CHAPTER-VI

Ni-borate catalyzed solvent free green synthesis of 2-substituted benzimidazole and 1, 2-disubstituited benzimidazole derivatives

6.1 Background of the present investigation

Benzimidazole, an organic N-containing heterocyclic scaffold has gained a lot of interest during the past few decades due to its versatile pharmaceutical properties in medicinal chemistry[1]. The benzimidazole ring serves as one of the privileged scaffolds for the development and synthesis of libraries of novel molecules with potential therapeutic value[2]. The first synthesis of benzimidazole derivatives was reported by Hobrecker in 1872[3] and the first pharmacological properties of benzimidazole derivatives were studied by Godmann and Hart in 1943[1]. Having recognized the biological and medicinal properties of the benzimidazole scaffold, a numerous synthetic methodology has been developed for the synthesis of benzimidazole derivatives[4-6]. A large variety of benzimidazole derivatives have been known to show diverse biological activities such as anti-cancer[3], anti-inflammatory[7], analgesic[8], anti-ulcer[9], proton-pump inhibitors[10], anti-microbial[11], antioxidant[12], antidiabetic[13], antiviral[14] and anticoagulants[15] etc. A large variety of benzimidazole derivatives have been synthesized and their therapeutic potential has been examined during the past few decades[16-19]. A numerous clinically approved drugs which contains the benzimidazole scaffolds such as albendazole (113)[20] (antihelmintics), carbendazim (114) (fungicidal)[21], telmisartan (115) (antihypertensives)[22] and astemizole (116) (antihistaminic)[23] are available in market (Fig 6.1.1). Among the diverse variety of benzimidazole derivatives, 1,2-disubstituted benzimidazole have attracted widespread interest due to their spacious applications in new drugs, including antihypertensive drugs (117)[24], $GABA_A$ receptor agonists (118)[25] and the hepatitis C virus (HCV) NS5B polymerase inhibitors (119)[26] (Fig 6.1.2). Interestingly and specifically, 1, 2-disubstituted benzimidazole derivatives have significant pharmacological utility[27]. A numerous literature is available for the synthetic methodology for the synthesis of benzimidazole and 1, 2-disubstituted benzimidazole derivatives[28-31]. The reported procedure however suffers from some serious drawbacks such as use of harsh reaction condition, expensive catalyst, use of hazardous solvent, low yield, long reaction time and less atom economy [32-34]. Therefore, looking at the diverse application of the benzimidazole scaffold, development of a highly efficient and green protocol for the synthesis of this highly therapeutic agent is a current demand for the synthetic chemist.

Hence, it was thought worthwhile to develop an efficient, economical and green methodology for the synthesis of benzimidazole derivatives. Thus, in this section, we are representing the synthesis of 2-substituted benzimidazole and 1,2-

disubstituted benzimidazole derivatives using unconventional and inexpensive Ni-borate catalyst under solvent free condition.

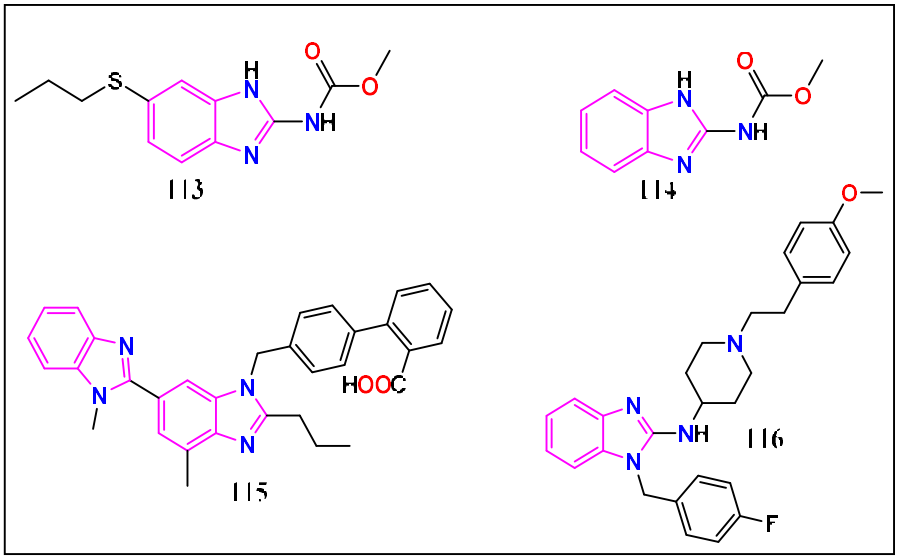


Fig. 6.1.1. Structures of some clinically approved drugs containing the benzimidazole scaffold

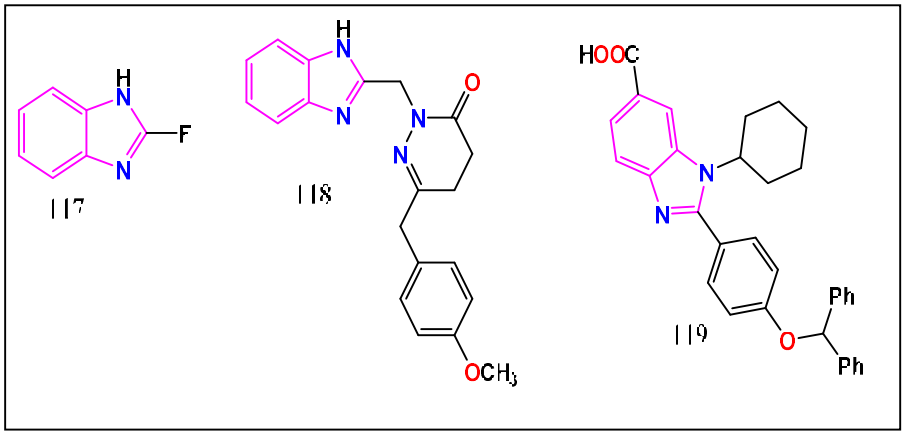
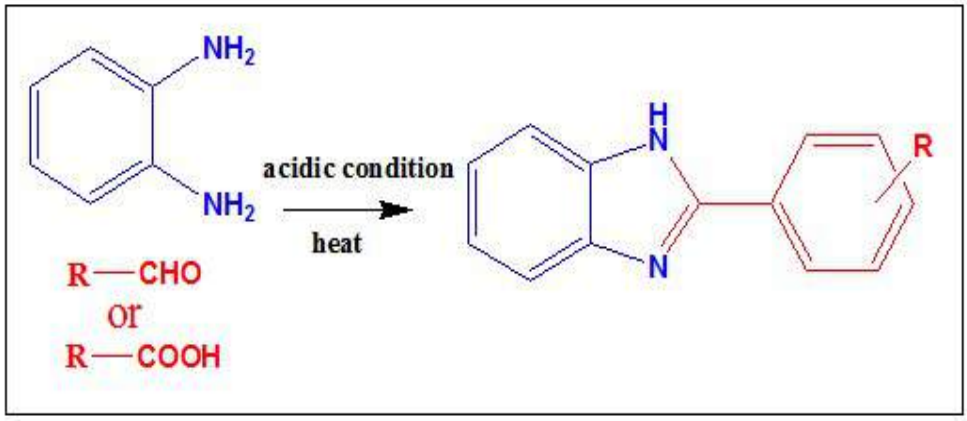


Fig. 6.1.2. Structures of some new drugs containing the benzimidazole scaffold

6.2 Results and discussions

6.2.1 2-Substituted benzimidazole derivatives

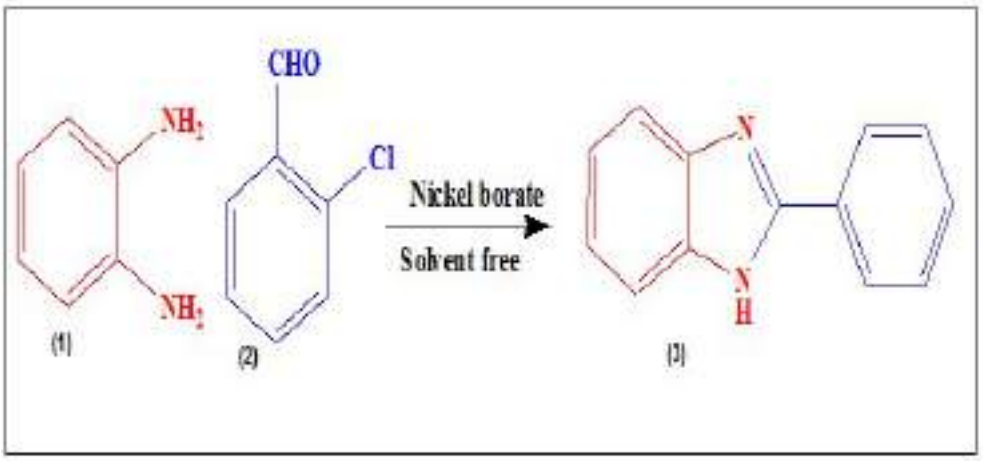
The classical method for the synthesis of 2-substituted benzimidazole derivatives involves the cyclization reaction of aromatic diamine with aldehydes, carboxylic acid or their derivatives at high temperature under strong acidic media[35] (Scheme 6.1.1).



