DEVELOPMENT OF NEW METHODOLOGIES IN ORGANIC SYNTHESIS USING RONGALITE, Pd(II) (2-AMINONICOTINALDEHYDE) COMPLEX AND METHYL 2-NITROSOBENZOATE

A THESIS SUBMITTED TO

NATIONAL INSTITUTE OF TECHNOLOGY
WARANGAL

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY
IN
CHEMISTRY
BY
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WARANGAL-506 004, TELANGANA, INDIA
May-2020

Dedicated to

…My Family and Supervisor

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CERTIFICATE

This is to certify that the research work presented in this thesis entitled **"Development of New Methodologies in Organic Synthesis Using Rongalite, Pd(II) (2-aminonicotinaldehyde) Complex and Methyl 2-nitrosobenzoate"** submitted by **Mr. Sanjeeva Thunga** for the degree of Doctor of Philosophy in Chemistry, National Institute of Technology, Warangal (Telangana), under my supervision and that the same has not been submitted elsewhere for a degree.

Date:15-05-2020
Place: NIT Warangal

Dr. K. Hari Prasad
Thesis Supervisor

DECLARATION

I hereby declare that the matter embodied in this thesis entitled **"Development of New Methodologies in Organic Synthesis Using Rongalite, Pd(II) (2-aminonicotinaldehyde) Complex and Methyl 2-nitrosobenzoate"** is based entirely on the results of the investigations and research work carried out by me under the supervision of **Dr. K. Hari Prasad**, Department of Chemistry, National Institute of Technology, Warangal. I declare that this work is original and has not been submitted in part or full, for any degree or diploma to this or any other University.

Sanjeeva

(Sanjeeva Thunga)

ACKNOWLEDGEMENTS

The work presented in this thesis would not have been possible without my close association with many people. I take this opportunity to extend my sincere gratitude and appreciation to all those who made this Ph.D., thesis possible.

It gives me an immense pleasure and delight to express my deep sense of gratitude to my research supervisor ***Dr. K. Hari Prasad***, Assistant Professor, Department of Chemistry, National Institute of Technology, Warangal for his inspiring and valuable guidance. His unfailing attention, unmitigated encouragement and co-operation have helped me in attaining my goal. It would have been impossible to achieve this goal without his able support and valuable advice. I consider myself fortunate that he has given me a decisive tune, a significant acceleration to my career. I will be thankful to him throughout my lifetime.

I am greatly indebted to ***Prof. N. V. Ramana Rao***, Director, National Institute of Technology, Warangalallowing me to submit my research work in the form of a thesis. I express my gratitude to ***Prof. T. Srinivasa Rao*** and ***Prof. G. R. C. Reddy***, formerDirectors, National Institute of Technology, Warangal for giving me the opportunity to carry out the research work.

My special words of thanks to ***Prof. P. V. Srilakshmi,*** Head, Department of Chemistry and ***Prof.K. V. Gobi, Prof. V. Rajeswar Rao, Prof. B. Rajitha,*** former Heads, Department of Chemistry, National Institute of Technology, Warangal for their valuable advice, help and support.

I express my sincere thanks to the Doctoral Scrutiny Committee (DSC) members, ***Prof. P. Nageswara Rao, Prof. V. Rajeswar Rao***, ***Dr. B. Srinivas,*** Department of Chemistry and ***Prof. N. Narasaiah***, Department of Materials & Metallurgical Engineering for their support and encouragement.

I take this opportunity to express thanks to ***Prof. B. Venkata Appa Rao (Retd)***, ***Prof. G. V. P. Chandramouli (Retd)***, ***Prof. I. Ajit Kumar Reddy (Retd)***, ***Prof. A. Ramachandraiah***, ***Prof. K. Laxma Reddy, Dr. Vishnu Shanker***, ***Dr. Venkatathri Narayanan***, ***Dr. D. Kashinath***, ***Dr. Raghu Chitta, Dr. B. Srinivas, Dr. S. Nagarajan, Dr. M. Raghasudha, Dr. C. Jugun Prakash, Dr. Ravinder Pawar*** for their suggestions and encouragement.

Financial assistance from the Government of India, Ministry of Human Resource Development ***(MHRD)*** in the form of fellowship is gratefully acknowledged.

My sincere thanks to ***Dr. Satheesh vanaparthi*** (Post-Doctoral Fellow) formar research scholar IIT Guwahati for his continuous support, suggetions in my entire Phd.

My sincere thanks to ***Dr. Rambabu. Chegondi, Dr. Vikram Gaddam, Dr. Amarender Goud Burra, Dr. Uday Kumar Ryakala, Dr. Kranthi Kumar, Radhika Cinsani, and V. Venkateshwarlu,*** all from CSIR-IICT Hyderabad for their immensive support and helpful in my Ph.D. tenure.

I am very delighted to work with my lovely colleagues and will miss organic research lab. My sincere thanks to ***Soumya Poshala, Naveen Kumar A, Sivaparwathi G, and Swath, J.*** for their support and encouragement through entire my Ph. D and this thesis would not have come to a successful completion, without the help of these members.

It gives me a great pleasure to express my gratitude to my colleagues and friends ***Dr. N. V. Bharat, Dr. S. Nagaraju, Dr. B. Paplal, Dr. B. Janardhan, Dr. G. Ramesh, Dr. V. Krishnaiah, Dr. V. Ravi Babu, Dr. L. Suresh, Dr. P. Sagar Vijay Kumar, Dr. M. Venkanna, Dr. G. Mallikarjun, Dr. K. Sujatha, Dr. B. Mayuri, Dr. Manjula Reddy, Dr. Varun. A, Dr. K. Ramaiah, Vinay Pogaku, N. Satyanarayana, M. Saikumar, Ch. Suman, V. Sunil Kumar, J. Paramehswara chary, M. Srikanth, P. Babji, K. Satish, Ch. Raju, K. Vijendar reddy, A. Bhargava Sai, T. Dhanunjay Rao, Ramesh ajmera, R. Venkatesh, S. Suresh, K. Shekar, G. Ambedhkar, G. Srinath, G. Sripal Reddy, K. Sampath, R. Hithavani, M. Sireesha, T. Shirisha, B. Sravanthi, P. Venkatesham, B. Prashanth, R. Varaprasad, R. Arun, B. Anjaiah, Akansha. Sangolkar, Dr. B. Rajitha, Dr. M. Nooka Raju, Dr, A. Rajini, Dr. K. Yugender goud, Dr. K. Vimal Kumar, Dr. M. Satyanarayana, Dr. Chaithanya kumar, Dr. M. Narsimha Reddy, Dr. P. Sreenu, Dr. K. Koteshwara Reddy, Dr. T. Ramesh, Dr. G. Srinivasa Rao, Dr. A. Ajay Kumar, Dr. R. Rajkumar, Dr. T. Surendar, Dr. B. Thirupaiah, Dr. B. Santosh Kumar and all the research scholars and scholar of various Departments*** for their good compensation and creating a nice atmosphere in and outside the laboratory and their encouragement and help during my research period.

Also, my sincere thanks to ***Narsimha K, Venkanna. K*** (NMR instrument operators) *and* ***Srinivas. B*** (Mass Spectrometer operator) for their support to characterize the synthesized compounds.

My special thanks to Non-teaching and technical supporting staff of Chemistry Department ***P. Heeralal, B. Sadanandam, T. Kiran, Md. Shaheen begum, G. Santhosh, J Praveen., K, Sreenivas. K, Keshavulu, A Rajini. V, Bhavani. and Kavya. K.*** for their help in every time needed.

It would be understatement to say that I would not be the person I am today without my family. I am extremely gratified to my father ***Sri. Chandraiah*** for his moral support and encouragement to never give up. I am also thankful to my mother ***Smt. Laxmi*** for her best wishes and blessings for my success. I would never forget the motivational, inspiring, enthusiastic behavior of my Brothers and sister-in-law's: ***Sammaiah and Sneha. Balu and Shirisha.*** Sister and Brother-in-law: ***Nirisha and Balraju*** for their support during this time. I express my thanks to inspired persons ***Dr. Bharath Kumar, Dr. Shobha rani.*** I express my thanks to **Mr. Peram Shyam Prasad** for his help in writing my thesis. I express my thanks to my friends ***P. Srikanth, P. Naveen, T. Ramu, K. Karnakar, B. Praveen, M. Vinod, M. Prabhakar, Akshay, R. Rajitha*** who were always there to help me in their way. I thankful to my whole Big family members, friends, and My Village people, for their constant support, cooperation, encouragement, love and affection whose blessings made the journey worth effort. I owe everything to them.

(Sanjeeva Thunga)

ABBREVIATIONS

ACN	Acetonitrile
AIDS	Acquired immune deficiency syndrome
AcOH	Acetic acid
BIM	Bisindolylmethanes
$(Bpin)_2$	Bis(pinacolato)diboron
BHT	Butylated hydroxytoluene
$CDCl_3$	Deuterated chloroform
CA	Capillary action
^{13}C NMR	Carbon nuclear magnetic resonance
$CuSO_4$	Copper sulphate
CTAB	Cetyltrimethylammonium bromide
CNS	Central nervous system
Cs_2CO_3	Cesium carbonate
COX-2	Cyclooxygenase-2
CuI	Cupper iodide
d	Doublet
dd	Doublet of doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	1,2-Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEA	Diethyl amine
DMSO-d_6	Deuterated dimethyl sulfoxide
DMF	*N*, *N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DIM	Diindolylmethanes
EtOH	Ethanol
Et_3N	Triethylamine
EtOAc	Ethyl acetate
FTIR	Fourier transform infrared
$FeCl_3$	Iron (III) chloride
GABA	γ-Amino butyric acid

h	:	Hours
HZ	:	Hertz
H_2O	:	Water
H_2O_2	:	Hydrogen peroxide
HCHO	:	Formaldehyde
HRMS	:	High-resolution mass spectrometry
HIV	:	Human immunodeficiency virus
J	:	Coupling constant
K_2CO_3	:	Potassium carbonate
IAA	:	Indole-3-acetic acid
$InCl_3$	:	Indium chloride
m	:	Multiplet
m-CPBA	:	meta-Chloroperoxybenzoic acid
MeOH	:	Methanol
min	:	Minutes
mg	:	Milligram
mL	:	Millilitre
mmol	:	Milli mole
M. P	:	Melting point
MW	:	Microwave Irradiation
$Rh_2(Oct)_4$	:	Rhodium(II)octanoate dimer
NaOAc	:	Sodium acetate
$NaHCO_3$	:	Sodium bicarbonate
ND	:	Not detected
NDA	:	Nitroso Diels-Alder reaction
NHC	:	*N*-Heterocyclic Carbene
NH_4OAc	:	Ammonium acetate
NADP	:	Nicotinamide adenine dinucleotide phosphate
NADPH	:	Reduced form of nicotinamide adenine dinucleotide Phosphate
NMR	:	Nuclear Magnetic Resonance
NMM	:	*N*-Methylmorpholine
NMO	:	*N*-Methylmorpholine *N*-oxide
NSAID	:	Non-steroidal anti-inflammatory agents
ORTEP	:	Oak Ridge Thermal Ellipsoid Plot
Ph	:	Phenyl
Pd	:	Palladium

Pd(OAc)$_2$: Pd(II)Palladium acetate
Pd(ANA) : Pd (II)-(2-aminonicotinaldehyde)
ppm : Parts per million
PSMS : Zinc bis[(phenylsulfonyl)methane sulfinate]
PTSA : *p*-Toluene sulfonic acid
q : Quartet
rt : Room temperature
s : Singlet
SAM : S-adenosylmethionine
SXRD : Single Crystal X-ray Diffraction
t : Triplet
TBHP : *tert*-Butyl hydroperoxide
TEA : Triethylamine
TEMPO : (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA : Trifluoro acetic acid
THF : Tetrahydrofuran
TLC : Thin Layer Chromatography
TMS : Tetramethyl silane
TPPMS : Sodium 3-(diphenylphosphino)benzenesulfonate
tpp-I$_2$: Triphenylphosphine-iodine
TON : Turnover number
UV-Vis : Ultraviolet-visible

Table of Contents

CHAPTER-I

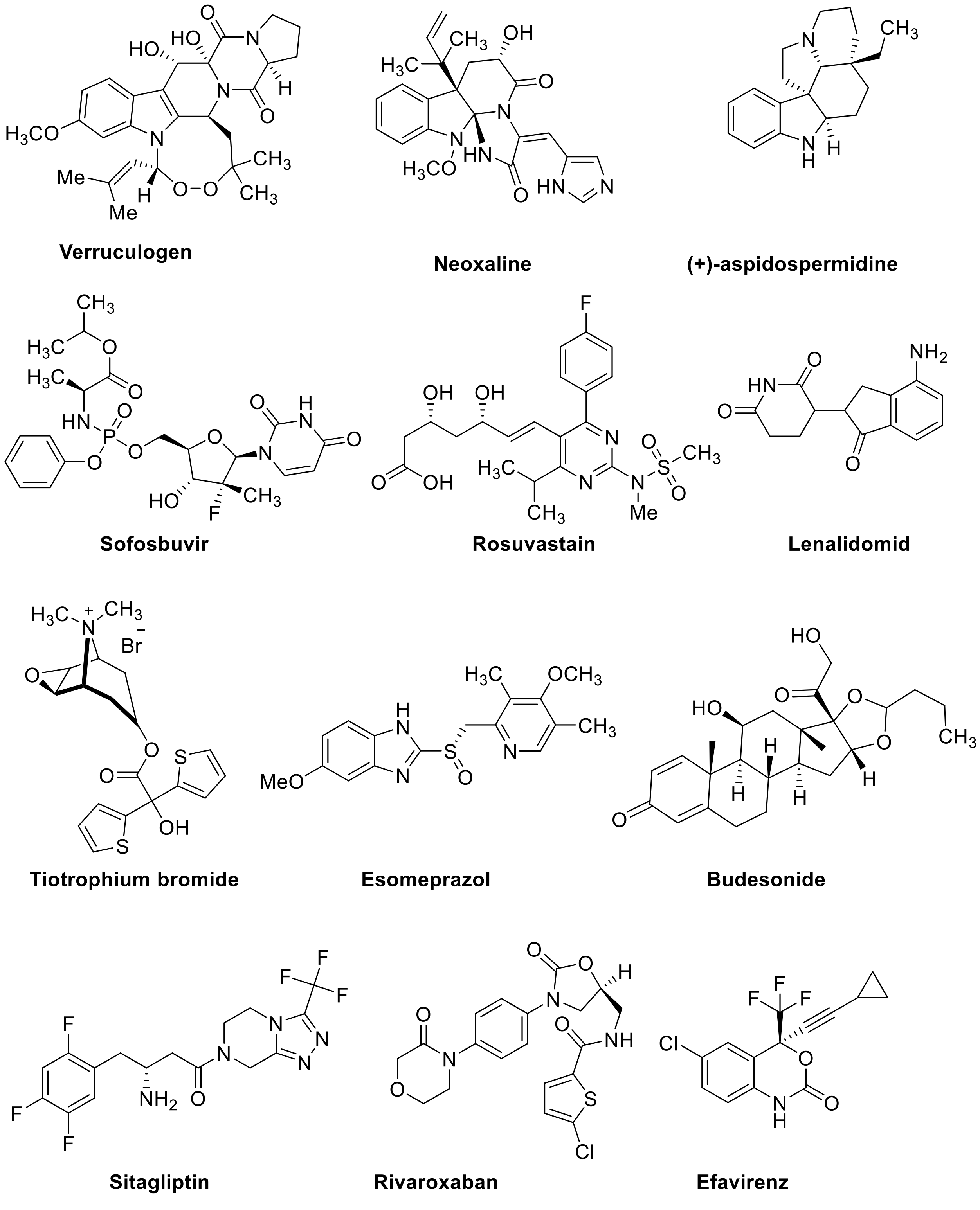
INTRODUCTION

1.1 Introduction

Development of new methodologies for the synthesis of nitrogen containing heterocycles has become thrust area because of their widespread applications in multi disciplinary fields ranging from natural products, engineering materials, agrochemicals to pharmaceuticals.[1-10] It is estimated that more than 50% of the published chemical literature contains heterocyclic structures and about 70% of all pharmaceutical products possess heterocyclic structural subunits, because of a favourable combination of drug-like properties. Of those, over 200 are currently marked to be drugs are undergoing clinical trials (Figure 1.1).[9,11] Thus, the chemistry of heterocycles is still a challenging research area to be explored by researchers across the globe.

Particularly, indoles and imidazo[1,2-*a*]pyridines are possessing wide spectrum of biological activities.[12-16] Keeping their promising biological activities and pharmaceutical applications, numerous methodologies are available for their synthesis. However, majority of the synthetic procedures involve use of toxic metals and harsh reaction conditions (more details are covered in chapter 2 and 3). For the past two decades green chemistry is playing a crucial role in minimizing the waste production and developing environment sustainable methodologies.[17] In this regard, green protocols such as one-pot approach, transition metal catalysis and metal-free conditions are the emerging techniques for the synthesis heterocyclic compounds under the green chemistry principles. Hence, the development of new synthetic routes for synthesis of heterocyclic compounds using mild and non-toxic reagents is a crucial goal for chemist.

Towards this goal, we have developed novel methods for the synthesis of heterocyclic compounds such as substituted indoles, imidazo[1,2-*a*]pyridines among others using commercially available, inexpensive and non-toxic reagents. In this chapter a brief introduction of indoles, imidazo[1,2-*a*]pyridines and the reagents used in this thesis were covered.



Verruculogen **Neoxaline** **(+)-aspidospermidine**

Sofosbuvir **Rosuvastain** **Lenalidomid**

Tiotrophium bromide **Esomeprazol** **Budesonide**

Sitagliptin **Rivaroxaban** **Efavirenz**

Figure 1.1. Some of the Important Pharmaceuticals Containing Heterocyclic Moieties.

1.1.1. Indoles

Indole gained immense popularity as a suitable candidate to be used in many drugs in at several pharmacological conditions, since its discovery in 1860s by Baeyer and co-workers while studying the structure of indigo. Indole is an aromatic heterocyclic organic compound with formula (C_8H_7N), fusion of a six-membered benzene and five-membered pyrrole ring at 2 and 3 positions. The unsubstituted indole is a colorless crystalline solid with an unpleasant odor.

The word indole is derived from the words *indigo* and *oleum* as it was first isolated through treatment of indigo dye with oleum.[18-20] It was first discovered by Adolf van Baeyer through pyrolysis of oxindole with zinc dust way back in 1866 while oxindole was obtained through reduction of isatin which itself is formed through oxidization of indigo, a naturally occurring insoluble dark blue dye found among the plant species of indigofera that itself is an example of bisindole. It was in the year 1869 that the formula of indole was proposed by Baeyer that now is accepted today.[21]

Indole with its peculiar and interesting molecular architecture attracted the attention of various organic and medicinal chemists to design derivatives for their respective fields (Figure 1.2).

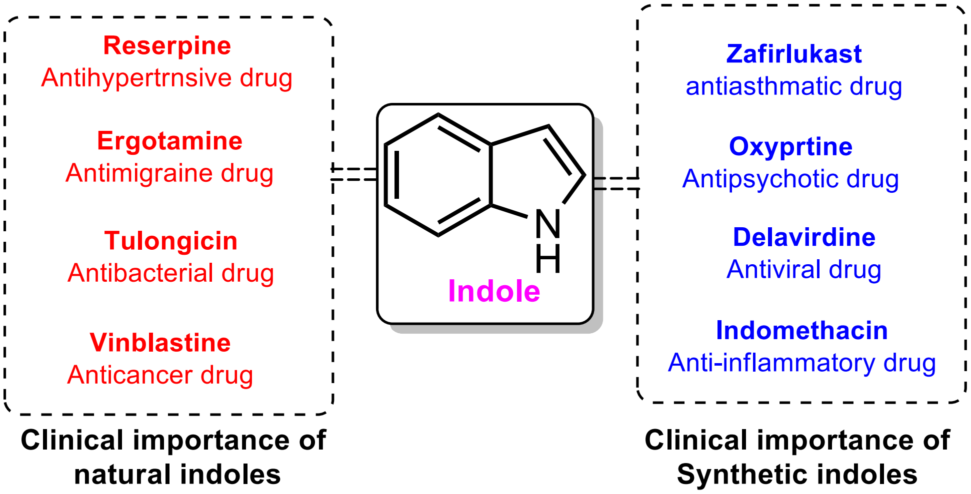
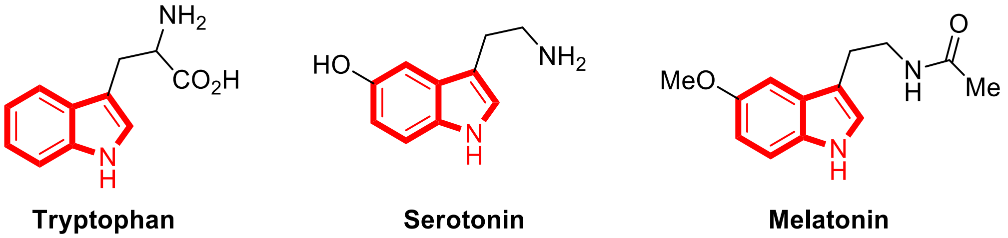


Figure 1.2. Applications of Inodole.

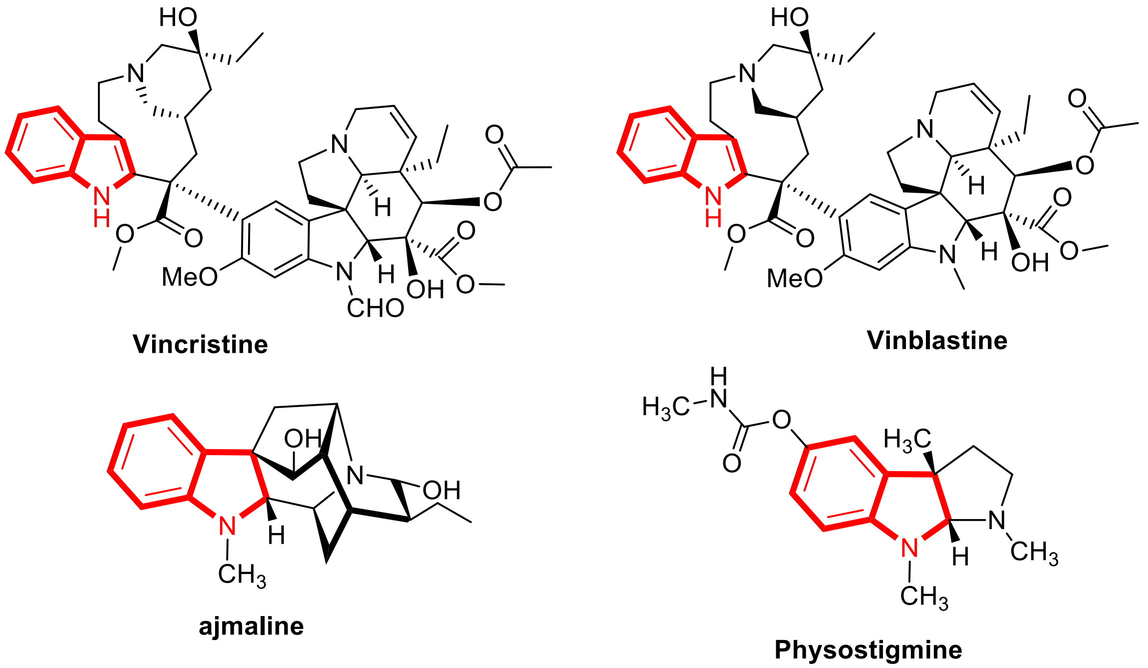
There exists a lot of literature on the electronic properties of indole that enable the synthesis of a number of indole derivatives via nucleophilic and electrophilic additions, C-H activation and cycloaddition.[22] This property of indole improves the portfolio for synthetic manipulation. Apart from all of these Indole is also an important phyto-constituent and is found in various plants species and is also produced by a variety of bacteria. Its natural occurrence can be traced to its presence in the essential amino acid tryptophan.[23] Indole-derived phyto-constituents and bacterial metabolites are a result of biosynthesis via coupling of tryptophan with other amino acids. It is because of all these reasons that indole or one of its derivatives became a constituent of flower perfumes, pharmacologically active indole alkaloids, and some animal hormones such as serotonin and melatonin (Figure 1.3).[24]



Tryptophan **Serotonin** **Melatonin**

Figure 1.3. Some of the Indol based bioactive compounds.

Some naturally occurring indole based vinca alkaloids have gained FDA approval, including vincristine, vinblastine, vinorelbine, and vindesine for anti-cancer chemotherapy drugs; ajmaline for antiarrhythmic activity; and physostigmine for glaucoma and Alzheimer's disease (AD) (Figure 1.4).[25a-c]

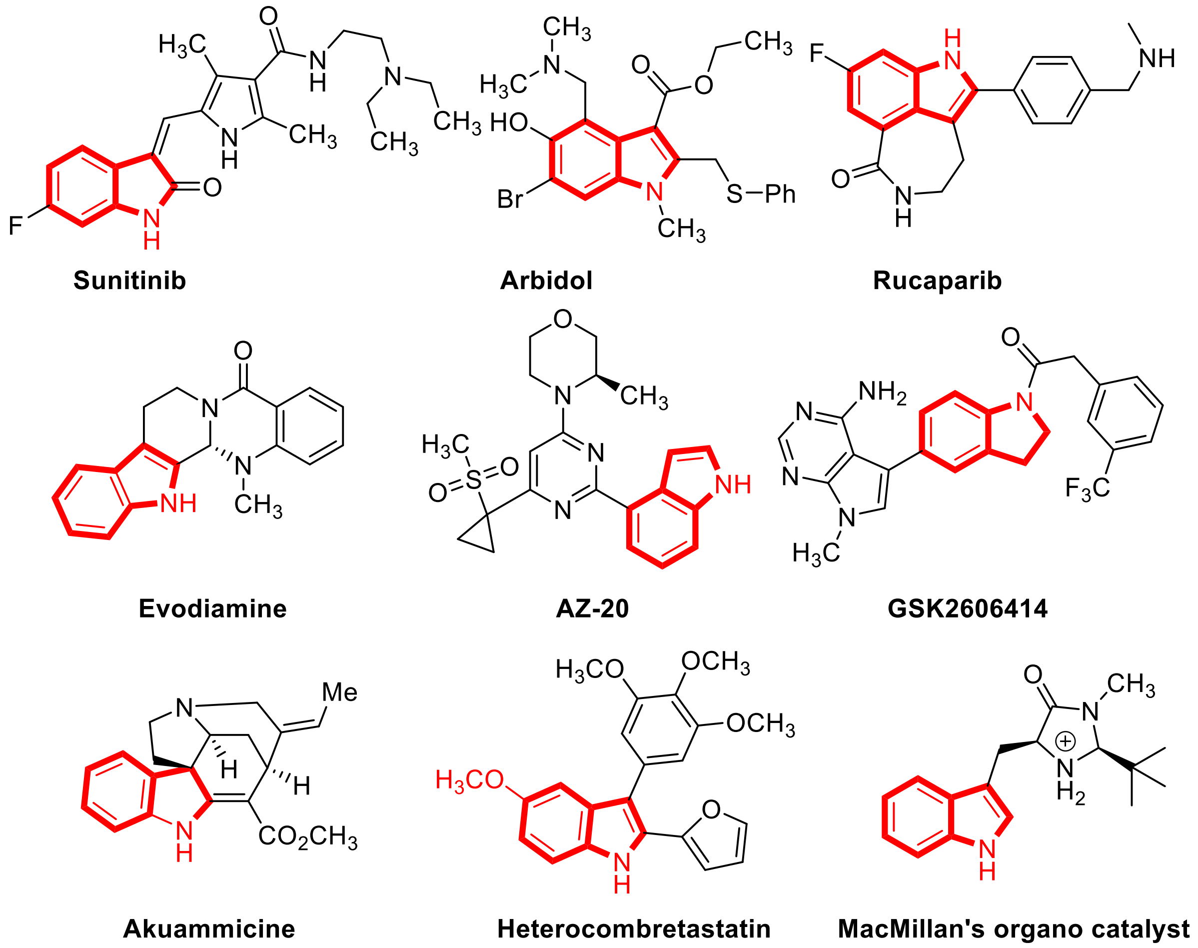


Vincristine **Vinblastine**

ajmaline **Physostigmine**

Figure 1.4. Some of the Indol alkaloids.

Taking inspiration from these natural compounds several synthetic drugs have been developed and released into the market as drug to treat various diseases (Figure 1.5).[26]



Sunitinib **Arbidol** **Rucaparib**

Evodiamine **AZ-20** **GSK2606414**

Akuammicine **Heterocombretastatin** **MacMillan's organo catalyst**

Figure 1.5. Some of the Pharmaceuticals Containing Indoles.

One of the most permeating heterocycles available in nature is the indole ring and forms backbone of many natural and biologically active compounds with high structural complexities. Thismade indole and its derivatives to be used continuously in wide ranging areas such agrochemicals, material sciences, pharmaceuticals, pigments and organo-catalysis (Figure 1.5).[27]

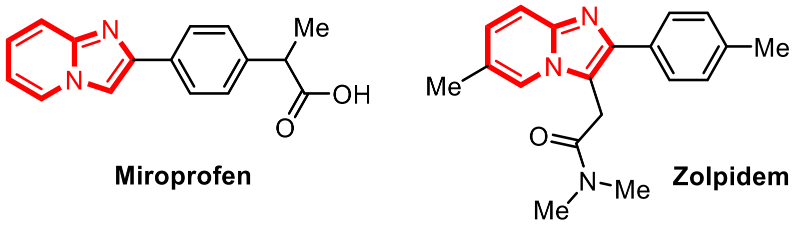
1.1.2. Imidazo[1,2-*a*]pyridines

Imidazole with its valuable therapeutic properties prompted chemists to synthesize a large number of novel chemotherapeutic agents like clotrimazole, ketoconazole, miconazole, sulconazole, tioconazole among others.Among the imidazoles system, imidazopyridines have been recognized as a privileged structure because of its diverse biological and pharmacological applications.[28-32] The two types of imidazopyridines that are commonly encountered are imidazo[1,2-*a*]pyridines and imidazo[1,5-*a*]pyridines (Figure 1.6).

Imidazo[1,2-*a*]Pyridines **Imidazo[1,5-*a*]Pyridines**

Figure 1.6. Core structure of imidazopyridines.

Here our primary focus of research interests has been imidazo[1,2-*a*]pyridines mainly due to their significant CNS activity, non-steroidal anti-inflammatory drugs (NSAIDs), GABA receptor agonists and their selective affinity towards benzodiazepine receptors without exhibiting any considerable negative side effects.[33] All of these properties make imidazoles an effective substitute for trivial benzodiazepine drugs and are used generally as sedatives, anti-convulsant, hypnotic anxiolytics and muscle relaxants. Furthermore, many drugs based on imidazo[1,2-*a*] pyridine such as Zolpidem, Alpidem and Saripidem etc., have been proved to be potent against pentylene tetrazole (PTZ) induced seizures (Figure 1.7).[34-36]



Miroprofen **Zolpidem**

Figure 1.7. Imidazo[1,2-*a*]pyridine Drugs.

On the other hand, both the imidazo[1,2-*a*] and imidazo[1,5-*a*]pyridine derivatives are used in optoelectronics as they exhibit an excited-state intramolecular proton-transfer process (ESIPT).[37]

1.2. Rongalite

Rongalite is scientifically called as sodium hydroxymethanesulfinate(SHM) (or) sodium formaldehyde sulfoxylate (Figure 1.8)[38] a crystalline industrial product that has been used as decolourizing agent for compounds like caramel, sugar juice etc.; and also used as bleaching agent in the dyeing and printing industry.[39] It is commonly used as an antidote against heavy metal poisoning involving Hg, Au, Cu, Ba, Sb, Pb and Bi.[40] It has been employed as a green reducing agent for reduction of metal salts,[41] aldehydes,[42] benzils[43] and nitroaromatics.[44] It is one of the important component in the preparation of veterinary medicines.[45] Rongalite is a traditional antioxidant, stabilizer and is used as one of the major component in the formulations in anticancer agents.[46]

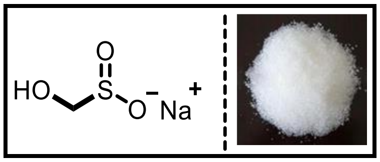
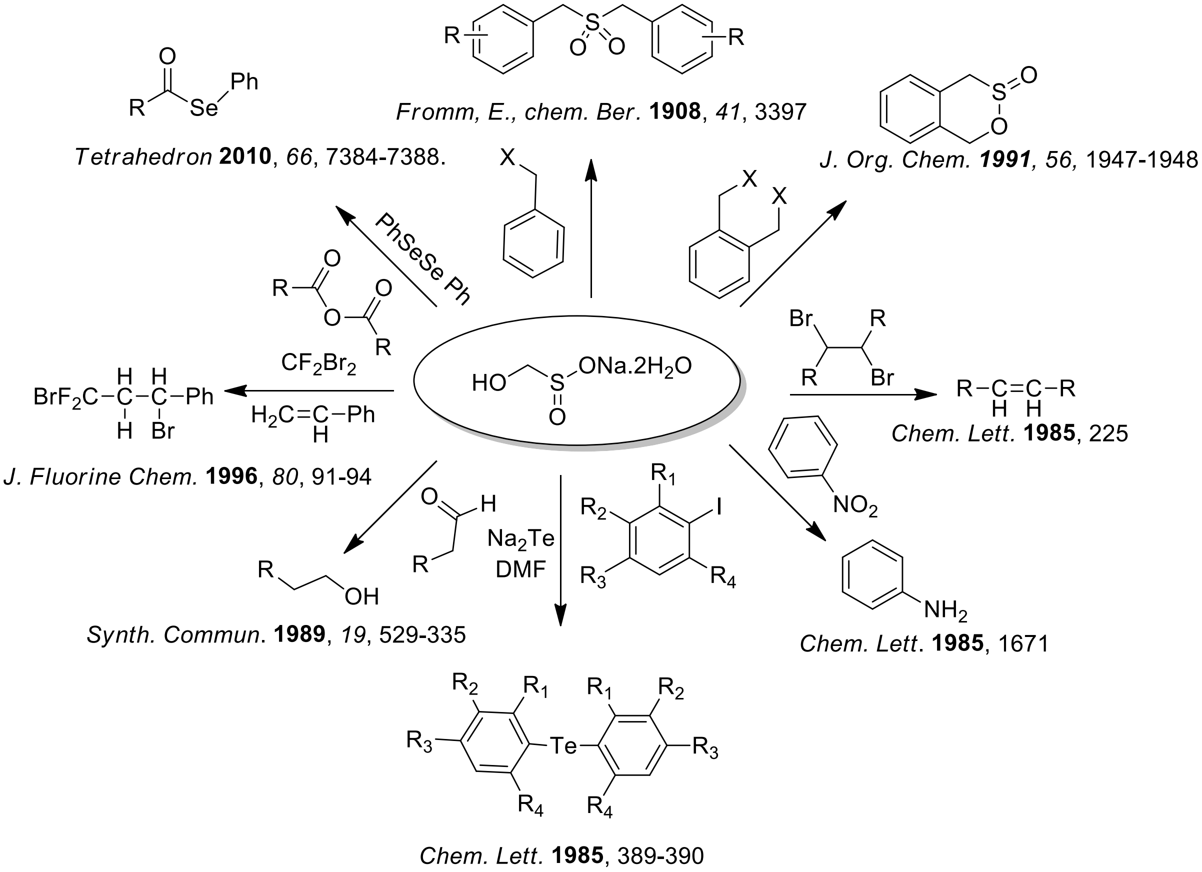


Figure 1.8. Structure Rongalite.

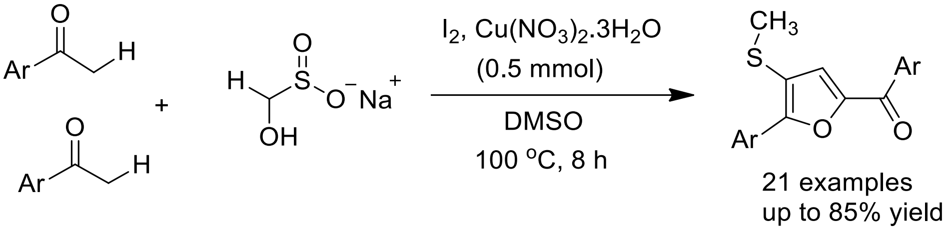
Kotha and co-workers extensively used the multifaceted reactivity of Rongalite in various organic transformations.[47] This reagent has been extensively utilized in the synthetic organic chemistry for the preparation of sulfides, sulfones, selenides, selenoesters, sultines, tellurides, thioesters, allylic alcohols and fluorine containing organic compounds (Scheme 1.1).[48]



Scheme 1.1

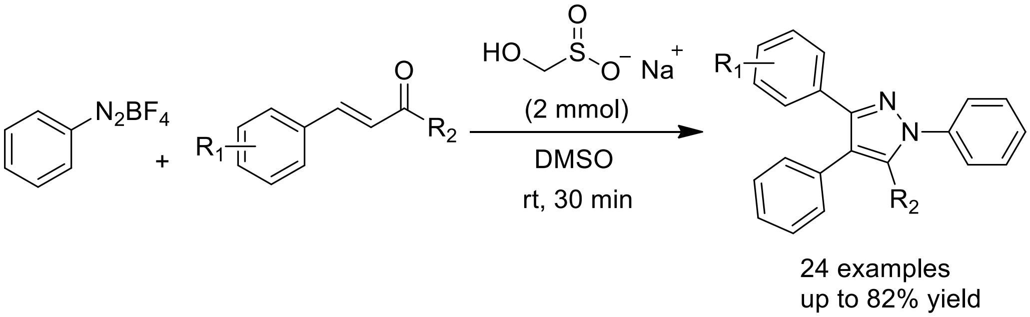
Some of the important organic transformations are listed below

Wang et al. developed a highly efficient method for the preparation of 2,4,5-trisubstituted furans via $I_2/Cu(NO_3)_2 \cdot 3H_2O$ catalyzed domino C(sp^3)-H activation from aryl methyl ketones in presence of rongalite. In this method rongalite donates C1 for the furans. This method gives rapid access to the library of (2-acyl-4 methylthio-5-aryl) furans (Scheme 1.2).[49]



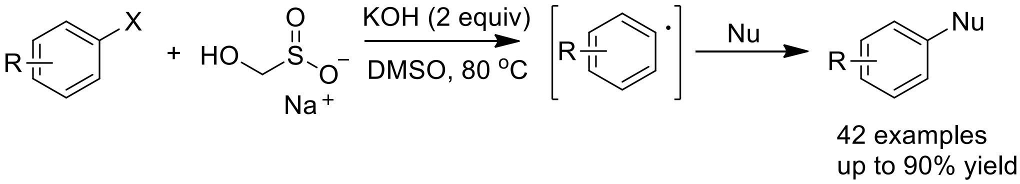
Scheme 1.2

Miao Wang et al. introduced a novel rongalite-promoted multi-component radical annulation reaction to obtain highly substituted pyrazoles from aryldiazonium salts and *α, β*-unsaturated carbonyls under transition metal-free conditions. In this method aryldiazonium salts plays a dual role of both the aryl and aryl hydrazine units (Scheme 1.3).[50]



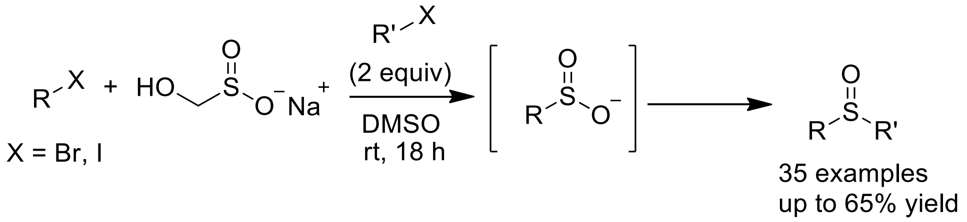
Scheme 1.3

Fazhi et al. introduced the transition-metal free electron-catalyzed reactions to obtain C−C, C−S, and C−P bonds through homolytic aromatic substitution or $S_{RN}1$ reactions from the aryl halides in the presence of sodium formaldehyde sulfoxylate. The antipsychotic drug, Quetiapine was synthesized on gram scale from the above described method (Scheme 1.4).[51]



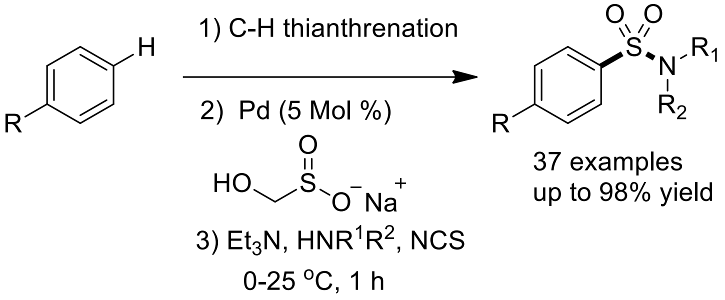
Scheme 1.4

Shavnya and co-workers developed a novel enroot for the telescoped synthesis of aliphatic sulfonamides, sulfonyl fluorides, and unsymmetrical sulfones on the basis of interrupted alkylation of rongalite with alkyl halides. The uniqueness of this protocol is mild reaction conditions, use inexpensive reagents, and they being air stable (Scheme 1.5).[52]



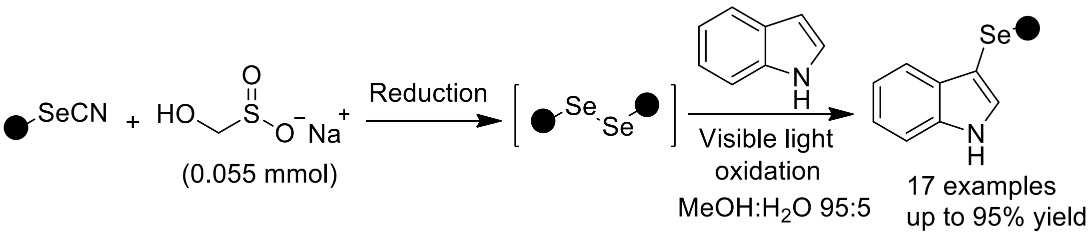
Scheme 1.5

Teppei et al. have been synthesized number of sulfonyl-derived arenes via site-selective two-step C−H sulfonation sequence via aryl sulfonium salts to access aryl sulphonamides. The described protocol involves sequential reaction of site-selective aromatic thianthrenation, palladium-catalyzed sulfonylation from sodium hydroxymethanelsulfinate (Rongalite) as a source of SO_2^{2-}. This approach delivers diverse number of sulfonyl-arenes, which are key intermediates in pharmaceuticals and agrochemicals (Scheme 1.6).[53]



Scheme 1.6

Recently, **Gabriela and co-workers** developed a novel multi-step continuous-flow system in order to synthesise active pharmaceutical ingredients (APIs), natural products and fine chemicals. In this method, selenylation of biologically important heterocyclic compounds was achieved by the combination of a chemical reduction and photochemical C(sp^2)-H activation by continuous-flow process (Scheme 1.7).[54]

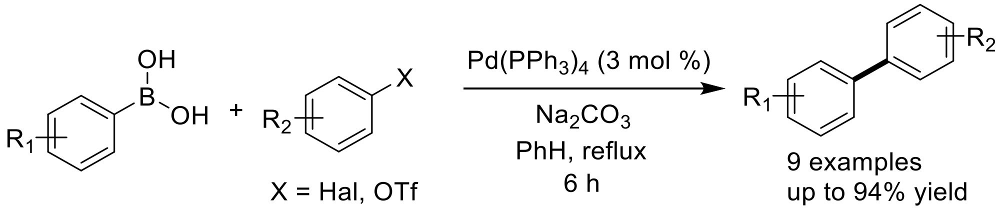


Scheme 1.7

1.3. Palladium Chemistry

Among the various methods available for Carbon-Carbon bond formation reactions, the cross-coupling reactions facilitated by transition-metal are currently leading in the synthetic chemistry.[55-56] Generally, transformations involving palladium (Pd) catalyst such as Suzuki-Miyaura, Heck, Songashira, Stille, Hiyama, Negishi, Kumada and Murashi are known for their versatility and usefulness can be employed both within the academic circles and industrial production plants.[57-64] These types of transition-metal catalyzed carbon-carbon bond forming processes makes up a lion's share of reactions in modern synthetic chemistry. These types of reactions were first discovered and developed during the 1970s thus giving a break away from the conventional reactions and enabled the cross coupling of substrates in ways that were never thought possible.[65] With time these reaction protocols are improved upon and thus provided a simple and efficient methodology for the new generation of chemists. Its importance was recognized by the Nobel committee in 2010 by awarding Richard F. Heck, Ei-ichiNegishi and Akira Suzuki Nobel Prize in Chemistry.[66]

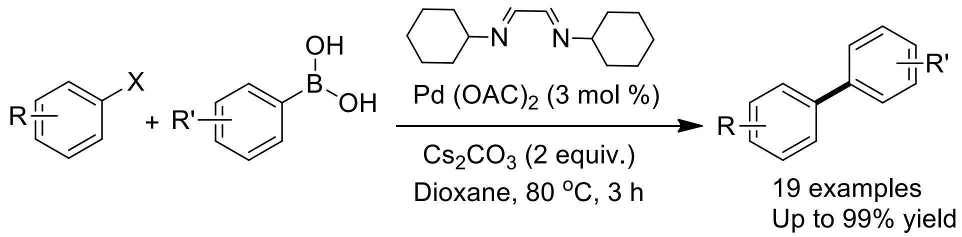
Within these wide-ranging cross-coupling reactions, the Suzuki-Miyaura and Heck cross-coupling reactions become popular from the last two decades. The Suzuki-Miyaura's reaction involves organo-boron compounds and organic halides catalyzed by Palladium rose to fame on account of their efficiency in the construction of carbon-carbon bonds (Scheme 1.8).[67] The factors that made this a possibility are i) commercial availability of starting materials, ii) mild reaction conditions, iii) no significant effect of steric hindrance, iv) easy removal of nontoxic boron containing by-products, v) broad functional groups compatibility, vi) water can be used a solvent or co-solvent among others.



Scheme 1.8

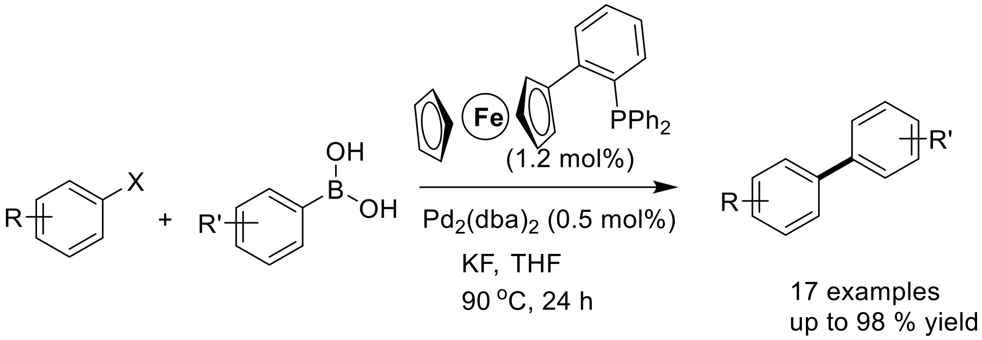
Some of the important Suzuki-Miyaura reactins are listed below

Nolan and research group developed a method for the Suzuki cross-coupling reaction between arylboronic acids and aryl halide in the presence of $Pd(OAc)_2$ and diazabutadiene ligand system in dioxane at 80 °C (Scheme 1.9).[68a]



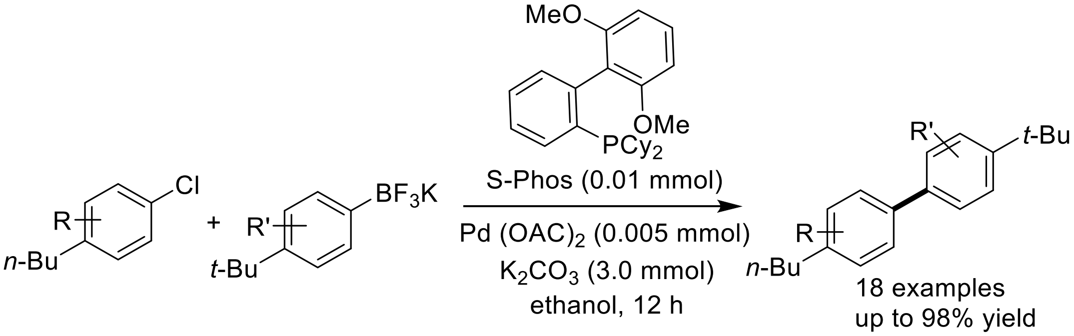
Scheme 1.9

Kwong et al. described the Suzuki cross coupling reaction between arylboronic acids and aryl halide in presence of metallic palladium and ferrocene-atteched triarylphosphine ligand in toluene at 90 °C (Scheme 1.10).^{68b}



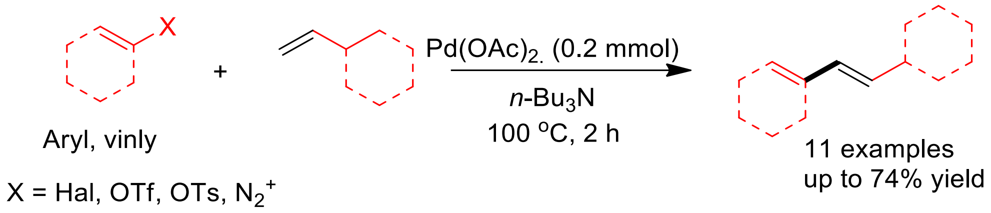
Scheme 1.10

Buchwald and co-worker explained the formation of highly hindered biaryls from aryl or heteroaryl halides and potassium aryl-or heterearyl trifluoroborates using palladium catalyst with S-Phos as supported ligand, K_2CO_3 as base in ethanol with excellent yields (Scheme 1.11).^{68c}



Scheme 1.11

Heck cross-coupling reaction was independently discovered by T. Mizoroki (1971) and R. F. Heck (1972), is generally known as the arylation of olefins catalyzed by palladium. This reaction involves an arylhalide and alkene in presence of catalytic amounts of palladium, and a base to afford the corresponding arylated alkene (Scheme 1.12).[69] It was initially started as a novel method for the preparation of stilbenes from styrenes and iodobenzene which subsequently developed into one of the most versatile and efficient methodologies to synthesize substituted olefins in the industrial domain.

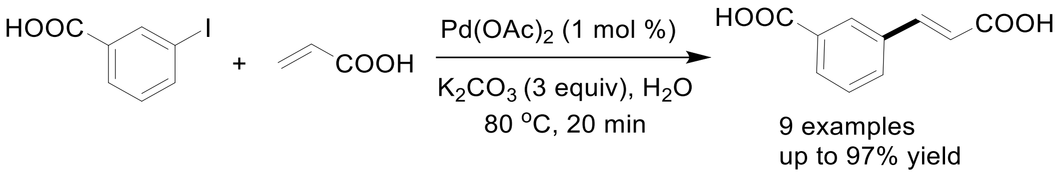


Scheme 1.12

It is because of these features that these reactions are used for the synthesis of a wide range of products in pharmaceutical industry while in the academic laboratories many natural and non-natural products are produced as agrochemical dendrimers, porphyrins, peptides and other materials.[70]

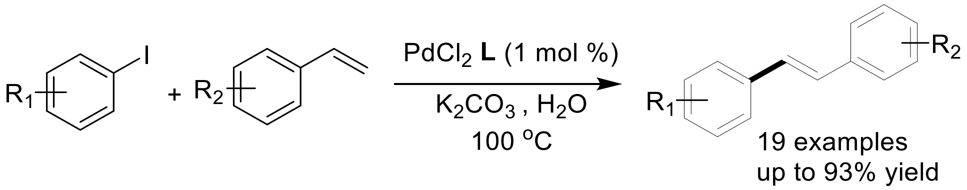
Some of the recent Heck cross-coupling reactions are listed below

Beletskaya and research group reported the first ligand-free palladium catalyzed Heck cross coupling reaction in aqueous medium. In this method they directly used commercially available $Pd(OAc)_2$ or $PdCl_2$ in the presence of some inorganic bases like K_2CO_3, $NaHCO_3$, NaOAc or amines. Initially it was reported in the use of acrylic acids (Scheme 1.13).[71]



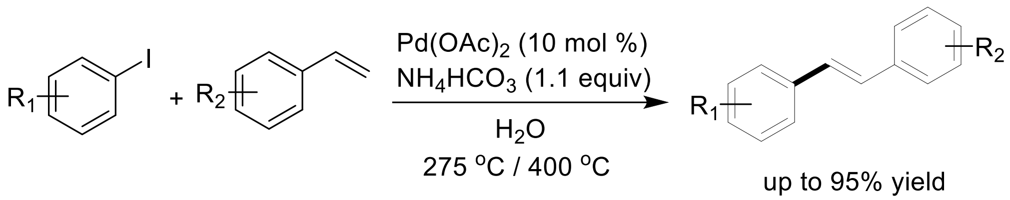
Scheme 1.13

Bumagin et al. developed a synthesis of stilbene derivatives with the reaction of styrene and aryl halides using $PdCl_2(o\text{-}Tol_3P)_2$ catalyst, K_2CO_3 in aqueous solution. From this method they have synthesised a library of stilbenes which they reported excellent yields (Scheme 1.14).[72]



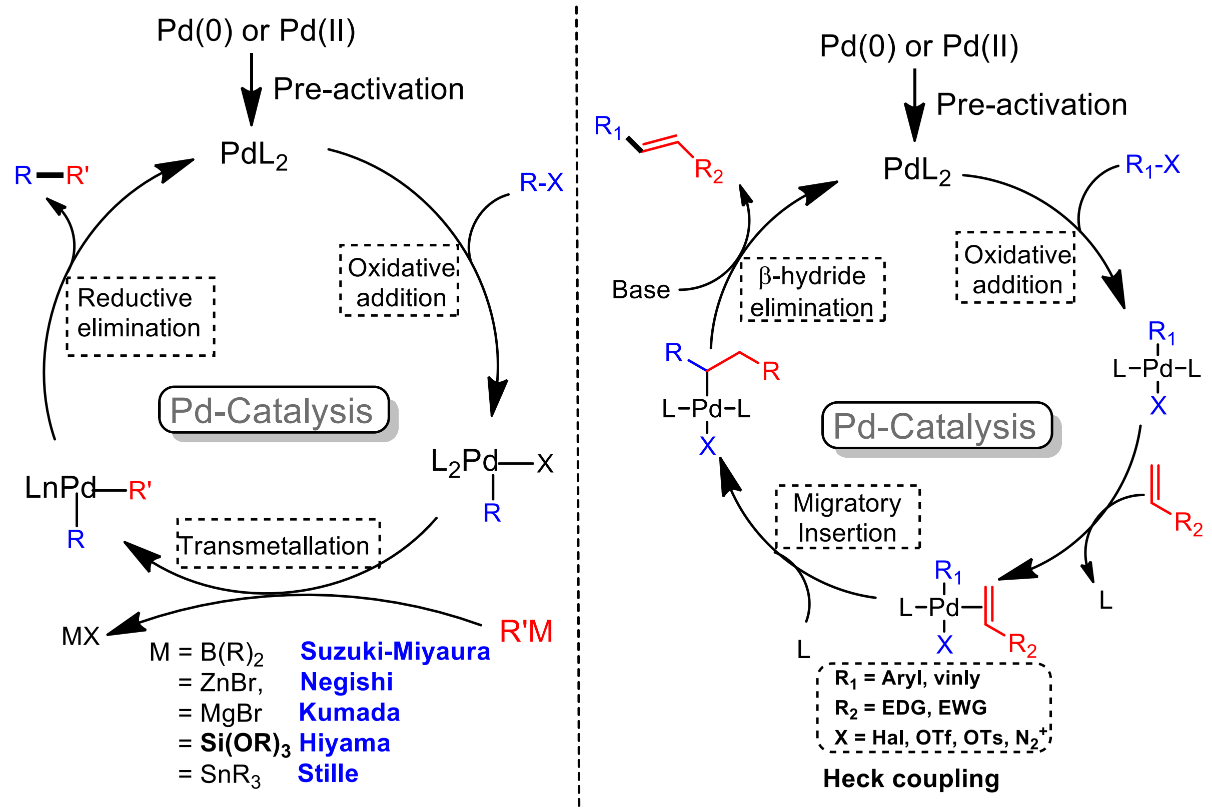
Scheme 1.14

Parsons and research group introduced homogenous ligand-free Pd(OAc)$_2$catalyzed Heck couplingprepare substituted stilbenes from iodobenzene and styrene in super critical water (Scheme 1.15).[73]



Scheme 1.15

A general catalytic cycle for the cross-coupling reaction of palladium, which involves oxidative addition transmetalation and reductive elimination sequences, is depicted in Scheme 1.16.[74]



Scheme 1.16

Like with any other reactions, these palladium cross-coupled reactions have been improved at various levels such as metal and its surrounded ligands, substrates, and reaction conditions to transform it to advanced level to accomplish green chemistry principles. The diverse coupling reactions use homogeneous palladium as catalyst whose importance became even more significant in case of Suzuki reaction as they provide high reaction rate, facilitates high selectivity, high yields and also high turnover numbers (TON).[75] In processes involving the use palladium catalyst, ligands such as phosphines,[76] dialkylbiarylphosphines,[77] diamines,[78] diphosphines,[79] dibenzylideneacetone,[80] carbenes,[81] Pincers,[82] bipyridines,[83] and pyridines,[84] (Figure 1.9) among others plays a crucial role such as enhancing the ability of catalyst to activate even weak leaving groups such as chloride, exhibiting higher TON and reaction rates.

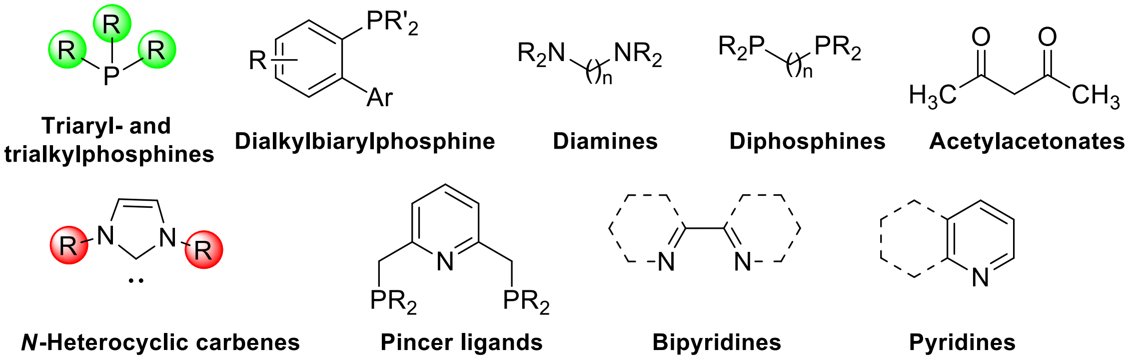


Figure 1.9. Ligands used in Palladium Catalyzed Reactions.

Quite recently a novel phosphorous free palladium catalyst has been designed that allows for higher activity, stability and substrate tolerance and even allows the reactions to be carried out under milder conditions.[85] In literature we found that only few pyridine based bidentate ligands for palladium catalyzed cross coupling reactions.[86] In continuation of our effort towards the sustainable chemistry to develop environmentally benign and commercially cheap catalyst, we searched for a robust, inexpensive and biologically relevant monodentate pyridine based-Pd(II)-catalysts for Suzuki-Miyaura and Heck couplings (Figure 1.10).[87]

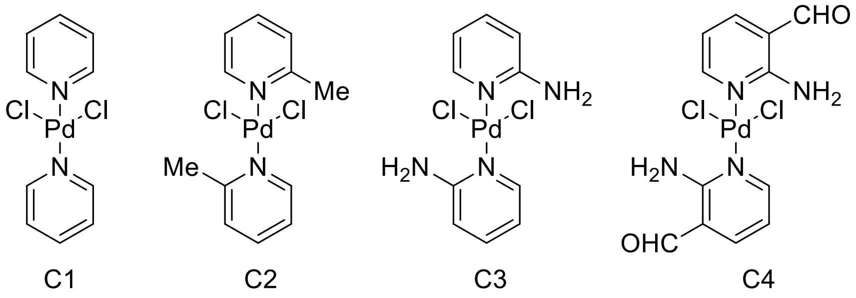


Figure 1.10. Palladium Pyridine Complexes.

1.4. C-Nitroso Compounds

Nitroso compounds (**R-N=O**) are important synthetic building blocks in organic synthesis. C-nitroso compounds are classified into nitrosoalkanes (R-NO; R = alkyl) and nitroso arenes (ArNO; Ar = aromatic), which plays an important role in various biological metabolic processes.[88] These nitroso compounds are indicators of some of the poisoning compounds (Figure 1.10).[89] For example, the detection of the nitroso benzene adduct of hemoglobin as a result of nitrobenzene poisoning[90] and the comprehensive studies show that some amine containing drugs may be metabolized to nitroso derivatives led to an amplified interest to pursue the fundamental biochemical properties of this fascinating class of *C*-nitroso compounds.[91-92]

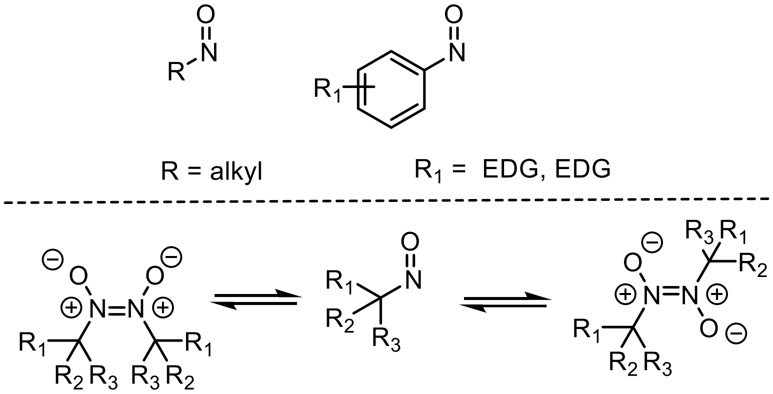


Figure 1.10. Dimerization of Nitroso Compounds.

Apart from the biological activity, one of the major advantages of cycloaddition reactions include their ability of regio-selective properties especially those involving nitroso compounds which themselves are readily available and can be used as starting materials in the synthesis of various natural product like molecules.[93] Some of the examples to this effect include synthesis of azasugars, asymmetric Diels-Alder reactions.[94-95] It was in the year 2011 that Bodnar and Miller reviewed hetero Diels-Alder reactions of acyl nitroso compounds with diene where they discovered the utility of the resultant oxazine rings in the synthesis of various biologically important molecules.[96] All of these experiments and the subsequent results points to the plethora of applications of nitroso derivatives in many of the present day ultra modern synthetic endeavors. Within these the utility of the N=O moiety can be regarded to know no bounds in the organic transformations including directing of many C-H functionalization reactions (Figure 1.11).[97]

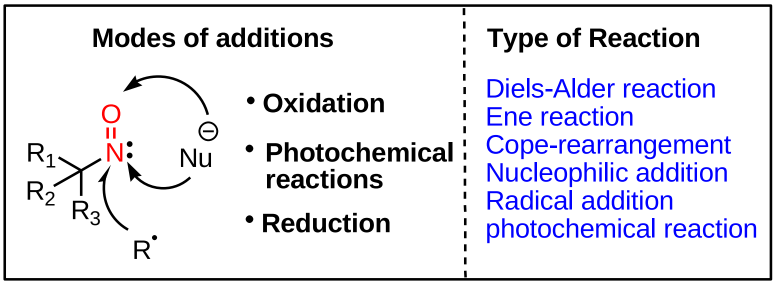
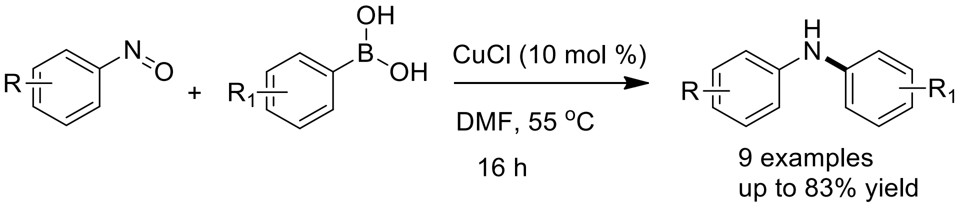


Figure 1.11. Reactivity of Nitroso Compound.

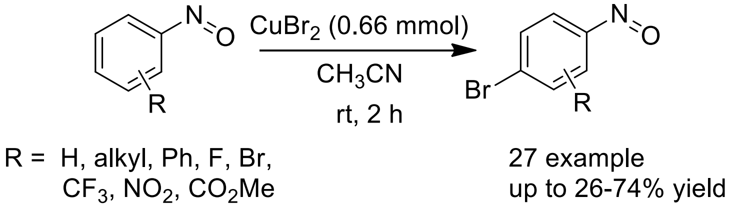
Some of the remarkable findings that involve nitroso compounds are discussed below.

Liebeskind and co-workers developed a copper-catalyzed reaction of aromatic nitroso compounds with arylboronic acids, which provided a novel synthetic diarylamine compounds (Scheme 1.11).[98]



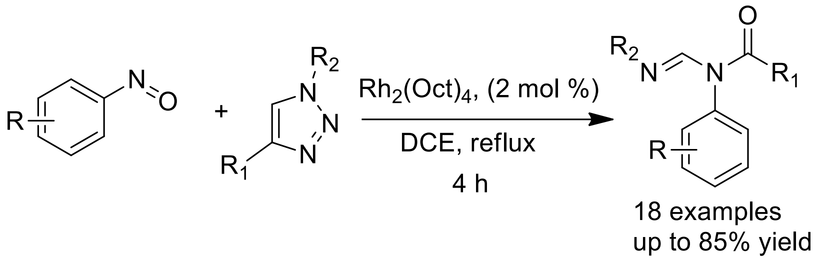
Scheme 1.11

Werfet al. developed a CuX2 catalyzed, mild, less-hazardous and regioselective halogenation for the synthesis of nitroso arenes (Scheme 1.12).[99]



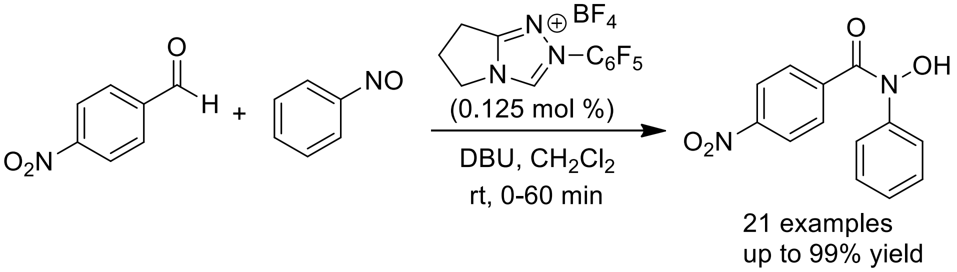
Scheme 1.12

Rui-Qiao et al. developed a new protocol of *N*-sulfonyl-1,2,3-triazoles with aromatic nitroso compounds to obtain *N*-acyl amidines in good to excellent yield. This methodology involved N-O bond cleavage by Rh-catalyzed decomposition of the corresponding triazole (Scheme 1.13).[100]



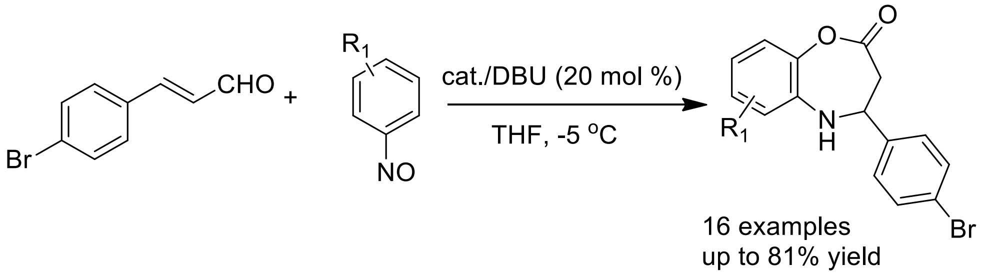
Scheme 1.13

Wong et al. introduced a metal-free condition for NHC-catalyzed amidation reaction of aldehydes with nitroso compounds in the presence of DBU to afford *N*-aryl hydroxamicacids (Scheme 1.14).[101]



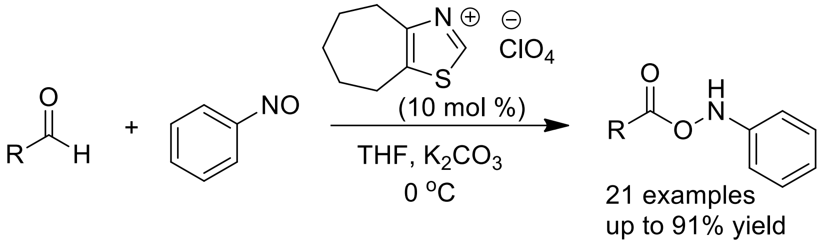
Scheme 1.14

Zhong and co-workers demonstrated ^{i}Pr-NHC catalyzed annulation of enol with nitroso arenes to furnish seven membered 4-azalactones under mild conditions. This reaction pathway follows 1,2-Bamberger-type rearrangement as a key step (Scheme 1.15).[102]



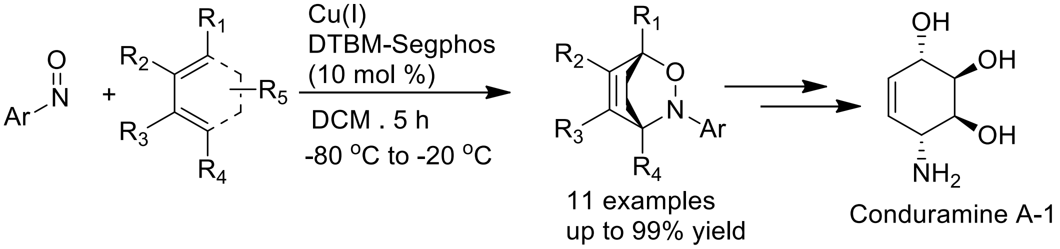
Scheme 1.15

Cheng Ma and co-workers in 2013, reported an NHC-catalyzed esterification reaction of various aldehydes with nitroso arenes, using thiazolium carbenes as a single dual-activation catalyst (Scheme 1.16).[103]



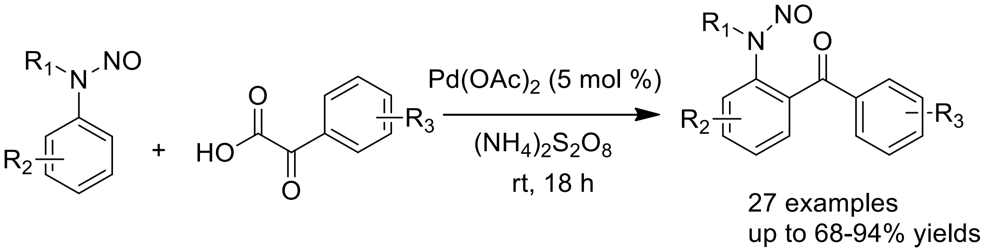
Scheme 1.16

Yamamoto et al. reported a Copper-SEGPHOS catalyzed enantio selective intermolecular Nitroso Diels-Alder reaction (NDA) reaction employing 6-methyl-2-nitrosopyridine and cyclic 1,3-dienes to obtain corresponding cycloadduct using this efficient method, the formal synthesis of conduramine A-1 and narciclasine were successfully synthesized (Scheme 1.17).[104]



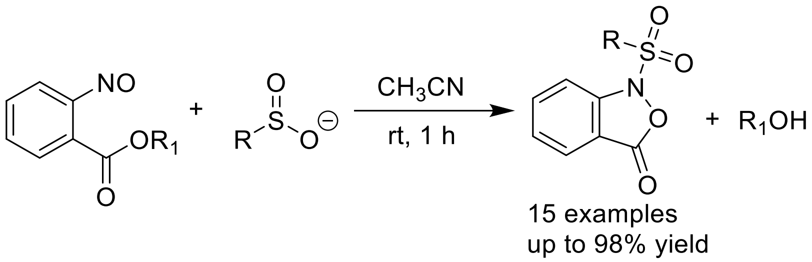
Scheme 1.17

Yinuo et al. reported ortho-acylation of *N*-nitroso anilines through the palladium-catalyzed oxidative C-H decarboxylative acylation of *N*-nitroso anilines based on ortho C-H activation strategy. This reaction involves α–oxocarboxylic acid as the acyl source and diammoniumpersulphate [$(NH_4)_2S_2O_8$] as an oxidant to furnish a library of *N*-nitroso-2-aminobenzophenones in good to excellent yields (Scheme 1.18).[105]



Scheme 1.18

Carroll and co-workers have developed a chemo selective ligation of sulfinic acids with aryl nitroso compounds in aqueous media under physiological pH. This method selectively converts sulfinic acid moieties into stable conjugates (Scheme 1.19).[106]



Scheme 1.19

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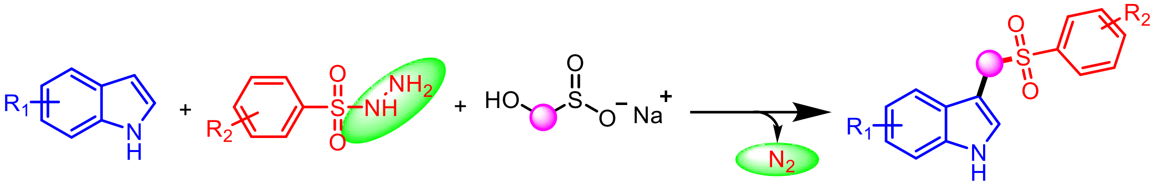
CHAPTER-II

One-Pot Three-Component Synthesis of 3-(phenylsulfonyl methyl) Substituted Indole Derivatives via C(sp^2)–H Functionalization



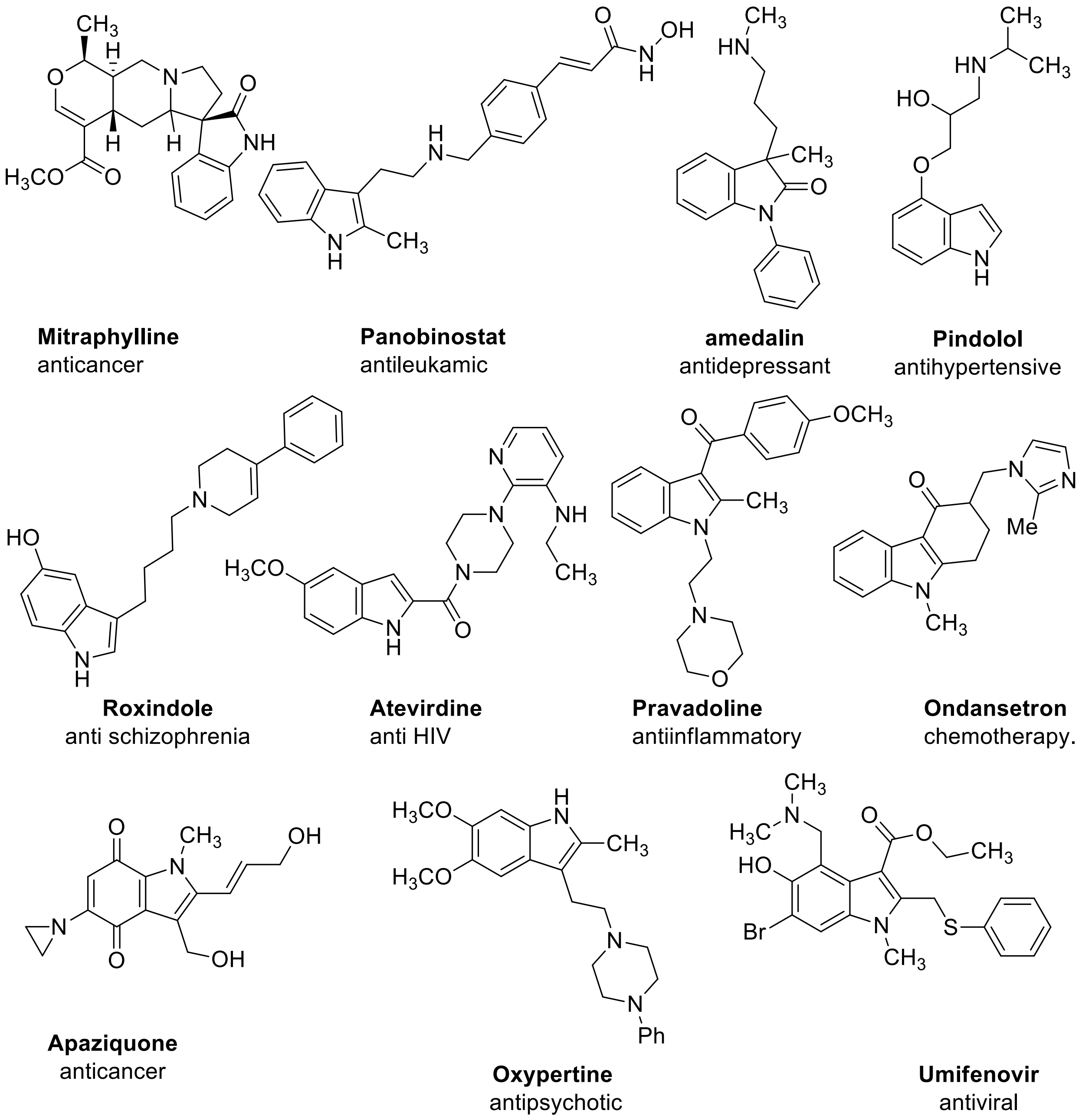
2.1. Introduction

There is mounting evidence that the nitrogen containing heterocycles have drawn much attention of researchers world over due to their utility as valuable intermediates for synthetic transformations as well as their wide ranging applications in pharmaceuticals, agrochemicals and material sciences.[1-5] Mainly, alkaloids, and terpenoids constitute passionate structures in the field of natural products.[6]

Particularly, nitrogen containing indole molecules are most common heterocyclic molecule where it is used in agriculture industrial, food flavorings, dyes, rubber chemical and adhesive sectors.[7] Of the more than ten thousand biologically active indole derivatives that have been synthesized till date, about 200 of them are involved directly in drugs are undergoing clinical trials. These indoles and their derivatives are the privileged structures as they bind selectively with the receptors.[8] Also, indole containing moieties exhibit numerous biological activities and are used in the treatment such as HIV,[9] cancer,[10] heart disease,[11] obesity[12] and allergies.[13]Also they are extensively used as cyclooxygenase-2 (COX-2) inhibitors (Figure 2.1).[14]

Over the years, complexity of indole derivatives increased and has inspired and influenced the development in synthetic chemistry.[15-17] Also it is well known in the field of chemistry as its stands at the pinnacle among all hetero aromatic compounds. In indole the C3 position will be protonated easily than *N*-atom even having the lone pair of electrons on it.

Because the lone pair of electrons on N-atom is not complacent due to delocalization of lone-pair circulates the total moiety from nitrogen atom to π-bond of C2-C3 carbon and also it renews easily in solvents due to thermodynamically stable and retention capacity in aromatic nature (Figure 2.2).[18] For this character and good fetching nature in indole it could able to participate in chemical reactions easily, like electrophilic substitution reactions, carbon lithiation, cycloaddition, oxidation, organometallic anion complexes, most probably the reactions occurs at C3 position only.[19a,b]



Mitraphylline
anticancer

Panobinostat
antileukamic

amedalin
antidepressant

Pindolol
antihypertensive

Roxindole
anti schizophrenia

Atevirdine
anti HIV

Pravadoline
antiinflammatory

Ondansetron
chemotherapy.

Apaziquone
anticancer

Oxypertine
antipsychotic

Umifenovir
antiviral

Figure 2.1. Biologically active Indole derivatives.

For the preparation of this indole and their substituted derivatives different conventional methods were used namely, Fisher indole synthesis, Julia indole synthesis, Larock indole synthesis, Baeyer-Emmerling indole synthesis, Bartoli indole synthesis, and Fukuyama synthesis.[20-22] Indole produces flowery smell when it is at small quantities and also it is present in some of flower scents, coal tar, and perfumes.[23] In addition it is involved in different types of biochemical reactions in human body.

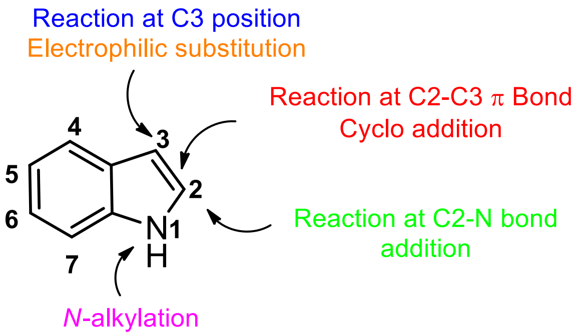


Figure 2.2. Reactivity of Indole.

The Core structure of this compound exhibit wide range of pharmaceutically and biologically active attributes and this indole chemistry has received a definite interest in alkaloid reserpine, which was introduced for treatment of central nervous system (CNS) including anxiety and mental disorders. For addressing of CNS disorders still these areas are investigated intensively in pharmaceuticals and also for their anti-inflammatory activity (Figure 2.3). [24]

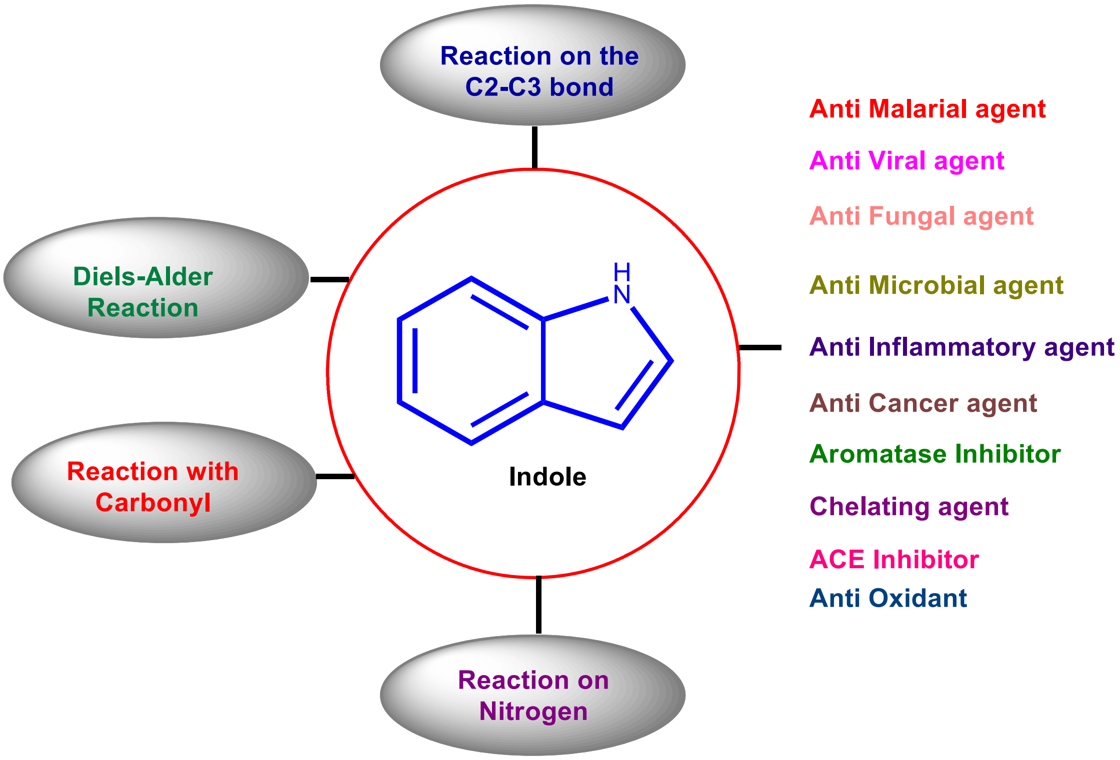
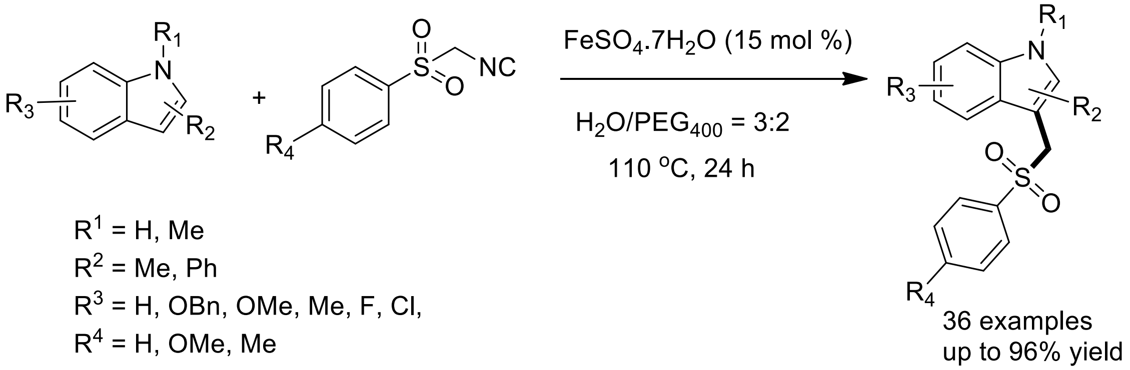


Figure 2.3. Various applications of indoles.

Over the past decade many reactions have been discovered in the synthesis of indole moieties with their regio selective functionalization at the C2-C3 position due to their immanent reactivity of the pyrrole core.[25] Till now the significance of the reaction progress was made to be, alkylation,[26] alkenylation,[27] alkynylation,[28] arylation,[29] acylation,[30] sulfuration,[31] and amination,[32] of indoles has been concluded. Also the sulfonyl methylated indoles are very common existed pharmacophores with their vast advantages in the pharmaceuticals.[18,33-34] Meanwhile the functionality of aryl sulfonyl moieties have esterified itself as a versatile synthetic intermediate, which can also be used to fulfil multiple functional group transformations.[35] Also much attention has been paid to make the sulfuration and sulfonylation of the indoles with their synthons of sulfonylhydrazines. However, the direct making of sulfonyl methylation of indole derivatives is still not much explored in the field of organic synthesis.[36]

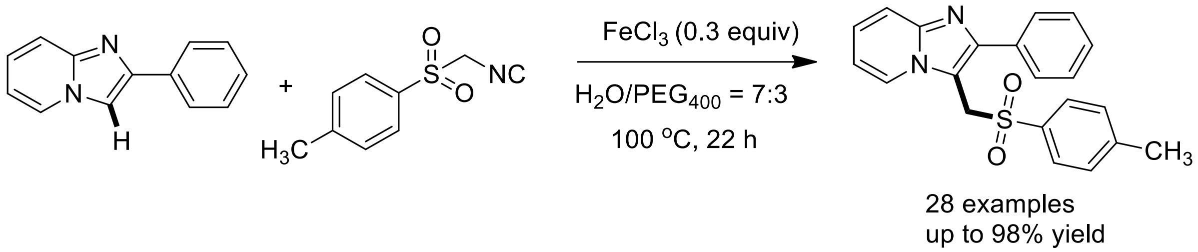
2.2. Reported Methods for the Synthesis of 3-((phenylsulfonyl)methyl)-1*H*-indole and its Derivatives

Hao et al. reported the C-H sulfonyl methylation of indoles using various *p*-toluene sulfonylmethyl isocyanide in presence of iron salts and polyethylene glycol 400 at 100 °C. In this protocol the regio-selective activation of C(sp^2)-H at C-3 position of indoles takes place giving the end product in good to excellent yield (Scheme 2.1).[37]



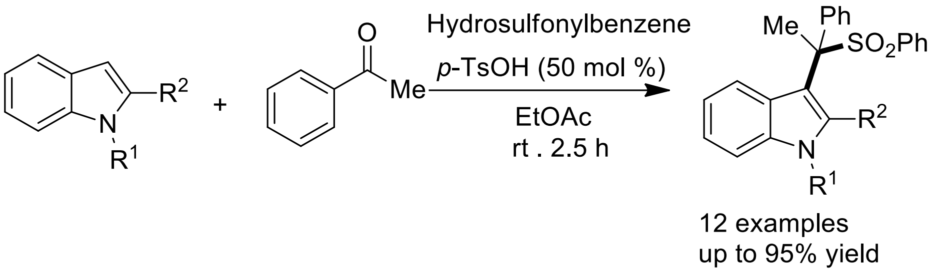
Scheme 2.1

The same group in 2016 developed a novel iron catalyzed tosylmethylation of imidazo[1,2-*a*]pyridines with *p*-toluene sulfonylmethyl isocyanide. This protocol opens new platform to the synthesis of functionalized imidazo[1,2-*a*] pyridine with high functional group compatibility (Scheme 2.2).[38]



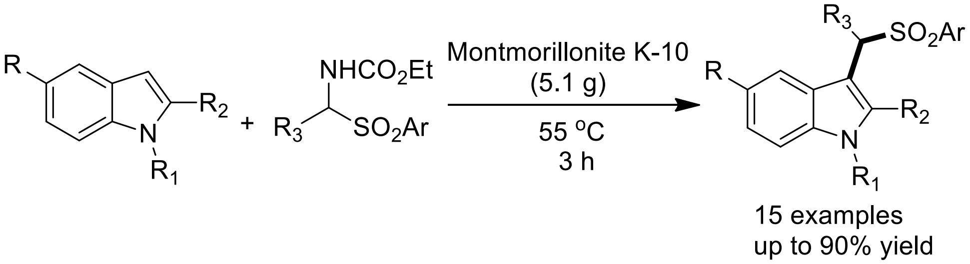
Scheme 2.2

Petrini et al. incorporated sulfonylmethylene moiety into3-(1-arylsulfonylalkyl) indoles by three-component condensation of indoles carbonyls, and arene sulfinic acids in EtOAc. The products obtained in this process undergo a Reformatsky reaction leading to alkyl 3-(3-indolyl) alkanoates and (3-indolyl) ketones (Scheme 2.3).[39]



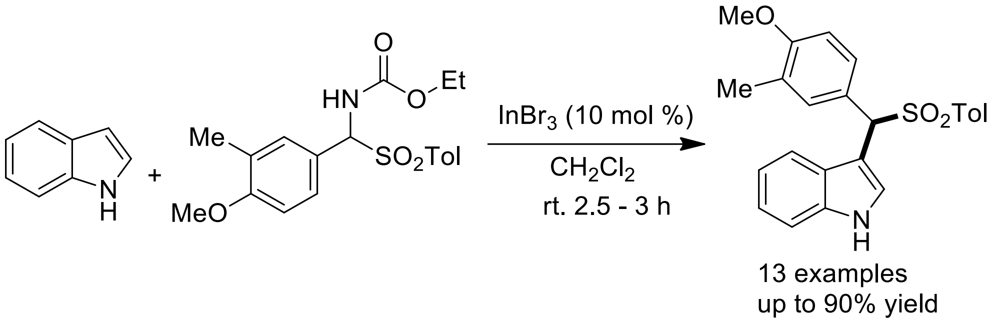
Scheme 2.3

Ballini et al. employed a procedure for the synthesis of 3-(1-arylsulfonylalkyl) indoles by montmorillonite K-10 catalyzed Friedel-Crafts reaction of indoles with R-amido sulfones under solvent-free conditions to obtain excellent yields. (Scheme 2.4).[40]



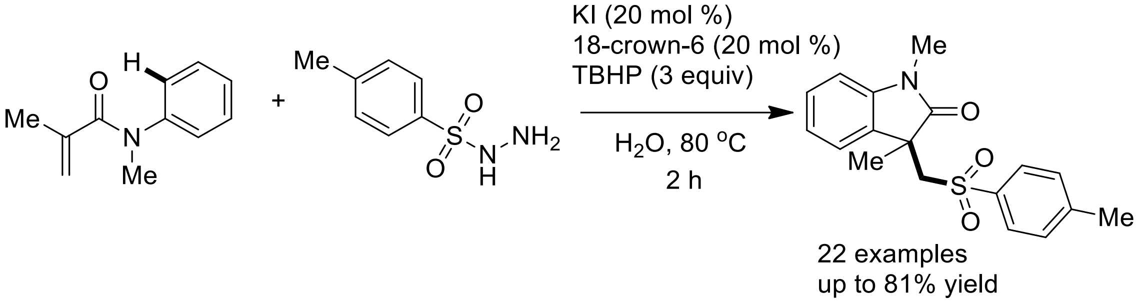
Scheme 2.4

Kim et al. introduced an efficient Friedel-Craft alkylation of heteroaromatic heterocyclic compounds catalyzed by $InBr_3$ with R-amido sulfones at ambient temperature in CH_2Cl_2. This methodology gives unsymmetrical or bis-symmetrical triaryl methanes in excellent yields (Scheme 2.5).[41]



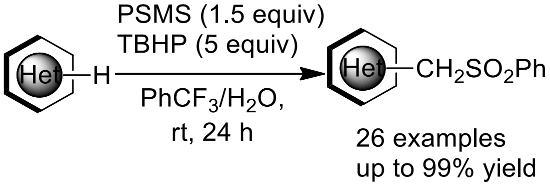
Scheme 2.5

Li et al. developed the green method for the synthesis of sulfonated oxindoles by potassium iodide promoted metal-free intra molecular oxidative arylsulfonylation of activated alkenes through direct aryl C(sp^2)-H functionalization. In this method sulfonyl hydrazides decomposed *in situ* to form sulfonyl radicals with the liberation of molecular nitrogen (Scheme 2.6).[42]



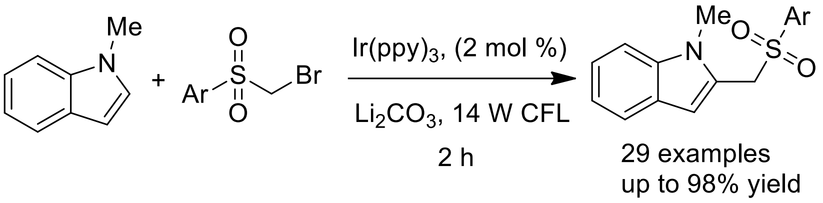
Scheme 2.6

Baran and co-workers developed a novel C-H functionalization method for the methylation of heteroarenes inspired from Nature’s methylating agent, S-adenosylmethionine (SAM), allowed for the design and development of zinc bis(phenylsulfonylmethanesulfinate) [PSMS]. The action of PSMS on a heteroarene generates a (phenylsulfonyl) methylated heterocyclic compounds with good to excellent yields (Scheme 2.7).[43]



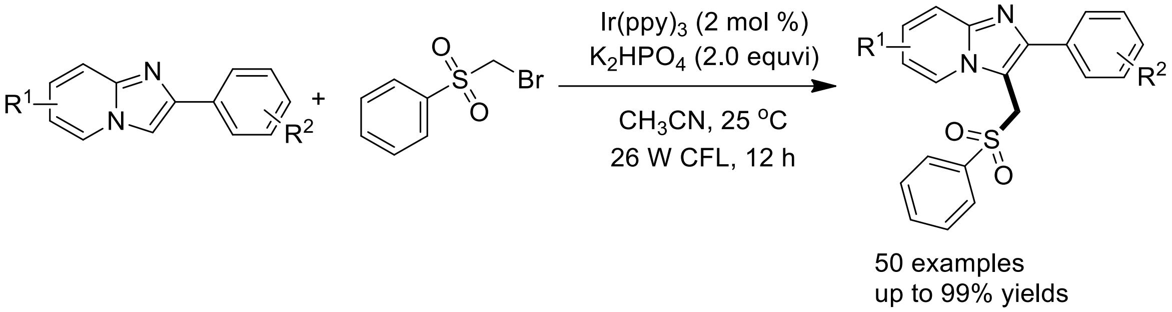
Scheme 2.7

Liet al. introduced (phenylsulfonyl)methylation electron-rich heteroarenes via radical mechanism promoted by visible-light from bromomethyl aryl sulfone derivatives. This novel route provides a platform to access various (phenylsulfonyl) methylated compounds (Scheme 2.8).[44]



Scheme 2.8

Zhang et al. developed C-H sulfonylmethylation of the imidazopyridines with the help of bromomethyl sulfones using mild conditions involving free radical generation in visible light. In this protocol he has provided an effective sulfonylmethylated imidazopyridines with high yields and functional group tolerance (Scheme 2.9).[45]

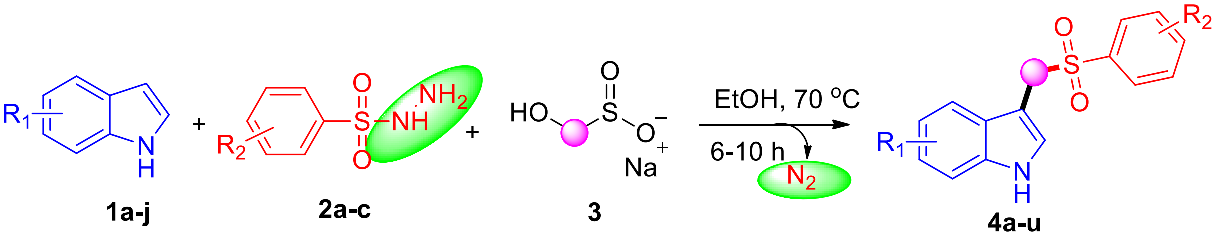


Scheme 2.9

A considerable attention has been received to the synthesis of indoles and functionalization of indoles at C2 and C3 position to increase the biological activity of the pyrrole core.[46] Much has already been done on alkenylation, arylation, alkynylation, amination, acylation, sulfuration, and alkylation of indoles. Whereas, sulfonyl methylated indoles are common pharmacophores with wide applications in pharmaceuticals.[18] Nevertheless, the direct sulfonyl methylation of indoles has only caught the imagination of only a few chemists.[47] Till date, only few reports are available for the direct synthesis of 3-(phenylsulfonyl methyl) substituted indoles. Therefore, introducing sulfonylmethylation group into the indole ring has the potential to attract many researchers in this direction.

2.3. Present Study

Herein we describe metal-free one-pot three-component synthesis of 3-(phenylsulfonyl methyl) substituted indoles via C(sp^2)-H functionalization in the presence of rongalite and sulfonylhydrazide. In this proposed methodology rongalite plays a dual role i.e., i) engaging *in situ* generation of formaldehyde, ii) acting as an electron donor. Sulfonylhydrazide acts as a sulfonyl donor after the removal of nitrogen gas (Scheme 2.10).



Scheme 2.10

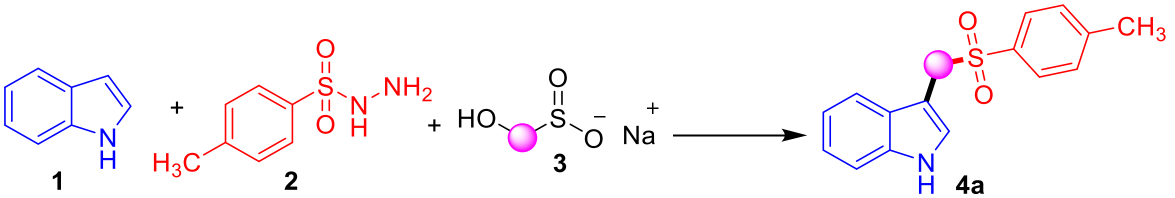
With this proposed methodology we can prepare various methylene bridged phenylsulfonyl indoles under environmentally benign condition i.e., metal free, less expensive, non-hazardous, and easily available reagents.

2.3.1. Results and Discussion

To validate our protocol for the synthesis of 3-(phenylsulfonyl methyl) substituted indole, we have begunwith the indole **1** (1.0 equiv), *p*-toluenesulfonyl hydrazide **2** (1.0 equiv) and rongalite **3** (2.0 equiv) in CH_3CN solvent (2 mL) at room temperature. Initially we have not observed any progress in the reaction which monitored by TLC. Even after stirring the reaction mixture at room temperature for 12 h. But the starting material was consumed at 70 °C and gave desired product 3-(tosylmethyl)-1*H*-indole **4** in 30% yield (Table 2.1, entries **1-4**).

These results prompted us to optimize the reaction conditions to improve the product yield by changing the reaction conditions. Hence, we focused on screening of various solvents. Then we have conducted the reactions in chlorinated solvents such as dichloromethane and chloroform, but these solvents failed to give the desired product (Table 2.1, entries 5-6). But dichloroethane gave target product in low yield; this may be attributed to the low boiling points of the solvents (Table 2.1, entry 7), this may not be the case with toluene which failed to give desired end product (Table 2.1, entries 8). We have further screened polar aprotic solvents such as nitromethane, THF, TEG, DMSO and DMF, except DMF everything else failed to give end product (Table 2.1, entries 9-13). Finally, we tested the same reaction in polar protic solvents i.e., methanol and ethanol, which surprisingly gave good results (Table 2.1, entries 14-15).

Table 2.1. Optimization of Reaction Condition.[a]

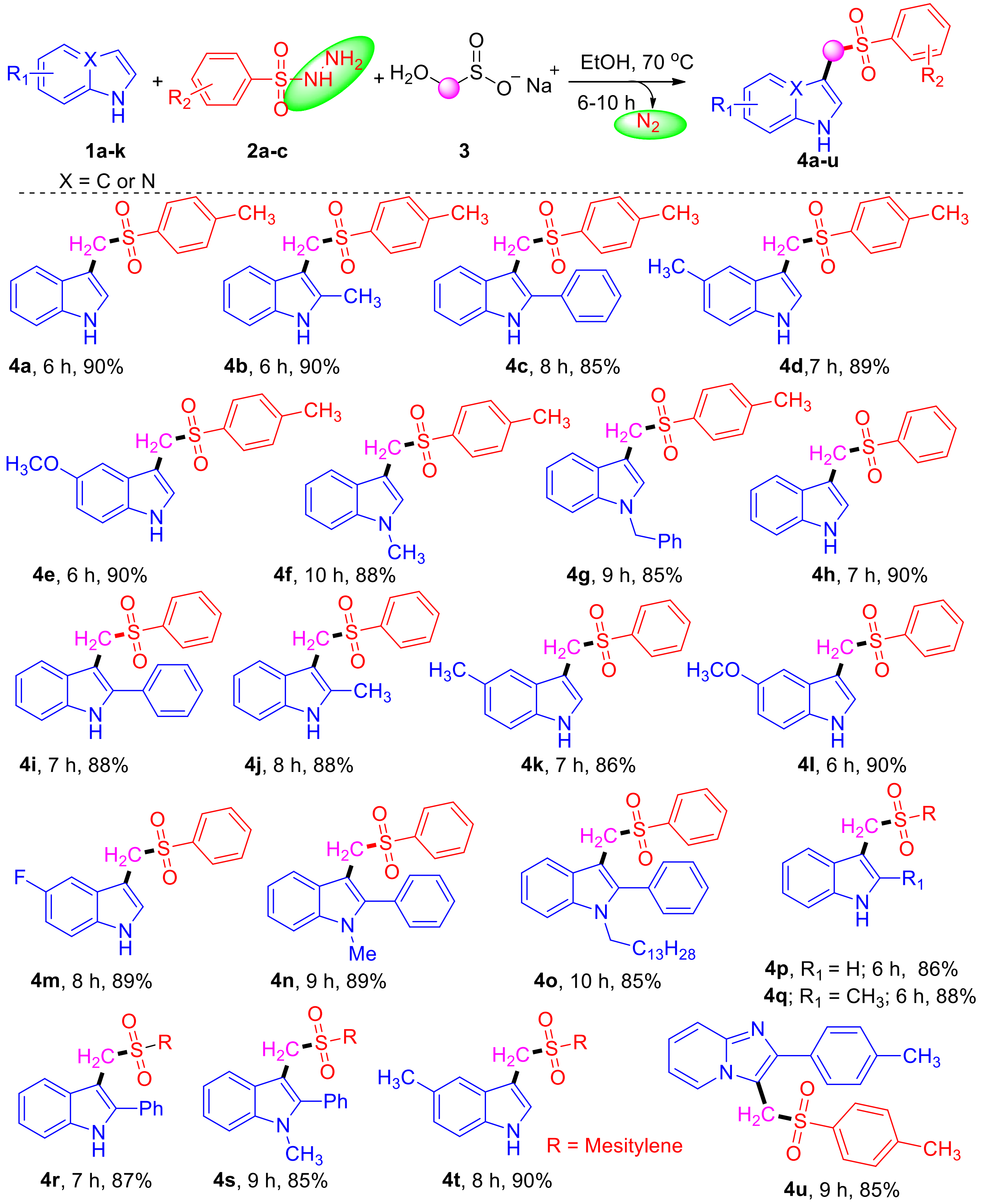


Entry	Solvent	Rongalite (equiv)	Temperature (°C)	Time (h)	Yield (%)[b]
1	CH_3CN	1.0	rt	12	n.d[d]
2	CH_3CN	1.0	50	12	20
3	CH_3CN	1.0	70	6	30
4	CH_3CN	1.0	80	6	30
5	CH_2Cl_2	1.0	45	12	n.d
6	$CHCl_3$	1.0	60	12	n.d
7	DCE	1.5	70[c]	10	20
8	Toluene	1.0	70	6	n.d
9	CH_3NO_2	1.0	70	10	n.d
10	THF	1.0	70	12	10
11	TEG	1.0	90	12	n.d
12	DMSO	1.0	90	12	n.d
13	DMF	1.0	90	12	40
14	MeOH	1.0	70	12	40
15	EtOH	1.0	70	12	50
16	EtOH	1.5	70	8	70
17	**EtOH**	**2.0**	**70**	**6**	**90**
18	EtOH	2.5	70	6	90
19	H_2O	1.0	90	12	n.d

[a] All the reactions were conducted on a 1 mmol scale of **1a** (1 mmol), **2a** (1 mmol) and **3** (2 mmol) in solvent (2 mL), otherwise mentioned. [b] Yield where reported is of isolated and purified product. [c] Reaction stirred at rt for 6 h then heated to 70 °C, [d] Not Detected.

