Supporting Information

Discovery, Optimization, and Characterization of Novel Chlorcyclizine Derivatives for the Treatment of Hepatitis C Virus Infection

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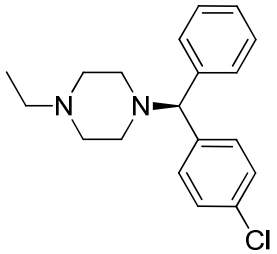
General Chemistry Methods. All air or moisture sensitive reactions were performed under positive pressure of nitrogen with oven-dried glassware. Anhydrous solvents such as dichloromethane, *N*,*N*-dimethylformamide (DMF), acetonitrile, methanol and triethylamine were purchased from Sigma-Aldrich (St. Louis, MO). Preparative purification was performed on a Waters semi-preparative HPLC system (Waters Corp., Milford, MA). The column used was a Phenomenex Luna C_{18} (5 micron, 30 x 75 mm; Phenomenex, Inc., Torrance, CA) at a flow rate of 45.0 mL/min. The mobile phase consisted of acetonitrile and water (each containing 0.1% trifluoroacetic acid). A gradient of 10% to 50% acetonitrile over 8 min was used during the purification. Fraction collection was triggered by UV detection at 220 nM. Analytical analysis was performed on an Agilent LC/MS (Agilent Technologies, Santa Clara, CA). Method 1: A 7-min gradient of 4% to 100% acetonitrile (containing 0.025% trifluoroacetic acid) in water (containing 0.05% trifluoroacetic acid) was used with an 8-min run time at a flow rate of 1.0 mL/min. Method 2: A 3-min gradient of 4% to 100% acetonitrile (containing 0.025% trifluoroacetic acid) in water (containing 0.05% trifluoroacetic acid) was used with a 4.5-min run time at a flow rate of 1.0 mL/min. A Phenomenex Luna C_{18} column (3 micron, 3 x 75 mm) was used at a temperature of 50 °C. Purity determination was performed using an Agilent diode array detector for both Method 1 and Method 2. Mass determination was performed using an Agilent 6130 mass spectrometer with electrospray ionization in the positive mode. ^{1}H NMR spectra were recorded on Varian 400 MHz spectrometers (Agilent Technologies, Santa Clara, CA). Chemical shifts are reported in ppm with undeuterated solvent (DMSO at 2.49 ppm) as internal standard for DMSO-d_6 solutions. All of the analogs tested in the biological assays have a purity of greater than 95% based on both analytical methods. High resolution mass spectrometry was recorded on Agilent 6210 Time-of-Flight (TOF) LC/MS system. Confirmation of molecular formula was accomplished using electrospray ionization in the positive mode with the Agilent Masshunter software (Version B.02). Enantiomerically pure compounds were purified to > 99% purity using supercritical fluid chromatography (SFC) preparative systems at Lotus Separations, LLC (Princeton, NJ, USA). Compounds **Rac-1**, **(S)-1**, and **(R)-1** were purchased from Albany Molecular Research (Albany, NY, USA). Compounds **Rac-2**, **(S)-2**, and **(R)-2** were purchased from MP Biomedicals (Santa Ana, CA, USA). Compounds **Rac-3** and **6** were purchased from Prestwick Chemical (France). Compound **Rac-5** was purchased from TimTec (Newark, DE, USA). Compound **Rac-7** was purchased from Biomol (Germany). Compounds **8** and **9** were purchased from Sigma-Aldrich (St. Louis, MO, USA). Compounds **Rac-36** and **Rac-37** were purchased from Vitas-M Laboratory (Netherlands).

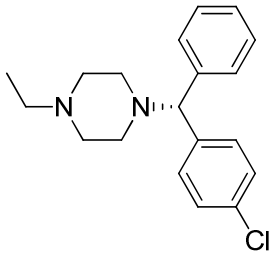
General Procedure A. A solution of amine **Rac-1**, **(S)-1** or **(R)-1** (0.105 mmol) in methanol (MeOH) (1.00 mL) was treated at room temperature with the corresponding aldehyde (0.525 mmol to 1.05 mmol, 5.0 to 10.0 equiv.), $NaBH_3CN$ (19.7 mg, 0.315 mmol, 3.0 equiv.) and acetic acid (0.018 mL, 0.315 mmol, 3.0 mmol). The reaction mixture was stirred at room temperature for 1 - 8 h and quenched with 1 N NaOH solution. The mixture was dried by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC.

General Procedure B. A solution of amine **Rac-1**, **(S)-1** or **(R)-1** (0.157 mmol) and the corresponding aldehyde or ketone (0.314 mmol, 2.0 equiv.) in ethanol (EtOH) (2.00 mL)

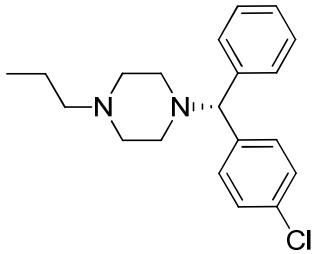
was treated at room temperature with titanium (IV) isopropoxide (0.092 mL, 0.314 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 10 min and then treated with $NaBH_3CN$ (49.3 mg, 0.785 mmol, 5.0 equiv.). The resulting mixture was stirred at room temperature for 1-8 h and quenched with 1 N NaOH. The mixture was dried by blowing air, re-dissolved in DMSO, filtered and purified by preparative HPLC to give the final product.



(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-ethylpiperazine ***((S)-10)****.* The title compound was prepared according to General Procedure A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (s, 1H), 7.50 – 7.29 (m, 8H), 7.29 – 7.19 (m, 1H), 4.54 (s, 1H), 3.42 (d, J = 12.23 Hz, 2H), 3.18 – 3.09 (m, 2H), 3.04 (q, J = 11.21 Hz, 2H), 2.84 (d, J = 13.01 Hz, 2H), 2.21 (q, J = 11.50 Hz, 2H), 1.18 (t, J = 7.27 Hz, 3H); LCMS RT (Method 1) = 4.566 min; RT (Method 2) = 3.035 min, m/z 315.1 [M+H$^+$].

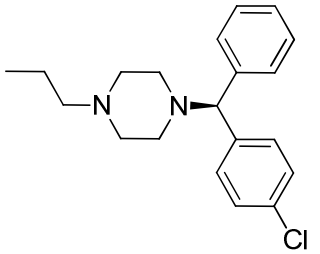


(R)-1-((4-Chlorophenyl)(phenyl)methyl)-4-ethylpiperazine ***((R)-10)****.* The title compound was prepared according to General Procedure A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (s, 1H), 7.48 – 7.27 (m, 8H), 7.27 – 7.18 (m, 1H), 4.52 (s, 1H), 3.40 (d, J = 11.93 Hz, 2H), 3.16 – 2.95 (m, 4H), 2.83 (d, J = 13.06 Hz, 2H), 2.19 (q, J = 11.58 Hz, 2H), 1.17 (t, J = 7.25 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.48; LCMS RT (Method 1) = 4.505 min, m/z 315.1 [M+H$^+$].