Scheme. 6.1.1. Synthetic methodology for the synthesis of 2-substituted benzimidazole derivatives

There are several modified methods such as hydroformylation of N-alkenyl phenylenediamines using rhodium catalyst[36], reductive cyclization of ortho-nitroaniline with aldehyde[37], dehydration coupling of 2-bromoaniline[35] and carbonylation-cyclization of ortho-phenylenediamines using Pd catalyst[38] have been reported in the literature. However, the above cited modified methods has several major limitations such as use of expensive catalyst, harsh reaction condition, low yield, long reaction time and tedious work-up procedures etc.

Therefore, in this section, we are discussing the catalytic efficiency of Ni-borate for the green synthesis of 2-substituted benzimidazole and 1, 2-disubstituted benzimidazole derivatives under solvent free condition. Thus, optimization of the reaction was carried out by choosing orthophenylenediamine (1) and 2-chlorobenzaldehyde (2) as model reactants for the synthesis of benzimidazole (3) and the reaction was performed in presence of different amount of the catalyst under solvent free condition at different reaction condition such as amount of catalyst, time and temperature. In a typical model reaction, orthophenylenediamine (1 mmol) and 2-chlorobenzaldehyde (1mmol) was thoroughly mixed and ground in a mortar with the help of pestle in presence of the catalyst (Scheme 6.1.2).



Scheme. 6.1.2. Model reaction for the synthesis of 2-substituted benzimidazole (3)

The reaction mixture was then transferred into a 50 ml round bottomed flask and was allowed to stirrer at room temperature with the help of magnetic stirrer for 2 hours. The progress of the reaction was monitored with the help of TLC using ethyl acetate: hexane (20:80) mixture and we observed that the reaction did not go for completion and we isolated the reactant only. Therefore, we carried out the reaction at 60 ºC and we found that a trace amount of the product was formed at this temperature (Table 6.1.1, entry 2). Further, we increased the reaction temperature to 80 ºC and we observed that the reaction proceeds well and gets completed at 80 ºC (Table 6.1.1, entry 3 and 4). After optimizing the reaction temperature, then we optimized the catalyst loading by varying the amount of catalyst for the same model reaction at optimized temperature and we observed that in absence of the catalyst no product has been formed (Table 6.1.2, entry 1). Then, we varied the amount of catalyst for the model reaction from 0.5 mol % to 4 mol % and we observed that the reaction proceeds well when the amount of the catalyst loading is 3 mol% (Table 6.1.2, entry 7). It was also observed that the increase and decrease of the catalyst loading has a remarkable effect on the yield of the product. An increase in the amount of catalyst loading from 3 mol % to higher result in the slight decrease of the yield of the product. However, decreases in the amount of catalyst loading from 3 mole% to less result in the significant decreases of the yield of the product. Thus, we observed that 3 mol % of catalyst loading at 80 ºC for 2 hours was the optimum condition for the model reaction.

Table. 6.1.1. Optimization of reaction temperature for the model reaction

Entry	Temperature	Yield[a] (%)
1	Room Temperature	Nil
2	60 ºC	Trace
3	70 ºC	25
4	**80 ºC**	**97**

*[a]isolated yield

Table. 6.1.2. Optimization of catalyst loading for the model reaction

Entry[a]	Amount of catalyst (mole %)	Time (hours)	Yield[b](%)
1	**0**	**2**	**Nil**
2	0.5	2	15
3	1.0	2	20
4	1.5	2	32
5	2.0	2	50
6	2.5	2	60
7	**3.0**	**2**	**97**
8	3.5	2	89
9	4	2	88

*[a]all the reaction were carried out using o-phenylenediamine (1, 1mmol) and aldehyde (2, 2 mmol) under solvent free condition at 120 ºC for 3 hours using Ni-borate catalyst (2.5 mole %) and [b]isolated yield

Having recognized the optimum condition for the studied reaction, we extended catalytic reaction with o-phenylenediamine and a range of differently substituted aromatic aldehydes bearing electron donating as well as electron withdrawing groups. We observed that all the aldehydes gave well to excellent yields under the optimized reaction condition (Table 6.1.3 and Fig 6.1.3).

Again, we checked the recyclability of the catalyst for the given reaction by collecting the used catalyst after each run and subsequently purifying the catalyst by washing with methanol. We found that the catalyst was effective till 4th run of the reaction and after 4th run the catalyst lost its activity and the yield of the product decrease drastically. Thus, from this study we can infer that the studied catalyst efficiently yielded the desired product up to 4th run (Table 6.1.4, Fig 6.1.4).

Table. 6.1.3. Isolated yield and melting point of the synthesized benzimidazole derivatives (3a-3j)

Entry[a]	Diamine substrate	Aldehyde	Product	Yield[b](%)	Melting point (ºC)
1	o-phenylenediamine	Benzaldehyde	3a	93	295-298
2	o-phenylenediamine	2-chlorobenzaldehyde	3b	97	230-234
3	o-phenylenediamine	4-chlorobenzaldehyde	3c	96	290-298
4	o-phenylenediamine	2-nitrobenzaldehyde	3d	98	228-232
5	o-phenylenediamine	4-nitrobenzaldehyde	3e	98	315-319
6	o-phenylenediamine	4-methoxybenzaldehyde	3f	95	224-228
7	o-phenylenediamine	2-hydroxybenzaldehyde	3g	96	239-241
8	o-phenylenediamine	2-hydroxy-3-methoxybenzaldehyde	3h	95	197-201
9	o-phenylenediamine	2-hydroxy-5-nitrobenzaldehyde	3i	96	238-241
10	o-phenylenediamine	2-hydroxy-5-bromobenzaldehyde	3j	95	252-256

*[a]all the reaction were carried out using o-phenylenediamine (1, 1mmol) and aldehyde (2, 1 mmol) under solvent free condition at 80 ºC for 2 hours using Ni-borate catalyst (3 mole %) and [b]isolated yield.

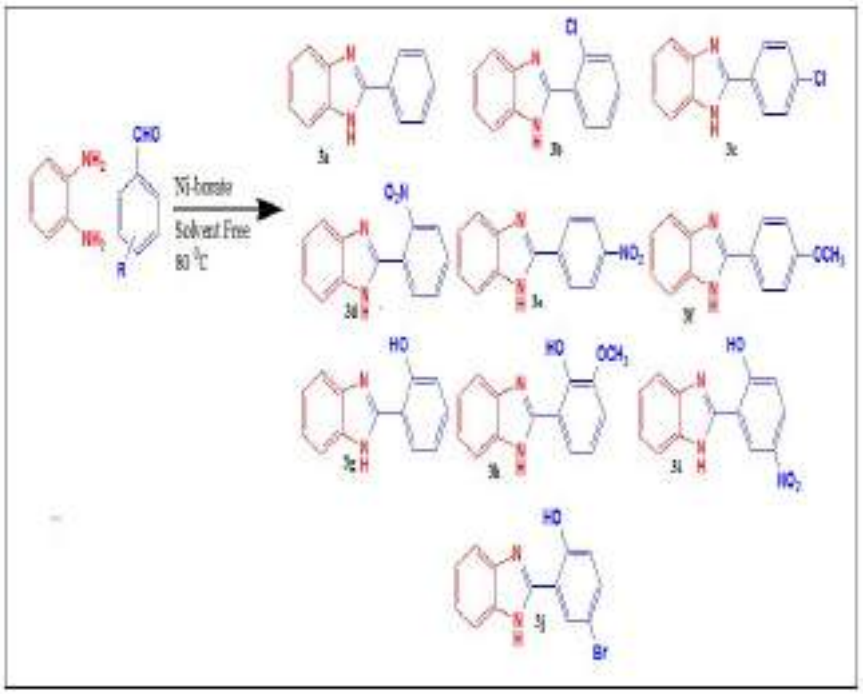


Fig. 6.1.3. Synthesized benzimidazole derivatives (3a-3j)

