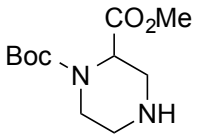
Experimental Section for "Discovery of Novel N-Aryl Piperazine CXCR4 Antagonists."

All reagents were purchased from commercial suppliers and used without further purification unless specified otherwise. Reaction progress was monitored by thin layer chromatography (TLC) on pre-coated glass plates (silica gel 60 F254, 0.25mm) or LC-MS (Varian C_8 analytical column with UV detection). All reactions were carried out under an argon atmosphere using dry solvents under anhydrous conditions unless otherwise noted. Compounds were purified by either flash chromatography using Sorbent Technologies silica gel (60Å, 230 x 400 mesh) or Redisep cartridges and a Teledyne ISCO Combiflash automated chromatography system. ^{1}H NMR and ^{13}C NMR were recorded on either a Varian 400 or 600 MHz instrument and chemical shifts were reported relative to residual deuterated solvent. Mass spectra were performed by the Emory University Mass Spectroscopy Center on either a VG 70-S Nier Johnson or JEOL instrument. LC/MS were recorded on an Agilent Technologies 6100 quadrupole instrument. Compound purity was established using combustion analysis by Atlantic Microlabs (Norcorss, GA) or using HPLC % purity by UV at 254 nM on an Agilent HPLC/LC-MS instrument (Varian C_8 analytical column, a = 85% MeOH/Water isocratic 1.0 ml/min, b= 75% Acetronitrile/Water isocratic 1.0 mL/min or c = 95% MeOH/Water isocratic 1.0 mL/min, d = 95% Acetonitrile/Water isocratic 1.0 mL/min).

(*S*)-5,6,7,8-tetrahydroisoquinolin-8-amine **24** was synthesized according to procedures found in the following reference: Boggs, S.; Elitzin, V.I.; Gudmunsson, K.; Martin, M.T.; Sharp, M.J. *Org. Proc. Res. Dev.* **2009**, *13*, 781-785.

The Boc protected amino-butyraldehydes **31** were synthesized according to the procedures provided in the following reference: Iradier, F.; Arrayas, R.G.; Carretero, J.C. *Org. Lett.* **2001**, *3*, 2957-2960.

Part I. Preparation of compounds in Scheme 1:

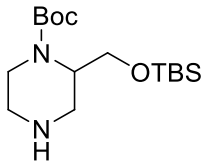


10

*Methyl 1-Boc-piperazine-2-carboxylate (**10**).*

A suspension of 1-Boc-piperazine-2-carboxylic acid (**9**, 2.0 g, 8.69 mmol), EDCI (1.99 g, 10.42 mmol) and DMAP (0.32 g, 2.61 mmol) in MeOH/CH_2Cl_2 (1:1) was stirred at 40^{o}C for 1.5 hr, then the resulting solution was cooled down to room temperature and stirred for another 4 hrs. After removing the solvent, the residue was dissolved in CH_2Cl_2. The solution was washed with H_2O (50 mL x 3). The combined aqueous was re-extracted with CH_2Cl_2 (40 mL x 3). All of the organics were combined, washed with 1 N $NaHCO_3$ (50 mL x 3) and brine, and finally dried over Na_2SO_4. The product, a colorless liquid,

was purified *via* flash chromatography, eluted with CH_2Cl_2 then 10% MeOH/CH_2Cl_2. R_f = 0.7 (10% MeOH/CH_2Cl_2, stained by phosphomolybdic acid (PMA)); yield - 84%; ^{1}H NMR (400Hz, $CDCl_3$): δ 1.45 (m, 9H), 2.69 (t, 1H, *J* = 12 Hz), 2.6-3.2 (m, 3H), 3.49 (t, 1H, *J* = 12.8 Hz), 3.755 (s, 3H), 3.83 (m, 1H), 4.52 (s, 0.5H), 4.69 (s, 0.5H); ESI-MS: m/z 245.1 $(M+H)^+$.



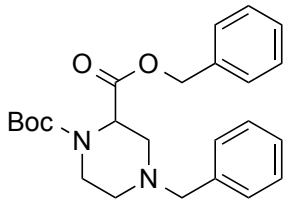
11

*tert-Butyl 2-(((tert-butyldimethylsilyl)oxy)methyl)piperazine-1-carboxylate(**11**).*

Step 1: Reduction of 1-Boc-piperazine-2-carboxylic acid to the corresponding alcohol
To a suspension of 1-Boc-piperazine-2-carboxylic acid (2.0 g, 8.69 mmol) in THF (100 ml) was added BH_3•Me_2S (2 M in THF) (16 ml) at 0 °C under argon. The resulting mixture was allowed to warm up to 45 °C and stirred overnight. The reaction was carefully quenched with MeOH in an ice-water bath. The mixture was partitioned between 1 N NaOH and Et_2O. The organic layer was washed with 1 N NaOH (120 mL x 3). The combined aqueous was re-extracted with Et_2O (30 mL x 3). All organics were combined, washed with brine (150 mL) and dried over Na_2SO_4. The crude mixture was purified *via* flash chromatography, eluted with CH_2Cl_2 then 10% MeOH/CH_2Cl_2t o give a viscous oil. R_f = 0.65 (10% MeOH/CH_2Cl_2, stained by phosphomolybdic acid); Yield: 71%; ^{1}H NMR (400Hz, $CDCl_3$): δ 1.46 (s, 9H), 2.19 (broad s, 1H), 2.6 (dq, 1H, J_1 = 13.2 Hz, J_2 = 12 Hz, J_3 = 4 Hz), 2.81 (dt, 1H, J_1 = 11.6 Hz, J_2 = 5.2 Hz), 3.21 (m, 1H), 3.4 (m, 2H), 4.02 (m, 4H), 4.792 (broad s, 1H); ESI-MS: m/z 173 ($M-CO_2$).

Step 2: TBS protection of the alcohol to give **11**.
The alcohol from previous step (1.32 g, 6.1 mmol) and imidazole (1.039 g, 15.26 mmol) in DMF (4.07 ml) was stirred at 0 °C for 45 min, to which TBS-Cl (1.84 g, 12.21 mmol) was added. The resulting mixture was stirred at 0 °C for 1 hr and then was allowed to warm up to room temperature, stirred overnight. The reaction was partitioned between H_2O and Et_2O, then the ether layer was washed with H_2O. The aqueous was combined and re-extracted with Et_2O. The combined organics were washed with brine and dried over Na_2SO_4. Product was purified *via* flash chromatography, eluted by 10% EtOAc/Hexanes then CH_2Cl_2 to give a pale yellow liquid. R_f = 0.55 (30% EtOAc/Hexanes, stained by phosphomolybdic acid); Yield: 89%; ^{1}H NMR (400Hz, $CDCl_3$): δ 0.09 (s, 3H), 0.111 (s, 3H), 0.911 (s, 9H), 1.47 (s, 9H), 2.616 (dq, 1H, J_1 = 13.2 Hz, J_2 = 4 Hz), 2.79 (dt, 1H, J_1 = 12 Hz, J_2 = 5.6 Hz), 3.19 (m, 1H), 3.34 (t, 1H, *J* = 14.4 Hz), 3.45 (dt, 1H, J_1 = 13.2 Hz, J_2 = 3.2 Hz), 3.89-4.14 (m, 4H), 4.812 (broad, s, 0.5H) 4.91 (broad s, 0.5H, -N***H***); ESI-MS: m/z 331 (M+H).

*2-Benzyl 1-(tert-butyl) 4-benzylpiperazine-1,2-dicarboxylate (**12**)*



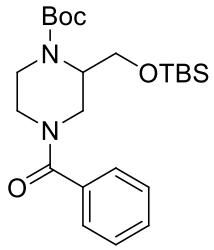
12

To a solution of 1 g rac-1-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (**9**, 4.3 mmoles) in 20 mL of anhydrous N,N-dimethylformamide was added 1.7g (12.3 mmoles) of granular potassium carbonate. The slurry was stirred for 1 hour, and then 1.3 mL (11 mmoles) of benzyl bromide was added and the mixture stirred for an additional 40 hours at room temperature. The reaction mixture was then diluted with water and extracted with ethyl ether. The organic layer was separated and washed with brine (NaCl(aq.)) solution twice. The organic layer was then dried over anhydrous sodium sulfate. Filtration, solvent removal and column chromatography (Hexanes:Ethyl acetate gradient) gave 1.49 g of a clear viscous oil (83% yield), which solidified upon standing.

Physical data for **12**: ^{1}H NMR (400Hz, $CDCl_3$): (1:1 ratio of rotomers) δ 1.38 (s, 4.5 H), 1.46 (s, 4.5 H), 2.06 (dt, 1H, J=3.2 Hz, J=12 Hz), 2.24 (dq, 1H, J=4 Hz, J=8.4 Hz), 2.73 (d, 0.5 H, J=11 Hz), 1.79 (d, 0.5 H, J=11 Hz), 3.24 (m, 1H), 3.32 (m, 1H), 3.49 (m, 2H), 3.76 (d, 0.5H, J=12 Hz), 3.86 (d, 0.5H, J=12Hz), 4.58 (s, 0.5 H), 4.78 (s, 0.5 H), 5.18 (m, 2H), 7.23 (m, 5H), 7.32 (m, 5H); LC-MS: 100% (254 nM) – 411 ($M+H^+$).

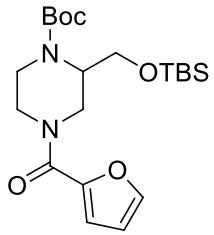
*General Procedure for Amide Formation of **13** and **14**.*

To a solution of **11** (1 eq.) in CH_2Cl_2 (0.2 M) was added ArCOCl (2 eq.) and Et_3N (2 eq.) at room temperature. The resulting solution was stirred overnight. After removal of CH_2Cl_2 on rotary evaporator, the solid was diluted with EtOAc and washed with H_2O, brine and dried over Na_2SO_4.

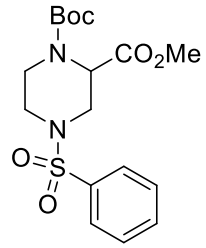


13

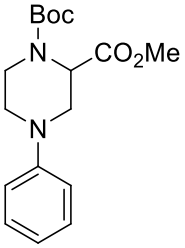
The product was purified *via* flash chromatography (5% EtOAc/Hexanes; 10% EtOAc/Hexanes; 20% EtOAc/Hexanes) to give a white solid 1-Boc-4-Benzoyl-piperazine-2-CH_2OTBS in 61 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ -0.013 (broad s, 6H), 0.754 (broad s, 9H), 1.467 (s, 9H), 3.034 (broad s, 2H), 3.24 (broad s, 1H), 3.507~3.946 (m, 5H), 4.499 (s, 1H); MS: m/z 435 (M+H).



The product was purified *via* flash chromatography (10% EtOAc/Hexanes; 20% EtOAc/Hexanes) to give a yellow liquid [1-Boc-4-Furoyl-piperazine-2-CH_2OTBS] in 61 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ -0.01 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 1.47 (s, 9H), 3.12 (broad s, 2H), 3.35 (broad s, 1H), 3.56 (broad s, 1H), 3.66 (t, 1H, J = 10 Hz), 3.96 (broad s, 1H), 4.11 (broad s, 1H), 4.36 (broad s, 1H), 4.61 (broad s, 1H), 6.46 (q, 1H, J_1 = 1.6 Hz), 7.08 (d, 1H, J = 2.8 Hz), 7.48 (dd, 1H, J_1 = 2 Hz, J_2 = 0.8 Hz); MS: m/z 325 (M-Boc+H), 425 (M+H); HRMS Calc. for $C_{21}H_{37}N_2O_5Si$ (M+H): 425.24663, Found: 425.24698.

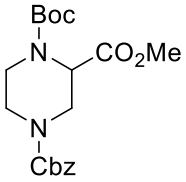


*1-(tert-Butyl) 2-methyl 4-(phenylsulfonyl)piperazine-1,2-dicarboxylate (**15**).* To a solution of methyl 1-Boc-piperazine-2-carboxylate (0.5 g, 2 mmol) in CH_2Cl_2 (10 ml) was added $PhSO_2Cl$ (0.53 ml, 4.1 mmol) and Et_3N (0.57 ml, 4.1 mmol) at room temperature. The resulting solution was stirred overnight .The reaction was washed with 1 N $NaHCO_3$ (40mL x 3), brine and dried over Na_2SO_4. The product was purified *via* flash chromatography (10% EtOAc/Hexanes; 20% EtOAc/Hexanes; 50% EtOAc/Hexanes) to give an off-white solid Methyl 1-Boc-4-benzenesulfonyl-piperazine-2-carboxylate in 91% yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.432 (m, 9H), 2.305 (dt, J_1 = 12 Hz, J_2 = 3.2 Hz), 2.484 (dd, 1H, J_1 = 11.6 Hz, J_2 = 4 Hz), 3.256 (td, 1H, J = 48.4), 3.6~4.05 (m, 5H), 4.245 (d, 1H, J = 11.6 Hz), 4.651 (s, 0.5H), 4.834 (s, 0.5H), 7.553 (m, 2H), 7.628 (m, 1H), 7.754 (m, 2H); MS: m/z 285.2 (M-Boc+H); HRMS Calc. for $C_{17}H_{24}O_6N_2NaS$ (M+Na): 407.12473, Found: 407.12567.



