Synthesis and Biological Activities of 2,6-Diaryl-3-methyl-4-piperidone Derivatives

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In the present study, a new series of 2,6-diaryl-3-methyl-4-piperidones was synthesized by Mannich reaction (condensation) of ethyl–methyl ketone, substituted aromatic aldehydes and ammonium acetate. Oximes and thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones were synthesized by reaction with hydroxylamine hydrochloride and thiosemicarbazide respectively. The chemical structures were confirmed by means of IR, ^{1}H-, ^{13}C-NMR and mass spectral data. The compounds were screened for acute toxicity, analgesic, local anaesthetic and antifungal activity. 2-(4-Methylphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one 2 exhibited the highest analgesic and local anaesthetic activity. The oximes and thiosemicarbazones were completely devoid of analgesic and local anaesthetic activity. 2-(4-Methylphenyl)-3-methyl-6-(4-hydroxyphenyl)-piperidin-4-oxime 21 and 2-(4-methoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime 17 exhibited potent antifungal activity against *Aspergillus niger*. Antifungal activity against *Candida albicans* was observed only with 2-(4-dimethylaminophenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime 20. 2,6-Diaryl-3-methyl-4-piperidones did not exhibit antifungal property.

Key words piperidone; oxime; thiosemicarbazone; analgesic; local anaesthetic; antifungal

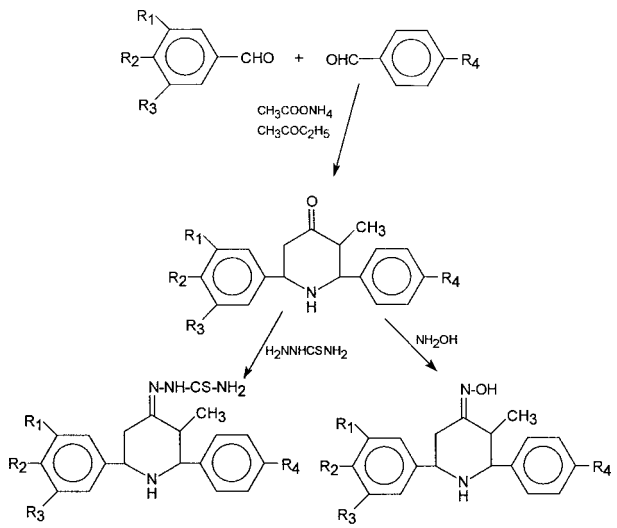
Piperidones were reported to possess analgesic,[1,2] anti-inflammatory,[1] central nervous system (CNS),[3—7] local anaesthetic,[3,8] anticancer[9] and antimicrobial activity.[10] Thiosemicarbazones[11—13] and oximes[14] were reported to be associated with antimicrobial activity. The earlier reports indicated that the biological activities of piperidones were associated with substitutions at 2, 3 and 6 positions.[3,4] The biological activity was found to be significant in compounds possessing aromatic substituents in 2 and/or 6 positions.[5,10] The presence of methyl substitution in 2 or 3 position[5,6] was also attributed to biological activities. Therefore, it was envisaged that a new series of 2,6-diaryl-3-methyl-piperidones and their corresponding, thiosemicarbazones and oximes would result in compounds of potent biological activities.

In the present study, a new series of 2,6-diaryl-3-methyl-4-piperidones was synthesized by Mannich reaction (condensation) of ethyl methyl ketone, substituted aromatic aldehydes and ammonium acetate. Oxime and thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones were synthesized by reaction with hydroxylamine hydrochloride and thiosemicarbazide respectively. The chemical structures were confirmed by means of IR, ^{1}H-, ^{13}C-NMR and mass spectral data. The compounds were screened for acute oral toxicity, analgesic, local anaesthetic and antifungal activity.

CHEMISTRY

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FTIR spectrometer MB104 with KBr pellets. ^{1}H-NMR spectra and ^{13}C-NMR were recorded on 400 MHz-Joel GSX 400 using DMSO-d_6 as solvent. The chemical shifts are reported as parts per million downfield from tetra methyl silane (Me_4Si). Mass spectra were recorded on Finningan MAT 8230. Microanalyses for C, H, N were performed in Heraeus CHN Rapid Analyzer. All the compounds gave satisfactory chemical analyses (±0.4%). The purity of the compounds were checked by TLC on SiO_2 gel (HF_{254}, 200 mesh) coated glass plates using (4 : 1) CCl_4: petroleum ether (40—60 °C) as mobile phase and visualized by iodine vapours. The spectral data are presented in Table 1.

