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Original Research Paper

SYNTHESIS, ANTIMICROBIAL AND ANTHELMINTIC ACTIVITY OF SOME NOVEL BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

The benzimidazoles are also known as benzoglyoxalines. Benzimidazole derivatives are very useful intermediates or subunits of the development of pharmaceutical or biological interest. Benzimidazole derivatives play vital role in biological field such as antimicrobial, antiviral, antidiabetic, and anticancer activity**.** Therapeutic significance of these clinically useful drugs in treatment of microbial infections encouraged the development of some more potent and significant compounds. With the purpose of finding new chemical entities with enhanced antimicrobial activity, series comprises 1 and 2-substituted-5-nitrobenzimidazole derivatives were synthesized. The presence of specific functional group were analyzed by IR spectroscopy. The determination of structure for the synthesized compounds by ^{1}H NMR and mass spectroscopy. Antimicrobial activity against bacteria and fungi was studied. The anthelmintic activity was evaluated on adult Indian earth worm *Pheretima posthuma.* The results of preliminary biological tests showed that of these compounds showed significant antimicrobial activity and anthelmintic activity.

Keywords: Benzimidazole, Antimicrobial activity, Anthelmintic activity, Ampicillin, Nalidixic acid, Piperazine citrate.

INTRODUCTION

Benzimidazole derivatives are very useful intermediates or subunits of the development of pharmaceutical or biological interest.[1] Benzimidazole derivatives are an important class of bioactive molecules in the field of drugs and pharmaceuticals.[2] Benzimidazole derivatives have found the application in diverse therapeutic areas including antiulcer, antihypertensive, antiviral, antifungal, anticancer, anti-histaminic[3], antitubercular[4], antiallergic[5,6], antioxidant[7,8], antimicrobial[9-11] and in vitro anti-HIV-1[12] activities etc. A compound containing benzimidazole and benzene rings have been used extensively for pharmaceutical purpose since 1960. 1-H-Benzimidazole rings, which exhibit remarkable basic characteristics due to their nitrogen content, comprise the active substances for several drugs. A number of biological activities have been attributed to these compounds[13.] This ring system is present in numerous antiparasitic, anithelemintic and anti-inflammatory drugs[14-16.] Also, some benzimidazole nucleosides, particularly 5,6-dichloro- benzimidazole-1-β- D-ribofuranoside (DRB) and its 2-substituted derivatives show activity against human cytomegalovirus[17.] It is also known that 5,6-dinitrobenzimidazole can substitute 5,6-dimethylbenzimidazole in the vitamin B_{12} molecule in *Corynebacterium diphteriae* and 2-trifluorobenzimidazoles are potent decouplers of oxidative phosphorylation in mitochondria. They are also inhibitors of photosynthesis, and some exhibit appreciable herbicidal activity[18.] Most recently, antiprotozoal activity of substituted 2-trifluorobenzimidazoles has been reported[19], consistent with several earlier studies on the anti-

giardial activity of various benzimidazole derivatives[20, 21].

MATERIALS AND METHODS

All the chemicals and reagents were of synthetic grade and commercially procured from S.D. Fine Chem. Ltd. (Mumbai, India). The melting points were determined using open capillary tubes and are uncorrected. Purity of the all synthesized compounds was checked by thin layer chromatography technique and iodine was used as visualizing agent. The k_{max} of the compounds was measured by IR spectra were recorded on FT-IR8400S, Fourier Transform (Shimadzu) Infrared spectrophotometer using KBr disk method. ^{1}H NMR spectra were recorded on JEOL (JNM-ECS400, 400 MHz) in dimethyl sulfoxide (DMSO-*d6*) using Tetramethyl silane as an internal standard. The mass spectra were recorded on a MicromassQ-TOF and Shimadzu LC–MS 2010A Mass spectrometer.

