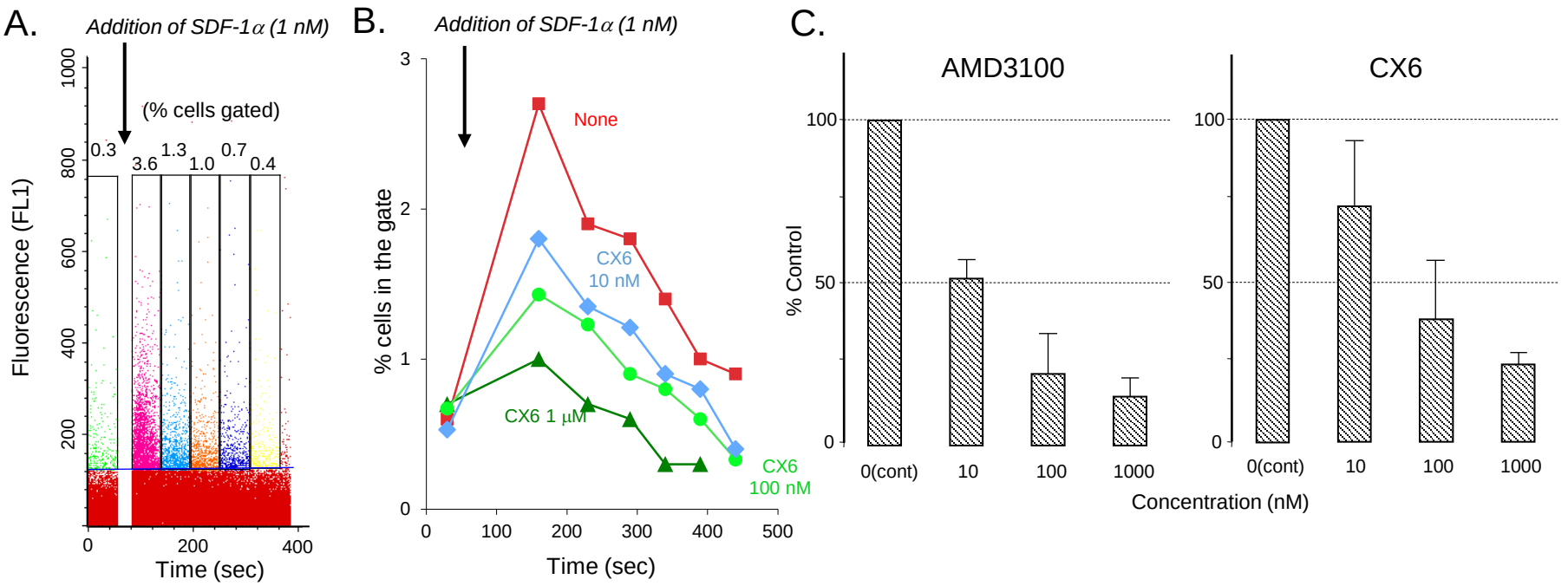

Figure S1. (A) Representative data showing calcium flux elicited by SDF-1α exposure. Changes in fluorescence (FL1) of Molt4 cells after exposure of SDF-1α was measured by flow cytometry using Fluo-4 DirectTM calcium reagent. Blue line indicates baseline. Square-gates were made above the baseline and the percent cell count in each gate was measured. As shown, the % cell counts in a gate increased after the exposure of SDF-1α (0.3% to 3.6%) and it went back to the original level after 300 seconds. **(B)** CX6 Inhibits Ca^{2+} flux in Molt4 cells. Molt4 cells pre-treated with CX6 at varying concentrations (10 nM ~ 1 mM) were exposed to SDF-1α at a concentration of 1 nM (black allow). Changes in the cytosolic Ca^{2+} level after SDF-1α exposure in samples pre-treated with CX6 (blue, right green and dark green) were measured and the IC_{50} was determined by comparison with the Ca^{2+} flux level in drug-free control samples (shown in red). **(C)** AMD3100 and CX6 inhibit calcium flux elicited by SDF-1α in a dose-response manner.

