SYNTHETIC AND ANTICONVULSANT STUDIES OF SOME NEW PYRIDINE DERIVATIVES

Thesis

Submitted in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

by

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June, 2013

DECLARATION

By the Ph.D. Research Scholar

I hereby declare that the Research Thesis entitled **"Synthetic and anticonvulsant studies of some new pyridine derivatives"** which is being submitted to the **National Institute of Technology Karnataka, Surathkal** in partial fulfillment of the requirements for the award of the degree of **Doctor of Philosophy** in **Chemistry** is a *bonafide report of the research work carried out by me*. The material contained in this Research Thesis has not been submitted to any University or Institution for the award of any degree.

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CERTIFICATE

This is to *certify* that the Research Thesis entitled **"Synthetic and anticonvulsant studies of some new pyridine derivatives"** submitted by **Mr. Shrikant** (Reg. No: CY10F03) as the record of the research work carried out by him is *accepted as the Research Thesis submission* in partial fulfillment of the requirements for the award of degree of Doctor of Philosophy.

Prof. A. Vasudeva Adhikari
Research Guide
Date:

Chairman – DRPC
Date:

DEDICATED TO MY

BELOVED PARENTS

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ABSTRACT

Epilepsy is a rapidly growing neurological disorder that affects about 1% of world's population. The present medications could able to control the seizure generation but none of the developed drugs are able to cure the disease completely. As a result, demand for new and efficient antiepileptic agents is growing day by day. In this connection, it was contemplated to synthesize new active antiepileptic agents.

Based on the literature survey, new DHP and imidazo[1,2-a]pyridine derivatives carrying biologically active pharmacophores (**P_{1-138}**) were designed as possible anticonvulsant agents. The newly designed compounds were later successfully synthesized following the appropriate synthetic routes. Further, their synthetic methods as well as purification techniques were established and their yields were optimized. They were later characterized by various spectral techniques such as FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral followed by elemental analyses. Finally, the target compounds were screened for their antiepileptic studies following Maximal Electroshock Seizure (MES) and subcutaneous Pentylene Tetrazole (scPTZ) methods. Further, the neurotoxicity study of target compounds was performed by Rotarod technique, in order to establish their toxicity profile. At the end, based on the *in vivo* results, their Structure-Activity Relationship (SAR) was discussed.

The *in vivo* results of preliminary anticonvulsant screening study indicated that newly synthesized DHPs carrying hydrazone and amide functionalities (**P_{1-40}**) are moderately active antiepileptic agents in MES method. On the other hand, significant activity was observed for new imidazo[1,2-a]pyridines (**P_{41-138}**) carrying various pharmacophores at position-2 and position-3. Particularly, those imidazo[1,2-a]pyridines carrying oxazolone, cyanopyridone, 1,2,3-triazole, 1,2,4-triazole and hydrazone groups exhibited pronounced activity. Interestingly, the Rotarod study revealed that most of the tested compounds are non-toxic, which further appreciated the choice of new derivatives as antiepileptic agents. Altogether, the suitably substituted new imidazo[1,2-a]pyridines carrying electron donor groups appeared as active templates for future development of new antiepileptic agents.

Key word: Dihydropyridine; Imidazo[1,2-a]pyridine; Anticonvulsant study; Neurotoxicity; SAR.

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ABBREVIATIONS

^{13}C NMR	: Carbon nuclear magnetic resonance
^{1}H NMR	: Proton nuclear magnetic resonance
AEDs	: Antiepileptic drugs
ASP	: Anticonvulsant screening program
ATR	: Attenuated total reflectance
$CDCl_3$	: Deuterated chloroform
CDS	: Chemical delivery system
CNS	: Central nervous system
CuI	: Cuprous iodide
DHP	: Dihydropyridine
DMF	: Dimethylformamide
DMSO-d_6	: Deuterated dimethyl sulfoxide
DNA	: Deoxyribonucleic acid
ED_{50}	: Effective dose
EEG	: Electroencephalography
EtOH	: Ethanol
Eq	: Equivalent
FTIR	: Fourier transform infrared spectroscopy
GABA	: Gama amino butyric acid
GAERS	: Genetic absence epilepsy rats from Strasbourg
HIV	: Human immunodeficiency virus
i.p.	: Intraperitonial
M.P.	: Melting point
MDC	: Methylene dichloride
MeOH	: Methanol
MES	: Maximal electroshock
MRI	: Magnetic resonance imaging
MS	: Mass spectroscopy
NADP	: Nicotinamide adenine dinucleotide phosphate
NIH	: National institute of health

ORTEP	: Oak ridge thermal ellipsoid plot program
PEG	: Polyethylene glycol
PI	: Protective index
QSAR	: Quantitative structure activity relationship
RNA	: Ribonucleic acid
SAR	: Structure activity relationship
scMET	: Subcutaneous Metrazole
scPTZ	: Subcutaneous pentylene tetrazole
SCXRD	: Single crystal X-ray diffraction
SEM	: Standard error of mean
$SOCl_2$	: Thionyl chloride
TD_{50}	: Median toxic dose
TLC	: Thin layer chromatography
WHO	: World health organization

CHAPTER-1

GENERAL INTRODUCTION

Abstract

This chapter includes a concise introduction to heterocyclic chemistry. It also covers a brief account on synthesis and pharmacological significance of important heterocyclic systems, viz. pyridine, triazole, pyrazole, oxazolone and pyrimidine derivatives, involved in the present work. Further, it deals with a brief note on epilepsy and its treatment, antiepileptic agents, different possible mechanism of their action, and screening methods. In the end, the broad objectives of the present work have been highlighted.

1.1 INTRODUCTION TO HETEROCLYCLES

Medicinal chemistry is an important part of science, which encompasses discovery, development, identification of therapeutics and interpretation of their mode of action in the body at the molecular level. Besides this, medicinal chemistry also involves the isolation, characterization and synthesis of compounds that can be used in medicine for the prevention, treatment and cure of the diseases, providing a chemical basis for the interdisciplinary field of therapeutics. For the better future of mankind, lots of efforts have been made to invent new medicinal agents. In this approach, many synthetic organic compounds have been developed as effective therapeutics. However, different side effects and toxicity of these new therapeutics limit their applicability as effective pharmaceutical agents. In addition, significant numbers of patients are becoming pharmaco-resistant to many such trivial drugs, which made the drug un-effective for such patients. Consequently, design and synthesis of new biologically active entities has developed as an active area of research in medicinal chemistry.

In earlier days, scientists have primarily concerned with the isolation of active agents found in the medicinal plants. However today, researchers in this field are mainly focusing their attention on the development of new synthetic compounds with enhanced bioactivity as therapeutics. Amongst various such agents, heterocyclic compounds are in the top because of their merits over other sources. Heterocycles can act both as biomimetics and pharmacophores and thereby making the molecule attractive. In fact, the lone pair of electrons present on hetero atom can involve in hydrogen bonding interactions with receptor sites, which bring about enhanced activities. Moreover, heteroatom such as nitrogen present in the ring can readily form

its hydrochloride salt, which is easily soluble in water. Because of these reasons along with their prime reactivity, heterocycles have emerged as eventual sources for the development of new medicinal drugs. Consequently, majority of modern pharmaceuticals are the derivatives of one or other heterocyclic systems. Due to the increasing significance of heterocyclic chemistry in the medicinal field, plenty of research activities, particularly on design and development of new heterocycles of pharmacological interest have gathered momentum, all over the world.

Many heterocyclic compounds occur widely in nature. A large number of them are essential to life and their functions are often of fundamental importance to living systems. Essential diet ingredients such as thiamin, riboflavin, nicotinamide, pyridoxal and two of the essential amino acids, viz. tryptophan and histidine are heterocycles. In addition, nucleic acids, haemoglobin, chlorophyll and many enzymes consist of heterocyclic systems.

It is well established that small modification in the structure of the targets can alter their physiochemical properties as well as their biological characters. Both steric and electronic factors are claimed to be major determinants in the variation of biological activity. Generally, factors such as presence of hydrophobic and hydrophilic groups, binding site and solubility of the molecules are desirable features to exhibit medicinal activity to a great extent. Stereochemistry of the molecule can also play an important function in their biological activity. These parameters have prime role in the discovery of new drugs in the modern pharmaceutical research.

An interesting feature of many heterocyclic compounds is that it is possible to incorporate many functional groups as substituents and also to introduce hetero atoms as a part of the ring system. For example, atoms of nitrogen can be included both as amino constituents and as the part of a ring. Accordingly, quite a large variety of heterocyclic compounds such as pyridine, pyrimidine, triazole, thiophene, imidazole, pyrazole, oxadiazole, thiadiazole, thiadiazine, quinoline, indole, purines, benzothiazole, benzodiazepine etc., have been designed, synthesized and extensively studied for their various pharmacological properties. The fast growing literature on heterocycles in recent years demonstrates their increasing importance in the field of pharmaceutical chemistry.

Amongst various heterocycles, pyridine is an important heterocyclic system which shows diverse biological properties. It is rather used as a precursor for the commercial synthesis of interesting pharmaceuticals and agrochemicals (Thirumurugan et al. 2010). Many pyridine derivatives find applications as active drugs and as important agricultural products such as herbicides, insecticides, fungicides, and plant growth regulators. In addition, pyridines also have significant applications outside the realm of bioactive ingredients. For instance, polymers made from pyridine-containing monomers possess wide commercial applications because of their unique optoelectronic properties and functions.

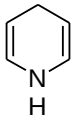
Dihydropyridine (DHP) is a reduced form of pyridine, carrying a free NH group in the ring system. DHP and its derivatives are known to chemists as well as biologists due to their broad spectrum of medicinal activities like anticonvulsant, antihypertensive, anti-inflammatory, hypnotic, antimycobacterial and anti-tubercular properties, since they display affinity for many diverse binding sites (Coburn et al. 1988). Interestingly, DHPs are the important class of calcium channel blockers and so, many DHPs have emerged as potential antihypertensive and antiepileptic drugs. Similarly, imidazo[1,2-a]pyridines, being condensed pyridine derivatives act selectively on Central Nervous system (CNS). They belong to 'non-benzodiazepine' class of drugs, as they possess selective affinity towards benzodiazepine receptors, despite they have entirely different chemical structures from classical benzodiazepines. Due to their GABAergic activity, they are explored as very good CNS agents. Therefore, they are acting as prominent anxiolytic, anticonvulsant, sedative and hypnotic agents. Interestingly, imidazo[1,2-a]pyridines display relatively less side effects when compared with those of classical benzodiazepines. These features attracted the attention of many scientists to design and develop new imidazo[1,2-a]pyridines as active substitutes for trivial benzodiazepine drugs (Najib 2006). Owing to the pharmacological importance of these pyridine derivatives, viz. dihydropyridines and imidazo[1,2-a]pyridines, in the present work it has been planned to focus on design, synthesis and anticonvulsant studies of new DHP and imidazo[1,2-a]pyridine based derivatives, that combine two or more bio-labile components together to give compact structures of better biological activity.

In additon to pyridine derivatives, certain nitrogen heterocycles like pyrazole, oxazolone, triazole and pyrimidine are also important pharmacologically active systems. They exhibit significant biological applications, including remarkable antiepileptic activity. Because of their well-established pharmacological importance, these heterocyclic systems have been included in our new design, as active pharmacophoric groups. In the following sections, a brief account on chemistry and biological importance of these heterocyclic systems has been highlighted.

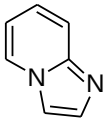
1.2 CHEMISTRY OF PYRIDINE AND ITS DERIVATIVES

Pyridine (**S-1**) is an important six membered heterocyclic system which resembles very much to the structure of benzene except one atom where carbon is replaced by nitrogen atom. It is a planar molecule, stable liquid with strong penetrating odour and is completely miscible with water. It plays a range of roles in organic reactions. It can act as a reagent, solvent or as a base in different reaction conditions. Pyridine is particularly used as a catalyst in reactions such as N- and O- acylation.

S-1



S-2



S-3

Pyridine was first isolated from bone pyrolysates. Pyridine and its simple alkyl derivatives were for a long time obtained from coal tar, in which they occur in good quantity. However, in recent years this source has been replaced by synthetic processes. For example, pyridine can be commercially synthesized by gas phase high temperature interaction of crotonaldehyde, formaldehyde, steam, air and ammonia over a silica-alumina catalyst with a yield of 60-70%.

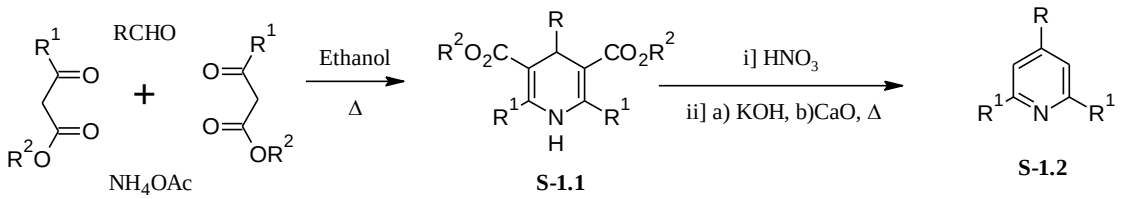
The dipole moment of pyridine is 1.57 D. As the resonance contributors and the electrostatic potential map indicate, the electron-withdrawing nitrogen is the negative end of the dipole. Unlike benzene, pyridine is readily undergoing nucleophilic substitution reaction at position-2 and position-4, because of the presence of electron withdrawing nitrogen atom in the ring. Due to the same reason, electrophilic substitution reaction is bit difficult on the pyridine ring; however, under forceful conditions, it undergoes at position-3.

Dihydropyridine (**S-2**) is a reduced form of pyridine carrying a free NH group and is found to block L-type calcium channels, selectively. Imidazo[1,2-a]pyridine (**S-3**) is another class of pyridine derivatives that carries biologically active imidazole and pyridine rings in a fused manner. It is well-established that imidazole derivatives exhibit good anticonvulsant activity (Matsumura et al. 2012; Emami et al. 2011; Hack et al. 2011). As a consequence, it is quite obvious to expect better antiepileptic property for its fused ring systems. Such union of imidazole and pyridine rings can lead to various possible imidazopyridine derivatives such as imidazo[1,2-a]pyridine, imidazo[1,2-b]pyridine, imidazo[4,5-b]pyridine and imidazo[1,5-a]pyridine, depending on the position of attachment. Among these various derivatives, imidazo[1,2-a]pyridine nucleus has its own significance in medicinal field. It is found to act selectively on GABA receptors and consequently, many of its derivatives are obtained as active therapeutics such as anxiolytic, anticonvulsant, sedative and hypnotic agents. Owing to the importance of DHP and imidazo[1,2-a]pyridine derivatives in the area of anticonvulsants, the present research work has been aimed at design and synthesis of new chemical entities carrying DHP and imidazo[1,2-a] pyridine as core moieties and evaluation of their antiepileptic property, with the hope that new molecules would show significant antiepileptic activity.

1.2.1 Synthesis

There are many ways of achieving the synthesis of a pyridine ring, few of them are mentioned below.

The well-known method, which is commonly used for the synthesis of pyridine is Hantzsch method (Hantzsch 1881). This reaction allows the preparation of dihydropyridine derivatives (**S-1.1**) by condensation of an aldehyde with two equivalents of a β-dicarbonyls in the presence of ammonia or ammonium acetate, as shown in Scheme 1.1. Subsequent oxidation (or dehydrogenation) of it gives pyridine-3,5-dicarbonyls, which can be decarboxylated to yield the corresponding pyridines (**S-1.2**).

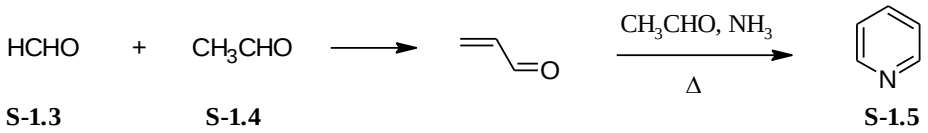


Where R^1, R^2=H, Methyl, Benzyl; R=Aryl

Scheme 1.1: Hantzsch pyridine synthesis

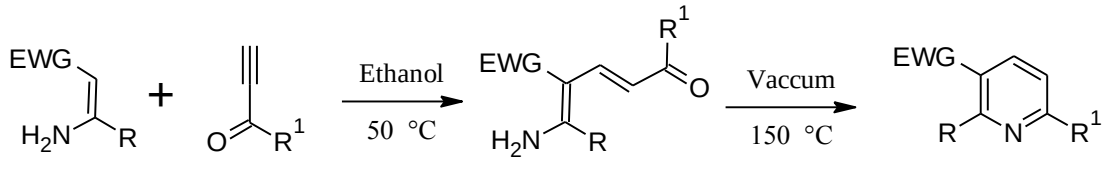
Here R^1 and R^2 are either identical or different. Presence of different groups leads to optically active stereo centre at C_4 of dihydropyridine ring.

The industrial production of pyridine is mainly achieved by Chichibabin method (Frank and Seven 1949). It involves condensation of aldehydes, ketones, α, β-unsaturated carbonyl compounds, or any combination of the above, with ammonia or its derivatives. In particular, unsubstituted pyridine (**S-1.5**) is synthesized from formaldehyde (**S-1.3**) and acetaldehyde (**S-1.4**) through Knovenagel condensation. This reaction is depicted in Scheme 1.2.



Scheme 1.2: Chichibabin pyridine synthesis

Another method for the pyridine synthesis is Bohlmann-Rahtz route, which allows the generation of substituted pyridines in two steps. Condensation of enamines (**S-1.6**) with ethynylketones (**S-1.7**) leads to an aminodiene intermediate (**S-1.8**) that upon heat-induced isomerization, undergoes a cyclodehydration to yield 2,3,6-trisubstituted pyridines (**S-1.9**). The general synthetic route is shown in Scheme 1.3.

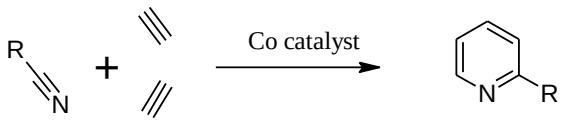


Where R, R^1= Alkyl or Aryl; EWG- Electron withdrawing group

Scheme 1.3: Bohlmann-Rahtz pyridine synthesis

The trimerization of a part of a nitrile molecule (**S-1.10**) and two parts of acetylene (**S-1.11**) into pyridine (**S-1.12**) is called Bonnemann pyridine synthesis (Scheme 1.4). The thermal activation requires high pressures and temperatures, the

photo-induced cycloaddition proceeds at ambient conditions with $CoCp_2(cod)$ (Cp = cyclopentadienyl, cod = 1,5-cyclooctadiene) as a catalyst, and can be performed even in water.

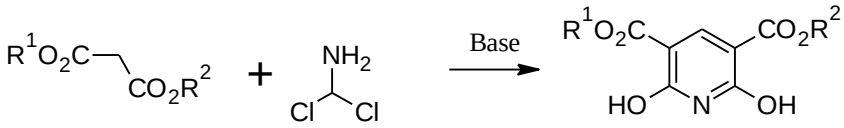


S-1.10 **S-1.11** **S-1.12**

Where R= Aliphatic or aromatic hydrocarbons

Scheme 1.4: Bonnemann cyclization

Gattermann-Skita synthesis (Gattermann and Skita 1916) is another method for the synthesis of pyridine ring (**S-1.15**), which involves the reaction of dialkyl malonates (**S-1.13**) with dichloromethylamines (**S-1.14**) under basic condition. The reaction is summarized in Scheme 1.5.

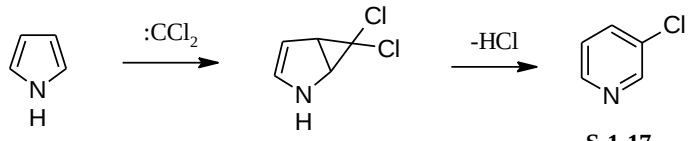


S-1.13 **S-1.14** **S-1.15**

Where R^1, R^2 = Appropriate alkyl chain

Scheme 1.5: Gattermann-Skita synthesis

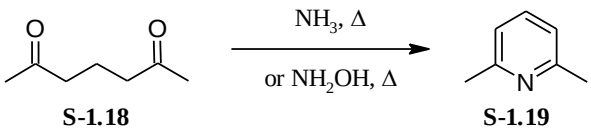
Ciamician-Dennstedt rearrangement (Jones and Rees 1969) is also an important route (Scheme 1.6) for the synthesis of pyridine (**S-1.17**), which involves ring expansion of pyrrole (**S-1.16**) in presence of dichlorocarbene.



S-1.16 **S-1.17**

Scheme 1.6: Synthesis of pyridine through Ciamician-Dennstedt rearrangement

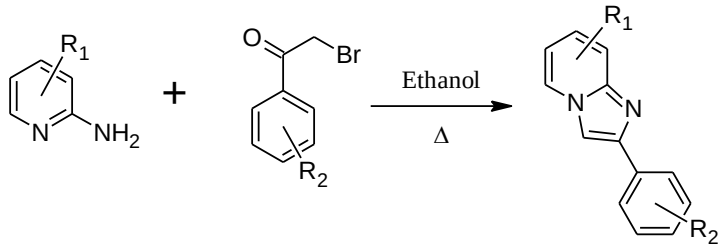
Pyridine (**S-1.19**) can be best synthesized by means of internal cyclization of 1,5-dicarbonyls (**S-1.18**) (Donohoe et al. 2011) in the presence of ammonia or hydroxylamine hydrochloride, as shown in Scheme 1.7.



S-1.18 **S-1.19**

Scheme 1.7: Synthesis of pyridine from 1,5-dicarbonyls

On the other hand, the condensed pyridine derivative, viz. imidazo[1,2-a] pyridines (**S-1.22**) can be conveniently synthesized by coupling 2-aminopyridine (**S-1.20**) with a phenacyl bromide (**S-1.21**) under refluxing condition (Gudmundson and Johns 2007). The general reaction sequence is shown in Scheme 1.8. This is a simple and routinely used method for their synthesis and so, in our present work, the same method has been selected for the synthesis of core imidazo[1,2-a]pyridine system.

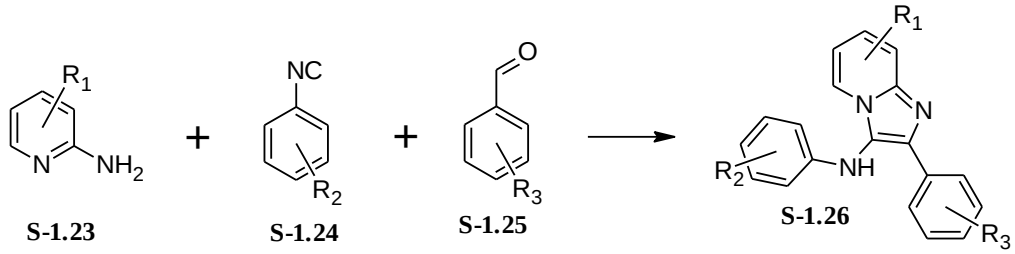


S-1.20 **S-1.21** **S-1.22**

Where R_1, R_2= H, Halogens, Alkyl, Alkoxy, Aryl

Scheme 1.8: Synthesis of imidazo[1,2-a]pyridines from 2-aminopyridines and phenacyl bromides

Imidazo[1,2-a]pyridines (**S-1.26**) can also be synthesized by means of one pot three component reaction that involves condensation of 2-aminopyridine (**S-1.23**) with phenyl isocyanide (**S-1.24**) and a suitable aldehyde (**S-1.25**) (Al-Tel et al. 2011), as shown in Scheme 1.9.

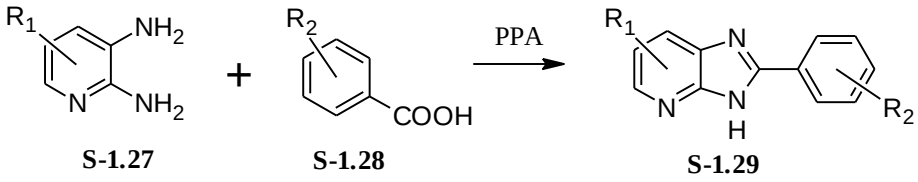


S-1.23 **S-1.24** **S-1.25** **S-1.26**

Where R_1, R_2, R_3= H, Halogens, Alkyl, Alkoxy, Aryl

Scheme 1.9: Synthesis of imidazo[1,2-a]pyridines from 2-aminopyridines, isocyanides and aldehydes

On the other hand, synthesis of imidazo[4,5-b]pyridines (**S-1.29**) is generally achieved by reacting 2,3-diaminopyridine (**S-1.27**) with a aromatic carboxylic acid (**S-1.28**) in presence of cyclizing agents such as polyphosphoric acids (Okubo et al. 2004). The general synthetic route is depicted in Scheme 1.10.



S-1.27 **S-1.28** **S-1.29**

Where R_1, R_2= H, Halogens, Alkyl, Alkoxy, Aryl

Scheme 1.10: Synthesis of imidazo[4,5-b]pyridines

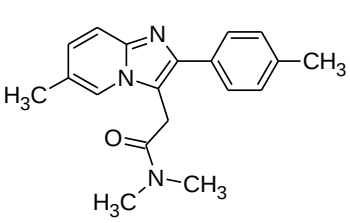
Amongst the various methods described above, the Hantzsch dihydropyridine synthesis method is quite convenient for the synthesis of DHP carrying appropriate functional groups. This method gives high yield and good purity for the products. So, in the present research work, it has been decided to synthesize new DHPs by this method. Further, it has been thought to synthesize new imidazo[1,2-a]pyridines from 2-aminopyridines, as explained in Scheme 1.8.

1.2.2 Biological importance

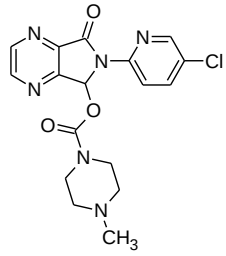
Among the numerous heterocyclic moieties of pharmacological interest, pyridine substructure is one of the most important heterocycles, found in various natural products, pharmaceuticals and functional materials (Thirumurugan et al. 2010). The pyridine ring is gifted with various activities, such as anticonvulsant (Tripathi et al. 2011), anti-inflammatory (Mader et al. 2008), antihypertensive (Arhancet et al. 2010), antimicrobial (El-borai et al. 2012), anti-tuberculosis (Kumar et al. 2010), antimalarial (Menezes et al. 2002), anticancer (Baviskar et al. 2011), anti-HIV (Gudmundson et al. 2009), etc. and is emerged as a major source for the development of new therapeutic agents.

Also, the pyridine plays a key role in several biological processes, most notably in the oxidation/reduction reaction. It is an important constituent in coenzyme nicotineamide adenine dinucleotide (NADP). Niacin and Pyridoxine are two important pyridine based vitamins, which have a vital role as the coenzyme in transaminase reaction. Nicotine is another pyridine derivative, which is highly toxic alkaloid and is the major active component in tobacco. Other alkaloids like Sedamine, Piperine, Anaferine, Lobeline contains piperidine core moiety whereas Trigonelline, Arecoline, Nornicotine, Anabasine, Anatabine, Actinidine and Pediculinne are containing pyridine core unit.

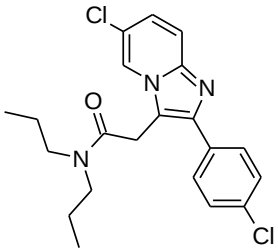
Many synthetic pyridine derivatives are important as therapeutic agents. There are quite a large number of pyridine based drugs in the market. Few such drugs which are acting as calcium channel blockers or GABA agonists (Saini et al. 2008; Sanger and Zivcovik 1994) are given below.



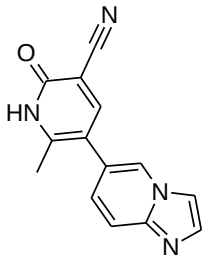
Zolpidem



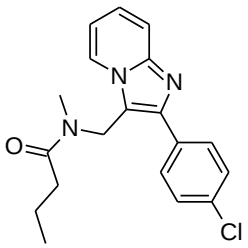
Zopiclone



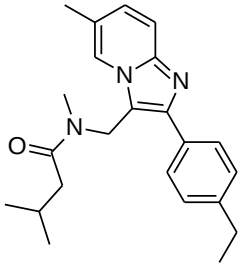
Alpidem



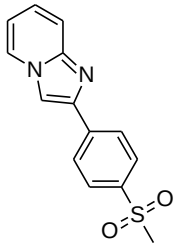
Olprinone



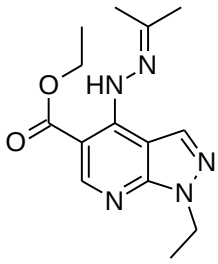
Saripidem



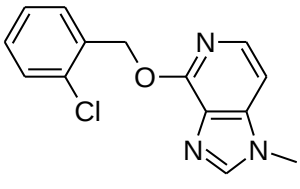
Necopidem



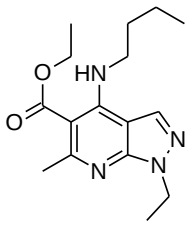
Zolimidine



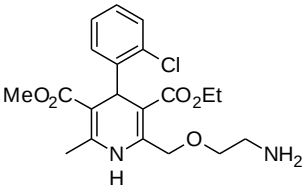
Etazolate



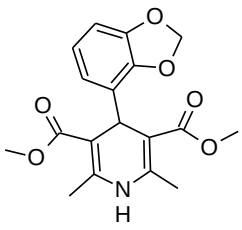
Bamaluzole



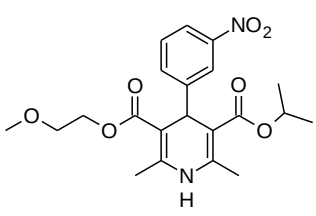
Tracazolate



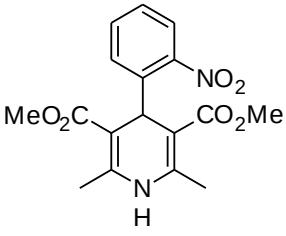
Amlodipine



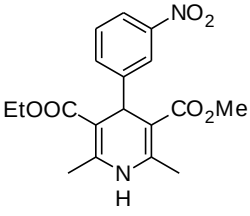
Oxodipine



Nimodipine



Nifedipine



Nitrendipine

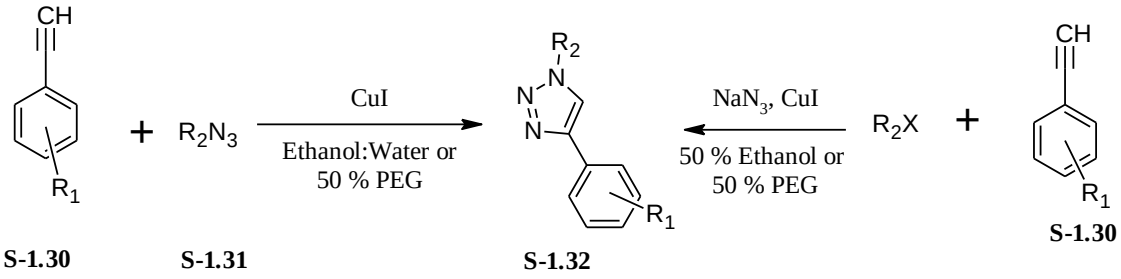
The detailed literature survey clearly shows that pyridine and its derivatives have vital role in the field of therapeutics. They display variety of biological activities, depending on the chemical structure and their affinity towards the receptors. However, with respect to anticonvulsant activity, dihydropyridine and imidazo[1,2-a]pyridine derivatives are in forefront, which is mainly due to their higher affinity towards calcium channel and GABA channels, respectively. In fact, majority of reported antiepileptic drugs (AEDs) exhibit their activity by stimulating either of these two sites. Keeping this in view, it has been thought of designing and synthesising new dihydropyridine derivatives due to their Ca^{2+} channel blocking property. Also, it has been contemplated to design and synthesize new imidazo[1,2-a]pyridine derivatives owing to their GABA agonist activity. Further, it is well-known fact that incorporation of certain active pharmacophoric groups into the parent ring will enhance the biological activity of the whole moiety. From the literature, it has been found that pyrazoline, oxazolone, pyrimidine and triazole derivatives exhibit remarkable antiepileptic activity. Against this background, it has been decided to include these heterocyclic groups along with the core pyridine nucleus in the new design, with the expectation of better anticonvulsant activity for the resulting molecules. In the following sections, the synthetic and biological importance of such heterocyclic groups has been discussed in brief.

1.3 CHEMISTRY OF TRIAZOLES

Triazole is an important five membered heterocyclic system, which attracts the attention of chemists and biologists due to its broad spectrum of pharmacological applications. Based on the position of nitrogen atoms in the ring system, triazoles can be broadly classified into two classes, viz. 1,2,3-triazoles and 1,2,4-triazoles. It is well-established that 1,2,4-triazole moiety possesses greater affinity towards epileptic receptors and thereby enhances the anticonvulsant property of its derivatives (Dawood et al. 2006; Mokrab et al. 2007). The presence of hydrogen bonding donor/acceptor groups on the 1,2,4-triazole moiety and the hydrophobic aryl unit attached to it, are the most probable reasons for their good bio-efficacy (Deng et al. 2011).

1.3.1 Synthesis

The 1,2,3-triazoles are extensively synthesized by means of 'Click Chemistry', wherein an alkyne (**S-1.30**) will be cyclized with an azide (**S-1.31**) to five membered 1,2,3-triazole system (Kolbe et al. 2001). This reaction is generally carried out in the presence of aqueous medium and hence, special precaution is not required. Usually CuI or $CuSO_4$ in presence of sodium ascorbate is used as a source of Cu^{+1} catalyst, which precisely results in 1,4-disubstituted 1,2,3-triazole derivatives (**S-1.32**) (Nolte et al. 2007). The reaction is summarized in Scheme 1.11.

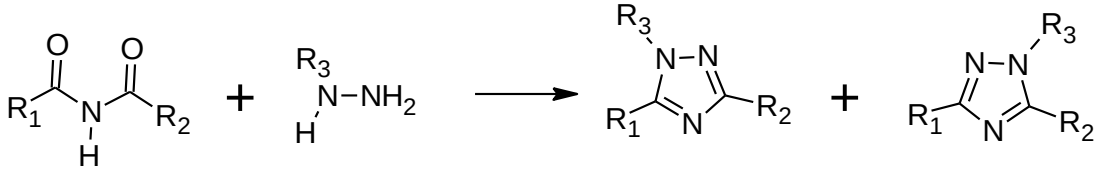


S-1.30 **S-1.31** **S-1.32** **S-1.30**

Where R_1= H, Halogens, NO_2, Alkyl; R_2= Benzyl, Alkyl, Phenacyl

Scheme 1.11: Synthesis of 1,2,3-triazoles

On the other hand, various methods have been established for the synthesis of 1,2,4-triazoles. Einhorn-Brunner reaction (Scheme 1.12) is one such method which involves cyclization of imides (**S-1.33**) with alkyl hydrazines (**S-1.34**) (Atkinson and Polya 1954). However, this method ends up with a mixture of isomeric 1,2,4-triazoles (**S-1.35** and **S-1.36**).

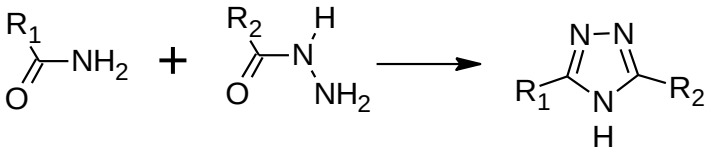


S-1.33 **S-1.34** **S-1.35** **S-1.36**

Where R_1, R_2, R_3= Alkyl or Aryl

Scheme 1.12: Einhorn-Brunner reaction

Pellizzari reaction (Bird and Wong 1974) is another method for the synthesis of 1,2,4-triazoles (**S-1.39**), wherein an amide (**S-1.37**) condenses with hydrazide (**S-1.38**), as shown in Scheme 1.13.

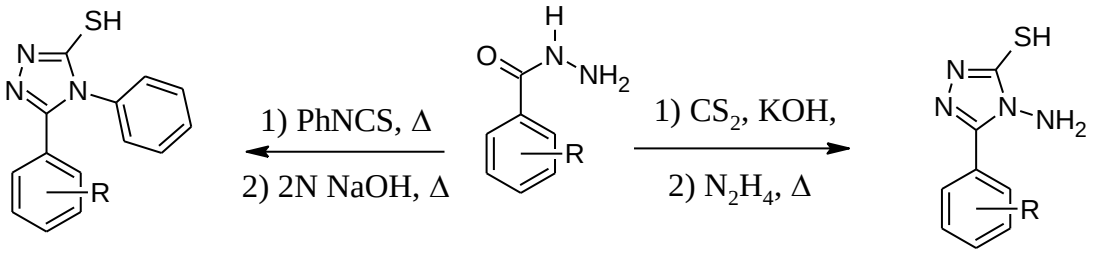


S-1.37 **S-1.38** **S-1.39**

Where R_1, R_2= Alkyl or Aryl

Scheme 1.13: Pellizzari reaction

Other trivial synthetic methods include cyclization of hydrazide (**S-1.40**) in presence of carbon disulphide and hydrazine, which gives 4-amino-1,2,4-triazole derivative (**S-1.41**). Similarly, the reaction of hydrazide with phenylisothiocyante followed by alkali treatment gives 4-phenyl 1,2,4-triazole-3-thiol (**S-1.42**) (Kumar et al. 2010). These reactions are depicted in Scheme 1.14.



S-1.42 **S-1.40** **S-1.41**

Where R= Halogen, Alkyl, Alkoxy, Heterocyclic

Scheme 1.14: Synthesis of 1,2,4-triazoles from hydrazides

The ease of conversion and selective formation of product in the above route makes it one of the convenient routes for the synthesis of 1,2,4-triazole derivatives. In our present study, the methods described in scheme 1.14 have been opted for the synthesis of required 1,2,4-triazoles, while Click chemistry has been selected for the synthesis of 1,2,3-triazoles.

1.3.2 Biological importance

During the last two decades the chemistry of 1,2,3-triazoles, 1,2,4-triazoles and their fused structures with other heterocyclic systems has received considerable attention owing to their synthetic and effective biological applications. Triazole nucleus is present as a core structural component in an array of drug categories (Kharb et al. 2011) such as antimicrobial (McAllister et al. 2012), anti-inflammatory (Shafi et al. 2012), antiepileptic, antiviral (Piotrowska et al. 2012), antineoplastic, antihypertensive (Siddiqui et al. 2011), antimalarial (Singh et al. 2012), antidepressant

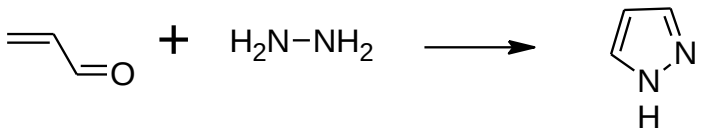
(Jubie et al. 2012), antiprotozoal (Durust et al. 2012), antihistaminic (Alagarsamy et al. 2008), antifungal (Sangeshetti and Shinde 2011) and anti-tubercular (Jordao et al. 2011), etc. The drugs Alprazolam and Estazolam that possess triazole moiety fused with benzodiazepine ring are very effective CNS agents, generally used against anxiety and convulsion. Also, various research articles have demonstrated that triazoles can act against both major and minor seizures (Kadaba 2003).

1.4 CHEMISTRY OF PYRAZOLES

Pyrazole is a five membered heterocyclic ring system possessing two nitrogen atoms adjacent to each other. It is a seat of diverse medicinal activities. Pyrazoline is a reduced form of pyrazole, while pyrazolone carries one keto group in the ring system. Further, depending on the position of keto group, they are classified as pyrazol-3-one and pyrazol-5-one.

1.4.1 Synthesis

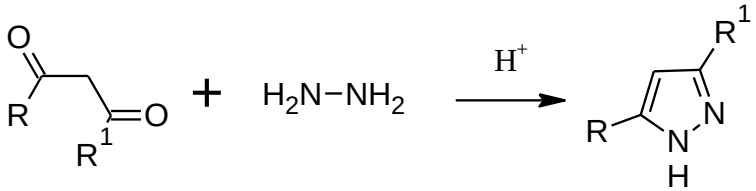
Unsubstituted pyrazole (**S-1.45**) can be synthesized by coupling α, β-unsaturated aldehyde (**S-1.43**) with hydrazine (**S-1.44**) and subsequent dehydrogenation (Schmidt and Dreger 2011), as summarized in Scheme 1.15.



S-1.43 **S-1.44** **S-1.45**

Scheme 1.15: Synthesis of pyrazole from conjugated aldehyde

Substituted pyrazoles (**S-1.47**) can be synthesized by Knorr pyrazole synthetic route (Scheme 1.16), which involves coupling of 1,3-dicarbonyls (**S-1.46**) with hydrazine hydrate (**S-1.44**) in presence of catalytic acid (Knorr 1883).

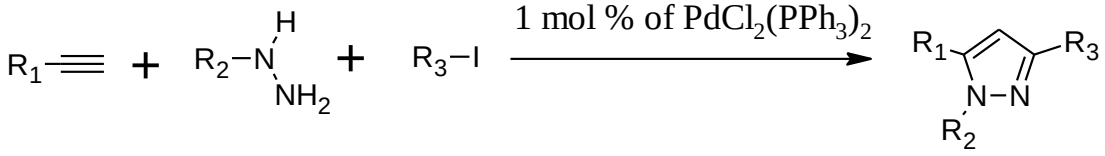


S-1.46 **S-1.44** **S-1.47**

Where R, R^1 = Alkyl or Aryl

Scheme 1.16: Knorr pyrazole synthesis

Also, one pot three component reaction of an alkyne (**S-1.48**) with a hydrazide (**S-1.49**) and an aryl iodide (**S-1.50**) in presence of Pd^{+2} catalyst yields substituted pyrazoles (**S-1.51**) (Ahmed et al. 2005). The reaction is depicted in Scheme 1.17.

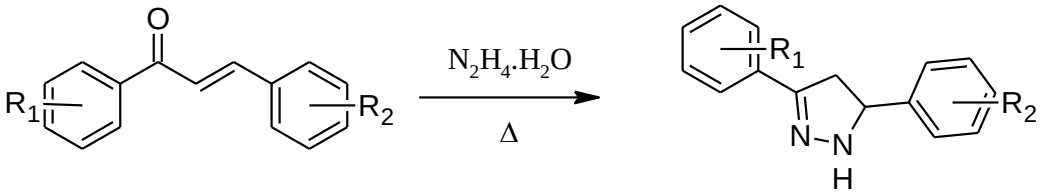


S-1.48 **S-1.49** **S-1.50** **S-1.51**

Where R_1, R_2, R_3= Alkyl or Aryl

Scheme 1.17: Synthesis of pyrazole from an alkyne

On the other hand, pyrazolines (**S-1.53**) can be effectively synthesized by reacting chalcones (**S-1.52**) with hydrazine hydrate under refluxing condition (Ozdemir et al. 2007), as given in Scheme 1.18.

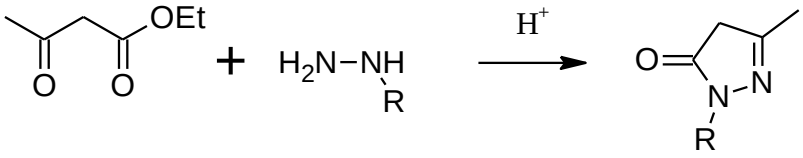


S-1.52 **S-1.53**

Where R_1, R_2= H, Alkyl, Alkoxy, Halogens

Scheme 1.18: Synthesis of pyrazoline from chalcone

Similarly, pyrazolones (**S-1.56**) are generally synthesized by reacting β-keto ester (**S-1.54**) with hydrazine or substituted hydrazine (**S-1.55**) in presence of trace of acid catalyst (Scheme 1.19).

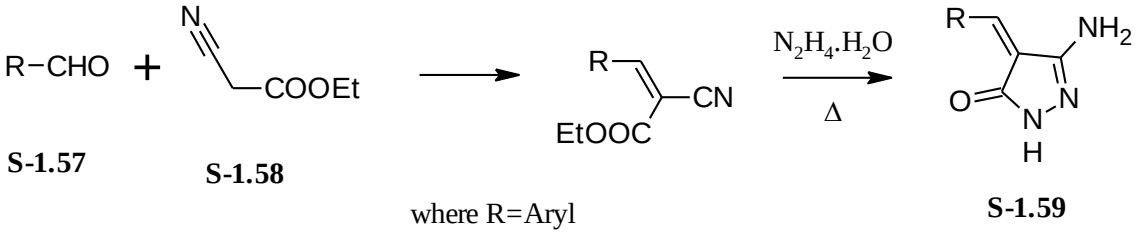


S-1.54 **S-1.55** **S-1.56**

where R=Aryl

Scheme 1.19: Synthesis of pyrazolone from β-keto ester

On the similar lines, pyrazolones (**S-1.59**) can also be synthesized by coupling an aldehyde (**S-1.57**) with an active methylene compound (**S-1.58**), followed by condensation with hydrazine. The reaction is summarized in Scheme 1.20.



Scheme 1.20: Synthesis of pyrazolone from ethyl cyanoacetate

Among above mentioned methods, synthesis of pyrazolines by cyclizing chalcones with hydrazine hydrate is a simple and straight forward reaction. Therefore, in the present work, it has been decided to synthesize pyrazolines by cyclizing chalcones with hydrazine hydrate, as given in Scheme 1.18 and pyrazolones by condensing aldehyde coupled ethyl cyanoacetate with hydrazine hydrate as mentoned in Scheme 1.20.

1.4.2 Biological importance

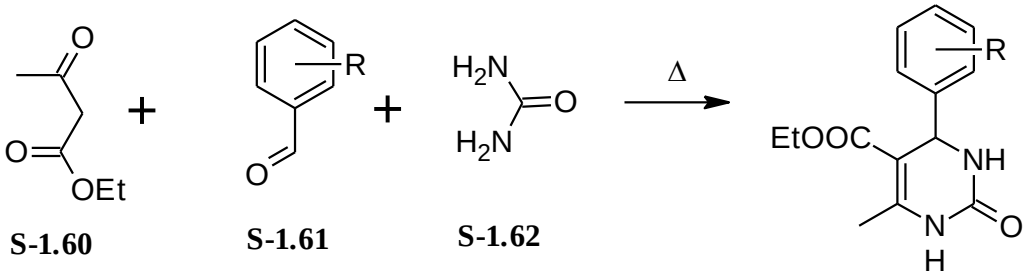
The biological applications of pyrazole and its derivatives are well reported in literature. They were shown to exhibit potential antimicrobial (Abdel-Wahab et al. 2012), anti-inflammatory (Khalil 2011), analgesic (Joshi et al. 2010), anticancer and anti-tubercular (Taj et al. 2011) activities. Particularly, many research articles evidenced the anticonvulsant activity of suitably substituted pyrazoles (Siddiqui et al. 2010; Amnerkar and Bhusari 2010). However, literature study revealed that pyrazoles were less explored towards antiepileptic screening study when compared to other pharmacological investigations.

1.5 CHEMISTRY OF PYRIMIDINES

Pyrimidine is important nitrogen containing six membered heterocyclic system that widely occurs in our body as either substituted or fused ring system including nucleotide and vitamins. Because of the presence of one more sp^2 hybridized nitrogen atom in the ring system, pyrimidine is less basic than pyridine. Because of the same reason, the electrophilic substitution reaction is much more difficult on pyrimidine ring system.

1.5.1 Synthesis

There are various methods available for the synthesis of pyrimidine derivatives (**S-1.63**). Among such method, Biginelli reaction is an important route, which involves cyclization of 1, 3-dicarbonyls (**S-1.60**) with an aldehyde (**S-1.61**) in presence of urea (**S-1.62**) or its derivatives (Kappe 1993), as shown in Scheme 1.21.



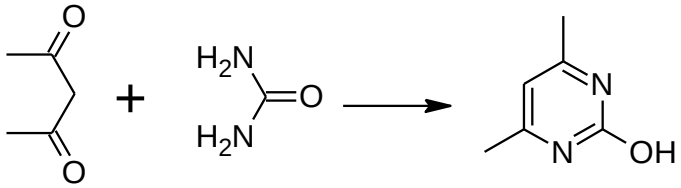
S-1.60 **S-1.61** **S-1.62**

where R= H, Halogen, Alkyl, Alkoxy **S-1.63**

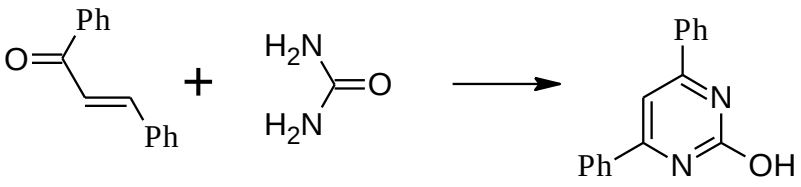
Scheme 1.21: Biginelli reaction

Pyrimidine (**S-1.66**) can also be synthesized by cyclizing 1,3-dicarbonyls (**S-1.64**) with 1,3-diaminocompounds (**S-1.65**). Similarly, treatment of chalcone (**S-1.67**) with 1,3-diamine derivative (**S-1.65**) yields diaryl pyrimidine (**S-1.68**), effectively (Bukhari et al. 2012). These reactions are summarized in Scheme 1.22.

The cyclization of chalcone is a simplest root for the synthesis of pyrimidine derivatives. This reaction can be performed by using readily available cheap chemicals. Because of these advantages, the chalcone cyclization has been chosen for the synthesis of new pyrimidine derivatives.



S-1.64 **S-1.65** **S-1.66**



S-1.67 **S-1.65** **S-1.68**

Scheme 1.22: Synthesis of pyrimidines from 1,3-diamino derivatives

1.5.2 Biological importance

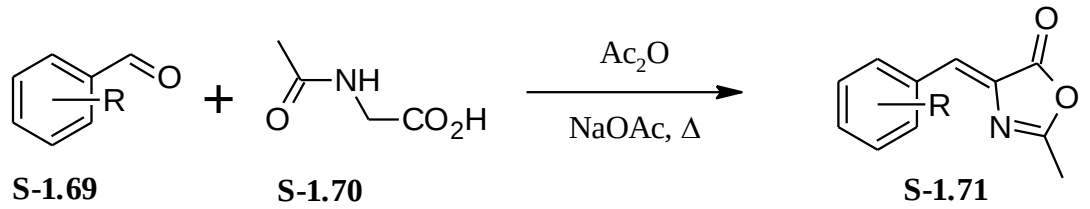
Being an integral part of DNA and RNA, pyrimidines and fused pyrimidines play an essential role in several biological processes and have considerable chemical and pharmacological importance. Particularly, the pyrimidine ring can be found in nucleoside antibiotics, antibacterials, cardio-vascular as well as agro chemical products. It is a chief chemical constituent in many synthetic therapeutics including barbiturates and the HIV drug zidovudine. They are the interesting group of compounds, as many of them possess wide-spread pharmacological properties such as anti-HIV (Guo et al. 2012), analgesic, anti-inflammatory (Hanna 2012), antiarrhythmic (Amr, et al. 2010), antitubercular (Matyugina et al. 2012) and anticancer (Pedeboscq et al. 2012) activities, in addition to potential antiepileptic property (Alam et al. 2010; Shaquiquzzaman et al. 2012).

1.6 CHEMISTRY OF OXAZOLONES

Oxazolone is an important heterocyclic system, which performs a significant role in the synthesis of many organic molecules including amino acids, thiamine (Ismail 1991), amides (Park et al. 1998), peptides (Palcut 2009), etc. Oxazolones possess many reactive sites in their structures, which allow diverse structural modifications. Consequently, it makes them excellent substrates for their use in diversity oriented synthesis (Jason et al. 2007).

1.6.1 Synthesis

Oxazolones (**S-1.71**) are extensively synthesized by Erlenmeyer reaction (Scheme 1.23) that was first described in 1893 by Friedrich Gustav Carl Emil Erlenmeyer. This reaction involves condensation of an aldehyde (**S-1.69**) with N-acetyl glycine (**S-1.70**) or N-aroyl glycine in the presence of acetic anhydride and sodium acetate. The reaction takes place via a Perkin condensation following the initial cyclization of the N-acetyl glycine to give the so-called Erlenmeyer azalactones. This is a straightforward reaction, which gives quantitative yield, and hence this method has been followed in the present work for the synthesis of new oxazolone derivatives.



S-1.69 **S-1.70** **S-1.71**

where R= H, X, Alkyl, Alkoxy, Nitro

Scheme 1.23: Erlenmeyer reaction

1.6.2 Biological importance

Many natural and synthetic oxazolone derivatives are reported to possess wide spectrum of biological activities. They display potential anticonvulsant (Wei et al. 2010; Khan et al. 2012), antimicrobial (Desai et al. 2009), anti-inflammatory (Goksen et al. 2007), anti-diabetic, antiobesity (Conway et al. 2009; Taile et al. 2009), anticancer (Sanchez et al. 2006), anti-HIV (Siddiqui et al. 2010), antiangiogenic (Perron-Sierra et al. 2002), sedative (Mesaik et al. 2004) and cardio-tonic activities (Pasha et al. 2007). Particularly, oxazolones are used as important intermediates in the synthesis of several small molecules, including amino acids, peptides, antimicrobial or anti-tumour compounds and various heterocyclic precursors.

From the above brief account on chemistry of various heterocyclic moieties, viz. pyridine, triazole, pyrazole, oxazole and pyrimidine, it is clear that they exhibit variety of pharmacological applications. Interestingly, they possess prominent antiepileptic activity, possibly due to their selective affinity and their capacity to involve in hydrogen bonding interactions with the receptors. Because of their prominent antiepileptic activity, it has been thought to design new hybrid heterocyclic moieties carrying DHP and imidazo[1,2-a]pyridine core nucleus and to screen them for preliminary *in vivo* anticonvulsant studies. In the following sections, a brief account on epilepsy, its treatment, antiepileptic agents, their possible mechanisms of action and anticonvulsant screening program (ASP) have been given.

1.7 ANTICONVULSANT STUDIES

1.7.1 Introduction

Our brain is the control centre of the body which is made up from millions of nerve cells called neurons. The neurons communicate with each other by means of small electrical signals. A seizure happens when there is a brief change or break in the way of electrical signals. Epilepsy is a disease that causes seizures to occur. Thus, epilepsy is a collective term used for about 40 different types of serious disorders of the brain characterized by excessive temporary neuronal discharge resulting in unprovoked seizures (Pessah et al. 2009). During a seizure, a person has movements or feelings that he or she cannot control. In epilepsy, the normal pattern of neuronal activity becomes disturbed, causing strange sensations, emotions or sometimes convulsions, muscle spasms, and loss of consciousness. Seizures sometimes do cause brain damage, particularly if they are severe.

A variety of different electrical or chemical stimuli can easily give rise to a seizure in any normal brain. The epileptic seizure always reflects abnormal hyper synchronous electrical activity of neurones caused by an imbalance between excitation and inhibition in the brain. Neurones are interconnected in a complex network in which each individual neurone is linked through synapses with hundreds of others. A small electrical current is discharged by neurones to release neurotransmitters of synaptic levels to permit communication with each other. More than hundred neurotransmitters or neuromodulators have been shown to play a role in neuronal excitation. However, the major excitatory neurotransmitter in the brain is L-glutamate and the major inhibitory neurotransmitter in the brain is gamma-amino butyric acid (GABA). An abnormal function of either of these could result in a seizure. An excited neurone will activate the next neurone whereas an inhibitory neurone will not. A normal neurone discharges repetitively at a low baseline frequency. If neurones are damaged, injured or suffered electrical or metabolic insult, a change in the discharge pattern may develop. In the case of epilepsy, regular low-frequency discharges are replaced by bursts of high-frequency discharges usually followed by periods of inactivity. An epileptic seizure is triggered when a whole population of neurons discharges synchronously in an abnormal way. This abnormal discharge may remain localized or it may spread to adjacent areas, recruiting more neurons as it spreads.

1.7.2 Types of epilepsy

The clinical classification of epilepsy recognizes two categories, viz. partial seizures and generalized seizures, although there are some overlaps and many varieties of each. A seizure is said to be partial if it is restricted to a regional disturbance. Partial seizures are those in which the discharge begins locally and often remains localized. These may produce relatively simple symptoms without loss of consciousnesses, such as involuntary muscle contractions, abnormal sensory experiences, autonomic discharge or they may cause more complex effects on consciousness, mood and behaviour.

Generalized seizures involve the whole brain, including the reticular system, thus producing abnormal electrical activity throughout both hemispheres. Immediate loss of consciousnesses is characteristic of generalized seizures (Bienvenu et al. 2002). The main categories are generalized tonic-clonic seizures (grand mal) and absence seizures (petit mal). A generalized tonic-clonic seizure consists of an initial strong contraction of the whole musculature, causing a rigid extensor spasm. Respiration stops, while defecation and salivation often occur. This tonic phase lasts for about few seconds and is followed by a series of violent, synchronous jerks, which gradually dies out in 2-4 minutes. Most types of epilepsy are characterized by more than one type of seizure. Patients with focal (or partial) epilepsy may have simple partial, complex partial and secondarily generalized tonic-clonic seizures. Thus, no seizure type is specific for a single type of epilepsy. Seizures are symptoms, and patients should be treated for a type of epilepsy, not for a type of seizure (Benbadis et al. 2001).

1.7.3 Causes of epilepsy

Approximately 1% of the world's population is suffering from epilepsy, which is the second most common neurological disorder after stroke. The cause of convulsions must be clearly understood through some precise observations. The type of seizure depends on the site of the focus in the brain. Epileptic attack can be caused by biochemical insults to the brain, such as hypoglycaemia, anoxia, hypocalcaemia, hyperventilation, water intoxication and sudden withdrawal of certain drugs such as barbiturates or alcoholic drinks. Epilepsy can also be caused by previous active pathology, such as birth trauma to the brain, during or following meningitis, trauma to the skull, cerebral abscesses, cerebral infarction, cerebral haemorrhage or

subarachnoid haemorrhage. Further analysis shows that the blockade of post-synaptic gamma-amino butyric acid receptors or an inhibition of GABA synthesis is the principal origin of brain discharge.

Epilepsy is not a hereditary disease. Therefore, it is clear that anyone can get epilepsy at any time in their lives. An epileptic attack can be triggered by a sensory stimulus, which is specific for individuals. On the other hand, maternal infections, poor nutrition, and oxygen deficiencies are some of the conditions that causes epilepsy in new born babies and children. However to date, there is no single unifying explanation on how these diverse factors cause seizures. Hence, it is difficult to determine the exact cause of epilepsy, even though it has been possible to investigate the physiological events which participate in the genesis of epilepsy.

1.7.4 Diagnosis of epilepsy

Pharmacologists have developed a number of different tests (Chadwick 1990 & Benbadis and Tatum 2001) to find out whether a person has epilepsy and, if so, what kind of seizures the person has. In some cases, people may have symptoms that look very much like a seizure but in fact are non-epileptic events caused by other disorders. Even physicians may not be able to tell the difference between these disorders and epilepsy without intensive testing. Some of the important methods of diagnosis have been discussed here below.

1.7.4.1 EEG monitoring

An electroencephalography (EEG) is the most common diagnostic test for epilepsy which records brain waves detected by electrodes placed on the scalp. This can detect abnormalities in the brain's electrical activity. People with epilepsy frequently have changes in their normal pattern of brain waves, even when they are not experiencing a seizure. However, in certain cases people retain their normal pattern of brain waves after certain time of epileptic seizures. In such cases, EEG becomes unable to detect abnormalities in the deep brain. Therefore, it is advisable to perform EEG within 24 hours of first epileptic attack.

1.7.4.2 Brain scanning

One of the most important ways of diagnosing epilepsy is through the use of brain scans. The most commonly used brain scans include computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI). CT and MRI scans reveal the structure of the brain, which can be useful for identifying brain tumours, cysts and other structural abnormalities. PET and an adapted kind of MRI called functional MRI (fMRI) can be used to monitor the brain's activity and detect abnormalities. Single photon emission computed tomography (SPECT) is a relatively new kind of brain scan that is sometimes used to locate seizures in the brain.

1.7.4.3 Blood test

An epileptic blood test measures the amount of the hormone prolactin present in the blood. It helps to determine whether a seizure is caused by epilepsy or another disorder. Physicians often take blood samples for testing, particularly when they are examining a child. These blood samples are frequently screened for metabolic or genetic disorders that may be associated with the seizures and also may be used to check for underlying problems such as infections, lead poisoning, anaemia and diabetes that may be causing or triggering the seizures. However, this test must be undertaken within 15-20 minutes of seizure to obtain valuable information.

1.7.4.4 Developmental, neurological and behavioral tests

Physicians often use tests devised to measure motor abilities, behaviour and intellectual capacity as a way to determine how the epilepsy is affecting that person. These tests also can provide clues about what kind of epilepsy the person has.

1.7.4.5 Medical history

Taking a detailed medical history, including symptoms and duration of the seizures, is also one of the best methods to diagnosis of the epilepsy.

1.7.5 Treatment for epilepsy

Different types of treatments are available for epilepsy. In medication, accurate diagnosis of the type of epilepsy is crucial for finding an effective treatment. Currently available treatments can control seizures in at least about 70-80 percent of people

affected with epilepsy. Once epilepsy is diagnosed, it is important to begin treatment as soon as possible.

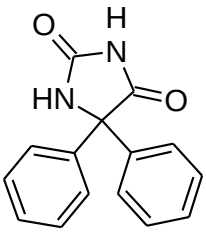
Currently, pharmacological treatment is the prime choice to cure or prevent seizures (Aiken and Brown 2000). Traditional drugs such as phenytoin (**S-1.72**), carbamazepine (**S-1.73**), benzodiazepine (**S-1.74**), ethosuximide (**S-1.75**), valproic acid (**S-1.76**) and phenobarbital (**S-1.77**) prevent seizures by either acting as $GABA_A$ receptor agonists or by blocking calcium or sodium channels (Macdonald and McLean 1986). These drugs are called "first generation" AED's, while those drugs which have been introduced recently are called "second generation" AED's (Löscher 1998), which have the same mechanism of action as first generation AEDs. Important therapeutics such as Felbamate (**S-1.78**), Gabapentin (**S-1.79**), Lamotrigine (**S-1.80**), Levetiracetam (**S-1.81**), Pregabalin (**S-1.82**), Tiagabine (**S-1.83**), Oxcarbazepine (**S-1.84**), Vigabatrin (**S-1.85**) and Zonisamide (**S-1.86**) are coming under second generation AEDs. About 60-70% of epileptic patients are treated by the above medications. The structures of these classical drugs are listed in Figure 1.1.

When seizures cannot be adequately controlled by medications, physicians may recommend surgery. Surgery for epilepsy ranges from small resections of the cerebral cortex, to the removal of one or more cerebral lobes, or of an entire hemisphere. In other instances, surgery disconnects epileptogenic tissue from adjacent cortex, or interrupts the large fibre bundles connecting both hemispheres. The size and location of the epileptogenic areas and their corresponding function determine the type and extent of surgery.

Studies have shown that, in some cases, children may experience fewer seizures, if they maintain a strict diet rich in fats and low in carbohydrates. This unusual diet, called the ketogenic diet, causes the body to break down fats instead of carbohydrates to survive. This condition is termed as ketosis.

1.7.6 Mechanism of action of antiepileptic drugs

The exact mechanism through which antiepileptic drugs (AEDs) work against epilepsy is still not clear. At the cellular level, three major mechanisms of action of antiepileptic drugs are recognised, viz. modulation of ion channels, enhancement of GABA inhibitory neurotransmission, and attenuation of glutamate mediated excitatory transmission (Kwan et al. 2001).



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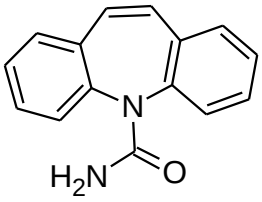

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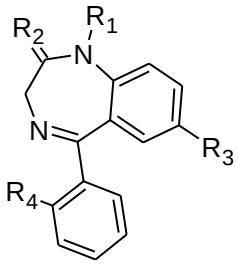

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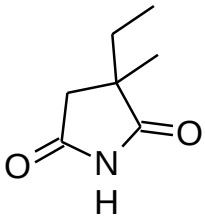

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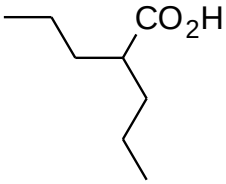

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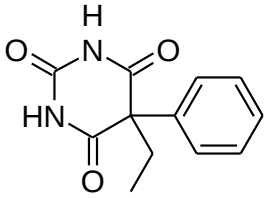

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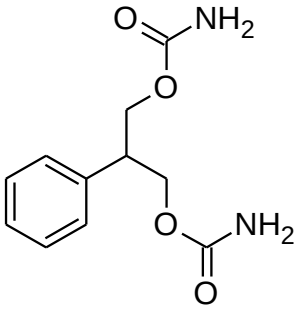

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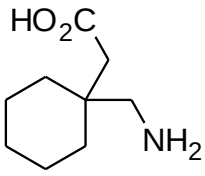

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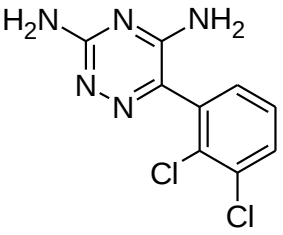

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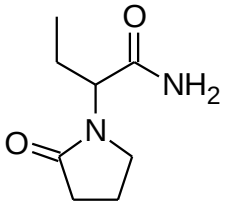

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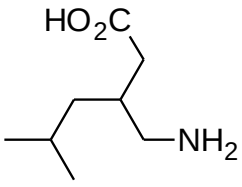

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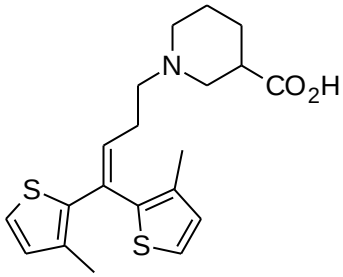

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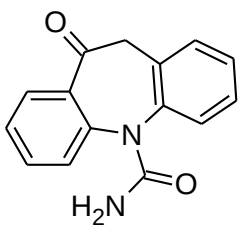

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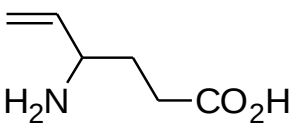

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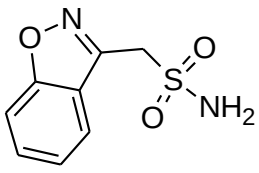

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Figure 1.1: Structures of important first and second-generation antiepileptic drugs.

1.7.6.1 Modulation of ion channels

The intrinsic excitability of the nervous system is ultimately controlled by voltage-gated ion channels, which regulate the flow of cations across the surface and internal cell membranes.

The sodium channel is arguably the most important and responsible for depolarization of the cell membranes and the characteristic upstroke of the neuronal action potential. Blockade of voltage-gated sodium channels is the most common mechanism of action amongst currently available AEDs (Deckers et al. 2003). Well established AEDs, phenytoin and carbamazepine are prototype sodium channel blockers and this mechanism is shared by the newer drugs lamotrigine, felbamate, topiramate and oxcarbazepine. These drugs mainly bind to the inactivated state of the sodium channel and produce a voltage- and frequency-dependent reduction in channel conductance, resulting in a limitation of repetitive neuronal firing with little or no effect on the generation of single action potentials (Kwan et al. 2001). Similar to sodium channels, voltage-gated calcium channels are also involved in depolarization, in response to action potential. Calcium channels are distributed throughout the nervous system on dendrites, cell bodies and nerve terminals. These channels represent a major target for AEDs.

1.7.6.2 Enhancement of inhibitory neurotransmission

GABA is the predominant inhibitory neurotransmitter in the mammalian central nervous system. Following synaptic release, GABA acts at three specific receptors, $GABA_A$, $GABA_B$, and $GABA_C$ (Deckers et al. 2003). The GABA belongs to the ligand-gated ion channel super-family and responds to GABA binding by increasing chloride conductance, resulting in neuronal hyperpolarization. GABA is removed from the synaptic cleft into localised nerve terminals and glial cells by specific transport molecules. Thereafter, GABA is either recycled to the readily releasable neurotransmitter pool or metabolized by the action of the mitochondrial enzyme GABA-transaminase, thereby completing the cycle. Phenobarbital and the benzodiazepines bind to distinct sites on the $GABA_A$ receptor complex and exert an allosteric influence on the opening of the chloride ion channel in response to GABA. Phenobarbital increases the duration of channel opening, while the benzodiazepines

increase the frequency of opening. Vigabatrin and tiagabin exert their antiepileptic actions by selective effects at the GABA synapse. The pictorial representation of ion channels and their mechanism of action is given in Figure 1.2.