Next, we examined the stoichiometry of the rongalite by varying it from 1.0 equivalent to 2.0 equivalents and found that 2 equivalents of rongalite is required to get better yields (Table, 2.1 entry 17). Finally, we have conducted same reaction in water but failed to give target product, this

Table 2.2. Substrate Scope for the Synthesis of 3-(phenylsulfonyl methyl) Indole Derivatives.[a,b]



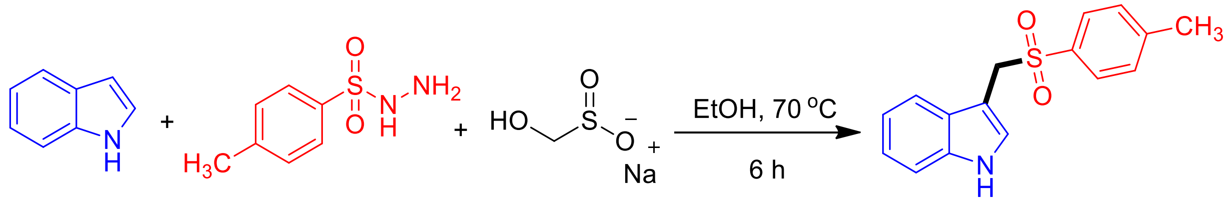
4a, 6 h, 90%
4b, 6 h, 90%
4c, 8 h, 85%
4d,7 h, 89%
4e, 6 h, 90%
4f, 10 h, 88%
4g, 9 h, 85%
4h, 7 h, 90%
4i, 7 h, 88%
4j, 8 h, 88%
4k, 7 h, 86%
4l, 6 h, 90%
4m, 8 h, 89%
4n, 9 h, 89%
4o, 10 h, 85%
4p, R_1 = H; 6 h, 86%
4q; R_1 = CH_3; 6 h, 88%
4r, 7 h, 87%
4s, 9 h, 85%
4t, 8 h, 90%
4u, 9 h, 85%

[a] All the reactions were conducted on a 1 mmol scale of **1a-k** (1 mmol), **2a-c** (1 mmol) and **3** (2 mmol) in solvent (2 mL). [b] Yields where reported is of isolated and purified product.

may be due to the solubility problem of substrates in water. The optimized condition for the above reaction is as follows, indole **1** (1.0 equiv) sulfonyl hydrazide **2** (1.0 equiv) and rongalite **3** (2.0 equiv) in ethanol (2 mL) at 70 °C for 6-10 h.

After optimized the reaction conditions for one-pot three-component synthesis of 3-(phenylsulfonyl methyl) substituted indoles (Table 2.1, entry **17**), then we have focused on the scope of the substrates and reagents. Interestingly, substitution on the indoles like Me, Ph, OMe, *N*-Ph-CH_2-, and F reacted with 4-methyl benzenesulfonohydrazide, and simple benzenesulfonohydrazide to furnish corresponding sulfonylmethyl indoles in good to excellent yields (Table 2.2, **4a-4g** and **4h-4m**). *N*-methyl indole and *N*-dodecyl indole derivatives also gave good yields (Table 2.2, **4n-40**). Similarly, 2,4,6-trimethylbenzenesulfonohydrazide reacted with different indoles and delivered the titled products in good yields (Table 2.2, **4p-4t**). Notably, the reaction between 2-(*p*-tolyl)imidazo[1,2-*a*]pyridine and 4-methyl benzenesulfonohydrazide was produced in excellent yield (Table 2.2, **4u**).

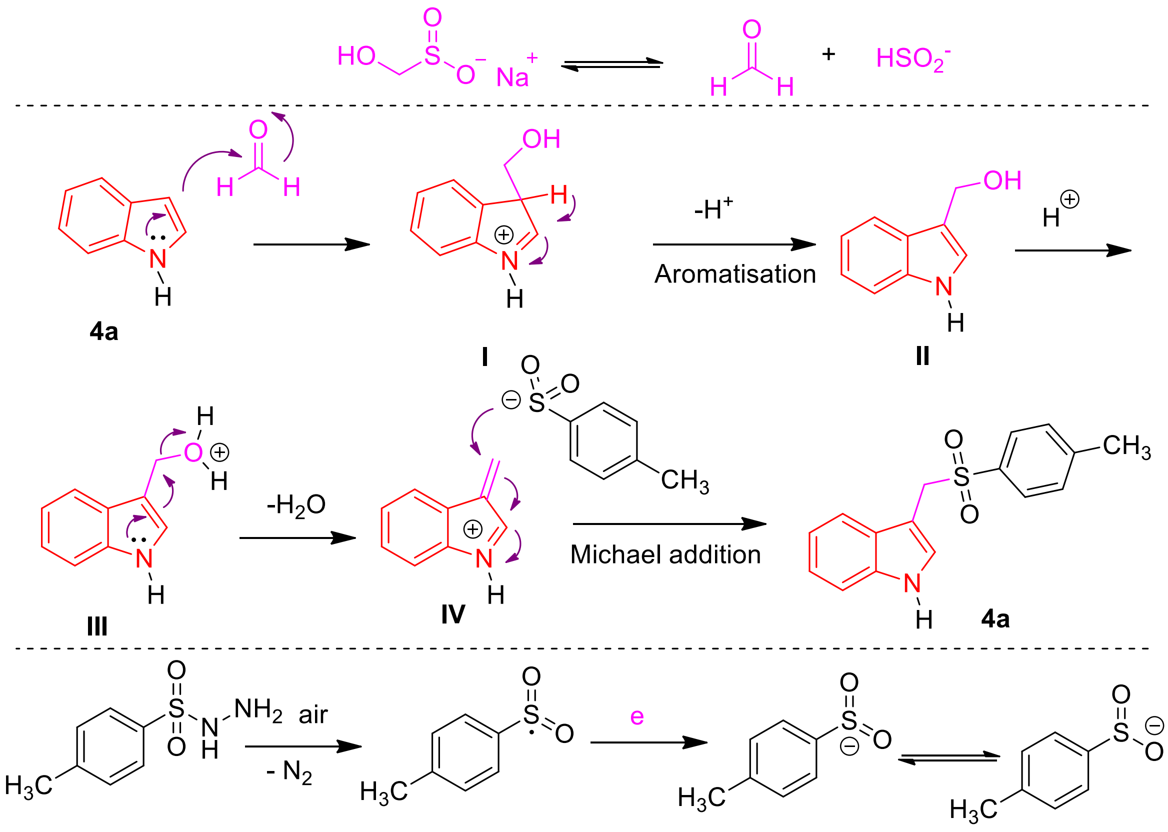
To examine the scalability of proposed method, we have conducted a reaction using Indole **1a** (1g, 8.54 mmol), 4-methylbenzenesulfonohydrazide **2a** (1.5g, 8.54 mmol) and rongalite **3** (2.01g, 17.08 mmol) which were dissolved in EtOH solvent and stirred at 70 °C and obtained target molecule **4a** in 70% yield (Scheme 2.12). This indicated that the method is also applicable for the gram scale reactions.



1a (1 g) **2a** (1.5 g) **3** (2.01 g) **4a** (1.72 g)

Scheme 2.12

A plausible reaction mechanism is proposed in Scheme 2.13 based on experimental observations and literature reports.[48-51]



Scheme 2.13

In this mechanism, the indole nitrogen lone pair of electrons are shifted to π bond and the π electrons are shifted to electrophilic carbon center of formaldehyde which generate *in situ* from the rongalite and forms the indole imminium intermediate (**I**). While deprotonation of intermediate **I** followed by aromatisation form the intermediate (**II**). Following the protonation and dehydration (-H_2O) of **III** it forms the intermediate (**IV**). Finally, conjugate addition by sulfonyl nucleophile which *in situ* generated from sulfonohydrazidevia Michael addition gives the final Compound **4a**. In this process sulfonyl nucleophile will be generated from the sulfonyl hydrazide and rongalite under thermal conditions.

All the synthesized compounds **4a-u** was characterized by the ^{1}H NMR, ^{13}C NMR and Mass spectral data. In the ^{1}H NMR spectrum, the peaks at δ 9.83 (s, 1H), corresponds to the single proton of indole NH, 7.46 (d, J = 6.8 Hz, 2H), and 7.11 (d, J = 7.2 Hz, 2H), four protons represent the phenyl of tosyl group. 7.16 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), and 6.57 (s, 1H) three protons are corresponding to indole ring. The peak at 4.41 (s, 2H) indicated methylene bridge, 3.64 (s, 3H), 2.30 (s, 3H) are corresponding to OCH_3, CH_3 protons respectively. ^{13}C NMR spectrum shows peak at δ 55.5, 54.7 and 21.5 are correspond to the carbon atoms of OCH_3, Bridges

CH_2, and CH_3 respectively. Further, the appearance of the peak at *m/z* 338.0829 in the HRMS spectrum indicates the formation of the compound **4e.** Finally, the structure of the compound **4e** and **4s** were confirmed by the single crystal X-RD (Figure 2.5, 2.6). The crystallographic data and structure refinement parameters of the compounds **4e** and **4s** were shown in Table 2.3.

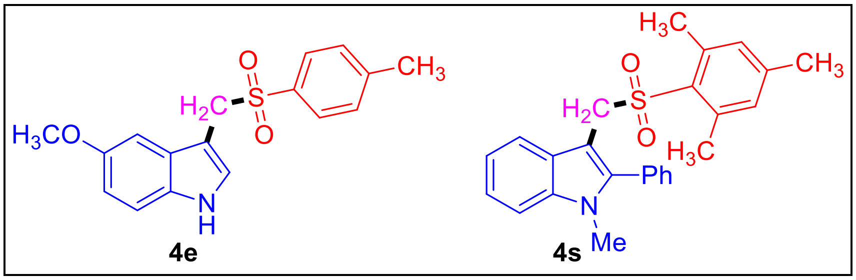


Figure 2.4

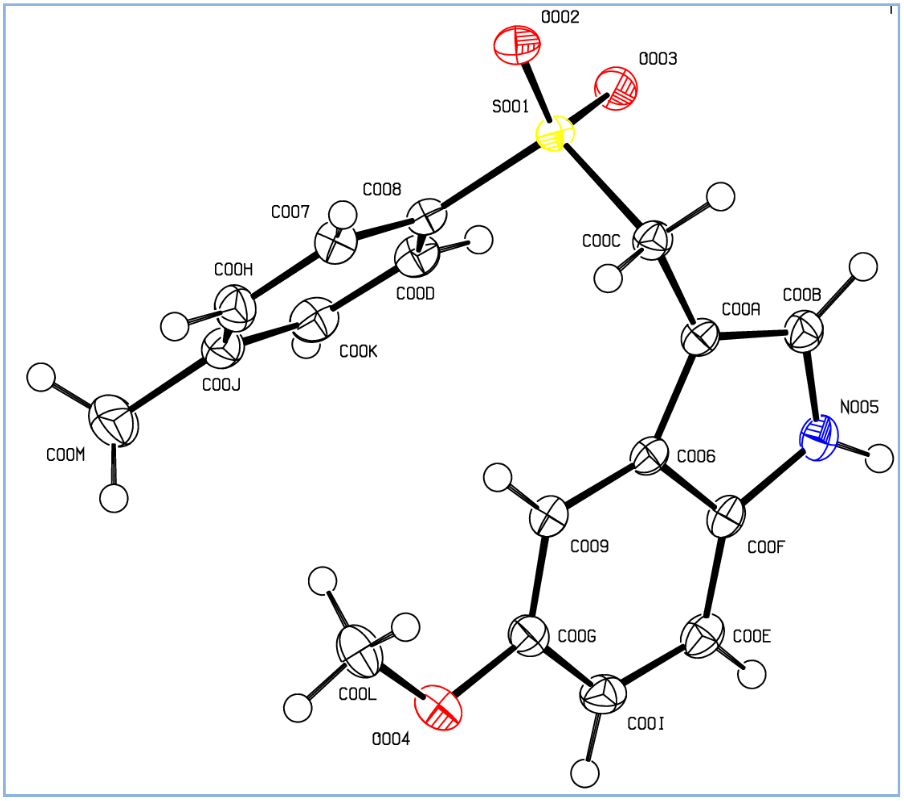


Figure 2.5. The ORTEP representation of the compound **4e**

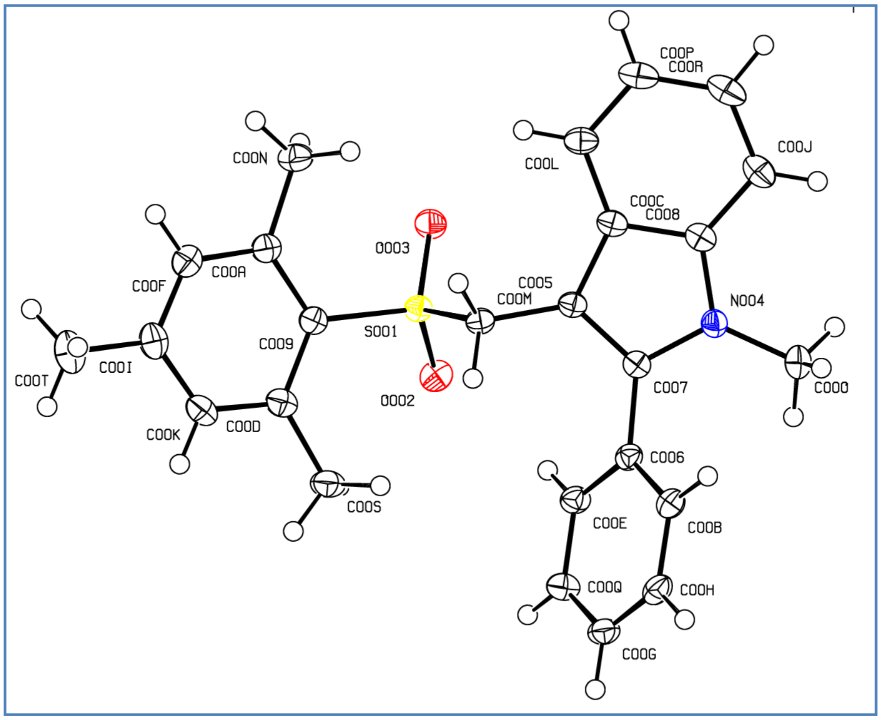


Figure 2.6. The ORTEP representation of the compound **4s**

Table 2.3. Crystallographic Data and Structure Refinement Parameters of the Compounds **4e** and **4s**

Identification code	**4e**	**4s**
Empirical formula	$C_{17}H_{17}NO_3S$	$C_{19}H_{21}NO_2S$
Formula weight	315.0929	327.4405
Crystal system	Monoclinic	Triclinic
Space group	*P*121/*c*1	*P*-1
T/K	93(2)	93 (2)
a/Å	10.6272(2)	8.4532(2)
b/Å	16.6924(2)	10.3709(2)
c/Å	9.0871(1)	12.4478(3)
α/°	90	96.935(2)
β/°	109.219(2)	104.121(2)
γ/°	90	102.127(2)

Z	4	4
Volume, V/Å^3	1522.15(4)	1017.51(4)
D_{calc}/ g/cm^3	1.376	1.317
F(000)	667.3	429.9
Absorption coefficient, μ/mm^{-1}	1.996	1.576
θ/° range for data collection	4.40 to 79.65	3.72 to 79.50
Index ranges	$-13 \leq h \leq 13$	$-10 \leq h \leq 10$
	$-21 \leq k \leq 21$	$-13 \leq k \leq 13$
	$-9 \leq l \leq 11$	$-15 \leq l \leq 15$
Parameters	209	267
R_1 ($I > 2\sigma(I)$)	0.0364	0.0390
wR_2 (all data)	0.0978	0.1065
Max. and min. transmission	0.819 and 0.787	0.854 and 0.828
Goodness–of–fit on F^2	1.031	1.023
CCDC	1975044	1975054

2.4. Conclusion

In conclusion a novel direct sulfonylmethylation of indoles/imidazopyridines by hydrazides to obtain bridged products has been described in this chapter. The proposed method delivers end products with high yields (85-90%). This method involves metal free, non-hazardous and less expensive bench chemical. Here rongalite is playing a dual role of both the *in situ* generation formalin and reducing agent, which makes this method green as the direct use of the formaldehyde or formalin solution in the reaction mixture which is the carcinogenic and harmful to human health. It is also observed that the reaction is also favourable to the synthesis in gram-scale reactions.

2.5. Experimental Section

2.5.1 General Information

All the starting compounds used in the reaction were purchased from Sigma-Aldrich, Spectrochem, SRL, and SD-Fine used as received. All the reagents are analytical grade and used directly without any further purification. All the reactions were performed in EtOH solvent. The conformation of the reactions was monitored using analytical on Thin Layer Chromatography (TLC) Merck silica gel G/GF $_{254}$ plates and used UV-Cabinet for visualization of compound spots on TLC plate. Purification of compounds using column chromatography where performed with the Rankem silica gel (60-120 mesh). Finding the melting points of solid compounds was determined by open capillaries using Stuart SMP30 melting point apparatus and is uncorrected. NMR (^{1}H and ^{13}C) spectra of all the synthesized compounds were recorded on Bruker AVANCE HD (400 MHz / 100 MHz) spectrometer using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The data of the compounds was recorded as chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations for the multiplicity as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. The mass spectrum analysis was recorded in Bruker- micro-TOF MS analyzer.

2.5.2. General Procedure for the Preparation of 3-(phenylsulfonyl methyl) Substituted Indole Derivatives (4a-u)

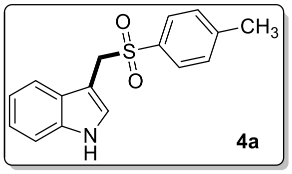
In a clean and dried round bottom flask, Indole **1a** (120 mg, 1.0 mmol), 4-methylbenzenesulfonohydrazide **2a** (190 mg, 1.0 mmol) and rongalite **3** (240 mg, 2.0 mmol) in ethanol (2 mL) were added. The reaction mixture was allowed to stir at 70 $^{\circ}$C. After completion of reaction (monitored by TLC) evaporate the solvent and the crude residue was extracted using ethyl acetate solvent (10 mL x 3) and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was separated using column chromatography with silica-gel (60-120 mesh) as stationary phase and eluting with ethyl acetate/hexanes solvents as mobile phase.

2.6. Spectral Data

3-(Tosylmethyl)-1*H*-indole (4a)[37&38]

Yield: 90%, brown colour solid, M.P. 166-167 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.08 (dd, J = 14.7, 7.6 Hz, 3H), 6.99 (s, 1H), 6.94 (t, J = 7.6 Hz, 1H), 4.44 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 135.8, 135.4, 129.5, 128.6, 127.0, 125.9, 122.5, 120.2, 118.6, 111.3, 103.0, 54.5, 21.6. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_2S$ [M+Na]$^+$ 308.0723, found 308.0715.

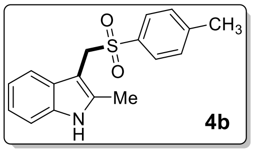


4a

2-Methyl-3-(tosylmethyl)-1*H*-indole (4b)[37]

Yield: 90%, white solid, M.P. 187-188 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 3H), 7.08 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 4.45 (s, 2H), 2.37 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 135.9, 135.5, 134.9, 129.5, 128.7, 128.2, 126.5, 121.6, 120.0, 118.0, 110.3, 99.4, 54.0, 21.6, 11.5. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}NO_2S$ [M+Na]$^+$322.088, found 322.0871.

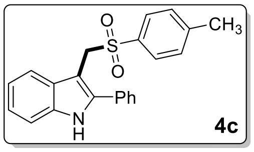


4b

2-Phenyl-3-(tosylmethyl)-1*H*-indole (4c) [37]

Yield: 85%, White crystalline solid, M.P. 211-212 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.43 (t, J = 8.2 Hz, 3H), 7.30 (s, 5H), 7.19 (s, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.04 (t, J = 7.4 Hz, 3H), 4.56 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.71, 135.49, 129.50, 128.81, 128.52, 128.30, 122.91, 120.62, 120.01, 110.81, 54.36, 21.60. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{19}NO_2S$ [M+Na]$^+$ 384.1036, found 384.1029.

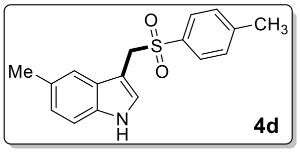


4c

5-Methyl-3-(tosylmethyl)-1*H*-indole (4d)

Yield: 89%, light brown solid, M.P. 131-133 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.18 (s, 1H), 7.02 – 6.95 (m, 2H), 6.93 (s, 1H), 4.50 (s, 2H), 2.40 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 135.5, 134.1, 129.4, 128.8,



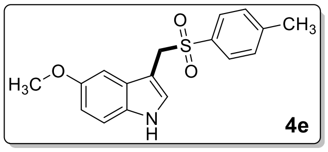
4d

125.9, 124.1, 118.2, 110.8, 102.6, 54.6, 21.6, 21.3. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}NO_2S$ $[M+Na]^+$ 322.0880, found 322.0868.

5-Methoxy-3-(tosylmethyl)-1*H*-indole (4e)[37]

Yield: 90%, brown solid, M.P. 155-157 °C.

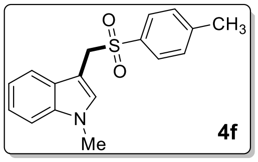
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.95 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.57 (s, 1H), 4.41 (s, 2H), 3.64 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 144.3, 135.4, 131.1, 129.4, 128.5, 127.3, 126.9, 112.4, 112.3, 101.6, 99.7, 55.5, 54.7, 21.5. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}NO_3S$ $[M+Na]^+$ 338.0829, found 338.0820.



1-Methyl-3-(tosylmethyl)-1*H*-indole (4f)

Yield: 88%, brown solid, M.P. 110-112 °C.

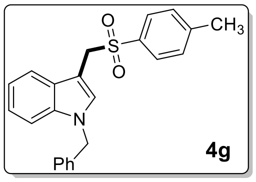
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.18 (m, 4H), 7.14 – 7.08 (m, 4H), 6.94 (s, 1H), 6.93 – 6.90 (m, 1H), 4.42 (s, 2H), 3.68 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 136.7, 135.6, 130.3, 129.5, 128.6, 127.6, 122.0, 119.8, 118.6, 109.4, 101.1, 54.5, 33.0, 21.6. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}NO_2S$ $[M+Na]^+$ 322.0880, found 322.0877.



1-Benzyl-3-(tosylmethyl)-1*H*-indole (4g)

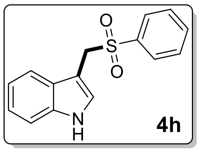
Yield: 85%, light yellow solid, M.P. 130-132 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.20 (qd, *J* = 4.9, 1.7 Hz, 3H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.07 – 7.02 (m, 3H), 6.98 – 6.93 (m, 3H), 6.86 (s, 1H), 5.15 (s, 2H), 4.43 (s, 2H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 137.0, 136.3, 135.2, 129.6, 129.4, 128.8, 128.7, 127.8, 126.8, 122.3, 120.1, 119.0, 109.9, 102.2, 54.5, 50.1, 21.6. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{21}NO_2S$ $[M+Na]^+$ 398.1193, found 398.1188.



3-((Phenylsulfonyl)methyl)-1*H*-indole (4h)[37]

Yield: 90%, brown crystalline solid, M.P. 148-150 °C.

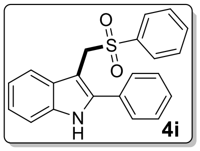


4h

^{1}H NMR (400 MHz, CDCl$_3$) δ 10.37 (s, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.2 Hz, 2H), 7.30 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 4.47 (s, 2H).^{13}C NMR (100 MHz, CDCl$_3$) δ 138.3, 135.7, 133.5, 128.9, 128.6, 126.9, 125.9, 122.5, 120.3, 118.5, 111.3, 102.7, 54.5. HRMS (ESI-TOF): m/z calcd for $C_{15}H_{13}NO_2S$ [M+Na]$^+$ 294.0567, found 294.0557.

2-Phenyl-3-((phenylsulfonyl)methyl)-1*H*-indole (4i)

Yield: 88%, light pink crystalline solid, M.P. 194-196 °C.

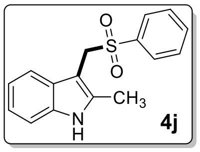


4i

^{1}H NMR (400 MHz, CDCl$_3$) δ 10.45 (s, 1H), 7.55 (d, J = 5.2 Hz, 2H), 7.47 (s, 2H), 7.41 – 7.34 (m, 5H), 7.31 (d, J = 5.2 Hz, 3H), 7.09 (t, J = 5.6 Hz, 1H), 6.98 (t, J = 5.6 Hz, 1H), 4.59 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.4, 138.8, 135.9, 133.4, 131.7, 128.8, 128.6, 128.5, 128.2, 128.1, 122.2, 119.9, 119.4, 111.3, 54.4. HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}NO_2S$ [M+Na]$^+$ 370.088, found 370.0874.

2-Methyl-3-((phenylsulfonyl)methyl)-1*H*-indole (4j)[43]

Yield: 88%, yellow solid, M.P. 148-150 °C.

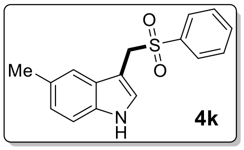


4j

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.88 (s, 1H), 7.56 (d, J = 7.2 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 5.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 6.86 (t, J = 7.2 Hz, 1H), 4.39 (s, 2H), 1.99 (s, 3H).^{13}C NMR (100 MHz, CDCl$_3$) δ 138.4, 136.3, 135.0, 133.4, 128.8, 128.6, 121.2, 119.7, 117.7, 110.5, 54.0, 11.3. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_2S$ [M+Na]$^+$ 308.0723, found 308.0719.

5-Methyl-3-((phenylsulfonyl)methyl)-1*H*-indole(4k)

Yield: 86%, brown colour solid, M.P. 103-105 °C.

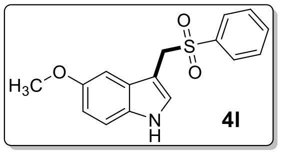


4k

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.29 (s, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.46 (t, J = 7.1 Hz, 1H), 7.29 (t, J = 7.2 Hz, 2H), 7.11 (d, J = 8.0 Hz, 1H), 6.88-6.857 (m, 3H), 4.42 (s, 2H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.4, 134.1, 133.5, 129.5, 128.8, 128.7, 127.2, 126.1, 124.1, 118.1, 111.0, 102.1, 54.6, 21.4. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_2S$ [M+Na]$^+$ 308.0723, found 308.0725.

5-Methoxy-3-((phenylsulfonyl)methyl)-1*H*-indole(4l)

Yield: 90%, crystalline solid, M.P. 118-120 °C.

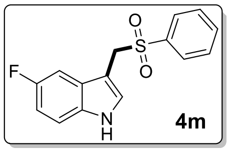


4l

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.46 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 2.8 Hz, 1H), 6.69 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 4.43 (s, 2H), 3.62 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.5, 138.3, 133.6, 130.8, 128.9, 128.7, 124.4, 126.6, 113.1, 112.2, 102.4, 99.8, 55.7, 54.6. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_3S$ [M+Na]$^+$ 324.0673, found 324.0666.

5-Fluoro-3-((phenylsulfonyl)methyl)-1*H*-indole (4m)

Yield: 89%, yellowish colour solid, M.P. 168-170 °C.

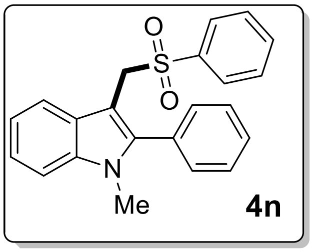


4m

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.89 (s, 1H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 6.6 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.23 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.02 (s, 1H), 6.95 (d, *J* = 9.6 Hz, 1H), 6.77 (t, *J* = 8.8 Hz, 1H), 4.46 (s, 2H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 158.8, 156.5, 138.6, 133.7, 132.9, 129.0, 128.6, 128.4, 112.7, 112.6, 110.2, 109.9, 103.6, 103.4, 54.32. HRMS (ESI-TOF): m/z calcd for $C_{15}H_{12}FNO_2S$ [M+Na]$^+$ 312.0473, found 312.0468.

1-Methyl-2-phenyl-3-((phenylsulfonyl)methyl)-1*H*-indole (4n)

Yield: 89%, crystalline solid, M.P. 179-181 °C.

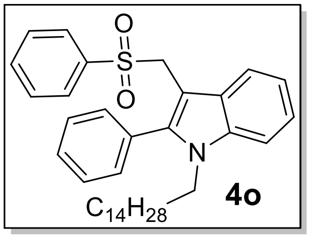


4n

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 – 7.47 (m, 4H), 7.33 – 7.25 (m, 6H), 7.21 – 7.16 (m, 1H), 7.06 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.01 – 6.98 (m, 2H), 4.42 (s, 2H), 3.44 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.0, 139.0, 137.1, 133.3, 130.4, 130.1, 128.9, 128.7, 128.6, 128.5, 122.4, 120.5, 120.0, 109.5, 100.0, 54.6, 31.0. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{19}NO_2S$ [M+Na]$^+$ 384.1036, found 384.1040.

2-Phenyl-3-((phenylsulfonyl)methyl)-1-tetradecyl-1*H*-indole (4o)

Yield: 85%, white solid, M.P. 54-56 °C.



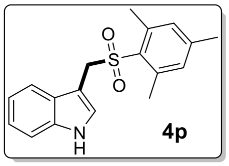
4o

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.43 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.21 – 7.16 (m, 2H), 7.10 – 7.05 (m, 1H), 6.92 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.87 (s, 1H), 4.44 (s, 2H), 3.95 (t, *J* = 7.2 Hz, 2H),1.67 (q, *J* = 7.2, 7.2 Hz, 2H), 1.17 (s, 22H), 0.81 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.3, 136.0, 133.4, 129.3, 128.7, 127.6, 121.9, 119.8, 118.7, 109.6, 54.5, 46.5, 31.9, 30.2, 29.7, 29.5, 29.4, 29.2, 26.9, 22.7, 14.2. HRMS (ESI-TOF): m/z calcd for $C_{29}H_{41}NO_2S$ $[M+Na]^+$ 490.2758, found 490.2745.

3-((Mesitylsulfonyl)methyl)-1*H*-indole (4p)

Yield: 90%, red solid, M.P. 151-153 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.94 (s, 1H), 6.86 – 6.77 (m, 2H), 6.68 (s, 2H), 4.36 (s, 2H), 2.24 (s, 6H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.9, 140.3, 136.0, 132.4, 131.8, 131.5, 127.1, 126.3, 121.6, 119.5, 118.2, 111.5, 53.9, 22.7, 20.8. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{19}NO_2S$ $[M+Na]^+$ 336.1036, found 336.1021.

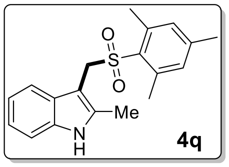


4p

3-((Mesitylsulfonyl)methyl)-2-methyl-1*H*-indole (4q)

Yield: 88%, red colour solid, M.P. 140-142 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 8.2 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.75 (s, 2H), 4.39 (s, 2H), 2.31 (s, 6H), 2.18 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 140.8, 135.9, 134.8, 132.8, 131.9, 128.4, 121.6, 120.1, 117.9, 110.2, 53.1, 22.8, 21.0, 11.5. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}NO_2S$ $[M+Na]^+$ 350.1193, found 350.1185.

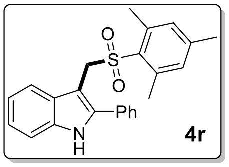


4q

3-((Mesitylsulfonyl)methyl)-2-phenyl-1*H*-indole (4r)

Yield: 86%, white solid, M.P. 173-175 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.26 (m, 5H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.64 (s, 2H), 4.59 (s, 2H), 3.18 (s, 6H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.9, 140.3, 139.4, 136.0, 132.7, 132.0, 128.9, 128.5,128.4, 128.1, 122.1, 119.8, 119.6, 111.4, 53.2, 22.6, 20.9. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{23}NO_2S$ $[M+Na]^+$ 412.1349, found 412.1340.

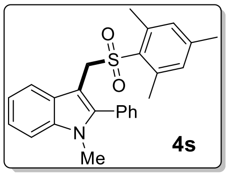


4r

3-((Mesitylsulfonyl)methyl)-1-methyl-2-phenyl-1*H*-indole (4s)

Yield: 85%, yellow crystalline solid, M.P. 161-163 °C.

^{1}HNMR (400 MHz, CDCl$_3$) δ 7.62 (d, J = 8.0 Hz, 1H), 7.33 – 7.23 (m, 4H), 7.21 – 7.17 (m, 1H), 7.09 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.03 – 6.99 (m, 2H), 6.67 (s, 2H), 4.42 (s, 2H), 3.45 (s, 3H), 2.19 (s, 3H), 2.13 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.7, 142.0, 140.9, 137.0 ,133.2, 130.5 ,130.2, 128.6, 128.4, 127.7, 122.3, 120.4, 120.1, 109.4 ,100.0, 53.5 ,31.0, 22.6, 21.0. HRMS (ESI-TOF): m/z calcd for $C_{25}H_{25}NO_2S$ [M+Na]$^+$ 426.1506, found 426.1495.

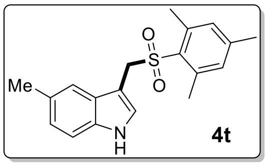


4s

3-((Mesitylsulfonyl)methyl)-5-methyl-1*H*-indole (4t)

Yield: 87%, pale pink colour solid, M.P. 125-127 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.17 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.4, 1.6 Hz, 1H), 6.75 (s, 2H), 6.73 (s, 1H), 4.42 (s, 2H), 2.32 (s, 6H), 2.21 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.1, 140.8, 134.0, 132.6, 131.9, 129.3,127.3, 126.0, 124.0, 118.0, 110.8, 102.4, 54.0, 22.89, 21.4, 21.0. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}NO_2S$ [M+Na]$^+$ 350.1193, found 350.1181.

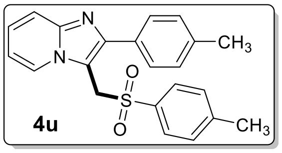


4t

2-(*p*-Tolyl)-3-(tosylmethyl)imidazo[1,2-*a*]pyridine (4u)[38]

Yield: 85%, gummy material.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.45 (d, J = 6.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.32 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.11-7.08 (m, 4H), 6.95 (t, J = 6.8 Hz, 1H), 4.85 (s, 2H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 138.3, 135.7, 133.5, 128.9, 128.6, 126.9, 126.0, 122.5, 120.3, 118.5, 111.3, 102.7, 54.5, 29.7. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{20}N_2O_2S$ [M+H]$^+$ Exact Mass: 377.1318, found 377.1317.



4u

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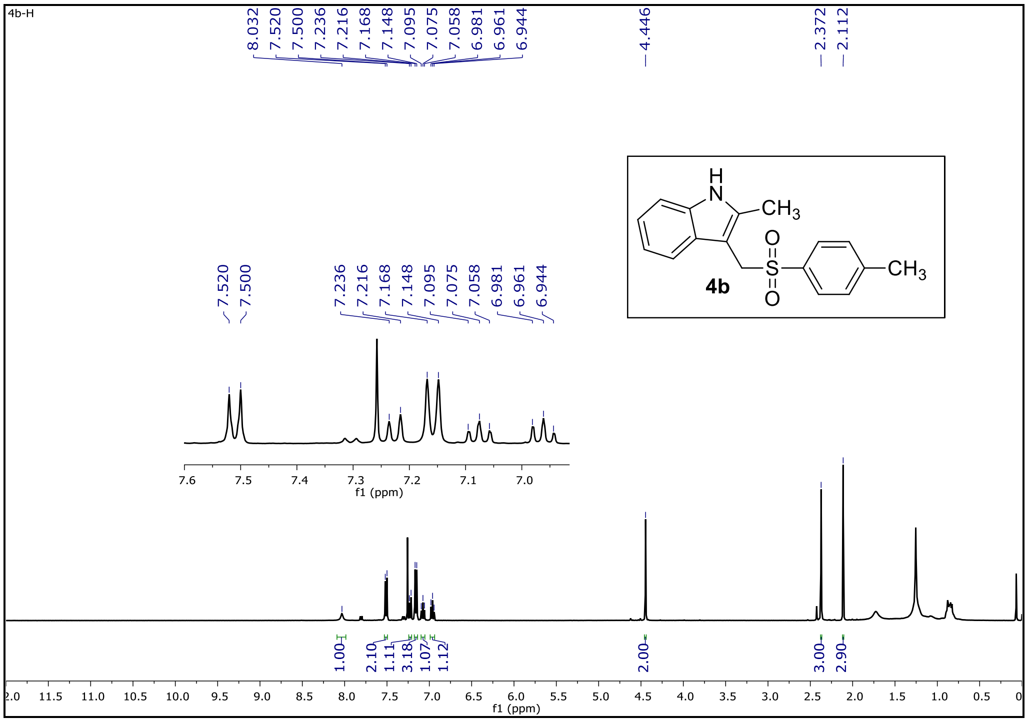
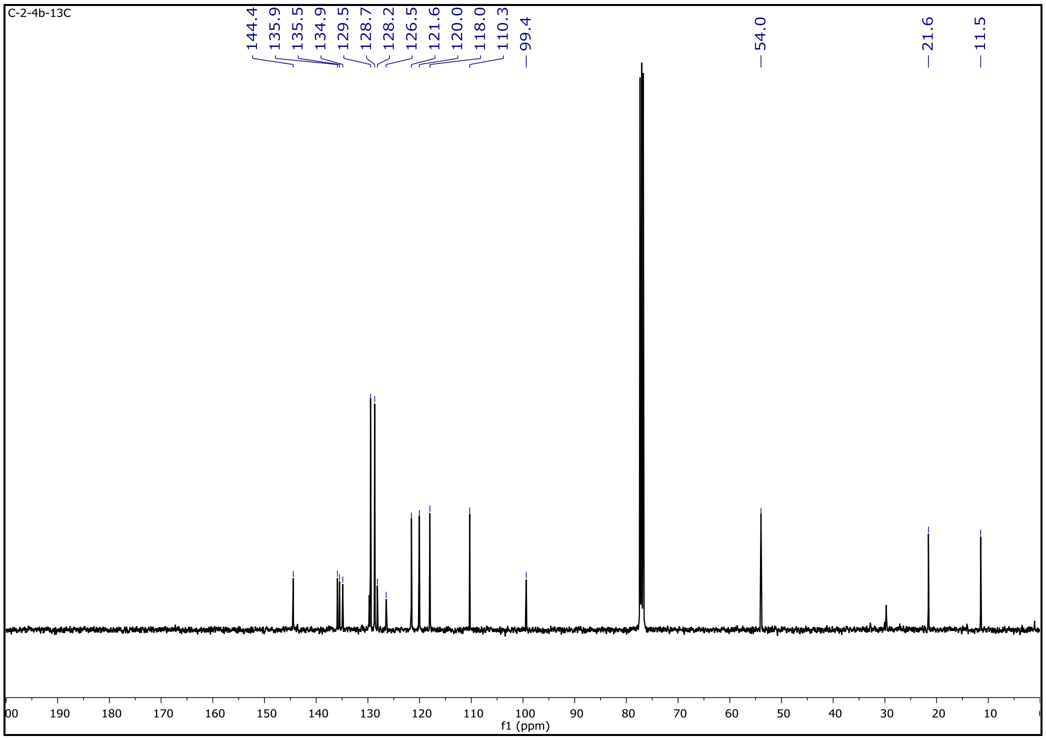
2.8. Selected NMR (^{1}H and ^{13}C) and Mass Spectra



^{1}H NMR spectrum of compound **4b**



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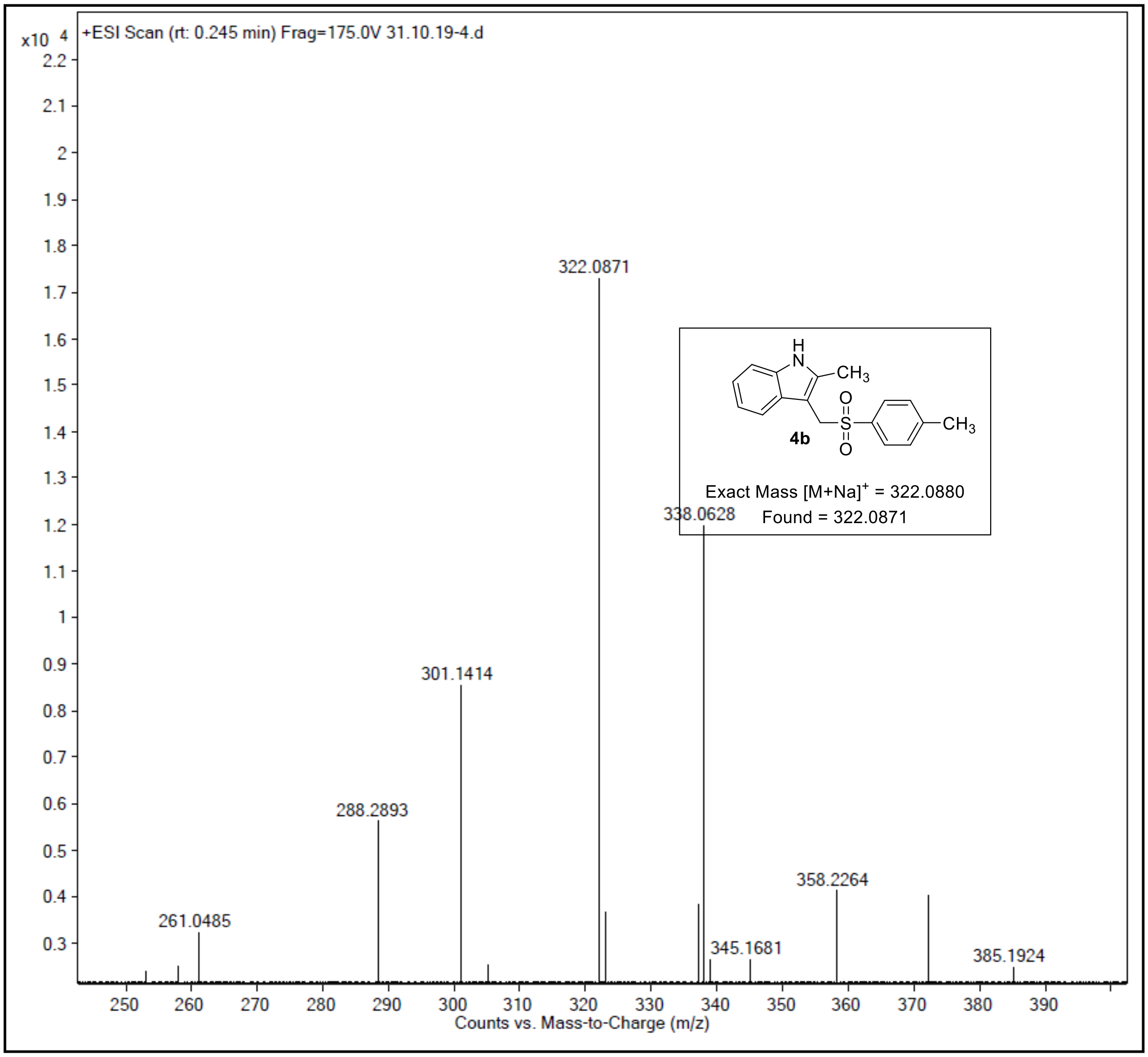
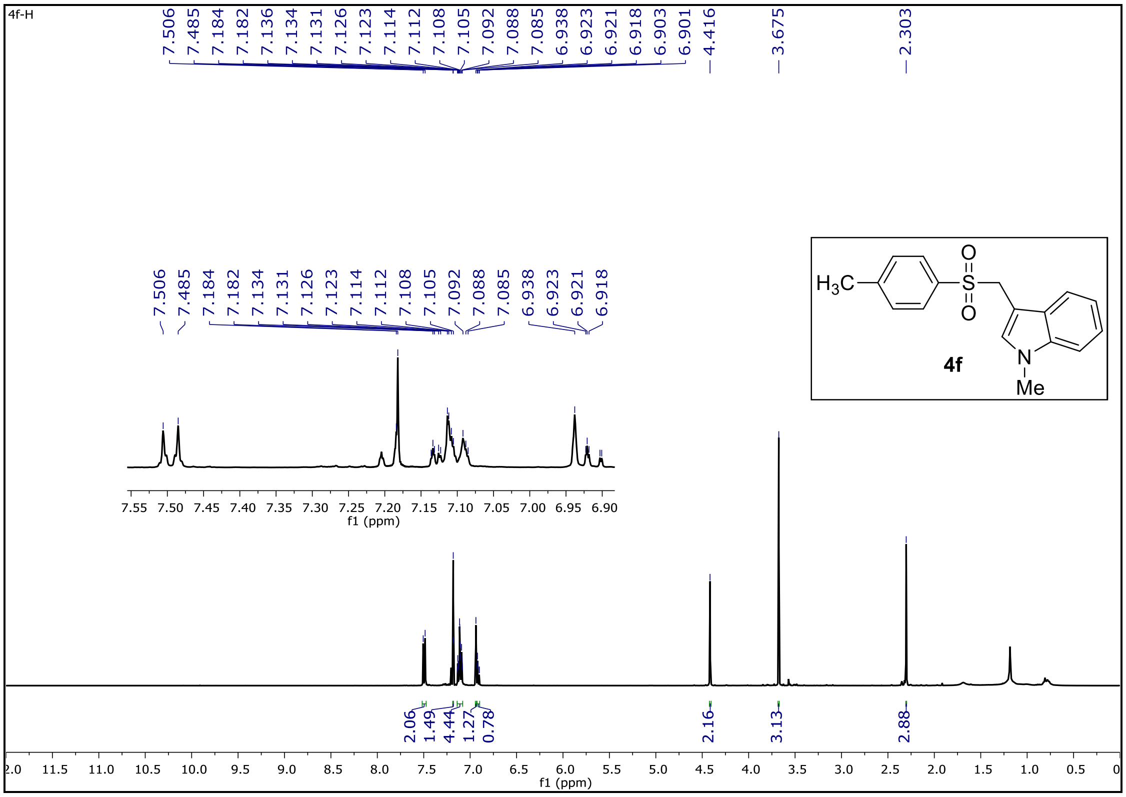
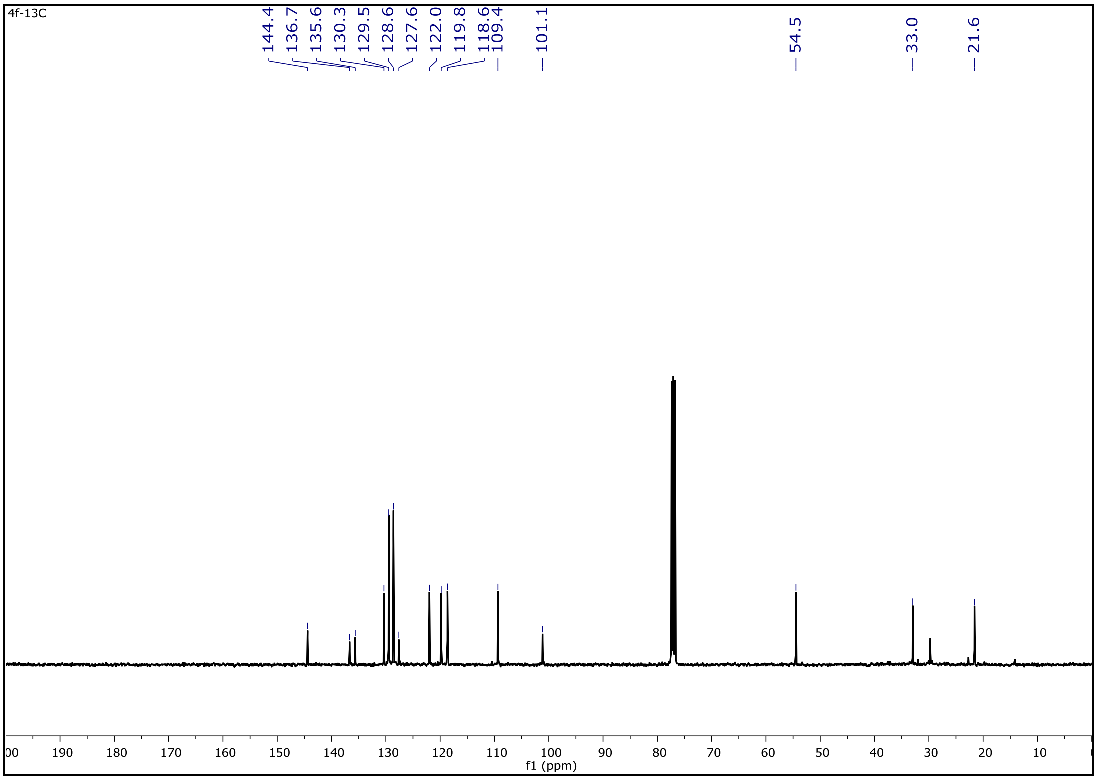


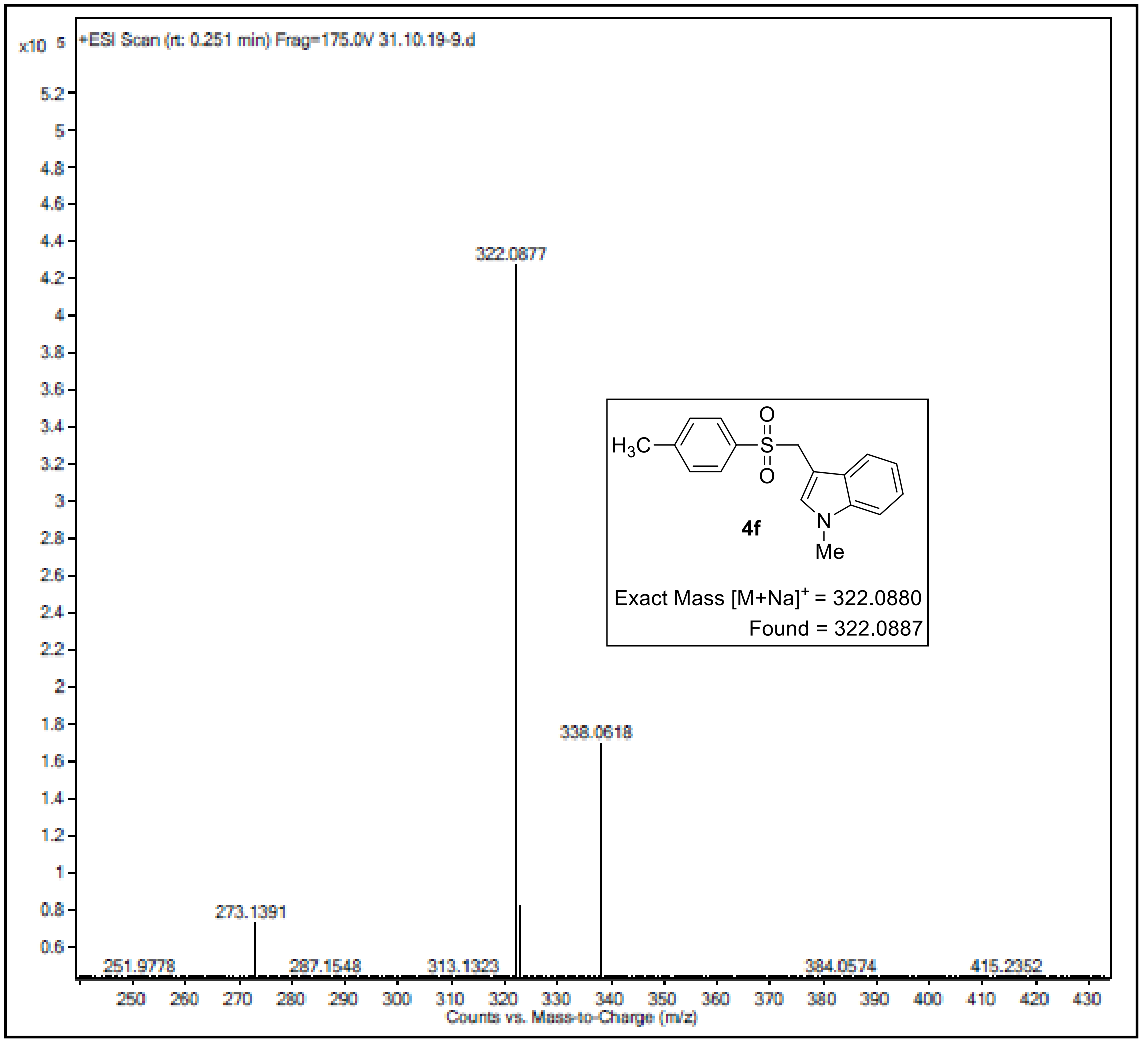
Mass spectrum of compound **4b**



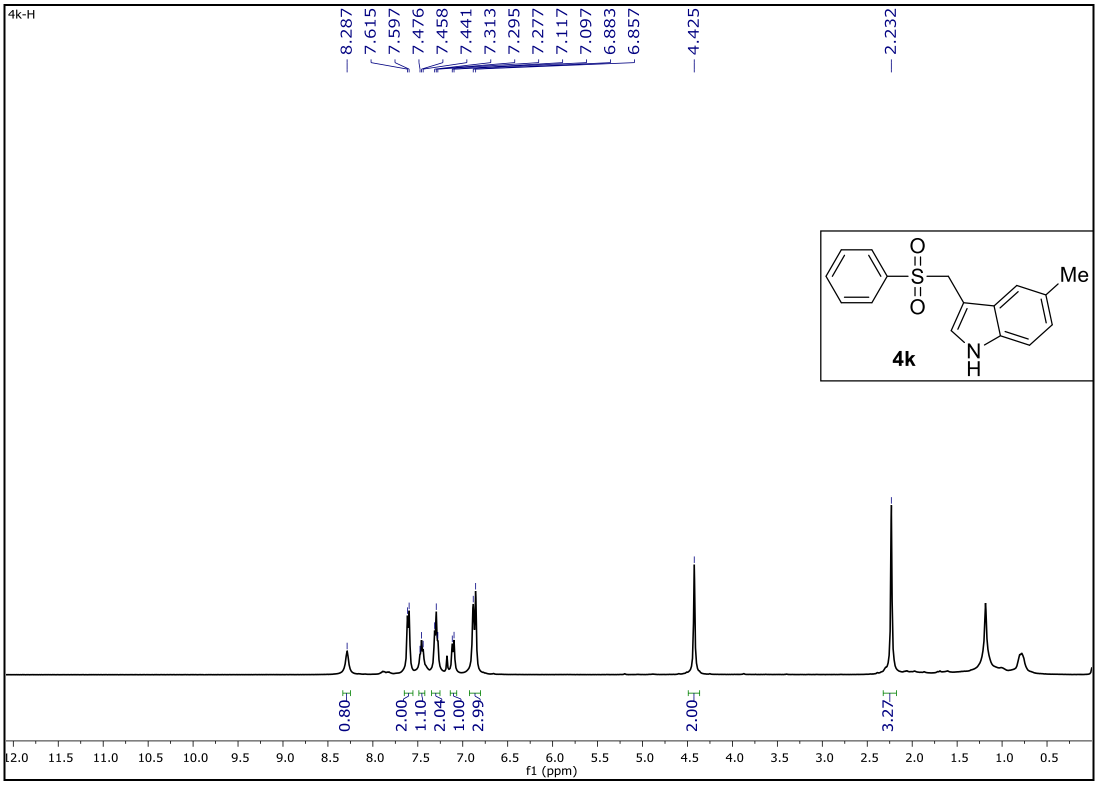
¹H NMR spectrum of compound **4f**



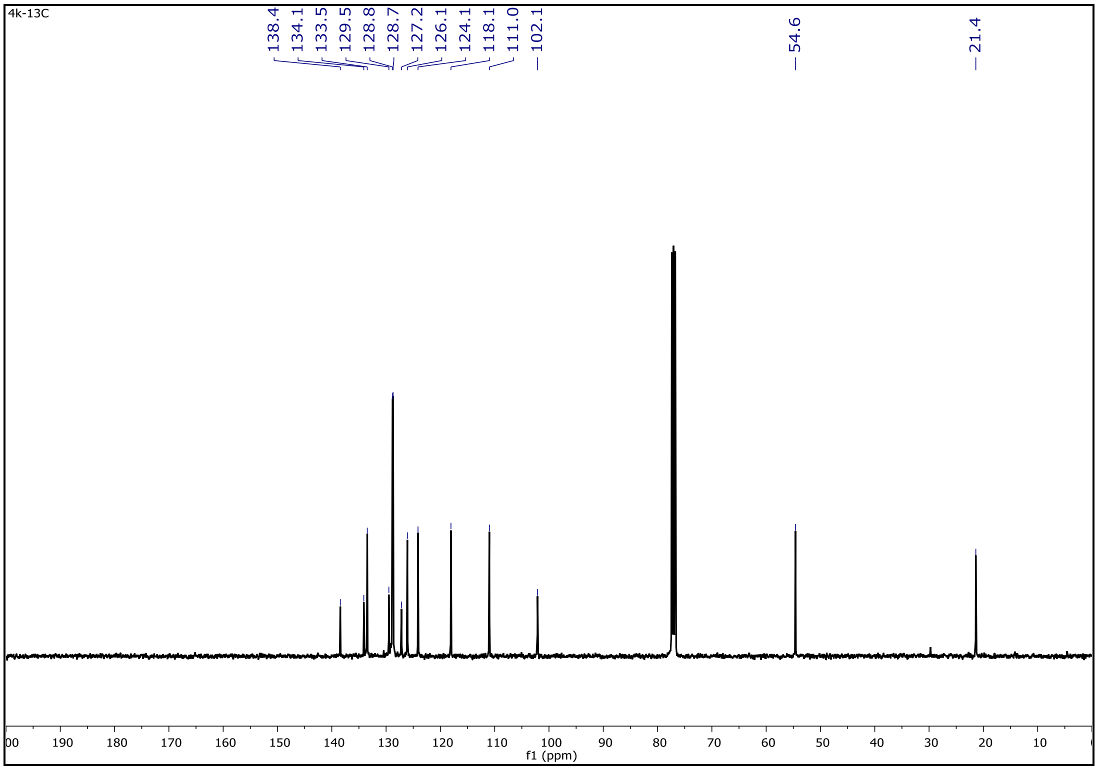
¹³C NMR spectrum of compound **4f**



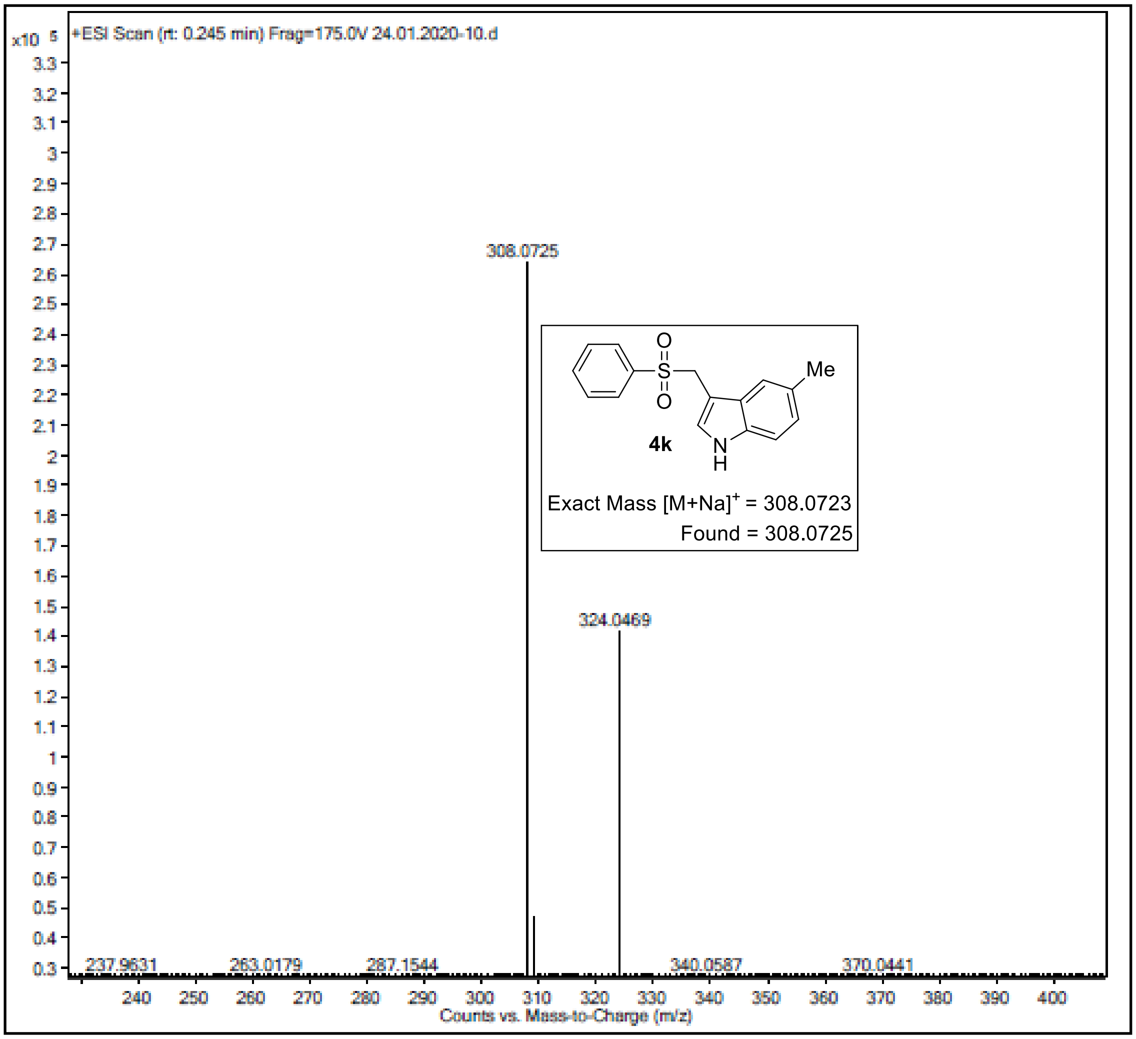
Mass spectrum of compound **4f**



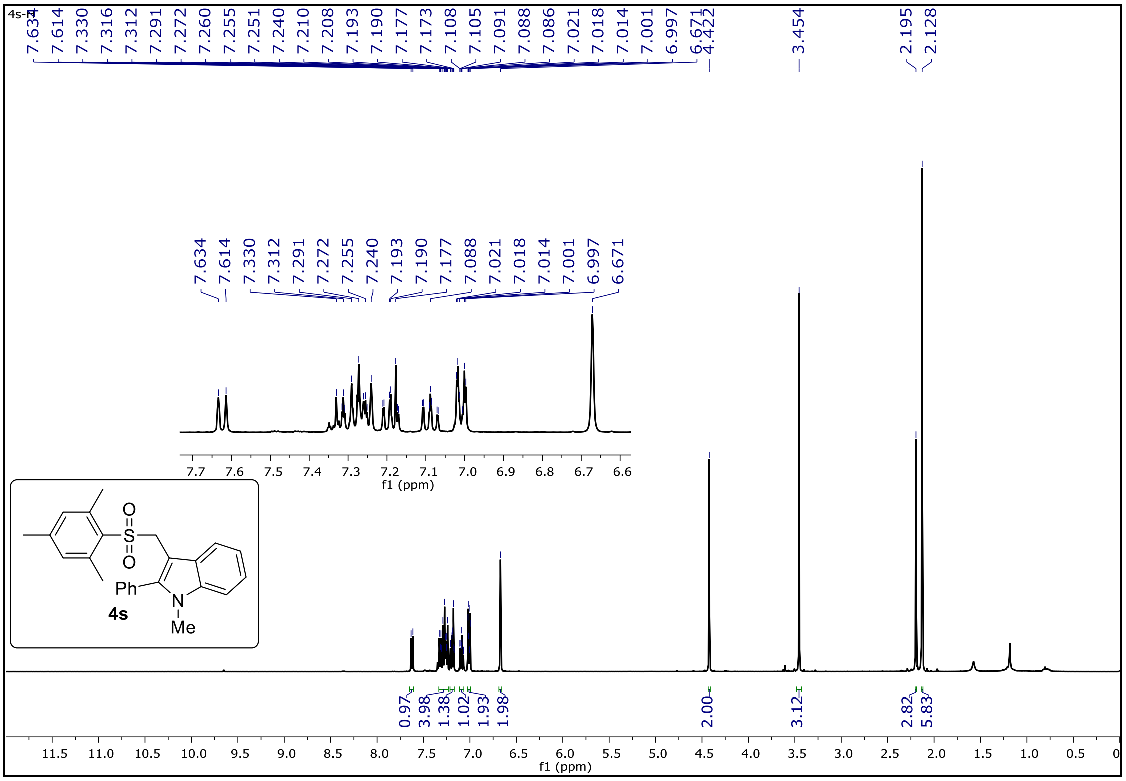
^{1}H NMR spectrum of compound **4k**



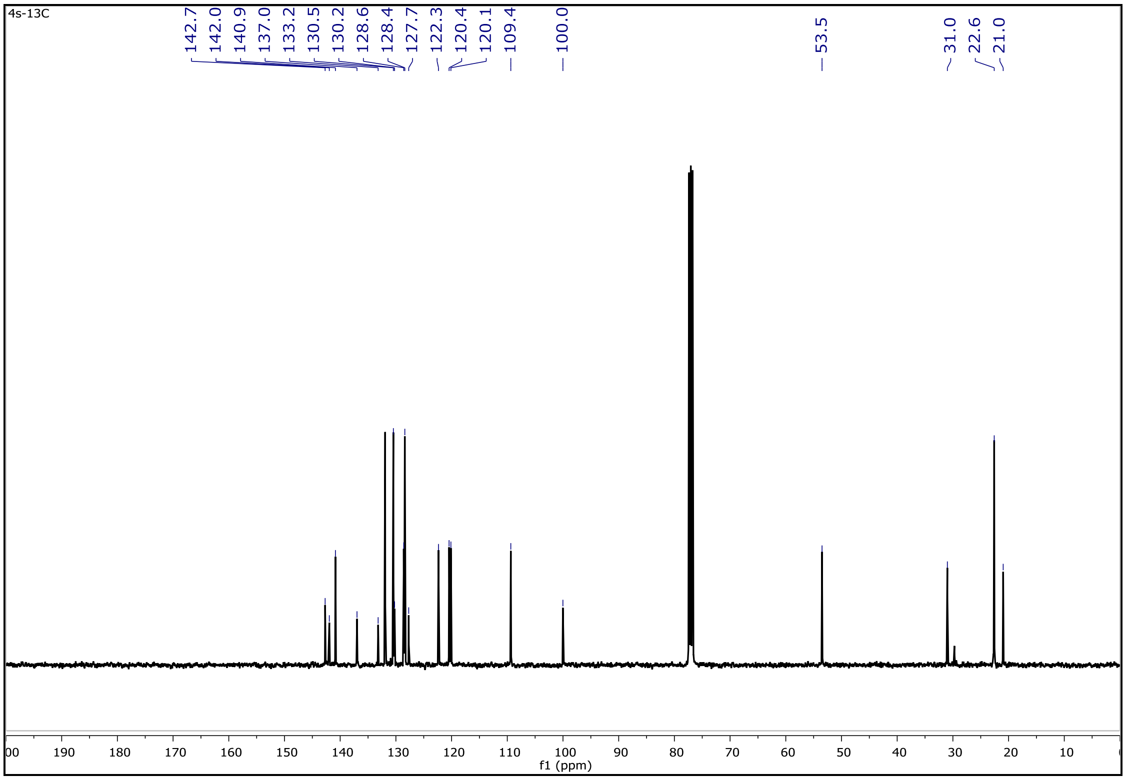
^{13}C NMR spectrum of compound **4k**



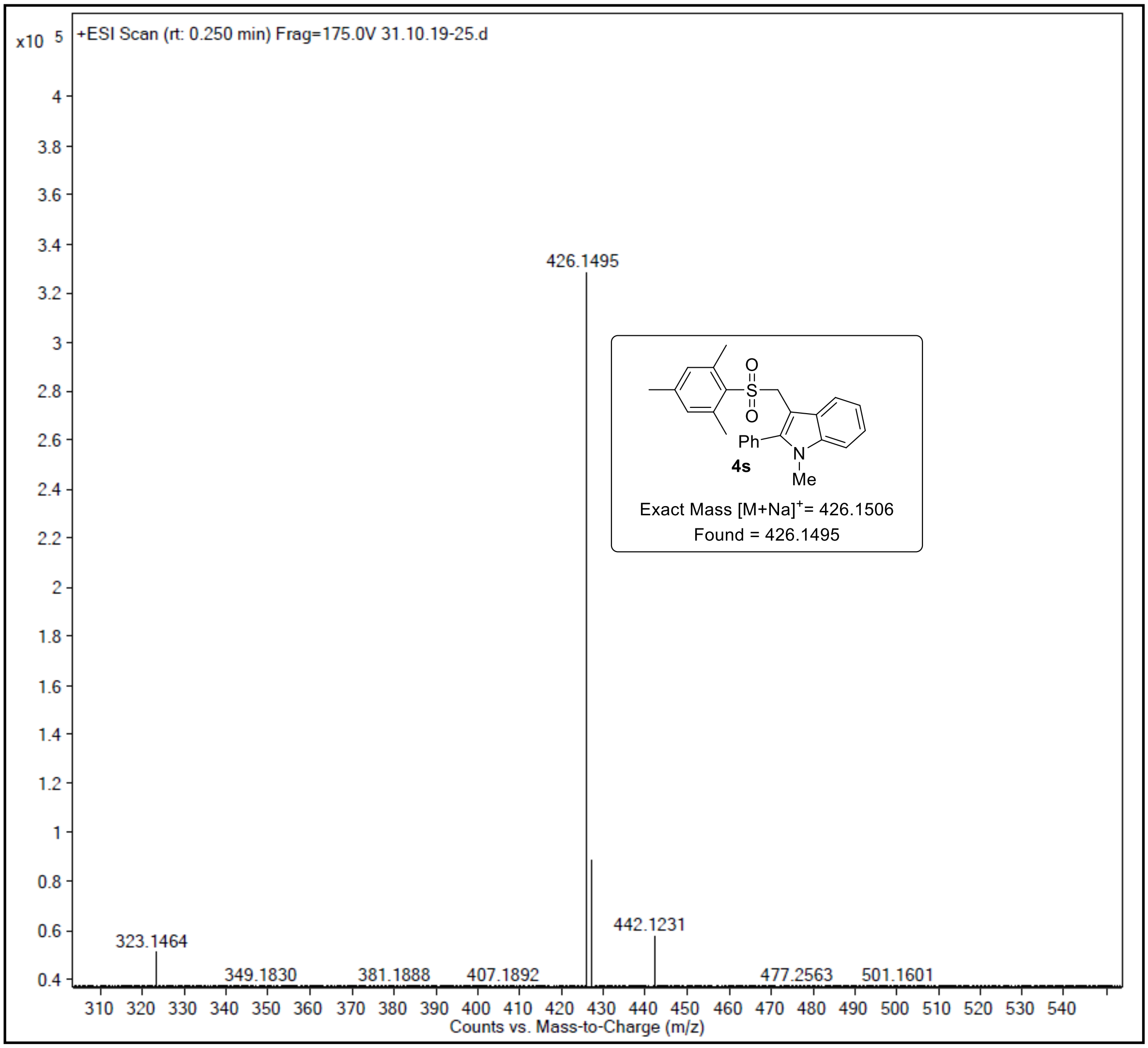
Mass spectrum of compound **4k**



^{1}H NMR spectrum of compound **4s**



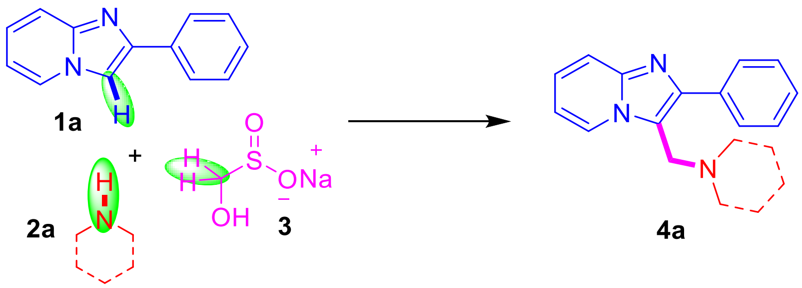
^{13}C NMR spectrum of compound **4s**



Mass spectrum of compound **4s**

CHAPTER-III
Section-A

One-Pot Aminomethylation of Imidazo[1,2-*a*]pyridineand Imidazo[2,1-*b*]thiazole Derivatives UsingSecondary Amines and Rongalite



3A.1. Introduction

Nitrogen bridge head-fused heterocycles containing an imidazole ring particularly, imidazo[1,2-*a*]pyridines are common structural motifs in pharmacologically important molecules, with diverse biological activities i.e., antiviral, analgesic, antifungal, antitumor, antibacterial, anti-inflammatory, antiprotozoal, antiapoptotic, antipyretic, anxioselectives, and hypnoselective activity.[1-10]

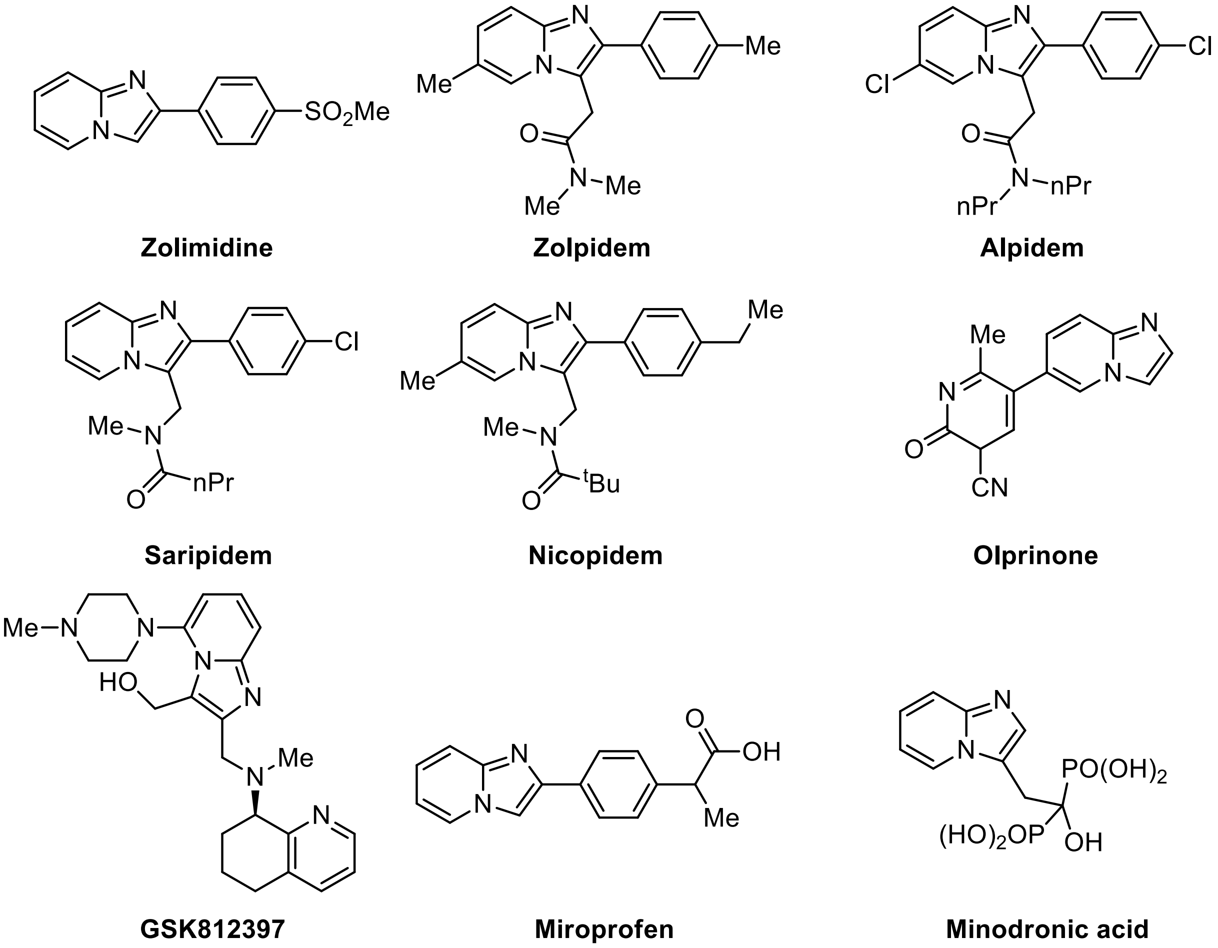


Figure 3A.1. Biologically Important Drugs Containing Imidazo[1,2-*a*]pyridine.

For the prevention of disease in humans, there are several drugs available in the market containing the imidazo[1,2-*a*]pyridine as core moiety namely, zolimidine (anti-peptic ulcer),[11] zolpidem (insomnia) alpidem, saripidem and necopidem (anxyolytic agent),[12-13] olprinone (cardiotonic agent),[14] drug GSK812397 which is optically active in nature and is used for the prevention of HIV.[15]

Recently some of the imidazo[1,2-*a*]pyridine are effectively used in the preparation of *N*-heterocyclic carbenes base catalyst PEPPSI™ (pyridine-enhanced precatalyst preparation stabilization and initiation) for Suzuki and Sonogashira reactions.[16] Among these, 2-phenylimidazo[l,2-*a*]pyridine derivatives are of significant synthetic interest due to their diverse biological activities ranging from anti-inflammatory to GABA-A inhibition.[17]

Along with nitrogen, Sulphur containing compounds are also regularly found in heterocyclic family which have different biological activities.[18-21] Benzo[*d*]imidazo[2,1-*b*]-thiazole and imidazo[2,1-*b*] thiazole fused heterocyclic compounds are very important building blocks in the synthetic and biologically active aspects of chemistry. This class of thiazoles are extensively used as antitumor agents, anti-allergic, antibacterial, antimicrobial agentsand also as kinase inhibitor and in PET imaging of Alzheimer patients' brains **(**Figure 3A.2).[22-26]

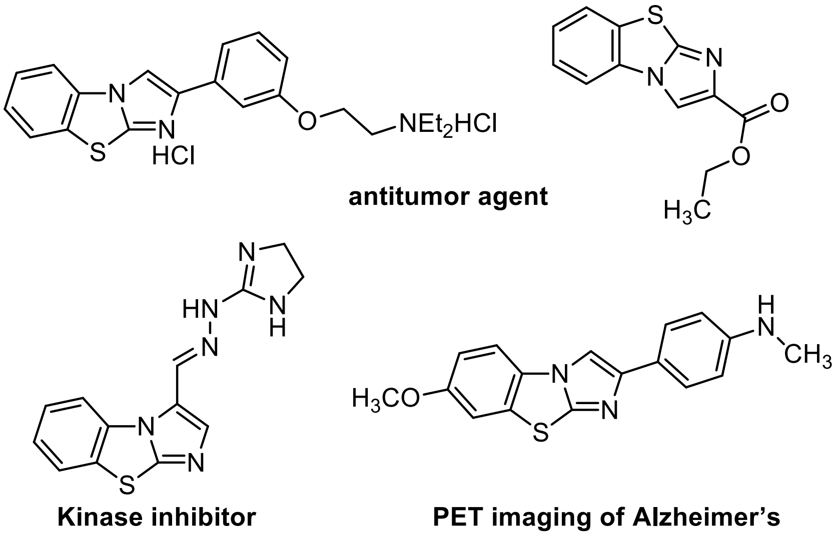


Figure 3A.2. Application of benzo[*d*]imidazo[2,1-*b*]thiazole derivatives.

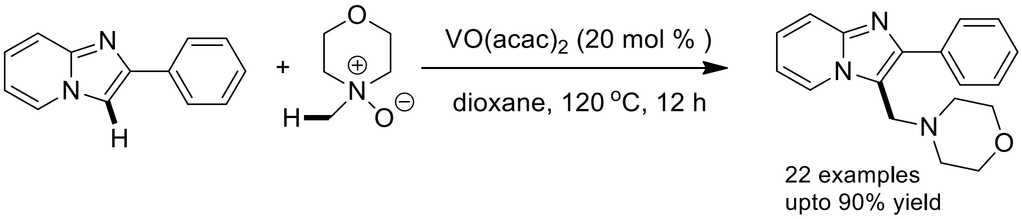
The hybrid molecules of imidazo-[1,2-*a*]pyridine and morpholine are key pharmacophores in various drugs and are biologically important molecules because of the presence of secondary amine thus enhancing their significance in the fields of agrochemicals and medicine.[27] Morpholine is a six member heterocyclic ring which is hydrophilic in nature and it will change the activity of the compound which it is attached to. It is present in Reboxetine drug which is used as antidepressant.[28-29]

Although, this class of compounds has promising biological activities, a few approaches have been developed for their synthesis.[30]

To prepare nitrogen bridgehead-fused phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine, aminomethylation is one of the best till date.[31] These compounds can be synthesised conventionally using Mannich reaction "an amino alkylation of an acidic proton with formaldehyde and any primary or secondary amine" where formaldehyde act as a methylene source.[32] Formalin solution is commonly known as formaldehyde is one of the important component in textile and resin industry, but it was banned due to its volatility high toxicity and also the US National Toxicology programme is described formaldehyde is known to be a human carcinogen.[33]

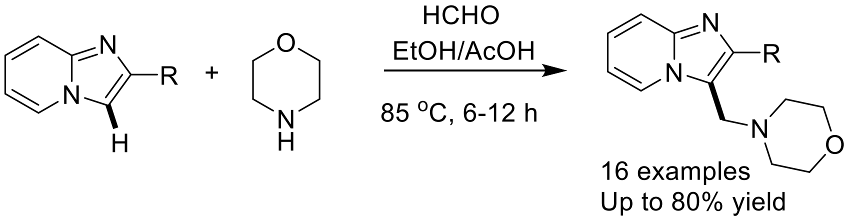
3A.2. Synthetic Methods for the Preparation of 4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine

Kaswan et al. developed a vanadium-catalyzed [VO(acac)$_2$]oxidative aminomethylation of imidazo[1,2-*a*]pyridines in the presence of NMO. Here NMO is acting both as a methylenating agent and oxidant. This method involves Mannich-type process to tertiary amines into heterocycles (Scheme 3A.1).[34]



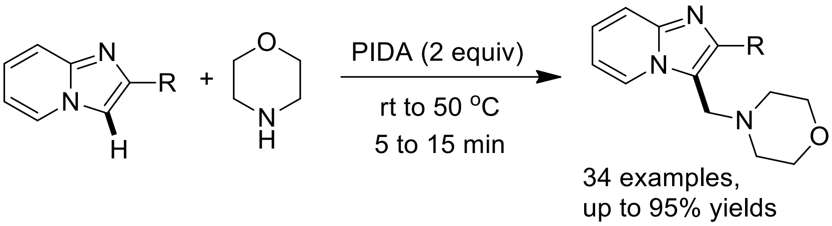
Scheme 3A.1

Bodke and co-workers synthesized a series of substituted 3-(morpholin-4-ylmethyl)-2-phenylimidazo[1,2-*a*] pyridine derivatives, where formalin was used as a methylenating agent in presence of catalytic amount of acetic acid at reflux condition (Scheme 3A.2).[35]



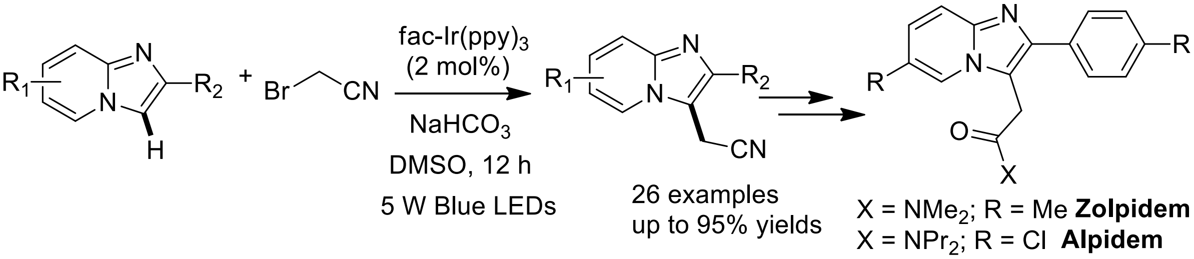
Scheme 3A.2

In 2017, **Hajra's research group** developed a novel aminomethylation C-3 of imidazopyridines with morpholine in the presence of (diacetoxyiodo)benzene (PIDA). This protocol is also applicable to electron rich indolizine, imidazo[2,1-*b*]thiazole, benzo[*d*]imidazo[2,1-*b*]thiazole, and indole. Notably, the morpholine is acting both as a source of methylene and nucleophile (Scheme 3A.3).[36]



Scheme 3A.3

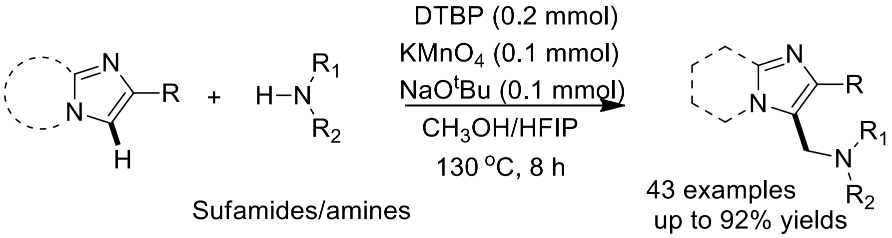
Sun and co-workers introduced visible-light promoted one-pot 3-cyanomethylation on imidazopyridines from imidazopyridines with bromoacetonitrile or iodo acetonitrile catalyzed by *fac*-Ir(ppy)3.



Scheme 3A.4

This method is operationally simple and tolerates wide variety of substituents on benzene or pyridine ring. Also, they have demonstrated this protocol for the synthesis of zolpidem and alpidem (Scheme 3A.4).[37]

Zhao et al. developed an efficient metal-free, one-pot syntheses of C3 sulfonamidomethylated imidazopyridines, which utilized commercially available reagent methanol as the main C-1 source. This method is widely tolerated substituted imidazopyridines and sulfamides/amines to afford the respective products in up to 92% yield (Scheme 3A.5).[38]



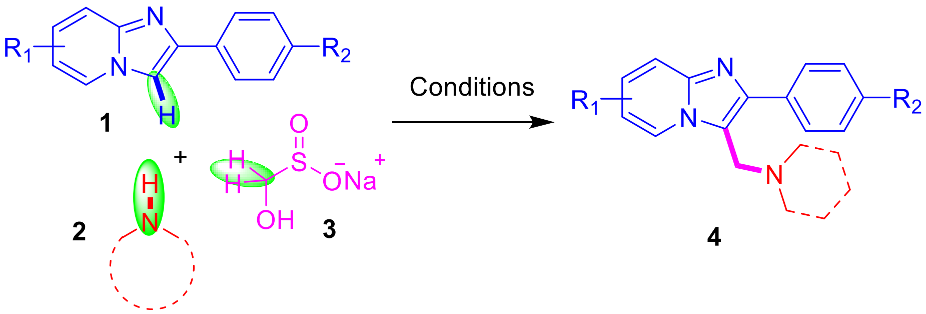
Scheme 3A.5

3A.3. Present Study

Considering the problems associated with use of toxic formalin solution, toxic metal catalysts and the importance of imidazo[1,2-*a*]pyridine-morpholine hybrids, we have developed one-pot three component reaction involving imidazo[1,2-*a*]pyridine, secondary amine and rongalite in ethanol to produce the desired compounds **4a-r** (Table 3A.2) and **6a-j** (Table 3A.3). The key step in this reaction is *in situ* generation of formaldehyde from rongalite.

3A.3.1. Results and Discussion

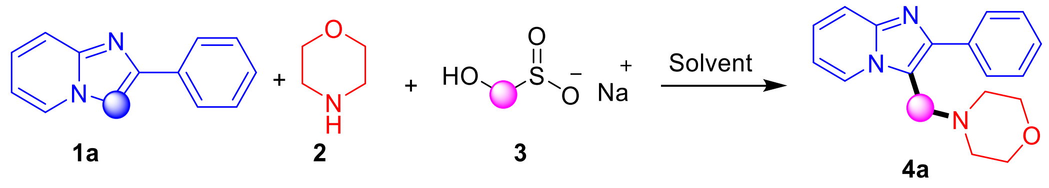
In the search for green formalin source, we have found that rongalite, a crystalline solid which can generate formaldehyde *in situ* without any danger.[39] Using this concept, we have developed a green one-pot synthesis of imidazo[1,2-*a*]pyridin-3-yl-methylmorpholine derivatives and a general Scheme is showed in Scheme 3A.5.



Scheme 3A.5

To validate our hypothesis a test reaction was conducted between imidazo[1, 2-*a*]pyridine **1a**, morpholine **2a** and rongalite in dichloromethane solvent. Initially, the reaction mixture was stirred at room temperature for 12 h, no change in starting material was observed (monitored by TLC). Then the reaction mixture was heated to 45 °C and surprisingly, formation of desired product **4a** was observed in low yield (Table 3A.1, entry 3). The product **4a** was purified and characterized by ^{1}H and ^{13}C and mass techniques.

Table 3A.1. Optimization of Reaction Condition.[a]



Entry	Solvent	Rongalite (equiv)	Temperature (°C)	Time (h)	Yield (%)[b]
1.	CH_2Cl_2	--	rt	12	n.d[c]
2.	CH_2Cl_2	1.0	rt	12	n.d
3.	CH_2Cl_2	1.0	45	12	10
4.	$CHCl_3$	1.0	65	12	20
5.	DCE	1.0	70	12	30
6.	Toluene	1.0	80	10	45
7.	CH_3CN	1.0	80	12	40
8.	THF	1.0	70	12	20
9.	1,4-Dioxane	1.0	70	12	20
10.	DMF	1.0	90	10	50
11.	DMSO	1.0	100	12	60
12.	MeOH	1.0	70	6	70
13.	EtOH	1.0	70	6	75
14.	EtOH	1.5	70	5	90
15.	EtOH	2.0	70	5	90
16.	H_2O	1.0	100	24	n.d

[a] All the reactions were conducted in 1 mmol scale of **1a** (1 mmol), **2a** (1mmol) and **3** (1.5 mmol) in solvent (2 mL), otherwise mentioned. [b] Yield where reported is of isolated and purified product. [c] Not Detected.

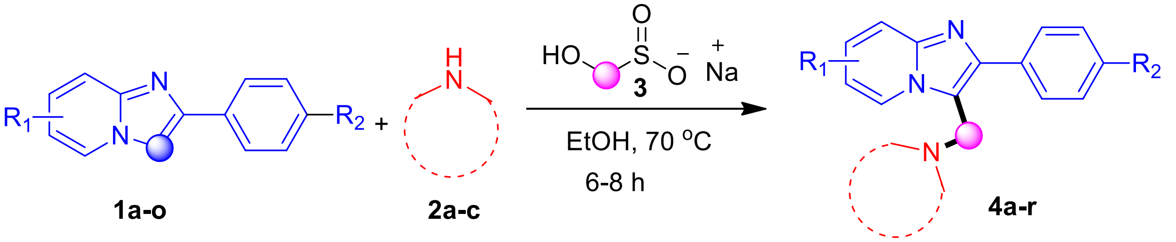
The above result provoked us to optimize the reaction conditions to improve the product yield by changing the reaction conditions and the results are tabulated in (Table 3A.1). Hence, we have focused on screening of solvents. Initially, reaction was conducted in chlorinated solvents such as chloroform and dichloroethane, but gave low yield (Table 3A.1, entries 4-5). It was observed from the entries 3-5 that temperature is playing role to furnish product in improvised yield, based on this we have conducted a reaction in toluene medium, but observed marginal increase in the yield. Later, we have changed the reaction medium to other polar aprotic solvents such as, CH_3CN, THF, dioxane, DMF and DMSO, which gave improved yields (Table 3A.1, entries 7-11). Finally, we have tested the same reaction in polar protic solvents i.e.; methanol and ethanol, surprisingly gave good yields (Table 3A.1, entries 12-13). Ethanol was found to be a best reaction medium among all the solvents tested to produce quantitative yield. To improve the product yield further, we shifted our focus to the stoichiometry of rongalite. Notably, changing the stoichiometry of rongalite from 1 mmol to 1.5 mmol gave 90% of product in less time, further increment of rongalite did not affect the yield (Table 3A.1, entries 14-15). Also, we were interested to test our protocol in water as reaction medium as water is universally accepted as green reaction medium but gave inferior results (Table 3A.1, entry 16).

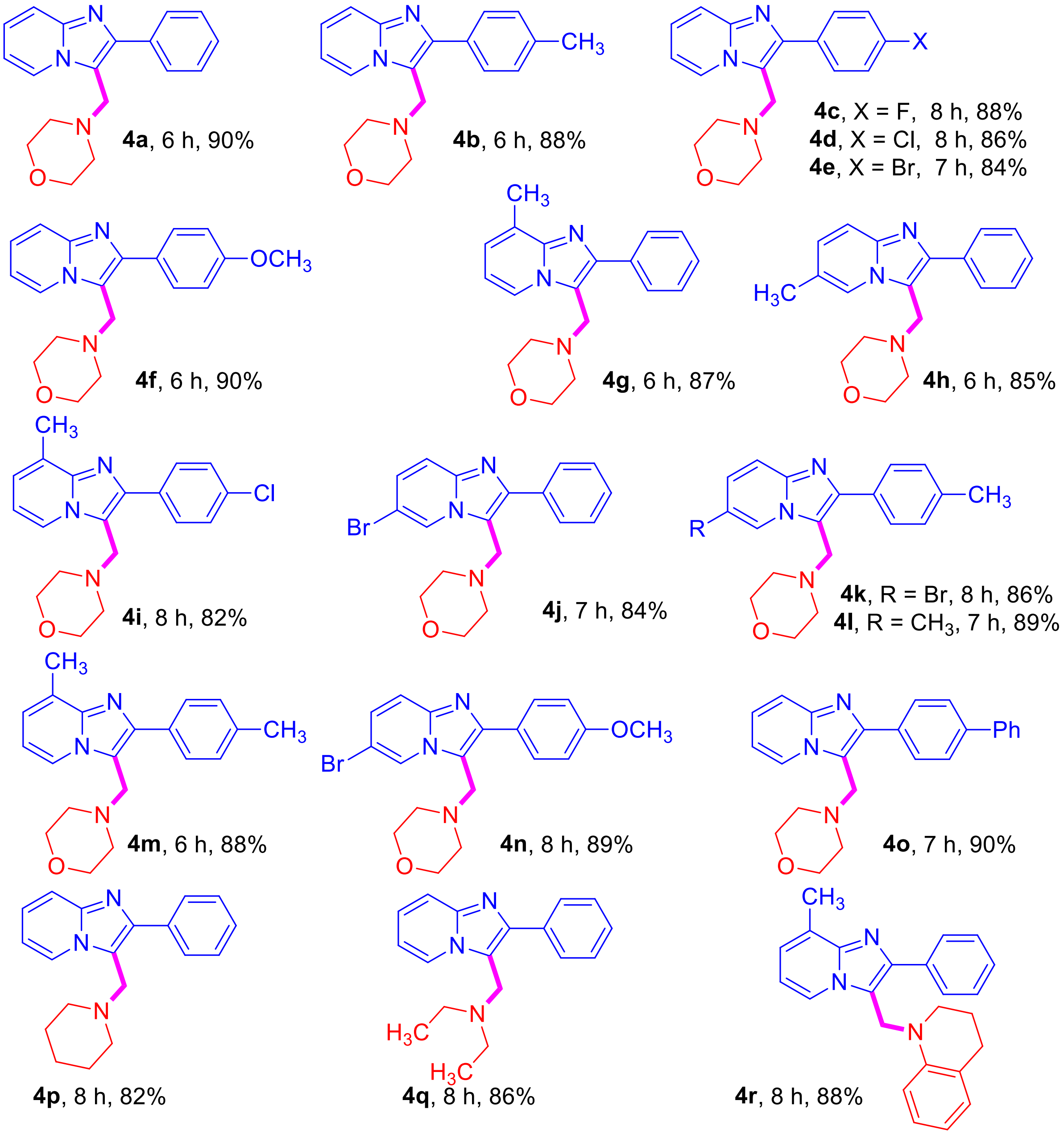
The optimized conditions for the above reaction is as follows, imidazo-[1, 2-*a*]pyridine **1a**, morpholine **2a** and rongalite **3** in ethanol (2 mL) at 70 ^{o}C for 6-8 h.

After optimized the reaction conditions for one-pot aminomethylation of imidazo-[1,2-*a*]pyridine with secondary amines then we have focused on the scope of the substrates and reagents, interestingly both the electron withdrawing and electron donating groups on the imidazo-[1,2-*a*]pyridine and secondary amines gave the corresponding bridged imidazo[1,2-a]pyridine-3-yl)methylmorpholine **4a-r** in good to excellent yields (Table 3A.2). All the synthesized compounds from the protocol were characterized by ^{1}H, and ^{13}C NMR spectroscopy and mass spectral data. The data of all the compounds were compared with the literature.

The reactivity of the substrates in this protocol is excellent by producing their products in moderate to excellent yields. The starting materials, imidazo-[1,2-*a*]pyridines which are used in this chapter, prepared from reported method using 2-aminiopyridine and phenacyl bromide in EtOH as solvent.[31] later, we have tested the substrate scope of the imidazopyridines. With electron releasing groups such as methyl, methoxy, phenyl and halogens (F, Cl, Br) on C-2-phenyl gave target compounds up to 90% yields (Table 3A.2, **4a-4f**). Substrates which have substitution on the pyridine ring also provided title products in excellent yields (Table 3A.2, **4g-4j).** Also, the substitution on both the pyridine ring and C-2-phenyl participated in this reaction and furnished the product in good yields (Table 3A.2, **4k-4o).** Later, we have tested our protocol with other secondary amines such as piperidine, *N*,*N*-diethylamine and 1,2,3,4-tetrahydro quinoline which gave satisfactory results (Table 3A.2, **4p-4r**).

Table 3A.2. One-pot Aminomethylation of Imidazo[1,2-*a*]pyridine Derivatives.[a,b]





4a, 6 h, 90%

4b, 6 h, 88%

4c, X = F, 8 h, 88%
4d, X = Cl, 8 h, 86%
4e, X = Br, 7 h, 84%

4f, 6 h, 90%

4g, 6 h, 87%

4h, 6 h, 85%

4i, 8 h, 82%

4j, 7 h, 84%

4k, R = Br, 8 h, 86%
4l, R = CH_3, 7 h, 89%

4m, 6 h, 88%

4n, 8 h, 89%

4o, 7 h, 90%

4p, 8 h, 82%

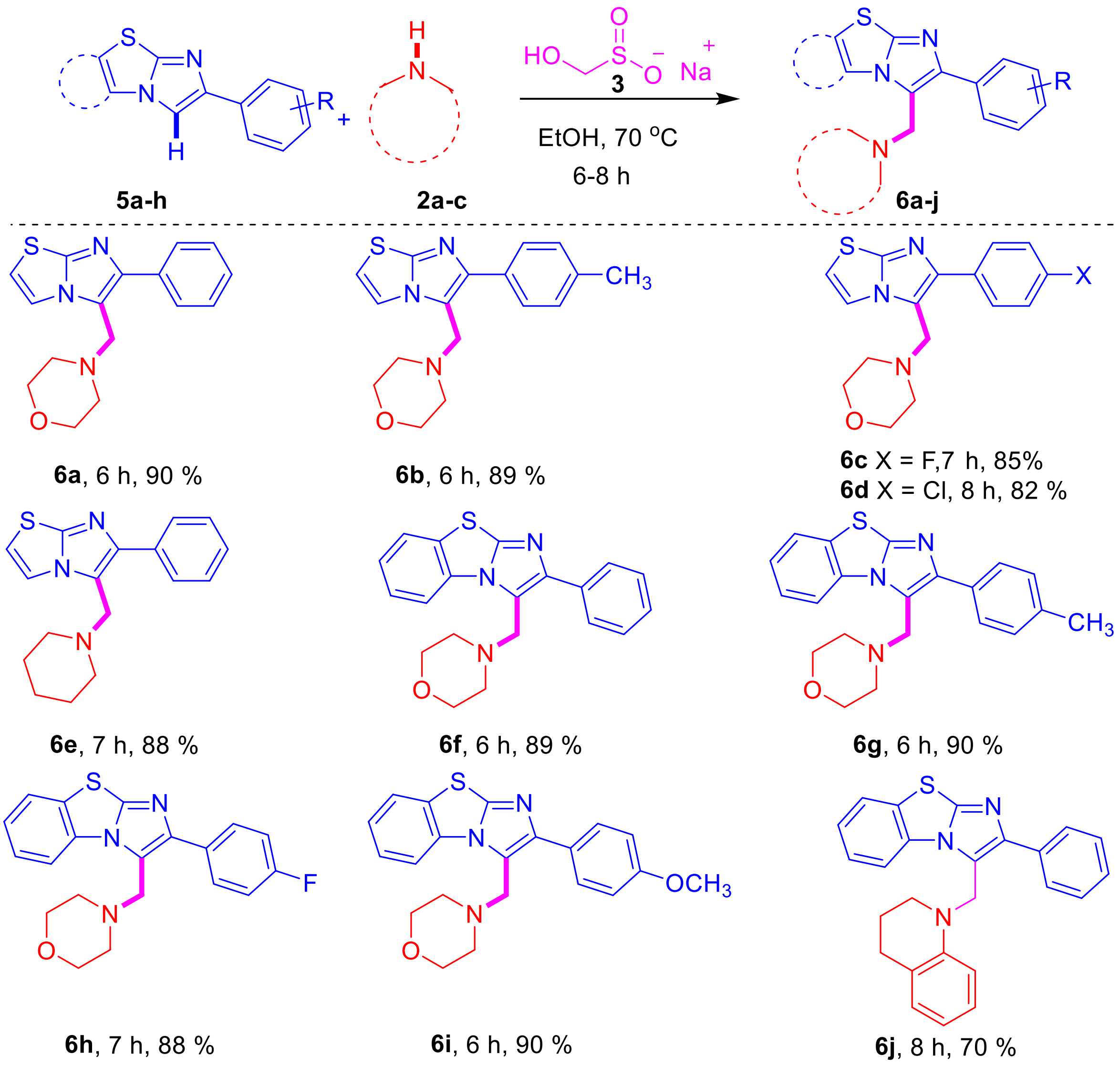
4q, 8 h, 86%

4r, 8 h, 88%

[a] All the reactions were conducted on a 1 mmol scale of **1a-o** (1.0 mmol), **2a-c** (1.0 mmol) and **3** (1.5 mmol) in solvent (2 mL), otherwise mentioned. [b] Yield where reported is of isolated and purified product.

Further, same reaction conditions were applied to other heteroarenes i.e., imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]-thiazole and the results are shown in table 3A.3. Similar reactivity pattern was observed with imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]-thiazole which gave the end products in acceptable yields (Table 3A.3, 6a-6j).

Table 3A.3. Aminomethylation Imidazo[2,1-*b*]thiazole Derivatives.[a,b]



6a, 6 h, 90 %

6b, 6 h, 89 %

6c X = F,7 h, 85%
6d X = Cl, 8 h, 82 %

6e, 7 h, 88 %

6f, 6 h, 89 %

6g, 6 h, 90 %

6h, 7 h, 88 %

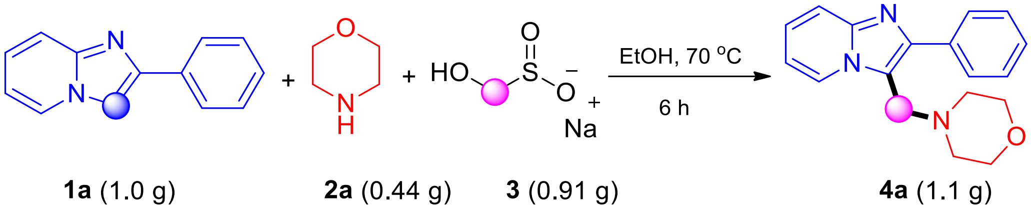
6i, 6 h, 90 %

6j, 8 h, 70 %

[a] All the reactions were conducted on a 1 mmol scale of **5a-h** (1 mmol), **2a-c** (1 mmol) and **3** (1.5 mmol) in solvent (2 mL), otherwise mentioned. [b] Yield where reported is of isolated and purified product.

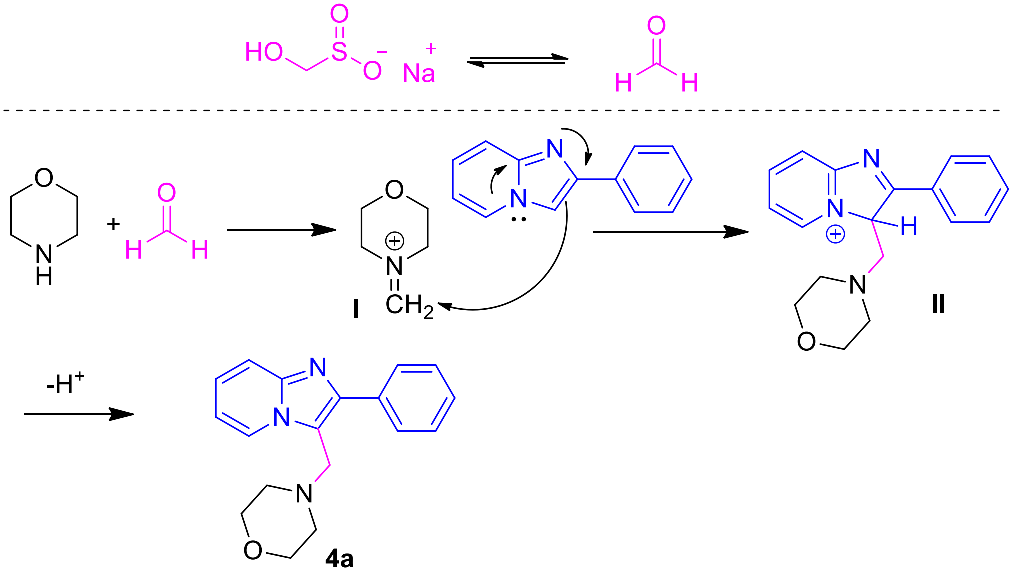
All the synthesized compounds (**4a-r** and **6a-j**) from the protocol were characterized by ^{1}H, and ^{13}C NMR spectroscopy and mass spectral data. The data of all the compounds were compared with the literature.

