New Avenues for the Synthesis of Some Biologically Relevant Nitrogen Containing Compounds

THESIS SUBMITTED IN PARTIAL FULFILLMENT FOR THE AWARD OF DEGREE

DOCTOR OF PHILOSOPHY

By

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Pratibha Verma

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Notations	Abbreviations
et al.	:et alia, Latin for "and others"
i.e.	:that is
e.g.	:Example
Ar	:Argon
[bmim][BF_4]	:1-butyl-3-methyl-imidazolium tetrafluoroborate
Bu^tOK	:Potassium tert-butoxide
$CHCl_3$	:Chloroform
CH_3CN	:Acetonitrile
$CMCSO_3H$	:sulfonated carboxymethylcellulose (SCMC)
chitosan@Fe_3O_4	: Chitosan supported Fe_3O_4
Cs_2CO_3	:Caesium carbonate
DCE	:Dichloroethane
DMSO	:Dimethylsulfoxide
DDQ	:2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
EDAX	:Energy dispersive X-ray
Fe_3O_4@Cu-$^{\beta}$-CD	:Fe_3O_4 particles modified by β-cyclodextrin
s-Fe_3O_4	:starch functionalized magnetite nanoparticles
EtOAc	:Ethyl acetate
Et_3N	:Triethyl amine
$Er(OTf)_3$	:Erbium((III) triflate
$FeCl_3$	:Iron(III) chloride
$FePO_4$	:Iron(III) phosphate
$H_5BW_{12}O_{40}$	:Tungstoboric acid
H_2O_2	:Hydrogen peroxide
h	:Hour(s)
I_2	:Iodine
IR	:Infrared radiation
In_2O_3	:Indium(III) oxide
KI	:Potassium iodide
$K_2S_2O_8$	:Potassium persulfate
K_2CO_3	:Potassium carbonate
$LnCl_3$	:Lanthanum chloride
MgO	:Magnesium oxide
MPMS	:Mission Planning and Monitoring System
mg	:Milligram
NH_2NH_2	:Hydrazine hydrate
NaOH	:Sodium hydroxide

NH_4OAc	:Ammonium acetate
$NH_4Fe(SO_4)_2$	:Ammonium iron(III) sulfate
$NiCl_2$	:Nickel(II) chloride
$NH_2OH.\ HCl$	:Hydroxyl amine hydrochloride
O_2	:Oxygen
P_2O_5	:Phosphorus pentoxide
P-TSA	:*p*-Toluenesulfonic acid
PEG-400	:Polyethylene glycol
P_2O_5/SiO_2	:P_2O_5 supported on SiO_2
$PhI(OAc)_2$	:2-Iodoxybenzoic acid
$[PVPH]ClO_4$	:poly(vinylpyrrolidonium) perchlorate
PCl_5	:Phosphorus pentachloride
RT	:Room temperature
$RuIII@CMC/Fe_3O_4$	:RuIII incorporated with magnetic nanosized CMC/Fe_3O_4 hybrid
$RHA[pmim]HSO_4$	:Brönsted acidic ionic liquid supported on rice husk ash
SnP_2O_7	:Tin Phosphates
SEM	:Scanning electron microscopy (SEM)
TBHP	:tert-Butyl hydroperoxide
TLC	:Thin-layer chromatography
TsOH	: *p*-Toluenesulfonic acid
TEM	:Transmission electron microscopy
TBHP	:*tert*–Butylhydroperoxide
THF	:Tetrahydrofuran
TAP-Cu	:Triazole-Phosphine-Copper
UHP	:Urea hydrogen peroxide
XRD	:X-ray diffraction (XRD) pattern
ZnO	:Zinc oxide
$ZnClO_4$	:Zinc perchlorate

Instrumentation and Materials

Melting points were measured using Buchi apparatus in open capillary tubes and are uncorrected. **IR spectra** were recorded on Perkin Elmer FT-IR Spectrophotometer. (ν_{max} expressed in cm^{-1}). **The ^{1}H and ^{13}C-NMR** spectra were recorded on Brucker-500 Avance Spectrometer in DMSO-d_6 and $CDCl_3$. Chemical shifts are given in δ ppm, using tetramethylsilane (TMS) as an internal standard. **X-ray diffraction (XRD)** patterns of dried powder samples were recorded on Rigaku Mini-X 600 (Japan) from 2θ value 10^0–90^0 (scan rate of 1^0 per min) with step size 0.02. **SEM analysis** was done by EVO - Scanning Electron Microscope MA15 / 18. Transmission electron microscopy (**TEM)** was carried out by using FEI-Tecnai-G2 electron microscope**. EDAX analysis** was analyzed by EDX (Oxford instrument; USA). **MPMS analysis** were carried out with a Quantum Design MPMS-3, over a temperature range 5–300 K and applied a magnetic field of ±2 T. **Thin-layer Chromatography (TLC)** was performed on glass plates (7.5 × 2.5 and 7.5 × 5.0 cm) coated with Merck silica gel GF 254 using various combinations of ethyl acetate and n-hexane as an eluent. Visualization of spots was accomplished either in iodine chamber or by exposure to UV light. Merck silica gel (100-200 mesh) was used for column chromatography (approximately 15-20 g per 1 g of the crude product).

All the chemicals and solvents were procured from Aldrich, USA and E. Merck, Germany and were used as received. The preparation and particulars of the substrates employed for the work undertaken are given in their respective chapters.

Preface

Nitrogen is a naturally occurring element that is essential for growth and development of both plants and animals. It is found in proteins, nucleic acids and in several other organic and inorganic compounds. A vast number of nitrogen containing heterocyclic compounds have found applications in pharmaceutical research, agriculture science and drug discovery. Nitrogen is a part of several functional groups such as amines, imines, amides, oximes etc. and biologically relevant heterocyclic compounds like pyrrole, pyridine, indole, benzimidazole, benzothaizole and benoxazole. In this context, the thesis entitled **"New Avenues for the Synthesis of Some Biologically Relevant Nitrogen Containing Compounds"** will introduce various aspects of synthesis of nitrogen containing organic compounds.

Chapter 1 will provide a general introduction and literature review of synthesis and applications of some main class of nitrogen containing organic compounds. **Chapter 2** will provide multi component synthesis of imidazopyrimidine derivatives in aqueous medium under ultrasound irradiation using starch functionalized magnetite nanoparticles as a green catalyst. **Chapter 3** will describe a facile and convenient synthetic approach for benzimidazole and benzothiazole by using UHP under solvent free conditions. **Chapter 4** will highlight the synthesis of pyrapyrazole using UHP under grinding method. **Chapter 5** will describe a simple and efficient method for the primary and secondary amide synthesis by using KI/ lactic acid catalytic system at reflux temperature.

CHAPTER 1

Over View of Nitrogen Containing Compounds

Chapter 1

Overview of Nitrogen Containing Organic Compounds

Nitrogen is a naturally occurring element that is essential structural moiety of all the living things and it is found in amino acids, nucleic acids, vitamins and hormones. They display an enormous structural diversity such as simple functional group, degrees of substitution and heterocyclic system. Nitrogen containing compounds represent as a core skeleton or exists alone in many biologically, pharmaceutically and synthetically active compounds. *N*-heterocyclic organic compounds are very important industrially, biologically and also used for the functioning of many developments in human society.

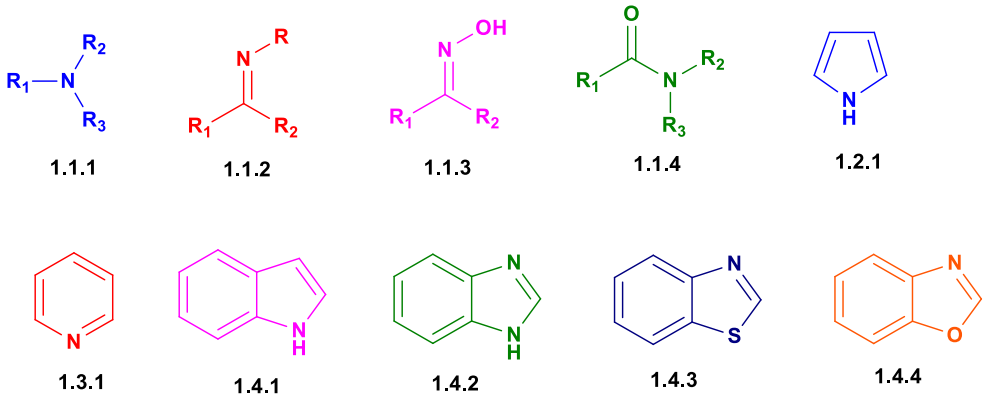


Figure 1.1 Nitrogen containing some main class of organic compounds

This chapter has covered some main class of nitrogen containing functional groups. Acyclic nitrogen containing compounds (1.1) like amine (1.1.1), imine (1.1.2), oxime (1.1.3), amides (1.1.4) and nitrogen containing five membered heterocyclic (1.2) pyrrole (1.2.1),

six membered (1.3) pyridine (1.3.1) and fused heterocycles (1.4) such as indoles (1.4.1), benzothiazoles (1.4.2) benzimidazoles (1.4.3) and benzoxazoles (1.4.4) (**Figure 1.1**).

1.1 Nitrogen containing acyclic compounds

1.1.1 Amines

Amines are the most important and widely focused organic compounds and derived from ammonia by replacing one, two or all the three protons by different carbon derivatives. Since amines are present in amino acids which involves in protein synthesis it shows that they are very important in survival of living beings. On the other hand amines are cornerstone in a variety of different industries such as dyes, drugs, surfactants, agrochemicals and plastics as auxiliaries for the rubber, textile, paper industries etc (Crozet et al. 2011).

Amines are also used in the synthesis of many drugs like Amphetamine which exists in two enantiomeric forms levoamphetamine and dextroamphetamine and are used in the treatment of attention deficit hyperactivity disorder (ADHD), obesity and narcolepsy. Chlorpheniramine is an antihistamine used to treat the symptoms of allergic conditions. Salmeterol is an adrenergic receptor agonist (LABA) used in the prevention of asthma symptoms and maintenance of chronic obstructive pulmonary disease (COPD) symptoms (**Figure 1.2**).

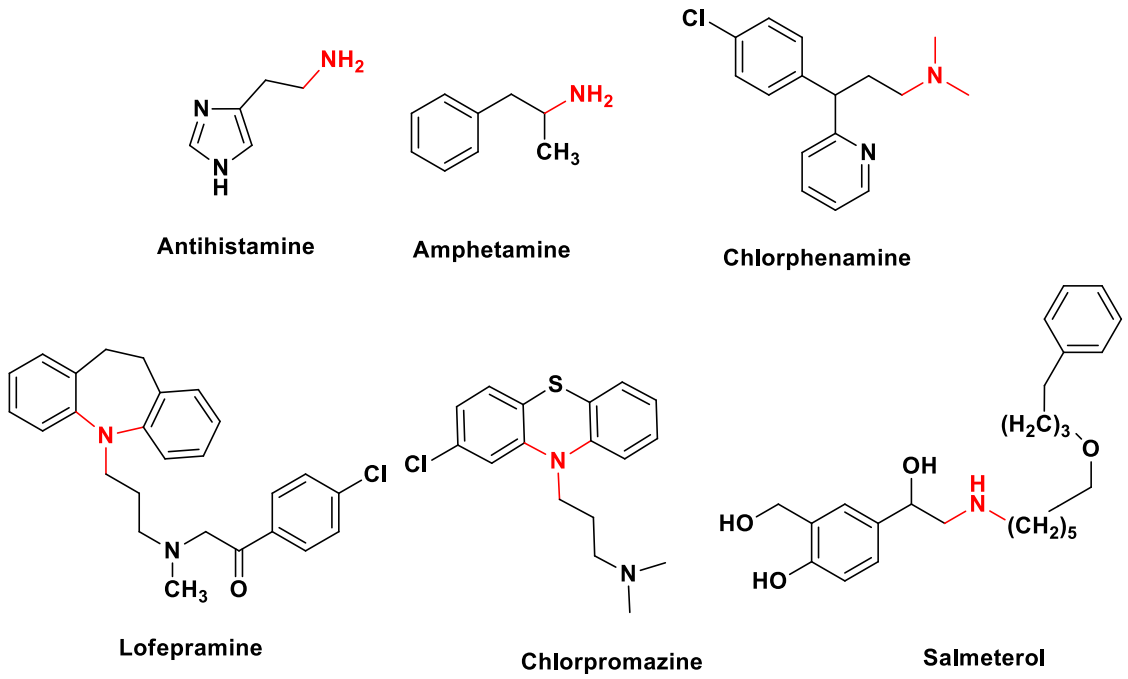
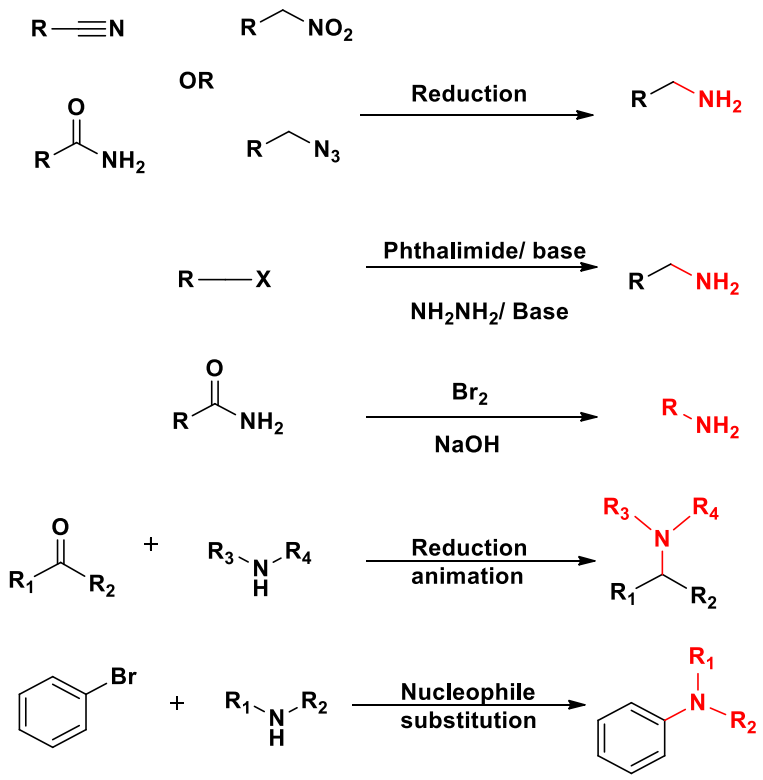


Figure 1.2 Some biological active drugs containing amine functional group

Primary amines are mainly synthesized by the reduction of amides (Bhunia et al. 2020), aliphatic and aromatic nitro compounds (Pehlivan et al. 2010, Orlandi et al. 2016, Goswamia et al. 2020), cyanides (Haddenhamet al. 2008)**,** azides (Lee et al. 2001, Lin et al. 2002) and different oximes (aldoximes and ketoximes) (Abiraj et al. 2004, Sadighnia et al. 2019) by using different reducing agents. Primary amines are also synthesized by Gabriel synthesis method, it involves the initial alkylation of potassium phthalimide to form *N*-alkyl phthalimide, which on hydrolysis provides corresponding primary amine as final product and also by Hofmann rearrangement (Loudon et al. 1984, Gibson et al. 1968).

Secondary and tertiary amines are directly prepared by the nucleophilic substitution of primary and secondary amines with the alkyl halides to give corresponding secondary and tertiary amines respectively. They are also prepared by reductive amination of aldehydes or ketones with primary and secondary amines (Varjosaari et al. 2017) (**Scheme 1.1**).



Scheme 1.1 Synthesis of primary, secondary and tertiary amines

1.1.2 Imines

An imine is a functional group, which is commonly referred to as azomethines or Schiff bases containing a carbon–nitrogen double bond and have general formula $R_2C=NR$, when R = H, the compound is a primary imine, when R is hydrocarbyl, the compound is a secondary imine. The term "imine" was coined by the German chemist Albert Ladenburg in 1883. Imines and its derivative have been documented as key intermediates for synthesizing nitrogen containing biologically active heterocycles and alkaloid (Martin 2009, Dai et al. 1999) (**Figure 1.3**).

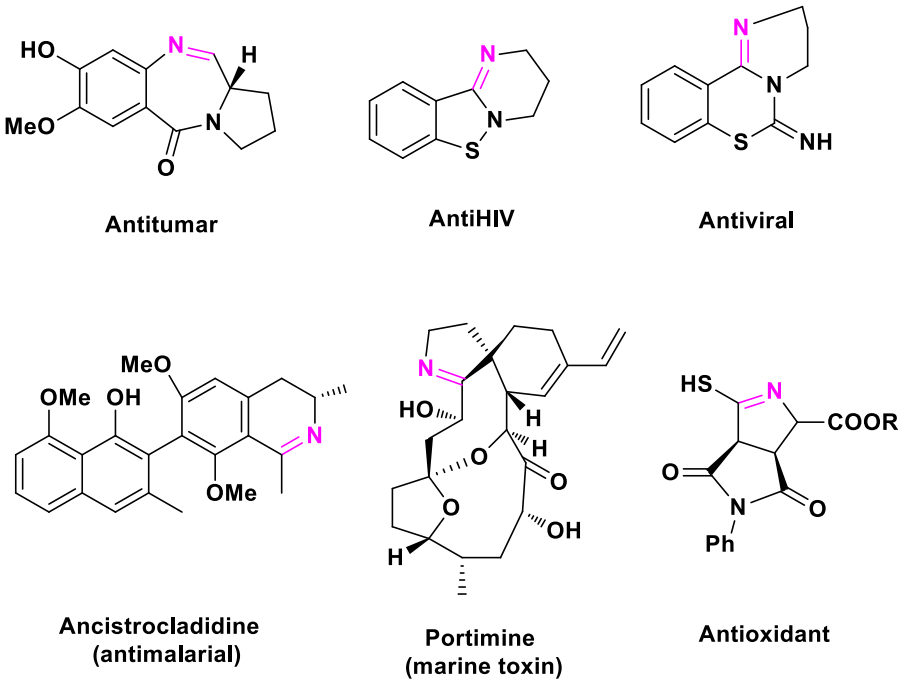
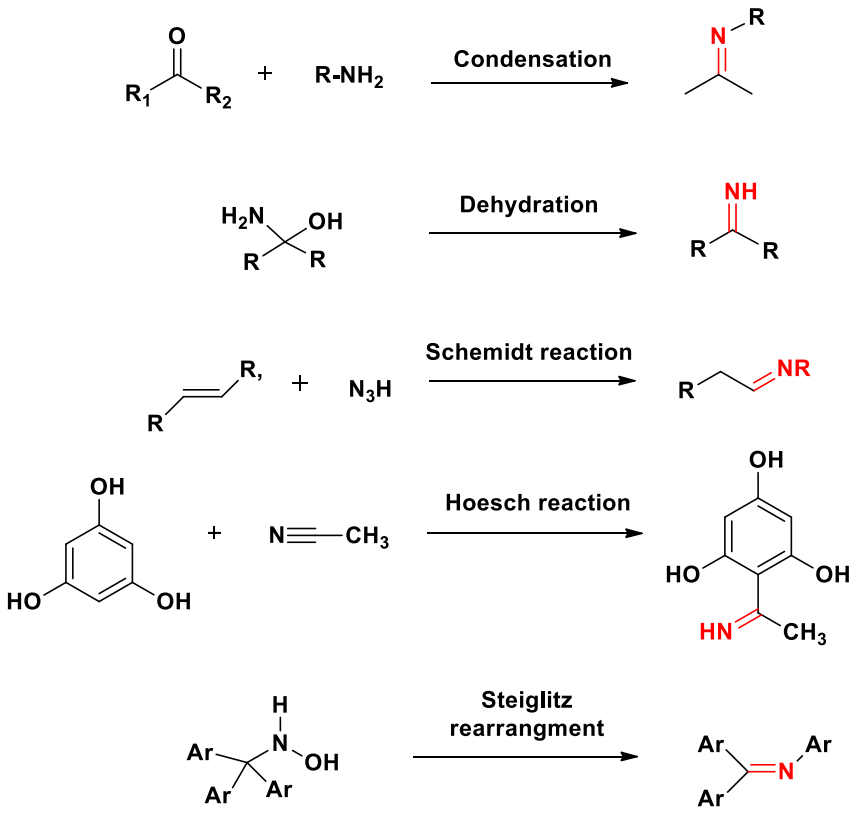


Figure 1.3 Some biological active drugs containing imine functional group

Traditionally primary imines are synthesized by condensation reaction of aldehydes with primary amines (Baruah et al. 2017, Ali et al. 2013). Secondary imines can be synthesized by condensation of ketones, which is less common due to low reactivity of ketones. Some other methods are also known like dehydration of hemiaminals (Shu et al. 2019), Stieglitz rearrangement in which trityl hydroxylamine (Ar_3CNHOH) rearranges to a triaryl imine**,** in the presence of catalyst PCl_5 (Sistietal. 1994). In Houben-Hoesh reaction nitriles react with arenes in the presence of acid gives carbonyls via imine intermediate and it is isolated as reaction intermediate (Yato et al. 1990) (**Scheme 1.2**).



Scheme 1.2 Synthesis of imine derivatives

1.1.3 Oximes

The name oxime is an abbreviation of oxy-imine, >C=N–OH. Two structures (A) and (B) (**Figure 1.4**) were proposed for the oxime group but on the basis of neutron diffraction study of dimethylglyoxime, the presence of –OH group has been established which favours the structure (A). In solid state, oximes are found to be associated by H-bonding O-H·····N. The presence of mild acidic hydroxyl group and slightly basic nitrogen atom makes the oxime group as an amphoteric in nature. In oxime carbon and nitrogen atoms are sp^2 hybridized. There is no free rotation about C=N, hence oximes of aldehyde and ketone exhibit geometrical isomerism.

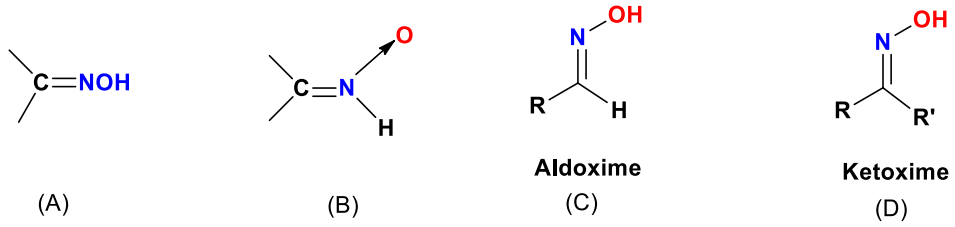


Figure 1.4 Structure (A & B) and classification (C & D) of oximes

Oxime is an important structural constituent, used as a building block for the synthesis of pharmaceuticals and agrochemicals (Ashani et al. 2008). Oxime compounds found extensive applications in different fields such as antidotes for nerve agents e.g. Pralidoxime, Obidoxime, Methoxime, Asoxime and Trimedoxime (**Figure 1.5**). Oximes are also found in antioxidants, insecticides, vasodilators, antimicrobial agents and inhibitors of P450. Diacetyloxime is used as an inhibitor of ATP-sensitive potassium ion channels

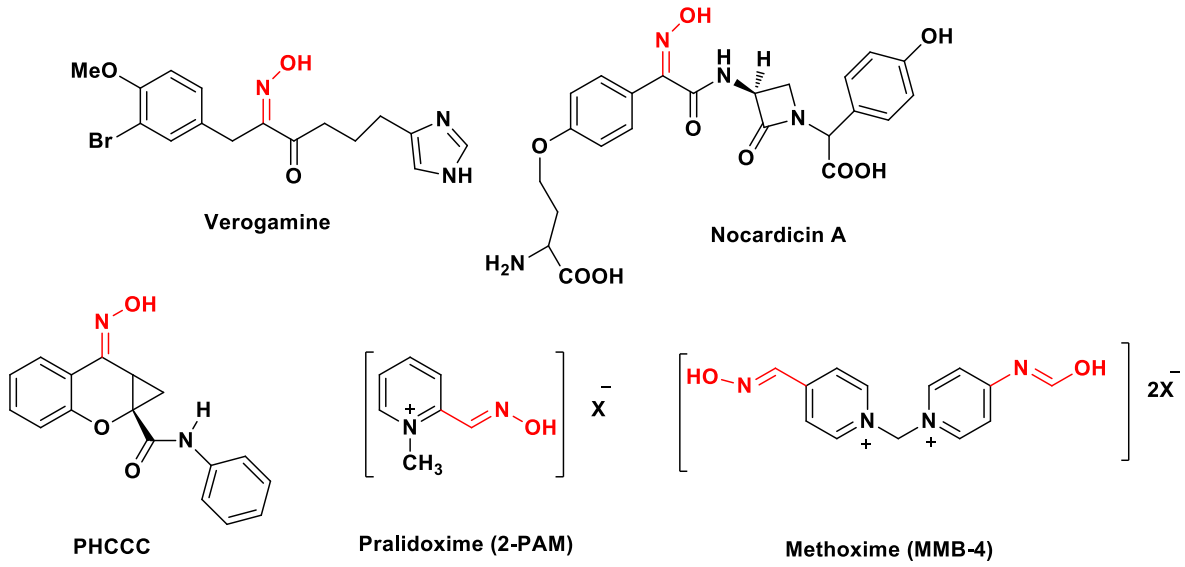
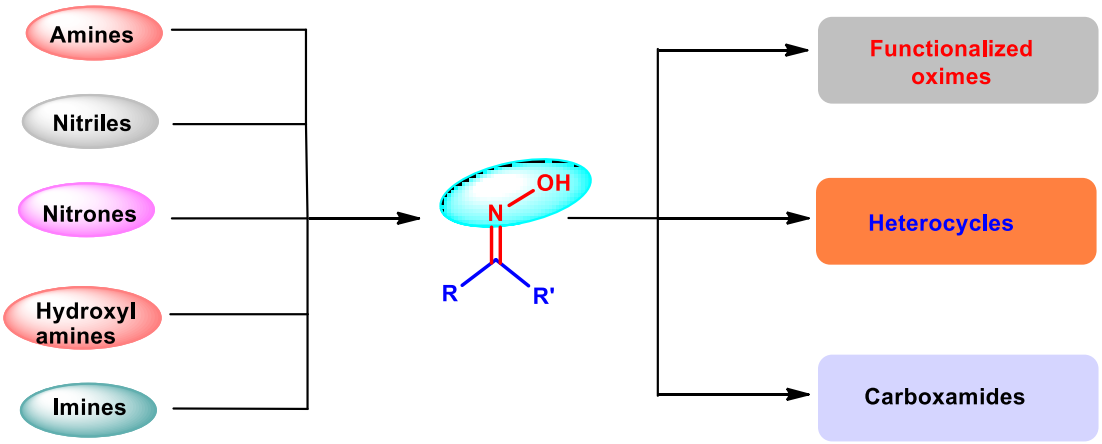


Figure 1.5 Examples of some drugs containing oxime group



Scheme 1.3 Synthesis and reactivity of oximes

(Tattersall 1993). Oximes have widely used in protecting carbonyls and different functional groups. Oxime is an important intermediate to convert different functional groups such as

amide (Martínez-Asencio et al. 2012), nitro, amine (Liu et al. 2019), isoxazolines (Zhu et al. 2019, Pohjakallio et al. 2009), isoquinolines (Deshmukh et al. 2019), hydroxylamine-*o*-ethers (Yamada et al. 1987) etc. into other functional groups (**Scheme 1.3**).

1.1.4 Amides

Amides are the compounds having general formula $RmE(O)nNR_1$ (R and R_1 are H or alkyl organic group) where E may be C, S, P and depending on E the corresponding amides are known as carboxamides (E=C, m=1 and n=1), sulfonamides (E=S, m=1 and n=2) and phosphoramides (E=P, m=2 and n=1). Amides represent an important class of compound in the agrochemicals, pharmaceutical, material science and chemical industries (Pattabiraman et al. 2011,Valeuretet al. 2009). Among them, carboxamide is usually found in nature and used in many drugs, natural products and polymers formation. Some examples are shown in **Figure 1.6**.

Traditionally, amides are synthesized by coupling reaction between carboxylic acid with an amine (primary and secondary) in the presence of some dehydrating agents (Grieco et al. 1979). Commonly this reaction is thermodynamically favorable and it has high activation energy because amine first deprotonating the carboxylic acid which reduces its reactivity. Therefore, carboxylic acid derivatives such as esters, acid chlorides and anhydride are used for amide synthesis (Ojeda-Porras et al. 2016, Wang et al. 2019).

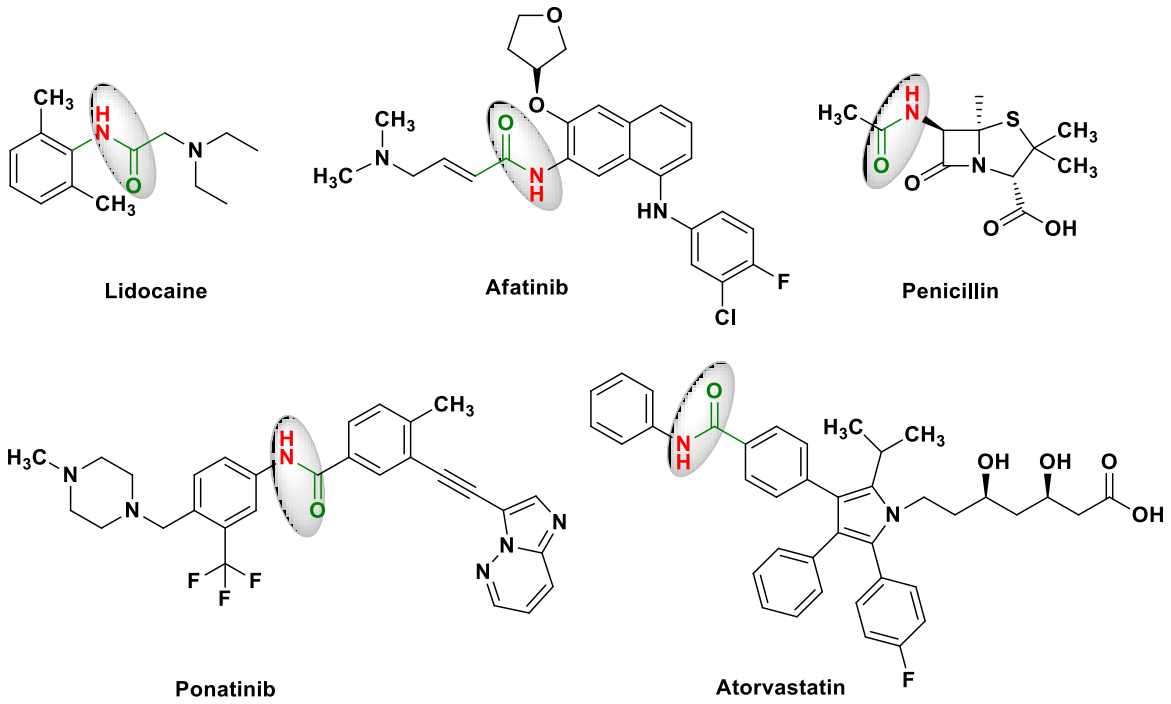
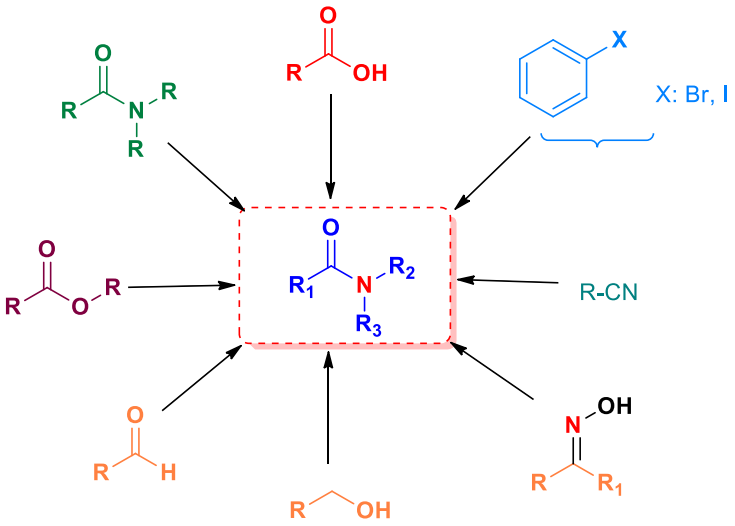


Figure 1.6 Examples of some drugs containing amide groups



Scheme 1.4 Amide bond formation through various substrates

Different name reactions are also known for amide synthesis such as Beckmann rearrangement in which oxime is converted into amide under acidic conditions (Hashimoto et al. 2007), "Ritter reaction", is used to convert a nitrile into amide using a strong acid (Jiang et al. 2014). "Schimdt reaction" is an acid-catalyzed reaction of hydrogen azide with different electrophiles (carbonyl compounds, tertiary alcohols or alkenes) (Smith 1948, Nyfeler et al. 2006). Multicomponent reaction between carbonyl compound, amine, isocyanide and carboxylic acid to give bis-amide,"Ugi reaction" (Yang et al. 2015), conversion of one amide to other by its reaction with an amine i.e. "transamidation" (Zhang et al. 2019), oxidative amidation of aldehydes or alcohols (Kamble et al. 2020) etc.

1.2 Nitrogen containing five membered cyclic compounds

1.2.1 Pyrrole

Pyrrole is a heterocyclic compound and an important chemical motif in various drugs, natural products, catalysts and advanced materials (Bhardwaj et al. 2015, Konar et al. 2017). In 1834 Runge isolated pyrrole from coal tar and the structure was correctly formulated by Baeyer in 1870. Pyrroles are active component of complex macrocycles, including the porphyrins of heme, chlorins, bacteriochlorins, chlorophyll, porphyrinogens (Senge et al. 2014).

Pyrroles are utilized as a substrate for polymerization process, corrosion inhibitor, preservative, solvent for resins and terpenes. It is used as a functional metarial in various

metallurgical process, luminescence chemistry, spectrochemical analysis and transition metal complex catalyst for uniform polymerization. Furthermore, some of the compounds are useful intermediates in the synthesis of biologically important naturally occurring alkaloids and synthetic heterocyclic derivatives (Estevez et al. 2010) **Figure 1.7**.

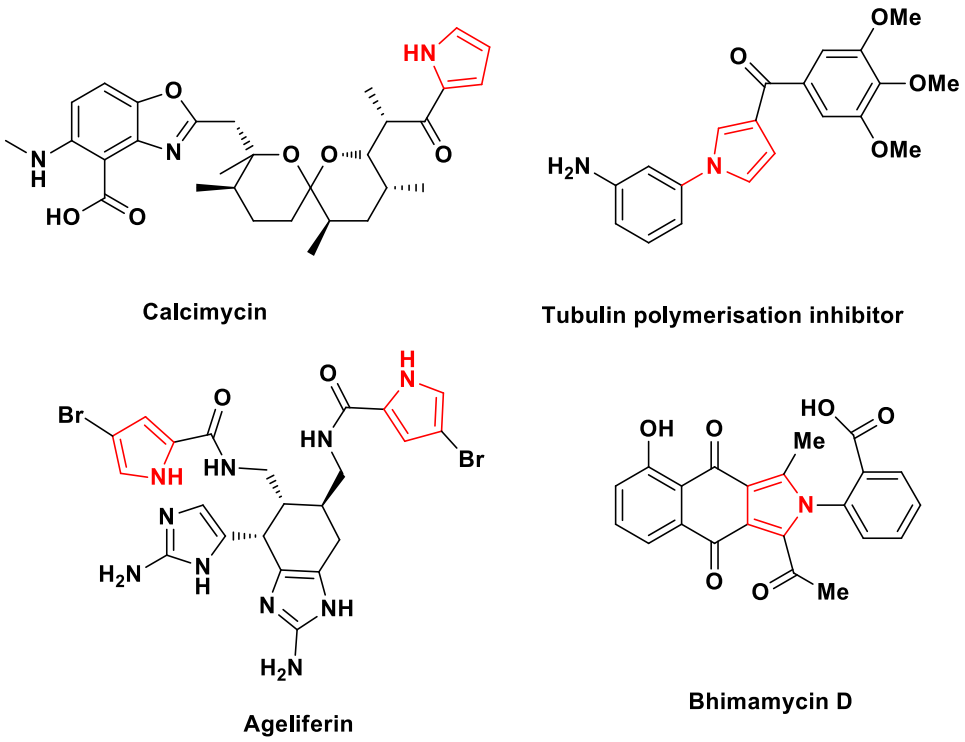
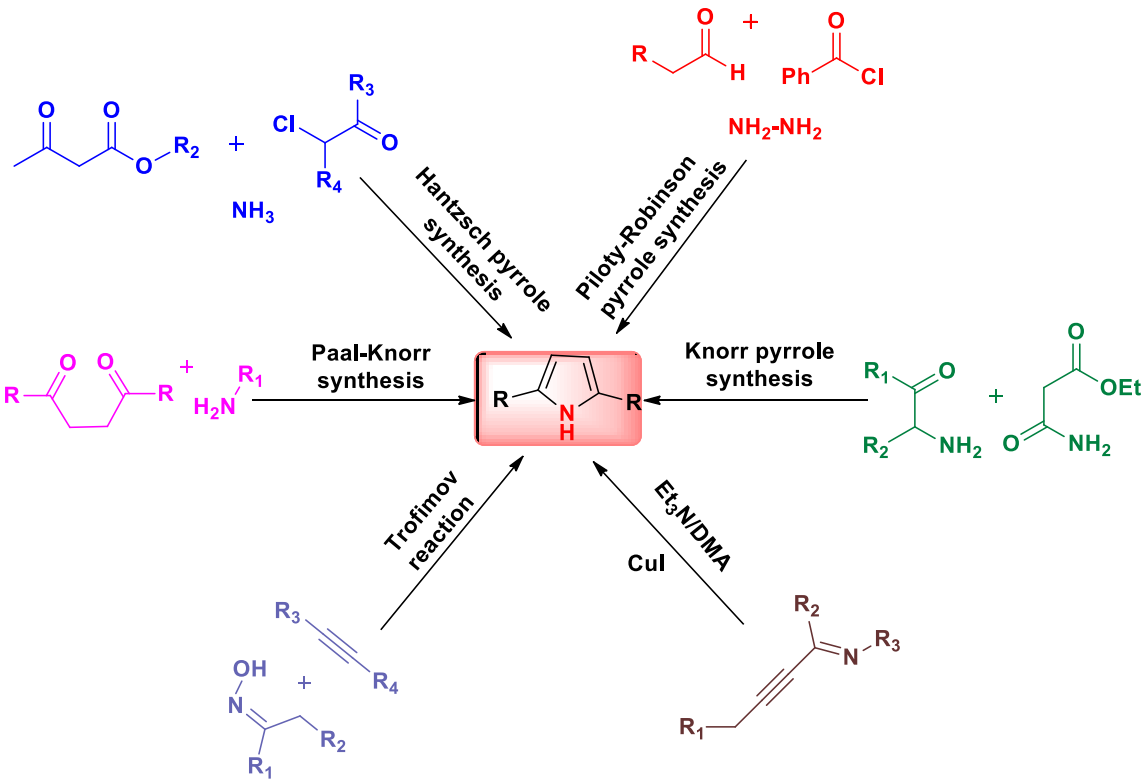


Figure 1.7 Few biologically active compounds containing pyrrole moiety

Pyrroles are synthesized by various methods such as by the reaction of 1,4-dicarbonyl compounds with ammonia or aromatic aliphatic amines (Akelis et al. 2016), ketones or secondary alcohols and β-amino alcohols (Krasniqi et al. 2019), α-amino-ketones react with active methylene compounds "Knorr pyrrole synthesis" (Ma et al. 2018),

three component condensation involving aldehyde and hydrazine hydrate "Piloty–Robinson pyrrole synthesis", ammonia and α-haloketones to give substituted pyrroles "Hantzsch pyrrole synthesis", reaction of oxime with alkynes "Trofimov reaction" (Schmidt et al. 2005) etc. **Scheme 1.5**.