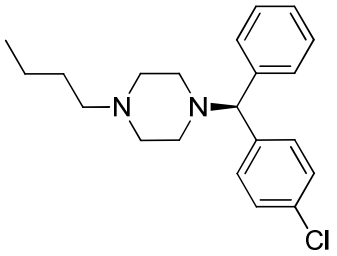


(R)-1-((4-Chlorophenyl)(phenyl)methyl)-4-propylpiperazine ***((R)-11)****.* The title compound was prepared according to General Procedure A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (d, J = 9.36 Hz, 1H), 7.49 – 7.29 (m, 8H), 7.29 – 7.20 (m, 1H), 4.54 (s, 1H), 3.42 (d, J = 12.10 Hz, 2H), 3.12 – 2.97 (m, 4H), 2.83 (d, J = 13.02 Hz, 2H), 2.29 – 2.16 (m, 2H), 1.69 – 1.54 (m, 2H), 0.89 (t, J = 7.38 Hz, 3H); ^{19}F NMR

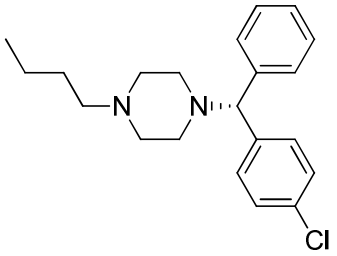
(376 MHz, DMSO-d_6) δ ppm -73.55; LCMS RT (Method 1) = 4.746 min, m/z 329.1 [M+H$^+$].



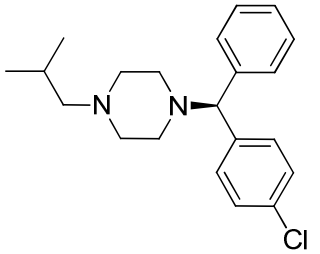
(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-propylpiperazine ***((S)-11)***. The title compound was prepared according to General Procedure B as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (s, 1H), 7.49 – 7.29 (m, 8H), 7.29 – 7.19 (m, 1H), 4.54 (s, 1H), 3.42 (d, J = 12.04 Hz, 2H), 3.12 – 2.97 (m, 4H), 2.83 (d, J = 12.71 Hz, 2H), 2.23 (q, J = 11.27 Hz, 2H), 1.69 – 1.54 (m, 2H), 0.89 (t, J = 7.37 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.46; LCMS RT (Method 1) = 4.817 min, m/z 329.1 [M+H$^+$].



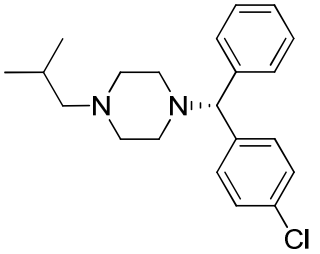
(S)-1-Butyl-4-((4-chlorophenyl)(phenyl)methyl)piperazine ***((S)-12)***. The title compound was prepared according to General Procedure A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (s, 1H), 7.49 – 7.29 (m, 8H), 7.29 – 7.19 (m, 1H), 4.53 (s, 1H), 3.43 (d, J = 10.81 Hz, 2H), 3.06 (dt, J = 5.09, 11.92 Hz, 4H), 2.83 (d, J = 13.08 Hz, 2H), 2.23 (td, J = 6.99, 11.94 Hz, 2H), 1.57 (tt, J = 6.23, 8.00 Hz, 2H), 1.30 (h, J = 7.36 Hz, 2H), 0.90 (t, J = 7.34 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.63; LCMS RT (Method 1) = 5.015 min, m/z 343.1 [M+H$^+$].



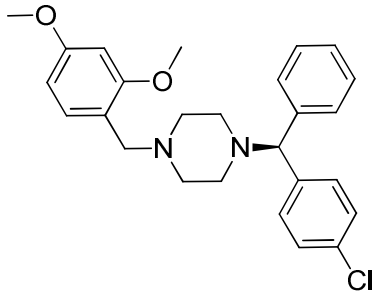
(R)-1-Butyl-4-((4-chlorophenyl)(phenyl)methyl)piperazine ***((R)-12)***. The title compound was prepared according to General Procedure A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (s, 1H), 7.49 – 7.29 (m, 8H), 7.29 – 7.19 (m, 1H), 4.53 (s, 1H), 3.43 (d, J = 12.96 Hz, 2H), 3.07 (dq, J = 4.91, 11.93 Hz, 4H), 2.87 – 2.79 (m, 2H), 2.29 – 2.16 (m, 2H), 1.64 – 1.51 (m, 2H), 1.30 (h, J = 7.40 Hz, 2H), 0.90 (t, J = 7.34 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.63; LCMS RT (Method 1) = 5.038 min, m/z 343.1 [M+H$^+$].



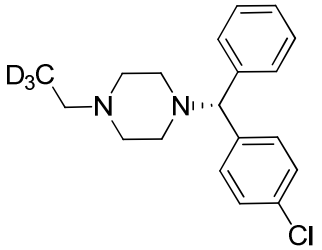
(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-isobutylpiperazine ***((S)-13)****.* The title compound was prepared according to General Procedure A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.92 (s, 1H), 7.47 – 7.28 (m, 8H), 7.27 – 7.18 (m, 1H), 4.54 (s, 1H), 3.45 – 3.36 (m, 2H), 3.05 (q, *J* = 11.14 Hz, 2H), 2.93 (dd, *J* = 5.50, 7.14 Hz, 2H), 2.82 – 2.74 (m, 2H), 2.37 – 2.25 (m, 2H), 2.00 (hept, *J* = 6.78 Hz, 1H), 0.91 (d, *J* = 6.60 Hz, 6H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.54; LCMS RT (Method 1) = 4.858 min, m/z 343.2 [M+H$^+$].



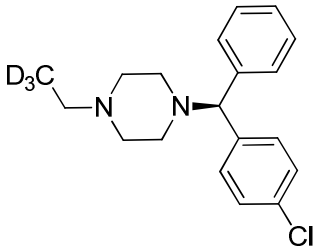
(R)-1-((4-Chlorophenyl)(phenyl)methyl)-4-isobutylpiperazine ***((R)-13)****.* The title compound was prepared according to General Procedure A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.92 (s, 1H), 7.49 – 7.30 (m, 8H), 7.29 – 7.20 (m, 1H), 4.56 (s, 1H), 3.42 (d, *J* = 11.68 Hz, 2H), 3.07 (q, *J* = 11.05 Hz, 2H), 2.95 (dd, *J* = 5.41, 7.28 Hz, 2H), 2.84 – 2.76 (m, 2H), 2.33 (q, *J* = 11.37 Hz, 2H), 2.02 (hept, *J* = 6.76 Hz, 1H), 0.93 (d, *J* = 6.58 Hz, 6H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.62; LCMS RT (Method 1) = 4.881 min, m/z 343.2 [M+H$^+$].



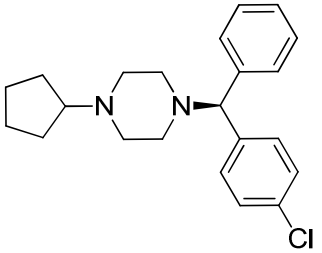
(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-(2,4-dimethoxybenzyl)piperazine ***((S)-14)****.* The title compound was prepared according to General Procedure B as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (s, 1H), 7.48 – 7.25 (m, 9H), 7.28 – 7.14 (m, 1H), 6.68 – 6.56 (m, 2H), 4.51 (s, 1H), 4.20 (d, *J* = 4.69 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.29 (d, *J* = 12.47 Hz, 1H), 3.07 (q, *J* = 10.83 Hz, 2H), 2.85 – 2.77 (m, 2H), 2.24 (s, 2H); LCMS RT (Method 1) = 5.552 min, m/z 437.1 [M+H$^+$].