General Procedure for Synthesis of 2-Substituted-5-Nitrobenzimidazole Derivatives

To a solution of 1eq. of 4-nitro-*o*-phenylenediamine and 1eq of corresponding aldehyde in ethanol, 4 eq. of $Na_2S_2O_5$ was added and the resulting mixture was reflux for 4 hours. After reaction mixture was cooled to room temperature, diethyl ether was added and the crude product was filtered off. The crude product was suspended in mixture of ethanol-diethyl ether several times until the powder was obtained analytically pure. *Synthesis of 2-(4-Chloro-phenyl)-5-nitro-1H-benzimidazole (A)*

To a solution of 4-nitro-o-phenylenediamine (0.001 mole, 0.15 g) and 4-chloro-benzaldehyde (0.001 mol, 0.14 g) in ethanol, $Na_2S_2O_5$ (0.001 mole, 0.76 g) was added and the resulting mixture was refluxed for 4 hours. After reaction mixture was cooled to room temperature, diethyl ether was added and the crude product was filtered off. The crude product was suspended in mixture of ethanol-diethyl ether several times until the powder was obtained analytically pure. Yield 68%; melting point 272 ^{0}C-274 ^{0}C; IR (KBr)(cm^{-1}): 3264 (N-H), 3066 (CH str.), 1362 (NO_2), 738 (Ar-Cl); ^{1}H-NMR (300 MHz, D_2O): δ 7.7-8.7 (m, 3H, benzimidazole ring), 4.8 (s, H, NH), 7.1-7.4 (m, 4H, ArH); Mass spectra m/z, 273(M)$^+$.

Synthesis of 2-(4-Fluoro-phenyl)-5-nitro-1Hbenzimidazole (B)

Synthetic procedure is same as described for 1A except 4- fluorobenzaldehyde (0.001 mole, 0.12 ml) used in place of 4-chlorobenzaldehyde. Yield 77%; melting point 221^{0}C- 222^{0}C; IR (KBr) (cm^{-1}): 3290 (N-H), 3065 (C-H str.), 1330 (NO_2), 1052 (Ar-F); ^{1}H-NMR (300 MHz, D2O): δ 7.8-8.5 (m, 3H, benzimidazole ring), 4.6 (s, H, NH), 7.3- 7.6 (m, 4H, ArH); Mass spectra m/z, 257(M)$^+$.

General Procedure for Synthesis of Mannich Bases

Equimolar quantity (0.02 mol) of secondary amine was added in to slurry containing the 2-substituted-5-nitro benzimidazole and (37%) formalin (1 mL) solution dissolved in 10 mL of DMSO (Dimethyl sulphoxide). The reaction mixture was stirred for 1 hour at room temperature and refrigerated for 24 hours. The products were separated, dried and recrystallized from ethanol.

N-{[2-(4-chlorophenyl)-5-nitro-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine (A1)

IR (KBr) (cm^{-1}): 1593 (C=N), 3065 (C-H str.Ar),1638 (C=C), 2865,2965 (C-H str.CH_2), 1315 (C-N str),1332 (NO_2), 736 (Ar-Cl) ; ^{1}H-NMR (300 MHz, D2O): δ 7.7-8.4 (m, 3H, benzimidazole ring), 4.27 (s, 2H, CH_2), 7.3- 7.6 (m, 4H, ArH) 2.71 and 3.42 (tand q, N-CH_2CH_3); Mass spectra m/z, 359 (M+1)$^+$.

N-{[2-(4-chlorophenyl)-5-nitro-1H-benzimidazol-1-yl]-methyl}-N-(propan-2-yl)-propan-2amine (A2)

IR (KBr)(cm^{-1}): 1582 (C=N), 3155 (C-H str.Ar),1598 (C=C), 2918 (C-H str.CH_2), 1353 (C-N str), 1337 (NO_2), 730 (Ar-Cl); Mass spectra *m/z*, 386 (M)$^+$, 387(M+1)$^+$.

2-(4-chlorophenyl)-5-nitro-1-(piperidin-1-ylmethyl)-1H-benzimidazole (A3)

IR (KBr)(cm^{-1}): 3051 (C-H str.Ar),1636 (C=C), 2939 (C-H str.CH_2),1568 (C=N str),1336 (NO_2), 697 (Ar-Cl) ; ^{1}H-NMR (300 MHz, D2O): δ 7.5-8.1 (m, 3H, benzimidazole ring), 4.11 (s, 2H, CH_2),

7.3- 7.6 (m, 4H, ArH),1.5-2.37(m,10H,piperidine) ;Mass spectra m/z, 370 $(M)^+$.

