

## Synthesis and Molecular Docking for Antiinflammatory Studies of 2-(Arylmethyl)-1-ethyl-1*H*-benzo[*d*]imidazol-5-amines

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1-Chloro-2,4-dinitrobenzene (**1**) was reacted with aliphatic amines (**2**) in ethanol as solvent under reflux condition for 16-24 h to form N-alkyl-2,4-dinitroaniline (**3**). Compound **3** undergoes reduction to form N-alkyl-4-nitrobenzene-1,2-diamine (**4**). Compound **4** was treated with carboxylic acid (**5**) to offer N-(2-(alkylamino)-5-nitrophenyl)-2-arylacamide (**6**) which on cyclization gave 2-(arylmethyl)-1-ethyl-5-nitro-1*H*-benzo[*d*]imidazole (**7**). Finally, compound **7** undergoes reduction give 2-(arylmethyl)-1-ethyl-1*H*-benzo[*d*]imidazol-5-amine (**8**). The synthesized compounds were characterized by using spectral analyses. The compounds synthesized were confirmed by spectral analyses. Molecular docking of 5COX with the ligand using docking server, predicted the compound to be a potential anti-inflammatory compound.

**Keywords:** N-alkyl-4-nitrobenzene-1,2-diamine, Benzimidazole, Antiinflammatory activity, Molecular docking.

### INTRODUCTION

Benzimidazole derivatives keep up a correspondence to most biologically active course of drugs, showing a broad range of actions. They prove selective neuropeptides YY1 receptor antagonists [1], antitumor agents [2], potent inhibitors of TIE-2 and VEGFER-2 tyrosine kinase receptors [3] and 5-HT3 antagonists [4]. Other benzimidazole compounds initiate commercial use in veterinarian medication as anthelmintic agents and in various human therapeutic areas such as handling of antihistaminic and ulcers [5].

Likewise, the common preparation of these compounds is by the condensation reaction of 1,2-phenylenediamine with carboxylic acids, carboxaldehydes [6,7], or their derivatives [8,9] such as, nitriles, chlorides and *ortho*-esters under strong acidic conditions. These have also been synthesized by combinatorial and solid phase approach [10,11]. Ammonium salts are economical, commercially available reagents for few organic alteration reactions such as halogenation of aromatic compounds and synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones [12]. A few articles also illustrate that benzimidazoles show antianxiety activity [13]. In view of biological importance of benzimidazole derivatives we have taken up the synthesis of 2-(arylmethyl)-1-ethyl-1*H*-benzo[*d*]imidazol-5-amines.