Finally, we have also tested our protocol in gram scale for the industrial applications with 1g scale and obtained in 73% yield (Scheme 3A. 6).



Scheme 3A. 6

The plausible reaction mechanism pathwayproposed for the one-pot Aminomethylation (Scheme 3A.7). In the first step, rongalite dissociates to generate formaldehyde *in situ*, which further reacts with the secondary amine, morpholine to form 4-methylenemorpholin-4-iminium intermediate **I**. Then C-2 double bond π electron of imidazo attack on iminium ion with the help of nitrogen lone pair to obtain intermediate **II**, finally re-aromatization of intermediate **II** with the loss of proton gave target molecule **4a**.



Scheme 3A.7

3A.3.2 Conclusion

In this chapter we have developed ametal-free one-pot aminomethylation to synthesize the hybrids of imidazopyridine/heteroarenes and morpholine in excellent yields. This method tolerates wide variety of substrates including electron donating, electron withdrawing, halogen and other substitutions on both the pyridyl and phenyl ring. The key point in this method is *in situ* generation of formaldehyde from rongalite. We have prepared 28 compounds in 80-90% yield. This protocol is also applicable to gram-scale reactions for industrial applications.

3A.4. Experimental Section

3A.4.1. General Information

All the starting materials 2-amino pyridines, and phenacyl bromides, morpholine, piperidine, rongalite and diethyl amine were purchased from Spectrochem, SD-Fine, Sigma-Aldrich, Finar, and SRL. All the used reagents are of analytical grade and were directly used without any further purification.The compounds imidazo[1,2-*a*]pyridine, imidazo[2,1-b]thiazole and benzo[*d*]imidazo[2,1-*b*]-thiazole are prepared according to the reported method and used after purification by column chromatography.[45] All the solvents used for this method were obtained from finar. For reaction monitoring TLC-Silica gel 60 GF_{254} were used with help of UV-Cabinet. Purification of compounds using column chromatography where performed with the Rankem silica gel (100-200 mesh). Melting point for solid compounds was recorded using Stuart SMP30 melting point apparatus. ^1H and ^{13}C NMR spectral data of all the synthesized compounds were recorded on Bruker Avance HD (400 MHz / 100 MHz) spectrometer using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The data of the compounds was recorded as chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations for the multiplicity as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. The mass spectrum analysis was recorded in Bruker- micro-TOF MS analyzer.

3A.4.2. General Procedures

General Procedure for the Preparation of Substituted (4-((2-phenylimidazo[1,2-a]pyridine-3-yl)methyl)morpholine) Derivatives (4a-r)

To a clean and oven dried round bottom flask were added imidazo[1,2-*a*] pyridine **1a** (200 mg, 1.0 mmol), morpholine **2a** (90.6 mg, 1.0 mmol), and rongalite **3** (184 mg, 1.5mmol) in ethanol solvent (2 mL). The reaction mixture was allowed to stir at 70 °C for 6-7 hours. After consumption of starting materials (monitored by TLC), solvent was evaporated and the crude residue was poured into water and extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over anhydrous sodium sulphate, concentrated under reduced pressure. The crude mixture was purified using column chromatography on silica-gel by eluting with ethyl acetate/hexanes solvent system used as mobile phase.

General Procedure for the Preparation of Substituted 4-((6-phenylimidazo[2,1-b]thiazol-5-yl)methyl)morpholine Derivatives (6a-e)

To a clean and oven dried round bottom flask were added 6-phenylimidazo[2,1-*b*]thiazole **5a** (200 mg, 1.0 mmol), morpholine **2a** (87 mg, 1.0 mmol), and rongalite **3** (176 mg, 1.5mmol) in ethanol (2 mL). The reaction mixture was allowed to stir at 70 °C for 6-7 hours. After consumption of starting materials (monitored by TLC), solvent was evaporated and the crude residue was poured into water and extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over anhydrous sodium sulphate, concentrated under reduced pressure. The crude mixture was purified using column chromatography on silica-gel by eluting with ethyl acetate/hexanes as mobile phase.

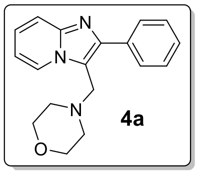
General Procedure for the Preparation of Substituted 4-((2-phenylbenzo[d]imidazo[2,1-b]thiazol-3-yl)methyl)morpholine Derivatives (6f-j)

To a clean and oven dried round bottom flask were added 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole **6a** (250 mg, 1.0 mmol), morpholine **2a** (86 mg, 1.0 mmol), and rongalite **3** (176.9 mg, 1.5 mmol) in ethanol (2 mL). The reaction mixture was allowed to stir at 70 °C for 6-7 hours. After consumption of starting materials (monitored by TLC), solvent was evaporated and the crude residue was poured into water and extracted with ethylacetate (10 mL x 3). The combined organic layers were dried over anhydrous sodium sulphate, concentrated under reduced pressure. The crude mixture was purified using column chromatography on silica-gel by eluting with ethyl acetate/hexanes solvents used as mobile phase.

3A.5. Characterization Data of Products

4-((2-Phenylimidazo[1,2-*a*]pyridine-3-yl)methyl)morpholine (4a)[41]

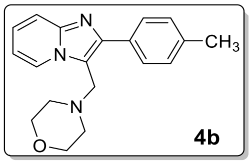
Yield: 90%, brown solid, M.P. 135-137 °C.



^{1}H NMR (400 MHz, CDCl$_3$) δ 8.40 (d, *J* = 6.8 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.38 (t, *J* = 7. 4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 4.4 Hz, 1H), 6. 81 (t, *J* = 6.8 Hz, 1H), 3.91 (s, 2H), 3.60 (t, *J* = 4.6 Hz, 4H), 2.41 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.3, 145.1, 134.4, 128.9, 128.45, 127.8, 125.3, 124.6, 117.3, 115.9, 111.9, 67.0, 53.2, 52.1. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_2S$ [M+Na]$^+$ 308.0723, found 308.0715.

4-((2-(*p*-Tolyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4b)[42]

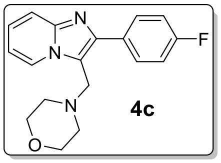
Yield: 88%, light greensolid, M.P. 114-116 °C.



^{1}HNMR (400 MHz, CDCl3) δ 8.35 (d, *J* = 6.8 Hz, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 10.4 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.77 (t, *J* = 6.8 Hz, 1H), 3.85 (s, 2H), 3.59 (t, *J* = 4.4 Hz, 4H), 2.38 (t, *J* = 4.6 Hz, 4H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 145.2, 145.0, 143.8, 137.6, 129.2, 128.8, 117.1, 115.6, 111.9, 67.0, 53.2, 52.1, 21.3. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_3O$ [M+H]$^+$ 308.1765, found 308.1754.

4-((2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4c)[41]

Yield: 88%, yellow solid, M.P. 172-174 °C.

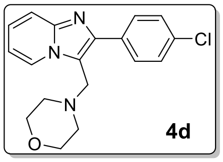


^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35(d, *J* = 6.8 Hz, 1H), 7.69 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 8.6 Hz, 2H), 6.78 (t, *J* = 7.0 Hz, 1H), 3.85 (s, 2H), 3.60 (t, *J* = 4.6 Hz, 4H), 2.39 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 163.8, 161.4, 145.0, 144.3, 130.6, 130.5, 125.2, 124.9, 117.3, 115.5, 115.3, 112, 66.9, 53.2, 52.0. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}FN_3O$ [M+H]$^+$ 312.1514, found 312.1506.

4-((2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4d)[41]

Yield: 86%, yellow solid, M.P. 153-155 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.37 (d, J = 6.8 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.20 (t, J = 8 Hz, 1H) 6.80 (t, J = 6.8 Hz, 1H), 3.88 (s, 2H), 3.60 (t, J = 4.6 Hz, 4H), 2.40 (t, J = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.9, 143.8, 134.0, 132.6, 130.1, 128.8, 125.3, 125.2, 117.2, 116.1, 112.3, 66.9, 53.2, 52.0. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}ClN_3O$ [M+H]$^+$ 328.1218, found 328.1210.

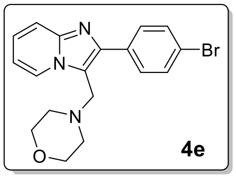


4d

4-((2-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4e)[34]

Yield: 84%, white solid, M.P. 161-163 °C

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.47 (d, J = 6.8 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.2 Hz, 1H), 6.92 (t, J = 6.8 Hz, 1H), 3.96 (s, 2H), 3.70 (t, J = 4.4 Hz, 4H), 2.49 (t, J = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.1, 140.0, 133.2, 131.7, 130.40, 125.2, 125.1, 122.1, 117.3, 116.1,112.3, 66.9, 53.2, 52.0. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}BrN_3O$ [M+H]$^+$ 372.0713, found 372.0724.

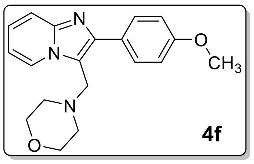


4e

4-((2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4f)[36]

Yield: 90%, light yellow liquid.

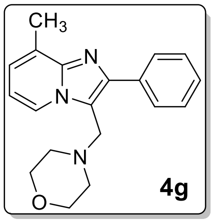
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.42 (d, J = 7.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 9.2 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.83 (t, J = 6.8 Hz, 1H), 3.95 (s, 2H), 3.86 (s, 3H), 3.67 (t, J = 4.6 Hz, 4H), 2.48 (t, J = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.4, 145.0, 144.9, 130.1, 126.8, 125.2, 124.6, 117.1, 115.3, 114.0, 111.9, 67.0, 55.3, 53.2, 52.2. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_3O_2$ [M+H]$^+$ 324.1714, found 324.1710.



4f

4-((8-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4g)[36]

Yield: 87%, white solid, M.P. 159-162 °C.



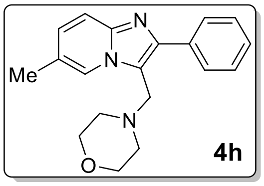
4g

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.23 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.0 Hz, 1H), 6.95 (d, J = 6.8 Hz, 1H), 6.68 (t, J = 6.8 Hz, 1H), 3.87 (s, 2H), 3.59 (t, J = 4.4 Hz, 4H), 2.59 (s, 3H), 2.39 (t, J = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.5, 145.0, 134.7, 129.1, 128.4, 127.6, 127.2, 123.4, 123.1, 116.3, 111.9, 67.0, 53.2, 52.2, 17.2. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_3O$ [M+H]$^+$ 308.1765, found308.1756.

4-((6-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4h)[38]

Yield: 85%, brown solid, M.P. 127-130 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 11.2 Hz, 1H), 3.90 (s, 2H), 3.64 (t, *J* = 4.4 Hz, 4H), 2.45 (t, *J* = 4.6 Hz, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 144.1, 134.5, 128.8, 128.4, 127.8, 127.7, 122.8, 121.6, 116.6, 115.7, 67.0, 53.2, 52.1, 18.6. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_3O$ $[M+H]^+$ 308.1765, found 308.1756.

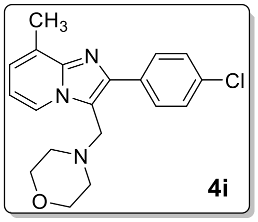


4h

4-((2-(4-Chlorophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4i)[43]

Yield: 83%, white solid, M.P. 177-179 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 6.8 Hz, 1H), 6.66 (t, *J* = 7.0 Hz, 1H), 3.81 (s, 2H), 3.57 (t, *J* = 4.6 Hz, 4H), 2.56 (s, 3H), 2.36 (t, *J* = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 143.7, 133.6, 133.3, 130.3, 128.6, 127.2, 123.6, 123.0, 116.4, 112.1, 66.9, 53.2, 52.1, 17.1. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{20}ClN_3O$ $[M+H]^+$ 342.1375, found 342.1368.

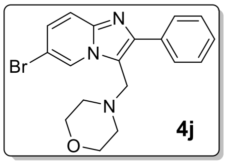


4i

4-((6-Bromo-2-phenylimidazo[1,2-*a*]pyridine-3-yl)methyl)morpholine (4j)[36]

Yield: 84%, yellow solid, M.P. 127-129 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 9.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.22 – 7.19 (m, 1H), 3.89 (s, 2H), 3.61 (t, *J* = 4.4 Hz, 4H), 2.40 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 143.5, 133.9, 128.8, 128.6, 128.1, 128.0, 125.5, 117.9, 116.3, 106.6, 66.9, 53.2, 52.1. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}BrN_3O$ $[M+H]^+$ 372.0713, found 372.0702.

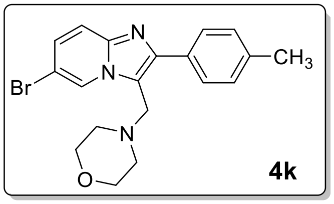


4j

4-((6-Bromo-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4k)[34]

Yield: 86%, white solid, M.P. 130-132 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 9.2 Hz, 1H), 7.23-7.18 (m, 3H), 3.88 (s, 2H), 3.60 (t, *J* = 4.6 Hz, 4H), 2.39 (t, *J* = 4.6 Hz, 4H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 143.2, 138.1, 130.4, 129.4, 129.3, 128.7, 128.3, 125.6, 125.5, 117.6, 116.1, 106.8,



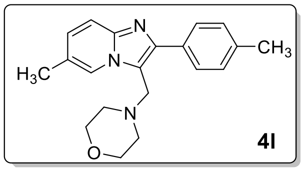
4k

66.9, 53.2, 52.1, 21.3. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_3O$ $[M+H]^+$ 386.0870, found 386.0859.

4-((6-Methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methl)morpholine (4l)[34]

Yield: 89%, white solid, M.P. 173-175 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 9.2 Hz, 1H), 3.84 (s, 2H), 3.59 (t, *J* = 4.4 Hz, 4H), 2.39 (t, *J* = 4 Hz, 4H), 2.32 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 144.0, 137.4, 131.6, 129.2, 129.1, 128.7, 127.8, 127.6, 122.8, 122.7, 121.4, 116.5, 115.4, 67.0, 53.2, 52.1, 21.4, 18.6. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{23}N_3O$ $[M+H]^+$ 322.1921, found 322.1915.

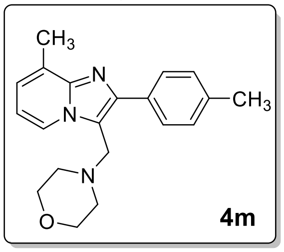


4l

4-((8-Methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4m)

Yield: 88%, yellow solid, M.P. 151-153 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.94 (d, *J* = 6.8 Hz, 1H), 6.66 (t, *J* = 6.8 Hz, 1H), 3.86 (s, 2H), 3.58 (t, *J* = 8.8 Hz, 4H), 2.58 (s, 3H), 2.38 (t, *J* = 3.8 Hz, 4H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 144.9, 137.4, 131.6, 129.2, 129.1, 127.0, 123.5, 123.3, 123.1, 123.0, 116.0, 67.0, 53.2, 52.2, 21.4, 17.1. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{23}N_3O$ $[M+H]^+$ 322.1921, found 322.1911.

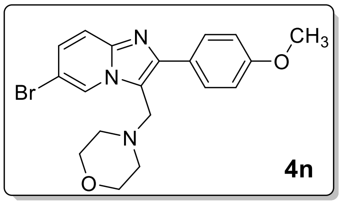


4m

4-((6-Bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)morpholine (4n)[32]

Yield: 89%, red colour solid, M.P. 138-140 °C.

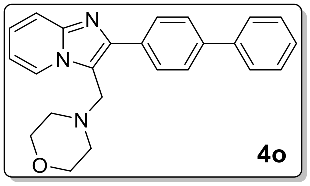
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 9.2 Hz, 1H), 7.23 (d, *J* = 11.2 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 2H), 3.79 (s, 3H), 3.62 (t, *J* = 4.6 Hz, 4H), 2.40 (t, *J* = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 145.6, 143.2, 130.1, 128.2, 128.1, 126.1, 125.5, 125.3, 117.6, 115.7, 114.2, 114.0, 106.6, 66.9, 53.2, 52.1. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{20}BrN_3O_2$ $[M+H]^+$ 402.0819, found 402.0819.



4n

4-((2-([1,1'-Biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (4o)

Yield: 90%, yellowish liquid.

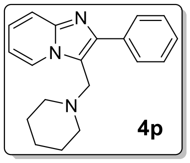


4o

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 6.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.81 (t, J = 6.8 Hz, 1H), 3.94 (s, 2H), 3.60 (t, J = 4.6 Hz, 4H), 2.44 (t, J = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 140.7, 140.6, 132.7, 129.3, 128.8, 127.5, 127.2, 127.1, 125.4, 125.3, 117.1, 116.1, 112.4, 67.0, 53.2, 52.1. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{23}N_3O$ $[M+H]^+$ 370.1921, found 370.1913.

2-Phenyl-3-(piperidin-1-ylmethl)imidazo[1,2-*a*]pyridine (4p)[43]

Yield: 82%, brown solid, M.P. 106-108 °C.

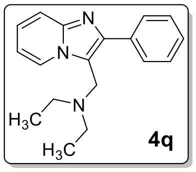


4p

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 6.8 Hz, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 9.2 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.82 (t, J = 6.8 Hz, 1H), 3.95 (s, 2H), 2.44 (t, J = 5.2 Hz, 4H), 1.56 (p, J = 5.5 Hz, 4H), 1.46 (q, J = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 144.8, 134.7, 128.9, 128.4, 127.6, 125.7, 124.4, 117.1, 116.9, 111.7, 54.2, 52.45, 26.0, 24.34. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}N_3$ $[M+H]^+$ 292.1815, found 292.1810.

***N*-Ethyl-*N*-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)ethanamine (4q)**[38]

Yield: 86%, yellowish liquid.

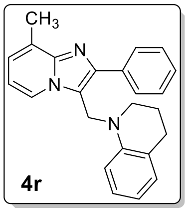


4q

^{1}H NMR (400 MHz,$CDCl_3$) δ 8.47 (d, J = 6.4 Hz, 1H), 7.70 (d, J = 7.2 Hz, 2H), 7.59 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.72 (t, J = 6.4 Hz, 1H), 3.99 (s, 2H), 2.44 (q, J = 6.8, 6.2 Hz, 4H), 0.90 (t, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 144.8, 134.6, 129.0, 128.4, 127.7, 127.6, 125.9, 125.7, 124.6, 124.5, 117.3, 117.1, 47.3, 46.4, 11.6, 11.5. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{21}N_3$ $[M+H]^+$ 280.1815, found 280.1808.

1-((8-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)-1,2,3,4-tetrahydroquinoline (4r)

Yield: 88%, brown solid, M.P. 177-179 °C.



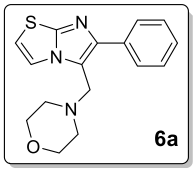
4r

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 6.8 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 7.18 (s, 1H), 6.90 (d, J = 6.8 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.55 (t, J = 6.8 Hz, 1H), 6.33 (d, J = 8.0 Hz, 1H), 4.24 (s, 2H), 3.20 (t, J = 5.4 Hz, 2H), 2.62 - 2.58 (m, 5H), 1.83 (q, J = 11.8, 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 128.7, 128.5, 128.4, 127.5, 127.3, 126.0, 122.1, 121.6, 118.9, 114.6, 112.1, 42.0, 29.2, 27.0, 22.1, 17.2. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{23}N_3$ [M+H]$^+$ 354.1972, found 354.1963.

4-((6-(*p*-Tolyl)imidazo[2,1-*b*]thiazol-5-yl)methyl)morpholine (6a)[36]

Yield: 90%, yellow colour solid, M.P. 135-137 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 9.4, 5.7 Hz, 3H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.25 (t, *J* = 7.0 Hz, 1H), 6.74 (d, *J* = 4.8 Hz, 1H), 3.81 (s, 2H), 3.62(t, *J* = 4.4 Hz, 4H), 2.42 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 146.0, 134.5, 128.5, 128.1, 127.4, 119.0, 118.1, 112.0, 66.9, 53.3, 52.9. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{17}N_3OS$ [M+H]$^+$ 300.1172, found 300.1159.

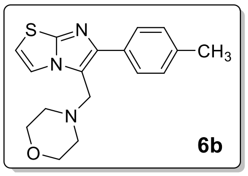


6a

4-((6-(*p*-Tolyl)imidazo[2,1-*b*]thiazol-5-yl)methyl)morpholine (6b)[36]

Yield: 89%, yellowish solid, M.P. 148-150 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 4.4 Hz, 1H), 3.92 (s, 2H), 3.72 (t, *J* = 4.6 Hz, 4H), 2.52 (t, *J* = 4.6 Hz, 4H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 144.5, 141.6, 132.5, 126.8, 124.5, 123.2, 114.3, 107.1, 61.9, 48.3, 47.9, 25.0. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{19}N_3OS$ [M+H]$^+$ 314.1329, found 314.1320.

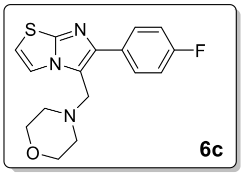


6b

6-(4-fluorophenyl)-5-(morpholinomethyl)imidazo[2,1-b]thiazole (6c)[44]

Yield: 85%, white solid, M.P. 197-198 °C.

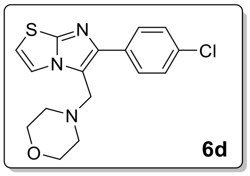
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 4.4 Hz, 1H), 7.70 (d, *J* = 3.36 Hz, 1H),7.12 (t, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 4.4 Hz, 1H), 3.84 (s, 2H), 3.70 (t, *J* = 4.6 Hz, 4H), 2.48 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 158.7, 156.3, 144.4, 140.4, 125.9, 125.0, 124.9, 114.1, 113.1, 110.8, 110.6, 107.4, 62.1, 48.4, 48.0.HRMS (ESI-TOF): m/z calcd for $C_{16}H_{16}FN_3OS$ [M+H]$^+$ 318.1078, found 318.1069.



6c

4-((6-(4-Chlorophenyl)imidazo[2,1-*b*]thizol-5-yl)methyl)morpholine (6d)

Yield: 82%, light pink solid, M.P. 191-192 °C.

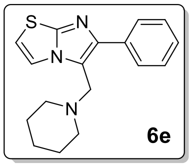


6d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 4.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 4.4 Hz, 1H), 3.8 (s, 2H), 3.70 (t, J = 4.4 Hz, 4H), 2.48 (t, J = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.6, 140.3, 128.5, 128.3, 124.5, 124.0, 114.1, 113.3, 107.5, 62.0, 48.4, 48.0. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{16}ClN_3OS$ $[M+H]^+$ 334.0783, found 334.0775.

6-Phenyl-5-(piperidin-1-ylmethyl)imidazo[2,1-*b*]thiazole (6e)

Yield: 80%, yellowish liquid.

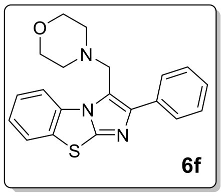


6e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 4.4 Hz, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 6.69 (d, J = 4.8 Hz, 1H), 3.7 (s, 2H), 2.34 (s, 4H), 1.48 (q, J = 5.5 Hz, 4H), 1.37 (q, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 145.4, 134.8, 128.4, 128.1, 127.1, 119.4, 119.3, 111.5, 54.3, 53.3, 26.0, 24.3. HRMS (ESI-TOF): m/z calcd for $C_{17}H_{19}N_3S$ $[M+H]^+$ 298.1380, found 298.1317.

4-((2-Phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)methyl)morpholine (6f)[36]

Yield: 89%, gummy material.

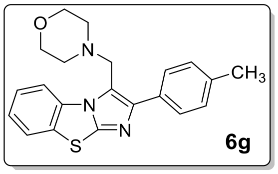


6f

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1H), 7.63 – 7.60 (m, 3H), 7.390 (m, 3H), 7.27 (t, J = 7.8 Hz, 2H), 3.95 (s, 2H), 3.59 (t, J = 4.6 Hz, 4H), 2.50 (t, J = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 146.9, 134.3, 133.6, 130.4, 128.6, 128.4, 127.6, 125.8, 124.5, 123.9, 115.5, 67.0, 53.0, 51.9. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{19}N_3OS$ $[M+H]^+$ 350.1329, found 350.1319.

4-((2-(*P*-Tolyl)benzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)methl)morpholine (6g)[36]

Yield: 90%, white solid, M.P. 169-171 °C.



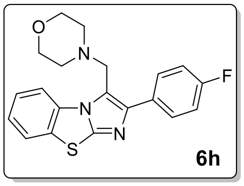
6g

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 6.8 Hz, 2H), 3.93 (s, 2H), 3.58 (t, J = 4.4 Hz, 4H), 2.48 (t, J = 4.4 Hz, 4H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 147.0, 137.3, 133.6, 131.4, 130.3, 129.2, 128.4, 125.8, 124.4, 123.9, 115.4, 67.0, 53.0, 51.95, 21.3. HRMS (ESI-TOF): m/z calcd for $C_{21}H_{21}N_3OS$ $[M+H]^+$ 364.1485, found 364.1475.

4-((2-(4-Fluorophenyl)benzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)methyl)morpholine (6h)[44]

Yield: 88%, white crystalline solid, M.P. 165-167 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.63 – 7.57 (m, 3H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 8.6 Hz, 2H), 3.93 (s, 2H), 3.60 (t, *J* = 4.6 Hz, 4H), 2.49 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 163.6, 161.2, 148.1, 146.1, 133.5, 130.3, 130.2, 125.9, 124.6, 124.0, 115.5, 115.4, 115.3, 66.9, 52.9, 51.9. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{18}FN_3OS$ [M+H]$^+$ 368.1235, found 368.1224.

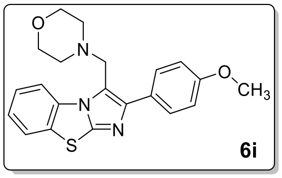


6h

4-((2-(4-Methoxyphenyl)benzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)methyl)morpholine (6i)

Yield: 85%, brown solid, M.P. 131-132 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 3.93 (s, 2H), 3.78 (s, 3H), 3.59 (t, *J* = 4.4 Hz, 4H), 2.46 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.2, 147.8, 146.8, 133.6, 130.3, 129.8, 126.8, 125.8, 124.4, 124.3, 123.9, 114.0, 113.8, 67.0, 55.4, 55.2, 53.0, 51.9. HRMS (ESI-TOF): m/z calcd for $C_{21}H_{21}N_3O_2S$ [M+H]$^+$ 380.1434, found 380.1427.

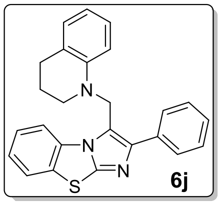


6i

3-((3, 4-Dihydroquinolin-1(2*H*)-yl) methyl)-2-phenylbenzo[*d*]imidazo [2, 1-*b*] thiazole (6j)

Yield: 70%, orange solid, M.P. 154-156 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74 – 7.66 (m, 3H), 7.50 – 7.48 (m, 1H), 7.41 (t, *J* = 6.6 Hz, 2H), 7.33 (d, *J* = 6.8 Hz, 1H), 7.28 – 7.24 (m, 3H), 6.91 – 6.81 (m, 2H), 6.51 (d, *J* = 8.2 Hz, 1H), 4.50 (s, 2H), 3.31 (t, *J* = 6.6 Hz, 2H), 2.72 (t, *J* = 7.0 Hz, 2H), 1.95 (q, *J* = 7.0, 6.4 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.0, 145.1, 142.9, 134.4, 133.1, 130.4, 128.7, 128.6, 127.4, 126.2, 126.2, 126.0, 124.1, 122.8, 122.5, 115.4, 115.3, 113.6, 42.0, 30.1, 26.90, 21.97. HRMS (ESI-TOF): m/z calcd for $C_{25}H_{21}N_3S$ [M+H]$^+$ 396.1536, found 396.1537.



6j

3A.6. References

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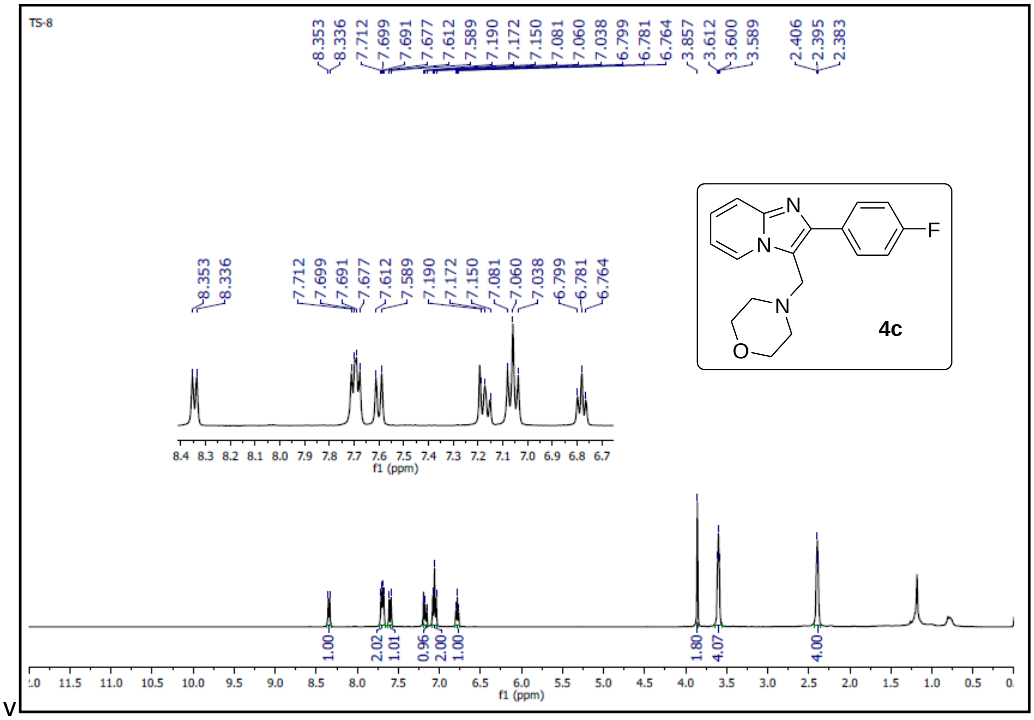
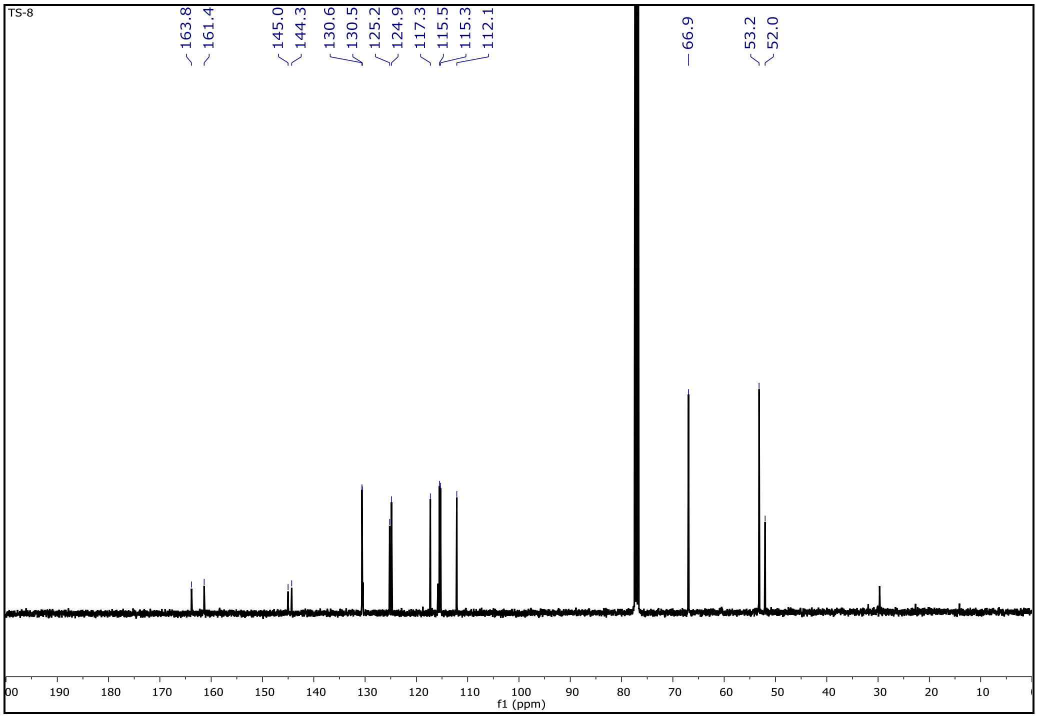
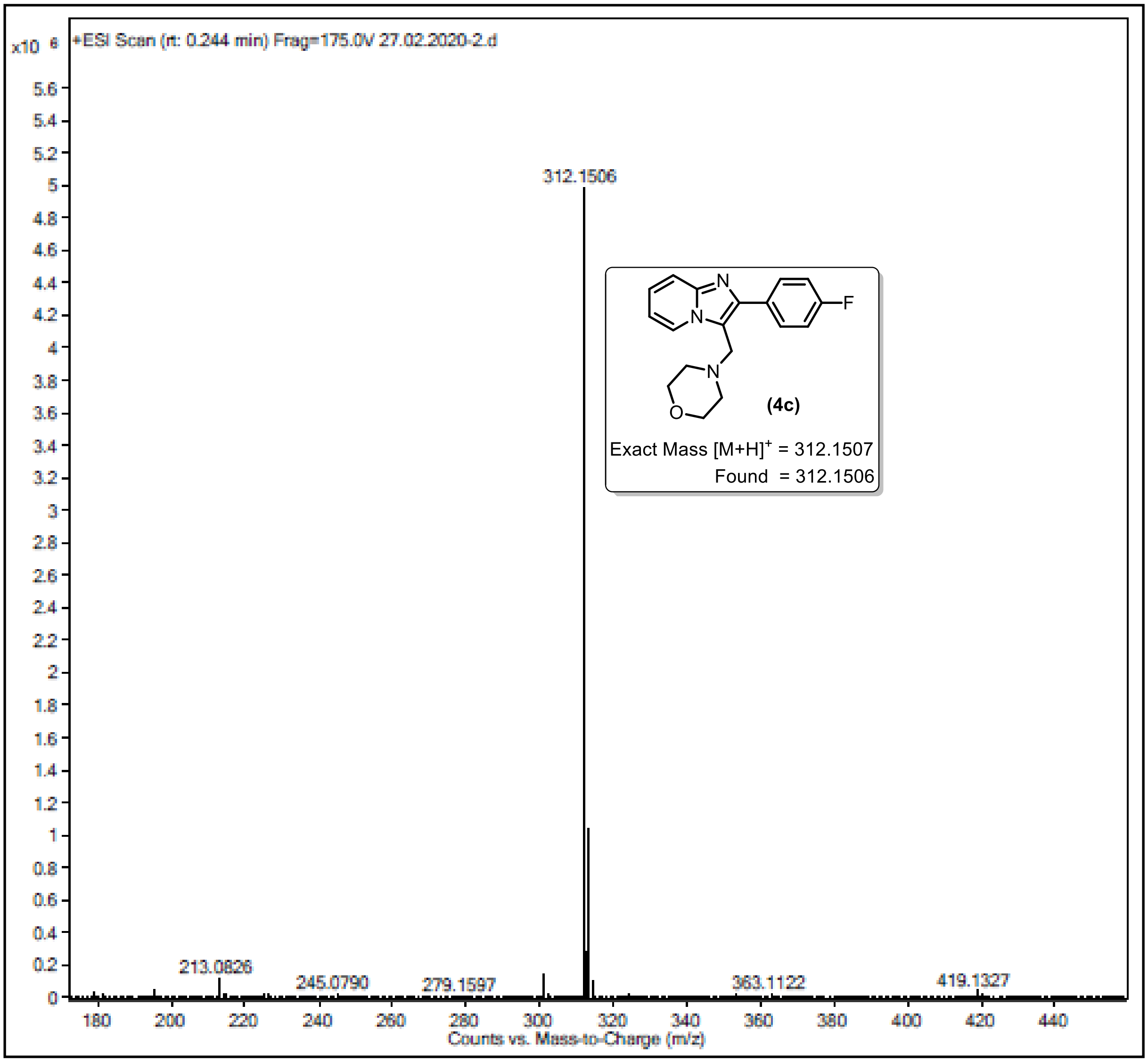
3A.7. Selected NMR (^{1}H and ^{13}C) and Mass Spectra



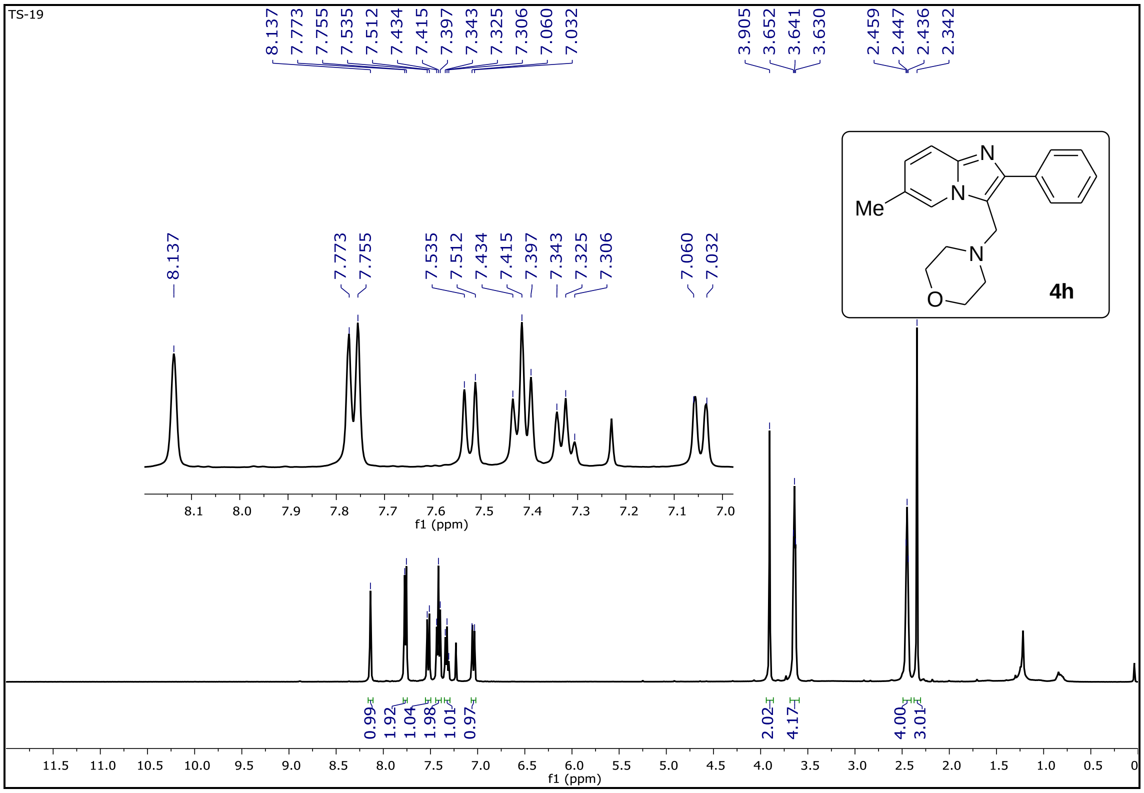
^{1}H NMR spectrum of compound **4c**



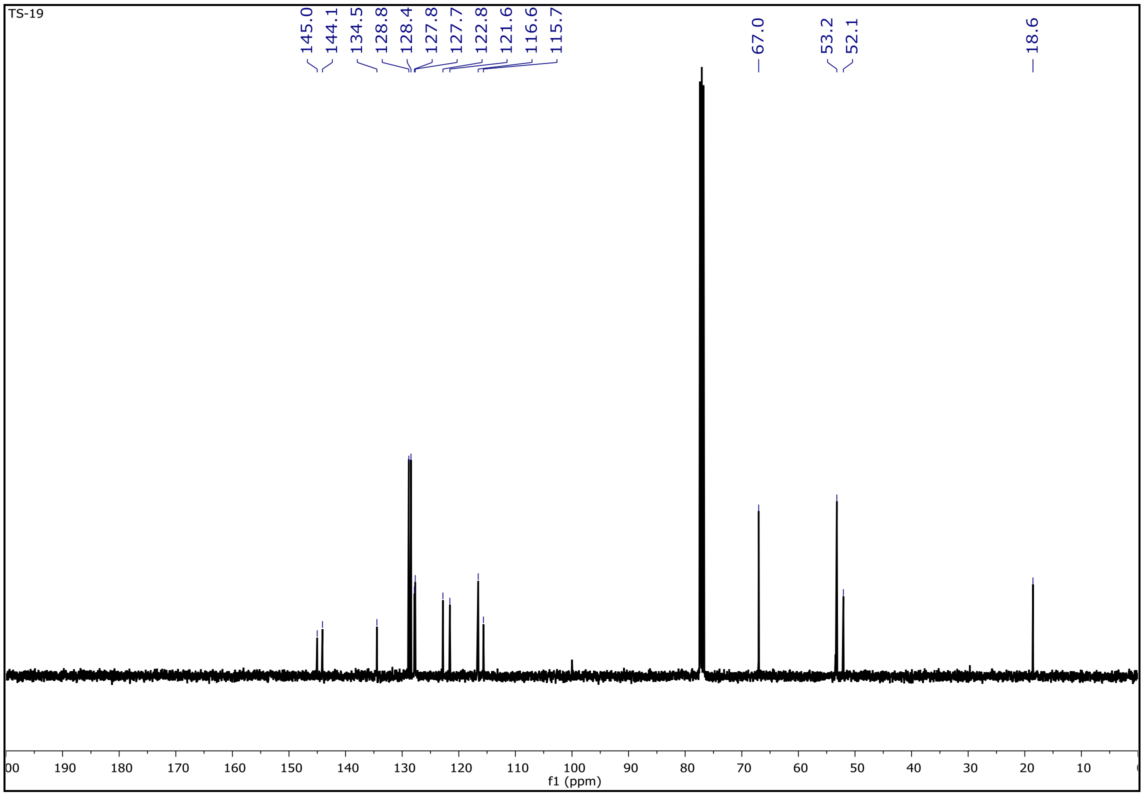
^{13}C NMR spectrum of compound **4c**



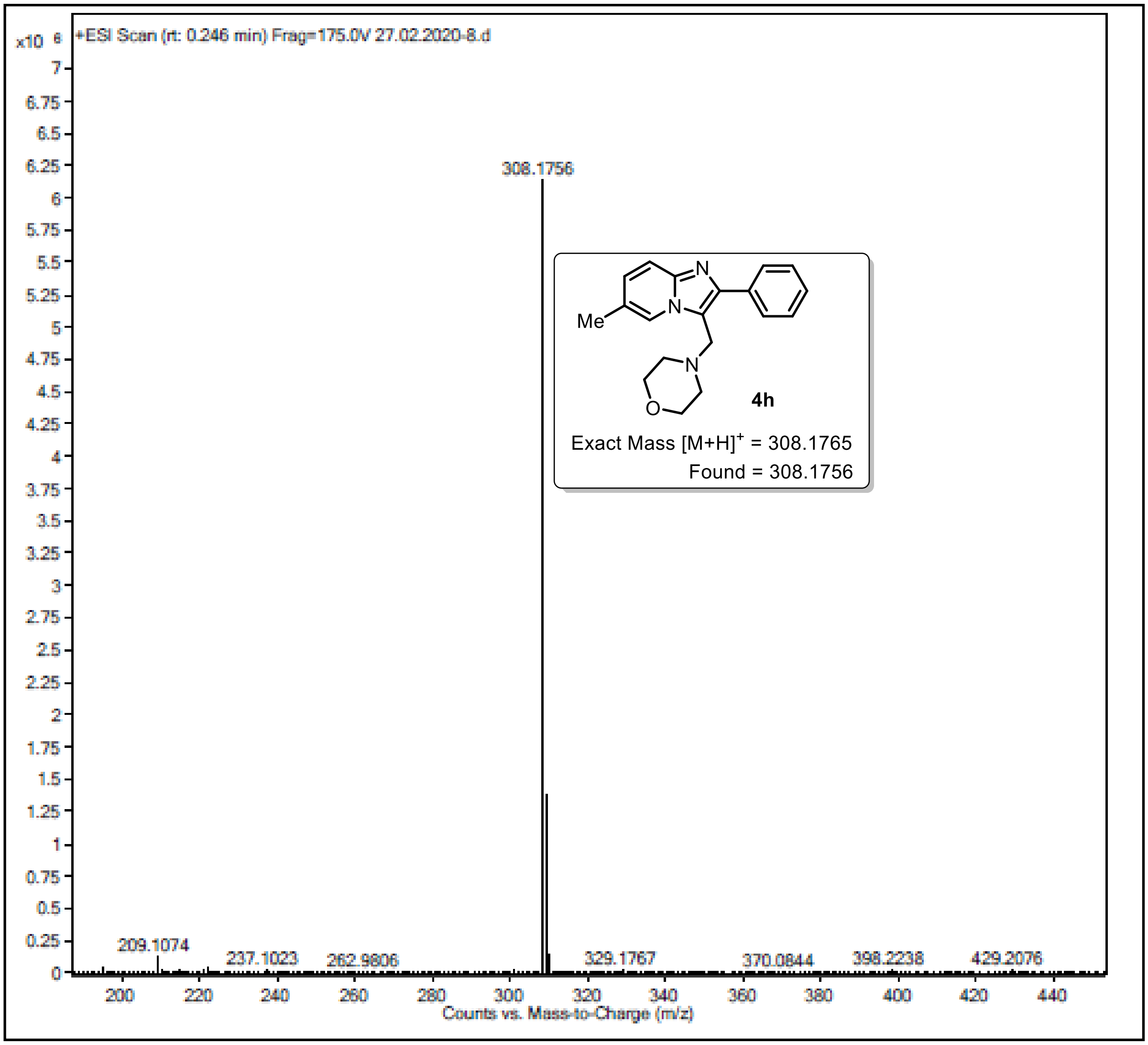
Mass spectrum of compound **4c**



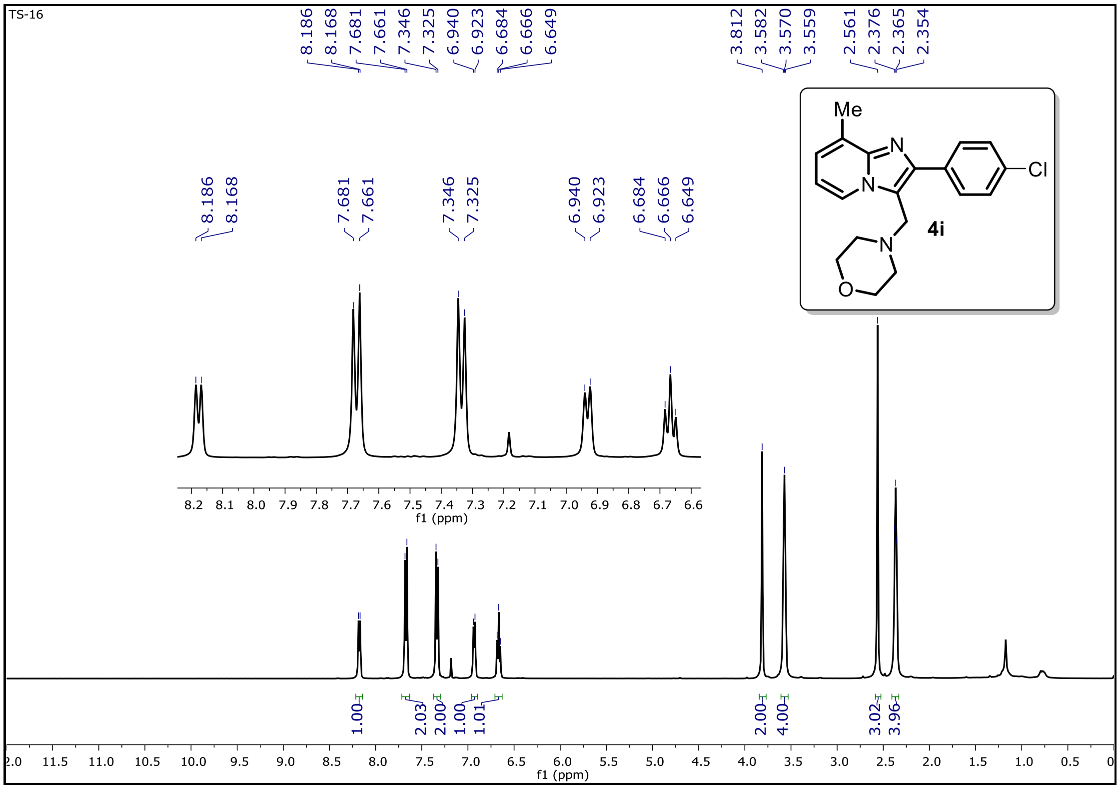
^{1}H NMR spectrum of compound **4h**



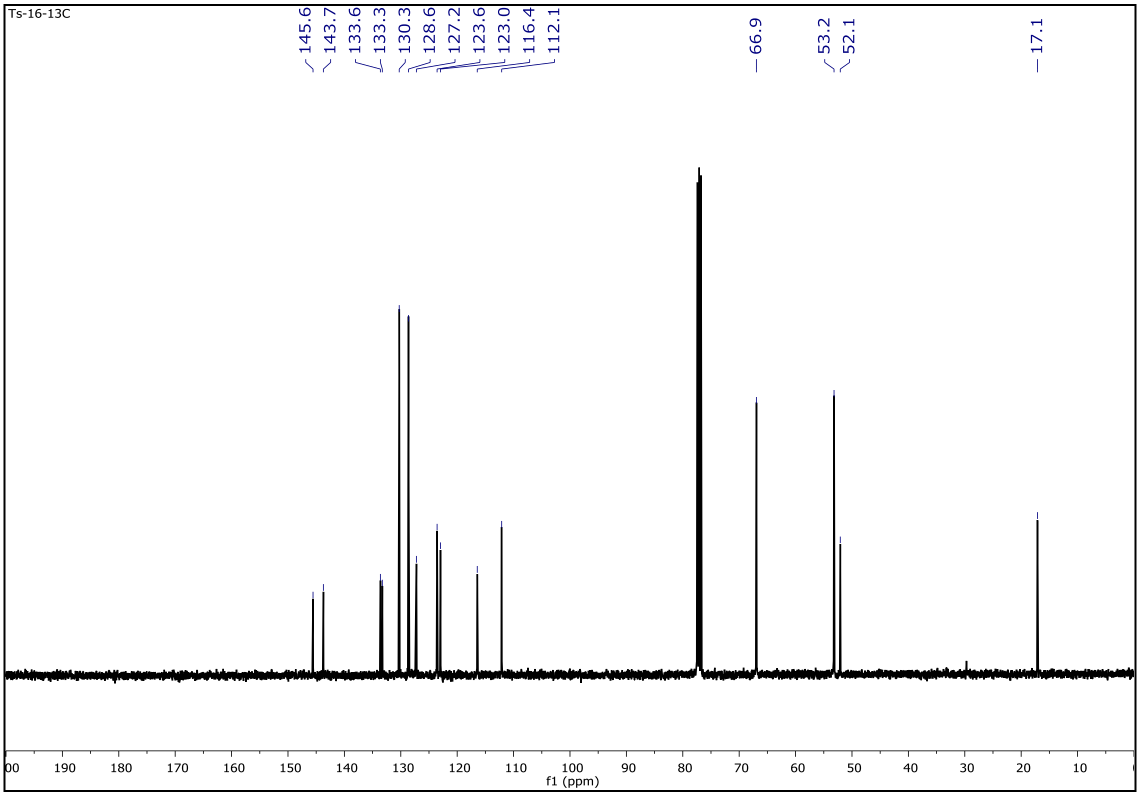
^{13}C NMR spectrum of compound **4h**



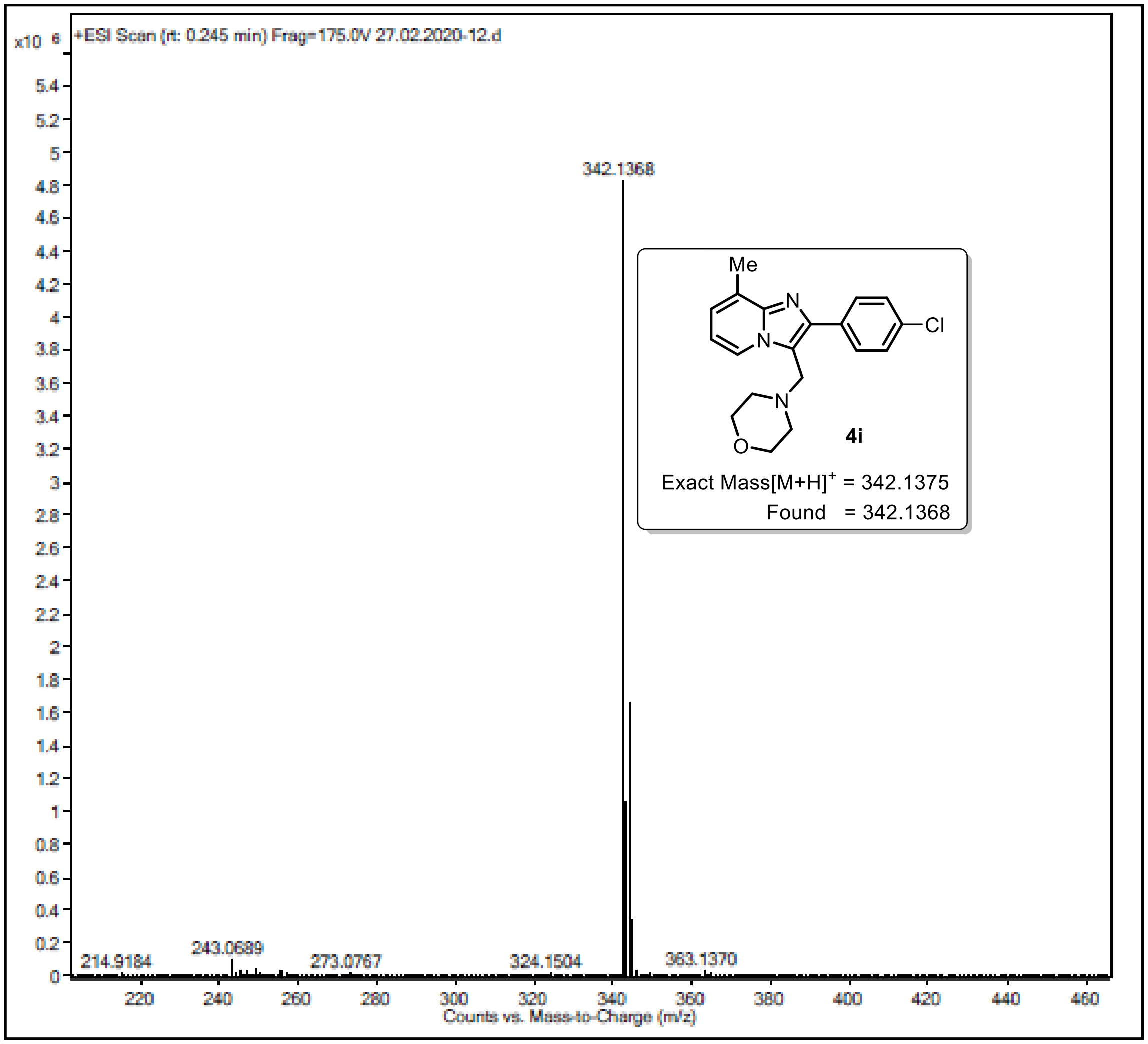
Mass spectrum of compound **4h**



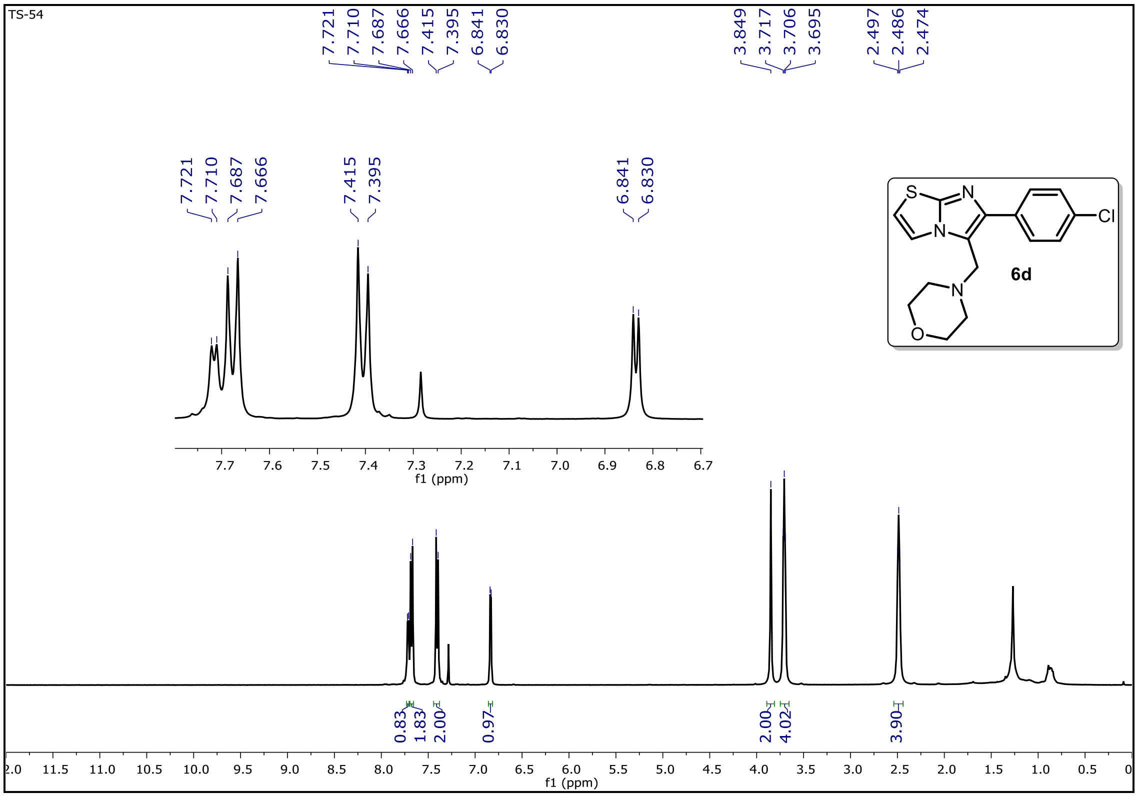
^{1}H NMR spectrum of compound **4i**



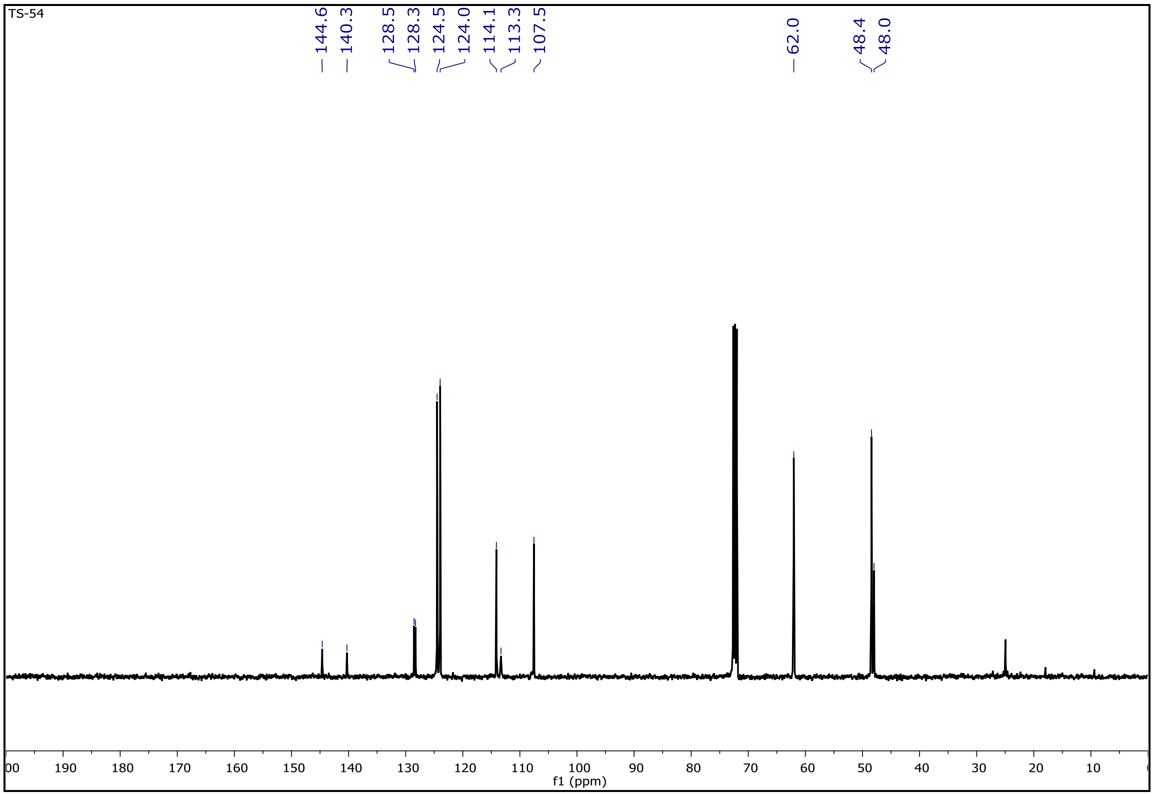
^{13}C NMR spectrum of compound **4i**



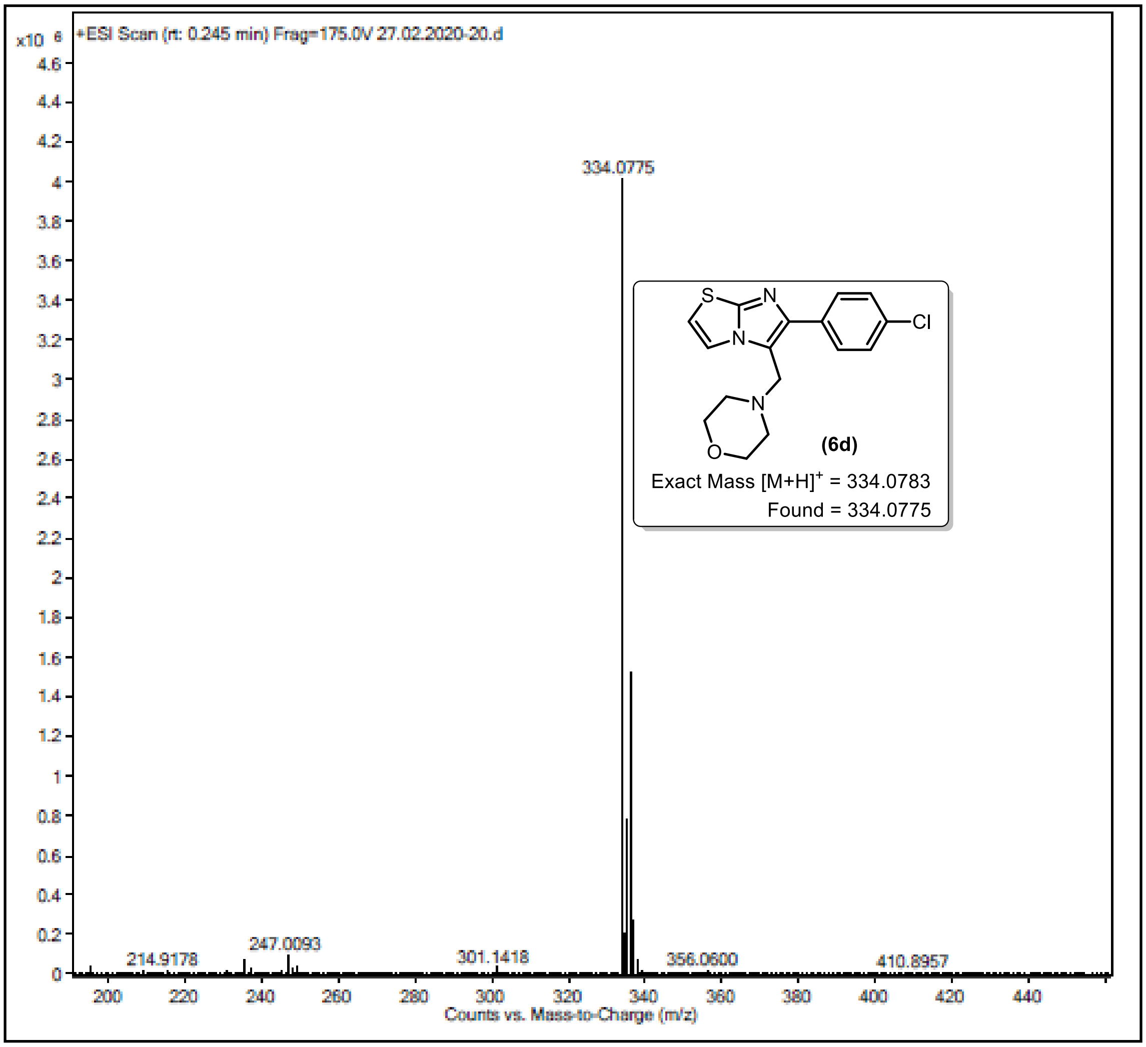
Mass spectrum of compound **4i**



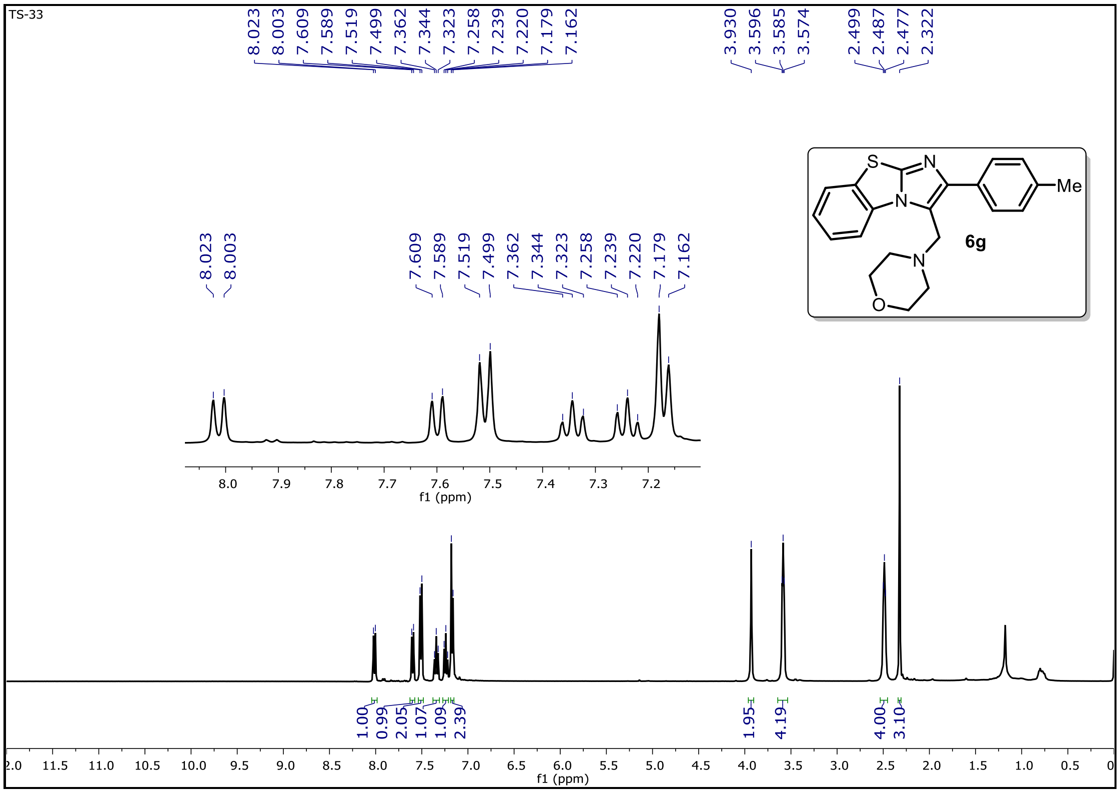
^{1}H NMR spectrum of compound **6d**



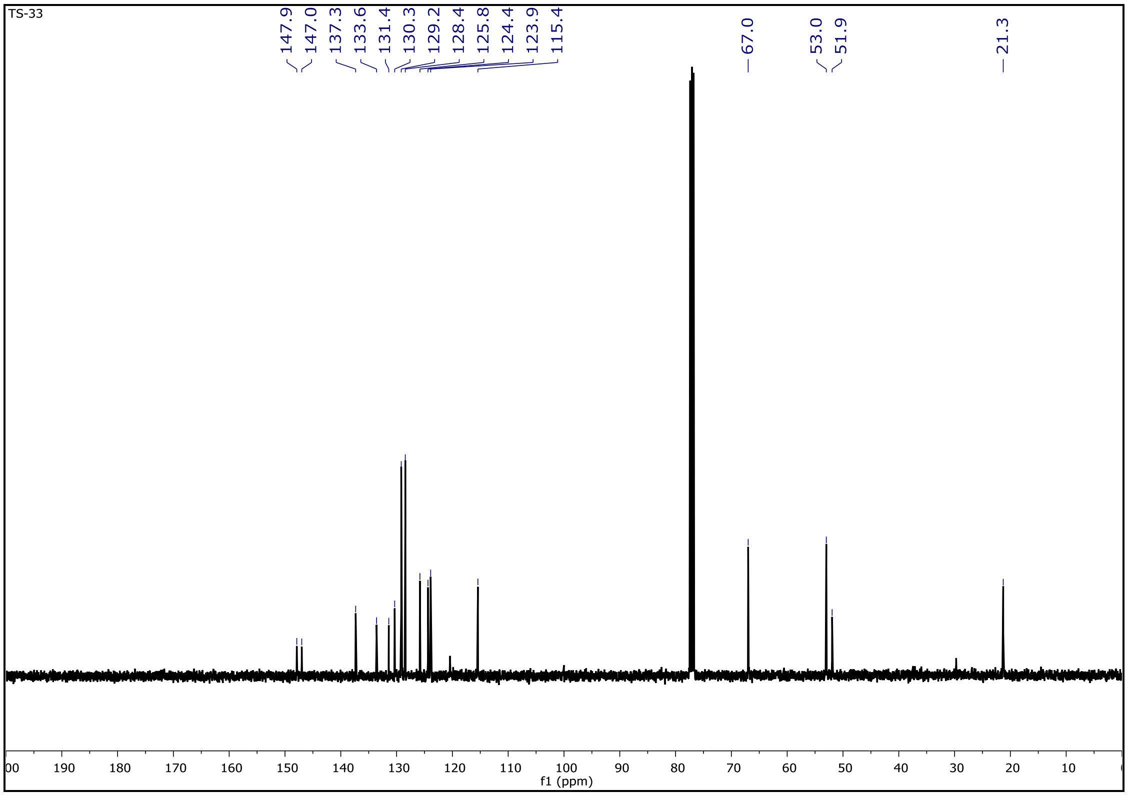
^{13}C NMR spectrum of compound **6d**



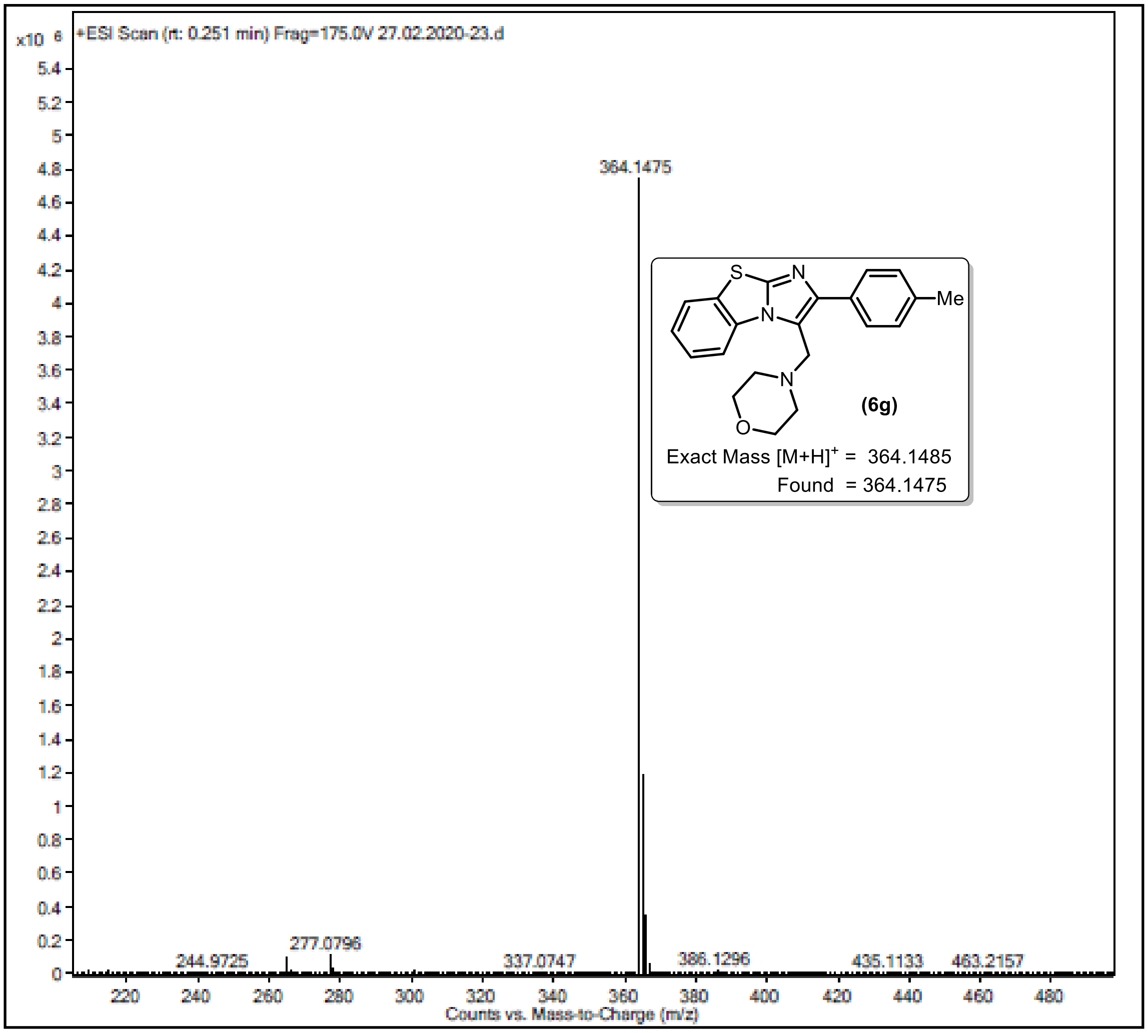
Mass spectrum of compound **6d**



^{1}H NMR spectrum of compound **6g**



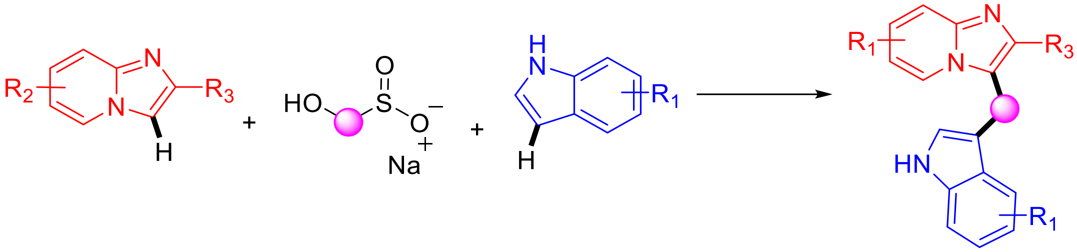
^{13}C NMR spectrum of compound **6g**



Mass spectrum of compound **6g**

CHAPTER-III
Section-B

Rongalite as a Methylenating Agent: Synthesis of Heterodiarylmethanes via Metal-Free Coupling between Imidazo[1,2-*a*]pyridines or Imidazo[2,1-*b*]thiazole and Indoles



3B.1. Introduction

Alkylated indoles are omnipresent in nature and are widely present in bioactive natural products and therapeutic drug molecules. Particularly, diarylmethane and its structural motifs are found in a wide variety of biologically active compounds and thus became an integral part of many promising pharmaceutical drugs.[1] Natural auxins are indole constituted phytohormones which regulate plant growth activity, cell division and root formation.[2-5] Indole-3-acetic acid (IAA) is a naturally occurring auxin can be found both in free and conjugated states among different plants and seeds. The fluctuating property of auxin in aqueous solution restricts its wide spread use. This prompted chemists to search for alternative auxin analogues.[6,7]

Bisindolylmethanes (BIMs) and their analogues are worth mentioning for their ability to exhibit wide range of biological activities,[8] diindolylmethane (DIM, **I**) which is a major metabolite of indole-3-carbinol and is produced from the glycoside glucobrassicin, which itself can be found in vegetables belonging to the family of brassicaceae like broccoli, cauliflower among others.[9] It has also been reported that this compound exhibits anti-oxidant,[10] anti-inflammatory,[11] anti-angiogenic,[12] anticancer properties.[13-15] Not only this but the compound is also used in the treatment of rare recurring respiratory disease - papillomatosis.[16] Other interesting fact about DIM is that it is used in stage I/II prostate cancer clinical trails[17] and is now up for phase III clinical study in the treatment of cervical dysplasia.[18]

Vibrindole (**II**) a metabolite of the marine *Vibrioparahaemolyticus*, shows potent antibacterial activity,[19] whereas, Sterptindole (**III**) is a metabolite of the common human intestinal bacterium *Streptococcus faecium* IB-37, and have DNA damaging and genotoxic properties.[20] Arsindoline B (**IV**) is isolated from Xiamen sea bacterium strain CB101 exhibited potent activity against the A-549 cancer cell lines.[21] Synthetic BIM analogs, such as bis(5-methylindol-3-yl)methane; (**VI**) and bis(5-bromoindol-3-yl) methane (**VII**) are reported to be inhibitors of the estrogeninduced growth of mammary tumors,[22-23] whereas, bis(indol-3-yl)- 4-methoxyphenylmethane (**V**) is an orphan nuclear receptor (Figure 3B.1).[24]

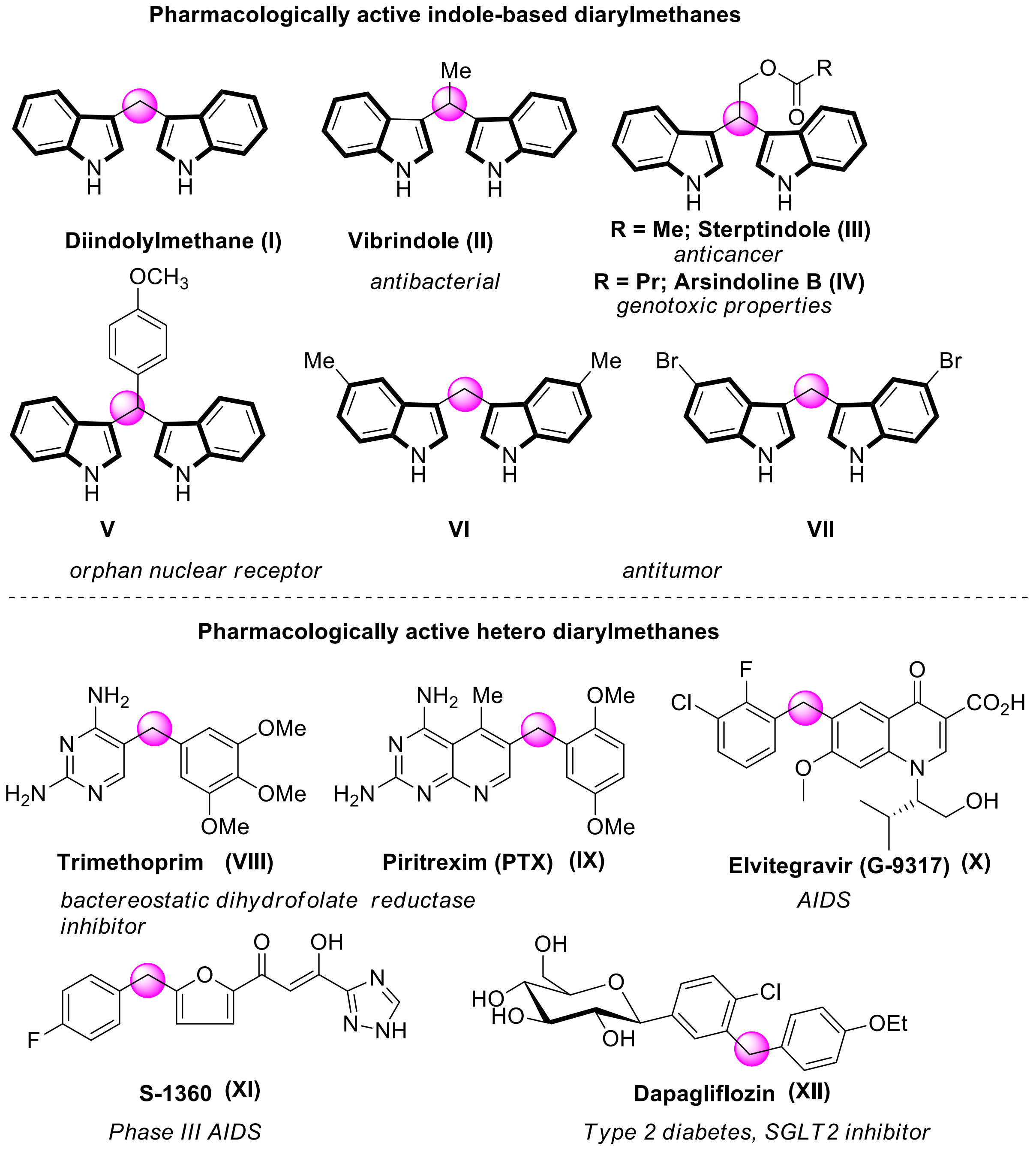


Figure 3B.1. Some of the Pharmaceutically-active Diarylmethane Compounds.

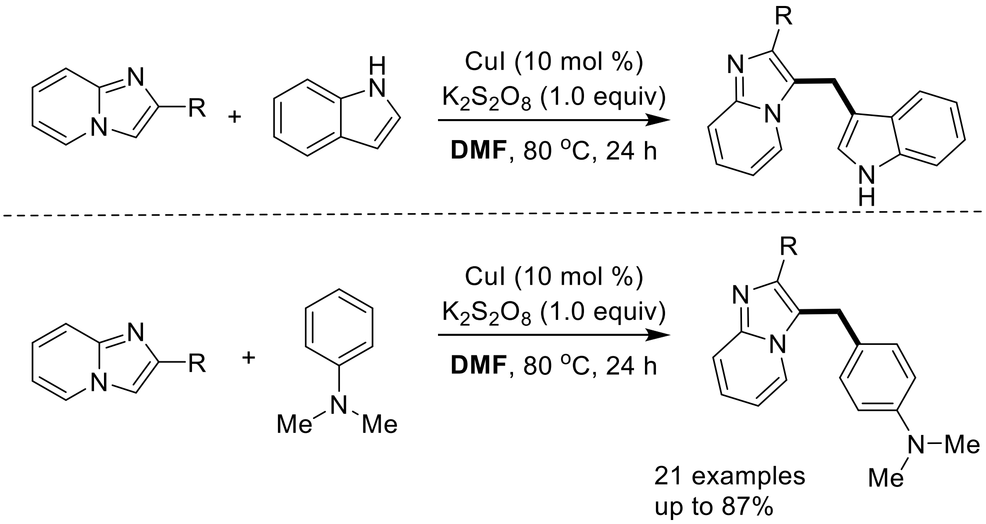
Recent studies also point to the ability of both DIM and 5-methoxy-diindolylmethane to be used as a potential radical scavenger against cancerous cells.[25] The diarylmethane substructure is present in Trimethoprim (TMP) **VIII** and piritrexim (PTX) **IX** which are used to treat a wide range of bacterial infections including treatment against opportunistic infections caused by pneumocystis carinii and toxoplasma gondii in patients with AIDS (Figure 3B.1).[26-27] Apart from the above mentioned properties, diarylmethane moiety plays a key role in a number of antiretroviral therapies targeting HIV1-integrase, which is the enzyme responsible for replication of HIV.[28] A few examples of these molecules that made their way to clinical development include Shionogi/GSK's S-1360 and Gilead Science's GS-9137 (Elviltegravir) which are currently in phase III clinical trials for the treatment of HIV.[29] The peculiar property of heterocyclic compounds to interact with biological systems through polar interactions that made them a topic of interest for the pharmaceutical industry.

Indoles and Imidazo[1,2-*a*]pyridines are nitrogen containing heterocyclic derivatives which have gained considerable attention from the synthetic chemists in the recent decades owing to their broad range of applications in the fields of pharmaceuticals, agrochemicals, natural products and material sciences.[30] These Indoles and imidazo[1,2-*a*]pyridine derivatives were studied for their different therapeutic activities like antibacterial,[31] anti-rhinoviral,[32] antifungal,[33] antiviral,[34] aromatise inhibition,[35] ligand peripheral benzodiazepine (PBD) receptors,[36] K^+ stimulated ATPase inhibition,[37] CDK inhibition,[38] bradykinin B2 receptor,[39] and b-amyloid (Ab) aggregate.[40]among others.

This nucleus is also a core structure for different drug formulations such as Zolpidem, olprinone, zolimidine, nicopidem, alpidem, and saripidem are regularly available in the drug market.[41] also some additional *N*-heterocyclic carbenes were synthesized on the basis of imidazo[1,2-*a*]pyridines.[42] Its reactivity pattern and synthetic applications are already covered in chapter-2 and chapter-3A.

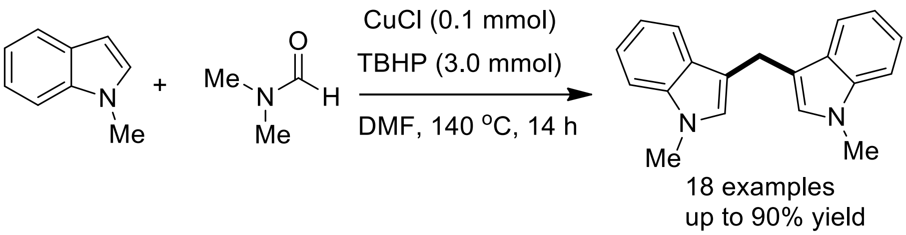
3B.2. Reported Methods for the Synthesis of Diarylmethane Derivatives

Hajra and research group developed a method for the synthesis of heterodiarylmethanes using imidazo[1,2-*a*]pyridine and indole in the presence of CuI as catalyst and DMF as methylenating agent. In this process he has exploited the DMF as reagent and as well as solvent (Scheme 3B.1).[43-44]



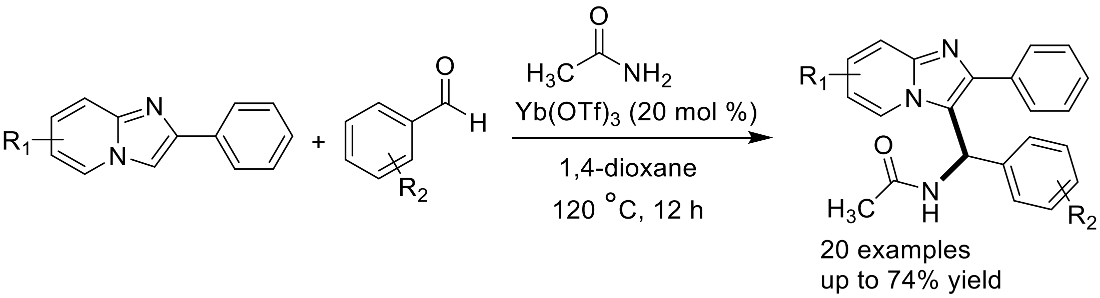
Scheme 3B.1

Fanet al. developed a method for the formation of diindolylmethane extensively from indoles and DMF in the presence of Cu(I) salt and *tert*-butyl hydrogen peroxide as an oxidant (Scheme 3B.2).[45]



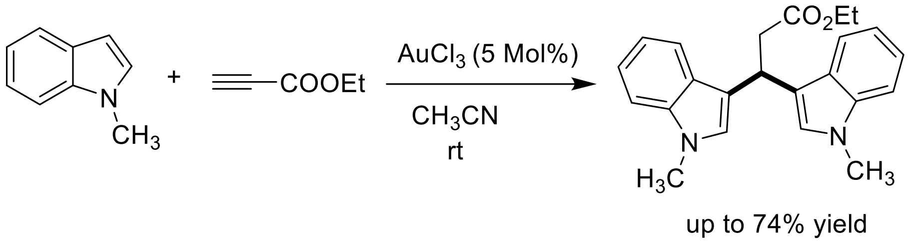
Scheme 3B.2

Anil Kumar and his research group developed $Yb(OTf)_3$ Promoted one-pot three component synthesis of diarylmethyl bis(imidazo[1,2-*a*]pyridine from imidazo[1,2-*a*]pyridines, acetamide and aldehyde. This method gave title products in good to excellent yields in 1,4-dioxane (Scheme 3B.3).[46]



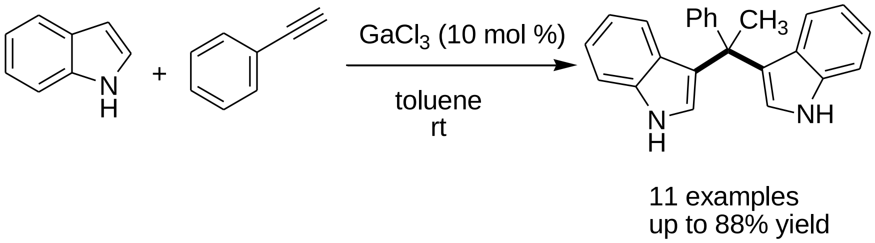
Scheme 3B.3

Chuan and co-workers studied the formation of ethyl 3, 3-di (1*H*-indol-3-yl)propanoate using indole and ethyl propionate in acetonitrile solvent. This reaction was catalyzed by $AuCl_3$ via double addition of indole with ethyl propiolate to furnish in good yields (Scheme 3B.4).[47]



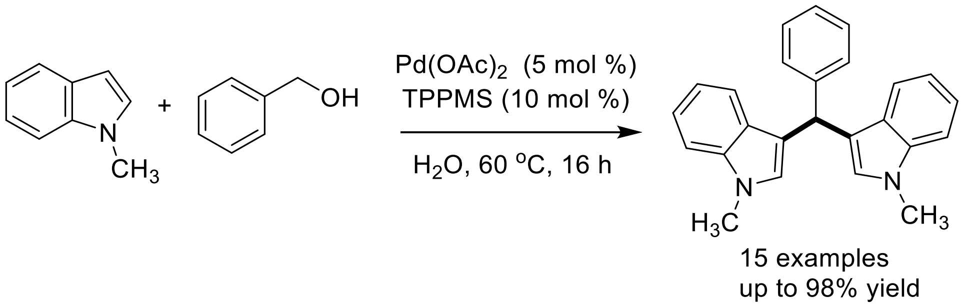
Scheme 3B.4

Yadav et al. introduced simple synthesis of bis(indolyl)phenylethanes in excellent yields usingphenyl acetylene and indoles catalyzed by 10 mol % of Gallium (III) halide in toluene as solvent (Scheme 3B.5).[48]



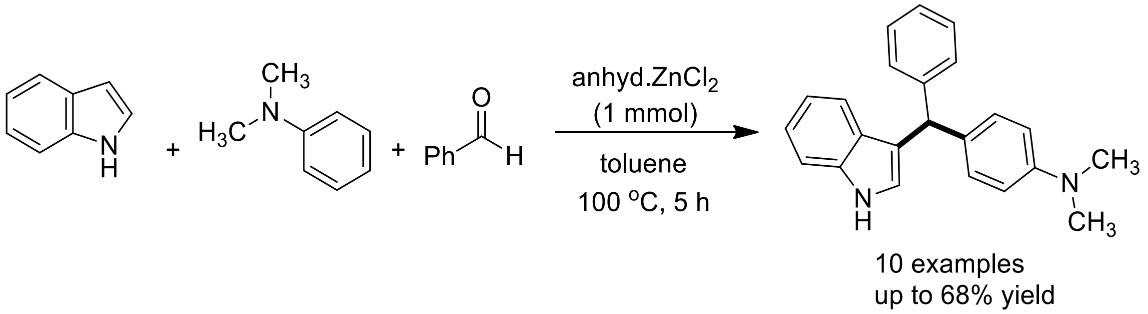
Scheme 3B.5

Hikawaet al. synthesized the selective bis(indolyl)methane by Pd(OAc)2 catalyzed C-H activation from indoles and benzyl alcohols in presence of water and 10 mol % of sodium diphenylphosphinobenzene-3-sulfonate (TPPMS) ligand obtained good yields (Scheme 3B.6).[49]



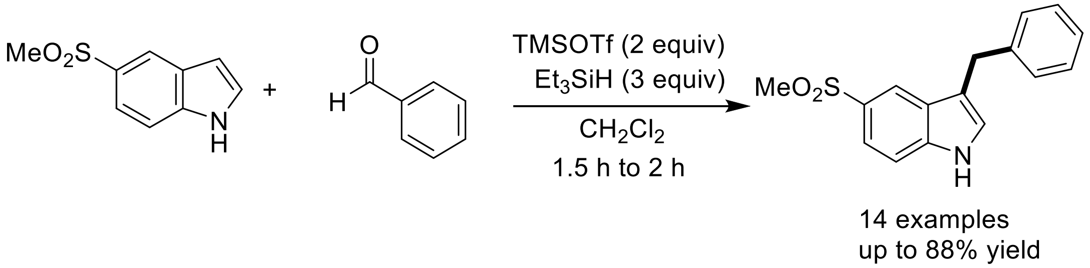
Scheme 3B.6

Ganesan et al. developed a novel protocol for the preparation of 4-((1*H*-indol-3-yl)methyl)-*N*,*N*-dimethylaniline by mixing of Indole with *N*,*N*- dimethylaniline and aldehyde or formaldehyde in the presence of anhydrous $ZnCl_2$ (Scheme 3B.7).[50]



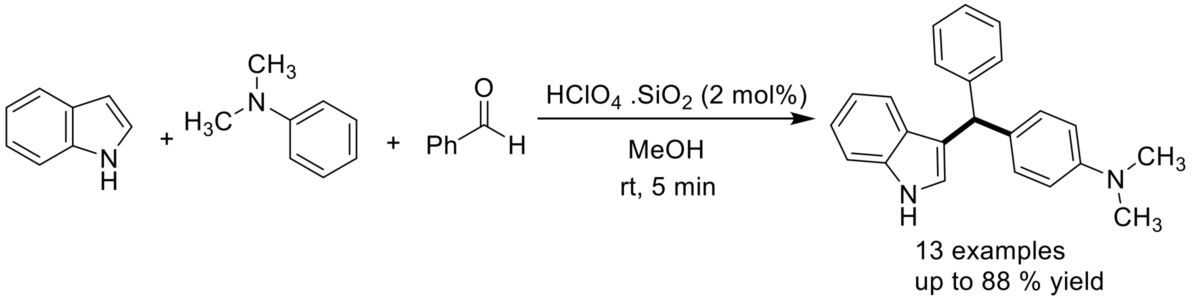
Scheme 3B.7

Campbell et al. introduced a protocol for the synthesis of 3-benzyl-1*H*-indoles using Trimethylsilyl trifluoromethanesulfonate and triethyl silane and DCM solvent produce in good yields (Scheme 3B.8**)**.[51]



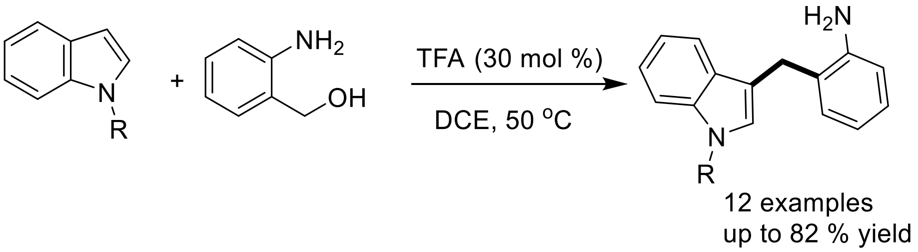
Scheme 3B.8

Atul Kumar et al. demonstrated operationally simple, silica supported perchloric acid ($HClO_4$-SiO_2) catalyzed reaction for the formation of 4-((1*H*-indol-3-yl)methyl)-*N*,*N*-dimethylaniline by the mixing of Indole, *N*,*N*-dimehyl amine, and aldehyde in methanol (Scheme 3B.9).[52]



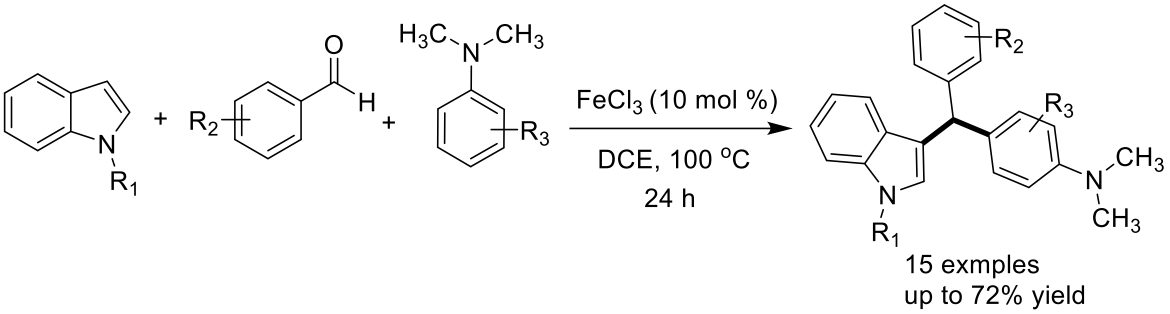
Scheme 3B.9

Jimmy Wu and his research group promoted a reaction for the formation of 2-((1*H*-indol-3-yl) methyl) aniline with mixing of indole and 2-amino benzyl alcohol catalyzed by 30 mol % of tri fluoroacetic acid in DCE solvent (Scheme 3B.10).[53]



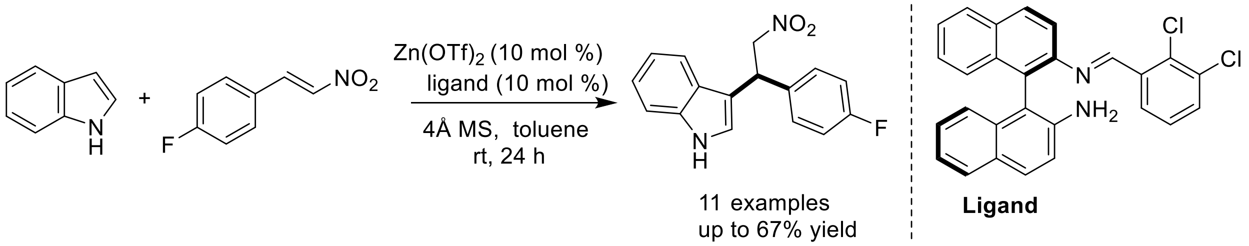
Scheme 3B.10

Wang and his research group developed the synthesis of 4-((1*H*-indol-3-yl)(phenyl)methyl)-*N*,*N*-dimethylaniline by mixing aniline, aldehyde, and indole catalyzed by 10 mol % $FeCl_3$ in DCM solvent (Scheme 3B.11).[54]



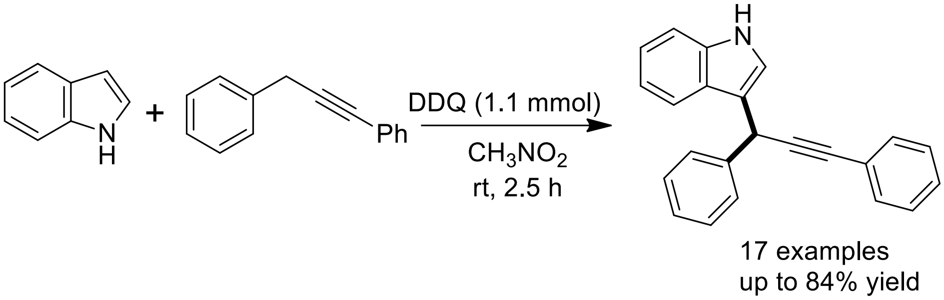
Scheme 3B.11

Yuan et al. effectively synthesised 3-(1-(4-fluorophenyl)-2-nitroethyl)-1*H*-indole from indole and nitro styrene in the presence of Zn $(OTf)_2$ catalyst and toluene as solvent (Scheme 3B.12).[55]



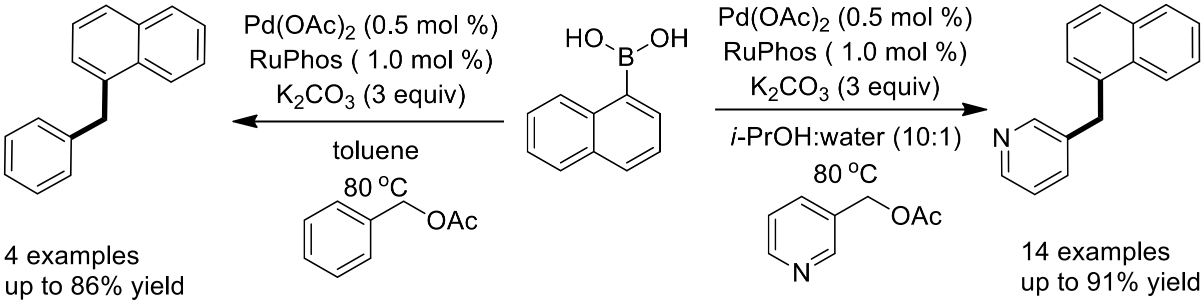
Scheme 3B.12

Venkateswarlu and his research group explained the formation of 3-(1,3-diphenylprop-2-yn-1-yl)-1*H*-indole from Indole and prop-1-yne-1,3-diyldibenzene. This reaction was catalyzed by DDQ in nitromethane solvent (Scheme 3B.13).[56]



Scheme 3B.13

Stewart et al. demonstrated the formation products 3-(naphthalen-1-ylmethyl) pyridine and 1-benzylnaphthalene from naphthalene-1-boronic acid reacts with pyridin-3-ylmethyl acetate or benzyl acetate, catalyzed by Pd $(OAc)_2$ and ligand obtained good yields (Scheme 3B.14).[57]



Scheme 3B.14

Literature survey reveals that most of the reported methods for the diarylmethanes involved use toxic metals which are environmentally hazardous and DMF as a methylating agent. Keeping in the view of green chemistry principles, we have developed a novel method to produce heterodiarylmethanes via metal-free coupling between imidazo[1,2-*a*]pyridines or imidazo[2,1-*b*]thiazole and indoles.

3B.3. Present Study

Considering the importance of these two classes of heterocyclic compounds and their hybrid molecules, we have developed a novel method of rongalite promoted metal-free one-pot synthesis of heterodiarylmethanes from imidazo[1,2-*a*]pyridines and indoles.

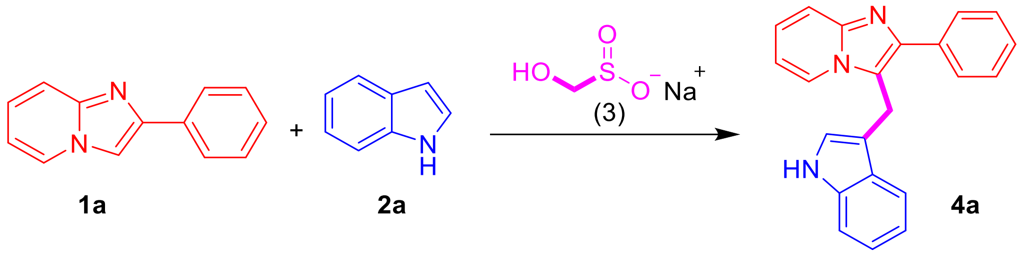
This chapter deals with the synthesis of the 3-((1*H*-indol-3-yl)methyl)-2-phenylimidazo[1,2-*a*]pyridine and 1-((1*H*-indol-3-yl)methyl)-2-phenylbenzo[*d*]pyrrolo[2,1-*b*]thiazole from their respective starting materials. Formaldehyde which is the source for methylene bridge was *in situ* generated by commercially inexpensive rongalite.[58]

3B.3.1. Results and Discussion

To test proposed hypothesis for the synthesis of the 3-((1*H*-indol-3-yl)methyl)-2-phenylimidazo[1,2-*a*]pyridine, we have started reaction by mixig imidazo[1,2-*a*]pyridine **1a**, indole **2a** and rongalite in CH_3CN and stirred at room temperature for 12 h. But there is no change was observed in the reaction progress (monitored by TLC), starting material was consumed when the reaction mixture was heated to 80 °C and gave desired compounds **4a** in less yield (Table 3B.1, entry 1-2). This fruitful result motivated us to go with further optimization to increase the yield of the products by changing the reaction conditions.