General Procedure for 3-Methyl-2,6-diaryl-piperidin-4-one (1—7) A mixture[15] of ethyl methyl ketone (0.1 mol), dried ammonium acetate (0.1 mol), *p*-chloro/*p*-hydroxy benzaldehyde (0.1 mol) and substituted benzaldehydes (0.1 mol) in ethanol (30 ml) and heated to simmering carefully. It was kept at room temperature for 12 h. Dry ether (50 ml) was added followed by concentrated hydrochloric acid (30 ml) and cooled in ice water. The precipitated hydrochloride was filtered and washed repeatedly with ethanol–ether (1 : 5) mixture. The hydrochloride was suspended in acetone, and made



R_1 = H, OCH_3; R_2 = H, CH_3, OCH_3, $N(CH_3)_2$; R_3 = H, OCH_3; R_4 = Cl, OH

Fig. 1. Synthetic Scheme

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Table 1. Spectral Data of the Synthesized Compounds

Compd	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ ppm	^{13}C-NMR (DMSO-d_6) δ ppm	EI-MS m/z
1	3025 (O–H), 2930 (N–H), 1722 (C=O), 828 (Ar–H)	11.21 (s, 1H; 4′-OH), 9.74 (s, 1H; NH), 6.62—7.87(m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 3.25—3.28 (m, 2H; 2,6-H), 2.04—2.28 (m, 3H; 3,5-H), 0.81 (s, 3H; 3-CH_3)	203.5, 191.1, 163.5, 158.3, 134.1, 133.7, 132.1, 131.2, 130.3, 128.5, 125.5, 115.6, 95.5, 64, 58.7, 46.1, 44.4, 40.1, 39.5, 38.8, 10.3	315 (M^+) (Calcd for $C_{18}H_{18}ClNO_2$: 315.8), 298, 279, 262, 244, 240, 227, 208, 199, 180, 167, 149, 138(B), 117, 103, 91, 77, 57, 51
2	2919 (N–H), 1722 (C=O), 817 (Ar–H)	9.81 (s, 1H; NH), 7.12—8.06 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 3.54—3.62 (m, 2H; 2,6-H), 2.62 (s, 3H; 4′-CH_3), 2.22—2.45 (m, 3H; 3,5-H), 0.84 (s, 3H; 3-CH_3)	203.3, 138.9, 134.1, 131.2, 130.6, 129.3, 128.8, 93.2, 63.9, 58.6, 46.1, 44.6, 40.1, 39.9, 38.8, 20.8, 10.3	313 (M^+) (Calcd for $C_{19}H_{20}ClNO$: 313.8), 293, 276, 261, 244, 242, 221, 208, 199, 181, 168, 167, 146, 138, 118(B), 115, 91, 89, 77, 55, 52
3	2936 (N–H), 1722 (C=O), 829 (Ar–H)	9.81 (s, 1H; NH), 7.45—7.91 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 4.1 (s, 3H; 4′-OCH_3), 3.5—3.64 (m, 2H; 2,6-H), 2.51—2.60 (m, 3H; 3,5-H), 0.83 (s, 3H; 3-CH_3)	203, 131.1, 130.5, 128.9, 114.1, 64, 55.4, 40.1, 39.9, 38.8, 10.4	329 (M^+) (Calcd for $C_{19}H_{20}ClNO_2$: 329.8), 311, 277, 261, 257, 241, 227, 208, 190, 176, 162, 148, 134(B), 117, 103, 91, 77, 56, 52
4	2934 (N–H), 1721 (C=O), 824 (Ar–H)	9.63 (s, 1H; NH), 7.55—8.07 (m, 7H; 2′,5′,6′,2″,3″,5″,6″-H), 3.91 (s, 6H; 3′,4′-OCH_3), 3.64—3.79 (m, 2H; 2,6-H), 2.54—2.68 (m, 3H; 3,5-H), 0.75 (s, 3H; 3-CH_3)	203.4, 134.3, 133.7, 131.2, 130.5, 128.8, 63.9, 58.6, 46.1, 44.3, 40.1, 39.9, 38.8, 10.3	359 (M^+) (Calcd for $C_{20}H_{22}ClNO_3$: 359.8), 335, 333, 303, 288, 279, 262, 240, 227, 220, 192, 180, 167, 140, 138(B), 117, 103, 77, 57, 55
5	2934 (N–H), 1721(C=O), 824 (Ar–H)	9.81 (s, 1H; NH), 7.49—7.78 (m, 6H; 2′,6′,2″,3″,5″,6″-H), 4.02 (s, 9H; 3′,4′,5′-OCH_3), 3.56—3.77 (m, 2H; 2,6-H), 2.45—2.69 (m, 3H; 3,5-H), 0.75 (s, 3H; 3-CH_3)	203.4, 134.2, 131.2, 130.5, 128.8, 63.9, 58.6, 46.1, 44.3, 40.1, 39.9, 38.8, 10.3	390 (M^+) (Calcd for $C_{21}H_{24}ClNO_4$: 389.8), 355, 332, 316, 294, 279, 262, 242, 228, 194, 168, 149(B), 138, 113, 112, 83, 71, 57
6	2938 (N–H), 1722 (C=O), 822 (Ar–H)	9.91 (s, 1H; NH), 7.18—8.04 (m, 8H; 2′,3′,5′,6′,2″,3″,5″, 6″-H), 3.67—3.78 (m, 2H; 2,6-H), 3.08 (s, 6H; 4′-N[CH_3]$_2$), 2.51—2.84 (m, 3H; 3,5-H), 0.75 (s, 3H; 3-CH_3)	203.4, 134.3, 133.7, 131.3, 130.6, 128.9, 111.2, 64.0, 58.7, 46.2, 44.4, 40.1, 39.9, 38.8, 10.3	342 (M^+) (Calcd for $C_{20}H_{23}ClN_2O$: 342.8), 332, 288, 275, 263, 245, 226, 202, 199, 180, 167, 151, 138(B), 117, 103, 89, 77, 57, 52
