Synthesis and Characterization of Some Nitrogen Heterocycles and Their Coordination Complexes

A Dissertation Submitted to the
Indian Institute of Technology Guwahati as
Partial Fulfillment for the Degree of Doctor of Philosophy
in Chemistry

by

Jugal Bori
Roll No. 126122043

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati – 781 039

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Dedicated to

My Parents

“Nothing in life is to be feared, it is only to be understood.”

-Marie Curie

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
GUWAHATI–781039

DECLARATION

I do hereby declare that the research work embodied in this thesis entitled "**Synthesis and Characterization of Some Nitrogen Heterocycles and Their Coordination Complexes**" is the outcome of research work carried out by me under the supervision of Prof. V. Manivannan, at the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India.

In keeping with the general practice of reporting scientific observations, due acknowledgments have been made wherever the work described is based on the findings of other investigators.

IIT Guwahati
March, 2020

Jugal Bori
(Roll. No. 126122043)


भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Dr. V. Manivannan
Professor
Department of Chemistry
Indian Institute of Technology
Guwahati-781039
Assam, INDIA

Ph: +91 361 258 2306 (O)
E-mail: mani@iitg.ac.in

CERTIFICATE

This is to certify that the research work presented in this thesis entitled "***Synthesis and Characterization of Some Nitrogen Heterocycles and Their Coordination Complexes***" is an authentic record of the results obtained from the research work carried out by **Mr. Jugal Bori**, a part-time student, under my supervision in the Department of Chemistry, Indian Institute of Technology Guwahati, India. This work is original and has not been submitted elsewhere for a degree.

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March, 2020

Prof. V. Manivannan
(Thesis Supervisor)

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Jugal Bori

PREFACE

This thesis contains five chapters. The Chapter 1 is the review chapter, where a literature report of synthetic approaches towards pyrimidines, imidazo[1,5-a]pyridines and imidazo[1,5-a]isoqinolines have been described. This chapter also highlights the materials and methods used for the synthesis and characterizations of compounds discussed in the thesis.

The Chapter 2 describes the synthesis of 2,4,6-tris(2-pyridyl)pyrimidine (**L1**), 2,4-bis(2-pyridyl)-6-(3-pyridyl)pyrimidine (**L2**) and 2,4-bis(2-pyridyl)-6-(4-pyridyl)pyrimidine (**L3**) from 2-cyanopyridine and respective acetylpyridines. This chapter also highlights the utility of **L1** as a ligand and by using **L1**, complexes of composition $[Ni(\mathbf{L1})(H_2O)_3](NO_3)_2\cdot 4H_2O$ (**1**), $[Ni(\mathbf{L1})_2](NO_3)_2\cdot 2H_2O$ (**2**) and $[Co(\mathbf{L1})_2](NO_3)_2\cdot 1.5H_2O$ (**3**) were isolated and structurally characterized.

In Chapter 3, the coordination chemistry of the ligand *N*-(3-(pyridine-2-yl)imidazo[1,5-a]pyridine-1-yl)picolinimidamide (**L4**) with nickel(II) has been described. Two binuclear Ni(II) complexes of composition $[Ni_2(\mathbf{L4})_2(Cl)_2(H_2O)_2]Cl_2\cdot 12H_2O$(**4**) and $[Ni_2(\mathbf{L4})_2(N_3)_3](N_3)\cdot 3H_2O$ (**5**) have been synthesized and characterized along with coligands Cl^- and N_3^-. The ligand **L4** acts as a bridging bis(bidentate) ligand each nickel center has pseudo-octahedral coordination geometry in both the complexes

In Chapter 4, a novel synthetic methodology has been described for construction of the imidazo[5, 1-a]isoquinoline nucleus from 1-isoquinolinemethylamine and various aldehydes by using selenium dioxide as an oxidant. When 1-isoqunolinemethylamine was employed without any aldehyde, 3-(1-isoquinolinyl)imidazo[5,1-a]isoquinoline (**IQ-1**) was isolated, which is fluorescent in nature.

In Chapter 5, a new convenient route for synthesis of 3-substituted-imidazo[1,5-a]pyridines has been described as well as the scope and limitations of the method is evaluated.

Abbreviations

a	Unit cell dimension a
b	Unit cell dimension b
c	Unit cell dimension c
α	Interfacial angle α in a unit cell
β	Interfacial angle β in a unit cell
γ	Interfacial angle γ in a unit cell
z	Unit cell formula units
λ	Wave length
ν	Wave number
μ	Absorption coefficient
ε	Molar extinction coefficient
τ	Geometric parameter applicable for five-coordinate structures as an index of trigonality between trigonal bipyramidal and rectangular pyramidal
δ	Chemical Shift in NMR
μ_{eff}	Effective Magnetic moment
H	Applied magnetic field
g	Lande splitting factor
A	Hyperfine splitting constant
Acac	Acetylacetonato
Bpy	2,2′-bipyridyl
BOP	Bis(2-oxo-3-oxazolidinyl)phosphine
BTC	Bis(trichloromethyl)carbonate
DABCO	1,4-Diazabyciclo[2.2.2]octane
Dba	Dibenzylideneacetone
DBU	1,8-Diazabyciclo

DCB	Dichlorobenzene
DCCD	1,3-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DMSO	Dimethyl sulfoxide
HMDS	1,1,1,3,3,3-hexamethyldisilizane
LDA	Lithium diisopropylamine
HOMO	Highest occupied molecular orbital
IR	Infrared
LUMO	Lowest unoccupied molecular orbital
NMR	Nuclear magnetic resonance
NIS	*N*-iodosuccinimide
ORTEP	Oak ridge thermal ellipsoid program
ppm	Parts per million
TBHP	t-Butylhydroperoxide
TEMPO	Tetramethylpiperidinyloxy
TFA	Trifluoroacetic(yl)
TFP	Tris(o-furyl)phosphine
TLC	Thin layer chromatography
Ts	Tosyl
T_3P	Propanephosphonic acid anhydride

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Chapter 1

Synthetic Approaches of Pyrimidine, Imidazo[1,5-*a*]pyridine and Imidazo[1,5-A]isoqinoline: A Review

1.1. Introduction

Heterocyclic compounds are one of the most important classes of organic chemistry. The name heterocycle follows the Greek word “heteros” which means “different”. These compounds are the largest class of known organic compounds. Heterocyclic compounds are carbocyclic compounds where atleast one atom other than carbon presents in the ring system. Generally, the hetero i.e. noncarbon atoms are nitrogen, oxygen and sulphur. Other heteroatoms such as Se, P, Si and B are also widely known [1-6]. Heterocyclic moieties are present in various medicines [7-9], pesticides [10], and many natural products [11-13]. These are also considerable interest because of their physiological activities [14], utility as synthetic intermediates, as ligands in coordination chemistry [15,16], as protecting groups and as catalysts in organic catalysis [17,18].

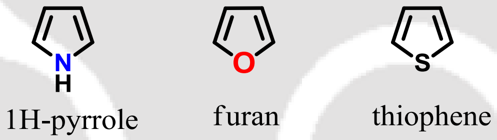


Figure 1.1. Examples of N, O and S-containing heterocycles.

1.2. Nitrogen-Containing Heterocycles

Nitrogen-containing heterocycles are also popularly known as azaheterocycles. Azaheterocycles are one of the largest classes of heterocyclic compounds, widely spread in nature and are very essential for survival of living organisms. In nature, the azaheterocycles such as haemoglobin and chlorophyll have fundamental importance to life. Furthermore, deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA), which are the genetic information carriers, composed of azaheterocycles like- adenine and guanine (purine bases), cytosine and thymine (pyrimidine bases) and uracil [19-23]. Again, azaheterocycles like morphine [24], penicillin, captopril and vincristine have been used as a medicinal drug for many decades. The five-membered, aromatic nitrogen heterocycles containing drugs are: atorvastatin, celecoxib cimetidine, fluconazole, losartan and many more.

Thus a vast number of nitrogen-containing heterocyclic building blocks have been found and are of a large varieties of applications in different fields of natural product chemistry, biologically active compounds, agriculture science, drug discovery, material and polymer sciences and recently coordination as well as catalytic chemistry [1,25-35]. Thus through the decades nitrogen-containing heterocycles have caught the interest of researchers. Substantial attention has been paid for the development of new synthetic methodologies to the nitrogen containing heterocyclic compounds. In this chapter, the literature on the synthesis of pyrimidine, imidazo[1,5-a]pyridine and imidazo[1,5-a]isoqinoline have been discussed.

1.3.Pyrimidine

Pyrimidine belongs to a significant class of azaheterocycles. It is a six-membered ring system of one diazine group, where the two N-atoms occupy the 1 and 3 positions of the ring. Three isomeric forms of diazines are possible according to the positions of the two nitrogen atoms. These are *o*-diazine or pyridazine, *m*-diazine or pyrimidine and *p*-diazine or pyrazine respectively [1].

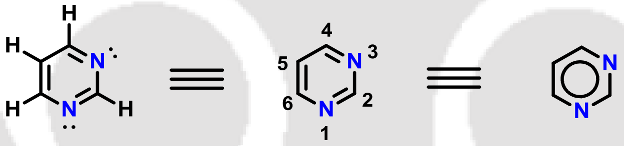
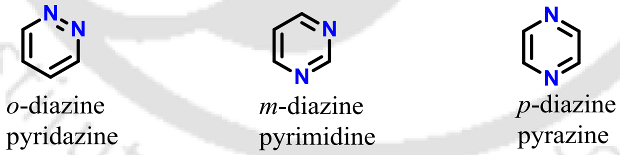


Figure 1.2. Pyrimidine moiety



o-diazine
pyridazine

m-diazine
pyrimidine

p-diazine
pyrazine

Figure 1.3. Three possible isomeric diazines.

Pyrimidine is a resonance hybrid of the following resonating structures.

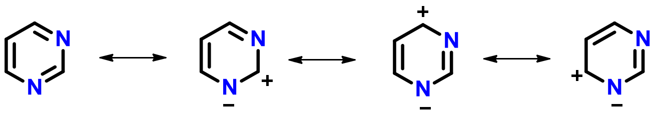


Figure 1.4. Possible resonance structures of pyrimidine.

The electron density of the pyrimidine ring is the highest at position 5 due to the ring deactivation of resonance. Thus the nucleophilic attack at positions 2, 4, and 6 of the pyrimidine ring is very much facilitated [1].

Pyrimidines are largely distributed among the natural products, pharmaceutical drugs, photochemical materials, polymers, inorganic catalysts and coordination chemistry [1,3,38-43]. Some examples of pharmaceutically important pyrimidines are trimethoprim [44], sulfadiazine [45], imatinib mesilate [46], capecitabine [47], orotate and HPI-2 [3]. There is a rich history for the development of synthetic methodologies for pyrimidines. Discovering new pyrimidine synthetic strategies always remains a vital field for researchers.

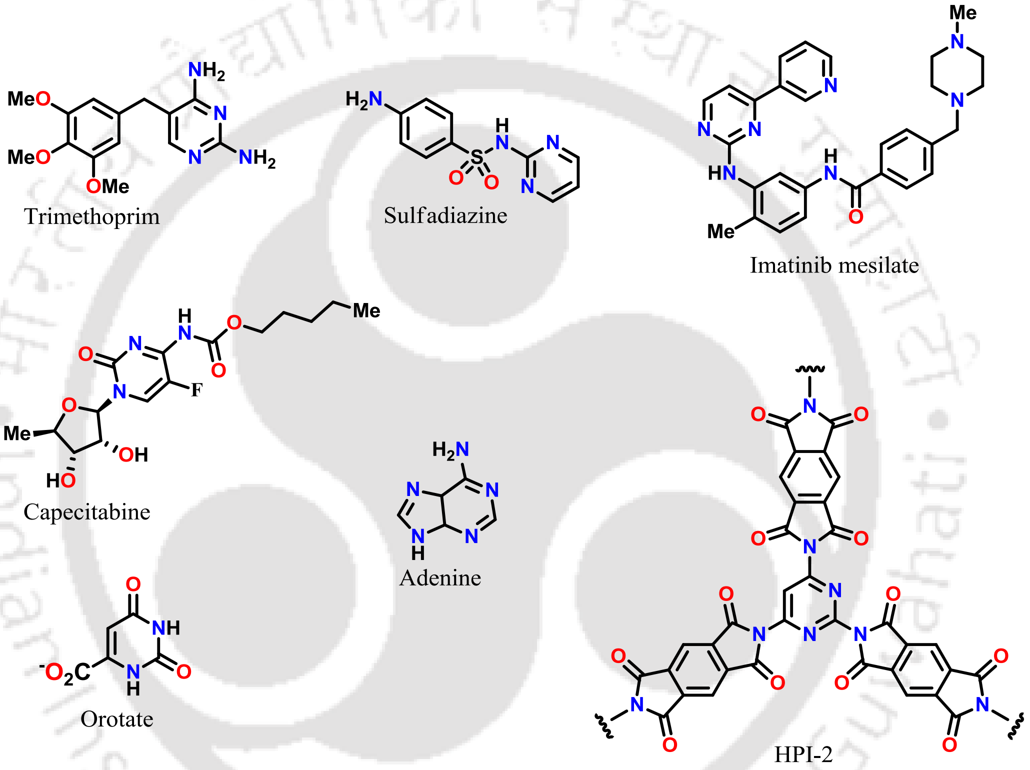
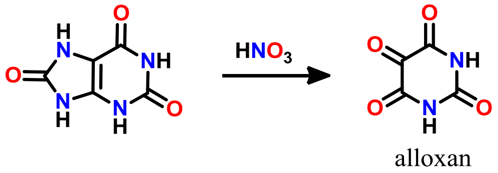


Figure 1.4. Some examples of bioactive pyrimidines.

1.4.Synthesis of Pyrimidine

In 1818, alloxan, the first pyrimidines was synthesized by Brugnatelli. It was synthesized by the degradation of uric acid with nitric acid [48]. Again, from propionitrile and potassium metal, Frankland and Kolbe synthesized the first pyrimidine cyanalkine in 1848 [49]. In 1899, Gabriel and Colman early reported the first isolation of pyrimidine by the pyrimidine-4-carboxylic acid decarboxylation [50].

Brugnatelli alloxan synthesis



Frankland and kolbe cyanalkine synthesis

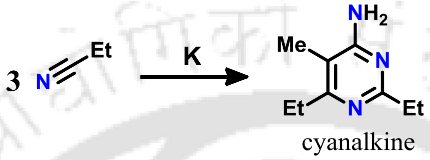


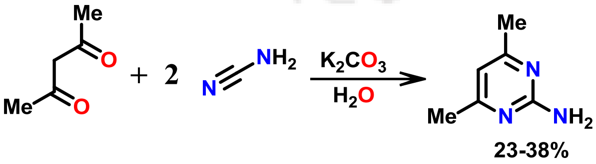
Figure 1.5. Synthesis of pyrimidines (early reports).

Since these early reports, a number of synthetic methodologies for the preparation of pyrimidines have been developed. Depending on the reagents involved on the synthesis of pyrimidines, the developed synthetic methodologies can be subcategorized as follows-

1. By C–N fragments.
2. N-C-N condensations.
3. Alternative Strategies.

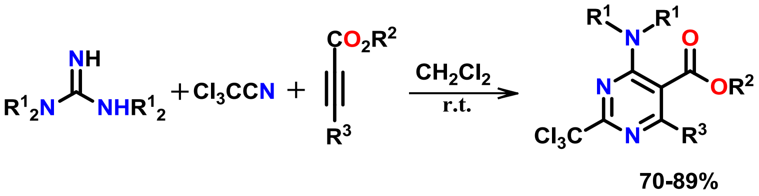
1.4.1. By C–N Fragments

It is a versatile process to the pyrimidine synthesis by utilizing the C–N fragments. Nitriles have been used in many synthetic strategies of pyrimidines because it has a common C–N source. Cyanamide is one of the most useful C–N sources in the pyrimidine synthesis. Cyanamide react with 2,4-pentanedione in water to give of 2-amino-4,6-dimethylpyrimidine after 8 hours in neutral condition [51].



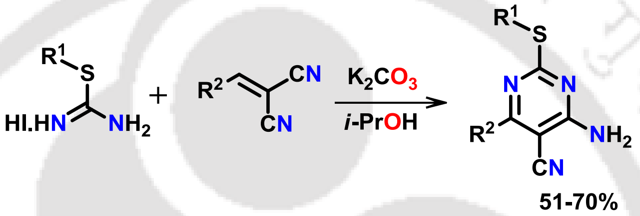
J. Org. Chem. 1984, **49**, 4072-4074.

Synthesis of trichloromethylated pyrimidines in good yields were described by a one-pot reaction between tetramethylguanidine or guanidine, trichloroacetonitrile and activated acetylenic esters [52].



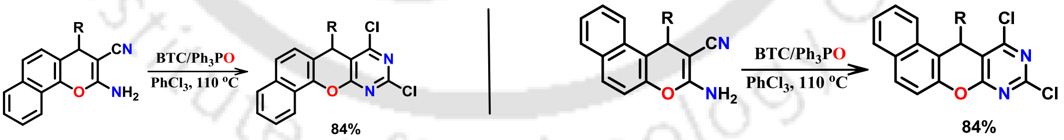
Tetrahedron Lett., 2016, **57**, 1733-1735.

Varieties of fused 2-alkylthiopyrimidines were synthesized from arylidenemalononitriles through simple condensation with different 2-alkylthiouronium halides with moderate to good yields, where anhydrous potassium carbonate was used as a catalyst [53].



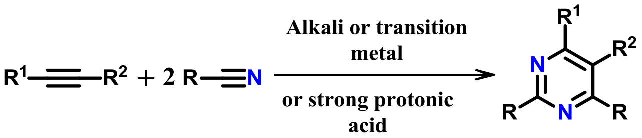
Synth. Commun., 2019, **49**, 395-403.

Different pyrano[2,3-*d*]pyrimidines were reported by the cyclizations of different chromenecarbonitriles. Cyclisation of 2-amino-4-aryl-4H- benzochromene-3-carbonitriles or 3-amino-1-aryl-1H-benzochromene-2-carbonitriles with bis(trichloromethyl) carbonate and triphenylphosphine oxide yields a series of 8,10-dichloro-7-aryl-7H- benzochromenopyrimidines and 9,11-dichloro-12-aryl-12H-benzochromenopyrimidines were described by the [54].

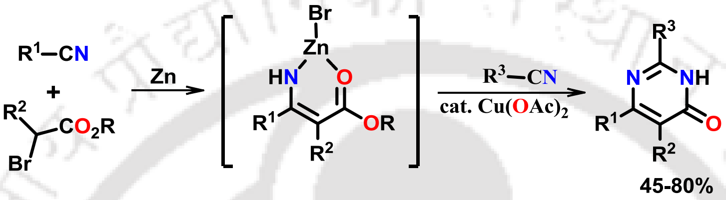


J. Chem. Res., 2014, **38**, 143-146.

From literature, in recent years several transition-metal-mediated/catalyzed cycloaddition reactions have been developed. The [2 + 2 + 2] intermolecular cycloaddition between nitriles and alkyne is one of the most simple and efficient methods of tetra- or trisubstituted pyrimidine synthesis in presence of an alkali or transition metal or a strong protonic acid (TfOH or H_3PO_4/BF_3) [55-60]. Again, Louie *et al*. reported that the FeI_2/Zn system can also be used successfully to the synthesis of bicyclic pyrimidines from alkyne nitriles and cyanamides [61].

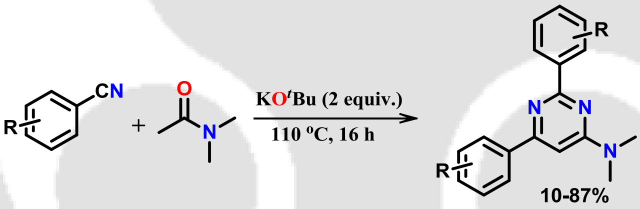


A one-pot synthetic strategy has described for the synthesis of a series of 2,5,6-trisubstituted pyrimidin-4-ones *via* Blaise followed by Pinner-type reaction. The intermediate, formed during the Blaise reaction react with the second nitrile chemoselectively with the Cu(OAc)$_2$ catalyst to afford pyrimidin-4-ones [62].



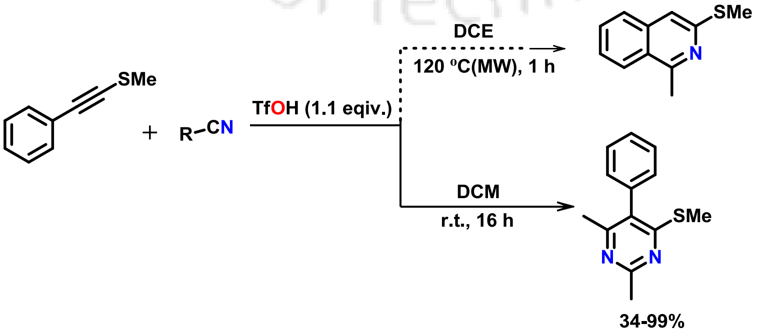
Org. Lett, 2012, **14**, 6358-6361.

Benzonitriles and aliphatic amides are used for one-step synthesis of multi-substituted 4-aminopyrimidines. KO^{t}Bu act as the promoter for the reaction [63].



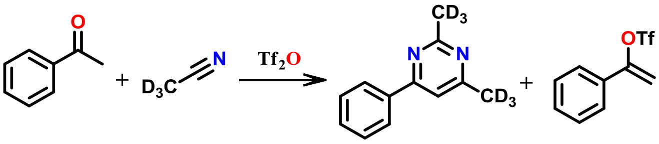
RSC Adv., 2015, **5**, 106444-106447.

Nitriles and ynamides or thioalkynes undergo cycloaddition reaction in metal-free condition for the synthesis of pyrimidine scaffolds. This is a acid-mediated regioselective reaction for orthogonal access of either pyrimidines or isoquinolines. [64].



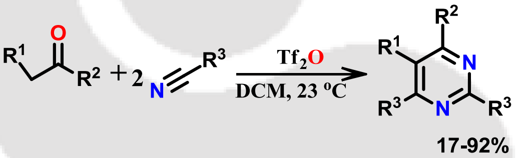
Nat. Commun., 2016, **7**, 10914.

The reaction between alkyl nitriles and aliphatic ketones in triflic anhydride was also reported for the formation of alkylpyrimidine [65].



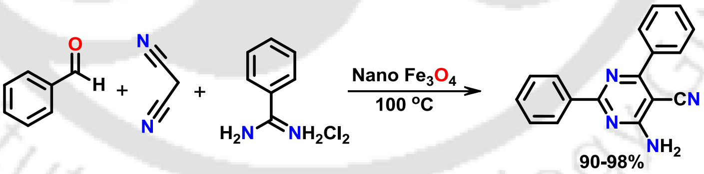
J. Am. Chem. Soc., 2012, **134**, 2706-2715.

MartKnez *et al*. reported a ketone-based pyrimidine synthetic strategy. Here 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidines were synthesized by the activation of various ketones with trifluoromethanesulfonic anhydride (Tf2O) followed by the reaction with two equivalents of nitriles. The all alicyclic and acyclic ketones were undergoing with this method to yield the desired product with good yields [66].



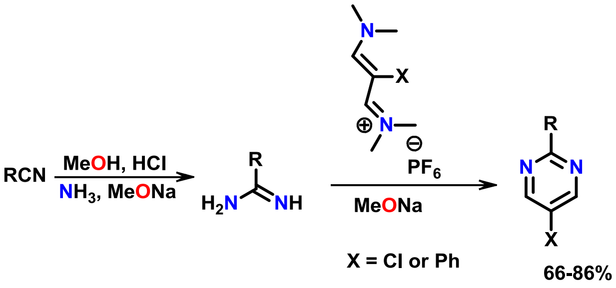
J. Org. Chem., 1992, **57**, 1627-1630.

Aromatic aldehydes, malonitrile, and benzamidine were undergoing condensation to synthesized the 2-phenyl-4-amino-5-cyano-6-arylpyrimidines. The condensation reaction was catalyzed by iron oxide [67].



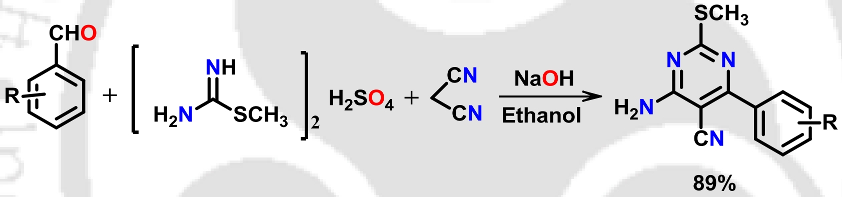
Chin. Chem. Lett., 2013, 24, 629-632.

Another one-pot process for the preparation of pyrimidines from simple nitrile has been demonstrated by Frutos and Wei. Direct condensation of amidine from the nitrile with 3-chloro- or 3-phenylvinamidinium gives the corresponding 2,5-disubstituted pyrimidines. However, the vinamidinium salts limit the scope of the reaction [68].



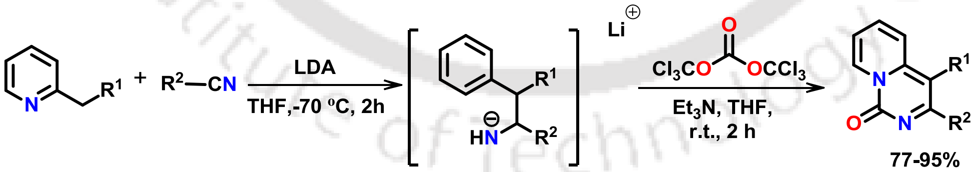
J. Org. Chem. Res. 2013, **78**, 5800-5803.

An efficient and facile multicomponent reaction synthetic method of thiosubstituted pyrimidines with nitrile has been reported. With the help of this multicomponent single step reaction, a series of 4-amino-6-aryl-2-alkylthiopyrimidine-5-carbonitriles were synthesized from aromatic aldehydes, malononitrile, and S-methylisothiouronium sulfate or S-benzylisothiourea hydrochloride in ethanolic NaOH [69].



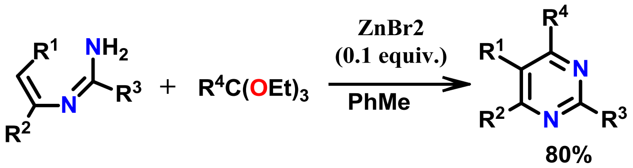
Res. Chem. Intermed., 2013, **39**, 3699-3707.

A three-component single-step coupling reaction of a nitrile, an α-acidic imine and triphosgene or carbon disulfide was developed for the synthesis of 3,4-fused pyrimidin-2-one and pyrimidin-2-thiones [70].



Eur. J. Org.Chem., 2009, **33**, 5738-5743.

Tri- and tetra-substituted pyrimidines from nitriles were described under catalyst and solvent-free conditions by the [5+1] annulation of enamidines. Here enamidines were prepared from nitriles, silanes and organolithium compounds where *N,N*-dimethylformamide dialkyl acetals as the C1 unit. Again polysubstituted pyrimidines were synthesized by using orthoesters as the C1 unit, $ZnBr_2$ as a catalyst in toluene or xylene under reflux conditions. Moreover, pyrido [2,3-*d*]pyrimidin-5-one frameworks has been formed by a ring-opening with [Mo(CO)$_6$] followed by ^{t}BuOK intramolecular cyclization [71].

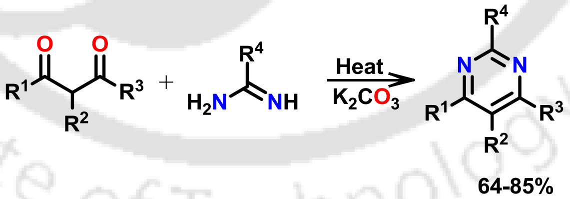


Eur. J. Org. Chem., 2011, **17**, 9385-9394.

1.4.2. N–C–N Condensations

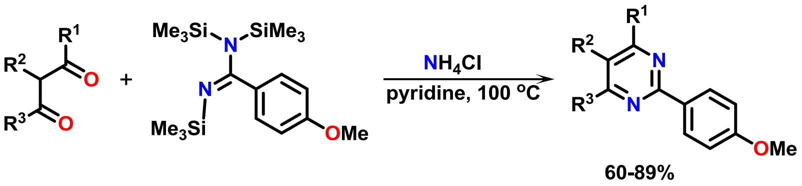
These succeed synthetic strategies involve the condensation of the compounds bearing N–C–N fragment and C–C–C fragments. Amidines or enamines are the most frequently used N–C–N fragments with the 1,3-dicarbonyl compounds and α,ß-unsaturated ketones or enones, the three-carbon fragments for the strategies [72-78]. While condensation could take place either by two-component or multicomponent reactions to afford the different pyrimidines. The recent progress in such reactions involving either greater variety in the resulting pyrimidines or on the use of alternative and more convenient and reactive 1,3-dicarbonyl substrates or on discovering new improved reaction conditions.

The historical Pinner reaction of pyrimidine synthesis by the condensation of 1,3-dicarbonyl compounds with amidines. Recently, many synthetic methodologies have been developed by following the same [72].



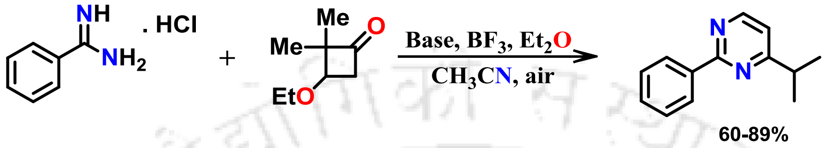
Ber. Dtsch. Chem. Ges, 1885, **18**, 2845-2852.

Ghosh and Katzenellenbogen prepared a series of 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidines by a modification to the Pinner pyrimidine synthesis [73].



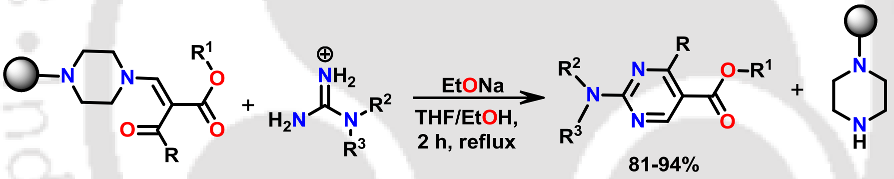
Heterocycl. Chem., 2002, **39**, 1101-1104.

Lewis acid-promoted [3+3] annulations, a transition metal-free, a direct and single-step methodology has been reported very recently for the synthesis of substituted pyrimidines. This [3+3] annulations strategy takes place between 3-ethoxycyclobutanones and enamines or amidines to produce a series of substituted pyrimidines [74].



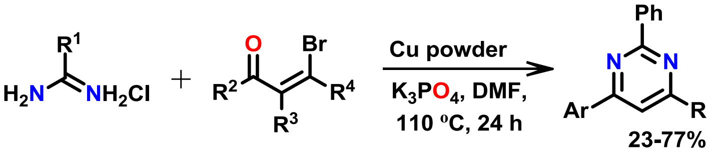
Adv. Synth. Catal., 2017, **359**, 952-958.

A resin capture and release strategy for the synthesis of 2,4,5-trisubstituted pyrimidines has described with microwave condition. *ß*-keto-esters and *ß*-keto-amides react through a cyclocondensation reaction with the help of a low-cost polymer under mild conditions to afford corresponding pyrimidines [75].



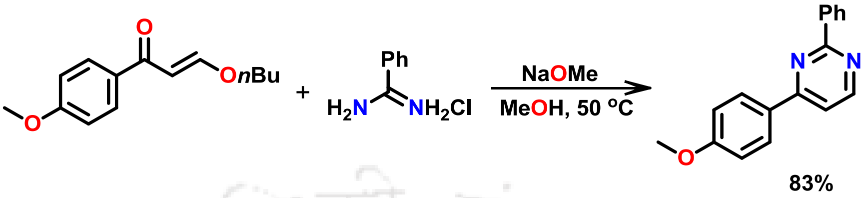
J. Comb.Chem., 2004, **6,** 105-111.

Most condensation strategies focus on reactive 1,3-dicarbonyl equivalents. ß-substituted-α,ß-unsaturated ketones are efficient precursors for the preparations of substituted pyrimidines. Cho and his co-workers reported that ß-bromo-α,ß-unsaturated ketones are very useful substrates for the pyrimidine synthesis. They allowed to condense ß-bromo-α,ß-unsaturated ketones with benzamidine or acetamidine in presence of Cu^0 catalyst for synthesizing corresponding pyrimidines [76].



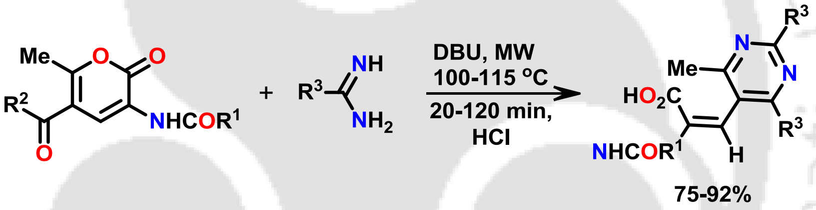
Synlett, 2015, **26**, 1081-1084.

Similarly, ß-*n*-butoxyenones such as (3-butoxy-1-(4-methoxyphenyl)prop-2-en-1-one) undergo condensation with benzamidine (benzimidamide hydrochloride) in basic conditions at 50^0C to form the corresponding pyrimidines [77].



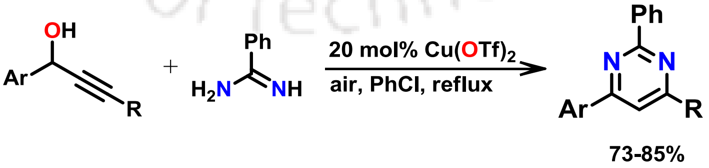
Org. Lett., 2012, **14**, 2536-2539.

In 1988, kvita *et al*. reported that amidines react with pyran-2-one nucleus and at C-2, C-4, and C-6 positions causing ring opening followed by recyclization into a pyrimidines. Thus 5-ethoxycarbonyl-2H-pyran-2-one with various amidines in presence of a base produces pyrano[2,3-d]pyrimidines under microwave-assisted conditions [78].



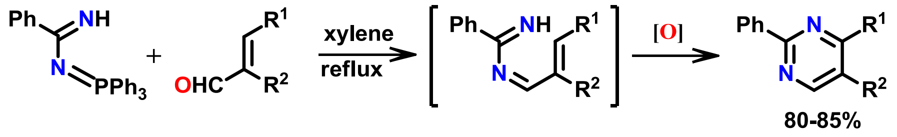
Tetrahedron Lett., 2009, **65**, 8216-8221.

In 2011, Zhan *et al*. reported a copper-catalyzed condensation reaction between benzamidine and propargyl alcohols for the preparation of corresponding pyrimidines. It provides a 3,4-dihydropyrimidine followed by the 6-*endo-dig* cyclization due to the nucleophilic substitution of the propargyl alcohol by the amidine. Then aerobic oxidation produces the corresponding pyrimidine in the same pot [79].



Synlett., 2011, **8**, 1179-1183.

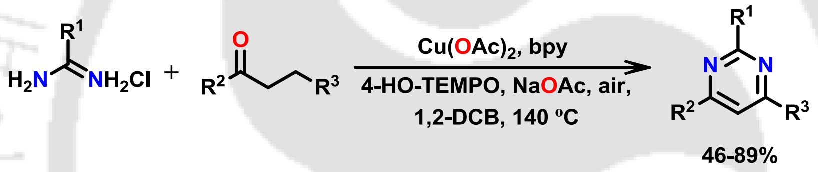
Iminophosphoranes and α, β-unsaturated aldehyde were used by Rossi *et al*. to afford 2,5-disubstituted and 2,4,5-trisubstituted pyrimidines *via* [3+3] approach. Pericyclization and autoxidation of the diazatriene intermediate afforded the corresponding pyrimidines with regiochemical control [80].



Synlett., 1999, **8**, 1265-1267.

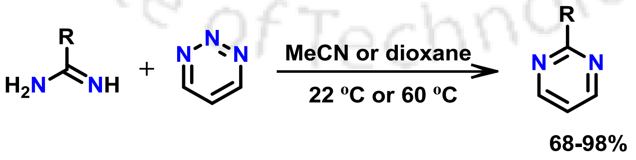
In 2016, Han reported that enones which were prepared from a saturated ketone in oxidative copper-catalyzed conditions undergo condensation with amidines to produce the corresponding 2,4-disubstituted and 2,4,6-trisubstituted pyrimidines. The oxidation of ketone to the corresponding enone proceeded through a single-electron transfer from the copper enolate.

In this method of pyrimidine synthesis oxidative dehydrogenation, annulations, oxidative aromatization of saturated ketones followed by annulation with amidines takes place [81].



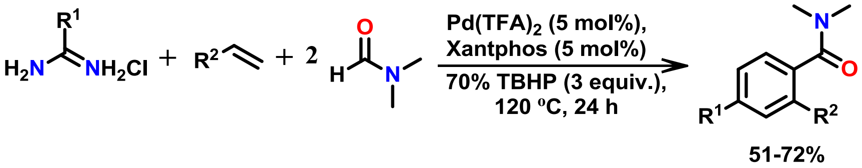
J. Org. Chem., 2016, **81**, 11994-12000.

In 2001, Anderson and Boger noticed a remarkably fast reaction strategy with superlative yields of pyrimidine synthesis from a thorough study of Diels–Alder cycloaddition reaction. The study was initiated with a wide range of unsubstituted 1,2,3-triazines and various amidines. The alkyl, aromatic, or heteroaromatic and aliphatic amidines and underwent in a few hours upon gentle heating to form the corresponding pyrimidines [82].



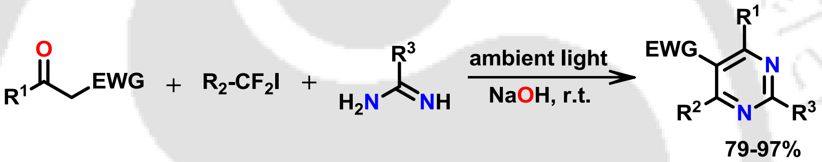
Org. Lett., 2011, **13**, 2492-2494.

Recently, Jiang and Wu demonstrated a highly effective four-component synthetic strategy for pyrimidine synthesis from amidine, styrene and *N*,*N*-dimethylformamide (DMF) under palladium catalysis oxidative process. Here an amidine chloride, a styrene derivative, and two molecules of DMF react for the formation of 2,4,5-trisubstituted pyrimidinecarboxamides [83].



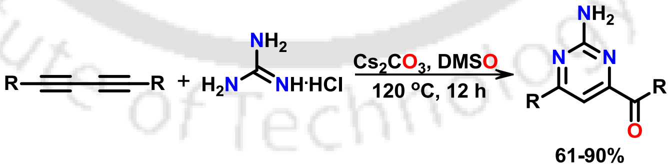
Angew. Chem., 2017, **129**, 1309-1314.

A photopromoted three-component [2+1+3] annulation reaction strategy has been described for the perfluoroalkylated pyrimidines synthesis. In this high-efficiency annulation reaction, active methylene compounds, perfluoroalkyl iodides, and guanidines or amidines were allowed to react in mild reaction conditions. It has a broad substrate scope, excellent functional group tolerance [84].



Org. Lett., 2017, **19**, 2358-2361.

A highly efficient one-pot synthesis of carbonyl 2-amino-pyrimidines has been described by the heterocyclization of 1,3-diynes and guanidine. In the [3+3] heterocyclization reaction 1,3-diynes act as a precursor of buta-1,2,3-trienes and guanidine serves as the N–C–N source in presence of Cs_2CO_3 and DMSO for the construction of pyrimidines [85].

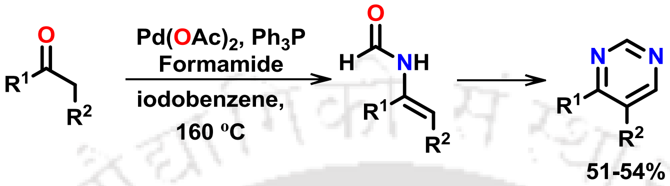


Chem. Commun., 2015, **51**, 9370-9373.

1.4.3. Alternative Strategies

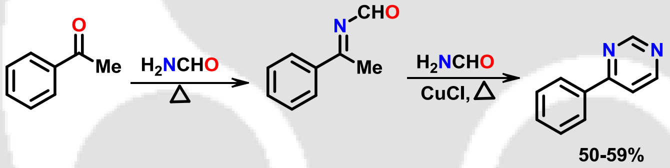
The methodologies of pyrimidine synthesis that do not depend on C–N or N–C–N fragments are categorized as alternative strategies. These methods involves either by nucleophilic addition to the electrophilic carbon generated by the activation of carbonyl moiety or by modification of existing pyrimidine compounds.

Ingebrigsten *et al*. have established a methodology for the synthesis of a variety of mono- and *di*-substituted pyrimidines from the condensation of two equivalents of formamide with ketones. However, the inclusion of catalytic palladium(II) acetate, triphenylphosphine, and iodobenzene as additives led to the removal of deleterious ammonium formate which was formed during the reaction [86].



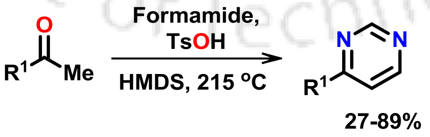
Heterocycles, 2005, **65**, 2593-2603.

In 1999, Helland and Lejon reported a simple synthetic method for the synthesis of 4-phenylpyrimidine by the reaction between acetophenone and 2 equivalent of formamide *via* the intermediate formyl imide. The concerted [4+2] cycloaddition reaction takes place under the cuprous chloride catalyst [87].



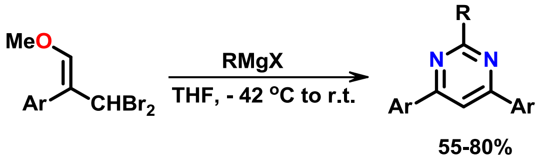
Heterocycles, 2005, **51**, 611-615.

Tyagarajan and Chakravarty described the synthesis of various 4-monosubstituted pyrimidines from ketones. The synthetic methodology used two equivalent of formamide with various aliphatic, aromatic, heteroaromatic and cyclic ketones in the presence of p-toluenesulfonic acid and 1,1,1,3,3,3-hexamethyldisilizane(HMDS) additives *via* microwave irradiation [88].



Tetrahedron Lett., 2005, **46**, 7889-7891.

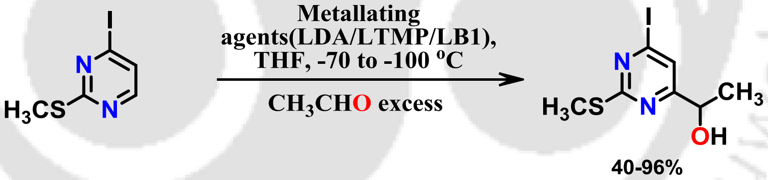
Kakiya *et al*. have synthesized some pyrimidine cores by using α,α-dibromo oxime ethers with various alkyl and aryl groups carrying Grignard reagents. Diazatriene, the intermediate forms by oximes with a Grignard reagent undergo a Neber-type cyclization followed by loss of methanol to afford the desired 2,4,6-trisubstituted pyrimidines [89].



J. Am. Chem. Soc., 2002, **124**, 9032-9033.

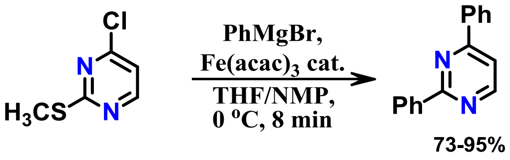
1.4.4. Modification of Existing Pyrimidines

Modification of existing pyrimidines has become a considerably important synthetic approach towards pyrimidines besides the advanced cross-coupling chemistry. Many of these synthetic strategies depend on inherent reactivity of the existing pyrimidine core and activated heterocycle cross-coupling has also additional importance [90-94]. Metalation and electrophilic trapping of pyrimidines which leads to new pyrimidines have been reported by Queguiner and co-worker in the year 1988. In this report, lithiation of 4-iodo-2-methylthiopyrimidine by different lithiating agents such as lithium diisopropylamide (LDA), lithium 2,2,6,6-tetramethylpiperidide (LTMP), or lithium *N*,*N*-*tert*-butyl(1-isopropyl)pentylamide(LB1) has been described to afford corresponding functionalized 4-iodo-2-methylthiopyrimidine followed by the reaction with various electrophiles [92].



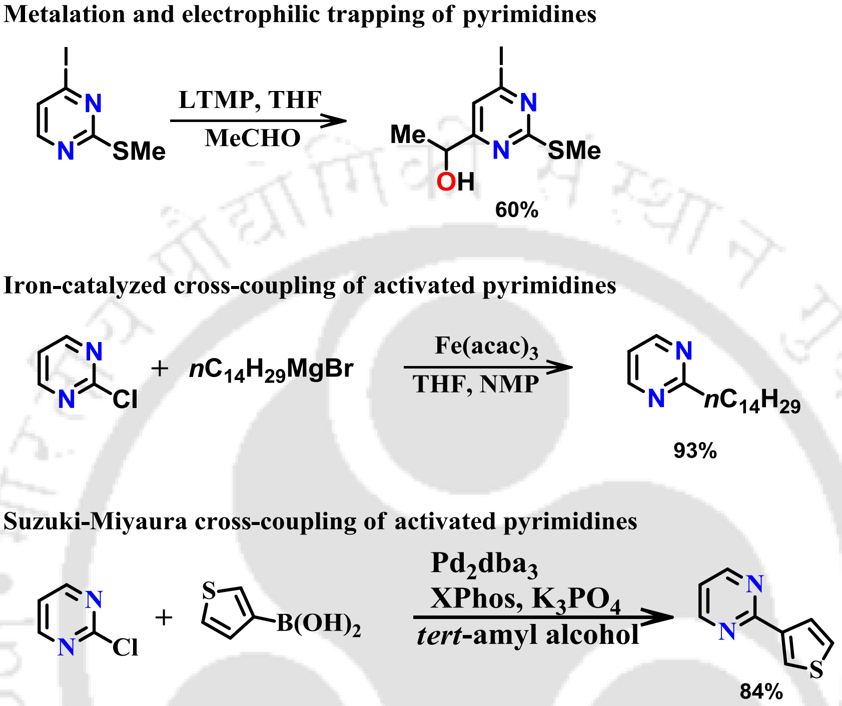
Tetrahedron, 1998, **54**, 9701-9710.

Another substituent modification on existing pyrimidines strategy has been reported as iron-catalyzed cross-coupling of activated pyrimidines. In this strategy, simple iron salts were used as precatalysts for a pyrimidine to undergo cross-coupling reactions with alkyl or aryl Grignard reagents, zincates, or aryl and heteroaryl organomanganese chlorides, triflates, and tosylates to synthesize corresponding new pyrimidines. The method has also been used for the first synthesis of the natural product montipyridine, which is a cytotoxic marine drug followed by consecutive cross-coupling processes in one pot [93].



J. Am. Chem. Soc., 2002, **124**, 13856-13863.

Suzuki–Miyaura couplings cross-coupling of activated pyrimidines has been reported as one of the new pyrimidine synthesis method from the existing pyrimidines. It describes the Suzuki-Miyaura cross-coupling reaction between heteroaryl boronic acids and esters in the presence of palladium precatalyst and monophosphine as the catalyst system [94].



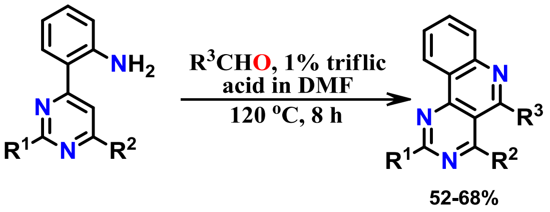
Metalation and electrophilic trapping of pyrimidines

Iron-catalyzed cross-coupling of activated pyrimidines

Suzuki-Miyaura cross-coupling of activated pyrimidines

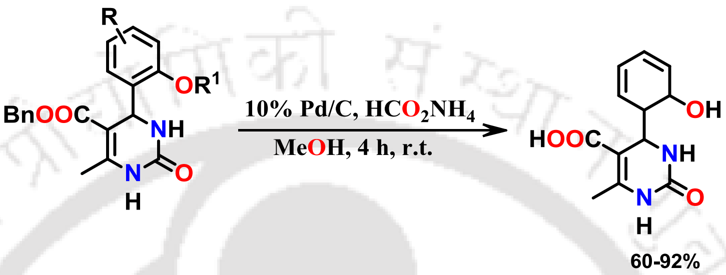
J. Am. Chem. Soc., 2007, **129**, 3358-3366.

Another synthetic strategy of pyrimidine annulated quinolones, based on the modified Pictet–Spengler reaction has been reported where deactivated pyrimidine rings acted as the nucleophilic partners whereas aryl amine served as the electrophilic partner. The nucleophilic partner 2-aminopyrimidine after attaching with the electrophile aryl amine undergoes Pictet–Spengler reaction with electron-withdrawing or electron-donating groups containing aldehydes to furnish pyrimido[5,4-*c*] quinolines followed by *pi*-cyclization [95].



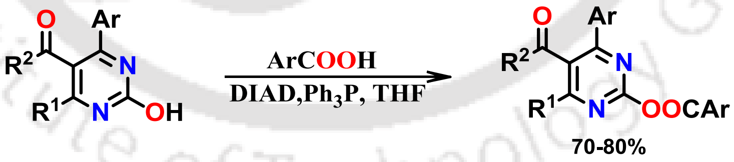
Tetrahedron, 2008, **64**, 8676-8684.

Funeriu *et al* has reported a strategy for synthesis of functionalized dihydro-pyrimido[4,3-*d*]coumarins, wherein (2-salicyl)-3,4-dihydropyrimidin-2-one 5-carboxylates were subjected to the palladium-catalyzed hydrogenolysis then dihydro-pyrimido[4,3-*d*]coumarins forms as a substituted pyramido product. Basic treatment of the hydrogenolysis reaction led to the isolation of the decarboxylated tricyclic oxo-bridged tetrahydro-pyrimidines [96].



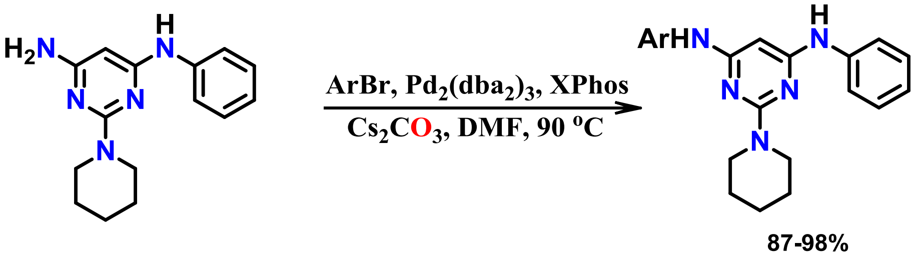
Tetrahedron, 2009, **65**, 5949-5957.

Xi-Cun Wang and Zheng-Jun Quan developed a novel, simple and efficient route for the synthesis of C2-multifunctionalized pyrimidines by following the Mitsunobu reaction. The various C2-multifunctionalized pyrimidines were synthesized by the dehydrogenation followed by Mitsunobu reaction of Biginelli 3,4-dihydropyrimidin-2(1H)-one. Here, alcohols, amines, phenols and carboxylic acids act as nucleophiles for 2-hydroxy pyrimidine to undergo Mitsunobu reaction. It is a readily accessible approach to prepare multifunctionalized pyrimidine scaffold for diversity-oriented synthesis [97].



Tetrahedron, 2011, **67**, 3267-3272.

The strategy for the synthesis of 2-dialkylamino-4-arylamino-6-aminopyrimidines from commercially available 4-amino-2,6-dichloropyrimidine has been reported. The method introduced a difficult access of secondary amines and arylamines to displace the 2- and 4-chloro groups [98].