Scheme 1.5 Synthesis of pyrrole and its derivatives

1.3 Nitrogen containing six membered cyclic compounds

1.3.1 Pyridine

Pyridine is an important heteroaromatic compound having diverse and potent biological properties (Quin et al. 2010, Altaf et al. 2015). A large amount of pyridine was obtained from natural sources via coal tar distillation. Pyridines are also occurred in many significant compounds e.g. vitamins niacin (vitamin B3) (Watts et al. 2008), pyridoxine (vitamin B6) and a number of alkaloids including nicotine, quinine etc. Pyridine structure present in a number of pharmaceuticalse such as anti-HIV, anticancer, antidiabetic, proton pump inhibitor (Kelgokmen et al. 2019) etc. **Figure 1.8.**

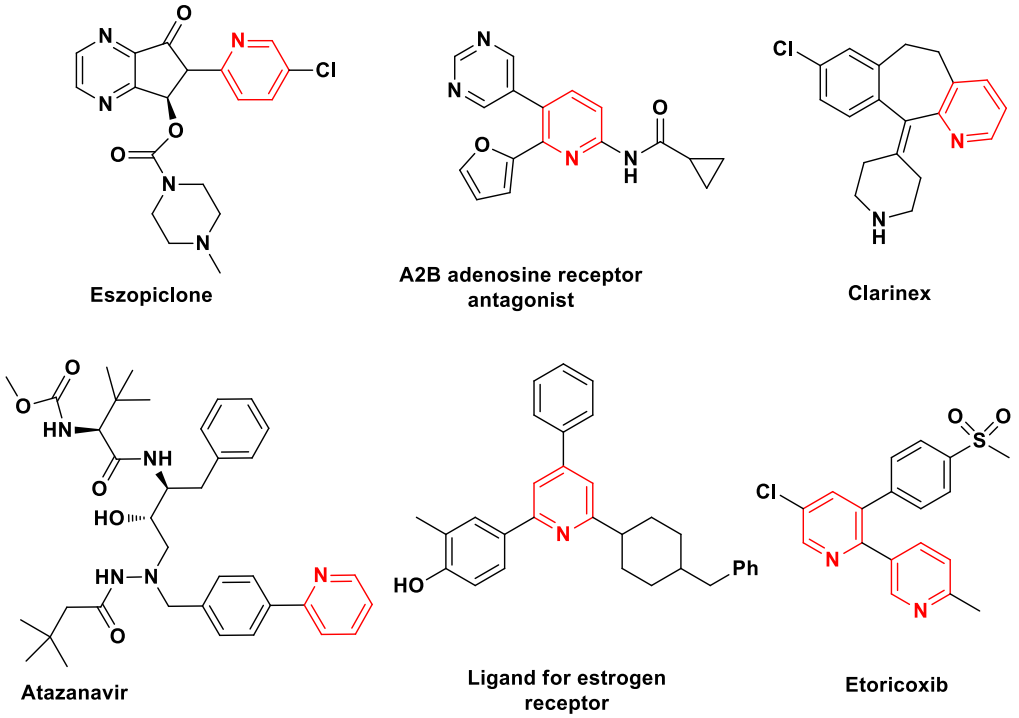
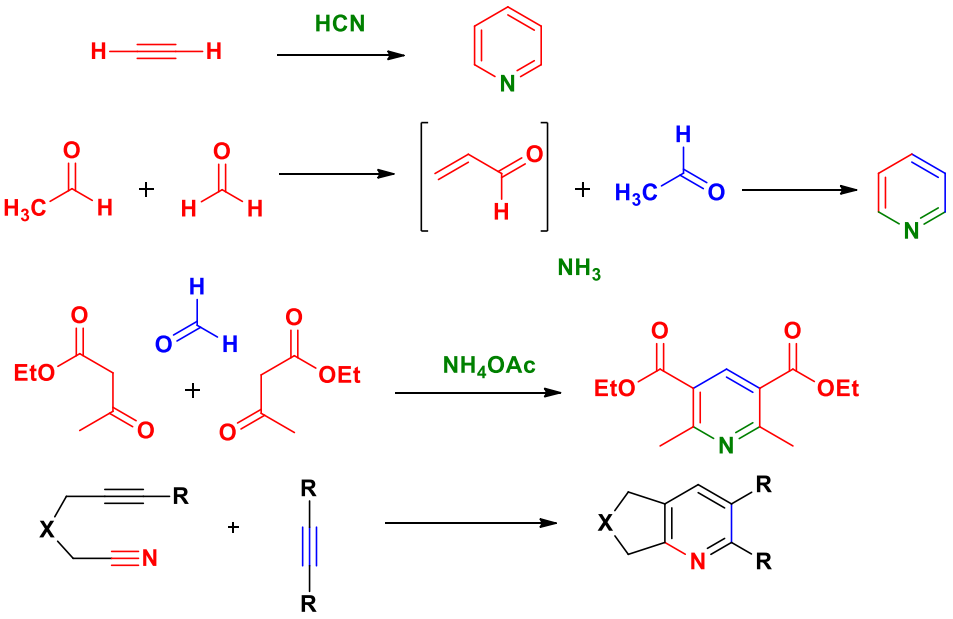


Figure 1.8 Representative compounds containing pyridine substructure

Pyridine was first synthesized in 1876 from acetylene and hydrogen cyanide (Hanmer et al. 1947). Pyridine have been synthesized by the Chichibabin pyridine synthesis and this method is still used in industries (Frank et al. 1949). Knoevenagel condensation reaction between aldehyde and formaldehyde gives acrolein after that acrolein condensed with acetaldehyde and ammonia to give dihydropyridine, which is oxidized with a solid-state catalyst gives pyridine (Jin et al. 2009). The Hantzsch pyridine synthesis is a multi-component organic reaction between an aldehyde, β-keto ester (2 equivalents) and nitrogen donor (ammonium acetate or ammonia) (Phillips 1949). Cycloaddition of alkynenitriles and alkynes gives pyridine (D'Souza et al. 2011) (**Scheme 1.6**).



Scheme 1.6 Synthesis of pyridine and its derivatives

1.4 Nitrogen containing fused heterocyclic compounds

1.4.1 Indole

Indole derivatives show diverse biological activities and widely distributed in natural products. Indole chemistry began to develop with the study of the indigo dye. Indigo can be converted to isatin and then oxindole derivatives. Indole derivatives have many biological properties such as anti-inflammatory, anticonvulsant, cardiovascular and antibacterial etc. In particular, 3-substituted indole derivatives play a key role in the synthesis of biologically active compounds (Agarwal et al. 2005, Demurtas et al. 2019, Estevão et al. 2010). Some of the biologically active indole representatives are shown in **Figure 1.9**.

Indoles and its derivatives were synthesized by different methods such as by the reaction of phenylhydrazine and carbonyl compounds (aldehyde or ketone) under acidic conditions known as "Fischer indole synthesis" (Saikia et al. 2019), in the presence potassium *tert*-butoxide-promoted dehydrogenation of indoline (MacDonough et al. 2015), 2-fluorotoluenes and benzonitriles in the presence of base (Mao et al. 2019), α-bromo-acetophenone and excess aniline to give 2-aryl-indole, "Bischler–Möhlauindole synthesis", an aniline and ketone bearing a thioether "Gassmanindole synthesis" (Li 2014), an *ortho*-iodoaniline and a disubstituted alkyne using palladium catalyst "Larockindole synthesis" (Shan et al. 2013), thermal decomposition of 3-aryl-2-azido-propenoic ester into an indole-2-carboxylic ester "Hemetsbergerindole synthesis" (Lehmann et al. 2009), from substituted

ortho-nitrocinnamic acid and iron powder in strongly basic solution "Baeyer–Emmerlingindole synthesis (Sánchez-Viesca et al. 2018) (**Scheme 1.7)**.

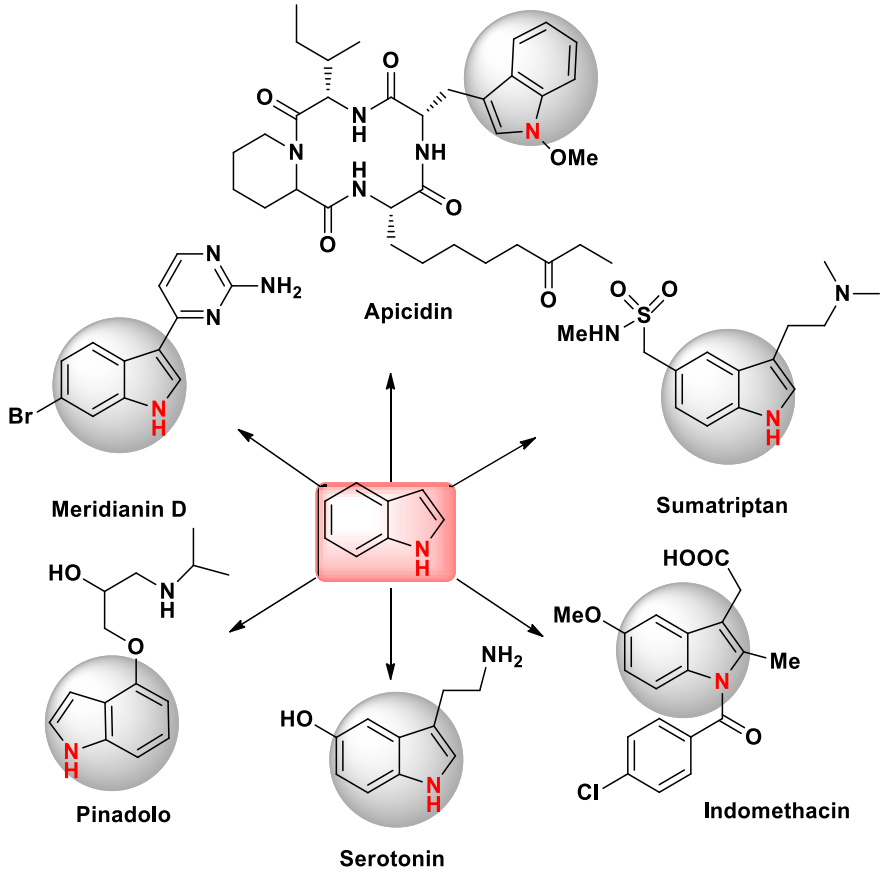
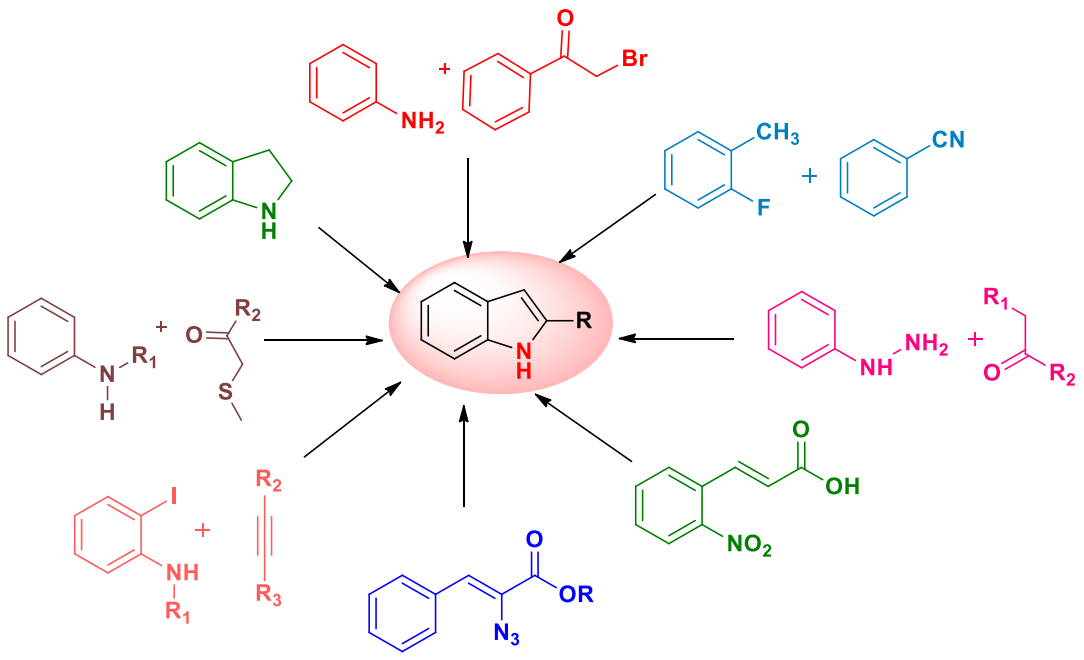


Figure 1.9 Examples of pharmacologically active indole derivatives



Scheme 1.7 Synthesis of indole and its derivatives

1.4.2 Benzothiazole

Benzothiazole has gained considerable attention because of their miscellaneous biological, pharmaceutical and interesting chemical applications (Rana et al. 2007). 2-Substituted benzothiazole derivatives have potential to use as antidiabetic, anti-inflammatory, antitumor, antifungal, anti-inflammatory, antiviral, antipsychotic, antiarrhythmic, neurodegenerative, mosquitocidal agents (Sever et al. 2019) imaging agents for Ca2þ channel antagonist, anti-HIV, antituberculosis, analgesia and diuretic activity etc. (Ali et al. 2013) **Figure 1.10**.

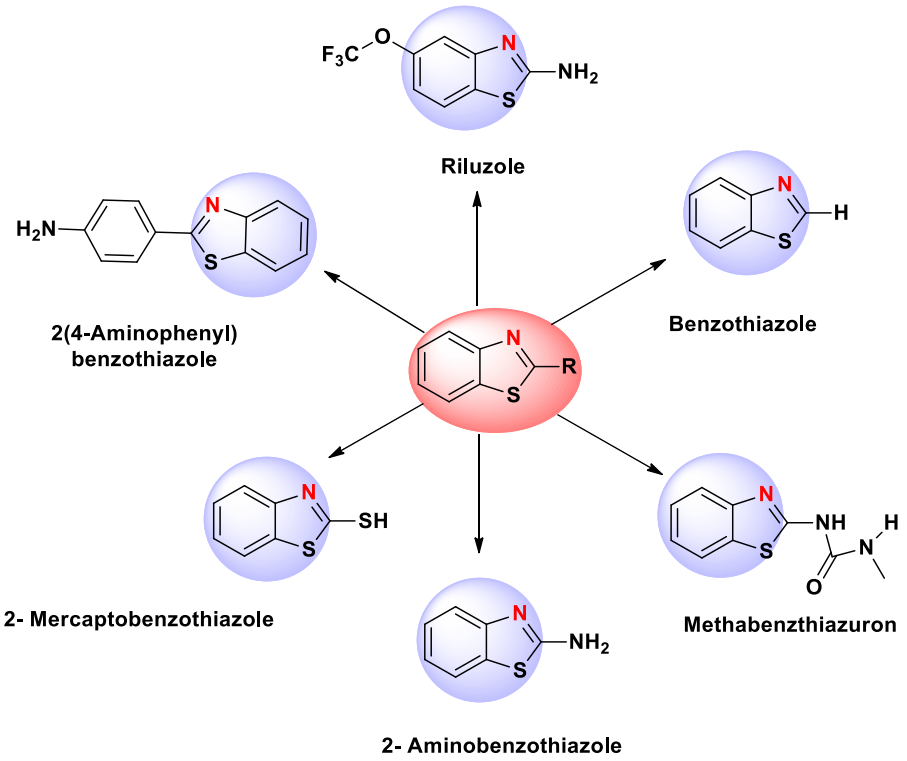
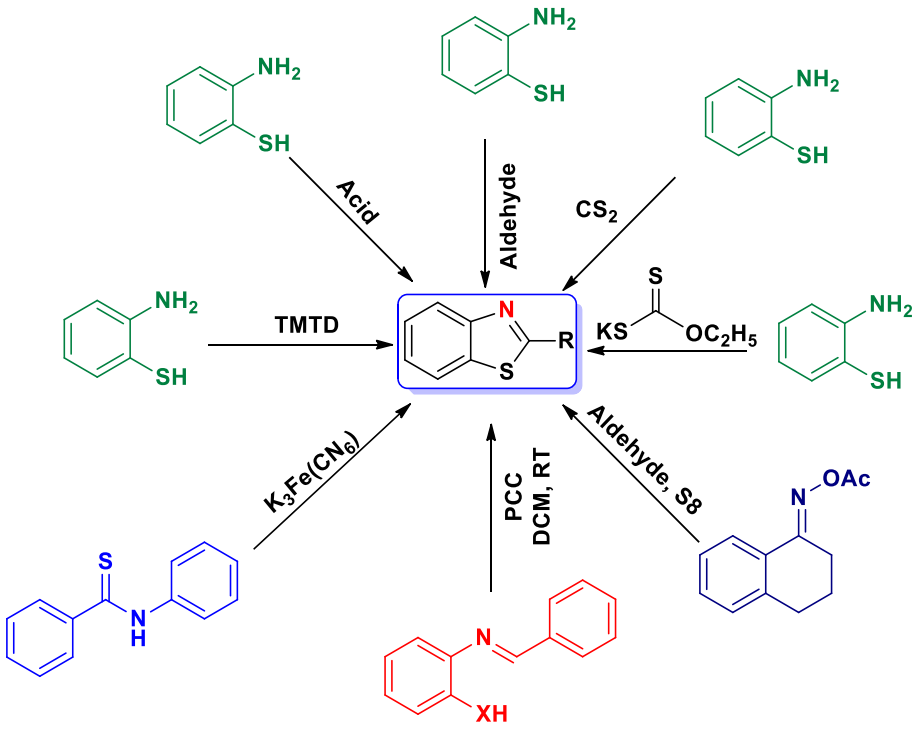


Figure 1.10 Few biologically active compounds containing benzothiazole moiety

Benzothiazoles are mainly synthesized by the reaction of 1,2-aminothiophenol with carbonyl compounds (Liu et al. 2020), 2-halogen substituted anilines and dithiocarbamates in the presence of *t*-BuOK. (Xu et al. 2017), oxidative cyclization of thiobenzanilinide by potassium cynohexaferrate (Voschino et al. 1989), oxidative cyclization of Schiff's base (Praveen et al. 2008), three-component reaction of cyclohexenoneoximes, aldehydes and elemental sulfur (Xu et al. 2019), tetramethylthiuram disulfide (TMTD) and *o*-aminothiophenol (Liu et al. 2017), arylthioureas undergoes intermolecular oxidative C-H bond functionalization in the presence of pyridine (Gao et al. 2019) (**Scheme 1.8).**



Scheme 1.8 Synthesis of benzothiazole and its derivatives

1.4.3 Benzimidazole

Benzimidazole is nitrogen containing heterocyclic moiety comprising of six-membered benzene ring fused with five-membered imidazole ring. Benzimidazole and its derivatives are the part of many biological active compounds and widely used as antihypertensive, anti-inflammatory, antibacterial, antiviral, antifungal, antihelmintic, anticancer (Najajreh 2019), antiulcer, antioxidant, psychoactive drugs, anticoagulants, proton pump inhibitors, immunomodulators, hormone modulators, antidepressants and antidiabetics etc. Benzimidazole derivatives exert their actions by interacting with vital

biological targets DNA minor groove, histamine receptors, β-tubulin, serotonin receptors etc. (Alaqeel 2017, Shaharyar et al. 2017) **Figure 1.11**.

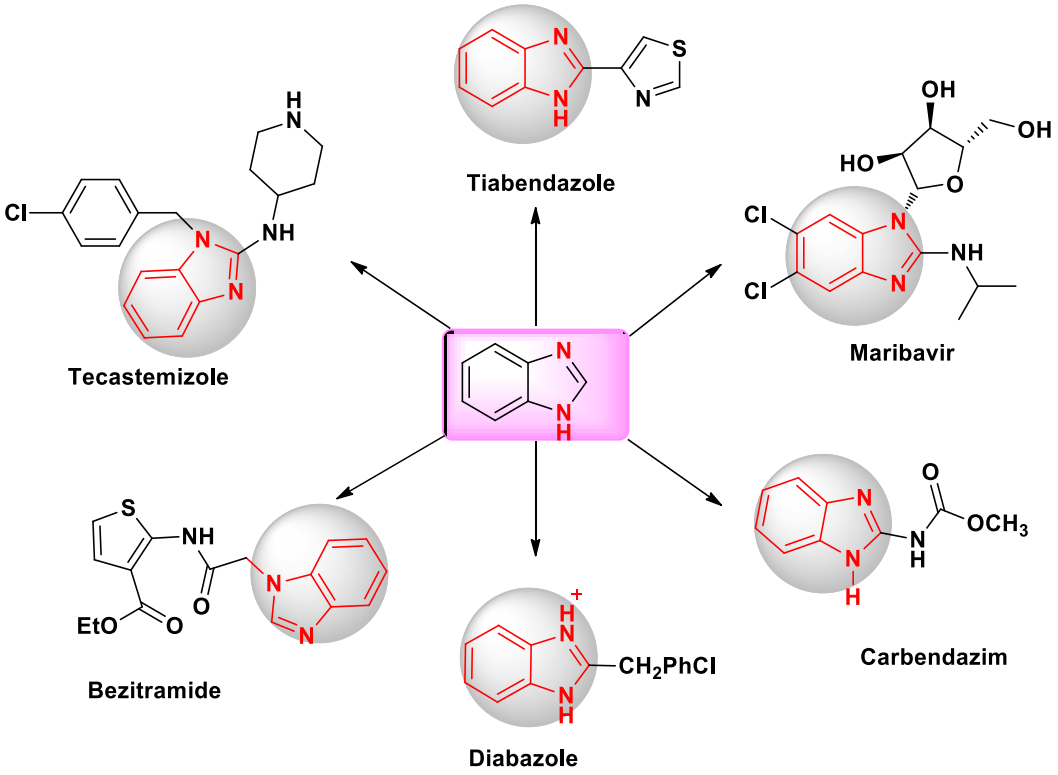
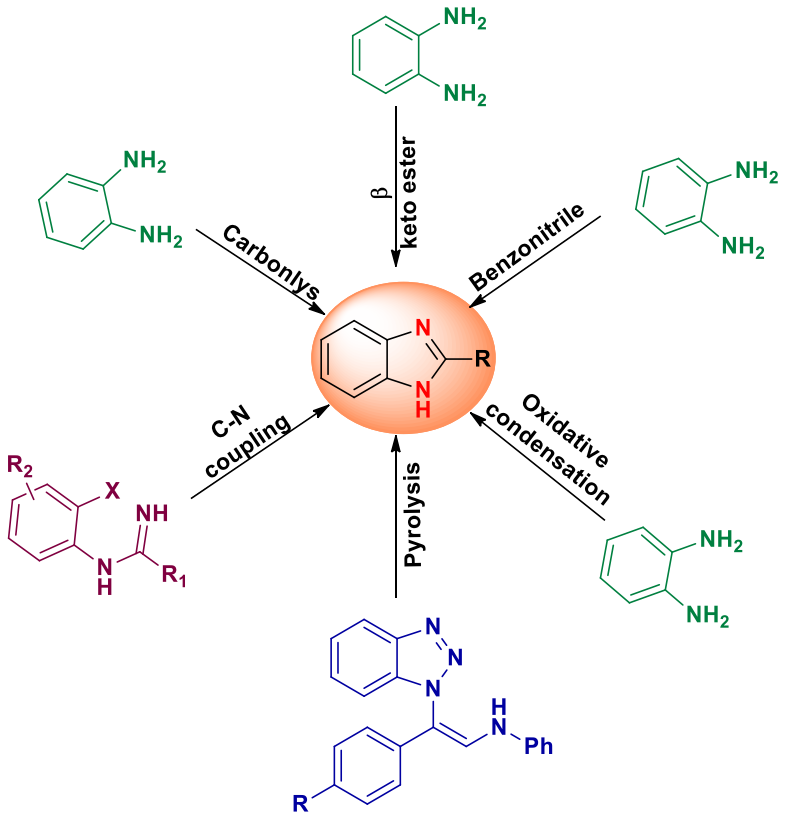


Figure 1.11 Few biologically active compounds containing benzimidazole moiety

Benzimidazole and its derivatives were prepared by different methods such as by the condensation reaction of *o*-phenylenediamine with carbonyls (Saberi et al. 2015, Gorepatilet al. 2013, Merroun et al. 2019), oxidative condensation reaction of alcohols, methyl arenes derivatives with *o*-phenylenediamine (Das et al. 2018, Chopra et al. 2019), oxidative cyclisation of *N*-aryl amidine intermediate resulting from aniline addition to a nitrile (Arnold et al. 2019, Xiang et al. 2013), one-pot intermolecular cross coupling of

o-haloacetoanilide with guanidines (Guo et al. 2019), intramolecular C(sp3)–H imination (Bose et al. 2019) and thermolysis of benzotriazole derivatives (Al-Awadi et al. 2008) (**Scheme 1.9**).



Scheme 1.9 Synthesis of benzimidazole and its derivatives

1.4.4 Benzoxazole

Benzoxazoles and their derivatives are aromatic heterocyclic compounds containing nitrogen and oxygen atoms which present in numerous natural products and attended as pharmacophores in drug discovery. Further, a number of benzoxazole derivatives are

recognized as a antimycobacterials, peroxisome proliferators activated receptor γ antagonists, cytotoxic natural products, cathepsin S inhibitors, 5-HT3 receptor antagonists, non-nucleoside reserve transcriptase inhibitors, elastase inhibitors, estrogen receptor-β agonists, antidiabetic antimicrobial, anti-cancer, anti-HIV, anticonvulsant, antiinflamatory, antinuclear and antitumor etc. (Kakkar et al. 2018, Vodnala et al. 2018) **Figure 1.12**.

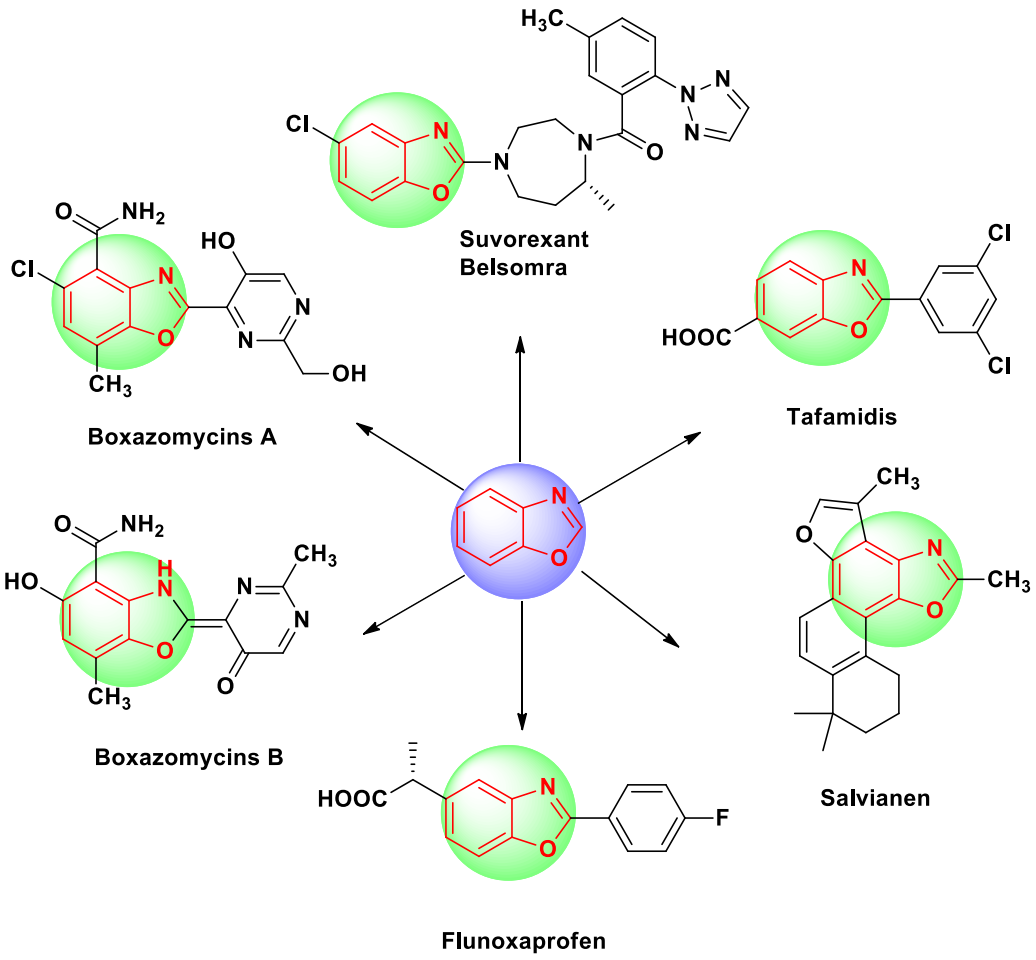
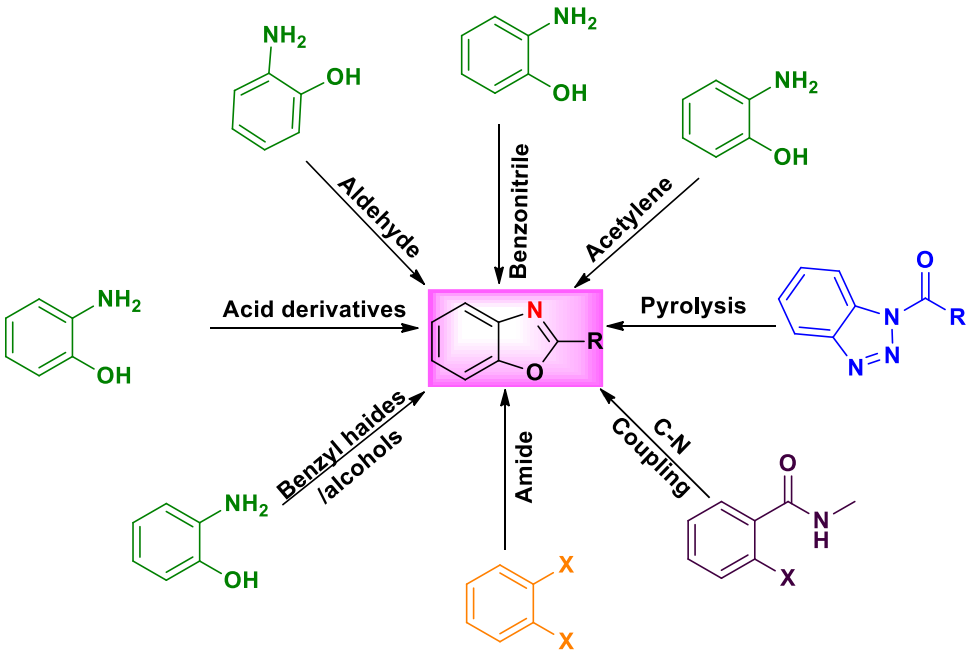


Figure 1.12 Few biologically active compounds containing benzoxazole moiety

Benzoxazole and its derivatives were prepared by different methods such as by the reaction of aldehyde/ carboxylic acids derivatives and 2-aminophenol under various conditions (Kumar et al. 2012, Niedduet al. 2012), oxidative condensation reaction between toluene/ benzyl alcohal/ benzyl amine/ styrene with 2-aminophenol (Doan et al. 2019, Safaei et al. 2018), one-pot intermolecular C-heteroatom coupling of N-(2-bromophenyl) benzamide (Singh et al. 2019), intermolecular cross coupling of 1,2-dihaloarenes with amide (Schuh et al. 2007), intramolecular C-N cross-coupling of 2-haloanilines with acyl halides/ thioacyl halides (Viirre et al. 2007), hydroamination of alkynes with 2-aminophenols (Oshimoto et al. 2019) benzotriazole rings cleavage (BtRC) of N-acyl benzotriazole gives benzoxazole derivative (Singh et al. 2017) (**Scheme 1.10**).



Scheme 1.10 Synthesis of benzoxazole and its derivatives

In view of importance of nitrogen containing organic compounds, our interest is to explore the chemistry (synthesis and structural characterization) of imidazopyrimidine, pyranopyrazoles, benzimidazole/ benzothaizole and amides. The studies have been described in the subsequent chapters 2-5. During the research period we have also synthesized the β–hydroxy ketones from α-methyl ketones and ninhydrin under microwave irradiations which is presented in last as an appendix.

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CHAPTER 2

Starch Functionalized Magnetite Nanoparticles: A Green, Biocatalyst for One-pot Multicomponent Synthesis of Imidazopyrimidine Derivatives in Aqueous Medium under Ultrasound Irradiation

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2.1 Introduction

Nitrogen-containing heterocyclic moieties get much more attention due to its biological, agrochemical and pharmaceutical properties. Imidazopyrimidines, which have two nitrogen-containing heterocyclic imidazole and pyrimidine core units, possess several biological activities (Wahe et al. 2003) like antioxidant, antibiotic, antiarrhythmic, anti-inflammatory, antiviral, antimicrobial, anti-diabetic, herbicidal, anti-cancer (Klutchko et al. 1998), calcium anagostic (Alajarin et al. 1994), antineoplastic (Badawey et al. 1995), anti-hepatitis B and as well as DNA-gyrase inhibitors and lipid peroxidation inhibitor properties (Le Corre et al. 2010, Neochoritis et al. 2011).

Several methods have been reported for the synthesis of imidazopyrimidine derivatives under different conditions and diverse catalysts like L-proline (Kalita et al. 2016), citric acid (Warekar et al. 2016), silica sulfuric acid (Wu et al. 2010), sulfamic acid (Yao et al. 2008), boric acid (Meshram et al. 2012), MgO (Sheibani et al. 2013), [PVPH]ClO_4 (Abedini et al. 2016), $ZnClO_4$ (Kaur et al. 2015), *P*-TSA (Reddy et al. 2014), NH_4OH (Hu et al. 2012), H_3PO_4–Al_2O_3 (Shaterian et al. 2014), RHA [pmim]HSO_4 (Shirini et al. 2016), Fe_3O_4@IM (Hemmati et al. 2016), [bmim][BF_4] (Yao et al. 2010).

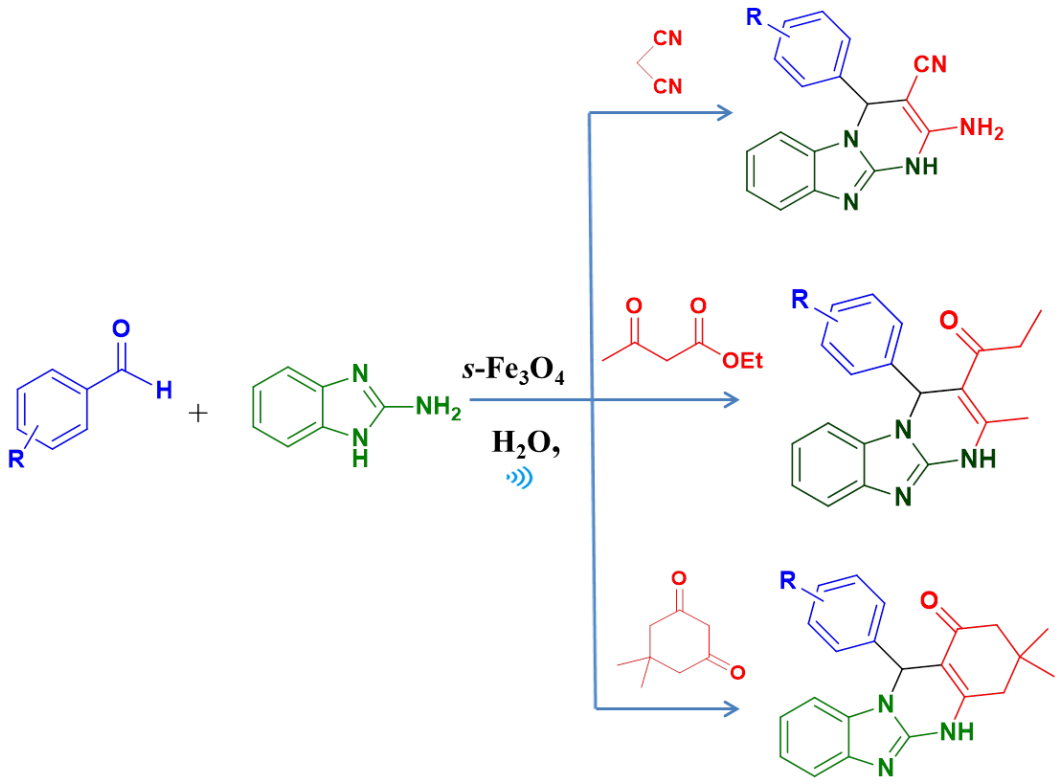
However these procedures suffer from comparatively harsh reaction conditions, longer reaction time, low yields and use of volatile organic solvents. Therefore, the development of an energy and environment efficient greener protocol for the synthesis of these heterocyclic compounds is always in demand.

In the last few decades, the construction of biologically active complex structures in a single step by multicomponent synthesis is one of the most promising areas of green chemistry. Successful implementation of this single step approach allows high atom economy, reduces reaction time, low cost due to lesser material consumption as compared to multi-step synthesis. However, limited methods have been reported for the synthesis of imidazopyrimidine derivatives via one pot. Imidazopyrimidines could be synthesized via multicomponent reaction (MCR) it reduces processing time, cost and waste materials. Another aspect of such green synthesis is the requirement of an alternative solvent like water (Khazaei et al. 2015, Rajarathinam et al. 2016, Komykhov et al. 2016, Tamaddon et al. 2014) supercritical CO_2, ethylene glycol (Survase et al. 2017, Nagarapu et al. 2013), ionic liquids (Velasco et al. 2015, Zhao et al. 2003), glycerol (Singh et al. 2016, Radatz et al. 2011) etc. which can be used instead of conventional volatile organic solvents. Among these, water is sustainable, non-toxic, inexpensive and can dissolve a variety of organic and inorganic compounds. In this respect, water has attracted much attention due to advantages in term of economic, ecological and environmental point of view. Since green synthesis procedures have generally been found to be relatively slower; therefore, workers have often

resorted to strong ultrasound irradiation (>20 Hz) for smooth conduct of the reaction. Ultrasound radiation brings physical and chemical changes due to the formation and destruction of cavitation space in the reaction mixture. Ultrasonic radiations are useful for all type of catalysts but are most effective for the catalysts which are intertwined or magnetic because ultrasound radiation helps to disperse the catalyst particulates in the reaction mixture equally (Zou et al. 2012, Tabassum et al. 2015, Cappelletti et al. 2015, Banerjee 2017, Noori et al. 2017).

Higher efficiency of green synthesis protocols for multicomponent synthesis can be achieved by using an appropriate nanocatalyst. Nowadays enzymes and biomolecules functionalized nanoparticles are being used extensively in organic synthesis as well as in biomedical sciences (Gupta et al. 2015, Gawande et al. 2012, Maleki et al. 2014, Subbiah et al. 2010, Mout et al. 2012). Functionalized nanocatalysts display improved stability against aggregation, thereby giving access to higher surface area and more catalytically active sites. Additionally, functionalization also influences the properties of active sites on the nanocatalyst (Singh et al. 2016). Because of this; the present investigation utilizes starch functionalized superparamagnetic magnetite nanoparticles for multicomponent synthesis of imidazopyridine derivatives. Starch is an excellent substrate for supporting the nanoparticles because it contains hydroxyl groups which stabilize the nanoparticles. Besides this, starch is an economical and biodegradable natural polymer of glucose. Utilization of such natural molecules for the functionalization of heterogeneous catalysts is

one of the most important thrust areas in green chemistry. To the best of our knowledge, the catalytic activity of starch functionalized magnetite nanoparticles for the one-pot multicomponent synthesis of imidazopyrimidine derivatives in aqueous medium under ultrasound irradiations has not been reported till date.



Scheme 2.1 *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidines

Moreover, superparamagnetic nanoparticles can be easily separated by placing magnet below the reaction vessel. The nanoparticles can then be reused by re-dispersing them again in fresh reaction medium after removal of the magnetic field. Thus, a new

dimension in organic synthesis for the devolvement of more efficient and green methodology for the synthesis of imidazopyridine derivatives (4) **(Scheme 2.1)** is achieved.

2.2 Results and Discussion

2.2.1 Nano-catalyst characterization

The starch functionalized superparamagnetic nanoparticles *s*-Fe_3O_4 were synthesized by co-precipitation method as reported by Prakash et al. and characterized by using different analytical and spectroscopic techniques (Singh et al. 2016). How starch was attached to the magnetite nanoparticles was investigated by FT-IR spectroscopy. The FT-IR spectrum of pure soluble starch shows characteristic peaks at 1,155 cm^{-1} for the stretching frequency of glycosidic C-O-C and 1,023 cm^{-1} for C-O bonds another peak, due to O-H stretching mode of starch, is observed at 3412 cm^{-1}. In contrast to this, the FT-IR of *s*-Fe_3O_4 displays the stretching frequencies of the C-O-C and C-O bonds at 1,150 and 1,025 cm^{-1} respectively and appearance of an intense peak at 584 cm^{-1} is due to the stretching frequency of Fe-O bond supports the formation of *s*-Fe_3O_4 (**Figure 2.1)**.

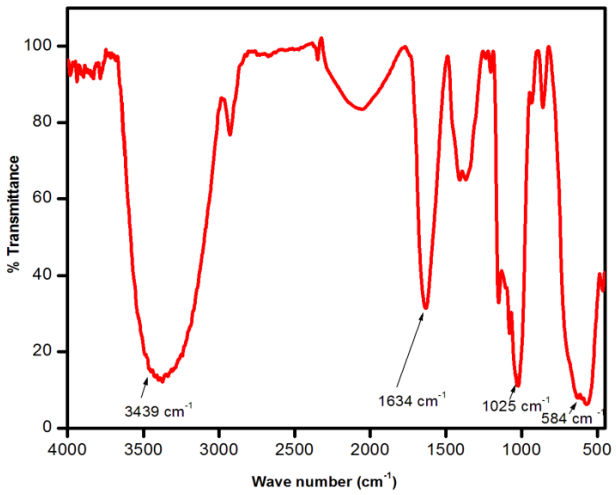


Figure 2.1 FT-IR of *s*-Fe_3O_4

The XRD diffraction spectrum of *s*-Fe_3O_4 is shown in **Figure 2.2**. The indexed planes (220), (311), (400), (422), (511), and (440) agree very well with the magnetite phase as per JCPDS card no-89-0688. The absence of any other peak indicates that only pure magnetite phase nanoparticles have been formed. Moreover, starch functionalization does not impact the XRD pattern of the magnetite phase. The SEM analysis of *s*-Fe_3O_4 was performed to investigate the effect of starch on magnetite particle morphology (**Figure 2.3**). The SEM image clearly shows the homogenous morphology and small particle size of *s*-Fe_3O_4. The presence of C, along with Fe and O in the Energy Dispersive X-Ray Analysis (EDAX), reaffirms the attachment of starch to magnetite (**Figure 2.4**). The TEM images *s*-Fe_3O_4 is spherical in nature and very fine particles in the case of *s*-Fe_3O_4 shows nano Fe_3O_4 are functionalized with starch (**Figure 2.5**).

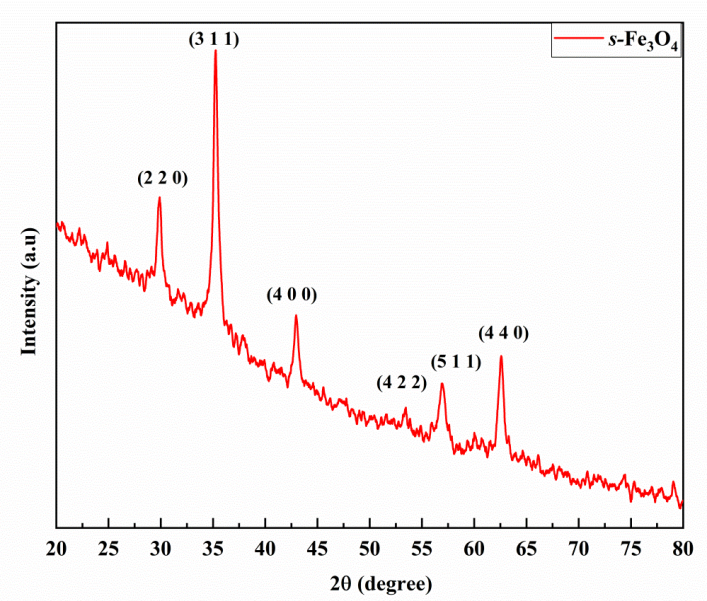


Figure 2.2 XRD pattern of *s*-Fe_3O_4

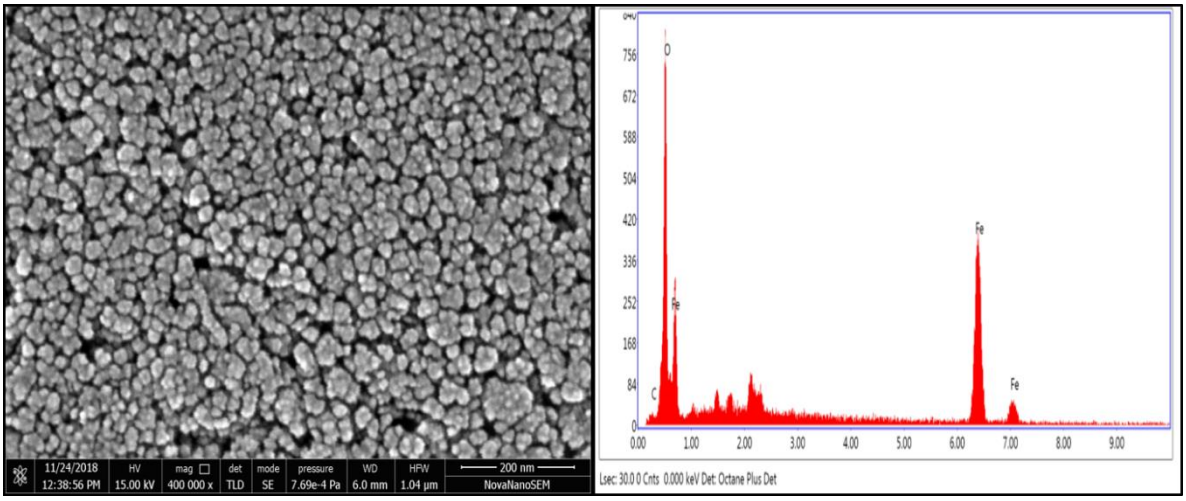


Figure 2.3 SEM image of *s*-Fe_3O_4

Figure 2.4 EDAX of *s*-Fe_3O_4.

