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Synthesis and Antiinflammatory Activity of 1-Aralkyl-2-Aryl-benzimidazoles

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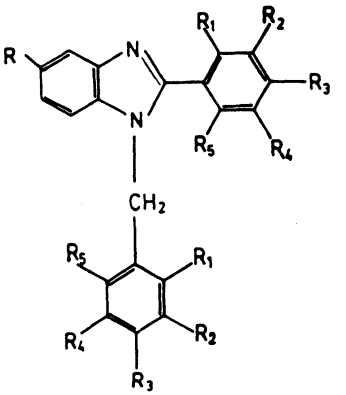
In the present work, we describe the synthesis and antiinflammatory activity of 1-aralkyl-2-aryl benzimidazoles.

INTRODUCTION

Several 2-substituted benzimidazoles are known to exhibit various biological activities.[1] Hence it was thought of considerable interest to synthesise new benzimidazole derivatives with a view to evaluate their antiinflammatory activity.

RESULTS AND DISCUSSION

In the synthesis of benzimidazole derivatives, aldehyde group of aromatic aldehyde is replaced by benzimidazole. These products were obtained in very



(a) $R_1 = H, R_2 = R_3 = R_4 = OCH_3, R_5 = H$ (b) $R_1 = R_2 = H, R_3 = Br, R_4 = R_5 = H,$

(c) $R_2 = NO_2, R_1 = R_3 = R_4 = R_5 = H,$ (d) $R_1 = R_4 = R_5 = H, R_2 = OCH_3, R_3 = OH,$

(e) $R_1 = R_2 = R_4 = R_5 = H, R_3 = CH(CH_3)_2$ (f) $R_1 = OH, R_2 = R_3 = H,$ $R_4, R_5 =$ Benz.

(g) $R_1, R_2 =$ Benz, $R_4, R_5 =$ Benz, $R_3 = H.$

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good yields. The structures of the products were established on the basis of UV,IR, ^{1}H NMR and mass spectroscopic data (Tables 1 and 2).

TABLE-1
PHYSICAL DATA OF COMPOUND 3 (a–g)

Compound	Reaction time	Yield (%)	m.p. (°C)	Molecular formula and other fragments
3a	6h	82	246	$C_{26}H_{28}O_6$ (M^+, 464) 312, 284 (100), 269, 211, 181
3b	5h	63	164	$C_{20}H_{14}N_2Br_2$ (M^+, 444), 443, 441, 172, 171, 170, 169 (100%), 90, 89
3c	6h	68	153	$C_{20}H_{14}N_4O_4$ (M^+, 374 (100)), 375 (M^+, +1), 240, 239, 192, 191, 136, 58.
3d	4h	65	182	$C_{22}H_{20}N_2O_4$ (M^+, 376), 377 (M^+, + 1), 268, 267, 340, 239, 238 (100), 137, 132
3e	6h	62	172	$C_{26}H_{28}N_2$ (M^+, 368), 235, 221, 134, 321 (100%), 131
3f	4h	80	168	$C_{28}H_{20}N_2O_2$ (M^+, 416), 300, 281, 259, 156, 144, 128
3g	9h	70	294	$C_{36}H_{24}N_2$ (M^+, 484), 307, 293, 291, 290 (100%), 289, 203, 189, 176, 145

Preliminary screenings for antiinflammatory activity of benzimidazole derivatives were carried out. Antiinflammatory effect of each compound was measured against simultaneously run controls using the method of winter *et al.*[2] Compounds were found to have significant antiinflammatory activity at 50 mg/kg dose (Table-3).333

Statistically it was suggested that there was no significant reduction in the oedema in all the groups administered with test drug after 1 h ($p < 0.05$). After 4 h there was significant reduction in the oedema in the most of groups administered with the test drug. In case of 3b, 3d and 3a the reduction in oedema was highly significant ($p > 0.001$) as comparable to phenyl butazone ($p > 0.005$) while in the test compound 3f ($p > 0.005$), 3c and 3e, the reduction was also significant ($p > 0.01$) but less than phenyl butazone ($p > 0.005$). After 24 h the reduction in oedema in most of the compounds is not very significant except phenyl butazone (Table-3).

