"Novel bivalent ligands for D2/D3 dopamine receptors: Significant co-operative gain in D2 affinity and potency".

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Experimental.

Analytical silica gel-coated TLC plates (Silica Gel 60 F_{254}) were purchased from EM Science and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 μM. ^{1}H NMR spectra were routinely obtained on varian 400 MHz FT NMR. The NMR solvent used was either $CDCl_3$ or CD_3OD as indicated. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc and were within ± 0.4% of the theoretical value.

Procedure A. Synthesis of (*S*)-2-chloro-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (2).

Chloroacetyl chloride (0.49 ml, 6.12 mmol) was added into a solution of compound (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.67 g, 3.06 mmol) and Et_3N (1.3 mL) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under N_2 atmosphere and then stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, brine, and the organic layer was dried over Na_2SO_4, evaporated, and purified by flash chromatography using ethyl acetate:hexane (1:4) solvent system to yield compound **2** (1.0 g, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.90-0.97 (m, 3H), 1.61-1.73 (m, 2H), 1.83-

2.12 (m, 2H), 2.58 -2.70 (m, 1H), 2.87 (dd, J_1 = 16.0 Hz, J_2 = 4.8 Hz 1H), 3.00-3.10 (m, 2H), 3.15-3.26 (m, 2H), 3.81 (s, 3H), 3.95-4.03 (m, 1H), 4.08-4.12 (m, 2H), 6.65-6.71 (m, 2H), 7.07-7.15 (m, 1H).

Synthesis of *N*-((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-(((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-*N*-propylacetamide (3).

A suspension of compound **2** (0.40 g, 1.35 mmol), potassium carbonate (0.56 g, 4.06 mmol) and (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.27 g, 1.22 mmol) in acetonitrile were refluxed for 3 h. The solvent was removed under vacuo. The residue was diluted with ethyl acetate, washed with water and brine. The organic layer was concentrated under vacuo and the crude reaction mixture was purified by column chromatography using solvent system ethyl acetate:methanol (9:1) to afford the product **3** (0.4 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79-0.95 (m, 6H), 1.40-1.68 (m, 6H), 1.82-2.04 (m, 3H), 2.51-2.73 (m, 5H), 2.82-3.20 (m, 7H), 3.43 (bs, 2H), 3.76-3.83 (m, 6H), 4.41-4.62 (m, 1H), 6.56-6.72 (m, 4H), 7.00-7.13 (m, 2H).

Procedure B. Synthesis of N^1,N^2-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^2-dipropylethane-1,2-diamine (4).

Compound **3** (0.40 g, 0.84 mmol) in anhydrous THF (15 mL) was added drop wise into a suspension of $LiAlH_4$ (0.32 g, 8.40 mmol) in anhydrous THF (15 ml) at 0 °C under N_2 atmosphere. The reaction mixture was refluxed for 3 h, cooled to room temperature and then cooled further to 0 °C. Saturated solution of NaOH in water (0.5 ml) was added drop wise to quench excess $LiAlH_4$. The reaction mixture was filtered, the solid was washed with ethyl acetate and the combined solvent was dried over Na_2SO_4. The solvent was removed under vacuo and the crude reaction mixture was purified by flash

chromatography using solvent system dichloromethane:methanol (9.5:0.5) to afford compound **4** (0.28 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87-0.92 (m, 6H), 1.44-1.58 (m, 8H), 2.03-2.07 (m, 2H), 2.47-2.56 (m, 5H), 2.61-3.02 (m, 10H), 3.68-3.69 (m, 1H), 3.80 (s, 6H), 6.62-6.75 (m, 4H), 7.07-7.10 (m, 2H).

Procedure C. Synthesis of (6*S*,6'*S*)-6,6'-(ethane-1,2-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (5).

To a stirring solution of **4** (0.28 g, 0.60 mmol) in anhydrous CH_2Cl_2 (15 mL), BBr_3 (6.0 mL, 6.0 mmol, 1.0 M solution in CH_2Cl_2) was added at -40 °C under nitrogen atmosphere. The reaction mixture was stirred at -40 °C for 2 h, then allowed to reach room temperature and stirring was continued for overnight. The reaction was quenched by the addition of saturated $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layer was dried over Na_2SO_4, evaporated under vacuo, and the crude product was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to afford compound **5** (0.12 g, 46%). $[\alpha]_D$ = -52.8 (c = 1, CH_3OH). M.p. 235-238 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-0.98 (m, 6H), 1.24-1.28 (m, 2H), 1.56-1.64 (m, 6H), 2.05 (m, 2H), 2.26-2.27 (m, 2H), 2.53 (m, 10H), 2.98-3.02 (m, 4H), 6.41-6.53 (m, 4H), 6.95-6.99 (m, 2H). The product was converted into corresponding dihydrochloride salt. Anal. Calcd for ($C_{28}H_{42}N_2O_3$. 2HCl) C, H, N.