Tetrahedron Lett., 2009, **50**, 5888-5893.

1.5.Imidazo[1,5-*a*]pyridines

Imidazole is a planar five-member ring system with two N atoms in 1 and 3 positions having the IUPAC name 1,3-diaza-2,4-cyclopentadiene and formula $C_3H_4N_2$. It is the simplest member of the imidazole family [99]. Imidazole was synthesized from glyoxal and ammonia in 1858 by a German Chemist named Heinrich Debus [100]. Pyridine is one of the most abundant six-membered nitrogen containing aromatic heterocycles with the formula moiety C_5H_5N. Structurally one methine (=CH−) group is replaced by a nitrogen atom from the benzene ring. These two azaheterocycles namely imidazole and pyridine are fused to form a new class of fused heterocycles which are popularly known as imidazo-pyridine in heterocyclic chemistry. The imidazo-pyridines comprise two isomers, imidazo[1, 2-*a*] pyridine and imidazo[1, 5-*a*] pyridine. Imidazo[1,5-*a*]pyridine is a fused 5:6 bicyclic system where one of the two nitrogen atom lie at the bridgehead 4-position and another at the 2-position of the five-membered ring [101]. The fused imidazole and pyridine ring systems (imidazopyridines) often shows valuable properties which are not typical for either of the separate moieties. For example, a popular soporific remedy, "Zolpidem" ("Ivadal"), is a functionalized imidazo[1, 2-*a*]pyridine. The imidazo[1,5-*a*]pyridines have been the subject of considerable interest because of their wide range of pharmaceutical, biological, medicinal applications and fluorescent chemistry [102-105].

1.6.Synthesis of Imidazo[1,5-*a*]pyridines

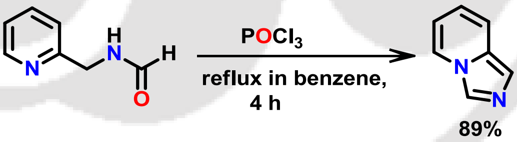
In 1955, the first synthesis of imidazo[1,5-*a*]pyridine was done by J. D. Bower and G. R. Ramage, by the cyclisation of 2-aminomethylpyridine with phosphoryl chloride [106]. Since the historical synthesis of imidazo[1,5-*a*]pyridines, it is a constantly active area of research and many important contributions describing a variety of synthetic strategies for the preparation of imidazo[1,5-*a*]pyridines have been published. These developed synthetic methodologies are classified into some subcategories like-

1. Vilsmeier–type cyclization
2. Transannulation of pyridotriazoles.
3. Multicomponent strategies.
4. Condensation reactions.

1.6.1. Vilsmeier–type Cyclizations

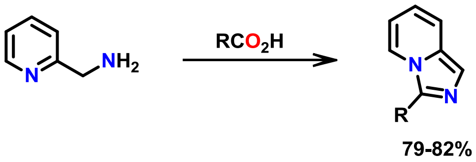
Most of the synthetic routes for imidazo[1,5-*a*]pyridines are involve either traditional Vilsmeier–type cyclizations of *N*-2-pyridylmethyl amides or cyclizations of *N*-2-pyridylmethyl thioamides with various reagents.

Bower and Ramage, in 1955 synthesized some imidazo[1,5-*a*]pyridines by the cyclisation of various 2-l′-acylaminoalkylpyridines by phosphoryl chloride. Cyclisation of 2-formamidomethylpyridines gave imidazo[1,5-*a*]pyridines which were unsubstituted at the 3-position, while substituents in this position were obtained by the use of acetyl, propionyl, and benzoyl derivatives of the amines. 1-Substituted imidazo[1,5-*a*]pyridines were obtained from the substituted 2-aminomethylpyridines [106].



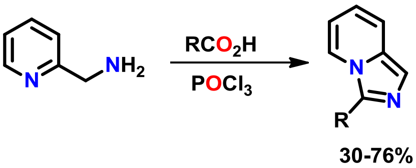
J. Chem. Soc., 1955, 2834-2837.

In the meantime, in 1963 Winterfeld and Franzke also reported a one spot strategy for the preparation of imidazo[1,5-*a*]pyridines from the 2-picolylamine by the use of carboxylic acid as the ring closure [107].



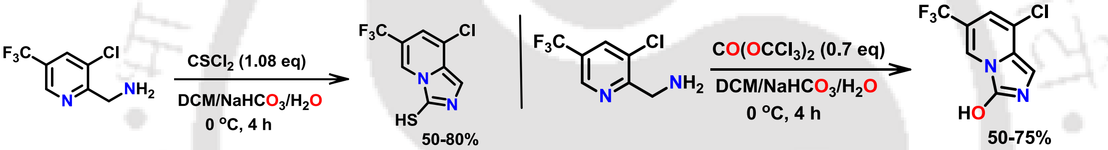
Angew. Chem., 1963, **75**, 1101-1102.

In 1979, Edwards has also reported the synthesis of imidazo[1,5-*a*]pyridines by the cyclization of amides from 2-aminomethyl pyridine. In this report, phosphorus trichloride in tetrahydrofuran or triethylamine is used at -20°C for the ring closure effect. It avoided the extensive tar formation of the reaction [108].



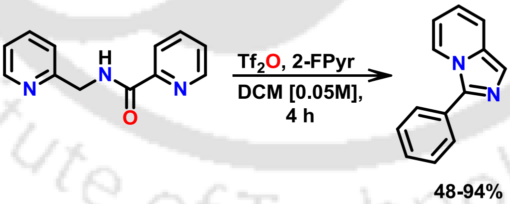
J. Heterocycl. Chem, 1979, **16**, 1349-1351.

A new method for the synthesis of imidazo[1,5-*a*]pyridines was developed by using 2,3-dichloro-5-(trifluoromethyl)pyridine. The intermediate aminomethyl-3-chloro-5 trifluoromethyl-pyridine react with triphosgene [bis(trichloromethyl)carbonate] or thiophosgene (thiocarbonyl chloride) to form the 3-substituted imidazo[1,5-*a*]pyridines. Here triphosgene and thiophosgene were act as a cyclization agent [109].



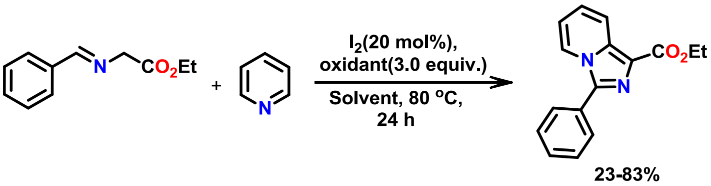
Rev. Roum. Chim., 2010, **55**, 689-695.

Imidazo[1,5-*a*]pyridines are synthesized using a mild cyclodehydration/aromatization reaction in presence of triflic anhydride (Tf_2O) and 2-methoxypyridine (2-MeOPyr) [110].



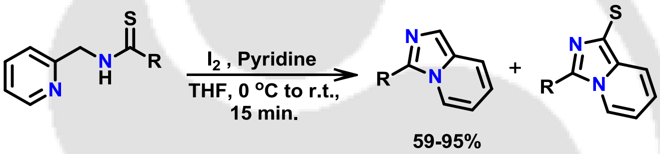
Org. Lett, 2013, **15**, 2290-2293.

An efficient I_2-mediated approach for the synthesis of imidazo[1,5-*a*]pyridines have been reported by Chen and his coworkers. The reaction of ethyl (E)-2-benzylideneamino acetate and pyridine has been described smoothly by using I_2 and TBPB as an oxidant for the facile synthesis of ethyl ester of 3-(phenyl)imidazo[1,5-*a*]pyridine-1-carboxylates. This methodology well described the limitation of the metal catalyst in 3-(phenyl)imidazo[1,5-*a*]pyridine synthesis. This represents an unprecedented 1,3-dipolar cycloaddition [111].



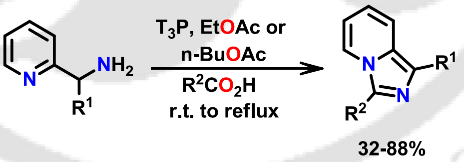
Asian J. Org. Chem., 2018, **7**, 1591-1594.

An iodine-mediated, cyclization strategy for the imidazo[1,5-*a*]pyridines synthesis promoted by oxidative desulfurization of thioamides has been reported. This method serves as a versatile synthetic method to generate 2-azaindolizines from of *N*-2-pyridylmethyl thioamides. In addition, with finely tuned absorption and emission i.e. fluorescent imidazo[1,5-*a*]pyridines were generated from the above-synthesised 2-azaindolizines by the developing of Suzuki-Miyaura coupling based protocol with transition-metal-catalyst [104].



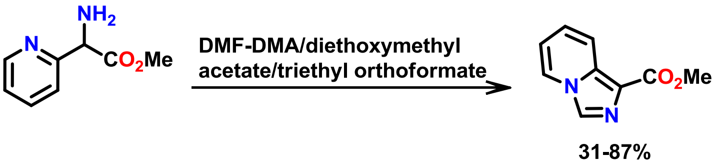
Org. Lett, 2006, **8**, 5621-5624.

Carboxylic acid and 2-methylaminopyridines react in a one-step to synthesis of imidazo[1,5-*a*]pyridines starting. By using propane phosphoric acid anhydride in ethyl or *n*-butyl acetate in this process introduce various substituents at 1- and 3-positions at reflux condition [112].



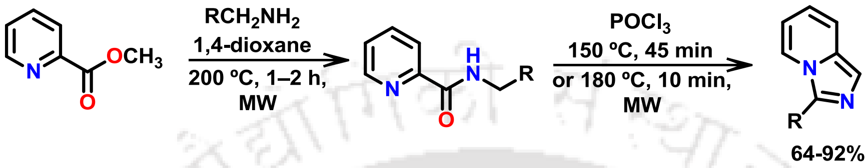
Tetrahedron Lett., 2009, **50**, 4916-4918.

Tisler and Kolar has described a new synthetic approach of alkyl(pyridyl-2')- or (quinolyl-2')glycinates to the corresponding imidazo[l,5-*a*]pyridines. They described the ethyl 2-amino-(pyridyl-2')acetate undergo cyclization with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA), or diethoxymethyl acetate or triethyl orthoformate to afforded the corresponding imidazo[l,5-*a*]pyridines [113].



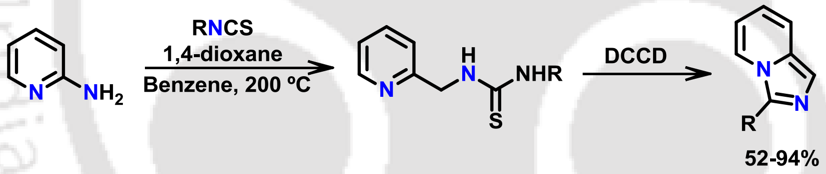
Z. Naturforsch. B, 1991, **46**, 1110-1112.

A microwave-assisted synthetic method of 3-substituted-imidazo[1,5-*a*]pyridines has reported. Here in anhydrous 1,4-dioxane, methyl picolinate and various amines react in microwave irradiation at 200 °C to give picolinamides, which again undergo cyclization in presence of phosphorus oxychloride in microwave at 150 °C for 45 min or at 180°C for 10 min and afforded the 3-substituted imidazo[1,5-*a*]pyridines [114].



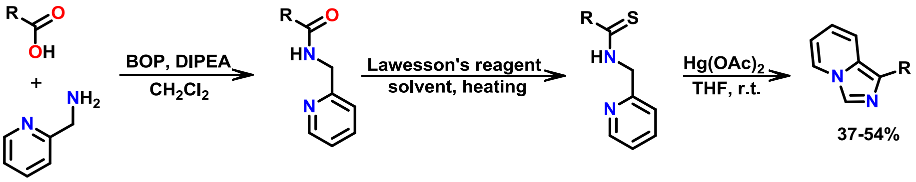
Tetrahedron Lett., 2010, **51**, 284-286.

A series of 3- substituted imidazo[1,5-*a*]pyridines have been synthesized by cyclodesufurization of a variety of *N*′-substituted-*N*-(2-pyridylmethyl)thioureas with decyclohexylcarbodiimide (DCCD). The *N*′-substituted-*N*-(2-pyridylmethyl)thioureas were prepared by reacting 2-aminomethylpyridine with the appropriate alkyl, aryl or aralkylisothiocyanic ester with in benzene at 20-50°C [115].



J. Heterocyclic Chem., 1980, **17**, 555-558.

A new method for the synthesis of starting from carboxylic acid and 2-methylaminopyridine react to obtained *N*-2-pyridylmethylamides, then generated the substituted imidazo[1,5-*a*]pyridines followed by the reaction with Lawesson's reagent and then mercury(II) acetate in THF. It has also been demonstrated that this heterocyclization was racemization free [116].

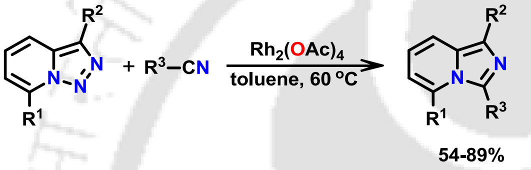


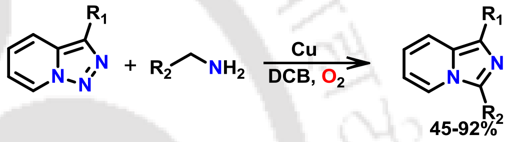
Synthesis, 2007, **17**, 2667-2673.

1.6.2. Transannulation of Pyridotriazoles

Most of the synthetic methods of imidazo[1,5-*a*]pyridines are depend on traditional Vilsmeier-type cyclizations. However, transannulation reactions have also become an indispensable methods for the synthesis of some imidazo[1,5-*a*]pyridines by making or breaking of C−C and C−hetero bonds.

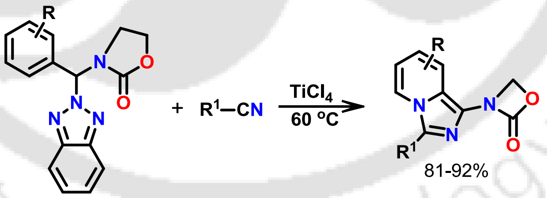
In 2007, Gevorgyan *et al*. developed an efficient, direct, Rh(II) metal-catalyzed transannulation of pyridotriazoles with nitriles for the synthesis of imidazopyridines. [117] Again, instead of rhodium, Adimurthy *et al*. reported a Cu(II) metal catalyzed transannulation of pyridotriazoles with benzyl amines and amino acids *via* the aerobic oxidative cyclization [118].





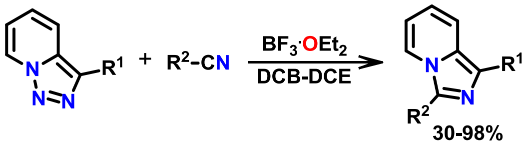
Angew. Chem. Int. Ed., 2007, **46**, 4757-4759. *Org. Lett*., 2016, **18**, 464-467.

A variety of 1-amido-3-aryl- and 1-amino-3-(alkyl)imidazo[1,5-*a*]pyridines has been synthesized from different 1-[amido(2-pyridinyl)methyl]benzotriazoles. The triazoles are undergone nucleophilic reaction with different aliphatic or aromatic cyanides at 60 °C in the presence of $TiCl_4$ to afford the respective imidazo[1,5-*a*]pyridines [119].



J. Org. Chem., 2001, **66**, 2862-2864.

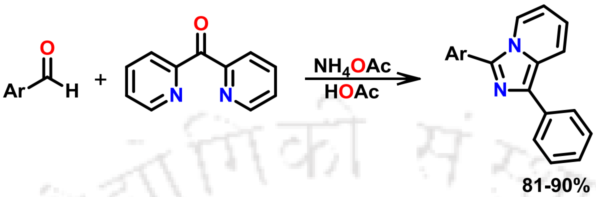
Another transannulation of pyridotriazoles under metal-free conditions for the imidazo[1,5-*a*]pyridines synthesis has been beautifully described with $BF_3·Et_2O$ as catalyst. Different substituted benzonitriles with commercially available different aliphatic as well as aromatic nitriles were amenable to this synthetic procedure [120].



J. Org. Chem., 2016, **81**, 9461-9469.

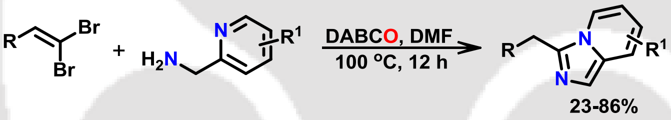
1.6.3. Multicomponent Strategies

A series of substituted (1-pyridyl)imidazo[1,5-*a*]pyridines have been reported by using the reactions of various aldehydes and dipyridyl ketone with ammonium acetate in hot acetic acid medium without the use of any metal-based catalysts [121].



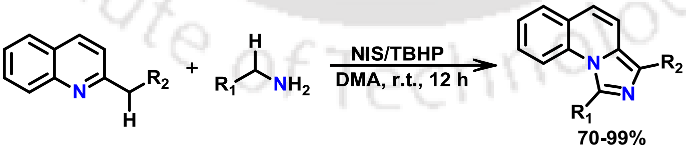
J. Org. Chem., 2005, **70**, 2353-2356.

A facile synthetic procedure has been reported with a mild inorganic base and moderate heating in DMF for the synthesis of imidazo[1,5-*a*]pyridines. 2-aminomethylpyridines and 1,1-dibromo-1-alkenes with the existing reaction conditions react to form a series of imidazo[1,5-*a*]pyridines. Thus the synthetic method found applications in synthetic organic chemistry [122].



Tetrahedron Lett., 2010, **51**, 828-831.

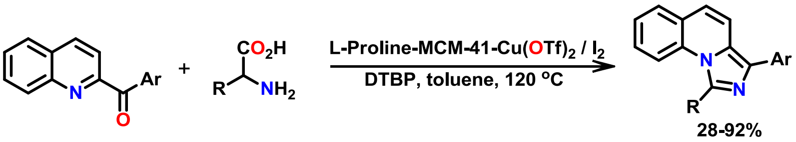
A synthetic protocol of metal-free sequential dual oxidative amination in ambient conditions has been reported for the production of imidazo[1,5-*a*]pyridines. The reaction was involved in two oxidative C–N couplings and one oxidative dehydrogenation [123].



Org. Lett., 2013, **15**, 2274-2277.

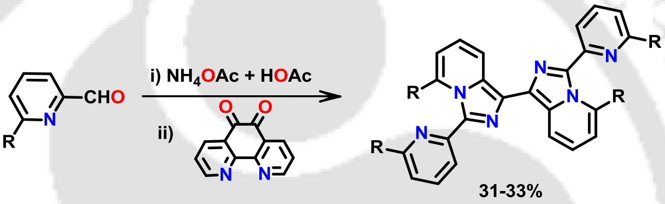
An efficient, inexpensive heterogeneous copper(II) catalyzed synthetic method has been reported for the synthesis of some drug-relevant biologically active 1,3-disubstituted imidazo[1,5-*a*]pyridines *via* decarboxylative cyclization of 2-benzoylpyridines and α-amino acids. The reaction has reported with 15 mol% of L-proline-functionalized MCM-41-supported copper(II) complex [L-Proline-MCM-41-

Cu(OTf)$_2$] and iodine at 120°C in toluene with the oxidant di-*tert*-butyl peroxide (DTBP) [124].



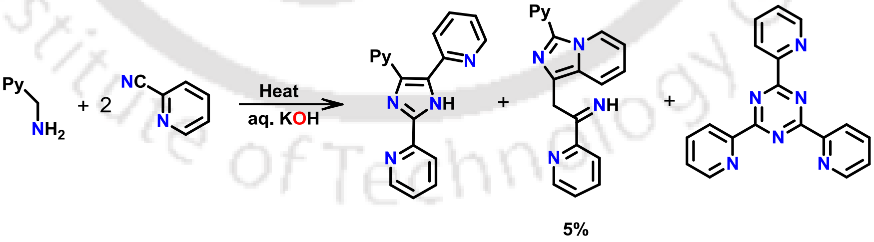
J. Organomet. Chem., 2019, **881**, 1-12.

A simple 'one-pot' condensation reaction of pyridine-2-carboxaldehydes and ammonium acetate in presence of acetic acid for the synthesis of biologically relevant imidazo[1,5-*a*]pyridine moiety has been described. In this reaction phenanthroline-5,6-dione has used as a oxidizing agent [125].



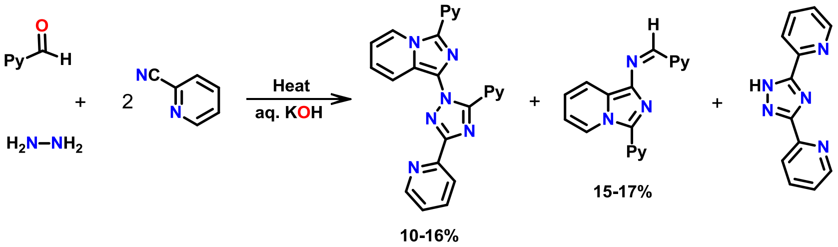
Tetrahedron Lett., 2012, **53**, 2719-2721.

A simple and efficient two-component synthetic strategy of imidazo[1,5-*a*]pyridine scaffold has been reported with picolylamine and cyanopyridine. The mixture of picolylamine and cyanopyridine with 1:2 ratios are heated followed by the treatment of aqueous KOH to afford the corresponding imidazo[1,5-*a*]pyridine along with imidazoles [126].



Tetrahedron Lett., 2009, **50**, 6264-6267.

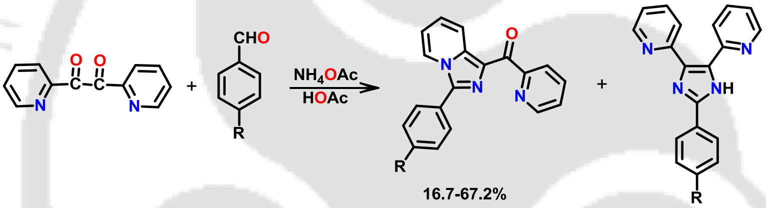
A synthetic method of 2-cyanopyridine, hydrazine hydrate and pyridinecarboxaldehydes has been reported for the synthesis of imidazo[1,5-*a*]pyridines. The mixture of 2-cyanopyridine and hydrazine hydrate are heated at 100°C followed by the reheating with pyridinecarboxaldehydes and aqueous KOH treatment to produce the corresponding imidazo[1,5-*a*]pyridines [127].



Tetrahedron Lett., 2012, **53**, 2420-2423

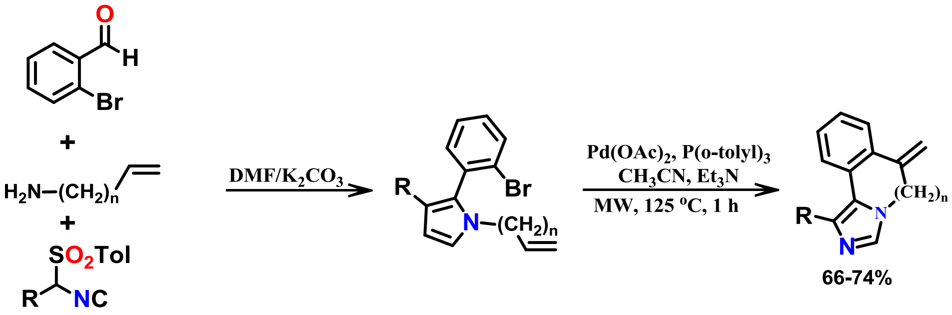
1.6.4. Condensation reactions

Bu *et al*. demonstrated a simple, facile, straight forward one-pot synthetic strategy for the preparation of a novel class of imidazo[1,5-*a*]pyridines by the use of ammonium acetate. In acetic acid medium, ammonium acetate was used to the benzaldehyde with 2,2′-pyridil for the preparation of different 1-(2-pyridoyl)-3-(phenyl)imidazo[1,5-*a*]pyridines [128].



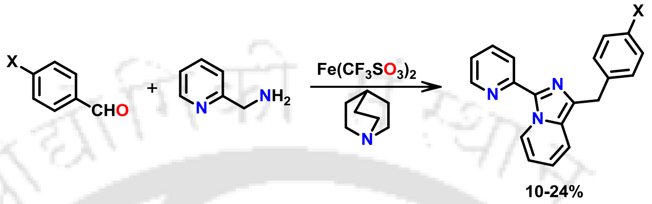
J. Org. Chem., 2003, **68**, 5415-5418.

Beebe has described the utilization of van Leusen synthetic methodology followed by an intramolecular Heck reaction for the synthesis of imidazo[1,5-*a*]pyridines and imidazo[1,5-*a*]azepines. This is a two steps synthetic strategy where an intermediate has been formed by the reaction between vinylogous bromide containing aldehydes and a double bond containing amines. The tosylmethylisocyanide (TosMIC) and base were added in room temperature for the cyclization. Then desired imidazo[1,5-*a*]pyridines or imidazo[1,5-*a*]azepines were prepared followed by the palladium-catalyzed Heck reaction [129].



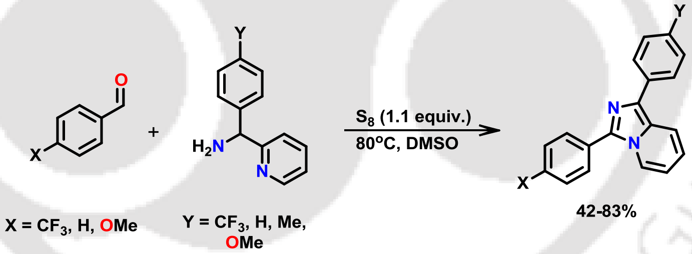
Tetrahedron Lett., 2006, **47**, 3225-3228.

An another condensation synthetic strategy of imidazo[1,5-*a*]pyridines has been described through the action of Fe^{2+} on imines. Here, benzaldehyde and 2-picolylamine undergo condensation reaction to produce the imines. The reaction is not occurring in case of *p*-OCH_3 and *p*-NO_2 benzaldehyde [130].



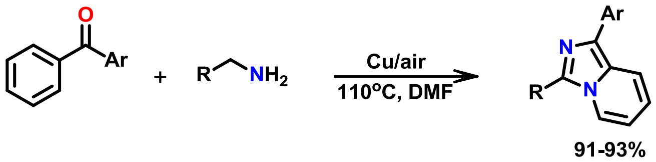
J. Org. Chem., 2017, **82**, 3820-3825.

Murai and Shibahara have developed an oxidative condensation-cyclization reaction with the help of elemental sulfur for the synthesis of different imidazo[1,5-*a*]pyridines. With various aldehydes and aryl-2-pyridylmethylamines were used to prepare a series of 1,3-diarylated imidazo[1,5-*a*]pyridines, where the elemental sulfur act as an oxidant in a catalyst-free condition [131].



J. Org. Chem., 2009, **74**, 3566-3568.

Xu and Wang well described a new and efficient synthetic tool *via* condensation–amination–oxidative dehydrogenation of imidazo[1,5-*a*]pyridines. The tandem reaction between pyridine ketone and benzylamine was catalysed by copper(II) under air to afford a wide range of 1,3-diarylated imidazo[1,5-*a*]pyridines [132].



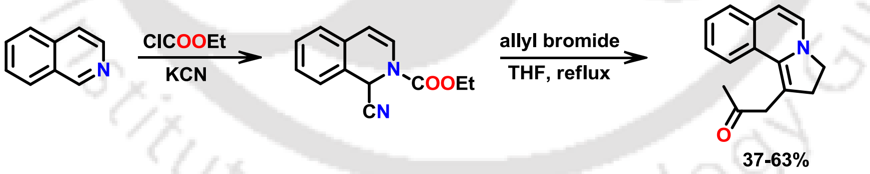
J. Org. Chem., 2015, **80**, 2431-2435.

1.7.Imidazo[5, 1-*a*]isoquinoline

Imidazo[5, 1-*a*]isoquinoline is an isoquinoline analogue of imidazo[1, 5-*a*]pyridine nucleus. Likewise imidazopyridine it is also a fused structure of imidazole and isoquinoline and it has two isomers of imidazo[2, 1-*a*]isoquinoline and imidazo[5, 1-*a*]isoquinoline. Similarly, imidazo[1,5-*a*]isoquinoline is a class of fused Tricyclic 5:6:6 system having one of the two nitrogen atoms lie at the bridgehead 4-position and other at the 2-position of the five-membered imidazole ring. From the literature synthesis of imidazo[1, 5-*a*]pyridine nucleus with varying substituents at pyridine has been reported. The quinoline analogue, imidazo[1, 5-*a*]quinoline has been well described in the field of synthetic as well as medicinal chemistry. However, its isoquinoline analogues are yet to be popularized. Although imidazo[2, 1-*a*]isoquinoline was successfully synthesized by Tominaga and Hosomi from pyridinium *N*-ylides or isoquinolium *N*-ylide in early 1987 [133]. But the imidazo[5, 1-*a*]isoquinoline has been mostly unnoticed so far. A very few synthetic reports have been reported for the synthesis of imidazo[5, 1-*a*]isoquinoline till to date.

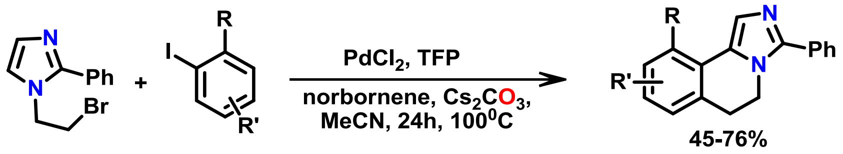
1.8. Synthesis of Imidazo[5, 1-*a*]isoquinoline

An indium-mediated synthetic protocol for the synthesis of allyl-substituted imidazo[5, 1-*a*]isoquinolines has been reported from the Reissert compounds of isoquinoline [134].



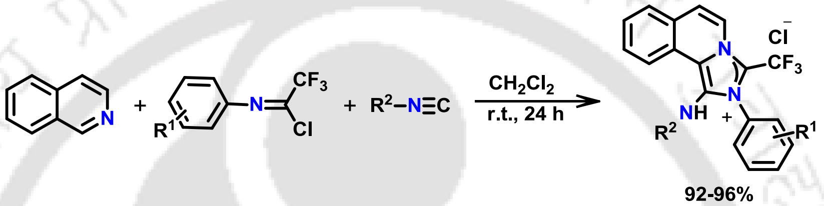
Bull. Korean Chem. Soc., 2010, **31**, 3031-3034.

Jafarpour and Ashtiani have provided an efficient, one step palladium-catalyzed/norbornene-mediated method where highly functionalized imidazoles undergo a sequential alkyl-aryl and aryl-heteroaryl coupling reaction to form the imidazo[5,1-*a*]isoquinoline scaffolds in presence of palladium and norbornene. A series of substituted imidazo[5,1-*a*]isoquinolines were synthesised with a wide variety of biological activities from *N*-bromoalkyl imidazoles and aryl iodides by using this synthetic methodology. These imidazo[5,1-*a*]isoquinolines motifs are not easily accessible [135].



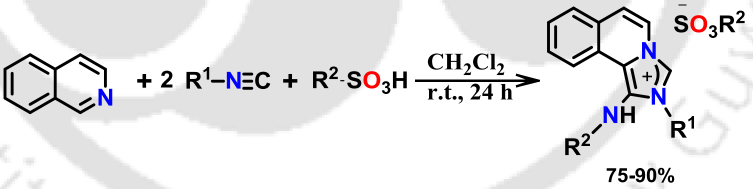
J. Org. Chem., 2009, **74**, 1364-1366.

A new class of novel 2*H*-imidazo[5,1-*a*]isoquinolinium chlorides were reported by Darehkordi et. al. from isoquinoline, trifluoroacetimidoyl chlorides and isocyanides. This high yields reactions were carried out in dry DCM and the synthesized compounds showed novel blue-light-emitting properties [136].



Synlett, 2018, **29**, 296-300.

An efficient pseudo-four-component condensation towards the synthesis of a series of 1-(amino)imidazo[5,1-*a*]isoquinolinium salts has been reported. In presence of different sulfonic acids isoquinoline react with various isocyanides to produce the respective (amino)imidazo[5,1-*a*]isoquinolinium salts. The reaction showed a good functional group tolerance [137].



J. Comb. Chem., 2008, **10**, 442-446.

The literature review explains the importance of nitrogen containing heterocycles and the various versatile synthetic methodologies particularly for pyrimidine, imidazo[1, 5-*a*]pyridine and imidazo[5, 1-*a*]isoquinoline. Due to the wide range of applications, a novel route remains always-valuable addition to the contemporary synthetic methodologies towards the above azaheterocycles.

1.9.Materials

2-Acetylpyridine, 3-acetylpyridine, 4-acetylpyridine, 2-cyanopyridine, 2-picolylamine, benzaldehyde, 2–hydroxybenzaldehyde, 2-methoxy-benzaldehyde, 3-methoxy-benzaldehyde, 4-methoxy-benzaldehyde, 2-naphthaldehyde, 9-anthracenaldehyde, 2-

bromobenzaldehyde, 3-bromobenzaldehyde, 4-bromobenzaldehyde, 2-chlorobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 2-nitrobenzaldehyde, 3-nitrobenzaldehyde, 4-nitrobenzaldehyde, 2-iodobenzaldehyde, 3-iodobenzaldehyde, 4-iodobenzaldehyde, 2-fluorobenzaldehyde, $CDCl_3$, and KBr were purchased from M/S Aldrich, USA. $Ni(NO_3)_2{\cdot}6H_2O$, $Co(NO_3)_2{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$, sodium azide, anhydrous $Na_2(SO)_4$, silica gel GF (< 0.02 mm), and KOH were purchased from Merck India. All the chemicals and solvents were of reagent grade and were used without further purifications.

1.10. Instrumentation and Methods

UV–Vis spectra were recorded in a Perkin-Elmer Lambda-750 UV–Vis spectrometer using 10 mm path length quartz cuvettes with the wavelength in the range of 250–800 nm for solutions obtained by dissolving a calculated amount of the sample in an appropriate solvent. A Perkin–Elmer Spectrum One FT–IR spectrometer (KBr, range 4000–250 cm^{-1}), has been used to record IR for moisture free samples. ^1H NMR and ^{13}C-NMR spectrums were recorded in a Varian Mercury plus 400 MHz, Bruker DPX FT-500 MHz and 600 NMR Spectrometer. The chemical shift values were recorded in parts per million (*ppm*) on the scale using tetramethylsilane (TMS) as a reference. ESI-Mass spectra and Melting points were recorded in Q-TOF/MS spectrometer and Buchi B-540 melting point apparatus respectively. Powder X-ray data was collected from high-power X-ray diffractometer (Rigaku TTRAX III, 18 kW) with Cu-Kα radiation(k = 1.54056 Å). Room temperature magnetic moments were measured using a Sherwood scientific magnetic susceptibility balance and EPR spectra using JEOL ESR spectrometer model JES-FA200.

1.10.1. X-Ray Crystallography

Single crystal X-ray data were collected by using Bruker SMART APEX–CCD diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å) and Rigaku Super Nova, single source at offset, Eos diffractometer. The intensity data were corrected for Lorentz and polarization effects and empirical absorption corrections was applied using SAINT program. All the structures were solved by direct methods using SHELXS–97 software. All the non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2, using SHELXL–97. The hydrogen atoms were included at the calculated positions and refined in the isotropic approximation.

1.10.2. Thermal Measurement

Thermogravimetric analysis (TGA) were were carried out in a Thermal Analyzer (Model Netzsch STA 449F3) under static nitrogen atmosphere. The temperature and sensitivity calibration was done at a heating rate of 10ºC/min by analyzing the TGA signal of the melting peak (Tm) of the pure substances; Indium (Tm = 431.8 K), Aluminum (Tm = 959.2 K), Gold (Tm = 1346.9 K), Tin (Tm = 508.4 K), and Zinc (Tm = 700.8 K) by using the same crucible (Alumina) and similar conditions.

1.10.3. Computational Methods:

The geometry optimisations were carried out using the density functional theory (DFT/TDDFT) method at the B3LYP level. The lanl2dz basis set was assigned for all the elements. All calculations were performed with Gaussian09 program [138] with the aid of Gauss View visualization program.

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Chapter 2

A New Route for the Synthesis of 2,4-Bis(2-pyridyl)-6-(pyridyl)pyrimidines: Synthesis and Characterization of Co(II), Ni(II) Complexes of 2,4,6-Tris(2-pyridyl)pyrimidine

Abstract

Using 2-acetylpyridine, sodium hydroxide and 2-cyanopyridine, 2,4,6-tris(2-pyridyl)pyrimidine (**L1**) was synthesized in good yield. Similarly, 2,4-bis(2-pyridyl)-6-(3-pyridyl)pyrimidine (**L2**) and 2,4-bis(2-pyridyl)-6-(4-pyridyl)pyrimidine (**L3**) were also synthesized by using respective acetylpyridine. 2-Acetylpyridine reacted with sodium hydroxide to produce 2-oxo-2-(2-pyridyl)-1-ethanide, which behaves as a nucleophile towards 2-cyanopyridine. All three pyrimidines are potential multidentate ligand and by using **L1** complexes of composition $[Ni(\mathbf{L1})(H_2O)_3](NO_3)_2{\cdot}4H_2O$ (**1**), $[Ni(\mathbf{L1})_2](NO_3)_2{\cdot}2H_2O$ (**2**) and $[Co(\mathbf{L1})_2](NO_3)_2{\cdot}1.5H_2O$ (**3**) were isolated and structurally characterized. In **1-3**, **L1** behaves as a tridentate pincer type ligand, DFT calculations performed on **L1–L3** indicate that energy difference between HOMO and LUMO is 4.544, 4.643 and 4.533 eV respectively.

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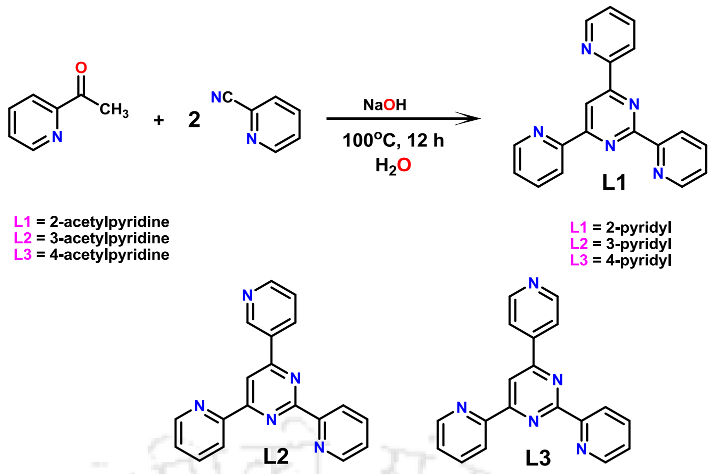
2.1. Introduction

Pyrimidine is an important six-membered diazaheterocycle, wherein two nitrogen atoms occupy 1 and 3 positions in the ring. A large number of pyrimidines are reported to have an important role in biological systems and find applications in medicinal activities [1–9]. As a consequence, synthesis of compounds containing pyrimidine nucleus remains an active area of research and various synthetic methods have been unveiled. After the historical synthesis of pyrimidine by Brugnatelli [10] and later by Kolbe [11], a wide range of synthetic strategies such as Pinner type synthesis [12–14], approaches like multicomponents [15–19], microwave [20, 21], cross-coupling [22, 23], condensation cyclization [24–29], different transition-metal or acid mediated cycloaddition [30–39], modified Pictet–Spengler [40] as well as Mitsunobu [41] reaction have expanded and improved the scopes of pyrimidine synthesis.

Suitably substituted pyrimidines were utilized as ligands due to its structural richness, electrochemical properties, and models for biological systems [42–44]. Over the years, some pyrimidine based ligands are used as intramolecular organizing chelating units, self-assembled supramolecular architectures and for their promising physicochemical properties [45–54]. Moreover some of metal (II) complexes of pyrimidines display antimicrobial properties [55, 56]. Polydentate *N*-donor ligands containing sp^2-hybridized nitrogen atoms, such as polypyridines [57–67], 2,4,6-tris-(2-pyridyl)-1,3,5-triazine [68–78] have frequently been the subject of many studies. On the other hand, pyrimidines substituted with pyridyl ring have received much less attention.

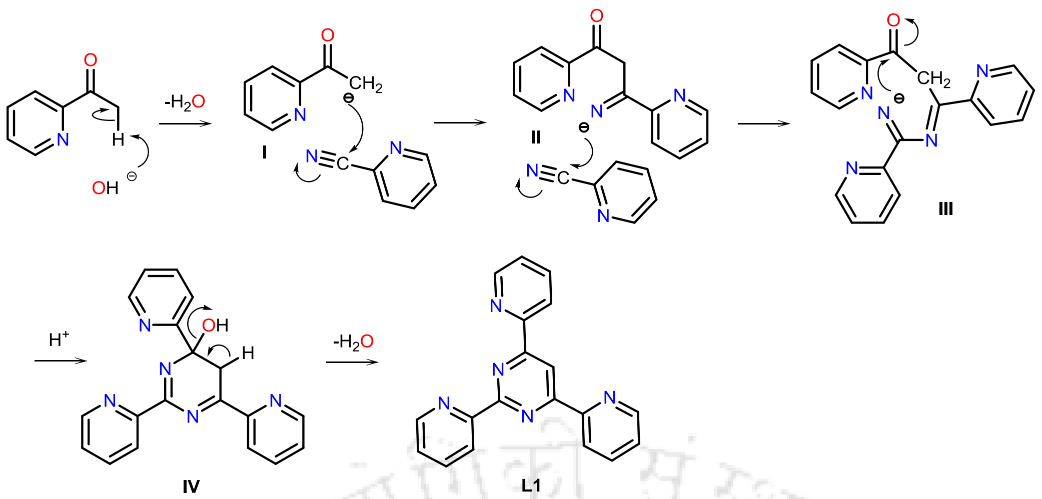
Nitriles are one of the most useful precursors for synthesis of many nitrogen heterocycles and have been used in synthetic strategies of pyrimidine nucleus. We also have reported synthesis of some nitrogen containing heterocycles by the reaction 2-cyanopyridine with suitable nucleophiles like picolylamines, hydrazine and imines [79-81]. As a continuation, a simple synthesis of 2,4,-bis(2-pyridyl)-6-(pyridyl)pyrimidines from the reaction of 2-cyanopyridine with 2-oxo-2-(pyridyl)-1-ethanides, generated from respective acetylpyridines and solid sodium hydroxide, has been described in this Chapter (Scheme 2.1). In addition, coordination chemistry of **L1** by the way of its mono- and bis- chelates has also been described.



Scheme 2.1. Synthesis of **L1**-**L3**.

2.2. Results and Discussion

Earlier it has been demonstrated that by reacting suitable nucleophiles with 2-cyanopyridine new heterocyclic compounds can be easily synthesized [79–81]. In the same direction, we have attempted the reaction of 2-oxo-2-(2-pyridyl)-1-ethanide (**I**) with 2-cyanopyridine in 1:2 ratio. The nucleophile **I** was obtained by grinding 2-actylpyridine with solid NaOH in 1:1.2 ratios, for about 30 minutes. The resultant viscous liquid reacted readily with 2-cyanopyridine in a neat hot mixture and then addition of water precipitated crude **L1**, which was purified by column chromatography. A plausible mechanism for the formation of **L1** is shown in Scheme 2.2. The nucleophile **I** attack the carbon atom of the nitrile group in 2-cyanopyridine resulting in the formation of (3-oxo-1,3-di(2-pyridyl)propylidene)amide ion (**II**), which then attack another molecule of 2-cyanopyridine, leading to adduct **III**. The amidinate nitrogen in **III**, now can link with the carbonyl carbon, forming the cyclic intermediate which abstract a proton to produce **IV**. Elimination of a water molecule from **IV** will yield the final product **L1**.



Scheme 2.2. Plausible mechanism for the formation of **L1**.

An attempt was made to evaluate the applicability of this method by using other two positional isomers of 2-acetylpyridine *viz.*, 3-acetylpyridine and 4-actylpyridine for the synthesis of respective pyrimidines. Indeed the reaction proceeded smoothly as anticipated from which **L2** and **L3** were respectively isolated in good yields. To the best of our knowledge, synthesis of **L2** and **L3** were not reported so far in the literature and these two new pyrimidines could be successfully synthesized by adopting this reaction strategy.

It is pertinent to note that synthesis of **L1** has been reported and the method involves thermal elimination of NH_3 from 2-methyl-2,4,6-tris(2′-pyridyl)-2-dihydro-s-triazine which in turn was prepared by reacting MeLi with 2-cyanopyridine [85]. Also, enaminones were reported to be formed from the reaction of ketones with aromatic nitriles in the presence of a copper catalyst system (CuI–2,2′-bipyridine–NaO^{t}Bu) in *N*,*N*-dimethylformamide [86]. The ^{1}H and ^{13}C NMR spectra are in agreement with their structures. ESI mass spectra of **L1-L3** show the presence of a characteristic $[M+H]^+$ peak at $m/z = 312.125$. Ligand **L1** shows a characteristic peak at ~9.4 δ in its ^{1}H NMR spectrum, assignable to the proton of the only aromatic C–H group present at the 5th position of the central pyrimidine nucleus.

2.3. Molecular Structures

Compound 2,4,6-tris(2-pyridyl)pyrimidine (**L1**) is a potential multidentate ligand which is isoelectronic with 4′-(2-pyridyl)-2,2′:6′,2′′-terpyridine (**ptpy**). Both have three pyridyl groups substituted at 2, 4 and 6 positions of central pyrimidine and pyridine rings and thus differ by replacement of a CH group with N atom in the central ring. Hence in order to evaluate the coordination mode of **L1**, synthesis of some transition metal complexes was attempted. Ligand **L1** was treated with nickel(II) nitrate in 1:1 and 1:2 ratios, yielding complexes of composition [Ni(**L1**)(H_2O)$_3$](NO_3)$_2$·4H_2O (**1**) and [Ni(**L1**)$_2$](NO_3)$_2$·2H_2O (**2**), respectively. With cobalt(II) nitrate, 1igand **L1** yielded [Co(**L1**)$_2$](NO_3)$_2$·1.5H_2O (**3**) as the only product in both 1:1 and 1:2 ratios. All the three complexes were characterized thoroughly and their molecular structures were established using single crystal X-ray diffraction studies.

The crystallographic data and refinement parameters are summarized in Table 1 and selected bond distances and angles are listed in Table 2 and 3, respectively.

Table 2.1. Crystallographic data of **1**–**3**.

	1	**2**	**3**
Formula	$C_{19}H_{13}N_7NiO_{13}$	$C_{38}H_{26}N_{12}NiO_7$	$C_{38}H_{26}N_{12}O_7Co$
CCDC number	1969163	1969164	1969165
Formula weight	606.05	820.14	821.14
T (K)	293 K	293(2)	296(2)
Crystal system	monoclinic	triclinic	triclinic
Space group	*C2/c*	*P-1*	*P-1*
a (Å)	14.4995(9)	8.7983(6)	8.8536(9)
b (Å)	15.0132(5)	13.6714(7)	13.6966(14)
c (Å)	12.2077(7)	15.8434(8)	15.8989(16)
α (°)	90.00	97.759(4)	98.402(3)
β (°)	98.782(6)	103.528(5)	103.957(3)
γ (°)	90.00	90.351(5)	90.379(3)
V (Å^3)	2626.3(2)	1834.48(18)	1849.2(3)
Z	4	1	1
D_{calcd} (g m^{-3})	1.533	1.473	1.461
μ (mm^{-1})	0.816	0.596	0.531
F(000)	1232.0	836.0	834
Reflections collected	2345	7594	7649
Unique reflections	1719	6009	5398
Goodness-of-fit (GOF)[a]	1.000	1.003	1.004
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	0.0690, 0.2063	0.0670, 0.1835	0.0767, 0.2223
R_1[b], wR_2[c] (all data)	0.0892 ,0.2313	0.0835,0.1985	0.1036, 0.2441

[a] GOF = $[\Sigma[w(F_0^2-F_c^2)^2]/M–N]^{1/2}$ (M = number of reflections, N = number of parameters refined). [b] $R_1 = \Sigma||F_0|-|F_c||\Sigma|F_0|$. [c] $wR_2 = [\Sigma [w(F_0^2-F_c^2)^2]/\Sigma [w(F_0^2)^2]]^{1/2}$.

In all **1-3**, **L1** acts as a tridentate ligand coordinating through the two nitrogen atoms (N_P) of 2-pyridyl rings substituted at 2 and 4 positions of the pyrimidine ring along with its nitrogen atom (N_M) situated at the third position. The nitrogen atom at position one in the pyrimidine ring and the 2-pyridyl ring substituted at the 6th position are free. The metal center has a distorted octahedral geometry with coordination environment of *mer*-$(N_M)(N_P)_2O_3$ in **1**, and *mer*-$(N_M)_2(N_P)_4$ in **2-3**. In **1-3**, the central Ni–N_M distances are shorter than the two terminal Ni–N_P distances, which may be due to the geometrical constraints on the ligand framework. However, with Pd(II) and Pt(II) ions **L1** has been reported to behave as a bidentate ligand, based on NMR studies [87].

Table 2.2: Selected bond distances (Å) in **1-3**.

Bond	**1**	**Bond**	**2**	**3**
Ni1–N1	2.213(4)	M–N1	2.119(3)	2.164(4)
Ni1–N2	2.067(5)	M–N2	1.980(3)	1.980(5)
Ni1–O1	2.013(6)	M–N3	2.127(3)	2.152(5)
Ni1–O2	2.154(4)	M–N6	2.131(3)	2.130(4)
		M–N7	1.985(3)	1.977(3)
		M–N8	2.126(3)	2.134(4)

Table 2.3: Selected bond angles (°) in **1-3**.

1		**2**		**3**	
N2–Ni1–N1	75.39(10)	N1–Ni1–N2	77.20(12)	N1–Co1–N2	77.00(14)
O1–Ni1–N1	104.61(10)	N1–Ni1–N3	154.53(13)	N1–Co1–N3	153.74(16)
O2–Ni1–N1	90.00(17)	N1–Ni1–N6	93.59(12)	N1–Co1–N6	94.13(13)
O1–Ni1–N2	180.00(1)	N1–Ni1–N7	100.73(12)	N1–Co1–N7	99.96(14)
N2–Ni1–O2	92.09(11)	N1–Ni1–N8	91.19(12)	N1–Co1–N8	94.97(14)
O1–Ni1–O2	87.91(11)	N2–Ni1–N3	77.51(13)	N2–Co1–N3	76.74(15)
N1–Ni1–N1a	150.8(2)	N2–Ni1–N6	100.61(13)	N2–Co1–N6	100.56(14)
O2a–Ni1–N1	91.06(17)	N2–Ni1–N7	177.14(12)	N2–Co1–N7	176.20(14)
O2–Ni1–O2a	175.8(2)	N2–Ni1–N8	104.65(13)	N2–Co1–N8	105.38(14)
		N3–Ni1–N6	93.93(12)	N3–Co1–N6	90.84(14)
		N3–Ni1–N7	104.64(13)	N3–Co1–N7	106.28(15)
		N3–Ni1–N8	92.31(12)	N3–Co1–N8	91.75(14)
		N6–Ni1–N7	77.46(13)	N6–Co1–N7	77.26(14)
		N6–Ni1–N8	154.72(13)	N6–Co1–N8	153.83(15)
		N7–Ni1–N8	77.26(13)	N7–Co1–N8	77.03(14)

Compound **1** crystallised in the space group *C*2/*c* and the asymmetric unit contain half molecule of $[Ni(\mathbf{L1})(H_2O)_3]$ ion along with one nitrate ion and two molecules of water. Ligand binds the Ni(II) ion in a tridentate fashion coordinating meridionally through the one nitrogen atom from the pyrimidine ring and two other nitrogen atoms from the 2-pyridyl rings that are substituted at the 2nd and 4th positions of the pyrimidine ring. The other three coordination sites are occupied by three water molecules. Two-fold axis of rotation passes through O1–Ni1–N2–C8–C9–C11, thus indicating that CH group and N atom of the central pyrimidine is disordered/exchanged, which also include the N3 atom of the pendent 2-pyridyl ring. A perspective view of [Ni(**L1**)(H_2O)$_3$] ion is shown in Figure 2.1. The square plane containing N1, N2, N1, and O1 atoms is planar and the bond parameters around the bivalent nickel are comparable to that found in [Ni(**ptpy**)(H_2O)$_3$] ion [88]. The Ni–N_M distance is shorter than Ni–N_P distances by 0.146(5)Å while the equatorial Ni–O1 bond is shorter by 0.141(6)Å than the axial Ni–O2 bond. The chelate bite N1–Ni–N2 is 75.39(10)°, other *cis* angle within the square plane is 104.61(10)° and the *trans* angle, O1–Ni–N2 is exactly linear as it coincide with the 2-fold rotational axis. The packing diagram shows the presence of O–H···O hydrogen bonding between the lattice water and nitrate ions. Significant among them are O2···O6, 2.73(1); O2···O3, 2.88(1); O7···O7, 1.90(5); O7···O6, 2.36(6); O4···O6, 2.99(1); O6···O3, 3.04(2); O6···O5, 2.89(1); O4···O6, 2.99(1); O6···O3, 3.04(2) and O5···O6, 2.89(1)Å. A perspective view of the packing diagram of **1** on viewing down the *c* – axis is shown in Figure 2.2.