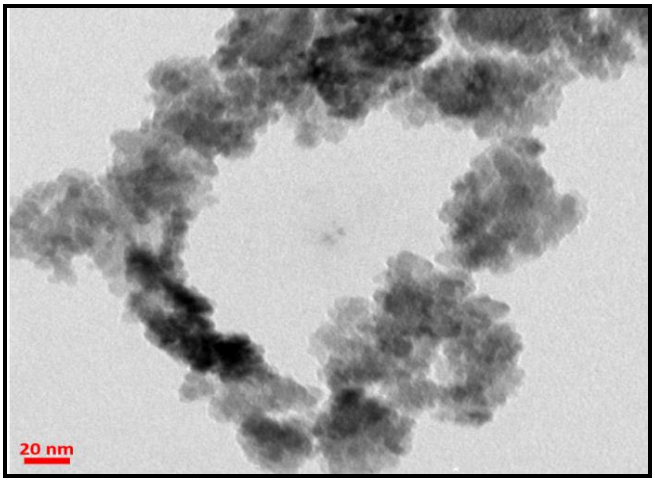


Figure 2.5 TEM image *s*-Fe_3O_4

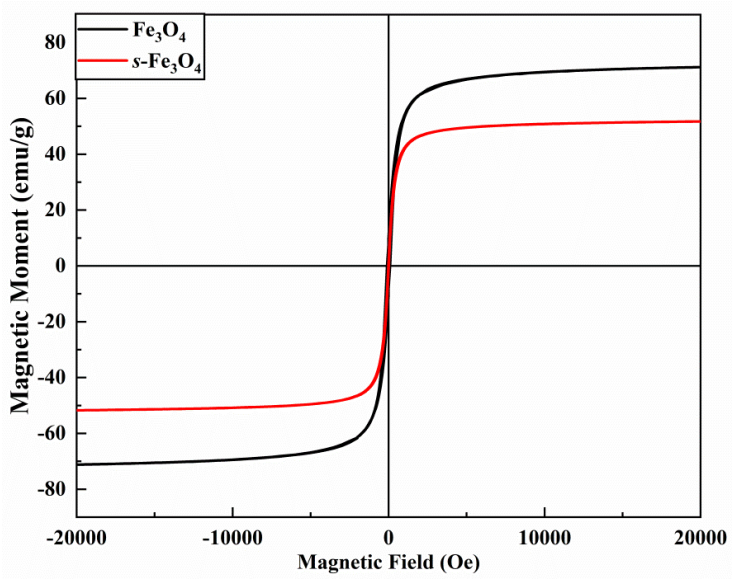


Figure 2.6 MPMS analysis; Magnetic moment versus magnetic field graph of Fe_3O_4 and *s*-Fe_3O_4

The magnetic properties of the starch functionalized magnetite nanoparticles were analyzed by Mission Planning and Monitoring System (MPMS) **Figure 2.6** shows the magnetization curve of *s*-Fe_3O_4. The absence of hysteresis loop shows that *s*-Fe_3O_4 is superparamagnetic. Furthermore, the magnetic moment of *s*-Fe_3O_4 (51.9 emu/g) is lower than Fe_3O_4 (71.3 emu/g) due to starch functionalization.

2.2.2 Optimization of Reaction Conditions

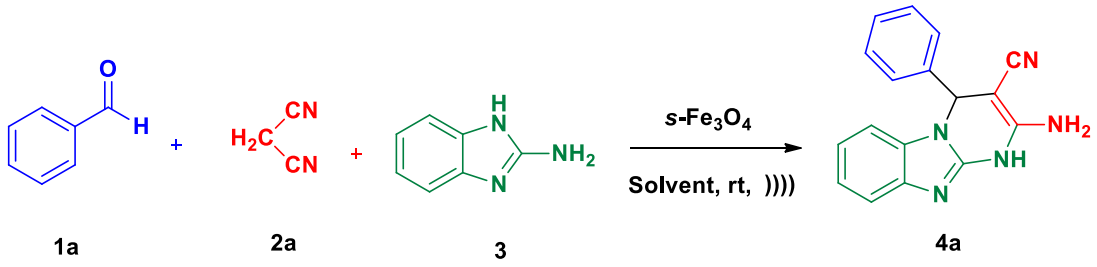
To establish the optimized conditions benzaldehyde (**1a**), malononitrile (**2a**) and 2-aminobenzimidazole (**3**) in (1.2: 1.2: 1 molar ratio) was chosen as a model reaction for the synthesis of imidazopyrimidine (**4a**).

The model reaction was carried out in reflux and ultrasound irradiation method to compare the effectiveness of this methodology. When model reaction was done under reflux, the reaction was completed in 2h and gave 80% yield of the product. While in ultrasound irradiation method it gave 98% of the product in 3 min because catalyst *s*-Fe_3O_4 was homogenized in reaction mixture by ultrasound irradiation so all other optimization was carried out by ultrasound method. To find a suitable solvent the model reaction was carried out with 5 mg of *s*-Fe_3O_4 in various solvents at room temperature under ultrasound irradiation. In non-polar solvents such as xylene, toluene, benzene no product was obtained after 1h (**Table 2.1, entries 1-3**). Polar-aprotic solvents such as 1,4-dioxane, acetonitrile, dichloromethane gave the imidazopyrimidine (**4a**) in 25-40% yield after one hour (**Table 2.1, entries 4-6**). In the case of polar- protic solvents like methanol, ethanol, and water

gave the product (**4a**) in 40-98% yield (**Table 2.1, entries 7-9**). The best result was obtained in water almost complete conversion of the reactants into the product (**4a**) was achieved with an isolated yield of 98% in 3 minutes (**Table 2.1, entry 9**). To understand the effectiveness of *s*-Fe_3O_4 nano catalyst in the synthesis of imidazopyrimidines some controlled experiments have been done with the model reaction under the same reaction conditions. The model reaction mixture was irradiated under ultrasound without catalyst *s*-Fe_3O_4 in water at r.t. However, there was no formation of 2-amino-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4a**) in 1h (**Table 2.1, entry 10**). In another controlled experiment, the reaction was also performed in the presence of starch only (no *s*-Fe_3O_4) but no product was formed in this case. The reaction was attempted with nano Fe_3O_4 (without starch functionalization) separately again, in this case, only 30% of the product was obtained under the same reaction conditions (**Table 2.1, entry 11, 12**).

Furthermore, optimization of catalyst loading was investigated with catalyst concentration 2, 3 and 4 mg gave 50%, 80%, and 98% yields of the desired product respectively (**Table 2.1, entries 13–15**), the results show that 4 mg of *s*-Fe_3O_4 was optimal and excessive amount of catalyst did not increase the rate and yield of the product. The product (**4a**) was characterized by spectral data (IR, ^1H, ^{13}C NMR) and confirmed by comparing with the reported.

Table 2.1 Evaluation of solvents and amount of the catalyst for the synthesis of 4a[a]



Entry	Solvent	Catalyst	Catalyst Amount (mg)	Time (min)	% Yield[b]
1	Xylene	*s*-Fe_3O_4	5	60	NA
2	Toluene	*s*-Fe_3O_4	5	60	NA
3	Benzene	*s*-Fe_3O_4	5	60	NA
4	1,4-Dioxane	*s*-Fe_3O_4	5	60	25
5	Acetonitrile	*s*-Fe_3O_4	5	40	35
6	Dichloromethane	*s*-Fe_3O_4	5	60	40
7	Ethanol	*s*-Fe_3O_4	5	40	50
8	Methanol	*s*-Fe_3O_4	5	60	40
9	Water	*s*-Fe_3O_4	5	3	98
10	Water	-	-	60	NA
11	Water	nano-Fe_3O_4	5	60	30
12	Water	Starch	5	60	NA
13	Water	*s*-Fe_3O_4	4	3	98

14	Water	*s*-Fe_3O_4	3	10	80
15	Water	*s*-Fe_3O_4	2	15	50

[a] **Reaction conditions:** Benzaldehyde 1a (1.2 mmol), malononitrile 2a (1.2 mmol) and 2-aminobenzimidazole 3 (1.0 mmol) in the presence of *s*-Fe_3O_4 at room temperature under ultrasound irradiation, [b]Isolated yield.

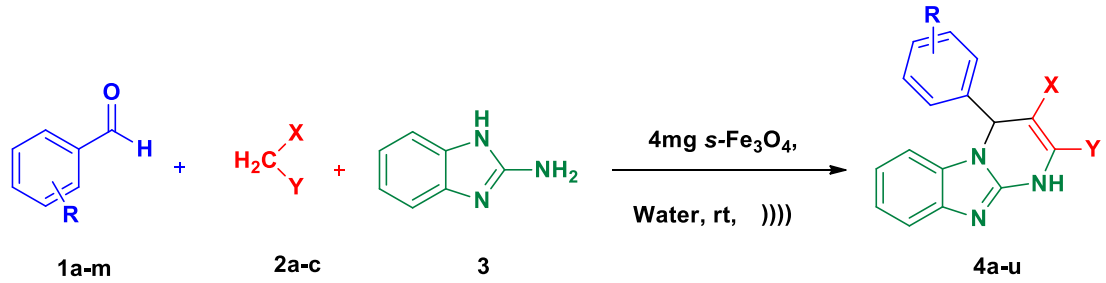
2.2.3 Substrate Scope

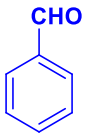
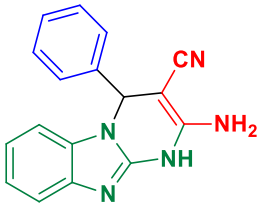
With optimized conditions in hand (**Table 1, entry 13**), the scope of this *s*-Fe_3O_4 catalyzed protocol was investigated with a variety of aromatic aldehydes such as benzaldehyde (**1a**), 2-methylbenzaldehyde (**1b**), 4-methoxybenzaldehyde (**1c**), 2-naphthaldehyde (**1d**), 2-nitrobenzaldehyde (**1e**), 4-nitrobenzaldehyde (**1f**), 2-chlorobenzaldehyde (**1g**), 3-chlorobenzaldehyde (**1h**), 4-chlorobenzaldehyde (**1i**), 2,3-dichlorobenzaldehyde (**1j**), 4-fluorobenzaldehyde (**1k**), 4-bromobenzaldehyde (**1l**) and malononirile (**2a**) with 2-aminobenzimidazole (**3**) which leads to a series of imidazopyrimidine derivatives viz. 2-amino-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4a**), 2-Amino-4-(o-tolyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile (**4b**), 2-amino-4-(4-methoxyphenyl)-1,4 dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3 carbonitrile (**4c**), 2-amino-4-(naphthalen-1-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (**4d**), 2-amino-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile **(4e)**, 2-amino-4-(4-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile **(4f)**, 2-amino-4-(2-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile **(4g),** 2-amino-4-(3-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-

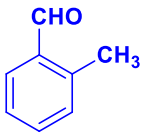
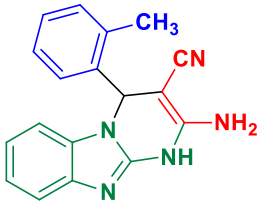
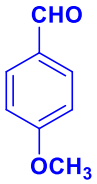
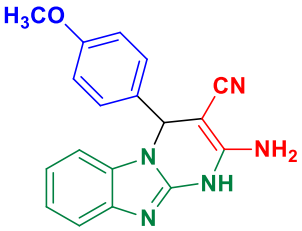
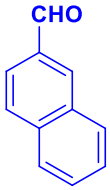
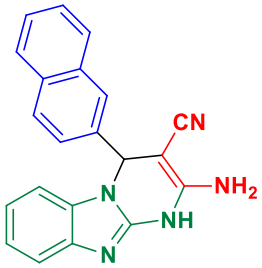
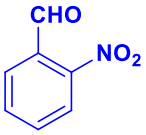
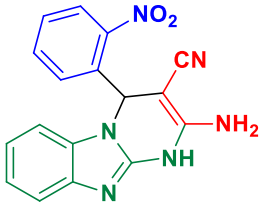
carbonitrile **(4h)**, 2-amino-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile **(4i)**, 2-amino-4-(2,3-dichlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile **(4j)**, 2-Amino-4-(4-fluorophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile **(4k),** 2-Amino-4-(4-bromophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3 carbonitrile **(4l)** in high-to-excellent yields. **Table 2.2**, reveal that nitro, chloro, fluoro, bromo electron-withdrawing groups on benzaldehyde leads to excellent yields in shorter reaction time than electro donating groups like methoxy, methyl. Further under the same optimized conditions the reaction of different active methylene compounds like ethyl acetoacetate (**2b**), dimedone (**2c**) with various aldehydes (**1**) and 2-aminobenzimidazole (**3**) 1-(2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (**4m**), 1-(4-(4-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3 yl)propan-1-one (**4n**), 1-(4-(4-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one **(4o),** 1-(2-methyl-4-(4-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one **(4p),** 3,3-dimethyl-12-phenyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one **(4q),** 12-(4-methoxyphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one **(4r),** 3,3-dimethyl-12-(naphthalen-2-yl)-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one **(4s),** 3,3-dimethyl-12-(4-nitrophenyl)-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one **(4t),** 12-(4-chorophenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-

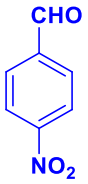
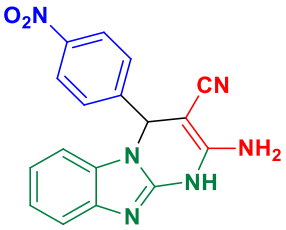
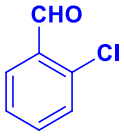
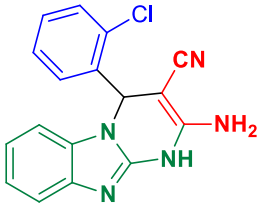
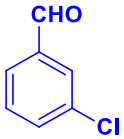
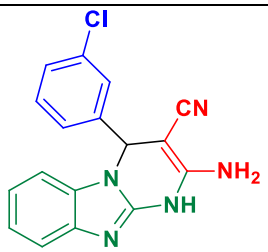
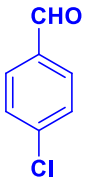
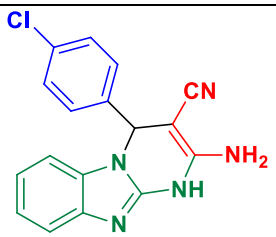
one **(4u),** gave desired products in excellent yields but it took slightly longer reaction time than malanonitrile. Excellent chemoselectivity is an important aspect of this reaction it gave only (**4**) as the major product in very high yields and the other possible product (**5**) was not observed in this methodology (**Scheme 2.2**).

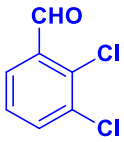
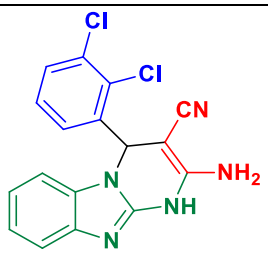
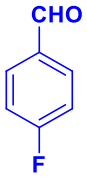
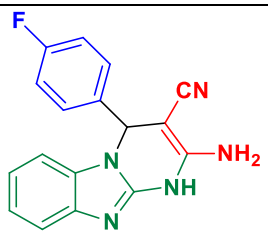
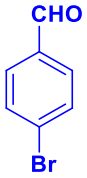
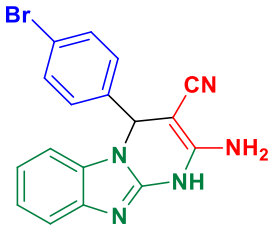
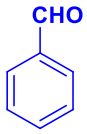
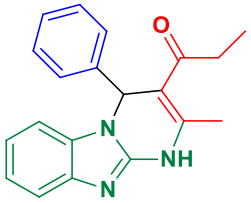
Table 2.2 Starch functionalized magnetite nanoparticles catalyzed the multicomponent synthesis of imidazopyrimidines (4a-u).

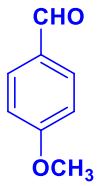
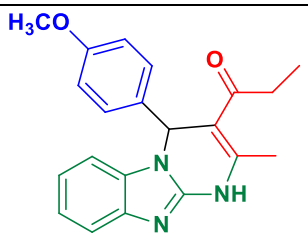
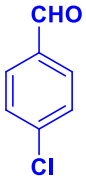
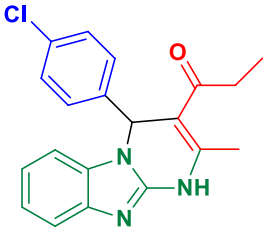
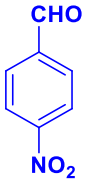
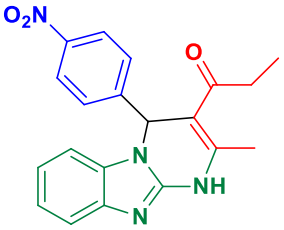
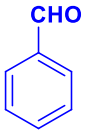
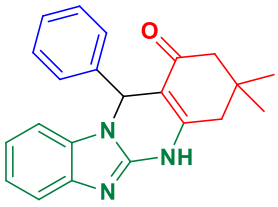


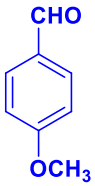
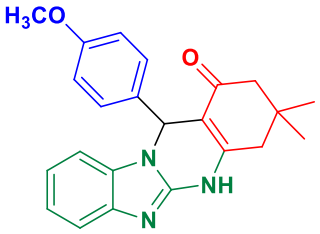
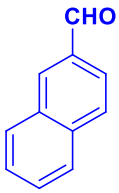
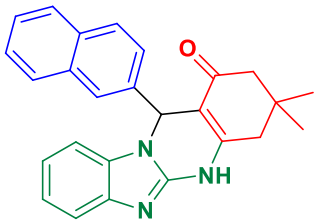
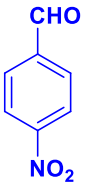
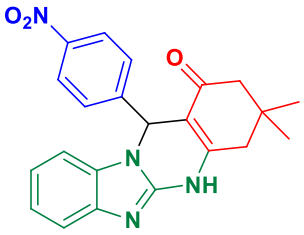
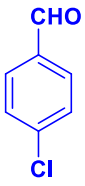
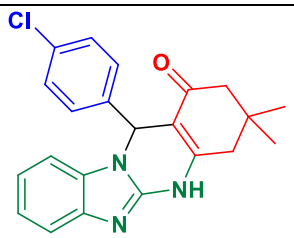
Entry	Reactant	Product	Time (min)	% Yield[b]
1	 1a	 4a	3	98

2	 1b	 4b	5	95
3	 1c	 4c	6	93
4	 1d	 4d	4	96
5	 1e	 4e	3	96

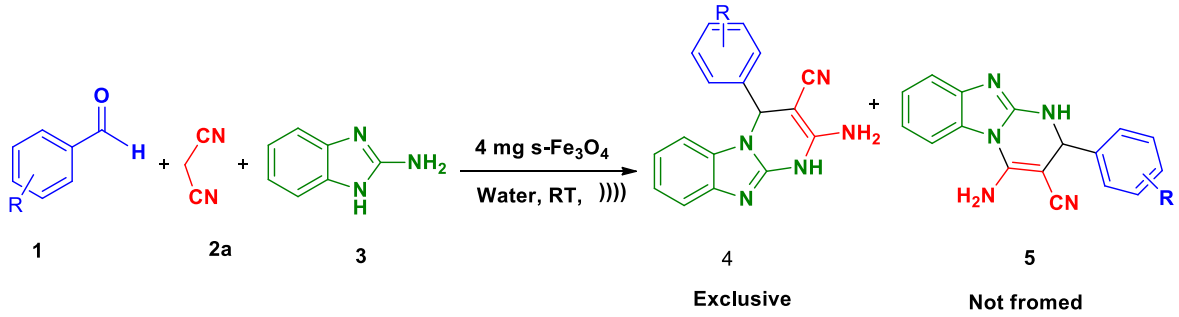
6	 1f	 4f	2	98
7	 1g	 4g	3	95
8	 1h	 4h	5	94
9	 1i	 4i	3	97

10	 1j	 4j	4	96
11	 1k	 4k	3	98
12	 1l	 4l	4	97
13	 1a	 4m	6	95

14	 1c	 4n	8	96
15	 1i	 4o	6	97
16	 1f	 4p	6	97
17	 1a	 4q	9	96

18	 1c	 4r	9	98
19	 1d	 4s	8	95
20	 1f	 4t	7	98
21	 1i	 4u	7	98

[a] **Reaction conditions:** Benzaldehyde derivatives 1a-l (1.2 mmol), active methylenic compounds 2a-c (1.2), 2-amino benzimidazole 3 (1.0 mmol) and *s*-Fe_3O_4 (4 mg) in 5 mL water under ultrasound irradiation method, b isolated yield



Scheme 2.2 Chemoselective synthesis of 4

2.2.4 Reusability of *s*-Fe_3O_4 nanocatalyst

The reusability of *s*-Fe_3O_4 nanocatalyst was also examined under the optimized reaction conditions up to 6 runs (**Figure 2.7**). The catalyst was separated by an external magnet after completion of the reaction, first washed with water and then methanol (3x10mL), dried at 60 ^oC and used in next reaction. The collected catalyst could be reused numerous times in the succeeding runs without a significant loss of catalytic activities. Comparison of XRD pattern (**Figure 2.9**) and FT-IR spectra (**Figure 2.8**) of the fresh and recycled catalyst *s*-Fe_3O_4 has shown that the reaction conditions do not affect the structure and chemical nature of the catalyst.

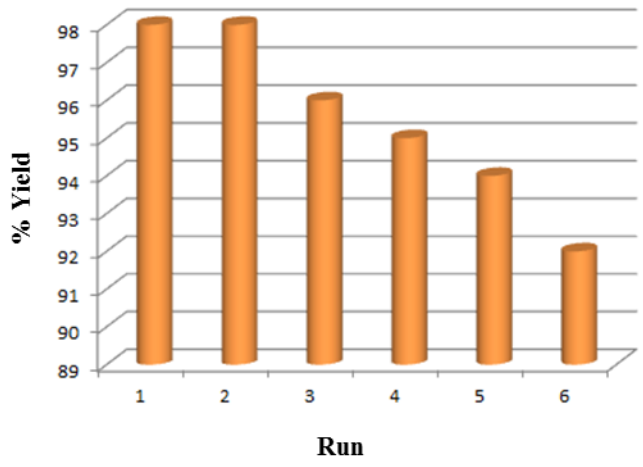


Figure 2.7 Recyclability of catalyst upto 6 runs

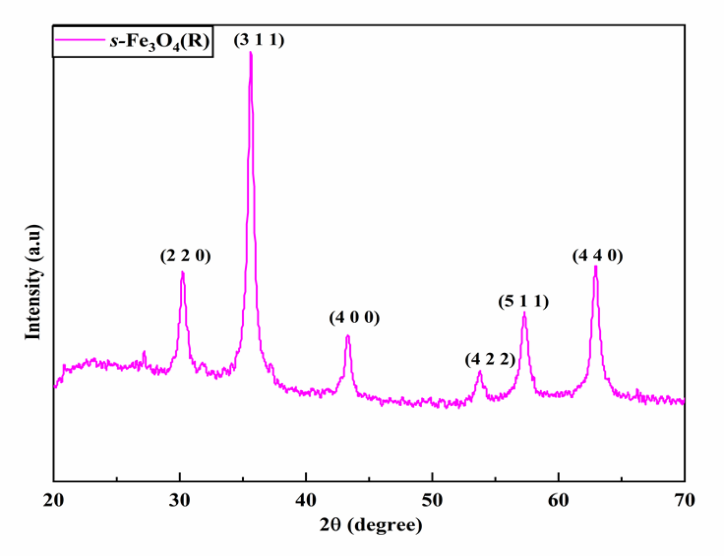


Figure 2.8 XRD pattern of reused *s*-Fe_3O_4

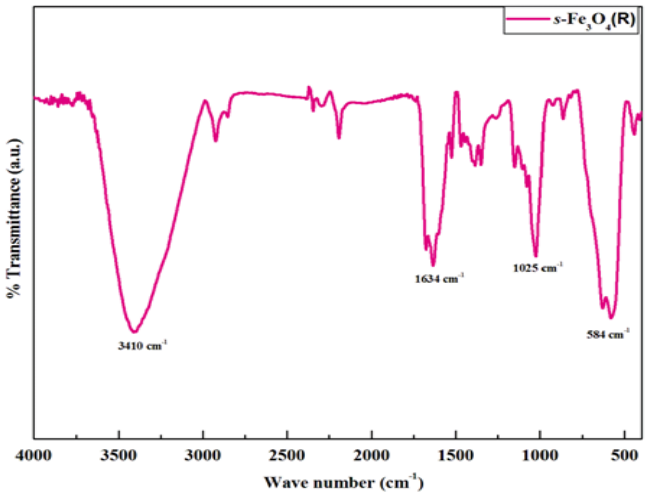


Figure 2.9 FT-IR of reused *s*-Fe_3O_4

2.2.5 Proposed Mechanism

A proposed mechanism for the *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidine based on the product analysis is shown in **Figure 2.10**. In the presence *s*-Fe_3O_4 catalyst the carbonyl group of aldehyde get polarized and its electrophillicity that help the condensation with malanonitrile to from arylidenemalononitrile intermediate (**I**) by Knoevenagel reaction. In the next step, Michael addition by ring nitrogen atom of 2-aminobenzimidazole (**3**) to arylidenenitrile (**I**) followed by intermolecular cyclization (**II**) *in situ* and gives the product (**4**).

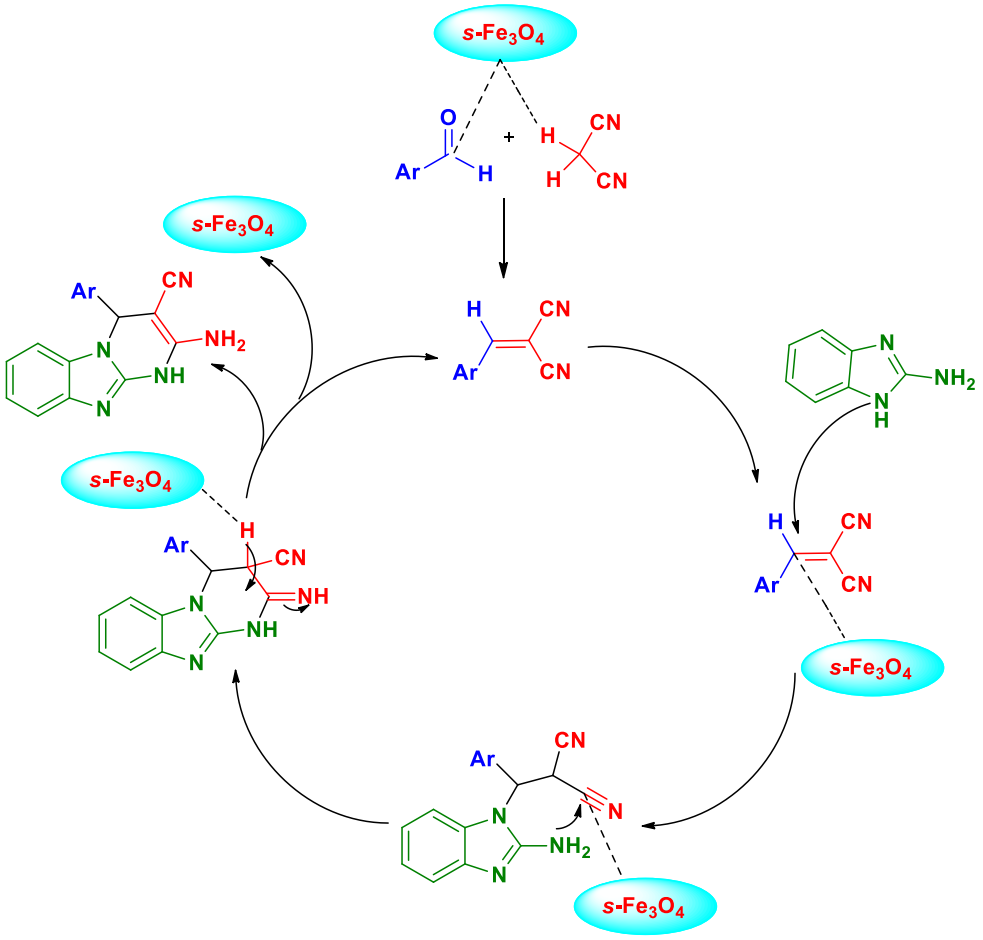


Figure 2.10 Plausible mechanism for *s*-Fe_3O_4 catalyzed synthesis of imidazopyrimidine

2.3 Experimental Section

2.3.1 General experimental procedure for the synthesis of imidazo pyrimidine derivatives (4a-u)

Aldehyde (1.2 mmol), active methylene compound (1.2 mmol), 2-aminobenzimidazole (1.0 mmol) and starch functionalized Fe_3O_4 (4 mg) were sonicated

in water (5 mL) and progress of the reaction was monitored by TLC. The catalyst was collected by an external magnet, after completion of the reaction. The reaction mixture was extracted with ethyl acetate (3×10 mL), washes with brine (3×10 mL) and dried over sodium sulphate. The solvent was evaporated under vacuum and the solid obtained was purified by recrystallization.

2.4 Analytical data

2-Amino-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4a) Yield 98%; yellow powder; m.p. 234–236°C; **IR** (KBr) 3354, 3115, 2176 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.57 (s, 1H, NH), 7.36-7.33 (t, 1H), 7.29-7.27(d, 2H), 7.23-7.22 (d, 1H), 7.13-7.10 (t, 1H), 7.02-6.99 (t, 1H), 6.79 (s, 2H), 5.21 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.39, 148.80, 143.13, 142.50, 128.89, 128.42, 127.60, 125.56, 123.12, 119.68, 118.85, 115.77, 112.02, 61.60, 52.89.

2-Amino-4-(o-tolyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile (4b) Yield 95%; white powder; m.p. 235–236°C; **IR** (KBr) 3398, 3348, 2185 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.33 (s, 1H, NH), 7.66-7.64 (d, 2H), 7.23-7.17 (m, 3H), 7.13-7.10 (t, 2H), 7.02–6.99 (t, 1H), 6.78 (s, 2H), 5.48 (s, 1H), 2.41 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.56, 148.97, 143.22, 139.70, 134.63, 130.34, 128.90, 127.45, 126.11, 126.09, 122.95, 119.50, 118.48, 115.60, 111.97, 61.42, 49.95, 18.52.

2-Amino-4-(4-methoxyphenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3 carbonitrile (4c) Yield 93%; white powder; m.p. 265–266°C; **IR** (KBr) 3392, 3343, 2179 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.49 (s, 1H, NH), 7.63-7.62 (d, 1H), 7.22-7.19 (t, 3H), 7.12-7.09 (t, 1H), 7.01-6.98 (t, 1H), 6.91-6.90 (d, 2H), 6.78 (s, 2H), 5.14 (s, 1H), 3.71 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 158.42, 151.27, 148.56, 143.13, 134.33, 128.81, 126.79, 122.80, 119.32, 118.70, 115.54, 113.53, 111.89, 61.82, 54.61, 52.27.

2-Amino-4-(naphthalen-1-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4d) Yield 96%; white powder; m.p. 228–229°C; **IR** (KBr) 3390, 3340, 2183 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.66 (s, 1H, 1NH), 7.93-7.88 (m, 4H), 7.78 (s, 1H), 7.66-7.64 (d, 1H), 7.52-7.50 (m, 1H), 7.47-7.45 (m, 1H), 7.24-7.23 (d, 1H), 7.14-7.10 (t, 1H), 7.02-6.99 (d, 1H), 6.86 (s, 2H), 5.41 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.21, 148.73, 143.00, 139.59, 132.09, 128.81, 128.19, 127.39, 127.06, 126.01, 125.73, 124.06, 123.89, 122.84, 119.38, 118.67, 115.58, 114.52, 111.93, 61.31, 53.10.

2-Amino-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4e) Yield 96%; brown powder; m.p. 233–235 °C; **IR** (KBr) 3319, 2182, 1670, 1645, 1565 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.59 (s, 1H, NH), 7.62-7.61 (d, 1H), 7.56-7.55 (d, 1H), 7.25-7.22 (t, 2H), 7.13-7.10 (t, 1H), 7.02-6.99 (t, 2H), 6.85 (s, 2H), 5.23 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.18, 148.88, 143.18,

141.47, 131.28, 128.84, 127.90, 123.12, 120.66, 119.69, 118.68, 115.79, 112.06, 60.99, 52.26.

2-Amino-4-(4-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4f) Yield 98%; brown powder; m.p.> 300 °C; **IR** (KBr) 3329, 2180, 1677, 1640, 1560 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.75 (s, 1H), 8.25-8.23 (d, 2H), 7.64-7.62 (d, 1H), 7.56-7.55 (d, 2H), 7.26-7.24 (d, 1H), 7.14-7.11 (t, 1H), 7.03-7.00 (t,1H), 6.95 (s, 2H), 5.44 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 150.97, 149.69, 148.99, 146.60, 128.76, 126.78, 123.63, 123.05, 119.63, 118.48, 115.77, 112.08, 60.15, 52.05.

2-Amino-4-(2-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4g) Yield 95%; white powder; m.p. 232-234°C; **IR** (KBr) 3425, 3310, 2190 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H, NH), 7.66-7.65 (d, 1H), 7.48 (s, 1H), 7.34 (s, 1H), 7.25-7.23 (d, 1H), 7.15-7.12 (t, 1H), 7.04-7.01 (t, 1H), 6.88 (s, 2H), 5.64 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.27, 149.14, 143.00, 138.86, 131.00, 129.33, 128.75, 128.03, 127.54, 123.08, 119.70,118.14,115.70, 112.07, 60.38, 50.45.

2-Amino-4-(3-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4h) Yield 94%; white powder; m.p. 240–242 °C; **IR** (KBr) 3255, 2190, 1680, 1635, 1540 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.60 (s, 1H, NH), 7.84-7.83 (d, 1H), 7.80-7.79 (d, 1H), 7.63-7.55 (m, 1H), 7.38-7.34 (d, 1H), 7.25-7.24 (d, 2H), 7.13-7.10

(t, 1H), 7.02-6.99 (t, 1H), 6.88 (s, 2H), 5.24 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.08, 148.74, 143.05, 141.73, 131.12, 130.92, 130.22, 128.75, 127.76, 122.89, 122.43, 120.47, 119.45, 118.55, 115.63, 111.97, 110.84, 60.88, 52.11.

2-Amino-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile (4i) Yield 97%; yellow powder; m.p. 234-235°C; **IR** (KBr) 3443, 3315, 2185 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.59 (s, 1H, NH), 7.63-7.61 (d, 1H), 7.43-7.42 (d, 2H), 7.31-7.29 (d, 1H), 7.24-7.22 (d, 1H), 7.13-7.12 (d, 1H), 7.02-7.00 (d, 1H), 6.86 (s, 2H), 5.25 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.11, 148.77, 143.07, 141.30, 131.97, 130.35,128.67, 128.24, 127.38, 122.94, 119.50, 118.58, 115.67, 111.99, 60.93, 51.78.

2-Amino-4-(2,3-dichlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile (4j) Yield 96%; white powder; m.p. 245–246°C; **IR** (KBr) 3422, 3310, 3208, 2902, 2198 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.48 (s, 1H, NH), 7.65 – 7.63 (m, 1H), 7.45-7.43 (d, 1H), 7.38-7.36 (d, 1H), 7.25-7.24 (d, 1H), 7.15-7.12(t, 1H), 7.04-7.01 (t, 1H), 6.88 (s, 2H), 5.63 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.30, 149.40, 143.08, 137.88, 133.25, 132.26, 129.75, 128.94, 127.87,123.40, 120.05, 118.22, 115.97, 112.09, 59.42, 50.34.

2-Amino-4-(4-fluorophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile (4k) Yield 98%; yellow powder; m.p. 266–268 °C; **IR** (KBr) 3424, 3314, 3206, 3052, 2890 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.57 (s, 1H, NH), 7.64-

7.62 (d, 1H), 7.34-7.31 (t, 1H), 7.24-7.17 (m, 3H), 7.13-7.10 (t, 1H) 7.02-7.00 (t, 1H), 6.84 (s, 2H), 5.25 (s, 1H); **^{13}C NMR** (125 Hz, DMSO-d_6) δ (ppm): 150.91, 149.11, 147.39, 144.58, 143.00, 132.31, 130.02, 128.74, 123.04, 122.42, 120.35, 120.35, 119.62, 118.51, 115.75, 112.05, 60.10, 51.84.

2-Amino-4-(4-bromophenyl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3 carbonitrile (4l) Yield 97%; yellow powder; m.p.> 300 °C; **IR** (KBr) 3326, 2185, 1675, 1470, 1420 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.59 (s, 1H, NH), 7.62-7.61 (d, 1H), 7.56-7.55 (d, 2H), 7.25-7.22 (t, 2H), 7.13-7.10 (t, 1H), 7.02-6.99 (t, 1H), 6.85 (s, 2H), 5.23 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 151.18, 148.88, 143.01, 141.79, 131.28, 128.84, 127.90, 123.12, 120.66, 119.69, 118.68, 115.79, 112.06, 60.06, 52.26.

1-(2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (4m) Yield 95%; White powder; m.p 288-289°C; **IR** (KBr) 3025, 2975, 2940, 1695, 1580 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.79 (s, 1H), 7.35-7.33 (m, 3H), 7.27-7.23 (m, 3H), 7.19-7.16 (t, 1H), 7.05-7.02 (t, 1H), 6.96-6.93 (t, 1H), 6.41 (s, 1H), 4.02-3.97 (m, 2H), 2.45 (s, 3H), 1.14-1.12 (t, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 164.74, 146.12, 145.18, 141.27, 131.12, 128.00, 127.43, 126.70, 121.43, 119.85, 116.38, 109.46, 97.58, 59.23, 55.09, 18.20, 13.53.

1-(4-(4-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (4n) Yield 96%; White powder; m.p. 270-274°C; **IR** (KBr) 3050, 2980, 2958, 1615, 1575, 1260 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.79 (s, 1H),

7.34-7.33 (d, 1H), 7.28-7.25 (m, 3H), 7.05-7.02 (t, 1H), 6.96-6.93 (t, 1H), 6.81-6.79 (d, 2H), 6.37 (s, 1H), 4.02–4.00 (m, 2H), 3.57 (s, 3H), 2.45 (s, 3H), 1.16-1.13 (t, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 165.23, 164.74, 158.13, 145.82,145.62, 145.14, 145.12, 141.81, 133.66, 131.00, 127.79, 127.62, 121.19, 119.63, 119.58, 116.23, 113.24, 113.14, 109.38, 97.68, 97.60, 58.99, 54.21, 50.29, 18.13, 13.59.

1-(4-(4-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (4o) Yield 97%; White powder; m.p. 267-268°C; **IR** (KBr) 3061, 2935, 2840, 1620, 1573, 1270 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.86 (s, 1H), 7.39-7.36 (t, 3H), 7.34-7.32 (t, 3H), 7.26-7.24 (d, 1H), 7.06-7.03 (t, 1H), 6.97-6.94 (t, 1H), 6.45 (s, 1H), 4.03-4.02 (t, 2H), 2.46 (s, 3H), 1.16-1.13 (t, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 165.58, 147.33, 145.92, 142.77, 141.51, 132.80, 131.93, 129.53, 128.90, 122.38, 120.77, 117.36,110.34, 97.98, 59.93, 55.74, 19.16, 14.57.

1-(2-methyl-4-(4-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-3-yl)propan-1-one (4p) Yield 97%; White powder; m.p. 276-278°C; **IR** (KBr) 3055, 2940, 2837, 1675, 1570, 1260 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.97 (s, 1H), 8.14-8.12 (d, 2H), 7.66-7.64 (d, 2H), 7.37-7.35 (d, 1H), 7.27-7.26 (d, 1H), 7.06-7.03 (t, 1H), 6.97-6.64 (t, 1H), 6.60 (s, 1H), 4.03-4.01(m, 2H), 2.47 (s, 3H), 1.16-1.14(t, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 165.42, 148.51, 146.98, 146.42, 144.73, 141.73, 130.83, 128.01, 123.20, 121.53, 119.94, 116.47, 109.27, 96.29, 59.04, 54.73, 17.89, 13.54.

3,3-Dimethyl-12-phenyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one (4q) Yield 96%; White powder; m.p.> 300 °C; **IR** (KBr) 3431, 2890, 1640, 1622, 1588 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.12 (s, 1H, NH), 7.36-7.32 (d, 3H), 7.25 (s, 3H), 7.15 (s, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 6.41 (s, 1H), 2.65-2.62 (d, 2H), 2.27-2.24 (d, 1H), 2.07-2.04 (d, 1H), 1.06 (s, 3H), 0.93 (s, 3H).

