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Synthesis, Antiinflammatory and Antibacterial Activities of Substituted Phenyl Benzimidazoles

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A new series of substituted benzimidazoles as 1-(substituted methyl)-2-(substituted phenyl) benzimidazoles were synthesized and characterized. The compounds were evaluated for anti-inflammatory and antibacterial activity. All the compounds exhibited significant to moderate antiinflammatory and antibacterial activities.

Key Words: Anti-inflammatory, Antibacterial, 2-Phenyl benzimidazole, Mannich bases.

INTRODUCTION

Benzimidazoles were reported to possess antimicrobial[1, 2], analgesic[3, 4], anti-inflammatory[3, 4], anti-HIV[5] and anticancer[6] activities. Heterocyclic[4] nucleus and amino group substituted at the 2-position of benzimidazole were reported to be associated with potent anti-inflammatory activity. Therefore it was envisaged that a new series of 1-methyl substituted-2-substituted phenyl benzimidazoles would result in compounds of potent antiinflammatory and antibacterial activities.

In the present study, the synthesis, antiinflammatory activity and antibacterial evaluation and structure-activity relationship of 1-(substituted methyl)-2-(substituted phenyl) benzimidazoles have been reported. The compounds were characterized by IR, ^{1}H NMR spectral and elemental analysis.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded (in KBr) on Bomem FT-IR spectrometer M.B. Serial. ^{1}H NMR spectra were recorded on 300 MHz Bruker DPX 300. The chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si). Microanalyses for C, H, N were performed in Heraeus CHN rapid analyzer.

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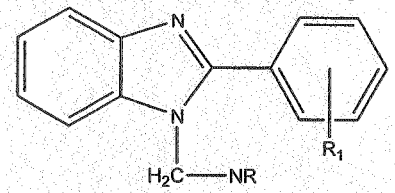
Synthesis of 2-(substituted phenyl) benzimidazole

A solution of substituted-benzoic acid (0.01 mol) and 1,2-phenylendiamine (0.01 mol) in 20 mL acetic acid was refluxed for 15 min; the precipitate obtained was recrystallized from 20% acetic acid. The product was filtered, dried in vacuum and recrystallized from DMF.

General method of synthesis of N-Mannich bases of 2-(substituted phenyl) benzimidazole (1–12)

N-Mannich bases of substituted-phenyl-benzimidazoles were prepared according to the following procedure. To a solution of 2-substituted phenyl benzimidazoles (0.005 mol) in 10 mL of ethanol, 0.005 mol of respective secondary amine and 0.005 mol formaldehyde were added with stirring for 1 h. Then the reaction mixture was refluxed for 20 min. On cooling, the product formed was filtered, dried in vacuum and recrystallized.

TABLE-1
PHYSICAL PARAMETERS OF N-MANNICH BASES OF SUBSTITUTED PHENYL BENZIMIDAZOLES



Cmpd. No.	NR	R^1	m.f.	m.p. (°C)	Yield (%)	Solvent for recrystallization
1	Morpholine	3-NO_2	$C_{18}H_{18}N_4O_3$	120–121	44	DMF-Ethyl acetate
2	Piperidine	3-NO_2	$C_{19}H_{20}N_4O_2$	161–162	52	Benzene
3	Piperazine	3-NO_2	$C_{18}H_{19}N_5O_2$	242–243	49	Chloroform
4	Imidazole	3-NO_2	$C_{17}H_{13}N_5O_2$	69–71	62	Ethyl acetate
5	Diphenyl amine	3-NO_2	$C_{26}H_{20}N_4O_2$	211–212	51	Ethyl acetate
6	Dimethyl amine	3-NO_2	$C_{16}H_{16}N_4O_2$	121–123	56	DMSO
7	4-Methyl piperazine	3-NO_2	$C_{19}H_{21}N_5O_2$	182–183	53	Chloroform
8	4-Ethyl piperazine	3-NO_2	$C_{20}H_{23}N_5O_2$	177–178	62	DMSO-Benzene
9	Piperazine	2-NH_2	$C_{18}H_{21}N_5$	211–212	51	Chloroform
10	Piperidine	2-NH_2	$C_{19}H_{22}N_4$	187–188	47	DMF
11	Diethyl amine	2-NH_2	$C_{18}H_{22}N_4$	134–135	32	Benzene
12	Piperazine	2,4-diCl	$C_{18}H_{18}N_4Cl_2$	178–179	36	DMSO

