New intermediates for the selective synthesis of 1-methyl-3-phenylpiperazine and some phenylpiperazine derivatives

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Abstract

New intermediates, 4-protected-1-alkyl-2-oxo-3-phenylpiperazines (**3a-e**) and 1-alkyl-2-oxo-3-phenylpiperazines (**6a-d**) for the selective synthesis of 1-alkyl-3-phenylpiperazines (**5a-e**) are described. First method involves the reduction of the 4-protected-1-alkyl-2-oxo-3-phenylpiperazine (**3a-e**) followed by deprotection giving the 1-alkyl-3-phenylpiperazine (**5a-e**). Second method involves the deprotection of 4-protected-1-alkyl-2-oxo-3-phenylpiperazine (**3a-e**) followed by reduction giving the 1-alkyl-3-phenylpiperazine (**5a-e**).

Keywords: 3-Phenylpiperazin-2-one, 4-benzyl-1-methyl-2-oxo-3-phenylpiperazine, 1-methyl-2-oxo-3-phenylpiperazine, protection, deprotection

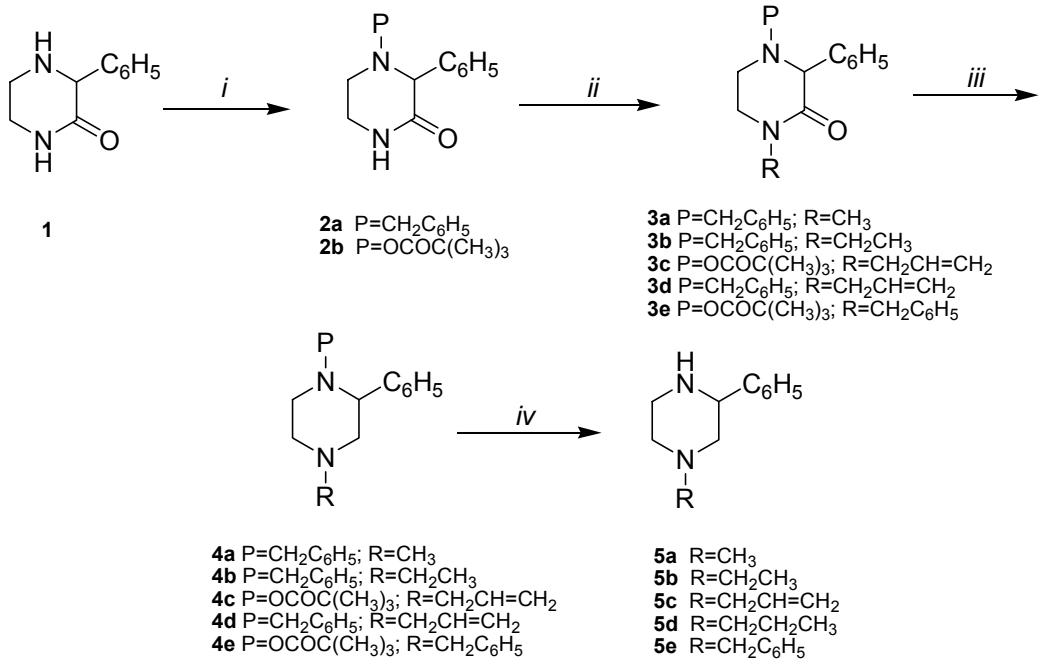
Introduction

1-Methyl-3-phenylpiperazine is an intermediate for the preparation of Mirtazapine, an antidepressant drug.[1] Several methods have been reported for the preparation of 1-methyl-3-phenylpiperazine. They have been prepared from 2-phenylpiperazine,[2] N- (2-chloroethyl)-N-methyl-β-chloro-β-phenylethylamine,[3] 2-chloroacetamide-N-methyl-2-phenylacetamide,[4] 1-benzyl-2-phenylpiperazine.[5,6] Our present work describes new intermediates such as 4-benzyl-1-methyl-2-oxo-3-phenylpiperazine [7] and 1-methyl-2-oxo-3-phenylpiperazine[7] for the preparation of 1-methyl-3-phenylpiperazine and some phenylpiperazine derivatives.

