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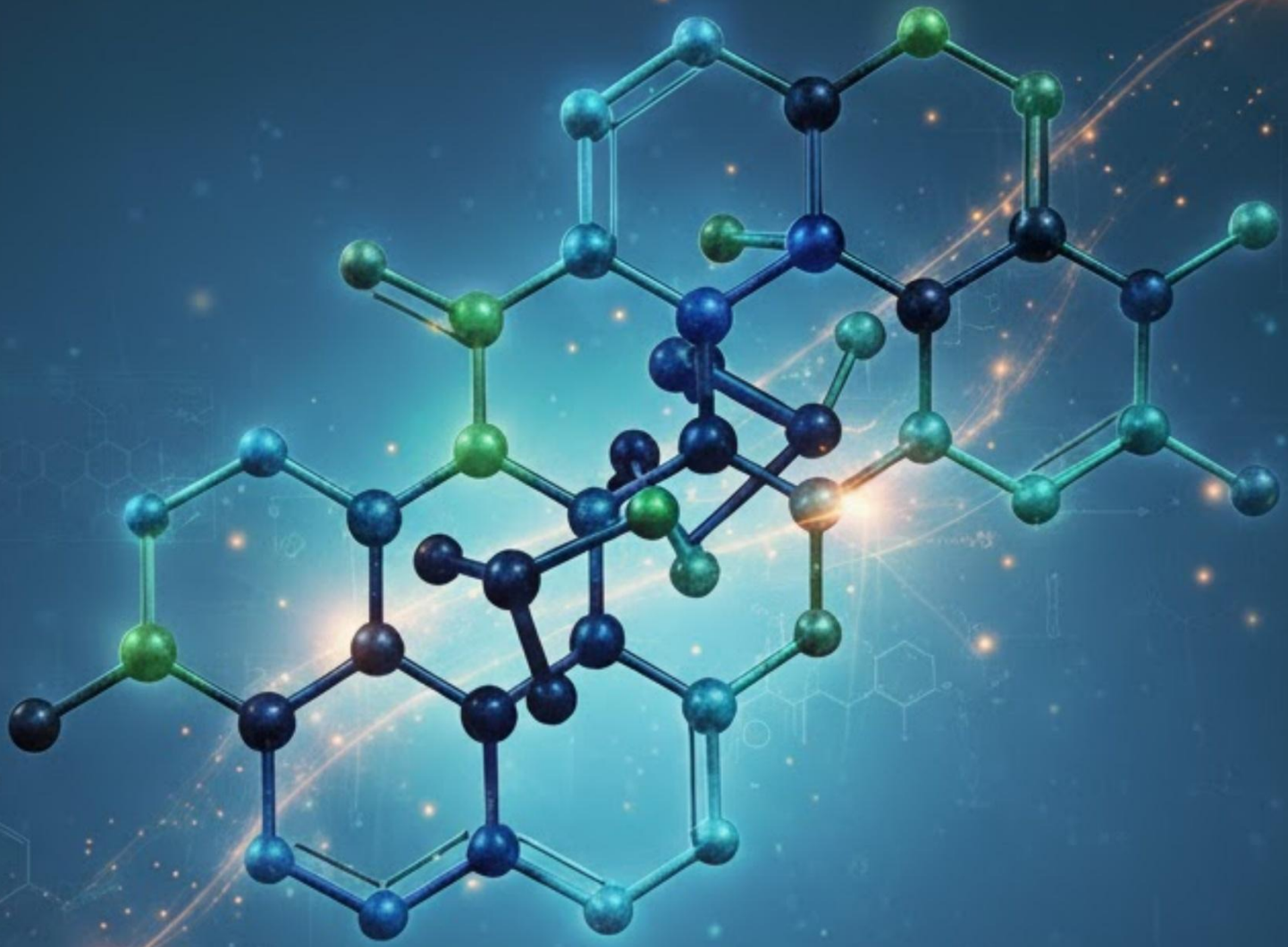

IMIDAZOPYRIDINE BASED N-FUSED HETEROCYCLES

Novel Design Strategies and Synthetic Methodologies

Dr. Suhas G. Patil

Bhumi Publishing, India

First Edition: January 2026

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(ISBN: 978-93-47587-44-3)

DOI: https://doi.org/10.5281/zenodo.18298367

Author

Dr. Suhas G. Patil

Associate Professor

Department: Chemistry,

S. R. M. Mahavidyalaya, Kudal, Dist.: Sindhudurg, Maharashtra, 416520

Contact No.: 9421147283

E-Mail: patilsg.patil@gmail.com

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Published by Bhumi Publishing,

a publishing unit of Bhumi Gramin Vikas Sanstha

Bhumi Publishing

Nigave Khalasa, Tal – Karveer, Dist – Kolhapur, Maharashtra, INDIA 416 207

E-mail: bhumipublishing@gmail.com

PREFACE

N-fused heterocycles are a rapidly advancing class of heterocycles whose distinctive structures, versatile reactivity, and broad biological activities make them important scaffolds in drug discovery, materials science and functional synthesis, driving ongoing innovation in their design and synthesis.

The book '*Imidazopyridine based N-Fused heterocycles: Novel Design Strategies and Synthetic Methodologies*' aim to provide a comprehensive, well-organized reference on the design principles, synthetic methodologies, and recent advancements in N-fused imidazole systems, with a focus on modern synthetic routes, mechanistic understanding and structure-based strategies.

Designed as a reference rather than a textbook, this volume provides concise, authoritative content for researchers, postgraduate students, and faculty, with a focus on standardized protocols, comparative synthetic strategies and representative examples reflecting recent advances in the field.

The book presents core principles of imidazole fusion chemistry, molecular design strategies, established and emerging synthetic methods, and key applications of N-fused imidazoles, with an emphasis on clarity, reproducibility, and effective use of schematics, mechanisms and tables for easy reference.

This book, based on extensive research in heterocyclic chemistry, has been thoroughly revised and expanded into a scholarly reference, incorporating recent literature and contemporary perspectives to reflect current trends and future directions in N-fused imidazole research.

It is hoped that this volume will serve not only as a dependable reference for existing researchers but also as an inspiration for further exploration and innovation in the chemistry of fused heterocyclic systems.

- Dr. Suhas G. Patil

ACKNOWLEDGEMENTS

The author expresses sincere gratitude to all those who have contributed, directly or indirectly, to the completion of this book entitled 'Imidazopyridine based N-Fused heterocycles: Novel Design Strategies and Synthetic Methodologies'. This work is the outcome of sustained academic engagement, research experience and scholarly interaction in the field of heterocyclic and medicinal chemistry.

The author is deeply thankful to mentors and teachers whose guidance, encouragement and critical insights have played a vital role in shaping scientific understanding and research perspective. Their continued support and intellectual influence have been instrumental throughout the academic journey that culminated in this reference work.

Grateful acknowledgement is extended to colleagues for their valuable discussions and constructive suggestions, which have enriched the content and broadened the scope of this book. The author also acknowledges the contributions of the wider scientific community, whose published research has provided a strong foundation and inspiration for this compilation.

The author sincerely thanks the institutional authorities and research facilities that provided the necessary academic environment, laboratory infrastructure and resources essential for research and scholarly writing. Appreciation is also extended to the publisher and editorial team for their professional support, guidance and efforts in bringing this work to publication.

Finally, the author expresses heartfelt gratitude to family members for their unwavering encouragement, patience and moral support throughout the course of this work. Their understanding and motivation have been a constant source of strength during the preparation of this book.

- Dr. Suhas G. Patil

TABLE OF CONTENT

LIST OF ABBREVIATIONS

Abbreviation	IUPAC name
NHCs	*N*-heterocyclic carbene
PDT	photodynamic therapy
OFET	Organic Thin Layer Field Effect Transistors
UV	Ultra violet
MCR	Multi-component reaction
DMAD	dimethyl but-2-ynedioate
NAH	*N*-acylhydrazone
LCMS	Liquid chromatography–mass spectrometry
HPLC	High performance liquid chromatography
COSY	Homonuclear correlation spectroscopy
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence
NOESY	Nuclear Overhauser Effect Spectroscopy
QSAR	Quantitative Structure-Activity Relationship
IC_{50}	Half-maximal inhibitory concentration
SAR	Structure Activity Relationship
DOX	Doxorubicin
CNS	Central Nervous System
scPTZ	Subcutaneous pentylenetetrazol
MES	Maximal electroshock induced seizure
TLC	Thin-Layer Chromatography
$POCl_3$	Phosphorous oxychloride
Ac_2O	Acetic anhydride
H_2SO_4	Sulphuric acid
PIDA	Phenyliodine-(III) diacetate
$NaOAc.3H_2O$	Sodium acetate Trihydrate
ppm	Parts per million
F. Wt	Formula Weight
MF	Molecular formula
TMS	Tetramethylsilane

EtOH	Ethanol
KOH	Potassium hydroxide
$Cu(OTf)_2$	Copper (II)Triflate
EtOAc	Ethyl acetate
ESI	Electrospray ionization
DMSO	Dimethyl sulfoxide
OLED	Organic light-emitting diodes
THF	Tetrahydrofuran
CH_2Cl_2	Dichloromethane
DMF	*N*,*N*-dimethyl formamide
Na_2SO_4	Sodium sulphate
K_2CO_3	Potassium carbonate
NBS	N-bromosuccinimide
NaOH	Sodium hydroxide
^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon-13 nuclear magnetic resonance
FTIR	Fourier transform Infra-red
m/z	Mass to charge ratio
rt	Room temperature
M.P.	Melting point
°C	Degree Celsius
%	Percentage
g	Gram
ml	Mili liter

CHAPTER 1

INTRODUCTION TO N-FUSED IMIDAZOLES

The heterocyclic compounds are considered privileged structures because they are present in many natural and synthetic compounds with interesting biological properties [1]. Moreover, it is known that about one third of the organic compounds discovered so far in nature are nitrogen-containing heterocycles. Among the nitrogen- containing heterocycles, the five-membered heterocyclic nuclei, such as imidazole, occupy a dominant place in the field of pharmaceutical and medicinal chemistry. In particular, the compounds containing a nitrogen bridgehead-fused heterocycle with an "imidazole" moiety represent a special class of biologically relevant compounds. The importance of imidazole-fused heterocyclic scaffolds is reflected in their use in the field of medicinal chemistry as an interesting template for the design, synthesis and development of biologically active molecules or drugs. Several examples of drugs and bioactive molecules that have an N-fused imidazole core in their molecular architecture can be found in the literature (Fig. 1.1). They exhibit a wide range of biological activities, including antibacterial, antifungal, antineoplastic, antidiabetic, antitumor, anxiolytic (alpidem), anti-ulcer, sedative, and anticancer properties [2]. Moreover, the applications of these *N*-fused heterocyclic compounds are not only limited to the field of medicine, but an increasing number of compounds are also used as solvents, catalysts, dyes, photographic sensitizers, antioxidants, etc. [3].

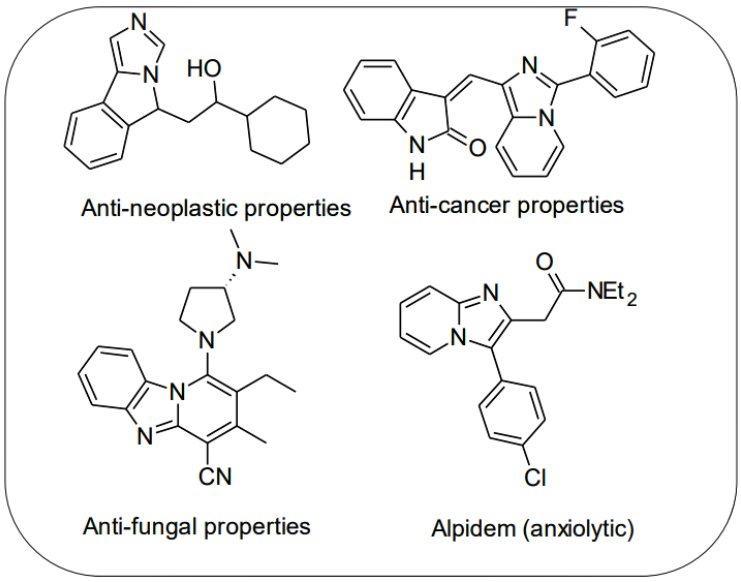


Figure 1.1: Pharmaceutically active compounds containing *N*-fused imidazole

The great reasons for widespread applications of *N*-fused imidazole-derived compounds are that their structures can be subtly manipulated to achieve a desired functional change. Many of them can be fitted into one of a few large groups of structures that have overall similarities in their

properties but significant variations within the group. Such variations may include differences in acidity or basicity, different polarity. Possible structural variations include the change of one heteroatom for another ring and different positioning of the same heteroatoms within the ring. So, to give an idea in a broader sense, the following assemblies of *N*-fused imidazoles have been outlined (Fig. 1.1).

1.1 Structures of *N*-fused imidazoles

There are several structural possibilities of ring systems containing an imidazole moiety fused to a five- or six-membered bicyclic 5-5, 5-6, and tricyclic 6-5-5, 6-6-5 ring in which the nitrogen atom is located at the ring junction. Fig. 1.2, depicts the structure of few imidazo fused heterocycles.

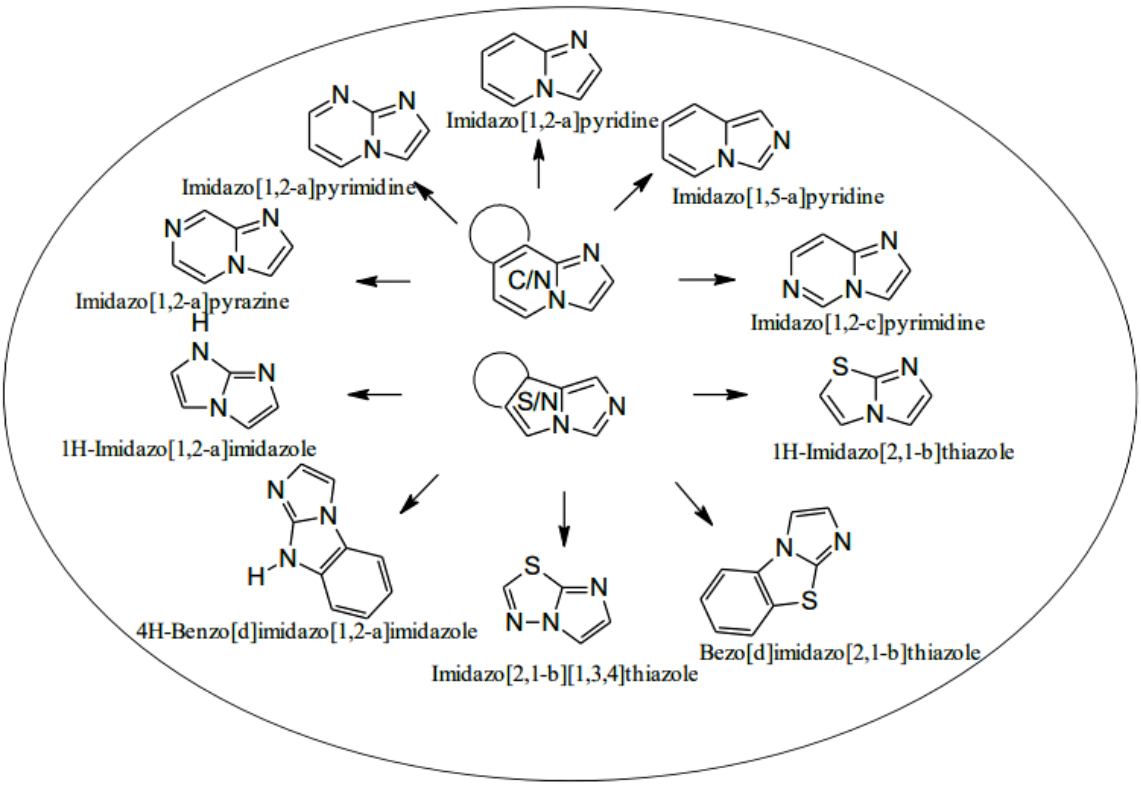


Figure 1.2: Imidazo fused-bicyclic, tricyclic ring systems with bridge head nitrogen

Among this wide range of fused imidazole ring systems, the imidazopyridine moiety is the most important in the field of natural products and pharmaceuticals. There are two forms of imidazopyridine A, B (Fig. 1.3) are common structural motifs found in various pharmacologically important molecules. However, the heterocyclic ring system imidazo[1,5-*a*]pyridine B is the focus of our interest as it is not only widely used in medicinal chemistry and drug synthesis but also in material science.

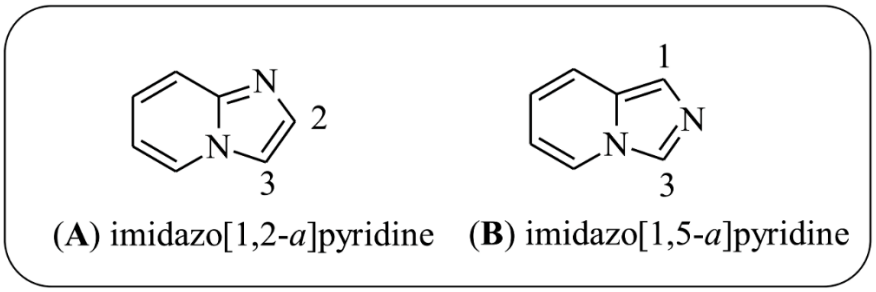


Figure 1.3: Regioisomers of imidazopyridine

1.2 Structure of imidazo[1,5-*a*]pyridine

Structurally, imidazo[1,5-*a*]pyridine is a fused bicyclic heteroaromatic ring system in which there are two heteroatoms, one in the five-membered ring and the other in the fused six-membered ring. Furthermore, both rings are linked by a single bond, with the nitrogen in bridgehead position of the "imidazole and/or pyridine" ring. Fig. 1.4 describes the naming and numbering of imidazo[1,5-*a*]pyridine according to the Hantzsch-Widman nomenclature [4], which starts with the highest-ranking heteroatom and progresses around the heterocycle to give the lowest position numbers to the remaining heteroatoms. The different substituents on both rings can play a crucial role in their spectral as well as biological properties.

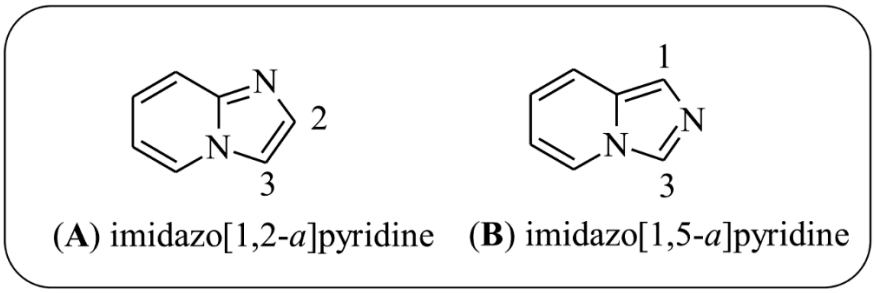


Figure 1.4: Structure of imidazo[1,5-*a*]pyridine

1.2.1 Tautomeric structure in imidazo[1,5-*a*]pyridine

As shown in Fig. 1.5 below, the two major players in the imidazo[1,5-*a*]pyridine resonance hybrid are those in which both the six- and five-membered rings are aromatic in character (mesomeric structures 1a and 1b) [5]. The latter also suggests that position 3 is rich in electron density, a structural argument that has been invoked to explain the high reactivity of this position towards electrophiles. Moreover, the introduction of an electron-withdrawing group (cyano, nitroso, nitro, carbonyl) at position 3 contributes to the stabilization of the π-electron density by placing a charge on the electronegative atom of the electron-withdrawing group (structures 2c-d), and in the process a positive charge on C-5 is formed by a mesomeric long-range effect (structure 2e).

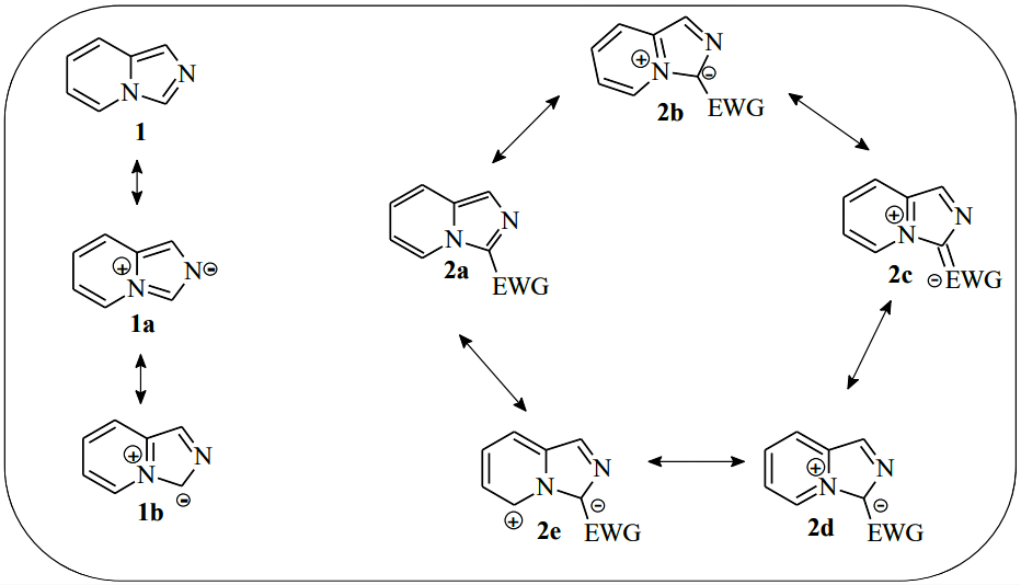


Figure 1.5: Resonance structures of imidazo[1,5-a]pyridine

1.3 Importance of imidazo[1,5-*a*]pyridine

Imidazo[1,5-*a*]pyridines are one of the most important and medicinally fascinating heterocyclic ring systems, serving as building blocks for the synthesis of important bioconjugates. In addition, they play a crucial role in many fields of research including pharmaceuticals [6] and material science [7]. Other applications of their derivatives have also been actively explored in the context of organic light-emitting diodes (OLEDs) [8], precursors of N-heterocyclic carbenes [9], and preparation of various metal complexes [10].

Another important property of imidazo[1,5-*a*]pyridine-derived heterocyclic compounds is their extraordinary participation in a variety of reactions. Depending on the pH of the medium, they can behave as acids or bases and form anions or cations. The ability of many imidazo[1,5-a]pyridines to form stable complexes with metal ions has great biochemical significance. All these results prove that imidazo[1,5-*a*]pyridines are excellent scaffolds for obtaining a variety of compounds and accelerate research activities.

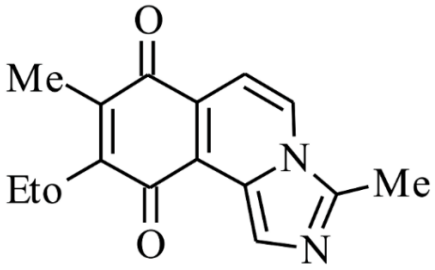
1.4 Present status of azaheterocyclic compounds

The chemistry of imidazo[1,5-*a*]pyridine-containing compound is the most important steaming field of organic chemistry, which has a wide range of applications from the biological and industrial point of view. Majority of pharmaceuticals, agrochemicals and complex organic compounds contain imidazo[1,5-*a*]pyridine as a core building unit. Some important applications of heterocyclic compounds containing imidazo[1,5- *a*]pyridine ring structure are discussed.

1.4.1 In natural product

Natural products are chemical compounds produced by a living organism and found in nature. They undergo both primary/secondary metabolites and biosynthesis, producing carbohydrates,

fatty acids, and polyketides. Heterocyclic compounds bearing an imidazo[1,5-*a*]pyridine unit are also among some natural products. In 2003, the first natural product containing an imidazo[1,5-*a*]quinolone scaffold was discovered by Petit and co-workers in the marine sponge Cribrochalina [11].The natural product, named Cribrostatin 6, shows promising anti-cancer and anti-inflammatory activity with a unique imidazo[1,5-*a*]isoquinolinedione structure (Fig. 1.6)



Cribrostatin

Figure 1.6: Imidazo[1,5-*a*]pyridine functionalized natural product

1.4.2 Applications in medicinal chemistry

As naturally occurring compounds containing imidazo[1,5-*a*]pyridine have found widespread clinical use, although nowadays the majority of pharmacologically active compounds are synthetic in nature. The remarkable ability of these fused nitrogen- containing heterocyclic nuclei to serve as both biomimetics and reactive pharmacophores (Fig. 1.7) has contributed significantly to their unique value as traditional key elements of numerous drugs.

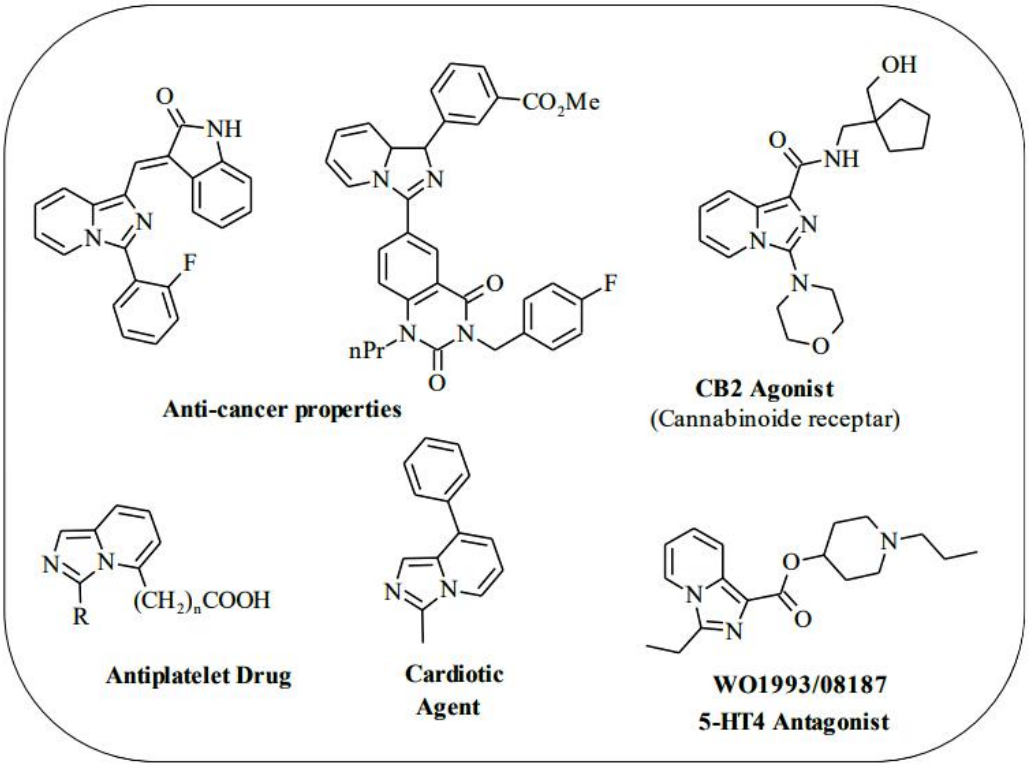


Figure 1.7: Medicinally active imidazo[1,5-*a*]pyridines

In this sense, the good old idea of screening large amounts of imidazo[1,5-*a*]pyridine-derived chemical compounds for biological activity has undergone a major transformation over the last three decades and has become a real hot topic in recent years. Central to this is the idea of virtual screening - either structure-based or ligand-based - where one can perform a preliminary in silico screening of millions of new molecules and come up with promising hits that are then developed and tested in the laboratory.

Due to this immense importance in medicinal fields, the development and functionalization of imidazo[1,5-*a*]pyridine has consequently attracted much effort from the medicinal and academic, and industrial chemical communities.

1.4.3 In catalysis

Catalysis plays a crucial role in providing fuels, fertilizers, pharmaceuticals, fine chemicals and many other commodities. It also helps in strengthening environmental protection. Recently, in the production of bulk chemicals, the traditional and environmentally unacceptable processes have been largely replaced by many catalytic alternatives, and *N*-heterocyclic carbenes (NHCs) are one of them (Fig. 1.8).

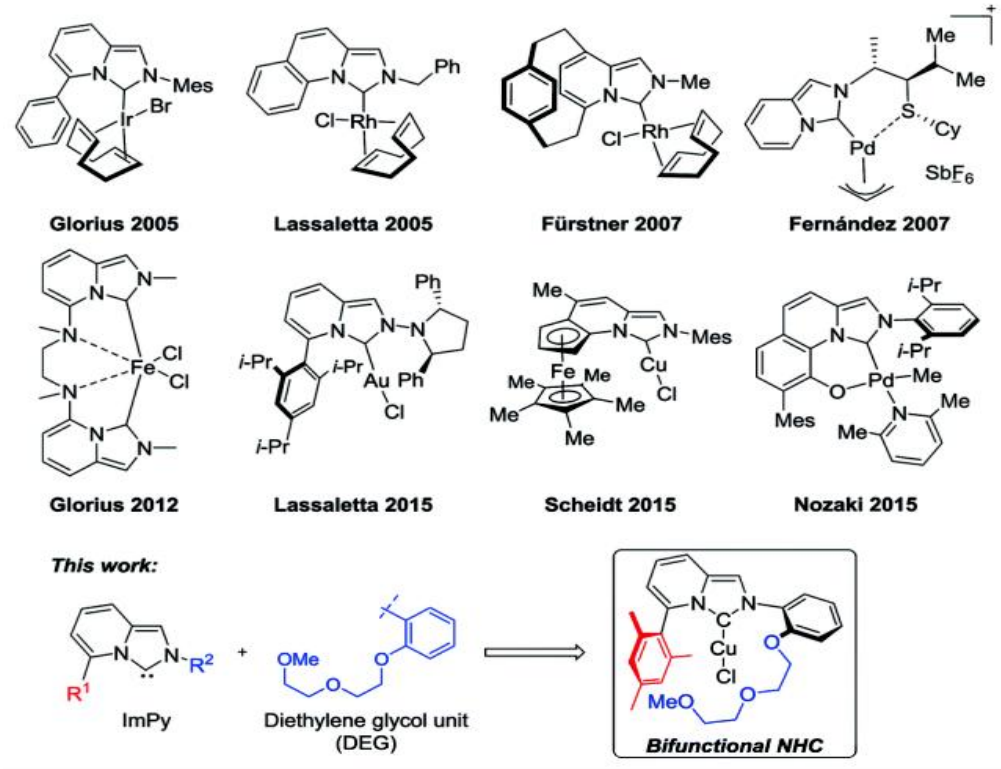


Figure 1.8: imidazo[1,5-a]pyridine metal complexes for catalysis

Compared to phosphine ligands, NHCs are superior as they possess a tremendous number of advantages such as cheap, non-toxic in nature, easy to prepare, possess thermal and oxidative stability [12a] and provide better steric protection for the active site within the inner metal

coordination sphere [12b]. In this regard, the imidazo[1,5-*a*]pyridine skeleton provides a versatile platform for the generation of new types of stable NHCs [13]. In addition, they have a tendency to bind more strongly to metals, leading to stable metal-carbon bonds, thus avoiding the need to use excess ligand in catalytic reactions, and they also show good resistance to dissociation from the metallic center. Thus, imidazo[1,5-*a*]pyridine-derived compounds are directed towards synthesis and sustained catalysis under mild conditions in interdisciplinary fields of coordination, inorganic, bioinorganic, organometallic, organic, photo and Electro-Chemistry through activation of a variety of small molecules with biological, environmental, or industrial significance.

