Design, Synthesis, and Characterization of Novel Small Molecules as Broad Range Anti-Schistosomal Agents

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Chemistry

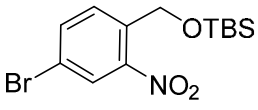
Chemicals were purchased from established commercial suppliers, including Sigma Aldrich (St. Louis, MO), Chembridge Corporation (San Diego, CA), ChemDiv (San Diego, CA), and Specs (Hopkinton, RI), Cayman (Ann Arbor, MI) and Pfaltz & Bauer (Waterbury, CT). The identity of all the tested compounds was confirmed by ^{1}H NMR and HPLC-MS, and the purity was ensured to be ≥ 95%.

General procedures. Unless otherwise indicated all reactions were conducted in standard commercially available glassware using standard synthetic chemistry methods and setup. All air- and moisture-sensitive reactions were performed under nitrogen atmosphere with dried solvents and glassware under anhydrous conditions. Starting materials and reagents were commercial compounds of the highest purity available and were used without purification. Solvents used for reactions were indicated as of commercial dry or extra-dry or analytical grade. Analytical thin-layer chromatograph (TLC) was carried out using silica gel 60 F_{254} TLC plates. TLC visualization was achieved with a UV lamp or by staining in an iodine chamber. Flash chromatography was done on a system using prepacked silica gel columns or using silica gel 60A (230-400 mesh) or with preparative thin-layer chromatography plates (1000 micron F_{254}), or using a Biotage Isolera One 2.2, using commercial columns that were pre-packed with Merck Kieselgel 60 (230– 400 mesh) silica gel. Solvent systems employed consisted of (EtOAc/Hex or DCM/MeOH or DCM/MeOH/Conc. NH_4OH). All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen. Final compounds for biological testing are all ≥95% purity as determined by HPLC-MS and ^{1}H NMR.

NMR. ^{1}H NMR experiments were recorded on Agilent DD2 400MHz spectrometers at ambient temperature. Samples were dissolved and prepared in deuterated solvents ($CDCl_3$, CD_3OD and $DMSOd_6$) with residual solvents being used as the internal standard in all cases. All deuterated solvent peaks were corrected to the standard chemical shifts ($CDCl_3$, d_H = 7.26 ppm; CD_3OD, d_H = 3.31 ppm; DMSO-d_6, d_H = 2.50 ppm). Spectra were all manually integrated after automatic baseline correction. Chemical shifts (*d*) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz). The proton spectra are reported as follows: d (multiplicity, coupling constant *J*, number of protons). The following abbreviations were used to explain the

multiplicities: app = apparent, b = broad, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, m = multiplet, s = singlet, t = triplet, ABq = AB quartet.

HPLC-MS. All samples were analyzed on Agilent 1290 series HPLC system comprised of binary pumps, degasser and UV detector, equipped with an auto-sampler that is coupled with Agilent 6150 mass spectrometer. Purity was determined via UV detection with a bandwidth of 170nm in the range from 230-400nm. The general LC parameters were as follows: Column - Zorbax Eclipse Plus C18, size 2.1 x 50 mm; Solvent A: 0.10 % formic acid in water, Solvent B: 0.00 % formic acid in acetonitrile; Flow rate – 0.7 mL/min; Gradient: 5 % B to 95 % B in 5 minutes and hold at 95 % B for 2 min; UV detector – channel 1 = 254 nm, channel 2 = 254 nm. Mass detector Agilent Jet Stream – Electron Ionization (AJS-ES).



*((4-bromo-2-nitrobenzyl)oxy)(tert-butyl)dimethylsilane (**6**):*

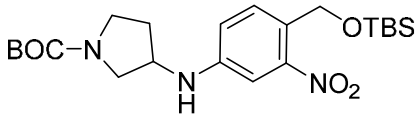
To a flame-dried 3-neck 250 mL RBF equipped with a stir bar and N_2 outlet, added 4-bromo-2-nitrobenzoic acid (13.68 g, 55.6 mmol), followed by anhydrous THF (56 mL). After thoroughly flushing the apparatus with N_2, the stirring solution was cooled to 0 ^oC and 223 mL of 1M BH_3THF (223 mmol) was added dropwise via addition funnel over 40 min. The reaction was allowed to warm to room temperature and stir for 18 hours. The reaction was then cooled to 0^oC and quenched upon slow addition of MeOH until bubbling ceased. The resulting solution was concentrated under reduced pressure to yield a yellow solid. The resulting solid was dissolved in EtOAc and washed with equal amounts of H_2O, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, decanted and concentrated in under reduced pressure to provide 12.41 g, 96.1 % of (4-bromo-2-nitrophenyl)methanol as a beige solid. The crude product was used in the next step without further purification. ^1H NMR (400 MHz, DMSO) δ 8.22 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 5.63 (t, J = 5.3 Hz, 1H), 4.77 (d, J = 5.2 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_7H_7BrNO_3$ [M+1]: 232.0, [M+3]: 234.0; found, 232.0, 234.0.

To a stirring solution of (4-bromo-2-nitrophenyl)methanol (12.30 g, 53.0 mmol) and tert-butyldimethylsilyl chloride (8.07, 53.6 mmol) in DMF (71.0 mL) at 0 ^oC, was added imidazole

(10.87g, 158 mmol) and the resulting reaction was allowed to slowly warm to room temperature. After 36 hours, 140 mL of H_2O was added, the resulting solution was extracted with hexanes (2 x 50 mL), the combined organic layers were washed with brine (2 x 100mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by flash chromatography, eluting with 100% hexanes, collecting 120 mL fractions. Fractions 1 to 6 were collected and concentrated under reduced pressure to yield 14.30 g, 77.8 % of **6** as a clear off yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.79 (s, 2H), 5.03 (d, *J* = 2.2 Hz, 2H), 0.95 (s, 10H), 0.13 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.75, 137.44, 136.76, 129.65, 127.36, 61.83, 25.85, 18.32, -5.46.

