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Synthesis and analgesic activity of some 1-benzyl-2-substituted-4,5-diphenyl-1H-imidazole derivatives

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Abstract

In this study, derivatives of 1-benzyl-2-substituted-4,5-diphenyl-1H-imidazole were synthesized and their analgesic activity assayed in two tests. 1,2,4,5-Tetrasubstituted imidazole compounds were obtained by the treatment of purified imidazole compounds with benzyl chloride in the presence of sodium hydride. The structure elucidation of the compounds was performed by IR, ^{1}H-NMR and mass spectroscopic data and elemental analysis results. Generally the prepared compound exhibited only moderate analgesic activity in mice at the dose of 100 mg/kg i.p.; however, a few of them exhibited good activity, almost equivalent to that of morphine at 1 mg/kg i.p. was observed. At the above dosage, no toxicity was observed for all compounds.
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Keywords: 1,2,4,5-Tetrasubstituted imidazole; Analgesic activity

1. Introduction

Imidazole nucleus forms the main structure of some well-known components of human organisms, i.e. the amino acid histidine, Vit-B_{12}, a component of DNA base structure and purines, histamine and biotin. It is also present in the structure of many natural or synthetic drug molecules, i.e. cimetidine, azomycin and metronidazole. Literature findings, especially on its analgesic [1] and anti-inflammatory [2,3] activities, has prompted us to synthesize similar compounds.

2. Chemistry

For the syntheses of 2-substituted-4,5-diphenyl imidazole derivatives, benzil and aldehyde derivatives were reacted with ammonium acetate in glacial acetic acid as described previously [4]. The obtained 2-substituted-4,5-diphenyl imidazole compounds were stirred with NaH in THF and refluxed by the addition of the benzyl chloride for 3–45 h (Scheme 1).

The structure elucidation of the prepared compounds was performed by IR, ^{1}H-NMR and mass spectral data and elemental analyses.

3. Experimental

3.1. Chemistry

Melting points of the compounds were determined using Stuart Scientific Smpl Melting Point apparatus and were reported uncorrected. Thin-Layer-Chromatography was performed on silica gel 60 GF_{254} and silica gel 60 G (Merck) (15:25) plates and spots were visualized by UV lamp. IR spectra were detected in KBr pellets using a Schimadzu-435 spectrophotometer. The ^{1}H-NMR spectra were recorded in DMSO-d_6 by Jeol-JNM-EX90A spectrometers using tetramethylsilane as an internal standard. Elemental analyses were performed by Carlo-Erba 1106 Analyser and results for C, H, N were within $\pm 0.4\%$ of calculated values. All the chemicals and solvents used in this study were of analytical grade (Merck, Sigma and Aldrich).

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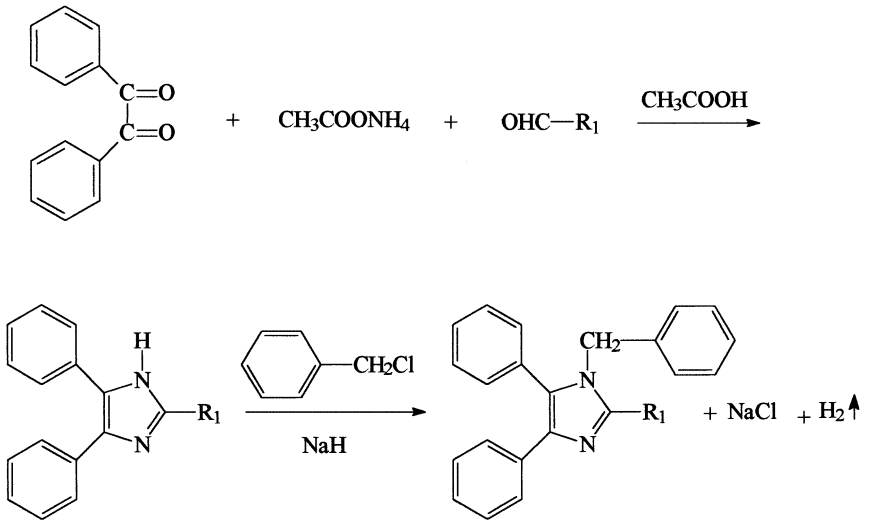

Scheme 1.

3.1.1. General procedure for the synthesis of 1-benzyl-2-substituted-4,5-diphenyl-1H-imidazoles

2-Substituted-4,5-diphenyl imidazoles (0.01 mol) [4] were stirred with 0.015 mol NaH in THF and refluxed by the addition of the benzyl chloride (0.015 mol) for 3–45 h. The content of the reaction vessel was evaporated. Residue was washed with water, dried and recrystallized from ethanol. Melting points and yields are collected in Table 1. Spectral data of the compounds are given in Table 2.