Table 6.1.4. Recyclability of the catalyst

Entry	Run	Yield[b] (%)
1	1	97
2	2	95
3	3	94
4	4	94
5	5	82
6	6	75

*[b]isolated yield

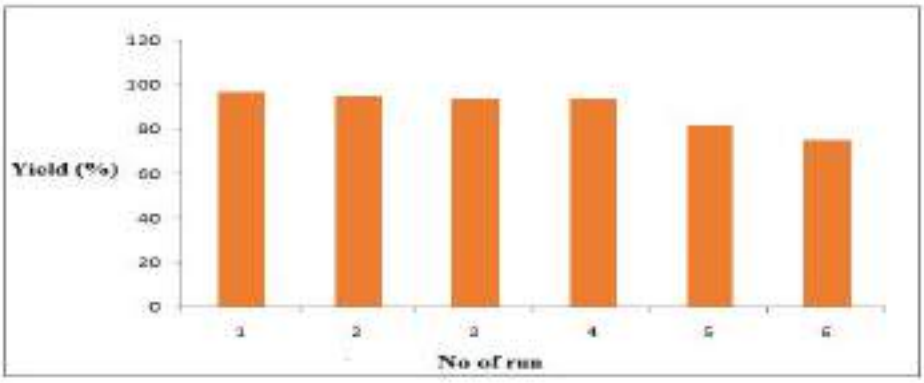
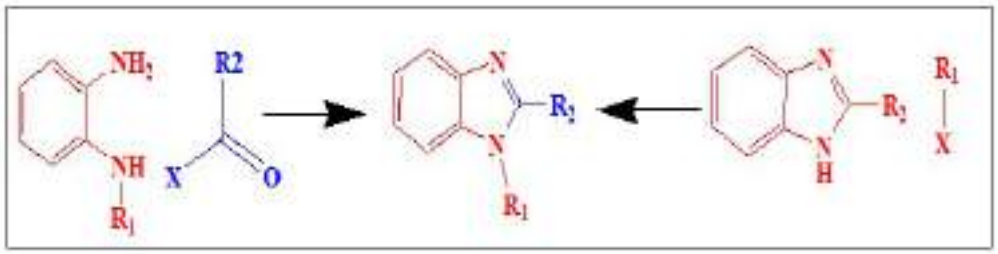


Fig. 6.1.4. Recyclability of the catalyst

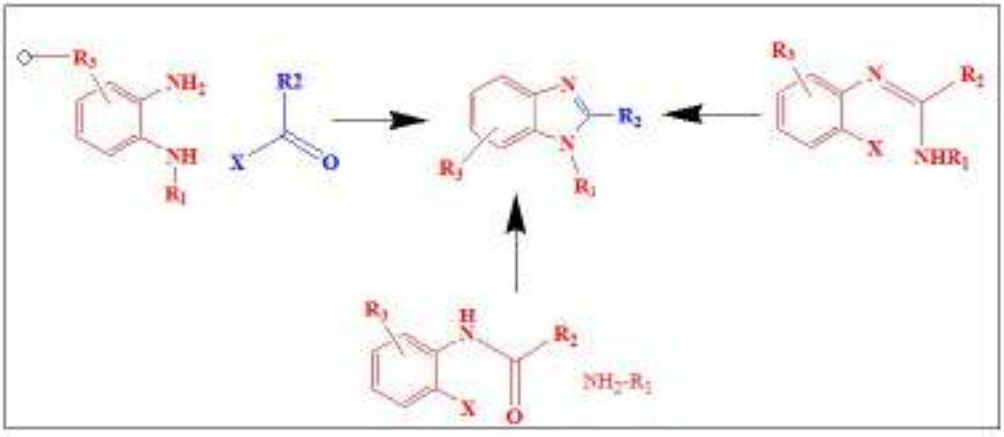
6.2.2 1, 2-disubstituted benzimidazole derivatives

1,2-disubstituted benzimidazole derivative represents a special class of the benzimidazole family and thus proven to be an important scaffold because of their diverse application in many fields such as drugs, dyes and polymers[39]. Undoubtedly, there are various methods for the synthesis of 1,2-disubstituted benzimidazole scaffold and the most common and traditional method involves the condensation of orthophenylene diamine with aldehyde or carboxylic derivatives. N-alkylation/N-arylation of benzimidazole serves as a frequent alternative for the synthesis of 1,2-disubstituted benzimidazole derivative[40] (Scheme 6.2.1).



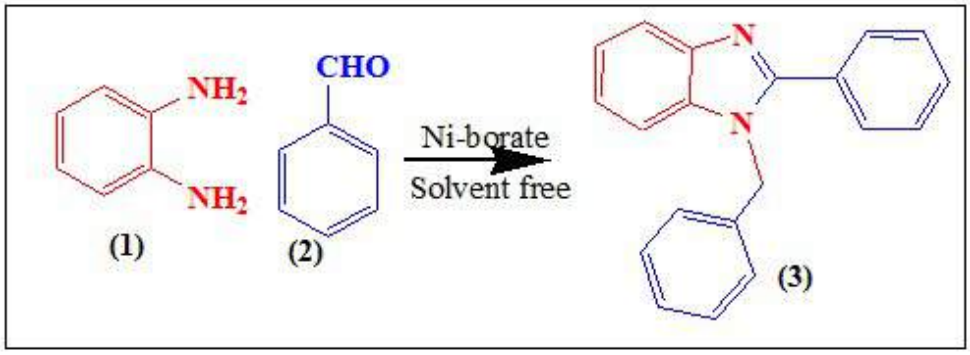
Scheme. 6.2.1. Classical method for the synthesis of 1,2-disubstituted benzimidazole

However, these methods are not very popular and suitable for the synthesis of 1,2-disubstituted benzimidazole as they are limited for few available substrates. Moreover, the traditional condensation method is not suitable for the synthesis of 1, 2-disubstituted benzimidazole derivatives because of the lack of difference between the two nitrogen atoms in the benzimidazole ring usually give rise to a mixture of regioisomers[27]. During the past few years, many improvements such as metal catalyzed aryl-amination and cascade arylamination/condensation methods have been formulated[41] (Scheme 6.2.2)



Scheme. 6.2.2. Modern methods for the synthesis of 1, 2-disubstituted benzimidazole derivatives.

Thus, the development and formulation of simple and region-selective synthesis of 1, 2-disubstituted benzimidazole derivatives have remains an active and emerging field of research. Therefore, in continuation to our research work for the synthesis of benzimidazole derivatives utilizing Ni-borate catalyst under solvent free condition, we were interested to examine the efficacy of the catalyst for the regioselective synthesis of 1,2-disubstituted benzimidazole derivatives. In order to optimize the reaction condition, orthophenylenediamine (1) and benzaldehyde (2) was chosen as a model reactant under solvent free condition (Scheme 6.2.3) using Ni-borate as a catalyst.



Scheme. 6.2.3. Model reaction for the synthesis of 1, 2-disubstituted benzimidazole.

For a model reaction, orthophenylenediamine (1 mmol) and benzaldehyde (2 mmol) was thoroughly mixed and ground in a mortar with the help of pestle in presence of the catalyst. The reaction mixture was then transferred into a 50 ml round bottomed flask and was allowed to stirrer at room temperature with the help of magnetic stirrer for 3 hours. The progress of the reaction was monitored with the help of TLC using ethyl acetate: hexane (20:80) mixture and we observed that the reaction did not go for completion and we isolated the reactant only. Therefore, we carried out the reaction at 80 ºC and we found that a trace amount of the product has been formed along with 2-substituted benzimidazole at this temperature (Table 6.2.1, entry 2). Further, we increased the reaction temperature to 120 ºC and we observed that the reaction proceeds well and gets completed at 120 ºC without formation of the side product (Table 6.2.1, entry 3 and 4)

Table 6.2.1. Optimization of reaction temperature for the model reaction

Entry	Temperature	Yield[a] (%)
1	Room Temperature	Nil
2	80 ºC	Trace
3	100 ºC	20
4	**120 ºC**	**96**