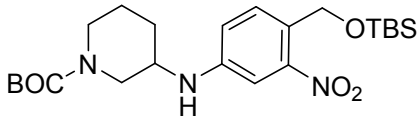
*Representative procedure for the Buchwald coupling of **6**.*

To a stirring solution of **6** (1.2 equiv.) in 1,4-dioxane (14.0 mL) at room temperature, added the appropriate N-BOC amine (1 equiv.), Cs_2CO_3 (3.5 equiv.) and (±)-BINAP (0.07 equiv.). A stream of N_2 gas was bubbled through the solution for 5 minutes, after which time $Pd(OAc)_2$ (0.07 equiv.) was added. The reaction was heated to reflux for 12 hours under positive N_2, cooled to room temperature, diluted with EtOAc, filtered over celite and the celite pad was washed with EtOAc. The resulting crude solution was concentrated under reduced pressure to yield a brown oil. Purification was accomplished by flash chromatography, eluting with solvent gradients of EtOAc and hexanes. Product containing fractions were collected and concentrated to yield the desired compounds of general structure **7**. The following compounds were prepared using the general method described above.

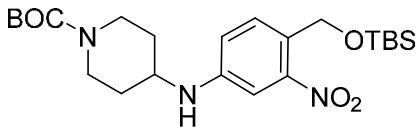


The following compound was prepared using the general method described above, employing *tert*-butyl 3-aminopyrrolidine-1-carboxylate as the N-BOC amine reagent. *tert-butyl-3-((4-(((tert-butyldimethylsilyl)oxy)methyl)-3-nitrophenyl)amino)pyrrolidine-1-carboxylate.* Orange solid: 927.6 mg, 70.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 2.7 Hz, 1H), 6.87 (dd, J = 8.6, 2.6 Hz, 1H), 4.97 (s, 2H), 4.07 (s, 1H), 3.97 (d, J = 6.6 Hz, 1H), 3.72 (s, 1H), 3.49 (s, 2H), 3.26 (dd, J = 34.7, 11.3 Hz, 1H), 2.22 (dtd, J = 13.3, 7.9, 5.6 Hz, 1H), 1.91 (s, 1H), 1.47 (s, 9H), 0.95 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 154.54, 147.33, 146.16, 129.07,

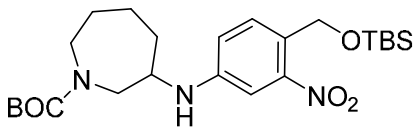
126.71, 118.51, 107.68, 79.66, 61.89, 52.95, 52.18, 51.86, 43.98, 43.70, 31.55, 30.95, 28.46, 25.91, 18.35, -5.44. ESI-MS (m/z): m/z calcd for $C_{18}H_{30}N_3O_5Si$ [M+1-C_4H_9]: 396.2; found, 396.2.



The following compound was prepared using the general method described above, employing *tert-butyl 3-aminopiperidine-1-carboxylate* as the N-BOC amine reagent. *tert-butyl-3-((4-(((tert-butyldimethylsilyl)oxy)methyl)-3-nitrophenyl)amino)piperidine-1-carboxylate.* Orange oil: 3.35 g, 57.9%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.95 (s, 2H), 3.89 (d, *J* = 9.2 Hz, 1H), 3.63 (d, *J* = 11.5 Hz, 1H), 3.43 (m, 1H), 3.16 (m, 1H), 3.00 (dd, *J* = 12.8, 7.3 Hz, 1H), 1.98 (m, 1H), 1.72 (m, 1H), 1.57 (d, *J* = 7.3 Hz, 2H), 1.43 (s, 9H), 0.93 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.02, 147.56, 146.24, 129.24, 126.40, 118.38, 107.96, 80.11, 62.07, 48.92, 48.82, 44.48, 30.423, 28.50, 26.06, 23.15, 18.50, -5.27. ESI-MS (m/z): m/z calcd for $C_{19}H_{32}N_3O_5Si$ [M+1-C_4H_9]: 410.2; found, 410.2.

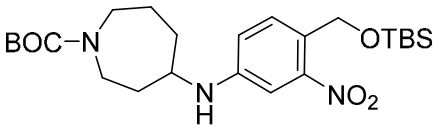


The following compound was prepared using the general method described above, employing *tert-butyl 4-aminopiperidine-1-carboxylate* as the N-BOC amine reagent. *tert-butyl-4-((4-(((tert-butyldimethylsilyl)oxy)methyl)-3-nitrophenyl)amino)piperidine-1-carboxylate.* Orange oil: 1.36 g, 71.1%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 1H), 7.27 (s, 1H), 6.86 (d, *J* = 10.9 Hz, 1H), 4.96 (s, 2H), 4.07 (m, 2H), 3.77 (d, *J* = 7.4 Hz, 1H), 3.47 (m, 1H), 2.95 (t, *J* = 12.6 Hz, 2H), 2.04 (m, 2H), 1.47 (s, 9H), 1.35 (m, 2H), 0.95 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.69, 148.41, 146.6, 129.04, 126.29, 118.56, 107.66, 79.73, 61.91, 50.15, 42.51, 32.09, 28.40, 25.91, 18.35, -5.44. ESI-MS (m/z): m/z calcd for $C_{19}H_{32}N_3O_5Si$ [M+1-C_4H_9]: 410.2; found, 410.2.

