Arch. Pharm. Res. (2013) 36:802–811
DOI 10.1007/s12272-013-0119-1

Archives of Pharmacal Research
www.springer.com/12272

RESEARCH ARTICLE

Synthesis of new 1-phenyl-2-(4-substituted-piperazin-1-yl)-propanol derivatives and evaluation of their antidepressant-like effects

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Published online: 18 April 2013

Abstract In this study, we synthesized eight novel 1-phenyl-2-(4-substituted-piperazin-1-yl)-propanol derivatives and evaluated their antidepressant-like activities. The chemical structures of the synthesised compounds were elucidated by spectroscopy and elemental analyses. Potential antidepressant-like effects of the test compounds (20 mg kg^{-1}) were investigated using the tail-suspension test and modified forced swimming test (MFST) in mice. Additionally, the spontaneous locomotor activity of the mice was assessed using the activity cage apparatus. Both the reference drug fluoxetine (20 mg kg^{-1}) and the test compounds **3a**–**3e** and **3g** significantly shortened the immobility time of the mice in both the behavioural tests. These test compounds also increased the swimming time in MFST without any change in the climbing duration. Compounds **3c**–**3e** and **3g** were significantly more potent in inducing these effects than **3a** and **3b**. None of the compounds changed the locomotor activities of the animals, thus antidepressant-like effects of test compounds were specific. The findings support those of previous studies that reported antidepressant-like activities of aryl alkanol piperazine derivatives.

Keywords Aryl alkanol piperazine · Tail-suspension test · Modified forced swimming test · Activity cage test · Fluoxetine

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Introduction

Depression is a potentially life-threatening disorder that affects people worldwide. The lifetime prevalence of this disease is estimated to be as high as 21 % of the general population in some developed countries. Depression can occur at any age from childhood to late life and has a tremendous cost to society as it causes severe distress and disruption of life and, if left untreated, can be fatal (Brigitta 2002; Cryan et al. 2002).

Drugs that increase the levels of monoamines in the synaptic clefts of the central nervous system have been used for the treatment of depression for many years. In the early years, depression was treated with tricyclic antidepressants and monoamine oxidase inhibitors (Rosenzweig-Lipson et al. 2007). However, the clinical applications of these drugs were limited due to their many side effects (Millan 2004). After the discovery of selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, and citalopram (Fig. 1), and selective noradrenaline reuptake inhibitors, such as reboxetine (Fig. 1), an important shift occurred in depression therapy. Drugs in these groups were found to be as effective as the traditional antidepressants but with fewer side effects because of their more specific mechanisms of action. Afterwards, dual serotonin-noradrenaline reuptake inhibitors (SNRIs), including venlafaxine, desvenlafaxine, and duloxetine (Fig. 1), which also have fewer side effects than traditional antidepressants, were discovered (Richelson 1994; Andrews et al. 1996; Lieberman 2003; Capriotti 2006; Rosenzweig-Lipson et al. 2007). Consequently, newer antidepressants, which inhibit the reuptake of serotonin, noradrenaline or both neurotransmitters, became the preferred drugs in psychiatry clinics because of their pharmacological advantages over the older drugs (Shelton 2003).

The remarkable antidepressant activity of compounds inhibiting serotonin and/or noradrenaline reuptake has directed researchers to develop a new series of chemicals acting as selective or dual inhibitors. The design of compounds carrying an aryloxy or alkoxy alkylamine substructure is a rational strategy for the synthesis of new antidepressants because, as seen in Fig. 1, all known antidepressants contain this common structural feature. Aryl alkanol piperazine derivatives fit this key structure well and, thus, are suitable compounds for evaluation of novel antidepressant drugs. Furthermore, several compounds in the aryl alkanol piperazine group were shown to inhibit the reuptake of serotonin and/or noradrenaline in previous studies (Li et al. 2006; Chen et al. 2009; Jianqi et al. 2010; Weng and Li 2010; Avram et al. 2012).

In the present study, prompted by the structural features and potential antidepressant-like activity of the aryl alkanol piperazines, we synthesised some novel 1-phenyl-2-(4-substituted-piperazin-1-yl)-propanol derivatives and evaluated their antidepressant-like profiles in animal models of depression.

Materials and methods

Chemistry

All chemicals were purchased from Merck (Darmstadt, Germany) or Sigma-Aldrich (St. Louis, MO, USA) Chemical companies. All melting points (M.p.) were determined by Electrothermal 9100 digital melting point apparatus and were uncorrected. ^{1}H NMR data was recorded by Bruker 500 MHz spectrometer. MS-ES, VG Quattro Mass spectrometer and Elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyzer.

Synthesis of 2-bromopropiophenone (**1**)

Propiophenone (150 mmol, 19.8 mL) and HBr (1 mL) were dissolved in 100 mL of chloroform and then bromine (165 mmol, 8.5 mL) in chloroform (20 mL) was added dropwise at room temperature. After completion of dropping, reaction mixture was stirred for an additional 2 h and then 100 mL of water was added. Chloroform phase was separated and the solvent was evaporated to give 2-bromopropiophenone as a liquid product. Yield; 93 %. M.p. not determined. IR (KBr) $\nu_{max}(cm^{-1})$: 3072–3028 (aromatic C–H), 2969–2924 (aliphatic C–H), 1698 (C=O), 1494–1443 (C=C), 1319–1094 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 1.92 (d, 3H, CH_3, $J = 6.60$ Hz), 5.31 (q, 1H, CH, $J = 6.60$ Hz), 7.42–7.58 (m, 3H, Ar–H), 8.02 (d, 2H, Ar–H, $J = 7.29$ Hz). MS-ES $[M + 1]^+$: m/z 214.1. For C_9H_9BrO calculated: 50.73 % C, 4.26 % H, 7.51 % N; found: 50.59 % C, 4.24 % H, 7.53 % N.