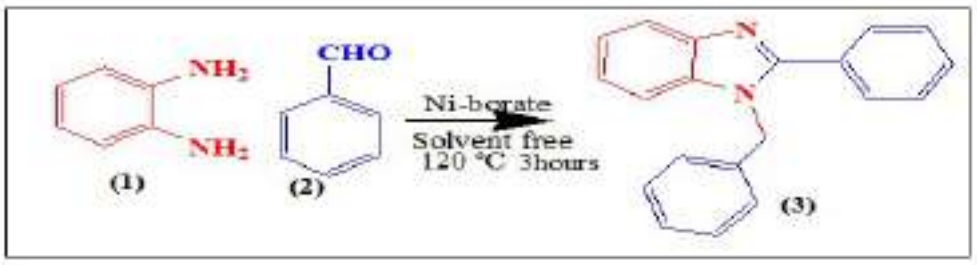
*[a]isolated yield

After optimizing the reaction temperature, then we optimized the catalyst loading by varying the amount of catalyst for the same model reaction at optimized temperature and we observed that in absence of the catalyst no product was isolated (Table 6.2.2, entry 1). Then, we varied the amount of catalyst for the model reaction from 0.5 mol % to 4 mol % and we observed that the reaction proceeds well when the amount of the catalyst loading is 2.5 mol % (Table 6.2.2, entry 7). It was also observed that the increase and decrease of the catalyst loading has a remarkable effect on the yield of the product. An increase in the amount of catalyst loading from 2.5 mol % to higher result in the slight decrease of the yield of the product. However, decrease in the amount of catalyst loading from 2.5 mol % to less resulted in the significant decrease of the yield of the product. Thus, were able to optimize the reaction condition as 2.5 mol % of catalyst at 120 ºC for 3 hours reaction time for the formation of 1, 2-disubstituted benzimidazole (3) (Scheme 6.2.4).

Table. 6.2.2. Optimization of catalyst loading for the model reaction

Entry[a]	Amount of catalyst (mole %)	Time (hours)	Yield[b](%)
1	**0**	**3**	**Nil**
2	0.5	3	10
3	1.0	3	22
4	1.5	3	37
5	2.0	3	66
6	**2.5**	**3**	**96**
7	3.0	3	92
8	3.5	3	80

*[a]all the reaction were carried out using o-phenylenediamine (1, 1mmol) and aldehyde (2, 2 mmol) under solvent free condition at 120 ºC for 3 hours using Ni-borate catalyst (2.5 mole %) and [b]isolated yield and [b]isolated yield



Scheme. 6.2.4. Optimization of reaction condition for model reaction to synthesize ($3a^{/}$-$3k^{/}$)

Table. 6.2.3. Isolated yield and melting point of the synthesized benzimidazole derivatives (3a/-3k/)

Entry[a]	Diamine substrate	Aldehyde	Product	Yield[b] (%)	Melting point (ºC)
1	o-phenylenediamine	Benzaldehyde	3a/	96	132-136
2	o-phenylenediamine	4-methylbenzaldehyde	3b/	94	126-129
3	o-phenylenediamine	3-nitrobenzaldehyde	3c/	98	166-170
4	o-phenylenediamine	4-nitrobenzaldehyde	3d/	98	188-192
5	o-phenylenediamine	4-methoxybenzaldehyde	3e/	95	125-129
6	o-phenylenediamine	4-hydroxybenzaldehyde	3f/	94	255-258
7	o-phenylenediamine	4-chlorobenzaldehyde	3g/	96	138-141
8	o-phenylenediamine	2-hydroxybenzaldehyde	3h/	95	205-208
9	o-phenylenediamine	2-hydroxy-5-nitrobenzaldehyde	3i/	98	-
10	o-phenylenediamine	Indole-3-Carboxaldehyde	3j/	94	233-237
11	o-phenylenediamine	2-chlorobenzaldehyde	3k/	96	-

*[a] all the reaction were carried out using o-phenylenediamine (1, 1mmol) and aldehyde (2, 2 mmol) under solvent free condition at 120 ºC for 3 hours using Ni-borate catalyst (2.5 mole %) and [b]isolated yield.

After optimizing the reaction condition for the model reaction, we extended the catalytic reaction with a range of differently substituted aromatic aldehydes bearing electron donating as well as electron withdrawing groups. We observed

that all the aldehydes furnished 1, 2-disubstituted products in good to excellent yield under the optimized reaction condition (Table 6.2.3 and Fig 6.2.1).

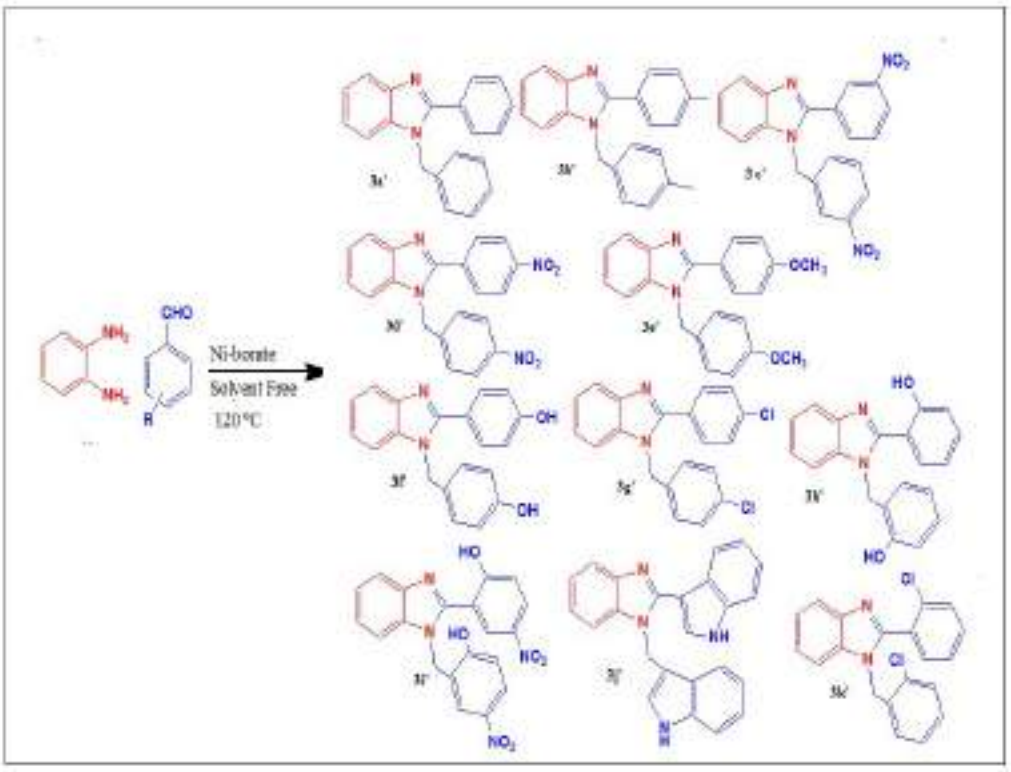


Fig. 6.2.1. Synthesized 1, 2-benzimidazole derivatives (3a/-3k/)

Again, we examined the recyclability of the catalyst for the given reaction and we recover the catalyst after each run and subsequently purifying the catalyst by washing with methanol. We found that the catalyst was effective till 3rd run of the reaction and after 3rd run the catalyst lost its activity and the yield of the product varied drastically. Thus, we can infer that the studied catalyst efficiently yielded the desired product up to 3rd run (Table 6.2.4, Fig 6.2.2).

Table. 6.2.4. Recyclability of the catalyst

Entry	Run	Yield[a] (%)
1	1	96
2	2	95
3	3	94
4	4	82
5	5	75

*[a]isolated yield

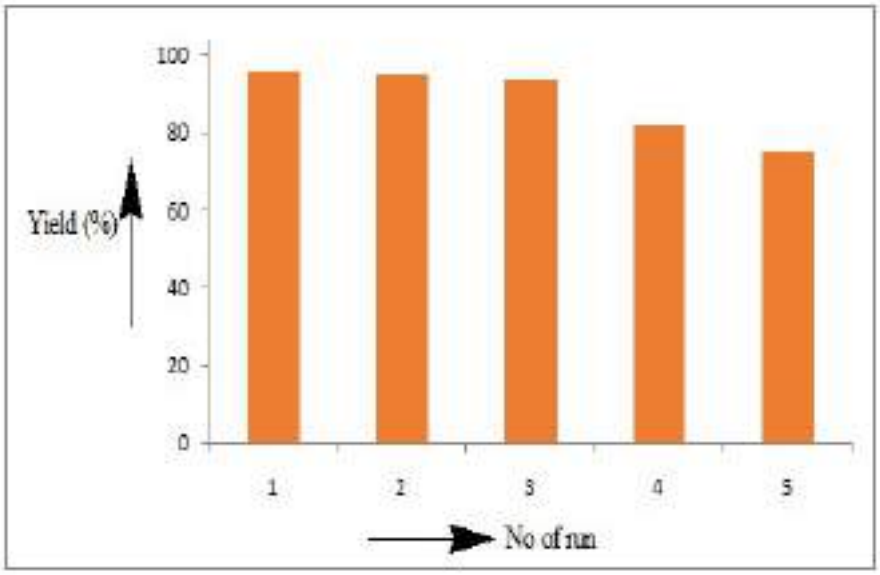


Fig. 6.2.2 Recyclability of the catalyst

6.3 Experimental Section

6.3.1 Materials

All starting materials of high purity for the synthesis of 2-substituted and 1, 2-disubstituted benzimidazole derivatives were purchased commercially and used as received. The FT-IR spectra of the prepared compounds were recorded in Bruker Alpha III spectrophotometer operating in the wave number region 4000 to 400 cm^{-1} in dry KBr. The melting points of the synthesized compounds were determined by open capillary method. ^{1}H-NMR spectra of the derivatives were recorded at room temperature on a FT-NMR (Bruker Advance-II 400 MHz) spectrometer by using DMSO-d_6 as solvents and chemical shifts are quoted in ppm downfield of internal standard tetramethylsilane(TMS).