Synthesis of (*S*)-ethyl 4-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-4-oxobutanoate (7a).

Compound (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.50 g, 2.26 mmol) was reacted with ethyl-4-chloro-4-oxobutyrate (**6a**) (0.42 ml, 2.94 mmol) and Et_3N (2.0 mL) in anhydrous CH_2Cl_2 (10 ml) by following procedure A. The crude product was

purified by flash chromatography using solvent system ethyl acetate:hexane (3:7) to yield compound **7a** (0.74 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-0.89 (m, 3H), 1.17-1.22 (m, 2H), 1.49-1.66 (m, 2H), 1.75-1.92 (m, 2H), 1.98-2.01 (m, 1H), 2.49-2.65 (m, 5H), 2.73-2.80 (m, 1H), 2.84-3.02 (m, 2H), 3.05-3.22 (m, 2H), 3.73-3.75 (d, *J* = 8.8 Hz, 3H), 3.92-4.58 (m, 3H), 6.57-6.64 (m, 2H), 6.98-7.07 (m, 1H).

Synthesis of (*S*)- ethyl 5-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-5-oxopentanoate (7b).

Compound (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.20 g, 0.92 mmol) was reacted with glutaric acid mono ethyl ester chloride (**6b**) (0.20 ml, 1.29 mmol) and Et_3N (0.5 mL) in CH_2Cl_2 (10 ml) following procedure A. The crude product was purified by flash chromatography using solvent system ethyl acetate:hexane (1:4) to yield pure compound **7b** (0.32 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-0.85 (m, 3H), 1.19-1.24 (m, 2H), 1.45-1.66 (m, 2H), 1.72-1.89 (m, 2H), 1.98-2.05 (m, 1H), 2.49-2.72 (m, 7H), 2.73-2.83 (m, 1H), 2.86-3.05 (m, 2H), 3.05-3.20 (m, 2H), 3.73-3.75 (d, *J* = 8.4 Hz, 3H), 3.92-4.55 (m, 3H), 6.57-6.65 (m, 2H), 6.98-7.04 (m, 1H).

Procedure D. Synthesis of (*S*)- ethyl 6-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-6-oxohexanoate (7c).

A mixture of adipic acid monoethyl ester **6c** (0.35 g, 1.99 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide.HCl (EDCI) (0.46 g, 2.39 mmol), 1-hydroxybenzotriazole hydrate (HOBT) (0.32 g, 2.39 mmol) and Et_3N (0.5 mL) in anhydrous dichloromethane (20 ml) was stirred at room temperature under nitrogen atmosphere for 1 hour. A solution of compound (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.17 g, 0.80 mmol) in anhydrous dichloromethane was added into the reaction

mixture under nitrogen atmosphere at room temperature and stirred for 20 hours. The reaction mixture was then diluted with dichlromethane, washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layer was removed under vacuo, dried over Na_2SO_4 and purified by column chromatography over silica gel using solvent system ethyl acetate : hexane (1:4) to afford the compound **7c** (0.25 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87-0.94 (m, 3H), 1.21-1.27 (m, 3H), 1.60-1.71 (m, 6H), 1.84-1.87 (m, 2H), 2.29-2.37 (m, 4H), 2.56-3.36 (m, 6H), 3.80-3.82 (d, 3H), 3.94-4.66 (m, 3H), 6.63-6.71 (m, 2H), 7.05-7.14 (m, 1H).

Synthesis of (*S*)- methyl 11-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-11-oxoundecanoate (7d).

To a stirring solution of acid **6d** (0.59 g, 2.96 mmol) in anhydrous CH_2Cl_2 (15 mL) was added Et_3N (1.0 mL), EDCI (1.32 g, 6.90 mmol) and HOBT (0.93 g, 6.90 mmol). The reaction mixture was stirred for overnight after addition of (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.50 g, 2.28 mmol) by following procedure D. The reaction mixture was purified by flash chromatography using solvent system ethyl acetate:hexane (1:4) to yield compound **7d** (0.65 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-0.87 (m, 3H), 1.16-1.31 (m, 6H), 1.50-1.64 (m, 6H), 1.75-1.94 (m, 2H), 2.19-2.31 (m, 4H), 2.50-2.58 (m, 1H), 2.69-2.77 (m, 1H), 2.83-3.12 (m, 4H), 3.58-3.59 (m, 3H), 3.73-3.75 (d, *J* = 8.0 Hz, 3H), 3.89-4.59 (m, 1H), 6.57-6.65 (m, 2H), 6.98-7.08 (m, 1H).

Procedure E. Synthesis of (*S*)-4-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-4-oxobutanoic acid (8a).