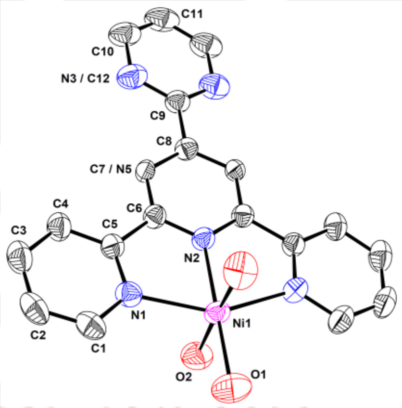


Figure 2.1. ORTEP (30% probability ellipsoids) diagram of [Ni(**L1**)(H_2O)$_3$] in **1**. Hydrogen atoms are omitted for clarity.

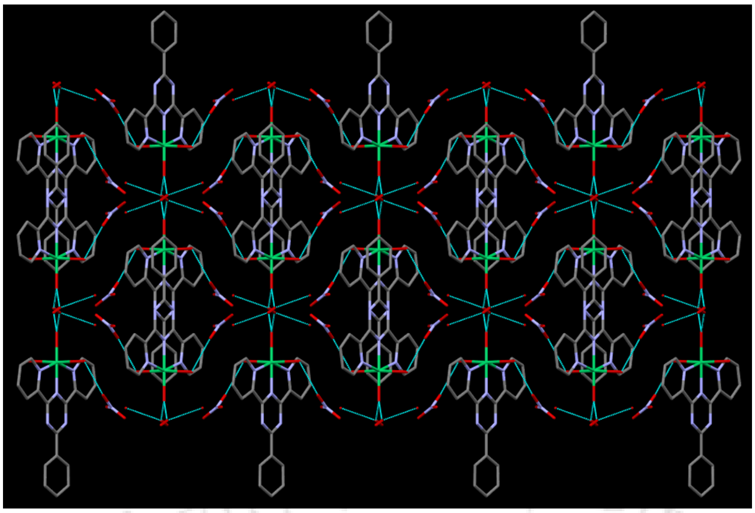


Figure 2.2. Packing diagram of **1** on viewing down the *c*-axis.

Compounds **2** and **3** are isostructural, both crystallized in *P1* space group and the asymmetric contain one [M(**L1**)$_2$] ion, two nitrate ions and two water molecules (in **2**), but 1.5 (in **3**) in the lattice, whose oxygen atoms are prolate. In **2**, two water molecules are disordered and were refined with variable site-occupation factors. One of the nitrate ions in both **2** and **3** is severely disordered with respect to an inversion center and the lattice water molecules appear prolate. The schematic diagram of [Co(**L1**)$_2$] ion is shown in Figure 2.3. The bivalent metal ion is surrounded by six nitrogen atoms from two tridentate ligand **L1**, having a distorted octahedral geometry around the metal ion. In both **L1** in **2**, uncoordinated nitrogen atom of the central pyrimidine ring is *anti* to nitrogen atom of the pendent 2-pyridyl ring, while one is *syn* and the other is *anti* in **3**. The central M–N$_M$ bond lengths lie in the range 1.980(3)–1.985(3)Å in **2**, and 1.977(3)–1.980(5)Å in **3**. The terminal M–N$_P$ bond distances lie in the range 2.119(3)–2.131(3)Å in **2**, 2.130(4)–2.164(4)Å in **3**. The chelate bite angles lie in the range 77.20(12)–77.51(13)° {in **2**} and 76.77(16)–77.28(14)° {in **3**} while the other *cis* angle lie in the range 91.19(12)–104.65(13)° {in **2**} and 90.83(14)–106.34(15)° {in **3**}. Among the *trans* angles N$_M$–M–N$_M$ angles are closer to linearity 177.14(12) {in **2**} and 176.15(14) {in **3**}, but the two N$_P$–M–N$_P$ deviate largely from linearity 154.53(13), 154.72(13) {in **2**} and 153.73(16), 153.89(15) {in **3**}.The central pyrimidine ring and its 6-position substituted 2-pyridyl ring deviate marginally from the planarity as inferred from the torsional angles N9–C26–C34–C35, 7.8(6)° and N4–C8–C15–C16, -9.7(6)° {in **2**} N9–C26–C34–N10, 8.0(7)° and N4–C7–C15–N5, -9.3(7)° {in **3**}.

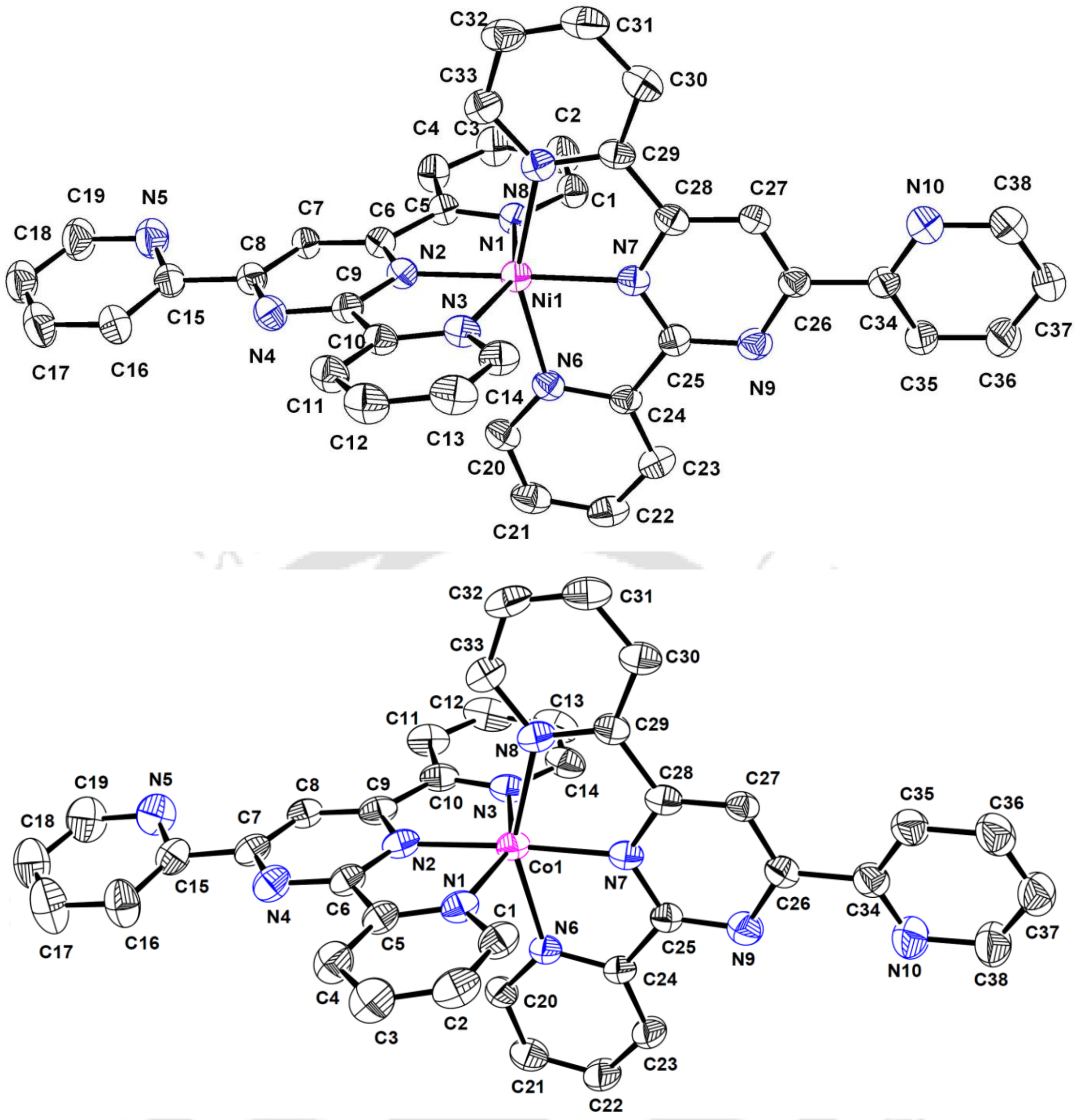


Figure 2.3. ORTEP (30% probability ellipsoids) of of [Ni(**L1**)$_2$] ion in **2** (above) and [Co(**L1**)$_2$] ion in **3**(below). Hydrogen atoms are omitted for clarity.

2.4. Spectra and Magnetism

In complexes **1-3** absorption bands due to *d*–*d* and intra-ligand charge transfer transition, respectively were observed in the visible and UV regions (Figure 2.4). In **1** the *d-d* band observed around 820 nm that tail into near-IR region is due to $^3A_{2g} \rightarrow {}^3T_{2g}$ and other *d-d* bands are obscured by the allowed intra-ligand transitions. In **2** three *d-d* bands were observed in the visible region can be assigned to $^3A_{2g} \rightarrow {}^3T_{2g}$ (835 nm) and $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ (596 nm), other (644 nm) may be due a spin-forbidden transition $^3A_{2g} \rightarrow {}^1E_g$. While in **3** two *d-d* bands observed at 840 and 738 nm could arise from $^4T_{1g}(F) \rightarrow {}^4T_{2g}$ having the electronic configuration $t_{2g}^4 e_g^3$ for the excited state and hence $^4T_{2g}$ should be strongly Jahn-Teller distorted. Therefore these two bands at 840 and 738 nm could be due to ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}$ transition with excited state Jahn-Teller distortion. Other bands at 517 and 469 nm could be due to ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition and splitting due to spin-orbit coupling in the excited state [89].

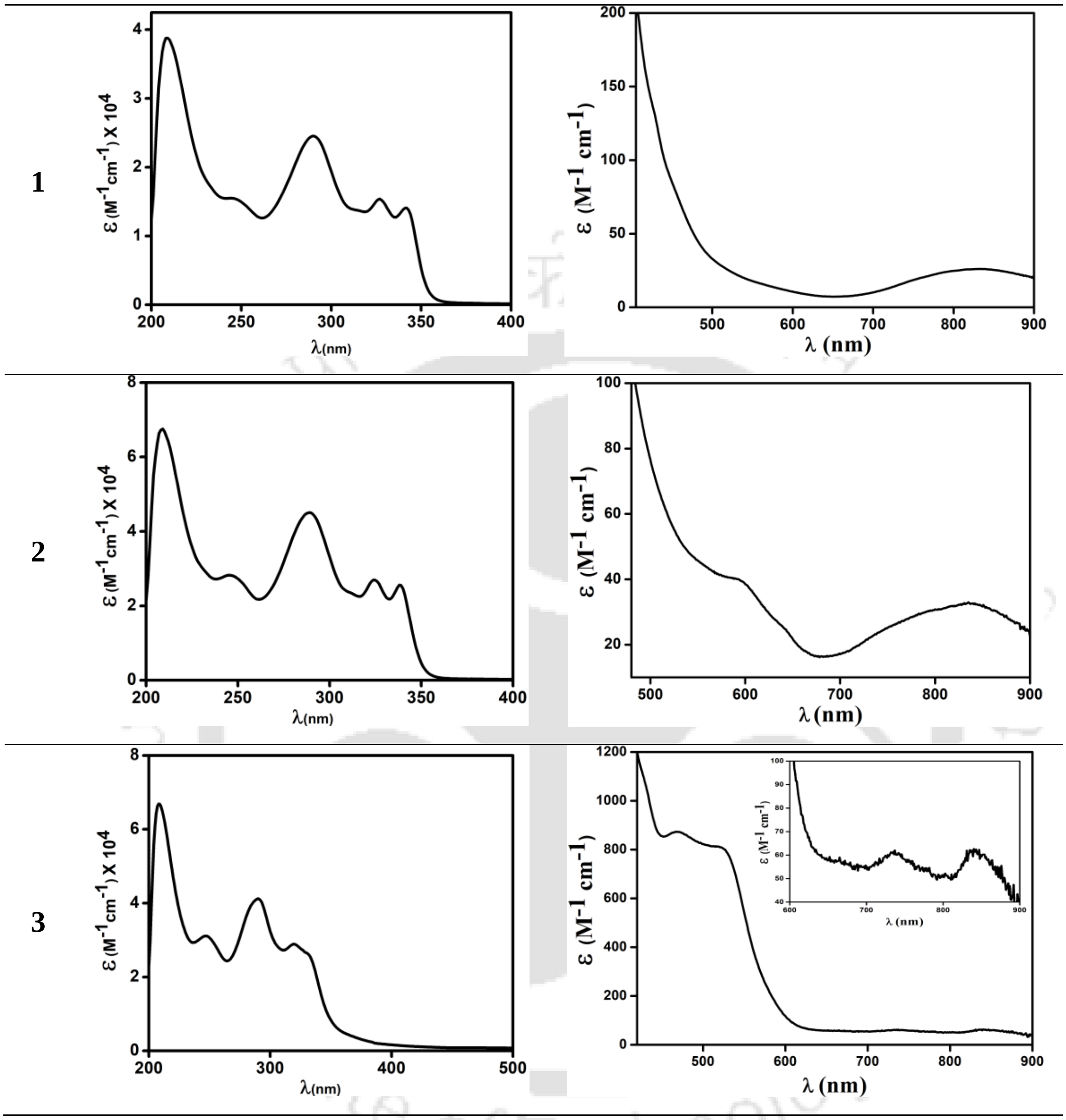
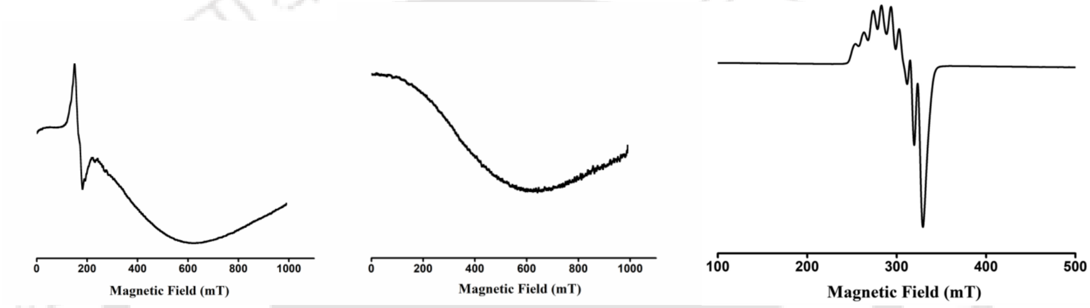


Figure 2.4. Electronic spectra of **1**–**3**.

The experimental room-temperature μ_{eff} values for the complexes **1**, **2** and **3** were 2.93, 3.64 and 4.93 BM respectively. The μ_{eff} value of **1** is slightly higher than that of $\mu_{s.o.}$ and is largely greater for **2**. The μ_{eff} value of the **3** is also higher than the calculated spin-only values and is suggestive of high spin nature of bivalent cobalt(II) ion. The trend $\mu_{eff} > \mu_{s.o.}$ indicate existence of spin-orbit coupling [90-91] in **2** and **3**. In frozen solution (1:3 methanol-acetonitrile) at 77K, X-band EPR spectral signals of complexes **1**–**2** were very weak and broad, but **1** exhibited a weak signal at g = 3.877.

Complex **3** exhibited a signal (Figure 4) at g_{ave} = 2.123 arising from lowest level $\pm\frac{1}{2}$ Kramers' doublet, having the hyperfine splitting by ^{59}Co (I = $\frac{7}{2}$) into eight lines with the constant A = 99 G. In ^{1}H NMR spectra, **1** and **2** exhibited paramagnetism induced broad signals for all the protons (in the δ range 7.8 – 15) of the bound ligand without hyperfine coupling. More number of peaks observed in **2** indicate the magnetically non-equivalent nature of two **L1** bound to Ni(II) center. This is consistent with the molecular structure that lacks symmetry which can equalize two coordinated ligands. Complex **3** did not show any signals for the protons of ligand **L1** bound to the high-spin Co(II) center implying a severe paramagnetic broadening effect on all protons.



1 **2** **3**

Figure 2.5. EPR spectra of **1-3** in frozen glass (1:3 methanol-acetonitrile) at 77K.

2.5. Computational Methods

The geometry was optimized by using the density functional theory (DFT) method at the B3LYP level for **L1–L3** and the 6-31g(+d,p) basis set was assigned for all elements. All calculations were performed with Gaussian09 program [92] and visualized using Gauss View program. From the DFT calculations it was clear that the energies of HOMO and LUMO of **L1-L3** differ marginally and in the case of **L1** calculated excitation energy for the transition from HOMO→LUMO (Figure 2.6), was found to be 282 nm (4.544 eV in vacuum). The difference in energy between HOMO and LUMO were respectively 4.643 and 4.533 eV in **L2** and **L3**. The experimental observation that UV-visible spectrum of **L1** in methanol exhibited an absorption band with λ_{max} = 291 nm, correlated well with the calculated value. The contours of molecular orbitals (Table 2.4) of **L1-L3** were nearly the same and the HOMO of **L1–L3** is a π-type orbital, has contributions from the central pyrimidine ring and mostly from one 2-pyridyl group, while LUMO is a π*-type orbital, has contributions from the central pyrimidine ring and rest of two pyridyl rings (excluding the one that is part of HOMO).

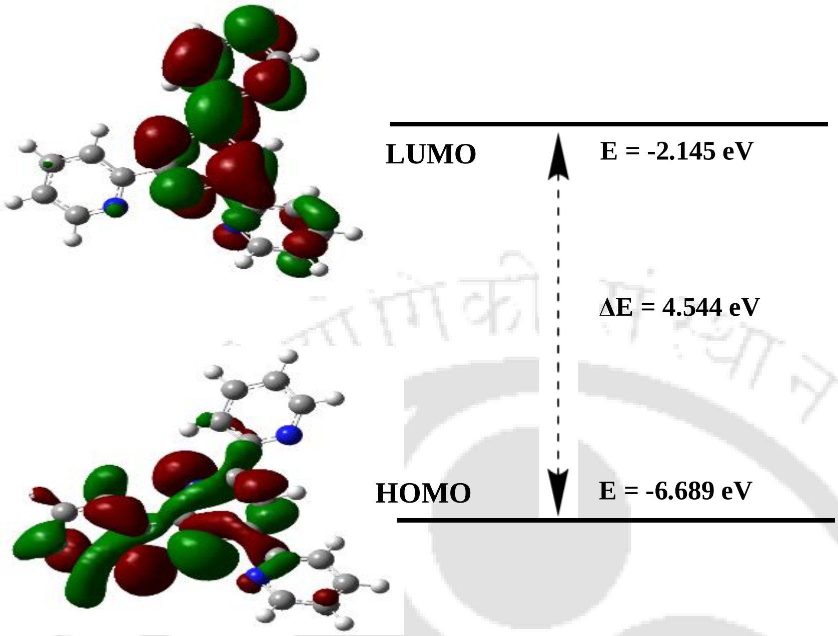
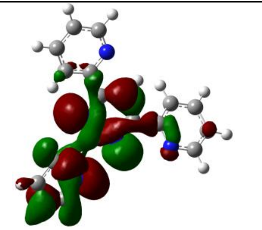
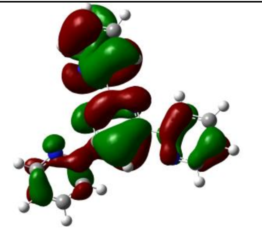
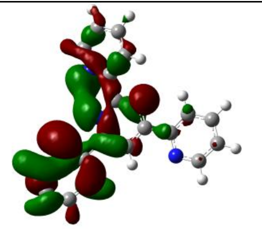
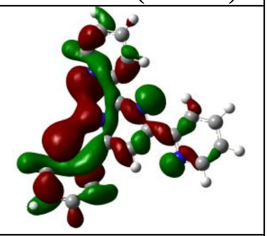
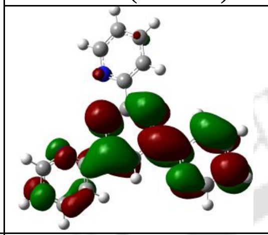
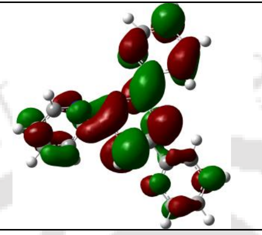
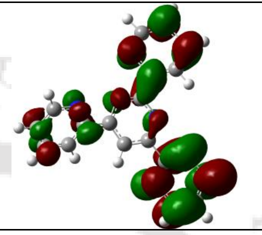
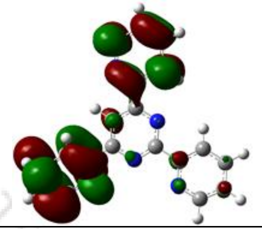
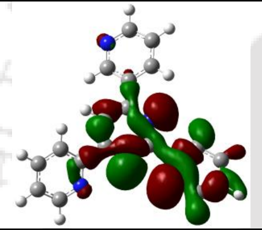
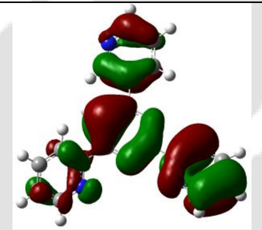
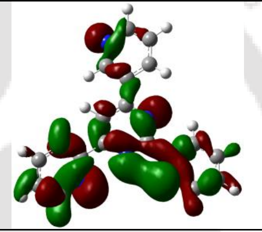
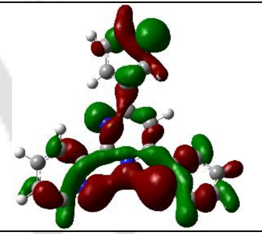
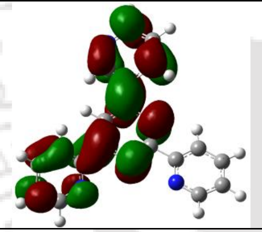
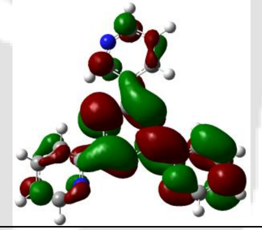
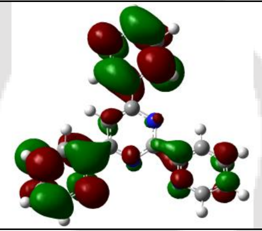
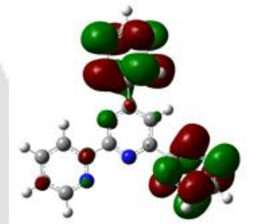
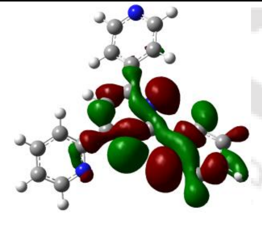
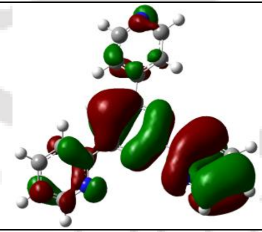
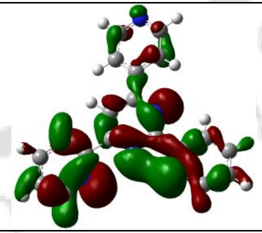
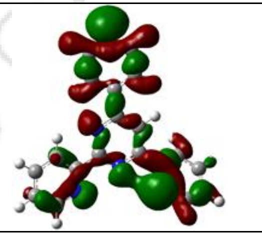
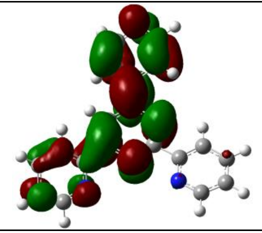
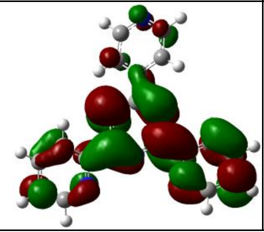
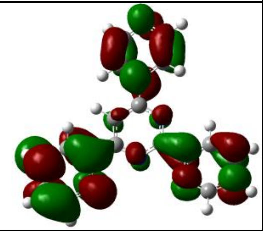
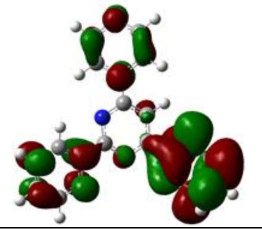


Figure 2.6. Energy level diagram depicting HOMO and LUMO of **L1**.

Table 2.4. Contour diagrams of frontier orbitals and their energies in **L1-L3**.

Molecular Orbitals (energy in eV)				
L1	HOMO (-6.6893)	HOMO-1 (-6.7705)	HOMO-2 (-7.0850)	HOMO-3 (-7.1501)
				
	LUMO (-2.1448)	LUMO+1 (-1.8400)	LUMO+2 (-1.1325)	LUMO+3 (-1.0177)
				
L2	HOMO (-6.4973)	HOMO-1 (-6.6031)	HOMO-2 (-6.9120)	HOMO-3 (-6.9803)
				
	LUMO (-1.8545)	LUMO+1 (-1.6392)	LUMO+2 (-0.8123)	LUMO+3 (-0.6993)
				
L3	HOMO (-6.5492)	HOMO-1 (-6.6842)	HOMO-2 (-6.6978)	HOMO-3 (-7.0426)
				
	LUMO (-1.9960)	LUMO+1 (-1.7149)	LUMO+2 (-0.8623)	LUMO+3 (-0.6855)
				

2.6. Conclusions

In summary, this Chapter describes a new efficient route for the synthesis of three 2,4,-bis(2-pyridyl)-6-(pyridyl)pyrimidines, by employing respective acetylpyridine, sodium hydroxide and 2-cyanopyridine. 2-Cyanopyridine readily reacted with 2-oxo-2-(2-pyridyl)-1-ethanide ion to yield 2,4,6-tris(2-pyridyl)pyrimidine (**L1**). The potential multidentate **L1** binds as a tridentate ligand to Ni(II) and Co(II) ions. The mono- and bis-chelated Ni(II) complexes were isolated by controlling the stoichiometry of the reactants and only the bis-chelated Co(II) complex formed, irrespective of the reactant ratios. Determination of the molecular structures of **1-3** revealed that the metal center has a distorted octahedral geometry with coordination environment of *mer*-$(N_M)(N_P)_2O_3$ in **1**, and *mer*-$(N_M)_2(N_P)_4$ in **2-3**. In general, the central Ni–N_M distances are shorter than the two terminal Ni–N_P distances. The HOMO is a π-type orbital, while LUMO is a π*-type, as inferred from the DFT calculations.

2.7. Syntheses and Spectral Data

2,4,6-Tris(2-pyridyl)pyrimidine (**L1**)

Powdered sodium hydroxide (0.40 g, 10 mmol) and 2-acetylpyridine (1.0 g, 8.25 mmol) were ground gently using a glass rod, in a round bottom flask until it became (~30 min) a viscous mixture. Then 2-pyridinecarbonitrile (1.72 g, 16.51 mmol) was added mixed using a glass rod until some red colored solid appeared and then the mixture was heated at 100°C in an oil bath for 12 h. To the cooled mixture, water (40 ml) was added and the precipitate obtained was separated by filtration and washed thoroughly with water. Then the precipitate was subjected to column chromatography (silica gel 60-120 mesh), **L1** was eluted using 60% ethylacetate in hexane. Yield: 1.93 g, (75%). Melting point 210°C. ESI-MS: m/z calcd for $C_{19}H_{13}N_5$, 311.117; found $(M^+ + H)$, 312.125. 500 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$): 9.43 (1H, s), 8.93 (1H, dd, 4.7, 1.7), 8.80 (2H, dd, 4.7, 1.7), 8.77 – 8.73 (3H, m), 7.92 (3H, dt, 13.6, 7.7), 7.45 (3H, ddd, 12.2, 7.5, 4.7). 126 MHz ^{13}C NMR (δ, $CDCl_3$): 165.04, 163.54, 155.41, 154.37, 150.21, 149.77, 137.12, 125.54, 124.96, 124.27, 122.38, 113.17. FTIR (KBr, cm^{-1}): 3424(b), 3054(w), 3007(w), 2923(w), 2853(w), 1648(w), 1579(vs), 1559(vs), 1534(s), 1468(s), 1431(w), 1395(w), 1366(vs), 1250(w), 1229(w), 1171(w), 1146(w), 1089(w), 1043(w), 994(w), 919(w), 853(w), 838(w), 794(w), 757(vs), 737(w), 667(w), 651(w), 627(w). UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$) MeOH solution]: 308(8710); 291(11470).

Other two compounds, 2,4-bis(2-pyridyl)-6-(3-pyridyl)pyrimidine (**L2**) and 2,4-bis(2-pyridyl)-6-(4-pyridyl)pyrimidine (**L3**) were synthesized by following the procedure described above for **L1**, by using 3-acetylpyridine and 4-acetylpyridine respectively.

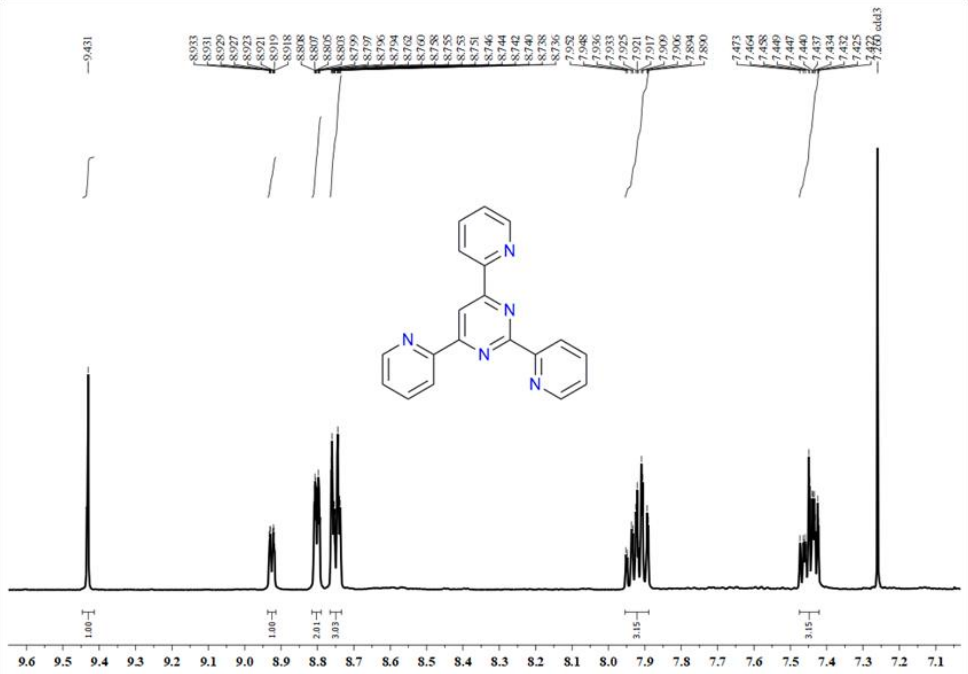


Figure 2.7. ^{1}H-NMR for 2,4,6-tri(pyridin-2-yl)pyrimidine (**L1**)

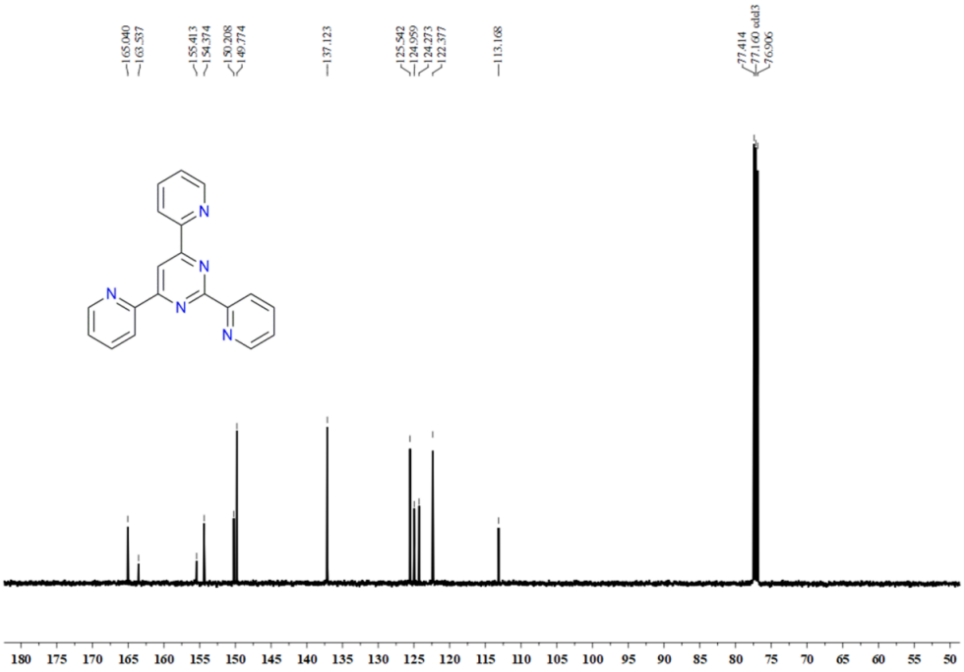
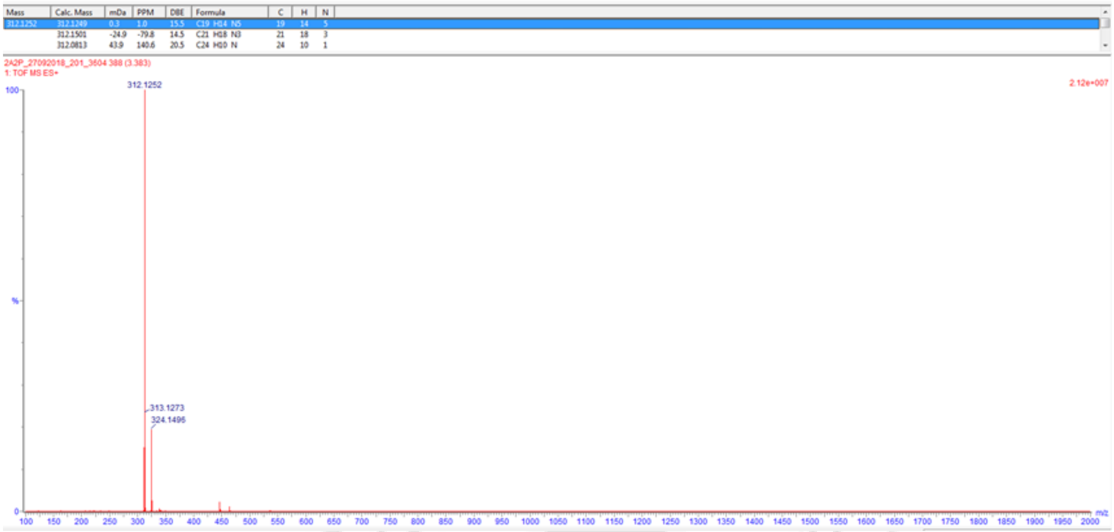


Figure 2.8. ^{13}C-NMR for 2,4,6-tri(pyridin-2-yl)pyrimidine (**L1**)



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N
312.1252	312.1249	0.3	1.0	15.5	C19 H14 N5	19	14	5
	312.1501	-24.9	-79.8	14.5	C21 H18 N3	21	18	3
	312.0813	43.9	140.6	20.5	C24 H10 N	24	10	1

Figure 2.9. ESI Mass spectrum for 2,4,6-tri(pyridin-2-yl)pyrimidine (**L1**)

2,4-Bis(2-pyridyl)-6-(3-pyridyl)pyrimidine (**L2**)

Yield: 1.86 g (72%).Melting point 212°C. ESI-MS: m/z calcd for $C_{19}H_{13}N_5$, 311.117; found (M^++H), 312.125. 500 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$):9.88 (1H, s), 9.55 (1H, s), 8.93 (1H, dd, 5.1, 2.9), 8.83 – 8.80 (1H, m), 8.80 – 8.75 (3H, m), 8.74 – 8.69 (1H, m), 8.67 – 8.60 (1H, m), 7.94 (1H, t, 7.7), 7.54 – 7.44 (3H, m). 126 MHz ^{13}C NMR (δ, $CDCl_3$):164.36, 163.22, 162.94, 153.92, 151.92, 151.64, 150.23, 149.71, 148.97, 137.43, 135.85, 134.93, 133.30, 132.74, 125.91, 123.87, 123.58, 122.15, 111.42. FTIR (KBr, cm^{-1}): 3399(b) (s), 2960(m), 2925(m), 2854(m), 1651(b), 1592(s), 1584(s), 1566(s), 1532(s), 1471(s), 1435(m), 1421(m), 1364(s), 1329(w), 1263(w), 1233(w), 1194(w), 1090(w), 1043(w), 1025(m), 995(w), 889(w), 798(s), 776(w), 744(s), 701(w), 666(w), 655(w), 617(w). UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$) MeOH solution]: 310(7490); 290(7970).

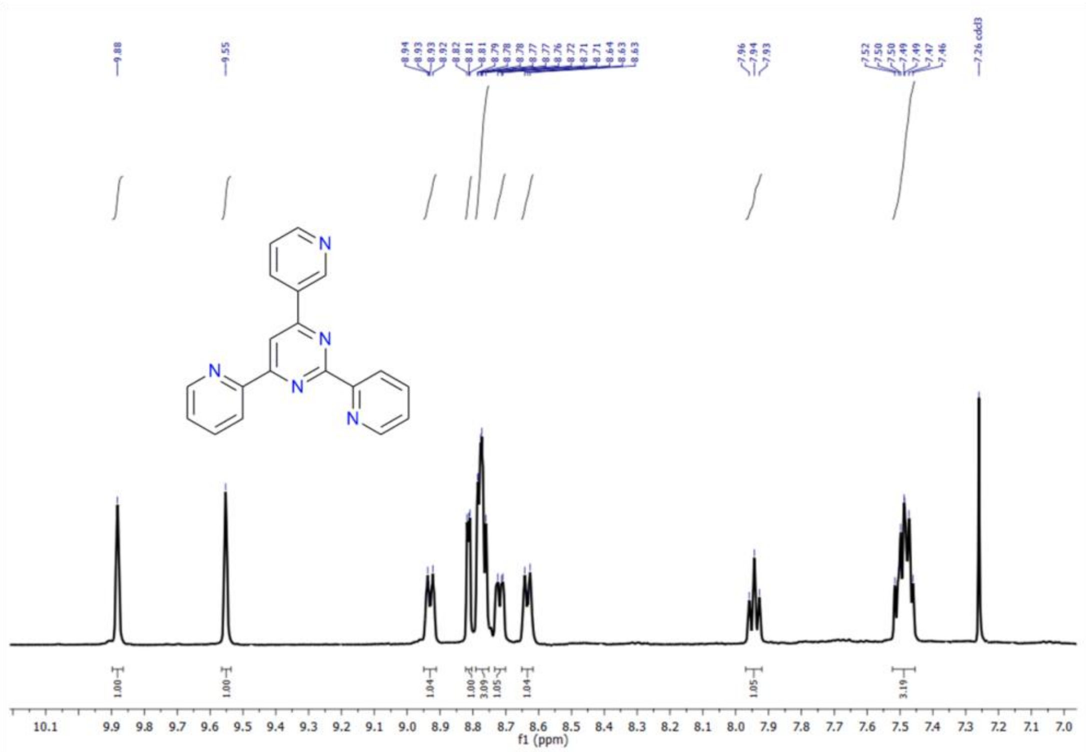


Figure 2.10. ^{1}H-NMR for 2,4-Bis(2-pyridyl)-6-(3-pyridyl)pyrimidine (**L2**)

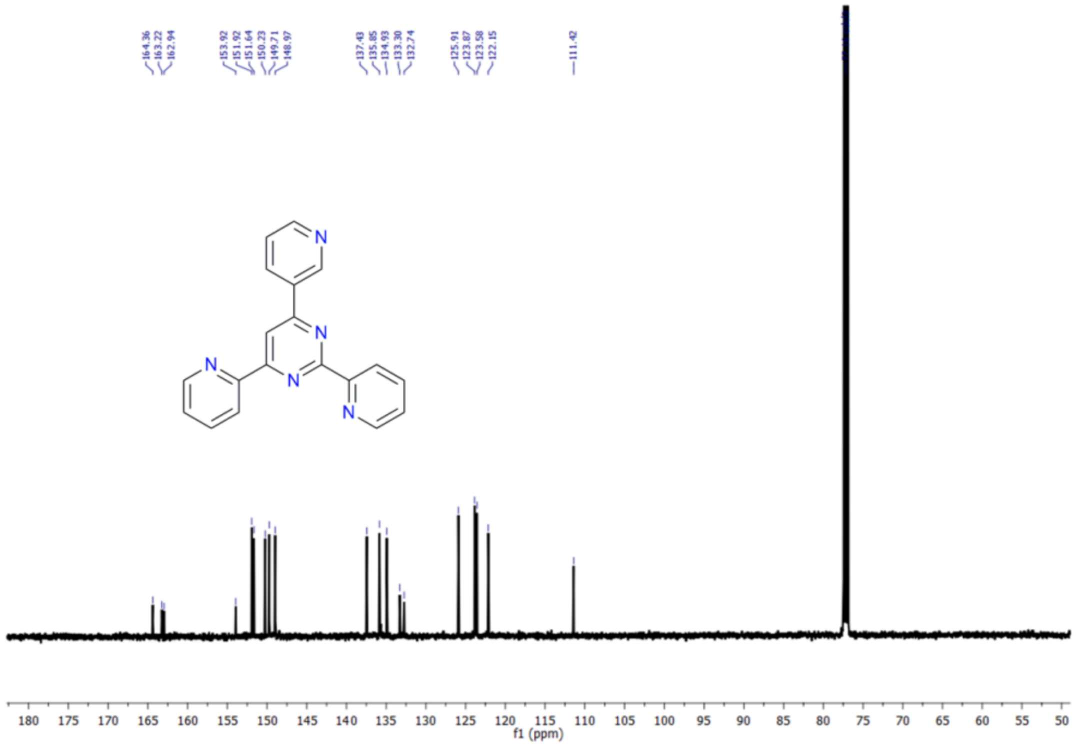
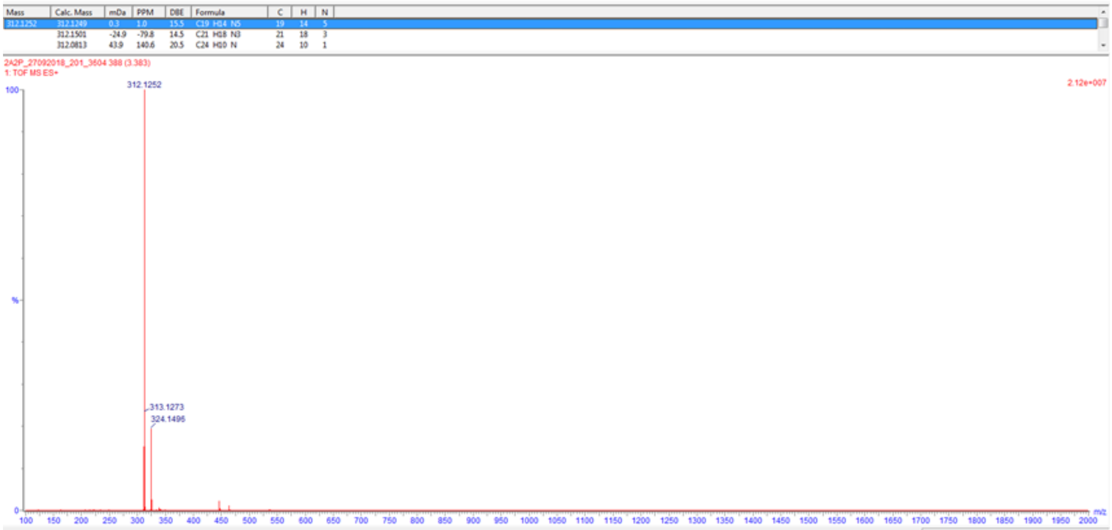


Figure 2.11. ^{13}C-NMR for 2,4-Bis(2-pyridyl)-6-(3-pyridyl)pyrimidine (**L2**)



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N
312.1252	312.1249	0.3	1.0	15.5	C19 H14 N5	19	14	5
	312.1501	-24.9	-79.8	14.5	C21 H18 N3	21	18	3
	312.0813	43.9	140.6	20.5	C24 H10 N	24	10	1

2A2P_27092018_201_3604 388 (3.383)
1: TOF MS ES+

Figure 2.12. ESI Mass spectrum for 2,4-Bis(2-pyridyl)-6-(3-pyridyl)pyrimidine (**L2**)

2,4-Bis(2-pyridyl)-6-(4-pyridyl)pyrimidine (L3)

Yield: 2.10 g (82%). Melting point 215°C. ESI-MS: m/z calcd for $C_{19}H_{13}N_5$, 311.117; found (M^++H), 312.125. 500 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$): 8.92 (1H, s), 8.89 – 8.84 (4H, m), 8.82 – 8.78 (1H, m), 8.74 (1H, d, 7.9), 8.54 (2H, dd, 4.5, 1.6), 8.22 (2H, dd, 4.5, 1.6), 7.97 (1H, td, 7.7, 1.8), 7.50 (1H, ddd, 7.5, 4.7, 1.1). 126 MHz ^{13}C NMR (δ, $CDCl_3$): 165.01, 163.34, 162.94, 153.68, 150.95, 150.68, 149.83, 144.96, 144.25, 137.51, 126.13, 122.36, 122.21, 121.39, 112.72. FTIR (KBr, cm^{-1}): 3367(b), 2956(m), 2919(m), 2851(m), 1730(m), 1594(s), 1581(s), 1555(s), 1529(s), 1470(s), 1433(w), 1396(m), 1368(m), 1318(w), 1263(w), 1218(w), 1153(w), 1090(w), 1061(w), 994(w), 895(m), 848(w), 797(w), 772(S), 742(m), 666(w), 646(w), 631(m). UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$) MeOH solution]: 307(8380); 292(9870).

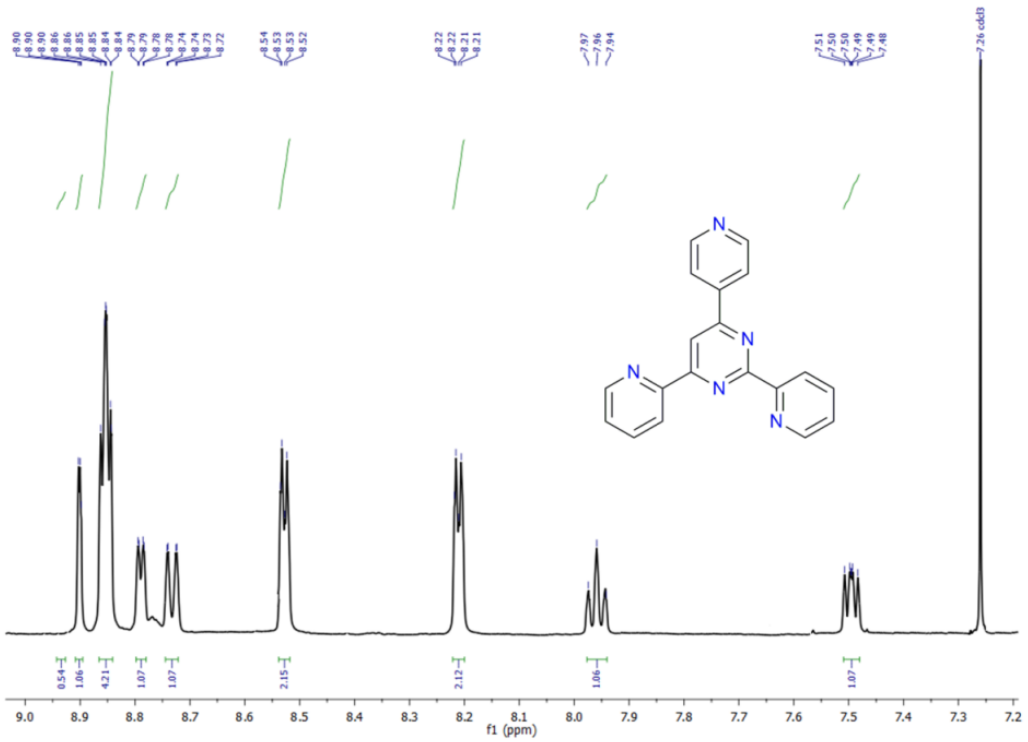


Figure 2.13. ^{1}H-NMR for 2,4-Bis(2-pyridyl)-6-(4-pyridyl)pyrimidine (**L3**)

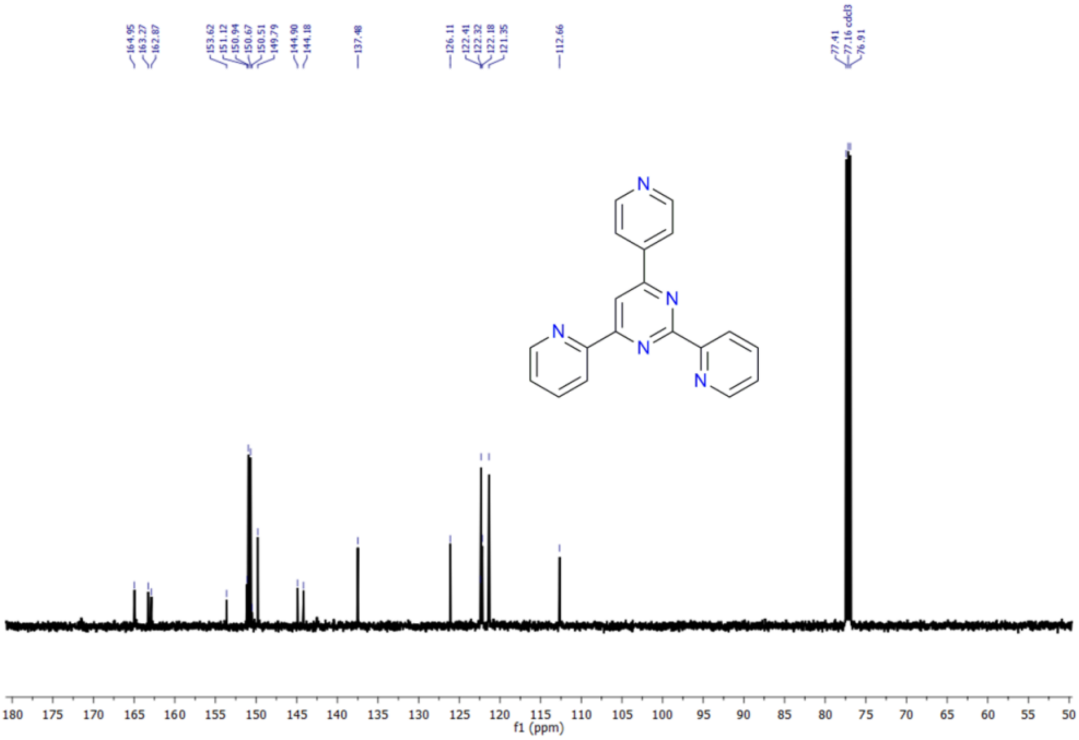
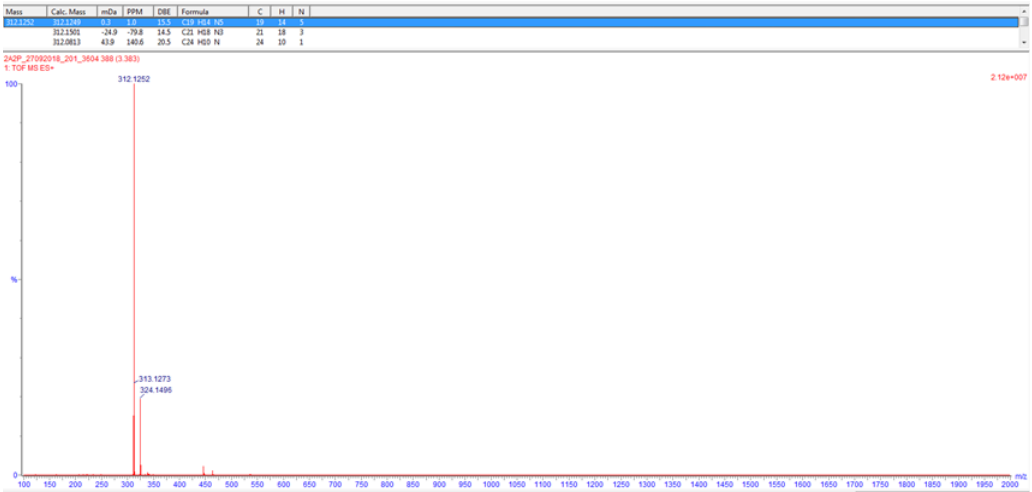


Figure 2.14. ^{13}C-NMR for 2,4-Bis(2-pyridyl)-6-(4-pyridyl)pyrimidine (**L3**)



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N
312.1252	312.1249	0.3	1.0	15.5	C19 H14 N5	19	14	5
	312.1501	-24.9	-79.8	14.5	C21 H18 N3	21	18	3
	312.0813	43.9	140.6	20.5	C24 H10 N	24	10	1

Figure 2.15. ESI Mass spectrum of 2,4-Bis(2-pyridyl)-6-(4-pyridyl)pyrimidine (**L3**)

[Ni(**L1**)$(H_2O)_3](NO_3)_2\cdot 4H_2O$ (**1**)

To **L1** (100 mg, 0.32 mmol) dissolved in methanol (30 mL), solid $Ni(NO_3)_2\cdot 6H_2O$ (94 mg, 0.32 mmol) was added and stirred for 6 h. The solution was kept at room temperature and block shaped crystals suitable for XRD studies, obtained after 7 days were collected and washed with ice-cold methanol. Yield: 130 mg, (69%). Anal. Calcd. for $C_{19}H_{27}N_7NiO_{13}$: C, 36.80; H, 4.39; N, 15.81. Found: C, 36.72; H, 4.34; N, 15.75%. FTIR (KBr, cm^{-1}): 3350(b), 2427(w), 1763(w), 1592(s), 1569(w), 1542(s), 1474(s), 1384(vs), 1266(w), 1237(w), 1186(w), 1159(w), 1093(w), 1029(w), 1029(w), 1015(s), 1001(w), 893(w), 862(w), 826(s), 796(w), 764(s), 749(w), 704(w), 674(w), 660(w), 659(w), 623(w). UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$) MeOH solution]: 830(26); 342(14070); 329(14930); 290(24540). 500 MHz ^{1}H NMR (δ, DMSO): 14.08 (1H, s) 13.79 (1H, s), 12.46 (1H, s), 10.75 (3H, s), 9.09 (3H, s), 7.87 (4H, s).

