Asian Journal of Chemistry Vol. 17, No. 4 (2005), 2674–2678

Synthesis, Antiinflammatory and Antibacterial Activities of 2-Hydroxyphenyl Benzimidazoles

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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 activity. All the compounds exhibited significant to moderate anti-inflammatory and antibacterial activities.

Key Words: Anti-inflammatory, Antibacterial, 2-Hydroxy-phenylbenzimidazole, 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 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. The compounds were characterized by IR, ^{1}H NMR spectral and elemental analysis. The compounds were investigated for anti-inflammatory activity by carrageenan induced rate paw edema method and antibacterial method by agar dilution method.

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. Microanalyses for C, H, N were performed in Heraeus CHN rapid analyzer.

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Analyses indicated by the symbols of the elements are within ±0.4% of the theoretical values. ^{1}H NMR and IR spectra were consistent with the assigned structures.

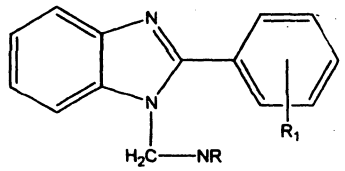
Synthesis of 2-(substituted phenyl)benzimidazole

A solution of substituted benzoic acid (salicylic acid/5-chloro-salicylic acid) and 1,2-phenylendiamine in equimolar ratio (0.01 mol) 20 mL acetic acid was refluxed for 15 min. The precipitate obtained was recrystallized with 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 (1–10)

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 formaldehyde (0.005 mol) 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 2-HYDROXYPHENYL BENZIMIDAZOLES



Compd. No.	NR	R^1	m.f.	m.p. (°C)	Yield (%)	Solvent for recrystallization
1	Piperazine	2-OH	$C_{18}H_{20}N_4O$	200–201	41	Chloroform
2	Piperidine	2-OH	$C_{19}H_{21}N_3O$	139–140	56	Ethylacetate
3	Diethylamine	2-OH	$C_{18}H_{21}N_3O$	136–137	43	DMSO
4	Morpholine	2-OH	$C_{18}H_{19}N_3O_2$	143–144	55	Chloroform
5	Diethanolamine	2-OH	$C_{18}H_{21}N_3O_3$	134–135	41	DMF
6	Piperazine	2-OH, 5-Cl	$C_{18}H_{20}N_4OCl$	150–151	42	Benzene
7	Piperidine	2-OH, 5-Cl	$C_{19}H_{21}N_3OCl$	132–133	45	DMSO
8	Diethylamine	2-OH, 5-Cl	$C_{18}H_{21}N_3OCl$	127–128	48	Chloroform
9	Diphenylamine	2-OH, 5-Cl	$C_{26}H_{21}N_3OCl$	120–121	32	DMF
10	4-Methylpiperazine	2-OH, 5-Cl	$C_{19}H_{22}N_4OCl$	162–163	56	DMSO

