



Synthesis and Biological Activity of Novel 2, 5-Disubstituted Benzimidazole Derivatives

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ABSTRACT

A new series of 2, 5 di-substituted benzimidazole derivatives have been synthesized. The structures of the synthesized compounds were confirmed by IR, ¹H NMR and Mass spectral analysis and they were evaluated for their antibacterial; *Proteus vulgaris* (NCTC 4635), *Klesibella pneumonia* (ATCC 29655), *Bacillus cereus* (NL98), and *Enterococcus faecium* (ATCC 29212) and antifungal (*Aspergillus niger* and *Aspergillus fumigatus*) activities by disc diffusion method. All of the synthesized compounds showed good antibacterial and antifungal activity. However the antibacterial and antifungal activity of the synthesized compounds against the tested organisms was found to be less than that of respective standard drug at tested dose level.

Keywords: O-phenylene diamine, Benzimidazole, Antibacterial, Antifungal.

INTRODUCTION

Benzimidazole ring system known to be possess numerous antimicrobial^[1-9], anti-inflammatory^[9], anthelmintic^[10], antiviral^[11-13] and anti-tumour^[14] properties. Therefore it was enabled that compounds containing benzimidazole nucleus would result in interesting of biological activities. In the present study 2-substituted benzimidazoles were synthesized by treating o-phenylene diamine with different carboxylic acids. Then they were subjected to nitration at room temperature to get 5-nitro 2-substituted benzimidazole derivatives. Finally they were reduced by using Zn/NaOH to get 5-amino 2-substituted benzimidazole derivatives. The structures of the synthesized compounds were confirmed by IR, ¹H NMR and Mass spectral analysis. The newly synthesized final compounds were screened for their antibacterial and antifungal activity.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes on melting point apparatus (Sunbim, Guna enterprises) and are uncorrected. The ¹H NMR spectra were recorded on Bruker-NMR 500 mHz using MeOD and DMSO – d₆ as solvent. Mass spectra were recorded on JEOL GC mate mass spectrometer. The IR spectra of the synthesized compounds

were recorded on Perkin-Elmer FT-IR spectrophotometer with KBr pellets. The UV spectra were recorded by using Double beam SHIMADZU 1700 UV spectrometer. The purity of the compounds was checked by TLC on pre-coated silica gel G plates by using methanol: water as a mobile phase and visualized in iodine vapour.

General Method for the Synthesis of 2-substituted benzimidazole derivatives^[14-15]

O-phenylene diamine (0.25 mol) and appropriate carboxylic acid (0.34 mol) was heated on a water bath at 100°C for 6-8 h. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled and basified to a pH of 7-8 by using 10% sodium hydroxide solution. The crude benzimidazole was filtered at the pump, washed with ice cold water. The crude product was dissolved in 400 ml of boiling water and 2 g of decolorizing carbon was added and digested for 15 min. The solution was filtered while hot, cooled the filtrate to about 10°C. The pure product was filtered, washed with 25 ml of cold water and dried at 100°C.

General Method for the Synthesis of 5-nitro 2-substituted benzimidazole derivatives^[16]

Conc. HNO₃ (7.5 ml) was placed in three necked round bottom flask fitted with a mechanical stirrer. The flask was immersed in ice cold water and added slowly conc. H₂SO₄ (7.5 ml) down the condenser with slow stirring. After the addition, 2-substituted benzimidazoles (0.028 mol) were added in a portion over a period of 1 h at such a rate that the temperature did not exceed 35°C. After continuous stirring for 12 h, the reaction mixture was poured very slowly over

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crushed ice with vigorous stirring. The formed product was filtered, washed with cold water and recrystallized from ethanol.

General Method for the Synthesis of 5-amino 2-substituted benzimidazole derivatives^[17]

A solution of 0.5 g of 5-nitro, 2-substituted benzimidazoles in 15 ml of rectified spirit was taken in round bottom flask. To this, 5 ml of 20 % sodium hydroxide and 2.5 g of zinc dust powder was added. The reaction mixture was refluxed until colour of the solution changed from deep red to colourless (about 4.5 h), the hot mixture was filtered. The zinc residue was returned to the flask and extracted with 10 ml of hot rectified spirit for two times. The extracts were combined and the solvent was removed under vacuum, yielded the brown solid and recrystallized from methanol.