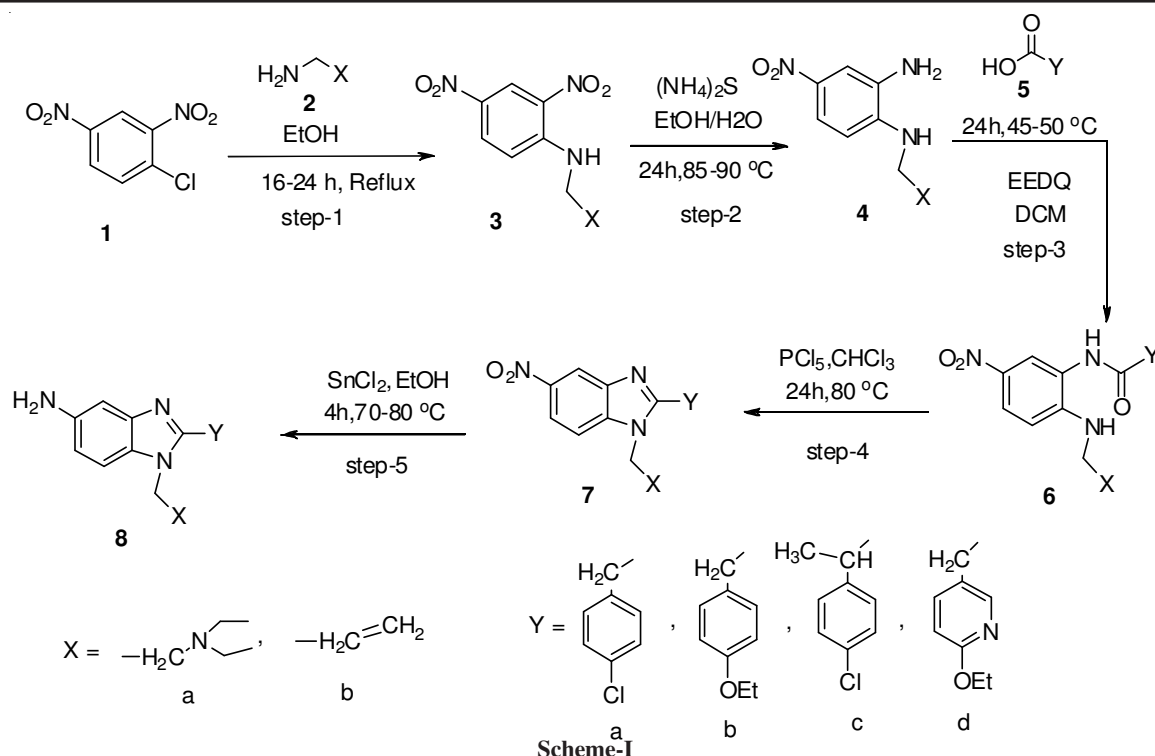
### EXPERIMENTAL

Melting points were uncorrected which were obtained in open capillary tubes in H<sub>2</sub>SO<sub>4</sub> bath. Thin layer chromatography was run on silica gel-G and visualization was done using UV light or iodine. IR spectra were recorded by Perkin-Elmer 1000 instrument in KBr pellets. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> solvent using tetramethylsilane as internal standard by 400 MHz spectrometer. By Jeol-JMS D-300 spectrometer, mass spectra were recorded. Starting materials which were used in this chapter were obtained by commercial sources and used as such.

Docking calculations were carried out using Docking Server. Docking calculations were carried out on 5COX (Cyclooxygenase) which plays a crucial role in inflammation with the ligand compound obtained from **Scheme-I** [14,15].

### RESULTS AND DISCUSSION

1-Chloro-2,4-dinitrobenzene (**1**) was reacted with aliphatic amine analogues (**2**) in ethanol as solvent under reflux condition for 16-24 h to form N-alkyl-2,4-dinitroaniline (**3**). Compound **3** undergoes selective reduction in the presence of (NH<sub>4</sub>)<sub>2</sub>S in EtOH as solvent at 80 °C for 24 h to form N-alkyl-4-nitrobenzene-1,2-diamine (**4**). Then **4** was treated with carboxylic



acid **5** in the presence of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) in dichloromethane as solvent at 45 °C for 48 h to yield N-[2-(alkylamino)-5-nitrophenyl]-2-arylacetaimide (**6**) which undergoes cyclization in the presence of  $\text{PCl}_5$  to give 2-(arylmethyl)-1-ethyl-5-nitro-1*H*-benzo[*d*]-imidazole (**7**). Finally, compound **7** undergoes reduction to change  $\text{---NO}_2$  group to  $\text{---NH}_2$  with  $\text{SnCl}_2$  in EtOH at room temperature for 3 h to give 2-(arylmethyl)-1-ethyl-1*H*-benzo[*d*]-imidazol-5-amine (**8**). The mass spectrum of the compound **8(a)** showed the molecular ion peak at  $m/z$  357 corresponding to molecular formula. The IR spectrum of the compound showed the absence of absorption for  $\text{---NH}$  group at  $3420\text{ cm}^{-1}$  and the  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) showed the signals at  $\delta$  0.8 for methyl protons,  $\delta$  2.5,  $\delta$  2.7,  $\delta$  4.2,  $\delta$  4.4, for  $\text{CH}_2$  protons,  $\delta$  4.8 for  $\text{---NH}_2$  ( $\text{D}_2\text{O}$  exchangeable),  $\delta$  7.2-8.8 aromatic protons. This data conforms the structure of **8(a)** and in the similar way the structures of others **8(b-e)** were confirmed.