7	3025 (O–H), 2930 (N–H), 1722 (C=O), 828 (Ar–H)	10.51 (s, 1H; 4″-OH), 9.64 (s, 1H; NH), 7.24—7.82 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 3.47—3.61 (m, 2H; 2,6-H), 2.62 (s, 3H; 4′-CH_3), 2.51—2.74 (m, 3H; 3,5-H), 0.74 (s, 3H; 3-CH_3)	204.6, 158.5, 139.1, 132.8, 130.7, 129.5, 128.6, 125.9, 115.6, 65.2, 64.8, 59.4, 46.6, 44.9, 40.3, 39.9, 21.1, 15.4, 10.6	295 (M^+) (Calcd for $C_{19}H_{21}NO_2$: 295.4), 293, 272, 262, 236, 222, 207, 195, 188, 174, 160, 147, 132, 118(B), 115, 91, 89, 77, 56, 52
8	3461 (NH_2), 3161 (O–H), 2976 (N–H), 1493 (C=S), 1091 (N–C–N), 828 (Ar–H)	11.21 (s, 1H; 4′-OH), 9.78 (s, 1H; NH), 8.15 (s, 1H; =N–NH), 7.01-7.98 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 6.73 (s, 2H; NH_2), 3.61—3.74 (m, 2H; 2,6-H), 2.53—2.76 (m, 3H; 3,5-H), 0.76 (s, 3H; 3-CH_3)	158, 134.3, 133.9, 131.2, 130.6, 129.3, 128.8, 115.7, 86.2, 84.1, 63.9, 58.6, 56.1, 46.1, 44.3, 40.9, 39.9, 38.8, 18.6, 12.2, 10.3	389 (M^+) (Calcd for $C_{19}H_{21}ClN_4OS$: 388.9), 381, 333, 316, 297, 278, 261, 240, 239, 210, 200, 168, 149, 148(B), 113, 112, 83, 70, 57
9	3424 (NH_2), 2974 (N–H), 1494 (C=S), 1091 (N–C–N), 816 (Ar–H)	9.69 (s, 1H; NH), 8.13 (s, 1H; =N–NH), 7.49—7.81 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 7.34 (s, 2H; NH_2), 3.44—3.61 (m, 2H; 2,6-H), 2.55 (s, 3H; 4′-CH_3), 2.42—2.51 (m, 3H; 3,5-H), 0.81 (s, 3H; 3-CH_3)	161, 131, 128.9, 79.3, 78.9, 64, 46, 40.1, 39.9, 38.8	386 (M^+) (Calcd for $C_{20}H_{23}ClN_4S$: 386.9), 361, 346, 321, 303, 289, 275, 261, 243, 232, 215, 191, 177, 167, 149, 128, 117, 91(B), 77, 57, 56
10	3420 (NH_2), 2935 (N–H), 1495 (C=S), 1092 (N–C–N), 828(Ar–H)	9.81 (s, 1H; NH), 8.04 (s, 1H; =N–NH), 7.36—7.91 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 6.96 (s, 2H; NH_2), 3.74 (s, 3H; 4′-OCH_3), 3.42—3.51 (m, 2H; 2,6-H), 2.51—2.80 (m, 3H; 3,5-H), 0.75 (s, 3H; 3-CH_3)	158, 130.9, 129.8, 128.6, 113.9, 79.1, 78.8, 64, 55.1, 40, 39.8, 38.9, 10.1	402 (M^+) (Calcd for $C_{20}H_{23}ClN_4OS$: 402.9), 333, 329, 308, 279, 262, 258, 227, 209, 190, 167, 162, 134(B), 117, 103, 77, 76, 55
11	3421 (NH_2), 2935 (N–H), 1495 (C=S), 1092 (N–C–N), 827 (Ar–H)	9.77 (s, 1H; NH), 8.17 (s, 1H; =N–NH), 7.41—8.01 (m, 7H; 2′,5′,6′,2″,3″,5″,6″-H), 7.28 (s, 2H; NH_2), 3.81 (s, 6H; 3′,4′-OCH_3), 3.39—3.48 (m, 2H; 2,6-H), 2.47—2.55 (m, 3H; 3,5-H), 0.80 (s, 3H; 3-CH_3)	160, 130.9, 128.7, 79.3, 78.9, 64, 50, 40.1, 39.9, 38.8, 10.2	432 (M^+) (Calcd for $C_{21}H_{25}ClN_4O_2S$: 432.9), 359, 333, 279, 262, 240, 228, 199, 183, 167, 149(B), 138, 113, 103, 71, 57
12	3442 (NH_2), 2940 (N–H), 1495 (C=S), 1092 (N–C–N), 828 (Ar–H)	9.81 (s, 1H; NH), 8.28 (s, 1H; =N–NH), 7.36—7.79 (m, 6H; 2′,6′,2″,3″,5″,6″-H), 7.19 (s, 2H; NH_2), 3.96 (s, 9H; 3′,4′,5′-OCH_3), 3.42—3.66 (m, 2H; 2,6-H), 2.54—2.77 (m, 3H; 3,5-H), 0.81 (s, 3H; 3-CH_3)	157, 131, 130.4, 128.7, 100, 79.3, 78.9, 65.2, 47.5, 40.1, 39.9, 38.8, 21.8, 10.2	463 (M^+) (Calcd for $C_{22}H_{27}ClN_4O_3S$: 463.1), 440, 424, 412, 368, 353, 334, 309, 280, 262, 253, 213, 188, 167, 149, 138(B), 105, 76, 57
13	3347 (NH_2), 2945 (N–H), 1495 (C=S), 1092 (N–C–N), 828 (Ar–H)	9.82 (s, 1H; NH), 8.25 (s, 1H; =N–NH), 7.42—7.86 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 6.72 (s, 2H; NH_2), 3.56—3.74 (m, 2H; 2,6-H), 2.72 (s, 6H; 4′-N[CH_3]$_2$), 2.45—2.67 (m, 3H; 3,5-H), 0.82 (s, 3H; 3-CH_3)	162, 134, 133.8, 131, 130.4, 128.6, 79.2, 78.9, 63.8, 58.5, 45.9, 44.2, 40, 39.8, 38.8, 10.1	415 (M^+), (Calcd for $C_{21}H_{26}ClN_5S$: 415.9), 411, 393, 369, 367, 333, 316, 299, 278, 262, 256, 222, 205, 188, 168, 165, 138(B), 117, 103, 77, 76, 51
14	3467 (NH_2), 3421 (O–H), 2922 (N–H), 1512 (C=S), 1069 (N–C–N), 816 (Ar–H)	11.51 (s, 1H; 4″-OH), 9.54 (s, 1H; NH), 8.15 (s, 1H; =N–NH), 6.94—7.34 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 6.68 (s, 2H; NH_2), 3.51—3.76 (m, 2H; 2,6-H), 2.78 (s, 3H; 4′-CH_3), 2.62—2.75 (m, 3H; 3,5-H), 0.89 (s, 3H; 3-CH_3)	160, 131.1, 130.5, 128.9, 114.1, 65, 55.4, 40.1, 39.9, 38.8, 10.4	368 (M^+) (Calcd for $C_{20}H_{24}N_4OS$: 368.5), 332, 320, 297, 278, 262, 256, 227, 208, 192, 168, 166, 148(B), 113, 105, 83, 70, 57