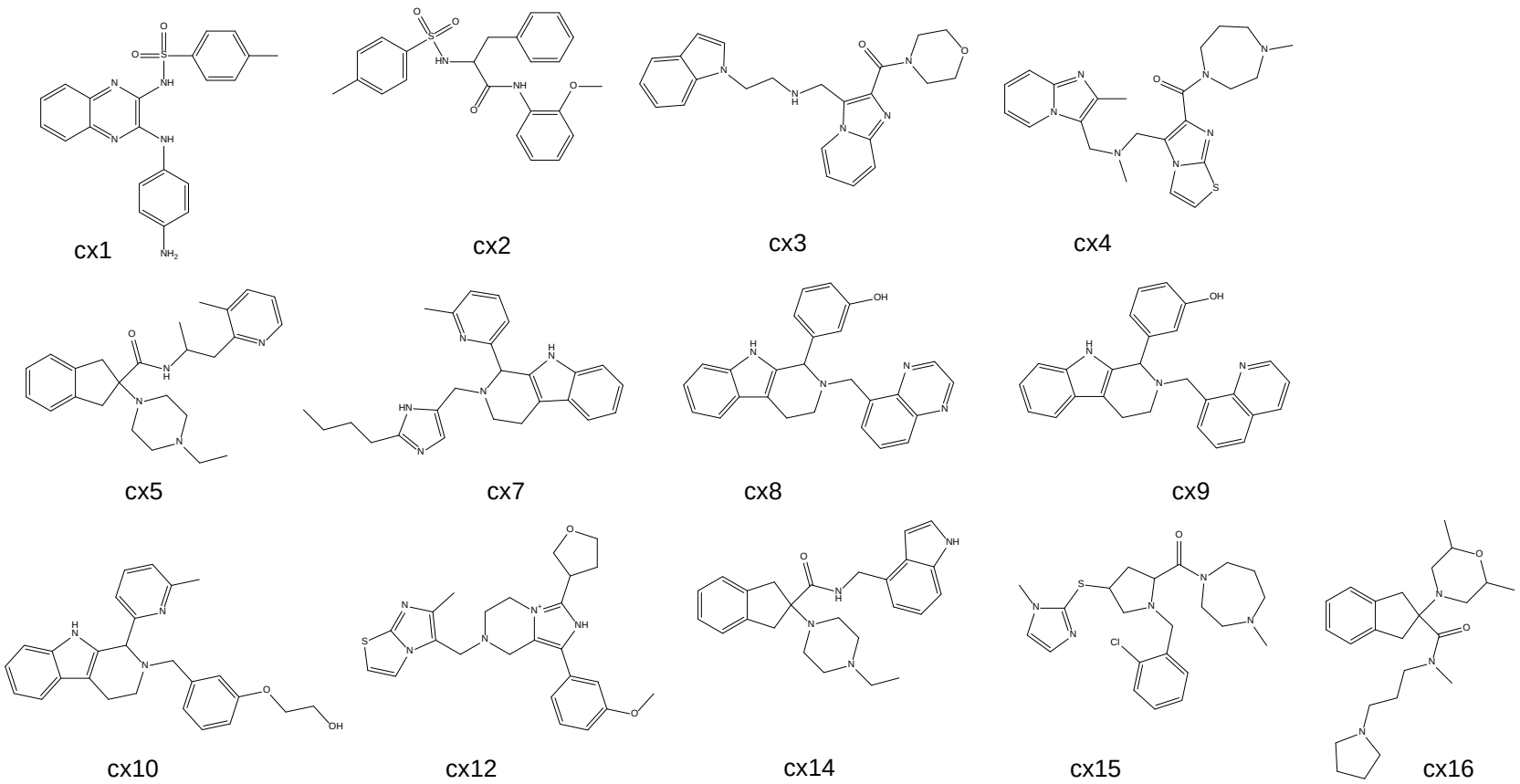

Figure S2. Structures of selected compounds found to be inactive in assays.