To a stirring solution of compound **7a** (0.74 g, 2.13 mmol) in 15 mL of mixed solvent (methanol:water = 5:2) was added lithium hydroxide (0.4 g, 16.8 mmol). The reaction

mixture was stirred overnight at room temperature under nitrogen atmosphere. The solvent methanol was removed under vacuo. The reaction mixture was washed with 15 mL of 6 N HCl. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over Na_2SO_4, and evaporated to yield **8a** (0.68 g, 99%) which was used in the next step without purification.

Synthesis of (*S*)-5-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-5-oxopentanoic acid (8b).

Compound **7b** (0.32 g, 0.89 mmol) was hydrolyzed in presence of LiOH (0.21 g, 8.90 mmol) by following procedure E to yield compound **8b** (0.28 g, 95%) which was used in the next step without purification.

Synthesis of (*S*)-6-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-6-oxohexanoic acid (8c).

Compound **7c** (1.0 g, 2.66 mmol) was hydrolyzed in presence of LiOH (0.64 g, 26.6 mmol) by following procedure E to yield compound **8c** (0.92 g, 99%) which was used in the next step without purification.

Synthesis of (*S*)-9-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-6-oxononanoic acid (8d).

Compound **7d** (0.65 g, 1.61 mmol) was hydrolyzed in presence of LiOH (0.38 g, 16.1 mmol) by following procedure E to yield compound **8d** (0.60 g, 95%) which was used in the next step without purification.

Synthesis of N^1,N^4-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^4-dipropylsuccinamide (9a).

To a stirring solution of acid **8a** (0.24 g, 1.10 mmol) in anhydrous CH_2Cl_2 (10 mL) was added Et_3N (1.0 mL), EDCI (0.63 g, 3.29 mmol) and HOBT (0.44 g, 3.29 mmol). The reaction mixture was stirred for overnight after addition of (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.24 g, 1.10 mmol) by following procedure D. The reaction mixture was purified by flash chromatography using solvent system ethyl acetate:hexane (7:3) to yield compound **9a** (0.27 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-0.94 (m, 6H), 1.59-2.24 (m, 12H), 2.59-3.27 (m, 12H), 3.80-3.97 (m, 7H), 4.61-4.63 (m, 1H), 6.64-6.70 (m, 4H), 7.05-7.14 (m, 2H).

Synthesis of N^1,N^5-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^5-dipropylglutaramide (9b).

To a stirring solution of acid **8b** (0.38 g, 1.14 mmol) in anhydrous CH_2Cl_2 (10 mL) was added Et_3N (1.0 mL), EDCI (0.55 g, 2.85 mmol) and HOBT (0.39 g, 2.85 mmol). The reaction mixture was stirred for overnight after addition of (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.21 g, 0.95 mmol) by following procedure D. The reaction mixture was purified by flash chromatography using solvent system ethyl acetate:hexane (7:3) to yield compound **9b** (0.32 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89-0.96 (m, 6H), 1.60-1.69 (m, 4H), 1.86-1.94 (m, 2H), 1.96-1.99 (m, 1H), 2.05-2.09 (m, 1H), 2.15-2.16 (d, *J* = 3.2 Hz, 6H), 2.58-2.67 (m, 2H), 2.82-2.87 (m, 2H), 2.92-3.28 (m, 8H), 3.81 (s, 3H), 3.83 (s, 3H), 3.87-3.97 (m, 1H), 4.62-4.64 (m, 1H), 6.65-6.72 (m, 4H), 7.07-7.16 (m, 2H).

Synthesis of N^1,N^6-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^6-dipropyladipamide (9c).

To a stirring solution of acid **8c** (0.39 g, 1.12 mmol) in anhydrous CH_2Cl_2 (15 mL) was added triethylamine (1.0 mL), EDCI (0.43 g, 2.24 mmol) and HOBT (0.30 g, 2.24 mmol). The reaction mixture was stirred for overnight after addition of (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.16 g, 0.75 mmol) following procedure D. The reaction mixture was purified by flash chromatography using solvent system ethyl acetate:hexane (3:7) to yield compound **9c** (0.24 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86-0.93 (m, 6H), 1.59-1.75 (m, 9H), 1.84-1.93 (m, 3H), 2.00-2.40 (m, 1H), 2.36-2.39 (m, 4H), 2.60-2.64 (m, 2H), 2.78-3.17 (m, 10H), 3.80 (s, 3H), 3.81 (s, 3H), 3.96-4.04 (m, 1H), 4.56-4.66 (m, 1H), 6.64-6.70 (m, 4H), 7.07-7.11 (m, 2H).

Synthesis of N^1,N^9-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^9-dipropylnonanediamide (9d).

