Int J Pharm Bio Sci 2014 Oct; 5(4): (P) 543 - 551

Research Article **Medicinal chemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF SOME NEW 2,6-DIARYLPIPERIDIN-4-ONE DERIVATIVES

R. SRIKANTH*[1], A. SIVARAJAN[2] AND B. SIVAKUMAR[3]

Analytical R&D, Gland Pharma Limited, Hyderabad-500 043, India
[1]Gland Pharma Limited, Near Gandimaisamma "X" Roads, D.P.Pally, Dundigal Post, Hyderabad – 500 043, India.
[2]Department of Chemistry, Government Arts College, Bharathidasan University, Tiruchirappali – 620 022.
[3]Orchid Chemicals and Pharmaceuticals Ltd, Sholinganallur, Chennai-600119, India

ABSTRACT

Acetic acid promoted one-pot Mannich type condensation involving long chain ketones results in the formation of 3-substituted or 3,5-disubstituted 2,6-diarylpiperidin-4-ones in moderate yields. In the absence of acetic acid, the reaction does not proceed to completion. The six member heterocyclic ring adopts a chair conformation, with equatorial disposition of all the substituents. Among the different derivatives of piperidine-4-one, derivatives containing tetrazole and semicarbazone are more potent than the alkyl derivatives against bacteria and fungi.

KEYWORDS: **2,6-diarylpiperidin-4-ones; *Mannich reaction*; semicarbazone; Antimicrobial activity.**

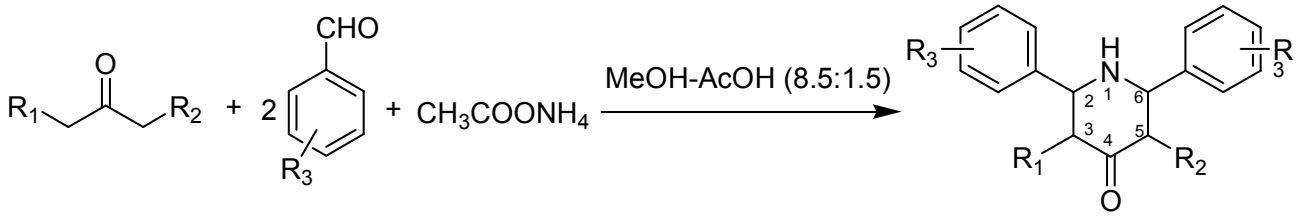
R. SRIKANTH
Gland Pharma Limited, Near Gandimaisamma "X" Roads,
D.P.Pally, Dundigal Post, Hyderabad – 500 043, India.

INTRODUCTION

Among the family of Nitrogen containing six membered heterocyles, the piperidine structural motif is ubiquitious in nature and often found to be naturally occurring bioactive compounds such as alkaloids.[1] Piperidin-3-one derivatives are used as precursors for the synthesis of antimalarial agents Febrifugine and Isofebrifugine.[2] Piperidin-4-ones mostly display varied and potent biological properties such as Antiviral, Antitumour,[3] Analgesic,[4] local Anaesthetic,[5,6] Depressant activities,[7–10] Antimicrobial, Fungicidal, Herbicidal, Insecticidal, Antihistaminic, Anti-inflammatory, Anticancer.[3] CNS stimulant and Recent reports suggest that compounds containing the piperidin-4-one moiety elicit excellent activity when aromatic substitutions are present at 2- and/or 6-positions.[3] Mannich reaction is one of the multicomponent reactions for the carbon-carbon and carbon-heteroatom sequential bond formation. Mannich type condensation involving aromatic aldehydes, ammonium acetate and ketones having two active methylene groups, resulting in the formation of 2,6-diarylpiperidin-4-ones, was first reported by Noller and Baliah.[11] However, a mixture of 2,6-diarylpiperidin-4-one and diazabicyclononane derivatives were obtained from the condensation of acetone, ammonia and arylaldehyde.[12,13] Later on, Jeyaraman and Baliah reported a similar condensation involving cyclohexanone resulting in the formation of azabicyclononanes.[14] To our knowledge, Mannich type condensation involving other linear ketones having long alkyl chains have not been reported in the literature. Recently, Thennarasu & Perumal reported the formation of 3-pentyl-2,6-diphenylpiperidin-4-one via Mannich-type condensation of octan-2-one, benzaldehyde and ammonium acetate in absolute ethanol.[15] However, the reaction did not proceed well in other organic solvents. Mannich type reactions catalyzed by proline derivatives, transition metal salts, organocatalysts, ionic liquids, and Lewis acids have been reported as efficient methods to prepare β-amino carbonyl compounds.[16-21] Very recently, Anderson and coworkers have shown that acetic acid can catalyze Nitro-Mannich reaction to give a variety of β-nitroamines[22]. These observations prompted us to examine whether acetic acid promotes the three-component Mannich type condensation and the subsequent formation of 2,6-diarylpiperidine-4ones. In this article, we report acetic acid catalyzed synthesis of some new 2,6-diarylpiperidin-4-ones. The conformational preferences of the products were analyzed as the heterocyclic ring is fully substituted. Antimicrobial and antifungal properties of 2,6-diarylpiperidin-4-one derivatives were also evaluated. The results of our study assume importance, that the conformation of biologically important piperidine derivatives is crucial to the key interactions with the receptors. The general synthetic scheme for the 2,6-diarylpiperidin-4-one and semicarbazone derivatives are shown in Scheme 1 & Scheme 2, respectively.