Table 1. Continued

Compd	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ ppm	^{13}C-NMR (DMSO-d_6) δ ppm	EI-MS *m/z*
15	3243 (NO–H), 2920 (N–H), 1652 (C=N), 828 (Ar–H)	11.12 (s, 1H; NOH), 10.26 (s, 1H; 4′-OH), 9.81 (s, 1H; NH), 6.46—7.98 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 3.62—3.86 (m, 2H; 2,6-H), 2.47—2.56 (m, 3H; 3,5-H), 0.85 (s, 3H; 3-CH_3)	153.2, 135.1, 134.6, 131.8, 130.9, 129.1, 128.9, 120.9, 115.6, 79.7, 66.1, 64.3, 59.2, 46.4, 44.7, 40.5, 39.9, 38.2, 28.2, 12.3, 10.6	330 (M^+) (Calcd for $C_{18}H_{19}ClN_2O_2$: 330.8), 316, 302, 299, 282, 263, 254, 239, 227, 208, 194, 176, 167, 142, 140(B), 115, 111, 89, 77, 57, 51
16	3229 (NO–H), 2922 (N–H), 1652 (C=N), 814 (Ar–H)	11.21 (s, 1H; NOH), 9.69 (s, 1H; NH), 7.17—7.75 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 3.52—3.65 (m, 2H; 2,6-H), 2.75 (s, 3H; 4′-CH_3), 2.51—2.65 (m, 3H; 3,5-H), 0.83 (s, 3H; 3-CH_3)	145, 131.1, 130.4, 128.9, 79.3, 78.9, 65, 50, 40.1, 39.9, 38.8	328 (M^+) (Calcd for: 328.8), 308, 291, 279, 263, 255, 243, 222, 208, 191, 172, 167, 149, 140, 120(B), 105, 91, 77, 69, 54
17	3306 (NO–H), 2936 (N–H), 1613 (C=N), 829 (Ar–H)	11.23 (s, 1H; NOH), 9.71 (s, 1H; NH), 7.37—7.98 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 3.84 (s, 3H; 4′-OCH_3), 3.48—3.56 (m, 2H; 2,6-H), 2.52—2.78 (m, 3H; 3,5-H), 0.85 (s, 3H; 3-CH_3)	159.8, 153.2, 134.9, 134, 133, 131.1, 130.5, 128.6, 113.9, 79.3, 78.6, 65.7, 59.2, 58.8, 55.2, 40.1, 39.9, 38.8, 37.9, 28, 12, 11.9	344 (M^+) (Calcd for $C_{19}H_{21}ClN_2O_2$: 344.8), 331, 312, 293, 279, 262, 244, 227, 205, 188, 177, 167, 140(B), 134, 115, 103, 77, 68, 55
18	3217 (NO–H), 2938 (N–H), 1599 (C=N), 826 (Ar–H)	11.17 (s, 1H; NOH), 9.76 (s, 1H; NH), 7.41—8.1 (m, 7H; 2′,5′,6′,2″,3″,5″,6″-H), 3.92 (s, 6H; 3′,4′-OCH_3), 3.52—3.76 (m, 2H; 2,6-H), 2.48—2.66 (m, 3H; 3,5-H), 0.86 (s, 3H; 3-CH_3)	150.8, 132, 131.9, 129.1, 128.4, 126.6, 77.3, 76.6, 63.7, 56.8, 54.2, 38.1, 37.8, 36.8, 35.9, 25.8, 9.9, 8.2	374 (M^+) (Calcd for $C_{20}H_{23}ClN_2O_3$: 374.8), 352, 348, 331, 302, 288, 276, 262, 240, 227, 209, 192, 177, 166, 140(B), 138, 115, 103, 77, 68, 55
19	3334 (NO–H), 2938 (N–H), 1598 (C=N), 827 (Ar–H)	11.12 (s, 1H; NOH), 9.82 (s, 1H; NH), 7.31—7.86 (m, 6H; 2′,6′,2″,3″,5″,6″-H), 3.91 (s, 9H; 3′,4′,5′-OCH_3), 3.61—3.82 (m, 2H; 2,6-H), 2.53—2.66 (m, 3H; 3,5-H), 0.85 (s, 3H; 3-CH_3)	150.8, 132, 131.9, 129.1, 128.4, 126.6, 77.3, 76.6, 63.7, 56.8, 54.2, 38.1, 37.8, 36.8, 35.9, 25.8, 9.9, 8.2	404 (M^+) (Calcd for $C_{21}H_{25}ClN_2O_4$: 404.9), 350, 347, 330, 279, 262, 248, 226, 209, 192, 167, 166, 140(B), 115, 103, 77, 68, 55