In this perspective, the development of versatile NHC ligands offers a major impact in areas where stereoselective synthesis is of great interest, such as in the pharmaceutical industry. The resulting chiral bidentate NHC-oxazoline ligands form stable complexes with rhodium(I), which are efficient catalysts for the enantioselective hydrosilylation of structurally diverse ketones [14] (Fig. 1.9).

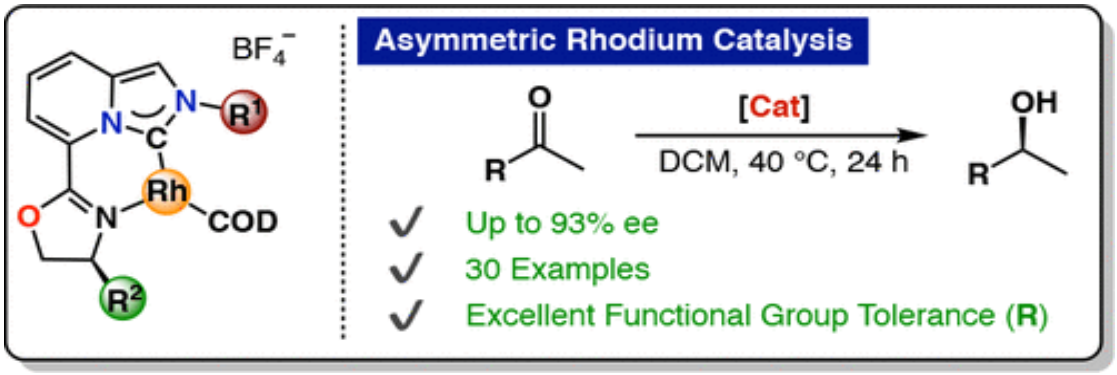


Figure 1.9: Application of imidazo[1,5-*a*]pyridine metal complexes in catalysis

1.4.4 In complexes of transition and main-group metals

The transition group metals have a strong reduction potential. The new compounds formed on complexation of these elements with imidazo[1,5-*a*]pyridine therefore highlighted the fundamental differences between their electronic properties and those of the lighter elements to an extent not previously apparent. In addition, they led to new structural and bonding insights and to the gradually growing realization that the chemistry of the heavier main-group elements resembles that of transition metal complexes rather than that of their lighter main-group relatives. The pyridyl derivative of imidazo[1,5-*a*]pyridine, i.e., 3-(pyridin-2-yl)imidazo[1,5-*a*]pyridine, can be readily complexed with several transition metals (Fig. 1.10) and fully characterized by X-ray crystallography and other typical spectroscopic methods [15].

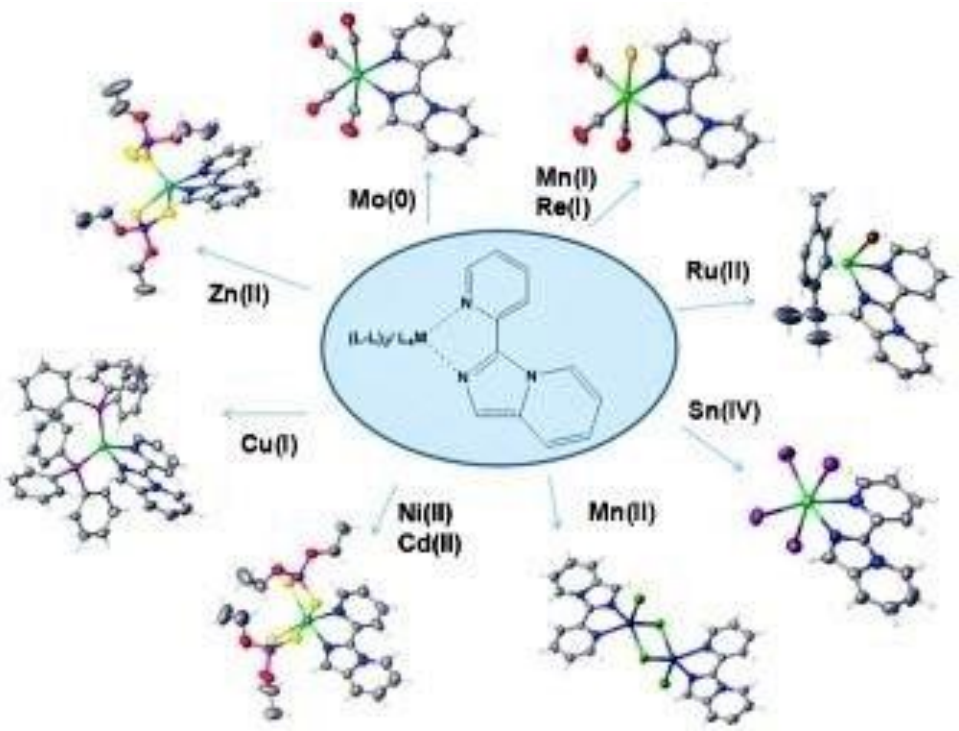


Figure 1.10: imidazo[1,5-*a*]pyridine functionalized metal complexes

1.4.5 In dyes and sensitizers

Dyes are colored substances that have an affinity for the substrate to which they are applied by absorbing some wavelengths of light more than others. They are a well- known class of organic compounds in which chromophoric groups are responsible for color by making energy changes in the delocalized electron cloud. This change always results in the compound by absorbing radiation in the visible color range.

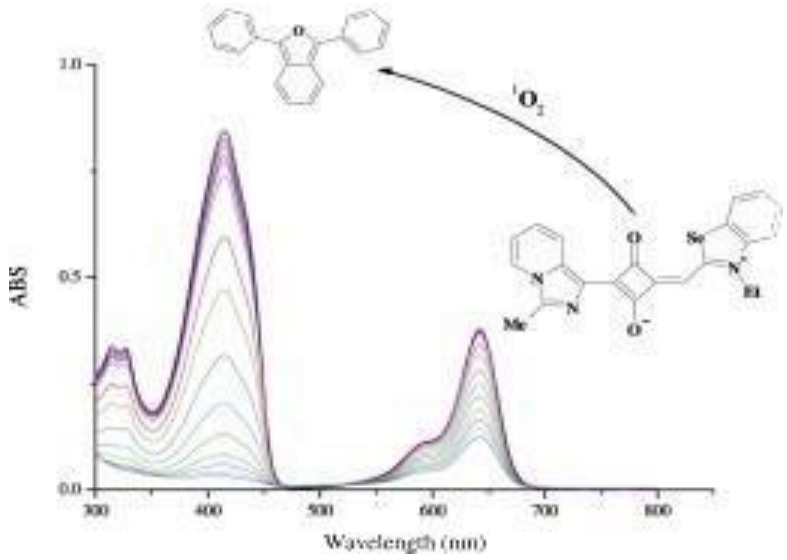


Figure 1.11: Imidazo[1,5-*a*]pyridines in dye applications

A very good example is considered to be an imidazo[1,5-*a*]pyridine-based heterocyclic structural unit consisting of a half-square [16]. It has the potential to be used as a sensitizer for

photodynamic therapy (PDT) due to its ability to generate singlet oxygen, which is achieved by condensation with several heterocyclic compounds possessing active methyl groups, resulting in a new class of unsymmetrical squaraines (Fig. 1.11).

1.4.6 Applications in Material Chemistry

1.4.6.1 In designing Electroluminescent/ photo luminescent material

The electroluminescence properties such as fluorescence or phosphorescence behaviour of the particular compound depend on the extent of conjugation. Increasing the extent of conjugation increases the mobility of π-electrons, which often increases the fluorescence intensity. Photoluminescence can often be greatly enhanced by introducing large bulky side groups to weaken the intermolecular interaction, and by introducing the fluorescent moiety into the backbone of the basic moiety.

Imidazo[1,5- *a*]pyridine [17] and its derivatives (Fig. 1.12) show different and tunable coordination motifs suitable for mono-, di- and tritopic coordination sites, as well as interesting optical properties: tunable luminescence [18], significant quantum yields, large Stokes shifts [19, 20] and strong halochromic effects.

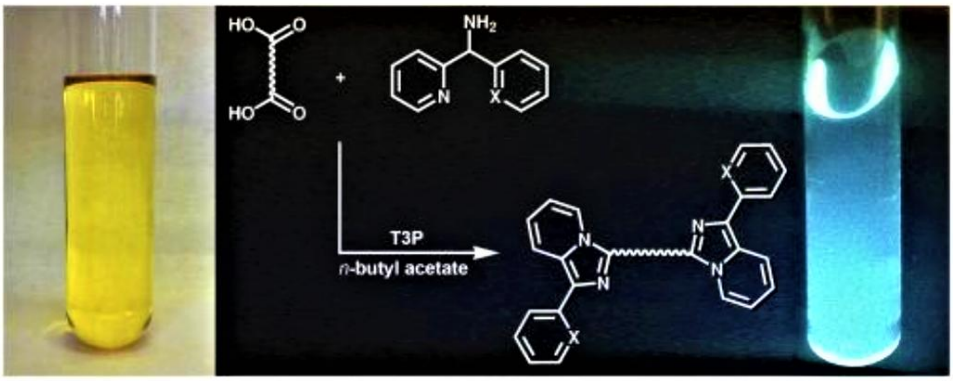


Figure 1.12: Photo luminescent imidazo[1,5-*a*]pyridines

1.4.6.2 In cell imaging (Laser scanning confocal microscopy)

Imidazo[1,5-*a*]pyridine-derived scaffolds serve as fluorescent labels for cell imaging applications and were studied by laser scanning confocal microscopy both *in vivo* on *Arabidopsis thaliana* seedlings and *in vitro* on mouse fibroblast cells. This fluorescent behavior developed in this particular moiety due to its functionalization by carboxylic group, which enhances its water solubility and provides an effective conjugation site [21]. (Fig. 1.13)

As mentioned earlier, imidazo[1,5-*a*]pyridines can exhibit tuning 'Stokes Shift' and intramolecular charge transfer character by varying the substituent groups [19]. The steady-state and nanosecond time-resolved emission studies of imidazo[1,5-*a*]pyridine- based novel donor-acceptor dyes with the large Stokes shift (ca. 140-200 nm) reveal that the dyes with a donor

group (average lifetimes of 0.65, 1.36, and 1.63 ns) present at the para position of the substituted phenyl group attached to the imidazopyridine core undergo reversible proton movement in chloroform than an acceptor group (average lifetimes of 3.50 and 4.06 ns). (Fig. 1.14)

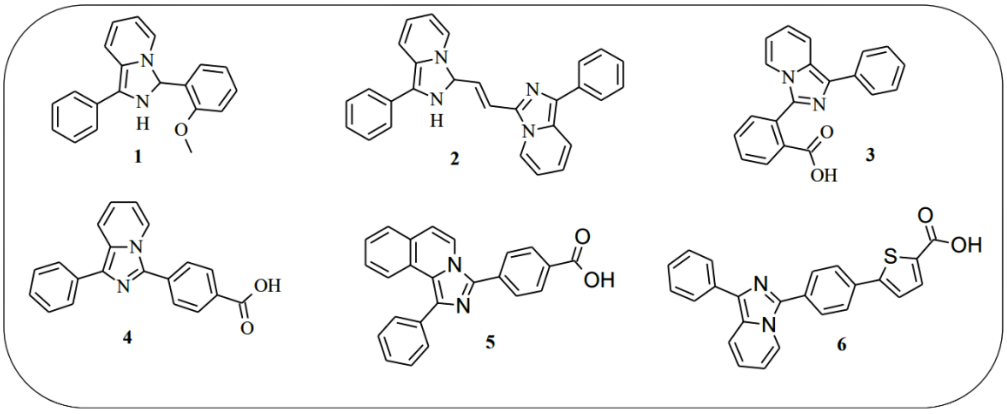


Figure 1.13: imidazo[1,5-*a*]pyridines having fluorescent activity

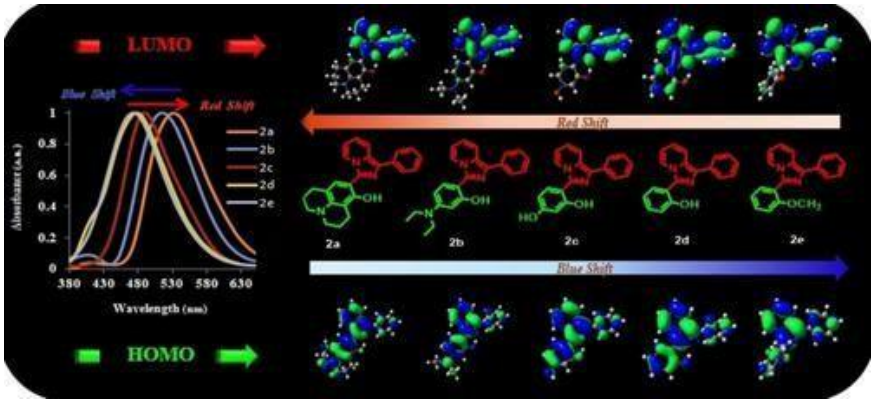


Figure 1.14: Fluorescent labelled imidazo[1,5-*a*]pyridines

1.4.6.3 In Optical materials and electronic devices

Organic light-emitting diodes (OLEDs) are the most successful organic electronics product on the market and continue to receive attention from academia and industry. imidazo[1,5-*a*]pyridines have been extensively studied for both OLED and organic thin-film field-effect transistors (OFET) and have demonstrated their versatility in molecular design for various functions. OLEDs, those of imidazo[1,5-*a*]pyridines [22] (Fig. 1.15) are not only thin and efficient, they also offer the best image quality ever and in the future can also be made transparent, flexible, foldable and even rollable and stretchable. OLEDs represent the future of display technology.

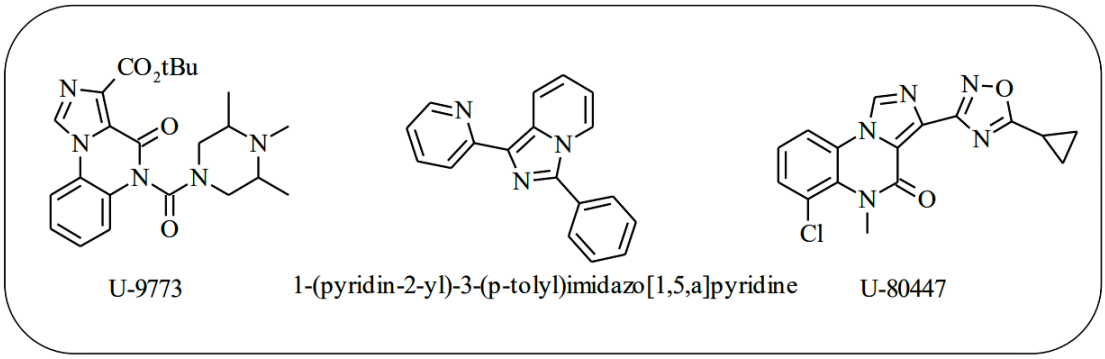


Figure 1.15: imidazo[1,5-*a*]pyridine derived OLEDs and FET

1.4.7 Miscellaneous applications

1.4.7.1 In Photochemistry

As we have already discussed, imidazo[1,5-*a*]pyridines behave chemically luminescent. This confirms their photoactive character and their preparation by photochemical route together with their use as templates for the preparation of metal complexes is highly justified. In an unexpected report, the photochemical transformation of imidazole derivatives containing the 5-hydroxy-2-methyl-4*H*-pyran-4-one moiety led to the synthesis of previously unknown imidazo[1,5-*a*]pyridine-5,8-dione derivatives (Fig. 1.16) in the presence of UV light [23]. Moreover, the derivatives of imidazo[1,5- *a*]pyridine ring systems have been used in Metal-Carbene-Templated Photochemistry [23b].

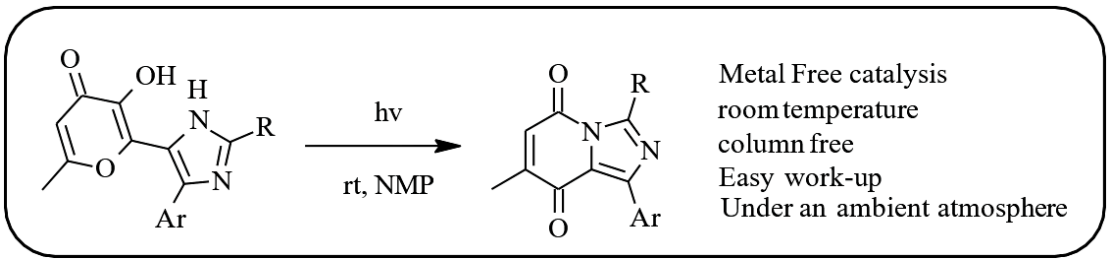


Figure 1.16: Photochemical synthesis of imidazo[1,5 a]pyridine ring

1.4.7.2 In building complex Heterocyclic structure

Due to the highly nucleophilic nature of the imidazo[1,5-*a*]pyridine ring, it can be readily converted to other complexed heterocycles such as benzo[d]furo[3,2-*b*]azepines by reacting with a carbonyl compound as an electrophile in the presence of dimethyl acetylenedicarboxylate [24]. The resulting fused heterocyclic compounds have partially fluorescent character and emit at long emission wavelengths, suggesting possible applications of the imidazo[1,5-*a*]pyridine ring as optical sensors. (Fig. 1.17)

Another striking result was observed in such MCR reactions [25] with ninhydrin giving corresponding 2-hydroxy-2-(imidazo[1,5-*a*]pyridin-1-yl)indene-1,3-diones. (Fig. 1.18) In this case, the uncatalyzed electrophilic substitution reaction involving C-1 (in 1) and the central

C=O (in ninhydrin) takes precedence over the three-component 1,4-dipolar cycloaddition reaction. This selectivity is probably due to the higher electrophilicity of the carbonyl carbon-2 in ninhydrin compared to that of the sp carbon atoms in DMAD, reinforced by the high nucleophilicity of carbon-1 in imidazo[1,5-*a*]pyridine.

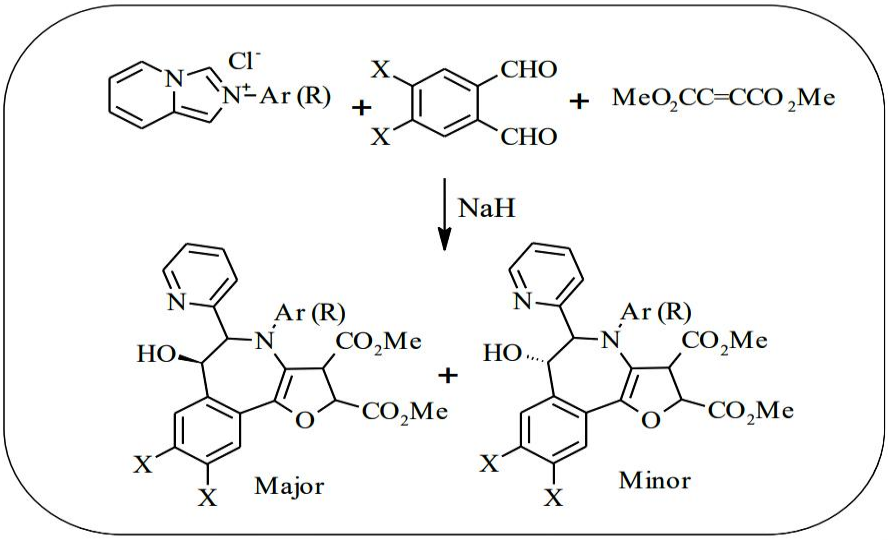


Figure 1.17: Synthesis of heterocyclic benzo[*d*]furo[3,2-*b*]azepines

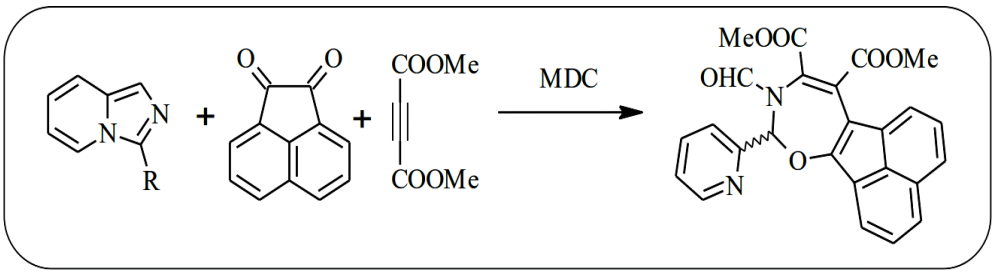


Figure 1.18: Synthesis of complex heterocyclic building blocks

These studies not only provided unique access to fused azepine derivatives that are difficult to access by other methods, but also opened a new avenue to complicated molecular skeletons. Besides, there has been a great proliferation of imidazo[1,5-*a*]pyridine-derived scaffolds in giant areas of liquid crystals, corrosion inhibitors, industrial biotechnology, photography, antioxidants, reprography, information storage, plastics and so on. All these findings have generated tremendous interest in the scientific community for the design and synthesis of new lead structures based on nitrogen-containing fused heterocyclic moieties in drug discovery programs.

1.5 Background and Scientific Rationale

Fused heterocycles form by far the largest of the classical divisions of organic chemistry and are of immense importance biologically, industrially, indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active

agrochemicals are derived from condensed heterocycles and modifiers used in industry. The search for simple and efficient methods to generate libraries of novel fused heterocyclic compounds is in demand. Especially, the fused heterocycles containing imidazo[1,5-*a*]pyridine moiety as they exhibit various biological activities. Therefore, the exploration and discovery of new potentially active imidazo[1,5-*a*]pyridines that are both safer and more effective is of utmost importance for both organic synthesis and medicinal chemistry.

Although an enormous number of research articles have been published in the past on the synthesis of imidazo[1,5-*a*]pyridines and their derivatives. However, the development of descent method is still of interest as it is one of the most important research endeavors in modern synthetic organic chemistry. In this regard, there is continuous demand of highly efficient methodologies. Thus, imidazo[1,5-*a*]pyridine- containing pharmacophores or polyfunctionalized units with a bridged "imidazole and/or pyridine" unit (Fig. 1.4) are of particular interest and proved difficult to prepare, mainly due to the commercial inaccessibility of the required starting materials. In this context, novel design strategies and advanced synthetic methodologies for N-fused imidazoles are systematically presented and critically discussed.

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CHAPTER- 2

SCALABLE ONE-POT APPROACH TO THE SYNTHESIS OF N-FUSED IMIDAZOLES MOIETY - IMIDAZO[1,5-A]PYRIDINE DERIVATIVES

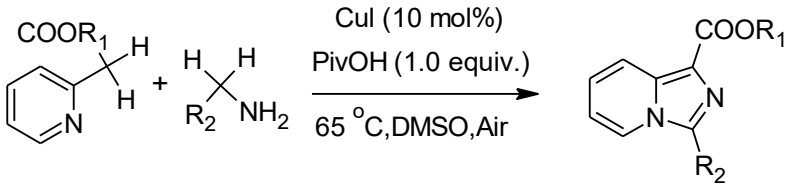
2.1 Introduction

The design and synthesis of new-sprung azahetrocylic ring systems are highly appreciated in modern drug discovery to achieve specific drug-receptor interactions [1]. Among them, imidazo[1,5-*a*]pyridine is one of the most important and medicinally fascinating heterocyclic ring systems, which serves as a building block for the synthesis of important bioconjugates. Moreover, they play a crucial role in many fields of research including pharmaceuticals [2] and materials science [3]. Other applications of their derivatives have also been explored in the context of organic light-emitting diodes (OLEDs) [4], precursors of *N*-heterocyclic carbenes [5], and the preparation of various metal complexes [6]. Due to the superior activity profile of imidazo[1,5-*a*]pyridine and its derivatives, the development of new versatile and efficient protocols for their synthesis is of continuing interest. The existing methods [7] mainly relied on the traditional dehydrative [8,9], desulfurative [10] and oxidative [11, 36a, 37] cyclization of 2-pyridinylmethylamine derivatives (with carbonyl compounds) in an intra/intermolecular manner. Another prominent tool is the direct C-H amination/cyclization strategy [12]. From a synthetic point of view, the imidazo[1,5-a]pyridine core can be achieved by various approaches involving the transition metals, such as Pd - [13] and Cu-catalyzed [14] reactions on different substrates or using a sensitive Lewis acid [15] or a stoichiometric amount of elemental sulfur (S8) [15] as oxidant or by oxidation of a Schiff base [16].

2.2 Synthesis of imidazo[1,5-*a*]pyridine using alkyl amines/amino acids

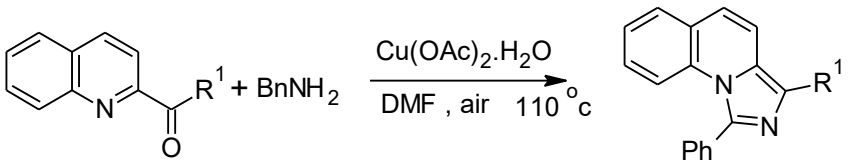
2.2.1 Transition metal catalyzed synthesis of imidazo[1,5-*a*]pyridine

Mohan Chandra *et al.* [17] described mild aerobic copper-catalyzed oxidative amination of C(sp3)-H bonds to construct imidazo[1,5-*a*]pyridine-1-carboxylate scaffolds with broad substrate scope (Scheme 2.1). Here the use of naturally abundant air as the sole oxidant proved to be efficient and selective. This methodology also survived for amino acid derivatives in the direct synthesis of functionalized imidazo[1,5-*a*]pyridines.



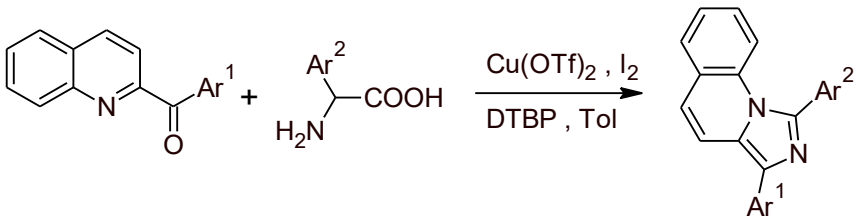
Scheme 2.1

Wang and co-workers [14] developed copper(II)-catalyzed efficient tandem condensation-amination-oxidative dehydrogenation process for the synthesis of 1,3-diarylated imidazo[1,5-*a*]pyridines between pyridine ketone and benzylamine using pure O_2 as oxidant (Scheme 2.2). The said synthetic protocol tolerates a wide range of substituents in good to excellent yields and can serve as a new tool for the synthesis of 1,3-diarylated imidazo[1,5-*a*]pyridines.



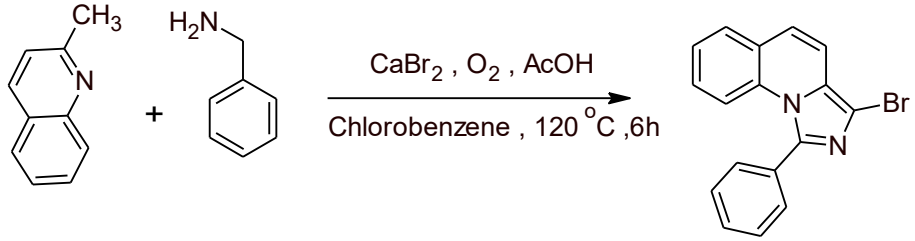
Scheme 2.2

Immediate next year in 2016, same group described a new dual copper/iodine co-catalyzed decarboxylative cyclization of α-amino acids and either 2-benzoyl pyridines/quinolines for the synthesis of 1,3-disubstituted imidazo[1,5-*a*]pyridines/quinolines (Scheme 2.3). This was an attractive alternative synthetic method and opens a new way for construction of 3-alkyl-1-arylimidazo[1,5-*a*]pyridines, which are difficult to access by existing methods.



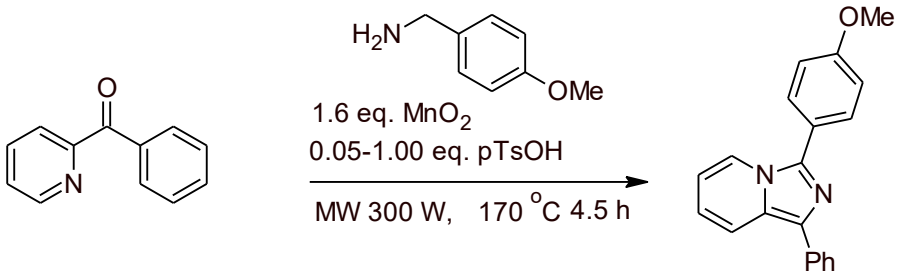
Scheme 2.3

Reddy and co-workers [18] developed an aerobic tandem copper-promoted double oxidative C–H amination and halogenation reaction of 2-methylazarenes with aliphatic amines or amino acids for the synthesis of imidazo[1,5-*a*]pyridines (Scheme 2.4). The use of $CuBr_2$ as catalyst as well as halogen source, and molecular oxygen acts as sole oxidant. The described protocol proves to be operationally simple and allows direct access to functionalized fused imidazoles in a one-pot procedure with good tolerance to functional-groups. Moreover, the synthetic usefulness of the synthesized imidazopyridines was tested and a good yield was observed in a Suzuki cross-coupling reaction.



Scheme 2.4

Very recently in 2019, a rapid and highly efficient microwave-assisted, MnO_2-catalysed and solvent-free method for the preparation of imidazopyridines and quinolines was developed by the Gottlich and co-workers group [19]. The use of activated MnO_2 as an oxidant for oxidative cyclization starting from the corresponding ketones and amines becomes an alternative route for the synthesis of new imidazo[1,5-*a*]pyridines and even imidazo[1,5-*a*]quinolones (Scheme 2.5). The synthesised compounds proved to be of great interest for both biological and technical applications

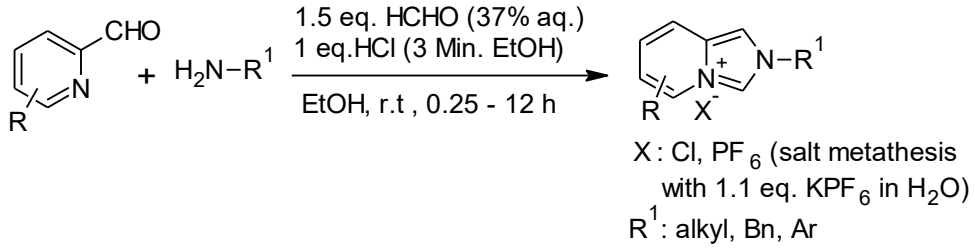


Scheme 2.5

2.2.2 Metal-free synthesis of imidazo[1,5-*a*]pyridines

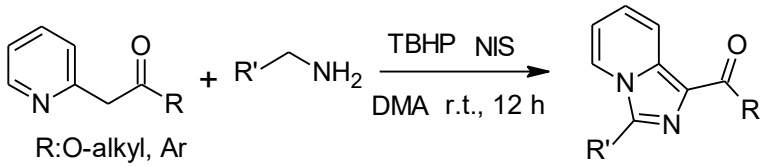
Complementary methods such as metal-free reaction conditions also play a crucial role in the preparation of the imidazo[1,5-*a*]pyridinyl architecture. In view of this, the research groups of Wang [12a] and Wei [12c] have independently investigated the synthesis of imidazo[1,5-*a*]pyridines by sequential dual oxidative amination of Csp^3-H bonds under metal-free conditions. Therefore, some representative cases have been considered and sequentially highlighted below.