Results and Discussion

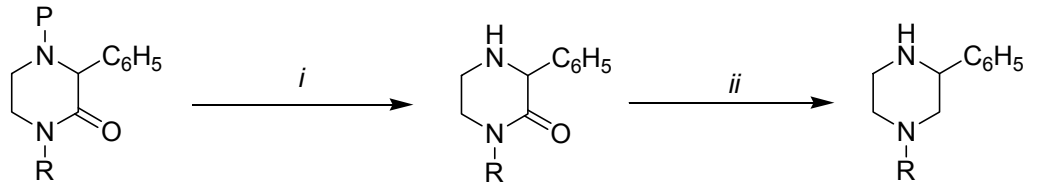
The method described by Roderick,[2] involves the methylation of 2-phenylpiperazine and this step afforded low yields because it was not selective and produces unwanted product 1,4-

dimethylpiperazine. By the route of Dolitzky,[3] the piperazine was made from *N*- (2-chloroethyl)-*N*-methyl-*β*-chloro-*β*-phenylethylamine and this method afforded by product 1-methyl-2-phenylpiperazine. This may be because of the non-selectivity in the reaction of starting material preparation. The method described by Guo,[5] involves the use of excess of lithium aluminum hydride,[7] for the unsubstituted amide reduction. We wish to report herein an improved procedure using new intermediates, which circumvents these problems. Different 1-alkyl-3-phenylpiperazines were prepared in two methods by simply changing the sequence of reduction and deprotection of the phenylpiperazine derivatives. First method involves the reduction of **3a-e** followed by the deprotection of **4a-e** to get 1-alkyl-3-phenylpiperazine **5a-e** (Scheme 1).



Scheme 1. *i.* Protection: for benzyl; $C_6H_5CH_2Cl$, $NaHCO_3$, DMF, 100 °C; for Boc. di-*tert*-butyl dicarbonate, $(C_2H_5)_3N$, CH_2Cl_2, rt. *ii.* RI, NaH, DMF, 25 °C. *iii*. $LiAlH_4$, THF, reflux. *iv.* deprotection: for benzyl; H_2, Pd-C, CH_3OH, CH_3COOH, rt; for Boc; 6N HCl, rt.

Second method involves the deprotection of **3a-c, e** followed by reduction of 1-alkyl-2-oxo-3-phenylpiperazines **6a-d** giving the 1-alkyl-3-phenylpiperazines **5a-c, e** (Scheme 2).



3a P=$CH_2C_6H_5$; R=CH_3
3b P=$CH_2C_6H_5$; R=CH_2CH_3
3c P=$OCOC(CH_3)_3$; R=$CH_2CH{=}CH_2$
3e P=$OCOC(CH_3)_3$; R=$CH_2C_6H_5$

6a R=CH_3
6b R=CH_2CH_3
6c R=$CH_2CH{=}CH_2$
6d R=$CH_2C_6H_5$

5a R=CH_3
5b R=CH_2CH_3
5c R=$CH_2CH{=}CH_2$
5e R=$CH_2C_6H_5$

Scheme 2. *i.* deprotection: for benzyl; H_2, Pd-C, acetic acid, rt. for Boc; 6N HCl, rt, *ii.* $LiAlH_4$, THF, reflux.

In summary, we report two different sequences of reactions, *viz.* lactam reduction and N^4-deprotection, or, initial N^4-deprotection followed by lactam reduction, provided the title compounds in good overall yield. However, the intermediates (**6a-d**) obtained by following the second method may be useful for making some biological important compounds owing to the available free NH group.

Experimental Section

General Procedures. All melting points were determined with Palmon melting point apparatus. ^{1}H-NMR spectra were recorded on a Bruker 300 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. Mass spectra were measured on Perkin Elmer PE SCIEX-API 2000 mass spectrometer. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument. Analytical HPLC[8] were run with Hypersil ODS Rx-C_{18} column at 210nm. "RT" denotes room temperature.

4-Benzyl-2-oxo-3-phenylpiperazine (2a). Benzyl chloride (75.0 g, 0.593 mol) was added to a suspension of **1** (100.0 g, 0.568 mol) obtained by the reported method (lit.[2] mp 138-140 °C) and sodium bicarbonate (100.0 g, 1.19 mol) in DMF (250 mL) and heated to 100 °C for 2 h. Cooled the mixture to 75 °C and water (500 ml) was added. Filtered the product and washed with water, dried, to yield **2a** (135.0 g, 89%) as a white solid; purity 99% (by HPLC); mp 225-226 °C (lit,[5] >210 °C); IR (KBr, cm^{-1}) 3181, 2891, 1678, 1602, 742, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.48-2.54 (m, 1H), 2.98-3.00 (m, 1H), 3.17 (d, 1H, *J*=13.5 Hz), 3.26-3.28 (m, 1H), 3.52-3.44 (m, 1H), 3.75 (d, 1H, *J*=13.5 Hz), 4.07 (s, 1H), 6.41 (bs, 1H), 7.20-7.30 (m, 5H), 7.32-7.41 (m, 3H), 7.54-7.55 (m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 46.1, 51.7, 63.7, 76.0, 132.3, 133.8, 132.8, 133.5, 134.3, 143.2, 144.6, 174.9; MS (ESI, *m/z*): 267.4 $[M+H]^+$. Anal. Calcd. For $C_{17}H_{18}N_2O$ (266.34): C, 76.66; H, 6.81; N, 10.52. Found: C, 76.70; H, 6.74; N, 10.45.