6.3.2 General procedure for the synthesis of 2-substituted benzimidazole:

In a typical reaction procedure, a mixture of orthophenylenediamine (1, 1 mmol), substituted benzaldehyde (2, 1.0 mmol) and Nickel borate (3 mol %) thoroughly ground and mixed in a mortar and pestle to make a homogenous mixture. The mixture was then transferred to a test tube. The reaction was heated at 80 ºC for 2 hours. The progress of the reaction was monitored by TLC using hexane/ethyl acetate (80:20) solvent. After completion of the reaction, the reaction mixture was dissolved in methanol and filtered. The filtrate was evaporated under vacuum and subsequently dried to afford desired product and the catalyst was recovered with simple filtration. The catalyst was again purified by washing with methanol and dried over an oven at 100 ºC for 2 hours for further use. All the synthesized compounds (3a-3j) were recrystallized from ethanol and have been

characterized by their analytical (yield and melting point value) and spectroscopic data (FT-IR and ^{1}HNMR) and compared with the literature value.

6.3.3 General procedure for the synthesis of 1, 2-disubstituted benzimidazole

The synthesis of 1, 2-disubstituted benzimidazole derivatives have been accomplished by grinding the mixture of orthophenylenediamine (1, 1 mmol) and substituted aromatic aldehydes (2, 2.0 mmol) in presence of Ni-borate catalyst (2.5 mole %) in agate mortar and pestle. The reaction mixture was then transferred into the borosil test tube and subjected to heating at 120 ºC for 3 hours. The progress of the reaction was monitored by TLC using hexane/ethyl acetate (80:20) solvent. After completion of the reaction, the reaction mixture was dissolved in methanol and filtered. The filtrate was evaporated under vacuum and subsequently dried to afford desired product and the catalyst was recovered with simple filtration. All the synthesized compounds ($3a^{/}$-$3k^{/}$) were recrystallized from ethanol and have been characterized by their analytical (yield and melting point value) and spectroscopic data (FT-IR and ^{1}HNMR) and compared with the literature value.

6.4. Conclusion

In summary, we have reported a novel and unconventional Ni-borate catalyst for the synthesis of 2-substituted and 1, 2-disubstituted benzimidazole derivatives under solvent free condition. The catalyst was found to be an efficient and versatile for the synthesis of above-mentioned derivatives under green chemical condition. This process is advantageous due to its simple operational procedure and easy work-up of the product with minimal use of the hazardous solvent.

6.5 Analytical and Spectroscopic data

6.5.1 2-substituted benzimidazole

6.5.1.1 2-Phenyl-1H-benzimidazole (3a): white solid, yield= 93%, melting point found (^{0}C) = 295-298, IR (KBr, cm^{-1}) υ_{max}:3446 (br, NH), 3003 (C-H, Aromatic), 1622(C=N), 1590, 1445 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 12.89 (S, 1H, OH), 8.15 (m, 2H, Ar-H), 7.52 (m, 2H, Ar-H), 7.46 (m, 3H, Ar-H), 7.17 (m, 2H, Ar-H).

6.5.1.2 2-(2-Chlorophenyl)-benzimidazole (3b): yellow solid, yield= 97%, melting point found (^{0}C) = 230-234, IR (KBr, cm^{-1}) υ_{max}:3444 (br, NH), 3031 (C-H, Aromatic), 1591(C=N), 1575, 1444 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 12.77 (S, 1H, NH), 7.91 (m, 1H, Ar-H), 7.65-7.56 (m, 3H, Ar-H), 7.52-7.49 (m, 2H, Ar-H), 7.17-7.23 (m, 2H, Ar-H).

6.5.1.3 2-(4-Chlorophenyl)-benzimidazole (3c): yellow solid, yield= 96%, melting point found (^{0}C) = 290-293, IR (KBr, cm^{-1}) υ_{max}:3442 (br, NH), 3036 (C-H, Aromatic), 1598(C=N), 1580, 1429 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 12.88 (S, 1H, NH), 8.13 (d, 2H, Ar-H), 7.64-7.49 (m, 4H, Ar-H), 7.20 (d, 2H, Ar-H).

6.5.1.4 2**-(2-Nitrophenyl)-benzimidazole (3d):** yellow solid, yield= 98%, melting point found (^{0}C) = 228-232, IR (KBr, cm^{-1}) υ_{max}:3428 (br, NH), 1620(C=N), 1528, 1457 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 13.08 (S, 1H, NH), 8.04-7.85 (m, 2H, Ar-H), 7.89-7.63 (m, 4H, Ar-H), 7.225 (brs, 2H, Ar-H).

6.5.1.5 2-(4-Nitrophenyl)-benzimidazole (3e): pale yellow solid, yield= 98%, melting point found (^{0}C) = 315-319, IR (KBr, cm^{-1}) υ_{max}:3420 (br, NH), 1604(C=N), 1520, 1451 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 13.20 (S, 1H, NH), 8.32 (d, 2H, Ar-H), 8.14 (d, 2H, Ar-H), 7.19-7.61 (m, 4H, Ar-H).

6.5.1.6 2**-(4-Methoxyphenyl)-benzimidazole (3f):** yellow solid; yield= 95%, melting point found (^{0}C) = 224-228, IR (KBr, cm^{-1}) υ_{max}:3342 (br, NH), 1605(C=N), 1506, 1459 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 12.68 (S, 1H, NH), 8.12 (d, 2H, Ar-H), 7.04-7.75 (m, 6H, Ar-H), 3.82 (s, 3H, -OCH_3).

6.5.1.7 2-(2-Hydroxyphenyl)-benzimidazole (3g): white solid;yield= 96%, melting point found (^{0}C) = 239-241, IR (KBr, cm^{-1}) υ_{max}:3330 (br, NH), 3054 (C-H, Aromatic),1598(C=N), 1528, 1490 (C=C, Aromatic), ^{1}HNMR (400 MHz,

DMSO d_6): δppm = 13.18 (S, 1H, NH), 12.98 (s, 1H, OH), 8.01 (m, 1H, Ar-H), 7.64 (m, 2H, Ar-H), 7.25-7.33 (m, 3H, Ar-H), 6.96-7.05 (m, 2H, Ar-H).

6.5.1.8 2**-(2-Hydroxy-3-methoxyphenyl)-benzimidazole (3h):** white solid; yield= 95%, melting point found (^{0}C) = 197-201, IR (KBr, cm^{-1}) υ_{max}:3152 (br, NH), 3004 (C-H, Aromatic), 1604(C=N), 1531, 1365 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 9.55 (S, 1H, NH), 8.80 (s, 1H, OH), 6.78-7.88 (m, 7H, Ar-H), 3.42 (s, 3H, -OCH_3).

6.5.1.9 2-(2-Hydroxy-5-nitrophenyl)-benzimidazole (3j): yellow solid; yield= 96%, melting point found (^{0}C) = 238-241, IR (KBr, cm^{-1}) υ_{max}:3284 (br, NH), 3000-2800 (OH), 1594(C=N), 1590, 1478 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 14.08 (S, 1H, NH), 9.18 (s, 1H, OH), 8.22 (d, 2H, Ar-H), 8.17 (d, 2H, Ar-H), 7.21-7.71 (m, 3H, Ar-H).