*1-(tert-Butyl) 2-methyl 4-phenylpiperazine-1,2-dicarboxylate (**16**)*. A mixture of Methyl 1-Boc-piperazine-2-carboxylate (1.837 g, 7.52 mmol), bromobenzene (0.728 ml, 6.84 mmol), $Pd_2(dba)_3$ (0.063 g, 0.068 mmol), DavePhos (0.032 g, 0.082 mmol) and Cs_2CO_3 (3.34 g, 10.25 mmol) in 1,4-Dioxane (15 ml, solvent was degassed for 40 min before using) with molecular sieves (4 A) was heated to 85 °C and stirred under argon for 24 hrs. After cooling to room temperature, the mixture was filtered through a plug of celite

and concentrated to a yellow oil which was purified *via* flash chromatography (5% EtOAc/Hexanes) to give a yellow viscous liquid Methyl 1-Boc-4-phenylpiperazine-2-carboxylate (2 g, 91 % yield). ^{1}H NMR (400Hz, $CDCl_3$): δ 1.476 (d, 9H, *J* = 17.6 Hz), 2.742 (dq, J_1 = 10 Hz, J_2 = 3.2 Hz), 2.922 (dt, 1H, J_1 = 12 Hz, J_2 = 4 Hz), 3.18~3.52 (m, 2H), 3.757 (s, 3H), 3.968 (dd, 1H, J_1 = 36.8 Hz, J_2 = 12.4 Hz), 4.142 (t, 1H, *J* = 12.8 Hz), 4.690 (s, 0.5H), 4.874 (s, 0.5H), 6.9 (m, 3H), 7.264 (m, 2H); ^{13}C NMR (100Hz, $CDCl_3$): δ 28.281, 40.829, 41.861, 48.333, 51.811, 52.024, 52.396, 54.471, 55.779, 80.566, 117.222, 120.769, 129.130; MS: m/z 321.1 (M+H); HRMS Calc. for $C_{17}H_{25}O_4N_2$ (M+H): 321.18088, Found: 321.18022.

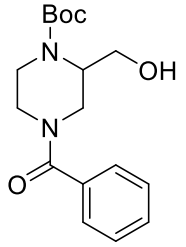


17

*4-Benzyl 1-(tert-butyl) 2-methyl piperazine-1,2,4-tricarboxylate (**17**).* To a solution of Methyl 1-Boc-piperazine-2-carboxylate (0.488 g, 1.998 mmol) and Et_3N (0.306 ml, 2.197 mmol) in CH_2Cl_2 (4.00 ml) was dropwise added Cbz-Cl (0.299 ml, 2.098 mmol) at 0 °C under argon. Upon the addition, the solution became cloudy, and the mixture was stirred at 0 °C for 2 hrs. Then the reaction was warmed up to room temperature and stirred for another 17 hrs. The reaction was quenched with saturated NH_4Cl. After the separation of two layers, the organic was washed with 1N $NaHCO_3$ (30 mL x 2), brine and dried over Na_2SO_4. The product was purified *via* flash chromatography (10% EtOAc/Hexanes; 20% EtOAc/Hexanes) to give a colorless liquid methyl 1-Boc-4-Cbz-piperazine-2-carboxylate (0.5468 g, 72.3 % yield). ^{1}H NMR (400Hz, $CDCl_3$): δ 1.347 (m, 9H), 2.7~3.4 (broad m, 3H), 3.4~4.2 (broad m, 5H), 4.583 (m, 2H), 5.064 (m, 2H), 7.244 (m, 5H); MS: m/z 279.1 (M-Boc+H), 401.2 (M+Na); HRMS Calc. for $C_{19}H_{26}O_6N_2Na$ (M+Na): 401.16831, Found: 401.16902.

General Procedure for the TBS deprotection

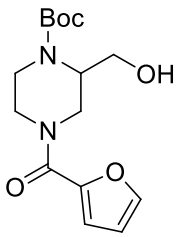
A solution of 1-Boc-4-acyl-piperazine-2-CH_2OTBS (1 eq.) and TBAF (1.0 M in THF) (2 eq.) was stirred at room temperature for 3 hrs. The reaction was taken up to EtOAc and washed with H_2O. The combined aqueous was re-extracted with EtOAc three times. The organics were combined, washed with brine and dried over Na_2SO_4.



*tert-Butyl 4-benzoyl-2-(hydroxymethyl)piperazine-1-carboxylate (**19**).*

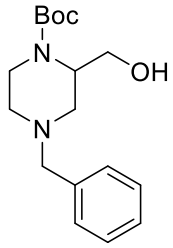
The product was purified *via* flash chromatography (CH_2Cl_2; 5% MeOH/CH_2Cl_2) to give a yellow liquid in 88 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.457 (s, 9H), 2.875 (broad s, 1H), 2.947 (t, 1H, *J* = 8.8 Hz), 3.033

(broad s, 1H), 3.262 (broad s, 1H), 3.593~4.304 (m, 5H), 4.712 (d, 1H, *J* = 12.8 Hz); MS: m/z 265 (M-^{t}Bu+H), 321 (M+1).



*tert-Butyl 4-(furan-2-carbonyl)-2-(hydroxymethyl)piperazine-1-carboxylate (**20**).*
The product was purified via flash chromatography (CH_2Cl_2; 5% MeOH/CH_2Cl_2) to give a yellow viscous liquid in 79 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.464 (s, 9H), 3.050~3.340 (broad m, 4H), 3.608 (broad s, 2H), 3.931 (broad s, 1H), 4.272 (broad s, 1H), 4.456 (broad s, 1H), 4.597 (broad s, 1H), 6.504 (q, 1H, J_2 = 1.6 Hz), 7.101 (dd, 1H, J_1 = 3.2 Hz, J_2 = 0.8 Hz), 7.501 (d, 1H, J_1 = 0.6 Hz); MS: m/z 634 (2M+Na); HRMS Calc. for $C_{19}H_{26}O_6N_2Na$ (M+Na): 333.16831, Found: 333.14171.

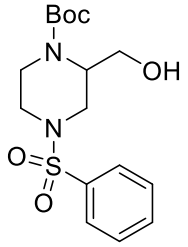
General Procedure for the reduction of ester to the corresponding alcohols
To a solution of Benzyl/Methyl 1-Boc-4-Acyl-piperazine-2-carboxylate (1 eq.) in THF/EtOH (1:1, 0.1 M) was added $CaCl_2$ (1.6 eq.), which was stirred at room temperature till the salt was all dissolved. The resulting solution was cooled down to 0 °C, to which was added $NaBH_4$ (4.25 eq.). The reaction mixture was stirred at 0 °C for 1.5 hrs then was warmed up to room temperature and stirred overnight. The reaction was carefully quenched with1N HCl and stirred till the bubbling settled. Then the aqueous was extracted with Et_2O three times. The combined organics were washed with H_2O, brine and dried over Na_2SO_4.



*tert-butyl 4-benzyl-2-(hydroxymethyl)piperazine-1-carboxylate (**18**).* A solution of 1.49 g (3.63 mmoles) of benzyl ester **12** and 0.77 g of calcium chloride dihydrate was formed in 20 mL of tetrahydrofuran and 20 mL of anhydrous ethanol. The reaction was stirred and cooled to 0oC. Next, 0.55 g of sodium borohydride was added. The reaction was warmed to room temperature and then stirred overnight. The reaction was quenched with water, extracted with ethyl acetate, and the organic layer was washed with brine. The aqueous layers were re-extracted with ethyl acetate and the organic layers were combined and dried over sodium sulfate. Filtration and solvent removal was followed by column chromatography (hexanes/ethyl acetate gradient) gave 0.63 g of a clear viscous oil (57% yield).

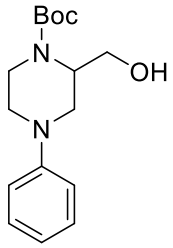
Physical data for **18**: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.45 (s, 9H), 2.09 (dt, 1H, J=4 Hz, J=11 Hz), 2.3 (ddd, 1H, J=1 Hz, J=4 Hz, J=12 Hz), 2.82 (d, 1H, J=10 Hz), 2.98 (dt, 1H, J=2 Hz, J=11 Hz), 3.4 (bs, 1H), 3.48 (d, 2H, J=3

Hz), 3.85 (ddd, 1H, J=1 Hz, J=4 Hz, J=11 Hz), 3.93 (dd, 1H, J=4 Hz, J=11 Hz), 4.07 (bs, 1H), 7.28 (m, 3H), 7.33 (m, 2H); LC-MS: 100% (254 nm) – 307 ($M+H^+$).



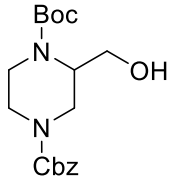
*tert-Butyl 2-(hydroxymethyl)-4-(phenylsulfonyl)piperazine-1-carboxylate (**21**).*

The final product was purified *via* flash chromatography (30% EtOAc/Hexanes; 50% EtOAc/Hexanes) to give an off-white foam in 68 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.415 (s, 9H), 1.956 (t, 1H, J = 6 Hz), 2.330 (dt, 1H, J_1 = 12 Hz, J_2 = 3.6 Hz), 2.402 (dd, 1H, J_1 = 12 Hz, J_2 = 3.6 Hz) 3.143 (t, 1H, J = 12 Hz), 3.684~3.980 (m, 5H) 4.242 (broad s, 1H), 7.554 (m, 2H), 7.624 (m, 1H), 7.747 (m, 2H); MS: m/z 257.0 (M-Boc+H), 379.0 (M+Na); HRMS Calc. for $C_{16}H_{24}O_5N_2SNa$ (M+Na): 379.12982, Found: 379.13076.



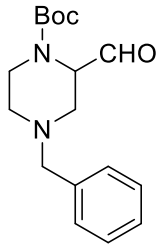
*tert-Butyl 2-(hydroxymethyl)-4-phenylpiperazine-1-carboxylate (**22**).*

The product was purified *via* flash chromatography (CH_2Cl_2; 10% MeOH/CH_2Cl_2) to give a yellow viscous liquid in 74.2 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.490 (s, 9H), 2.775 (dt, 2H, J_1 = 11.6 Hz, J_2 = 4 Hz), 2.910 (dd, 1H, J_1 = 12.8 Hz, J_2 = 4 Hz), 3.304 (t, 1H, J = 11.6 Hz), 3.466 (d, 1H, J = 11.6 Hz) 3.678 (d, 1H, J = 12 Hz) 3.881 (broad s, 2H), 3.995 (d, 1H, J = 11.2 Hz), 4.274 (s, 1H), 6.922 (m, 3H), 7.276 (m, 2H); ^{13}C NMR (100Hz, $CDCl_3$): δ 28.341, 40.829, 49.194, 50.146, 53.524, 62.069, 80.274, 116.911, 120.500, 129.145, 151.310; MS: m/z 293.2 (M+H); HRMS Calc. for $C_{16}H_{25}O_3N_2$ (M+H): 293.18570, Found: 293.18570.



*4-Benzyl 1-(tert-butyl) 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (**23**).*

The product 1-Boc-4-Cbz-piperazine-2-CH_2OH was purified via flash chromatography (10% EtOAc/Hexanes; 30% EtOAc/Hexanes) to give a color less liquid in 81% yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.436 (m, 9H), 2.973 (broad bump, 4H), 3.557 (broad s, 2H), 3.838 (broad s, 1H), 3.985 (broad s, 1H), 4.150 (broad s, 1H) 5.124 (m, 2H), 7.326 (m, 5H); MS: m/z 251.2 (M-Boc+H), 373.4 (M+Na); HRMS Calc. for $C_{18}H_{26}O_5N_2Na$ (M+Na): 373.17339, Found: 373.17415.