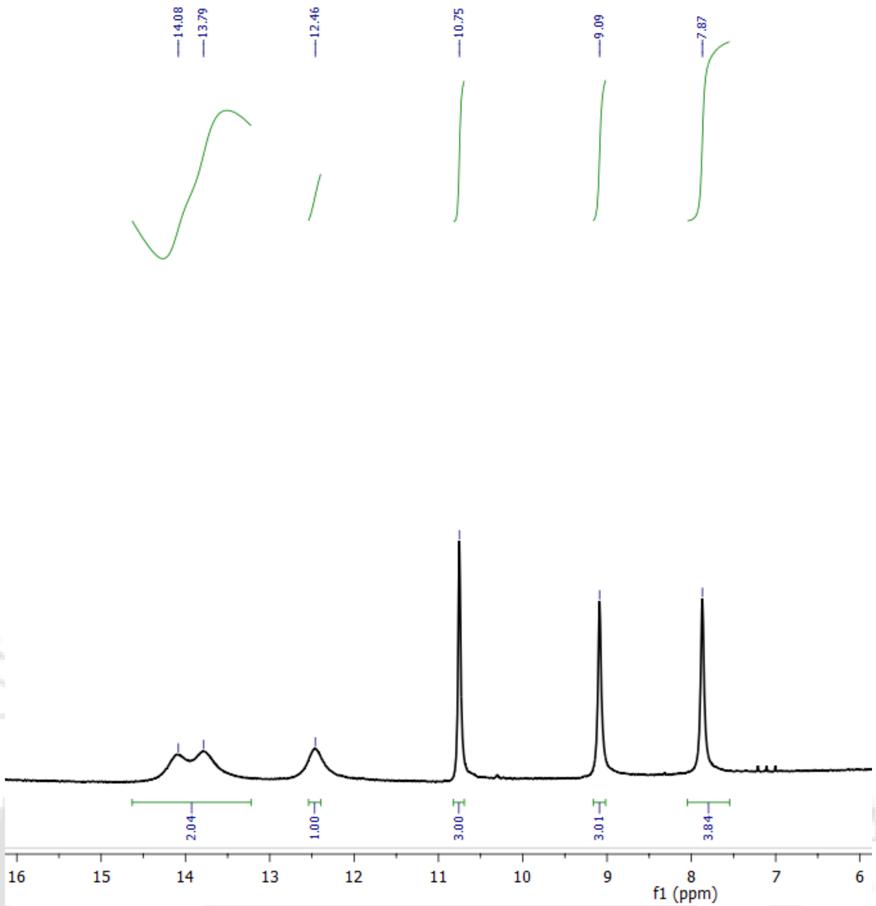


Figure 2.16. ^{1}H NMR spectrum of **1**.

[Ni(**L1**)$_2$](NO$_3$)$_2$·2H$_2$O (**2**)

To **L1** (100 mg, 0.32 mmol) dissolved in methanol (15 mL), solid Ni(NO$_3$)$_2$·6H$_2$O (46 mg, 0.16 mmol) was added and stirred for 6 h. The solution was kept at room temperature and block shaped crystals suitable for XRD studies, obtained after 7 days were collected and washed with ice-cold methanol. Yield: 120 mg, (80%). Anal. Calcd. for $C_{38}H_{30}N_{12}NiO_8$: C, 54.24; H, 3.59; N, 19.98. Found: C, 54.05; H, 3. 05; N, 19.84%. FTIR (KBr, cm^{-1}): 3368(b), 2427(w), 1763(w), 1591(s), 1569(w), 1542(s), 1475(m), 1384(vs), 1266(w), 1237(w), 1159(w), 1094(w), 1046(w), 1029(w), 1015(s), 1001(w), 892(w), 862(w), 840(w), 826(w), 796(w), 764(s), 750(w), 674(w), 660(w), 639(w). UV–Vis [λ_{max}, nm (ε, M^{-1}cm^{-1}) MeOH solution]: 835(33); 644(23); 596(40); 339(25490); 325(26900); 289(45050). 500 MHz ^{1}H NMR (δ, DMSO): 13.15 (1H, s), 13.82 (1H, s), 13.14 (1H, s), 12.91 (1H, s), 12.51 (1H, s), 11.92 (1H, s), 10.75 (1H, s), 10.31 (1H, s), 9.06 (2H, d, 15.3), 7.87 (3H, s).

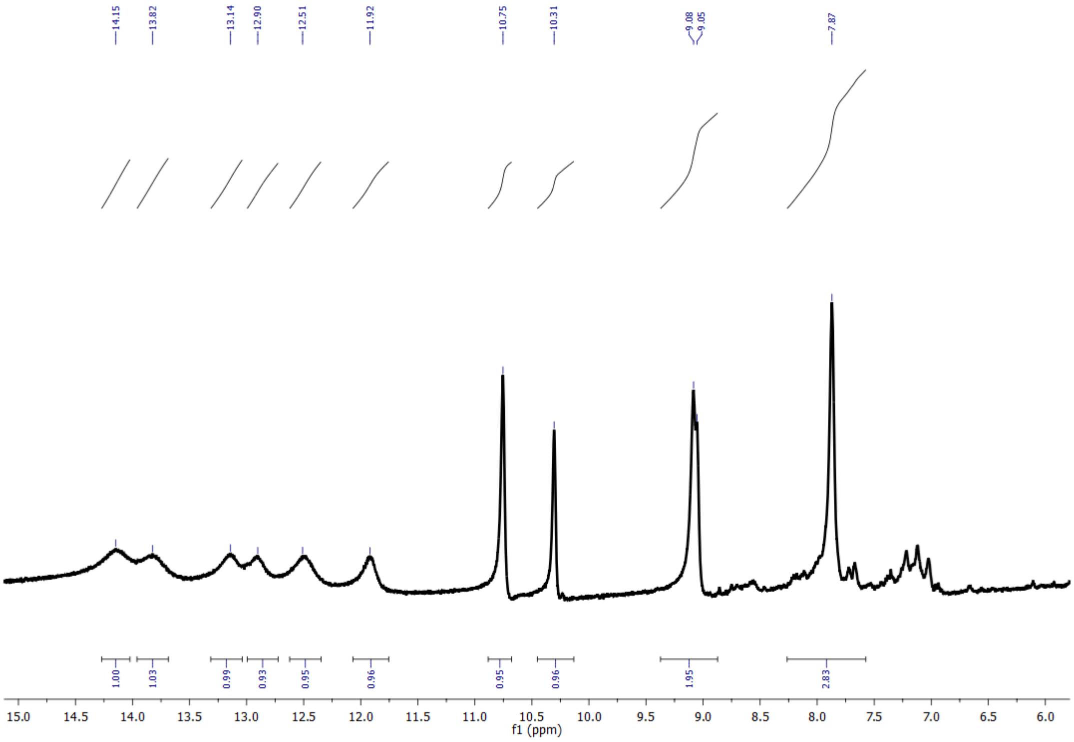


Figure 2.17. ^{1}H NMR spectrum of **2**.

[Co(**L1**)$_2$](NO$_3$)$_2$·1.5H$_2$O **(3)**

To **L1** (100 mg, 0.32 mmol) dissolved in methanol (15 mL), solid Co(NO$_3$)$_2$·6H$_2$O (47 mg, 0.16 mmol) was added and stirred for 6 h. The solution was kept at room temperature and block shaped crystals suitable for XRD studies, obtained after 7 days were collected and washed with ice-cold methanol. Yield: 126 mg, (82%). Yield: 58 mg, (82%). Anal. Calc. for $C_{38}H_{29}N_{12}CoO_{7.5}$: C, 54.81; H, 3.51; N, 20.19. Found: C, 54.75; H, 3.47; N, 20.07%. FTIR (KBr, cm^{-1}): 3368(b), 2426(w), 1763(w), 1589(s), 1566(w), 1537(s), 1474(w), 1384(vs), 1265(w), 1236(w), 1158(w), 1093(w), 1045(w), 1014(s), 893(w), 861(w), 840(w), 826(w), 796(w), 762(s), 750(w), 671(w), 659(w), 637(w). UV–Vis [λ_{max}, nm (ε, M^{-1}cm^{-1}) MeOH solution]: 840(63); 738(61); 517(812); 469(873); 320(28890); 290(41210).

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Chapter 3

Synthesis and Characterization of Binuclear Nickel(II) Complexes Using *N*-(3-(Pyridine-2-yl)imidazo[1,5-*a*]pyridine-1-yl)picolinimidamide

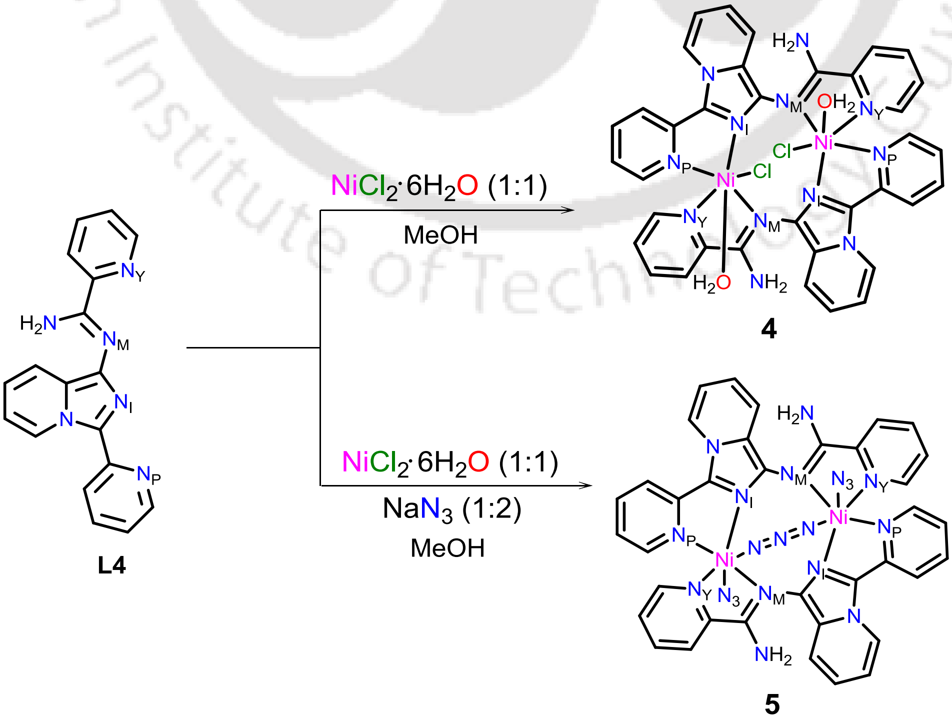
Abstract

Two new binuclear Ni(II) complexes of composition $[Ni_2(\mathbf{L4})_2(Cl)_2(H_2O)_2]Cl_2\cdot12H_2O$ (**4**), and $[Ni_2(\mathbf{L4})_2(N_3)_3](N_3)\cdot5H_2O$,(**5**) {**L4** = *N*-(3-(pyridine-2-yl)imidazo[1,5-a]pyridine-1-yl)picolinimidamide} have been synthesized and characterized. Complex **4** was obtained by treating **L4** with $NiCl_2\cdot6H_2O$, in 1:1 ratios and in the synthesis of complex **5**, two equivalent of NaN_3 was used additionally. Structural characterization revealed that the nickel center has pseudo-octahedral coordination geometry in both the complexes with **L4** acting as a bridging bis(bidentate) ligand. In **5**, out of the three coordination azide ions, two are bound as a monodentate fashion and the third one in μ-1,3(end-to-end) bridging fashion.

3.1. Introduction

Coordination chemistry of nickel(II) with multidentate nitrogen based ligands has attracted particular attention and such complexes has been found have a role in bioinorganic chemistry [1,2] or act also as catalysts [3,4]. An increasing effort has been committed in recent years, to the mono- or *di*-nuclear nickel complexes with imidazole-based tridentate pincer NNN type ligand [5-9]. Nickel(II) complexes of nitrogen based multidentate chelating ligands have been extensively used as these ligands [10-14] exhibit varying coordination modes. This, allow homo- and/or heteronuclear metal complexes with different stereochemistry [15,16]. Different binuclear nickel complexes with pseudo halide- [17-20], azido- [18-37], cyanato- [38-42], and thicyanato- bridged [43-52], complexes have been reported with reference to relationship between coordination mode and magnetic behavior. Although some imidazo[1,5-*a*]pyridines have been used for the synthesis of bivalent nickel homoleptic [53], tris-chelate [54] and square planar complexes [55] but dinuclear nickel complexes has not been reported so far.

In continuation of Chapter 2 wherein bivalent mononuclear complexes of Ni(II) and Co(II) complexes of 2,4,6-tris(2-pyridyl)pyrimidine (**L1**) have been described, in this Chapter synthesis, characterization and structural aspects of two binuclear Ni(II) complexes of *N*-(3-(2-pyridyl)imidazo[1,5-*a*]pyridiyl)picolinimidamide (**L4**), along with coligands such as Cl$^-$ and N_3^- have been described.



3.2. Results and Discussion

Compound **L4** is a potential multidentate ligand and hence has been used to synthesize nickel(II) complexes of compositions [Ni_2(**L4**)$_2$(Cl)$_2$(H_2O)$_2$]Cl_2·12H_2O (**4**) and [Ni_2(**L4**)$_2$(N_3)$_3$](N_3)·5H_2O (**5**). Complex **4** has been isolated from the reaction of **L4** with $NiCl_2$·6H_2O in methanol and under the same conditions in presence of two equivalents of sodium azide, complex **5** was isolated. Both complexes were isolated in the solid form and characterized thoroughly by FTIR and UV-Vis spectroscopies, room temperature magnetic moment and thermogravimetric analysis.

3.3. Molecular Structures

The molecular structures of both **4** and **5** were established using single-crystal X-ray diffraction studies, crystallographic data are listed in Table 3.1, selected bond distances and angles are listed respectively in Tables 3.2 and 3.3. Complex **4** crystallized in $P2_1/c$ space group and the asymmetric unit contain the complex ion [Ni_2(**L4**)$_2$(Cl)$_2$(H_2O)$_2$] along with two chloride ions and twelve water molecules in the lattice. Both molecules of **L4** coordinate in bis(bidentate) fashion to two nickel centers and thus forming a dinickel entity. Each nickel center is chelated by N_PN_I from one molecule of **L4** and by N_MN_Y from another molecule of **L4** {N_I = imidazo nitrogen; N_M = imidamide nitrogen; N_P = pyridyl nitrogen; N_Y = picolinimidamide nitrogen}. Other two coordination sites are occupied by one chloride ion and one water molecule (O_W). A perspective view of [Ni_2(**L4**)$_2$(Cl)$_2$(H_2O)$_2$] unit is shown in Figure 3.1. Thus the metal center has a distorted octahedral geometry coordinated by six different types of donor atoms with a *cis*-*cis*-*cis*-(N_PN_I)(N_MN_Y)(O_WCl) orientation. Also it can be mentioned that one face of the octahedron is occupied by $N_PN_IN_Y$ and the opposite face by N_MO_WCl group of atoms, as a consequence N_P, N_I and N_Y are respectively *trans* to N_M, O_W and Cl. The Ni–N bond lengths lie within a small range of 2.054(7) to 2.097(6) Å. The Ni–N_Y distance in Ni1 nucleus is longer than Ni–N_Y distance in Ni2 nucleus by 0.016(5) Å, while Ni–N_Y distances at both Ni1 and Ni2 nucleus are nearly same. The non-bonded Ni···Ni distance is 4.531(1) Å. The 3-(pyridine-2-yl)imidazo[1,5-*a*]pyridine and 1-picolinimidamide moieties of both coordinated ligands are twisted along C7–N4 and C30–N10 bonds. The torsional angle at N2–C7–N4–C13 and N8–C30–N10–C31 respectively are 108.2(9)° and 103.9(8)°.

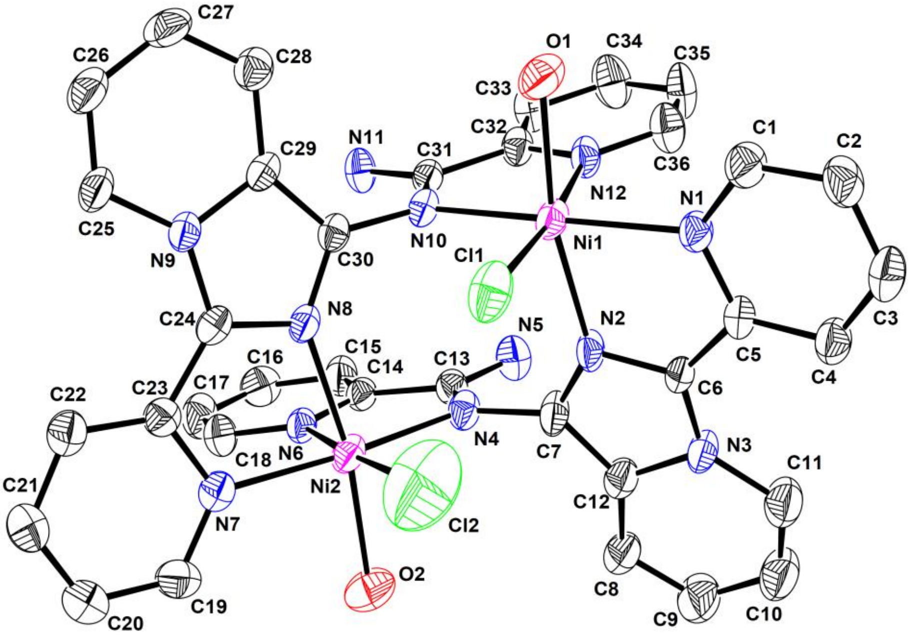


Figure 3.1. ORTEP (30% probability ellipsoids) of [Ni_2(**L4**)$_2$(Cl)$_2$(H_2O)$_2$] ion in **4**, hydrogen atoms omitted for clarity.

Two units of [Ni_2(**L4**)$_2$(Cl)$_2$(H_2O)$_2$] entity are linked with O1 of one entity with O2 of the other by a bifurcated H-bonding through two uncoordinated chloride ions Cl3 and Cl4, present in the lattice. Thus O1···Cl3···O2···Cl4 linkage has a diamond-like shape with the non-bonded distances of O1···Cl3, 3.106(8); O1···Cl4, 3.147(9); O2···Cl4, 3.059(9); and O2···Cl3, 3.050(8) Å. This non-bonded intermolecular distance is O1···O2, 3.528(8) Å. The Cl2 coordinated to the Ni1 center and Cl4 are H-bonded to O11, having non-bonded distances of Cl2···O11, 2.630(9) and O11···Cl4, 3.158(8) Å. Coordinated Cl1 remains free from weak intermolecular interactions but the lattice Cl3 and Cl4 are additionally involved hydrogen bonding with the lattice water *viz*., Cl3···O10, 3.071(5); Cl4···O11, 3.158(8) and Cl4···O14, 2.938(5) Å. The nitrogen atom of the amidine group is involved in hydrogen bonding with two water molecules O6 and O7 having the non-bonded contacts N5···O6, 2.958(7) and N5···O7, 3.005(9) Å. Hydrogen-bonding between water molecule O6 with O5, O5 with O12 having a non-bonded distance of O6···O5, 3.005(4)Å and O5···O12, 3.036(5)Å are present. Notable hydrogen bonding interaction among the other lattice water molecules are O3···O4, 2.940(4); O4···O12, 2.818(4); O4···O13, 2.861(5); O5···O6, 3.005(4); O5···O8, 2.941(6); O5···O12, 3.036(5); O7···O14, 2.989(5); O8···O9, 2.721(4); O8···O14, 2.765(4); O9···O9, 2.961(7); O9···O10, 2.840(7); O10···O13, 2.999(5) and

O13···O14, 2.808(5) Å. A packing diagram viewing down the *a* – axis is shown in Figure 3.2.

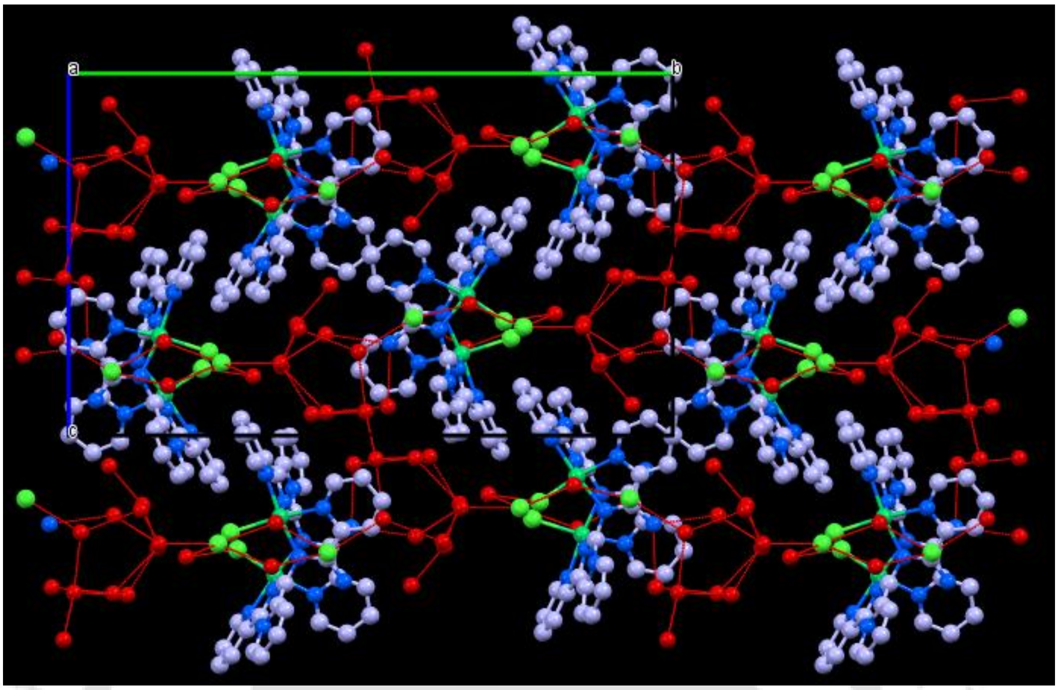


Figure 3.2. Packing diagram of **4** viewing down the *a* – axis.

Table 3.1. Crystallographic data of the complexes **4** and **5**.

	4	**5**
Formula	$C_{36}H_{32}N_{12}Ni_2Cl_4O_{14}$	$C_{36}H_{38}N_{24}Ni_2O_5$
Formula weight	1115.92	1004.32
T (K)	293 K	293
Crystal system	monoclinic	monoclinic
Space group	P 21/c	I 2/c
a (Å)	10.6415(5)	15.8707(4)
b (Å)	27.8109(18)	13.1541(4)
c (Å)	16.6814(7)	20.8019(6)
α (°)	90.00	90.00
β (°)	94.031(4)	101.042(2
γ (°)	90.00	90.00
V (Å^3)	4924.6(4)	4262.3(2)
Z	4	4
D_{calcd} (g m^{-3})	1.505	1.565
μ (mm^{-1})	1.054	0.958
F(000)	2272.0	2072.0
Reflections collected	19137	8663
Unique reflections	8724	3967
Goodness-of-fit (GOF)[a]	1.078	1.061
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	0.1451, 0.2018	0.0697, 0.1098
R_1[b], wR_2[c] (all data)	0.0916,0.1748	0.0536,0.1007

[a]GOF = [a]GOF = $[\Sigma[w(F_0^2-F_c^2)^2]/M–N]^{1/2}$ (M = number of reflections, N = number of parameters refined). [b]$R_1 = \Sigma||F_0|-|F_c||\Sigma|F_0|$. [c]$wR_2 = [\Sigma [w(F_0^2-F_c^2)^2]/\Sigma [w(F_0^2)^2]]^{1/2}$.

Table 3.2. Selected bond distances (Å) in **4** and **5.**

4		**5**	
Ni1–N1	2.097(6)	Ni1–N1	2.102(3)
Ni2–N7	2.096(7)	Ni1–N2	2.071(3)
Ni1–N2	2.070(6)	Ni1–N4	2.069(3)
Ni2–N8	2.068(6)	Ni1–N6	2.111(3)
Ni1–N10	2.073(6)	Ni1–N7	2.190(4)
Ni2–N4	2.054(7)	Ni1–N9	2.059(4)
Ni2–N6	2.081(7)		
Ni1–N12	2.053(7)		
Ni1–O1	2.093(5)		
Ni2–O2	2.090(6)		
Ni1–Cl1	2.420(3)		
Ni2–Cl2	2.123(7)		

Table 3.3. Selected bond angles (°) in **4** and **5.**

4		**5**	
N1–Ni1–N2	78.3(2)	N1–Ni1–N2	78.00(12)
N1–Ni1–N10	173.1(3)	N1–Ni1–N4	170.90(13)
N1–Ni1–N12	95.8(3)	N1–Ni1–N6	94.17(13)
N1–Ni1–O1	90.6(2)	N1–Ni1–N7	93.63(13)
N1–Ni1–Cl1	89.8(2)	N4–Ni1–N9	90.02(14)
N2–Ni1–N10	98.7(2)	N2–Ni1–N9	171.99(14)
N2–Ni1–N12	91.6(3)	N6–Ni1–N9	97.90(12)
N2–Ni1–O1	92.1(2)	N2–Ni1–O1	91.55(14)
N2–Ni1–Cl1	92.1(2)	N4–Ni1–N6	77.70(12)
N10–Ni1–N12	78.0(2)	N2–Ni1–N6	91.34(12)
N10–Ni1–O1	92.1(2)	N7–Ni1–N9	93.91(14)
N10–Ni1–Cl1	96.47(19)	N4–Ni1–N7	94.04(13)
N12–Ni1–O1	87.1(3)	N12–Ni1–N7	84.35(13)
N12–Ni1–Cl1	173.78(19)	N6–Ni1–N7	170.11(12)
O1–Ni2–Cl1	90.3(2)		
N4–Ni2–N6	78.5(3)		
N4–Ni2–N7	174.1(3)		
N4–Ni2–N8	98.3(3)		
N4–Ni2–O2	91.9(3)		
N4–Ni2–Cl2	93.3(3)		
N6–Ni2–N7	96.3(3)		
N6–Ni2–N8	92.6(2)		
N6–Ni2–O2	88.3(3)		
N6–Ni2–Cl2	171.5(3)		
N7–Ni2–N8	79.0(3)		
N7–Ni2–O2	90.7(3)		
N7–Ni2–Cl2	91.9(3)		
N8–Ni2–O2	169.8(3)		
N8–Ni2–Cl2	91.1(3)		
O2–Ni2–Cl2	89.5(3)		

Complex **5** crystallized in *I*2/*c* space group and the asymmetric unit contains half molecule each of the complex and lattice azide ions as well as 2·5 molecules of H_2O

with the overall composition being [Ni_2(**L4**)$_2$(N_3)$_3$](N_3)·5H_2O. Both molecules of **L4** coordinate in bis(bidentate) fashion to two nickel centers and thus forming a dinickel entity. Each nickel center is chelated by N_PN_I from one molecule of **L4** and by N_MN_Y from another molecule of **L4** {N_I = imidazo nitrogen; N_M = imidamide nitrogen; N_P = pyridyl nitrogen; N_Y = picolinimidamide nitrogen}. Other two coordination sites are occupied by one monodentate azide (N_A) and one azide bound in μ-1,3(end-to-end) bridging fashion (N_B). A perspective view of [Ni_2(**L4**)$_2$(N_3)$_3$] unit is shown in Figure 3.3. Each nickel center has a distorted octahedral geometry coordinated by five different types of donor atoms with a *cis-cis-cis*-(N_PN_I)(N_MN_Y)(N_BN_A) orientation. Also it can be mentioned that one face of the octahedron is occupied by $N_PN_IN_Y$ and the opposite face by $N_MN_BN_A$ group of atoms, as a consequence N_P, N_I and N_Y are respectively *trans* to N_M, N_B and N_A. The Ni–N bond lengths lie in a larger range of 2.059(4) to 2.190(4) Å while compared with the range found in **4**. The non-bonded Ni···Ni distance is 4.523(1) Å is marginally longer than that observed in **4** with a difference of 0.008(1) Å, implying effect of the constraint imposed by **L4**. The 3-(pyridine-2-yl)imidazo[1,5-a]pyridine and 1-picolinimidamide moieties of the coordinated ligand is twisted along C12–N4 bond with the torsional angle at N2–C12–N4–C13 being 105.0(4)°.

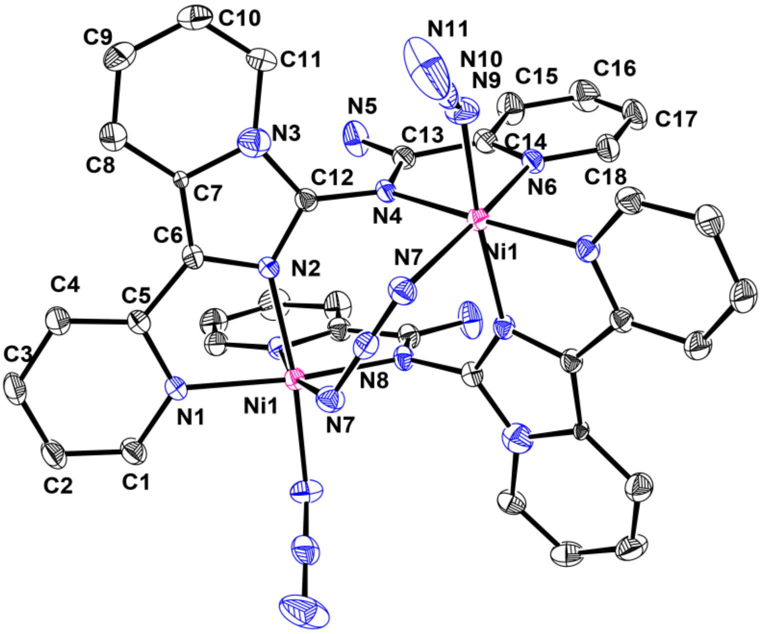


Figure 3.3. ORTEP (30% probability ellipsoids) of [Ni_2(**L4**)$_2$(N_3)$_3$] ion in **5**, hydrogen atoms omitted for clarity.

The crystal lattice consists of hydrogen bonding interaction among the terminal azide nitrogen atom that is coordinated in mono-dentate fashion to a lattice water molecule having a non-bonded distance of O1···N11, 2.830(8) Å. The azide that is bound in *μ*-1,3(end-to-end) bridging fashion remains free from weak intermolecular interactions. The amidine NH_2 group acts as hydrogen bond donor to azide ion as well as to a water molecule, both present in lattice with non-bonded contacts N5···N12, 2.981(5); N5···N13, 3.046(5) and N5···O2, 2.994(6) Å. Other significant hydrogen bonding interactions exhibited by lattice water molecules are: O1···O1, 2.823(9); O1···O2, 2.841(7); O2···O3, 2.755(7) and O2···N12, 2.799(6) Å. These three water molecules *viz.*, O1, O2 and O3 form a channel and a packing diagram viewing down the *c* – axis is shown in Figure 3.4.

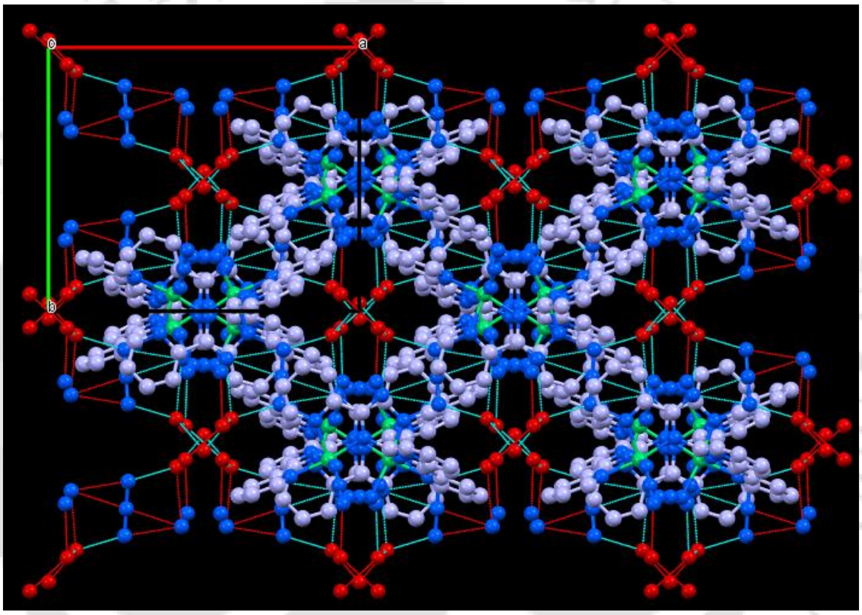


Figure 3.4. Packing diagram of **5** viewing down the *c* – axis.

3.4. Spectra and Magnetism

In complexes **4** and **5** absorption bands due to *d–d* and intra-ligand charge transfer transition, respectively were observed in the visible and UV regions (Figure 3.5). Two spin-allowed *d-d* bands for each of the two complexes were observed in the visible region and the other may be obscured by the allowed intra-ligand transitions. In **4** the *d-d* band observed around 942 nm that tail into near-IR region is due to $^3A_{2g} \rightarrow {}^3T_{2g}$ and the same is observed around 905 nm, in **5**. Difference in the absorption maximum is consistent with the strong field nature of azide ion compared to water and chloride ion. In both **4** and **5**, the *d-d* transition $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ has been observed respectively at 540 and 545 nm.

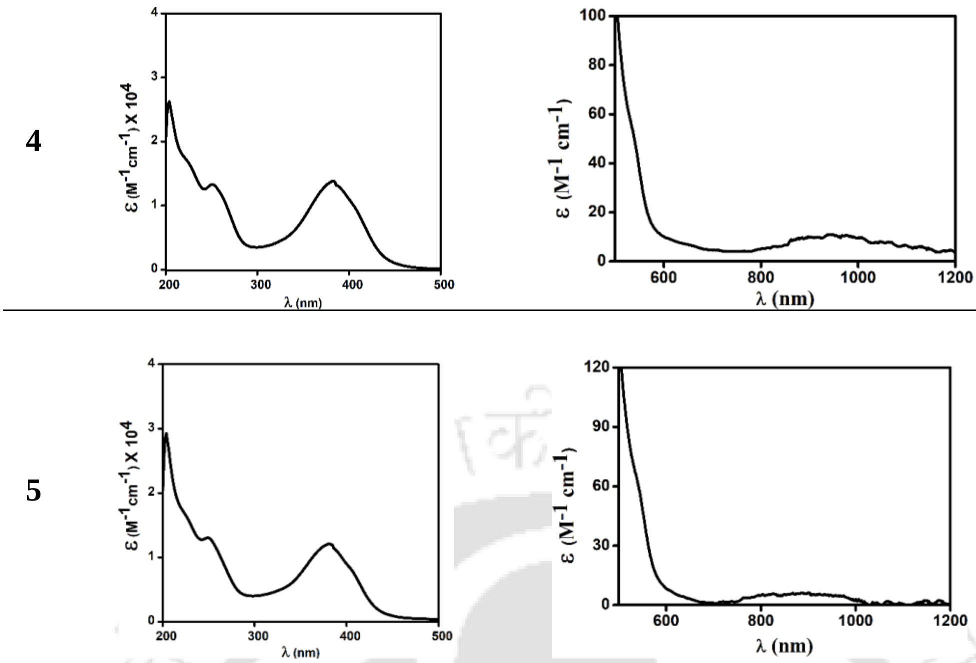
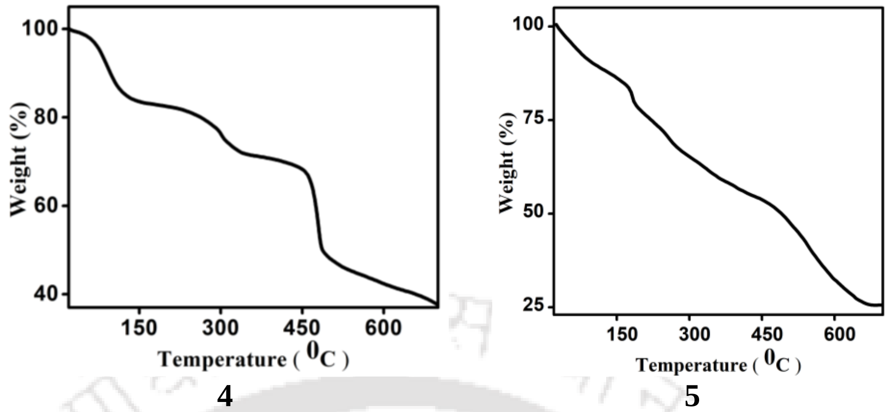


Figure 3.5. Electronic spectra of **4** and **5**.

The calculated μ_{eff} values of **4** and **5** were respectively 3.23 and 3.54 BM per nickel. The μ_{eff} values are largely greater than that of the calculated spin-only values in both the complexes and may be due to spin-orbit coupling and/or ferromagnetic interaction between the two metals. The complexes **4** and **5** did not show any EPR signals in frozen solution (1:3 methanol-acetonitrile) at 77K. In ^{1}H NMR spectra, the complex **5** exhibited paramagnetism induced broad signals (in the δ range 12.5 – 17.5) for protons that lie closer to the metal centres of the bound ligands without hyperfine coupling. Signals of rest of the protons that are farther from metal centers exhibited sharp signals in the aromatic region. This is consistent with the molecular structure of **5**. However, complex **4** did not show any signals in ^{1}H NMR, due to inherent shimming problem in this complex.

3.5. Thermogravimetric Analysis (TGA)

TG profile of **4** and **5** were recorded in the temperature range 25-700°C and were shown in Figure 3.6. The profile of **4** shows the loss of twelve water molecules occur in single step (found 18.49%, *ca*. 18.51%) in the temperature range of 40–130°C having a mid-point temperature of 91.4°C. In the case of **5**, the weight loss five water molecules occur in the range 40–95°C having a mid-point temperature at 72.5°C (found 8.54%, *ca*. 8.53%). In the second step weight loss corresponding to four azide ions (found 17.41, *ca*. 17.44%), occur in the temperature range 150–210°C with the midpoint temperature at 181.7°C.



4 **5**

Figure 3.6. The TGA profile of **4** and **5**.

3.6. Conclusions

In this chapter, two binuclear metal complexes of composition $[Ni_2(\mathbf{L4})_2(Cl)_2(H_2O)_2]Cl_2 \cdot 12H_2O$ (**4**), and $[Ni_2(\mathbf{L4})_2(N_3)_3](N_3) \cdot 5H_2O$,(**5**) have been synthesized and characterized with the nitrogen based chelating ligand (**L4**), along with coligands such as Cl^- and N_3^-. The ligand **L4** acts as a bridging bis(bidentate) ligand the nickel center has pseudo-octahedral coordination geometry in both the complexes. Each nickel center has a distorted octahedral geometry coordinated by different types of donor atoms with a *cis*-*cis*-*cis*-$(N_PN_I)(N_MN_Y)(O_WCl)$ orientation in **4** and *cis*-*cis*-*cis*-$(N_PN_I)(N_MN_Y)(N_BN_A)$ orientation in **5**. The 3-(pyridine-2-yl)imidazo[1,5-*a*]pyridine and 1-picolinimidamide moieties of coordinated ligands are twisted along C7–N4 and C30–N10 bonds in **4** and along C12–N4 bond in **5**.

3.7. Synthesis and Spectral Data

$[Ni_2(\mathbf{L4})_2(Cl)_2(H_2O)_2]Cl_2 \cdot 12H_2O$ (**4**)

To **L4** (100 mg, 0.32 mmol) dissolved in methanol (10 mL) solid $NiCl_2 \cdot 6H_2O$ (76 mg, 0.32 mmol) was added and stirred for 6 h. The reaction mixture was filtered and red colored filtrate was left undisturbed at room temperature. The red blocks of crystals of **4** suitable for XRD studies, deposited were red colored collected after 7 days and washed with ice-cold methanol. Yield: 146 mg, (88%). Anal. Calcd. for $C_{36}H_{56}Cl_4N_{12}Ni_2O_{14}$: C, 37.93; H, 4.95; N, 14.74. Found: C, 37.87; H, 4.90; N, 14.65%. FTIR (KBr, cm^{-1}): 3368(b), 1649(s), 1601(s), 1584(s), 1568(s), 1535(w), 1521(w), 1488(s), 1468(w), 1446(m), 1418(w), 1351(w), 1313(w), 1271(w), 1250(m), 1193(w), 1170(w), 1153(w), 1106(w), 1073(w), 1015(w), 973(w), 872(w), 801(w), 770(w), 747(m), 689(m), 642(w), 628(w), 588(w), 423(w). UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$) MeOH solution]: 942(11); 540(52); 384(13820); 252(13370).

$[Ni_2(\mathbf{L4})_2(N_3)_3](N_3)\cdot5H_2O$ (**5**)

To **L4** (100 mg, 0.32 mmol) dissolved in methanol (10 mL) solid $NiCl_2\cdot6H_2O$ (76 mg, 0.32 mmol) and sodium azide (42 mg, 65 mmol) were added and stirred for 6 h. The reaction mixture was filtered and red colored filtrate was left undisturbed at room temperature. The red blocks of crystals of **5** suitable for XRD studies, deposited were red colored collected after 7 days and washed with ice-cold methanol. Yield: 127 mg, (79%). Anal. Calcd. for $C_{36}H_{38}N_{24}Ni_2O_5$: C, 43.06; H, 3.81; N, 33.47. Found: C, 43.00; H, 3.76; N, 33.41%.500 MHz ^{1}H NMR (δ, DMSO): 16.94, 15.43, 13.67, 9.87, 9.04, 8.76 – 8.47, 8.39 – 8.08, 7.93, 7.52, 7.33, 7.17, 6.98, 6.55 (assignment of protons could not be done). FTIR (KBr, cm^{-1}): 3356(b), 3173(w), 2063(s), 2036(s), 2025(s), 1665(m), 1632(m), 1599(m), 1587(m), 1571(m), 1534(w), 1519(w), 1489(s), 1460(w), 1447(m), 1419(w), 1353(w), 1305(w), 1269(w), 1250(w), 1192(w), 1165(w), 1148(w), 1109(w), 1077(w), 1059(w), 1015(w), 971(w), 877(w), 803(w), 776(w), 772(w), 748(w), 733(w), 693(w), 642(w), 458(w), 424(w). UV–Vis [λ_{max}, nm (ε, $M^{-1}cm^{-1}$) MeOH solution]: 664(10); 542(14); 488(30); 382(12180); 252 (13240).

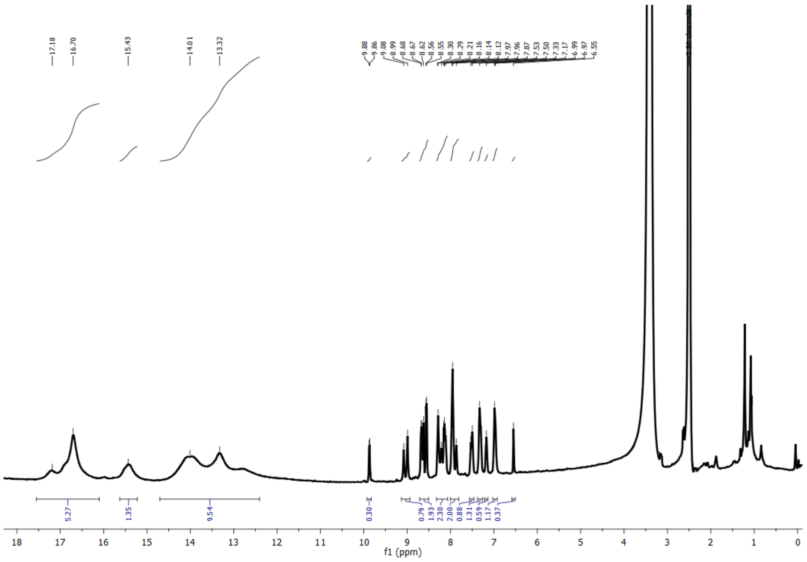


Figure 3.7. ^{1}H NMR spectrum of **5**.

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Chapter 4

Synthesis of Imidazo[5, 1-*a*]isoquinoline and Its 3-Substituted Analogues Including the Fluorescent 3-(1-Isoquinolinyl)imidazo[5,1-*a*]isoquinoline

Abstract: Compounds having imidazo[5,1-*a*]isoquinoline nucleus have been synthesised. Selenium dioxide oxidation of a mixture of various aldehydes and 1-isoquinolinemethylamine produced respective 3-substituted imidazo[5,1-*a*]isoquinolines in good yields. When 1-isoquinolinemethylamine was employed without any aldehyde, 3-(1-isoquinolinyl)imidazo[5,1-*a*]isoquinoline (**IQ-1**) was isolated. This **IQ-1** is fluorescent and all the compounds were thoroughly characterized. Molecular structures of **IQ-1** and 3-(2-hydroxyphenyl)imidazo[5,1-*a*]isoquinoline (**IQ-4**) have been confirmed by single crystal X-ray diffraction technique.

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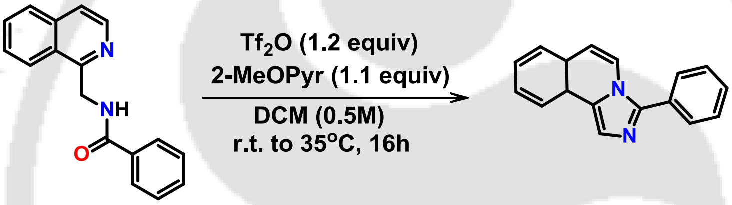
* This work has been published in:

J. Bori, N. Behera S. Mahata and V. Manivannan, *ChemistrySelect* 2017, **35**, 11727-11731.

4.1. Introduction

Imidazo[1,5-*a*]pyridine is a class of bicyclic 5:6 heterocyclic system with one bridgehead nitrogen atom and having imidazole fused to a benzene ring [1]. The synthesis of imidazo[1,5-*a*]pyridine nucleus with varying substituents at pyridine [2,3], including thromboxane A_2 synthetase inhibitors [4], positive ionotropic agents [5], as well as at 3-position of imidazole rings have been reported [6-11], Syntheses of its quinoline analogue imidazo[1,5-*a*]quinoline, have been reported and some of them are having medicinal applications [12-18].

However its isoquinoline analogue, imidazo[5,1-*a*]isoquinoline has been mostly unnoticed so far. Synthesis of 3-phenylimidazo[5,1-*a*]isoquinoline has been described as a part of the general method of preparing imidazo[1,5-*a*]azines [19].



It is also relevant to note that cribrostatin 6 (Figure 4.1) isolated from the species *Cribrochalina sp.* having a tricyclic imidazo[5,1-*a*]isoquinolinedione moiety, has been found to exhibit anti-cancer properties [20] and its total synthesis has been described [21-23].

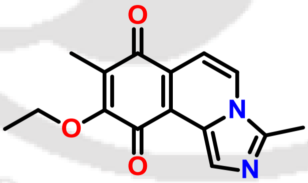
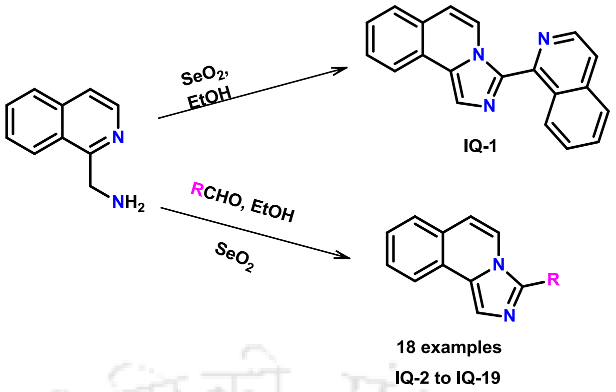


Figure 4.1. Cribrostatin **6**.

This Chapter describes a facile synthesis of a series of 3-substituted imidazo[5,1-*a*]isoquinolines. This is achieved by selenium dioxide oxidation of a mixture of 1-isoquinolinemethylamine and various aldehydes (Scheme 4.1). One of the isolated products, 3-(1-isoquinolinyl)imidazo[5,1-a]isoquinoline (**IQ-1**), exhibits fluorescence in most of the common solvents.