To a stirring solution of acid **8d** (0.60 g, 1.54 mmol) in anhydrous CH_2Cl_2 (15 mL) was added Et_3N (1.0 mL), EDCI (0.74 g, 3.85 mmol) and HOBT (0.51 g, 3.85 mmol). The reaction mixture was stirred for overnight after addition of (*S*)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (**1**) (0.28 g, 1.28 mmol) by following procedure D. The reaction mixture was purified by flash chromatography using solvent system ethyl acetate:hexane (3:7) to yield compound **9d** (0.52 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-0.87 (m, 6H), 1.17-1.32 (m, 6H), 1.56-1.60 (m, 8H), 1.75-1.94 (m, 4H), 2.18-2.28 (m, 4H), 2.55 (m, 2H), 2.70-3.15 (m, 10H), 3.73 (s, 3H), 3.75 (s, 3H), 3.89-3.92 (m, 1H), 4.52-4.56 (m, 1H), 6.57-6.64 (m, 4H), 6.99-7.07 (m, 2H).

Synthesis of N^1,N^4-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^4-dipropylbutane-1,4-diamine (10a).

Compound **9a** (0.27 g, 0.51 mmol) was reacted with $LiAlH_4$ (0.19 g, 5.13 mmol) in THF (20 ml) by following procedure B. The crude product was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to yield compound **10a** (0.21 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87-0.95 (m, 6H), 1.11-1.17 (m, 3H), 1.54-1.70 (m, 7H), 2.05-2.24 (m, 3H), 2.46-2.60 (m, 7H), 2.72-3.04 (m, 10H), 3.80 (s, 6H), 6.64-6.72 (m, 4H), 7.06-7.11 (m, 2H).

Synthesis of N^1,N^5-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^5-dipropylpentane-1,5-diamine (10b).

Compound **9b** (0.16 g, 0.29 mmol) was reacted with $LiAlH_4$ (0.11 g, 2.99 mmol) in THF (15 ml) by following procedure B. The crude product was purified by flash chromatography using solvent system ethyl acetate:hexane (9:1) to yield compound **10b** (0.19 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 6H), 1.08 (t, *J* = 6.8 Hz, 4H), 1.47-1.61 (m, 7H), 2.06 (bs, 2H), 2.50-3.02 (m, 19H), 3.81 (s, 6H), 6.65-6.73 (m, 4H), 7.07-7.11 (t, *J* = 8.0 Hz, 2H).

Synthesis of N^1,N^6-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^6-dipropylhexane-1,6-diamine (10c).

Compound **9c** (0.20 g, 0.36 mmol) was reacted with $LiAlH_4$ (0.14 g, 3.60 mmol) in THF (15 ml) by following procedure B. The crude product was purified by flash chromatography using solvent system ethyl acetate:methanol (9:1) to yield compound **10c** (0.15 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 6H), 1.25-1.35 (m, 8H), 1.45-1.64 (m, 10H), 2.05-2.10 (m, 2H), 2.48-3.00 (m, 14H), 3.81 (s, 6H), 6.65-6.72 (m, 4H), 7.07-7.10 (t, *J* = 8.0 Hz, 2H).

Synthesis of N^1,N^9-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^9-dipropylnonane-1,9-diamine (10d).

Compound **9d** (0.52 g, 0.88 mmol) was reacted with $LiAlH_4$ (0.33 g, 8.80 mmol) in THF (15 ml) by following procedure B. The crude product was purified by flash chromatography using solvent system dichloromethane:methanol (9.5:0.5) to yield compound **10d** (0.40 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-0.97 (t, *J* = 6.8 Hz, 6H), 1.28 (bs, 8H), 1.60-1.62 (m, 2H), 1.82-1.95 (m, 10H), 2.50-2.56 (m, 4H), 2.97-3.23 (m, 12H), 3.51 (m, 2H), 3.61-3.62 (m, 2H), 3.74 (s, 6H), 6.58-6.67 (m, 4H), 7.01-7.08 (m, 2H).

Synthesis of (6*S*,6'*S*)-6,6'-(butane-1,4-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (11a).

Compound **10a** (0.21 g, 0.43 mmol) was reacted with BBr_3 (4.3 mL, 4.30 mmol, 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (15 mL) by following procedure C. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to afford compound **11a** (0.11 g, 56%). $[\alpha]_D$ = -33.0 (c = 1, CH_2Cl_2). M.p. 114-117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88-0.93 (m, 6H), 1.14 (t, *J* = 6.4 Hz, 4H), 1.22-1.26 (m, 7H), 1.43 (s, 4H), 1.52-1.68 (m, 4H), 2.13-2.15 (m, 1H), 2.48-2.62 (m, 4H), 2.71-2.96 (m, 5H), 3.04-3.10 (m, 1H), 6.61-6.64 (m, 2H), 6.94-6.98 (m, 2H). The product was converted into corresponding dioxalate salt. Anal. Calcd for ($C_{30}H_{47}N_2O_{3.5}$.2$(COOH)_2$) C, H, N.

