CHAPTER-3

ONE POT REDUCTIVE SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES FROM 2-NITRO ANILINE AND AROMATIC ALDEHYDES

III.1. Benzimidazole

The benzo derivative of imidazole is referred to as benzimidazole (Bansal, 2002) having chemical formula $C_7H_6N_2$. Although benzimidazole is the commonest name of the parent compound of the series, other names such as 1*H*-Benzo[d]imidazole and 1*H*-1, 3-benzimidiazole (Figure III.1) are often used. Benzimidazole ring exists in two equivalent tautomeric forms (Figure III.2). It is an important heterocyclic aromatic organic compound. Among heterocyclic pharmacophores, this bicyclic ring system is quite common. It is a vital Pharmacophore and privileged structure, owing to their extensive recurrence in bioactive compounds. In spite of great interest in ligands and structural chemistry of benzimidazole, medicinal chemistry, biological activities, development and synthesis of novel molecules with therapeutic values are the leading attractiveness in this field [1].

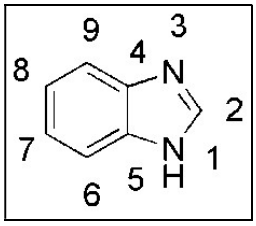


Figure III.1. 1*H*-1, 3-benzimidiazole.

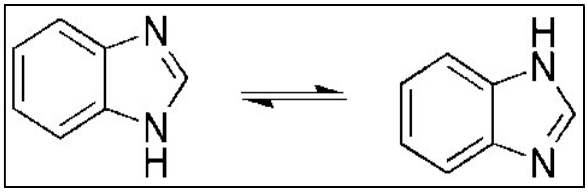


Figure III.2. Equivalent tautomeric forms of benzimidazole.

Benzimidazole is whitish solid having characteristic odor with the melting point 172 ^{o}C and boiling point 360 ^{o}C. It is freely soluble in alcohol, sparingly soluble in ether, practically insoluble in benzene, petroleum ether but soluble in aqueous solutions of acids and strong alkalis [2].

III. 2. Natural occurrences

The benzimidazole nucleus does not appear to occur very widespread in nature. The 5, 6-di methyl-1-(α-D-ribofuranosyl)benzimidazole ring system was discovered in 1948 as an integral part of the structure of vitamin B12 [3] (Figure III.3).

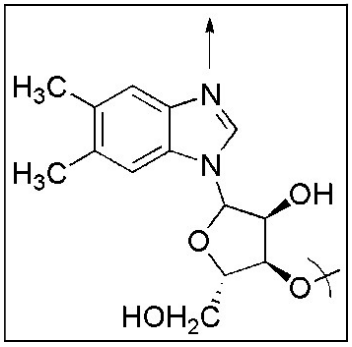


Figure III.3. 5, 6-di methyl-1-(α-D-ribofuranosyl)benzimidazole ring system in vitamin B12.

III.3. Medicinal and biological activities of benzimidazole derivatives

The early 1950s was a significant period to unlock the biological importance of benzimidazole-containing structures [4, 5, 6] and the closely-related purines (Figure III.4). Subsequently pharmaceutical, veterinary and agrochemical products were discovered including thiabendazole, cimetidine, azomycin, metronidazole, misonidazole, and chlotrimazole, antihistamines, astemizole and the anti-ulcerative omeprazole) [7]. These biological activities include anti-cancer [8], bactericidal [9], fungicidal [10-11], analgesic [12] anti-viral properties [13] and some have cardiovascular applications [14] while some derivatives have been synthesized and evaluated for inhibition of HIV-1 infectivity [15]. Most recently, the anti-protozoal activity of substituted 2-trifluoro benzimidazole has been reported [16]. It was also suggested that the benzimidazole derivatives may selectively and irreversibly inhibit the absorption of glucose by helminths and produce degenerative changes in the intestinal tract of nematodes and in the absorptive cells of cystodes. Thus benzimidazole-based drugs exhibit a wide range of different biological activities, as a result of changing the groups on the core structure, as shown below (Figure III.5).

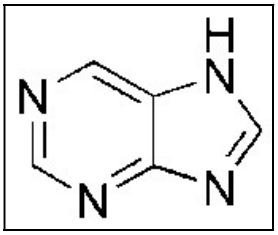


Figure III. 4. Purine ring

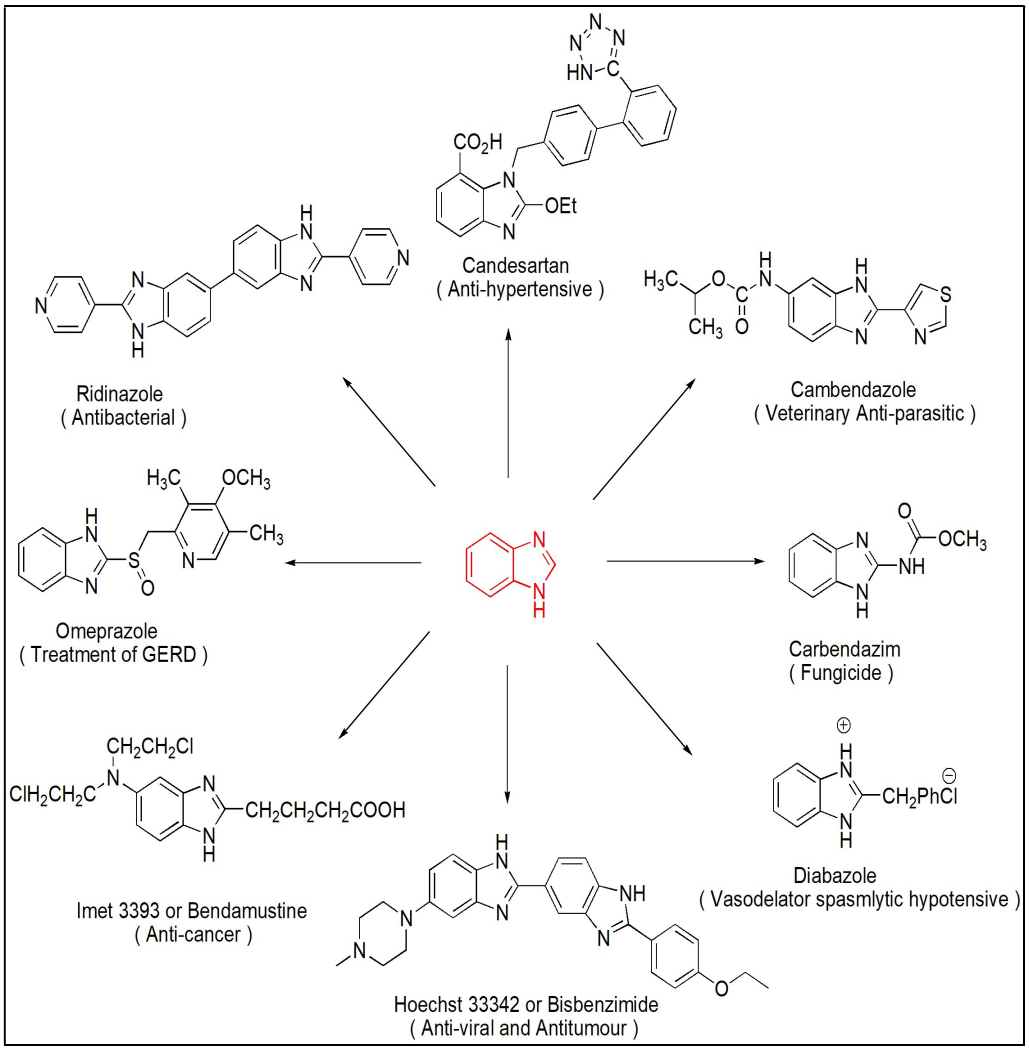
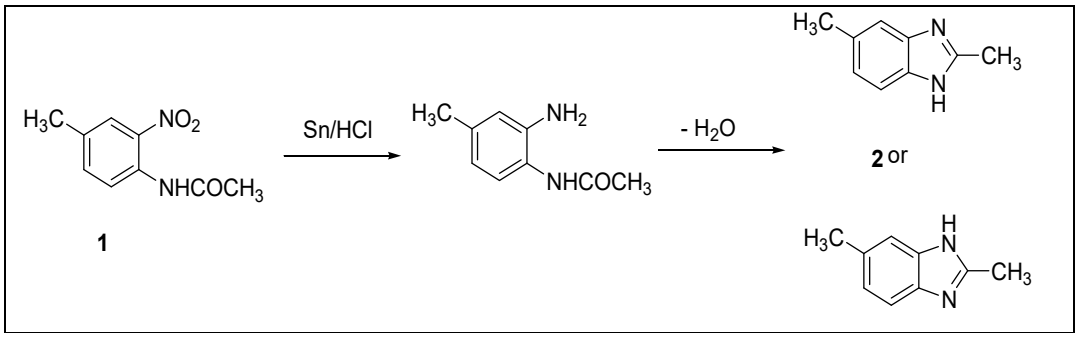


Figure III.5. Varity of drugs containing benzimidazole ring.

III.4. Memoir of foremost synthesis of Benzoimidazole derivatives

In 1872, first benzimidazole was prepared by Hoebrecker [17], who obtained 2, 5-dimethylbenzimidazole (2) by the reduction and dehydration of 2-nitro-4-methylacetanilide (1) (Scheme III.1).

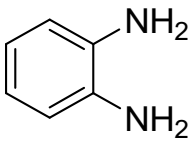


Scheme III.1. Hoebrecker method for synthesis of benzimidazole derivatives.

III.5. Synthesis of Benzoimidazole derivatives

Literature unveiled that, there has been a lot of work done in last few years to synthesize benzimidazoles ring. This indicated clearly the worth of benzimidazoles ring for a Chemist, a Researcher or an Industrialist. To amplify the scope of synthesis of benzimidazole ring, researchers were used various paths. Here a number of different synthetic methods for benzimidazoles have been grouped according to the starting material.