Hutt *et al* [20] developed a multicomponent coupling reaction for the synthesis of imidazo[1,5-*a*]pyridinium ions in high yields under mild conditions with substituted picolinaldehydes, amines and formaldehyde (Scheme 2.6). This method of high order condensations, which allows the incorporation of various functionalities and chiral substituents, provides access to polydentate NHC ligands useful for a variety of applications.



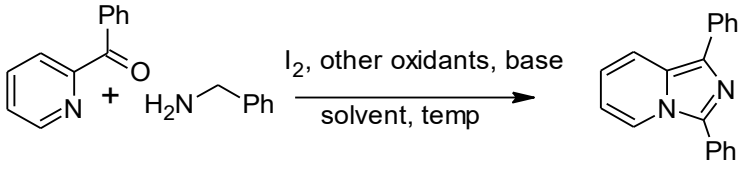
Scheme 2.6

A group of Wang and co-workers [21] succeeded in synthesizing imidazo[1,5-*a*]pyridines in very good yields by transition metal-free and sequential dual oxidative amination of C(sp^3)-H bonds under ambient conditions (Scheme 2.7). The process described involves the removal of six hydrogen atoms under two oxidative C-N couplings and an oxidative dehydrogenation process.



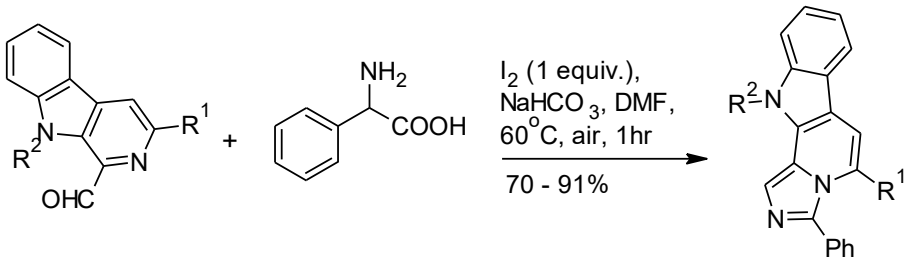
Scheme 2.7

Chang and co-workers [22] established a transition metal-free sp^3-C-H amination reaction for the synthesis of imidazo[1,5-*a*]pyridine using 2-pyridyl ketones and alkylamines as substrates (Scheme 2.8). Here, they rapidly prepared a variety of imidazo[1,5-*a*]pyridine derivatives in a one-pot method using sodium acetate (NaOAc) and iodine-mediated oxidative annulations of readily available substrates. Furthermore, the said protocol was successively translated into the synthesis of a series of 1-(2-pyridyl)imidazo[1,5-*a*]pyridine cysteine protease inhibitors from the corresponding di-2-pyridyl ketones and substituted benzylamines with satisfactory yields.



Scheme 2.8

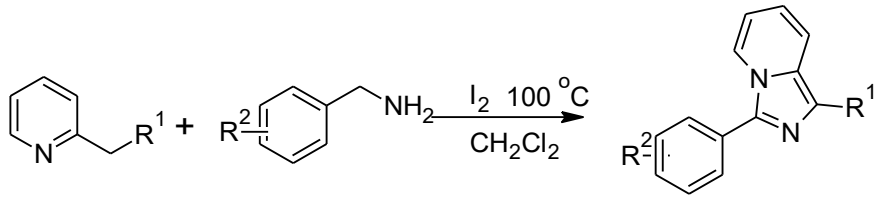
On similar ground of iodine catalysed reaction, a group of Singh and co-workers [23] developed a rapid gram scale synthetic strategy for an alkaloid scaffold 1-formyl-*b*-carboline (useful in the synthesis of kumujian C). The said method has great synthetic potential and provides alternative routes for the construction of a variety of β-carbolines fused and substituted via the decarboxylative oxidation of natural □-amino acids. In addition to the advantages, they also pointed out the limitations of the methodology for oxidative amination with benzylamines. NMOM and NBn(2-NO_2) deprotection and that was recorded for the first time in β-carbolines under the influence of iodine (Scheme 2.9).



Scheme 2.9

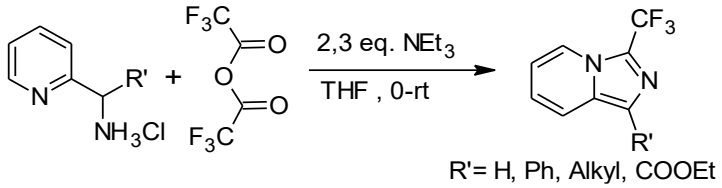
Su *et al.*[24] developed a general and efficient protocol for the synthesis of imidazo[1,5-*a*]pyridines by an I_2-mediated sequential dual oxidative C(sp^3)-H amination of ethylpyridin-2-ylacetates with benzylamines (Scheme 2.10). The use of metal- and peroxide-free reaction conditions under oxidative dehydrogenation and two C-N couplings leads to moderate to

excellent yields without the use of extra additives. The reaction is therefore sufficiently valuable to initiate and deepen.



Scheme 2.10

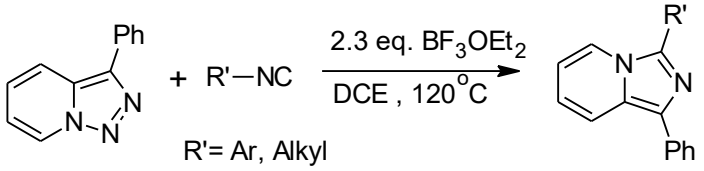
Another important transition metal-free strategy in the design and synthesis of imidazo[1,5-a]pyridines was described by Schafer *et al.*[25] *via* the condensation reaction of heterocyclic benzylamines using TFAA as trifluoromethylating reagent (Scheme 2.11). He illustrated single as well as two-step synthesis of trifluoromethylated imidazo-fused *N*-heterocycles from heterocyclic benzyl (pseudo)halides using trifluoroacetamide as trifluoromethylating reagent proceeds *via* alkylation followed by dehydrative cyclization.



Scheme 2.11

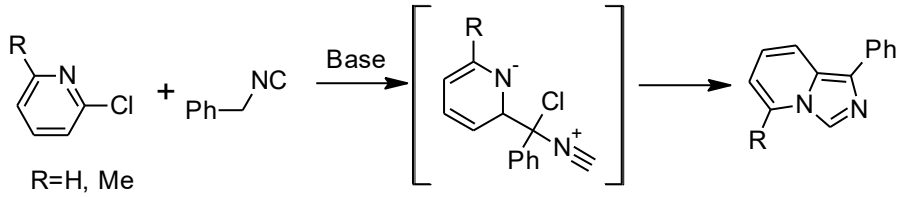
2.3 Synthesis of imidazo[1,5-*a*]pyridine using nitriles/isonitriles

In year 2016, Joshi *et al.*[26] described a denitrogenative transannulation method in which pyridotriazoles and nitriles are reacted in the presence of Lewis acid catalyst $BF_3 \cdot Et_2O$ to give the desired imidazo[1,5-*a*]pyridines (Scheme 2.12). The said protocol explains the crucial role of the combination of solvents (dichlorobenzene-dichloroethane) in obtaining quantitative yields of imidazo[1,5-*a*]pyridines under metal-free conditions.



Scheme 2.12

Li *et al.* [27] developed a rapid route to imidazo[1,5-a]pyridines from metallated arylmethylisonitriles via condensation reactions with 2-chloropyridine-like precursors (Scheme 2.13). Furthermore, they mentioned advantages over the existing protocol in analogous additions to a chloroquinoline, a pyrimidine, and imidoyl chlorides to generate an imidazo[1,5-*a*]quinoline, an imidazo- [1,5-*a*]pyrimidine, and imidazoles, respectively.



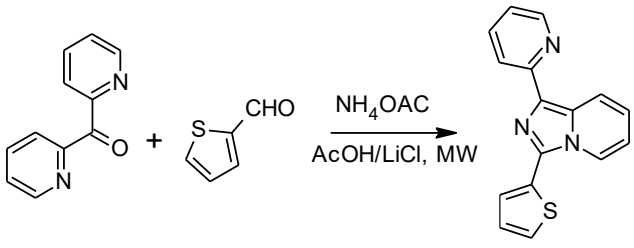
Scheme 2.13

Recently, in 2018, a novel strategy for the synthesis of a series of unprecedented tetrazole-linked imidazo[1,5-*a*]pyridines from simple and readily available building blocks were reported by Kurhade et al [28]. They achieved the targeted heterocyclic scaffolds by following an azido-Ugi-deprotection reaction followed by an acetic anhydride-mediated *N*-acylation cyclization process (Scheme 2.14). The usefulness of the methodology is exemplified by various R3 substitutions using commercial anhydrides, acid chlorides and acids as acyl components. Furthermore, the scope for post-modification reactions is explored through an improved three-step synthesis of a guanylate cyclase stimulator.

Scheme 2.14

2.4 Synthesis of imidazo[1,5-*a*]pyridine using ammonium acetate

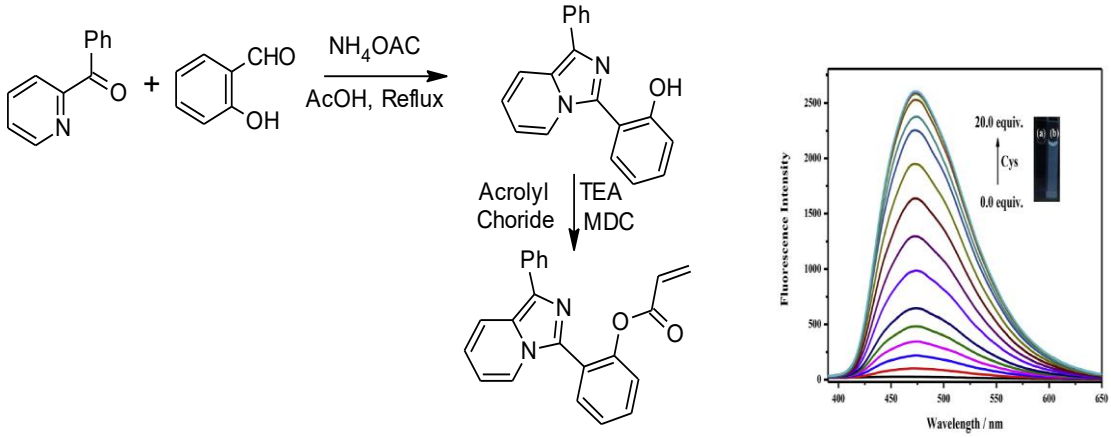
Among the various efficient synthetic methods for the preparation of imidazo[1,5-*a*]pyridine nucleus, the multicomponent condensation reactions involving an aldehyde and 2-cyanopyridine [29] or pyridyl ketones, aromatic aldehydes and ammonium acetate in acetic acid [30] are highly appreciated. A team of Rahmati and co-workers [31] reported a microwave-assisted lithium chloride-catalyzed one-pot multicomponent synthesis of imidazo[1,5-*a*]pyridines using various aromatic aldehydes and dipyridyl ketone with ammonium acetate in good yields (Scheme 2.15).



Scheme 2.15

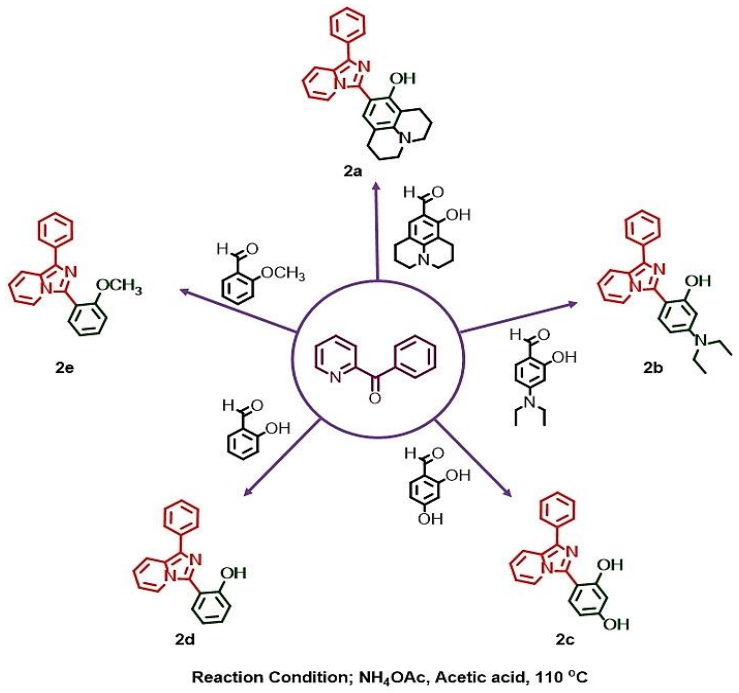
H. Sheng *et al.* [32] developed a new imidazo [1,5-a]pyridine-based fluorescent probe, named MZC-AC, which is used for the detection of cysteine (Cys) based on an excited-state

intramolecular proton transfer (ESIPT) mechanism (Scheme 2.16). MZC-AC was designed using an imidazo [1,5-a]pyridine derivative (MZC) as the chromophore and an acrylate group as the recognition site which imparts a dramatic fluorescence enhancement (85-fold) and a large Stokes shift (166 nm). Significantly, MZC-AC can be used to detect Cys in living cells because it is highly sensitive and selective for Cys over homocysteine (Hcy) and glutathione (GSH).



Scheme 2.16

Sekar and co-workers [33] designed and synthesized novel donor-acceptor dyes based on imidazo[1,5-*a*]pyridine with the large Stokes shift (ca. 140-200 nm) by keeping the phenyl group at position 1 constant and substituting the different donor at position 3 for the large Stokes shift (Scheme 2.17).

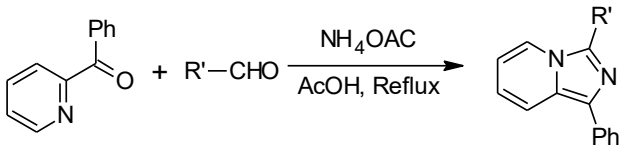


Scheme 2.17: Synthesis of dyes

Further during the fine tuning of the photophysical properties such as density functional theory (DFT) calculations [(B3LYP/6-311++G(d, p)] and natural bond orbital (NBO) analyzes provide

the information of the structural as well as the electronic properties of the dyes. Moreover, the large difference in dipole moment (ca. 1.57-21.55 D) leads to a strong nonlinear optical (NLO) property. All these studies bring new insights into coupled ICT and proton transfer reactions, which will be useful for further research and promising applications in sensing the polarity or H-bonding of microenvironments similar to those of biological ones.

Another interesting route for the synthesis of novel 1,3-diarylated imidazo[1,5-*a*]pyridine derivatives was described by Volpi and co-workers [34] by the easy-to-scale one-pot condensation of phenyl(pyridin-2-yl)methanone with natural aldehydes obtained directly by steam distillation and solvent extraction (Scheme 2.18). Optical study of the fluorescent 1,3-diarylated-imidazo[1,5-*a*]pyridine derivatives and characterization of the extracted aldehydes by various techniques enables the design of new compounds suitable for pharmaceutical, downshifting, microscopy and electronic applications.



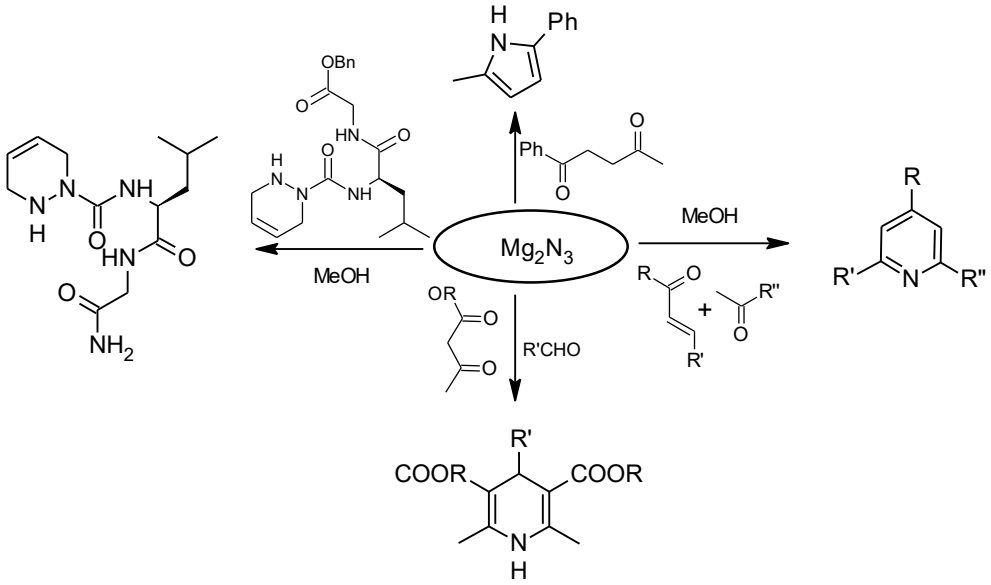
Scheme 2.18

All these, reports on synthesis of imidazo[1,5-*a*]pyridine highlight's straightforward way to construct imidazo[1,5-*a*]pyridine ring system under decarboxylative cyclic annulation of amines [35] or α-amino acids [36, 37] with 2-pyridyl carbonyl compounds. Encouraged by these previous successes and in continuation of our exploits on development of novel approaches towards bio-logically active compounds [38], we hypothesized to develop a rapid, more practical and eco-friendly technique by rendering descent nitrogen source for the shaping of imidazo[1,5-*a*]pyridine ring structure.

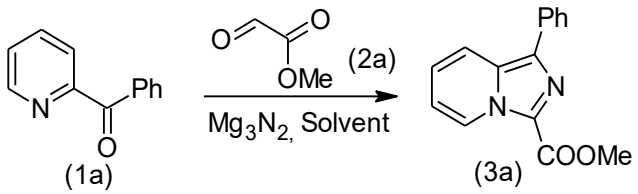
Thus, while rooming around to accomplish the goal, we are looking for such substance that befalls as a surrogate for ammonia. The scrutiny of literature reveals that magnesium nitride (Mg_3N_2), became a convenient source of ammonia when used in protic media and renders magnesium salt with the potential to act as a catalyst [39a]. Moreover, recent articles on Mg_3N_2, exposes its applicability in the synthesis of diverse azaheterocyclic ring systems [39]. (Scheme 2.19)

This chapter, demonstrates a new methodology for a Mg_3N_2-assisted one-pot annulation reaction towards synthesis of 1,3-disubstituted imidazo[1,5-*a*]pyridines using 2-pyridyl ketone and ethyl/methyl glyoxylates in protic solvent. The rational motive behind use of glyoxalate is the highest degree of electrophilicity and the prepared imidazo[1,5-*a*]pyridine carboxylates are predisposed to various synthetic manipulations into a complex architecture. To date, to our

knowledge, there is no entry in the literature describing the applicability of Mg_3N_2 in the synthesis of imidazo[1,5-*a*]pyridinyl carboxylates.



Scheme 2.19: Synthetic methods describing usage of Mg_2N_3 in heterocycles synthesis

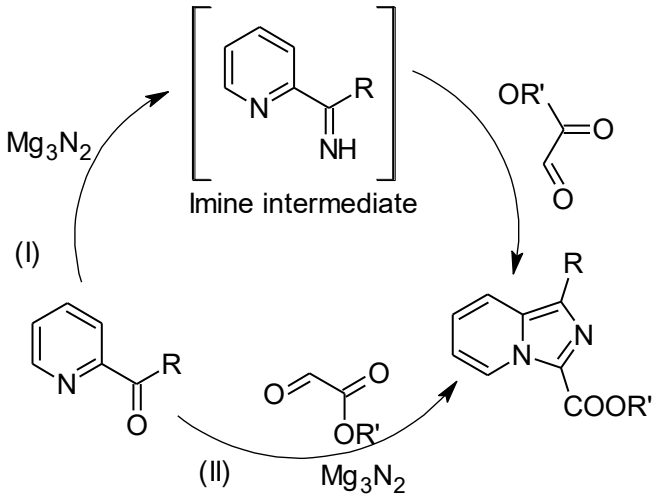


Scheme 2.20

2.5 Synthetic Performance and Optimization

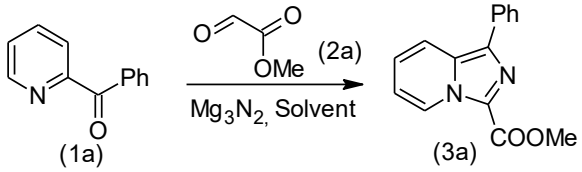
It involves synthesis of commercially unavailable 2-pyridyl ketones prepared by Grignard reaction of 2-pyridylmagnesium chloride and *N*,*N*-dialkylalkyl/arylamides according to known procedure [40a] and whose characterization data agrees with the literature [40]. To establish the best reaction conditions at which the dehydrative annulation would proceed smoothly, during stepwise formation of the desired 1,3-disubstituted imidazo[1,5-*a*]pyridines via an intermediate 2-pyridinyl methylimine, 2-pyridylphenyl ketone (1a) as model substrate is reacted with Mg_3N_2 and then immediately treated them with ethyl glyoxalate (2a) for cyclization without isolation. (Scheme 2.21, Route I) The said reaction establishes only partial conversion at both room temperature and high temperature. (Table 2.21, entries 1-4) This refers to incomplete formation of the ketoimine, which may be due to slow evolution of the ammonia or the ammonia would simply escape. Another possibility is complexation of the free Mg salt with 2-imidopyridine [41], which resists nucleophilic attack on the aldehyde.

The employment of closed system with the use a sealed tube ends with a satisfactory conversion but results into extended reaction time at ambient temperature. (Table 2.1, entry 5) Reaction rate could be enhanced with moderate heating, stimulating the formation of 3a in excellent yields (Table 2.1, entry 6)



Scheme 2.21: Mg_3N_2 assisted (I) stepwise and (II) one-pot annulation reaction in synthesis of imidazo[1,5-*a*]pyridine

Table 2.1: Optimization study in one pot synthesis of 3a



Sr No	Solvent	Time in Hrs	Temp ℃	% yield[a]
1	MeOH	24	25	40[b]
2	EtOH	24	25	48[b]
3	MeOH	24	60	54[b]
4	EtOH	24	75	63[b]
5	EtOH	12	25	65[c]
6	EtOH	08	60	80[c]
7	MeOH:water (8:2)	04	60	85[c]
8	EtOH:water (8:2)	04	80	92[c]
9	EtOH:water (8:2)	04	80	80[d]
10	EtOH:water (8:2)	04	80	81[e(7d)]
11	EtOH:water (8:2)	04	80	92[f]

[a]Reaction conditions- 2-pyridyl phenyl ketone (1a, 1 mol), Mg_3N_2 (1 mol), Methyl glyoxalate (2a, 1 mol), Solvent (3 ml), [b]Open flask, [c]Sealed tube, [d]Aq. Ammonia (1 mol), [e]NH_4OAc (1 mol), [f]Mg_3N_2 (1.5 mol).

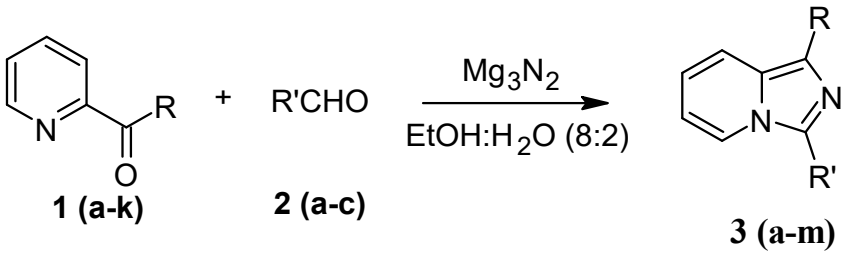
The results presented in Table 2.1 show that the solvent combination plays a crucial role in the transformation at hand (Table 2.1, entries 7-11). Attempts to use other nitrogen sources (Table 2.1, entries 9-10) showed no progress in improving the proportion of 3a over Mg_3N_2. When the amount of Mg_3N_2 was increased to 1.5 equivalents, the yield remained the same (Table 2.1, entry 11). Thus, the optimum reaction condition was achieved by using 1a (1 equivalent), Mg_3N_2 (1 equivalent) and methyl glyoxalate 2a (1 equivalent) in EtOH: water (8:2) as solvent system to obtain the maximum yield of 3a (Table 2.1, entry 8)

As shown in Table 2.2, this methodology tolerates a range of 2-pyridyl ketones (1a-k) bearing alkyl/aryl or heteroaryl functionality. All of these substrates were readily converted to the expected imidazo[1,5-*a*]pyridines (3a-m) by reacting them exclusively with aldehydes (2a-c) in the same pot, and no anomalies were observed. Encouragingly, the sterically hindered 2-(3-methyl)pyridyl ketones (Table 2.2, entries 2,4,6,8,10) also function well under the standard conditions, giving the corresponding products in good yields. It is noteworthy that the electronic nature of the substituents on aroyl (Table 2.2, entries 1-2 and 11-12), heteroaroyl (Table 2.2, entries 3-4) as well as acyl (Table 2.2, entries 5-10) did not significantly affect the rate of product formation, clearly demonstrating higher efficiency and greater generality of the present protocol. It is noteworthy that in the long run, synthesis of 3a could be successfully carried out at five-gram scale, confirming the synthetic practicability of the present method.

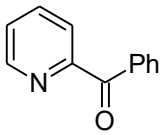
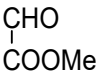
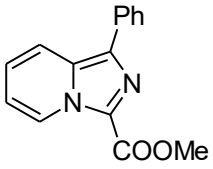
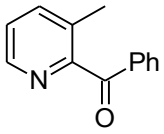
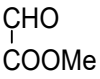
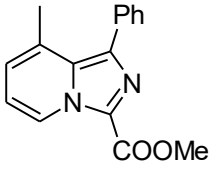
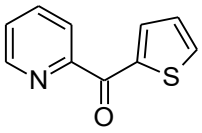
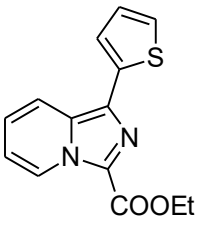
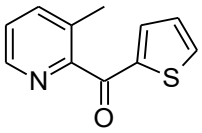
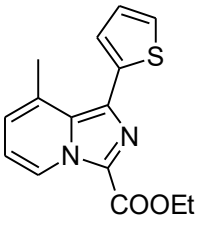
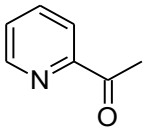
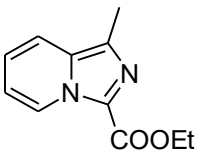
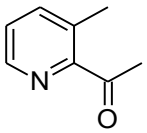
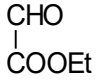
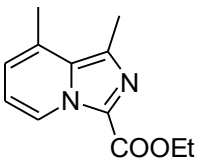
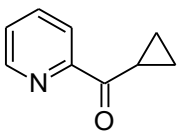
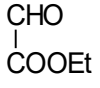
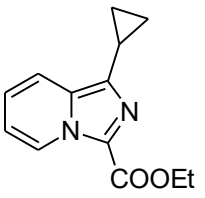
2.6 Synthetic Procedure for preparation of imidazo[1,5-*a*]pyridine deravetives (3a-m)

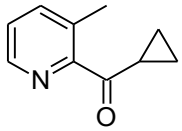
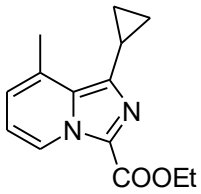
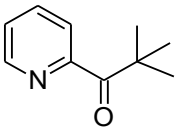
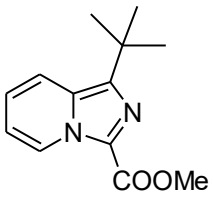
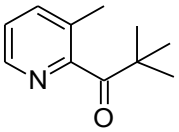
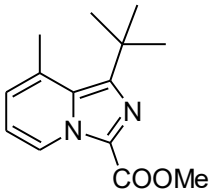
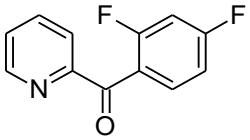
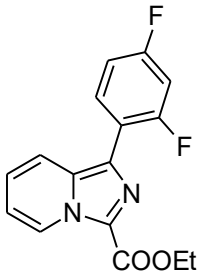
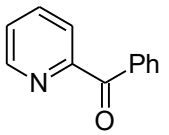
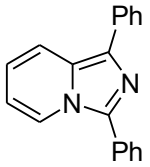
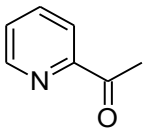
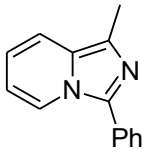
A mixture of 2-pyridyl ketones 1 (1 mol), aldehyde 2 (1 mol) and Mg_3N_2 (0.100 g, 1 mol) in EtOH:water (8:2) (3 ml) in a 5 ml sealed tube is stirred at 80 °C for the time indicated in Table 2.1. After complete consumption of ketone 1 (monitored by TLC), the reaction mixture is allowed to cool to room temperature, quenched with ice-cold water (10 ml), and extracted with EtOAc (3 x 15 ml). The combined organic layer is dried over Na_2SO_4, the solvent removed in vacuo and the product purified by silica gel column chromatography using a mixture of EtOAc and n-hexane as eluent to give the corresponding product 3.