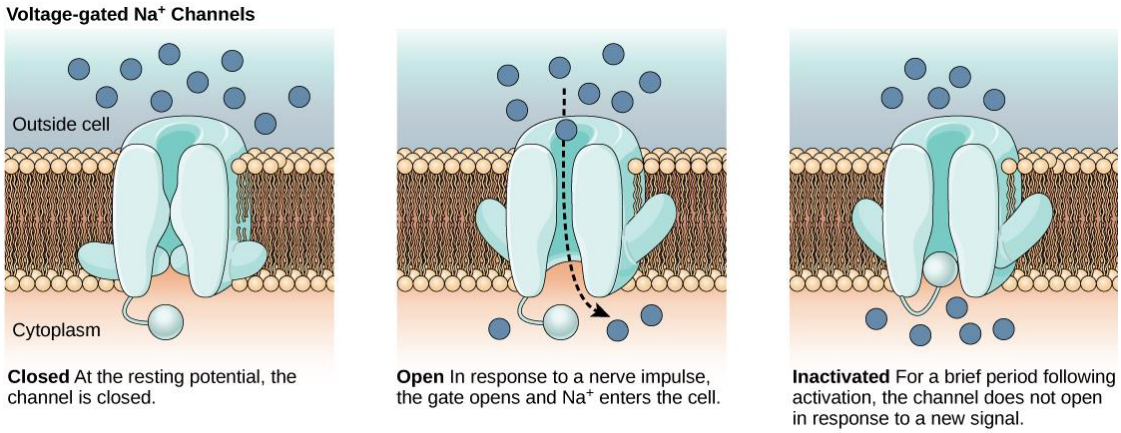


Figure 1.2: Pictorial representation of ion channels and their mechanism of action

1.7.6.3 Attenuation of excitatory neurotransmission

Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Following synaptic release, it exerts its effects on both ionotropic and metabotropic receptor types. The ionotropic glutamate receptors are arguably the best characterized and are classified into three subtypes, (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) AMPA, kainite and (N-Methyl-D-aspartic acid or N-Methyl-D-aspartate) NMDA, which form ligand-gated ion channels permeable to sodium and depending on subtype and subunit composition, calcium ions. The AMPA and kainite subtypes are implicated in fast excitatory neurotransmission, whereas the NMDA receptor, quiescent at resting membrane potential, is recruited during periods of prolonged depolarization (Kwan et al. 2001). None of the currently available AEDs exert its pharmacological effects solely by an action on the glutamatergic system (Deckers et al. 2003). However, blockade of the NMDA subtype of glutamate receptor has been reported to contribute to the antiepileptic effects of felbamate.

However, this classification has limited value because the majority of AEDs possess more than one mechanism of action, which may account for their efficacy and it is also the fact that some of the clinically used drugs have not been linked with a specific site of the brain, and the exact mechanisms of many AEDs remain unknown.

1.7.7 Anticonvulsant screening

The anticonvulsant screening program (ASP) involves a combination of mechanistic, non-mechanistic and 'seizure-type' approach to identify potential compounds for the treatment of seizures. The initial screening procedures are broad and non-mechanistic and serve to identify CNS and minimal neurotoxic activity of the compound. Once identified in the initial non-mechanistic screens, the activity of compounds is then differentiated using 'syndrome-specific' animal seizure models. Finally, advanced studies are used to identify proconvulsant potential of compounds, tolerance to the anticonvulsant effects, and possible molecular targets that can contribute to a mechanism of action of compounds.

The *in vivo* animal models are the majorly used and widely accepted methods for the identification of preliminary anticonvulsant property in a newly synthesized compound. The maximal electroshock (MES) (Krall et al. 1978) and subcutaneous pentylene tetrazole (scPTZ) (Clark et al. 1984) screening methods are the two important and routinely used animal models for the anticonvulsant studies. Therefore, these two methods have been selected for evaluating antiepileptic property of targeted DHP and imidazo[1,2-a]pyridine entities. Other few methods for the screening studies include 6 Hz model, metrazole, strychnine and picrotoxin induced seizure methods. Further, Rotarod technique (Dunham and Miya 1957) has been selected for the toxicity study of new derivatives. The procedures of these *in vivo* studies are discussed in detail in Chapter 4.

These initial screening procedures are broad and non-mechanistic and they serve to identify CNS and minimal neurotoxic activity of the compound. Based on the potency of the molecules in preliminary antiepileptic studies, the compounds can be taken further for the detailed antiepileptic studies. The detailed screening involves the identification of time to peak pharmacodynamics effect (TPE), wherein effective doses (ED_{50}), median toxic doses (TD_{50}) and protective index (PI) will be calculated. The *in vitro* studies will be generally used for the identification of mechanism of action of target compound, which followed by proconvulsant, behavioural and metabolism studies. In our present study, we mainly focus on synthesis of new active DHP and imidazo[1,2-a]pyridine derivatives, and their preliminary anticonvulsant evaluation.

Depending on the potency of the molecules in the preliminary screening study, it has been planned to carry out the detailed pharmacological studies in the near future.

1.8 AN OVERVIEW OF THE PRESENT WORK

At present, there are about 40-50 antiepileptic drugs are available in the market. However, none of these drugs are able to cure the disease completely. All the drugs are rather concerned only on control of the seizure, which is causing epilepsy. Therefore, in most of the cases epileptic patients are advised to take continuous medications for years together. Such intake of drugs for long period certainly induces many side effects on the body. This scenario in the field of epilepsy significantly demands the development of new efficient antiepileptic agents which can overcome the limitations of present anticonvulsant therapy. So, lots of research on synthesis and antiepileptic investigation of new chemical entities are going on all over the globe.

In search of new efficient anticonvulsant agents with better activity, it has been planned to design and synthesize several new dihydropyridine and imidazo[1,2-a] pyridine derivatives containing suitable pharmacophores, following appropriate synthetic routes. It has contemplated to characterize the new compounds by various spectral methods such as FTIR, ^{1}H NMR, ^{13}C NMR, mass spectrometry followed by elemental analyses. Further, it is aimed to screen the new target compounds in order to investigate their *in vivo* anticonvulsant property following MES, and scPTZ methods and to study their neurotoxicity by Rotarod technique.

In the next chapter, a detailed literature survey on the reported anticonvulsant activity of various derivatives of heterocycles such as DHP, imidazo[1,2-a]pyridine, triazole, pyrimidine, pyrazole, followed by amide and hydrazones, have been discussed. Further, it includes the scope and objectives of the present work. At the end, the designs of new target compounds have been discussed in detail.

CHAPTER-2

LITERATURE SURVEY, SCOPE, OBJECTIVES AND DESIGN OF NEW PYRIDINE DERIVATIVES

Abstract

This chapter describes a thorough literature survey on the anticonvulsant profile of various derivatives of heterocycles such as DHP, imidazo[1,2-a]pyridine, triazole, pyrimidine, pyrazole, oxazole as well as different amides and hydrazones. It also includes the scope and objectives of the present research work. Further, it encompasses the design of new pyridine derivatives as possible anticonvulsant agents, based on the literature survey.

2.1 INTRODUCTION

In the previous chapter, the chemistry and medicinal importance of dihydropyridine and imidazo[1,2-a]pyridine derivatives have been discussed. These pyridine derivatives were found to display variety of CNS related activities, including antiepileptic property. In fact, epilepsy is a major neurological disorder of brain, characterized by unprovoked, recurring seizures that disrupt the nervous system and can cause mental and physical dysfunction, as explained in the previous chapter. A global health campaign against epilepsy by World Health Organisation (WHO) found that about 50 million people worldwide affected by this neurological disorder (Karakurt et al. 2010) and every year about 2.4 million such new cases are added to these figures (Daras et al. 2007). Regrettably, the cellular mechanism of human epilepsy is still uncertain and hence the present drug therapy is rather concerned only with control of epileptic symptoms than curing (Kenda et al. 2004). Though there are more than 40 different AEDs presently in clinical use, still about 30% of patients experience uncontrolled seizures and they are pharmaco-resistant to the available treatment (Picot et al. 2008). Further, present therapy for seizure requires continuous medication for long period, which in turn associated with many adverse side effects such as nausea, ataxia, drowsiness, hyperplasia, etc. (Naithani et al. 2010; Lin et al. 1997). These observations clearly demonstrate the scope and need for the development of new anticonvulsant agents having improved seizure control along with better tolerability. In this direction, the present research plan is originated with an intention of developing new antiepileptic agents having improved bioactivity.

2.2 LITERATURE SURVEY

During the past four decades, effective research has been carried out in order to develop new therapeutics against epilepsy. As a result, many new antiepileptic drugs such as Phenytoin, Benzodiazepines, Carbamazepine, Phenobarbital, etc. have been invented in the middle of 20th century. However, a variety of dose dependent side effects and toxic property restricted their applicability as effective drugs. In the late 1990s, many new drugs such as Felbamate, Tiagabine, Gabapentine, Pregabatrin, Zonisamide, etc. have been developed as effective substitutes for trivial drugs. These newer drugs came up with improved efficiency and exhibited minimal side effects when compared with earlier medications. Nevertheless, they are also not free from certain side effects and hence search for new effective drugs without any side effect is still continues. As a result, design and development of new synthetic anticonvulsant agents gathered momentum all over the world.

According to the literature survey, pyridine derivatives, particularly dihydropyridine and imidazo[1,2-a]pyridines were found as effective structural scaffolds for the development of new anticonvulsant agents. Moreover, the presence of certain active pharmacophores such as hydrazone, amide, imine, triazole, pyrimidine, pyrazolone and oxazolone generally enhances the anticonvulsant activity when they are included in a suitable molecular framework (Kucukguzel et al. 2000; Deng et al. 2011). In the following pages, a brief account of important literature reports available on the antiepileptic activity of various agents carrying above-mentioned pharmacophores was discussed. Further, their structure-activity relationships (SAR) were highlighted.

2.2.1 Pyridines

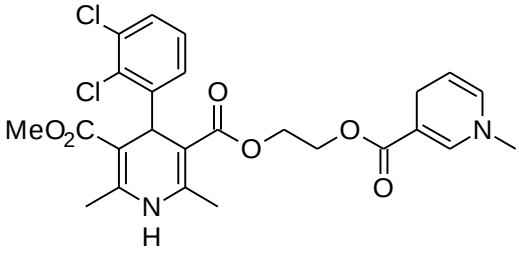
Pyridine and its derivatives find wide range of applications in medicinal chemistry due to their variety of biological activities. They were reported to possess anticonvulsant, anti-inflammatory (Liu et al. 2012), antihypertensive (Schleifer 1999), cardiodepressant (Budriesi et al. 2008), anticoagulant (Kumar et al. 2011), anti-HIV (Kawasuji et al. 2012), antitubercular (Moraski et al. 2012), hypnotic (Menegatti et al. 2006), anti-platelet (Ihmaid et al. 2012) and anticancer (Brzozowski et al. 2012), etc. activities. They were also known as enzyme inhibitors such as protein kinase inhibitor (Kendall et al. 2012). Various dihydropyridine derivatives such as Amlodipine,

Azelnidipine, Benidipine, Clinidipine, Clevidipine, Felodipine are potent antihypertensive as well as anticonvulsant drugs. Similarly, imidazo[1,2-a]pyridines like zolpidem, Alpidem, Saripidem and DS-1 are effective CNS agents. They are acting as hypnotic, anxiolytic, anticonvulsant and sedatives. Some important literatures on anticonvulsant activity of pyridine derivatives, viz. dihydropyridines and imidazo[1,2-a]pyridines are given below.

2.2.1.1 Dihydropyridines

Dihydropyridines are the important class of compounds acting as calcium channel blockers. Their various derivatives show prominent anticonvulsant and antihypertensive activities. In the following section, few significant literatures on antiepileptic activity study of various DHPs have been discussed.

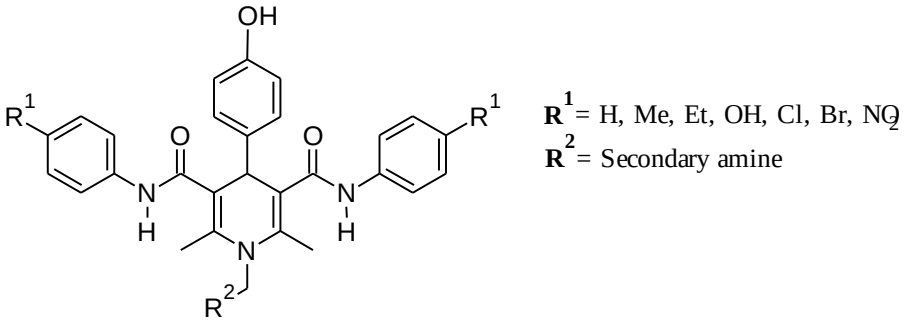
The anticonvulsant profile of well-known calcium channel blocker, Felodipin was evaluated in the year 1996 by Yiu and Knaus. With the expectation of better and selective antiepileptic activity, they coupled Felodipin with Bodor's lipophilic [(1-methyl-1,4-dihydropyrid-3-yl)-carbonyl]oxy(amino) chemical delivery system (CDS) (**S-2.1**), since CDS would enhance the selective drug delivery to the brain. This new compound displayed selective activity in MES method while it remained inactive in scPTZ screening study. Also, they found that this moiety would enter into brain very readily and then undergo facile oxidation to pyridinium species. Finally, the hydrolysis of this pyridinium derivative gives an active moiety responsible for anticonvulsant activity. Also, it was found that the efficacy of the coupled molecule is proportional to the rate with which the molecule undergoes hydrolysis upon reaching the brain.



S-2.1

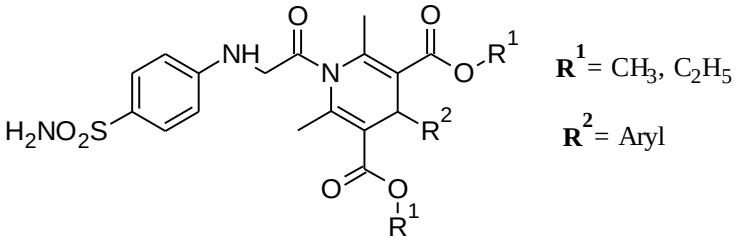
A new series of dihydropyridines carrying amide groups at position-3 and position-5 (**S-2.2**) was synthesized and evaluated for their anticonvulsant activity by Pattan and co-workers (2010). The compound possessing 5-aminotetrazole unit,

attached to DHP nitrogen and electron rich aryl systems at position-3 and position-5 exhibited prominent results in MES, scPTZ and Strychnine-induced convulsion screening methods.



S-2.2

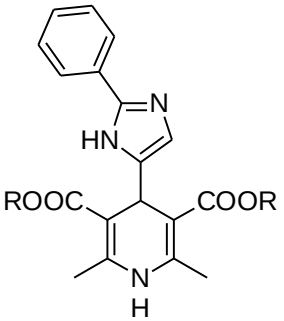
A research group headed by Subudhi (2009) evaluated new dihydropyridine based amides as potential anticonvulsant agents. According to them, presence of sulphonamide group at N_1 position of DHP ring would enhance their anticonvulsant activity. Also, they found that presence of electron donating aryl substituent at position-4 of DHP improves the activity. Compound **S-2.3** possessing sulphonamide group at N_1 position and electron rich vanillin group at position-4 emerged as lead compound.



S-2.3

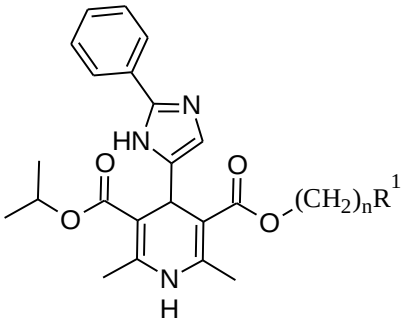
A research article by Navidpour and his co-workers (2004) described the design, synthesis and anticonvulsant evaluation of new 3,5-disymmetrically substituted (**S-2.4**) and unsymmetrically substituted 4-imidazolyl-1,4-dihydropyridines (**S-2.5**). They found the increased antiepileptic activity when alkyl chain length of two similar ester groups at position-3 and position-5 was increased. However, when a bulky group was included at these positions, the activity decreased. Compound possessing propyl chain showed very good result similar to reference drug, nifedipine. In contrast, for asymmetrical esters, increasing the length of the methylene chain

resulted in decreased activity. Compound carrying cyclohexyl group showed better activity among asymmetrical ester derivatives.



R= Me, Et, Propyl, t-Butyl

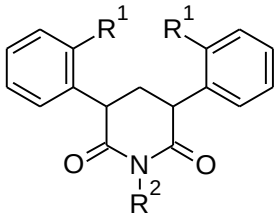
S-2.4



R^{1}= Phenyl, Cyclohexyl; **n**= 0-4

S-2.5

Recently, Babu et al. (2012) reported design and synthesis of a new series of 3,5-diarylpiperidin-2,6-dione derivatives (**S-2.6**) as prominent anticonvulsant agents. Compounds carrying unsubstituted NH group or those compounds, which contain NH_2 group, attached in the position of R_2, exhibited smaller ED_{50} values (10-11.5 mg/kg), which are comparable with standard drug carbamazepine. It was also observed that the substituents on two aryl rings have impact on the activity of the resulting molecules. Unsubstituted phenyl rings end up with enhanced activity while substitution by chloro group leads to lowering of antiepileptic activity. Based on the results, they found that free NH group of glutarimide moiety is responsible for hydrogen bonding interaction. Thus substitution of it by any group resulted in decreased activity.



R^{1}= H, Cl

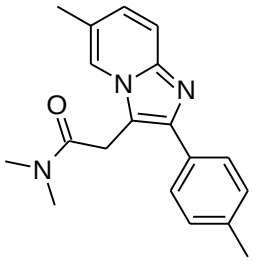
R^{2}= H, CH_3, Ph, Benzyl, NH_2, Tolyl

S-2.6

2.2.1.2 Imidazo[1,2-a]pyridines

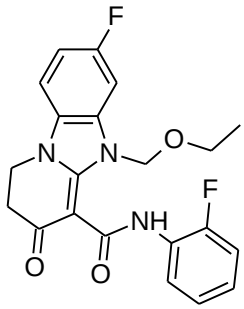
Imidazo[1,2-a]pyridine is a condensed pyridine derivative, known by its selective GABA agonist activity. Because of its GABA affinity, its derivatives display variety of CNS related activities such as anxiolytic, anticonvulsant, sedative and hypnotics. Few articles focussing on antiepileptic evaluation of imidazo[1,2-a]pyridines have been highlighted below.

Zolpidem (**S-2.7**) is a well-known non-benzodiazepine GABA agonist acting mainly as sedative and hypnotic agent. It is proved that Zolpidem can act as anticonvulsant agent also (Kralic et al. 2002; Rudolph et al. 1999). Recently, Vlainic and Pericic (2010) compared the hypnotic and anticonvulsant potency of Zolpidem by various experimental methods. They found that at lower doses (0.1-10 mg/kg), Zolpidem exhibits potential anticonvulsant activity. They also studied the anticonvulsant property by taking adult and aged mice in order to find the age-dependency of the drug. They found that at lower doses, the drug is not age-dependent.



S-2.7

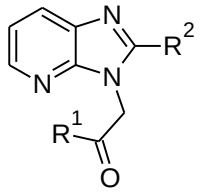
In an important study, Dubinsky and co-workers (2002) compared the pharmacological properties of an anxiolytic drug, RWJ-51204 (**S-2.8**), with those of full and partial $GABA_A$ agonists. The drug was shown to possess remarkable anticonvulsant activity when screened *in vivo* by scPTZ method. It exhibited antiepileptic activity with an ED_{50} value of 0.04 mg/kg, whereas its ED_{50} value for motor impairment was found to be 27 mg/kg, indicating about 700-fold separation between efficacy and motor impairment.



S-2.8

Anticonvulsant profile of new 2-phenyl imidazo[4,5-b]pyridine-3-carboxamides/esters (**S-2.9**) was investigated by Tomczuk et al (1991). They designed and synthesized the target molecules based on molecular disconnection hypothesis.

Compounds possessing phenyl substituent at second position of imidazo[4,5-b] pyridine ring were found to be inactive. On the other hand, those with 3-substituted phenyl substituents are moderately active, while 4-substituted phenyl analogues, particularly, 4-halophenyl derivatives showed enhanced activities. Further, compounds possessing ester and carboxylic acid groups at third position were inactive while those containing amide groups were found to be active against scPTZ induced seizure test. An acetamide derivative containing 4-chlorophenyl group at second position emerged as most active derivative among tested compounds.

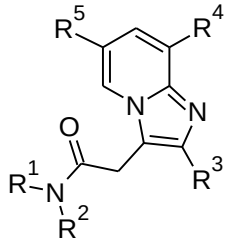


R^{1} = H, OMe, OEt, NH_2, Substituted amines

R^{2} = Aryl

S-2.9

The appropriate structural requirement for a imidazo[1,2-a]pyridine derivative (**S-2.10**) to bind selectively into benzodiazepine receptor was investigated by Denora and his co-workers (2008). They observed that variation at position-2 and position-8 are crucial for making imidazo[1,2-a]pyridines as either selective central benzodiazepine or peripheral benzodiazepine receptor binders. Based on their series of reactions, it was found that substitution at position-8 by a lipophilic unit and position-2 by a 4-halophenyl group makes the molecule more selective towards central benzodiazepine receptor. Incorporation of hydrophilic groups such as hydroxyl, amine, carboxylic, etc. at *para* position of phenyl ring at position-2 makes the molecule more selective towards peripheral benzodiazepine receptor.



R^{1} = Me, H, Propyl;**R**^{2} = Propyl, Butyl, Pheny

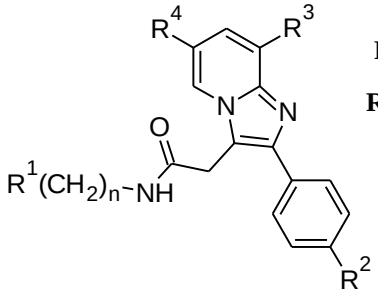
R^{3} = Aryl

R^{4} = Cl, $NHCOCH_2CO_2H$; **R**^{5} = H, Cl

S-2.10

A research group led by Trapani (2003) synthesized new alpidem analogues (**S-2.11**) containing GABA and glycine moiety. They evaluated their GABA/benzodiazepine binding affinity by means of detailed *in vitro* and *in vivo*

studies. The logP (lipophilicity) values of the target compounds were found to be above 2.1 (which is minimum lipophilicity required for a molecule to pass the blood brain barrier). From the *in vitro* study by radioligand binding assay, they found that new compounds possess greater selectivity towards GABA receptors. These results further supported by their *in vivo* study, wherein satisfactory results were obtained in scPTZ screening method. Authors observed that, presence of GABA or glycine moiety in the molecule at position-3 enhanced their activity when compared with compounds with simple carboxylate groups at position-3 of imidazo[1,2-a]pyridines.



R^{1} = CO_2Et, Propyl; **n**= 0, 1, 3
R^{2} = H, Cl; **R**^{3} = H, Cl; **R**^{4} = Cl

S-2.11

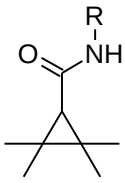
From the above literature survey, it is clear that dihydropyridine and imidazo[1,2-a]pyridines containing appropriate pharmacophores are prominent anticonvulsant agents. Keeping this in view, the present research work is aimed at design and development of new DHPs and imidazo[1,2-a]pyridines carrying suitable pharmacophores as possible anticonvulsant agents. Further, based on medicinal importance of hydrazone, triazole, oxazolone, pyrazole etc., it has been decided to incorporate above mentioned organic entities with DHPs and imidazo[1,2-a]pyridines using proper reaction routes. It is hoped that, such new organic compounds would come out as good anticonvulsant agents with enhanced activity. A brief account of literatures on the medicinal importance of different pharmacophoric systems such as amides, hydrazones, triazoles, pyrazoles, pyrimidines and oxazolones is highlighted below.

2.2.2 Amides and hydrazones

Amides and hydrazones are important groups that are responsible for enhanced anticonvulsant activity of many organic compounds. Important AEDs such as acetazolamide, zonisamide, and topiramate are containing amide functionality in their structure. The hydrogen bonding capability of hydrazone and amide functional groups

are found to be responsible for their improved activity. Several heterocyclic hydrazones were reported to possess various biological activities viz. antimicrobial (Osorio et al. 2012), anti-inflammatory (El-Sayed et al. 2011), analgesic (Eissa et al. 2009), anticonvulsant (Tripathi et al. 2011), antitubercular (Pathak et al 2012), antiplatelet (Silva et al. 2004), anticancer (Altintop et al. 2012), antiviral (Kumar et al. 2010) and antimalarial (Walcourt et al. 2004) activities. Interestingly, aryl hydrazones with terminal electron donating groups were shown to possess enhanced hydrogen bonding capabilities, which influence significantly on their anticonvulsant activity (Dimmock et al. 2000). Similarly, amides are also shown to possess wide spectrum of biological activities, such as anticonvulsant (Azam et al. 2009; Shimshoni et al. 2008) anti-inflammatory (Raghavendra et al. 2012; Takahashi et al. 2012), antimicrobial (Padmavathi et al. 2011), anti-tubercular (Thomas et al. 2011) as well as anticancer (Lu et al. 2010) properties. In the following section, a brief literature-survey on anticonvulsant profile of amides and hydrazones are highlighted.

In pioneering studies, Shimshoni et al. (2008) designed and synthesized new tetramethyl cyclopropane carboxamide derivatives (**S-2.12**) as potential anticonvulsant agents. They compared the potency of the new molecules with standard drug valproic acid. They synthesized new compounds by replacing valproic group of standard drug by tetramethyl cyclopropane carboxamide and observed diminished activity for the synthesized compounds in MES method. However, compound possessing amide and sulphonamide groups showed similar ED_{50} value as zonisamide and emerged as potent derivatives among screened molecules.

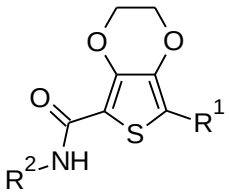


R= Aryl, Benzyl

S-2.12

Anticonvulsant activity of new 3,4-ethylenedioxythiophene derivatives containing amide and thioamide pharmacophores (**S-2.13**) was evaluated by Kulandasamy et al. in the year 2010. Many of the newly synthesized amide derivatives exhibited activity at a dose of 100 mg/kg when screened by 6Hz method. From Rotarod-toxicity study, they found that the compounds are non-toxic at all tested

doses. Further, amides obtained from electron rich xylidine and aniline moieties exhibited enhanced activity.

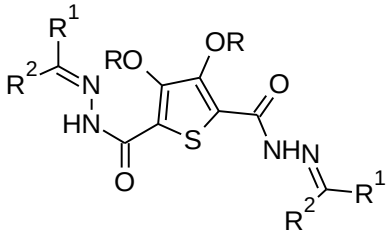


$\mathbf{R^1}$ = CO_2Et, CO_2H, COPh

$\mathbf{R^2}$ = Aryl

S-2.13

In an effort to study the anticonvulsant activity of certain hydrazone derivatives, Kulandasamy et al. (2009) have synthesized new thiophene based bishydrazones as prominent anticonvulsant agents. They varied the alkoxy chain length at position-3 and position-4 of thiophene ring (**S-2.14**) and found that propyloxy derivative exhibited very good activity. In addition, they introduced different aryl groups at position-2 and position-5 via hydrazone linkage. According to authors, compounds carrying hydroxyphenyl and nitrophenyl moieties displayed the highest activity.



R=Propyl, Heptyl, Benzyl

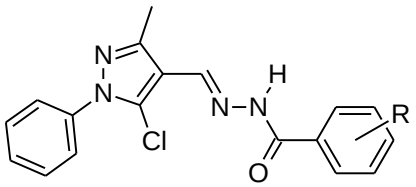
$\mathbf{R^1}$ = H, CH_3; $\mathbf{R^2}$ = Aryl, Heterocyclic

S-2.14

Various research groups such as Yogeeswari et al. (2004, 2005), Dimmock et al. (1993, 1996), Pandeya et al. (2002) and Aggarwal et al. (2004) studied anticonvulsant activity of about 250 new semicarbazones carrying different heterocyclic systems and reported their SAR studies. They found that the substitution in the aryl ring by halogens increases potency in the MES screening. Amongst the different tested compounds, most of them exhibited good activity in the preliminary screening and even some of the selected compounds from this series entered into the next phase of the pharmacological studies. The potent compounds were found to act by blocking the voltage-gated sodium ion channels in neuron cells.

In search of new potent anticonvulsant agents, Kaushik et al. (2010) synthesized new N'-[(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene] 2/4-

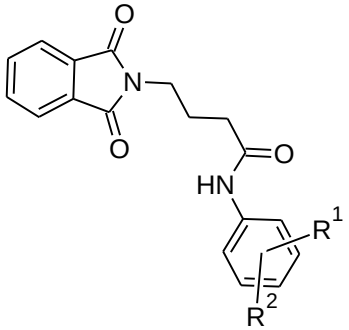
substituted hydrazones (**S-2.15**) as anticonvulsant agents. The preliminary screening results by MES and scPTZ methods showed that most of the tested compounds were short-acting anticonvulsants (0.5 hour). They found enhanced activity when *para* position of phenyl ring was substituted by electron withdrawing groups. They also calculated logP values for selected compounds and the results indicated the lipophilic nature of the compounds.

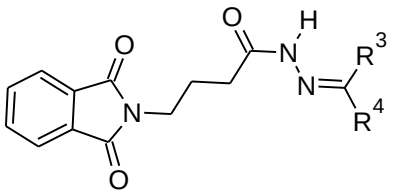


R= Aryl, Benzyl

S-2.15

New phthalimide coupled GABA amides (**S-2.16**) and hydrazones (**S-2.17**) were evaluated as potent anticonvulsant agents by Ragavendran and co-workers (2007). All the tested compounds were inactive in MES method, while many compounds displayed activity in scPTZ method at doses ranging from 30 to 300 mg/kg. In addition, they screened final compounds by ipPIC method and obtained very good results at a small dose of 30 mg/kg. Moreover, they calculated lipophilicity of the target molecules and found that lipophilicity alone cannot account for differences in anticonvulsant activity but rather a better fit into a putative molecular target due to favourable steric interactions. The comparative study of a series of amides with corresponding hydrazones revealed that amides are more potent as well as more toxic than hydrazones. In the study, compounds containing electron donating methyl substituents emerged as lead moieties.





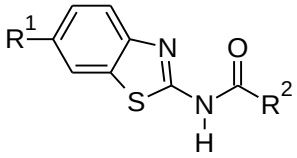
R^{1}= H, Me, Cl;**R**^{2}= F, Cl, Br, Me, CF$_3$

R^{3}= H, Me, Et, Ph;**R**^{4}= Aryl

S-2.16 **S-2.17**

Recently, Hassan et al. (2012) synthesized new N-(substituted benzothiazol-2-yl) amides (**S-2.18**) and evaluated them as prominent anticonvulsant agents. The final

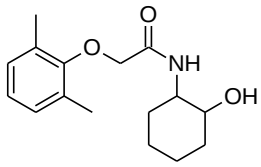
compounds exhibited selective activity in MES method, which is a measure of ability of a compound to act against generalized toni-clonic seizures. The amide obtained from 3-phenoyl propylamine was emerged as lead compound that exhibited rapid onset and long duration of action at a small test dose of 30 mg/kg. Unlike other screened compounds, it also showed activity in scPTZ method, which is a measure of ability of a compound to raise seizure threshold.



R^{1}= H, Cl, Br;**R**^{2}= Alkyl, Aryl

S-2.18

A research group headed by Pekala (2011) synthesized and investigated anticonvulsant property of new 2-(2,6-dimethylphenoxy)-N-(2-hydroxycyclohexyl) acetamides. The time to peak effect (TPE) assay of new compounds revealed that certain compounds such as **S-2.19** exhibited activity 15 min after sample administration, showing that the synthesized compounds itself are anticonvulsant active but not their any metabolites. In addition, the various possible stereo-isomers of **S-2.19** were isolated and it was found that each isomer displayed different extent of activity. Its *in vivo* anticonvulsant results indicated that stereochemistry plays an important role in biological activity of any compound. The electrophysiological study showed that **S-2.19** acts by blocking sodium currents as well as by enhancing GABA effect.



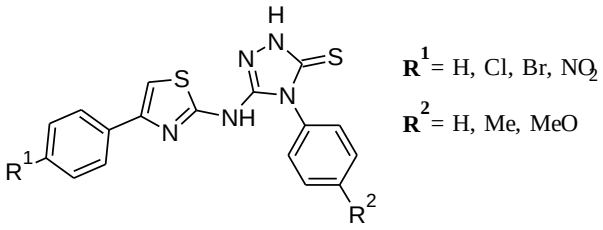
S-2.19

On the basis of literature reports on biological applications of amides and hydrazones, it can be concluded that incorporation of such functionalities achieves enhanced anticonvulsant activity. Owing to their importance, in the present research work it has been decided to include these pharmacophoric groups at suitable positions of DHP and imidazo[1,2-a]pyridine, to achieve enhanced activity.

2.2.3 Triazoles

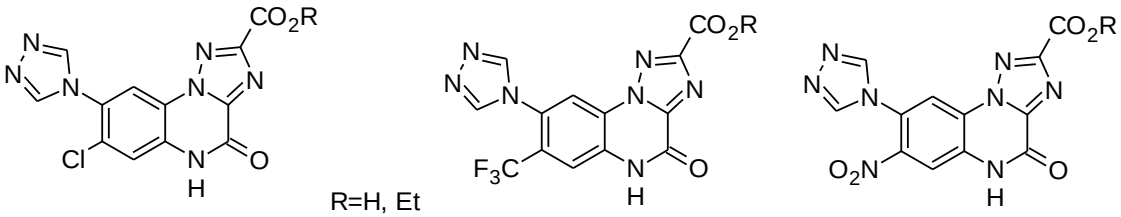
Triazole is an important five membered heterocyclic system, which exhibit variety of biological activities. Particularly, triazole is found to possess greater affinity towards epileptic receptors, probably due to their hydrogen bonding capabilities (Deng et al. 2011). In the following pages, few important literatures involving anticonvulsant investigation of various triazoles have been highlighted.

Siddiqui and Ahsan (2010) evaluated the anticonvulsant profile of triazoles carrying thiazoles (**S-2.20**) by introducing necessary groups such as hydrogen bonding donors, distal ring and hydrophobic unit at suitable positions. They observed the enhanced activity for compounds carrying nitro substituted aryl group, but they exhibited high toxicity. According to authors, the presence of electron withdrawing groups on thiazole ring and electron donating aryl systems on triazole group has enhanced the activity. In particular, those possessing halophenyl group and alkyl/alkoxyphenyl group, respectively on thiazole and triazole moieties exhibited the highest activity at 30 mg/kg dose.



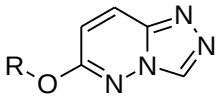
S-2.20

Catarzi et al. reported synthesis and anticonvulsant activity of new triazole based organic compounds as selective AMPA receptor antagonists in 2004. Based on their previous paper on SAR studies (Catarzi et al. 2001), they obtained **S-2.21** as potent AMPA antagonist. However, due to very close resemblance of AMPA and KA receptors, **S-2.21** also displayed affinity towards KA receptor. In search of selective AMPA antagonists, they further replaced 7-chloro group of **S-2.21** by various substituents and found that trifluoromethyl (**S-2.22**) and nitro (**S-2.23**) groups are effective to make the molecule more selective towards AMPA receptor. In addition, enhanced activity was observed when they incorporated carboxylic acid group on triazole moiety, while relatively less activity was found for corresponding ethyl esters.



S-2.21 **S-2.22** **S-2.23**

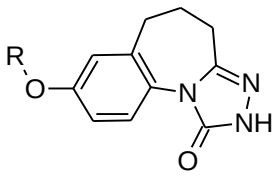
A research group headed by Guan (2010) synthesized a series of 6-alkoxy/aryloxy-[1,2,4]triazolo[4,3-b]pyridazine derivatives (**S-2.24**) as potent anticonvulsant agents. They observed very good results for all the tested compounds in MES method. Further, they noticed that compound possessing 2,4-dichlorophenyl substituted analogue showed the highest activity with ED_{50}=17.3 mg/kg which is very close to widely prescribed antiepileptic drug Phenobarbital. This compound exhibited greater margin of safety (HD_{50}/ED_{50}=43.2) which is much higher than any other prototype drug whose HD_{50}/ED_{50} values are much less than 20.



R= n-Alkyl, Aryl

S-2.24

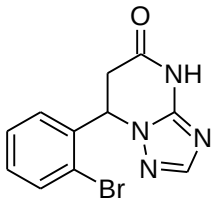
Recently, novel 8-alkoxy-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepin-1-ones (**S-2.25**) were successfully synthesized as new anticonvulsant agents by Piao and his colleagues (2011). They obtained good results for those compounds which possess haloaryl substituents, wherein the order of reactivity was F>Cl>Br. Also, among all compounds, *meta* substituted derivatives exhibited more activity than *ortho* substituted analogues which in turn more active than *para* substituted compounds. These new compounds showed diminished activity against chemically induced seizure model (scPTZ). *Meta*-fluoro substituted derivative was obtained as the most active antiepileptic agent of the series with ED_{50}= 17.6 mg/kg.



R= n-Alkyl, Benzyl, Aryl

S-2.25

Deng and co-workers (2011) described the synthesis and anticonvulsant activity of 7-(substituted-phenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-ones and their derivatives. They found that new compounds are potent molecules against electrically induced seizures. The most active compound **S-2.26** exhibited ED_{50} of 19.7 mg/kg, which is very close to that of marketed drugs such as phenytoin and carbamazepine, while better than that of phenobarbital and sodium valproate. Similarly, it's TD_{50}=684.7 mg/kg value is higher than those of the above standard drugs. The SAR study of new molecules revealed that presence of halogen substituted aryl rings would enhance the anticonvulsant property considerably. They also replaced triazole by imidazole, pyrazole and phenyl imidazole, in order to compare the bio-activity of these molecules. Amongst these tested compounds, triazole derivatives showed the highest activity. Pyrazole analogues also exhibited similar activity, but they induced higher toxicity which led to lower protective index (PI). In addition, the potency of compound **S-2.26** was further investigated in other seizure models such as scPTZ, ISO (Isoniazid), 3-MP (3-Mercaptopropionic acid), TSC (Thiosemicarbazide), and BIC (Bicuculline) induced screening tests. They observed constant activity in all the animal models, confirming the potency of the molecule. This observation also indicated that compound **S-2.26** may act by different mechanism of action.



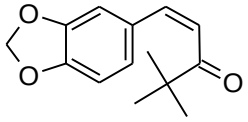
S-2.26

From the above literature survey, it is clear that triazole is an important pharmacophore that contributes significantly in enhancing anticonvulsant activity of their derivatives. Against this background, it has been decided to design new imidazo[1,2-a]pyridine derivatives carrying active triazole moiety together with various other substituents such as halogens, alkyl, alkoxy, aryl, etc. at suitable positions. It is hoped that incorporation of triazole moiety would improve the antiepileptic property of resulting molecules.

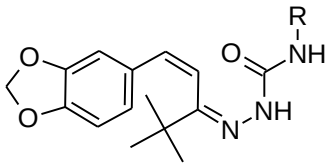
2.2.4 Pyrazoles

Pyrazole is an important five membered heterocyclic system possessing a wide spectrum of biological activities. However, they are less explored compounds for anticonvulsant studies. Nevertheless, very good anticonvulsant results were reported for various pyrazole and its derivatives in the literature. Some of the important literatures on their anticonvulsant study have been given below.

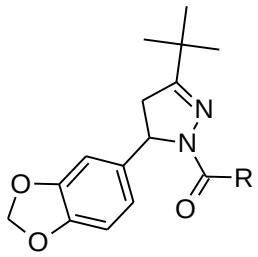
Recently, Aboul-Enein and co-workers (2012) reported the synthesis and anticonvulsant property of new aryl chalcones (**S-2.27**), their semicarbazones (**S-2.28**) and pyrazoline derivatives (**S-2.29**). They found that the anticonvulsant activity has increased drastically for pyrazolines and semicarbazones when compared with their precursor chalcones. Compound possessing N-(4-bromobenzoyl) group on pyrazoline moiety appeared as a highly potent molecule with ED_{50} value of 110 mg/kg without exhibiting any neurotoxicity.



S-2.27



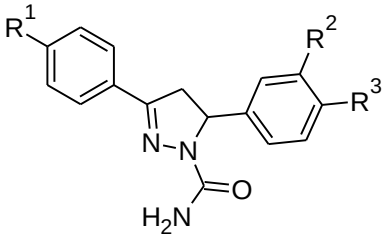
S-2.28



R= H, Aryl

S.2.29

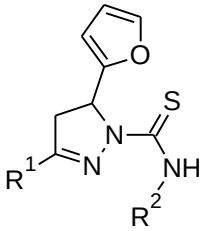
While searching for new pyrazole based anticonvulsant agents, Siddiqui and his colleagues (2010) synthesized new substituted 3,5-diphenyl-2-pyrazoline-1-carboxamide derivatives (**S-2.30**) and evaluated their anticonvulsant activity. According to them, many compounds exhibited complete protection against seizures when the screening was carried out at 100 and 300 mg/kg doses. Certain compounds displayed good results even at a small dose of 30 mg/kg with a rapid onset of action (30 min). It was observed that substitution at position-5 of pyrazole moiety has influenced the activity significantly rather than substitution at position -3. However, compounds possessing haloaryl groups at both the positions showed very good activity at 30 mg/kg dose.



$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$ = H, Me, MeO, Cl, Br, F, NO_2

S-2.30

A research group headed by Ozdemir (2007) investigated anticonvulsant property of new furan coupled 1-N-substituted pyrazolines (**S-2.31**) and found that compounds possessing furan moiety at both position-3 and position-5 displayed enhanced activity. Further, substitution of pyrazoline with various aryl, alkyl and sulphonamide groups at N-1 position resulted in increased activity and maximum activity was observed for compound carrying N-methyl sulphonamide group.

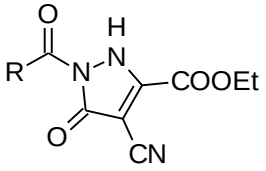


$\mathbf{R^1}$ = Phenyl, 2-Furyl

$\mathbf{R^2}$ = CH_3, C_2H_5, C_3H_7, Ph

S-2.31

Abdel-Aziz et al. (2009) synthesized various classes of pyrazolone derivatives (**S-2.32**) and evaluated anticonvulsant and antidepressant activities of newly synthesized molecules. Most of the compounds displayed remarkable anticonvulsant activity at a small test dose of 20 and 30 mg/kg. At 30 mg/kg, compounds carrying thiophene and indole groups showed comparable activity to phenytoin sodium. These new compounds were shown to act against clonic seizures induced by pentylene tetrazole.

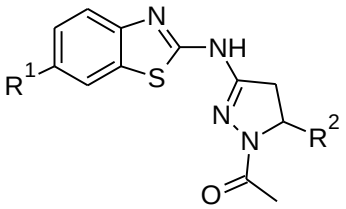


R= Phenyl, Thiophen-2-yl, Indol-2-yl, Pyridin-2-yl

S-2.32

A new series of pyrazolines carrying aminobenzothiazole moiety (**S-2.33**), synthesized by Amnerkar and Bhusari (2010) was shown to possess good anticonvulsant activity in MES as well as scMET methods. The most active compound

carrying 4-chlorophenyl group exhibited ED_{50} of 25.49 μmol/kg and high protective index of 4.86. Using 3D QSAR study, the influence of electron donor, hydrogen bond donor-acceptors and hydrophobic groups on the anticonvulsant activity was also analyzed.

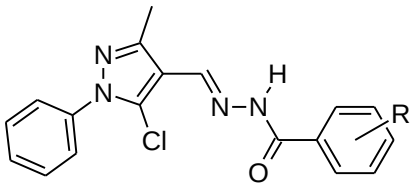


R^{1} = H, Me, NO_2, Cl

R^{2} = Aryl

S-2.33

Kaushik and co-workers (2010) reported the synthesis and *in vivo* anticonvulsant activity of certain N'-[(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene] 2/4-substituted hydrazides (**S-2.34**). They observed that most of the tested compounds exhibited activity in both MES and scPTZ methods at doses 30-300 mg/kg. Majority of compounds showed 70-80% more activity at 0.5 hour than that after 4 hours of drug administration, indicating their rapid onset and short duration of action. Also, they calculated the logP value and found that the new compounds are quite lipophilic in nature. Further, they observed enhanced activity for compounds carrying electron withdrawing substituents on phenyl ring of hydrazone moiety.



R= Aryl, Benzyl

S-2.34

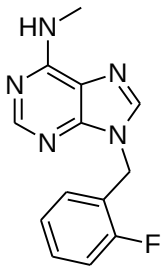
Based on the above findings, it can be concluded that pyrazole is an active moiety in enhancing the anticonvulsant activity. Therefore, it has been thought of including pyrazole moiety along with pyridine and imidazo[1,2-a]pyridine scaffolds in our new design. It is expected that combination of these two groups would enhance the anticonvulsant property significantly.

2.2.5 Pyrimidines

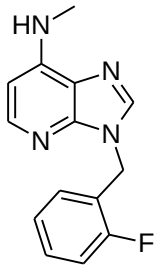
Pyrimidine, being a basic nucleus of DNA and RNA, is found to be associated with diverse biological activities. There are a large number of reports available on various pharmacological applications of pyrimidine derivatives in the literature.

Among various pharmacological activities, the anticonvulsant property of pyrimidines is noteworthy. Few important research reports on anticonvulsant activity of pyrimidine derivatives have been discussed below.

Anticonvulsant profile of some fused pyrimidines such as pyrazolopyrimidine, pyrolopyrimidine, triazolopyrimidines were investigated by Kelley and co-workers (1995). They replaced/modified the imidazole ring of purine by pyrole, pyrazole and triazole rings, but they got relatively less activity for all new derivatives than original purine. They confirmed that an imidazopyrimidine nucleus of purine (**S-2.35**) is essential structural feature for better activity. Interestingly, their earlier research (Kelley et al. 1988) established that imidazopyridines (**S-2.36**) are also equally active as imidazopyrimidines.

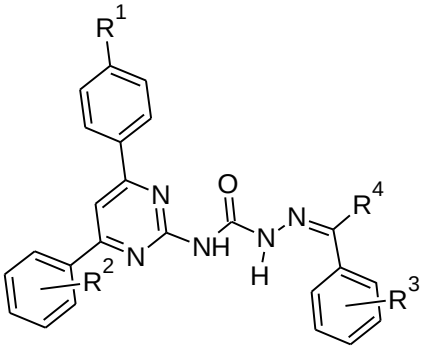


S-2.35



S-2.36

Alam and his colleagues (2010) synthesized new N-(4,6-substituted diphenylpyrimidin-2-yl) semicarbazones (**S-2.37**) and screened their anticonvulsant activity by MES and scPTZ methods. In their study, they observed good activity for compounds possessing electron donating and electron withdrawing substituents, respectively on two aryl rings at position-3 and position-5 of pyrimidine moiety. Further, *para* substituted derivatives showed higher activity than *meta* and *ortho* substituted analogues. They also found that substitution of amine group of 2-aminopyrimidine ring by thiosemicarbazone has no effect on their activity. Most of the tested compounds showed less toxicity when compared with that of established drugs. Compound possessing 4-chlorophenyl and 3,4-dimethoxyphenyl substituents displayed the highest activity with a dose of 30 mg/kg at both 0.5 and 4 hours intervals.

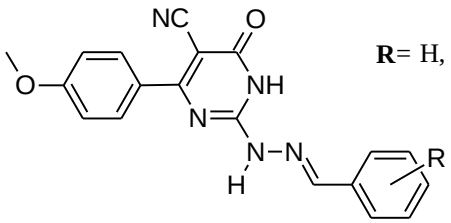


R^{1} = F, Cl; **R**^{2} = Me, MeO, NO_2

R^{3} = Me, MeO, NO_2, Cl; **R**^{4} = H, Me

S-2.37

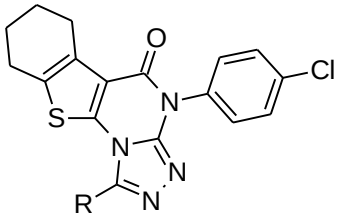
Recently, Shaquiquzzaman and co-workers (2012) designed and synthesized new 2,4-diaryl-5-carbonitrile-6-pyrimidones (**S-2.38**) as effective antiepileptic agents. The active compounds showed rapid onset and short duration of action as they were found to be more active at 0.5 hour duration than 4 hour post sample administration. Also, most of the tested compounds were non-toxic up to 300 mg/kg, when compared with toxicity of phenytoin (100 mg/kg). Compound possessing hydroxyl and fluoro substituents displayed the highest antiepileptic activity in MES method at a dose of 30 mg/kg, without exhibiting any toxicity up to 300 mg/kg dose.



R= H, F, Cl, Br, OH, OMe, NO_2, NMe_2

S-2.38

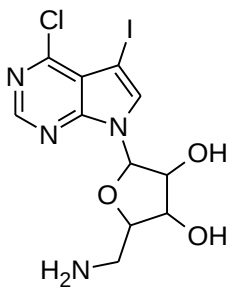
A series of triazolo[4,3-a]tetrahydrobenzo(b)thieno[3,2-e]pyrimidine-5(4H)-ones (**S-2.39**) were synthesized as new anticonvulsant agents by Gupta and his colleagues (2009). They screened the title compounds to establish CNS activity and found comparable activity with that of standard drug diazepam at 5 mg/kg dose for many compounds. Later, they screened the compounds by scPTZ method at various doses and observed that tested compounds are active at the dose levels of 6.0-11.0 mg/kg. The compound carrying propyl chain protected the animal completely from scPTZ induced clonic convulsion at a dose of 6.0 mg/kg (ED_{50}= 4.4 mg/kg) and appeared as most potent anticonvulsant agent.



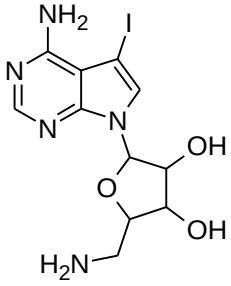
R= H, CH_2Cl, alkyl, aryl, benzyl, NH_2, SH, NHPh

S-2.39

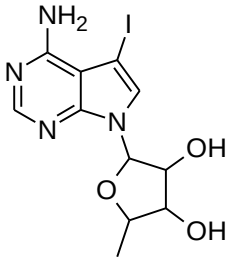
Several adenosine kinase inhibitors (AKI) were shown to possess significant anticonvulsant activity as reported by Erion (1993) and Jacobson et al. 1992). In this approach, variety of new pyrrolo[2,3-d]pyrimidine nucleoside analogues were designed and synthesized by Ugarkar and his colleagues (2000). These molecules displayed very good enzyme inhibition and anti-seizure activities when compared to standard drugs. However, the rank order of *in vivo* anticonvulsant activity did not strongly correlate with the order of potency in the *in vitro* enzyme inhibition assay. Thus, they predicted that the variation in the molecular substituents result in substantial changes in pharmacokinetic properties such as clearance rate, brain penetration, or accessibility to the intracellular enzyme. Presence of halogen at position-5 and electron rich groups at position-4 resulted in enhanced activity. Interestingly, **S-2.40** and **S-2.41** were found to be the most potent AKIs reported to date (IC_{50} < 0.001 μM), while, **S-2.42** showed the highest anticonvulsant activity with ED_{50} value of 0.3 mg/kg.



S-2.40



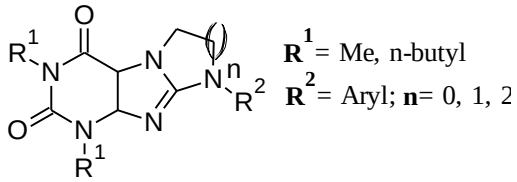
S-2.41



S-2.42

Drabczynska et al. (2006) described the synthesis and anticonvulsant activity of N-aryl-substituted imidazo-, pyrimido-, and 1,3-diazepino[2,1-f]purinediones (**S-2.43**). At first, they examined their adenosine receptor affinity by radioligand binding assay. They varied the number of carbon of a cyclic ring system in order to compare the activity profile of imidazole, pyrimidine and diazepine. They observed the highest activity for those possessing pyrimidine nuclei. The compounds possessing

halogens and hydroxyl groups displayed good results. Interestingly, significant antiepileptic activity was observed for new derivatives carrying aryl substituents, while no activity was found for unsubstituted analogues. In the *in vivo* study also, pyrimidine derivatives displayed enhanced activity when compared to corresponding imidazole and diazepines. Particularly, aryl rings possessing hydroxyl and halo groups showed improved activity. However, most of the compounds were found to be toxic and so, the authors presumed that further structural modification of **S-2.43** would end up with non-toxic anticonvulsant agents.



S-2.43

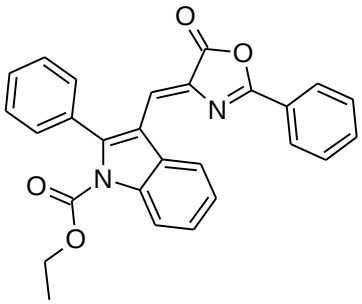
The above literature reports on anticonvulsant activity of pyrimidine derivatives clearly confirm the importance of pyrimidine nucleus in showing enhanced antiepileptic property. So, in our present study, it has been contemplated to synthesize new heterocyclic hybrids carrying imidazo[1,2-a]pyridine and pyrimidine moieties, with the expectation of good activity for resulting compact molecules.

2.2.6 Oxazoles

Oxazole is a seat of diverse medicinal activities. It possesses many reactive sites in its ring system, which enables many structural modifications. Such structural flexibility makes it one of the major intermediates for the synthesis of variety of chemical derivatives. Due to its variety of medicinal applications, they are considered to be important pharmacophoric group. Oxazolone, being a derivative of oxazole also plays a vital role in enhancing biological activity of its derivatives. In the following section, a few literature reports on synthesis and antiepileptic study of certain important oxazole derivatives have been highlighted.

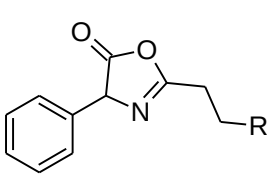
Recently, Khan and his colleagues (2012) investigated anticonvulsant potency of new indole containing oxazolone derivatives. They screened the compounds by MES and scPTZ methods at different test doses. Compound (**S-2.44**) exhibited good protection against seizures when screening was carried out at 100 and 300 mg/kg

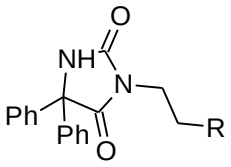
doses. Further, it was noticed that similar results were obtained when oxazolone moiety was replaced by pyrazolone group.



S-2.44

In search of new oxazolone based anticonvulsant agents, Dhanawat et al. (2012) reported design, synthesis and antiepileptic screening of some new substituted piperazine and aniline derivatives of 5-phenyloxazolidin-2,4-diones (**S-2.45**) and 5,5-diphenylimidazolidin-2,4 diones (**S-2.46**). From the SAR study it was concluded that the alkyl chain length present between imide and amine nitrogens has crucial role in deciding the activity. According to authors, compounds possessing ethylene spacer group showed better activity than that containing methylene chain. In addition, compounds carrying *para*-chloro and *para*-fluoro substituents displayed enhanced activity. Further, compounds with substituted anilines exhibited good results when compared to those carrying piperazine moiety.

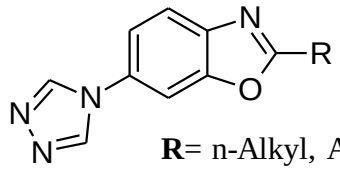




R= Substituted anilines/piperazines

S-2.45 **S-2.46**

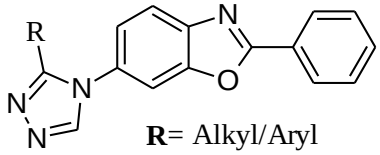
Wei et al. (2009) reported the synthesis and anticonvulsant activity of new benzoxazole derivatives carrying triazole moiety (**S-2.47**). All the tested compounds exhibited activity in MES method indicating their ability to control seizure spread, effectively. Many compounds displayed complete protection at 100 mg/kg, without exhibiting neurotoxicity up to 300 mg/kg doses. It was noticed that the activity increases with increase in alkyl chain length and replacement of alkyl chain with unsubstituted phenyl ring brought about better activity.



R= n-Alkyl, Aryl

S-2.47

In continuation of the previous work, Wei and his colleagues (2010) further derivatized the above active scaffold by incorporating various alkyl/aryl groups on triazole moiety, keeping phenyl ring at second position of benzoxazole (**S-2.48**). Most of the new derivatives exhibited complete protection against seizures at 100 mg/kg and were found to be non-toxic up to 300 mg/kg dose. The compounds carrying halogens and electron donating methyl and methoxy groups on aryl ring displayed significant activity.



R= Alkyl/Aryl

S-2.48

The above said literature reports clearly indicate the importance of dihydropyridines and imidazo[1,2-a]pyridines as potential antiepileptic agents and they appear as important scaffolds for the development of new antiepileptic agents with improved activity. Further, it was also seen that presence of various pharmacophoric groups such as amides, hydrazones, pyrazolines, triazoles, pyrimidines and oxazoles were shown to enhance the anticonvulsant property of the resulting molecules, significantly. Keeping this in view, it has been planned to design new DHP and imidazo[1,2-a]pyridine derivatives carrying above mentioned pharmacophoric groups at suitable positions. It is hoped that new hybrid compounds resulting from the union of these heterocyclic systems would enhance the antiepileptic property of the resulting molecules considerably without producing any toxicity. During their course of action, they may bind with the receptor site effectively and help to cross the blood brain barrier to suppress the seizures.

2.3 SCOPE AND OBJECTIVES OF THE WORK

Currently, most of the active therapeutic agents present in the market are obtained from synthetic sources. Though the synthetic drugs exhibit prominent activity, majority of them are displaying toxicity and many side effects. Unfortunately, the proper mechanism of drug action in the body is remaining mystery for many such synthetic drugs. Further, the costs of several drugs are now sky-rotating. So, investigation of pharmacological applications of simple molecules is an active area of research. Currently, there is an extensive research going on all over the world to synthesise and to develop the new effective drugs.

Antiepileptic research is one such active research area, which is mainly dealing with development of new potential synthetic AEDs. At present, there are about 50 well-established drugs available in the market to fight against epilepsy, which is one of the most dangerous neurological diseases. These drugs are able to control the epilepsy, either by acting on sodium/calcium ion channels or acting as GABA agonists, however none of the established drugs are found effective in curing epileptic patients completely. Moreover, the exact mechanisms of action of several traditional AEDs are still uncertain to the mankind. Further, it is regret to find that about 30-40 % of epileptic patients are resistant to available medications. These observations clearly demonstrate the scope and need for the development of new anticonvulsant agents having improved seizure control along with better tolerability.

In this context, the present research work is aimed at design, synthesis of new pyridine derivatives as potential anticonvulsant agents. The projected research work may lead to the development of new anticonvulsant agents, which may further grow to contribute interesting drugs. It has been expected that newly synthesized molecules will be suppressors for different types of seizures with long durability and less toxicity. The proposed target molecules and their intermediates may be explored for their applications in other research areas like development of new pesticides, herbicides, polymers, dyes, additives for various commercial products or corrosion control as inhibitors etc. Pyridine being electron withdrawing system can be a good monomer for donor-acceptor type conjugated polymers which may find applications in optoelectronics. Recently, novel pyridine based polymers were reported as good non-linear optical materials (Vishnumurthy, et al. 2011). The outcome of the present

research studies, particularly, structure-activity relationship data may help the future researchers for the development of new types of drugs in coming days. The results of our research may be useful in understanding the mechanism of drug action.

Based on the wide scope of the work and a detailed literature survey, following main objectives have been intended in the present research work.

- Design of new dihydropyridine and imidazo[1,2-a]pyridine derivatives containing active hydrazone, amide, triazole, pyrazole, oxazolone, pyrimidine and imine pharmacophoric groups at suitable positions
- Synthesis of newly designed target molecules and development of their synthetic and purification methods
- Characterization of newly synthesized compounds by FTIR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral techniques followed by elemental analysis
- Anticonvulsant study of newly synthesized compounds following MES and scPTZ methods, and toxicity study by Rotarod technique
- Structure-activity relationship study of the tested compounds

In conclusion, the present research work, involving design, synthesis, characterization of new dihydropyridine as well as imidazo[1,2-a]pyridine derivatives and evaluation of their anticonvulsant activity is aimed at development of new active anticonvulsants, which may come out as potent drug in future. Moreover, the study adds some more data to the chemistry of new dihydropyridine as well as imidazo[1,2-a]pyridine derivatives. Its utility may be explored in other areas of applications also.

2.4 DESIGN OF NEW PYRIDINE DERIVATIVES

Design of new synthetic compounds with appropriate therapeutic importance is a major challenge in medicinal chemistry. Molecular modification could be a productive source for the design of new biologically active molecules (Kraus 1983). As described earlier, pyridine is an important nitrogen containing heterocyclic system possessing wide range of biological applications. It appears to be the best suitable core moiety for the development of new antiepileptic agents, as many pyridine derivatives have been reported in literature as significant anticonvulsants. The dihydropyridines and imidazo[1,2-a]pyridines are the two major class of pyridine derivatives attracted the antiepileptic researchers due to their affinity towards calcium ion and GABA channels, respectively.

The brief literature survey given above clearly reveals the importance of DHPs and imidazo[1,2-a]pyridines along with other pharmacophores such as amides, hydrazones, pyrazolines, triazoles, pyrimidines etc., as prominent antiepileptic agents. Owing to their pharmacological applications as antiepileptic agents, in our present study, new DHP and imidazo[1,2-a]pyridines carrying various above mentioned pharmacophoric groups have been designed. The design strategies of the new target molecules are discussed in the following paragraphs.

2.4.1 Design of new dihydropyridines

A detailed literature reports on structure-activity relationship study of 1,4-DHP system reveals that un-substituted free NH group in DHP ring is crucial for better activity with respect to any medicinal property. Further, presence of methyl groups at position-2 and position-6, ester groups at position-3 and position-5, and an aryl ring at position-4 are essential structural features for prominent biological effect (Pedemonte et al. 2007; Triggle 2003). In addition, for better anticonvulsant activity, it is desirable to have two aryl rings at suitable positions in the target chemical entity to increase the Van der Waal's fore of attraction with the binding receptor unit (Yogeeswari et al. 2005). Further, presence of a functional group possessing hydrogen bonding capability would enhance the efficacy of resulting molecule to a higher extent. It is well-known that the nitrogen and oxygen atoms present in the amides and hydrazone functionalities are acting as hydrogen bond donor and acceptors, respectively, thereby enhancing the interactions with the amino acid of receptors. Based on these observations, we have designed new dihydropyridine derivatives carrying amide and azomethine groups derived from various aromatic/heteroaromatic aldehydes and ketones, with the anticipation that newly designed molecules would show good anticonvulsant property. In Figure 2.1(a), the design of new DHPs carrying hydrazone functionality has been summarized. Similarly, another series of amide derivatives has been designed, wherein hydrazone group is replaced with amide functionality, as shown in Figure 2.1(b).

2.4.2 Design of new imidazo[1,2-a]pyridines

Recently**,** imidazopyridines containing aryl substituent at position-2 were shown to possess good CNS activity (Farkas et al. 2011; Trapani et al. 2005). Based

on this result, imidazo[1,2-a]pyridine moiety can be considered as a good scaffold for the development of future CNS agents. Further, a detailed structure-activity relationship study on imidazo[1,2-a]pyridines (Denora et al. 2008) revealed that, substitutions of the ring at position-8 by a hydrophobic unit and the position-2 by a 4-halophenyl group are the crucial key factors for making the molecule more selective towards benzodiazepine receptors. Inspired by this observation, it has been planned to design new imidazo[1,2-a]pyridines containing 4-fluoro substituted aryl ring at position-2 and a methyl group as a hydrophobic unit at position-8 of the ring, with the expectation of improved anticonvulsant activity for the resulting molecules. It is surprising to see that, very few research articles on anticonvulsant activity of imidazo[1,2-a]pyridine derivatives are available in the literature, despite its well-established CNS activity. This has further prompted us to design, and synthesize new imidazo[1,2-a]pyridine derivatives and to evaluate their anticonvulsant activity. As observed from the general structure of established drugs such as Zolpidem, Alpidem, Saripidem, DS-1, etc, it is clear that, the substituent present at position-3 of imidazo[1,2-a]pyridine ring plays a key role in deciding the potency of the resulting molecules. In this context, the imidazo[1,2-a]pyridine scaffold has been derivatized at position-3 with different heterocyclic pharmacophoric groups. It has also been decided to keep alkyl and alkoxy substituted aryl groups at position-2 along with 4-fluorophenyl moiety, in order to study the effect of inductive and electronic factors on the activity. In the same way, it has been planned to synthesize some new imidazo[1,2-a]pyridines carrying bromo substituent on pyridine moiety. The new design is depicted in Figure 2.2.

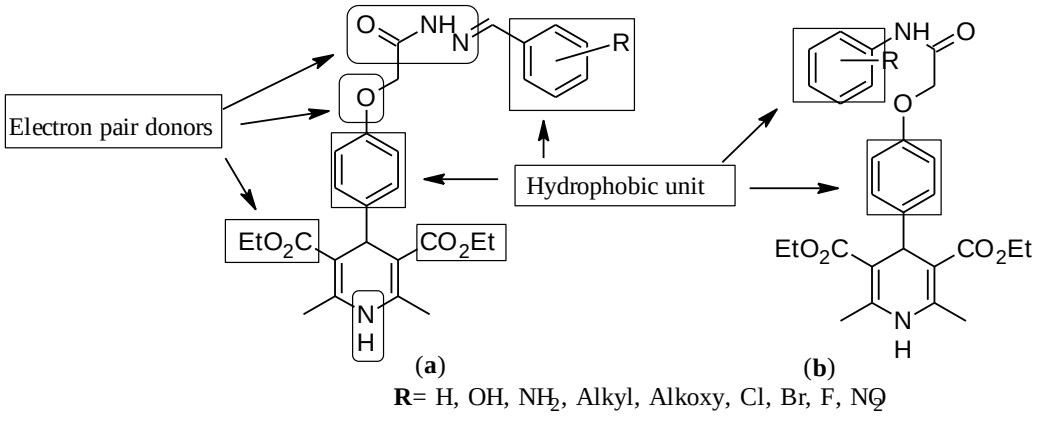
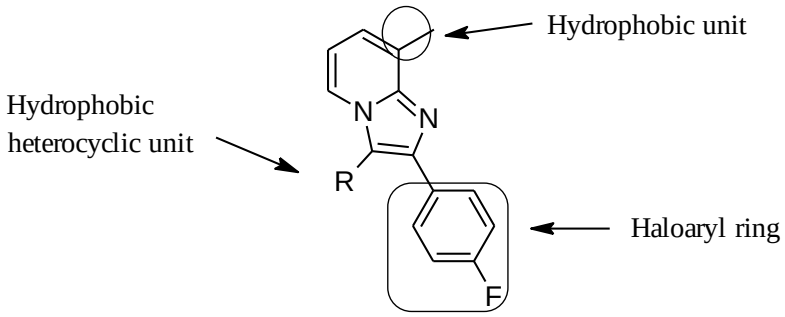


Figure 2.1: Design of new DHPs carrying (a) hydrazone and (b) amide functionalities

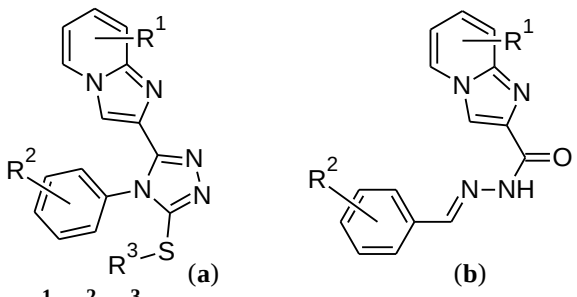
As described earlier, the heterocyclic systems such as pyrimidines, pyrazolines, triazoles and oxazolones are anticonvulsant active systems. Therefore, these moieties have been incorporated at position-3 of imidazo[1,2-a]pyridine ring, to form new heterocyclic hybrid molecules (Figure 2.2). These new chemical entities are expected to show enhanced anticonvulsant activity as they contain two or more active moieties in a single framework.



R= Pyrazoline, Pyrimidine, Triazole, Cyanopyridine, Imine, Oxazolone

Figure 2.2: Design of new imidazo[1,2-a]pyridines carrying active pharmacophores

From the forgoing account, it is clear that imidazo[1,2-a]pyridine and 1,2,4-triazole units are important heterocyclic systems, which are responsible for better anticonvulsant activity of their derivatives. However, there is no literature report available on the synthesis and antiepileptic studies of imidazo[1,2-a]pyridines carrying 1,2,4-triazole unit at position-2. Against this background, it has been thought of designing new heterocyclic hybrids carrying 1,2,4-triazole unit at second position of imidazo[1,2-a]pyridine scaffold. The new design is summarized in Figure 2.3(a). Further, since hydrazone is an important functional group that accounts for enhanced anticonvulsant property, it has been planned to design new imidazo[1,2-a]pyridine-2-carboxylic hydrazones. The general structure of hydrazones is given in Figure 2.3(b).