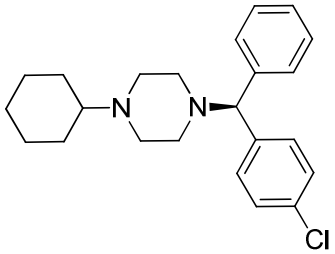
(R)-1-((4-Chlorophenyl)(phenyl)methyl)-4-ethyl(2,2,2-d_3)piperazine (***(R)-15***). The title compound was prepared according to General Procedure A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.14 (s, 1H), 7.46 (ddt, J = 6.6, 4.4, 2.1 Hz, 2H), 7.43 – 7.38 (m, 4H), 7.34 (t, J = 7.6 Hz, 2H), 7.29 – 7.20 (m, 1H), 4.55 (d, J = 4.6 Hz, 1H), 3.55 (d, J = 10.9 Hz, 2H), 3.22 – 2.97 (m, 3H), 2.86 (t, J = 10.7 Hz, 2H), 2.21 (dd, J = 20.2, 11.1 Hz, 3H). LCMS RT (Method 1) = 4.630 min, m/z 317.2 [M+H$^+$].



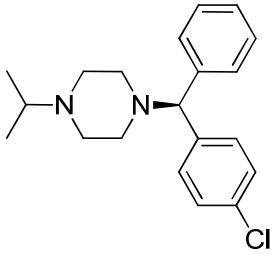
(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-ethyl(2,2,2-d_3)piperazine (***(S)-15***). The title compound was prepared according to General Protocol A as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.19 (s, 1H), 7.46-7.44 (m, 2H), 7.43 – 7.38 (m, 4H), 7.34 (t, J = 7.3 Hz, 2H), 7.27 – 7.23 (m, 1H), 4.57 (d, J = 4.3 Hz, 1H), 3.49 (d, J = 10.1 Hz, 2H), 3.24 – 2.95 (m, 3H), 2.86 (t, J = 10.1 Hz, 2H), 2.24 (dd, J = 20.3, 11.0 Hz, 3H). LCMS RT (Method 1) = 4.671 min, m/z 317.2 [M+H$^+$].



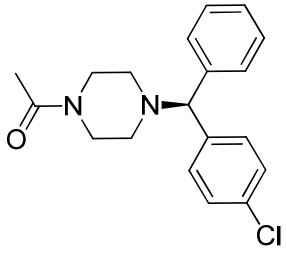
(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-cyclopentylpiperazine (***(S)-16***). The title compound was prepared according to General Procedure B as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (s, 1H), 7.50 – 7.29 (m, 8H), 7.31 – 7.20 (m, 1H), 4.55 (s, 1H), 3.57 – 3.40 (m, 3H), 3.16 – 3.02 (m, 2H), 2.85 (d, *J* = 12.86 Hz, 2H), 2.28 – 2.14 (m, 2H), 2.04 – 1.90 (m, 2H), 1.73 – 1.47 (m, 6H); LCMS RT (Method 1) = 4.871 min; RT (Method 2) = 3.149 min, m/z 355.1 [M+H$^+$].



(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-cyclohexylpiperazine ***((S)-17)****.* The title compound was prepared according to General Procedure B as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.08 (s, 1H), 7.50 – 7.29 (m, 8H), 7.29 – 7.20 (m, 1H), 4.54 (s, 1H), 3.17 – 3.04 (m, 3H), 2.86 (d, J = 12.75 Hz, 2H), 2.25 (q, J = 11.46 Hz, 2H), 2.03 (d, J = 11.14 Hz, 2H), 1.81 (d, J = 12.56 Hz, 2H), 1.61 (d, J = 12.82 Hz, 1H), 1.40 – 1.16 (m, 4H), 1.15 – 1.01 (m, 1H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.56; LCMS RT (Method 1) = 5.048 min; m/z 369.2 [M+H$^+$].

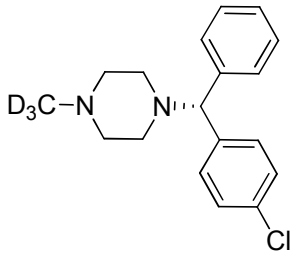


(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-isopropylpiperazine ***((S)-18)****.* A solution of (*S*)-1-((4-chlorophenyl)(phenyl)methyl)piperazine (**(S)-1**, 30.0 mg, 0.105 mmol) and acetone (60.8 mg, 1.05 mmol) in EtOH (2.00 mL) was treated at room temperature with TsOH (2.98 mg, 0.016 mmol). After stirring for 10 min, $NaBH_3CN$ (65.7 mg, 1.05 mmol) was added. The resulting reaction mixture was stirred overnight and quenched with 1 N NaOH solution. The mixture was dried by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC to give **(S)-18** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.05 (s, 1H), 7.50 – 7.29 (m, 8H), 7.29 – 7.20 (m, 1H), 4.55 (s, 1H), 3.51 – 3.40 (m, 3H), 3.08 (q, J = 11.33 Hz, 2H), 2.87 (d, J = 12.96 Hz, 2H), 2.23 (q, J = 11.23 Hz, 2H), 1.24 (d, J = 6.56 Hz, 6H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.56; LCMS RT (Method 1) = 4.688 min, m/z 329.1 [M+H$^+$].

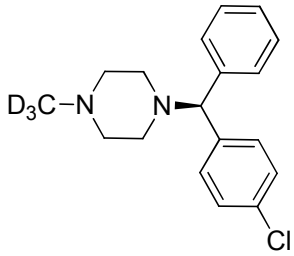


(S)-1-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethanone ***((S)-19)****.* A solution of (*S*)-1-((4-chlorophenyl)(phenyl)methyl)piperazine (**(S)-1**, 30.0 mg, 0.105 mmol) in CH_2Cl_2 (2.00 mL) was treated at room temperature with acetyl chloride (16.4 mg, 0.209 mmol) and Et_3N (0.044 mL, 0.314 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was dried by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC to give **(S)-19** as the TFA salt. ^{1}H NMR (400 MHz,

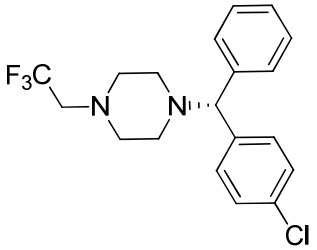
DMSO-d_6) δ ppm 9.38 (s, 1H), 7.47 – 7.40 (m, 2H), 7.43 – 7.35 (m, 4H), 7.32 (t, J = 7.8 Hz, 2H), 7.27 – 7.21 (m, 1H), 4.55 (s, 1H), 3.40 (m, 2H), 3.17 (q, J = 9.8 Hz, 2H), 2.88 (d, J = 11.7 Hz, 2H), 2.12 (d, J = 8.3 Hz, 2H), 1.75 (s, 3H). LCMS RT (Method 1) = 4.123 min, m/z 329.1 [M+H$^+$].



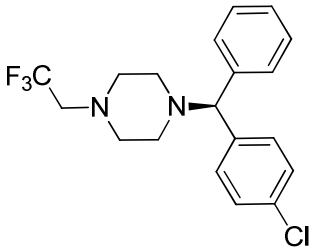
*(R)-1-((4-Chlorophenyl)(phenyl)methyl)-4-methyl(d_3)piperazine (**(R)-20**)*. A solution of (*R*)-1-((4-chlorophenyl)(phenyl)methyl)piperazine (**(R)-1**, 50.0 mg, 0.174 mmol) in THF (1.00 mL) and H_2O (0.500 mL) was treated at room temperature with NaOH (7.00 mg, 0.174 mmol) and MeI-d_3 (10.9 µL, 0.174 mmol). The reaction mixture was stirred at 65 ºC for 2 h. The mixture was dried by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC to give **(R)-20** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (s, 1H), 7.48 – 7.39 (m, 2H), 7.44 – 7.35 (m, 4H), 7.33 (t, J = 7.6 Hz, 2H), 7.28 – 7.19 (m, 1H), 4.51 (s, 1H), 3.38 (m, 2H), 3.08 (q, J = 10.8 Hz, 2H), 2.83 (d, J = 12.9 Hz, 2H), 2.19 (d, J = 8.5 Hz, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -73.60. LCMS RT (Method 1) = 4.484 min, m/z 304.1 [M+H$^+$].