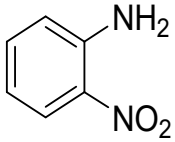
A. From-



+

- Aliphatic / Aromatic carboxylic acid
- Acid chloride
- Aldehydes
- Ketones
- Nitrile
- Ester
- Acid anhydrides
- Urea
- Lactone

B. From-



+

- Aryl aldehydes
- Carboxylic acid
- Alcohol
- Activated methyl group

C. Through C-H functionalization-

D. Through C-X functionalization-

E. Miscellaneous work

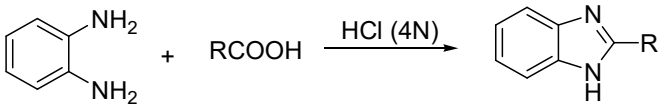
F. Green Protocols

III.5.A.i. By the reaction with Aliphatic / Aromatic carboxylic acid

The prevalent laboratory method for preparation benzimidazoles is Phillip's method [18], involves the condensation of o-diaminobenzenes with carboxylic acids or its derivatives (Scheme III.2), including heating the reagents together in the presence of concentrated hydrochloric acid. E. Wundt et al [19] and Von Niemantowski et al [20] also walked in a similar path.

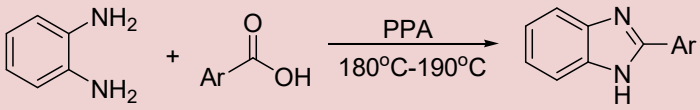
In the presence of catalyst polyphosphate ester (PPA) at 180-190ºC, Maleki *et al*., condensed *o*-phenylenediamine with aromatic carboxylic acid and got 77% yield of 2-arybenzimidazole (Scheme III.3)[21]. Room temperature is also sufficient to synthesize 2-substituted benzimidazole derivatives and gives about 83% yield, which was proven by Venkateswarlu *et al*., from the reaction of o-phenylenediamine and substituted benzoic acid in the presence of lanthanum chloride in acetonitrile (Scheme III.4). [22]

Scheme III.2



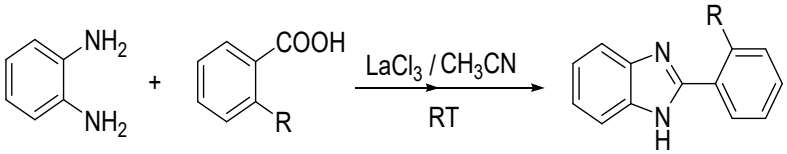
Phillip's method.

Scheme III.3



Synthesis of 2-arybenzimidazole using polyphosphate ester (PPA) as a catalyst.

Scheme III.4



Synthesis of 2-substituted benzimidazole derivatives in the presence of lanthanum chloride and acetonitrile.

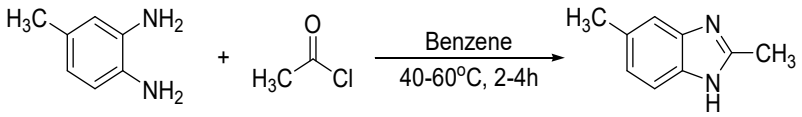
III.5.A.ii. By the reaction with acid chloride

Most reactions between o-phenylenediamines and acid chlorides to give benzimidazoles have been carried out with aroyl chlorides. Since benzimidazoles have no grouping in the l-position may undergo acylation with acid chlorides leads to benzimidazoles or monoacylated or diacylated o-phenylenediamines, depending upon experimental conditions.

Acetyl chloride with 5-methyl-1, 2- diaminophenyl in benzene medium have been condensed by Benguer *et al*. at 40 to 60 ºC for 2 to 3 h it gives 2,6-dimethyl benzimidazole with 71% yield (Scheme III.5) [23].

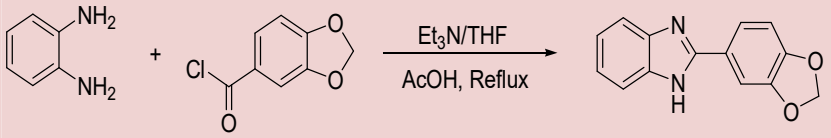
A novel antitumor agent, 2-phenyl-(3, 4-methylenedioxy)benzimidazol Kadri *et al.* had synthesized from *o*-phenylenediamine and 1,3-benzodioxole-5-carbonyl chloride, by stirring at 0°C in triethylamine and THF for 1 h. The residue got from the reaction was refluxed with acetic acid for 12 h to obtain the desired product in 46-59% yield (Scheme III.6) [24].

Scheme III.5



Synthesis of 2,6-dimethyl benzimidazole from acetyl chloride with 5-methyl-1, 2- diaminophenyl in benzene medium.

Scheme III.6



Synthesis of 2-phenyl-(3, 4-methylenedioxy)benzimidazol from *o*-phenylenediamine and 1,3-benzodioxole-5-carbonyl chloride in Et_3N/THF.

III.5.A.iii. By the reaction with aldehydes

The condensation of phenylenediamines with aldehydes is achieved by various reported conditions. Since an oxidation is involved, the reaction is best carried out under oxidative conditions. This oxidation may be brought about by the air or, more

conveniently, by the use of other oxidizing agents. Smith, Rao and Ratnam *et al*., reported synthesis of 2-aryl benzimidazole from o-phenylenediamine and aryl aldehydes, in the presence of the oxidising agents like- cupric acetate, mercuric oxide, chlorine, lead tetraacetate, manganese dioxide, Nickel peroxide at room temperature. This eco-friendly method gives about 85% yield. (Scheme III.7)[25].

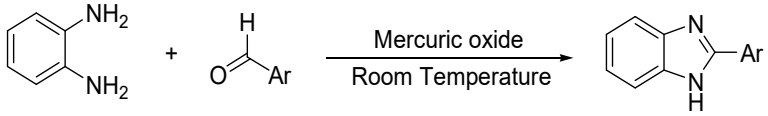
In the presence of silica phenyl sulfonic acid as a solid, heterogeneous catalyst Veisi *et al*., synthesized 2-aryl-benzimidazole by reacting *o*-phenylenediamine and aromatic aldehyde in water, gives 67% yield of 2-aryl –benzimidazole.(Scheme III.8**)** [26].

Varala *et al*., used L-proline to synthesized 2-aryl-5-alkyl-benzimidazoles by the condensation of o-phenylenediamine with aromatic aldehydes in chloroform medium to get a yield of 72-95% at ambient temperature (Scheme III.9**)** [27].

With the help of heterogeneous catalyst Amberlite IR-120 (strongly acidic cation exchange resin), Sharma *et al.,* synthesized 2, 5-substituted-benzimidazoles by the reacting 4-substituted-o-phenylenediamine with the substituted aldehydes, the media is ethanol and water solution (2:1). This method gives a 72% yield. The catalyst is recyclable without loss of activity (Scheme III.10**)** [28].

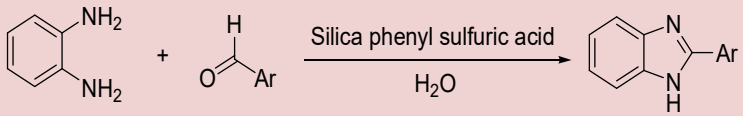
With a good yield of 81%, Ravi *et al.,* selectively synthesized 1,2,4,5-tetrasubstituted benzimidazoles by using 4,5- substituted o-phenylenediamine and substituted aldehydes at room temperature in presence of Zn-proline, a water-soluble and recyclable Lewis acid catalyst (Scheme III.11**)** [29].

Scheme III.7



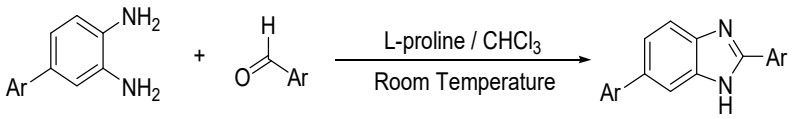
Synthesis of 2-aryl benzimidazole using oxidising agents.

Scheme III.8



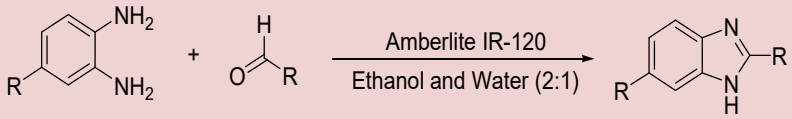
Using silica phenyl sulfonic acid synthesis of 2-aryl - benzimidazole in water medium.

Scheme III.9



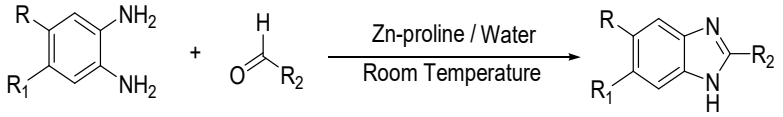
L-proline mediated synthesis of 2-aryl-5-alkyl-benzimidazoles.

Scheme III.10



Synthesis of 2, 5-substituted-benzimidazoles using amberlite IR-120 in ethanol and water solution (2:1).

Scheme III.11

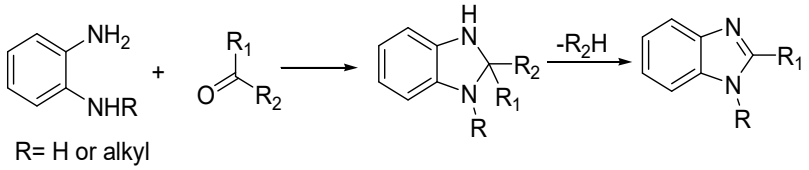


Selective synthesis of 1, 2, 4, 5-tetrasubstituted benzimidazoles at room temperature by using Zn-proline.