R^{1}, **R**^{2}, **R**^{3}= H, Halogen, Alkyl, Aryl, Heterocyclic

Figure 2.3: General structures of new imidazo[1,2-a]pyridine core carrying (a) triazoles and (b) hydrazones

Accordingly, the following five series of newly designed DHP and imidazo[1,2-a]pyridine derivatives have been planned to synthesize:

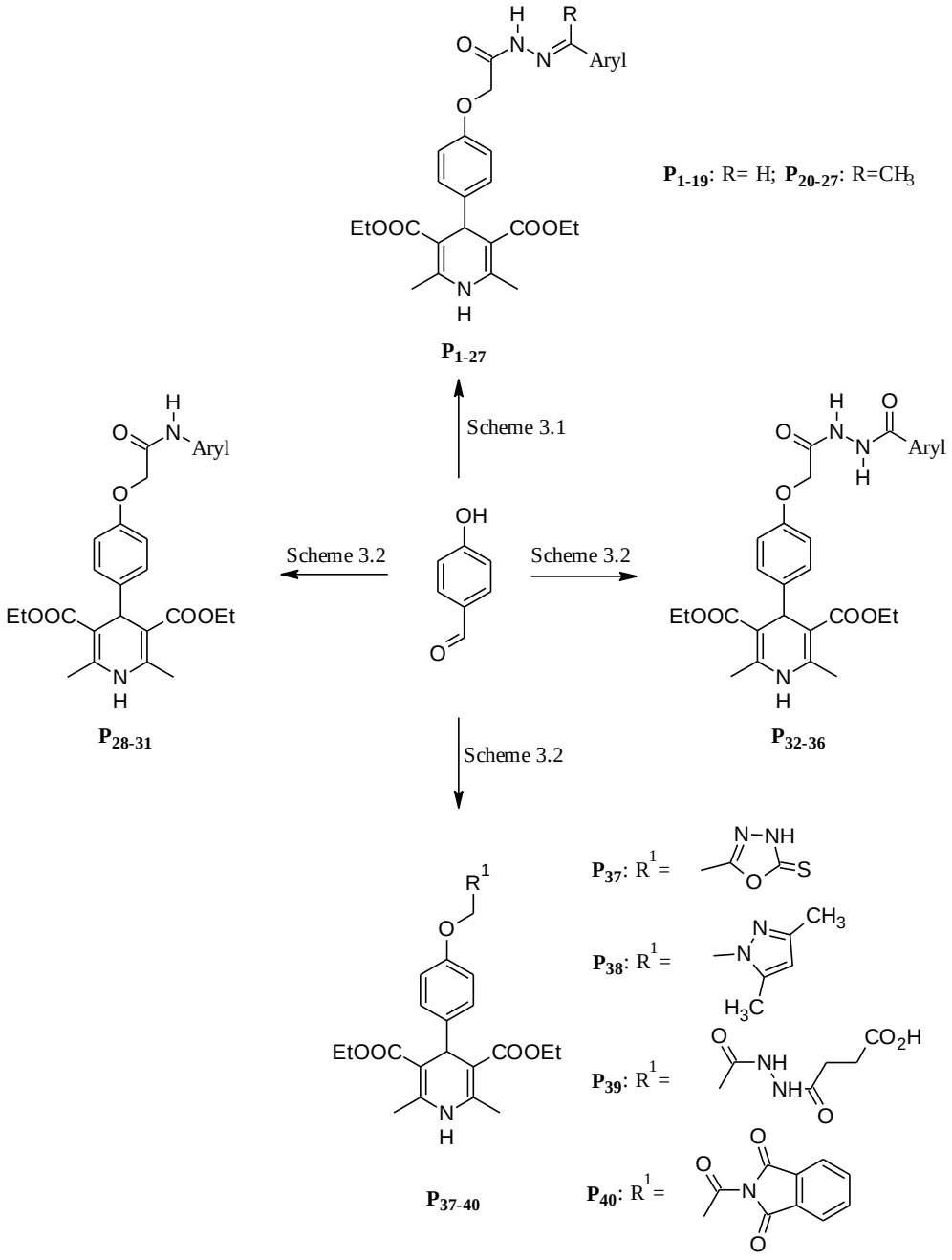
(i) New DHP derivatives carrying hydrazone and amide functionalities (**P_{1-40}**)

(ii) New imidazo[1,2-a]pyridine-3-carboxaldehyde derivatives (**P_{41-64}**)

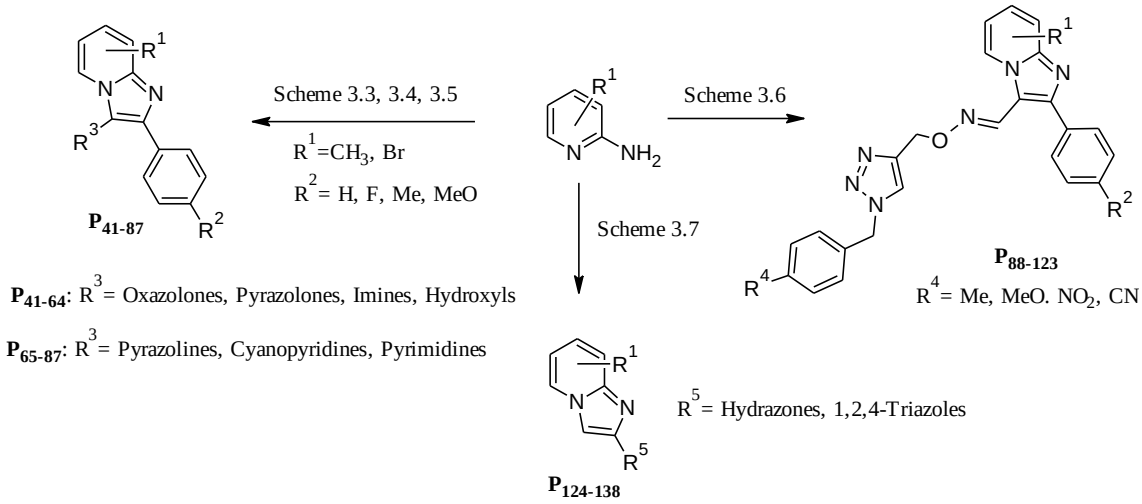
(iii) New chalcone derivatives containing imidazo[1,2-a]pyridines (**P_{65-87}**)

(iv) New imidazo[1,2-a]pyridines carrying (1,2,3-triazol-4-yl)methyl oxime (**P_{88-123}**)

(v) New imidazo[1,2-a]pyridine-2-carbohydrazide derivatives (**$P_{124-138}$**)



Scheme 2.1: New DHP derivatives **P_{1-40}**



Scheme 2.2: New imidazo[1,2-a]pyridine derivatives $\mathbf{P_{41\text{-}138}}$

In the present work, above five new series of derivatives have been synthesized following appropriate synthetic routes. The synthetic routes for the target compounds, $\mathbf{P_{1\text{-}138}}$ have been summarized in Scheme 2.1 and Scheme 2.2, the details of which are given in the next chapter.

The newly designed pyridine derivatives have been synthesized by adopting appropriate synthetic routes starting from simple organic compounds. The purification methods for the newly synthesized compounds have been established and accordingly they have been purified. Column chromatography and re-crystallization techniques have been used for the purification of targets. The purified compounds are then characterized by various spectral techniques such as FTIR, ^{1}H NMR, ^{13}C NMR, mass spectrometry followed by elemental analysis. The structures of selected target compounds were confirmed by their single crystal XRD studies. Further, the *in vivo* anticonvulsant screening study of all target compounds has been carried out following MES and scPTZ methods, by taking suitable doses of test samples. Furthermore, their neurotoxicity study has been performed by Rotarod method. The synthetic strategies and characterization data of new compounds have been discussed in **Chapter-3**, while, their screening data along with detailed SAR has been discussed in **Chapter 4**. Finally, important research outcomes have been highlighted in **Chapter 5**.

CHAPTER-3

SYNTHESIS AND CHARACTERIZATION OF NEW PYRIDINE DERIVATIVES

Abstract

In this chapter, the experimental protocols leading to synthesis of new DHP and imidazo[1,2-a]pyridine based derivatives carrying suitable pharmacophores have been elaborated. In addition, their structural characterization has been discussed in detail. Further, it includes the physiochemical properties as well as characterization data of new compounds.

3.1 INTRODUCTION

In the previous chapter, design of five new series of DHP and imidazo[1,2-a] pyridine derivatives has been discussed in detail. This chapter describes their synthesis and structural characterization. Generally, the synthesis of any organic compound may be achieved by various possible reaction sequences. However, stabilization of an energy efficient, cheap and simple reaction path for the synthesis is a great challenge in organic chemistry. The reaction condition such as solvent, temperature and purity of the precursors plays an important role in various conversions. In the present study, the newly designed molecules were synthesized by stabilizing the appropriate synthetic routes for each series and the reaction conditions were optimized to get maximum yield. They were purified with appropriate techniques, for which required solvent systems were identified. The pure products were then characterized by various spectral techniques and elemental analysis. In the following sections, the synthetic strategy for the new compounds and their characterization data are discussed in detail.

3.2 MATERIALS AND METHODS

All the chemicals used in the present work were procured from Sigma Aldrich and Spectrochem. All the solvents used were of analytical grade. They were purchased and used as such without any further purification. The progress of the reaction was monitored by thin layer chromatography, performed on a Silica gel 60 F254 coated aluminium sheet. Melting points were determined on open capillaries using a Stuart SMP3 (BIBBY STERLIN Ltd. UK) apparatus and were uncorrected. Infrared spectra were recorded on a Nicolet Avatar 5700 FTIR (Thermo Electron Corporation). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-400 MHz FT-NMR spectrometer using TMS as internal reference and DMSO-d_6, $CDCl_3$ as solvent. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd) and multiplet (m). The

coupling constant (*J*) values were expressed in Hz. Elemental analyses were performed on a Flash EA1112 CHNS analyzer (Thermo Electron Corporation). Mass spectra (ESI) were recorded on Waters ZQ-4000 liquid chromatography-mass spectrometer.

3.3 SYNTHETIC METHODS

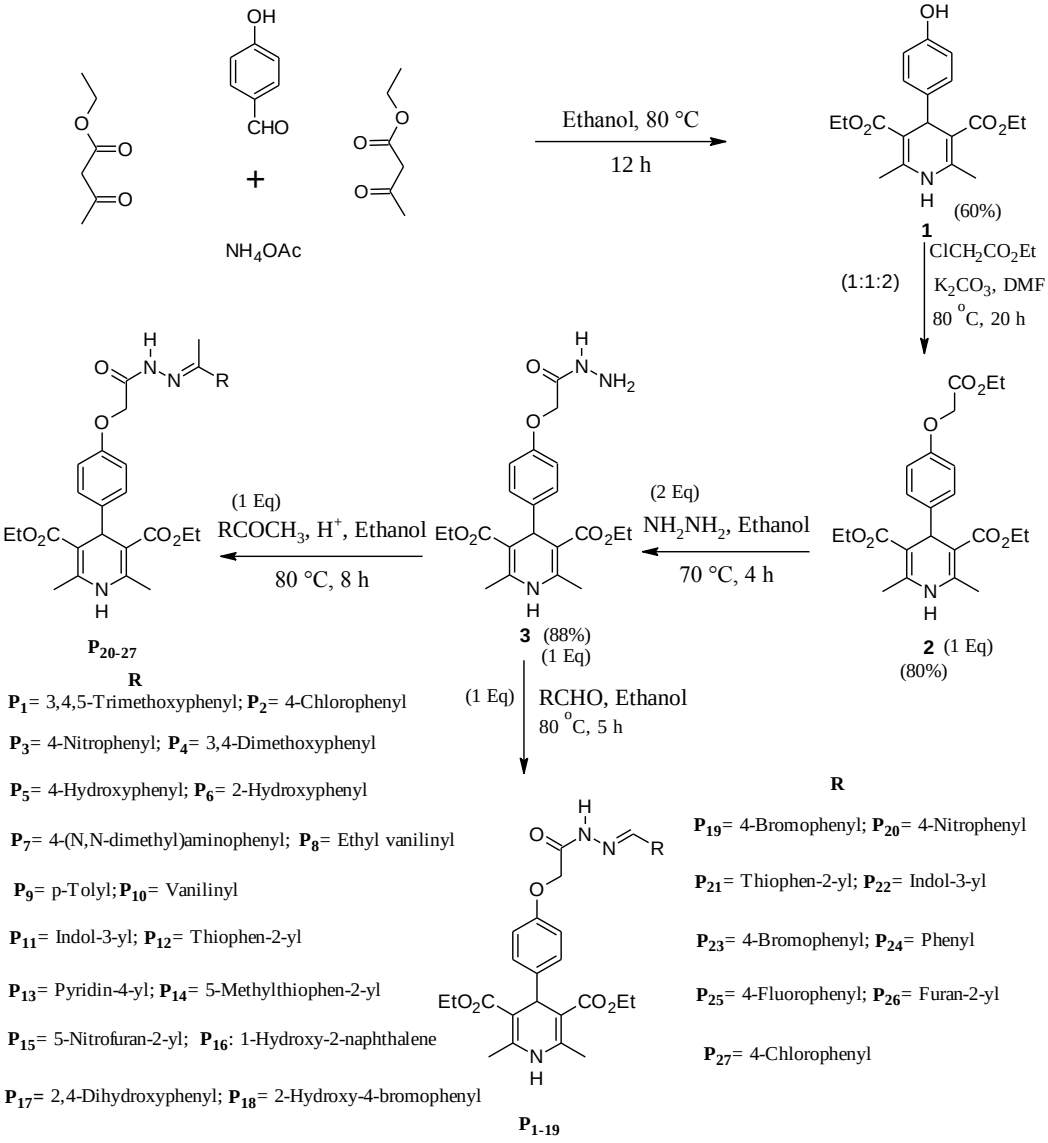
In the present study, new dihydropyridine (DHP) and imidazo[1,2-a]pyridine derivatives containing an appropriate pharmacophoric group such as hydrazone, amide triazole, pyrimidine, oxazolone and pyrazole functionalities in a single molecular framework, were synthesized. Dihydropyridine ring was synthesized by means of Hantzsch Pyridine synthesis method (Fassihi et al. 2009), while imidazo[1,2-a] pyridine nucleus was constructed following earlier reported procedure (Gudmundson and Johns, 2007).

3.3.1 Synthesis of new DHPs ($\mathbf{P_{1\text{-}40}}$)

In this series, forty new DHPs were synthesized by coupling various aryl moieties with dihydropyridine ring via hydrazone ($\mathbf{P_{1\text{-}27}}$) and amide ($\mathbf{P_{28\text{-}40}}$) linkages. The synthetic routes for $\mathbf{P_{1\text{-}27}}$ and $\mathbf{P_{28\text{-}40}}$ are summarized in Scheme 3.1 and Scheme 3.2, respectively.

3.3.1.1 Chemistry

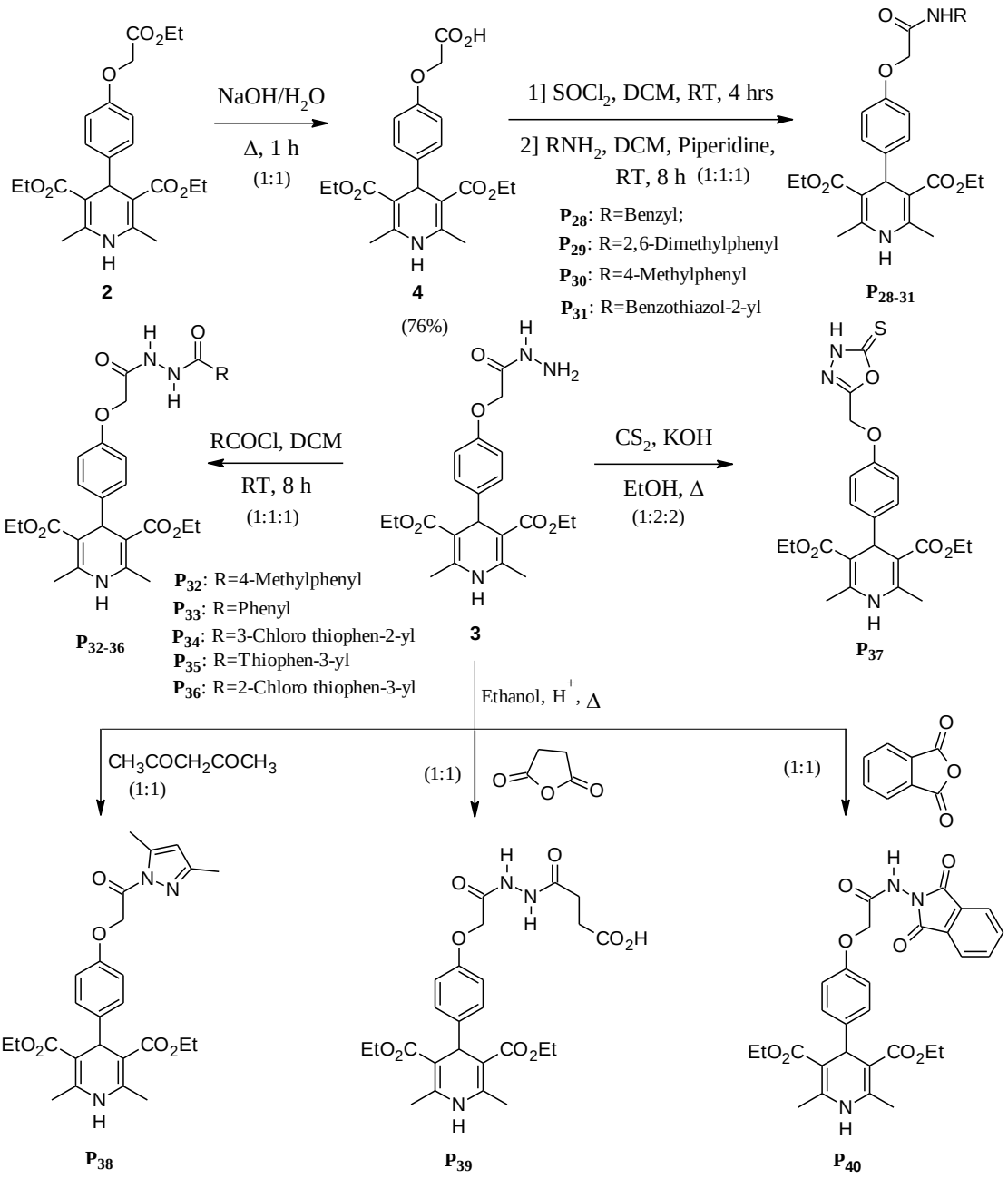
The key dihydropyridine derivative **1** was prepared following Hantzsch method, from 4-hydroxybenzaldehyde by refluxing it with two equivalents of ethyl acetoacetate and ammonium acetate in ethanol medium. The hydroxyl group was alkylated with ethyl chloroacetate in DMF medium under nitrogen atmosphere to obtain the product **2**. Under similar mild conditions, only phenolic OH group, but not NH group of DHP ring undergoes alkylation. The resulting ester **2** was converted to its hydrazide **3** through nucleophilic substitution reaction by refluxing it with hydrazine hydrate in ethanol for about 4 h. Under this condition, stable ester groups on DHP ring remained intact without participating in the reaction. The hydrazide **3** was used as an active scaffold for the synthesis of various target derivatives. The target hydrazones $\mathbf{P_{1\text{-}19}}$ and $\mathbf{P_{20\text{-}27}}$ were obtained by condensing hydrazide **3** with various aldehydes and ketones, in ethanol medium with trace of acid catalyst, respectively.



Scheme 3.1: Synthetic route for hydrazones $\mathbf{P_{1\text{-}27}}$

The alkaline hydrolysis of ester **2** afforded the corresponding acid **4** which was later conveniently converted to acid chloride and coupled with various amines to obtain amides $\mathbf{P_{28\text{-}31}}$ in good yield. Another set of amides $\mathbf{P_{32\text{-}36}}$ was obtained by coupling hydrazide **3** with different acid chlorides in presence of piperidine base. In another series, the intermediate **3** was cyclized to form 1,3,4- oxadiazole-2-thiol $\mathbf{P_{37}}$ by treating compound **3** with carbon disulfide and potassium hydroxide and subsequent neutralization. On the other hand, hydrazide **3** was condensed with acetyl acetone in alcoholic medium containing trace of glacial acetic acid to obtain pyrazole derivative $\mathbf{P_{38}}$. Finally, intermediate **3** was treated with succinic anhydride and phthalic

anhydride under acidic medium, to achieve **P_{39}** and **P_{40}**, respectively in good yield. Interestingly, reaction of **3** with succinic anhydride led to ring opening reaction and resulted in an carboxylic acid derivative **P_{39}**, while that with phthalic anhydride resulted in substituted pthalimide derivative **P_{40}**.



Scheme 3.2: Synthesis of DHP derivatives **P_{28-40}**

3.3.1.2 Results and discussion

The newly synthesized target compounds were characterized by various spectral methods. Formation of DHP ring was confirmed by FTIR spectrum of **1**

(Figure 3.2), where it showed prominent peaks at 3337 cm^{-1} and 1656 cm^{-1}, due to NH/OH and ester carbonyl groups, respectively. This was also confirmed by its ^1H NMR spectrum (Figure 3.3), wherein it displayed singlets at δ 9.09 and δ 8.71 ppm, which are attributed to phenolic OH and NH protons of DHP ring, respectively. Further, appearance of a multiplet and a triplet at δ 4.04 and δ 1.15 ppm, respectively corresponds to two OCH_2CH_3 groups attached to DHP ring, in turn it supports the structure. Another characteristic singlet at δ 4.74 ppm was observed corresponding to C_4 proton, which also support the proposed structure of **1**. In ^1H NMR spectrum of compound **2** (Figure 3.5), disappearance of OH peak at δ 9.09 ppm clearly established that phenolic hydroxyl group was undergone alkylation but not NH group of DHP ring. To further confirm the site of alkylation among two reactive sites, single crystal SCXRD analysis was performed for one of the title compounds $\mathbf{P_{38}}$, wherein the structure corresponds to O-alkylated product. Its crystallographic data are tabulated in Table 3.3 while its ORTEP diagram is given in Figure 3.1. The FTIR spectrum of compound **2** is given in Figure 3.4.

Conversion of ester **2** to a key intermediate **3** was verified by FTIR spectrum of hydrazide **3** (Figure 3.6), wherein, shifting of carbonyl stretching frequency from 1739 cm^{-1} to lower frequency 1656 cm^{-1} was observed. Also its ^1H NMR spectrum (Figure 3.7) displayed two singlets at δ 9.24 and δ 4.28 ppm confirming the presence of hydrazidic NH and NH_2 groups. Formation of various hydrazones $\mathbf{P_{1\text{-}19}}$ and $\mathbf{P_{20\text{-}27}}$ from hydrazide **3** was evidenced by their FTIR and ^1H NMR spectra. ^1H NMR spectrum of $\mathbf{P_1}$ showed a new peak at δ 7.89 ppm which corresponds to –N=CH- proton, in the place of a singlet at δ 4.28 ppm due to NH_2 group, confirming its structure. Further, its mass spectrum showed molecular ion peak at 596.1, corresponding to M+H peak of the compound. On the other hand, the ^1H NMR spectrum of $\mathbf{P_{20}}$ (Figure 3.9) exhibited a new peak at δ 2.31 ppm corresponding to allylic methyl group that confirms its formation. Similar pattern of peaks was observed for remaining compounds of the series. The physiochemical properties of final compounds are tabulated in Table 3.1. The FTIR, ^{13}C NMR and mass spectra of compound $\mathbf{P_{20}}$ are given in Figure 3.8, 3.10 and 3.11, respectively.

Table 3.1: Physiochemical properties of compounds $\mathbf{P_{1\text{-}27}}$

Compound	R	Mol. Formula	M.P. (^{o}C)	Yield (%)
P_1	3,4,5-Trimethoxyphenyl	$C_{31}H_{37}N_3O_9$	212-214	88
P_2	4-Chlorophenyl	$C_{28}H_{30}ClN_3O_6$	246-248	90
P_3	4-Nitrophenyl	$C_{28}H_{30}N_4O_8$	244-246	91
P_4	3,4-Dimethoxyphenyl	$C_{30}H_{35}N_3O_8$	213-215	92
P_5	4-Hydroxyphenyl	$C_{28}H_{31}N_3O_8$	237-239	87
P_6	2-Hydroxyphenyl	$C_{28}H_{31}N_3O_7$	270-272	92
P_7	4-(N,N-dimethyl) aminophenyl	$C_{28}H_{31}N_3O_7$	217-219	81
P_8	Ethylvanilinyl	$C_{30}H_{35}N_3O_8$	207-209	86
P_9	4-Methylphenyl	$C_{29}H_{33}N_3O_6$	251-253	90
P_{10}	Vanilinyl	$C_{29}H_{33}N_3O_8$	213-215	85
P_{11}	Indole-3-yl	$C_{30}H_{32}N_4O_6$	231-233	88
P_{12}	Thiophen-2-yl	$C_{26}H_{29}N_3O_6S$	261-263	83
P_{13}	Pyridin-4-yl	$C_{27}H_{30}N_4O_6$	216-218	91
P_{14}	5-Methylthiophen-2-yl	$C_{27}H_{31}N_3O_6S$	261-263	88
P_{15}	5-Nitrofuran-2-yl	$C_{26}H_{28}N_4O_9$	231-233	84
P_{16}	1-Hydroxy-2-naphthalene	$C_{32}H_{33}N_3O_7$	260-262	88
P_{17}	2,4-Dihydroxyphenyl	$C_{28}H_{31}N_3O_8$	271-273	81
P_{18}	2-Hydroxy-4-bromophenyl	$C_{28}H_{30}BrN_3O_7$	248-250	89
P_{19}	4-Bromophenyl	$C_{28}H_{30}BrN_3O_6$	235-237	90
P_{20}	4-Nitrophenyl	$C_{29}H_{32}N_4O_8$	225-227	91
P_{21}	Thiophen-2-yl	$C_{27}H_{31}N_3O_6S$	218-220	83
P_{22}	Indol-3-yl	$C_{31}H_{34}N_4O_6$	226-228	89
P_{23}	4-Bromophenyl	$C_{29}H_{32}BrN_3O_6$	144-146	90
P_{24}	Phenyl	$C_{29}H_{33}N_3O_6$	215-217	87
P_{25}	4-Fluorophenyl	$C_{29}H_{32}FN_3O_6$	191-193	91
P_{26}	Furan-2-yl	$C_{27}H_{31}N_3O_7$	161-163	92
P_{27}	4-Chlorophenyl	$C_{29}H_{32}ClN_3O_6$	205-207	91

In FTIR spectrum of **4**, appearance of new broad peak at 3000-3300 cm^{-1} and a shift in carbonyl stretching frequency from 1739 to 1723 cm^{-1} clearly confirms the hydrolysis of ester **2** into acid **4**. This was further supported by ^{1}H NMR spectrum, wherein, a quartet and a triplet peaks that correspond to ester group disappeared. The freshly prepared acid chloride intermediate was directly used for next step without purification as it is highly reactive. The formation of amides, viz. $\mathbf{P_{28}}$ was confirmed by its FTIR spectrum, wherein a new peak at 1672 cm^{-1} corresponding to amide group appeared. More evidence was obtained by its ^{1}H NMR spectrum, wherein a new peak at δ 9.31 ppm due to amidic proton was observed. Similarly, its ^{13}C NMR spectrum exhibited characteristic peaks at 169.2 and 167.5 ppm, corresponding to ester and amide carbonyl groups, respectively. Further, it also showed other significant peaks at 62.5, 43.3 and 14.3 ppm corresponding to alkoxy and ethoxy groups, respectively. Formation of another set of amides $\mathbf{P_{32\text{-}36}}$ from hydrazide **3** was proved by their ^{1}H NMR spectra. A downfield shift in peak from δ 9.24 to δ 10.19 ppm in ^{1}H NMR spectrum of $\mathbf{P_{32}}$ that corresponds to amide NH proton, confirmed its structure. Similar pattern of peaks were observed for remaining amide derivatives of the series also.

Conversion of hydrazide **3** to 1,3,4 oxadiazole $\mathbf{P_{37}}$ was evidenced by its FTIR and ^{1}H NMR spectra, wherein carbonyl and amine stretching peaks disappeared and new characteristic peak at δ 14.65 ppm that corresponds to tautomeric NH proton of 1,3,4-oxadiazole ring appeared. Similarly, conversion of hydrazide to pyrazole derivative $\mathbf{P_{38}}$ was validated by its FTIR spectrum (Figure 3.12) where peaks correspond to hydrazide group disappeared. Moreover, its ^{1}H NMR spectrum (Figure 3.13) showed two new peaks at δ 2.45 and 2.19 ppm attributing to two allylic methyl groups attached to pyrazole ring. In FTIR spectrum of $\mathbf{P_{39}}$, a new broad peak at 3390 cm^{-1} and shift of carbonyl stretching frequency to 1718 cm^{-1} were observed, confirming the presence of carboxylic group. A new peak at δ 12.08 ppm in ^{1}H NMR spectrum confirms the ring opening of succinic anhydride. Disappearance of NH_2 peak at δ 4.28 ppm in $\mathbf{P_{40}}$ clearly established the conversion of hydrazide **3** to phthalimide derivative $\mathbf{P_{40}}$. Further, its ^{13}C NMR spectrum displayed three carbonyl peaks at δ 167.8, 166.9 and 164.9 ppm, which clearly confirms the proposed structure. Finally, structures of all the target compounds were confirmed by analysing their FTIR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The spectral data of all the title compounds

are summarized in the experimental section and their physical data are tabulated in Table 3.2. The ^{13}C NMR and mass spectra of compound **P_{38}** are given in Figure 3.14 and 3.15, respectively.

Table 3.2: Physical properties of compounds **P_{28-40}**

Compound	R	Mol. Formula	M.P. (^oC)	Yield (%)
P_{28}	Benzyl	$C_{28}H_{32}N_2O_6$	164-166	82
P_{29}	2,6-Dimethylphenyl	$C_{29}H_{34}N_2O_6$	175-177	78
P_{30}	4-Methylphenyl	$C_{28}H_{32}N_2O_6$	115-117	84
P_{31}	Benzothiazol-2-yl	$C_{28}H_{29}N_3O_6S$	97-99	80
P_{32}	4-Methylphenyl	$C_{29}H_{33}N_3O_7$	118-120	76
P_{33}	Phenyl	$C_{28}H_{31}N_3O_7$	144-146	78
P_{34}	3-Chlorothiophen-2-yl	$C_{26}H_{28}ClN_3O_7S$	131-133	80
P_{35}	Thiophen-3-yl	$C_{26}H_{29}N_3O_7S$	147-149	82
P_{36}	2-Chlorothiophen-3-yl	$C_{26}H_{28}ClN_3O_7S$	137-139	79
P_{37}	-	$C_{22}H_{25}N_3O_6S$	172-174	72
P_{38}	-	$C_{26}H_{31}N_3O_6$	181-183	78
P_{39}	-	$C_{25}H_{31}N_3O_9$	83-185	82
P_{40}	-	$C_{29}H_{29}N_3O_8$	139-141	80

3.3.1.3 Experimental procedures

In the following section, the appropriate synthetic methodology followed for the synthesis of various intermediates and target compounds of **P_{1-40}** were given. Further, their characterization data are also included.

Procedure for synthesis of diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate **(1):** A mixture of 4-hydroxybenzaldehyde (2 g, 16.3 mmol) ethyl acetoacetate (2.1 mL, 32.7 mmol) and ammonium acetate (1.9 g, 24.5 mmol) in 20 mL of ethanol was refluxed for 12 h. The reaction mixture was cooled on ice bath and solid separated was filtered, washed with ethanol and dried under vacuum. The product was recrystallized using ethanol/DMF mixture. Yield 60%, M.P. 239-241 ^oC. FTIR (ATR, cm^{-1}): 3337, 2980, 1656, 1221. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09 (s, 1H, OH), 8.71 (s, 1H, NH), 6.94-6.91 (d, 2H, ArH, *J*=12.0 Hz), 6.59-6.56 (d, 2H, ArH, *J*=12.0 Hz), 4.74 (s, 1H, CH_2), 4.04-3.92 (m, 4H, CH_2), 2.23 (s, 6H, CH_3),

1.15-1.11 (t, 6H, CH_3, *J*=8.0 Hz). MS (m/z): 346.4. Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.91; H, 6.69; N, 4.05.

Procedure for synthesis of diethyl 4-(4-(2-ethoxy-2-oxoethoxy)phenyl)-2,6-dimethyl 1,4-dihydropyridine-3,5-dicarboxylate (**2**): To a clear solution of **1** (3 g, 8.7 mmol) in 30 mL of DMF, ethyl chloroacetate (1.1 mL, 9.01 mmol) and K_2CO_3 (2.4 g, 17.3 mmol) were added with stirring. The reaction mixture was stirred at 100 °C for 20 h under nitrogen and cooled to room temperature. It was then quenched to ice cold water with stirring. Resulting solid was filtered, washed with water and dried. This was recrystallized from hot ethanol. Yield 80%, M.P. 105-107 ^oC. FTIR (ATR, cm^{-1}): 3351, 2979, 2905, 1739, 1686, 1492, 1201. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.73 (s, 1H, NH), 7.04-7.02 (dd, 2H, ArH, *J*=6.8, 2.0 Hz), 6.74-6.72 (dd, 2H, ArH, *J*=6.8, 2.0 Hz), 4.78 (s, 1H, CH), 4.66 (s, 2H, OCH_2), 4.16-4.11 (q, 2H, OCH_2, *J*=14.2, 6.8 Hz), 4.00-3.93 (m, 4H, OCH_2), 2.23 (s, 6H, CH_3), 1.20-1.16 (t, 3H, CH_3, *J*=7.2 Hz), 1.13-1.10 (t, 6H, CH_3, *J*=7.0 Hz). MS (m/z): 432.2. Anal. Calcd. for $C_{23}H_{29}NO_7$: C, 64.02; H, 6.77; N, 3.25. Found: C, 63.86; H, 6.74; N, 3.23.

Procedure for synthesis of 2-(4-(3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydro pyridin-4-yl)phenoxy) acetic acid hydrazide (**3**): A mixture of compound **2** (2.5 g, 5.8 mmol) and hydrazine hydrate (0.5 mL, 10 mmol) in ethanol (25 mL) was refluxed for 4 h. It was then cooled to room temperature to get crude hydrazide **3**. The resulting solid was filtered, washed with ethanol and recrystallized from ethanol/DMF mixture. Yield 90%, M.P. 191-193 ^oC. FTIR (ATR, cm^{-1}): 3348, 3288, 3224, 3099, 2978, 1672, 1656, 1498, 1203. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.24 (s, 1H, CONH), 8.73 (s, 1H, NH), 7.03-7.01 (m, 2H, ArH), 6.77-6.75 (m, 2H, ArH), 4.78 (s, 1H, CH), 4.39 (s, 2H, OCH_2), 4.28 (s, 2H, NH_2), 4.00-3.94 (m, 4H, OCH_2), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.0 Hz). MS (m/z): 418.1. Anal. Calcd. for $C_{21}H_{27}N_3O_6$. C, 60.42; H, 6.52; N, 10.07. Found: C, 60.28; H, 6.54; N, 10.06.

General procedure for synthesis of hydrazones (**P_{1-19}, P_{20-27}**)**:** To a clear solution of **3** (0.5 g, 1.2 mmol) in ethanol (10 mL), 1.2 mmol of aldehyde / ketone was added and refluxed for 5 h. Catalytic amount (0.2 mL) of glacial acetic acid was used for the synthesis of **P_{20-27}**. Resulting solid was filtered, washed with ethanol and finally recrystallized from methanol/chloroform mixture. Similarly, other final compounds

were also recrystallized from methanol/chloroform system. Their characterization and spectral data are given below.

Diethyl 4-(N'-(3,4,5-trimethoxybenzylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_1**): FTIR (ATR, cm^{-1}): 3352, 3000, 2941, 1663, 1620, 1492, 1211. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.2 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.89 (s, 1H, CH), 7.07-6.72 (m, 6H, ArH), 5.06 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.00-3.96 (m, 4H, CH_2), 3.79 (s, 6H, OCH_3), 3.68 (s, 3H, OCH_3), 2.23 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=8.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.2, 168.7, 157.3, 148.8, 145.1, 136.4, 131.4, 126.8, 125.4, 119.7, 116.5, 112.2, 102.4, 68.7, 62.5, 56.7, 43.3, 18.4, 16.3. MS (m/z) 596.1. Anal. Calcd. for $C_{31}H_{37}N_3O_9$: C, 62.51; H, 6.26; N, 7.05. Found: C, 62.40; H, 6.23; N, 7.02.

Diethyl 4-(N'-(4-chloro benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_2**): FTIR (ATR, cm^{-1}): 3285, 3231, 3058, 2957, 1660, 1610, 1217. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.2 (s, 1H, CONH), 8.73 (s, 1H, NH), 7.97 (s, 1H, CH), 7.72-7.70 (d, 2H, ArH, *J*=7.2 Hz), 7.50-7.48 (d, 2H, ArH, *J*=7.2 Hz), 7.07-7.05 (d, 2H, ArH, *J*=8.8 Hz), 6.81-6.79 (d, 2H, ArH, *J*=8.8 Hz), 5.09 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.03-3.96 (m, 4H, CH_2), 2.33 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=8.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.4, 163.4, 158.7, 145.3, 136.7, 134.6, 132.0, 127.1, 123.2, 119.1, 116.5, 112.4, 101.9, 68.7, 62.9, 43.2, 18.1, 16.5. MS (m/z) 540.1. Anal. Calcd. for $C_{28}H_{30}ClN_3O_6$: C, 62.28; H, 5.60; N, 7.78. Found: C, 62.11; H, 5.58; N, 7.75.

Diethyl 4-(N'-(4-nitro benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_3**): FTIR (ATR, cm^{-1}): 3309, 3237, 1667, 1608, 1224. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.80 (s, 1H, CONH), 8.73 (s, 1H, NH), 8.09 (s, 1H, CH), 8.28-6.75 (m, 8H, ArH), 5.09 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.02-3.93 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=7.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.2, 163.7, 161.4, 146.7, 135.7, 134.2, 132.4, 127.3, 123.4, 118.5, 116.5, 112.9, 101.9, 68.7, 63.1, 43.2, 18.1, 16.5. MS (m/z) 551.2. Anal. Calcd. for $C_{28}H_{30}N_4O_8$. C, 61.08; H, 5.49; N, 10.18. Found: C, 60.92; H, 5.49; N, 10.14.

Diethyl 4-(N'-(3,4-dimethoxy benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_4**): FTIR (ATR, cm^{-1}): 3230, 3094, 2969, 1667, 1612, 1496, 1221, 1122. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.35 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.95 (s, 1H, CH), 7.29-6.72 (m, 7H, ArH), 5.04 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.01-3.94 (m, 4H, CH_2), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.6 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 172.4, 165.2, 161.4, 158.4, 146.5, 134.7, 131.8, 123.4, 120.4, 118.5, 117.2, 102.8, 69.1, 62.3, 58.4, 43.2, 18.2, 16.5. MS (m/z) 566.6. Anal. Calcd. for $C_{30}H_{35}N_3O_8$. C, 63.70; H, 6.24; N, 7.43. Found: C, 63.52; H, 6.24; N, 7.41.

Diethyl 4-(N'-(4-hydroxy benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_5**): FTIR (ATR, cm^{-1}): 3384, 3282, 3224, 1662, 1609, 1222. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.28 (s, 1H, CONH), 9.44 (s, 1H, NH), 8.72 (s, 1H, CH), 7.86 (s, 1H, OH), 7.25-6.71 (m, 8H, ArH), 5.02 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.02-3.93 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 170.4, 164.2, 161.4, 158.4, 146.8, 134.7, 132.4, 127.3, 123.4, 118.5, 117.2, 102.4, 69.1, 62.8, 43.2, 18.2, 16.5. MS (m/z) 522.3. Anal. Calcd. for $C_{28}H_{31}N_3O_7$. C, 64.48; H, 5.99; N, 8.06. Found: C, 64.33; H, 5.95; N, 8.02.

Diethyl 4-(N'-(2-hydroxy phenyl)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_6**): FTIR (ATR, cm^{-1}): 3354, 3280, 3225, 1657, 1614, 1218. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.04 (s, 1H, CONH), 8.73 (s, 1H, NH), 8.53 (s, 1H, OH), 8.28 (s, 1H, CH), 7.68-6.73 (m, 8H, ArH), 5.01 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.00-3.94 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=8.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.7, 166.9, 157.3, 148.3, 145.0, 136.3, 131.1, 126.4, 119.3, 116.2, 113.7, 101.9, 66.5, 58.9, 43.2, 18.1, 14.1. MS (m/z) 522.2. Anal. Calcd. for $C_{28}H_{31}N_3O_7$. C, 64.48; H, 5.99; N, 8.06. Found: C, 64.35; H, 5.92; N, 8.03.

Diethyl 4-(N'-(4-dimethylamino benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_7**): FTIR (ATR, cm^{-1}): 3286, 3228, 1663, 1605, 1222. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.15 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.85 (s, 1H, CH), 7.49-6.70 (m, 8H, ArH), 4.99 (s, 1H, CH), 4.78 (s, 2H,

OCH_2), 4.02-3.93 (m, 4H, CH_2), 2.95 (s, 6H, CH_3), 2.33 (s, 6H, CH_3), 1.15-1.10 (t, 6H, CH_3, *J*=8.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 171.4, 164.5, 158.9, 151.3, 146.7, 137.6, 133.2, 132.7, 127.3, 123.5, 118.9, 116.4, 112.9, 101.9, 68.7, 63.3, 44.3, 43.2, 18.1, 16.6. MS (m/z) 549.2. Anal. Calcd. for $C_{30}H_{36}N_4O_6$. C, 65.68; H, 6.61; N, 10.21. Found: C, 65.54; H, 6.62; N, 10.17.

Diethyl 4-(N'-(4-hydroxy-3-ethoxy benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P$_8$**): FTIR (ATR, cm^{-1}): 3308, 3226, 1675, 1602, 1212. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.27 (s, 1H, CONH), 9.37 (s, 1H, OH), 8.72 (s, 1H, NH), 7.85 (s, 1H, CH), 7.23-6.79 (m, 7H, ArH), 5.02 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.07-3.93 (m, 6H, OCH_2), 2.32 (s, 6H, CH_3), 1.35-1.31 (t, 3H, CH_3, *J*=7.2 Hz), 1.14-1.10 (t, 6H, CH_3, *J*=9.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.1, 163.8, 158.7, 151.2, 149.2, 138.6, 134.7, 127.3, 124.6, 118.5, 117.2, 113.4, 102.4, 69.1, 64.3, 62.8, 43.2, 18.2, 16.5, 14.7. MS (m/z) 566.2. Anal. Calcd. for $C_{30}H_{35}N_3O_8$. C, 63.70; H, 6.24; N, 7.43. Found: C, 63.53; H, 6.21; N, 7.41.

Diethyl 4-(N'-(4-methyl benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P$_9$**): FTIR (ATR, cm^{-1}): 3291, 3232, 3099, 2997, 1662, 1612, 1219. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.41 (s, 1H, CONH), 8.73 (s, 1H, NH), 7.95 (s, 1H, CH), 7.57-6.72 (m, 8H, ArH), 5.03 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.02-3.93 (m, 4H, CH_2), 2.32 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=9.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.5, 163.2, 158.9, 151.8, 142.9, 139.6, 137.6, 132.4, 132.7, 129.4, 122.3, 116.4, 101.9, 69.3, 64.2, 43.2, 18.1, 16.6. MS (m/z) 520.2. Anal. Calcd. for $C_{29}H_{33}N_3O_6$. C, 67.04; H, 6.40; N, 8.09. Found: C, 66.87; H, 6.39; N, 8.02.

Diethyl 4-(N'-(4-hydroxy-3-methoxy benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P$_{10}$**): FTIR (ATR, cm^{-1}): 3459, 3318, 3247, 1676, 1612, 1217. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.28 (s, 1H, CONH), 9.44 (s, 1H, OH), 8.72 (s, 1H, NH), 7.86 (s, 1H, CH), 7.25-6.71 (m, 7H, ArH), 5.02 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.00-3.94 (m, 4H, CH_2), 3.77 (s, 3H, OCH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=9.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 171.2, 163.4, 158.5, 152.5, 147.3, 142.7, 136.7, 132.9, 128.7, 123.2, 121.3, 118.5, 116.6, 113.1, 101.9, 68.7, 62.9, 56.7, 43.3, 18.1, 16.5. MS (m/z)

552.3. Anal. Calcd. for $C_{29}H_{33}N_3O_8$. C, 63.15; H, 6.03; N, 7.62. Found: C, 63.03; H, 5.96; N, 7.57.

Diethyl 4-(N'-(1H-indol-3-yl)methylene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{11}**): FTIR (ATR, cm^{-1}): 3259, 3201, 3089, 2977, 1675, 1610, 1216. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.52 (s, 1H, CONH), 11.12 (s, 1H, NH), 8.72 (s, 1H, NH), 8.04 (s, 1H, CH), 7.78-6.82 (m, 9H, ArH), 5.07 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.01-3.94 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=9.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.3, 167.5, 159.8, 152.5, 142.3, 138.4, 132.2, 130.5, 128.7, 125.7, 122.1, 120.9, 118.6, 116.5, 114.7, 112.1, 106.4, 102.1, 67.1, 61.8, 42.0, 18.1, 14.3. MS (m/z) 545.6. Anal. Calcd. for $C_{30}H_{32}N_4O_6$. C, 66.16; H, 5.92; N, 10.29. Found: C, 66.02; H, 5.90; N, 10.25.

Diethyl 4-(N'-(thiophen-2-yl methylene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{12}**): FTIR (ATR, cm^{-1}): 3303, 3218, 3067, 2977, 1671, 1641, 1216. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.14 (s, 1H, CONH), 8.73 (s, 1H, NH), 8.16 (s, 1H, CH), 7.65-6.70 (m, 7H, ArH), 4.95 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.04-3.94 (m, 4H, CH_2), 2.33 (s, 6H, CH_3), 1.14-1.09 (t, 6H, CH_3, *J*=9.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.4, 164.5, 158.2, 142.3, 140.3, 138.4, 132.2, 130.7, 128.1, 126.3, 124.5, 123.7, 122.1, 120.9, 117.7, 114.3, 102.3, 67.8, 62.1, 42.3, 18.1, 14.5. MS (m/z) 512.6. Anal. Calcd. for $C_{26}H_{29}N_3O_6S$. C, 61.04; H, 5.71; N, 8.21. Found: C, 60.92; H, 5.68; N, 8.22.

Diethyl 4-(N'-(pyridin-4-ylmethylene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{13}**): FTIR (ATR, cm^{-1}): 3301, 3259, 2975, 1665, 1607, 1222. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.76 (s, 1H, CONH), 8.73 (s, 1H, NH), 7.96 (s, 1H, CH), 7.65-6.74 (m, 8H, ArH), 5.07 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.02-3.94 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.09 (t, 6H, CH_3, *J*=9.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.6, 162.8, 158.3, 147.6, 146.9, 141.3, 140.3, 132.2, 131.3, 125.7, 121.5, 117.7, 114.3, 102.3, 67.8, 62.1, 42.5, 18.1, 14.3. MS (m/z) 507.2. Anal. Calcd. for $C_{27}H_{30}N_4O_6$. C, 64.02; H, 5.97; N, 11.06. Found: C, 63.87; H, 5.98; N, 11.02.

Diethyl 4-(N'-((5-methylthiophen-2-yl)methylene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{14}**): FTIR (ATR, cm^{-1}): 3291, 3231,

3027, 2975, 1665, 1605, 1219. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.34 (s, 1H, CONH), 8.72 (s, 1H, NH), 8.06 (s, 1H, CH), 7.22-6.69 (m, 6H, ArH), 4.91 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.01-3.93 (m, 4H, CH_2), 2.44 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.09 (t, 6H, CH_3, *J*=9.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 166.8, 163.1, 158.7, 141.3, 140.3, 138.6, 131.3, 128.6, 125.7, 116.4, 114.2, 102.4, 67.8, 63.1, 41.8, 18.1, 15.2, 14.3. MS (m/z) 526.2. Anal. Calcd. for $C_{27}H_{31}N_3O_6S$. C, 61.70; H, 5.94; N, 7.99. Found: C, 61.55; H, 5.89; N, 7.97.

Diethyl (N'- 4-((5-nitrofuran-2-yl)methylene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{15}**): FTIR (ATR, cm^{-1}): 3301, 3234, 3065, 2974, 1674, 1611, 1213. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.89 (s, 1H, CONH), 8.73 (s, 1H, NH), 7.94 (s, 1H, CH), 7.78-6.72 (m, 6H, ArH), 5.02 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 3.99-3.94 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.15-1.10 (t, 6H, CH_3, *J*=9.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 173.1, 164.5, 158.5, 154.3, 152.7, 136.7, 135.4, 132.9, 123.2, 121.3, 118.8, 116.4, 101.8, 68.7, 63.1, 42.9, 18.2, 16.5. MS (m/z) 541.2. Anal. Calcd. for $C_{26}H_{28}N_4O_9$. C, 57.77; H, 5.22; N, 10.37. Found: C, 57.59; H, 5.19; N, 10.39.

Diethyl (N'-4-((1-hydroxynaphthalen-2-yl)methylene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{16}**): FTIR (ATR, cm^{-1}): 3306, 3263, 3058, 2978, 1664, 1617, 1219. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.78 (s, 1H, CONH), 9.41 (s, 1H, OH), 8.74 (s, 1H, NH), 8.19 (s, 1H, CH), 7.93-6.88 (m, 10H, ArH), 5.05 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.03-3.91 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=9.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 173.8, 164.8, 161.3, 158.5, 151.8, 143.2, 135.4, 132.7, 131.7, 126.4, 123.6, 121.3, 116.9, 114.7, 102.3, 68.7, 62.9, 42.8, 18.2, 16.6. MS (m/z) 572.1. Anal. Calcd. for $C_{32}H_{33}N_3O_7$. C, 67.24; H, 5.82; N, 7.35. Found: C, 67.12; H, 5.79; N, 7.29.

Diethyl 4-(N'-(2,4-dihydroxy benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{17}**): FTIR (ATR, cm^{-1}): 3380, 3229, 3094, 2973, 1661, 1621, 1223. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.21 (s, 1H, CONH), 9.92 (s, 1H, OH), 9.76 (s, 1H, OH), 8.71 (s, 1H, NH), 8.15 (s, 1H, CH), 7.46-6.30 (m, 7H, ArH), 4.95 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.01-3.93 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.09 (t, 6H, CH_3, *J*=9.6 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm):

169.1, 165.4, 161.4, 158.3, 149.2, 133.6, 131.2, 128.2, 124.7, 122.4, 115.7, 113.7, 109.7, 102.0, 66.4, 59.8, 41.2, 18.2, 14.1. MS (m/z) 538.3. Anal. Calcd. for $C_{28}H_{31}N_3O_8$. C, 62.56; H, 5.81; N, 7.82. Found: C, 62.48; H, 5.76; N, 7.79.

Diethyl 4-(N'-(5-bromo-2-hydroxybenzylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{18}**): FTIR (ATR, cm^{-1}): 3325, 3272, 3013, 2976, 1671, 1612, 1212. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.06 (s, 1H, CONH), 10.32 (s, 1H, OH), 8.73 (s, 1H, NH), 8.21 (s, 1H, CH), 7.81-6.72 (m, 7H, ArH), 5.05 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 3.99-3.95 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=9.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.3, 164.6, 159.2, 149.5, 142.3, 133.6, 131.4, 125.2, 124.7, 123.2, 119.7, 115.7, 113.7, 109.7, 102.0, 66.4, 59.8, 41.2, 18.2, 14.1. MS (m/z) 600.6. Anal. Calcd. for $C_{28}H_{30}BrN_3O_7$. C, 56.01; H, 5.04; N, 7.00. Found: C, 55.92; H, 5.05; N, 6.96.

Diethyl 4-(N'-(4-bromo benzylidine)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{19}**): FTIR (ATR, cm^{-1}): 3307, 3272, 3058, 2957, 1667, 1610, 1228. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.55 (s, 1H, CONH), 8.73 (s, 1H, NH), 7.96 (s, 1H, CH), 7.65-6.73 (m, 8H, ArH), 5.04 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.02-3.93 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.09 (t, 6H, CH_3, *J*=9.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 173.8, 165.2, 158.5, 151.8, 142.9, 135.4, 132.7, 131.2, 126.4, 114.7, 102.3, 68.7, 62.9, 42.8, 18.2, 16.6. MS (m/z) 584.1. Anal. Calcd. for $C_{28}H_{30}BrN_3O_6$. C, 57.54; H, 5.17; N, 7.19. Found: C, 57.41; H, 5.15 N, 7.15.

Diethyl 4-(-N'-(1-(4-nitrophenyl)ethylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{20}**): FTIR (ATR, cm^{-1}): 3309, 3237, 1667, 1497, 1224. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.1 (s, 1H, CONH), 8.77 (s, 1H, NH), 8.26-8.23 (d, 2H, ArH, *J*=12.0 Hz), 8.08-8.05 (d, 2H, ArH, *J*=12.0 Hz), 7.06-6.78 (m, 4H, ArH), 5.14 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.00-3.97 (m, 4H, CH_2), 2.31 (s, 3H, CH_3), 2.24 (s, 6H, CH_3), 1.16-1.11 (t, 6H, CH_3, *J*=10.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.9, 166.9, 163.8, 161.4, 156.3, 147.2, 144.9, 140.6, 134.4, 128.3, 115.2, 113.7, 102.0, 65.0, 58.9, 37.8, 18.2, 14.1. 13.4. MS (m/z) 565.7. Anal. Calcd. for $C_{29}H_{32}N_4O_8$: C, 61.69; H, 5.71; N, 9.92. Found: C, 61.61; H, 5.67; N, 9.88.

Diethyl 4-(N'-(1-(thiophen-2-yl)ethylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{21}**): FTIR (ATR, cm^{-1}): 3294, 3094, 2969, 1689, 1652, 1206. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 10.81 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.58-6.70 (m, 7H, ArH), 4.97 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.01-3.94 (m, 4H, CH_2), 2.26 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.2, 164.5, 160.2, 155.8, 136.7, 134.3, 133.2, 128.7, 123.5, 121.7, 117.4, 115.3, 102.1, 64.6, 59.8, 40.2, 18.1, 14.4. 13.3. MS (m/z) 526.3. Anal. Calcd. for $C_{27}H_{31}N_3O_6S$. C, 61.70; H, 5.94; N, 7.99. Found: C, 61.57; H, 5.92; N, 7.93.

Diethyl 4-(N'-(1-(1H-indol-3-yl)ethylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{22}**): FTIR (ATR, cm^{-1}): 3277, 3210, 3080, 2966, 1684, 1641, 1209. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 11.42 (s, 1H, CONH), 10.55 (s, 1H, NH), 8.72 (s, 1H, NH), 8.56-6.76 (m, 9H, ArH), 5.11 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.02-3.94 (m, 4H, CH_2), 2.27 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.11 (t, 6H, CH_3, *J*=7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 170.4, 167.3, 164.5, 156.5, 138.4, 136.8, 134.2, 128.7, 126.9, 124.1, 120.7, 114.2, 113.5, 102.1, 67.1, 59.3, 42.0, 18.1, 14.3. 13.7. MS (m/z) 559.1. Anal. Calcd. for $C_{31}H_{34}N_4O_6$. C, 66.65; H, 6.13; N, 10.03. Found: C, 66.53; H, 6.12; N, 10.04.

Diethyl 4-(N'-(1-(4-bromophenyl)ethylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{23}**): FTIR (ATR, cm^{-1}): 3295, 3237, 2976, 1687, 1648, 1202. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 10.84 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.86-6.72 (m, 8H, ArH), 5.07 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.02-3.94 (m, 4H, CH_2), 2.25 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.2, 166.7, 162.3, 158.9, 138.5, 136.1, 134.7, 131.4, 128.7, 126.9, 116.3, 114.2, 102.1, 67.1, 59.7, 42.1, 18.1, 14.4. 13.3. MS (m/z) 598.2. Anal. Calcd. for $C_{29}H_{32}BrN_3O_6$. C, 58.20; H, 5.39; N, 7.02. Found: C, 58.10; H, 5.39; N, 6.98.

Diethyl 4-(N'-(1-phenylethylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{24}**): FTIR (ATR, cm^{-1}): 3296, 3218, 2976, 1684, 1618, 1208. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 10.78 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.79-6.72 (m, 9H, ArH), 5.07 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.02-3.94

(m, 4H, CH_2), 2.25 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.2, 166.4, 159.7, 135.4, 134.7, 132.2, 130.4, 123.5, 121.7, 118.9, 117.3, 116.4, 102.1, 67.4, 59.7, 42.1, 18.1, 14.4. 13.3. MS (m/z) 520.3. Anal. Calcd. for $C_{29}H_{33}N_3O_6$. C, 67.04; H, 6.40; N, 8.09. Found: C, 66.89; H, 6.36; N, 8.05.

Diethyl 4-(N'-(1-(4-fluorophenyl)ethylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{25}**): FTIR (ATR, cm^{-1}): 3342, 2976, 1693, 1642, 1207. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 10.79 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.85-6.72 (m, 8H, ArH), 5.07 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.02-3.94 (m, 4H, CH_2), 2.24 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.9, 166.8, 156.4, 147.2, 134.4, 128.3, 115.2, 113.7, 102.0, 66.0, 62.3, 38.2, 18.2, 14.1. 13.4. MS (m/z) 538.2. Anal. Calcd. for $C_{29}H_{32}FN_3O_6$. C, 64.79; H, 6.00; N, 7.82. Found: C, 64.81; H, 5.95; N, 7.79.

Diethyl 4-(N'-(1-(furan-2-yl)ethylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{26}**): FTIR (ATR, cm^{-1}): 3282, 2956, 1683, 1632, 1217. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 10.74 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.67-6.57 (m, 7H, ArH), 4.99 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.02-3.94 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 2.17 (s, 3H, CH_3), 1.14-1.11 (t, 6H, CH_3, *J*=7.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.2, 164.2, 156.4, 154.3, 147.2, 142.7, 141.8, 126.4, 124.8, 123.1, 114.2, 113.7, 102.2, 66.7, 60.4, 39.2, 18.2, 14.2. 13.4. MS (m/z) 510.4. Anal. Calcd. for $C_{27}H_{31}N_3O_7$. C, 63.64; H, 6.13; N, 8.25. Found: C, 63.56; H, 6.15; N, 8.23.

Diethyl 4-(N'-(1-(4-chlorophenyl)ethylidene)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{27}**): FTIR (ATR, cm^{-1}): 3295, 3237, 2976, 1687, 1648, 1202. ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 10.84 (s, 1H, CONH), 8.72 (s, 1H, NH), 7.86-6.72 (m, 8H, ArH), 5.07 (s, 1H, CH), 4.78 (s, 2H, OCH_2), 4.02-3.94 (m, 4H, CH_2), 2.25 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.2, 166.4, 162.3, 160.2, 158.7, 135.1, 134.2, 132.6, 123.4, 121.5, 118.6, 117.3, 116.3, 102.1, 67.4, 59.7, 42.1, 18.1, 14.4. 13.3. MS (m/z) 554.2. Anal. Calcd. for $C_{29}H_{32}ClN_3O_6$. C, 62.87; H, 5.82; N, 7.58. Found: C, 62.91; H, 5.80; N, 7.56.

Procedure for the synthesis of 2-(4-(3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl)phenoxy)acetic acid **(4):** To a solution of ester **2** (1 g, 2.32 mmol), in 10 mL of ethanol, sodium hydroxide (0.1 g, 2.5 mmol, 10 mL) solution was added. The resulting solution was refluxed for one hr. It was then cooled to room temperature and neutralized with conc. HCl. The crude compound **4** was recrystallized from methanol-chloroform mixture. Yield 76%, M.P. 176-178 ^{o}C. FTIR (ATR, cm^{-1}): 3242, 2982, 2912, 1723, 1671, 1203. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.74 (s, 1H, NH), 7.04-7.02 (d, 2H, ArH, *J*=8.0 Hz), 6.73-6.71 (d, 2H, ArH, *J*=8.0 Hz), 4.78 (s, 1H, CH), 4.58 (s, 2H, OCH_2), 4.00-3.97 (m, 4H, CH_2), 2.24 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=7.2 Hz). MS (m/z): 404.4. Anal. Calcd. for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.46; H, 6.24; N, 3.42.

*Procedure for synthesis of diethyl 4-(4-(2-chloro-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate***:** To a solution of compound **4** (1 g, 2.32 mmol) in methylene dichloride (10 mL), thionyl chloride (0.35 mL, 4.64 mmol) was added followed by one drop of DMF. The resulting solution was stirred at 50 ^{o}C for about 4 h. The solvent was evaporated under reduced pressure and the resulting crude product was taken as such for next step without any purification.

General procedure for synthesis of amides (**P_{28-31}**)**:** The intermediate acid chloride (0.1 g, 0.22 mmol) was dissolved in 5 mL of methylene dichloride and reacted with different amines (0.22 mmol) in presence of piperidine (0.02 mL, 0.22 mmol). This reaction mixture was stirred at room temperature for 8 h. The precipitated product was filtered, washed well with methylene dichloride and dried. All the crude products were recrystallized from ethanol-DMF mixture. Same procedure was followed for the synthesis of **P_{32-36}**, wherein hydrazide intermediate **3** was condensed with different acid chlorides. Their characterization and spectral data are as follows.

Diethyl 4-(4-(2-(benzylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{28}**): FTIR (ATR, cm^{-1}): 3392 (br), 2960, 2872, 1672, 1663, 1203. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.31 (s, 1H, CONH), 8.75 (s, 1H, NH), 7.76-6.77 (m, 9H, ArH), 4.87 (s, 1H, CH), 4.62 (s, 2H, OCH_2), 4.24 (s, 2H, NCH_2), 4.01-3.93 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.2, 167.5, 157.3, 141.8, 142.1, 134.4, 126.8, 125.4,

116.0, 112.2, 68.7, 62.5, 43.3, 16.4, 14.3. MS (m/z): 493.6. Anal. Calcd. for $C_{28}H_{32}N_2O_6$. C, 68.28; H, 6.55; N, 5.69. Found: C, 68.20; H, 6.53; N, 5.62.

Diethyl 4-(4-(2-(2,6-dimethylphenylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{29}**): FTIR (ATR, cm^{-1}): 3350, 3091, 2981, 1672, 1666, 1195. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.04 (s, 1H, CONH), 8.74 (s, 1H, NH), 7.82-6.80 (m, 7H, ArH), 4.86 (s, 1H, CH), 4.62 (s, 2H, OCH_2), 4.01-3.96 (m, 4H, CH_2), 2.32 (s, 6H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.10 (t, 6H, CH_3, *J*=7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.2, 167.6, 157.4, 141.2, 137.3, 134.2, 129.8, 126.7, 124.2, 114.5, 113.1, 66.8, 61.4, 43.2, 16.3, 14.7, 14.2. MS (m/z): 507.4. Anal. Calcd. for $C_{29}H_{34}N_2O_6$. C, 68.76; H, 6.76; N, 5.53. Found: C, 68.64; H, 6.73; N, 5.52.

Diethyl 4-(4-(2-(p-toluidino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{30}**): FTIR (ATR, cm^{-1}): 3315, 3091, 2981, 2923, 1686, 1667, 1235. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.83 (s, 1H, CONH), 8.74 (s, 1H, NH), 7.78-6.76 (m, 8H, ArH), 4.88 (s, 1H, CH), 4.63 (s, 2H, OCH_2), 4.01-3.95 (m, 4H, CH_2), 2.32 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 1.14-1.11 (t, 6H, CH_3, *J*=6.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 169.3, 167.4, 158.1, 143.4, 138.3, 135.7, 129.7, 121.5, 114.3, 112.5, 66.8, 61.7, 43.2, 24.3, 16.4, 14.2. MS (m/z): 493.4. Anal. Calcd. for $C_{28}H_{32}N_2O_6$. C, 68.28; H, 6.55; N, 5.69. Found: C, 68.14; H, 6.53; N, 5.62.

Diethyl 4-(4-(2-(benzothiazol-2-ylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{31}**): FTIR (ATR, cm^{-1}): 3315, 3150, 3066, 2981, 1672, 1215. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.12 (s, 1H, CONH), 8.75 (s, 1H, NH), 7.78-6.68 (m, 8H, ArH), 4.84 (s, 1H, CH), 4.62 (s, 2H, OCH_2), 4.00-3.96 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.14-1.11 (t, 6H, CH_3, *J*=7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 176.2, 169.3, 167.2, 155.6, 150.2, 148.7, 134.6, 130.2, 125.6, 124.3, 122.3, 114.5, 112.4, 66.7, 61.7, 42.9, 16.3, 14.2. MS (m/z): 536.4. Anal. Calcd. for $C_{28}H_{29}N_3O_6S$. C, 62.79; H, 5.46; N, 7.85. Found: C, 62.64; H, 5.43; N, 7.82.

Diethyl 4-(N'-(4-methyl benzoyl)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{32}**): FTIR (ATR, cm^{-1}): 3346, 3226, 3056, 2982, 1674, 1648, 1212. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.19 (s, 2H, CONH), 8.74 (s, 1H, NH), 7.78-7.76 (d, 2H, ArH, *J*=8.0 Hz), 7.29-7.27 (d, 2H, ArH, *J*=8.0 Hz),

7.06-7.04 (d, 2H, ArH, *J*=8.4 Hz), 6.84-6.82 (d, 2H, ArH, *J*=8.4 Hz), 4.80 (s, 1H, CH), 4.56 (s, 2H, OCH_2), 4.01-3.95 (m, 4H, CH_2), 2.35 (s, 3H, CH_3), 2.24 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=7.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.2, 166.9, 165.3, 155.9, 145.0, 141.7, 129.6, 128.9, 127.4, 114.0, 112.0, 66.1, 58.9, 39.7, 20.9, 18.1, 14.1. MS (m/z): 536.6. Anal. Calcd. for $C_{29}H_{33}N_3O_7$. C, 65.03; H, 6.21; N, 7.85. Found: C, 64.91; H, 6.19; N, 7.83.

Diethyl 4-(N'-(benzoyl)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{33}**): FTIR (ATR, cm^{-1}): 3345, 3234, 3056, 2979, 1689, 1645, 1210. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.36 (s, 1H, CONH), 10.16 (s, 1H, CONH), 8.74 (s, 1H, NH), 7.95-6.83 (m, 9H, ArH), 4.80 (s, 1H, CH), 4.57 (s, 2H, OCH_2), 4.01-3.96 (m, 4H, CH_2), 2.24 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.2, 166.9, 165.4, 155.9, 145.1, 141.5, 131.2, 128.7, 127.3, 114.1, 112.2, 66.1, 58.7, 39.7, 18.1, 14.1. MS (m/z): 522.3. Anal. Calcd. for $C_{28}H_{31}N_3O_7$. C, 64.48; H, 5.99; N, 8.06. Found: C, 64.39; H, 5.92; N, 8.02.

Diethyl 4-(N'-(3-chloro thiophene-2-carbonyl)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{34}**): FTIR (ATR, cm^{-1}): 3342, 3238, 3017, 2965, 1664, 1645, 1212. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.24 (s, 1H, CONH), 10.18 (s, 1H, CONH), 8.74 (s, 1H, NH), 7.95-6.85 (m, 6H, ArH), 4.79 (s, 1H, CH), 4.58 (s, 2H, OCH_2), 4.01-3.95 (m, 4H, CH_2), 2.24 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=7.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.2, 166.6, 161.2, 155.8, 140.9, 138.1, 135.0, 129.8, 129.2, 114.1, 112.2, 67.1, 58.8, 40.0, 16.3, 14.2. MS (m/z): 562.7. Anal. Calcd. for $C_{26}H_{28}ClN_3O_7S$. C, 55.56; H, 5.02; N, 7.48. Found: C, 55.49; H, 5.02; N, 7.42.

Diethyl 4-(N'-(thiophene-2-carbonyl)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{35}**): FTIR (ATR, cm^{-1}): 3348, 3242, 3009, 2965, 1669, 1647, 1209. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.19 (s, 1H, CONH), 10.11 (s, 1H, CONH), 8.74 (s, 1H, NH), 7.82-6.81 (m, 7H, ArH), 4.81 (s, 1H, CH), 4.54 (s, 2H, OCH_2), 4.01-3.96 (m, 4H, CH_2), 2.24 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.2, 166.6, 161.2, 155.8, 142.8, 138.1, 137.4, 129.8, 114.2, 112.3, 67.1, 58.8, 39.8, 16.3, 14.2. MS (m/z): 528.6. Anal. Calcd. for $C_{26}H_{29}N_3O_7S$. C, 59.19; H, 5.54; N, 7.96. Found: C, 59.08; H, 5.52; N, 7.91.

Diethyl 4-(N'-(2-chloro thiophene-3-carbonyl)-2-phenoxyacetohydrazide)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{36}**): FTIR (ATR, cm^{-1}): 3332, 3213, 2997, 2946, 1665, 1643, 1202. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.23 (s, 1H, CONH), 10.14 (s, 1H, CONH), 8.74 (s, 1H, NH), 7.80-6.84 (m, 6H, ArH), 4.82 (s, 1H, CH), 4.54 (s, 2H, OCH_2), 4.00-3.95 (m, 4H, CH_2), 2.24 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=7.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.2, 166.4, 164.8, 156.2, 141.3, 139.4, 137.6, 134.5, 129.8, 128.7, 118.9, 114.3, 112.3, 67.3, 58.8, 40.2, 16.3, 14.2. MS (m/z): 562.9. Anal. Calcd. for $C_{26}H_{28}ClN_3O_7S$. C, 55.56; H, 5.02; N, 7.48. Found: C, 55.48; H, 4.98; N, 7.45.