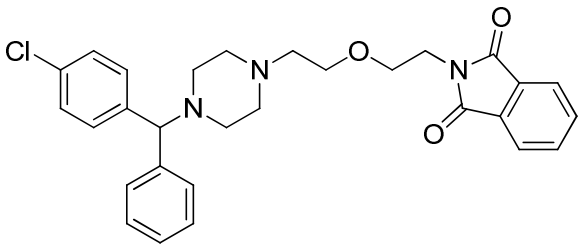
*(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-methyl(d_3)piperazine (**(S)-20**)*. A solution of (*S*)-1-((4-chlorophenyl)(phenyl)methyl)piperazine (**(S)-1**, 30.0 mg, 0.105 mmol) in THF (1.00 mL) and H_2O (0.500 mL) was treated at room temperature with NaOH (4.20 mg, 0.105 mmol) and MeI-d_3 (6.50 µL, 0.105 mmol). The reaction mixture was stirred at 65 ºC for 2 h. The mixture was dried by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC to give **(S)-20** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.35 (s, 1H), 7.45 – 7.40 (m, 2H), 7.45 – 7.34 (m, 4H), 7.30 (t, J = 7.7 Hz, 2H), 7.27 – 7.19 (m, 1H), 4.50 (s, 1H), 3.36 (m, 2H), 3.00 (q, J = 10.0 Hz, 2H), 2.81 (d, J = 12.1 Hz, 2H), 2.20 (d, J = 8.3 Hz, 2H). LCMS RT (Method 1) = 4.501 min, m/z 304.1 [M+H$^+$].



(R)-1-((4-Chlorophenyl)(phenyl)methyl)-4-(2,2,2-trifluoroethyl)piperazine ***((R)-21)***. 2,2,2-Trifluoroethyl trifluoromethanesulfonate (24.3 mg, 0.105 mmol) was added to a stirred mixture of (*R*)-1-((4-chlorophenyl)(phenyl)methyl)piperazine (**(R)-1**, 30.0 mg, 0.105 mmol), K_2CO_3 (28.9 mg, 0.209 mmol) and acetonitrile (1.00 mL). The reaction mixture was stirred at room temperature for 5 h. The mixture was dried by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC to give **(R)-21** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.20 (s, 1H), 7.48 (ddt, J = 6.5, 4.3, 2.2 Hz, 2H), 7.45 – 7.39 (m, 4H), 7.35 (t, J = 7.3 Hz, 2H), 7.30 – 7.21 (m, 1H), 4.57 (d, J = 4.8 Hz, 1H), 3.57 (d, J = 10.1 Hz, 2H), 3.23 – 2.99 (m, 3H), 2.95 (s, 2H), 2.20 (m, 3H). LCMS RT (Method 1) = 4.846 min, m/z 369.1 [M+H$^+$].

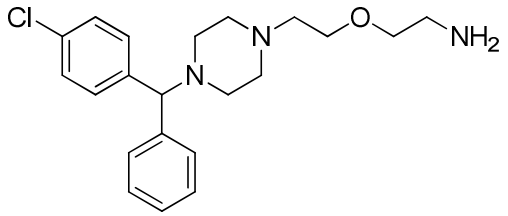


(S)-1-((4-Chlorophenyl)(phenyl)methyl)-4-(2,2,2-trifluoroethyl)piperazine ***((S)-21)***. 2,2,2-Trifluoroethyl trifluoromethanesulfonate (24.3 mg, 0.105 mmol) was added to a stirred mixture of (*S*)-1-((4-chlorophenyl)(phenyl)methyl)piperazine (**(S)-1**, 30.0 mg, 0.105 mmol), K_2CO_3 (28.9 mg, 0.209 mmol) and acetonitrile (1.00 mL). The reaction mixture was stirred at room temperature for 5 h. The mixture was dried by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC to give **(S)-21** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.18 (s, 1H), 7.45 (m, 2H), 7.46 – 7.39 (m, 4H), 7.34 (t, J = 7.5 Hz, 2H), 7.31 – 7.25 (m, 1H), 4.55 (d, J = 4.5 Hz, 1H), 3.55 (d, J = 10.0 Hz, 2H), 3.25 – 2.99 (m, 3H), 2.91 (s, 2H), 2.21 (m, 3H). LCMS RT (Method 2) = 3.160 min, m/z 369.1 [M+H$^+$].

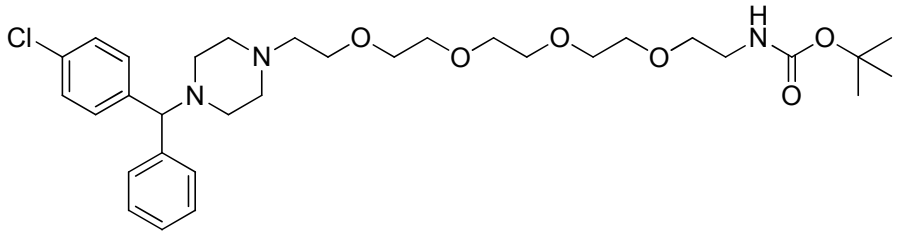


2-(2-(2-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)ethyl)isoindoline-1,3-dione ***(Rac-22)***. A solution of 2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)ethanol, 2·HCl (**Rac-5,** 250 mg, 0.667 mmol) in THF (10.0 mL) was added Et_3N (0.279 mL, 2.00 mmol) at room temperature. The mixture was stirred for 15 min,

then phthalimide (147 mg, 1.000 mmol) and triphenylphosphine (262 mg, 1.00 mmol) were added to the mixture followed by diisopropyl azodicarboxylate (0.130 mL, 0.667 mmol). The reaction mixture was stirred at room temperature for 4 h, after which LCMS analysis showed product formation. Reaction mixture was concentrated to dryness and residue purified by preparative HPLC to give **Rac-22** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.42 (s, 1H), 7.72 (m, 4H), 7.46 (d, J = 8.4 Hz, 2H), 7.44 – 7.38 (m, 4H), 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 4.53 (s, 1H), 3.73 (d, J = 4.8 Hz, 4H), 3.58 (t, J = 5.2 Hz, 4H), 3.14 (d, J = 11.2 Hz, 2H), 3.04 – 2.97 (m, 2H), 2.82 (d, J = 12.8 Hz, 2H), 2.28 (m, 2H). LCMS RT (Method 1) = 5.205 min, m/z 505.7 [M+H$^+$].

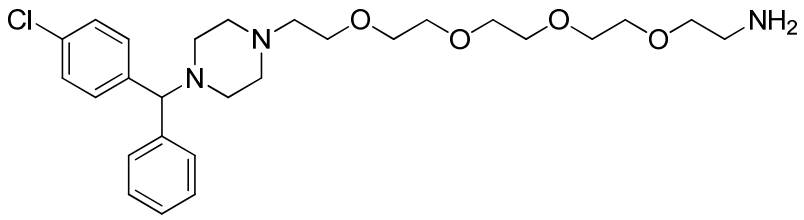


*2-(2-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)ethanamine (**Rac-23**).* Hydrazine (0.181 mL, 5.77 mmol) was added to a solution of 2-(2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)ethyl)isoindoline-1,3-dione (**Rac-22**, 97.0 mg, 0.192 mmol) in EtOH (3.00 mL). The reaction mixture was stirred at 60.0 °C for 3 h, after which LCMS analysis showed completion. The reaction mixture was concentrated under reduced pressure and residue purified by preparative HPLC, to give **Rac-23** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.39 (s, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.41 – 7.38 (m, 4H), 7.35 (t, J = 7.8 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 4.55 (s, 1H), 3.77 (d, J = 4.6 Hz, 2H), 3.55 (t, J = 5.0 Hz, 4H), 3.19 (d, J = 11.0 Hz, 2H), 3.09 – 2.95 (m, 2H), 2.80 (d, J = 11.5 Hz, 2H), 2.25 (m, 2H). LCMS RT (Method 1) = 3.959 min, m/z 374.7 [M+H$^+$].