**Preparation of N'-(2,4-dinitro-phenyl)-N,N-diethyl-ethane-1,2-diamine (3a):** To a stirred solution of 1-chloro-2,4-dinitrobenzene (10 mmol) in EtOH (15 mL) was added *N,N*-diethyl ethylene diamine (12 mmol) at room temperature and then refluxed for 16 h. It was diluted with water (20 mL) and made alkaline to  $\text{pH} = 10$  using conc.  $\text{NH}_3$  to obtain yellow solid. The yellow solid thus obtained was filtered and dried under vacuum to afford 90 % of N'-(2,4-dinitro-phenyl)-N,N-diethyl-ethane-1,2-diamine (**3a**) as a yellow solid.

m.p.: 180-186 °C; IR (KBr pellets):  $3465\text{ cm}^{-1}$  (broad,  $\text{---NH}$  group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  1.1 (t, 6H,  $\text{---CH}_3$ ), 2.6 (q, 4H,  $\text{---CH}_2$ ), 2.8 (t, 2H,  $\text{---CH}_2$ ), 3.2 (t, 2H,  $\text{---CH}_2$ ), 6.8-9.2 (m, 3H, Ar-H), 9.1 (s, 1H,  $\text{---NH}$ ,  $\text{D}_2\text{O}$  exchangeable);  $M^+1$ : 282.

**Preparation of allyl-(2,4-dinitrophenyl)amine (3b):** To a stirred solution of 1-chloro-2,4-dinitrobenzene (10 mmol) in ethanol (30 mL) was added allyl amine (12 mmol) at room

temperature. The reaction mixture was heated to reflux (80 °C) for 24 h. It was cooled to 0 °C and made alkaline with aqueous  $\text{NH}_3$  solution up to  $\text{pH} = 8$ , to obtain 70 % of allyl-(2,4-dinitrophenyl)amine as a yellow solid. It was filtrated and dried well.

m.p.: 175-177 °C; IR (KBr pellets):  $3468\text{ cm}^{-1}$  (broad,  $\text{---NH}$  group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  3.8 (d, 2H,  $\text{---CH}_2$ ), 5.2 (t, 2H,  $\text{---CH=CH}$ ), 6.2-7.4 (m, 3H, Ar-H), 7.2 (s, 2H,  $\text{---NH}$ ,  $\text{D}_2\text{O}$  exchangeable);  $M^+1$ : 223.

**Preparation of N-(2-diethylamino-ethyl)-4-nitro-benzene-1,2-diamine (4a):** To a stirred solution of N'-(2,4-dinitro-phenyl)-N,N-diethyl-ethane-1,2-diamine **3a** (10 mmol) in EtOH (10 mL) was added a pre-mixed solution of aqueous ammonium sulphide (48-50 %) (30 mmol) in EtOH (50 mL) and water (25 mL), at 60 °C for 30 min and then heated to 80-85 °C for 20 h. It was cooled to 0 °C and adjusted to  $\text{pH} = 1$  using 2 N HCl. The reaction contents were evaporated, made alkaline using conc.  $\text{NH}_3$  and extracted with dichloromethane ( $2 \times 30\text{ mL}$ ). The combined organic layer was washed with water (15 mL), brine solution (15 mL), dried over (anhyd.  $\text{Na}_2\text{SO}_4$ ) and concentrated. The crude compound was purified by column chromatography over silica gel (100-200 mesh) using a gradient of 0-10 % of MeOH:  $\text{CHCl}_3$  as eluent to afford 55 % of N-(2-diethylamino-ethyl)-4-nitro-benzene-1,2-diamine (**4a**) as a yellow solid.

m.p.: 182-184 °C; IR (KBr pellets):  $3455\text{ cm}^{-1}$  (broad,  $\text{---NH}$  group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  1.1 (t, 6H,  $\text{---CH}_3$ ), 2.6 (q, 4H,  $\text{---CH}_2$ ), 2.8 (t, 2H,  $\text{---CH}_2$ ), 3.2 (t, 2H,  $\text{---CH}_2$ ), 3.4 (s, 2H,  $\text{---NH}$ ,  $\text{D}_2\text{O}$  exchangeable), 5.1 (s, 1H,  $\text{---NH}$ ,  $\text{D}_2\text{O}$  exchangeable), 6.5-7.8 (m, 3H, Ar-H);  $M^+1$ : 252.