Procedure for synthesis of diethyl 4-(4-((5-mercapto-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{37}**)**:** An ethanolic KOH (0.1 g in 10 mL C_2H_5OH) solution was prepared and hydrazide **3** (0.5 g, 1.21 mmol) was added to it. The resulting solution was cooled to 5 ^{o}C and to this carbon disulphide (0.2 mL, 2.42 mmol) was added while stirring. This mixture was stirred at room temperature for about one hour and then heated under reflux condition for 6 h. The resulting potassium salt was filtered and washed with ethanol. The salt was dissolved in water and acidified with dil. HCl under stirring. The resulting solid was filtered and recrystallized from methanol-chloroform mixture. FTIR (ATR, cm^{-1}): 3334, 3082, 2933, 1662, 1492, 1213. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.65 (br, 1H, CSNH), 8.74 (s, 1H, NH), 7.076-7.054 (d, 2H, ArH, *J*=8.8 Hz), 6.87-6.85 (d, 2H, ArH, *J*=8.8 Hz), 5.15 (s, 1H, CH), 4.79 (s, 2H, OCH_2), 4.00-3.94 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.13-1.00 (t, 6H, CH_3, *J*=7.6 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 178.0, 166.9, 159.6, 155.3, 145.1, 141.9, 128.4, 114.1, 101.9, 59.5, 58.1, 38.9, 18.1, 14.1. MS (m/z): 460.3. Anal. Calcd. for $C_{22}H_{25}N_3O_6S$. C, 57.50; H, 5.48; N, 9.14. Found: C, 57.38; H, 5.47; N, 9.14.

Procedure for the synthesis of diethyl 4-(4-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**P_{38}**)**:** An ethanolic solution of **3** (0.5 g, 1.21 mmol) and acetyl acetone (0.43 mL, 1.21 mmol) was refluxed in presence of catalytic amount (0.2 mL) of glacial acetic acid for 5 h. Upon completion of the reaction, the mixture was cooled, filtered and recrystallized from methanol-chloroform mixture. FTIR (ATR, cm^{-1}): 3337, 2977, 2926, 1720, 1687,

1491, 1264. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.73 (s, 1H, NH), 7.05-7.02 (m, 2H, ArH), 6.79-6.76 (m, 2H, ArH), 6.21 (s, 1H, ArH), 5.39 (s, 2H, OCH_2), 4.80 (s, 1H, CH), 4.02-3.94 (m, 4H, CH_2), 2.45 (s, 3H, CH_3), 2.23 (s, 6H, CH_3), 2.19 (s, 3H, CH_3), 1.14-1.11 (t, 6H, CH_3, *J*=7.2 Hz).). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.1, 166.9, 155.9, 152.3, 145.0, 143.5, 141.0, 128.2, 113.8, 111.1, 101.9, 65.8, 58.9, 38.8, 18.1, 14.1, 13.5. MS (m/z): 482.2. Anal. Calcd. for $C_{26}H_{31}N_3O_6$. C, 64.85; H, 6.49; N, 8.73. Found: C, 64.73; H, 6.47; N, 8.74.

Procedure for synthesis of 4-(2-(2-(4-(3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl)phenoxy)acetyl)hydrazinyl)-4-oxobutanoic acid **(P_{39}):** A mixture of **3** (0.5 g, 1.21 mmol), succinic anhydride (0.11 g, 1.21 mmol) in 10 mL of ethanol was refluxed in presence of 0.1 mL of glacial acetic acid for 6 h. After complete reaction, pH of the reaction mixture was made alkaline by adding sodium bicarbonate solution. The product was extracted with ethyl acetate and aqueous layer was neutralized with dil. HCl. Resulting solid was filtered and recrystallized from ethanol. FTIR (ATR, cm^{-1}): 3390 (br), 2978, 1718, 1658, 1221. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 12.08 (s, 1H, OH), 9.99 (s, 1H, CONH), 9.81 (s, 1H, CONH), 8.73 (s, 1H, NH), 7.04-7.02 (d, 2H, ArH, *J*=8.4 Hz), 6.79-6.77 (d, 2H, ArH, *J*=8.4 Hz), 4.78 (s, 1H, CH), 4.48 (s, 2H, OCH_2), 4.01-3.95 (m, 4H, CH_2), 2.43-2.42 (t, 2H, CH_2, *J*=3.2 Hz), 2.38-2.37 (t, 2H, CH_2, *J*=3.2 Hz), 2.23 (s, 6H, CH_3), 1.14-1.11 (t, 6H, CH_3, *J*=7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.8, 166.8, 164.7, 156.1, 145.2, 141.1, 135.8, 113.9, 102.3, 65.9, 63.9, 58.9, 38.9, 18.1, 14.1. MS (m/z): 518.2. Anal. Calcd. for $C_{25}H_{31}N_3O_9$. C, 58.02; H, 6.04; N, 8.12. Found: C, 57.92; H, 6.02; N, 8.09.

Procedure for the synthesis of diethyl 4-(4-(2-(1,3-dioxoisoindolin-2-ylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **(P_{40}):** A solution of **3** (0.5 g, 1.21 mmol) and phthalic anhydride (0.2 g, 1.35 mmol) in 10 mL of ethanol containing 0.2 mL of glacial acetic acid was refluxed for 6 h with stirring. Upon completion of reaction, the reaction mixture was cooled, filtered and washed with ethanol and recrystallized from methanol-chloroform mixture. FTIR (ATR, cm^{-1}): 3224, 2981, 1668, 1222. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.24 (s, 1H, CONH), 8.73 (s, 1H, NH), 7.78-6.80 (s, 8H, ArH), 4.79 (s, 1H, CH), 4.55 (s, 2H, OCH_2), 4.00-3.96 (m, 4H, CH_2), 2.23 (s, 6H, CH_3), 1.15-1.11 (t, 6H, CH_3, *J*=7.0 Hz).

^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.8, 166.9, 164.9, 156.0, 145.0, 141.1, 135.6, 123.8, 113.9, 102.3, 65.9, 63.9, 58.9, 38.9, 18.1, 14.1. MS (m/z): 548.5. Anal. Calcd. for $C_{29}H_{29}N_3O_8$. C, 63.61; H, 5.34; N, 7.67. Found: C, 63.52; H, 5.32; N, 7.63.

Table 3.3: Crystallographic data of compound **P_{38}**

Crystal Data	
Empirical formula	$C_{26}H_{31}N_3O_6$
Formula weight	481.54
Space group	P 21/c
a (Å)	9.7280(6)
b (Å)	16.2565(11)
c (Å)	15.7224(11)
Volume (Å^3)	2482.6(3)
Angle α, β, γ	90, 93.146(3), 90
Z	4
Crystal density (g/cm^3)	1.288
F_{000}	1024
μ (mm^{-1})	0.092
Radiation wavelength	0.71073
Radiation source	Fine-focus sealed tube
h max	12
k max	20
l max	19
N_{ref}	4868
wR_2 (Reflections)	0.1257 (4868)
R(reflections)	0.0443(3991)
Theta (max)	26.0

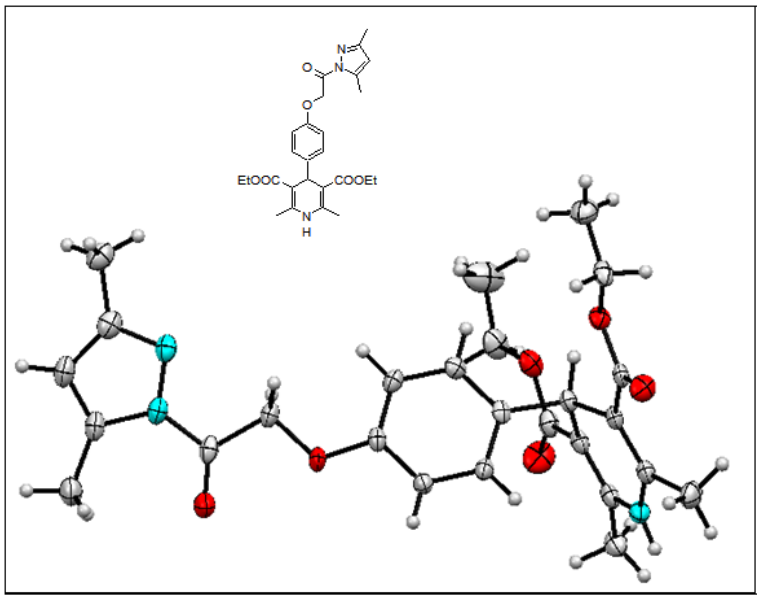


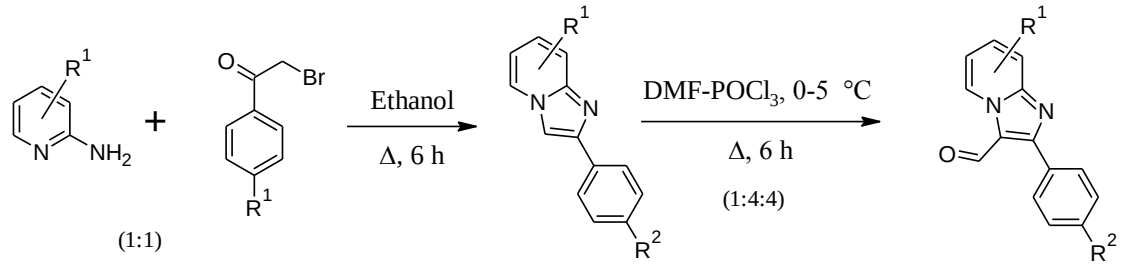
Figure 3.1: ORTEP diagram of compound **P_{38}**

3.3.2 Synthesis of new imidazo[1,2-a]pyridine-3-carboxaldehyde derivatives (P_{41-64})

In the following section, synthetic protocols for the preparation of new imidazo[1,2-a]pyridine-3-carboxaldehyde derivatives (**P_{41-64}**) have been given. This series includes twenty four compounds containing various pharmacophoric groups such as oxazolone, pyrazolone, hydroxyl and imine groups at third position of imidazo[1,2-a]pyridine scaffold.

3.3.2.1 Chemistry

The reaction sequence involving the synthesis of required imidazo[1,2-a]pyridine-3-carboxaldehydes is given in Scheme 3.3. The core imidazo[1,2-a]pyridine nuclei **5a-g** were conveniently synthesized following reported procedure, by coupling 2-aminopyridines with different freshly prepared phenacyl bromides under reflux condition. These cyclic products were then made to undergo Vilsmeier–Haack formylation, selectively at free nucleophilic carbon centre on imidazole ring to get the corresponding aldehydes **6a-g** with reasonable yield.

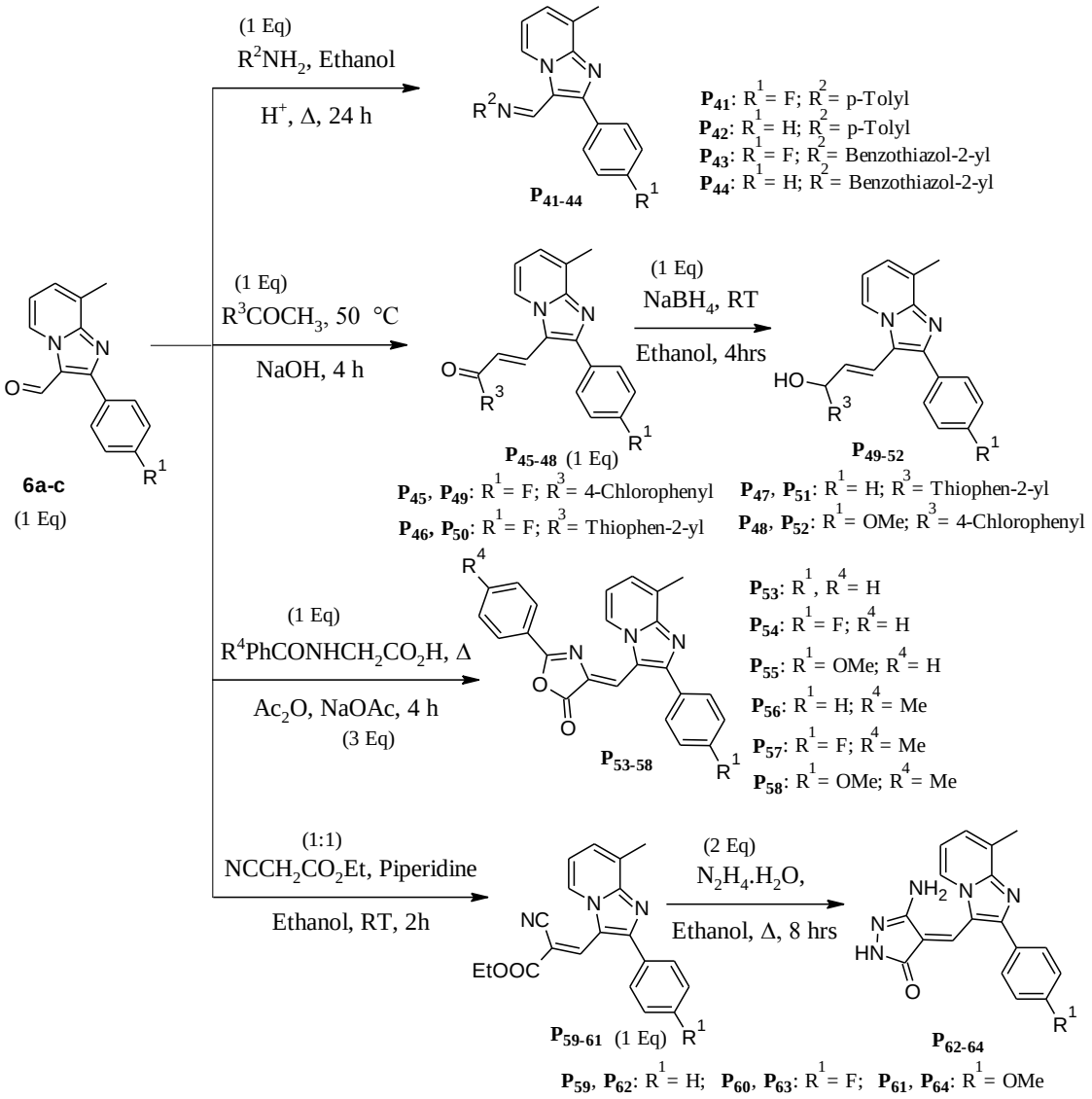


5a, 6a: R^1=8-Me; R^2=H
5b, 6b: R^1=8-Me; R^2=F
5c, 6c: R^1=8-Me; R^2=Me
5d, 6d: R^1=8-Me; R^2=MeO
5e, **6e**: R^1=6-Br; R^2=H
5f, **6f**: R^1=6-Br; R^2=F
5g, **6g**: R^1=6-Br; R^2=Me

Scheme 3.3: Synthesis of imidazo[1,2-a]pyridine-3-carboxaldehydes **6a-g**

The synthetic routes for final compounds **P_{41-64}** are depicted in Scheme 3.4. The imines **P_{41-44}** were obtained by condensing aldehydes **6a-b** with appropriate aromatic amines in presence of catalytic amount of sulphuric acid at 80 ^oC for 24 h. Further, the chalcone derivatives **P_{45-48}** were obtained by treating aldehydes **6a-c** with various substituted acetophenones under basic media and those were later reduced to corresponding hydroxyl derivatives **P_{49-52}** using sodium borohydride at room temperature. In another series, oxazolones **P_{53-58}** were obtained in good yield by

treating substituted/unsubstituted hippuric acids with aldehydes **6a-c**, in presence of sodium acetate and acetic anhydride under reflux condition. Finally, aldehydes **6a-c** were coupled with ethyl cyanoacetate in presence of piperidine to obtain intermediates $\mathbf{P_{59\text{-}61}}$, which were later successfully cyclised to target pyrazolone derivatives $\mathbf{P_{62\text{-}64}}$ by reacting with hydrazine hydrate. The intermediates as well as target compounds were purified by recrystallization or column chromatographic technique and were characterized by various spectral studies.



Scheme 3.4: Synthetic routes for target compounds $\mathbf{P_{41\text{-}64}}$

3.3.2.2 Results and discussion

The structures of new compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy followed by elemental analysis studies. Synthesis of core

imidazo[1,2-a]pyridine derivative **5a** was confirmed by its FTIR spectrum, where the peak corresponding to amine group of 2-amino-3-picoline and carbonyl functionality of phenacyl bromide disappeared. Also, a new characteristic peak at 1638 cm^{-1} corresponding to C=N stretching of the ring was observed, which clearly demonstrated the cyclization. Similarly, the ^{1}H NMR spectrum of **5a** displayed a singlet at δ 2.65 ppm corresponding to CH_3 group attached to pyridine ring along with other required aromatic peaks, but no peaks corresponding to amine group was observed. Formylation of core ring was clearly established by the observation of new carbonyl stretching peak at 1678 cm^{-1} in FTIR spectrum of **6a**. This was further confirmed by its ^{1}H NMR spectrum, wherein it displayed a singlet at δ 9.98 ppm, corresponding to aldehydic proton. Moreover, a peak at δ 8.73 ppm that corresponds to CH proton at position-3 of the ring disappeared upon formylation, indicating the electrophilic attack at position-3. The ^{1}H NMR spectrum of intermediate **5b** and **6b** are given in Figure 3.16 and 3.17, respectively.

Conversion of aldehyde to Schiff base was confirmed by the FTIR spectrum of $\mathbf{P_{41}}$, wherein the carbonyl peak due to aldehyde disappeared, while a new peak corresponding to C=N stretching appeared at 1607 cm^{-1}. Similarly, in its ^{1}H NMR spectrum, a singlet peak at δ 10.07 ppm due to CH=N proton appeared, which further confirms the conversion. A peak at 1647 cm^{-1} was observed in FTIR spectrum of chalcone $\mathbf{P_{45}}$, which is due to stretching vibration of conjugated carbonyl group. Upon reduction, this carbonyl peak has disappeared in FTIR spectrum of $\mathbf{P_{49}}$, indicating the conversion of C=O to CHOH. Later, this reduction was further confirmed by its ^{1}H NMR spectrum, where a new peak at δ 2.02 ppm appeared due to hydroxyl group. Also, three double doublets appeared at δ 6.76, 6.14, 5.38 ppm due to CH=CH and allylic protons, respectively. This clearly shows that only carbonyl group has undergone reduction while double bond is intact. FTIR spectrum of oxazolone derivative $\mathbf{P_{53}}$ showed a carbonyl peak at 1777 cm^{-1}, indicating the presence of cyclic lactone ring. Also, appearance of another peak at 1640 cm^{-1} due to C=N stretching of oxazolone further supported the proposed structure. Additional evidence was obtained by its ^{13}C NMR spectrum where two characteristic peaks at δ 168.5 and 165.4 ppm due to carbonyl and C=N carbons of oxazolone moiety, respectively were observed.

Table 3.4: Physical data of target compounds **P_{41-64}**

Sl.No.	R_1	$R_2/R_3/R_4$	Mol. Formula	M.P. (^oC)	Yield (%)
P_{41}	F	p-Tolyl	$C_{22}H_{18}FN_3$	147-149	70
P_{42}	H	p-Tolyl	$C_{22}H_{19}N_3$	107-109	72
P_{43}	F	Benzothiazolyl	$C_{22}H_{15}FN_4S$	176-178	68
P_{44}	H	Benzothiazolyl	$C_{22}H_{16}N_4S$	132-134	70
P_{45}	F	4-Chlorophenyl	$C_{23}H_{16}ClFN_2O$	227-229	80
P_{46}	F	Thiophen-2-yl	$C_{21}H_{15}FN_2OS$	216-218	72
P_{47}	H	Thiophen-2-yl	$C_{21}H_{26}N_2OS$	192-194	72
P_{48}	OMe	4-Chlorophenyl	$C_{24}H_{19}ClN_2O_2$	225-227	78
P_{49}	F	4-Chlorophenyl	$C_{23}H_{18}ClFN_2O$	146-148	72
P_{50}	F	Thiophen-2-yl	$C_{21}H_{17}FN_2OS$	195-197	72
P_{51}	H	Thiophen-2-yl	$C_{21}H_{28}N_2OS$	150-152	76
P_{52}	OMe	4-Chlorophenyl	$C_{24}H_{21}ClN_2O_2$	144-146	71
P_{53}	H	H	$C_{24}H_{17}N_3O_2$	125-127	67
P_{54}	F	H	$C_{24}H_{16}FN_3O_2$	187-189	71
P_{55}	OMe	H	$C_{25}H_{19}N_3O_3$	189-191	65
P_{56}	H	Me	$C_{25}H_{19}N_3O_2$	121-123	69
P_{57}	F	Me	$C_{25}H_{18}FN_3O_2$	192-194	71
P_{58}	OMe	Me	$C_{26}H_{21}N_3O_3$	175-177	68
P_{59}	H	-	$C_{20}H_{17}N_3O_2$	129-131	82
P_{60}	F	-	$C_{20}H_{16}FN_3O_2$	165-167	86
P_{61}	OMe	-	$C_{21}H_{19}N_3O_3$	172-174	80
P_{62}	H	-	$C_{18}H_{15}N_5O$	141-143	78
P_{63}	F	-	$C_{18}H_{14}FN_5O$	187-189	75
P_{64}	OMe	-	$C_{19}H_{17}N_5O_2$	162-164	82

Finally, conversion of aldehydes **6a-d** into ester derivatives **P_{59}** was confirmed by FTIR spectrum of **P_{59}**, wherein characteristic peaks due to nitrile and carboxylic esters were observed at 2218 and 1710 cm^{-1}, respectively. Its ^1H NMR spectrum showed a singlet at δ 8.31 ppm due to vinylic CH proton, a quartet and a triplet at δ 4.08 and 1.08 ppm due to ethyl carboxylate group. Similarly, the cyclization of ester

analogues $\mathbf{P_{59\text{-}61}}$ to pyrazolones $\mathbf{P_{62\text{-}64}}$ was confirmed by their FTIR and ^{1}H NMR spectral studies. The peaks due to nitrile and ester of $\mathbf{P_{59}}$ disappeared in FTIR spectrum of $\mathbf{P_{62}}$, while new peaks at 3303 and 3176 cm^{-1} appeared due to amine and amide NH groups, respectively. The peak due to cyclic conjugated amide carbonyl has appeared at relatively lower stretching frequency (1607 cm^{-1}), which is due to conjugation involved with cyclic carbamide group and exocyclic double bond. Its ^{1}H NMR spectrum displayed two singlets at δ 9.89 and 6.84 ppm due to NH and NH_2 groups, respectively confirming the conversion. Similarly, all target compounds were well-characterized by ^{1}H NMR, ^{13}C NMR and mass spectral studies. The analytical data of all final compounds are summarized in experimental section, while their physical data are tabulated in Table 3.4. The FTIR, ^{1}H NMR, ^{13}C NMR and mass spectra of compound $\mathbf{P_{63}}$ are given in Figure 3.18, 3.19, 3.20 and 3.21, respectively.

3.3.2.3 Experimental procedures

The general synthetic protocol for the synthesis of intermediates and the target compounds $\mathbf{P_{41\text{-}64}}$ are explained in the following paragraphs.

General procedure for the synthesis of imidazo[1,2-a]pyridines **5a-g**: A mixture of 2-amino-3-methyl pyridine (2 g, 18.5 mmol) and freshly prepared phenacyl bromide (3.68 g, 18.5 mmol) in 20 mL of ethanol was refluxed for 6 h. The reaction mixture was cooled to room temperature and the solid separated was filtered, washed with ethanol and finally recrystallized from chloroform to obtain pure product. Similarly, other derivatives were also recrystallized from chloroform.

8-Methyl-2-phenylimidazo[1,2-a]pyridine (**5a**): Yield 82%, M.P. 186-188 ^{o}C. FTIR (ATR, cm^{-1}): 3094, 2946, 1638, 1598, 1492, 1225. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.74-7.40 (m, 9H, ArH), 2.65 (s, 3H, CH_3). MS (m/z): 208.9. Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.75; H, 5.80; N, 13.46.

2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridine (**5b**): Yield 84%, M.P. 256-258 ^{o}C. FTIR (ATR, cm^{-1}): 3082, 2943, 1640, 1594, 1494, 1228. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.73-7.38 (m, 8H, ArH), 2.65 (s, 3H, CH_3). MS (m/z): 227.2. Anal. Calcd. for $C_{14}H_{11}FN_2$: C, 74.32; H, 4.90; N, 12.38. Found: C, 74.21; H, 4.87; N, 12.36.

8-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine (**5c**): Yield 80%, M.P. 274-276 ^{o}C. FTIR (ATR, cm^{-1}): 3084, 2956, 1634, 1567, 1498, 1228. ^{1}H NMR (DMSO-d_6, 400

MHz, δ ppm): 8.73-7.32 (m, 8H, ArH), 2.65 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). MS (m/z): 223.4. Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.00; H, 6.32; N, 12.58.

2-(4-Methoxylphenyl)-8-methylimidazo[1,2-a]pyridine (**5d**): Yield 86%, M.P. 245-247 ^oC. FTIR (ATR, cm^{-1}): 3084, 2972, 1636, 1581, 1494, 1225. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.73-7.40 (m, 8H, ArH), 3.98 (s, 3H, OMe), 2.65 (s, 3H, CH_3). MS (m/z): 239.4. Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.52; H, 5.90; N, 11.76.

6-Bromo-2-phenylimidazo[1,2-a]pyridine (**5e**): Yield 90%, M.P. 284-286 ^oC. FTIR (ATR, cm^{-1}): 3076, 2897, 1630, 1584, 1494, 1226. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.98 (s, 1H, ArH), 8.76 (s, 1H, ArH), 7.64-7.62 (d, 1H, ArH, *J*=9.2 Hz), 7.51-7.49 (d, 1H, ArH, *J*=9.2 Hz), 7.38-6.98 (m, 5H, ArH). MS (m/z): 274.1. Anal. Calcd. for $C_{13}H_9BrN_2$: C, 57.17; H, 3.32; N, 10.26. Found: C, 57.09; H, 3.30; N, 10.25.

6-Bromo-2-(4-fluorophenyl)imidazo[1,2-a]pyridine (**5f**): Yield 89%, M.P. 243-245 ^oC. FTIR (ATR, cm^{-1}): 3080, 2923, 1632, 1588, 1487, 1226. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.98 (s, 1H, ArH), 8.75 (s, 1H, ArH), 7.69-7.67 (d, 2H, ArH, *J*=8.0 Hz), 7.64-7.62 (d, 1H, ArH, *J*=8.8 Hz), 7.50-7.48 (d, 1H, ArH, *J*=8.8 Hz), 7.28-7.26 (d, 2H, ArH, *J*=8.0 Hz). MS (m/z): 291.8. Anal. Calcd. for $C_{13}H_8BrFN_2$: C, 53.63; H, 2.77; N, 9.62. Found: C, 53.52; H, 2.28; N, 9.61.

6-Bromo-2-(4-methylphenyl)imidazo[1,2-a]pyridine (**5g**): Yield 87%, M.P. 285-287 ^oC. FTIR (ATR, cm^{-1}): 3083, 2975, 1636, 1592, 1467, 1226. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.98 (s, 1H, ArH), 8.77 (s, 1H, ArH), 7.64-7.62 (d, 1H, ArH, *J*=9.2 Hz), 7.54-7.52 (d, 2H, ArH, *J*=8.4 Hz), 7.51-7.48 (d, 1H, ArH, *J*=9.2 Hz), 7.14-7.12 (d, 2H, ArH, *J*=8.4 Hz), 2.34 (s, 3H, CH_3). MS (m/z): 288.1. Anal. Calcd. for $C_{14}H_{11}BrN_2$: C, 58.56; H, 3.86; N, 9.76. Found: C, 58.48; H, 3.87; N, 9.75.

General procedure for the synthesis of imidazo[1,2-a]pyridine-3-carboxaldehydes (**6a-g**): Vilsmeier-Haack complex was prepared by adding $POCl_3$ (2.3 mL, 25.4 mmol) drop-wise to a dry RB flask containing DMF (1.85 mL, 25.4 mmol) at 0-5 ^oC. Later, a clear solution of **5a** (1.5 g, 6.35 mmol) in 10 mL of DMF was added to the resulting complex at a stretch. The resulting solution was stirred at 80 ^oC for about 6 h. The container was cooled to room temperature and quenched to ice cold water while

stirring. The solid product **6a** obtained was filtered, washed with excess of water and then purified by column chromatographic technique using ethyl acetate:hexane (1:9) system. Similar procedure was followed for the synthesis of other derivatives **6b-g**.

8-Methyl-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (**6a**): Yield 65%, M.P. 131-133 ^{o}C. FTIR (ATR, cm^{-1}): 3023, 2845, 1678, 1642, 1603, 1483, 1225. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.98 (s, 1H, CHO), 9.42-9.41 (d, 1H, ArH, *J*=6.4 Hz), 7.59-7.57 (m, 2H, ArH), 7.54-7.51 (m, 1H, ArH), 7.25-7.22 (m, 3H, ArH), 7.18-7.16 (m, 1H, ArH), 2.62 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 188.8, 160.2, 152.1, 137.4, 134.7, 129.6, 128.9, 127.4, 124.6, 123.1, 116.5, 16.5. MS (m/z): 237.1. Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.13; H, 5.10; N, 11.88.

2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridine-3-carbaldehyde (**6b**): Yield 65%, M.P. 197-199 ^{o}C. FTIR (ATR, cm^{-1}): 3017, 2848, 1682, 1645, 1603, 1480, 1224. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.99 (s, 1H, CHO), 9.43-9.42 (d, 1H, ArH, *J*=6.8 Hz), 7.99-7.96 (m, 2H, ArH), 7.59-7.57 (m, 1H, ArH), 7.41-7.39 (m, 2H, ArH), 7.38-7.23 (m, 1H, ArH), 2.62 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 189.2, 162.7, 159.8, 152.3, 136.5, 134.8, 129.6, 122.2, 117.5, 16.6. MS (m/z): 255.1. Anal. Calcd. for $C_{15}H_{11}FN_2O$: C, 70.86; H, 4.36; N, 11.02. Found: C, 70.74; H, 4.34; N, 11.03.

8-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (**6c**): Yield 68%, M.P. 162-164 ^{o}C. FTIR (ATR, cm^{-1}): 3033, 2898, 1684, 1638, 1607, 1512, 1432, 1225. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.99 (s, 1H, CHO), 9.45-9.43 (d, 1H, ArH, *J*=7.6 Hz), 7.69-7.67 (d, 2H, ArH, *J*=8.4 Hz), 7.57-7.55 (m, 1H, ArH), 7.14-7.10 (m, 3H, ArH), 2.62 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). MS (m/z): 251.4. Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.67; H, 5.63; N, 11.20.

2-(4-Methoxyphenyl)-8-methylimidazo[1,2-a]pyridine-3-carbaldehyde (**6d**): Yield 65%, M.P. 147-149 ^{o}C. FTIR (ATR, cm^{-1}): 3023, 2918, 1687, 1634, 1600, 1484, 1226. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.98 (s, 1H, CHO), 9.40-9.38 (d, 1H, ArH, *J*=6.8 Hz), 7.76-7.73 (d, 2H, ArH, *J*=8.8 Hz), 7.58-7.56 (m, 1H, ArH), 7.26-7.21 (m, 3H, ArH), 4.03 (s, 3H, OMe), 2.62 (s, 3H, CH_3). MS (m/z): 267.3. Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.02; H, 5.31; N, 10.53.

6-Bromo-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (**6e**): Yield 62%, M.P. 180-182 ^{o}C. FTIR (ATR, cm^{-1}): 3018, 2933, 1684, 1632, 1570, 1483, 1226. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.99 (s, 1H, CHO), 9.27 (s, 1H, ArH), 7.62-7.60 (d, 1H, ArH, *J*=8.8 Hz), 7.51-7.49 (d, 1H, ArH, *J*=8.8 Hz), 7.38-7.02 (m, 5H, ArH). MS (m/z): 302.3. Anal. Calcd. for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.30. Found: C, 55.72; H, 3.02; N, 9.29.

6-Bromo-2-(4-fluorophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (**6f**): Yield 62%, M.P. 197-199 ^{o}C. FTIR (ATR, cm^{-1}): 3012, 2954, 1681, 1628, 1582, 1471, 1223. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.99 (s, 1H, CHO), 9.26 (s, 1H, ArH), 7.68-7.66 (d, 2H, ArH, *J*=8.0 Hz), 7.62-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.51-7.48 (d, 1H, ArH, *J*=9.2 Hz), 7.24-7.22 (d, 2H, ArH, *J*=8.0 Hz). MS (m/z): 320.3. Anal. Calcd. for $C_{14}H_8BrFN_2O$: C, 52.69; H, 2.53; N, 8.78. Found: C, 52.58; H, 2.54; N, 8.78.

6-Bromo-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (**6g**): Yield 67%, M.P. 222-224 ^{o}C. FTIR (ATR, cm^{-1}): 3045, 2976, 1687, 1629, 1523, 1483, 1226. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.99 (s, 1H, CHO), 9.27 (s, 1H, ArH), 7.61-7.59 (d, 1H, ArH, *J*=8.8 Hz), 7.54-7.52 (d, 2H, ArH, *J*=8.4 Hz), 7.50-7.48 (d, 1H, ArH, *J*=8.8 Hz), 7.18-7.16 (d, 2H, ArH, *J*=8.4 Hz). MS (m/z): 315.9. Anal. Calcd. for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89. Found: C, 57.04; H, 3.52; N, 8.88.

General procedure for the synthesis of Schiff bases (**P_{41-44}**): The imidazo[1,2-a]pyridine-3-carbaldehyde **6a** (0.5 g, 2.4 mmol) was dissolved in 8 mL of ethanol and treated with toluidine (0.26 g, 2.5 mmol) in presence of a drop of sulphuric acid. The above ethanolic reaction mixture was refluxed for 24 h. After completion of reaction, the resulting solid product **P_{42}** was filtered, washed with ethanol and finally Schiff bases **P_{41-44}** were recrystallized from methanol-chloroform mixture. Their characterization data are as follows:

1-[2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]-N-(4-methylphenyl) methanimine (**P_{41}**): FTIR (ATR, cm^{-1}): 3054, 2912, 1607, 1512, 1224. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.07 (s, 1H, CH=N), 9.52-9.51 (d, 1H, ArH, *J*=4.0 Hz), 7.85-7.02 (m, 10H, ArH), 2.73 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.3, 160.3, 152.7, 148.7, 142.3, 138.6, 136.5, 131.8, 129.6, 127.6, 122.2,

117.5, 104.3, 18.4, 16.6. MS (m/z): 344.2. Anal. Calcd. for $C_{22}H_{18}FN_3$: C, 76.95; H, 5.28; N, 12.24. Found: C, 76.86; H, 5.30; N, 12.23.

N-(4-Methyl phenyl)-1-(8-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)methanimine (**P_{42}**): FTIR (ATR, cm^{-1}): 3056, 2918, 1612, 1602, 1532, 1226. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.06 (s, 1H, CH=N), 9.53-9.52 (d, 1H, ArH, *J*=4.4 Hz), 7.87-6.94 (m, 11H, ArH), 2.72 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.2, 152.7, 148.5, 142.6, 138.5, 136.54, 131.8, 129.6, 128.4, 127.1, 123.2, 117.8, 105.2, 18.3, 16.6. MS (m/z): 326.2. Anal. Calcd. for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.07; H, 5.89; N, 12.90.

N-(1,3-Benzothiazol-2-yl)-1-[2-(4-fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl] methanimine (**P_{43}**): FTIR (ATR, cm^{-1}): 3048, 2992, 2907, 1617, 1597, 1532, 1224. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.04 (s, 1H, CH=N), 9.53-9.52 (d, 1H, ArH, *J*=5.2 Hz), 7.85-7.02 (m, 10H, ArH), 2.73 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.6, 162.8, 158.4, 145.7, 141.7, 134.4, 129.6, 128.3, 126.6, 114.2, 104.7, 18.6. MS (m/z): 386.9. Anal. Calcd. for $C_{22}H_{15}FN_4S$: C, 68.38; H, 3.91; N, 14.50. Found: C, 68.25; H, 3.90; N, 14.51.

N-(1,3-Benzothiazol-2-yl)-1-(8-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl) methan imine (**P_{44}**): FTIR (ATR, cm^{-1}): 3032, 3003, 2914, 1619, 1585, 1553, 1225. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.04 (s, 1H, CH=N), 9.53-9.52 (d, 1H, ArH, *J*=4.8 Hz), 7.85-6.87 (m, 11H, ArH), 2.72 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.4, 158.8, 144.9, 141.8, 133.9, 129.6, 128.5, 126.8, 114.2, 104.1, 18.4. MS (m/z): 386.9. Anal. Calcd. for $C_{22}H_{16}N_4S$: C, 71.71; H, 4.38; N, 15.21. Found: C, 71.60; H, 4.39; N, 15.20.

General procedure for the synthesis of chalcones (**$P_{45\text{-}48}$**): An aqueous solution of NaOH (1.1 eq. in 3 mL of water) was added drop-wise to the ethanolic solution of an appropriate acetophenone (1.1 eq.) with stirring. This was later treated with a appropriate imidazo[1,2-a]pyridine-3-aldehyde (1.0 eq.) and heated at 50 ^oC for 4 h. The precipitated chalcone was filtered off, washed well with ethanol and finally were recrystallized from chloroform. The spectral data of **$P_{45\text{-}48}$** are summarised below.

1-(4-Chlorophenyl)-3-[2-(4-fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]prop-2 -en-1-one (**P_{45}**): FTIR (ATR, cm^{-1}): 3040, 2916, 1647, 1623, 1577, 1477, 1215. ^1H

NMR ($CDCl_3$, 400 MHz, δ ppm): 8.92-8.90 (d, 1H, Pyridine CH, *J*=6.4 Hz), 7.95-7.91 (d, 1H, CH=C, *J*=15.2 Hz), 7.83-7.79 (d, 1H, C=CH, *J*=15.2 Hz), 7.64 (m, 4H, ArH), 7.52 (m, 1H, ArH), 7.30-7.28 (d, 2H, ArH, *J*=7.2 Hz), 7.15-7.09 (m, 3H, ArH), 2.69 (s, 3H, CH_3). MS (m/z): 391.3. Anal. Calcd. for $C_{23}H_{16}ClFN_2O$: C, 70.68; H, 4.13; N, 7.17. Found: C, 70.55; H, 4.12; N, 7.15.

3-[2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]-1-(thiophen-2-yl)prop-2-en-1-one (**P_{46}**): FTIR (ATR, cm^{-1}): 3023, 2937, 1652, 1610, 1562, 1490, 1215. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.93-8.91 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.80-7.76 (d, 1H, CH=C, *J*=14.8 Hz), 7.68-7.64 (d, 1H, C=CH, *J*=14.8 Hz), 7.86- 6.91 (m, 9H, ArH), 2.68 (s, 3H, CH_3). MS (m/z): 363.1. Anal. Calcd. for $C_{21}H_{15}FN_2OS$: C, 69.59; H, 4.17; N, 7.73. Found: C, 69.51; H, 4.15; N, 7.75.

3-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-1-(thiophen-2-yl) prop-2-en-1-one (**P_{47}**): FTIR (ATR, cm^{-1}): 3053, 2941, 1650, 1629, 1598, 1469, 1217. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.93-8.91 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.98-7.94 (d, 1H, CH=C, *J*=15.6 Hz), 7.87-7.83 (d, 1H, C=CH, *J*=15.6 Hz), 7.80- 6.76 (m, 10H, ArH), 2.69 (s, 3H, CH_3). MS (m/z): 345.1. Anal. Calcd. for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13. Found: C, 73.10; H, 4.66; N, 8.12.

1-(4-Chlorophenyl)-3-[2-(4-methoxyphenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]prop-2-en-1-one (**P_{48}**): FTIR (ATR, cm^{-1}): 3052, 2924, 1651, 1619, 1583, 1492, 1215. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.92-8.90 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.95-7.91 (d, 1H, CH=C, *J*=15.2 Hz), 7.84-7.80 (d, 1H, C=CH, *J*=15.2 Hz), 7.83- 6.92 (m, 10H, ArH), 2.69 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). MS (m/z): 402.8. Anal. Calcd. for $C_{24}H_{19}ClN_2O_2$: C, 71.55; H, 4.75; N, 6.95. Found: C, 71.42; H, 4.76; N, 6.97.

General procedure for the synthesis of **$P_{49\text{-}52}$**: The ethanolic solution (6 mL) of chalcone **P_{45}** (0.4 g, 1.02 mmol) was stirred with sodium borohydride (0.04 g, 1.02 mmol) at room temperature for about 4 h. Upon completion of reaction, the solvent was removed under reduced pressure and was quenched to ice-cold water while stirring. The reaction mass was neutralised to get solid product that was filtered, washed with excess of water, dried and finally recrystallized from ethanol. Other derivatives **$P_{50\text{-}52}$** were also synthesized following similar procedure and they were recrystallized from ethanol. The characterization data of **$P_{49\text{-}52}$** are given below.

1-(4-Chlorophenyl)-3-[2-(4-fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]prop-2-en-1-ol (**P_{49}**): FTIR (ATR, cm^{-1}): 3169, 2917, 2840, 1609, 1490, 1399, 1244. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.07-8.06 (d, 1H, ArH, *J*=6.8 Hz), 7.78-6.78 (m, 10H, ArH), 6.76-6.72 (dd, 1H, CH=CH-, *J*=16.0, 1.2 Hz), 6.14-6.08 (dd, 1H, CH=CH, *J*=6.8, 16.0 Hz), 5.38-5.36 (dd, 1H, CHOH, *J*=1.2, 6.8 Hz), 2.67 (s, 3H, CH_3), 2.02 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 159.7, 142.5, 132.1, 131.6, 129.8, 127.9, 124.3, 122.4, 121.8, 118.3, 117.6, 116.2, 115.3, 112.3, 75.2, 73.8, 36.8, 19.6. MS (m/z): 393.0. Anal. Calcd. for $C_{23}H_{18}ClFN_2O$: C, 70.32; H, 4.62; N, 7.13. Found: C, 70.21; H, 4.60; N, 7.12.

3-[2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]-1-(thiophen-2-yl)prop-2-en-1-ol (**P_{50}**): FTIR (ATR, cm^{-1}): 3114, 2918, 2834, 1603, 1499, 1369, 1222. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.13-8.11 (d, 1H, ArH, *J*=6.8 Hz), 7.84-6.72 (m, 9H, ArH), 6.85-6.81 (d, 1H, CH=CH, *J*=16.0 Hz), 6.29-6.24 (dd, 1H, CH=CH-, *J*=6.4, 16.0 Hz), 5.61-5.59 (d, 1H, CHOH, *J*=6.4 Hz), 2.64 (s, 3H, CH_3), 2.10 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 160.1, 147.8, 142.3, 141.2, 132.4, 131.1, 129.5, 124.7, 121.6, 119.2, 117.6, 115.3, 113.9, 112.3, 71.7, 69.3, 37.1, 19.6. MS (m/z): 364.9. Anal. Calcd. for $C_{21}H_{17}FN_2OS$: C, 69.21; H, 4.70; N, 7.69. Found: C, 69.10; H, 4.68; N, 7.70.

3-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-1-(thiophen-2-yl) prop-2-en-1-ol (**P_{51}**): FTIR (ATR, cm^{-1}): 3107, 2935, 2842, 1599, 1499, 1369, 1222. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.12-8.10 (d, 1H, ArH, *J*=6.8 Hz), 7.83-6.71 (m, 10H, ArH), 6.84-6.82 (d, 1H, CH=CH, *J*=16.0 Hz), 6.28-6.23 (dd, 1H, CH=CH-, *J*=6.4, 16.0 Hz), 5.60-5.58 (d, 1H, CHOH, *J*=6.4 Hz), 2.63 (s, 3H, CH_3), 2.08 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 159.4, 147.4, 142.7, 141.2, 132.4, 130.0, 126.7, 124.7, 123.8, 121.9, 119.7, 117.9, 115.4, 112.6, 71.0, 69.3, 36.9, 19.6. MS (m/z): 365.1. Anal. Calcd. for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09. Found: C, 72.69; H, 5.23; N, 8.10.

1-(4-Chlorophenyl)-3-[2-(4-methoxyphenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]prop-2-en-1-ol (**P_{52}**): FTIR (ATR, cm^{-1}): 3165, 2917, 2840, 1609, 1490, 1399, 1244. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.04-8.02 (d, 1H, ArH, *J*=6.8 Hz), 7.78-6.70 (m, 10H, ArH), 6.75-6.71 (dd, 1H, CH=CH-, *J*=0.8, 16.0 Hz), 6.14-6.08 (dd, 1H, CH=CH,

J=6.8, 16.0 Hz), 5.34-5.32 (dd, 1H, CHOH, J=0.8 Hz, 6.8 Hz), 3.83 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.04 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 159.0, 141.2, 131.8, 130.2, 129.4, 127.6, 123.6, 122.4, 118.1, 117.5, 113.9, 112.0, 74.9, 72.7, 55.3, 36.6, 19.6. MS (m/z): 405.1. Anal. Calcd. for $C_{24}H_{21}ClN_2O_2$: C, 71.19; H, 5.23; N, 6.92. Found: C, 71.06; H, 5.21; N, 6.93.

General procedure for the synthesis of oxazolones (**P$_{53\text{-}58}$**): A solution of an appropriate aldehyde **6a** (0.5 g, 2.1 mmol) and hippuric acid (0.37 g, 2.1 mmol) in 10 mL of acetic anhydride containing sodium acetate (0.62 g, 6.3 mmol) was stirred at 80 ^{o}C for 4 h. After completion of reaction, the product was quenched into ice-cold water while stirring. The reaction mixture was neutralised to obtain solid product, which was then filtered, washed with excess of water, dried and recrystallized from methanol. Similar procedure and purification technique were followed for compounds **P$_{53\text{-}58}$** and their characterization data are listed in the following sections.

4-[(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)methylidene]-2-phenyl-1,3-oxazol-5 (4H)-one (**P$_{53}$**): FTIR (ATR, cm^{-1}): 3110, 3051, 2914, 1777, 1640, 1484, 1365, 1265. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.03-8.01 (d, 1H, ArH, *J*=6.8 Hz), 7.68 (s, 1H, CH), 7.49-6.84 (m, 12H, ArH), 2.72 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.5, 165.4, 145.3, 142.1, 134.3, 132.6, 129.7, 128.4, 127.4, 126.5, 123.8, 122.8, 122.0, 120.3, 119.5, 112.4, 19.3. MS (m/z): 379.9. Anal. Calcd. for $C_{24}H_{17}N_3O_2$: C, 75.97; H, 4.52; N, 11.08. Found: C, 75.88; H, 4.50; N, 11.07.

4-{[2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl] methylidene}-2-phenyl-1,3-oxazol-5(4H)-one (**P$_{54}$**): FTIR (ATR, cm^{-1}): 3097, 3032, 2942, 1773, 1634, 1492, 1364, 1265. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.04-8.02 (d, 1H, ArH, *J*=6.0 Hz), 7.76-7.74 (d, 2H, ArH, *J*=8.4 Hz), 7.67 (s, 1H, CH), 7.48-6.89 (m, 9H, ArH), 2.71 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.2, 164.8, 159.7, 144.5, 142.3, 138.5, 131.8, 129.5, 128.7, 127.3, 123.2, 119.8, 116.7, 112.4, 19.1. MS (m/z): 398.2. Anal. Calcd. for $C_{24}H_{16}FN_3O_2$: C, 72.54; H, 4.06; N, 10.57. Found: C, 72.40; H, 4.05; N, 10.58.

4-{[2-(4-Methoxyphenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]methylidene}-2-phenyl-1,3-oxazol-5(4H)-one (**P$_{55}$**): FTIR (ATR, cm^{-1}): 3117, 3058, 2830, 1783, 1647, 1603, 1482, 1336, 1226. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.04-8.02 (d, 1H, ArH,

J=6.8 Hz), 7.69 (s, 1H, ArH), 7.53-7.51 (d, 2H, ArH, *J*=8.0 Hz), 7.48-6.87 (m, 9H, ArH), 3.87 (s, 3H, CH_3), 2.71 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.2, 163.3, 160.1, 146.3, 142.4, 137.9, 131.4, 129.9, 128.7, 128.0, 127.1, 123.6, 116.1, 113.7, 56.1, 19.2. MS (m/z): 410.1. Anal. Calcd. for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.20; H, 4.65; N, 10.27.

2-(4-Methylphenyl)-4-[(8-methyl-2-phenylimidazo [1,2-a]pyridin-3-yl)methylidene]-1,3-oxazol-5(4H)-one (**P_{56}**): FTIR (ATR, cm^{-1}): 3111, 3049, 2915, 1779, 1641, 1485, 1366, 1256. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.04-8.02 (d, 1H, ArH, *J*=6.8 Hz), 7.68 (s, 1H, CH), 7.54-7.52 (d, 2H, ArH, *J*=8.4 Hz), 7.48-6.86 (m, 9H, ArH), 2.73 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.9, 162.5, 146.9, 143.7, 139.7, 134.4, 131.3, 129.6, 128.8, 127.4, 123.6, 113.5, 24.3, 19.1. MS (m/z): 394.3. Anal. Calcd. for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.21; H, 4.88; N, 10.66.

4-{[2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]methylidene}-2-(4-methyl phenyl)-1,3-oxazol-5(4H)-one (**P_{57}**): FTIR (ATR, cm^{-1}): 3107, 3057, 1772, 1644, 1600, 1479, 1364, 1224. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.04-8.02 (d, 1H, ArH, *J*=7.2 Hz), 7.73-7.71 (d, 2H, ArH, *J*=8.8 Hz), 7.68 (s, 1H, CH), 7.53-7.51 (d, 2H, ArH, *J*=7.6 Hz), 7.48-7.47 (d, 1H, ArH, J=5.2 Hz), 7.32-7.31 (d, 2H, ArH, *J*=8.8 Hz), 7.29-7.28 (d, 1H, ArH, *J*=5.2 Hz), 7.21-7.19 (d, 2H, ArH, *J*=7.6 Hz), 2.73 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.8, 163.1, 159.7, 144.3, 142.5, 139.6, 135.3, 132.1, 129.7, 128.4, 123.1, 121.9, 116.7, 113.1, 24.3, 19.3. MS (m/z): 412.2. Anal. Calcd. for $C_{25}H_{18}FN_3O_2$: C, 72.98; H, 4.41; N, 10.21. Found: C, 72.90; H, 4.40; N, 10.22.

4-((2-(4-Methoxyphenyl)-8-methylimidazo[1,2-a]pyridin-3-yl) methylene)-2-p-tolyl oxazol-5(4H)-one (**P_{58}**): FTIR (ATR, cm^{-1}): 3056, 2918, 2833, 1772, 1644, 1601, 1479, 1364, 1223. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.04-8.02 (d, 1H, ArH, *J*=6.8 Hz), 7.68 (s, 1H, CH), 7.53-7.11 (m, 10H, ArH), 3.89 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.2, 161.3, 160.1, 145.2, 142.7, 140.2, 137.2, 129.5, 128.1, 126.4, 124.5, 122.3, 115.2, 114.2, 56.1, 24.3, 19.3. MS (m/z): 424.4. Anal. Calcd. for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.59; H, 4.98; N, 9.93.

General procedure for the synthesis of ester **P_{59-61}**: The aldehyde **6a** (1 g, 4.23 mmol) was treated with ethyl cyanoacetate (0.5 g, 4.42 mmol) in presence of piperidine (0.38 g, 4.42 mmol) and stirred their ethanolic solution (10 mL) for 2 h. The solid product **P_{59}** thus obtained was collected by filtration and it was recrystallized from methanol-chloroform mixture. Similarly other compounds were also synthesized and purified. The characterization data of **P_{59-61}** are as follows.

Ethyl 2-cyano-3-(8-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)prop-2-enoate (**P_{59}**): FTIR (ATR, cm^{-1}): 3124, 2971, 2912, 2218, 1710, 1575, 1472, 1221. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.63-8.61 (d, 1H, ArH, *J*=6.8 Hz), 8.31 (s, 1H, CH), 7.87-6.78 (m, 7H, ArH), 4.08 (m, 2H, CH_2), 2.72 (s, 3H, CH_3), 1.08-1.06 (t, 3H, CH_3, *J*=7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.7, 159.3, 142.4, 141.6, 134.7, 129.7, 128.4, 127.6, 123.2, 121.4, 115.6, 113.9, 94.2, 61.2, 19.1, 14.2. MS (m/z): 332.5. Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.40; H, 5.19; N, 12.67.

Ethyl 2-cyano-3-[2-(4-fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl] prop-2-enoate (**P_{60}**): FTIR (ATR, cm^{-1}): 3124, 2971, 2912, 2218, 1710, 1575, 1472, 1221. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.63-8.61 (d, 1H, ArH, *J*=6.8 Hz), 8.34 (s, 1H, CH), 7.92-7.02 (m, 6H, ArH), 4.06 (m, 2H, CH_2), 2.72 (s, 3H, CH_3), 1.08-1.06 (t, 3H, CH_3, *J*=7.6 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 167.7, 162.1, 143.2, 141.4, 134.7, 130.4, 129.7, 127.3, 123.2, 120.8, 116.8, 115.6, 114.7, 94.5, 61.2, 19.1, 14.2. MS (m/z): 332.5. Anal. Calcd. for $C_{20}H_{16}FN_3O_2$: C, 68.76; H, 4.62; N, 12.03. Found: C, 68.67; H, 4.60; N, 12.04.

Ethyl 2-cyano-3-[2-(4-methoxyphenyl)-8-methylimidazo[1,2-a]pyridin-3-yl] prop-2-enoate (**P_{61}**): FTIR (ATR, cm^{-1}): 3138, 2970, 2921, 2218, 1712, 1592, 1478, 1224. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.62-8.61 (d, 1H, ArH, *J*=6.8 Hz), 8.33 (s, 1H, CH), 7.82-6.81 (m, 6H, ArH), 4.04 (m, 2H, CH_2), 3.81 (s, 3H, OMe), 2.73 (s, 3H, CH_3), 1.08-1.06 (t, 3H, CH_3, *J*=7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 168.1, 159.4, 143.9, 142.3, 134.5, 129.1, 128.4, 127.3, 123.2, 121.5, 120.8, 116.8, 114.3, 94.7, 61.2, 56.7, 19.1, 14.4. MS (m/z): 362.7. Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.71; H, 5.28; N, 11.64.

General procedure for the synthesis of 3-amino-pyrazolone derivatives **P_{62-64}**: The intermediate **P_{59}** (0.6 g, 1.81 mmol) was refluxed with hydrazine hydrate (0.18 g, 3.62 mmol) in ethanolic media (8 mL) for about 8 h. On completion of reaction, the mixture was cooled to allow complete precipitation of product, that was later filtered and recrystallized from methanol. Other derivatives were also obtained by adopting the same procedure and recrystallized from methanol. Their characterization data are given below.

5-Amino-4-[(8-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)methylidene]-2,4-dihydro-3H-pyrazol-3-one (**P_{62}**): FTIR (ATR, cm^{-1}): 3303, 3176, 2961, 2900, 1607, 1528, 1349, 1213. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.89 (s, 1H, NH), 9.27-9.25 (d, 1H, ArH, *J*=7.2 Hz), 8.14 (s, 1H, CH), 7.81-6.98 (m, 7H, ArH), 6.84 (s, 2H, NH_2), 2.53 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.3, 151.2, 142.7, 139.6, 134.1, 132.3, 131.7, 130.2, 129.1, 128.5, 127.8, 123.4, 116.5, 111.0, 16.4. MS (m/z): 318.3. Anal. Calcd. for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found: C, 67.98; H, 4.77; N, 22.05.

5-Amino-4-{[2-(4-fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl]methylidene}-2,4-dihydro-3H-pyrazol-3-one (**P_{63}**): FTIR (ATR, cm^{-1}): 3331, 3184, 2910, 1607, 1528, 1486, 1345, 1220. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.91 (s, 1H, NH), 9.27-9.25 (d, 1H, ArH, *J*=6.8 Hz), 8.21 (s, 1H, CH), 7.79-6.93 (m, 7H, ArH), 6.85 (s, 2H, NH_2), 2.54 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.1, 144.9, 143.0, 130.7, 126.1, 125.2, 124.4, 117.1, 115.5, 112.9, 16.5. MS (m/z): 336.5. Anal. Calcd. for $C_{18}H_{14}FN_5O$: C, 64.47; H, 4.21; N, 20.88. Found: C, 64.38; H, 4.23; N, 20.85.

5-Amino-4-{[2-(4-methoxyphenyl)-8-methylimidazo[1,2-a]pyridin-3-yl] methylidene}-2,4-dihydro-3H-pyrazol-3-one (**P_{64}**): FTIR (ATR, cm^{-1}): 3334, 3176, 2910, 1607, 1530, 1489, 1337, 1223. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.91 (s, 1H, NH), 9.26-9.25 (d, 1H, ArH, *J*=6.8 Hz), 8.22 (d, 1H, CH), 7.86-7.07 (m, 6H, ArH), 6.86 (s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 2.53 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 165.1, 158.3, 151.1, 144.3, 142.5, 134.3, 133.2, 129.7, 128.2, 127.4, 123.4, 122.5, 121.2, 115.7, 112.3, 56.3, 16.4. MS (m/z): 348.2. Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.63; H, 4.91; N, 20.18.

3.3.3 Synthesis of new chalcone derivatives containing imidazo[1,2-a]pyridines ($\mathbf{P_{65-87}}$)

In this series, the new imidazo[1,2-a]pyridine hybrids carrying pyrazoline, cyanopyridine, cyanopyridone and pyrimidine systems were synthesized and characterized by spectroscopic techniques as well as elemental analysis.

3.3.3.1 Chemistry

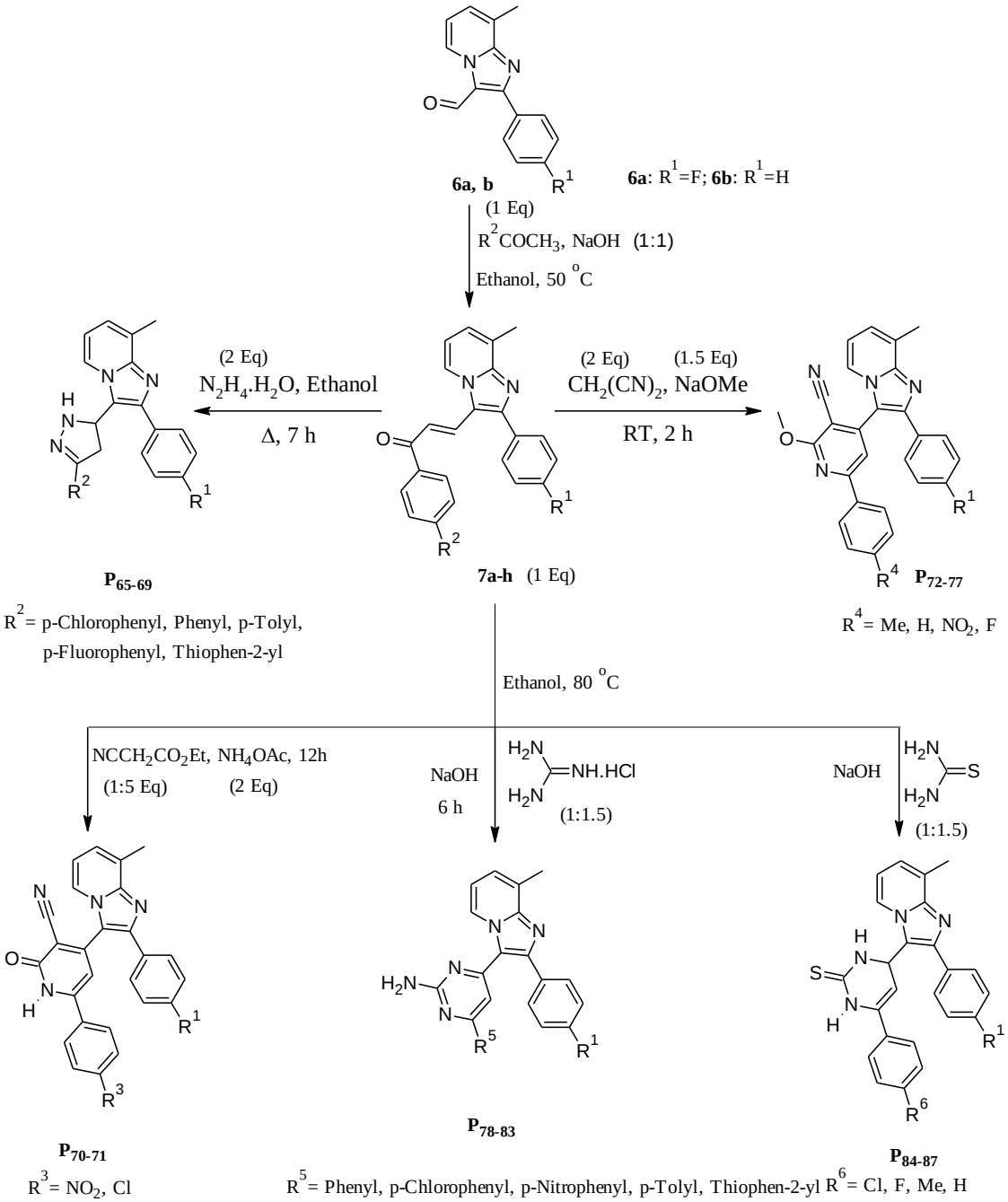
The reaction sequence involving the synthesis of required final compounds is given in Scheme 3.5. The aldehydes **6a, b** were reacted with different acetophenones under alcoholic NaOH media to obtain the key chalcone intermediates **7a-h**. These chalcones were used as active scaffolds for the synthesis of target compounds $\mathbf{P_{65-69}}$, $\mathbf{P_{70-71}}$, $\mathbf{P_{72-77}}$, $\mathbf{P_{78-83}}$, $\mathbf{P_{84-87}}$ carrying different heterocyclic systems.

A new series of pyrazolines $\mathbf{P_{65-69}}$ was synthesized by refluxing chalcones **7a-h** with hydrazine hydrate under ethanolic media. Further, 3-cyano-2-pyridones $\mathbf{P_{70-71}}$ were conveniently obtained by refluxing chalcones with ethyl cyanoacetate and ammonium acetate under alcoholic media for about 12 h. Similarly, 2-methoxy-3-cyano pyridines $\mathbf{P_{72-77}}$ were synthesized with good yield by stirring chalcones **7a-h** with malononitrile at room temperature in sodium methoxide solution. The latter two reactions involve the Michael addition of active methylene compounds to conjugated double bond, followed by internal cyclization. Finally, 2-amino pyrimidines $\mathbf{P_{78-83}}$ and pyrimidin-2-thiones $\mathbf{P_{84-87}}$ were obtained by refluxing chalcones **7a-h** with guanidine hydrochloride and thiourea, respectively in presence of alcoholic NaOH. Further, all the newly synthesised final compounds were purified by either recrystallization or column chromatographic techniques.

3.3.3.2 Results and discussion

The structures of new intermediates and final compounds synthesized by above mentioned routes were confirmed by various spectral techniques like FTIR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy followed by elemental analysis. The conversion of aldehyde **6a-b** into chalcones was confirmed by the comparative study of their FTIR spectra. The shift in carbonyl stretching frequency of **6a** from 1678 to 1647 cm^{-1} upon reacting it with acetophenone, confirmed the formation of chalcone **7a**. Also, appearance of two doublets in ^{1}H NMR spectrum at δ 7.95 and 7.83 ppm corresponds

to protons of conjugated alkenes, further supported the proposed structure of chalcone. The coupling constant value (*J*) for these olefinic protons was calculated to be 15.2 Hz. Similarly, for all other chalcones (**7b-h**), the '*J*' values are in the range of 14.4-16 Hz, indicating that they are stereo-selective and attained trans (*E*) configuration.



Scheme 3.5: Synthesis of new imidazo[1,2-a]pyridine derivatives $\mathbf{P_{65\text{-}87}}$

FTIR spectrum of pyrazoline analogue **P_{65}** showed a new peak at 3241 cm^{-1} for NH stretching. Also, its ^{1}H NMR spectrum displayed a singlet at δ 9.34 ppm, corresponding to pyrazoline NH proton. Moreover, three doublets of doublets (dd) were observed for ABX type of pyrazoline ring protons at δ 5.65, 3.41 and 3.09 ppm, which is a characteristic feature of pyrazoline systems that reveals the proposed structure. Formation of 3-cyano-2-pyridone derivative **P_{70}** was well documented from its FTIR spectrum, which showed characteristic peaks at 2213 cm^{-1} corresponding to nitrile functionality and at 1637 cm^{-1} for cyclic amide carbonyl group. Similarly, FTIR spectrum (Figure 3.22) of 3-cyano-2-methoxypyridine analogue **P_{73}** exhibited appropriate peaks at 2218 and 1576 cm^{-1} respectively, for nitrile and pyridine C=N stretching. Its ^{1}H NMR spectrum (Figure 3.23) showed two prominent singlets at δ 8.04 and 4.18 ppm corresponding to single aromatic proton of cyanopyridine ring and the methoxy group, respectively.

Conversion of chalcone **7a** into 2-amino pyrimidine derivative **P_{78}** was evidenced by the appearance of a new peak in its FTIR spectrum at 3306 cm^{-1} corresponding to amine group. Also, its ^{1}H NMR spectrum showed a singlet at δ 5.24 ppm confirming the proposed structure. However, treatment of chalcones **7a-h** with thiourea resulted in non-aromatic pyrimidine thiones **$P_{84\text{-}87}$**. This was confirmed by FTIR spectrum of **P_{84}** wherein, a signal at 3176 cm^{-1} that corresponds to NH stretching frequency was observed. Furthermore, its ^{1}H NMR spectrum displayed two singlets at δ 10.02 and 9.07 ppm confirming the presence of two NH groups. Also, two doublets at δ 6.06 and 5.12 ppm were observed for vinylic and allylic protons, respectively of the pyrimidine ring which further supported the proposed structure. Moreover, in all above conversions, the cyclization was evidenced by the complete disappearance of two singlets corresponding to conjugated alkenyl protons of chalcones. In the same way, the formation of other derivatives was also confirmed. In addition, the structures of target compounds were further established using ^{13}C NMR, mass spectral and elemental analyses. The detailed synthetic procedure and characterization data of all these individual compounds are discussed in experimental section. The physical parameters of the final compounds are tabulated in Table 3.5. The ^{13}C NMR and mass spectra of compound **P_{73}** are given in Figure 2.24 and 2.25, respectively.

Table 3.5: Physical data of final compounds **P_{65-87}**

Sl. No.	R_1	$R_2/R_3/R_4/R_5/R_6$	Yield (%)	M.P. (^oC)	Mol. Wt. (g)
P_{65}	F	4-Chlorophenyl	72	105-107	404.8
P_{66}	F	Phenyl	74	230-232	370.4
P_{67}	H	p-Tolyl	70	220-222	366.4
P_{68}	H	4-Fluorophenyl	74	231-233	370.4
P_{69}	H	Thiophen-2-yl	68	157-159	358.4
P_{70}	F	NO_2	62	278-280	465.4
P_{71}	F	Cl	67	183-185	454.9
P_{72}	F	Me	58	237-239	448.5
P_{73}	F	H	60	186-188	434.4
P_{74}	F	NO_2	52	302-304	479.5
P_{75}	H	F	63	203-205	434.4
P_{76}	H	NO_2	60	284-286	461.4
P_{77}	H	Me	62	220-222	430.5
P_{78}	F	4-Chlorophenyl	72	248-250	429.8
P_{79}	F	4-Nitrophenyl	68	184-186	440.4
P_{80}	F	p-Tolyl	75	138-140	409.5
P_{81}	F	Phenyl	72	173-175	395.4
P_{82}	H	Thiophen-2-yl	68	117-119	383.5
P_{83}	H	p-Tolyl	75	115-117	391.5
P_{84}	F	Cl	62	145-147	448.9
P_{85}	F	H	60	218-220	414.5
P_{86}	H	Me	64	147-149	410.5
P_{87}	H	F	60	173-175	414.5

3.3.3.3 Experimental procedures

The general synthetic protocols for the preparation of intermediates and the new target compounds **P_{65-87}** are described in the following paragraphs.

General procedure for the synthesis of chalcones **7a-h**: An aqueous solution of NaOH (1.1 eq. in 3 mL of water) was added drop-wise to the ethanolic solution of an appropriate acetophenone (1.1 eq.) with stirring. This was later treated with a suitable

imidazo[1,2-a]pyridine-3-aldehyde (1.0 eq.) and was heated at 50 ^{o}C for 4 h. The precipitated chalcone was filtered off, washed well with ethanol and finally was recrystallized from chloroform.

1-(4-Chlorophenyl)-3-(2-(4-fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl) prop-2-en-1-one (**7a**): Yield 80%. FTIR (ATR, cm^{-1}): 3040, 2916, 1647, 1623, 1577, 1477, 1215. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.92-8.90 (d, 1H, Pyridine CH, *J*=6.4 Hz), 7.95-7.91 (d, 1H, CH=C, *J*=15.2 Hz), 7.83-7.79 (d, 1H, C=CH, *J*=15.2 Hz), 7.64 (m, 4H, ArH), 7.52 (m, 1H, ArH), 7.30-7.28 (d, 2H, ArH, *J*=7.2 Hz), 7.15-7.09 (m, 3H, ArH), 2.69 (s, 3H, CH_3). MS (m/z): 391.3. Anal. Calcd. for $C_{23}H_{16}ClFN_2O$: C, 70.68; H, 4.13; N, 7.17. Found: C, 70.58; H, 4.12; N, 7.15.