Then we have focused on screening of solvents. Initially, we have conducted the reaction in acetonitrile but due to unsatisfactory yields we moved to chlorinated solvents such as dichloromethane, chloroform and dichloroethane, but even these solvents gave poor yields (Table 3B.1 entres 3-5). We have further screened toluene, THF, methanol and ethanol which gave moderate yields (Table 3B.1 entries 6-10). Surprisingly, DMF gave 65% yield in 5 h (Table 3B.1 entry 11). This led us to check the stoichiometry of rongalite and tried reaction with 1.5 and 2 equivalents and latter one furnished product in 90% yield (Table 3B.1 entrie 12-13).

Table 3B.1. Optimization of Reaction Condition.[a]

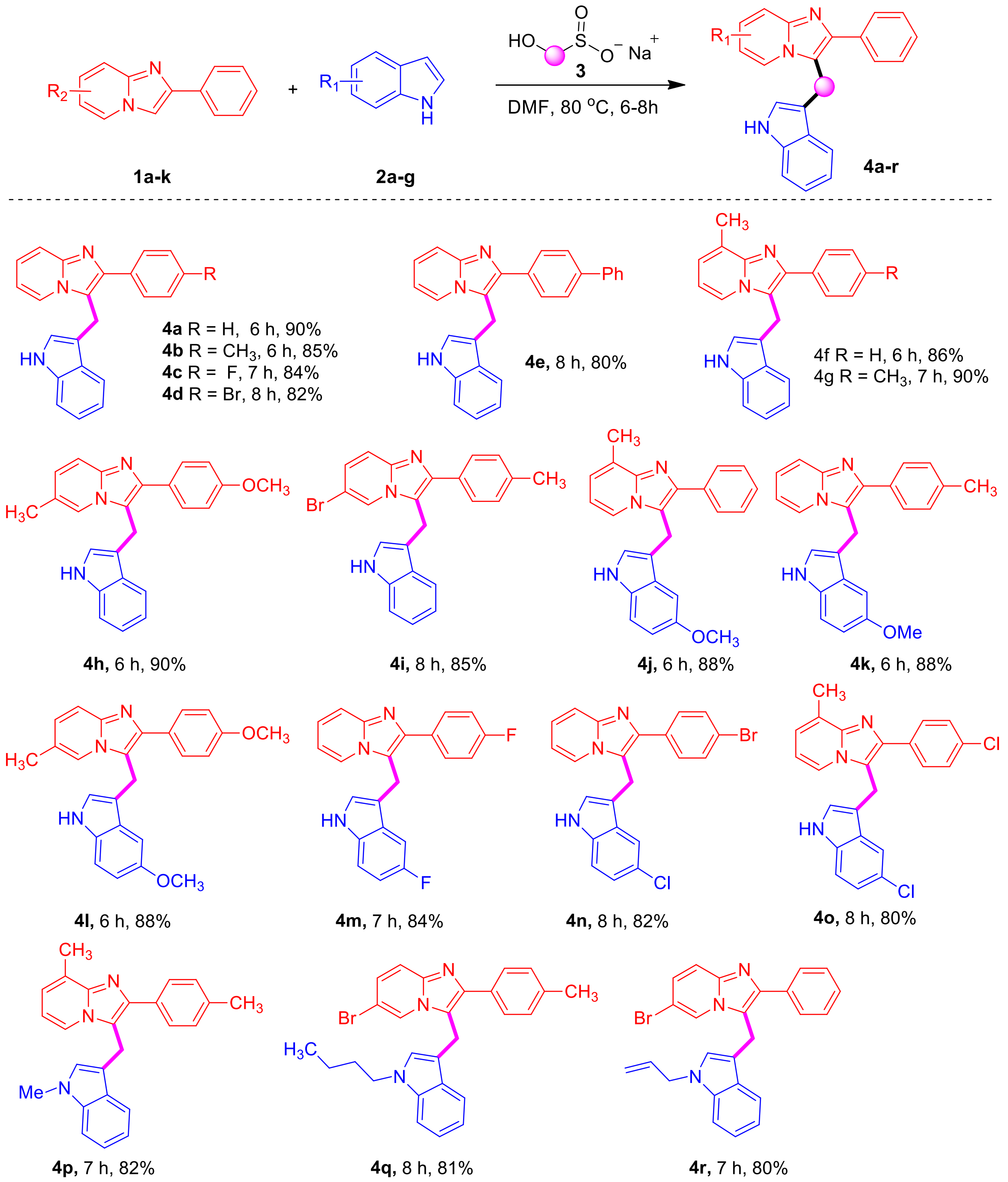


Entry	Solvent	Rongalite (equiv)	Temperature (°C)	Time (h)	Yield (%)[b]
1.	CH_3CN	1.0	rt	12	n.d
2.	CH_3CN	1.0	70	6	40
3.	CH_2Cl_2	1.0	45	12	10
4.	$CHCl_3$	1.0	65	12	10
5.	DCE	1.0	70	12	10
6.	Toluene	1.0	80	10	45
7.	THF	1.0	70	12	20
8.	1,4-Dioxane	1.0	70	12	20
9.	MeOH	1.0	70	6	50
10.	EtOH	1.0	70	6	55
11.	DMF	1.0	70	5	65
12.	DMF	1.5	70	5	75
13.	**DMF**	**2.0**	**80**	**5**	**90**
14.	DMSO	2.0	80	10	40
15.	H_2O	2.0	80	24	n.d

[a] All the reactions were conducted on a 1 mmol scale of **1a** (1 mmol), **2a** (1 mmol) and **3** (2 mmol) in solvent (3 mL), otherwise mentioned. [b] Yields where reported is of isolated and purified product. [c] Not Detected.

Unfortunately, DMSO, a polar and high boiling solvent gave less yield (Table 3B.1 entry 14). Green solvent H_2O is insufficient for this methodology (Table 3B.1 entry 15). Thus, DMF is found to be a best reaction medium among all the solvents tested to produce title compound in excellent yield. The stabilized condition for the synthesis of diarylmethane is as follows, imidazo [1,2-*a*]pyridine **1** (1.0 mmol), indole **2** (1.0 mmol), and rongalite **3** (2 mmol) in DMF solvent (2 mL) at 5 h.

Table 3B.2. Reaction of Substituted Imidazo[1,2-*a*]pyridine with Indoles.[a,b]

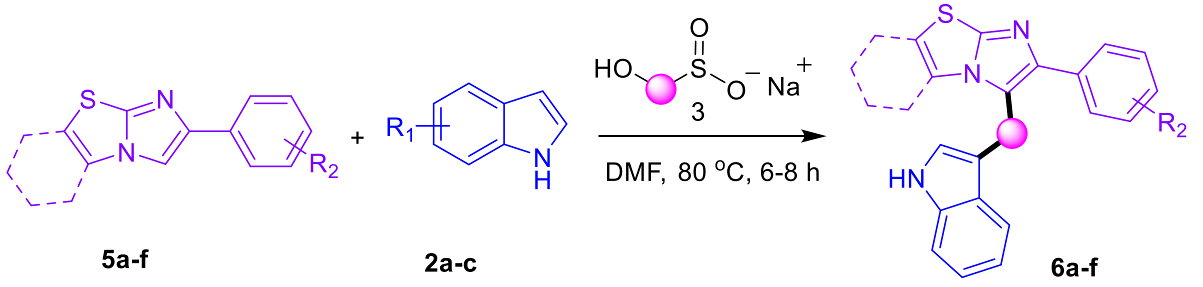


[a]All the reactions were conducted on a 1 mmol scale of **1a-k** (1 mmol), **2a-g** (1 mmol) and **3** (2 mmol) in DMF solvent (2 mL). [b]Yields where reported is of isolated and purified product.

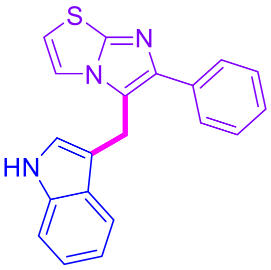
After optimized the reaction conditions for metal-free coupling heterodiarylmethanes via between imidazo[1,2-*a*]pyridines, indoles and rongalite in DMF, then we have concentrated on the scope of the substitutions on both the imidazo[1,2-*a*]pyridines, indoles results are showed in Table 3B.2. Fortunately, the substitution such as methyl, F, Br, Ph, methoxy and Cl on both the imidazo-

[1,2-*a*]pyridine and indoles are well tolerated and gave the corresponding 3-((1*H*-indol-3-yl)methyl)-2-phenylimidazo[1,2-*a*]pyridine derivative in good to excellent yields (Table 3B.2, **4a-4o**) and also *N*-methyl, *N*-butyl, *N*-allyl indoles reacted with imidazo-[1,2-*a*]pyridine and gave good yields (Table 3B.2 **4p-4r**).

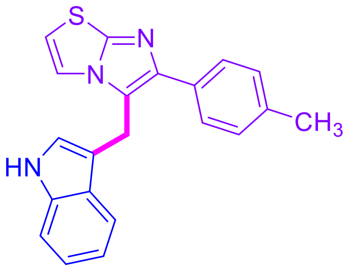
Table 3B.3. Reaction of Simple or Benzo[*d*]pyrrolo[2,1-*b*]thiazoles with Indoles



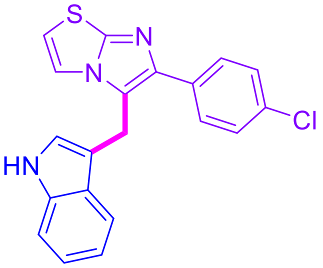
5a-f **2a-c** **6a-f**



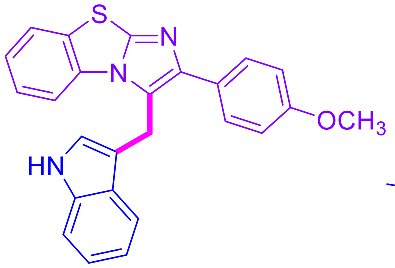
6a, 6 h, 90%



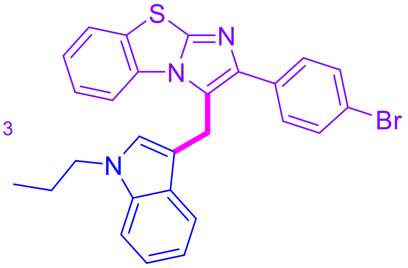
6b, 6 h, 88%



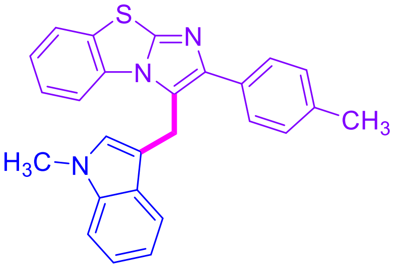
6c, 7 h, 82%



6d, 8 h, 86%



6e, 7 h, 84%

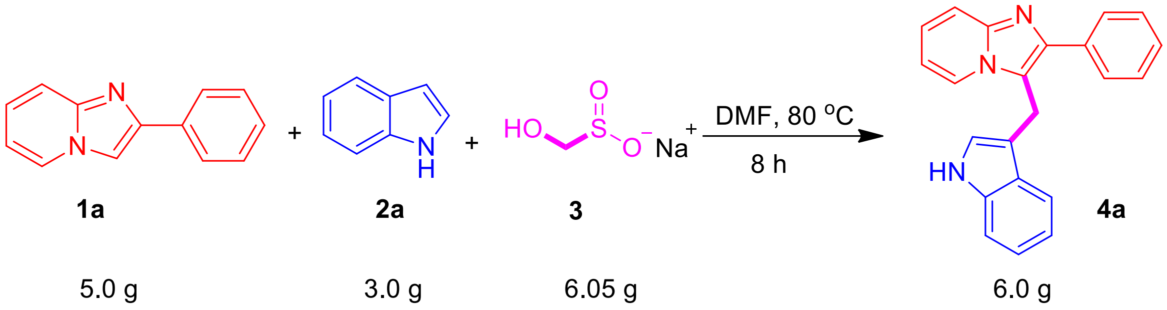


6f, 6 h, 82%

[a]All the reactions were conducted on a 1 mmol scale of **5a-f** (1 mmol), **2a-c** (1 mmol) and **3** (2 mmol) in DMF solvent (2 mL). [b]Yields where reported is of isolated and purified product.

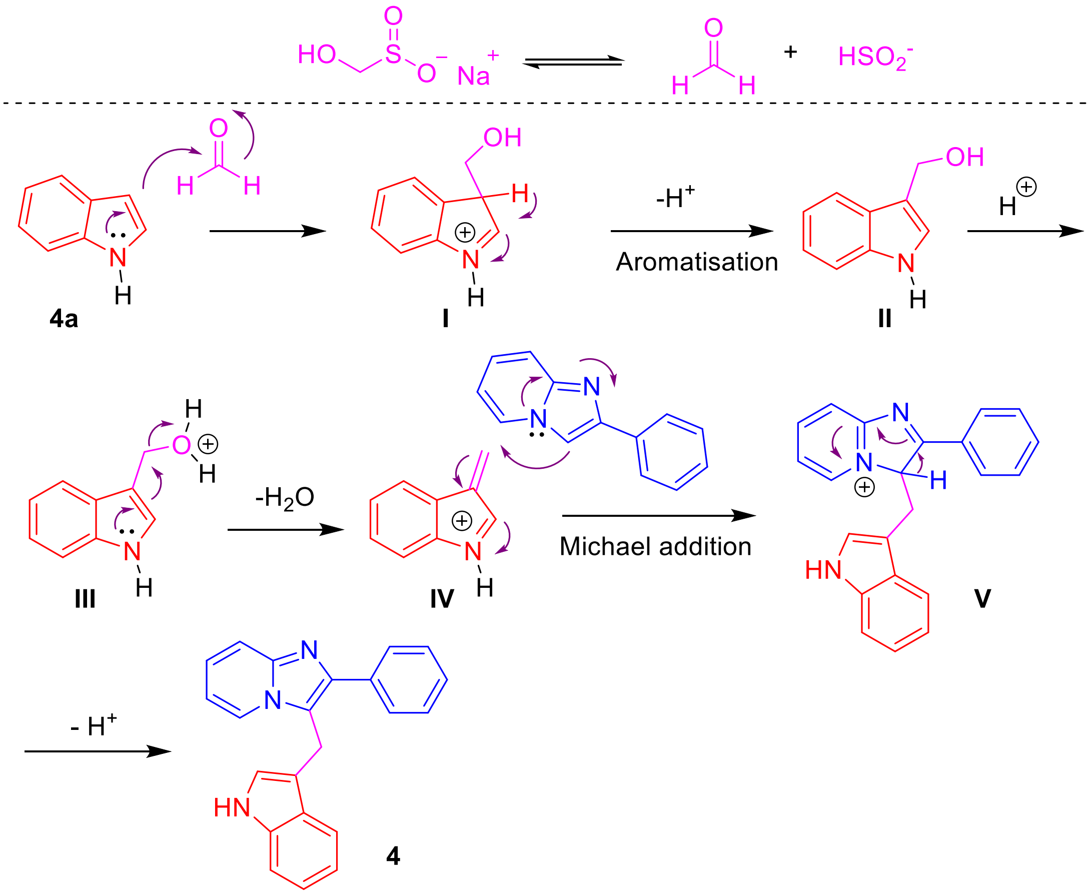
Further, the above methodology was extended to synthesis other heteroarene i.e., imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]-thiazole. These substrate also showed similar reactivity patterns of imidazo[1, 2-*a*]pyridines and furnished title compounds in excellent yield (Table 3B.3, **6a-6f**).All the synthesized compounds from this methodology was characterized by ^{1}H, ^{13}C NMR and mass spectral data.

Finally, we have tested our method in gram scale for the industrial applications with 5g scale and obtained 72% yield (Scheme 3B.15).



Scheme 3B.15

The plausible reaction mechanism pathway is proposed for the heterodiarylmethanes via metal-free coupling between imidazo[1,2-*a*]pyridines or imidazo[2,1-*b*]thiazole and indoles, based on experimental observations.



Scheme 3B.16

In the first step, rongalite dissociates and generate formaldehyde *in situ*, which further reacts with C-2 position of indole to form an intermediate **I**, which further re-aromatises to form stable (1*H*-indol-3-yl) methanol compound **II**. Upon dehydration of intermediate **II** yields a Michael acceptor 3-methylene-3*H*-indole **IV**. Then imidazo[1,2-*a*]pyridine π-electrons attack on 3-methylene-3*H*-indole **IV** via michael addition to form intermediate **V**, which further undergoes aromatization to furnish desired product **4** (Scheme 3B.16).

3B.4. Conclusion

In this chapter we have described a metal-free synthesis of heterodiaryls of 3-((1*H*-indol-3-yl)methyl)-2-phenylimidazo[1,2-*a*]pyridine and 1-((1*H*-indol-3-yl)methyl)-2-phenylbenzo[*d*]pyrrolo[2,1-*b*]thiazole from their respective starting materials. The substrate scope of this methodology is well studied and 24 compounds were synthesized accordingly. This method involves metal free, non-hazardous and less expensive bench chemical. Here rongalite is acting as a formaline source. It is also observed that the reaction is also favourable to the synthesis in gram-scale reactions.

3B.5.Experimental Section

3B.5.1.General Information

All the starting materials i.e., 2-amino pyridines, phenacyl bromides, morpholine, piperidine, rongalite and diethyl amine were purchased from Spectrochem, SD-Fine, Sigma-Aldrich, Finar, and SRL. All the used reagents were of analytical grade and were directly used without any further purification. The compounds imidazo[1,2-*a*]pyridine, imidazo[2,1-b]thiazole and benzo[*d*]imidazo[2,1-*b*]-thiazole are prepared according to the reported methods and used after purification by column chromatography.[59] All the solvents used for this method were obtained from Finar. For reaction monitoring TLC-Silica gel 60 GF_{254} was used with the help of UV-Cabinet. Purification of compounds using column chromatography which was performed with the Rankem silica gel (100-200 mesh). Melting point for solid compounds were recorded using Stuart SMP30 melting point apparatus. ^{1}H and ^{13}C NMR spectral data of all the synthesized compounds was recorded on Bruker AVANCE HD (400 MHz / 100 MHz) spectrometer using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The data of the compounds was recorded as chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations for the multiplicity as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. The mass spectrometry analysis was recorded in Bruker- micro-TOF MS analyser.

3B.5.2. General procedure for the Preparation of Substituted 3-((1H-indol-3-yl)methyl)-2-phenylimidazo[1,2-*a*]pyridine (4a-4r)

To a clean and dry round bottom flask equipped with magnetic bead were added imidazo-[1, 2-*a*] pyridine **1a** (200 mg, 1.0 mmol), indole **2a** (122 mg, 1.0 mmol), and rongalite **3** (245 mg, 2 mmol) in 2 mL of DMF solvent. The reaction mixture was allowed to stir at 80 °C for 6-8 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into an ice-cold water and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was separated using column chromatography with silica-gel (100-200 mesh) by eluting with ethyl acetate / hexanes as a mobile phase.

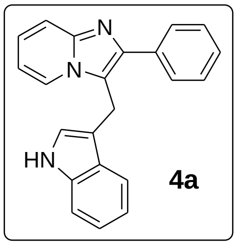
3B.5.2.1. General Procedure for the Preparation of Substituted 5-((1*H*-indol-3-yl)methyl)-6-phenylimidazo[2,1-*b*]thiazole and 3-((1*H*-indol-3-yl)methyl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole Derivatives (6a-6f)

To a clean and dry round bottom flask equipped with magnetic bead were added indole **2a (**170 mg, 1.0 mmol), 6-phenylimidazo[2,1-*b*]thiazole or 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole **5a** (200 mg, 1.0 mmol), and rongalite **3** (236 mg, 2 mmol) in DMF solvent (2 mL). The reaction mixture was allowed to stir at 80 °C for 6-8 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into an ice-cold water and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was separated using column chromatography with silica-gel (100-200 mesh) by eluting with ethyl acetate / hexanes as a mobile phase.

3B.6. Characterization Data of Products

3-((1*H*-Indol-3-yl)methyl)-2-phenyl*H*-imidazo[1,2-*a*]pyridine (4a)[32]

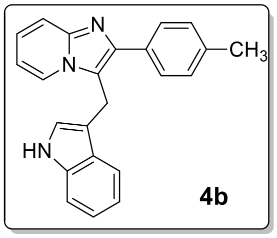
Yield: 90%, brown solid, M.P. 160-162 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.82 (t, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.37 (m, 3H), 7.3 (t, *J* = 7.3 Hz, 1H), 7.19 (dd, *J* = 12.9, 6.0 Hz, 2H), 6.70 (t, *J* = 6.7 Hz, 1H), 6.63 (s, 1H), 4.55 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 140.9, 134.9, 132.3, 126.8, 126.3, 125.9, 125.0, 122.6, 122.0, 120.5, 120.2, 117.7, 116.7, 115.3, 114.5, 110.4, 109.6, 108.9, 27.8. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{17}N_3$ [M+H]$^+$324.1502, found 324.1503.

3-((1*H*-Indol-3-yl)methyl)-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine (4b)

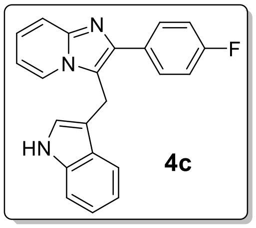
Yield: 85%, brown solid, M.P. 106-108 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.69 (d, *J* = 6.5 Hz, 1H), 7.63 (t, *J* = 7.3 Hz, 3H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 18.3, 7.6 Hz, 4H), 6.59 (t, *J* = 6.4 Hz, 1H), 6.51 (s, 1H), 4.44 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 142.8, 137.6, 136.8, 131.2, 129.4, 128.1, 126.9, 124.4, 123.8, 122.5, 122.1, 119.7, 118.6, 118.0, 117.1, 112.2, 111.5, 111.0, 21.3, 20.7. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{19}N_3$ [M+H]$^+$ 338.1659, found 338.1654.

3-((1*H*-Indol-3-yl)methyl)-2-(4-fluorophenyfl)*H*-imidazo[1,2-*a*]pyridine(4c)

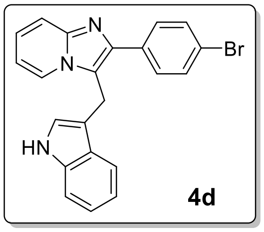
Yield: 84%, white solid, M.P. 178-180 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.75 – 7.70 (m, 3H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.18 (d, *J* = 4.8 Hz, 1H), 7.15 – 7.08 (m, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.64 (t, *J* = 6.7 Hz, 1H), 6.54 (s, 1H), 4.44 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 161.4, 144.3, 141.5, 136.8, 129.9, 126.8, 124.9, 123.9, 122.6, 122.0, 119.8, 118.5, 118.2, 117.0, 115.8, 115.6, 112.6, 111.5, 110.7. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{16}FN_3$ [M+H]$^+$ 342.1408, found 342.1401.

3-((1*H*-Indol-3-yl)methyl)-2-(4-bromophenyl)*H*-imidazo[1,2-*a*]pyridine(4d)

Yield: 82%, brown solid, M.P. 193-195 °C.

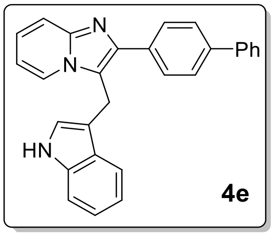


4d

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.40 (s, 2H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.10 (t, *J* = 8.9 Hz, 2H), 6.61 (t, *J* = 6.6 Hz, 1H), 6.49 (s, 1H), 4.42 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.6, 141.6, 136.8, 133.1, 131.9, 129.7, 126.8, 124.8, 123.8, 122.7, 122.0, 121.9, 119.8, 118.5, 117.2, 112.5, 111.5, 110.7, 20.7. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{16}BrN_3[M+H]^+$ 402.0608, found 402.0609 (Br peak 404.0592).

3-((1*H*-Indol-3-yl)methyl)-2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridine (4e)

Yield: 80%, brown solid, M.P. 101-103 °C.

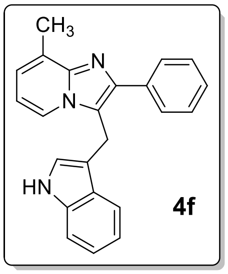


4e

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.50 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 6.8 Hz, 1H), 7.66 (t, *J*= 7.3 Hz, 2H), 7.60 (t, *J* = 8.5 Hz, 4H), 7.44 – 7.36 (m, 3H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.20 – 7.11 (m, 2H), 6.64 (t, *J* = 6.7 Hz, 2H), 6.59 (s, 1H), 4.56 (s, 2H). ^{13}C NMR (100 MHz, DMSO+CDCl$_3$) δ 144.4, 141.9, 140.5, 140.1, 137.0, 133.4, 128.9, 128.6, 127.4, 127.2, 126.9, 124.6, 124.1, 122.5, 121.9, 119.1, 118.9, 118.3, 116.9, 112.3, 111.8, 109.7, 20.8. HRMS (ESI-TOF): m/z calcd for $C_{28}H_{21}N_3$ $[M+H]^+$ 400.1815, found 400.1794.

3-((1*H*-Indol-3-yl)methyl)-8-methyl-2-phenyl*H*-imidazo[1,2-*a*]pyridine(4f)[32]

Yield: 86%, brown solid, M.P. 142-144 °C.



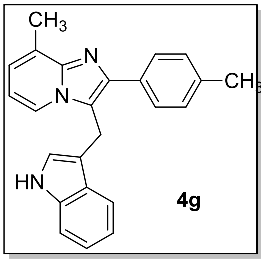
4f

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.32 (s, 1H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 7.1 Hz, 3H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 5.0 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 6.8 Hz, 1H), 6.50 (t, *J* = 6.8 Hz, 1H), 6.47 (s, 1H), 4.41 (s, 2H), 2.62 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.1, 142.5, 136.7, 134.5, 128.6, 128.4, 127.6, 127.2, 127.0, 123.2, 122.4, 122.1, 121.7, 119.6, 118.7, 118.6, 112.2, 111.4, 111.2, 20.8, 17.3. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{19}N_3$ $[M+H]^+$ 338.1659, found 338.1647.

3-((1*H*-Indol-3-yl)methyl)-8-methyl-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine(4g)

Yield: 90%, brown solid, M.P. 195-197 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.58 (dd, J = 12.1, 7.4 Hz, 2H), 7.32 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.09 (d, J = 7.2 Hz, 1H), 6.91 (d, J = 6.8 Hz, 1H), 6.54 (t, J = 6.8 Hz, 2H), 4.43 (s, 2H), 2.64 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.7, 142.1, 137.6, 136.7, 129.4, 128.3, 127.0, 123.6, 122.4, 122.1, 121.7, 119.6, 118.6, 118.4, 112.3, 111.4, 111.2, 21.3, 20.7, 17.3. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{21}N_3$ [M+H]$^+$ 352.1815, found 352.1815.

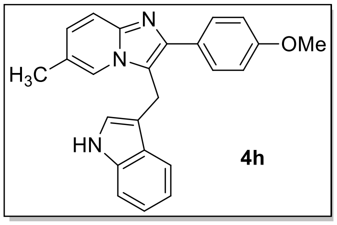


4g

3-((1*H*-Indol-3-yl)methyl)-2-(4-methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridine (4h)

Yield: 90%, light brown solid, M.P. 121-123 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.29 (s, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.58 (s, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 6.61 (s, 1H), 4.48 (s, 2H), 3.80 (s, 3H), 2.21 (s, 3H).^{13}C NMR (100 MHz, CDCl$_3$) δ 159.4, 143.2, 141.8, 136.9, 129.4, 128.0, 126.9, 126.2, 122.5, 122.3, 122.1, 121.3, 119.7, 118.6, 117.3, 116.1, 114.2, 111.5, 111.1, 55.3, 20.7, 18.3. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{21}N_3O$ [M+H]$^+$ 368.1765, found 368.1764.

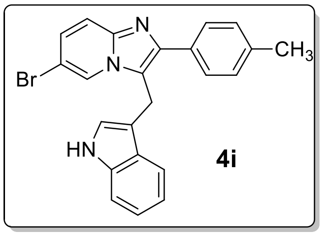


4h

3-((1*H*-Indol-3-yl)methyl)-6-bromo-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine(4i)

Yield: 85%, brown solid, M.P. 151-153 °C.

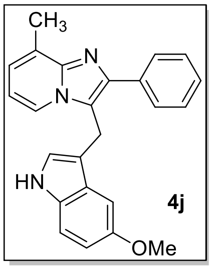
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.57 (s, 1H), 7.91 (s, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 9.5 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.7 Hz, 5H), 6.57 (s, 1H), 4.48 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.8, 143.0, 138.0, 136.9, 130.8, 129.5, 128.0, 127.6, 126.8, 123.7, 122.6, 122.0, 199.7, 118.6, 118.5, 117.7, 111.6, 110.4, 106.9, 21.3, 20.8. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{18}BrN_3$ [M+H]$^+$ 416.0764, found 416.0740. (Br peak 418.0722).



4i

3-((5-Methoxy-1*H*-indol-3-yl)methyl)-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine(4j)

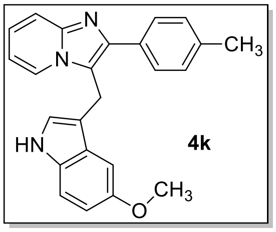
Yield: 88%, brown solid, M.P. 98-100 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.76 (d, *J* = 6.9 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 3H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.17 – 7.11 (m, 3H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.66 (td, *J* = 6.8, 0.8 Hz, 1H), 6.60 – 6.57 (m, 1H), 4.43 (s, 2H), 3.74 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 144.1, 137.9, 131.8, 129.5, 128.2, 127.2, 124.8, 123.8, 122.7, 118.1, 116.9, 112.8, 112.5, 112.1, 110.5, 100.2, 55.9, 21.3, 20.7. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{21}N_3O$ $[M+H]^+$ 368.1765, found 368.1758.

3-((5-Methoxy-1*H*-indol-3-yl)methyl)-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine(4k)

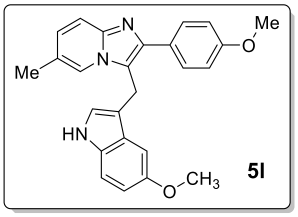
Yield: 88%, brown solid, M.P. 191-193 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.70 – 7.67 (m, 2H), 7.57 (t, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.12 – 7.07 (m, 1H), 6.90 (d, *J* = 6.8 Hz, 1H), 6.86 – 6.84 (m, 2H), 6.53 (t, *J* = 6.8 Hz, 2H), 4.41 (s, 2H), 3.73 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 144.8, 142.1, 136.7, 129.6, 127.0, 123.3, 122.5, 122.0, 121.6, 119.7, 118.6, 118.0, 114.1, 112.2, 111.4, 55.3, 20.8, 17.3. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{21}N_3O$ $[M+H]^+$ 368.1765, found 368.1759.

3-((5-Methoxy-1*H*-indol-3-yl)methyl)-2-(4-methoxyphenyl)-6-methyl*H*-imidazo[1,2-*a*]pyridine (4l)

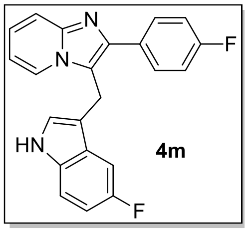
Yield: 88%, brown solid, M.P. 163-166 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.60 (s, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.04 (dd, *J* = 10.9, 5.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 3H), 6.60 (s, 1H), 4.43 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 154.2, 131.9, 129.4, 128.2, 127.2, 122.8, 121.4, 117.3, 116.0, 114.2, 112.8, 112.2, 110.6, 100.3, 55.9, 55.3, 20.7, 18.3. HRMS (ESI-TOF): m/z calcd for $C_{25}H_{23}N_3O_2$ $[M+H]^+$ 398.1870, found 398.1854.

3-((5-Fluoro-1*H*-indol-3-yl)methyl)-2-(4-fluorophenyl)*H*-imidazo[1,2-*a*]pyridine(4m)

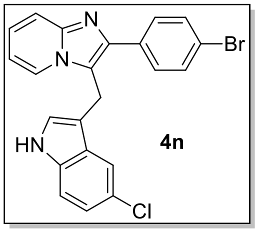
Yield: 84%, brown solid, M.P. 180-182 °C.



^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 10.10 (s, 1H), 7.81 (d, *J* = 6.8 Hz, 1H), 7.73 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.38 (d, *J* = 4.2 Hz, 2H), 7.27 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.86 (td, *J* = 9.0, 1.8 Hz, 1H), 6.73 (t, *J* = 6.7 Hz, 1H), 6.67 (s, 1H), 4.41 (s, 2H). ^{13}C NMR (100 MHz, DMSO+$CDCl_3$) δ 163.6, 158.6, 144.2, 141.2, 133.6, 130.4, 129.9, 127.0, 126.9, 124.9, 124.3, 124.1, 118.4, 116.8, 115.7, 115.5, 112.5, 110.2, 110.0, 109.6, 103.2, 102.9, 20.5. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{15}F_2N_3$ $[M+H]^+$ 360.1314, found 360.1301.

2-(4-Bromophenyl)-3-((5-chloro-1*H*-indol-3-yl)methyl)*H*-imidazo[1,2-*a*]pyridine(4n)

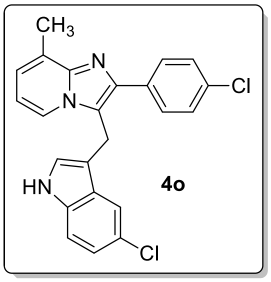
Yield: 82%, brown solid, M.P. 196-198 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.71 (d, *J* = 6.8 Hz, 1H), 7.60 (t, *J* = 9.3 Hz, 3H), 7.43 (t, *J* = 9.5 Hz, 3H), 7.30 (s, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.06 (dd, *J* = 8.5, 1.6 Hz, 1H), 6.66 (t, *J* = 6.7 Hz, 1H), 6.54 (s, 1H), 4.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 141.6, 137.1, 132.9, 131.9, 129.7, 128.6, 125.4, 124.9, 123.7, 122.6, 122.1, 120.6, 119.4, 118.2, 117.3, 112.6, 111.5, 111.0, 20.6. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{15}BrClN_3$ $[M+H]^+$ 436.0218, found 436.0227. (Br peak 438.0207).

3-((5-Chloro-1*H*-indol-3-yl)methyl)-2-(4-chlorophenyl)-8-methyl*H*-imidazo[1,2-*a*]pyridine(4o)

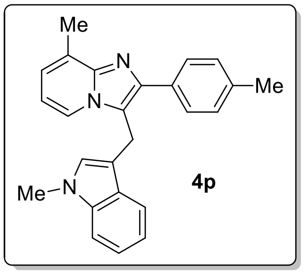
Yield: 80%, red colour solid, M.P. 191-193 °C.



^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 10.74 (s, 1H), 7.85 – 7.74 (m, 3H), 7.46 – 7.34 (m, 4H), 7.02 (d, *J* = 6.4 Hz, 1H), 6.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.78 – 6.68 (m, 2H), 4.50 (s, 2H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, DMSO+$CDCl_3$) δ 144.6, 137.4, 133.2, 129.7, 128.8, 127.2, 126.7, 125.5, 123.5, 122.1, 119.5, 119.3, 112.7, 111.6, 110.0, 20.6, 17.0. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{17}Cl_2N_3$ $[M+H]^+$ 406.0880, found 406.0886.

8-Methyl-3-((1-methyl-1*H*-indol-3-yl)methyl)-2-*p*-tolyl*H*-imidazo[1,2 *a*]pyridine(4p)

Yield: 82%, brown solid, M.P. 111-113 °C.

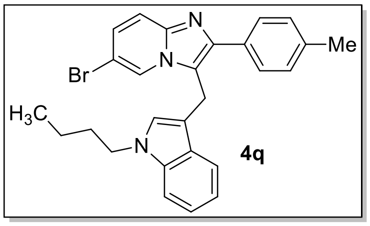


4p

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.21(t, *J* = 7.5 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.52 (t, *J* = 6.8 Hz, 1H), 6.42 (s, 1H), 4.42 (s, 2H), 3.57 (s, 3H), 2.64 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.0, 142.6, 137.5, 137.3, 131.8, 129.3, 128.2, 127.4, 127.2, 126.7, 122.9, 122.0, 121.6, 119.1, 118.8, 118.4, 112.0, 109.9, 32.7, 21.3, 20.7, 17.3. HRMS (ESI-TOF): m/z calcd for C$_{25}$H$_{23}$N$_3$ [M+H]$^+$ 366.1972, found 366.1976.

6-Bromo-3-((1-butyl-1*H*-indol-3-yl)methyl)-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine(4q)

Yield: 81%, brown solid, M.P. 105-107 °C.

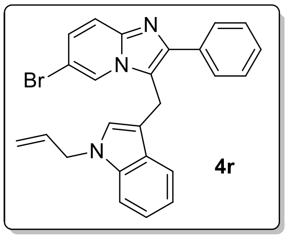


4q

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.58 (dd, *J* = 8.6, 4.8 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.21 (dd, *J* = 6.9, 4.4 Hz, 3H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.54 (s, 1H), 4.50 (s, 2H), 4.00 (t, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 1.71 (dt, *J* = 14.6, 7.1 Hz, 2H), 1.26 – 1.20 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.0, 143.1, 137.8, 136.9, 131.1, 129.5, 128.1, 127.4, 125.7, 123.8, 122.0, 119.2, 118.9, 118.6, 118.0, 109.8, 108.7, 106.7, 46.1, 32.2, 21.3, 20.9, 20.1, 13.7. HRMS (ESI-TOF): m/z calcd for C$_{27}$H$_{26}$BrN$_3$ [M+H]$^+$ 472.1390, found 472.1380 (Br peak 474.1363).

3-((1-Allyl-1*H*-indol-3-yl)methyl)-6-bromo-2-phenyl*H*-imidazo[1,2-*a*]pyridine (4r)

Yield: 80%, red colour solid, M.P. 104-106 °C.

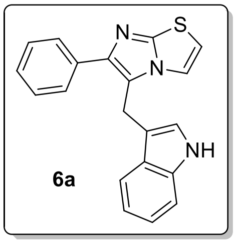


4r

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.59 (dd, *J* = 8.7, 4.3 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.22 (dd, *J* = 9.6, 1.5 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.57 (s, 1H), 5.90 (ddd, *J* = 22.2, 10.4, 5.3 Hz, 1H), 5.14 (d, *J* = 10.2 Hz, 1H), 4.99 (d, *J* = 17.9 Hz, 1H), 4.62 (d, *J* = 5.2 Hz, 2H), 4.53 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.0, 143.2, 137.1, 134.0, 133.3, 128.8, 128.2, 128.0, 127.5, 127.4, 125.7, 123.8, 123.3, 119.5, 118.9, 118.8, 118.1, 117.3, 110.0, 109.4, 106.8, 48.8, 20.8. HRMS (ESI-TOF): m/z calcd for C$_{25}$H$_{20}$BrN$_3$ [M+H]$^+$ 442.0921, found 442.0911 (Br peak 444.0893).

3-((6-Phenylimidazo[2,1-*b*]thiazol-5-yl)methyl)-1*H*-indole (6a)

Yield: 90%, red colour solid, M.P. 62-65 °C.

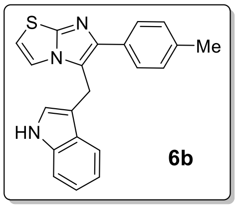


6a

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (s, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.46 (d, J = 7.9 Hz, 1H), 7.33 – 7.26 (m, 3H), 7.20 (t, J = 7.4 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.08 – 7.03 (m, 1H), 6.94 (d, J = 4.5 Hz, 1H), 6.65 (s, 1H), 6.55 (d, J = 4.5 Hz, 1H), 4.36 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.3, 143.7, 136.7, 134.6, 128.7, 127.5, 127.2, 126.9, 122.5, 122.3, 120.4, 119.7, 118.6, 117.6, 112.1, 111.9, 111.5, 21.6. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{15}N_3S$ [M+H]$^+$ 330.1067, found 330.1055.

3-((6-*p*-Tolylimidazo[2,1-*b*]thiazol-5-yl)methyl)-1*H*-indole (6b)

Yield: 88%, brown solid, M.P. 168-170 °C.

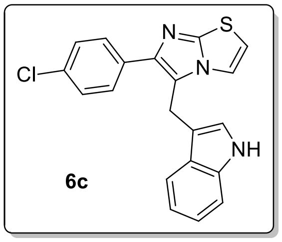


6b

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.68 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 4.5 Hz, 1H), 6.63 (s, 1H), 6.51 (d, J = 4.5 Hz, 1H), 4.38 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.2, 143.8, 137.0, 136.7, 131.8, 129.4, 127.4, 126.9, 122.4, 122.3, 120.2, 119.6, 118.6, 117.6, 111.9, 111.8, 111.5, 21.5, 21.3. HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}N_3S$ [M+H]$^+$ 344.1223, found 344.1213.

3-((6-(4-Chlorophenyl)imidazo[2,1-*b*]thiazol-5-yl)methyl)-1*H*-indole (6c)

Yield: 82%, orange colour solid, M.P. 130-131 °C.



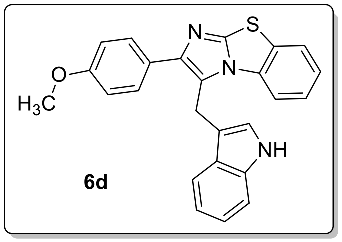
6c

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.42 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 4.5 Hz, 1H), 6.62 (s, 1H), 6.55 (d, J = 4.5 Hz, 1H), 4.32 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.5, 142.5, 136.7, 133.1, 128.8, 128.7, 126.8, 122.6, 122.2, 120.7, 119.8, 118.5, 117.5, 112.5, 111.5. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{14}ClN_3S$ [M+H]$^+$ 364.0677, found 364.0671.

3-((1*H*-Indol-3-yl)methyl)-2-(4-methoxyphenyl)benzo[*d*]imidazo[2,1-*b*]thiazole (6d)

Yield: 86%, brown solid, M.P. 120-125 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16 (s, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.55 (dd, J = 7.8, 5.7 Hz, 3H), 7.35 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.16 – 7.10 (m, 2H), 7.02 (dd, J = 11.5, 4.1 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 6.66 (s, 1H), 4.53 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.1, 146.7, 144.0, 136.9, 133.0, 130.3, 128.7, 126.7, 126.2, 124.3, 124.1, 122.7, 122.6, 121.4, 119.8, 118.6, 114.2, 113.6, 112.5, 111.6, 55.3, 22.1. HRMS (ESI-TOF): m/z calcd for C$_{25}$H$_{19}$N$_3$OS [M+H]$^+$ 410.1329, found 410.1323.

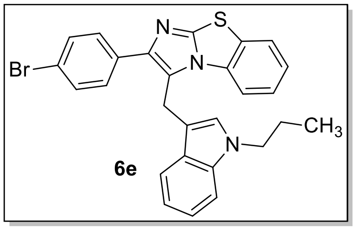


6d

2-(4-Bromophenyl)-3-((1-propyl-1*H*-indol-3-yl)methyl)benzo[*d*]imidazo[2,1-*b*]thiazole (6e)

Yield: 84%, orange colour solid, M.P. 139-140 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (dt, J = 13.6, 6.7 Hz, 3H), 7.52 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.33 (t, J = 6.8 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 7.15 (d, J = 7.1 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.61 (s, 1H), 4.55 (s, 14H), 3.88 (t, J = 7.0 Hz, 2H), 1.64 (dd, J = 14.4, 7.2 Hz, 2H), 0.67 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.1, 137.0, 132.7, 132.5, 131.9, 130.3, 128.9, 127.0, 126.4, 126.2, 124.8, 124.2, 122.7, 122.2, 121.7, 119.3, 118.7, 113.9, 110.0, 109.9, 48.0, 23.4, 22.2, 11.3. HRMS (ESI-TOF): m/z calcd for C$_{27}$H$_{22}$BrN$_3$S [M+H]$^+$ 500.0798, found 500.0802.

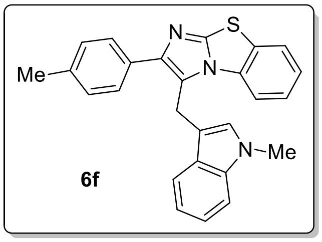


6e

3-((1-Methyl-1*H*-indol-3-yl)methyl)-2-(*p*-tolyl)benzo[*d*]imidazo[2,1-*b*]thiazole (6f)

Yield: 82%, brown solid, M.P. 191-193 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 8.4 Hz, 1H), 7.26 (t, J = 7.9 Hz, 2H), 7.15 (dd, J = 10.4, 4.6 Hz, 2H), 7.12 – 7.05 (m, 3H), 6.58 (s, 1H), 4.56 (s, 2H), 3.58 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.7, 144.2, 137.1, 133.0, 131.2, 130.4, 129.4, 127.3, 126.2, 124.3, 124.1, 122.1, 122.0, 119.2, 118.7, 113.7, 110.9, 109.6, 32.8, 22.1, 21.3. HRMS (ESI-TOF): m/z calcd for C$_{26}$H$_{21}$N$_3$S [M+H]$^+$ 408.1536, found 408.1536.



6f

3B.7. References

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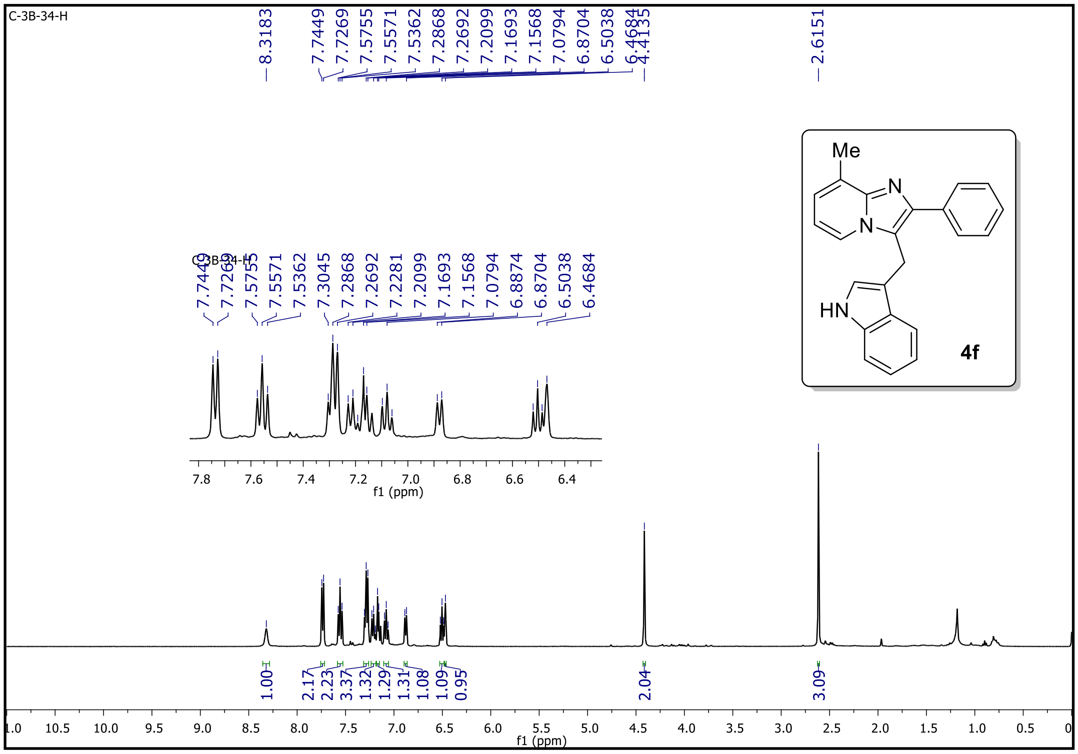
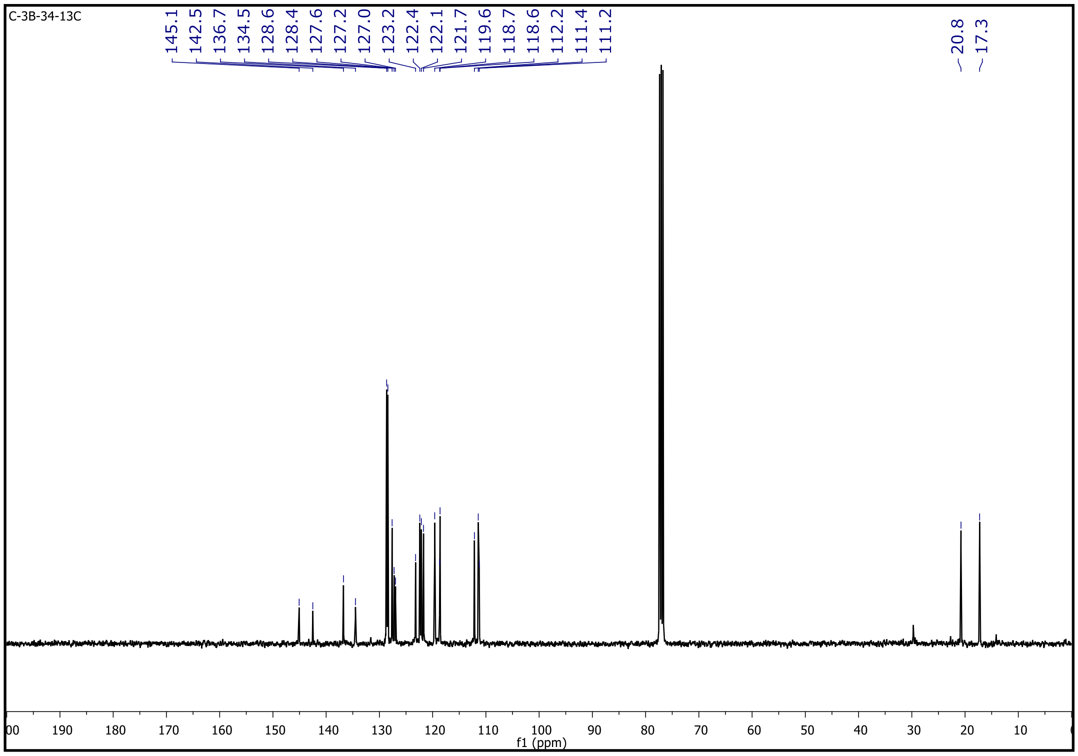
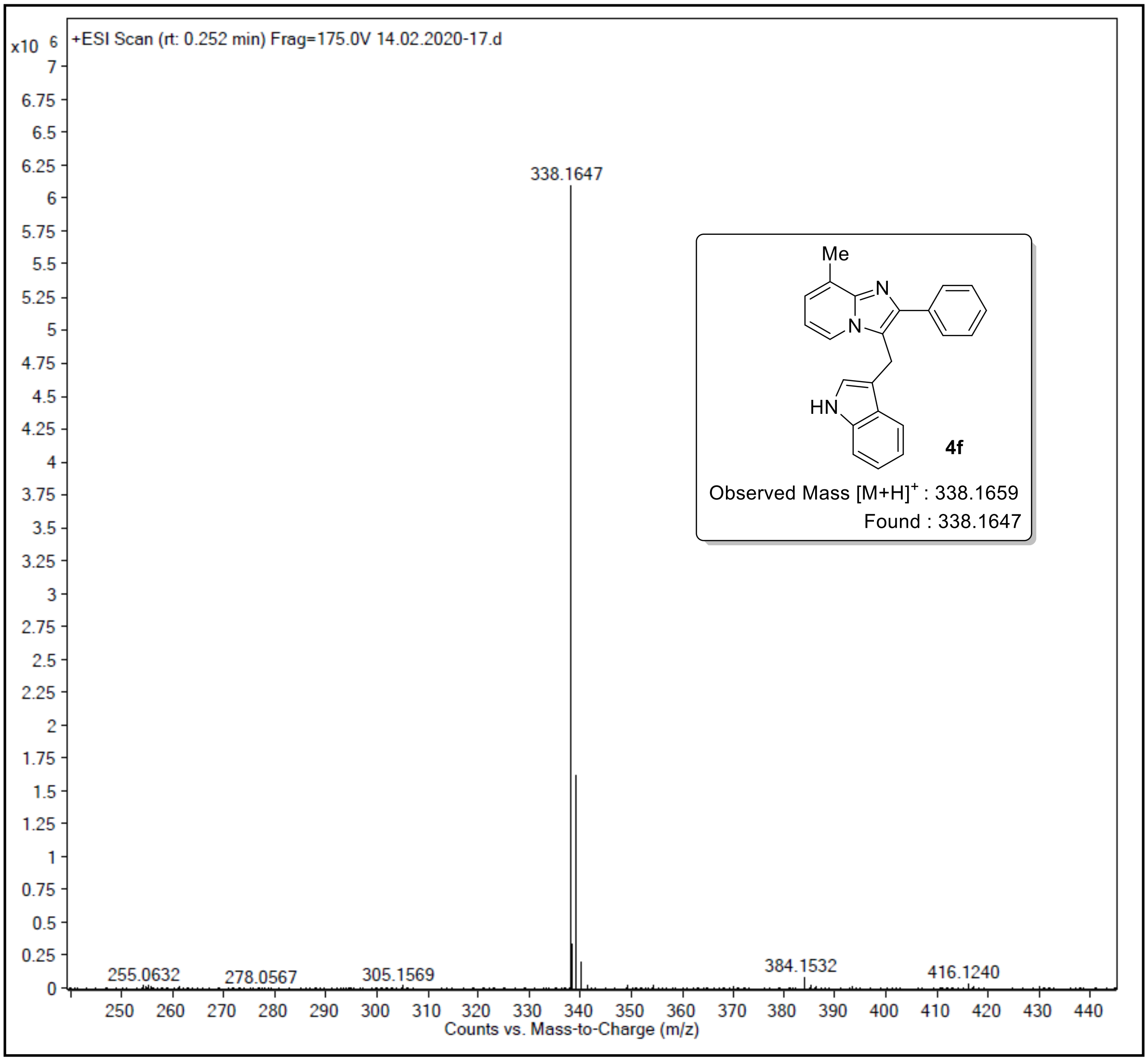
3B.8. Selected NMR (^{1}H and ^{13}C) and mass Spectra



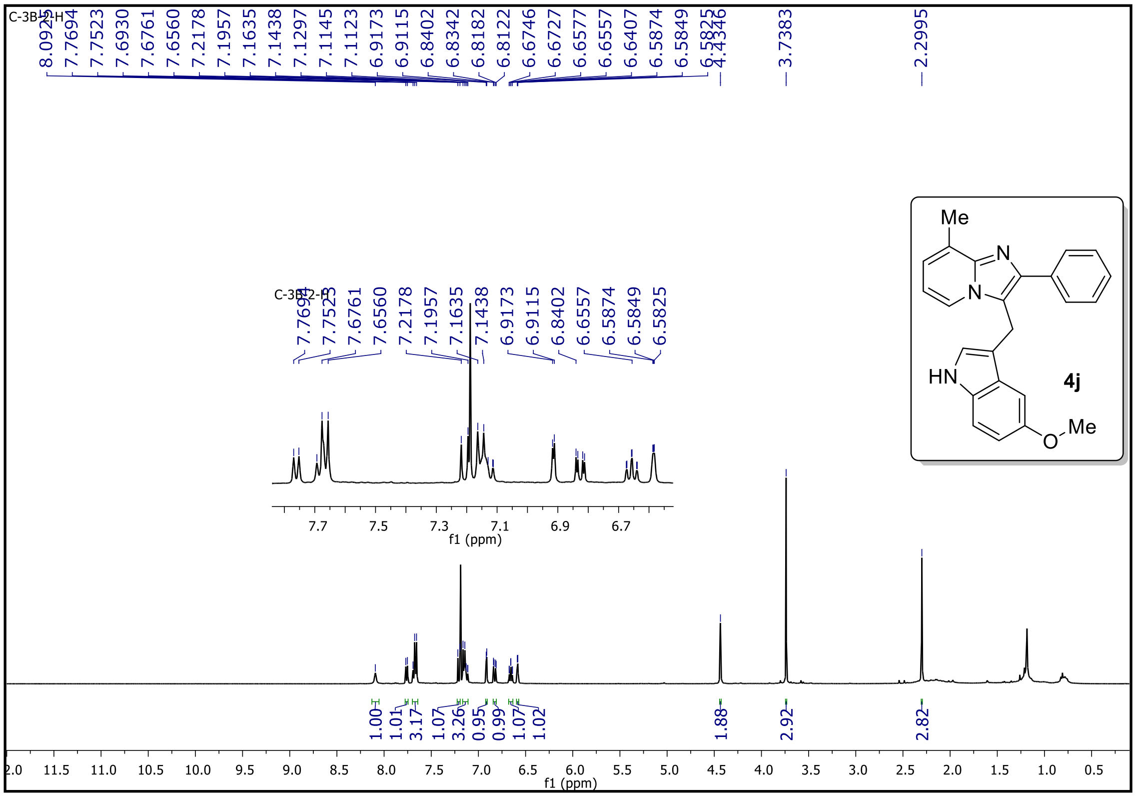
^{1}H NMR spectrum of compound **4f**



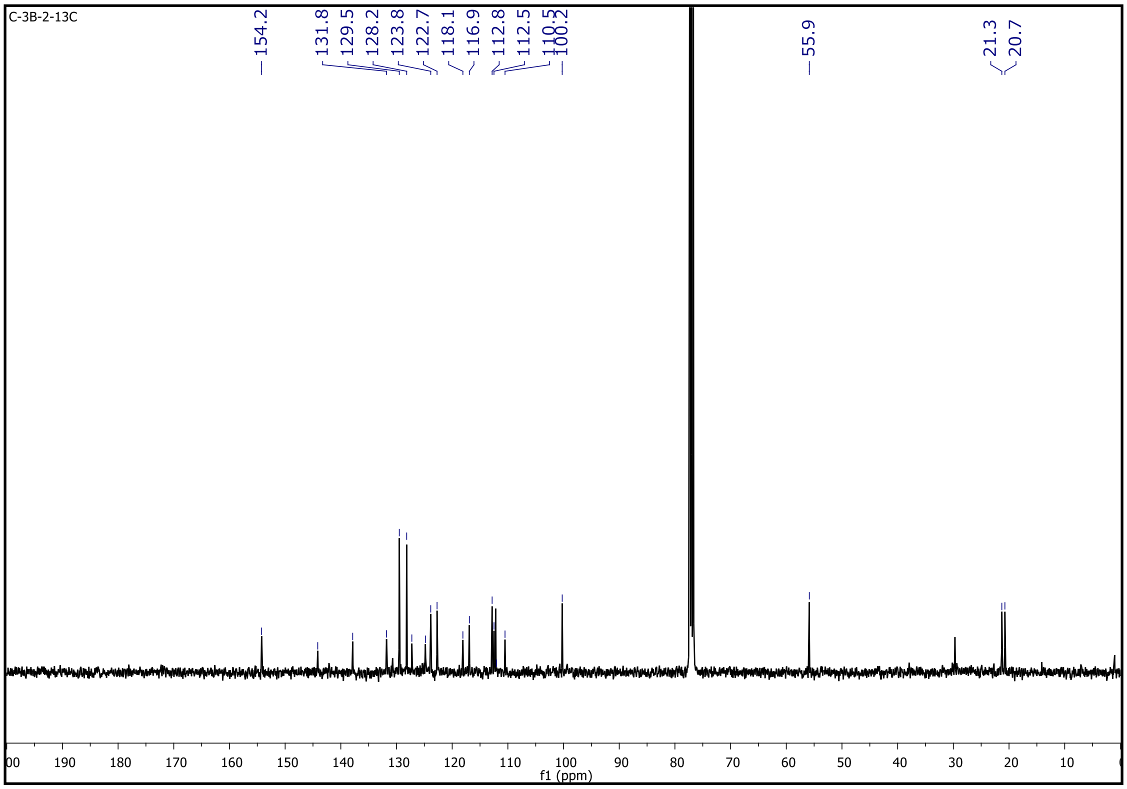
^{13}C NMR spectrum of compound **4f**



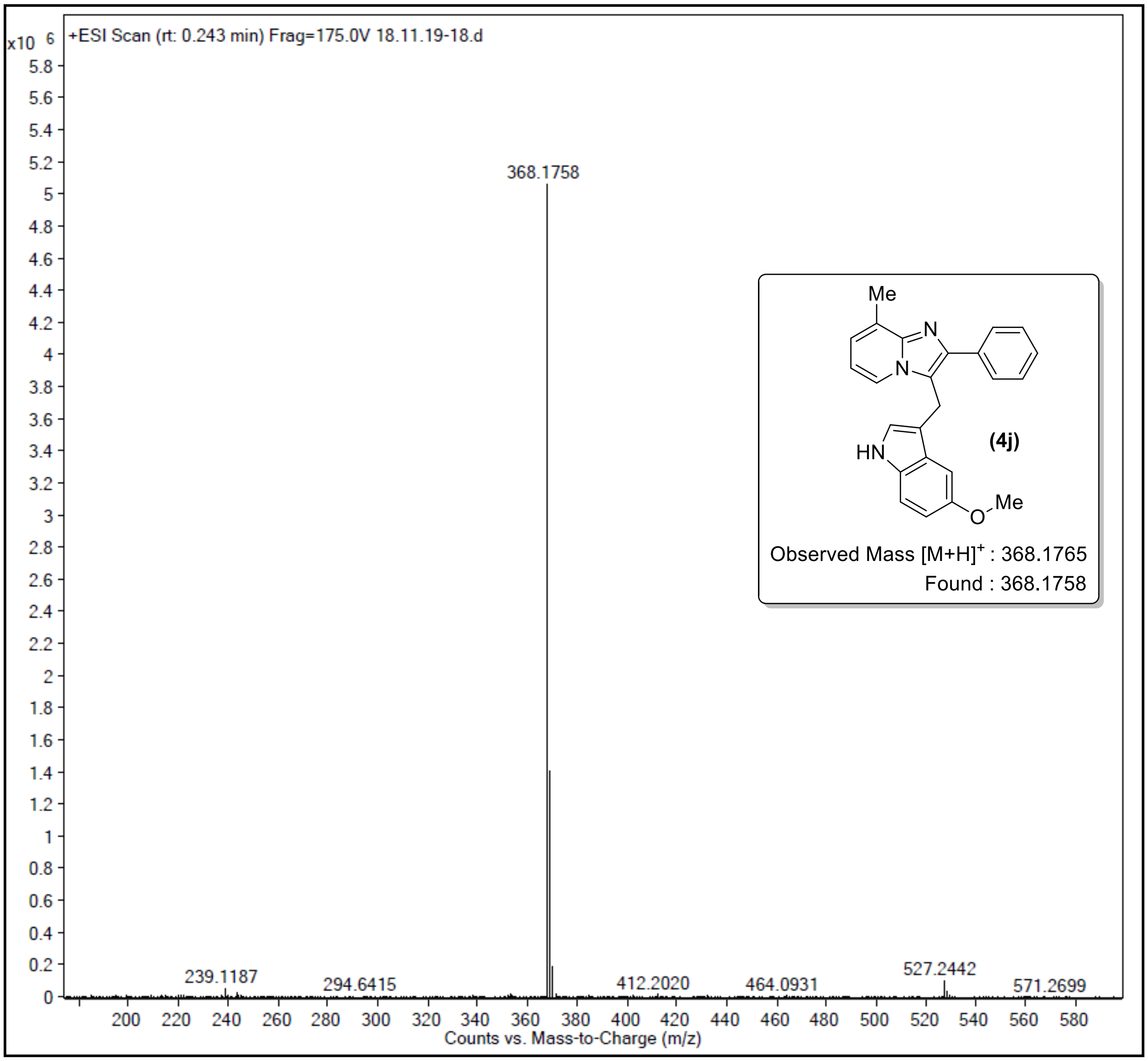
Mass spectrum of compound **4f**



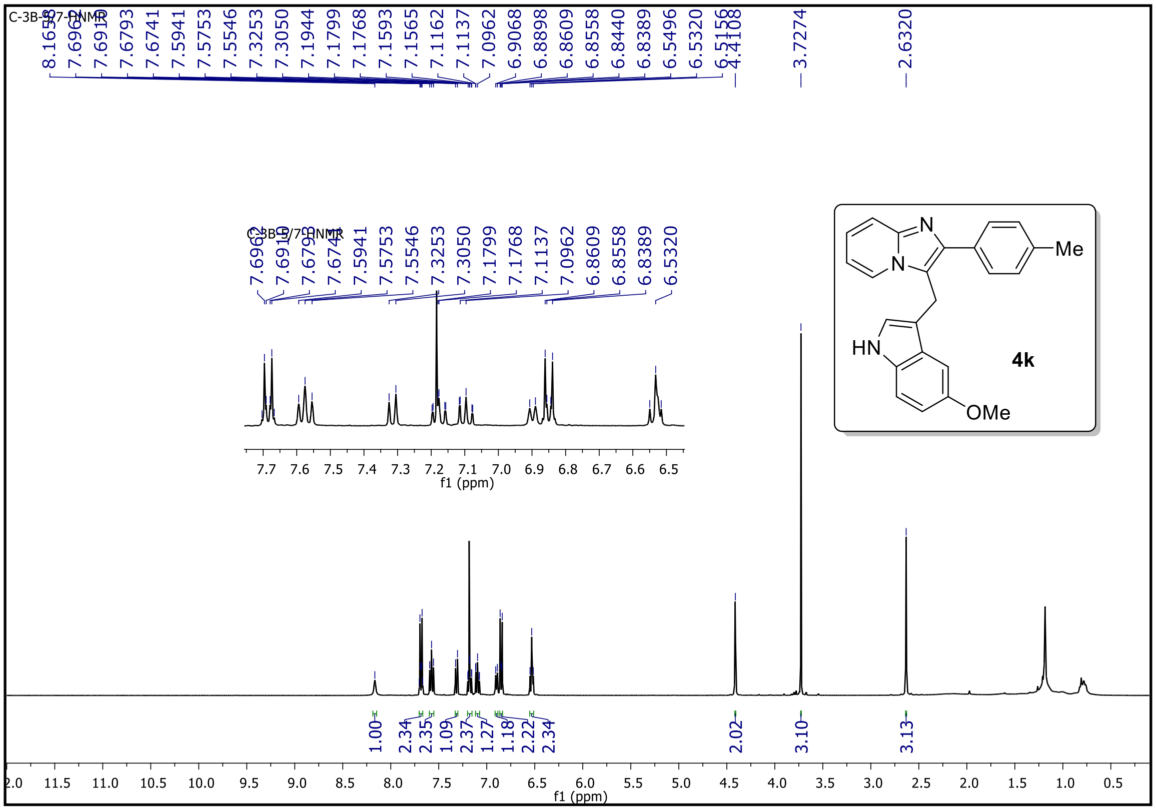
^{1}H NMR spectrum of compound **4j**



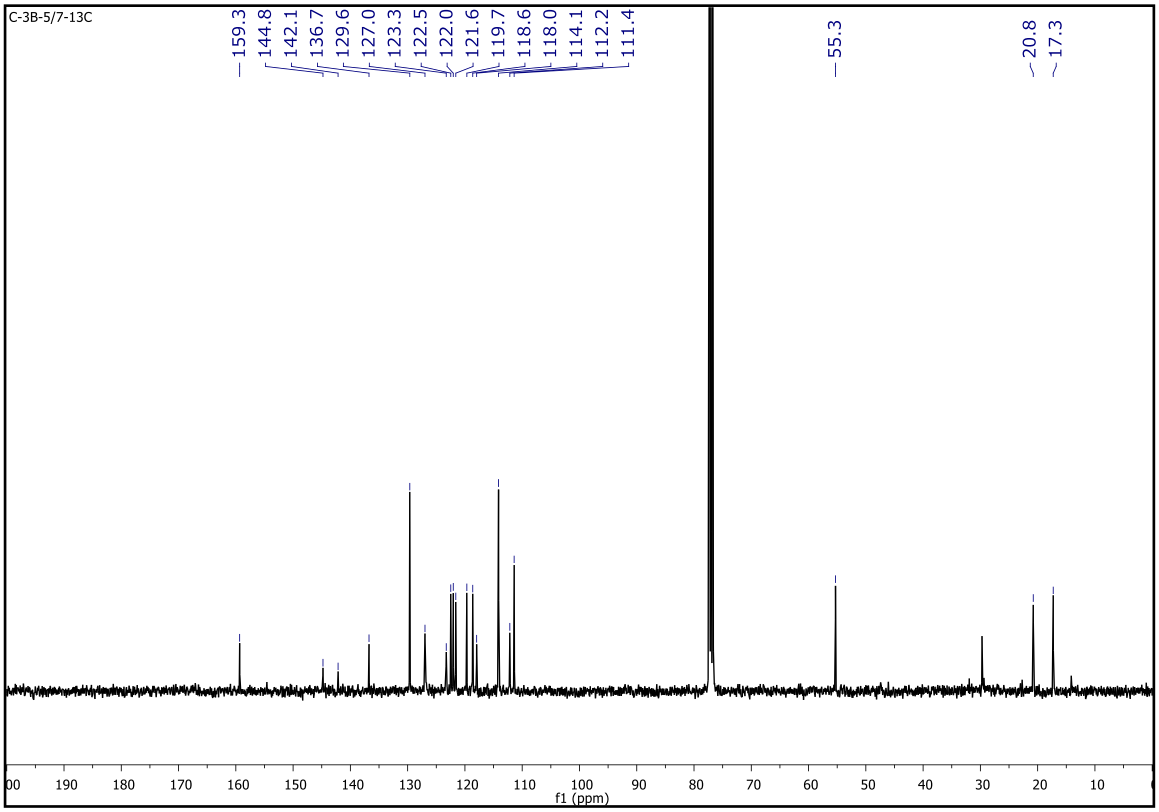
^{13}C NMR spectrum of compound **4j**



Mass spectrum of compound **4j**



^{1}H NMR spectrum of compound **4k**



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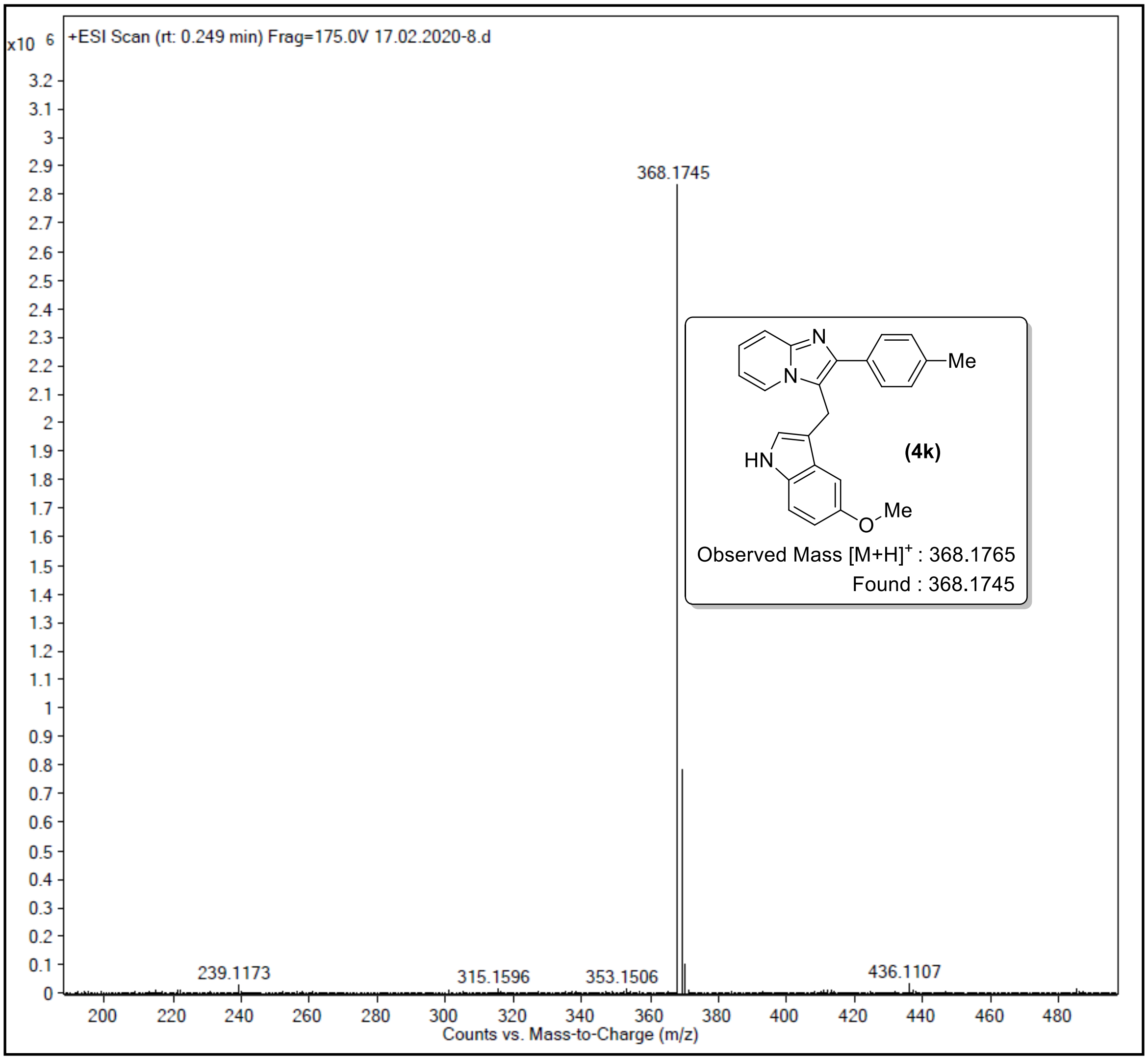
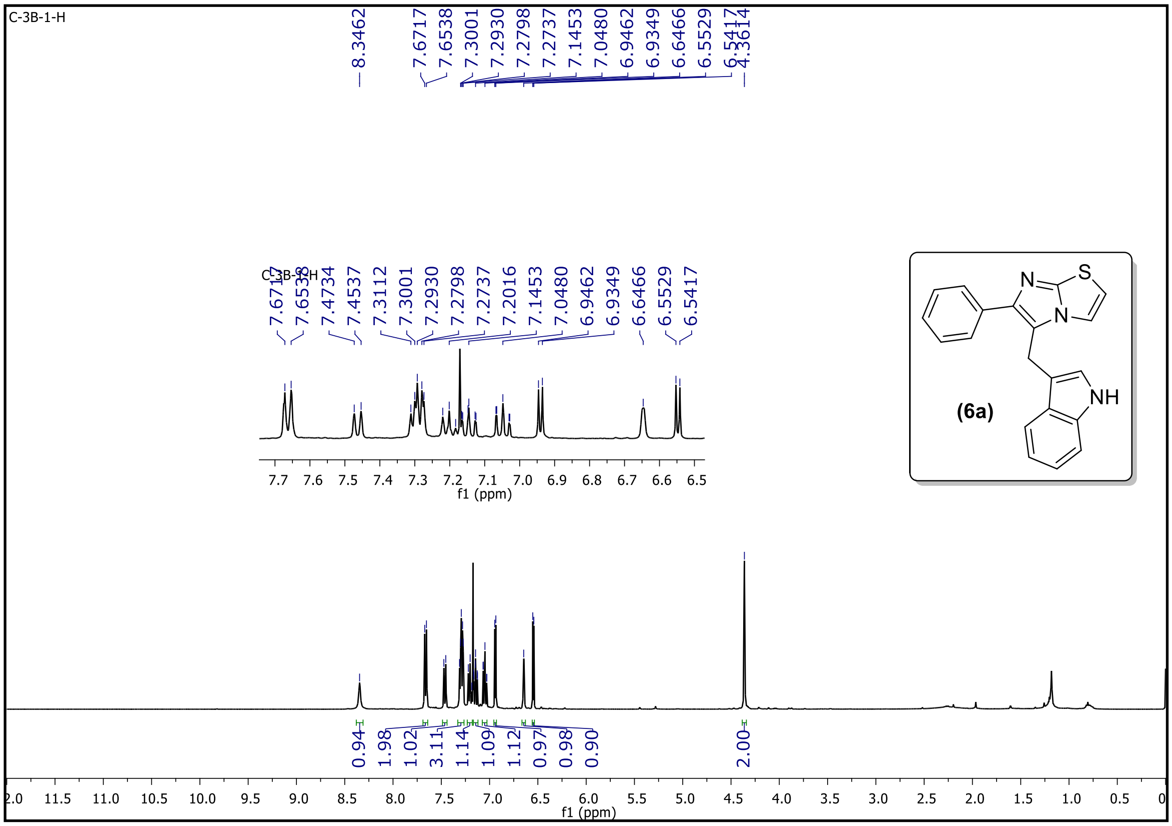
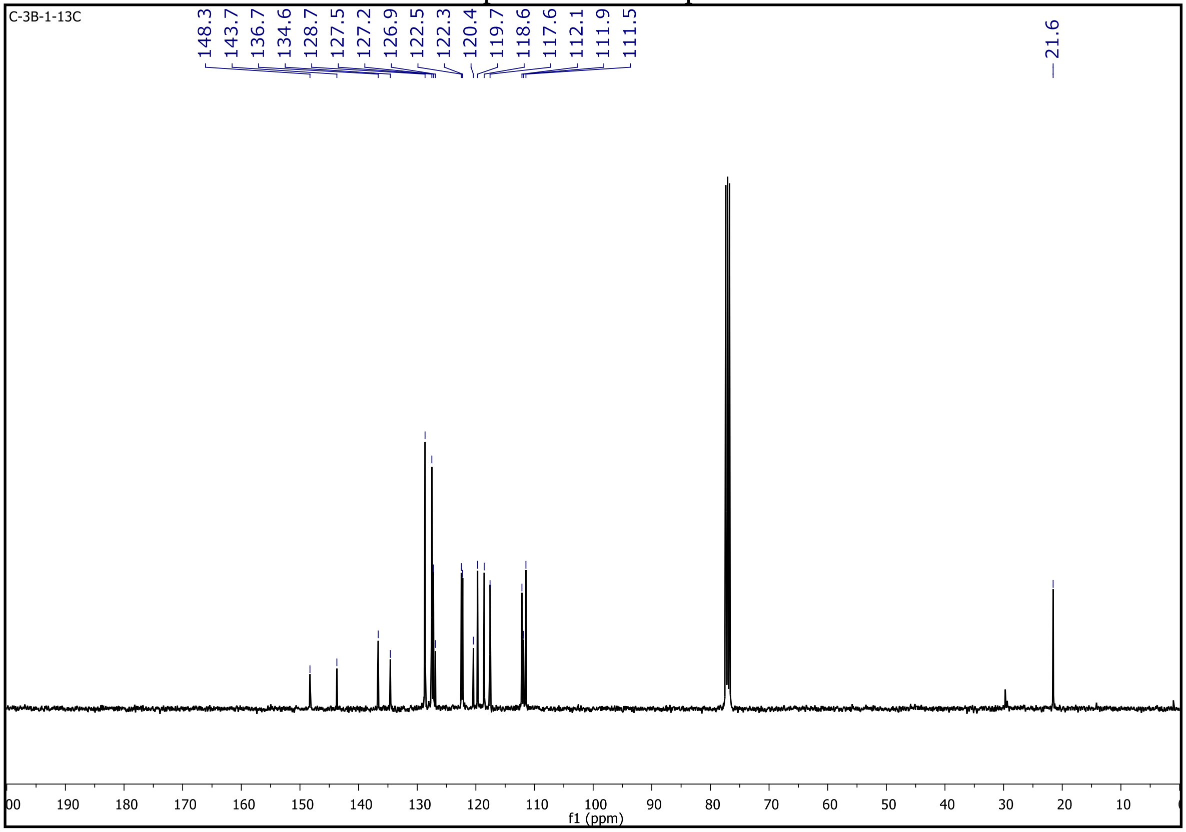


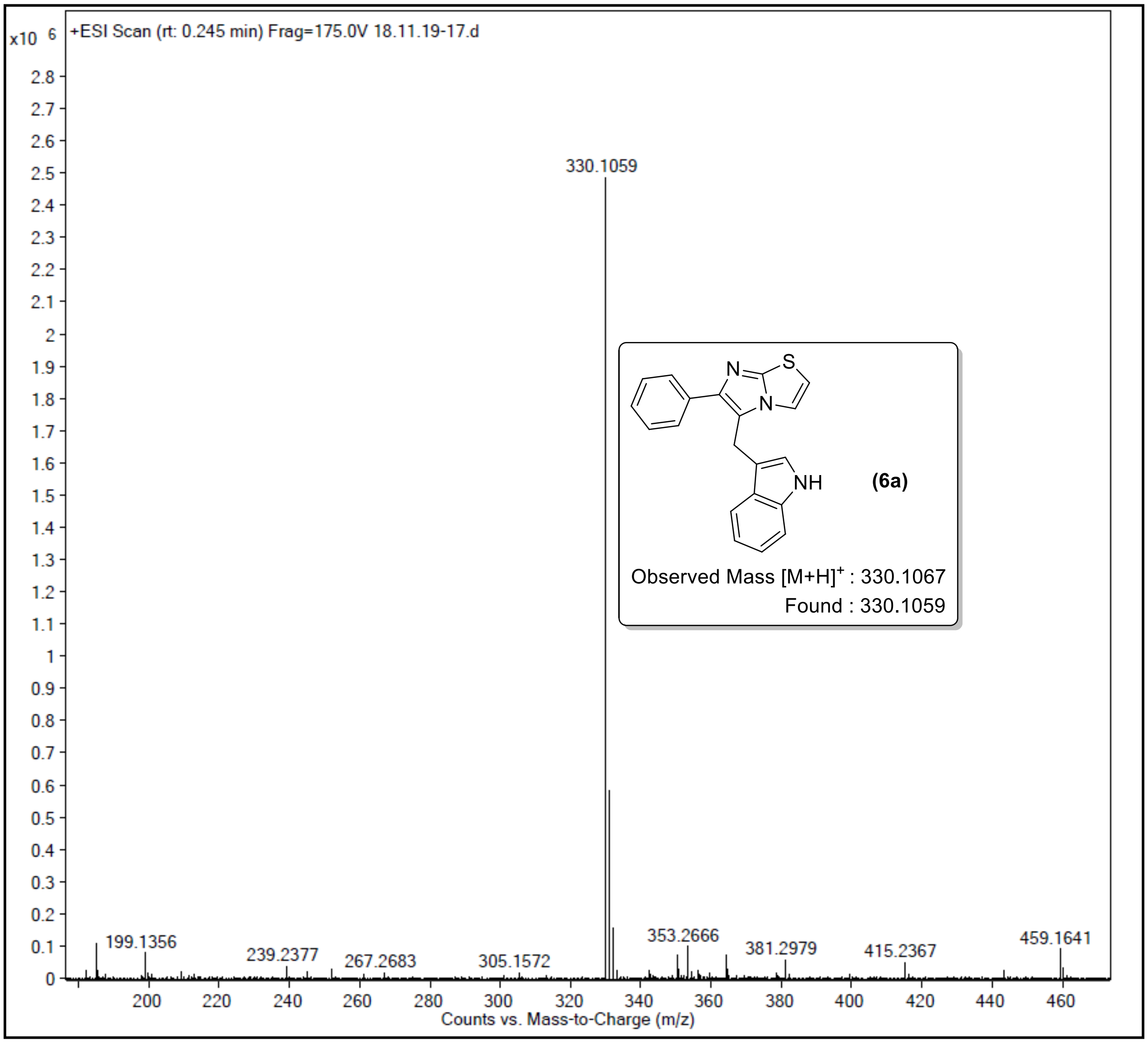
Mass spectrum of compound **4k**



^{1}H NMR spectrum of compound **6a**

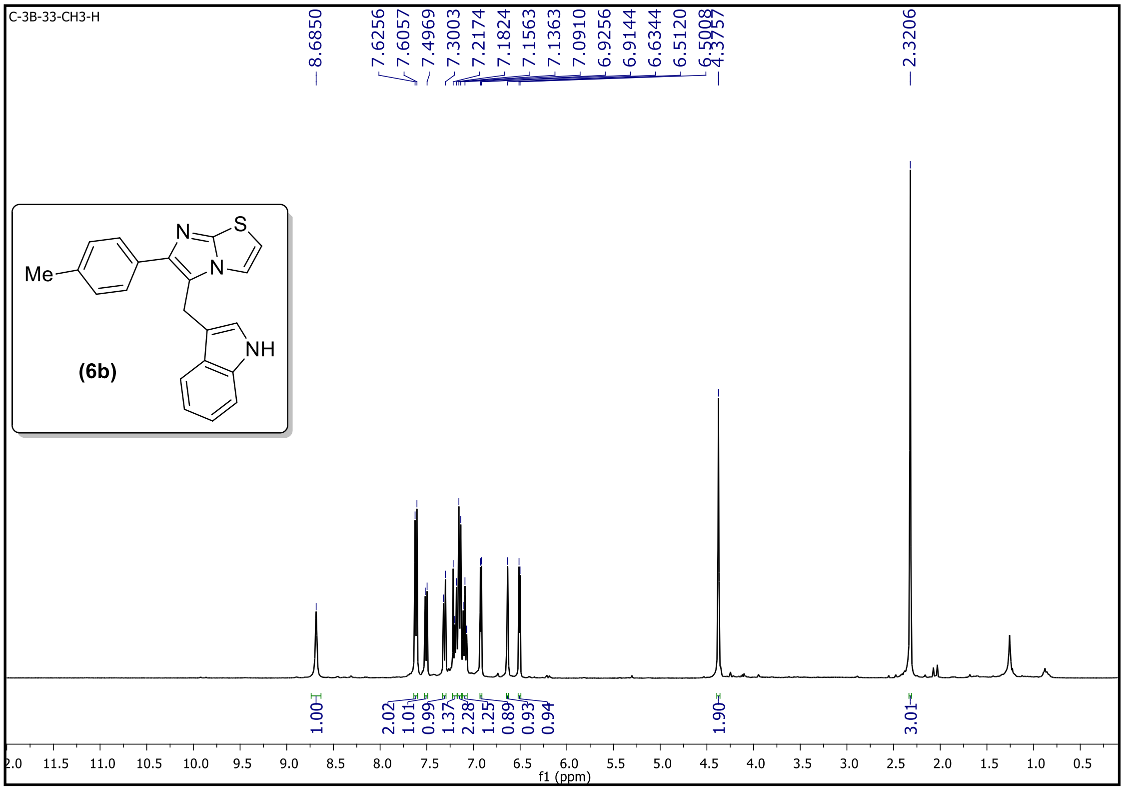


^{13}C NMR spectrum of compound **6a**

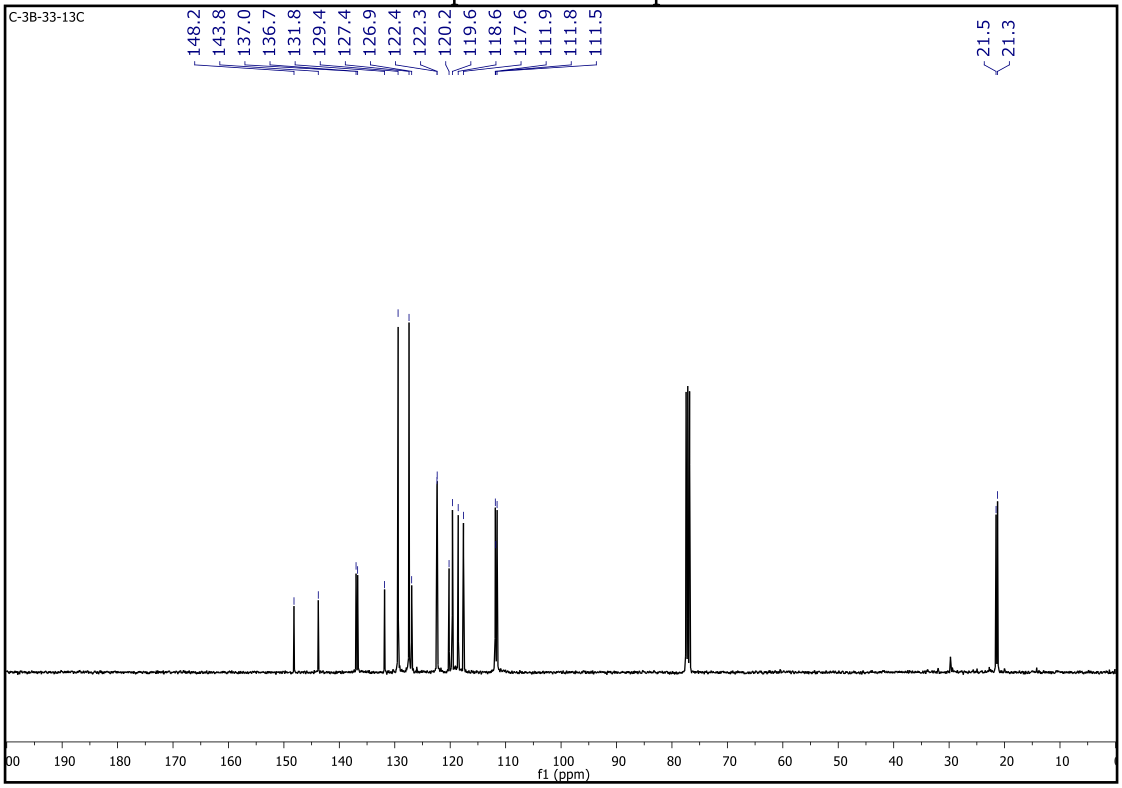


Observed Mass $[M+H]^+$: 330.1067
Found : 330.1059

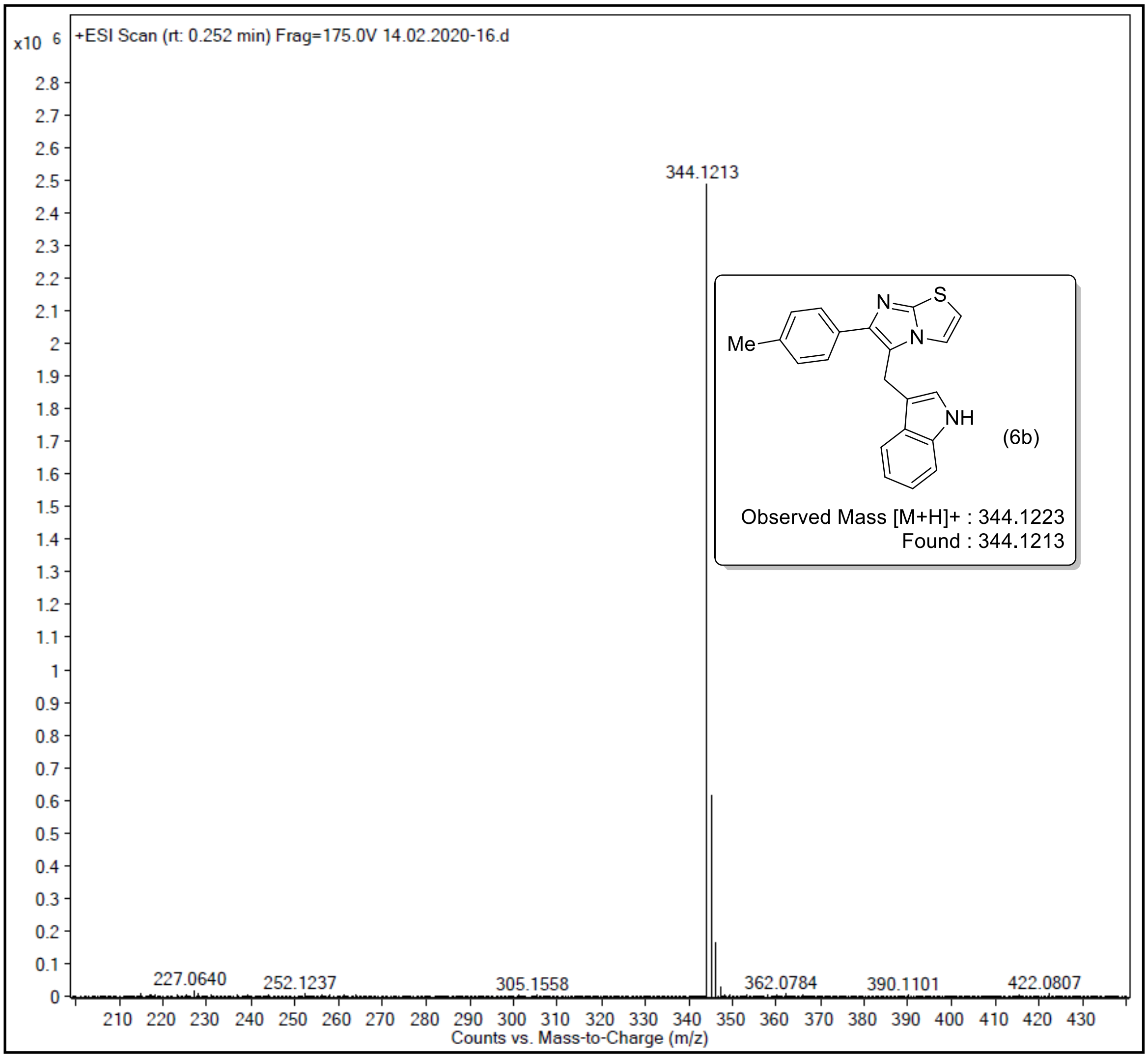
Mass spectrum of compound **6a**



^{1}H NMR spectrum of compound **6b**



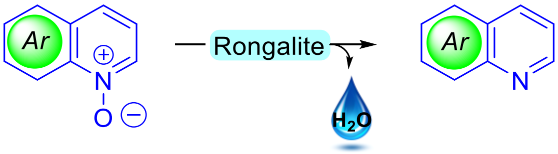
^{13}C NMR spectrum of compound **6b**



Mass spectrum of compound **6b**

CHAPTER-IV

Facile Metal-Free Deoxygenation of Aromatic Amine *N*-Oxides Using Rongalite



4.1. Introduction

The chemoselective deoxygenation of organic compounds like heteroaromatic *N*-oxides and sulfoxides are of paramount importance due to the formation of intermediates with enormous applications in asymmetric synthesis and it is one of the remarkable area in the synthetic organic chemistry for synthesis of functionalized heterocycles.[1] Tremendous attention has been devoted to the development of the field of chemistry dealing with *N*-Oxides in the recent decades.[2] Due to the presence of more electron density on the oxygen atom and weak bonding between nitrogen and oxygen (N-O), it is extensively used as oxidant of alkynes catalyzed by transition metal complexes such as Au, Pt, Pd, etc.[3] These amine *N*-oxides are found to have enormous applications, for instance, it can be used as an oxidants, intermediates, starting material, ligands, directing groups and organo catalyst in synthetic chemistry.[4]

Also these are acquitting as Lewis base in nature for directing the functional groups and it allows the alternative C-H activation strategy using this as directing group metal catalyzed C-H functionalization of their alternatives.[5] *N*-Oxide shows wide range of applications in the synthetic and heterocyclic chemistry including the functional group interconversions, alkylation (using alkylating reagents) and benzylation (direct cross coupled with the toluene derivatives).[6a-g] Furthermore direct amination, sulfonylation and chlorination on the quinolone *N*-oxide or pyridine *N*-oxide can also be carried out under mild conditions.[7] Sometimes C-8 selective coupling may also occur because of the formation of heteroaryl-heteroaryl bond.[8] This is the significant strategy to obtain homo and heterodimeric motifs involving it as a catalyst in the reaction,[9] in material sciences,[10] and in drug discovery.[11] The chemical interactions between nitrogen and oxygen atoms in *N*-oxide are very significant in terms of reactivity and these *N*-oxides have gained appreciable attention in the field of drug metabolism, medicinal and pharmaceutical industry.[12]

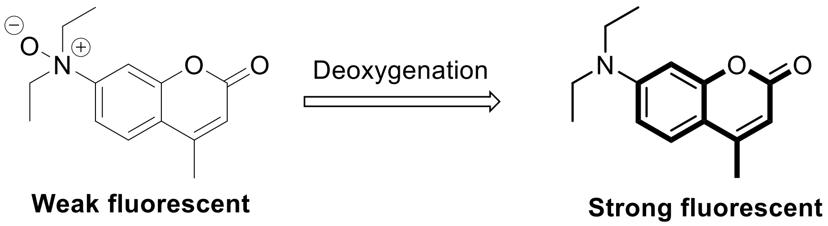


Figure 4.1. Deoxygenation of *N*-oxide Promoted turn-on Fluorescent Probe.

Recently, fluorescent probes which are based on deoxygenation of *N*-oxide for their sensing in their non-metal and metal species allied in their biological assay[12a-c] as shown in the Figure 4.1.[13]

Wilson et al. reported *N*-oxide based pharmaceutical agents, where by these molecules are recommended as less toxic prodrug for the treatment of cancer. In this protocol the active *N*-oxide based drug undergoes chemoselective deoxygenation by metabolic reduction to release the naked drug to cure the diseases (Figure 4.2)[14]

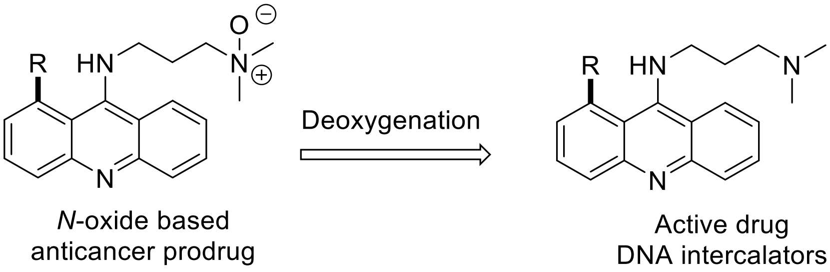


Figure 4.2. *N*-oxides Based Anticancer Prodrugs.

N-oxides can be used as an efficient substrates to introduce regioselective functionalization on those which cannot accomplish directly on their parent heterocyclic molecules.[15] Also, *N*-oxides are very important precursors in the synthetic functional group transformations and modification of their structures which not accessible by any other methods and also they could serve as reagent for protecting some functional groups, oxidations, and metal-ligand complexes.[16]

In particular, quinolines, isoquinolines, and pyridine derivatives would play an immense role in the organic synthesis, material sciences, industrial, agricultural, as a catalyst, pharmaceutical, and medicinal chemistry.[17] Generally the pyridine containing components play a vital role in the numerous pharmaceutical, agricultural, and drug deliver products. These are often found in variety of naturally available compounds, like pyridoxine, niacin, alkaloids and NADPH/NADP.[18] Along with pyridines, quinoline derivatives also received much importance from both the synthetic and industrial domain.[19] For instance, the drug nalidixic acid is an antibiotic drug which can be used for the treatment against the gram +ve and gram –ve bacteria.[20] The quinine is quinolines derivative which occur naturally and it has broadly used in the malaria treatment.[21] One of *N*-heterocyclic quinoline and its derivatives is well acknowledged by the biological as well as synthetic chemists and this moiety possess wide applications as pharmaceuticals and drugs.[22] In this class of quinolines, pyranoquinolines are well known feminine compounds which constitute the basic scaffolding of alkaloids of their biological importance (Figure 4.3).[23-25]

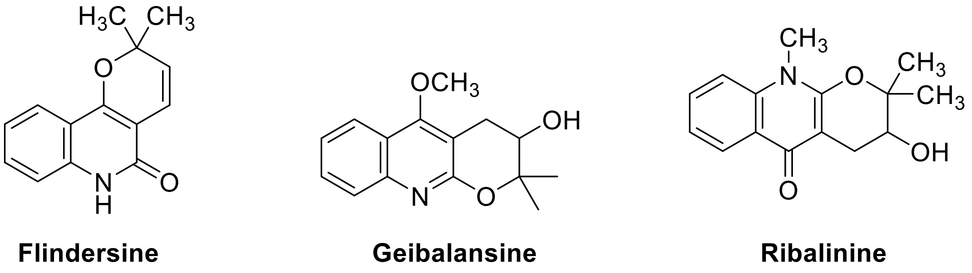


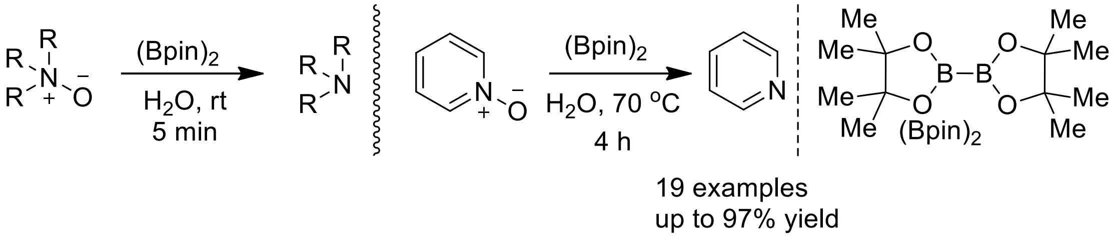
Figure 4.3. Importance of Quinolines.

Due to great synthetic applications of *N*-oxides, deoxygenation of the amine *N*-oxides after the required transformation is obvious and crucial to get the parent compounds. There are many known ways available for the synthesis of *N*-oxides from their corresponding amines, which mostly includes peracids and metal-based oxidations.[26-27]

Thus selective and mild deoxygenation of the amine *N*-oxide transformation is significant not only in synthetic organic chemistry, but also in biology and their drug metabolism.[28] Also the chemo selective reduction to amine transformation is a very eminent transformation in the presence of other functional group for the preparation of nitrogenous heterocyclic aromatic compound.[29] To achieve this conversion of *N*-oxide to amine there are some conventional methods which includes, trivalent phosphorous compounds,[30a] baker's yeast,[30b] sulphur based compounds.[31]or employ use of some excess metals such as Zn or Fe.[32] Additionally, some of catalytic procedures have also been developed utilizing transition metals in presence of H_2 gas.[33]

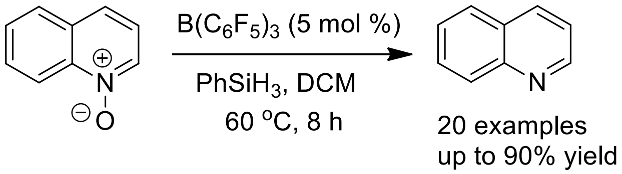
4.2. Reported Methods for the Deoxygenation of *N*-Oxides to Amines

Kokatla et al. developed a methodology for the facile reduction of amine *N*-oxide using diborane reagents in excellent yields in water. In this method reduces alkylamino and aniline *N*-oxides occure extremely fast, where as pyridyl-*N*-oxides undergo slower reduction. The reaction is tolerant of a wide variety of functionalities such as hydroxyl, thiol, and cyano groups, as well as halogens (Scheme 4.1).[34]



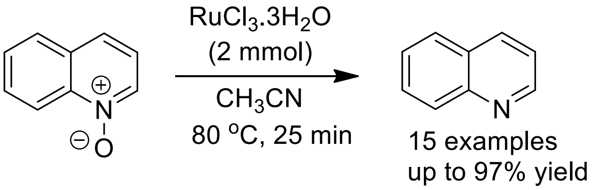
Scheme 4.1

Ding et al. developed an efficient strategy based on the Lewis acid promoted *N*-oxide deoxygenation using the $B(C_6F_5)_3$ with the help of reducing agent, hydro silanes. This methodology is applicable for the aromatic *N*-oxide to corresponding aromatic products in good yields (Scheme 4.2).[35]



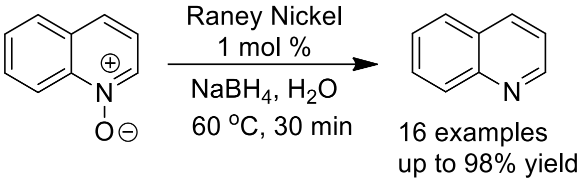
Scheme 4.2

Sandhu and research group reported an efficient method for the deoxygenation of *N*-oxides, such as *N*-arylnitrone, *N*-heteroarene, azoxybenzene *N*-oxides using the ruthenium (III) chloride to get their corresponding reduced products in good to moderate yields (Scheme 4.3).[36]



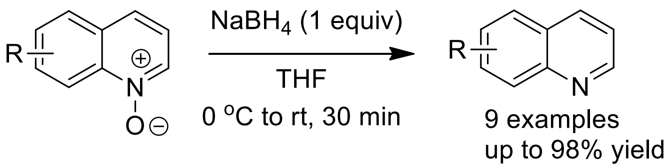
Scheme 4.3

Ramakrishna and research group studied an efficient transformation of aromatic and aliphatic *N*-oxide to their respective amines using raney nickel with sodiumborohydride in water as solvent (Scheme 4.4).[37]



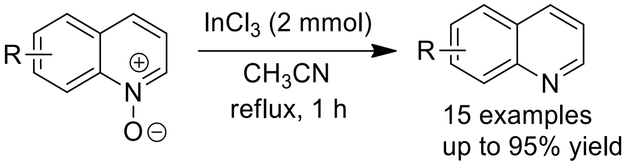
Scheme 4.4

Iyengar and research group investigated the process for deoxygenation of the heteroaromatic *N*-oxides to their respected amines using LiCl/ $NaBH_4$ (Scheme 4.5).[38]



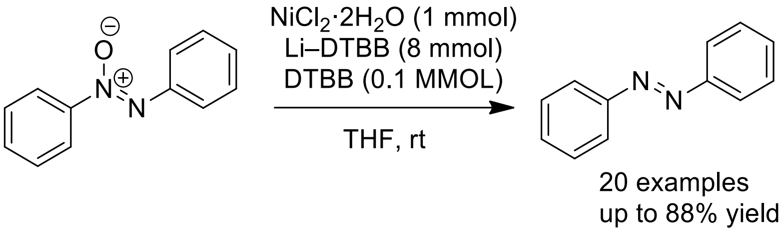
Scheme 4.5

Sandhu and research group scrutinized the process of deoxygenation of *N*-oxides, such as azaxybenzenes, *N*-heteroarenes, *N*-arylnitrones, *N*-oxides to their corresponding amines by using indium trichloride at ambient temparatures in acetonitrile solvent and it obtained good to moderate yields (Scheme 4.6).[39]



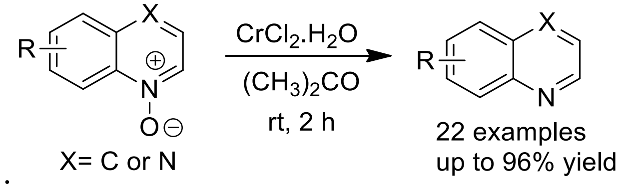
Scheme 4.6

Yus et al. examined the reduction properties of amine *N*-oxides, azo, azoxy compounds, and some aromatic hydrazines using catalytic amount of nickel salt with 4,4'-di-*tert*-butylbiphenyl (DTBB) in THF solvent to produce their amine in excellent yields (NiCl2 2H2O-Li-DTBB). (Z)-1,2-diphenyldiazene 1-oxide (Scheme 4.7).[40]



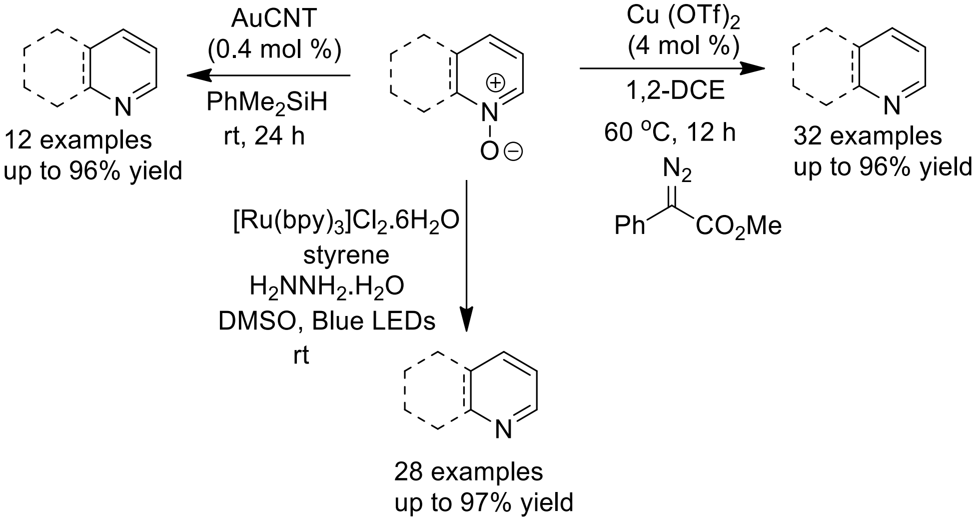
Scheme 4.7

Akita et al. developed a chromium-based reagent for deoxygenation of amine *N*-oxides of pyrazine, pyridine, quinolines using chromium (II) chloride to get good to excellent yields acetone used as solvent (Scheme 4.8).[41]



Scheme 4.8

Recent past has witnessed that the methodologies based on ruthenium, copper and gold catalytic system are emerging for the deoxygenation of *N*-oxides to give better yield and TON.