2-(4-chlorophenyl)-1-(morpholin-4-ylmethyl)-5-nitro-1H-benzimidazole (A4)

IR (KBr)(cm-1): 3151 (C-H str.Ar),1625 (C=C), 2890 (C-H str.CH_2),1489 (C=N str),1328 (NO_2), 713 (Ar-Cl) ; ^{1}H-NMR (300 MHz, D2O): δ 7.2-8.5 (m, 3H, benzimidazole ring), 4.13 (s, 2H, CH_2), 7.3- 7.6 (m, 4H, ArH), 2.37 (d,4H,morpholine), 3.67 (d,4H,morpholine); Mass spectra m/z, 495$(M)^+$.

N-{[2-(4-Fluoro-phenyl)-5-nitro-1H-benzimidazol-1-yl]-methyl}-N-ethylethanamine (B1)

IR (KBr)(cm^{-1}): 3165 (C-H str.), 1337 (NO_2), 1055 (Ar-F); ^{1}H-NMR (300 MHz, D2O): δ 7.8-8.5 (m, 3H, benzimidazole ring), 4.16 (s, 2H, CH_2), 7.3-7.6 (m, 4H, ArH);Mass spectra m/z, 342 $(M)^+$,343$(M+1)^+$

N-{[2-(4-Fluoro-phenyl)-5-nitro-1H-benzimidazol-1-yl]-methyl}-N-(propan-2-yl)-propan-2-amine (B2)

IR (KBr) (cm^{-1}): 1591 (C=N), 3085 (C-H str.Ar),1534 (C=C), 2978 (C-H str.CH_2), 1337 (NO_2), 1055 (Ar-F); Mass spectra m/z,370$(M)^+$, 371 $(M+1)^+$

2-(4-Fluoro-phenyl)-5-nitro-1-(piperidin-1-ylmethyl)-1H-benzimidazole (B3)

IR (KBr) (cm^{-1}): 3051 (C-H str.Ar), 1556 (C=C), 2850 (C-H str.CH_2),1630 (C=N str), 1340 (NO_2), 1045 (Ar-F); ^{1}H-NMR (300 MHz, D_2O): δ 7.7-8.3 (m, 3H, benzimidazole ring), 4.13 (s, 2H, CH_2), 7.2- 7.5 (m, 4H, ArH), 1.7-2.5 (m,10H,piperidine); Mass spectra m/z, 354$(M)^+$.

2-(4-Fluoro-phenyl)-1-(morpholin-4-ylmethyl)-5-nitro-1H-benzimidazole (B4)

IR (KBr) (cm^{-1}): 3085 (C-H str. Ar), 1630 (C=C), 2928 (C-H str.CH_2), 1458 (C=N str), 1332 (NO_2), 1054 (Ar-F) ; ^{1}H-NMR (300 MHz, D_2O): δ 7.4-8.6 (m, 3H, benzimidazole ring), 4.12 (s, 2H, CH_2), 7.1- 7.5 (m, 4H, ArH), 1.59 (d,4H,morpholine), 3.69 (d, 4H, morpholine); Mass spectra m/z, 356(M).

Anthelmintic Activity[22, 23]

The anthelmintic activity was evaluated on adult Indian earth worm *Pheretima posthuma* due to its anatomical resemblance with the intestinal roundworm parasites of human beings. The activity was carried out using Mathew *etal* method. Four groups of Indian earth worms each containing six earthworms approximately of equal size was used for the study. Each group of earth worms were treated with vehicle (1% CMC), synthesized compounds (10, 50, 100 mg/ml conc.) and piperazine citrate (15 mg/ml). Observations were made for the time taken for paralysis and death of individual worms (Table 2). Paralysis was said to occur when the worms do not revive even in normal saline. Death was concluded when the worms lost their motility, followed with fading away of their body colour.

Antimicrobial Activity

The anti microbial activities of the synthesized compounds were determined by the agar dilution method. All bacteria were grown on Mueller-Hinton agar (Hi-media) plates (37^0C, 24 hours).The synthesized compounds were subjected to antimicrobial screening by cup-plate method for zone of inhibition. The antibacterial activity was tested against various gram-positive and gram negative bacteria compared with standard drug ampicillin and nalidixic acid using solvent control. The microorganism selected for antimicrobial activity were *Staphylococcus aureus* (NTCC-6571)**,** *Bacillus subtilis* (B_2), *Echerichia coli* (TG_1) 4**,** *Sulmonella typhi*. The results were described in the Table 3.