3.2. Pharmacology

3.2.1. Materials

For toxicity and analgesic activity tests, all compounds were dissolved in dimethylsulfoxide (DMSO). Morphine sulfate as opioid agonist and naloxone hydrochloride as opioid antagonist were used as pharmacological standards, similarly dissolved in DMSO.

3.2.2. Acute lethal toxicity

The method of Lorke [10] was used for acute lethal toxicity tests. No mortality was observed after the injection of a dose of 100 mg/kg. Therefore, only a predictive LD_{50} value for each compound was calculated, i.e. $LD_{50} > 100$ mg/kg i.p.

3.2.3. Analgesic activity

Analgesic activity experiments were carried out using Swiss albino mice of both sexes weighing 23–36 g. For primary testing three animals were injected i.p. with each compound; for the active compounds of the primary testing the test was repeated with a group of six animals. The analgesic activity was determined by mechanical (Tail-Clip) and thermal (52.5°C hot water) methods as described previously [11,12]. A control response was also obtained by the intraperitonial administration of DMSO alone. Injection volumes were not more than 0.1 ml at each case. Latencies were measured after 30 min of intraperitonial injections of compounds at doses of 100 mg/kg and percent variation was calculated respect to control response. In order to avoid irreversible damage to the tail structures of animals, a maximum latency of 15 s was imposed for Tail-Clip test, if no response occurred within that time (cutoff time). The mean latency was calculated for each compound. Using the latency, analgesia determined by both mechanical and thermal methods was expressed as a percentage of maximum effect where [12]:

$$\%\ \text{Analgesia} = \left[\frac{\text{postdrug latency} - \text{predrug latency}}{\text{cutoff time} - \text{predrug latency}}\right] \times 100 \quad (1)$$

The reference drugs, morphine sulfate and naloxone hydrochloride, were used i.p. at doses of 1 and 0.4 mg/kg, respectively.

3.2.4. Analysis of data

Results were expressed as means ± standard error of means. Statistical significance relative to controls were determined by Tukey's HSD test, with $P < 0.05$. Statistical calculations have been performed by Minitab statistic program package (version 11.12).

Table 1
Some characteristics of the compounds

Compound	R_1	Yield (%)	Experimental m.p. (°C)	Literature m.p. (°C)	Formula	Molecular mass
1	H	42	116	117–8 [5]	$C_{22}H_{18}N_2$	310.38
2	CH_3	40	120	137–8 [5]	$C_{23}H_{20}N_2$	324.41
3	Ph	42	160–2	164 [6]	$C_{28}H_{22}N_2$	386.48
4	Ph–*o*-OH	41	147–8	–	$C_{28}H_{22}N_20$	402.48
5	Ph–*m*-OH	45	130	–	$C_{28}H_{22}N_20$	402.48
6	Ph–*p*-OH	43	134–5	–	$C_{28}H_{22}N_20$	402.48
7	Ph–*o*-OCH_3	62	187–90	–	$C_{29}H_{24}N_2O$	416.50
8	Ph–*m*-OCH_3	42	128–9	–	$C_{29}H_{24}N_2O$	416.50
9	Ph–*p*-OCH_3	87	153–5	–	$C_{29}H_{24}N_2O$	416.50
10	Ph–*o*-NO_2	74	166–7	–	$C_{28}H_{21}N_3O_2$	431.47
11	Ph–*m*-NO_2	47	115–6	–	$C_{28}H_{21}N_3O_2$	431.47
12	Ph–*p*-NO_2	63	168–71	–	$C_{28}H_{21}N_3O_2$	431.47
13	Ph–*p*-$N(CH_3)_2$	52	155–7	–	$C_{30}H_{27}N_3$	429.54
14	Ph–3,4-(OCH_2O)	82	148–50	–	$C_{29}H_{22}N_2O_2$	430.49
15	Ph–*o*-Cl	48	144–7	–	$C_{28}H_{21}N_2Cl$	420.92
16	Ph–*m*-Cl	54	152–4	–	$C_{28}H_{21}N_2Cl$	420.92
17	Ph–*p*-Cl	49	162–6	–	$C_{28}H_{21}N_2Cl$	420.92
18	Ph–*o*-CH_3	53	123–5	124–5 [7]	$C_{29}H_{24}N_2$	400.50
19	Ph–*m*-CH_3	47	135–7	–	$C_{29}H_{24}N_2$	400.50
20	Ph–*p*-CH_3	92	163–6	162 [8]	$C_{29}H_{24}N_2$	400.50
21	Ph–*o*-Br	62	140–2	–	$C_{28}H_{21}N_2Br$	465.37
22	Ph–*m*-Br	87	155–7	–	$C_{28}H_{21}N_2Br$	465.37
23	Ph–*p*-Br	64	170–4	–	$C_{28}H_{21}N_2Br$	465.37
24	2-Furyl	52	156–8	156–7 [9]	$C_{26}H_{20}N_2O$	376.44
25	Ph–*m*-OCH_3, *p*-OH	45	243–7	–	$C_{29}H_{24}N_2O_2$	423.50
26	Ph–*m*,*p*-$(OCH_3)_2$	42	168	–	$C_{30}H_{26}N_2O_2$	446.53
27	Ph–*o*,*p*-$(CH_3)_2$	72	160–3	–	$C_{30}H_{26}N_2$	414.53
28	Ph–*o*,*m*,*p*-$(OCH_3)_3$	65	132–4	–	$C_{31}H_{28}N_2O_3$	476.55