6.5.1.10 2-(2-Hydrox-5-bromophenyl)-benzimidazole (3k): yellow solid; yield= 95%, melting point found (^{0}C) = 252-256, IR (KBr, cm^{-1}) υ_{max}:3364 (br, NH), 3065 C-H Aromatic), 1612(C=N), 1438 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 10.28 (S, 1H, 0H), 8.89 (s, 1H, NH), 6.72-7.52 (m, 7H, Ar-H).

6.5.2 1, 2-disubstituted benzimidazole

6.5.2.1 1-benzyl-2-phenyl-1H-benzo[d]imidazole (3a$^/$): white solid; yield= 96%, melting point found (^{0}C) = 132-136, IR (KBr, cm^{-1}) υ_{max}: 2924, 2853 (C-H Aromatic), 1632(C=N), 1469 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 7.71-7.25 (m, 3H, Ar-H), 7.27-7.19 (m, 5H, Ar-H), 6.98 (d, 2H, Ar-H), 5.16 (S, 2H, -CH_2).

6.5.2.2 1-(4-methylbenzyl-2-p-tolyl-1H-benzo[d]imidazole (3b$^/$): white solid; yield= 94%, melting point found (^{0}C) = 126-129, IR (KBr, cm^{-1}) υ_{max}: 2959, 2937 C-H Aromatic), 1626, 1587 (C=N), 1480 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 7.64 (d, 1H, Ar-H), 7.58 (d, 2H, Ar-H), 7.38 (d, 1H, Ar-H), 7.33-7.19 (m, 4H, Ar-H), 7.04-6.85 (m, 4H, Ar-H), 5.48 (S, 2H, -CH_2), 2.35 (s, 3H, CH_3), 2.20 (S, 3H, CH_3).

6.5.2.3 1-(3-nitrobenzyl)-2-(3-nitrophenyl-1H-benzo[d]imidazole (3c$^/$): yellow solid; yield= 98%, melting point found (^{0}C) = 166-170, IR (KBr, cm^{-1}) υ_{max}: 2882 C-H Aromatic), 1637(C=N), 1536, 1471 (C=C, Aromatic), ^{1}HNMR (400 MHz,

DMSO d_6): δppm = 8.82 (s, 1H, Ar-H), 8.41 (d, 2H, Ar-H), 8.25 (d, 1H, Ar-H), 7.77-7.7.3 (m, 2H, Ar-H), 7.61-7.59 (m, 2H, Ar-H), 7.26-7.24 (m, 2H, Ar-H), 5.20 (S, 2H, -CH_2).

6.5.2.4 1-(4-nitrobenzyl)-2-(4-nitrophenyl-1H-benzo[d]imidazole (3d′): bright yellow solid; yield= 98%, melting point found (^{0}C) = 188-192, IR (KBr, cm^{-1}) υ_{max}: 3107 (C-H Aromatic), 1634, 1607 (C=N), 1540 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 8.32 (d, 2H, Ar-H), 8.23 (d, 2H, Ar-H), 8.10 (d, 2H, Ar-H), 7.88 (d, 1H, Ar-H), 7.62 (d, 1H, Ar-H), 7.28-7.20 (m, 2H, Ar-H), 7.02 (d, 2H, Ar-H), 5.18 (S, 2H, -CH_2).

6.5.2.5 1-(4-methoxybenzyl)-2-(4-methoxyphenyl-1H-benzo[d]imidazole (3e′): white solid; yield= 95%, melting point found (^{0}C) = 125-129, IR (KBr, cm^{-1}) υ_{max}: 2937 C-H Aromatic), 1626, 1587 (C=N), 1480, 1458 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 7.66 (d, 3H, Ar-H), 7.43 (d, 1H, Ar-H), 7.21-7.18 (m, 2H, Ar-H), 7.06 (d, 2H, Ar-H), 6.95(d, 2H, Ar-H), 6.82 (d, 2H, Ar-H), 5.39 (S, 2H, -CH_2), 3.81 (s, 3H, -OCH_3), 3.66 (s, 3H, -OCH_3).

6.5.2.6 1-(4-hydroxybenzyl) -1H-benzo[d]imidazol-2-yl)phenol (3f′): yellow solid; yield= 94%, melting point found (^{0}C) = 255-258, IR (KBr, cm^{-1}) υ_{max}: 2922 (C-H Aromatic), 1621, 1578 (C=N), 1506, 1463 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm =10.77 (s,1H, -OH), 9.58 (s, 1H, -OH), 7.82 (d, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 7.74 (d, 2H, Ar-H), 7.54-7.51 (m, 2H, Ar-H), 7.12 (d, 2H, Ar-H), 6.94 (d, 2H, Ar-H), 6.65 (d, 2H, Ar-H) 5.61 (S, 2H, -CH_2).

6.5.2.7 1-(4-chlorobenzyl)-2-(4-chlorophenyl-1H-benzo[d]imidazole (3g′): white solid; yield= 96%, melting point found (^{0}C) = 138-141, IR (KBr, cm^{-1}) υ_{max}: 3070, 2847 C-H Aromatic), 1627, 1568 (C=N), 1505, 1462 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 7.71 (d, 3H, Ar-H), 7.60 (d, 2H, Ar-H), 7.46 (d, 1H, Ar-H), 7.32 (d, 2H, Ar-H), 7.26-7.24 (m, 2H, Ar-H), 7.01 (d, 2H, Ar-H), 5.54 (S, 2H, -CH_2).

6.5.2.8 2-(1-(2-hydroxybenzyl)-1H-benzo[d]imidazol-2-yl)phenol (3h′): yellow solid; yield= 95%, melting point found (^{0}C) = 205-208, IR (KBr, cm^{-1}) υ_{max}: 2923, 2852 (C-H Aromatic), 1635(C=N), 1495(C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 11.08 (s, 1H, -OH), 9.75 (s, 1H, -OH), 7.71 (d, 1H, Ar-H), 7.41-7.36 (m, 3H, Ar-H), 7.01 (d, 2H, Ar-H), 6.94-6.88 (m, 1H, Ar-H), 6.78 (d, 1H, Ar-H), 6.58-6.39 (m, 2H, Ar-H), 5.42 (S, 2H, -CH_2).

6.5.2.9 2-(1-(2-hydroxy-5-nitrobenzyl)-1H-benzo[d]imidazol-2-yl)-4-nitrophenol (3i/): yellow solid, yield= 98%, IR (KBr, cm^{-1}) υ_{max}: 2922, 2852 (C-H Aromatic), 1635, 1590 (C=N), 1481 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 13.98 (s, 2H, -OH), 9.11 (s, 2H, Ar-H), 8.77 (d, 2H, Ar-H), 8.21 (dd, 2H, Ar-H), 7.56-7.48 (m, 4H, Ar-H), 5.36 (S, 2H, $-CH_2$).

6.5.2.10 1-((1*H*-Indol-3-yl)methyl)-2-(1*H*-indol-3-yl)-1*H*-benzimidazole (3j/): brown solid, yield= 94%, melting point found (^{0}C) = 233-238, IR (KBr, cm^{-1}) υ_{max}: 3032 C-H Aromatic), 1612, 1598(C=N), 1256 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 10.20 (s, 1H, -OH), 9.45 (s, 1H, -OH), 8.72 (s, 1H, Ar-H), 8.35 (t, 1H, Ar-H), 7.82 (d, 1H, Ar-H), 7.63 (s, 1H, Ar-H), 7.44-7.41 (m, 1H, Ar-H), 7.42 (t, 1H, Ar-H), 7.35-7.29 (m, 2H, Ar-H), 7.28-7.25 (m, 3H, Ar-H), 7.08-7.04 (m, 2H, Ar-H), 6.84 (t, 1H, Ar-H), 5.67 (S, 2H, $-CH_2$).

6.5.2.11 1-(2-chlorobenzyl)-2-(2-chlorophenyl-1H-benzo[d]imidazole (3l/): white solid, yield= 96%, IR (KBr, cm^{-1}) υ_{max}: 3065 (C-H Aromatic), 1638 (C=N), 1446 (C=C, Aromatic), ^{1}HNMR (400 MHz, DMSO d_6): δppm = 7.93 (m, 1H, Ar-H), 7.72 (m, 2H, Ar-H), 7.68-7.65 (m, 4H, Ar-H), 7.62 (t, 1H, Ar-H), 7.56-7.50 (m, 2H, Ar-H), 7.32-7.27 (m, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 5.43 (s, 2H, $-CH_2$).