III.5.A.iv. By the reaction with ketones

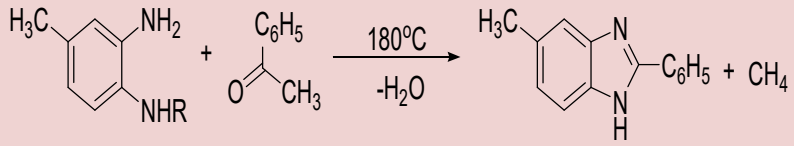
Elderfield and Kreysa, investigated the reaction of o-phenylenediamines with a number of ketones.(Scheme III.12). *o*-Phenylenediamine reacts with ketones to form 2- disubstituted benzimidazolines, these decompose under the influence of heat with the formation of a 2-substituted benzimidazole and a hydrocarbon. The decomposition of unsymmetrically substituted benzimidazoline may lead to formation of two different benzimidazoles depending upon whether the substituent R_1 or the substituent R_2 is eliminated preferentially. By heating 3, 4-diaminotoluene with acetophenone at 180^{o}C for some time Ladenburg and Rugheimer have obtained 2-phenyl-5 (or 6)-methylbenzimidazole. Here the methyl group eliminated preferentially (Scheme III.13).

Scheme III.12



Synthesis of di-substituted benzimidazole from ketone.

Scheme III.13

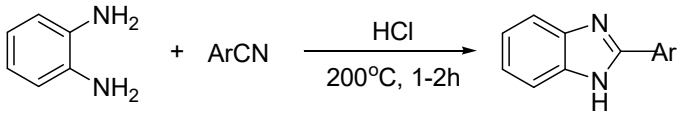


Synthesis of 2-phenyl-5-methylbenzimidazole by 3,4-diaminotoluene with acetophenone.

III.5.A.v. By the reaction with nitrile

Hollies and Wagner obtained 2-substituted benzimidazole by the reaction of o-phenylenediamine with the substituted nitrile at 200 ºC for 1 to 2 h and gives 77% yield (Scheme III.14) [30].

Scheme III.14

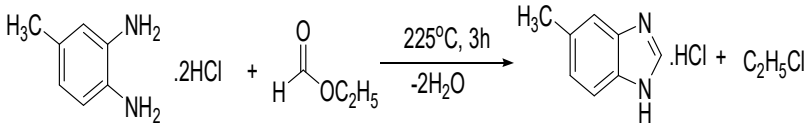


Synthesis of 2-substituted benzimidazole by *o*-phenylenediamine with substituted nitrile.

III.5.A.vi. By the reaction with ester

Reaction of o-phenylenediamines with esters also gives benzimidazoles. Von Niementowski first investigated the reaction of esters and o-phenylenediamines to give benzimidazoles. Equimolecular amounts of 3,4-diaminotoluene dihydrochloride and ethyl formate when heated in a sealed tube for 3 h at 225 °C give 84% of 5(or 6)-methylbenzimidazole hydrochloride [31] (Scheme III.15). The product is not further alkylated by the ethyl chloride formed. Ethyl acetate under the same conditions gives only a poor yield of 2, 5(or 2,6)-dimethylbenzimidazole, and poor yields of benzimidazoles would probably be obtained from esters of acids of higher molecular weight.

Scheme III.15

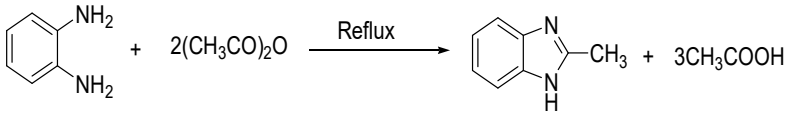


Synthesis of 5(or 6)-methylbenzimidazole by 3,4-diaminotoluene dihydrochloride and ethyl formate.

III.5.A.vii. By the reaction with acid anhydrides

Literature survey has revealed that depending on the conditions acid anhydrides and *o*-phenylenediamines will lead to benzimidazoles or to N, N-diacylphenylenediamines. It was formerly thought that o-phenylenediamine yields benzimidazoles with acids and diacyl derivatives with acid anhydrides; however, this was shown to be incorrect. Time appears to be a decisive factor and if the refluxing is continued long enough benzimidazoles may be obtained, usually in good yields. *o*-Phenylenediamines when reflux for several hours with acetic anhydride is completely converted to 2-methylbenzimidazole [31] (Scheme III.16).

Scheme III.16

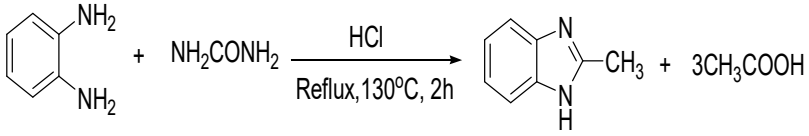


Synthesis of 2-methylbenzimidazole from o-Phenylenediamines and acetic anhydride.

III.5.A.viii. By the reaction with urea

By refuxing o-phenylenediamine and urea in amyl alcohol solution until the evolution of ammonia ceased, Mistry and Guha have obtained a 95% yield of 2(3H)-benzimidazolone. [31] On refluxing o-phenylenediamine with urea in the presence of hydrochloric acid at 130 ºC for 2 h gives a 78% yield of benzimidazole (Scheme III.17) [32] .

Scheme III.17

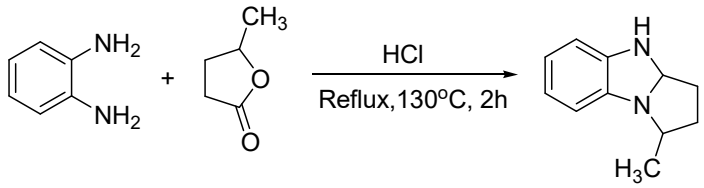


Synthesis of benzimidazole by o-phenylenediamine and urea.

III.5.A.ix. By the reaction with lactone

On refluxing Valerolactone (5-methyldihydrofuran-2(3H)-one) with o-phenyllenediamine at 130 ºC for 1 to 2 h in the presence hydrochloric acid gives 76% yield of 1,2-(1- methyltrimethylene) benzimidazole (Scheme III.18) [33] .

Scheme III.18



Synthesis of 1, 2-(1- methyltrimethylene) benzimidazole by *o*-phenyllenediamine and Valerolactone.

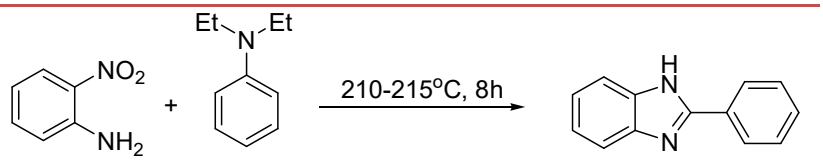
III.5.B.i. By the reaction with aldehydes

2-Nitroanilines were also used for one pot synthesis of 2- arylbenzimidazoles under different reaction conditions. Nishioka et al. have obtained of 2-phenylbenzimidazole (3) from 2-nitro aniline (23) and N, N-diethylaniline (24) by heating them at 210-215°C for 8h (Scheme III.19) [34]. one-pot reduction triggered heterocyclization of 2- nitroanilines (23) or 1,2-dinitroarenes to 2-phenylbenzimidazoles (3) in excellent yield when refluxed in presence of indium/AcOH in ethyl acetate, (Scheme III.20) [35].

The reductive cyclization of o-nitroarylamine with aldehyde using sodium dithionite ($Na_2S_2O_4$) have been reported by Oda et al. The reaction was accelerated by addition of H_2O for the one-Pot Synthesis of N-1- and C-2-substituted benzimidazole [36].

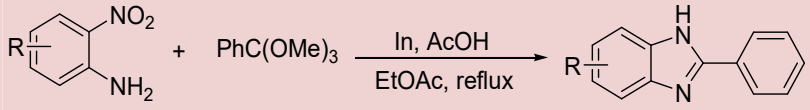
M. P. Surpur et al., reported one-pot synthesis of benzimidazoles from o-nitroanilines under microwaves via a reductive cyclization by using $Na_2S_2O_4$ in water-DMF medium and it took only 2 minutes to produce 65-92% product. (Scheme III.21) [37].

Scheme III.19



Synthesis of 2-phenylbenzimidazole from 2-nitro aniline and N,N-diethylaniline

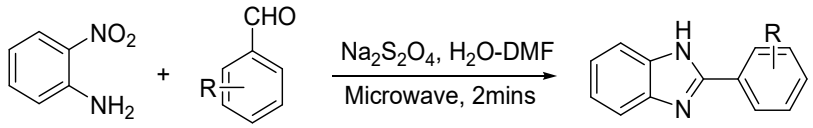
Scheme III.20



R= Me, OMe, Br, I

Heterocyclization of 2- nitroanilines or 1, 2-dinitroarenes to 2-phenylbenzimidazoles.

Scheme III.21

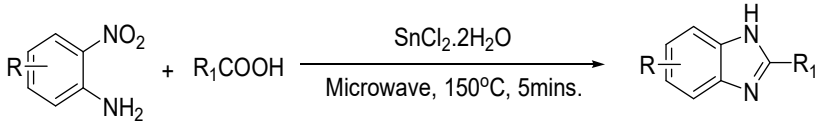


Synthesis of benzimidazoles from o-nitroanilines under microwaves.

III.5.B.ii. By the reaction with carboxylic acids

David S. VanVliet et al. have reported that by using stannous chloride and microwave irradiation of 2-nitroaniline with various carboxylice acids gives 2-substituted benzimidazoles. (scheme III.22) [38].

Scheme III.22

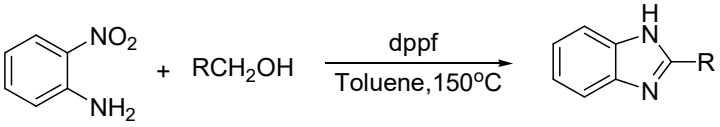


Synthesis of 2-substituted benzimidazoles by using stannous chloride and microwave irradiation.

III.5.B.iii. By the reaction with alcohols

Iron-catalyzed heterocyclizations from 2- nitroanilines and benzylic alcohols in the presence of dppf [1, 10- bis(diphenylphosphino)-ferrocene] at 150 °C to form benzimidazoles using hydrogen transfer reaction have been reported by Haihong Huang et al. [39]. (Scheme III.23).