Scheme 4.9

Reduction of N-O bonds also reported with the help of Cu triflates, Gold nano particle, and Ru/Ir based photocatalyst to producing the desired free amines in good to excellent yields (Scheme 4.9).[42]

Literature survey reveals that all the transformation of the amine *N*-oxide to their corresponding amine in the proceedings has potential application in organic synthesis. Despite of the availability of various methods for this transformation many of them encumbered with functional group incompatibility problems i) stoichiometric amounts of reagents, ii) use of transition metals, iii) use of PPh_3, PCl_3, iv) less functional compatibility, v) tedious workup procedures.

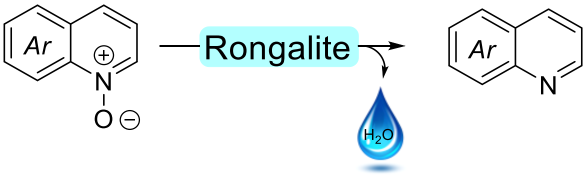
Hence, a simple, mild and inexpensive method for the selective conversion of amine *N*-oxides to the corresponding amines continues to be synthetically desirable.

4.3. Present Study

Chapter 4 describes the development of a novel method to convert the amine *N*-oxides to their respective amines under mild reaction conditions. In the present investigation an attempt has been made to introduce a green, commercially less expensive, non-hazardous and easily available reducing agent rongalite for the N-O reduction.

4.3.1. Results and Discussion

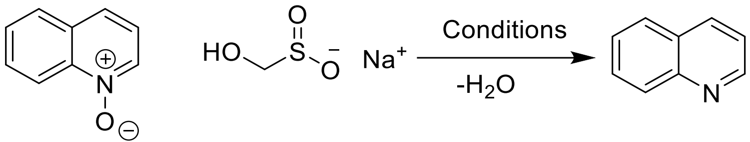
En route to the development of reduction of amine *N*-oxides to their respected amines with rongalite is depicted in the scheme 4.10.



Scheme 4.10

To examine our proposed method for *N*-O reduction with rongalite, we have started with quinoline *N*-oxides **1a** along with rongalite **2** in acetonitrile at room temperature and results are presented in table 4.1.

Table 4.1. Optimization of Reaction Condition for the Deoxygenation of *N*-oxides.[a]



1a **2** **3a**

Entry	Solvent	Rongalite (equiv)	Temperature (°C)	Time (h)	Yield (%)[b]
1.	CH_3CN	--	rt	12	n.d[c]
2.	CH_3CN	1.0	rt	12	n.d
3.	CH_3CN	1.0	70	10	30
4.	CH_2Cl_2	1.0	45	10	n.d
5.	$CHCl_3$	1.0	65	6	n.d
6.	DCE	1.0	70	10	20
7.	THF	2.0	70	12	10
8.	Toluene	1.0	80	8	30
9.	CH_3NO_2	1.0	70	10	n.d
10.	MeOH	1.0	70	6	30
11.	EtOH	1.0	70	6	30
12.	DMSO	1.0	70	8	50
13.	DMF	1.0	80	10	65
14.	DMF	1.5	80	10	70
15.	DMF	2.0	80	8	85
16.	DMF	3.0	80	8	85

[a] All the reactions were conducted on a 1 mmol scale of **1a** (1 mmol) and **2** (2 mmol) in 2 mL of solvent otherwise mentioned. [b] Yield where reported is of isolated and purified product. [c] Not Detected.

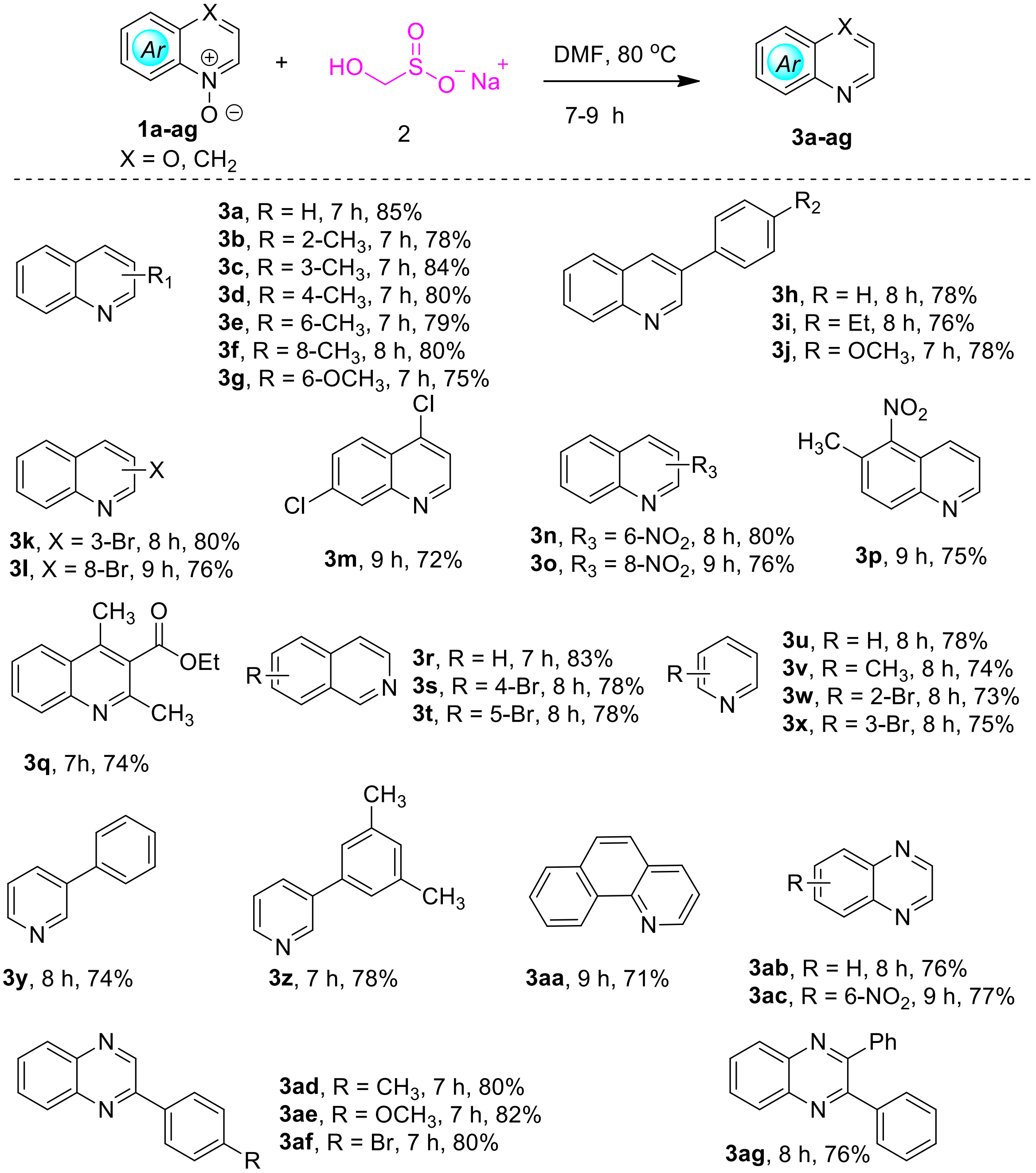
In the beginning, we have not observed any progress in the reaction (monitored by TLC) even after stirring the reaction mixture at room temperature for 12 h. But the formation of product was observed at 70 ^{o}C and gave desired product quinolone **3a** in 30% yield (Table 4.1 entry 3), this could be attributed by the release of electron from the rongalite under heating.[43]

The compound **3a** was confirmed by NMR and Mass spectral data. The above result motivated us to optimise reaction condition to improve the yield of the products. Later, we have concentrated on the effect of reaction medium on product yield, to test this we have then conducted reactions in a library solvent starting from nonpolar to polar solvent for the betterment of product yields. Except DMSO, all other solvents gave inferior results (Table 4.1, entries 4-12). Notably, the reaction in DMF gave better N-O reduction product in 65% compare to other solvents (Table 4.1, entry 13). Further we have studied the stoichiometric ratio of rongalite surprisingly, higher amounts of rongalite furnished titled product in 85% yield. (Table 4.1, entries 14-15). Further increamnt of reducing agent rongalite did not improve the yield of the product (Table 4.1, entry 16). Thus, DMF is found to be a best reaction medium among all the solvents tested to produce title compound in excellent yield (Table 4.1, entry 15).

After having the optimized reaction conditions at hand, we have moved to the check the compatibility of various pyridine *N*-oxides, other aromatic *N*-oxides with the demonstrated method. All that *N*-oxides were reduced and produced their corresponding amines in good to excellent yields (70-85%) in 6-10 h at 80 ^{o}C showed in Table 4.2. The substrates which have electron donating groups such as CH_3, OCH_3, were well tolerated to undergo the reduction with rongalite (Table 4.2, **3a-3g**). Nitro substitution on aromatic *N*-oxides also participated in reduction process to obtain the respective pyridines in good to excellent yields (Table 4.2, **3n-3p**), also substituted phenyl groups on quinoline also produced good yields (Table 4.2, **3h-3j**).

It is worth mentioning that, halogen containing *N*-oxides are readily deoxygenated without further dehalogenation, (Table 4.2, **3k-3l**). steric crowding by two chlorine atoms does not deter their reduction and also the steric crowding by disubstitution on *N*-oxides does not deter the reduction (Table 4.2, **3m**) although quinoline carboxylate gave good yield (Table 4.2, **3q**). Interestingly, isoquinoline *N*-oxides also participated in the process to give the parent molecules in excellent yields (Table 4.2, **3r-3t**), Notably, N-O bond of less reactive pyridine and quinoxaline *N*-oxides also cleaved under this condition to obtain reduced products in excellent yields (Table, **3u-3ag**). All the reduced amines were characterized by ^{1}H, ^{13}C NMR and mass spectral data.

Table 4.2. Library of Synthesised Deoxygenated Products.[a,b]



3a, R = H, 7 h, 85%
3b, R = 2-CH_3, 7 h, 78%
3c, R = 3-CH_3, 7 h, 84%
3d, R = 4-CH_3, 7 h, 80%
3e, R = 6-CH_3, 7 h, 79%
3f, R = 8-CH_3, 8 h, 80%
3g, R = 6-OCH_3, 7 h, 75%

3h, R = H, 8 h, 78%
3i, R = Et, 8 h, 76%
3j, R = OCH_3, 7 h, 78%

3k, X = 3-Br, 8 h, 80%
3l, X = 8-Br, 9 h, 76%

3m, 9 h, 72%

3n, R_3 = 6-NO_2, 8 h, 80%
3o, R_3 = 8-NO_2, 9 h, 76%

3p, 9 h, 75%

3q, 7h, 74%

3r, R = H, 7 h, 83%
3s, R = 4-Br, 8 h, 78%
3t, R = 5-Br, 8 h, 78%

3u, R = H, 8 h, 78%
3v, R = CH_3, 8 h, 74%
3w, R = 2-Br, 8 h, 73%
3x, R = 3-Br, 8 h, 75%

3y, 8 h, 74%

3z, 7 h, 78%

3aa, 9 h, 71%

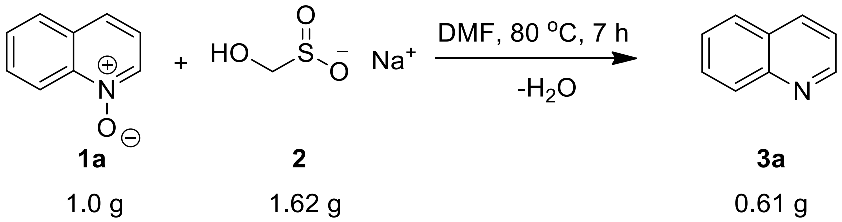
3ab, R = H, 8 h, 76%
3ac, R = 6-NO_2, 9 h, 77%

3ad, R = CH_3, 7 h, 80%
3ae, R = OCH_3, 7 h, 82%
3af, R = Br, 7 h, 80%

3ag, 8 h, 76%

[a] All the reactions were conducted on a mmol scale of **1 a-ag** (1 mmol), **2** (2 mmol) and in DMF solvent (2 mL), otherwise mentioned. [b] Yield where reported is of isolated and purified product.

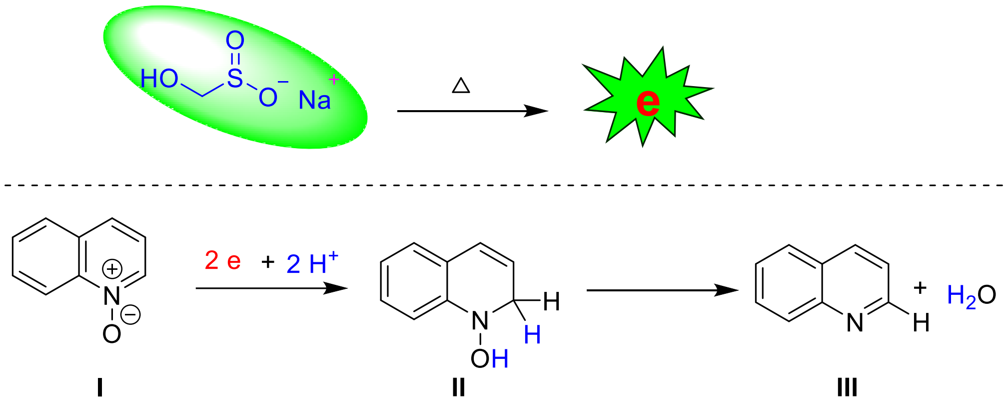
We have then focused on applying the optimized condition for the gram scale. We carried out a reaction on quinoline *N*-oxide (1g, 6.88 mmol), and rongalite (1.62g, 13.71 mmol) which were dissolved in DMF solvent (10 mL) and stirred at 80 °C for 7 hours and obtained **3a** in 70% yield (0.61g, Scheme 4.11).



Scheme 4.11

4.3.2. Reaction Mechanism

The plausible reaction mechanism pathway is proposed for the chemoselective reduction of amine *N*-oxide based on the literature reports and experimental observations. In the first step, rongalite decomposes to release electrons under thermal condition, then these electron attacks at electrophilic centre at C-2 position in presence of protons to give intermediate **II**. Finally, the intermediate **II** converts to target amine up on dehydration (Scheme 4.12).



Scheme 4.12

4.4. Conclusion

In this chapter we have introduced a chemo-selective metal-free, non-hazardous and less expensive deoxygenation of *N*-oxides using rongalite. From this method a library of **33** compounds were synthesized with wide variety of functional groups. This method is amicable with most of the functional groups and able to produce end products in good to excellent yields.

4.5. Experimental Section

4.5.1. General Information

All the starting materials pyridines, quinolones, isoquinolines, quinoxolines rongalite was purchased from Spectrochem, SD-Fine, Sigma-Aldrich, Finar, and SRL. All the used reagents are analytical grade and were directly used without any further purification. The *N*-oxide compounds are prepared using reported methods.[26] All the solvents used for this method was obtained from Finar. For reaction monitoring TLC-Silica gel 60 GF_{254} were used with help of UV-Cabinet. Purification of compounds using column chromatography where performed with the Rankem silica gel (100-200 mesh). Melting point for solid compounds was recorded using Stuart SMP30 melting point apparatus. FT-IR spectra recorded on Perkin Elmer IR Spectrometer. ^{1}H and ^{13}C NMR spectral data of all the synthesized compounds were recorded on Bruker AVANCE HD (400 MHz / 100 MHz) spectrometer with using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The data of the compounds was recorded as chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations for the multiplicity as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. The mass spectrum analysis was recorded in Bruker- micro-TOF MS analyser.

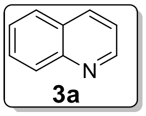
4.5.2. General Procedure for the Deoxygenation of Amine *N*-oxide to Amine (3a-3ag)

To a clean and oven dried round bottom flask amine *N*-oxide **1a** (150 mg, 1.0 mmol) and rongalite **2** (244 mg, 2.0 mmol) were added in DMF solvent (2 mL). The reaction mixture was allowed to stir at 80 °C for 6-8 hours. After completion of reaction (monitored by TLC) the reaction mixture was transferred into an ice-cold water and extracted by using ethyl acetate (10 mL x 3) and dried over anhydrous sodium sulphate, filtered again evaporated under reduced pressure. The crude mixture was purified on column chromatography using silica-gel (60-120 mesh) by eluting with ethyl acetate/ hexanes solvents mixture.

4.8. Characterization Data of Products

Quinoline (3a)[50]

Yield: 85%, colourless liquid.

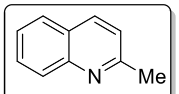


3a

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.93 (dd, J = 4.1, 1.6 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.40 (dd, J = 8.3, 4.2 Hz, 1H).^{13}C NMR (100 MHz, CDCl$_3$) δ 150.4, 148.3, 136.1, 129.5, 128.3, 127.8, 126.6, 121.1.

2-Methylquinoline (3b)[42c]

Yield: 78%, colourless liquid.

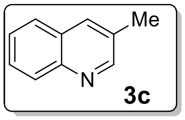


3b

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.0, 147.8, 136.2, 129.5, 128.5, 127.5, 126.5, 125.7, 122.0. 25.3. HRMS (ESI-TOF): m/z calcd for $C_{10}H_9N$ $[M+H]^+$ 144.0815, found 144.0817.

3-Methylquinoline (3c) [42c]

Yield: 84%, pale yellow liquid.

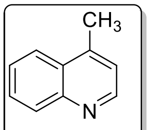


3c

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.79 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 2.54 (s, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 152.4, 146.5, 134.7, 130.5, 129.1, 128.4, 128.1, 127.1, 126.6, 18.7.

4-Methylquinoline (3d) [42c]

Yield: 80%, yellow liquid.



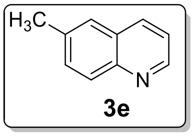
3d

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.68 (d, J = 4.3 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 4.1 Hz, 1H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.1, 147.9, 144.4, 129.9, 129.1, 128.3, 126.3, 123.8, 121.9, 18.6.

6-Methylquinoline (3e)[42c]

Yield: 79%, wine red liquid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.85 (d, J = 2.7 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 11.3 Hz, 2H), 7.36 (dd, J = 8.2, 4.2 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.5, 146.8, 136.4, 135.4, 131.8, 129.1, 128.3, 126.6, 121.1, 21.6.

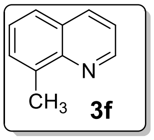


3e

8-Methylquinoline (3f)[45]

Yield: 80%, yellow liquid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.86 (dd, J = 4.0, 1.5 Hz, 1H), 8.03 (dd, J = 8.2, 1.4 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 6.9 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.29 (dd, J = 8.2, 4.2 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.2, 147.3, 137.1, 136.4, 129.7, 128.3, 126.3, 125.9, 120.8, 18.2.

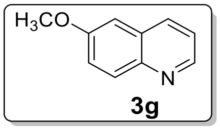


3f

6-Methoxyquinoline (3g)[46b]

Yield: 75%, pale yellow liquid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.75 (s, 1H), 8.00 (d, J = 9.0 Hz, 2H), 7.39 – 7.27 (m, 2H), 7.04 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 157.3, 147.8, 142.6, 135.2, 130.5, 129.5, 122.0, 105.8, 55.9.

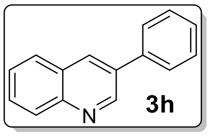


3g

3-Phenylquinoline (3h)[49]

Yield: 78%, gummy material.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.11 (s, 1H), 8.22 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.2 Hz, 3H), 7.51 (d, J = 7.5 Hz, 1H), 7.45 (t, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.9, 147.3, 137.9, 133.3, 129.5, 129.2, 128.2, 128.1, 127.5, 127.1.

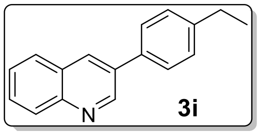


3h

3-(4-Ethylphenyl)quinolines (3i)[49]

Yield: 76%, Pale yellow solid, M.P. 86-88 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.07 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.57 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.45 – 7.40 (m, 1H), 7.22 (d, J = 8.1 Hz, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.18 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.9, 147.1, 144.4, 135.1, 133.8, 132.9, 129.3, 129.1, 128.7, 128.1, 128.0, 127.3, 127.0, 28.6, 15.6.

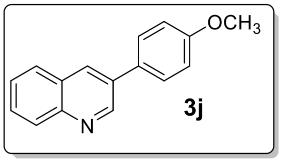


3i

3-(4-Methoxyphenyl)quinolines (3j)[49]

Yield: 78%, Pale yellow solid, M.P. 85-87 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 2.1 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 149.7, 146.9, 133.5, 132.5, 130.2, 129.1, 128.5, 128.1, 127.9, 127.0, 114.7, 55.4.

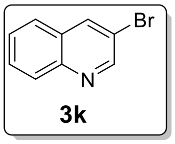


3j

3-Bromoquinoline (3k)[42c]

Yield: 80%, yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 2.0 Hz, 1H), 8.31 (d, J = 1.4 Hz, 1H), 8.09 (d, J = 8.9 Hz, 1H), 7.73 (t, J = 7.5 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 146.3, 137.3, 129.8, 129.5, 129.1, 127.7, 127.0, 117.1. HRMS (ESI-TOF): m/z calcd for $C_{10}H_9N$ $[M+H]^+$ 144.0815, found 144.0817.

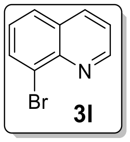


3k

8-Bromoquinoline (3l)[46a]

Yield: 76%, colourless oily liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 2.6 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.39 (dd, J = 8.2, 4.2 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 145.2, 136.7, 133.2, 129.6, 127.8, 127.1, 124.7, 121.9.

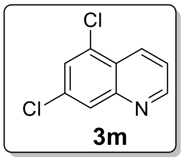


3l

4,7-Dichloroquinoline (3m)[50]

Yield: 72%, colour less solid, M.P. 79-81°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 4.7 Hz, 1H), 8.16 (dd, J = 15.0, 5.4 Hz, 2H), 7.60 (dd, J = 9.0, 2.0 Hz, 1H), 7.49 (d, J = 4.7 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 149.3, 142.9, 136.6, 128.7, 128.6, 125.6, 125.0, 121.4. HRMS (ESI-TOF): m/z calcd for $C_9H_5Cl_2N$ $[M+H]^+$ 197.9879, found 197.9889.

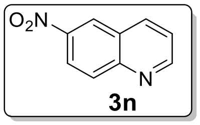


3m

6-Nitroquinoline (3n) [47]

Yield: 75%, yellow solid, M.P. 150-152 °C.

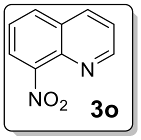
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (dd, J = 4.1, 1.4 Hz, 1H), 8.74 (s, 1H), 8.42 (dd, J = 9.2, 2.3 Hz, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.20 (d, J = 9.2 Hz, 1H), 7.53 (dd, J = 8.3, 4.2 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 150.2, 145.6, 137.9, 131.4, 127.1, 124.6, 122.9, 122.9.



3n

8-Nitroquinoline (3o)[48]

Yield: 74%, yellow solid, M.P. 90-91 °C.

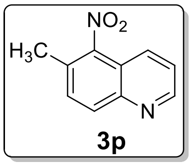


3o

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 2.7 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 7.9 Hz, 2H), 7.65 (t, J = 7.9 Hz, 1H), 7.59 (dd, J = 8.4, 4.2 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 139.5, 136.2, 132.1, 129.1, 125.3, 123.8, 122.8.

6-Methyl-5-nitroquinoline (3p)[51]

Yield: 75%, white crystalline solid, M.P. 114-116 °C.

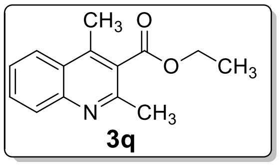


3p

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 3.0 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.48 (dd, J = 8.6, 4.2 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 146.4, 132.3, 131.8, 130.1, 129.2, 123.2, 120.4, 18.2. HRMS (ESI-TOF): m/z calcd for $C_{10}H_8N_2O_2$ $[M+H]^+$ 189.0666, found 189.0673.

Ethyl2,4-dimethylquinoline-3-carboxylate (3q)[52]

Yield: 74%, yellow sticky solid.

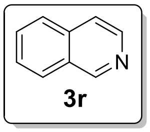


3q

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 2.74 (s, 3H), 2.68 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 154.3, 130.4, 128.8, 128.1, 126.6, 125.9, 124.1, 61.8, 23.4, 15.8, 14.3.

Isoquinoline (3r)[45]

Yield: 83%, yellow liquid.

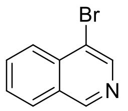


3r

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.44 (d, J = 5.8 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.55 (d, J = 5.8 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 142.9, 135.7, 130.6, 130.3, 128.6, 127.6, 127.2, 126.4, 120.4.

4-Bromoisoquinoline (3s)[53]

Yield: 78%, white solid, M.P. 42-45 °C.

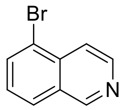


3s

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.10 (s, 1H), 8.65 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.6, 144.4, 135.0, 134.0, 129.6, 127.8, 127.4, 121.5, 119.4.

5-Bromoisoquinoline (3t)[42c]

Yield: 78%, White solid, M.P. 85-87 °C.

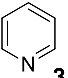


3t

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.18 (s, 1H), 8.58 (d, J = 6.0 Hz, 1H), 7.95 – 7.88 (m, 3H), 7.42 (t, J = 7.8 Hz, 1H) ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.7, 144.6, 134.7, 131.7, 129.7, 128.2, 127.9, 125.9, 119.7.

Pyridine (3u)[42b]

Yield: 78%, colourless liquid.

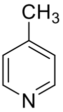


3u

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.61 (d, J = 4.2 Hz, 2H), 7.67 (tt, J = 7.8, 1.7 Hz, 1H), 7.27 (dd, J = 7.6, 5.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.7, 135.9, 123.7.

4-Methylpyridine (3v)[55]

Yield: 74%, colourless liquid.

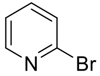


3v

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.45 (d, J = 5.8 Hz, 2H), 7.09 (d, J = 5.0 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.5, 147.0, 124.6, 20.9.

2-Bromopyridine (3w)[42b]

Yield: 73%, colourless liquid.

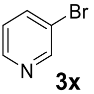


3w

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.31 (d, J = 4.5 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.21–7.17 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.5, 143.0, 139.7, 129.2, 123.7.

3-Bromopyridine (3x)[54]

Yield: 75%, Colourless liquid.

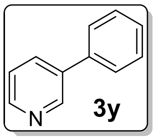


3x

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.62 (s, 1H), 8.46 (d, J = 4.0 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.14 (dd, J = 7.9, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.0, 147.8, 138.7, 124.8, 121.0.

3-Phenylpyridine (3y)[49]

Yield: 74%, pale yellow solid, M.P. 161-163 °C.

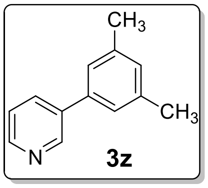


3y

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.78 (s, 1H), 8.52 (s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.40 (t, J = 7.1 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.4, 148.3, 137.8, 136.7, 134.43, 129.1, 128.1, 127.2, 123.6.

3-(3,5-Dimethylphenyl)pyridine (3z)[56]

Yield: 78%, yellow liquid.

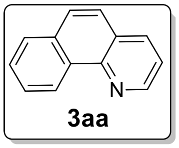


3z

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.75 (s, 1H), 8.49 (d, J = 4.1 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.27 (dd, J = 7.6, 4.9 Hz, 1H), 7.11 (s, 2H), 6.97 (s, 1H), 2.31 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.2, 148.1, 138.7, 137.8, 137.0, 134.5, 129.8, 125.1, 123.5, 21.4. HRMS (ESI-TOF): m/z calcd for $C_{13}H_{13}N$ [M+H]$^+$ 184.1128, found 184.1122.

Benzo[*h*]quinoline (3aa)[45]

Yield: 71%, white solid, M.P. 50-52 °C.

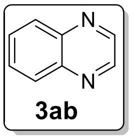


3aa

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.31 (d, J = 8.0 Hz, 1H), 9.01 (dd, J = 4.3, 1.6 Hz, 1H), 8.18 (dd, J = 8.0, 1.6 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.77 – 7.66 (m, 3H), 7.53 (dd, J = 8.0, 4.4 Hz, 1H).^{13}C NMR (100 MHz, CDCl$_3$) δ 148.7, 146.5, 136.0, 133.7, 131.4, 128.3, 127.9, 127.2, 126.5, 125.3, 124.4, 121.8.

Quinoxaline (3ab)[45]

Yield: 76%, wine red liquid.

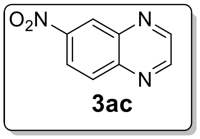


3ab

H NMR (400 MHz, CDCl$_3$) δ 8.84 (s, 1H), 8.11 (dd, J = 6.3, 3.3 Hz, 1H), 7.76 (dd, J = 6.3, 3.3 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.9, 142.9, 130.0, 129.41. HRMS (ESI-TOF): m/z calcd for $C_8H_6N_2$ [M+H]$^+$ 131.0611, found 131.0602.

6-Nitroquinoxaline (3ac)[57]

Yield: 77%, orange colour solid, M.P. 176-177 °C



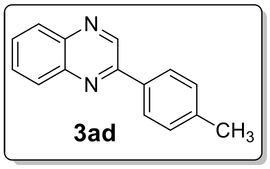
3ac

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.04 (dd, J = 4.6, 2.5 Hz, 3H), 8.57 (dd, J = 9.2, 2.4 Hz, 1H), 8.30 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.0, 147.7, 147.1, 145.4, 141.9, 131.4, 126.0, 123.5.

2-(*p*-Tolyl)quinoxaline (3ad)[58]

Yield: 80%, brown solid, M.P. 91-92 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.34 (s, 1H), 8.15 (dd, J = 19.7, 7.4 Hz, 4H), 7.82 – 7.74 (m, 2H), 7.40 (d, J = 7.5 Hz, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.2, 142.3, 141.3, 140.6, 133.9, 130.3, 129.9, 129.5, 129.4, 129.0, 127.5, 21.4. HRMS (ESI-TOF): m/z calcd for $C_{15}H_{12}N_2$ [M+H]$^+$ 221.1080, found 221.1076.

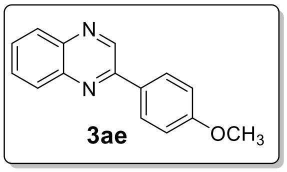


3ad

2-(4-Methoxyphenyl)quinoxaline (3ae)[58]

Yield: 82%, white solid, M.P. 100-102 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.29 (s, 1H), 8.17 (d, J = 8.8 Hz, 2H), 8.10 (t, J = 9.0 Hz, 2H), 7.78 – 7.68 (m, 2H), 7.08 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.5, 151.4, 143.1, 142.3, 141.2, 130.2, 129.2, 129.0, 114.6, 114.1, 55.4. HRMS (ESI-TOF): m/z calcd for $C_{15}H_{12}N_2O$ [M+H]$^+$ 237.1030, found 237.1021.

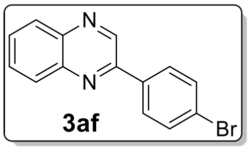


3ae

2-(4-Bromophenyl)quinoxaline (3af)[58]

Yield: 80%, white solid, M.P. 132-134 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.30 (s, 1H), 8.16 – 8.11 (m, 2H), 8.09 (d, J = 8.5 Hz, 2H), 7.78 (pd, J = 6.9, 1.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.7, 142.8, 142.3, 141.6, 135.6, 132.4, 130.5, 129.9, 129.6, 129.1, 129.0, 125.0. HRMS (ESI-TOF): m/z calcd for $C_{14}H_9BrN_2$ [M+H]$^+$ 285.0029, found 285.0025.

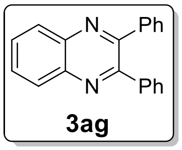


3af

2,3-Diphenylquinoxaline (3ag)[45]

Yield: 76%, white solid, M.P. 123-125 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.19 (dd, J = 6.3, 3.5 Hz, 2H), 7.78 (dd, J = 6.4, 3.4 Hz, 2H), 7.52 (d, J = 6.3 Hz, 4H), 7.39 – 7.31 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.5, 141.2, 139.0, 130.0, 129.9, 129.2, 128.9, 128.3. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{14}N_2$ [M+H]$^+$ 283.1237 found 283.1229.



3ag

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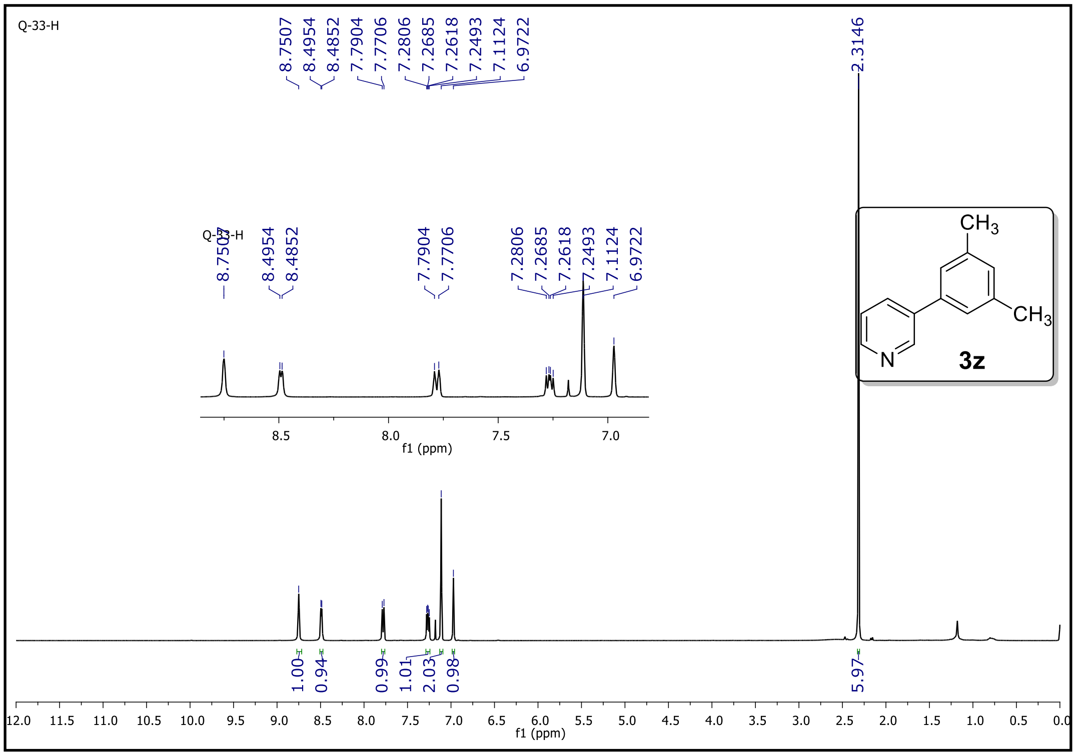
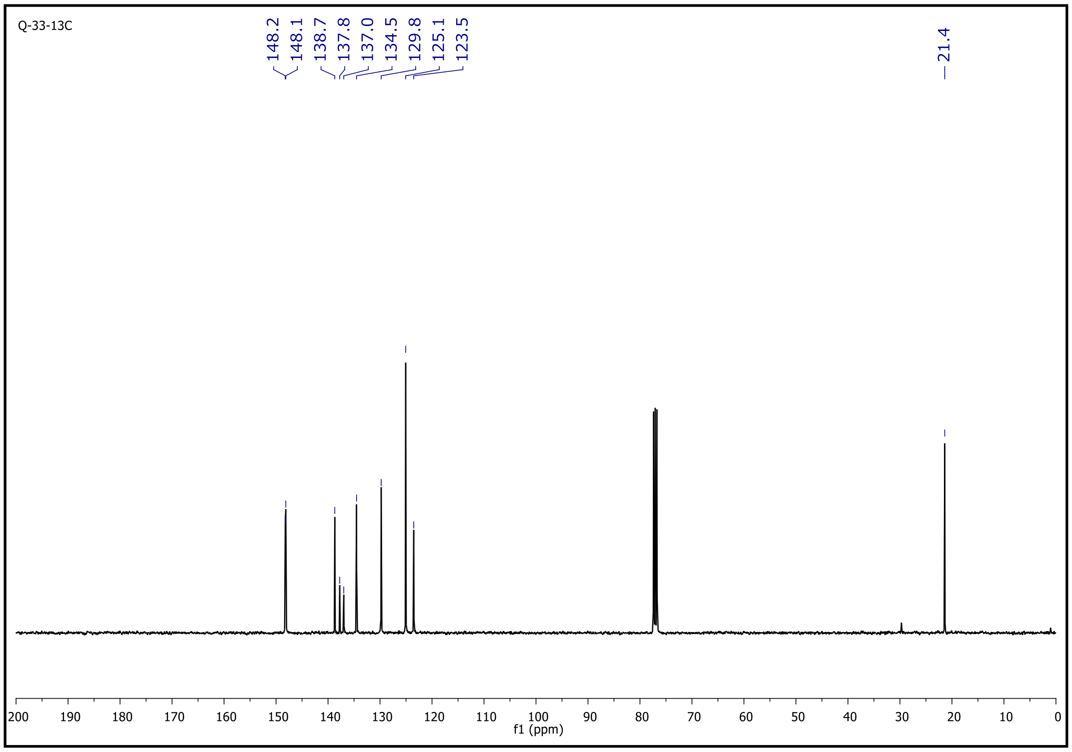
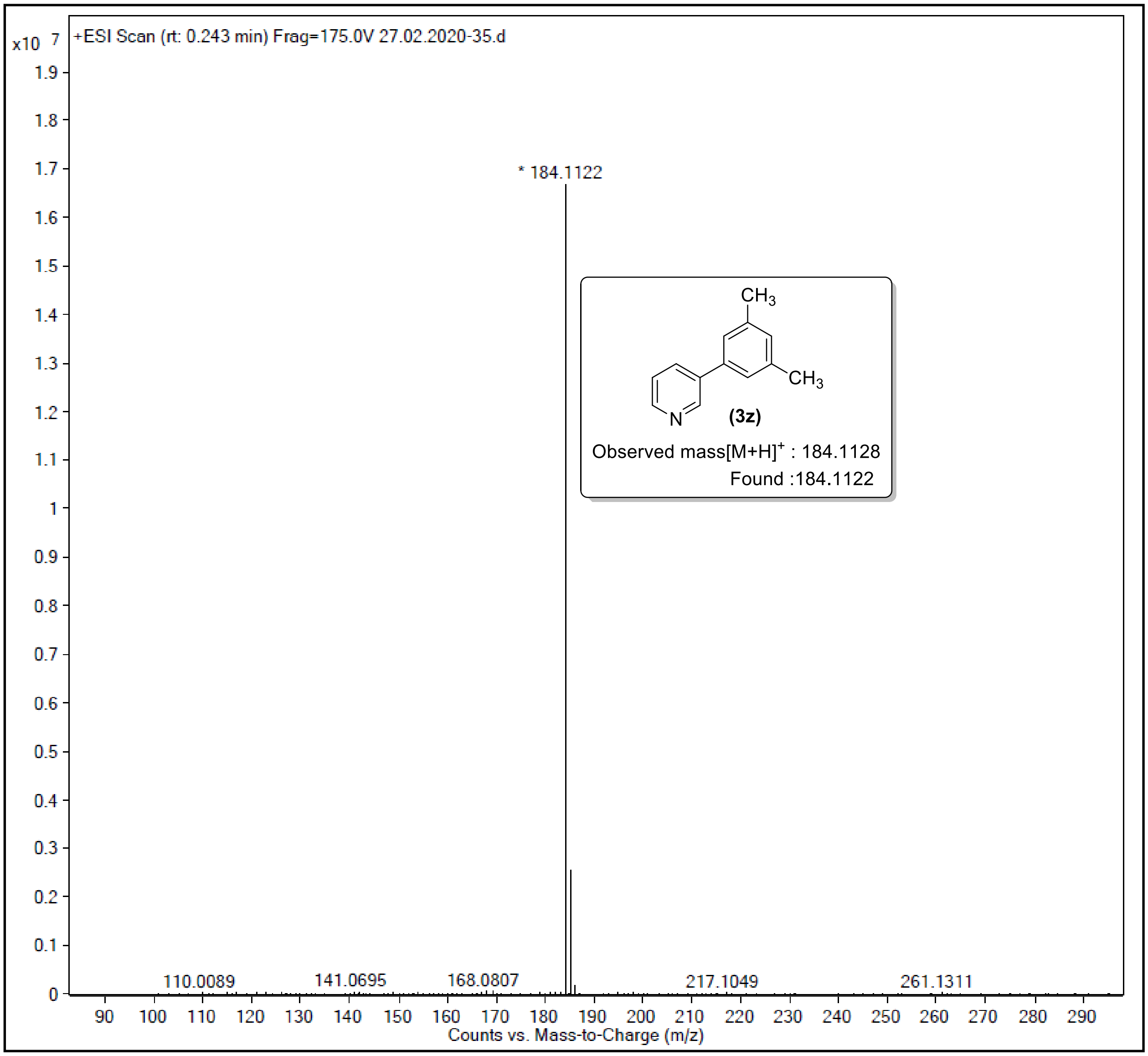
4.7. Selected NMR (^{1}H and ^{13}C) and Mass Spectra



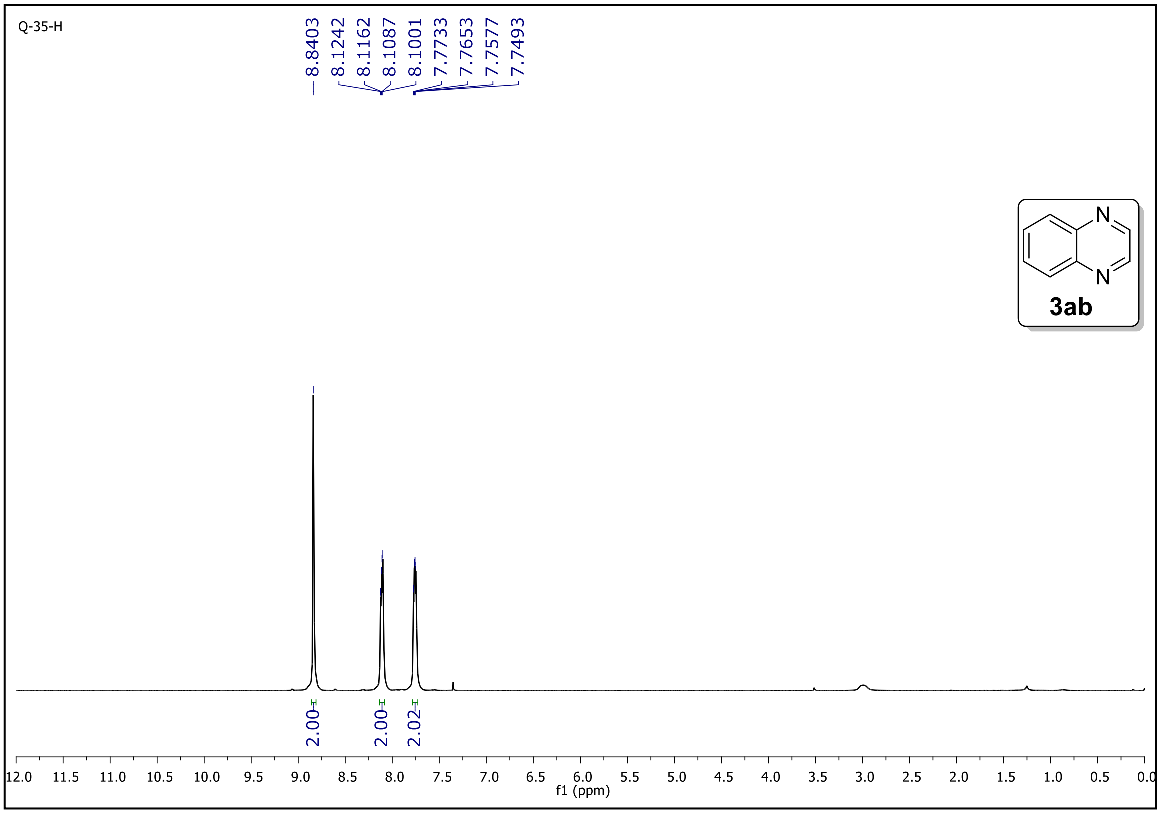
^{1}H NMR spectrum of compound **3z**



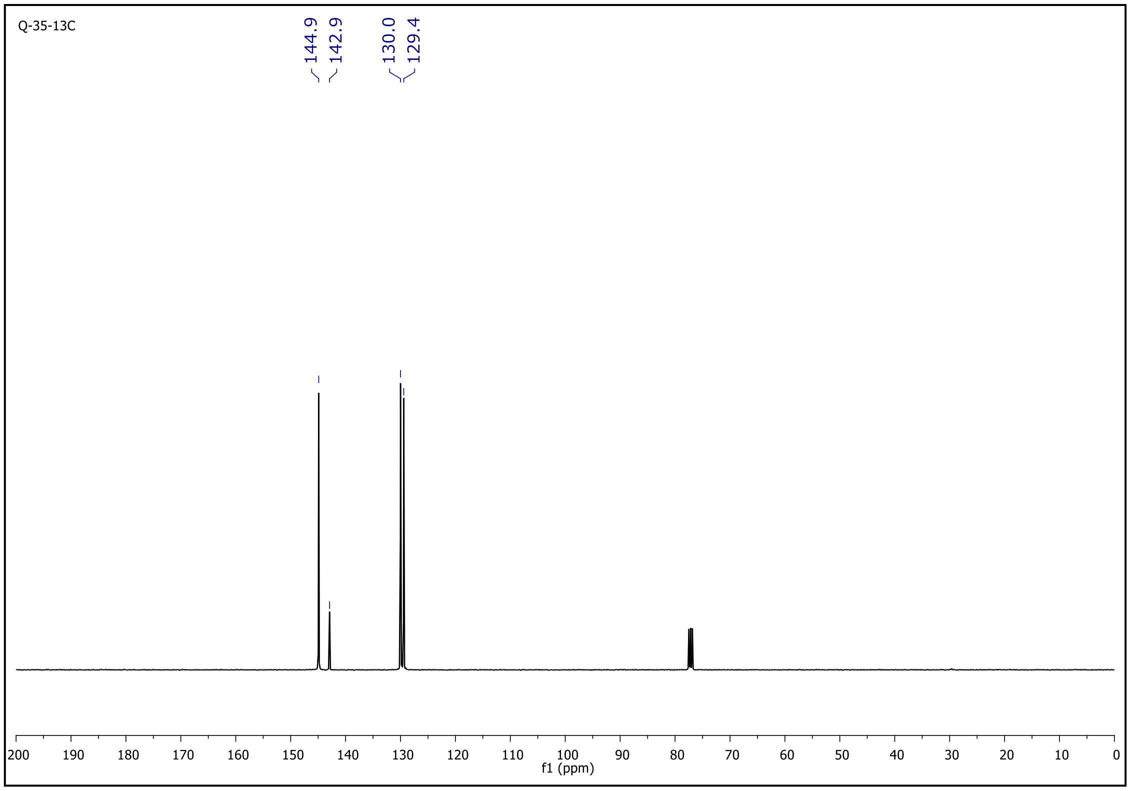
^{13}C NMR spectrum of compound **3z**



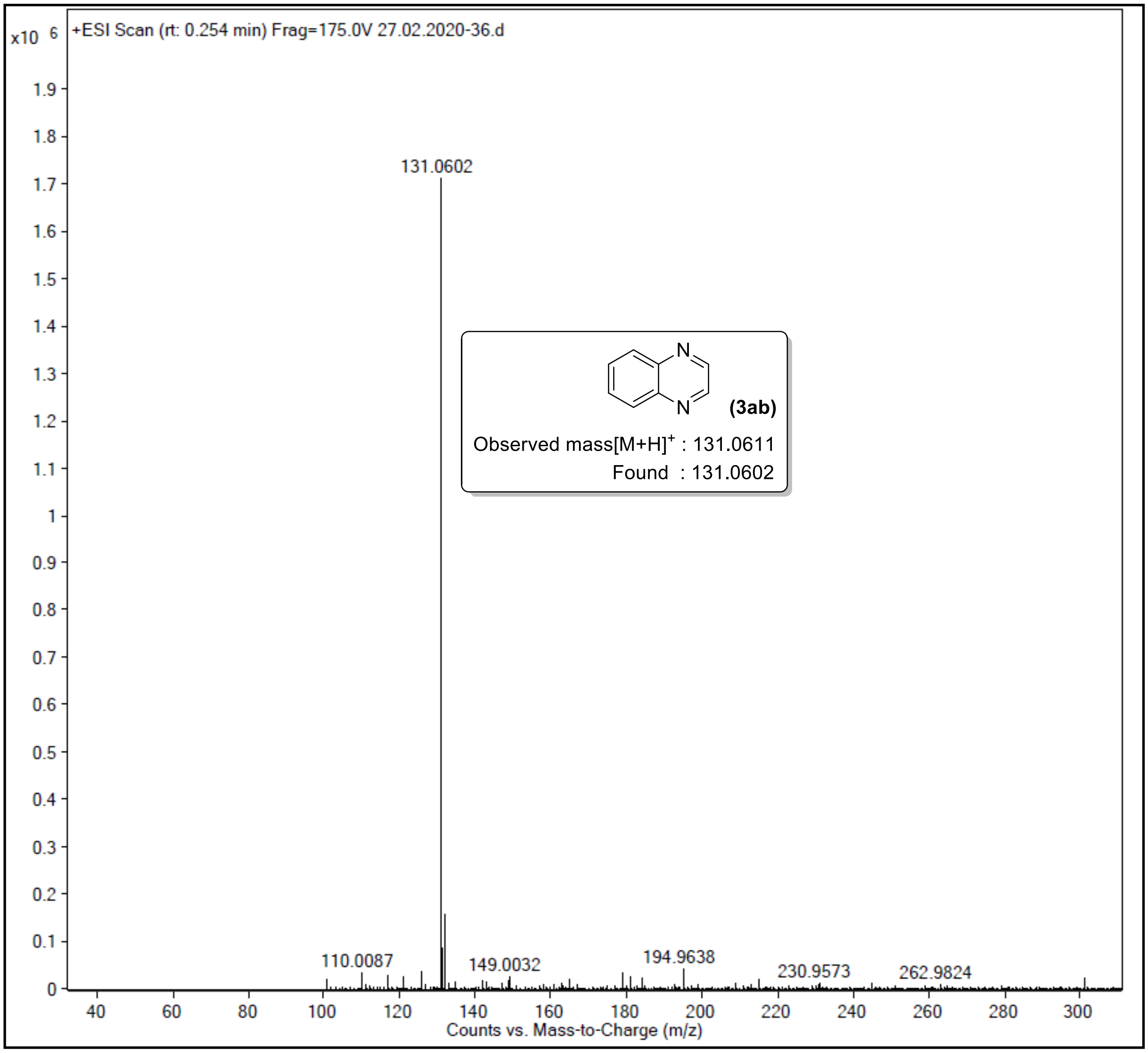
Mass spectrum of compound **3z**



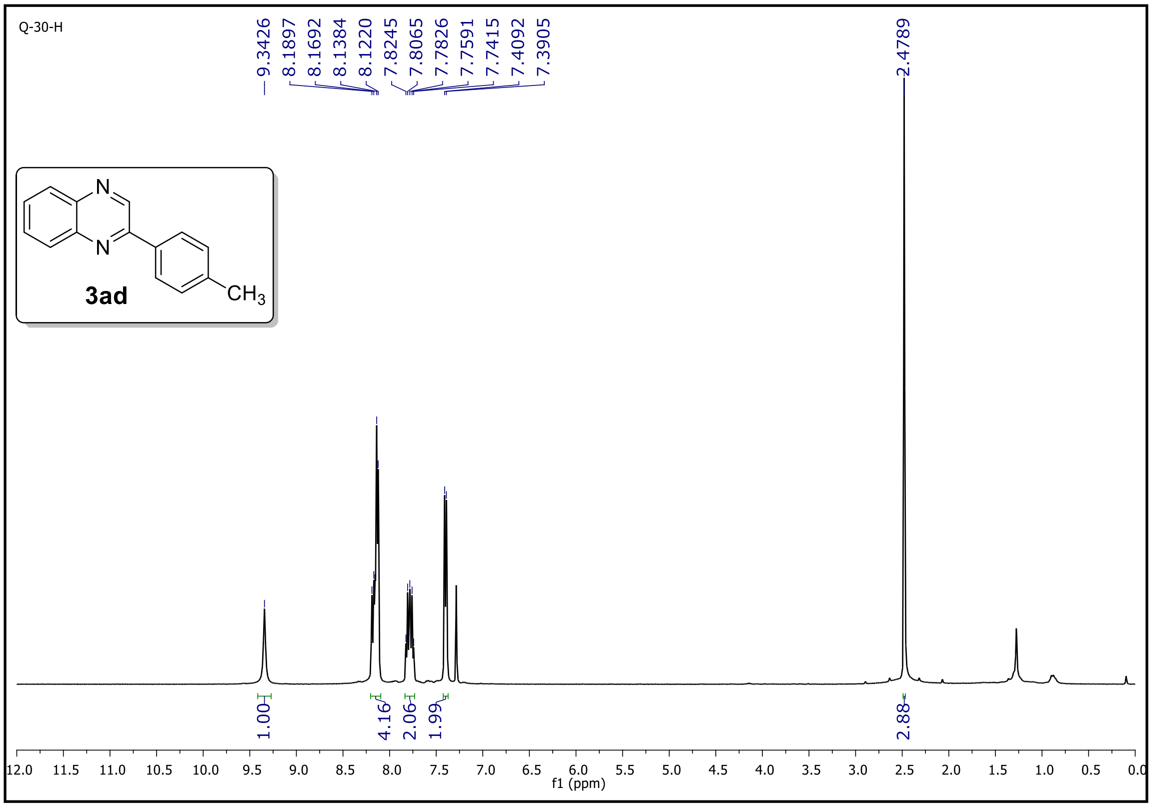
^{1}H NMR spectrum of compound **3ab**



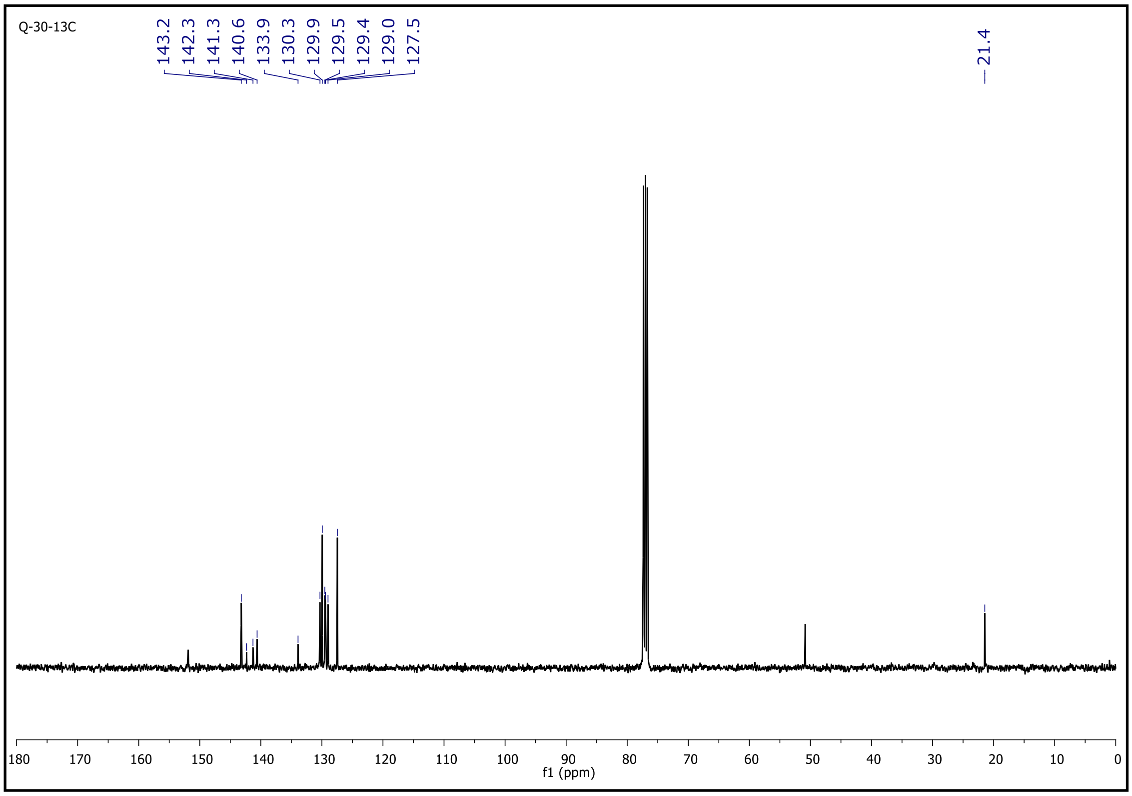
^{13}C NMR spectrum of compound **3ab**



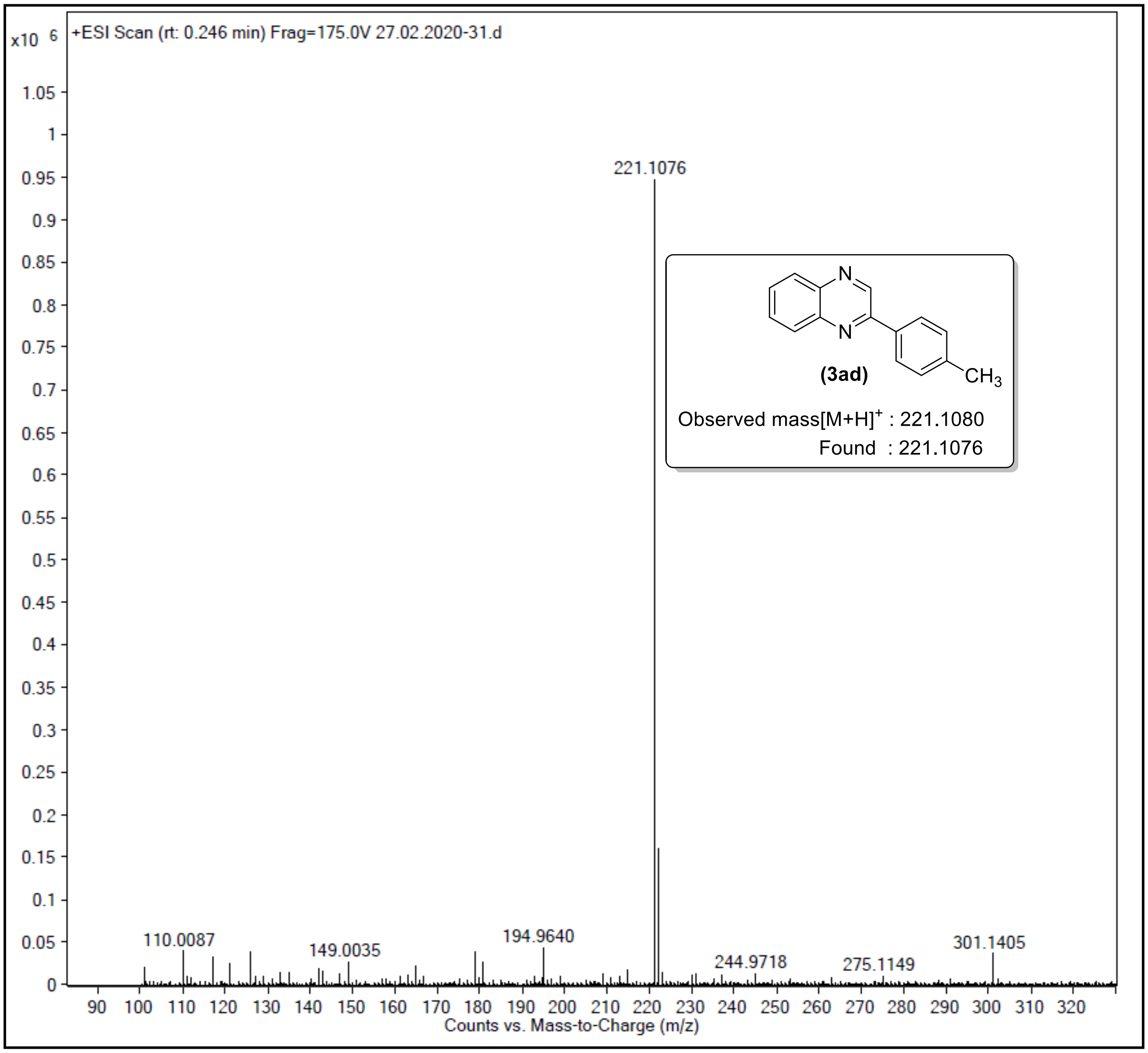
Mass spectrum of compound **3ab**



^{1}H NMR spectrum of compound **3ad**

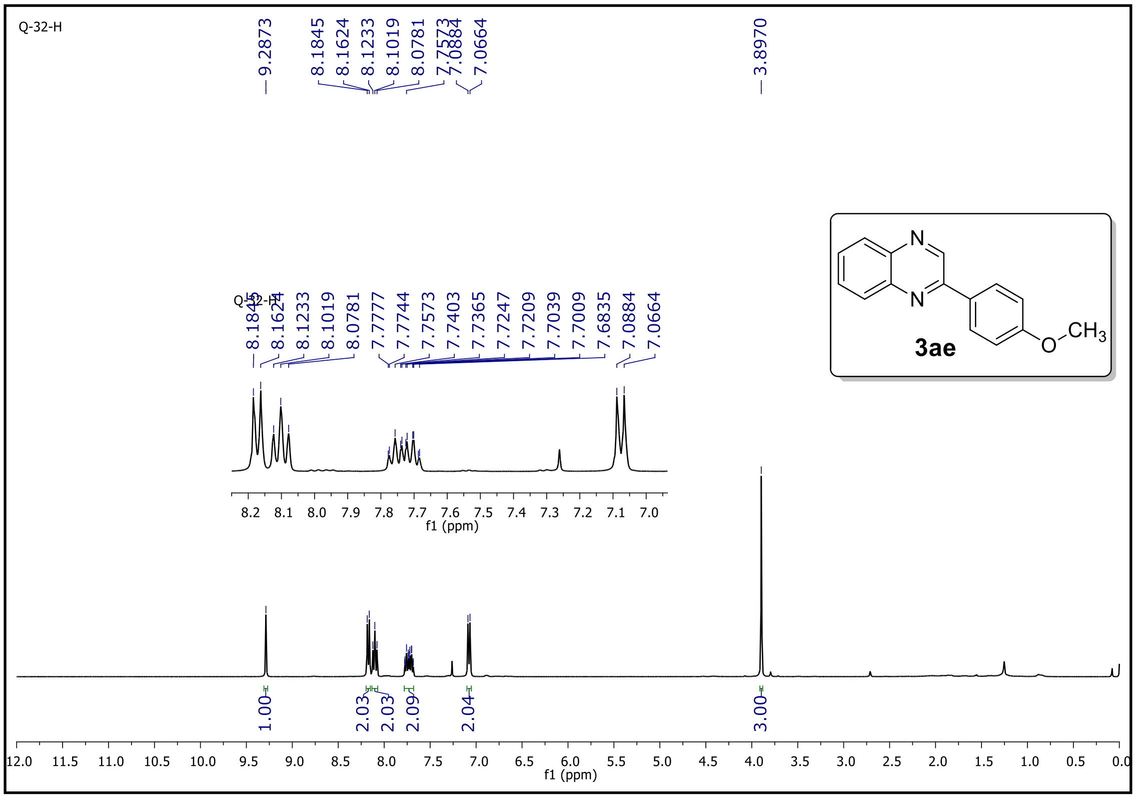


^{13}C NMR spectrum of compound **3ad**

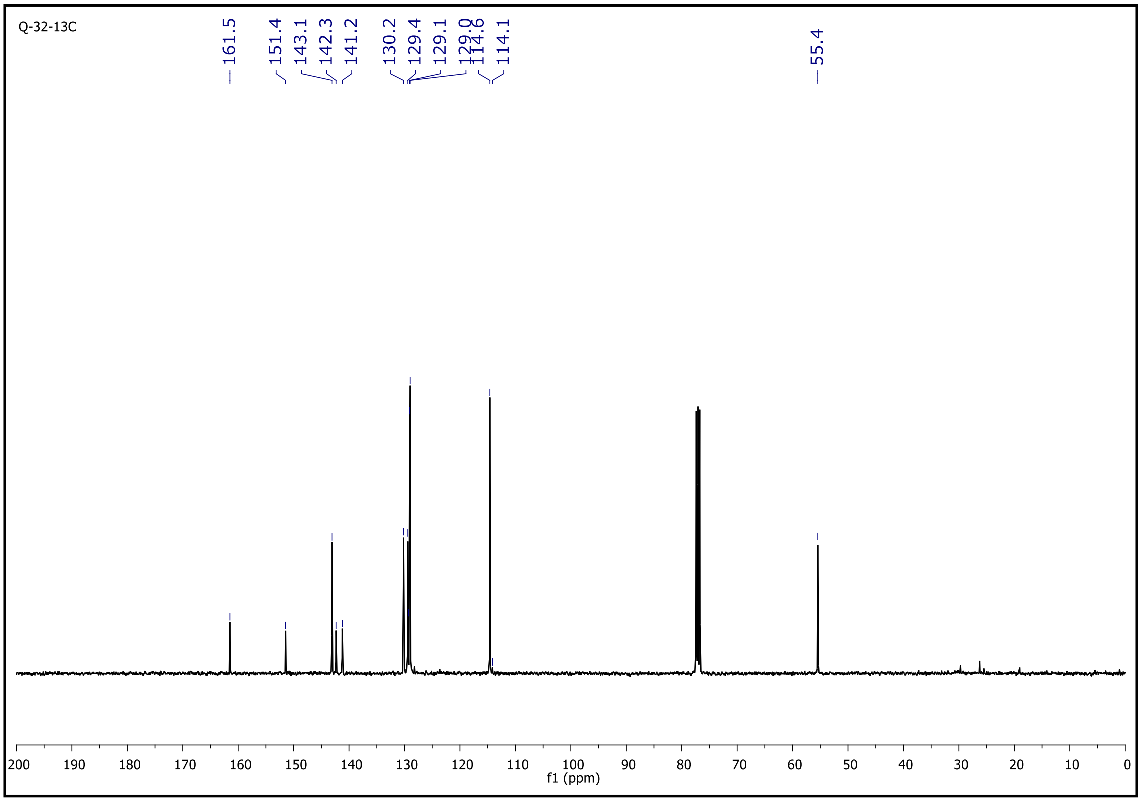


Observed mass$[M+H]^+$: 221.1080
Found : 221.1076

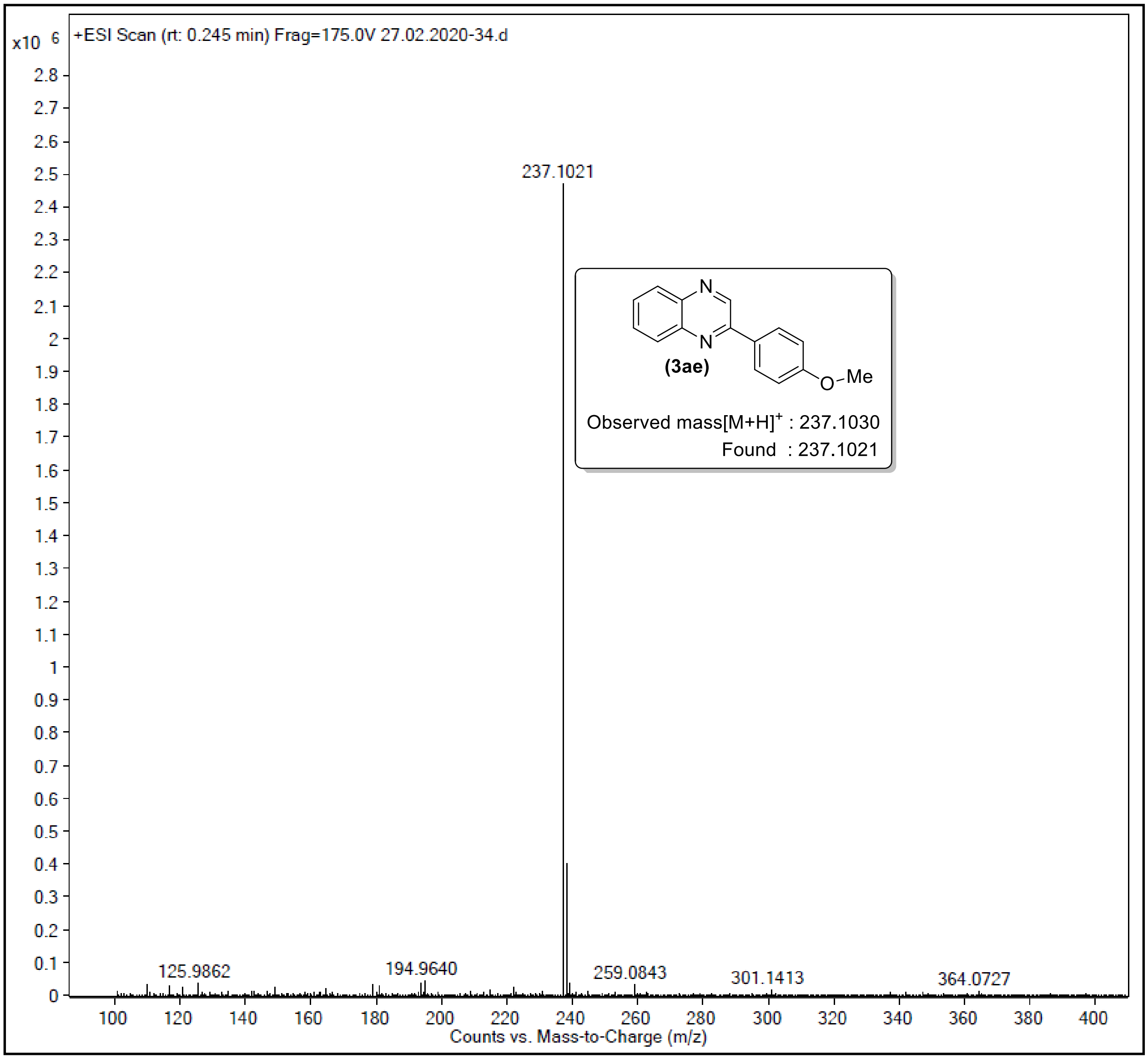
Mass spectrum of compound **3ad**



^{1}H NMR spectrum of compound **3ae**

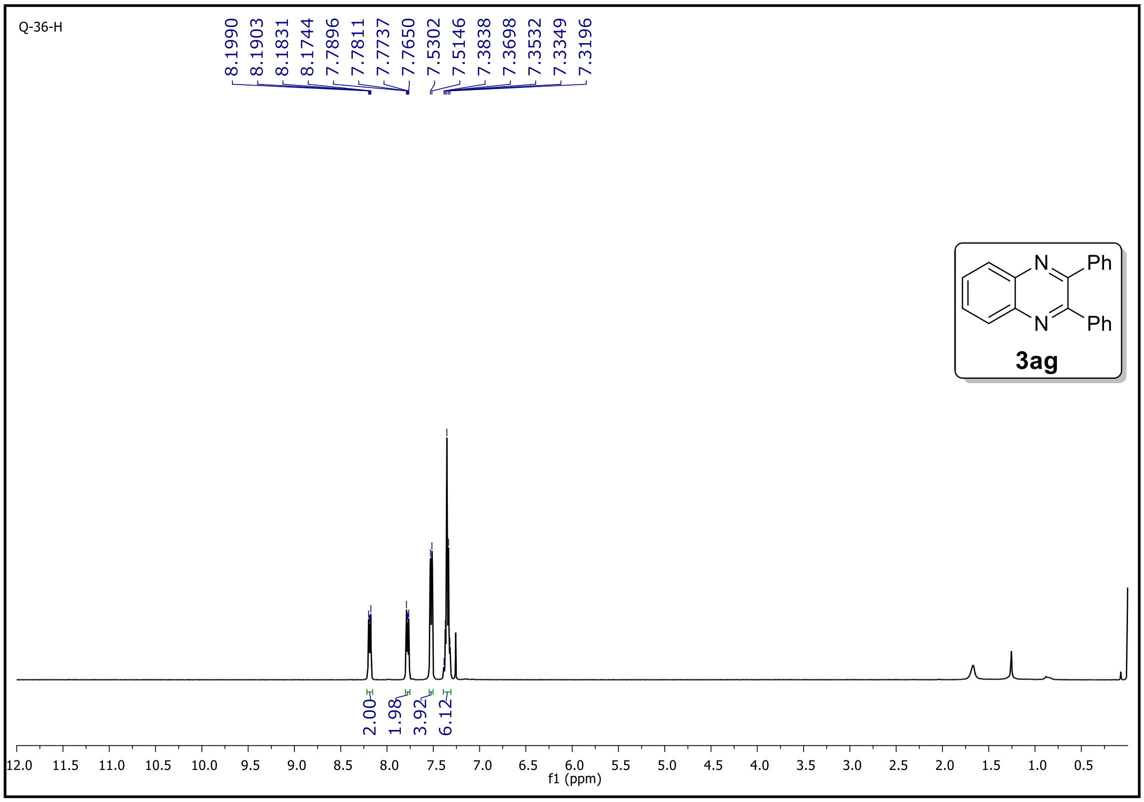


^{13}C NMR spectrum of compound **3ae**

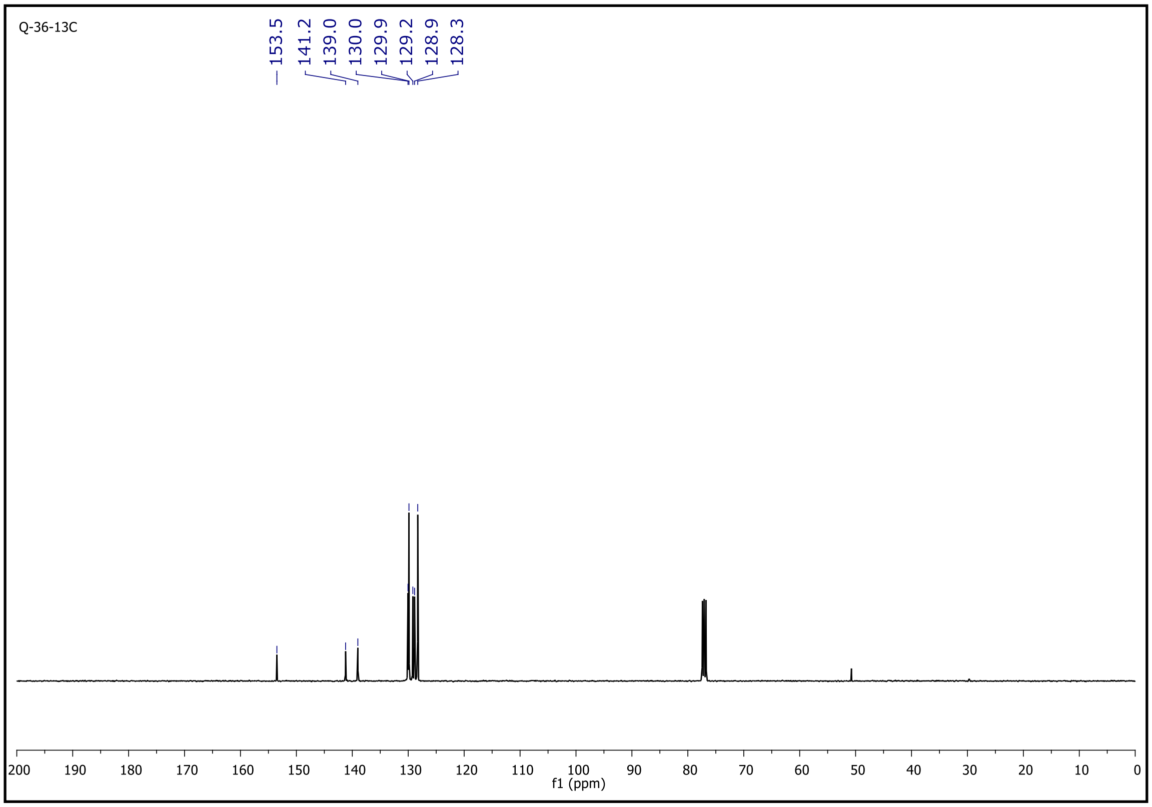


Observed mass$[M+H]^+$: 237.1030
Found : 237.1021

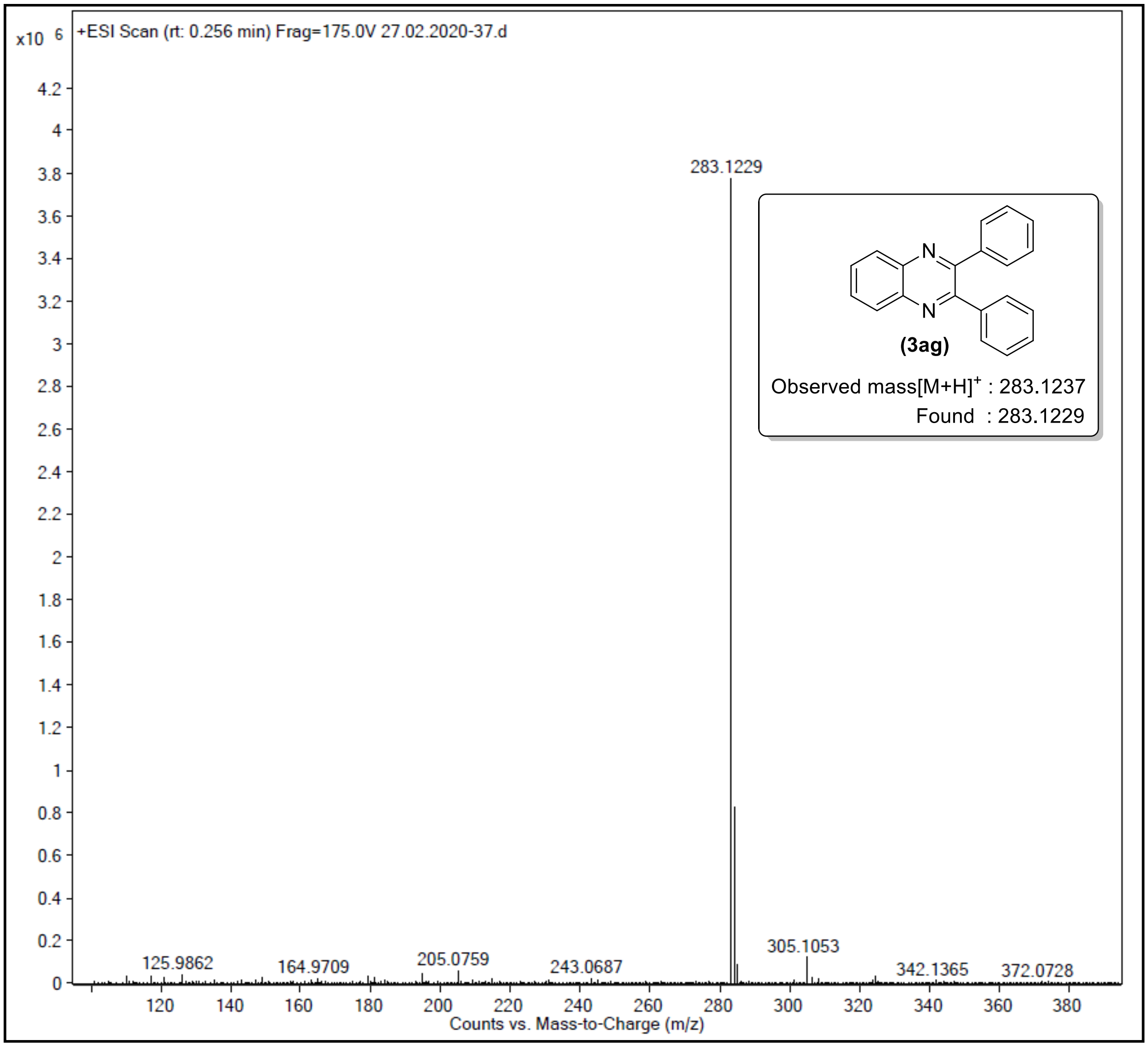
Mass spectrum of compound **3ae**



^{1}H NMR spectrum of compound **3ag**



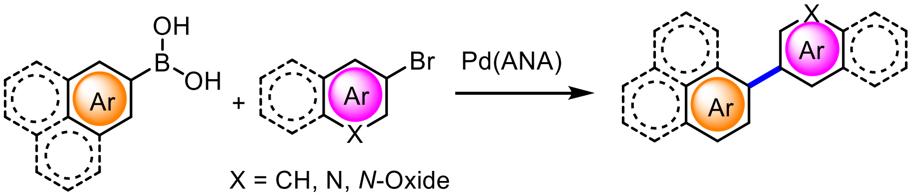
^{13}C NMR spectrum of compound **3ag**



Mass spectrum of compound **3ag**

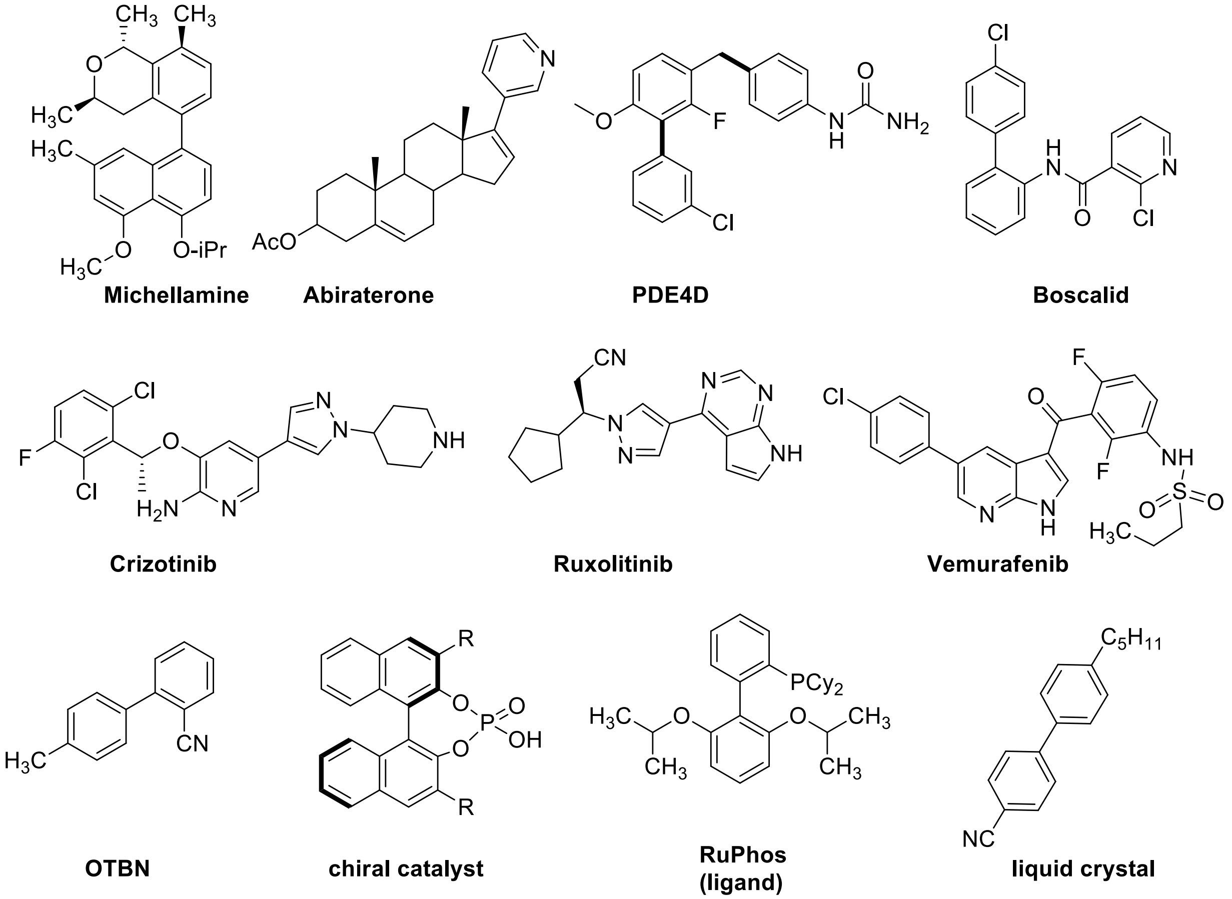
CHAPTER-V
Section-A

Pd(II)ANA Complex Catalyzed Cross-Coupling Reaction Between Arylboronic Acids and Arylbromides



5A.1. Introduction

Transition-metal-catalyzed C-C bond formation reactions play a vital role in the field of modern organic synthesis because of their unique reactivity with transition metals allow access to unconventional transformations with high selectivity and efficiency.[1] These reactions are the most important synthetic tools for organic chemists and are indispensable to synthesis of building blocks for various biologically active products including pharmaceuticals, supra molecular chemistry, material sciences and catalysis.[2]


Michellamine Abiraterone PDE4D Boscalid

Crizotinib Ruxolitinib Vemurafenib

OTBN chiral catalyst RuPhos (ligand) liquid crystal

Figure 5A.1. Some of Important Functional Biaryl Compounds.

The C-C bond formation reactions which involves transition-metal catalysts include Suzuki,[3] Heck,[4] Sonogashira,[5] Stille,[6] Hiyama,[7] Negishi,[8] Kumada,[9] and Murahashi reactions.[10] Among these, palladium-catalyzed cross-couplings Suzuki-Miyaura is the leading methodologies for the construction of C-C bond in the synthesis of biaryls become popular because of its wide applications in various fields such as antibacterial,[11] aniviral,[12] antihypertensive,[13] anticancer,[14] antidiabetic,[15] antimicrobial,[16] and diuretic[17] (Figure 5A.1).

Suzuki-Miyaura reaction was discovered by Suzuki-Miyaura in 1979, which involves a reaction between arylboronic acid with aryl halide. Majorly, this reaction involves use of various organoboranes and different type of organic electrophiles which include halides, pseudo-halide, triflates in the presence of palladium and base. This protocol provides biaryl compounds predominately with high selectivity and quantitative yields.[18]

In this decade, the Suzuki cross-coupling of organoboronic acid, organoborane,[19] organoboronate esters,[20] KF_4-borates[21] and aryl halides has been massively employed to unsymmetrical biaryls *via* sp^2-sp^2 linkage since its initial reporting by Akira Suzuki.[3] Suzuki-Miyaura coupling reaction has many advantages which includes i) mild conditions, ii) commercially available starting materials, iii) high functional group tolerance, iv) easy isolation. Homo-biaryl and hetero-biaryl compound can be synthesized selectively from this method depending up on the reqirement and reaction conditions. There has been a deep-rooted interest in the exploration of palladium complexes due to their wide use as homogeneous and heterogeneous catalyst for carbon-carbon bond formation reactions in high turnover numbers (TON).[22]

5A.2.Reported Methods for the Suzuki Cross-Coupling Reaction

There are several transition metal catalyzed reports on Suzuki-Miyaura cross-couple reactions ranging from iron to palladium (Figure 5A.2).

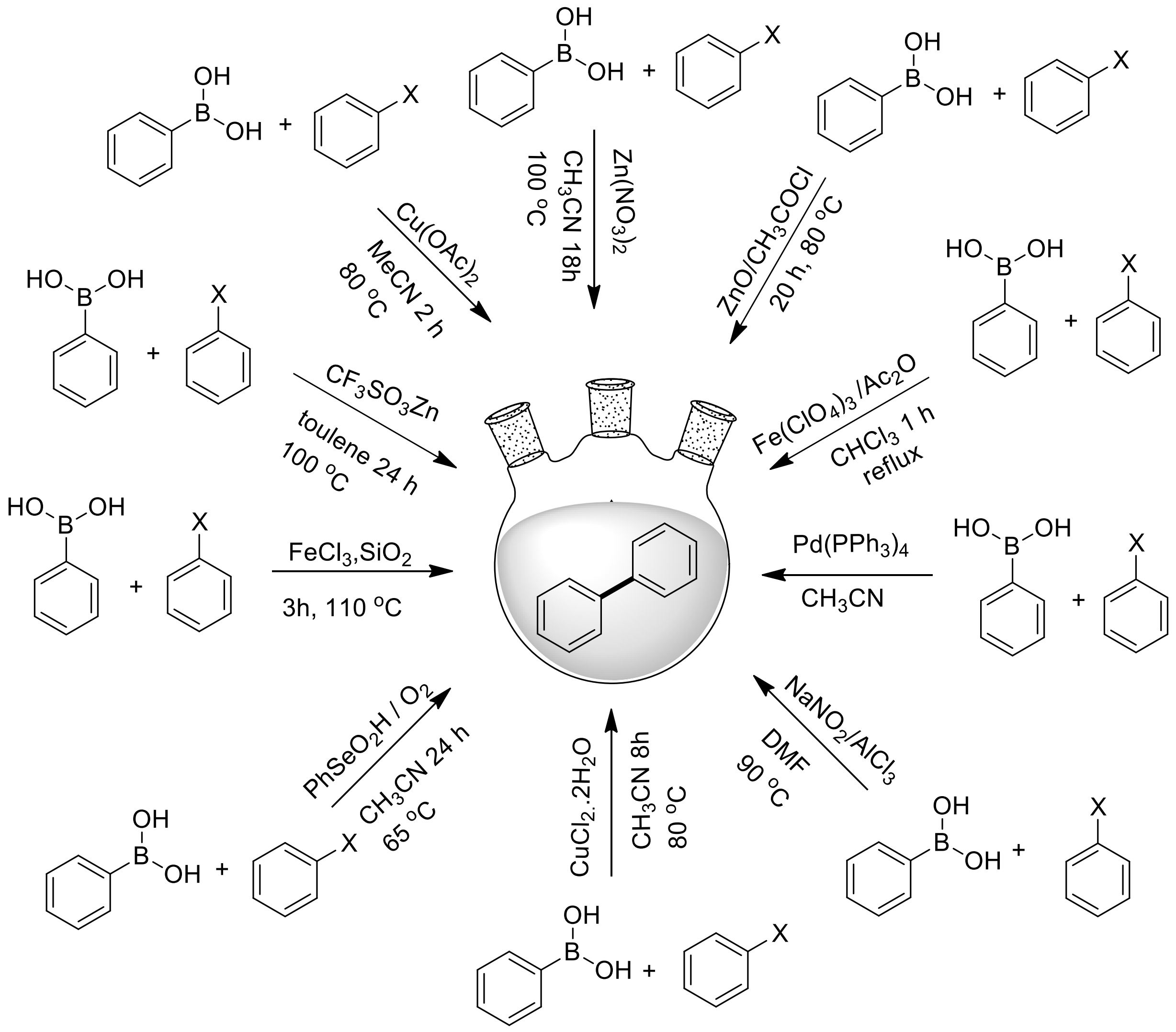
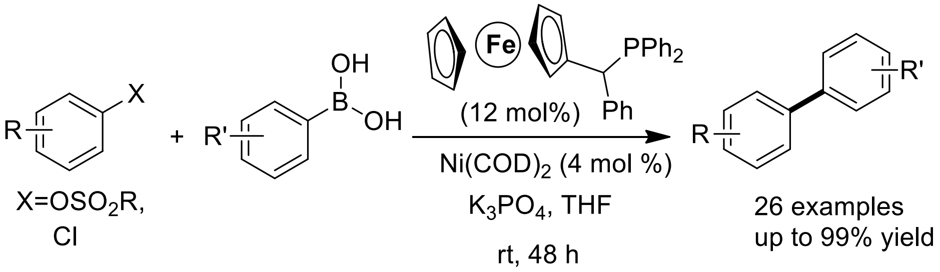


Figure 5A.2. Different Metal Catalyzed Suzuki-Miyaura Cross-Coupling Reactions.

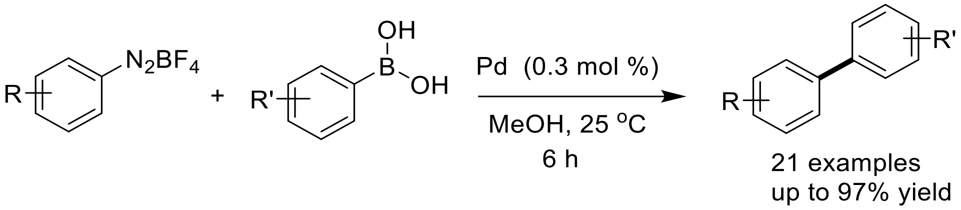
Palladium catalyzed Suzuki-Miyaura reaction has particularly gained more attention compared to the other transition metal catalysis, herein some of the reports are discussed below.

Tanget et al. established the Suzuki-Miyaura cross coupling reaction between arylsulfonates and arylboronic acids in the presence of an Ni(0) metal and commercially available ferrocenylmethylphosphine ligand to obtain the biphenyl in excellent yields (Scheme 5A.1).[23a]



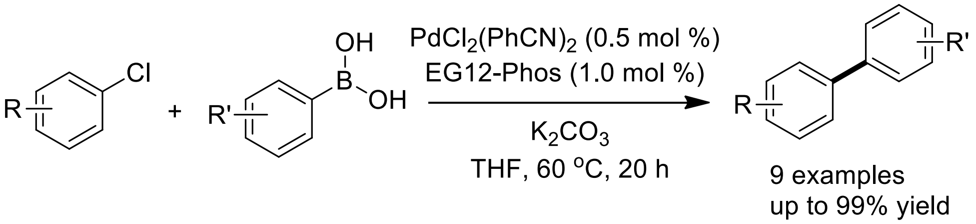
Scheme 5A.1

Xing et al. developed a novel method for the synthesis of biaryl via Suzuki-Miyaura cross coupling reactions from arylboronic acids and arenediazonium salts in the presence of palladium nanoparticles supported by aluminium-hydroxide. This catalyst furnished title products in excellent yields at 25 °C in methanol (Scheme 5A.2).[23b]



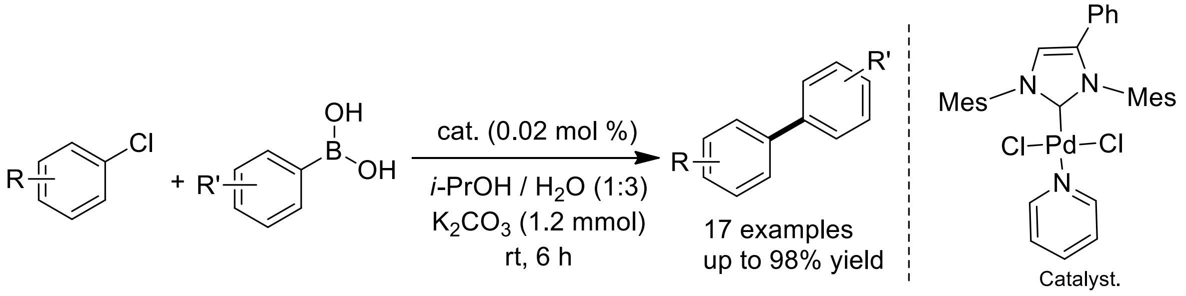
Scheme 5A.2

Tsuji and co-workers empoyed the suzuki-Miyaura cross coupling reaction to obtain biaryl derivatives with aryl boronic acids and aryl halide using phosphine having dodeca [ethylene glycol (EG12)] ligand supported palladium catalyst (Scheme 5A.3).[23c]



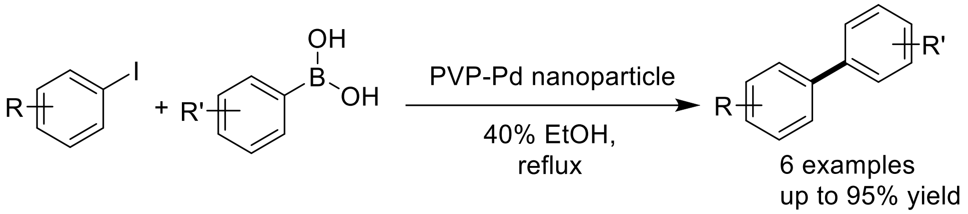
Scheme 5A.3

Rajabiand et al. developed a new method for biphenyls from arylboronic acids and different activated and non-activated aryl halides in the presence of Pd-NHC catalytic system. The advantage of this method is low catalyst loading and high product yields (Scheme 5A.4).[23d]



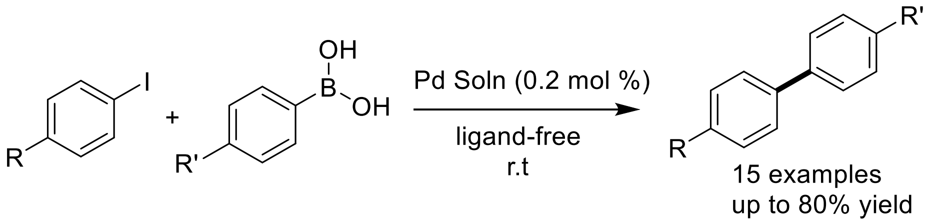
Scheme 5A.4

El-Sayed and research group expanded the Suzuki-Miyaura cross coupling by employing the poly (*N*-vinyl-2-pyrrolidone) (PVP) stabilised palladium nanoparticles. It is an efficient catalyst for the preparation of substituted biaryl with good yields in aqueous medium (Scheme 5A.5).[23e]



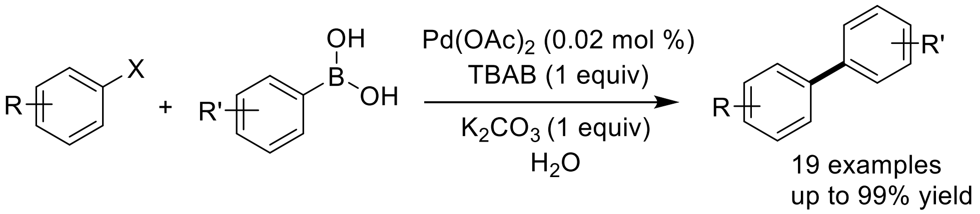
Scheme 5A.5

A ligand-free high yielding Suzuki-Miyaura reaction was developed by **Nicholas and research group** for biphenyls using simple and inexpensive catalytic materials. In this reaction they used para-substituted arylboronic acids and aryl halides in the presence aqueous solution of palladium, the coupling reactions proceeded rapidly at room temperature (Scheme 5A.6).[23f]



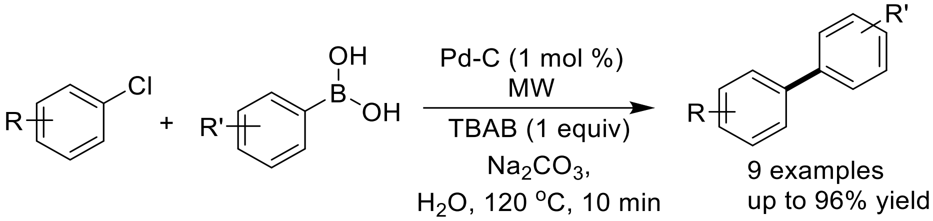
Scheme 5A.6

Badone et al. enlarged the suziki cross coupling reaction with aryl or vinly boronic acids with aryl halides in the presence of palladium acetate catalyst which was supported by the tetrabutylammonium bromide in water medium obtained good yields (Scheme 5A.7).[23g]



Scheme 5A.7

Leadbeater and co-workers developed a charcoal supported palladium catalyst (Pd/C) for cross coupling of arylboronic acids and aryl halides under the microwave heating to obtain biaryls in good yield (Scheme 5A.8).[23h]



Scheme 5A.8

5A.3. Present Study

A number of modifications have been appeared in palladium complexity to increase the efficacy of the catalyst including activity, stability, and functional group compatibility.[24] The ligands which are used in most of the catalysts are phosphenes,[25] *N*-Heterocyclic carbenes (NHCs)[26] and bidentate P, N ligands.[27] Recent past has witnesed a tremendous increment in the ways to develop and design novel phosphorus-free palladium catalysts for robust, active, higher turnover number and functional group tolerance at low costs.[28] In literature we found that only few pyridine based bidentate ligands for palladium catalyzed cross-coupling reactions.[29]

Pyridine is a simplest heterocycle that closely resembles benzene structure, where a benzene methine (=CH-) group replaced with nitrogen atom to form a six membered aromatic heterocycle with chemical formula C_5H_5N.[30]

The lone pair of nitrogen of pyridine, which is not a part of the resonance in sp^2 orbital in the same plane and doesn't contribute to the aromatic behaviour of pyridine but greatly influence the chemical environment of the ring. The available "free" lone pair thus could be utilized by "N" in several ways suiting for chemical reactions either on pyridine ring or as Lewis base to form coordinate bond with Lewis acids (Figure 5A.3). It is usually a weak monodentate ligand having capability to bind metal in different proportions to produce the range of metal complexes. A rich literature of pyridine coordinated complexes of transition metals has grown over the years. Pyridine and its numerous derivatives have been under investigation of inorganic chemists in design and preparation of numerous metal complexes of their interest. The further design of pyridine ligand explored in polypyridine system fusing two or more pyridine moieties to result in chelating multidentate ligands. Such as bipyridine, a fused two pyridine rings system, is a worth mention in transition metal chemistry.[31]

This interprets to strong electrostatic interactions of pyridine lone pair to metal *d*-orbitals. Despite being neutral, pyridine causes moderately large *d*-orbital splitting implying strong bonding interaction to metal centres. Apart from nitrogen lone pair orbitals, the ring π-electron is also capable of bonding interaction to metal ions. Moreover, delocalized π* anti-bonding orbitals can act as acceptor of metal electron density (Figure 5A.3). The pyridine can also indulge in hydrogen bonding and π-π stacking-like weak interactions. Thus, pyridine is enriched with multiple orbitals for bonding interactions with metal ions.[32]

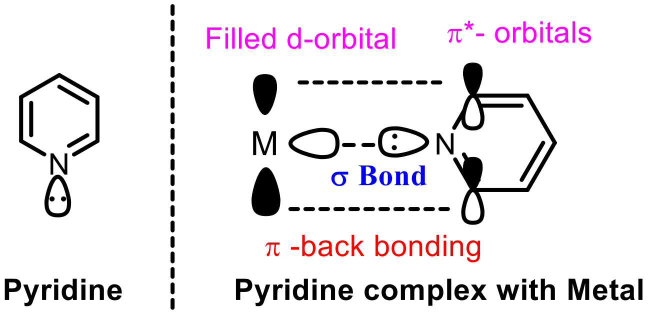
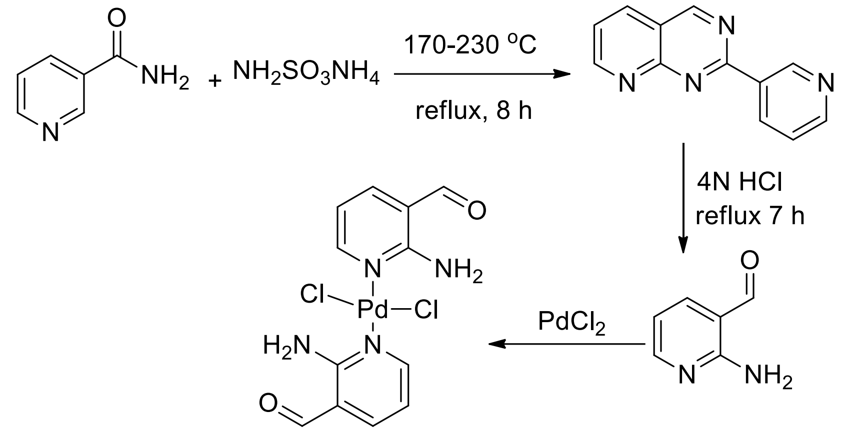


Figure 5A.3. ChemicalProperties of Pyridines.