Spectral data of synthesized compounds

Compound SY₁: yield = 37.94%, mp 162°C, R_f = 0.79, $\lambda_{\max}$ (MeOH) 280.50, 242.5. IR (KBr) cm^{-1} 3369.99 (N-H str), 3100.50 (Ar C-H str), 2539.91 (S-H str), 1661.54 (Ar C=C ring str), 1556.06 (C=N str). ¹H NMR (MeOD) δ : 7.70 (m, 2H; Ar-H- C₄ & C₇), 7.26 (m, 2H; Ar-H- C₅ & C₆), 5.0 (s, 1H; broad, NH), 3.82 (s, 2H; CH₂), 1.5 (s, 1H; SH). EI-MS m/z 163.82 (Calcd for C₈H₈N₂S: 164.22).

Compound SY₂: yield = 39.94%, mp 112°C, R_f = 0.85, $\lambda_{\max}$ (MeOH) 275.50, 210.0. IR (KBr) cm^{-1} 3363.57 (N-H str), 3032.10 (Ar C-H str), 2667.83 (C-H str), 1632.61 (C=C ring str), 1591.92 (C=N str), 1320.5 (C-H ben gem-dimethyl), 1272.31 (C-N str), 1114.79 (C-C skeletal str). ¹H NMR (MeOD) δ : 7.70 (m, 2H; Ar-H- C₄ & C₇), 7.26 (m, 2H; Ar-H- C₅ & C₆), 5.0 (s, 1H; broad, NH), 3.12 (m, 1H; CH of iso propyl), 1.29 (d, 6H; 2CH₃ of iso propyl). EI-MS m/z : 159.90 (Calcd for C₁₀H₁₂N₂: 160.21).

Compound SY₃: yield = 54.02%, mp 114°C, R_f = 0.83, $\lambda_{\max}$ (MeOH) 293.50, 238.0. IR (KBr) cm^{-1} 3192.57 (C-H str), 3288.94 (N-H str), 3032.75 (Ar C-H str), 1632.86 (C=C ring str), 1590.16 (C=N str), 1272.45 (C-N str). ¹H NMR (MeOD) δ : 7.70 (m, 2H; Ar-H- C₄ & C₇), 7.26 (m, 2H; Ar-H- C₅ & C₆), 5.0 (s, 1H; broad, NH), 2.55 (t, 2H; CH₂), 1.62 (m, 2H; CH₂), 1.33 (m, 2H; CH₂), 0.96 (t, 3H; methyl, C₁₁). EI-MS m/z : 174.24 (Calcd for C₁₁H₁₄N₂: 170.24).

Compound SY₄: yield = 35.37%, mp 248°C, R_f = 0.30, $\lambda_{\max}$ (MeOH) 294.50. IR (KBr) cm^{-1} 3514.74 (N-H asy str primary amine), 3463.63 (N-H sy str primary amine), 3358.60 (N-H str secondary amine), 2968.78 (Ar C-H str), 1621.12 (N-H ben), 1274.47 (C-N str). ¹H NMR (MeOD) δ : 7.70 (m, 2H; Ar-H- C₄ & C₇), 7.23-7.26 (m, 2H; Ar-H- C₅, C₆ & C₂, C₆'), 6.52 (m, 2H; Ar-H- C₃ & C₅'), 5.0 (s, 1H; broad, NH), 4.0 (s, 2H; NH₂). EI-MS m/z : 209.18 (Calcd for C₁₃H₁₁N₃: 209.24).