RESULT AND DISCUSSSION

Chemical Synthesis

All the synthesized compounds were first purified by successive recrystallization using appropriate solvents**.** The purity of the synthesized compounds was checked by performing thin layer chromatography and determining melting points. Then the synthesized compounds were subjected to spectral analysis such as IR, NMR and Mass Spectra to confirm the structures. All the analytical details show satisfactory results. All the mass spectra showed the molecular ion peaks for their respective molecular weights apart from fragmentation profile.

Antimicrobial Evaluation

The *in vitro* antimicrobial activity was performed using the cup plate method with different strains of bacteria. Ampicillin and nalidixic acid were used as positive control for bacteria. The results of the final compounds for preliminary antibacterial testing are shown in table 3. The results revealed that the majority of the synthesized compounds showed varying degree of inhibition against the tested microorganisms. In general, the inhibitory activity against the Gram-positive bacteria was higher than that of the Gram-negative bacteria. The chloro substitutions at the 4-position of phenyl ring of 2-(4-chlorophenyl)-1-(morpholin-4-ylmethyl)-5-nitro-1*H*-benzimidazoleand2-(4-chlorophenyl)-5-nitro-1-(piperidin-1-ylmethyl)-1H-benzimidazol-ein the molecule of nitro benzimidazole has the best overall antibacterial profile. The fluoro substituents on phenyl ring at nitro benzimidazole displayed least activity. The compounds showed activity which is comparable with control against bacterial strains in increasing order of 4- Cl> 4-F. This shows that *para* position with lipophilic group may be important to exhibit significant activity as antimicrobial agents. It is quite evident from the above sequence that the compound A3 which contain nitro group (strong electron withdrawing group) at *para* position and a 4-chloro substituent is highly active. The activity decreasing as the electron withdrawing ability of the substituent decreased. The derivatives A3 and A4 exhibited good activity in comparison to the standard.

Anthelmintic Activity

All the synthesized compounds showed significant anthelmintic activity. Among the synthesized compounds2-(4-chlorophenyl)-5-nitro-1-(piperidin-1-ylmethyl)-1H-benzimidazole (A3) showed potential anthelminitic activity 0.981+0.201&1.017+0.159 minutes for paralysis and death respectively when compared with the standard piperazine citrate.

CONCLUSION

The proposed substituted benzimidazole derivatives A [1-4] and B [1-4] were synthesized and evaluated for their antimicrobial and anthelmintic activity. All of the synthesized compounds were found to be active as anthelmintic and antimicrobial agents. Among all the titled compounds, [A3] significantly showed very high anthelmintic activity and [A4] showed moderate antimicrobial activity. Compound [B3] being the most potent compound of this series when compared with the standard drug which means that electron withdrawing group is essential for anthelmintic activity. The significant findings of the present research work in this manuscript may be utilized by the researchers for development of better anthelmintic and antimicrobial agents for future.

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Scheme I: The synthetic route of the target compounds.

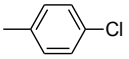
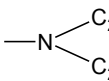
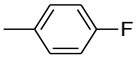
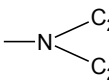
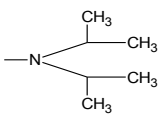
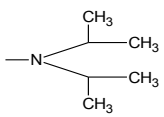
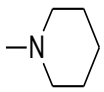
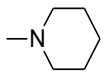
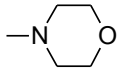
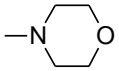
Compound No	R	R^1	Compound No	R	R^1
A1			B1		
A2			B2		
A3			B3		
A4			B4		

Table 1: Physiochemical properties of the synthesized compounds

Compd.	Mol. Formula	Mol. Wt	mp	R_f Value	%Yield
A1	$C_{18}H_{19}ClN_4O_2$	358.82	198	0.342	56
A2	$C_{20}H_{23}ClN_4O_2$	386.87	230	0.461	61
A3	$C_{19}H_{19}ClN_4O_2$	370.83	210	0.387	52
A4	$C_{18}H_{17}ClN_4O_3$	494.96	215	0.293	69
B1	$C_{18}H_{19}FN_4O_2$	342.36	201	0.340	57
B2	$C_{20}H_{23}FN_4O_2$	370.42	211	0.354	72
B3	$C_{19}H_{19}FN_4O_2$	354.37	208	0.285	66
B4	$C_{18}H_{17}FN_4O_3$	356.35	222	0.326	69