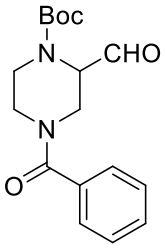


*tert-Butyl 4-benzyl-2-formylpiperazine-1-carboxylate (**24**).*

To a solution of 0.62 g (2 mmoles) of alcohol xx in 20 mL of dichloromethane was added 1.45 g of Dess-Martin Periodane, 0.96 g of sodium bicarbonate and 10 drops of water. The reaction was stirred at room temperature overnight. The reaction was filtered over celite with additional dichloromethane and the solvent was removed under vacuum. The residue was taken up in ethyl ether and washed with 1M sodium persulfate (aq.) and brine solutions. The organic layer was then separated and dried over sodium sulfate. Filtration, solvent removal, and filtration over silica gel with 3:1-heaxanes/ethyl acetate solution gave 0.435 g of a vivid-yellow, viscous oil (68% yield). Physical data for **24**: ^{1}H NMR (400Hz, $CDCl_3$): (1:1 mixture of rotomers) δ 1.43 (s, 4.5H), 1.48 (s, 4.5 H), 2.11 (dt, 1H, J=4 Hz, J=12 Hz), 2.27 (d, 1H, J=12 Hz), 2.7 (d, 0.5 H, J=10 Hz), 2.78 (d, 0.5H, J=10 Hz), 3.06 (t, 0.5H, J=11 Hz), 3.15 (t, 0.5H, J=11 Hz), 3.3 (d, 1H, J=12 Hz), 3.44 (dd, 1H, J=4 Hz, J=14 Hz), 3.56 (dd, 1H, J=4 Hz, J=14 Hz), 3.78 (d, 0.5 H, J=13 Hz), 3.9 (d, 0.5H, J=13 Hz), 4.38 (s, 0.5H), 4.58 (s, 0.5H), 7.29 (m, 3H), 7.33 (m, 2H), 9.51 (d, 1H, J=10 Hz); LC-MS: 94% (254 nm) – 305 ($M+H^+$).

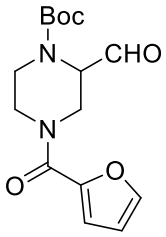
General oxidation of alcohols to corresponding aldehydes *via* Swern oxidation

To a solution of oxalyl chloride (2.25 eq.) in CH_2Cl_2 (0.2 M) was added DMSO (4.5 eq.) slowly at -78 °C under argon. The resulting mixture was stirred for 30 min. A solution of the alcohol (1 eq.) in CH_2Cl_2 (0.2 M) was slowly added to the reaction mixture at -78 °C and stirred for 1 hr, then Et_3N (4.5 eq.) was dropwise added. After the addition was complete, the reaction mixture was stirred at -78 °C for 1 hr and was warmed up to 0 °C, and stirred for another 2 hrs. Reaction was quenched by sat. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organics were washed with H_2O, brine and dried over Na_2SO_4.



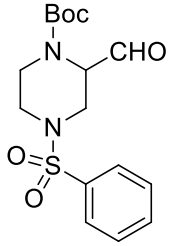
*tert-Butyl 4-benzoyl-2-formylpiperazine-1-carboxylate (**25**).*

The product was purified *via* flash chromatography (CH_2Cl_2; 5% MeOH/CH_2Cl_2) to give pale yellow viscous liquid in 98 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.436 (m, 9H), 2.941~5.174 (broad bumps, 7H), 7.39 (m, 5H), 9.607 (broad s, 1H); MS: m/z 263.1 ($M-^{t}Bu+H$).



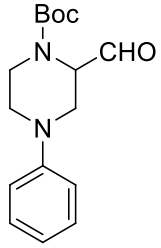
*tert-Butyl 2-formyl-4-(furan-2-carbonyl)piperazine-1-carboxylate (**26**).*

The product was purified *via* flash chromatography (CH_2Cl_2; 5% MeOH/CH_2Cl_2) to give pale yellow viscous liquid in 83 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.47 (m, 9H), 3.224 (broad s, 42H), 3.377 (broad d, 1H, *J* = 11.2 Hz), 3.914 (broad dd, 1H, J_1 =38 Hz, J_2 = 10.8 Hz), 4.359 (broad s, 1H), 4.562 (broad s, 0.5H), 4.739 (broad s, 0.5H), 5.021 (broad s, 1H), 6.492 (q, 1H, *J* = 1.6 Hz), 7.082 (d, 1H, *J* = 3.2 Hz), 7.487 (dd, 1H, J_1 = 2 Hz, J_2 = 0.8 Hz), 9.626 (s, 1H); ^{13}C NMR (100Hz, $CDCl_3$): δ 28.201, 41.042, 42.362, 60.445, 61.731, 81.336, 111.600, 117.632, 144.118, 159.318; MS: m/z 253.2 (M-^{t}Bu+H); HRMS Calc. for $C_{15}H_{21}O_5N_2Na$ (M+H): 309.14450, Found: 309.14424;



*tert-Butyl 2-formyl-4-(phenylsulfonyl)piperazine-1-carboxylate (**27**).*

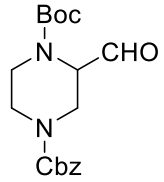
The final product was purified *via* flash chromatography (30% EtOAc/Hexanes; 50% EtOAc/Hexanes) to give a yellow liquid in 94 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.416 (m, 9H), 2.335 (dt, 1H, J_1 = 11.6 Hz, J_2 = 3.6 Hz), 2.586 (dd, 1H, J_1 = 12 Hz, J_2 = 4.8 Hz), 3.132 (broad d, 1H, *J* = 41.6 Hz) 3.600 (broad d, 1H, *J* = 20.4 Hz), 3.951 (dd, 2H, J_1 = 52.8 Hz, J_2 = 12 Hz) 4.245 (td, 1H, J_1 = 12 Hz, J_2 = 2 Hz), 4.499 (broad s, 0.5H), 4.686 (broad s, 0.5H), 7.578 (m, 2H), 7.633 (m, 1H), 7.752 (m, 2H), 9.593 (s, 1H); ^{13}C NMR (100Hz, $CDCl_3$): δ 28.102, 40.177, 41.414, 44.099, 45.260, 59.243, 60.419, 81.374, 127.779, 129.278, 133.340, 134.998, 197.484; HRMS Calc. for $C_{16}H_{22}O_5N_2SNa$ (M+Na): 377.11417, Found: 377.11521.



*tert-Butyl 2-formyl-4-phenylpiperazine-1-carboxylate (**28**).*

The product was purified *via* flash chromatography (10% EtOAc/Hexanes) to give a yellow liquid in 95 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.492 (m, 9H), 2.798 (broad s, 1H), 3.002 (d, 1H, *J* = 12.4 Hz), 3.269 (m, 1H), 3.396 (dd, 1H, J_1 = 30.8 Hz, J_2 = 9.6 Hz) 4.073 (m, 2H) 4.515 (s, 0.5H), 4.717 (s, 0.5H), 6.933 (m, 3H),

7.283 (m, 2H), 9.685 (s, 1H); MS: m/z 235.1 (M-^{t}Bu+H); HRMS Calc. for $C_{16}H_{22}O_3N_2$ (M): 290.16249, Found: 290.16228.

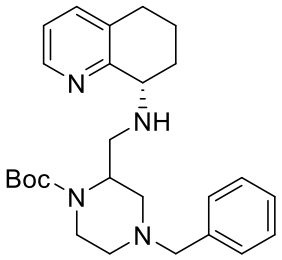


*4-Benzyl 1-(tert-butyl) 2-formylpiperazine-1,4-dicarboxylate (**29**).*

The product was purified *via* flash chromatography (30% EtOAc/Hexanes) to give pale yellow viscous liquid in 97 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.457 (m, 9H), 3.15 (broad m, 3H), 3.95 (broad s, 2H), 4.63 (broad m, 2H), 5.121 (s, 2H), 7.329 (m, 5H), 9.574 (s, 1H); MS: m/z 293.0 (M-^{t}Bu+H); HRMS Calc. for $C_{18}H_{24}O_5N_2Na$ (M+Na): 371.15774, Found: 371.15842.

General procedure for reductive amination of aldehydes and **30** to generate **31**-**36.**

A solution of the aldehyde (1 eq.) and **30** (1.5 eq.) in $ClCH_2CH_2Cl$ (0.15 M) was stirred at room temperature for 6 hrs. $NaBH(OAc)_3$ (95%) (1.6 eq.) was added. The resulting mixture was stirred overnight. The reaction was quenched with 1 N K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organics were washed with 1 N K_2CO_3 three times, brine and dried over Na_2SO_4.

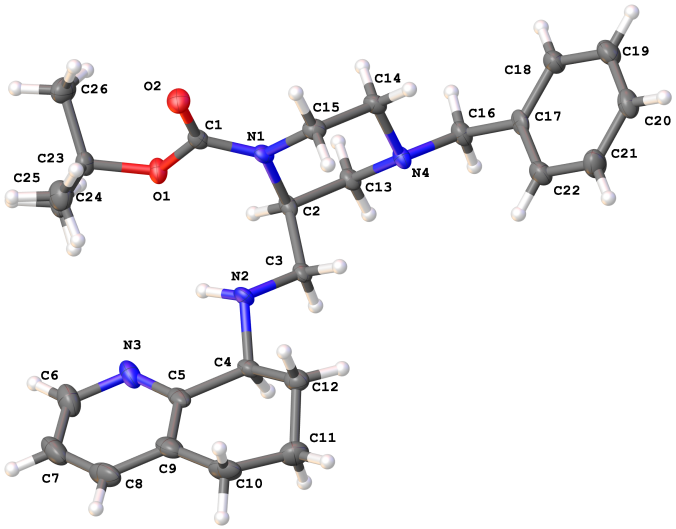


*tert-Butyl 4-benzyl-2-(R/S-(((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**31a-(S,R); 31b-(S,S)**).* To a solution of 5 mmoles of crude aldehyde **24** in 30 mL of 1,2-dichloromethane, generated from reducing benzyl ester 12 (2.15 g, 5.24 mmoles) with 10 mL of diisobutylaluminum hydride solution (1M in toluene) at -78oC, was added 0.9 g (6.1 mmoles) of *S*-amine **30** followed by stirring for 90 minutes at room temperature. Next, 2.38 g of sodium triacetoxyborohydride was added and the reaction was stirred at room temperature for 48 hours. The reaction was diluted with dichloromethane followed washing with NaOH (1N, aq.) and NaCl (aq.) solutions. The organic layerds were dried over sodium sulfate. The organics were filtered and the solvent removed under vacuum. Column chromatography (dichloromethane/methanol/ammonium hydroxide (90:10:0.1) gave a total of 1.907 g of the following make up – 0.948 g of an upper Rf spot assigned as **31a** (S,R), 0.461 g of a lower Rf spot as a white crystalline solid assigned as **31b** (S,S) based on a x-ray crystal structure, and 0.498 g of a mixture of **31a** and **31b** (83% yield for 2 steps from ester **12**).

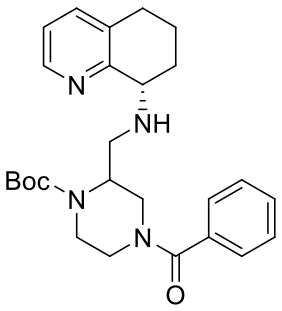
Physical data for **31b**: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.37 (s, 9H), 1.7 (m, 1H), 1.78 (m, 1H), 1.97 (m, 2H), 2.1 (dd, 2H, J=4Hz, J=12Hz), 2.72 (m, 3H), 2.86 (d, 1H, J=12Hz), 3.05 (m, 3H), 3.44 (s, 2H), 3.84 (d, 2H, J=9Hz),

4.16 (s, 1H), 7.03 (dd, 1H, J=5Hz, J=8Hz), 7.22 (m, 2H), 7.27 (m, 3H), 7.33 (dt, 1H, J=1Hz, J=8Hz), 8.34 (dt, 1H, J=1Hz, J=5Hz).

X-ray Structure of 31b:

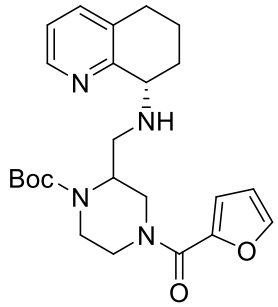


Experimental. Single colourless prism-shaped crystals of **31b** were re-crystallized from a mixture of dichloromethane, diethyl ether and ethanol. A suitable crystal (0.97 × 0.16 × 0.16 mm^3) was selected and mounted on a loop paratone oil on a Bruker APEX-II CCD diffractometer. The crystal was kept at T = 110(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXS-97** (Sheldrick, 2008) structure solution program, using the Dual Space solution method. The model was refined with version 2013-4 of **ShelXL-97** (Sheldrick, 2008) using Least Squares minimisation. **Crystal Data.** $C_{26}H_{36}N_4O_2$, M_r = 436.59, monoclinic, $P2_1$ (No. 4), a = 11.142(3) Å, b = 9.544(2) Å, c = 22.568(5) Å, β = 91.096(4)°, $\alpha = \gamma$ = 90°, V = 2399.4(10) Å^3, T = 110(2) K, Z = 4, Z' = 2.000, μ (MoK$_\alpha$) = 0.077), 27433 reflections measured, 10867 unique (R_{int} = 0.0585) which were used in all calculations. The final wR_2 was 0.1659 (all data) and R_1 was 0.0635 (I > 2(I)).