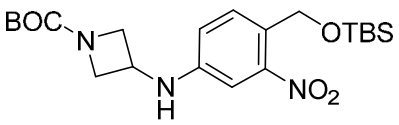


The following compound was prepared using the general method described above, employing *tert-butyl 3-aminoazepane-1-carboxylate* as the N-BOC

amine reagent. *tert-butyl-3-((4-(((tert-butyldimethylsilyl)oxy)methyl)-3-nitrophenyl)amino)azepane-1-carboxylate.* Orange oil: 713.2 mg, 66.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 1H), 7.22 (s, 2H), 6.89 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.93 (s, 1H), 4.77 (d, *J* = 8.7 Hz, 2H), 4.00 (d, *J* = 8.2 Hz, 1H), 3.67 (m, 2H), 3.53 (m, 2H), 3.40 (m, 1H), 3.14 (m, 1H), 2.01 (m, 2H), 1.74 (m, 4H), 1.47 (s, 9H), 0.93 (s, 9H), 0.09 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.85, 147.43, 146.63, 128.96, 127.38, 118.46, 107.84, 79.78, 61.86, 53.47, 52.13, 48.94, 34.21, 28.55, 28.41, 25.90, 22.24, 18.38, -5.44. ESI-MS (m/z): m/z calcd for $C_{20}H_{34}N_3O_5Si$ [M+1-C_4H_9]: 424.2; found, 424.2.



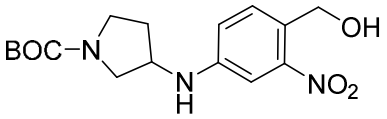
The following compound was prepared using the general method described above, employing *tert-butyl 4-aminoazepane-1-carboxylate* as the N-BOC amine reagent. *tert-butyl-4-((4-(((tert-butyldimethylsilyl)oxy)methyl)-3-nitrophenyl)amino)azepane-1-carboxylate.* Orange oil: 669.1 mg, 61.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 1H), 7.19 (s, 1H), 6.78 (dd, *J* = 8.6, 1.3 Hz, 1H), 4.94 (s, 2H), 3.85 (s, 1H), 3.66 (d, *J* = 14.5 Hz, 1H), 3.46 (s, 4H), 3.26 (s, 1H), 2.12 (d, *J* = 15.3 Hz, 1H), 1.96 (d, *J* z= 14.7 Hz, 1H), 1.86 (m, 1H), 1.66 (m, 2H), 1.52 (m, 1H), 1.46 (s, 9H), 0.93 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.51, 147.38, 145.50, 129.04, 127.53, 118.872, 108.35, 79.54, 61.92, 46.53, 45.80, 43.03, 34.50, 32.77, 28.49, 25.91, 24.68, 18.36, -5.44. ESI-MS (m/z): m/z calcd for $C_{20}H_{34}N_3O_5Si$ [M+1-C_4H_9]: 424.2; found, 424.2.



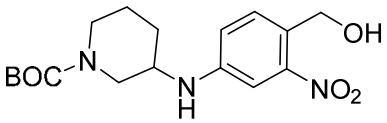
The following compound was prepared using the general method described above, employing *tert-butyl 3-aminoazetidine-1-carboxylate* as the N-BOC amine reagent. *tert-butyl-3-((4-(((tert-butyldimethylsilyl)oxy)methyl)-3-nitrophenyl)amino)azetidine-1-carboxylate.* Orange oil: 175.0 mg, 39.4%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.81 6.81 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.97 (s, 2H), 4.34 (m, 3H), 4.24 (m, 1H), 3.75 (dd, *J* = 9.2, 4.5 Hz, 2H), 1.45 (s, 9H), 0.95 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.10, 148.29, 145.41, 129.20, 127.62, 118.45, 107.74, 79.90, 61.86, 56.63, 43.07, 28.33, 25.90, 18.34, -544. ESI-MS (m/z): m/z calcd for $C_{17}H_{28}N_3O_5Si$ [M+1-C_4H_9]: 382.2; found, 382.2.

Representative procedure for the silyl deprotection of compound 7.

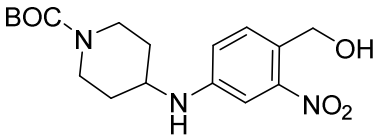
To a stirring solution of **7** in THF (40 mL) at -10 ^{o}C, was added a 1.0 M Tetrabutylammonium Fluoride (1.2 equiv) solution in THF dropwise over 8 minutes and the resulting reaction was allowed to slowly warm to room temperature. After 2 hours, 50 mL of brine and 50 mL of EtOAc were added to quench the reaction. Layers were separated and washed organic with brine (3 x 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by flash chromatography, eluting with a solvent gradient of EtOAc/hexanes. Product containing fractions were collected and concentrated to yield the desired compounds. The following compounds were prepared using the general method described above.



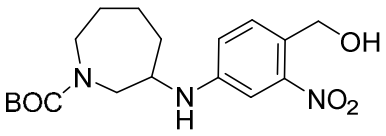
tert-butyl-3-((4-(hydroxymethyl)-3-nitrophenyl)amino)pyrrolidine-1-carboxylate. Orange solid: 591.7 mg, 86.7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 2.6 Hz, 1H), 6.83 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.76 (d, *J* = 6.9 Hz, 2H), 4.08 (m, 1H), 3.71 (s, 1H), 3.48 (s, 2H), 3.27 (dd, *J* = 34.0, 10.4 Hz, 1H), 2.60 (t, *J* = 6.9 Hz, 1H), 2.23 (dtd, *J* = 13.1, 7.9, 5.5 Hz, 1H), 1.92 (s, 1H), 1.47 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 154.71, 149.17, 147.28, 132.14, 125.17, 118.43, 108.24, 79.93, 62.58, 53.01, 52.25, 51.96, 51.67, 44.13, 43.81, 31.67, 31.08, 28.61. ESI-MS (m/z): m/z calcd for $C_{12}H_{16}N_3O_5$ [M+1-C_4H_9]: 282.1; found, 282.1.