**Preparation of N'-allyl-4-nitro-benzene-1,2-diamine (4b):** To a stirred solution of allyl-(2,4-dinitrophenyl) amine (**3b**) (10 mmol) in ethanol (20 mL) was added a mixture of ammonium sulphide (30 mmol), ethanol (20 mL) and water (20 mL) slowly drop-wise at 50 °C. After the addition the reac-

tion mixture was heated to 90 °C for 20 h. It was cooled to 0 °C, acidified with 2 N HCl up to pH 2, distilled off the solvent from it and made alkaline with aqueous NH<sub>3</sub> solution up to pH 8. From which the product was isolated by extraction with EtOAc (2 × 30 mL). The organic layer was washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), evaporated under reduced pressure and the residue was purified by flash column chromatography over silica gel (100-200 mesh) using a gradient mixture of 1.5 % of methanol + chloroform as eluent to afford 75 % of N'-allyl-4-nitro-benzene-1,2-diamine (**4b**) as a white red colour gummy material.

m.p.: 165-167 °C; IR (KBr pellets): 3459 cm<sup>-1</sup> (broad, -NH group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 3.8 (d, 2H, -CH<sub>2</sub>), 5.1 (t, 2H, -CH=CH), 5.1 (s, 2H, -NH, D<sub>2</sub>O exchangeable), 6.2 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.4-7.6 (m, 3H, Ar-H); M<sup>+</sup>1: 193.

**Preparation of 2-aryl-N-[2-((2-(diethylamino)ethyl)-amino)-5-nitrophenyl]acetamide (6a-d):** To a solution of **6a** (10 mmol) in dichloromethane was added **5a-5d** (12 mmol) and EEDQ (10 mmol) and the resulting mixture was heated to reflux (50 °C) for 24 h. Reaction mass was diluted with dichloromethane (30 mL) and basify with aqueous NH<sub>3</sub> solution pH 8. Dichloromethane layer was washed with water (25 mL), brine solution (10 mL), dried over anhydrous sodium sulphate, filtrated and concentrated to obtain the crude material. The crude material was purified over silica gel (100-200 mesh) column chromatography using 2 % CH<sub>3</sub>OH + CHCl<sub>3</sub> as eluent to get 45-55 % yield of gummy material **6a-6d**.

**2-(4-Chlorophenyl)-N-[2-((2-(diethylamino)ethyl)-amino)-5-nitrophenyl]acetamide (6a):** m.p.: 182-184 °C; IR (KBr pellets): 3443 cm<sup>-1</sup> (broad, -NH group), 1689 cm<sup>-1</sup> (broad, -NH-CO group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 1.1 (t, 6H, -CH<sub>3</sub>), 2.7 (q, 4H, -CH<sub>2</sub>), 2.9 (t, 2H, -CH<sub>2</sub>), 3.3 (t, 2H, -CH<sub>2</sub>), 3.8 (s, 2H, CO-CH<sub>2</sub>), 5.9 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 7.6 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.5-8.2 (m, 7H, Ar-H); M<sup>+</sup>1: 405.

**N-[2-((2-(Diethylamino)ethyl)amino)-5-nitrophenyl]-2-(4-ethoxyphenyl)acetamide (6b):** m.p.: 190-192 °C; IR (KBr pellets): 3446 cm<sup>-1</sup> (broad, -NH group), 1684 cm<sup>-1</sup> (broad, -NH-CO group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 1.1 (t, 6H, -CH<sub>3</sub>), 1.5 (t, 3H, -CH<sub>3</sub>), 2.5 (q, 4H, -CH<sub>2</sub>), 2.9 (t, 2H, -CH<sub>2</sub>), 3.1 (t, 2H, -CH<sub>2</sub>), 3.7 (s, 2H, CO-CH<sub>2</sub>), 4.0 (t, 2H, -OCH<sub>2</sub>), 5.5 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.8 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.5-8.2 (m, 7H, Ar-H); M<sup>+</sup>1: 415.

**2-(4-Chlorophenyl)-N-[2-((2-(diethylamino)ethyl)-amino)-5-nitrophenyl]acetamide (6c):** m.p.: 195-197 °C; IR (KBr pellets): 3448 cm<sup>-1</sup> (broad, -NH group), 1684 cm<sup>-1</sup> (broad, -NH-CO group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 1.0 (t, 6H, -CH<sub>3</sub>), 1.8 (q, 4H, -CH<sub>2</sub>), 2.5 (d, 3H, -CH<sub>3</sub>), 2.7 (t, 2H, -CH<sub>2</sub>), 3.2 (t, 2H, -CH<sub>2</sub>), 3.7 (t, 1H, CO-CH), 5.2 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.8 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.5-8.1 (m, 7H, Ar-H); M<sup>+</sup>1: 419.