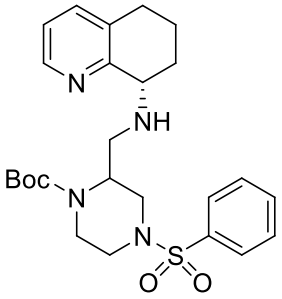


*tert-Butyl 4-benzoyl-2-(R/S-(((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**32**).* The crude mixture was purified *via* flash chromatography (CH_2Cl_2; 3% MeOH/CH_2Cl_2 to yield a yellow solid in 89 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.394 (s, 4.5H), 1.470 (s, 4.5H) 1.684 (broad s, 2H), 2.024 (broad s, 2H), 2.35 (broad s, 1H), 2.731~3.4 (broad m, 7H), 3.45~4.55 (broad m, 5H), 7.052 (m, 1H),

7.359 (m, 6H), 8.360 (broad s, 1H); MS: m/z 451.3 (M+H); HRMS Calc. for $C_{26}H_{35}O_3N_4$ (M+H): 451.27037, Found: 451.26998.

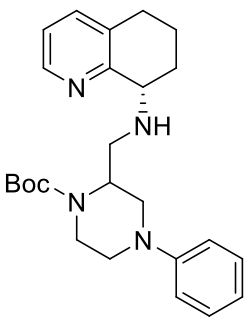


*tert-Butyl 4-(furan-2-carbonyl)-2-(R/S-(((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**33**).* The crude mixture was purified *via* flash chromatography (CH_2Cl_2; 2% MeOH/CH_2Cl_2) to yield a yellow solid in 79 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.414 (s, 4.5H), 1.478 (s, 4.5H) 1.643~2.079 (m, 4H), 2.5~3.5 (m, 8H), 3.750 (m, 1H), 3.992 (broad s, 1H), 4.26 (broad s, 1H), 4.45 (broad s, 1H), 4.579~4.752 (m, 1H), 6.472 (m, 1H), 7.045 (m, 2H), 7.346 (d, 1H, *J* = 7.6 Hz), 7.490 (d, 1H, *J* = 15.6 Hz), 8.349 (t, 1H, *J* = 4.4 Hz); MS: m/z 441.2 (M+H); HRMS Calc. for $C_{24}H_{33}O_4N_4$ (M+H): 441.24963, Found: 441.24936.

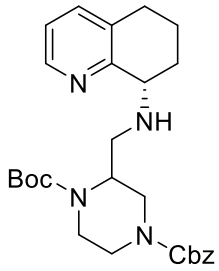


*tert-Butyl 4-(phenylsulfonyl)-2-(R/S-(((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**34**).*

The crude mixture was purified *via* flash chromatography (CH_2Cl_2; 3% MeOH/CH_2Cl_2) to yield a yellow solid in 93 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.322 (s, 4.5H), 1.398 (s, 4.5H) 1.713~2.6 (m, 7H), 2.702~3.187 (m, 5H), 3.678~4.002 (m, 4H), 4.161 (s, 0.5H), 4.248 (s, 0.5H), 7.055 (dq, 1H, J_1 = 7.2 Hz, J_2 = 2.4 Hz), 7.368 (t, 1H, *J* = 8.8 Hz), 7.53 (m, 2H), 7.599 (m, 1H), 7.74 (d, 1H, *J* = 8.4 Hz), 8.375 (d, 1H, *J* = 4.4 Hz); MS: m/z 487.2 (M+H); HRMS Calc. for $C_{25}H_{35}O_4N_4S$ (M+H): 487.23735, Found: 487.23713.



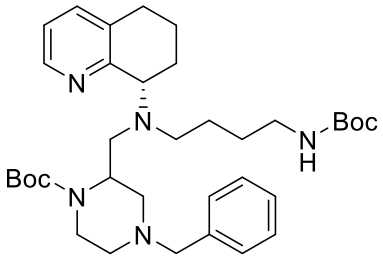
*tert-Butyl 4-phenyl-2-(R/S-(((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**35**).* The crude mixture was purified *via* flash chromatography (CH_2Cl_2; 3% MeOH/CH_2Cl_2) to yield a yellow solid in 93 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.422 (s, 4.5H), 1.499 (s, 4.5H) 1.749 (m, 2H), 2.017 (m, 3H), 2.783 (m, 5H), 3.163 (m, 2H), 3.490 (broad d, 1H, *J* = 11.6 Hz), 3.697~4.022 (m, 3H), 4.262 (broad, 1H), 6.859 (dt, 1H, J_1 = 7.2 Hz, J_2 = 2.4 Hz), 6.946 (t, 2H, *J* = 8 Hz), 7.062 (m, 1H), 7.260 (t, 2H, *J* = 8 Hz), 7.368 (t, 1H, *J* = 6.4 Hz), 8.382 (d, 1H, *J* = 4.4 Hz); MS: m/z 423.2 (M+H); HRMS Calc. for $C_{25}H_{35}O_2N_4$ (M+H): 423.27545, Found: 423.27505.



*4-Benzyl 1-(tert-butyl) 2-(R/S-(((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**36**).* The crude mixture was purified *via* flash chromatography (CH_2Cl_2; 3% MeOH/CH_2Cl_2) to yield a yellow liquid in 93 % yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.400 (s, 4.5H), 1.468 (s, 4.5H) 1.625~2.021 (m, 4H), 2.519 (broad s, 1H), 2.684~3.017 (m, 7H), 3.719~4.321 (m, 5H), 5.152 (m, 2H), 7.042 (m, 1H), 7.336 (m, 6H), 8.336 (s, 1H); MS: m/z 481.0 (M+H); HRMS Calc. for $C_{27}H_{37}O_4N_4$ (M+H): 481.28093, Found: 481.28176.

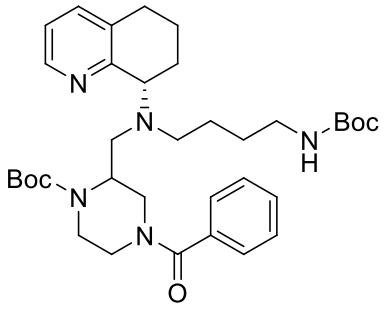
General procedure for reductive amination with **37**.

To a solution of a suitable secondary amine (**31**-**36**) and **37** (2 eq.) in CH_2Cl_2 (0.1 M) was added AcOH (2.3 eq.) at room temperature. The resulting solution was stirred for 1.5 hrs. After the addition of $NaBH(OAc)_3$ (95%) (2 eq.), the mixture was stirred overnight. The reaction was washed with 1 N K_2CO_3 three times. The aqueous was re-extracted with CH_2Cl_2. The combined organics were washed with brine and dried over Na_2SO_4.

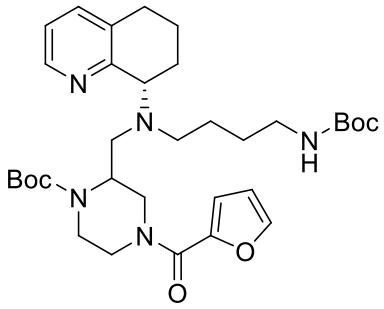


*tert-Butyl 4-benzyl-2-(R-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**38a**) and tert-Butyl 4-benzyl-2-(S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**38b**).* Physical data for **38a**: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.41 (s, 9H), 1.45 (s, 9H), 1.61 (m,2H), 1.77 (t, 2H, J=9Hz), 1.92 (m, 2H), 2.03 (d, 1H, J=4Hz), 2.06 (d, 1H, J=4Hz), 2.43 (m, 1H), 2.52 (d, 2H, J=11 Hz), 2.64 (m, 1H), 2.79 (m, 1H), 3.1 (m, 4H), 3.31 (t, 1H, J=11 Hz), 3.4 (d, 1H, J=13Hz), 3.72 (bs, 1H), 4.01 (m, 1H), 6.93

(dd, 1H, J=5Hz, J=8Hz), 7.09 (d, 2H, J=6Hz), 7.22 (m, 3H), 7.3 (d, 1H, J=7Hz), 8.43 (d, 1H, J=4Hz); LC-MS: 100% r.t.=7.3 mins. (254 nm) for $M+H^+$ (608).
Physical data for **38b**: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.42 (s, 9H), 1.43 (s, 9H), 1.47 (m, 2H), 1.65 (m, 1H), 1.75 (m, 1H), 1.89 (m, 2H), 2.06 (m, 2H), 2.64 (m, 2H), 2.77 (m, 2H), 2.95 (t, 1H, J=12Hz), 3.08 (s, 2H), 3.25 (m, 1H), 3.28 (d, 1H, J=13Hz), 3.55 (d, 1H, J=13Hz), 3.72 (d, 1H, J=11Hz), 3.9 (bs, 1H), 3.98 (q, 1H, J=6Hz), 7.01 (dd, 1H, J=5Hz, J=8Hz), 7.22 (m, 1H), 7.27 (m, 4H), 7.32 (d, 1H, J=8Hz), 8.38 (dd, 1H, J=1Hz, J=4Hz); LC-MS: 98% r.t.=7.01 mins. (254 nm) for $M+H^+$ (608).

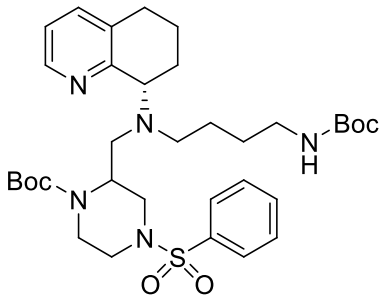


*tert-Butyl 4-benzoyl-2-(R-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**39a**) and tert-Butyl 4-benzoyl-2-(R-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**39b**).* The product was purified *via* flash chromatography (CH_2Cl_2; 2% MeOH/CH_2Cl_2; 5% MeOH/CH_2Cl_2; 10% MeOH/CH_2Cl_2) to give two diastereomers (URF and LRF) with a 1:1 ratio with a total yield of 92%. Physical data of **URF** (**39a**): ^{1}H NMR (400Hz, $CDCl_3$): δ 1.416~2.1 (m, 22H), 2.15~5 (m, 20H), 7.005 (q, 1H, *J* = 4.4 Hz), 7.342 (m, 6H), 8.362 (broad s, 1H); MS: m/z 622.5 (M+H); Physical data of the **LRF** (**39b**): ^{1}H NMR (400Hz, $CDCl_3$): δ 1.407~2.0 (m, 22H), 2.4~5.2 (m, 20H), 7.009 (t, 1H, *J* = 5.2 Hz), ~7.32 (broad m, 6H), 8.375 (broad s, 1H); MS: m/z 622.5 (M+H).

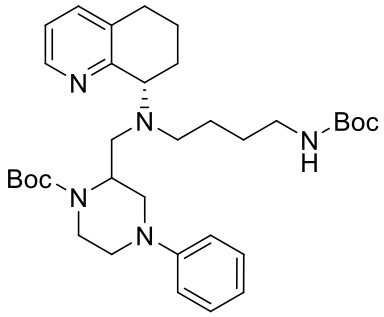


*tert-Butyl 2-(R/S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)-4-(furan-2-carbonyl)piperazine-1-carboxylate (**40a/b**).* The product was purified *via* flash chromatography (CH_2Cl_2; 2% MeOH/CH_2Cl_2; 10% MeOH/CH_2Cl_2) to give a yellow liquid in 93 % yield, which is a mixture of both diastereomers. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.421 (d, 9H, *J* = 4.4 Hz), 1.470 (d, 9H, *J* = 4.8 Hz) 1.277~1.632 (m, 5H), 1.869 (broad s, 2H), 2.20~2.74 (m, 4H), 2.75~3.5 (m, 7H), 3.854 (borad s, 2H), 4.101 (broad s, 1H), 4.28 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.8 Hz), 4.67 (broad m, 2H), 6.454 &

6.483 (s & s, 1H with ~1:2 ratio), 6.964 (m, 1H), 7.039 (d, 1H, *J* = 3.2 Hz), 7.28 (m, 1H), 7.485 (d, 1H, *J* = 8.8 Hz), 8.329 (m, 1H); MS: m/z 612.3 (M+H); HRMS Calc. for $C_{33}H_{50}O_6N_5$ (M+H): 612.37556, Found: 612.37519.