20	3335 (NO–H), 2979 (N–H), 1599 (C=N), 827 (Ar–H)	11.14 (s, 1H; NOH), 9.82 (s, 1H; NH), 7.32—7.88 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 3.47—3.64 (m, 2H; 2,6-H), 2.81 (s, 6H; 4′-$N[CH_3]_2$), 2.48—2.68 (m, 3H; 3,5-H), 0.8 (s, 3H; 3-CH_3)	152.9, 134.8, 133.7, 131.2, 130.6, 128.9, 115.9, 96.2, 91.6, 79.4, 78.7, 65.9, 64.2, 59.8, 58.8, 46.2, 44.5, 41, 40.3, 39.9, 38, 35.5, 27.9, 19.7, 12.1, 10.4, 6.8	357 (M^+) (Calcd for $C_{20}H_{24}ClN_3O$: 357.9), 351, 349, 333, 317, 298, 276, 264, 227, 208, 192, 179, 166, 140(B), 138, 115, 103, 77, 68, 55
21	3215 (NO–H), 3010 (O–H), 2938 (N–H), 1600 (C=N), 818 (Ar–H)	11.09 (s, 1H; NOH), 10.15 (s, 1H; 4′-OH), 9.68 (s, 1H; NH), 6.59—7.55 (m, 8H; 2′,3′,5′,6′,2″,3″,5″,6″-H), 3.49—3.68 (m, 2H; 2,6-H), 2.72 (s, 3H; 4′-CH_3), 2.48—2.64 (m, 3H; 3,5-H), 0.84 (s, 3H; 3-CH_3)	153.2, 138.5, 132.9, 129.8, 128.9, 115.1, 79.2, 78.8, 66.2, 40, 39.7, 38.9, 37.9, 27.9, 20.7, 11.9	310 (M^+) (Calcd for $C_{19}H_{22}N_2O_2$: 310.4), 308, 291, 279, 262, 256, 236, 222, 207, 189, 172, 167, 149(B), 132, 120, 105, 91, 71, 57, 54

alkaline using strong ammonia solution. On dilution with excess of water, the base was precipitated which was filtered, vacuum dried and recrystallized from absolute alcohol.

2-(4-Hydroxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one **1**: Yield=73.4%, mp 218—220 °C, *Rf* value=0.84. *Anal.* Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.74; N, 4.44. Found: C, 68.51; H, 5.89; N, 4.71.

2-(4-Methylphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one **2**: Yield=94.4%, mp 250—252 °C, *Rf* value=0.82. *Anal.* Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46. Found: C, 73.04; H, 6.26; N, 4.22.

2-(4-Methoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one **3**: Yield=86.1%, mp 230—232 °C, *Rf* value=0.82. *Anal.* Calcd for $C_{19}H_{20}ClNO_2$: C, 69.20; H, 6.11; N, 4.25. Found: C, 69.48; H, 5.99; N, 4.18.

2-(3′,4-Dimethoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one **4**: Yield=48.9%, mp 264—266 °C, *Rf* value=0.91. *Anal.* Calcd for $C_{20}H_{22}ClNO_3$: C, 66.76; H, 6.16; N, 3.89. Found: C, 66.61; H, 6.34; N, 3.66.

2-(3,4,5-Trimethoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one **5**: Yield=32.5%, mp 250—252 °C, *Rf* value=0.62. *Anal.* Calcd for $C_{21}H_{24}ClNO_4$: C, 64.71; H, 6.21; N, 7.19. Found: C, 64.60; H, 6.36; N, 7.31.

2-(4-Dimethylaminophenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one **6**: Yield=43.9%, mp 198—200 °C, *Rf* value=0.66. *Anal.* Calcd for $C_{20}H_{23}ClN_2O$: C, 70.08; H, 6.76; N, 8.17. Found: C, 69.88; H, 6.51; N, 8.29.

