



# Synthesis, Spectral Analysis, DFT and Antimicrobial of Some Novel Benzimidazole Derivatives

C. M. Mahalakshmi

Assistant Professor, Department of Chemistry, Faculty of Science  
Krishnasamy College of Science, Arts and Management for Women,  
Cuddalore, Tamil Nadu, India

## ABSTRACT

Two novel 2-substituted benzimidazole derivatives were synthesized from 2-chloromethyl-1H-benzimidazole and 2-(2-chlorophenyl)-1H-benzo[d]imidazole with 1H-1,2,4-triazol-3-amine. Their structures were characterized by Infrared spectroscopy, Nuclear magnetic resonance, ( $^1\text{H}$ ,  $^{13}\text{C}$ ), Elemental analysis. Density functional theory (DFT) studies were performed using the B3LYP/6-31G (d, p) basis set to expand imminent into their structural properties. All the synthesized compounds were screened for antimicrobial activity against a panel of selected bacterial and fungal strains using ciprofloxacin and fluconazole as standards.

**Keywords:** 2-chloromethyl-1H-benzimidazole, 2-(2-chlorophenyl)-1H-benzo[d]imidazole, 1H-1,2,4-triazol-3-amine, IR & NMR spectral data, DFT and Antimicrobial efficiency

## 1. INTRODUCTION

N-heterocycles represent the largest and manifold family of organic compounds and play a significant role in biology and technology, for instance as building blocks of DNA and amino acids or as natural and artificial dyes and pigments. Among them Benzimidazole derivatives possessed various biological activities such as anticancer<sup>1</sup>, antihypertensive<sup>2</sup>, anthelmintic<sup>3,4</sup>, antiprotozoal<sup>5-6</sup>, antimicrobial<sup>7-11</sup>. Benzimidazole in an extension of well-elaborated imidazole system has been used as carbon skeletons for N-heterocyclic carbenes. The most prominent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serve as an

axial ligand for cobalt in vitamin B<sub>12</sub><sup>12</sup>. Furthermore, the relative ease of preparation and great activity of some of benzimidazole derivatives make them promising precursors for preparation of variety of biologically active compounds. Furthermore, benzimidazole moiety is a crucial template in medicinal chemistry, because of its wide range of therapeutic areas. Optimization of substituent around the benzimidazole nucleus has resulted in many drugs like albendazole, mebendazole, thiabendazole as anthelmintic, omeprazole, lansoprazole, pantoprazole as proton pump inhibitors. Though all seven positions in the benzimidazole nucleus can be substituted with a variety of chemical entities, but most of the biologically active benzimidazole base compounds been functional groups at 1, 2 and (or) 5 (or) 6 positions. Based on these findings the aim of this study was to synthesize a novel products of benzimidazole derivatives derived from 2-chloromethyl-1H-benzimidazole and 2-(2-chlorophenyl)-1H-benzo[d]imidazole and screened for antimicrobial activities. The synthesized compounds were characterized by IR, NMR ( $^1\text{H}$ ,  $^{13}\text{C}$ ), CHN analysis.

## 2. Materials and Methods

Melting points (mp) were recorded on open capillary melting point apparatus and are uncorrected. IR spectra were recorded in AVATAR 330 FT-IR Thermo Nicolet spectrophotometer (range 4000–400  $\text{cm}^{-1}$ ) as KBr pellets.  $^1\text{H}$  NMR spectra were recorded with a Bruker AMX-400 spectrometer operating at

400 MHz spectrometer at room temperature, using TMS as internal standard.  $^{13}\text{C}$ NMR spectra were recorded on the same instrument at 100 MHz and are referenced using the central line of the solvent signal ( $\text{CDCl}_3$ , DMSO- $d_6$  septet at  $\delta = 39.5$  ppm). Elemental analyses (C, H and N) were performed with a Perkin Elmer 2400 Series II CHN Analyzer. Thin layer chromatography was carried out on (Fluka) Silica Gel. All the chromatographic purifications were performed with silica gel 60 (100-200 or 200-400 mesh), whereas all TLC (Silica gel) was performed on silica gel coated (Merk Kiesel 60 GF-254, 0.2 mm thickness) sheets. All reagents and solvents commercially obtained (Sigma-Aldrich®, Himedia®) were used directly and without further purification.

### 3. Results and Discussion

#### 3.1 Chemistry

The synthesis of two novel benzimidazole derivatives were carried out as depicted in scheme-1. A broad band at  $3408\text{cm}^{-1}$  is ascribed to N-H stretching frequency of the imidazole moiety. A strong band at  $2925\text{cm}^{-1}$  is due to the (C-H) stretching frequencies. Hence the IR data illustrate the formation of the benzimidazole derivatives. In  $^1\text{H}$ NMR spectrum of compound 1a and 1b show broad singlet in the region of 12.15 ppm which is due to free NH group present. A singlet at 3.97 ppm (1a) shows the presence of methylene group in 2-chloromethyl-1H-benzimidazole derivatives. Aromatic protons appeared as multiplet at 7.56-6.76ppm show the presence of 2-(2-chlorophenyl)-1H-benzo[d]imidazole derivatives. On focusing the  $^{13}\text{C}$ NMR spectral assignments, the aromatic carbon signal is appeared at 123.2ppm (1b) and 44.7 ppm show the presence of methylene carbon of 2-chloromethyl-1H-benzimidazole moiety(1a).