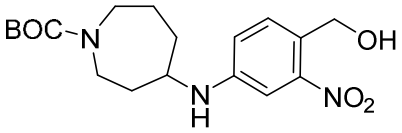
tert-butyl-3-((4-(hydroxymethyl)-3-nitrophenyl)amino)piperidine-1-carboxylate. Orange oil: 2.14 g, 89.7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.75 (d, *J* = 4.3 Hz, 2H), 4.04 (m, 1H), 3.90 (dd, *J* = 12.7, 3.0 Hz, 1H), 3.62 (m, 1H), 3.46 (m, 1H), 3.20 (m, 1H), 3.05 (dd, *J* = 13.2, 7.5 Hz, 1H), 2.59 (m, 1H), 1.99 (m, 1H), 1.74 (m, 1H), 1.59 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.42, 149.11, 147.07, 132.05, 124.51, 118.01, 108.08, 80.02, 62.45, 48.66, 48.55, 30.17, 28.34, 22.92. ESI-MS (m/z): m/z calcd for $C_{13}H_{18}N_3O_5$ [M+1-C_4H_9]: 296.1; found, 296.1.



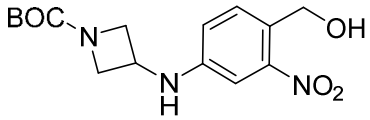
tert-butyl-4-((4-(hydroxymethyl)-3-nitrophenyl)amino)piperidine-1-carboxylate. Orange oil: 863.4 mg, 86.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.75 (d, *J* = 5.1 Hz, 2H), 4.08 (m, 2H), 3.89 (m, 1H), 3.47 (3, 1H), 2.95 (t, *J* = 13.5 Hz, 2H), 2.58 (t, *J* = 6.9 Hz, 1H), 2.04 (d, *J* = 11.6 Hz, 2H), 1.47 (s, 9H), 1.36 (d, *J* = 9.6 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.68, 149.13, 147.05, 132.04, 124.52, 118.30, 107.99, 79.81, 62.46, 50.04, 42.40, 31.99, 28.40. ESI-MS (m/z): m/z calcd for $C_{13}H_{18}N_3O_5$ [M+1-C_4H_9]: 296.1; found, 296.1.



tert-butyl 3-((4-(hydroxymethyl)-3-nitrophenyl)amino)azepane-1-carboxylate. Orange oil: 462.1 mg, 87.4%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.6 Hz, 1H), 7.23 (s, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 4.94 (s, 1H), 4.73 (d, *J* = 5.3 Hz, 2H), 3.67 (m, 2H), 3.55 (m, 2H), 3.43 (m, 1H), 3.16 (m, 1H), 2.55 (s, 1H), 2.02 (m, 1H), 1.78 (d, *J* = 10.7 Hz, 2H), 1.68 (d, *J* = 11.9 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.69, 149.15, 147.38, 132.07, 123.89, 118.36, 108.10, 79.93, 62.57, 53.58, 51.89, 48.94, 32.65, 28.57, 28.40, 22.20. ESI-MS (m/z): m/z calcd for $C_{14}H_{20}N_3O_5$ [M+1-C_4H_9]: 310.1; found, 310.1.



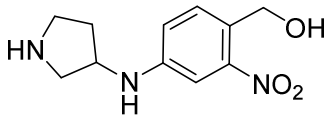
tert-butyl 4-((4-(hydroxymethyl)-3-nitrophenyl)amino)azepane-1-carboxylate. Orange oil: 426.0 mg, 85.5%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 4.74 (d, *J* = 5.8 Hz, 2H), 3.97 (m, 1H), 3.68 (m, 1H), 3.47 (m, 4H), 3.28 (m, 1H), 2.57 (t, *J* = 6.3 Hz, 1H), 2.14 (d, *J* = 14.0 Hz, 1H), 1.90 (m, 2H), 1.68 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.40, 149.10, 146.99, 131.99, 124.34, 118.28, 108.14, 79.60, 62.45, 53.11, 46.58, 42.99, 34.65, 32.76, 28.48, 24.63. ESI-MS (m/z): m/z calcd for $C_{14}H_{20}N_3O_5$ [M+1-C_4H_9]: 310.1; found, 310.1.



tert-butyl 3-((4-(hydroxymethyl)-3-nitrophenyl)amino)azetidine-1-carboxylate. Orange oil: 84.6 mg, 80.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.2 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 2H), 4.41 (d, *J* = 6.4 Hz, 1H), 4.34 (dd, *J* = 8.9, 6.4 Hz, 2H), 4.25 (m, 1H), 3.75 (dd, *J* = 8.9, 4.6 Hz, 2H), 2.58 (t, *J* = 5.9 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.25, 149.15, 146.53, 132.24, 126.08, 118.46, 108.31, 80.19, 62.57, 56.74, 43.15, 28.50. ESI-MS (m/z): m/z calcd for $C_{14}H_{20}N_3O_5$ [M+1-C_4H_9]: 268.1; found, 268.1.