Table 2.2: One-pot synthesis of imidazo[1,5-*a*]pyridine[a]



1 (a-k) **2 (a-c)** **3 (a-m)**

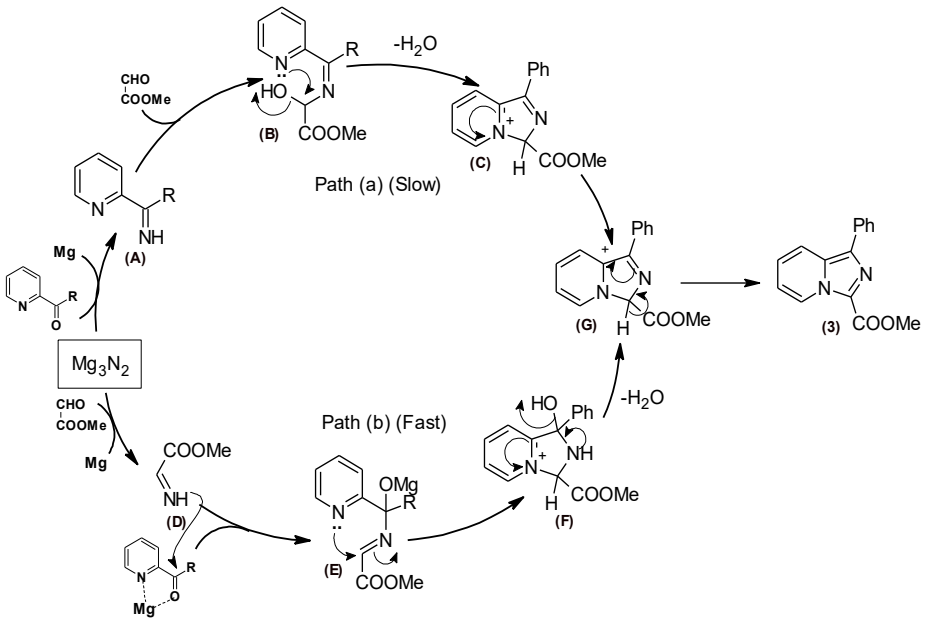
Sr No	Ketone (1)	RCHO (2)	Product (3)	Reaction time (hrs)	% Yield[b]
1	 (1a)	 (2a)	 (3a)	4	92
2	 (1b)	 (2a)	 (3b)	5	85
3	 (1c)	 (2b)	 (3c)	4.5	90
4	 (1d)	 (2b)	 (3d)	5.5	83
5	 (1e)	 (2b)	 (3e)	5	87
6	 (1f)	 (2b)	 (3f)	5.5	75
7	 (1g)	 (2b)		3	88

			(3g)		
8	 (1h)	 (2b)	 (3h)	4	80
9	 (1i)	 (2a)	 (3i)	5.5	78
10	 (1j)	 (2a)	 (3j)	6	72
11	 (1k)	 (2b)	 (3k)	4	83
12	 (1a)	PhCHO (2c)	 (3l)	4	85[9]
13	 (1e)	PhCHO (2c)	 (3m)	3.5	63[41]

[a]Reaction condition- 2-pyridyl ketone (**1**, 1 mol), Mg_3N_2 (1mol), aldehyde (**2**, 1 mol), EtOH: water (8:2) (3 ml), at 80°C, [b]Isolated yields

2.7 Mechanism

Based on the above experimental results and the latest mechanistic studies on the role of Mg_3N_2 in azaheterocylic chemistry [39], the plausible mechanism as depicted in Scheme 2.2. The plausible explanation for the one-pot annulation between 2-pyridyl ketone and aldehyde is attributed to the synchronous formation of two types of imines such as ketoimine A (pathway-a) and aldimine D (pathway-b). Owing to the highest degree of electrophilic character of aldehyde compared to ketone, the formation of aldimines derived from ethyl glyoxylate/aldehyde is very favorable and therefore pathway (b) seems to be more feasible than pathway (a). As a result, previously released Mg salts can coordinate with 2-pyridyl ketone [41d], which leads to the formation of the intermediate E upon nucleophilic attack of the aldimine D. This becomes G upon successive intramolecular cyclization to intermediate F, followed by the release of a water molecule. Finally, intermediate G rapidly tautomerizes to the more stable imidazo[1,5-*a*]pyridine (3) as solitary product.



Scheme 2.22: Plausible mechanistic rationalization for the synthesis of Imidazo[1,5-*a*]pyridine

2.8 Overview and Key Takeaways

This demonstrates a novel and efficient strategy in terms of cost and ease of use for the synthesis of diverse and functionalized imidazo[1,5-*a*] pyridines through an unprecedented annulation of readily available 2-pyridyl ketones and Mg_3N_2 as a secondary nitrogen/amine source. Mg_3N_2 has demonstrated valuable and unique reactivity with a completely different set of chemical transformations that meet the needs of academia and industry. Moreover, it would be possible to convert the synthesized imidazo[1,5-*a*]pyridine-3-carboxylates into more complex heterocycles via a systematic approach.

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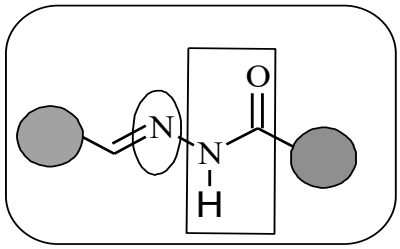
CHAPTER 3

AZOMETHINE-DERIVATIVES OF PHENYLIMIDAZO[1,5-A]PYRIDINES (N-FUSED IMIDAZOLES): NOVEL SYNTHETIC STRATEGIES

3.1 Introduction

Recent developments in the field of complex-organic chemistry have increased the interest in Hydrazide/hydrazone complexes generally known as 'Schiff base hydrazone'. (Fig. 3.1) It has been known that many of these complexes may act as lead for biologically important species [1–5]. The interest in the study of Schiff base hydrazones have gained great importance because of their complex structural linker, may represent a promising tool for developing of potential active agents as well as their vast occurrence in drugs and natural products.[6-11] Besides the diverse pharmacological properties of Schiff base derived hydrazones, they play an important role in inorganic chemistry due to easy formation of stable coordination complexes with most transition metal ions.

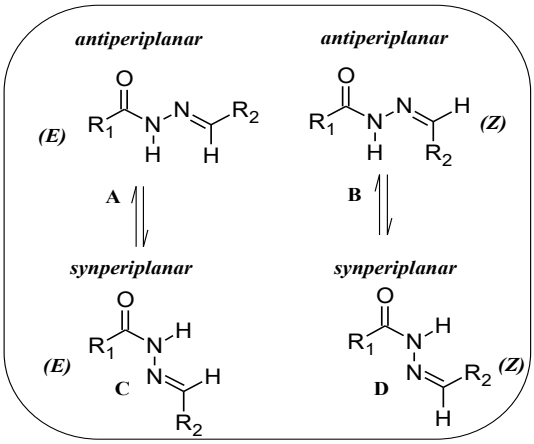


Hydrazide/hydrazone Scaffol

Figure 3.1

3.2 Structure of hydrazide/hydrazone

The bioactive *N*-acylhydrazone (NAH) moiety has been identified in a great number of lead compounds that act on different types of molecular targets [12–15]. Because of the assemblage of amide and imine functions, NAH compounds may exist as C=N double bond stereoisomers (E/Z) and as syn/antiperiplanar conformers about the amide CO-NH bond (Scheme 3.1) [16].



Scheme 3.1: General structure and stereochemistry of NAH

3.3 Applications of hydrazide/hydrazone

Hydrazide–hydrazones attract the attention of medicinal chemists due to the fact that they contain azomethine (–NH–N=CH–) group linked to carbonyl (>C=O) group. This azomethine is mainly responsible for their medicinal applications and attributed to modify them into several heterocyclic scaffolds [17] such as coumarins [18], azetidin-2-ones [19], 1,3,4-oxadiazolines [20], 1,3-benzothiazin-4-ones [21b] and 1,3-thiazolidin-4-ones [21a]. (Fig. 3.2) Moreover, the significance of hydrazones was extensively used for the synthesis of transition metal chelators.[22]

Figure 3.2: Applications of Acid-hydrazide in construction of various heterocycles

The principal synthetic method used in preparation of hydrazide–hydrazone and their derivatives is the heating of appropriate hydrazides of carboxylic acids with diverse aldehydes or ketones in various organic solvent. The structure elucidation of hydrazide–hydrazone derivatives can be easily done on the basis of different spectral techniques. According to the IR spectra, there were three characteristic bands observed in functional group region. The characteristic peak appears for C=N, C=O and NH group at around 1550 cm^{-1}, 1650 cm^{-1} and 3050 cm^{-1} respectively. In ^{1}H NMR spectra, two types of characteristic singlets of hydrazide–hydrazones were observed. One is in the range of δ 8–9 ppm and the second singlet is around δ 10–13 ppm, which correspond to =CH and NH groups, respectively. In the ^{13}C NMR spectra, the signal for =CH group usually appears around δ 145–160 ppm, whereas the carbonyl (>C=O) group appears in the range of δ 160–170 ppm [21-23].

Hydrazones have an attractive therapeutic approach, which is widely applied in the treatment of many diseases. In recent years, many medicinal chemists synthesized several hydrazide–hydrazones and evaluated there *in vitro* as well as *in vivo* assays for various biological activities

viz. anticancer [24], anti-inflammatory [25], anticonvulsant [26], antiviral [27], and antiprotozoal [28] activities. Additionally, their detailed theory and applications of entirely prepared compounds have appeared in several reviews [29] and monographs, where the structural elucidation of hydrazide–hydrazones derivative probes from various analytical tools such as FT-IR, ^{1}H, ^{13}C NMR and 2D NMR (COSY, HMBC, HSQC and NOESY) spectroscopy. Thus, on the basis of medicinal application of hydrazide–hydrazones, we broadly classified them into different categories and briefly taken into account bellow.

3.3.1 Anti-microbial activity

The exploitation of diverse synthetic scaffolds against various infectious diseases has led to rapid emergence of resistivity against different bacteria. Therefore, the search for anti-microbials is a never-ending task. Consequently, there has been immense research on hydrazide–hydrazones and in scientific literature the most frequently encountered biological properties of these classes of compounds are the anti-microbial activity. The comprehensive chemotherapeutic agents containing typical hydrazide–hydrazone moiety is free or sometimes linked with heterocyclic ring system. Fig. 3.3 illustrates few examples of nitrofurazone [30], furazolidone [31], and nitrofurantoin [32] which are widely used as anti-microbial agents.

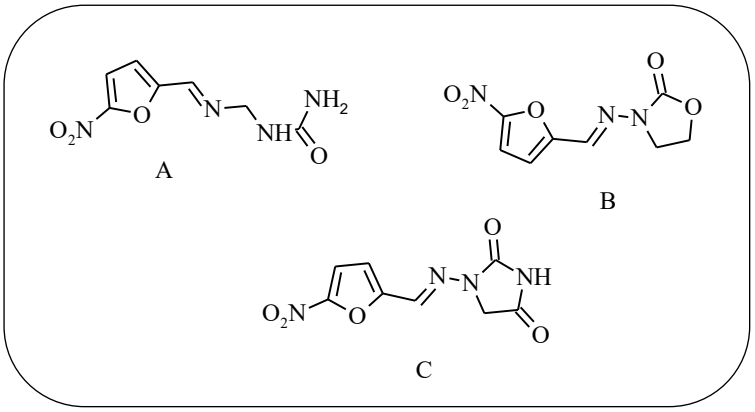


Figure 3.3

3.3.2 Anti-bacterial Activity

Anti-bacterial as well as antiviral activity is completely associated with the compounds that provincially kill bacteria and virus or slow down their rate of growth, without being extensively toxic to nearby tissues. Substantiation to antibacterial activity, the molecular structure of the compound is also extremely important in fighting infectious diseases. There has been immense research on hydrazide–hydrazone as anti-bacterial agents.

Group of Rane *et al.* [33] were synthesized hydrazine derivatives of chloropyrrole in 2010 and evaluated their antibacterial activity against different bacterial strains using broth dilution technique. (Fig. 3.4) Besides the synthesized 1*H*-pyrrole-2-carbohydrazide derivatives few compounds shows activity equivalent to the standard drug ciprofloxacin.

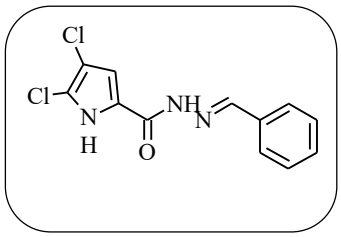
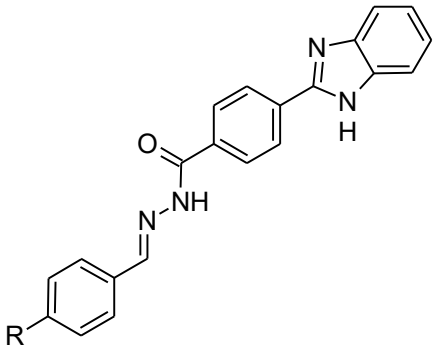


Figure 3.4

Ozkay *et al.* [34] reported the antibacterial activity of twelve novel benzimidazole derivatives bearing hydrazone moiety against six different gram-negative and four different gram-positive bacterial strains. Most of the test compounds found to be significantly effective against *Proteus vulgaris, Staphylococcus typhimurium, Klebsiella pneumoniae and Pseudomonas aeruginosa* gram-negative bacterial strains. At the same time the toxicity of the most effective compounds was established by performing Brine–Shrimp lethality assay. (Fig. 3.5)



Entry	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**
R	H	OH	NMe_2	Cl	Br	F	Me	**OMe**	NO_2	CF_3	COOH	CN

Figure 3.5

Govindasami *et al.* [35] synthesized vanillin based hydrazine derivatives (Fig. 3.6) and characterized by ^{1}HNMR, ^{13}CNMR, LCMS, FT-IR and HPLC techniques. The synthesized hydrazone derivatives were further checked for their antibacterial activity specifically against *Staphylococcus aureus* and *Pseudomonas aeruginosa* by paper disc diffusion method against.

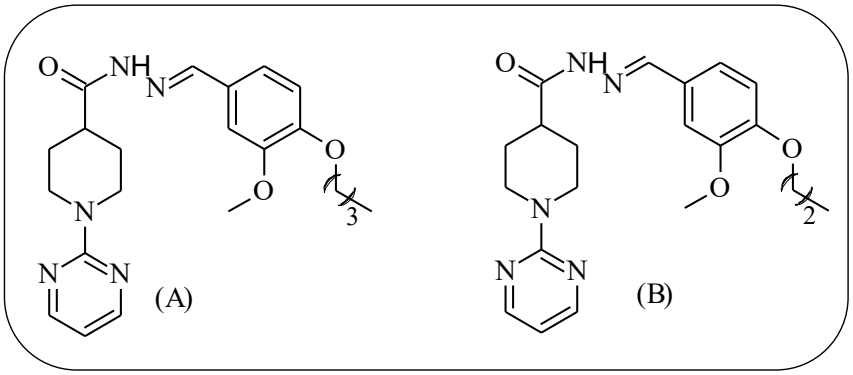


Figure 3.6

Lee *et al.* [36] discovered a new series of hydrazones (Fig. 3.7) having a novel 4-hydrazonomethyl-benzene-1,3-diol core structure. The prepared compound exhibited high binding affinity to SAKAS III and highly selective antimicrobial activities against *S. aureus* and methicillin-resistant *S. aureus*, with minimal inhibitory concentration values of 1–2 µg/ml.

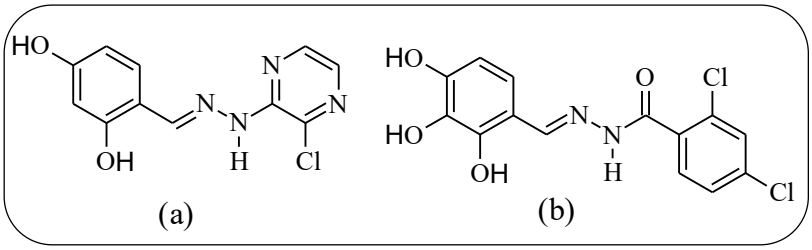


Figure 3.7

Kumar *et al.* [37] synthesized various benzylidene-hydrazides (Fig. 3.8) and tested, various *in vitro* activities, such as antibacterial, antifungal and antiviral activities. The screening results contraindicate the compound bearing chloro and nitro substituents are the most active ones. Additionally, the multi-target QSAR model was effective for synthesized derivatives in describing the antimicrobial (antibacterial and antifungal) activity over the one-target QSAR models.

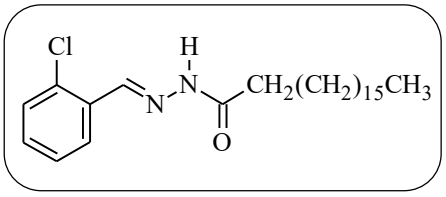


Figure 3.8

A group of Abdel-Wahab *et al.* [38] were used 1-(5-methyl- 2-phenyl-1*H* -imidazol-4-yl)ethanone as a precursor for the synthesis of different hydrazone (Fig. 3.9) derivatives. They were screened and described various types of antimicrobials, antioxidant, anti-hemolytic, and cytotoxic activities of newly synthesized compounds.

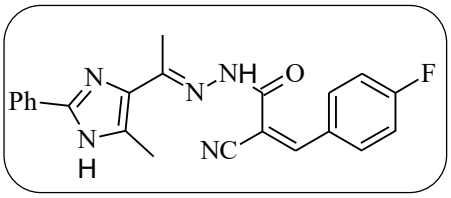


Figure 3.9

Two different groups Xaiver *et al.* [39a] and Kodisundaram *et al.* [39b] synthesized similar kind of novel hydrazide–hydrazones and were tested for *in vitro* anti-bacterial activity against different bacterial strains (Gram negative bacteria: *S. thypimurium*, *E. coli*, *Vibrio cholerae*, *S. typhi*, *P. aeruginosa*, and *K. pneumonia*, and Gram-positive bacteria: *B. subtilis* and *S. aureus*).

Among the synthesized derivatives, it is worth to mention few compounds which showed good to moderate activity against all bacterial strains. (Fig. 3.10)

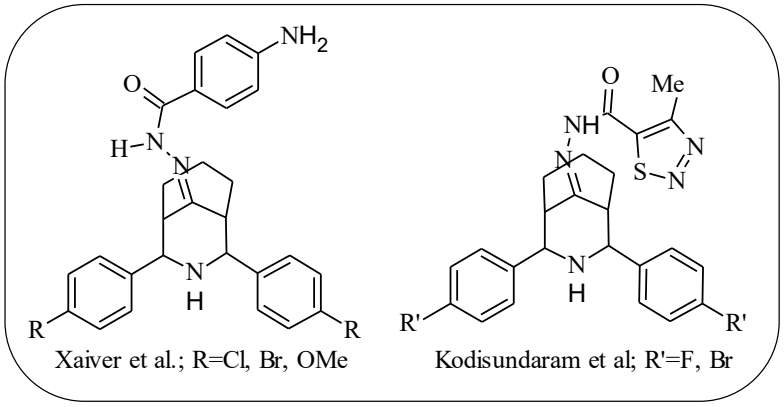


Figure 3.10: Ferrocenyl hydrazones with Anti-bacterial activity

Maguene *et al.* in [40] reported the synthesis and evaluation of in vitro Mycobacterium tuberculosis activities of a series of twenty-five Ferrocenyl hydrazones (Fig. 3.11) derived compounds of nicotine and pyrazine, pyridinyl, quinolyl and acridinyl functionality. In particular ferrocenyl acylhydrazones (I) and ferrocenylquinoxaline amide (II) showed interesting antimycobacterial activities.

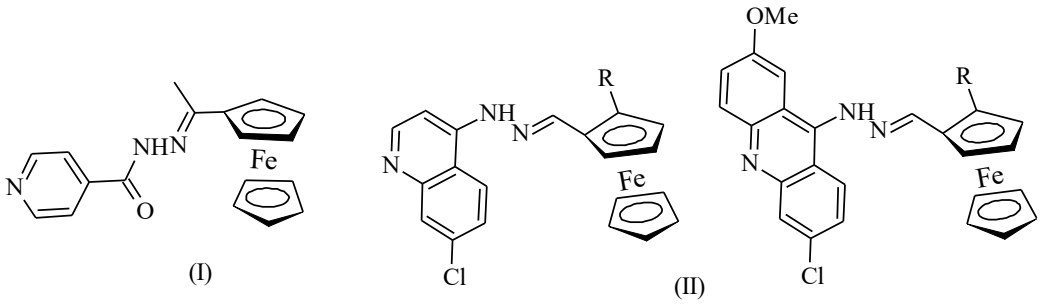


Figure 3.11

In same year, another group of Mahajan *et al.* [41] synthesized ferrocene-based hydrazone derivatives (Fig. 3.12) and disclosed for its *in vitro* significant activity (MIC = 2.5–5 μg/ml) against *Mycobacterium tuberculosis*. Also they claimed that such hybrid compounds provide an efficient approach for future pharmacological developments to fight against tuberculosis and found to be an interesting alternative in endemic area where malaria and tuberculosis coexist.

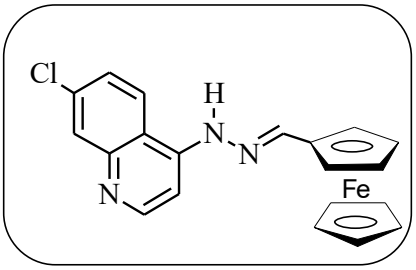


Figure 3.12

Recently Smith and co-workers [42] described that incorporation of isonicotinyl and pyrazinyl ferrocenyl-derived complexes of hydrazide–hydrazone supports promising antimicrobial activities than existing antimicrobial therapies than the non-ferrocenyl compound in order to alter their biological activities favorably. (Fig. 3.13)

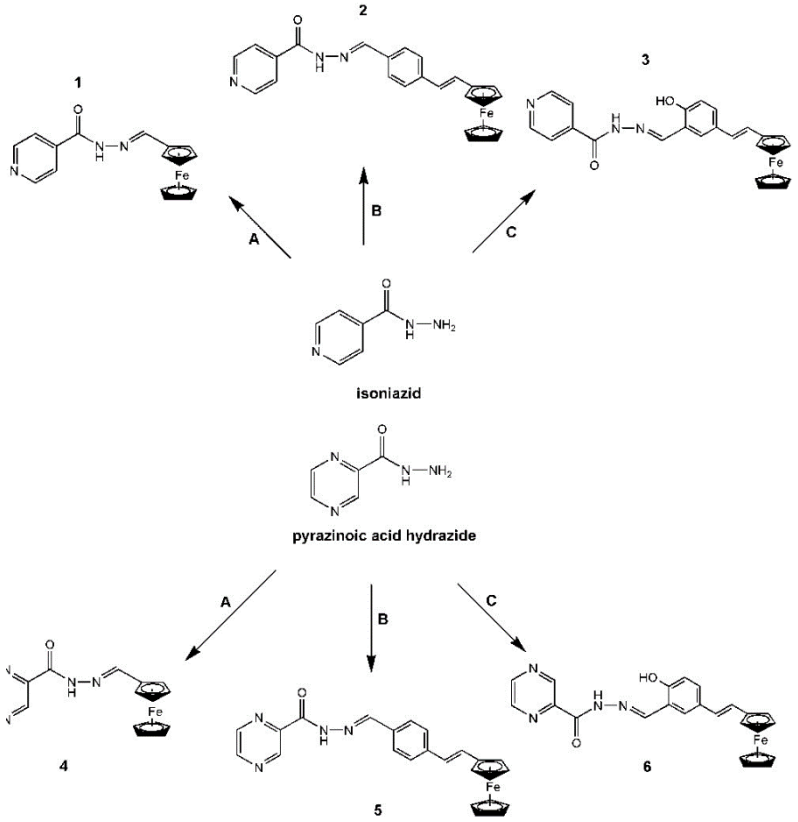


Figure 3.13

3.3.3 Anti-fungal activity

Özkay *et al.* [43] in 2010 discovered benzimidazole derivatives bearing hydrazones as anti-fungal agents against three species of yeasts: *Candida albicans*, *Candida glabrata*, and *Candida tropicalis*. (Fig. 3.14) The compounds bearing halogenated substituent's (Cl and Br) are most active against these fungi (MIC = 50–100 μg/ml) where as the activity against *C. tropicalis*, the MICs of the synthesized compounds (MIC = 50 μg/ml) were equal to the MIC of ketoconazole used as control (MIC = 50 μg/ml).

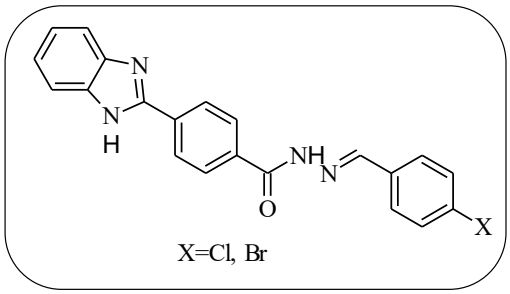


Figure 3.14

In succeeding year, similar research was performed by Kumar *et al.* [44] by developing new hydrazide–hydrazones of 4-chlorophenylsulfonyl acid. (Fig. 3.15) The synthesized derivatives were tested for anti-fungal activity on the basis of the measurement of the zone of inhibition growth against *C. albicans* and *Aspergillus niger*. Out of synthesized derivatives, only three compounds (A, B and C) showed promising anti-fungal activity compared with the clotrimazole, which was used as positive control. In the case of compound A, the anti-fungal activity (ZOI = 31 mm) was greater than the activity of clotrimazole (ZOI = 30 mm) against *C. albicans.*

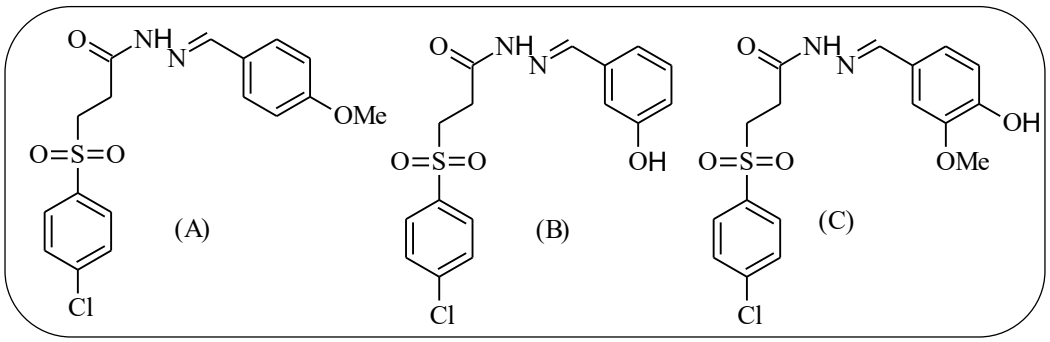


Figure 3.15: 4-chlorophenylsulfonyl Hydrazide–hydrazones with antibacterial activity.

Shirinzadeh *et al.* [45] synthesized indole based hydrazide–hydrazones and subjected to anti-fungal assays against *C. albicans*. They revealed that two compounds bearing pyridyl and anisyl functionalities are good anti-fungal activity ((a): MIC = 6.25 μg/ml and (b): 12.5 μg/ml, respectively), but weaker than for fluconazole (MIC = 0.78 μg/ml) as an internal standard. (Fig. 3.16)

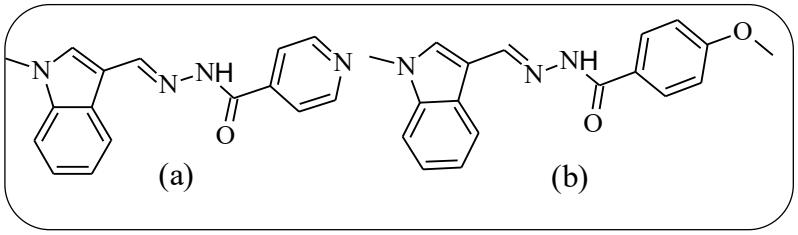


Figure 3.16

3.3.4 Anti-tubercular activity

Tuberculosis remains a major cause of death and illness, despite the fact that it is a curable and treatable disease, therefore development of new anti-tubercular agents is become a hot topic of 21st century. A survey of scientific literature reveals that several hydrazide–hydrazones synthesized during last few years possess interesting anti-tubercular activity.[46] (Fig. 3.17) Additionally, according to the latest report by John *et al.*[47] it is worth to mention that the 2-hydroxy-1-naphthaldehyde isonicotinoyl hydrazone act as a novel inhibitor of methionine aminopeptidases.

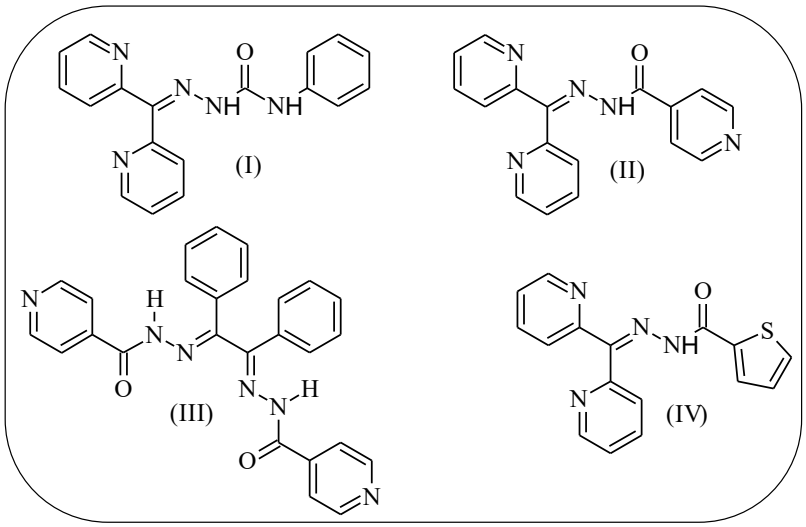


Figure 3.17: Hydrazide–hydrazones with interesting mycobacterium tuberculosis

As like anti-fungal activity, another interesting property of indole derived hydrazide–hydrazones were described by Cihan-Üstündağ and Çapan [48] *via* synthesizing and evaluating series of indole containing hydrazide–hydrazone scaffold for *in vitro* anti-tubercular activity (Fig. 3.18). Its anti-mycobacterial activity was tested against *M. tuberculosis* H37Rv ATCC 27294 with the use of rifampicine as a control and they noted that the synthesized derivatives are weaker in activity (MIC > 6.25 μg/ml) than reference substance (MIC = 0.125 μg/ml).

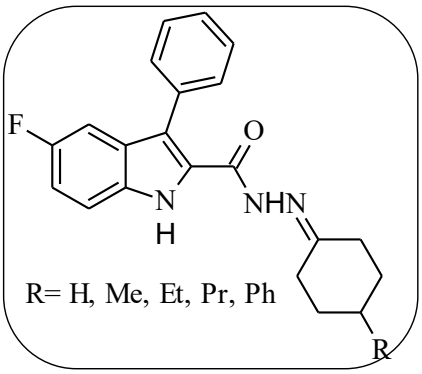


Figure 3.18: Indole derived hydrazide–hydrazone with antitubercular activity

Further Velezheva *et al.* [49] designed and synthesized one more series of indole derived hydrazide–hydrazones and evaluated them against two *M. tuberculosis* strains (H37Rv and CN-40). It was observed that, the hydrazide–hydrazone derivative appeared in Figure 3.19 is the most potent among examined compounds (MIC=0.05 μg/ml) against the *M. tuberculosis* H37Rv strain. It was almost equality active to that of positive control isoniazid in this assay. Besides, this compound, unlike isoniazid, showed significant activity against isoniazid resistant *M. tuberculosis* CN-40 strain. Other synthesized derivatives also displayed high anti-tubercular activity.

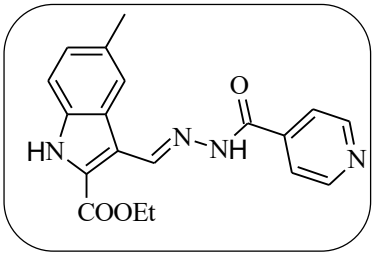


Figure 3.19: Novel indole derivatives with significant antitubercular activity

3.3.5 Anti-protozoal activity

Protozoal diseases are highly prevalent in tropical countries affecting human and animal populations' and causing suffering and death. Hayat *et al.* [50] reported the *in-vitro* antiamoebic activity of hydrazones (Fig. 3.20) against the HM1:IMSS strain of Entamoeba histolytica. The compounds are reported to have IC_{50} value of 0.03 and 0.04μM respectively.