The onset of action was found to be after 1 h and the activity reached its peak at 4 h. The above discussion also suggests that presence of 2 bromo group on benzene ring leads to increase in activity. Compound (3a) having three methoxy groups and compound (3a) one methoxy and one hydroxy group in benzene ring also increase activity but less than bromo compound (3b). Compounds having nitro group and isopropyl group possessed less activity. Compound having one hydroxy and 4,5-benzene fused system possessed more activity but less than bromo, trimethoxy, methoxy and hydroxyl derivatives. The results suggested that compounds 3b, 3a, 3d have more antiinflammatory activity than standard phenyl butazone.

TABLE-2
SPECTRAL DATA OF COMPOUNDS 3(a–g)[5, 6]

Com. No.	λ_{max}	ν_{max} (cm^{-1})	δ
3a	223.6, 252, 309.2 nm	1590, 1432, 1296, 1274, 1236, 1180, 1130 and 1010	3.88 (6H, *S*, 2 × OCH_3), 4.0 (12H, *S*, 4 × OCH_3), 3.76 (2H, *S*, NCH_2—Ar), 7.18 (2H, *d*, J = 1 Hz, m-coupled —H), 7.22 (2H, *d*, J = 1 Hz, m-coupled H), 7.50 (2H, br, *S*, Ar—H), 7.55 (2H, br, *S*, Ar—H).
3b	223.6, 255.2, 290	1600, 1460, 1402, 1325, 795	5.40 (2H, *S*, N—CH_2—Ar), 7.15–7.45 (4H, *d*, *d*, J = 8, 2 Hz Ar—H adjacent to Br), 7.55–7.65 (6H, *dd*, J = 8, 2 Hz, Ar—H), 6.95 (2H, *d*, J = 8 Hz).
3c	218.8, 242.8, 263.2	1616, 1530, 1448, 1266, 1252, 1164, 1094, 934	5.6 (2H, *S*, N—CH_2—Ar), 7.55 (1H, *d*, J = 8 Hz, o-coupled H), 7.65 (1H, *d*, J = 8 Hz, o-coupled H), 7.72 (1H, *d*, J = 8 Hz, o-coupled H), 7.35 (4H, br *m*, ArH of benzimidazole nucleus), 7.95 (1H, *dd*, J = 8H, 2 Hz, Ar—H), 8.05 (1H, *dd*, J = 8, 2 Hz, Ar—H), 8.35 (1H, *dd*, J = 8, 2Hz, Ar—H), 8.02 (1H, *d*, J = 2Hz), 8.55 (1H, *d*, J = 2 Hz, m-coupled H), 8.23 (1 H, *dd*, J = 8, 2 Hz, Ar—H).
3d		3450, 1616, 1540, 1480, 1435, 1290, 1260, 1130, 1050, 820	5.45 (2H, *S*, N—CH_2—Ar), 3.78 (6H, S, 2 × OCH_3), 6.52 (1H, d, J = 8 Hz, o-coupled—H), 6.78 (1H, *d*, J = 8 Hz, o-coupled Ar—H), 6.92 (1H, *d*, J = 8 Hz, o-coupled Ar—H), 7.20 (1H, *d*, J = 8 Hz, o-coupled Ar—H), 6.65 (1H, *d*, J = 0.5 Hz, m-coupled Ar—H), 7.30 (1H, *d*, J = 0.5 Hz, m-coupled Ar—H), 7.35 (3H, br *m*, Ar—H), 7.75 (1H, br *m* ArH), 8.62 (1H, br *S*, OH), 9.15 (1H, br *S*, OH).
3e		1620, 1430, 1410, 1380, 1274, 1220, 1028, 874, 737	1.60 (2H, br *m*, benzylic H), 2.55 (12H, br *S*, 4 × CH_3), 5.35 (2h, *S*, N—CH_3—Ar), 7.15 (6H, br *m*, Ar—H), 7.55 (6H, br *m*, Ar—H).
3f	226, 319.2, 382.8	3500–3450 ν(OH), 1622, 1356, 1326, 1250, 1118, 748	4.80 (2H, *S*, N—CH_2—Ar), 7.15 (2H, *d*, J = 8 Hz, o-coupled H), 7.35 (2H, *d*, J = 8 Hz, o-coupled H), 7.75 (2H, *d*, J = 8 Hz, o-coupled H), 7.85 (2H, *d*, J = 8 Hz, o-coupled H), 7.20 (2H, *m*, Ar—H), 7.45 (2H, *m*, Ar—H), 7.65 (4H, br *m*, Ar—H), 8.20 (1H, *S*, OH) 8.35 (1H, *S*, OH).
3g	220.4, 248.8, 271, 307.2	1591, 1451, 1399, 1369, 1333, 1031, 928, 889, 849	6.20 (2H, *S*, N—CH_2—Ar), 6.95 (2H, *dd*, J = 8.0, 1.5 Hz Ar—H), 7.05 (2H, *dd*, J = 8, 1.5 Hz, Ar—H), 7.30 (2H, *dd*, J = 8, 1.5 Hz, Ar —H), 7.60 (7H, br *S*, Ar—H), 7.75 (1H, *S*, Ar—H), 7.85 (1H, *S*, Ar—H), 8.10 (2H, *dd*, J = 8, 1.5, Ar—H), 8.5 (1H, *dd*, J = 8, 1.5, Ar—H), 8.75 (2H, *dd*, J = 8, 1.5, Ar—H), 8.20 (2H, *dd*, J = 8, 1.5 Hz, Ar—H).