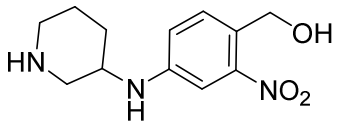
<u>*Representative procedure for the tertbutylcarbamate deprotection.*</u>

To a flame dried 50 mL RBF equipped with a stir bar and N_2 outlet was added the BOC-protected amine (1 equiv.), followed by anhydrous DCM (0.2 M). After thoroughly flushing the apparatus with N_2, the stirring solution was cooled to -10 ^{o}C. After 10 minutes, neat BF_3OEt_2 (3 equiv.) was added dropwise over 6 minutes. Upon addition, the yellow solution turned bright red followed by a red oil precipitating from solution. The reaction was allowed to warm to room temperature and stir for 1 hour at which point the reaction was quenched with 5 mL of saturated $NaHCO_3$. The orange aqueous layer was extracted with a 1:3 mixture of isopropanol to chloroform (6 x 20 mL), dried organic extracts over Na_2SO_4, and concentrated *in vacuo*. Purification was accomplished by flash chromatography, eluting with a solvent gradient of EtOAc/hexanes. Product containing fractions were collected and concentrated to yield the desired compounds of general structure **8**. The following compounds were prepared using the general method described above.

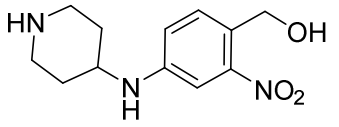


*(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol (**9a**).* Red oil: 320.1 mg, 77.0%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.5, 2.4 Hz, 1H), 4.76 (s, 2H), 3.99 (s, 1H), 3.18 (dd, J = 11.6, 6.1 Hz, 1H), 3.07 (dt, J = 11.3, 7.4 Hz, 1H), 2.96 (ddd, J = 11.4, 8.2, 5.8 Hz, 1H), 2.79 (dd, J = 11.7, 3.9 Hz, 1H), 2.19 (dt, J = 15.3, 7.2 Hz, 1H), 1.70 (m, 1H). ^{13}C NMR (400 MHz, CD_3OD) δ 149.99, 149.29, 131.33, 125.48, 118.71, 108.64, 61.84, 54.44, 52.86, 45.93, 33.21. ESI-MS (m/z): m/z calcd for

$C_{11}H_{15}N_3O_3$ [M+1]: 238.1; found, 238.1. HRMS (EI): m/z calcd for $C_{11}H_{15}N_3O_3$ [M+1]: 238.1186; found, 238.1186.



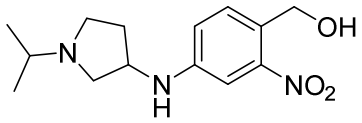
(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol. ***(10a)*** Orange oil: 1.33 g, 87.4%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.75 (s, 2H), 3.49 (m, 1H), 3.05 (dt, *J* = 13.0, 3.9 Hz, 1H), 2.70 (ddd, *J* = 12.6, 11.1, 3.3 Hz, 1H), 2.51 (dd, *J* = 12.3, 9.4 Hz, 1H), 2.09 (dd, *J* = 13.1, 3.5 Hz, 1H), 1.87 (m, 1H), 1.67 (m, 1H), 1.50 (m, 1H). ^{13}C NMR (400 MHz, CD_3OD) δ 150.14, 149.07, 131.42, 125.08, 118.51, 108.32, 61.86, 51.13, 50.03, 46.37, 31.42, 25.19. ESI-MS (m/z): m/z calcd for $C_{12}H_{17}N_3O_3$ [M+1]: 252.1; found, 252.1. HRMS (EI): m/z calcd for $C_{12}H_{17}N_3O_3$ [M+1]: 252.1343; found, 252.1341.



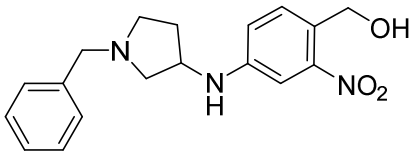
(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol. Orange oil: 609.1 mg, 99.0%. ^{1}H NMR (300 MHz, CD_3OD) δ 7.44 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.75 (s, 2H), 3.51 (m, 1H), 3.20 (dt, *J* = 7.0, 3.3 Hz, 2H), 2.87 (td, *J* = 12.4, 2.3 Hz, 2H), 2.09 (dd, *J* = 13.6, 3.3 Hz, 2H), 1.48 (ddd, *J* = 13.8, 11.3, 3.8 Hz, 2H). ^{13}C NMR (400 MHz, CD_3OD) δ 150.12, 149.22, 131.37, 124.61, 118.52, 108.49, 61.90, 50.81, 45.78, 33.59. ESI-MS (m/z): m/z calcd for $C_{12}H_{17}N_3O_3$ [M+1]: 252.1; found, 252.1. HRMS (EI): m/z calcd for $C_{12}H_{17}N_3O_3$ [M+1]: 252.1343; found, 252.1345.

Representative procedure for reductive amination reactions.

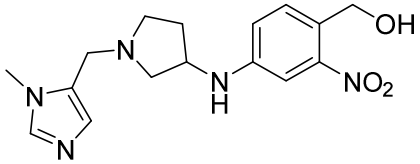
To a stirring solution of amine (1 equiv.) in 1,2-DCE (0.1 M), added the appropriate aldehyde or ketone (1.5 equiv.). After stirring for 1 hour at room temperature, $NaBH(OAc)_3$ (2.5 equiv) was added. The reaction was allowed to stir for 12-24 hours, at which point, reaction was quenched upon addition of 1.0 ml of saturated $NaHCO_3$ and 1.0 mL of EtOAc. Layers were separated then the aqueous portion was extracted EtOAc (3 x 10 mL). Combined organic fractions, dried over Na_2SO_4, and concentrated under reduced pressure. Purification crude product was carried out via by flash chromatography to afford the desired compounds of general structure **4**. The following compounds were prepared using the general method described above.