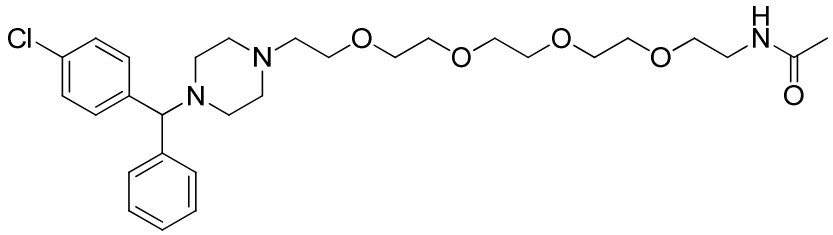


*tert-Butyl (14-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-3,6,9,12-tetraoxatetradecyl)carbamate (**Rac-24**).* A solution of 2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)ethanol, 2·HCl (**Rac-5**, 250 mg, 0.558 mmol) in DMF (5.00 mL) was treated with a 60% dispersion in mineral oil of NaH (89.0 mg, 2.23 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and room temperature for 30 min. To this mixture was added a solution of tert-butyl (2-(2-(2-bromoethoxy)ethoxy)ethyl)carbamate (174 mg, 0.558 mmol) in DMF (1.00 mL) and the resulting mixture allowed to stir overnight. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. Crude residue was purified by preparative HPLC, to give **Rac-24** as the TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45 – 7.37 (m, 4H), 7.37 – 7.18 (m, 5H), 4.44 (s, 1H), 3.86 (t, J = 4.4 Hz, 2H), 3.63 – 3.48 (m, 14H), 3.29 (s, 4H), 2.91 (s, 9H),

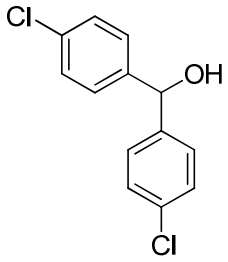
1.43 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -75.78. LCMS RT (Method 1) = 5.372 min, m/z 607.7 [M+H$^+$].



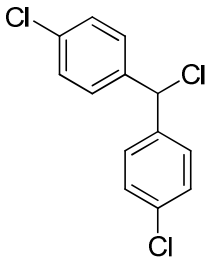
14-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)-3,6,9,12-tetraoxatetradecan-1-amine ***(Rac-25)***. A solution of tert-butyl (14-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-3,6,9,12-tetraoxatetradecyl)carbamate (**Rac-24**, 0.217 g, 0.358 mmol) in CH_2Cl_2 (10.0 mL) was treated with trifluoroacetic acid (5.00 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 10 min and room temperature for 30 min, after which LCMS analysis showed completion. The reaction mixture was concentrated and the crude residue was purified by preparative HPLC, to give **Rac-25** as the TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.95 (s, 2H), 7.51 – 7.41 (m, 4H), 7.38 – 7.25 (m, 4H), 4.57 (s, 1H), 3.79 (dd, J = 11.2, 6.6 Hz, 4H), 3.70 – 3.49 (m, 9H), 3.58 (s, 7H), 3.36 (d, J = 4.8 Hz, 2H), 3.17 (s, 3H), 3.00 (s, 5H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.78. LCMS RT (Method 1) = 3.916 min, m/z 507.2 [M+H$^+$].



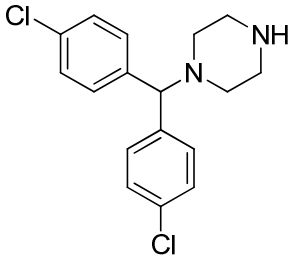
N-(14-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)-3,6,9,12-tetraoxatetradecyl)acetamide ***(Rac-26)***. A solution of 14-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-3,6,9,12-tetraoxatetradecan-1-amine (**Rac-25**, 14.0 mg, 0.028 mmol) in CH_2Cl_2 (1.00 mL) and Et_3N (0.019 mL, 0.138 mmol) was treated with acetyl chloride (1.97 µL, 0.028 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 10 min and room temperature for 30 min, after which LCMS analysis showed completion. The reaction mixture was concentrated and the crude residue was purified by preparative HPLC, to give **Rac-26** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (s, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.41 – 7.35 (m, 5H), 7.32 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 4.51 (s, 1H), 3.71 (s, 2H), 3.53 (d, J = 4.8 Hz, 4H), 3.46 (hept, J = 2.5 Hz, 4H), 3.42 (s, 4H), 3.36 (t, J = 5.9 Hz, 2H), 3.28 (s, 4H), 3.17 (tq, J = 14.7, 9.0, 7.4 Hz, 4H), 2.79 (d, J = 12.7 Hz, 2H), 2.27 (s, 2H), 1.78 (s, 3H). LCMS RT (Method 1) = 4.538 min, m/z 549.7 [M+H$^+$].



bis(4-Chlorophenyl)methanol. A solution of bis(4-chlorophenyl)methanone (**27**, 3.00 g, 11.9 mmol) in MeOH (15.0 mL) was treated at 0 ^{o}C in portions with $NaBH_4$ (0.678 g, 17.9 mmol). The reaction mixture was stirred at 0 ^{o}C for 15 min, allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with ice, diluted with H_2O and extracted with EtOAc. The organic layer was separeted, dried over $MgSO_4$ and concentrated to give the title compound as a white solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.31 (d, J = 8.8 Hz, 4H), 7.28 (d, J = 8.7 Hz, 4H), 5.78 (d, J = 3.2 Hz, 1H), 2.26 (d, J = 3.5 Hz, 1H). LCMS RT (Method 2) = 3.733 min, m/z 254.5 [M+H$^+$].

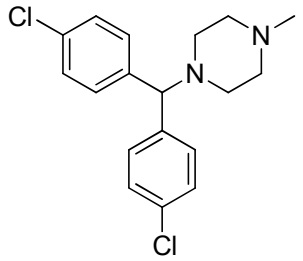


*4,4'-(Chloromethylene)bis(chlorobenzene) (**28**).* bis(4-Chlorophenyl)methanol (3.00 g, 11.8 mmol) was dissolved in CH_2Cl_2 (10.0 mL), to this was added 3-4 drops of DMF followed by thionyl chloride (2.60 mL, 35.6 mmol). The resulting reaction mixture was allowed to stir at room temperature for 45 min, after which TLC anlysis (20% EtOAc in Hex) showed completion. Reaction mixture was concentrated under reduced pressure to afford **28** as a white solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 – 7.27 (m, 8H), 6.06 (s, 1H). LCMS RT (Method 2) = 3.932 min, m/z 272.6 [M+H$^+$].