Synthesis of (6*S*,6'*S*)-6,6'-(pentane-1,5-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (11b).

Compound **10b** (0.19 g, 0.43 mmol) was reacted with BBr_3 (3.8 mL, 3.80 mmol, 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (15 mL) by following procedure C. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to

afford compound **11b** (0.90 g, 47%). $[\alpha]_D$ = -43.6 (c = 1, CH_2Cl_2). M.p. 200-202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 6H), 1.07-1.11 (t, *J* = 7.2 Hz, 6H), 1.47-1.65 (m, 6H), 2.11-2.13 (m, 2H), 2.52-2.99 (m, 18H), 6.58 (d, *J* = 8.0 Hz, 2H), 6.66-6.68 (d, *J* = 7.2 Hz, 2H), 6.96-6.70 (t, *J* = 7.6 Hz, 2H). The product was converted into corresponding dihydrochloride salt. Anal. Calcd for ($C_{31}H_{47.4}N_2O_{2.7}$.2HCl) C, H, N.

Synthesis of (6*S*,6'*S*)-6,6'-(hexane-1,6-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (11c).

Compound **10c** (0.20 g, 0.38 mmol) was reacted with BBr_3 (3.8 mL, 3.8 mmol, 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (15 mL) by following procedure C. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to afford compound **11c** (0.11 g, 58%). $[\alpha]_D$ = -38.0 (c = 1, CH_3OH). M.p. 191-193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 6H), 1.21-1.30 (m, 8H), 1.45-1.62 (m, 10H), 2.05-2.10 (m, 2H), 2.47-2.59 (m, 8H), 2.71-2.96 (m, 6H), 6.59 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.97-7.00 (t, *J* = 7.6 Hz, 2H).

^{1}H NMR of HCl salt (CD_3OD, 400MHz): δ 1.04 (t, *J* =7.2 Hz, 6H), 1.23 (t, *J* = 7.2Hz,0.7H,$CH_3COOCH_2\underline{CH_3}$), 1.51 (bs, 4H),1.72-1.95 (m,10H), 2.00(s, 0.6H, $\underline{CH_3}COOCH_2CH_3$), 2.34-2.37 (m, 2H), 2.60-2.69 (m, 2H), 3.04-3.25 (m,14H), 3.68-3.76 (m, 2H), 4.09 (q,*J* = 6.4Hz, 0.4H,$CH_3COO\underline{CH_2}CH_3$), 6.61 (d,*J* =8.0 Hz, 2H), 6.64 (d,*J* =8.0 Hz, 2H), 6.96 (t, *J* = 7.2 Hz, 2H).

The product was converted into corresponding dihydrochloride salt. Anal. Calcd for ($C_{33.2}H_{54.6}N_2O_{4.1}$.2HCl) C, H, N.

Synthesis of (6*S*,6'*S*)-6,6'-(nonane-1,9-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (11d).

Compound **10d** (0.37 g, 0.66 mmol) was reacted with BBr_3 (6.6 mL, 6.60 mmol, 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (15 mL) by following procedure C. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to afford compound **11d** (0.10 g, 29%). $[\alpha]_D$ = -62.4 (c = 1, CH_2Cl_2). M.p. 180-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.8 Hz, 6H), 1.28 (bs, 10H), 1.51-1.64 (m, 10H), 2.02-2.16 (m, 2H), 2.46-2.98 (m, 18H), 6.59-6.63 (m, 4H), 6.93-6.97 (m, 2H), 7.40 (bs, 2H). The product was converted into corresponding dihydrochloride salt. Anal. Calcd for ($C_{35}H_{58}N_2O_4$.2HCl) C, H, N.

Procedure F. Synthesis of *N*^{1},*N*^{7}-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*^{1},*N*^{7}-dipropylheptanediamide (12a).

To a stirring solution of EDCI.HCl (437 mg, 2.28 mmol), in dichloromethane (10 mL), heptanedioic acid (91 mg, 0.57 mmol) was added followed by addition of amine **1** (250 mg, 1.14 mmol), HOBT (308 mg, 2.28 mmol) and Et_3N (0.48 mL, 3.42 mmol). After stirring for 24 hours water was added into the reaction mixture and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with water, brine and evaporated in vacuo. The crude product was purified by silica gel column chromatography using solvent system dichloromethane:methanol (9:1) to afford compound **12a** (526 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.72-1.08 (m, 6H), 1.10-2.20 (m, 16H), 2.22-3.45 (m, 16H), 3.81 (s, 3H), 3.83 (s, 3H), 6.44-6.85 (m, 4H), 6.90-7.25 (m, 2H).

Synthesis of *N*^{1},*N*^{10}-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*^{1},*N*^{10}-dipropyldecanediamide (12b).