The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *propan-2-one* as the ketone reagent. *(4-((1-isopropylpyrrolidin-3-yl)amino)-2-nitrophenyl)methanol (**9b**)*. Orange oil: 48.5 mg, 63%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.67 (s, 2H), 3.91 (ddd, *J* = 13.2, 7.7, 4.8 Hz, 1H), 3.22 (dt, *J* = 3.3, 1.7 Hz, 1H), 2.95 (dd, *J* = 10.0, 7.1 Hz, 1H), 2.69 (ddd, *J* = 9.5, 7.7, 6.4 Hz, 1H), 2.58 (ddd, *J* = 9.5, 7.7, 6.4 Hz, 1H), 2.42 (dd, *J* = 10.0, 4.9 Hz, 1H), 2.35 (sept, *J* = 8.0 Hz, 1H), 2.23 (dtd, *J* = 14.2, 8.0, 6.1 Hz, 1H), 1.61 (m, 1H), 1.03 (t, *J* = 6.6 Hz, 6H). ESI-MS (m/z): m/z calcd for $C_{14}H_{22}N_3O_3$ [M+1]: 280.2; found, 280.2.

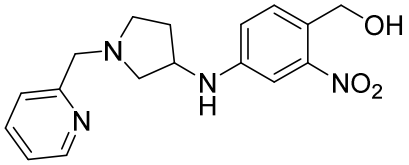


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *benzaldehyde* as the aldehyde reagent. *((4-((1-benzylpyrrolidin-3-yl)amino)-2-nitrophenyl)methanol (**9c**)*. Orange solid: 77.5 mg, 95%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, *J* = 8.5 Hz, 1H), 7.28 (m, 4H), 7.21 (m, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 6.82 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.72 (s, 2H), 3.95 (m, 1H), 3.60 (ABq, Δ ν_{AB} = 12.6 Hz, J_{AB}= 8.7 Hz, 2H), , 2.89 (dd, *J* = 9.9, 6.9 Hz, 1H), 2.69 (dd, *J* = 14.8, 8.7 Hz, 1H), 2.55 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.44 (dd, *J* = 9.9, 4.7 Hz, 1H), 2.28 (m, 1H), 1.64 (m , 1H). ESI-MS (m/z): m/z calcd for $C_{18}H_{22}N_3O_3$ [M+1]: 328.2; found, 328.2. HRMS (EI): m/z calcd for $C_{18}H_{22}N_3O_3$ [M+1]: 328.1656; found, 328.1665.

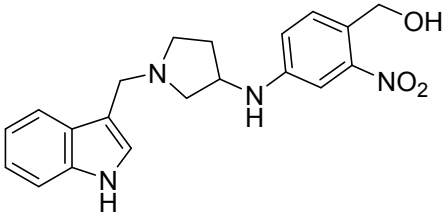


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *1-methyl-1H-imidazole-5-carbaldehyde* as the aldehyde reagent. *(4-((1-((1-methyl-1H-imidazol-5-yl)methyl)pyrrolidin-3-yl)amino)-2-*

*nitrophenyl)methanol (**9d**)*. Orange oil: 37.6 mg, 54%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.82 (s, 1H), 6.79 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.66 (s, 2H), 3.92 (s, 1H), 3.63 (s, 3H), 3.61 (d, *J* = 4.0 Hz, 3H), 2.83 (dd, *J* = 9.7, 6.8 Hz, 1H), 2.69 m, 1H), 2.50 (m, 1H), 2.44 (dd, *J* = 9.8, 4.4 Hz, 1H), 2.25 (m, 1H), 1.62 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{16}H_{21}N_5O_3$ [M+1]: 332.2; found, 332.2. HRMS (EI): m/z calcd for $C_{16}H_{21}N_5O_3$ [M+1]: 332.1717; found, 332.1706.

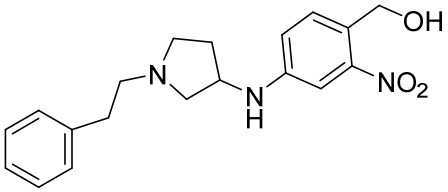


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *pyridine-2-carboxaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(pyridin-2-ylmethyl)pyrrolidin-3-yl)amino)phenyl)methanol (**9e**)*. Orange oil: 26.0 mg, 32%. ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.80 (td, *J* = 7.7, 1.8 Hz, 1H), 7.49 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.31 (ddd, *J* = 7.6, 5.0, 1.2 Hz, 1H), 7.17 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.73 (s, 2H), 4.07 (m, 1H), 3.95 (ABq, $\Delta \nu_{AB}$ = 9.7 Hz, J_{AB}= 13.7 Hz, 2H), 3.11 (dd, *J* = 10.2, 6.7 Hz, 1H), 2.98 (m, 1H), 2.81 (m, 1H), 2.72 (dd, *J* = 10.3, 4.4 Hz, 1H), 2.36 (m, 1H), 1.78 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{17}H_{20}N_4O_3$ [M+1]: 329.2; found, 329.2. HRMS (EI): m/z calcd for $C_{17}H_{20}N_4O_3$ [M+1]: 329.1608; found, 329.1603.