12-(4-methoxyphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one (4r) Yield 98%; White powder; m.p.> 300 °C; **IR** (KBr) 3432, 2892, 1645, 1620, 1590 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.00 (s, 1H, NH), 8.17 (s, 1H), 7.33-732 (d, 1H), 7.23-7.21 (d, 2H), 7.17-7.15 (d, 1H), 7.03-7.00 (t, 1H), 6.93-6.90 (t, 1H), 6.75-6.73 (s, 1H), 6.30 (s, 1H), 3.64 (s, 3H), 2.60-2.56 (d, 2H), 2.23-2.20 (d, 1H), 2.06-2.02 (d, 1H), 1.06 (s, 3H), 0.94 (s, 3H).

3,3-dimethyl-12-(naphthalen-2-yl)-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one (4s) Yield 95%; White powder; m.p.> 300 °C; **IR** (KBr) 3427, 2923, 2992, 1647, 1576 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.11 (s, 1H, NH), 8.15 (s, 1H), 7.96 (s, 1H), 7.84-7.83 (d, 1H), 7.74-7.69 (m, 1H), 7.44-7.29 (m, 4H), 7.19-7.18 (d, 1H), 7.00-6.97 (t, 1H), 6.89-6.86 (t, 1H), 6.53 (s, 1H), 2.64-2.54 (m,2H), 2.24-2.21 (d, 1H), 2.05-2.01 (d, 1H), 1.07 (s, 3H), 0.93 (s, 3H).

3,3-dimethyl-12-(4-nitrophenyl)-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one (4t) Yield 98%; White powder; m.p.> 300 °C; **IR** (KBr) 3542, 3043, 1645, 1600, 1590 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.28 (s, 1H), 8.12-

8.11 (d, 2H), 7.61-7.60 (d, 2H), 7.40-7.38 (d, 1H), 7.22-7.21 (d, 1H), 7.08-7.05 (t, 1H), 6.98-6.95 (t, 1H), 6.59 (s, 1H), 2.66-2.63 (t, 1H), 2.55-2.54 (t, 1H), 2.28-2.25 (d, 1H), 2.07-2.04 (d, 1H), 1.05 (s, 3H), 0.90 (s, 3H).

12-(4-chorophenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one3 (4u) Yield 98%; White powder; m.p.> 300 °C; **IR** (KBr) 3442, 2956, 1646, 1617, 1590, 1569 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 11.03 (s, 1H, NH), 8.18 (s, 1H), 7.34-7.30 (m, 2H), 7.22-7.19 (t, 2H), 7.14-7.12 (d, 1H), 7.03-7.00 (t, 1H), 6.93-6.90 (t, 1H), 2.60-2.57 (d, 1H), 2.39-2.36 (d, 1H), 2.24-2.20 (d, 1H), 2.07-2.04 (d, 1H), 1.07 (s, 3H), 0.94 (s, 3H).

2.5 Spectral data of product for few products

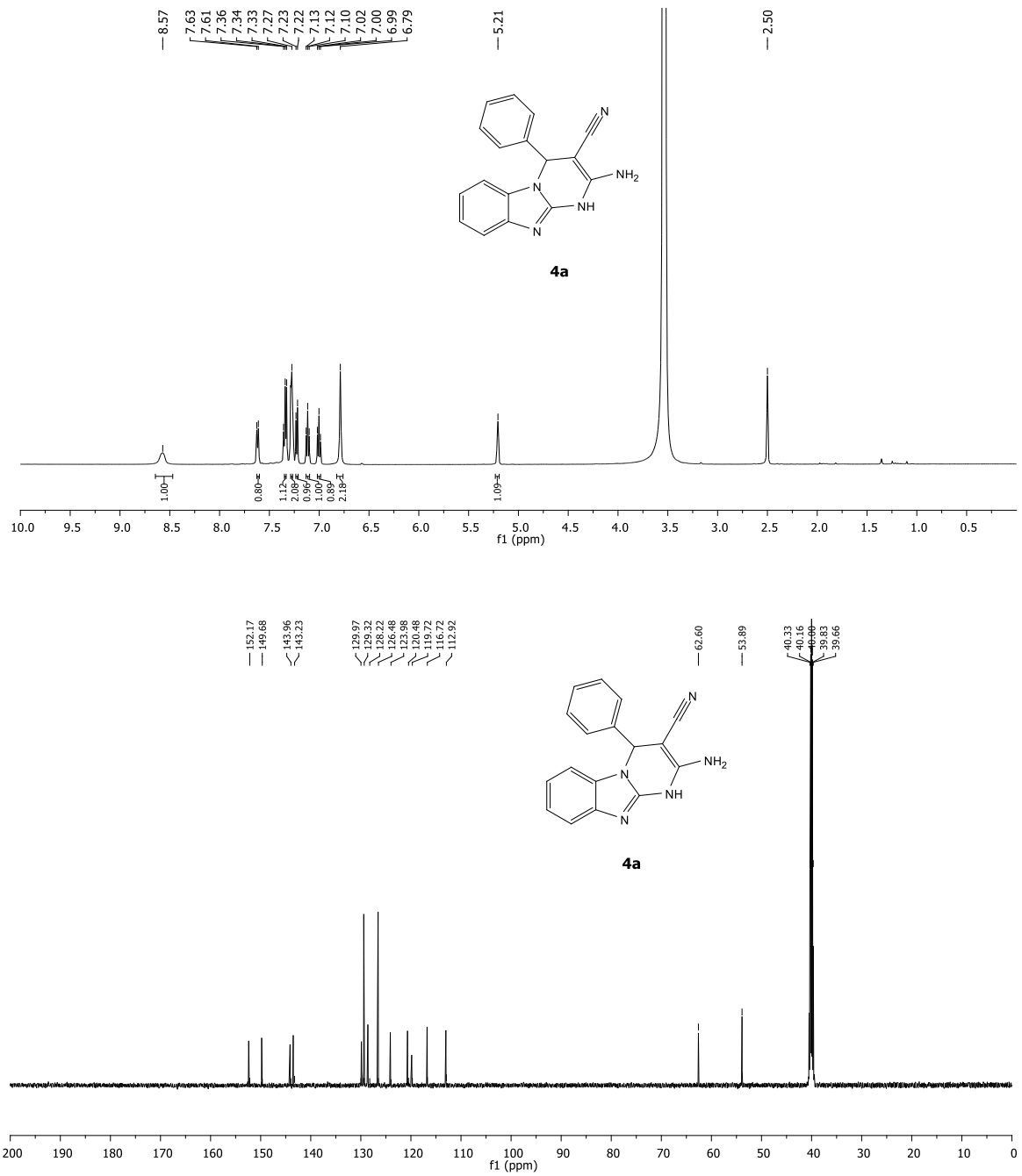


Figure 2.11 ^{1}H NMR & ^{13}C NMR of 2-Amino-4-phenyl-1,4 dihydrobenzo[4,5]imidazo [1,2-a]pyrimidine-3-carbonitrile (4a)

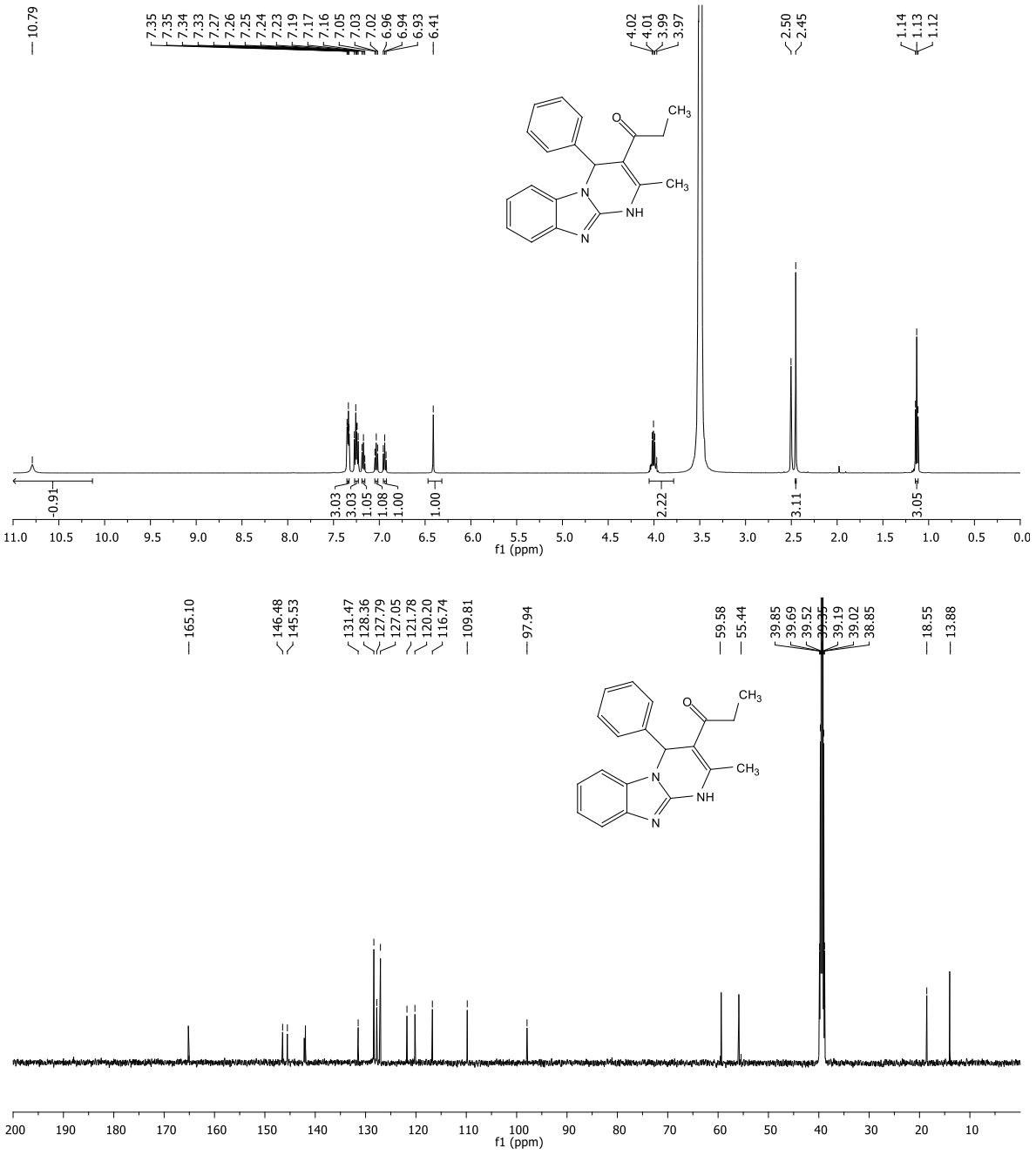


Figure 2.12 ^{1}H NMR & ^{13}C NMR of 2-Amino-4-phenyl-1,4 dihydrobenzo[4,5]imidazo [1,2-a]pyrimidine-3-carbonitrile (4m)

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CHAPTER 3

Developing a Sustainable Metal and Catalyst Free Chemoselective Synthesis of Benzimidazole and Benzothiazole under Controlled Reaction Conditions via Solid-State Oxidative Cyclization

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3.1 Introduction

Nitrogen and sulphur containing heterocycles such as benzimidazole, benzothiazole and there derivatives occupy an important place in both medicinal and industrial chemistry for human welfare (Kanwal et al. 2019, Prajapati et al. 2014). These compounds play an important role in the metabolism of all living cells. Benzimidazole and benzothiazole derivatives exhibit numerous significant in biological activities such as antiallergic (Nakano et al. 2000), anticancer (Azam et al. 2015), antimicrobial (Pawar et al. 2004), antiulcer (Patil et al. 2008), antifungal (Shi et al. 2019), antihistaminic (Mavrova et al. 2007), antiviral (Budow et al. 2009), anti-inflammatory (Lazer et al. 1987), antihypertensive (Kubo et al. 1993), antidiabetic (Vinodkumar et al. 2008), anti HIV (Roth et al. 1997), antiprotozoal (Navarrete-Vázquez et al. 2001), anti-hepatitis B virus (Li et al. 2006), anti-tumor (Denny et al. 1990), anti-oxidant (Kus et al. 2004) and antitrichinellosis activity (Mavrova et al. 2010) (**Figure 3.1**). Moreover, these derivatives have remarkable applications in material science, polymer and dye synthesis (Berrada et al. 2002) and also found pervasive application in fluorescence (Shao et al. 2009), chemosensing (Singh et al. 2007), crystal engineering (Li et al. 2007) and corrosion science (Roque et al. 2008).

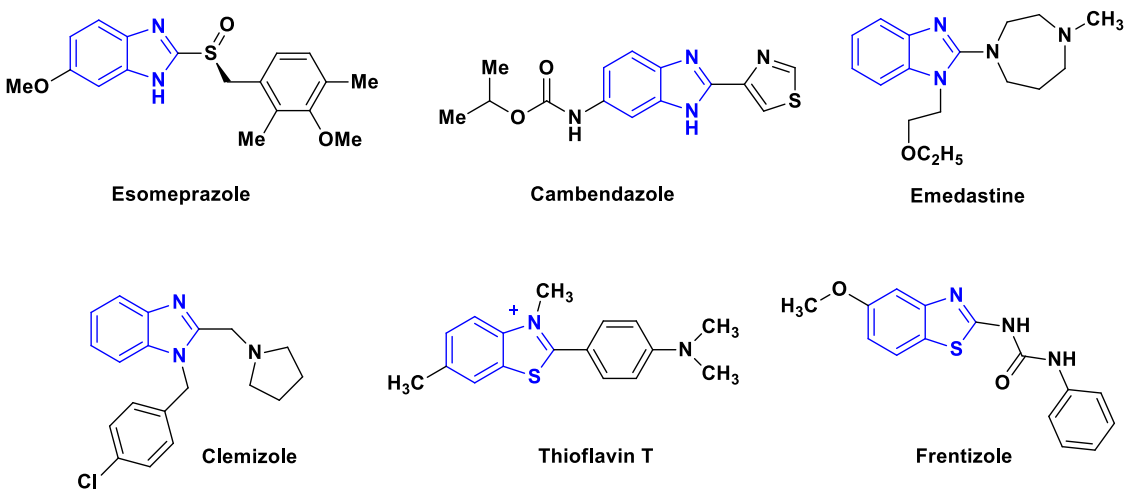


Figure 3.1 Some pharmacologically active benzimidazole and benzothiazole compounds

Several distinctive synthetic methods have been reported for achieving benzimidazoles and benzothiazoles due to their wide range of applications in organic chemistry as intermediates and ligands for the asymmetric catalysis. Traditionally, these fused heterocycles have been synthesized by the condensation of aldehydes with *o*-phenylenediamine/ 2-aminothiophenol in the presence of different catalysts and oxidants like K-10 (Landge et al. 2008), I_2 (Aniket et al. 2015), glycerol (Radatz et al. 2011), PEG-400 (Mekala et al. 2015), lactic acid (Yu et al. 2016), glyoxylic acid (Pawar et al. 2008), thiamine hydrochloride (Lei et al. 2012), $FeCl_3$ (Liu et al. 2012), $FePO_4$ (Behbahani et al. 2012), SnP_2O_7 (Merroun et al. 2019), $NH_4Fe(SO_4)_2$ (Khazaei et al. 2016), $NiCl_2$ (Bera et al. 2019), P_2O_5/SiO_2 (Shaterian et al. 2011), Indion 190 Resin (Reddy et al. 2011), $NiFe_2O_4@SiO_2@$amino glucose (Fekri et al. 2018), nano In_2O_3 (Santra et al. 2012), Ir/TiO_2 (Fukutake et al. 2018), Zn-Proline (Ravi et al. 2007), ZnO (Sharma et al. 2015), Cu/Al_2O_3

(Pogula et al. 2017), $LnCl_3$ (Zhang et al. 2012), $SnCl_4$ (Mirjalili et al. 2019), $Er(OTf)_3$ (Cano et al. 2016), $MnO_2/ZrCl_4$ (Wang et al. 2014), UiO-66-$NHSO_3H$ (Homaee et al. 2019), laccase (Maphupha et al. 2018), SDS micelles (Bahrami et al. 2010), ZrO_2-b-cyclodextrin (Girish et al. 2015), Cu(I) glycosyltriazole (Mishra et al. 2019), TAP-Cu (Xu et al. 2017), silica@ytterbium (Samanta et al. 2018), chitosan@Fe_3O_4 (Maleki et al. 2014) and natural wool@Fe_2O_4 nanoparticles (Shaabani et al. 2017). Bose *et. al.*, have reported synthesis of 1,2-disubstituted benzimidazoles via an intramolecular C(sp3)–H imination with PhI– mCPBA (Bose et al. 2019) and Chopra *et. al.*, have reported visible light promoted synthesis of 2-substituted benzimidazole (Chopra et al. 2019). Recently the formation of 2-substituted, 1,2-disubstituted benzimidazoles from *o*-phenylenediamine and alcohol using manganese catalyst in strong basic medium have been reported by Srimani and coworkers (Das et al. 2018). Most of these existing methods require metal catalysts, bases, solvents, stoichiometric amount of oxidants, higher reaction temperature and longer reaction time etc. However green sustainable method for selective synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles/ benzothiazoles is highly desirable.

UHP is a white crystalline solid, soluble in water, stable at room temperature and easy to handle. UHP is an important oxidizing reagent widely used in various organic transformations such as synthesis of amides by the hydrolysis of cyano group, epoxidation of double bond, thiols to disulfides, secondary alcohols to ketones, sulfides to sulfoxides

and sulfones, pyridine to pyridine-N-oxide. Dakin and Baeyer–Villiger oxidation reaction was also carried out in the presence of UHP as well as chemoselective ipso- hydroxylation of arylboronic acids (Laha et al. 2001, Varma et al. 1999, Marcantoni et al. 1995, Gupta et al. 2016).

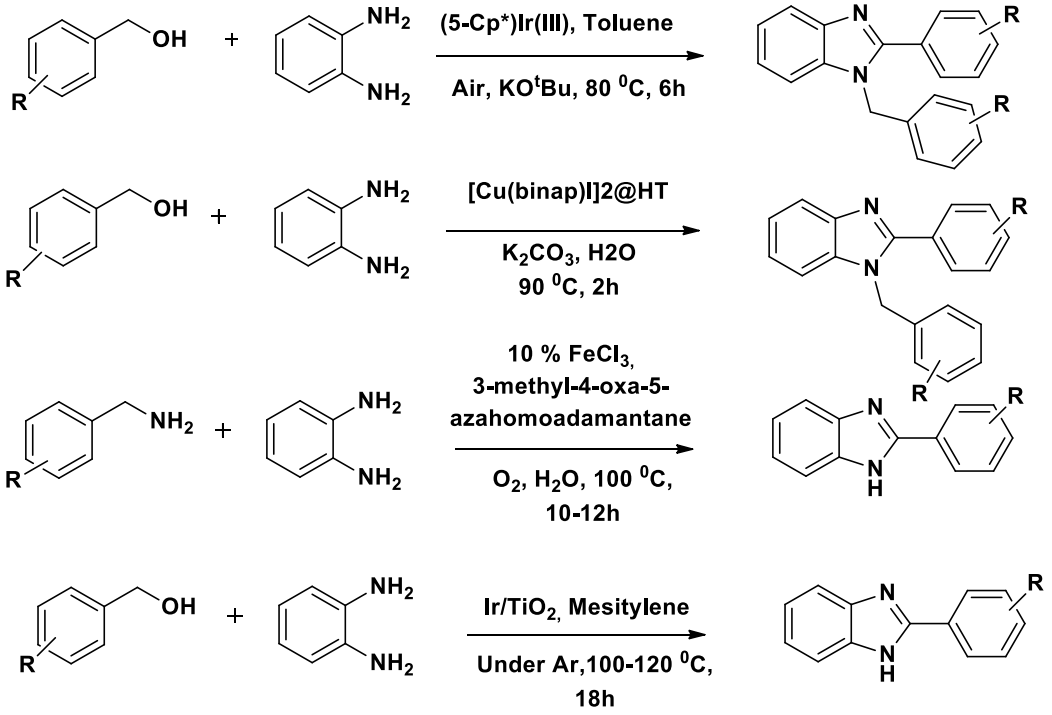
Green chemistry has become an important tool in the field of synthetic organic chemistry. In organic synthesis transition metal catalysts and volatile organic solvents are replaced by green catalysts and solvents like water, ionic liquids, bio-based green solvents (poly ethylene glycol and glycerol), supercritical carbon dioxide or reaction in solvent free condition (Singh et al. 2016, Datta et al. 2012, Mohira et al. 2019). Reactions in neat condition (i.e in solid state) are ideal because solvent free condition reduces environmental pollution and cost of the solvents. Alternative energy source for the chemical reactions is another concern of green chemistry, utilization of non-classical energy sources such as mechanochemical ball milling technique, ultrasound, microwave irradiation and UV light radiation in order to save energy and time. In grinding method reaction starts with the transfer of the very small amount of mechanical energy which is generated by grinding the reactants in a mortar and pestle in solvent free condition and leads to the formation of the product. Since it has several advantages in terms of environmental impact, effectiveness, requires no special apparatus, cost of solvents & energy sources and easiness of the reaction protocol (Hematinezhad et al. 2019, Zangade et al. 2019, Abdelrazek et al. 2019).

Methyl arenes are naturally available cheap and abundant starting materials used in the development of organic transformations. Fundamental challenges in the oxidation of

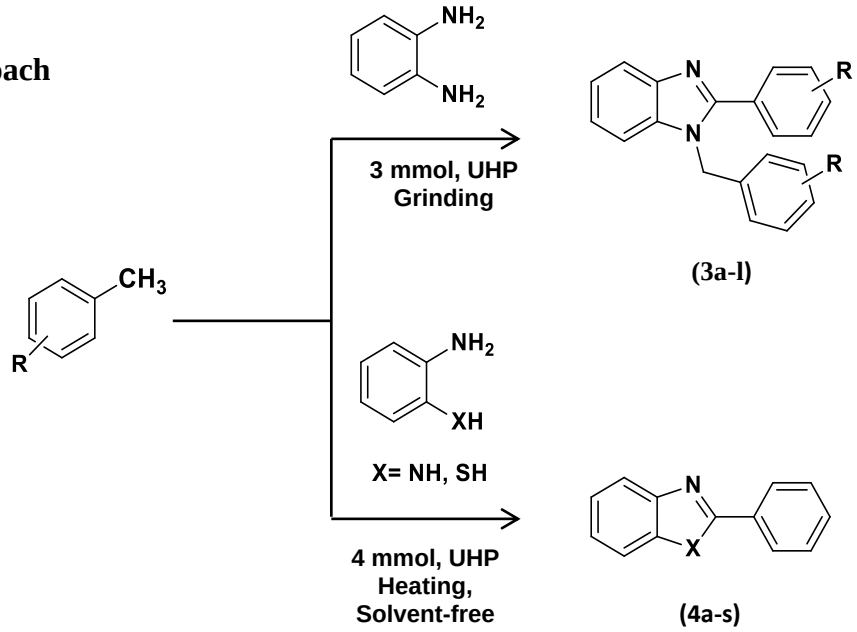
methyl arenes which involves C-H bond activation. Chemoselective oxidation of toluene under controlled reaction conditions is still challenging because different oxidized products are formed like benzyl alcohol, benzaldehyde and benzoic acid but under harsh reaction conditions it gave over oxidized product benzoic acid. These are very important starting material in synthetic organic chemistry and industrial point of view (Mahyari et al. 2014, Gaster et al. 2017, Shaabani et al. 2008).

In continuation of our efforts towards development of simple, eco-friendly reaction protocols for organic transformations (Verma et al. 2019, Chauhan et al. 2018), here we report a practical and sustainable protocol for the chemoselective synthesis of 1,2–disubstituted benzimidazoles, 2-substituted benzimidazoles/ benzothiazoles by urea hydrogen peroxide complex (UHP) initiated oxidative coupling of methyl arenes with *o*-phenylenediamine/ 2-aminothiophenol in one pot by varying reaction parameters. To the best of our knowledge synthesis of these fused heterocycles directly from methyl arenes and 1,2-diaminebenzene/ 2-aminothiphenol in the presence of UHP by oxidative coupling has not been reported. A comparison of the previous and present methodologies is illustrated in **Scheme 3.1**.

Previous approaches



Present approach



Scheme 3.1 An illustration of the previous and present reports for the synthesis of 1,2-disubstituted benzimidazole and 2- substituted benzimidazole/ benzothiazoles derivatives.

3.2 Results and discussion

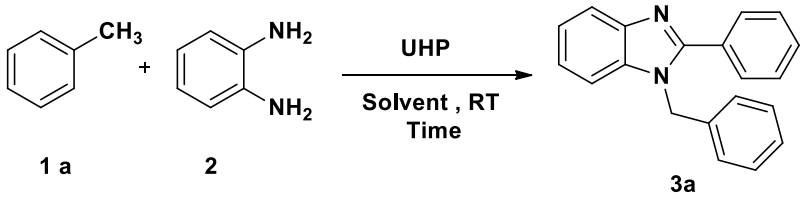
3.2.1 Optimization of Reaction Conditions

To optimize the reaction conditions for the synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles a model reaction was carried out using toluene **1a** (2.0 mmol) and *o*-phenylenediamine **2** (1.0 mmol) in the presence of UHP (2.0 mmol). Various reaction parameters were optimized like solvent, amount of UHP, reaction temperature on the model reaction.

At the outset, the optimization experiments were carried out with the model reaction at room temperature by stirring in different polar and non-polar solvents and the progress of the reaction was monitored by TLC. Non-polar solvents (xylene, toluene) gave negligible amount of product even after 2h stirring at room temperature (**Table 3.1, entry 1 and 2**). However polar aprotic solvents like tetrahydrofuran, chloroform, acetonitrile and 1,4-dioxane gave the product (**3a**) but the yield was very low (15-20%) (**Table 3.1, entries 3-6**). However polar protic solvents like water, methanol and ethanol also gave desired product in better yield (30-40%) (**Table 3.1, entries 7-9**). In order to improve the yield of the product an attempt was made under grinding in solvent-free condition to our surprise it gave 70% yield of product in shorter reaction time 25 min (**Table 3.1, entry 10**). Furthermore, UHP loading was also investigated with 0, 3, 6, 8 mmol, without UHP no product was obtained, with 3 equiv. of UHP it gave 92 % yield (**Table 3.1, entries 11-15**) while further increasing the amount of the UHP did not increase the % yield of the product in all cases it gave exclusively 1,2-disubstituted benzimidazoles. In case of grinding at

room temperature the molar ratio of the reactants were also varied by taking 1 mmol of toluene and 1 or 2 mmoles of *o*-phenylenediamine with UHP gave only 1,2-disubstituted benzimidazole.

Table 3.1 Optimization of reaction conditions for the synthesis of 1,2-disubstituted benzimidazole[a]



S. No	Solvent[b]	UHP (mmol)	Reaction Condition at rt	Time (min)	Yield [%] [c]
1	Benzene	2	Stirring	120	10
2	Toluene	2	Stirring	120	10
3	THF	2	Stirring	120	15
4	$CHCl_3$	2	Stirring	120	20
5	CH_3CN	2	Stirring	120	15
6	1, 4 dioxin	2	Stirring	120	20
7	Water	2	Stirring	60	40
8	Methanol	2	Stirring	60	30
9	Ethanol	2	Stirring	60	40
10	Solvent-free	2	Grinding	25	70

11	Solvent-free	-	Grinding	25	NR
12	Solvent-free	3	Grinding	25	92
13	Solvent-free	6	Grinding	25	92
14	Solvent-free	8	Grinding	25	92
15	Solvent-free	3	Grinding	40	92

[a]**Reaction conditions:** Toluene **1a** (2.0 mmol), *o*-phenylenediamine **2** (1.0 mmol) and UHP at room temperature. [b] 2 mL solvent, [c] % isolated yield .

So the optimal conditions for chemoselective synthesis of 1,2-disubstituted benzimidazole are toluene (2.0 mmol), *o*-phenylenediamine (1.0 mmol) and UHP (3.0 mmol) under grinding at room temperature in solvent-free condition. The product (**3a**) was characterized by spectral data (IR, ^{1}H, ^{13}C NMR) and confirmed by comparing with the reported.

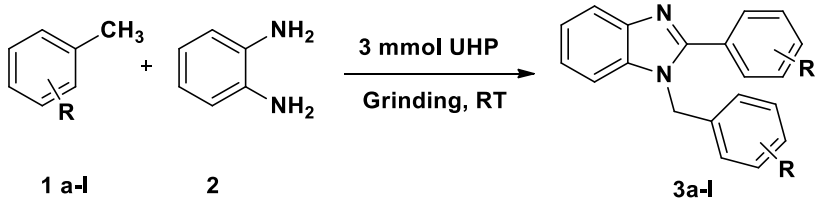
3.2.2 Substrates Scope for 1,2-disubstituted benzimidazoles

After finding the optimized reaction conditions (**Table 3.1, entry 12**), a variety of methyl arenes containing electron donating groups like 4- methoxy, 4-N,N- dimethyl, 3,4-dimethoxy, 2- hydroxyl as well as electron withdrawing groups such as 2-chloro, 3-chloro, 4-bromo and 4-flouro with *o*-phenylenediamine were used to explore the generality and substrate scope of this protocol. Toluene (**1a**), 1-methoxy-4-methylbenzene (**1b**), N,N,4-trimethylaniline (**1c**), 1,2-dimethoxy-4-methylbenzene (**1d**), *o*-cresol (**1e**), 1-chloro-3-methylbenzene (**1f**), 1-chloro-2-methylbenzene (**1g**), 1-bromo-4-methylbenzene (**1h**),

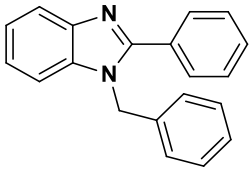
1-fluoro-4-methylbenzene (**1i**), 2-methylnaphthalene (**1j**), 2-methylfuran (**1k**), 2-methylpyridine (**1l**) with *o*-phenylenediamine (**2**) gave compound **(3**) viz. 1-benzyl-2-phenyl-1H-benzo[d]imidazole (**3a**), 1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (**3b**), 4-(1-(4-(dimethylamino)benzyl)-1H-benzo[d]imidazol-2-yl)-N,N-dimethylaniline (**3c**), 1-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (**3d**), 2-(1-(2-hydroxybenzyl)-1H-benzo[d]imidazol-2-yl)phenol **(3e),** 1-(3-chlorobenzyl)-2-(3-chlorophenyl)-1H-benzo[d]imidazole **(3f),** 1-(2-chlorobenzyl)-2-(2-chlorophenyl)-1H-benzo[d]imidazole **(3g),** 1-(4-bromobenzyl)-2-(4-bromophenyl)-1H-benzo[d]imidazole **(3h)**, 1-(4-fluorobenzyl)-2-(4-fluorophenyl)-1H-benzo[d]imidazole **(3i)**, 2-(naphthalen-2-yl)-1-(naphthalen-2-ylmethyl)-1H-benzo[d]imidazole **(3j)**, 2-(furan-2-yl)-1-(furan-2-ylmethyl)-1H-benzo[d]imidazole (**3k**) and 2-(pyridin-2-yl)-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazole **(3l)** in good to excellent yield (86-94%) in shorter reaction time (20-30 min). The chemical structures of the synthesized compounds were established from their spectral data. The structure of the products along with their reaction time and yields are summarized in (**Table 3.2**).

To our delight the present method is compatible with a wide range of functional groups and the nature of the functional group does not affect the yield of the reaction. When *o*-aminothiophenol was treated with toluene under the same optimized condition no product, i.e. 1,2- benzothiazole was obtained while starting material was remained as such.

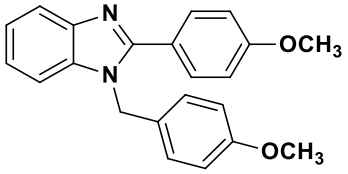
Table 3.2 Synthesis of 1,2-disubstituted benzoimidazoles (3a-l)



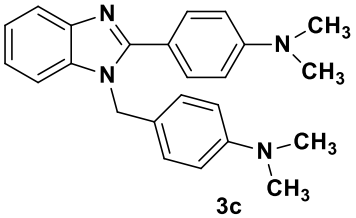
1 a-l 2 3a-l



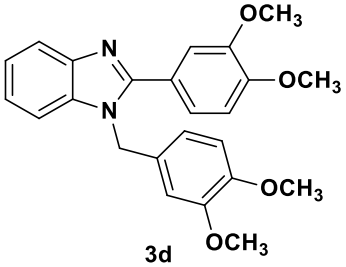
3a
(92%, 25 min)



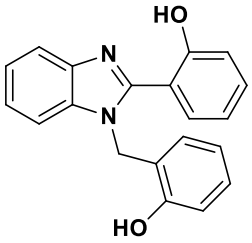
3b
(90%, 20 min)



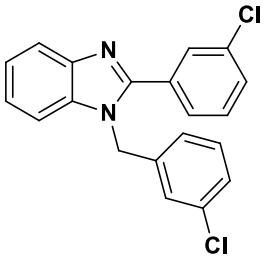
3c
(93%, 20 min)



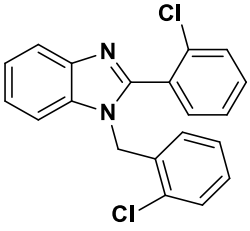
3d
(94%, 25 min)



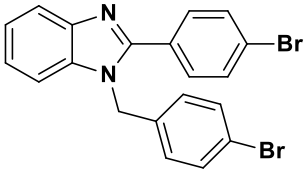
3e
(89%, 20 min)



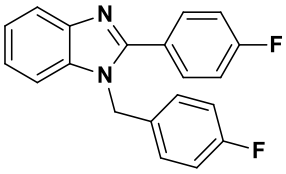
3f
(87%, 20 min)



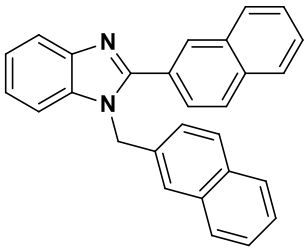
3g
(88%, 22 min)



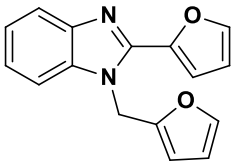
3h
(86%, 20 min)



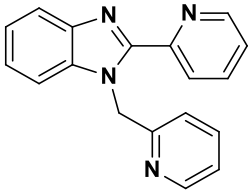
3i
(88%, 20 min)



3j
(91%, 25 min)



3k
(89%, 30 min)



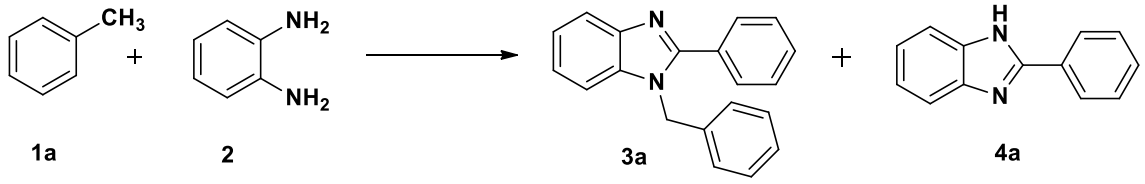
3l
(88%, 30 min)

[a]**Reaction conditions**: Toluene derivatives 1a-l (2 mmol) , *o*-phenylenediamine 2 (1.0 mmol) and of UHP (3 mmol) were grinded in solvent free condition at room temperature . [b] % yield

In order to obtain 2-substituted benzimidazole the model reaction was grinded with higher amounts of UHP and also for longer time up to 60 min but exclusively 1,2-disubsituted benzimidazole was obtained. UHP shows very interesting results by varying reaction temperature and amount of the oxidant in solvent-free condition. Model reaction mixture was stirred with 3 mmol of UHP at room temperature but no product was obtained while starting material was remained as such (**Table 3.3, entry 1**). As temperature of the reaction increases, yield of 3a decreases while yield of 4a increases. The reaction temperature was increased up to 100 ^{0}C with 3 mmol of UHP it gave a mixture of 3a and 4a (**Table 3.3, entries 2-6**). The reaction was also carried out with different loading of UHP (4-6 mmol) at 80 ^{0}C, with 4 mmol of the UHP, exclusively 2-substituted benzimidazole 4a was obtained in 92% yield (**Table 3.3, entry 7**). Further increase in UHP amount by 6 mmol there is no improvement in % yield of 4a (**Table 3.3, entry 8**) and at higher temperature 100 ^{0}C with 4 mmol of UHP no significant improvement in the % yield of 4a

was obtained (**Table 3.3, entry 9**). The product (**4a**) was characterized by spectral data (IR, ^{1}H, ^{13}C NMR) and confirmed by comparing with the reported.

Table 3.3 Effect of temperature and amount of the oxidant on the model reaction



S. No	Oxidant (UHP)	Temperature (^{o}C)	Product (3a)[b]	Product (4a)[c]
1	3 mmol	RT	NR	NR
2	3 mmol	50	60	30
3	3 mmol	60	45	43
4	3 mmol	70	32	58
5	3 mmol	80	15	72
6	3 mmol	100	12	76
7	4 mmol	80	-	92
8	6 mmol	80	-	92
9	4 mmol	100	-	92

[a]**Reaction conditions:** Toluene **1**(1.0 mmol), *o*-phenylenediamine **2** (1.0 mmol) and UHP were treated at different temperature without solvent. [b] % yield of 3a. [c] % yield of 4a.

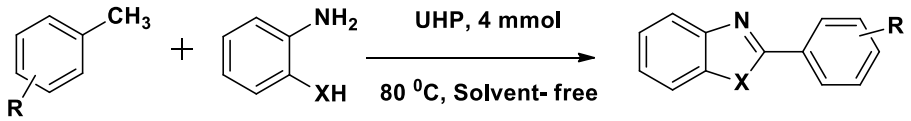
So the optimized conditions for chemoselective synthesis of 2-phenylbenzimidazole is toluene (1 mmol), *o*-phenylenediamine (1.0 mmol) and UHP (4.0 mmol) at 80 ^{0}C in solvent-free condition (**Table 3.2, entry 7)**.

3.2.3 Substrates Scope for 2-substituted benzimidazole/ benzothiazoles

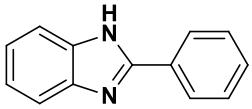
Having been encouraged by the observation, we extended the synthesis of 2-substituted benzimidazoles/ benzothiazoles by using different methyl arene derivatives with 1,2-diaminobenzene/ 2-aminothiophenol. All methyl arenes carrying either electron donating (methoxy, methyl, N,N dimethyl) or electron-withdrawing (nitro, chloro, fluoro, bromo) gave chemoselective 2-substituted benzimidazoles like 2-phenyl-1H-benzo[d]imidazole (**4a**), 2-(1H-benzo[d]imidazol-2-yl)-3-bromophenol (**4b**), 2-(4-nitrophenyl)-1H-benzo[d]imidazole (**4c**), 2-(4-chlorophenyl)-1H-benzo[d]imidazole (**4d**), 2-(4-bromophenyl)-1H-benzo[d]imidazole (**4e**), 2-(4-fluorophenyl)-1H-benzo[d]imidazole (**4f**), 2-(naphthalen-2-yl)-1H-benzo[d]imidazole **(4g)** and 2-(pyridin-2-yl)-1H-benzo[d]imidazole (**4h**). Under the same optimized condition 2-substituted benzothiazoles also achieved in excellent yield. Methyl arenes derivatives and 2-aminothiophenol gave benzothiazole derivatives viz 2-phenylbenzo[d]thaizole (**4i**), 2-(4-methoxyphenyl)benzo[d]thaizole (**4j**), 4-(benzo[d]thiazol-2-yl)-N,N-dimethylaniline (**4k**), 2-(3,4 dimethoxyphenyl)benzo[d]thaizole (**4l**), 2-(4-nitrophenyl)benzo[d]thaizole (**4m**), 2-(4-bromophenyl)benzo[d]thaizole (**4n**), 2-(4-chlorophenyl)benzo[d]thaizole **(4o)**, 2-(4-fluorophenyl)benzo[d]thaizole (**4p**), 2-(naphthalen-2-yl)benzo[d]thaizole (**4q**), 2-(furan-2-

yl)benzo[d]thaizole (**4r**) and 2-(pyridin-2-yl)benzo[d]thaizole (**4s**) in good to excellent yield (**Table 3.4**). 2-Aminothiophenol gave excellent yield in shorter reaction time than *o*-phenylenediamine because sulfur is more nucleophile than nitrogen atom.