Scheme III.23

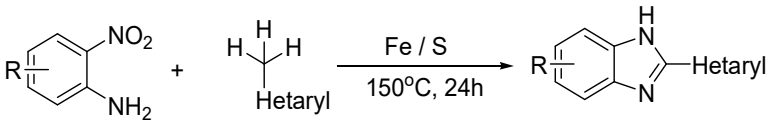


Benzimidazole synthesis 2- nitroanilines and benzylic alcohols in the presence of dppf.

III. 5. B. iv. By the reaction with active methyl group:

Direct coupling of 2-nitroaniline and the methyl group bearing a 2, 4-picolyl or 2-benzimidazolyl substituent providing 2-hetarylbenzimidazoles. The reaction employs a catalytic amount of iron sulfide generated in situ from the elements under solvent-free conditions (scheme III.24) [40].

Scheme III.24

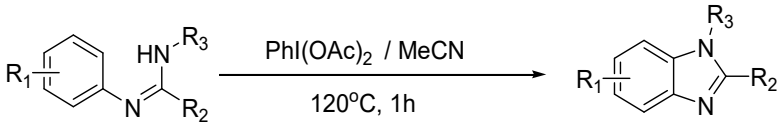


Synthesis of 2-hetarylbenzimidazoles from 2-nitroaniline and the methyl group.

III.5.C. Through C-H functionalisation:

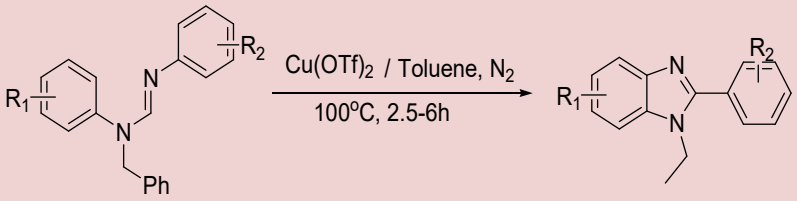
From literature I came to know that there are few routes to derivatives of benzimidazoles from C-H bond functionalization. Ya-Qiu Long et al. [41]. presented the TEMPO promoted synthesis of multisubstituted benzimidazoles via metal-free oxidative C-N coupling between the sp3 C-H and free N−H of readily available N-benzyl/alkyl-1, 2- phenylenediamines. The same group have also reported that iodine (III) promoted metal free selective oxidative annulations of aryl amidines for the synthesis of multisubstituted benzimidazoles through C(sp2)−N bond formation in polar solvent (Scheme III.25) [42]. Tharmalingam Punniyamurthy et al. shown the copper (II)-mediated synthesis of 2-aryl-N-benzylbenzimidazoles from N-benzyl bisarylhydrazones via C-H functionalization (Scheme III.26) [43].

Scheme III.25



Multisubstituted benzimidazoles synthesis through C(sp2)−N bond formation.

Scheme III.26

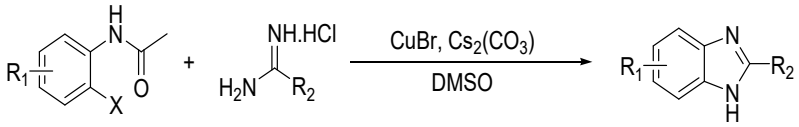


Copper (II)-mediated synthesis of 2-aryl-N-benzylbenzimidazoles from N-benzyl bisarylhydrazones via C-H functionalization.

III.5.D. Through C-X functionalisation

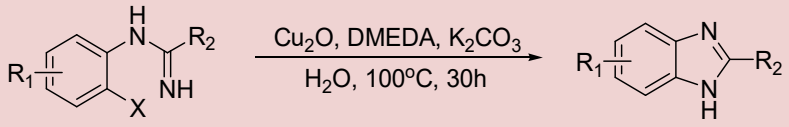
A well known transition metal catalyzed C-X functionalization for the organic transformations are in CuBr catalyzed synthesis of 2-substituted benzimidazoles from *o*-haloacetanilide derivatives and amidine hydrochloride under ligand free conditions (Scheme III.27),[44]. CuI/L-Proline catalyzed synthesis of substituted benzimidazoles by coupling of aqueous ammonia with 2-iodoacetanilides, [45] CuI catalyzed synthesis of N-substituted benzimidazoles [46]. Cu_2O in combination with a simple diamine derivative (DMEDA) catalyzed synthesis organic chemistry. There are few numbers of literature report where the transition metals play excellent catalytic role for the synthesis of substituted benzimidazoles by C-X bond activation such as, palladium catalyzed synthesis of benzimidazoles using aryl amination chemistry, [47] of substituted benzimidazoles by intramolecular N-arylation in water (Scheme III.28), [48] palladium catalyzed synthesis of substituted benzimidazoles from N-(o-halophenyl)-imidoyl chlorides and the corresponding imidates using variety of N-nucleophiles. [49] Recently, Carsten Bolm et al. have reported KOH/DMSO mediated transition metal free synthesis of benzimidazoles by intramolecular N-arylation of amidine, [50] copper or palladium catalyzed the formation of 2-aminobenzimidazoles through intramolecular C-N bond formation between an aryl halide and a guanidine moiety[51].

Scheme III.27



CuBr catalyzed synthesis of 2-substituted benzimidazoles.

Scheme III.28



X= Cl, Br, I

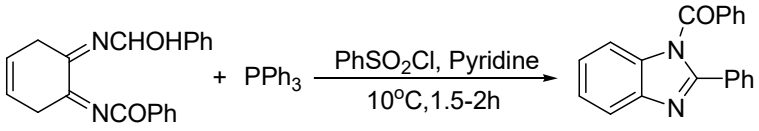
Synthesis of benzimidazoles by intramolecular N-arylation.

III. 5. E Miscellaneous work:

Some miscellaneous works are also presented here:

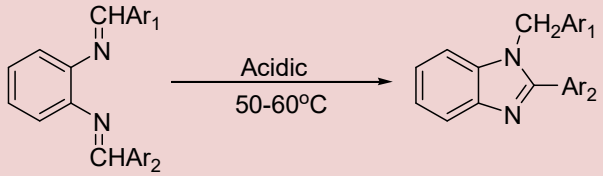
Scheme III.29

R. S. Kumar *et al.*[52]



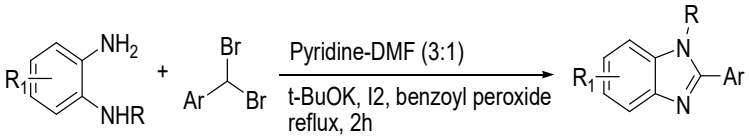
Scheme III.30

Dianils *et al.*[53]



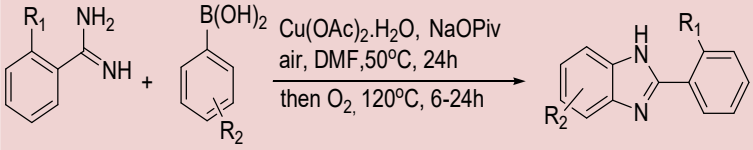
Scheme III.31

Kanchugarakoppal S. Rangappa *et al.*[54]



Scheme III.32

Jieping Zhu *et al.*[55]

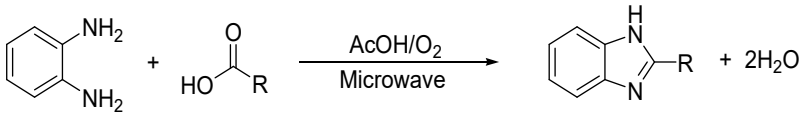


III. 5. F. Green Approaches

E-factor or environmental factor was also present in researcher's mind during their work. As for example, in 2010 Davood Azarifar *et al*., got 2-substituted-benzimidazole with 77% yield by the reaction of o- phenylenediamine with a carboxylic acid using microwaves. This method is promoted to green chemistry and avoided using of hazardous solvents (Scheme III.33) [56]. Kabeer A. Shaikh et al., 2012 have been efficiently synthesized Benzimidazoles in high yields by treatment of 1, 2- diamine with aldehydes using the metal coordinate complex K4[Fe(CN)6] as a catalysis. The method was carried out under solvent free condition via oxidation of carbon-nitrogen bond which is green, mild and inexpensive process (Scheme III.34) [57]. M. Rekha et al., studied catalytic activity of alumina, zirconia, manganese oxide/alumina, and manganese oxide/zirconia in the condensation reaction between *o*-phenylenediamine and an aldehyde or a ketone to synthesise 2-substituted benzimidazoles and 1, 5-disubstituted benzodiazepines respectively and found to be simple and economical (Scheme III.35) [58]. In the presence of polyethyleneglycol-400

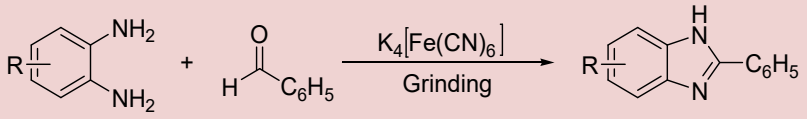
(PEG-400) Mita D. Khunt *et al*., refluxed o-phenylenediamine with substituted aldehydes for 1.5 to 2 h gives 76% yield of 2-substituted-benzimidazole. PEG is a green and eco-friendly solvent (Scheme III.36) [59].

Scheme III.33



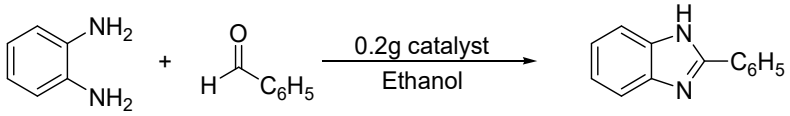
Synthesis of 2-substituted-benzimidazole from *o*-phenylenediamine with a carboxylic acid using microwaves.

Scheme III.34



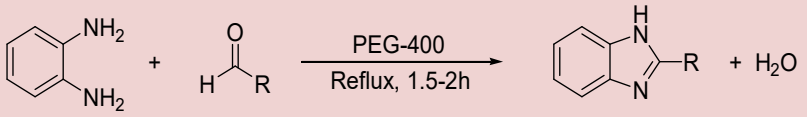
Synthesis of benzimidazoles by 1, 2- diamine with aldehydes using the metal coordinate complex as a catalyst.