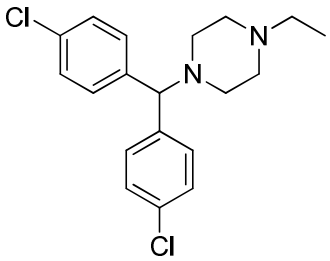


*1-(bis(4-Chlorophenyl)methyl)piperazine (**29**).* A solution of 4,4'-(chloromethylene)bis(chlorobenzene) (**28**, 80.0 mg, 0.295 mmol) in THF (10.0 mL) was treated with piperazine (38.1 mg, 0.442 mmol) followed by K_2CO_3 (81.0 mg, 0.589 mmol). A catalytic amount of tetrabutylammonium iodide (10.9 mg, 0.029 mmol) was added to the mixture. The reaction mixture was refluxed for 8 h, after which LCMS analysis showed completion. The reaction mixture was concentrated and re-disolved in

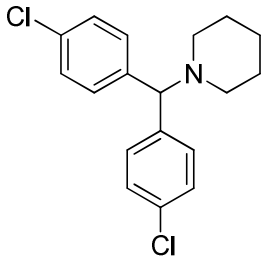
EtOAc. The organic layer was washed three times with saturated $NaHCO_3$ solution, dired over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative HPLC, to give **29** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.50 (s, 2H), 7.43 (d, J = 8.7 Hz, 4H), 7.39 (d, J = 8.6 Hz, 4H), 4.56 (s, 1H), 3.11 (s, 4H), 2.46 (s, 4H). LCMS RT (Method 1) = 4.760 min, m/z 322.7 [M+H$^+$].



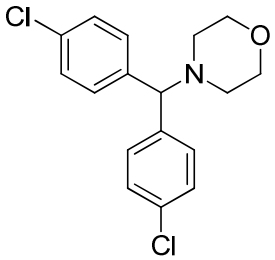
*1-(bis(4-Chlorophenyl)methyl)-4-methylpiperazine (**30**).* To a stirred solution of 4,4'-(chloromethylene)bis(chlorobenzene) (**28**, 0.800 g, 2.95 mmol) in THF (10.0 mL) was added K_2CO_3 (0.814 g, 5.89 mmol), 1-methylpiperazine (0.654 mL, 5.89 mmol) and catalytic potassium iodide (73.0 mg, 0.442 mmol). The reaction was heated to 100 ^{o}C for 48 h. The reaction mixture was partitioned between EtOAc and H_2O, the layers separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated. Crude mixture was purified by flash column chromatography: silica gel with a gradient of 0-5% MeOH in CH_2Cl_2 to afford **30** as a free-base oil, which was then mixed in a 1:1 ratio with oxalic acid to form the oxalate salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.41 (d, J = 8.6 Hz, 4H), 7.34 (d, J = 8.5 Hz, 4H), 4.33 (s, 1H), 2.32 (s, 4H), 2.27 (s, 4H), 2.14 (s, 3H). LCMS RT (Method 1) = 4.843 min, m/z 336.9 [M+H$^+$].



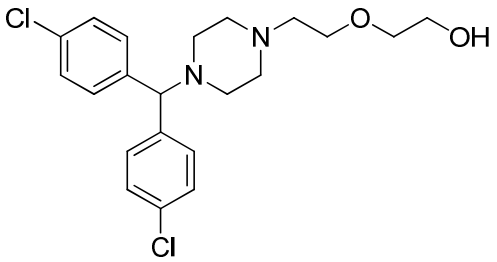
*1-(bis(4-Chlorophenyl)methyl)-4-ethylpiperazine, (**31**).* A solution of 4,4'-(chloromethylene)bis(chlorobenzene) (**28**, 160 mg, 0.589 mmol) in THF (10.0 mL) was treated with 1-ethylpiperazine (101 mg, 0.884 mmol) followed by K_2CO_3 (163 mg, 1.18 mmol). A catalytic amount of tetrabutylammonium iodide (21.8 mg, 0.059 mmol) was added, and the resulting reaction mixture was heated to 100 ^{o}C for 48 hours. The reaction mixture was partitioned between EtOAc and H_2O, the layers separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated. Crude mixture was purified by flash column chromatography: silica gel with a gradient of 0-5% MeOH in CH_2Cl_2 to afford **31** as a free-base oil, which was then mixed in a 1:1 ratio with oxalic acid to form the oxalate salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.44 (d, J = 8.8 Hz, 4H), 7.40 (d, J = 8.8 Hz, 4H), 4.57 (s, 1H), 3.11 – 3.02 (m, 2H), 2.80 (s, 8H), 2.24 (s, 2H), 1.17 (t, J = 7.2 Hz, 3H). LCMS RT (Method 1) = 5.029 min, m/z 350.7 [M+H$^+$].



*1-(bis(4-Chlorophenyl)methyl)piperidine (**32**).* A solution of 4,4'-(chloromethylene)bis(chlorobenzene) (**28**, 80.0 mg, 0.295 mmol) in THF (10.0 mL) was treated with piperidine (37.6 mg, 0.442 mmol) followed by K_2CO_3 (81.0 mg, 0.589 mmol) and a catalytic amount of tetrabutylammonium iodide (10.9 mg, 0.029 mmol). The resulting reaction mixture was refluxed for 8 h, after which LCMS analysis showed product formation. The reaction mixture was concentrated and then taken up in EtOAc. The organic layer was washed three times with saturated $NaHCO_3$ solution, brine, dired over $MgSO_4$, filtered and concentrated to an oil. The crude product was purified by preparative HPLC, to afford **32** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.96 (s, 1H), 7.67 (d, J = 8.3 Hz, 3H), 7.58 (d, J = 8.1 Hz, 3H), 7.43 – 7.33 (m, 2H), 5.71 (d, J = 9.3 Hz, 1H), 3.24 – 3.16 (m, 2H), 2.94 – 2.86 (m, 2H), 1.89 – 1.80 (m, 2H), 1.71 – 1.66 (m, 3H), 1.45 – 1.36 (m, 1H). LCMS RT (Method 1) = 4.584 min, m/z 321.7 [M+H$^+$].

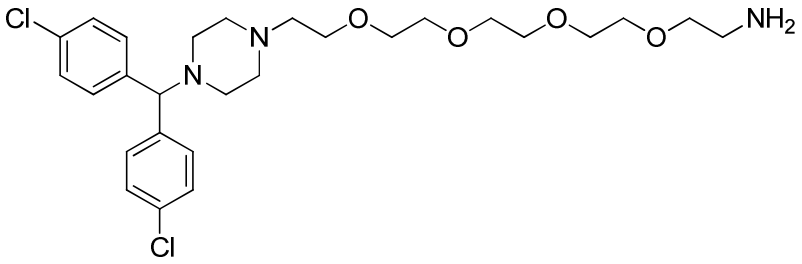


*4-(bis(4-Chlorophenyl)methyl)morpholine (**33**).* A solution of 4,4'-(chloromethylene)bis(chlorobenzene) (**28**, 50.0 mg, 0.184 mmol) in acetonitrile (6.00 mL) was treated with morpholine (48.1 mg, 0.552 mmol). The reaction mixture was refluxed for 3 h. The mixture was concentrated and purified by preparative HPLC to afford **33** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.46 – 7.41 (m, 4H), 7.40 – 7.35 (m, 4H), 4.36 (s, 1H), 3.59 (s, 4H), 3.11 (s, 1H), 2.26 (s, 4H). LCMS RT (Method 1) = 4.728 min, m/z 323.3 [M+H$^+$].