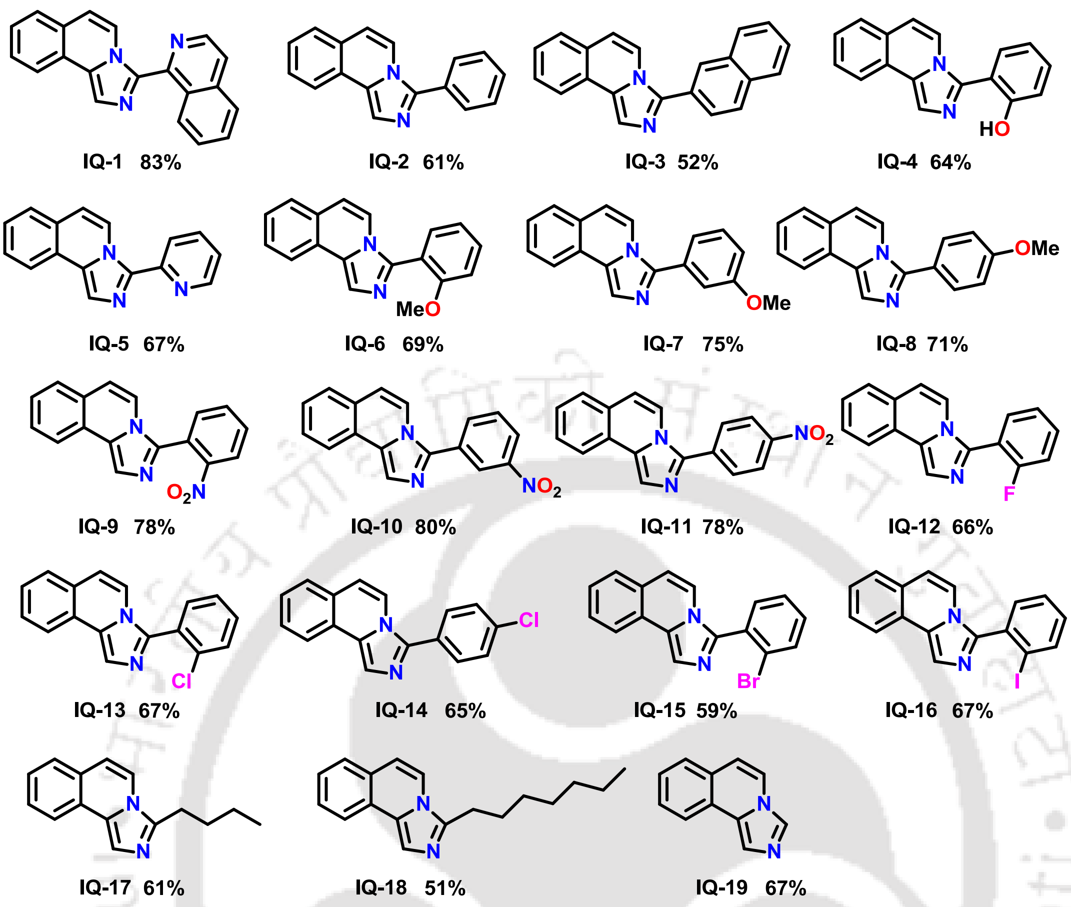


Scheme 4.1. Synthesis of imidazo[5,1-*a*]isoquinolines.

4.2. Results and Discussion

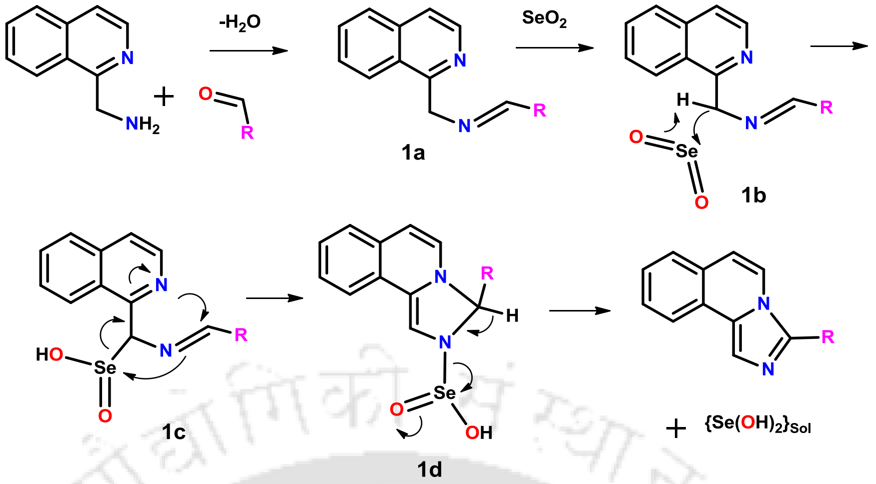
Stirring the 1:1 mixture of 1-isoquinolinylmethanamine [24,25] and selenium dioxide in ethanol at room temperature afforded a red colored solution. From the solution, **IQ-1** was isolated as yellow solid after the work up and column chromatographic purification. Presumably during course of the reaction, 1-isoquinolinylcarboxaldehyde was generated by selenium dioxide which in presence of 1-isoquinolinylmethanamine condensed to yield *N*-(1-isoquinolinylmethylene)-1-(2-quinolinyl)methanamine. Oxidation of this Schiff's base by selenium dioxide could yield the isolated product **IQ-1**.

This prompted us to examine the nature of the reaction of a mixture of various aldehydes and 1-isoquinolinylmethanamine with selenium dioxide. Indeed this reaction proceeded in the anticipated direction and a series of 3-substituted imidazo[5,1-*a*]isoquinolines were isolated in good yields. In all these reactions, **IQ-1** (10-20%) was also formed as a minor product and all 3-substituted imidazo[5,1-*a*]isoquinolines were isolated in their pure form after column chromatography and were thoroughly characterized. This reaction has wider applicability as is evident from Scheme 4.2. The reaction proceeded smoothly, best yield was obtained for **IQ-1** itself and its formation in small quantities along with other entries are consistent. Different kinds of aldehydes such as formaldehyde, aliphatic, aromatic, heterocyclic as well as aromatic ring carrying electron withdrawing and donating groups at *ortho*, *meta* and *para* positions have been used and yielded the respective products in moderate to good yields.



Scheme 4.2. Scope of synthesis of imidazo[5,1-*a*]isoquinolines.

A plausible mechanism has been proposed in Scheme 4.3. The aldehyde and 1-isoquinolinylmethanamine condense to form the Schiff base **1a**. The active methylene proton in **1a** being abstracted by SeO_2 and remain linked to the same carbon [26] as shown in **1b** to form the **1c**, which is a alkylseleninic acid [27-29]. The nucleophilic attack by the nitrogen lone pair of isoquinoline ring on the imine bond and subsequent migration of electrons of this bond on to selenium accompanied by breaking the Se–C bond could lead to the intermediate **1d** [30]. Dissociation of the proton at the tetrahedral carbon, migration of the resultant electron pair on to the C–N bond, transfer of the N–Se bond pair to selenium resulting in its reduction to its bivalent state accompanied by dissociation of $Se(OH)_2$ could lead to the product.



Scheme 4.3. Plausible mechanism of the reaction.

All the compounds have been thoroughly characterized using elemental analysis, ^{1}H and ^{13}C NMR spectroscopy and ESI-Mass spectrometric techniques. All these data are unequivocally consistent with the respective structures. In general, presence of singlet in the δ range 7.7–8.3, corresponding to the proton of imidazole ring and a doublet around 6.9–7.1 to the proton of the fused isoquinoline ring in ^{1}H NMR, indicate the presence of imidazo[5,1-*a*]isoquinoline nucleus. The molecular ion $[M^{+}+H]$ peak of **IQ-1** and **IQ-4** were observed at *m*/*z* values of 296.088 and 261.063, respectively.

4.3. Molecular Structures

The molecular structure of both **IQ-1** and **IQ-4** were confirmed by single crystal X-ray diffraction method and the relevant crystallographic data are listed in Table 4.1.

Table 4.1. Crystallographic Data for **IQ-1** and **IQ-4**.

	IQ-1	**IQ-4**
Formula	$C_{20}H_{13}N_3$	$C_{17}H_{12}N_2O$
CCDC No.	1578482	1578481
Formula weight	295.33	260.29
T, K	293(2)	293(2)
Cryst syst	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1/n$
a, Å	3.8459(3)	13.5682(13)
b, Å	13.4462(10)	6.4556(4)
c, Å	27.427(2)	15.6396(13)
α, deg	90.00	90.00
β, deg	90.00	112.372(10)
γ, deg	90.00	90.00
V, Å^3	1418.36(19)	1266.76(18)
Z	4	4
Dcalcd, gcm^{-3}	1.383	1.365
μ, mm^{-1}	0.084	0.087
GOF^a on F^2	1.000	1.003
R[I > 2σ(I)]	$^bR_1 = 0.0852$; $^cwR_2 = 0.1769$	$^bR_1 = 0.0782$; $^cwR_2 = 0.1542$
Rindices (all data)	$^bR_1 = 0.1278$; $^cwR_2 = 0.2001$	$^bR_1 = 0.1251$; $^cwR_2 = 0.2075$

^{a} GOF = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M =number of reflections, N = number of parameters refined). $^b R_1 = \sum \| F_0 | - | Fc \| / \sum | F_0 |$. $^c wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{1/2}$.

Compound **IQ-1** crystallized in $P2_1P2_1P2_1$ space group while **IQ-4** in $P2_1/n$. A schematic view of both has been shown in Figure 4.2 and 4.3. In **IQ-1**, the angle formed between the two rings containing the atoms C12N3C13C14C15C20 and C2N1C1C11N2 is 45.8°. The packing diagram is dominated by $\pi \cdots \pi$ interactions between imidazo[5,1-*a*]isoquinoline rings (with a distance of 3.55Å between two N1C2N2C11C1 rings) and isoquinoline rings (with a distance of 3.53Å between two N1C2N2C11C1 rings). The significant non-bonding interaction present in **IQ-4** is hydrogen bonding interaction between phenolic group and the imidazole nitrogen having the non-bonded contact of O1···N1, 2.618(6)Å.

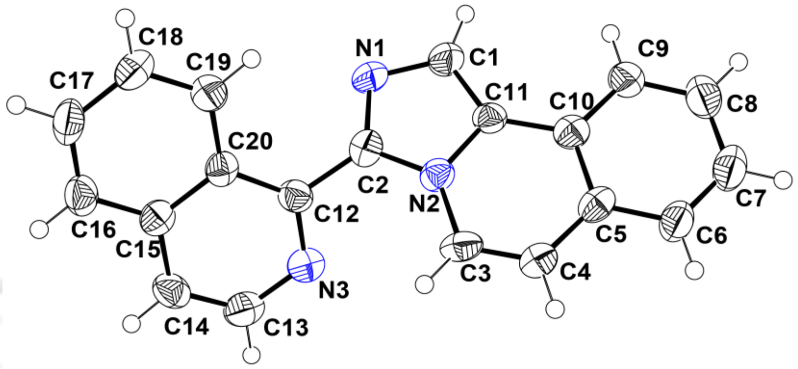


Figure 4.2. ORTEP (50% probability ellipsoids) diagram of **IQ-1**.

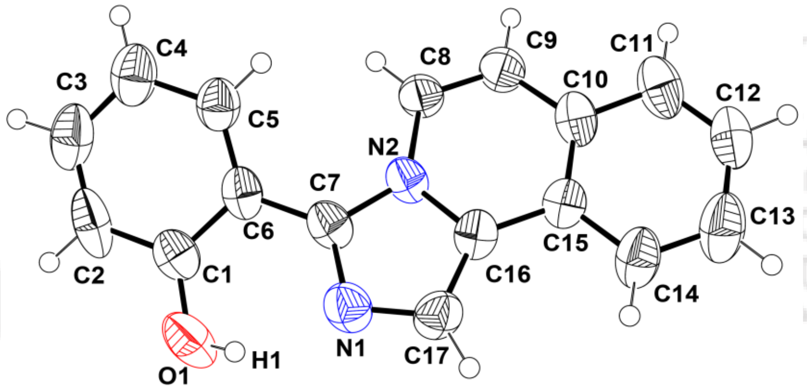


Figure 4.3. ORTEP (50% probability ellipsoids) diagram of **IQ-4**.

4.4. Powder X-ray Diffraction

Powder X-ray diffraction pattern of **IQ-1** was collected in order to ascertain the nature of the bulk sample. The experimentally observed powder pattern matched (Figure 4.4) with that of calculated from the single crystal X-ray data, proving uniformity of bulk sample with that of the single crystal.

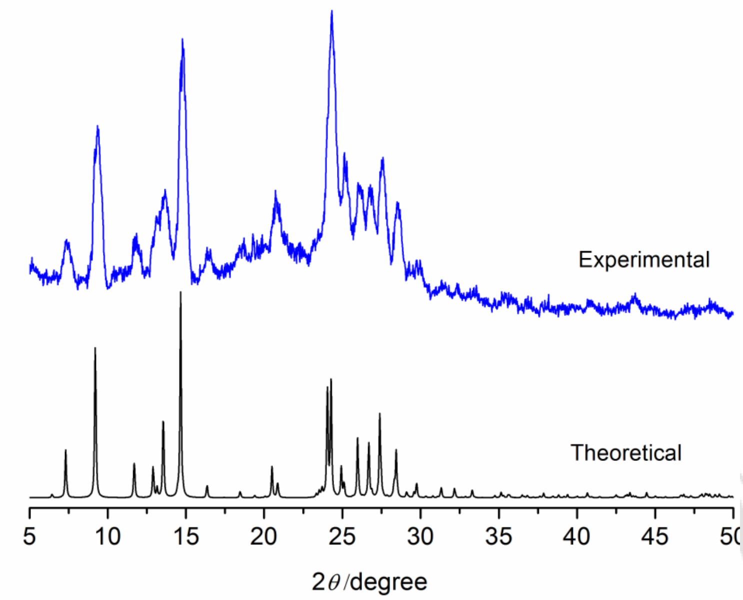
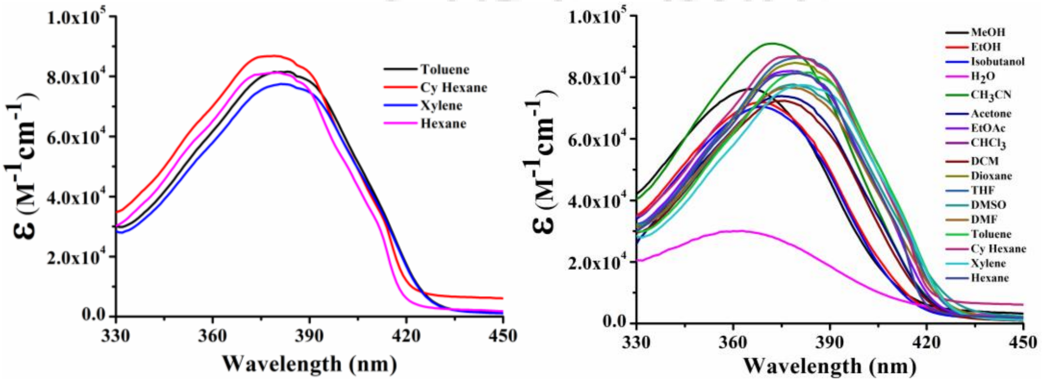


Figure 4.4. Powder X-ray diffraction patterns of **IQ-1**.

4.5. UV-Vis and Emission spectra

UV-Vis spectra of **IQ-1** have been recorded in various solvents such as MeOH, ethanol, isobutanol, CH_3CN, acetone, ethylacetate, chloroform, dichloromethane, dioxane, THF, DMSO, DMF, H_2O, cyclohexane, toluene, hexane and xylene. In polar and non polar solvents absorbance maximum lies in range 365-383 nm (Figure 4.5). While going from polar protic → polar → aprotic nonpolar solvents, absorbance maximum got shifted from 363 → 372 → 383 nm. In the higher energy region, a peak ~260nm having a shoulder at ~250 nm was observed in MeOH, EtOH, isobutanol, CH_3CN, THF, cyclohexane, hexane and H_2O.



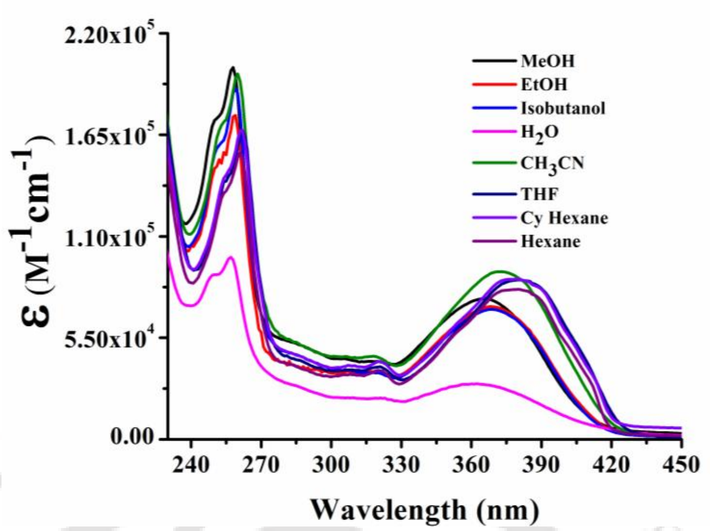


Figure 4.5. UV-Visible spectra of **IQ-1**.

Upon excitation at 365 nm, **IQ-1** showed emission maximum in the range 425-470 nm in polar and non-polar solvents (Figure 4.6). In ethyl acetate, chloroform, dioxane, tetrahydrofuran, cyclohexane, hexane, xylene and toluene, the emission peak appearing at ~407-430 nm, was accompanied by two other peaks. Whereas, only single emission peak ~445-470nm was observed in rest of solvents. Among all the solvents employed, **IQ-1** shows very weak emission at 470 nm in H_2O.

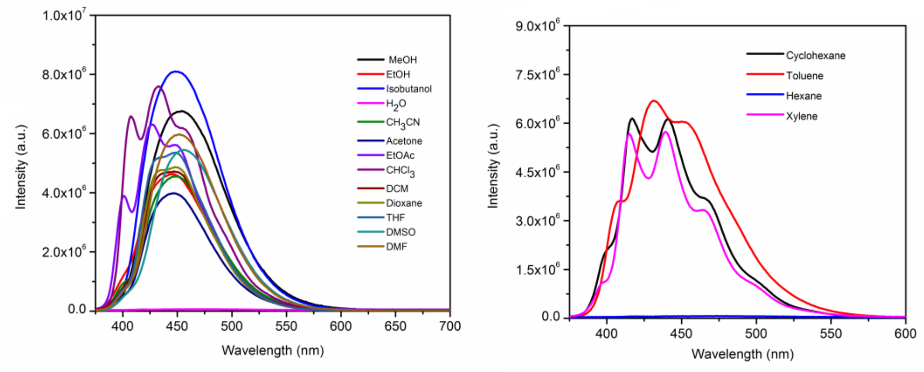


Figure 4.6. Fluorescence spectra of **IQ-1** in polar and non polar solvents.

4.6. Computational Method

In order to understand the origin of optical spectra, DFT/TDDFT calculations were performed on **IQ-1** molecule. The LUMO has more contribution from the 1-isoquinolinyl ring and HOMO has more contribution from the imidazo[5,1-*a*]isoquinoline nucleus (Figure 4.7). The energy gap between LUMO and HOMO is

~3.78 eV, which is in agreement with observed absorption spectrum. The lower wavelength absorption might arise out of HOMO-1 to LUMO transition.

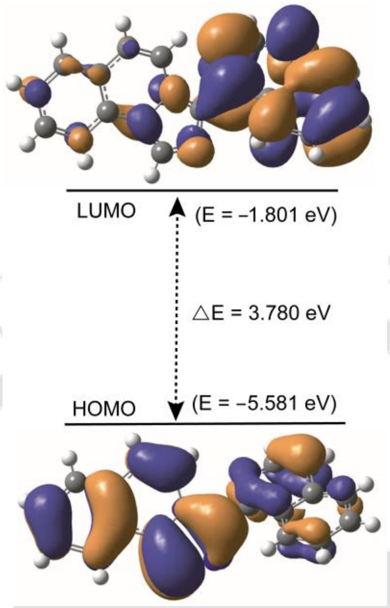


Figure 4.7. Energy level diagram, HOMO and LUMO of **IQ-1**.

4.7. Conclusions

In this chapter, a method for the construction of imidazo[5,1-*a*]isoquinoline nucleus from 1-isoquinolinemethylamine and various aldehydes have been described. Using this procedure a series 3-substituted imidazo[5,1-*a*]isoquinolines were synthesized. Compound 3-(1-Isoquinolinyl)imidazo[5,1-*a*]isoquinoline is fluorescent in nature. This method is applicable to wide variety of substrates and we believe that imidazo[5,1-*a*]isoquinoline moiety can easily be incorporated in substrates having a aldehyde group provided other functionalities are stable towards selenium dioxide. These compounds with suitably substituted groups could find their utility in various fields.

4.8. Synthesis and Spectral Data

3-(1-Isoquinolinyl)imidazo[5,1-*a*]isoquinoline (IQ-1)

A mixture of 1-isoquinolinylmethanamine (0.150 g, 0.949 mmol) and selenium dioxide (0.105 g, 0.946 mmol) in ethanol (6 mL) was stirred at room temperature. After 3 h, the reaction mixture was quenched by shaking with 20 ml of saturated aqueous sodium thiosulfate solution and left to stand for 20 min. The solution was filtered, washed three times with ethanol, filtrate and washings were combined. The ethanol was removed using rotary evaporator, extracted with ethyl acetate and again evaporated to dryness. The crude product was subjected to column chromatography over silica gel, eluted with 5% ethyl acetate in hexane and from the eluent a light yellow solid was obtained. Yield: 0.232g (83%). mp: 116 °C. ESI-MS: *m/z* calcd for $C_{20}H_{13}N_3$ 295.111 found $(M^+ + H)$ 296.088. Elemental analysis (%) calcd for $C_{20}H_{13}N_3$: C 81.34, H 4.44, N 14.23; found: C 81.27, H 4.40, N 14.17. 600 MHz ^1H NMR (δ (*J*, Hz), DMSO-d_6): 9.30(1H, d, 8.4), 9.13(1H, d, 7.8), 8.68(1H, d, 5.4), 8.36(1H, d, 7.8), 8.33(1H, s), 8.07(1H, d, 8.4), 7.96(1H, d, 5.4), 7.85–7.81(2H, m), 7.76(1H, t, 7.5), 7.65(1H, t, 7.5), 7.57(1H, t, 7.5), 7.17(1H, d, 7.8). 151 MHz ^{13}C NMR (δ, DMSO-d_6): 148.44, 141.34, 137.67, 136.94, 130.63, 129.70, 128.60, 128.22, 127.93, 127.81, 127.37, 127.22, 127.13, 126.39, 123.88, 123.58, 122.98, 121.56, 120.94, 113.88.

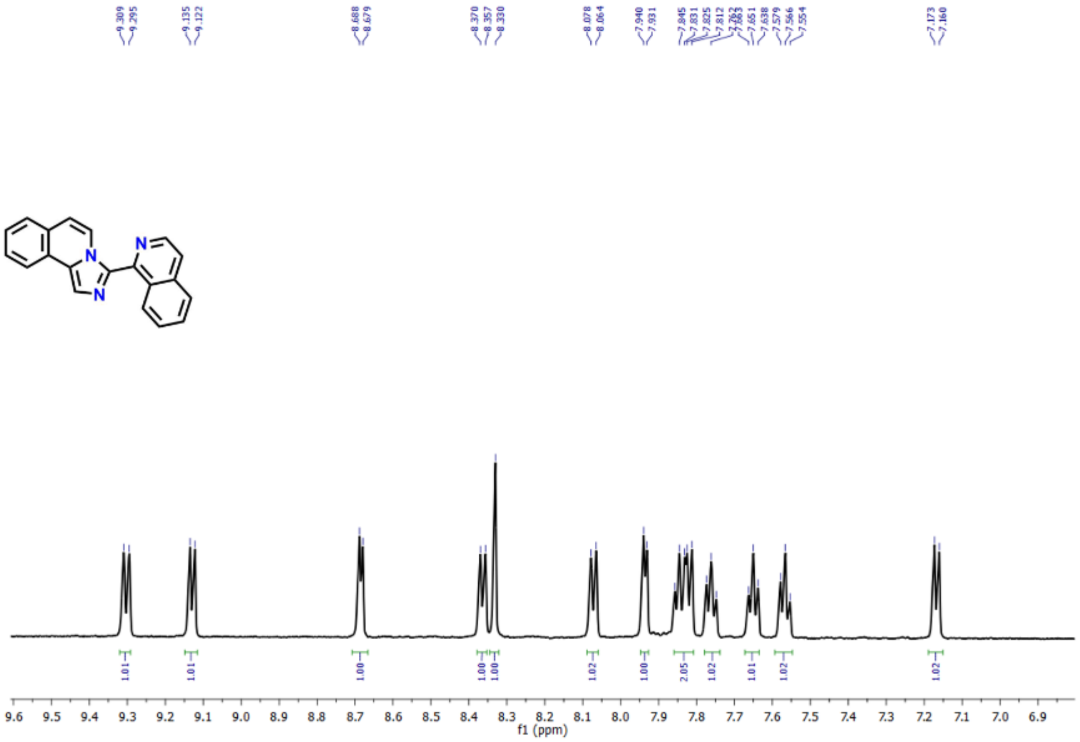


Figure 4.8. ^1H NMR spectrum of **IQ-1**

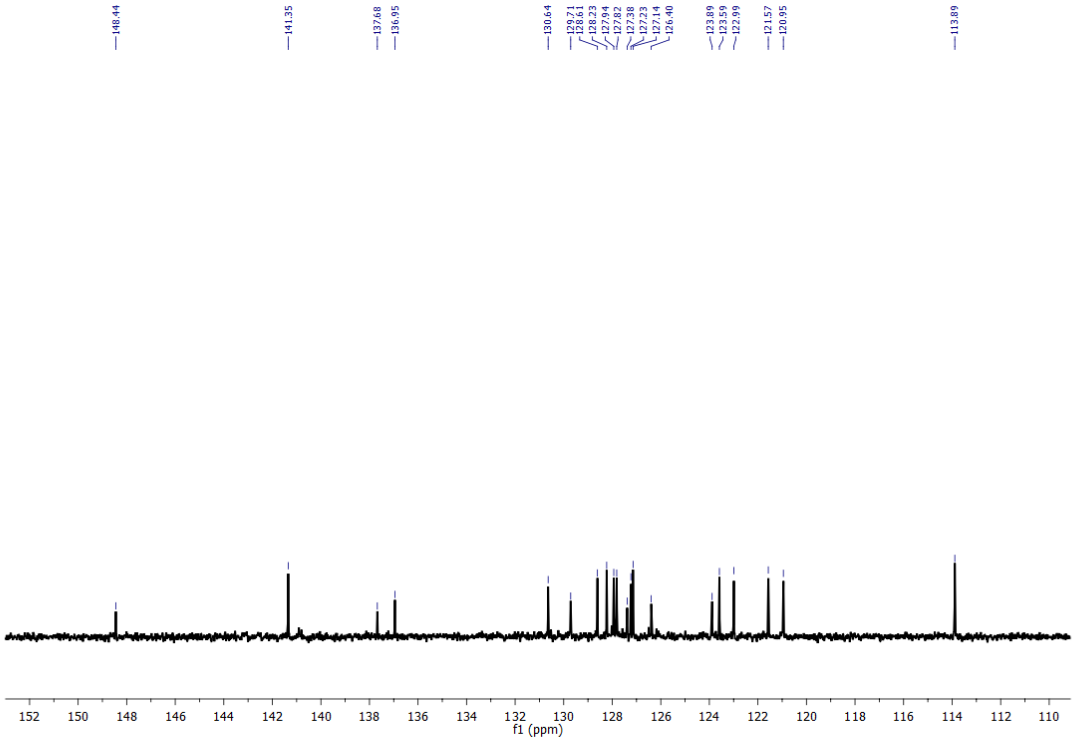


Figure 4.9. ^{13}C NMR spectrum of **IQ-1**

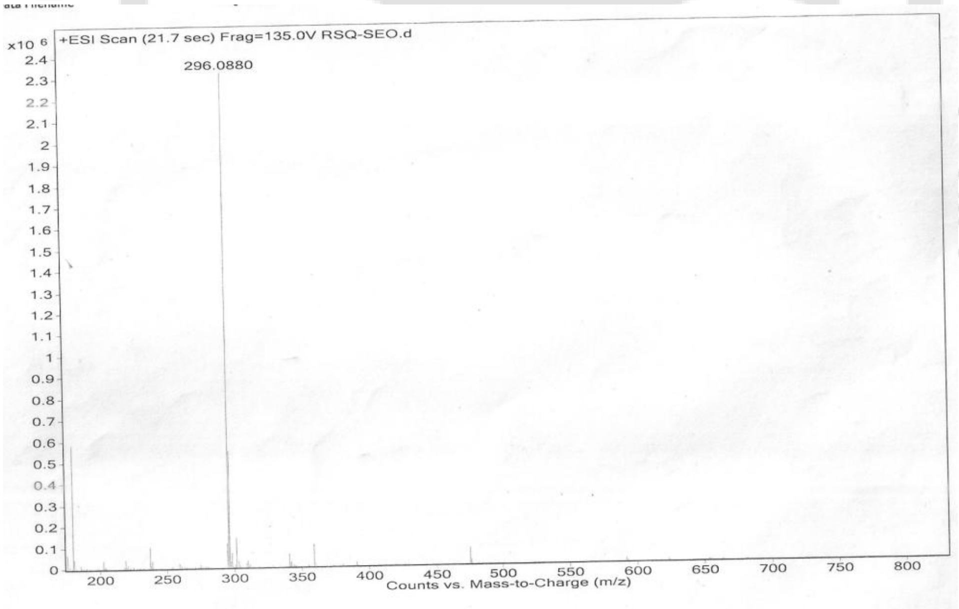


Figure 4.10. ESI Mass spectrum of **IQ-1**

3-Phenylimidazo[5,1-*a*]isoquinoline (**IQ-2**)

A mixture of 1-isoquinolinylmethanamine (0.150 g, 0.949 mmol) and benzaldehyde (0.100 g, 0.949 mmol) was stirred in ethanol for 5 min and then solid selenium dioxide (0.105 g, 0.946 mmol) was added and stirred at room temperature. After stirring for 5 h, the reaction mixture was quenched by shaking with 20 ml of saturated aqueous sodium thiosulfate solution and left to stand for 20 min. Then the mixture was filtered and washed 3 to 4 times with ethyl acetate then solvent was removed from the combined filtrate and washings. The crude mixture was subjected to column chromatography over silica gel, eluted with 3% ethyl acetate in hexane and from the eluent a light yellow solid was obtained. In addition, a small amount of **IQ-1** was eluted with 5% ethyl acetate in hexane. Yield: 0.141g (61%). mp. 155°C. ESI-MS: *m/z* calcd for $C_{17}H_{12}N_2$ 244.100 found (M^++H) 245.112: Elemental analysis (%) calcd for $C_{17}H_{12}N_2$: C 83.58, H 4.95, N 11.47; found: C 83.50, H 4.92, N 11.44. 600 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.07(1H, d, 7.8), 8.02(1H, d, 7.8), 7.94(1H, s) 7.80(2H, d, 7.2), 7.59(1H, d, 7.8), 7.56–7.52(3H, m), 7.47(1H, t, 7.5), 7.43(1H, t, 7.2), 6.80(1H, d, 7.2). 151 MHz ^{13}C NMR (δ, DMSO-d_6): δ 148.47, 141.39, 136.97, 130.68, 129.74, 128.65, 128.27, 127.97, 127.86, 127.27, 127.18, 126.41, 123.62, 123.03, 121.62, 120.99, 113.92.

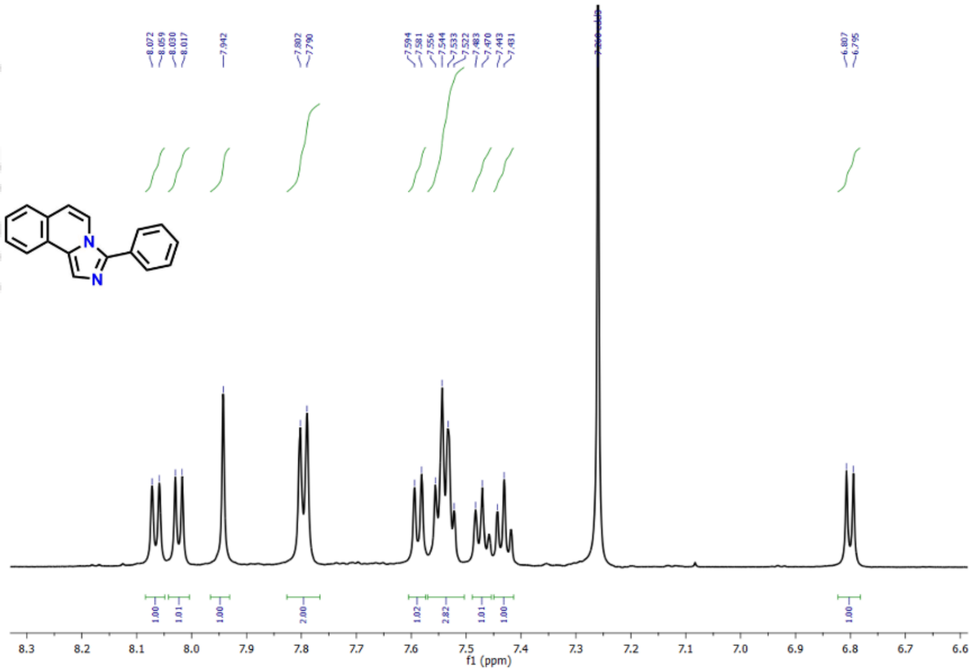


Figure 4.11. ^{1}H NMR spectrum of **IQ-2**

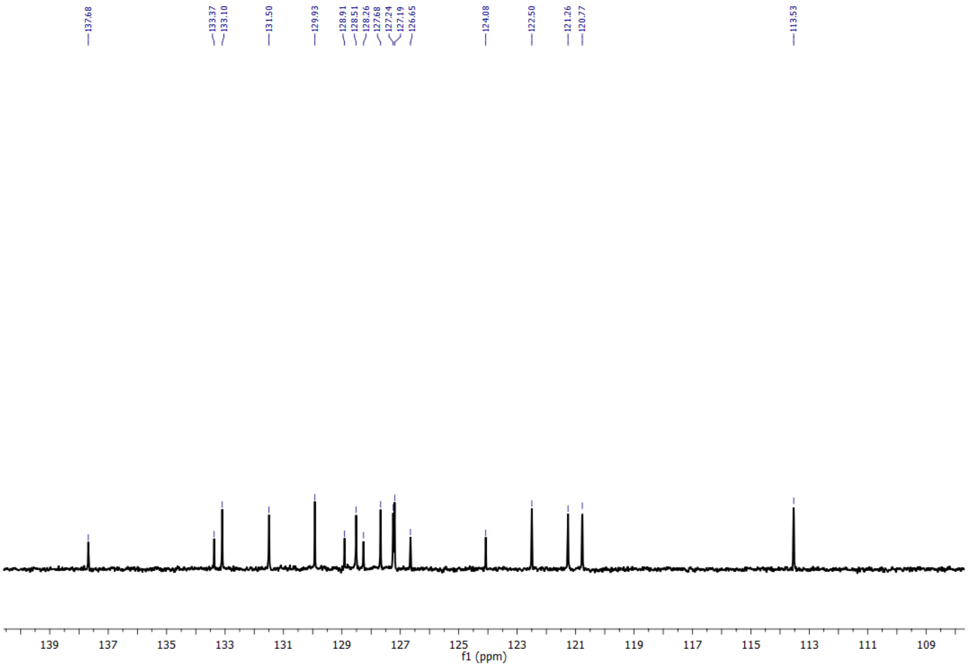


Figure 4.12. ^{13}C NMR spectrum of **IQ-2**

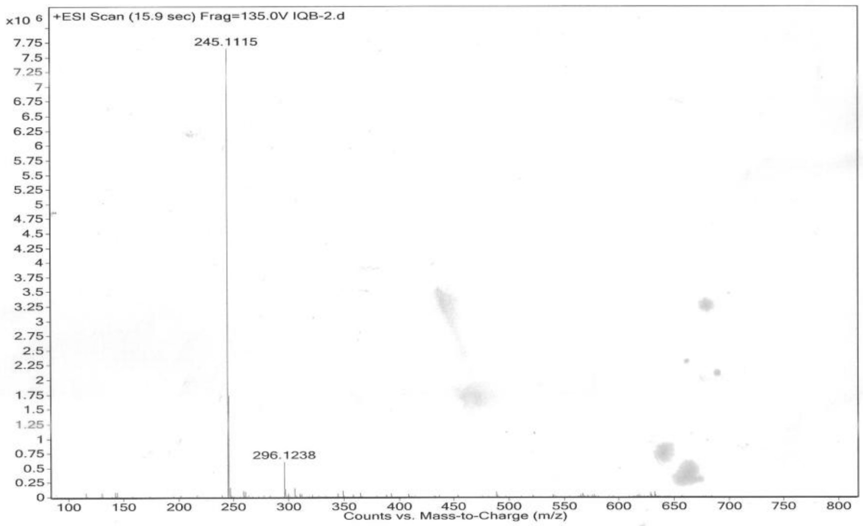


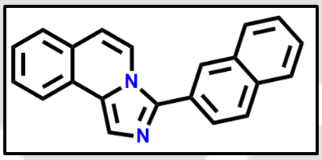
Figure 4.13. ESI Mass spectrum of **IQ-2**

All other compounds (**IQ-3** to **IQ-19**) were synthesized by adopting the same procedure described for **IQ-2** by using 0.95 mmol of respective aldehyde. 2-naphthaldehyde (**IQ-3**); salicylaldehyde (**IQ-4**); 2-pyridinecarboxaldehyde (**IQ-5**); 2-methoxybenzaldehyde (**IQ-6**); 3-methoxybenzaldehyde (**IQ-7**); 4-methoxybenzaldehyde (**IQ-8**); 2-nitrobenzaldehyde (**IQ-9**); 3-nitrobenzaldehyde (**IQ-10**); 4-nitrobenzaldehyde (**IQ-11**); 2-fluorobenzaldehyde (**IQ-12**); 2-chlorobenzaldehyde (**IQ-13**); 4-chlorobenzaldehyde (**IQ-14**); 2-bromobenzaldehyde

(**IQ-15**); 2-iodobenzaldehyde (**IQ-16**); 1-pentanal (**IQ-17**); 1-octanal (**IQ-18**) aq. formaldehyde (**IQ-19**). Compounds **IQ-3** to **IQ-11** were eluted with 7% ethyl acetate in hexane and **IQ-12** to **IQ-19** were with 3% ethyl acetate in hexane. In all cases, small amount of **IQ-1** formed was eluted with 5% ethyl acetate in hexane.

3-(2-Naphthalenyl)imidazo[5,1-*a*]isoquinoline (IQ-3)

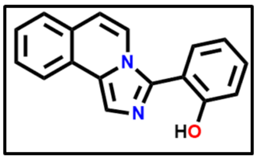
Yield: 0.145g (52%). ESI-MS: *m/z* calcd for $C_{21}H_{14}N_2$ 294.116 found (M^++H) 295.124. Elemental analysis (%) calcd for $C_{21}H_{14}N_2$: C 85.69, H 4.79, N 9.52; found: C 85.59, H 4.75, N 9.50. 500 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.26(1H, s), 8.13(1H, d, 7.5), 8.09(1H, d, 8.0), 8.01(2H, d,s, 8.5), 7.95–7.91(3H, m), 7.60(1H, d, 8.0), 7.55(3H, m), 7.45(1H, td, 7.7, 1.2), 6.84(1H, d, 7.5). 126 MHz ^{13}C NMR (δ, $CDCl_3$): 140.89, 133.20, 133.17, 129.44, 128.77, 128.45, 128.22, 127.76, 127.42, 127.21, 126.99, 126.94, 126.91, 126.75, 126.63, 125.80, 124.99, 122.45, 120.76, 120.62, 114.14.



IQ-3

3-(2-Hydroxyphenyl)imidazo[5,1-*a*]isoquinoline (IQ-4)

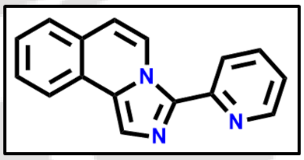
Yield: 0.158g (64%). mp. 148°C. ESI-MS: *m/z* calcd for $C_{17}H_{12}N_2O$ 260.095 found (M^++H) 261.063. Elemental analysis (%) calcd for $C_{17}H_{12}N_2O$: C 78.44, H 4.65, N 10.76; found: C 78.36, H 4.61, N 10.72. 600 MHz ^{1}H NMR (δ (*J*, Hz), DMSO-d_6): 10.44(OH, very broad), 8.17(1H, d, 7.8), 8.03(1H, s), 7.69(1H, d, 7.7), 7.65(1H, d, 7.8), 7.55(1H, t, 7.5), 7.48(2H, m), 7.36(1H, t, 7.2), 7.04(1H, d, 8.4), 7.00–6.96(2H, m). 126 MHz ^{13}C NMR (δ, DMSO-d_6): 155.46, 138.90, 131.00, 130.68, 128.34, 128.28, 127.10, 127.07, 126.64, 124.28, 122.56, 122.40, 120.34, 119.43, 116.54, 116.27, 112.76. Single crystals suitable for X-ray diffraction studies were grown by slow evaporation of methanol solution of **IQ-4**.



IQ-4

3-(2-Pyridyl)imidazo[5,1-*a*]isoquinoline (IQ-5)

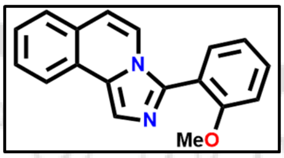
Yield: 0.156g (67%). mp. 162°C. ESI-MS: *m/z* calcd for $C_{16}H_{11}N_3$ 245.095 found (M^++H) 246.097. Elemental analysis (%) calcd for $C_{16}H_{11}N_3$: C 78.35, H 4.52, N 17.13; found: C 78.36, H 4.49, N 17.10. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 9.74(1H, d, 7.2), 8.67(1H, s), 8.37(1H, d, 8.0), 8.12(1H, d, 7.6), 7.99(1H, s), 7.81(1H, t, 7.8), 7.65(1H, d, 7.6), 7.55(1H, t, 7.2), 7.47(1H, t, 7.2), 7.28–7.23(1H, s){along with $CDCl_3$ peak}, 6.94(1H, d, 7.2). 151 MHz ^{13}C NMR (δ, $CDCl_3$): 151.18, 148.41, 138.28, 136.82, 130.84, 128.26, 127.62, 127.38, 127.03, 124.78, 124.67, 122.81, 122.54, 122.31, 121.24, 114.14.



IQ-5

3-(2-Methoxyphenyl)imidazo[5,1-*a*]isoquinoline (IQ-6)

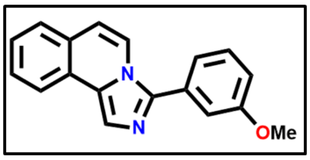
Yield: 0.182g (69%). ESI-MS: *m/z* calcd for $C_{18}H_{14}N_2O$ 274.111 found (M^++H) 275.120. Elemental analysis (%) calcd for $C_{18}H_{14}N_2O$: C 78.81, H 5.14, N 10.21; found: C 78.75, H 5.09, N 10.16. 600 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.08(1H, d, 8.4), 7.98(1H, s), 7.62(1H, d, 7.8), 7.59(1H, d, 7.8), 7.49–7.46(3H, m), 7.42(1H, t, 7.2), 7.13(1H, t, 7.5), 7.06(1H, d, 8.4), 6.75(1H, d, 7.2), 3.81(3H, s). 101 MHz ^{13}C NMR (δ, DMSO-d_6): 157.04, 138.39, 132.16, 131.20, 128.35, 128.34, 127.09, 127.07, 126.65, 124.27, 122.39, 122.33, 120.85, 120.69, 118.64, 112.69, 111.89, 55.51.



IQ-6

3-(3-Methoxyphenyl)imidazo[5,1-*a*]isoquinoline (IQ-7)

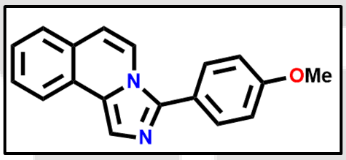
Yield: 0.192g (75%). ESI-MS: *m/z* calcd for $C_{18}H_{14}N_2O$ 274.111 found (M^++H) 275.120. Elemental analysis (%) calcd for $C_{18}H_{14}N_2O$: C 78.81, H 5.14, N 10.21; found: C 78.73, H 5.11, N 10.14. 500 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.04(2H, dd, 7.6, 3.25), 7.92(1H, s), 7.56(1H, d, 8.0), 7.53–7.50(1H, m), 7.44–7.39(2H, m), 7.34(2H, d, 7.5), 7.01–6.98(1H, m), 6.78(1H, d, 7.5), 3.89(3H, s). 126 MHz ^{13}C NMR (δ, $CDCl_3$): 160.27, 141.09, 131.51, 130.18, 129.68, 128.68, 127.24, 127.21, 127.18, 125.26, 122.71, 121.00, 120.86, 120.63, 115.38, 114.21, 113.85, 55.67.



IQ-7

3-(4-Methoxyphenyl)imidazo[5,1-*a*]isoquinoline (**IQ-8**)

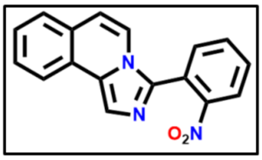
Yield: 0.186g (71%). mp. 155°C. ESI-MS: *m/z* calcd for $C_{18}H_{14}N_2O$ 274.111 found (M^++H) 275.120. Elemental analysis (%) calcd for $C_{18}H_{14}N_2O$: C 78.81, H 5.14, N 10.21; found: C 78.70, H 5.11, N 10.16. 500 MHz ^1H NMR (δ (*J*, Hz), $CDCl_3$):8.19(1H, d, 8.0), 8.14(1H, d, 7.5), 8.04(1H, s), 7.74(3H, t, 8.1), 7.57(1H, t, 7.5), 7.47(1H, t, 7.5), 7.13(2H, d, 9.0), 6.99(1H, d, 7.5), 3.85(3H, s). 126 MHz ^{13}C NMR (δ, DMSO-d_6): 159.65, 140.32, 129.63, 128.45, 127.05, 126.99, 126.60, 124.44, 122.33, 122.24, 121.22, 120.75, 114.42, 113.53, 55.30.



IQ-8

3-(2-Nitrophenyl)imidazo[5,1-*a*]isoquinoline (**IQ-9**)

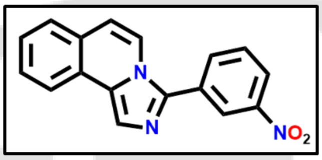
Yield: 0.215g (78%). mp. 200°C. ESI-MS: *m/z* calcd for $C_{17}H_{11}N_3O_2$ 289.085 found (M^+ +H) 290.097. Elemental analysis (%) calcd for $C_{17}H_{11}N_3O_2$: C 70.58, H 3.83, N 14.53; found: C 70.50, H 3.80, N 14.46. 600 MHz ^1H NMR (δ (*J*, Hz), $CDCl_3$): 8.19(1H, d, 8.4), 8.10(1H, d, 7.8), 7.97(1H, s), 7.80(1H, t, 7.5), 7.76(1H, d, 6.6), 7.70(1H, t, 7.8), 7.61(1H, d, 7.8), 7.57(1H, t, 7.8), 7.46(1H, t, 7.5), 7.42(1H, d, 7.2), 6.82(1H, d, 7.2). 151 MHz ^{13}C NMR (δ, $CDCl_3$): 149.14, 136.16, 133.65, 133.30, 130.74, 129.70, 128.88, 127.50, 127.40, 127.18, 125.27, 125.20, 125.01, 122.86, 121.28, 119.93, 114.76.



IQ-9

3-(3-Nitrophenyl)imidazo[5,1-*a*]isoquinoline (**IQ-10**)

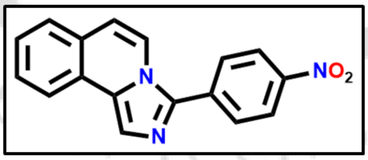
Yield: 0.219g (80%). mp. 188°C. ESI-MS: *m/z* calcd for $C_{17}H_{11}N_3O_2$ 289.085 found (M^++H) 290.093. Elemental analysis (%) calcd for $C_{17}H_{11}N_3O_2$: C 70.58, H 3.83, N 14.53; found: C 70.53, H 3.78, N 14.48. 400 MHz ^{1}H NMR (δ (*J*, Hz), DMSO-d_6): 8.59(1H, s), 8.34(1H, d, 7.6), 8.30(2H, d, 7.2), 8.25(1H, d, 7.6), 8.19(1H, s), 7.84(1H, t, 8.2), 7.78(1H, d, 7.6), 7.60(1H, t, 7.6), 7.51(1H, t, 7.6), 7.13(1H, d, 7.6). 151 MHz ^{13}C NMR (δ, $CDCl_3$): 148.83, 138.59, 134.37, 132.11, 130.51, 130.41, 129.06, 127.71, 127.40, 127.16, 125.02, 123.60, 122.87, 122.85, 121.74, 120.09, 115.31.



IQ-10

3-(4-Nitrophenyl)imidazo[5,1-*a*]isoquinoline (**IQ-11**)

Yield: 0.215g (78%). mp. 223°C. ESI-MS: *m/z* calcd for $C_{17}H_{11}N_3O_2$ 289.085 found (M^++H) 290.095. Elemental analysis (%) calcd for $C_{17}H_{11}N_3O_2$: C 70.58, H 3.83, N 14.53; found: C 70.52, H 3.77, N 14.50. 400 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.41(2H, d, 8.8), 8.12–8.07(2H, m), 8.04–8.02(3H, m), 7.65(1H, d, 8.0), 7.59(1H, t, 6.8), 7.50(1H, t, 8.0), 6.95(1H, d, 7.6). 151 MHz ^{13}C NMR (δ, $CDCl_3$): 147.47, 138.63, 136.31, 130.77, 128.97, 128.55, 127.68, 127.22, 127.06, 124.79, 124.42, 122.76, 122.12, 120.09, 115.25.

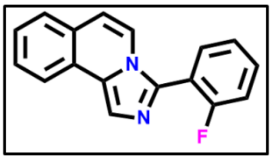


IQ-11

3-(2-Fluorophenyl)imidazo[5,1-*a*]isoquinoline (**IQ-12**)

Yield: 0.159g (66%). mp. 130°C. ESI-MS: *m/z* calcd for $C_{17}H_{11}N_2F$ 262.091 found (M^++H) 263.100. Elemental analysis (%) calcd for $C_{17}H_{11}N_2F$: C 77.85, H 4.23, N 10.68; found: C 77.77, H 4.18, N 10.62. 600 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 8.09(1H, d, 7.8), 8.00(1H, s), 7.77–7.74(1H, m), 7.63(1H, dd, 7.5, 3.9), 7.61(1H, d, 7.8), 7.55(1H, t, 7.5), 7.52–7.48(1H, m), 7.45(1H, t, 7.5), 7.34(1H, t, 7.5), 7.28–

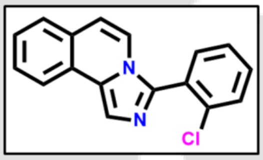
7.24(1H, t, 9.3){along with $CDCl_3$ peak}, 6.83(1H, d, 7.5). 151 MHz ^{13}C NMR (δ, $CDCl_3$): 161.03, 136.25, 132.55, 131.44, 131.39, 129.82, 128.60, 127.30, 127.21, 125.06, 122.69, 121.43, 118.44, 118.34, 116.45, 116.30, 113.97.