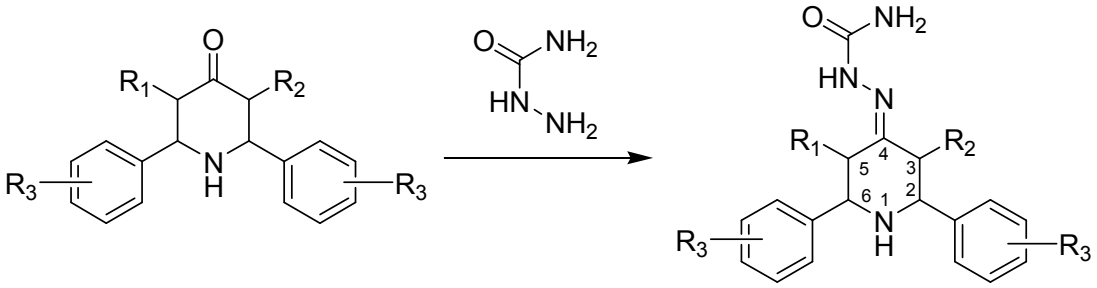
Scheme 1

General synthetic scheme of 2,6-diarypiperidin-4-one derivatives



Scheme 2

General synthetic scheme of semicarbazone derivatives of 2,6-diarypiperidin-4-one



MATERIALS AND METHODS

Melting points were determined on a Mettler toledo apparatus and uncorrected. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance spectrometer at 400 and 100 MHz, respectively. The DEPT, H,H-COSY, ^{1}H-^{13}C HMBC and ^{1}H-^{13}C HSQC spectra were recorded by employing the standard pulse programs built in the Bruker Avance NMR 400 MHz spectrometer and Jeol NMR 500MHz spectrometer. IR spectra were obtained on a Perkin-Elmer Spectrum paragon 1000 spectrometer. The UV-Vis spectra were obtained using Perkin-Elmer lambda-20 spectrophotometer. The molecular mass was determined using PE SCIEX API 4000 mass spectrometer.

EXPERIMENTAL

General method for the synthesis of substituted 2,6-diarylpiperidin-4-ones title compounds (1-7):

Aromatic aldehyde (0.2 mol), octan-2-one or octan-3-one (0.1 mol; E. Merck) and ammonium acetate (7.7g, 0.1 mol) were added to glacial acetic acid-methanol (15:85 v/v) mixture (100 mL) placed in a round-bottom flask. The contents of the flask were heated under reflux in an oil-bath for 6-12 h and the formation of 2,6-diarylpiperidin-4-ones were monitored by diluting an aliquot of the reaction mixture in ether and adding a drop of conc. HCl to obtain the precipitates of the corresponding salts. Heating was stopped when the reaction mixture developed amber colour. The solution was left standing overnight and the precipitate formed was separated by filtration. The white solids obtained were purified further by crystallization from methanol.

General method for the preparation of semicarbazone derivatives title compounds (8-11):

A mixture of 2,6-diarylpiperidin-4-one (0.01 mol) and semicarbazide (0.01 mol) dissolved in methanol (40 mL) was refluxed on a steam bath for 1-2 hrs with continuous stirring. The contents were cooled and poured into crushed ice. The precipitate obtained was filtered, washed with water and vacuum dried.