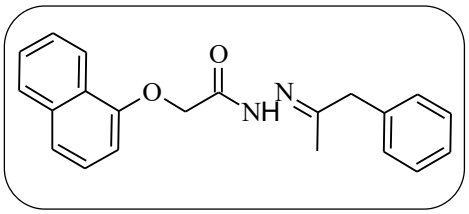


Figure 3.20

Vaio *et al.* [51] synthesized hydrazone derivatives, where the halogenated-benzylidene-carbohydrazide presented the lowest potency whereas cyano and nitro benzylidene-carbohydrazide (Fig. 3.21) showed the most promising profile with low toxicity (0% of cell death) in *in vitro* trypanocidal evaluation, cytotoxicity assays. Further molecular modeling and SAR/QSAR studies of these new series of *N*-phenylpyrazole benzylidene-carbohydrazides revealed that bulky R-substituents decreased the potency whereas hydrophobic and hydrogen bond acceptor R_1-substituents increased it.

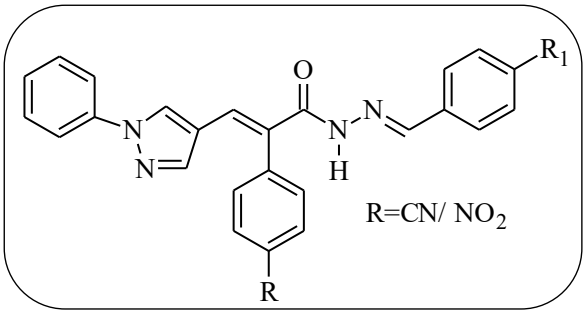


Figure 3.21

Siddiqui *et al.* [52] described synthesis of pyridyl functionalized the hydrazones and azoles and screened for *in vitro* antiamoebic activity against HM1:IMSS strain of *Entamoeba histolytica.* Among the prepared compounds, hydrazone derivatives methoxy and nitro were found to be better inhibitors of growth of *E. histolytica* than the reference drug metronidazole. (Fig. 3.22)

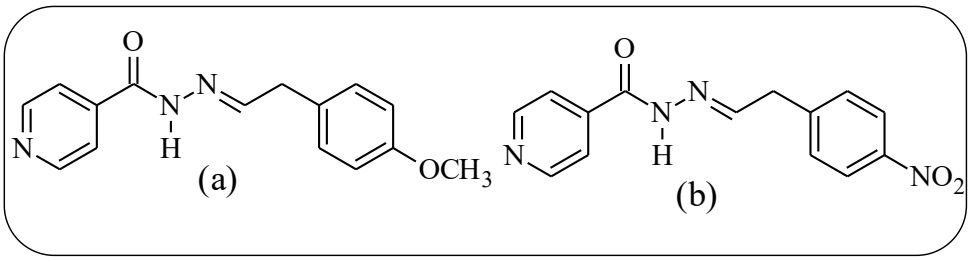


Figure 3.22

Romeiro *et al.* in year 2009 [53] reported the structural design, synthesis, trypanocidal activity and docking studies of novel quinoxaline-*N*-acylhydrazone (NAH) derivatives. The synthesized hydrazone derivatives (Fig. 3.23) become cruzain inhibitors candidates, a cysteine protease essential for the survival of *Trypanosoma cruzi* within the host cell.

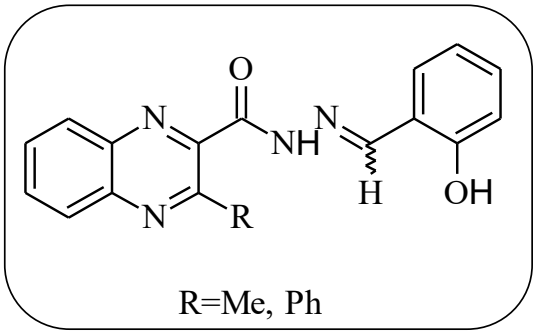


Figure 3.23

3.3.6 Anti-cancer Activity

Cancer is a lethal group of diseases with a high level of penetrating potency affecting almost every organ of the body. The main causes for failure of many chemically and mechanically unrelated anticancer agents in chemotherapy is the lack of response from the cancer cells, which can lead to recurrence of disease or even death.[54] Also higher doses of anticancer drugs during its clinical administration to overcome resistance led drug-induced toxicities. All these factors responsible in synthesizing and testing of newer anti-cancer agents for its efficacy both *in vitro* and *in vivo* to overcome drug resistance.

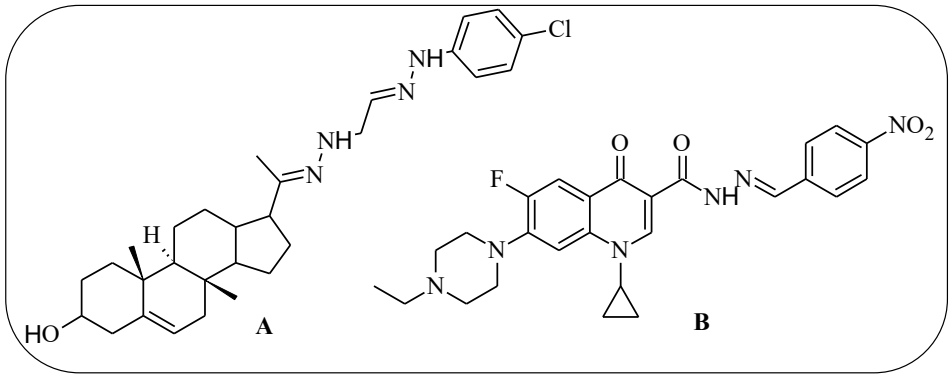


Figure 3.24

Some of currently used anti-cancer agents are known to contain hydrazide–hydrazone moiety. For instance, Ciprofloxacin acyl hydrazone (Fig. 3.24(B)), was found to exhibit extensive anti-tumor activities in liver cancer cells (SMMC-7221), leukemia cells (L1210) and human promyelocytic leukemia cells.[55] Mohareb *et al.* [56] authenticated as a new and patent small molecule scaffolds derived from Pregnenolone structure of cyanide acetyl hydrazone derivatives (Fig. 3.24) and claimed for potential anti-cancer agents.

Moreover, recent research on the hetero cyclic hydrazo-hydrazide skeleton, became much more attractive and promising for the devise of anti-cancer agents. For instance, the hetero cyclic hydrazo-hydrazide compounds containing both furan and coumarin ring systems have found to be been a productive and potent than doxorubicin (DOX) against resistant Panc-1 cells. [57] (Fig. 3.25)

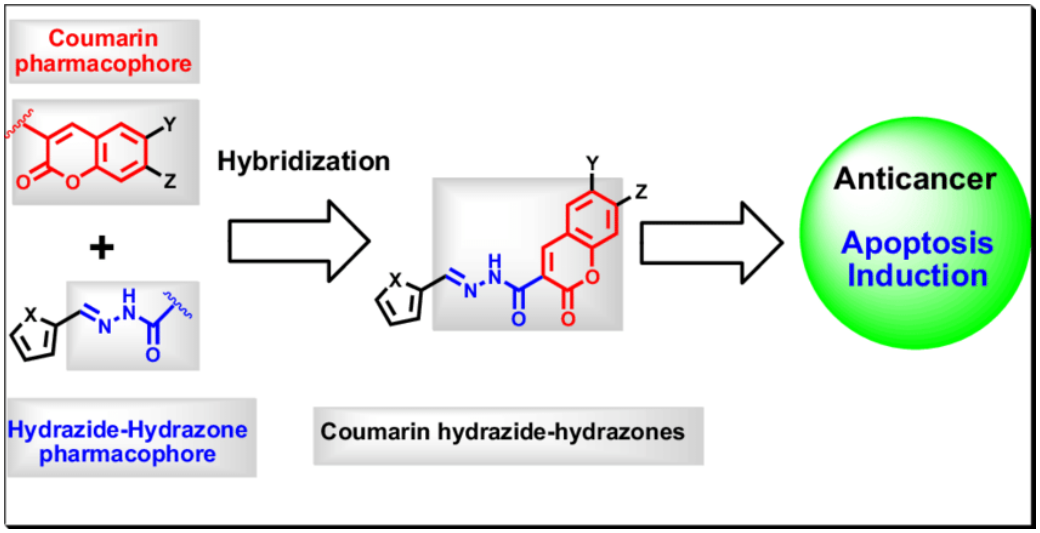


Figure 3.25

Kumar *et al.* [58] synthesized various bis(indolyl) based hydrazones and evaluated for their cytotoxicity against selected human cancer cell lines. *N*-(*p*-chlorobenzyl) and bromo substituents (Fig. 3.26) was found to be the most potent against multiple cancer cell lines (IC_{50}=1.0 µM, MDA-MB-231).

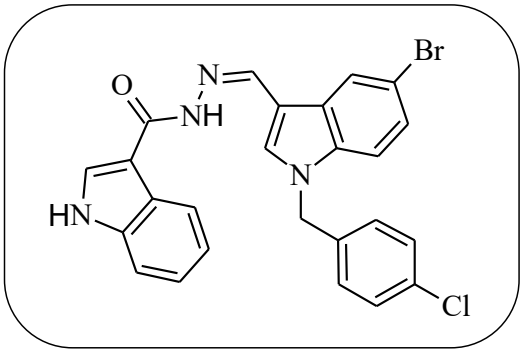


Figure 3.26

In year 2010, copper based hydrazone derivatives are reported by Fan *et al*.[59] Further they maid copper complex of (*E*)-*N*′-(2-hydroxybenzylidene)-1-(4-tert- butylbenzyl)-3-phenyl-1*H*-pyrazole-5-carbohydrazide, (Fig. 3.27) which exhibited an advantage in selectivity and efficacy over the others against integrin β4 in H322 lung carcinoma cell lines.

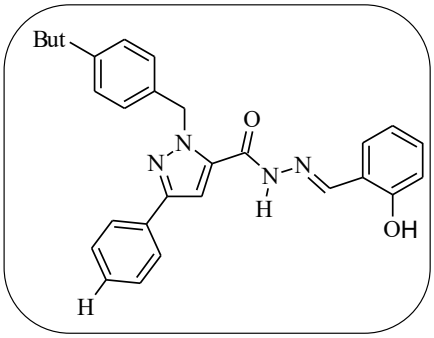


Figure 3.27

3.3.7 Cardioprotective activity

Despite the intensive drug research cardiovascular diseases still remain the leading cause of mortalities worldwide. El-Sabbagh *et al.* [60] synthesized octahydroquinazoline hydrazones (Fig. 3.28) and reported them to be potential hypotensive agents. The activity was attributed to α-blockage.

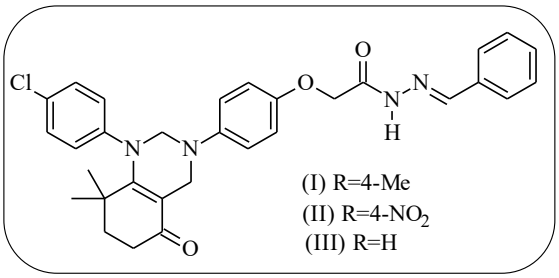


Figure 3.28

3.3.8 Anti-platelet activity

Anti-platelets decrease platelet aggregation, hold back the formation of thrombus. Jordao *et al.* [61] synthesized hydrazone derivatives (Fig. 3.29) and evaluated them for *in-vitro* anti-platelet activity.

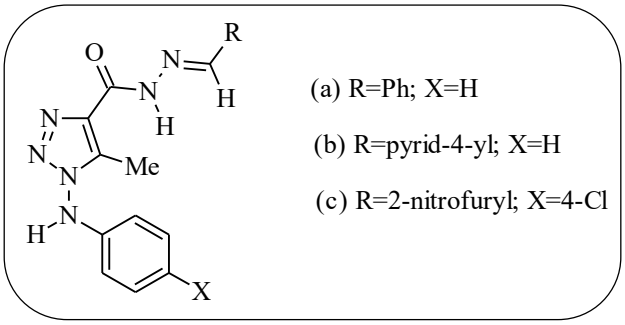


Figure 3.29

3.3.9 Anti-parasitic activity

Ali *et al.* [62] evaluated the *in-vitro* anti-parasitic activity of hydrazone derivatives (Fig. 3.30) against Ctenocephalides felis and Rhipicephalus sanguineusas. LD50 of 0.39 and 0.28 µg/tick has been reported.

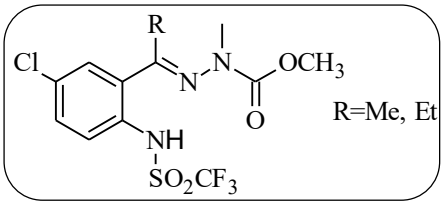


Figure 3.30

3.3.10 Anti-inflammatory

Much work has been done describing the analgesic and anti-inflammatory potential of hydrazides. Harnandez *et al.* [63] reported analgesic and anti-inflammatory activity of furoxanyl-*N*-acylhydrazones (Fig. 3.31) (furoxanyl-NAH) by applying molecular hybridization approach and confirmed that both these hybrid derivatives do not have additional LOX- or COX-inhibition activities.

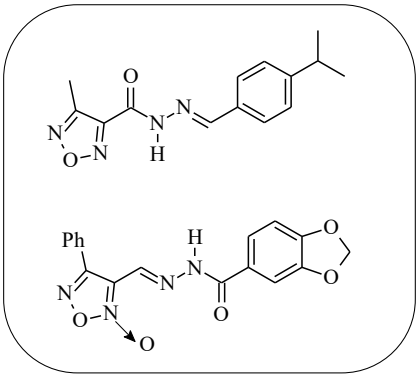


Figure 3.31

Moldovan *et al.* [64] synthesized novel acyl-hydrazones derivatives bearing 2-aryl-thiazole moiety (Fig. 3.32) by the condensation between derivatives of 4-(2-aryl-thiazol-4-ylmethoxy)-benzaldehyde and 4-[2-(4-methyl-2-phenyl-thiazole- 5-yl)-2-oxo-ethoxy] carboxylic acid hydrazides and tested *in vivo* for their anti-inflammatory activity, in an acute experimental inflammation. Further they evaluated acute phase bone marrow response and phagocytes' activity.

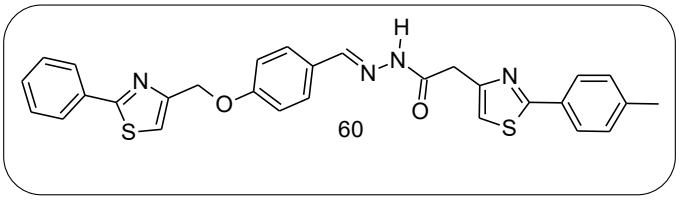


Figure 3.32

Series of new benzo-thiophene derivatives were synthesized, characterized and their anti-inflammatory studies with inhibition of 50.2% have been developed by Isloor *et al.* [65]. The hydrazone derivative (fig. 3.33) is found to be more potent in anti-inflammatory studies than other benzo-thiophene derivatives.

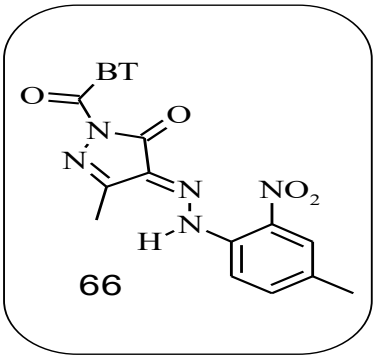


Figure 3.33

3.3.11 Central Nervous System (CNS) Activity

Hydrazones are reported to have activity against various illnesses of central nervous system. Hydrazones (Fig. 3.34) synthesized by Gage *et al.* [66] have been evaluated for inhibition of PDE10A- a phosphodiesterase responsible for neurological and psychological disorder such as Parkinson's, Schizophrenia and Huntington's disease.

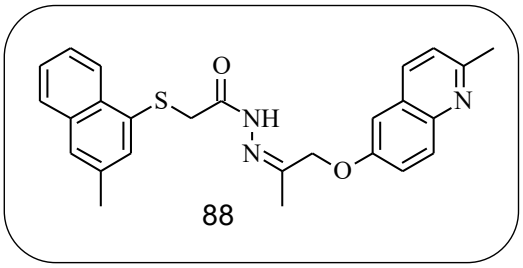


Figure 3.34

Kaushik *et al.* [67] reported the anti-convulsant potential of some *N*'-[(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene] 2/4-substituted hydrazides against maximal electroshock induced seizure (MES) and subcutaneous pentylenetetrazol (scPTZ) induced seizure models in mice.

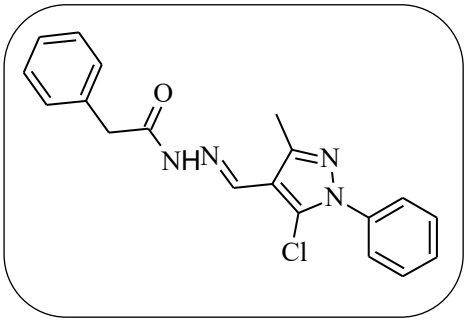


Figure 3.35

The compound shown in figure 3.35 having long duration of action and a rapid onset of action. During this study the administered doses of test compounds are 30, 100, and 300 mg/kg body weight and the anticonvulsant activity was recorded for each 0.5 and 4 hrs of time intervals after the drug administration.

A group of Emami and co-workers [68] were developed series of phenacyl triazole hydrazones as new anticonvulsant agents, based on the hybridization of (arylalkly) triazole and aroyl hydrazone scaffolds. (Fig. 3.36) Further *in vivo* anti-convulsant evaluation of synthesized compounds by using MES and PTZ tests revealed that they are more effective in MES model respect to PTZ test. Additionally molecular docking studies with different targets (NMDA, AMPA, GABAA and sodium channel), postulated that the prepared hydrazones acted mainly *via* GABAA receptors.

Figure 3.36

3.3.12 Hydrazide/hydrazone in click Chemistry

In radiopharmaceutical chemistry ‘click reactions of hydrazide/hydrazone’ have plays crucial role in designing ligands for metal complexation or for coupling pre-labeled radionuclide complexes with a targeting biomolecule [69-71]. The former approaches cut down the exposure of biomolecules to harsh conditions (i.e., pH, temperature) required for complexation. So to improve the site-specific labeling of the metal atom in radiopharmaceutical, the ‘‘prelabel, then click’’ strategy allows efficient incorporation of radiometals into sensitive biomolecules.

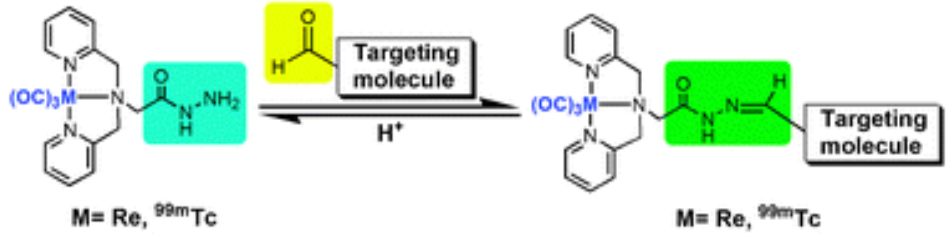


Figure 3.37

Benny and co-workers [72] were described a facile method *via* incorporation of $M(CO)_3$ (M = Re, 99mTc) based radiopharmaceuticals from various aldehydes and hydrazides as potential

coupling partners. They mentioned both synthetic routes, 'prelabel, then click' as well as 'click, then chelate', produces identical products in high yields. The potential highlighted click strategy is lacking in metal-hydrazide/-hydrazone interactions. (Fig. 3.37)

All above study of various hydrazide-hydrazones with presence of diverse heterocyclic moiety have shown to possess the stimulatory and/or inhibitory effects on different contractile states and targeted delivery under assorted environments. However, the pharmacological properties of such compounds together with imidazo pyridine substituents were rarely evaluated.

Fraga and co-workers [73] described the design, synthesis and pharmacological evaluation of novel imidazo[1,2-*a*]pyridine-*N*-glycinylhydrazone derivatives. Further *in vitro* pharmacological evaluation of the synthesized compounds showed that substitution of the *N*-phenylpyrazole core present in earlier lead, were altered by modifying it with a bioisosteric imidazo[1,2-*a*]pyridine scaffold generated anti-TNF-a compounds and that were more potent as SB-203580, a p38 MAPK inhibitor. (Fig. 3.38)

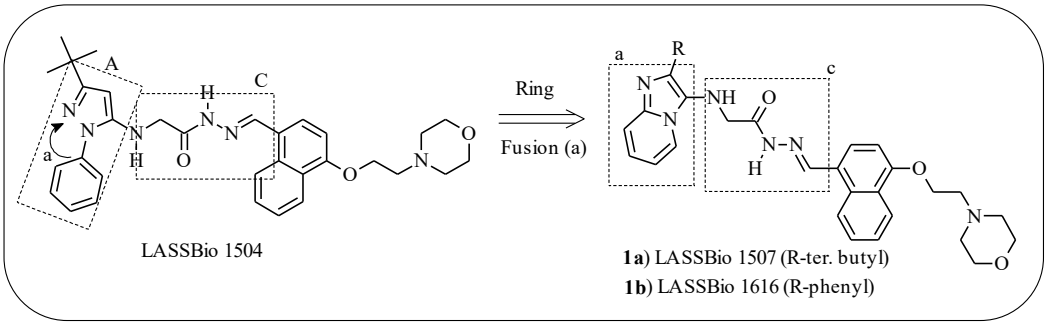


Figure 3.38

Ulloora *et al.* [74] reported facile synthesis of new imidazo[1,2-*a*]pyridines carrying biologically active hydrazone functionality (Fig. 3.39). The *in vivo* anticonvulsant study of synthesized target compounds were carried out following maximal electroshock seizure and subcutaneous pentylene tetrazole methods. Most of the new compounds displayed remarkable anticonvulsant properties, where as compound carrying hydrogen bond donor groups, *viz*. hydroxyl and amine moieties, exhibited complete protection against seizure and their results are comparable to that of standard drug diazepam.

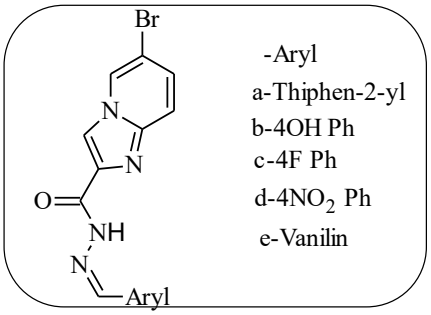


Figure 3.39

Very recently Reena Kumari *et al.* [75] studied corrosion inhibition activity by electrochemical measurement of 6-bromo-(4,5-dimethoxy-2-nitrophenyl) methylidene]imidazo[1,2-*a*]pyridine-2-carbohydrazide on mild steel in 0.5M HCl solution at temperature 303K. (Fig. 3.40) The outcome of said findings discloses that the inhibition efficiency increases and corrosion rate decreases with increase in inhibitor concentration.

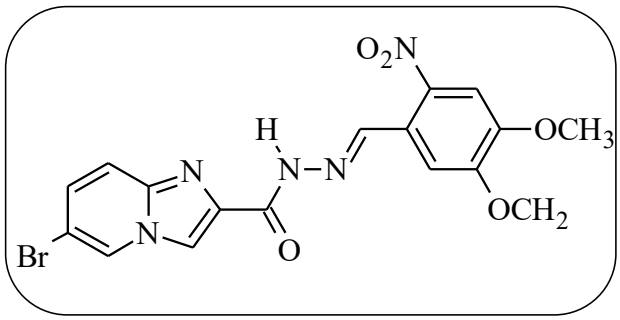


Figure 3.40

Turan-Zitouni *et al.* [76] have been synthesized ten different novel imidazo[1,2-*a*] pyrazine-2-carboxylic acid arylidenehydrazide derivatives and evaluated for their antinociceptive activity. Compound shown in figure 3.41 bearing 5-benzylidene moiety was determined as the most active compound.

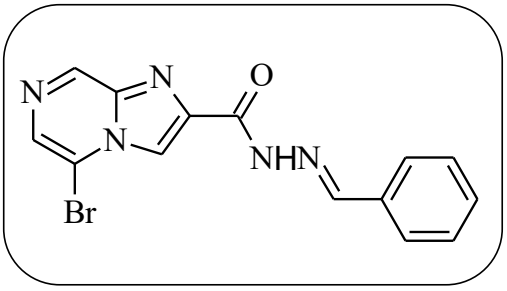


Figure 3.41

Another group of Edraki and co-workers [77] were designed and synthesized novel series of imidazo[1,2-*a*]pyridine 2-carbohydrazide derivatives bearing different arylidene pendantrs and evaluated for their inhibitory activity against mushroom Tyrosinase. (Fig. 3.42) The evaluation study showed that the compounds bearing 4-hydroxy and 3-nitro groups on the arylidene pendant exhibited the best Tyrosinase inhibitory activity with IC_{50} values of 7.19 and 8.11 μM, respectively against kojic acid as reference drug (IC50 = 9.64±0.5 μM).

The synthesis of 5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidine-hydrazone derivatives in six elaborate steps from commercially available 2-aminopyrimidine were described by Maringanti and co-workers [78] and screened for their *in vitro* antimicrobial activity. Compounds revealed in figure 3.43, were found to excellent anti-bacterial activity with zone of inhibition 30–33 mm against *E. coli* (Gram negative bacteria) and *S. aureus* (Gram positive bacteria). Also these

compounds displayed superior antibacterial activity against *P. aeruginosa* (Gram negative bacteria) and *S. pyogenes* (Gram positive bacteria with zone of inhibition 22–25 mm.

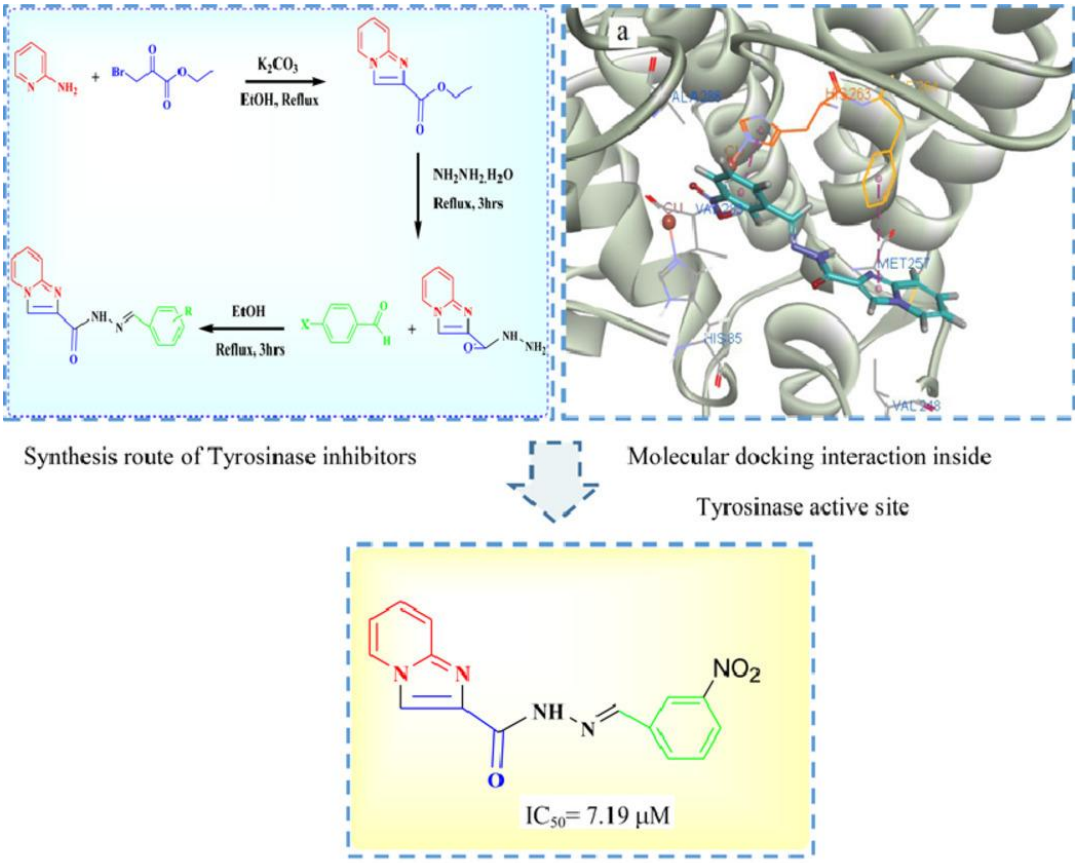


Figure 3.42

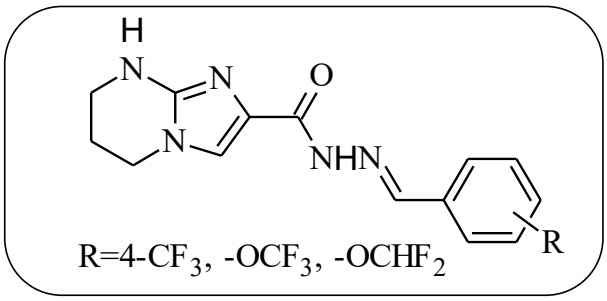
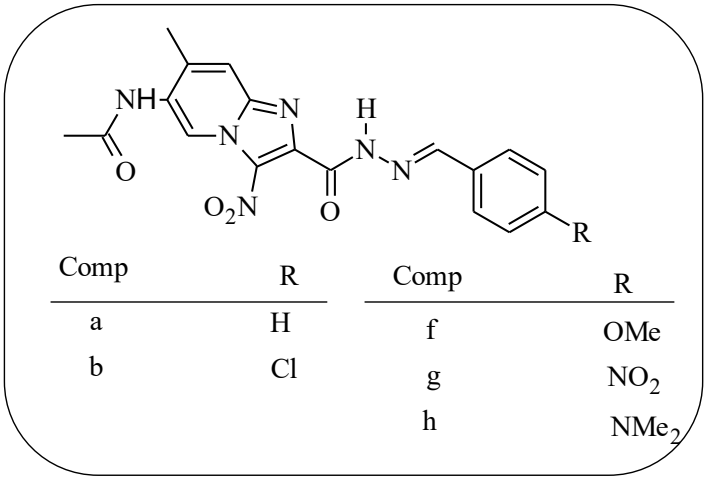


Figure 3.43

Kaplancikli *etal*.[79] prepared new hydrazide derivatives bearing imidazo[1,2-*a*]pyridine moiety and evaluated for anti-candidal activity. Out of all synthesized derivatives few compounds showed promising anti-candidal activities, when compared with Ketoconazole as reference drug. The compounds shown in figure 3.44, a**,** g, h showed similar antifungal activity against *Candida glabrata* (clinical isolate); also compounds b, f, g, h showed similar antifungal activities against *Candida zeylanoides* (NRLL Y-1774).



Comp	R	Comp	R
a	H	f	OMe
b	Cl	g	NO_2
		h	NMe_2

Figure 3.44

Another series of arylidene hydrazide compounds were synthesized by Berin Karaman and co-workers[80] from [6-(4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl] acetic acid hydrazide. The newly synthesized compounds were subjected to *in vitro* disease-oriented anti-tumor screening, where compound showed in figure 3.45, is most potent and displayed broad spectrum anti-proliferative activity against all of the tested cell lines with $\log_{10}GI_{50}$ values between −4.41 and −6.44.