IQ-13

3-(2-Chlorophenyl)imidazo[5,1-*a*]isoquinoline (**IQ-13**)

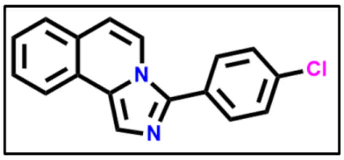
Yield: 0.150g (67%). mp.110 °C. ESI-MS: *m/z* calcd for $C_{17}H_{11}N_2Cl$ 278.061 found (M^++H) 279.054. Elemental analysis (%) calcd for $C_{17}H_{11}N_2Cl$: C 73.25, H 3.98, N 10.05; found: C 73.17, H 3.94, N 10.01. 400 MHz ^1H NMR (δ (*J*, Hz), DMSO-d_6): 8.25(1H, d, 7.6), 8.11(1H, s), 7.76(1H, d, 7.6), 7.71(1H, d, 8.0), 7.67–7.64(1H, m), 7.62–7.59(3H, m), 7.58–7.56(1H, m), 7.50(1H, t, 7.6), 7.03(1H, d, 7.5). 151 MHz ^{13}C NMR (δ, DMSO-d_6): 137.68, 133.37, 133.10, 131.50, 129.93, 128.91, 128.51, 128.26, 127.68, 127.24, 127.19, 126.65, 124.08, 122.50, 121.26, 120.77, 113.53.



IQ-14

3-(4-Chlorophenyl)imidazo[5,1-*a*]isoquinoline (**IQ-14**)

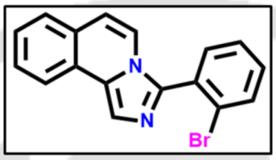
Yield: 0.141g (65%). mp. 155°C. ESI-MS: *m/z* calcd for $C_{17}H_{11}ClN_2$ 278.061 found (M^++H) 279.068: Elemental analysis (%) calcd for $C_{17}H_{11}N_2Cl$: C 73.25, H 3.98, N 10.05; found: C 73.20, H 3.92, N 10.00. 500 MHz ^1H NMR (δ (*J*, Hz), $CDCl_3$): δ 8.06(1H, d, 8.0), 7.96–7.94(2H, m), 7.74(2H, d, 8.5), 7.59(1H, d, 7.8), 7.56–7.50(3H, m), 7.44(1H, td, 7.8, 1.0), 6.82(1H, d, 7.5). 126 MHz ^{13}C NMR (δ, $CDCl_3$):140.06, 135.18, 129.85, 129.82, 129.50, 128.90, 128.84, 128.76, 127.39, 127.27, 127.13, 125.20, 122.75, 121.10, 120.55, 114.63, 114.58.



IQ-14

3-(2-Bromophenyl)imidazo[5,1-*a*]isoquinoline (**IQ-15**)

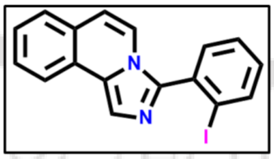
Yield: 0.160g (59%). mp. 103°C. ESI-MS: *m/z* calcd for $C_{17}H_{11}N_2Br$ 322.011 found (M^++H) 323.018. Elemental analysis (%) calcd for $C_{17}H_{11}N_2Br$: C 63.18, H 3.43, N 8.67; found: C 63.13, H 3.40, N 8.63. 400 MHz ^{1}H NMR (δ (*J*, Hz), DMSO-*d*$_6$): 8.24(1H, d, 8.0), 8.09(1H, s), 7.86(1H, d, 8.0), 7.76(1H, d, 8.0), 7.61–7.48(6H, m), 7.02(1H, d, 7.2). 151 MHz ^{13}C NMR (δ, DMSO-*d*$_6$): 139.72, 133.46, 133.41, 131.59, 131.39, 128.98, 128.63, 127.92, 127.30, 127.24, 125.06, 124.56, 122.78, 121.24, 120.48, 113.91.



IQ-15

3-(2-Iodophenyl)imidazo[5,1-*a*]isoquinoline (**IQ-16**)

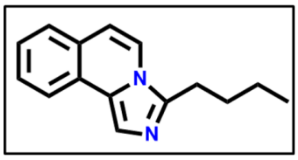
Yield: 0.230g (67%). mp. 113°C. ESI-MS: *m/z* calcd for $C_{17}H_{11}N_2I$ 369.997 found (M^++H) 371.004. Elemental analysis (%) calcd for $C_{17}H_{11}N_2I$: C 55.16, H 3.00, N 7.57; found: C 55.09, H 2.97, N 7.55. 400 MHz ^{1}H NMR (δ (*J*, Hz), DMSO-*d*$_6$): 8.24(1H, d, 8.0), 8.08(2H, d, 6.8), 7.75(1H, d, 8.0), 7.60(2H, t, 7.5), 7.55–7.47(3H, m), 7.35(1H, t, 7.6), 7.01(1H, d, 7.6). 101 MHz ^{13}C NMR (δ, DMSO-*d*$_6$): 141.73, 139.59, 135.50, 132.97, 131.99, 129.01, 128.96, 128.18, 127.64, 127.12, 124.55, 122.94, 121.63, 120.63, 113.91, 100.64.



IQ-16

3-Butylimidazo[5,1-*a*]isoquinoline (**IQ-17**)

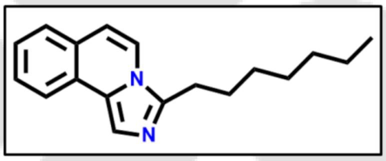
Yield: 0.141g (61%). ESI-MS: *m/z* calcd for $C_{15}H_{16}N_2$ 224.131 found (M^++H) 225.140: Elemental analysis (%) calcd for $C_{15}H_{16}N_2$: C 80.32, H 7.19, N 12.49; found: C 80.33, H 7.20, N 12.30. 500 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 7.98(1H, d, 8.0), 7.73(1H, s), 7.59(1H, d, 7.5), 7.55(1H, d, 7.5), 7.50–7.47(1H, m), 7.40–7.37(1H, m), 6.77(1H, d, 7.5), 3.05–2.91(2H, m), 1.83(2H, m), 1.45(2H, m), 0.97(3H, m). 126 MHz ^{13}C NMR (δ, $CDCl_3$): 141.92, 128.53, 128.32, 127.22, 126.84, 126.75, 125.41, 122.47, 119.94, 118.91, 113.53, 29.73, 26.58, 22.73, 14.06. (Some grease remained as impurity in the NMR spectra)



IQ-17

3-Heptylimidazo[5,1-*a*]isoquinoline (**IQ-18**)

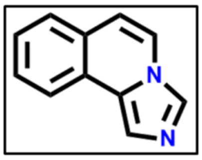
Yield: 0.128g (51%). ESI-MS: *m/z* calcd for $C_{18}H_{22}N_2$ 266.178 found (M^++H) 267.181: Elemental analysis (%) calcd for $C_{18}H_{22}N_2$: C 81.16, H 8.32, N 10.52; found: C 81.18, H 8.35, N 10.40. 500 MHz ^{1}H NMR (δ (*J*, Hz), $CDCl_3$): 7.98(1H, d, 6.5), 7.75(1H, s), 7.61(1H, d, 6.0), 7.58(1H, d, 6.5), 7.51–7.47(1H, m), 7.40–7.37(1H, m), 6.78(1H, d, 6.5), 3.00–2.97(2H, m), 1.84(2H, m), 1.45–1.27(8H, m), 0.88–0.85(3H, m). 126 MHz ^{13}C NMR (δ, $CDCl_3$):141.85, 128.50, 128.21, 127.17, 126.83, 126.69, 125.34, 122.43, 119.82, 118.64, 113.61, 31.86, 29.50, 29.17, 27.61, 26.71, 22.76, 14.22. (Some grease remained as impurity in the NMR spectra)



IQ-18

Imidazo[5,1-a]isoquinoline (**IQ-19**)

Yield: 0.168g (67%). ESI-MS: *m/z* calcd. for $C_{11}H_8N_2$ 168.069 found (M^++H) 169.076: Elemental analysis (%) calcd for $C_{11}H_8N_2$: C 78.55, H 4.79, N 16.66; found: C 78.50, H 4.76, N 16.45. 600 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$):δ 8.11(1H, s), 8.02(1H, d, 7.8), 7.82(1H, s), 7.75(1H, d, 7.8),7.58(1H, d, 7.8), 7.52(1H, t, 7.5), 7.43(1H, t, 7.5), 6.81(1H, d, 7.2).151 MHz ^{13}C NMR(δ, $CDCl_3$): 130.32, 128.71, 128.54, 127.45, 127.39, 127.32, 125.03, 122.82, 121.14, 120.68, 114.27.



IQ-19

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Annexure

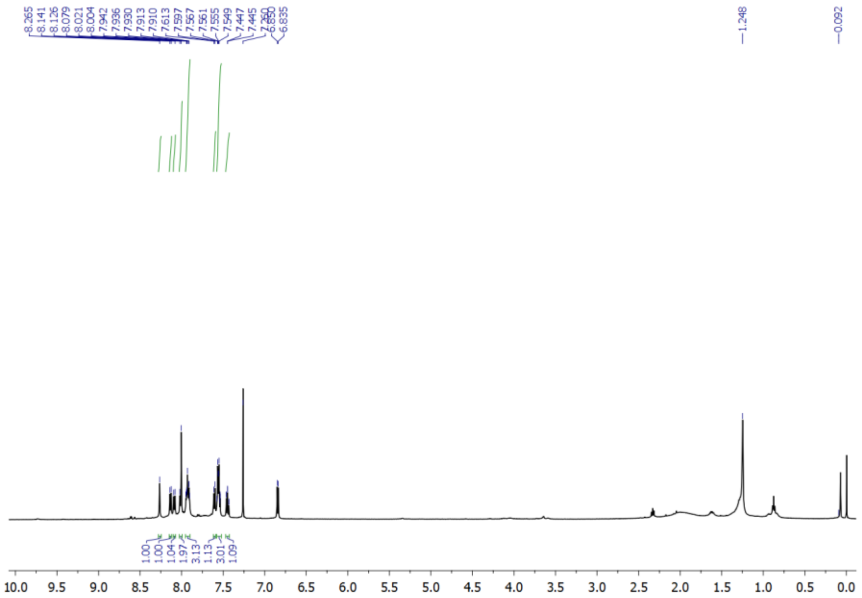


Figure 4.14. ^{1}H NMR spectrum of **IQ-3**.

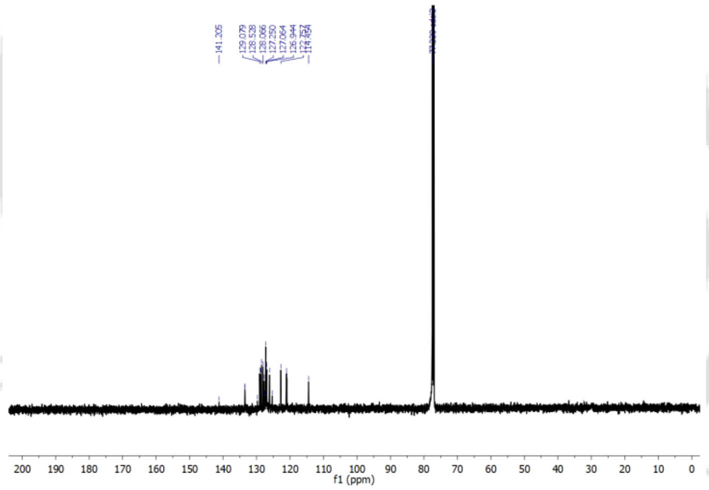


Figure 4.15. ^{13}C NMR spectrum of **IQ-3**.

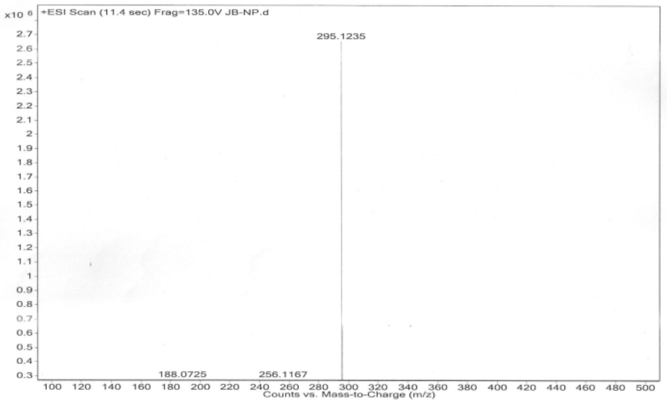


Figure 4.16. ESI Mass spectrum of **IQ-3**.

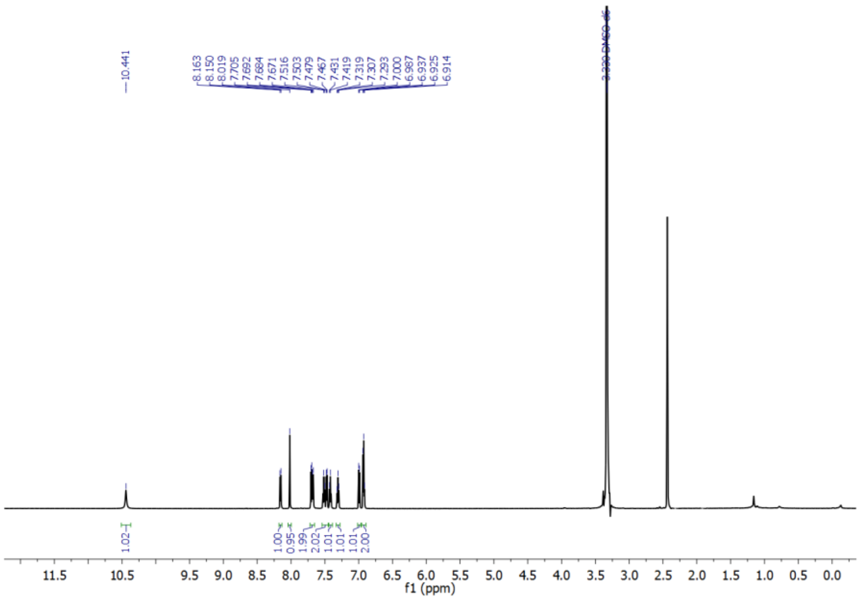


Figure 4.17. ^{1}H NMR spectrum of **IQ-4**.

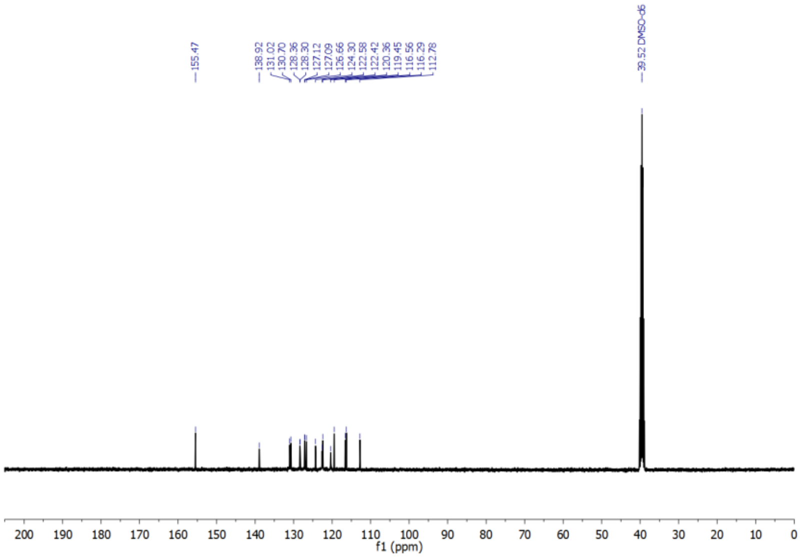


Figure 4.18. ^{13}C NMR spectrum of **IQ-4**.

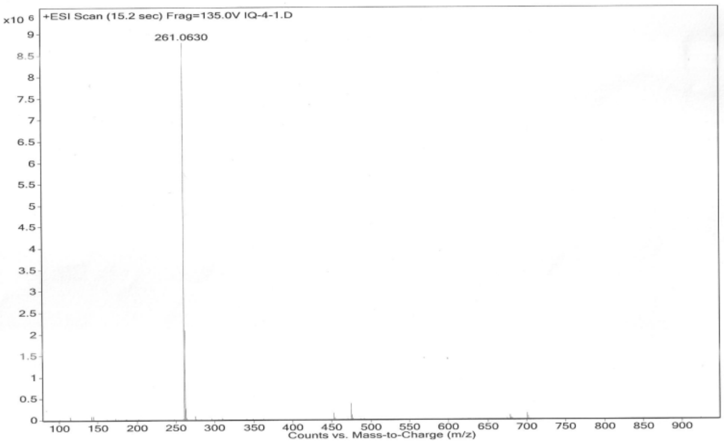


Figure 4.19. ESI Mass spectrum of **IQ-4**.

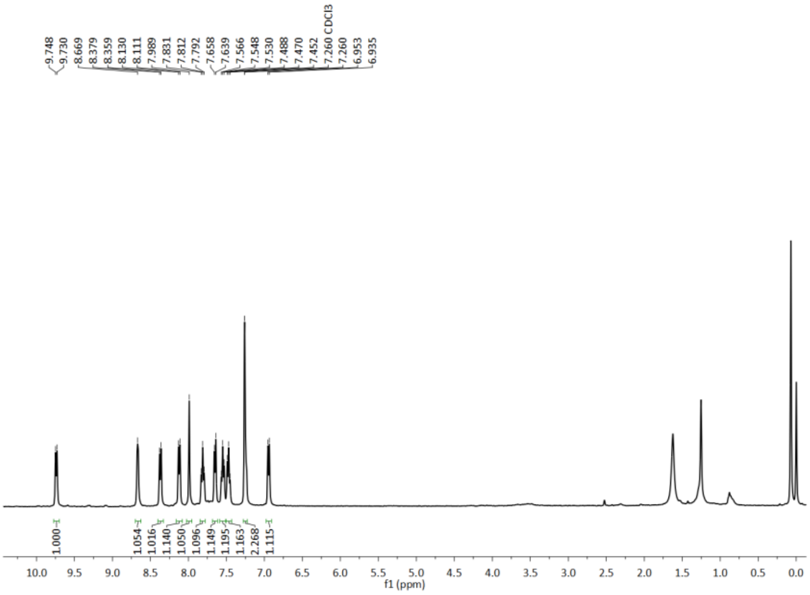


Figure 4.20. ^{1}H NMR spectrum of **IQ-5**.

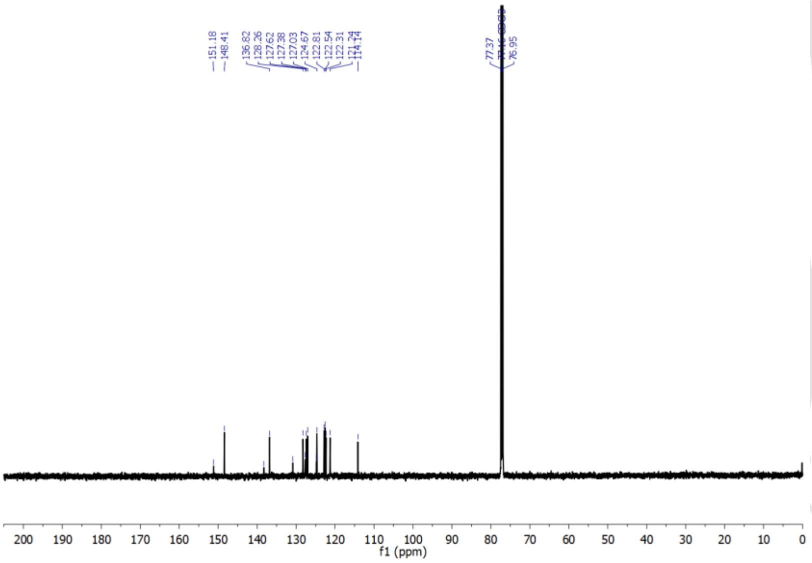


Figure 4.21. ^{13}C NMR spectrum of **IQ-5**.

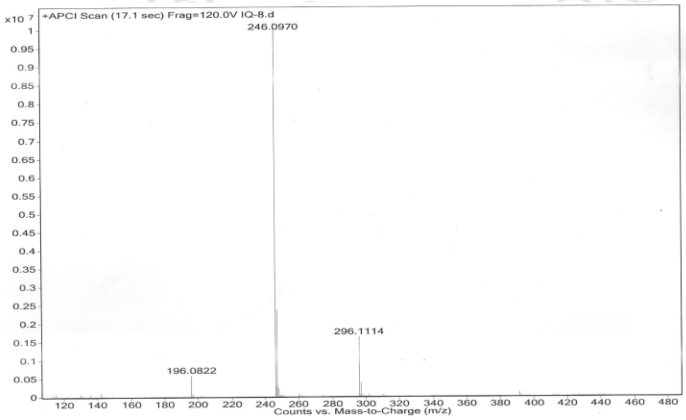


Figure 4.22. ESI Mass spectrum of **IQ-5**.

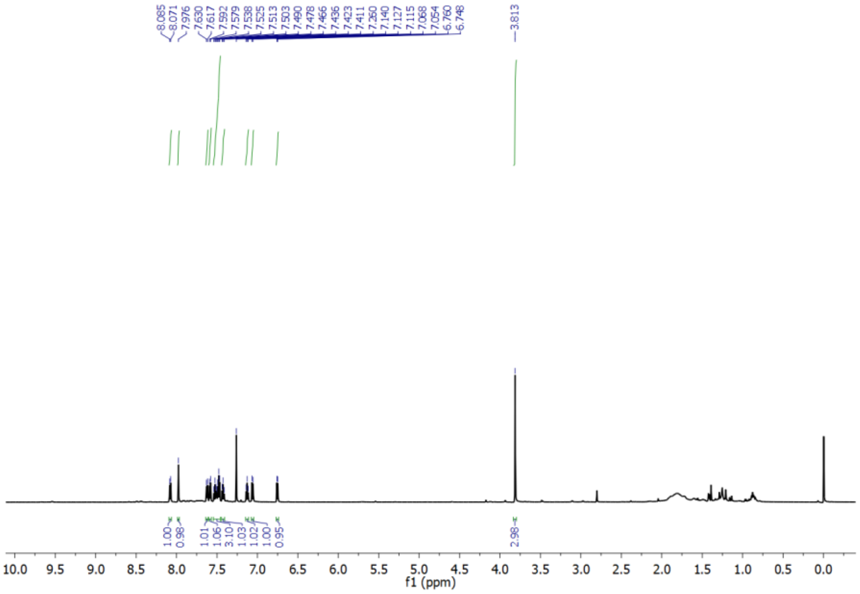


Figure 4.23. ^{1}H NMR spectrum of **IQ-6**.

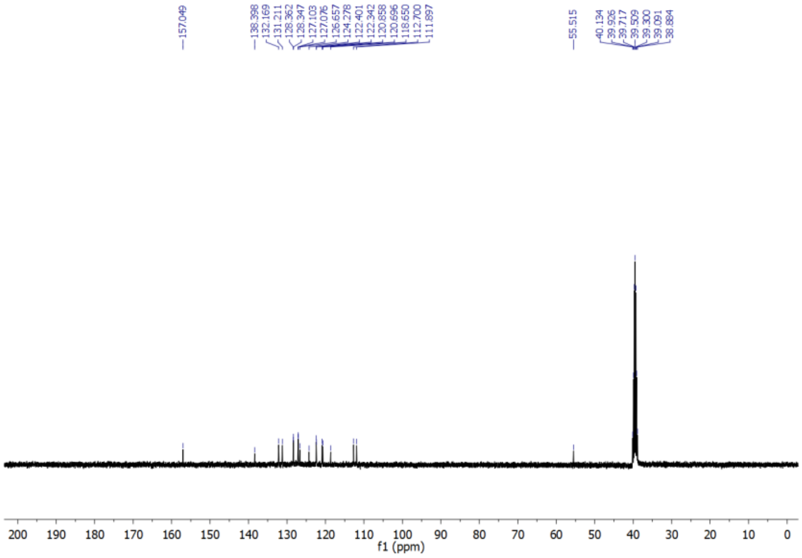


Figure 4.24. ^{13}C NMR spectrum of **IQ-6**.

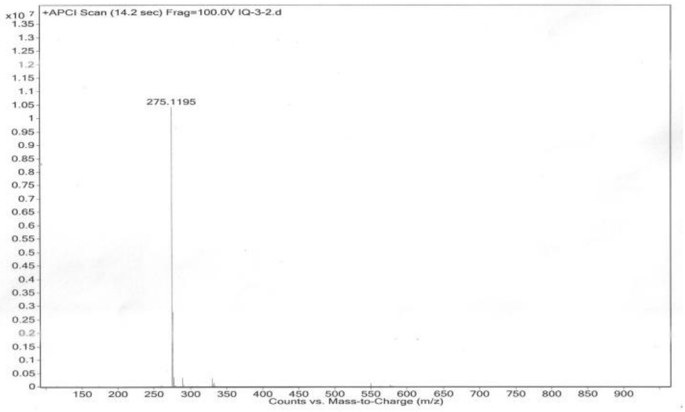


Figure 4.25. ESI Mass spectrum of **IQ-6**.

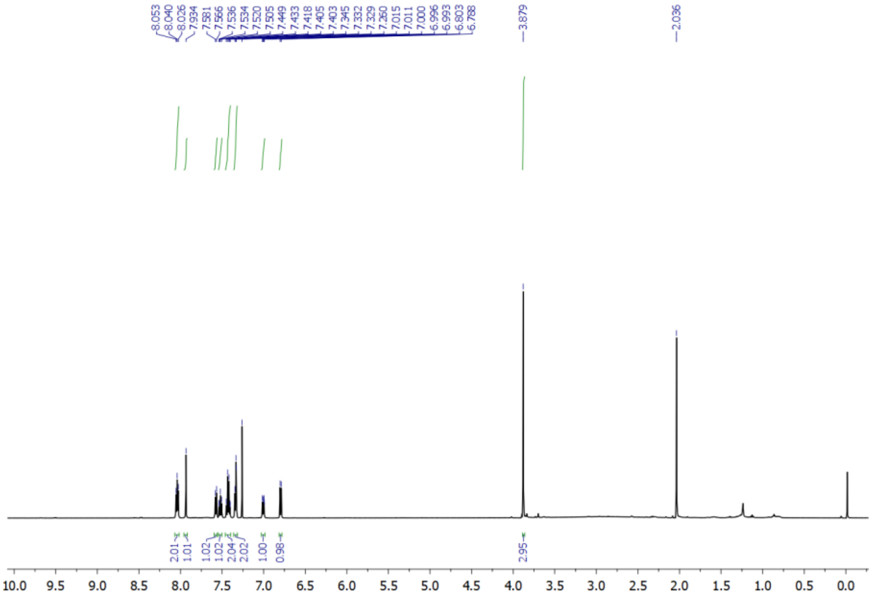


Figure 4.26. ^{1}H NMR spectrum of **IQ-7**.

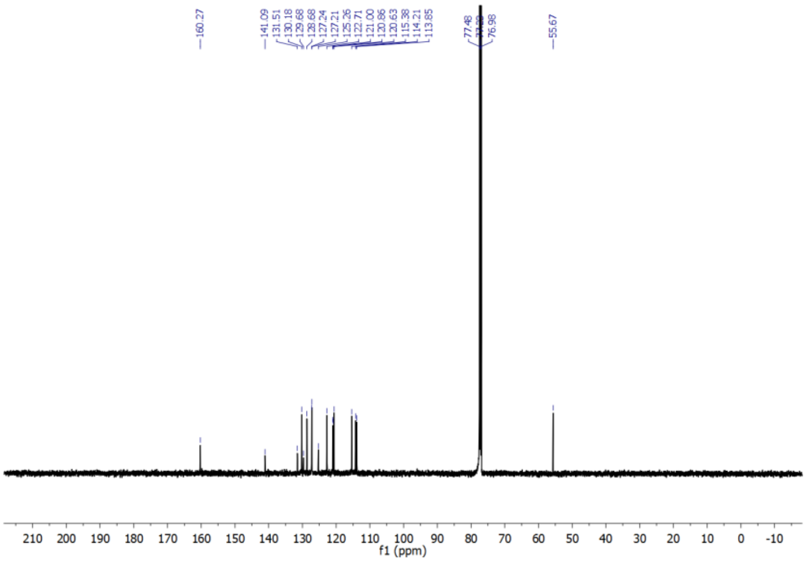


Figure 4.27. ^{13}C NMR spectrum of **IQ-7**.

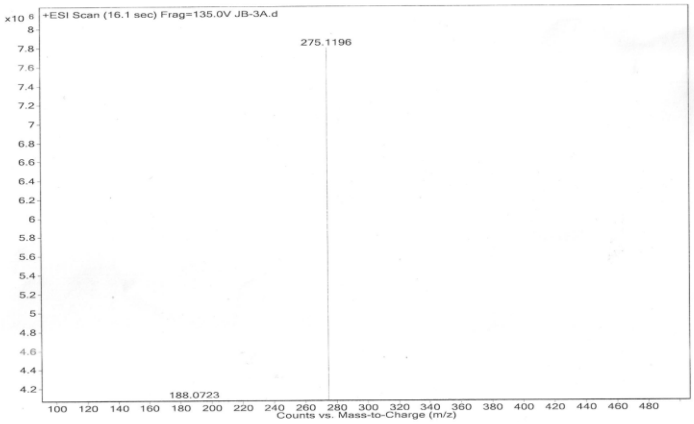


Figure 4.28. ESI Mass spectrum of **IQ-7**.

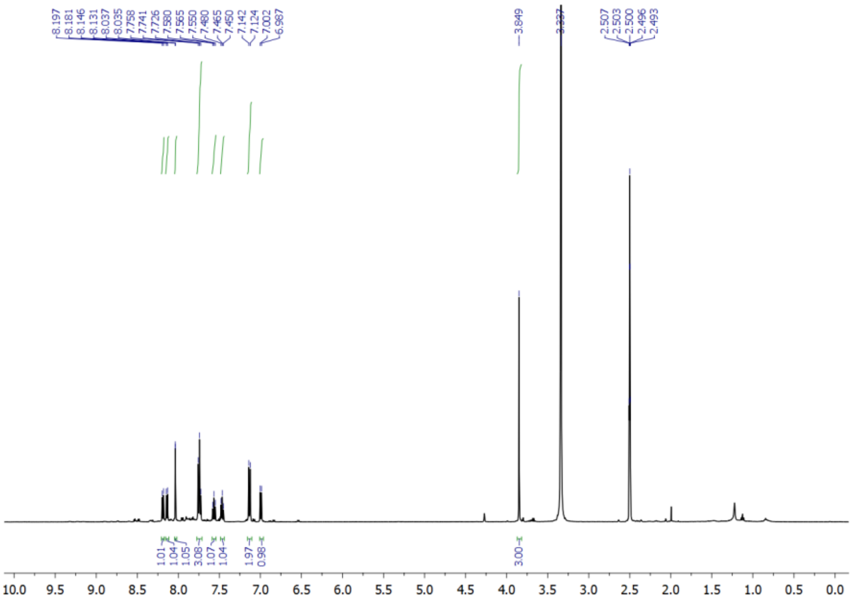


Figure 4.29. ^{1}H NMR spectrum of **IQ-8**.

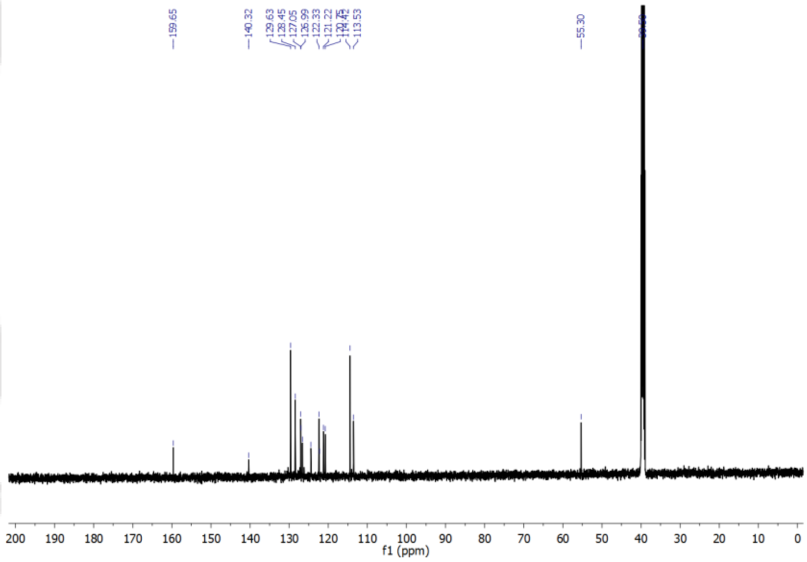


Figure 4.30. ^{13}C NMR spectrum of **IQ-8**.

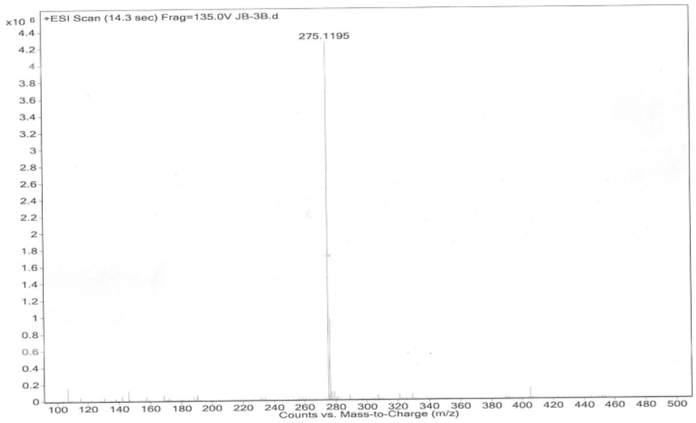


Figure 4.31. ESI Mass spectrum of **IQ-8**.

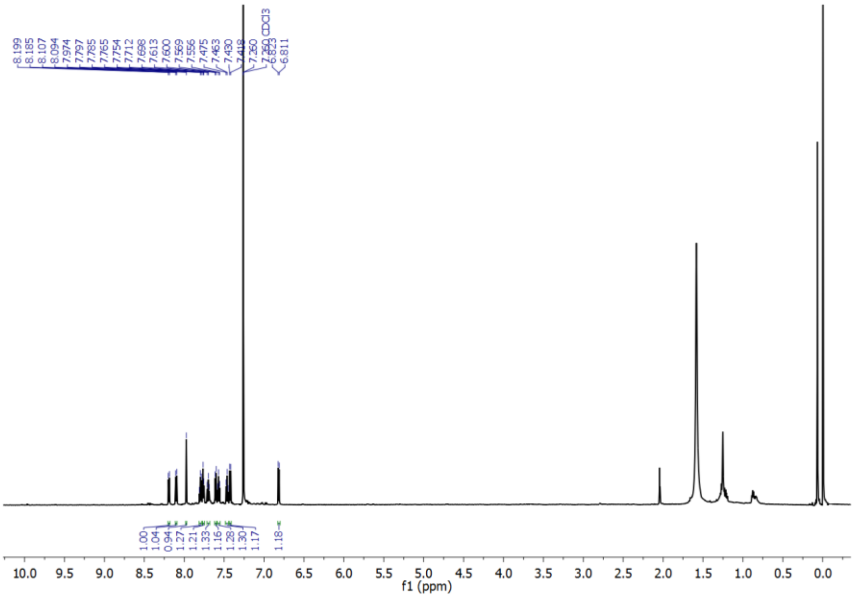


Figure 4.32. ^{1}H NMR spectrum of **IQ-9**.

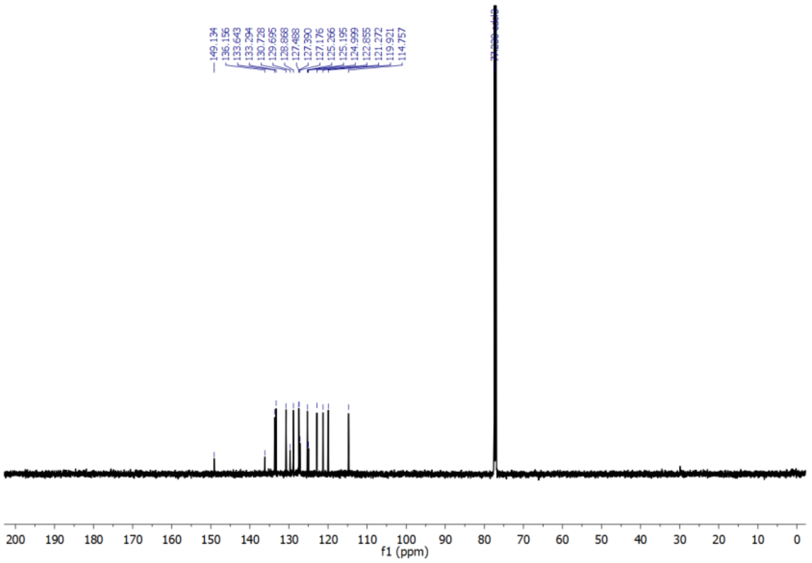


Figure 4.33. ^{13}C NMR spectrum of **IQ-9**.

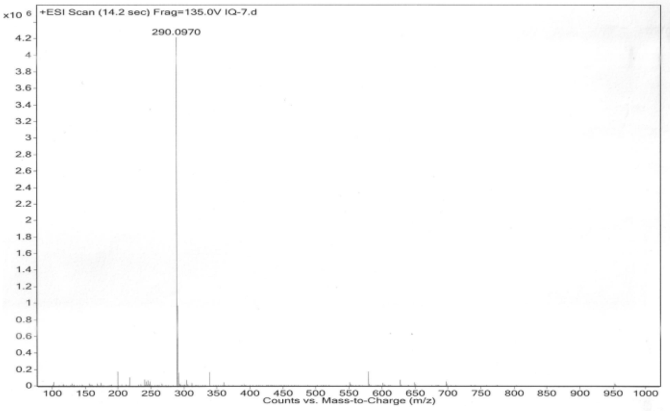


Figure 4.34. ESI Mass spectrum of **IQ-9**.

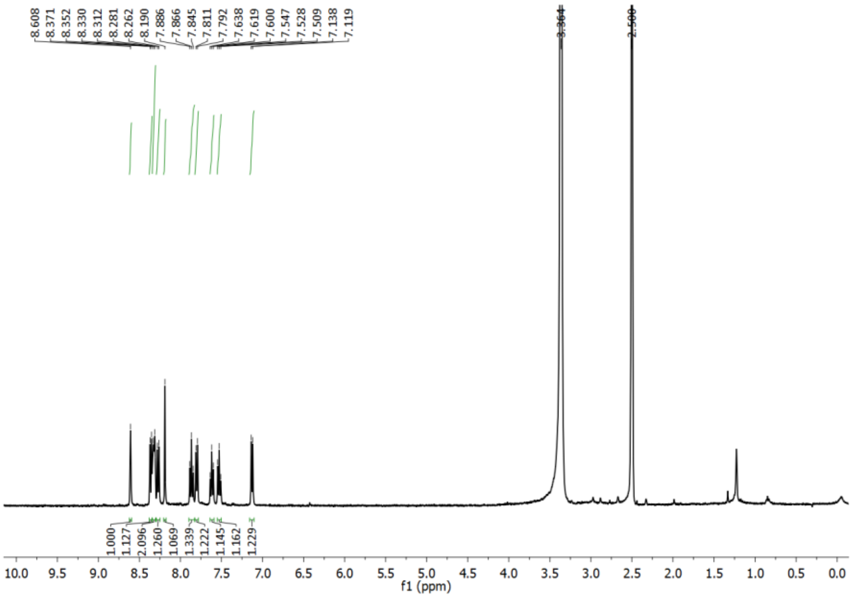


Figure 4.35. ^{1}H NMR spectrum of **IQ-10**.

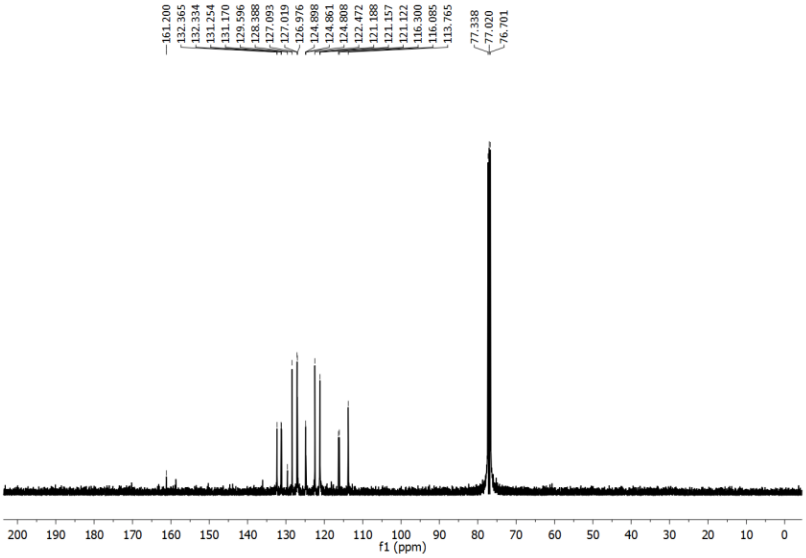


Figure 4.36. ^{13}C NMR spectrum of **IQ-10**.

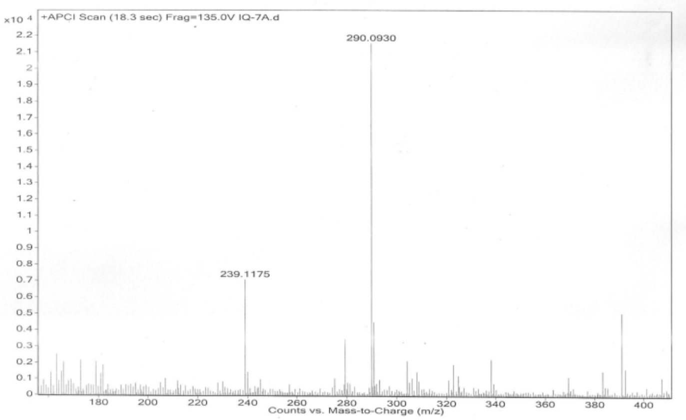


Figure 4.37. ESI Mass spectrum of **IQ-10**.

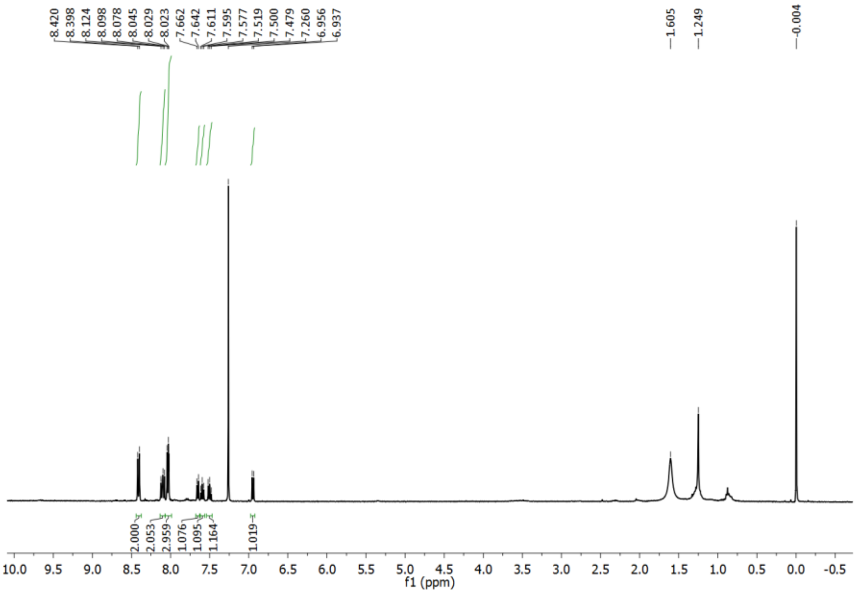


Figure 4.38. ^{1}H NMR spectrum of **IQ-11**.

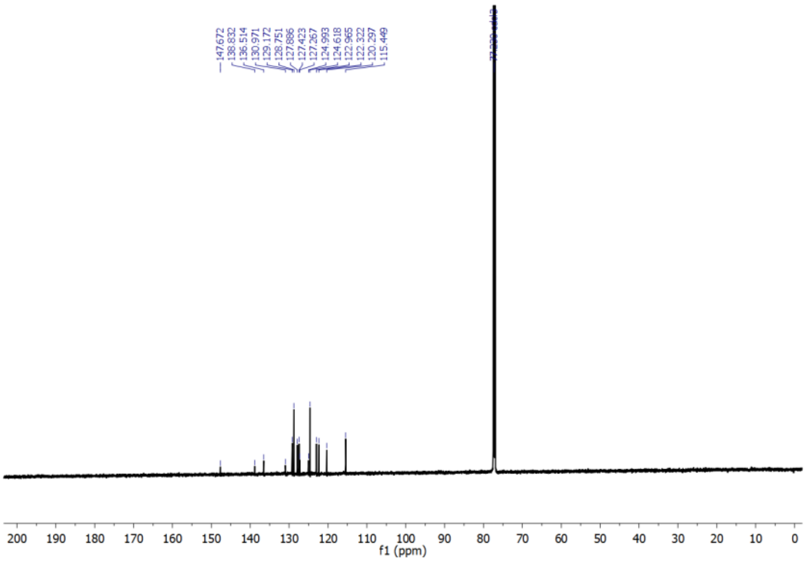


Figure 4.39. ^{13}C NMR spectrum of **IQ-11**.

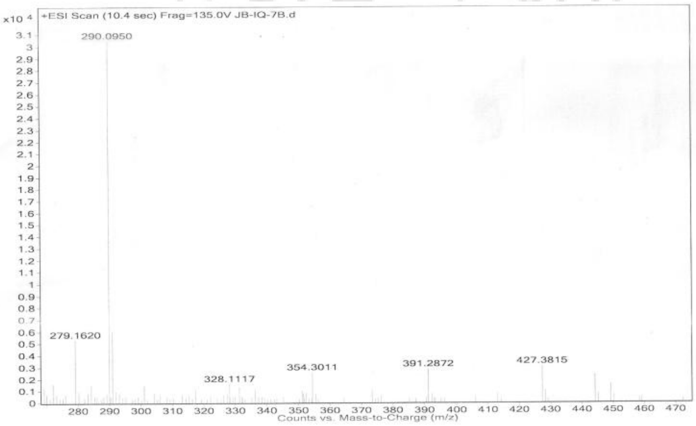


Figure 4.40. ESI Mass spectrum of **IQ-11**.

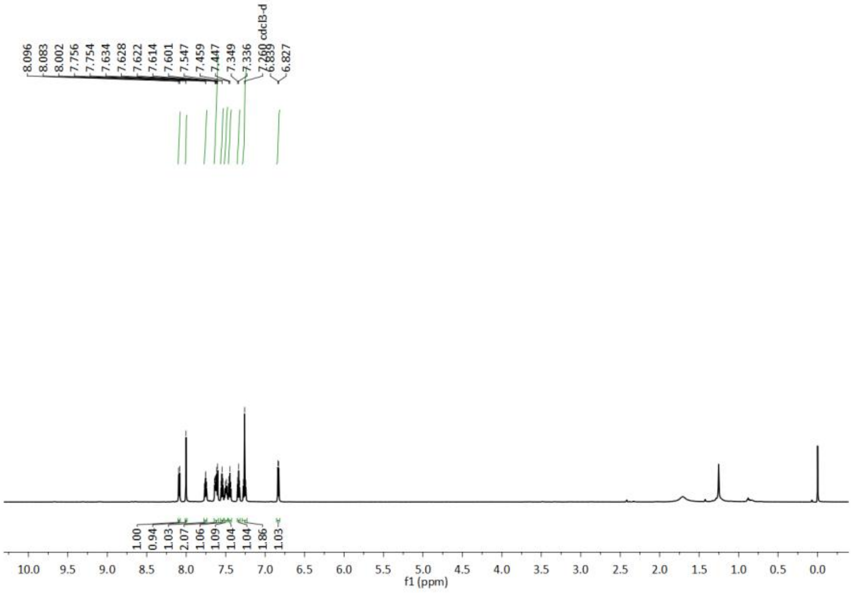


Figure 4.41. ^{1}H NMR spectrum of **IQ-12**.

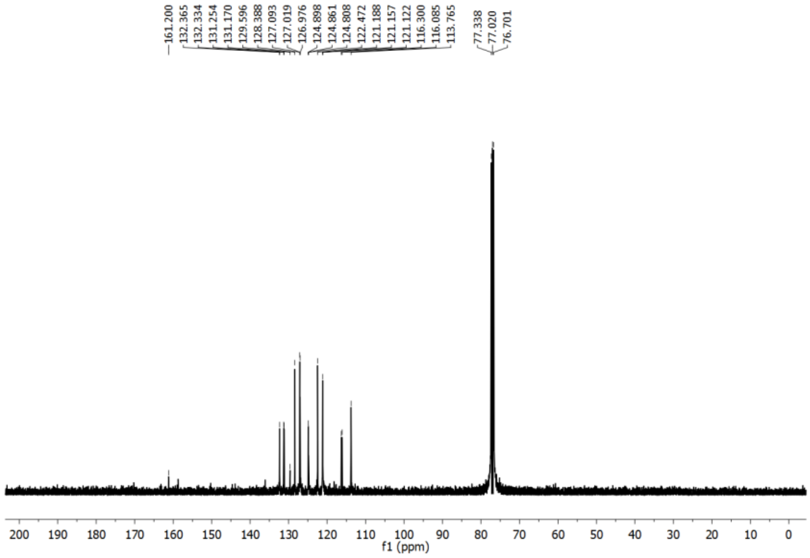


Figure 4.42. ^{13}C NMR spectrum of **IQ-12**.

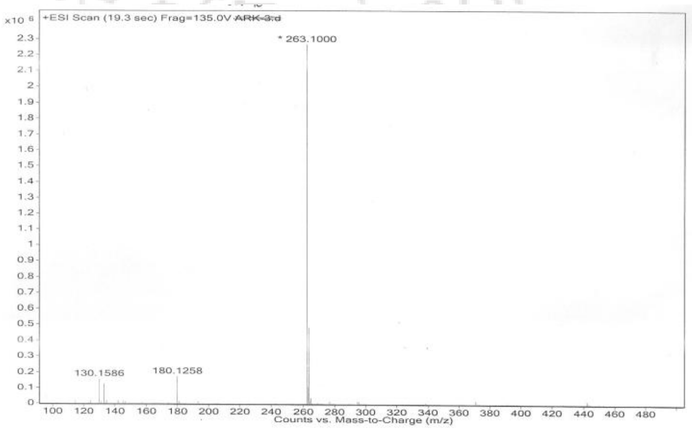


Figure 4.43. ESI Mass spectrum of **IQ-12**.

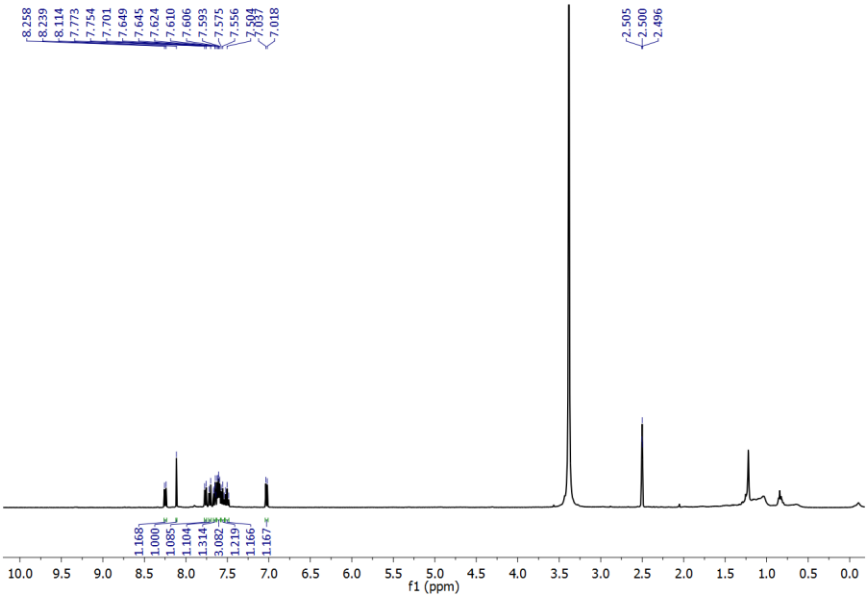


Figure 4.44. ^{1}H NMR spectrum of **IQ-13**.

