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SYNTHESIS OF PHENYL HYDRAZINE SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY

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ABSTRACT:

2-Chloromethyl benzimdazole is formed by condensation of o-phenylene diamine with chloroacetic acid. It is then subjected to halide substitution with phenylhydrazines to get the matching NN' disubstituted hydrazines. In vitro anti-inflammatory activity and microbiological screening were performed on the produced compounds.

INTRODUCTION:

Benzimidazole derivatives are an important class of nitrogen containing heterocycles and were reported to possess a wide spectrum of biological properties such as antibacterial, analgesic, anti-inflammatory, antifungal and antimalarial activities. Although a number of drugs are available in the market, thirst for discovering new antimicrobial drugs with better pharmacokinetic profile, and lesser toxicity has become main objectives in the field of medicinal chemistry due to fast development of microbial resistance towards the existing molecules. Despite a number of drugs being in clinical use, search for new NSAIDS is still relevant because the existing molecules suffer from the drawback of adverse effects such as gastric ulceration, inhibition of platelet function, alterations in the renal function, hypersensitivity reactions etc.

RESULTS AND DISCUSSION:

Chemistry: 2- Chloro-methyl benz-imidazoles were prepared by Condensation of O-phenylene diamines with Chloroacetic acid. 2- [(2-phenyl-hydrazinyl) methyl] - 1H- benz-imidazole were prepared by the halide replacement of substituted 2- chloro-methyl benz-imidazole with Phenyl hydrazinyl ring.

Antimicrobial activity:

a) Antibacterial activity:

The antibacterial activity of newly synthesized benzimidazole derivatives has been evaluated against Gram positive *Staphylococcus aureus and Enterobacter cocci and Gram negative Escherichia coli* and *Shigella* species by disc diffusion method. The standards used are Norfloxacin and Gatifloxacin. The antibacterial data is given in the table- 1. b)

Antifungal activity: *Aspergillus niger and Aspergillus flavus:* The antifungal activity of newly synthesized benzimidazole derivatives have been evaluated against *Aspergillus niger and Aspergillus flavus* the standard used is Clotrimazole and Amphotericin B. The antifungal data is given in the table- 2.

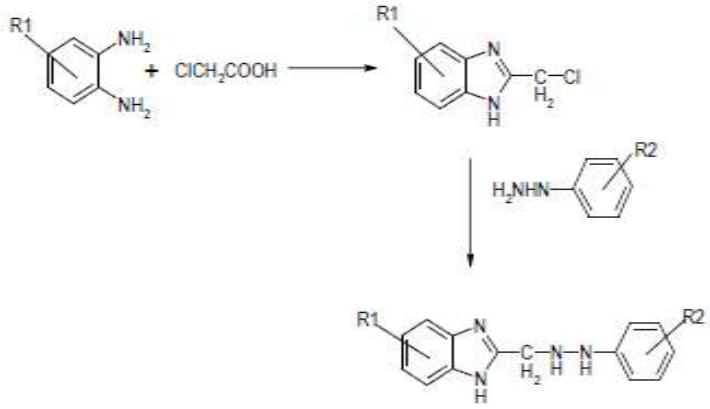
CONCLUSION:

The observation of other compounds revealed that the substitution of 6-nitro group in benzimidazole ring increases the antibacterial activity. All compounds have shown antibacterial activity against Gram positive bacteria as well as gram negative bacteria namely *Staphylococcus aureus*, *Enterococci* and *Escherichia coli Shigella (Gram negative).* The 6-nitro derivative of benzimidazole shows good activity against *Aspergillus niger* and *Aspergillus flavus.*.

Experimental:

Melting points of the synthesized compounds were determined by open capillary method and were uncorrected. IR spectral analysis was carried out using FTIR-8400S, SHIMADZU at M.S.Ramaiah College of Pharmacy, Bangalore. 1HNMR spectral data was obtained from Indian Institute of Sciences, Bangalore. The instrument used was amx-400 and the solvent used was deuterated chloroform. The mass spectral data were recorded from LCMS 2010A, SHIMADZU provided by UWIN Global Services**,** Bangalore.