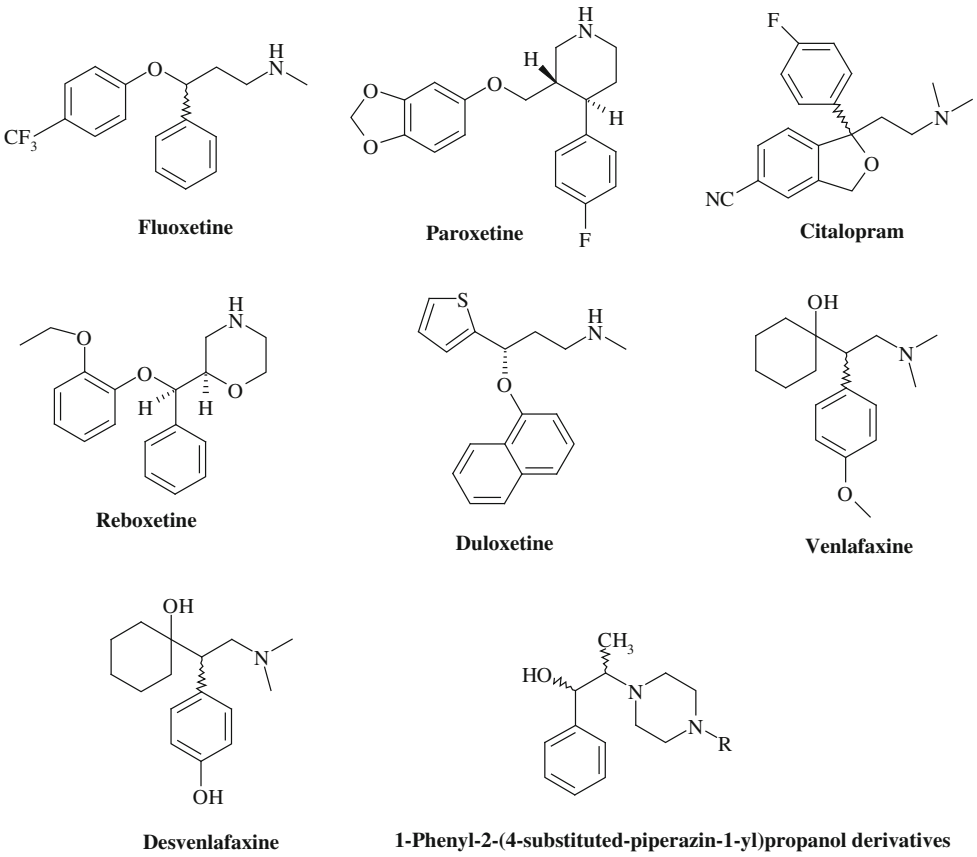


Fig. 1 Chemical structures of some antidepressant drugs and synthesized compounds that carry aryloxy or alkoxy alkylamine main structure

General synthesis of 1-phenyl-2-(4-substituted-piperazin-1-yl)propanone derivatives (**2a**–**2h**)

2-Bromopropiophenone (10 mmol, 2.13 g), appropriate N-substituted piperazine derivative (10 mmol), and K_2CO_3 (10 mmol, 1.38 g) were dissolved in acetone and refluxed for 6 h. After evaporation of solvent, the residue was washed with water, dried, and recrystallized from ethanol if it was obtained in solid form. Otherwise, the oily residue was extracted with ethyl acetate dried on anhydrous sodium sulfate and used in next step after evaporation of the solvent.

*1-Phenyl-2-(4-phenyl-piperazin-1-yl)propanone (**2a**)*

Yield; 84 %. M.p. 104 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3069–3031 (aromatic C–H), 2974–2926 (aliphatic C–H), 1703 (C=O), 1483–1435 (C=C), 1324–1086 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.83 (d, 3H, CH_3, $J = 6.96$ Hz), 2.58–3.23 (m, 8H, piperazine), 4,34 (q, H, CH, $J = 6.94$ Hz), 7.03–7.15 (m, 5H, Ar–H), 7.43–7.57 (m, 3H, Ar–H), 8.03 (2H, d, Ar–H, $J = 7.88$ Hz). MS-ES $[M + 1]^+$: *m/z* 295.6. For $C_{19}H_{22}N_2O$ calculated: 77.52 % C, 7.53 % H, 9.52 % N; found: 77.46 % C, 7.49 % H, 9.50 % N.

*1-Phenyl-2-[4-(4-methyl-phenyl)piperazin-1-yl]propanone (**2b**)*

Yield; 79 %. M.p. 109 °C. 3074–3036 (aromatic C–H), 2968–2923 (aliphatic C–H), 1700 (C=O), 1478–1427 (C=C), 1341–1093 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.85 (d, 3H, CH_3, $J = 6.97$ Hz), 2.58–3.23 (m, 8H, piperazine), 4,32 (q, H, CH, $J = 6.96$ Hz), 6.88 (2H, d, Ar–H, $J = 8.24$ Hz), 7.01 (2H, d, Ar–H, $J = 8.26$ Hz), 7.40–7.57 (m, 3H, Ar–H), 8.01 (2H, d, Ar–H, $J = 7.69$ Hz). MS-ES $[M + 1]^+$: *m/z* 309.2. For $C_{20}H_{24}N_2O$ calculated: 77.89 % C, 7.84 % H, 9.08 % N; found: 78.02 % C, 7.79 % H, 9.02 % N.

*1-Phenyl-2-[4-(4-chloro-phenyl)piperazin-1-yl]propanone (**2c**)*

Yield; 81 %. M.p. 169 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3064–3038 (aromatic C–H), 2977–2923 (aliphatic C–H), 1702 (C=O), 1484–1432 (C=C), 1327–1081 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.83 (d, 3H, CH_3, $J = 7.06$ Hz), 2.59–3.21 (m, 8H, piperazine), 4,31 (q, H, CH, $J = 7.04$ Hz), 6.94 (2H, d, Ar–H, $J = 8.32$ Hz), 7.03 (2H, d, Ar–H, $J = 8.32$ Hz), 7.41–7.56 (m, 3H, Ar–H), 8.00 (2H, d, Ar–H, $J = 7.83$ Hz). MS-ES $[M + 1]^+$: *m/z* 329.8. For $C_{19}H_{21}ClN_2O$ calculated: 69.40 % C, 6.44 % H, 8.52 % N; found: 69.23 % C, 6.46 % H, 8.55 % N.

*1-Phenyl-2-[4-(4-fluoro-phenyl)piperazin-1-yl]propanone (**2d**)*

Yield; 85 %. M.p. 172 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3075–3039 (aromatic C–H), 2968–2919 (aliphatic C–H), 1701 (C=O), 1484–1433 (C=C), 1332–1091 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.83 (d, 3H, CH_3, $J = 7.01$ Hz), 2.56–3.24 (m, 8H, piperazine), 4,31 (q, H, CH, $J = 7.09$ Hz), 6.94 (2H, d, Ar–H, $J = 8.21$ Hz), 7.02 (2H, d, Ar–H, $J = 8.22$ Hz), 7.41–7.56 (m, 3H, Ar–H), 8.01 (2H, d, Ar–H, $J = 7.66$ Hz). MS-ES $[M + 1]^+$: *m/z* 313.2. For $C_{19}H_{21}FN_2O$ calculated: 73.05 % C, 6.78 % H, 8.97 % N; found: 72.99 % C, 6.80 % H, 8.92 % N.