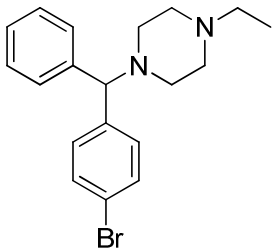


*2-(2-(4-(bis(4-Chlorophenyl)methyl)piperazin-1-yl)ethoxy)ethanol (**34**).* A solution of 1-(bis(4-chlorophenyl)methyl)piperazine (**29**, 100 mg, 0.311 mmol) in H_2O (1.50 mL) was treated with K_2CO_3 (86.0 mg, 0.623 mmol) and tetrabutylammonium chloride (87.0

mg, 0.311 mmol). The resulting mixture was stirred at room temperature for 15 min, then 2-(2-chloroethoxy)ethanol (38.8 mg, 0.311 mmol) in acetonitrile (1.50 mL) was added to the mixture. The resulting reaction mixture was heated to 100 °C for 2 h, after which LCMS analysis showed completion. The reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. Residue was purified by preparative HPLC to afford **34** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.34 (s, 1H), 7.47 – 7.36 (m, 8H), 4.58 (s, 1H), 3.72 (t, J = 4.9 Hz, 2H), 3.55 – 3.49 (m, 4H), 3.49 – 3.42 (m, 4H), 3.13 (d, J = 11.5 Hz, 3H), 2.80 (d, J = 12.9 Hz, 2H), 2.27 (t, J = 12.2 Hz, 2H). LCMS RT (Method 1) = 4.716 min, m/z 410.4 [M+H$^+$].

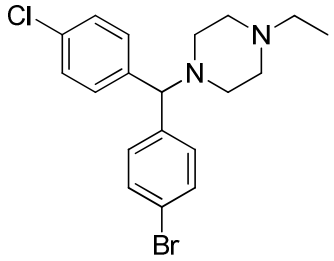


*14-(4-(bis(4-Chlorophenyl)methyl)piperazin-1-yl)-3,6,9,12-tetraoxatetradecan-1-amine (**35**)*. A solution of 2-(2-(4-(bis(4-chlorophenyl)methyl)piperazin-1-yl)ethoxy)ethanol (**34**, 250 mg, 0.518 mmol) in DMF (5.00 mL) was treated with a 60% dispersion in mineral oil of NaH (83.0 mg, 2.07 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 10 min and room temperature for 30 min. To this mixture was then added a solution of tert-butyl (2-(2-(2-bromoethoxy)ethoxy)ethyl)carbamate (162 mg, 0.518 mmol) in DMF (1.00 mL) and the resulting reaction mixture allowed to stir overnight. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layers were separated, dried over $MgSO_4$, filtered and concentrated. The residue was taken up in CH_2Cl_2 (10.0 mL) and treated with trifluoroacetic acid (5.00 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 10 min and room temperature for 30 min. The reaction mixture was concentrated and purfied by preparative HPLC to afford **35** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (s, 1H), 7.77 (s, 3H), 7.47 – 7.37 (m, 7H), 4.58 (s, 1H), 3.72 (t, J = 4.9 Hz, 2H), 3.61 – 3.43 (m, 14H), 3.45 – 3.40 (m, 2H), 3.30 (d, J = 5.1 Hz, 2H), 3.13 (d, J = 10.5 Hz, 2H), 2.97 (h, J = 5.6 Hz, 2H), 2.80 (d, J = 12.8 Hz, 2H), 2.28 (t, J = 12.4 Hz, 2H). LCMS RT (Method 1) = 4.208 min, m/z 541.5 [M+H$^+$].

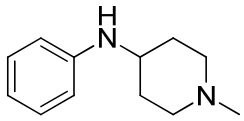


*1-((4-Bromophenyl)(phenyl)methyl)-4-ethylpiperazine (**Rac-38**)*. To a solution of 1-((4-bromophenyl)(phenyl)methyl)piperazine (**Rac-36**, 50.0 mg, 0.151 mmol) in MeOH (2.00 mL) was added acetaldehyde (33.2 mg, 0.755 mmol), $NaBH_3CN$ (28.5 mg, 0.453 mmol) and acetic acid (0.026 mL, 0.453 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with 1 N NaOH solution. The mixture was dried

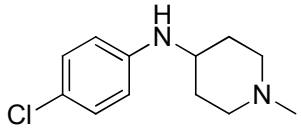
by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC to afford **Rac-38** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 7.57 – 7.49 (m, 2H), 7.40 (tq, J = 6.4, 4.2, 3.5 Hz, 4H), 7.34 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 4.53 (d, J = 4.7 Hz, 1H), 3.56 (dt, J = 10.4, 5.3 Hz, 1H), 3.19 – 3.08 (m, 1H), 3.13 (s, 1H), 3.08 – 2.97 (m, 1H), 2.84 (d, J = 12.2 Hz, 2H), 2.27 – 2.14 (m, 2H), 1.25 (d, J = 6.6 Hz, 2H), 1.18 (t, J = 7.3 Hz, 3H). LCMS RT (Method 1) = 4.594 min, m/z 360.3 [M+H$^+$].



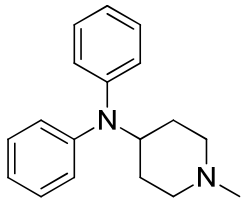
*1-((4-Bromophenyl)(4-chlorophenyl)methyl)-4-ethylpiperazine (**39**).* To a solution of 1-((4-bromophenyl)(4-chlorophenyl)methyl)piperazine (**Rac-37**, 50.0 mg, 0.151 mmol) in MeOH (2.00 mL) was added acetaldehyde (33.2 mg, 0.755 mmol), $NaBH_3CN$ (28.5 mg, 0.453 mmol) and acetic acid (0.026 mL, 0.453 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with 1 N NaOH solution. The mixture was dried by blowing air, re-disolved in DMSO, filtered and purified by preparative HPLC to afford **Rac-38** as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (s, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.47 – 7.33 (m, 6H), 4.59 (d, J = 6.6 Hz, 1H), 3.41 (d, J = 12.3 Hz, 2H), 3.13 (s, 2H), 3.03 (q, J = 11.3, 10.8 Hz, 2H), 2.83 (d, J = 12.8 Hz, 2H), 2.20 (t, J = 12.2 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H). LCMS RT (Method 1) = 4.950 min, m/z 394.7 [M+H$^+$].



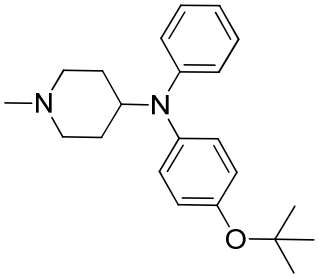
*1-Methyl-N-phenylpiperidin-4-amine (**42**).* A solution of aniline (**40**, 500 mg, 5.37 mmol) and 1-methylpiperidin-4-one (1.24 mL, 10.7 mmol) in MeOH (10.0 mL) was treated at room temperature with acetic acid (0.615 mL, 10.7 mmol). After stirring for 10 min, $NaBH_3CN$ (1.69 g, 26.8 mmol) was added, and the resulting reaction mixture allowed to stir overnight. A 2 N NaOH solution was then added to adjust the pH to ~10. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography: silica gel with 0-100% EtOAc in hexanes to get rid of the first peak. Then 20% MeOH in CH_2Cl_2 to afford **42** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.12 (m, 2H), 6.63 (m, 2H), 6.54 (m, 1H), 3.42 (d, J = 7.3 Hz, 1H), 3.24 (m, 1H), 2.84 (d, J = 9.7 Hz, 2H), 2.27 (s, 3H), 2.08 (t, J = 10.2 Hz, 2H), 2.05 (m, 2H), 1.42 (m, 2H). LCMS RT (Method 2) = 2.171 min, m/z 191.3 [M+H$^+$].