4-*tert*-Butoxycarbonyl-2-oxo-3-phenylpiperazine (2b). Di-*tert*-butyl dicarbonate (126.4 g, 0.58 mol) was added to a suspension **1** (100.0 g, 0.568 mol) and triethylamine (72.72 g, 0.72 mol) in dichloromethane (1000 mL) at 10°C and stirred at RT for 15 h. The reaction mixture was washed

with water and evaporated. The residue was treated with cyclohexane (500 mL). Filtered the product and washed with cyclohexane, dried, to yield **2b** (125.0 g, 80%) as a white solid; mp 152-153 °C; IR (KBr, cm^{-1}) 3197, 2986, 1690, 1674, 1602, 1395, 737, 699; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.27-3.34 (m, 2H), 3.48-3.52 (m, 1H), 3.92-4.04 (m, 1H), 5.71 (s, 1H), 6.65 (bs, 1H), 7.28-7.44 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 28.8, 37.9, 41.1, 60.7, 81.4, 127.5, 128.3, 129.0, 137.9, 154.3, 170.1; MS (ESI, *m/z*): 277.2 $[M+H]^+$. Anal. Calcd. For $C_{15}H_{20}N_2O_3$ (276.33): C, 65.20; H, 7.30; N, 10.14. Found: C, 65.12; H, 7.34; N, 10.18.

General procedure for alkylation of 4-protected-2-oxo-3-phenylpiperazines (2a-b). 4-Benzyl-1-methyl-2-oxo-3-phenylpiperazine (3a). Under N_2 atmosphere, **2a** (100.0 g, 0.376 mol) was added portion wise to a suspension of sodium hydride (15.3 g, 65% dispersed in mineral oil, 0.41 mol) in anhydrous DMF (250 mL) at 10-15 °C over a period of 1 h. A solution of methyl iodide (64.0 g, 0.45 mol) in anhydrous DMF (65 mL) was added slowly by maintaining the temperature below 25 °C and the stirring was continued for 1 h. The reaction mass was poured slowly into cold water (1000 mL) and product was extracted with toluene (800mL), the combined organic solution was washed with water and concentrated. The residue was treated with cyclohexane (200mL) at 10 °C for 1 h. Filtered the product to yield **3a** (98.5 g, 94%) as a light yellow solid; purity 99% (by HPLC); mp 101-102 °C; IR (KBr, cm^{-1}) 2935, 2805, 1646, 1602, 733, 697; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.54-2.58 (m, 1H), 2.99 (s, 3H), 3.03-3.05 (m, 1H), 3.17 (d, 1H, *J*=13.5 Hz), 3.15-3.20 (m, 1H), 3.22-3.60 (m, 1H), 3.75 (d, 1H, *J*=13.4 Hz), 4.08 (s, 1H), 7.26-7.32 (m, 6H), 7.35-7.40 (m, 2H), 7.55 (d, 2H, *J*=7.4 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 35.1, 46.9, 48.9, 59.3, 71.5, 127.7, 128.2, 128.8, 129.2, 129.5, 138.4, 139.7, 168.7; MS (ESI, *m/z*): 281.2 $[M+H]^+$. Anal. Calcd. For $C_{18}H_{20}N_2O$ (280.36): C, 77.11; H, 7.19; N, 9.99. Found: C, 77.03; H, 7.22; N, 9.96.

4-Benzyl-1-ethyl-2-oxo-3-phenylpiperazine (3b). This compound was prepared in a similar way to **3a**, using compound **2a** (8.0 g, 30.07 mmol) and ethyl bromide, as a light yellow solid (8.13 g, 92%); mp 88-89 °C; IR (KBr, cm^{-1}) 2937, 2818, 1648, 1602, 742, 699; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, *J*=7.2 Hz), 2.50-2.54 (m, 1H), 3.03-3.13 (m, 1H), 3.15-3.18 (m, 2H), 3.34-3.38 (m, 1H), 3.46-3.53 (m, 2H), 3.72-3.77 (d, 1H, J=13.4 Hz), 4.04 (s, 1H), 7.21-7.38 (m, 8H), 7.52 (d, 2H, *J*=7.4 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 12.1, 41.8, 45.7, 46.6, 58.8, 71.0, 127.2, 127.7, 128.3, 128.7, 129.0, 137.9, 139.5, 167.6; MS (ESI, *m/z*): 295.3 $[M+H]^+$. Anal. Calcd. For $C_{19}H_{22}N_2O$ (294.39): C, 77.52; H, 7.53; N, 9.52. Found: C, 77.46; H, 7.50; N, 9.56.