Decanedioic acid (115 mg, 0.57 mmol) was reacted with amine **1** (250 mg, 1.14 mmol), in presence of EDCI.HCl (437 mg, 2.28 mmol), HOBT (308 mg, 2.28 mmol) and Et_3N (0.48

mL, 3.42 mmol) following procedure F. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to afford compound **12b** (538 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.74-1.05 (m, 6H), 1.12-2.15 (m, 22H), 2.22-3.48 (m, 16H), 3.81 (s, 3H), 3.83 (s, 3H), 6.52-6.82 (m, 4H), 7.02-7.18 (m, 2H).

Synthesis of N^1,N^{12}-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^{12}-dipropyldodecanediamide (12c).

Dodecanedioic acid (131 mg, 0.57 mmol) was reacted with amine **1** (250 mg, 1.14 mmol), in presence of EDCI.HCl (437 mg, 2.28 mmol), HOBT (308 mg, 2.28 mmol) and Et_3N (0.48 mL, 3.42 mmol) by following procedure F. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9.5:0.5) to afford compound **12c** (606 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.74-1.02 (m, 6H), 1.15-2.02 (m, 22H), 2.20-2.40 (m, 4H), 2.52-2.72 (m, 2H), 2.74-3.40 (m, 10H), 3.81 (s, 3H), 3.83 (s, 3H), 6.56-6.80 (m, 4H), 7.00-7.22 (m, 2H).

Synthesis of N^1,N^{14}-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^{14}-dipropyltetradecanediamide (12d).

Tetradecanedioic acid (147 mg, 0.57 mmol) was reacted with amine **1** (250 mg, 1.14 mmol), in presence of EDCI.HCl (437 mg, 2.28 mmol), HOBT (308 mg, 2.28 mmol) and Et_3N (0.48 mL, 3.42 mmol) by following procedure F. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9.5:0.5) to afford compound **12d** (603 mg, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78-1.02 (m, 6H), 1.04-2.02 (m, 30H), 2.20-2.42 (m, 4H), 2.50-3.40 (m, 12H), 3.81 (s, 3H), 3.83 (s, 3H), 6.56-6.82 (m, 4H), 7.01-7.22 (m, 2H).

Synthesis of N^1,N^7-bis((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^7-dipropylheptane-1,7-diamine (13a).

Compound **12a** (500 mg, 0.89 mmol) was reacted with $LiAlH_4$ (338 mg, 8.9 mmol) in THF (15 mL) by following procedure B. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to afford compound **13a** (381 mg, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 6.0 Hz, 6H), 1.00-1.80 (m, 17H), 1.94-2.48 (m, 2 H), 2.50-3.20 (m, 17H), 3.81 (s, 6H), 6.66 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 7.2 Hz, 2H), 7.09 (t, *J* = 10.4 Hz, 2H).

Synthesis of N^1,N^{10}-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^{10}-dipropyldecane-1,10-diamine (13b).

Compound **12b** (520 mg, 0.86 mmol) was reacted with $LiAlH_4$ (326 mg, 8.60 mmol) in THF (15 mL) by following procedure B. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9:1) to afford compound **13b** (372 mg, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, *J* = 7.2 Hz, 6H), 1.06-1.90 (m, 23H), 2.02-2.38 (m, 2H), 2.40-3.40 (m, 17H), 3.79 (s, 6H), 6.65 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 2H).

Synthesis of N^1,N^{12}-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^{12}-dipropyldodecane-1,12-diamine (13c).

Compound **12c** (544 mg, 0.86 mmol) was reacted with $LiAlH_4$ (326 mg, 8.60 mmol) in THF (15 mL) following procedure B. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9.5:0.5) to afford compound **13c** (404 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 7.2 Hz, 6H), 1.06-

1.96 (m, 27H), 1.98-2.20 (m, 2H), 2.30-3.20 (m, 17H), 3.81 (s, 6H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 2H).

Synthesis of N^1,N^{14}-*bis*((*S*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-N^1,N^{14}-dipropyltetradecane-1,14-diamine (13d).

Compound **12d** (550 mg, 0.83 mmol) was reacted with $LiAlH_4$ (315 mg, 8.30 mmol) in THF (15 mL) by following procedure B. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (9.5:0.5) to afford compound **13d** (442 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 7.2 Hz, 6H), 1.02-1.80 (m, 31H), 2.00-2.38 (m, 2H), 2.30-3.20 (m, 17H), 3.81 (s, 6H), 6.65 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 2H).

Synthesis of (6*S*,6'*S*)-6,6'-(heptane-1,7-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (14a).