In continuation of our efforts towards the sustainable chemistry employing metal catalysis under green reaction conditions,[33] we searched for a robust, inexpensive and biologically relevant monodentate pyridine based-Pd(II)-catalysts for Suzuki-Miyaura coupling reaction.[34] Water is ubiquitous in nature and a desirable medium for chemical reactions which falls in line with the principles of green chemistry.[35] In the process of catalyst preparation we employed use of Pd (II) chloride and 2 equiv of 2-aminonicotinaldehyde ligand in alcohol for 2 h under refluxing condition, there is change in colour of the solution from pink to yellow which is an indication for completion of reaction (Scheme 5A.9).[36]



Scheme 5A.9

After confirming the formation of palladium (II) 2-aminonicotinaldehyde, we prepared different types of pyridine ligand **C1-C4** (Figure 5A.4) using same procedure.

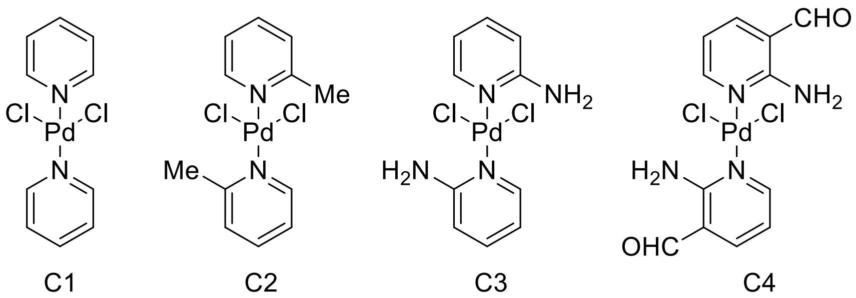
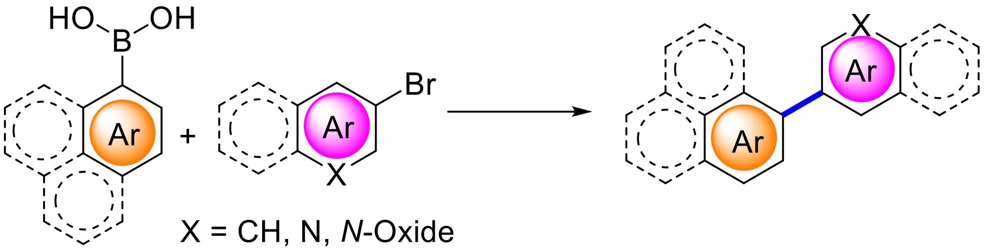


Figure 5A.4. Palladium Pyridine Complexes.

Herewith, we report an efficient, less expensive, easily accessible, air-stable Pd(II)-(2-aminonicotinaldehyde) [Pd(II)-ANA] complex **C4** as a complementary catalyst for the Suzuki-Miyaura reaction with low catalyst loading in water.

5A.3.1. Results and Discussion

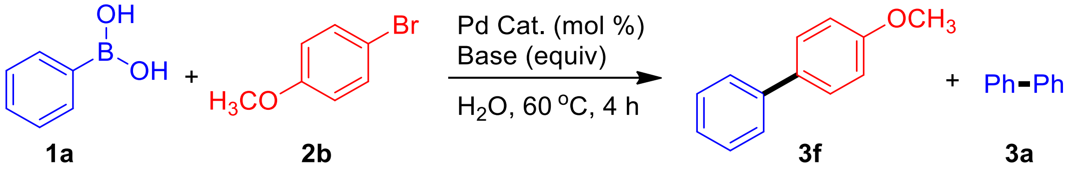
To validate our proposed hypothesis for the synthesis of biaryls via palladium (II) catalyzed Suzuki-Miyaura cross-coupling reaction, we have started with arylboronic acids and arylbromides in presence of Pd(II) complex of pyridine and base, a pictroial diagram is showe in Scheme 5A.10.



Scheme 5A.10

In our initial screening experiments, the reaction between phenylboronic acid **1a** and 4-bromo anisole **2b** with catalysts **C1-C4** was investigated to optimize the reaction conditions, and only the key facts are reported in Table 5A.1.

Table 5A.1. Optimization of the Reaction Conditions.[a]



Entry	Catalyst (mol %)	Base (equiv)	Yield[b]	
			3f	3a
1	C1	Cs_2CO_3	78	20
2	C2	Cs_2CO_3	83	16
3	C3	Cs_2CO_3	80	18
4	**C4**	**Cs_2CO_3**	**96**	**n.d**[f]
5	C4	K_2CO_3	90	n.d
6	C4	Na_2CO_3	88	10
7	C4	KO^{t}Bu	95	n.d
8	C4	$NaHCO_3$	86	Trace
9	C4	NaOH	22	n.d
10	C4	Cs_2CO_3	52[c]	n.d
11	C4	Cs_2CO_3	80[d]	n.d
12	C4	Cs_2CO_3	78[e]	n.d

[a]Reaction Conditions: Phenylboronic acid **1a** (0.5 mmol), 4-bromo anisole **2b** (0.5 mmol), catalyst (1 mol %), base (0.5 equiv), water (1.0 mL) at 60 °C. [b]Yields are of isolated pure products. [c]Room temperature, [d]40 °C, [e]Base 0.3 equiv., [f]Not detected.

Firstly, we have initiated the optimization of the reaction conditions using phenylboronic acid **1a** and 4-bromo anisole **2b** and we are delighted to observe that the formation of corresponding cross-coupled product **3f** in 78% along with the self coupled product of boronic acid **3a** (20%) employing 1.0 mol % of Pd(II) complex of pyridine **C1** and 0.5 equivalents of Cs_2CO_3 in water (Table 5A.1, entry 1). These results prompted us to optimize the reaction conditions to improve the product yield by changing the different pyridine based ligands on palladium metal and reaction conditions.

The Pd(II) complexes of 2-methylpyridine **C2**, 2-aminopyridine **C3** were successful to yield the cross-coupled product **3f** in 80-83% along with the self-coupled product **3a** in 16-18% (Table 5A.1, entry 2-3). Inspiringly, we found that the yield was improved to 96% by use of Pd(II) complex of 2-aminonicotinaldehyde **C4**, this catalyst was found to be highly active and gave unsymmetrical biphenyl **3f** as a solo product. (Table 5A.1, entry 4).

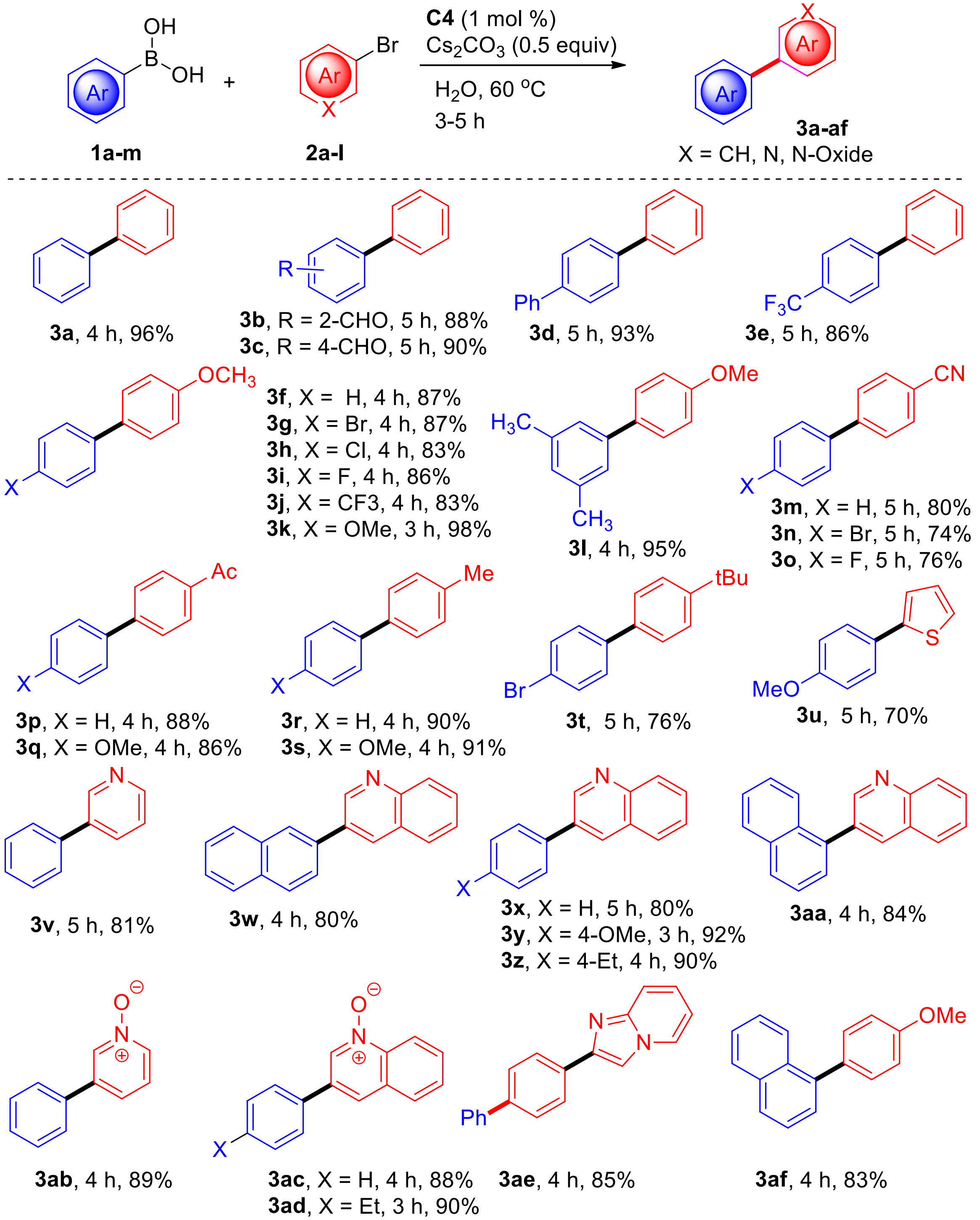
The effect of various bases on the model reaction were also screened (Table 1, entries 5-8). Notably, K_2CO_3, Na_2CO_3, KO^tBu and $NaHCO_3$ gave the desired product **3f** in 86-95% yield, whereas NaOH gave cross-coupled product in low yields 22% (Table 5A.1, entry 9). Lowering the reaction temperature or the amount of the base showed the inferior results (Table 5A.1, entries 10-12).With the preferred conditions for the Suzuki reaction in hand, we next examined the scope of the substrates and synthesised a library of compounds listed in Table 2. Intiated with a substituted arylboronic acids **1a-m** and bromobenzene **2a-l** as substrates.

The phenylboronic acid **1a** readily reacted with bromobenzene **2a** to deliver biphenyl **3a** in 96% yield. Notably, electron withdrawing groups on boronic acid (**1b** and **1c**) did not hamper the reaction yields (**3b-c**). The 4-biphenylboronic acid **1d** was similarly reacted to produce *para*-terphenyl **3d** in 93%. It was observed that the halogen substituted arylboronic acids were also reacted smoothly to give the corresponding cross-coupled products **3g-j**, **3n-o** in good yields (Table 5A.2, 83-87%). Whereas, phenyl and electron rich arylboronic acids gave marginally high yields with various bromobenzenes (**3k-m**, **3p-s**).

We also found that 4-bromo boronic acid **1f** reacted with 4-*tert*-butyl bomobenzene **2f** to furnish the desired substituted biphenyl **3t** at 76% of yield. Further, the protocol was extended to explore the substrate scope of heteroaryl bromides. The 2-bromothiophene readily reacted with 4-bromo anisole **2b** and yielded desired product **3u** in 70%. Likewise, 3-bromopyridine and 3-

bromoquinoline **2h-2i** cross-coupled with various arylboronic acids to deliver desired products **3v-aa** in good yields (80-90%). It is worth noting that the pyridine *N*-oxide and quinoline *N*-oxide derivatives also smoothly gave cross-coupled products **3ab-ad** without deoxygenation of *N*-oxides.

Table 5A.2. Reaction of Diverse Arylboronic Acids 1 and Aryl bromides 2[a,b]



3a, 4 h, 96%

3b, R = 2-CHO, 5 h, 88%
3c, R = 4-CHO, 5 h, 90%

3d, 5 h, 93%

3e, 5 h, 86%

3f, X = H, 4 h, 87%
3g, X = Br, 4 h, 87%
3h, X = Cl, 4 h, 83%
3i, X = F, 4 h, 86%
3j, X = CF3, 4 h, 83%
3k, X = OMe, 3 h, 98%

3l, 4 h, 95%

3m, X = H, 5 h, 80%
3n, X = Br, 5 h, 74%
3o, X = F, 5 h, 76%

3p, X = H, 4 h, 88%
3q, X = OMe, 4 h, 86%

3r, X = H, 4 h, 90%
3s, X = OMe, 4 h, 91%

3t, 5 h, 76%

3u, 5 h, 70%

3v, 5 h, 81%

3w, 4 h, 80%

3x, X = H, 5 h, 80%
3y, X = 4-OMe, 3 h, 92%
3z, X = 4-Et, 4 h, 90%

3aa, 4 h, 84%

3ab, 4 h, 89%

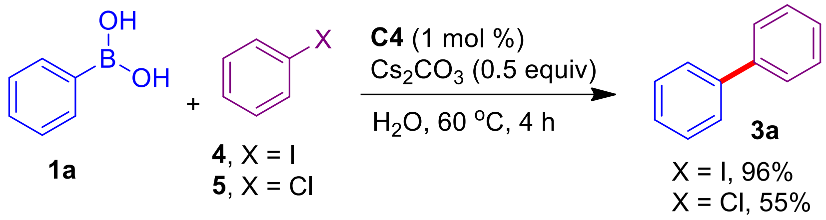
3ac, X = H, 4 h, 88%
3ad, X = Et, 3 h, 90%

3ae, 4 h, 85%

3af, 4 h, 83%

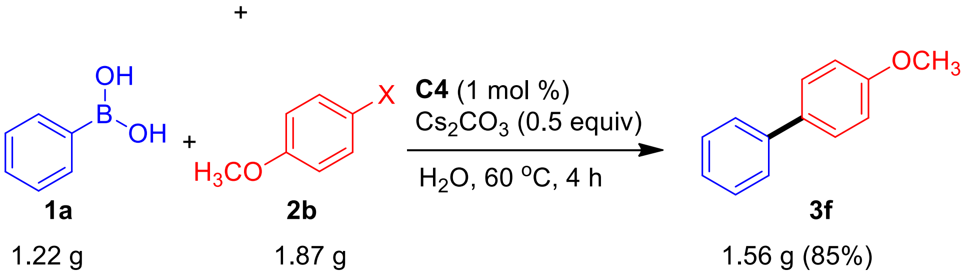
[a] Reaction Condition: Boronic acid **1a-m** (0.5 mmol), bromobenzene **2a-l** (0.5 mmol), catalyst **C4** (1 mol %), Cs_2CO_3 (0.5 equiv), H_2O (1.0 mL) at 60 °C. [b] Yields are of isolated pure products.

Also, we found that 4-imidazopyridine bromobenzene **2l** with boronic acid and *para*-methoxy with naphthal boromic acid delivered cross-coupled biphenyls **3ae-3af** in 83% and 85% yields respectively. Furthermore, we extended the optimized protocol to investigate the reactivity of other halobenzenes and found that the iodobenzene **4** was comparable to the bromobenzene (Scheme 5A.11). Whereas, Chlorobenzene **5** gave less yield compared to bromo and iodo benzenes.



Scheme 5A.11

Finally, we investigated the efficiency of this protocol for gram scale reaction using phenylboronic acid **1a** and 4-bomo anisole **2b** under the standard condition, gave **3f** in 85% of yield (Scheme 5A.12).



Scheme 5A.12

5A.4. Conclusion

We conclude by saying that we have synthesized an efficient, easily accessible, air-stable Pd(II)ANA-catalyzed Suzuki-Miyaura coupling reaction in water at moderate temperature to produce different substituted or unsymmetrical biaryls with functional group diversities. The protocol is simple and efficient at low catalyst loading. The protocol demonstrated at gram scale preparation of biphenyl derivatives for commercial applications.

5A.5. Experimental Section

5A.5.1. General Information

All the compounds used in development of Suziki-Miyaura cross coupling like Boronic acids, halobenzenes, K_2CO_3, Na_2CO_3, KO^{t}Bu, $NaHCO_3$, NaOH, and Cs_2CO_3 were purchased from Sigma-Aldrich, Spectrochem, SRL, and SD-Fine used as received. Catalysts **C1-C4** were synthesised as reported below. All reactions were performed in pure water (>5 MΩ cm @ 25 °C, total organic content <30ppb). The reactions were monitored by analytical TLC on 200 µm aluminium-foil-backed silica gel plates. The column chromatography was performed with 100-200 mesh silica gel. Finding the melting points of solid compounds was done with open capillaries using Stuart SMP30 melting point apparatus and is uncorrected. NMR (^{1}H and ^{13}C) spectra of all the synthesized compounds were recorded on Bruker AVANCE HD (400 MHz /100 MHz) spectrometer. Using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and dd = doublet of doublets.

5A.5.2. General Procedure for the Reaction of Arylboronic Acids and Halobenzenes

In an oven dried 10 mL round bottom flask were added arylboronic acid **1a** (125 mg, 1.0 mmol), halobenzene **2a** (191.7 mg, 1.0 mmol), Cs_2CO_3 (167 mg, 0.5 equiv) and catalyst **C4** (43 mg, 1 mol%) in water (2 mL). The reaction mixture was allowed to stir at 60 °C. After completion of reaction (monitored by TLC) the crude residue was extracted into in ethylacetate (10 mL x 3) and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was separated using silica-gel column chromatography by eluting with ethylacetate/hexanes.

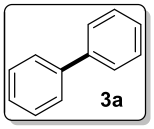
5A.5.3. General Procedure for the Preparation of the Catalysts C1-C4[36]

The freshly purified ligand (120 mg, 1 mmol) and palladium (II) chloride (87 mg, 0.5 mmol) were dissolved in 10 mL of anhydrous acetonitrile and refluxed for 30 min. The colour of the reaction mixture changed from pink to yellow. After completion of the reaction, the solid reaction mixture was washed with acetonitrile/Diethy eher and dried under vacuum to produce pure product.

5A.6. Characterization Data of Products

1,1'-Biphenyl (3a)[37a]

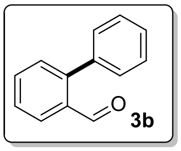
Yield: 96%, white solid, M.P. 68-69 ºC.


3a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 4H), 7.53 (t, *J* = 7.5 Hz, 4H), 7.44 (t, *J*= 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 128.9, 127.4, 127.3.

1,1’-Biphenyl-2-carbaldehyde (3b)[37a]

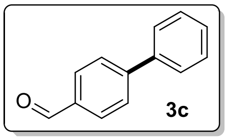
Yield: 88%, yellow liquid.


3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.51(d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 3H), 7.39 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 146.0, 137.8, 133.7, 130.8, 130.1, 128.5, 128.1, 128.0, 127.9, 127.7. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{14}O$ $[M+H]^+$ 223.1125, found 223.1131.

1,1’-Biphenyl-4-carbaldehyde (3c)[37a]

Yield: 90%, white solid, M.P. 169-170 ºC.

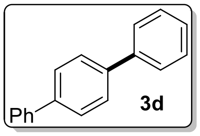

3c

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.88 (d, *J* = 7.3 Hz, 2H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 6.8 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 147.2, 139.7, 135.2, 130.3, 129.0, 128.5, 127.7, 127.4.

1,1’:4’,1’’-Terphenyl (3d)[37j]

Yield: 93%, white solid, M.P. 200-201 ºC.

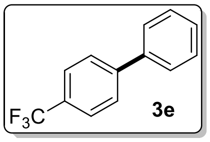
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.55 (m, 8H), 7.39 (t, *J* = 7.4 Hz, 4H), 7.29 (t, *J* = 7.3 Hz, 2H).


3d

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 140.1, 128.8, 127.4, 127.1. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{14}O$ $[M+H]^+$ 223.1125, found 223.1131.

4-(Trifluoromethyl)-1,1’-biphenyl (3e)[37j]

Yield: 86%, white solid, M.P. 69-70 °C.

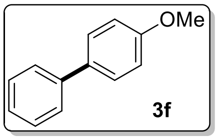


3e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 4H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 139.8, 129.0, 128.2, 127.4, 127.3, 125.7.

4-Methoxy-1,1'-biphenyl (3f)[37a]

Yield: 96%, white solid, M.P. 86-87 °C.

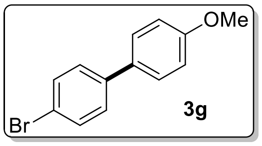


3f

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 8.1 Hz, 4H), 7.34 (t, *J* = 7.1 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 140.8, 133.8, 128.7, 128.2, 126.8, 126.7, 114.2, 55.4.

4-Bromo-4'-methoxy-1,1'-biphenyl (3g)[37j]

Yield: 87%, white solid, M.P. 140-141 °C.

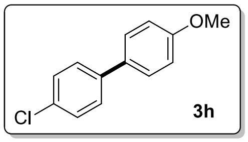


3g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 139.8, 132.5, 131.8, 128.3, 128.0, 120.8, 114.3, 55.4.

4-Chloro-4'-methoxy-1,1'-biphenyl (3h)[37a]

Yield: 83%, white solid, M.P. 112-113 °C.

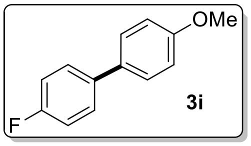


3h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.4, 6.3 Hz, 4H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 139.3, 132.7, 132.5, 128.9, 128.0, 127.9, 114.3, 55.4.

4-Fluoro-4'-methoxy-1,1'biphenyl (3i)[37j]

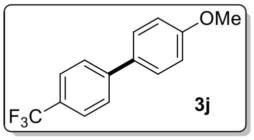
Yield: 86%, white solid, M.P. 90-91 °C.



3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 9.5 Hz, 4H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 7.7 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 160.9, 159.1, 137.0, 132.9, 128.3, 128.2, 128.0, 115.6, 115.4, 114.3, 55.4.

4-Methoxy-4’-(trifluoromethyl)-1,1’-biphenyl (3j)[37h]



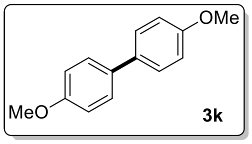
3j

Yield: 83%, white solid, M.P. 124-125 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.56 (m, 4H), 7.47 (d, J = 8.1 Hz, 2H), 6.93 (d, J = 8.1 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 144.3, 132.2, 128.4, 126.9, 125.7, 114.4, 55.4.

4,4’-Dimethoxy-1,1’-biphenyl (3k)[37f]

Yield: 98%, white solid, M.P. 137-138 °C.

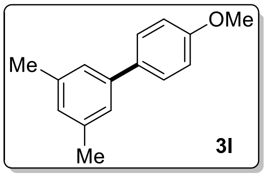


3k

^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 7.40-7.36 (m, 2H), 6.88-6.84 (m, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 158.7, 133.2, 127.6, 114.2, 55.30.

4’-Methoxy-3,5-dimethyl-1,1’-biphenyl (3l)

Yield: 92%, colourless liquid, M.P. 137-138 °C.

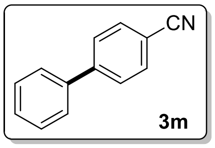


3l

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.7 Hz, 2H), 7.08 (s, 2H), 6.86 (dd, J = 5.2 Hz, 3.4 Hz, 3H), 3.73 (s, 3H), 2.27 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 140.9, 138.2, 134.0, 128.4, 128.2, 124.7, 114.1, 55.4, 21.5.

1,1’-Biphenyl]-4-carbonitrile (3m)[37a]

Yield: 80%, pale yellow solid, M.P. 88-89 °C.

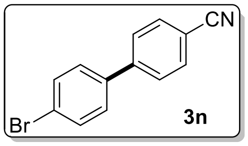


3m

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 7.46 – 7.39 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 139.2, 132.6, 129.1, 128.7, 127.8, 127.2, 119.0, 110.9.

4’-Bromo[1,1’-biphenyl]-4-carbonitrile (3n)

Yield: 74%, white solid, M.P. 145-146 °C.

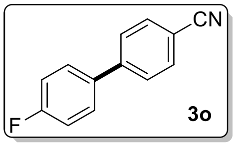


3n

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.2 Hz, 2H), 7.58-7.53 (m, 4H), 7.38 (d, J = 7.1 Hz, 2H).^{13}C (100 MHz, $CDCl_3$) δ 144.4, 138.1, 132.7, 132.3, 128.8, 127.5, 123.2, 118.8, 111.4.

4'-Fluoro-[1,1'-biphenyl]-4-carbonitrile (3o)[37k]

Yield: 76%, white solid, M.P. 115-116 °C.

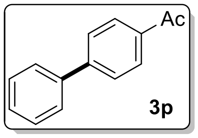


3o

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 6.3 Hz, 2H), 7.10 (t, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 164.4, 162.0, 144.7, 135.3, 132.7, 129.0, 128.9, 127.6, 118.9, 116.3, 116.0, 111.0.

1-([1,1'-Biphenyl]-4-yl)ethanone (3p)[37a]

Yield: 88%, white solid, M.P. 120-121 °C.

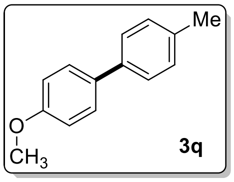


3p

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.8, 145.7, 139.8, 135.9, 128.9, 128.3, 127.3, 26.7.

1-(4'Methoxy-[1,1'-biphenyl]-4-yl)ethanone (3q)

Yield: 86%, white solid, M.P. 156-157 °C.

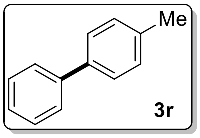


3q

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.7, 160.0, 145.4, 135.3, 132.2, 129.0, 128.4, 126.6, 114.4, 55.4, 26.6.

4-Methyl-1,1'-biphenyl (3r)[37j]

Yield: 90%, yellow gummy liquid.

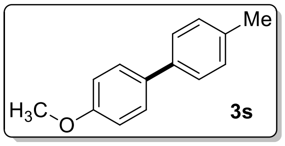


3r

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.2, 138.4, 137.1, 129.5, 128.8, 127.0, 21.2.

4-Methoxy-4'-methyl-1,1'-biphenyl (3s)[37g]

Yield: 91%, white solid, M.P. 111-112 °C.

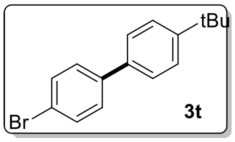


3s

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.0, 138.0, 136.4, 133.8, 129.5, 128.0, 126.6, 114.2, 55.4, 21.1.

4-Bromo-4'-(*tert*-butyl)-1,1'-biphenyl (3t)

Yield: 91%, white solid, M.P. 140-141 °C.

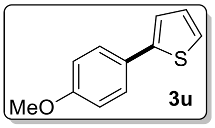


3t

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.47 (dd, J = 5.1 Hz, 2.4 Hz, 4H), 7.43 (d, J = 8.4 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 140.0, 137.1, 131.8, 128.6, 126.6, 125.9, 121.2, 34.6, 31.4.

2-(4-Methoxyphenyl)thiophene (3u)[1a]

Yield: 76%, colourless liquid, M.P. 140-141 °C.

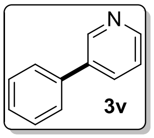


3u

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 2H), 7.28 (m, 3H), 6.87 (d, J = 7.6 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 158.9, 142.0, 128.8, 127.6, 126.3, 126.1, 118.9, 114.2, 55.3.

3-Phenylpyridine (3v)[37l]

Yield: 81%, Pale yellow solid, M.P. 162-163 °C.



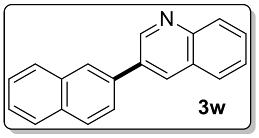
3v

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.52 (s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.40 (t, J = 7.1 Hz, 2H), 7.34 (d, J = 6.5 Hz, 1H), 7.29 (t, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 137.8, 136.7, 134.4, 129.1, 128.1, 127.2, 123.6.

3-(Naphthalen-2-yl)quinoline (3w)

Yield: 80%, yellow solid, M.P. 111-112 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.42 (s, 1H), 8.18 (d, J = 9.0 Hz, 2H), 7.99 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 7.1 Hz, 1H), 7.91 (d, J = 7.7 Hz, 2H), 7.84 (d, J = 8.5 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.57-7.50 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.1, 135.1, 133.8, 133.7, 132.9, 129.6, 129.1, 128.3, 128.1, 128.08, 127.8, 127.2, 126.7, 126.6, 126.5, 125.2.

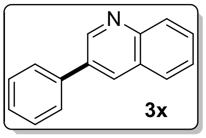


3w

3-Phenylquinoline (3x)[37g]

Yield: 80%, pale yellow gummy liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.22 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.1 Hz, 3H), 7.51 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.3, 137.9, 133.9, 133.3, 129.5, 129.2, 128.2, 128.0, 127.5, 127.1.

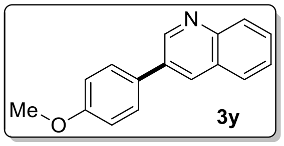


3x

3-(4-Methoxyphenyl)quinoline (3y)[37g]

Yield: 92%, pale yellow solid, M.P. 84-86 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 2.1 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.59 (t, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 149.7, 146.9, 133.5, 132.5, 130.2, 129.1, 128.5, 128.1, 127.9, 127.0, 114.7, 55.4.

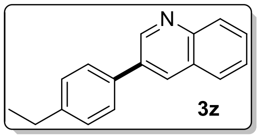


3y

3-(4-Ethylphenyl)quinoline (3z)[37g]

Yield: 90%, pale yellow solid, M.P. 85-86 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, *J* = 2.1 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.57 (t, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.1, 144.4, 135.1, 133.8, 132.9, 129.3, 129.1, 128.7, 128.1, 128.0, 127.3, 127.0, 28.6, 15.6.

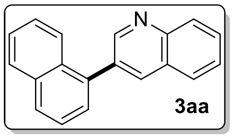


3z

2-(Naphthalen-1-yl)quinoline (3aa)[37c]

Yield: 80%, brown liquid.

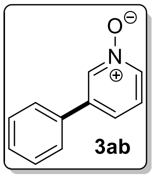
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.17 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.88-7.82 (m, 2H), 7.78 (t, *J* = 7.7 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.53-7.41 (m, 4H), 7.37 (t, *J* = 7.4 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 147.2, 136.4, 136.3, 133.9, 133.8, 131.7, 129.7,129.3, 128.7, 128.6, 128.0, 127.8, 127.1, 126.7, 126.2, 125.5, 125.4.



3aa

3-Phenylpyridine-1-oxide (3ab)

Yield: 89%, yellow liquid.

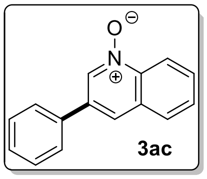


3ab

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.13 (d, *J* = 6.2 Hz, 1H), 7.46-7.38 (m, 6H), 7.28 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 137.6, 135.1, 134.2, 129.4, 126.9, 125.9, 125.0.

3-Phenylquinoline-1-oxide (3ac)[37e]

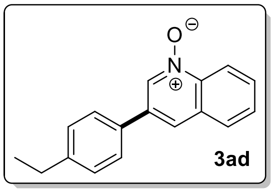
Yield: 88%, white solid, M.P. 104-105 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.75 (d, *J* = 8.6 Hz, 1H), 8.01 – 7.90 (m, 2H), 7.78 (t, *J* = 7.4 Hz, 1H), 7.68 (m, 3H), 7.53 (t, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 135.8, 135.1, 135.0, 130.3, 129.4, 129.2, 129.0, 128.4, 127.1, 123.8, 119.7.

3-(4-Ethylphenyl)quinolines-1-oxide (3ad)[37e]

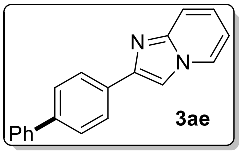
Yield: 90%, yellow solid, M.P. 122-123 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.74 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 9.1 Hz, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 140.2, 135.1, 134.9, 133.2, 130.4, 130.0, 129.1, 128.9, 128.3, 127.0, 123.2, 119.7, 28.6, 15.5.

2-([1,1'-Biphenyl]-4-yl)imidazo[1,2-a]pyridine (3ae)

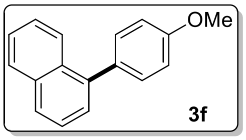
Yield: 85%, white solid, M.P. 150-151 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.8 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.90 (s, 1H), 7.70-7.64 (m, 5H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.81 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 140.7, 131.9, 128.8, 127.5, 127.0, 126.5, 125.6, 125.1, 117.5, 112.7, 108.3. HRMS (ESI) *m/z* $[M+H]^+$ calcd, for $C_{19}H_{14}N_2$+H 271.1230, found: 271.1184.

1-(4-Methoxyphenyl) naphthalene (3af)[37c]

Yield: 83%, white solid, M.P. 137-138 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 12.9 Hz, 8.3 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.44-7.31 (m, 6H), 6.95 (d, *J* = 8.0 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 139.9, 133.9, 133.2, 131.9, 131.2, 128.3, 127.4, 126.9, 126.1, 126.0, 125.7, 125.4, 113.7, 55.4.

5A.8. References

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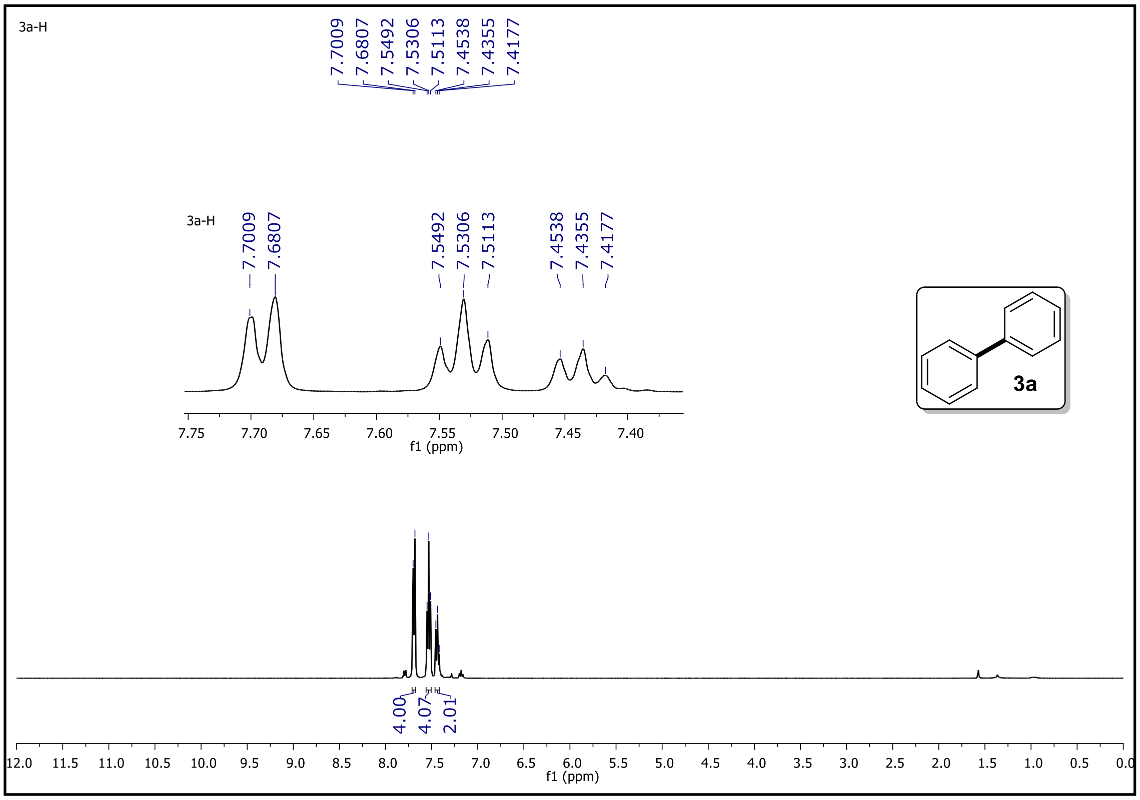
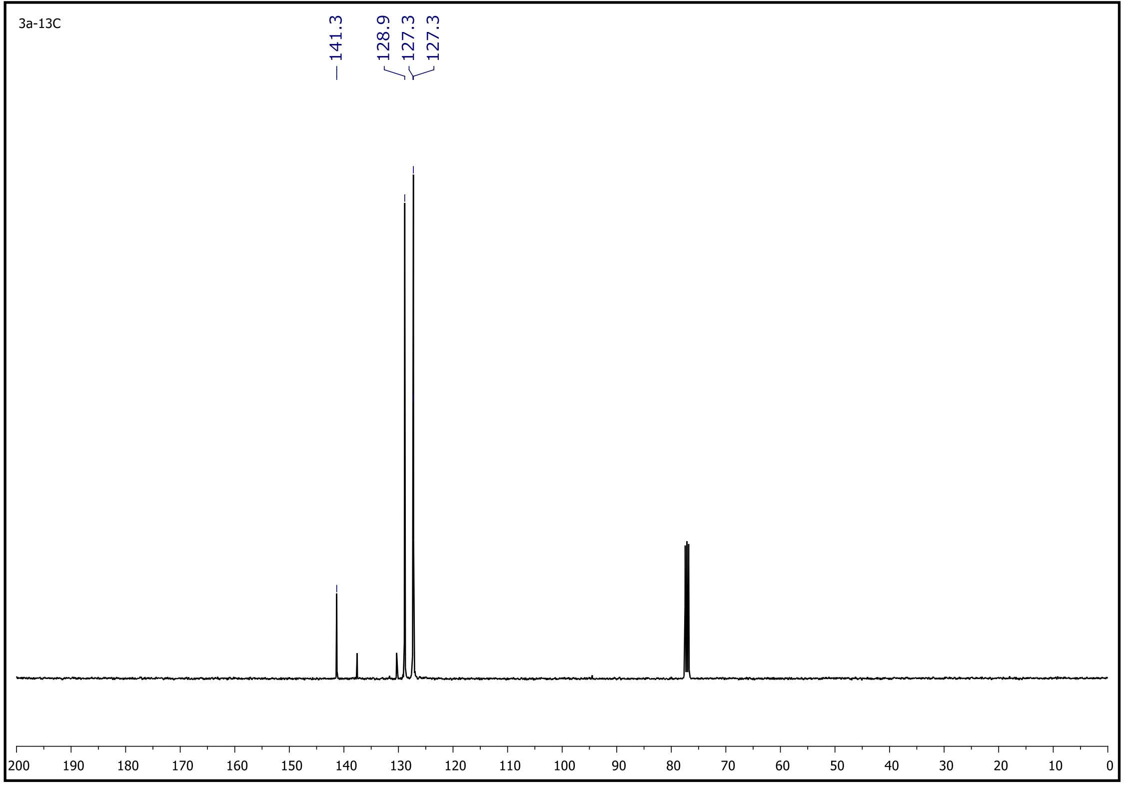
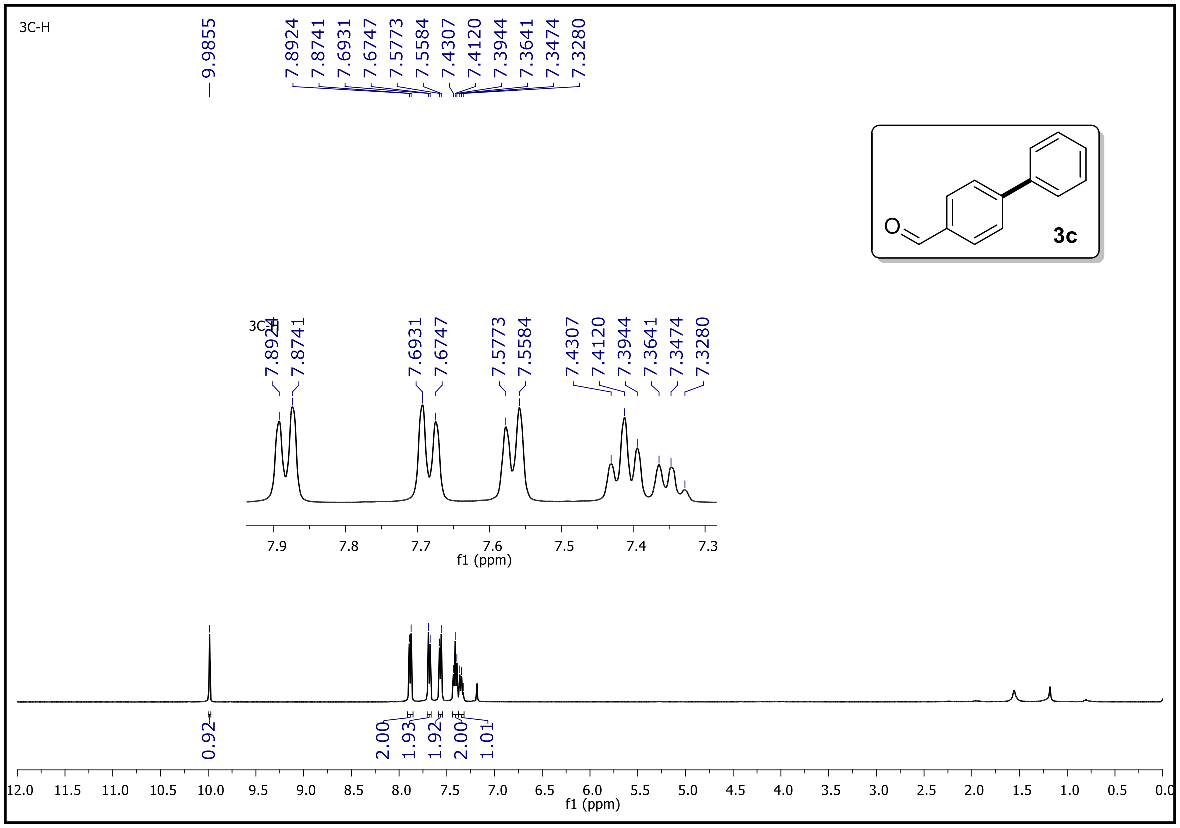
5A.9. Selected (^{1}H and ^{13}C) NMR Spectra



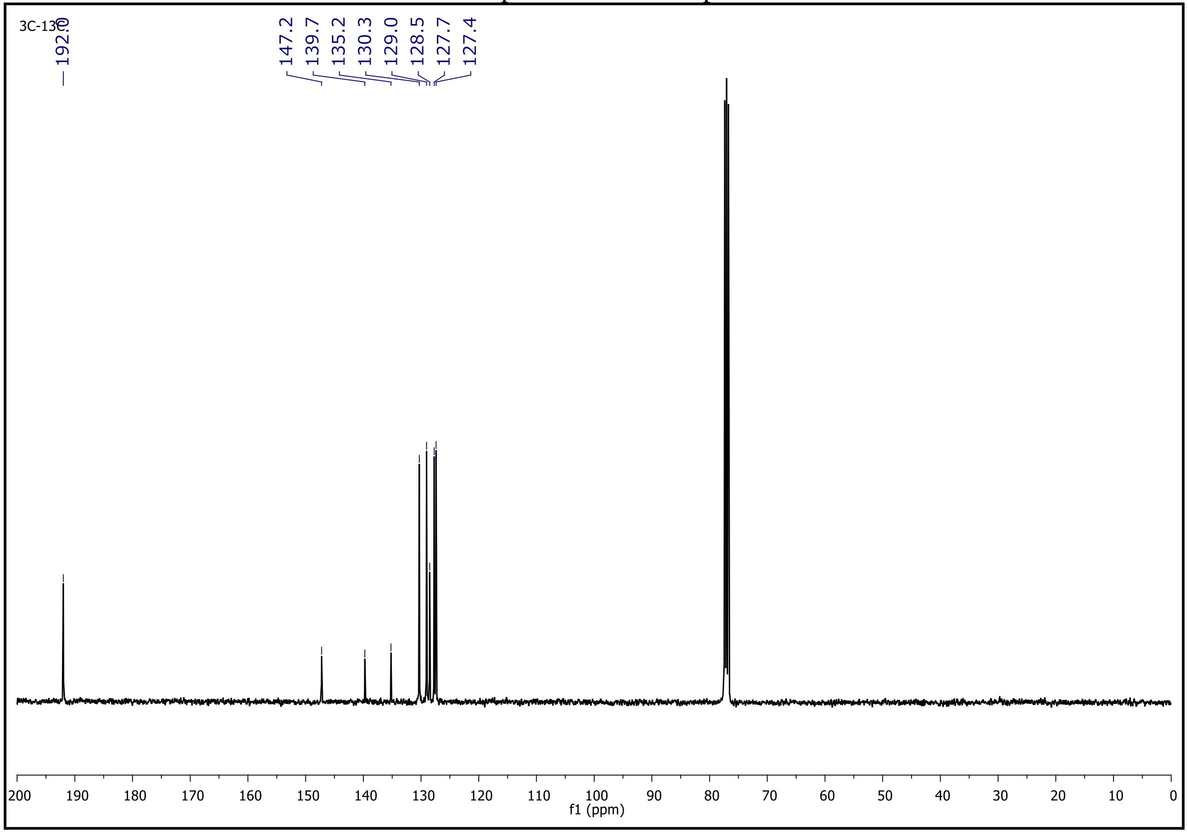
^{1}H NMR spectrum of compound **3a**



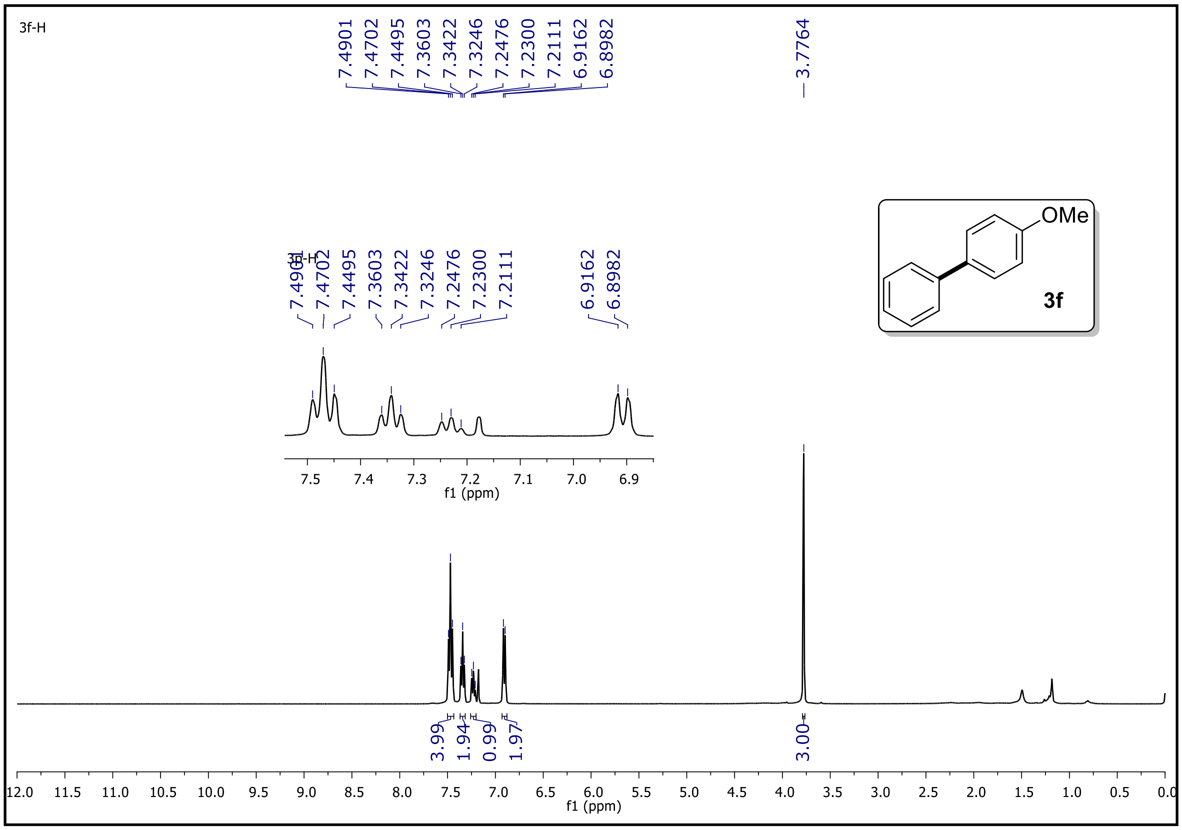
^{13}C NMR spectrum of compound **3a**



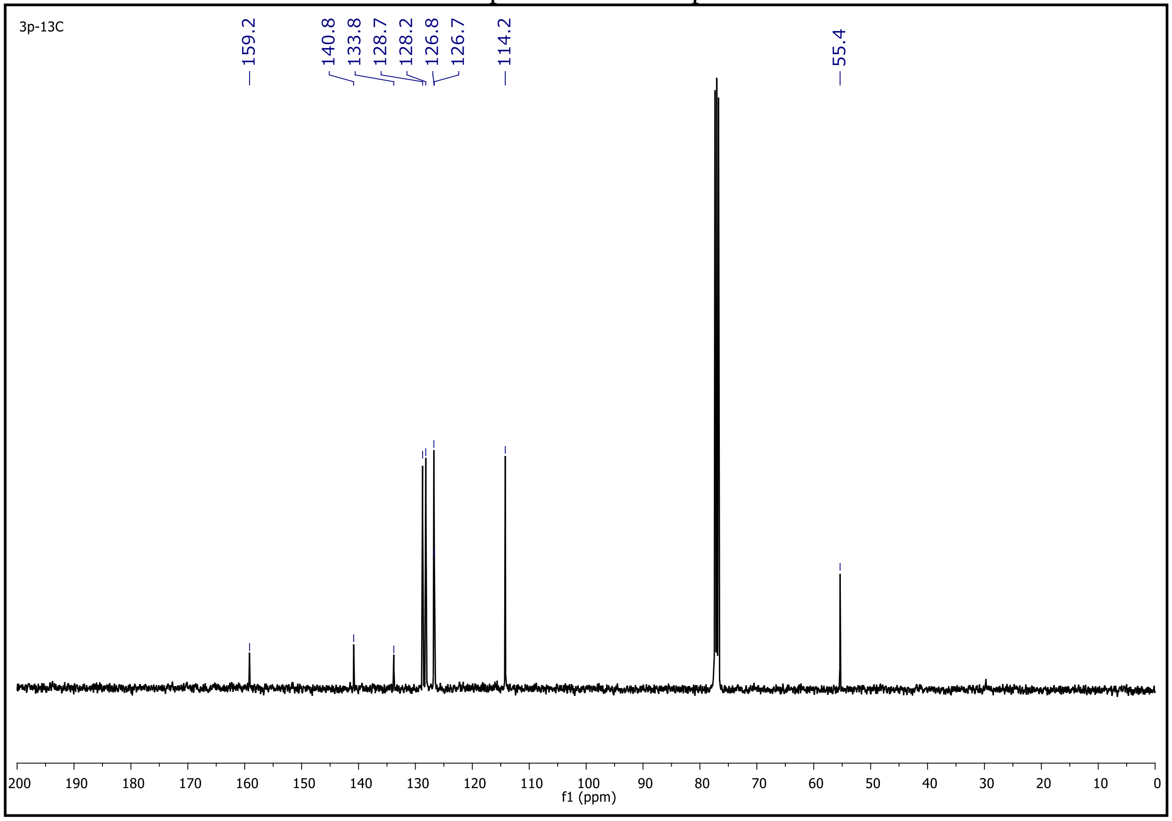
^{1}H NMR spectrum of compound **3c**



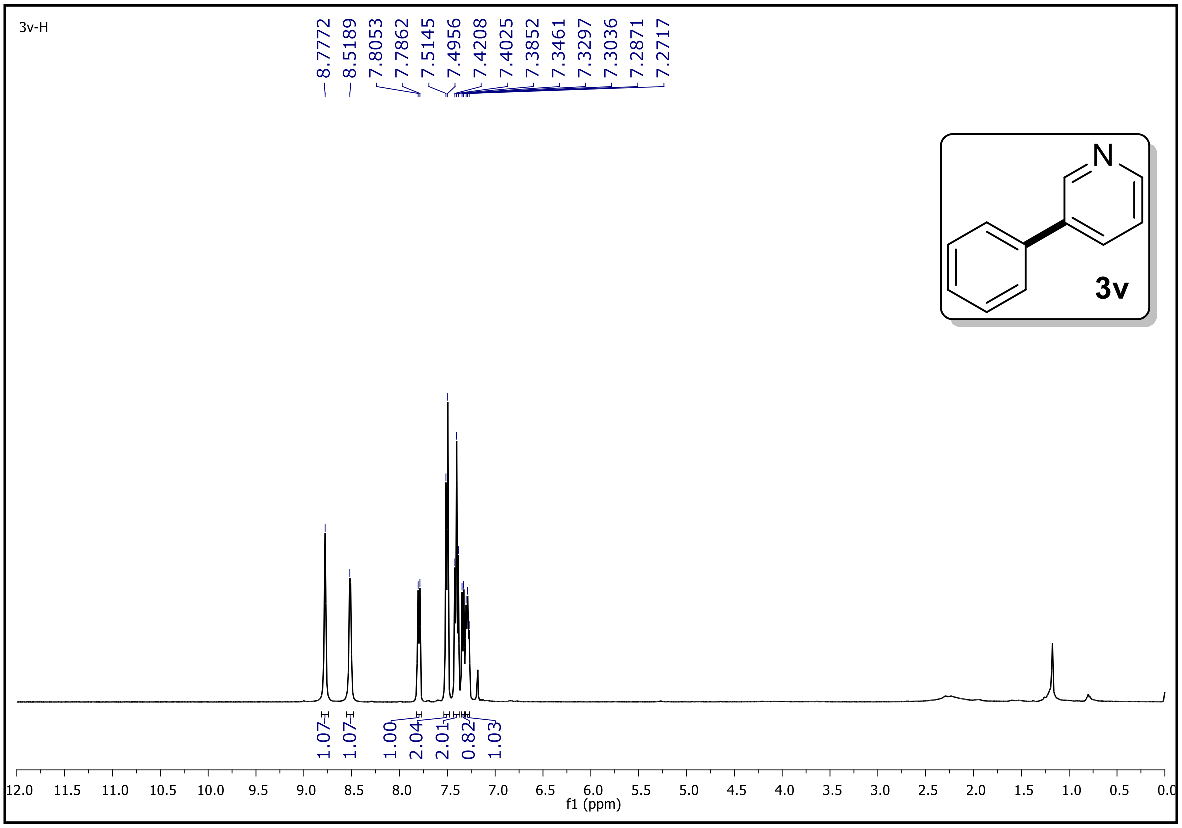
^{13}C NMR spectrum of compound **3c**



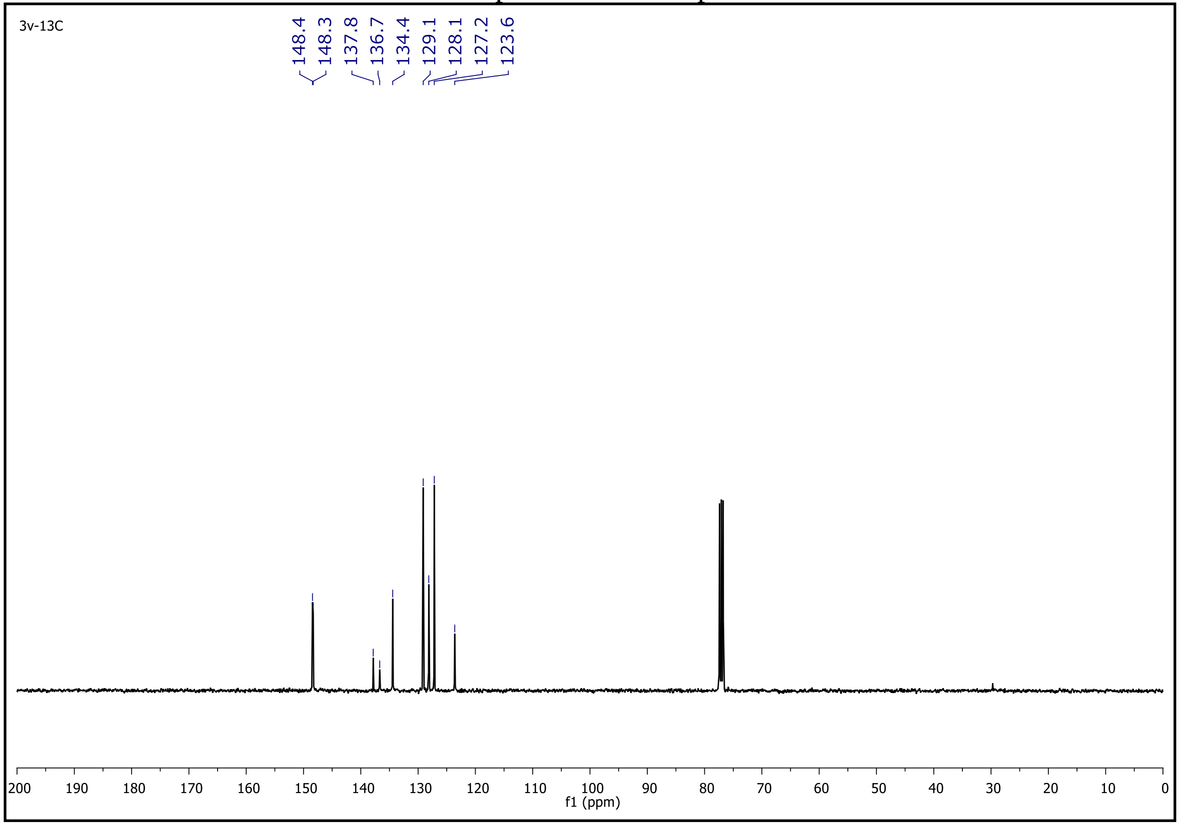
^{1}H NMR spectrum of compound **3f**



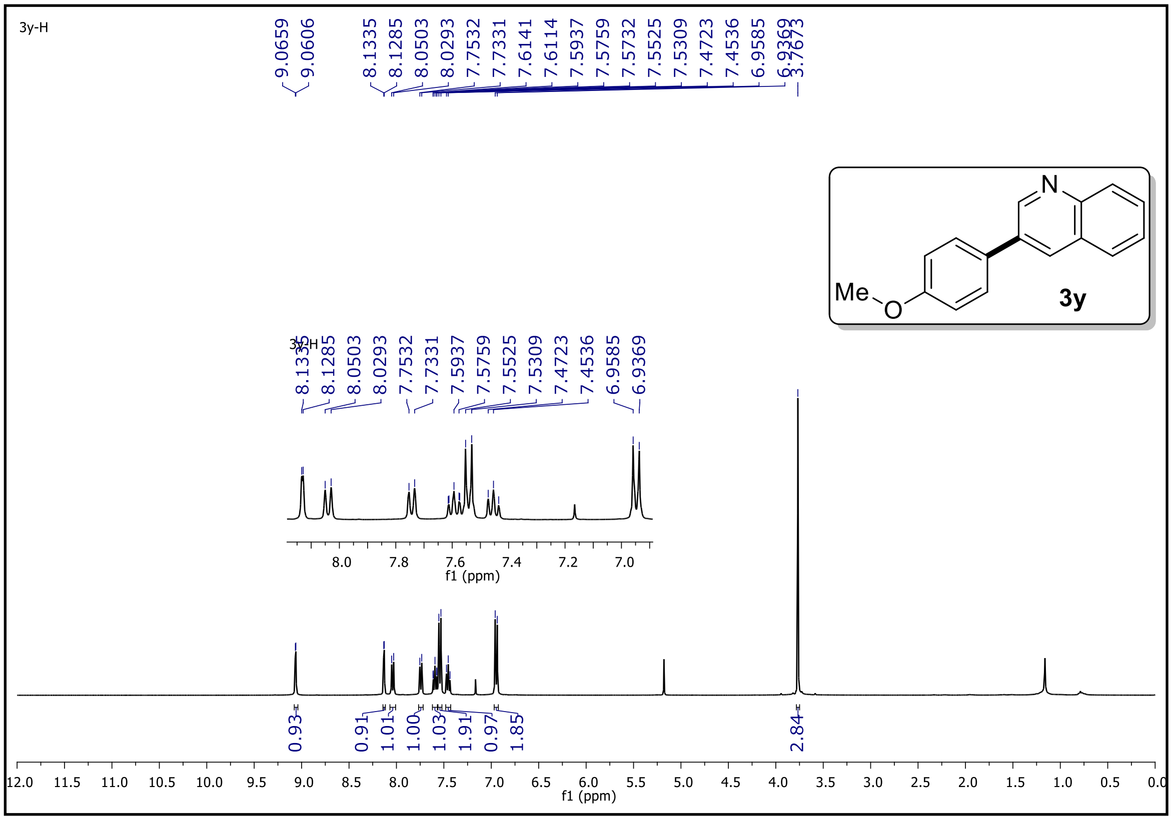
^{13}C NMR spectrum of compound **3f**



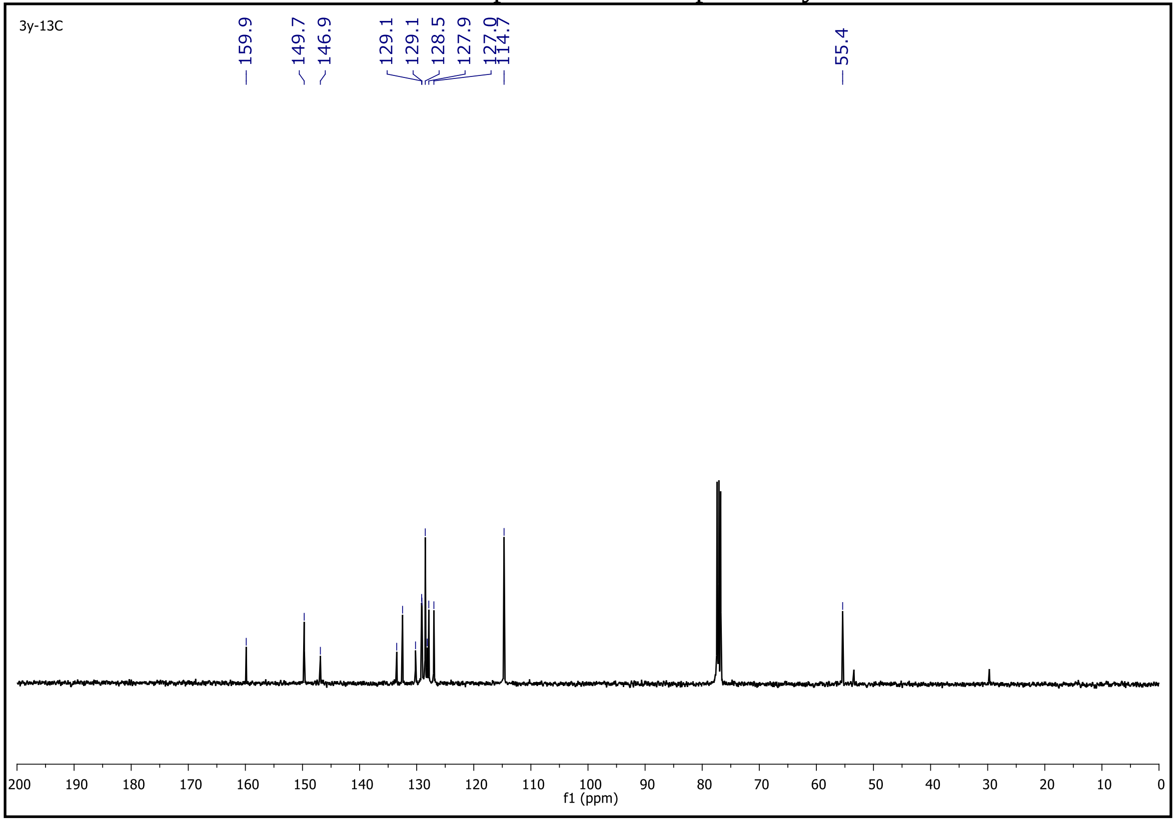
^{1}H NMR spectrum of compound **3v**



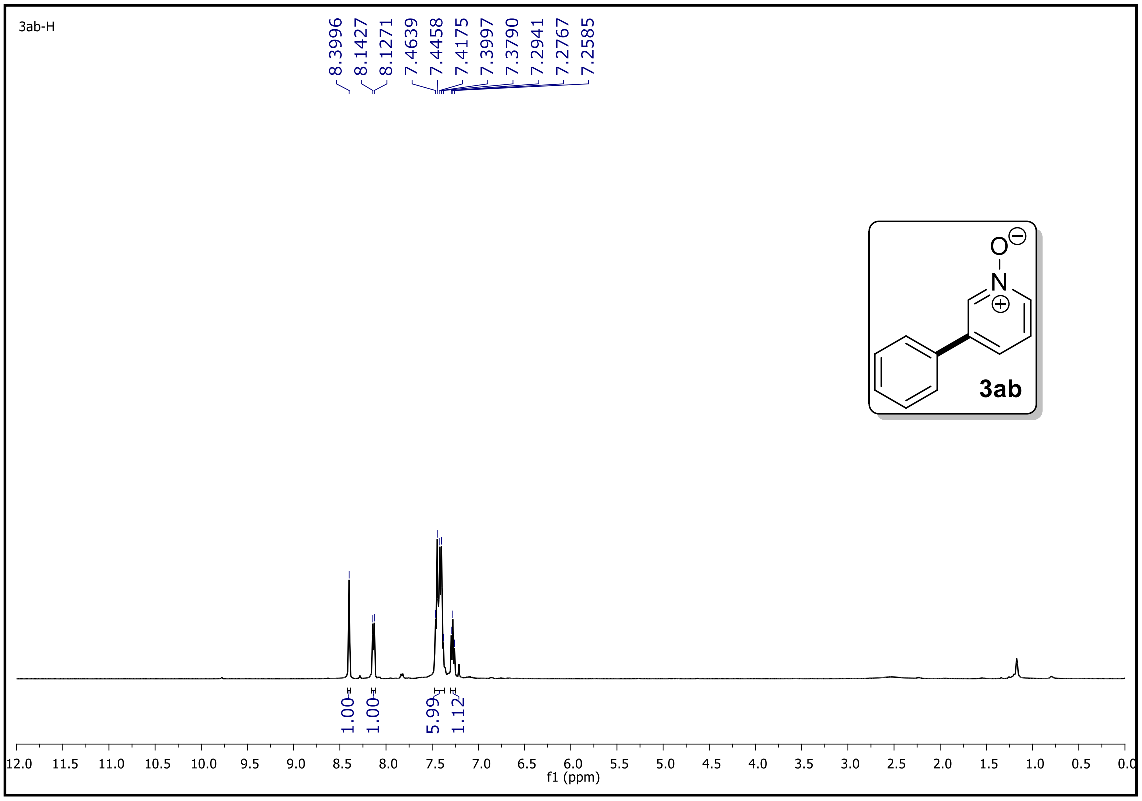
^{13}C NMR spectrum of compound **3v**



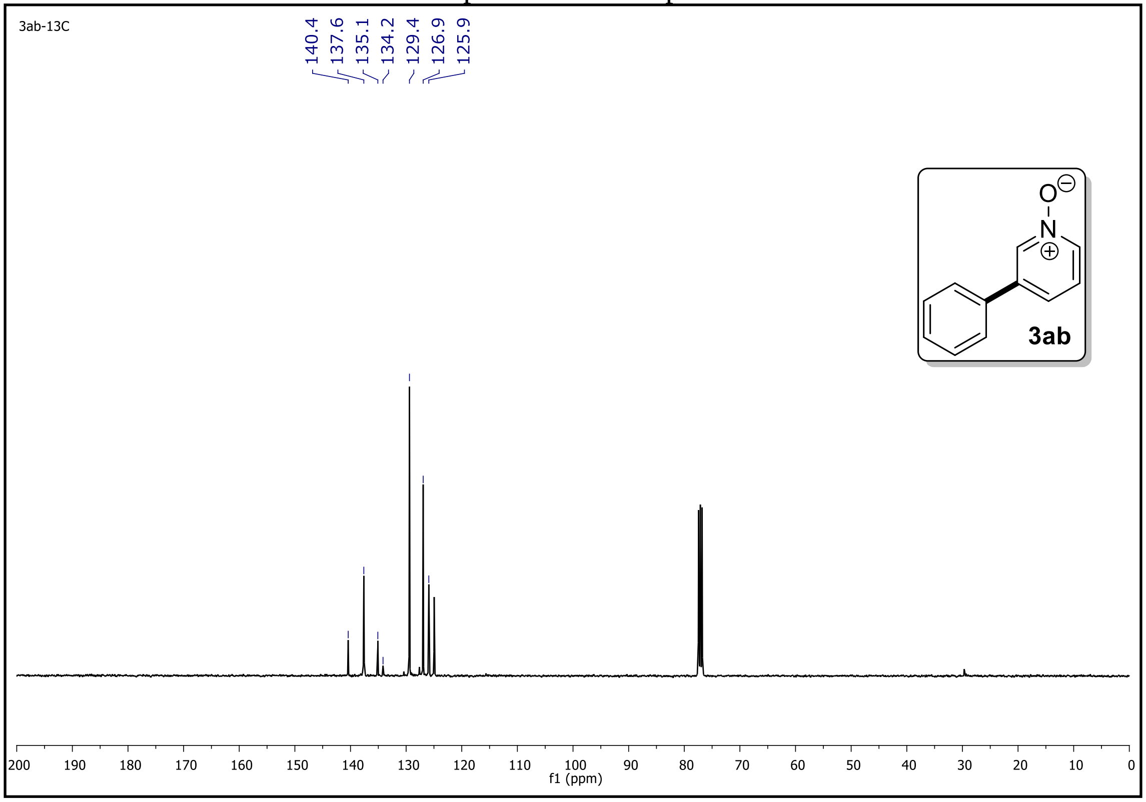
^{1}H NMR spectrum of compound **3y**



^{13}C NMR spectrum of compound **3y**



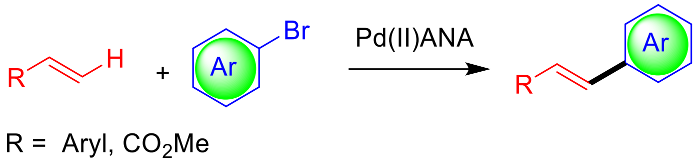
^{1}H NMR spectrum of compound **3ab**



^{13}C NMR spectrum of compound **3ab**

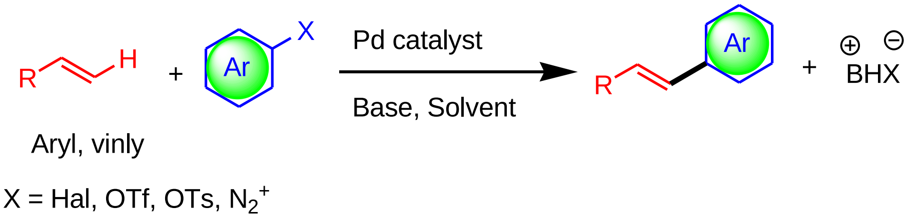
CHAPTER-V
Section-B

An Efficient Protocol for Phosphine-Free Heck Reactions Using Pd(II)ANA Complex



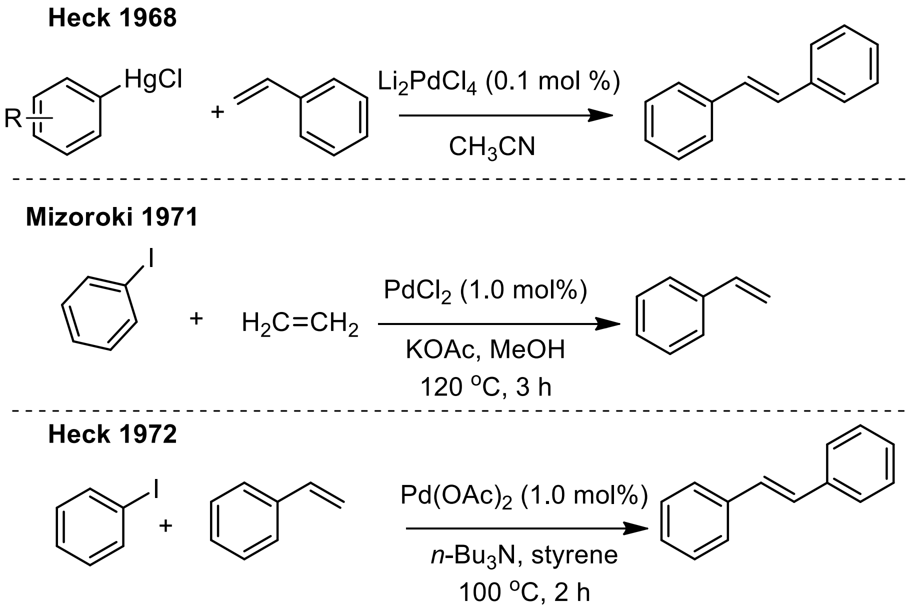
5B.1. Introduction

Mizoroki-Heck reaction, also known as Heck cross-coupling reaction was discovered in the 1970s and has grabbed the attention of industry and academia on account of its efficiency and simplicity. It employs Palladium-catalyzed cross-coupling of olefins with aryl or vinyl halides, known as the Heck- Mizoroki reaction (Scheme 5B.1), is one of the prime tools for carbon-carbon bond formation in organic synthesis. Its journey has started in the late 1960 by Heck. In 1968, Richard F. Heck reported a series of consecutive publications on palladium-mediated coupling of organomercury compounds to different olefins (Scheme 5B. 2).[1]



Scheme 5B.1

In these reports, Heck used stoichiometric ratio of palladium, but based on his initial findings, he also reported that this reaction could be achieved with a catalytic amount of Li_2PdCl_4 in presences of co-catalyst $CuCl_2$, [1a] However, this methodology became less popular due to the problems associated with the use of toxic organo mercury compounds and expensive palladium.



Scheme 5B.2

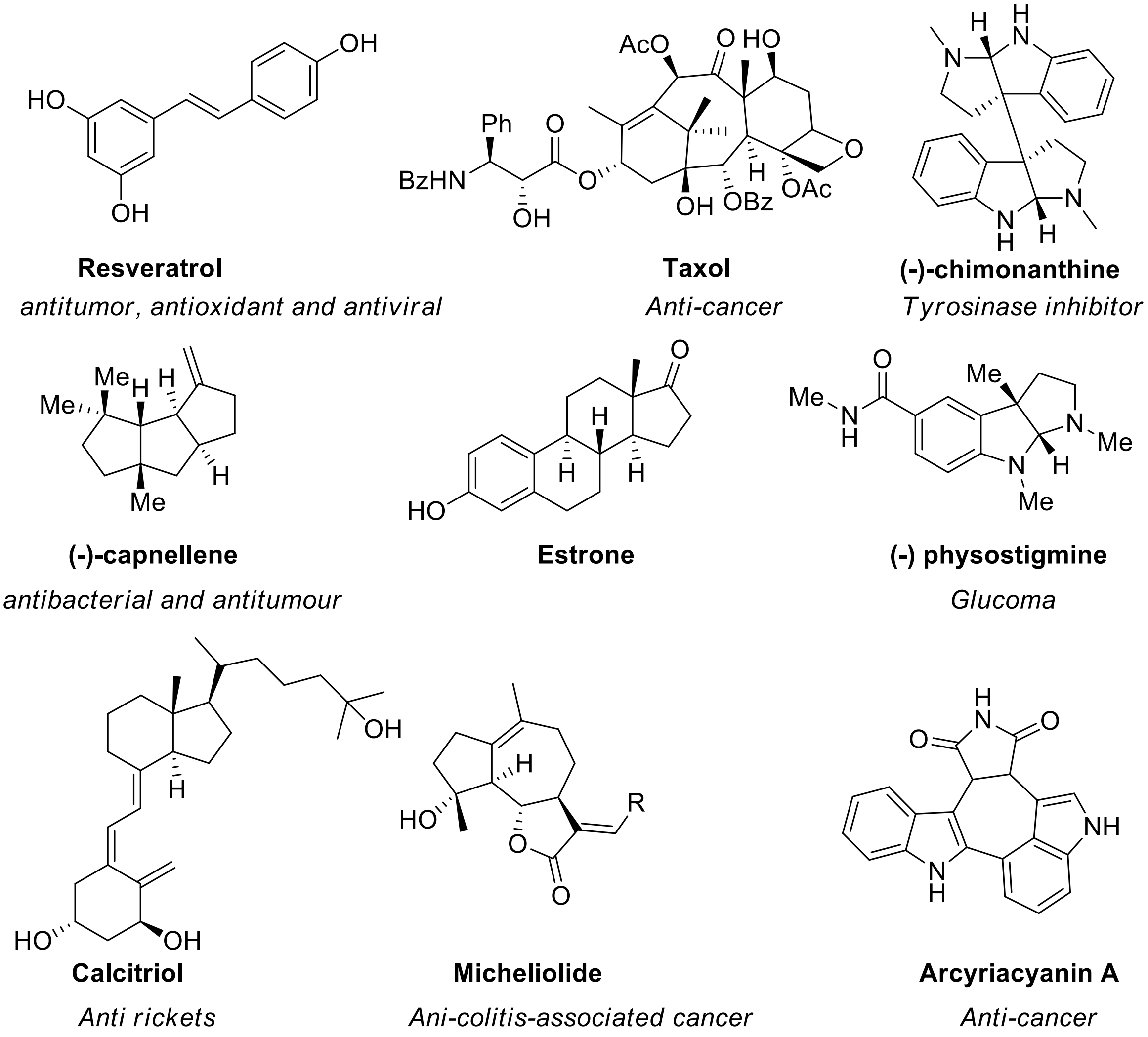
Later, Tsutomu Mizoroki realized the potential of this synthetic transformation and reported the first example of this reaction using aryl iodides in 1971.[2] Subsequently even Heck proposed a new catalytic version of his earlier process whilst replacing aryl mercury compounds with aryl halides all under much milder reaction conditions compared to those prescribed by Mizoroki.[3] This led to the emergence of the now well-known Heck–Mizoroki reaction.

Heck-Mizoroki reactions were extensively used and were developed upon over the years to include various substrates mainly on account of high efficiency and tolerance to a wide variety of functional groups. It still is one of the most sought after reaction mechanism by synthetic organic chemists especially for the formation of carbon-carbon bonds.[4] It importance can be gauged from the fact that in the year 2010 Richard F. Heck was awarded the Nobel Prize in chemistry, along with Ei-ichi Negishi and Akira Suzuki, for their work in the development of Pd-catalyzed cross-coupling reactions in organic synthesis.[5]

Heck coupling reaction is abode to many sensitive functional groups such as unprotected amino, aldehyde, ketone, hydroxyl, carboxy, ester, nitro and cyano groups.[6] The multifaceted Heck couplings has been comprehensively used in all branches of sciences including bioactive natural products, pharmaceuticals, agrochemicals and material sciences.[7-15] Some of the important natural products which are synthesized using multiple Heck Couplings as a key step are shown in the Figure 5B.1.

Catalyst used is often anything containing palladium, even in homeopathic doses, and other metals can perform the task in the absence of palladium.[16] The conditions required for this reaction i.e, reaction media, ligands around the catalyst are well studied. A worth remembering fact is that even a minute variation in the structure of substrate, ligands, nature of base temperature and pressure can lead to many unpredictable outcomes. Even some of the commercially used ligands that were used in some of the complex and sophisticated transformations may at times fail in the simplest of the cases.

The classical Heck reaction is typically performed with 1-5 mol% of a palladium catalyst along with a phosphine ligand in the presence of a suitable base. Primary role of phosphine ligands is to support palladium in its zero-oxidation state in the form of stable PdL_4 or PdL_3 species.



Resveratrol
antitumor, antioxidant and antiviral

Taxol
Anti-cancer

(-)-chimonanthine
Tyrosinase inhibitor

(-)-capnellene
antibacterial and antitumour

Estrone

(-) physostigmine
Glucoma

Calcitriol
Anti rickets

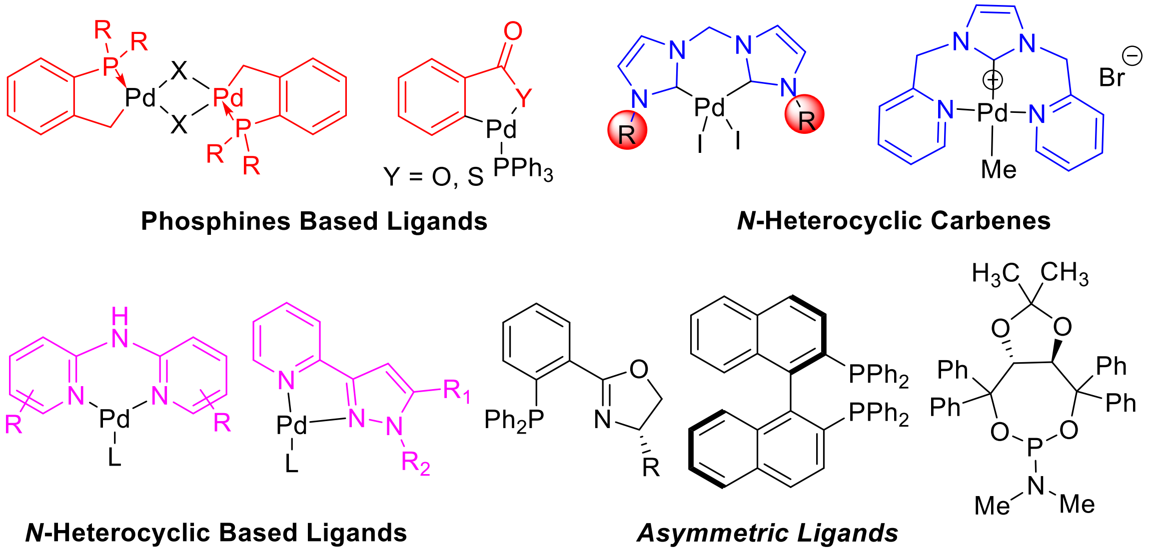
Micheliolide
Ani-colitis-associated cancer

Arcyriacyanin A
Anti-cancer

Figure 5B.1. Some of the biologically important compounds synthesized using Heck coupling.

The phosphine-assisted approach is the classical and well-established method which gives excellent results in a majority of the cases. But the reasons to explore for new methodologies are i) lower reactivity of fully ligated palladium complexes, ii) Phosphine ligands are expensive, toxic, air sensitive, and unrecoverable which in turn is Burden for large-scale applications in industries. Despite having robustness and efficiency, the coupling partners of aryl halides and triflates still have some limitations, under these conditions, the maximum turnover numbers (TON) are only 20-100 and large-scale industrial application are not practical.

A number of different approaches were developed for the synthesis of more efficient catalytic systems in the recent years. But certain limitations prop up with respect to TON number, reactivity toward deactivated aryl bromides and aryl chlorides which are readily available. Some of remedies that emerged include use of sterically bulky and electron rich phosphines, nitrogen, nucleophilic carbene ligands, sulfur based palladacycles (Figure 5B.2).[17-21]



Phosphines Based Ligands

***N*-Heterocyclic Carbenes**

***N*-Heterocyclic Based Ligands**

Asymmetric Ligands

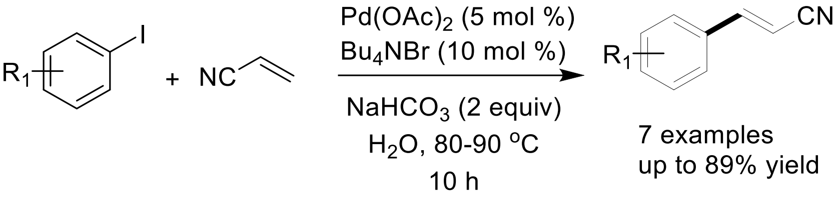
Figure 5B.2. Ligands used in Palladium Catalyzed Reactions.

All of these catalyst systems suffer from drawbacks of one or the other kind, such as high ligand sensitivity toward air and moisture, the tedious multistep synthesis and hence the rising cost of the ligands, and the use of various additives. On the other hand, the operationally and economically more advantageous ligand-free Heck reaction catalyst systems remain extremely rare.[22-25]

Recent past witnessed that most of the developments in heck couplings involve the use of both activated and unactivated aryl chlorides.[26-29] On the other hand, majority of these reactions require harsh reaction conditions like high temperature, long reaction time, high catalyst load. However, that inactivated aryl chlorides are hesitant to participate catalytic cycles due its intrinsic property of strong C-Cl bond.[30] Many reports were published for the developing of Heck cross coupling reactions in the presence of palladium catalyst along with different ligands. Thus, a search for the development of robust, inexpensive, functional group compatible ligand for heck cross-coupling is challenging for the chemist till date. All of these limitations make it an obligation upon the chemists to search for even more efficient and milder catalytic systems to see to it that the Heck cross-coupling reactions are put to good use especially in the reactions involving aryl chloride substrates.

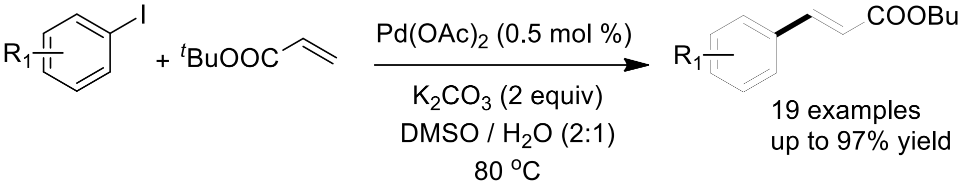
5.B.2. Reported Methods for the Heck Cross-Coupling Reactions

Zhao et al. employed Heck arylation of acrylonitrile and aryl iodides in the presence of catalytic amounts of $Pd(OAc)_2$ and Bu_4NBr in water at 80-90 °C to obtain stereoselective (*E*)-cinnamonitrile. A library of substituted (*E*)-cinnamonitriles were obtained in good yields under mild conditions (Scheme 5B.3)[31]



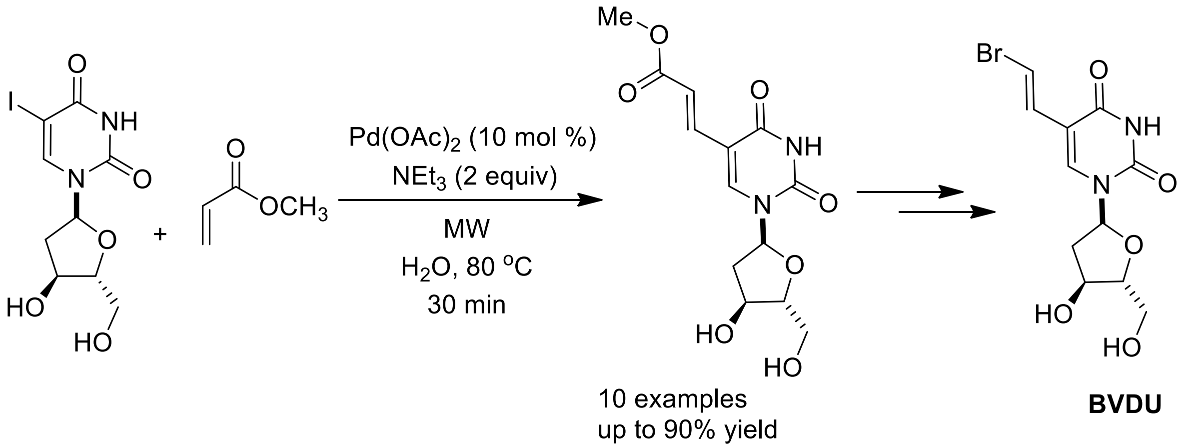
Scheme 5B.3

Amini et al. introduced an efficient ligand-free Heck Cross-coupling reaction of aryl iodides and bromides with terminal olefins under aerobic conditions by palladium acetate in water. In this report the authers observed the following points, both the base and the solvent showed significant influence on the efficiency of the reaction, K_2CO_3 is the best base and solvent should be a mixture of (2:1) H_2O/DMSO (Scheme 5B.4).[32]



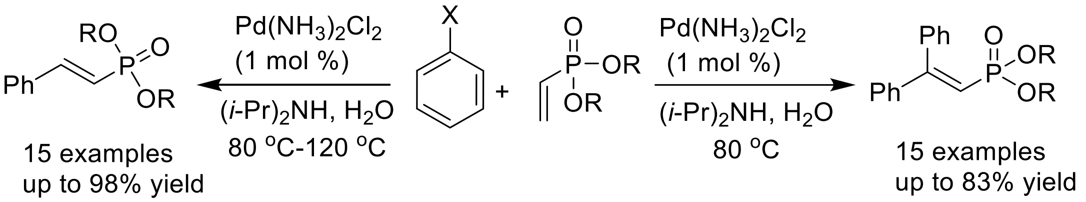
Scheme 5B. 4

Herve et al. developed an effective ligand-free HCR in water under microwave irradiation. From this method 5-iodo-2′-deoxyuridines were acrylated by $Pd(OAc)_2$, NEt_3 base in water. Continuation they synthesized the Antiviral drug BVDU ((*E*)-5-(2-bromovinyl)-2-deoxyuridine) in high yield (Scheme 5B.5).[33]



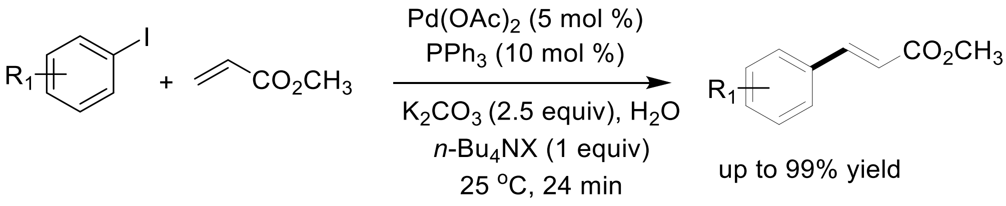
Scheme 5B.5

Tsai and research group reported palladium catalyzed operationally simplest method for mono and double Mizoroki-HCR with different aryl halides and vinyl phosphonates using $^{i}Pr_2NH$ as base in water under aerobic conditions. In this method, they found that 0.1-1.0 mol % of Pd-catalyst is enough to convert aryl halides to desired products. Also, PdNPs are *in situ* generated for the catalytic activity (Scheme 5B.6)[34]



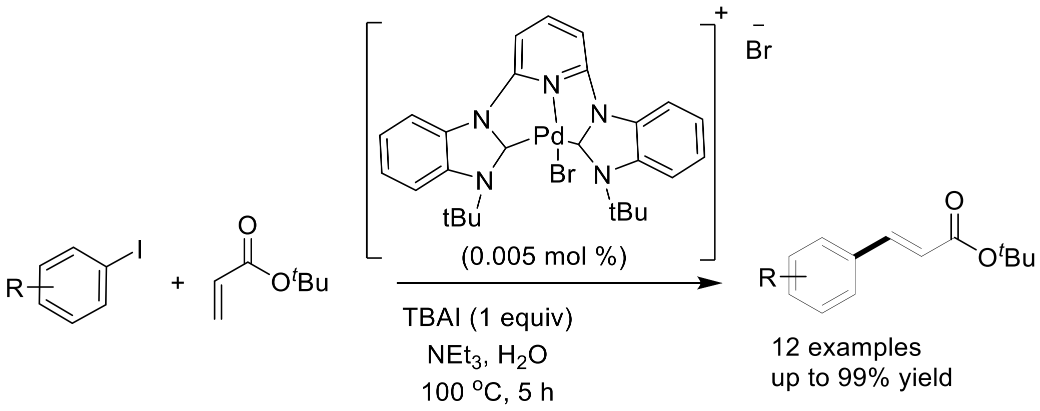
Scheme 5B.6

In 1994, **Jeffery et al.** developed Pd-catalyzed Heck coupling reaction using different solvents and quaternary ammonium salts. He found that the use of QX salts lead to increased reaction stability in aqueous solvents at room temperature and afforded excellent yields. It is the first reaction for the significant use of phosphine ligand in H_2O as solvent (Scheme 5B.7).[35]



Scheme 5B.7

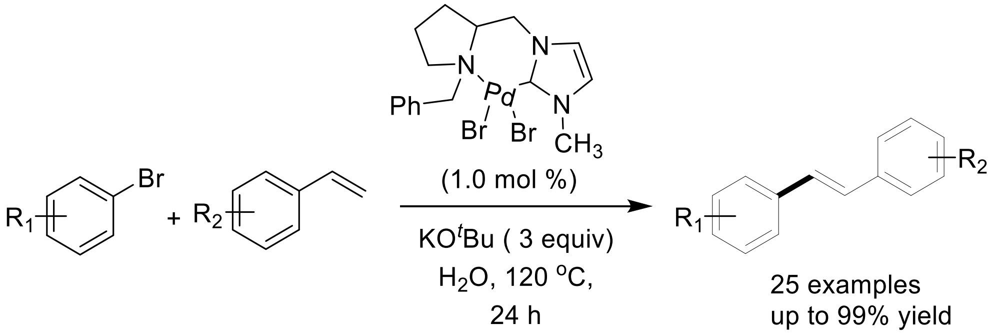
N-Heterocyclic carbene (NHC) ligands have the similar or same electronic characteristic feature to that of phosphine. Also, it has a high sigma donor ligand combined with the limited π-donor properties. These NHC were extremely used and has emerged as alternative to phosphines.[36] Unlike phosphines, these NHC tend to be easily prepared and have high functionalization and are moisture, temperature and air stable. Also, it could bind with metals tightly in all oxidant states.[37]



Scheme 5B.8

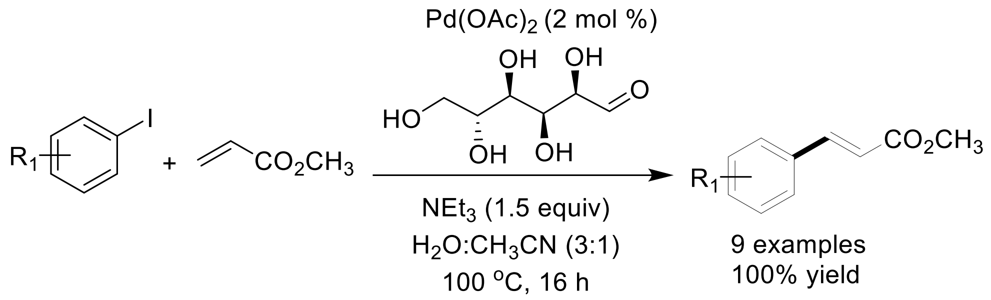
Wanh et al. reported a method for the development of HCR using pyridine-bridged bisbenzimidazoledinene-Pd-pincer complex in water as solvent. Here they used various aryl iodides with different substituted *t*-butyl acrylate afford the good yield. This catalyst tolerated various electronic properties of substituted functional groups in arenes (Scheme 5B.8).[38]

Shao and research group developed HCR using various substituted aryl bromides which includes bromo-pyridines and bromothiophenes with styrene or acrylates producing good to excellent yields in the presence of proline-derived palladium catalyst. Also, this catalyst is moisture and air stable (Scheme 5B.9).[39]



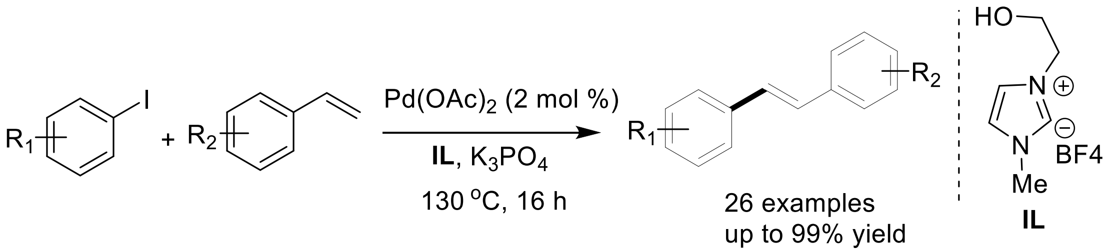
Scheme 5B.9

Recently, **Camp et al.** developed eco-friendly carbohydrate based ligands that *in situ*-generate palladium(0) nanoparticles for HCR to replace the expensive and toxic ligand. This catalytic system involve $Pd(OAc)_2$, glucose and NEt_3 in CH_3CN solvent to afford desired products in good to excellent yields. The hydroxyl groups of glucose molecule stabilizes Pd(0)NPs (Scheme 5B.10).[40]



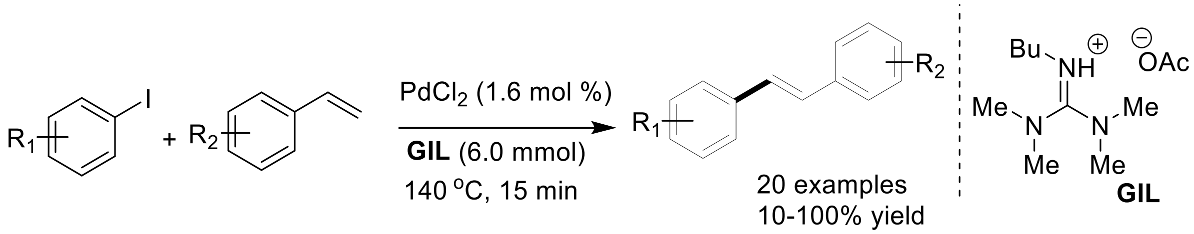
Scheme 5B.10

In 2006, **Lei Wang and research group** developed HCR using an efficient and reusable palladium catalyst and functionalized ionic liquid,1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate [HEmim][BF4] as a solvent and K_3PO_4 used as base. The olefination of bromoarene and iodoarenes with olefins delivered the corresponding stilbenes in excellent yield (Scheme 5B.11).[41]



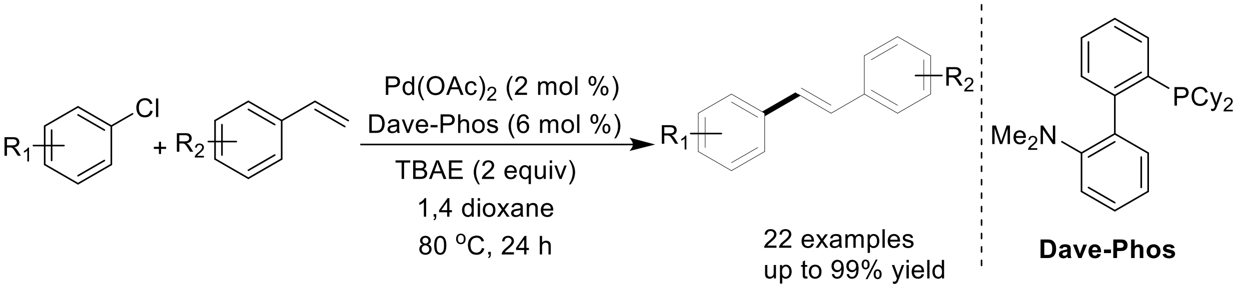
Scheme 5B.11

Zhang and research group extensively studied the formation of stilbene derivatives in HCR by palladium catalyst and Bronsted acid-base ionic liquids (GILs) which is based on acetic acid and guanidine. These GILs are showing multiple roles during the reaction such as reaction medium and as a base (Scheme 5B.12).[42]



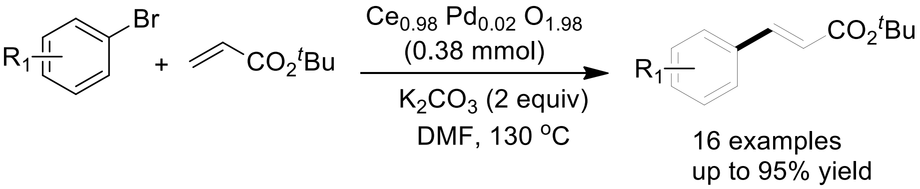
Scheme 5B.12

Hua-Jian et al. established HCR using efficient palladium catalyst along with Dava-Phos ligand and *n*-Bu_4NOAc as base to achieve biaryl in good to excellent yields. This catalytic system has proven to be efficient for inactivated aryl chlorides also (Scheme 5B.13).[43]



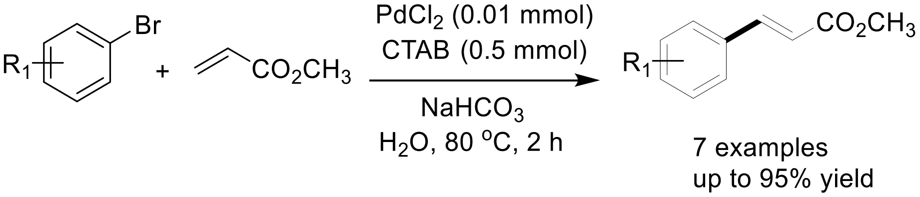
Scheme 5B.13

Sanjay kumar et. al. introduced a novel heterogeneous catalyst of Palladium substituted in cerium dioxide in the form of a solid solution ($Ce_{0\cdot98}$ $Pd_{0\cdot02}$ $O_{1\cdot98}$), which exhibits high activity and 100% trans-selectivity for the Heck reactions of aryl bromides including heteroaryl with olefins under this ligand-free protocol. Also, the catalyst can be recovered and is reusable without loss of its activity (Scheme 5B.14).[44]



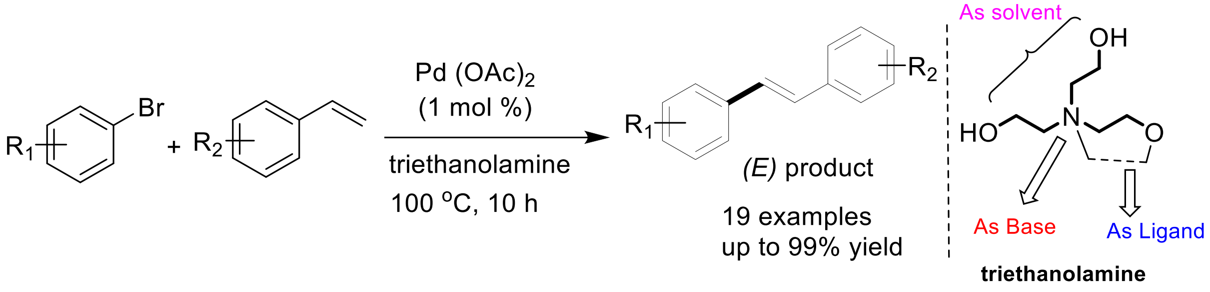
Scheme 5B.14

Bhattacharya et al. discovered a facile surfactant mediated Heck cross-couplings in water using ligand-free Pd-catalysts. The method which involves nanometric palladium colloids, is user friendly, less hazardous, and synthetically as efficient as conventional procedures using organic solvents. They used additives cetyltrimethylammonium bromide (CTAB) for the full conversion of reaction and afford biaryl in good yield (Scheme 5B.15).[45]



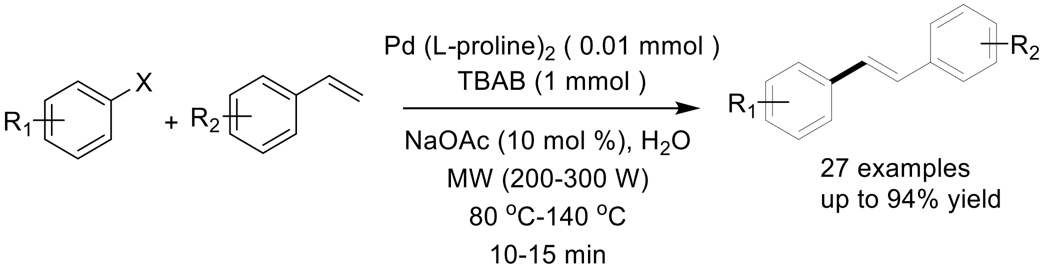
Scheme 5B.15

Lei Wang and research group effectively utilized the multifunctional triethanolamine ligand which is used as ligand, base, solvent and catalytic medium for phosphane-free palladium-catalyzed Heck reactions. The substrates of iodo and bromoarenes are olefinated to corresponding products in excellent yields in the presence of palladium acetate catalyst in triethanolamine without any additive. In addition, the multi-fuctional triethanolamine could be recovered and reused without significant loss of its reactivity (Scheme 5B.16).[46]



Scheme 5B.16

Allam et al. described a Pd(*L*-proline)$_2$ complex mediated phosphine-free Heck reaction for the synthesis of stilbene products under the microwave irradiation. This methodology is versatile and provides excellent yields of products in short reaction times and minimizes costs, operational hazards and environmental pollution (Scheme 5B.17).[47]



Scheme 5B.17

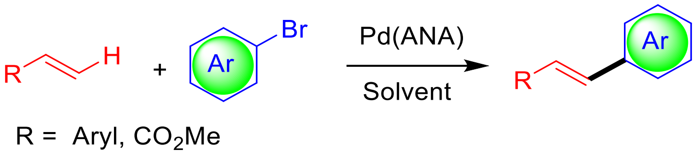
The past decade has seen a large-scale use of Heck cross-coupling of styrene and aryl halides mainly to unsymmetrical stilbene derivatives *via* sp^2-sp^2 linkage. Apart from this many other applications and methodologies were formulated for the development of intramolecular Heck coupling reactions.[48]

The study of Heck- cross coupling reactions revealed their use of ligands has not been entirely beneficial on account of its toxicity and moisture sensitivity. These reactions are found to be even more challenging in the C-C bond development.