**N-[2-((2-(Diethylamino)ethyl)amino)-5-nitrophenyl]-2-(6-ethoxypyridin-3-yl)acetamide (6d):** m.p.: 180-182 °C; IR (KBr pellets): 3453 cm<sup>-1</sup> (broad, -NH group), 1685 cm<sup>-1</sup> (broad, -NH-CO group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 1.1 (t, 6H, -CH<sub>3</sub>), 1.4 (t, 3H, -CH<sub>3</sub>), 2.5 (q, 4H, -CH<sub>2</sub>), 2.8 (t, 2H, -CH<sub>2</sub>), 3.2 (t, 2H, -CH<sub>2</sub>), 3.7 (s, 2H, CO-CH<sub>2</sub>), 4.1 (t, 2H,

-OCH<sub>2</sub>), 5.6 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.8 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.6-8.1 (m, 6H, Ar-H); M<sup>+</sup>1: 416.

**Preparation of 2-(4-chlorophenyl)-N-[2-((2-(diethylamino)ethyl)amino)-5-nitrophenyl]propanamide (6e):** To a solution of **4b** (10 mmol) in dichloromethane was added 4-chlorophenyl acetic acid (**5a**) (12 mmol) and EEDQ (10 mmol) and the resulting mixture was heated to reflux (50 °C) for 24 h. Reaction mass was diluted with dichloromethane (30 mL) and basify with aqueous NH<sub>3</sub> solution pH 8. Dichloromethane layer was washed with water (25 mL), brine solution (10 mL), dried over anhydrous sodium sulphate, filtrated and concentrated to obtain the crude material. The crude material was purified over silica gel (100-200 mesh) column chromatography using 2 % methanol + CHCl<sub>3</sub> as eluent to get 55 % yield of gummy material **6e**.

m.p.: 175-177 °C; IR (KBr pellets): 3446 cm<sup>-1</sup> (broad, -NH group), 1682 cm<sup>-1</sup> (broad, -NH-CO group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 3.2 (d, 2H, -CH<sub>2</sub>), 3.9 (s, 2H, -CH<sub>2</sub>), 5.2 (t, 2H, -CH=CH), 6.9 (s, 1H, -NH, D<sub>2</sub>O exchangeable), 6.4-7.6 (m, 7H, Ar-H), 10.1 (s, 1H, -NH, D<sub>2</sub>O exchangeable); M<sup>+</sup>1: 356.

**Preparation of 2-(arylmethyl)-1-ethyl-5-nitro-1*H*-benzo[d]imidazole 7(a-d):** To a solution of **6(a-d)** (10 mmol) in CHCl<sub>3</sub> (50 mL) was added PCl<sub>5</sub> (20 mmol) and heated to reflux (80 °C) for 24 h. Reaction mass was cooled to room temperature and basify with aqueous NH<sub>3</sub> solution. Then CHCl<sub>3</sub> layer was separated and washed with water (20 mL), brine solution (20 mL), dried over anhydrous sodium sulphate solution, filtrated and concentrated to obtain the crude product **7(a-d)**.

**2-[2-(4-Chlorobenzyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl]-N,N-diethylethanamine (7a):** m.p.: 200-202 °C; IR (KBr pellets): 3052 cm<sup>-1</sup> (stretching, -CH group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 0.8 (t, 6H, -CH<sub>3</sub>), 2.5 (q, 4H, -CH<sub>2</sub>), 2.7 (t, 2H, -CH<sub>2</sub>), 4.2 (t, 2H, -CH<sub>2</sub>), 4.4 (s, 2H, -CH<sub>2</sub>), 7.2-8.8 (m, 7H, Ar-H); M<sup>+</sup>1: 387.