1-Allyl-4-*tert*-butoxycarbonyl -2-oxo-3-phenylpiperazine (3c). This compound was prepared in a similar way to **3a**, using compound **2b** (8.0 g, 28.98 mmol) and allyl bromide, as a light yellow liquid (8.2 g, 92%); IR (neat, cm^{-1}) 3083, 1698, 1658, 1392, 721, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.23-3.28 (m, 2H), 3.32-3.36 (m, 1H), 3.85-3.97 (m, 2H), 4.19-4.21 (m, 1H), 5.15-5.21(m, 2H), 5.71-5.79 (m, 2H), 7.29-7.38 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 28.1, 37.7, 44.8, 49.0, 60.6, 80.7, 118.0, 125.2, 126.6, 127.5, 127.9, 128.3, 133.1, 137.4, 153.7, 166.3; MS (ESI, *m/z*): 317.3 $[M+H]^+$. Anal. Calcd. For $C_{18}H_{24}N_2O_3$ (316.39): C, 68.33; H, 7.65; N, 8.85. Found: C, 68.40; H, 7.58; N, 8.82.

1-Allyl-4-benzyl-2-oxo-3-phenylpiperazine (3d). This compound was prepared in a similar way to **3a**, using compound **2a** (8.0 g, 30.07 mmol) and allyl bromide, as a yellow oil (8.37 g, 91%); IR (neat, cm^{-1}) 3084, 2804, 1649, 1603, 754, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.51-2.53 (m, 1H), 3.01-3.14 (m, 1H), 3.16-3.20 (m, 2H), 3.48-3.52 (m, 1H), 3.75-3.80 (d, 1H, *J*=13.4 Hz), 3.98-4.05 (m, 2H), 4.10 (s, 1H), 5.17-5.23 (m, 2H), 5.71-5.84 (m, 1H), 7.28-7.41 (m, 8H), 7.57(m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 45.8, 46.6, 49.3, 58.8, 71.0, 117.8, 127.2, 127.8, 128.3, 128.7, 129.0, 132.3, 137.8, 139.2, 162.5, 168.0; MS (ESI, *m/z*): 307.5 $[M+H]^+$. Anal. Calcd. For $C_{20}H_{22}N_2O$ (306.40): C, 78.40; H, 7.24; N, 9.14. Found: C, 78.51; H, 7.22; N, 9.10.

1-Benzyl-4-*tert*-butoxycarbonyl-2-oxo-3-phenylpiperazine (3e). This compound was prepared in a similar way to **3a**, using compound **2b** (8.0 g, 28.98 mmol) and benzyl bromide, as a light brown oil (9.75 g, 92%); IR (neat, cm^{-1}) 3062, 2877, 1676, 1603, 1389, 729, 702; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.20-3.23 (m, 1H), 3.32-3.36 (m, 2H), 3.93 (m, 1H), 4.49 (d, 1H, *J*=14.5 Hz), 4.85 (d, 1H, *J*=14.5 Hz), 5.78 (s, 1H), 7.27-7.41 (m, 10H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 28.6, 38.8, 45.3, 50.4, 60.9, 81.3, 127.9, 128.1, 128.4, 128.6, 128.7, 128.9, 129.1, 129.4, 129.5, 138.1, 154.3, 162.8, 167.2; MS (ESI, *m/z*): 367.2 $[M+H]^+$. Anal. Calcd. For $C_{22}H_{26}N_2O_3$ (366.45): C, 72.11; H, 7.15; N, 7.64. Found: C, 72.18; H, 7.18; N, 7.61.