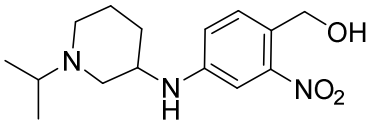


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *1H-indole-3-carbaldehyde* as the aldehyde reagent. *(4-((1-((1H-indol-3-yl)methyl)pyrrolidin-3-yl)amino)-2-nitrophenyl)methanol (**9f**)*. Orange oil: 59.8mg, 34%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.35 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.26 (s, 1H), 7.16 (d, *J* = 2.5 Hz, 1H), 7.11 (td, *J* = 7.5, 1.2 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.74 (s,

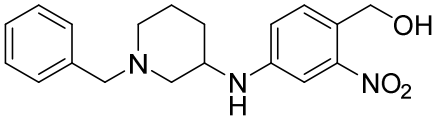
2H), 4.04 (m, 1H), 3.98 (s, 2H), 3.13 (dd, *J* = 11.0, 5.8 Hz, 1H), 2.91 (m, 1H), 2.82 (m, 1H), 2.66 (dd, *J* = 10.1, 4.8 Hz, 1H), 2.35 (s, 1H), 1.71 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}N_4O_3$ [M+1]: 367.2; found, 367.2. HRMS (EI): m/z calcd for $C_{20}H_{22}N_4O_3$ [M+1]: 367.1765; found, 367.1771.



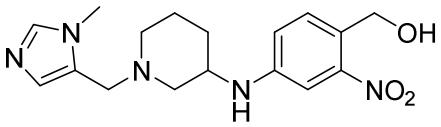
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-phenylacetaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-phenethylpyrrolidin-3-yl)amino)phenyl)methanol (**9g**)*. Orange oil: 51.2 mg, 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.28 (m, 2H), 7.20 (m, 3H), 6.77 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.45 (d, *J* = 7.9 Hz, 1H), 4.01 (m, 1H),2.96 (td, *J* = 8.6, 4.1 Hz, 1H), 2.79 (m, 2H), 2.71 (m, 3H), 2.39 (m, 2H), 1.68 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{23}N_3O_3$ [M+1]: 342.2; found, 342.2. HRMS (EI): m/z calcd for $C_{19}H_{23}N_3O_3$ [M+1]: 342.1812; found, 342.1814.



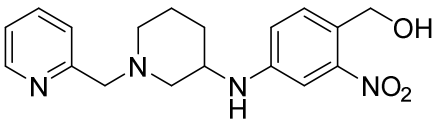
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *propan-2-one* as the ketone reagent. *(4-((1-isopropylpiperidin-3-yl)amino)-2-nitrophenyl)methanol (**10b**)*. Orange oil: 59.4 mg, 98%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.67 (s, 2H), 3.92 (m, 1H), 2.84 (dd, *J* = 9.8, 6.9 Hz, 1H), 2.61 (ddd, *J* = 9.3, 7.9, 6.3 Hz, 1H), 2.50 (ddd, *J* = 9.4, 7.8, 6.2 Hz, 1H), 2.22 (m,3H), 2.37 (dd, *J* = 9.8, 4.8 Hz, 1H), 1.69 (tt, *J* = 13.8, 6.8 Hz, 1H), 1.60 (dddd, *J* = 12.8, 8.0, 6.2, 4.7 Hz, 1H) 0.86 (dd, *J* = 6.6, 1.3 Hz, 6H). ESI-MS (m/z): m/z calcd for $C_{15}H_{24}N_3O_3$ [M+1]: 294.2; found, 294.2.



The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *benzaldehyde* as the aldehyde reagent. *(4-((1-benzylpiperidin-3-yl)amino)-2-nitrophenyl)methanol (**10c**).* Orange oil: 34.2 mg, 50%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.30 (d, *J* = 8.5 Hz, 1H), 7.21 (m, 4H), 7.15 (m, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.64 (s, 2H), 3.44 (s, 2H), 3.40 (m, 1H), 2.88 (d, *J* = 11.2 Hz, 1H), 2.63 (d, *J* = 11.0 Hz, 1H), 2.03 (t, *J* = 9.4 Hz, 1H), 1.83 (m, 2H), 1.62 (m, 2H), 1.21 (m, 1H). ^{13}C NMR (400 MHz, CD_3OD) δ 148.61, 147.73, 137.00, 129.94, 129.12, 127.90, 126.96, 123.39, 117.09, 106.96, 62.60, 60.48, 57.92, 53.05, 48.86, 29.72, 23.11. ESI-MS (m/z): m/z calcd for $C_{19}H_{23}N_3O_3$ [M+1]: 342.2; found, 342.2. HRMS (EI): m/z calcd for $C_{19}H_{23}N_3O_3$ [M+1]: 342.1812; found, 342.1822.

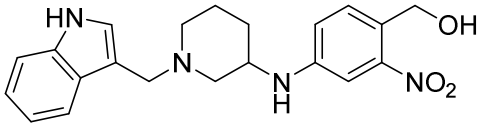


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *1-methyl-1H-imidazole-5-carbaldehyde* as the aldehyde reagent. *(4-((1-((1-methyl-1H-imidazol-5-yl)methyl)piperidin-3-yl)amino)-2-nitrophenyl)methanol (**10d**).* Orange oil: 47.0 mg, 68%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.73 (s, 1H), 4.65 (s, 2H), 3.44 (ABq, $\Delta\nu_{AB}$ = 11.8, Hz, J_{AB}= 14.0 Hz, 2H), 3.38 (m, 1H), 2.82 (d, *J* = 10.7 Hz, 1H), 2.60 (d, *J* = 11.2 Hz, 1H), 2.08 (t, *J* = 10.2 Hz, 1H), 1.87 (m, 2H), 1.69 m, 1H), 1.53 (m, 1H), 1.26 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{17}H_{23}N_5O_3$ [M+1]: 346.2; found, 346.2. HRMS (EI): m/z calcd for $C_{17}H_{23}N_5O_3$ [M+1]: 346.1874; found, 346.1876.