**2-[2-(4-Ethoxybenzyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl]-N,N-diethylethanamine (7b):** m.p.: 205-207 °C; IR (KBr pellets): 3042 cm<sup>-1</sup> (Stretching, -CH group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 0.8 (t, 6H, -CH<sub>3</sub>), 1.3 (t, 3H, -CH<sub>3</sub>), 2.4 (q, 4H, -CH<sub>2</sub>), 2.6 (t, 2H, -CH<sub>2</sub>), 4.0 (t, 2H, -CH<sub>2</sub>), 4.1 (t, 2H, -OCH<sub>2</sub>), 4.4 (s, 2H, CO-CH<sub>2</sub>), 6.8-8.8 (m, 7H, Ar-H); M<sup>+</sup>1: 415.

**2-[2-{1-(4-Chlorophenyl)ethyl}-5-nitro-1*H*-benzo[d]imidazol-1-yl]-N,N-diethylethanamine (7c):** m.p.: 208-210 °C; IR (KBr pellets): 3048 cm<sup>-1</sup> (Stretching, -CH group); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 0.8 (t, 6H, -CH<sub>3</sub>), 1.8 (d, 3H, -CH<sub>3</sub>), 2.4 (q, 4H, -CH<sub>2</sub>), 2.6 (t, 1H, -CH), 4.0 (t, 2H, -CH<sub>2</sub>), 4.5 (t, 2H, -CH<sub>2</sub>), 7.1-8.8 (m, 7H, Ar-H); M<sup>+</sup>1: 401.

**2-[2-((6-Ethoxypyridin-3-yl)methyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl]-N,N-diethylethanamine (7d):** m.p.: 203-205 °C; IR (KBr pellets): 3040 cm<sup>-1</sup> (Stretching, -CH group); -NH group; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS): δ 0.7 (t, 6H, -CH<sub>3</sub>), 1.3 (t, 3H, -CH<sub>3</sub>), 2.4 (q, 4H, -CH<sub>2</sub>), 2.6 (t, 2H, -OCH<sub>2</sub>), 4.2 (t, 4H, -CH<sub>2</sub>), 4.4 (s, 2H, -CH<sub>2</sub>), 6.8-8.6 (m, 6H, Ar-H); M<sup>+</sup>1: 398.

**Preparation of 1-allyl-2-(4-chlorobenzyl)-5-nitro-1*H*-benzo[d]imidazole (7e):** To a solution of **6(a-d)** (10 mmol) in

$\text{CHCl}_3$  (50 mL) was added  $\text{PCl}_5$  (20 mmol) and heated to reflux (80 °C) for 24 h. Reaction mass was cooled to room temperature and basified with aqueous  $\text{NH}_3$  solution, Then  $\text{CHCl}_3$  layer was separated and washed with water (20 mL), brine solution (20 mL), dried over anhydrous sodium sulphate solution, filtrated and concentrated to obtain the crude product **7 (a-d)**.

m.p.: 207-209 °C; IR (KBr pellets): 3044  $\text{cm}^{-1}$  (Stretching, -CH group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  3.0 (d, 2H, - $\text{CH}_2$ ), 3.2 (s, 2H, - $\text{CH}_2$ ), 5.2 (t, 2H, - $\text{CH}=\text{CH}$ ), 6.2-7.8 (m, 7H, Ar-H);  $M^+1$ : 328.

**Preparation of 2-(arylmethyl)-1-ethyl-1H-benzo[d]imidazol-5-amine 8(a-d):** To a solution of **7(a-d)** (10 mmol) in ethanol was added  $\text{SnCl}_2$  (30 mmol) and conc. HCl (catalytic amount) and the resulting mixture was heated to 70-80 °C for 4 h. Reaction mass was cooled to 0 °C and basified using aqueous NaOH solution (5 mL) to pH 9. Aqueous layer was extracted with EtOAc (2 × 50 mL). Combined EtOAc layer was washed with water (20 mL), brine solution (20 mL), dried over anhydrous sodium sulphate, filtrated and concentrated to obtain the crude product. The crude material was purified over silica gel (100-200 mesh) column chromatography with 2.5 %  $\text{CH}_3\text{OH} + \text{CHCl}_3$  as eluent.