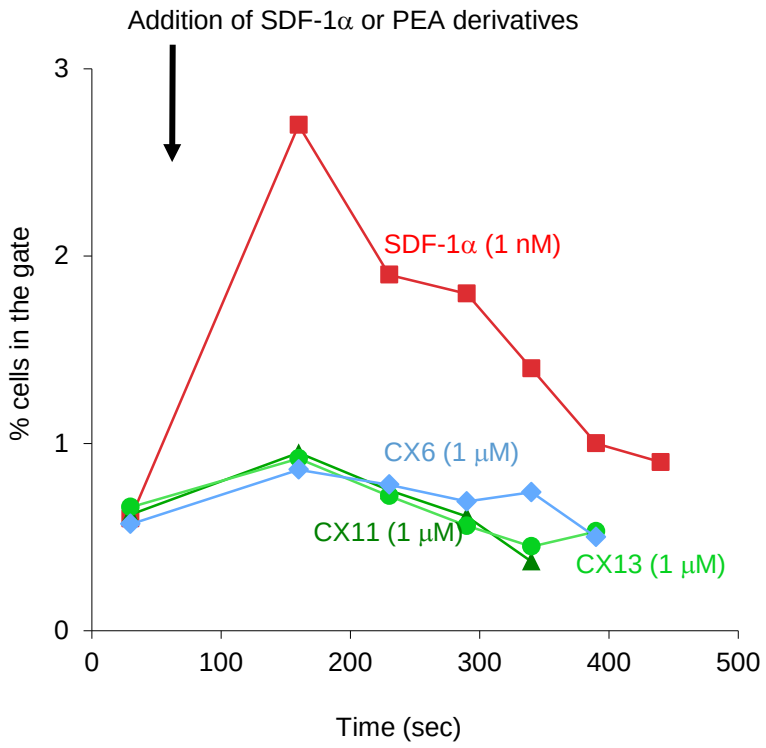

Figure S3. CX6/CX11/CX13 are antagonists. The change in intracellular Ca^{2+} level after exposure of a CX-compound was determined. Molt4 cells (without pre-treatment) were exposed to 1 mM of CX6 (right blue), CX11 (dark green), CX13 (right green) and 1 nM of SDF-1α (red). As shown, cytosolic Ca^{2+} level after the SDF-1α exposure (red) increased Ca^{2+} level but the exposures of CX-compounds did not induce Ca^{2+} flux in cells, suggesting that the PEA derivatives are not agonists.

Experimental Procedure for CX6:

Synthesis of Ethyl 1-cyclopentylpiperidine-3-carboxylate (1): To a stirred solution of cyclopentanone (0.10 mL, 1 equiv.) in CH_2Cl_2 (10 mL) was added ethyl nipecotate (0.19 mL, 1.05 equiv.), AcOH (0.098 mL, 1.5 equiv.), $NaBH(OAc)_3$ (362 mg, 1.5 equiv.) under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched by adding saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 X 20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using 0 to 8% MeOH in CH_2Cl_2 as the eluent to furnish ethyl 1-cyclopentylpiperidine-3-carboxylate **1** as a transparent yellow oil (208 mg, 81%). R_f = 0.47 (6% MeOH in CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.13-4.08 (q, 2H), 3.12 (d, 1H, J = 11.02 Hz), 2.91 (d, 1H, J = 11.24 Hz), 2.55-2.49 (m, 2H), 2.06 (t, 1H, J = 10.96 Hz), 1.96-1.91 (m, 2H), 1.89-1.79 (m, 2H), 1.69-1.60 (m, 3H), 1.56-1.47 (m, 3H), 1.44-1.33 (m, 3H), 1.23 (t, 3H, J = 7.39 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.18, 67.36, 60.04, 54.21, 52.33, 41.80, 30.17, 27.03, 24.55, 23.98, 14.07.

Synthesis of 1-Cyclopentylpiperidine-3-carbaldehyde (2): To a stirred solution of ethyl 1-cyclopentylpiperidine-3-carboxylate **1** (150 mg, 1 equiv.) in anhydrous CH_2Cl_2 (8 mL) at -78 °C under an argon atmosphere was added DIBAL-H (1M solution in CH_2Cl_2, 0.80 mL, 1.2 equiv.) dropwise over 5 min. The mixture was continued to stir at -78 °C for 1 h and quenched by slow addition of MeOH (0.5 mL) followed by 15% w/v potassium sodium tartrate (5 mL). The resulting mixture was allowed to warm to room temperature, stirred vigorously for 1 h, and filtered through a pad of Celite. After the mixture was washed with CH_2Cl_2, the filtrate was partitioned between water and CH_2Cl_2. The organic layer was washed with brine, dried over

Na_2SO_4, filtered, and concentrated to afford the desired crude product. The crude product was purified by column chromatography using 0 to 8% MeOH in CH_2Cl_2 as the eluent to furnish 1-cyclopentylpiperidine-3-carbaldehyde **2** as a transparent yellow oil (90 mg, 75%). R_f = 0.44 (6% MeOH in CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.65 (s, 1H), 2.98 (d, 1H, J = 9.94 Hz), 2.72-2.69 (m, 1H), 2.55-2.43 (m, 2H), 2.27 (t, 1H, J = 10.4 Hz), 2.12 (t, 1H, J = 9.2 Hz), 1.85-1.82 (m, 3H), 1.73-1.61 (m, 3H), 1.54-1.52 (m, 3H), 1.43-1.33 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.75, 67.53, 52.62, 52.12, 48.42, 30.31, 30.26, 24.16, 24.05.