3-(2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl)-1-phenylprop-2-en-1-one (**7b**): Yield 78%. FTIR (ATR, cm^{-1}): 3052, 2924, 1651, 1619, 1583, 1492, 1215. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.92-8.90 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.94-7.90 (d, 1H, CH=C, *J*=14.8 Hz), 7.82-7.78 (d, 1H, C=CH, *J*=14.8 Hz), 7.81-7.79 (d, 2H, ArH, *J*=7.2 Hz), 7.53-7.46 (m, 3H, ArH), 7.42-7.41 (d, 2H, ArH, *J*=7.2 Hz), 7.32-7.04 (m, 4H, ArH), 2.69 (s, 3H, CH_3). MS (m/z): 357.2. Anal. Calcd. for $C_{23}H_{17}FN_2O$: C, 77.51; H, 4.81; N, 7.86. Found: C, 77.40; H, 4.80; N, 7.87.

3-(2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl)-1-p-tolylprop-2-en-1-one (**7c**): Yield 81%. FTIR (ATR, cm^{-1}): 3047, 2932, 1649, 1621, 1592, 1469, 1216. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.93-8.91 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.93-7.90 (d, 1H, CH=C, *J*=15.2 Hz), 7.83-7.80 (d, 1H, C=CH, *J*=15.2 Hz), 7.79-7.77 (d, 2H, ArH, *J*=7.6 Hz), 7.67-7.10 (m, 8H, ArH), 2.69 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). MS (m/z): 371.3. Anal. Calcd. for $C_{24}H_{19}FN_2O$: C, 77.82; H, 5.17; N, 7.56. Found: C, 77.74; H, 5.17; N, 7.55.

3-(2-(4-Fluorophenyl)-8-methylimidazo[1,2-a]pyridin-3-yl)-1-(4-nitrophenyl) prop-2-en-1-one (**7d**): Yield 72%. FTIR (ATR, cm^{-1}): 3053, 2941, 1650, 1629, 1598, 1469, 1217. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.93-8.91 (d, 1H, Pyridine CH, *J*=7.2 Hz), 8.14-8.12 (d, 2H, ArH, *J*=8.0 Hz), 7.96-7.92 (d, 1H, CH=C, *J*=15.6 Hz), 7.87-7.83 (d, 1H, C=CH, *J*=15.6 Hz), 7.80- 7.78 (d, 2H, ArH, *J*=7.2 Hz), 7.64-7.62 (d, 2H, ArH, *J*=8.0 Hz), 7.51 (m, 1H, ArH), 7.41-7.18 (m, 3H, ArH), 2.69 (s, 3H, CH_3). MS (m/z):

402.1. Anal. Calcd. for $C_{23}H_{16}FN_3O_3$: C, 68.82; H, 4.02; N, 10.47. Found: C, 68.73; H, 4.00; N, 10.46.

1-(4-Fluorophenyl)-3-(8-methyl-2-phenylimidazo[1,2-a] pyridin-3-yl)prop-2-en-1-one (**7e**): Yield 80%. FTIR (ATR, cm^{-1}): 3049, 2925, 1648, 1621, 1584, 1492, 1216. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.92-8.91 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.93-7.89 (d, 1H, CH=C, *J*=14.8 Hz), 7.83-7.79 (d, 1H, C=CH, *J*=14.8 Hz), 7.84-7.82 (d, 2H, ArH, *J*=7.6 Hz), 7.54-7.03 (m, 9H, ArH), 2.68 (s, 3H, CH_3). MS (m/z): 357.2. Anal. Calcd. for $C_{23}H_{17}FN_2O$: C, 77.51; H, 4.81; N, 7.86. Found: C, 77.53; H, 4.80; N, 7.87.

3-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-1-(thiophen-2-yl) prop-2-en-1-one (**7f**): Yield 72%. FTIR (ATR, cm^{-1}): 3023, 2937, 1652, 1610, 1562, 1490, 1215. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.93-8.91 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.92-7.88 (d, 1H, CH=C, *J*=14.8 Hz), 7.83-7.79 (d, 1H, C=CH, *J*=14.8 Hz), 7.63-7.60 (dd, 1H, ArH, *J*=7.2, 3.2 Hz), 7.53-6.98 (m, 9H, ArH), 2.68 (s, 3H, CH_3). MS (m/z): 345.3. Anal. Calcd. for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13. Found: C, 73.17; H, 4.68; N, 8.12.

3-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-1-p-tolylprop-2-en-1-one (**7g**): Yield 70%. FTIR (ATR, cm^{-1}): 2997, 2892, 1650, 1617, 1584, 1492, 1215. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.93-8.91 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.91-7.87 (d, 1H, CH=C, *J*=15.6 Hz), 7.82-7.78 (d, 1H, C=CH, *J*=15.6 Hz), 7.62-7.60 (d, 2H, ArH, *J*=7.2 Hz),7.54 (m, 1H, ArH), 7.49-6.98 (m, 8H, ArH), 2.68 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). MS (m/z): 353.6. Anal. Calcd. for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.80; H, 5.72; N, 7.94.

3-(8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-1-(4-nitrophenyl) prop-2-en-1-one (**7h**): Yield 69%. FTIR (ATR, cm^{-1}): 3032, 2932, 1654, 1628, 1584, 1517, 1445, 1216. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.93-8.92 (d, 1H, Pyridine CH, *J*=7.2 Hz), 8.12-8.10 (d, 2H, ArH, *J*=8.0 Hz), 7.94-7.90 (d, 1H, CH=C, *J*=15.6 Hz), 7.84-7.80 (d, 1H, C=CH, *J*=15.6 Hz), 7.71-7.69 (d, 2H, ArH, *J*=7.2 Hz), 7.62-7.60 (d, 2H, ArH, *J*=8.0 Hz), 7.53 (m, 1H, ArH), 7.28-7.25 (dd, 1H, ArH, *J*=6.8, 3.2 Hz), 7.16-7.03 (m, 3H, ArH), 2.68 (s, 3H, CH_3). MS (m/z): 384.8. Anal. Calcd. for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.02; H, 4.46; N, 10.95.

General procedure for the synthesis of pyrazoline derivatives **P_{65-69}**: A solution of chalcone **7a** (0.15 g, 38.46 mmol) and hydrazine hydrate (0.04 g, 80 mmol) in ethanol (5 mL) was refluxed for 7 h. Upon completion of conversion, the reaction flask was cooled overnight in deep freezer and the resulting solid product was isolated by filtration. The compounds **P_{65-69}** were recrystallized in methanol-chloroform mixture to get pure products.

3-(3-(4-Chlorophenyl)-4,5-dihydropyrazol-5-yl)-2-(4-fluorophenyl)-8-methyl-imidazo [1,2-a]pyridine (**P_{65}**): FTIR (ATR, cm^{-1}): 3241, 3029, 2914, 1612, 1593, 1497, 1224. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.34 (s, 1H, NH), 8.19-8.17 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.77-7.75 (d, 2H, ArH, *J*=8.0 Hz), 7.76-7.75 (m, 3H, ArH), 7.37-7.08 (m, 5H, ArH), 5.65-5.61 (dd, 1H, -CH-, *J*=4, 12 Hz), 3.41-3.35 (dd, 1H, CH-, *J*=4, 18 Hz), 3.09-3.03 (dd, 1H, -CH-, *J*=8, 16 Hz), 2.66 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 162.6, 153.7, 145.3, 142.6, 136.4, 135.3, 134.8, 132.2, 130.7, 129.2, 122.6, 115.7, 43.1, 38.6, 16.5. MS (m/z) 405.4. Anal. Calcd. for $C_{23}H_{18}ClFN_4$: C, 68.23; H, 4.48; N, 13.84. Found: C, 68.11; H, 4.50; N, 13.85.

2-(4-Fluorophenyl)-8-methyl-3-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)imidazo[1,2-a] pyridine (**P_{66}**): FTIR (ATR, cm^{-1}): 3243, 3031, 2915, 1593, 1486, 1238. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.29 (s, 1H, NH), 8.19-8.17 (d, 1H, pyridine CH, *J*=6.4 Hz), 7.84-7.82 (d, 2H, ArH, *J*=7.2 Hz), 7.54-7.51 (m, 1H, ArH), 7.48-7.40 (m, 4H, ArH), 7.34-7.07 (m, 4H, ArH), 5.65-5.61 (dd, 1H, -CH-, *J*=4, 11.6 Hz), 3.40-3.35 (dd, 1H, -CH_2-, *J*=4, 16 Hz), 3.05-2.99 (dd, 1H, -CH_2-, *J*=6, 18 Hz), 2.66 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 163.1, 153.4, 145.5, 142.1, 135.7, 134.6, 131.4, 129.5, 128.6, 123.7, 121.4, 116.0, 43.2, 38.6, 16.6. MS (m/z) 371.2. Anal. Calcd. for $C_{23}H_{19}FN_4$: C, 74.58; H, 5.17; N, 15.13. Found: C, 74.51; H, 5.18; N, 15.12.

8-Methyl-2-phenyl-3-(3-p-tolyl-4,5-dihydro-1H-pyrazol-5-yl) imidazo[1,2-a]pyridine (**P_{67}**): FTIR (ATR, cm^{-1}): 3347, 3069, 2970, 1624, 1585, 1400, 1250. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.32 (s, 1H, NH), 8.20-8.19 (d, 1H, ArH, *J*=6.8 Hz), 7.76-7.74 (d, 2H, ArH, *J*=7.6 Hz), 7.53-7.37 (m, 5H, ArH), 7.32-6.98 (m, 4H, ArH), 5.66-5.62 (dd, 1H, -CH-, *J*=4, 12 Hz), 3.41-3.36 (dd, 1H, -CH_2-, *J*=4, 16 Hz), 3.31-3.26 (dd, 1H, -CH_2-, *J*=4, 14.4 Hz), 2.66 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 152.6, 145.7, 143.2, 142.5, 134.6, 133.7, 131.4, 129.6, 127.4, 124.9, 121.5,

43.5, 38.6, 16.5. MS (m/z) 367.3. Anal. Calcd. for $C_{24}H_{22}N_4$: C, 78.66; H, 6.05; N, 15.29. Found: C, 78.54; H, 6.03; N, 15.30.

3-(3-(4-Fluorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)-8-methyl-2-phenyimidazo[1,2-a] pyridine (**P_{68}**): FTIR (ATR, cm^{-1}): 3241, 3053, 1618, 1591, 1401, 1219. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.29 (s, 1H, NH), 8.23-8.21 (d, 1H, ArH, *J*=6.8 Hz), 7.82-7.80 (d, 2H, ArH, *J*=7.2 Hz), 7.54-7.40 (m, 5H, ArH), 7.32-7.01 (m, 4H, ArH), 5.62-5.58 (dd, 1H, -CH-, *J*=3.2, 12 Hz), 3.41-3.37 (dd, 1H, -CH_2-, *J*=4.8, 12.4 Hz), 3.06-3.02 (dd, 1H, CH_2, *J*=4, 12 Hz), 2.67 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 165.3, 153.2, 146.3, 142.3, 135.7, 134.2, 131.7, 130.1. 127.9, 123.5, 115.6, 43.6, 38.5, 16.6. MS (m/z) 371.4. Anal. Calcd. for $C_{23}H_{19}FN_4$: C, 74.58; H, 5.17; N, 15.13. Found: C, 74.50; H, 5.17; N, 15.15.

8-Methyl-2-phenyl-3-(3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl) 1H-imidazo [1,2-a]pyridine (**P_{69}**): FTIR (ATR, cm^{-1}): 3250, 3078, 2914, 1634, 1585, 1490, 1240. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.30 (s, 1H, NH), 8.23-8.21 (d, 1H, Pyridine CH, *J*=6.8 Hz), 7.65-6.98 (m, 10H, ArH), 5.64-5.60 (dd, 1H, -CH-, *J*=4, 12 Hz), 3.42-3.38 (dd, 1H, CH_2-, *J*=4, 12 Hz), 3.08-3.04 (dd, 1H, ArH, *J*=3.2, 12 Hz), 2.67 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 156.3, 147.3, 143.2, 134.8, 133.2, 130.2, 128.4, 125.6, 122.5, 121.7, 43.5, 38.6, 16.5. MS (m/z) 359.1. Anal. Calcd. for $C_{21}H_{18}N_4S$: C, 70.36; H, 5.06; N, 15.63. Found: C, 70.28; H, 5.07; N, 15.61.

General procedure for the synthesis of 3-cyano-2-pyridones (**$P_{70\text{-}71}$**): An appropriate chalcone (1eq.) was refluxed with ethyl cyanoacetate (1 eq.) and ammonium acetate (5 eq.) in ethanol media for 12 h. Upon completion of reaction, the reaction flask was cooled to facilitate complete precipitation. The crude product thus obtained was filtered and was purified by column chromatographic method by taking ethyl acetate and hexane (2:8) as eluting system.

4-(2-(4-Fluorophenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl)-6-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**P_{70}**): FTIR (ATR, cm^{-1}): 3141, 3061, 2928, 2213, 1637, 1595, 1503, 1216. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 10.05 (s, 1H, NH), 8.42-8.40 (d, 1H, ArH, *J*=6.8 Hz), 8.34-8.32 (d, 2H, ArH, *J*=7.6 Hz), 8.07-8.06 (d, 2H, ArH, *J*=7.2 Hz), 7.73-7.71 (d, 2H, ArH, *J*=7.6 Hz), 7.61 (s, 1H, ArH), 7.53-7.50 (m, 3H, ArH), 7.08-7.02 (m, 1H, ArH), 2.71 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$):

170.1, 162.3, 161.5, 157.8, 147.9, 145.4, 143.7, 141.3, 136.3, 129.6, 127.9, 123.1, 121.6, 116.7, 105.2, 16.7. MS (m/z) 466.2. Anal. Calcd. for $C_{26}H_{16}FN_5O_3$: C, 67.09; H, 3.46; N, 15.05. Found: C, 67.01; H, 3.45; N, 15.06.

6-(4-Chlorophenyl)-4-(2-(4-fluorophenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl)-2-oxo -1,2-dihydropyridine-3-carbonitrile (**P_{71}**): FTIR (ATR, cm^{-1}): 3153, 3069, 2934, 2220, 1643, 1587, 1496, 1215. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.98 (s, 1H, NH), 8.42-8.40 (d, 1H, ArH, *J*=7.2 Hz), 7.83-7.81 (d, 2H, ArH, *J*=7.6 Hz), 7.75-7.73 (d, 2H, ArH, *J*=7.2 Hz), 7.60 (s, 1H, ArH), 7.54-7.08 (m, 6H, ArH), 2.71 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 165.9, 163.6, 155.3, 145.6, 142.2, 135.3, 133.7, 131.5, 128.6, 122.9, 116.2, 104.8, 16.5. MS (m/z) 455.6. Anal. Calcd. for $C_{26}H_{16}ClFN_4O$: C, 68.65; H, 3.55; N, 12.32. Found: C, 68.57; H, 3.55; N, 12.34.

General procedure for the synthesis of 2-methoxy-3-cyanopyridines **$P_{72\text{-}77}$**: The chalcone **7a** (0.5 g, 1.35 mmol) was added slowly to a freshly prepared sodium methoxide solution (6.75 mmol of sodium in 20 mL of methanol) with stirring. Later, malononitrile (0.13 g, 2.0 mmol) was added drop-wise at room temperature and the stirring was continued until the product separates out. The solid product was collected by filtration and later was recrystallized from methanol-chloroform mixture. Same procedure and recrystallization system were followed for the synthesis of other derivatives **$P_{73\text{-}77}$**.

4-(2-(4-Fluorophenyl)-8-methyl-imidazo[1,2-a] pyridin-3-yl)-2-methoxy-6-p-tolyl nicotinonitrile (**P_{72}**): FTIR (ATR, cm^{-1}): 3054, 2918, 2854, 2220, 1582, 1541, 1496, 1244, 1031. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.02-7.98 (m, 2H, ArH), 7.85-7.83 (d, 1H, ArH, *J*=6.8 Hz), 7.64-7.48 (m, 5H, ArH), 7.13-6.79 (m, 4H, ArH), 4.24 (s, 3H, OCH_3), 2.72 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 164.7, 163.3, 160.6, 158.6, 145.7, 136.5, 130.9, 130.2, 129.5, 128.7, 127.6, 126.8, 125.2, 123.1, 115.4, 114.3, 113.5, 94.8, 54.3, 16.5, 13.4. MS (m/z) 449.2. Anal. Calcd. for $C_{28}H_{21}FN_4O$: C, 74.98; H, 4.72; N, 12.49. Found: C, 75.02; H, 4.70; N, 12.48.

4-(2-(4-Fluorophenyl)-8-methyl-imidazo[1,2-a] pyridin-3-yl)-2-methoxy-6-phenyl nicotinonitrile (**P_{73}**): FTIR (ATR, cm^{-1}): 2918, 2854, 2218, 1576, 1541, 1447, 1245, 1031. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.24-8.22 (dd, 2H, ArH, *J*=6.4, 3.2 Hz), 8.16-8.14 (d, 1H, ArH, *J*=6.8 Hz), 8.04 (s, 1H, ArH), 7.65-6.88 (m, 9H, ArH), 4.18 (s,

3H, OCH_3), 2.60 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 164.5, 163.1, 160.6, 158.4, 145.5, 142.3, 136.4, 130.9, 130.0, 129.5, 128.9, 127.4, 126.5, 125.1, 122.8, 115.6, 114.3, 113.2, 94.6, 54.5, 16.5. MS (m/z) 435.2. Anal. Calcd. for $C_{27}H_{19}FN_4O$: C, 74.64; H, 4.41; N, 12.90. Found: C, 74.53; H, 4.40; N, 12.88.

4-(2-(4-Fluorophenyl)-8-methyl-imidazo[1,2-a] pyridin-3-yl)-2-methoxy-6-(4-nitro phenyl)nicotinonitrile (**P_{74}**): FTIR (ATR, cm^{-1}): 3032, 2908, 2843, 2215, 1586, 1542, 1223, 1042. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.34-8.32 (d, 2H, ArH, *J*=8.0 Hz), 8.15-8.13 (d, 2H, ArH, *J*=8.0 Hz), 7.85-7.84 (d, 1H, ArH, *J*=6.4 Hz), 7.63-7.59 (m, 2H, ArH), 7.52 (s, 1H, ArH), 7.16-7.82 (m, 4H, ArH), 4.26 (s, 3H, OCH_3), 2.72 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 165.2, 162.9, 158.4, 152.7, 147.3, 142.5, 135.9, 129.6, 128.5, 123.9, 122.2, 121.5, 117.2, 116.7, 109.7, 94.2, 54.8, 16.7. MS (m/z) 480.3. Anal. Calcd. for $C_{27}H_{18}FN_5O_3$: C, 67.64; H, 3.78; N, 14.61. Found: C, 67.55; H, 3.77; N, 14.63.

6-(4-Fluorophenyl)-2-methoxy-4-(8-methyl-2-phenyl-imidazo [1,2-a]pyridin-3-yl) nicotinonitrile (**P_{75}**): FTIR (ATR, cm^{-1}): 3023, 2917, 2856, 2219, 1593, 1547, 1217, 1034. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.98-7.94 (m, 2H, ArH), 7.84-7.82 (d, 1H, ArH, *J*=6.4 Hz), 7.65-7.63 (m, 2H, ArH), 7.39 (s, 1H, ArH), 7.37-6.79 (m, 7H, ArH), 4.22 (s, 3H, OCH_3), 2.73 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 166.2, 162.3, 158.7, 151.4, 142.7, 134.5, 131.8, 129.8, 128.4, 127.6, 122.4, 117.5, 116.3, 109.7, 94.1, 55.2, 16.6. MS (m/z) 435.7. Anal. Calcd. for $C_{27}H_{19}FN_4O$: C, 74.64; H, 4.41; N, 12.90. Found: C, 74.65; H, 4.42; N, 12.88.

2-Methoxy-4-(8-methyl-2-phenyl-imidazo [1,2-a]pyridin-3-yl)-6-(4-nitrophenyl) nicotinonitrile (**P_{76}**): FTIR (ATR, cm^{-1}): 3032, 2918, 2853, 2216, 1576, 1521, 1225, 1040. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.33-8.31 (d, 2H, ArH, *J*=7.6 Hz), 8.14-8.12 (d, 2H, ArH, *J*=7.6 Hz), 7.84-7.82 (d, 1H, ArH, *J*=6.8 Hz), 7.62-7.60 (d, 2H, ArH, *J*=7.6 Hz), 7.53 (s, 1H, ArH), 7.41-7.36-6.94 (m, 5H, ArH), 4.23 (s, 3H, OCH_3), 2.73 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 158.3, 150.7, 148.6, 143.2, 134.8, 133.2, 129.7, 128.6, 127.8, 122.7, 121.4, 117.6, 110.3, 94.2, 55.4, 16.7. MS (m/z) 462.4. Anal. Calcd. for $C_{27}H_{19}N_5O_3$: C, 70.27; H, 4. 15; N, 15.18. Found: C, 70.13; H, 4.16; N, 15.18.

2-Methoxy-4-(8-methyl-2-phenyl-imidazo[1,2-a]pyridin-3-yl)-6-p-tolyl nicotinonitrile (**P_{77}**): FTIR (ATR, cm^{-1}): 3022, 2918, 2854, 2218, 1576, 1541, 1244, 1031. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.89-7.87 (d, 2H, ArH, *J*=8.0 Hz), 7.65-7.63 (d, 1H, ArH, *J*=6.8 Hz), 7.44 (s, 1H, ArH), 7.37-6.78 (m, 9H, ArH), 4.22 (s, 3H, OCH_3), 2.72 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 165.4, 157.8, 151.3, 143.6, 137.2, 134.7, 133.6, 129.4, 128.1, 127.5, 122.3, 118.2, 109.6, 93.9, 55.5, 16.6, 13.4. MS (m/z) 431.2. Anal. Calcd. for $C_{28}H_{22}N_4O$: C, 78.12; H, 5. 15; N, 13.01. Found: C, 78.04; H, 5.14; N, 13.00.

General procedure for the synthesis of pyrimidine derivatives **$P_{78\text{-}83}$** and **$P_{84\text{-}87}$**: An alcoholic solution of suitable chalcone **7a** (0.5 g, 1.35 mmol) and guanidine hydrochloride (0.15 g, 1.62 mmol) was made alkaline by adding NaOH (2.0 mmol). The resulting solution was refluxed for 6 h to afford complete cyclization of chalcone to pyrimidines **$P_{78\text{-}83}$**. The solid product obtained upon cooling was filtered and dried. Similar procedure was adopted for synthesis of compounds pyrimidine thiones **$P_{84\text{-}87}$**, wherein, thiourea (0.15 g, 2.0 mmol) was made use instead of guanidine hydrochloride. All the pyrimidine derivatives were recrystallized from methanol-chloroform mixture and their characterization data are summarized below.

4-(4-Chlorophenyl)-6-(2-(4-fluorophenyl)-8-methyl-imidazo [1,2-a]pyridin-3-yl) pyrimidin-2-amine (**P_{78}**): FTIR (ATR, cm^{-1}): 3306, 3192, 1627, 1579, 1530, 1492, 1232, 1154. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.28-8.26 (d, 1H, ArH, *J*=6.8 Hz), 7.85-7.83 (d, 2H, ArH, *J*=7.2 Hz), 7.66 (s, 1H, ArH), 7.47-7.41 (m, 5H, ArH), 7.08-6.89 (m, 3H, ArH), 5.24 (s, 2H, NH_2), 2.72 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 166.3, 162.5, 161.7, 159.8, 142.8, 134.5, 132.4, 131.3, 129.8, 129.2, 128.6, 123.4, 122.6, 116.1, 95.8, 16.7. MS (m/z) 430.7. Anal. Calcd. for $C_{24}H_{17}ClFN_5$: C, 67.06; H, 3.99; N, 16.29. Found: C, 66.91; H, 3.99; N, 16.30.

4-(2-(4-Fluorophenyl)-8-methyl-imidazo[1,2-a] pyridin-3-yl)-6-(4-nitrophenyl) pyrimidin-2-amine (**P_{79}**): FTIR (ATR, cm^{-1}): 3361, 3056, 1637, 1600, 1530, 1409, 1225, 1157. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.28-8.26 (d, 1H, ArH, *J*=7.2 Hz), 8.16-8.14 (d, 2H, ArH, *J*=8.0 Hz), 7.85-7.83 (d, 2H, ArH, *J*=7.6 Hz), 7.65 (s, 1H, ArH), 7.52-7.50 (d, 2H, ArH, *J*=8.0 Hz), 7.48 (m, 1H, ArH), 7.37-7.35 (d, 2H, ArH, *J*=7.6 Hz), 7.04-7.01 (dd, 1H, ArH, *J*=6.8, 3.2 Hz), 5.27 (s, 2H, NH_2), 2.72 (s, 3H,

CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 162.4, 161.5, 160.0, 149.3, 142.2, 139.7, 135.2, 130.4, 129.8, 128.4, 127.6, 122.9, 121.2, 116.5, 96.4, 16.8. MS (m/z) 441.4. Anal. Calcd. for $C_{24}H_{17}FN_6O_2$: C, 65.45; H, 3.89; N, 19.08. Found: C, 65.38; H, 3.87; N, 19.10.

4-(2-(4-Fluorophenyl)-8-methyl-imidazo [1,2-a]pyridin-3-yl)-6-p-tolylpyrimidin-2-amine (**P_{80}**): FTIR (ATR, cm^{-1}): 3342, 3028, 1624, 1587, 1527, 1408, 1227, 1146. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.28-8.26 (d, 1H, ArH, *J*=6.8 Hz), 7.82-7.80 (d, 2H, ArH, *J*=7.2 Hz), 7.64 (s, 1H, ArH), 7.48-7.43 (m, 5H, ArH), 7.14-7.12 (d, 2H, ArH, *J*=7.2 Hz), 6.98-6.96 (m, 1H, ArH), 5.22 (s, 2H, NH_2), 2.72 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 163.4, 162.5, 159.7, 143.1, 138.7, 134.7, 129.5, 128.6, 127.8, 122.3, 116.7, 96.5, 16.6. MS (m/z) 410.2. Anal. Calcd. for $C_{25}H_{20}FN_5$: C, 73.33; H, 4.92; N, 17.10. Found: C, 73.21; H, 4.90; N, 17.11.

4-(2-(4-Fluorophenyl)-8-methyl-imidazo [1,2-a]pyridin-3-yl)-6-phenylpyrimidin-2-amine (**P_{81}**): FTIR (ATR, cm^{-1}): 3178, 3027, 1624, 1563, 1534, 1492, 1400, 1224, 1154. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.27-8.26 (d, 1H, ArH, *J*=6.8 Hz), 7.82-7.80 (d, 2H, ArH, *J*=7.6 Hz), 7.64 (s, 1H, ArH), 7.47-7.40 (m, 5H, ArH), 7.28-6.96 (m, 4H, ArH), 5.21 (s, 2H, NH_2), 2.73 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 167.6, 163.4, 162.8, 160.1, 142.7, 134.7, 133.8, 131.8, 129.3, 128.6, 127.5, 122.5, 121.7, 116.4, 96.6, 16.6. MS (m/z) 396.2. Anal. Calcd. for $C_{24}H_{18}FN_5$: C, 72.90; H, 4.59; N, 17.71. Found: C, 72.78; H, 4.58; N, 17.71.

4-(8-Methyl-2-phenyl-imidazo[1,2-a]pyridin-3-yl)-6-(thiophen-2-yl)pyrimidin-2-amine (**P_{82}**): FTIR (ATR, cm^{-1}): 3334, 3024, 2911, 1574, 1502, 1398, 1250, 1156. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.26-8.25 (d, 1H, ArH, *J*=6.4 Hz), 7.65 (s, 1H, ArH), 7.64-7.62 (dd, 1H, ArH, *J*=6.8, 2.8 Hz), 7.55 (m, 1H, ArH), 7.46-7.37 (m, 4H, ArH), 7.13-7.06 (m, 3H, ArH), 6.98-6.95 (dd, 1H, ArH, *J*=6.4, 2.8 Hz), 5.09 (s, 2H, NH_2), 2.70 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 167.6, 133.4, 159.8, 143.1, 139.3, 134.7, 133.5, 129.3, 128.6, 127.4, 122.9, 96.3, 24.3, 16.7. MS (m/z) 384.6. Anal. Calcd. for $C_{22}H_{17}N_5S$: C, 68.91; H, 4.47; N, 18.26. Found: C, 68.79; H, 4.45; N, 18.25.

4-(8-Methyl-2-phenyl-imidazo[1,2-a]pyridin-3-yl)-6-p-tolylpyrimidin-2-amine (**P_{83}**): FTIR (ATR, cm^{-1}): 3257, 3037, 1627, 1593, 1523, 1485, 1412, 1226, 1151. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.27-8.25 (d, 1H, ArH, *J*=6.8 Hz), 7.68-7.66 (d, 2H, ArH,

J=7.6 Hz), 7.63 (s, 1H, ArH), 7.48-7.43 (m, 3H, ArH), 7.27-7.16 (m, 5H, ArH), 6.97 (m, 1H, ArH), 5.17 (s, 2H, NH_2), 2.72 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 167.3, 132.4, 158.4, 142.6, 141.1, 134.3, 133.7, 129.7, 128.3, 127.6, 125.4, 123.1, 122.5, 121.6, 96.5, 16.6. MS (m/z) 392.3. Anal. Calcd. for $C_{25}H_{21}N_5$: C, 76.70; H, 5.41; N, 17.89. Found: C, 76.60; H, 5.40; N, 17.91.

6-(4-Chlorophenyl)-4-(2-(4-fluorophenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl)-3,4-dihydropyrimidine-2(1H)-thione (**P_{84}**): FTIR (ATR, cm^{-1}): 3176, 2930, 1550, 1494, 1455, 1222. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 10.02 (s, 1H, NH), 9.07 (s, 1H, NH), 8.17-8.15 (d, 1H, ArH, *J*=6.4 Hz), 7.91-7.89 (d, 2H, ArH, *J*=7.2 Hz), 7.72-7.70 (d, 2H, ArH, *J*=6.8 Hz), 7.58-7.56 (d, 2H, ArH, *J*=7.2 Hz), 7.20-7.16 (m, 3H, ArH), 6.93 (m, 1H, ArH), 6.06-6.05 (d, 1H, CH, *J*=2.4 Hz), 5.12-5.12 (d, 1H, CH, *J*=2.4 Hz), 2.72 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 179.6, 163.2, 150.3, 145.6, 143.1, 135.2, 134.1, 132.7, 129.8, 128.6, 127.5, 122.4, 116.7, 95.8, 49.2, 16.5. MS (m/z) 449.7. Anal. Calcd. for $C_{24}H_{18}ClFN_4S$: C, 64.21; H, 4.04; N, 12.48. Found: C, 64.08; H, 4.02; N, 12.50.

4-(2-(4-Fluorophenyl)-8-methyl-imidazo [1,2-a]pyridin-3-yl)-6-phenyl-3,4-dihydro pyrimidine-2(1H)-thione (**P_{85}**): FTIR (ATR, cm^{-1}): 3176, 2943, 1637, 1554, 1481, 1276. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 10.01 (s, 1H, NH), 9.50 (s, 1H, NH), 8.17-8.15 (d, 1H, ArH, *J*=6.0 Hz), 7.84-7.82 (d, 2H, ArH, *J*=7.2 Hz), 7.36-7.32 (m, 5H, ArH), 7.13-7.04 (m, 3H, ArH), 6.94-6.92 (dd, 1H, ArH, *J*=6.8, 2.8 Hz), 6.08-6.07 (d, 1H, CH, *J*=3.2 Hz),), 5.17-5.16 (d, 1H, CH, *J*=3.2 Hz), 2.71 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 180.4, 163.2, 150.2, 144.3, 142.6, 134.9, 128.9, 127.6, 126.3, 122.4, 116.7, 95.8, 49.3, 16.5. MS (m/z) 415.3. Anal. Calcd. for $C_{24}H_{19}FN_4S$: C, 69.54; H, 4.62; N, 13.52. Found: C, 69.42; H, 4.61; N, 13.49.

4-(8-Methyl-2-phenyl-imidazo [1,2-a]pyridin-3-yl)-6-p-tolyl-3,4-dihydropyrimidine-2 (1H)-thione (**P_{86}**): FTIR (ATR, cm^{-1}): 3192, 2954, 1617, 1573, 1492, 1271. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 10.01 (s, 1H, NH), 9.52 (s, 1H, NH), 8.18-8.16 (d, 1H, ArH, *J*=6.8 Hz), 7.54-7.52 (d, 2H, ArH, *J*=7.2 Hz), 7.43 (m, 1H, ArH), 7.38-7.30 (m, 4H, ArH), 7.18-7.08 (m, 3H, ArH), 6.97 (m, 1H, ArH), 6.11-6.10 (d, 1H, CH, *J*=2.8 Hz), 5.14-5.13 (d, 1H, CH, *J*=2.8 Hz), 2.66 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 180.1, 150.2, 144.3, 142.6, 137.6, 134.7, 133.6, 129.7, 128.1,

127.4, 126.8, 122.3, 96.1, 49.2, 16.7. MS (m/z) 411.4. Anal. Calcd. for $C_{25}H_{22}N_4S$: C, 73.14; H, 5.40; N, 13.65. Found: C, 73.01; H, 5.41; N, 13.66.

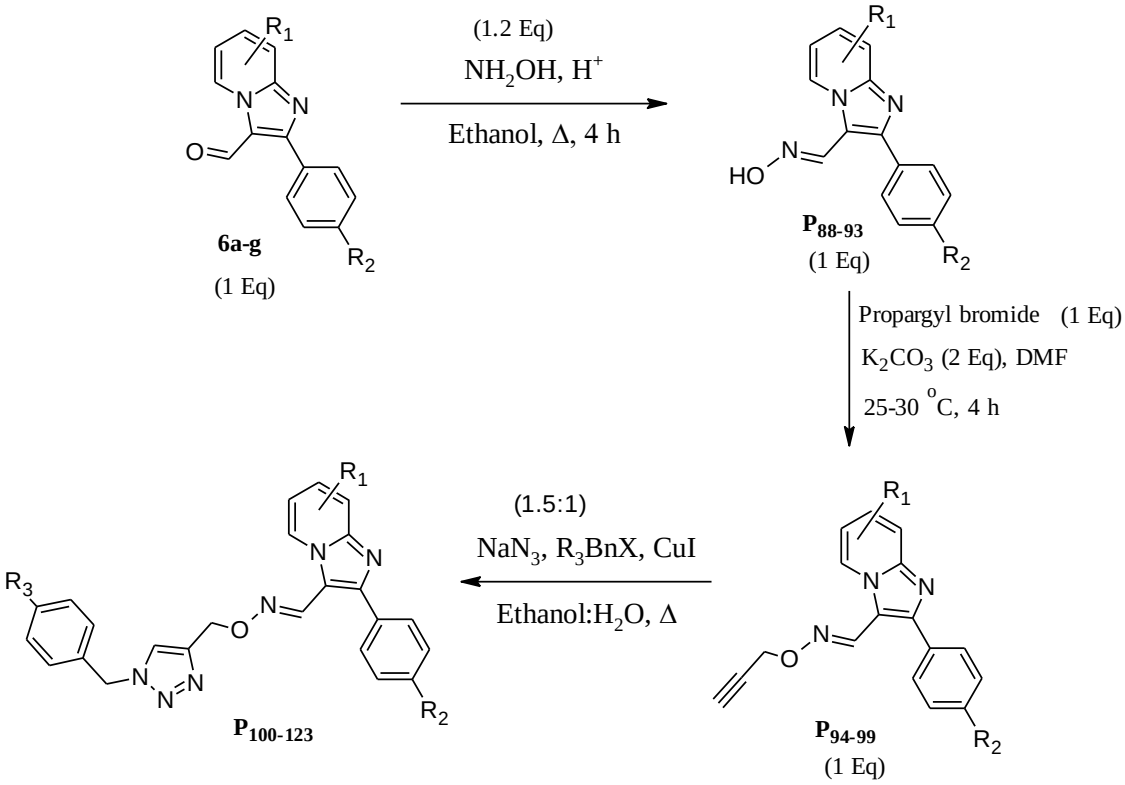
6-(4-Fluorophenyl)-4-(8-methyl-2-phenyl-imidazo [1,2-a]pyridin-3-yl)-3,4-dihydro pyrimidine-2(1H)-thione (**P_{87}**): FTIR (ATR, cm^{-1}): 3192, 2964, 1625, 1554, 1486, 1269. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 10.01 (s, 1H, NH), 9.52 (s, 1H, NH), 8.17-8.15 (d, 1H, ArH, *J*=6.8 Hz), 7.84-7.82 (d, 2H, ArH, *J*=7.2 Hz), 7.48 (m, 1H, ArH), 7.39-7.34 (m, 4H, ArH), 7.21-7.19 (d, 2H, ArH, *J*=7.2 Hz), 7.03-6.95 (m, 2H, ArH), 6.04-6.04 (d, 1H, CH, *J*=2.4 Hz), 5.19-5.18 (d, 1H, CH, *J*=2.4 Hz), 2.70 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 180.3, 162.3, 150.1, 144.4, 142.5, 134.2, 133.7, 129.7, 128.5, 127.2, 126.6, 122.7, 115.8, 96.5, 49.3, 16.5. MS (m/z) 415.3. Anal. Calcd. for $C_{24}H_{19}FN_4S$: C, 69.54; H, 4.62; N, 13.52. Found: C, 69.45; H, 4.63; N, 13.51.

3.3.4 Synthesis of new imidazo[1,2-a]pyridines carrying (1,2,3-triazol-4-yl) methyl oxime (**$P_{88\text{-}123}$**)

Synthesis of twenty four new imidazo[1,2-a]pyridines carrying 1,2,3-triazole moiety was achieved via Click chemistry during which, twelve new oximes were synthesized as new intermediates.

3.3.4.1 Chemistry

The reaction sequence involving the synthesis of required intermediates and title compounds is given in Scheme 3.6. The imidazo[1,2-a]pyridine-3-aldehydes **6a-g** were converted into oximes **$P_{88\text{-}93}$** by reacting them with hydroxyl amine hydrochloride in presence of acid catalyst. The hydroxyl group of oximes **$P_{88\text{-}93}$** were alkylated with propargyl bromide in presence of potassium carbonate to obtain active scaffolds **$P_{94\text{-}99}$**. Finally, the alkyne intermediates **$P_{94\text{-}99}$** were cyclised to new 1,2,3-triazole derivatives **$P_{100\text{-}123}$** by means of one pot multi-component 'Click Chemistry' cyclization, wherein alkynes were treated with sodium azide and an appropriate benzyl halide in presence of 10 mol % of copper iodide as catalyst. These newly synthesized compounds were later purified by column chromatography technique by taking petroleum ether and ethyl acetate solvent systems.



Scheme 3.6: Synthesis of new heterocyclic hybrids **$P_{100\text{-}123}$** carrying imidazo[1,2-a]pyridine and 1,2,3-triazole moieties.

3.3.4.2 Results and discussion

The structures of newly synthesized intermediates and target compounds were confirmed by their FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral followed by elemental analysis studies. The conversion of aldehyde **6a** to oxime **P_{89}** was confirmed by their FTIR and ^{1}H NMR spectral studies. In FTIR spectrum of **P_{89}** (Figure 3.26), the peak due to carboxaldehyde group of **6a** disappeared, while two new prominent peaks at 3105 and 1614 cm^{-1} corresponding to hydroxyl and imine groups, respectively were observed that clearly confirms the conversion. This conversion was further evidenced by its ^{1}H NMR spectrum (Figure 3.27), wherein it showed two singlet peaks at δ 11.38 and 8.43 ppm, corresponding to hydroxyl and CH=N protons, respectively. Also, its mass spectrum (Figure 3.29) showed molecular ion peak at 270.4, which is corresponding to M+H peak of the molecule. Disappearance of hydroxyl peak and appearance of a new peak at 3270 cm^{-1} corresponding to alkyne CH stretching in FTIR spectrum (Figure 3.30) of compound **P_{95}** clearly confirm the alkylation of **P_{89}** with

propargyl bromide. Another prominent peak at 2197 cm^{-1} corresponding to C-C triple bond stretching in its FTIR spectrum further confirms its formation. ^{1}H NMR spectrum (Figure 3.31) of **P_{95}** displayed two new prominent peaks at δ 4.85 and 3.53 ppm corresponding to CH_2 and CH protons of propargyl group, respectively. Further, the ^{13}C NMR spectrum (Figure 3.32) of **P_{95}** showed peaks at δ 80.0, 77.7 and 61.5ppm corresponding to two alkyne carbons and one methylene carbons, respectively.

Similarly, the cyclization of alkyne **P_{95}** to 1,2,3-triazole **P_{106}** was confirmed by spectral analysis. The ^{1}H NMR spectrum (Figure 3.34) of **P_{106}** showed two singlets at δ 8.46 and 8.37 ppm, corresponding to CH=N and a single aromatic proton of 1,2,3-triazole moiety, respectively. Also, two more characteristic singlets at δ 5.77 and 5.30 ppm, corresponding to two methylene groups present in the molecule were observed. Its ^{13}C NMR spectrum (Figure 3.35) displayed two typical peaks at δ 66.9, 51.7 ppm attributing to two methylene carbons, which further support the proposed structure. Similarly, structures of other new intermediates were also confirmed based on their spectral analysis. The analytical and characterization data of the intermediates and the final compounds are summarised in the experimental section, while their physical data are tabulated in Table 3.6. The ^{13}C NMR spectrum of compound **P_{89}** is given in Figure 3.28, while mass spectra of compound **P_{95}** and **P_{106}** are given in Figure 3.33 and 3.36, respectively. Similarly, the ^{1}H NMR, ^{13}C NMR and mass spectra of compound **P_{117}** are given in Figure 3.37, 3.38 and 3.39, respectively.

3.3.4.3 Experimental procedures

The procedures employed for the synthesis of new derivatives **$P_{88\text{-}123}$** are given below.

General procedure for the synthesis of oximes (**$P_{88\text{-}93}$**): The imidazo[1,2-a]pyridine-3-aldehyde **6a** (1 g, 4.2 mmol) was treated with hydroxyl amine hydrochloride (0.35 g, 5.0 mmol) under ethanolic media in the presence of catalytic sulphuric acid as dehydrating agent. The resulting solution was refluxed for about 4 h. Upon completion of reaction, the mixture was cooled to room temperature and the solid product was isolated through filtration. The product was washed with excess of ethanol, dried and finally recrystallized from methanol. Other oximes **$P_{89\text{-}93}$** were also synthesized following the same procedure and recrystallized from methanol.

Table 3.6: Physical data of target compounds $\mathbf{P_{88\text{-}123}}$

Sample	R_1	R_2	R_3	Mol. formula	M.P. (^oC)	Yield (%)
P_{88}	3Me	H	-	$C_{15}H_{13}N_3O$	251-254	84
P_{89}	3Me	F	-	$C_{15}H_{12}FN_3O$	227-229	80
P_{90}	3Me	Me	-	$C_{16}H_{15}N_3O$	261-263	83
P_{91}	5Br	H	-	$C_{14}H_{10}BrN_3O$	241-243	80
P_{92}	5Br	F	-	$C_{14}H_9BrFN_3O$	251-253	82
P_{93}	5Br	Me	-	$C_{15}H_{12}BrN_3O$	244-246	88
P_{94}	3Me	H	-	$C_{18}H_{15}N_3O$	161-163	82
P_{95}	3Me	F	-	$C_{18}H_{14}FN_3O$	151-154	82
P_{96}	3Me	Me	-	$C_{19}H_{17}N_3O$	145-147	87
P_{97}	5Br	H	-	$C_{17}H_{12}BrN_3O$	164-166	84
P_{98}	5Br	F	-	$C_{17}H_{11}BrFN_3O$	158-160	84
P_{99}	5Br	Me	-	$C_{18}H_{14}BrN_3O$	155-157	82
P_{100}	3Me	H	Me	$C_{26}H_{24}N_6O$	157-159	72
P_{101}	3Me	H	MeO	$C_{26}H_{24}N_6O_2$	197-199	74
P_{102}	3Me	H	NO_2	$C_{25}H_{21}N_7O_3$	224-226	80
P_{103}	3Me	H	CN	$C_{26}H_{21}N_7O$	232-234	81
P_{104}	3Me	F	Me	$C_{26}H_{23}FN_6O$	163-165	77
P_{105}	3Me	F	MeO	$C_{26}H_{23}FN_6O_2$	213-216	74
P_{106}	3Me	F	NO_2	$C_{25}H_{20}FN_7O_3$	207-209	78
P_{107}	3Me	F	CN	$C_{26}H_{20}FN_7O$	>300	77
P_{108}	3Me	Me	Me	$C_{27}H_{26}N_6O$	149-151	80
P_{109}	3Me	Me	MeO	$C_{27}H_{26}N_6O_2$	155-157	78
P_{110}	3Me	Me	NO_2	$C_{26}H_{23}N_7O_3$	208-210	76
P_{111}	3Me	Me	CN	$C_{27}H_{23}N_7O$	232-235	80
P_{112}	5Br	H	Me	$C_{25}H_{21}BrN_6O$	214-216	84
P_{113}	5Br	H	MeO	$C_{25}H_{21}BrN_6O_2$	218-220	80
P_{114}	5Br	H	NO_2	$C_{24}H_{18}BrN_7O_3$	219-221	82
P_{115}	5Br	H	CN	$C_{25}H_{18}BrN_7O$	227-229	79
P_{116}	5Br	F	Me	$C_{25}H_{20}BrN_6O$	233-235	75
P_{117}	5Br	F	MeO	$C_{25}H_{20}BrFN_6O_2$	161-163	82
P_{118}	5Br	F	NO_2	$C_{24}H_{17}BrFN_7O_3$	209-211	81
P_{119}	5Br	F	CN	$C_{25}H_{17}BrFN_7O$	235-237	78
P_{120}	5Br	Me	Me	$C_{26}H_{23}BrN_6O$	141-143	80
P_{121}	5Br	Me	MeO	$C_{26}H_{23}BrN_6O_2$	173-175	74
P_{122}	5Br	Me	NO_2	$C_{25}H_{20}BrN_7O_3$	207-209	70
p_{123}	5Br	Me	CN	$C_{26}H_{20}BrN_7O$	212-215	71

8-Methyl-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde oxime (**P_{88}**): FTIR (ATR, cm^{-1}): 3112, 2975, 1611, 1568, 1495, 1283. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.38 (s, 1H, OH), 9.09-9.07 (d, 1H, ArH, *J*=7.2 Hz), 8.42 (s, 1H, -CH=N), 7.41-7.38 (m, 2H, ArH), 7.35-7.33 (d, 1H, ArH, *J*=9.6 Hz), 7.21-7.02 (m, 4H, ArH), 2.54 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.4, 145.6, 136.1, 130.0, 124.4, 122.7, 121.3, 119.8, 116.2, 114.9, 113.2, 16.4. MS (m/z): 252.8. Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.57; H, 5.24; N, 16.70.

2-(4-Fluorophenyl)-8-methyl-imidazo[1,2-a]pyridine-3-carbaldehyde oxime (**P_{89}**): FTIR (ATR, cm^{-1}): 3105, 2922, 1614, 1488, 1448, 1384, 1257. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.38 (s, 1H, OH), 9.09-9.07 (d, 1H, ArH, *J*=7.2 Hz), 8.43 (s, 1H, -CH=N), 7.79-7.75 (m, 2H, ArH), 7.37-7.02 (m, 4H, ArH), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.4, 161.0, 145.6, 139.8, 131.0, 126.3, 125.8, 125.6, 115.5, 114.1, 113.9, 16.4. MS (m/z): 270.4. Anal. Calcd. for $C_{15}H_{12}FN_3O$: C, 66.91; H, 4.49; N, 15.60. Found: C, 66.77; H, 4.50; N, 15.58.

8-Methyl-2-p-tolyl-imidazo[1,2-a]pyridine-3-carbaldehyde oxime (**P_{90}**): FTIR (ATR, cm^{-1}): 3105, 2922, 2868, 1614, 1488, 1448, 1257. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.36 (s, 1H, OH), 9.08-9.06 (d, 1H, ArH, *J*=7.2 Hz), 8.40 (s, 1H, -CH=N), 7.73-7.71 (d, 2H, ArH, *J*=7.6 Hz), 7.35-7.33 (d, 1H, ArH, *J*=9.2 Hz), 7.14-7.12 (d, 2H, ArH, *J*=7.6 Hz), 7.10-7.08 (d, 1H, ArH, *J*=9.2 Hz), 2.57 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.6, 145.6, 136.4, 130.3, 124.3, 122.4, 121.7, 116.3, 115.1, 113.9, 113.1, 16.4, 13.4. MS (m/z): 266.1. Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.30; H, 5.70; N, 15.82.

6-Bromo-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde oxime (**P_{91}**): FTIR (ATR, cm^{-1}): 3101, 3059, 2826, 1639, 1497, 1449, 1261. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.40 (s, 1H, OH), 9.21 (s, 1H, ArH), 8.42 (s, 1H, -CH=N), 7.63-7.60 (d, 1H, ArH, *J*=9.6 Hz), 7.51-7.48 (d, 1H, ArH, *J*=9.6 Hz), 7.31-6.96 (m, 5H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.3, 143.7, 130.4, 125.6, 123.8, 121.4, 117.7, 116.1, 114.2, 113.3. MS (m/z): 316.8. Anal. Calcd. for $C_{14}H_{10}BrN_3O$: C, 53.19; H, 3.19; N, 13.29. Found: C, 53.04; H, 3.17; N, 13.30.

6-Bromo-2-(4-fluorophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde oxime (**P_{92}**): FTIR (ATR, cm^{-1}): 3089, 2974, 1636, 1599, 1496, 1420, 1227. ^{1}H NMR (DMSO-d_6, 400

MHz, δ ppm): 11.40 (s, 1H, OH), 9.22 (s, 1H, ArH), 8.44 (s, 1H, -CH=N), 7.81-7.79 (d, 2H, ArH, *J*=8.4 Hz), 7.63-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.51-7.48 (d, 1H, ArH, *J*=9.2 Hz), 7.20-7.18 (d, 2H, ArH, *J*=8.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.3, 159.8, 144.3, 130.4, 125.7, 121.4, 119.6, 117.8, 116.7, 114.5, 113.4. MS (m/z): 335.2. Anal. Calcd. for $C_{14}H_9BrFN_3O$: C, 50.32; H, 2.71; N, 12.58. Found: C, 50.19; H, 2.70; N, 12.60.

6-Bromo-2-p-tolyl-imidazo[1,2-a]pyridine-3-carbaldehyde oxime (**P$_{93}$**): FTIR (ATR, cm^{-1}): 3085, 2967, 2811, 1607, 1563, 1494, 1422, 1283. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.40 (s, 1H, OH), 9.21 (s, 1H, ArH), 8.40 (s, 1H, -CH=N), 7.63-7.60 (d, 1H, ArH, *J*=9.6 Hz), 7.54-7.52 (d, 2H, ArH, *J*=8.0 Hz), 7.51-7.48 (d, 1H, ArH, *J*=9.6 Hz), 7.15-7.13 (d, 2H, ArH, *J*=8.0 Hz), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.6, 143.7, 129.3, 125.7, 123.6, 121.8, 120.1, 117.8, 116.4, 115.3, 113.4. MS (m/z): 330.9. Anal. Calcd. for $C_{15}H_{12}BrN_3O$: C, 54.56; H, 3.66; N, 12.73. Found: C, 54.50; H, 3.65; N, 12.71.

General procedure for the synthesis of alkynes **P$_{94\text{-}99}$**: A mixture of oxime **P$_{88}$** (0.5 g, 1.99 mmol), propargyl bromide (0.24 g, 2.0 mmol) and potassium carbonate (0.55 g, 4.0 mmol) in DMF (10 mL) was stirred at 25-30 ^{o}C for 4 h. On completion of reaction, the mixture was quenched into ice-cold water while stirring. The resulting solid product **P$_{94}$** was filtered, washed with 5 % NaOH solution followed by excess of water and dried. The product was purified by column chromatography using hexane and ethyl acetate (9.5:0.5) eluting system. Similar procedure and purification technique were followed for the synthesis of other derivatives **P$_{95\text{-}99}$**.

8-Methyl-2-phenyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-prop-2-ynyl oxime (**P$_{94}$**): FTIR (ATR, cm^{-1}): 3259, 3114, 2915, 2203, 1597, 1487, 1443, 1259. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.07 (d, 1H, ArH, *J*=7.2 Hz), 8.49 (s, 1H, -CH=N), 7.39-6.94 (m, 7H, ArH), 4.85 (s, 2H, CH_2), 3.53 (s, 1H, CH), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.4, 146.4, 141.7, 131.2, 125.7, 124.4, 122.7, 119.7, 116.4, 114.8, 113.1, 79.8, 77.6, 61.4, 16.4. MS (m/z): 290.3. Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.63; H, 5.24; N, 14.50.

2-(4-Fluorophenyl)-8-methylH-imidazo[1,2-a]pyridine-3-carbaldehyde-O-prop-2-ynyl oxime (**P_{95}**): FTIR (ATR, cm^{-1}): 3270, 3118, 3022, 2922, 2197, 1603, 1527, 1485, 1394, 1230. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.07 (d, 1H, ArH, *J*=6.8 Hz), 8.50 (s, 1H, -CH=N), 7.79-7.76 (m, 2H, ArH), 7.35-7.09 (m, 4H, ArH), 4.85-4.84 (d, 2H, CH_2, *J*=2.4 Hz), 3.53 (s, 1H, CH), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.5, 161.1, 147.7, 146.2, 141.1, 131.0, 126.5, 125.9, 124.4, 116.0, 115.6, 114.2, 112.7, 80.0, 77.7, 61.5, 16.4. MS (m/z): 308.2. Anal. Calcd. for $C_{18}H_{14}FN_3O$: C, 70.35; H, 4.59; N, 13.67. Found: C, 70.21; H, 4.60; N, 13.66.

8-Methyl-2-p-tolyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-prop-2-ynyl oxime (**P_{96}**): FTIR (ATR, cm^{-1}): 3210, 3010, 2915, 2185, 1601, 1489, 1412, 1257. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.07 (d, 1H, ArH, *J*=6.8 Hz), 8.48 (s, 1H, -CH=N), 7.56-7.54 (d, 2H, ArH, *J*=8.4 Hz), 7.35-7.33 (d, 1H, ArH, *J*=8.8 Hz), 7.21-7.18 (d, 2H, ArH, *J*=8.4 Hz), 7.08-7.06 (d, 1H, ArH, *J*=8.8 Hz), 4.85 (s, 2H, CH_2), 3.53 (s, 1H, CH), 2.57 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 163.5, 149.3, 146.1, 140.7, 129.5, 127.1, 124.2, 122.3, 119.2, 116.3, 113.4, 80.0, 77.5, 61.4, 16.4, 13.3. MS (m/z): 304.1. Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.10; H, 5.64; N, 13.83.

6-Bromo-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-prop-2-ynyl oxime (**P_{97}**): FTIR (ATR, cm^{-1}): 3215, 3084, 2923, 2196, 2866, 1599, 1482, 1428, 1249. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.99 (s, 1H, ArH), 8.51 (s, 1H, -CH=N), 7.62-7.60 (d, 1H, ArH, *J*=8.8 Hz), 7.50-7.48 (d, 1H, ArH, *J*=8.8 Hz), 7.32-6.98 (m, 5H, ArH), 4.87 (s, 2H, CH_2), 3.54 (s, 1H, CH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.1, 147.2, 145.6, 140.1, 130.6, 126.4, 124.5, 123.1, 121.9, 118.5, 115.8, 113.4, 80.1, 77.6, 61.4. MS (m/z): 355.7. Anal. Calcd. for $C_{17}H_{12}BrN_3O$: C, 57.65; H, 3.41; N, 11.86. Found: C, 57.51; H, 3.39; N, 11.87.

6-Bromo-2-(4-fluorophenyl)-imidazo [1,2-a]pyridine-3-carbaldehyde-O-prop-2-ynyl oxime (**P_{98}**): FTIR (ATR, cm^{-1}): 3215, 2921, 2833, 2194, 1601, 1481, 1408, 1245. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.99 (s, 1H, ArH), 8.51 (s, 1H, -CH=N), 7.79-7.77 (d, 2H, ArH, *J*=8.4 Hz), 7.62-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.56-7.54 (d, 1H, ArH, *J*=9.2 Hz), 7.18-7.16 (d, 2H, ArH, *J*=8.4 Hz), 4.86 (s, 2H, CH_2), 3.53 (s, 1H, CH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.1, 159.8, 147.8, 145.1, 139.8,

131.3, 127.2, 123.2, 121.0, 119.2, 116.3, 113.4, 80.0, 77.6, 61.4. MS (m/z): 372.9. Anal. Calcd. for $C_{17}H_{11}BrFN_3O$: C, 54.86; H, 2.98; N, 11.29. Found: C, 54.73; H, 2.99; N, 11.27.

6-Bromo-2-p-tolyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-prop-2-ynyl oxime (**P_{99}**): FTIR (ATR, cm^{-1}): 3270, 3118, 3022, 2922, 2184, 1603, 1527, 1485, 1394, 1230. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.99 (s, 1H, ArH), 8.51 (s, 1H, -CH=N), 7.62-7.60 (d, 1H, ArH, *J*=8.8 Hz), 7.56-7.54 (d, 2H, ArH, *J*=8.0 Hz), 7.50-7.48 (d, 1H, ArH, *J*=8.8 Hz), 7.18-7.16 (d, 2H, ArH, *J*=8.0 Hz), 4.86 (s, 2H, CH_2), 3.53 (s, 1H, CH), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.3, 146.7, 145.1, 140.2, 130.9, 127.2, 125.6, 122.8, 121.3, 118.6, 116.5, 113.4, 80.0, 77.7, 61.4, 13.4. MS (m/z): 369.4. Anal. Calcd. for $C_{18}H_{14}BrN_3O$: C, 58.71; H, 3.83; N, 11.41. Found: C, 58.57; H, 3.84; N, 11.40.

General procedure for the synthesis of imidazo[1,2-a]pyridines carrying1,2,3-triazole **$P_{100\text{-}123}$**: A mixture of alkyne derivative **P_{94}** (0.5 g, 1.73 mmol), sodium azide (0.17 g, 2.6 mmol), and 4-methyl benzyl bromide (0.32 g, 1.73 mmol) was dissolved in 10 mL of 50% ethanol. Cuprous iodide (10mol %) was added to the above reaction mixture and stirred at 60-70 ^{o}C for 12 h. After completion of reaction, the mixture was cooled to room temperature and then quenched to ice-water with stirring. The separated solid product **P_{100}** was later collected by filtration, washed with excess of cold water and dried. The crude residue was purified over silica gel column using methanol-chloroform eluting system to obtain the pure product. Similar procedure was followed for other derivatives **$P_{101\text{-}123}$** also.

8-Methyl-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{100}**): FTIR (ATR, cm^{-1}): 3117, 3024, 2920, 2861, 1598, 1484, 1349, 1254. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=7.2 Hz), 8.48 (s, 1H, -CH=N), 8.35 (s, 1H, ArH), 7.58-7.56 (d, 2H, ArH, *J*=7.6 Hz), 7.42 (m, 2H, ArH), 7.37-7.35 (d, 1H, ArH, *J*=9.6 Hz), 7.32-7.02 (m, 6H, ArH), 5.77 (s, 2H, CH_2), 5.33 (s, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.4, 139.6, 131.2, 130.7, 128.5, 126.3, 125.1, 123.3, 121.9, 115.6, 114.7, 113.4, 66.8, 51.7, 16.3, 13.4. MS (m/z): 437.4. Anal. Calcd. for $C_{26}H_{24}N_6O$: C, 71.54; H, 5.54; N, 19.25. Found: C, 71.42; H, 5.54; N, 19.23.

8-Methyl-2-phenyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{101}**): FTIR (ATR, cm^{-1}): 3114, 3018, 2943, 2882, 1598, 1465, 1254. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=6.4 Hz), 8.48 (s, 1H, -CH=N), 8.37 (s, 1H, ArH), 7.54-7.52 (d, 2H, ArH, *J*=8.8 Hz), 7.46 (m, 2H, ArH), 7.36-7.34 (d, 1H, ArH, J=9.2 Hz), 7.32-6.98 (m, 6H, ArH), 5.77 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.7, 154.4, 140.2, 131.4, 130.7, 127.8, 126.3, 125.4, 123.9, 122.4, 121.5, 116.4, 115.7, 113.9, 66.8, 64.0, 51.4, 16.3. MS (m/z): 453.7. Anal. Calcd. for $C_{26}H_{24}N_6O_2$: C, 69.01; H, 5.35; N, 18.57. Found: C, 68.87; H, 5.34; N, 18.58.

8-Methyl-2-phenyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{102}**): FTIR (ATR, cm^{-1}): 3117, 3024, 2920, 2861, 1598, 1521, 1343, 1258. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.07 (d, 1H, ArH, *J*=6.8 Hz), 8.46 (s, 1H, -CH=N), 8.37 (s, 1H, ArH), 7.85-7.83 (d, 2H, ArH, *J*=8.0 Hz), 7.47-7.45 (d, 2H, ArH, *J*=8.0 Hz), 7.15-7.04 (m, 7H, ArH), 5.77 (s, 2H, CH_2), 5.29 (s, 2H, CH_2), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.4, 161.0, 140.5, 130.9, 128.7, 126.3, 125.9, 123.6, 115.5, 114.0, 66.8, 51.7, 16.3. MS (m/z): 468.3. Anal. Calcd. for $C_{25}H_{21}N_7O_3$: C, 64.23; H, 4.53; N, 20.97. Found: C, 64.10; H, 4.54; N, 20.97.

8-Methyl-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-[1-(4-cyanobenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{103}**): FTIR (ATR, cm^{-1}): 3093, 2934, 2886, 2198, 1599, 1546, 1361, 1248. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=7.2 Hz), 8.47 (s, 1H, -CH=N), 8.39 (s, 1H, ArH), 8.13-8.11 (d, 2H, ArH, *J*=8.0 Hz), 7.57-7.55 (d, 2H, ArH, *J*=8.0 Hz), 7.36-7.34 (d, 1H, ArH, *J*=9.2 Hz), 7.01 (m, 6H, ArH), 5.76 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.6, 149.8, 139.4, 131.7, 130.4, 125.2, 124.7, 123.1, 121.2, 118.2, 117.5, 115.0, 114.1, 66.9, 51.6, 16.3. MS (m/z): 448.9. Anal. Calcd. for $C_{26}H_{21}N_7O$: C, 69.78; H, 4.73; N, 21.91. Found: C, 69.63; H, 4.72; N, 21.94.

2-(4-Fluorophenyl)-8-methyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methyl benzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{104}**): FTIR (ATR, cm^{-1}): 3117, 2976, 2834, 1603, 1512, 1257. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H,

ArH, *J*=6.8 Hz), 8.46 (s, 1H, -CH=N), 8.34 (s, 1H, ArH), 7.55-7.53 (d, 2H, ArH, *J*=8.0 Hz), 7.48-7.46 (d, 2H, ArH, *J*=8.4 Hz), 7.36-7.34 (d, 1H, ArH, *J*=9.2 Hz), 7.24-7.22 (d, 2H, ArH, *J*=8.0 Hz), 7.20-7.18 (d, 2H, ArH, *J*=8.4 Hz), 7.07-7.05 (d, 1H, ArH, *J*=9.2 Hz), 5.77 (s, 2H, CH_2), 5.29 (s, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.3, 140.1, 137.6, 132.6, 130.4, 129.4, 125.4, 123.3, 121.8, 121.1, 118.6, 115.6, 66.8, 51.7, 16.3, 13.4. MS (m/z): 455.6. Anal. Calcd. for $C_{26}H_{23}FN_6O$: C, 68.71; H, 5.10; N, 18.49. Found: C, 68.58; H, 5.08; N, 18.49.

2-(4-Fluorophenyl)-8-methyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{105}**): FTIR (ATR, cm^{-1}): 3108, 3012, 2934, 1600, 1532, 1365, 1255. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=7.2 Hz), 8.46 (s, 1H, -CH=N), 8.34 (s, 1H, ArH), 7.56-7.54 (d, 2H, ArH, *J*=8.4 Hz), 7.51-7.49 (d, 2H, ArH, *J*=7.6 Hz), 7.36-7.34 (d, 1H, ArH, *J*=9.6 Hz), 7.24-7.19 (m, 4H, ArH), 7.06-7.04 (d, 1H, ArH, *J*=9.6 Hz), 5.76 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.2, 159.4, 152.8, 130.8, 129.3, 127.8, 125.8, 124.1, 123.2, 122.4, 121.0, 118.3, 115.7, 66.8, 64.3, 51.4, 16.3. MS (m/z): 471.8. Anal. Calcd. for $C_{26}H_{23}FN_6O_2$: C, 66.37; H, 4.93; N, 17.86. Found: C, 66.23; H, 4.92; N, 17.85.

2-(4-Fluorophenyl)-8-methyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-nitro benzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{106}**): FTIR (ATR, cm^{-1}): 3117, 3024, 2920, 2861, 1598, 1484, 1349, 1254. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=7.2 Hz), 8.46 (s, 1H, -CH=N), 8.37 (s, 1H, ArH), 8.15-8.13 (d, 2H, ArH, *J*=8.0 Hz), 7.55-7.05 (m, 8H, ArH), 5.77 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.3, 159.3, 147.5, 140.5, 130.9, 128.7, 126.3, 126.0, 115.3, 114.0, 66.9, 51.7, 16.3. MS (m/z): 487.4. Anal. Calcd. for $C_{25}H_{20}FN_7O_3$: C, 61.85; H, 4.15; N, 20.20. Found: C, 61.71; H, 4.13; N, 20.21.

2-(4-Fluorophenyl)-8-methyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-cyano benzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{107}**): FTIR (ATR, cm^{-1}): 3120, 3031, 2878, 2208, 1602, 1532, 1448, 1251. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=7.6 Hz), 8.47 (s, 1H, -CH=N), 8.41 (s, 1H, ArH), 8.21-8.19 (d,

2H, ArH, *J*=7.2 Hz), 7.57-7.55 (d, 2H, ArH, *J*=7.6 Hz), 7.36-7.34 (d, 1H, ArH, *J*=9.6 Hz), 7.31-7.29 (d, 2H, ArH, *J*=7.2 Hz), 7.21-7.19 (d, 2H, ArH, *J*=7.6 Hz), 7.08-7.05 (d, 1H, ArH, *J*=9.6 Hz), 5.79 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.6, 149.5, 140.6, 132.3, 131.5, 126.0, 124.7, 123.2, 121.5, 119.8, 118.7, 114.0, 67.0, 51.5, 16.3. MS (m/z): 466.6. Anal. Calcd. for $C_{26}H_{20}FN_7O$: C, 67.09; H, 4.33; N, 21.06. Found: C, 67.01; H, 4.33; N, 21.08.

8-Methyl-2-p-tolyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methylbenzyl)-1H -1,2,3-triazol-4-yl]methyl oxime (**P_{108}**): FTIR (ATR, cm^{-1}): 3109, 2987, 2838, 1598, 1525, 1462, 1254. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=7.6 Hz), 8.45 (s, 1H, -CH=N), 8.36 (s, 1H, ArH), 7.46-7.44 (d, 2H, ArH, *J*=8.0 Hz), 7.43-7.41 (d, 2H, ArH, *J*=8.8 Hz), 7.36-7.34 (d, 1H, ArH, *J*=9.6 Hz), 7.20-7.17 (m, 4H, ArH), 7.09-7.07 (d, 1H, ArH, *J*=9.6 Hz), 5.76 (s, 2H, CH_2), 5.28 (s, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.34 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.1, 141.0, 136.4, 131.9, 130.7, 129.4, 125.3, 124.5, 122.2, 120.1, 118.7, 116.2, 115.1, 66.8, 51.7, 16.3, 13.6, 13.4. MS (m/z): 451.3. Anal. Calcd. for $C_{27}H_{26}N_6O$: C, 71.98; H, 5.82; N, 18.65. Found: C, 71.86; H, 5.83; N, 18.64.

8-Methyl-2-p-tolyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methoxybenzyl) 1H-1,2,3-triazol-4-yl]methyl oxime (**P_{109}**): FTIR (ATR, cm^{-1}): 3111, 3008, 2887, 1598, 1546, 1483, 1254. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=8.0 Hz), 8.46 (s, 1H, -CH=N), 8.34 (s, 1H, ArH), 7.52-7.50 (d, 2H, ArH, *J*=8.4 Hz), 7.45-7.43 (d, 2H, ArH, *J*=7.6 Hz), 7.36-7.34 (d, 1H, ArH, *J*=9.2 Hz), 7.22-7.20 (d, 2H, ArH, *J*=8.4 Hz), 7.18-7.16 (d, 2H, ArH, *J*=7.6 Hz), 7.10-7.08 (d, 1H, ArH, *J*=9.2 Hz), 5.76 (s, 2H, CH_2), 5.29 (s, 2H, CH_2), 3.98 (s, 3H, OCH_3), 2.57 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.1, 158.3, 142.1, 133.9, 130.1, 129.7, 125.7, 124.3, 123.8, 122.4, 120.1, 119.1, 117.0, 66.9, 64.3, 51.7, 16.3, 13.3. MS (m/z): 467.4. Anal. Calcd. for $C_{27}H_{26}N_6O_2$: C, 69.51; H, 5.62; N, 18.01. Found: C, 69.38; H, 5.63; N, 18.02.