TABLE-2
SPECTRAL AND ELEMENTAL ANALYSES OF N-MANNICH BASES OF SUBSTITUTED PHENYL BENZIMIDAZOLES

Cmpd. No.	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ: ppm	% of Carbon		% of Nitrogen	
			Calcd.	Found	Calcd.	Found
1	1431 (C—N), 1361 (N—H)	7.29–7.94 (8H, m, Ar-H), 4.23–4.38 (2H, m, CH_2), 2.36–2.51 (8H, m)	63.9	63.54	16.56	16.21
2	1425 (C—N), 1321 (N—H)	7.4–8.221 (8H, m, Ar-H), 4.06–4.19 (2H, m, CH_2), 2.19–2.32 (10H, mCH_2)	67.85	67.56	16.66	16.97
3	1476 (C—N), 1355 (N—H)	7.28–7.93 (8H, m, Ar-H), 5.23–5.41 (1H, m, NH), 4.06–4.22 (2H, m, CH_2), 2.64–2.87 (8H, m)	64.09	64.38	20.77	20.45
4	1452 (C—N), 1342 (N—H)	7.26–7.9 (8H, m, Ar-H), 6.43–6.6 (1H, m, 2′-CH), 6.17–6.32 (2H, m, 4′, 5′ —CH), 4.29–4.41 (2H, m, CH_2)	63.94	63.65	21.94	21.62
5	1478 (C—N), 1371 (N—H)	7.14–7.77 (8H, m, Ar-H), 5.41–5.57 (10H, m, $(C_6H_5)_2$), 4.2–4.36 (2H, m, CH_2)	74.28	74.55	13.33	13.67
6	1465 (C—N), 1339 (N—H)	7.29–7.93 (8H, m, Ar-H), 4.37–4.55 (2H, m, CH_2), 2.1–2.32 (6H, s, $(CH_3)_2$)	64.86	64.56	18.91	18.58
7	1428 (C—N), 1369 (N—H)	7.33–8.04 (8H, m, Ar-H), 4.34–4.48 (2H, m, CH_2), 2.39–2.53 (8H, m), 2.03–2.17 (3H, s, N-CH_3)	64.95	64.64	19.94	19.59
8	1446 (C—N), 1369 (N—H)	7.28–7.9 (8H, m, Ar-H), 4.4–4.52 (2H, m, CH_2), 2.28–2.41 (8H, m), 1.82–1.94 (5H, m, C_2H_5)	65.75	65.53	19.17	19.51
9	1446 (C—N), 1349 (N—H)	7.25–7.69 (m, 8H, Ar-H), 5.11–5.23 (m, 1H; NH), 4.14–4.25 (m, 2H; CH_2), 2.17–2.32 (m, 8H), 1.96–2.09 (s, 2H; NH_2)	70.35	70.69	22.8	22.46
10	1436 (C—N), 1323 (N—H)	7.19–7.74 (m, 8H, Ar-H), 4.28–4.37 (m, 2H; CH_2), 2.43–2.56 (m, 10H), 2.1–2.23 (m, 2H; NH_2)	74.5	74.13	18.3	18.66
11	1483 (C—N), 1392 (N—H)	7.36–7.82 (m, 8H, Ar-H), 4.33–4.41 (m, 2H; CH_2), 2.31–2.46 (m, 10H, $(C_2H_5)_2$), 2.03–2.14 (m, 2Hl NH_2)	73.46	73.78	19.04	19.39
12	1439 (C—N), 1385 (N—H)	7.34–7.8 (m, 7H, Ar-H), 5.43–5.56 (m, 1H; NH), 4.31–4.42 (m, 2H; CH_2)	59.85	59.53	15.51	15.24