Compound SY₅: yield = 31.38%, mp 254°C, R_f = 0.58, $\lambda_{\max}$ (MeOH) 273.0, IR (KBr) cm^{-1} 3114.22 (N-H str), 3062.21 (Ar C-H str), 1604.17 (C-C skeletal str), 1541.85 (N-O asy str), 1349.62 (N-O sym str), 1288.31 (C-N str). ¹H NMR (MeOD) δ : 8.25 (m, 2H; Ar-H- C₃ & C₅'), 7.74 (m, 2H; Ar-H- C₂ & C₆'), 7.70 (m, 2H; Ar-H- C₄ & C₇), 7.26 (m, 2H; Ar-H- C₅ & C₆), 5.0 (s, 1H; broad, NH). EI-MS m/z : 238.95 (Calcd for C₁₃H₉N₃O₂: 239.23).

Compound SY₆: yield = 54.79%, mp 185°C, R_f = 0.81, $\lambda_{\max}$ (MeOH) 280.0, IR (KBr) cm^{-1} 3072.23 (Ar C-H str), 2933.61 (S-H str), 1683.23 (C=C ring str), 1584.92 (N-O asy str), 1348.72 (N-O sym str), 1537.17 (C=N str), 846.68 (C-N str), 763.10 (N-O ben), 715.23 (C-S str). ¹H NMR (MeOD) δ : 8.63 (s, 1H; Ar-H- C₄), 8.19 (d, 1H; Ar-H- C₆), 7.96 (d, 1H;

Ar-H- C₇), 5.0 (s, 1H; broad, NH), 3.82 (s, 2H; CH₂), 1.5 (s, 1H; SH). EI-MS m/z : 209.11 (Calcd for C₈H₇N₃O₂S: 209.22).

Compound SY₇: yield = 31.53%, mp 96°C, R_f = 0.69, $\lambda_{\max}$ (MeOH) 233.0, IR (KBr) cm^{-1} 3384.19 (N-H str), 3098.25 (Ar C-H str), 1612.71 (N-H ben), 1538.03 (N-O asy str), 1348.03 (N-O sym str), 1217.67 (C-N str), 883.21 (C=C ring str). ¹H NMR (MeOD) δ : 8.63 (s, 1H; Ar-H- C₄), 8.19 (d, 1H; Ar-H- C₆), 7.96 (d, 1H; Ar-H- C₇), 5.0 (s, 1H; broad, NH), 3.12 (m, 1H; CH of isopropyl), 1.29 (d, 6H; 2CH₃ of isopropyl). EI-MS m/z : 204.88 (Calcd for C₁₀H₁₁N₃O₂: 205.21).

Compound SY₈: yield = 26.59%, mp 124°C, R_f = 0.84, $\lambda_{\max}$ (MeOH) 244.0, IR (KBr) cm^{-1} 3651.02 (N-H str), 3098.41 (Ar C-H str), 1541.67 (N-O asy str), 1344.16 (N-O sym str), 1209.52 (C-N str), 892.90 (C=C ring str). ¹H NMR (MeOD) δ : 8.63 (s, 6H; Ar-H- C₄), 8.19 (d, 1H; Ar-H- C₅), 7.96 (d, 1H; Ar-H- C₇), 5.0 (s, 1H; broad, NH), 2.55 (t, 2H; CH₂), 1.62 (m, 2H; CH₂), 1.33 (m, 2H; CH₂), 0.96 (t, 2H; CH₃). EI-MS m/z : 219.04 (Calcd for C₁₁H₁₃N₃O₂: 219.24).

