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Synthesis, Antiinflammatory and Antibacterial Activities of 4-Substituted Phenyl Benzimidazoles

J.T. LEONARD, L. JEYASEELI†, O.S. RAJESH, K. MURUGESH†, R. SIVAKUMAR and V. GUNASEKARAN*

Department of Pharmaceutical Chemistry, Vel's College of Pharmacy, Chennai-600 117, India
E-mail: alabarae@yahoo.com

A new series of substituted benzimidazoles as 1-(substituted methyl)-2-(substituted phenyl) benzimidazoles were synthesized and characterized by IR, ^{1}H NMR and elemental analysis. The compounds were evaluated for antiinflammatory and antibacterial activities. All the compounds exhibited significant to moderate anti-inflammatory and antibacterial activities.

Key Words: Antiinflammatory, 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 antiinflammatory 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-methyl substituted-2-substituted phenyl benzimidazoles were reported.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded (in KBr) on Bomem FTIR 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.

Synthesis of 2-(substituted phenyl)benzimidazole

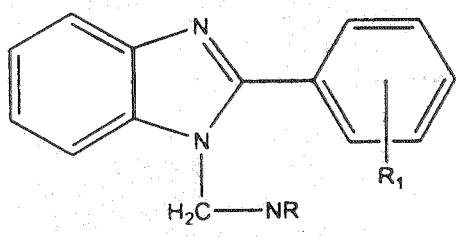
A solution of substituted benzoic acid (0.01 mol) and 1,2-phenylenediamine (0.01 mol) in 20 mL acetic acid was refluxed for 15 min; the precipitate obtained was recrystallized from 20% acetic acid. The product was filtered, dried in vacuum and recrystallized from DMF.

[b]Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700 032, India.

Synthesis of N-Mannich bases of 2-(substituted phenyl)benzimidazole (1–13)

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 VARIOUS SUBSTITUTED N-MANNICH BASES OF SUBSTITUTED PHENYLBENZIMIDAZOLES



Compd. No.	NR	R^1	m.f.	m.p. (°C)	Yield (%)	Solvent for recrystallization
1	Morpholine	4-Cl	$C_{18}H_{18}N_3OCl$	190–191	43	Benzene
2	Piperidine	4-Cl	$C_{19}H_{20}N_3Cl$	174–175	51	Ethyl acetate
3	Piperazine	4-Cl	$C_{18}H_{19}N_4Cl$	182–184	41	DMSO
4	Imidazole	4-Cl	$C_{17}H_{13}N_4Cl$	174–175	48	Chloroform
5	Diphenylamine	4-Cl	$C_{26}H_{20}N_3Cl$	235–236	44	Benzene
6	Dimethylamine	4-Cl	$C_{16}H_{16}N_3Cl$	219–220	59	DMSO
7	Diethanolamine	4-Cl	$C_{18}H_{20}N_3O_2Cl$	81–83	54	DMF
8	Diethylamine	4-Cl	$C_{18}H_{20}N_3Cl$	249–250	41	Ethyl acetate
9	Morpholine	4-NH_2	$C_{18}H_{20}N_4O$	130–131	43	DMSO
10	Piperazine	4-NH_2	$C_{18}H_{21}N_5$	109–110	39	Chloroform
11	Diphenylamine	4-NH_2	$C_{26}H_{22}N_4$	120–121	54	Ethyl acetate
12	4-Methylpiperazine	4-NH_2	$C_{19}H_{23}N_5$	116–117	42	Benzene
13	4-Ethylpiperazine	4-NH_2	$C_{20}H_{25}N_5$	105–106	52	DMF