Synthesis of *tert*-Butyl 2-bromoethylcarbamate (3): To a stirred solution of 2-bromoethylamine hydrobromide (200 mg, 1 equiv.) in MeOH (8 mL) was added Et_3N (1.4 mL, 10.3 equiv.) followed by $(Boc)_2O$ (426 mg, 2 equiv.) under an argon atmosphere. The reaction mixture was stirred under reflux for 1 h, then at room temperature for 14 h. The solvent was removed under vacuum and the obtained residue was dissolved in dichloromethane and washed successively with a 1M HCl, a saturated $NaHCO_3$ and brine solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using 0 to 1% MeOH in CH_2Cl_2 as the eluent to furnish *tert*-butyl 2-bromoethylcarbamate **3** as a colorless oil (183 mg, 84%). R_f = 0.37 (1% MeOH in CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.95 (brs, 1H), 3.52 (t, 2H, J = 5.66 Hz), 3.44 (t, 2H, J = 5.48 Hz), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.05, 79.5, 42.31, 32.85, 28.31.

Synthesis of *tert*-Butyl (2-(piperidin-1-yl)ethyl)carbamate: To a stirred solution of piperidine (0.13 mL, 2 equiv.) and K_2CO_3 (277 mg, 3 equiv.) in dry DMF (5 mL) was added *tert*-butyl 2-bromoethylcarbamate **3** (150 mg, 1 equiv.) under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under vacuum and the

obtained residue was dissolved in ethyl acetate and washed with water (2 X 10 mL) and brine solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using 0 to 2% MeOH in CH_2Cl_2 as the eluent to furnish *tert*-butyl (2-(piperidin-1-yl)ethyl)carbamate as a transparent yellow oil (119 mg, 78%). R_f = 0.43 (2% MeOH in CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.02 (brs, 1H), 3.20-3-17 (m, 2H), 2.39 (t, 2H, J = 6.22 Hz), 2.34 (brs, 4H), 1.59-1.52 (m, 4H), 1.48-1.40 (m, 2H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.91, 78.88, 57.75, 54.26, 37.16, 28.34, 25.86, 24.31.

Synthesis of 2-(Piperidin-1-yl)ethanamine (4): *tert*-Butyl (2-(piperidin-1-yl)ethyl)carbamate (100 mg) was dissolved in 3N aq. HCl (2 mL) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was made alkaline by addition of 2N NaOH up to pH 8 and the alkaline solution was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford 2-(piperidin-1-yl)ethanamine **4** as a transparent yellow oil (49 mg, 88%). R_f = 0.32 (3% methanolic ammonia (5%) in CH_2Cl_2). The product was used for the next reaction without any further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.71 (t, 2H, J = 6.42 Hz), 2.35-2.26 (m, 6H), 1.53-1.48 (m, 4H), 1.39-1.34 (m, 2H), 1.31 (brs, 2H).

Synthesis of *N*-((1-Cyclopentylpiperidin-3-yl)methyl)-2-(piperidin-1-yl)ethanamine (5): To a stirred solution of 1-cyclopentylpiperidine-3-carbaldehyde **2** (40 mg, 1 equiv.) and 2-(piperidin-1-yl)ethanamine **4** (31 mg, 1.1 equiv.) in absolute EtOH (3 mL) was added Ti(^{i}PrO)$_4$ (0.19 mL, 3 equiv.) dropwise under argon. The reaction mixture was stirred at room temperature for 15 h. $NaBH_4$ (25 mg, 3 equiv.) was then added and the resulting mixture was stirred for an