**2-(4-Chlorobenzyl)-1-[2-(diethylamino)ethyl]-1H-benzo[d]imidazol-5-amine (8a):** m.p.: 220-222 °C; IR (KBr pellets): 3420  $\text{cm}^{-1}$  (broad, -NH group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  0.8 (t, 6H, - $\text{CH}_3$ ), 2.5 (q, 4H, - $\text{CH}_2$ ), 2.7 (t, 2H, - $\text{CH}_2$ ), 4.2 (t, 2H, - $\text{CH}_2$ ), 4.4 (s, 2H, - $\text{CH}_2$ ), 4.8 (s, 2H, -NH,  $\text{D}_2\text{O}$  exchangeable), 7.2-8.8 (m, 7H, Ar-H);  $M^+1$ : 357.

**1-[2-(Diethylamino)ethyl]-2-(4-ethoxybenzyl)-1H-benzo[d]imidazol-5-amine (8b):** m.p.: 212-214 °C; IR (KBr pellets): 3426  $\text{cm}^{-1}$  (broad, -NH group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  0.8 (t, 6H, - $\text{CH}_3$ ), 1.3 (t, 3H, - $\text{CH}_3$ ), 2.4 (q, 4H, - $\text{CH}_2$ ), 2.6 (t, 2H, - $\text{CH}_2$ ), 4.0 (t, 2H, - $\text{CH}_2$ ), 4.1 (t, 2H, - $\text{OCH}_2$ ), 4.4 (s, 2H, - $\text{CO-CH}_2$ ), 4.8 (s, 2H, -NH,  $\text{D}_2\text{O}$  exchangeable), 6.8-8.8 (m, 7H, Ar-H);  $M^+1$ : 367.

**2-[1-(4-Chlorophenyl)ethyl]-1-(2-(diethylamino)ethyl)-1H-benzo[d]imidazol-5-amine (8c):** m.p.: 219-221 °C; IR (KBr pellets): 3424  $\text{cm}^{-1}$  (broad, -NH group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  0.8 (t, 6H, - $\text{CH}_3$ ), 1.8 (d, 3H, - $\text{CH}_3$ ), 2.4 (q, 4H, - $\text{CH}_2$ ), 2.6 (t, 1H, -CH), 4.0 (t, 2H, - $\text{CH}_2$ ), 4.5 (t, 2H, - $\text{CH}_2$ ), 4.8 (s, 2H, -NH,  $\text{D}_2\text{O}$  exchangeable), 7.1-8.8 (m, 7H, Ar-H);  $M^+1$ : 371.

**1-[2-(Diethylamino)ethyl]-2-((6-ethoxypyridin-3-yl)methyl)-1H-benzo[d]imidazol-5-amine (8d):** m.p.: 222-224 °C; IR (KBr pellets): 3414  $\text{cm}^{-1}$  (broad, -NH group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  0.7 (t, 6H, - $\text{CH}_3$ ), 1.3 (t, 3H, - $\text{CH}_3$ ), 2.4 (q, 4H, - $\text{CH}_2$ ), 2.6 (t, 2H, - $\text{OCH}_2$ ), 4.2 (t, 4H, - $\text{CH}_2$ ), 4.4 (s, 2H, - $\text{CH}_2$ ), 4.8 (s, 2H, -NH,  $\text{D}_2\text{O}$  exchangeable), 6.8-8.6 (m, 6H, Ar-H);  $M^+1$ : 368.

**Preparation of 1-allyl-2-(4-chlorobenzyl)-1H-benzo[d]imidazol-5-amine (8e):** To a solution of **7(a-d)** (10 mmol) in ethanol was added  $\text{SnCl}_2$  (30 mmol) and conc HCl (catalytic amount) and the resulting mixture was heated to 70-80 °C for

4 h. Reaction mass was cooled to 0 °C and basified using aqueous NaOH solution (5 mL) to pH 9. Aqueous layer was extracted with EtOAc (2 × 50 mL). Combined EtOAc layer was washed with water (20 mL), brine solution (20 mL), dried over anhydrous sodium sulphate, filtrated and concentrated to obtain the crude product. The crude material was purified over silica gel (100-200 mesh) column chromatography with 2.5 %  $\text{CH}_3\text{OH} + \text{CHCl}_3$  as eluent.

m.p.: 225-227 °C; IR (KBr pellets): 3453  $\text{cm}^{-1}$  (broad, -NH group);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  2.9 (d, 2H, - $\text{CH}_2$ ), 3.1 (s, 2H, - $\text{CH}_2$ ), 4.9 (s, 2H, -NH,  $\text{D}_2\text{O}$  exchangeable), 5.1 (t, 2H, - $\text{CH}=\text{CH}$ ), 6.2-7.8 (m, 7H, Ar-H);  $M^+1$ : 328.

