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Original Article

Synthesis, characterization and evaluation of new benzimidazole derivatives

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ABSTRACT

A series of new benzimidazole derivatives have been synthesized by simple condensation (Schiff reaction) reaction between benzimidazole derivatives and substituted aromatic aldehydes. All these compounds were characterized by FT-IR, ^{1}HNMR, Mass spectral and TLC analysis thus compounds were screened for antibacterial and antifungal activities respectively. The antibacterial activities were compared with the standard drug such as norfloxacin and antifungal activities were compared with fluconazole. Among synthesized compounds, the compound with 4 – chloro IV b on the aromatic ring possessing good antibacterial activity, however lower than standard norfloxacin and the compound with 4 – dimethyl amine group IV d showed better antifungal activity; almost similar to that of standard, fluconazole thus they could be promising candidates for novel drugs.

Keywords: Benzimidazole, Schiff Base, ^{1}HNMR, FTIR, Antibacterial and Antifungal

INTRODUCTION

Recent observations suggest that substituted Benzimidazoles and related heterocycles possess potential activity with lower toxicities in the chemotherapeutic approach in human beings. The antimicrobial agents are amongst the most important and frequently used group of drugs to treat disorders of microbes. The incorporation of an imidazole nucleus, a biologically accepted pharmacophore, in the benzimidazole molecule has made it a versatile heterocycle possessing a wide spectrum of biological activities including antimicrobial [1, 2], antiproliferative [4,5], anti-inflammatory [6,7], antidiabetic [9], antihypertensive [10], antitubercular [13], antipsychotic [12] and antiviral [11].

Benzimidazole nucleus is also found in a variety of naturally occurring compounds such as vitamin B_{12} and its derivatives and it is structurally similar to purine bases. Benzimidazoles are widely used as drugs such as omeprazole, pantoprazole, lansoprazole: proton pump inhibitor, mebendazole, thiabendazole: antihelmintic, Domperidone: antidopaminergic and rifaximin: anticancer. Since azomethine linkage has also shown antimicrobial activity.

The title compounds were synthesized by treating 5- Nitro 2- substituted benzimidazole with substituted aromatic aldehydes to get a new series of benzimidazole derivatives (scheme – 1). The purity of the synthesized compounds was tested by TLC and the structures were confirmed on the basis of IR, ^{1}HNMR and Mass spectral data. The antimicrobial and antifungal activity of the novel compounds were tested by cup plate method using norfloxacin and fluconazole as standard drug.

MATERIAL AND METHOD

Synthesis of benzimidazole derivatives involved following steps. In the first step, ortho phenylene diamine was condensed with carboxylic acid like para amino benzoic acid in the presence of HCL to give 2- substituted benzimidazole (II). In the next step, 2- substituted benzimidazole (II) was treated with nitric acid and sulphuric acid to give 5-Nitro 2- substituted benzimidazole (III) which was further reacted with different substituted aromatic aldehydes in the presence of glacial acetic acid and ethanol as solvent to get [4- substituted (5- nitro – benzimidazol – 2 – yl) phenyl] – 1 – phenylmethanimine (IV a – d).

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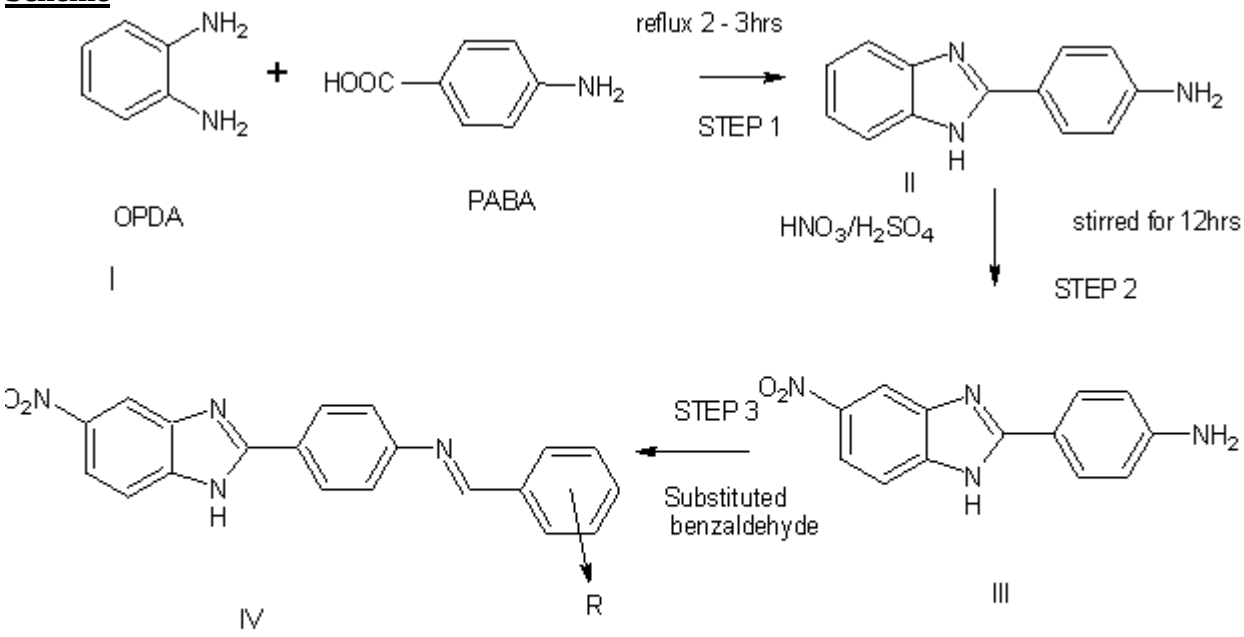
The melting points of newly synthesized compounds were determined with an electro thermal melting point apparatus. The homogeneity of all newly synthesized compounds was checked by TLC on silica gel G coated plates using ethyl acetate: hexane (7:3) solvent system. IR spectra (KBR pellet) were recorded on FTIR paragon 500 (Perkin Elmer) instrument. ^{1}HNMR spectra were recorded on JEOL, GSX_ 400 FT NMR instrument at 400 MHZ in $CDCl_3$ and chemical shifts (δ) are reported in ppm relative to tetramethylsilane as an internal standard.