*1-Phenyl-2-[4-(4-nitro-phenyl)piperazin-1-yl]propanone (**2e**)*

Yield; 87 %. M.p. 164 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3071–3028 (aromatic C–H), 2977–2934 (aliphatic C–H), 1701 (C=O), 1479–1431 (C=C), 1319–1094 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.85 (d, 3H, CH_3, $J = 7.11$ Hz), 2.63–3.29 (m, 8H, piperazine), 4.30 (q, H, CH, $J = 7.17$ Hz), 7.41–7.56 (m, 3H, Ar–H), 7.86 (2H, d, Ar–H, $J = 8.42$ Hz), 8.02–8.11 (4H, m, Ar–H). MS-ES $[M + 1]^+$: *m/z* 340.2. For $C_{19}H_{21}N_3O_3$ calculated: 67.24 % C, 6.24 % H, 12.38 % N; found: 67.36 % C, 6.25 % H, 12.41 % N.

*1-Phenyl-2-(4-cyclohexyl-piperazin-1-yl)propanone (**2f**)*

Yield; 77 %. M.p. 106 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3068–3034 (aromatic C–H), 2971–2927 (aliphatic C–H), 1701 (C=O), 1483–1435 (C=C), 1321–1083 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.81 (d, 3H, CH_3, $J = 7.05$ Hz), 1.09–1.27 (m, 6H, cyclohexyl), 1.64–1.97 (m, 4H, cyclohexyl), 2.18–2.27 (m, H, cyclohexyl), 2.49–2.83 (m, 8H, piperazine), 4.36 (q, H, CH, $J = 7.06$ Hz), 7.41–7.56 (m, 3H, Ar–H), 8.01 (2H, d, Ar–H, $J = 7.93$ Hz). MS-ES $[M + 1]^+$: *m/z* 301.4. For $C_{19}H_{28}N_2O$ calculated: 75.96 % C, 9.39 % H, 9.32 % N; found: 75.88 % C, 9.36 % H, 9.30 % N.

*1-Phenyl-2-[4-(2-hydroxy-ethyl)piperazin-1-yl]propanone (**2g**)*

Yield; 74 %. M.p. not determined. IR (KBr) $\nu_{max}(cm^{-1})$: 3294 (O–H), 3073–3036 (aromatic C–H), 2971–2937 (aliphatic C–H), 1700 (C=O), 1486–1428 (C=C), 1325–1088 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.81 (d, 3H, CH_3, $J = 7.02$ Hz), 2.44–2.81 (m, 10H, CH_2 and piperazine), 3.66 (t, 2H, $J = 7.16$ Hz), 4.00–4.08 (b, H, O–H), 4.35 (q, H, CH, $J = 7.04$ Hz), 7.40–7.56 (m, 3H, Ar–H), 8.01 (2H, d, Ar–H, $J = 7.88$ Hz). MS-ES

$[M + 1]^+$: *m/z* 263.2. For $C_{15}H_{22}N_2O_2$ calculated: 68.67 % C, 8.45 % H, 10.68 % N; found: 68.56 % C, 8.43 % H, 10.64 % N.

*1-Phenyl-2-[4-(2-dimethylamino-ethyl)piperazin-1-yl]propanone (**2h**)*

Yield; 76 %. M.p. not determined. IR (KBr) $\nu_{max}(cm^{-1})$: 3075–3033 (aromatic C–H), 2976–2929 (aliphatic C–H), 1703 (C=O), 1481–1426 (C=C), 1332–1093 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.83 (d, 3H, CH_3, $J = 6.97$ Hz), 2.15 (s, 6H, 2xCH_3), 2.34–2.37 (m, 4H, CH_2CH_2), 2.47–2.82 (m, 8H, piperazine), 4.33 (q, H, CH, $J = 7.02$ Hz), 7.41–7.55 (m, 3H, Ar–H), 8.00 (2H, d, Ar–H, $J = 7.84$ Hz). MS-ES $[M + 1]^+$: *m/z* 290.3. For $C_{17}H_{27}N_3O$ calculated: 70.55 % C, 9.40 % H, 14.52 % N; found: 70.39 % C, 9.37 % H, 14.56 % N.

General synthesis of 1-phenyl-2-(4-substituted-piperazin-1-yl)propanol derivatives (**3a**–**3h**)

The intermediates **2a**–**2h** (5 mmol) were dissolved in methanol and $NaBH_4$ (10 mmol) was added in several portions. Reaction was monitored by TLC until the starting material disappeared. After evaporation of solvent, the residue was washed with water, dried, and recrystallized from ethanol to give **3a**–**3g**. Compound **3h** was obtained as an oily residue and its purification was performed by extracting in ethyl acetate.

*1-Phenyl-2-(4-phenyl-piperazin-1-yl)propanol (**3a**)*

Yield; 69 %. M.p. 127 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3246 (O–H), 3042–3024 (aromatic C–H), 2978–2921 (aliphatic C–H), 1456–1432 (C=C), 1321–1083 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.84 (d, 3H, CH_3, $J = 7.16$ Hz), 2.59–3.22 (m, 9H, CH and piperazine), 4,32 (d, H, CH, $J = 8.31$ Hz) 5.08–5.14 (b, H, –OH), 7.01–7.14 (m, 5H, Ar–H), 7.26–7.41 (m, 5H, Ar–H). MS-ES $[M + 1]^+$: *m/z* 297.5. For $C_{19}H_{24}N_2O$ calculated: 76.99 % C, 8.16 % H, 9.45 % N; found: 77.16 % C, 8.18 % H, 9.38 % N.

*1-Phenyl-2-[4-(4-methyl-phenyl)piperazin-1-yl]propanol (**3b**)*

Yield; 72 %. M.p. 112 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3242 (O–H), 3044–3027 (aromatic C–H), 2970–2927 (aliphatic C–H), 1458–1433 (C=C), 1321–1086 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.83 (d, 3H, CH_3, $J = 7.18$ Hz), 2.32 (s, 2H, CH_3), 2.62–3.24 (m, 9H, CH and piperazine), 4.30 (d, H, CH, $J = 8.27$ Hz) 5.07–5.13 (b, H, –OH), 6.86 (2H, d, Ar–H, $J = 8.32$ Hz), 6.98 (2H, d, Ar–H, $J = 8.34$ Hz), 7.25–7.39 (m, 5H, Ar–H). MS-ES $[M + 1]^+$: *m/z* 311.4. For $C_{20}H_{26}N_2O$ calculated: 77.38 % C, 8.44 % H, 9.02 % N; found: 77.73 % C, 8.43 % H, 9.07 % N.

*1-Phenyl-2-[4-(4-chloro-phenyl)piperazin-1-yl]propanol (**3c**)*

Yield; 74 %. M.p. 186 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3236 (O–H), 3056–3031 (aromatic C–H), 2976–2934 (aliphatic C–H), 1452–1433 (C=C), 1318–1086 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.83 (d, 3H, CH_3, $J = 7.15$ Hz), 2.60–3.28 (m, 9H, CH and piperazine), 4.30 (d, H, CH, $J = 8.26$ Hz), 5.02–5.11 (b, H, –OH), 6.93 (m, 2H, Ar–H, $J = 8.37$ Hz), 6.99 (2H, d, Ar–H, $J = 8.35$), 7.26–7.42 (m, 5H, Ar–H). MS-ES $[M + 1]^+$: *m/z* 331.8. For $C_{19}H_{23}ClN_2O$ calculated: 68.97 % C, 7.01 % H, 8.47 % N; found: 68.74 % C, 7.02 % H, 8.42 % N.