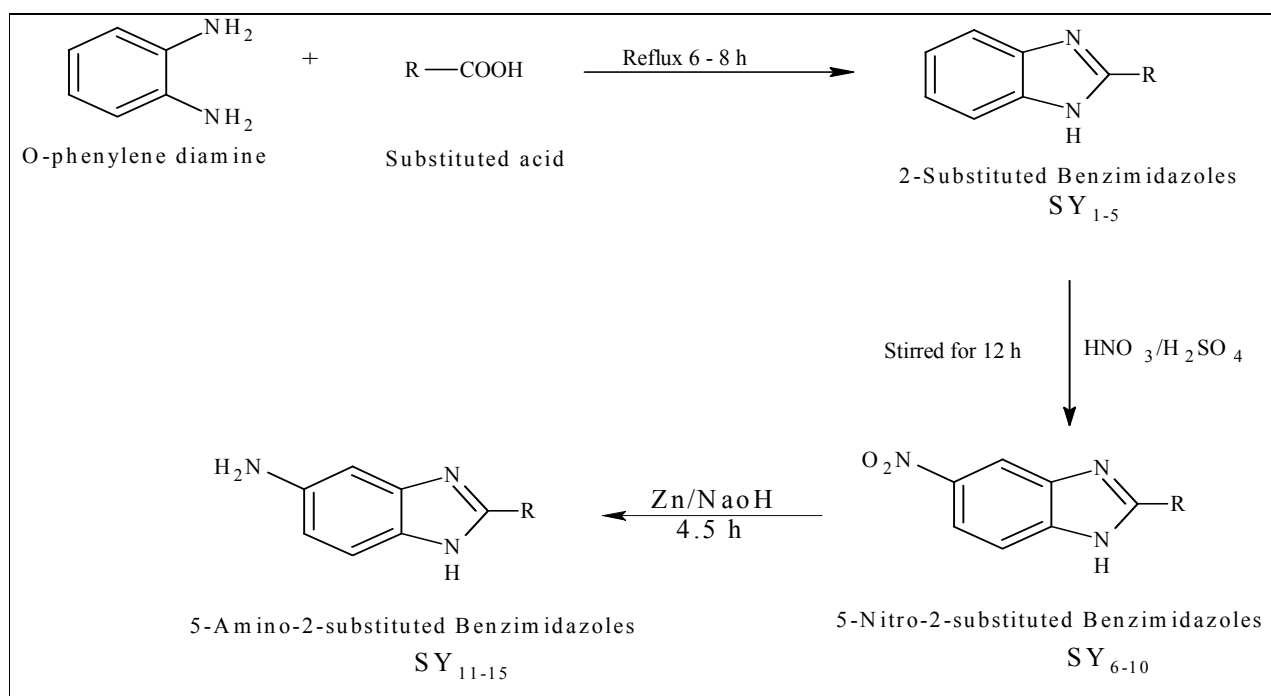
Compound SY₉: yield = 30.09%, mp 216°C, R_f = 0.81, $\lambda_{\max}$ (MeOH) 313.0, IR (KBr) cm^{-1} 3418.50 (N-H sym str primary amine), 3322.70 (N-H str secondary amine), 3072.36 (Ar C-H str), 1644.22 (N-H ben), 1532.92 (N-O asy str), 1344.12 (N-O sym str), 1231.34 (C-N str). ¹H NMR (MeOD) δ : 8.63 (s, 1H; Ar-H- C₄), 8.19 (d, 1H; Ar-H- C₆), 7.96 (d, 1H; Ar-H- C₇), 7.23 (m, 2H; Ar-H- C₂ & C₆'), 6.52 (m, 2H; Ar-H- C₃ & C₅'), 5.0 (s, 1H; broad, NH), 4.0 (s, 1H; NH₂). EI-MS m/z : 254.12 (Calcd for C₁₃H₁₀N₄O₂: 254.24).

Compound SY₁₀: yield = 39.54%, mp 226°C, R_f = 0.58, $\lambda_{\max}$ (MeOH) 267.5, IR (KBr) cm^{-1} 3114.32 (N-H str), 3061.87 (Ar C-H str), 1698.28 (N-O asy str), 1604.29 (N-H ben), 1349.69 (N-O sym str), 877.69 (C-N str). ¹H NMR (MeOD) δ : 8.63 (s, 1H; Ar-H- C₄), 8.25 (m, 2H; Ar-H- C₃ & C₅'), 8.19 (d, 1H; Ar-H- C₆), 7.96 (d, 1H; Ar-H- C₇), 7.74 (m, 1H; Ar-H- C₂ & C₆'), 5.0 (s, 1H; broad, NH). EI-MS m/z : 284.12 (Calcd for C₁₃H₈N₄O₄: 284.22).