8-Methyl-2-p-tolyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{110}**): FTIR (ATR, cm^{-1}): 3118, 3021, 1603, 1587, 1484, 1254. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=7.6 Hz), 8.48 (s, 1H, -CH=N), 8.40 (s, 1H, ArH), 8.11-8.09 (d, 2H, ArH, *J*=7.6 Hz), 7.46-

7.44 (d, 2H, ArH, *J*=8.4 Hz), 7.36-7.34 (d, 1H, ArH, *J*=9.2 Hz), 7.31-7.29 (d, 2H, ArH, *J*=7.6 Hz), 7.19-7.17 (d, 2H, ArH, *J*=8.4 Hz), 7.08-7.06 (d, 1H, ArH, *J*=9.2 Hz), 5.78 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.3, 161.6, 141.3, 132.5, 130.3, 126.2, 124.3, 123.2, 120.4, 119.8, 118.7, 114.0, 67.1, 51.6, 16.3, 13.3. MS (m/z): 482.6. Anal. Calcd. for $C_{26}H_{23}N_7O_3$: C, 64.85; H, 4.81; N, 20.36. Found: C, 64.72; H, 4.80; N, 20.36.

8-Methyl-2-p-tolyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-[1-(4-cyanobenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{111}**): FTIR (ATR, cm^{-1}): 3113, 3041, 2896, 2198, 1608, 1554, 1467, 1256. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.03 (d, 1H, ArH, *J*=8.0 Hz), 8.47 (s, 1H, -CH=N), 8.39 (s, 1H, ArH), 8.11-8.09 (d, 2H, ArH, *J*=7.6 Hz), 7.45-7.43 (d, 2H, ArH, *J*=8.0 Hz), 7.37-7.35 (d, 1H, ArH, *J*=8.8 Hz), 7.32-7.30 (d, 2H, ArH, *J*=7.6 Hz), 7.20-7.18 (d, 2H, ArH, *J*=8.4 Hz), 7.11-7.09 (d, 1H, ArH, *J*=8.8 Hz), 5.78 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.3, 149.6, 141.5, 131.9, 130.6, 126.2, 125.7, 123.2, 122.5, 120.4, 119.8, 118.7, 115.3, 66.8, 51.7, 16.3, 13.4. MS (m/z): 462.5. Anal. Calcd. for $C_{27}H_{23}N_7O$: C, 70.27; H, 5.02; N, 21.24. Found: C, 70.15; H, 5.00; N, 21.26.

6-Bromo-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{112}**): FTIR (ATR, cm^{-1}): 3108, 2976, 2834, 1600, 1487, 1328. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09 (s, 1H, ArH), 8.50 (s, 1H, -CH=N), 8.45 (s, 1H, ArH), 7.62-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.56-7.54 (d, 1H, ArH, *J*=9.2 Hz), 7.48-7.46 (d, 2H, ArH, J=7.6 Hz), 7.41-7.03 (m, 7H, ArH), 5.56 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.4, 154.3, 145.5, 130.6, 129.5, 126.0, 125.1, 122.4, 120.4, 119.8, 118.3, 116.0, 114.6, 66.8, 51.7, 14.4. MS (m/z): 502.2. Anal. Calcd. for $C_{25}H_{21}BrN_6O$: C, 59.89; H, 4.22; N, 16.76. Found: C, 59.75; H, 4.21; N, 16.77.

6-Bromo-2-phenyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methoxybenzyl) 1H-1,2,3-triazol-4-yl]methyl oxime (**P_{113}**): FTIR (ATR, cm^{-1}): 3111, 3022, 2976, 1603, 1502, 1432, 1251. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09 (s, 1H, ArH), 8.49 (s, 1H, -CH=N), 8.47 (s, 1H, ArH), 7.63-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.57-7.54 (d, 1H, ArH, J=9.2 Hz), 7.51-7.49 (d, 2H, ArH, *J*=7.2 Hz), 7.42-7.38 (m, 2H, ArH), 7.22-7.06

(m, 5H, ArH), 5.56 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 3.98 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.4, 155.1, 145.5, 130.6, 129.5, 126.0, 125.1, 124.3, 122.4, 120.4, 118.3, 116.0, 114.6, 66.8, 64.3, 51.7. MS (m/z): 518.9. Anal. Calcd. for $C_{25}H_{21}BrN_6O_2$: C, 58.04; H, 4.09; N, 16.24. Found: C, 57.91; H, 4.11; N, 16.24.

6-Bromo-2-phenyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{114}**): FTIR (ATR, cm^{-1}): 3116, 3082, 2876, 1603, 1522, 1487, 1337, 1243. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.08 (d, 1H, ArH, *J*=2.8 Hz), 8.50 (s, 2H, -CH=N, ArH), 8.21-8.19 (d, 2H, ArH, *J*=7.6 Hz), 7.62-7.59 (d, 1H, ArH, *J*=9.6 Hz), 7.56-7.54 (d, 1H, ArH, *J*=9.6 Hz), 7.35-7.32 (m, 2H, ArH), 7.21-7.19 (d, 2H, ArH, *J*=7.6 Hz), 7.15-7.02 (m, 3H, ArH), 5.57 (s, 2H, CH_2), 5.31 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.0, 161.1, 154.5, 130.6, 129.2, 126.5, 124.8, 124.3, 122.2, 120.2, 118.3, 116.2, 66.9, 51.7. MS (m/z): 532.9. Anal. Calcd. for $C_{24}H_{18}BrN_7O_3$: C, 54.15; H, 3.41; N, 18.42. Found: C, 54.01; H, 3.41; N, 18.40.

6-Bromo-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-[1-(4-cyanobenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{115}**): FTIR (ATR, cm^{-1}): 3114, 3067, 2891, 2207, 1607, 1487, 1319, 1241. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.09 (d, 1H, ArH, *J*=2.0 Hz), 8.48 (s, 1H, -CH=N), 8.44 (s, 1H, ArH), 8.10-8.09 (d, 2H, ArH, *J*=7.2 Hz), 7.62-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.57-7.54 (d, 1H, ArH, *J*=9.2 Hz), 7.39-7.35 (m, 2H, ArH), 7.23-7.21 (d, 2H, ArH, *J*=7.2 Hz), 7.15-7.08 (m, 3H, ArH), 5.56 (s, 2H, CH_2), 5.32 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.0, 154.5, 150.2, 131.0, 129.8, 127.6, 123.4, 122.3, 121.6, 119.2, 118.3, 116.2, 66.8, 51.4. MS (m/z): 513.1. Anal. Calcd. for $C_{25}H_{18}BrN_7O$: C, 58.60; H, 3.54; N,19.14. Found: C, 58.51; H, 3.55; N, 19.13.

6-Bromo-2-(4-fluorophenyl)-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methyl benzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{116}**): FTIR (ATR, cm^{-1}): 3114, 2954, 2834, 1603, 1529, 1487, 1318, 1237. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.04 (d, 1H, ArH, *J*=2.0 Hz), 8.49 (s, 1H, -CH=N), 8.42 (s, 1H, ArH), 7.72-7.70 (d, 2H, ArH, *J*=8.0 Hz), 7.62-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.56-7.54 (d, 1H, ArH, *J*=9.2 Hz), 7.49-7.47 (d, 2H, ArH, *J*=7.6 Hz), 7.24-7.22 (d, 2H, ArH, *J*=8.0 Hz), 7.18-7.16 (d, 2H, ArH, *J*=7.6 Hz), 5.56 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 2.33 (s, 3H, CH_3). ^{13}C

NMR (DMSO-d_6, 100 MHz, δ ppm): 162.3, 159.4, 139.8, 131.4, 126.3, 125.4, 124.2, 122.0, 121.1, 120.4, 118.6, 116.2, 66.8, 51.6, 13.3. MS (m/z): 521.1. Anal. Calcd. for $C_{25}H_{20}BrFN_6O$: C, 57.81; H, 3.88; N, 16.18. Found: C, 57.71; H, 3.87; N, 16.19.

6-Bromo-2-(4-fluorophenyl)-imidazo[1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methoxy benzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{117}**): FTIR (ATR, cm^{-1}): 3111, 2987, 1602, 1485, 1315, 1242. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.08 (d, 1H, ArH, *J*=2.8 Hz), 8.50 (s, 2H, -CH=N, ArH), 7.99-7.96 (m, 3H, ArH), 7.59-7.57 (m, 3H, ArH), 7.42-7.23 (m, 4H, ArH), 5.55 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 4.03 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.0, 154.0, 140.5, 130.9, 128.7, 126.3, 126.0, 125.9, 123.6, 115.6, 114.0, 66.8, 64.2, 51.7. MS (m/z): 536.3. Anal. Calcd. for $C_{25}H_{20}BrFN_6O_2$: C, 56.09; H, 3.77; N,15.70. Found: C, 56.00; H, 3.75; N, 15.68.

6-Bromo-2-(4-fluorophenyl)-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-nitro benzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{118}**): FTIR (ATR, cm^{-1}): 3080, 2873, 1603, 1523, 1487, 1338, 1231. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.08 (d, 1H, ArH, *J*=2.4 Hz), 8.50 (s, 2H, -CH=N, ArH), 8.21-8.19 (d, 2H, ArH, *J*=7.6 Hz), 7.77-7.75 (d, 2H, ArH, *J*=7.6 Hz), 7.62-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.56-7.54 (d, 1H, ArH, *J*=9.2 Hz), 7.23-7.21 (d, 2H, ArH, *J*=7.6 Hz), 7.20-7.18 (d, 2H, ArH, *J*=7.6 Hz), 5.57 (s, 2H, CH_2), 5.31 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.0, 161.1, 154.5, 130.6, 129.4, 126.6, 124.8, 124.3, 122.4, 120.0, 118.4, 116.1, 66.9, 51.7. MS (m/z): 552.1. Anal. Calcd. for $C_{24}H_{17}BrFN_7O_3$: C, 52.38; H, 3.11; N,17.82. Found: C, 52.31; H, 3.09; N, 17.82.

6-Bromo-2-(4-fluorophenyl)-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-cyano benzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{119}**): FTIR (ATR, cm^{-1}): 3114, 2918, 2201, 1608, 1488, 1319, 1234. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09 (s, 1H, ArH), 8.49 (s, 1H, -CH=N), 8.46 (s, 1H, ArH), 8.11-8.09 (d, 2H, ArH, *J*=7.2 Hz), 7.76-7.74 (d, 2H, ArH, *J*=8.0 Hz), 7.63-7.60 (d, 1H, ArH, *J*=9.6 Hz), 7.56-7.54 (d, 1H, ArH, *J*=9.6 Hz), 7.22-7.20 (d, 2H, ArH, *J*=7.2 Hz), 7.16-7.14 (d, 2H, ArH, *J*=8.0 Hz), 5.57 (s, 2H, CH_2), 5.32 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.2, 154.4, 150.2, 131.0, 129.7, 127.6, 123.4, 122.3, 121.8, 119.2, 118.4, 116.2, 66.8, 51.3.

MS (m/z): 531.2. Anal. Calcd. for $C_{25}H_{17}BrFN_7O$: C, 56.62; H, 3.23; N,18.49. Found: C, 56.49; H, 3.24; N, 18.50.

6-Bromo-2-p-tolyl-imidazo[1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{120}**): FTIR (ATR, cm^{-1}): 3114, 3084, 2853, 1606, 1520, 1422, 1341, 1248. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.04 (d, 1H, ArH, *J*=2.4 Hz), 8.47 (s, 1H, -CH=N), 8.42 (s, 1H, ArH), 7.63-7.60 (d, 1H, ArH, *J*=8.8 Hz), 7.56-7.54 (d, 1H, ArH, *J*=8.8 Hz), 7.51-7.49 (d, 2H, ArH, *J*=7.6 Hz), 7.48-7.46 (d, 2H, ArH, *J*=8.0 Hz), 7.21-7.15 (m, 4H, ArH), 5.56 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 2.34 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.8, 141.2, 136.4, 132.1, 130.6, 129.5, 125.3, 124.4, 122.0, 120.1, 118.7, 116.2, 115.1, 66.8, 51.7, 13.6, 13.4. MS (m/z): 517.1. Anal. Calcd. for $C_{26}H_{23}BrN_6O$: C, 60.59; H, 4.50; N,16.31. Found: C, 60.50; H, 4.51; N, 16.30.

6-Bromo-2-p-tolyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{121}**): FTIR (ATR, cm^{-1}): 3078, 2930, 2836, 1605, 1480, 1245. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.05-9.04 (d, 1H, ArH, *J*=2.8 Hz), 8.48 (s, 1H, -CH=N), 8.45 (s, 1H, ArH), 7.64-7.61 (d, 1H, ArH, *J*=9.2 Hz), 7.57-7.54 (d, 1H, ArH, *J*=9.2 Hz), 7.53-7.51 (d, 2H, ArH, *J*=8.4 Hz), 7.49-7.47 (d, 2H, ArH, *J*=7.2 Hz), 7.23-7.21 (d, 2H, ArH, *J*=8.4 Hz), 7.18-7.17 (d, 2H, ArH, *J*=7.2 Hz), 5.56 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 4.02 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.3, 154.0, 139.4, 131.8, 130.7, 129.4, 126.4, 124.5, 122.1, 120.1, 118.7, 116.2, 114.8, 66.8, 64.3, 51.7, 13.5. MS (m/z): 532.9. Anal. Calcd. for $C_{26}H_{23}BrN_6O_2$: C, 58.76; H, 4.36; N,15.81. Found: C, 58.64; H, 4.36; N, 15.82.

6-Bromo-2-p-tolyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{122}**): FTIR (ATR, cm^{-1}): 3078, 3010, 2846, 1607, 1537, 1482, 1345, 1245. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09 (s, 1H, ArH), 8.50 (s, 2H, -CH=N, ArH), 8.21-8.19 (d, 2H, ArH, *J*=8.4 Hz), 7.63-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.56-7.54 (d, 1H, ArH, *J*=9.2 Hz), 7.49-7.47 (d, 2H, ArH, *J*=7.6 Hz), 7.21-7.19 (d, 2H, ArH, *J*=8.4 Hz), 7.18-7.16 (d, 2H, ArH, *J*=7.6 Hz), 5.56 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.9, 160.8, 154.5, 130.9, 128.9, 126.6, 124.7, 122.6, 121.8, 120.4, 118.4, 116.6, 66.8, 51.7,

13.5. MS (m/z): 547.6. Anal. Calcd. for $C_{25}H_{20}BrN_7O_3$: C, 54.96; H, 3.69; N, 17.94. Found: C, 54.82; H, 3.68; N, 17.94.

6-Bromo-2-p-tolyl-imidazo [1,2-a]pyridine-3-carbaldehyde-O-[1-(4-cyanobenzyl)-1H-1,2,3-triazol-4-yl]methyl oxime (**P_{123}**): FTIR (ATR, cm^{-1}): 3114, 3017, 2910, 2196, 1601, 1480, 1244. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.09-9.08 (d, 1H, ArH, *J*=2.0 Hz), 8.48 (s, 1H, -CH=N), 8.46 (s, 1H, ArH), 8.11-8.09 (d, 2H, ArH, *J*=8.0 Hz), 7.63-7.61 (d, 1H, ArH, *J*=9.2 Hz), 7.56-7.53 (d, 1H, ArH, *J*=9.2 Hz), 7.47-7.46 (d, 2H, ArH, *J*=7.2 Hz), 7.20-7.18 (d, 2H, ArH, *J*=8.0 Hz), 7.18-7.16 (d, 2H, ArH, *J*=7.2 Hz), 5.56 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.0, 154.6, 150.2, 131.2, 129.6, 127.6, 125.4, 123.3, 122.6, 121.8, 119.2, 118.4, 116.2, 66.8, 51.6, 13.3. MS (m/z): 527.7. Anal. Calcd. for $C_{26}H_{20}BrN_7O$: C, 59.32; H, 3.83; N,18.63. Found: C, 59.20; H, 3.84; N, 18.64.

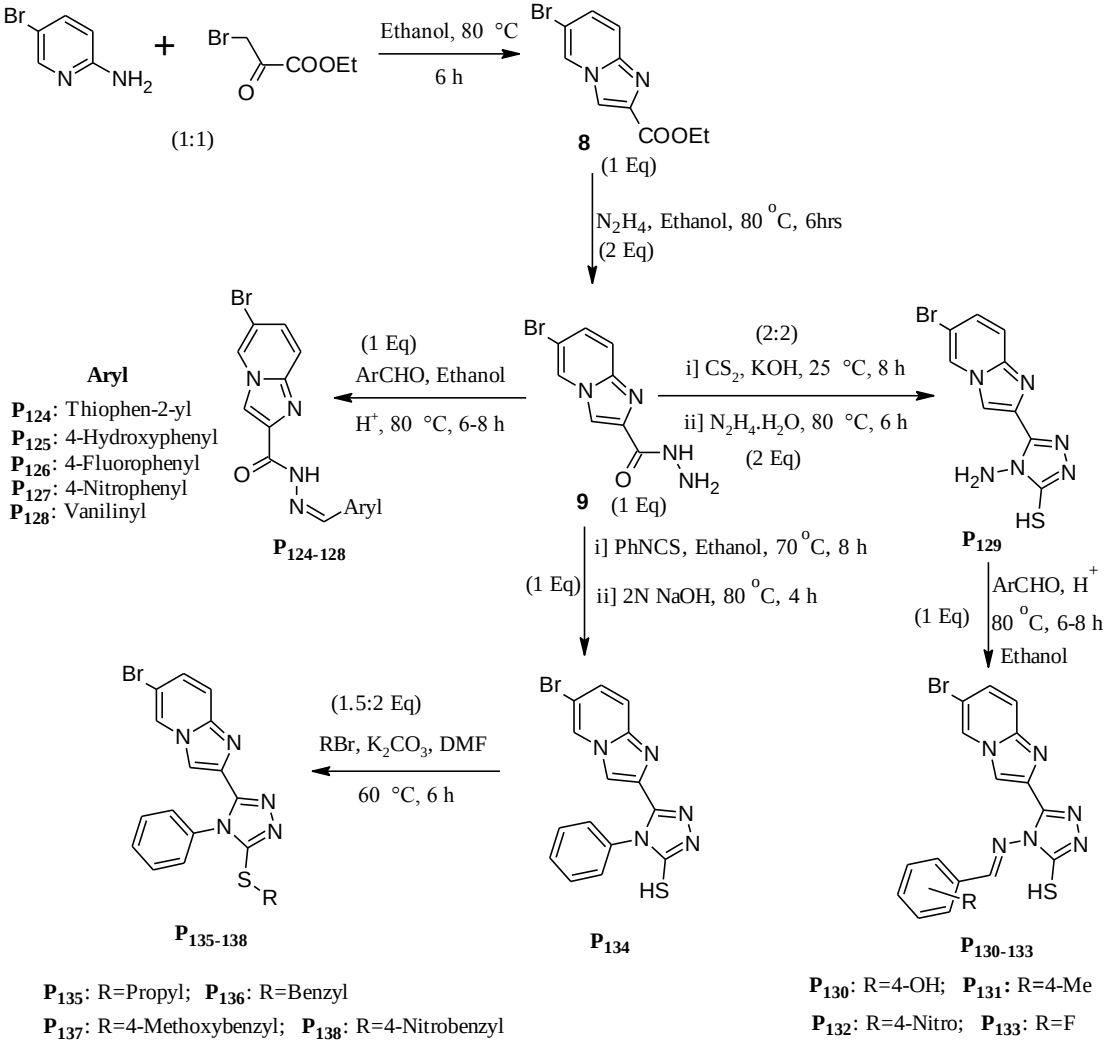
3.3.5 Synthesis of new imidazo[1,2-a]pyridine-2-carbohydrazide derivatives (**$P_{124\text{-}138}$**)

Fifteen new 6-bromoimidazo[1,2-a]pyridine derivatives carrying hydrazone (**$P_{124\text{-}128}$**) and 1,2,4-triazole pharmacophores (**$P_{129\text{-}138}$**) were synthesized by simple reaction routes.

3.3.5.1 Chemistry

The reaction sequence employed for the synthesis of target hydrazones **$P_{124\text{-}128}$**, and 1,2,4-triazole derivatives **$P_{130\text{-}133}$**, **$P_{135\text{-}138}$** is given in Scheme 3.7. The imidazo[1,2-a]pyridine-2-carboxylate derivative **8** was synthesized by refluxing 5-bromo-2-aminopyridine with ethyl bromopyruate in ethanol medium. The solid ester product thus obtained was later refluxed with hydrazine hydrate to attain active scaffold hydrazide **9**. The hydrazide **9** was reacted with appropriate aromatic aldehydes in presence of a drop of conc. sulphuric acid as a dehydrating agent, to get a set of hydrazones **$P_{124\text{-}128}$**. On the other hand, hydrazide **9** was stirred at room temperature with carbon disulfide and potassium hydroxide to obtain corresponding potassium carbodithioate. The potassium salt thus obtained *in situ*, was later cyclised to 4-amino-4H-1,2,4-triazole-3-thiol derivative **P_{129}** by refluxing with hydrazine hydrate under ethanol media for 6 h. The free amine group of **P_{129}** was condensed with different aromatic aldehydes in presence of acidic catalyst to get Schiff bases **$P_{130\text{-}133}$**. Similarly, hydrazide **9** was refluxed with phenyl isothiocyanate under ethanol medium to get

thiosemicarbazide intermediate that was later cyclised to 4-phenyl-1,2,4-triazole-3-thiol derivative **P_{134}** by stirring with 2N NaOH at 80 ^{o}C. The free thiol group of **P_{134}** was alkylated with appropriate alkyl/benzyl halides in presence of potassium carbonate to afford alkylated 1,2,4-triazoles **$P_{135\text{-}138}$**. All the newly synthesized intermediates and target compounds were purified by either recrystallization or by column chromatography technique.



Scheme 3.7: Synthetic routes for target compounds **$P_{124\text{-}138}$**

3.3.5.2 Results and discussion

The structures of new derivatives were confirmed by their FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral studies followed by elemental analysis data. The cyclization of 5-bromo-2-aminopyridine into 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (**8**) was

confirmed by their FTIR and ^{1}H NMR spectral studies. In the FTIR spectrum of compound **8**, the peaks due to amine and ketonic groups of starting materials, viz. 5-bromo-2-aminopyridine and ethyl bromopyruvate, respectively disappeared, while a new peak at 1697 cm^{-1} corresponding to ester carbonyl group appeared. Similarly, its ^{1}H NMR spectrum displayed two singlets at δ 8.94 and 8.37 ppm, corresponding to two aromatic protons present at position-5 and position-3, respectively. These two protons resonated at down field, because of the inductive field effect offered by adjacent electronegative nitrogen atom. Also, appearance of a quartet and a triplet at δ 4.00 and 0.96 ppm clearly confirms the presence of ethyl carboxylate group. In the FTIR spectrum of **9**, new peaks at 3448, 3256 and 3159 cm^{-1} have appeared corresponding to hydrazidic NH and NH_2 groups, respectively. On the other hand, a downshift in the carbonyl stretching frequency was observed from 1697 to 1677 cm^{-1}, when ester was converted to hydrazide. The ^{1}H NMR spectrum of compound **9** showed a new peak at δ 9.89 ppm corresponding to CONH proton, while NH_2 peak appeared at δ 4.28 ppm. The complete disappearance of quartet and a triplet peak of ethyl carboxylate group of compound **8** and appearance of two characteristic peaks corresponding to NH and NH_2 protons, clearly confirm the conversion of **8** to **9**.

In the FTIR spectrum of $\mathbf{P_{124}}$, the peak due to NH_2 group of hydrazide **9** has disappeared, while peak due to NH stretching has shifted from 3448 to 3297 cm^{-1}. Similarly, the carbonyl stretching peak has shifted from 1677 to 1670 cm^{-1}, upon coupling with thiophene-2-aldehyde, which evidences the formation of hydrazone $\mathbf{P_{124}}$. In the same way, a down field shift was observed in the ^{1}H NMR spectrum of compound $\mathbf{P_{124}}$ for NH peak, while a new prominent peak has appeared at δ 8.55 ppm corresponding to vinylic proton of imine group, which clearly confirms the proposed structure. This was further evidenced by its mass spectral data wherein a mass peak of 350.7 (M+H) was observed which is in accordance with its molecular formula $C_{13}H_9BrN_4OS$.

The cyclization of hydrazide **9** into 4-amino-1,2,4-triazole-3-thiol $\mathbf{P_{129}}$ was confirmed by its ^{1}H NMR spectrum (Figure 3.41), which showed characteristic peaks at δ 13.88 and 5.91 ppm corresponding to tautomaric HN(C=S) and NH_2 protons, respectively. The appearance of peak at δ 13.88 ppm due to NH group clearly shows that keto tautomeric form of triazole is more stable than thiol form. In the ^{1}H NMR

spectrum of **P_{130}**, the amine peak of **P_{129}** at δ 5.91 ppm has disappeared, while a new peak has appeared at δ 9.51 ppm that corresponds to CH=N proton, confirming the conversion of amine into imine. Appearance of another new peak at δ 10.41 ppm corresponding to phenolic group further confirms the conversion. Synthesis of 4-phenyl-1,2,4-triazol-3-thiol derivative **P_{134}** was evidenced by its ^{1}H NMR spectrum, where peaks due to NH and NH_2 protons of hydrazide **9** have disappeared, while new peaks corresponding to phenyl ring and thiol group present on triazole ring have appeared at δ 7.5-7.1 and 2.07 ppm, respectively. Upon alkylation with propyl bromide, the ^{1}H NMR spectrum of product **P_{135}** displayed three characteristic peaks at δ 3.88, 1.67 and 0.97 ppm corresponding to two methylene and the terminal methyl groups of propyl chain. Its ^{13}C NMR spectrum showed peaks at δ 53.0, 20.77, 10.86 ppm attributing to those alkyl protons, respectively confirming the conversion. In the same way, the structures of all the final compounds were confirmed by their characterization data and are summarized in the experimental section. The physio-chemical properties of these target compounds are tabulated in Table 3.7. The FTIR, ^{13}C NMR and mass spectra of compound **P_{129}** are given in Figure 3.40, 3.42 and 3.43, respectively.

Table 3.7: Physical data of target compounds **$P_{124\text{-}138}$**

Sample	R/Aryl	Mol. Formula	Yield (%)	M.P. (^{o}C)
P_{124}	Thiophen-2-yl	$C_{13}H_9BrN_4OS$	86	277-279
P_{125}	4-Hydroxyphenyl	$C_{15}H_{11}BrN_4O_2$	88	>300
P_{126}	4-Fluorophenyl	$C_{15}H_{10}BrFN_4O$	91	>300
P_{127}	4-Nitrophenyl	$C_{15}H_{10}BrN_5O_3$	82	>300
P_{128}	Vanilinyl	$C_{16}H_{13}BrN_4O_3$	85	257-260
P_{129}	-	$C_9H_7BrN_6S$	78	239-242
P_{130}	4-Hydroxy	$C_{16}H_{11}BrN_6OS$	82	213-215
P_{131}	4-Methyl	$C_{17}H_{13}BrN_6S$	84	231-234
P_{132}	4-Nitro	$C_{16}H_{10}BrN_7O_2S$	79	>300
P_{133}	4-Fluoro	$C_{16}H_{10}BrFN_6S$	85	>300
P_{134}	-	$C_{15}H_{10}BrN_5S$	80	138-140
P_{135}	Propyl	$C_{18}H_{16}BrN_5S$	86	181-184
P_{136}	Benzyl	$C_{22}H_{16}BrN_5S$	82	163-165
P_{137}	4-Methoxybenzyl	$C_{23}H_{18}BrN_5OS$	76	207-210
P_{138}	4-Nitrobenzyl	$C_{22}H_{15}BrN_6O_2S$	75	264-267

3.3.5.3 Experimental procedures

In the following sections, the synthetic procedures and the characterization data of target compounds **$P_{124-138}$** are given.

Procedure for the synthesis of ethyl 6-bromo-imidazo[1,2-a]pyridine-2-carboxylate (**8**): A mixture of 5-bromo-2-aminopyridine (1 g, 5.78 mmol) and ethyl bromopyruvate (1.13 g, 5.78 mmol) in 15 mL of ethanol was refluxed for 6 h. The solvent was removed under reduced pressure and resulting crude product was quenched into ice cold water with stirring. The solid product was isolated by filtration and dried. The product was later recrystallized from ethyl acetate to obtain pure product.

Yield 84%, M.P. 63-65 ^{o}C. FTIR (ATR, cm^{-1}): 2897, 2846, 1697, 1538, 1213. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.94 (s, 1H, ArH), 8.37 (s, 1H, CH), 7.56-7.53 (d, 1H, ArH, *J*=12 Hz), 7.38-7.35 (d, 1H, ArH, *J*=12 Hz), 4.00-3.97 (q, 2H, CH_2, *J*=8, 4 Hz), 0.96-0.91 (t, 3H, CH_3, *J*=10 Hz). ^{13}NMR (100 MHz, DMSO-d_6, δ ppm): 169.7, 150.7, 142.7, 139.3, 124.1, 123.3, 117.6, 115.3, 61.8, 13.8. MS (m/z): 270.1. Anal. Calcd. for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.55; H, 3.38; N, 10.40.

Procedure for the synthesis of 6-bromo-imidazo[1,2-a]pyridine-2-carbohydrazide (**9**): The ethyl carboxylate derivative **8** (0.8 g, 2.97 mmol) was refluxed with hydrazine hydrate (0.3g, 6.0 mmol) in ethanolic media for about 6 h. Upon completion of reaction, the reaction mixture was cooled in deep freezer so as to get solid product **9**, that later was filtered, dried and recrystallized from ethanol.

Yield 81%, M.P. 183-186 ^{o}C. FTIR (ATR, cm^{-1}): 3448, 3256, 3159, 3065, 1677, 1627, 1561, 1476, 1279. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.89 (s, 1H, NH), 8.60 (s, 1H, ArH), 8.23 (s, 1H, CH), 7.77-7.44 (d, 1H, ArH, *J*=9.2 Hz), 7.19-7.17 (d, 1H, ArH, *J*=9.2 Hz), 4.28 (s, 2H, NH_2). ^{13}NMR (100 MHz, DMSO-d_6, δ ppm): 165.3, 150.8, 140.3, 138.7, 126.3, 124.7, 118.7, 116.4. MS (m/z): 257.3. Anal. Calcd. for $C_8H_7BrN_4O$: C, 37.67; H, 2.77; N, 21.97. Found: C, 37.63; H, 2.75; N, 21.98.

General procedure for the synthesis of hydrazones (**$P_{124-128}$**): The hydrazide **9** (0.5 g, 1.96 mmol) was treated with thiophene-2-aldehyde (0.22 g, 1.96 mmol) in 10 mL of ethanol solution. A drop of concentrated sulphuric acid was added as a dehydrating

agent and the solution was refluxed for 6 h. The reaction vessel was cooled to room temperature and the precipitated product was collected by filtration. The product was washed well with ethanol and was purified by column chromatographic technique using methanol-chloroform eluting system. Remaining derivatives **$P_{125-128}$** were also synthesized following similar procedures.

6-Bromo-N'-(thiophen-2-ylmethylene)-imidazo [1,2-a]pyridine-2-carbohydrazide (**P_{124}**): FTIR (ATR, cm^{-1}): 3297, 3077, 2925, 1670, 1592, 1549, 1476, 1199. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.89 (s, 1H, NH), 8.96 (s, 1H, ArH), 8.55 (s, 1H, CH), 8.46 (s, 1H, CH), 7.63-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.51-7.48 (d, 1H, ArH, *J*=9.2 Hz), 7.39-7.18 (m, 3H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.3, 158.2, 146.7, 141.8, 139.2, 131.2, 129.2, 127.1, 118.9, 117.6, 115.8, 107.3. MS (m/z): 350.6. Anal. Calcd. for $C_{13}H_9BrN_4OS$: C, 44.71; H, 2.60; N, 16.04. Found: C, 44.76; H, 2.61; N, 16.04.

N'-(4-Hydroxybenzylidene)-6-bromo-imidazo[1,2-a]pyridine-2-carbohydrazide (**P_{125}**): FTIR (ATR, cm^{-1}): 3323, 3283, 3092, 1668, 1599, 1516, 1434, 1274. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.90 (s, 1H, NH), 9.05 (s, 1H, OH), 8.96 (s, 1H, ArH), 8.57 (s, 1H, CH), 8.47 (s, 1H, CH), 7.71-7.69 (d, 2H, ArH, *J*=8.0 Hz), 7.63-7.60 (d, 1H, ArH, *J*=8.4 Hz), 7.51-7.49 (d, 1H, ArH, *J*=8.4 Hz), 7.22-7.20 (d, 2H, ArH, *J*=8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.3, 161.6, 150.2, 146.7, 142.3, 139.0, 130.7, 129.3, 127.4, 118.6, 116.1, 115.7, 107.3. MS (m/z): 360.3. Anal. Calcd. for $C_{15}H_{11}BrN_4O_2$: C, 50.16; H, 3.09; N, 15.60. Found: C, 50.08; H, 3.09; N, 15.61.

N'-(4-Fluorobenzylidene)-6-bromo-imidazo[1,2-a]pyridine-2-carbohydrazide (**P_{126}**): FTIR (ATR, cm^{-1}): 3300, 3137, 3070, 1665, 1600, 1552, 1488, 1201. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.94 (s, 1H, NH), 8.96 (s, 1H, ArH), 8.58 (s, 1H, CH), 8.46 (s, 1H, CH), 7.76-7.74 (d, 2H, ArH, *J*=8.4 Hz), 7.63-7.60 (d, 1H, ArH, *J*=9.6 Hz), 7.51-7.48 (d, 1H, ArH, *J*=9.6 Hz), 7.30-7.28 (d, 2H, ArH, *J*=8.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.2, 161.8, 158.1, 147.0, 142.4, 139.1, 131.0, 129.5, 127.4, 118.3, 115.9, 107.1. MS (m/z): 361.9. Anal. Calcd. for $C_{15}H_{10}BrFN_4O$: C, 49.88; H, 2.79; N, 15.51. Found: C, 49.79; H, 2.78; N, 15.51.

N'-(4-Nitrobenzylidene)-6-bromo-imidazo[1,2-a]pyridine-2-carbohydrazide (**P_{127}**): FTIR (ATR, cm^{-1}): 3297, 3077, 2925, 1670, 1592, 1549, 1476, 1334, 1199. ^{1}H NMR

(DMSO-d_6, 400 MHz, δ ppm): 11.95 (s, 1H, NH), 8.96 (s, 1H, ArH), 8.59 (s, 1H, CH), 8.46 (s, 1H, CH), 8.12-8.10 (d, 2H, ArH, *J*=8.4 Hz), 7.63-7.60 (d, 1H, ArH, *J*=9.2 Hz), 7.51-7.48 (m, 3H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.3, 161.9, 160.2, 147.3, 142.6, 139.3, 131.4, 128.9, 127.4, 118.7, 116.1, 107.2. MS (m/z): 389.2. Anal. Calcd. for $C_{15}H_{10}BrN_5O_3$: C, 46.41; H, 2.60; N, 18.04. Found: C, 46.32; H, 2.60; N, 18.03.

N'-(4-Hydroxy-3-methoxybenzylidene)-6-bromo-imidazo [1,2-a]pyridine-2-carbo hydrazide (**P_{128}**): FTIR (ATR, cm^{-1}): 3382, 3327, 3063, 2934, 1670, 1583, 1464, 1231. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 11.93 (s, 1H, NH), 9.10 (s, 1H, OH), 8.96 (s, 1H, ArH), 8.58 (s, 1H, CH), 8.45 (s, 1H, CH), 7.63-7.61 (d, 1H, ArH, *J*=8.8 Hz), 7.51-7.48 (d, 1H, ArH, *J*=8.8 Hz), 7.46-7.44 (d, 1H, ArH, *J*=7.6 Hz), 7.36 (s, 1H, ArH), 7.31-7.30 (d, 1H, ArH, *J*=7.6 Hz), 3.98 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 164.2, 161.4, 154.3, 150.2, 146.8, 142.3, 139.4, 130.6, 129.0, 127.5, 120.3, 118.6, 116.4, 107.2, 64.2. MS (m/z): 390.8. Anal. Calcd. for $C_{16}H_{13}BrN_4O_3$: C, 49.38; H, 3.37; N, 14.40. Found: C, 49.27; H, 3.38; N, 14.40.

Procedure for the synthesis of 4-amino-5-(6-bromoimidazo[1,2-a]pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**P_{129}**): An ethanolic solution of KOH was prepared by dissolving 0.2 g (3.6 mmol) of KOH in 10 mL of ethanol. To this solution, hydrazide **9** (0.5 g, 1.96 mmol) and carbon disulfide (0.3 g, 3.94 mmol) were added and the resulting mixture was stirred at ambient temperature for about 8 h to get potassium salt. Later, this mixture was stirred with hydrazine hydrate (0.2 g, 4 mmol) at reflux condition for 6 h. Upon completion of reaction, the solvent was removed and quenched in to ice cold water. The mixture was neutralized with hydrochloric acid to get solid product that later isolated by filtration. All the products were recrystallized from methanol-chloroform mixture.

FTIR (ATR, cm^{-1}): 3098, 2916, 2771, 1636, 1501, 1410, 1319, 1167. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.88 (s, 1H, H-NC=S), 9.06 (s, 1H, ArH), 8.55 (s, 1H, CH), 7.76-7.74 (d, 1H, ArH, *J*=8.4 Hz), 7.16-7.14 (d, 1H, ArH, *J*=8.4 Hz), 5.91 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 166.1, 142.7, 131.4, 129.3, 127.5, 118.4, 114.9, 106.8. MS (m/z): 312.7. Anal. Calcd. for $C_9H_7BrN_6S$: C, 34.74; H, 2.27; N, 27.01. Found: C, 34.64; H, 2.26; N, 27.02.

General procedure for the synthesis of Schiff bases (**$P_{130-133}$**): A mixture of triazole **P_{129}** (0.4 g, 1.29 mmol) with 4-hydroxy benzaldehyde (0.19 g, 1.5 mmol) in 10 mL of ethanol was refluxed for 6 h in presence of a drop of concentrated sulphuric acid. The product **P_{130}** that precipitated out during the course of reaction was filtered, washed with ethanol and dried. The crude product was recrystallized from ethylene dichloride to obtain pure compound. Similarly, other derivatives were also synthesized and recrystallized from ethylene dichloride.

4-((3-(6-Bromo-imidazo [1,2-a]pyridin-2-yl)-5-mercapto-4H-1,2,4-triazol-4-ylimino) methyl)phenol (**P_{130}**): FTIR (ATR, cm^{-1}): 3412, 3068, 2884, 2740, 1620, 1502, 1417, 1319, 1148, 1109. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.12 (s, 1H, NH), 10.41 (s, 1H, OH), 9.51 (s, 1H, CH), 9.07 (s, 1H, ArH), 8.40 (s, 1H, CH), 7.86-7.83 (d, 2H, ArH, *J*=8.8 Hz), 7.75-7.73 (d, 1H, ArH, *J*=8.4 Hz), 7.66-7.64 (d, 2H, ArH, *J*=8.8 Hz), 7.45-7.43 (d, 1H, ArH, *J*=8.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 177.1, 163.2, 161.9, 144.2, 132.0, 130.1, 129.1, 127.5, 122.7, 118.4, 115.7, 107.5. MS (m/z): 416.3. Anal. Calcd. for $C_{16}H_{11}BrN_6OS$: C, 46.28; H, 2.67; N, 20.24. Found: C, 46.15; H, 2.66; N, 20.24.

4-(4-Methylbenzylidene amino]-5-(6-bromoimidazo[1,2-a]pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**P_{131}**): FTIR (ATR, cm^{-1}): 3343, 2978, 2885, 2765, 1629, 1521, 1418, 1319, 1259, 1148. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.12 (s, 1H, NH), 9.51 (s, 1H, CH), 9.10 (s, 1H, ArH), 8.41 (s, 1H, CH), 7.75-7.70 (m, 3H, ArH), 7.45-7.43 (d, 1H, ArH, *J*=8.0 Hz), 7.23-7.21 (d, 2H, ArH, *J*=8.4 Hz), 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 176.5, 166.5, 163.2, 161.7, 145.0, 143.4, 131.4, 129.4, 127.5, 122.3, 121.4, 118.1, 115.1, 107.5, 14.3. MS (m/z): 414.1. Anal. Calcd. for $C_{17}H_{13}BrN_6S$: C, 49.40; H, 3.17; N, 20.33. Found: C, 49.28; H, 3.16; N, 20.34.

4-(4-Nitrobenzylideneamino)-5-(6-bromoimidazo [1,2-a]pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**P_{132}**): FTIR (ATR, cm^{-1}): 3189, 3031, 2954, 2834, 2772, 1618, 1545, 1247, 1164. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.15 (s, 1H, NH), 9.52 (s, 1H, CH), 9.17 (s, 1H, ArH), 8.41 (s, 1H, CH), 8.17-8.15 (d, 2H, ArH, *J*=8.8 Hz), 7.55-7.53 (d, 1H, ArH, *J*=9.2 Hz), 7.51-7.49 (d, 2H, ArH, *J*=8.8 Hz), 7.45-7.43 (d, 1H, ArH, *J*=9.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 176.5, 167.5, 164.3, 161.8, 160.4, 144.5, 143.2, 131.8, 131.0, 128.9, 127.8, 122.8, 116.7, 107.6. MS (m/z): 445.7. Anal.

Calcd. for $C_{16}H_{10}BrN_7O_2S$: C, 43.26; H, 2.27; N, 22.07. Found: C, 43.15; H, 2.25; N, 22.06.

4-(4-Fluorobenzylideneamino)-5-(6-bromoimidazo [1,2-a]pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**P_{133}**): FTIR (ATR, cm^{-1}): 3203, 3048, 2950, 2803, 2734, 1631, 1587, 1510, 1417, 1237. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.13 (s, 1H, NH), 9.51 (s, 1H, CH), 9.12 (s, 1H, ArH), 8.41 (s, 1H, CH), 7.86-7.84 (d, 2H, ArH, *J*=8.4 Hz), 7.51-7.49 (d, 1H, ArH, *J*=8.8 Hz), 7.45-7.43 (d, 1H, ArH, *J*=8.8 Hz), 7.37-7.35 (d, 2H, ArH, *J*=8.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 174.1, 165.4, 163.1, 159.6, 144.5, 142.7, 134.6, 129.7, 123.4, 121.3, 119.4, 115.4, 107.6. MS (m/z): 418.4. Anal. Calcd. for $C_{16}H_{10}BrFN_6S$: C, 46.06; H, 2.42; N, 20.14. Found: C, 45.94; H, 2.43; N, 20.14.

Procedure for the synthesis of 5-(6-bromoimidazo[1,2-a]pyridin-2-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**P_{134}**): The hydrazide **9** (0.5 g, 1.96 mmol) was refluxed with phenyl isothiocyanate (0.27 g, 1.96 mmol) in ethanol (10 mL) medium for 8 h. The resulting thiosemicarbazide derivatives was isolated through filtration, washed well with ethanol and dried. This intermediate was later treated with 2 mL of aqueous 2N NaOH and the resulting solution was stirred at 80 ^{o}C for about 4 h. The reaction mixture was cooled to room temperature and quenched to ice cold water while stirring. The mixture was neutralized with conc. hydrochloric acid and the precipitate thus obtained was filtered, washed with excess of cold water. The pure product **P_{134}** was obtained by recrystallizing crude compound from ethanol.

FTIR (ATR, cm^{-1}): 3073, 2361, 1648, 1595, 1529, 1501, 1454, 1357, 1232. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.96 (s, 1H, ArH), 8.42 (s, 1H, CH), 7.63-7.61 (d, 1H, ArH, *J*=9.6 Hz), 7.53-7.10 (m, 6H, ArH), 2.07 (s, 1H, SH). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 142.3, 139.2, 138.6, 129.4, 128.6, 130.0, 127.6, 124.7, 118.4, 115.7, 107.0. MS (m/z): 372.9. Anal. Calcd. for $C_{15}H_{10}BrN_5S$: C, 48.40; H, 2.71; N, 18.81. Found: C, 48.27; H, 2.70; N, 18.80.

General procedure for the synthesis of **$P_{135\text{-}138}$**: A mixture of **P_{134}** (0.4 g, 1.07 mmol), propyl bromide (0.2 g, 1.6 mmol) and potassium carbonate (0.3 g, 2.17 mmol) in dry DMF (10 mL) was stirred at 60 ^{o}C for 6 h. The reaction mixture was later quenched into ice-water with stirring. The precipitated product was filtered, washed with water

and dried. The compound was purified by column chromatography using hexane: ethyl acetate eluent system. In the same way, other compounds were synthesized and purified.

6-Bromo-2-(4-phenyl-5-(propylthio)-4H-1,2,4-triazol-3-yl)-imidazo [1,2-a]pyridine (**P_{135}**): FTIR (ATR, cm^{-1}): 3091, 2966, 2873, 1577, 1494, 1387, 1229. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.88 (s, 1H, ArH), 8.40 (s, 1H, CH), 7.60-7.18 (m, 7H, ArH), 3.88-3.83 (t, 2H, SCH_2, *J*=9.0 Hz), 1.67-1.59 (m, 2H, CH_2), 0.97-0.93 (t, 3H, CH_3, *J*=7.6 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.6, 154.6, 148.1, 143.6, 141.2, 130.7, 129.8, 126.0, 124.8, 122.6, 118.1, 113.7, 107.1, 53.0, 20.77, 10.86. MS (m/z): 415.3. Anal. Calcd. for $C_{18}H_{16}BrN_5S$: C, 52.18; H, 3.89; N, 16.90. Found: C, 52.03; H, 3.88; N, 16.90.

2-(5-(Benzylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-6-bromoimidazo [1,2-a]pyridine (**P_{136}**): FTIR (ATR, cm^{-1}): 3056, 2916, 1634, 1578, 1492, 1213. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.88 (s, 1H, ArH), 8.39 (s, 1H, CH), 7.54-7.10 (m, 12H, ArH), 4.84 (s, 2H, SCH_2). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.3, 160.2, 154.7, 148.6, 143.3, 130.6, 129.7, 127.4, 126.3, 125.0, 123.5, 118.7, 117.0, 115.6, 107.2, 68.4. MS (m/z): 463.6. Anal. Calcd. for $C_{22}H_{16}BrN_5S$: C, 57.15; H, 3.49; N, 15.15. Found: C, 57.06; H, 3.48; N, 15.14.

2-(5-(4-Methoxybenzyl thio)-4-phenyl-4H-1,2,4-triazol-3-yl)-6-bromoimidazo[1,2-a] pyridine (**P_{137}**): FTIR (ATR, cm^{-1}): 3000, 2938, 2834, 1632, 1579, 1503, 1238. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.87 (s, 1H, ArH), 8.39 (s, 1H, CH), 7.64-7.62 (d, 2H, ArH, *J*=8.4 Hz), 7.54-7.52 (d, 1H, ArH, *J*=9.2 Hz), 7.51-7.08 (m, 8H, ArH), 4.82 (s, 2H, SCH_2), 4.03 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.3, 159.6, 153.9, 147.6, 140.4, 138.7, 130.3, 128.7, 127.5, 124.3, 122.6, 121.0, 119.8, 107.6, 68.5, 63.7. MS (m/z): 493.5. Anal. Calcd. for $C_{23}H_{18}BrN_5OS$: C, 56.10; H, 3.68; N, 14.22. Found: C, 56.01; H, 3.69; N, 14.22.

2-(5-(4-Nitrobenzyl thio)-4-phenyl-4H-1,2,4-triazol-3-yl)-6-bromoimidazo[1,2-a] pyridine (**P_{138}**): FTIR (ATR, cm^{-1}): 3066, 1638, 1585, 1503, 1334, 1279. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.89 (s, 1H, ArH), 8.40 (s, 1H, CH), 8.14-8.12 (d, 2H, ArH, *J*=8.4 Hz), 7.64-7.62 (d, 2H, ArH, *J*=8.4 Hz), 7.54-7.52 (d, 1H, ArH, *J*=9.6 Hz), 7.51-7.09 (m, 6H, ArH), 4.85 (s, 2H, SCH_2). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm):

163.2, 161.2, 158.7, 154.6, 146.8, 140.1, 131.9, 19.8, 127.5, 125.4, 123.5, 121.5, 120.3, 119.5, 107.3, 68.6. MS (m/z): 508.6. Anal. Calcd. for $C_{22}H_{15}BrN_6O_2S$: C, 52.08; H, 2.98; N, 16.56. Found: C, 51.96; H, 2.99; N, 16.55.

The spectrograms of selected new intermediates and target compounds are given below.