*1-Phenyl-2-[4-(4-fluoro-phenyl)piperazin-1-yl]propanol (**3d**)*

Yield; 63 %. M.p. 144 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3241 (O–H), 3053–3027 (aromatic C–H), 2962–2924 (aliphatic C–H), 1453–1417 (C=C), 1328–1096 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.83 (d, 3H, CH_3, $J = 7.12$ Hz), 2.61–3.31(m, 9H, CH and piperazine), 4.31 (d, H, CH, $J = 8.24$ Hz), 4.99–5.11 (b, H, –OH), 6.92 (m, 2H, Ar–H, $J = 8.26$ Hz), 6.98 (2H, d, Ar–H, $J = 8.28$ Hz), 7.25–7.41 (m, 5H, Ar–H). MS-ES $[M + 1]^+$: *m/z* 315.4. For $C_{19}H_{23}FN_2O$ calculated: 72.58 % C, 5.57 % H, 8.91 % N; found: 72.44 % C, 5.56 % H, 8.89 % N.

*1-Phenyl-2-[4-(4-nitro-phenyl)piperazin-1-yl]propanol (**3e**)*

Yield; 81 %. M.p. 182 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3248 (O–H), 3047–3018 (aromatic C–H), 2974–2931 (aliphatic C–H), 1458–1411 (C=C), 1336–1070 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.85 (d, 3H, CH_3, $J = 7.16$ Hz), 2.63–3.29 (m, 9H, CH and piperazine), 4.30 (d, H, CH, $J = 8.17$ Hz), 5.02–5.09 (b, H, –OH), 7.25–7.41 (m, 5H, Ar–H), 7.86 (2H, d, Ar–H, $J = 8.42$ Hz), 8.09 (2H, d, Ar–H, $J = 8.48$ Hz). MS-ES $[M + 1]^+$: *m/z* 342.4. For $C_{19}H_{23}N_3O_3$ calculated: 66.84 % C, 6.79 % H, 12.31 % N; found: 66.76 % C, 6.77 % H, 12.36 % N.

*1-Phenyl-2-(4-cyclohexyl-piperazin-1-yl)propanol (**3f**)*

Yield; 66 %. M.p. 101 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3216 (O–H), 3051–3024 (aromatic C–H), 2972–2938 (aliphatic C–H), 1454–1416 (C=C), 1329–1077 (C–N and C–O).

^{1}H NMR (500 MHz, DMSO-d_6): 0.79 (d, 3H, CH_3, $J = 7.25$ Hz), 1.07–1.29 (m, 6H, cyclohexyl), 1.61–1.92 (m, 4H, cyclohexyl), 2.18–2.30 (m, H, cyclohexyl), 2.48–2.82 (m, 9H, CH and piperazine), 4.24 (d, H, CH, $J = 8.26$ Hz), 5.11–5.26 (b, H, –OH), 7.25–7.37 (m, 5H, Ar–H). MS-ES $[M + 1]^+$: *m/z* 303.5. For $C_{19}H_{30}N_2O$ calculated: 75.45 % C, 10.00 % H, 9.26 % N; found: 75.81 % C, 9.98 % H, 9.31 % N.

*1-Phenyl-2-[4-(2-hydroxy-ethyl)piperazin-1-yl]propanol (**3g**)*

Yield; 69 %. M.p. 109 °C. IR (KBr) $\nu_{max}(cm^{-1})$: 3292 (O–H), 3198 (O–H), 3062–3033 (aromatic C–H), 2981–2914 (aliphatic C–H), 1462–1418 (C=C), 1338–1082 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.78 (d, 3H, CH_3, $J = 7.21$ Hz), 2.47–2.83 (m, 11H, CH_2, CH and piperazine), 3.64 (t, 2H, $J = 7.16$ Hz), 3.98–4.06 (b, H, O–H), 4.25 (d, H, CH, $J = 8.14$ Hz), 5.06–5.18 (b, H, –OH), 7.26–7.37 (m, 5H, Ar–H). MS-ES $[M + 1]^+$: *m/z* 265.4. For $C_{15}H_{24}N_2O_2$ calculated: 68.15 % C, 9.15 % N, 10.60 % N; found: 68.26 % C, 9.13 % H, 10.53 % N.

*1-Phenyl-2-[4-(2-dimethylamino-ethyl)piperazin-1-yl]propanol (**3h**)*

Yield; 71 %. M.p. not determined. IR (KBr) $\nu_{max}(cm^{-1})$: 3226 (O–H), 3042–3017 (aromatic C–H), 2970–2941 (aliphatic C–H), 1459–1413 (C=C), 1341–1083 (C–N and C–O). ^{1}H NMR (500 MHz, DMSO-d_6): 0.79 (d, 3H, CH_3, $J = 7.29$ Hz), 2.14 (s, 6H, 2xCH_3), 2.33–2.38 (m, 4H, CH_2CH_2), 2.47–2.80 (m, 9H, CH and piperazine), 4.24 (d, H, CH, $J = 8.19$ Hz), 5.09–5.18 (b, H, –OH), 7.25–7.37 (m, 5H, Ar–H). MS-ES $[M + 1]^+$: *m/z* 292.5. For $C_{17}H_{29}N_3O$ calculated: 70.06 % C, 10.03 % H, 14.24 % N; found: 70.09 % C, 10.03 % H, 14.40 % N.

Pharmacology

Animals

Adult BALB/c mice, weighing approximately 30–35 g, were used for the experiments. All animals were kept under a 12-h light/12-h dark cycle (lights on at 8:00 a.m.) at a constant temperature of 25 ± 1 °C. These temperature, sound, and light conditions were maintained during the experiments. To ensure adaptation to the new environment, mice were housed in the laboratory for at least 48 h before the experimental session. Food was withdrawn 12 h before the experiments in order to avoid any possible interference of the food with the absorption of the test substances. Water was allowed ad libitum. All experimental procedures were performed in accordance with protocols approved by the Local Ethical Committee on Animal Experimentation of Anadolu University, Eskişehir, Turkey.

Administration of compounds

The mice were assigned randomly into following treatment groups: a control group, a reference drug-treated group, and eight test compounds-treated groups. All of the groups consisted of seven animals. The reference drug fluoxetine (20 mg kg^{-1}, Sigma-Aldrich Chemical Company, St. Louis, MO, USA), control solution (sunflower oil), and the test compounds (20 mg kg^{-1}) were given orally three times 24, 5, and 1 h before the behavioural tests (Sanmukhani et al. 2011).