Compound SY₁₁: yield = 44.04%, mp 261°C, R_f = 0.78, $\lambda_{\max}$ (MeOH, DMSO) 275.0, IR (KBr) cm^{-1} 3552.00 (N-H asy str primary amine), 3416.86 (N-H sym str primary amine), 3376.18 (N-H str secondary amine), 2468.00 (S-H str), 1622.56 (N-H ben), 1225.49 (C-N str), 746.41 (C-S str). ¹H NMR (DMSO - d₆) δ : 7.31 (d, 1H; Ar-H- C₇), 6.70 (s, 1H; Ar-H- C₄), 6.62 (d, 1H; Ar-H- C₆), 5.0 (s, 1H; NH), 4.03 (s, 2H; CH₂), 3.48 (s, 2H; NH₂), 1.68 (s, 1H; SH). EI-MS m/z : 179.14 (Calcd for C₈H₉N₃S: 179.24).

Compound SY₁₂: yield = 91.96%, mp 220°C, R_f = 0.79, $\lambda_{\max}$ (MeOH, DMSO) 272.5, IR (KBr) cm^{-1} 3587.00 (N-H asy str primary amine), 3218.00 (N-H str secondary amine), 2343.00 (C-H str), 1635.00 (N-H ben), 1385.00 (C-N str), 1129.00 (C-H inplane ben). ¹H NMR (DMSO - d₆) δ : 7.31 (d, 1H; Ar-H- C₇), 6.69 (s, 1H; Ar-H- C₄), 6.61 (d, 1H; Ar-H- C₆), 5.0 (s, 1H; NH), 3.48 (s, 2H; NH₂), 3.40 (m, 1H; CH of isopropyl), 1.24 (m, 6H; CH₃ of isopropyl). EI-MS m/z : 175.18 (Calcd for C₁₀H₁₃N₃: 175.23).

Compound SY₁₃: yield = 93.02%, mp 238°C, R_f = 0.80, $\lambda_{\max}$ (MeOH, DMSO) 366.0, IR (KBr) cm^{-1} 3573.00 (N-H asy str primary amines), 3393.00 (N-H str secondary amines), 2175.00 (C-H str), 1648.00 (N-H ben), 1397.00 (C-N str). ¹H NMR (DMSO - d₆) δ : 7.31 (d, 1H; Ar-H- C₇), 6.69 (s, 1H; Ar-H- C₄), 6.61 (d, 1H; Ar-H- C₆), 5.0 (s, 1H; NH), 3.48 (s, 2H; NH₂), 2.86 (t, 2H; CH₂), 1.72 (m, 2H; CH₂), 1.30 (m, 2H; CH₂), 0.90 (t, 3H; CH₃). EI-MS m/z : 189.22 (Calcd for C₁₁H₁₅N₃: 189.25).



Scheme 1: Synthetic scheme of 5-amino 2-substituted benzimidazole derivatives.

Compound	R
SY ₁ , SY ₆ , SY ₁₁	CH ₂ SH
SY ₂ , SY ₇ , SY ₁₂	CH(CH ₃) ₂
SY ₃ , SY ₈ , SY ₁₃	CH ₂ CH ₂ CH ₂ CH ₃
SY ₄ , SY ₉ , SY ₁₄	C ₆ H ₅ N
SY ₅ , SY ₁₀ , SY ₁₅	C ₆ H ₄ NO ₂

Compound SY₁₄: yield = 86.36%, mp 255°C, R_f = 0.72, $\lambda_{\max}$ (MeOH, DMSO) 366.0, IR (KBr) cm^{-1} 3579.00 (N-H asy str primary amine), 3369.00 (N-H str secondary amine), 1645.00 (N-H ben), 1429.00 (C-N str), 866.00 (C-H ben). ¹H NMR (DMSO - d₆) δ : 7.85 (m, 2H; Ar-H- C₂ & C₆'), 7.43 (d, 1H; Ar-H- C₇), 6.85 (s, 1H; Ar-H- C₄), 6.76 (d, 1H; Ar-H- C₆), 6.59 (m, 2H; Ar-H- C₁₀ & C₁₂), 5.0 (s, 1H; NH), 3.99 (s, 2H; NH₂), 3.58 (s, 2H; NH₂). EI-MS m/z : 224.20 (Calcd for C₁₃H₁₂N₄: 224.26).