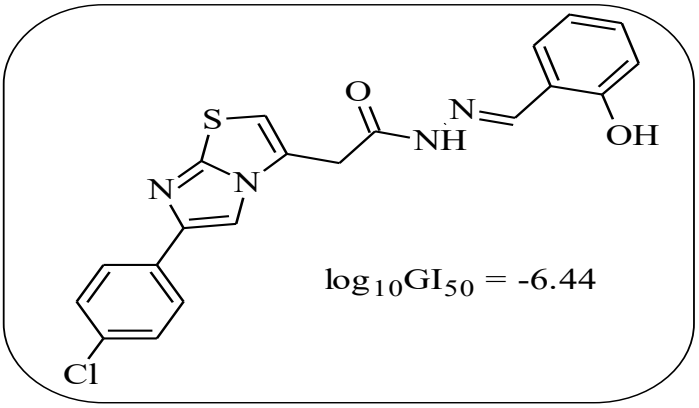
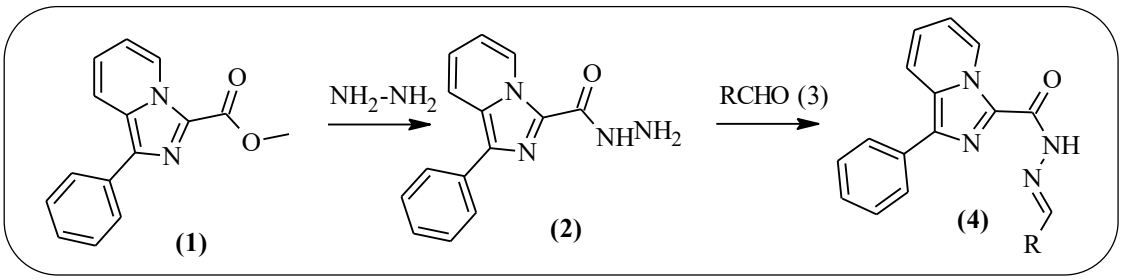


Figure 3.45

All aforesaid evidences demonstrate that, due to the multifarious biological and clinical applications, hydrazide-hydrazones are one of the most popular intermediates in the synthesis of medicinal active scaffolds. Thus, with the aim of obtaining novel hydrazide-hydrazones having a wide spectrum of pharmaceutical applications, we wish report in this chapter the synthesis of a series of imidazo[1,5-*a*]pyridine derived hydrazide-hydrazones together with their use in a series of heterocyclic transformations.

Nowadays hydrazide-hydrazones have attracted a great deal of interest due to their biological activities and their potential applications as pharmacological agents. Moreover, their derivatives are privileged structures and attracted considerable attention in the fields of biological sciences

for assemblage of active molecules. Several derivatives of the hydrazide-hydrazone in combination with hetrocyclic compound exhibited potent biological activities in medicinal chemistry. Out of several heterocyclic ring system imidazo[1,5-*a*]pyridine derived hydrazide-hydrazones has received considerable attention among synthetic chemists and the molecules bearing this structural feature have been found to display a wide range of biological activities. This chapter demonstrates the synthesis of a series of imidazo[1,5-*a*]pyridine derived hydrazide-hydrazones by reacting imidazo[1,5-*a*] pyridine hydrazide with diverse aldehyde. (Scheme 3.2)



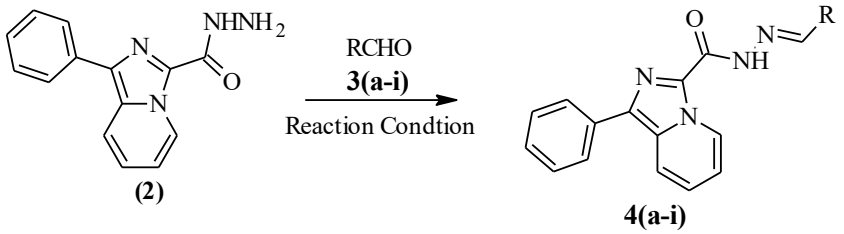
Scheme 3.2

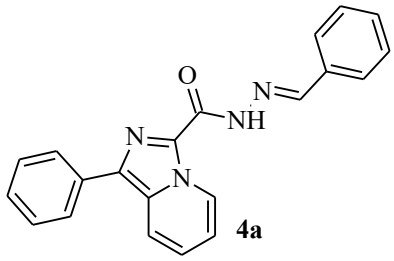
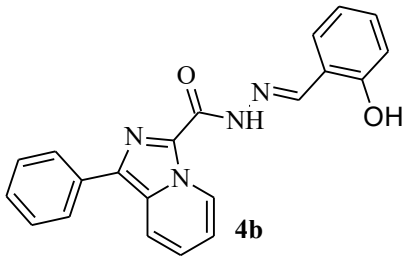
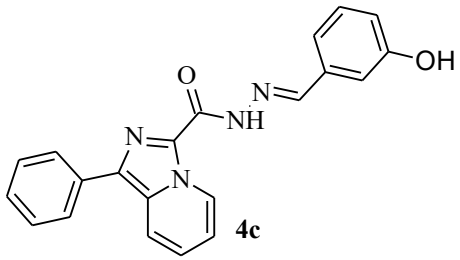
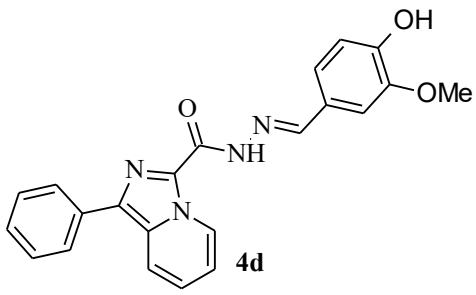
3.4 Ultrasound-Mediated Versus Conventional Synthetic Approach

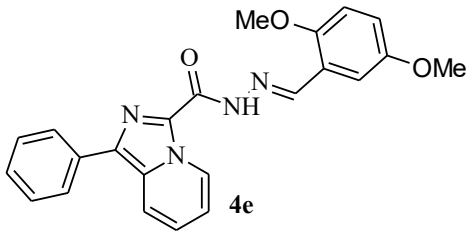
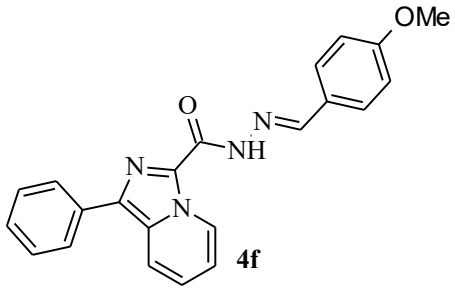
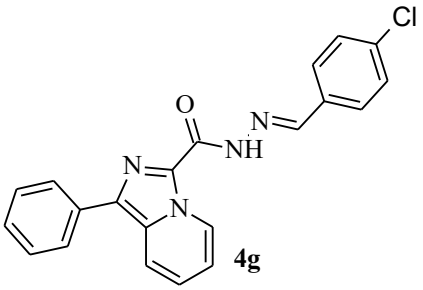
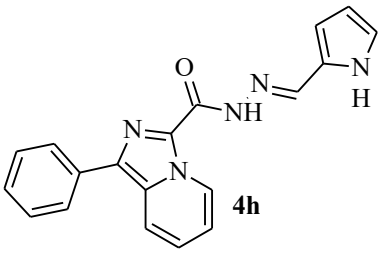
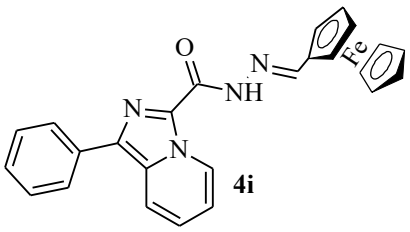
The general synthetic approach for preparation of target hydrazone and their derivatives are depicted in scheme 3.2. In the first step equimolar quantity of ethyl 1-phenylimidazo [1,5-*a*]pyridine-3-carboxylate (1) (2.0 mmol) and hydrazine hydrate (4.0 mmol) in ethanol (5.0ml) are refluxed for 4h. After completion of reaction on TLC, the excess of solvent is evaporated and obtained white colored solid is filtered by diluting with water. The yield of crude product (2) is 95% and chosen as key material for further study without extra purification.

For the sake of obtaining greater transformation of imidazo[1,5-*a*]pyridine derived hydrazide (2) and aldehydes (3) into azomethine with a good yield, nucleophilic addition-elimination reaction is applied. All results are summarized in table 3.1 by reacting diverse aromatic aldehydes (3) to get the final product 1-phenylimidazo[1,5-*a*]pyridine-3- acetohydrazide analogues (4a-i). Finally all synthesized molecules are purified by column chromatography. Purity is identified by TLC (Thin-Layer Chromatography) under UV (Ultra Violet) light exposure and recorded the yields. The total yields of novel hydrazones compounds are ranges within (70-92)% vary among each compound. All compounds are found to be stable in atmospheric condition for extended period of time and are easily soluble in polar solvents such as dimethyl sulfoxide (DMSO) and *N*, *N*-dimethyl formamide (DMF).

Table 3.1: Synthesis of imidazo[1,5-*a*]pyridine derived hydrazide-hydrazones



Sr. No.	RCHO (3)	Product (4)	Time in min Conventional[a]	Time in min Sonication[b]	(%) Yield[c] Conventional[a]	(%) Yield[c] Sonication[b]	MP (^{0}C)
1	Ph	 **4a**	300	30	90	92	178-180
2	2-OHPh	 **4b**	320	30	88	92	200-202
3	3-OHPh	 **4c**	300	35	85	84	250-252
4	4-OH,3-OMePh	 **4d**	350	45	73	72	208-212

5	2,5-diOMePh	 **4e**	400	45	82	85	176-178
6	4-OMePh	 **4f**	300	45	86	88	182-184
7	4-ClPh	 **4g**	300	30	89	90	258-260
8	Pyrrole	 **4h**	320	45	70	75	204-206
9	Ferroene	 **4i**	300	40	75	78	220-222

Reaction Condition: [a]Conventional: (**2**) (1.0 mol), aldehyde (1.1mol), AcOH (2 drops) Ethanol (5ml) were fluxed for 4-5 hrs.

[b]Sonication: (**2**) (1.0 mol), aldehyde (1.1mol), AcOH (2 drops) Ethanol (5ml) were sonicated at 50 °C for 30-45 min.

[c]Yields were recorded after column chromatography

3.4.1 Synthetic Procedure for Preparation of 1-phenylimidazo[1,5-*a*]pyridine-3-carbohydrazide (2):

An oven dried round bottom flask is charged with ethyl 1-phenylimidazo [1,5-a]pyridine-3-carboxylate (**1**) (2.0 mmol) and hydrazine hydrate (4.0 mmol) in ethanol (5.0ml). The resulting mixture is refluxed for 5h. After completion of reaction on TLC, the excess of solvent is evaporated and obtained white colored solid is filtered by diluting with water. On given plenty of water wash product is oven dried at 50°C and characterized. Its recorded spectral data: ^{1}H NMR (400 MHz, DMSO-d^6) δ 9.04 (bs, 1H, -CO-NH), 8.75-8.73 (d, 1H, pyridinyl), 7.97-7.74 (m, 2H), 7.57-7.54 (m, 2H), 7.41-7.37 (m, 2H), 7.34-7.29 (m,2 H), 6.94-6.91 (t, 1H), 4.39 (bs, 2H, NH_2), ^{13}C NMR (100 MHz, DMSO-d^6) δ 161.0, 145.3, 133.9, 128.8, 128.6, 126.9, 117.0, 114.8, 113.3 (Ar-C).

3.4.2 Synthetic Procedure for Preparation of hydrazide-hydrazones:

Equimolar quantities of acid hydrazide and corresponding aromatic aldehydes are dissolved in ethanol (25 ml) in a 100 ml round bottomed flask and few drops of conc. Acetic acid are added. The resulting solution is processed as per conditions given in table 3.1 until clear solution gets ppted. The reaction is monitored throughout by TLC using chloroform-methanol (9:1) as mobile phase. The spots are located under iodine vapour/UV light. After completion of the reaction, excess of ethanol is removed under reduced pressure and the crude product is diluted with ice water and extracted with EtOAc (3 X 10 ml). The organic extracts are dried over anhydrous sodium sulphate and the solvent is concentrated. The crude product purified by column chromatography with hexane:EtOAc (5:1) as eluent. The solid obtained is recrystallized from ethanol.

3.5 Overview and Key Takeaways

The rate of reaction depends on the nucleophilicity of hydrazide itself and the structure of the carbonyl compounds. Due to the carbonyl carbon atom connection with electronic group (substituents on aryl or heteroaryl rings), it increases the carbon atomic charge density, reduced nucleophilic reagent's ability to attack it and slowed down the reaction rate. Further the use of sonication plays crucial role in getting better conversion than conventional method and that improves reaction rate with temperature.

3.9 References

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Spectral Data (3a – 3m)

1) Methyl 1-phenylimidazo[1,5-*a*]pyridine-3-carboxylate (3a)

Yellow solid

R_f 0.45 (n-hexane /EtOAc 8 : 2)

Yield: 92%

MF / FWt: $C_{15}H_{12}N_2O_2$/252

MP: 139–141 ℃

IR (KBr, cm^{-1}): 3044 and 2955 (C-H, str.), 1674 (C=O, str.), 1492, 1473 (C=C), 1385, 1340 (C-N), 1224, 1159 (C-O, str.), 917, 753, 743, 700

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (ddd, *J*= 6.8, 1.2, 0.8 Hz, 1H), 7.78-7.73 (m, 3H), 7.47-7.43 (m, 4H), 7.05 (td, *J*= 7.2, 1.2 Hz, 1H), 3.8 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 153.5, 147.1, 134.3, 130.0, 128.7, 128.3, 128.1, 127.7, 117.4, 114.2, 51.3

Elemental analysis: Theoretical % C, 71.42; % H, 4.79; % N, 11.10,

Observed: % C, 71.40; % H, 4.80; % N, 11.08

MS (ESI): m/e 252 (M^+).

2) Methyl 8-methyl-1-phenylimidazo[1,5-*a*]pyridine-3-carboxylate (3b)

Beige solid

R_f 0.50 (n-hexane /EtOAc 8 : 2)

Yield: 85%

MF / FWt: $C_{16}H_{14}N_2O_2$/266

MP: 148–150 ℃

IR (KBr, cm^{-1}): 2954 and 2892 (C-H, str.), 1680 (C=O, str.), 1521, 1491 (C=C), 1378, 1328 (C-N), 1243, 1221 (C-O, str.), 1152, 784, 754.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (dd, *J*=6.8, 1.2 Hz, 1H), 7.76-7.74 (m, 2H), 7.47-7.41 (m, 3H), 7.26-7.24 (m, 1H), 6.99 (t, *J*=6.8 Hz, 1H), 3.80 (s, 3H), 2.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 152.9, 147.2, 134.4, 130.1, 128.6, 127.4, 127.1, 126.0, 114.2, 51.2, 17.1

Elemental analysis: Theoretical % C, 72.16; % H, 5.30; % N, 10.52

Observed: % C, 72.19; % H, 5.34; % N, 10.49

MS (ESI): m/e 266 (M^+).

3) Ethyl 1-(2-thionyl)imidazo[1,5-*a*]pyridine-3-carboxylate (3c)

Beige solid

R_f 0.46 (n-hexane /EtOAc 8 : 2)

Yield: 90%

MF / FWt: $C_{16}H_{14}N_2O_2$/272

MP: 99–101 ℃

IR (KBr, cm^{-1}): 3034 (C-H, str.), 1694 (C=O, str.), 1496, 1446 (C=C), 1338, 1231, 1228 (C=O), 1157, 1086, 1046 (Ar C-C), 963, 852, 720.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (dd, *J*=7.2, 1.2 Hz, 1H), 8.04 (dd, *J*=3.6, 1.2 Hz, 1H), 7.70-7.68 (m, 1H), 7.47 (dd, *J*=4, 1.2 Hz, 1H), 7.42-7.38 (m, 1H), 7.15-7.13 (m, 1H), 7.00-6.96 (m, 1H), 4.55 (q, *J*=7.2 Hz, 2H), 1.47 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 146.8, 146.6, 136.6, 129.8, 128.5, 128.2, 128.1, 127.3, 117.1, 113.9, 110.8, 60.8, 14.4

Elemental analysis: Theoretical % C, 61.75; % H, 4.44; % N, 10.29

Observed: % C, 61.79; % H, 4.40; % N, 10.25

MS (ESI): m/e 272 (M^+).

4) Ethyl 1-(2-thionyl)-8-methylimidazo[1,5-*a*]pyridine-3-carboxylate (3d)

Off-white powder

R_f 0.51 (n-hexane /EtOAc 8 : 2)

Yield: 83%

MF / FWt: $C_{15}H_{14}N_2O_2S$ /286

MP: 98–100 ℃

IR (KBr, cm^{-1}): 2984, 2969 and 2945 (C-H, str.), 1683 (C=O, str.), 1458, 1442 (C=C), 1394, 1328, 1271 (C-O), 1154, 1068, 1001, 952, 928, 807, 746, 697.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (d, *J*=6.8 Hz,1H), 7.99 (dd, *J*=3.6, 1.2 Hz, 1H), 7.47 (dd, 1H), 7.21 (d, *J*=6.8 Hz, 1H), 7.15 (dd, *J*=4, 1.2 Hz,1H), 6.92 (t, *J*=6.8 Hz, 1H), 4.50 (q, *J*=7.2 Hz, 2H), 2.67 (s, 3H), 1.46 (t, *J*=7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 147.1, 146.1, 136.8, 129.7, 127.9, 127.2, 127.1, 127.0, 126.1, 114.0, 60.6, 16.9, 14.3

Elemental analysis: Theoretical % C, 62.92; % H, 4.93; % N, 9.78

Observed: % C, 62.95; % H, 5.00; % N, 9. 80

MS (ESI): m/e 286 (M^+).

5) Ethyl 1-methylimidazo[1,5-*a*]pyridine-3-carboxylate (3e)

Off-white powder

R_f 0.41 (n-hexane /EtOAc 8 : 2)

Yield: 87%

MF / FWt: $C_{11}H_{12}N_2O_2$ /204

MP: 119–120 ℃

IR (KBr, cm^{-1}): 2979, 2951 and 2928 (C-H, str.), 1692 (C=O, str.), 1497, 1459 (C=C), 1385, 1267 (C-O), 1153, 1060, 951, 879, 756, 704.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (d, *J*=6.8 Hz, 1H), 7.57 (d, 1H), 7.34-7.30 (m, 1H), 6.93 (t, *J*=6.8 Hz, 1H), 4.41 (q, *J*=7.2 Hz, 2H), 2.67 (s, 3H), 1.41 (t, *J*=7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.7, 146.8, 127.8, 127.4, 116.5, 113.5, 112.5, 60.2, 16.6, 14.4

Elemental analysis: Theoretical % C, 64.69; % H, 5.93; % N, 13.72

Observed: % C, 64.70; % H, 5.90; % N, 13.70

MS (ESI): m/e 204 (M^+).

6) Ethyl 1,8-dimethylimidazo[1,5-*a*]pyridine-3-carboxylate (3f)

Off-white powder

R_f 0.41 (n-hexane /EtOAc 8 : 2)

Yield: 70%

MF / FWt: $C_{14}H_{14}N_2O_2$/218

MP: 110–112 ℃

IR (KBr, cm^{-1}): 2994, 2980, 2957 and 2947 (C-H), 1718, 1693 (C=O, str.), 1546 (C=N), 1484, 1452 (C=C), 1393, 1345, 1291 (C-O), 1140, 1092, 1058, 1021, 748, 710.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (d, *J*=6.8 Hz, 1H), 7.18 (dt, *J*=7.2, 1.2 Hz,1H), 6.89 (t, *J*=7.2 Hz, 1H), 4.45 (q, *J*=7.2 Hz, 2H), 2.74 (s, 3H), 2.62 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 152.1, 147.0, 128.6, 126.4, 125.7, 113.5, 112.9, 60.2, 17.0, 16.7, 14.4.

Elemental analysis: Theoretical % C, 66.04; % H, 6.47; % N, 12.84

Observed: % C, 66.00; % H, 6.50; % N, 12.89

MS (ESI): m/e 218 (M^+).

7) Ethyl 1-cyclopropylimidazo[1,5-*a*]pyridine-3-carboxylate (3g)

Pale yellow solid

R_f 0.42 (n-hexane /EtOAc 8 : 2)

Yield: 88%

MF / FWt: $C_{13}H_{14}N_2O_2$/230

MP: 98–100 ℃

IR (KBr, cm^{-1}): 3082, 2984 and 2955 (C-H, str.), 1675 (C=O, str.), 1536 (C=N), 1413 (C=C), 1341 (C-O), 1088, 1055, 768.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (ddd, *J* = 7.2, 1.2, 0.8 Hz, 1H), 7.56 (dd, 1H), 7.36-7.32 (m, 1H), 6.94 (td, *J*=7.2, 1.2 Hz, 1H), 4.48 (q, 2H), 2.87 (quin, 1H), 1.46 (t, *J*=7.2 Hz, 3H), 1.22 (dt, 2H), 1.10 (dt, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 158.1, 147.1, 127.9, 127.7, 116.4, 113.2, 60.2, 14.5, 9.

Elemental analysis: Theoretical % C, 67.81; % H, 6.13; % N, 12.17

Observed: % C, 67.85; % H, 6.10; % N, 12.15

MS (ESI): m/e 230 (M^+).

8) Ethyl 1-cyclopropyl-8-methylimidazo[1,5-*a*]pyridine-3-carboxylate (3h)

Off-white powder

R_f 0.38 (n-hexane /EtOAc 8 : 2)

Yield: 80%

MF / FWt: $C_{14}H_{16}N_2O_2$/244

MP: 105–108 ℃

IR (KBr, cm^{-1}): 2999, 2976 and 2934 (C-H, str.), 1676 (C=O, str.), 1559 (C=N), 1412 (C=C), 1381, 1338, 1236 (C-O), 1185, 1086, 901, 779, 756.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15-9.13 (m, 1H), 7.11 (dd, 1H), 6.82 (t, *J*=6.8 Hz, 1H), 4.47 (q, *J*=7.2 Hz, 2H), 2.84 (quin, 1H), 2.54 (s, 3H), 1.46 (t, *J*=7.2 Hz, 3H, -CH_3), 1.30-1.19 (m, 3H), 1.07-1.04 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 157.4, 147.4, 126.4, 125.6, 113.1, 60.1, 16.9, 14.5, 10.1.

Elemental analysis: Theoretical % C, 68.83; % H, 6.60; % N, 11.47

Observed: % C, 68.80; % H, 6.65; % N, 11.50

MS (ESI): m/e 244 (M^+).

9) Methyl 1-tert-butylimidazo[1,5-*a*]pyridine-3-carboxylate (3i)

Pale yellow solid

R_f 0.32 (n-hexane /EtOAc 8 : 2)

Yield: 78%

MF / FWt: $C_{13}H_{16}N_2O_2$/232

MP: 126–128 ℃

IR (KBr, cm^{-1}): 2984 and 2946 (C-H, str.), 1683 (C=O, str.), 1516, 1474 (C=C), 1344, 1250 (C-O), 1140, 1052, 1029, 914, 885, 750, 747, 722.

^1H NMR (400 MHz, $CDCl_3$): δ 9.32 (ddd, *J*=7.2, 1.2, 0.8 Hz), 7.71-7.68 (m, 1H), 7.38-7.34 (m, 1H), 6.98 (td, *J*=6.8, 1.2 Hz, 1H), 3.99 (s, 3H), 1.53 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 161.5, 145.4, 128.2, 121.1, 117.2, 113.7, 112.1, 51.1, 34.6, 29.5.

Elemental analysis: Theoretical % C, 67.22; % H, 6.94; % N, 12.06

Observed: % C, 67.20; % H, 7.00; % N, 12.10

MS (ESI): m/e 232 (M^+).

10) Methyl 1-tert-butyl-8-methylimidazo[1,5-*a*]pyridine-3-carboxylate (3j)

Beige solid

R_f 0.32 (n-hexane /EtOAc 8 : 2)

Yield: 72%

MF / FWt: $C_{14}H_{18}N_2O_2$/246

MP: 112–114 ℃

IR (KBr, cm^{-1}): 2952 and 2929 (C-H, str.), 1759, 1714 (C=O, str.), 1651 (C=N), 1474, 1392 (C=C), 1343, 1237, 1185 (C-O), 1098, 1074, 773, 747.

^1H NMR (400 MHz, $CDCl_3$): δ 9.16 (dd, *J*=6.8, 1.2 Hz, 1H), 7.14-7.12 (m, 1H), 6.86 (t, *J*=6.8 Hz, 1H), 3.98 (s, 3H), 2.63 (s, 3H), 1.53 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 161.7, 145.5, 127.2, 125.9, 113.6, 112.3, 52.9, 51.0, 34.7, 29.5, 26.1.

Elemental analysis: Theoretical % C, 68.27; % H, 7.37; % N, 11.37

Observed: % C, 68.30; % H, 7.40; % N, 11.40

MS (ESI): m/e 246 (M^+).

11) Ethyl 1-(2,4-difluorophenyl)imidazo[1,5-*a*]pyridine-3-carboxylate (3k)

Beige solid

R_f 0.32 (n-hexane /EtOAc 8 : 2)

Yield: 83%

MF / FWt: $C_{16}H_{12}F_2N_2O_2$/302

MP: 177 °C

IR (KBr, cm^{-1}): 2978 and 2939 (C-H, str.), 1685 (C=O, str.), 1497, 1393 (C=C), 1337, 1217 (C-O), 1169, 1135, 1043, 1008, 768, 753.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (d, *J*=7.2 Hz,1H), 7.77 (d, *J*=6.8 Hz, 1H), 7.64-7.52 (m, 1H), 7.49-7.42 (m, 1H), 7.14-7.07 (m, 1H), 7.01-9.98 (m, 1H), 6.93-6.88 (m, 1H), 4.31 (q, *J*=7.2 Hz, 2H), 1.26 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 155.4, 145.4, 124.4, 123.6, 111.1, 60.8, 14.4.

Elemental analysis: Theoretical % C, 63.57; % H, 4.00; % N, 9.27

Observed: % C, 63.60; % H, 4.05; % N, 9.30

MS (ESI): m/e 302 (M^+).

12) 1,3-diphenylimidazo[1,5-*a*]pyridine[9] (3l)

Yellow solid

R_f 0.35 (n-hexane /EtOAc 8 : 2)

Yield: 85%

MF / FWt: $C_{19}H_{14}N_2$/270

MP: 112-114 °C

IR (KBr, cm^{-1}): 2978 and 2939 (C-H str.), 1655 (C=N), 1497 (C=C), 1393, 1337, 1217 (C-N), 1169, 1135, 1043, 1008, 768, 753.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H), 7.89 (d, *J* = 5.5 Hz, 2H), 7.80 (s, 5H), 7.55 (d, *J* = 5.5 Hz, 2H), 7.50 (d, *J*= 5.5 Hz, 2H), 7.29 (s, 1H), 6. 80 (s, 1H), 6.52 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 134.5, 132.0, 130.1, 129.0, 128.6, 128.3, 128.2, 127.5, 126.3, 126.1, 121.4, 120.0, 119.4, 113.2.

Elemental analysis: Theoretical % C, 84.42; % H, 5.22; % N, 10.36

Observed: % C, 84.49; % H, 5.20; % N, 10.40

MS (ESI): m/e 270 (M^+).

13) 1-Methyl-3-phenylimidazo[1,5-*a*]pyridine[41] (3m)

Pale yellow oil

R_f 0.40 (n-hexane /EtOAc 8 : 2)

Yield: 63%

MF / FWt: $C_{14}H_{12}N_2$/208

IR (KBr, cm^{-1}): 3024 and 2982 (C-H, str.), 1648 (C=N), 1495 (C=C), 1370, 1256 (C-N), 1078, 943, 741, 719, 692.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28-8.14 (m, 2H), 7.95-7.89 (m, 2H), 7.37-7.33 (m, 2H), 7.26-7.22 (m, 1H), 6.97 (d, *J*=6.8 Hz, 1H), 6.72 (t, *J*=6.8 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 143.7, 133.7, 128.8, 127.9, 126.4, 126.0, 124.6, 124.2, 112.7, 109.6, 17.1.

Elemental analysis: Theoretical % C, 80.74; % H, 5.81; % N, 13.45

Observed: % C, 80.75; % H, 5.79; % N, 13.50

MS (ESI): m/e 208 (M^+).