Behavioural tests

Tail-suspension test (TST)

To assess the antidepressant-like activities of the test compounds, the tail-suspension test (TST) was conducted according to the method described previously (Steru et al. 1985). Each mouse was individually suspended 30 cm above the floor using adhesive tape placed approximately 1 cm from the tip of its tail. Mice were considered immobile only when they hung passively and were completely motionless. The total duration of immobility was measured with a stopwatch during the last 4 min of a 6-min test period (Can et al. 2012).

Modified forced swimming test (MFST)

The modified forced swimming test (MFST) was performed as described elsewhere (Tanaka and Telegdy, 2008; Cryan et al. 2002; Can et al. 2011). The mice were forced to swim individually in a glass cylinder (diameter, 12 cm; height, 30 cm) containing 20 cm of water at 25 ± 1 °C. One day prior to the test, mice were exposed to a pre-test for 15 min with no behavioural observation. Twenty-four hours after the pre-test, the mice were tested under the same conditions for 5 min (test session). During the test session, the times spent swimming (horizontal movement on the surface of the water and crossing into another quadrant), climbing (upward-directed movements of the forepaws along the side of the swim chamber) and immobility (the movement required just to keep the head above the water) in 5-s intervals were recorded by a stopwatch.

Activity cage test

The spontaneous locomotor activities of the mice were evaluated using an activity cage apparatus (Ugo Basile,

No.7420, Varese, Italy) containing 2 pairs of 16 photocells under a transparent cover. Interruptions in light beams to the photocells during horizontal and vertical movements of the animals were recorded automatically for 4 min (Votava et al. 2005).

Statistical analyses

Statistical analyses of the experimental data were performed using GraphPad Prism 3.0 software (GraphPad Software, San Diego, CA, USA). The data used in the statistical analyses were obtained from seven animals for each of the groups. The effects of the test compounds on the behavioural parameters of the animals were analysed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. The data are presented as the mean ± standard error of the mean (SEM). Differences between groups were considered statistically significant at a level of $p < 0.05$.

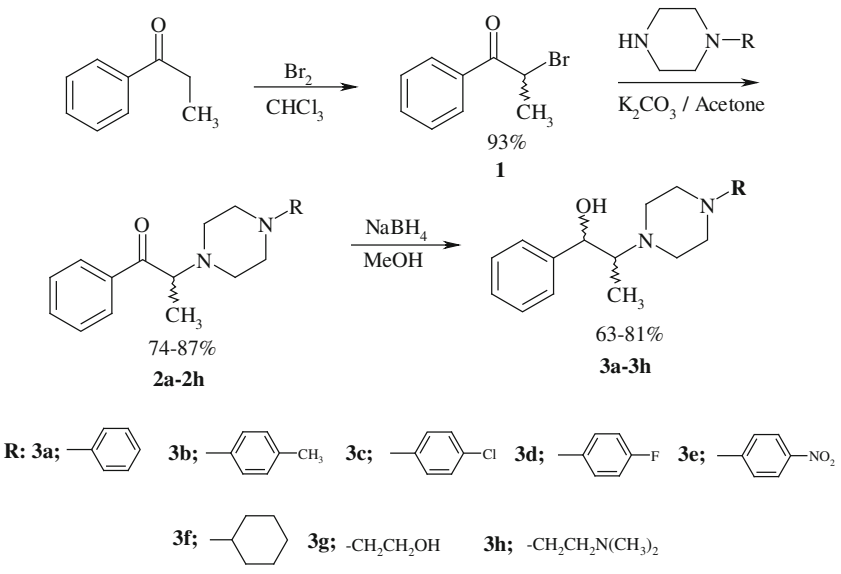
Results and discussion

Chemistry

In this study, we synthesised new 1-phenyl-2-(4-substituted-piperazin-1-yl)-propanol derivatives and investigated their antidepressant-like activities. The target compounds were synthesised in three steps (Scheme 1). Firstly, propiophenone was brominated in chloroform to give 2-bromopropiophenone (compound **1**), which was then reacted with corresponding-N-substituted piperazines to produce 1-phenyl-2-(4-substituted-piperazin-1-yl)-propanone derivatives (compounds **2a**–**2h**). Finally, compounds **2a**–**2h** were reduced by $NaBH_4$ in methanol to produce 1-phenyl-2-(4-substituted-piperazin-1-yl)-propanol derivatives (compounds **3a**–**3h**). Due to the presence of two chiral carbons in their structures, the target compounds were obtained as diastereomers. The structures of the compounds were assigned on the basis of spectroscopic and analytical data. The infrared (IR) spectra were very informative about the structures of the target compounds. The disappearance of the characteristic stretching absorptions for ketone carbonyl group (C=O) at approximately 1700 cm^{-1} and the appearance of stretching bands for O–H bonds at approximately 3216–3292 cm^{-1} indicated the successful reduction of ketone to alcohol. Stretching absorption at approximately 1077–1341 cm^{-1} was recorded for C–N and C–O bonds. In the ^1H nuclear magnetic resonance (NMR) spectra, the methyl group appeared at 0.78–0.84 ppm as a doublet. Protons of piperazine and C–H gave a peak together at approximately 2.47–3.31 ppm as multiplets. C–H protons, which are bonded to O–H groups, were observed at 4.25–4.32 ppm as doublets. Protons of the O–H were observed at 5.02–5.26 ppm as broad peaks. The other peaks, belonging to aromatic and aliphatic protons of variable side chains, were observed at the estimated areas. In the mass spectra, the observed M + 1 peaks agreed with the calculated molecular weights of the synthesised compounds. The results of elemental analyses for C, H, and N were within the calculated values for the compounds.

Pharmacology

The potential antidepressant-like activities of the new phenyl alkanol piperazine derivatives were next evaluated, using TST and MFST. Furthermore, the effects of the



Scheme 1 Synthesis of 1-phenyl-2-(4-substituted-piperazin-1-yl)-propanol derivatives (**3a**–**3h**)

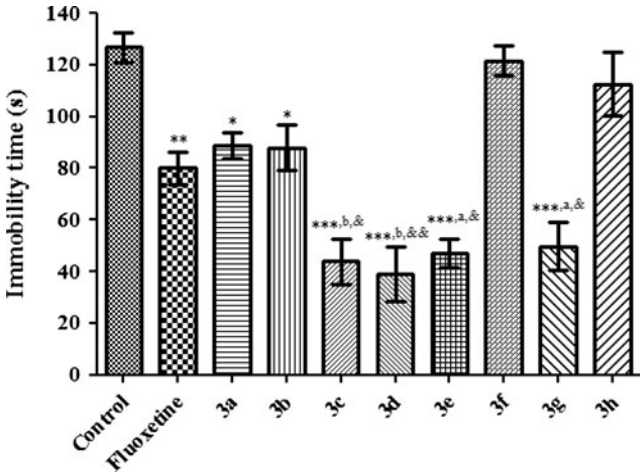


Fig. 2 Effects of the test compounds on immobility time of mice in the TSTs. Values are given as mean ± SEM. Significance against control values, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; significance against compound **3a** treated group, $^{a}p < 0.05$, $^{b}p < 0.01$; significance against compound **3b** treated group, $^{\&}p < 0.05$, $^{\&\&}p < 0.01$. One-way ANOVA, post hoc Tukey test, $n = 7$

compounds on spontaneous locomotor activities were evaluated using the activity cage apparatus.