Scheme III.35



M. Rekha et al. synthesis of 2-substituted benzimidazoles from *o*-phenylenediamine and an aldehyde or a ketone.

Scheme III.36



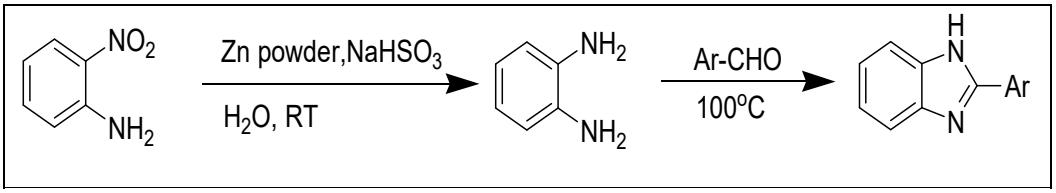
Synthesis of 2-substituted-benzimidazole using PEG-400.

From the above discussion it is clear that one of the most important precursors of medicinal and biological ring is benzimidazole, which can be synthesized in various ways. Different researchers from different countries tried a lot to search the best path to synthesize it. Till now many are working on it. I am also searching a route to avoid hazardous, expensive chemicals, time consuming method and organic solvent to provide a scheme to synthesize the privileged ring.

III. 6. Present Work

We report a simple and mild one-pot method for the synthesis of 2-substituted benzimidazoles (Scheme III.37) from 2-nitroanilines and aromatic aldehyde via reductive cyclocondensation process with the help of suitable metal, Zn and metal salt

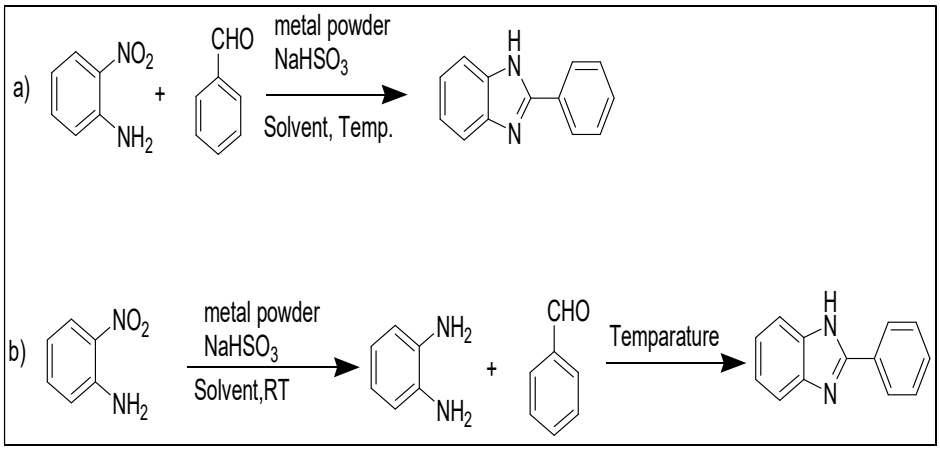
$NaHSO_3$ at 100°C in water. $NaHSO_3$ is a non-hazardous, easily available, inexpensive weakly acidic species having pKa value 6.97 which helps to trigger the reaction in the presence of Zn. Adduct formation ability of it with the aldehydes, may help cyclocondensation in the present protocol. Key features of this draft are very good to excellent yields in reasonably short reaction times, high atom economy, and use of readily available starting material, operational simplicity and easy workup process.



Scheme III.37. General scheme for the synthesis of benzimidazole derivatives.

III.6.A. Results and discussion

For screening the reaction, 2-nitroaniline and benzaldehyde was selected as model substrates for intended transfiguration. Initially we performed the reaction of *o*-nitroaniline with benzaldehyde in water at room temperature for 1h on a magnetic stirrer in presence of the combination of Fe powder and sodium bisulphite. The reaction yielded only the diamine (*o*-phenylenediamine). The yield of diamine decreases with a rise in temperature and benzimidazole was undetected (Table III.1, scheme III.38a). The scheme was also tried (Scheme III.38a) without using $NaHSO_3$ (Table III.1, entry 4), but it failed to produce the diamine even at a trace amount. Thus, it is obvious that, as a hydrogen ion's source $NaHSO_3$ plays a vital role to reduce nitro to amine.



Scheme III.38. Two different plans for the synthesis of benzimidazole derivatives.

Table III.1. [a]Reaction (Scheme-2a) condition optimization.

Entry	Time (h)	Temperature (^oC)	Additive (3 mmol)	Yield of diamine	Yield of Benzimidazole
1	1	RT	$NaHSO_3$	70	Nil
2	1	60	$NaHSO_3$	44	Nil
3	1	80	$NaHSO_3$	25	Nil
4	1	RT	-	Nil	Nil

[a]Reaction of *o*-nitrobenzaldehyde (1 mmol), Fe (3mmol), in water on magnetic stirrer.

With this experimental data we followed our scheme III.38b. In this process *o*-nitroaniline was reduced to 1, 2-diamine with Zn and $NaHSO_3$ in presence of water at room temperature and the process was completed within 5 minutes. It was followed by the addition of benzaldehyde with continuous stirring at 100 ^oC. As a solvent, water was first screened (Scheme III.38b, Table III.2, entry 4), and very surprisingly no product was isolated in its absence (Table III.2, entry 5). Further, being the most easily available and most significantly its green nature has really enriched the objective of the present investigation.

The presence of metal is the necessary requirement for the initial reduction of the nitro compound (Table III.2, entry 8) and in comparison to Fe and Cu, Zn is estimable in terms of yield of the product and the time of completion of reaction (Table III.2, entries 4, 6, 7). We also tried the scheme at different temperature; finally at 100 ^oC temperature the desired product, benzimidazole was isolated as a single compound (Table III.2, entry 7). Further we optimized the amount of Zn and $NaHSO_3$ required (Table III.3). Further investigation towards the optimization of the process revealed that a 3 mmol Zn and 6 mmol $NaHSO_3$, (Table III.3) under atmospheric pressure at 100^oC yielded the best result to produce the desired benzimidazole in 1h (compared with Table III.2, entries 7, 14, 15)

Table III. 2. [a]Reaction (**Scheme III. 38b**) conditions optimization.

Entry	Metal	Solvent	Time(min.)	Temperature(^{o}C)	Yield (%)[b]
1	Fe	DMF	60	100	68
2	Fe	DMSO	60	100	60
3	Fe	Toluene	60	100	56
4	Fe	H_2O	60	100	80
5	Fe	-	60	100	Nil
6	Cu	H_2O	60	100	75
7	Zn	H_2O	60	100	94
8	-	H_2O	60	100	Nil
9	Zn	H_2O	60	RT	Nil
10	Zn	H_2O	60	80	50
11	Zn	H_2O	60	60	Nil
12	Zn	H_2O	60	40	Nil
13	Zn	H_2O	90	100	95
14	Zn	H_2O	45	100	87
15	Zn	H_2O	120	100	94

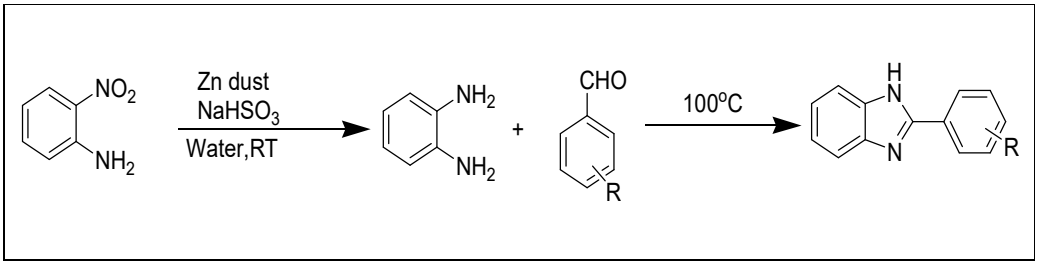
[a]Reaction of o-nitrobenzaldehyde (1 mmol), Zn (3mmol), $NaHSO_3$ (6 mmol) in water on magnetic stirrer. [b]Isolated yield of benzimidazole.

Table III. 3. [a]Optimization of amount of Zn and $NaHSO_3$.

Entry	Zn (mmol)	$NaHSO_3$ (mmol)	Time (min)	Yield (%)[b]
1	3	3	60	54
2	3	4	60	62
3	3	5	60	82
4	3	6	60	94
5	3	7	60	94
6	2	6	60	75

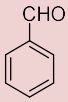
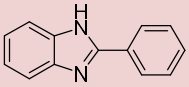
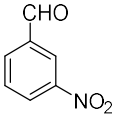
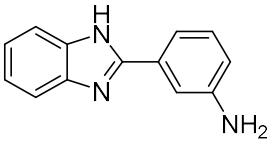
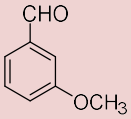
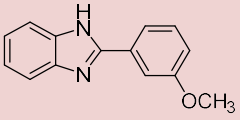
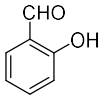
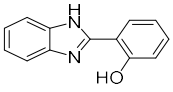
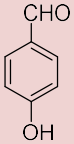
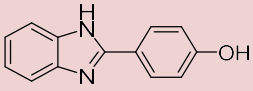
[a]Reaction of *o*-nitrobenzaldehyde (1mmol), Zn (2-3 mmol), $NaHSO_3$ (4-7 mmol) in water on magnetic stirrer at 100^{o}C. [b]Isolated yield.