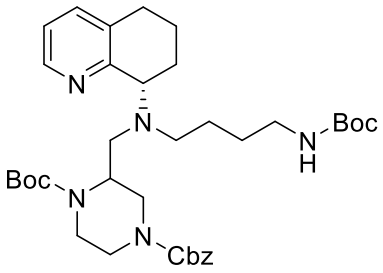


*tert-Butyl 2-(R-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)-4-(phenylsulfonyl)piperazine-1-carboxylate (**41a**) and tert-Butyl 2-(S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)-4-(phenylsulfonyl)piperazine-1-carboxylate (**41b**).* The product was purified *via* flash chromatography (CH_2Cl_2; 1% MeOH/CH_2Cl_2; 2% MeOH/CH_2Cl_2; 8% MeOH/CH_2Cl_2) to give two diastereomers (URF and LRF) with a ~1:1 ratio in total yield of 87%. Physical data of the **URF** (**41a**): ^{1}H NMR (400Hz, $CDCl_3$): δ 1.411 (s, 9H), 1.468 (s, 9H) 1.724~2.4 (m, 8H), 2.602~2.827 (m, 4H), 3.058 (m, 4H), 3.475~3.647 (m, 5H), 3.8~4.15 (m, 4H), 7.124 (dd, 1H, J_1 = 7.6 Hz, J_2 = 4.8 Hz), 7.328 (d, 1H, *J* = 7.6 Hz), 7.546 (m, 2H), 7.613 (m, 1H), 7.764 (d, 2H, *J* = 7.2 Hz), 8.418 (d, 1H, *J* = 4.4 Hz); MS: m/z 658.2 (M+H); HRMS Calc. for $C_{34}H_{52}O_6N_5S$ (M+H): 658.36328, Found: 658.36365. Physical data of the **LRF** (**41b**): ^{1}H NMR (400Hz, $CDCl_3$): δ 1.364 (s, 9H), 1.431 (s, 9H) 1.483~1.574 (m, 3H),1.693 (m, 1H), 1.888 (q, 1H, *J* = 10 Hz), 1.998~2.196 (m, 6H), 2.484 (m, 1H), 2.668 (d, 1H, *J* = 15.6 Hz), 2.79~3.142 (m, 7H), 3.603 (d, 1H, *J* = 11.2 Hz), 3.865 (d, 1H), 3.95~4.098 (m, 3H), 7.023 (dd, 1H, J_1 = 7.6 Hz, J_2 = 4.8 Hz), 7.338 (d, 1H, *J* = 7.6 Hz), 7.548 (m, 2H), 7.618 (m, 1H), 7.758 (d, 2H, *J* = 7.2 Hz), 8.390 (d, 1H, *J* = 4.4 Hz); MS: m/z 658.2 (M+H); HRMS Calc. for $C_{34}H_{52}O_6N_5S$ (M+H): 658.36328, Found: 658.36346.



*tert-Butyl 2-(R/S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)-4-phenylpiperazine-1-carboxylate (**42a/b**).* The product was purified *via* flash chromatography (10% EtOAc/Hexanes; 15% EtOAc/Hexanes; 30% EtOAc/Hexanes; 10% MeOH/CH_2Cl_2) to give a mixture of both diastereomers in 62.7 % yield as a yellow viscous liquid. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.422 (d, 9H, *J* = 2.4 Hz), 1.487 (s, 9H), 1.378~1.57 (m, 3H), 1.579~2.05 (m, 5H), 2.485~3.096 (m, 10H), 3.202 (t, 1H, *J* = 11.6 Hz), 3.454 (m, 1H), 4.009 (m, 4H), 6.838 (m, 2H), 6.958 (m, 2H), 7.24 (m, 3H), 8.210

(d, 0.5H), 8.391 (d, 0.5H, *J* = 3.2 Hz); MS: m/z 594.4 (M+H), 594.4 (M+H); HRMS Calc. for $C_{34}H_{52}O_4N_5$ (M+H): 594.40004, Found: 594.40059.



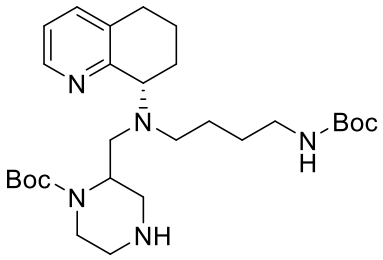
37

*4-Benzyl 1-(tert-butyl) 2-(R-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**37a**) and 4-Benzyl 1-(tert-butyl) 2-(S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**37b**).*

The products were purified *via* flash chromatography (20% EtOAc/Hexanes; 30% EtOAc/Hexanes; 40% EtOAc/Hexanes; 5% MeOH/CH_2Cl_2) to give two diastereomers (URF and LRF) in total yield of 83%.

Physical data of the **37a**: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.366 (broad, 5H), 1.416 (s, 9H), 1.463 (s, 9H), 1.465~2.221 (m, 3H), 2.316 (broad t, 1H, *J* = 6.8 Hz), 2.526~2.697 (broad m, 3H), 2.76 (dd, 1H, J_1 = 13.6 Hz, J_2 = 4.8 Hz), 2.952 (broad m, 5H), 3.243 (t, 1H, *J* = 13.2 Hz), 3.75~4.45 (m, 5H), 5.106 (broad m, 2H), 6.998 (dd, 1H, J_1 = 7.6 Hz, J_2 = 5.2 Hz), 7.307 (m, 6H), 8.374 (broad s, 1H); MS: m/z 652.4 (M+H); HRMS Calc. for $C_{36}H_{54}O_6N_5$ (M+H): 652.40686, Found: 652.40649.

Physical data of the **37b**: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.345 (s, 18H), 1.388 (broad, 3H), 1.4~1.96 (broad m, 5H), 2.2-3.2 (m, 11H), 3.6-4.15 (m, 4H), 4.246 (d, 1H, *J* = 13.2 Hz), 5.080 (broad m, 2H), 6.914 (dd, 1H, J_1 = 7.6 Hz, J_2 = 4.8 Hz), 7.22 (m, 6H), 8.282 (d, 1H, *J* = 4.4 Hz); MS: m/z 652.4 (M+H); HRMS Calc. for $C_{36}H_{54}O_6N_5$ (M+H): 652.40686, Found: 652.40641.



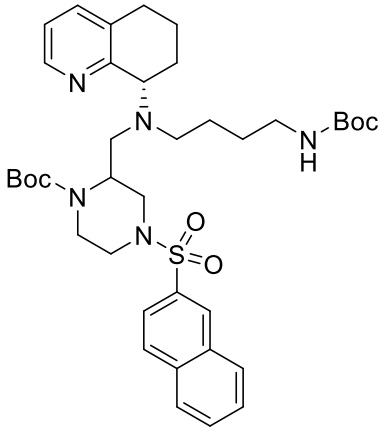
tert-Butyl 2-(R-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate.

To a solution of **37a** (2.73 g, 4.19 mmol) in MeOH (84 ml) was added Pd on carbon (0.0446 g, 0.419 mmol) under argon in a Parr hydrogenator. The flask was carefully charged with H_2 (45 psi) and the reaction mixture was left on the hydrogenolysis shaker at room temperature for 20 hrs. The reaction

was filtered through a celite pad and the filtrated was condensed on rotavap. The pale yellow foam in 94 % yield was used for next step without further purification.

General procedure for sulfonamide formation to generate **38a**, **39a** and **40a**

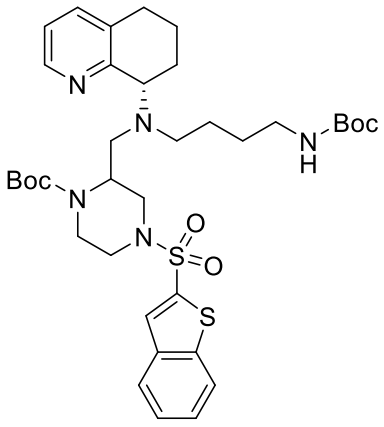
To a solution of the intermediate (1 eq.), which was obtained by hydrogenolysis, in CH_2Cl_2 (0.2 M) was added the sulfonyl chlorides (2 eq.) and triethylamine (2 eq.) at room temperature. The resulting solution was stirred overnight. After removal of CH_2Cl_2 on rotavap, the solid was diluted with EtOAc and washed with H_2O (twice), 1 N NaOH (twice), brine and dried over Na_2SO_4.



38a

*tert-Butyl 2-(((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)-4-(naphthalen-2-ylsulfonyl)piperazine-1-carboxylate (**38a**)*.

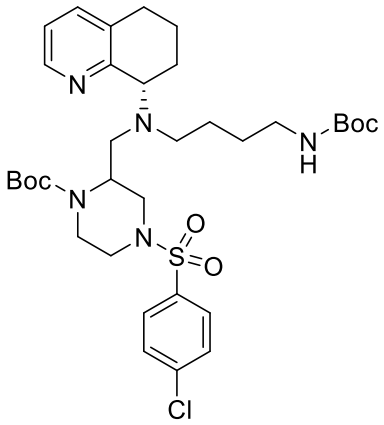
The product was purified *via* preparative TLC (5% MeOH/CH_2Cl_2) to give a yellow foam **38a** in 55.9% yield. ^{1}H NMR (600Hz, $CDCl_3$): δ 1.400 (s, 18H), 1.779 (q, 2H, *J* = 10.8 Hz), 1.993 (m, 1H), 2.167~2.295 (m, 4H), 2.370 (broad s, 1H), 2.592 (broad s, 1H), 2.623~2.792 (m, 2H), 3.058 (broad s, 4H), 3.604 (t, 1H, *J* = 13.2 Hz), 3.7 (broad s, 1H), 3.8~4.158 (broad m, 4H), 4.7 (broad s, 1H), 7.033 (dd, 1H, J_1 = 7.2 Hz, J_2 = 4.8 Hz), 7.333 (d, 1H, *J* = 7.8 Hz), 7.634 (m, 2H), 7.751 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.2 Hz), 7.918 (d, 1H, *J* = 7.8 Hz), 7.986 (dd, 2H, J_1 = 13.2 Hz, J_2 = 8.4 Hz), 8.328 (s, 1H), 8.431 (d, 1H, *J* = 3.6 Hz); HRMS Calc. for $C_{38}H_{54}O_6N_5{}^{32}S_1$ (M+H): 708.37893, Found: 708.37815.



39a

*tert-Butyl 4-(benzo[b]thiophen-2-ylsulfonyl)-2-(((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**39a**)*

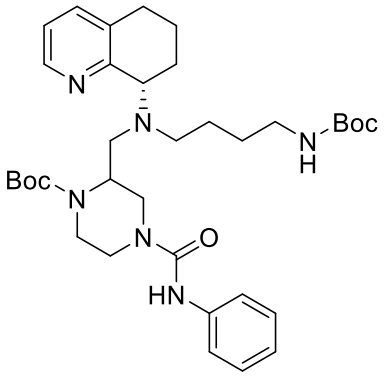
The product was purified *via* preparative TLC (5% MeOH/CH_2Cl_2) to give a yellow foam **39a** in 59.3% yield. ^{1}H NMR (600Hz, $CDCl_3$): δ 1.399 (s, 18H), 1.760 (q, 2H, *J* = 12 Hz), 1.969 (broad s, 1H), 2.198 (m, 2H), 2.391 (m, 2H), 2.486 (dd, 1H, J_1 = 10.8 Hz, J_2 = 3.6 Hz), 2.583~2.794 (m, 5H), 3.053 (broad s, 4H), 3.586 (t, 1H, *J* = 12 Hz), 3.695 (broad s, 1H), 3.8~4.141 (broad m, 5H), 4.7 (broad s, 1H), 7.029 (dd, 1H, J_1 = 6.6 Hz, J_2 = 4.2 Hz), 7.329 (d, 1H, *J* = 7.8 Hz), 7.481 (m, 2H), 7.817 (s, 1H), 7.864 (d, 1H, *J* = 7.8 Hz), 7.908 (d, 1H, *J* = 7.2 Hz), 8.421 (d, 1H, *J* = 2.4 Hz); HRMS Calc. for $C_{36}H_{52}O_6N_5{}^{32}S_2$ (M+H): 714.33536, Found: 714.33452.



40a

*tert-Butyl 2-(((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)-4-((4-chlorophenyl)sulfonyl)piperazine-1-carboxylate (**40a**)*

The product was purified *via* ISCO (12g cartridge, 1.5→5.5% MeOH/CH_2Cl_2) to give a yellow foam **40a** in 50.4% yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.406 (s, 18H), 1.758 (q, 2H, *J* = 10.4 Hz), 1.964 (broad s, 1H), 2.128~2.369 (m, 5H), 2.565~2.789 (m, 5H), 3.049 (broad s, 4H), 3.566 (m, 2H), 3.8~4.126 (broad m, 5H), 4.7 (broad s, 1H), 7.024 (dd, 1H, J_1 = 7.2 Hz, J_2 = 4.8 Hz), 7.324 (d, 1H, *J* = 7.2 Hz), 7.514 (d, 2H, *J* = 8.4 Hz), 7.696 (d, 2H, *J* = 8.4 Hz), 8.413 (d, 1H, *J* = 4 Hz); MS: m/z 692.2 (M+H); HRMS Calc. for $C_{34}H_{51}O_6N_5Cl^{32}S_1$ (M+H): 692.32431, Found: 692.32416.



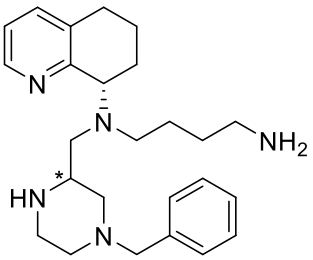
41a

*tert-Butyl 2-(((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)-4-(phenylcarbamoyl)piperazine-1-carboxylate (**41a**)*

The product was purified *via* ISCO (12g cartridge, 1.5→7.5% MeOH/CH_2Cl_2) to give a white foam **41a** in 69.5% yield. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.39 (s, 9H), 1.49 (s, 9H), 1.64~1.72 (broad m, 2H), 1.88 (broad m,1H), 2.04 (broad m, 1H), 2.14 (broad m, 1H), 2.39 (m, 2H), 2.60~3.03 (m, 10H), 3.95 (m, 3H), 4.37 (broad m, 2H), 4.52 (broad s, 1H), 4.68 (broad s, 1H), 6.99 (t, 2H, *J* = 8 Hz), 7.24 (m, 3H), 7.35 (m, 2H), 8.13 (borad s, 1H); MS: m/z 637.4 (M+H); HRMS Calc. for $C_{35}H_{53}O_5N_6Cl$ (M+H): 637.40720, Found: 637.40726.