General procedure for reduction of 4-protected-1-alkyl-3-phenylpiperazines (3a-e). 4-Benzyl-1-methyl-3-phenylpiperazine (4a). Under N_2 atmosphere, **3a** (90.0 g, 0.321 mol) was added slowly to a suspension of $LiAlH_4$[9] (14.6 g, 0.384 mol) in anhydrous THF (450 mL) at 10-15 °C over a period of 1 h and refluxed for 6 h. The excess $LiAlH_4$ was destroyed at 0 °C with water (14.6 mL), 15% NaOH (14.6 mL) and water (42.8 mL). After filtration, the filtrate was evaporated to dryness and water (300 mL) was added. Filtered the product to yield **4a** (80.0 g, 94%) as a light yellow solid; purity 98% (by HPLC); mp 79-80 °C; IR (KBr, cm^{-1}) 2932, 2788, 1599, 740, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.15-2.22 (m, 2H), 2.23-2.28 (m, 1H), 2.99 (s, 3H), 2.80-2.85 (m, 2H), 2.86 (d, 2H, *J*=13.4 Hz), 3.44 (dd, 1H, *J*=10.5, 2.9 Hz), 3.82 (d, 1H, *J*=13.4 Hz), 7.19-7.30 (m, 6H), 7.40-7.38 (m, 2H), 7.50-7.52 (m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 46.3, 52.3, 55.7, 59.4, 64.6, 67.9, 127.2, 127.9, 128.4, 128.5, 129.0, 129.2, 139.5, 142.5; MS (ESI, *m/z*): 267.4 $[M+H]^+$. Anal. Calcd. For $C_{18}H_{22}N_2$ (266.38): C, 81.16; H, 8.32; N, 10.52. Found: C, 81.02; H, 8.44; N, 10.54.

4-Benzyl-1-ethyl-3-phenylpiperazine (4b). This compound was prepared in a similar way to **4a**, using compound **3b** (5.0 g, 17.0 mmol), as a light yellow oil (4.52 g, 95%); IR (neat, cm^{-1}) 2945, 2805, 1603, 1470, 736, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06 (t, 3H, *J*=7.2 Hz), 2.05-2.19 (m, 2H), 2.23-2.31 (m, 1H), 2.36-2.44 (m, 2H), 2.84-2.92 (m, 4H), 3.41-3.44 (m, 1H), 3.78 (d, 1H, *J*=13.4 Hz), 7.19-7.37 (m, 8H), 7.49-7.51 (m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 12.4, 52.3, 52.6, 53.3, 59.5, 62.4, 67.8, 127.1, 127.9, 128.4, 128.5, 128.8, 129.0, 129.2, 139.5, 142.7; MS (ESI, *m/z*): 281.3 $[M+H]^+$. Anal. Calcd. For $C_{19}H_{24}N_2$ (280.41): C, 81.38; H, 8.63; N, 9.99. Found: C, 81.24; H, 8.62; N, 10.14.

1-Allyl-4-*tert*-butoxycarbonyl-3-phenylpiperazine (4c). This compound was prepared in a similar way to **4a**, using compound **3c** (5.0 g, 15.82 mmol), as a light yellow oil (3.72 g, 78%) after purification by silica gel (100-200 mesh) column chromatography [AcOEt-hexane (1:9)];

IR (neat, cm^{-1}) 3063, 1694, 1603, 1392, 1300, 722, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.13-2.14 (m, 1H), 2.31-2.37 (m, 1H), 2.79-2.83 (m, 2H), 3.03-3.08 (m, 2H), 3.39-3.43 (m, 1H), 3.92-3.96 (m, 1H), 5.17-5.26 (m, 3H), 5.86-5.88 (m, 1H), 7.24-7.43 (m, 3H), 7.46 (m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 28.8, 40.4, 53.7, 53.8, 55.2, 62.2, 80.3, 118.6, 127.2, 127.8, 128.7, 135.2, 140.8, 155.4; MS (ESI, *m/z*): 303.3 $[M+H]^+$. Anal. Calcd. For $C_{18}H_{26}N_2O_2$ (302.41): C, 71.49; H, 8.67; N, 9.26. Found: C, 71.28; H, 8.79; N, 9.29.

1-Allyl-4-benzyl -3-phenylpiperazine (4d). This compound was prepared in a similar way to **4a**, using compound **3d** (5.0 g, 16.33 mmol), as a light yellow solid (4.20 g, 88%); mp 86-88 °C. IR (KBr, cm^{-1}) 3062, 2795, 1603, 741, 701; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.07-2.14 (m, 1H), 2.18-2.30 (m, 2H), 2.81-2.90 (m, 4H), 2.97-2.99 (m, 2H), 3.40 (dd, 1H, *J*=10.4, 2.7 Hz), 3.79 (dd, 1H, *J*=13.4 Hz), 5.10-5.16 (m, 2H), 5.73-5.84 (m, 1H), 7.21-7.36 (m, 8H), 7.49 (d, 2H, J=7.4 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 52.2, 53.6, 59.4, 62.1, 62.4, 67.8, 118.7, 127.2, 127.9, 128.4, 128.5, 128.8, 129.0, 129.2, 135.1, 139.4, 142.6; MS (ESI, *m/z*): 293.1 $[M+H]^+$. Anal. Calcd. For $C_{20}H_{24}N_2$ (292.42): C, 82.15; H, 8.27; N, 9.58. Found: C, 82.04; H, 8.30; N, 9.66.