additional 3 h at room temperature. The reaction was then quenched by pouring into aqueous ammonia, the resulting inorganic precipitate was filtered off, and washed with CH_2Cl_2 (10 mL). The organic layer was separated and washed with 1N NaOH, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using 0 to 2% methanolic ammonia (5%) in CH_2Cl_2 as the eluent to afford *N*-((1-cyclopentylpiperidin-3-yl)methyl)-2-(piperidin-1-yl)ethanamine **5** as a yellow gummy solid (54 mg, 84%). R_f = 0.52 (2% methanolic ammonia (5%) in CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.03 (d, 1H, J = 10.8 Hz), 2.96 (d, 1H, J = 11.08 Hz), 2.68-2.61 (m, 2H), 2.48-2.44 (m, 3H), 2.40 (t, 2H, J = 6.39 Hz) 2.34 (brs, 4H), 1.89-1.72 (m, 5H), 1.68-1.61 (m, 3H), 1.58-1.46 (m, 9H), 1.43-1.34 (m, 4H), 0.92-0.81 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.79, 58.50, 57.68, 54.60, 53.17, 46.63, 36.17, 30.33, 29.34, 26.0, 25.23, 24.41, 24.11. LRMS-ESI (*m*/*z*) 316.5 $[M + Na]^+$.

Synthesis of 3-((((1-Cyclopentylpiperidin-3-yl)methyl)(2-(piperidin-1yl)ethyl)amino) methyl) phenol (6 or CX6): To a stirred solution of *N*-((1-cyclopentylpiperidin-3-yl)methyl)-2-(piperidin-1-yl)ethanamine **5** (20 mg, 1 equiv.) in CH_2Cl_2 (4 mL) was added 3-hydroxybenzaldehyde (9 mg, 1.05 equiv.), AcOH (6 µL, 1.5 equiv.), $NaBH(OAc)_3$ (21 mg, 1.5 equiv.) under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched by adding saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 X 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using 10% methanolic ammonia (5%) in CH_2Cl_2 as the eluent to obtain 3-((((1-cyclopentylpiperidin-3-yl)methyl)(2-(piperidin-1-yl)ethyl)amino)methyl) phenol **6** as a brown solid (21 mg, 78%). R_f = 0.46 (10% methanolic ammonia (5%) in CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (t, 1H, J = 8.0 Hz), 6.87 (s, 1H), 6.72-6.67 (m, 2H), 3.52 (d, 1H, J = 14 Hz), 3.39 (d, 1H, J = 13.6 Hz), 2.73-2.67 (m, 2H), 2.63-2.59 (m, 2H), 2.61 (s, 2H), 2.44 (t, 2H, J = 6.8 Hz), 2.40 (brs, 4H), 1.93-1.85 (m, 5H), 1.71-1.66 (m, 3H), 1.60-1.52 (m, 9H), 1.45-1.38 (m, 4H), 0.86-0.79 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.80, 141.12, 129.01, 119.97, 166, 114.26, 67.72, 59.38 (d), 57.00 (d) 54.68, 52.75, 51.62, 40.88, 29.40, 28.23, 28.02, 25.33, 23.94. LRMS-ESI (*m*/*z*) 400.6 $[M + H]^+$. HRMS-ESI (m/z) [M + H]+ calculated for (C25H41N3O+H), 400.3328; found, 400.3327. HPLC purity 97.24 %, t_R = 13.57 min [HPLC Condition: YMC-Pack ODS-A Column (5 μM, 250 X 4.6 mm); gradient flow at 1mL/min; injection volume 5 μL; single detection wavelength at λ = 214 nm; column temperature = 30°C; Mobile phase: solvent A: acetonitrile with 0.05% TFA, solvent B: water with 0.05% TFA; gradient elution: t = 0-5 min (gradient flow from 1% to 10% solvent A), t = 5-25 min (gradient flow from 10% to 90% solvent A), t = 25-30 min (90:10 = solvent A:B).

Characterization of CX21 (*N*- ((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-*N*-((1-cyclopentyl-piperidin-3-yl)methyl)-2-(piperidin-1-yl)ethanamine): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (dd, 1H, J = 3.14, 6.24 Hz), 7.53 (dd, 1H, J = 3.04, 6.11 Hz), 7.17-7.15 (m, 2H), 3.97 (q, 2H, J = 16.02 Hz), 2.88 (d, 1H, J = 8.58 Hz), 2.79-2.74 (m, 3H), 2.53-2.49 (m, 3H), 2.46-2.41 (m, 4H), 2.42 (d, 2H, J = 6.27 Hz), 2.03-1.91 (m, 1H), 1.80-1.65 (m, 8H), 1.61-1.50 (m, 6H), 1.47-1.41 (m, 3H), 1.35-1.23 (m, 2H), 0.93-0.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.33, 144.07, 134.01, 121.47, 118.82, 110.62, 67.54, 61.83, 57.49, 57.22, 54.38, 53.39, 53.25, 34.77, 30.22 (d), 29.14, 25.82, 24.72, 24.13, 24.04 (d). LRMS-ESI (*m*/*z*) 424.6 $[M + H]^+$; HRMS-ESI (m/z) $[M + H]^+$ calculated for ($C_{26}H_{41}N_5$+H), 424.3440; found, 424.3439. HPLC purity 98.30 %, t_R = 13.63 min.