6.6 Supporting spectra

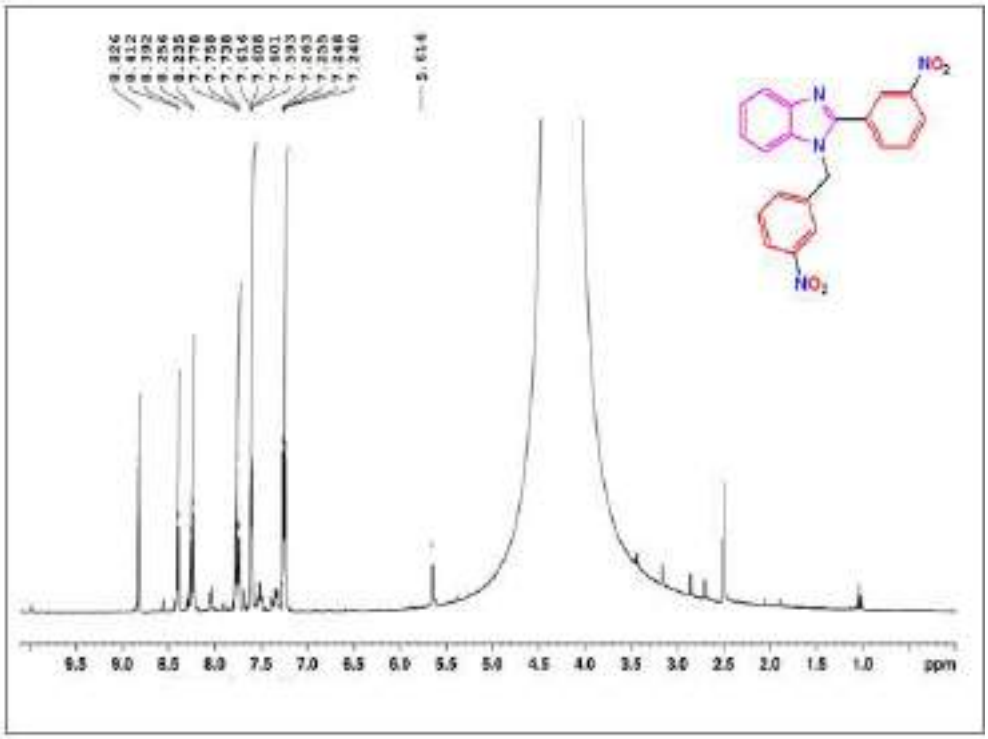


Fig.6.6.1. [1]HNMR of 1-(3-nitrobenzyl)-2-(3-nitrophenyl-1H-benzo[d]imidazole (3c/)

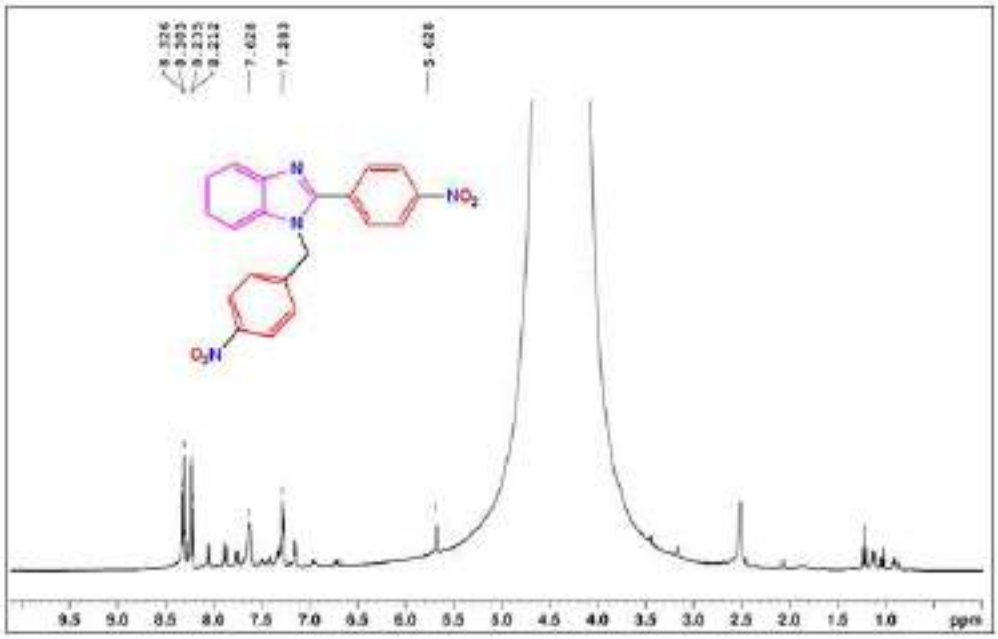


Fig.6.6.2. [1]HNMR of 1-(4-nitrobenzyl)-2-(4-nitrophenyl-1H-benzo[d]imidazole (3d/)

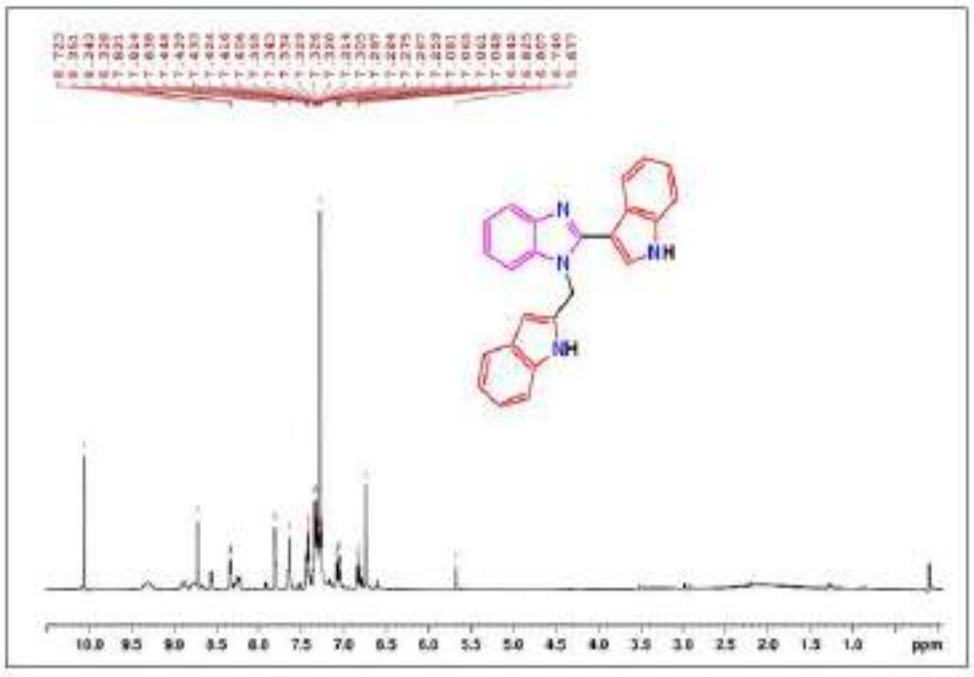


Fig.6.6.3. [1]HNMR of 1-((1*H*-Indol-3-yl)methyl)-2-(1*H*-indol-3-yl)-1*H*-benzimidazole (3j/)

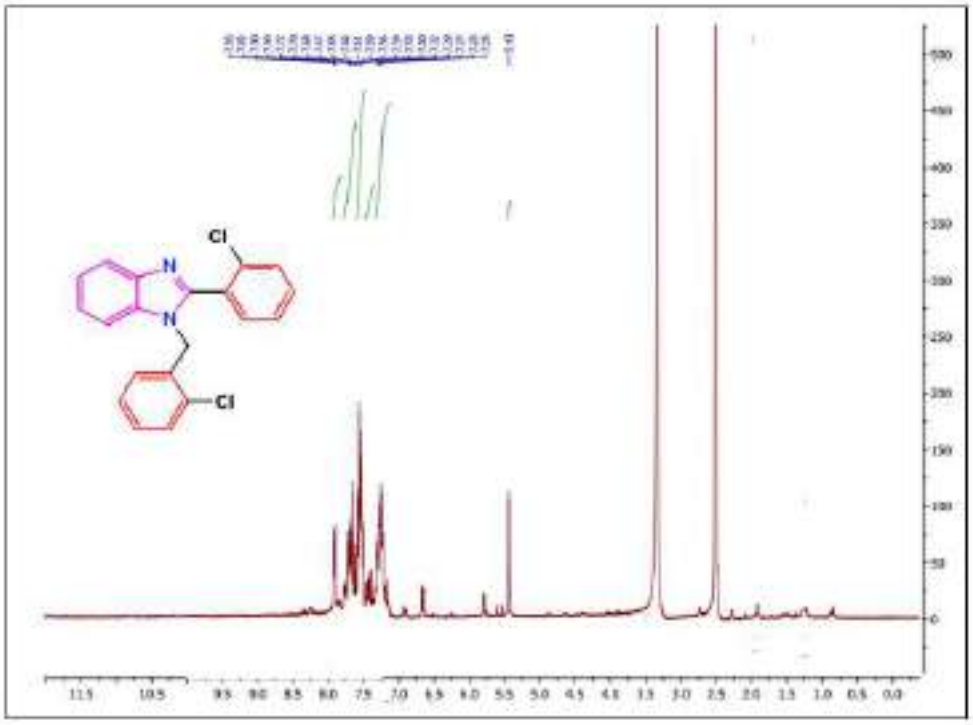


Fig 6.6.4. [1]HNMR of 1-(2-chlorobenzyl)-2-(2-chlorophenyl-1H-benzo[d]imidazole (3l/)

6.7 References

(1) B. Pathare, T. Bansode., *Results in Chemistry*, **2021**, *3*, 100200.