CHEMISTRY

IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra were consistent with the assigned structures.

3-Butyl-5-methyl-2,6-bis(4-methoxyphenyl)piperidin-4-one, 1

IR (KBr, υ = cm^{-1}): 3420 (NH), 2955 & 2933 (CH), 1708 (C=O), 1512, 1457 (aromatic C=C) stretching. 1H-NMR ($CDCl_3$ 400 MHz, ppm): δ 7.34 (dd, 1H, ArH, J = 8.5 & 1.4 Hz), 6.86 (dd, ArH, J = 8.6 & 1.4 Hz), 3.60 (d, C-2H, 1H, J=10.4 Hz), 3.51 (d, C-6H, 1H, J =10.3 Hz), 3.27 (m, C-3H, 1H), 2.65-2.76 (m, C-5H, 1H), 0.80 (d, 3H, C-5CH_3, J = 6.6 Hz), 1.62-1.66 & 1.20-1.35 (m, 2H, C$H_2$$CH_2CH_2CH_3$), 1.11-1.16 (m, 2H, CH_2C$H_2$$CH_2CH_3$), 0.93-0.97 (m, 2H, CH_2CH_2C$H_2$$CH_3$), 0.78 (t, 3H, CH_2CH_2CH_2CH_3, J = 7.2 Hz), 3.79 & 3.80 (OCH_3, 2 x s). ^{13}C-NMR ($CDCl_3$, 100 MHz, ppm): δ 210.9 (C=O), 159.5, 133.4, 129.2, 129.1, 114.3, 114.1 30.6 (C6), 25.0 (C3), 23.1 (C4), 14.1 (C5), 13.7 (C7). MS (m/z): 382.0 (M+1).

3-Butyl-5-methyl-2,6-bis(3,4-dimethoxyphenyl)piperidin-4-one, 2

IR (KBr, υ = cm^{-1}): 3411, 2955, 2936, 1716, 1519, 1466, 1264, 1155. ^{1}H-NMR ($CDCl_3$, 500MHz, ppm): 7.01 (m, 2H, ArH), 6.93 (t, 1H, ArH), 6.94 (t, 1H, ArH), 6.83 (d, 1H, ArH, J=2.8 Hz), 6.81 (d, 1H, ArH, J=2.8 Hz), 3.61 (d, C-2H, 1H, J =10.3 Hz), 3.51 (d, C-6H, 1H, J =10.3Hz), 2.68-2.81 (m, 1H, C-5H) 0.83 (d, 3H, C-5CH_3, J=6.8 Hz), 1.65-1.67 & 1.31-1.36 (m, 2H, C$H_2$$CH_2CH_2CH_3$), 1.12-1.18 (m, 2H, $CH_2C$$H_2$$CH_2CH_3$), 0.92-1.00 (m, 2H, $CH_2CH_2C$$H_2$$CH_3$), 0.76 (t, 3H, $CH_2CH_2CH_2C$$H_3$, J=7.4 Hz), 3.88 & 3.92 O-CH_3 (2 x s, 6H, 2 x OCH3). ^{13}C-NMR ($CDCl_3$, 125MHz, ppm): 149.0, 148.7, 134.4, 120.3, 120.1, 110.8, 110.6, 110.4, 30.1, 24.8, 22.9, 20.8, 14.0, 10.7; O-CH_3 (55.9-56.0). MS (m/z): 442 (M+1).

3-Butyl-5-methyl-2,6-bis(3,4,5-trimethoxyphenyl)piperidin-4-one, 3

IR (KBr, υ = cm^{-1}): 3433, 3318, 2936, 1701, 1593, 1464, 1234, 1127. ^{1}H-NMR ($CDCl_3$, 500MHz, ppm): 6.67-6.66 (m, 4H, ArH), 3.57 (d, 1H, C-2H, J = 10.5 Hz), 3.47 (d, 1H, C-6H, J = 10.2 Hz), 2.67-2.79 (m, 1H, C-5H), 2.01 (d, 1H, C-3H), 0.83 (d, 3H, C-5CH_3, J=6.6 Hz), 1.65-1.73 (m, 2H, C$H_2$$CH_2CH_2CH_3$), 1.12-1.22 (m, 2H, $CH_2C$$H_2$$CH_2CH_3$), 0.95-1.03 (m, 2H, $CH_2CH_2C$$H_2$$CH_3$), 0.78 (t, 3H, $CH_2CH_2CH_2C$$H_3$, *J*=7.2 Hz), 3.83 & 3.88 (2 x s, 12H, 4 x O-CH_3). ^{13}C NMR ($CDCl_3$, 125MHz, ppm): 210.7 (C=O), 153.3, 137.7, 137.6, 104.8, 104.6 57.6, 56.3, 56.2, 30.1, 24.7, 22.8, 13.9, 10.7. MS (m/z): 502.2 (M+1).