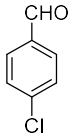
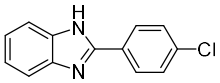
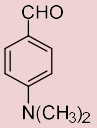
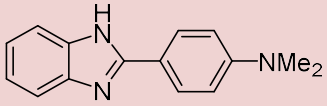
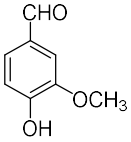
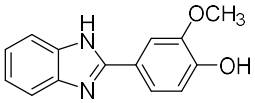
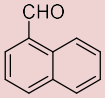
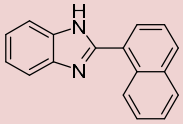
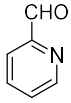
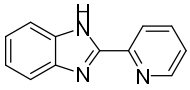
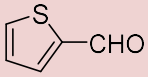
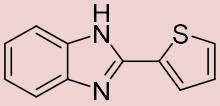
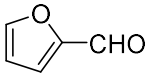
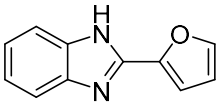
Now the optimized procedure is followed for all of the reactions listed in Table III.4. Staggering part of our reaction is chemoselective reduction of nitro to amine. We really enthralled and exhilarated on observing Table III.4 entry 3, 4, 5, 6, 7, 8 that reducible groups remain intact after completion of the reaction. The reaction took place smoothly to produce corresponding benzimidazole in moderate to high yields (Table III.4).



Scheme III.39. Synthesis of benzimidazole derivatives with different aromatic aldehydes at optimum condition.

Table III.4. [a]Zn and $NaHSO_3$ mediated reduction to amines.

Entry	Reactant	Product	Time (min)	Yield (%)[b]
1			50	93
2			70	83
3			80	90
4			50	85
5			45	89

6			90	87
7			60	90
8			70	94
9			45	93
10			80	90
11			50	87
12			60	89

[a]Reaction of nitro compound (1mmol), Zn (3 mmol), $NaHSO_3$ (6 mmol) in water at 100 ^oC for different time intervals on magnetic stirrer. [b]Isolated yields.

III.6.B. Probable Mechanism

From the above observation we can propose a possible mechanism and tentative intermediates for the above developed protocol is shown below.

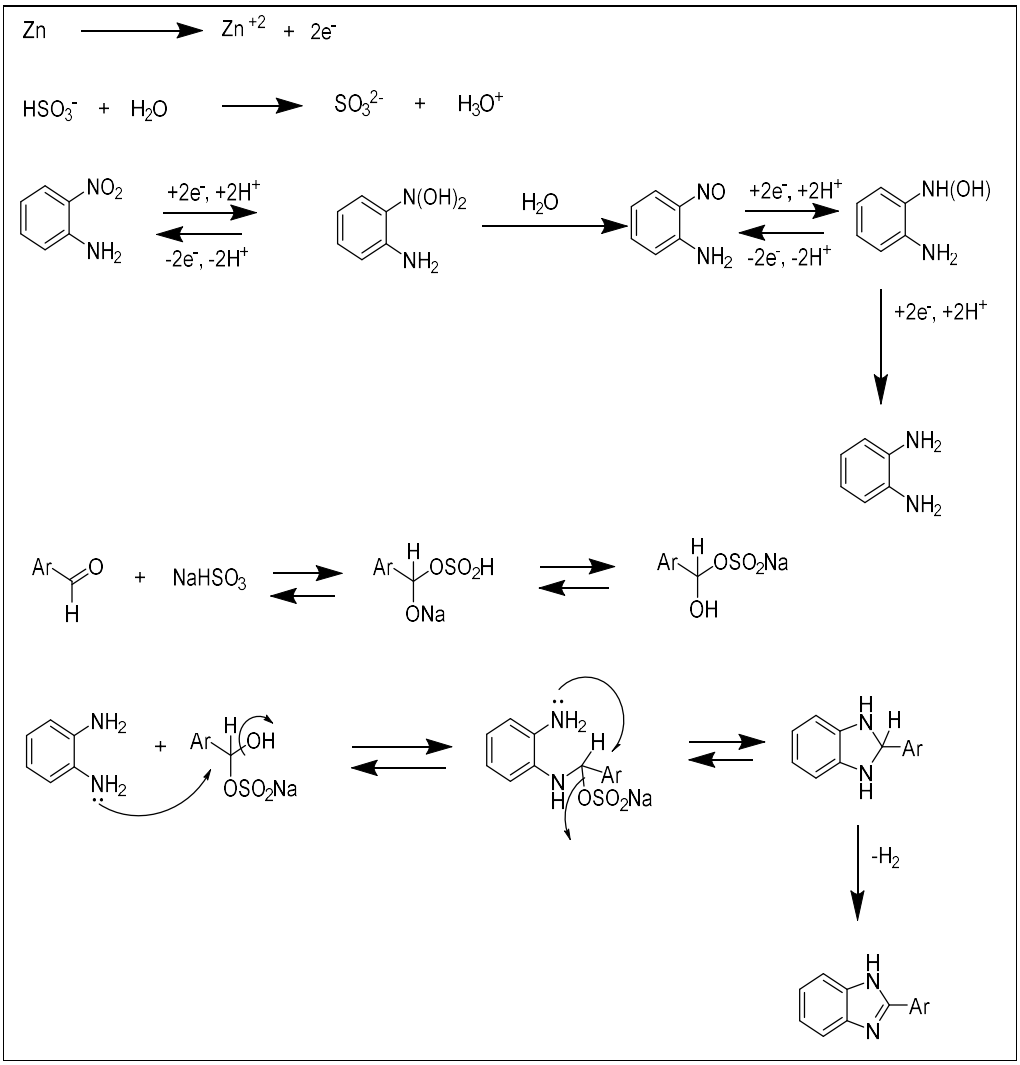


Figure III.6. Proposed mechanism for the synthesis of benzimidazole derivatives.

III.6.C. Conclusion

We have developed a novel and efficient protocol through one pot reductive cyclocondensation of 2-nitroaniline with aromatic aldehydes to benzimidazole with $Zn/NaHSO_3$ in water. The fascinating part of our method in comparison to the conventional methods is its simplicity, cost effectiveness, environmentally benign approach and a less time consuming process. We also earn that $Zn/NaHSO_3$ in water is also a better chemoselective reducing system to reduce nitro to amine. Thus, it

could potentially be complementary to the existing methods for the synthesis of biologically active benzimidazoles moiety.

III.6.D. Experimental

III.6.D.i. Chemicals

All the chemicals and solvents used in the study were purchased from commercial sources of Sigma Aldrich and SD Fine chemical company and were used without further purification unless stated. The organic solvents used were of analytical or spectroscopic grade. Before using, the solvents were dried and freshly distilled using the standard procedures whenever anhydrous solvents were required.

III.6.D.ii. General Information

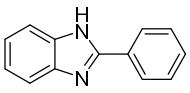
^{1}H NMR and ^{13}C NMR were recorded using 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

III.6.D.iii. General procedure for the synthesis of Benzimidazole derivatives from o-nitrianiline and benzaldehyde derivatives

In a round bottom flask 2-nitro aniline (1 mmol), Zn powder (3 mmol), $NaHSO_3$ (6 mmol) in 20 mL water at room temperature was stirred on a magnetic stirrer. After 10 minutes aromatic aldehyde added into it and at 100 ^{o}C temperature the mixture was stirred on a magnetic stirrer for 30 minutes. One cotton ball was present on the mouth of the round bottom flask during the process of reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the metallic part was filtered off. The filtrate was poured into 100 mL ice cold water and extracted with ethyl acetate, washed several times with water. After that we evaporate the solvent, subsequently column chromatography was done over basic alumina using petroleum ether/ethyl acetate (3:1) as eluent to afford the pure benzimidazole derivatives. The spectroscopic data (^{1}H NMR, ^{13}C NMR) of this compound are in good agreement with those reported.

III.6.D.iv. Spectroscopy data of synthesized benzimidazole derivatives

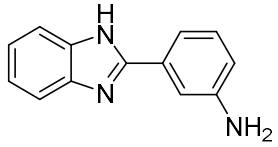
2-phenyl-1H-benzimidazole[1]



Pale yellow solid ($C_{13}H_{10}N_2$): Melting point: 292-295 ^{o}C. IR, KBr (cm^{-1}): 694, 1252, 1560, 3058; ^{1}H NMR (300 MHz), dmso-d^{6}, (ppm): δ, 7.19-7.22 (m, 2H), 7.46-7.61

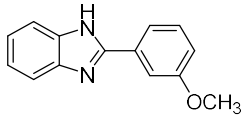
(m, 5H), 8.18-8.21 (m, 2H), 12.89 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 122.7, 126.9, 129.4, 130.3, 130.6, 151.63.

2-(3-amino phenyl)-1H-benzimidazole



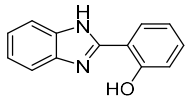
Light brown ($C_{13}H_{11}N_3$): Melting point: >290 ^{o}C. IR, KBr (cm^{-1}): 810, 1518.8, 1655.8, 3090.7, 3370.4; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 4.02-4.07 (s,2H), 7.22-7.29 (m, 2H), 7.57(d, 1H, J=7.5Hz), 7.71 (d, 1H, J=7.5Hz), 7.80-7.86 (m, 1H), 8.29-8.32 (m, 1H), 8.60 (d, 1H, J=7.8Hz), 8.99-9.01 (m, 1H) 13.27 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 112.1, 119.7, 121.2, 122.6, 123.7, 124.6, 131.1, 132.1, 132.9, 135.5, 144.0, 148.8, 149.5.

2-(3-Methoxy phenyl)-1H-benzimidazole[1]



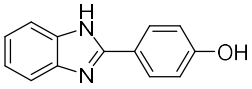
Yellow solid (C $_{14}$H $_{12}$N $_2$O): Melting point: 196-198^{o}C. IR, KBr (cm^{-1}): 830.30, 1655.8, 3067.6; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 3.86 (s, 3H), 7.03-7.07 (m, 1H), 7.18-7.23 (m, 2H), 7.43-7.48 (m, 1H), 7.60 (s, 2H), 7.74-7.77 (m, 2H), 12.9 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 55.7, 111.8, 111.8, 116.3, 119.2, 122.5, 130.5, 131.9, 151.5, 160.1.