4. Results and discussion

4.1. Pharmacology

Results of Tail-Clip and thermal analgesic tests were presented in Table 3. At the thermal algesic test all compounds gave a rather poor response; only compounds **21** and **25** exhibited a moderate activity. Better results were obtained at the Tail-Clip algesic test, with about one third of assayed compounds giving a moderate or good response. Particularly compounds **4** and **10** ranged not far from morphine. All compounds tested in the present study were also found to have low lethal toxicity, since their LD_{50} values were greater than 100 mg/kg i.p.

Table 2
Spectral data of the compounds

Compound	IR (KBr, cm^{-1})	^{1}H-NMR (90 MHz) (DMSO-d_6) δ(ppm)	EI-MS (m/z)
1	1625, 1493 (C=N and C=C), 1357 (C–N), 722, 695 (monosubstituted benzene)	5.14 (2H, s, $-CH_2-$), 6.99–7.54 (15H, m, Ar–H), 8.04 (1H, s, imidazole C_2–H)	310, 219, 165, 116, 103, 91 (%100), 89, 77, 65
2	1599, 1521, 1493 (C=N and C=C), 1362 (C–N), 739, 694 (monosubstituted benzene)	2.38 (3H, s, imidazole C_2–CH_3), 5.08 (2H, s, $-CH_2-$), 6.95–7.55 (15H, m, Ar–H)	
3	1601, 1478, 1447 (C=N and C=C), 1350 (C–N), 770, 695 (monosubstituted benzene)	5.15 (2H, s, $-CH_2-$), 6.68–7.71 (20H, m, Ar–H)	386, 295, 192, 165, 103, 91 (%100), 89, 77, 65
4	3408 (O–H), 1621, 1582, 1527 (C=N and C=C), 1390 (C–N), 1314, 1156 (C–O), 1225 (O–H), 774 (1,2-disubstituted benzene), 745, 695 (monosubstituted benzene)	5.38 (2H, s, $-CH_2-$), 7.18–8.20 (19H, m, Ar–H), 11.696 (1H, s, OH)	
5	3370 (O–H), 1601, 1495, 1446 (C=N and C=C), 1387 (C–N), 1268 (C–O), 1223, 1117 (O–H), 952, 861, 793 (1,3-disubstituted benzene), 732, 693 (monosubstituted benzene)	5.11 (2H, s, $-CH_2-$), 6.81–7.62 (19H, m, Ar–H), 11.65 (1H, s, OH)	
6	3696 (O–H), 1607–1439 (C=N and C=C), 1383 (C–N), 1316–1228 (C–O), 1197–1128 (O–H), 831 (1,4-disubstituted benzene), 735, 694 (monosubstituted benzene)	5.25 (2H, s, $-CH_2-$), 7.16–7.26 (2H, d, $J = 8.90$, Ar–H C_3–C_5 of p-OH phenyl), 7.31–7.71 (15H, m, Ar–H), 8.08–8.17 (2H, d, $J = 8.79$, Ar–H C_2–C_6 of p-OH phenyl), 12.58 (1H, s, OH)	