TABLE-2
THE SPECTRAL AND ELEMENTAL ANALYSES OF N-MANNICH BASES OF 2-HYDROXYPHENYL BENZIMIDAZOLES

Compd. No.	IR (KBr) cm^{-1}	^1H HMR ($CDCl_3$) δ : ppm	Carbon (%)		Nitrogen (%)	
			Calcd.	Found	Calcd.	Found
1	1438 ν(C—N), 1386 ν(N—H),	7.84–7.96 (m, 1H, —OH), 7.14–7.79 (m, 8H, Ar—H), 5.54–5.65 (m, 1H; NH), 4.14–4.25 (m, 2H; CH_2), 2.15–2.28 (8H, m)	70.12	70.44	18.18	18.51
2	1463 ν(C—N), 1385 ν(N—H),	7.78–7.9 (m, 1H; —OH), 7.08–7.69 (m, 8H, Ar—H), 4.431–4.42 (m, 2H, CH_2), 2.53–2.68 (10H, m)	74.26	74.58	13.68	13.37
3	1489 ν(C—N), 1380 ν(N—H),	7.6–7.73 (m, 1H, —OH), 6.94–7.52 (m, 8H, Ar—H), 4.36–4.48 (m, 2H; CH_2), 2.28–2.46 (10H, m)	73.22	73.49	14.23	14.60
4	1492 ν(C—N), 1358 ν(N—H),	7.66–7.8 (m, 1H; —OH), 7.04–7.59 (m, 8H, Ar—H), 4.21–4.32 (m, 2H; CH_2), 2.15–2.28 (m, 8H)	69.90	69.56	13.59	13.25
5	1459 ν(C—N), 1364 ν(N—H),	7.71–7.82 (s, 1H; —OH), 7.01–7.662 (m, 8H, Ar—H), 3.43–3.52 (s, 2H; $(—OH)_2$), 2.26–2.39 (m, 8H, $(C_2H_4)_2$)	66.05	66.39	12.84	12.50
6	1472 ν(C—N), 1388 ν(N—H),	7.85–7.96 (s, 1H; —OH), 7.15–7.72 (m, 7H, Ar—H), 5.44–5.59 (m, 1H; NH), 4.31–4.44 (m, 2H; CH_2), 2.28–2.41 (m, 8H)	62.89	62.53	16.30	16.66
7	1457 ν(C—N), 1373 ν(N—H),	7.72–7.83 (s, 1H; —OH), 7.18–7.6 (m, 7H, Ar—H), 4.23–4.37 (m, 2H; CH_2), 2.17–2.29 (m, 10H)	66.57	66.31	12.26	12.55
8	1434 ν(C—N), 1346 ν(N—H),	7.76–7.88 (s, 1H; —OH), 7.11–7.65 (m, 7H, Ar—H), 4.42–4.51 (m, 2H; CH_2), 2.25–2.38 (s, 10H, $C_2H_5)_2$)	65.36	65.02	12.70	12.41
9	1422 ν(C—N), 1365 ν(N—H),	7.7–7.83 (s, 1H; —OH), 7.06–7.62 (m, 7H, Ar—H), 5.65–5.78 (s, 10H; $(C_6H_5)_2$) 4.31–4.4 (m, 2H; CH_2)	73.16	73.48	9.84	9.53
10	1428 ν(C—N), 1344 ν(N—H),	7.81–7.9 (s, 1H; —OH), 7.29–7.73 (m, 7H, Ar—H), 4.45–4.62 (m, 2H; CH_2), 2.36–2.48 (m, 8H), 1.35–1.43 (s, 3H; CH_3)	63.78	63.43	15.66	15.32

Antiinflammatory activity

The 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:

% 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 respectively). The results are tabulated in Table-3.

TABLE-3
ANTIINFLAMMATORY ACTIVITY OF N-MANNICH BASES OF 2-HYDROXYPHENYL BENZIMIDAZOLES

Compd. No.	mg kg^{-1} p.o.	% Inhibition of edema	Compd. No.	mg kg^{-1} p.o.	% inhibition of edema
1	25	13.9*	**6**	25	14.8*
	50	26.2†		50	28.9†
2	25	16.5*	**7**	25	15.6*
	50	32.7*		50	30.8†
3	25	21.2*	**8**	25	24.2†
	50	41.8*		50	49.5*
4	25	11.2*	**9**	25	25.1†
	50	22.6‡		50	50.6*
5	25	23.9*	**10**	25	21.7†
	50	47.4‡		50	44.1*

*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, Klebsiella 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
2-HYDROXYPHENYL BENZIMIDAZOLES

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

RESULTS AND DISCUSSION

All the synthesized compounds were evaluated for the antiinflammatory and antibacterial activities. In both the evaluations, compounds with the methoxy compounds with the methoxy substitutions at R^1 produced better activity than the nitro substitutions. In the antiinflammatory study compounds with diethylamino, diethanolamino, diphenylamino and 4-methyl piperazino substitutions (**3, 5, 8, 9** and **10**) 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 piperazine, diethanolamino and diphenylamino substitutions (**1, 5** and **9**) at NR position produced good antibacterial activity while other compounds were moderately active.

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(*Received*: 28 January 2005; *Accepted:* 25 July 2005) AJC-4309