2-(4-Methylphenyl)-3-methyl-6-(4-hydroxyphenyl)-piperidin-4-one **7**: Yield=53.4%, mp 196—198 °C, *Rf* value=0.83. *Anal.* Calcd for $C_{19}H_{21}NO_2$: C, 79.25; H, 7.17; N, 4.74. Found: C, 79.44; H, 7.02; N, 4.57.

General Procedure for 3-Methyl-2,6-diaryl-piperidin-4-thiosemicarbazone (8—14) A mixture of 3-methyl-2,6-diaryl-piperidin-4-one (0.01 mol) and thiosemicarbazide (0.01 mol) dissolved in ethanol (30 ml) was refluxed on a steam bath for 3 h with continuous stirring. The contents were cooled and poured into crushed ice. The precipitate obtained was filtered, washed with water, vacuum dried and recrystallized from absolute alcohol.

2-(4-Hydroxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-thiosemicarbazone **8**: Yield=52.5%, mp 170—172 °C, *Rf* value=0.66. *Anal.* Calcd for $C_{19}H_{21}ClN_4OS$: C, 58.68; H, 5.44; N, 14.41. Found: C, 58.92; H, 5.09; N, 14.27.

2-(4-Methylphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-thiosemicarbazone **9**: Yield=64.7%, mp 206—208 °C, *Rf* value=0.78. *Anal.* Calcd for $C_{20}H_{23}ClN_4S$: C, 62.09; H, 5.99; N, 14.48. Found: C, 61.91; H, 6.22; N, 14.56.

2-(4-Methoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-thiosemicarbazone **10**: Yield=73.6%, mp 218—220 °C, *Rf* value=0.91. *Anal.* Calcd for $C_{20}H_{23}ClN_4OS$: C, 59.62; H, 5.75; N, 13.91. Found: C, 59.88; H, 5.91; N, 13.67.

2-(3,4-Dimethoxyphenyl)-3-methyl-6-(4-chlorophenyl)-

piperidin-4-thiosemicarbazone **11**: Yield=78.9%, mp 188—190 °C, *Rf* value=0.68. *Anal.* Calcd for $C_{21}H_{25}ClN_4O_2S$: C, 58.27; H, 5.82; N, 12.94. Found: C, 57.98; H, 5.98; N, 13.24.

2-(3,4,5-Trimethoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-thiosemicarbazone **12**: Yield=76.4%, mp 172—175 °C, *Rf* value=0.89. *Anal.* Calcd for $C_{22}H_{27}ClN_4O_3S$: C, 57.07; H, 5.88; N, 12.10. Found: C, 57.29; H, 6.12; N, 11.98.

2-(4-Dimethylaminophenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-thiosemicarbazone **13**: Yield=63.5%, mp 216—218 °C, *Rf* value=0.41. *Anal.* Calcd for $C_{21}H_{26}ClN_5S$: C, 60.65; H, 6.30; N, 16.84. Found: C, 60.41; H, 6.15; N, 16.99.

2-(4-Methylphenyl)-3-methyl-6-(4-hydroxyphenyl)-piperidin-4-thiosemicarbazone **14**: Yield=50.9%, mp 152—154 °C, *Rf* value=0.75. *Anal.* Calcd for $C_{20}H_{24}N_4OS$: C, 65.19; H, 6.56; N, 15.20. Found: C, 64.91; H, 6.47; N, 15.38.

General Procedure for 3-Methyl-2,6-diaryl-piperidin-4-oxime (15—21) A mixture of 3-methyl-2,6-diaryl-piperidin-4-one (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) dissolved in ethanol (30 ml) was refluxed on a steam bath for 30 min. The contents were cooled and poured into crushed ice. The precipitated obtained was filtered, washed with water, vacuum dried and recrystallized from absolute alcohol.

2-(4-Hydroxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime **15**: Yield=57.5%, mp 196—198 °C, *Rf* value=0.82. *Anal.* Calcd for $C_{18}H_{19}ClN_2O_2$: C, 65.36; H, 5.79; N, 8.47. Found: C, 65.44; H, 5.85; N, 8.63.

2-(4-Methylphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime **16**: Yield=64.7%, mp 238—240 °C, *Rf* value=0.72. *Anal.* Calcd for $C_{19}H_{21}ClN_2O$: C, 69.41; H, 6.44; N, 8.52. Found: C, 69.29; H, 6.58; N, 8.77.

2-(4-Methoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime **17**: Yield=73.6%, mp 230—232 °C, *Rf* value=0.62. *Anal.* Calcd for $C_{19}H_{21}ClN_2O_2$: C, 66.19; H, 6.14; N, 8.13. Found: C, 65.89; H, 6.30; N, 8.29.

2-(3,4-Dimethoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime **18**: Yield=75.4%, mp 236—238 °C, *Rf* value=0.48. *Anal.* Calcd for $C_{20}H_{23}ClN_2O_3$: C, 64.09; H, 6.18; N, 7.48. Found: C, 63.82; H, 6.37; N, 7.33.

2-(3,4,5-Trimethoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime **19**: Yield=69.3%, mp 238—240 °C, *Rf* value=0.41. *Anal.* Calcd for $C_{21}H_{25}ClN_2O_4$: C, 62.29; H, 6.22; N, 6.92. Found: C, 62.19; H, 6.38; N, 7.09.