The TST and MFST tests are widely accepted behavioural models for the screening of antidepressant-like activity. These tests are sensitive to antidepressant drugs and treatment with antidepressants decreases the immobility time of the animals in both the tests (Porsolt et al. 1977; Steru et al. 1985; Brocardo et al. 2008; Girish et al. 2012). Moreover, MFST provides additional information about the possible mechanisms of antidepressant action (Detke and Lucki 1996; Cryan et al. 2002; Akhtar et al. 2005; Aksoz et al. 2008; Nakatomi et al. 2008; Can et al. 2011). In MFST, evaluation of the active behaviours of animals (climbing and swimming) contributes to an estimation of the probable neurotransmitters involved in the antidepressant-like action. Antidepressant drugs that mainly activate the noradrenergic system reduce immobility and increase climbing behaviour, whereas drugs that mainly stimulate the serotonergic system decrease immobility and increase swimming behaviour (Detke and Lucki 1996; Cryan et al. 2002). In the present study, compounds **3a**, **3b**, **3c**, **3d**, **3e**, and **3g** and the reference drug fluoxetine significantly decreased the immobility time of the animals in TST (Fig. 2). Compounds **3c**, **3d**, **3e**, and **3g** were significantly more effective than compounds **3a** and **3b** in terms of this antidepressant-like activity. The antidepressant-like activities of these compounds observed in TST were confirmed by the results of MFST (Fig. 3). Moreover, the observed decrease in the immobility time and increase in the swimming time of the mice without any change in the climbing duration in MFST indicated that the antidepressant-like effects of compounds **3a**, **3b**, **3c**, **3d**, **3e**, and **3g** may be related to serotonergic rather than noradrenergic mechanisms in the central nervous system (Detke and Lucki 1996; Cryan et al. 2002; Can et al. 2012). However, the involvement of the serotonergic system in the exhibited antidepressant-like activity must be confirmed with further detailed studies.

In addition, drugs that increase locomotor activity may give a 'false positive' result in TST and MFST, whereas drugs that decrease locomotion may give a 'false negative' result (Borsini and Meli 1988; Brocardo et al. 2008). Therefore, the activity cage test was performed in order to rule out these probabilities. As illustrated in Fig. 4, the test compounds had no effect on the total number of horizontal or vertical locomotor activities of the mice. Thus, antidepressant-like effects of test compouds were specific.

The structure–activity relationship (SAR) study revealed that the antidepressant-like activity of compounds **3a**–**3h** was sensitive to the nature of the substituents at the fourth position of the piperazine ring. The significant antidepressant-like activity of compounds **3a**–**3e**, which carry phenyl or 4-substituted phenyl groups on their piperazine ring, indicated the impact of the compound's lipophilicity on its pharmacological activity because these compounds have a greater lipophilicity than the inactive compounds **3f** and **3h**, which contain cyclohexane and dimethylaminoethyl side chains, respectively. Lipophilicity is a key property of a drug that influences its ability to reach its target by transmembrane diffusion and therefore influences its biological activity (Testa et al. 2000; Patil et al. 2010). The importance of this property increases for drugs targeting the central nervous system because they need to have sufficient lipophilicity to allow them to cross the blood–brain barrier and, therefore, display pharmacological activity (Alavijeh et al. 2005). In addition to lipophilicity, the electron characteristics of the substituents in compounds **3a**–**3e** influenced their pharmacological activity. The antidepressant-like effects of compounds **3c**–**3e** that had electron withdrawing substituents such as chloro, fluoro, and nitro seemed to be significantly stronger than those of the unsubstituted compound **3a** and compound **3b** with an electron donating methyl group substituent. This is an interesting finding suggesting that the electron density on the piperazine ring is very important for a compound's pharmacological activity. Thus, it may be declared that electron-withdrawing substituents decrease the electron density on the piperazine ring and increase the antidepressant-like activity. Another interesting observation was the significant antidepressant-like activity of compound **3g**. This compound carried a 2-hydroxyethyl group instead of a phenyl substituent at the fourth position of the piperazine ring. According to the above explanations, including the relationships between antidepressant-like activity and physicochemical features such as lipophilicity and electron