3-Butyl-5-methyl-2,6-bis(4-dimethylaminophenyl)piperidin-4-one, 4

IR (KBr, υ = cm^{-1}): 3409, 2953, 2871, 1716, 1616, 1528, 1445, 1356. ^{1}H-NMR ($CDCl_3$, 500MHz, ppm): 7.27 (d, 1H, ArH, J=8.6 Hz), 6.69 (d, 1H, ArH, J=8.6 Hz), 4.80 (brs, 1H, NH), 3.59 (d, 1H, C-2H, *J*=10.4 Hz), 3.49 (d, 1H, C-6H, J=10.3 Hz), 2.74-2.82 (m, 1H, C-5H), 0.81 (d, C-5CH_3, J=6.3Hz), 1.62-1.64 & 1.22-1.32 (m, 2H, C$H_2$$CH_2CH_2CH_3$), 1.12-1.18 (m, 2H, $CH_2C$$H_2$$CH_2CH_3$), 0.95-1.04 (m, 2H, $CH_2CH_2C$$H_2$$CH_3$), 0.76 (t, 3H, $CH_2CH_2CH_2C$$H_3$, J=7.4Hz), 2.91 & 2.92 (2 x s, 6H, 2 x N-CH_3). ^{13}C-NMR ($CDCl_3$, 125MHz, ppm): 211.8 (C=O), 150.3, 129.8, 128.6, 128.5, 112.6 30.1, 24.9, 23.0, 21.0, 14.1, 10.7. MS (m/z): 408.2 (M+1).

3-Pentyl-2,6-diphenylpiperidin-4-one, 5

IR (KBr, υ = cm^{-1}): 3063 (=C-H), 3033, 2923, 2854, 1713 (C=O), 1457. ^{1}H-NMR ($CDCl_3$, 400MHz, ppm): δ 7.47-7.26 (m, 10H, Ar-H), 4.26 (brs, 1H, NH), 4.08 (d, 1H, C-6H, J=8.8 Hz), 3.71 (d, 1H, C-2H, J=10.2 Hz), 2.72-2.62 (dd, 2H, H5 merged with m, 1H, H3), 2.08 (s, 1H, NH), 1.61-1.65 (m, 2H, C$H_2$$CH_2CH_2CH_2CH_3$), 1.25-1.38 (m, 2H, $CH_2C$$H_2$$CH_2CH_2CH_3$), 1.07-1.15 (m, 2H, $CH_2CH_2C$$H_2$$CH_2CH_3$), 0.97-0.99 (m, 2H, $CH_2CH_2CH_2C$$H_2$$CH_3$), 0.77 (t, 3H, $CH_2CH_2CH_2CH_2C$$H_3$ J=7.6 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz, ppm): δ 209.0 (C=O), 143.8, 141.8, 128.6, 128.5, 128.0, 127.9, 126.5, 67.2, 61.8, 57.0, 51.5, 31.9, 27.3, 24.6, 22.3, 13.9. MS (m/z, EI+): 322 (M+1), 321(M+).