Compound SY₁₅: yield = 39.14%, mp 277°C, R_f = 0.76, $\lambda_{\max}$ (MeOH, DMSO) 270.0, IR (KBr) cm^{-1} 3559.00 (N-H asy str primary amine), 3432.00 (N-H sym str primary amine), 3206.00 (N-H str secondary amine), 1632.00 (N-H ben), 1596.00 (N-O str). ¹H NMR (DMSO - d₆) δ : 8.28 (m, 2H; Ar-H- C₃ & C₅'), 8.02 (m, 2H; Ar-H- C₂ & C₆'), 7.44 (d, 1H; Ar-H- C₇), 6.91 (s, 1H; Ar-H- C₄), 6.82 (d, 1H; Ar-H- C₆), 5.0 (s, 1H; NH), 3.58 (s, 2H; NH₂). EI-MS m/z : 254.12 (Calcd for C₁₃H₁₀N₄O₂: 254.24).

Antimicrobial Activity^[2]

The synthesized compounds were tested for antimicrobial activity by disc diffusion method. They were dissolved in DMSO and sterilized by filtering through 0.45 μ m millipore filter. Final inoculums of 100 μ l suspension containing 10⁸ CFU/ ml of each bacterium and fungus used. Nutrient agar (antibacterial activity) and sabouraud's dextrose agar medium (antifungal activity) was prepared and sterilized by an autoclave (121°C and 15 lbs for 20 min) and transferred to previously sterilized petridishes (9 cm in diameter). After solidification, petriplates were inoculated with bacterial organisms in sterile nutrient agar medium at 45°C, and fungal

organisms in sterile sabouraud's dextrose agar medium at 45°C in aseptic condition. Sterile Whatmann filter paper discs (previously sterilized in U.V. lamp) were impregnated with synthesized compounds at a concentration of 25; 100 mg/disc were placed in the organism-impregnated petri plates under sterile condition. The plates were left for 30 min to allow the diffusion of compounds at room temperature. Antibiotic discs of ciprofloxacin (100 μ g /disc) and ketaconazole (100 μ g /disc) were used as positive control, while DMSO used as negative control. Then the plates were incubated for 24 h at 37 $\pm$ 1°C for antibacterial activity and 48 h at 37 $\pm$ 1°C for antifungal activity. The zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around the each disc.

RESULTS AND DISCUSSION

The structure of the synthesized compounds were established by spectral (IR, ¹H NMR and Mass) analysis data. The NH band (3463-3114 cm^{-1}) and NH proton signal (5.0 ppm) of 2-substituted benzimidazole in IR and ¹H NMR spectrum respectively in the synthesized compounds, (SY₁-SY₅) confirmed the formation of benzimidazole nucleus. In SY₁, ¹H NMR spectrum showed a 2 proton singlet at δ 1.5 and δ 3.82 for 3 protons confirmed the presence of methane thiol group. In SY₂, multiplet at δ 3.12 for 1 proton and doublet at δ 1.29 for 6 protons indicated the formation of iso-propyl group. In SY₃, two triplets at δ 2.55 and 0.96 for 5 protons and two multiplet at δ 1.62 and δ 1.37 for 4 protons indicated the presence of butyl group. In SY₄, two multiplet at δ 7.23-7.26 and δ 6.52 for 4 protons and a singlet at δ 4.0 for 2 protons indicated the presence of amino phenyl group. In the case of SY₅, two multiplet at δ 8.25 and δ 7.74 for 4 protons indicated the substitution of nitro phenyl group at C₂ of benzimidazole nucleus. The presence of nitro group in SY₆-SY₁₀ was ascertained from strong bands at 1584 -1532 cm^{-1} and 1345 cm^{-1} corresponding to asymmetric and symmetric O=N=O stretch respectively.