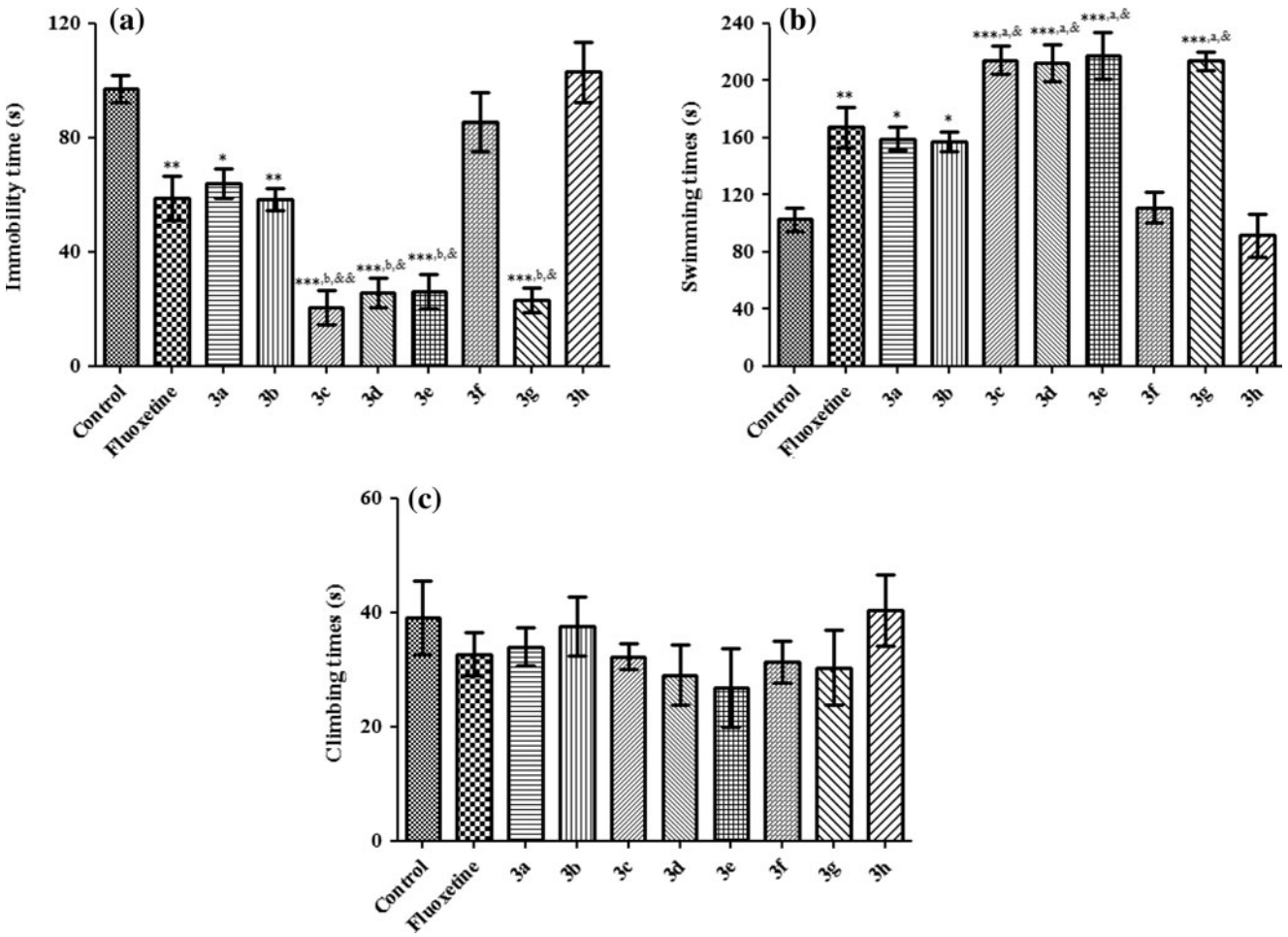


Fig. 3 Effects of the test compounds on immobility (**a**), swimming (**b**) and climbing (**c**) times of mice in the MFSTs. Significance against control values, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; significance against compound **3a** treated group, $^{a}p < 0.05$, $^{b}p < 0.01$; significance against compound **3b** treated group, $^{\&}p < 0.05$, $^{\&\&}p < 0.01$. One-way ANOVA, post hoc Tukey test, $n = 7$

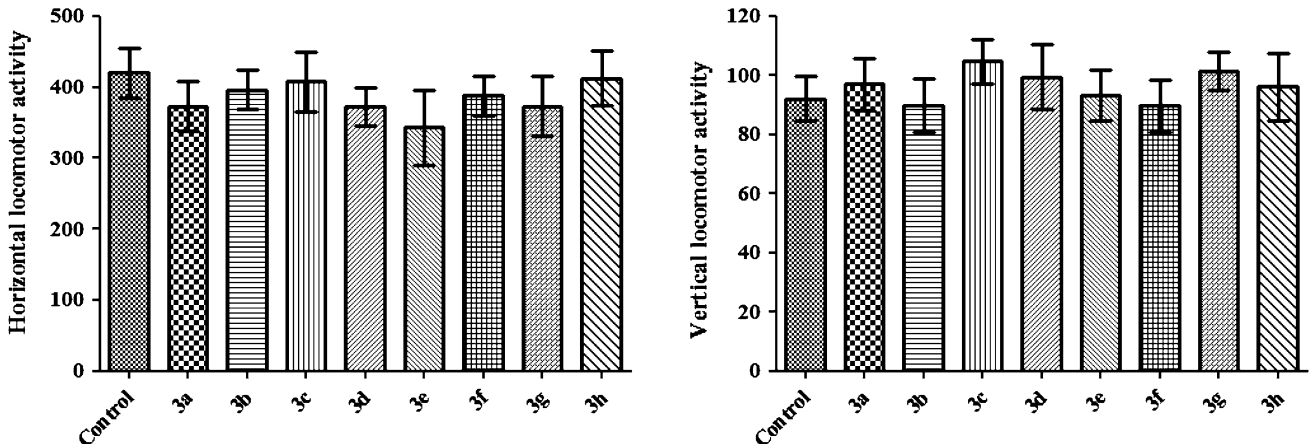


Fig. 4 Effects of the test compounds on spontaneous locomotor activity parameters of mice in the activity cage tests. Values are given as mean ± SEM. One-way ANOVA, post hoc Tukey's test, $n = 7$

density, compound **3g** was not expected to possess notable pharmacological activity. Thus, additional physicochemical properties of this compound should be described. The distinctive feature of compounds **3g** in the series was its second free hydroxyl group, which enabled easier interaction with biomolecules via hydrogen bonds. Hence, it

may be suggested that the greater hydrogen bonding capacity of compound **3g** compared with that of the other derivatives improved its activity. This suggestion can also be proposed for the pharmacologically active compounds **3c**–**3e**, which bear chloro, fluoro, and nitro substituents and are able to form hydrogen bonds with biomolecules.

Conclusion

In the present study, eight novel compounds that are members of the aryl alkanol piperazine group were synthesised and their antidepressant-like activities were investigated. Previously reported similar compounds have been suggested to have serotonergic and/or noradrenergic mechanisms of action (Li et al. 2006; Chen et al. 2009; Jianqi et al. 2010; Weng and Li, 2010; Avram et al. 2012). In this study, in vivo pharmacological studies indicated that most of the synthesised compounds possessed significant antidepressant-like activity, which seemed to be related to a serotonergic mechanism of action. An SAR study revealed that compounds **3c**–**3e** and **3g**, which had 4-chloro phenyl, 4-fluoro phenyl, 4-nitro phenyl and or 2-hydroxyethyl groups on the nitrogen of their piperazine ring, displayed the strongest antidepressant-like activity. These results supported previously reported antidepressant-like activities of aryl alkanol piperazine derivatives and confirmed the antidepressant-like activity of these types of compounds once more (Li et al. 2006; Chen et al. 2009; Jianqi et al. 2010; Weng and Li 2010; Avram et al. 2012).

References

Akhtar, M., K.K. Pillai, and D. Vohora. 2005. Effect of thioperamide on modified forced swimming test-induced oxidative stress in mice. *Basic & Clinical Pharmacology & Toxicology* 97: 218–221.

Aksoz, E., T. Aksoz, S.S. Bilge, F. Ilkaya, S. Celik, and H.B. Diren. 2008. Antidepressant-like effects of echo-planar magnetic resonance imaging in mice determined using the forced swimming test. *Brain Research* 1236: 194–199.

Alavijeh, M.S., M. Chishty, M.Z. Qaiser, and A.M. Palmer. 2005. Drug metabolism and pharmacokinetics, the blood-brain barrier, and central nervous system drug discovery. *NeuroRx* 2: 554–571.