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

Compd. No.	IR $\nu(cm^{-1})$	^1H HMR ($CDCl_3$) δ: ppm	% of Carbon		% of Nitrogen	
			Calcd.	Found	Calcd.	Found
1	1453 (CN), 1335 (NH)	7.07–7.81 (8H, m, Ar-H), 4.07–4.19 (2H, m, CH_2), 2.15–2.28 (8H, m)	65.96	12.82	65.73	12.49
2	1446 (C—N), 1349 (N—H)	7.15–7.88 (8H, m, Ar-H), 4.11–4.25 (2H, m, CH_2), 2.34–2.45 (10H, m)	70.05	70.36	12.9	12.58
3	1427 (C—N), 1343 (N—H)	7.26–7.82 (8H, m, Ar-H), 4.62–4.7 (1H, m, NH), 4.23–4.31 (2H, m, CH_2), 2.03–2.14 (8H, m)	66.16	66.44	17.15	17.44
4	1446 (C—N), 1328 (N—H)	7.1–7.83 (8H, m, Ar-H), 6.63–6.78 (1H, m, 2′-CH), 6.14–6.31 (2H, m, 4′,5′-CH), 4.26–4.42 (2H, m, CH_2)	66.13	66.41	18.15	18.47
5	1475 (C—N), 1335 (N—H)	7.14–7.9 (8H, m, Ar-H), 5.78–5.92 (10H, m, $(C_6H_5)_2$), 4.61–4.85 (2H, m, CH_2)	76.19	76.48	10.25	10.62
6	1425 (C—N), 1354 (N—H)	7.12–7.64 (8H, m, Ar-H), 4.2–4.32 (2H, m, CH_2), 2.06–2.15 (6H, s, $(CH_3)_2$)	67.26	67.52	14.71	14.42
7	1432 (C—N), 1373 (N—H)	7.4–8.03 (8H, m, Ar-H), 4.47–4.61 (2H, m, CH_2), 3.37–3.52 (2H, m, $(OH)_2$), 2.26–2.39 (8H, m, $(C_2H_4)_2$)	62.52	62.23	12.15	12.42
8	1489 (C—N), 1372 (N—H)	7.22–7.86 (8H, m, Ar-H), 4.16–4.28 (2H, m, CH_2), 2.18–2.34 (10H, m, $(C_2H_5)_2$)	68.91	68.63	13.39	13.71
9	1426 (C—N), 1392 (N—H)	7.25–7.96 (8H, m, Ar-H), 4.18–4.29 (2H, m, CH_2), 2.21–2.38 (8H, m), 2.03–2.16 (2H, m, NH_2)	70.12	70.43	18.18	18.53
10	1465 (C—N), 1352 (N—H)	7.36–7.79 (8H, m, Ar-H), 5.11–5.21 (1H, m, NH) 4.32–4.49 (2H, m, CH_2), 2.34–2.47 (8H, m), 2.13–2.25 (2H, m, NH_2)	70.35	70.01	22.8	22.47
11	1479 (C—N), 1368 (N—H)	7.12–7.89 (8H, m, Ar-H), 5.65–5.88 (10H, m, $(C_6H_5)_2$), 4.32–4.48 (2H, m, CH_2), 2.31–2.46 (2H, m, —NH_2)	80.0	79.71	14.35	14.72
12	1429 (C—N), 1335 (N—H)	7.07–7.83 (8H, m, Ar-H), 4.37–4.49 (2H, m, CH_2), 2.26–2.38 (8H, m), 2.06–2.17 (2H, m, NH_2), 1.88–1.96 (3H, m, —CH_3)	71.02	71.36	21.08	22.12
13	1446 (C—N), 1368 (N—H)	7.25–7.97 (8H, m, Ar-H), 4.27–4.39 (2H, m, CH_2), 2.47–2.55 (8H, m), 2.17–2.26 (2H, m, —NH_2), 1.94–2.07 (5H, m, C_2H_5)	71.64	71.31	20.89	21.23

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
ANTIINFLAMMATORY ACTIVITY OF N-MANNICH BASES OF SUBSTITUTED PHENYL BENZIMIDAZOLES (CARRAGEENAN INDUCED RAT PAW EDEMA METHOD)

Compd. No.	mg kg^{-1} p.o.	% Inhibition of edema	Compd. No.	mg kg^{-1} p.o.	% Inhibition of edema
1	25	11.6*	8	25	15.2*
	50	22.1*		50	31.1†
2	25	08.4‡	9	25	14.8*
	50	16.5*		50	28.5*
3	25	14.6*	10	25	16.6*
	50	28.8*		50	31.9*
4	25	24.9†	11	25	22.8*
	50	49.6‡		50	44.5†
5	25	26.3†	12	25	17.1*
	50	52.2‡		50	34.2†
6	25	27.2†	13	25	21.8†
	50	54.6*		50	42.5*
7	25	13.0*			
	50	24.5*			

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

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 and 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)

Compd. No.	Minimum inhibitory concentration (drug concentrations in μg/mL)					
	S. aureus	*B. pumillus*	*S. typhi*	*E. coli*	*K. pneumoniae*	*Ps. aeruginosa*
1	25	25	50	50	50	25
2	50	50	25	100	100	50
3	25	6.25	50	100	12.5	12.5
4	25	25	50	50	12.5	25
5	25	50	50	100	50	50
6	50	12.5	12.5	50	25	12.5
7	12.5	25	25	100	25	25
8	25	12.5	50	50	50	12.5
9	25	50	25	100	25	50
10	100	25	50	100	25	25
11	50	25	100	50	50	100
12	50	50	12.5	50	12.5	50
13	50	25	50	50	25	25

RESULTS AND DISCUSSION

All the synthesized compounds were characterized by IR, ^{1}H NMR and element analysis. Analysis indicated by the symbols of the elements are within ±0.4% of the theoretical values. The symmetrical compounds were also evaluated for anti-inflammatory and antibacterial activities. 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 imidazole, diphenylamino and dimethylamino substitutions (**4, 5, 6** and **11**) at NR position produced good antiinflammatory activity whereas other compounds were moderately active at the dose level of 50 mg/kg. In the antibacterial evaluation compounds with piperazino, dimethylamino, diethylamino and 4-methyl piperazino substitutions (**3, 6, 8** and **12**) at NR position produced good antibacterial activity while other compounds were moderately active.

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