#### 3.2 General procedure for synthesis of compounds 1a and 1b:

##### 3.2.1 N-((1H-benzo[d]imidazol-2-yl)methyl)-1H-1,2,4-triazol-3-amine.(1a);

2-Chloromethyl-1H-benzimidazole (1.665g, 0.01mol) and  $\text{K}_2\text{CO}_3$  (0.02mol, 2.76g) were stirred at room temperature in dimethyl formamide (25 ml) for half an hour and pinch of KI was added. After that 1H-1,2,4-triazol-3-amine (0.840g, 0.01mol) was added to reaction mixture which was refluxed for 14 hours until TLC showed completion of reaction. The reaction mixture was poured into water (20ml) and the mixture was extracted with ethylacetate. The organic extracts was washed with water, dried over anhydrous

sodium sulphate and concentrated to obtain crude product. The residue was crystallised from diethyl ether to give pure compound at room temperature. Yield 50%; yellow solid; mp  $470\text{ }^\circ\text{C}$ ; FT-IR (KBr):  $\nu_{\text{max}}$  3408 (NH), 3057, 2925, 1643 (C=N), 1486, 1286,  $867\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 12.78 (s, 1H, benzimidazolic NH), 12.15 (s, 1H, triazolic NH), 7.56 (dd,  $J=5.2\text{ Hz}$ ,  $J=3.6\text{ Hz}$ , 2H) C4H & C7H (benzimidazole), 7.25 (m, 2H, C5H & C6H (benzimidazole), 7.63 (s, 2H), 7.06 (s, NH), 3.97 (s, 2H),  $^{13}\text{C}$  NMR (100.63 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 163.0, 146.6, 141.1, 137.4, 137.6, 123.4, 123.0, 115.8, 44.7: Anal. Calcd. For  $\text{C}_{10}\text{H}_{10}\text{N}_6$ : C, 56.07; H, 4.71; N, 39.23 Found: C, 55.07; H, 4.91; N, 38.23.

##### 3.2.1. N-(2-(1H-benzo[d]imidazol-2-yl) phenyl)-1H-1, 2, 4-triazol-4-amine(1b);

2-(2-Chlorophenyl)-1H-benzo[d]imidazole (2.2867g, 0.01mol) and  $\text{K}_2\text{CO}_3$  (0.02mol, 2.76g) were stirred at room temperature in dimethyl formamide (25 ml) for half an hour and pinch of KI was added. After that 1H-1, 2, 4-triazol-3-amine (0.840g, 0.01mol) was added to reaction mixture which was refluxed for 21 hours until TLC showed completion of reaction. The reaction mixture was poured into water (20ml) and the mixture was extracted with ethylacetate. The organic extracts was washed with water, dried over anhydrous sodium sulphate and concentrated to obtain crude product. The residue was crystallised from diethyl ether to give pure compound at room temperature. Yield 40%; yellow solid; mp  $5700\text{ }^\circ\text{C}$ ; FT-IR (KBr):  $\nu_{\text{max}}$  3488 (NH), 3011, 2922, 1615 (C=N), 1488, 1299,  $1182\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) ; 13.03 (s, 1H, benzimidazolic NH), 7.56-6.76 (m, 8H), 7.09 (s, NH), 12.33 (s, Triazole NH) , 7.64 (s, 1H);  $^{13}\text{C}$  NMR (100.63 MHz, DMSO- $d_6$ ): $\delta$  (ppm):158.6, 154.3, 146.6, 144.2, 141.8, 128.6, 125.2, 123.6, 119.0, 116.7, 115.8, 107.7. Anal. Calcd. For  $\text{C}_{15}\text{H}_{12}\text{N}_6$ : C, 65.21; H, 4.38; N, 30.42 Found: C, 65.23; H, 4.40; N, 30.50.