Table 2: Anthelmintic activity of Benzimidazole Derivatives

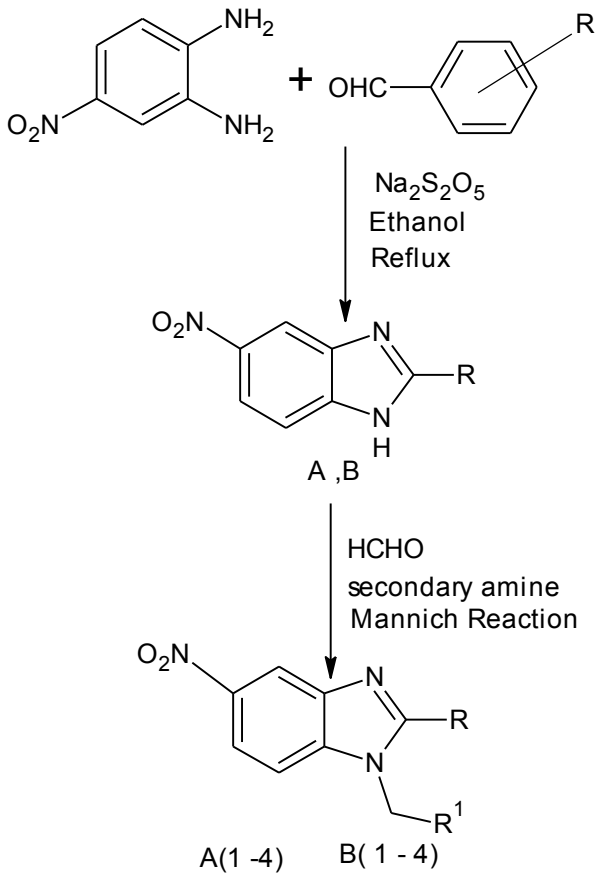
Compound No.	Concentration	Parameter	
		Time taken for paralysis in minutes	Time taken for death in minutes
A1	100	1.89+0.116	2.09+0.304
	50	3.99+0.330	4.62+0.124
	10	12.56+0.729	12.12+0.534
A2	100	1.77+0.191	2.91+0.298
	50	4.01+0.49	4.25+0.910
	10	11.13+0.98	11.98+0.99
A3	100	0.981+0.201	1.017+0.159
	50	30.125+0.315	3.975+0.294
	10	12.60+0.616	13.90+0.761
A4	100	1.80+0.406	2.18+0.340
	50	3.91+0.419	4.95+0.451
	10	11.06+0.325	11.87+0.782
B1	100	2.01+0.227	2.69+0.401
	50	4.09+0.541	4.92+0.224
	10	11.76+0.339	12.22+0.616
B2	100	1.07+0.341	1.91+0.301
	50	3.91+0.56	4.01+0.954
	10	11.53+0.98	11.97+0.899
B3	100	1.00+0.281	1.37+0.159
	50	31.17+0.367	4.275+0.414
	10	11.77+0.671	12.88+0.671
B4	100	1.89+0.515	2.58+0.540
	50	4.01+0.229	4.99+0.625
	10	12.06+0.125	12.87+0.701
Piperazine Citrate	15	42.55 ± 0.52	48.12 ± 0.471

Table 3: Antibacterial activity of compounds

Compound	Mean Zone Inhibition (in mm)a			
	Gram-Positive Bacteria		Gram-Negative Bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*S. typhi*
A1	28	29	22	20
A2	23	26	----	18
A3	38	31	23	14
A4	35	30	18	12
B1	15	-------	10	13
B2	16	17	15	12
B3	22	25	------	14
B4	11	10	15	-----
Ampicillin	38	28	20	------
NalidixicAcid	-------	-------	28.20	28.20

Values are mean (n = 3)
Ampicillin (10 µg/disc) and Nalidixic acid (30 µg/disc) used as positive reference; synthesized compounds (300 µg/disc)'–' indicates no sensitivity or mean inhibition zone diameter lower than 7 mm

SCHEME



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