Scheme 1



COMPOUND	R^1	R^2
3A	H	H
3B	H	-4-NO_2
3C	H	-2,4 NO_2
3D	H	-4-Cl
3E	6-NO_2	H
3F	6-NO_2	-4-NO_2
3G	6-NO_2	-2,4 NO_2
3H	6-NO_2	-4-Cl

TABLE 1: ANTIBACTERIAL ACTIVITY DATA OF THE SYNTHESIZED COMPOUNDS

Compound	R^1	R^2	Antibacterial activity zone of inhibition in (mm)			
			S.aureus (Gram +ve)	*Entrococci* (Gram +ve)	*E. coli* (Gram - ve)	*Shigella* (Gram - ve)
2a	H	H	10	08	07	11
2b	H	-4-NO_2	11	09	08	10
2c	H	-2,4 NO_2	12	09	12	10
2d	H	-4Cl	14	09	10	05
2e	6-NO_2	H	15	12	10	07
2f	6-NO_2	-4N O_2	15	10	11	09
2g	6-NO_2	-2,4 NO_2	13	10	12	05
2h	6-NO_2	-4Cl	12	05	10	05
Norfloxacin	-	-	22	20	25	16
Gatifloxacin	-	-	24	20	24	18
Control (DMF)	-	-	Nl	Nl	Nl	Nl

NOTE: - Average zone diameter in mm of triplicates

General procedure for preparation of phenyl hydrazines 3**:** To a solution of Hydrazine hydrate (0.2mol, 10ml.), hydrochloric acid (10ml) was added dropwise in such a manner that the temperature of solution was maintained at 5-10º C, followed by

NOTE: - Average zone diameter in mm of triplicates ethylene glycol (40 ml) and then substituted aniline (0.087mol) was added. The mixture was refluxed for 2 hours, cooled to room temperature. The separated solid was filtered, dried and recrystalized from ethanol. The yields ranged from 50 – 65%.

General procedure for synthesis of substituted 2- (chloro- methyl)- 1H-benz-imidazole 4, 5, 6**:** The o-phenylene diamine (0.01mol) was dissolved in 4N HCl and chloroacetic acid (0.01mol) was added. The mixture was refluxed for 4 hours, cooled and on neutralization with sodium bicarbonate,

TABLE 2: ANTIBACTERIAL ACTIVITY DATA OF THE SYNTHESIZED COMPOUNDS

Compound	R^1	R^2	Antifungal activity zone of inhibition in (mm)	
			Aspergillus niger	*Aspergillus flavus*
3a	H	H	05	08
3b	H	-4-NO_2	08	09
3c	H	2,4NO_2	05	09
3d	H	-4Cl	09	09
3e	6-NO_2	H	10	12
3f	6-NO_2	-4NO_2	10	10
3g	6-NO_2	-2,4 NO_2	08	10
3h	6-NO_2	-4Cl	07	10
Clotrimoxazol	-	-	13	17
Amphotericin B	-	-	15	18
Control (DMF)	-	-	Nl	Nl

NOTE: - Average zone diameter in mm of triplicates

the product was precipitated. It was filtered, washed with water, dried and recrystalized from ethyl acetate or aqueous ethanol. The yields ranged from 30 –60 %. The spectral data is given below-

Data- 1: IR (KBr): 3249,3213 (N-H str), 1512 (N-H bend), 3056, 3008 (Ar ,C-H str), 1469, 1443 (C=C str), 2950 (CH2 str), 819 (C-Cl) 1HNMR (MeOD): 3.5 (2H, CH2), 12.0 (1H, NH benzimidazole), 7.3 (2H Ar-benzimidazole), 7.6 (2H, Ar-benzimidazole). Mass: M/e-167 (M+), 169 (M+2) and other important peaks are 149, 119.

General procedure for synthesis of 2-[(2-phenylhydrazinyl) methyl} - 1H- benzimidazole7**:** To the ethanolic solution of 2-Chloromethylbenzimidazoles (0.02mol) phenylhydrazine (0.0217mol) were added and it was refluxed for 5 hr. hot mixture was poured in crushed ice with constant stirring. Separated solid was filtered, dried, and recrystallized from ethanol. The yields ranged from 45-65 %. The spectral data is given below-

Data- 2: IR (KBr): 3487, 3404 (N-H str), 1510 (N-H bend), 3053 (Ar, C-H str), 2887, 2817 (CH2 str), 1469, 1436 (C=C str). 1HNMR (CDCl3): 3.6 (2H, CH2), 4. 2 (1H N-H hydrazinyl), 4.5 (1H N-H hydrazinyl), 12.0 (1H, NH Ar-benzimidazole), 8.3 (4H Ar-benzimidazole), 7.8 (5H, phenyl), Mass: M/e-237 (M+) and other important peaks are 124, 109.

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