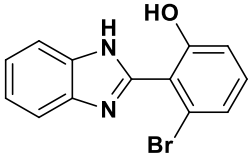
Table 3.4 Synthesis of 2- substituted benzoheterocycles (4a-s)



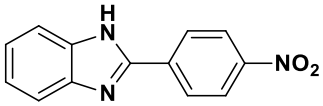
1a-k 2 4a-4s



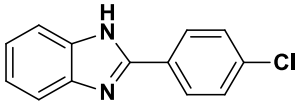
4a
(92%, 20 min)



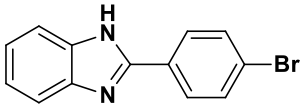
4b
(85%, 30 min)



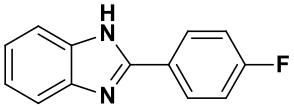
4c
(87%, 25 min)



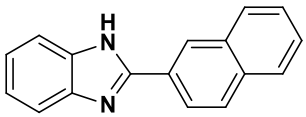
4d
(87%, 26 min)



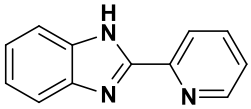
4e
(87%, 25 min)



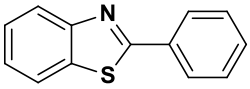
4f
(92%, 22 min)



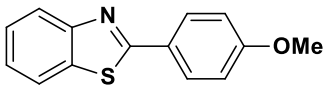
4g
(89%, 25 min)



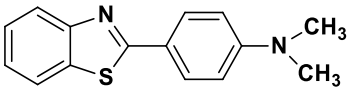
4h
(88%, 25 min)



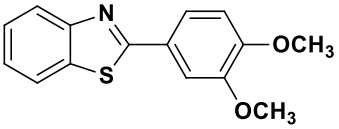
4i
(93%, 15 min)



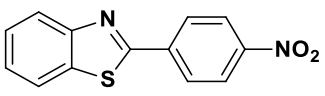
4j
(89%, 10 min)



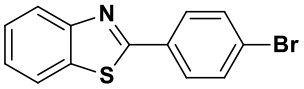
4k
(86%, 10 min)



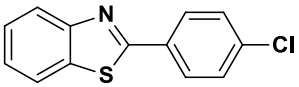
4l
(85%, 10 min)



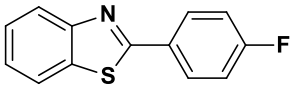
4m
(86%, 10 min)



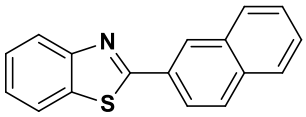
4n
(88%, 10 min)



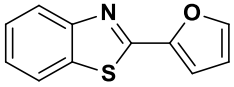
4o
(85%, 10 min)



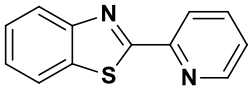
4p
(85%, 15 min)



4q
(90%, 15 min)



4r
(88%, 15 min)

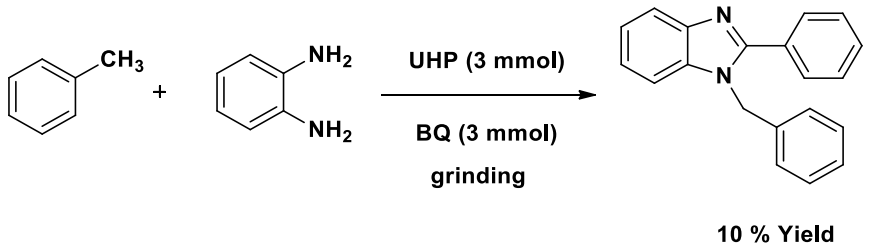


4s
(92%, 15 min)

[a]**Reaction conditions** toluene derivatives **1a-o** (1 mmol) *o*-phenylenediamine or *o*-aminothiophenol **2** (1 mmol) and UHP (4 mmol) were fused at 80 ^{0}C. [b] % yield of the reaction

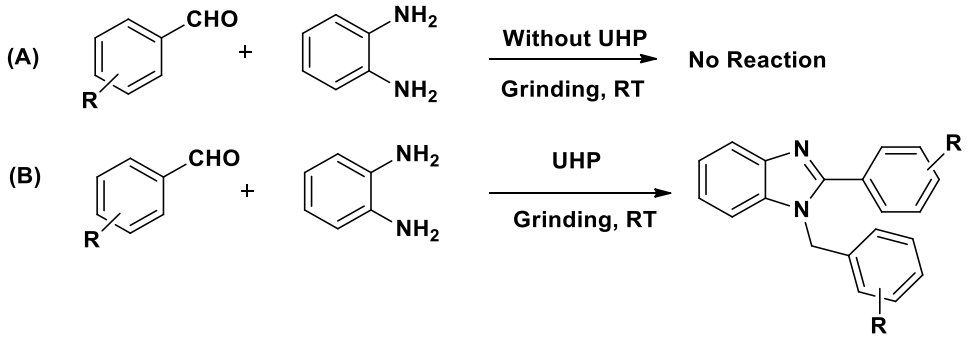
3.3 Controlled Experiments and Mechanistic studies

In order to establish the reaction mechanism, some controlled experiments were performed, when the model reaction was carried in the presence of UHP (3 mmol) under grinding condition with radical scavenger 1,4-benzoquinone (Zhao et al. 2018) (3 mmol), only 10% of the desired product (**3a**) (**Scheme 3.2**) was obtained. This observation shows that the reaction proceeds through radical pathway. When toluene (1.0 mmol), alone was treated with UHP (3.0 mmol) under grinding at room temperature it gave selectively benzaldehyde.



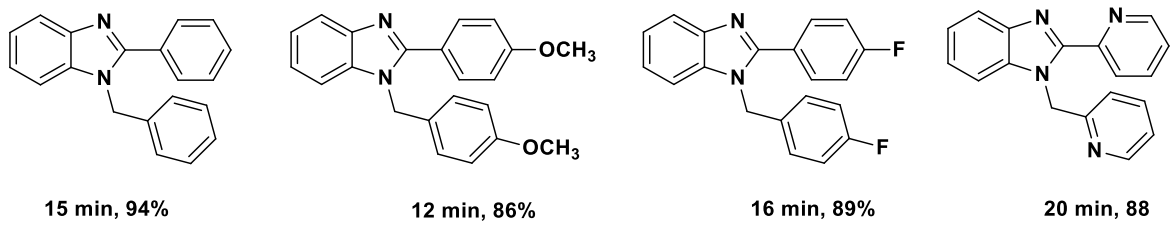
Scheme 3.2 Control experiment using benzoquinone as radical trapping agents

In order to investigate the role of UHP in condensation reaction a controlled experiment was performed by the reaction of benzaldehyde with *o*-phenylenediamine under grinding in the absence of UHP at room temperature. This reaction did not provide the desired product even after 2 hrs **(Scheme 3.3, A)**. When the same reaction was carried out in the presence of UHP it gave the product (**3a**) in **94%** yield **(Scheme 3.3, B)**. In fact, not only benzaldehyde, but also many other substituted benzaldehydes underwent condensation with *o*-phenylenediamine (**2**) and provided products in good yields (**Table 3.5**). These results show that UHP taking part not only in the oxidation of methyl arenes to aldehyde but also in the cyclization step.



Scheme 3.3 Controlled experiment with and without UHP

Table 3.5 Conversion of aldehyde derivatives into corresponding 1,2-disubstituted benzimidazoles.



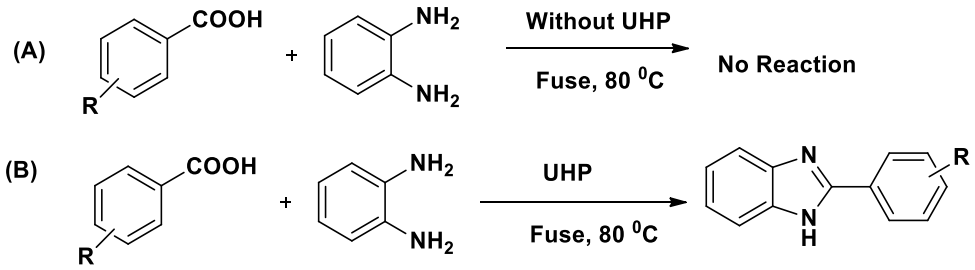
[a]**Reaction condition** benzaldehyde derivatives (1.0 mmol), *o*-phenylenediamine (1.0 mmol) and UHP (3 mmol) were grinded at room temperature. .[b] % yield of the product.

3.3.1 Plausible Reaction Mechanism

A proposed mechanism for the synthesis of 1,2-disubstituted benzimidazole is shown in **Figure 3.2**. In the initial step, decomposition of UHP gives hydrogen peroxide and urea. Hydrogen peroxide gives radical path for the oxidation of methyl arenes via hydroxyl radical ($HO^{\bullet}$). After oxidation, aldehyde (**A**) undergoes condensation reaction with *o*-phenylenediamine and forms diamine (**B**). Intra molecular cyclization followed by 1, 3 hydride shift (**C**) affords final product (**3**). Reaction mechanism for 2-substituted benzimidazole, in initial step aldehyde derivatives react with OH radical give acid derivatives (**D**) which undergoes condensation reaction with *o*-phenylenediamine to form amine (**E**) and intra molecular cyclization affords product (**4**). The formation of reaction intermediate aldehyde derivative (**A)** and benzoic acid derivative (**D**) were confirmed ^{1}H NMR and ^{13}C NMR.

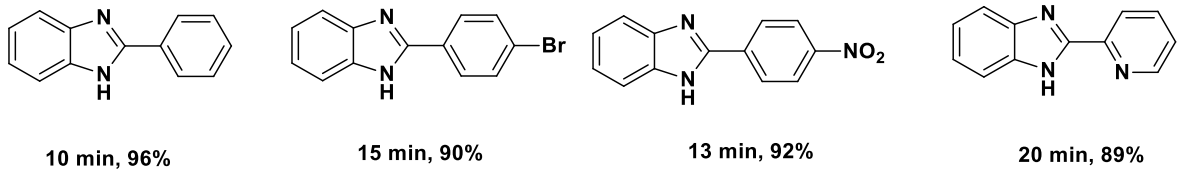
When toluene (1.0 mmol) alone was treated with UHP (3.0 mmol) at 80 ^{0}C it gave completely benzoic acid. To understand the path of the reaction and the role of UHP in the

synthesis of 2-substituted benzimidazole, controlled experiments were performed by the reaction of benzoic acid with *o*-phenylenediamine at 80 ^{0}C in the absence of UHP at room temperature. This reaction did not provide the desired product even after 2 hrs (**Scheme 3.4, A**). When the same reaction was carried out in the presence of UHP it gave the product (**4a**) in **96 %** yield (**Scheme 3.6, B**). In fact, not only benzoic acid, but also many other substituted benzoic acid underwent condensation with *o*-phenylenediamine (**2**) and provided products in good yields (**Table 3.6**). These results show that UHP taking part not only in the oxidation of methyl arenes to benzoic acid but also in the cyclization step.



Scheme 3.4 Controlled experiment with and without UHP

Table 3.6 Conversion of benzoic acid derivatives into corresponding 2-substituted benzimidazoles



10 min, 96% | 15 min, 90% | 13 min, 92% | 20 min, 89%

Reaction conditions: Benzoic acid derivatives (1.0 mmol), *o*-phenylenediamine (1.0 mmol) and UHP were fused at 80^{0}C, [b] % yield of the product.

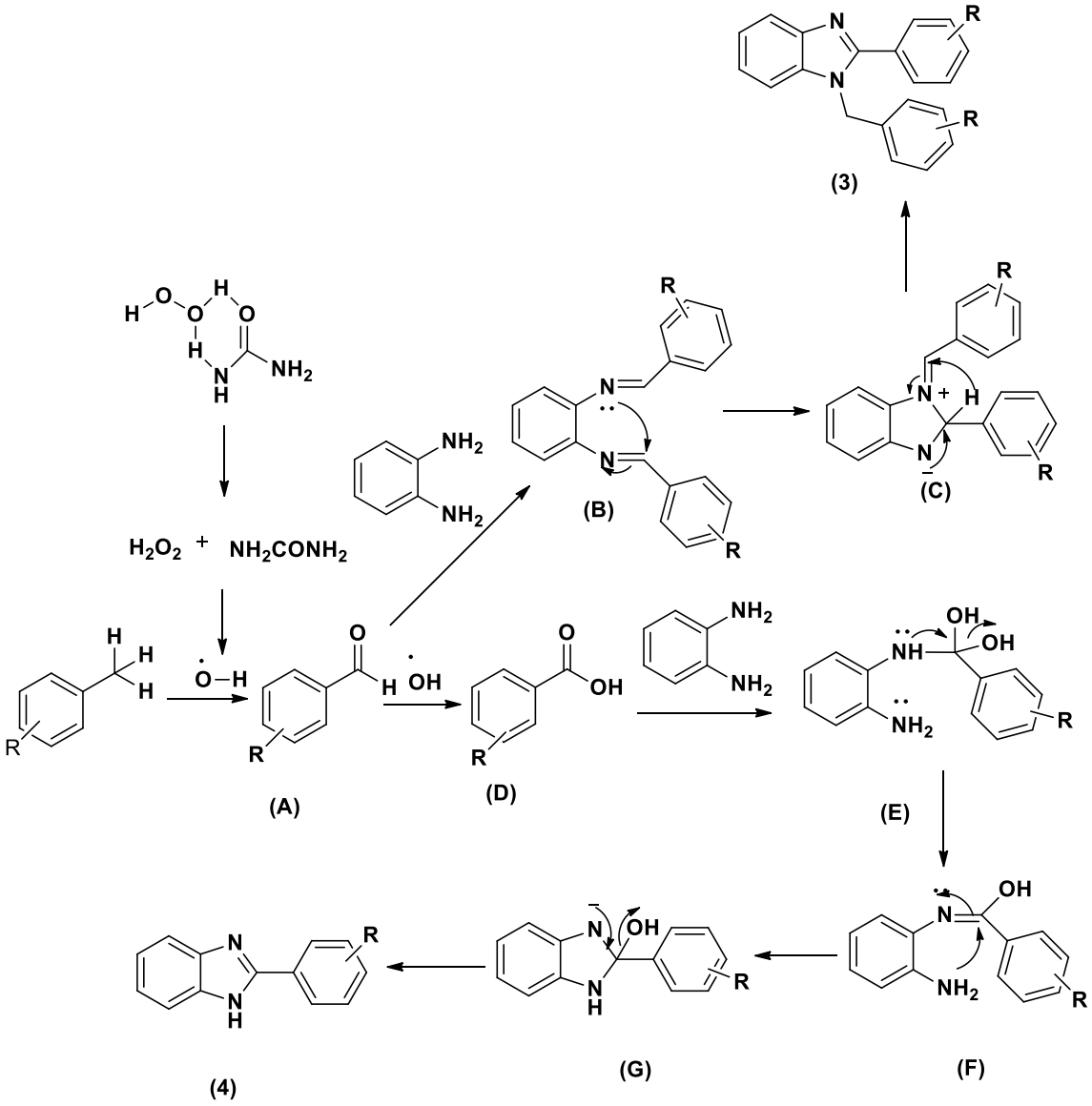


Figure 3.2 Proposed mechanism for the formation of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles

3.4 Gram-scale synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles

To establish the potential synthetic application of this methodology the synthesis of 1-benzyl-2-phenyl-1H-benzo[d]imidazole (**3a**) was carried out on gram scale with toluene (**1a**) (2.13 mL, 20 mmol) and *o*-phenylenediamine (**2**) (1 g, 10 mmol) using of UHP (3 mmol) under optimized reaction conditions it gave desired products (**3a**) in 90% yield (5.2 g). 2-Phenyl-1H-benzo[d]imidazole (**4a**) was also synthesized on gram scale toluene (**1a**) (2.13 mL, 20 mmol), *o*- phenylenediamine (**2**) (2 g, 20 mmol) and 4 mmol of UHP at 80 ^{0}C without solvent, gave 88 % (4.98 g) yield of (**4a**).

3. 5 Experimental Section

3.5.1 General Procedure for the Synthesis of 1,2-Disubstituted Benzimidazole (3a-3l)

A mixture of appropriate methyl arene derivatives (2.0 mmol), *o*-phenylenediamine (1.0 mmol) and UHP (3.0 mmol) were taken in mortar and pestle and ground continuously for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), evaporated under reduced pressure and purified by column chromatography over silica gel (60-120 mesh) with ethyl acetate/hexane solvent system to obtain pure desired products.

3.5.2 General Procedure for the Synthesis of 2-substituted benzimidazoles and benzothiazoles (4a-4s)

o-Phenylenediamine (1.0 mmol), methyl arenes (1.0 mmol) and UHP (4 mmol) were heated at 80 ^{0}C in solvent-free condition. The progress of the reaction was monitored by TLC. After completion of the reaction, mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), evaporated under reduced pressure and purified by column chromatography over silica gel (60-120 mesh) with ethyl acetate/hexane solvent system to obtain pure desired products.

The ^{1}H NMR and ^{13}C NMR of the 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles/ benzothiazoles were compared with literature reports.

3.6 Analytical data

3.6.1 Analytical data of 1,2-disubstituted benzimidazoles and 2-disubstituted benzimidazoles/ benzothiazoles

1-benzyl-2-phenyl-1H-benzo[d]imidazole (3a) Yield 92%; White powder; m.p. 132-133 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.81-7.79 (d, 2H), 7.63-7.61(d, 2H), 7.40- 7.37 (t, 3H), 7.27-7.22 (m, 4H), 7.18-7.13 (m, 2H) , 7.04-7.02 (d, 2H), 5.39 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 154.22, 143.20, 136.40, 136.06, 130.11, 129.88, 129.26, 129.04, 128.72, 127.76, 125.97, 123.01, 122.65, 120.00, 110.38, 48.28.

1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3b) Yield 90%; White powder; m.p. 128-130 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.78- 7.77 (d, 1H),

7.58- 7.56 (d, 2H), 7.22-7.21 (d, 1H), 7.15- 7.14 (d, 2H) 6.97-6.96 (d, 2H) 6.91-6.89 (d, 2H), 6.79-6.78 (d, 2H), 5.32 (s, 2H) 3.78 (s, 3H) 3.72 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 160.86, 159.00, 153.99, 142.93, 135.89, 130.69, 128.35, 127.20, 122.71, 122.50, 122.40, 119.65, 114.41, 114.17, 110.34, 55.35, 55.27, 47.87.

4-(1-(4-(dimethylamino)benzyl)-1H-benzo[d]imidazol-2-yl)-N,N-dimethylaniline (3c) Yield 93%; Yellow powder; m.p. 255 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.84-7.83 (d, 1H), 7.66-7.64 (d, 2H), 7.29-7.26 (t, 1H), 7.22-7.19 (t, 2H), 7.05-7.03 (d, 2H), 6.76-6.75 (d, 2H), 6.71-6.69 (d, 2H), 5.39 (s, 2H), 3.03 (s, 6H), 2.95 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 151.21, 149.97, 143.20, 130.30, 126.92, 124.30, 122.15, 119.21, 112.79, 111.80, 110.37, 48.05, 40.52, 40.18.

1-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (3d) Yield 94%; White powder; m.p. 174-175 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.86-7.85 (d, 2H), 7.38-7.28 (m, 6H), 6.93-6.91 (d, 1H), 6.81-6.80 (d, 1H), 6.66 (s, 1H), 5.40 (s, 2H), 3.92 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 3.77(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 154.12, 150.50, 149.53, 149.11, 148.58, 136.32, 129.11, 122.91, 122.66, 121.86, 119.78, 118.12, 112.36, 111.54, 110.99, 110.26, 109.04, 55.98, 55.96, 55.92, 55.86, 48.17.

2-(1-(2-hydroxybenzyl)-1H-benzo[d]imidazol-2-yl)phenol (3e) Yield 89%; White powder; m.p. 210-212 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 9.48 (s, 1H), 7.69-7.67 (d, 1H), 7.55-7.54 (d, 1H), 7.37-7.35 (d, 1H), 7.23-7.18 (m, 2H), 7.05-7.02 (t, 3H) 6.99-6.97 (d, 1H), 6.89-6.87 (d, 1H), 6.74- 6.71 (t, 1H), 6.61-6.58 (t, 1H), 6.55-6.53 (d, 1H), 5.49 (s, 2H); **^{13}C NMR** (125 MHz, DMSO) δ (ppm):157.71, 153.80, 151.25, 139.72,

134.74, 130.52, 127.94, 126.88, 125.54, 121.65, 118.74, 117.72, 117.15, 114.57, 112.50, 109.60, 44.30.

1-(2-chlorobenzyl)-2-(2-chlorophenyl)-1H-benzo[d]imidazole (3f) Yield 87%; White powder; m.p. 159-160 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.43-841 (d, 2H), 7.90-788 (d, 1H), 7.51(m, 2H), 7.43 (m,2H), 7.34 (m, 2H), 7.32 (m, 2H), 7.27 (s, 2H), 6.65 (s, 1H), 5.37 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 151.50, 149.00, 143.04, 132.09, 129.88, 129.56, 128.95, 127.73, 127.09, 123.09, 123.35, 122.69, 120.33, 110.50, 45.68.

1-(3-chlorobenzyl)-2-(3-chlorophenyl)-1H-benzo[d]imidazole (3g) Yield 88%; White powder; m.p. 202-204 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.93-7.91 (d, 1H), 7.73-7.71 (m, 2H), 7.49 -7.47 (t, 3H), 7.36-7.33 (m, 4H), 7.27–7.24 (m, 2H), 7.14-7.12 (d, 2H), 5.48 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 154.08, 142.98, 136.40, 136.04, 130.03, 129.96, 129.31, 129.08, 128.78, 127.81, 126.00, 123.09, 122.74, 120.00, 110.56, 77.31, 77.06, 76.81, 48.51.

1-(4-bromobenzyl)-2-(4-bromophenyl)-1H-benzo[d]imidazole (3h) Yield 86%; White powder; m.p. 160-162 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.87 (d, 1H), 7.60 (d, 2H), 7.52 (d, 2H), 7.46 (d, 2H), 7.33 (t, 1H), 7.26 (d, 1H), 7.19 (d, 1H), 6.96 (d, 2H), 5.37 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 152.91, 143.13, 135.89, 132.33, 130.52, 128.84, 127.48, 123.06, 121.90, 120.22, 110.27, 47.84.

1-Benzyl-5-fluoro-2-phenyl-1 H-benzo[d]imidazole (3i) Yield 88%; White powder; m.p. 110-112 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.10-8.07 (m, 2H), 7.65-7.63 (d, 3H), 7.27-7.26 (t, 3H), 7.26-715 (m, 4H), 5.40 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm):

164.73, 162.77, 161.32, 153.08, 143.09, 135.90, 131.25, 127.66, 126.20, 123.23, 120.10, 116, 110.30, 47.72.

2-(naphthalen-2-yl)-1-(naphthalen-2-ylmethyl)-1H-benzo[d]imidazole (3j) Yield 91%; White powder; m.p. 124-125 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.92 (d, 2H), 7.72 (d, 4H), 7.49 (s, 4H), 7.34 (s, 4H), 7.25 (d, 3H), 7.13 (d, 3H), 5.48 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 154.14, 143.04, 136.34, 135.98, 129.90, 129.25, 129.02, 128.72, 127.75, 125.94, 123.03, 122.68, 119.94, 110.50, 48.34.

2-(furan-2-yl)-1-(furan-2-ylmethyl)-1H-benzo[d]imidazole (3k) Yield 89%; White powder; m.p. 88-89 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.79-7.77 (d, 1H), 7.64 (s, 1H), 7.50-7.48 (t, 2H), 7.32-7.28 (m, 2H), 7.22- 7.21 (d, 1H), 6.60 (s, 1H), 6.27-6.23 (d, 2H), 5.63 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 149.54, 145.34, 143.90, 142.91, 142.60, 135.43, 123.19, 122.87, 119.75, 112.86, 112.01, 110.47, 109.94, 108.31, 41.62.

2-(pyridin-4-yl)-1-(pyridin-4-ylmethyl)-1H-benzo[d]imidazole (3l) Yield 88%; Yellow powder; m.p. 293-294 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.93-7.91 (d, 1H), 7.73-7.71 (d, 2H), 7.50-7.46 (m, 3H), 7.36-7.33 (t, 2H), 7.27-7.25(t, 2H), 7.14-7.12 (t, 2H), 5.48 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 143.00, 138.34, 134.82, 133.99, 130.53, 130.36, 129.87, 127.46, 126.30, 126.03, 125.62, 122.85, 122.36, 110.50, 45.58.

2-phenyl-1H-benzo[d]imidazole (4a) Yield 92%; Yellow powder; m.p. 293-294 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.92 (s, 1H), 8.19 -8.18 (d, 2H), 7.67 (s, 1H), 7.57-7.54 (t, 3H), 7.50-7.47 (t, 1H), 7.21 (s, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 150.75, 143.32, 134.51, 129.37, 128.47, 125.95, 122.07, 121.22, 118.36, 110.83.

2-(1H-benzo[d]imidazol-2-yl)-3-bromophenol (4b) Yield 85%; Yellow powder; m.p. 252-254 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 13.04 (s, 1H), 8.56 (s, 1H), 7.50 (d, 2H), 7.44 (d, 1H), 7.38-7.37 (s, 1H), 7.26 (s, 1H), 6.96-6.94 (d, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 162.32, 160.30, 141.99, 136.03, 134.25, 128.25, 120.51, 119.54, 110.48,

2-(4-nitrophenyl)-1H-benzo[d]imidazole (4c) Yield 87%; Yellow powder; m.p. >300 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 13.28 (s, 1H), 8.41 (s, 4H), 7.66 (d, 2H), 7.26 (d, 2H); **^{13}C NMR** (125 MHz, DMSO) δ (ppm): 149.46, 148.27, 144.28, 136.49, 135.53, 127.85, 124.76, 124.08, 122.79, 119.91, 112.28.

2-(4-chlorophenyl)-1H-benzo[d]imidazole (4d) Yield 87%; Yellow powder; m.p. > 300 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 12.99 (s, 1H, NH), 8.20-8.18 (d, 2H), 7.64-7.54 (m, 4H), 7.22-7.12 (d, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 149.62, 143.21, 134.03, 133.96, 128.54, 127.61, 122.25, 121.33, 118.43, 110.90.

2-(4-bromophenyl)-1H-benzo[d]imidazole (4e) Yield 87%; Yellow powder; m.p. >300 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.43-8.39 (t, 4H), 7.66 (s, 2H), 7.28-7.26 (d, 2H); **^{13}C NMR** (125 MHz, DMSO) δ (ppm): 143.30, 132.67, 129.32, 128.68, 125.03, 118.61.

2-(4-fluorophenyl)-1H-benzo[d]imidazole (4f) Yield 92%; Yellow powder; m.p. 256-258 °C; **^{1}H NMR** (500 MHz, $CDCl_3$ & DMSO) δ (ppm): 8.46 (s, 1H), 8.13-8.12(d, 4H), 7.81-7.76 (t, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$ & DMSO) δ (ppm): 150.17, 143.38, 134.64, 131.21, 128.79, 127.73, 123.20, 122.34, 121.39, 118.47, 110.79.

2-(naphthalen-2-yl)-1H-benzo[d]imidazole (4g) Yield 89%; Yellow powder; m.p. 260-262 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.81 (s, 1H), 8.39 (s, 1H), 8.26 (d, 1H), 8.00 (t, 2H), 7.63-7.54 (m, 2H), 7.19 (d, 1H), 6.99 (t, 1H), 6.75 (d, 1H), 6.59 (t, 1H), 5.25 (s, 1H); **^{13}C NMR** (125 MHz, DMSO) δ (ppm): 155.69, 143.62, 134.71, 133.93, 133.84, 132.32, 130.24, 128.16, 127.86, 127.38, 127.24, 127.00, 126.29, 123.42, 116.48, 115.79, 114.30.

2-(pyridin-4-yl)-1H-benzo[d]imidazole (4h) Yield 88%; White powder; m.p. 260-262 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.33 (s, NH, 1H), 8.66-8.65 (d, 1H), 8.51-8.47 (d, 1H), 7.91-7.89 (m, 2H), 7.46-7.45 (d, 1H), 7.39-7.38 (d, 1H), 7.31-7.30 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 150.81, 149.05, 148.43, 144.44, 137.42, 124.62, 123.95, 122.70, 121.81, 120.15, 111.27.

2-phenylbenzo[d]thaizole (4i) Yield 93%; Yellow powder; m.p. 115-116 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.05-8.02 (m, 2H), 7.87-85 (d, 1H), 7.45-7.42 (m, 4H), 7.35-7.32 (t, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 168.08, 154.18, 154.18, 135.06, 133.68, 130.98, 129.03, 127.58, 123.26, 125.20, 123.22, 121.63.

2-(4-methoxyphenyl)benzo[d]thaizole (4j) Yield 89%; Yellow powder; m.p. 134-125 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.06-8.00 (m, 3H), 7.88 (d, 1H), 7.47 (t, 1H), 7.35 (t, 1H), 7.00 (d, 2H), 3.89 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 167.87, 161.94, 154.23, 134.86, 129.12, 126.46, 126.19, 124.78, 122.82, 121.50, 114.38, 55.46.

4-(benzo[d]thiazol-2-yl)-N,N-dimethylaniline (4k) Yield 86%; Yellow powder; m.p. 170-171 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.97 (t, 3H), 7.84 (d, 1H), 7.43 (t, 1H),

7.30 (t, 1H), 6.75 (d, 2H), 3.05 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 167.87, 161.94, 154.23, 134.86, 129.12, 126.46, 126.19, 124.78, 122.82, 121.50, 114.38, 55.46.

2-(3,4-dimethoxyphenyl)benzo[d]thaizole (4l) Yield 85%; Yellow powder; m.p. 132-134 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.97 (d, 1H), 7.81 (d, 1H), 7.65 (d, 1H), 7.60 - 7.47 (m, 1H), 7.47-7.36 (m, 1H), 7.34-7.25 (m, 1H), 6.88 (d, 1H), 3.96 (s, 3H), 3.89 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 167.91, 126.70, 126.25, 124.90, 122.85, 121.52, 121.16, 111.03, 109.80, 56.11.

2-(4-nitrophenyl)benzo[d]thaizole (4m) Yield 86%; Yellow powder; m.p. 230-231 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.29 (s, 2H), 8.22 (s, 2H), 8.08 (d, 1H), 7.90 (d, 1H), 7.54-7.44 (m, 1H), 7.44-7.34 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 164.85, 154.12, 139.19, 135.54, 128.25, 126.92, 126.23, 124.32, 123.94, 121.84.

2-(4-bromophenyl)benzo[d]thaizole (4n) Yield 88%; Yellow powder; m.p. 132-134 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.01 (d, 1H), 7.90 (d, 2H), 7.85 (d, 1H), 7.60-7.53 (m, 2H), 7.45 (s, 1H), 7.35 (d, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 166.70, 154.07, 135.04, 132.55, 132.23, 128.91, 126.50, 125.43, 123.32, 121.66.

2-(4-chlorophenyl)benzo[d]thaizole (4o) Yield 85%; Yellow powder; m.p. 110-112 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.01 (d, 1H), 7.97 (d, 2H), 7.84 (d, 1H), 7.47-7.37 (m, 3H), 7.34 (t, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 166.60, 154.08, 137.03, 135.06, 132.13, 129.26, 128.71, 126.47, 125.40, 123.30, 121.64.

2-(4-fluorophenyl)benzo[d]thaizole (4p) Yield 85%; Yellow powder; m.p. 101-103°C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.02 (d, 3H), 7.84 (d, 1H), 7.44 (t, 1H), 7.33

(t, 1H), 7.13 (t, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 166.73, 165.45, 154.09, 135.04, 129.51, 126.41, 125.24, 123.18, 121.61, 116.24, 116.07.

2-(naphthalen-2-yl)benzo[d]thaizole (4q) Yield 90%; Yellow powder; m.p. 123-125 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.52 (s, 1H), 8.17-8.15 (m, 1H), 8.07-8.05 (d, 1H), 7.93-7.82 (m, 4H), 7.51-7.45 (m, 3H), 7.37-7.34 (t, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 168.14, 154.20, 135.16, 134.62, 133.22, 131.00, 128.84, 127.89, 127.61, 127.48, 126.91, 126.41, 125.22, 123.26, 121.66.

2-(furan-2-yl)benzo[d]thaizole (4r) Yield 88%; Yellow powder; m.p. 104-105 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.99 (d, 1H), 7.83 (d, 1H), 7.60-7.49 (m, 1H), 7.45-7.38 (m, 1H), 7.34 (s, 1H), 7.13 (d, 1H), 6.54 (d, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 157.57, 153.79, 148.79, 144.70, 134.30, 126.48, 125.20, 123.15, 121.57, 112.53, 111.42.

2-(pyridin-2-yl)benzo[d]thaizole (4s) Yield 92%; Yellow powder; m.p. 133-135 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.71 (d, 1H), 8.40 (d, 1H), 8.12 (d, 1H), 7.99 (d, 1H), 7.87 (t, 1H), 7.53 (d, 1H), 7.42 (d, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 169.37, 154.27, 151.40, 149.65, 137.00, 136.11, 126.26, 125.63, 125.25, 123.56, 122.00, 120.75.

3.6.2 Spectral data of product (1-benzyl-2-phenyl-1H-benzo[d]imidazole (3a)

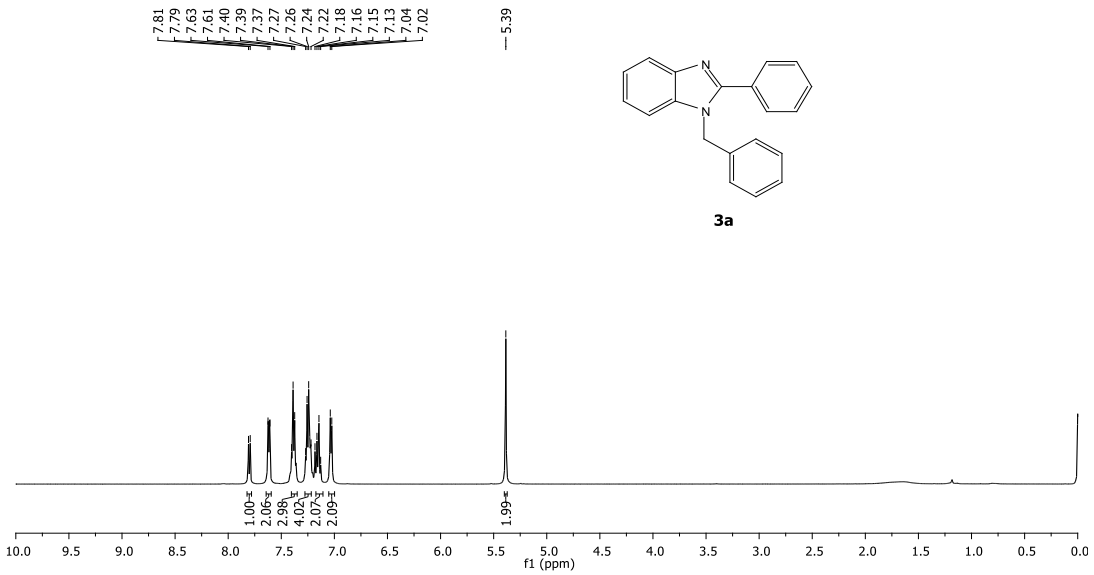


Figure 3.3 ^{1}H NMR of 1-benzyl-2-phenyl-1H-benzo[d]imidazole (3a)

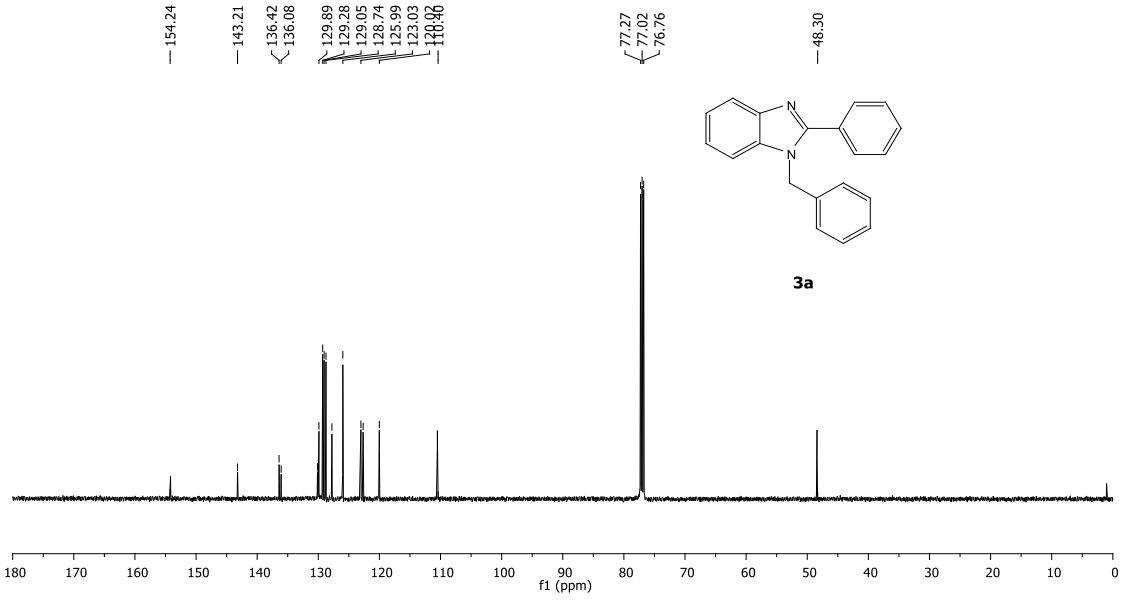


Figure 3.4 ^{13}C NMR of 1-benzyl-2-phenyl-1H-benzo[d]imidazole (3a)

3.6.3 Spectral data of product 2-phenyl-1H-benzo[d]imidazole (4a)

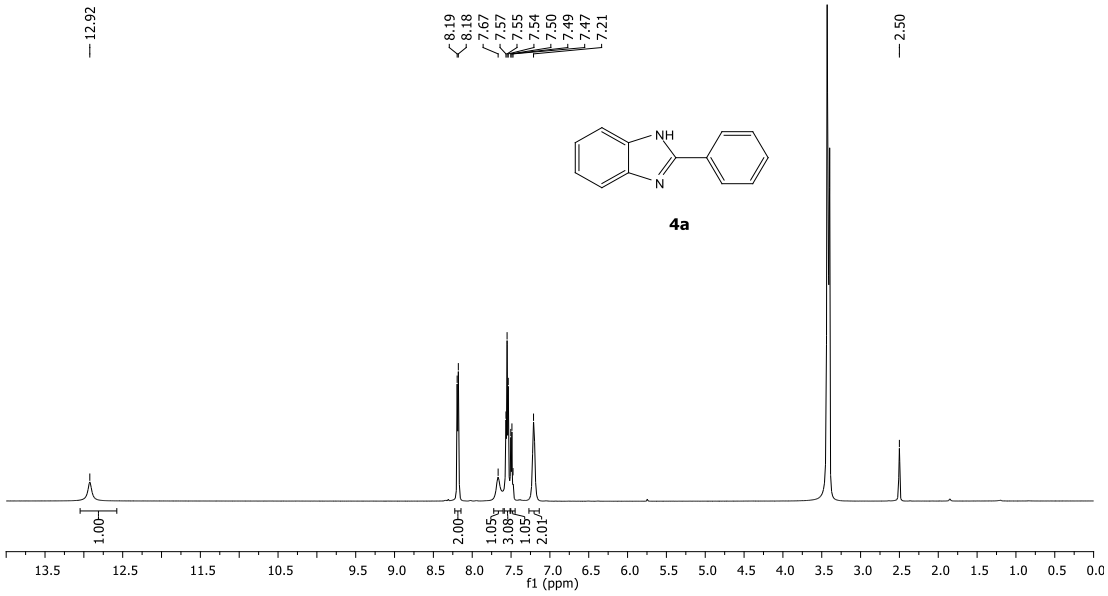


Figure 3.5 ^{1}H of 2-phenyl-1H-benzo[d]imidazole

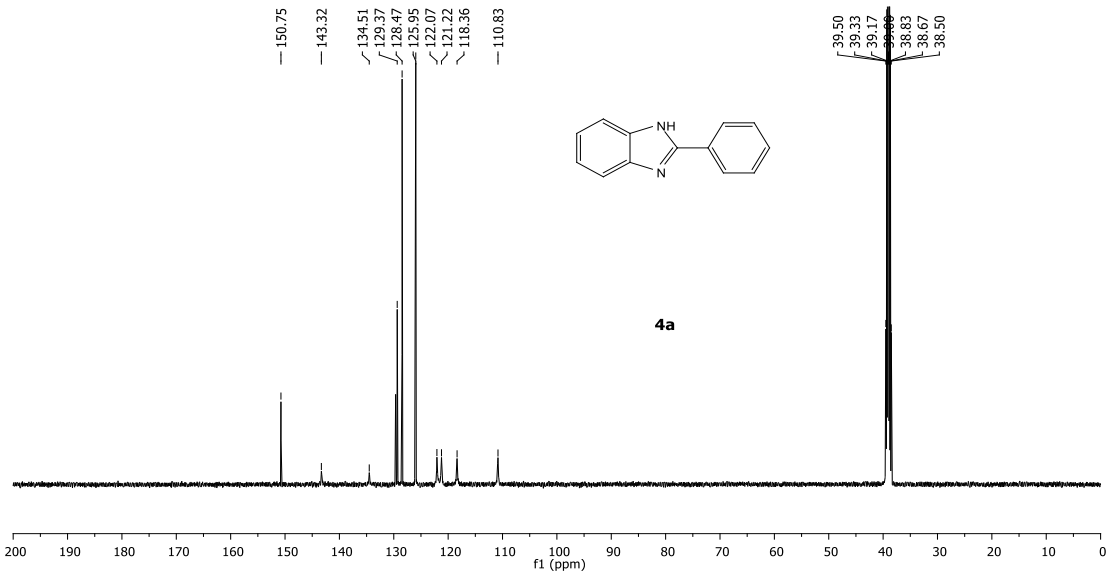


Figure 3.6 ^{13}C NMR of 2-phenyl-1H-benzo[d]imidazole

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CHAPTER 4

Urea Hydrogen Peroxide Initiated Synthesis of Pyranopyrazoles through Oxidative Coupling under Base and Metal-Free Conditions by Physical Grinding Method

Chapter 4

Urea Hydrogen Peroxide Initiated Synthesis of Pyranopyrazoles through Oxidative Coupling under Base and Metal Free Conditions by Physical Grinding Method

4.1 Introduction

Pyranopyrazoles are very important class of fused polycyclic organic compounds which have two heterocyclic pyrane and pyrazole core units. Pyranopyrazole and its derivatives are attractive target heterocyclic molecules due to its potency and wide range of biological and pharmacological activities including analgesic (Kamel 2015), anti-pyretic (Ismail et al. 2007), antimicrobial (Mamaghani et al. 2019), antioxidant, antitumor (Wang et al. 2000), fungicidal (Liu et al. 2012), insecticidal, antibacterial (Aslam et al. 2018), anti-HIV (Patil et al. 1993), herpetic (Gudmundsson et al. 2005), molluscicidal (Abdelrazek et al. 2007), antidepressants (Abdel-Aziz et al. 2009), cardiovascular, anticancer (Mohamed et al. 2010), anti-inflammatory (Zaki et al. 2014), hypoglycemic (Zonouz et al. 2012), Chk1 kinase 10 inhibitory (Gogai et al. 2009) shown in **Figure 4.1.**

Increasing demand of pyrazoles in the biological and pharmaceutical field scientists are always looking for new protocol for its synthesis. Therefore, a large number of methods have been reported in the presence of various homogenous/ heterogeneous, acidic or basic catalysts such as amberlyst A21 (Bihani et al. 2013), molecular sieves (Gujar et al. 2014), lipase (Bora et al. 2013), L-proline (Mecadon et al. 2011), meglumine (Guo et al. 2013),

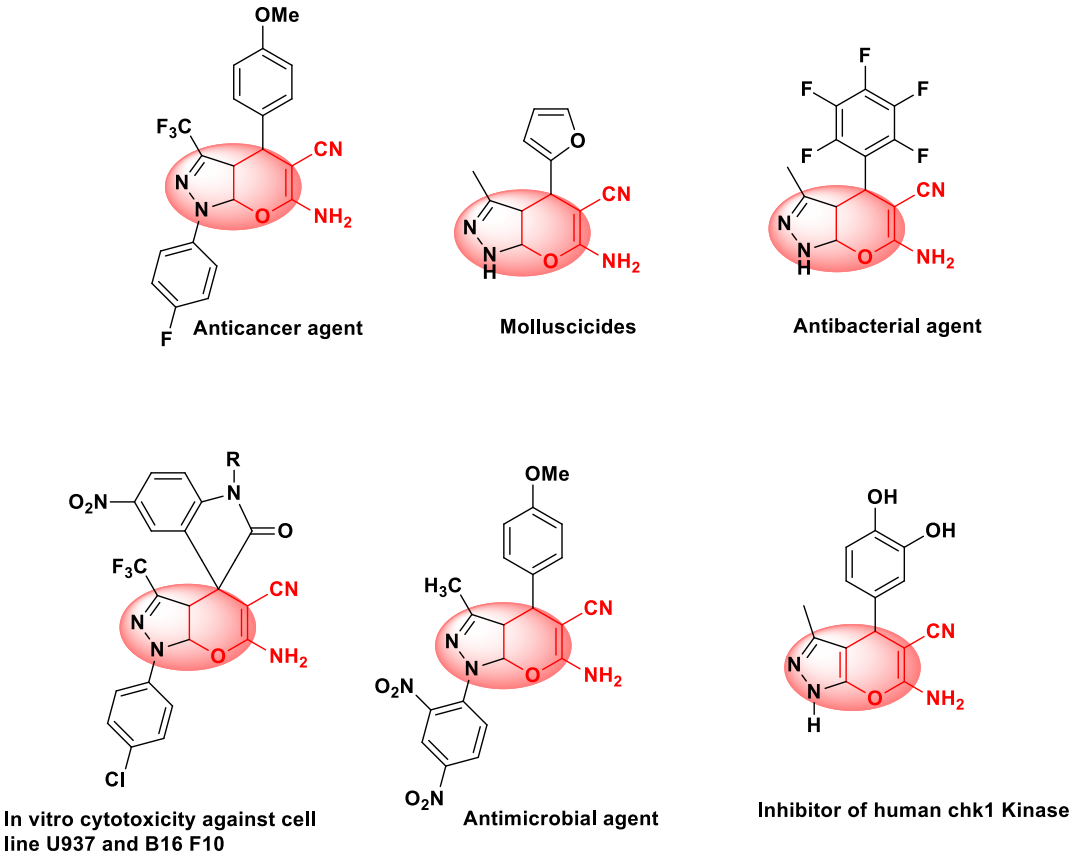


Figure 4.1 Structures of some biologically active 1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles

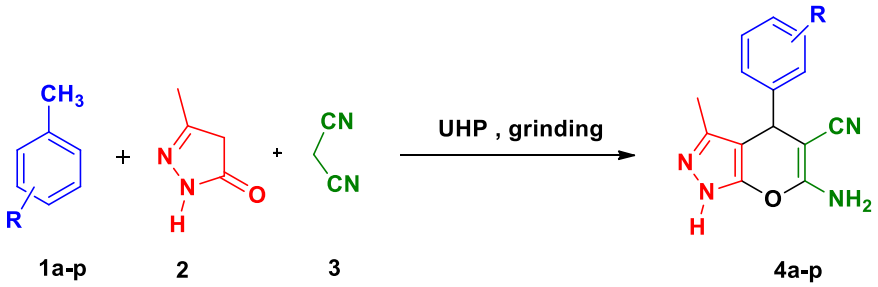
per-6-amino-β-cyclodextrin (Kanagaraj et al. 2010), sodium ascorbate (Kiyani et al. 2018), silica sodium carbonate (Eskandari et al. 2014), $CMCSO_3H$ (Ali et al. 2019), alpha-casein (Milani et al. 2019), theophylline (Mohamadpour 2019), saccharin (Mohamadpour et al. 2018), morpholinium glycolate (Shaikh et al. 2018), [Bmim]OH (Srivastava et al. 2013), $[Et_3NH][HSO_4]$ (Nimbalkar et al. 2017), sodium citrate (Laroum et al. 2017), bovine serum albumin (Dalal et al. 2016), cetyltrimethylammonium chloride (Wu et al. 2013),

cocamidopropyl betaine (Tamaddon et al. 2014), $H_5BW_{12}O_{40}$ (Heravi et al. 2018), RuIII@CMC/Fe_3O_4 (Chen et al. 2019), Fe_3O_4@Cu-β-CD (Mirhashemi et al. 2019), Polypyrrole/Fe_3O_4/CNT (Hojati et al. 2018), $Ag_3[PMo_{12}O_{40}]$ (Tamimi et al. 2019). Photo and electrochemical induced methods have also been reported for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Tripathi et al. 2017, Upadhyay et al. 2017). However, more proficient and biocompatible catalysts are desirable which cover the issues of environmental safety and high atom economy.