*DMSO-d_6; + $CDCl_3$ + DMSO –d_6: # $CDCl_3$

TABLE-3
ANTIINFLAMMATORY EFFECT OF TEST DRURG 3 (a–f) ON CARRAGENIN INDUCED PAWS OEDEMA IN ALBINO MICE

S. No.	Test drugs	Percentage reduction of oedema ± S.E.		
		1 h	4 h	24 h
1.	Phenyl butazone	29.06 ± 1.91	64.66 ± 1.88[b]	80.12 ± 1.70[c]
2.	3a	26.19 ± 1.30	77.80 ± 0.32[c]	89.01 ± 0.65[b]
3.	b	25.77 ± 0.48	77.02 ± 0.40[c]	88.36 ± 0.66[b]
4.	c	36.15 ± 1.59	75.81 ± 0.58[a]	72.35 ± 0.98
5.	d	23.47 ± 1.98	74.16 ± 0.93[c]	81.87 ± 0.58[b]
6.	e	38.18 ± 0.68	70.83 ± 0.86[a]	75.63 ± 1.38
7.	f	24.05 ± 1.53	70.66 ± 0.86[b]	80.15 ± 1.58[b]

$p > 0.05$, a: $p > 0.01$, b: $p > 0.005$, c: $p > 0.001$; dose 50 mg/kg.

EXPERIMENTAL

M.p.s were taken in open capillary and are uncorrected. The compounds were routinely detected for their purity by TLC on silica gel G. IR spectra (KBr) were recorded on a Hitachi 295 spectrophotometer and PMR spectra (DMSO d_6) on F.T. JeOL (100 MHz) and F.T. Bruker Ac 200 MHz spectrometer using TMS as internal standard.

Antiinflammatory activity: A freshly prepared 1% suspension of carragenin in 0.9% saline was infected under planter aponeurosis of the right paw of the mice by the reported method.[2] One group of six mice was kept as control and animals of other groups of six each were treated with test drugs in a dose of 50 mg/kg. One group received the standard drug phenyl butazone. The volume of foot was measured by the micropipette method[3] and percentage reduction of oedema was calculated at 1 h, 4 h and 24 h.

General Procedure: To the *o*-phenylene diamine hydrochloride (0.01 mol) dissolved in minimum amount of glacial acetic acid was added with stirring, appropriate aromatic aldehyde (0.02 mol) and the reacstion mixture was heated on water bath for 4–9 h. It was poured into-ice cold water and neutralized with ammonia to give solid which was crystallised from organic solvents (3a methanol, 3b ethanol, 3c ethyl acetate and petoleum ether, 3d methanol and dichloromethane, 3e acetone and petroleum ether, 3f petroleum ether).

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