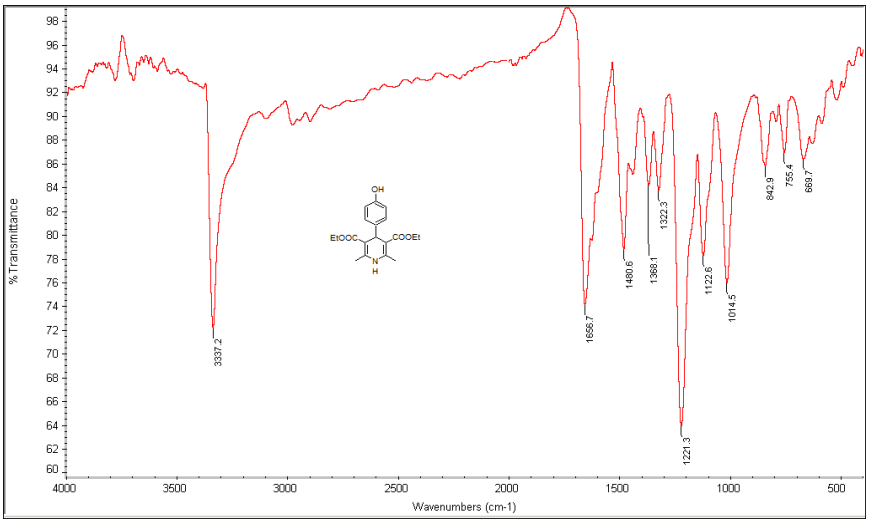


Figure 3.2: FTIR Spectrum of compound **1**

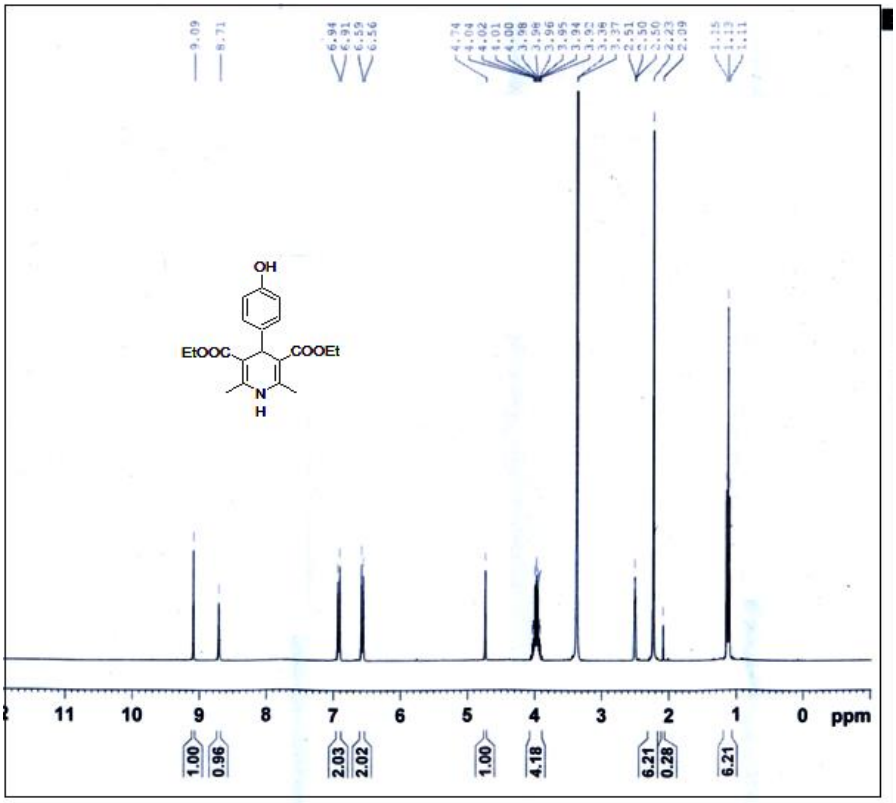


Figure 3.3: ^{1}H NMR spectrum of compound **1**

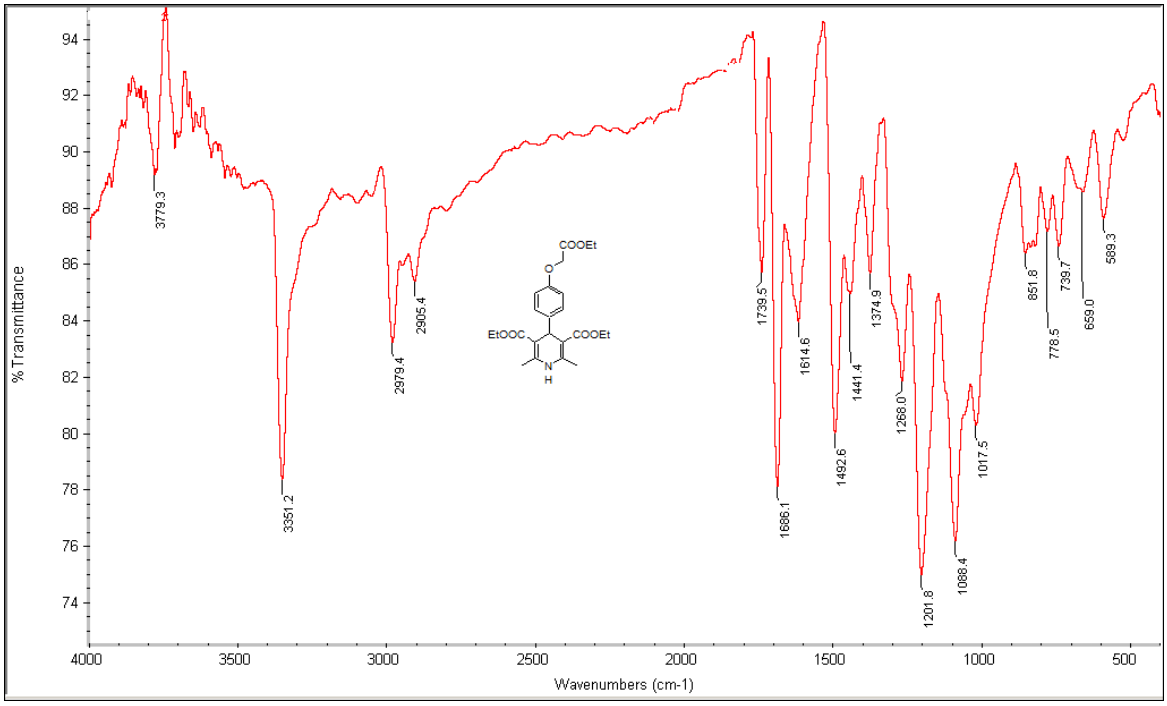


Figure 3.4: FTIR spectrum of compound **2**

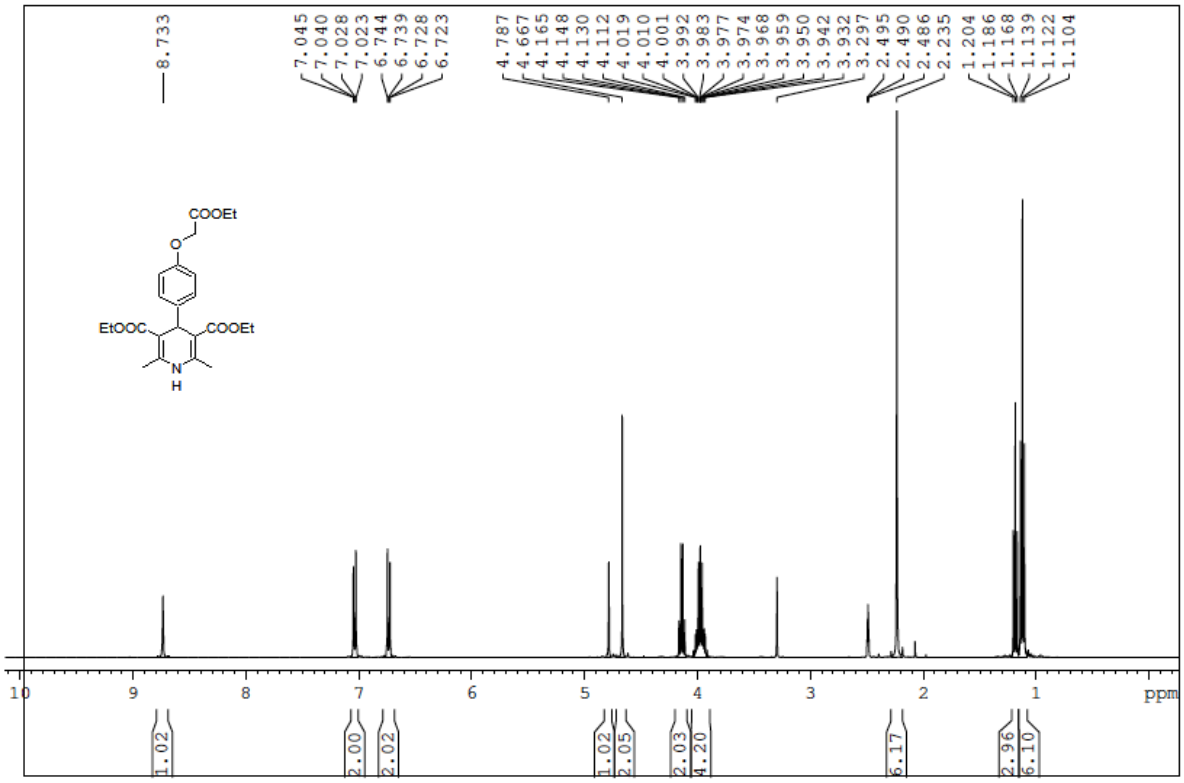


Figure 3.5: ^{1}H NMR spectrum of compound **2**

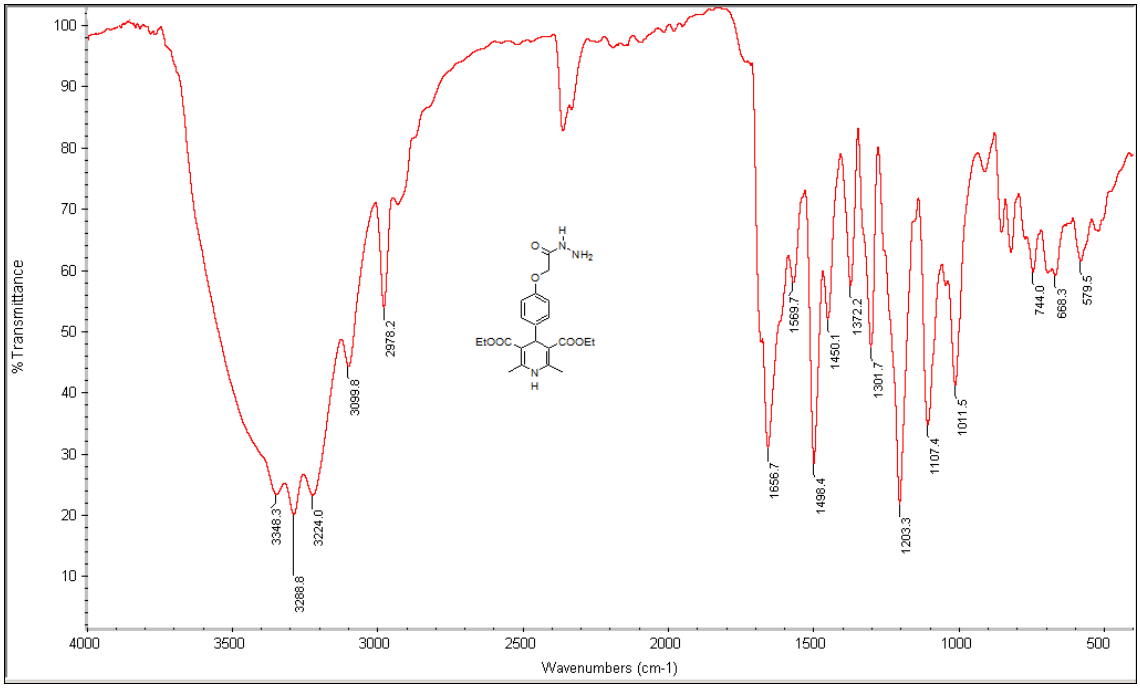


Figure 3.6: FTIR Spectrum of compound **3**

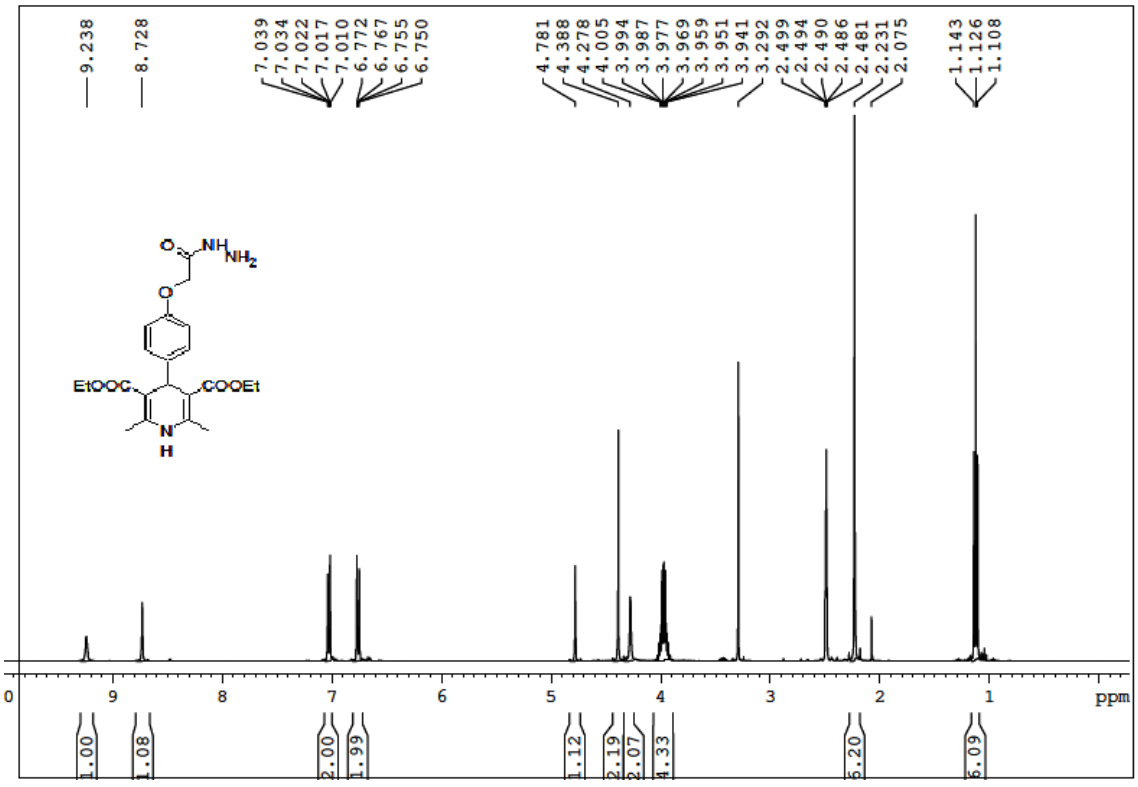


Figure 3.7: ^{1}H NMR spectrum of compound **3**

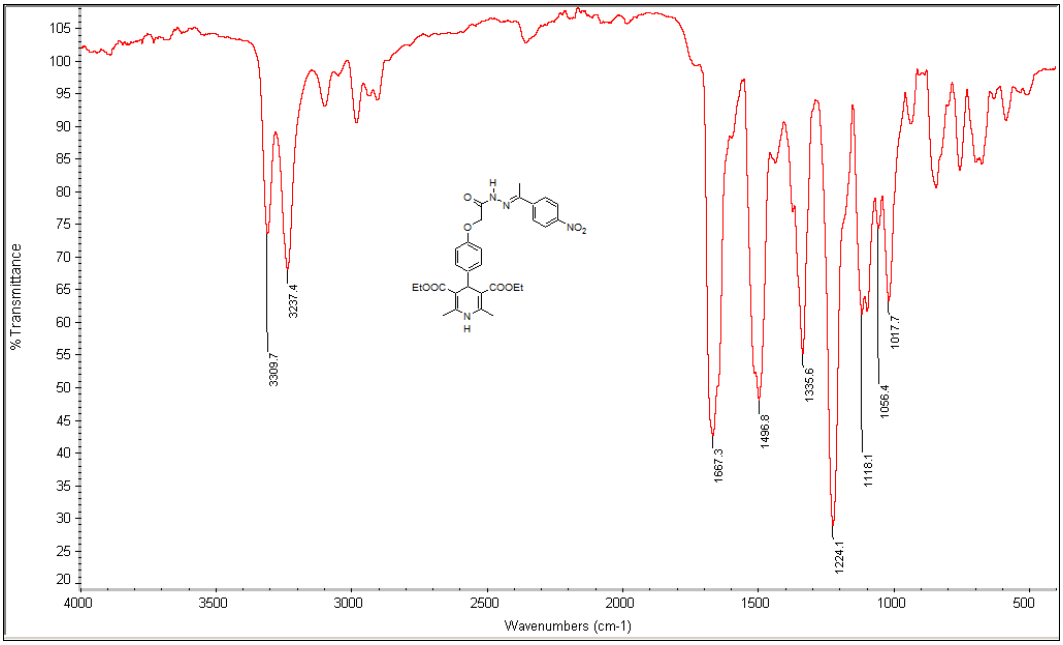


Figure 3.8: FTIR spectrum of compound **P_{20}**

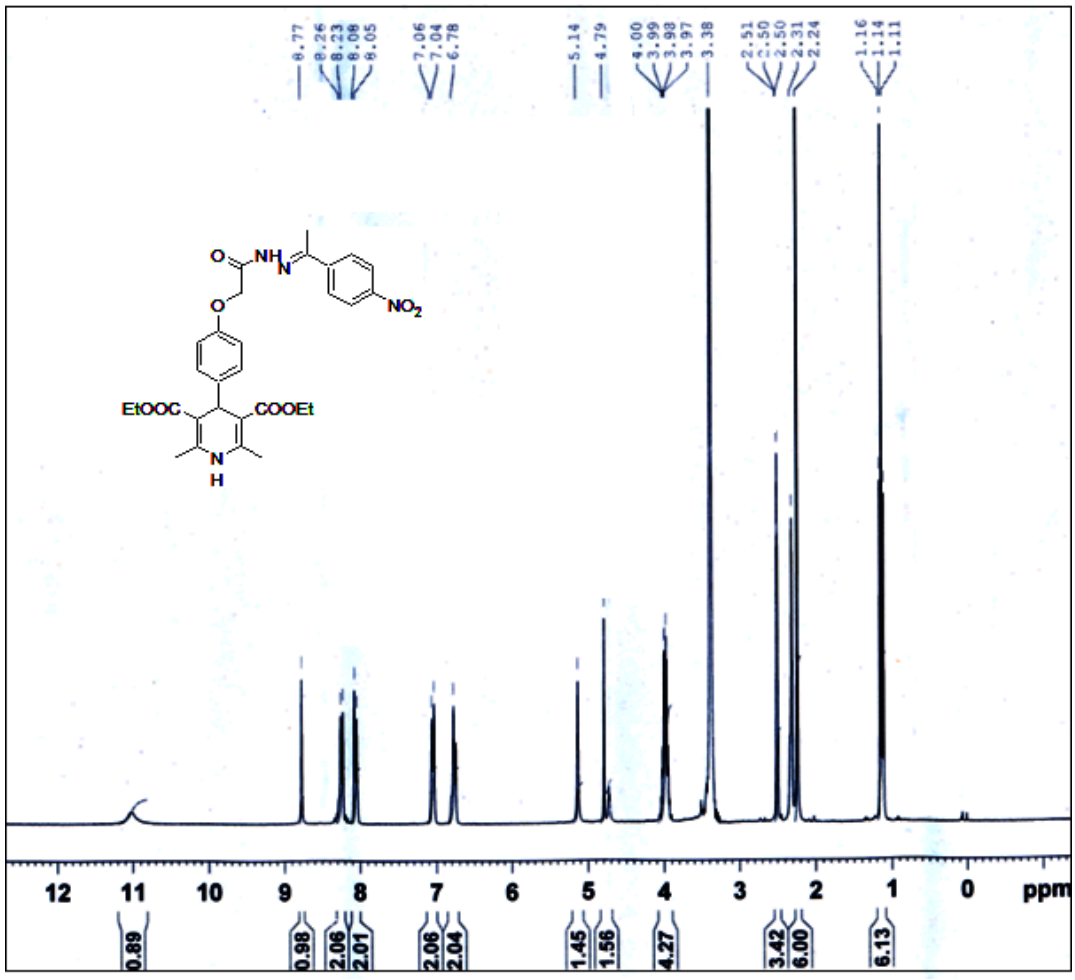


Figure 3.9: ^{1}H NMR spectrum of compound **P_{20}**

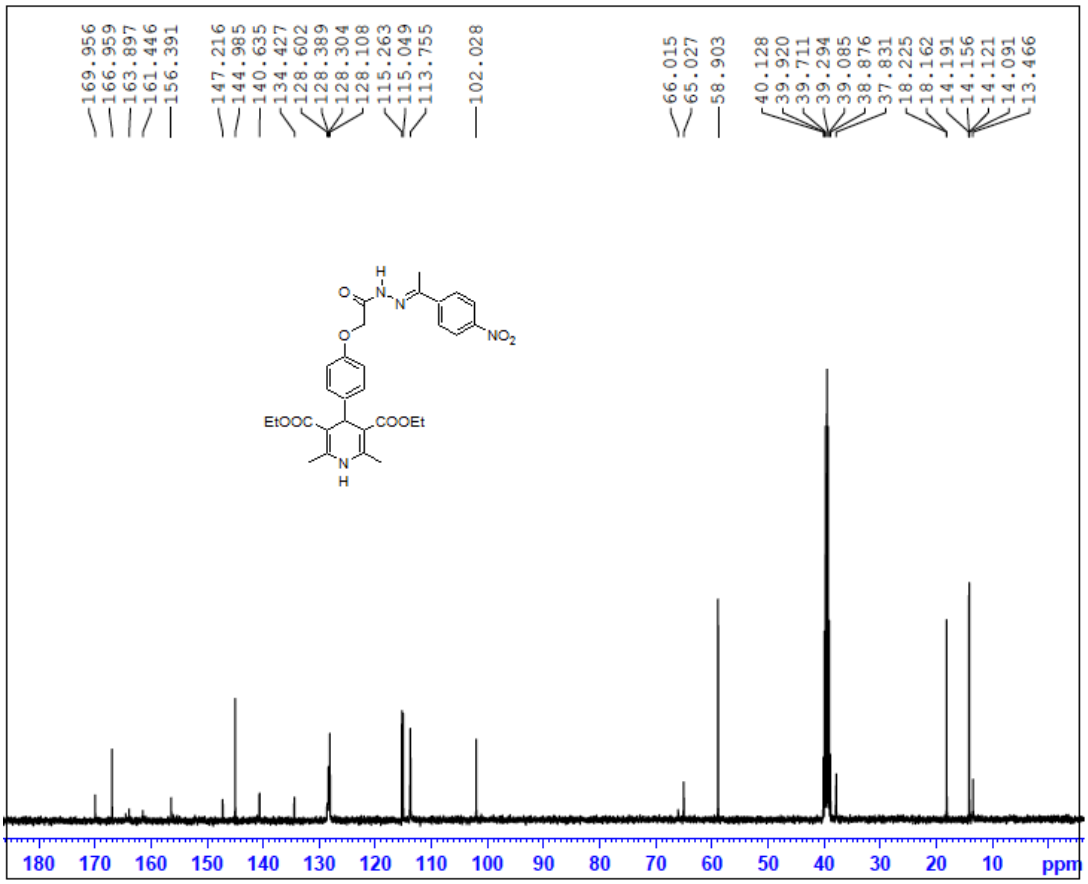


Figure 3.10: ^{13}C NMR spectrum of compound **P_{20}**

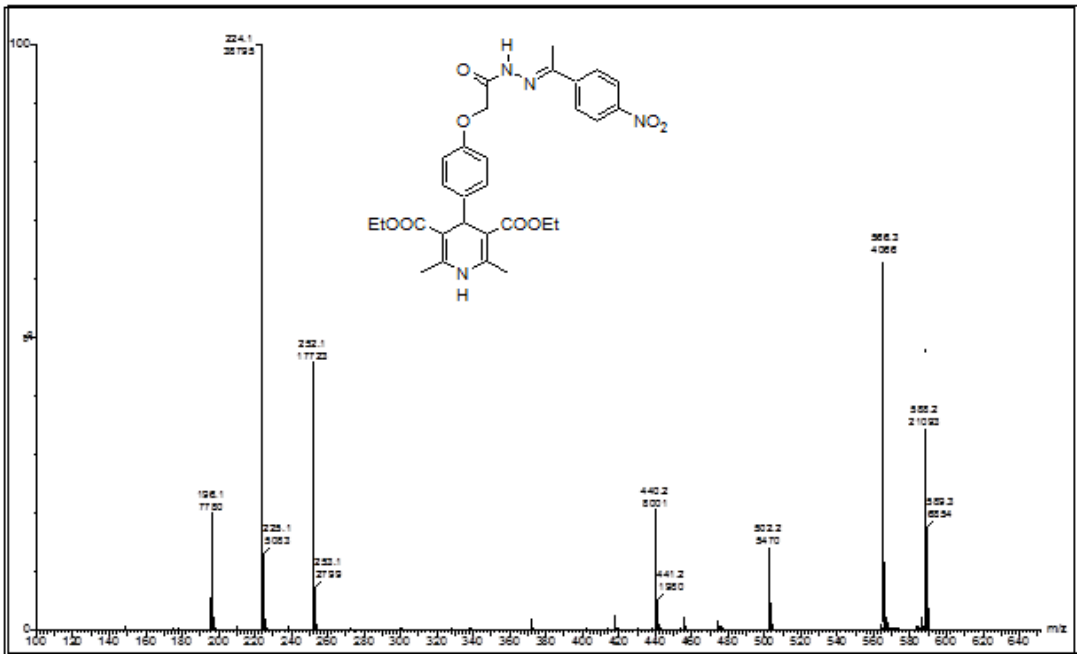


Figure 3.11: Mass spectrum of compound **P_{20}**

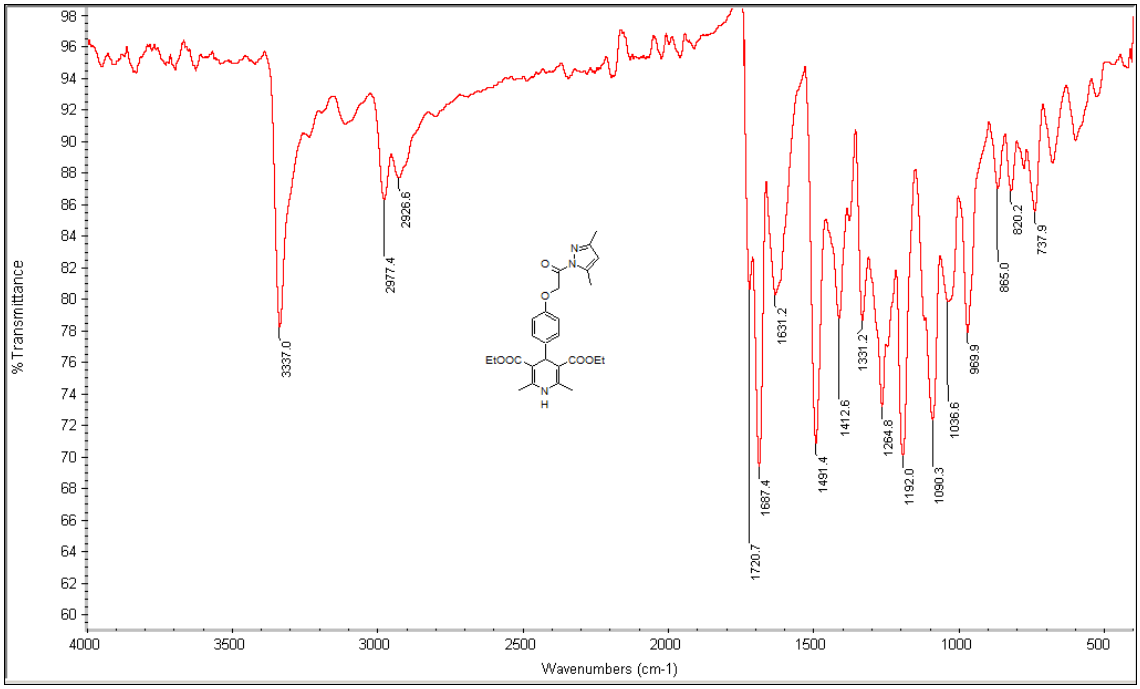


Figure 3.12: FTIR Spectrum of compound **P_{38}**

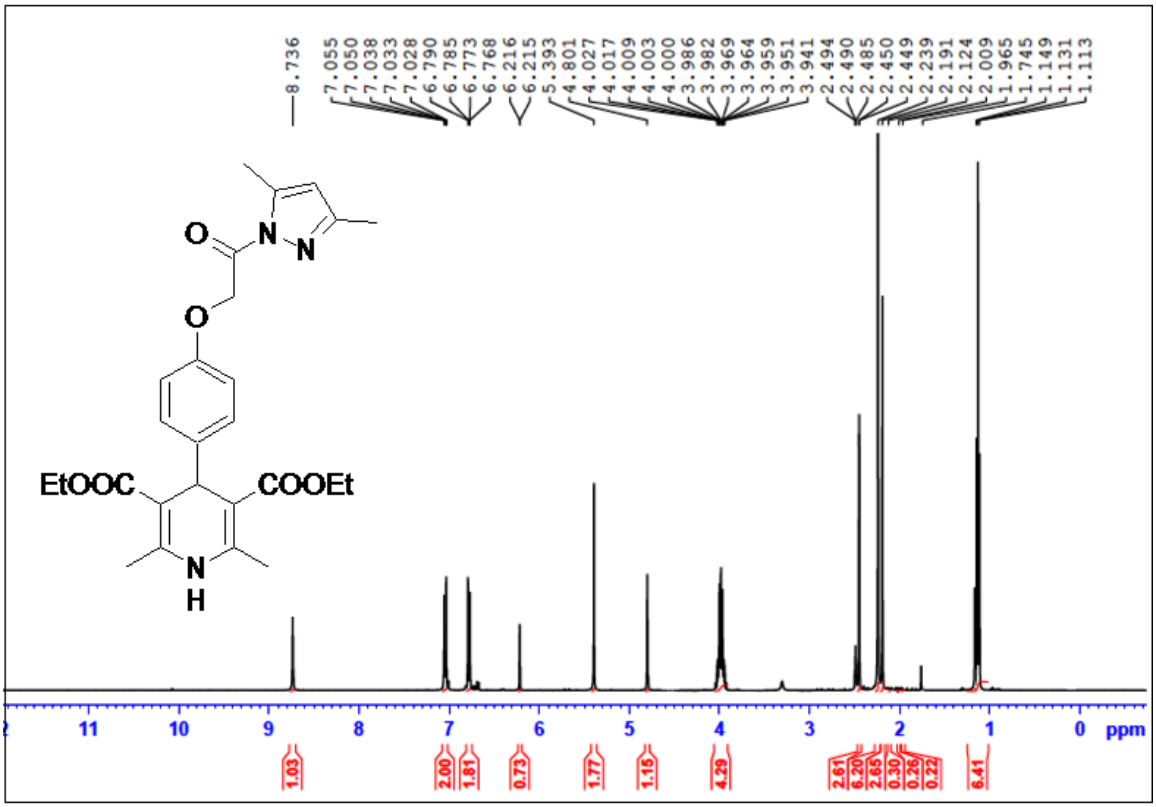


Figure 3.13: ^{1}H NMR spectrum of compound **P_{38}**

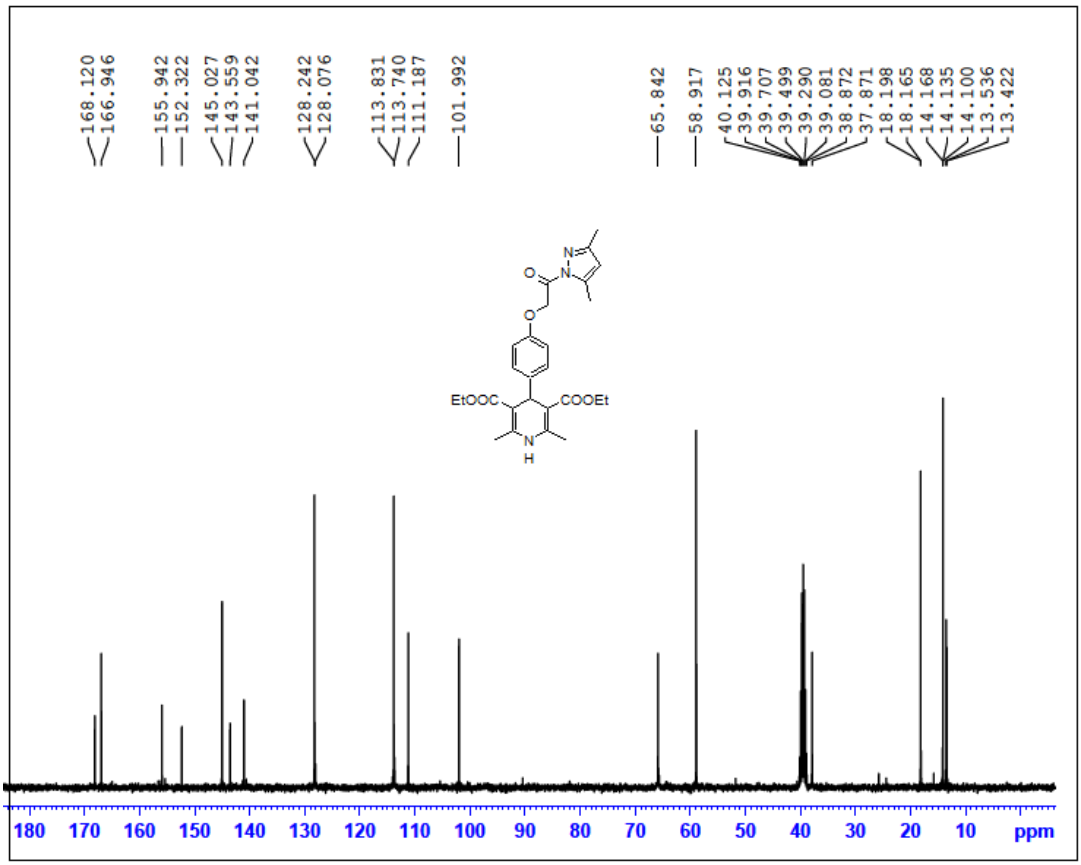


Figure 3.14: ^{13}C NMR spectrum of compound **P_{38}**

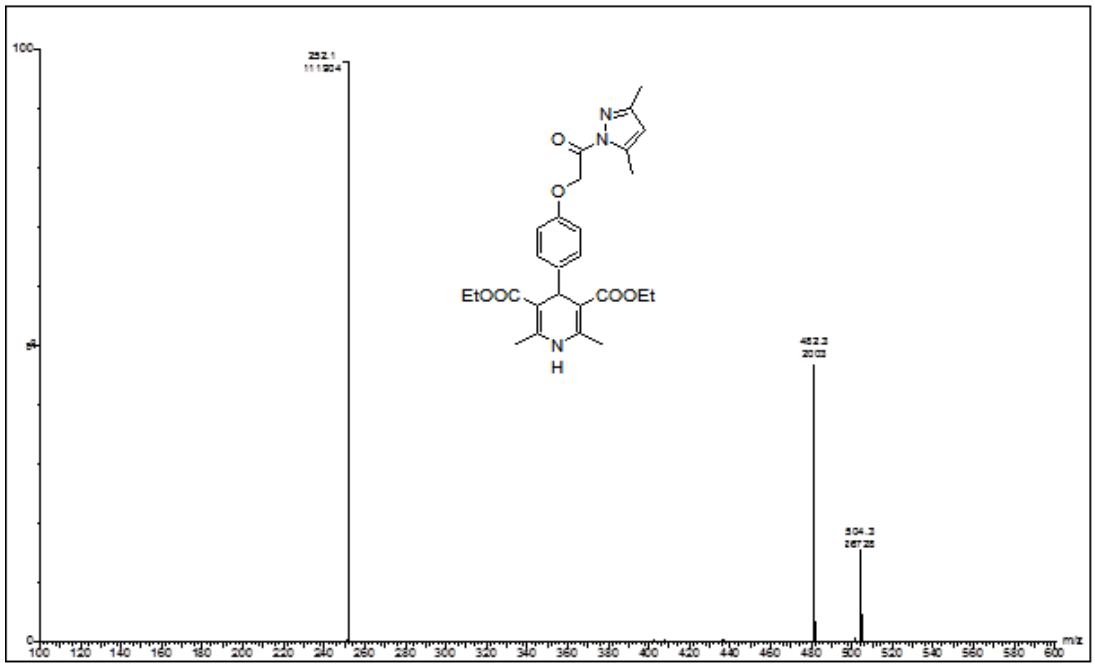


Figure 3.15: Mass spectrum of compound **P_{38}**

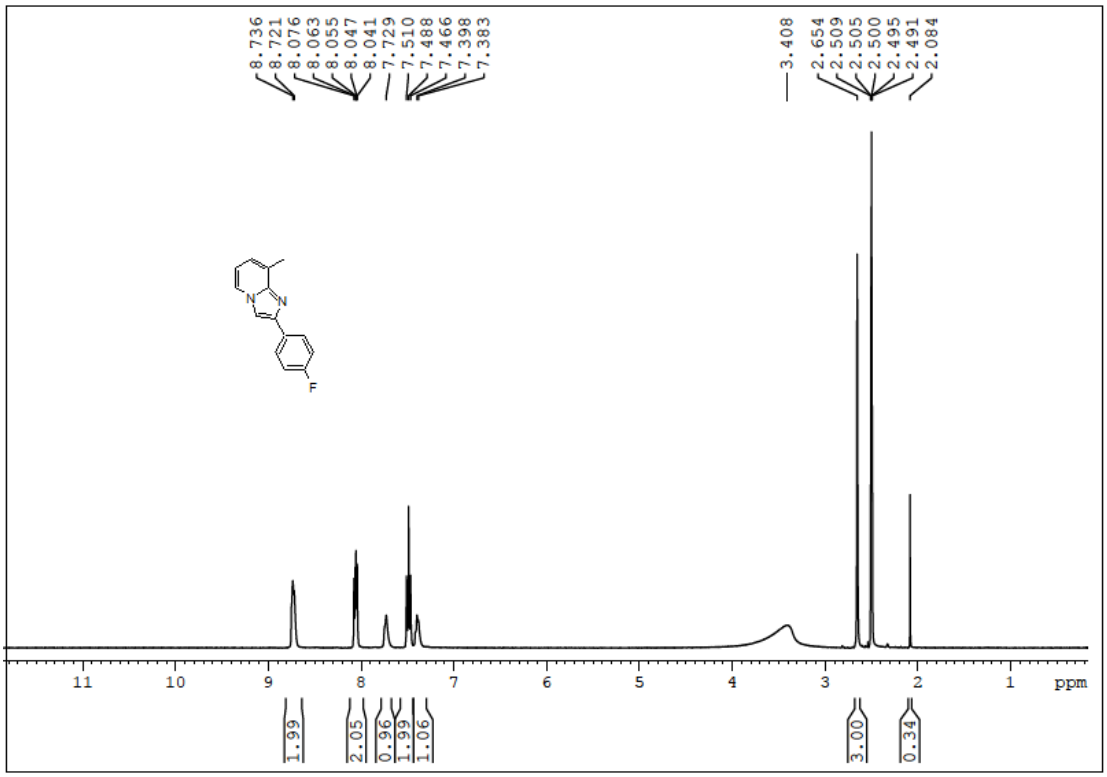


Figure 3.16: ^{1}H NMR spectrum of compound **5b**

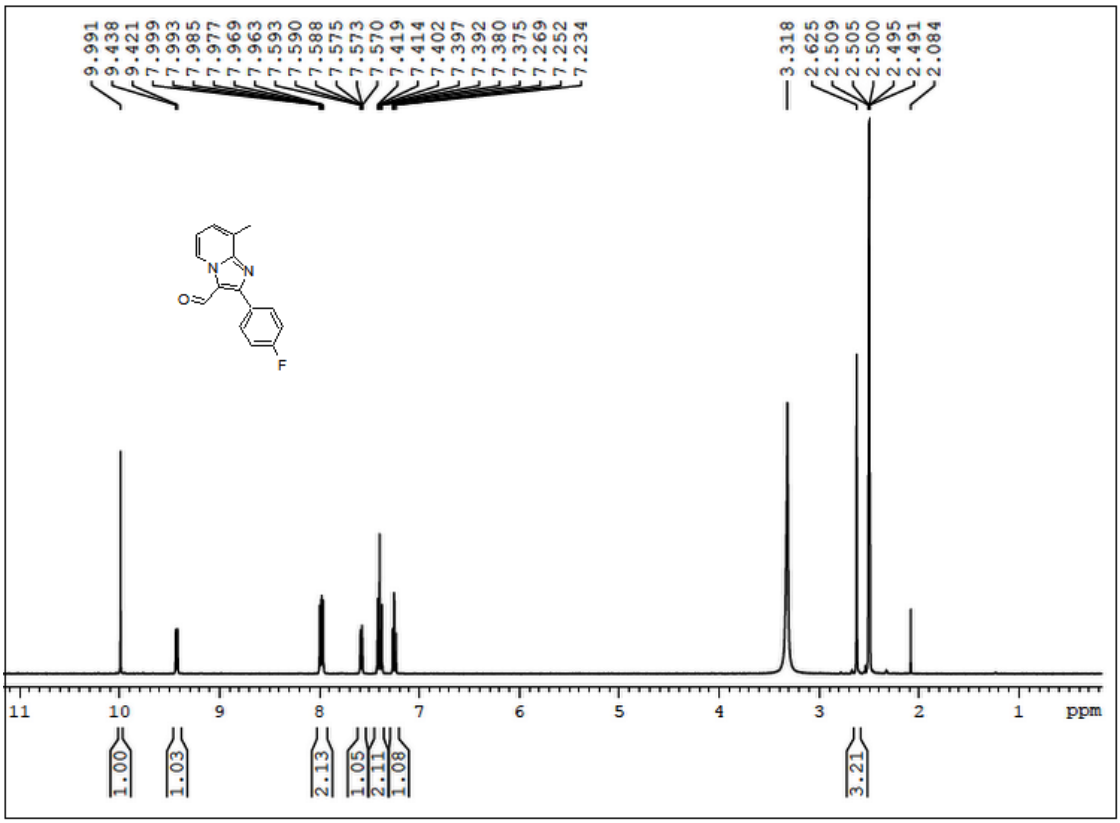


Figure 3.17: ^{1}H NMR spectrum of compound **6b**

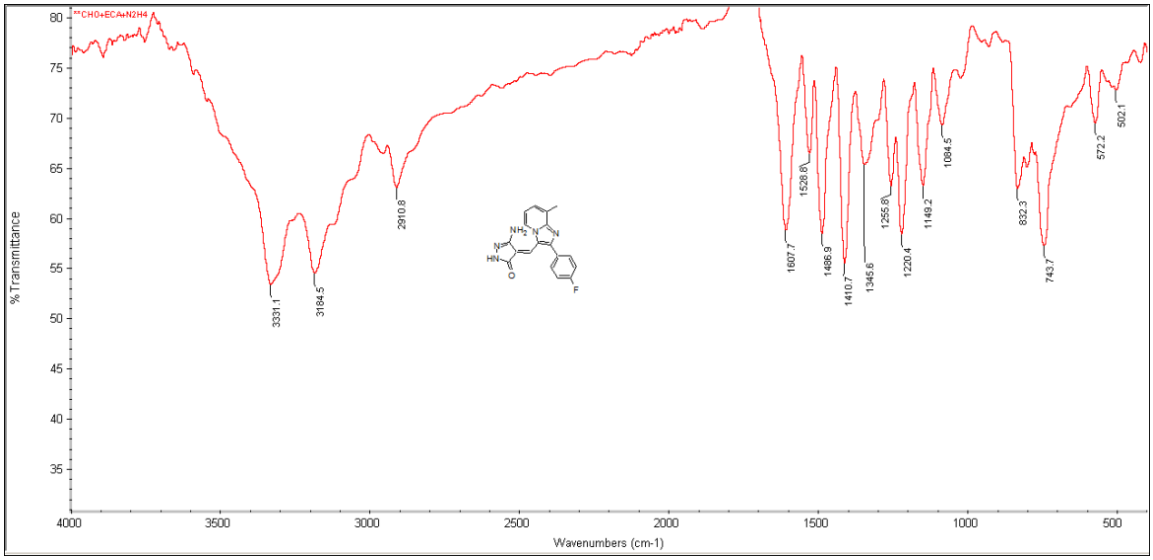


Figure 3.18: FTIR spectrum of compound **P_{63}**

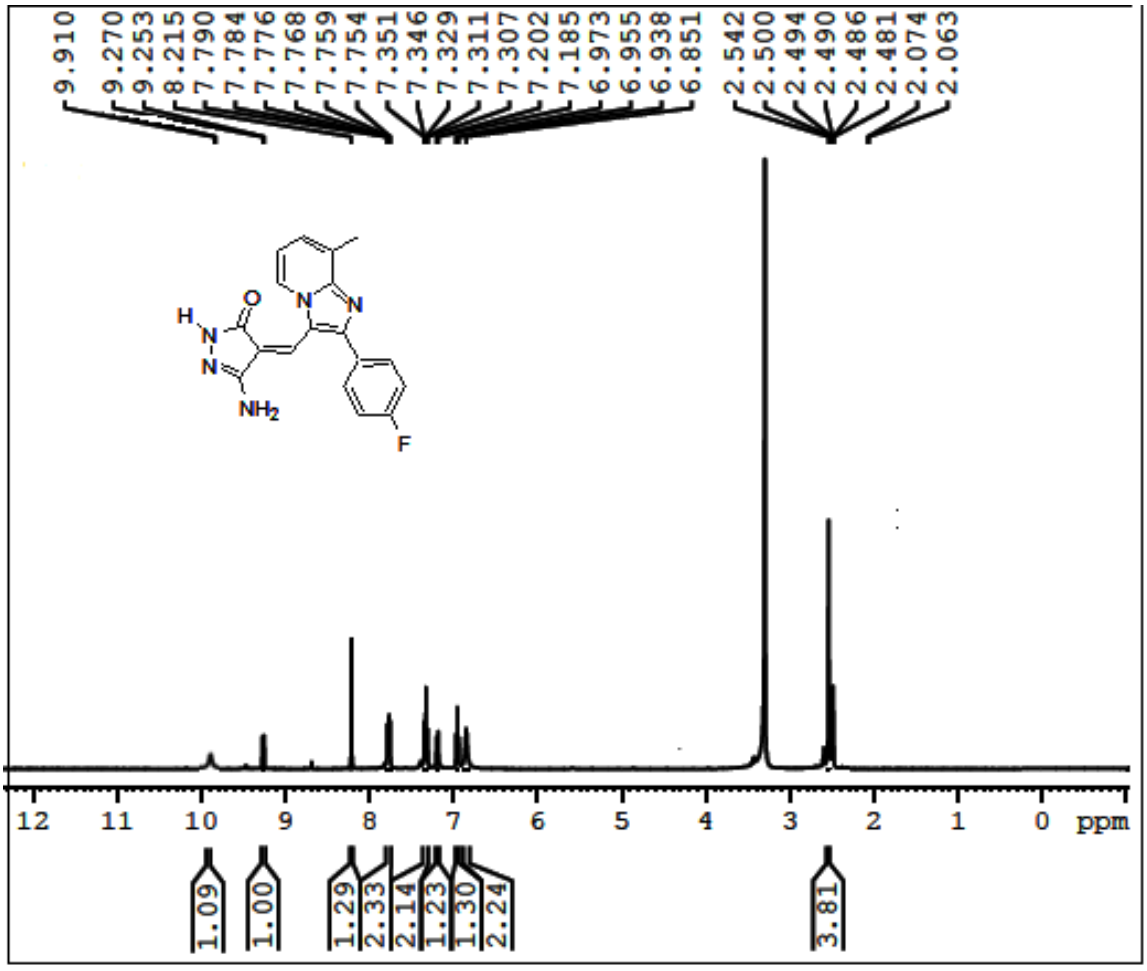


Figure 3.19: ^{1}H NMR spectra of compound **P_{63}**

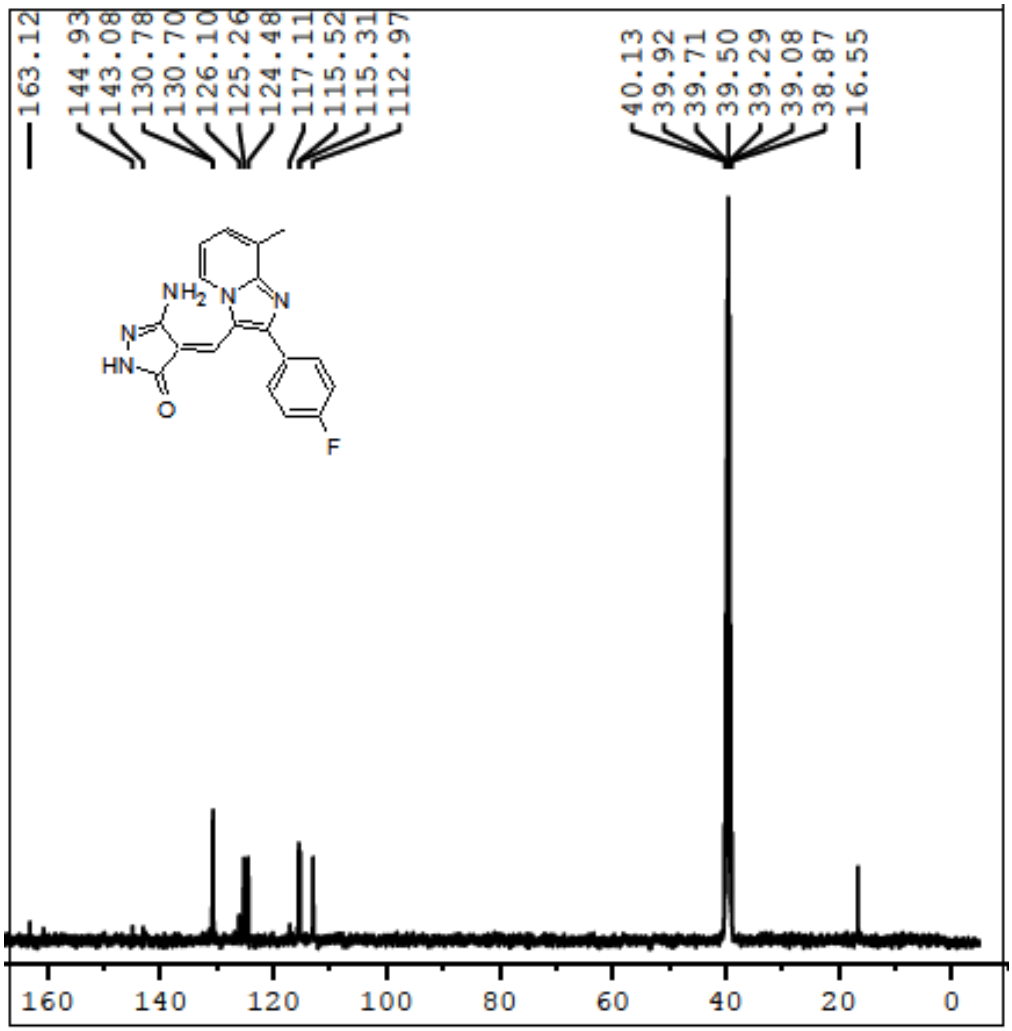


Figure 3.20: ^{13}C NMR spectrum of compound **P_{63}**

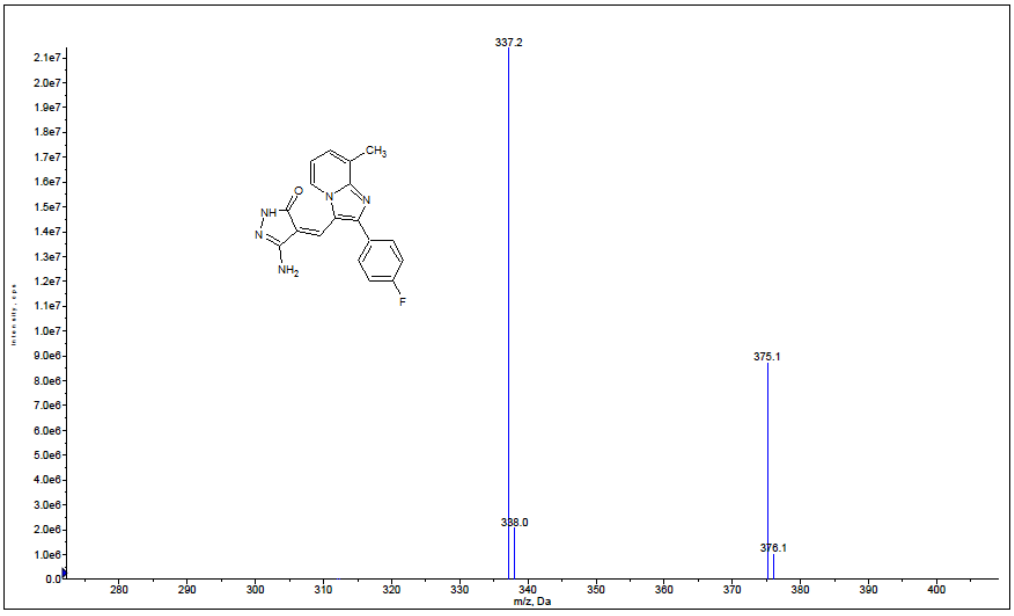


Figure 3.21: Mass spectrum of compound **P_{63}**

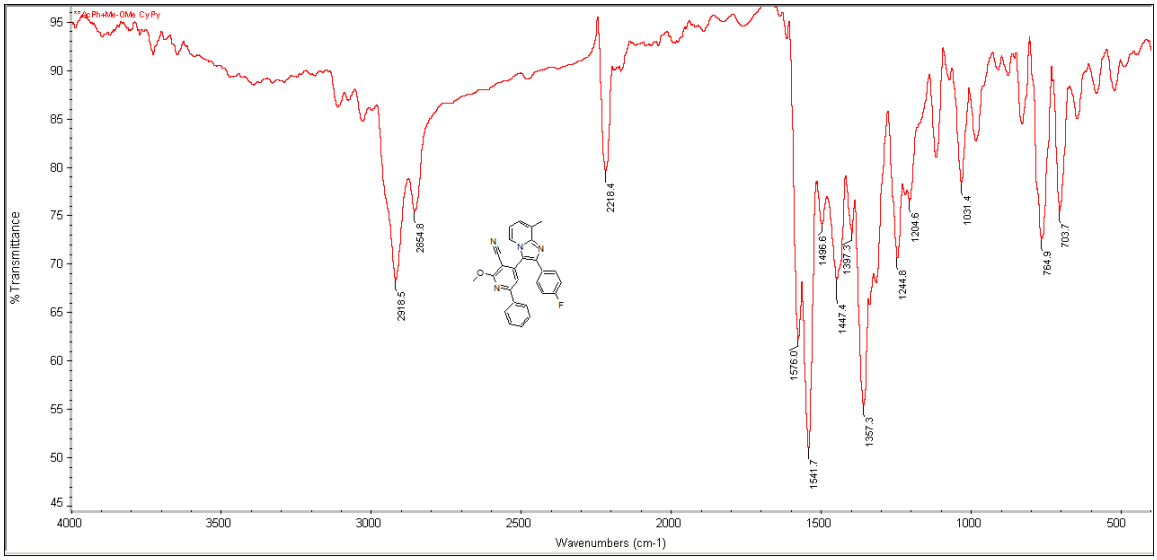


Figure 3.22: FTIR spectrum of compound **P_{73}**

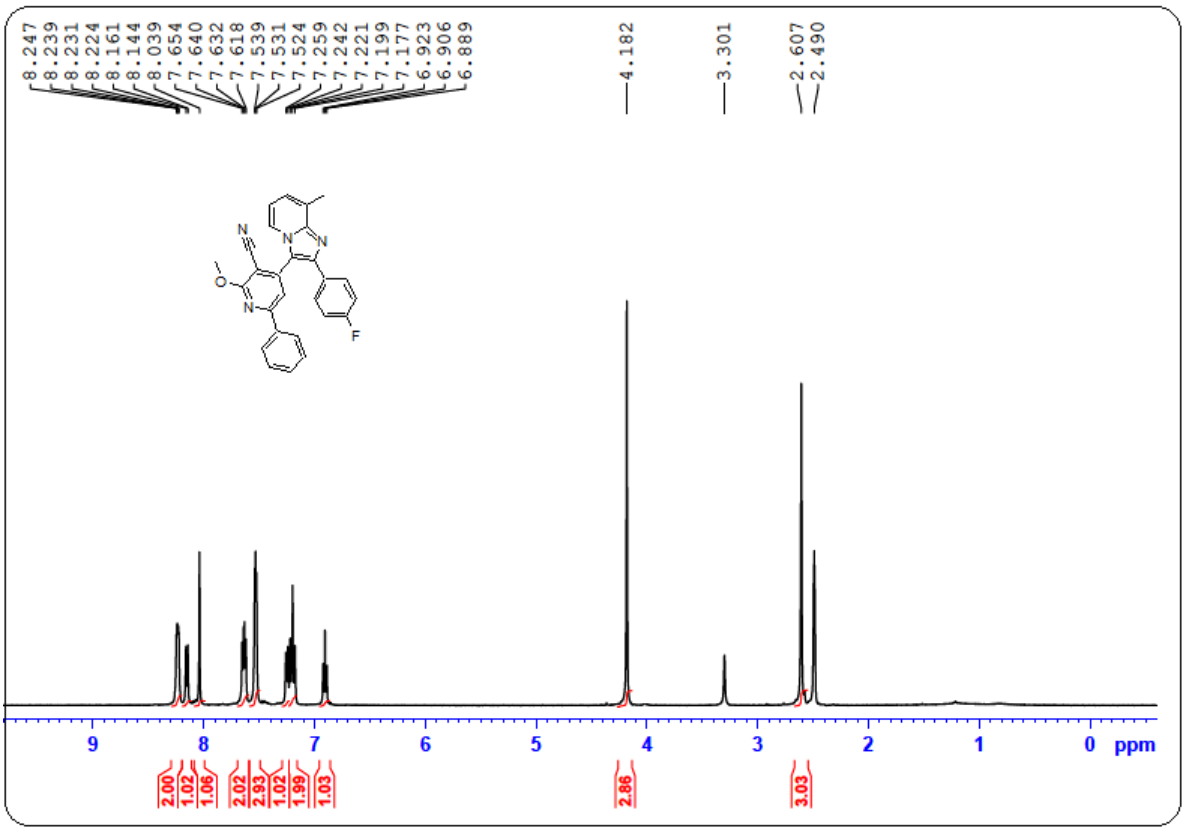


Figure 3.23: ^{1}H NMR spectrum of compound **P_{73}**

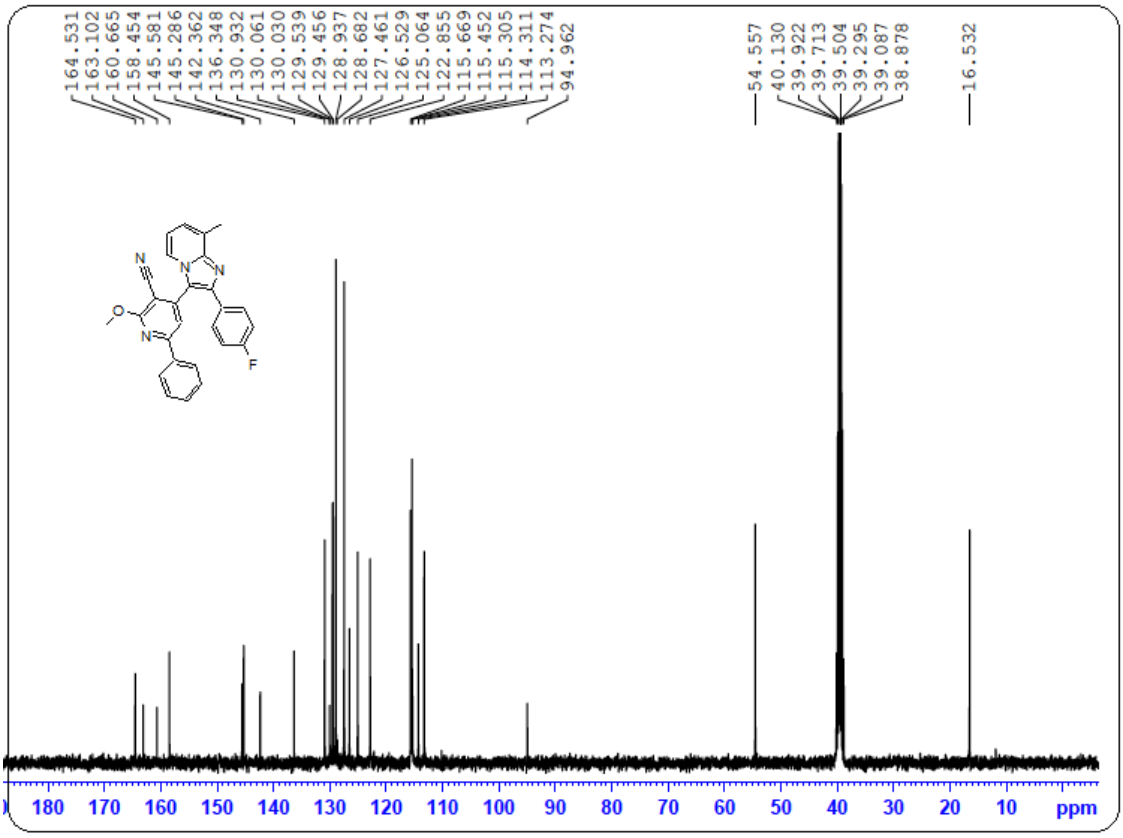


Figure 3.24: ^{13}C NMR spectrum of compound **P_{73}**

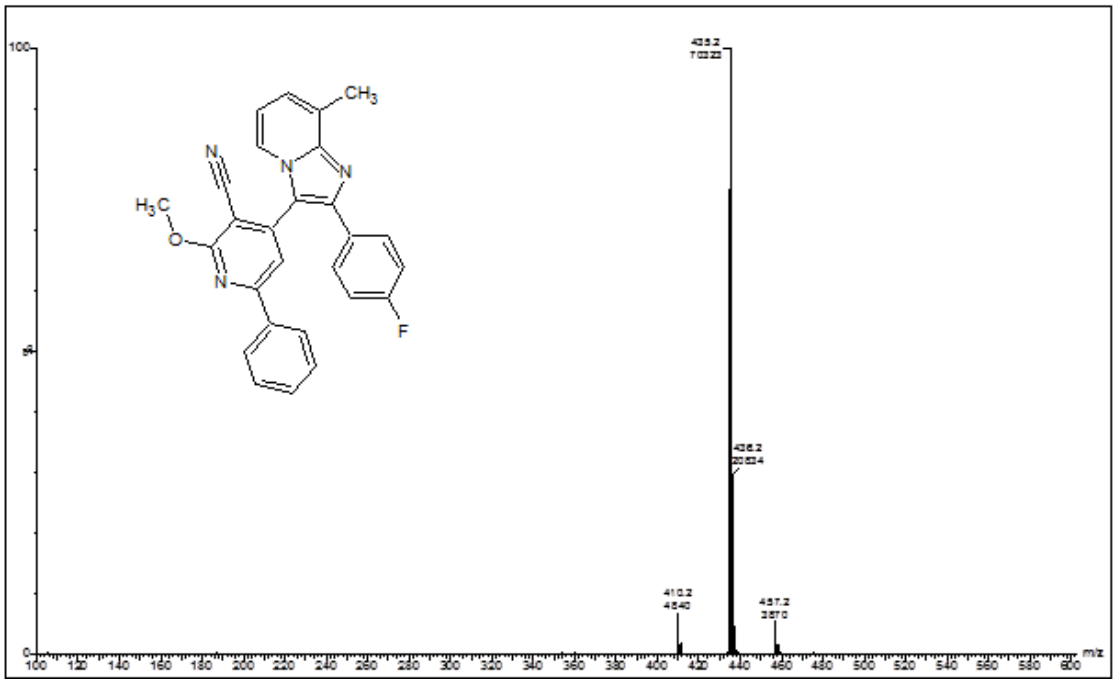


Figure 3.25: Mass spectrum of compound **P_{73}**

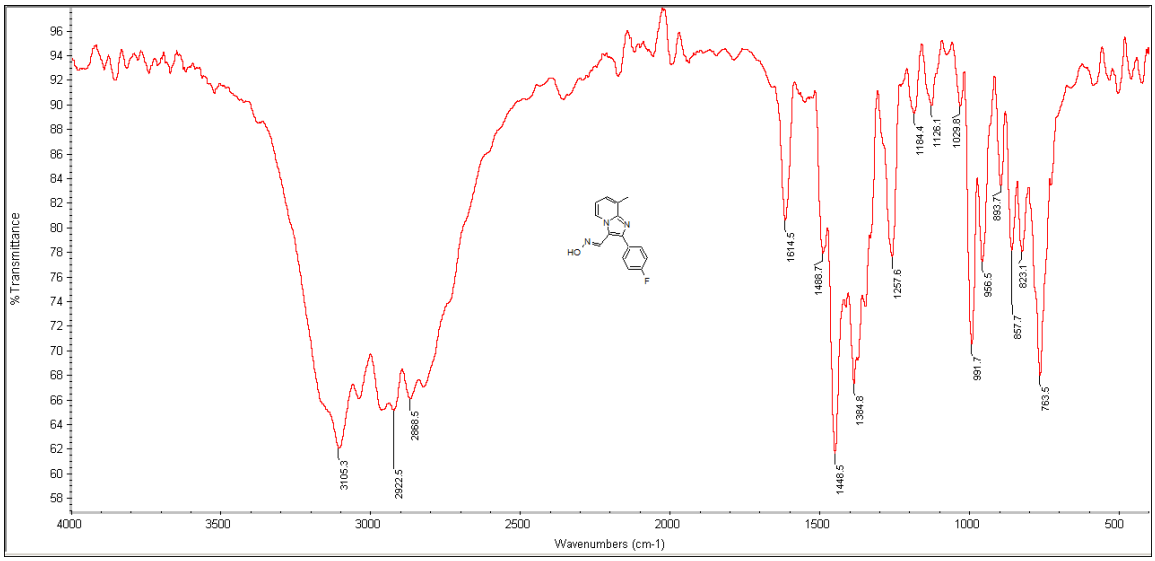


Figure 3.26: FTIR spectrum of compound **P_{89}**

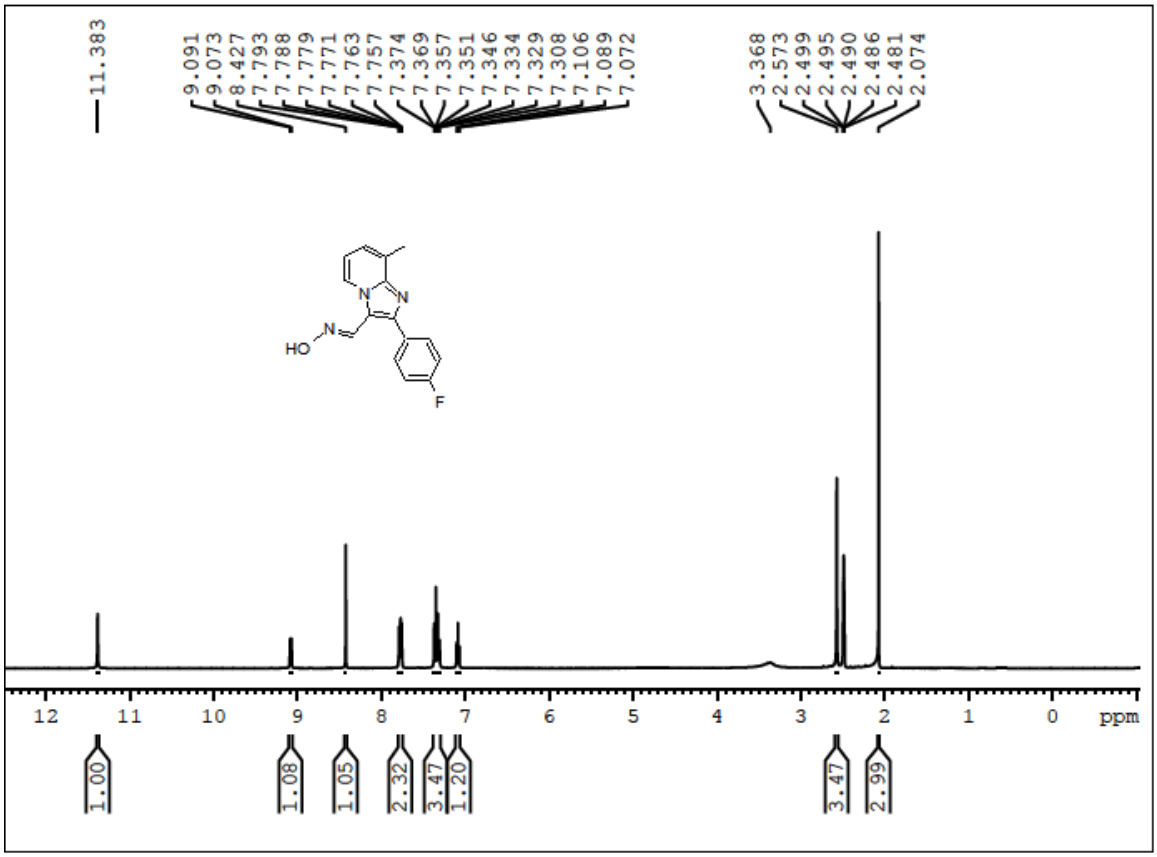


Figure 3.27: ^{1}H NMR spectrum of compound **P_{89}**

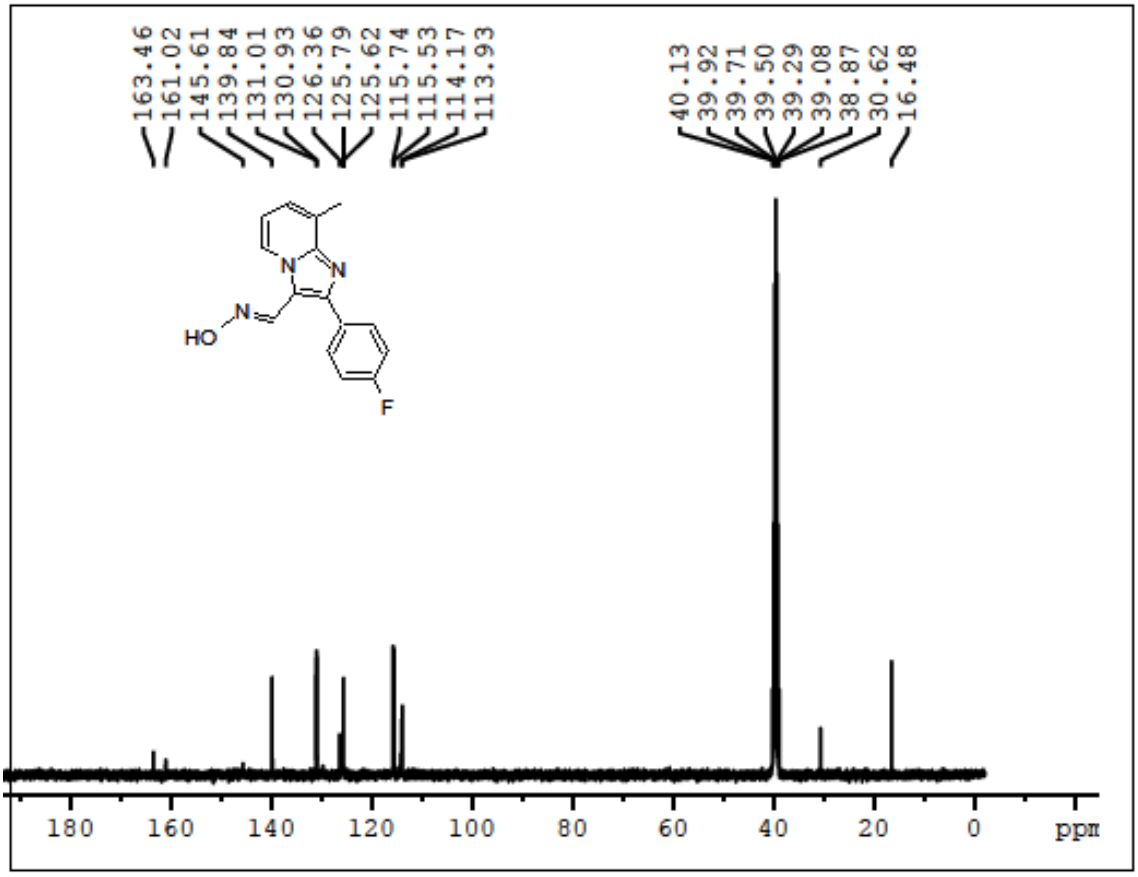


Figure 3.28: ^{13}C NMR spectrum of compound **P_{89}**

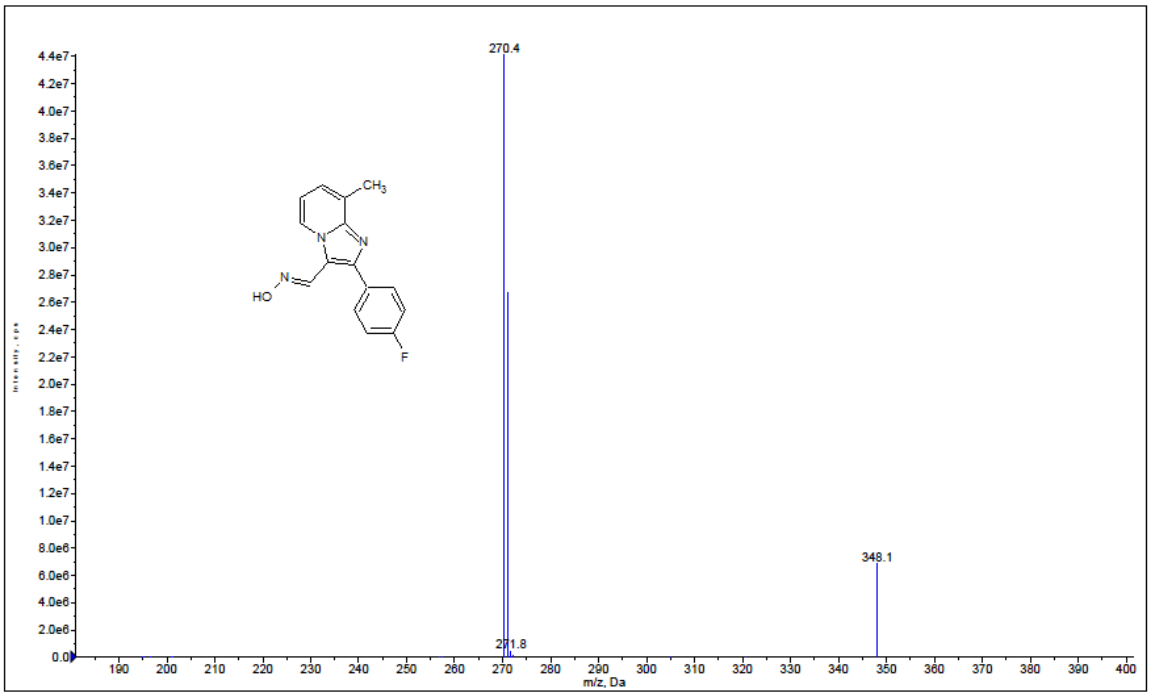


Figure 3.29: Mass spectrum of compound **P_{89}**

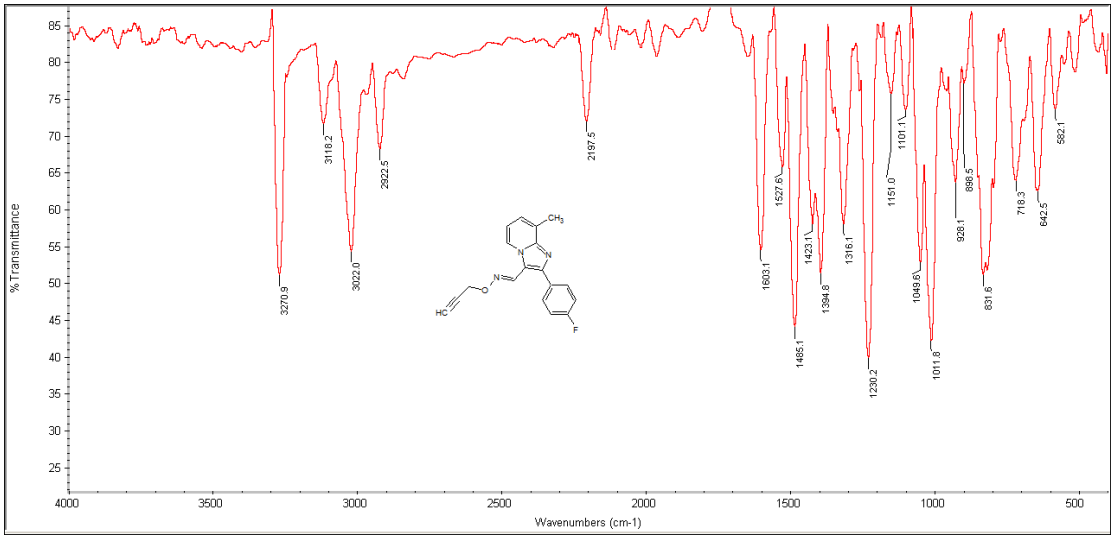


Figure 3.30: FTIR spectrum of compound **P_{95}**

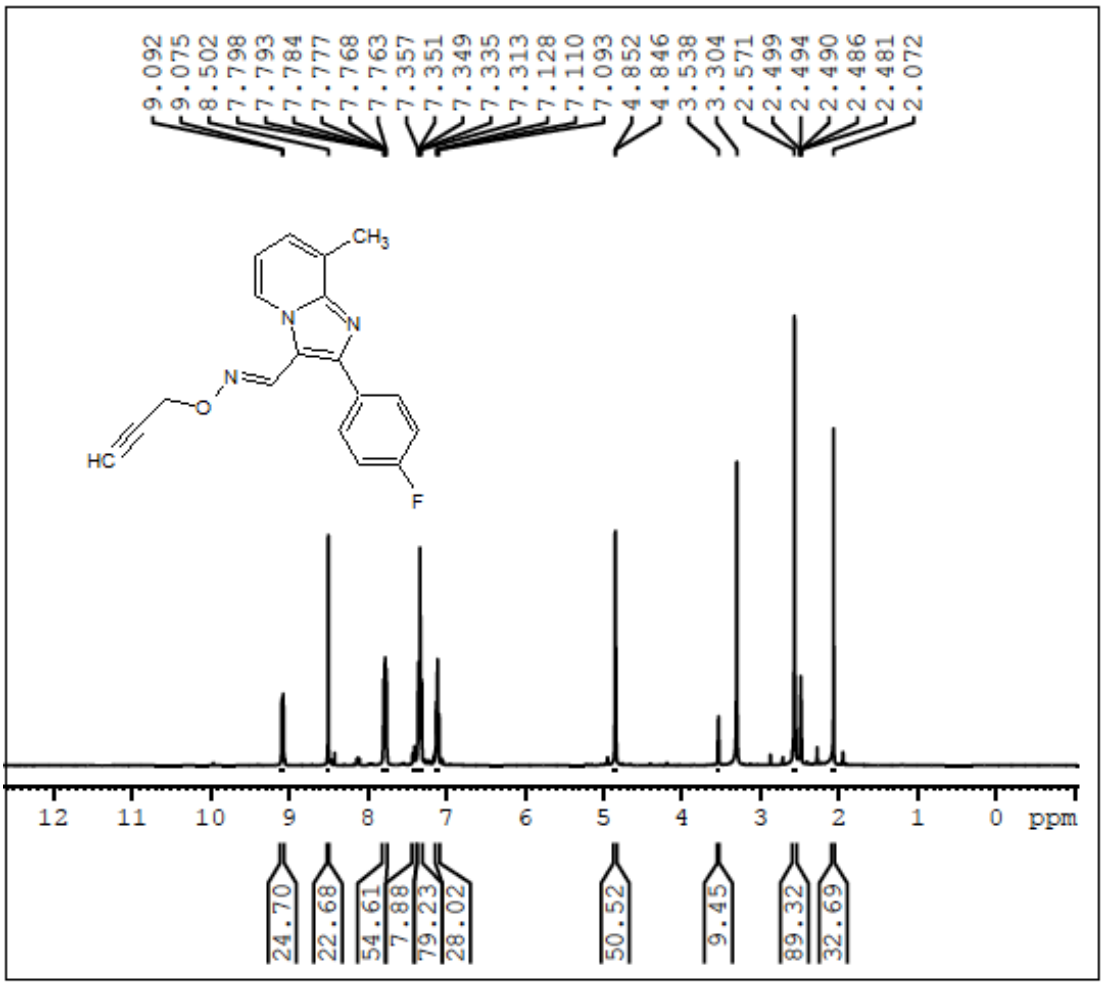


Figure 3.31: ^{1}H NMR spectrum of compound **P_{95}**

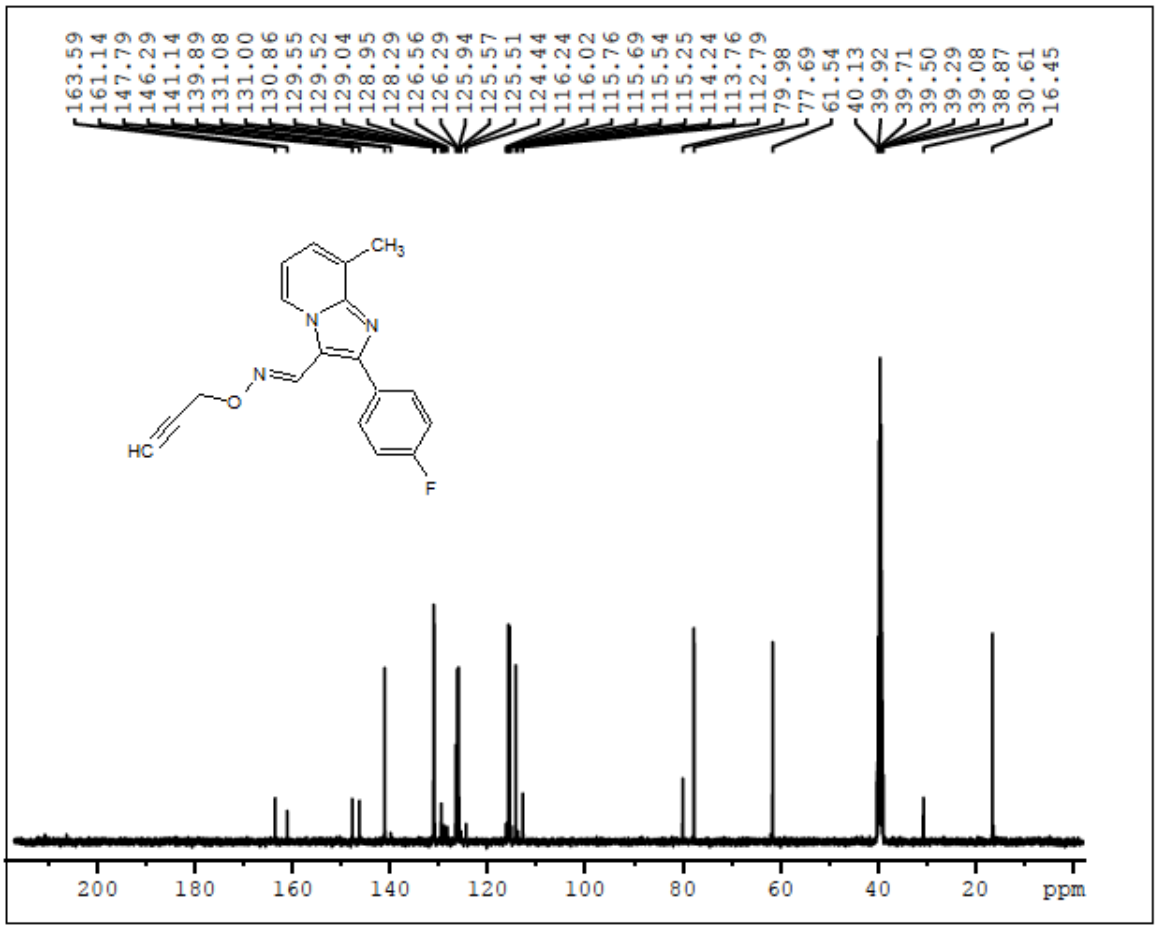


Figure 3.32: ^{13}C NMR spectrum of compound **P_{95}**

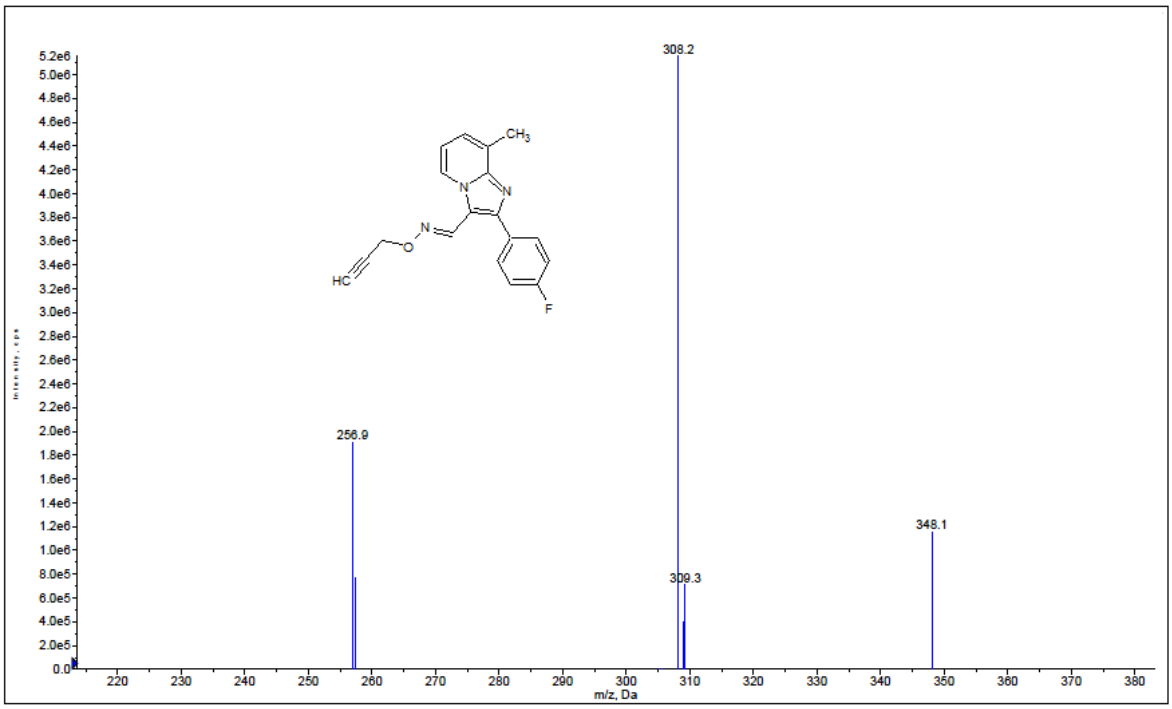


Figure 3.33: Mass spectrum of compound **P_{95}**

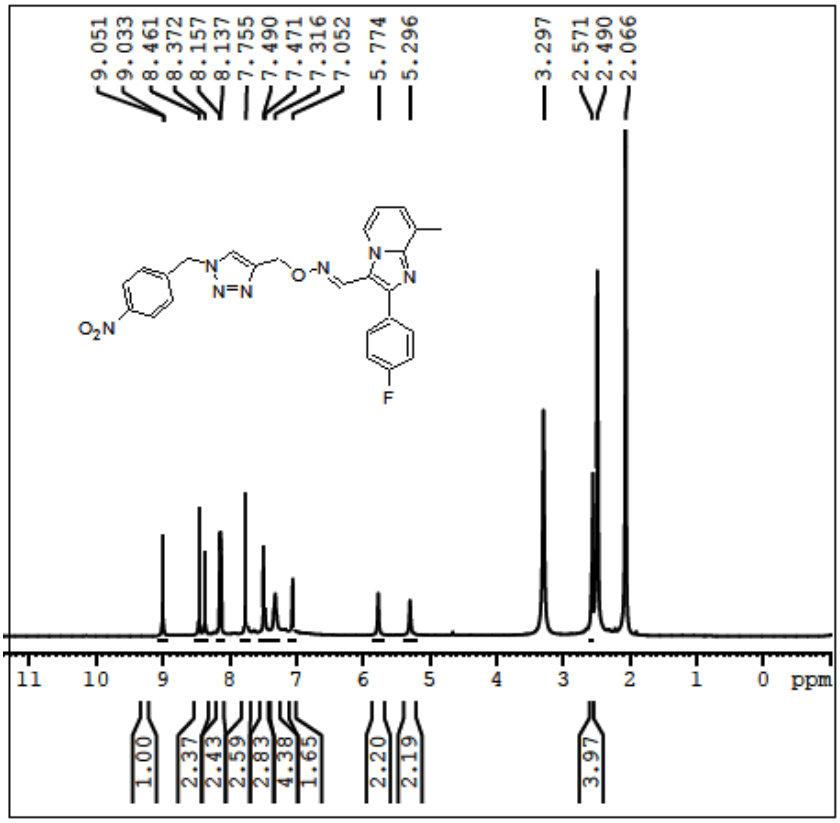


Figure 3.34: ^{1}H NMR spectrum of compound $\mathbf{P_{106}}$

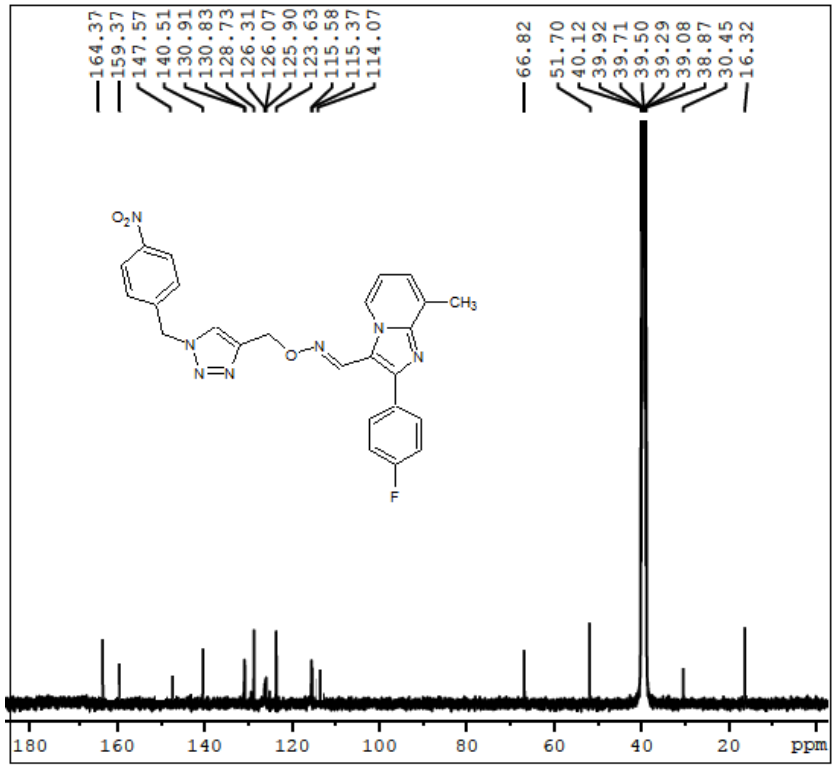


Figure 3.35: ^{13}C NMR spectrum of compound $\mathbf{P_{106}}$

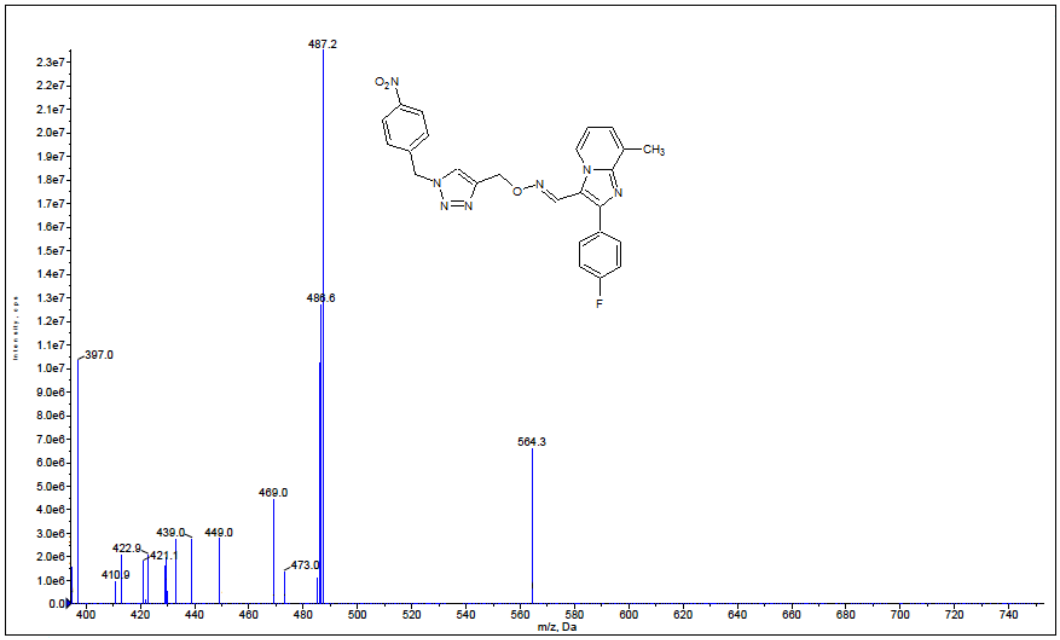


Figure 3.36: Mass spectrum of compound $\mathbf{P_{106}}$

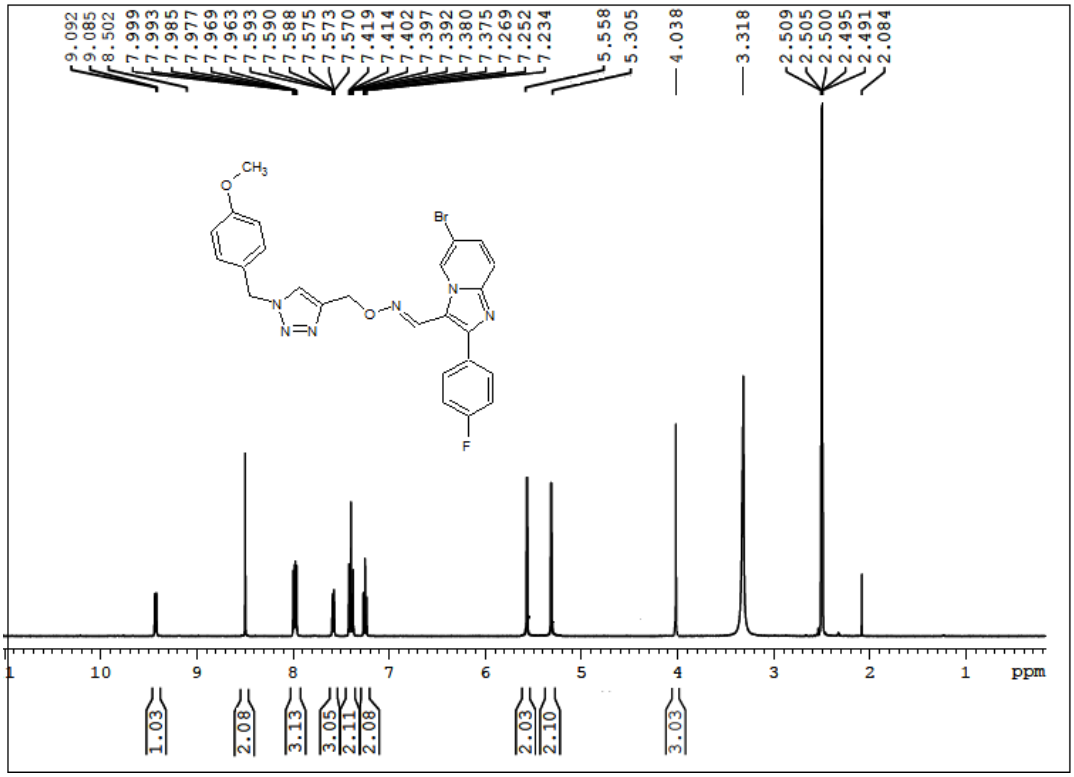


Figure 3.37: ^{1}H NMR spectrum of compound $\mathbf{P_{117}}$

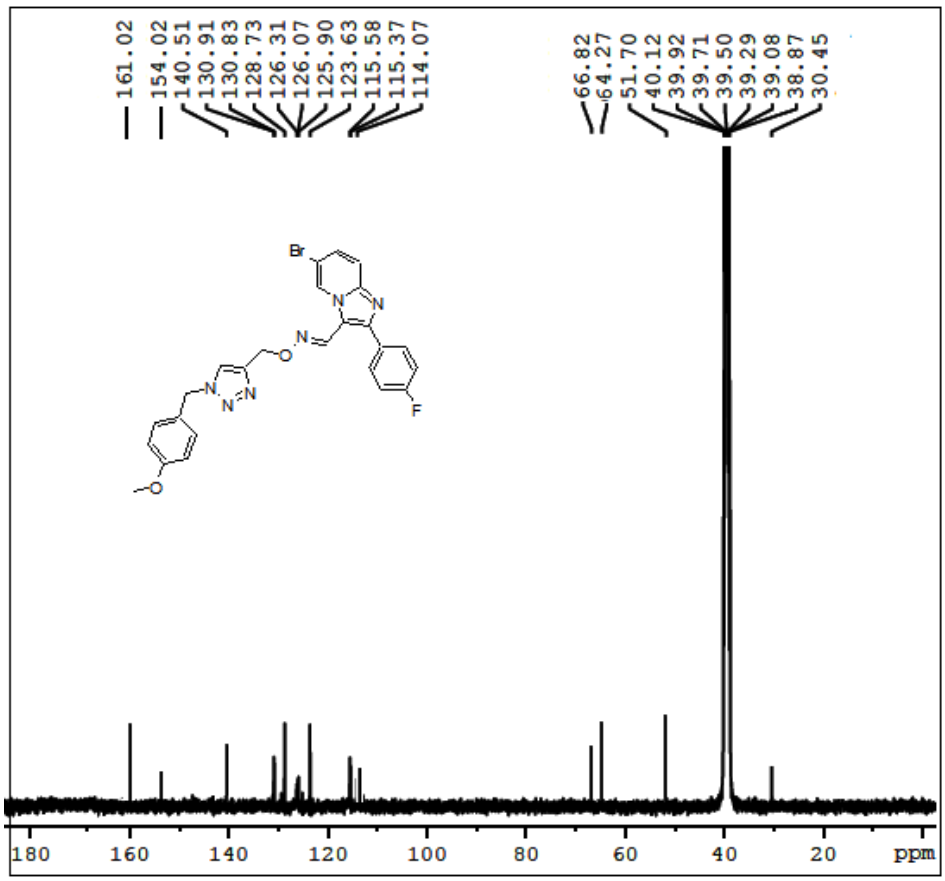


Figure 3.38: ^{13}C NMR spectrum of compound **P_{117}**

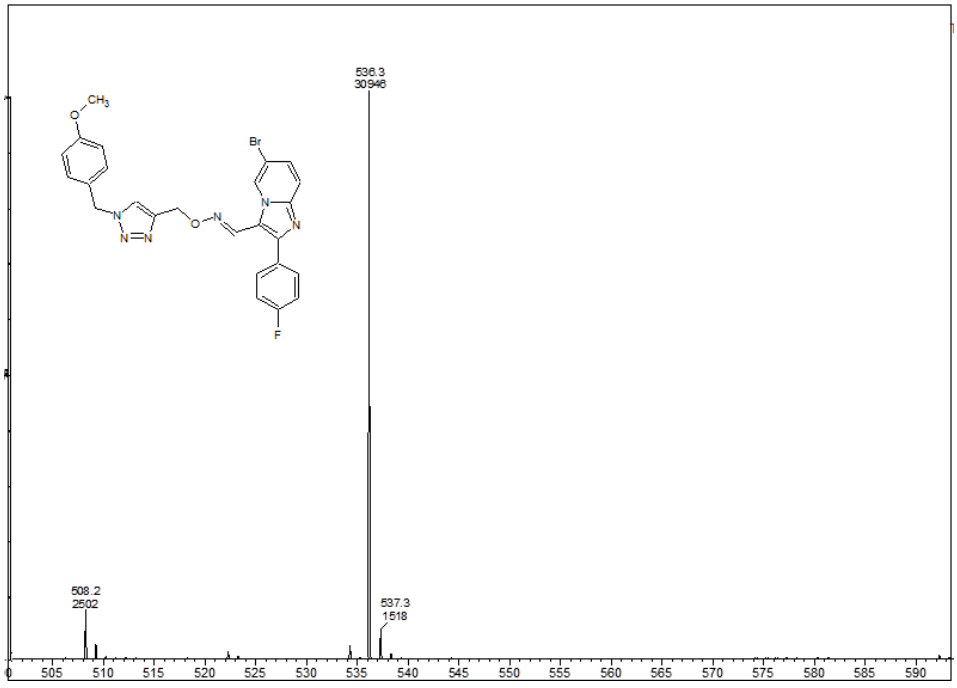


Figure 3.39: Mass spectrum of compound **P_{117}**

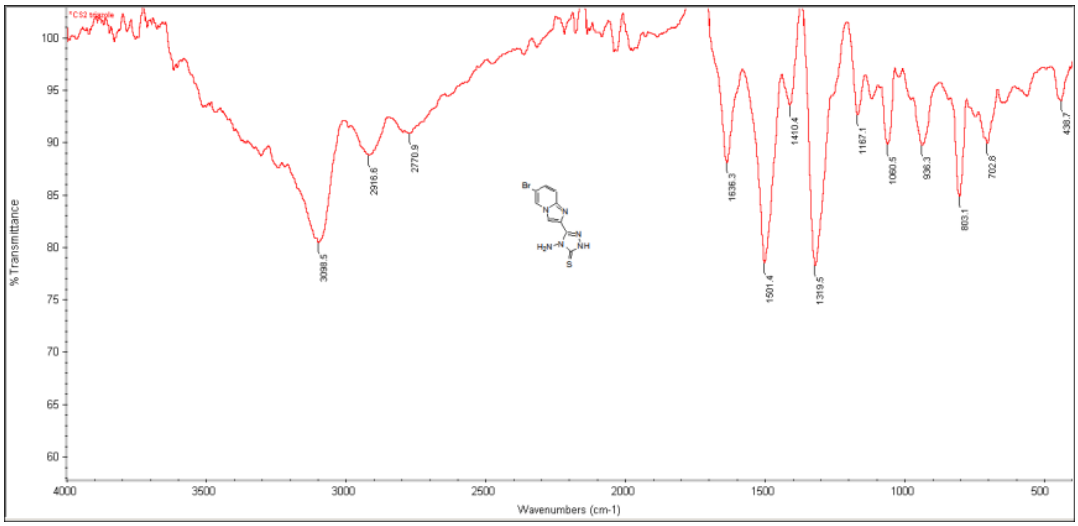


Figure 3.40: FTIR spectrum of compound **P_{129}**

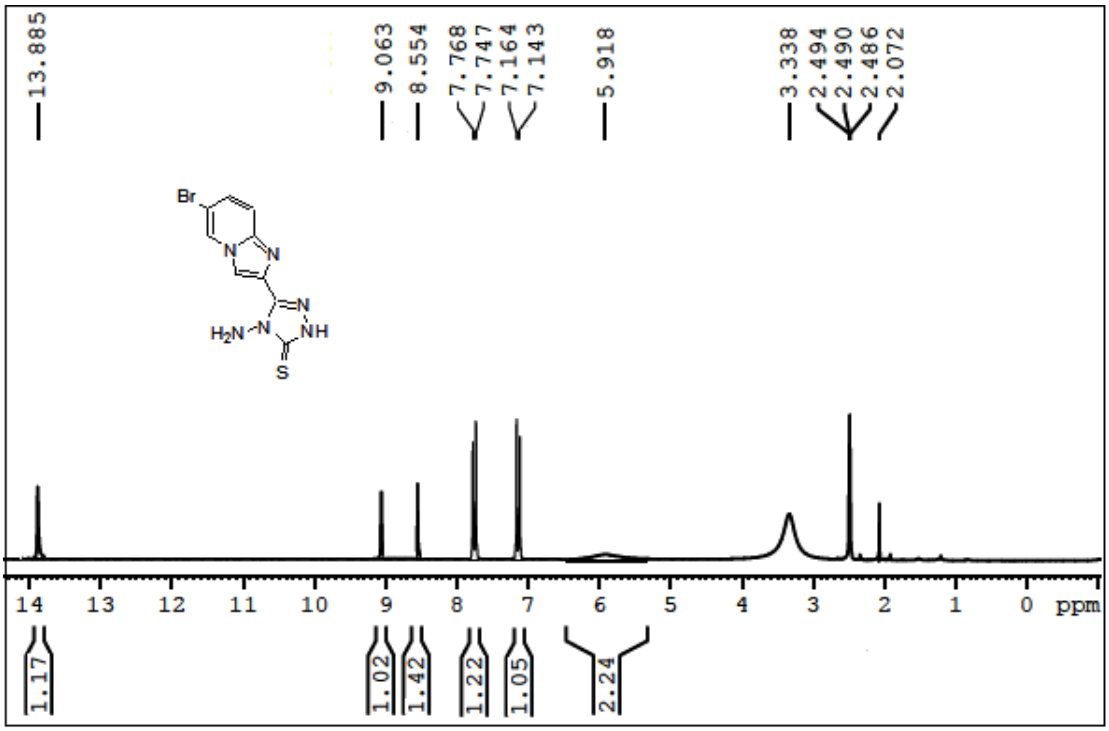


Figure 3.41: ^{1}H NMR spectrum of compound **P_{129}**

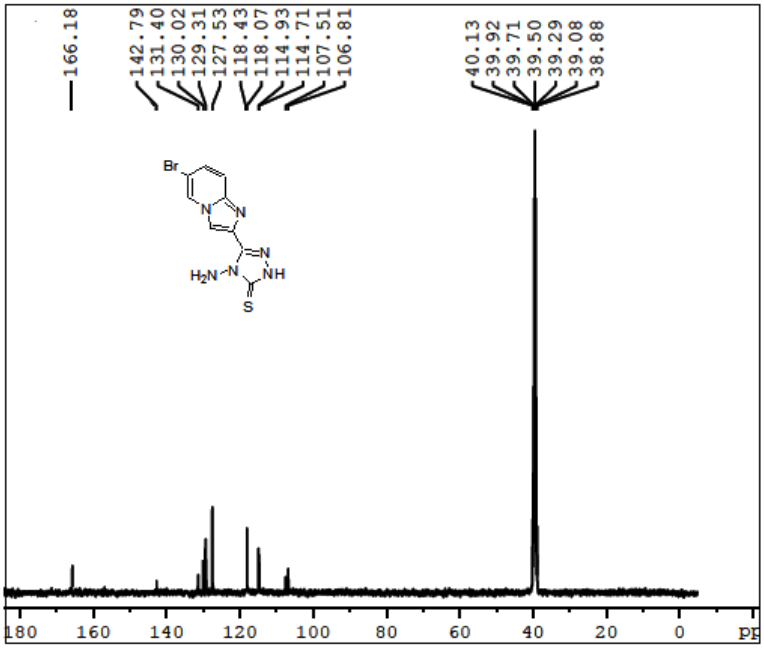


Figure 3.42: ^{13}C NMR spectrum of compound $\mathbf{P_{129}}$

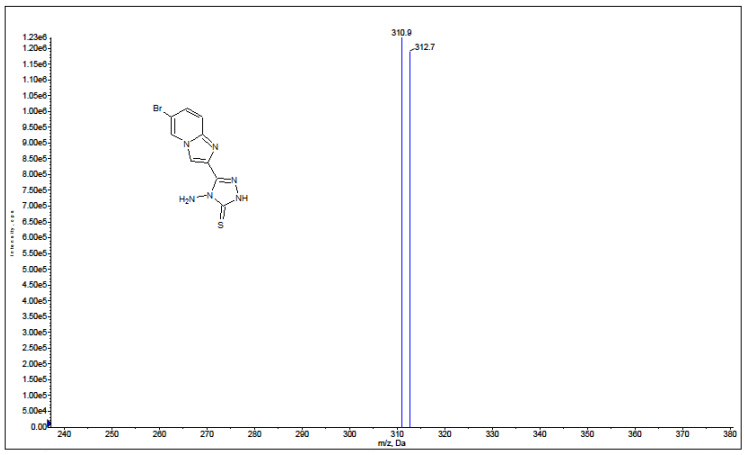


Figure 3.43: Mass spectrum of compound $\mathbf{P_{129}}$

3.4 CONCLUSIONS

In conclusion, new dihydropyridine ($\mathbf{P_{1\text{-}40}}$) and imidazo[1,2-a]pyridine ($\mathbf{P_{41\text{-}138}}$) derivatives carrying various pharmacophores, viz. hydrazone, amide, triazole, pyrazole, oxazolone, and pyrimidine were successfully synthesized following appropriate synthetic routes. The purification techniques and the solvent systems for purification of the new compounds were established. The various physical parameters such as melting point, yield etc. of target compounds were determined. Further, the structural characterization of new compounds was performed by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, SCXRD followed by elemental analysis methods.

CHAPTER-4

ANTICONVULSANT STUDIES OF NEW PYRIDINE DERIVATIVES

Abstract

This chapter describes a detailed account on anticonvulsant screening of newly synthesized DHP and imidazo[1,2-a]pyridine derivatives. It also includes the results of anticonvulsant screening and their discussion in detail.

4.1 INTRODUCTION

The choice of appropriate models for the initial screening of a potential anticonvulsant agent is one of the most important steps in the successful search for new AEDs. Although modern cellular neurophysiological and biochemical approaches have made it possible to identify molecular targets of AEDs, the *in vitro* testing is not likely to replace screening in animal models. *In vitro* systems cannot model the specific pharmacodynamic actions required for seizure protection since they do not assess the multidimensional parameter space, which includes the target molecules and other critical biomolecules (Castel-Branco et al. 2009). Also, *in vitro* testing does not assess bioavailability, brain accessibility and local delivery to the target. Therefore, only animal test systems can select compounds that are inherently anticonvulsant and are able to access the relevant brain targets (Rogawski 2006).

At present, preclinical animal studies are indispensable in exploring the efficacy and safety of an investigational AED before its introduction in human volunteers (White 2003; Löscher and Schmidt 1994). For practical reasons, experimental research on new AEDs has mostly been carried out on normal mice and rats in which seizures were induced by chemical or electrical means (Engel and Schwartzkroin 2006; White et al. 2006). Indeed, with respect to screening purposes, electrically or chemically induced seizures have advantages over most genetic models since seizure-susceptible animal species may lead to an exaggeration of the anticonvulsant potency of a new drug (Löscher and Schmidt 1994).

The maximal electroshock (MES) (Krall et al. 1978) and subcutaneous pentylenetetrazole (scPTZ) (Clark et al. 1984) screening methods are the two important and routinely used *in vivo* animal models for the anticonvulsant studies, because the seizure induction in these two models is simple and the predictive value for detecting clinically effective AEDs is high. The active compounds identified by these two methods were also found to show similar anticonvulsant effects in different genetic models of absence epilepsy such as Genetic Absence Epilepsy Rats from

Strasbourg (GAERS) or lethargic mice. This clearly suggests that there is no need to use chronic models in the search for new AEDs (Löscher 2002), while MES and scPTZ methods itself will serve their purpose of detecting new anticonvulsant agents. Therefore, these two methods are recognized as the "gold standards" in the early stages of testing. They are claimed to detect new bioactive chemical entities affording protection to generalized tonic-clonic seizures and generalized absence seizures, respectively. Almost all clinically significant AEDs are protective in at least one of these two models (Dawidowski et al. 2012). So, compounds found to be effective in either of these seizure methods are termed as potential anticonvulsants (Więckowski et al. 2012). Against this background, in our study the target compounds were screened for their *in vivo* antiepileptic property following MES and scPTZ methods. Further, their toxicity study was carried out by Rotarod method (Dunham and Miya 1957) that measures motor impairment.

4.2 EXPERIMENTAL PROTOCOL

The *in vivo* screening studies were carried out at National Institute of Health (NIH-NINDS), USA and Srinivas College of Pharmacy, Valachil, Mangalore. The experimental data are summarized in Table 4.1-4.6, wherein the figures indicate the minimal concentration of sample required to cause either protection or toxicity in at least 50% of tested animals. The detailed experimental procedures used for anticonvulsant screening and toxicity studies of the title compounds are described below.

4.2.1 Maximal Electroshock Seizure (MES) test

The samples were injected to mice by suspending them in 2% solution of Tween 80. Phenytoin was used as standard drug to compare the effectiveness of target samples. Groups of six male NMRI mice (18–30 g each) were used to screen the samples. Electrical stimuli of 0.2 s in duration (50 mA at 60 Hz) were delivered via corneal electrodes. Animals were previously administered with the suitable concentration of test compound. In the first series of compounds, standard test doses of 30, 100 and 300 mg/kg were used for the analysis, while in 2^{nd}, 4^{th} and 5^{th} series, three test doses, viz. 20, 40 and 100 mg/kg were used, as these compounds were found to be reactive in small doses itself. On the other hand, a kind of sedative effect was observed

for certain compounds of series 3 at higher test doses (above 100 mg/kg). Therefore, the test dose was reduced to 10 mg/kg, wherein compounds exhibited remarkable antiepileptic activity without showing any sedative property. Anticonvulsant activity was assessed 0.5 and 4 hours after i.p. injection of test samples. In the analysis, decrease in the duration of the hind limb tonic extensor phase was used as positive criterion for deciding antiepileptic potency of the tested compounds.

4.2.2 Subcutaneous Pentylene Tetrazole (scPTZ) test

Similar to MES method, a group of six mice were taken for scPTZ screening by using diazepam as a standard drug. The same test doses as taken for MES study were used for all the series of compounds. A standard dose of 85 mg/kg of Pentylene Tetrazole (Metrazol) was injected subcutaneously after 0.5 and 4 h of drug administration, so as to induce convulsion. These animals were placed in isolation cages to minimize stress and were observed for the next 30 min to see the absence of a seizure. Delay in onset of clonic phase was considered as criterion for anticonvulsant evaluation.

4.2.3 Neurotoxicity study by Rotarod method

Rotarod test was performed to detect the motor deficit in mice. Animals were divided in groups of 4 animals and trained to stay on an accelerating rotarod that rotates at 10 revolutions per minute. The rod diameter was 3.2 cm. Trained animals (able to stay on the rotarod for at least two consecutive periods of 90 s) were given an i.p. injection of the test compounds. For DHP derivatives, 30, 100 and 300 mg/kg doses were used, while in other serieses, 20, 40 and 100 mg/kg dose levels were used for the toxicity studies. In series-3, 10, 50 and 100 mg/kg doses were used for the toxicity evaluation. Neurological deficit was indicated by the inability of the animal to maintain equilibrium on the rotating rod for at least 1 min in each of the three trials. The dose at which animal fell off the rod, was determined.

4.3 RESULTS AND DISCUSSION

In the following sections, the *in vivo* anticonvulsant screening results of new DHP and imidazo[1,2-a]pyridine derivatives were discussed in detail. Further, their structure-activity relationships have been discussed briefly.

4.3.1 Anticonvulsant study of new pyridine derivatives (P_{1-138})

4.3.1.1 Dihydropyridines (P_{1-40})

In this series, the screening study was carried out by taking three different test doses such as 30, 100 and 300 mg/kg. The screening results of hydrazones (P_{1-27}) are tabulated in Table 4.1 while that of amides (P_{28-40}) are summarized in Table 4.2.

Among the screened compounds, the compounds P_5, P_{9-11}, P_{16}, P_{22}, P_{25} and P_{27} exhibited their activity after 4 hour i.p. injection of test samples, where as they were inactive at 0.5 hour interval. This clearly showed that they have slow onset of action. Amongst arylhydroxy derivatives, compound P_5 containing 4-hydroxy substituent displayed good activity at 100 mg/kg dose. However, its ortho-hydroxyphenyl analogue P_6 was inactive even at high test dose of 300 mg/kg. Similarly, 2,4-dihydroxyphenyl derivative P_{17} did not show any activity. Based on these observations, it can be concluded that a p-hydroxyphenyl group attached to hydrazone linkage is an activity-enhancing moiety. Further, it was observed that presence of an electron donating methoxy group adjacent to hydroxy functionality (as in P_{10}) does not influence on the activity of P_5. However, replacement of methoxy by ethoxy as in P_8 caused loss of activity. This could be probably due to steric effect exerted by the bulky ethoxy group. Also, a hydroxynaphthalene derivative P_{16} showed activity at a dose of 100 mg/kg, confirming the importance of hydroxyl group in enhancing the activity. It was also observed that the presence of electron rich aryl systems like 4-methyl phenyl (P_9), indole (P_{11}, P_{22}) displayed activity at 4 hours with a dose of 300 mg/kg. These screening results clearly showed that the hydrazone group carrying an electron rich aryl moiety is an essential structural requirement for good anticonvulsant activity.

Interestingly, 4-fluorophenyl derivative P_{25} exhibited significant activity at 100 mg/kg dose. However, replacement of fluoro by chloro as in P_{27} made it less potent (300 mg/kg), while the bromo derivative P_{23} was found to be inactive. Thus, as the size of halogen increases, their anticonvulsant activity follows the reverse order. Moreover, the active samples showed significant activity only in MES method but not in scPTZ mode, at all tested doses. This clearly shows that new DHP derivatives are capable of preventing seizure spread effectively. Finally, the Rotarod toxicity measurement results of tested compounds indicated that all the final DHP based hydrazone derivatives were non-toxic even at a high dose of 300 mg/kg. This non-

toxic nature of new DHPs prompted us to synthesize and screen another series of DHPs carrying anticonvulsant active amide pharmacophore.

Table 4.1: Anticonvulsant and toxicity screening results of $\mathbf{P_{1\text{-}27}}$

Sample Name	MES[a]		scPTZ[a]		Toxicity[a]	
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
P_1	-	-	-	-	-	-
P_2	-	-	-	-	-	-
P_3	-	-	-	-	-	-
P_4	-	-	-	-	-	-
P_5	-	100	-	-	-	-
P_6	-	-	-	-	-	-
P_7	-	-	-	-	-	-
P_8	-	-	-	-	-	-
P_9	-	300	-	-	-	-
P_{10}	-	100	-	-	-	-
P_{11}	-	300	-	-	-	-
P_{12}	-	-	-	-	-	-
P_{13}	-	-	-	-	-	-
P_{14}	-	-	-	-	-	-
P_{15}	-	-	-	-	-	-
P_{16}	-	100	-	-	-	-
P_{17}	-	-	-	-	-	-
P_{18}	-	-	-	-	-	-
P_{19}	-	-	-	-	-	-
P_{20}	-	-	-	-	-	-
P_{21}	-	-	-	-	-	-
P_{22}	-	300	-	-	-	-
P_{23}	-	-	-	-	-	-
P_{24}	-	-	-	-	-	-
P_{25}	-	100	-	-	-	-
P_{26}	-	-	-	-	-	-
P_{27}	-	300	-	-	-	-
Phenytoin	30	30	×	×	100	100
Sodium valproate	×	×	300	-	-	-

[a]Doses of 30, 100, 300 mg/kg of the compounds were administered and the protection as well as toxicity were measured after 0.5 and 4.0 hours. The figures indicate the minimal concentration of sample required to cause either protection or toxicity in more than 50 % of mice. The dash (-) indicates the absence of activity/toxicity, while '×' denotes 'not tested'.

Table 4.2: Anticonvulsant and toxicity screening data of $\mathbf{P_{28\text{-}40}}$

Sample name	MES[a]		scPTZ[a]		Toxicity[a]	
	0.5 hr	4.0 hr	0.5 hr	4.0 hr	0.5 hr	4.0 hr
P_{28}	-	-	-	-	-	-
P_{29}	-	-	-	-	-	-
P_{30}	-	300	-	-	-	-
P_{31}	-	100	-	300	-	-
P_{32}	-	100	-	-	-	-
P_{33}	-	-	-	-	-	-
P_{34}	-	-	-	-	-	-
P_{35}	-	100	-	-	-	-
P_{36}	-	-	-	-	-	-
P_{37}	-	-	-	-	-	-
P_{38}	-	-	-	-	-	-
P_{39}	-	300	-	-	-	-
P_{40}	-	-	-	-	-	-
Phenytoin	30	30	×	×	100	100
Sodium valproate	×	×	300	-	-	-

[a]Doses of 30, 100, 300 mg/kg of the compounds were administered and the protection as well as toxicity were measured after 0.5 and 4.0 hours. The figures indicate the minimal concentration of sample required to cause either protection or toxicity in more than 50 % of mice. The dash (-) indicates the absence of activity/toxicity, while '×' denotes 'not tested'.

On the similar line, another set of new DHPs containing amides $\mathbf{P_{28\text{-}40}}$ were screened for *in vivo* antiepileptic as well as toxicity studies and their results are summarized in Table 4.2. This activity data is also found to be similar to that of hydrazones $\mathbf{P_{1\text{-}27}}$, wherein amides possessing electron rich systems, viz. $\mathbf{P_{30\text{-}32}}$, $\mathbf{P_{35}}$ and $\mathbf{P_{39}}$ showed moderate anticonvulsant activity. These results evidenced that, amide group possessing electron rich systems like thiophene, benzothiazole, tolyl groups enhance the anticonvulsant property of the resulting molecules. A phenyl derivative $\mathbf{P_{28}}$ did not show any activity while 4-methylphenyl analogues $\mathbf{P_{30}}$ and $\mathbf{P_{32}}$ exhibited activities at 300 and 100 mg/kg, respectively. This may be due to inductive effect of methyl group on the ring which increases the electron strength of the resulting molecules. On the other hand, 2,6-dimethylphenyl derivative $\mathbf{P_{29}}$ failed to show any activity, despite the presence of two electron donating methyl groups. This observation is predicted to be due to steric hindrance around amide functionality offered by two

vicinal methyl groups. Interestingly, when phenyl ring was replaced by benzothiazole moiety as in **P_{31}**, the activity was enhanced (100 mg/kg) significantly. An amide derivative **P_{35}**, obtained from thiophene-2-acid chloride showed considerable activity at a dose of 100 mg/kg. However chloro substituted thiophene derivatives (**P_{34}** and **P_{36}**) were found to be inactive. Finally, a carboxylic acid derivative **P_{39}** exhibited antiepileptic activity at 300 mg/kg, might be due to its capacity to involve in hydrogen bonding interactions with receptor. Similar to hydrazones, amide derivatives also displayed enhanced activity in MES method when compared with that in scPTZ method. Only compound **P_{31}** showed activity in scPTZ method at relatively higher dose (300 mg/kg). Interestingly, these DHPs were also found to be non-toxic up to 300 mg/kg. Though they were non-toxic in nature, their moderate activity restricted us from further synthesizing new DHPs carrying appropriate functionalities.

4.3.1.2 Imidazo[1,2-a]pyridine-3-carboxaldehyde derivatives ($P_{41\text{-}64}$)

Owing to the well-known CNS applications of various imidazo[1,2-a]pyridine derivatives, twenty four new imidazo[1,2-a]pyridine derivatives carrying suitable pharmacophoric groups (**$P_{41\text{-}64}$**) were synthesized and screened for *in vivo* anticonvulsant study. In this section, the anticonvulsant profile of a set of imidazo[1,2-a]pyridines carrying active heterocycles at position-3 was discussed. The antiepileptic property of these new compounds were examined at 0.5 and 4 hour after i.p. injection of test sample by taking doses of 20, 40 and 100 mg/kg. Also, the active target compounds were subjected to neurotoxicity study following Rotarod method by taking above mentioned test doses and the screening results are tabulated in Table 4.3.

In MES screening method, compound **P_{43}** possessing benzothiazole ring displayed activity at 100 mg/kg after 4 hours of sample injection, while compound **P_{58}** containing oxazolone ring showed activity at a smaller dose of 40 mg/kg. Interestingly, new compounds displayed significant activity in scPTZ method when compared to their activity in MES method. This is a clear indicative of their ability to elevate the seizure threshold (Stables and Kupferberg 1997). Further, compounds **P_{41}**, **$P_{43\text{-}44}$**, **P_{46}**, **P_{50}**, **P_{52}**, **$P_{54\text{-}55}$**, **$P_{57\text{-}58}$**, **P_{61}** and **$P_{63\text{-}64}$** showed significant antiepileptic activity in PTZ method. Particularly, compounds **P_{54}** and **$P_{57\text{-}58}$** containing oxazolone moiety exhibited complete protection at a dose of 20 mg/kg. Further, they showed activity in

both the intervals (0.5 and 4 hour), indicating their rapid onset and long duration of anticonvulsant action. On the other hand, compounds **P_{41}**, **P_{43}**, **P_{55}** and **P_{63}** showed activity at a dose of 40 mg/kg where as compounds **P_{44}**, **P_{46}**, **P_{50}**, **P_{52}**, **P_{61}** and **P_{64}** exhibited anticonvulsant activity at relatively high test dose of 100 mg/kg.

Based on general observations on structure-activity relationship, it appears that the presence of electron donating substituent at position-4 of phenyl ring attached at C-2 of imidazo[1,2-a]pyridine nucleus results in enhanced anticonvulsant activity. In particular, presence of fluoro (as in **P_{41}**, **P_{43}**, **P_{50}**, **P_{54}**, **P_{57}** and **P_{63}**) and methoxy (as in **P_{55}**, **P_{58}**, **P_{61}** and **P_{64}**) groups led to significant activity when compared with those of un-substituted phenyl derivatives. Amongst various imidazo[1,2-a]pyridine derivatives, oxazolone analogues were emerged as lead compounds. Particularly, compounds **P_{57}** and **P_{58}** possessing tolyl substituent on oxazolone pharmacophore displayed enhanced activity when compared with that possessing phenyl substituent (as in **P_{54}** and **P_{55}**). Thus, as electron donating strength of substituents present on oxazolone moietyincreases, their anticonvulsant activity also enhances. Further, the pyrazolone derivatives **$P_{62\text{-}64}$** were found to be more active than their precursors **$P_{59\text{-}61}$**. This may be due to their capacity to involve in hydrogen bonding interactions with cellular receptors. In the same way, reduction of chalcones to corresponding hydroxyl derivatives enhanced their antiepileptic activity significantly. This was confirmed by comparing the activity of chalcones **$P_{45\text{-}48}$** with corresponding hydroxyl derivatives **$P_{49\text{-}52}$**, wherein **P_{46}** showed activity at 100 mg/kg after 4 hr, while **P_{50}** exhibited activity in 0.5 hr duration itself. Similarly, compound **P_{48}** was inactive at all tested doses, whereas its reduced analogue **P_{52}** exhibited activity at 100 mg/kg after 4 h of sample administration.

The neurotoxicity screening results indicated that most of the tested compounds were non-toxic at tested doses 20, 40 and 100 mg/kg. Only compounds **P_{43}** and **P_{63}** showed toxic character at a high dose of 100 mg/kg. On the basis of the observed results, it can be concluded that, new imidazo[1,2-a]pyridines are non-toxic anticonvulsant agents. Compounds **P_{57}** and **P_{58}** possessing tolyl substituted oxazolone moiety emerged as lead compounds by displaying prominent anticonvulsant activity in PTZ method at a dose of 40 and 20 mg/kg, respectively.

Table 4.3: Anticonvulsant and toxicity screening results of target compounds $\mathbf{P_{41\text{-}64}}$

Sample	MES[a]		scPTZ[a]		Neurotoxicity study[a]	
	0.5	4.0	0.5	4.0	0.5	4.0
P_{41}	-	-	40	-	-	-
P_{42}	-	-	-	-	×	×
P_{43}	-	100	40	100	-	100
P_{44}	-	-	100	-	-	-
P_{45}	-	-	-	-	×	×
P_{46}	-	-	-	100	×	×
P_{47}	-	-	-	-	×	×
P_{48}	-	-	-	-	×	×
P_{49}	-	-	-	-	×	×
P_{50}	-	-	100	-	-	-
P_{51}	-	-	-	-	-	-
P_{52}	-	-	-	100	-	-
P_{53}	-	-	-	-	×	×
P_{54}	-	-	20	100	-	-
P_{55}	-	-	40	100	-	-
P_{56}	-	-	-	-	×	×
P_{57}	-	-	20	40	-	-
P_{58}	40	-	20	40	-	-
P_{59}	-	-	-	-	×	×
P_{60}	-	-	-	-	×	×
P_{61}	-	-	-	100	-	-
P_{62}	-	-	-	-	×	×
P_{63}	-	-	40	100	-	100
P_{64}	-	-	100	-	×	×
Phenytoin	20	20	×	×	100	100
Diazepam	×	×	20	20	-	-

[a]Doses of 20, 40, 100 mg/kg of the compounds were administered and the protection as well as toxicity were measured after 0.5 and 4.0 hours. The figures indicate the minimal concentration of sample required to cause either protection or toxicity in more than 50 % of mice. The dash (-) indicates the absence of activity/toxicity, while '×' denotes 'not tested'.

4.3.1.3 Chalcone derivatives containing imidazo[1,2-a]pyridines (P_{65-87})