The development of efficient, biocompatible and environmentally friendly protocol is getting incredible attention in synthetic organic chemistry. Successful implementation of the multicomponent single step approach allows low cost due to lesser material consumption, reduces reaction time, high atom economy compared to multi-step synthesis (Vachan et al. 2020, Paprocki et al. 2018). Moreover, the current research in organic chemistry is focused on the development of green methods to avoid environment pollution. In this context, recently many organic transformations were performed using green solvents, ionic liquids, deep eutectic solvents, solvent-free reactions etc (Pazoki et al. 2020, Zaharani et al. 2020, Saavedra et al. 2020, Gui et al. 2020).

We wish to report the simple and efficient environmentally benign synthesis of dihydropyrano[2,3-c]pyrazole which has a promising frontier field of research in medicinal, organic and combinatorial chemistry. Dihydropyrano[2,3-c]pyrazoles have been synthesized by methyl aryl derivatives, 4-methylpyrazolone and malanonitrile in the

presence of UHP via one-pot three-component reactions under physical grinding method at room temperature (**Scheme 4.1**).



Scheme 4.1 UHP initiated synthesis of dihydropyrano[2,3-c]pyrazoles

4.2 Results and Discussion

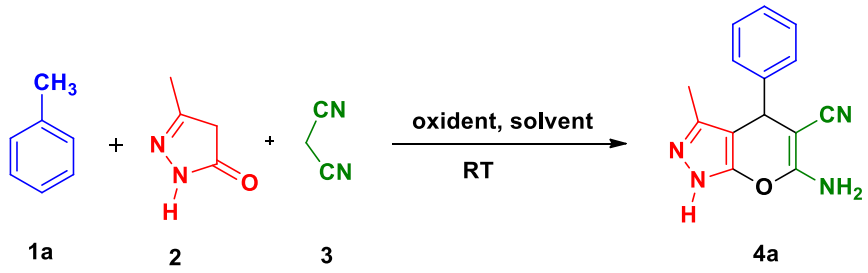
4.2.1 Optimization of Reaction Conditions

The stoichiometric ratio of toluene (**1a**), 4-methylpyrazolone (**2**) malononitrile (**3**) were chosen as a model reaction for the synthesis of dihydropyrano[2,3-c]pyrazole (**4a**). Different reaction parameters were optimized like solvents, oxidants and amount of the oxidant at room temperature.

To find an appropriate solvent different polar and non-polar solvents were tested in the presence of UHP (4 mmol). In non-polar solvents such as toluene, xylene, benzene no product was formed after 60 min (**Table 4.1, entries 1-3**). Polar-aprotic solvents such as 1,4-dioxane, acetonitrile, dichloroethane, DMSO gave the trace amount of the product dihydropyrano[2,3-c]pyrazoles (**4a**) even after 60 min (**Table 4.1, entries 4-7**). In the case of polar- protic solvents like methanol, ethanol and water gave the product (**4a**) in 35-60 %

yield (**Table 4.1, entries 8-10**). Just to avoid the solvent, the reaction was tried in solvent-free condition under grinding to our surprise it gave 88 % yield of the product in 15 min (**Table 4.1, entry 11**). The model reaction of toluene (**1a**), methylpyrazolone (**2**) malononitrile (**3**) was also investigated with different organic/ inorganic oxidising agents such as oxone, H_2O_2, TBHP, $K_2S_2O_8$ and benzoyl peroxide under grinding for 15 min at room temperature it gave the desired product (**4a**) but the yield of the product was poor (**Table 4.1, entries, 12-16**). Out of all tested oxidants UHP was found to be the best. The amount of the oxidant UHP was also examined, when the reaction was carried out in the absence of UHP, it did not provide the desired product even after an hour. Increasing the amount of UHP from 1 to 3 mmol, % yield of the reaction increases from 20-88 % (**Table 4.1 entries, 17-21**). There was no further increase in the % yield when more than 3 mmol of UHP was used.

Table 4.1 Optimization of reaction conditions[a]



Entry	Solvent	Oxidant (mmol)	Reaction condition	Time (min)	Yield (%)[b]
1	Toluene	UHP (4)	Stirring	60	NA
2	Xylene	UHP (4)	Stirring	60	NA

3	Benzene	UHP (4)	Stirring	60	NA
4	1,4- Dioxane	UHP (4)	Stirring	60	Traces
5	Acetonitrile	UHP (4)	Stirring	60	Traces
6	DCE	UHP (4)	Stirring	60	Traces
7	DMSO	UHP (4)	Stirring	60	Traces
8	Methanol	UHP (4)	Stirring	60	35
9	Ethanol	UHP (4)	Stirring	60	40
10	Water	UHP (4)	Stirring	60	60
11	-	UHP (4)	Grinding	15	88
12	-	Oxone (4)	Grinding	15	30
13	-	H_2O_2 (4)	Grinding	15	40
14		TBHP (4)	Grinding	15	50
15	-	$K_2S_2O_8$ (4)	Grinding	15	40
16	-	Benzoyl Peroxide (4)	Grinding	15	38
17	-	UHP (0)	Grinding	15	NA
18	-	UHP (1)	Grinding	15	20
19	-	UHP (2)	Grinding	15	60
20	-	UHP (3)	Grinding	15	88
21	-	UHP (6)	Grinding	15	89

[a] **Reaction conditions:** Toluene **1a** (1.0 mmol), methylpyrazolone **2** (1.0 mmol) malononitrile **3** (1 mmol) were grind/stirring together in the room temperature, [b] Isolated yield.

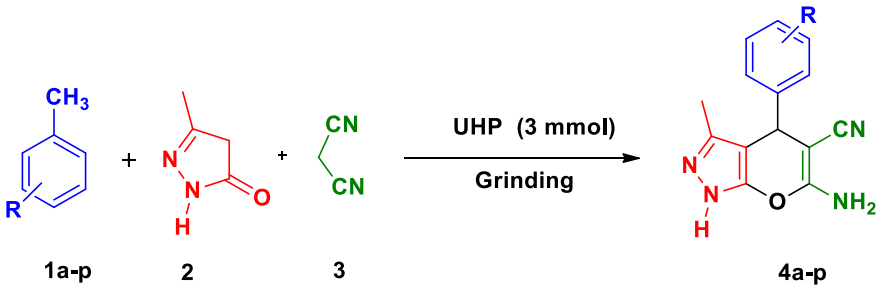
Toluene (**1a**, 1.0 mmol), methylpyrazolone (**2**, 1.0 mmol), malononitrile (**3**, 1.0 mmol) with UHP (3.0 mmol) under grinding at room temperature was found to be the optimum condition for the synthesis of dihydropyrano[2,3-c]pyrazole (**4a**).

4.2.2 Substrates Scope

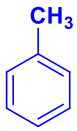
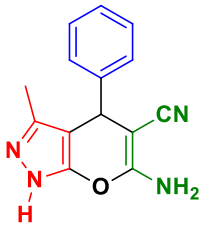
With the optimized conditions (**Table 4.1, entry 20**), the substrate scope of this methodology was explored with different methyl aryl derivatives. Coincidentally, methyl arenes with different electron donating as well as electron withdrawing groups such as 1-methoxy-4-methylbenzene (**1b**), p-xylene (**1c**), o-xylene (**1d**), N,N,4-trimethylaniline (**1e**), 2-methoxy-5-methylphenol (**1f**), 1-fluoro-4-methylbenzene (**1g**), 1-chloro-4-methylbenzene (**1h**), 1-chloro-3-methylbenzene (**1i**), 1-chloro-2-methylbenzene (**1j**), 1-bromo-4-methylbenzene (**1k**), 1-nitro-4-methylbenzene (**1l**), 1-methyl-3-nitrobenzene (**1m**), 1-methyl-2-nitrobenzene (**1n**), 2-methylnaphthalene (**1o**), 2-methylfuran (**1p**) malanonitrile (**2**) and 4-methylpyrazole (**3**) to give product *viz.*6-amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4b**), 6-amino-3-methyl-4-(p-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4c**), 6-amino-3-methyl-4-(o-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4d**), 6-amino-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4e**), 6-amino-4-(3-hydroxy-4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4f**), 6-amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4g**), 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4h**), 6-amino-4-(3-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5carbonitrile

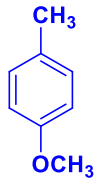
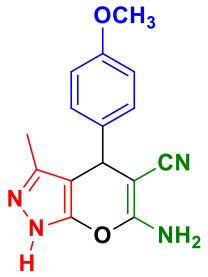
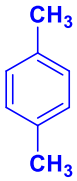
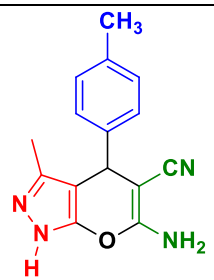
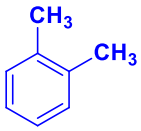
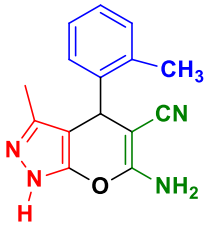
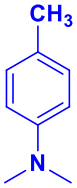
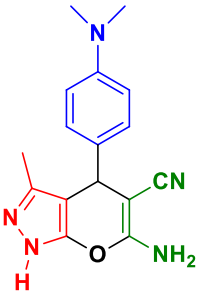
(**4i**), 6-amino-4-(2-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4j**), 6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4k**), 6-amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4l**), 6-amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4m**), 6-amino-3-methyl-4-(2-nitrophenyl)-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (**4n**), 6-amino-3-methyl-4-(naphthalen-2-yl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4o**) and 6-amino-4-(furan-2-yl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4p**) underwent subsequent transformation smoothly in good to excellent yields (80-88%). Interestingly, different positions of the substituent (ortho, meta and para) in aromatic ring did not affect the yield of the product.

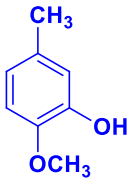
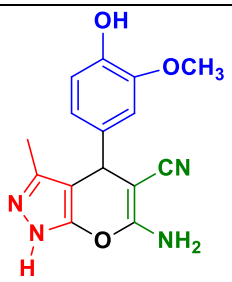
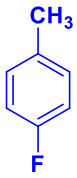
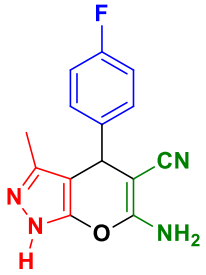
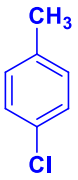
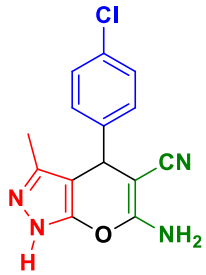
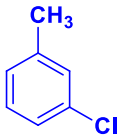
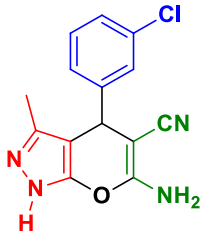
Table 4.2 Synthesis of dihydropyrano[2,3-c]pyrazole (4a-p)

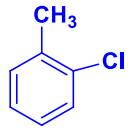
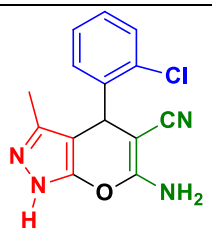
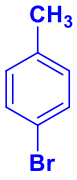
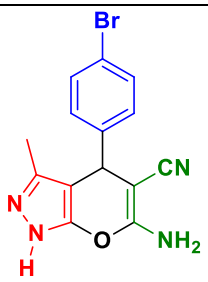
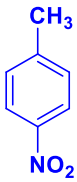
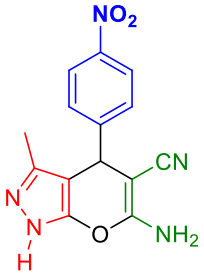
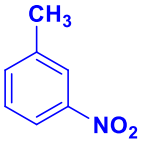
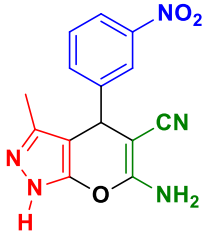


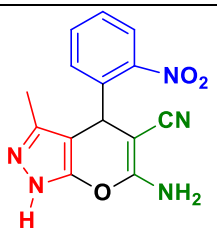
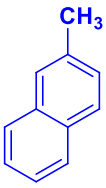
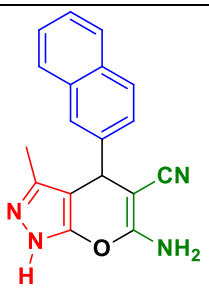
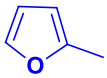
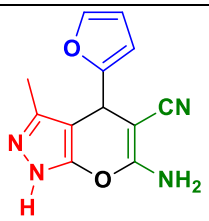
1a-p 2 3 4a-p

Entry	Reactant	Product	Time (min)	% Yield[b]
1	 1a	 4a	15	88

2	 1b	 4b	20	88
3	 1c	 4c	17	88
4	 1d	 4d	20	85
5	 1e	 4e	20	88

6	 1f	 4f	20	84
7	 1g	 4g	20	82
8	 1h	 4h	22	85
9	 1i	 4i	20	84

10	 1j  4j	20	82
11	 1k  4k	20	85
12	 1l  4l	20	84
13	 1m  4m	20	86

14	 1n	 4n	20	80
15	 1o	 4o	20	82
16	 1p	 4p	25	83

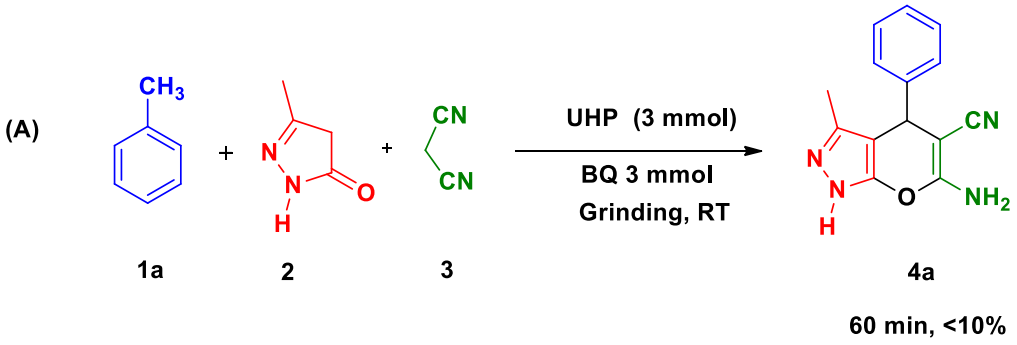
[a] **Reaction conditions**: Toluene **1a** (1.0 mmol), methylpyrazolone **2** (1.0 mmol) malononitrile **3** (1 mmol) and UHP (3 mmol) were grind together in the room temperature, [b] Isolated yield

4.3 Mechanistic Studies

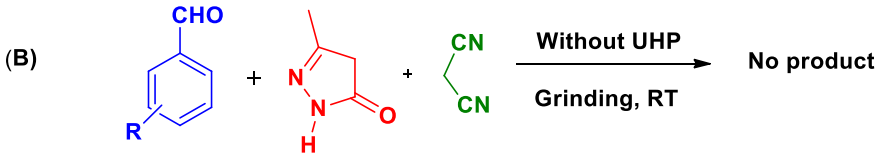
4.3.1 Controlled Experiments

In order to find the reaction mechanism, controlled experiments were carried out with model reaction, in presence of radical scavenger benzoquinone (BQ) under optimized reaction conditions (**Scheme 4.2, A**) less than 10% of the product was obtained. The result

shows that reaction goes via radical path. To investigate the role of urea-hydrogen peroxide complex in Knoevenagel condensation of benzaldehyde, methylpyrazolone and malanonitrile reaction was performed in the absence of UHP under grinding at room temperature in solvent-free condition (**Scheme 4.2, B**). This reaction did not provide the desired product even after 2 hrs. However, when the same reaction was carried out in the presence of UHP desired product was obtained in good yield (**Scheme 4.2, C**). These results indicate that UHP takes part not only in the oxidation of methyl arene to aldehyde but also in Knoevenagel-Micheal condensation reaction **Table 4.3.**



Scheme 4.2 Control experiments using benzoquinone as radical trapping agents



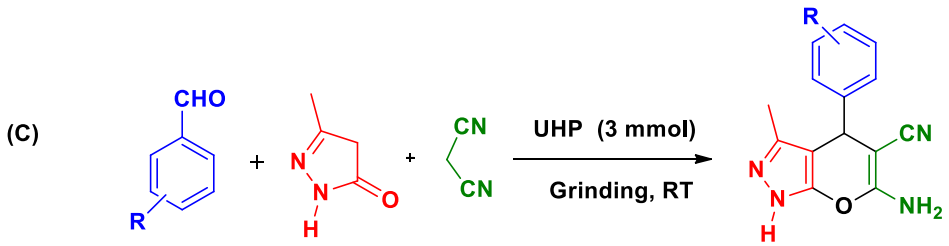
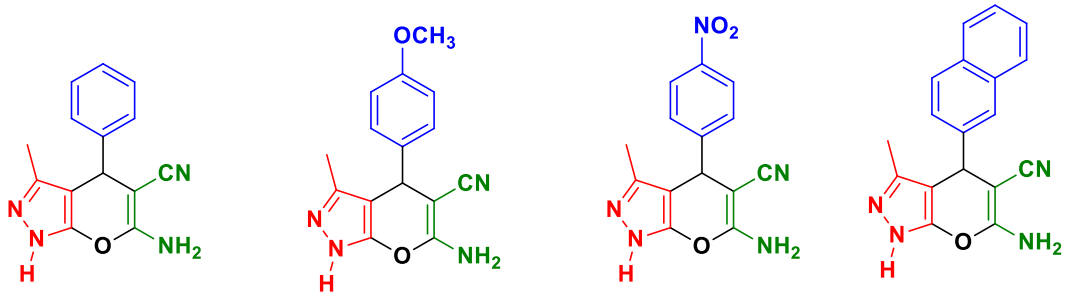


Table 4.3 Synthesis of pyranopyrazoles derivatives from aldehyde derivatives



[a] **Reaction conditions**: Benzaldehyde derivatives (1.0 mmol), methylpyrazolone **2** (1.0 mmol) malononitrile **3** (1 mmol) and UHP (3 mmol) were grind together in the room temperature, [b] Isolated yield.

4.3.2 Plausible Reaction Mechanism

On the basis of literature and our findings a plausible mechanism is predicted in **Figure 4.2**. The reaction is initiated by oxidation of methyl arene derivatives that selectively gave aldehyde derivatives which react with malanonitrile to from benzylidene adduct (**A**). In the second step, in the presence of OH radical methyl pyrazole gave radical intermediate (**B**). Then, (**B**) methyl pyrazole radical abstracts a hydrogen form benzylidene adduct to form intermediate (**C**). Intermediate (**C**) undergoes intermolecular cyclization and gives final product (**4**).

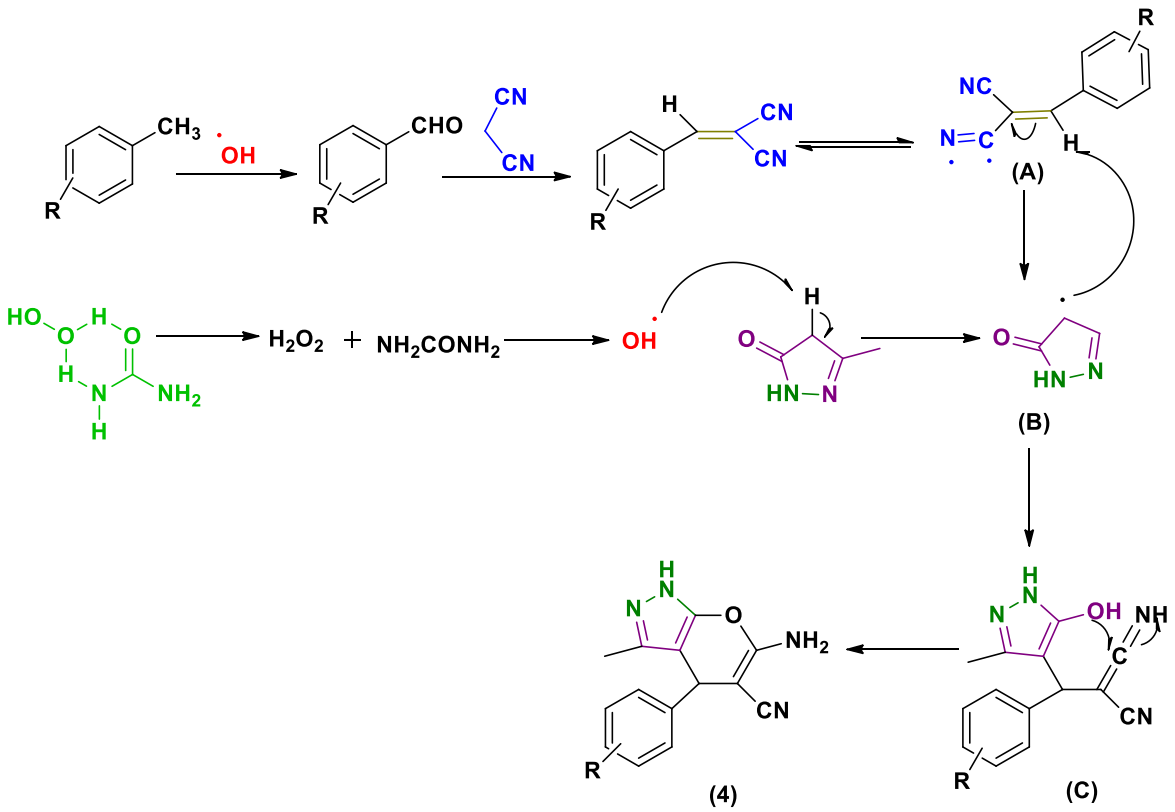


Figure 4.2 Plausible mechanism for the UHP induced dihydropyrano[2,3-c]pyrazole

4.4 Experimental

4.4.1 General procedure for the synthesis of the dihydropyrano[2,3-c]pyrazoles (4a-p)

Methyl arene (1 mmol), malanonitrile (1 mmol), 3-methylpyrazolone (1.0 mmol) and UHP (3 mmol) were grinded in mortar and pestle at room temperature. The progress of reaction was monitored by TLC. After completion of the reaction crushed ice was added into the reaction mixture and stirred for 15 min. The solid obtained was filtered and dried under vacuum, the crude product was recrystallized from ethanol to afford the pure products.

4.4.2 Spectral data of the compounds

6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4a)

Yield 88 %; White solid; m.p. 210-211 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.10 (s, 1H), 7.33-7.20 (t, 2H), 7.24-7.21 (m, 1H), 7.18-7.16 (d, 2H), 6.87 (s, 2H), 4.59 (s, 1H), 1.78 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.04, 154.94, 144.63, 135.74, 128.61, 127.64, 126.91, 120.96, 97.82, 57.36, 36.41, 9.90.

6-amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4b) Yield 88 %; White solid; m.p. 210-211; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.07 (s, 1H), 7.09-7.07 (d, 2H), 6.88-6.86 (d, 2H), 6.82 (s, 2H), 4.54 (s, 1H), 3.73 (s, 3H), 1.78 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.16, 157.43, 154.23, 135.97, 135.02, 127.97, 120.32, 113.24, 97.37, 57.09, 54.47, 34.93, 9.24.

6-amino-3-methyl-4-(p-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4c)

Yield 88 %; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.08 (s, 1H), 7.11 (d, 2H), 7.04-7.03 (d, 2H), 6.85 (s, 2H), 4.53 (s, 1H), 2.26 (s, 3H), 1.77 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.62, 154.61, 141.35, 135.58, 135.40, 128.86, 127.22, 120.70, 97.58, 57.18, 20.92, 9.63.

6-amino-3-methyl-4-(o-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4d)

Yield 85%; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.21 (s, 1H), 8.20 (s, 1H), 8.11 (d, 1H), 7.46 (s, 1H), 7.37 (d, 1H), 7.06 (s, 2H), 4.83 (s,

1H), 2.10 (s, 3H), 1.80 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.67, 154.18, 151.61, 151.28, 145.91, 145.10, 135.44, 128.33, 123.41, 122.50, 120.01, 96.08, 55.45, 35.42, 9.83, 9.25.

6-amino-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4e) Yield 88 %; White solid, m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.04 (s, 1H), 6.97 (d, 2H), 6.77 (s, 2H), 6.66 (d, 2H), 4.46 (s, 1H), 2.86 (s, 6H), 1.79 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.08, 154.31, 148.74, 135.01, 131.55, 127.49, 120.50, 111.83, 97.71, 57.51 38.83, 38.67, 34.89, 9.30.

6-amino-4-(3-hydroxy-4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4f) Yield 84 %; Off-white solid; m.p. 227-228 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): δ 12.09, 8.94 (s, 1H, OH), 6.77 (s, 2H), 6.72, 6.71-6.69 (m, 2H), 6.55 - 6.53 (m, 1H), 4.49 (s, 1H), 3.70 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.13, 147.77, 145.61, 136.22, 135.83, 121.39, 120.18, 115.85, 112.00, 98.35, 58.13, 56.05, 40.24, 40.07, 36.23, 10.25.

6-amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4g) Yield 82 %; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz DMSO-d6) δ (ppm): 12.13 (s, 1H), 7.21-7.19 (m, 2H), 7.15-7.12 (d, 2H), 6.91 (s, 2H), 4.63 (s, 1H), 1.78 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.44, 160.35, 159.51, 154.23, 140.17, 135.17, 128.86, 120.23, 114.77, 114.60, 97.01, 56.62, 34.96, 9.24.

6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4h) Yield 85 %; White solid; m.p. 252-253 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.15 (s, 1H), 7.38-7.36 (d, 2H), 7.20-7.18 (d, 2H), 6.95 (s, 2H, NH_2), 4.63 (s, 1H), 1.79 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm):161.37, 155.17, 143.95, 136.15, 131.70, 129.84, 128.93, 121.15, 97.66, 57.18, 36.01, 10.21.

6-amino-4-(3-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4i) Yield 84 %; White solid; m.p. 210-212 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.10 (s, 1H), 7.30 (d, 2H), 7.21 (d 1H), 7.16 (d, 2H), 6.87 (s, 2H), 4.59 (s, 1H), 1.77 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.40, 154.29, 143.96, 135.12, 127.96, 126.99, 126.26, 120.33, 97.17, 56.71, 39.33, 39.17, 39.00, 38.83, 38.67, 35.76, 9.25.

6-amino-4-(2-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4j) Yield 82 %; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.15 (s, 1H), 7.40 (d, 1H), 7.31 (d, 1H), 7.25 (t, 1H), 7.18 (d, 1H), 6.93 (s, 2H), 5.06 (s, 1H), 1.76 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d6) δ (ppm): 161.82, 155.47, 141.36, 136.01, 132.49, 131.22, 130.05, 129.17, 128.29, 120.96, 97.36, 56.29, 33.97, 10.01.

6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4k) Yield 85 %; White solid; m.p. 249-250 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.15 (s, 1H), 7.51 (d, 2H), 7.14 (d, 2H), 6.94 (s, 2H), 4.62 (s, 1H), 1.80 (s, 3H); **^{13}C NMR (**125 MHz, DMSO-d_6**)** δ (ppm): 160.45, 154.24, 143.42, 135.24, 130.91, 129.28, 119.30, 96.66, 56.23, 38.50, 35.17, 9.28.

6-amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4l) Yield 84 %; White solid; m.p. 277-280 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.10-8.09 (d, 2H), 7.37-7.35 (d, 2H), 4.94 (s, 1H), 2.10 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.45, 154.24, 143.42, 135.24, 130.91, 129.91, 120.20, 119.30, 96.66, 56.23, 10.22.

6-amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4m) Yield 86 %; White solid; m.p. 210-212; ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.21 (s, 1H), 8.12 (s, 1H), 8.02 (s, 1H), 7.77-7.57 (m, 2H), 7.04 (s, 2H), 4.88 (s, 1H), 1.81 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.61, 148.36, 147.29, 136.36, 134.84, 130.71, 122.37, 97.13, 56.64, 36.12, 10.22.

6-amino-3-methyl-4-(2-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4n) Yield 80 %; White solid; m.p. 187-188 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.21 (s, 1H), 7.85 (d, 1H), 7.66 (s, 1H), 7.49 (d, 1H), 7.33 (d, 1H), 7.03 (s, 2H), 5.11 (s, 1H), 1.77 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.71, 154.49, 148.68, 137.10, 135.28, 132.87, 130.80, 127.85, 123.11, 119, 95.90, 55.60, 30.96, 9.00.

6-amino-3-methyl-4-(naphthalen-2-yl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4o) Yield 82 %; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.14 (s, 1H), 7.87 (d, 3H), 7.77 (s, 1H), 7.57-7.38 (m, 2H), 7.25 (d, 1H), 6.96 (s, 2H), 4.79 (s, 1H), 1.76 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.46,

155.38, 142.23, 136.38, 133.35, 132.67, 128.93, 128.14, 126.78, 126.55–126.05, 121.35, 97.94, 57.63, 37.04, 10.24.

6-amino-4-(furan-2-yl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4p)

Yield 83 %; Black solid; m.p. 218-220 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) 12.17 (s, 1H), 7.54 (t, 1H), 6.96 (s, 2H), 6.37-6.39 (m, 1H), 6.18 (d, 1H), 4.78 (s, 1H), 1.98 (s, 3H), **^{13}C NMR** (125 MHz, DMSO-d_6) 161.9, 156.1, 155.2, 142.7, 136.3, 136.1, 121.0, 110.7, 106.1, 95.5, 54.4, 30.2, 10.0.

4.4.3 Spectral data of product 4a

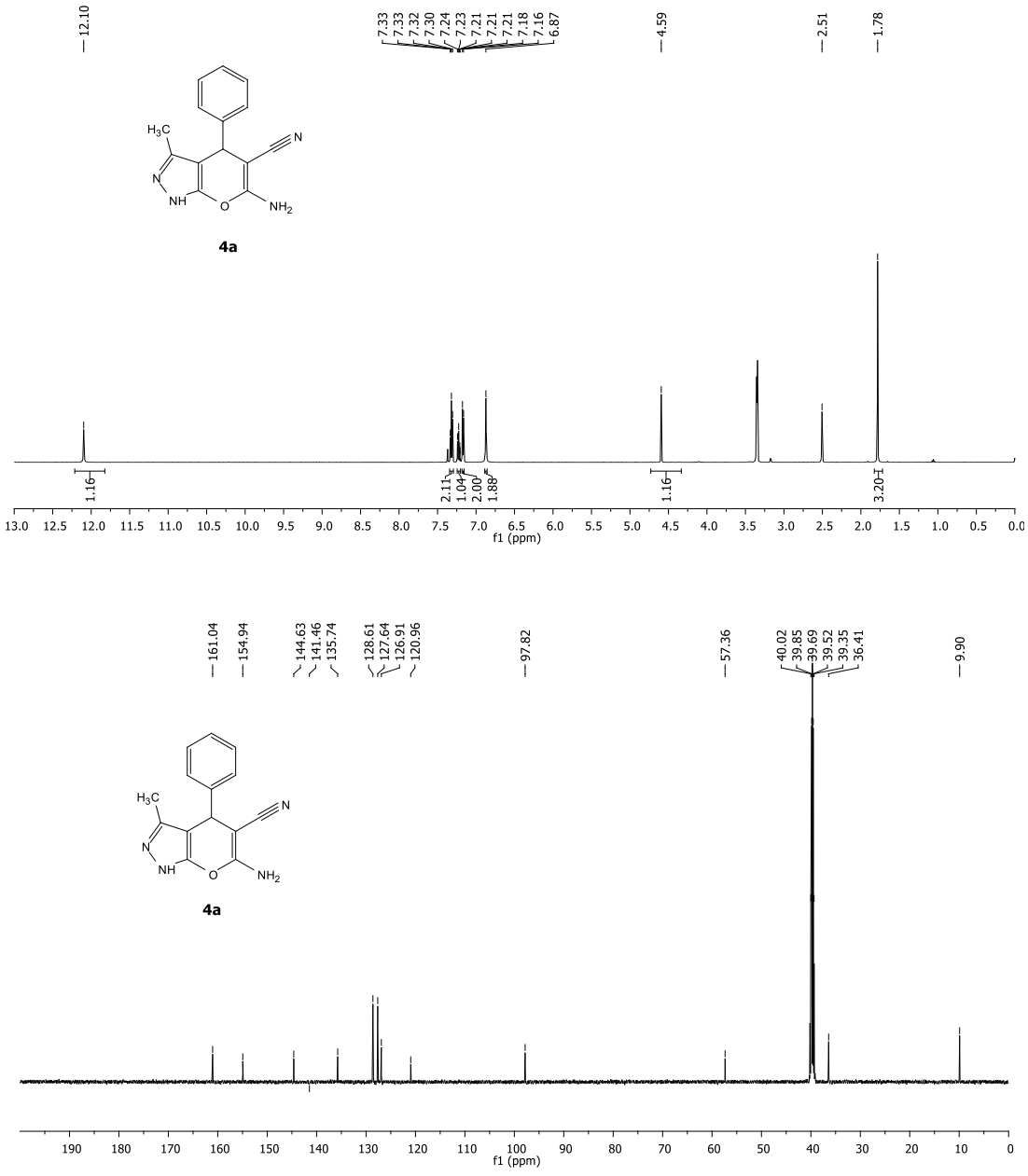


Figure 4.3 ^{1}H & ^{13}C NMR of 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4a)

4.5 References

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CHAPTER 5

Lactic acid/ KI Catalyzed One-Pot Tandem Beckmann Rearrangement of Carbonyls in Metal-Free Condition

Chapter 5

Lactic acid/ KI Catalyzed One-Pot Tandem Beckmann Rearrangement of Carbonyls in Metal-Free Condition

5.1 Introduction

Amides are considered as an essential privileged structure in natural products and pharmaceutical compounds and also play a vital role in the elaborating protein and peptide synthesis. The organic compounds containing amide groups have broadly investigated due to industrial purpose for synthesizing color pigments, detergent, lubricants, cosmetics, treatment of drinking and sewage water and used in polymer chemistry for the lactam synthesis (Naik et al. 2015, Asif 2016, Carey et al. 2006, García et al. 2010, Pattabiraman et al. 2011, Hu et al. 2019). Some valuable commercial drugs which contain amide group are shown in **Figure 5.1.**

Traditionally amides are synthesized by coupling of ammonia with acid derivatives e.g., acid chloride, acid anhydride and esters etc. Hydrolysis of cyanide and transamidation are also important methods for the synthesis of amides derivatives (Dunetz et al. 2016, Gawande et al. 2013, Mylavarapu et al. 2007, Mishra et al. 2018). Different name reactions are also reported as the alternative methods for amide synthesis. Beckmann reaction is one of the most intriguing method due to its peculiar properties (Valizadeh et al. 2014, Eshghiet al. 2006, Reinares-Fisac et al. 2019, Tamaddon et al. 2007).

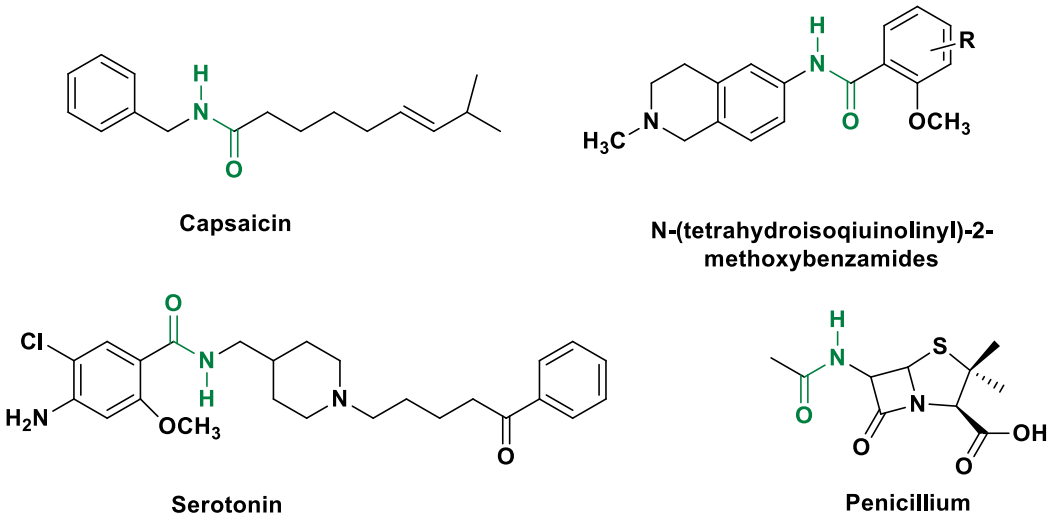


Figure 5.1 Some examples of bioactive substituted amides.

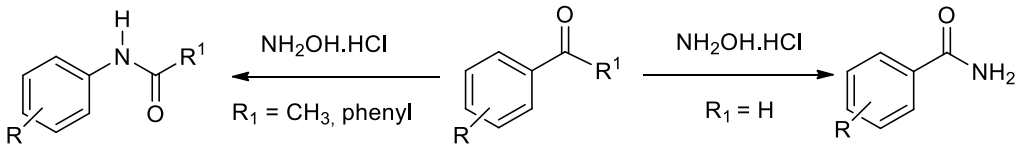
Beckmann reaction is generally catalyzed by strong lewis and bronsted acids at high temperature. A large variety of catalysts have been used for the synthesis of amides such as Al_2O_3/CH_3SO_3H (Sharghi et al. 2001), $(NH_4)_2S_2O_8$ (Mahajan et al. 2016), $SiO_2@H_2SO_4$ (Eshghi et al. 2007), SiO_2@HCOOH (Kuksenok et al. 2016), TsOH (Hyodo et al. 2018), Cs_2CO_3 (Wang et al. 2014), $FeCl_3$ (Gowda et al. 2011), $Sc(OTf)_3$ (Allam et al. 2011), Zn (Kumari et al. 2017), Cu(II) (Rezaei et al. 2017), Ru(II) (Kanchanadevi et al. 2015), Rh (Raja et al. 2014), Pd(II) (Rostamnia et al. 2016, Ali et al. 2010), nano-sulfated titania (Hosseini-Sarvari et al. 2011), Fe_3O_4 (KarimKoshteh et al. 2017), ionic liquid (Rani et al. 2016, Khalafi-Nezhad et al. 2014) etc. Some non-conventional microwave irradiation (Eshghi et al. 2003), ultrasound-assisted, electrochemical (Ke et al. 2019) and photocatalytic (Chen et al. 2019) methods have also been reported. Although, most of these

methods have their own benefits and drawbacks like harsh reaction conditions, expensive metallic catalysts, harmful non-volatile organic solvents, non-recyclability of catalyst, long reaction time, tedious reaction workup and low yield of the products. Considering the above facts, the development of an environmentally efficient and greener protocol for the synthesis of the amides is still in demand and we have directed our studies towards finding a suitable green catalystic system for the synthesis of primary and secondary amides.