Compound **13a** (350 mg, 0.64 mmol) was reacted with BBr_3 (6.4 mL, 6.40 mmol, 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (12 mL) by following procedure C. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (4:1) to yield **14a** (212 mg, 64%). $[\alpha]_D$ = (-) 47.2 (c = 0.5, CH_2Cl_2). Mp: 50-55 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, *J* = 7.2 Hz, 6H), 1.15-1.72 (m, 16H), 2.02-2.18 (m, 2 H), 2.40-2.68 (m, 10H), 2.70-3.12 (m, 8H), 6.59 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 2H). Anal. Calcd for ($C_{33}H_{50}N_2O_2$.2HCl) C, H, N.

Synthesis of (6*S*,6'*S*)-6,6'-(decane-1,10-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (14b).

Compound **13b** (350 mg, 0.61 mmol) was reacted with BBr_3 (6.1 mL, 6.10 mmol, 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (12 mL) by following procedure C. The reaction mixture was

purified by flash chromatography using solvent system dichloromethane:methanol (4:1) to yield **14b** (196 mg, 59%). $[\alpha]_D$ = (-) 53.1 (c = 1, CH_2Cl_2). Mp: 64-69 ^oC. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 7.2 Hz, 6H), 1.10-1.80 (m, 22H), 2.00-2.28 (m, 2H), 2.29-3.24 (m, 18H), 6.58 (d, *J* = 7.6 Hz, 2H), 6.67 (d, *J* = 7.6 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 2H). Anal. Calcd for ($C_{36}H_{56}N_2O_2$.2HCl) C, H, N.

Synthesis of (6*S*,6'*S*)-6,6'-(dodecane-1,12-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (14c).

Compound **13c** (350 mg, 0.58 mmol) was reacted with BBr_3 (5.8 mL, 5.80 mmol, 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (12 mL) by following procedure C. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (17:3) to afford compound **14c** (190 mg, 57%). $[\alpha]_D$ = (-) 42.2 (c = 1, MeOH). Mp (HCl salt): 115-120 ^oC. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, *J* = 7.2 Hz, 6H), 1.08-1.42 (m, 16H), 1.63-1.98 (m, 10 H), 2.30-2.58 (m, 4H), 2.72-3.20 (m, 14H), 3.40-3.58 (m, 2H), 5.25 (s, C*H*$_2Cl_2$), 6.54 (d, *J* =7.6 Hz, 2H), 6.69 (d, *J* = 7.6 Hz, 2H), 6.91 (t, *J* = 8.0 Hz, 2H). Anal. Calcd for ($C_{39.2}H_{62.4}Cl_{2.4}N_2O_2$.2HCl) C, H, N.

Synthesis of (6*S*,6'*S*)-6,6'-(tetradecane-1,14-diyl*bis*(propylazanediyl))*bis*(5,6,7,8-tetrahydronaphthalen-1-ol) (14d).

Compound **13d** (350 mg, 0.55 mmol) was reacted with BBr_3 (5.5 mL, 5.50 mmol, 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (12 mL) by following procedure C. The reaction mixture was purified by flash chromatography using solvent system dichloromethane:methanol (17:3) to afford compound **14d** (197 mg, 59%). $[\alpha]_D$ = (-) 34.0 (c = 1, MeOH). Mp (HCl salt): 118-123 ^oC. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, *J* = 7.2 Hz, 6H), 1.06-1.50 (m, 16H), 1.51-2.01 (m, 9H), 2.20-2.72 (m, 11H), 2.76-3.20 (m, 11H), 3.24-3.62 (m, 2H), 5.25 (s, C*H*$_2Cl_2$), 6.55

(d, *J* =7.6 Hz, 2H), 6.68 (d, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 8.0 Hz, 2H). Anal. Calcd for ($C_{41.1}H_{66.2}Cl_{2.2}N_2O_2$.2HCl) C, H, N.

***S*-(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-nonyl-propyl-amine (15).**

To a stirring solution of amine **1** (200 mg, 0.91 mmol) in 1,2 dichloroethane (10 mL), nonanal (143 mg, 1.01 mmol) and acetic acid (52 µL, 0.91 mmol) were added. The reaction mixture was stirred for 0.5 hour and then $NaCNBH_3$ (86 mg, 1.37 mmol) was added into it. The reaction mixture was further stirred for 12 hours and extracted with dichloromethane (3 x 25 mL). The combined organic layer was washed with water, brine and evaporated in vacuo. The crude product was purified by silica gel column chromatography using solvent system ethylacetate:hexane (1:4) to afford compound **15** (123 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 7.2 Hz, 6H), 1.16-1.60 (m, 18H), 1.96-2.10 (m, 1H), 2.40-2.58 (m, 5H), 2.68-3.08 (m, 3H), 3.81 (s, 3H), 6.65 (d, *J* = 8 Hz, 1H), 6.71 (d, *J* = 8 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H).

(*S*)-6-(Nonyl-propyl-amino)-5,6,7,8-tetrahydro-naphthalen-1-ol (16).