5B.3. Present Study

Recent past has witnessed a tremendous increment in ways to develop and design novel phosphorus-free palladium catalysts for robust, active, higher turnover number and functional group tolerance at low costs.[49] In literature we found that only few pyridines based bidentate ligand for palladium catalyzed cross coupling reactions.[50]

In continuation of our efforts toward the sustainable chemistry employing metal catalysis under green reaction conditions,[51] we searched for a robust, inexpensive and biologically relevant monodentate pyridine based-Pd (II)-catalysts for Heck-cross coupling reaction.[52] Herewith, we report an efficient, less expensive, easily accessible, air-stable Pd (II)-(2-aminonicotinaldehyde) [Pd (II)-ANA] complex **C4** as a complementary catalyst for the Heck-cross coupling reaction with low catalyst (Schem 5B.18).



Scheme 5B.18

5B 3.1. Results and Discussions

Our journey begun to explore the feasibility of Pd(II)-(2-aminonicotinaldehyde) [Pd(II)-ANA)] to catalyze the Mizoroki-Heck coupling under mild condition. To validate our proposed methodology, a model reaction was conducted between styrene **2a** and 1-(4-bromophenyl) ethanone **1b** with catalysts **C1-C4** (Figure 5B.3) and base, and here only the key facts are reported in table 5B.1.

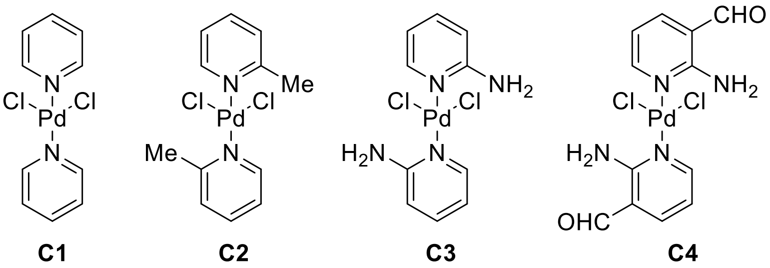
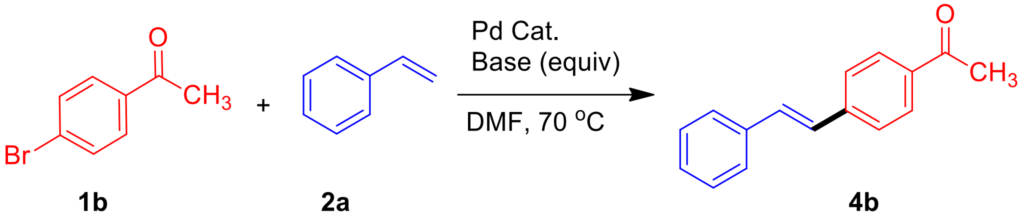


Figure 5B.3

Firstly, we have initiated optimization of reaction conditions with the aid of reaction between styrene **2a** and 1-(4-bromophenyl)ethanone **1b** employing 1.0 mol % of Pd(II) complex of pyridine **C1** and 0.5 equivalents of Cs_2CO_3 in DMF and we are delighted to observe that the formation of corresponding cross-coupled product **4b** in 50%. These results prompted us to optimize the reaction conditions to improve the product yield by changing different pyridine based ligands on palladium metal and reaction conditions. The Pd(II) complexes of 2-methylpyridine **C2**, 2-aminopyridine **C3** were successful to yield the cross-coupled product **4b** in 60-65% respectively (Table 5B.1, entry 1-3), Inspiringly, we found that the yield was improved to 85% with the use of Pd(II) complex of 2-aminonicotinaldehyde **C4** and gave unsymmetrical stilbene **4b** (Table 5B.1, entry 4). Other solvents such as chlorinated polar and nonpolar solvents were also used to improve the reaction yield but failed to give so.

Table 5B.1. Optimization of the Reaction Conditions.[a, b]



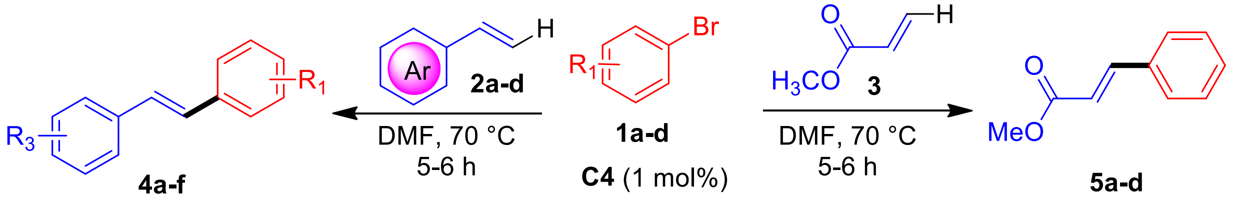
Entry	Catalyst (mol %)	Base (equiv)	Yield[b]
1	C1	K_2CO_3	50
2	C2	K_2CO_3	60
3	C3	K_2CO_3	65
4	**C4**	Cs_2CO_3	**85**
5	C4	K_2CO_3	70
6	C4	Na_2CO_3	60
7	C4	KO^{t}Bu	55
8	C4	$NaHCO_3$	50
9	C4	NaOH	20
10	C4	Cs_2CO_3	60

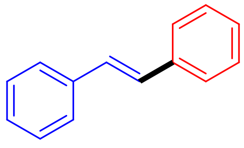
[a]Reaction Conditions: Styrene **2a** (0.5 mmol), 1-(4-bromophenyl)ethanone **1b** (0.5 mmol), catalyst (1 mol %), base (0.5 equiv), DMF (1.0 mL) at 70 °C. [b]Yields are of isolated pure products.

The effect of various bases on the model reaction were also screened (Table 5B.1entries 5-8). Notably, K_2CO_3, Na_2CO_3, KO^{t}Bu and $NaHCO_3$ gave the desired product **4b** in less yield, 50-

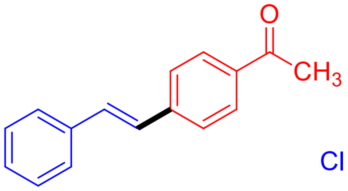
70% respectively compared to entry 4. However, NaOH gave cross-coupled product in very low yield 20% (Table 5B entry 9). Surprisingly, the less baic Cs_2CO_3 gave inferior results (Table 5B., entry 10).Thus, the optimizations are as follows, catalyst Pd(II) complex of 2-aminonicotinaldehyde **C4**, K_2CO_3 in 70 °C.

Table 5B.2. Substrate Scope of the Styrene and Acrylates Aryl Olefination.[a b]

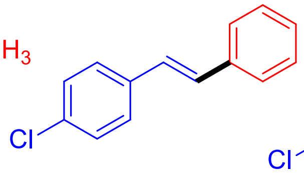




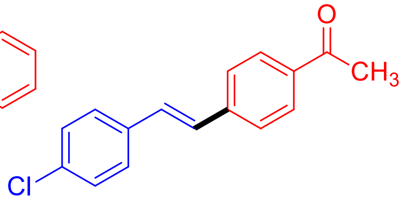
4a, 5 h, 85%



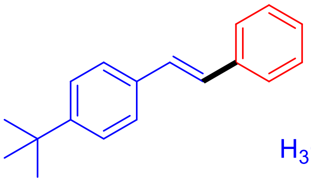
4b, 5 h, 82%



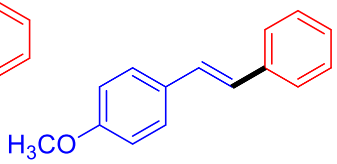
4c, 6 h, 82%



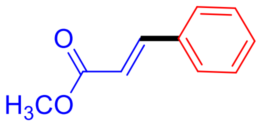
4d, 6 h, 80%



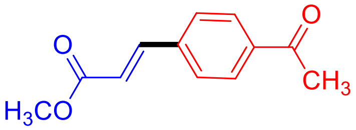
4e, 5 h, 84%



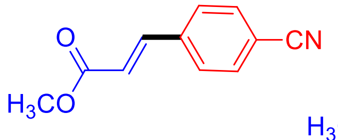
4f, 5 h, 85%



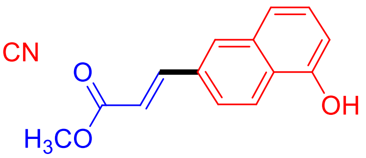
5a, 6 h, 85%



5b, 5 h, 81%



5c, 7 h, 79%



5d, 5 h, 80%

[a]Reaction Condition: arylbromide **1a-d** (0.5 mmol), styrene **2a-d** (0.5 mmol), (or) **3** (0.5 mmol), catalyst **C4** (1 mol %), Cs_2CO_3 (0.5 equiv), DMSO (1.0 mL) at 70 °C. [b]Yields are of isolated pure products.

With the preferred conditions for the Heck reaction in hand, we next examined the scope of the substrates and synthesized a library of compounds listed in Table 5B.2. Initially reactions with substituted bromobenzene **1a-d** and styrene **2a-d** were examined. Bromobenzene **1a** readily reacted with styrene **2a** to form stilbene **4a** in 85%. Electron withdrawing group on bromo benzene does not alter product yield **4d** (Table 5B.2).

Notably, chloro substitution on styrenes is well tolerated and gave the corresponding **4c** in 82%. Also, bulky *t*-butyl and electron donating group i.e., methoxy on styrene actively involved in olefination reaction and provided **4e** and **4f** in yields 84%, 85% repectively (Table 5B.2). Similarly, bromobezene and its substituted bromobenzene readily reacted with methylacrylate **3** and furnished **5a-5d** in 79-85% yield (Table 5B.2). Even unprotected hydroxyl group on bromonaphthalene is also an active partners in this protocol **5d (**(Table 5B.2).

5B.4. Conclusion

To conclude, we have developed an efficient, easily accessible, air-stable, inexpensive Pd(II)-(2-aminonicotinaldehyde) [Pd(II)-ANA] for aromatic-olefination via Heck-cross coupling. From these method we can synthesis symmetrical and unsymmetrical stilbene derivatives can be achieved effectively. One of the other reactive partners in heck coupling is also well tolerated. Unprotected hydroxyl goup on bromonaphthalene did not affect the reaction yield, so this could be a potential method for the synthesis of bioactive resveratrol. This protocol is operationally simple and efficient at low catalyst loading.

5B.5. Experimental Section

5B.5.1. General Information

All the compounds used in development of Heck-cross coupling like aryl bromide, styrene, methacrylate and K_2CO_3, Na_2CO_3, KO^{t}Bu, $NaHCO_3$, NaOH, and Cs_2CO_3 were purchased from Sigma-Aldrich, Spectrochem, SRL, Avra synthesis and SD-Fine were used as received. Catalysts **C1-C4** were synthesised as reported below. All the reactions were performed in pure water (>5 MΩ cm @ 25 °C, total organic content <30ppb). Reactions were monitored by analytical TLC on 200 µm aluminium-foil-backed silica gel plates. The column chromatography was performed with 100-200 mesh silica gel. Finding the melting points of solid compounds was determined by open capillaries using Stuart SMP30 melting point apparatus and is uncorrected. NMR (^{1}H and ^{13}C) spectra of all the synthesized compounds were recorded on Bruker AVANCE HD (400 MHz / 100 MHz) spectrometer using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The data accounted is as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and dd = doublet of doublets.

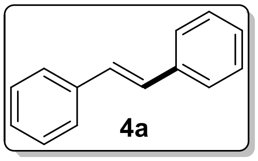
5B.5.2. General Procedure for the Reaction of Styrene and Halobenzenes

To an oven dried 10 mL round bottom flask were added aryl bromide **1a** (165.8 mg, 1.0 mmol), styrene **2a** (110 mg, 1.0 mmol), Base (0.5 equiv) and catalyst **C4** (4.4 mg, 1mol %) in DMF solvent (1 mL). The reaction mixture was allowed to stir at 70 °C for completion. After completion of reaction (monitored by TLC) the crude residue was extracted into in ethyl acetate (10 mL x 3) and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was separated using silica-gel column chromatography by eluting with ethyl acetate /hexanes as mobile phase.

5B.6. Characterization Data of Products

(E)-1,2-Diphenylethene (4a)[53]

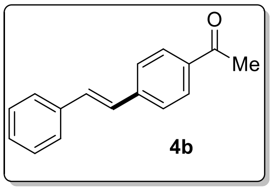
Yield: 85%, white crystalline solid, M.P. 125-126 °C.


4a

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, J = 7.5 Hz, 4H), 7.36 (t, J = 7.5 Hz, 4H), 7.26 (t, J = 7.3 Hz, 2H), 7.11 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.5, 128.6, 128.5, 127.9, 127.4.

(E)-1-(4-Styrylphenyl)ethanone (4b)[54]

Yield: 82%, pink colour solid, M.P. 143-144 °C.

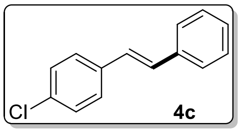


4b

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 17.0 Hz, 1H), 7.16 (d, J = 16.3 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.5, 142.0, 136.7, 136.0, 131.5, 128.9, 128.8, 128.3, 127.5, 126.8, 126.5, 26.6. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{14}O$ $[M+H]^+$ 223.1125, found 223.1131.

(E)-1-Chloro-4-styrylbenzene (4c)[55]

Yield: 82%, white solid, M.P. 128-130 °C.



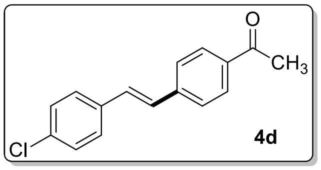
4c

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.09 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.0, 135.9, 133.2, 129.3, 128.9, 128.8, 127.9, 127.7, 127.4, 126.6.

(E)-1-(4-(4-chlorostyryl)phenyl)ethanone (4d)[56]

Yield: 80%, white crystalline solid, M.P. 142-144 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 16.3 Hz, 1H), 7.03 (d, J = 16.4 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.5, 141.6, 136.1, 135.2, 130.10, 134.0, 130.1, 129.0, 128.9, 128.1, 128.0, 126.6, 26.6. HRMS (ESI-TOF): m/z calcd for C$_{16}$H$_{13}$ClO [M+H]$^+$ 257.0735, found 257.0739.

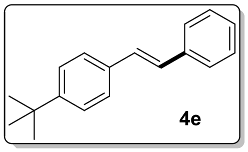


4d

(E)-1-(Tert-butyl)-4-styrylbenzene (4e)[57]

Yield: 84%, white solid, M.P. 87-90 °C.

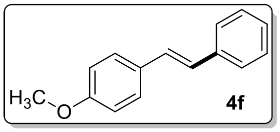
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 7.1 Hz, 2H), 7.16 (t, J = 7.1 Hz, 1H), 7.01 (s, 2H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.8, 137.6, 134.6, 128.7, 128.5, 128.1, 128.0, 127.6, 127.4, 126.4, 126.3, 125.6, 34.7, 31.3.


4e

(E)-1-methoxy-4-styrylbenzene (4f)[54]

Yield: 85%, white solid, M.P. 132-134 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.4 Hz, 2H), 7.19 - 7.18 (m, 1H), 7.00 (d, J = 16.3 Hz, 1H), 6.90 (d, J = 16.3 Hz, 1H), 6.83 (d, J = 8.2 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.3, 137.7, 128.7, 128.2, 127.7, 127.2, 126.6, 126.3, 114.1, 55.3. HRMS (ESI-TOF): m/z calcd for C$_{15}$H$_{14}$O [M+H]$^+$ 211.1125, found 211.1125.

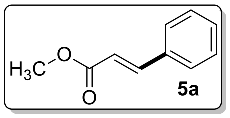


4f

Methyl cinnamate (5a)[58]

Yield: 85%, white solid, M.P. 55-58 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, J = 16.0 Hz, 1H), 7.55 (d, J = 3.7 Hz, 2H), 7.41 (t, J = 6.0 Hz, 3H), 6.47 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H).^{13}C NMR (100 MHz, CDCl$_3$) δ 166.5, 143.6, 135.2, 128.6, 128.5, 127.9, 115.1, 52.0. HRMS (ESI-TOF): m/z calcd for C$_{10}$H$_{10}$O$_2$ [M+H]$^+$ 162.0761, found 162.0721.

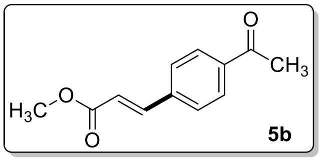


5a

(E)-Methyl 3-(4-acetylphenyl)acrylate (5b)[59]

Yield: 81%, white crystalline solid, M.P. 109-111 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 16.0 Hz, 1H), 7.63 (d, J = 7.9 Hz, 2H), 6.55 (d, J = 16.1 Hz, 1H), 3.84 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 167.0, 143.3, 138.7, 138.0, 128.9, 128.2, 120.3, 51.9, 26.7. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{12}O_3$ $[M+H]^+$ 205.0866, found 205.0864.

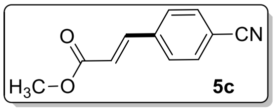


5b

(E)-Methyl 3-(4-cyanophenyl)acrylate (5c)[60]

Yield: 79%, white crystalline solid, M.P. 101-103 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 6.45 (d, J = 16.1 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 143.6, 139.5, 132.1, 128.8, 118.6, 115.1, 111.8, 52.0.

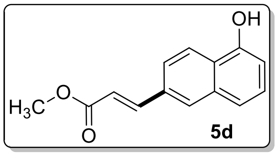


5c

(E)-methyl 3-(5-hydroxynaphthalen-2-yl)acrylate (5d)

Yield: 80%, yellow solid, M.P. 168-170 °C.

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.74 – 7.66 (m, 2H), 7.59 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 10.7 Hz, 2H), 6.43 (d, J = 16.0 Hz, 1H), 5.39 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 153.5, 143.6, 135.4, 134.6, 127.1, 126.2, 125.7, 124.2, 122.9, 121.1, 115.1, 110.6, 52.0. HRMS (ESI-TOF): m/z calcd for $C_{14}H_{12}O_3$ $[M+Na]^+$ 251.0686, found 251.0659.



5d

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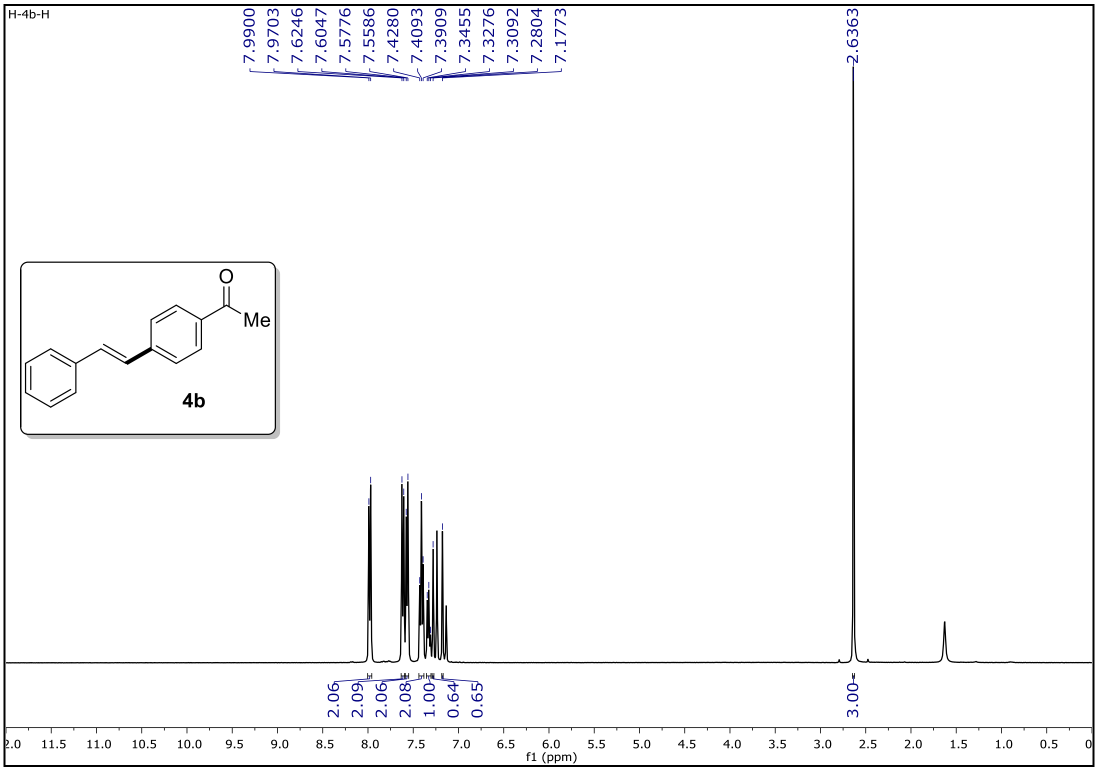
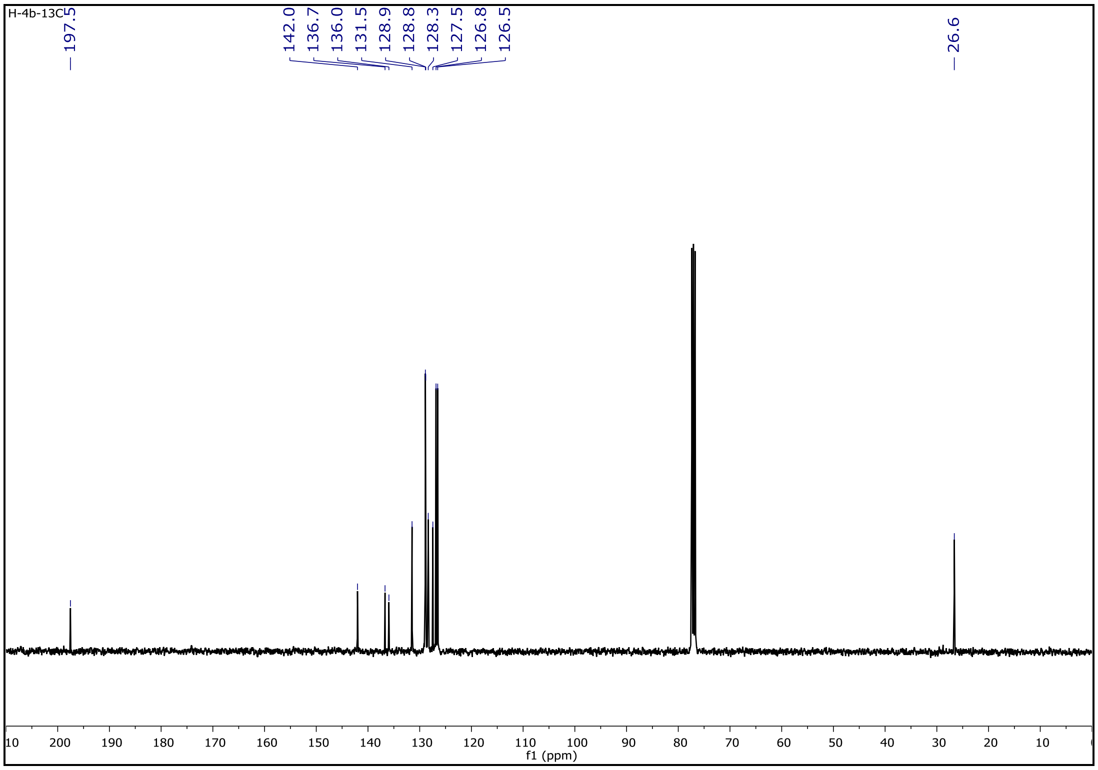
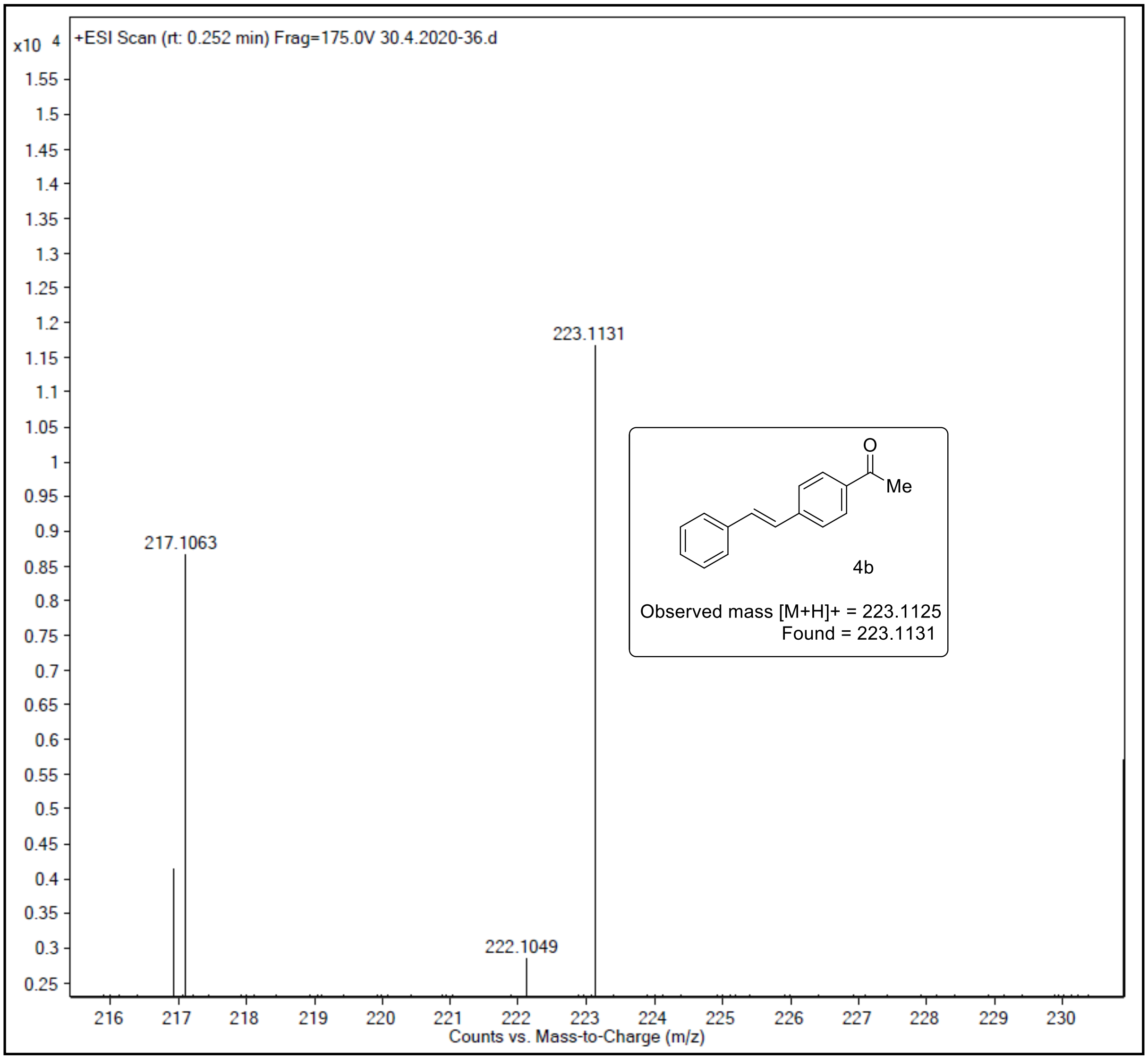
5B.7. Selected NMR (^{1}H and ^{13}C)



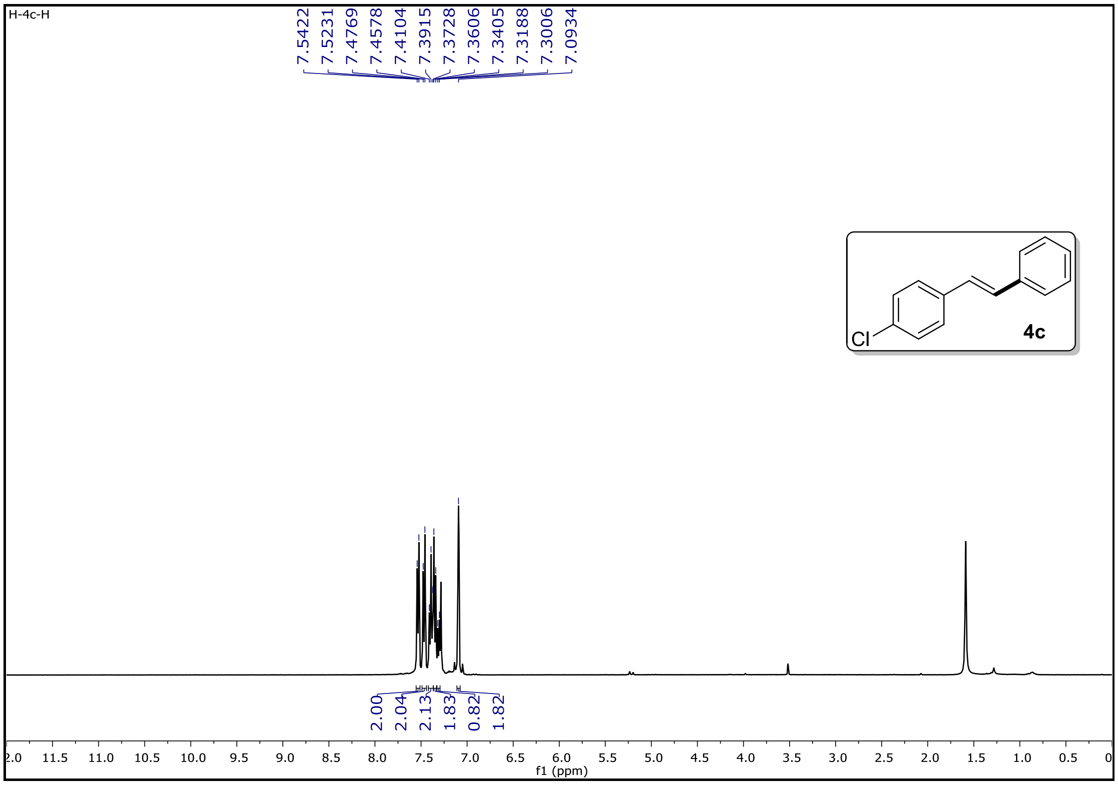
^{1}H NMR spectrum of compound **4b**



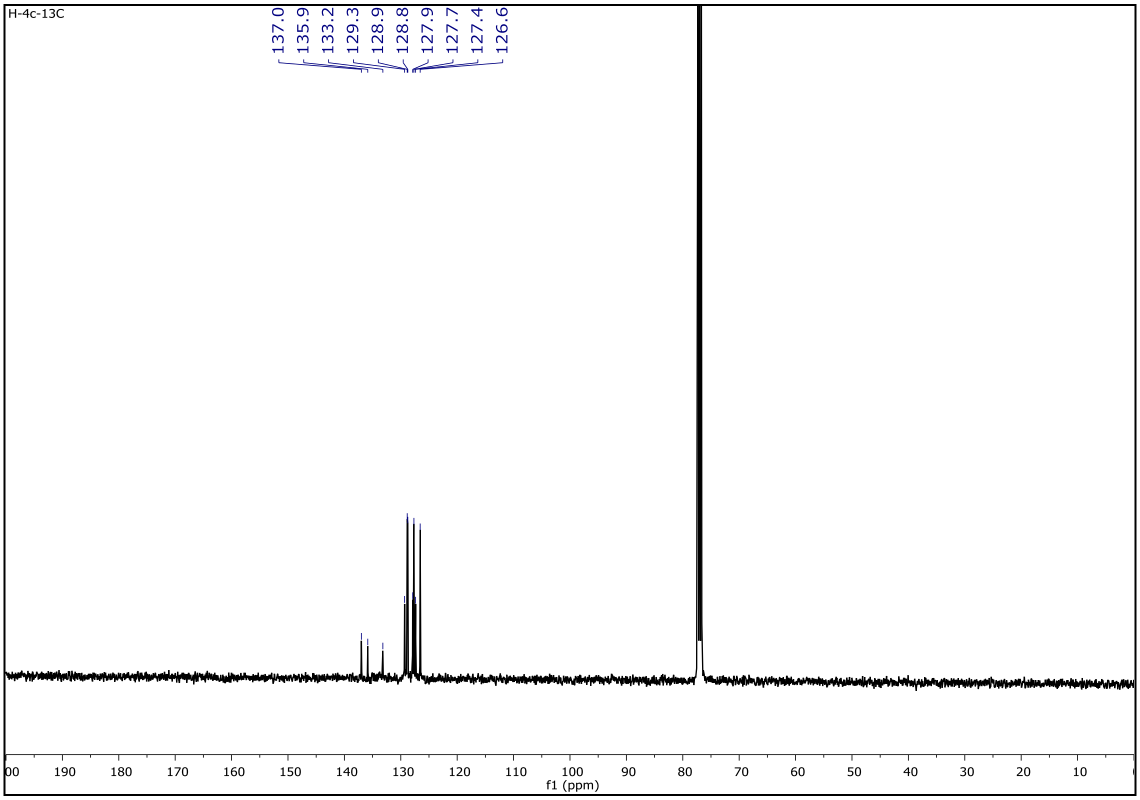
^{13}C NMR spectrum of compound **4b**



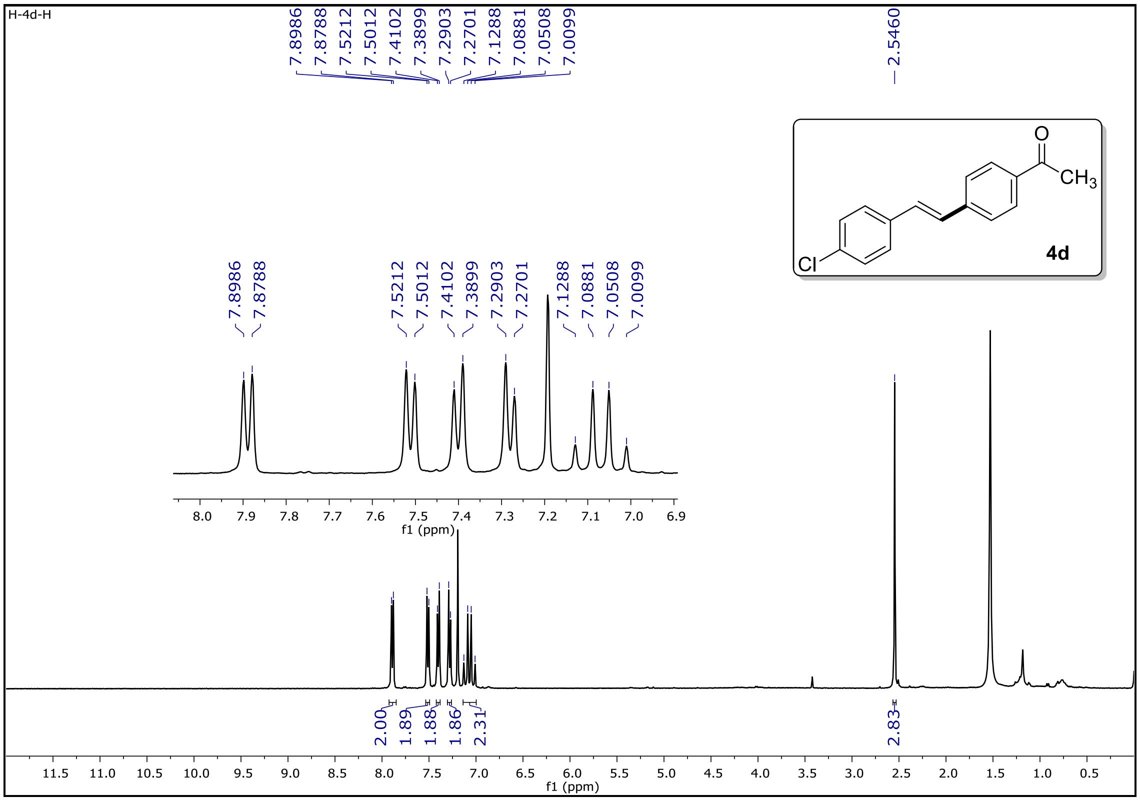
Mass spectrum of compound **4b**



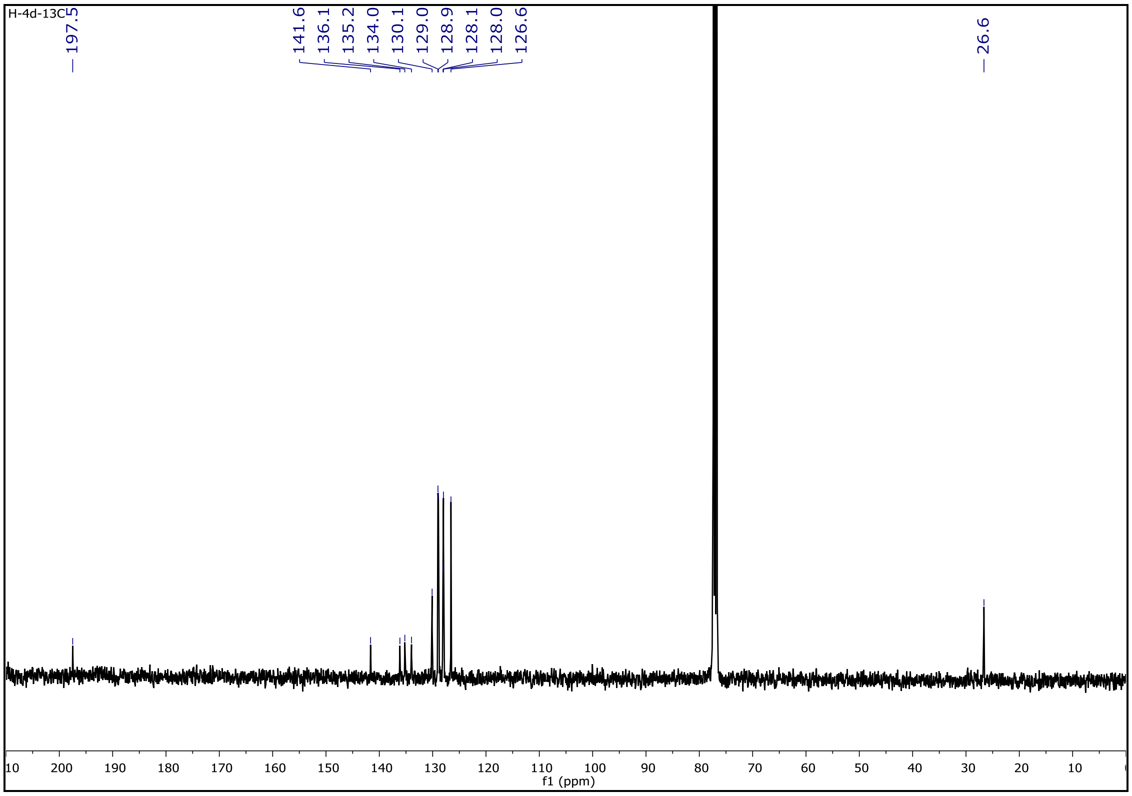
^{1}H NMR spectrum of compound **4c**



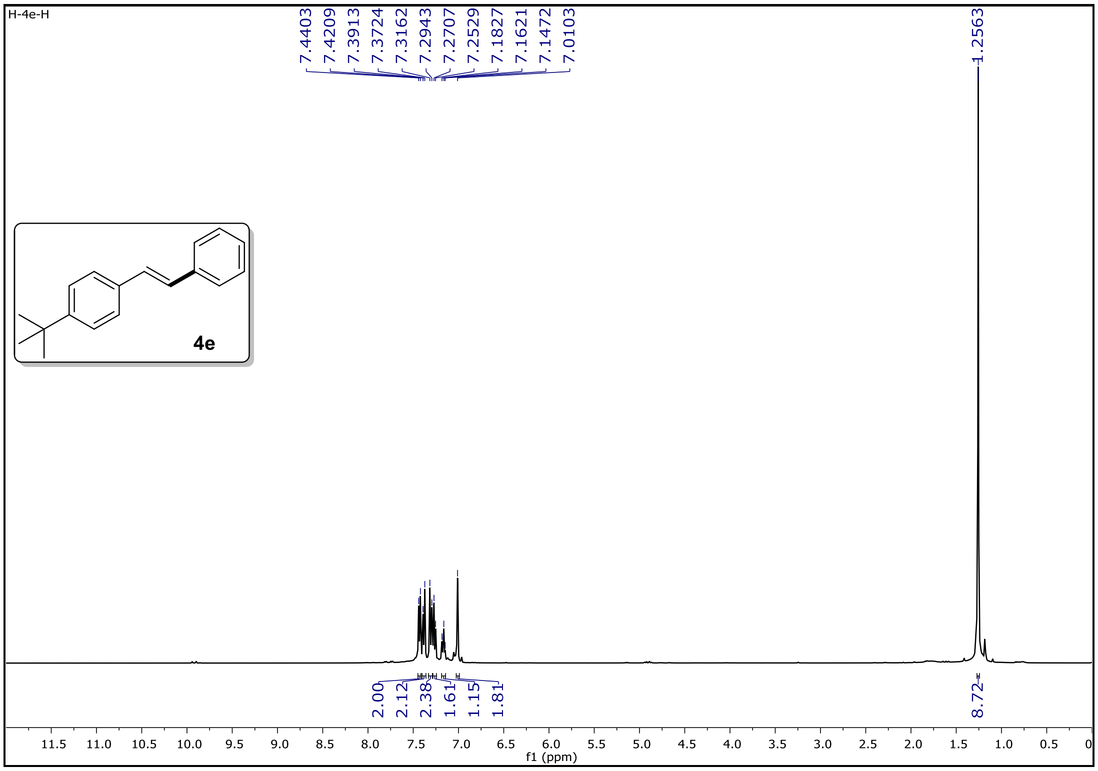
^{13}C NMR spectrum of compound **4c**



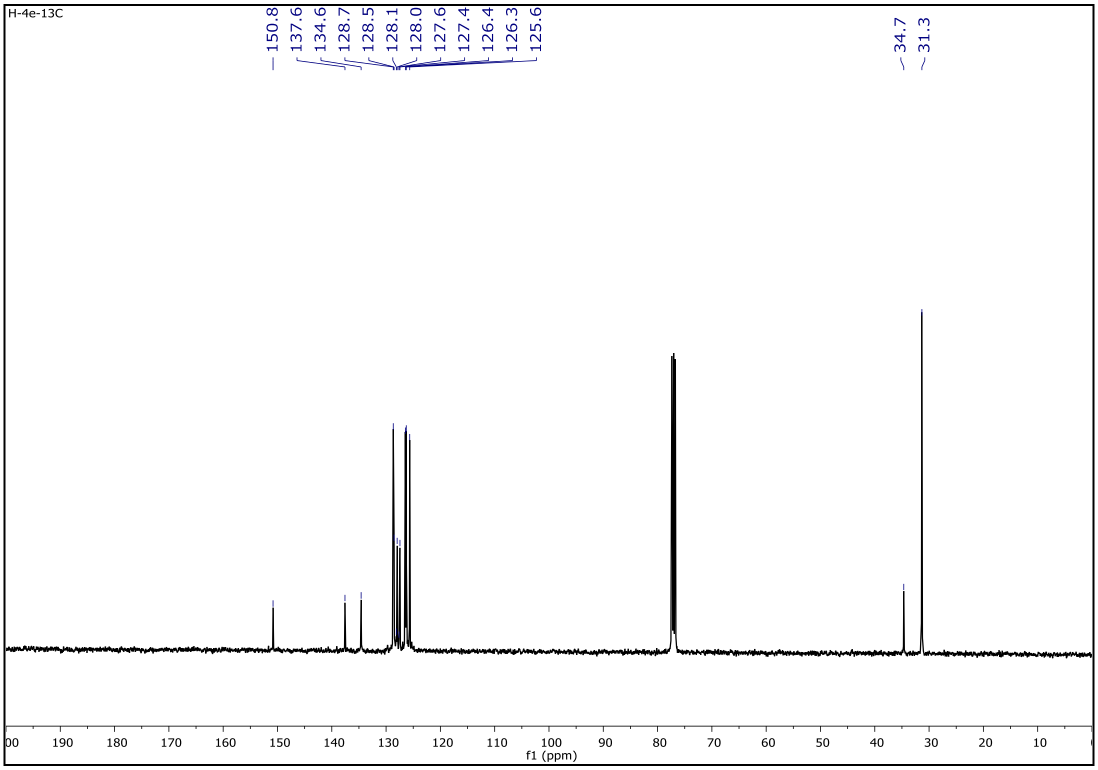
^{1}H NMR spectrum of compound **4d**



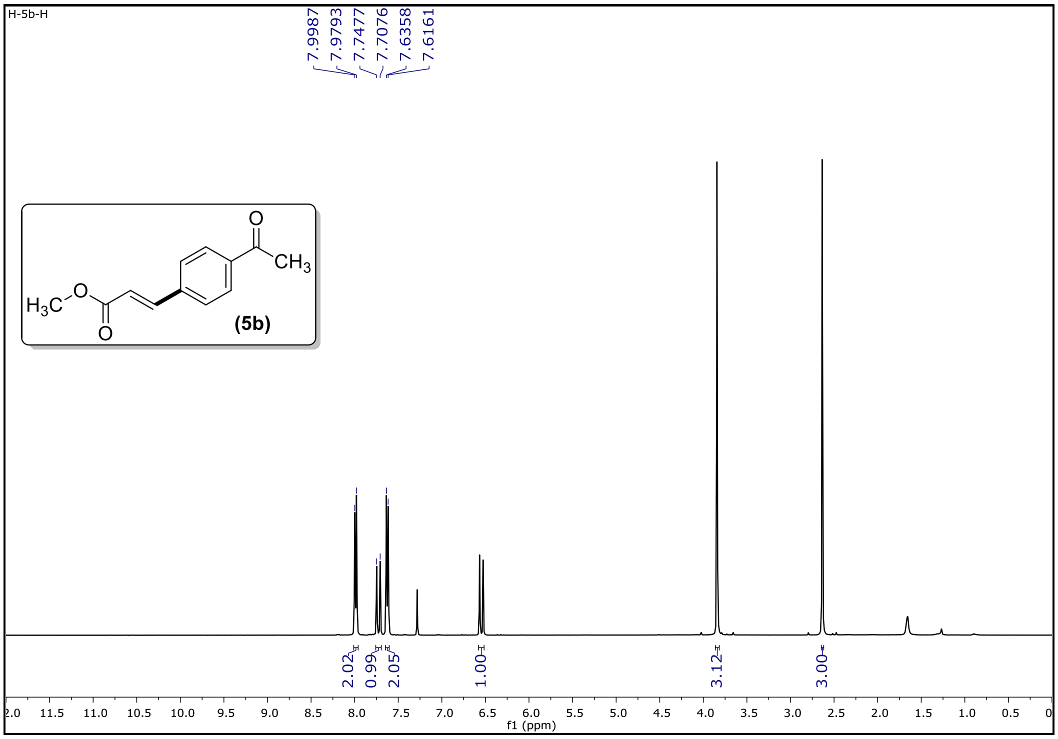
^{13}C NMR spectrum of compound **4d**



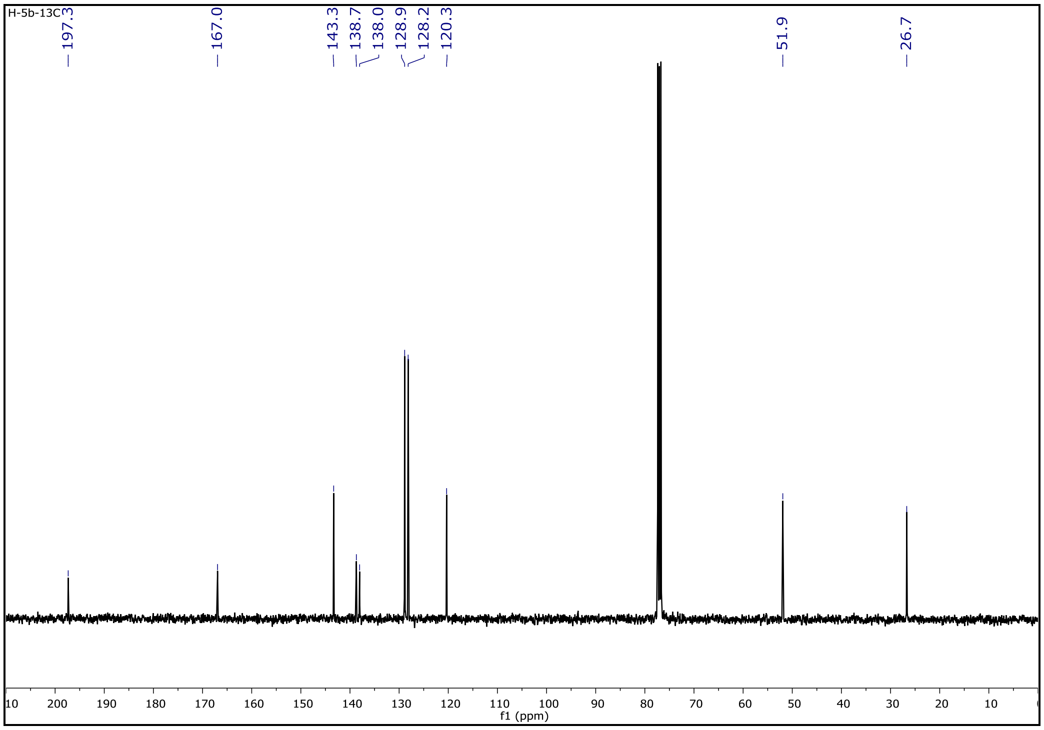
^{1}H NMR spectrum of compound **4e**



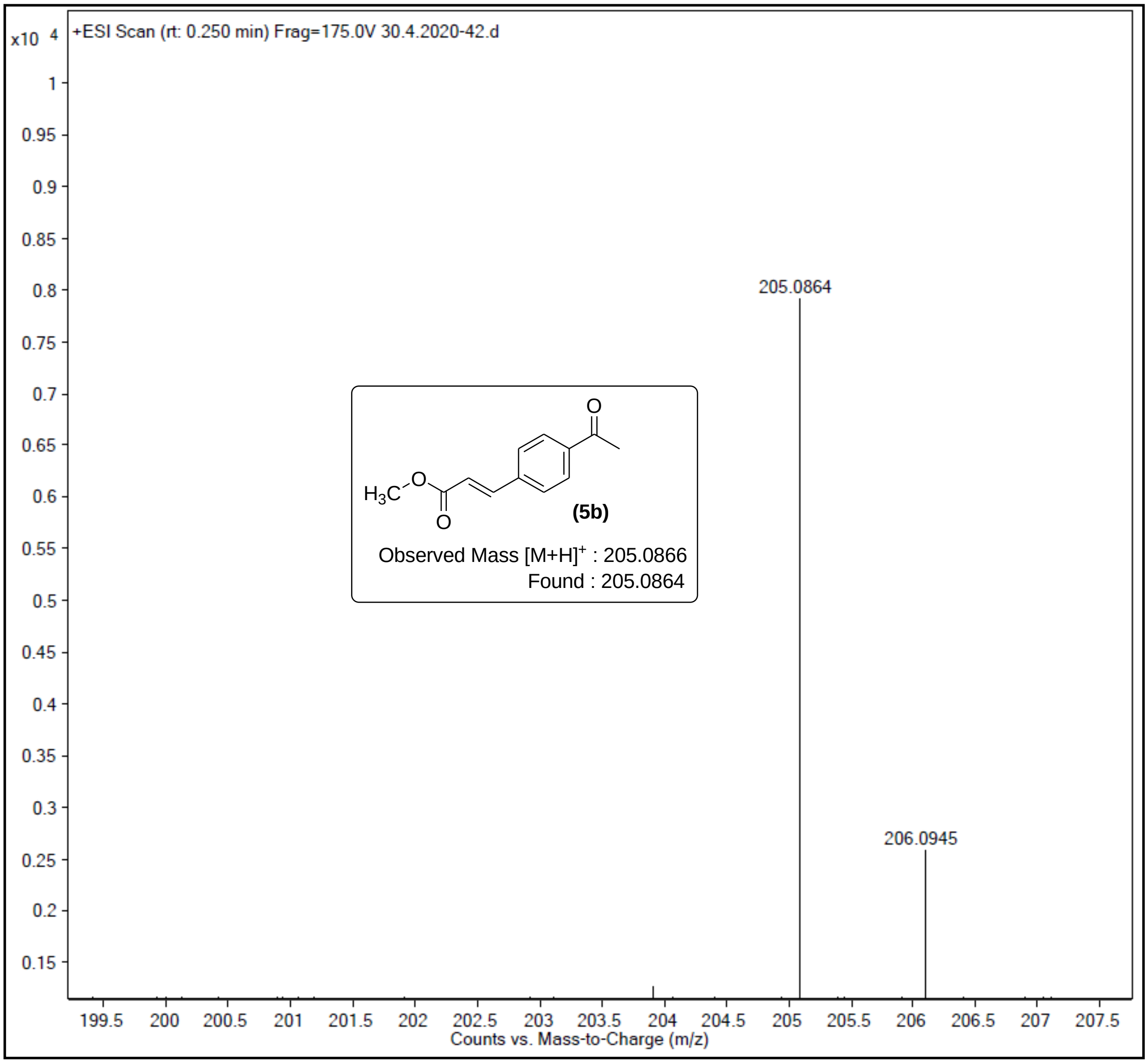
^{13}C NMR spectrum of compound **4e**



^{1}H NMR spectrum of compound **5b**



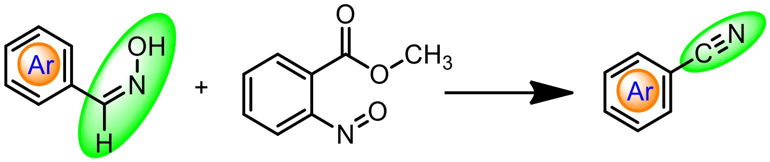
^{13}C NMR spectrum of compound **5b**



Mass spectrum of compound **5b**

CHAPTER-VI

Synthesis of Benzonitrile from Benzaldehyde Oximes Using Methyl 2-Nitrosobenzoate as Dehydrating Agent



6.1 Introduction

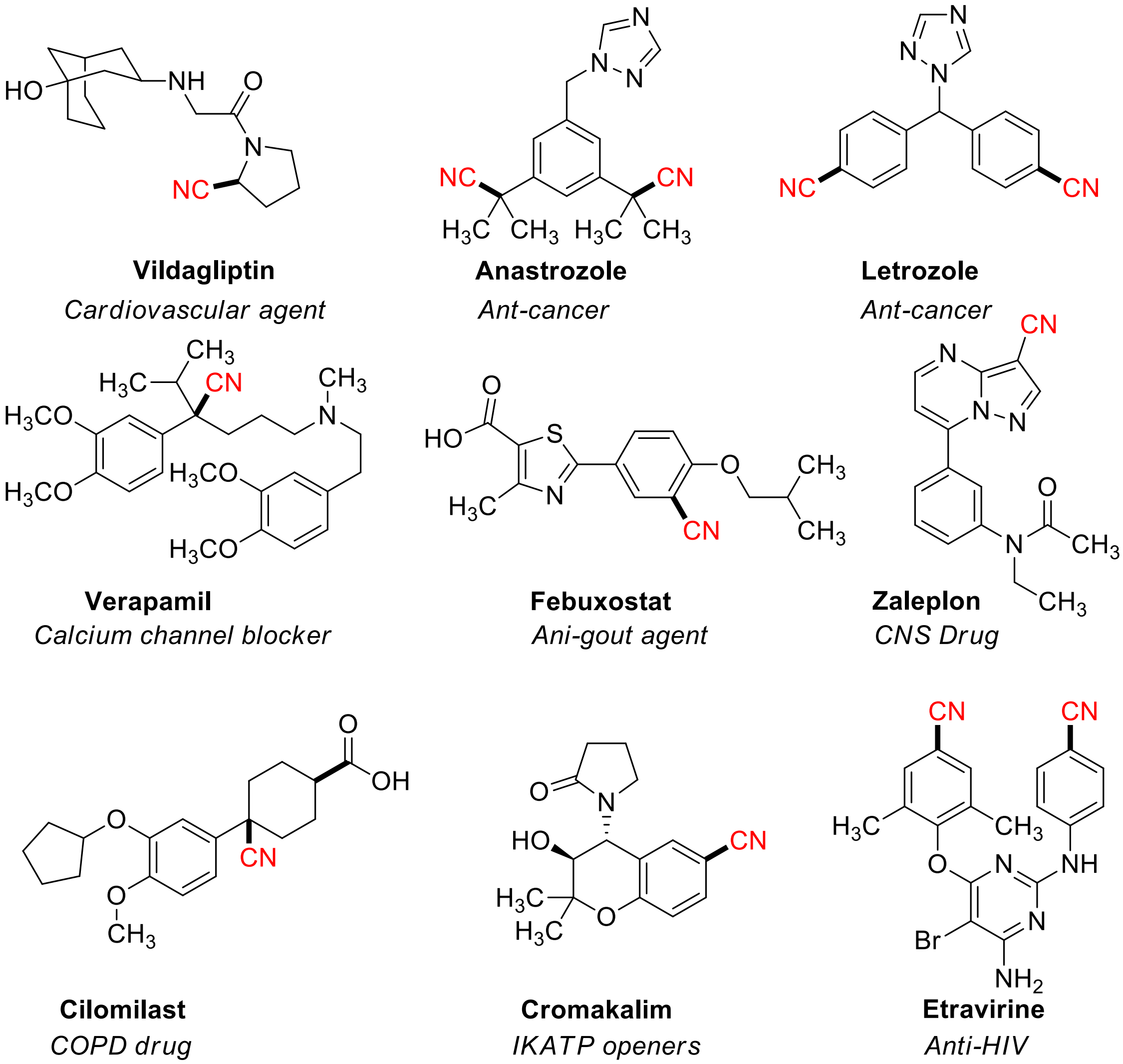
The cyano functionality is an important synthon in many natural products, dyes, herbicides, agrochemicals, functional materials and various fine chemicals.[1] They also play a major role in drug design because of its unique electron withdrawing and hydrogen bond acceptor properties. Several reports explained their crystal structure showing hydrogen bonds between nitrogen in nitrile group and amino acid which bound to the backbone to the protein.[2] Para-substituted benzonitrile will show superior inductive properties and it supposes to strong polarise to the aromatic ring.[3]

Trends identifying the roles of the nitrile in medical agents have emerged as the number of nitrile-containing pharmaceuticals has increased. Coupled with the increasing number of nitrile-containing agents, there have been structural advances that provide insight into the binding of small molecule inhibitors.[4] Nitrile containing pharmaceutical drugs are found abundantly which by itself reflects upon its biocompatibility properties.[5] The important point to note is that the nitrile group does not show much electrophilic properties towards free nucleophiles this includes even glutathione.[6] But this nitriles group is activated nearby electron withdrawing groups.[7] An example to the same involves activation-electrophilic additions used in the case of many aminonitriles which are used for diabetes and osteoporosis.

One of the important features of nitrile group is that it is robust and stable thus making its metabolism difficult.[8] This makes drugs having nitrile group to just pass through the body without undergoing any changes.[9] Thus before the actual metabolism of drugs takes place, formation of glucuronides,[10] conjugation with glutathione,[11] *N*-dealkylation,[12] *N*-acetylation,[13] hydrolysis,[10] and oxidation[14] occurs at sites that are remote from the nitrile and all of this happens without modifying the nitrile group.

Many pharmaceutical drugs have nitriles as a component within them and they range from vildagliptin, which is an anti diabetic drug to anastrozole which is regarded as one of the best drugs out there to treat breast cancer. Nitrile groups has mimicking properties ranging from those of substrates for enzymes to the one where nitrile actually decreases susceptibility to oxidative metabolism in the liver.[15]

For example, many of the recently released drugs like Vildagliptin (antidiabetic),[16] 1,2-diarylimidazolesv (anti-inflammatory),[17a] benzamidines (fibrinogen antagonists),[17b] thiazole (Superoxide inhibitor),[17c] tetrazole derivatives (antipicornavirus),[17d] and pyrimidines (anti asthama drug),[17e] have nitriles in them. And many other are at various stages of development and are used in the treatment of a variety of diseases (Figure 6.1).[18] In addition, nitriles are extensively used for conversion into useful functionalities such as amides, amines, esters, carboxylic acids, tetrazoles and other heterocycles.[19]



Vildagliptin
Cardiovascular agent

Anastrozole
Ant-cancer

Letrozole
Ant-cancer

Verapamil
Calcium channel blocker

Febuxostat
Ani-gout agent

Zaleplon
CNS Drug

Cilomilast
COPD drug

Cromakalim
IKATP openers

Etravirine
Anti-HIV

Figure 6.1. Examples of Pharmaceutically Important Nitrile Containing Molecules.

Nitriles also extensively used in polymer chemistry to make material such as super glue (methyl cyanoacrylate) and nitrile rubber, a latex-free laboratory and medical gloves. Nitrile rubber is also widely used as automotive and other seals since it is resistant to fuels and oils.[20]

Recently, nitrile functionality has been exploited as a promising directing group for metal catalyzed C-H activation reactions.[21]

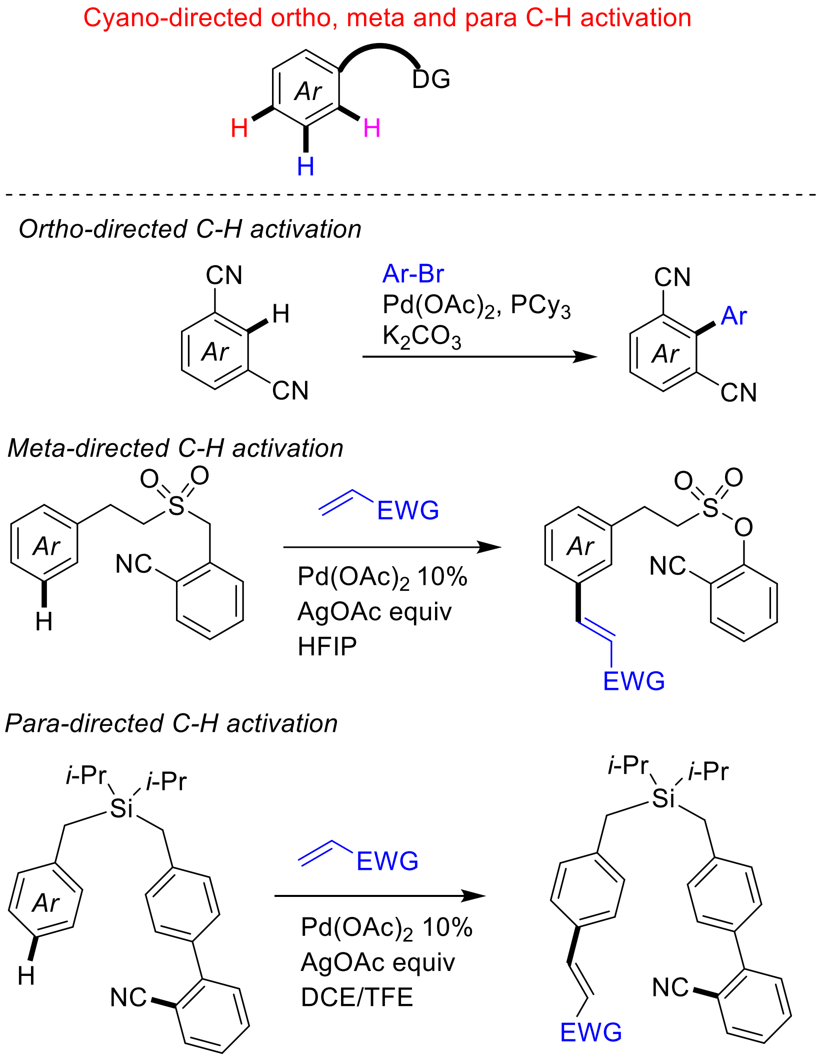
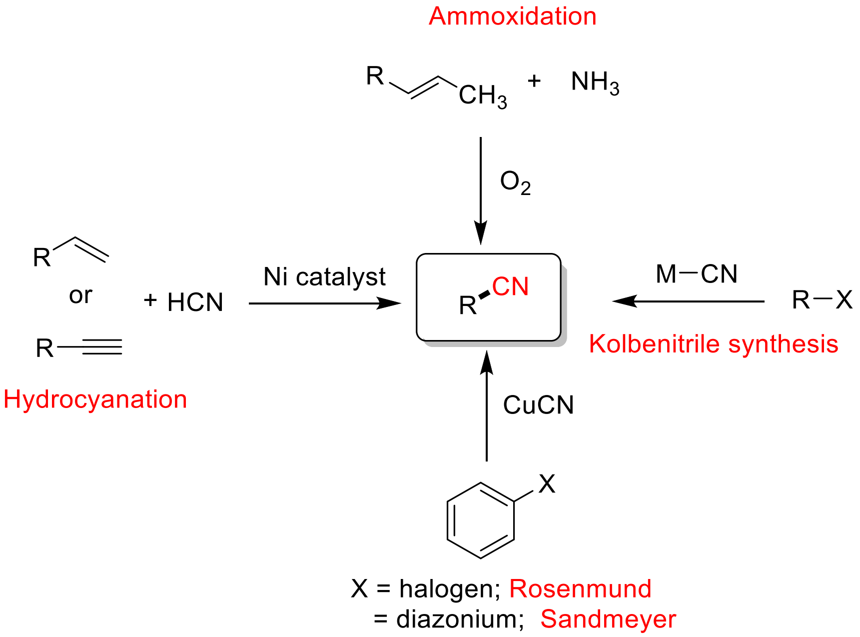


Figure 6.2. Nitrile Directed C-H Activation.

Also, nitriles are commonly used as a solvent to conduct the reactions such as acetonitrile and benzonitrile in both the academic and industrial circles. There is a considerable difference between benzonitriles and acetonitrile in terms of reactivity as benzonitriles does not have labile hydrogen in α position to nitrile function and where as acetonitrile has this labile hydrogen in the α position to the nitrile function. Thus, acetonitrile would allow to react more species than that Benzonitrile for their potentially stabilization. It has high dipole movement and dielectric constant when compared with other aromatic solvents. Also, it has low vapour pressure and it is best solvent to be used if there is the possibility of changes in concentration due to the evaporation.

6.2. Reported Methods for the Formation of Benzonitriles

One of the classical methods for the synthesis of nitriles involves the nucleophilic substitution reaction of alkyl halides with cyanide source including ammoxidation, hydrocyanation, Kolbe nitrile synthesis, Rosenmund-von braun reaction, and Sandmeyer diazonium salts reaction (Scheme 6.1).[22-24]

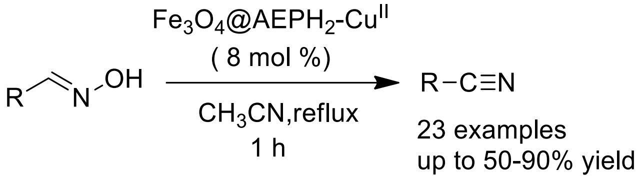


Scheme 6.1

However, these methods involve use of stoichiometric amount of reagents, tedious workup procedures, nonavailability of starting materials and the hazardousness associated with metal cyanide limit the practical utility of this approach.[26] Thus, other methods such as the dehydration of aldoximes remain a promising method. Some of the recently reported methods for aldoxime dehydration involve classical dehydrating agents which are discussed bellow.

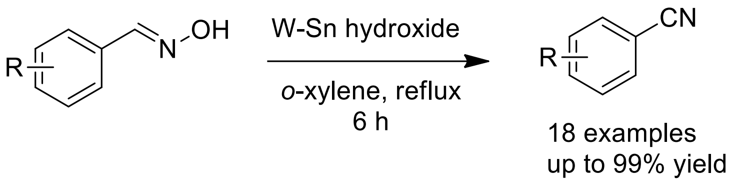
6.2.1 Metal Catalyzed Dehydration of Aldoximes

Akhlaghinia and research group developed a simple and direct synthetic method for the formation of Benzonitriles from their corresponding benzadoximes by using Cu^{II}immobilized 2-aminoethyl dihydrogen phosphate (Fe_3O_4@$AEPH_2$-Cu^{II}). It allows for convertion of variety of aldoximes including aliphatic, aromatic and hetero aromatic aldoximes in excellent yields (Scheme 6.2).[27]



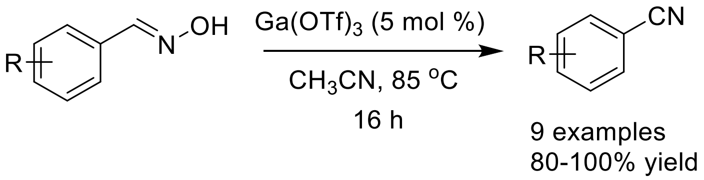
Scheme 6.2

Yamaguchi et al. studied the synthesis of benzonitrile formation from the dehydration of respective aldoximes up on treatment with Tungsten-Tin mixed Hydroxides (W- Sn hydroxide). This heterogeneous catalytic system effectively converts aldehyde to the aldoximes followed by dehydration (Scheme 6.3).[28]



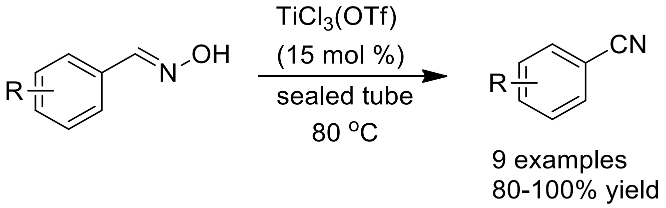
Scheme 6.3

Surya Prakash and Olahet research group developed a methodology for the synthesis of benzonitriles from their corresponding aldoximes by Gallium (III) triflate and obtained the end products in excellent yields (Scheme 6.4).[29]



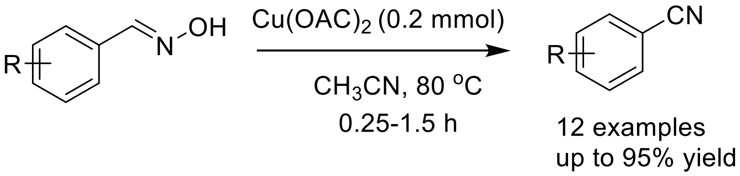
Scheme 6.4

Iranpoor et al. demonstrated a titanium catalyzed conversion of aldoxime to cyanide in good yields. In this reaction HCl is also involved in dehydration of aldoximes which was *in situ* generated from Triflate (Scheme 6.5).[30]



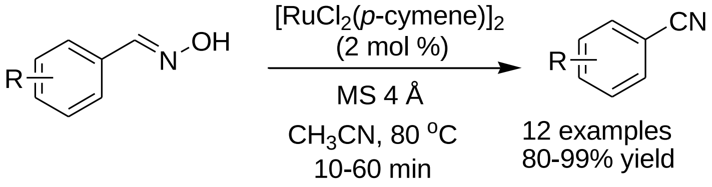
Scheme 6.5

Xiao-Yun et al. studied the synthesis of benzonitriles from bezaldoximes using various transition metal salts and found that Cu (II) acetate in acetonitrile at 80 °C is the best condition to obtain nitriles in good excellent yields (Scheme 6.6).[31]



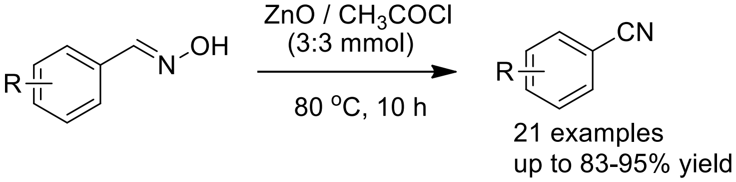
Scheme 6.6

Yang et al. developed a method for dehydration of aldoxims using ruthenium salts i.e., Ru catalysts like $Ru_3(CO)_{12}$, $RuCl_2(PPh_3)_3$, $[RuCl_2(p\text{-cymene})]_2$to in the presence of 4Å molecular sieves to get the the nitriles in good yields (Scheme 6.7).[32]



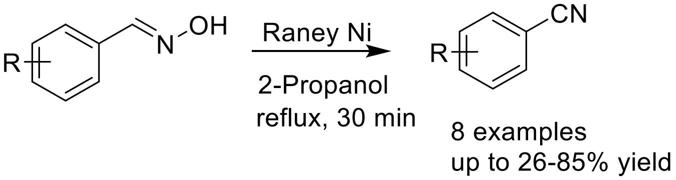
Scheme 6.7

Sarvari et al. studied the synthesis of benzonitrile from aldoximes using metal oxide like ZnO with the CH_3COCl. In this process acetic acid is a by product and this acidic medium is a problem for other functional groups present on substrate (Scheme 6.8).[33]



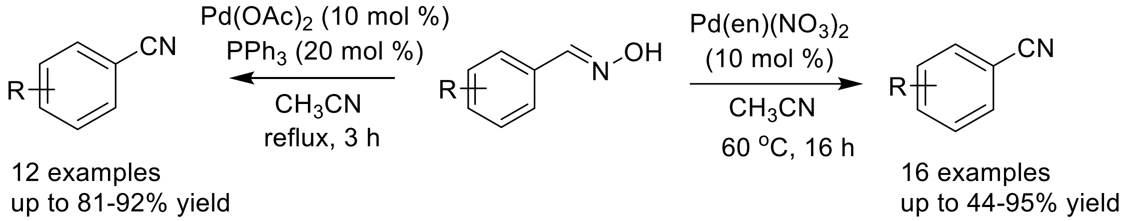
Scheme 6.8

Zuidema et al. prepared substituted benzonitriles from their oximes using Raney nickel in 2-propanol at reflux condition. This method delivers good to excellent yields of nitriles (Scheme 6.9).[34]



Scheme 6.9

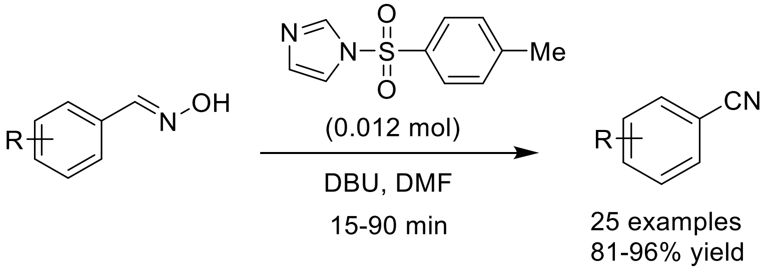
In recent past, palladium metal played a major role not only in cross-coupling but also in the other synthetic transformations. In connection to this **Kim et al.** have elaborated the synthesis of benzonitrile from corresponding aldoximes using palladium catalyst with additives and it is the first result to produce the nitriles from aldoximes (Scheme 6.10). Later, **Tambaraet al.** havedeveloped $Pd(en)(NO_3)_2$ catalyst for the formation of nitriles from corresponding aldoximes (Scheme 6.10).[35-36]



Scheme 6.10

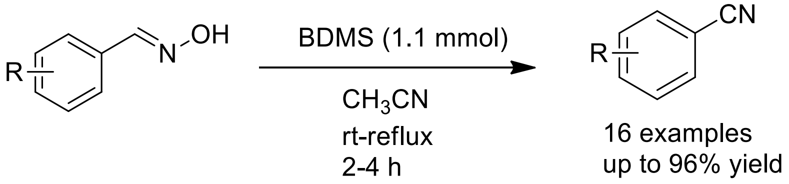
6.2.2. Non-Metal Catalyzed Dehydration of Aldoximes

Navid et al. described imidazole base dehydrating i.e., *N*-(*p*-toluenesulfonyl) imidazole, and 8-Bromocaffeine agent for the synthesis of benzonitrile from the benzaldoxime by DBU as base in DMF solvent. This process is suitable for both the conventional heating and microwave conditions (Scheme 6.11).[37]



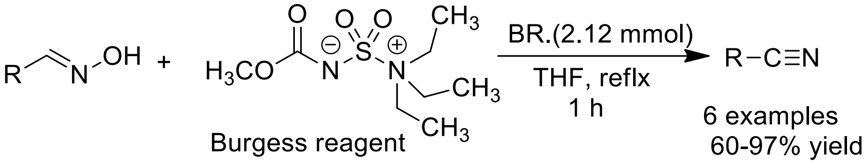
Scheme 6.11

Yadav et al. developed the sulphur based dehydrating reagent Bromodimethylsulfonium bromide for converting aldehydeoximes and primary amides into their corresponding nitriles in good yields (Scheme 6.12).[38]



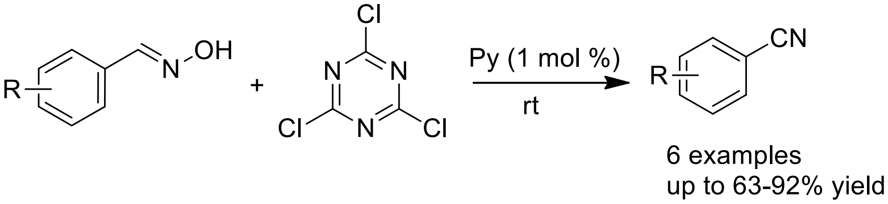
Scheme 6.12

Miller et al. synthesized benzonitrile from their corresponding the aldoximes in various conditions using the "Burgess reagent" also known as methyl N(triethylammonium-sulfonyl) carbamate in THF solvent at reflux conditions to give excellent yields (Scheme 6.13).[39]



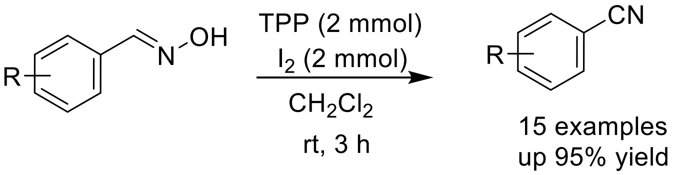
Scheme 6.13

Chakrabarti et al. monitored the condition for the synthesis of benzonitrile from their oximes using 2,4,6-Trichloro-s-triazine (Cyanuric Chloride) and delivered good to excellent yields (Scheme 6.14).[40]



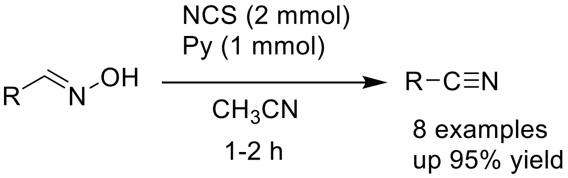
Scheme 6.14

Narsaiah et al. succeeded in developining a new method involving triphenylphosphine-iodine reagent system for converting oximes to their nitriles in CH_2Cl_2 solvent (Scheme 6.15).[41]



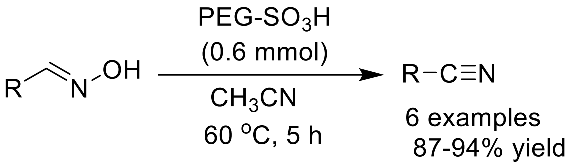
Scheme 6.15

Gołębiewskiet and research group synthesized the substituted benzonitrile from their corresponding oximes in the presence of the *N*-Chlorosuccinimide and pyridine base. In this reaction CH_3CN used as the solvent and gave good yield (Scheme 6.16).[42]



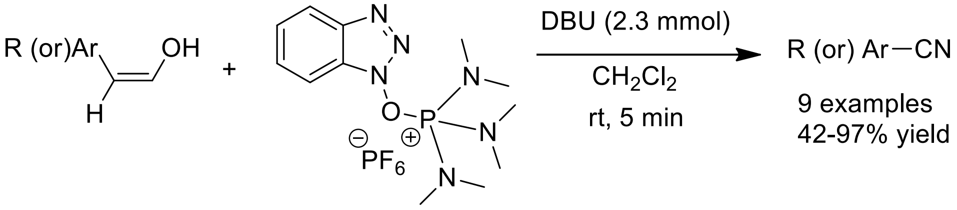
Scheme 6.16

Wang et al. developed the conventional method for the synthesis of benzonitriles from their oximes by polymer supported catalyst such as polyethylene glycol (PEG) and their sulfonic acid (PEG-SO_3H) to obtain good yields (Scheme 6.17).[43]



Scheme 6.17

Lakshman et al. developed a phosphorus based dehydrating agent (BOP) for converting aldoxime to nitrile in the presence of DBU in dichloromethane (Scheme 6.18).[44]



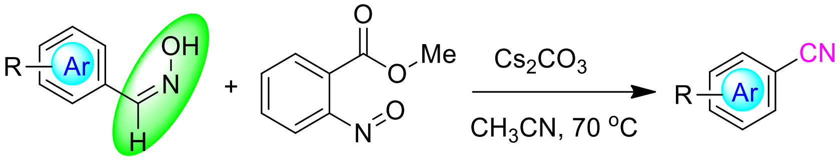
Scheme 6.18

And also some of the recently reported methods for aldoxime dehydration involve classical dehydrating agents includes organoselenium,[45] triethylamine sulfurdioxide,[46] Montmorillonite KSF,[47] $NaICl_2$/aq. NH_3,[48] Ga(III)OAc/MeCN,[49] chlorotriphenylphosphonium chloride,[50] Dimethyl dithiocarbonate[51] by Preyssler's Anion and $[NaP_5W_{30}O_{110}]$.[52] Direct conversion of aldehydes to nitriles is also reported.[53]

Though conventional methods are plenty in number and are used almost everywhere, they suffer from some limitations in the form of increased costs due to the need for the use of excess amounts of reagents, highly toxic compounds are formed, the reactions conditions themselves are harsh, tedious and most importantly the yield is only sub optimal. Unfortunately, the common dehydrating agents are insufficient for this purpose and more active reagents are required.

6.3. Present Study

After going through the literature for converting aldoximes to the nitrile *via* dehydration step, we found some key obeservations i.e., most of the methods involve the use of transition metal which are toxic, and metal-free methods have some of the limitations like use of expensive reagents, harsh reaction conditions, low yields, tedious workup procedures and use of excess reagents. Unfortunately, the common dehydrating agents are insufficient to make this study and more active reagents are required. Hence, the development of new synthetic routes using mild and non-toxic reagents have gained much interest from last decade from an environmental point of view. Therefore, the design of environmentally benign reactions is a crucial goal for chemist. In this context, aryl nitroso compounds are found to be a chemoselective ligating agents for sulfonic acids, where nitroso group act as an electrophilic center.[54]



1a-ab **2** **3a-ab**

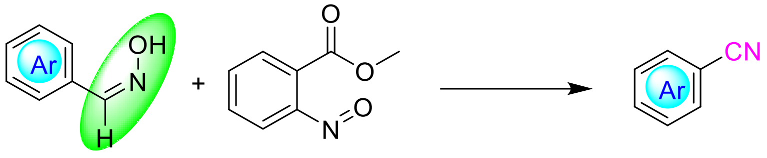
Scheme 6.19

Herein, we are reporting the “methyl 2-nitrosobenzoate”, a novel mild dehydrating agent for converting aldoximes to the corresponding nitriles and general route is showed in Scheme 6.19. In order to investigate the dehydrating property of methyl 2-nitrosobenzoate **2**, we have selected benzaldoxime **1a** as a model substrate for the optimization of reaction condition. The starting material of aldoximes required for this method were prepared from corresponding aldehydes and hydroxylamine hydrochloride using reported procedure.[55]

6.3.1. Results and Discussion

Benzaldoxime **1a** (1.0 mmol) was reacted with methyl 2-nitrosobenzoate **2** (1.0 mmol) using different solvents (2 mL) at different temperatures to optimize the reaction conditions to access desired nitrile **3a**. The results were shown in table 6.1. When the reaction was performed at room temperature in acetonitrile in the absence of both the methyl 2-nitrosobenzoate **2** and base, product **3a** was not formed, the aldoxime was not consumed even after 24 h at 70 °C and prolonged time resulted in the hydrolysis of aldoxime (entries 1 and 2). Even addition of the base to the reaction mixture did not give nitrile **3a** (entries 3 and 4). However, starting material was consumed in the presence of methyl 2-nitrosobenzoate **2** and triethylamine at 70 °C and gave desired product in 55% (Table 6.1, entry 5). Other bases such as piperidine, DBU, DABCO and KO^{t}Bu gave poor yields (Table 6.1, entries 6-9). It was reported in the literature that use of strong base accelerates the hydration of nitriles to the corresponding primary amides and lower the yields and weak bases give better yields.[56]

Table.6.1. Screening of Reaction Condition for Dehydration of Benzaldoxime by Methyl2-nitrosobenzoate.[a]



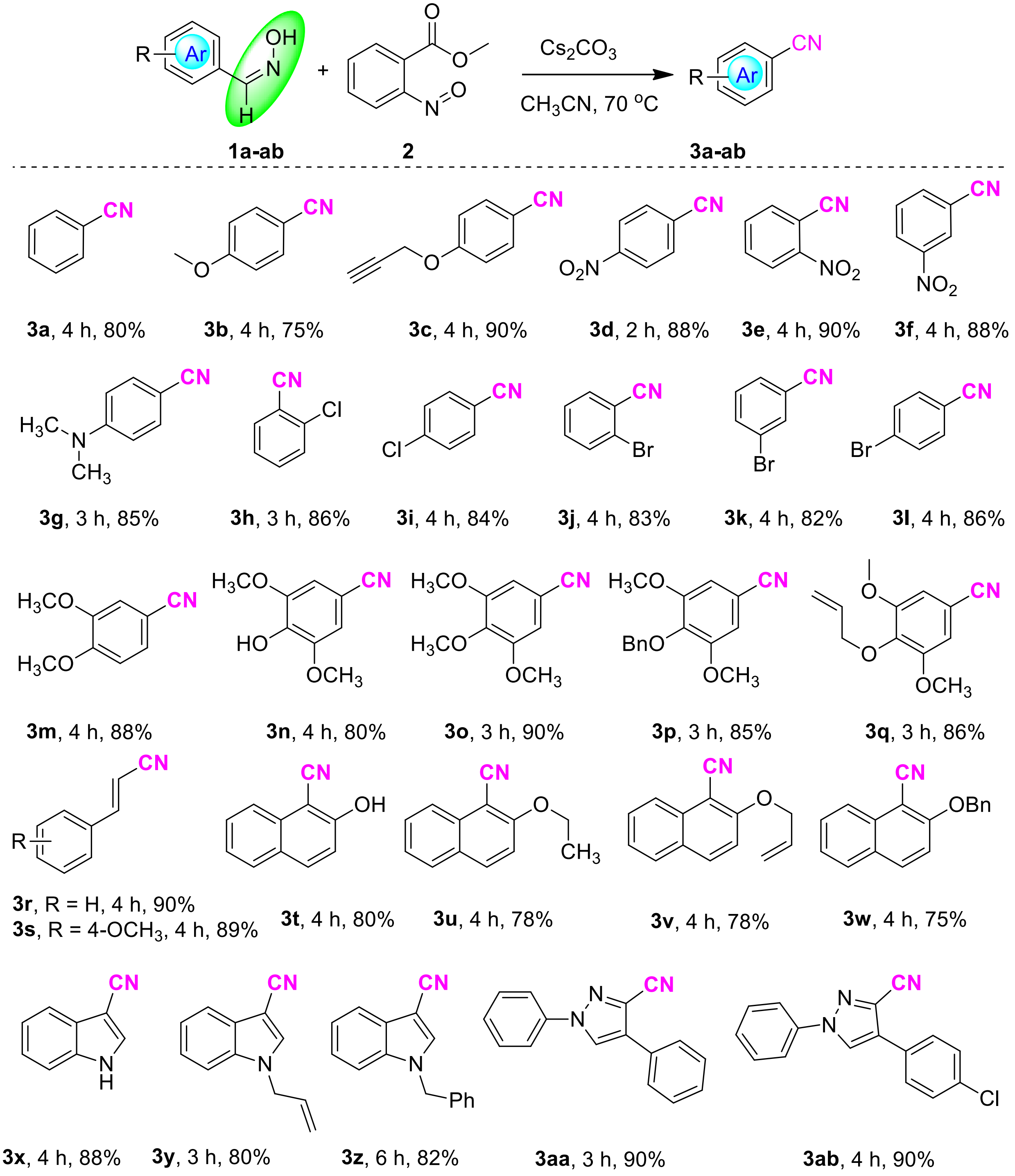
1a **2** **3a**

Entry	Base, Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	CH_3CN[c]	r.t	24	n.d.[e]
2	CH_3CN[c]	70	24	n.d.
3	Et_3N, CH_3CN[d]	r.t	24	n.d.
4	Et_3N, CH_3CN[d]	70	24	n.d.
5	Et_3N, CH_3CN	70	6	55
6	Piperidine, CH_3CN	70	4	60
7	DBU, CH_3CN	70	4	55
8	DABCO, CH_3CN	70	4	65
9	KO^tBu, CH_3CN	70	4	50
10	aq. NaOH, CH_3CN	70	4	40
11	K_2CO_3, CH_3CN	70	2	60
12	Cs_2CO_3, CH_3CN	70	2	**90**
13	Cs_2CO_3, CH_3CN	80	3	80
14	Cs_2CO_3, THF	70	3	70
15	Cs_2CO_3, 1,4-dioxane	70	8	50
16	Cs_2CO_3, Toluene	70	6	64

[a]Reactions were carried out using **1a** (1.0 mmol), **2** (1.0 mmol) and base (1.0 mmol) in solvent (2.0 mL), otherwise mentioned. [b]Yield where reported is of isolated and purified product. [c]Reaction was conducted in absences of methyl 2-nitrosobenzoate **2** and base. [d]Reaction was conducted in absence of methyl 2-methylnitrosobenzoate **2**. [e]Not detetcted.

Our results support the same, use of Cs_2CO_3 in acetonitrile solvent at 70 °C furnished **3a** in 80% yield (entry 12) and increasing the temperature did not improve the yield. (entry 13). Then several solvents, such as, THF, 1,4-dioxane and toluene were screened (entries 14-16), and the results showed that acetonitrile was found to be the best choice. The effect of various inorganic bases on the model reaction was also investigated (entries 10-12). It is clear that the Cs_2CO_3 gave the best result.

Table 6.2. Substrate Scope of the Dehydration Methodology Using methyl 2-nitrosobenzoate and Cs_2CO_3.[a,b]



1a-ab + **2** → **3a-ab**

3a, 4 h, 80% **3b**, 4 h, 75% **3c**, 4 h, 90% **3d**, 2 h, 88% **3e**, 4 h, 90% **3f**, 4 h, 88%

3g, 3 h, 85% **3h**, 3 h, 86% **3i**, 4 h, 84% **3j**, 4 h, 83% **3k**, 4 h, 82% **3l**, 4 h, 86%

3m, 4 h, 88% **3n**, 4 h, 80% **3o**, 3 h, 90% **3p**, 3 h, 85% **3q**, 3 h, 86%

3r, R = H, 4 h, 90%
3s, R = 4-OCH_3, 4 h, 89% **3t**, 4 h, 80% **3u**, 4 h, 78% **3v**, 4 h, 78% **3w**, 4 h, 75%

3x, 4 h, 88% **3y**, 3 h, 80% **3z**, 6 h, 82% **3aa**, 3 h, 90% **3ab**, 4 h, 90%

[a] All the reactions were conducted on a 1 mmol scale. [b] Yield of isolated and column purified product.

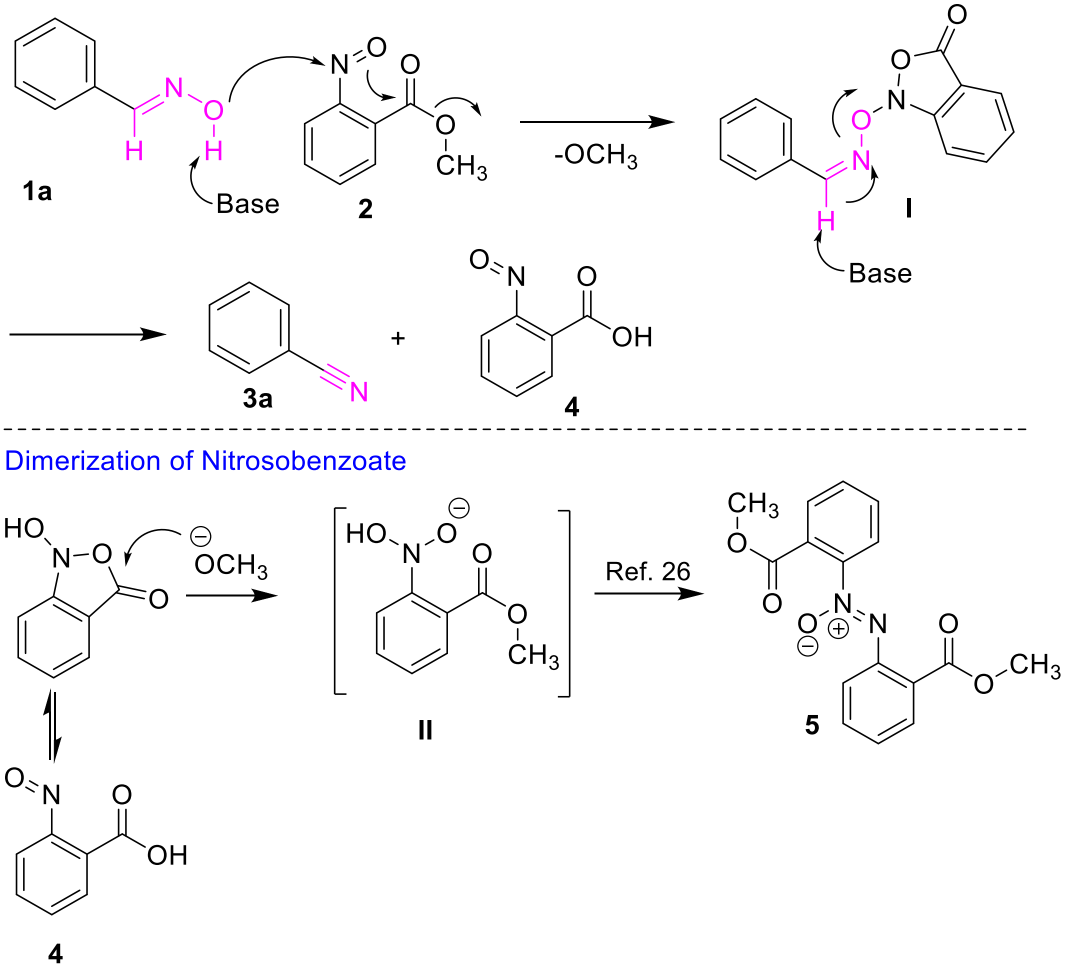
With the optimized reaction conditions at hand, we explored for a techniques to convert a wide variety of aromatic aldoximes to corresponding nitriles in high yields Table 6.2.

Dehydration of benzaldoxime proceeded fast under these conditions (Table 6.2, **3a**). It is worthnoting that electronic effect of the substituents on aromatic aldoxime had little impact on the product yield (Table 6.2, **3b-3g**).

It was observed that the halogen substituted aldoximes were reacted smoothly to give the corresponding nitriles in good yields (Table 6.2, **3h-3i**). Notably, *trans*-cinnamaldoximes were also compatible with the reaction conditions without any *cis*/*trans* isomerization of the double bonds (Table 6.2, **3r-3s**). To our delight, the unprotected hydroxyl and amine substituted aldoximes also reacted efficiently without causing any side reaction (Table 6.2, **3n**, **3t** and **3x**). Napthaldoximes and indole-3-oximes underwent dehydration in good yields (Table 6.2, **3t-3w**). In addition, as a typical heteroaromatic aldoxime, pyrazole-3-carbaldehyde oxime was smoothly converted into pyrazole-3-carbonitrile in good yield (Table 6.2, **3aa**, **3ab**). Unfortunately, aliphatic aldoximes donot undergo dehydration with our optimized reaction condition. All the structures of the products were characterized by FT-IR, ^{1}H and ^{13}CNMR spectroscopy.

6.3.2. Reaction Mechanism

A possible reaction mechanism was proposed in Scheme 6.20 for conversion of benzaldoxime to nitrile using methyl 2-nitrosobenzoate **2** based on literature reports.[44] Upon deprotonation of oxime **1a** by Cs_2CO_3 reaction could occur at the nitrogen atom of methyl 2-nitrosobenzoate **2** with the elimination of methoxide to form intermediate **I**, which was subsequently attacked by the base to form the corresponding nitrile compound and nitroso benzoic acid **4** **(**Scheme 6.20**)**. Although, nitroso benzoic acid **4** was unable to isolate by column chromatography but was confirmed by mass spectrum (*m/z* =152.05). Nitroso benzoic acid **4** again attacks by methoxide ion in basic condition to form intermediate **II.** There is mounting evidence that 2-substituted nitroso benzoates undergo dimerization in basic condition to afford compound **5**.[57] Then we separated the Dimer compound from the reaction mixture and this dimer **5** is characterized by ^{1}H NMR, ^{13}C NMR and Mass spectral data.



Scheme 6.20

6.4. Conclusion

To conclude, a facile methodology for the conversion of aldoximes into nitriles is described. Using methyl 2-nitrosobenzoate, aldoximes were converted under mild reaction conditions into the desired nitriles in excellent yields and in less reaction time. Furthermore, the reaction is widely applicable for aromatic and heteroaromatic aldoximes, and in fact it works well with different aldoximes and occurs keeping the geometrical integrity of alkene substrates unchanged. The methyl 2-nitrosobenzoate assisted conversion of oximes to nitriles proceeded in shorter times and with good yields. This methodology can be readily applied to wide variety of aromatic and heteroaromatic aldoximes for their conversion into desired nitriles.

6.5. Experimental Section

6.5.1. General Information

Reactions were conducted in screw-cap glass vials, with Teflon-lined caps. The conformation of the reactions was monitored using analytical Thin Layer Chromatography (TLC) on Merck silica gel G/GF$_{254}$ plates and used UV-Cabinet for visualization of compound spots on TLC plate. All the starting materials for preparation of aldoximes were purchased from Sigma-Aldrich, SRL, Spectrochem, SD-Fine and Avra and were used as received. All the reagents are of analytical grade and used directly without any further purification. CH_3CN solvent was distilled over CaH_2. Purification of compounds using column chromatography was performed with the Rankem silica gel (60-120 mesh). NMR (^{1}H and ^{13}C) spectra of all the synthesized compounds were recorded on Bruker AVANCE HD (400 MHz / 100 MHz) spectrometerusing$CDCl_3$and DMSO-d_6(deutrated) as solvents and TMS as an internal standard. The data of the compounds was recorded as chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations for the multiplicity as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet.

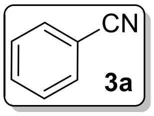
6.5.2. General Procedure for the Preparation Nitriles (3a-3ab)

To a solution of the substrate **1a** (120 mg, 1.0 mmol) in dry acetonitrile (2 mL) in round bottom flask were added methyl 2-nitrosobenzoate **2** (163 mg, 1.0 mmol) and Cs_2CO_3 (320 mg, 1.0 mmol) under a nitrogen atmosphere. The mixture was allowed to stir 70 ^{o}C, until TLC indicated complete reaction. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel using *n*-hexane and ethyl acetate solvents as mobile phase.

6.6 Characterization Data of Products

Benzonitrile (3a)

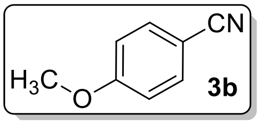
Yield: 80%, Colourless liquid, IR (KBr) neat: 2231 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.50 (m, 3H), 7.41-7.37 (t, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8, 132.2, 129.2, 118.9, 112.4.

4-MethoxyBenzonitrile (3b)

Yield: 80%, Colourless liquid, IR (KBr) neat: 2221 cm^{-1}.

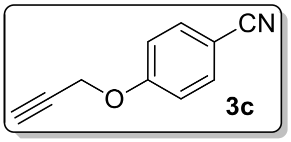


3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78(d, *J*= 8, 1H), 7.52(d, *J* = 8, 1H),6.95(d, *J* = 8, 1H), 6.87 (d, *J* = 8, 1H),3.81 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 139.3, 119.4, 109.2, 102.3, 56.6.

4-(Prop-2-yn-1-yloxy)benzonitrile (3c)

Yield: 85%, white solid, IR (KBr) neat: 2226 cm^{-1}, M.P. 138-139 °C.

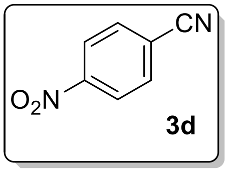


3c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.68 (d, *J* = 2.4 Hz, 2H), 2.50 (t, *J* = 2.4 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 134.0, 118.9, 115.7, 105.0, 76.6, 55.9.

4-Nitrobenzonitrile (3d)

Yield: 92%, white solid, IR (KBr) neat: 2211 cm^{-1}, M.P. 143-145 °C.

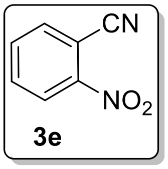


3d

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 124.3, 118.4, 116.7.

2-Nitrobenzonitrile (3e)

Yield: 90%, white solid, IR (KBr) neat: 2232 cm^{-1}, M.P. 109-111 °C.

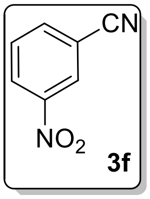


3e

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.36 (d, *J* = 12 Hz, 1H), 7.97-7.95 (d, *J* = *8* Hz, 1H), 7.87-7.86(t, *J* = 4Hz, 1H), 7.40-7.36 (t, *J* = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 134.3,133.7,128.5, 125.6,114.9, 108.2.

3-Nitrobenzonitrile (3f)

Yield: 88%, white solid, IR (KBr) neat: 2233 cm^{-1}, M.P. 118-110 °C.

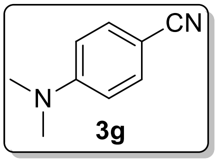


3f

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.41 (d, *J* = 7.8 Hz, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 138.1, 130.2, 128.1, 127.3, 127. 3, 125.4, 115.1.

4-(Dimethylamino)benzonitrile (3g)

Yield: 80%, white solid, IR (KBr) neat: 2211 cm^{-1}, M.P. 71-73 °C.

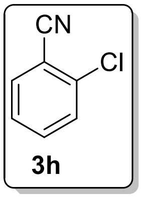


3g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47(d, J = 8 Hz, 2H), 6.4 (d, J = 8 2 Hz, 2H), 3.0(s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 133.4, 120.8, 111.4, 97.3, 39.9. HRMS (ESI-TOF): m/z calcd for $C_9H_{10}N_2[M+H]^+$ 147.0924, found 147.0925.

2-Chlorobenzonitrile (3h)

Yield: 92%, white solid, IR (KBr) neat: 2223 cm^{-1}, M.P. 48-50 °C.

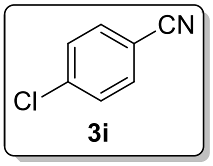


3h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.9 Hz, 1H), 7.51-7.44 (m, 2H), 7.31 (t, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 134.0, 130.1, 127.2, 116.0, 113.3.

4-Clorobenzonitrile (3i)

Yield: 82%, solid, IR (KBr) neat: 2232 cm^{-1}, M.P. 92-94 °C.

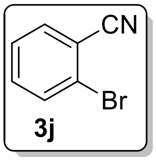


3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 133.4, 129.7, 118.0, 110.8.

2-Bromobenzonitrile (3j)

Yield: 85%, white solid, IR (KBr) neat: 2228 cm^{-1}, M.P. 56-57 °C.

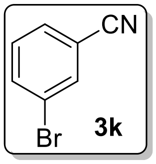


3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.64 (m, 2H), 7.51-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 134.0, 133.2, 127.7, 125.2, 117.2, 115.8.

3-Bromobenzonitrile (3k)

Yield: 82%, white solid, IR (KBr) neat: 2233 cm^{-1}, M.P. 41-42 °C.

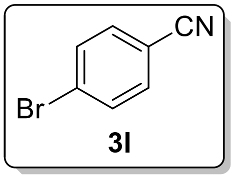


3k

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 3.3 Hz, 1H), 7.70-7.66 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.8, 130.7, 122.9, 117.3, 114.2.

4-Bromobenzonitrile (3l)

Yield: 86%, white solid, IR (KBr) neat: 2108 cm^{-1}, M.P. 112-113 °C.

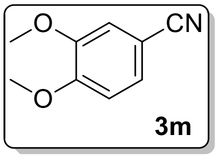


3l

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 133.4, 132.7, 128.0, 118.1, 111.2.

3,4-Dimethoxybenzonitrile (3m)

Yield: 88%, white solid, IR (KBr) neat: 2211 cm^{-1}, M.P. 64-66 °C.

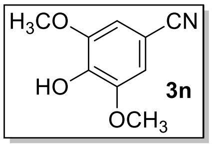


3m

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22 (dd, J = 8.3, 1.8 Hz, 1H), 7.01 (d, J = 1.7 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.9, 149.2, 126.5, 119.3, 113.9, 111.2, 103.9, 56.2.

4-Hydroxy-3,5-dimethoxybenzonitrile (3n)

Yield: 80%, white solid, IR (KBr) neat: 2211 cm^{-1}, M.P. 130-131 °C.

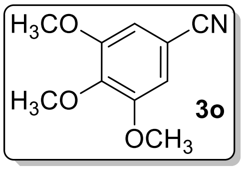


3n

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.90 (s, 2H), 5.99 (s, 1H), 3.94 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.2, 139.3, 119.4, 109.2, 102.3, 56.6. HRMS (ESI-TOF): m/z calcd for $C_9H_9NO_3$ [M+H]$^+$ 180.0662, found 180.0665.

3,4,5-Trimethoxybenzonitrile (3o)

Yield: 90%, white solid, IR (KBr) neat: 2211 cm^{-1}, M.P. 89-91 °C.

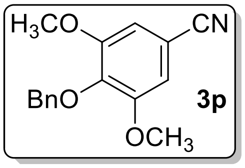


3o

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.80 (s, 2H), 3.83 (s, 3H), 3.81 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.6, 142.3, 119.0, 109.4, 106.7, 61.1, 56.4. HRMS (ESI-TOF): m/z calcd for $C_{10}H_{11}NO_3$ [M+H]$^+$ 194.0819, found 194.0820.

4-(Benzyloxy)-3,5-dimethoxybenzonitrile (3p)

Yield: 82%, white gummy solid, IR (KBr) neat: 2231 cm^{-1}.

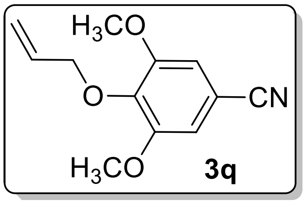


3p

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, J = 6.5 Hz, 2H), 7.36-7.31 (m, 3H), 6.84 (s, 2H), 5.08 (s, 2H), 3.84 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.6, 140.8, 136.7, 128.9, 127.5, 127.0, 119.0, 106.8, 106.5, 75.2, 56.1.