Table 1: Antimicrobial activity of the synthesized compounds by disc diffusion method (SY₁₁ – SY₁₅)

Organisms	Diameter of Zone of inhibition in mm											Ket 100 (µg)	Cip 100 (µg)
	SY ₁₁		SY ₁₂		SY ₁₃		SY ₁₄		SY ₁₅				
	25 (mg)	100 (mg)	25 (mg)	100 (mg)	25 (mg)	100 (mg)	25(mg)	100 (mg)	25 (mg)	100 (mg)			
<i>B. cereus</i>	11	17	17	25.5	12	14	10	14.8	18	26	----	30	
<i>P. vulgaris</i>	12	18.5	12	15	21	25	11	16.4	12	17	----	28	
<i>K.pneumonia</i>	13	15	14	17	18	22.5	21	26	22	26.5	----	29	
<i>E. faecium</i>	15	18	14	17.6	11	14	17	21	17	24	----	28	
<i>A. niger</i>	14	17.5	19	22	14	26	15	19.5	12	16.4	30	----	
<i>A. fumigatus</i>	15	17	20	21	15	16	11	16.7	13	18	27	----	

(Ket = Ketoconazole, Cip = Ciprofloxacin, *P. vulgaris* = *Proteus vulgaris*, *K. pneumonia* = *Klesibella pneumonia*, *B. Cereus* = *Bacillus cereus*, *E. faecium* = *Enterococcus faecium*, *A. niger* = *Aspergillus niger* and *A. fumigatus* = *Aspergillus fumigatus*)

Further a strong intensity signal at 1231-846 cm⁻¹ was attributed to the C-N stretching for aromatic nitro compounds. Spectrum of SY₆-SY₁₀ in the aromatic region indicated that the three chemical environments at δ 8.63, 8.19 and 7.96, instead of two regions which were present in SY₁-SY₅. The presence of primary amino group in SY₁₁-SY₁₅ was ascertained from strong bands at 3500 cm⁻¹ and 3400 cm⁻¹ corresponding to asymmetric and symmetric H-N-H stretch respectively. Further a strong signal at 1648-1622 cm⁻¹ was attributed to N-H bending for primary amino group. In SY₁₁-SY₁₅, a singlet at δ 3.48 for 2 protons indicated the presence of primary amino group. In the mass spectrum of the synthesized compounds produced (M⁺) molecular ion peaks at 163.82, 159.90, 174.24, 209.18, 238.95, 209.11, 204.88, 219.04, 254.12, 284.12, 179.24, 175.23, 189.25, 224.26, 254.24 values for SY₁-SY₁₅ respectively corresponds to their molecular formulas.

The synthesized compounds were evaluated for *in-vitro* antibacterial activity against gram negative bacteria *Proteus vulgaris* (NCTC 4635), *Klesibella pneumonia* (ATCC 29655) and gram positive bacteria *Bacillus cereus* (NL98), *Enterococcus faecium* (ATCC 29212). These are the agents commonly causes urinary tract infection, nosocomial infection, biliary tract infection. The gram negative organism *Klesibella pneumonia* causes pneumonia, bronco pneumonia and bronchitis infection. The gram negative organisms *Bacillus cereus* and *Enterococcus faecium* cause endocarditis, bacteremia, meningitis and septicemia. From the biological data, it was evident that the compound SY₁₅ was found to be more active against *Klesibella pneumonia* (ATCC 29655), *Bacillus cereus* (NL98), and *Enterococcus faecium* (ATCC 29212); where as compound SY₁₃ was found to be more active against *Proteus vulgaris* (NCTC 4635). Compound SY₁₂ was found to be more active against *Aspergillus niger* and *Aspergillus fumigatus*. However the antimicrobial activity of the synthesized compounds against the tested organisms was found to be less than that of respective standard drug at tested dose level. In future study the activity of the compounds may be manipulated by introducing unsaturation or heterocyclic ring at C₂ of benzimidazole.

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