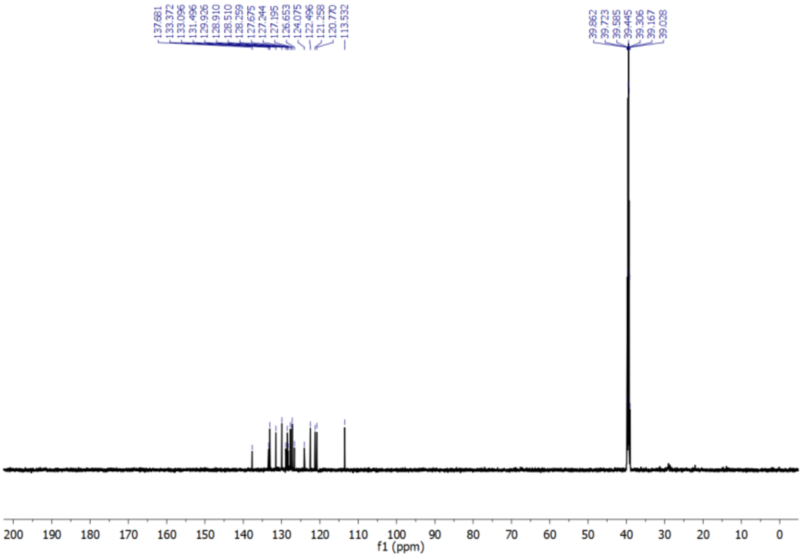


Figure 4.45. ^{13}C NMR spectrum of **IQ-13**.

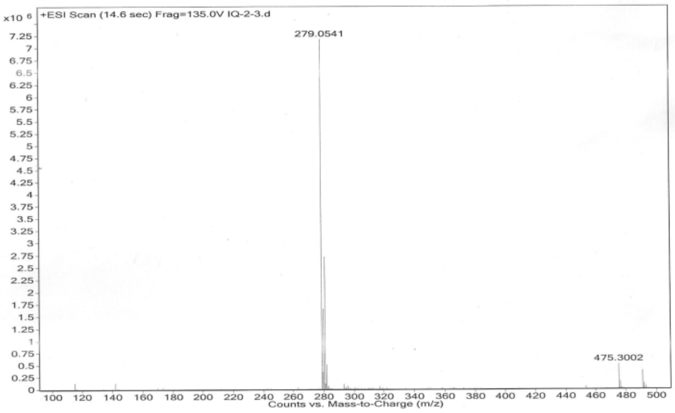


Figure 4.46. ESI Mass spectrum of **IQ-13**.

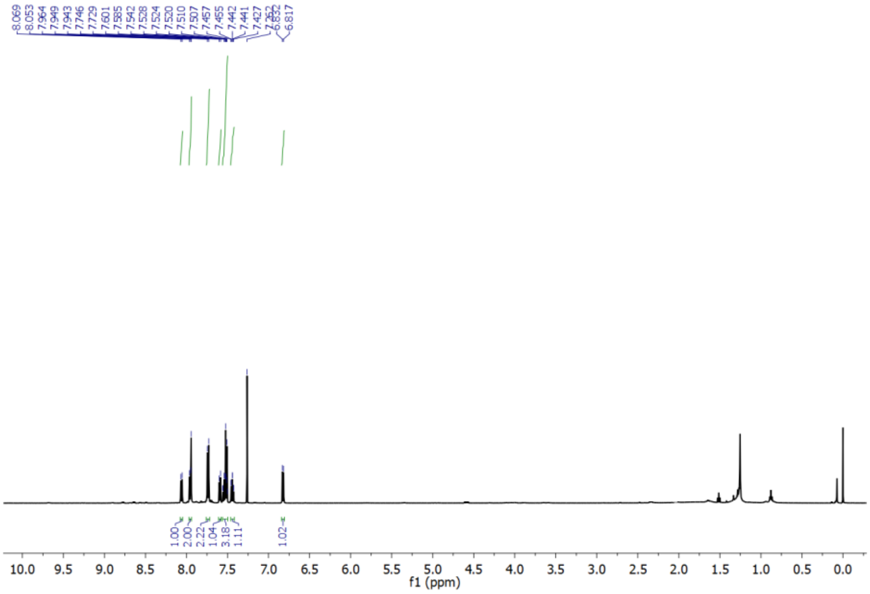


Figure 4.47. ^{1}H NMR spectrum of **IQ-14**.

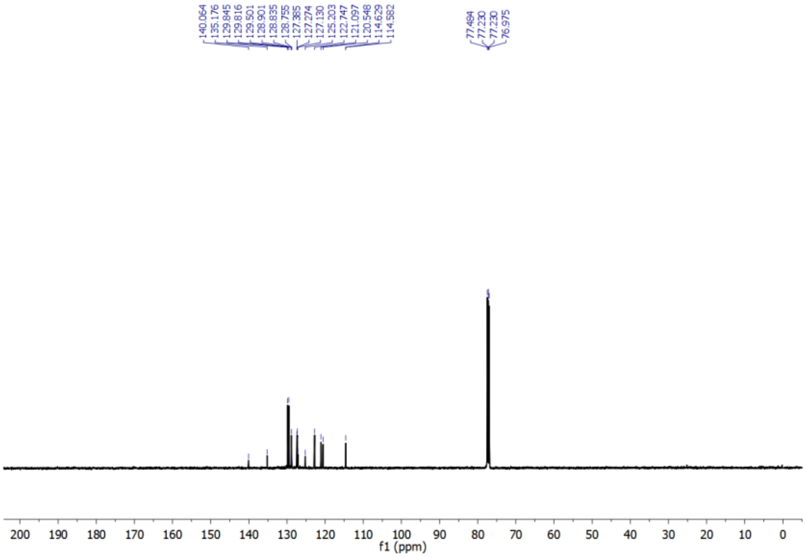


Figure 4.48. ^{13}C NMR spectrum of **IQ-14**.

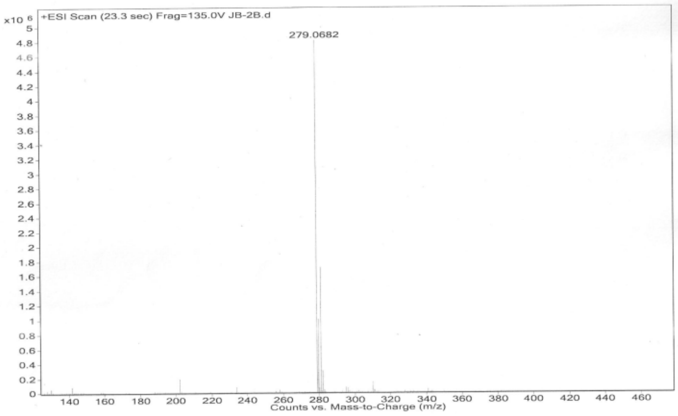


Figure 4.49. ESI Mass spectrum of **IQ-14**.

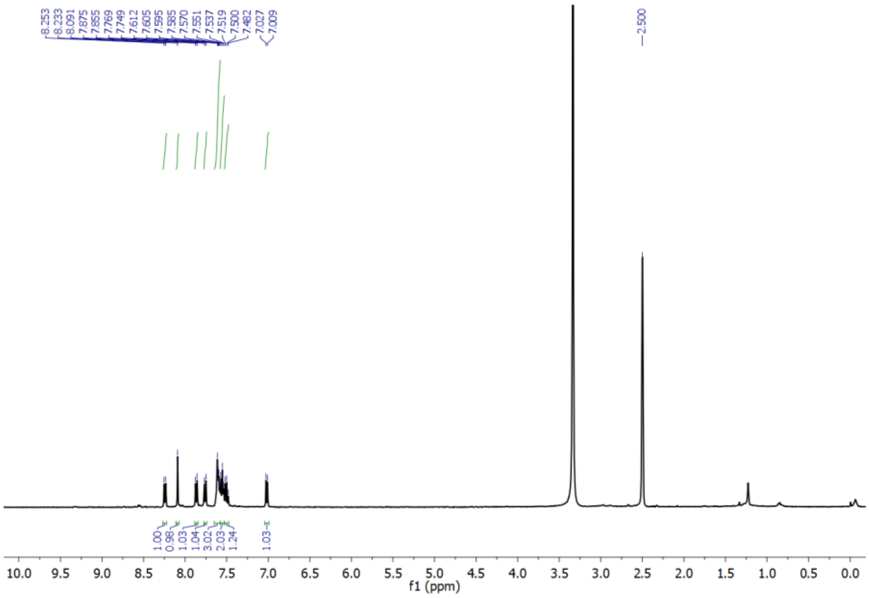


Figure 4.50. ^{1}H NMR spectrum of **IQ-15**.

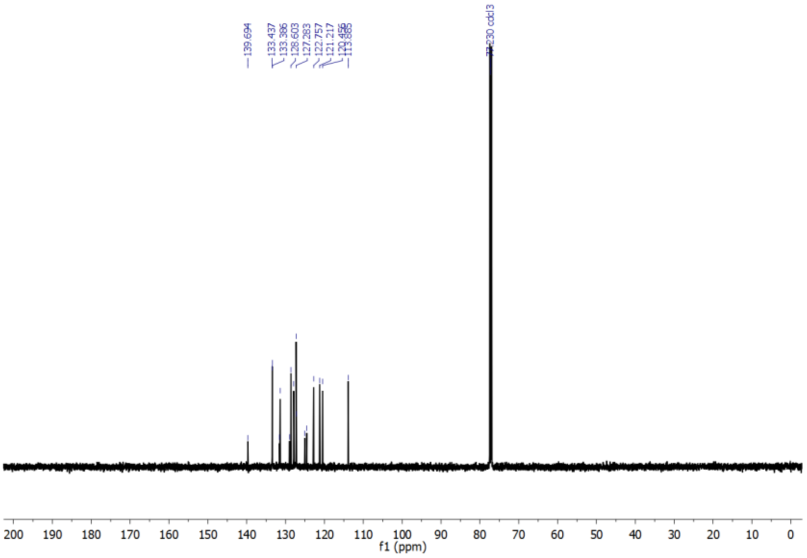


Figure 4.51. ^{13}C NMR spectrum of **IQ-15**.

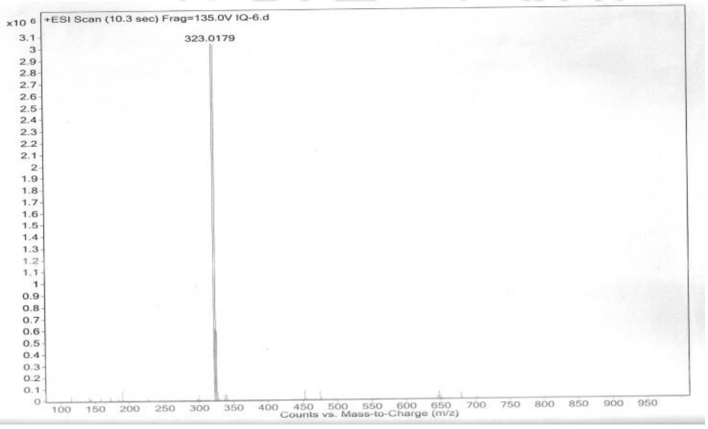


Figure 4.52. ESI Mass spectrum of **IQ-15**.

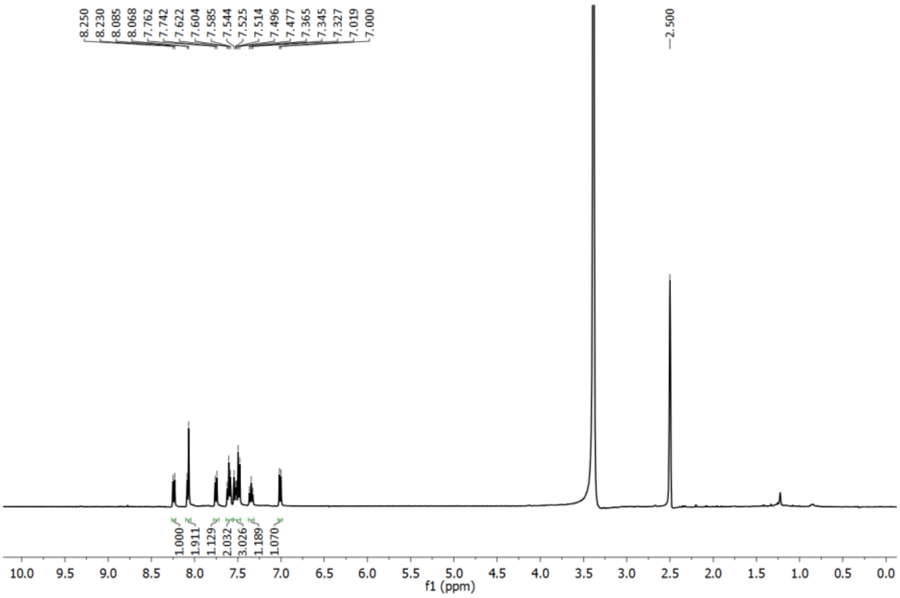


Figure 4.53. ^{1}H NMR spectrum of **IQ-16**.

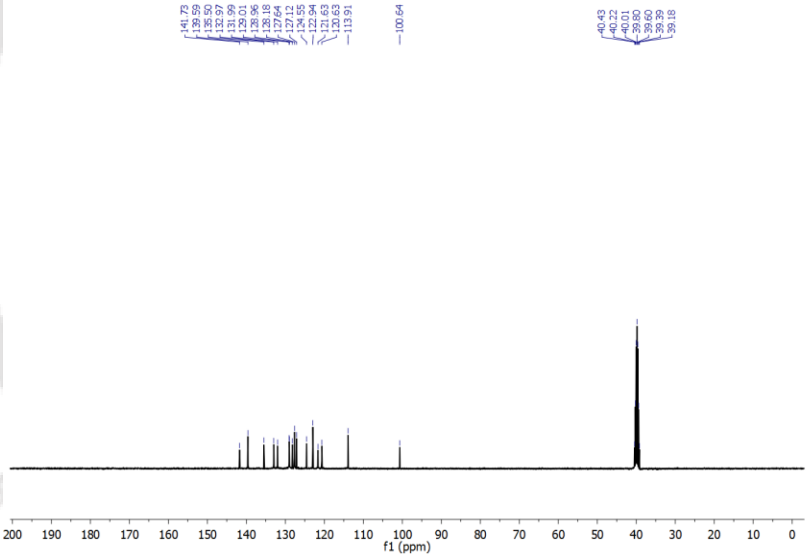


Figure 54. ^{13}C NMR spectrum of **IQ-16**.

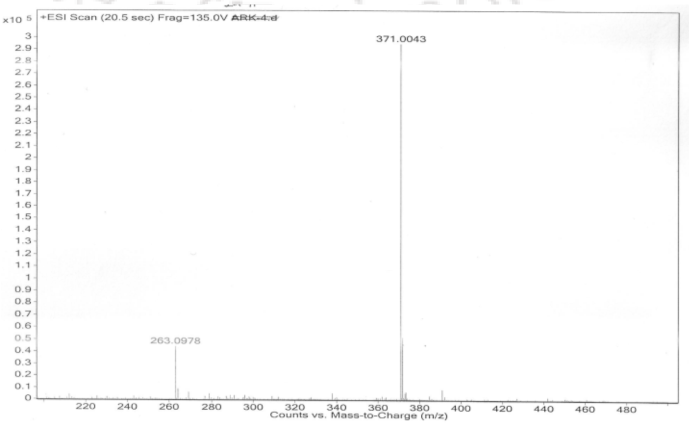


Figure 4.55. ESI Mass spectrum of **IQ-16**.

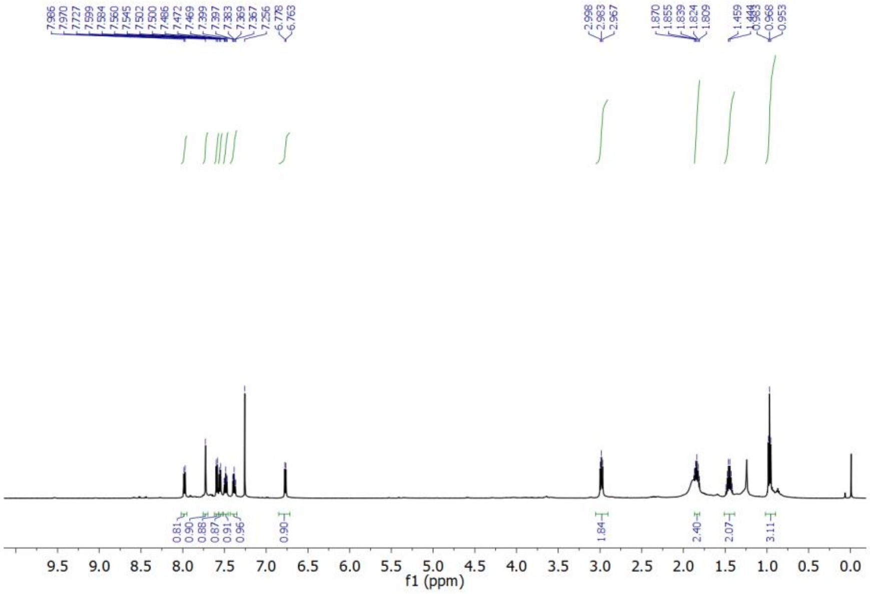


Figure 4.56. ^{1}H NMR spectrum of **IQ-17**.

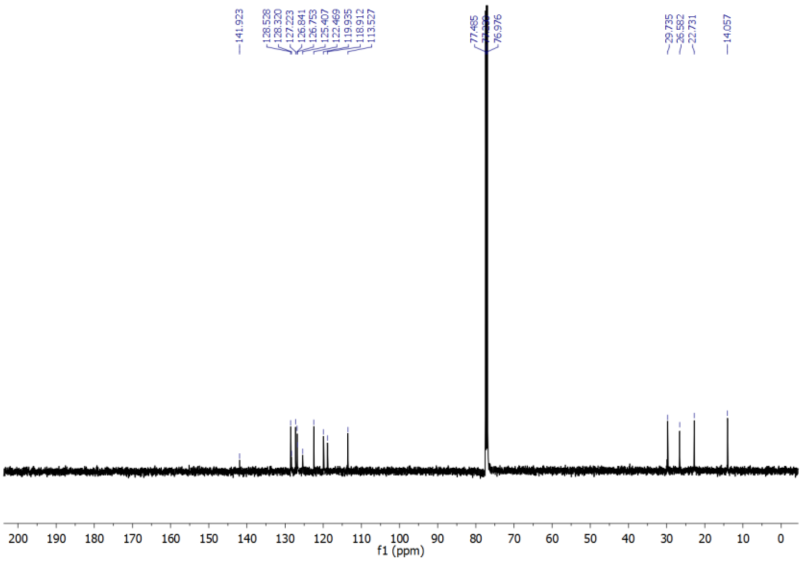


Figure 4.57. ^{13}C NMR spectrum of **IQ-17**.

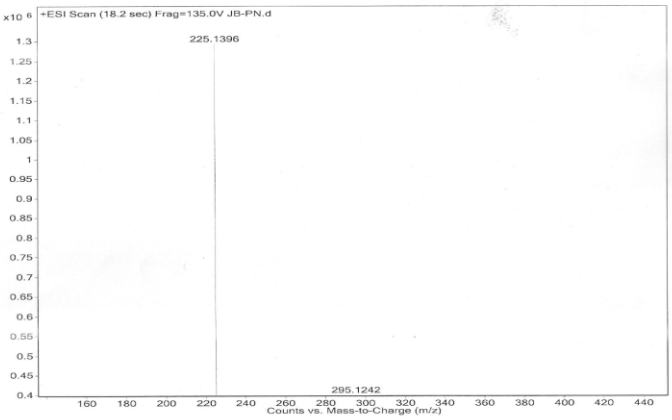


Figure 4.58. ESI Mass spectrum of **IQ-17**.

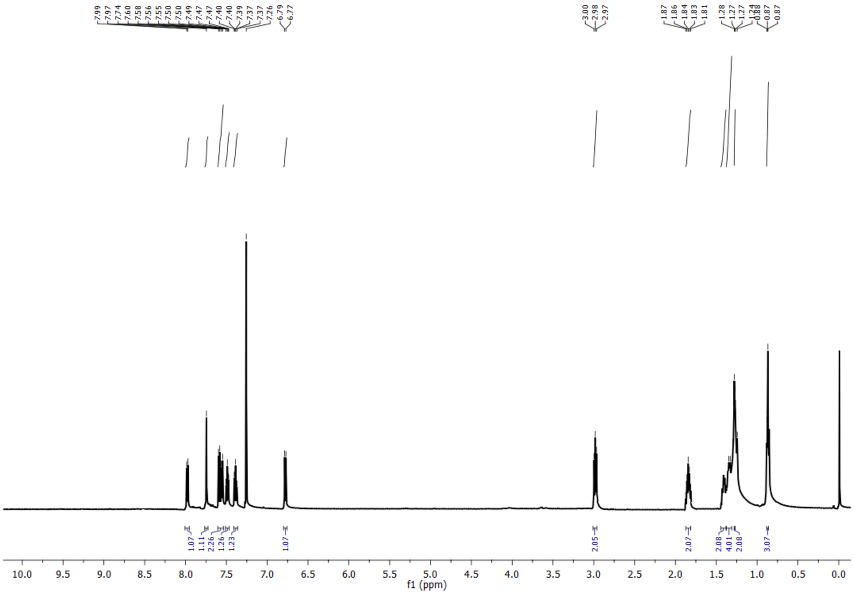


Figure 4.59. ^{1}H NMR spectrum of **IQ-18**.

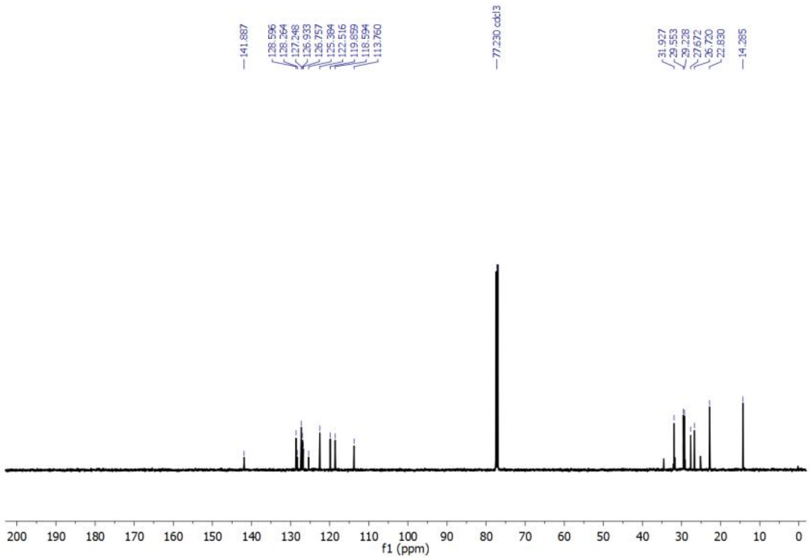


Figure 4.60. ^{13}C NMR spectrum of **IQ-18**.

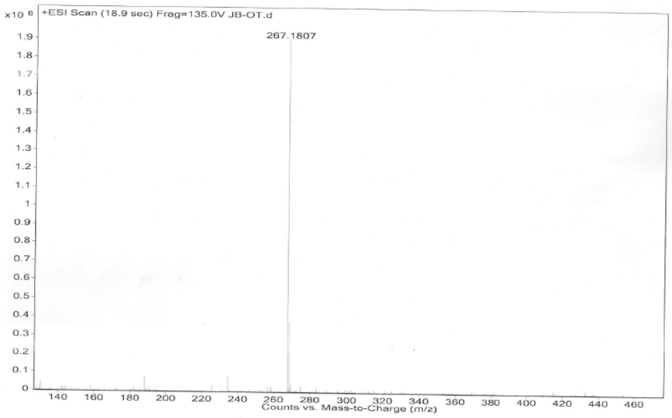


Figure 4.61. ESI Mass spectrum of **IQ-18**.

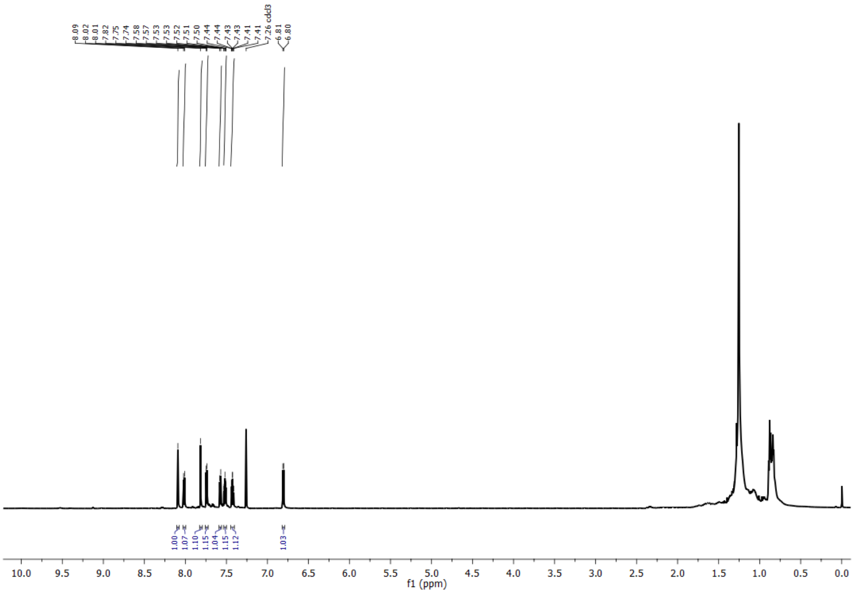


Figure 4.62. ^{1}H NMR spectrum of **IQ-19**.

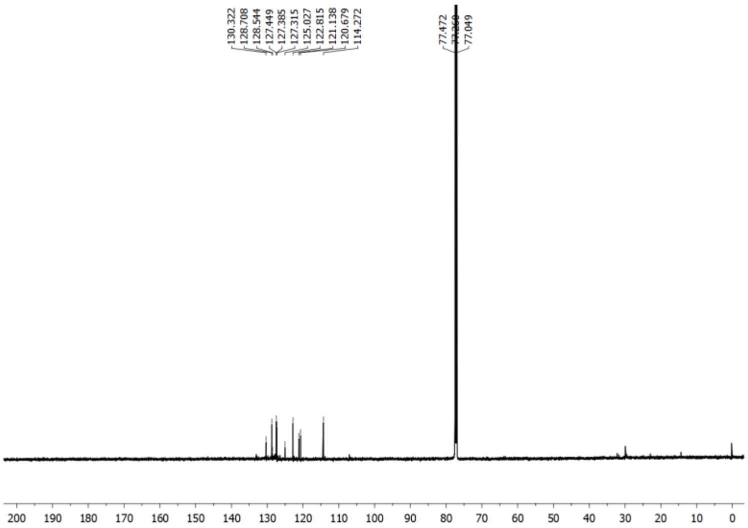


Figure 4.63. ^{13}C NMR spectrum of **IQ-19**.

Figure 4.63. ESI Mass spectrum of **IQ-19**

Chapter 5

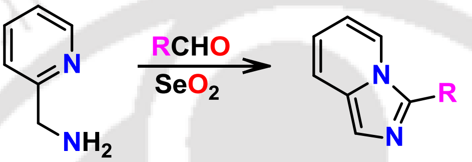
A New Synthetic Route for 3-Substituted Imidazo[1,5-*a*]pyridines

Abstract

A new convenient route for synthesis of 3-substituted-imidazo[1,5-*a*]pyridines has been described as well as the scope and limitations of the method is evaluated. By reacting 2-picolylamine and different aldehydes in presence of selenium dioxide as the oxidant, a series of 3-substituted imidazo[1,5-*a*]pyridines were isolated in good yields. Different kinds of aldehydes such as aliphatic, aromatic, heterocyclic as well as aromatic ring carrying some substituents have been used.

5.1. Introduction

In Chapter 4, 1-isoquinolinemethylamine was used as a nucleophile with various aldehydes in presence of SeO_2 for the synthesis of a series of 3-substituted imidazo[5,1-*a*]isoquinolines. This has inspired to study the reaction of 2-picolylamine with various aldehydes in presence of SeO_2. This Chapter describes such reaction involving 2-picolylamine and various aldehydes in presence of SeO_2 which lead to a facile formation of imidazo[1,5-*a*]pyridines (Scheme 5.1).



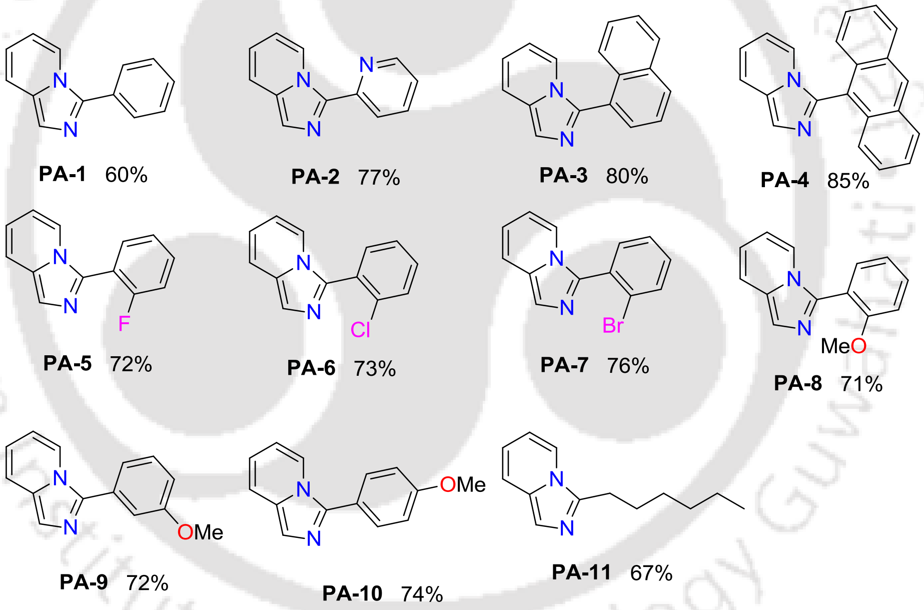
PA-1 to PA-11

Scheme 5.1. Synthesis of 3-substituted imidazo[5,1-*a*]pyridines.

5.2. Results and Discussion

An attempt was made to evaluate the applicability of the synthetic methodology described in the previous Chapter by using 2-picolylamine with various aldehydes in presence of SeO_2. Indeed, the reaction proceeded smoothly with some aldehydes yielding the desired product, but for some aldehydes the reaction did not yield expected products. Thus stirring the 1:1 mixture of 2-picolylamine and various aldehydes in presence of selenium dioxide in ethanol at room temperature afforded the respective imidazo[5,1-*a*]pyridines (Scheme 5.2). As observed with the case of 1-isoquinolinemethylamine, 3-(pyridin-2-yl)imidazo[1,5-*a*]pyridine (5-10%) was also formed as a minor product along with expected product.

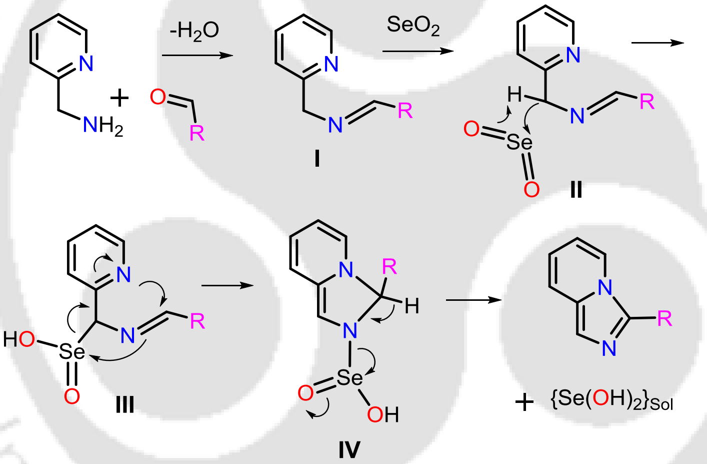
An attempt was made to synthesize similar series of 3-substituted imidazo[1,5-*a*]pyridines by using aldehydes studied in the Chapter 4. Aldehydes such as aromatic, heterocyclic, aliphatic as well as phenyl ring with –OMe group at *ortho*, *meta* and *para* positions yielded the respective products. In the case of phenyl ring with F, Cl and Br substituted at *ortho* position yielded respective imidazo[5,1-*a*]pyridines, but *meta* and *para* substituted fluoro-, chloro-, bromo- and all the three nitro-benzaldehydes did not yield respective imidazo[5,1-*a*]pyridines. Since for the formation of imidazo[5,1-*a*]pyridine nucleus, a prior reaction between the aldehyde and 2-picolylamine to generate the Schiff's base is essential. There are two competing species *viz.*, Schiff's base and the 2-picolylamine itself. It is probable that in case of *meta* and *para* substituted fluoro-, chloro-, bromo- and three nitro- benzaldehydes, 2-picolylamine could have reacted with SeO_2 well before the formation of Schiff's bases and hence did not yield respective imidazo[5,1-*a*]pyridines, but 3-(pyridin-2-yl)imidazo[1,5-*a*]pyridine was found to be formed as a major product with 40-45% yields and the desired product was found in very negligible amount, thus could not be isolated. From these reactions products **PA-1** to **PA-11** (Scheme 5.2) were isolated in good yields, among these imidazo[1,5-*a*]pyridines **PA-4** and **PA-11** are unreported so far in the literature and only **PA-2** exhibits fluorescence which has been already been discussed elsewhere [1].



Scheme 5.2. Scope of synthesis of imidazo[5,1-*a*]pyridines.

All the compounds have been thoroughly characterized using elemental analysis, ^{1}H and ^{13}C NMR spectroscopy and ESI-Mass spectrometric techniques. All these data are consistent with the respective structures. The presence of a singlet in the δ range 7.27–8.30 *ppm*, corresponding to the proton of imidazole ring and two distinct triplets around 6.69–6.89 *ppm* corresponding to the proton of the fused pyridine ring in ^{1}H NMR, is characteristic of imidazo[5,1-*a*]pyridine nucleus.

Plausible mechanistic steps involved in the reaction have been proposed in Scheme 5.3. At first, the 2-picolylamine undergoes a condensation reaction with the aldehydes to form the Schiff base (**I**). The active methylene proton in (**I**) being abstracted by SeO_2 as shown in (**II**) [2] and forms the alkylseleninic acid (**III**) [3-5]. Then a nucleophilic attack on the imine bond takes place by the nitrogen lone pair of 2-picolylamine ring and subsequent migration of electrons to selenium leads to the intermediate **IV** accompanied by breaking of Se–C bond [6]. Dissociation of the proton at the tetrahedral carbon, migration of the resultant electron pair on to the C–N bond, transfer of the N–Se bond pair to selenium resulting in its reduction to its bivalent state accompanied by dissociation of $Se(OH)_2$ could lead to the product. All the compounds were thoroughly characterized by using FTIR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.



Scheme 5.3. Plausible mechanism.

5.3. Conclusions

In this chapter, a new one pot synthetic route for the synthesis of imidazo[5,1-*a*]pyridine nucleus has been described and the scope and limitations of the method is evaluated. By using this procedure with 2-picolylamine and different aldehydes in presence of selenium dioxide as the oxidant, a series of 3-substituted imidazo[1,5-*a*]pyridines were isolated in good yields.

5.4. Synthesis and spectral data

3-Phenylimidazo[1,5-*a*]pyridine (PA-1)

A mixture of 2-picolylamine (0.150g, 1.39mmol) and benzaldehyde (0.147g, 1.39mmol) was stirred in ethanol for about 5 min and then solid selenium dioxide

(0.185 g, 1.66 mmol) was added to the mixture and was allowed to stir at room temperature. After stirring for 3 h, saturated sodium thiosulphate (20 mL) solution was added, stirred well and then allowed to stand for 20 min. The mixture was filtered and washed 3 to 4 times with ethylacetate. The filtrate and washing were collected, evaporated to dryness and then extracted several times with ethyl acetate. The solvent was removed from the extract and was subjected to column chromatography over silica (60-120 mesh). The yellow colored solid compound was eluted with 7% ethyl acetate in hexane. Yield: 0.162 g (61%). ESI-MS: *m/z* calcd for $C_{13}H_{10}N_2$, 194.084; found (M^++H) 195.087. Elemental analysis (%) calcd for $C_{13}H_{10}N_2$: C 80.39, H 5.19, N 14.42; found: C 80.32, H 5.15, N 14.36. 500 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$): 8.16 (1H, dd, 7.5, 1.4), 7.65 (2H, dd, 7.5, 1.5), 7.42 (2H, t, 7.4), 7.38 – 7.30 (2H, m), 7.27 (1H, d, 1.4 s), 6.89 (1H, td, 7.5, 1.6), 6.69 (1H, td, 7.5, 1.4).126 MHz^{13}C NMR (δ, $CDCl_3$):133.43, 131.63, 130.21, 130.11, 129.17, 128.93, 128.52, 128.16, 121.54, 120.35, 119.12, 119.06, 113.46.

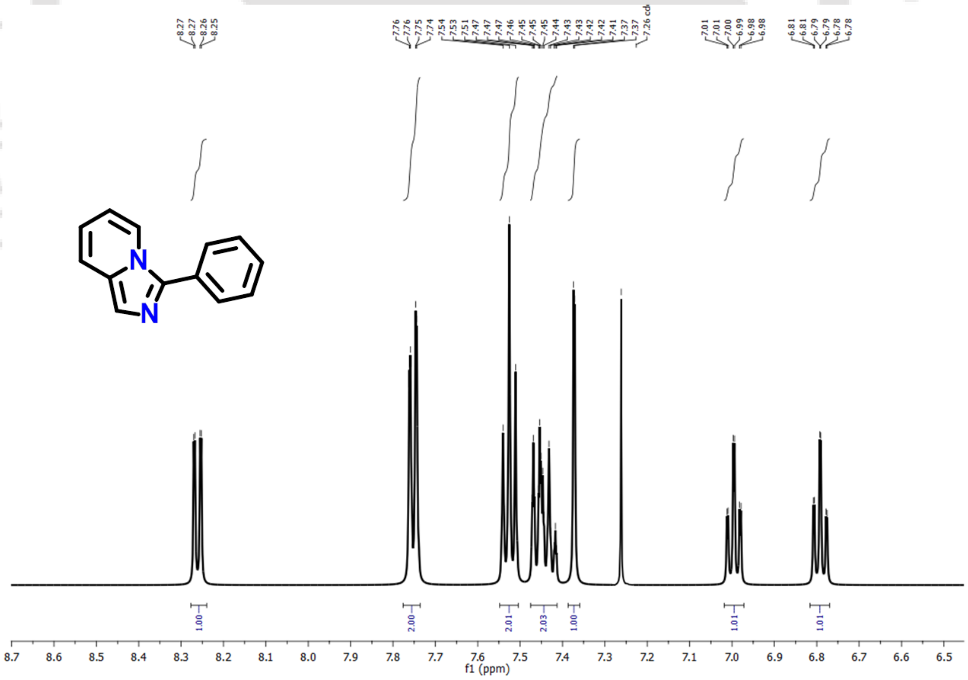


Figure 5.1. ^{1}H NMR spectrum of **PA-1**.

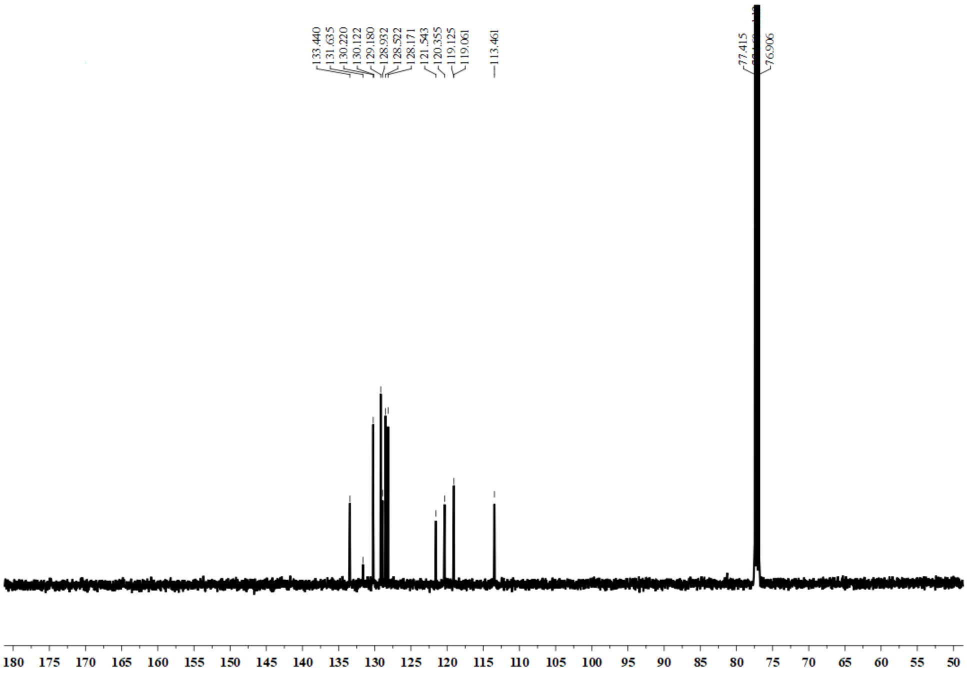
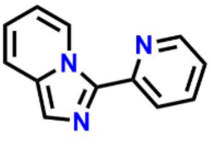


Figure 5.2. ^{13}C NMR spectrum of **PA-1**.

All other compounds were synthesized by following the same procedure by using appropriate aldehydes. Spectral data are given below:

3-(2-Pyridyl)imidazo[1,5-*a*]pyridine(PA-2)

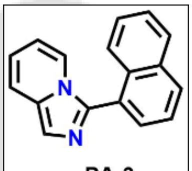
Yield: 0.208 g (77%). ESI-MS: *m*/*z* calcd for $C_{12}H_9N_3$ 195.080; found (M^++H) 196.086. Elemental analysis (%) calcd for $C_{12}H_9N_3$: C 73.83, H 4.65, N 21.52; found: C 73.86, H 4.60, N 21.46. 500 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$):9.96 (1H, ddd, 7.3, 2.0, 1.0), 8.64 (1H, ddd, 4.9, 1.8, 0.9), 8.35 (1H, dt, 8.1, 1.0), 7.78 (1H, ddd, 8.1, 7.5, 1.8), 7.60 (1H, d, 0.7 s), 7.54 (1H, dt, 9.1, 1.2), 7.20 (1H, ddd, 7.5, 4.9, 1.2), 6.87 (1H, ddd, 9.0, 6.4, 1.0), 6.74 (1H, ddd, 7.6, 6.5, 1.3).126 MHz ^{13}C NMR (δ, $CDCl_3$): 151.15, 148.28, 136.71, 135.48, 133.03, 126.17, 121.90, 121.77, 120.97, 120.36, 118.15, 113.75.



PA-2

3-(Naphthalen-1-yl)imidazo[1,5-*a*]pyridine(PA-3)

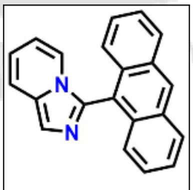
Yield: 0.271 g (80%).mp: 175 °C. ESI-MS: *m*/*z* calcd for $C_{17}H_{12}N_2$ is 244.100 found (M^++H) 245.107.Elemental analysis (%) calcd for $C_{17}H_{12}N_2$: C 83.58, H 4.95, N 11.47; found: C 83.52, H 4.90, N 11.41.500 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$):8.39 (1H, dd, 7.3, 1.0), 8.26 (1H, d, 0.7), 7.99 (1H, d, 8.5), 7.95 – 7.88 (3H, m), 7.61 (1H, d, 0.7), 7.57 – 7.49 (3H, m), 6.76 (1H, ddd, 9.1, 6.3, 0.8), 6.60 (1H, ddd, 7.4, 6.4, 1.2).126 MHz ^{13}C NMR (δ, $CDCl_3$):138.40, 133.50, 133.29, 131.94, 128.95, 128.37, 127.98, 127.92, 126.84, 126.79, 126.78, 125.85, 121.64, 121.05, 119.06, 119.04, 113.40.



PA-3

3-(Anthracen-9-yl)imidazo[1,5-*a*]pyridine(PA-4)

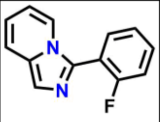
Yield: 0.347 g (85%). mp: 146°C. ESI-MS: *m*/*z* calcd for $C_{21}H_{14}N_2$ is 294.116 found (M^++H) 295.124. Elemental analysis (%) calcd for $C_{21}H_{14}N_2$: C 85.69, H 4.79, N 9.52; found: C 85.60, H 4.75, N 9.48.500 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$):8.65 (1H, s), 8.10 (2H, d, 8.5), 7.84 (1H, d, 0.7), 7.63 (1H, dt, 9.2, 1.1), 7.52 – 7.46 (2H, m), 7.44 – 7.35 (4H, m), 7.15 (1H, dd, 7.2, 1.0), 6.78 (1H, ddd, 9.2, 6.3, 0.9), 6.39 (1H, ddd, 7.3, 6.4, 1.1).126 MHz ^{13}C NMR (δ, $CDCl_3$):161.05, 159.06, 148.55, 133.65, 132.34, 132.32, 131.89, 131.02, 130.95, 125.01, 124.98, 122.49, 122.44, 121.00, 119.19, 118.54, 118.44, 118.32, 116.37, 116.20, 112.97.



PA-4

3-(2-Fluorophenyl)imidazo[1,5-*a*]pyridine(PA-5)

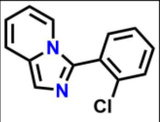
Yield: 0.212 g (72%). mp: 86°C. ESI-MS: *m*/*z* calcd for $C_{13}H_9FN_2$ is 212.23 found (M^++H) 213.0828. 500 MHz ^{1}H NMR (δ (J, Hz), $CDCl_3$): 7.46 – 7.43 (1H, m), 7.39 (1H, td, 7.4, 1.7), 7.16 (1H, d, 9.1), 7.14 – 7.09 (1H, m), 7.01 – 6.84 (1H, m), 6.43 (1H, dd, 9.1, 6.4), 6.27 – 6.23 (1H, m).126 MHz ^{13}C NMR (δ, $CDCl_3$):152.228, 137.02, 133.40, 133.30, 131.05, 131.03, 127.80, 124.33, 122.26, 120.07, 119.12, 118.56, 112.73.



PA-5

3-(2-Chlorophenyl)imidazo[1,5-*a*]pyridine(PA-6)

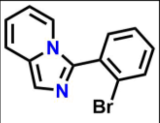
Yield: 0.232 g (73%). ESI-MS: *m/z* calcd for $C_{13}H_9ClN_2$ is 228.68 found (M^++H) 229.0545. 500 MHz ^1H NMR (δ (J, Hz), $CDCl_3$): 7.62 – 7.56 (3H, m), 7.54 – 7.48 (2H, m), 7.44 – 7.37 (2H, m), 6.75 (1H, dd, 9.1, 6.4), 6.55 (1H, t, 6.8). 126 MHz ^{13}C NMR (δ, $CDCl_3$):135.82, 134.33, 133.14, 131.22, 130.74, 130.07, 129.56, 127.23, 122.26, 120.29, 119.07, 118.50, 112.69.



PA-6

3-(2-Bromophenyl)imidazo[1,5-*a*]pyridine (PA-7)

Yield: 0.288 g (76%). ESI-MS: *m/z* calcd for $C_{13}H_9BrN_2$ is 273.13 found (M^++H) 274.9957. 500 MHz ^1H NMR (δ (J, Hz), $CDCl_3$):7.73 (1H, dd, 8.1, 1.1), 7.61 – 7.57 (2H, m), 7.56 (1H, dd, 7.6, 1.7), 7.51 (1H, dt, 9.2, 1.1), 7.46 (1H, td, 7.5, 1.2), 7.38 – 7.34 (1H, m), 6.77 (1H, ddd, 9.2, 6.4, 0.9), 6.57 (1H, ddd, 7.4, 6.5, 1.1). 126 MHz ^{13}C NMR (δ, $CDCl_3$):137.02, 133.40, 133.30, 131.67, 131.05, 131.03, 127.80, 124.33, 122.26, 120.07, 119.12, 118.56, 112.73.

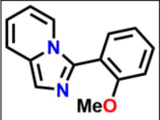


PA-7

3-(2-Methoxyphenyl)imidazo[1,5-*a*]pyridine (PA-8)

Yield: 0.220 g (71%). ESI-MS: *m/z* calcd for $C_{14}H_{12}N_2O$ is 224.26 found (M^++H) 225.10. 500 MHz ^1H NMR (δ (J, Hz), $CDCl_3$): 7.61 (2H, ddt, 6.1, 4.0, 1.4), 7.57 (1H, d, 1.0), 7.51 – 7.44 (2H, m), 7.11 (1H, td, 7.5, 1.1), 7.05 (1H, dd, 8.4, 1.0), 6.73 (1H, ddd, 9.1, 6.3, 1.0), 6.51 (1H, ddd, 7.4, 6.3, 1.2), 3.81 (3H, s).126 MHz ^{13}C NMR (δ,

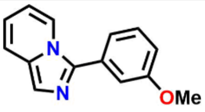
$CDCl_3$):157.40, 136.24, 132.61, 131.34, 130.81, 123.27, 121.25, 120.08, 119.33, 118.69, 118.37, 111.99, 111.29, 55.57.



PA-8

3-(3-Methoxyphenyl)imidazo[1,5-*a*]pyridine (PA-9)

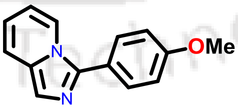
Yield: 0.224 g (72%).ESI-MS: *m/z* calcd for $C_{14}H_{12}N_2O$ is 224.26 found (M^++H) 225.11. 500 MHz ^1H NMR (δ (J, Hz), $CDCl_3$):8.29 (1H, dd, 1.0, 7.2), 7.55 (1H, d, 0.6), 7.48 (1H, td, 1.1, 9.1), 7.44 - 7.40 (1H, m), 7.39 - 7.34 (1H, m), 6.98 (1H, ddd, 1.1, 2.6, 8.2), 6.72 (1H, ddd, 0.8, 6.3, 9.1), 6.56 (1H, ddd, 1.1, 6.3, 7.3), 3.88 (3H, s). 126 MHz ^{13}C NMR (δ, $CDCl_3$): 160.23, 138.22, 131.78, 130.06, 121.71, 120.65, 120.04, 118.94, 114.95, 113.40, 113.23, 55.57.



PA-9

3-(4-Methoxyphenyl)imidazo[1,5-*a*]pyridine(PA-10)

Yield: 0.230 g (74%). ESI-MS: *m/z* calcd for $C_{14}H_{12}N_2O$ is 224.26 found (M^++H) 225.10. 500 MHz ^1H NMR (δ (J, Hz), $CDCl_3$):8.17 (1H, d, 7.3), 7.73 – 7.68 (2H, m), 7.51 (1H, s), 7.45 (1H, d, 9.1), 7.06 – 7.01 (1H, m), 6.68 (1H, dd, 9.1, 6.3), 6.52 (1H, dd, 10.0, 3.6), 3.87 (3H,s). 126 MHz ^{13}C NMR (δ, $CDCl_3$):159.97, 138.35, 131.38, 129.52, 123.01, 121.46, 120.29, 118.88, 118.56, 114.52, 112.95, 55.48.