Characterization of CX22 (*N*-((1-cyclopentylpiperidin-3-yl)methyl)-*N*-((2,3-dihydrobenzo [*b*][1,4]dioxin-5-yl)methyl)-2-(piperidin-1-yl)ethanamine): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (dd, 1H, *J* = 1.69, 7.37 Hz), 6.78-6.71 (m, 2H), 4.22 (s, 4H), 3.54 (d, 2H, *J* = 3.11 Hz), 3.14 (d, 1H, *J* = 10.30 Hz), 2.96 (d, 1H, *J* = 10.70 Hz), 2.58-2.52 (m, 2H), 2.41 (t, 3H, *J* = 7.76, 13.98 Hz), 2.33 (brs, 4H), 2.25 (d, 2H, *J* = 6.88 Hz), 1.84-1.76 (m, 5H), 1.67-1.62 (m, 4H), 1.56-1.52 (m, 6H), 1.44-1.38 (m, 5H), 0.80-0.72 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.02, 141.64, 128.52, 122.02, 120.25, 115.27, 67.79, 64.08, 59.56, 58.04, 57.43, 54.95, 53.39, 52.28, 52.09, 34.81, 30.45, 30.38, 29.70, 25.93, 25.39, 24.32, 24.14. LRMS-ESI (*m*/*z*) 442.5 $[M + H]^+$; HRMS-ESI (m/z) $[M + H]^+$ calculated for ($C_{27}H_{43}N_3O_2$+H), 442.3434; found, 442.3427. HPLC purity 97.00 %, t_R = 14.36 min.

Characterization of CX23 (*N*-((1-cyclopentylpiperidin-3-yl)methyl)-2-(piperidin-1-yl)-*N*-(quinolin-2-ylmethyl)ethanamine): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, 1H, *J* = 8.48 Hz), 8.02 (1H, *J* = 8.48 Hz), 7.77 (d, 1H, *J* = 7.72 Hz), 7.69 (d, 1H, *J* = 13.16 Hz), 7.65 (t, 1H, *J* = 7.90, 14.94 Hz), 7.47 (t, 1H, *J* = 7.79, 15.01 Hz), 3.91 (q, 2H, *J* = 14.58 Hz), 3.17 (d, 1H, *J* = 10.76 Hz), 2.94 (d, 1H, *J* = 10.89 Hz), 2.69-2.57 (m, 2H), 2.45-2.42 (t, 3H, *J* = 7.57, 14.76 Hz), 2.32-2.26 (m, 6H), 1.85-1.73 (m, 5H), 1.67-1.57 (m, 4H), 1.52-1.50 (p, 6H), 1.42-1.33 (m, 5H), 0.76-0.67 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.58, 147.35, 135.91, 129.09, 128.83, 127.40, 127.31, 125.81, 120.99, 67.73, 62.37, 59.81, 57.98, 57.28, 54.89, 53.31, 52.12, 34.86, 30.45, 30.39, 29.61, 25.90, 25.31, 24.28, 24.12. LRMS-ESI (*m*/*z*) 435.5 $[M + H]^+$; HRMS-ESI (m/z) $[M + H]^+$ calculated for ($C_{28}H_{42}N_4$+H), 435.3488; found, 435.3479. HPLC purity 98.17 %, t_R = 13.63 min.