Spectra of synthesized compounds (Representative)

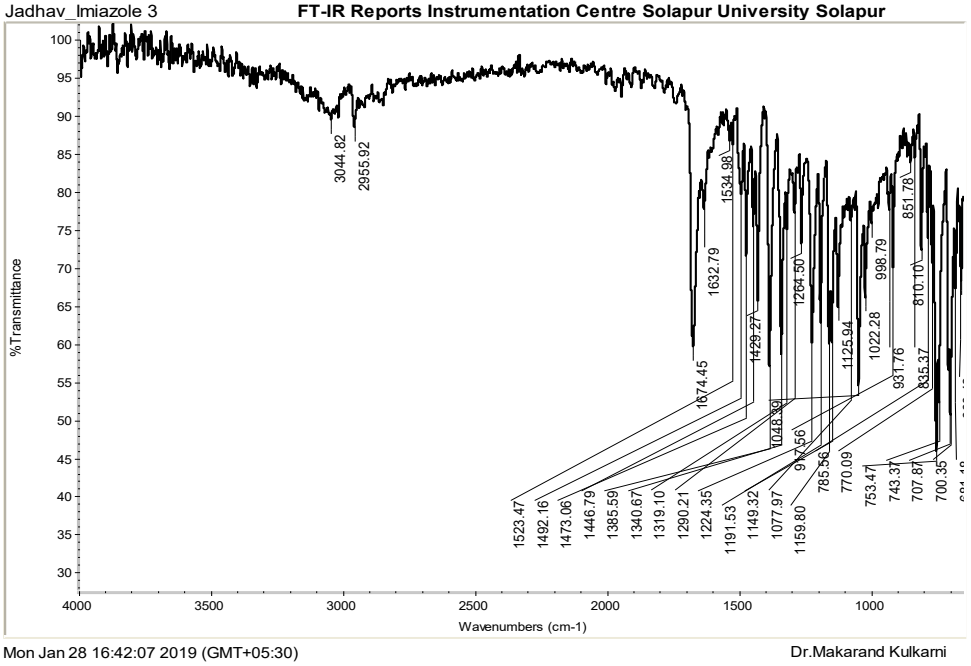

Figure 2.1: IR Spectrum of Methyl 1-phenylimidazo[1,5-a]pyridine-3-carboxylate (3a)

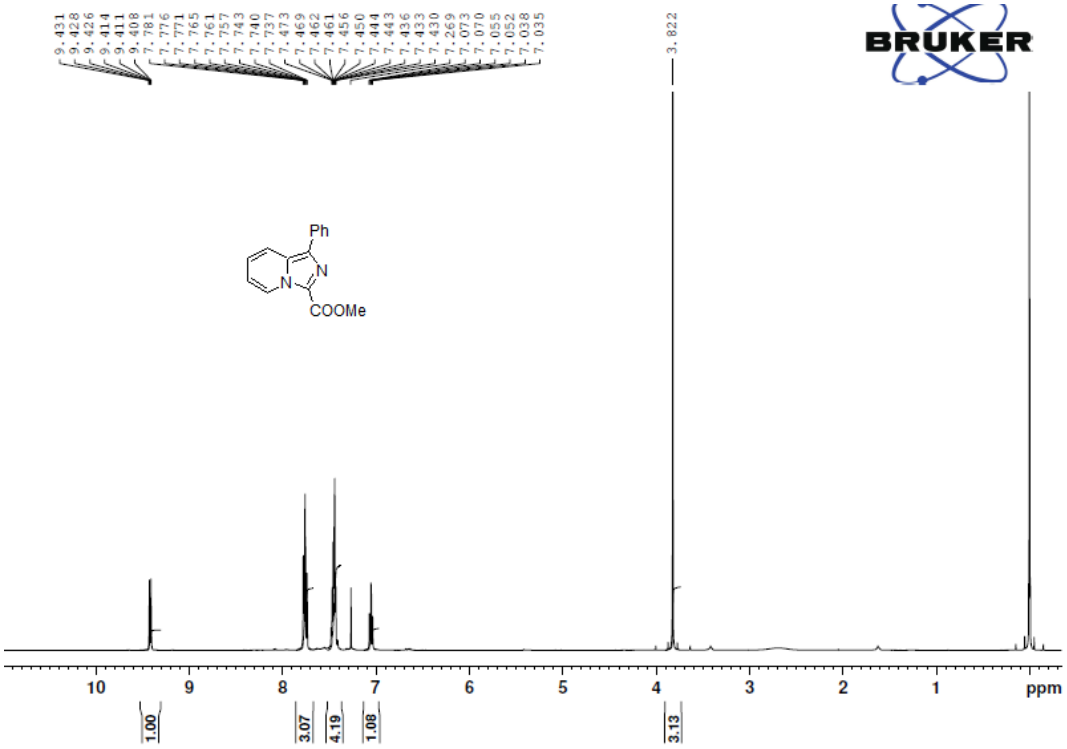

Figure 2.2: ^{1}H NMR spectrum of Methyl 1-phenylimidazo[1,5-a]pyridine-3-carboxylate (3a)

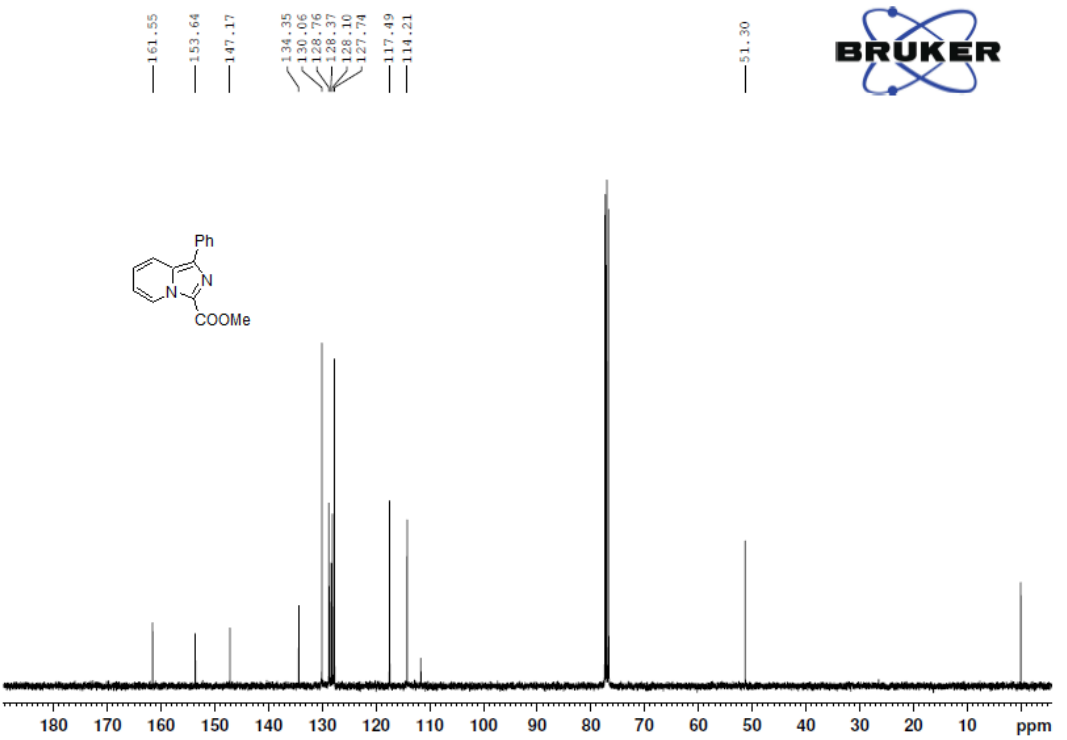

Figure 2.3: ^{13}C NMR spectrum of Methyl 1-phenylimidazo[1,5-a]pyridine-3-carboxylate (3a)

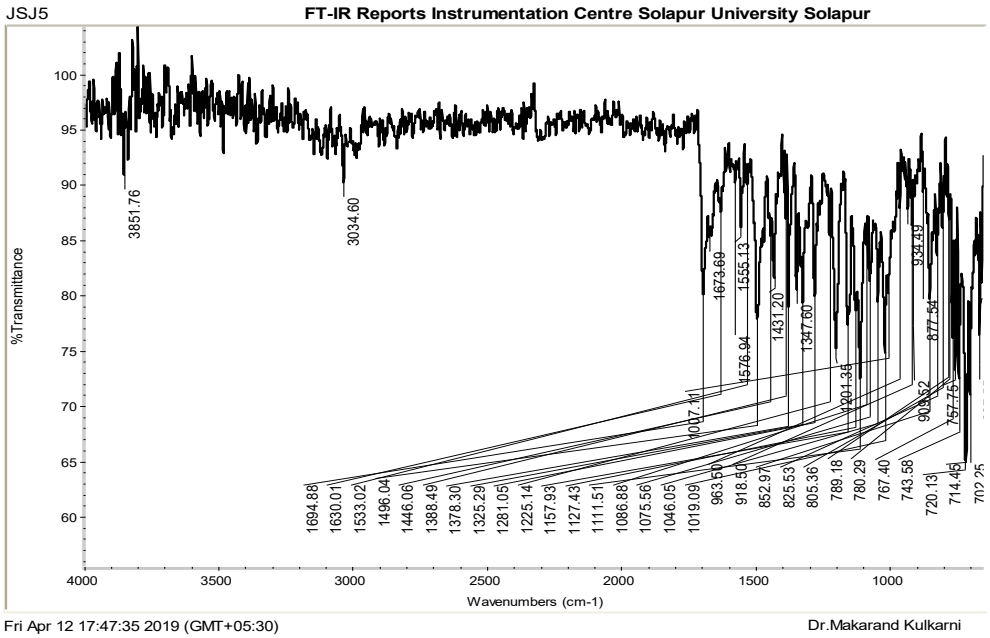

Figure 2.4: IR spectrum of Ethyl 1-(2-thionyl)imidazo[1,5-a]pyridine-3-carboxylate (3c)

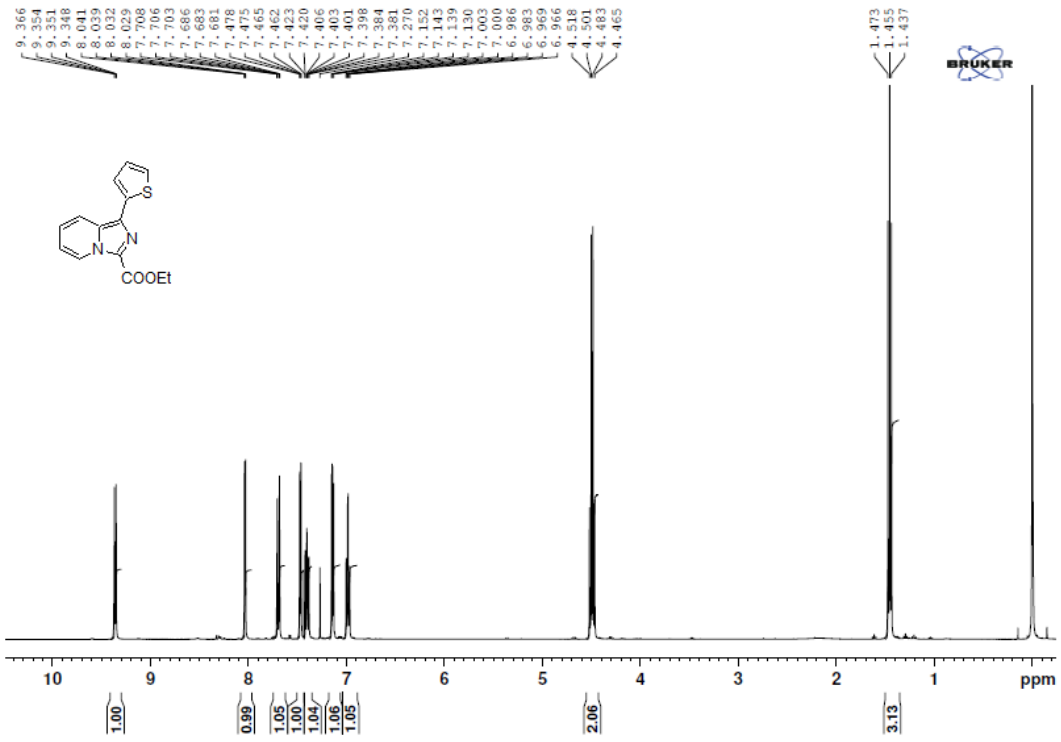

Figure 2.5: ^{1}H NMR spectrum of Ethyl 1-(2-thionyl)imidazo[1,5-a]pyridine-3-carboxylate (3c)

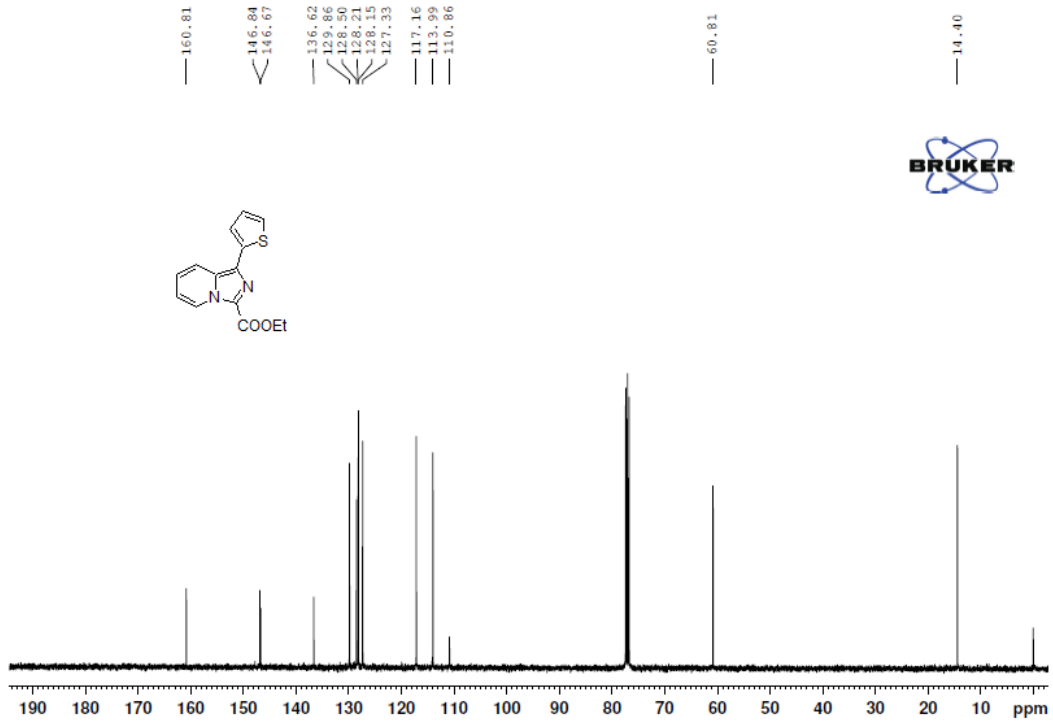

Figure 2.6: ^{13}C NMR spectrum of Ethyl 1-(2-thionyl)imidazo[1,5-a]pyridine-3-carboxylate (3c)

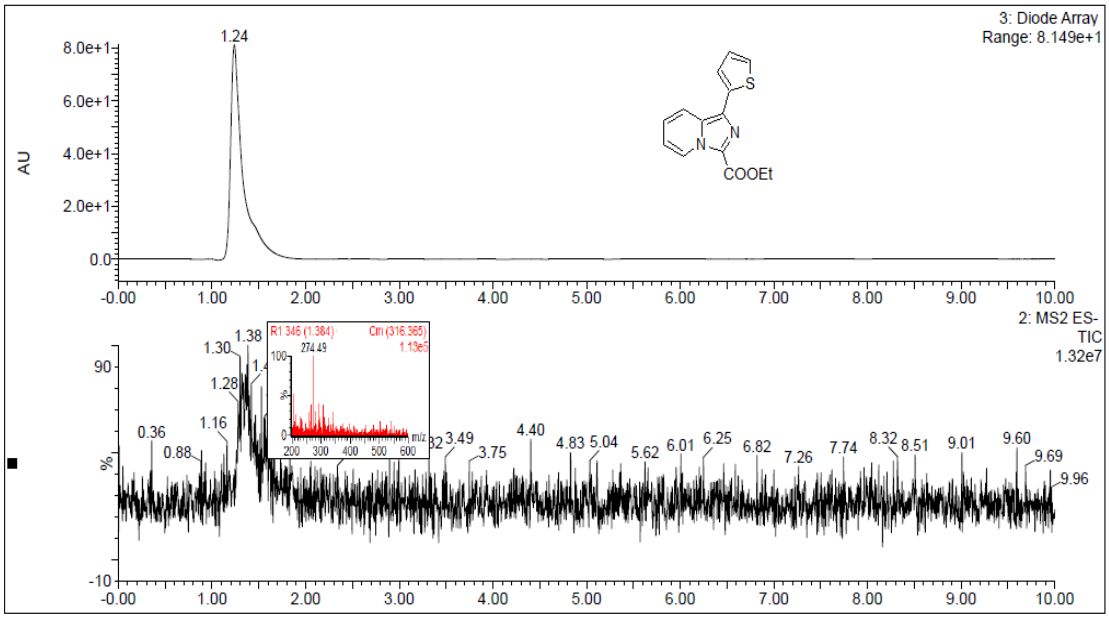

Figure 2.7: Mass spectrum of Ethyl 1-(2-thionyl)imidazo[1,5-a]pyridine-3-carboxylate (3c)

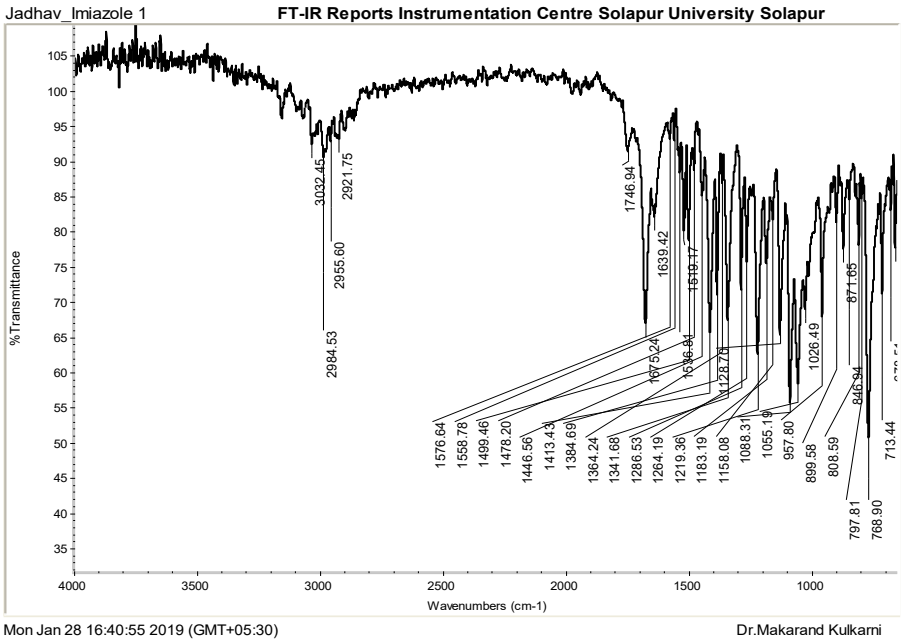

Figure 2.8: IR spectrum of Ethyl 1-cyclopropylimidazo[1,5-a]pyridine-3-carboxylate (3g)

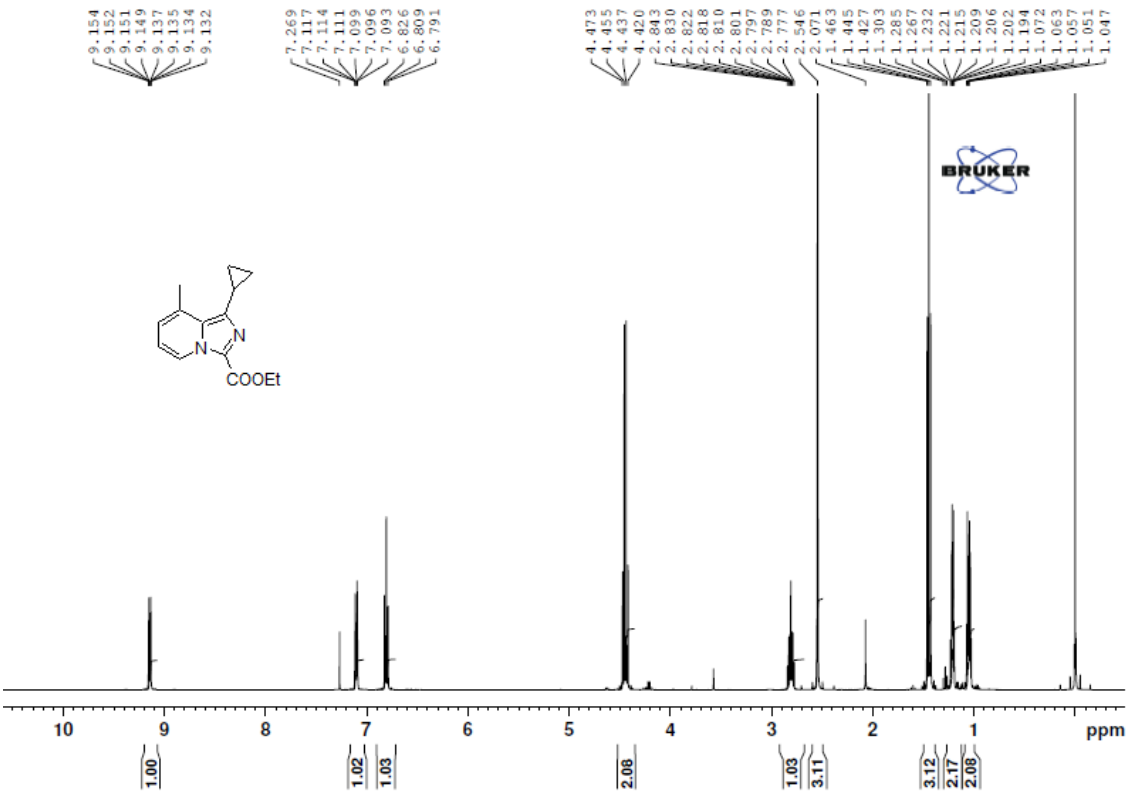

Figure 2.9: ^{1}H NMR spectrum of Ethyl 1-cyclopropylimidazo[1,5-a]pyridine-3-carboxylate (3g)

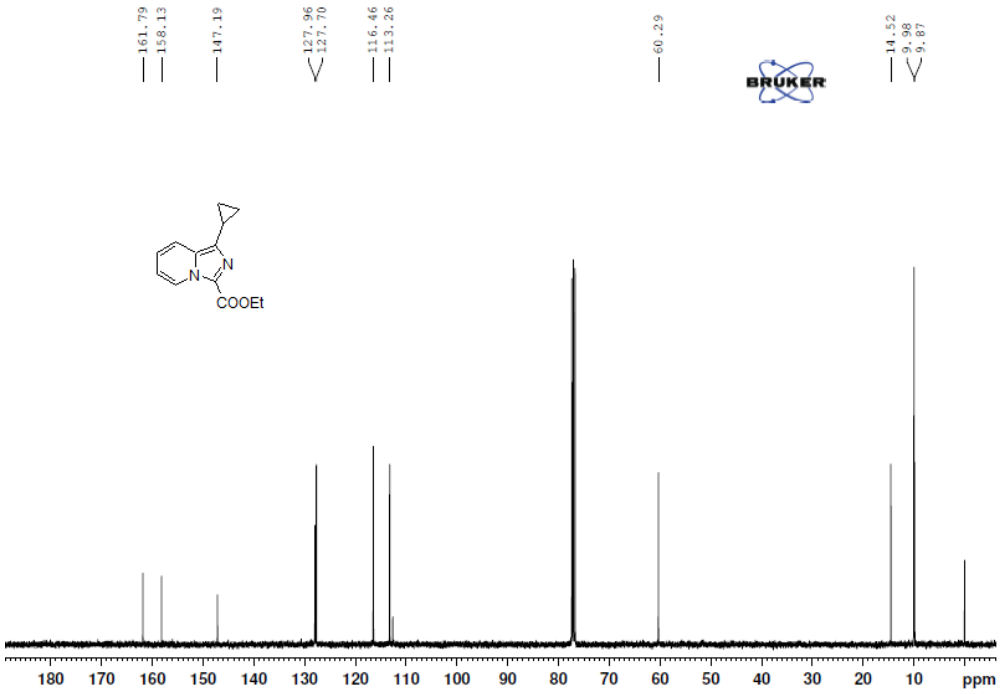

Figure 2.10: ^{13}C NMR spectrum of Ethyl 1-cyclopropylimidazo[1,5-a]pyridine-3-carboxylate (3g)

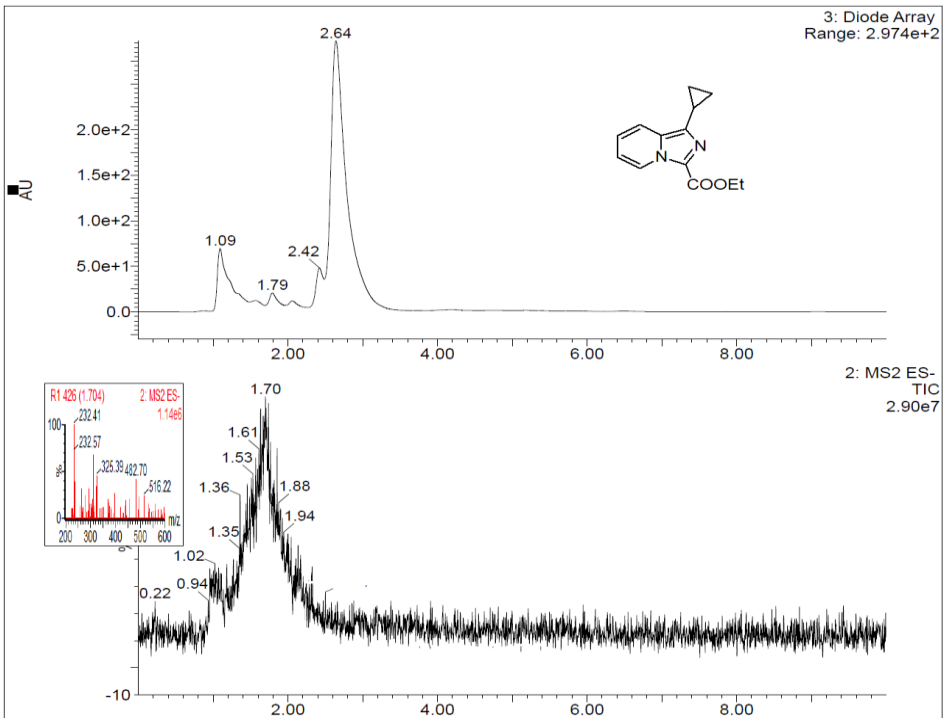

Figure 2.11: Mass spectrum of Ethyl 1-cyclopropylimidazo[1,5-a]pyridine-3-carboxylate (3g)

Spectral Data (4a – 3i)

1] 1-phenyl-*N*'-[(*E*)-phenylmethylidene]imidazo[1,5-*a*]pyridine-3-carbohydrazide (4a):

Yield: 92%

MF / FWt: $C_{21}H_{16}N_4O$/340.37

MP: 178-180 °C

IR (KBr, cm^{-1}): 3109.6, 2940.9, 1604.8, 1591.6, 1436.2, 1212.2, 1185.3, 1080.9, 976.6.

^1H NMR (400 MHz, DMSO-d^6): δ 11.76-11.45 (bd, 1H, -CO-NH), 8.79 (bd, 1H, pyridinyl), 7.93 (m, 1H), 7.79 (m, 2H), 7.65-7.63 (m, 2H), 7.40-7.36 (m, 7H), 6.99 (m, 1H).

^{13}C NMR (100MHz, DMSO-d^6): δ 160.4, 148.2, 145.5, 134.3, 128.9, 127.6, 117.1, 100.9, 95.5 (Ar-C).

MS (ESI): m/e 340 (M^+).

2] *N*'-[(*E*)-(2-hydroxyphenyl)methylidene]-1-phenylimidazo[1,5-*a*]pyridine-3-carbohydrazide (4b):

Yield: 92%

MF / FWt: $C_{21}H_{16}N_4O_2$/356.37

MP: 200-202 °C

IR (KBr, cm^{-1}): 3375.9, 3061.9, 3011.7, 2948.3, 1628.5, 1605.1, 1464.8, 1308.3, 1126.3, 1105.3, 1025.0.

^1H NMR (400 MHz, DMSO-d^6): δ 11.66 (bs, 1H, -CO-NH), 11.18 (bs, 1H, -OH), 8.84 (s, 1H, pyridinyl), 8.17 (s, 1H), 7.81-7.80 (m, 2H), 7.65-7.63 (m, 1H), 7.41-7.37 (m, 5H), 7.21 (s, 1H), 6.86 (m, 1H), 682 (m, 2H).

^{13}C NMR (100MHz, DMSO-d^6): δ 157.9, 148.7, 146.9, 145.9, 133.6, 131.7, 130.0, 129.0, 128.7, 127.7, 119.5, 118.7, 117.2, 1163.7, 114.2, 113.9 (Ar-C).

MS (ESI): m/e 356 (M^+).

3] *N*'-[(*E*)-(3-hydroxyphenyl)methylidene]-1-phenylimidazo[1,5-*a*]pyridine-3-carbohydrazide (4c):

Yield: 84%

MF / FWt: $C_{21}H_{16}N_4O_2$/356.37

MP: 250-252 ℃

IR (KBr, cm^{-1}): 3350.7, 3046.4, 2983.2, 1638.5, 1606.5, 1576.7, 1390.8, 1281.7, 1219.8, 1177.8, 1066.0, 1020.0.

^{1}H NMR (400 MHz, DMSO-d^6): δ 11.67-11.25 (bd, 1H, -CO-NH), 9.35 (m, 1H, pyridinyl), 8.81 (m, 1H), 7.96-7.74 (m, 3H), 7.63-7.60 (m, 1H), 7.39-7.28 (m, 4H), 6.97 (m, 2H), 6.92 (m, 2H), 6.76 (m, 1H).

^{13}C NMR (100MHz, DMSO-d^6): δ 157.8, 148.3, 145.2, 135.3, 133.8, 128.8, 127.4, 127.0, 119.2, 117.1, 114.6, 113.8, 113.4 (Ar-C).

MS (ESI): m/e 356 (M^+).

4] *N*'-[(1*E*)-(3-hydroxy-4-methoxyphenyl)methylene]-1-phenylimidazo[1,5-*a*] pyridine-3-carbohydrazide (4d):

Yield: 72%

MF / FWt: $C_{22}H_{18}N_4O_3$/386.40

MP: 208-212 ℃

IR (KBr, cm^{-1}): 3402.6, 3012.7, 2921.2, 1614.8, 1643.8, 1602.8, 1446.2, 1304.6, 1185.3, 1095.8, 1011.1, 980.3

^{1}H NMR (400 MHz, DMSO-d^6): δ 11.85-11.60 (bd, 1H, -CO-NH), 9.59-9.40 (m, 1H, pyridinyl), 8.73-8.58 (m, 1H), 7.86-7.84 (m, 2H), 7.75-7.73 (m, 1H), 7.47-7.33 (m, 4H), 6.07 (m, 1H), 6.84 (bs, 1H), 6.63-6.53 (m, 1H), 3.84-3.55 (bd, 3H, OMe).

^{13}C NMR (100MHz, DMSO-d^6): δ 158.8, 147.3, 145.1, 135.8, 133.4, 129.0, 127.1, 127.0, 119.0, 117.4, 114.8, 114.0, 113.4 (Ar-C), 56.7 (-OMe).

MS (ESI): m/e 380 (M^+).

5] *N*'-[(*E*)-(2,5-dimethoxyphenyl)methylidene]-1-phenylimidazo[1,5-*a*]pyridine-3-carbohydrazide (4e):

Yield: 85%

MF / FWt: $C_{23}H_{20}N_4O_3$/400.42

MP: 176-178 ℃

IR (KBr, cm^{-1}): 3000.1, 2910.5, 1621.0, 1606.5, 1435.0, 1321.9, 1178.5, 1126.3, 1010.1, 898.3.

^{1}H NMR (400 MHz, DMSO-d^6): δ 12.08-11.59 (bd, 1H, -CO-NH), 8.90-877 (d, 1H, pyridinyl), 8.33-8.22 (d, 1H), 7.78 (m, 4H), 7.59 (m, 1H), 7.45-7.19 (m, 5H), 6.86-6.73 (m, 2H), 3.74-3.70 (s, 6H).

^{13}C NMR (100MHz, DMSO-d^6): δ 153.6, 144.3, 141.2, 129.8, 129.2, 122.6, 115.6, 113.7, 109.1, 100.0 (Ar-C), 56.7 (-OMe).

MS (ESI): m/e 400 (M^+).

6] *N*'-[(*E*)-(4-methoxyphenyl)methylidene]-1-phenylimidazo[1,5-*a*]pyridine-3-carbohydrazide (4f):

Yield: 88%

MF / FWt: $C_{22}H_{18}N_4O_2$/370.40

MP: 182-184 ℃

IR (KBr, cm^{-1}): 3011.3, 2822.2, 2835.0, 1664.8, 1625.1, 1561.1, 1421.3, 1107.7, 1080.7, 920.7.

^{1}H NMR (400 MHz, DMSO-d^6): δ 11.68-11.36 (bs, 1H, -CO-NH), 8.77-8.62 (s, 1H, pyridinyl), 7.91 (s, 1H), 7.80 (m, 2H), 7.64-7.62 (m, 2H), 7.37 (m, 4H), 6.98-6.90 (m, 3H), 6.65 (s, 1H), 3.77 (s, 3H, -OMe).

^{13}C NMR (100MHz, DMSO-d^6): δ 161.3, 157.2, 148.1, 145.6, 133.7, 117.1, 114.4, 113.9 (Ar-C), 55.5 (-OMe).