*General procedure for Boc-deprotection to generate **48**-**53a/b** and **54a**-**57a***

To a solution of the Boc-protected starting material (1 eq.) in CH_2Cl_2 (0.15 M) was added TFA (32 eq.) at room temperature. The resulting solution was stirred for overnight. The reaction was neutralized by NaOH to pH~13, and washed with 1 N NaOH three times. The combined aqueous was re-extracted with CH_2Cl_2 three times. The organics were combined, washed with brine and dried over Na_2SO_4. TLC (20% MeOH/CH_2Cl_2 with 2% NH_4OH) of the crude reaction mixture showed a new spot. The crude mixture was purified *via* flash chromatography, eluted by 10% MeOH/CH_2Cl_2 then 20% MeOH/CH_2Cl_2 with 2% NH_4OH, to give the desired product.

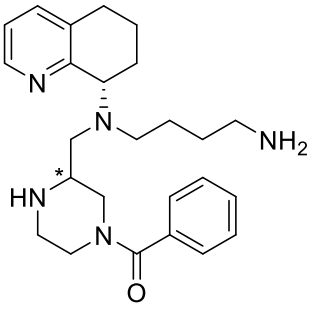


48

*N^1-(((R)-4-Benzylpiperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**48a**) and N^1-(((R)-4-Benzylpiperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**48b**).*

Physical data for **48a**: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.25 (s, 2H), 1.43 (m, 4H), 1.72 (m, 4H), 1.99 (m, 2H), 2.17 (t, 1H, J=9Hz), 2.48 (m, 2H), 2.73 (m, 10H), 3.03 (d, 1H, J=12Hz), 3.27 (bs, 3H), 3.47 (d, 2H, J=4Hz), 4 (dd, 1H, J=6Hz, J=10Hz), 7.04 (dd, 1H, J=5Hz, J=8Hz), 7.29 (m, 5H), 7.33 (d, 1H, J=8Hz), 8.39 (d, 1H, J=4Hz); LC-MS: 88% r.t. 5.43 min. (254 nm) for $M+H^+$ (408.3).

Physical data for **48b**: ^{1}H NMR (400Hz, $CDCl_3$): δ 1.42 (m, 3H), 1.66 (m, 1H), 1.77 (q, 2H, J=10Hz), 1.96 (m, 1H), 2.05 (m, 1H), 2.16 (t, 1H, J=9 Hz), 2.47 (m, 4H), 2.61 (m, 4H), 2.69 (m, 4H), 2.83 (m, 2H), 2.99 (d, 1H, J=12Hz), 3.48 (d, 2H, J=4Hz), 3.95 (dd, 1H, J=6Hz, J=9Hz), 7.05 (dd, 1H, J=5Hz, J=8Hz), 7.24 (m, 1H), 7.29 (m, 4H), 7.33 (d, 1H, J=8Hz), 8.43 (d, 1H, J=4Hz); LC-MS: 97% r.t. 5.45 min. (254 nm) for $M+H^+$ (408.3).

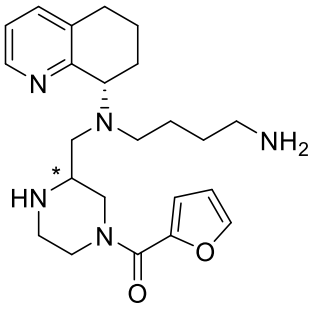


49

*(3-(R-((4-Aminobutyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazin-1-yl)(phenyl)methanone (**49a**) and (3-(S-((4-Aminobutyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazin-1-yl)(phenyl)methanone (**49b**).*

49a was obtained in 65% yield as a light brown foam. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.44-3.2 (m, 24H), 3.53 (dd, 1H, J_1 = 40.4 Hz, J_2 = 13.6 Hz), 4.0 (d, 1H, J = 36.4 Hz), 4.52 (dd, 1H, J_1 = 36.4 Hz, J_2 = 9.6 Hz), 7.03 (broad s, 1H), 7.38 (m, 6H), 8.38 (broad d, 1H, J = 36.4 Hz); MS: m/z 422.3 (M+H); HRMS Calc. for $C_{25}H_{36}ON_5$ (M+H): 422.29144, Found: 422.29099; Purity is determined by LC-MS: Area% 100.00 (Retention time: 2.02).

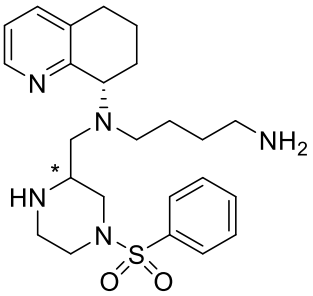
49b was obtained in 63 % yield as a viscous, yellow oil. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.25-3.11 (m, 20H), 3.15-3.7 (m, 5H), 3.95 (d, 1H, J = 48 Hz), 4.46 (broad t, 1H, J = 12.4 Hz), 7.05 (broad s, 1H), 7.360 (m, 6H), 8.45 (broad d, 1H, J = 37.6 Hz); MS: m/z 422.3 (M+H); HRMS Calc. for $C_{25}H_{36}ON_5$ (M+H): 422.29144, Found: 422.29096; Purity is determined by LC-MS: Area% 100.00 (Retention time: 2.18).



50a/b

*(3-(R-((4-Aminobutyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazin-1-yl)(furan-2-yl)methanone (**50b**)*

Compound **50b** was obtained in 90% yield as a light brown solid. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.4 (s, 1H), 1.55-2.28 (m, 8H), 2.44-3.2 (m, 12H), 3.72 (m, 2H), 3.91 (m, 1H), 4.03 (m, 1H), 4.44 (d, 2H, J = 12.8 Hz), 6.47 (m, 1H), 7.01 (d, 1H, J = 3.2 Hz), 7.15 (dd, 1H, J_1 = 7.6 Hz, J_2 = 4.8 Hz), 7.40 (d, 1H, J = 7.6 Hz), 7.48 (m, 1H), 8.66 (d, 1H, J = 4 Hz); MS: m/z 412.2 (M+H); HRMS Calc. for $C_{23}H_{34}O_2N_5$ (M+H): 412.27070, Found: 412.27061; Purity is determined by LC-MS: Method 1 (75-95% MeOH over 5.5 min) Area% 100.00 (Retention time: 1.34); Method 2 (50-95% MeOH over 5.5 min) Area% 100.00 (Retention time: 1.29).

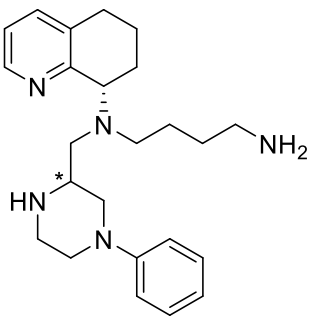


51a/b

*N^1-(S-(4-(Phenylsulfonyl)piperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**51a**) and N^1-(R-(4-(Phenylsulfonyl)piperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**51b**).*

51a was obtained in 80% yield as a yellow foam. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.39-1.49 (m, 4H), 1.65-1.84 (m, 4H), 1.93-2.19 (m, 6H), 2.34 (dt, 1H, J_1 = 10.8 Hz, J_2 = 2.8 Hz), 2.66 (m, 8H), 2.92 (m, 2H), 3.48 (d, 1H, J = 10.4 Hz), 3.58 (d, 1H, J = 11.6 Hz), 3.97 (dd, 1H, J_1 = 9.2 Hz, J_2 = 5.2 Hz), 7.02 (dd, 1H, J_1 = 7.6 Hz, J_2 = 4.8 Hz), 7.31 (d, 1H, J = 7.2 Hz), 7.48 (m, 2H), 7.56 (m, 1H), 7.69 (m, 2H), 8.38 (d, 1H, J = 3.6 Hz); ^{13}C NMR (100Hz, $CDCl_3$): δ 21.900, 27.052, 28.114, 29.305, 31.164, 41.956, 44.923, 46.550, 49.964, 53.572, 54.243, 55.165, 61.420, 121.452, 127.719, 128.917, 132.680, 133.811, 135.328, 136.546, 146.663, 158.328; MS: m/z 458.2 (M+H); HRMS Calc. for $C_{24}H_{36}O_2N_5S$ (M+H): 458.25842, Found: 458.25859; Purity is determined by LC-MS: Method 1 (75-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.43); Method 2 (25-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.49).

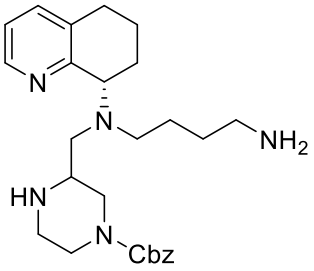
51b was obtained in 54% yield as a yellow foam. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.383 (broad s, 2H), 1.64-1.87 (m, 6H), 2.04-2.16 (m, 2H), 2.4-2.93 (m, 13H), 3.19 (broad m, 1H), 3.53 (m, 3H), 3.91 (dd, 1H, J_1 = 9.6 Hz, J_2 = 6 Hz), 7.14 (dd, 1H, J_1 = 7.6 Hz, J_2 = 4.8 Hz), 7.41 (d, 1H, J = 8 Hz), 7.53 (m, 2H), 7.61 (m, 1H), 7.71 (s, 1H), 7.73 (s, 1H), 8.67 (d, 1H, J = 4 Hz); ^{13}C NMR (100Hz, $CDCl_3$): δ 21.619, 22.010, 25.591, 25.705, 28.926, 39.331, 43.098, 44.577, 50.423, 52.274, 52.870, 59.926, 74.637, 122.305, 127.419, 129.206, 133.113, 134.145, 135.605, 137.616, 147.179, 156.754; MS: m/z 458.2 (M+H); HRMS Calc. for $C_{24}H_{36}O_2N_5S$ (M+H): 458.25842, Found: 458.25872; Purity is determined by LC-MS: Method 1 (75-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.43); Method 2 (75% MeOH ISO over 3 min) Area% 100.00 (Retention time: 0.43).



52a/b

*N^1-(R/S-(4-Phenylpiperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**52a/b**).*

52a/b was obtained in 91% yield as a yellow solid. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.35-1.9 (m, 7H), 1.92-2.15 (m, 5H), 2.45-3.1 (m, 10H), 3.16 (m, 1H), 3.46 (m, 2H), 4.00 (m, 1H), 6.84 (m, 3H), 7.03 (m, 1H), 7.22 (t, 2H, *J* = 7.2 Hz), 7.32 (m, 1H), 8.39 (m, 0.5H) 8.54 (dd, 0.5H, J_1 = 53.2 Hz); ^{13}C NMR (100Hz, $CDCl_3$): δ 22.177, 28.061, 28.228, 28.929, 29.252, 29.529, 29.620, 31.202, 51.736, 53.666, 54.524, 61.944, 116.395, 116.680, 116.782, 119.881, 120.507, 121.744, 121.979, 129.335, 129.403, 129.460, 134.342, 136.937, 146.838, 159.049; MS: m/z 394.3 (M+H); HRMS Calc. for $C_{24}H_{36}N_5$ (M+H): 394.29652, Found: 394.29602; Purity is determined by LC-MS: Method 1 (25-95% MeOH over 5.5 min) Area% 100.00 (Retention time: 1.56); Method 2 (50-95% MeOH over 5.5 min) Area% 100.00 (Retention time: 0.44).

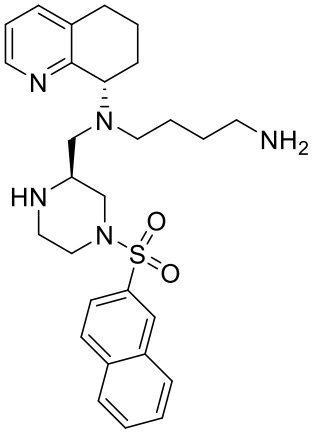


53a/b

*Benzyl 3-(S-((4-aminobutyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**53a**) and Benzyl 3-(R-((4-aminobutyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**53b**).*

53a was obtained in 72% yield as a yellow foam. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.39-1.50 (m, 4H), 1.66 (m, 1H), 1.79 (m, 1H), 1.96 (m, 2H), 2.15-2.9 (m, 20H), 3.99 (m, 3H), 5.09 (broad s, 2H), 7.01 (dd, 1H, J_1 = 7.2 Hz, J_2 = 4.8 Hz), 7.32 (m, 6H), 8.388 (broad s, 1H); ^{13}C NMR (100Hz, $CDCl_3$): δ 21.838, 26.981, 27.779, 29.292, 41.738, 44.323, 45.382, 47.789, 53.992, 55.312, 61.322, 66.988, 74.717, 121.298, 121.449, 127.803, 127.899, 128.394, 133.868, 136.371, 136.536, 136.701, 146.616, 155.239; MS: m/z 451.8 (M+H); HRMS Calc. for $C_{26}H_{38}O_2N_5$ (M+H): 452.30200, Found: 452.30194; Purity is determined by LC-MS: Method 1 (50-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.56); Method 2 (75-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.63).