Recently, green solvents (e.g. polyethylene glycol, fluorous compounds, ionic liquids, water) and bio-based solvents (fatty acid, ethyl lactate, glycerol, *p*-cymene) got much more attention due to eco-compatibility and sustainability of the reactions. In continuation of this, lactic acid is also used as solvent which is widely used in the agricultural, food, pharmaceutical, textile and cosmetic industries. Commercial lactic acid is produced naturally by fermentation of carbohydrates such as glucose, sucrose or lactose it is white, odorless, non-toxic bio-based weak acid pKa is 3.7, in solution lactic acid can lose a proton from the acidic group, producing the lactate ion $CH_3CH(OH)COO^-$. Recently, Bodireddy *et al.* has developed green and efficient multicomponent reactions (MCR) catalysed by lactic acid (Bodireddy et al. 2016, Gupta et al. 2015, Yu et al. 2016). Due to its unique properties, it is continuously used in organic synthesis as a catalyst as well as solvent.

Iodine containing molecules (such as molecular iodine, potassium iodide and sodium iodine) plays a vital role in organic synthesis due to its various benefits. Various

type of organic reaction e.g. Michael addition, Aldol reaction, esterification, one-pot multicomponent reactions and oxidation reactions etc. are catalyzed by iodine, KI or hypervalent iodine containing molecules (Chen et al. 2017, Song et al. 2015, Zhang et al. 2018, Yoshimura et al. 2013). Potassium iodide is less toxic, cheaper and environmental friendly as compare to molecular iodine. In view of the above, herein, we disclose the use of lactic acid/ KI as an efficient catalytic system for the synthesis of amides by one-pot tandem Beckmann rearrangement under metal and solvent free condition (**Scheme 5.1**).



Scheme 5.1 Conversion of aldehydes/ ketones to amides via Beckmann rearrangement

5.2 Results and discussion

5.2.1 Optimsation of reaction conditions

At the outset, Beckmann reaction of benzaldehyde (**1a**) was investigated with hydroxylamine hydrochloride (**2**) (molar ratio 1: 1.2) in the presence of KI/ lactic acid catalytic system in order to optimize reaction conditions. The consequences of different parameters including solvents, type of catalyst, catalyst loading, reaction temperature and reaction time were studied.

Several solvents were tested in the presence of KI/ lactic acid (0.5/1 equiv.) for the synthesis of benzamide. Reactions were performed in both polar protic (ethanol, methanol and water), polar aprotic (acetonitrile, dichloroethane) and also in non-polar solvents (xylene, toluene) at 80 ^{o}C. In case of polar solvents it gave (30-60%) yield of the product (**Table 5.1, entries 1-5**) while in case of non-polar solvents very poor yield only 10% was obtained (**Table 5.1, entries 6-7**). The results were not satisfactory and show that these solvents were not efficient for the conversion of carbonyl to amide in excellent yield. To our great delight, a significant improvement was observed when the reaction was proceeded without additional solvent at 80 ^{o}C reaction was completed in 2h with 90% yield of the product (3a) it indicates that the extent of conversion was independent of solvent (**Table 5.1, entry 8**). After optimizing solvents, different iodine containing compouds (molecular iodine, sodium iodide, lithium iodide and 2-iodoxybenzoic acid) in the presence of lactic acid were also applied for the amide synthesis and we got (10-60%) yield of the product in 5 h (**Table 5.1, entries 12-15**). The results indicate that KI/ lactic acid found the best catalytic system (**Table 5.1, entry 9)**.

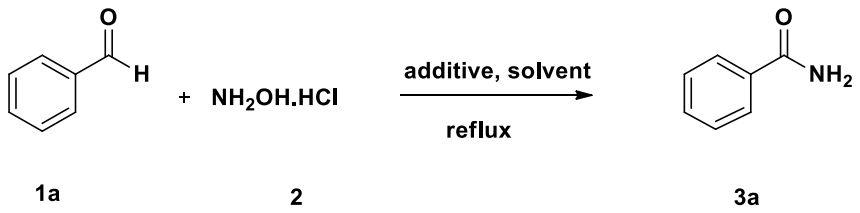
In order to optimize the amount of the catalyst we started optimization of catalyst KI with 1 equiv. of lactic acid, the first experiment was carried out in the absence of KI and the reaction did not afford the final product (3a) and stopped after intermediate formation (oxime) (**Table 5.1, entry 11**). Next we increased the amount of KI (0.2-0.7 equiv.) and got 45-91% yield of the product in 2h. These results show that increasing the amount of KI from 0 to 0.5 equiv affects the yield of amide, but further any increment in

the amount of KI from 0.5 to 0.7 did not make any significant difference in the yield of the product (**Table 5.1, entries 16-18**). Next the amount of the lactic acid was also optimized (0.5-2 equiv.) with 0.5 equiv. of KI, in the absence of lactic acid no product was obtained (**Table 5.1, entry 10**) and the best result was obtained when the reaction was performed with 1 equiv. of lactic acid (**Table 5.1, entry 8**). This also shows that tuning of the equivalent of KI and lactic acid had an effect on the yield of 3a and it is essential for this reaction (**Table 5.1, entry 19, 20**).

To find out the effect of temperature, the model reaction was carried out at different temperatures by using KI/ lactic acid (0.5/1 equiv.). At room temperature, no desired product was obtained but the yield of the product (3a) was improved as the temperature was increased (40-80^{0}C) and observed maximum yield 90% at 80^{0}C. Further increase in temperature did not improve the yield of the product (**Table 5.1, entries 21-24**).

The results show a combination of lactic acid and KI was found efficient to catalyze Beckmann reaction in a high yield. So the optimized conditions for Beckmann reaction is benzaldehyde (1.0 mmol), hydroxylamine hydrochloride (1.2 mmol) in the presence of KI/ lactic acid (0.5/1equiv.) catalytic system at 80 ^{0}C was the optimum condition for the synthesis of benzamide.

Table 5.1 Optimization of different reaction conditions on the yield of 3a[a]



1a 2 3a

Entry	Solvent	Catalyst (equiv.)	Time (h)	Temp.	Yield[%][b]
1	Acetonitrile	KI /Lactic acid (0.5/1)	5	80	30
2	Dichloro-Methane	KI /Lactic acid (0.5/1)	5	80	30
3	Ethanol	KI /Lactic acid (0.5/1)	3	80	40
4	Methanol	KI /Lactic acid (0.5/1)	3	80	32
5	Water	KI /Lactic acid (0.5/1)	3	80	60
6	Xylene	KI /Lactic acid (0.5/1)	5	80	10
7	Toluene	KI /Lactic acid (0.5/1)	5	80	10
8	-	KI /Lactic acid (0.5/1)	2	80	90
9	-	-	2	80	NR
10	-	KI (0.5)	2	80	NR
11	-	Lactic acid (1)	2	80	NR
12	-	I_2/Lactic acid (0.5/1)	5	80	30
13	-	LiI/Lactic acid (0.5/1)	5	80	10

14	-	NaI/ Lactic acid (0.5/1)	5	80	10
15	-	IBX /Lactic acid (0.5/1)	5	80	60
16	-	KI/ Lactic acid (0.2/1)	5	80	45
17	-	KI/ Lactic acid (0.4/1)	5	80	80
18	-	KI /Lactic acid (0.7/1)	2	80	91
19	-	KI /Lactic acid (0.5/0.5)	2	80	40
20	-	KI /Lactic acid (0.5/2)	2	80	90
21	-	KI/ Lactic acid (0.5/1)	2	RT	NA
22	-	KI /Lactic acid (0.5/1)	2	40	30
23	-	KI/ Lactic acid (0.5/1)	2	60	67
24	-	KI/ Lactic acid (0.5/1)	2	100	90

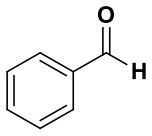
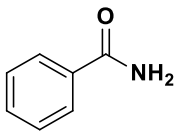
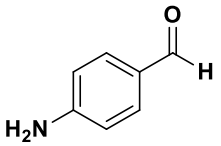
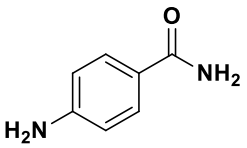
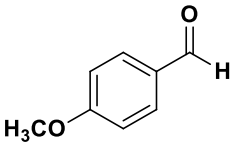
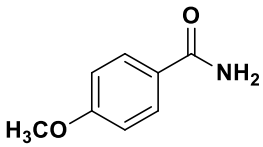
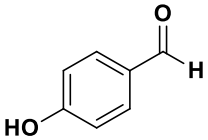
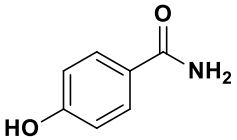
[a] **Reaction condition:**Benzaldehyde **1a** (1.0 mmol), hydroxylamine hydrochloride **2** (1.2 mmol) in 0.2 mL solvents and with different catalytic system. [b] Isolated yield.

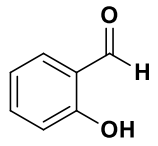
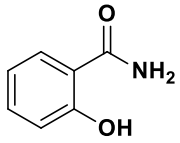
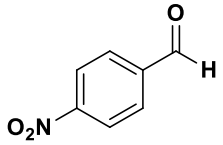
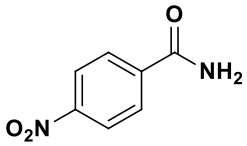
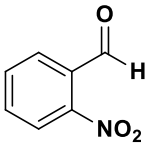
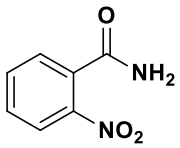
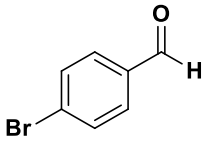
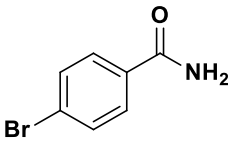
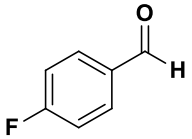
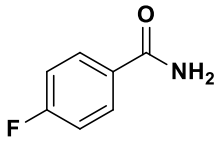
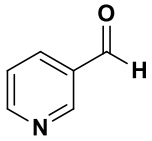
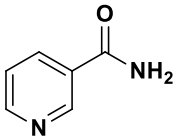
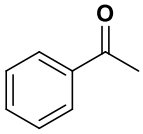
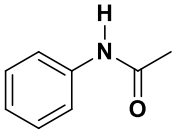
5.2.2. Substrate Scope

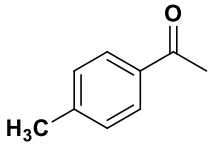
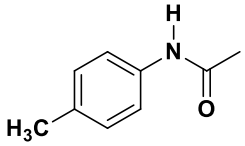
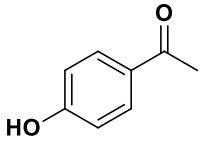
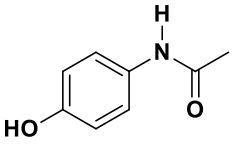
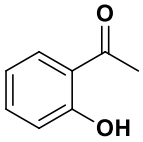
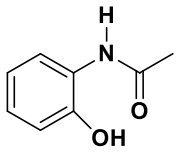
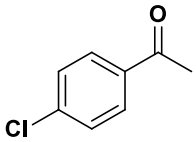
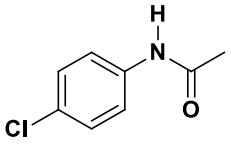
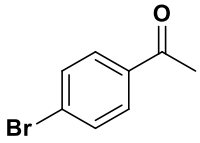
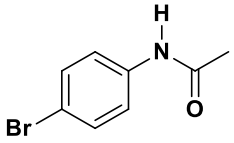
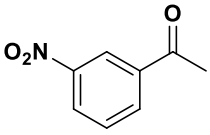
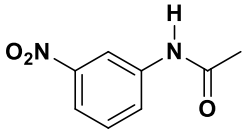
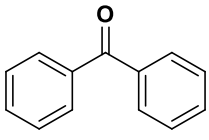
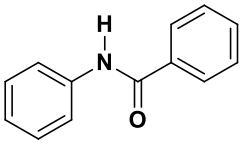
With the established optimized reaction conditions in hand, we examined the scope and compatibility of the aromatic aldehydes such as benzaldehyde (**1a**), 4-aminobenzaldehyde (**1b**), 4-methoxybenzaldehyde (**1c**), 4-hydroxybenzaldehyde (**1d**), 2-hydroxybenzaldehyde (**1e**), 4-nitrobenzaldehyde (**1f**), 2-nitrobenzaldehyde (**1g**), 4-bromobenzaldehyde (**1h**), 4-fluorobenzaldehyde (**1i**) and nicotinaldehyde (**1j**) gave corresponding primary amide benzamide (**3a**), 4-aminobenzamide (**3b**),

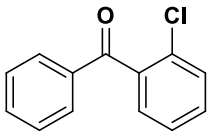
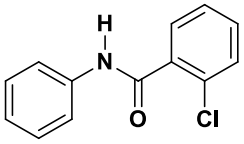
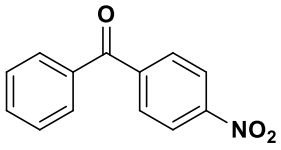
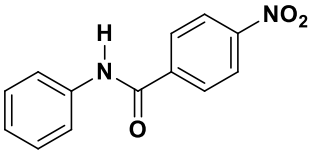
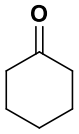
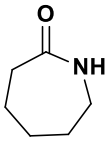
4-methoxybenzamide (**3c**), 4-hydroxybenzamide (**3d**), 2-hydroxybenzamide (**3e**), 4-nitrobenzamide (**3f**), 2-nitrobenzamide (**3g**), 4-bromobenzamide (**3h**), 4-fluorobenzamide (**3i**) and nicotinamide (**3j**) in good to excellent yield. Aromatic aldehyde containing electron-withdrawing group gave the desired product in excellent yield in shorter reaction time than the electrondonating groups (**Table 5.2**).

Table 5.2 Synthesis of substituted primary and secondary amides[a]

Entry	Reactant	Product	Time (h)	Yield [%][b]
1	 1a	 3a	2	90
2	 1b	 3b	2.5	86
3	 1c	 3c	2.5	85
4	 1d	 3d	2.5	88

5	 1e	 3e	2.5	87
6	 1f	 3f	2	90
7	 1g	 3g	2	91
8	 1h	 3h	2	89
9	 1i	 3i	2	87
10	 1j	 3j	2.5	84
11	 1k	 3k	2.5	92

12	 1l	 3l	2.5	90
13	 1m	 3m	2.5	88
14	 1n	 3n	2.5	87
15	 1o	 3o	2	85
16	 1p	 3p	2	87
17	 1q	 3q	2	89
18	 1r	 3r	2	87

19	 1s	 3s	2	88
20	 1t	 3t	2	89
21	 1u	 3u	2.5	85

[a]**Reaction conditions**: Aromatic aldehydes/ ketones **1** (1.0 mmol), hydroxylamine hydrochloride **2** (1.2 mmol) and KI /Lactic acid (0.5/1equiv.) were heated at 80 ^{0}C. [b] Isolated yield.

Due to the achievement of the above methodology in primary amide synthesis, this methodology was also applied for the synthesis of a secondary amides from ketones. Various aromatic ketone such as acetophenone (**1k**) *p*-methylacetopheone (**1l**), *p*-hydroxyacetophenone (**1m**), *o*-hydroxyacetophenone (**1n**), *p*-chloroacetophenone (**1o**), *p*-bromoacetophenone (**1p**), *m*-nitroacetophenone (**1q**), benzophenone (**1r**), 2-chlorobenzophenone (**1s**), 4-nitrobenzophenone (**1t**) and aliphatic cyclic ketone cyclohexanone gave secondary amides *N*-phenylacetamide (**3k**), *N*-(p-tolyl)acetamide (**3l**), *N*-(4-hydroxyphenyl)acetamide (**3m**), *N*-(2-hydroxyphenyl)acetamide (**3n**), *N*-(4-chlorophenyl)acetamide (**3o**), *N*-(4-bromophenyl)acetamide (**3p**), *N*-(3-nitrophenyl)acetamide (**3q**), *N*-phenylbenzamide (**3r**), (2-chlorophenyl)(phenyl)methanone

(**3s**), (4-nitrophenyl)(phenyl)methanone (**3t**), azepan-2-one (**3u)** respectively in excellent yield. Acetophenone derivatives with electron-donating and electron-withdrawing substituents could be accommodated to afford amides in excellent yields (85–92%) (**Table 5.2 entries 11-21**).

5.2.3 Appilcation of this methodology (Synthesis of Paracetamol and caprolactum)

To demonstrate the utility of this mild method, we accomplish the synthesis of Paracetamol, a commercial analgesics and antipyretics is used for the treatment of pain and fever directly from aldehyde. Excitingly 4-hydroxy acetophenone gave 88% of the Paracetamol (**3m**) under the optimized conditions in 2h. This methodology is also useful for the synthesis of caprolactum (**3u**), yield 85 % in 2.5h from cyclohexanone which is used for the synthesis of polymer Nylon 6 and several medicinally active drugs such as pentylenetetrazol, meptazinol and laurocapram etc. These examples illustrate the potential synthetic utility of this method.

5.2.4 Plausible reaction Mechanism

A plausible reaction pathway for the conversion of carbonyl derivatives into the corresponding amides is outlined in (**Figure 5.2**). Firstly, combination of lactic acid and KI gives hydrogen iodide, which polarizes the carbonyl group that facilitates the reaction with hydroxylamine hydrochloride and gave oxime (**I**), which upon dehydration produces cyanide (**II**) and then the hydrolysis of cyanide gives amide derivatives **(3**).

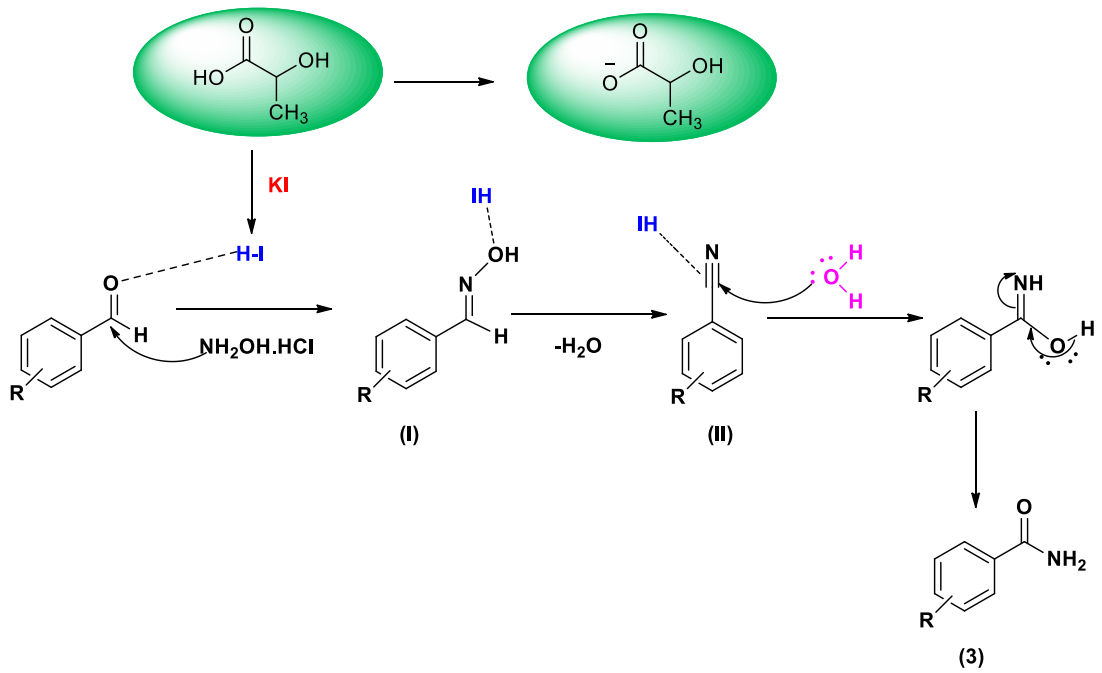


Figure 5.2 A plausible reaction pathway for the conversion of aldehyde derivatives to amides.

5.3 Experimental section

5.3.1 General procedure for the synthesis of amides

A mixture of aldehyde/ketone (1.0 mmol), hydroxylamine hydrochloride (1.2 mmol) and KI/ lactic acid (0.5/1equiv) was stirred at 80 ^{0}C for the appropriate time. The progress of reaction was monitored by thin-layer chromatography (n hexane: ethyl acetate). After completion, the reaction mixture was allowed to cool to room temperature and diluted with ethylactate and washed with water, organic layer was dried over sodium sulfate, concentrated and purified through column chromatography (Hexane: ethyl acetate).

5.4 Analytical data

5.4.1 Analytical data of primay and secondary amide

Benzamide (3a) Yield 90 %; White solid; m.p. 128-129 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.80 -7.79 (d, 2H) 7.50-7.49 (t, 1H), 7.44-7.41 (t, 2H), 6.20 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 169.59, 133.35, 131.96, 128.59, 127.31.

4-Aminobenzamide (3b) Yield 86 %; White solid; m.p.180- 181 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.62-7.61 (d, 2H), 6.90 (s, 2H), 6.55-6.54 (d, 2H), 5.60 (s, 1H, NH_2); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 168.30, 151.74, 129.23, 121.00, 112.60.

4-Methoxybenzamide (3c) Yield 85 %; White solid; m.p. 166-167 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.77-7.75 (d, 2H), 6.92-6.90 (d, 2H), 3.83 (s, 3H), 1.64 (s, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 169.59, 163.30, 129.97, 126.27, 114.50, 56.12.

4-Hydroxybenzamide (3d) Yield 88 %; White solid; m.p. 161-162 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 9.94 (s, 1H, OH), 7.74-7.74 (d, 2H), 7.07 (s, 2H), 6.78-6.77 (d, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 167.27, 159.73, 129.05, 124.56, 114.26.

2-Hydroxybenzamide (3e) Yield 87 %; White solid; m.p. 140-141 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.91 (s, 1H, OH), 8.37 (s, 2H, NH_2) 7.82-7.80(t, 1H), 7.40-7.37 (m, 1H), 6.88- 6.85 (t, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 171.8, 160.63, 134.02, 128.00, 118.40, 117.24, 114.28.

4-Nitrobenzamide (3f) Yield 90 %; White solid; m.p. 199-201 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.30-8.29 (d, 2H), 8.10-8.08 (d, 2H), 7.72 (s, 2H**)**; **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 165.67, 148.54, 139.47, 128.38, 122.92.

2-Nitrobenzamide (3g) Yield 91 %; White solid; m.p. 176-177 ^{0}C; **^{1}H NMR** (125 MHz, DMSO-d_6) δ (ppm): 8.15 (s, 2H), 8.00-7.99 (d, 1H), 7.78-7.75(t, 1H), 7.69-7.63(m, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 166.66, 146.73, 132.83, 132.07, 130.12, 128.33, 123.44.

4-Bromobenzamide (3h) Yield 89 %; White solid; m.p. 190-191 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.81-7.80 (d, 2H), 7.67-7.65 (d, 2H), 7.45 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 166.42, 132.89,130.73, 129.09, 124.50.

4-Fluorobenzamide (3i) Yield 87 %; White solid; m.p. 155-156 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.18 (s, 2H), 7.60-7.57 (d, 2H), 7.09-7.07 (d, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 164.57, 149.66, 128.92, 127.97, 115.58.

Picolinamide (3j) Yield 84 %; White solid; m.p. 110-112 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 9.04 (s, 2H), 8.70-8.69 (d, 1H), 8.21-8.17 (m, 1H), 7.61 (s, 4H), 7.50-7.47(d, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 166.00, 151.39, 148.19, 134.65, 129.18, 122.89.

N-Phenylacetamide (3k) Yield 92 %; White solid; m.p. 114-115 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.62 (s, 1H), 7.43-7.42 (d, 2H), 7.24-7.21 (t, 2H), 7.04-7.02(t, 1H), 2.08

(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 168.82, 137.96, 128.76, 124.26, 120.25, 24.29.

N-(p-Tolyl)acetamide (3l) Yield 90 %; White solid; m.p. 152-153 ^{0}C; **^{1}H NMR** (500 MHz $CDCl_3$) δ (ppm): 7.45 (s, 1H), 7.35-7.34 (d, 2H), 7.09-7.07 (d, 2H), 2.28 (s, 3H), 2.12(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 168.82, 137.89, 128.76, 124.26, 120.25, 24.29.

N-(4-Hydroxyphenyl)acetamide (3m) Yield 88 %; White solid; m.p. 169-170 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 9.71 (s, 1H), 9.38 (s, 1H), 7.29-7.27 (d, 2H), 6.67-6.65 (d, 2H), 1.96 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 168.32, 153.12, 130.68, 121.18, 115.04, 23.49.

N-(2-Hydroxyphenyl)acetamide (3n) Yield 87 %; White solid; m.p. 207-208 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.50-7.47 (d, 1H), 7.45-7.44 (d, 1H), 7.12-7.08 (d, 1H) 7.08- 6.98 (d, 1H), 2.60 (s, 3H), 2.02 (s, 1H), 1.22 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 171.16, 155.52, 154.10, 134.88, 127.26, 120.60, 119.68, 115.49, 21.02.

N-(4-Chlorophenyl)acetamide (3o) Yield 85 %; White solid; m.p. 178-179 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.39-7.37 (d, 2H), 7.21-7.20 (d, 2H), 2.11(s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 168.25, 151.02, 136.40, 129.00, 121.04, 24.56.

N-(4-Bromophenyl)acetamide (3p) Yield 87 %; White solid; m.p. 168-169 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 10.07 (s, 1H), 7.57-7.45 (d, 4H), 2.03 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 168.04, 138.19, 131.00, 120.39, 114.03, 23.54.

N-(3-Nitrophenyl)acetamide (3q) Yield 94 %; White solid; m.p. 155-156 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.34 (s, 1H), 7.94-7.92 (s, 1H), 7.69 (s, 1H), 7.46 (t, 1H), 2.22 (s, 3H), 1.64 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 168.77, 148.61, 138.65, 129.49, 125.49, 125.03, 118.72, 118.72, 114.31, 24.25.

N-Phenylbenzamide (3r) Yield 89 %; White solid; m.p. 162-163 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.86-7.84 (d, 3H), 7.63-7.62 (d, 2H), 7.55-7.52 (t, 1H), 7.48-7.45(t, 2H), 7.37-7.34 (t, 2H), 7.15-7.12 (t, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 165.74, 137.90, 135.00, 131.83, 129.09, 128.78, 127.00, 124.57, 120.19.

N-(2-Chlorophenyl)benzamide (3s) Yield 87%; White solid; m.p. 97-98 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.58-8.59 (d, 1H), 8.45 (s, 1H), 7.93-7.91(t, 2H), 7.59-7.57(m, 1H), 7.53-7.50 (t, 2H), 7.42-7.41 (d, 1H), 7.35-7.32 (t, 1H), 7.10-6.99 (t, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 165.26, 134.73, 134.61, 132.17, 129.01, 128.93, 127.87, 127.07, 124.73, 121.49.

N-(4-Nitrophenyl)benzamide (3t) Yield 89 %; White solid; m.p. 97-98 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.27-8.26 (d, 2H), 8.07-8.05 (d, 2H), 7.98-7.96 (m, 1H), 7.56-7.55 (d, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 165.25, 159.37, 157.31, 135.23, 127.58, 121.99, 115.54.

azepan-2-one (3u) Yield 85 %; White solid; m.p. 54-56 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 7.52 (s, 1H), 3.19-3.16 (m, 2H), 2.21 (t, 2H), 1.72-1.60 (m, 4H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 172.9, 42.0, 31.4, 22.1, 20.8

5.5 Spectral data of few products

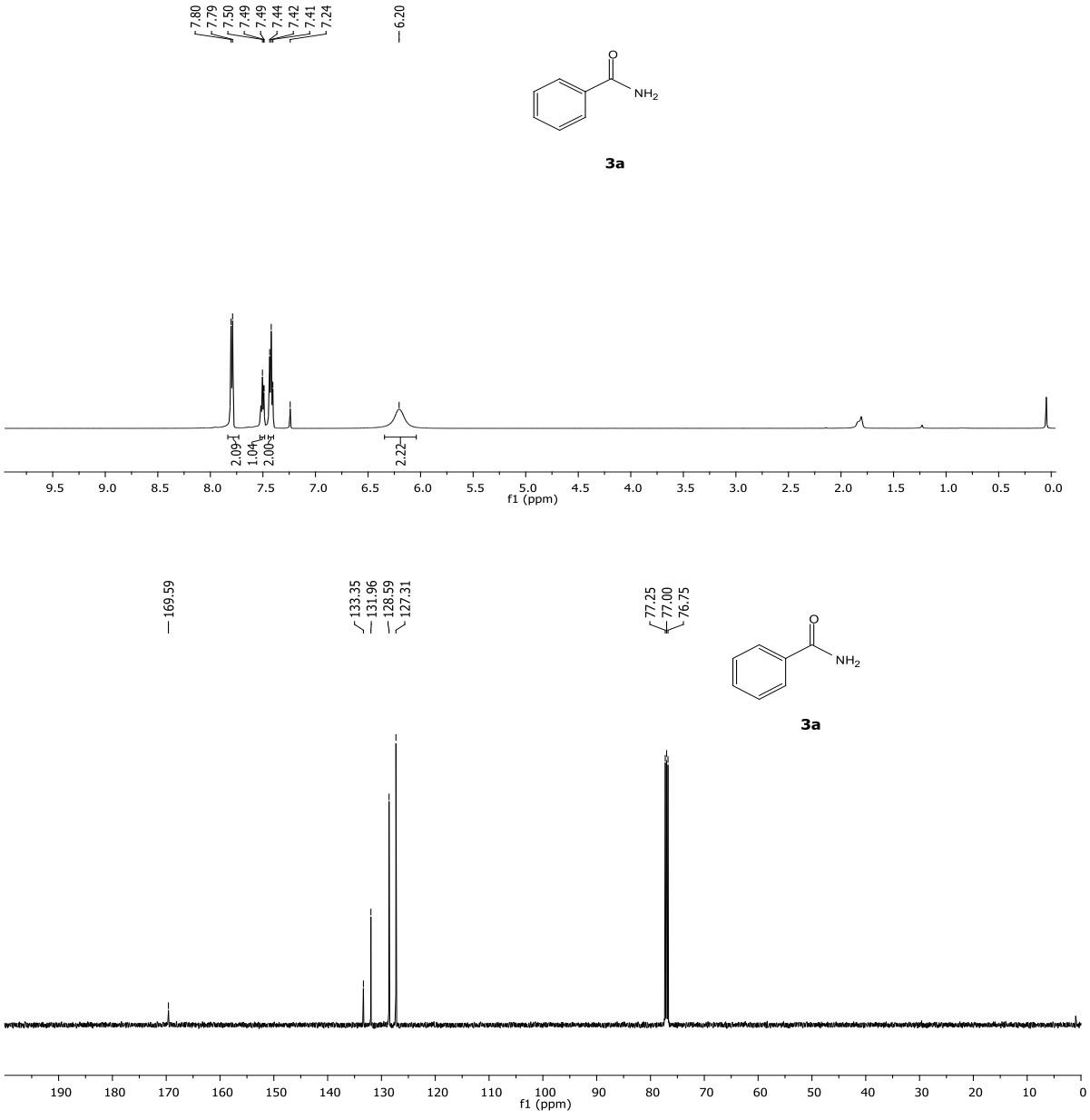


Figure 5.3 ^{1}H and ^{13}C NMR of benzamide (3a)

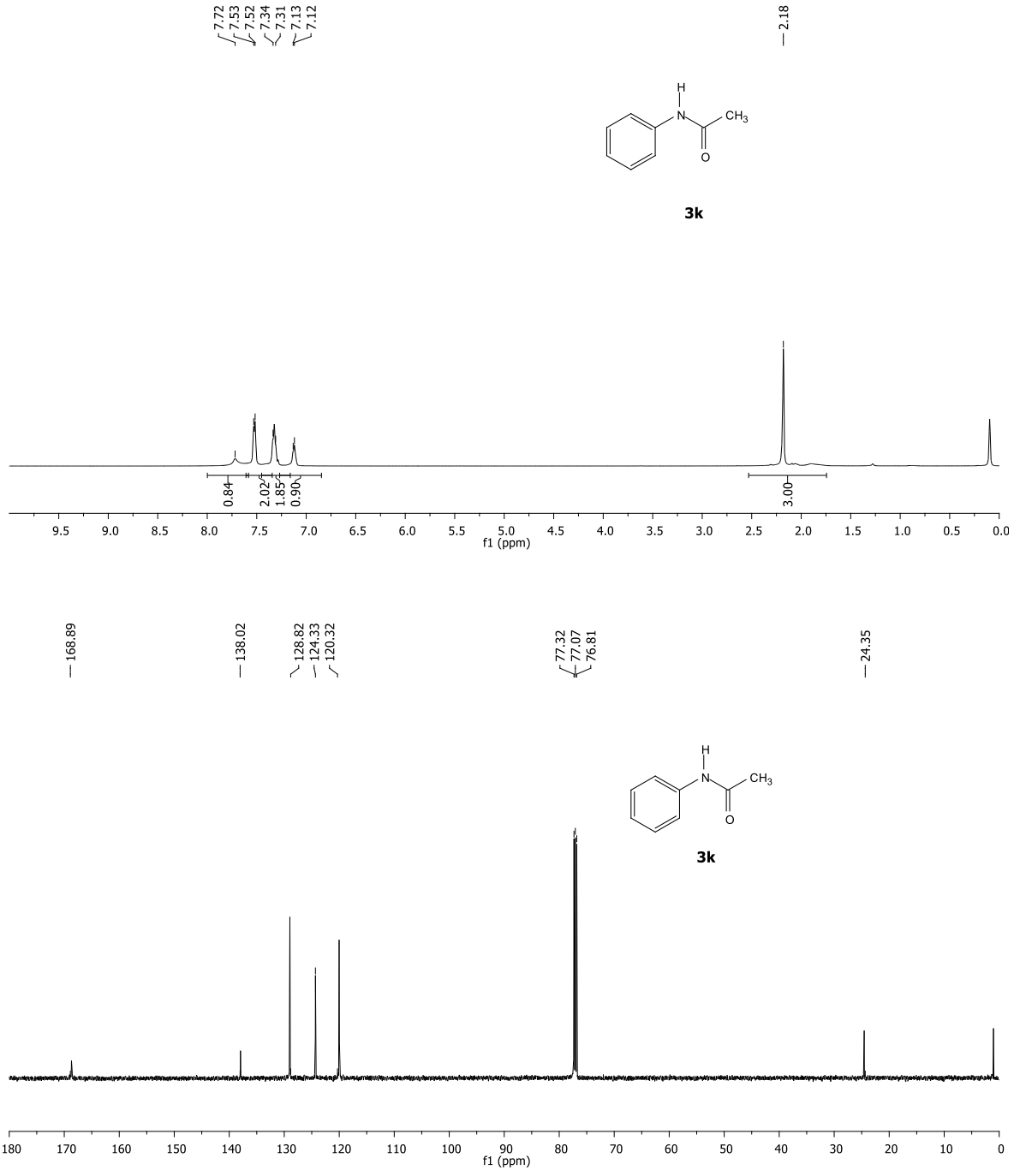


Figure 5.4 ^{1}H and ^{13}C NMR of *N*-Phenylacetamide (3k)

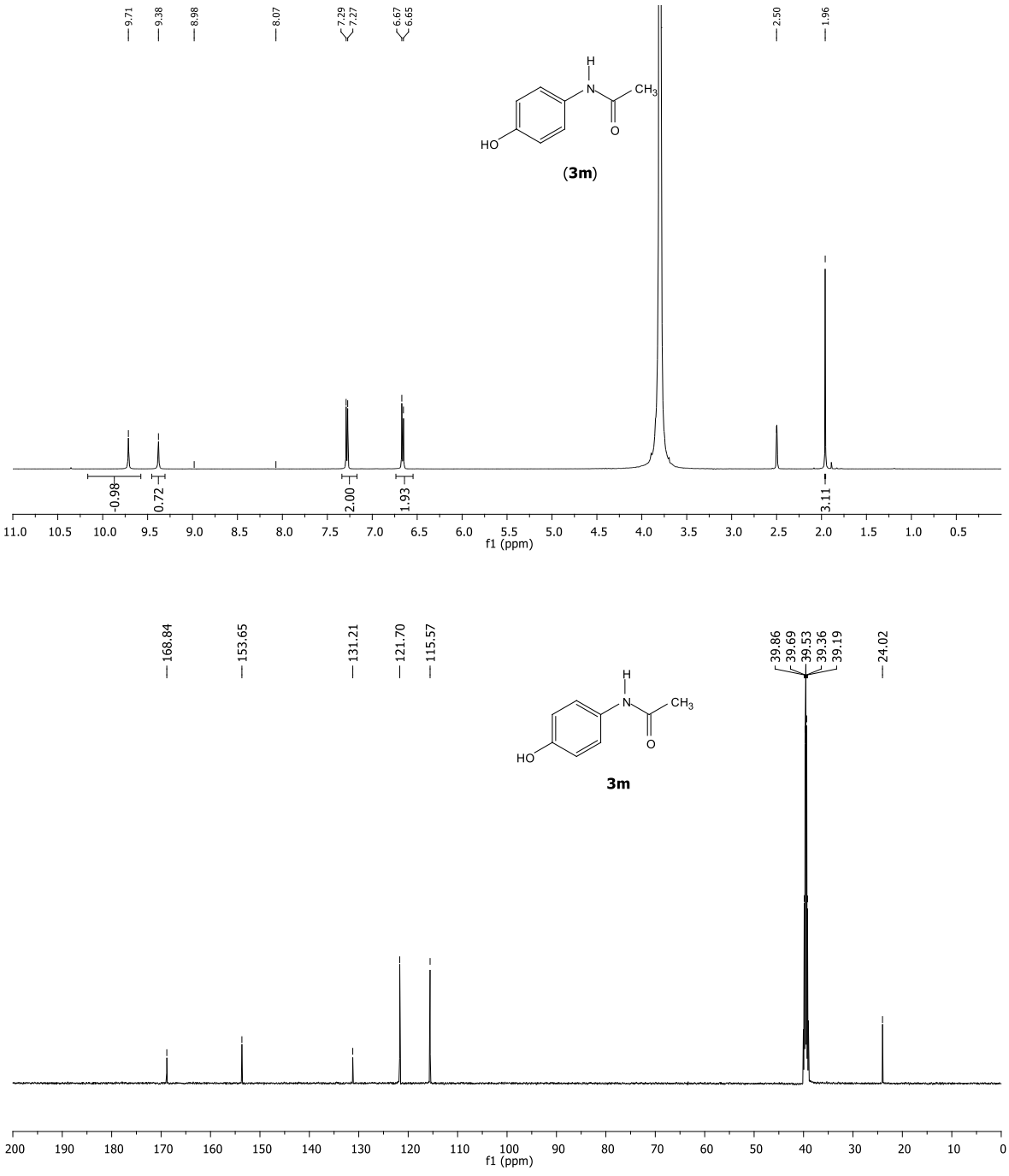


Figure 5.5 ^{1}H and ^{13}C NMR of *N-(*4-Hydroxyphenyl)acetamide (3m)

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APPENDIX

Appendix

DABCO Catalyzed Synthesis of β-Hydroxy Ketones Derived from α-Methyl Ketones and Ninhydrin under Microwave Irradiations

Introduction

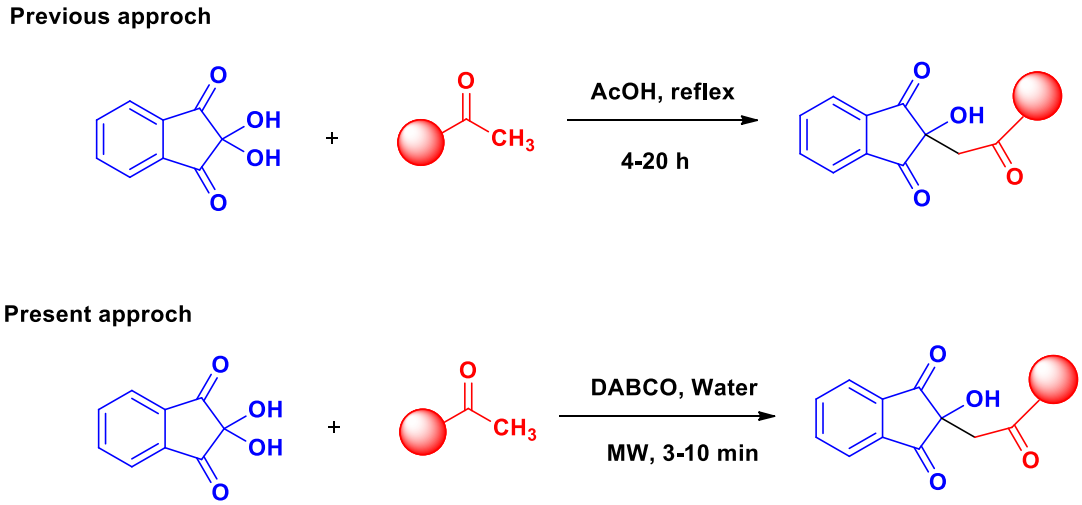
Ninhydrin is a privileged structural constituent which is involved as intermediates for the synthesis of an extensive range of pharmaceutically and biologically active compounds (Ziarani et al. 2015). Ninhydrin have highly activated carbonyl at C-2 position which readily reacts with carbon, nitrogen, oxygen and sulfur nucleophiles which results in the formation of C-C, C-N, C-O and C-S bonds respectively (Etman et al. 2011, Naskar et al. 2010, Mohammadizadeh et al. 2016, Ukhin et al. 2013, Chen et al. 2016). There are ample of name reactions for C-C bond construction but among them cross aldol condensation are most widely used. Isatin undergoes cross aldol reaction with ketones to give many biologically and pharmaceutically active products (Lu et al. 2015, Gao et al. 2012, Tiwari et al. 2016). In 2017, Hao and et al. reported β–hydroxyl ketones as a precursor for the synthesis of indole derivatives (Lan et al. 2017). It inspired us to carry out the cross aldol condensation reaction of ninhydrin with alkyl/ aryl methyl ketones to synthesis β–hydroxyl ketones. The literature survey reveals that only two reports are available for the reaction of ninhydrin with alkyl methyl ketones in glacial acetic acid (Carotti et al. 1985, Kneubuehler et al. 1995).