#### 3.3 Computational analysis of 1a and 1b:

The optimized molecular structures of compounds 1a and 1b calculated using DFT at B3LYP/6-311G (d,p) basis set is shown in Fig. 2. Frontier molecular orbitals can offer a reasonable qualitative prediction of the excitation properties and the ability of electron support. The highest molecular orbital (HOMO) is outermost higher energy orbital containing electrons so it act as an electron donor. The lowest unoccupied molecular orbital is the lowest energy orbital that has the room to accept electrons so it acts as an electron



acceptor. The HOMO and LUMO are also very determine the molecular reactivity. The energies of the HOMO and LUMO orbitals of the compound 1a and 1b are calculated using B3LYP/6-311G(d,p) levels and shown in fig 3. In frontier energy molecular orbital diagram (Fig. 3), the HOMO is distributed on heterocyclic rings (especially electron donating like methyl group substituents) for all compound 1a. In frontier energy molecular orbital diagram (Fig. 3), the HOMO is distributed on heterocyclic rings (especially electron donating like methyl group substituents) and phenyl ring in second position of benzimidazole for all compounds 1b. The energy gap values of HOMO and LUMO for the compounds 1a and 1b are shown in Table-1.

### 3.4 Antimicrobial activity

The preliminary screenings of the synthesized compounds (1a and 1b) against bacterial strains and fungal strains were carried out by using Agar well diffusion method and serial dilution method (minimum inhibitory concentration). The bacterial viz., Gram positive [*Staphylococcus aureus* ATCC-25833 (*S. aureus*), *Bacillus Subtilis* ATCC-461 (*B. Subtilis*), and Gram negative [*Klebsiella pneumonia* ATCC-15499 (*K. Pneumonia*), *Salmonella typhi* ATCC-24930 (*S. typhi*), *Pseudomonas. Auruginosa* ATCC-27853 (*P. Auruginosa*), *Escherichia coli* ATCC-25840 (*E. coli*)] also *Candida albicans* ATCC-3130 (*C. Albicans*), *Candida-6* ATCC-3315, *Rhizopus* ATCC-2920 (*Sp. Rhizopus*), *Aspergillus Flavus* ATCC-470 (*A. Flavus*), *Aspergillus Niger* ATCC-591 (*A. Niger*), *Mucor* fungal strains are used for this study. Ciprofloxacin and Fluconazole are used as standards (positive control) for bacterial and fungal strains, respectively. Compound 1a has good activity against *B. subtilis*, less activity against *K. pneumonia* and moderate activity against *S. typhi*, *s. aureus*, *P. Auruginosa* and *E. coli* pathogenic bacteria and they are found to be the active compounds against *Candida albicans* fungi. The antimicrobial activities in terms of minimum inhibitory concentration (MIC) of compounds (1a and 1b) are depicted in Table-2 & 3.

## 4. CONCLUSION

Two new 2-Chloromethyl-1H-benzimidazole/2-(2-chlorophenyl)-1H-benzo[d]imidazole derivatives were synthesized in reasonably good yields. They were characterized by IR, <sup>1</sup>H, <sup>13</sup>C NMR and elemental analysis. All the newly synthesized compounds were tested for antibacterial and antifungal activity by agar

popular quantum chemical parameters which well diffusion and serial dilution method. Among the screened samples, compound 1a exhibited as most active against bacterial strain *E. Coli* and compound 1b exhibited as most active against fungal strain *C. Albicans* compared to other synthesized compounds.

## REFERENCES

- Starcevic, K., & Krajai, M (2007), *Bioorg. Med. Chem.* 15, 4419, (2007).
- Sharma, M. C., Kohli D. V, Sharma, A. D, (2010), *Der Pharmacia Sinica* . 1, 104.
- Dubay. R., Abuza. S., Sharma. S., Chatterjee. R. K & Katiyar. J. C (1985), *J. Med. Chem.* 28, 1748.
- Mavrova. A. T., Denkova. P. S., Tsenor. Y. A., Anichina. K. K., (2007). *Bioorg. Med. Chem.* 15, 6291.
- Navarette-Vazquez. G., Cedilla. R., Hernandez-Campos. A., Vepez. A, Hernandez-Iuis. F., (2001). *Bioorg. Med. Chem.* 11, 187.
- Katiyar. S. K. Gorden. V. R., McLaughlin. G. L., Edlind. J. D., (1994), *Antimicrob. Agents. Chemother.* 38, 2986.
- Goker. H., Kus. C., Buykin. D. W., Vildiz. S., Altanlar. N., (2002) *Bioorg. Med. Chem.* 10, 258.
- Desai. K. G., Desa. K. R., (2006), *Bioorg. Med. Chem.* 14, 8271.
- Kazimierzuk. Z., Uperoft. J. A., Uperoft. P., Gorska. S., Starosciak. S., Laudy. A., (2002), *Acta Biochim. Polon.* 49, 185.
- Mohammad. B. G., Hussien. M. A., Abdel-Alim. A. A., Hashem. A, (2006), *Arch. Pharm. Res.* 29, 26.
- Pawar. N. S., Dalal D.S., Shimpi. S. R., Mahulikar. P. P., (2004), *Eur. J. Pharm. Sci.* 21, 115,
- Ito. K., Kagaya. H., Fukuda. E., Yoshino. K., Nose. T., (1982), *Arzneim. Forsch. Drug Res.* 32, 49.