3-Pentyl-2,6-bis(3,4-dimethoxyphenyl)piperidin-4-one, 6

IR (KBr, υ = cm^{-1}): 3404, 2936, 2854, 1714, 1593, 1519, 1469, 1264. ^{1}H-NMR ($CDCl_3$, 500MHz ppm): δ 6.82-6.98 (m, 6H, ArH), 4.01 (dd, C-2H & C-5H, *J*= 12.0 & 2.8 Hz), 3.64 (d, C-2H, J= 10.9 Hz), 2.71-2.76 (t, 1H, C-3H, J= 12.6 Hz,), 2.57-2.61 (dd, 1H, J = 12.6 & 3.2 Hz), 2.59-2.64 (m, 2H, C-5H), 3.87, 3.90 & 3.93 (3 x s, 9H, 3 x OCH_3), 1.57-1.64 & 1.00-1.04 (m, 2H, C$H_2$$CH_2CH_2CH_2CH_3$), 1.23-1.32 (m, 2H, $CH_2C$$H_2$$CH_2CH_2CH_3$), 1.12-1.18 (m, 2H, $CH_2CH_2C$$H_2$$CH_2CH_3$), 1.07-1.12 (m, 2H, $CH_2CH_2CH_2C$$H_2$$CH_3$), 0.79 (t, 3H, $CH_2C$$H_2$$CH_2CH_2C$$H_3$, J= 7.2 Hz). ^{13}C-NMR ($CDCl_3$, 125MHz, ppm): 209.4 (C=O), 149.1, 148.8, 135.1, 134.2, 120.4, 118.7, 111.2, 110.9, 110.6, 109.7 55.9, 56.0 (OCH_3), 24.1(C7), 27.4(C8), 22.5(C9), 32.0(C10), 14.1(C11). MS (m/z): 442 (M+1).

Ethyl-2,6-bis(3,4,5-trimethoxyphenyl)-5-[(1-methyl-1H-tetrazolyl-5-yl)thio]-4-oxopiperidine3-carboxylate, 7

IR (KBr, υ = cm^{-1}): 3431, 3508 (NH), 2940 (CH), 1748, 1737, 1714 (C=O), 1594, and 1459. ^{1}H-NMR ($CDCl_3$, 400MHz, ppm): 6.66-7.27 (m, Aromatic protons), 5.06 (d, 1H, C-2H, J=10.9 Hz), 4.40 (d, 1H, C-6H, J=10.6 Hz), 4.16 (d, 1H, C-3H, J=10.8 Hz), 4.13-4.07 (m, 2H, -OCH_2), (d, CH_2S), 3.94 (d,

1H, C-5H, J=10.9 Hz), 4.12 (q, 2H, CH_3CH_2, J=7.4 Hz), 1.14 (t, 2H, CH_3CH_2, J=7.1 Hz), 3.82 (s, 3H, N-CH_3), 3.80, 3.81, 3.82, 3.85 & 3.87 (5 x s, 18H, 6 x -OCH_3). ^{13}C-NMR ($CDCl_3$, 100MHz, ppm): 197.0 (C=O), 153.4, 153.2, 138.2, 138.1, 134.9, 133.9, 104.9, 104.5, COO (166.8), Tetrazole (154.5), O-CH_3 (60.9, 60.8, 56.3), N-CH_3 (33.8), CH_3CH_2O (61.4), CH_3CH_2O (14.2). MS (m/z): 618.3 (M+1).

(E)-1-(2,6-diphenyl-3-pentyl-4-ylidene) semicarbazone, 8

IR (KBr, υ = cm^{-1}): 3427, 3370 (NH_2), 3290, 3174 (NH), 2953, 2927 (C-H), 1588 (C=N), 1476, 1280, 1084, 755, 701. ^{1}H-NMR (DMSO-d_6, 500MHz, ppm): δ 10.67 (s, 1H, NH), 10.5 (bs, 1H, NH), 9.79 (d, 1H, NH), 8.30 (s, 1H, NH), 7.38-7.79 (m, 10H, ArH), 4.56 (t, 1H, C-2H, J = 10.3 Hz), 4.44 (t, 1H, C-6H, J = 10.3 Hz), 3.58-3.48 (m, 2H, C-5H), 3.12 (t, 1H, J = 14.3 Hz), 2.47 (t, 1H), 1.51-1.49 (m, 2H, $CH_2CH_2CH_2CH_2CH_3$), 1.21-0.97 (m, 6H, $CH_2(CH_2)_3CH_3$), 0.71 (t, 3H, $CH_2(CH_2)_3CH_3$). ^{13}C-NMR (DMSO-d_6, 125MHz, ppm): δ 179.90 (C=O), 149.95, 136.38, 135.56, 129.97, 129.75, 129.50, 129.09, 128.81, 65.78, 60.10, 44.92, 32.18, 31.87, 25.79, 25.53, 22.31, 14.33. ESI-MS: m/z (M^++1) 395.2.