2-(2-Hydroxy phenyl)-1H-benzimidazole[1]



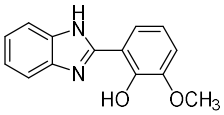
White solid ($C_{13}H_{10}N_2O$): Melting point: 238-240^{o}C. IR, KBr (cm^{-1}): 799, 1590, 3047.3, 3327.9; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 6.99-7.06 (m, 2H), 7.28-7.41(m, 3H), 7.66 (br band, 2H), 8.06 (d, 1H, J=7.8Hz), 13.18 (s, 2H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 111.9, 113.0, 117.6, 118.4, 119.5, 122.9, 123.6, 126.6, 132.2, 152.1, 158.4.

2-(4-Hydroxy phenyl)-1H-benzimidazole[1]



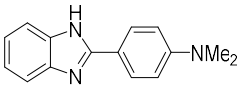
White solid ($C_{13}H_{10}N_2O$): Melting point: 253–255 ^oC. IR, KBr (cm^{-1}): 1565, 3360, 3570; ^1H NMR (300 MHz), dmso-d^6, (ppm): δ, 6.7-6.75 (m, 2H), 6.91-6.97 (m, 2H), 7.33 (s, 2H), 7.79-7.85 (m, 2H), 9.94 (s, 1H, -OH), 12.47 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6: δ, 111.6, 121.5, 122.1, 128.6, 152.2, 159.6.

2-(2-hydroxy-3-methoxy phenyl)-1H-benzimidazole[3]



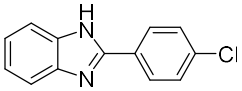
Light yellow ($C_{14}H_{12}N_2O_2$) IR, KBr (cm^{-1}): 743, 1422, 1593, 3067, 3336; ^1H NMR (300 MHz), dmso-d^6, (ppm): δ, 3.82 (s, 3H), 6.92-6.97 (m, 1H), 7.06-7.09 (m, 1H), 7.25-7.31 (m, 2H), 7.61-7.64 (m, 3H), 13.25 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 56.1, 112.9, 114.2, 117.9, 119.2, 123.3, 148.7, 149.0, 152.3.

2-(4-*N, N*-dimethyl phenyl)-1H-benzimidazole[1]



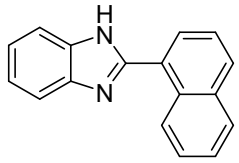
Yellow solid ($C_{15}H_{13}N_3$): Melting point: 277-279 ^oC. IR, KBr (cm^{-1}): 1459, 1518, 1605, 3391; ^1H NMR (300 MHz), dmso-d^6, (ppm): δ, 6.84 (2H, d, Ar, J = 7.8Hz), 7.43 (2H, m, Ar, J = 4Hz), 7.70 (2H, m, Ar, J = 4Hz), 8.21 (2H, d, Ar, J = 7.8 Hz), 15.2 (1H, s, NH); ^{13}C NMR (DMSO, 100 MHz)/δ ppm: 39.5, 107.8, 111.8, 113.2, 125.1, 129.1, 131.5, 149.8, 153.2.

2-(4-hydroxy, 3-methoxy phenyl)-1H-benzimidazole[2]



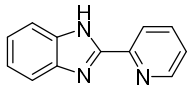
Colorless solid ($C_{13}H_9N_2Cl$): Melting point:290-292^oC IR, KBr (cm^{-1}): 754, 950, 1268, 1410, 1440, 3038; ^1H NMR (500 MHz), dmso-d^6, (ppm): δ, 7.20 (m, 2H), 7.49-7.64 (m, 4H), 8.15 (d, 2H), 12.9 (s, 1H, -NH); ^{13}C NMR (100 MHz), dmso-d^6, (ppm): δ, 111.1, 118.6, 121.9, 126.2, 128.6, 129.5, 130.0, 134.8, 143.5, 151.0.

2- (Napthyl-1yl)-1H-benzimidazole[3]



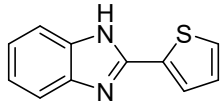
Pale yellow solid ($C_{17}H_{12}N_2$): Melting point: 196-198°C. IR, KBr (cm^{-1}): 774.4, 1560, 3057; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 7.19-7.23 (m, 2H), 7.52-7.66 (m, 4H), 7.61(d, 1H, J= 6.6 Hz), 7.96-8.05 (m, 3H), 9.06 (d, 1H, J=8.1 Hz), 12.89 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 111.8, 119.5, 122.0, 123.1, 125.7, 126.8, 127.5, 127.9, 128.3, 128.8, 130.6, 130.9, 134.0, 134.9, 144.3, 151.8.

2-(Pyridin- 2yl)-1H-benzimidazole[2]



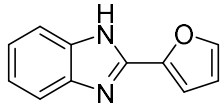
Yellow solid ($C_{12}H_9N_3$): Melting point: 240-242°C. IR, KBr (cm^{-1}): 926, 1275, 1410, 1444, 3041; ^{1}H NMR (500 MHz), dmso-d^6, (ppm): δ, 7.2 (d, 2H), 7.57 (m, 4H), 8.45 (d, 1H), 8.63 (d,1H), 9.3 (s, 2H), 13.0 (s, 1H, -NH); ^{13}C NMR (100 MHz), dmso-d^6, (ppm): δ, 112.3, 122.6, 124.6, 126.6, 134.3, 147.9, 149.3, 151.0.

2-(Thiophene-2yl)-1H-benzimidazole[4]



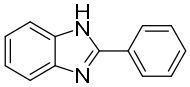
Pale yellow solid ($C_{11}H_8N_2S$): Melting point: >290°C. IR, (KBr) cm^{-1}: 743, 1423, 1571, 3051; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 7.2-7.24 (m, 3H), 7.57(br band, 2H), 7.71 (d, 1H, J=0.9 Hz), 7.73 (d, 1H, J=0.9 Hz), 12.94 (s, 1H, -NH). ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 111.6, 119.0, 122.2, 122.9, 127.1, 128.7, 129.1, 134.1, 147.4.

2-(Furan-2-yl)-1H- benzimidazole[4]



Light yellow solid ($C_{11}H_8N_2O$): Melting point: 267- 270°C, IR, KBr (cm^{-1}): 738, 979, 1417, 1525, 1655, 3058; ^{1}H NMR (300 MHz), dmso-d^6, (ppm): δ, 6.71-6.76 (m, 1H), 7.18-7.22 (m, 3H), 7.54-7.57 (s, 2H), 7.93-7.97 (m, 1H), 12.94 (s, 1H, -NH); ^{13}C NMR (75 MHz), dmso-d^6, (ppm): δ, 110.9, 112.7, 122.7, 144.1, 145, 146.

III. 6. D. v. Scan copy of 1 H NMR and 13C NMR of benzimidazole derivatives



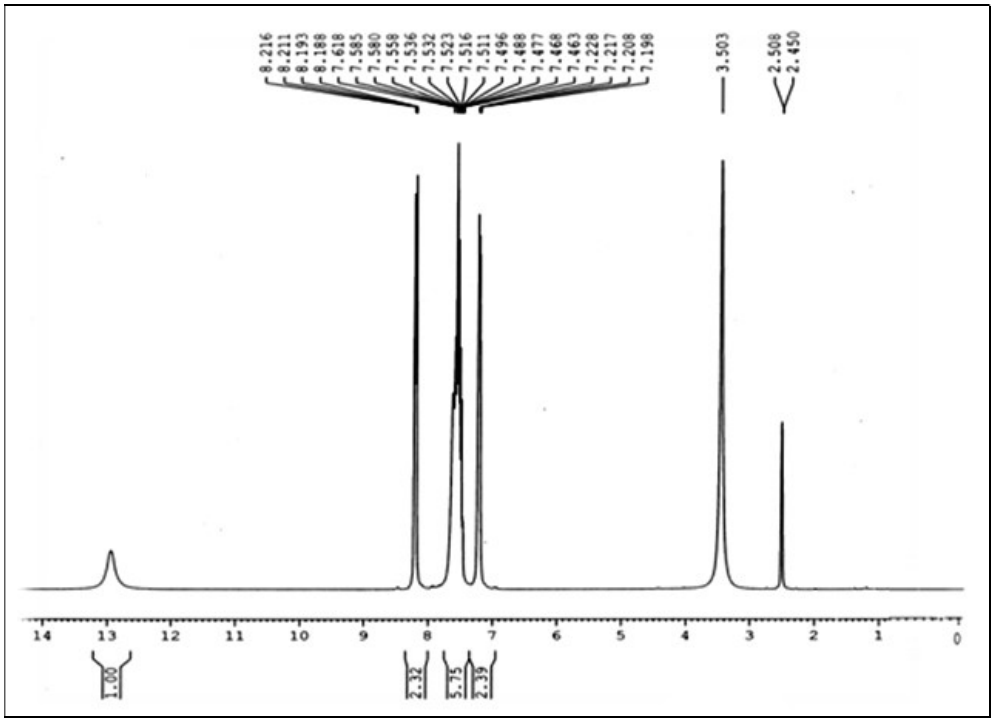


Figure III.7. [1]HNMR of 2-phenyl-1H-benzimidazole

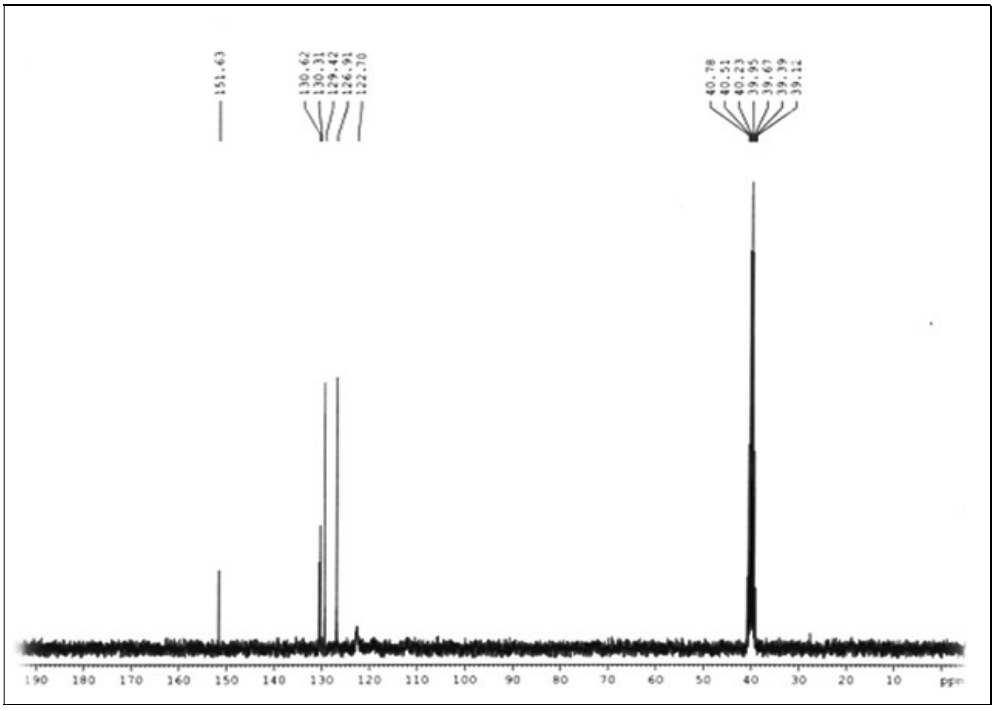
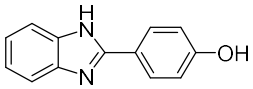