Characterization of CX24 (*N*-((1-cyclopentylpiperidin-3-yl)methyl)-*N*-(2,3-dimethoxy-benzyl)-2-(piperidin-1-yl)ethanamine): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03-6.96 (m 2H), 6.78

(dd, 1H, *J* = 1.38, 7.70 Hz), 3.83 (s, 3H), 3.77 (s, 3H), 3.58 (q, 2H, *J* = 14.17 Hz), 3.12 (d, 1H, *J* = 10.61 Hz), 2.95 (d, 1H, *J* = 10.90 Hz), 2.60-2.51 (m, 2H), 2.43-2.39 (m, 3H), 2.32 (brs, 4H), 2.23 (d, 2H, *J* = 6.86 Hz), 1.85-1.73 (m, 5H), 1.68-1.61 (m, 4H), 1.54-1.49 (p, 6H), 1.41-1.34 (m, 5H), 0.78-0.68 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.44, 147.37, 133.91, 123.42, 122.06, 110.43, 67.76, 60.55, 59.56, 58.04, 57.38, 55.57, 54.93, 53.36, 53.12, 52.00, 34.84, 30.44 (d), 29.66, 25.90, 25.36, 24.30, 24.12. LRMS-ESI (*m*/*z*) 444.6 $[M + H]^+$; HRMS-ESI (m/z) $[M + H]^+$ calculated for ($C_{27}H_{45}N_3O_2$+H), 444.3590; found, 444.3583. HPLC purity 97.78 %, t_R = 14.68 min.

Characterization of CX25 *(N*-((1-cyclopentylpiperidin-3-yl)methyl)-*N*-(2-methoxybenzyl)-2-(piperidin-1-yl)ethanamine: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 1H, *J* = 7.42 Hz), 7.16 (t, 1H, *J* = 7.65, 14.18 Hz), 6.90 (t, 1H, *J* = 7.46, 14.89 Hz), 6.81 (d, 1H, *J* = 8.14 Hz), 3.77 (s, 3H), 3.57 (s, 2H), 3.14 (d, 1H, *J* = 10.77 Hz), 2.94 (d, 1H, *J* = 10.86 Hz), 2.59-2.49 (m, 2H), 2.45-2.39 (m, 3H), 2.33 (brs, 4H), 2.23 (d, 2H, *J* = 6.40 Hz), 1.87-1.77 (m, 5H), 1.69-1.62 (m, 4H), 1.56-1.49 (p, 6H), 1.40-1.34 (m, 5H), 0.80-0.71 (m. 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.46, 129.65, 128.21, 127.23, 120.11, 109.90, 67.78, 59.65, 58.05, 57.46, 55.12, 54.93, 53.38, 52.79, 52.13, 34.84, 30.43 (d), 29.69, 25.90, 25.37, 24.31, 24.12. LRMS-ESI (*m*/*z*) 414.6 $[M + H]^+$; HRMS-ESI (m/z) $[M + H]^+$ calculated for ($C_{26}H_{43}N_3O$+H), 414.3484; found, 414.3478. HPLC purity 95.59 %, t_R = 13.84 min.

Characterization of CX27 (3-((((1-cyclopentylpiperidin-3-yl)methyl)(2-(piperidin-1-yl) ethyl)amino)methyl)-2-methoxyphenol): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.96-6.90 (m, 2H), 6.79 (dd, 1H, *J* = 2.20, 7.37 Hz), 3.76 (s, 3H), 3.58 (q, 2H, *J* = 14.00 Hz), 3.14 (d, 1H, *J* = 10.57 Hz), 2.97 (d, 1H, *J* = 10.82 Hz), 2.58-2.50 (m, 2H), 2.45-2.39 (m, 3H), 2.34 (brs, 4H), 2.24 (d, 2H, *J* = 6.91 Hz), 1.88- 1.75 (m, 5H), 1.69-1.63 (m, 4H), 1.56-1.50 (p, 6H), 1.42-1.37 (m, 5H),

0.79-0.71 (m. 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.79, 145.72, 133.01, 124.31, 121.66, 114.01, 67.77, 61.32, 59.54, 57.99, 57.27, 54.92, 53.30, 51.86, 34.71, 30.37 (d), 29.66, 25.81, 25.29, 24.26, 24.12. LRMS-ESI (*m*/*z*) 430.6 $[M + H]^+$; HRMS-ESI (m/z) $[M + H]^+$ calculated for ($C_{26}H_{43}N_3O_2$ +H), 430.3434; found, 430.3423. HPLC purity 96.24 %, t_R = 13.26 min.

Purity of Compounds purchased from ChemBridge: CX11, CX13, CX20 and CX26 were purchased from ChemBridge, and have ≥ 95% purity determined by LC-MS as provided in the compound characterization information from ChemBridge.