1-Benzyl-4-*tert*-butoxycarbonyl -3-phenylpiperazine (4e). This compound was prepared in a similar way to **4a**, using compound **3e** (5.0 g, 13.66 mmol), as a light yellow oil (3.82 g, 79%) after purification by silica gel (100-200 mesh) column chromatography [AcOEt-hexane (1:9)]; IR (neat, cm^{-1}) 2809, 1682, 1602, 1392, 737, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.15-2.19 (m, 1H), 2.38-2.43 (m, 1H), 2.78-2.82 (m, 1H), 2.99-3.06 (m, 1H), 3.26-3.30 (m, 1H), 3.44 (d, 1H, *J*=13.2 Hz), 3.57 (d, 1H, *J*=13.2 Hz), 3.88-3.93 (m, 1H), 5.23 (s, 1H), 7.21-7.36 (m, 8H), 7.41 (d, 2H, *J*=7.4 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 28.9, 31.7, 40.3, 53.8, 55.4, 63.6, 80.3, 127.2, 127.6, 128.1, 128.5, 128.7, 129.6, 138.3, 140.9, 155.4; MS (ESI, *m/z*): 353.3 $[M+H]^+$. Anal. Calcd. For $C_{22}H_{28}N_2O_2$ (352.47): C, 74.97; H, 8.01; N, 7.95. Found: C, 74.80; H, 8.15; N, 7.98.

1-Methyl-3-phenylpiperazine (5a). The mixture of **4a** (60.0 g, 0.226 mol), 5% Pd-C (3.0 g, 50% wet),[10] methanol (300 mL) and acetic acid (50 mL) was hydrogenated with H_2 (100 psi.) at 25-30 °C for 5 h, filtered and the filtrate was evaporated to dryness. Dissolved the residue in water (150 mL), pH adjusted to 11.5 with 40% NaOH and extracted with toluene (240 mL). Combined organic solution was concentrated to dryness and the product was precipitated with cyclohexane. Filtered to yield **5a** (36.2 g, 91%) as a light yellow solid; purity 99.9% (by HPLC); mp 58-60 °C (lit,[6] 53-55°C); IR (KBr, cm^{-1}) 3253, 2942, 2816, 2792, 1603, 761, 703; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.76 (bs, 1H), 1.92-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.31 (s, 3H), 2.80-2.89 (m, 2H), 3.01-3.11 (m, 2H), 3.87 (dd, 1H, *J*=10.6, 2.7 Hz), 7.27-7.41 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 46.6, 46.7, 55.6, 60.8, 63.7, 127.3, 127.9, 128.8, 142.9; MS (ESI, *m/z*): 177.0 $[M+H]^+$. Anal. Calcd. For $C_{11}H_{16}N_2$ (176.26): C, 74.96; H, 9.15; N, 15.89. Found: C, 74.90; H, 9.22; N, 15.88.

1-Ethyl-3-phenylpiperazine (5b). This compound was prepared in a similar way to **5a**, using compound **4b** (3.0 g, 10.71 mmol), as a light yellow liquid (1.83 g, 90%); IR (neat, cm^{-1}) 3268, 2944, 2809, 1603, 1470, 756, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, *J*=7.2 Hz), 1.95-1.98 (m, 1H), 2.02-2.13 (m, 1H), 2.45 (q, 2H, *J*=7.2Hz), 2.91-2.97 (m, 2H), 3.06-3.10 (m, 2H),

3.87-3.91 (dd, 1H, *J*=10.4, 2.7 Hz), 7.20-7.32 (m, 3H), 7.34-7.41 (m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 12.2, 46.5, 52.9, 53.1, 60.7, 61.4, 127.4, 127.8, 128.0, 128.6, 128.7, 128.9, 142.9; MS (ESI, *m/z*): 191.2 $[M+H]^+$. Anal. Calcd. For $C_{12}H_{18}N_2$ (190.28): C, 75.74; H, 9.53; N, 14.72. Found: C, 75.60; H, 9.61; N, 14.79.

1-Allyl-3-phenylpiperazine (5c). Compound **4c** (3.0 g, 9.93 mmol) was treated with 6N HCl (12 mL) at 25-30°C for 4 h. Adjusted the pH to 11.5 with 40% NaOH and the aqueous solution was extracted with dichloromethane (30 mL), evaporated to dryness to yield **5c** as a light yellow liquid (1.76 g, 88%); IR (neat, cm^{-1}) 3069, 2886, 1603, 1471, 761, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.98 (br, 1H), 3.56-3.68 (m, 6H), 3.72-3.84 (m, 2H), 4.85-4.88 (m, 1H), 5.51-5.63 (m, 2H), 5.95-6.09 (m, 1H), 7.49-7.54 (m, 3H), 7.69-7.71(m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 41.8, 47.0, 52.5, 57.1, 59.7, 125.6, 127.4, 128.7, 129.8, 130.8, 132.0; MS (ESI, *m/z*): 203.3 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{18}N_2$ (202.30): C, 77.18; H, 8.97; N, 13.85. Found: C, 77.31; H, 8.88; N, 13.81.