Experimental Procedure:

Scheme



Here R = 4- OH, 4- N $(CH_3)_2$, 4- H and 4-Cl

SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES

Step-1: **Synthesis of 2- substituted benzimidazole (II):** Ortho phenylenediamine (1mol) was made to condense with carboxylic acid (1mol) like (aspirin salicylic acid and para amino benzoic acid) in presence of ring closing agents like hydrochloric acid. The mixture was kept for reflux and progress of the reaction. On completion of reaction, the reaction mixture was cooled and poured on to crushed ice. The cooling mixture was made basic by the gradual addition of sodium hydroxide solution. The filtered and recrystallized from hot water decolourised with charcoal if necessary.
Percentage Yield- 70%, **M.P.** 182-184°C, **Rf**-0.7 (ethyl acetate and hexane)

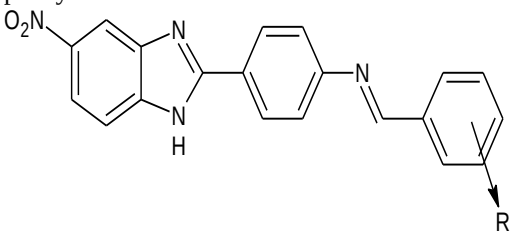
Step-2: **Synthesis of 5- nitro 2- substituted benzimidazole (III):** Conc. HNO3 (7.5ml) was placed in three necked round bottom flask fitted with mechanical stirrer. The flask was immersed in ice cold water and add slowly conc. H2SO4 (7.5ml) down the condenser with low stirring. After the addition of 2- substituted benzimidazole (0.28mol) were added in a portion over the period of 1hr at such a rate that the temperature not exceeds 35^{o}C. After continuous stirring for 12hrs the reaction was poured very slowly over crushed ice with vigorous stirring. The formed product was filtered and washed with cold water and recrystallized from ethanol.
Percentage Yield- 65%, **M.P.** 175-180°C, **Rf**-0.7 (ethyl acetate and hexane)

Step-3: **Synthesis of [4-substituted (5-nitro–benzimidazol-2–yl) phenyl]–1phenylmethanimine (IV):** The 5-nitro 2-substituted benzimidazole (III, 0.01mol) and appropriate aromatic aldehydes (0.015mol) in

alcohol (20ml) with 2 to 3 drops of acetic acid, heated under reflux on a water bath for one hour. The solvent was removed to possible extent by distillation under reduced pressure. The product thus obtained was filtered, washed with water, dried and purified by recrystallization from suitable solvent to produce the compounds IV (a-d). The physical data of these benzimidazole derivatives were given in table1

RESULTS AND DISCUSSION

Table 1: Physical data of [4– substituted – (5-nitro – benzimidazol – 2 yl) phenyl] – 1 – phenylmethanimine.