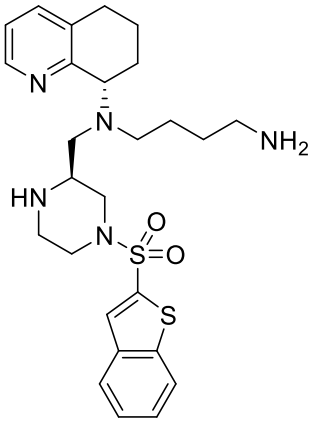
53b was obtained in 90% yield as a yellow foamy solid. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.25-2.13 (m, 8H), 2.39-3.38 (m, 20H), 3.99 (m, 3H), 5.11 (broad s, 2H), 7.14 (dd, 1H, J_1 = 7.2 Hz, J_2 = 4.8 Hz), 7.34 (m, 5H), 7.4 (d, 1H, *J* = 7.8 Hz), 8.64 (d, 1H, *J* = 4.2 Hz); ^{13}C NMR (100Hz, $CDCl_3$): δ 21.563, 25.826, 26.417, 29.140, 39.689, 43.430, 43.952, 46.400, 50.856, 52.493, 52.823, 60.167, 67.277, 74.676, 122.288, 127.830, 128.036, 128.463, 134.487, 136.371, 137.526, 147.098, 156.628; MS: m/z 451.8 (M+H); HRMS Calc. for $C_{26}H_{38}O_2N_5$ (M+H): 452.30200, Found: 452.30162; Purity is determined by LC-MS: Method 1 (50-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.54); Method 2 (75-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.63).



54a

*N^1-(((S)-4-(Naphthalen-2-ylsulfonyl)piperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**54a**).*

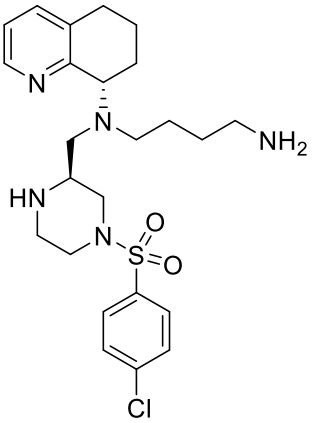
54a was obtained in 41.8% yield as a yellow foam. ^{1}H NMR (600Hz, $CDCl_3$): δ 1.45 (m, 3H), 1.65 (m, 1H), 1.74 (dq, 1H, J_1 =10.2 Hz, J_2 = 2.4 Hz), 1.94 (m, 3H), 2.2 (t, 1H, J =11.4 Hz), 2.42 (dt, 1H, J_1 =10.8 Hz, J_2 = 2.4 Hz), 2.55 (m, 2H), 2.62-2.84 (m, 11H), 2.99 (dd, 1H, J_1 =9.6 Hz, J_2 = 2.4 Hz), 3.55 (d, 1H, J = 10.8 Hz), 3.64 (d, 1H, J = 10.8 Hz), 3.96 (dd, 1H, J_1 =10.2 Hz, J_2 = 6 Hz), 7.02 (dd, 1H, J_1 =7.8 Hz, J_2 = 4.8 Hz), 7.29 (d, 1H, J = 7.2 Hz), 7.59 (t, 1H, J = 7.8 Hz), 7.63 (t, 1H, J = 7.2 Hz), 7.69 (dd, 1H, J_1 =8.4 Hz, J_2 = 1.2 Hz), 7.89 (d, 1H, J = 4.2 Hz), 7.93 (t, 2H, J = 10.2 Hz), 8.27 (s, 1H), 8.38 (d, 1H, J = 3.6 Hz); ^{13}C NMR (150Hz, $CDCl_3$): δ 21.824, 26.844, 29.278, 30.241, 41.367, 44.681, 46.634, 50.017, 54.157, 55.394, 61.721, 121.614, 122.962, 127.473, 127.844, 128.752, 128.944, 129.095, 129.137, 132.135, 132.561, 133.909, 134.817, 136.769, 146.575, 157.949, 173.296, 181.411; MS: m/z 508.2 (M+H); HRMS Calc. for $C_{28}H_{38}O_2N_5{}^{32}S_1$ (M+H): 508.27462, Found: 508.37309; Purity is determined by LC-MS: Method 1 (50-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.600); Method 2 (75-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.524).



55a

*N^1-(((S)-4-(Benzo[b]thiophen-2-ylsulfonyl)piperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**55a**).*

55a was obtained in 70% yield as a yellow foam. ^{1}H NMR (600Hz, $CDCl_3$): δ 1.42-1.53 (m, 5H), 1.67 (m, 1H), 1.76 (dq, 1H, J_1 =10.2 Hz, J_2 = 3 Hz), 1.95 (m, 1H), 1.99 (m, 1H), 2.25 (t, 1H, J = 12 Hz), 2.52-2.73 (m, 12H), 3.03 (dd, 1H, J_1 =9 Hz, J_2 = 2.4 Hz), 3.53 (d, 1H, J = 10.2 Hz), 3.62 (d, 1H, J = 10.8 Hz), 3.99 (dd, 1H, J_1 =10.2 Hz, J_2 = 6 Hz), 7.01 (dd, 1H, J_1 =7.8 Hz, J_2 = 4.8 Hz), 7.29 (d, 1H, J =7.8 Hz), 7.46 (m, 2H), 7.74 (s, 1H), 7.83 (d, 1H, J =7.8 Hz), 7.87 (d, 1H, J =7.8 Hz), 8.41 (d, 1H, J =3.6 Hz); ^{13}C NMR (150Hz, $CDCl_3$): δ 21.838, 26.789, 29.278, 30.199, 41.339, 44.626, 46.648, 50.017, 53.387, 54.294, 55.298, 61.693, 121.614, 122.494, 125.458, 127.088, 129.315, 133.826, 136.192, 136.769, 137.787, 141.665, 146.685, 157.921, 173.270, 181.328; MS: m/z 514.2 (M+H); HRMS Calc. for $C_{26}H_{36}O_2N_5{}^{32}S_2$ (M+H): 514.23104, Found: 514.22933; Purity is determined by LC-MS: Method 1 (50-95% MeOH over 3 min) Area% 97.97 (Retention time: 0.575); Method 2 (75-95% MeOH over 3 min) Area% 95.63 (Retention time: 0.491).

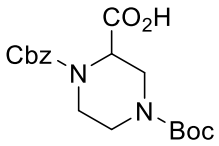


56a

*N^1-(((S)-4-((4-Chlorophenyl)sulfonyl)piperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**56a**)*

56a was obtained in 84% yield as an off-white foam. ^{1}H NMR (400Hz, $CDCl_3$): δ 1.42-1.55 (m, 4H), 1.65-1.88 (m, 3H), 1.94-2.04 (m, 2H), 2.24 (t, 1H, J = 12.8 Hz), 2.36 (m, 1H), 2.56-2.86 (m, 12H), 3.03 (d, 1H, J = 12 Hz), 3.46 (d, 1H, J = 10.4 Hz), 3.55 (d, 1H, J = 11.2 Hz), 7.05 (dd, 1H, J_1 =7.6 Hz, J_2 = 4.4 Hz), 7.34 (d, 1H, J = 7.2 Hz), 7.47 (d, 2H, J = 8.4 Hz), 7.64 (d, 2H, J = 8.8 Hz), 8.42 (d, 1H, J = 4 Hz); MS: m/z 492.2 (M+H); HRMS Calc. for $C_{24}H_{35}O_2N_5ClS$ (M+H): 492.21945, Found: 492.21945; Purity is determined by LC-MS: Method 1 (50-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.583); Method 2 (75-95% MeOH over 3 min) Area% 100.00 (Retention time: 0.562).

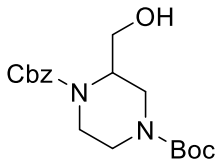
Part 2. Procedures for compounds synthesized in Scheme 2.



59

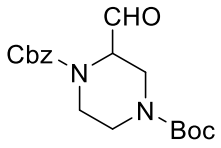
*1-((Benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**59**).*

A solution of piperazine-1,3-dicarboxylic acid 1-tert-butyl ester (**58**, 14.55 g, 63.2 mmol) in 1,4-dioxane (211 mL) water (105 mL) and triethylamine (22 mL, 2.5 eq) was cooled to 0ºC. Benzyl carbonochloridate (12.93 g, 76 mmol, 1.2 eq) was added dropwise over the course of 5 minutes. The reaction was allowed to warm to room temperature and was tracked by LCMS. After one hour the reaction was diluted with 1N HCl and then extracted with DCM (3 times). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (approx. 23 g). The material was used in the next step crude.



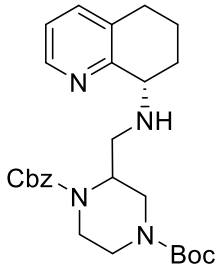
*1-Benzyl 4-(tert-butyl) 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (**60**).*

A solution of 1-((benzyloxy)carbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (**59**, aprox 23 g, 63 mmol) in THF (316 mL, .2M) was cooled to 0^{o}C. Borane dimethylsulfide (11.1 mL, 110 mmol, 1.75 eq) was added drop wise over the course of 5 minutes. The reaction was allowed to warm to room temperature and was tracked by LCMS. After stirring overnight the reaction was diluted with brine and then extracted with DCM (3 times). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 1-benzyl 4-tert-butyl 2-(hydroxymethyl) piperazine-1,4-dicarboxylate (**60**, 21 g, 95% yield over two steps). Physical data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 5.12 (d, *J* = 2.3 Hz, 2H), 4.36 – 4.07 (m, 2H), 4.04 – 3.78 (m, 2H), 3.66 – 3.50 (m, 2H), 3.16 – 2.72 (m, 4H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.08, 154.98, 136.47, 128.78, 128.41, 128.19, 80.86, 67.76, 67.29, 52.77, 42.89, 39.84, 28.54. HRMS Calc'd for $C_{15}H_{27}O_5N_2$ 351.19145; found [M+H] 351.19204.



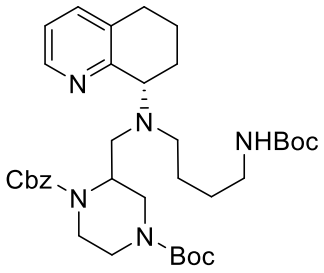
*1-Benzyl 4-(tert-butyl) 2-formylpiperazine-1,4-dicarboxylate (**61**).*

To a solution of 1-benzyl 4-tert-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (**60**, 21 g, 60 mmol) dissolved in DCM (300 mL, .2M) was added PCC (19.38 g, 90 mmol, 1.5 eq). The reaction was tracked by LCMS. After stirring overnight the reaction mixture was triturated with diethyl ether until no more solid (chromium waste) crashed out. The suspension was then filtered and the solution concentrated down to afford 1-benzyl 4-tert-butyl 2-formylpiperazine-1,4-dicarboxylate (approx. 20g). The material was used in the next step crude.



*1-Benzyl 4-(tert-butyl) 2-(R/S-(((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**62**).*

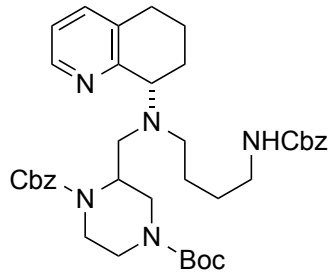
To a solution of 1-benzyl 4-tert-butyl 2-formylpiperazine-1,4-dicarboxylate (**61**, 15.9 g, 45.6 mmol) dissolved in CH_2Cl_2 (456 mL, 0.1M) was added (S)-5,6,7,8-tetrahydroquinolin-8-amine (**30**, 8.45 g, 57.0 mmol, 1.25 eq). The mixture was stirred at room temperature for 30 minutes, at which point sodium triacetoxyborohydride (14.51 g, 68.5 mmol, 1.5 eq) was added. The reaction was complete after 2 hours as monitored by LCMS. The mixture was diluted with 5 mL of 10% NaOH and 50 mL of brine. The fractions were separated and the aqueous phase extracted with CH_2Cl_2 (3 times). The organic layers were combined dried over anhydrous sodium sulfate, filtered and concentrated. The crude mixture was then purified on a 80 gram combiflash column with a gradient from 0-20% MeOH in CH_2Cl_2 to afford 1-benzyl 4-tert-butyl-2-((((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4,dicarboxylate (12.5 g, 57% yield). ^{1}H NMR (400Hz, $CDCl_3$): δ 1.40 (s, 9H), 1.49-1.79 (m, 1H), 1.79-1.95 (m, 1H), 2.58-3.11 (m, 7H), 3.46-3.61 (m, 1H), 3.64-3.76 (m, 1H), 3.81-3.95 (m, 4H), 4.11-4.30 (m, 2H), 5.05-5.12 (m, 2H), 6.98 (dd, J = 7.7, 4.7 Hz, 1H), 7.15-7.38 (m, 6H), 8.22-8.31 (m, 1H); ^{13}C NMR (150Hz, $CDCl_3$): δ 19.75, 28.49, 28.96, 39.61, 42.75, 44.14, 45.12, 51.89, 52.82, 60.55, 67.51, 67.60, 80.32, 122.00, 128.09, 128.59, 128.70, 132.53, 136.71, 136.99, 146.85, 146.97, 155.12, 157.50.