Figure III.8. [13]CNMR of 2-phenyl-1H-benzimidazole



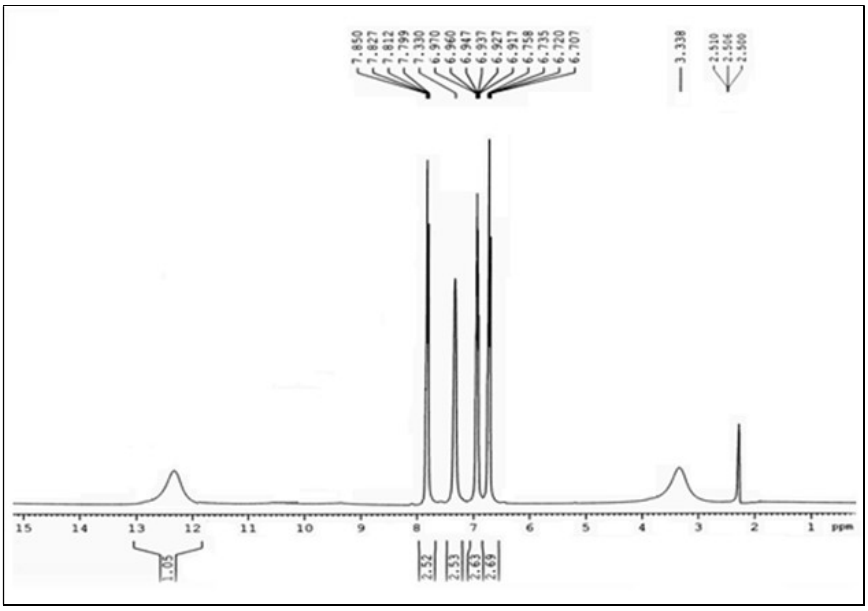


Figure III.9. [1]HNMR of 2-(4-Hydroxy phenyl)-1H-benzimidazole.

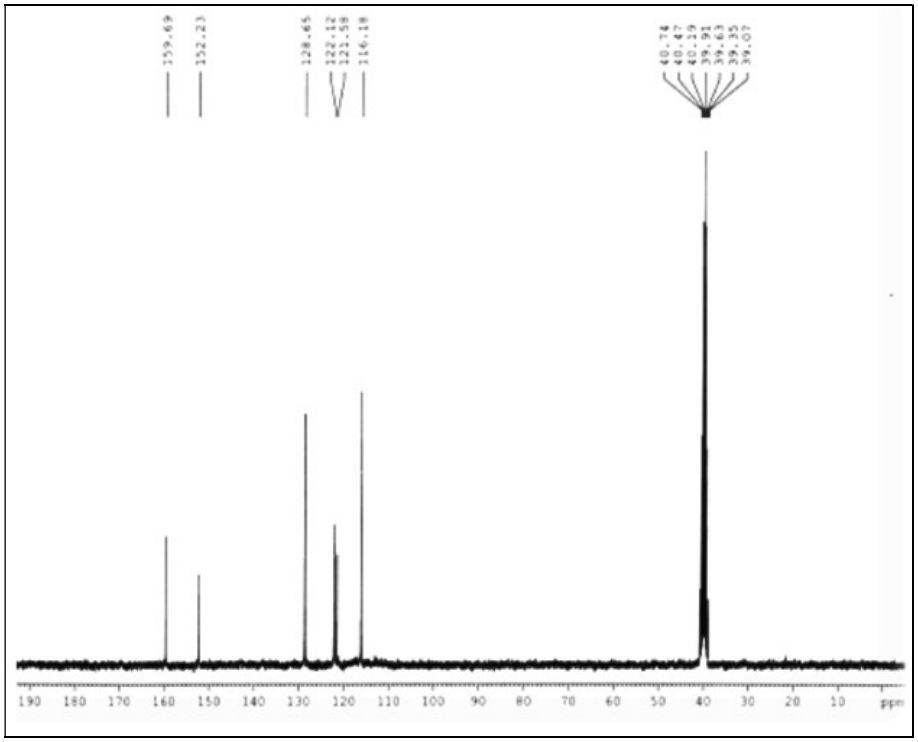
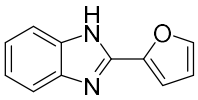


Figure III.10. [13]CNMR of 2-(4-Hydroxy phenyl)-1H-benzimidazole.



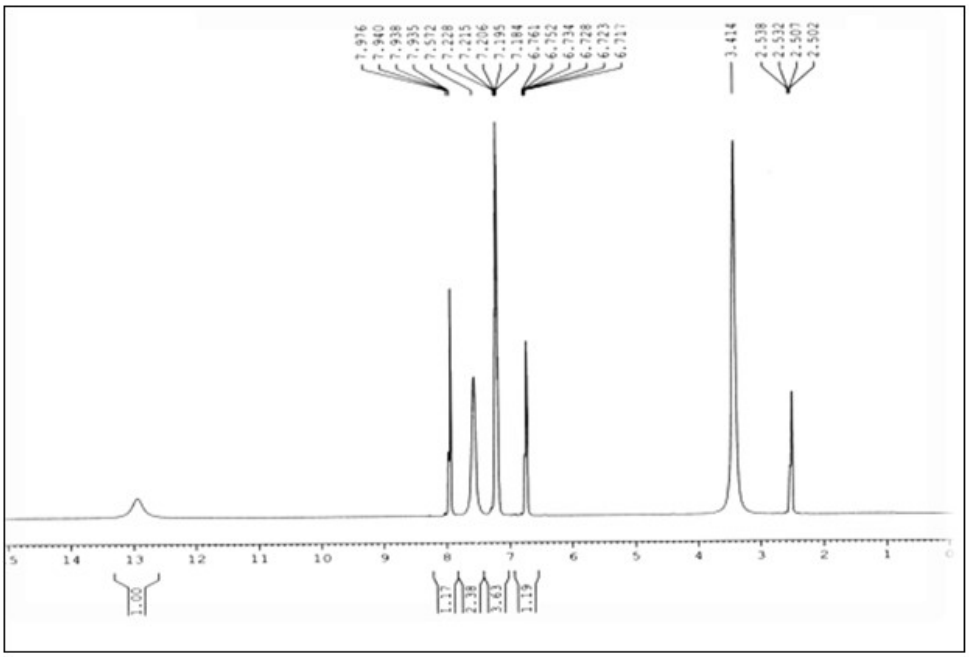


Figure III.11. [1]HNMR of 2-(Furan-2-yl)-1H- benzimidazole.

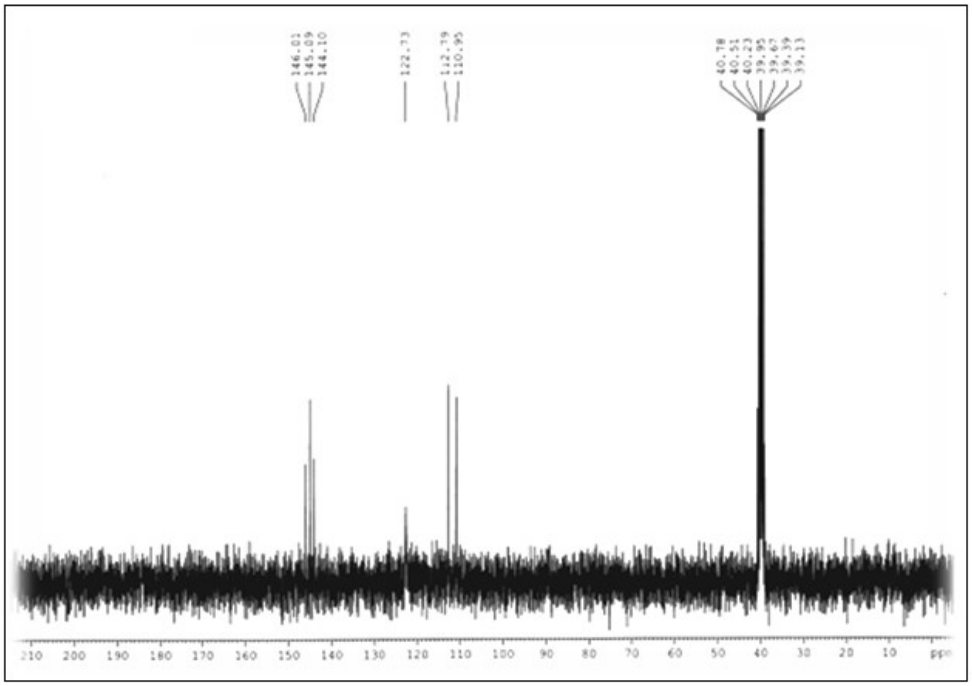


Figure III.12. [13]CNMR of 2-(Furan-2-yl)-1H- benzimidazole.

I.G. References

References are given in BIBLIOGRAPHY under Chapter III.