



## A Green Synthesis of Benzimidazole Derivatives & Antibacterial Activity

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**Abstract :** A simple catalyst free synthetic method has been developed by the synthesis of Benzimidazole derivatives from 2-chloro benzimidazole and different types of amine derivatives using PEG-400 green solvent at room temperature. This method is simple, ecofriendly, rapid and generates 2-amino benzimidazole derivatives and good yield without use any catalysts. Newly synthesized compounds were screened for their antibacterial activity against E.Coli, Bacillus, Pseudomonas, S.aureus. The structure of benzimidazole derivatives were confirmed by using IR, <sup>1</sup>H NMR, Mass spectroscopy.

**Keywords :** 2-(chloromethyl)-1H-benzo[d]imidazole, catalyst free, PEG-400, Green synthesis.

### Introduction:

Benzimidazole is an important heterocyclic organic compound. It is having important pharmacophore and a privileged structure in medicinal chemistry. Benzimidazole derivatives is used in different ways such as antifungal<sup>1</sup>, antitubercular<sup>2</sup>, antioxidant, antiallergic<sup>3</sup>, antiparasitic<sup>4</sup>, herbicidal agent, human and veterinary medicine, anti-HIV<sup>5</sup>, anti-histaminic, anti-ulcer<sup>6</sup>, cardiotoxic, antihypertensive, antiviral, anticancer<sup>7</sup> activities. We now designed and synthesized a series of novel benzimidazole derivatives from 2-(chloromethyl)-1H-benzo[d]imidazole by applying the principles of green chemistry using PEG-400<sup>8</sup> as an alternative reaction medium. PEG is non-toxic, Inexpensive, potentially recyclable and water soluble, which facilitates it is easily removal from the reaction product.

### Experimental:

All the chemicals were used as purchased from sigma-Aldrich, Avra Laboratories. Solvents and reagents were obtained from commercial sources. TLC analyses were done on plastic sheets coated with silica gel G and spotting was done using Iodine/UV lamp. IR spectra were recorded on a Perkin Elmer model 1000 instrument in KBr Pellet. <sup>1</sup>H NMR was recorded in CDCl<sub>3</sub>/DMSO-d<sub>6</sub> using 400 MHz varian Gemini spectrometer and TMS as reference standard. Mass spectra were recorded on an Agilent-LCMS instrument.

### General procedure for the preparation of 4a:

A mixture of 3(0.6gr,10mmol),6-Benzylaminopurine (0.9gr,10mmol), K<sub>2</sub>CO<sub>3</sub>(1gr,20mmol), KI(0.3gr,3mmol) and different solvent such as Acetonitrile/1,4Dioxane/THF/ETOH/MeOH/DMF was heated at 80-100°C for 2-4 hr. the progress of reaction was monitored by TLC, after completion of reaction, mixture was diluted with water and extracted with Ethyl Acetate (2x25ml). The combined organic layer was washed with

water, brine and then dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The organic layer was distilled under reduced pressure, gave respectively 4a. [scheme 1, Table 1]

### General procedure for the preparation of 4(a-j) under PEG-400:

A mixture of powdered anhydrous K<sub>2</sub>CO<sub>3</sub> (1 gr, 20mmol), PEG-400, KI (0.3gr, 3mmol) and 6-Benzyl amino purine/different amine derivatives (10 mmol) was taken in a mortar and ground with a pestle for few minutes. To this mixture, starting material 3(10 mmol) was added and the whole mixture was ground with pestle in the mortar at room temperature. After sometime monitored by TLC after then, mixture was treated with ice-cold water (50ml). Product separated by filtration, washed with water and dried to obtain products of 4(a-j) room temperature. After sometime monitored by TLC after then, mixture was treated with ice-cold water (50 ml). Product separated by filtration, washed with water, and dried to obtain products of 4(a-j). In this products some compounds already reported such as