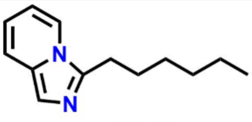


PA-10

3-Hexylimidazo[1,5-*a*]pyridine(PA-11)

Yield: 0.187 g (67%). ESI-MS: *m/z* calcd for $C_{13}H_{18}N_2$ is 202.14 found (M^++H) 203.15. 500 MHz ^1H NMR (δ (J, Hz), $CDCl_3$): 8.90 (1H, d, 4.5), 8.01 (1H, d, 7.9), 7.97 (1H, dd, 7.6, 1.7), 7.49 (1H, dd, 4.9, 1.1), 7.48 (1H, s), 2.71 – 2.63 (2H, m), 1.90 (2H,dt, 14.9, 7.4), 1.58 (6H, dt, 7.2, 3.7), 1.13 (3H, t, 7.0).126 MHz ^{13}C NMR (δ,

$CDCl_3$):152.39, 149.93, 142.73, 136.87, 124.02, 123.29, 118.47, 115.58, 36.46, 31.01, 27.87, 22.48, 14.08.



PA-11

References

[1] F. Shibahara, E. Yamaguchi, A. Kitagawa, A. Imai and T. Murai, *Tetrahedron*, 2009, **65**, 5062–5073.

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[3] K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, 1973, **95**, 2697–2699.

[4] D. M. Freudendahl, S. Santoro, S. A. Shahzad, C. Santi and T. Wirth, *Angew. Chem. Int. Ed.*, 2009, **48**, 8409–8411.

[5] C. K. Banks and C. S Hamilton, *J. Am. Chem. Soc.*, 1940, **62**, 1859–1860.

[6] L. Yu, H. Li, X. Zhang, J. Ye, J. Liu, Q. Xu and M. Lautens, *Org. Lett.*, 2014, **16**, 1346–1349.

Annexure

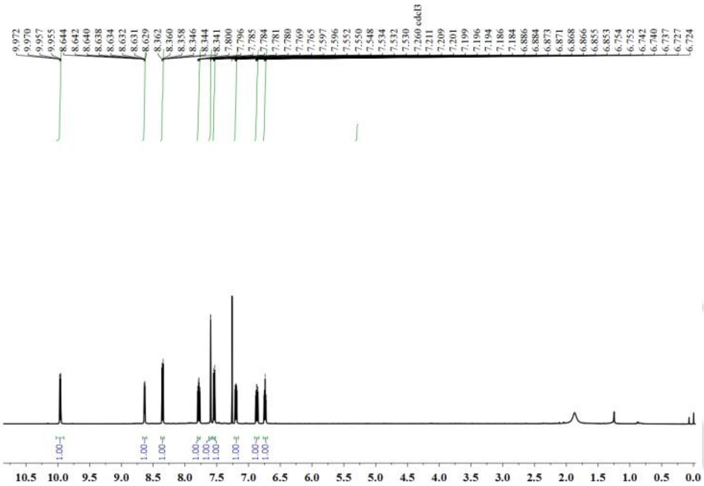


Figure 5.3. ^{1}H NMR spectrum of **PA-2**.

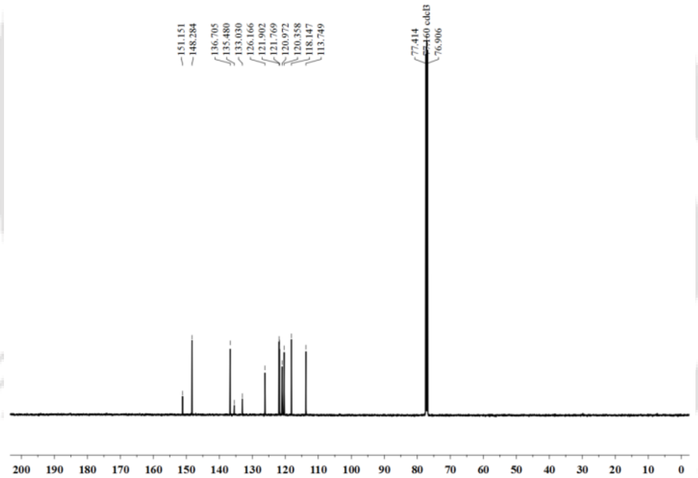


Figure 5.4. ^{13}C NMR spectrum of **PA-2**.

Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N
196.0860	196.0875	-1.5	-7.6	9.5	C12 H10 N3	12	10	3
	196.0623	23.7	120.9	10.5	C10 H6 N5	10	6	5
	196.1126	-26.6	-135.7	8.5	C14 H14 N	14	14	1

196_24082018_187_3352 400 (3.486)
1: TOF MS ES+

Figure 5.5. ESI mass spectrum of **PA-2**.

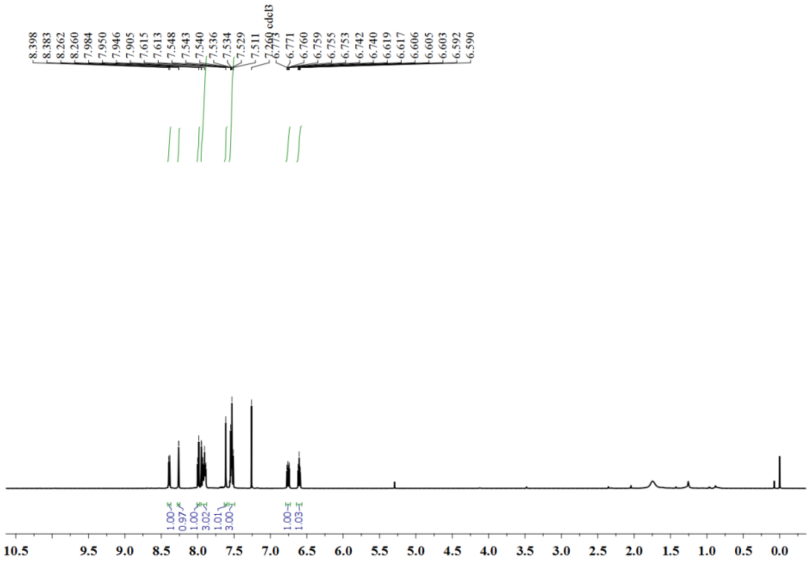


Figure 5.6. ^{1}H NMR spectrum of **PA-3**.

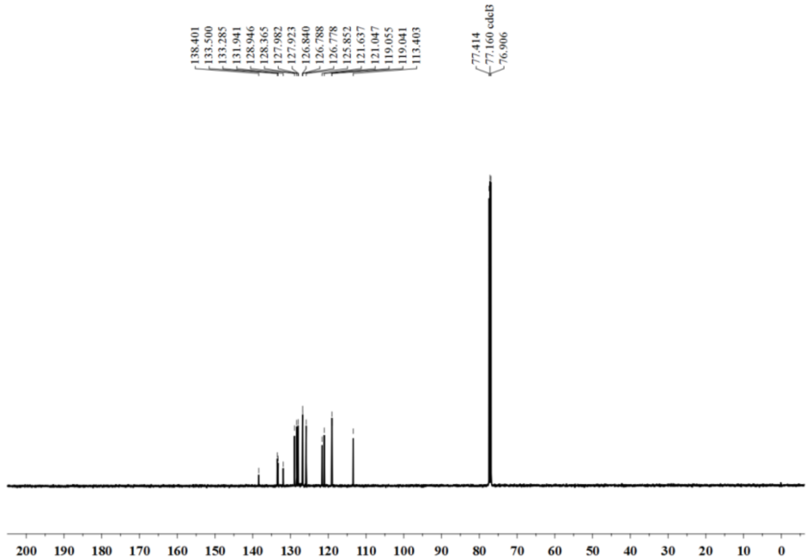
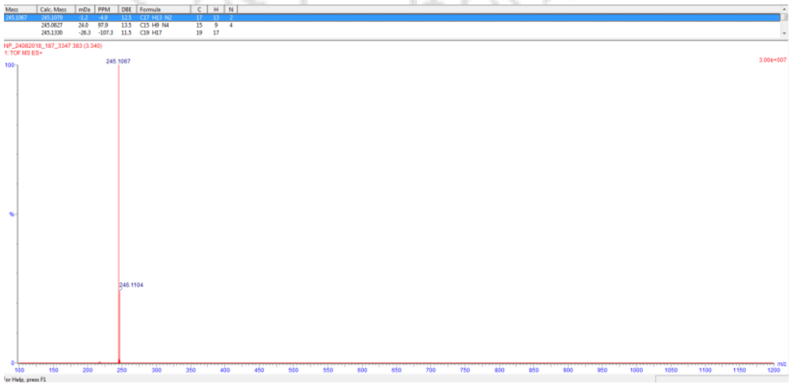


Figure 5.7. ^{13}C NMR spectrum of **PA-3**.



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N
245.1067	245.1079	-1.2	-4.9	12.5	C17 H13 N2	17	13	2
	245.0827	24.0	97.9	13.5	C15 H9 N4	15	9	4
	245.1330	-26.3	-107.3	11.5	C19 H17	19	17	

NP_24082018_187_3347 383 (3.340)
1: TOF MS ES+

Figure 5.8. ESI mass spectrum of **PA-3**.

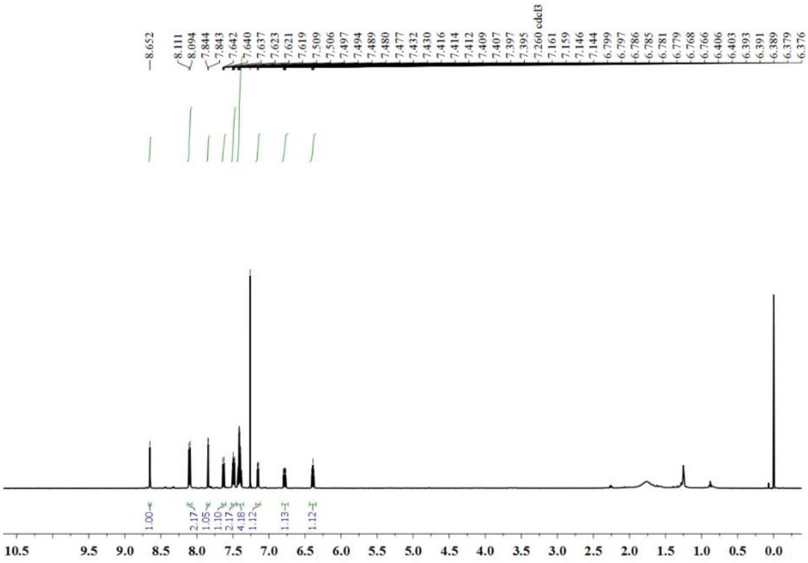


Figure 5.9. ^{1}H NMR spectrum of **PA-4**.

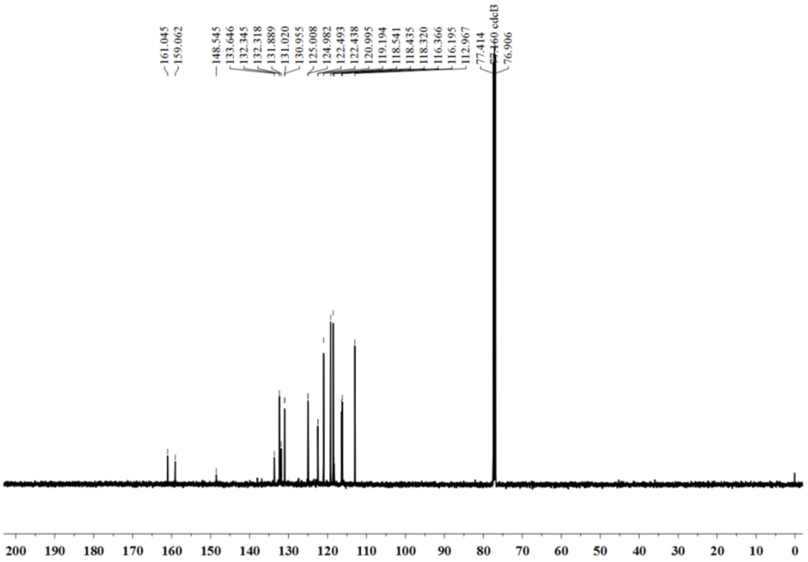
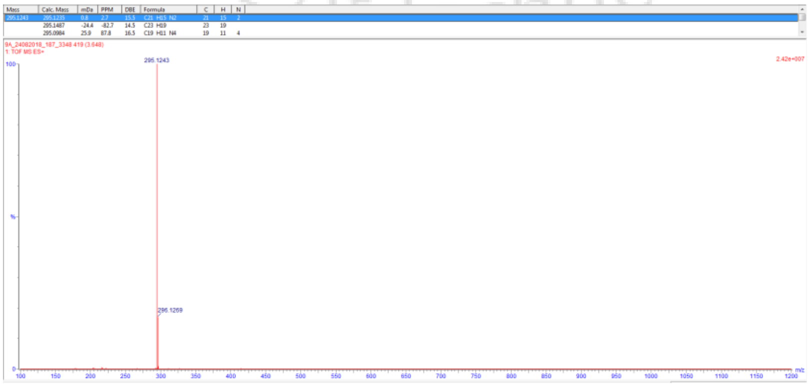


Figure 5.10. ^{13}C NMR spectrum of **PA-4**.



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N
295.1243	295.1235	0.8	2.7	15.5	C21 H15 N2	21	15	2
	295.1487	-24.4	-82.7	14.5	C23 H19	23	19	
	295.0984	25.9	87.8	16.5	C19 H11 N4	19	11	4

Figure 5.11. ESI mass spectrum of **PA-4**.

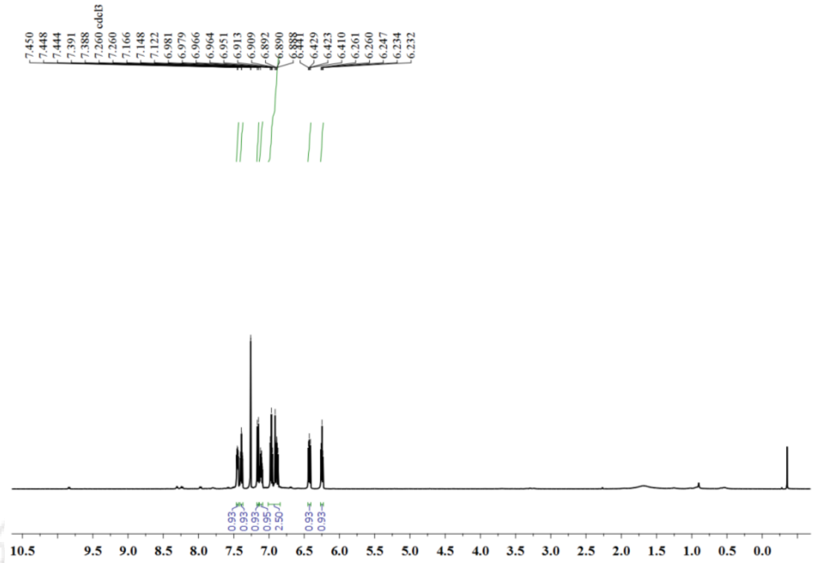


Figure 5.12. ^{1}H NMR spectrum of **PA-5**.

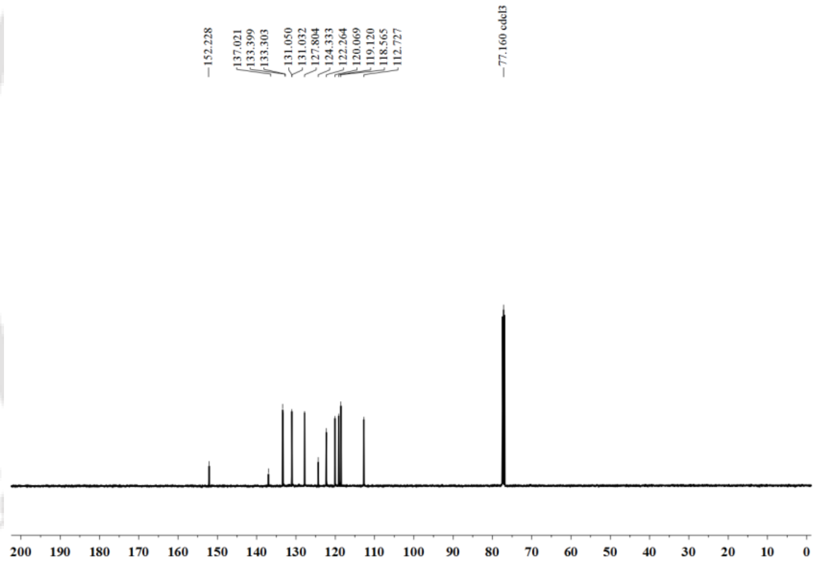
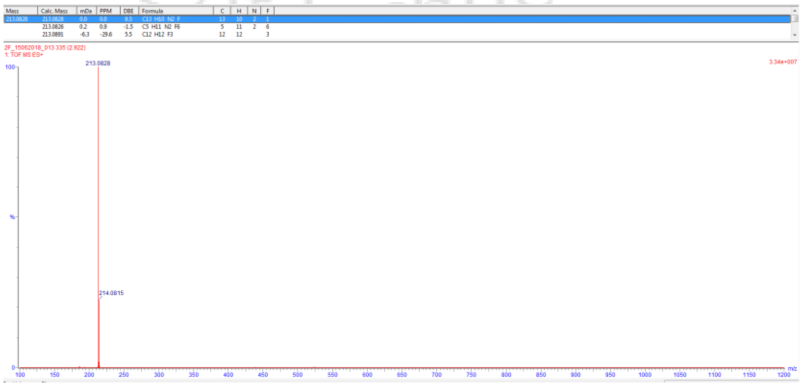


Figure 5.13. ^{13}C NMR spectrum of **PA-5**.



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N	F
213.0828	213.0828	0.0	0.0	9.5	C13 H10 N2 F	13	10	2	1
	213.0826	0.2	0.9	-1.5	C5 H11 N2 F6	5	11	2	6
	213.0891	-6.3	-29.6	5.5	C12 H12 F3	12	12		3

2F_15062018_013 335 (2.922)
1: TOF MS ES+

Figure 5.14. ESI mass spectrum of **PA-5**.

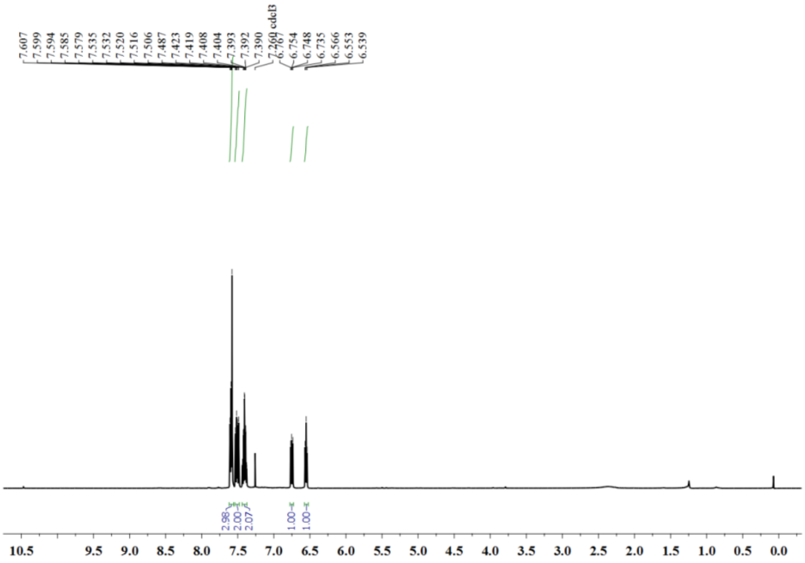


Figure 5.15. ^{1}H NMR spectrum of **PA-6**.

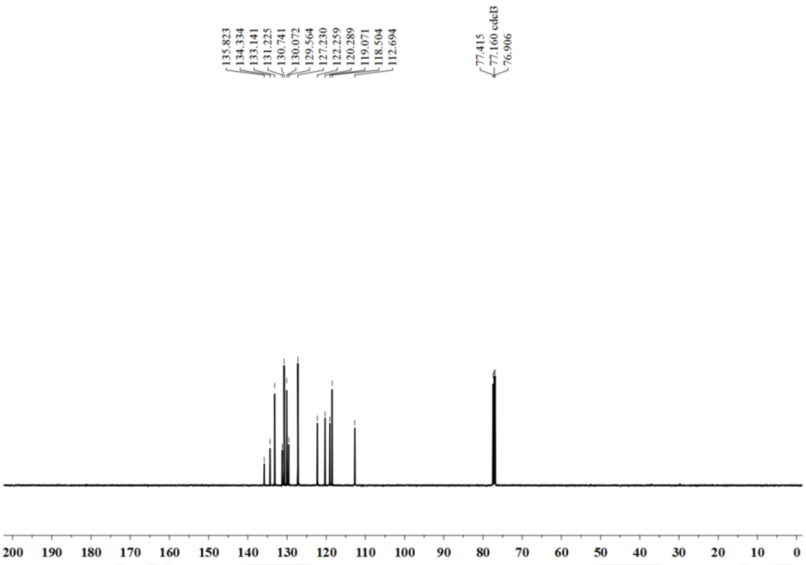


Figure 5.16. ^{13}C NMR spectrum of **PA-6**.

Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N	Cl
229.0545	229.0551	-0.6	-2.6	4.5	C12 H15 Cl2	12	15		2
	229.0533	1.2	5.2	9.5	C13 H10 N2 Cl	13	10	2	1
	229.0514	3.1	13.5	14.5	C14 H5 N4	14	5	4	

Figure 5.17. ESI mass spectrum of **PA-6**.

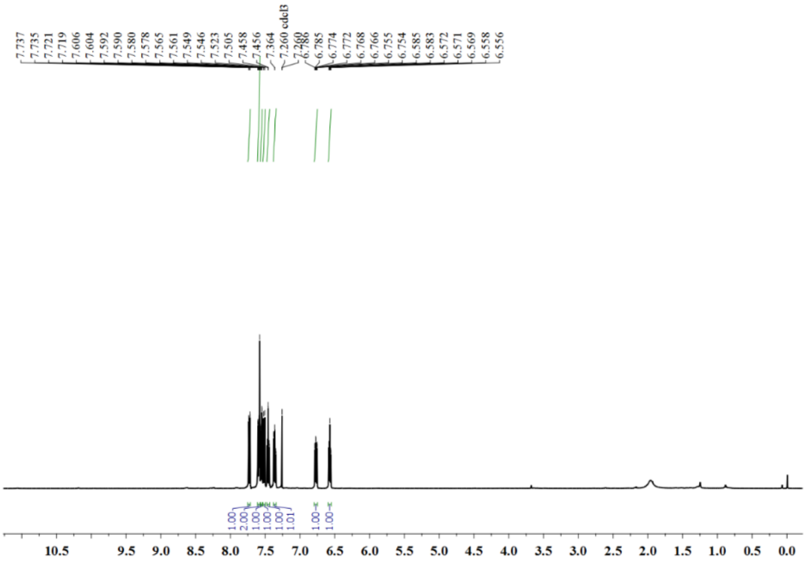


Figure 5.18. ^{1}H NMR spectrum of **PA-7**.

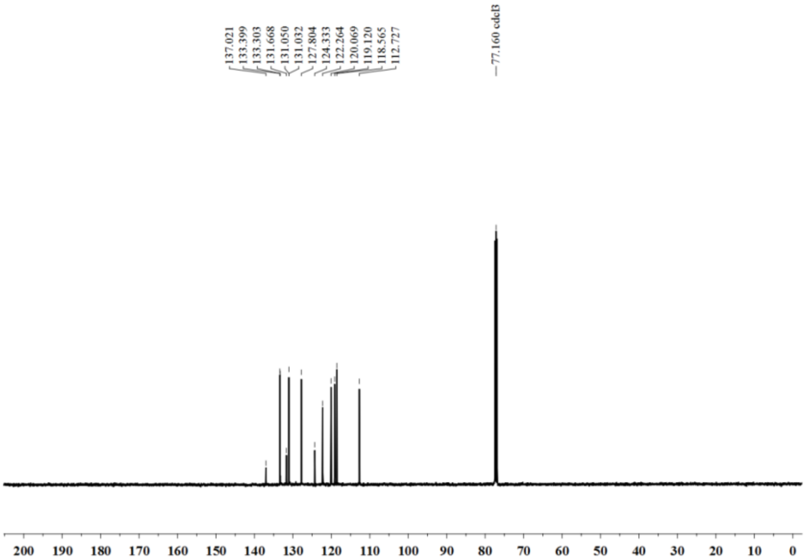


Figure 5.19. ^{13}C NMR spectrum of **PA-7**.

Figure 5.20. ESI mass spectrum of **PA-7**.

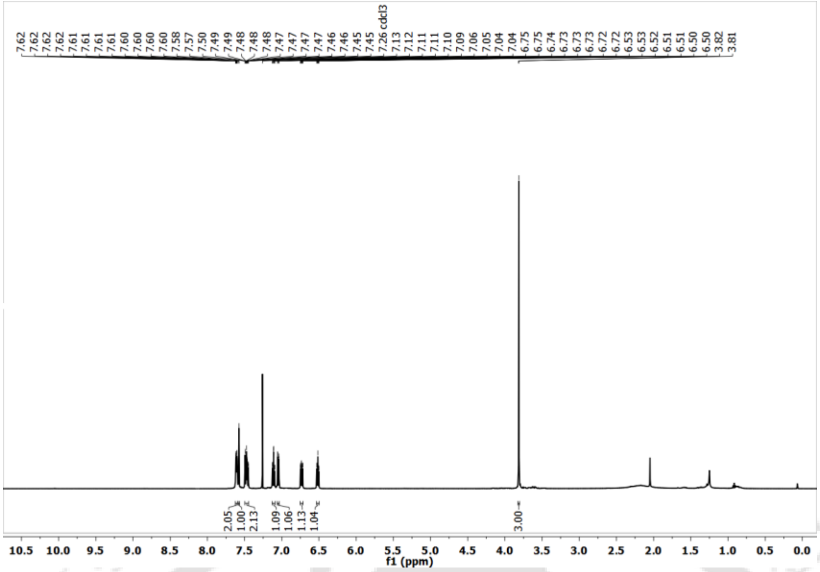


Figure 5.21. ^{1}H NMR spectrum of **PA-8**.

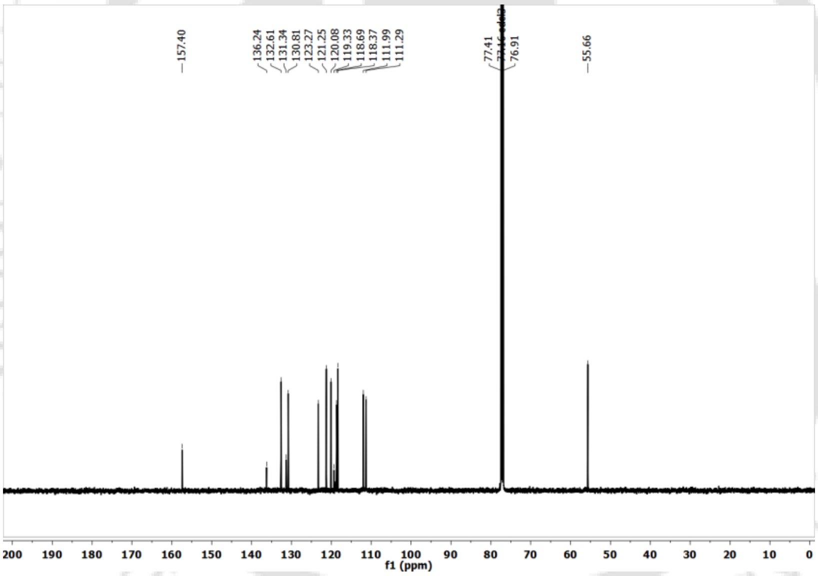
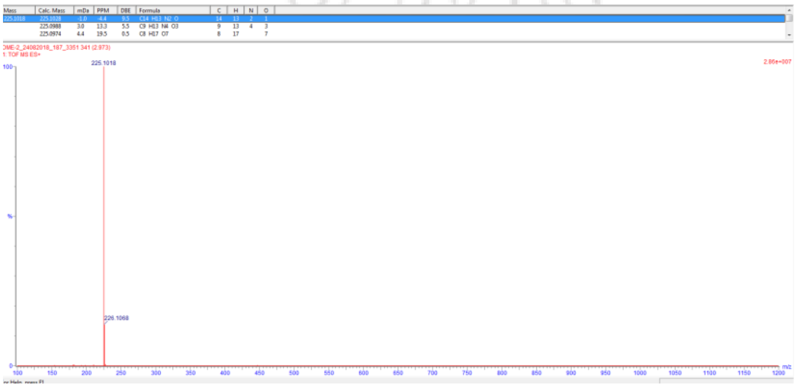


Figure 5.22. ^{13}C NMR spectrum of **PA-8**.



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N	O
225.1018	225.1028	-1.0	-4.4	9.5	C14 H13 N2 O	14	13	2	1
	225.0988	3.0	13.3	5.5	C9 H13 N4 O3	9	13	4	3
	225.0974	4.4	19.5	0.5	C8 H17 O7	8	17		7

Figure 5.23. ESI mass spectrum of **PA-8**.

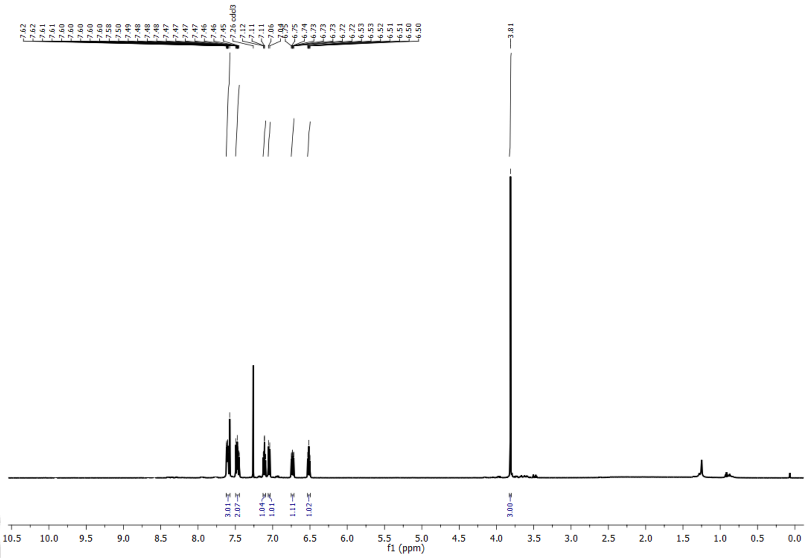


Figure 5.24. ^{1}H NMR spectrum of **PA-9**.

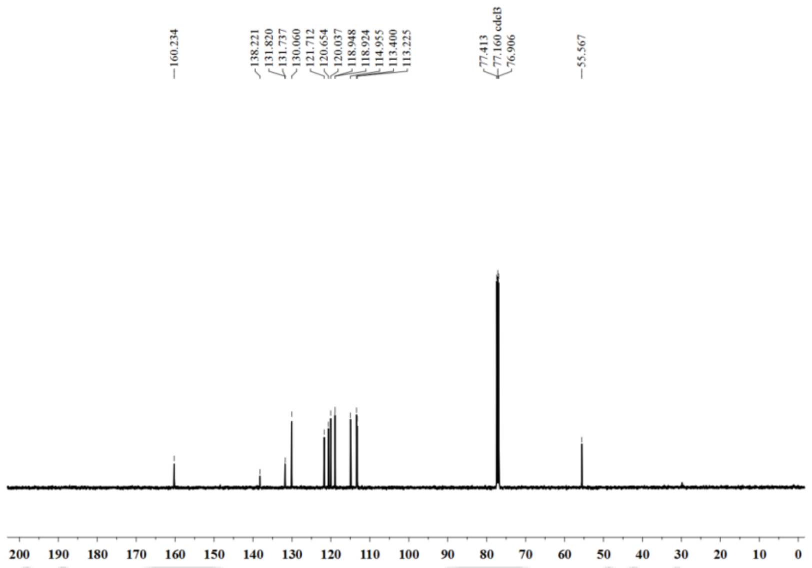
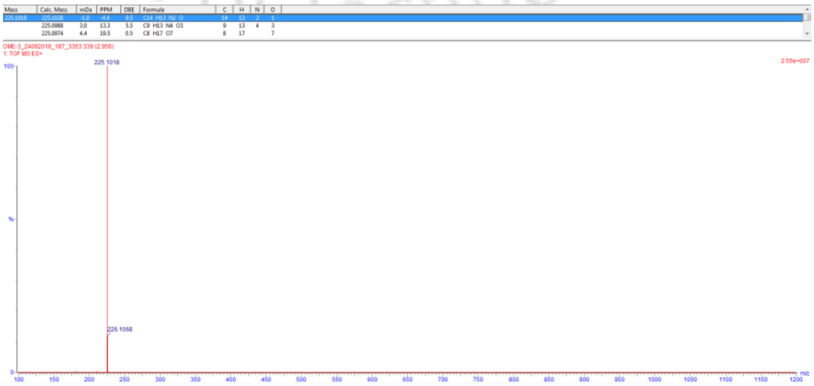


Figure 5.25. ^{13}C NMR spectrum of **PA-9**.



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N	O
225.1018	225.1028	-1.0	-4.4	9.5	C14 H13 N2 O	14	13	2	1
	225.0988	3.0	13.3	5.5	C9 H13 N4 O3	9	13	4	3
	225.0974	4.4	19.5	0.5	C8 H17 O7	8	17		7

OME-3_24082018_187_3353 339 (2.956)
1: TOF MS ES+

Figure 5.26. ESI mass spectrum of **PA-9**.

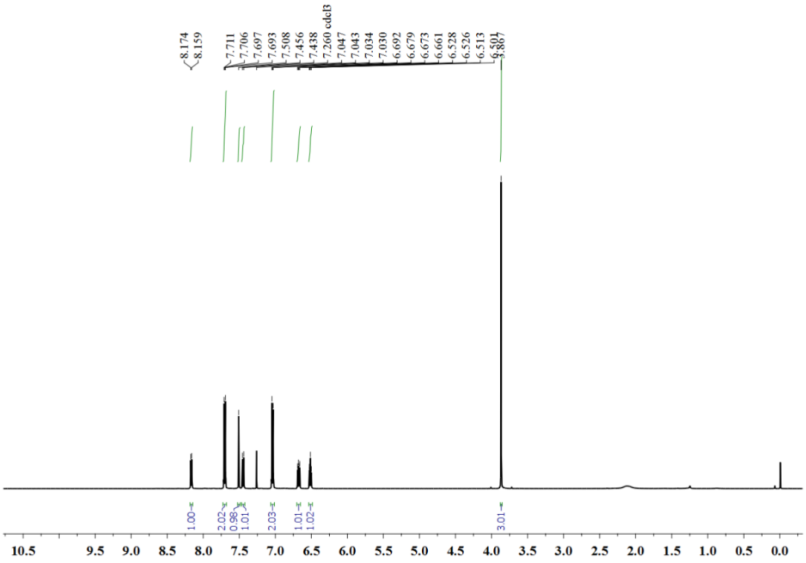


Figure 5.27. ^{1}H NMR spectrum of **PA-10**.

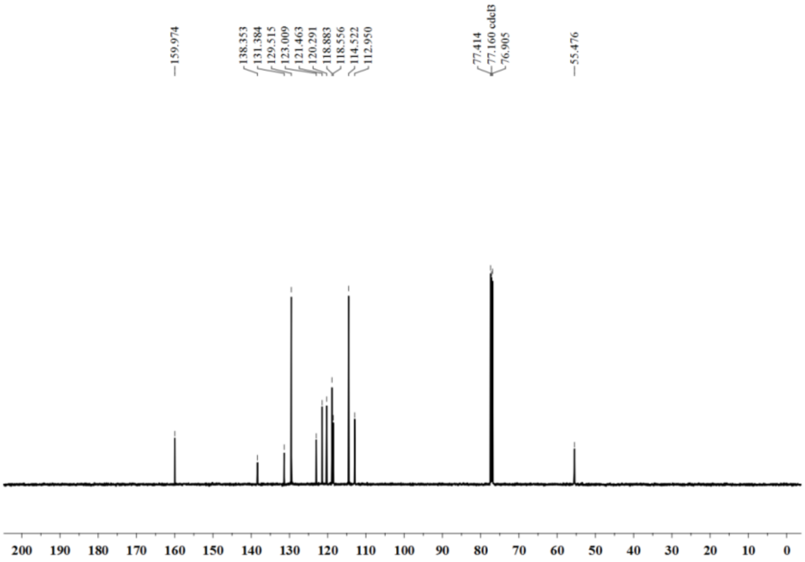
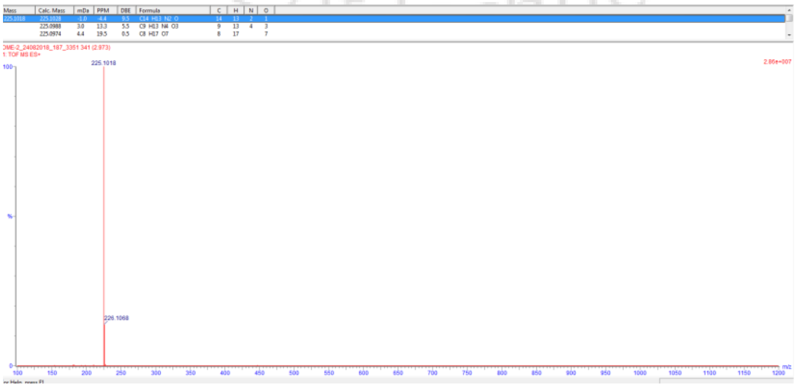


Figure 5.28. ^{13}C NMR spectrum of **PA-10**.



Mass	Calc. Mass	mDa	PPM	DBE	Formula	C	H	N	O
225.1018	225.1028	-1.0	-4.4	9.5	C14 H13 N2 O	14	13	2	1
	225.0988	3.0	13.3	5.5	C9 H13 N4 O3	9	13	4	3
	225.0974	4.4	19.5	0.5	C8 H17 O7	8	17		7

Figure 5.29. ESI mass spectrum of **PA-10**.

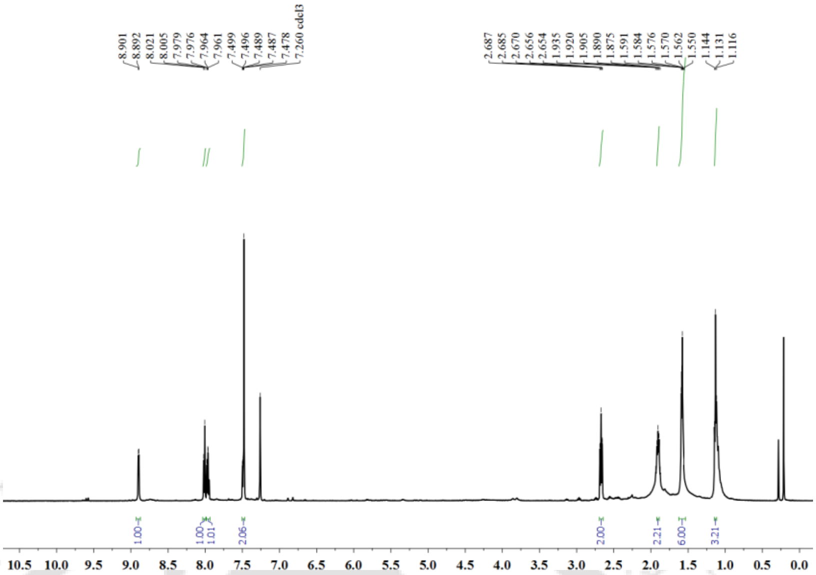


Figure 5.30. ^{1}H NMR spectrum of **PA-11**.

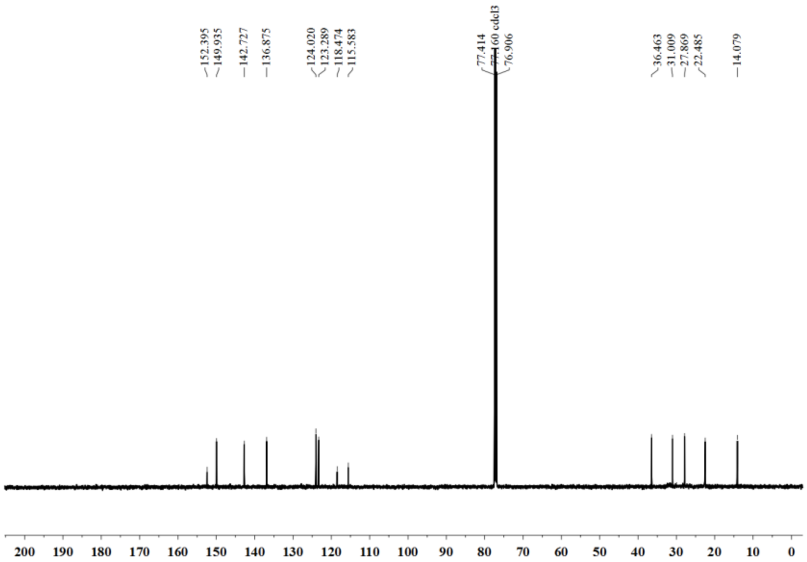
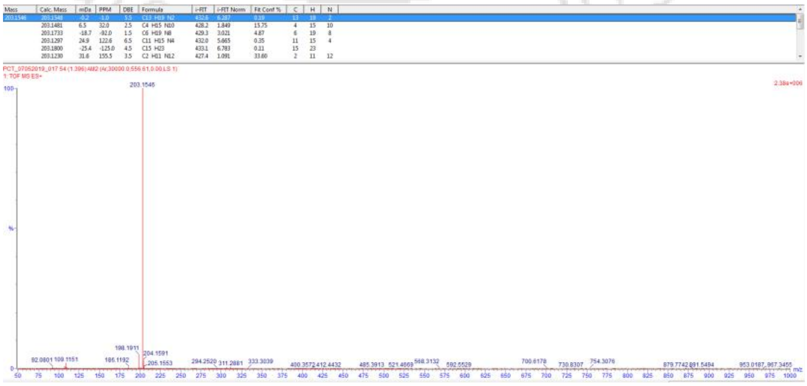


Figure 5.31. ^{13}C NMR spectrum of **PA-11**.



Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N
203.1546	203.1548	-0.2	-1.0	5.5	C13 H19 N2	432.6	6.287	0.19	13	19	2
	203.1481	6.5	32.0	2.5	C4 H15 N10	428.2	1.849	15.75	4	15	10
	203.1733	-18.7	-92.0	1.5	C6 H19 N8	429.3	3.021	4.87	6	19	8
	203.1297	24.9	122.6	6.5	C11 H15 N4	432.0	5.665	0.35	11	15	4
	203.1800	-25.4	-125.0	4.5	C15 H23	433.1	6.783	0.11	15	23	
	203.1230	31.6	155.5	3.5	C2 H11 N12	427.4	1.091	33.60	2	11	12

PCT_07062019_017 54 (1.396) AM2 (Ar,30000.0,556.61,0.00,LS 1)
1: TOF MS ES+

Figure 5.32. ESI mass spectrum of **PA-11.**

Thesis Summary and Future Perspectives

This dissertation has a total of five chapters out which Chapter 1 is a review chapter on the synthesis of pyrimidine, imidazo[1,5-*a*]pyridine amd imidazo[5,1-*a*]isoquinoline. In Chapter 2, we have described a novel synthetic method for the synthesis of 2,4,6-tris(2-pyridyl)pyrimidine (**L1**), 2,4-bis(2-pyridyl)-6-(3-pyridyl)pyrimidine (**L2**) and 2,4-bis(2-pyridyl)-6-(4-pyridyl)pyrimidine (**L3**) by reacting respective acetylpyridines, sodium hydroxide and 2-cyanopyridine. The coordination chemistry of 2,4,6-tris(2-pyridyl)pyrimidine (**L1**) was also revealed towards Co(II), Ni(II) by synthesizing the complexes of composition $[Ni(\mathbf{L1})(H_2O)_3](NO_3)_2{\cdot}4H_2O$ (**1**), $[Ni(\mathbf{L1})_2](NO_3)_2{\cdot}2H_2O$ (**2**) and $[Co(\mathbf{L1})_2](NO_3)_2{\cdot}1.5H_2O$ (**3**) where **L1** behaves as a tridentate pincer type ligand. Both **L2** and **L3** can also be used for their transition metal chemistry. Thus, it would find wide future application in synthesis as well as coordination chemistry.

In Chapter 3 we have studied the coordination chemistry of the ligand *N*-(3-(pyridine-2-yl)imidazo[1,5-*a*]pyridine-1-yl)picolinimidamide (**L4**) with nickel(II). Two binuclear metal complexes of composition $[Ni_2(\mathbf{L4})_2(Cl)_2(H_2O)_2]Cl_2{\cdot}12H_2O$ (4), and $[Ni_2(\mathbf{L4})_2(N_3)_3](N_3){\cdot}5H_2O$,(**5**) have been synthesized and structurally characterized with the nitrogen based chelating ligand (**L4**), along with coligands such as Cl^- and N_3^-. Thus, these types of nitrogen based chelating ligand would find application towards transition metal chemistry as well as catalytic chemistry.

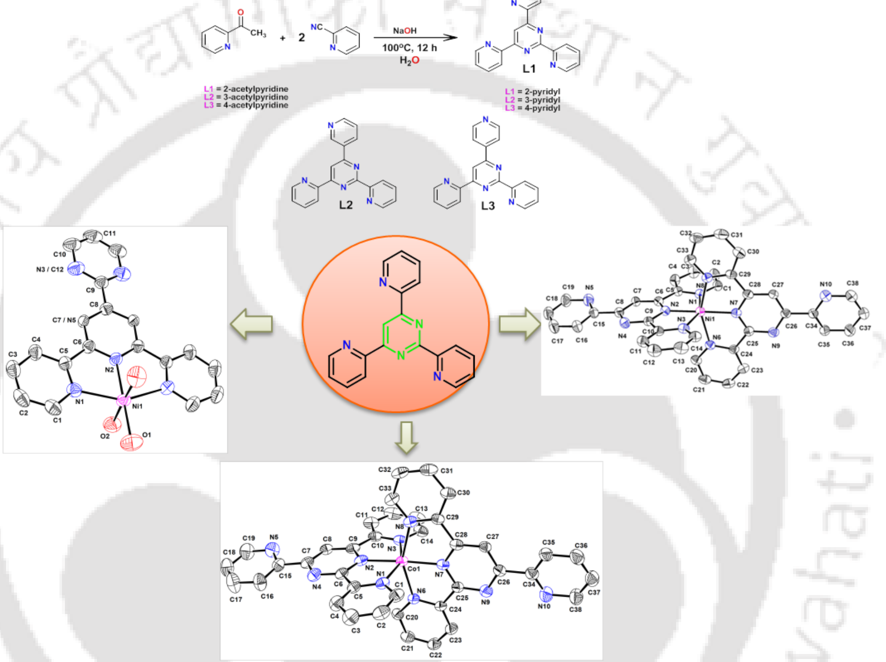
Finally, the Chapter 4 and Chapter 5, demonstrates a novel synthetic methodology towards the synthesis of imidazo[5, 1-*a*]isoquinoline and imidazo[1,5-*a*]pyridine nucleus respectively. Different kinds of aldehydes were react with respective 1-isoqunolinemethylamine and 2-picolylamine in presence of the oxidant selenium dioxide to yielded the respective products. This method is applicable to wide variety of substrates and I believe that imidazo[5,1-*a*]isoquinoline and imidazo[1,5-*a*]pyridine moiety can easily be incorporated in substrates having a aldehyde group provided other functionalities are stable towards selenium dioxide. Further, I believe, these synthesised compounds with suitably substituted groups could find their utility in various fields.

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Thesis Outlook

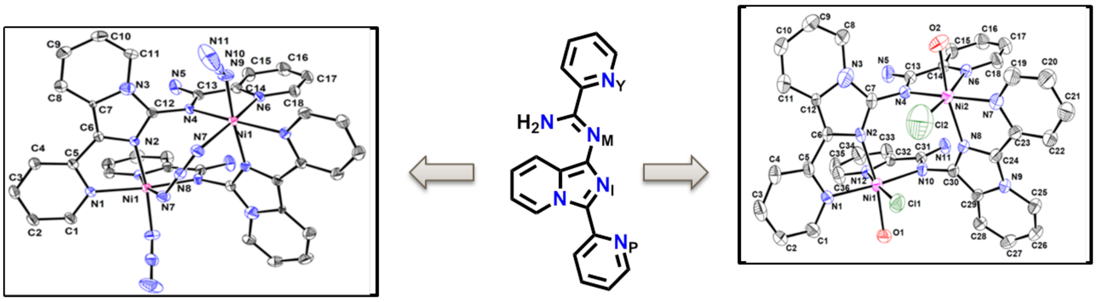
Chapter 2

A New Route for the Synthesis of 2,4-Bis(2-pyridyl)-6-(pyridyl)pyrimidines: Synthesis and Characterization of Co(II), Ni(II) Complexes of 2,4,6-Tris(2-pyridyl)pyrimidine



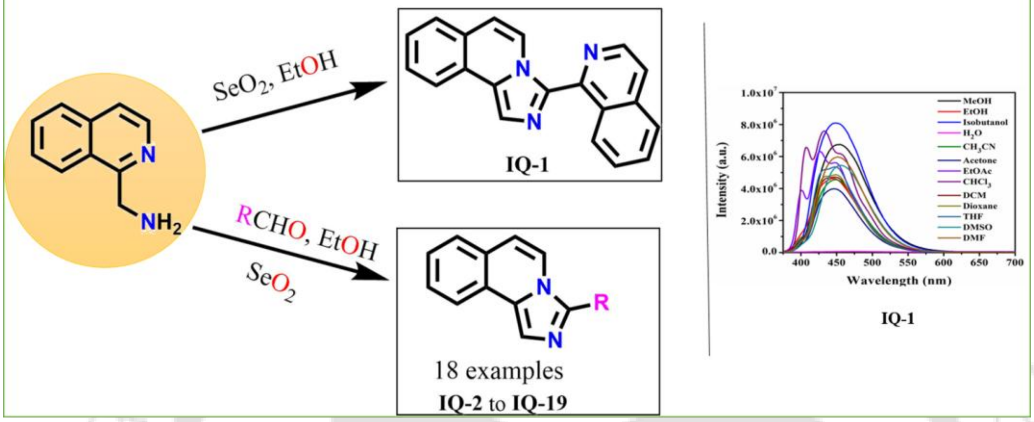
Chapter 3

Synthesis and characterization of nickel (II) complexes of N-(3-(pyridine-2-yl)imidazo[1,5-a]pyridine-1-yl)picolinimidamide



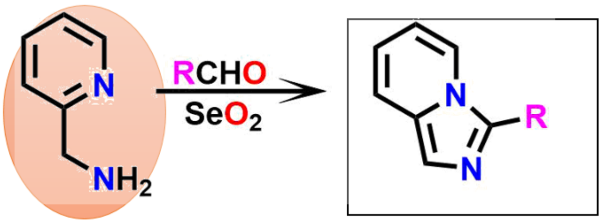
Chapter 4

Synthesis of Imidazo[5, 1-*a*]isoquinoline and Its 3-Substituted Analogues Including the Fluorescent 3-(1-Isoquinolinyl)imidazo[5,1-*a*]isoquinoline



Chapter 5

A New Synthetic Route for 3-substituted imidazo[1,5-*a*]pyridines



PA-1 to PA-11

List of Publications

1. J. Bori, N. Behera, S. Mahata and V. Manivannan, *ChemistrySelect*, 2017, **2**, 11727–11731.
2. J. Bori, S. Mahata and V. Manivannan, *Inorg. Chim. Acta* 2020, **506**, 119506.