4-(Allyloxy)-3,5-dimethoxybenzonitrie (3q)

Yield: 86%, white gummy solid, IR (KBr) neat: 2241 cm^{-1}.

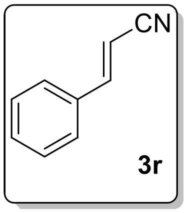


3q

^{1}H NMR (400 MHz,$CDCl_3$) δ 6.88 (s,2H), 6.08 (dd, J = 10.3, 6.1 Hz, 1H), 5.33 (dd, J = 17.2, 1.5 Hz, 1H), 5.23 (d, J = 9.1Hz, 1H), 4.60 (d, J = 6.1 Hz, 2H), 3.89 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 142.2. 133.8, 118.4, 106.6, 74.2, 56.3.

Cinnamonitrile (3r)

Yield: 90%, white solid, IR (KBr) neat: 2253 cm^{-1}, M.P. 35-36 ˚C.

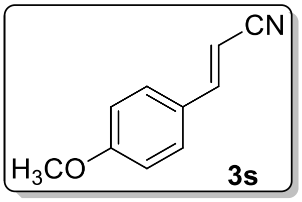


3r

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.38 (m, 6H), 5.88 (d, J = 16.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.3, 116.9, 127.4, 129.1, 131.2, 133.5, 134.1, 150.6.

P-Methoxycinnamonitrile (3s)

Yield: 89%, white solid, IR (KBr) neat: 2203 cm^{-1}, M.P. 62-65 ˚C.



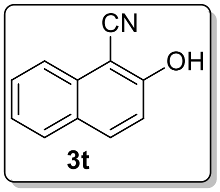
3s

^{1}H NMR (400 MHz,$CDCl_3$) δ 7.42 (d,J = 8.7 Hz, 2H), 7.36 (d,J = 16.6 Hz, 1H), 6.94 (d,J = 8.8 Hz, 2H), 5.74 (d, J = 16.6 Hz, 1H), 3.87 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 150.1, 129.1, 126.5, 118.7, 114.5, 93.4, 55.5.

2-Hydroxy-1-napthaonitrile (3t)

Yield: 90%, white solid, IR (KBr) neat: 2282 cm^{-1}, M.P. 156-158 ˚C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1H), 7.97(d, J = 6.4Hz,1H), 7.85 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.21 (s, 1H), 5.37 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 132.9, 132.6, 128.1, 124.3, 122.8, 117.6, 115.4.

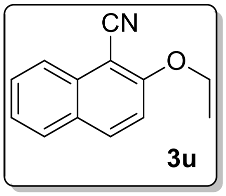


3t

2-Ethoxy-1-napthonitrile (3u)

Yield: 78%, white gummy solid, IR (KBr) neat: 2213 cm^{-1}.

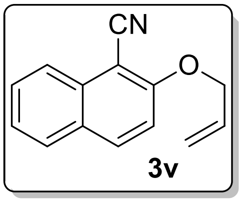
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.67–7.61 (m, 1H), 7.48–7.43 (m, 1H), 7.26 (s, 1H), 4.33 (q, J = 7.0 Hz, 2H), 1.54 (t, J = 7.0 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 133.9, 133.7, 129.1, 128.4, 125.1, 124.2, 115.8, 113.1, 95.8, 65.4, 14.8.



3u

2-(Allyloxy)-1-naphthonitrile (3v)

Yield: 78%, white gummy solid, IR (KBr) neat: 2236 cm^{-1}.

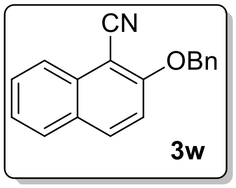


3v

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.28 (s, 1H), 6.12 (ddd, J = 21.0, 10.3, 5.0 Hz, 1H), 5.55 (d, J = 16.1 Hz, 1H), 5.39 (d, J = 10.6 Hz, 1H), 4.86 (d, J = 5.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 134.8, 133.7, 132.0, 129.2, 128.4, 125.2, 124.2, 118.5, 113.5, 96.0, 70.1.

2-(Benzyloxy)-1-naphthonitrile (3w)

Yield: 75%, white sticky solid, IR (KBr) neat: 2234 cm^{-1}.

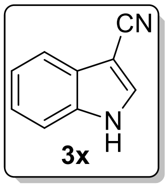


3w

H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 6.7 Hz, 2H), 7.45 (d, J = 7.3 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.35 (d, J = 7.3 Hz, 1H), 7.29 (s, 1H), 5.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 136.8, 133.6, 132.8, 128.9, 128.0, 127.1, 127.0, 124.3, 122.6, 117.3, 115.8, 86.5, 70.3

1*H*-Indole-3-carbonitrile (3x)

Yield: 88%, white solid, IR (KBr) neat: 2221 cm^{-1}, M.P. 180-182 °C.

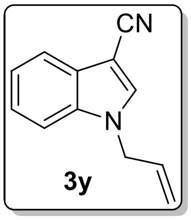


3x

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65(s, 1H), 7.80 (d, J= 8.48 Hz, 1H), 7.75(s, 1H), 7.47(d, J = 6.1 Hz, 1H), 7.40 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) δ 134.9, 132.0, 127.0, 124.3, 122.4, 119.7, 115.9, 112.1.

1-Allyl-1*H*-indole-3-carbonitrile (3y)

Yield: 80%, colour less liquid, IR (KBr) neat: 2224 cm^{-1}.

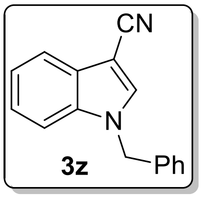


3y

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 1H),7.62 (s, 1H),7.40 (d, J= 7.6 Hz, 1H),7.36-7.29 (m, 2H), 6.04-5.94 (m, 1H), 5.33 (d, J = 6.2 Hz, 1H), 5.18 (d, J = 8.0 Hz 1H), 4.78 (d, J = 8.1 Hz 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 134.7, 131.6, 128.0, 123.9, 122.2, 120.0, 119.1, 115.9, 110.7, 86.1, 49.5.

1-Benzyl-1*H*-indole-3-carbonitrile (3z)

Yield: 82%, yellow liquid, IR (KBr) neat: 2233 cm^{-1}.



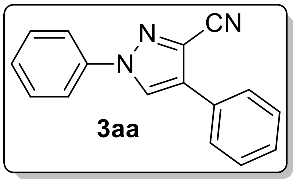
3z

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 (d, J = 12 Hz, 1H), 7.61 (s, 1H), 7.38-7.28(m, 7H), 7.15 (d, J = 8.0 Hz 2H), 5.34(s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.6, 135.2, 135.0, 129.2, 128.5, 128.0, 127.1, 124.0, 122.3, 120.0, 115.8, 110.8, 86.3, 50.9.

1,4-Diphenyl-1*H*-pyrazole-3-carbonitrile (3aa)

Yield: 90%, white sticky solid, IR (KBr) neat: 2228 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.28 (s, 1H), 8.00 (dd, J = 6.8, 1.6 Hz, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.45-7.30 (m, 6H).^{13}C NMR (100 MHz, CDCl$_3$) δ 138.8, 133.6, 130.4, 129.8, 129.0, 128.2, 126.8, 119.8, 114.2. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{11}N_3$[M+H]$^+$ 246.1033, found 246.1039.

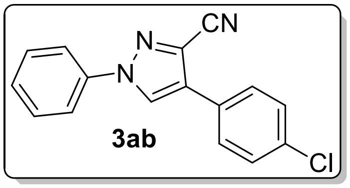


3aa

4-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-3-carbonitrile (3ab)

Yield: 90%, white sticky solid, IR (KBr) neat: 2221 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.40 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H), 7.77 (d, J=7.7 Hz, 2H), 7.56 (t, J = 7.9 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.7, 133.6, 129.8, 129.21, 128.2, 119.8. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{10}ClN_3$ [M+H]$^+$ 280.0643, found 280.0644.

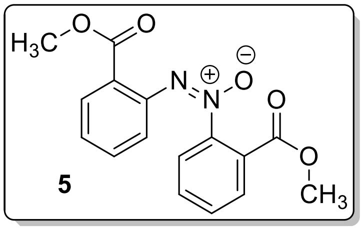


3ab

Compound (5)

(*Z*)-1,2-bis(2-(Methoxycarbonyl)phenyl)diazene oxide

Orange colour solid: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (td, J = 7.8, 1.2 Hz, 2H), 7.83 (dd, J = 7.7, 1.4 Hz, 1H), 7.65-7.61 (m, 1H), 7.60-7.57 (m, 1H), 7.52 (td, J = 7.6, 1.1 Hz, 1H), 7.38-7.35 (m, 1H), 7.35-7.30 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.8, 165.4, 133.1, 132.5, 130.6, 130.4, 130.3, 127.4, 125.7, 124.3, 124.0, 122.5, 52.8, 52.4. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{14}N_2O_5$[M+Na]$^+$ 337.0803, found 337.8110.



5

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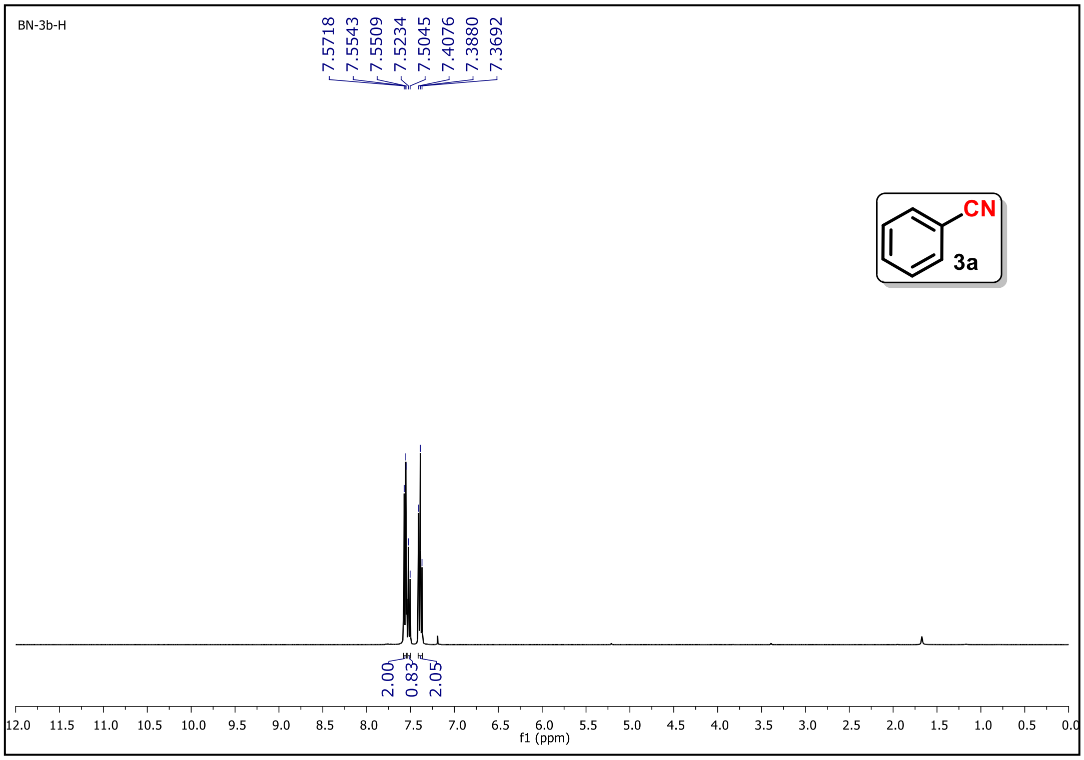
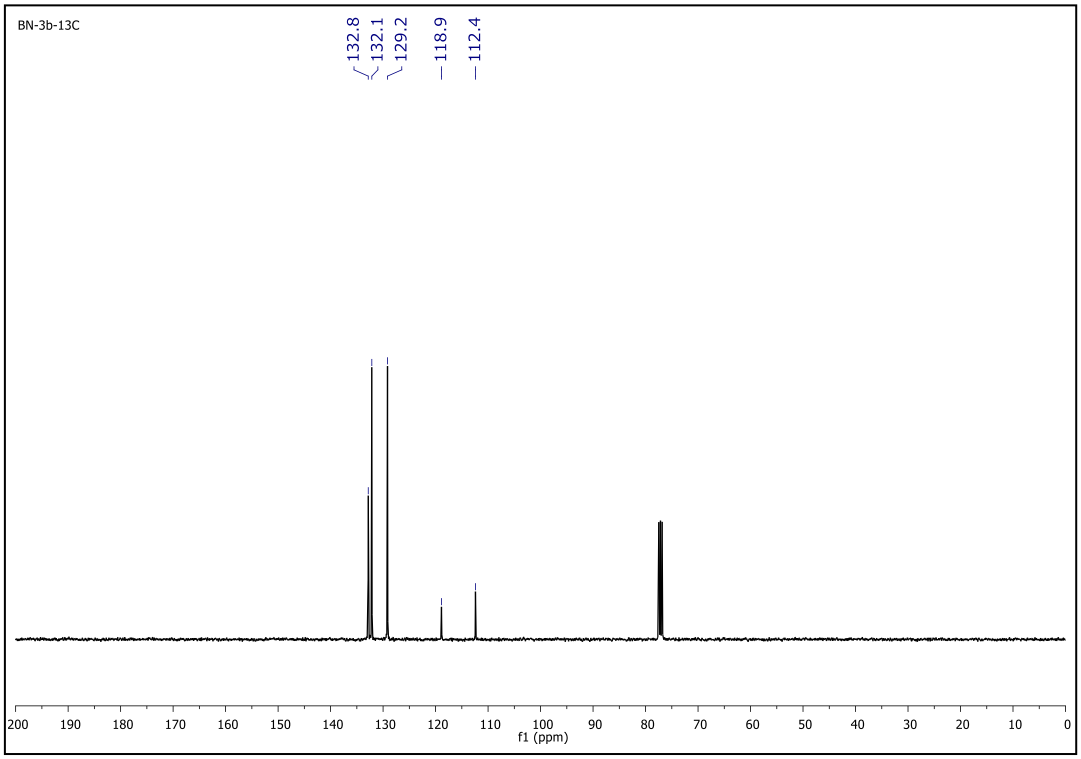
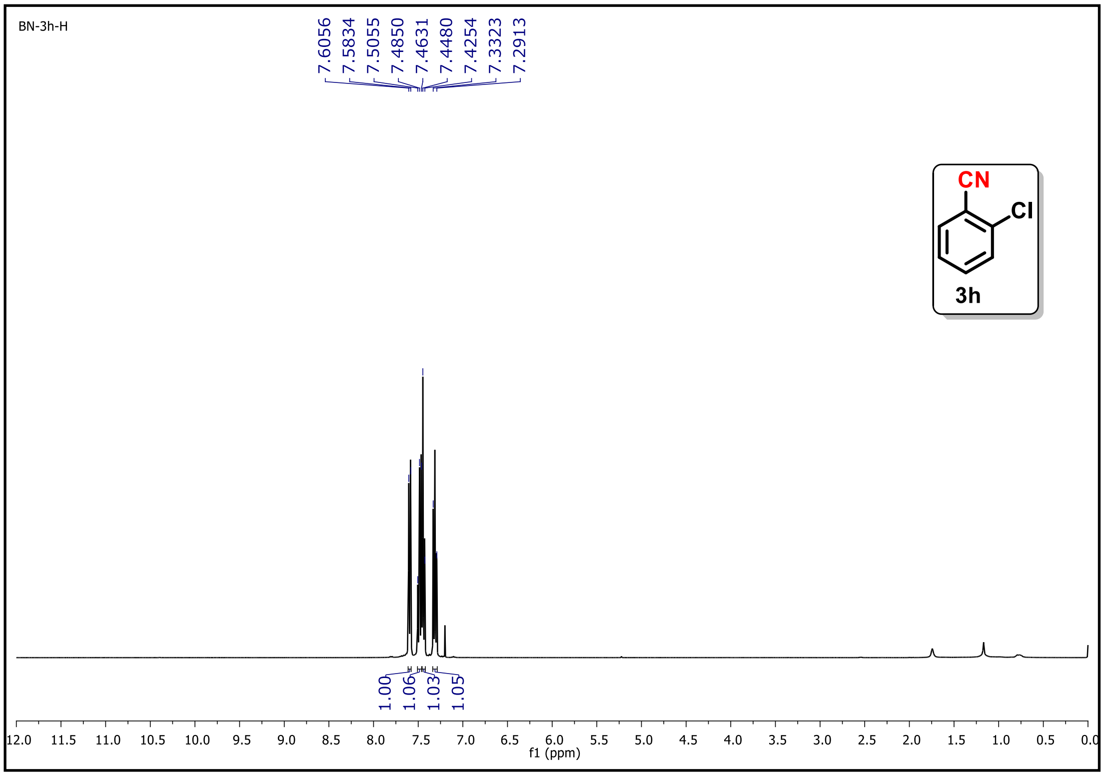
6.8. Selected NMR (^{1}H and ^{13}C) and Mass Spectra



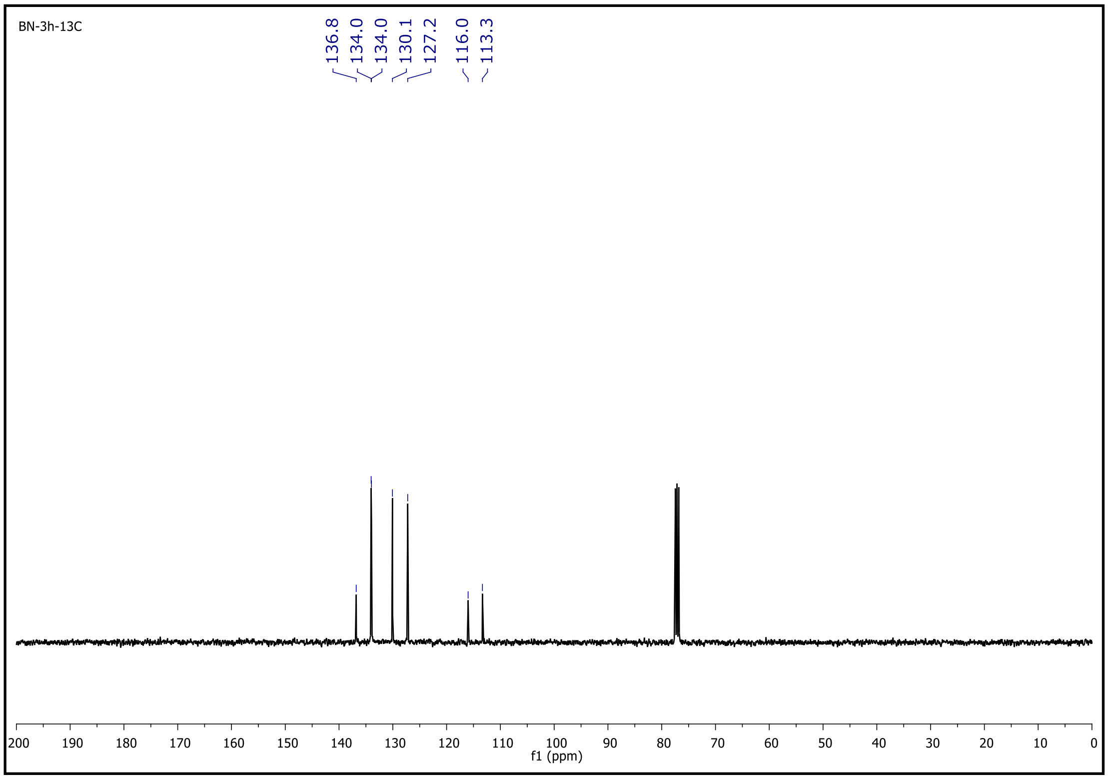
^{1}H NMR spectrum of compound **3a**



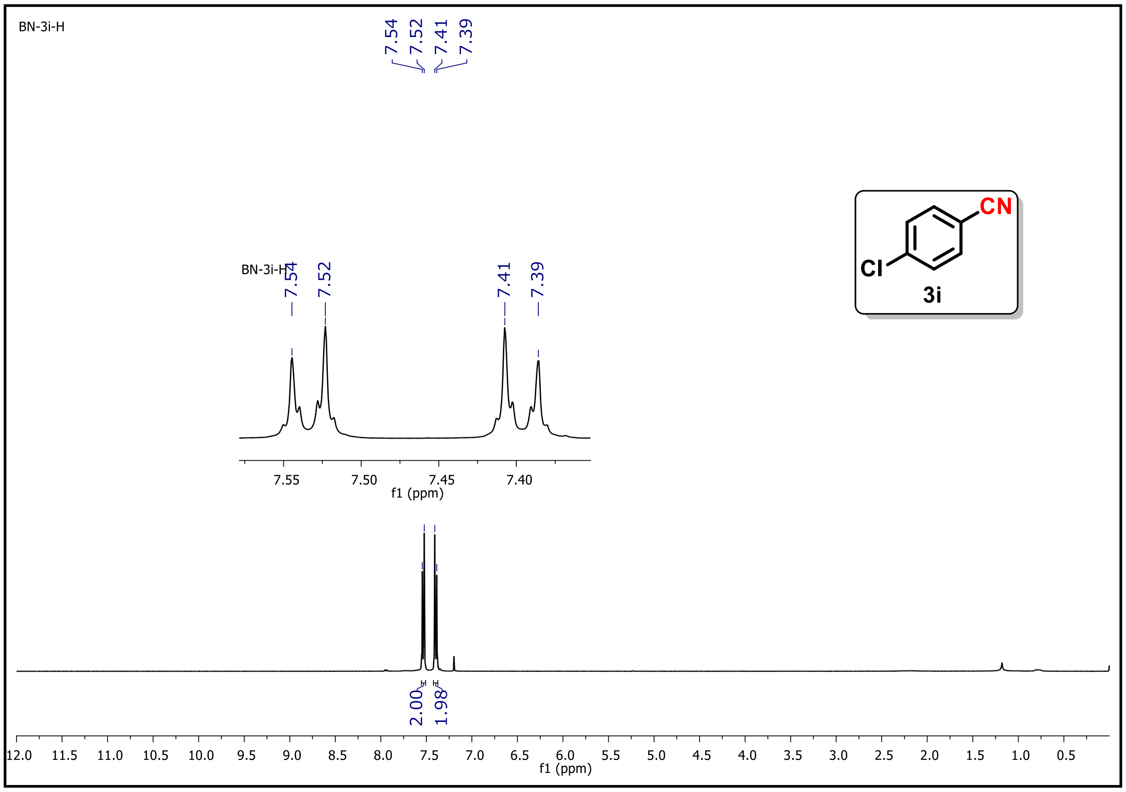
^{13}C NMR spectrum of compound **3a**



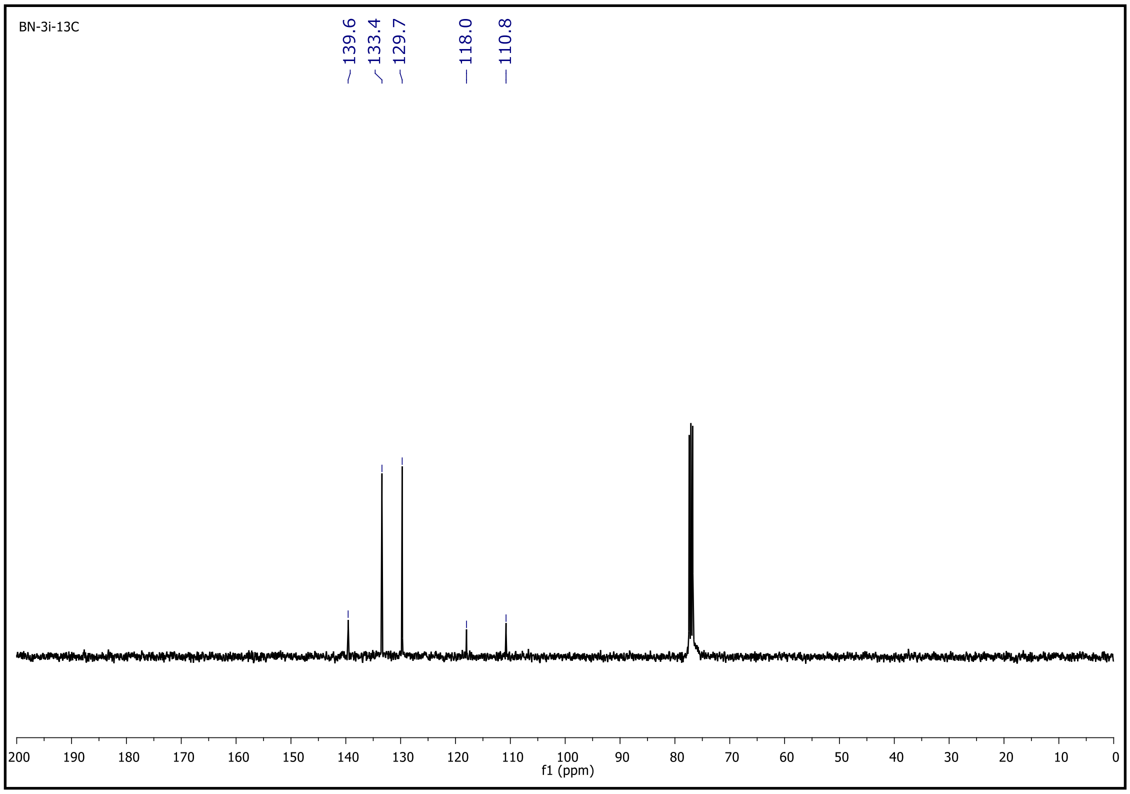
^{1}H NMR spectrum of compound **3h**



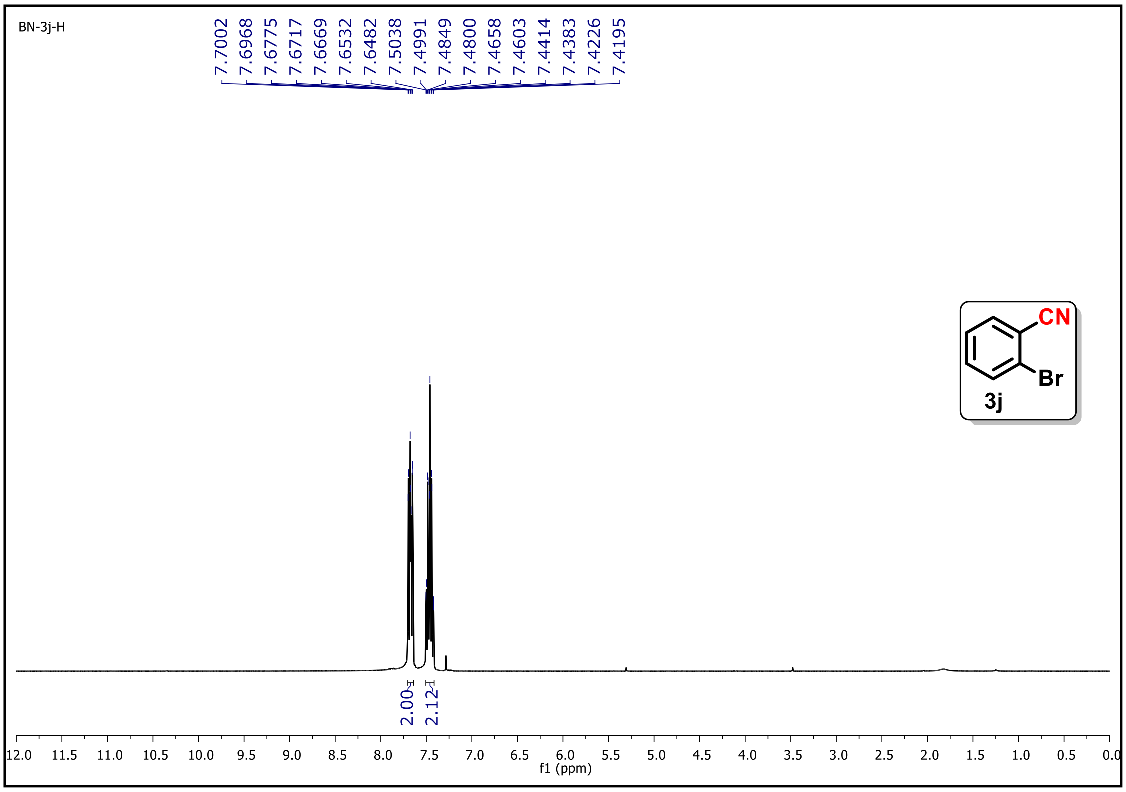
^{13}C NMR spectrum of compound **3h**



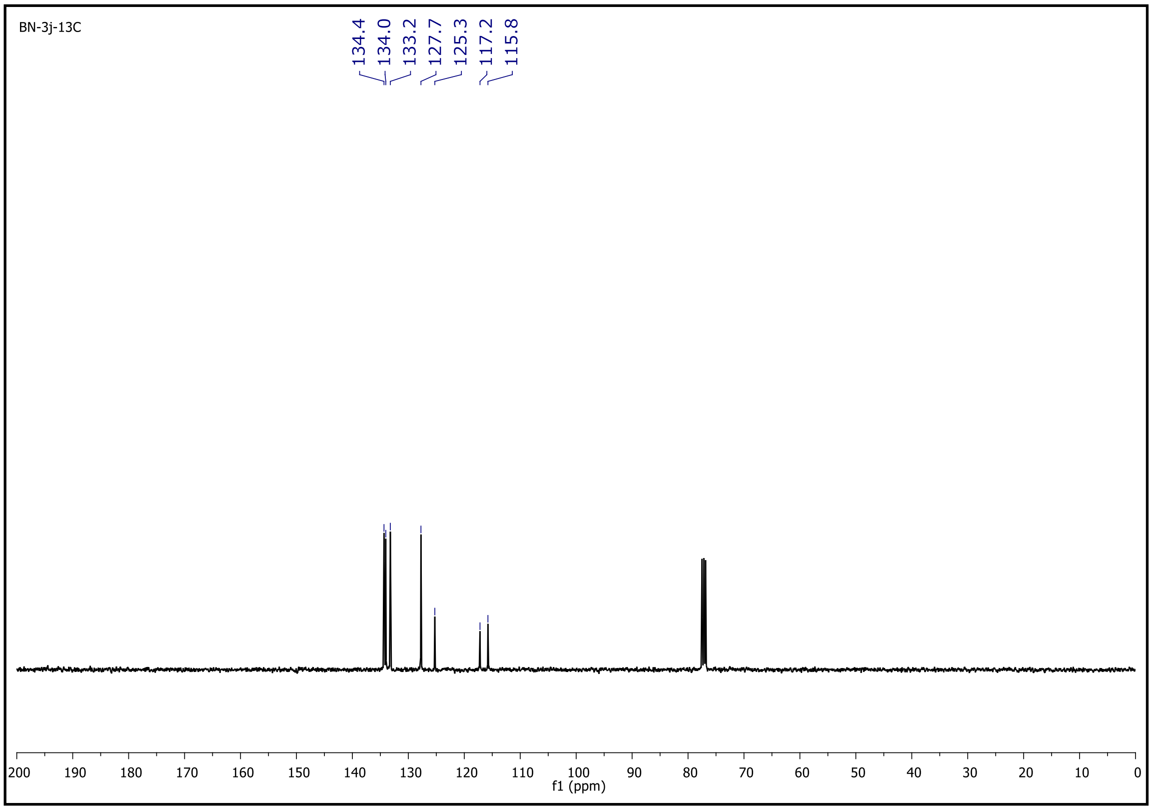
^{1}H NMR spectrum of compound **3i**



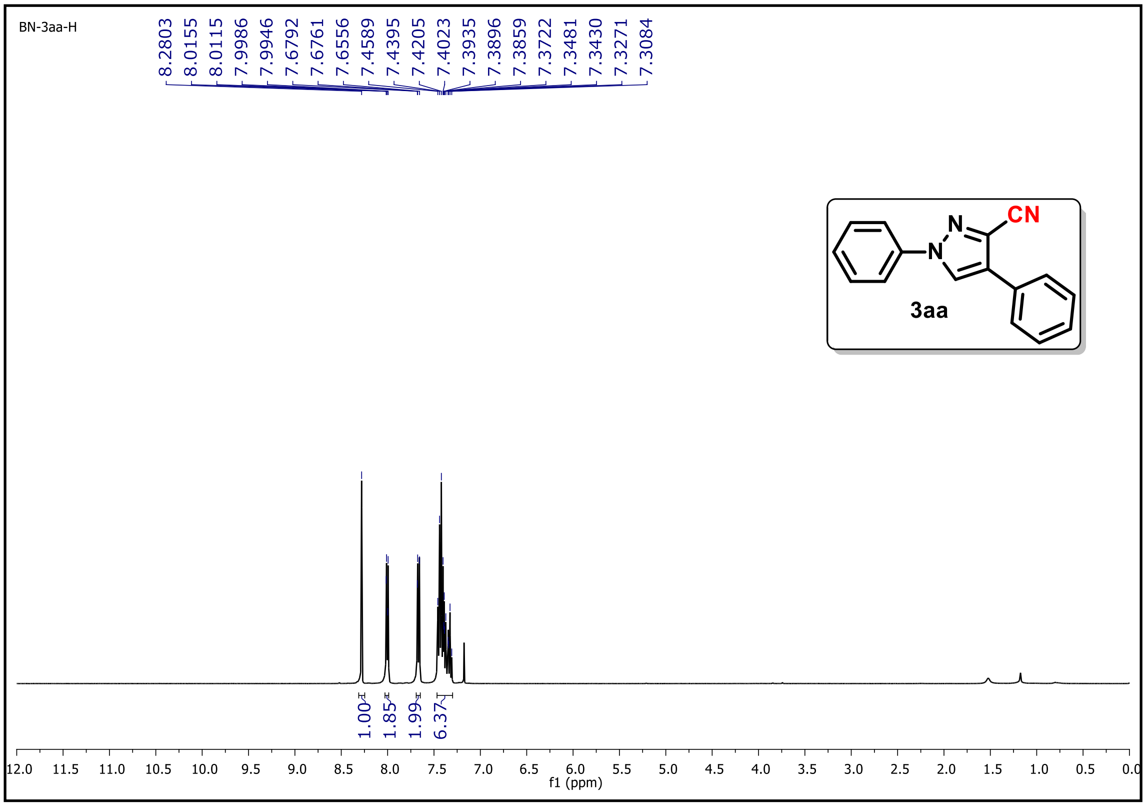
^{13}C NMR spectrum of compound **3i**



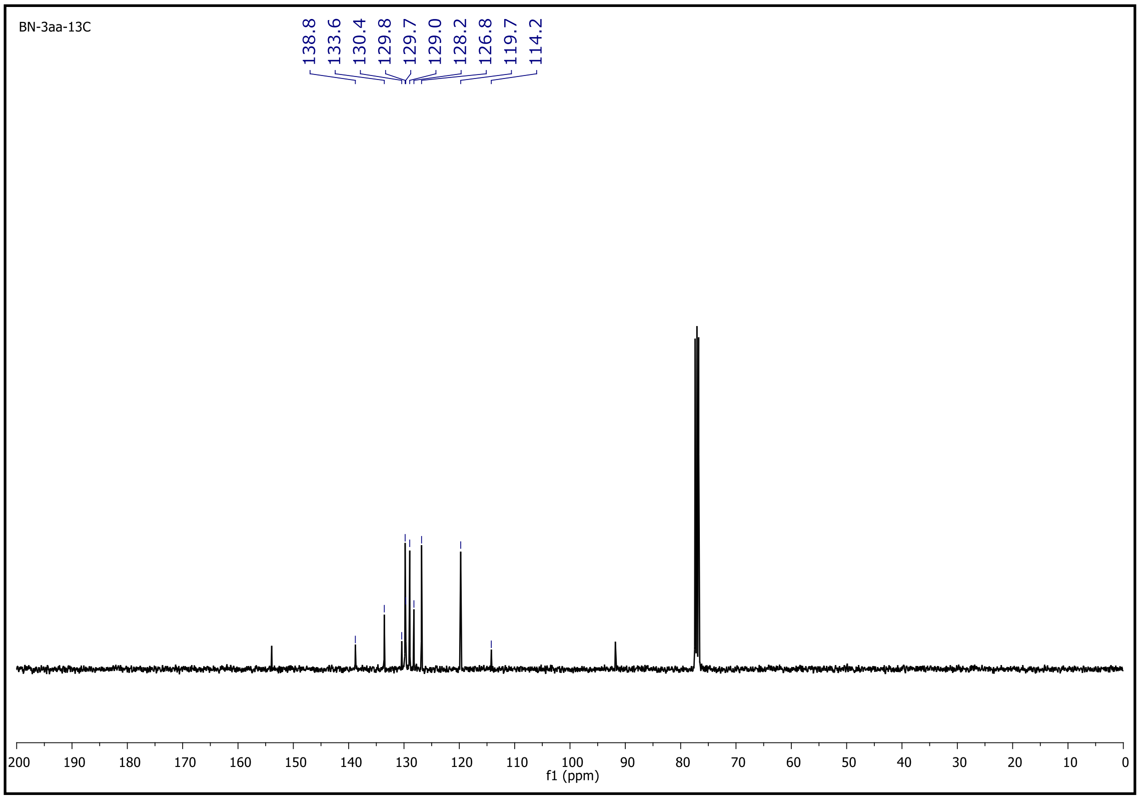
^{1}H NMR spectrum of compound **3j**



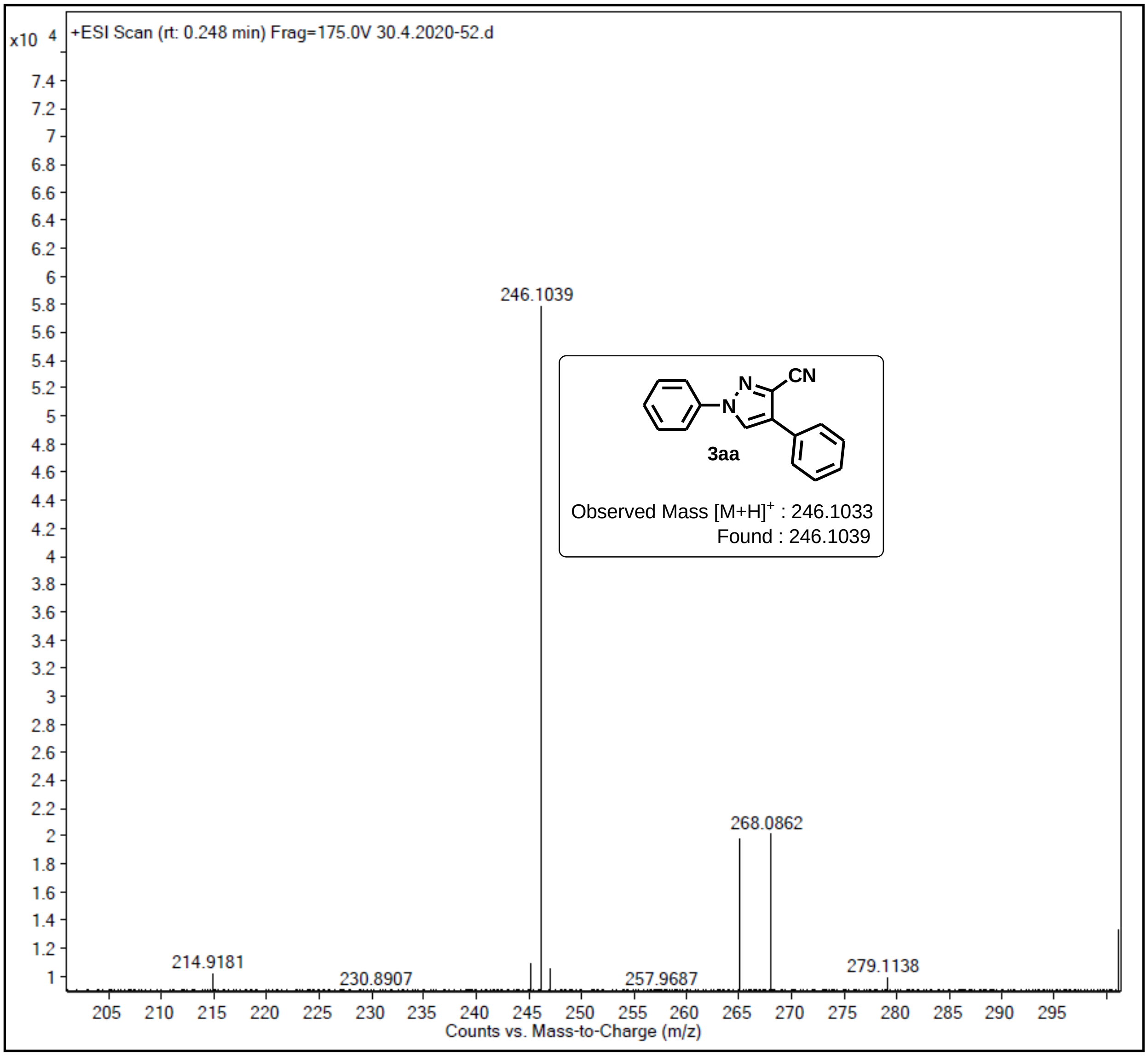
^{13}C NMR spectrum of compound **3j**



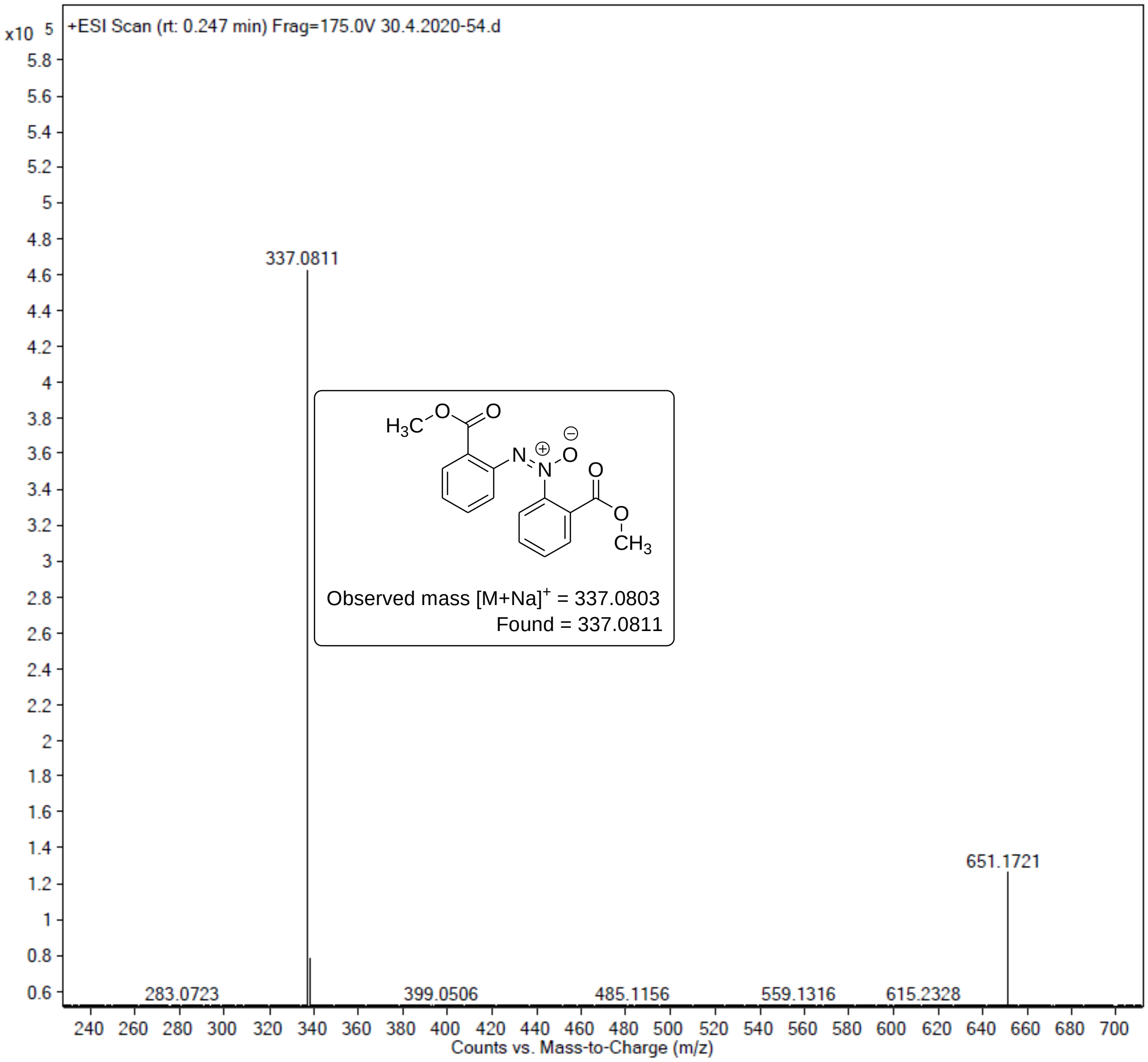
^{1}H NMR spectrum of compound **3aa**



^{13}C NMR spectrum of compound **3aa**



Mass spectrum of compound **3aa**



Mass spectrum of compound **5**

SUMMARY

CHAPTER-I

Introduction

The literature survey, objectives and prerequisites of the present study are presented in the chapter. Apart from this, a brief introduction of rongalite and its synthetic applications in various fields is discussed.[1] Sodium hydroxy methanesulfinatedihydrate (SHM), also called as rongalite. It is an industrial product that has been used as a bleaching agent in the dye and printing industry, it acts as an antidote against heavy metal poisoning, antioxidant in formulations and green reagent in organic chemistry.[2-4]

Palladium-catalyzed cross-coupling, reactions of arylboronic acid with aryl halide, known as the Suzuki-Miyaura reaction, which is the leading methodologies for the construction of C-C bond in the synthesis of biaryl and their applications in various fields. Recent past has witnessed a tremendous increment in ways to develop and design novel phosphorus-free palladium catalysts for robust, active, higher turnover number and functional group tolerance at low costs. Development of phosphine-free palladium complexes and their application in the C-C bond formation.

Also, we have discussed the importance of nitrile compounds and their synthesis from the corresponding aldoximes by environmentally benign dehydrating agents.

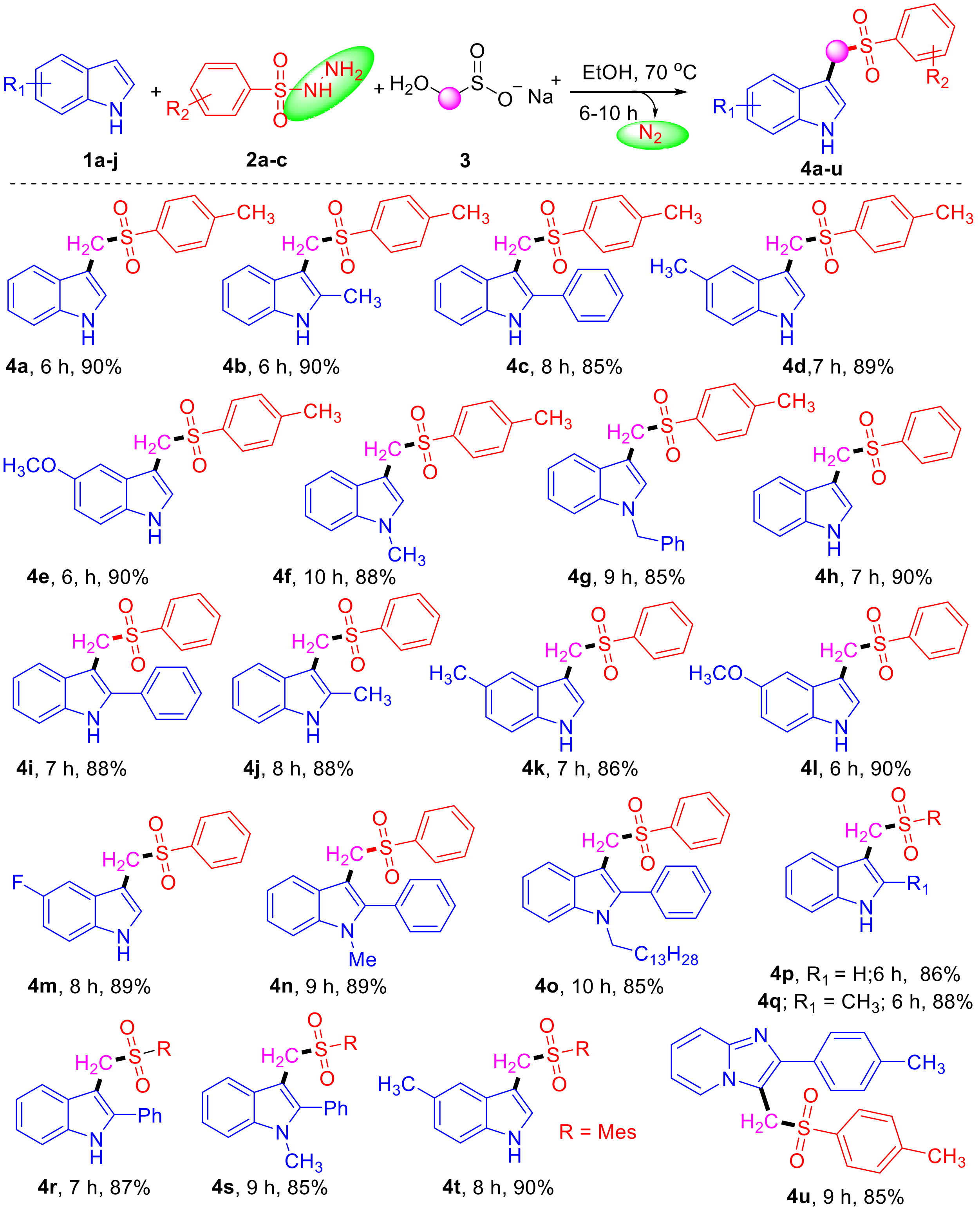
The structures of the synthesized compounds were characterized by FT-IR, NMR, Mass spectral and single crystal X-ray diffraction methods. All the compounds described in the thesis were synthesized using conventional methods.

CHAPTER-II

One-Pot Three-Component Synthesis of 3-(phenylsulfonyl methyl) Substituted Indole Derivatives via C(sp^2)–H Functionalization

The indole synthon is the most common heterocyclic moiety found in many natural and pharmaceutical agents.[5] Indoles and its derivatives are considered “privileged structures” as they tend to bind with many receptors.[6] A considerable attention has been received in the synthesis of indoles and functionalization of indoles at C-2 and C-3 position to increase the biological activity of the pyrrole core.[7] Much has already been done on alkenylation, arylation, alkynylation, amination, acylation, sulfuration, and alkylation of indoles. Whereas, sulfonyl methylated indoles

Table 2.1. One-pot 3-(phenylsulfonyl methyl) Substituted Indole Derivatives.



1a-j **2a-c** **3** **4a-u**

4a, 6 h, 90% **4b**, 6 h, 90% **4c**, 8 h, 85% **4d**,7 h, 89%

4e, 6, h, 90% **4f**, 10 h, 88% **4g**, 9 h, 85% **4h**, 7 h, 90%

4i, 7 h, 88% **4j**, 8 h, 88% **4k**, 7 h, 86% **4l**, 6 h, 90%

4m, 8 h, 89% **4n**, 9 h, 89% **4o**, 10 h, 85%

4p, R_1 = H;6 h, 86%

4q; R_1 = CH_3; 6 h, 88%

4r, 7 h, 87% **4s**, 9 h, 85% **4t**, 8 h, 90% **4u**, 9 h, 85%

are common pharmacophores with wide applications in pharmaceuticals.[8] Nevertheless, the direct sulfonyl methylation of indoles has only caught the imagination of only a few chemists.[9] Therefore, introducing sulfonyl methylation group into the indole ring has the potential to attract the many researchers in this direction. Herewith, we report a metal-free one-pot three-component synthesis of 3-(phenylsulfonyl methyl) substituted indole derivatives with tosylhydrazides in the presence of rongalite (Table 2.1).

The optimized reaction conditions are as follows, to an equimolar solution of indoles **1a** with tosylhydrazides **2a** in ethanol was added rongalite **3** (2 equiv) and the reaction mixture was stirred at 70 °C for 6-8 hours to produce the desire products **4a** up to 90% yields. (Table 2.1). Further, we have extended the optimized protocol of 3-(phenylsulfonyl methyl)indoles derivatives **4a-u** with tosylhydrazides **2a-c** in the presence of rongalite. (Table 2.1).

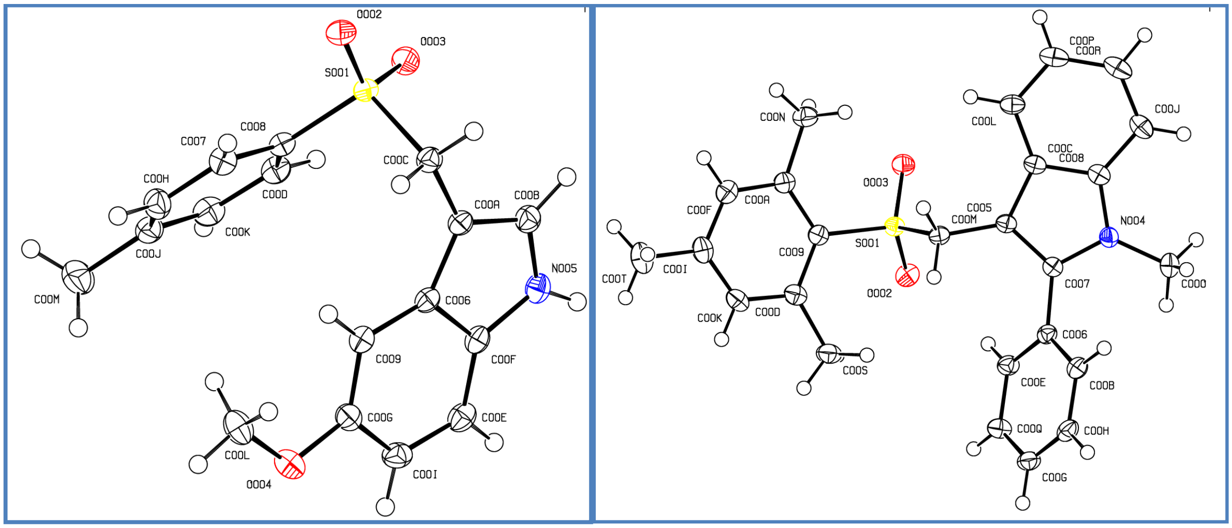


Figure 2.1: ORTEP Representation of Compounds **4e** and **4s**.

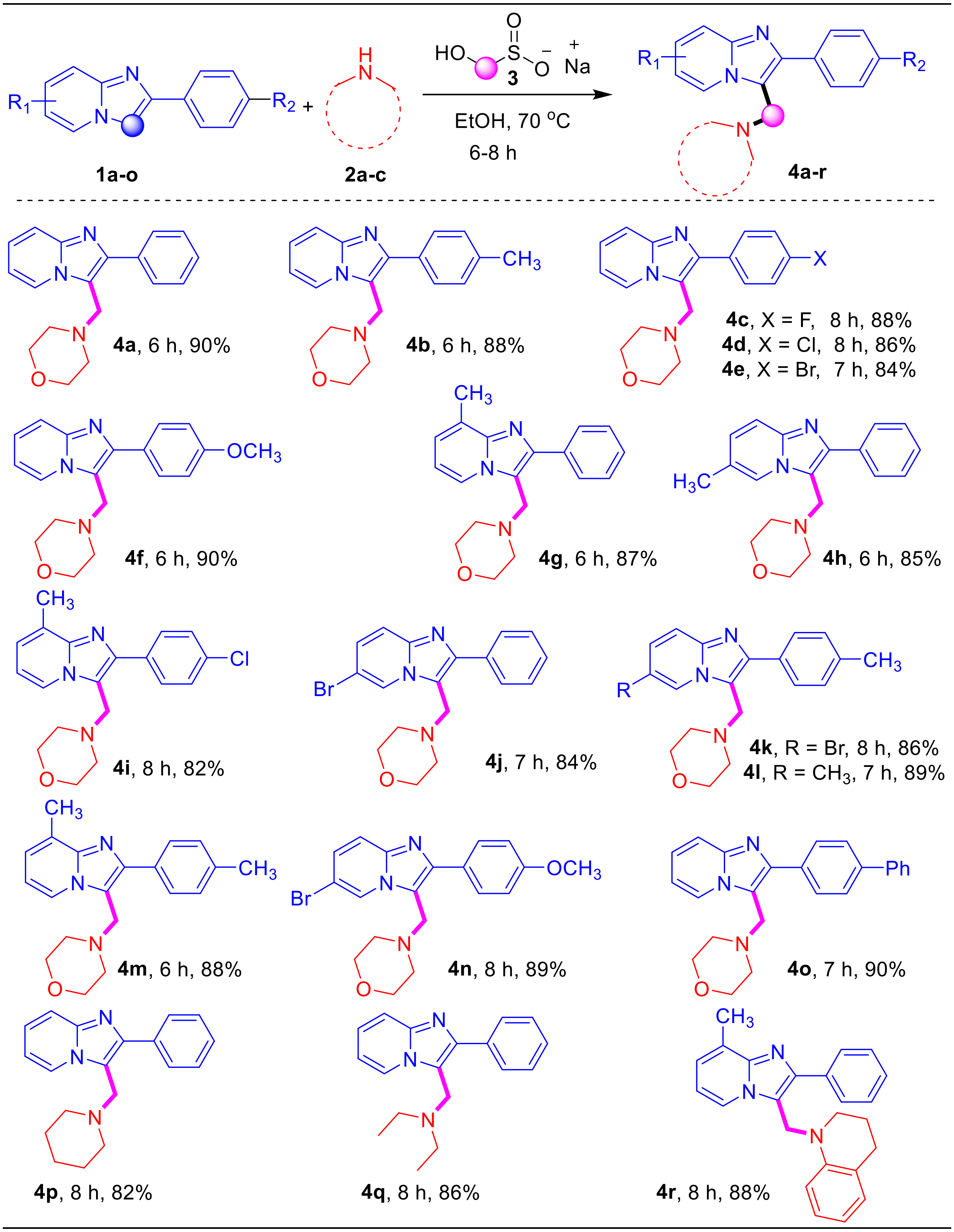
Here we have synthesized 21 compounds with good to excellent yields by using present protocol.

CHAPTER-IIIA

One-Pot Aminomethylation of Imidazo[1,2-*a*]pyridine and imidazo[2,1-*b*]thiazole Derivatives Using Secondary Amines and Rongalite

Imidazo[1,2-*a*]pyridines are important heterocyclic compounds and are known for their wide ranging biological activities and are building blocks in drugs such as Zolpidem , Olprinone, Zolimidine and show some pharmacological activities like being antibacterial, antiviral, antifungal, anti-inflammatory, analgesic and aromatise-inhibitors.[10] Alteration in the structural component leads to change in the activity of the compound. The hybrid molecules of imidazo-[1,2-*a*]pyridine and morpholine are key pharmacophores in various drugs and are biologically important molecules because of the presence of secondary amine thus enhancing their significance in the fields of agro chemicals and medicine.[11]

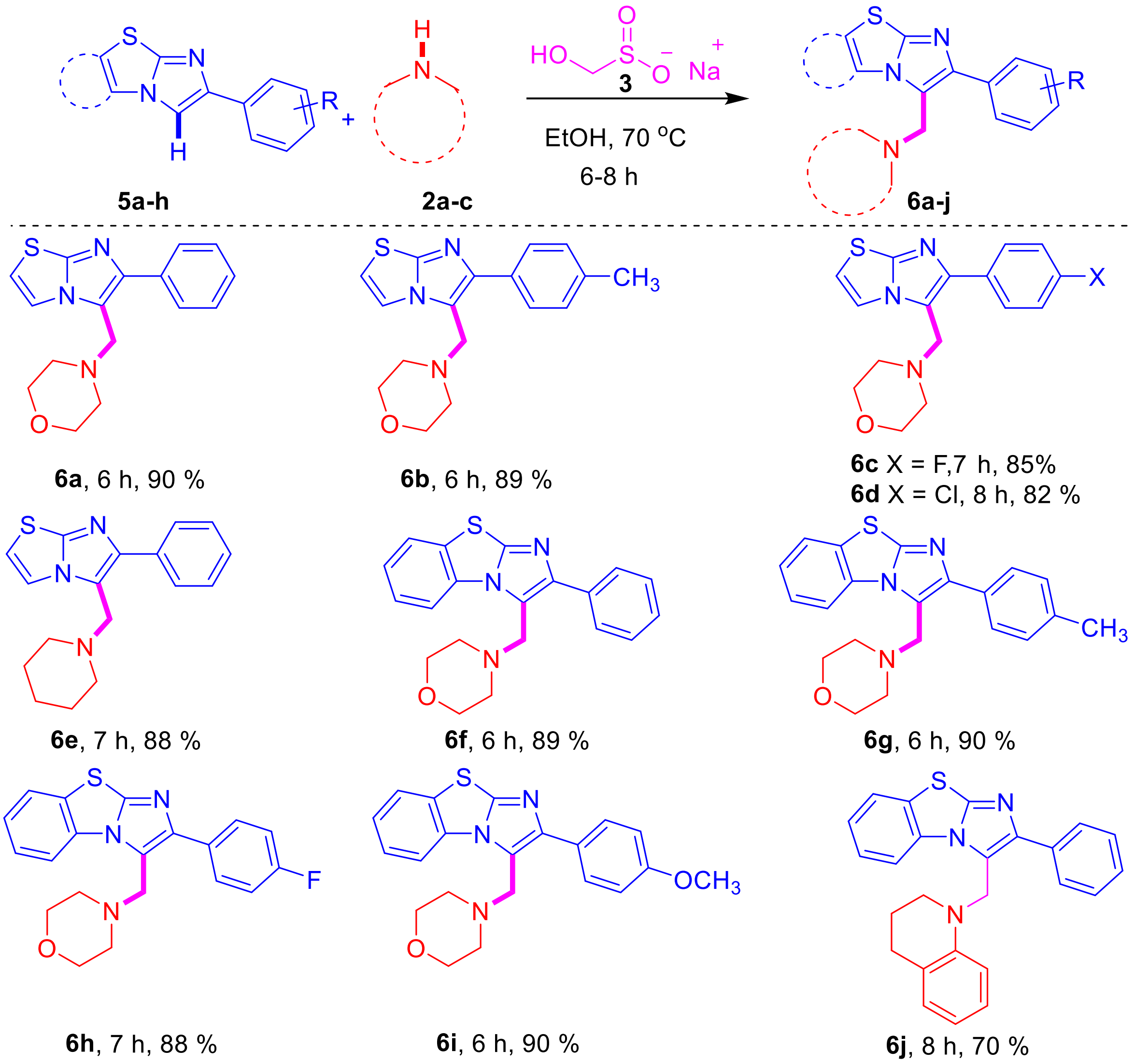
Table 3A.1. One-pot Aminomethylation of Imidazo[1,2-*a*]pyridine Derivatives.



Considering the importance of imidazo[1,2-*a*]pyridine-morpholine hybrids, we have developed one-pot three component reaction involving imidazo[1,2-*a*]pyridine, secondary amine and rongalite in ethanol to produce the desired compounds **4a-r** (Table 3A.1) and **6a-j** (Table 3A.2). The key step in this reaction is *in situ* generation of formaldehyde from rongalite.

The optimized reaction conditions are as follows, to an equimolar solution of imidazopyridines (1 mmol) and morpholine (secondary amine, 1 mmol) in ethanol solvent, 1.5 mmol of rongalite was added and the reaction mixture was stirred at 70 °C for 6-8 h to produce the desired products **4a-r** up to 90% yields (Table 3A.1). Further, we have extended the optimized protocol of aminomethylation by rongalite in the presence of secondary amine to the various 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole to obtain **6a-j** (Table 3A.2).

Table 3A.2. Aminomethylation of 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazolederivatives.



6a, 6 h, 90 %

6b, 6 h, 89 %

6c X = F,7 h, 85%
6d X = Cl, 8 h, 82 %

6e, 7 h, 88 %

6f, 6 h, 89 %

6g, 6 h, 90 %

6h, 7 h, 88 %

6i, 6 h, 90 %

6j, 8 h, 70 %

CHAPTER-III-B

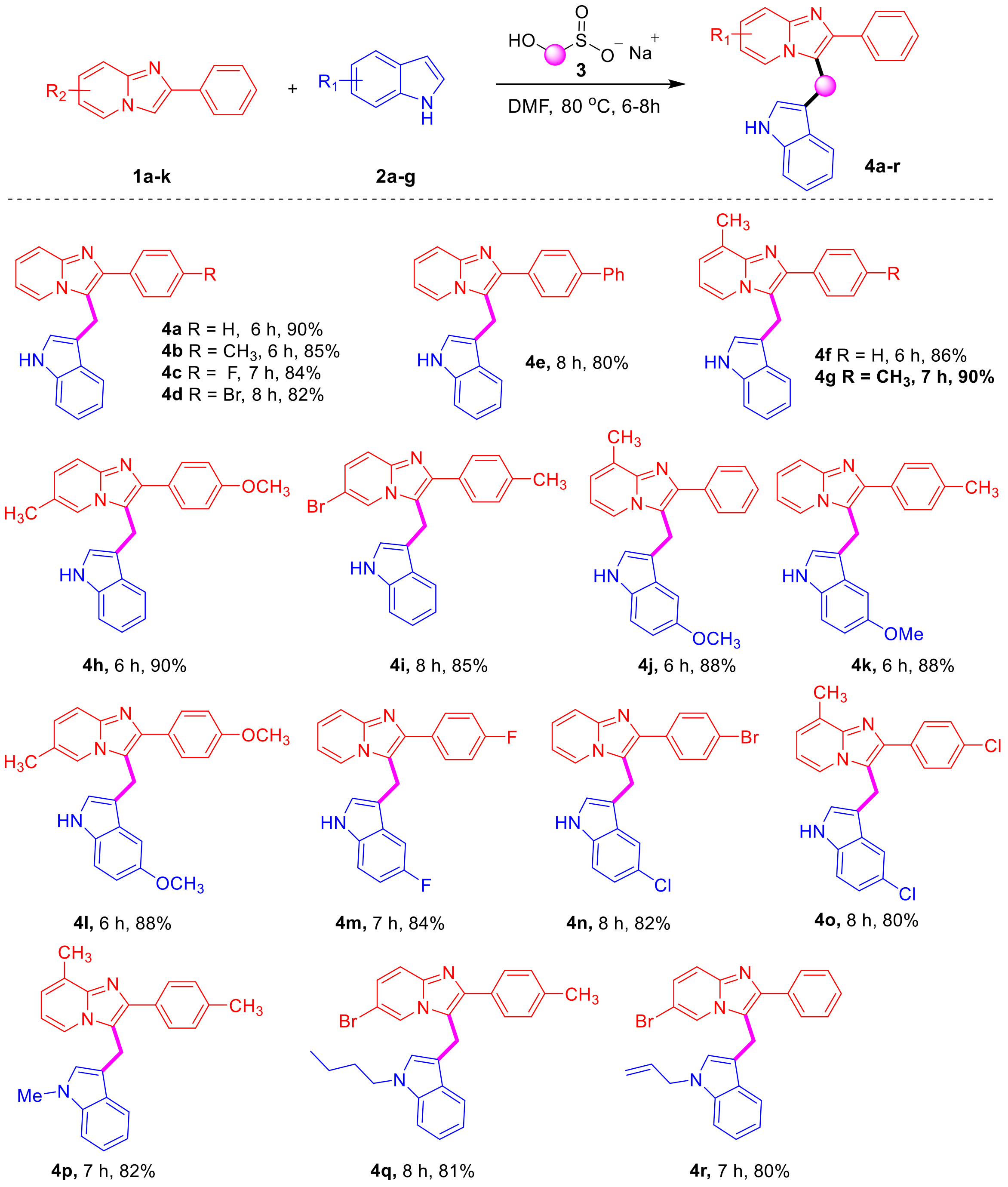
Rongalite as a Methylenating Agent: Synthesis of Heterodiarylmethanes via Metal-Free Coupling Between Imidazo[1,2-*a*]pyridines, imidazo[2,1-*b*]thiazole and Indoles

Diarylmethanes are important compounds which are frequently encountered in many biologically and pharmaceutically active compounds.[12] One of the well-known method for the synthesis of this class of compounds is transition metal-catalyzed cross-coupling reaction from the prefunctionalized substrates.[13] Among others, imidazo[1,2-*a*]pyridine derivatives and indole derivatives have gained much attention from the synthetic chemists due to their wide ranging applications.[14]

Considering the importance of these two classes of heterocyclic compounds and their hybrid molecules we have developed a novel method of rongalite promoted metal-free one-pot synthesis of heterodiarylmethanes from imidazo[1,2-*a*]pyridines and indoles. The optimized reaction conditions are as follows, to an equimolar solution of imidazo[1,2-*a*]pyridines and indole in DMF solvent add 2.0 mmol of rongalite to the reaction mixture and stirred at 80 ^{o}C for 4-5 h to produce the desire products **4a-r** up to 90% yields. Derivatives were showed in (Table 3B.1).

Further, the above methodology was extended to synthesis other heteroarene i.e., imidazo[2,1-*b*]thiazole, benzo[*d*]imidazo[2,1-*b*]-thiazole. These substrate also showed similar reactivity patterns of imidazo[1, 2-*a*]pyridines and furnished title compounds in excellent **6a-f** (Table 3B.2).

Table 3B.1. Synthesis of Heterodiaryl Methanes from Imidazo[1,2-*a*]pyridines and Indoles.



4a R = H, 6 h, 90%
4b R = CH_3, 6 h, 85%
4c R = F, 7 h, 84%
4d R = Br, 8 h, 82%

4e, 8 h, 80%

4f R = H, 6 h, 86%
4g R = CH_3, 7 h, 90%

4h, 6 h, 90%

4i, 8 h, 85%

4j, 6 h, 88%

4k, 6 h, 88%

4l, 6 h, 88%

4m, 7 h, 84%

4n, 8 h, 82%

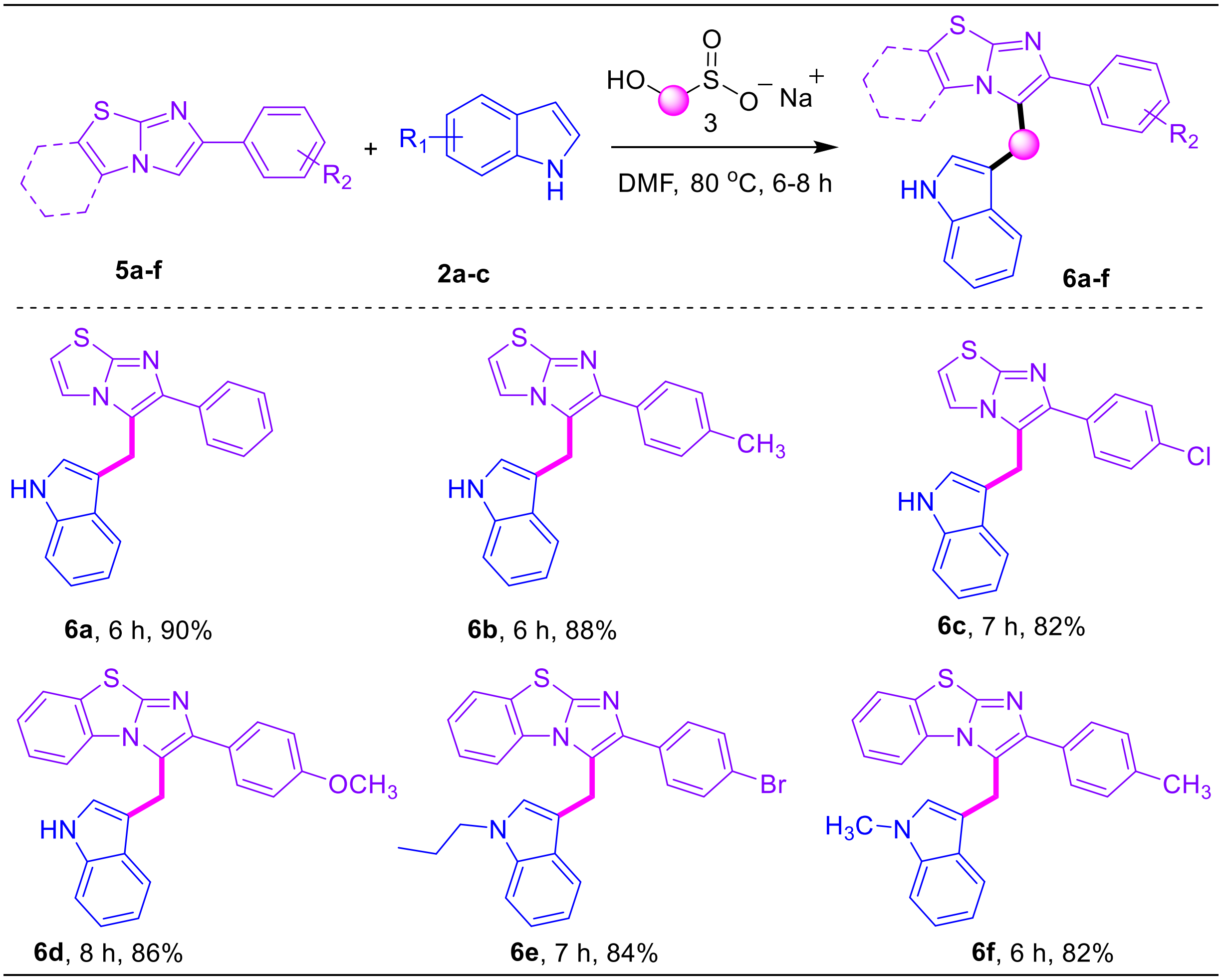
4o, 8 h, 80%

4p, 7 h, 82%

4q, 8 h, 81%

4r, 7 h, 80%

Table 3B.3. Reaction of Simple or Benzo[*d*]pyrrolo[2,1-*b*]thiazoles with Indoles

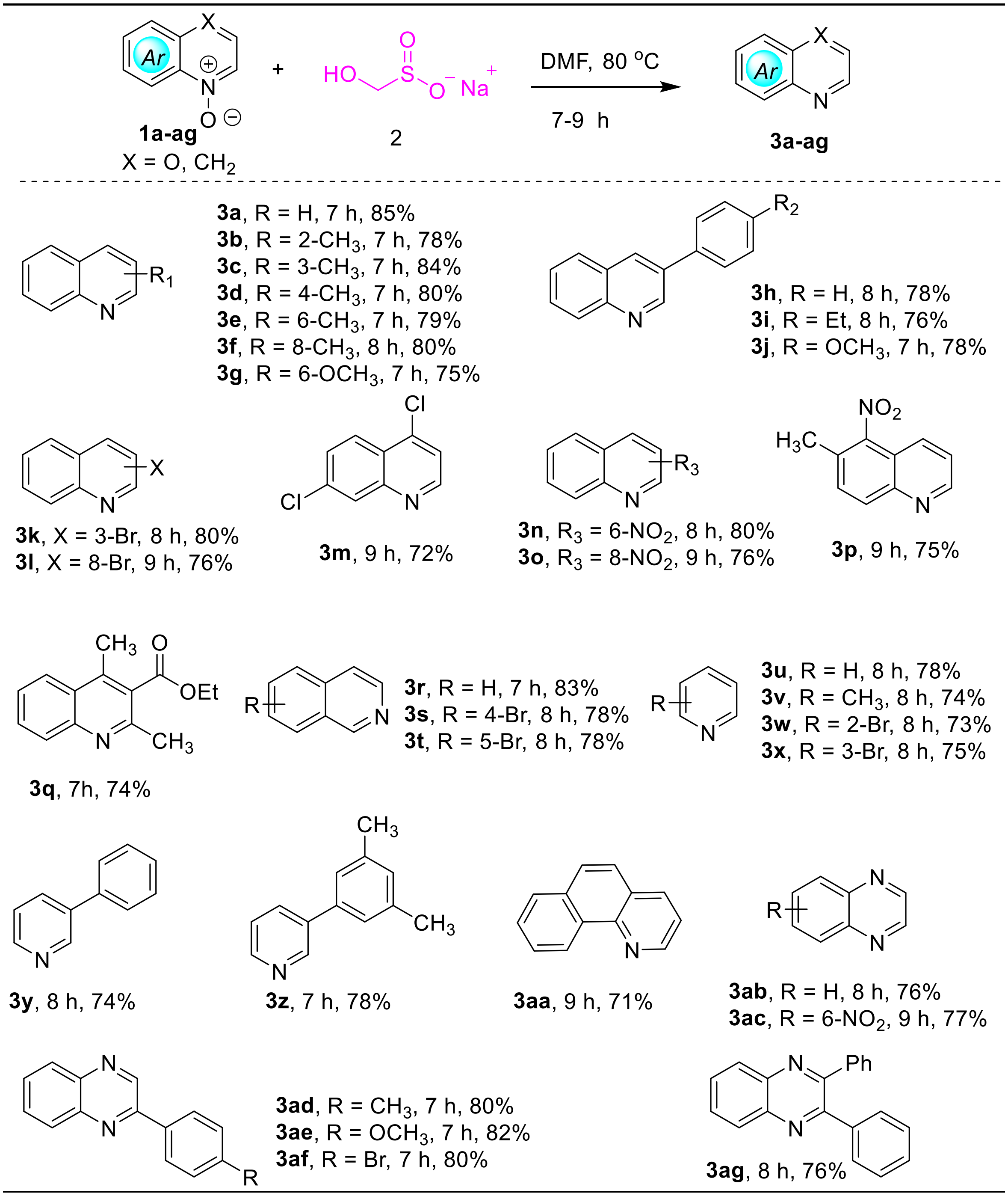


CHAPTER-IV

Facile Metal-Free Deoxygenation of Aromatic Amine *N*-oxides Using Rongalite

Pyridine *N*-oxides are frequently encountered in organic synthesis[15] which could serve as temporary protecting groups to alter the reactivity towards electrophilic substitution and C–H activation of aromatics, and also require their easy removal after completing desired functions.[16] The reduction of N-O bond of amine *N*-oxides to corresponding amine is an important synthetic route that has found considerable application in the field of organic synthesis.[17] In order for this a great number of synthetic methodologies have been developed for the reduction of amine *N*-oxide to amine, whereas most of which suffer from use of metals, harsh reaction conditions, less compatibility of functional groups, tedious work-up procedures and also from low yields and less selectivity.[18] The development of new synthetic routes employing metal free non-toxic reagents have gained much interest from last decade.

Table 4.1. Deoxygenation of Pyridine *N*-Oxide by Rongalite.



3a, R = H, 7 h, 85%
3b, R = 2-CH_3, 7 h, 78%
3c, R = 3-CH_3, 7 h, 84%
3d, R = 4-CH_3, 7 h, 80%
3e, R = 6-CH_3, 7 h, 79%
3f, R = 8-CH_3, 8 h, 80%
3g, R = 6-OCH_3, 7 h, 75%

3h, R = H, 8 h, 78%
3i, R = Et, 8 h, 76%
3j, R = OCH_3, 7 h, 78%

3k, X = 3-Br, 8 h, 80%
3l, X = 8-Br, 9 h, 76%

3m, 9 h, 72%

3n, R_3 = 6-NO_2, 8 h, 80%
3o, R_3 = 8-NO_2, 9 h, 76%

3p, 9 h, 75%

3q, 7h, 74%

3r, R = H, 7 h, 83%
3s, R = 4-Br, 8 h, 78%
3t, R = 5-Br, 8 h, 78%

3u, R = H, 8 h, 78%
3v, R = CH_3, 8 h, 74%
3w, R = 2-Br, 8 h, 73%
3x, R = 3-Br, 8 h, 75%

3y, 8 h, 74%

3z, 7 h, 78%

3aa, 9 h, 71%

3ab, R = H, 8 h, 76%
3ac, R = 6-NO_2, 9 h, 77%

3ad, R = CH_3, 7 h, 80%
3ae, R = OCH_3, 7 h, 82%
3af, R = Br, 7 h, 80%

3ag, 8 h, 76%

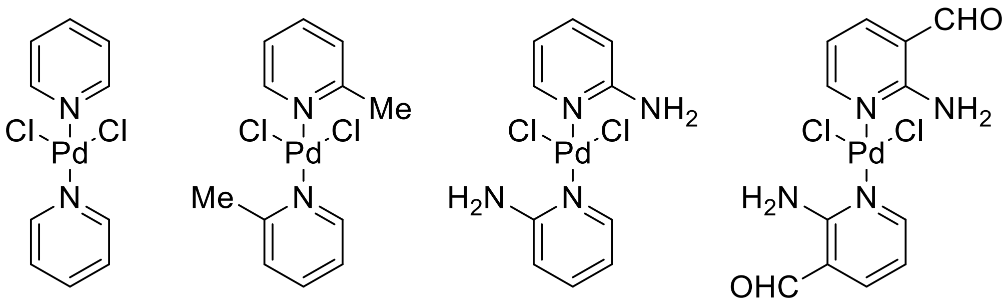
Therefore, the design of environmentally benign methods is needed now more than ever before. In this context, we have developed metal-free method which involve the use of commercially cheap reducing agent rongalite under mild conditions. The optimized condition as follows, 1 mmol of amine *N*-oxide reacted with the 2 mmol of rongalite in DMF solvent at 80 °C to produce the deoxygenated product in good yields (Table 4.1).

CHAPTER-VA

Pd(II)ANA Complex Catalyzed Cross-Coupling Reaction between Arylboronic Acids and Arylbromides

The direct carbon-carbon bond formation reactions are the most important synthetic tools for organic chemists[19] as they play vital role in the synthesis of building blocks for various biologically active products, material sciences, supramolecular chemistry and catalysis.[20] Palladium-catalyzed cross-coupling reactions of arylboronic acid with aryl halide, known as the Suzuki-Miyaura reaction, which is the leading methodologies for the construction of C-C bond in the synthesis of biaryl became popular because of its wide applications in various fields.A number of modifications have been appeared in palladium complexity to increase the efficacy of the catalyst including activity, stability, and functional group compatibility.[21] Recent past has witnessed a tremendous increment in ways to develop and design novel phosphorus free palladium catalysts for robust, active, higher turnover number and functional group tolerance at low costs.[22]

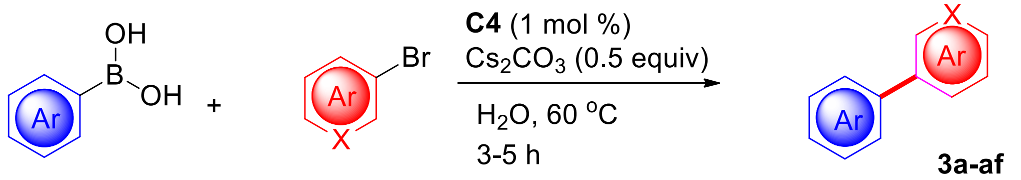
Keeping the importance of Suzuki-Miyaura reaction in the mind, we have searched for a robust, inexpensive and biologically relevant monodentate pyridine based-Pd(II)-catalysts for Suzuki-Miyaura coupling reaction and found.



C1 **C2** **C3** **C4**

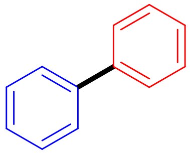
Figure 5A.1. Pyridine Based-Pd(II) Complxes.

Table 5A.1. Pd(II)ANA-Catalyzed Suzuki-Miyaura Coupling to Access Biaryl Derivatives.

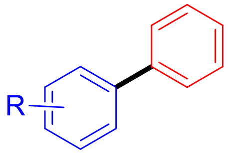


1a-m **2a-l** **3a-af**

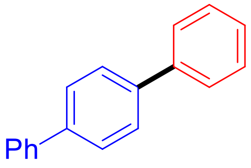
X = CH, N, *N*-Oxide



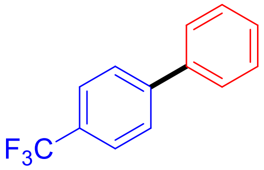
3a, 4 h, 96%



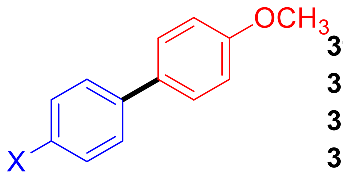
3b, R = 2-CHO, 5 h, 88%
3c, R = 4-CHO, 5 h, 90%



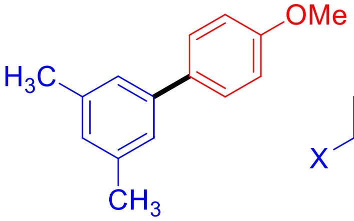
3d, 5 h, 93%



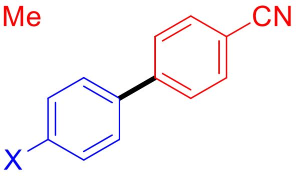
3e, 5 h, 86%



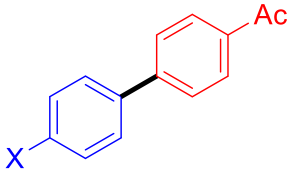
3f, X = H, 4 h, 87%
3g, X = Br, 4 h, 87%
3h, X = Cl, 4 h, 83%
3i, X = F, 4 h, 86%
3j, X = CF_3, 4 h, 83%
3k, X = OMe, 3 h, 98%



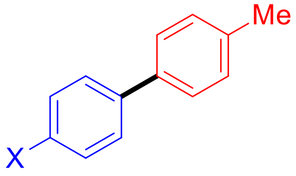
3l, 4 h, 95%



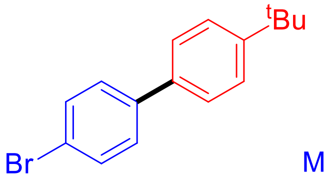
3m, X = H, 5 h, 80%
3n, X = Br, 5 h, 74%
3o, X = F, 5 h, 76%



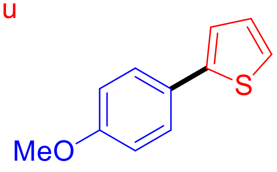
3p, X = H, 4 h, 88%
3q, X = OMe, 4 h, 86%



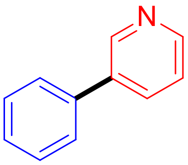
3r, X = H, 4 h, 90%
3s, X = OMe, 4 h, 91%



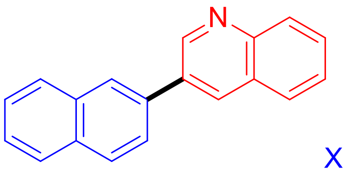
3t, 5 h, 76%



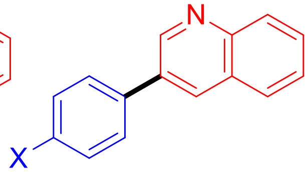
3u, 5 h, 70%



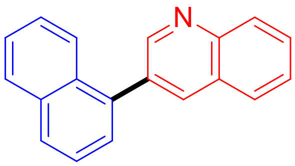
3v, 5 h, 81%



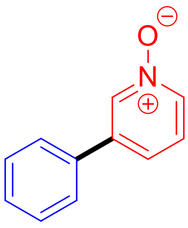
3w, 4 h, 80%



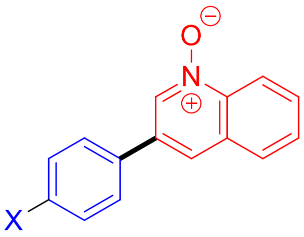
3x, X = H, 5 h, 80%
3y, X = 4-OMe, 3 h, 92%
3z, X = 4-Et, 4 h, 90%



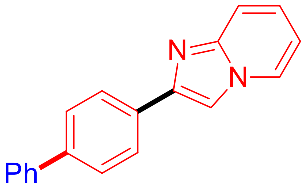
3aa, 4 h, 84%



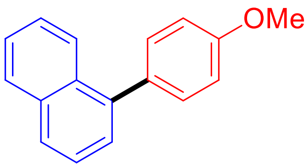
3ab, 4 h, 89%



3ac, X = H, 4 h, 88%
3ad, X = Et, 3 h, 90%



3ae, 4 h, 85%



3af, 4 h, 83%

In this chapter, we report an efficient, less expensive, easily accessible, air-stable Pd(II)-(substituted pyridine) complex as a complementary catalysts (C1-C4) for the Suzuki-Miyaura reaction (Fig. 5A.1). Later we found that Pd(II)-(2-aminonicotinaldehyde) complex [Pd(II)-ANA, **C4**] gave desired biaryl derivative from corresponding phenylboronic acids and aryl bromides in water (Table 5A.1). Water is ubiquitous in nature and a desirable medium for chemical reactions which falls in line with the principles of green chemistry has been used.

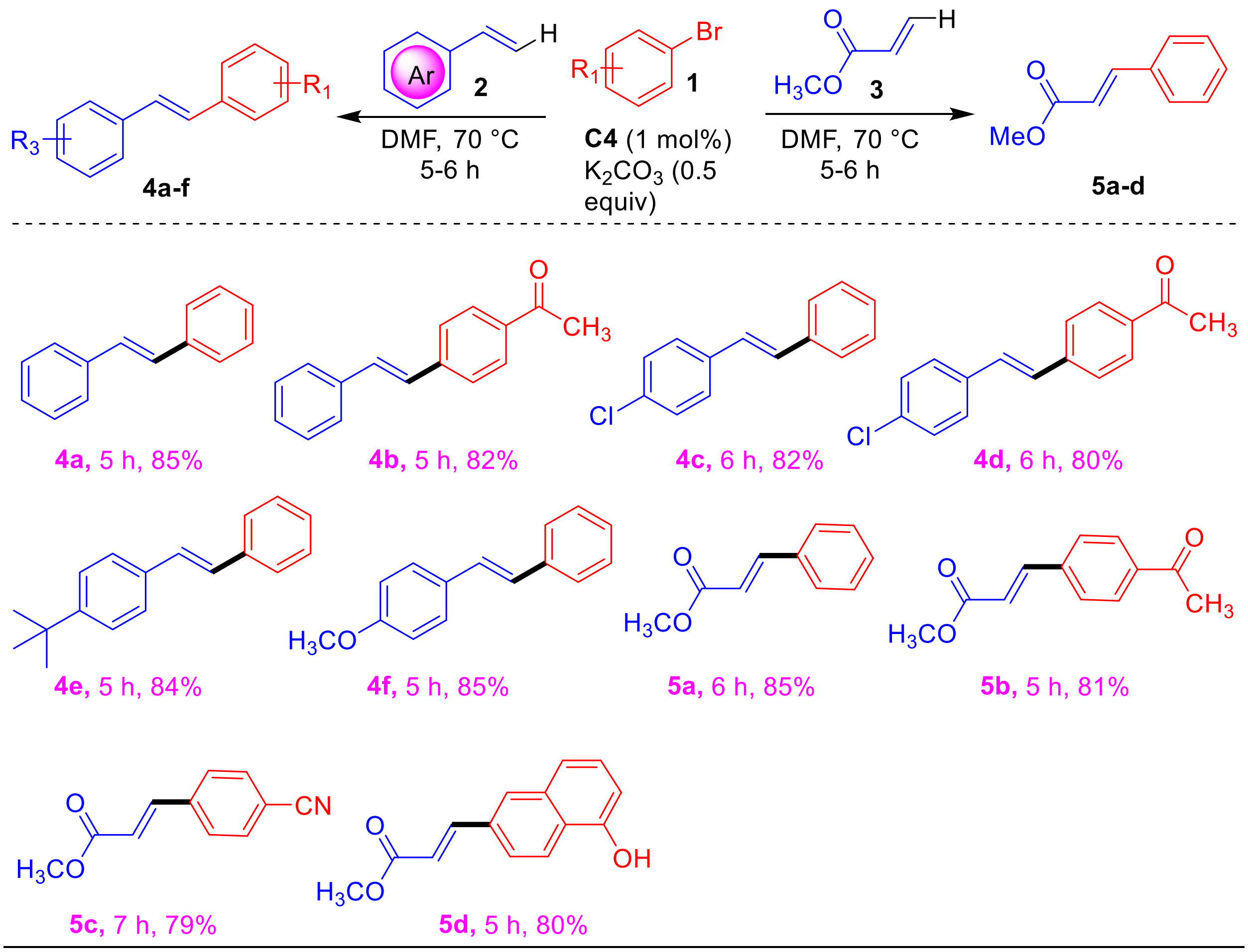
In our initial screening experiments, the reaction between phenylboronic acid **1a** and 4-bromoanisole **2b** with catalysts C1-C4 (Figure 5A.1) were investigated to optimize the reaction conditions to obtain **3f** (Table 5A.1). After several examinations, Pd(II) complex of 2-aminonicotinaldehyde (**C4)** catalyst was found to be highly active and gave unsymmetrical biphenyl **3f** as a solo product. With the preferred conditions for the Suzuki reaction in hand, we next examined the scope of the substrates and synthesized a library of compounds. The optimized condition as follows, an equimolar amounts of aryl bromides **2a-l** and boronic acids**1a-m** in water was added catalyst **C4** (0.01 equiv), Cs_2CO_3(0.5 equiv) and the reaction mixture was stirred at 60 ^oC to obtain the desired cross-coupled products **3a-3ag** in good to excellent yields (Table 5A.1).

CHAPTER-VB

An Efficient Protocol for Phosphine-Free Heck Reactions using Pd(II)ANA Complex

The Heck reaction is considered to be one of the most important synthetic tools to modify olefins with high selectivity and efficiency.[23] From the last few decades chemist have utilized this tool to synthesize a wide range of the complex molecules including pharmaceuticals and natural products.[24] Tuning various ligands around the transition metal, Heck reactions could be optimized to perform under mild conditions to achieve desired product in excellent yields.[25] We aimed in this chapter to develop phosphine free Heck-coupling reaction. The optimized condition as follows, an equimolar amounts of aryl bromides **1a-d** with styrene **2a-d** or methyl acrylate **3** in DMF was add catalyst **C4** (0.01 equiv.) and Cs_2CO_3 (0.5 equiv.) and stirred at 70 ^oC to form the desired highly substituted alkenes **4a-f**and **5a-d** in 85% yields (Table 5B.1).

Table 5B.1. Pd(II)ANA-Catalyzed Heck coupling to access substituted olefin derivatives.



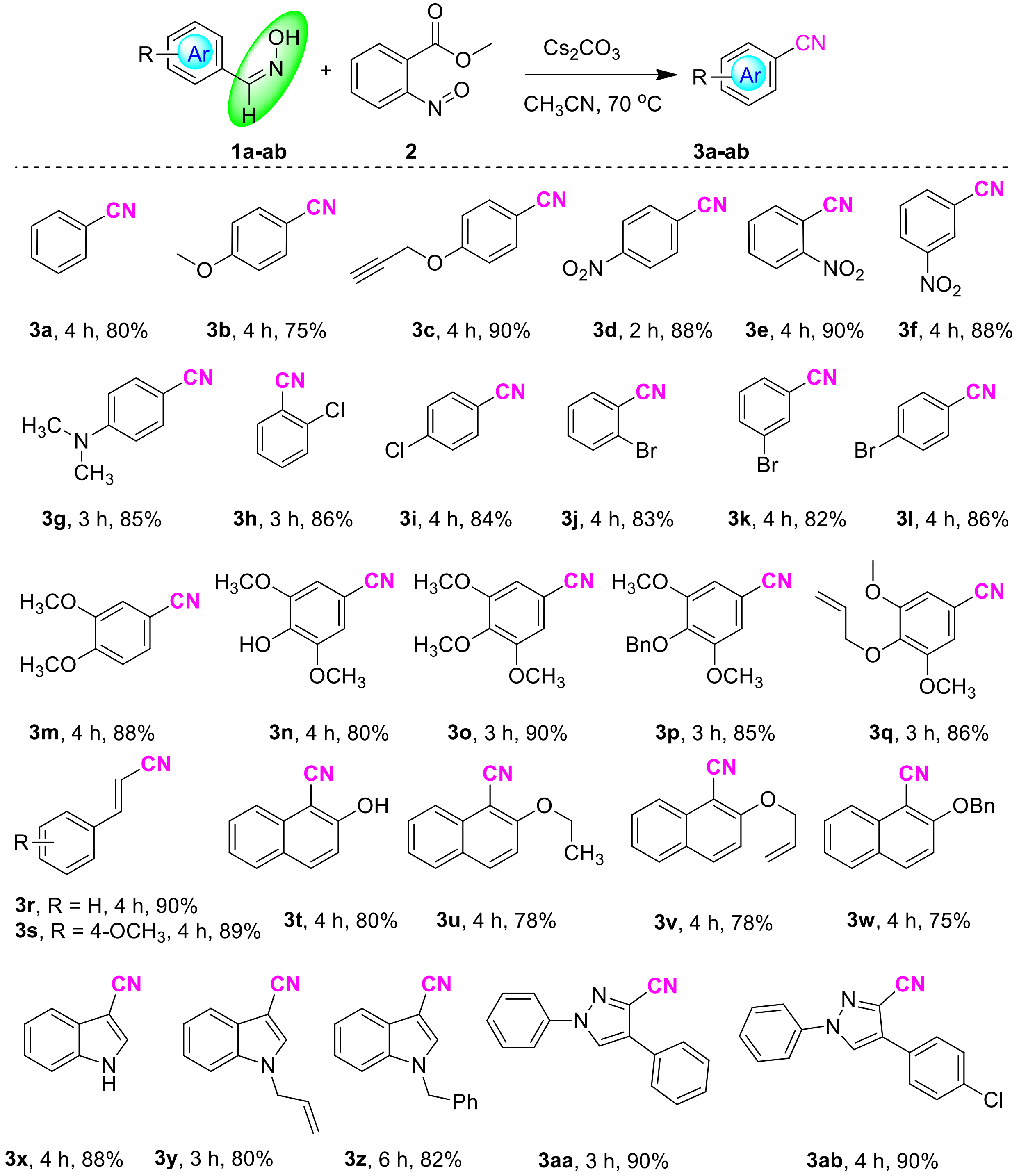
CHAPTER-VI

Synthesis of Benzonitrile from Benzaldehyde Oximes Using Methyl 2-nitrosobenzoate as Dehydrating Agent

Nitriles are particularly useful synthons endowed with multifaceted properties that serve as precursors in several functional group transformations. The cyano groups are building blocks of many natural products, agrochemicals, pharmaceuticals and Dyes.[26] They also play a significant role in hydrogen bonding to certain biological receptors.[27]

Recently, nitrile functionality has been exploited as a promising directing group for metal catalyzed C-H activation reactions.[28] Unfortunately, the common dehydrating agents are insufficient for this purpose and more active reagents are required. Hence, the development of new synthetic routes using mild and non-toxic reagents is a new emerging field in organic synthesis. In this context, aryl nitroso compounds are found to be a chemo-selective ligating agent for sulfonic acids, where nitroso group act as an electrophilic center.[29] We have utilized the electrophilic nature of nitroso group to act as dehydrating agent for converting aldoxime to corresponding nitriles.

Table 6.1. Substrate Scope of the Dehydration Methodology Using Methyl 2-nitrosobenzoate



1a-ab **2** **3a-ab**

3a, 4 h, 80% **3b**, 4 h, 75% **3c**, 4 h, 90% **3d**, 2 h, 88% **3e**, 4 h, 90% **3f**, 4 h, 88%

3g, 3 h, 85% **3h**, 3 h, 86% **3i**, 4 h, 84% **3j**, 4 h, 83% **3k**, 4 h, 82% **3l**, 4 h, 86%

3m, 4 h, 88% **3n**, 4 h, 80% **3o**, 3 h, 90% **3p**, 3 h, 85% **3q**, 3 h, 86%

3r, R = H, 4 h, 90%
3s, R = 4-OCH_3, 4 h, 89% **3t**, 4 h, 80% **3u**, 4 h, 78% **3v**, 4 h, 78% **3w**, 4 h, 75%

3x, 4 h, 88% **3y**, 3 h, 80% **3z**, 6 h, 82% **3aa**, 3 h, 90% **3ab**, 4 h, 90%

Herein, we report the methyl 2-nitrosobenzoate, a novel mild dehydrating agent for the synthesis of nitriles from aldoximes.

The target nitrile compounds were synthesized from an equimolar mixture of aldoximes, methyl 2-nirosobenzoate and Cs_2CO_3 in dry acetonitrile under nitrogen atmosphere at 70 °C. The green protocol described in this chapter for the synthesis of nitriles offers excellent yields under mild conditions and therefore this protocol can be widely applied. Various substituted aryl aldoxime substrates undergo this dehydrative transformation smoothly. We have synthesized 28 nitriles by using present protocol and summarized in Table 6.1.

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APPENDICES

List of Publications

Published

1. Methyl 2-Nitrosobenzoate: A Simple Dehydrating Agent for the Synthesis of Nitriles from Aldoximes.
   Sanjeeva Thunga, Soumya Poshala, and Hari Prasad Kokatla, *ChemistrySelect* **2018**, *3*, 4425-4429.

2. An efficient Pd(II)-(2-aminonicotinaldehyde) complex as complementary catalyst for the Suzuki-Miyaura coupling in water.
   Sanjeeva Thunga, Soumya Poshala, Naveen kumar Anugu, Ramaiah Konakanchi, Satheesh Vanaparthi and Hari Prasad Kokatla, *Tetrahedron L*ett. **2019**, *60*, 2046-2048.

3. In Situ Generation of Copper Nanoparticles by Rongalite and Their Use as Catalyst for Click Chemistry in Water.
   Soumya Poshala, **Sanjeeva Thunga,** Saikumar Manchala, and Hari Prasad Kokatla. *ChemistrySelect* **2018**, *3*, 13759-13764.

4. A Facile One-Pot Synthesis of 2,2,2-Trichloroacetates Through Acid-Catalyzed Deimination and Its Applications.
   Soumya Poshala, **Sanjeeva Thunga**, Sivaparwathi Golla, Vanaparthi Satheesh and Hari Prasad Kokatla, *ChemistrySelect* **2019**, *4*, 10466–10470.

Manuscripts under preparation

1. One-Pot Three-Component Synthesis of 3-(phenylsulfonyl methyl) Substituted Indole Derivatives via C(sp^2)-H Functionalization.
   Sanjeeva Thunga and Hari Prasad Kokatla.

2. One-Pot Aminomethylation of Imidazo[1,2-*a*]pyridine and imidazo[2,1-*b*]thiazole Derivatives Using Secondary Amines and Rongalite.
   Sanjeeva Thunga and Hari Prasad Kokatla.

3. Rongalite as a Methylenating Agent: Synthesis of Heterodiarylmethanes via Metal-free Coupling between Imidazo[1,2 *a*]pyridines or imidazo[2,1-*b*]thiazole and Indoles.
   Sanjeeva Thunga and Hari Prasad Kokatla.

4. Facile Metal-free Deoxygenation of Aromatic Amine *N*-oxides By Using Rongalite.
   Sanjeeva Thunga and Hari Prasad Kokatla.

PAPERS PRESENTED IN INTERNATIONAL AND NATIONAL CONFERENCES

International

1. **Synthesis of imidazo pyridine derivatives containing secondary amine nucleus**
   ***International conference on "Advances in Chemical Sciences and Technologies-2019* (ACST-2019).** During 23-25, September 2019. Organized by Department of chemistry, National Institute of Technology. Warangal, Telangana.

2. **Facile Synthesis of Nitriles From aldoximes by using Methyl 2-nitrosobenzoate as dehydrating agent**

   ***International Conference on "Chemistry for Sustainable Future, (CFSF-2018*)** During 7th-9th, August 2018. Organized by Department of chemistry, Palamuru University, Mahbubnagar, Telangana.

3. **An Efficient Synthesis of 2-Substituted Quinazolin-4(3H)-ones catalysed by Pd(II) chloride**
   International conference on "Advanced Functional Materials (ICFAM-2017) During 18-20, December 2017. Organized by department of chemistry, RGUKT, Basar, Nirmal, Telangana.

National

1. **Pd (II) Ligand Catalysed Suzuki-Coupling reaction in Presence of aqueous medium**
   ***National XIV J-NOST (J- National Organic Symposium Trust) conference for research scholar*s** during 28th Nov - 1st Dec 2018. at CSIR-Indian Institute of Chemical Technology, Hyderabad, Telangana, India.
2. **Pd (II) Ligand Catalysed Heck-Coupling reaction in Presence of aqueous medium**
   TEQIP-III sponsored National conference on Emerging Trends in Instrumental Methods of chemical Analysis (ETIMCA-2019). During 30-31st January 2019. Organized by Department of Chemistry, NIT Warangal. Telangana.

3. **Facile Metal-free Deoxygenation of Aromatic Amine N-oxides By Using Rongalite.**

   National Conference on Recent Development in Chemical Sciences and Allied Technologies (RDCST-2017). During 29-30th June, 2017. Organized by Department of chemistry, National Institute of Technology Warangal, Telangana.

4. **Methyl 2-Nitrosobenzoate: A Simple Dehydrating Agent for the Synthesis of Nitriles from Aldoximes.**

   UGC sponsored Two Day National Seminar on "Recent Trends and Challenges in Chemical Sciences (RTCCS). During 24th-25th March, 2017. Organized by Kakatiya University, Warangal Telangana.

5. **Facile Synthesis of Nitriles From aldoximes**
   National Conference on "Frontiers in chemical sciences and technologies" (FCST-2016) during 28th-29th January 2016, organized by the Department of Chemistry, NIT Warangal. Telangana.

6. **An Efficient Synthesis of 2-Substituted Quinazolin-4(3H)-ones catalysed**
   UGC Sponsored National Seminar on "Recent Advances in Chemistry" (RAC-2015). During 30-31, March 2015. Organized by Department of Chemistry, Kakatiya University, Warangal, Telangana.

7. **Phosphine-free Pd (II) Ligand Catalysed Suzuki-Coupling reactions**

   National conference on drug discovery and development in chemistry applications in pharma industry (DDDC-2015). During 14th-15th September 2015. Organized by Department of chemistry, Sri Venkateshwara University, Tirupati, Andhra Pradesh.

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