1-Propyl-3-phenylpiperazine (5d). This compound was prepared in a similar way to **5a**, using compound **4d** (3.0 g, 10.27 mmol), as a light yellow liquid (1.92 g, 92%); IR (neat, cm^{-1}) 3257, 2935, 2807, 1603, 755, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J*=7.2 Hz), 1.50-1.53 (m, 2H), 1.95-2.11 (m, 2H), 2.29-2.34(m, 2H), 2.85-2.93 (m, 2H) 3.04-3.09 (m, 2H), 3.85 (dd, 1H, *J*=10.4, 2.7 Hz), 7.24-7.33 (m, 3H), 7.37-7.40 (m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 12.4, 20.2, 46.6, 53.6, 60.8, 61.3, 61.9, 127.2, 127.4, 127.8, 128.4, 128.7, 143.0; MS (ESI, *m/z*): 205.2 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{20}N_2$ (204.31): C, 76.42; H, 9.87; N, 13.71. Found: C, 76.58; H, 9.90; N, 13.52.

1-Benzyl-3-phenylpiperazine (5e). This compound was prepared in a similar way to **5c**, using compound **4e** (3.0 g, 8.52 mol), as a light yellow solid (1.93 g, 90%); mp 55-56 °C (lit,[2] 55-63 °C); IR (KBr, cm^{-1}) 3244, 2802, 1602, 761, 741, 701, 696; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.99 (bs, 1H), 2.05-2.13 (m, 1H), 2.21-2.26 (m, 1H), 2.84-2.94 (m, 2H), 3.07-3.11 (m, 2H), 3.57 (s, 2H), 3.91 (dd, 1H, *J*=10.4, 2.7 Hz), 7.24-7.38 (m, 10H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 46.6, 53.6, 60.8, 61.6, 63.8, 127.5, 127.9, 128.7, 128.8, 129.7, 138.3, 143.0; MS (ESI, *m/z*): 253.1 $[M+H]^+$. Anal. Calcd. For $C_{17}H_{20}N_2$ (252.35): C, 80.91; H, 7.99; N, 11.10. Found: C, 80.98; H, 7.96; N, 11.06.

1-Methyl-2-oxo-3-phenylpiperazine (6a). The mixture of **3a** (15.0 g, 53.57 mmol), 5% Pd-C (3.0 g, 50% wet) and acetic acid (90 mL) was hydrogenated with H_2 (100 psi.) at 25-30 °C for 5 h, filtered and the filtrate was evaporated to dryness. Dissolved the residue in water (75 mL), pH adjusted to 10.5 with 20% NaOH and extracted with dichloromethane (150 mL). Combined organic solution was concentrated to dryness to yield **6a** (10.0 g, 98%) as light yellow oil; IR (neat, cm^{-1}) 3301, 2925, 2865, 1640, 1588, 738, 699; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.99 (bs, 1H), 3.03 (s, 3H), 3.05-3.19 (m, 2H), 3.31-3.55 (m, 2H), 4.58 (s, 1H), 7.27-7.42 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 35.1, 41.5, 50.6, 64.2, 128.0, 128.7, 140.3, 169.1; MS (ESI, *m/z*): 191.0 $[M+H]^+$. Anal. Calcd. For $C_{11}H_{14}N_2O$ (190.24): C, 69.45; H, 7.42; N, 14.73. Found: C, 69.54; H, 7.35; N, 14.75.

1-Ethyl-2-oxo-3-phenylpiperazine (6b). This compound was prepared in a similar way to **6a**, using compound **3b** (2.5 g, 8.50 mmol), as a light yellow oil (1.64 g, 95%); IR (neat, cm^{-1}) 3312, 2934, 2873, 1639, 1451, 752, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.19 (t, 3H, *J*=7.2 Hz), 2.10 (bs, 1H), 3.02-3.10 (m, 1H), 3.13-3.20 (m, 1H), 3.27-3.37 (m, 1H), 3.39-3.44 (m, 1H), 3.47-3.58 (m, 2H), 4.55 (s, 1H), 7.27-7.40 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 12.6, 41.5, 42.4, 47.7, 64.1, 128.4, 128.6, 128.7, 128.8, 129.3, 140.4, 168.5; MS (ESI, *m/z*): 205.2 $[M+H]^+$. Anal. Calcd. For $C_{12}H_{16}N_2O$ (204.27): C, 70.56; H, 7.90; N, 13.71. Found: C, 70.34; H, 7.92; N, 13.74.