*N-(4-Chlorophenyl)-1-methylpiperidin-4-amine (**43**).* A solution of 4-chloroaniline (**41**, 500 mg, 3.92 mmol) and 1-methylpiperidin-4-one (0.905 mL, 7.84 mmol) in MeOH (10.0 mL) was treated at room temperature with acetic acid (0.449 mL, 7.84 mmol). After stirring for 10 min, $NaBH_3CN$ (1.69 g, 26.8 mmol) was added, and the resulting reaction mixture allowed to stir overnight. A 2 N NaOH solution was then added to adjust the pH to ~10. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography: silica gel with 0-100% EtOAc in hexanes to get rid of the first peak. Then 20% MeOH in CH_2Cl_2 to afford **43** as a as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.44 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.55 (m, 1H), 3.42 (d, J = 7.0 Hz, 1H), 3.24 (m, 1H), 2.80 (d, J = 9.7 Hz, 2H), 2.27 (s, 3H), 2.08 (t, J = 10.5 Hz, 2H), 2.00 (m, 1H), 1.42 (m, 2H). LCMS RT (Method 2) = 2.345 min, m/z 225.1 [M+H$^+$].

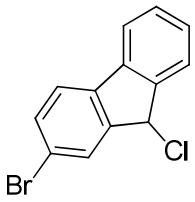


*1-Methyl-N,N-diphenylpiperidin-4-amine (**44**).* A mixture of 1-methyl-*N*-phenylpiperidin-4-amine (**42**, 141 mg, 0.741 mmol), iodobenzene (0.165 mL, 1.48 mmol), $Pd(OAc)_2$ (16.6 mg, 0.074 mmol), BINAP (50.8 mg, 0.082 mmol), and potassium *tert*-butoxide (104 mg, 0.926 mmol) (1.0 M solution in THF, 0.167 mL) in toluene (0.200 mL) was stirred at 110 ºC for 4 h. The reaction was cooled to room temperature and treaed with Si-Thiol. The mixture was dried by blowing air, re-dissolved in DMSO, filtered and purified by preparative HPLC to give **44** as the TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.15 (s, 1H), 7.35 – 7.22 (m, 4H), 7.14 – 6.96 (m, 2H), 6.97 (d, J = 7.5 Hz, 1H), 6.85 – 6.78 (m, 3H), 4.07 (tt, J = 11.8, 3.7 Hz, 1H), 3.66 (d, J = 11.8 Hz, 2H), 2.80 (d, J = 21.5 Hz, 5H), 2.72 (s, 2H), 2.15 (d, J = 14.1 Hz, 2H). LCMS RT (Method 1) = 4.218 min, m/z 267.2 [M+H$^+$].

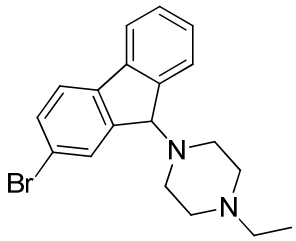


*N-(4-(tert-Butoxy)phenyl)-1-methyl-N-phenylpiperidin-4-amine (**45**).* A mixture of *N*-(4-chlorophenyl)-1-methylpiperidin-4-amine (**43**, 30.0 mg, 0.133 mmol), iodobenzene (0.030 mL, 0.267 mmol), $Pd(OAc)_2$ (3.00 mg, 0.013 mmol), BINAP (9.14 mg, 0.015 mmol), and potassium *tert*-butoxide (18.7 mg, 0.167 mmol) (0.167 mmol, 1.0 M solution in THF, 0.167 mL) in toluene (0.200 mL) was stirred at 110 ºC for 4 h. The reaction was cooled to room temperature and treaed with Si-Thiol. The mixture was dried by blowing air, re-dissolved in DMSO, filtered and purified by preparative HPLC to give the final

product as a TFA salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 7.33 – 7.24 (m, 4H), 7.12 – 6.99 (m, 4H), 6.97 (d, J = 7.5 Hz, 1H), 4.07 (tt, J = 11.5, 3.5 Hz, 1H), 3.66 (d, J = 11.3 Hz, 2H), 2.91 (s, 9H), 2.80 (m, 5H), 2.70 (s, 2H), 2.11 (d, J = 14.1 Hz, 2H). LCMS RT (Method 1) = 4.656 min, m/z 339.1 [M+H$^+$].



*2-Bromo-9-chloro-9H-fluorene (**47**).* A solution of 2-bromo-9*H*-fluoren-9-one (**46**, 1.00 g, 3.86 mmol) in MeOH (5.00 mL) was treated at 0 ^{o}C with $NaBH_4$ (0.219 g, 5.79 mmol). The resulting reaction mixture was stirred at room temperature overnight. The reaction was quenched with ice water and extracted into EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give the intermediate alcohol 2-bromo-9*H*-fluoren-9-ol as white solid (0.920 g, 91%). A solution of this intermediate alcohol 2-bromo-9*H*-fluoren-9-ol (500 mg, 1.91 mmol) in concentrated HCl (10.0 mL, 329 mmol) was treated at with calcium chloride (298 mg, 2.68 mmol). The resulting reaction mixture was refluxed for 4 h. The reaction was cooled to room temperature and extracted into EtOAc. The organic layer was separated and dried over $MgSO_4$, filtered and concentrated to give **47** a white solid, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.83 (m, 2H), 7.75 (d, J = 1.9 Hz, 1H), 7.68 – 7.55 (m, 2H), 7.47 – 7.33 (m, 2H), 5.53 (s, 1H). LCMS RT (Method 2) = 3.974 min, m/z 280.6 [M+H$^+$].



*1-(2-Bromo-9H-fluoren-9-yl)-4-ethylpiperazine (**48**).* A solution of 2-bromo-9-chloro-9*H*-fluorene (**47**, 100 mg, 0.358 mmol) in THF (10.0 mL) was treated at with 1-ethylpiperazine (0.068 mL, 0.537 mmol) followed by K_2CO_3 (99.0 mg, 0.715 mmol), and a catalytic amount of tetrabutylammonium iodide (13.2 mg, 0.036 mmol). The resulting reaction mixture was refluxed for 8 h, after which LCMS analysis showed product formation. The reaction mixture was concentrated and the residue taken up in EtOAc, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. Crude residue was purified by flash column chromatography: silica gel with a gradient of 0-20% MeOH in CH_2Cl_2 to give **48** as a colorless oil which was converted into the oxalic acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.93 – 7.80 (m, 2H), 7.76 (d, J = 1.8 Hz, 1H), 7.69 – 7.57 (m, 2H), 7.49 – 7.34 (m, 2H), 5.10 (s, 1H), 3.06 – 3.01 (m, 4H), 2.73 (s, 4H), 1.24 (s, 2H), 1.19 – 1.10 (m, 3H). LCMS RT (Method 1) = 4.598 min, m/z 358.2 [M+H$^+$].

Table S1 Pharmacokinetic data for compound **30** in the mouse model. Concentrations were measured using UPLC-MS/MS methods. The results are means from n = 3 mice. SD: standard deviation.

Sampling time (h)	Compound **30**, 10 mg/kg, i.p.				
	Plasma Concentration		Liver Concentration		Liver/Plasma Ratio
	(μM)	SD	(μM)	SD	
0	0	-	0	-	-
0.083	5.29	0.55	56.9	4.76	11
0.25	3.66	0.24	53.9	5.25	15
0.5	3.36	0.17	39.6	3.39	12
1	3.58	0.42	34.6	5.38	10
2	2.38	0.20	32.9	2.50	14
4	1.88	0.60	25.0	3.00	13
7	1.19	0.32	21.3	3.39	18
24	0.23	0.12	5.29	1.77	23

Table S2. Antiviral activity of CCZ analogues against dengue virus

Compound	DENV-RVPs EC_{50} (μM)	ATPlite CC_{50} (μM)	Selective Index
(S)-10	11.6	> 31.6	> 2.72
30	4.62	17.5	3.79
Lycorine HCl	0.0406	> 31.6	778