Antiinflammatory activity

This activity was performed by following the procedure of Winter *et al.*[7] on groups of six animals each. Edema was induced in the rats by injecting

carrageenan (0.05 mL, 1% (w/v) in 0.9% saline) into the sub-plantar tissue of the right hind paw. One group was kept as control and treated with propylene glycol. The animals of standard drug and drug treated groups were pretreated with standard drug and test compounds given orally 1 h before the carrageenan injection, respectively. The paw volume (mL) was measured before carrageenan injection and 0, 1, 2, and 3 h thereafter, using plethysmometer. The percentage antiinflammatory activity was calculated according to formula given below:

$$\% \text{ antiinflammatory activity} = (1 - V_t/V_c) \times 100$$

where V_t and V_c are the volumes of edema in drug treated and the control groups, respectively. The results are tabulated in Table-3.

TABLE-3
ANTI-INFLAMMATORY ACTIVITY OF N-MANNICH BASES OF SUBSTITUTED PHENYL-BENZIMIDAZOLES (CARRAGEENAN INDUCED RAT PAW EDEMA METHOD)

Cmpd. No.	mg kg^{-1} p.o.	% Inhibition of edema	Cmpd. No.	mg kg^{-1} p.o.	% Inhibition of edema
1	25	20.1*	**7**	25	21.2*
	50	39.7†		50	41.9†
2	25	17.4*	**8**	25	22.2*
	50	34.5*		50	44.6†
3	25	14.3†	**9**	25	25.6†
	50	28.2*		50	49.2*
4	25	11.6*	**10**	25	22.3†
	50	22.9*		50	44.5*
5	25	09.2†	**11**	25	13.6†
	50	17.6*		50	27.9*
6	25	18.2‡	**12**	25	13.6‡
	50	36.5*		50	26.4*

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

Antibacterial activity

All the compounds were screened *in-vitro* for their antibacterial activity[8] against *Staphylococcus aureus, Escherichia coli, Bacillus pumillus, Salmonella typhi, Klebseilla pneumoniae, Pseudomonas aeruginosa* by agar dilution method[9] at 100 μg/mL concentration using DMSO as solvent control. After 24 h of incubation at 37°C, the MIC was measured. The results are tabulated in Table-4.

TABLE-4
ANTIBACTERIAL ACTIVITY OF N-MANNICH BASES OF SUBSTITUTED PHENYL-BENZIMIDAZOLES (AGAR DILUTION METHOD)

Cmpd.	Minimum inhibitory concentration (drug concentrations in μg/mL)					
No.	*S. aureus*	*B. pumillus*	*S. typhi*	*E. coli*	*K. pneumoniae*	*Ps. aeruginosa*
1	25	25	50	50	50	25
2	25	50	25	100	100	50
3	25	25	12.5	100	12.5	25
4	12.5	25	12.5	50	12.5	25
5	25	50	25	100	100	50
6	50	25	50	100	12.5	25
7	25	50	25	100	25	50
8	50	50	25	100	50	50
9	25	12.5	25	50	25	25
10	25	50	50	100	50	50
11	25	12.5	25	50	25	12.5
12	25	25	50	100	25	12.5

RESULTS AND DISCUSSION

All the synthesized compounds were characterized by ^{1}H NMR, IR and elemental analyses. Analyses indicated by the symbols of the elements are within ±0.4% of the theoretical values. In both the evaluations compounds with the methoxy substitutions at R^1 produced better activity than the nitro substitutions. In the antiinflammatory study compounds with morpholine, piperazine, piperidine, 4-methyl piperazine and 4-ethyl piperazine substitutions (**1, 7, 8, 9** and **10**) at NR position produced good antiinflammatory activity where as other compounds were moderately active at the dose level of 50 mg/kg. In the antibacterial evaluation compounds with imidazole, piperazine and diethylamino substitutions (**3, 4, 9, 11** and **12**) at NR position produced good antibacterial activity while other compounds were moderately active.

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