(E)-1-(2,6-bis(3,4-dimethoxyphenyl)-3-pentylpiperidin-4-ylidene) semicarbazone, 9

IR (KBr, υ = cm^{-1}): 3428, 3355 (NH_2), 3261, 3184 (-NH), 2958, 2933 (-CH-Ar), 1590, 1521 (C=N), 1495, 1463, 1269, 1146, 1021. ^{1}H-NMR (DMSO-d_6, 400MHz, ppm): δ 10.63 (bs, 1H, NH), 9.58 (d, 1H, NH), 8.29 (s, 1H, NH), 7.82-7.65 (d, 1H, NH), 7.25-6.93 (m, 6H, ArH), 4.43 (t, 1H, J = 10.9 Hz), 4.31 (t, 1H, J = 10.9 Hz), 3.77 (s, 6H, O-CH_3), 3.73 (s, 6H, O-CH_3), 3.51 (m, 2H), 3.13 (m, 1H), 1.55 (m, 2H, C-5H), 1.23-1.01 (m, 6H), 0.73 (t, 3H). ^{13}C-NMR (DMSO-d_6, 100MHz, ppm): δ 179.87, 150.47, 149.72, 149.28, 148.99, 128.76, 127.82, 122.84, 121.79, 113.00, 111.69, 65.76, 60.06, 56.39, 56.11, 56.02, 45.05, 32.54, 31.86, 25.92, 25.49, 22.39, 14.35. ESI-MS: m/z (M^++1) 515.4.

(E)-1-(2,6-bis(3,4-dimethoxyphenyl)-3-butyl-5-methylpiperidin-4-ylidene) semicarbazone, **10**

IR (KBr, υ = cm^{-1}): 3429 (-NH), 2956, 2935 (-CH-Ar), 1597, 1519 (C=N), 1464, 1268, 1145, 1024. ^{1}H-NMR (DMSO-d_6, 400MHz, ppm): δ 8.14 & 7.99 (2bs, 2H, NH_2), 7.93 (s, 1H, NH), 7.10 (d, 1H, NH), 6.92-6.85 (m, 6H, ArH), 3.78 (d, 1H), 3.72 (s, 6H), 3.69 (s, 6H), 3.32 (m, 1H), 2.83-2.76 (m, 2H), 1.51 (m, 2H), 1.12-0.82 (m, 4H), 0.68 (d, 3H), 0.65 (t, 3H). ^{13}C-NMR (DMSO-d_6, 100MHz, ppm): δ 178.05, 172.57, 151.10, 149.67, 149.08, 149.05, 148.66, 143.02, 127.45, 122.72, 120.52, 120.38, 112.01, 111.88, 111.70, 108.95, 56.19, 56.11, 56.06, 55.97, 29.84, 24.92, 22.78, 21.59, 14.26, 11.34. ESI-MS: m/z (M^++1) 515.4.

(E)-1-(2,6-bis(4-methoxyphenyl)-3-butyl-5-methylpiperidin-4-ylidene) semicarbazone, 11

IR (KBr, υ = cm^{-1}): 3423, 3178 (NH), 2956, 2934 (-CH-Ar), 1612 1517 (C=N), 1440, 1254, 1183, 1032, 833. ^{1}H-NMR (DMSO-d_6, 400MHz, ppm): δ 11.13 (s, 1H, NH), 10.48 (d, 1H, NH), 9.57 (d, 1H, NH), 7.80 (d, 1H, NH), 7.20-6.95 (m, 8H, ArH), 4.43 (t, 1H, *J* = 10.35 Hz), 4.33 (t, 1H, *J* = 10.85 Hz), 3.81-3.77 (d, 6H, OCH_3), 3.55 (d, 1H, *J* = 12.6 Hz), 3.44 (m, 1H), 1.46 (m, 1H), 1.33 (m, 1H), 1.22 (m, 2H), 1.13 (d, 3H, merged with CH_2 proton), 1.09-1.01 (m, 2H), 0.77 (t, 3H). ^{13}C-NMR (DMSO-d_6, 100MHz, ppm): δ 162.90, 152.9, 149.7, 149.3, 149.1, 129.0, 121.5, 112.8, 111.8, 111.7, 65.6, 60.0, 56.39, 56.4, 56.3, 56.03, 56.01, 43.06, 31.94, 31.24, 29.1, 25.89, 25.69, 22.42, 14.36. ESI-MS: m/z (M^++1) 455.3.