However, there are some shortcomings of these reported methods like harsh reaction condition, high reaction temperature, longer reaction time, tedious workup, low yield and use of a hazardous solvent. Thus the development of a new facial and rapid protocol for the synthesis of β-hydroxyl ketones is still in demand and challenging.

Recently, a great deal of attention has been paid to the development of simple and efficient methodologies for the synthesis of organic compounds in water. Water is environmentally and economically favorable; it is the most abundant solvent on earth and also, its unique and unusual physical and chemical properties enhance its reactivity and selectivity compared to organic solvents (Nagaraju et al. 2017, Shaabani et al. 2018, Gawande et al. 2013, Khazaei et al. 2015, Guo et al. 2019, Yang et al. 2018, Zhang et al. 2018, Rostami et al. 2018, Li et al. 2017). Water has advantages over many traditional organic solvents for being non-toxic, easily available, the reactions occur under mild conditions and usually easy to handle in workup processes.

Organocatalyst has emerged as a valuable and attractive tool for the synthesis of molecules through construction of new bonds. Organocatalytic formation of carbon-carbon bond provides a convenient methodology for constructing basic molecular frameworks and valuable building blocks. Recently, nitrogen-based oganocatalyst like bicyclic Lewis bases 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triazabicyclodecene (TBD) etc. have found extensive applications in organic transformations. DABCO has emerged as a base (Shi et al. 2008, Bhagat et al. 2017, Wen

et al. 2014), catalyst (Biswas et al. 2016, Keyume et al. 2014, Chong et al. 2014, Zhang et al. 2017) acts as a nucleophile (Chung et al. 2011, Meshram et al. 2012) and bulky ligand (Li et al. 2004, Han et al. 2011) for various organic reactions. DABCO is an inexpensive, easily available, non-toxic and exceedingly soluble in water so it is easy to separate from the product.



Scheme 1 An illustration of the previous and present reports for synthesis of 2- substituted-2-hydroxy-indan-1,3-diones

Herein, we disclose a simple, greener, environment friendly and highly efficient microwave induced synthesis of 2-substituted-2-hydroxy-indan-1,3-diones using water as a solvent and catalyzed by DABCO through the cross aldol condensation in good to excellent yields. A comparison of the previous and present strategies is illustrated in **Figure 1**.

Results and Discussion

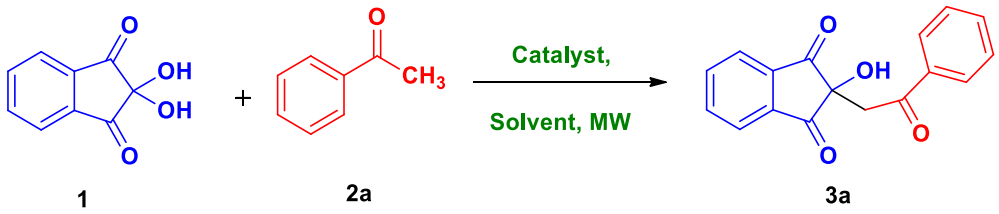
In order to achieve the optimized reaction conditions, various parameters like the effect of solvent, catalyst and mol% of the catalyst were examined in detail by choosing the model reaction of ninhydrin (**1**) and acetophenone (**2a**). To begin with, the model reaction was undertaken by conventional heating at 80 ^{0}C in acetonitrile without using any catalyst and as expected no product was obtained even after 24 h. The model reaction was then carried out with 10 mol% of DABCO as a catalyst, 40% of the product was observed in 2.5h. Just to avoid the solvent, reaction was tried with 10 mol% of DABCO at 80 ^{0}C without solvent and by grinding at room temperature for 1h but unfortunately no product was observed. It shows that solvent has a notable impact on the yield of the product. To our surprise when the reaction was carried out in the presence of DABCO (10 mol%) in acetonitrile under microwave irradiation (300W, 80 ^{0}C) the product yield was increased to 70% in 10 min (**Table 1, entry 1**). A further increase in reaction time and amount of the catalyst did not improve the yield. Microwave irradiation gave the best result in short span of time so all further optimization were carried out under microwave irradiations.

To investigate the effect of different solvents the model reaction was undertaken in various solvents under microwave irradiation using with10 mol% of DABCO as a catalyst. In the presence of non-polar solvents like toluene, xylene (**Table 1, entries 5-6**) no product was obtained while in polar solvents like methanol, ethanol and water provided good yield of product (**Table 1, entries 2-4**), among all tested solvents water and ethanol gave 100%

conversion. From the environment benign green synthesis point of view volatile organic solvents (VOS) should be replaced by green solvents so we preferred water than ethanol.

Further different catalysts were also screened for this transformation, the model reaction was microwave irradiated for 60 min with 10 mol% of Et_3N, piperidine, urea, Cs_2CO_3, *p*-TSA in water gave the desired product in low yield (40-60%), (**Table 1, entries 7-11**) while C_2H_5ONa, TiO_2, K-10 (**Table 1, entries 12-14**) didn't give any trace of the product. Among all the tested catalysts, DABCO gave the best result in lesser time. The catalyst loading was also optimized with DABCO concentration i.e. 0, 2, 5, 7 and 8 mol% (**Table 1, entries 15-19**) the results show that 8 mol% catalyst loading is optimum for the reaction, a decrease in the mol% of the catalyst amount resulted in diminished yield and any further increase of catalyst amount did not show any significant improvement in rate of the reaction and yield. The formation of product (**3a**) was confirmed by IR and NMR spectra. IR spectrum shows peaks at 3354 and 1749, 1710, 1674 cm^{-1} for OH and carbonyl groups respectively. In ^1H NMR ($CDCl_3$) shows a singlet at δ 3.43 (1H, D_2O exchangeable) for 2-hydroxyl and a singlet at 3.93 (2H) for β-methylenic protons. Appearance of singlet for methelynic protons shows that they are in same magnetic environment and are orthogonal to the indandione ring.

Table 1 Effect of the solvents, catalysts on the yield of the product 3a[a]



Entry	Solvent	Catalyst	Loading of the catalyst (mol%)	Time(min)	% Yield[b]
1	Acetonitrile	DABCO	10	10	70
2	Methanol	DABCO	10	5	80
3	Ethanol	DABCO	10	3	93
4	Water	DABCO	10	3	95
5	Toluene	DABCO	10	60	NR
6	Xylene	DABCO	10	60	NR
7	Water	Triethylamine	10	60	40
8	Water	Piperdine	10	60	40
9	Water	Urea	10	60	60
10	Water	Cs_2CO_3	10	60	60
11	Water	p-TSA	10	60	50
12	Water	C_2H_5ONa	10	60	NR
13	Water	TiO_2	10	60	NR
14	Water	K-10	10	60	NR

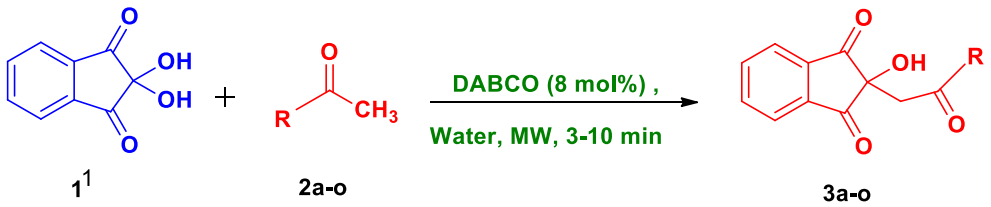
15	Water	-	0	60	NR
16	Water	DABCO	2	3	20
17	Water	DABCO	5	3	60
18	Water	DABCO	7	3	75
19	Water	DABCO	8	3	95

[a]**Reaction conditions**: Ninhydrin (**1**) (1.0 mmol), acetophenone (**2a**) (1.0 mmol) and catalyst in 5 mL of solvent were irradiated in microwave.[b]Isolated yield.

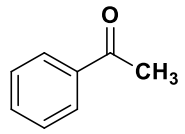
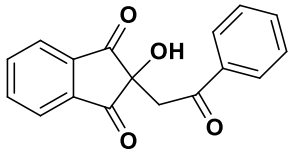
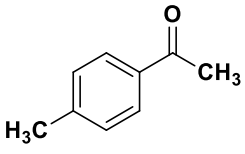
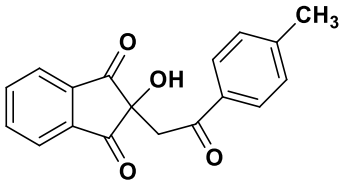
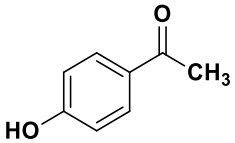
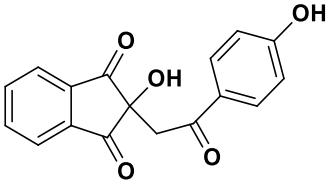
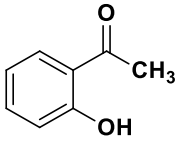
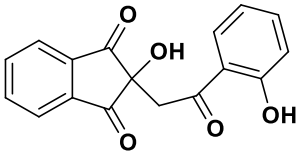
With these encouraging results and having the optimized reaction conditions, the scope and the applicability of this methodology was examined on various aromatic and aliphatic α-methyl ketones (**2**) with ninhydrin (**1**). Acetophenones (**1a**), 4-methyl acetophenones (**1b**), 4-hydroxy acetophenones (**1c**), 2-hydroxy acetophenones (**1d**), 2- naphthalenones (**1e**), 4-amino acetophenones (**1f**) 4-fluoro acetophenones (**3g**), 4-chloro acetophenones (**3h**), 4-bromo acetophenones (**3i**), 3-nitro acetophenones (**3j**), 2-acetyl thiophene (**3k**), 2-acetyl pyridine (**3l**), acetyl cyclopropene (**3m**) gives 2-Hydroxy-2-(2'-oxo-2'-phenylethyl)indan-1,3-dione (**3a**), 2-Hydroxy-2-(2'-oxo-2'-(4-tolyl)ethyl)indan-1,3-dione (**3b**), 2-Hydroxy-2-(2'-(4-hydroxyphenyl)-2'-oxoethyl)indan-1,3-dione (**3c**), 2-Hydroxy-2-(2-(2-hydroxyphenyl)-2-oxoethyl)-1H-indene-1,3(2H)-dione (**3d**), 2-Hydroxy-2-(2-(naphthalen-1-yl)-2-oxoethyl)-1H-indene-1,3(2H)-dione (**3e**), 2-(2-(4-Aminophenyl)-2-oxoethyl)-2-hydroxy-1H-indene-1,3(2H)-dione (**3f**), 2-(2-(4-Fluorophenyl)-2-oxoethyl)-2-hydroxy-1H-indene-1,3(2H)-dione (**3g**), 2-(2-(4-Cholrophenyl)-2-oxoethyl)-2-hydroxy-1H-indene-1,3(2H)-dione (**3h**), 2-(2-(4-

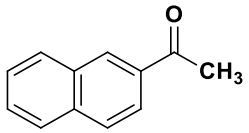
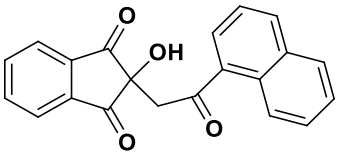
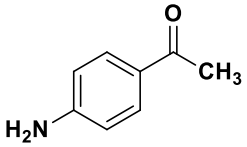
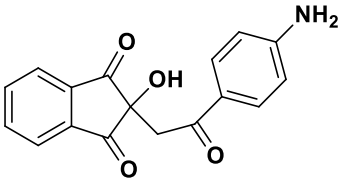
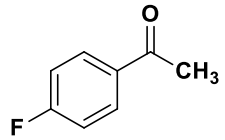
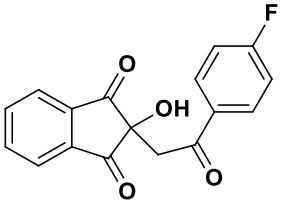
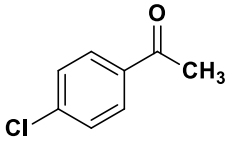
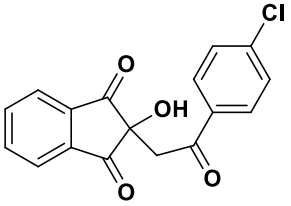
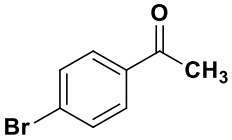
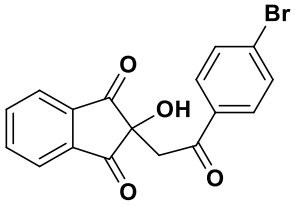
Bromophenyl)-2-oxoethyl)-2-hydroxy-1H-indene-1,3(2H)-dione (**3i**), 2-Hydroxy-2-(2-(3-nitrophenyl)-2-oxoethyl)-1H-indene-1,3(2H)-dione (**3j**), 2-Hydroxy-2-(2-oxo-2-(thiophen-2-yl)ethyl)-1H-indene-1,3(2H)-dione (**3k**), 2-Hydroxy-2-(2-oxo-2-(pyridin-2-yl)ethyl)-1H-indene-1,3(2H)-dione (**3l**), 2-(2-Cyclopropyl-2-oxoethyl)-2-hydroxy-1H-indene-1,3(2H)-dione (**3m**), 2-Hydroxy-2-(2-oxobutyl)-1H-indene-1,3(2H)-dione (**3n**), 2-Hydroxy-2-(4-methyl-2-oxopentyl)-1H-indene-1,3(2H)-dione (**3o)**. Acetophenones with electron withdrawing group e.g. flouro, chloro, bromo and nitro (**Table 2, entries 7-10**) provided slightly higher yields in lesser time than electron releasing groups like alkyl, hydroxyl and amino (**Table 2, entries 2-6**). Higher rate of reaction in case of electron withdrawing substituents may be due to better stabilization of the enolate ions and makes it better nucleophile. We have employed the *o*-hydroxyl acetophenone as the ketone substrate (2d), but no annulated product was observed. Further under optimized conditions 2-acetyl thiophene and 2-acetyl pyridine (**Table 2, entries 11 and 12**) also gave desired product in good to excellent yields, on the other hand aliphatic and cyclic ketones also gave the products in good yields but took longer reaction time 7-10 min (**Table 2, entries 13-15**). The structures of all the synthesized compounds (**3a-o**) were characterized by CHN analysis, ^{1}H and ^{13}C NMR spectroscopy.

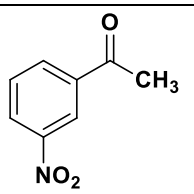
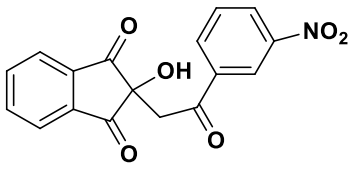
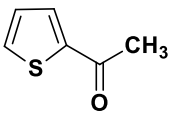
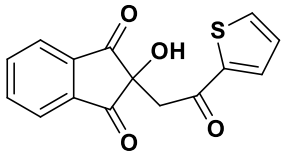
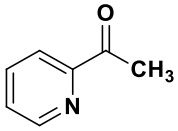
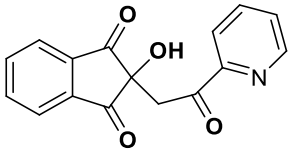
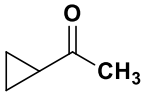
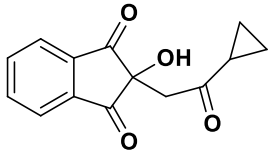
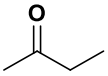
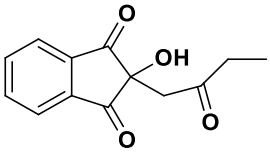
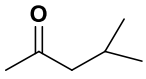
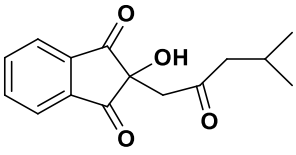
Table 2 Synthesis of **3a-o** under microwave irradiation method[a]



1[1] 2a-o 3a-o

Entry	Substrate	Product	Time (min)	Yield (%)[b]
1	 2a	 3a	3	95
2	 2b	 3b	5	85
3	 2c	 3c	6	82
4	 2d	 3d	6	84

5	 2e	 3e	5	85
6	 2f	 3f	5	86
7	 2g	 3g	3	96
8	 2h	 3h	4	92
9	 2i	 3i	4	90

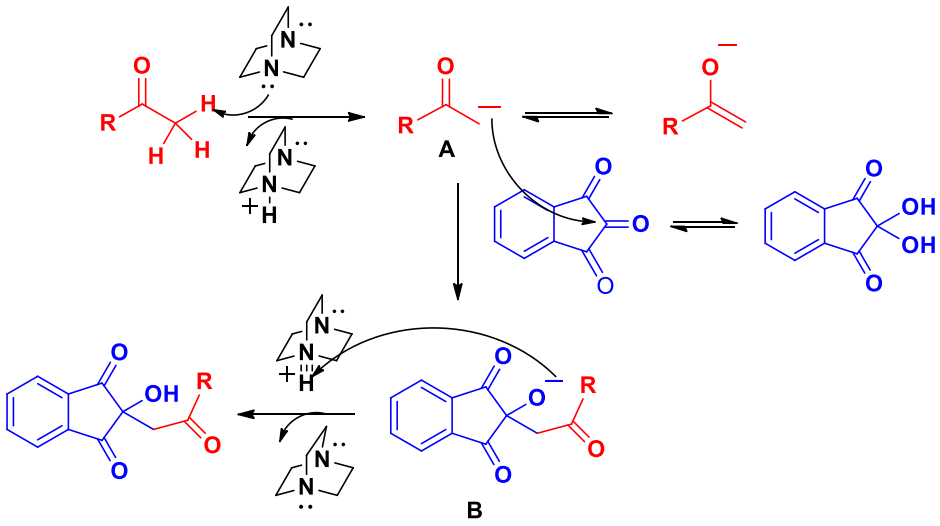
10	 2j	 3j	5	92
11	 2k	 3k	8	89
12	 2l	 3l	8	88
13	 2m	 3m	7	82
14	 2n	 3n	10	85
15	 2o	 3o	10	85

[a]**Reaction conditions:** Ninhydrin (1.0 mmol), aryl/alkyl methyl ketone (1.0 mmol) and DABCO (8 mol %) in 5 mL of water were irradiated in microwave. [b]Isolated yield.

A plausible mechanism for the DABCO catalyzed cross aldol condensation reaction shown in Scheme 1. DABCO abstracts acidic proton from α-methyl ketones and from

enolate (**A**) followed by attack at the C-2 position of ninhydrin and from (**B**) which subsequently abstract proton from protonated DABCO and from desired products.

To demonstrate the potential synthetic application of this protocol the synthesis of (**3a**) was carried out on gram scale with 5g (0.028 mol) of ninhydrin and 3.26 ml (0.028) mol of acetophenone using 8 mol% DABCO in water under microwave irradiation gave 3a in (7.22 g) 92% yield and also comparable to the yield obtained in mg scale (**Table 2, entry 1**).



Scheme 1 Plausible mechanism of the cross-aldol reaction

Experimental section

General procedure for the preparation 2-susbtituted-2-hydroxy indan-1,3-dione derivatives (3a-o)

A mixture of ninhydrin **1** (1.0 mmol), aryl/alkyl methyl ketone **2** (1.0 mmol) and DABCO (8 mol %) in water (5 mL) was placed in round bottom flask and irradiated in microwave oven at 300 W, 80 ^{0}C. The progress of reaction was monitored by TLC using *n*-hexane/ethyl acetate and after the completion of reaction, solvent was evaporated under vaccum. The crude products were purified by silica gel column chromatography using ethyl acetate- hexane solvent system to afford the pure β–hydroxy ketones (3a-o).

Analytical data

2-Hydroxy-2-(2'-oxo-2'-phenylethyl)indan-1,3-dione (3a)

Yield 95%; Light yellow; m.p. 107-108 ^{0}C; **^{1}H NMR** ($CDCl_3$) δ (ppm): 8.05-8.04 (m, 2H), 7.90-7.89 (m, 2H), 7.84-7.82 (d, 2H), 7.57-7.54 (t, 1H), 7.43-7.40 (t, 2H), 3.91 (s, 2H), 3.41 (s, 1H, OH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 198.47, 197.57, 140.91, 136.88, 135.01, 134.34, 129.05, 128.61, 124.80, 124.56, 73.66, 44.49; **Elemental analysis**: Calc. (%) for $C_{17}H_{12}O_4$ (280.27): C 72.85, H 4.32; Found (%): C 72.50, H 4.72.

2-Hydroxy-2-(2'-oxo-2'-(4-tolyl)ethyl)indan-1,3-dione (3b)

Yield 85%; White solid; m.p. 140-142 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.03-8.01 (m, 2H), 7.88-7.86 (m, 2H), 7.22-7.70 (d, 2H), 7.19-7.18 (d, 2H), 3.89 (s, 2 H), 3.65 (s, 1H,

OH), 2.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 198.71, 197.14, 145.08, 140.99, 136.03, 132.69, 129.38, 128.40, 124.15, 73.48, 43.47, 21.18; **Elemental analysis**: Calc. (%) for $C_{18}H_{14}O_4$ (294.30): C 73.46, H 4.79; Found (%): C 73.85, H 4.74.

2-Hydroxy-2-(2'-(4-hydroxyphenyl)-2'-oxoethyl)indan-1,3-dione (3c)

Yield 82%; White solid; m.p. 138-140 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.54 (s, 1H, OH), 8.02 (s, 4H), 7.77-7.76 (d, 2H), 6.83-6.81 (d, 2H), 6.77 (s, 1H, OH), 3.84 (s, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 199.50, 195.71, 163.08, 141.04, 136.38, 131.08, 126.56, 123.71, 115.61, 72.72, 43.91; **Elemental analysis**: Calc. (%) for $C_{17}H_{12}O_5$ (296.27): C 68.91, H 4.08; Found (%): C 68.52, H 4.19.

2-Hydroxy-2-(2'-(2-hydroxyphenyl)-2'-oxoethyl)indan-1,3-dione (3d)

Yield 84%; Yellowish solid; m.p. 131-132 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.21 (s, 1H, OH), 8.05-8.03 (m, 2H), 7.92-7.90 (m, 2H), 7.70 (s, 1H), 7.47-7.41(t, 1H), 6.90-6.83 (m, 2H), 3.95 (s, 2H), 3.37 (s, 1H, OH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 202.06, 197.86, 162.32, 140.90, 137.32, 136.26, 130.22, 124.26, 119.33, 118.63, 72.14, 43.63; **Elemental analysis**: Calc. (%) for $C_{17}H_{12}O_5$ (296.27): C 68.91, H 4.08; Found (%): C 68.50, H 4.03.

2-Hydroxy-2-(2'-(naphthalen-1-yl)-2'-oxoethyl)indan-1,3-dione (3e)

Yield 85%; Yellowish solid; m.p. 110-112 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.39 (s, 1H), 8.05 (s, 2H), 7.89 (s, 3H), 7.80 (s, 3H), 7.58-7.52 (d, 2H), 4.06 (s, 2H), 3.54 (s, 1H,

OH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 198.26, 197.01, 141.01, 136.19, 135.91, 132.46, 132.27, 130.63, 129.68, 128.99, 128.63, 127.78, 126.99, 124.21, 123.31, 73.57, 44.01; **Elemental analysis**: Calc. (%) for $C_{21}H_{14}O_4$ (330.33): C 76.35, H 4.27; Found (%): C 75.98, H 4.24.

2-(2'-(4-Aminophenyl)-2'-oxoethyl)-2-hydroxy-indan-1,3-dione (3f)

Yield 86%; Pale Yellow; m.p. 160-162 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.00 (s, 4H), 7.57-7.56 (d, 2H), 6.68 (s, 1H), 6.53-6.51 (d, 2H), 6.21 (s, 2H), 3.75 (s, 2H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 198.88, 193.48, 153.98, 140.41, 135.51, 130.20, 122.93, 121.83, 112.02, 72.10, 43.00; **Elemental analysis**: Calc. (%) for $C_{17}H_{13}NO_4$ (295.29): C 69.14, H 4.43; Found (%): C 68.74, H 4.48.

2-(2'-(4-Fluorophenyl)-2'-oxoethyl)-2-hydroxy-indan-1,3-dione (3g)

Yield 96%; Brown solid; m.p. 114-115 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.05-8.03 (m, 2H), 7.91-7.89 (m, 2H), 7.87-7.84 (m, 2H), 7.09-7.06 (t, 2H), 3.89 (s, 2H), 3.51 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 198.17, 195.43, 167.28, 165.24, 140.95, 136.24, 131.07, 131.00, 124.20, 116.04, 115.86, 73.33, 43.85; **Elemental analysis**: Calc. (%) for $C_{17}H_{11}FO_4$ (298.27): C 68.46, H 3.72; Found (%): C 68.09, H 3.66.

2-(2'-(4-Cholrophenyl)-2'-oxoethyl)-2-hydroxy-indan-1,3-dione (3h)

Yield 92%; Brown solid; m.p. 180-181 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.03-8.02 (d, 2H), 7.90-7.89 (d, 2H), 7.76-7.74 (d, 2H), 7.38-7.36 (d, 2H), 3.88 (s, 2H), 3.54 (s, 1H,

OH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 198.14, 195.86, 140.94, 136.26, 133.43, 131.51, 129.66, 129.08, 124.21, 73.32, 43.88; **Elemental analysis**: Calc. (%) for $C_{17}H_{11}ClO_4$ (314.72): C 64.88, H 3.52; Found (%): C 65.28, H 3.55.

2-(2'-(4-Bromophenyl)-2'-oxoethyl)-2-hydroxy-indan-1,3-dione (3i)

Yield 90%; Yellow solid; m.p. 150-152 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.98-7.97 (d, 2H), 7.84-7.83 (d, 2H), 7.64-7.63 (d, 2H), 7.49-7.47 (d, 1H), 3.90 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 198.47, 196.10, 140.91, 136.15, 133.68, 131.95, 129.69, 129.31, 124.10, 73.19, 44.01; **Elemental analysis**: Calc. (%) for $C_{17}H_{11}BrO_4$ (359.17): C 56.85, H 3.09; Found (%): C 56.52, H 3.15.

2-Hydroxy-2-(2'-(3-nitrophenyl)-2'-oxoethyl)indan-1,3-dione (3j)

Yield 92%; White solid; m.p. 160-162 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H), 8.43-8.41 (d, 1H), 8.17- 8.15 (d, 1H), 8.07- 8.05 (m, 2H), 7.94-7.92 (m, 2H), 7.66 - 7.63 (t, 1H), 3.95 (s, 2H), 3.31 (s, 1H, OH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 197.75, 194.71, 148.55, 140.80, 136.45, 133.67, 130.27, 127.74, 124.39, 123.41, 73.24, 43.93; **Elemental analysis**: Calc. (%) for $C_{17}H_{11}NO_6$ (325.27): C 62.77, H 3.40; Found (%): C 62.36, H 3.37.

2-Hydroxy-2-(2'-oxo-2'-(thiophen-2-yl)ethyl)indan-1,3-dione (3k)

Yield 89%; Yellow solid; m.p. 144-145 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.03 (s, 1H), 7.88-7.83 (t, 4H), 7.56-7.54 (d, 1H), 7.42-7.41 (d, 1H), 4.14 (s, 1H, OH), 3.99 (s,

2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 198.51, 197.06, 140.95, 136.08, 134.97, 133.97, 128.63, 128.24, 124.10, 73.32, 44.08; **Elemental analysis**: Calc. (%) for $C_{15}H_{10}O_4S$ (286.30): C 62.92, H 3.52; Found (%): C 62.52, H 3.46.

3.1.2-Hydroxy-2-(2'-oxo-2'-(pyridin-2-yl)ethyl)indan-1,3-dione (3l)

Yield 88%; White solid; m.p. 108-110 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.67-8.66 (d, 1H), 8.04-7.99 (m, 3H), 7.90-7.88 (m, 2H), 7.56-7.54 (t, 1H), 7.33 (s, 1H), 3.61 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 198.87, 197.51, 151.98, 148.35, 139.96, 138.03, 136.51, 127.82, 124.18, 122.77, 74.75, 44.79; **Elemental analysis**: Calc. (%) for $C_{16}H_{11}NO_4$ (281.26): C 68.32, H 3.94; Found (%): C 67.94, H 3.88.

2-(2'-Cyclopropyl-2'-oxoethyl)-2-hydroxy-indan-1,3-dione (3m)

Yield 82%; White solid; m.p. 116-118 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.94-7.82 (d, 4H), 4.21 (s, 1H), 3.43 (s, 2H), 1.86 (s, 1H), 0.91-0.87 (s, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 208.13, 198.52, 140.76, 136.07, 123.96, 72.99, 47.57, 20.38, 11.62; **Elemental analysis**: Calc. (%) for $C_{14}H_{12}O_4$ (244.24): C 68.84, H 4.95; Found (%): C 69.25, H 4.93.

2-Hydroxy-2-(2'-oxobutyl)indan-1,3-dione (3n)

Yield 85%; White solid; m.p. 128-129 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.98 -7.93 (t, 2H), 7.86-7.84 (t, 2H), 3.26 (s, 1H), 3.21 (s, 2H), 2.16 (d, 2H), 1.42-1.41 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 210.78, 198.20, 140.58, 136.11, 123.91, 75.55, 51.23,

28.93, 11.09; **Elemental analysis**: Calc. (%) for $C_{13}H_{12}O_4$ (232.23): C 67.23, H 5.20; Found (%): C 67.60, H 5.23.

2-Hydroxy-2-(4'-methyl-2'-oxopentyl)indan-1,3-dione (3o)

Yield 85%; White solid; m.p. 165-166 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.99-7.98 (d, 2H), 7.86-7.85 (d, 2H), 3.76 (s, 1H, OH), 3.26 (s, 2H), 2.24-2.23 (d, 2H), 2.00-1.96 (m, 1H), 0.82-0.81 (d, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 208.52, 198.35, 140.80, 136.22, 124.12, 73.14, 51.42, 47.27, 24.52, 22.34; **Elemental analysis**: Calc. (%) for $C_{15}H_{16}O_4$ (260.29): C 68.22, H 6.20; Found (%): C 68.82, H 6.23.

Spectral data of product (3a)

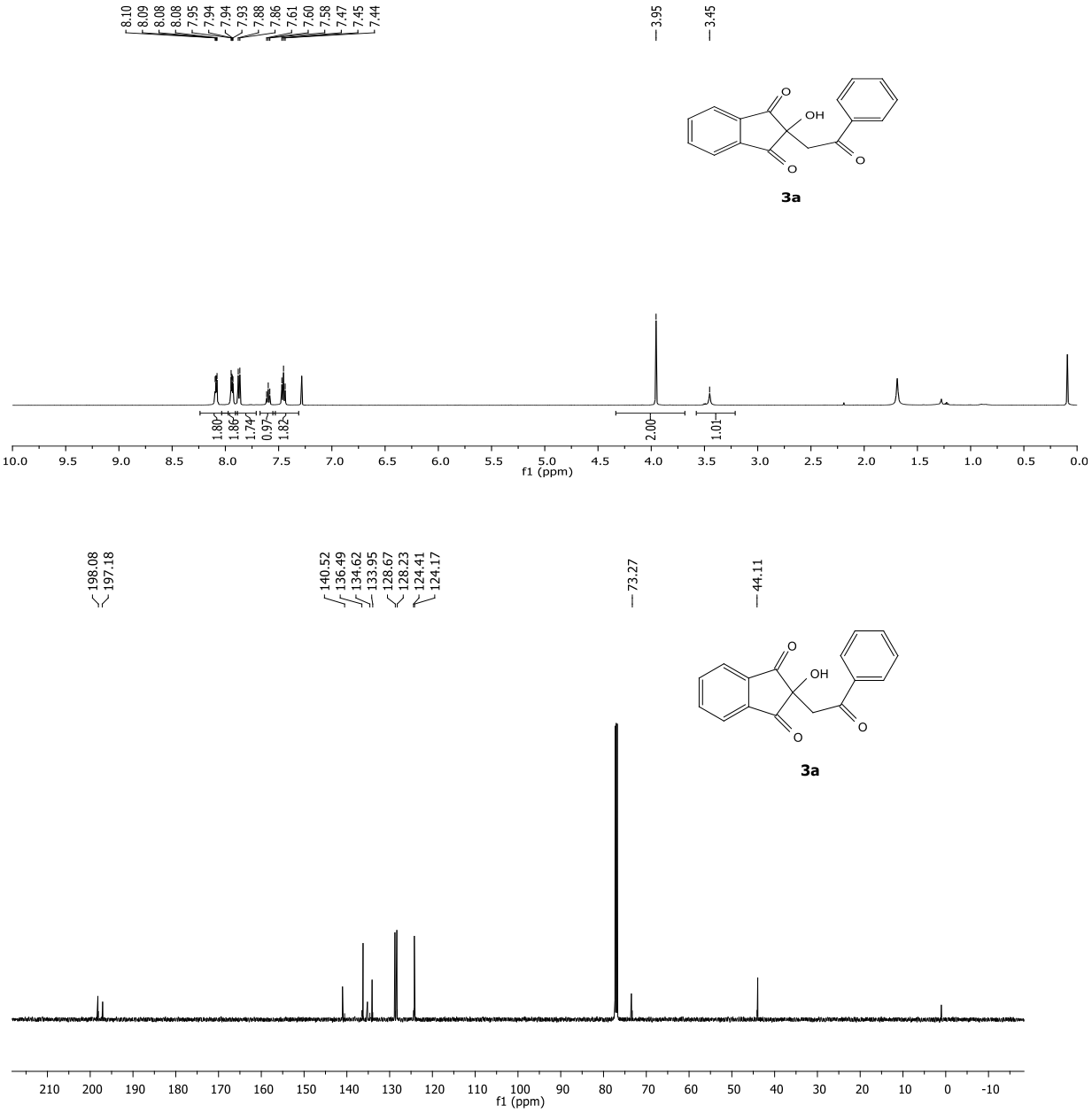


Figure ^{1}H and ^{13}C NMR of 2-Hydroxy-2-(2'-oxo-2'-phenylethyl)indan-1,3-dione (3a)

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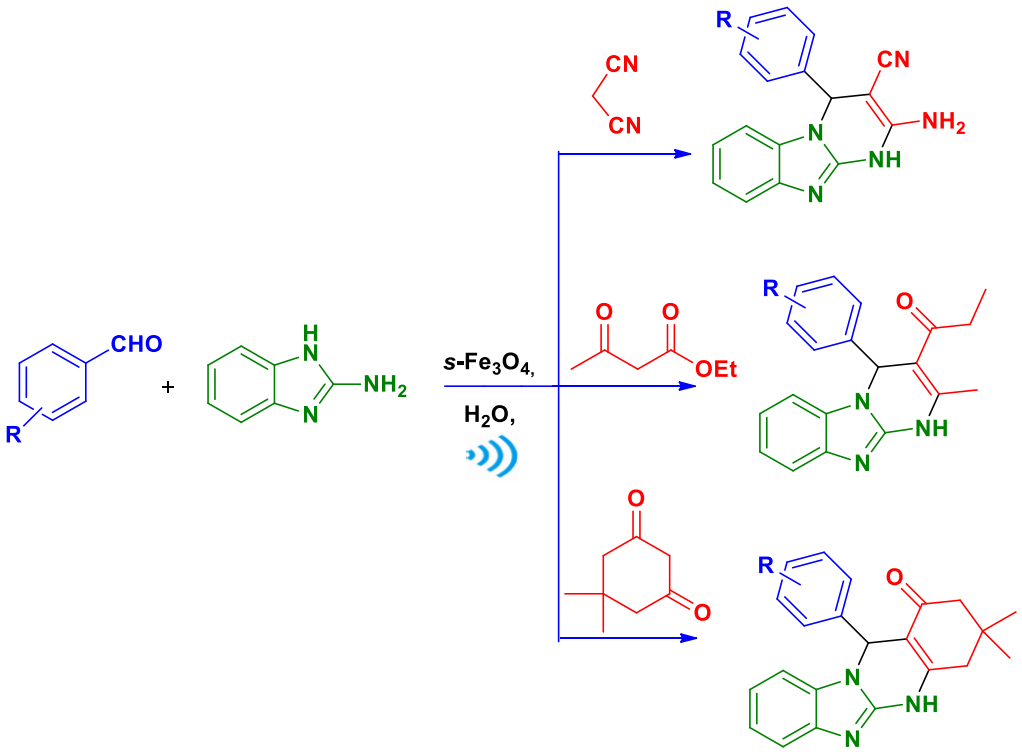
SUMMARY AND CONCLUSIONS

Summary and Conclusions

The thesis entitled, "New Avenues for the Synthesis of Some Biologically Relevant Nitrogen Containing Compounds" embodies the synthesis and reactivity of biologically important compounds containing nitrogen atoms. The content of the thesis has been divided into five chapters.

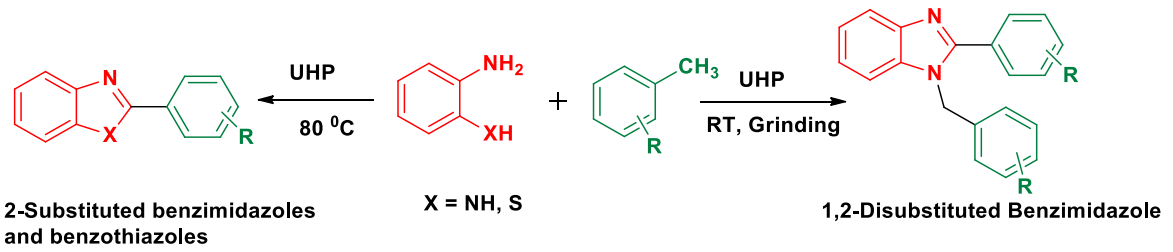
Chapter 1 provides a general introduction and literature review of some main class of nitrogen containing organic compounds such as amine, imine, oxime, amides, pyrrole, pyridine and fused heterocycles indoles, imidazopyrimidine, pyranopyrazoles, benzimidazole, benzoxazoles and benzothaizole.

Chapter 2 describes ultrasound induced chemoselective green synthesis of imidazopyrimidine from aldehyde derivatives, malanonitrile and 2-aminobenzimidazole and the reaction was catalyzed by starch functionalized superparamagnetic nanoparticles (*s*-Fe_3O_4). The syntheses were successfully achieved by domino Knoevenagel–Michael reaction in water with variety of aldehyde and active methylene compounds. The developed method is simple, efficient and provides good to excellent yields in short span of time (**Scheme A**).



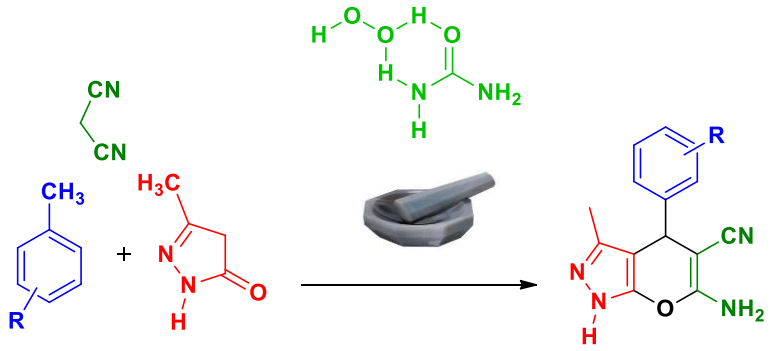
(**Scheme A**)

Chapter 3 exploits a highly efficient, practical and environmentally benign approach for the synthesis of 1,2-disubstitituted benzimidazole and 2-substitited benzimidazole/ benzothaizole from *o*-phenylenediamine/ aminothiophenol and methyl arenes derivatives under different reaction conditions. Herein we have developed a rapid and facile method to achieve the fused heterocycles using simple urea hydrogen peroxide under catalyst-free condition at room temperature. The methodology shows extensive functional group tolerance and good to excellent yield in short span of time (**Scheme B**).



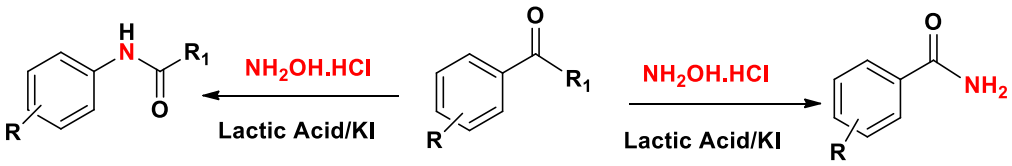
(**Scheme B**)

Chapter 4 illustrates a high yielding and environment benign synthesis of pyranopyrazoles derivatives using urea hydrogen peroxide (UHP) under physical grinding method. The present methodology offers several benefits such as available green and cheap starting materials, solvent-free, mild reaction conditions, high atom-economy, excellent yields and easy isolation of products without column chromatographic separation (**Scheme C**).



(**Scheme C**)

Chapter 5 presents an efficient synthesis of primary and secondary amide through Beckmann reaction. This reaction was catalyzed lactic acid and potassium iodide catalyst system. The highlights of present methodology is low-cost starting material, high atom-economic strategy, simple with cleaner reaction profile, high yield of products in shorter reaction time which builds a genuinely green protocol (**Scheme D**).



R_1 = H, CH_3, phenyl

(**Scheme D**)

LIST OF RESEARCH PUBLICATIONS

List of Publications

Verma, P., S. Pal, S. Chauhan, A. Mishra, I. Sinha, S. Singh and V. Srivastava, "Starch functionalized magnetite nanoparticles: A green, biocatalyst for one-pot multicomponent synthesis of imidazopyrimidine derivatives in aqueous medium under ultrasound irradiation," *Journal of Molecular Structure*, **1203** (2020) 127410.

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