1-Allyl-2-oxo-3-phenylpiperazine (6c). This compound was prepared in a similar way to **5c**, using compound **3c** (2.5 g, 7.91 mmol), as a light yellow oil (1.53 g, 90%); IR (neat, cm^{-1}) 3309, 3083, 2865, 1638, 1490, 751, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.99 (bs, 1H), 2.88-2.95 (m, 1H), 3.09-3.17 (m, 1H), 3.19-3.22 (m, 1H), 3.32-3.49 (m, 1H), 4.07 (d, 2H, *J*=6.0 Hz), 4.61 (s, 1H), 5.20-5.26 (m, 2H), 5.81-5.97 (m, 1H), 7.28-7.40 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 41.6, 47.9, 49.7, 64.3, 118.2, 128.0, 128.7, 132.9, 140.3, 168.8; MS (ESI, *m/z*): 217.2 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{16}N_2O$ (216.28): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.06; H, 7.58; N, 12.98.

1-Benzyl-2-oxo-3-phenylpiperazine (6d). This compound was prepared in a similar way to **5c**, using compound **3e** (2.5 g, 6.83 mmol), as a light yellow oil (1.59 g, 88%); IR (neat, cm^{-1}) 3313, 2862, 1645, 753, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.91 (bs, 1H), 2.96-3.00 (m, 1H), 3.20-3.24 (m, 1H), 3.42-3.46 (m, 1H), 3.69-3.72 (m, 1H), 4.67 (s, 2H), 5.31 (s, 1H), 7.20-7.49 (m, 10H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 41.6, 47.5, 50.7, 64.2, 127.9, 128.0, 128.4, 128.6, 128.7, 128.9, 129.0, 129.1, 129.3, 129.4, 137.1, 139.7, 168.7; MS (ESI, *m/z*): 267.1 $[M+H]^+$. Anal. Calcd. For $C_{17}H_{18}N_2O$ (266.34): C, 76.66; H, 6.81; N, 10.52. Found: C, 76.50; H, 6.83; N, 10.54.

General method for the preparation of 1-alky-3-phenylpiperazine (5a-c, e) by the reduction of 1-alkyl-2-oxo-3-phenylpiperazines (6a-d). 1-Methyl-3-phenylpiperazine (5a). Under N_2 atmosphere, **6a** (9.0 g, 47.36 mmol) was added slowly to a suspension of $LiAlH_4$ (3.1 g, 81.58mmol) in anhydrous THF (100 mL) at 10-15 °C over a period of 1 h and then refluxed for 6 h. The excess $LiAlH_4$ was destroyed at 0 °C with water (3.1 mL), 15% NaOH (3.1 mL) and water (9.3 mL). After filtration, the filtrate was evaporated to dryness and dissolved the residue in water (25 mL). Acidified the solution to pH 2.0 with 15% HCl and washed the solution with toluene (20 mL). Basified to pH 10.5 with 20% NaOH. The aqueous solution was extracted with dichloromethane (100 mL); the combined organic solution was evaporated. The residue was treated with cyclohexane (20 mL) to yield **5a** (7.4 g, 84%) as a light yellow solid; purity 99.5% (by HPLC), mp 58-59 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1,80 (bs, 1H), 1.96-2.03 (m, 1H), 2.13-2.18 (m, 1H), 2.31 (s, 3H), 2.80-2.89 (m, 2H), 3.06-3.10 (m, 2H), 3.86 (dd, 1H, *J*=10.6, 2.7 Hz), 7.23-7.40 (m, 5H); MS (ESI, *m/z*): 177.0 $[M+H]^+$. Similarly, by following the same procedure **5b, 5c and 5e** can be prepared.

Acknowledgements

Authors thank the management of Aurobindo Pharma Limited, Hyderabad for permission to publish this work. Authors also thank the Analytical Research Department for their valuable contribution to this work.

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8. HPLC analyses were carried out only for compounds 2a, 3a, 4a and 5a. Retention times were 12.1, 13.1, 10.3 and 6.5 respectively (CH_3CN: 0.05 M KH_2PO_4).
9. Lithium aluminum hydride reacts violently with water, liberating hydrogen, incompatible with strong oxidizing agents. Reactions to be carried out in anhydrous conditions.
10. Palladium on carbon is flammable, pyrophoric after activation with hydrogen. It should always be kept at inert atmosphere.