*1-Benzyl 4-(tert-butyl) 2-(R/S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**64a/b**).*

To a solution of 1-benzyl 4-tert-butyl 2-((((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate from the previous step (**62**, 2.5 g, 5.2 mmol) in DCE (52 ml, .1 M) was added tert-butyl (4-oxobutyl)carbamate (**37**, 1.17 g, 6.2 mmol, 1.2 eq) After stirring at room temperature for 30 minutes sodium triacetoxyborohydride (1.65 g, 7.80 mmol, 1.5 eq) was added as one portion. The reaction was tracked by LCMS and went to completion overnight. The mixture was filtered and then partitioned between water and DCM. The aqueous layer was basified and extracted with DCM (3 times). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude mixture was then purified on a 40 gram combiflash column with a step wise gradient from 0 to 15%

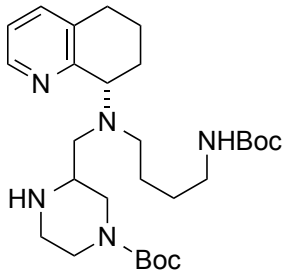
MeOH in DCM to afford 1-benzyl 4-tert-butyl 2-(R/S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**64a/b**, 2.13 g, 63% yield) as a mixture of diasteromers.



*1-benzyl 4-(tert-butyl) 2-(S-((4-(((benzyloxy)carbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**65a**) and 1-benzyl 4-(tert-butyl) 2-(R-((4-(((benzyloxy)carbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**65b**).*

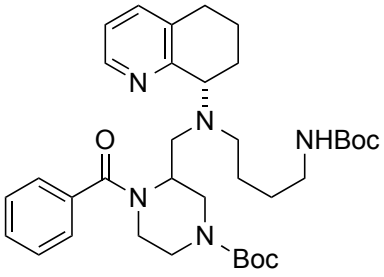
To a solution of 1-benzyl 4-tert-butyl 2-(R/S-(((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**62**, 2.0 g, 4.2 mmol) in DCM (42 ml, .1 M) was added benzyl (4-oxobutyl)carbamate (**63**, 1.38 g, 6.2 mmol, 1.5 eq) After stirring at room temperature for 30 minutes sodium triacetoxyborohydride (1.54 g, 7.3 mmol, 1.75 eq) was added as one portion. The reaction was tracked by LCMS and went to completion overnight. The mixture was filtered and then partitioned between water and DCM. The aqueous layer was basified and extracted with DCM (3 times). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude mixture was then purified on a 40 gram combiflash column with a step wise gradient from 0 to 15% MeOH in DCM to afford separate diastereomers of 1-benzyl 4-tert-butyl 2-(((4-(((benzyloxy)carbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**65**, 2.0 g, 70% combined yield).

Physical data for 1-benzyl 4-tert-butyl 2-(*R*-((4-(((benzyloxy)carbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate **65b** (LRF, 0.9 g)
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 – 8.22 (m, 1H), 7.52 – 7.15 (m, 11H), 7.05 (d, *J* = 7.7 Hz, 1H), 5.20 – 4.93 (m, 4H), 4.32 – 3.62 (m, 4H), 3.31 – 2.87 (m, 5H), 2.85 – 2.53 (m, 5H), 1.98 – 1.80 (m, 2H), 1.81 – 1.49 (m, 3H), 1.38 (s, 9H). HRMS calc'd for $C_{40}H_{48}O_6N_5$ 686.39121; found 686.39195 [M+H]
Physical data for 1-benzyl 4-tert-butyl 2-(*S*-((4-(((benzyloxy)carbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate **65a** URF (1.1g): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 – 8.37 (m, 1H), 7.37 – 7.22 (m, 11H), 7.00 (dd, *J* = 7.7, 4.7 Hz, 1H), 5.17 – 4.98 (m, 4H), 4.31 – 3.72 (m, 4H), 3.21 – 2.49 (m, 10H), 2.48 – 2.16 (m, 1H), 1.99 – 1.73 (m, 1H), 1.63 (m, 1H), 1.41 (s, 9H), 1.31 – 1.13 (m, 2H). HRMS calc'd for $C_{40}H_{48}O_6N_5$ 686.39121; found 686.39189 [M+H].



*4-(tert-butyl) 2-(R/S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**66a/b**).*

To a solution of 1-benzyl 4-tert-butyl 2-(R/S-((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1,4-dicarboxylate (**64a/b**, 1.7 g, 2.6 mmol) in EtOH (26 ml, .1 M) and AcOH (2.6 ml) was added Pd/C (170 mg, 10% by weight). The reaction was then hydrogenated under a 50 psi atmosphere of H_2 via a parr hydrogenator overnight. Upon completion the H_2 was purged under vacuum and then flushed with argon. The crude reaction mixture was then filtered through two fluted pieces of filter paper and concentrated in vacou. The mixture was then diluted with brine and DCM followed by basification with 10% NaOH. The layers were separated and the aqueous layer extracted with DCM (3 times). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford the crude mixture of diasteromers tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (1.34 g, 99% yield) which was taken on without further purification.

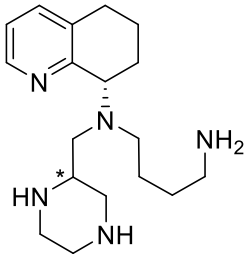


*tert-Butyl (S)-4-benzoyl-3-(((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**67a**).*

Prepared by general acylation procedure from diastereomeric mixture **66a/b** and purified on a 4 gram Combiflash column with a gradient of 0-12% MeOH in CH_2Cl_2 (137 mg, 67% combined yield over two steps). HRMS Calc. for $C_{35}H_{52}O_5N_5$ (M+H): 622.39630, Found: 622.39652.

*tert-Butyl (R)-4-benzoyl-3-(((4-((tert-butoxycarbonyl)amino)butyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazine-1-carboxylate (**67b**).*

Prepared by general acylation procedure from diastereomeric mixture **66a/b** and purified on a 4 gram combiflash column with a gradient of 0-12% MeOH in CH_2Cl_2 (106 mg, 67% combined yield over two steps). HRMS Calc. for $C_{35}H_{52}O_5N_5$ (M+H): 622.39630, Found: 622.39647.

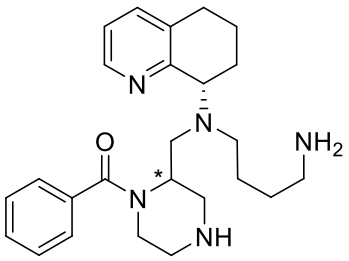


*N^1-(R-piperazin-2-ylmethyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**68a**) and N^1-(S-piperazin-2-ylmethyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine (**68b**).*

Prepared by general Boc deprotection procedure in trifluoroacetic acid from **65a** and **65b** respectively. Taken on crude to the hydrogentation procedure for each material described previously in the preparation of **66a/b**.

For **68b** - Purified on 4 gram combiflash column with a gradient of 3-20% MeOH (3.5N NH_4) in DCM to afford: **68b** (LRF) (26 mg, 44% yield over two steps): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 – 8.36 (m, 1H), 7.46 – 7.26 (m, 1H), 7.11 – 6.98 (m, 1H), 3.95 (tq, *J* = 14.8, 8.4, 7.8 Hz, 1H), 3.16 – 3.01 (m, 1H), 2.98 – 2.35 (m, 14H), 2.12 – 1.84 (m, 2H), 1.84 – 1.55 (m, 3H), 1.54 – 1.32 (m, 4H), 1.32 – 1.10 (m, 2H), 0.94 – 0.67 (m, 2H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 157.59, 147.09, 137.46, 134.66, 122.26, 60.97, 54.31, 51.70, 49.26, 45.43, 45.13, 40.68, 29.49, 28.64, 26.53, 23.52, 21.87. LCMS 95% MeOH:H_2O w/ .1% formic acid >95% pure rt= 0.403. HRMS calc'd for $C_{18}H_{32}N_5$ 318.26522; found 318.26517 [M+H].

For **68a** (URF): (58 mg, 89% yield over two steps) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 – 8.25 (m, 1H), 7.41-7.25 (m, 1H), 7.11 – 6.94 (m, 1H), 3.99 (q, *J* = 7.8, 7.3 Hz, 1H), 3.38 (d, *J* = 3.7 Hz, 2H), 3.28 – 2.28 (m, 13H), 2.26 – 1.80 (m, 2H), 1.80 – 1.28 (m, 4H), 1.28 – 0.96 (m, 4H), 0.96 – 0.64 (m, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 157.58, 147.05, 137.37, 134.40, 122.20, 61.92, 53.66, 50.43, 49.23, 45.92, 45.48, 40.37, 29.89, 29.43, 26.60, 21.96, 14.34. LCMS 95% MeOH:H_2O w/ .1% formic acid >95% pure rt= 0.413. HRMS calc'd for $C_{18}H_{32}N_5$ 318.26522; found 318.26521 [M+H].



*(2-(R-((4-aminobutyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazin-1-yl)(phenyl)methanone (**69a**) and (2-(S-((4-aminobutyl)((S)-5,6,7,8-tetrahydroquinolin-8-yl)amino)methyl)piperazin-1-yl)(phenyl)methanone (**69b**).*

Prepared by general Boc-deprotection procedure from materials **67a** and **67b**.

69a was purified on 4 gram Combiflash column with a gradient of 3-20% MeOH (3.5N NH_4) in CH_2Cl_2 (42 mg, 62% yield). ^{1}H NMR (400Hz, $CDCl_3$): δ 1.12-1.3 (m, 2H), 1.43-1.67 (m, 7H), 1.67-1.82 (m, 1H), 1.83-2.09 (m, 1H), 2.11-2.46 (m, 1H), 2.49-3.00 (m, 9H), 3.18 (t, J = 11.3 Hz, 1H), 3.29 (d, J = 13.3 Hz, 1H), 3.34-3.43 (m, 2H), 3.62-3.82 (m, 2H), 4.05-4.20 (m, 1H), 4.22-4.37 (m, 1H), 4.72-4.84 (m, 1H), 6.99-7.10 (m,

1H), 7.29-7.42 (m, 5H), 7.41-7.56 (m, 1H), 8.37-8.52 (m, 1H); ^{13}C NMR (100Hz, $CDCl_3$): δ 18.67, 21.93, 24.56, 26.00, 28.68, 29.45, 39.10, 41.50, 45.93, 46.35, 50.99, 51.86, 121.92, 127.01, 127.56, 128.83, 129.65, 132.21, 137.03, 147.16; MS: m/z (M+H) ; HRMS Calc. for $C_{25}H_{36}O_1N_5$ (M+H): 422.29144, Found: 422.29169; Purity is determined by LC-MS: 75% MeOH over 3 min) Area% 100.00 (Retention time:).

69b was purified on 4 gram Combiflash column with a gradient of 3-20% MeOH (3.5N NH_4) in CH_2Cl_2 (49 mg, 80% yield). ^{1}H NMR (400Hz, $CDCl_3$): δ 0.97~1.24 (m, 2H), 1.30~1.76 (m, 7H), 1.76-2.08 (m, 1H), 2.41~2.53 (m, 1H), 2.53~2.89 (m, 9H), 2.89~3.12 (m, 1H); 3.17~3.37 (m, 2H), 3.48~3.68 (m, 2H), 4.03~4.19 (m, 1H),), 4.33 (d, J = 10.8 Hz, 1H), 4.53~4.67 (m, 1H), 7.01 (dd, J = 7.7, 4.7 Hz, 1H), 7.32 (dt, J = 12.1, 6.3 Hz, 4H), 7.36~7.41 (m, 2H), 8.38 (s, 1H); ^{13}C NMR (150Hz, $CDCl_3$): δ 21.83, 26.61, 28.59, 29.39, 29.78, 31.65, 42.34, 45.94, 51.78, 53.07, 54.79, 61.18, 121.57, 127.01, 128.57, 129.43, 136.63, 146.78, 159.01, 171.64; MS: m/z (M+H) ; HRMS Calc. for $C_{25}H_{36}O_1N_5$ (M+H): 422.29144, Found: 422.29156; Purity is determined by LC-MS: 75% MeOH over 3 min) Area% 100.00 (Retention time: 1.947).