Molecular docking of 5COX (cyclooxygenase) with ligand using docking server, predicted a free energy of -4.51 kcal/mol making the title compound a probable potent anti-inflammatory compound. Inhibition constant was 490.36  $\mu\text{M}$  which predicts that the ligand is going to inhibit enzyme. The interaction between the first ligand and the target enzyme are presented in the Fig. 1. Tables 1-3 shows the interaction energies and various bonds involved in the substrate binding to the ligand.

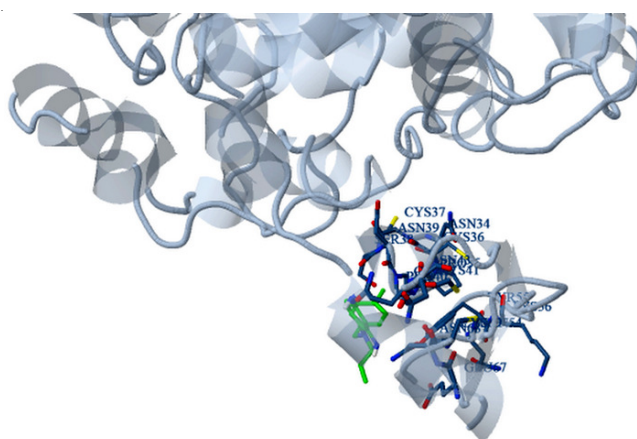


Fig. 1. Interaction between the ligand and the target enzyme

TABLE-2  
DECOMPOSED INTERACTION ENERGIES (kcal/mol)

Hydrogen bonds	Polar	Hydrophobic	Other
TYR55 (-0.7878)	ASN68 (-0.9031)	PRO40 (-1.3755)	SER38 (-0.8517)
GLN42 (-0.4032)	—	—	—

## Conclusion

Facile synthesis of the title compounds benzimidazole amines was achieved. Molecular docking of 5COX with ligand showed that the benzimidazole amine compound synthesized was a potent anti-inflammatory compounds.

TABLE-1  
ESTIMATED DIFFERENT PHYSICAL PARAMETERS BETWEEN SECOND LIGAND AND THE ENZYME

Est. free energy of binding	Est. inhibition constant ( $K_i$ )	vdW + Hbond + desolv energy	Electrostatic energy	Total Intermolec. energy	Frequency	Interact. surface
-4.51 kcal/mol	490.36 $\mu\text{M}$	-5.67 kcal/mol	+0.01 kcal/mol	-5.66 kcal/mol	50 %	510.746



TABLE-3  
INTERACTING BONDS BETWEEN THE LIGAND AND THE ENZYME

Hydrogen bonds		Polar		Hydrophobic		Other	
N' ()	GLN42 (CD,	H4 ()	GLN42	C1 ()	PRO40	C4 ()	SER38
[2.63]	NE2, OE1)	[2.29]	(NE2, OE1)	[3.78]	(CB)	[3.57]	(CB, OG)
N3 ()	TYR55 (OH)	H5 ()	GLN42	C6 ()	PRO40	C15 ()	SER38
[3.33]		[2.19]	(OE1)	[3.71]	(CB)	[3.48]	(CB, OG)
		H7 ()	TYR55			C16 ()	SER38
		[3.74]	(OH)			[3.47]	(CB, OG)
		N3 ()	ASN68			C11 ()	SER38
		[3.27]	(ND2, OD1)			[3.44]	(OG)
		H7 ()	ASN68			C12 ()	SER38
		[2.62]	(ND2, OD1)			[3.42]	(OG)
						C13 ()	SER38
						[3.43]	(OG)
						C14 ()	SER38
						[3.45]	(OG)
						H4 ()	GLN42
						[2.99]	(CD)
						H5 ()	GLN42
						[3.35]	(CD)
						C2 ()	GLN42
						[3.84]	(OE1)
						C7 ()	TYR55
						[3.87]	(OH)
						N3 ()	ASN68
						[3.88]	(CG)
						H7 ()	ASN68
						[3.52]	(CG)
						C1 ()	ASN68
						[3.82]	(ND2)

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