Compound	R	Mol. formula	Melting point	% Yield
IVa	4 – OH	$C_{20}N_4O_3H_{15}$	192	70
IVb	4 – Cl	$C_{20}N_4O_2H_{12}Cl$	195	78
IVc	4 – H	$C_{20}N_4H_{13}O_2$	190	60
IVd	4- $N(CH_3)_2$	$C_{20}N_5O_2H_{18}$	198	72

Compound IV a: IR (KBr, cm-1): 3240 (O-H), 3060(C-H aromatic), 2932 (C-H str in CH_2), 1592 (C=N), 1159 (N-O):
MS (EI). m/z 359 (M+1)
^{1}H-NMR ($CDCl_3$) δ: 10.1 (s, 1H, cyclic NH), 8.0 – 7.0 (s and d, 11H, aromatic-H); 8.3(s, 1H, CH); 5.35 (s, 1H, OH),
Compound IV b: IR (KBr, cm-1): 3066(C-H aromatic), 2950 (C-H str in CH_2), 1613 (C=N), 1159 (N-O)
MS (EI). m/z 377 (M+1)
^{1}H-NMR ($CDCl_3$) δ: 9.8 (s, 1H, cyclic NH), 8.2 – 7.1 (s and d, 11H, aromatic-H); 8.0 (s, 1H, CH);
Compound IV c: IR (KBr, cm-1): 3040(C-H aromatic), 1592 (C=N), 1159 (N-O):
MS (EI). m/z 343 (M+1)
^{1}H-NMR ($CDCl_3$) δ: 10.0 (s, 1H, cyclic NH), 8.3 – 7.0 (s and d, 12H, aromatic-H); 7.8(s, 1H, CH);
Compound IV d: IR (KBr, cm-1): 3050(C-H aromatic), 2900 (C-H str in CH_2), 1595 (C=N),
MS (EI). m/z 386 (M+1)
^{1}H-NMR ($CDCl_3$) δ: 9.7 (s, 1H, cyclic NH), 8.2 – 7.0 (s and d, 11H, aromatic-H); 8.3(s, 1H, CH); 2.45 (s, 6H, CH_3)

Antimirobial Activity: The synthesized compounds IV a – d were tested in vitro for antibacterial activity against gram positive S. aureus and gram negative E. coli by cup plate agar diffusion method in nutrient agar medium with an incubation of 24 hrs at 37^{o}C. The zone of inhibition was measured in millimeters using 50, 100 and 150 µg/ml concentrations of synthesized compounds. Norfloxacin was used as reference and DMF was used as a control. The antifungal activity of the compounds was assayed against C. albican by cup plate method in dextrose agar media with an incubation of 48hrs at 28^{o}C. The zone of inhibition was measured in millimeters using 50, 100 and 150 µg/ml concentraction of synthesized compounds. Fluconazole was used as reference and DMF was used both as a solvent and as a control.

RESULTS AND DISCUSSION

Table 2: Antibacterial activity of synthesized compounds

Compound	Zone of inhibition (mm)					
	S. aureus			E. coli		
	Concentration (ppm)			Concentration (ppm)		
	50µg/ml	100µg/ml	150µg/ml	50µg/ml	100µg/ml	150µg/ml
IVa	11	13	14	10	12	14
IVb	13	15	16	12	15	16
IVc	08	10	11	10	9	11
IVd	13	14	15	12	14	15
norfloxacin	15	17	19	16	18	20

Table 3: Antifungal activity of synthesized compounds

Compound	Zone of inhibition (mm)		
	C.albicans		
	Concentration (ppm)		
	50µg/ml	100µg/ml	150µg/ml
IVa	12	14	15
IVb	13	14	16
IVc	19	21	23
IVd	21	23	24
fluconazole	24	25	27

Antibacterial screening results presented in **table 2,** revealed that all compounds tested showed some degree of antibacterial activity. The compounds exhibited zone of inhibition of 8- 16mm in diameter, whereas standard, norfloxacin showed a zone of inhibition of 15- 20mm in diameter against S. aureus and E. coli different concentration respectively. The minimum activity was shown by the compound IVc having unsubstituted aromatic ring. When substitution was made in the aromatic ring, activity started increasing. Among synthesized compounds, compound IVb and IVd showed good activity against both the strains. IVa was less active against both the strains. The screening results showed that aromatic ring having a substitution at the para position by chlorine, and dimethyl amine group showed an increase in activity. The results of antifungal activity of the test compounds IVa-d were found to be quite different from their antibacterial activity. Sensitivity of the selected fungal pathogens to synthetic compounds IVa-d was determined in vitro at three concentrations (50, 100 and 150 µg/ml). The compounds exhibited zone of inhibition of 12-24mm in diameter where as standard, fluconazole showed a zone of inhibition of 24- 27mm in diameter against C. albicans. The antifungal screening results presented in table 3. The test compound IVd showed better activity against both the strains.

CONCLUSION

In conclusion, a series of benzimidazole derivatives have been synthesized successfully in appreciable yields and screened for their in vitro antimicrobial activity. From the antibacterial activity study, it was observed that compound IVc showed minimum activity and compound IVb and IVd showed better activity. Thus, it was concluded that among all benzimidazole derivatives, antibacterial activity decreases when there is unsubstituted and it increases with chlorine and dimethyl amine on aromatic ring. From the antifungal activity study, it was observed that compound IVd showed better activity against the strain. Thus, it was concluded that the compound having P- dimethyl amine substituent is the more potent than other substitutes.

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