A stirring solution of methoxy compound **15** (100 mg, 0.29 mmol) was refluxed with 48% aqueous HBr (10 mL) for 6 hours. The reagent was removed in vacuo and crude product was washed with diethylether and recrystallized from ethanol to furnish HBr salt of amine **16** (98 mg, 82%). $[\alpha]_D$ = -12.3 (c = 1, CH_3OH). M.p. 84-89 °C. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.88 (t, *J* = 6 Hz, 3H), 0.96 (t, *J* = 5.6 Hz, 3H), 1.16-1.90 (m, 18H), 2.24-2.38 (m, 1H), 3.02-3.40 (m, 8H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H). Anal. Calcd for ($C_{22}H_{37.6}NO_{1.3}$.HBr) C, H, N.

(S)-6-((9-Phenylnonyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol (19):

Into a stirring solution of (S)-6-(propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (60 mg, 0.29 mmol) **17** in methanol (5ml), 9-phenylnonanal **18** (63.85 mg, 0.29 mmol) was added at room temperature. The reaction mixture was stirred for 1 hour and then $NaCNBH_3$ (33 mg, 0.52 mmol) was added into the solution. After stirring for overnight, the mixture was concentrated, quenched by addition of saturated solution of $NaHCO_3$ and it was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer was washed with brine and finally purified by silica gel column chromatography (Hexane/EtOAc, 9:1) to yield (68 mg, 60%) of pure compound **19** as colorless oil**.** $[\alpha]_d$ = - 13.8 (c = 1, **CH_3OH**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.21-1.38 (m, 12H), 1.49-1.68 (m, 7H), 2.05-2.18 (m, 1H), 2.50-2.64 (m, 6H), 2.74-2.93 (m, 3H), 6.28 (t, *J* = 7.2 Hz, 2H), 6.96 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 6.8 Hz, 3H), 7.24-7.28 (m, 2H). The product, **3** was converted into corresponding hydrobromide salt. Anal. ($C_{28}H_{41}NO \cdot 1.0\ HBr \cdot 1.0\ H_2O$) : C, H, N.

Evaluation of potency in binding to and activating dopamine D2 and D3 receptors

Binding potency was monitored by inhibition of [^{3}H]spiroperidol (16.2 Ci/mmole, Perkin-Elmer) binding to DA rD2 and rD3 receptors expressed in HEK-293 cells, in a buffer containing 0.9% NaCl under conditions corresponding to our 'high [radioligand] protocol' as described by us previously.[1, 2] Observed IC_{50} values were converted to inhibition constants (K_i) by the Cheng–Prusoff equation.[1] Functional activity of test compounds in activating dopamine hD2 and hD3 receptors expressed in CHO cells was measured by stimulation of [^{35}S]GTPγS (1250 Ci/mmole, Perkin-Elmer) binding in comparison to stimulation by the full agonist DA as described by us previously.[1]

Elemental analysis report of the target compounds.

Compound number	Calculated			Found		
	C	H	N	C	H	N
5. 2HCl. H_2O	63.75	8.41	5.31	63.93	8.41	4.95
11a. $2(COOH)_2.1.5H_2O$	60.79	7.65	4.17	60.67	7.77	3.93
11b. 2HCl. $0.7H_2O$	65.99	8.82	4.96	65.91	8.75	5.04
11c. 2HCl. $0.3C_4H_{10}O$. $1.8H_2O$	64.28	9.20	4.52	64.40	8.84	4.15
11d. 2HCl. $2H_2O$	65.30	9.39	4.35	64.91	8.85	4.38
14a. 2HCl. $1.2H_2O$	65.92	9.12	4.66	65.95	9.00	4.55
14b. 2HCl. $1.2H_2O$	67.21	9.46	4.35	67.29	9.30	4.35
14c. 2HCl. $1.2CH_2Cl_2$	62.63	8.63	3.73	62.17	8.96	3.81
14d. 2HCl. $1.1CH_2Cl_2$	64.00	8.91	3.63	63.58	9.23	3.62
16. HBr.$0.3H_2O$	63.24	9.31	3.35	63.16	8.93	3.32
19. 1.0 HBr · 1.0 H_2O	66.39	8.36	2.77	66.71	8.76	2.77

1. Ghosh, B.; Antonio, T.; Reith, M. E.; Dutta, A. K. Discovery of 4-(4-(2-((5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)ethyl)piperaz in-1-yl)quinolin-8-ol and its analogues as highly potent dopamine D2/D3 agonists and as iron chelator: in vivo activity indicates potential application in symptomatic and neuroprotective therapy for Parkinson's disease. *J Med Chem* 53, 2114-25.
2. Zhen, J.; Antonio, T.; Dutta, A. K.; Reith, M. E. Concentration of receptor and ligand revisited in a modified receptor binding protocol for high-affinity radioligands: [3H]Spiperone binding to D2 and D3 dopamine receptors. *J Neurosci Methods* 188, 32-8.