MS (ESI): m/e 370 (M^+).

7] *N*'-[(*E*)-(4-Chlorophenyl)methylidene]-1-phenylimidazo[1,5-*a*]pyridine-3-carbohydrazide (4g):

Yield: 90%

MF / FWt: $C_{21}H_{15}ClN_4O$/374.84

MP: 258-260 ℃

IR (KBr, cm^{-1}): 3051.3, 2972.2, 2885.0, 1654.8, 1625.1, 1441.1, 1331.3, 1207.7, 1104.5, 1080.7, 920.7, 887.1.

^{1}H NMR (400 MHz, DMSO-d^6): δ 11.81-11.57 (bd, 1H, -CO-NH), 8.76 (s, 1H, pyridinyl), 8.11 (m, 1H), 7.95-7.78 (m, 4H), 7.66-7.15 (m, 6H), 7.00 (s, 2H).

^{13}C NMR (100MHz, DMSO-d^6): δ 145.7, 144.1, 128.8, 127.0, 122.5, 117.1, 108.1 (Ar-C).

MS (ESI): m/e 375 (M^+).

8] **1-phenyl-*N*'-[(*E*)-1 *H* -pyrrol-2-ylmethylidene]imidazo[1,5-*a*]pyridine-3-Carbohydrazide (4h):**

Yield: 75%

MF / FWt: $C_{19}H_{15}N_5O$/329.35

MP: 204-206 ℃

IR (KBr, cm^{-1}): 3254.0, 3063.9, 2922.2, 1617.7, 1442.5, 1226.2, 969.1, 756.6.

^{1}H NMR (400 MHz, DMSO-d^6): δ 11.44 (bs, 1H, -CO-NH), 11.24 (bs, 1H, -NH), 8.75-8.73 (d, 1H, pyridinyl), 7.82-7.80 (m, 3H), 7.63-7.61 (d, 1H), 7.40-7.34 (m, 4H), 7.00-6.99 (t, 1H), 6.85 (s, 1H, pyrrole), 6.37 (s, 1H, pyrrole), 6.07 (s, 1H, pyrrole).

^{13}C NMR (100MHz, DMSO-d^6): δ 157.5, 146.3, 145.8, 140.5, 133.5, 128.9, 128.6, 127.5, 127.2, 126.9, 122.9, 117.0, 114.6, 113.8, 109.6 (Ar-C).

MS (ESI): m/e 329 (M^+).

9] 1-phenyl-*N*'-[(*E*)-1*H*-ferrocen-2-ylmethylidene]imidazo[1,5-*a*]pyridine-3-carbohydrazide (4i):

Yield: 78%

MF / FWt: $C_{25}H_{20}N_4OFe$/449

MP: 220-222 °C

IR (KBr, cm^{-1}): 3261.4, 2937.1, 2885.2, 1682.9, 1621.4, 1591.6, 1438.0, 1222.6, 920.7, 756.6.

^1H NMR (400 MHz, DMSO-d^6): δ 11.64-11.21 (bd, 1H, -CO-NH), 8.78-8.48 (bd, 1H), 7.74 (m, 4H), 7.41-7.39 (m, 4H), 7.00 (s, 1H), 4.60 (s, 2H, ferrocene), 4.38 (s, 2H, ferrocene), 4.14 (s, 5H, ferrocene).

^{13}C NMR (100MHz, DMSO-d^6): δ 164.2, 156.4, 153.8, 149.6, 139.6, 129.0, 128.6, 126.9, 117.0, 114.4 (Ar-C), 70.8, 69.4, 68.1 (ferrocene).

MS (ESI): m/e 449 (M^+).

Spectra of synthesized compounds (Representative)

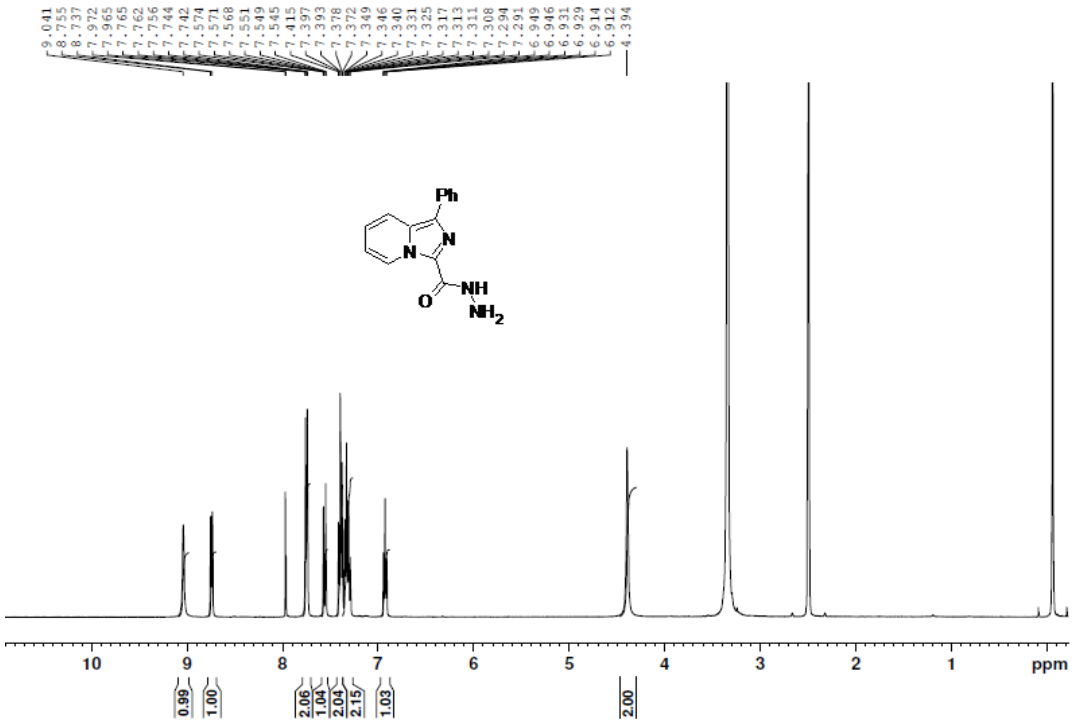

Figure 3.46: ^1H NMR Spectrum of 1-phenylimidazo[1,5-*a*]pyridine-3-carbohydrazide (2)

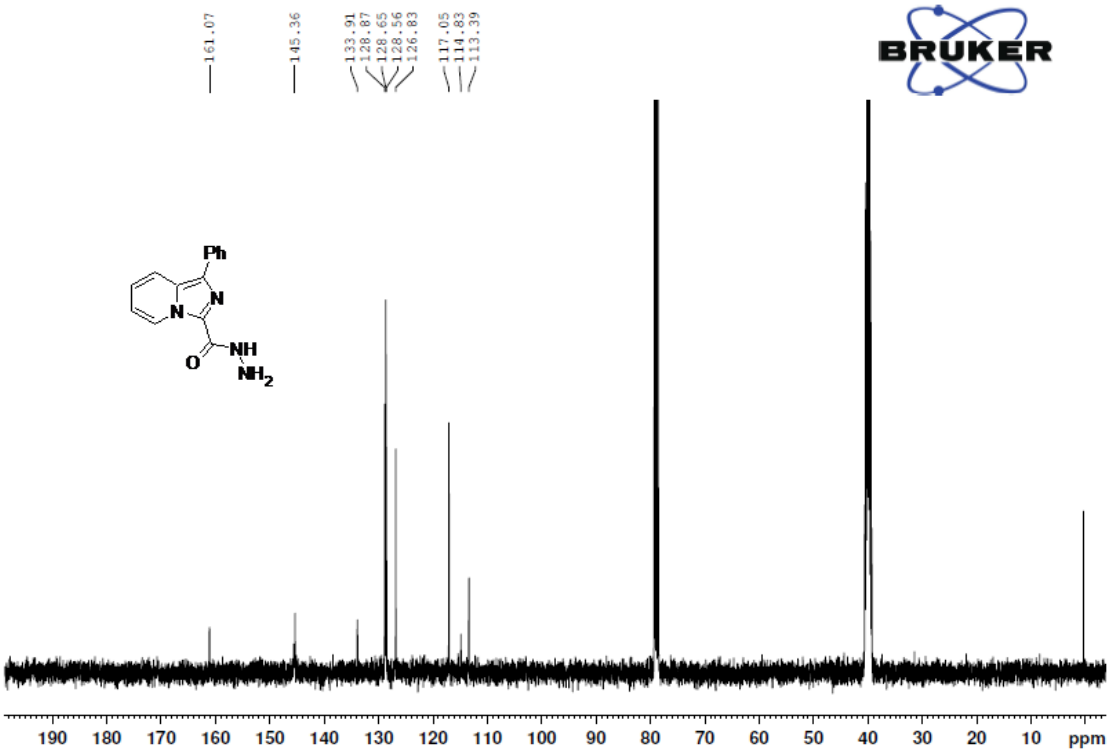

Figure 3.47: ^{13}C NMR Spectrum of 1-phenylimidazo[1,5-*a*]pyridine-3-carbohydrazide (2)

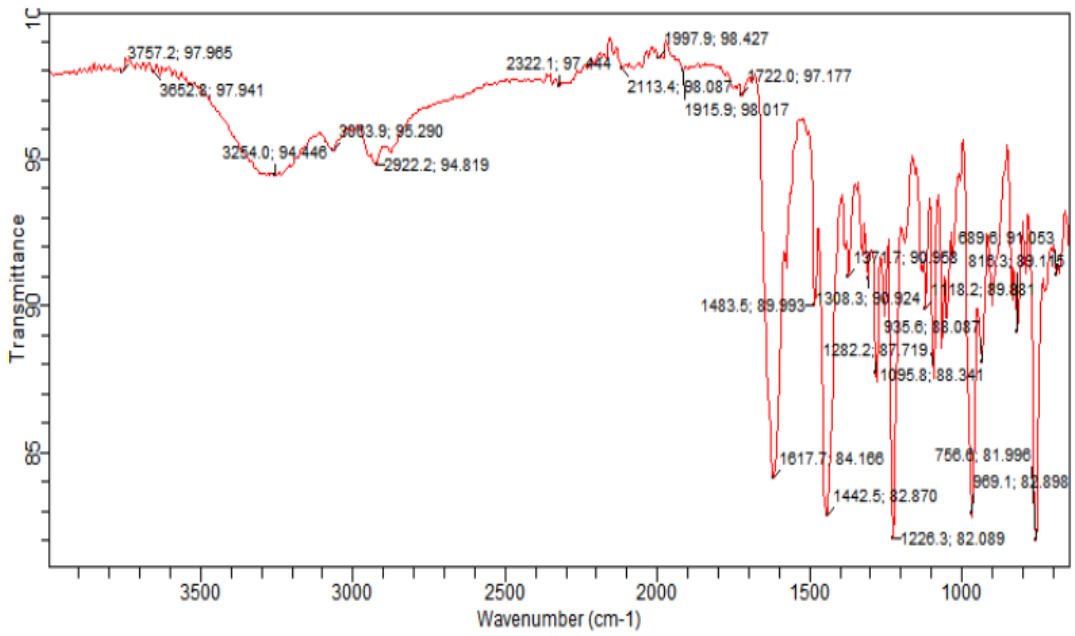

Figure 3.48: IR Spectrum of 1-phenyl-*N*'-[(*E*)-1*H*-pyrrol-2-ylmethylidene]imidazo [1,5-*a*]pyridine-3-Carbohydrazide (4h)

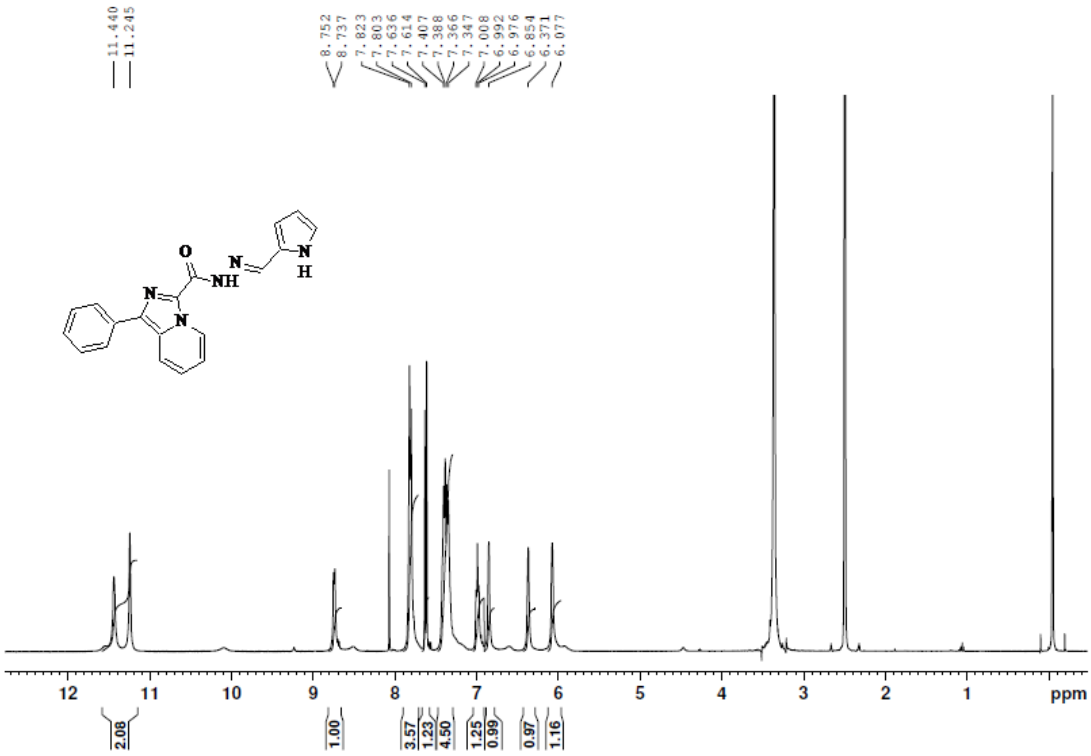

Figure 3.49: ^{1}H NMR Spectrum of 1-phenyl-*N*'-[(*E*)-1*H*-pyrrol-2-ylmethylidene]imidazo [1,5-*a*]pyridine-3-Carbohydrazide (4h)

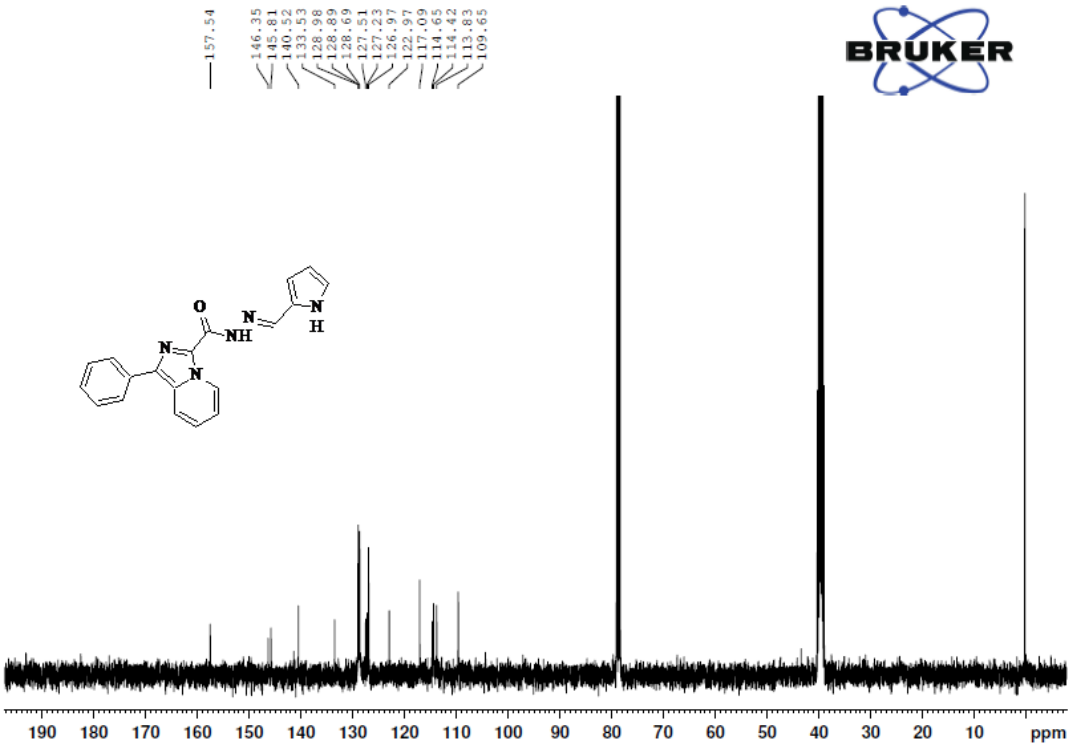

Figure 3.50: ^{13}C NMR Spectrum of 1-phenyl-*N*'-[(*E*)-1*H*-pyrrol-2-ylmethylidene]imidazo [1,5-*a*]pyridine-3-Carbohydrazide (4h)

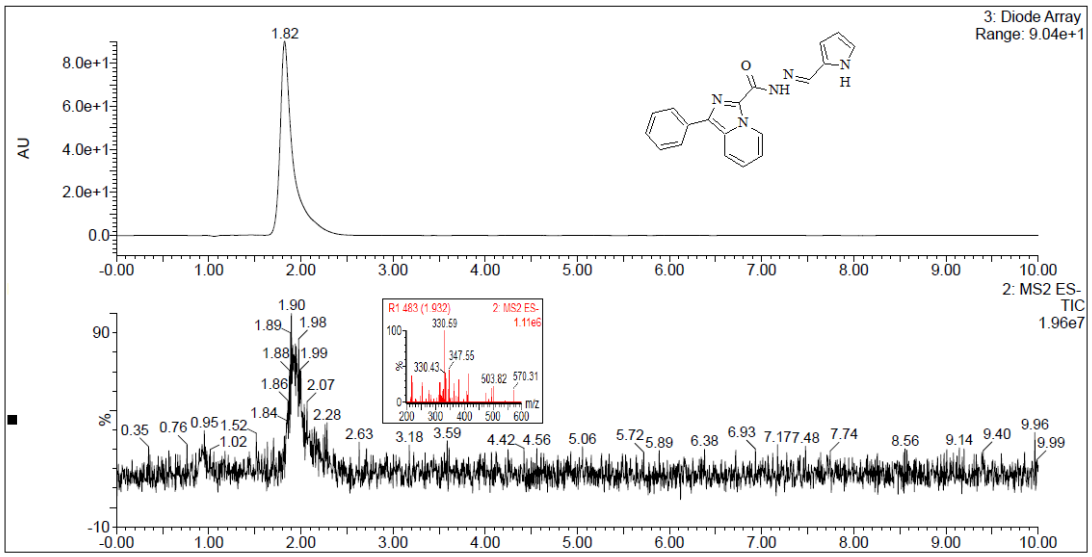

Figure 3.51: Mass Spectrum of 1-phenyl-*N*'-[(*E*)-1*H*-pyrrol-2-ylmethylidene]imidazo [1,5-*a*]pyridine-3-Carbohydrazide (4h)

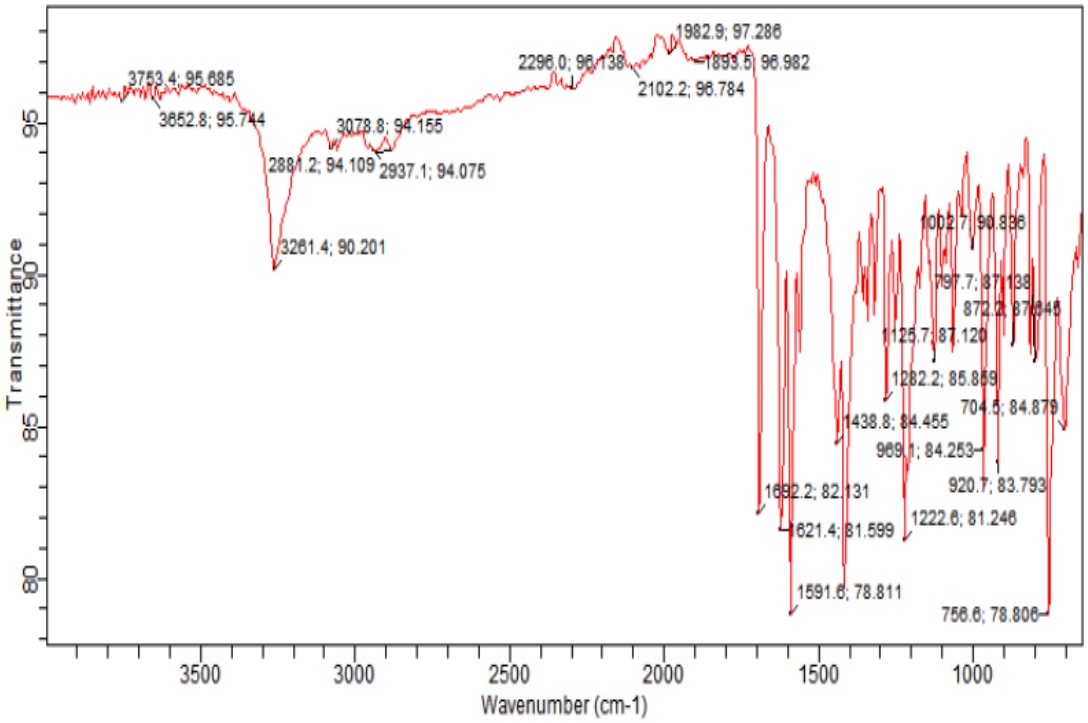

Figure 3.52: IR Spectrum of 1-phenyl-*N*'-[(*E*)-1*H*-ferrocen-2-ylmethylidene]imidazo [1,5-*a*]pyridine-3-carbohydrazide (4i)

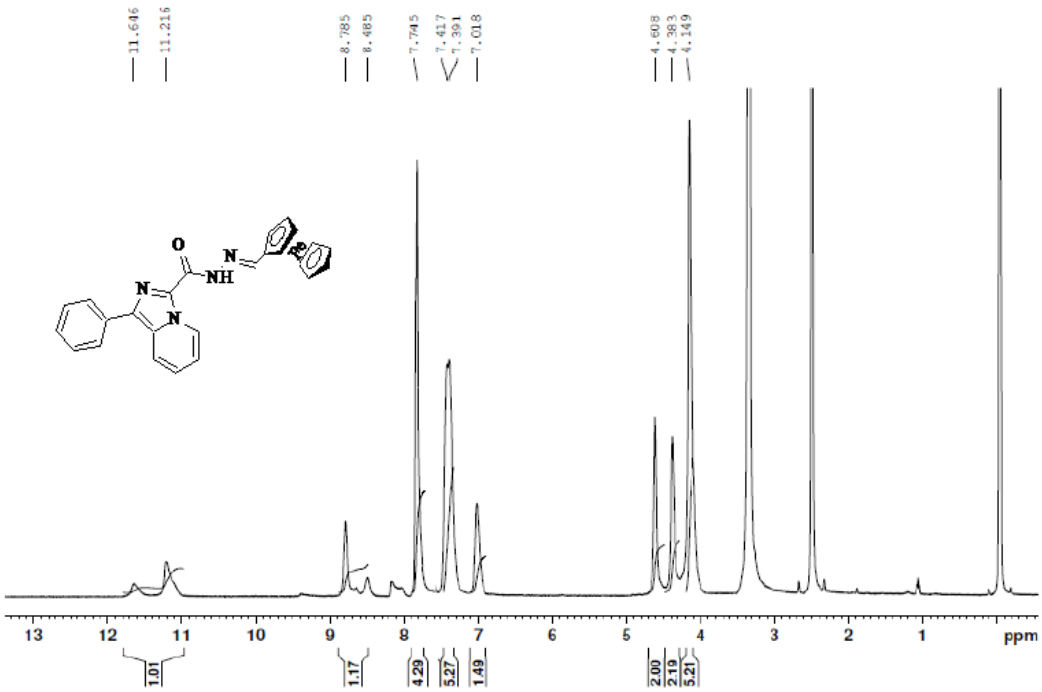

Figure 3.53: ^{1}H NMR Spectrum of 1-phenyl-*N*'-[(*E*)-1*H*-ferrocen-2-ylmethylidene]imidazo [1,5-*a*]pyridine-3-carbohydrazide (4i)

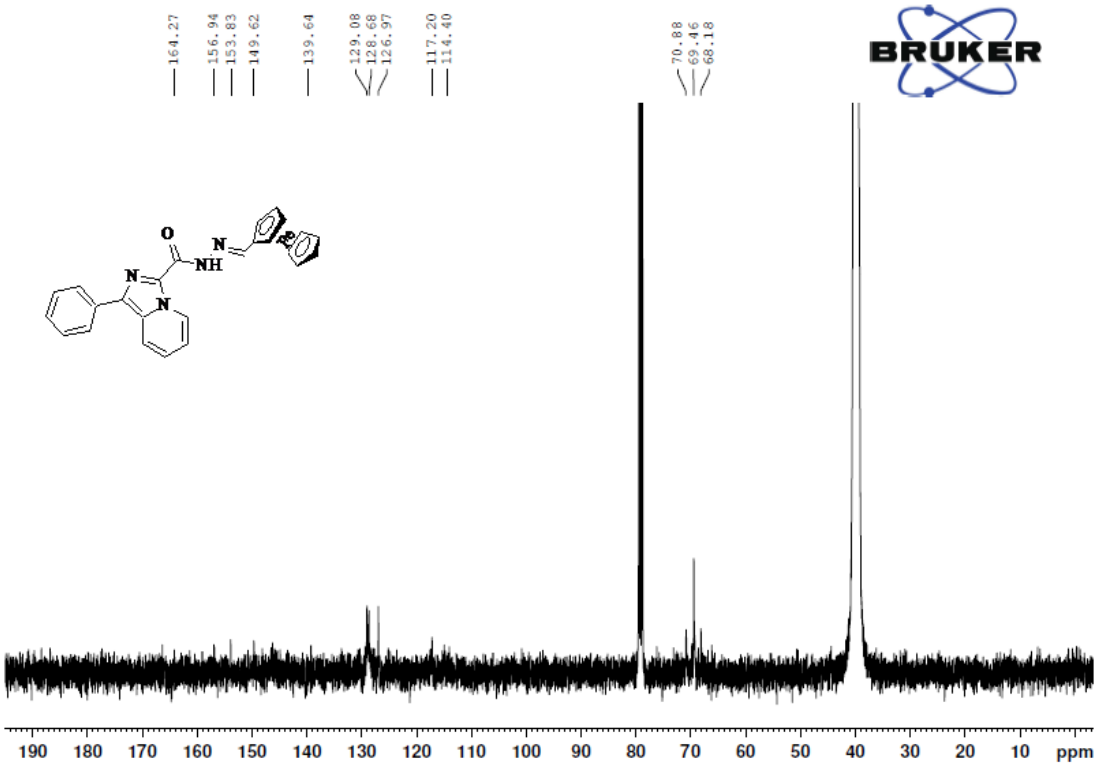

Figure 3.54: ^{13}C NMR Spectrum of 1-phenyl-*N*'-[(*E*)-1*H*-ferrocen-2-ylmethylidene]imidazo [1,5-*a*]pyridine-3-carbohydrazide (4i)

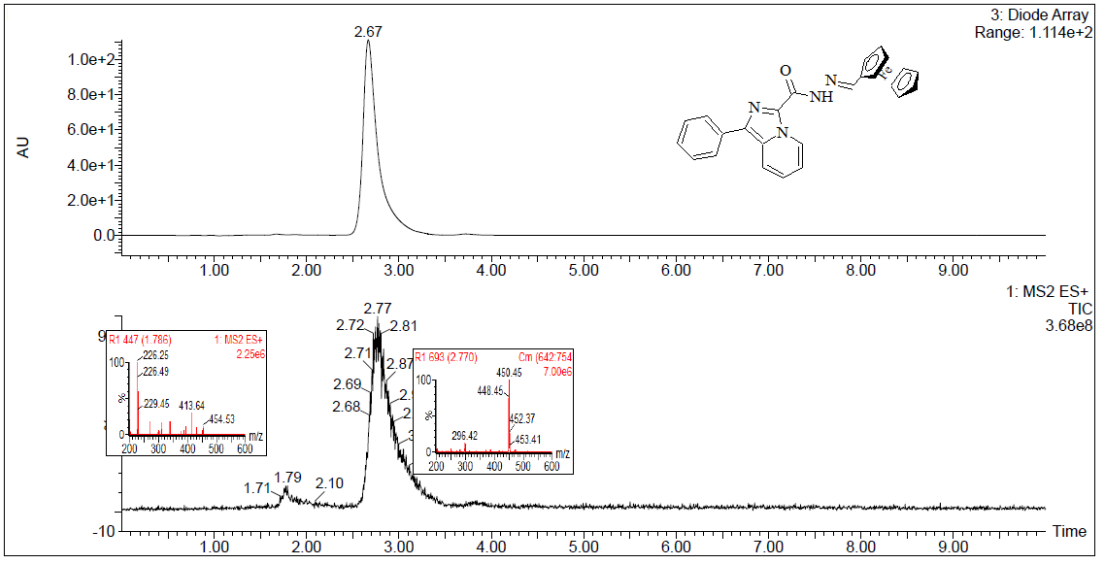

Figure 3.55: Mass Spectrum of 1-phenyl-*N*'-[(*E*)-1*H*-ferrocen-2-ylmethylidene]imidazo [1,5-*a*]pyridine-3-carbohydrazide (4i)

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Novel Design Strategies and Synthetic Methodologies
(ISBN: 978-93-47587-44-3)

About Author

Dr. Suhas G. Patil
Associate Professor
Department of Chemistry,
S. R. M. Mahavidyalaya, Kudal, Dist.: Sindhudurg, Maharashtra, 416520

Dr. Suhas G. Patil is currently working as an Associate Professor in the Department of Chemistry at S. R. M. Mahavidyalaya, Kudal, Sindhudurg, Maharashtra. He brings with him nearly 28 years of rich teaching experience at both undergraduate and postgraduate levels, contributing significantly to academic development and student mentoring. Dr. Patil obtained his M.Sc. degree in Organic Chemistry from the University of Mumbai, subsequently qualifying the State Eligibility Test (SET). He earned his Ph.D. in Chemistry from the University of Mumbai, where his research work strengthened his expertise in advanced chemical sciences.

Dr. Patil has an active research profile and has published eleven research papers in reputed refereed journals, including three papers indexed in Scopus, reflecting the quality and impact of his scholarly contributions. He is a co-author of the book Mechanisms and Applications of Physical Organic Chemistry, published by Infinite Research, which serves as a valuable academic resource. He has also served as the co-editor of the book Innovations and Research in Science and Technology, Volume III, published by Bhumi Publishing, highlighting his editorial and academic leadership.

In addition, Dr. Patil has presented research papers at several national and international conferences and has successfully completed five minor research projects funded by the University of Mumbai. His research interests include natural products, heterocyclic chemistry, medicinal chemistry, and catalysis, areas in which he continues to guide and inspire young researchers.

Contact details: Mobile No. 9421147283; E-mail: patilsg.patil@gmail.com

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ISBN 978-93-475-8744-3
9 789347 587443