4-((1H-benzo[d]imidazol-2-yl)methyl)morpholine<sup>9</sup>, 2-(piperidin-1-ylmethyl)-1H-benzo[d]imidazole<sup>10</sup>, 2-(piperazin-1-ylmethyl)-1H-benzo[d]imidazole<sup>11</sup>, 2-(pyrrolidin-1-ylmethyl)-1H-benzo[d]imidazole<sup>12</sup>, 2-((4-methylpiperazin-1-yl)methyl)-1H-benzo[d]imidazole<sup>13</sup>, N-((1H-benzo[d]imidazol-2-yl)methyl)-1-phenylmethanamine<sup>14</sup>, N-((1H-benzo[d]imidazol-2-yl)methyl)-N-ethylethanamine<sup>15</sup>, N-((1H-benzo[d]imidazol-2-yl)methyl)butan-1-amine<sup>16</sup>. [Scheme 2, Table 2]

### N-((1H-benzo[d]imidazol-2-yl)methyl)-N-benzyl-7H-purin-6-amine (4a):

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 7.41ppm (d, 1H, Ar-H), 7.23(t, 1H, Ar-H), 7.23(t, 1H, Ar-H), 7.41(d, 1H, Ar-H), 5.4(s, 1H, NH), 4.9(s, 1H, CH<sub>2</sub>), 5.8(s, 1H, CH<sub>2</sub>), 12.5(d, 1H, NH), 8.5(d, 1H, CH), 7.9(s, 1H, CH), 7.25(d, 1H, Ar-H), 7.30(t, 1H, Ar-H), 7.28(t, 1H, Ar-H), 7.30(t, 1H, Ar-H), 7.26(d, 1H, Ar-H). <sup>13</sup>C NMR (400 MHz, DMSO-d<sub>6</sub>): 139.2ppm, 118.6, 127.3, 127.3, 118.6, 139.2, 143.6, 60.1, 57.8, 140.1, 129.6, 130.4, 129.2, 130.4, 129.6, 169.7, 124.5, 150.2, 153.9, 155.3 .

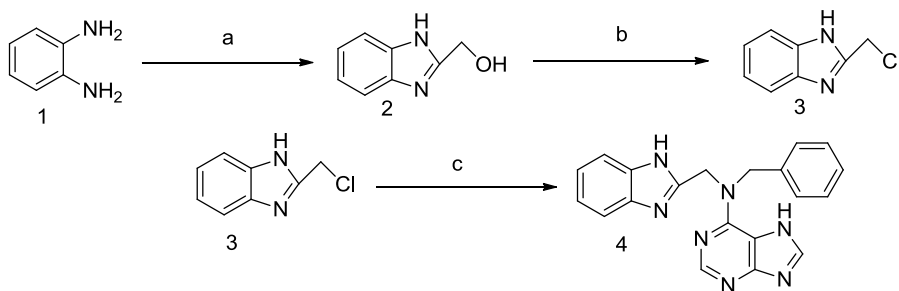
### N-((1H-benzo[d]imidazol-2-yl) methyl) butan-2-amine (4j):

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 7.41ppm (d, 1H, Ar-H), 7.23(t, 1H, Ar-H), 7.23(t, 1H, Ar-H), 7.41(d, 1H, Ar-H), 5.4(s, 1H, NH), 4.9 (d, 2H,CH<sub>2</sub>), 3.2(m, 1H, NH), 2.91(m, 1H, CH), 1.57(m, 1H, CH<sub>2</sub>), 1.23(d, 3H, CH<sub>3</sub>), 0.97(t, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (400MHz, DMSO-d<sub>6</sub>):139.2ppm, 118.6, 127.3, 127.3, 118.6, 139.2, 143.6, 49.3, 58.7, 33.2, 23.8, 11.9 .