RESULTS AND DISCUSSION

Among the different catalysts[16-21] reported to promote Mannich reaction, Lewis acids and mineral acids could not be used as catalysts in our study as they react with ammonia. Considering the high cost of other inorganic catalysts, and the problems posed by organocatalysts during workup, we decide to use glacial acetic acid as the catalyst for the one-pot three-component reaction. When the condensation of octan-2-one, benzaldehyde and ammonium acetate was carried out in methanol-acetic acid (85:15 v/v) medium, the three-component Mannich-type condensation underwent smoothly and gave the corresponding 2,6-diarylpiperidin-4-one. The

presence of acetic acid improved the yield significantly to 68% as compared to the 51% yield obtained under uncatalyzed conditions[4]. In order to extend the applicability of this method obtain hitherto unknown 2,6-diarylpiperidin-4-ones, we used a set of different aryl aldehydes and ketones with a long aliphatic chain. Only in the presence of 15% acetic acid in methanol, several aryl aldehydes condensed with ammonia and octan-2-one/octan-3-one and yielded the corresponding 2,6-diarylpiperidin-4-ones. In the absence of acetic acid, the reactions did not proceed to the completion even after refluxing the reaction mixture for several days. It is imperative to note that the lower yields and longer reaction times (Table 1) correlate with the electron deficient nature of aryl aldehydes used.

Table 1
Analytical data of Compounds (1-7) – 2,6-diarylpiperidin-4-one derivatives

Entry	R_1	R_2	R_3	Reaction Time (h)	Yield %	m.p (°C)	ESI Mass (Calculated)
1	CH_3	$CH_3(CH_2)_3$	4-OCH_3	32	70	102-103	382.0 (381.5)
2	CH_3	$CH_3(CH_2)_3$	3,4-$(OCH_3)_2$	17	71	101-102	442.0 (441.6)
3	CH_3	$CH_3(CH_2)_3$	3,4,5-$(OCH_3)_3$	8	75	102 – 104	502.2 (501.6)
4	CH_3	$CH_3(CH_2)_3$	4-$N(CH_3)_2$	8	72	100-101	408.2 (407.6)
5	H	$CH_3(CH_2)_4$	H	12	68	97-98	321.0 (321.4)
6	H	$CH_3(CH_2)_4$	3,4-$(OCH_3)_2$	1.0	72	100 -102	442.0 (441.6)
7	COOEt	N-Methyl tetrazol-2-yl	3,4,5-$(OCH_3)_3$	8.0	75	103-104	618.3 (617.7)

Table 2
Analytical data of Compounds (8-11) – Semicarbazone derivatives

Entry	R_1	R_2	R_3	Reaction Time (h)	Yield %	m.p (°C)	ESI Mass (Calculated)
8	H	$CH_3(CH_2)_4$	H	1.0	65	218	395.2
9	CH_3	$CH_3(CH_2)_3$	3,4-$(OCH_3)_2$	1.5	66	208	515.4 (M+1) 514Da
10	H	$CH_3(CH_2)_4$	3,4-$(OCH_3)_2$	1.5	68	212	515.4 (M+1) 514Da
11	CH_3	$CH_3(CH_2)_3$	4-OCH_3	1.0	70	206	455.3 (M+1) 454 Da

The structure determination was done using physical and spectral data, and by comparison with data reported in the literature.[11-16] A combination of ^{1}H NMR, ^{13}C NMR, and ^{1}H-^{13}C HSQC experiments provided information for the unambiguous assignment of various signals and on the stereo-chemical nature of the title compounds. For instance, the IR spectrum of compound 1 displays the amine NH stretching at 3420 cm^{-1}. The ketone carbonyl vibration occurs at ~1708 cm^{-1} and indicates the formation of a cyclic ketone. The ketone carbonyl resonance at 210.9 in the ^{13}C NMR spectrum of 1 confirms the presence of the heterocyclic compound 1. The ^{1}H NMR spectrum of 1 shows a broad peak at ~3.27 ppm that can be ascribed to the NH proton of a secondary amine. D_2O induced proton exchange diminishes the intensity of the peak at ~3.27 ppm confirming the exchangeability of the NH proton. The spacial disposition of various substituents in piperidone derivatives were deduced from spectroscopic and computational data. Specifically, the vicinal coupling constants, determined for the different protons in the piperidine ring are in the range from 10.2 to 12.6 Hz (Table III). These observations clearly suggest a rigid-chair conformation for the heterocyclic ring, an axial orientation for the hydrogen atoms and an equatorial orientation for the aryl and alkyl substituents.