(2) O. O. Ajani, D. v. Aderohunmu, C. O. Ikpo, A. E. Adedapo, I. O. Olanrewaju., *Arch Pharm (Weinheim)*, **2016**, *349* (7), 475–506.

(3) A. R. Katritzky, X. Lan, J. Z. Yang, O. v. Denisko., *Chemical Reviews*, **1998**, *98* (2), 409–548.

(4) Z. Wang, X. Deng, S. Xiong, R. Xiong, J. Liu, L. Zou, X. Lei, X. Cao, Z. Xie, Y. Chen, Y. Liu, X. Zheng, G. Tang., *Natural Product Research*, **2018**, *32* (24), 2900–2909.

(5) G. R. Morais, E. Palma, F. Marques, L. Gano, M. C. Oliveira, A. Abrunhosa, H. V. Miranda, T. F. Outeiro, I. Santos, A. Paulo., *Journal of Heterocyclic Chemistry*, **2017**, *54* (1), 255–267.

(6) V. Onnis, M. Demurtas, A. Deplano, G. Balboni, A. Baldisserotto, S. Manfredini, S. Pacifico, S. Liekens, J. Balzarini., *Molecules*, **2016**, *21* (5), 579.

(7) R. Sharma, A. Bali, B. B. Chaudhari., *Bioorganic & Medicinal Chemistry Letters*, **2017**, *27* (13), 3007–3013.

(8) M. M. Vandeputte, K. van Uytfanghe, N. K. Layle, D. M. st. Germaine, D. M. Iula, C. P. Stove., *ACS Chemical Neuroscience*, **2021**, *12* (7), 1241–1251.

(9) A. Noor, N. G. Qazi, H. Nadeem, A. ullah Khan, R. Z. Paracha, F. Ali, A. Saeed., *Chemistry Central Journal*, **2017**, *11* (85), 1–13.

(10) T. Iwahi, H. Satoh, M. Nakao, T. Iwasaki, T. Yamazaki, K. Kubo, T. Tamura, A. Imada., *Antimicrobial Agents and Chemotherapy*, **1991**, *35* (3), 490–496.

(11) N. S. El-Gohary, M. I. Shaaban., *European Journal of Medicinal Chemistry*, **2017**, *131*, 255–262.

(12) M. Taha, A. Mosaddik, F. Rahim, S. Ali, M. Ibrahim, N. B. Almandil., *Journal of King Saud University - Science*, **2020**, *32* (1), 191–194.

(13) B. Dik, D. Coşkun, E. Bahçivan, K. Üney., *Turkish Journal of Medical Sciences*, **2021**, *51* (3), 1585.

(14) A. Kanwal, M. Ahmad, S. Aslam, S. A. R. Naqvi, M. J. Saif., *Pharmaceutical Chemistry Journal*, **2019**, *53* (3), 179–187.

(15) H. Yang, Y. Ren, X. Gao, Y. Gao., *Chemical Research in Chinese Universities*, **2016**, *32* (6), 973–978.

(16) Y. Bansal, O. Silakari., *Bioorganic & Medicinal Chemistry*, **2012**, *20* (21), 6208–6236.

(17) K. P. Barot, S. Nikolova, I. Ivanov, M. D. Ghate., *Mini-Reviews in Medicinal Chemistry*, **2013**, *13* (10), 1421–1447.

(18) W. Akhtar, M. F. Khan, G. Verma, M. Shaquiquzzaman, M. A. Rizvi, S. H. Mehdi, M. Akhter, M. M. Alam., *European Journal of Medicinal Chemistry*, **2017**, *126*, 705–753.

(19) E. Mulugeta, Y. Samuel., *Biochemistry Research International*, **2022**, *2022* (Article ID 7255299).

(20) J. Horton., *Parasitology*, **2000**, *121* (Suppl. 1), S113–S132.

(21) S. Singh, N. Singh, V. Kumar, S. Datta, A. B. Wani, D. Singh, K. Singh, J. Singh., *Environmental Chemistry Letters*, **2016**, *14* (3), 317–329.

(22) P. Gosse., *Vascular Health and Risk Management*, **2006**, *2* (3), 195–201.

(23) D. M. Richards, R. N. Brogden, R. C. Heel, T. M. Speight, G. S. Avery., *Drugs*, **1984**, *28* (1), 38–61.

(24) H. Iqbal, A. K. Verma, P. Yadav, S. Alam, M. Shafiq, D. Mishra, F. Khan, K. Hanif, A. S. Negi, D. Chanda., *Frontiers in Pharmacology*, **2021**, *12* (Article ID 611109).

(25) H. Y. Aboul-Enein, A. A. El Rashedy., *Current Drug Therapy*, **2013**, *8* (3), 145–154.

(26) T. Ishida, T. Suzuki, S. Hirashima, K. Mizutani, A. Yoshida, I. Ando, S. Ikeda, T. Adachi, H. Hashimoto., *Bioorganic & Medicinal Chemistry Letters*, **2006**, *16* (7), 1859–1863.

(27) B. A. Reddy., *E-Journal of Chemistry*, **2010**, *7(1)* (Article ID 601929), 222–226.

(28) M. Nardi, S. Bonacci, N. H. Cano, M. Oliverio, A. Procopio., *Molecules*, **2022**, *27* (5), 1751.

(29) M. Taha, A. Ahmad Khan, F. Rahim, S. Imran, M. Salahuddin, N. Uddin, K. Mohammed Khan, S. Adnan Ali Shah, A. Zafar, Z. Amiruddin Zakaria., *Arabian Journal of Chemistry*, **2022**, *15* (1), 103505.

(30) Y. Chen, F. Xu, Z. Sun., *RSC Advances*, **2017**, *7* (70), 44421–44425.

(31) P. Thapa, P. M. Palacios, T. Tran, B. S. Pierce, F. W. Foss., *The Journal of Organic Chemistry*, **2020**, *85* (4), 1991–2009.

(32) D. Kumar, D. N. Kommi, R. Chebolu, S. K. Garg, R. Kumar, A. K. Chakraborti., *RSC Advances*, **2013**, *3* (1), 91–98.

(33) Y. R. Girish, K. S. Sharath Kumar, K. N. Thimmaiah, K. S. Rangappa, S. Shashikanth., *RSC Advances*, **2015**, *5* (92), 75533–75546.

(34) R. Chebolu, D. N. Kommi, D. Kumar, N. Bollineni, A. K. Chakraborti., *Journal of Organic Chemistry*, **2012**, *77* (22), 10158–10167.

(35) C. T. Brain, S. A. Brunton., *Tetrahedron Letters*, **2002**, *43* (10), 1893–1895.

(36) D. Anastasiou, E. M. Campi, H. Chaouk, W. R. Jackson., *Tetrahedron*, **1992**, *48* (36), 7467–7478.

(37) H. Naeimi, N. Alishahi., *Organic Chemistry International*, **2012**, *2012* (Article ID 498521), 1–5.

(38) R. J. Perry, B. D. Wilson., *Journal of Organic Chemistry*, **1993**, *58* (25), 7016–7021.

(39) M. J. Plater, P. Barnes, L. K. McDonald, S. Wallace, N. Archer, T. Gelbrich, P. N. Horton, M. B. Hursthouse., *Organic & Biomolecular Chemistry*, **2009**, *7* (8), 1633–1641.

(40) K. Das, A. Mondal, D. Srimani., *Journal of Organic Chemistry*, **2018**, *83* (16), 9553–9560.

(41) B. Zou, Q. Yuan, D. Ma., *Angewandte Chemie International Edition*, **2007**, *46* (15), 2598–2601.