In this series, the preliminary screening study was carried out by taking three test doses such as 20, 40 and 100 mg/kg, initially. The tested compounds exhibited very good protection against epilepsy at all these doses. However, sedative symptoms were observed for certain compounds when screening was carried out at 100 mg/kg dose. It is well known fact that the CNS activities such as antiepileptic, sedative, anxiolytic properties of imidazo[1,2-a]pyridines are dose dependant (Vlainic and Pericic 2010). Therefore, to avoid such interference of sedative effect with antiepileptic property, the dose levels were reduced to 10 mg/kg, wherein only anticonvulsant activity was observed without any sedative symptoms. Further, their toxicity study was carried out by Rotarod method, by taking three different test doses (10, 50 and 100 mg/kg). The screening results of MES, scPTZ and Rotarod toxicity studies are summarized in Table 4.4. The data represents the duration of tonic and clonic phases in MES and scPTZ methods.

In MES method, among pyrazoline derivatives **P_{65-69}**, compound **P_{66}** carrying fluoro substituent at para position on aryl ring attached to position-2 of imidazo[1, 2-a]pyridine group displayed the enhanced activity with latency period of 10.97±1.74 sec, which is significant when compared with that of control (2.18±0.47). Similarly, another fluoro derivative **P_{65}** also showed good anticonvulsant activity (9.15±1.01). However, replacement of fluoro by hydrogen as in **P_{67-69}** resulted in decreased anti-epileptic efficacy of the molecules. The cyanopyridone derivatives **P_{70-71}** displayed better activity irrespective of substituents present on the molecule indicating that cyanopyridone is an active moiety (Rogawski 2011). In contrast, little less activity was observed for 2-methoxy-3-cyanopyridines **P_{72-77}** when compared with cyanopyridone analogues. Here also, compounds **P_{72}** and **P_{73}** displayed good results owing to the presence of fluoro substituent on aryl ring (halo-aryl) attached to imidazopyridine moiety. In spite of halo-aryl group present in **P_{73}**, it resulted relatively less activity, which may be attributed to the presence of electron withdrawing nitro group (Yamamoto et al. 2006). Further, 2-amino pyrimidine **P_{78-83}** and pyrimidine 2-thiones **P_{84-87}** showed similar trend in their results, wherein compounds **P_{82}** and **P_{87}** containing thiophene and fluoro groups displayed enhanced activity.

Table 4.4: Anticonvulsant and toxicity screening results of target compounds $\mathbf{P_{65\text{-}87}}$

Sample	MES test[a]		scPTZ test[a]		Toxicity study[b]	
	Duration of tonic Extension	Latency (onset of clonus)	Onset times in secs (Mean±SEM)		0.5 hr	4.0 hr
			Conic	Tonic		
Control	15.35±0.60	2.18±0.47	59.2±1.108	385.5±10.90	×	×
Diazepam	-	13.17±1.29	-	-	-	-
P_{65}	7.21±1.30	9.45±1.01	158.7±1.542	542.2±6.745	-	-
P_{66}	6.54±1.14	10.97±1.74	149.3±2.246	528.2±4.854	-	-
P_{67}	7.22±1.32	9.28±1.11	126.7±1.745	532.5±4.808	×	×
P_{68}	7.15±1.07	9.25±1.15	79.32±1.233	426.8±3.232	×	×
P_{69}	7.27±1.11	9.33±1.25	117.7±1.054	530.8±5.510	-	-
P_{70}	6.61±1.21	10.88±1.31	171.8±2.227	641.5±6.076	-	-
P_{71}	6.54±1.14	10.97±1.74	129.2±4.175	544.7±8.774	-	100
P_{72}	9.84±1.17	7.94±1.53	335.3±4.580	611.5±8.449	-	-
P_{73}	7.77±1.01	9.90±1.41	171.5±1.839	596.0±9.640	-	-
P_{74}	7.01±1.15	9.13±1.01	115.7±0.849	469.2±6.091	×	×
P_{75}	6.96±1.23	10.77±1.33	90.87±1.706	456.7±4.550	-	-
P_{76}	8.52±1.41	8.72±1.36	79.32±1.236	426.8±3.234	-	-
P_{77}	6.85±1.06	10.90±1.44	170.7±1.745	595.7±8.464	-	-
P_{78}	9.88±0.98	7.95±1.50	109.7±1.606	480.2±3.842	×	×
P_{79}	8.67±1.01	8.80±1.32	85.330±1.706	435.8±3.736	×	×
P_{80}	8.15±1.71	8.16±1.21	171.4±1.742	593.2±8.467	-	-
P_{81}	8.27±1.37	8.11±1.43	115.7±0.8493	469.2±6.091	-	-
P_{82}	8.71±1.25	8.86±1.50	79.50±1.232	426.8±3.219	-	-
P_{83}	8.52±1.41	8.72±1.36	90.83±1.706	454.7±4.550	-	-
P_{84}	7.77±1.01	9.90±1.41	82.50±1.708	435.0±3.941	×	×
P_{85}	8.13±1.76	8.04±1.25	107.0±4.325	479.7±7.223	-	-
P_{86}	7.45±1.51	9.75±1.32	79.34±1.235	426.5±3.232	-	-
P_{87}	6.87±1.12	10.91±1.45	90.83±1.706	454.7±4.550	-	-

[a]Results are expressed as Mean ± SEM; (n=6). MES and PTZ tests were carried out at 10 mg/kg dose. The mice were examined 0.5 hour post i.p. injection of test samples. [b]Toxicity study was carried out by Rotarod method at a 10, 50 and 100 mg/kg doses. The values indicate the minimum dose required to exhibit toxicity in at least 50 % of mice. (-) indicates the absence of toxicity, while '×' means 'not tested'.

On the other hand, the title compounds exhibited better results in PTZ induced anticonvulsant screening test than that of MES method. Many compounds especially, **P_{65}**, **P_{66}**, **P_{70}**, **P_{73}**, **P_{82}** and **P_{87}** produced good protection against epilepsy at tested dose (10 mg/kg). In PTZ method also, compounds with fluoro substituent on aryl ring displayed delayed onset of clonus-tonus phases, indicating their anticonvulsant efficacy. Particularly, a cyanopyridine derivative **P_{72}**, possessing an electron donating methyl group along with fluoro-aryl moiety exhibited the highest activity with complete protection against seizures. Further, 2-amino pyrimidine derivatives were found to be more active than corresponding pyrimidine-2-thiones, possibly due to more hydrogen bond donor capacity of amine group.

All the tested compounds except compound **P_{70}** were found to be non-toxic at both the intervals.The toxicity of **P_{70}** is might be due to the presence of nitro group in the molecule. This compound remained non-toxic at 0.5 hour interval, indicating that the compound has slow onset of toxicity. Other tested compounds were non-toxic at all tested doses (10, 50 and 100 mg/kg), indicating that they are potential candidates for antiepileptic activity.

When we correlate the structures of the tested samples and their activity, it appears that presence of 4-fluorophenyl group at position-2 of imidazo[1,2-a]pyridine ring is responsible for enhanced anticonvulsant activity. Additionally, the *in vivo* results also indicated that the presence of heterocyclic systems at position-3 improved their efficacy. Further, the presence of electron rich aryl and halophenyl substituents on these heterocyclic systems resulted in improved activity whereas less activity was observed for those possessing electron withdrawing groups. Similarly, motor impairment study showed that electron withdrawing groups such as nitro substituent induces toxicity.

4.3.1.4 Imidazo[1,2-a]pyridines carrying (1,2,3-triazol-4-yl) methyl oxime ($P_{88\text{-}123}$)

In this series twenty four new target 1,2,3-triazole derivatives (**$P_{100\text{-}123}$**) were synthesized, in addition to twelve new intermediates (**$P_{88\text{-}99}$**). These new thirty six new derivatives were screened for their *in vivo* antiepileptic as well as toxicity studies by taking three different test doses, viz. 20, 40 and 100 mg/kg. The screening results are summarized in Table 4.5.

Table 4.5: Antiepileptic and toxicity data of final compounds **P_{88-123}**

Sample	MES[a]		scPTZ[a]		Toxicity results[a]	
	0.5	4.0	0.5	4.0	0.5	4.0
1	2	3	4	5	6	7
P_{88}	-	-	-	-	-	-
P_{89}	-	-	-	40	-	-
P_{90}	-	40	20	40	-	-
P_{91}	-	-	-	-	-	-
P_{92}	-	-	40	40	-	-
P_{93}	-	100	20	20	-	-
P_{94}	-	-	-	100	-	-
P_{95}	-	-	-	100	-	-
P_{96}	20	40	20	20	-	-
P_{97}	-	-	-	-	-	-
P_{98}	-	-	40	-	-	-
P_{99}	-	20	20	20	-	-
P_{100}	-	-	-	-	-	-
P_{101}	-	40	40	100	-	-
P_{102}	-	-	-	-	-	-
P_{103}	-	-	-	40	-	-
P_{104}	-	-	-	40	-	-
P_{105}	-	-	40	40	-	-
P_{106}	-	-	-	40	100	100
P_{107}	-	-	-	40	100	100
P_{108}	-	-	-	-	-	-
P_{109}	-	100	40	100	-	-
P_{110}	40	40	20	20	-	-
P_{111}	-	-	-	100	-	100
P_{112}	-	-	-	-	-	-
P_{113}	-	-	-	40	-	-
P_{114}	-	40	20	40	-	-
P_{115}	-	100	20	20	-	-

1	2	3	4	5	6	7
P_{116}	-	-	-	100	-	-
P_{117}	-	-	-	-	-	-
P_{118}	-	100	40	100	-	100
P_{119}	-	100	-	100	-	100
P_{120}	-	-	40	100	-	-
P_{121}	-	-	-	40	-	-
P_{122}	40	100	20	20	-	-
P_{123}	-	-	40	40	-	-
Phenytoin	20	20	×	×	100	100
Diazepam	×	×	20	20	-	-

[a]Doses of 20, 40, 100 mg/kg of the compounds were administered and the protection as well as toxicity were measured after 0.5 and 4.0 hours. The figures indicate the minimal concentration of sample required to cause either protection or toxicity in more than 50 % of mice. The dash (-) indicates the absence of activity/toxicity, while '×' denotes 'not tested'.

In MES method, compounds **P_{90}**, **P_{93}**, **P_{96}**, **P_{99}**, **P_{101}**, **P_{109}**, **P_{110}**, **P_{114}**, **P_{115}**, **P_{118}**, **P_{119}** and **P_{122}** were found to be active antiepileptic agents. Amongst them, compounds **P_{96}**, **P_{110}** and **P_{122}** displayed reasonably good activity in both the durations 0.5 and 4 hr, indicating that they possess rapid onset and long duration of action. Other active compounds showed their activity only after 4 h, which demonstrated their slow onset of action. The final compounds exhibited more activity in scPTZ method than that of MES method, indicating their ability to raise the seizure threshold effectively (Stables and Kupferberg 1997). In scPTZ method, many tested compounds exhibited rapid onset and long duration of action by displaying activity in both 0.5 and 4 hours durations. Particularly, compounds **P_{93}**, **P_{96}**, **P_{99}**, **P_{110}**, **P_{115}** and **P_{122}** exhibited complete protection against seizure at 20 mg/kg.

From the screening results, it can be seen that substitution by electron donating methyl group on phenyl ring present at position-2 of imidazo[1,2-a]pyridine enhances the anticonvulsant property of new oximes **P_{90}**, **P_{93}** and their alkylated derivatives **P_{96}**, **P_{99}**. Substitution of phenyl ring by fluoro group as in compounds **P_{89}**, **P_{92}**, **P_{95}**, **P_{98}** resulted in moderate activity, whereas less activity was observed for unsubstituted phenyl derivatives **P_{88}**, **P_{91}**, **P_{94}**, and **P_{97}**. Similar trend was observed for 1,2,3-triazole derivatives **$P_{100\text{-}123}$** also. Interestingly, when electron donating methyl group was

introduced to imidazo[1,2-a]pyridine nuclei, the enhanced antiepileptic property was observed for compounds **$P_{100\text{-}111}$** carrying electron rich benzyl substituted triazoles. Amongst **$P_{100\text{-}111}$**, the triazoles carrying methoxybenzyl analogues **P_{101}**, **P_{105}** and **P_{109}** were found to be more active than corresponding methyl derivatives **P_{100}**, **P_{104}** and **P_{108}**, while less activity was observed for those containing electron withdrawing groups such as nitro and nitrile moieties. However, the compound **P_{110}** carrying nitro group showed complete protection from seizures and appeared as one of the lead compound. On the other hand, contradictory results were observed for 6-bromoimidazo[1,2-a]pyridine carrying triazoles **$P_{112\text{-}123}$**, wherein presence of electron withdrawing substituents such as 4-nitrobenzyl (**P_{114}**, **P_{118}** and **P_{122}**) or 4-cyanobenzyl group (**P_{115}**, **P_{119}** and **P_{123}**) on triazole moiety enhances the activity. Here also, substitution of imidazo[1,2-a]pyridine ring by 4-methylphenyl ring at position-2 resulted in improved antiepileptic activity. Complete protection was observed for compounds **P_{115}** and **P_{123}** containing cyanobenzyl and nitrobenzyl substituents, respectively.

Results of neurotoxicity study revealed that majority of tested compounds are non-toxic at all the tested doses. However, compounds **P_{106}**, **P_{107}**, **P_{111}**, **P_{118}** and **P_{119}** were found to be toxic at relatively high dose (100 mg/kg). From the screening results, it can be concluded that neither imidazo[1,2-a]pyridine nucleus nor 1,2,3-triazole ring is responsible for their toxicity, but their neurotoxic nature is mainly attributed to the presence of substituents in the hybrid molecules. Further, it was observed that molecules containing electron withdrawing nitro (**P_{106}**, **P_{118}**) and nitrile substitutents (**P_{107}**, **P_{111}**, **P_{119}**) attached to benzyl ring have exhibited toxicity.

4.3.1.5 Imidazo[1,2-a]pyridine-2-carbohydrazide derivatives ($P_{124\text{-}138}$)

In this series, fifteen new imidazo[1,2-a]pyridine-2-carbohydrazide derivatives (**$P_{124\text{-}138}$**) were screened for their *in vivo* antiepileptic and toxicity studies by taking 20, 40 and 100 mg/kg doses. The results are tabulated in Table 4.6. The anticonvulsant results indicated that compounds **P_{125}**, **P_{126}**, **P_{129}**, **P_{130}**, **P_{133}**, **P_{134}** and **P_{135}** were active in MES method, while all the tested compounds except **P_{132}** and **P_{138}** were active in scPTZ method. Among MES active compounds, hydrazones carrying electron donating groups were found to be more active than those containing electron

withdrawing substituents. Compound **P_{129}** carrying 4-amino-1,2,4-triazole moiety displayed the highest activity at both the intervals (0.5 and 4 h) indicating its fast onset and long duration of action. On the other hand, most of the compounds exhibited prominent activity in both the intervals as indicated by the results of PTZ method, which clearly shows that they can raise seizure threshold effectively (Stables and Kupferberg 1997). Compounds **P_{125}** and **P_{129}** exhibited complete protection from seizure at 20 mg/kg dose and appeared as lead derivatives of this series.

The *in vivo* results indicated that the presence of electron donating groups on aryl moiety enhances the anticonvulsant property remarkably. This was evidenced by the hydrazone derivatives (**$P_{124\text{-}128}$**), wherein compound **$P_{124\text{-}126}$** and **P_{128}** carrying electron donating groups were more active than compound **P_{127}** that contains nitrophenyl moiety. The compound **P_{125}** carrying 4-hydroxyphenyl group exhibited complete protection from seizure at 20 mg/kg, which may be attributed to the presence of hydrogen bond donating hydroxyl group in the molecule. Similarly, 4-amino-1,2,4-triazole derivative **P_{129}** carrying hydrogen bond donor as well as acceptor groups showed similar activity (100 % protection) in scPTZ method. Coupling of the amine group with various aldehydes has led to decrease in anticonvulsant activity. This clearly confirms the importance of amine group for enhanced anticonvulsant activity. In Schiff bases **$P_{130\text{-}133}$**, the presence of electron donating groups, viz. hydroxyphenyl, tolyl and fluorophenyl groups caused good activity, as observed in compounds **$P_{130\text{-}131}$** and **P_{133}**, respectively. In the same way, another 1,2,4-triazole-3-thiol derivative **P_{134}** also displayed good activity at 40 mg/kg. The same extent of activity was retained when the thiol group was alkylated with propyl group. However, replacement of propyl chain by aryl rings resulted in considerable decrease in their activity. The reason may be attributed to the fact that the presence of more bulky groups might disturb the direct ligand-receptor interaction by inducing steric hindrance on the moiety.

Table 4.6: Anticonvulsant and toxicity screening results of final compounds **$P_{124-138}$**

Sample	MES[a]		scPTZ[a]		Toxicity results[a]	
	0.5	4.0	0.5	4.0	0.5	4.0
P_{124}	-	-	40	40	-	-
P_{125}	-	40	20	20	-	-
P_{126}	40	-	20	40	-	-
P_{127}	-	-	100	100	-	-
P_{128}	-	-	40	40	-	-
P_{129}	20	40	20	20	-	-
P_{130}	-	40	40	40	-	-
P_{131}	-	-	-	100	-	-
P_{132}	-	-	-	-	-	-
P_{133}	40	-	40	100	-	-
P_{134}	-	100	40	40	-	-
P_{135}	-	40	40	40	-	-
P_{136}	-	-	100	100	-	-
P_{137}	-	-	-	100	-	-
P_{138}	-	-	-	-	-	-
Phenytoin	20	20	×	×	100	100
Diazepam	×	×	20	20	-	-

[a]Doses of 20, 40, 100 mg/kg of the compounds were administered and the protection as well as toxicity were measured after 0.5 and 4.0 hours. The figures indicate the minimal concentration of sample required to cause either protection or toxicity in more than 50 % of mice. The dash (-) indicates the absence of activity/toxicity, while '×' denotes 'not tested'.

The toxicity study revealed that new imidazo[1,2-a]pyridines are non-toxic at all the tested doses. So, the new compounds can be considered as non-toxic anticonvulsants. In conclusion, the linking of imidazo[1,2-a]pyridines with triazole and hydrazone moieties resulted in improved activity without producing any toxicity up to 100 mg/kg. Particularly, those hybrids possessing electron donating and hydrogen bond donor/acceptor groups exhibited pronounced activity. The compounds **P_{125}** and **P_{129}** exhibited complete protection and so, they can be considered as active templates for future anticonvulsant studies.

4.4 CONCLUSIONS

The newly synthesized DHP and imidazo[1,2-a]pyridine derivatives were screened for their preliminary *in vivo* anticonvulsant study following MES and scPTZ methods at various doses. Further, the neurotoxicity study of these compounds was performed by Rotarod technique. It was observed that DHP derivatives carrying electron rich aryl systems displayed the activity at 300 mg/kg, without exhibiting any neurotoxicity. On the other hand, imidazo[1,2-a]pyridines displayed their antiepileptic activity at smaller doses itself. Few of the synthesized imidazo[1,2-a]pyridine derivatives exhibited complete protection against seizures and appeared as lead derivatives. As a general observation, presence of aryl groups carrying fluoro, methyl and methoxy groups at position-2 of imidazo[1,2-a]pyridine ring enhanced their activity significantly.

CHAPTER-5

SUMMARY AND CONCLUSIONS

Abstract

This chapter includes the summary of the entire research work and important conclusions drawn from the results of series of experiments.

5.1 SUMMARY AND CONCLUSIONS

The epilepsy is second major neurological disease of brain, after stroke that affects about 1% of world's population. It appears more severe, since the available medications are only able to control the disease, while they fail to cure the disease completely. The various side effects of the AEDs limit their applicability and so, hunt for effective new AEDs has increased enormously. Eventually, design and development of new efficient antiepileptic agents has become an active research area.

In this context, the present research work mainly focused on design and synthesis of new DHP and imidazo[1,2-a]pyridine derivatives as effective anticonvulsant agents, due to well-established calcium channel blocking and GABA agonist capability of DHP and imidazo[1,2-a]pyridine derivatives, respectively. Further, based on literature supports, various pharmacophores such as hydrazones, amides, triazoles, pyrazolines, oxazolones and pyrimidines were incorporated in the new design along with DHPs and imidazo[1,2-a]pyridine core moiety, with the hope of getting enhanced antiepileptic activity.

Accordingly, following five new series of target compounds were synthesized through multistep organic synthetic routes.

(i) DHP derivatives carrying hydrazone and amide functionalities (**P_{1-40}**)
(ii) Imidazo[1,2-a]pyridine-3-carboxaldehyde derivatives (**P_{41-64}**)
(iii) Chalcone derivatives containing imidazo[1,2-a]pyridines (**P_{65-87}**)
(iv) Imidazo[1,2-a]pyridines carrying (1,2,3-triazol-4-yl)methyl oxime (**P_{88-123}**)
(v) Imidazo[1,2-a]pyridine-2-carbohydrazide derivatives (**$P_{124-138}$**)

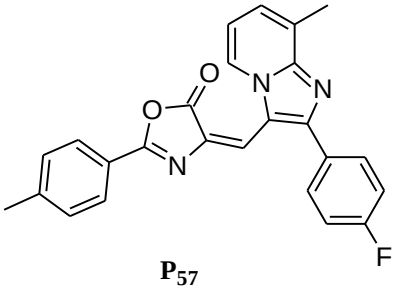
The newly synthesized compounds were purified by recrystallization and/or column chromatography techniques and their synthetic methods were established. The structures of new intermediates and target compounds were confirmed by various spectral and elemental analysis studies. Further, X-ray crystallographic study was carried out for few compounds in order to elucidate their final structure.

The newly synthesized target compounds were screened for their *in vivo* anticonvulsant study following MES and scPTZ methodologies, by taking phenytoin and diazepam as standard drugs, respectively. Also, their neurotoxic profile was explored by Rotarod technique at three different test doses. In screening study of DHPs (**P_{1-40}**), three standard doses, i.e. 30, 100 and 300 mg/kg were used, while relatively small doses, i.e. 20, 40 and 100 mg/kg were employed for the screening study of imidazo[1,2-a]pyridines (**P_{41-64}** and **P_{88-138}**), as they were found to be more active at lower doses itself. A single dose of 10 mg/kg was fixed for imidazo[1,2-a]pyridines **P_{65-87}**, since sedative symptoms were observed at higher dose (100 mg/kg) for few tested compounds. Based on the results of preliminary *in vivo* studies, **P_{57}**, **P_{58}**, **P_{93}**, **P_{96}**, **P_{99}**, **P_{110}**, **P_{115}**, **P_{122}**, **P_{125}** and **P_{129}** were identified as active lead compounds.

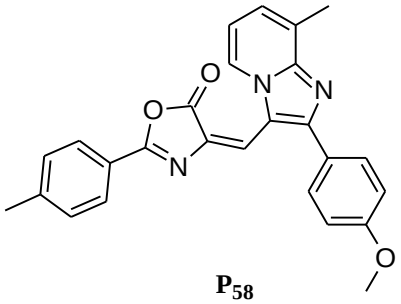
Following important conclusions have been drawn from the present research work.

- Newly designed compounds **P_{1-138}** were successfully synthesized. Their synthetic methods as well as purification techniques were established and their structures were confirmed by various spectral studies. Their *in vivo* antiepileptic study by MES and scPTZ methods indicated that the new DHPs display moderate activity in MES method, while imidazo[1,2-a]pyridines exhibit better activity in scPTZ method than that in MES method.
- The Rotarod study clearly showed that most of the newly synthesized compounds are non-toxic at tested doses. Thus, the new compounds can be considered as non-toxic anticonvulsant agents. Only few imidazo[1,2-a]pyridines exhibited toxicity at higher doses (100 mg/kg), which clearly shows that neither imidazo[1,2-a] pyridine, nor the pharmacophore, is responsible for their toxicity, but they rely mainly upon the nature of substituents present on whole moiety.
- The nature of substituents at position-2 and position-3 of imidazo[1,2-a]pyridines were found to be crucial in deciding the efficacy of a molecule. Compounds possessing 4-fluorophenyl, 4-tolyl and 4-anisolyl groups at position-2 exhibited enhanced activity. Similarly, incorporation of pyrazoline, cyanopyridone, triazole, oxazolone and pyrimidine heterocyclic rings at position-3 was found to enhance their anticonvulsant activity significantly.

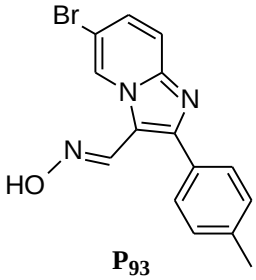
- Imidazo[1,2-a]pyridines **P_{65}** and **P_{66}** carrying pyrazoline group, **$P_{70\text{-}72}$** carrying cyanopyridine ring, **P_{54}**, **P_{55}**, **P_{57}**, **P_{58}** containing oxazolone moiety, **$P_{92\text{-}93}$**, **P_{96}**, **P_{99}**, **P_{101}**, **$P_{109\text{-}110}$**, **$P_{114\text{-}115}$** **P_{118}**, **P_{120}** and **P_{122}** bearing 1,2,3-triazoles at position-3 displayed very good seizure protection at lower doses. Similarly, imidazo[1,2-a]pyridines carrying hydrazone (**$P_{124\text{-}128}$**) and 1,2,4-triazole system (**$P_{129\text{-}131}$**, **$P_{133\text{-}137}$**) at position-2 showed remarkable antiepileptic protection in scPTZ method.
- Compounds **P_{57}**, **P_{58}**, **P_{93}**, **P_{96}**, **P_{99}**, **P_{110}**, **P_{115}**, **P_{122}**, **P_{125}** and **P_{129}** exhibited complete protection from seizure at lower doses (20 and 40 mg/kg) itself. The structures of these lead compounds are given below.



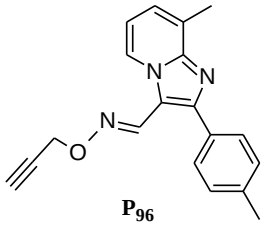
P_{57}



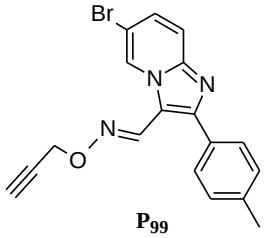
P_{58}



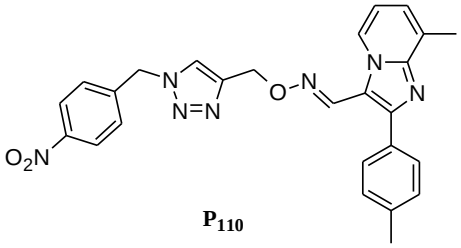
P_{93}



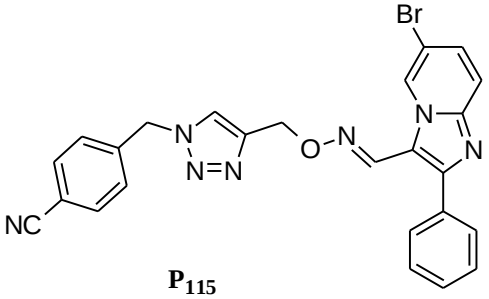
P_{96}



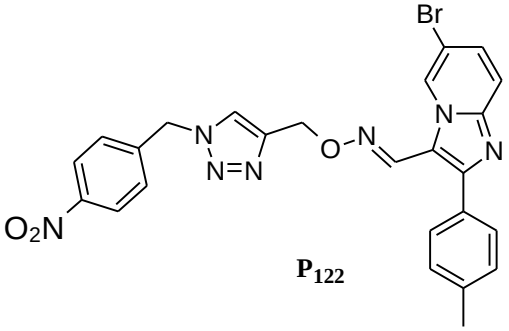
P_{99}



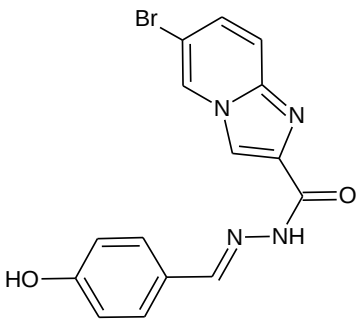
P_{110}



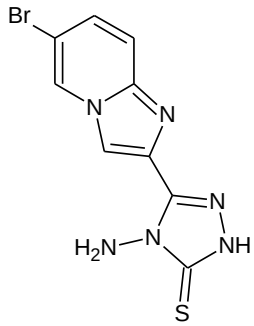
P_{115}



P_{122}



P_{125}



P_{129}

Thus, the present research work identified a few antiepileptic agents, which displayed complete seizure protection in scPTZ method and non-toxicity in Rotarod study. The lead compounds obtained in the present work can be taken for further detailed antiepileptic study that may result in development of new effective AEDs in near future. Furthermore, proper structural modification of imidazo[1,2-a]pyridines may bring about enhancement in their antiepileptic activity to a desired level. Also, the new derivatives may possess other medicinal properties, which may be explored by various screening techniques. The new derivatives may also find utility in other research areas such as polymer, agrochemicals, photo-electronics etc.

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List of publications

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[1] Shrikanth Ulloora, Airody Vasudeva Adhikari, "Synthesis, characterization and biological study of some new dihydropyridine derivatives." International Conference on Vistas in Chemistry (ICVC-2011), Indira Ghandhi Centre for Atomic Research (IGCAR), Kalpakkam, Chennai, India, October 11-13, 2011.

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List of Publications

1. Shrikanth Ulloora, Santhosh Kumar, Ramakrishna Shabaraya, Airody Vasudeva Adhikari. "New Dihydropyridine derivatives: Anti-inflammatory, analgesic and docking studies." *Med. Chem. Res.*, 2013, 22 (04), 1549-1562.
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