2-(4-Dimethylaminophenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime **20**: Yield=71.3%, mp 222—224 °C, *Rf* value=0.52. *Anal.* Calcd for $C_{20}H_{24}ClN_3O$: C, 67.12; H, 6.76; N, 11.74. Found: C, 66.94; H, 6.99; N, 11.66.

2-(4-Methylphenyl)-3-methyl-6-(4-hydroxyphenyl)-piperidin-4-oxime **21**: Yield=45.2%, mp 152—154 °C, *Rf* value=0.74. *Anal.* Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.81; H, 7.22; N, 9.31.

PHARMACOLOGY

The synthesized compounds were evaluated for analgesic, local anaesthetic and antifungal activity. Acute oral toxicity test was performed for all the synthesized compounds as per organization of economic co-operation and development (OECD) guidelines. Statistical analysis (ANOVA followed by Dunnett's *t*-test) was performed for analgesic activity to ascertain the significance of the exhibited activity. The test compounds and the standard drugs were administered in the form of a suspension (1% carboxy methyl cellulose as vehicle) in the same route of administration.

Animals Inbred wistar albino mice (20—30 g) was used. They were kept in colony cages at 25±2 °C, relative humidity 45—55% under 12 h light and dark cycle. The animals were fed with standard animal feed and water *ad libitum*. All the animals were acclimatized for a week before use. Small frogs (*Rana tigrina*; 100—150 g) was procured locally and used on the same day.

Acute Oral Toxicity Acute oral toxicity[16] was performed as per OECD-423 guidelines (acute toxic class method). Wistar albino mice (n=3) of either sex selected by random sampling technique was used for the study. The animals were kept fasting for 3—4 h providing only water, after which the test compounds (suspended in olive oil) were administered orally at the dose level of 5 mg/kg by intragastric tube and observed for 3 d. If mortality was observed in 2—3 animals, then the dose administered was assigned as toxic dose. If mortality was observed in one animal, then the same dose was repeated again to confirm the toxic dose. If mortality was not observed, the procedure was repeated for further higher doses such as 50, 300 and 2000 mg/kg.

Analgesic Activity The analgesic activity[17] was determined by tail immersion method. Wistar albino mice (n=6) of either sex selected by random sampling technique was used for the study. Diclofenac sodium at the dose of 20 mg/kg was administered as standard drug for comparison. The test compounds at 2 dose levels (30 and 60 mg/kg) were administered orally by intragastric tube. The animals were held in position by a suitable restrainer with the tail extending out and the tail (up to 5 cm) was then dipped in a beaker of water maintained at 55±0.5 °C. The time in seconds taken to withdraw the tail clearly out of water was taken as the reaction time. The first reading (0 min) was taken immediately after the administration of the test compound and subsequent reaction time was recorded at 30, 60, 120 and 180 min after the administration of compounds. A cut off point of 15 s was observed to prevent the tail damage. The data are presented in Table 2.

Local Anaesthetic Activity The local anaesthetic activity[18] was determined by nerve block anaesthesia in frogs (n=6). The animal was decerebrated and the upper part of the spinal cord was destroyed with a pithing needle. The abdomen was cut open and all the abdominal organs was removed, so that a pouch (sac) was made to expose the spinal nerves. The animal was fixed on a frog board with two of its hind legs hanging free from the board. The right leg was immersed in a beaker containing 0.1 N hydrochloric acid and the time taken for the absence of withdrawal was noted. The same procedure was repeated for the left leg also. The sac was filled with 2 ml of the test compounds at 0.5, 1, 2% w/v (suspended in 1% carboxy methyl cellulose) and the absence of withdrawal reflex was observed at the interval of 30 s. The leg was washed with normal saline between exposure to acid. Lignocaine (0.5, 1, 2% w/v) was taken as the standard drug for comparison. The data are presented in Table 3.

Antifungal Activity The antifungal activity[19] of the compounds was tested against *C. albicans* and *A. niger* using sabourand dextrose agar medium. The sterilized (antoclaved at 120° for 30 min) medium (40—50°) was inoculated