7	1603–1441 (C=N and C=C), 1354 (C–N), 1253–1020 (C–O–C), 748 (1,2-disubstituted benzene), 770, 702 (monosubstituted benzene)	3.36 (3H, s, OCH_3), 4.89 (2H, s, $-CH_2-$), 7.05–7.40 (19H, m, Ar–H)	
8	1600–1426 (C=N and C=C), 1351 (C–N), 1226, 1051 (C–O–C), 952, 886, 793 (1,3-disubstituted benzene), 724, 694 (monosubstituted benzene)	3.66 (3H, s, OCH_3), 5.15 (2H, s, $-CH_2-$), 6.75–7.51 (19H, m, Ar–H)	
9	1605–1447 (C=N and C=C), 1349 (C–N), 1244, 1174, 1072 (C–O–C), 836 (1,4-disubstituted benzene), 770, 694 (monosubstituted benzene)	3.76 (3H, s, OCH_3), 5.12 (2H, s, $-CH_2-$), 6.69–7.50 (15H, m, Ar–H), 6.93–7.03 (2H, d, $J = 8.90$, Ar–H C_3–C_5 of p-OCH_3 phenyl), 7.52–7.62 (2H, d, $J = 8.90$, Ar–H C_2–C_6 of p-OCH_3 phenyl)	416, 325, 103, 91 (%100), 89, 77, 65
10	1601, 1573 (C=N and C=C), 1523, 1355 (N=O), 1326 (C–N), 750 (1,2-disubstituted benzene), 729, 696 (monosubstituted benzene)	5.02 (2H, s, $-CH_2-$), 6.71–8.16 (19H, m, Ar–H)	
11	1612, 1575 (C=N and C=C), 1523, 1349 (N=O), 1308 (C–N), 953, 812, 775 (1,3-disubstituted benzene), 740, 700 (monosubstituted benzene)	5.22 (2H, s, $-CH_2-$), 6.77–8.46 (19H, m, Ar–H)	
12	1598–1549 (C=N and C=C), 1517, 1339 (N=O), 1291 (C–N), 772 (1,4-disubstituted benzene), 732, 696 (monosubstituted benzene)	5.24 (2H, s, $-CH_2-$), 6.72–7.53 (15H, m, Ar–H), 7.92–8.02 (2H, d, $J = 9.13$, Ar–H C_2–C_6 of p-NO_2 phenyl), 8.21–8.31 (2H, d, $J = 9.01$, Ar–H C_3–C_5 of p-NO_2 phenyl)	
13	1679–1490 (C=N and C=C), 1335 (C–N), 813 (1,4-disubstituted benzene), 763, 695 (monosubstituted benzene)	3.00 (6H, s, $N(CH_3)_2$), 5.21 (2H, s, $-CH_2-$), 6.76–8.06 (19H, m, Ar–H)	
14	1622–1452 (C=N and C=C), 1353, 1330 (C–N), 1252, 1221, 1035 (C–O–C cyclic ether), 876, 813 (1,2,4-trisubstituted benzene), 762, 699 (monosubstituted benzene)	5.12 (2H, s, $-CH_2-$), 6.05 (2H, s, $-OCH_2O-$), 6.69–7.50 (18H, m, Ar–H)	
15	1600–1460 (C=N and C=C), 1350 (C–N), 1069 (C–Cl), 760 (1,2-disubstituted benzene), 777, 695 (monosubstituted benzene)	4.90 (2H, s, $-CH_2-$), 6.67–7.57 (19H, m, Ar–H)	
16	1598–1453 (C=N and C=C), 1362–1329 (C–N), 1071 (C–Cl), 911, 830, 790 (1,3-disubstituted benzene), 756, 693 (monosubstituted benzene)	5.16 (2H, s, $-CH_2-$), 6.71–7.70 (19H, m, Ar–H)	

Table 2 (*Continued*)