## Results and Discussion:

### Scheme-1:

O-phenylene di amine (1) was treated with glycolic acid in presence of 4N HCL at reflux condition for 4hr obtained previously reported 1H-benzo[d]imidazole-2-yl)methanol<sup>17</sup>(2). Latter on treatment with SOCl<sub>2</sub> at room temperature for 2hr, obtained already reported 2-(chloromethyl)-1H-benzo[d]imidazole<sup>18</sup>(3). The reaction of (3) with 6-Benzyl amino purine, K<sub>2</sub>CO<sub>3</sub>, and KI under refluxing different solvents such as Acetonitrile, DMF, 1,4-Dioxane, MeOH, ETOH, THF, PEG-400, after then resulted in the formation of N-((1H-benzo[d]imidazol-2-yl)-N-benzyl-7H-purin-6-amine.



**Reagents & conditions:** a: glycolic acid, 4N HCl, reflux for 4hr b: SOCl<sub>2</sub>, room temperature for 2hr c: K<sub>2</sub>CO<sub>3</sub>, KI, Acetonitrile, DMF, 1,4-Dioxane, THF, MeOH, ETOH, PEG-400, 6-benzyl amino purine.

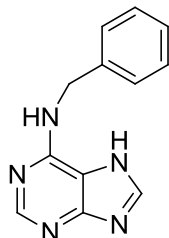
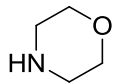
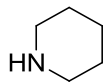
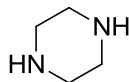

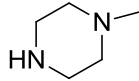
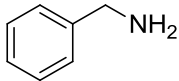
The reaction of (3) with 6-benzyl amino purine in presence of different solvents and different reaction conditions, reaction is monitored by TLC and subsequent workup yielded product identical with one to each one, in all respects characterized by comparison with IR, M.P Data. PEG-400 use as a solvent, obtained good yield compared to remaining all solvent systems.


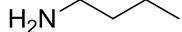
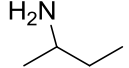
Entry	Solvent	Time/min.	Yield(%)
1	Solvent-free	600	-
2	Acetonitrile	160	74
3	DMF	175	68
4	THF	200	80
5	1,4-Dioxane	190	82
6	MeOH	225	60
7	ETOH	210	65
8	PEG-400	40	96

### Scheme-2:

Reaction between 3 and 6-Benzyl amino purine in the presence of PEG-400 we obtained good yield and less time. PEG-400 has been found to be a general one and has been extended to different nitrogen nucleophilic substrates such as 6-Benzyl amino purine, Isobutyl amine, Piperidine, Morpholine, pyrrolidine, Benzyl amine, Diethylamine, Piperazine, Methyl piperazine, n-Butyl amine.

**Table-2: Preparation of Benzimidazole derivatives in presence of PEG-400 Solvent.**

S.no.	Starting material	Reactent	Product	Time/min.	Yield(%)
1	3		4a	50min.	88
2	3		4b	30min.	94
3	3		4c	35min.	90
4	3		4d	45min	80
5	3		4e	30min.	84
6	3		4f	50min.	88
7	3		4g	70min.	72

8	3		4h	35min.	80
9	3		4i	78min.	85
10	3		4j	85min	90

### Biological Activity:

Newly synthesized compounds were screened for antibacterial activity study purpose micro-organisms employed were Gram positive (Bacillus, S.aureus), Gram negative (E.Coli, Pseudomonas).

**Table-3: Antibacterial activity (Diameters in mm of zone of inhibition)**

s.no.	product	E.Coli(mm)	Bacillus(mm)	S.aureus(mm)	Pseudomonas
1	4a	24	28	20	21
2	4b	25	22	18	16
3	4c	22	19	13	12
4	4d	16	17	14	18
5	4e	13	11	10	10
6	4f	11	11	<10	<10
7	4g	12	10	13	10
8	4h	13	10	11	11
9	4i	15	13	13	12
10	4j	16	18	19	14

### Conclusion:

In summary, we have developed a simple and efficient method for preparation of new Benzimidazole derivatives in solution phase and also under catalyst-free conditions using PEG-400 at room temperature. Present protocol has several advantages, particularly catalyst-free condition, during workup, water was used which is free from organic solvent, readily available catalyst.

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