Andrews, J.M., P.T. Ninan, and C.B. Nemeroff. 1996. Venlafaxine: a novel antidepressant that has a dual mechanism of action. *Depression* 4: 48–56.

Avram, S., C. Buiu, D. Duda-Seiman, C. Duda-Seiman, F. Borcan, and D. Mihailescu. 2012. Evaluation of the pharmacological descriptors related to the induction of antidepressant activity and its prediction by QSAR/QRAR methods. Mini review. *Medicinal Chemistry* 12: 467–476.

Brigitta, B. 2002. Pathophysiology of depression and mechanisms of treatment. *Dialogues in Clinical Neuroscience* 4: 7–20.

Borsini, F., and A. Meli. 1988. Is the forced swimming test a suitable model for revealing antidepressant activity? *Psychopharmacology (Berlin)* 94: 147–160.

Brocardo, P.S., J. Budni, M.P. Kaster, A.R. Santos, and A.L. Rodrigues. 2008. Folic acid administration produces an antidepressant-like effect in mice: evidence for the involvement of the serotonergic and noradrenergic systems. *Neuropharmacology* 54: 464–473.

Can, O.D., M.D. Altintop, U.D. Ozkay, U.I. Uçel, B. Doğruer, and Z.A. Kaplancikli. 2012. Synthesis of thiadiazole derivatives bearing hydrazone moieties and evaluation of their pharmacological effects on anxiety, depression, and nociception parameters in mice. *Archives of Pharmacal Research* 35: 659–669.

Can, O.D., I.B. Ismail, Y. Oztürk, N. Oztürk, I. Potoğlu-Erkara, G. Sagratini, M. Ricciutelli, S. Vittori, and F. Maggi. 2011. New antidepressant drug candidate: *Hypericum montbretti* extract. *Natural Product Research* 25: 1469–1472.

Capriotti, T. 2006. Update on depression and antidepressant medications. *Journal of the Academy of Medical-Surgical Nurses* 15: 241–246.

Chen, K.X., Z.G. Li, H.Y. Xie, J.R. Gao, and J.W. Zou. 2009. Quantitative structure-activity relationship analysis of aryl alkanol piperazine derivatives with antidepressant activities. *European Journal of Medicinal Chemistry* 44: 4367–4375.

Cryan, J.F., A. Markou, and I. Lucki. 2002. Assessing antidepressant activity in rodents: recent developments and future needs. *Trends in Pharmacological Sciences* 23: 238–245.

Detke, M.J., and I. Lucki. 1996. Detection of serotonergic and noradrenergic antidepressants in the rat forced swimming test: the effects of water depth. *Behavioural Brain Research* 73: 43–46.

Girish, C., V. Raj, J. Arya, and S. Balakrishnan. 2012. Evidence for the involvement of the monoaminergic system, but not the opioid system in the antidepressant-like activity of ellagic acid in mice. *European Journal of Pharmacology* 682: 118–125.

Jianqi, L.I., Kai, G.A.O., and Na, L.V. 2010. Benzothiophene alkanol piperazine derivatives and their use as antidepressant. W.O. Patent 2010/000198.

Li, J.Q., L.Y. Huang, W.X. Dong, Z.J. Weng, H. Jin, X.L. Ni, S.J. Zhang, C.F. Huang, and F.H. Gu. 2006. Synthesis of α-aryl-1-piperazinealkanol derivatives and determination of their activity as serotonin re-uptake inhibitors, noradrenaline re-uptake inhibitors and their activity as antidepressants. *Chinese Journal of Medicinal Chemistry* 16: 270–276.

Lieberman, J.A. 2003. History of the use of antidepressants in primary care. Primary Care Companion. *Journal of Clinical Psychiatry* 5: 6–10.

Millan, M.J. 2004. The role of monoamines in the actions of established and "novel" antidepressant agents: a critical review. *European Journal of Pharmacology* 500: 371–384.

Nakatomi, Y., C. Yokoyama, S. Kinoshita, D. Masaki, H. Tsuchida, H. Onoe, H. Yoshimoto, and K. Fukui. 2008. Serotonergic mediation of the antidepressant-like effect of the green leaves odor in mice. *Neuroscience Letters* 436: 167–170.

Patil, M., R. Hunoor, and K. Gudasi. 2010. Transition metal complexes of a new hexadentate macroacyclic N_2O_4-donor Schiff base: inhibitory activity against bacteria and fungi. *European Journal of Medicinal Chemistry* 45: 2981–2986.

Porsolt, R.D., A. Bertin, and M. Jalfre. 1977. Behavioral despair in mice: a primary screening test for antidepressants. *Archives Internationales de Pharmacodynamie et de Therapie* 229: 327–336.

Richelson, E. 1994. Pharmacology of antidepressants—characteristics of the ideal drug. *Mayo Clinic Proceedings* 69: 1069–1081.

Rosenzweig-Lipson, S., C.E. Beyer, Z.A. Hughes, X. Khawaja, S.J. Rajarao, J.E. Malberg, Z. Rahman, R.H. Ring, and L.E. Schechter. 2007. Differentiating antidepressants of the

future: efficacy and safety. *Pharmacology & Therapeutics* 113: 134–153.

Sanmukhani, J., A. Anovadiya, and C.B. Tripathi. 2011. Evaluation of antidepressant like activity of curcumin and its combination with fluoxetine and imipramine: an acute and chronic study. *Acta Poloniae Pharmaceutica* 68: 769–775.

Shelton, R.C. 2003. Classification of antidepressants and their clinical implications. Primary Care Companion. *Journal of Clinical Psychiatry* 5: 27–32.

Steru, L., R. Chermat, B. Thierry, and P. Simon. 1985. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology (Berlin)* 85: 367–370.

Tanaka, M., and G. Telegdy. 2008. Involvement of adrenergic and serotonergic receptors in antidepressant-like effect of urocortin 3 in a modified forced swimming test in mice. *Brain Research Bulletin* 77: 301–305.

Testa, B., P. Crivori, M. Reist, and P.A. Carrupt. 2000. The influence of lipophilicity on the pharmacokinetic behavior of drugs: concepts and examples. *Perspectives in Drug Discovery and Design* 19: 179–211.

Votava, M., L. Hess, J. Slíva, M. Krsiak, and V. Agová. 2005. Dexmedetomidine selectively suppresses dominant behavior in aggressive and sociable mice. *European Journal of Pharmacology* 523: 79–85.

Weng, Z., and J. Li. 2010. Synthesis and antidepressant activity of optical isomers of 2-(4-benzylpiperazin-1-yl)-1-(5-chloro-6-methoxynaphthalen-2-yl) propan-1-ol (SIPI5056). *Bioorganic & Medicinal Chemistry Letters* 20: 1256–1259.