Table 3
Vicinal coupling constant values of protons in the piperidine ring

Entry	H(2)	H(3)	H(5)	H(6)
1	10.4 Hz	Overlapped multiplet	Overlapped multiplet	10.3 Hz
2	10.3 Hz	Overlapped multiplet	Overlapped multiplet	10.3 Hz
3	10.5 Hz	Overlapped multiplet	Overlapped multiplet	10.2 Hz
4	10.4 Hz	Overlapped multiplet	Overlapped multiplet	10.3 Hz
5	10.2 Hz	Overlapped multiplet	Overlapped multiplet	8.8 Hz
6	10.9 Hz	12.6 Hz	15.4 Hz & 3.0 Hz	12.1 Hz
7	10.9 Hz	10.8 Hz	10.9 Hz	10.6 Hz

In vitro Antimicrobial assay

The 2,6-diarylpiperidin-4-ones and their semicarbazone derivatives (1-11) were screened in vitro for their potency against bacterial strains such as S. aureus, E. coli, P. aeruginosa, and S. pyogenes, and fungal strains such as C. albicans and A. flavus.[23] The in vitro activities of the test compounds were studied using agar plates containing Sabourauds dextrose broth (Himedia, Mumbai) for fungi and in Nutrient broth (Himedia, Mumbai) for bacteria. Three fixed concentrations of the test compounds were tested against each microbial species. The antibacterial and antifungal potencies of the test compounds were compared with gentamycin (bacteria) and ketaconozole (fungi). The relative antimicrobial potencies of test compounds are expressed as the area of zone of inhibition and summarized in Table IV.

A clear distinction between the in vitro antibacterial and antifungal activity profiles of the 2,6-diarylpiperidin-4-ones and their semicarbazone derivatives (1-11) is that all the derivatives display very good antifungal activity while only some of them show antibacterial activity. This marked antifungal activity could only be attributed to the high hydrophobic content of this family of compounds and the piperidine ring system. The compounds containing semicarbazone moiety are relatively less active against bacteria as compared to the piperidin-4-one derivatives, presumably due to the strong interaction of the former with the agar medium, which hinders their diffusion in agar medium. The subtle variations in the antibiotic activity of the test compounds could arise from the difference in the nature of the substituents as well as their spatial disposition with respect to the heterocyclic ring system.

Table 4
Antimicrobial activity of the synthesized compounds

Compd	Conc	Zone of inhibition in mm*					
	(µg/well)	Antibacterial activity				Antifungal activity	
	in DMF	*P. aeruginosa*	*E. coli*	*S. pyogenes*	*S. aureus*	*C. albicans*	*A. flavus*
1	600	10	8	17	8	8	15
2	600	10	10	9	8	11	18
3	600	12	8	NA	NA	12	16
4	600	8	10	NA	11	10	13
5	600	10	11	NA	8	15	12
6	600	9	7	8	11	15	13
7	600	8	8	12	12	13	15
8	600	10	6	NA	6	14	13
9	600	6	6	NA	6	14	12
10	600	6	6	NA	6	12	12
11	600	7	8	11	10	16	17
Gentamycin	600	18	17	17	17	-	-
Ketaconozole	600	-	-	-	-	17	19
Control	-	-	-	-	-	-	-
(DMF)							
***Diameter of well (bore size) - 6 mm**							
NA = Not active							

CONCLUSION

To the best of our knowledge, this is the first report on acetic acid promoted condensation of aryl aldehyde, ammonia and long chain ketones resulting in the formation of 2,6-diarylpiperidin-4-ones, which could not be synthesized using conventional protocols. The enhanced yield observed in the case of 5 clearly shows the catalytic activity of acetic acid. Three semicarbazone derivatives 2,6-diarylpiperidin-4-one could be isolated in pure form. Bulky substituents oblige the heterocyclic ring to adopt a twist-boat conformation. The spectrum of antimicrobial efficacy displayed by the newly synthesized piperidin-4-one derivatives indicates the importance of nature, size and functional groups for potent activity against bacteria and fungi. All the compounds exhibit a very good antifungal activity rather than antibacterial activity. These results provide the basis for further development potent antimicrobial agents in the future.

ACKNOWLEDGEMENT

The authors wish to thank the management of Gland Pharma limited for providing facility to carry out this work and take this opportunity to acknowledge the synthesis R & D team of Gland Pharma.

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