Table 2. Analgesic Activity of the Compounds by Tail Immersion Method

Compound	Dose (mg/kg)	Pain reaction time in s (mean±S.E.M.)					
		0 min	30 min	60 min	90 min	120 min	180 min
1	30	3.8±0.61	4.6±0.43[b]	7.6±0.43[b]	7.6±0.22[b]	6±0.22[b]	3.5±0.22
	60	3.1±0.45	6.3±0.43[b]	10.3±0.43[b]	10.6±0.16[b]	5.8±0.17[b]	5.8±0.32[b]
2	30	3±0.43	6.6±0.16[b]	9.6±0.22[b]	10.1±0.32[b]	6.8±0.61[b]	4.6±0.22[b]
	60	2.6±0.55	8.5±0.56[b]	10.3±0.43[b]	12.8±0.61[b]	10±0.59[b]	5.6±0.5[b]
3	30	3±0.62	4.3±0.43[b]	6±0.58[b]	7±0.26[b]	4.8±0.31[b]	3.6±0.43
	60	2.8±0.31	4.8±0.31[b]	8.8±0.61[b]	9±0.26[b]	7.3±0.22[b]	4.6±0.43[b]
4	30	2.6±0.21	3.8±0.31[b]	5.6±0.34[b]	6±0.28[b]	7±0.53[b]	4±0.53[a]
	60	2.6±0.34	5.3±0.43[b]	7.1±0.32[b]	9.3±0.43[b]	10.6±0.68[b]	7±0.53[b]
5	30	2.8±0.31	4.6±0.34[b]	4.8±0.61[b]	6.3±0.35[b]	7.6±0.34[b]	4.6±0.53[b]
	60	2.3±0.47	3.8±0.3[b]	5.5±0.34[b]	6.8±0.3[b]	7.3±0.61[b]	5±0.22[b]
6	30	2.6±0.21	4.3±0.21[b]	4.5±0.34[b]	5.6±0.33[b]	6.5±0.28[b]	3.8±0.58
	60	2.6±0.21	4.6±0.21[b]	5.8±0.3[b]	8±0.25[b]	6.3±0.61[b]	3.6±0.21
7	30	3±0.25	4.8±0.3[b]	5.8±0.16[b]	6.3±0.43[b]	5.3±0.31[b]	3.8±0.68
	60	3.1±0.25	5.8±0.3[b]	7.3±0.33[b]	8.5±0.22[b]	5.8±0.56[b]	4.3±0.55[a]
Control	—	2.6±0.21	2.6±0.21	2.8±0.16	2.6±0.21	2.3±0.16	2.6±0.36
Diclofenac	20	2.8±0.16	6.8±0.3[b]	10±0.25[b]	11.8±0.3[b]	14±0.16[b]	12.3±0.43[b]

Significance levels: *a*) $p<0.01$, *b*) $p<0.001$ compared to control.

Table 3. Local Anaesthetic Activity of the Compounds by Nerve Block Anaesthesia

Compound	Concentration	Mean absence of foot withdrawal reflex in s
Lignocaine	0.5%	82.50
	1%	75
	2%	60
1	0.5%	405
	1%	345
	2%	300
2	0.5%	112.50
	1%	90
	2%	67.50
3	0.5%	270
	1%	225
	2%	210
4	0.5%	195
	1%	150
	2%	135
5	0.5%	135
	1%	112.50
	2%	82.50
6	0.5%	345
	1%	225
	2%	210
7	0.5%	330
	1%	240
	2%	210

Table 4. Antifungal Activity of the Compounds by Disc Diffusion Method

Compound	Zone of inhibition (mm)	
	Aspergillus niger	*Candida albicans*
8	9	—
9	11	—
10	10	—
11	10	—
12	9	—
13	9.5	—
15	13	—
16	17	—
17	19	—
18	11	—
19	14	—
20	16	19
21	19	—
Ketoconazole	19	20

(1 ml/100 ml of medium) with the suspension of the microorganism (matched to McFarland barium sulphate standard) and poured into a petridish to give a depth of 3—4 mm. The paper impregnated with the test compounds (1 mg/ml in dimethyl sulphoxide) was placed on the solidified medium. The plates were preincubated for 1 h at room temperature and incubated at 37 °C for 48 h for antifungal activity. Ketoconazole (100 μg/disc) was used as standard. The observed zone of inhibition is presented in Table 4.

RESULTS AND DISCUSSION

Compounds **1**—**4**, **8**—**12**, **14**—**20** did not cause mortality up to 2000 mg/kg and were considered as safe (x-unclassified). Compounds **5**—**7**, **13**, **17**, **18** and **21** produced mortality at 2000 mg/kg and they were considered as class-4 compounds.

Compounds **1**—**7** exhibited significant analgesic and local anaesthetic activity. Graded dose response was observed for the active compounds. 2-(4-Methylphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one **2** exhibited the highest analgesic and local anaesthetic activity. It was observed that when the 4-keto functionality was condensed to form thiosemicarbazones (**8**—**14**) or oximes (**15**—**21**), the resulting compounds did not exhibit analgesic and local anaesthetic activity. The predominant and stable configuration[20] of 2,6-diaryl-3-substituted-piperidones is chair form with the substituents in the equatorial positions. The analgesic and local anaesthetic activity of compounds **1**—**7** may be attributed to this favourable configuration. The introduction of thiosemicarbazino (**8**—**14**) or oxime (**15**—**21**) substitution probably leads to unfavourable configuration of the molecules resulting in compounds completely devoid of analgesic and local anaesthetic activity. Therefore, the 4-keto moiety of

the present series of piperidones seems to play a vital role in the analgesic and local anaesthetic activity of the compounds.

Compounds **8**—**13**, **15**—**21** exhibit antifungal activity against *A. niger*. Antifungal activity against *C. albicans* was only observed with 2-(4-dimethylaminophenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime **20**. 2-(4-Methylphenyl)-3-methyl-6-(4-hydroxyphenyl)-piperidin-4-oxime **21** and 2-(4-methoxyphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-oxime **17** was found to exhibit equivalent antifungal activity against *A. niger* compared to ketoconazole. The compounds with 4-keto group (**1**—**7**) did not exhibit antifungal activity.

In the present series of compounds, the oxime substitution at the 4 position and 4-dimethylamino phenyl substitution at the 2 position seems to play a vital role in the activity against *C. albicans*. The activity against *A. niger* was significantly higher for oximes (**15**—**21**) than the corresponding thiosemicarbazones (**8**—**14**). The presence of thiosemicarbazino or oxime functionality at the 4-position of the present series of piperidones seems to possess an important role in the antifungal activity of the compounds.

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