Compound	IR (KBr, cm^{-1})	^{1}H-NMR (90 MHz) (DMSO-d_6) δ(ppm)	EI-MS (m/z)
17	1600–1415 (C=N and C=C), 1357, 1333 (C–N), 1086 (C–Cl), 775 (1,4-disubstituted benzene), 760, 692 (monosubstituted benzene)	5.15 (2H, s, $-CH_2-$), 6.79–7.74 (19H, m, Ar–H)	
18	1601–1445 (C=N and C=C), 1351 (C–N), 758 (1,2-disubstituted benzene), 775, 692 (monosubstituted benzene)	2.19 (3H, s, CH_3), 4.89 (2H, s, $-CH_2-$), 6.52–7.51 (19H, m, Ar–H)	
19	1603–1453 (C=N and C=C), 1356 (C–N), 913, 870, 805 (1,3-disubstituted benzene), 736, 693 (monosubstituted benzene)	2.39 (3H, s, CH_3), 5.23 (2H, s, $-CH_2-$), 6.78–7.55 (19H, m, Ar–H)	
20	1599–1450 (C=N and C=C), 1348 (C–N), 766 (1,4-disubstituted benzene), 730, 700 (monosubstituted benzene)	2.40 (3H, s, CH_3), 5.23 (2H, s, $-CH_2-$), 6.77–7.68 (19H, m, Ar–H)	
21	1601–1440 (C=N and C=C), 1355, 1334 (C–N), 1069 (C–Br), 750 (1,2-disubstituted benzene), 771, 692 (monosubstituted benzene)	4.88 (2H, s, $-CH_2-$), 6.69–7.75 (19H, m, Ar–H)	
22	1598–1453 (C=N and C=C), 1362 (C–N), 1068 (C–Br), 886, 818, 790 (1,3-disubstituted benzene), 724, 693 (monosubstituted benzene)	5.16 (2H, s, $-CH_2-$), 6.73–7.83 (19H, m, Ar–H)	
23	1620–1445 (C=N and C=C), 1357 (C–N), 1068 (C–Br), 829 (1,4-disubstituted benzene), 774, 692 (monosubstituted benzene)	5.15 (2H, s, $-CH_2-$), 6.796–7.811 (19H, m, Ar–H)	
24	1599, 1492 (C=N and C=C), 1335 (C–N), 1025 (C–O furyl), 762, 695 (monosubstituted benzene)	4.89 (2H, s, $-CH_2-$), 6.87–7.67 (18H, m, Ar–H)	
25	3845 (O–H), 1600, 1543, 1509 (C=N and C=C), 1350 (C–N), 1257, 1219 (O–H), 1177, 1141 (C–O Ar–O–CH_3), 1069, 1027 (C–O Ar–OH), 912, 763 (1,2,4-trisubstituted benzene), 730, 694 (monosubstituted benzene)	3.52 (3H, s, OCH_3), 5.17 (2H, s,$-CH_2-$), 6.82–7.65 (18H, m, Ar–H), 12.54 (1H, s, OH)	
26	1691, 1528 (C=N and C=C), 1352, 1322 (C–N), 1174, 1143, 1020 (C–O Ar–O–CH_3), 915, 807 (1,2,4-trisubstituted benzene), 728, 697 (Monosubstituted benzene)	3.21 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 5.13 (2H, s, $-CH_2-$), 7.12–7.40 (18H, m, Ar–H)	
27	1599–1470 (C=N and C=C), 1347 (C–N), 915, 796 (1,2,4-trisubstituted benzene), 728, 691 (Monosubstituted benzene)	2.36 (3H, s, CH_3), 2.49 (3H, s, CH_3), 5.08 (2H, s, $-CH_2-$), 6.78–7.65 (18H, m, Ar–H)	
28	1602–1449 (C=N and C=C), 1353 (C–N), 1291, 1228, 1094 (C–O–C), 868 (1,2,3,4-tetrasubstituted benzene), 757, 694 (Mono substituted benzene)	3.73–3.81 (9H, t, OCH_3), 4.92 (2H, s, $-CH_2-$), 6.62–7.44 (17H, m, Ar–H)	

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Table 3
Analgesic activities of the compounds

Compound	Thermal algesic test		Mechanical (Tail-Clip) algesic test	
	% Analgesia	Standard error	% Analgesia	Standard Error
1	5.02	8.30	28.03	36.20
2	−9.38	4.58	–	–
3	8.31	2.99	14.22	9.10
4	17.23	16.80	46.15	21.01
5	12.19	10.60	−4.10	6.32
6	2.93	2.46	2.23	1.95
7	−0.99	2.98	−0.91	3.03
8	14.55	16.20	8.49	8.49
9	−6.06	6.35	20.20	16.70
10	9.21	7.05	45.51	16.70
11	0.79	3.24	35.60	20.80
12	6.09	6.19	15.44	17.40
13	−4.84	8.97	3.85	3.85
14	19.76	0.53	2.20	4.95
15	−13.89	10.00	2.38	2.38
16	3.57	3.57	23.81	11.90
17	12.10	8.30	−5.37	5.30
18	10.32	5.20	13.10	11.40
19	−0.03	5.92	28.85	15.80
20	8.26	3.05	0.70	0.65
21	26.41	13.30	2.38	2.38
22	14.70	6.82	4.76	4.76
23	−3.51	3.62	7.86	5.98
24	2.38	2.38	−5.13	5.13
25	22.74	7.75	35.49	20.50
26	−2.56	2.56	2.20	6.44
27	8.83	6.16	−5.27	3.98
28	3.02	6.15	−5.76	3.01
Morphine	70.20	17.40	67.20	17.00
Morphine + naloxone	12.40	2.25	18.00	10.00

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