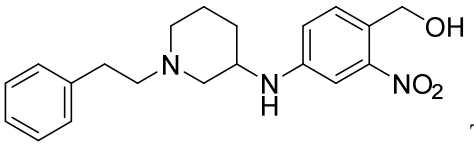


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *pyridine-2-carboxaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(pyridin-2-ylmethyl)piperidin-3-yl)amino)phenyl)methanol (**10e**).* Orange

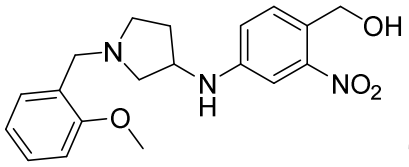
oil: 26.8 mg, 42%. ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (d, *J* = 5.2 Hz, 1H), 7.82 (m, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.31 (m, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.73 (m, 1H), 3.67 (ABq, $\Delta\nu_{AB}$ = 24.0 Hz, J_{AB}= 13.7 Hz, 2H), 3.56 (m, 1H), 2.92 (d, *J* = 10.1 Hz, 1H), 2.66 (m, 1H), 2.30 (m, 1H), 2.11 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.67 (m, 1H), 1.43 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{18}H_{22}N_4O_3$ [M+1]: 343.2; found, 343.2. HRMS (EI): m/z calcd for $C_{18}H_{22}N_4O_3$ [M+1]: 343.1765; found, 343.1766.



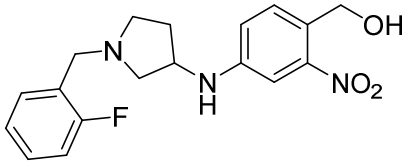
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *1H-indole-3-carbaldehyde* as the aldehyde reagent. *(4-((1-((1H-indol-3-yl)methyl)piperidin-3-yl)amino)-2-nitrophenyl)methanol* ***(10f)***. Orange oil: 21.1 mg, 54%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (ddd, *J* =7.9, 1.2, 0.8 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.27 (dt, *J* =7.9, 0.9 Hz, 1H), 7.20 (s, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 7.02 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 6.96 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.64 (s, 2H), 3.91 (ABq, $\Delta\nu_{AB}$ = 6.4 Hz, J_{AB}= 13.5 Hz 2H), 3.49 (m, 1H), 3.14 (d, *J* = 13.8 Hz, 1H), 2.93 (d, *J* = 13.3 Hz, 1H), 2.36 (m, 1H), 2.17 (m, 1H), 1.87 (d, *J* = 12.5 Hz, 1H), 1.76 (m, 1H), 1.61 (m, 1H), 1.25 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{21}H_{24}N_4O_3$ [M+1]: 381.2; found, 381.2. HRMS (EI): m/z calcd for $C_{21}H_{24}N_4O_3$ [M+1]: 381.1921; found, 381.1925.



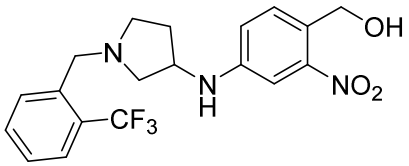
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-phenylacetaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-phenethylpiperidin-3-yl)amino)phenyl)methanol* ***(10g)***. Orange oil: 16.7 mg, 24%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (d, *J* = 8.5 Hz, 1H), 7.13 (s, 6H), 6.82 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.64 (s, 2H), 3.48 (m, 1H), 3.07 (d, *J* = 11.0 Hz, 1H), 2.90 (d, *J* = 10.7 Hz, 1H), 2.77 (m, 2H), 2.69 (m, 2H), 2.28 (m, 1H), 2.09 (m, 1H), 1.90 (m, 1H), 1.81 – 1.72 (m, 3H), 1.64 (m, 1H), 1.32 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{20}H_{25}N_3O_3$ [M+1]: 356.2; found, 356.2. HRMS (EI): m/z calcd for $C_{20}H_{25}N_3O_3$ [M+1]: 356.1969; found, 356.1972.



The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-methoxybenzaldehyde* as the aldehyde reagent. *(4-((1-(2-methoxybenzyl)pyrrolidin-3-yl)amino)-2-nitrophenyl)methanol* ***(11a)***. Orange oil: 9.1 mg, 35%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (d, *J* = 8.5 Hz, 1H), 7.25 (m, 2H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.86 (td, *J* = 7.5, 1.0 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.66 (s, 2H), 4.03 (m, 1H), 3.90 (s, 2H), 3.77 (s, 3H), 3.20 (dd, *J* = 10.7, 4.4 Hz, 1H), 2.99 (m, 1H), 2.89 (m, 1H), 2.72 (dd, *J* = 10.7, 4.4 Hz, 14H), 2.32 (dt, *J* = 14.8, 8.0 Hz, 11H), 1.74 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{23}N_3O_4$ [M+1]: 358.2; found, 358.3. HRMS (EI): m/z calcd for $C_{19}H_{23}N_3O_4$ [M+1]: 358.1761; found, 358.1774.

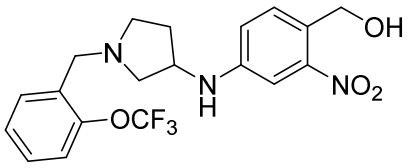


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-fluorobenzaldehyde* as the aldehyde reagent. *(4-((1-(2-fluorobenzyl)pyrrolidin-3-yl)amino)-2-nitrophenyl)methanol* ***(11b)***. Orange oil: 11.7 mg, 47%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (m, 2H), 7.30 (m, 1H), 7.16 (m, 2H), 7.08 (m, 1H), 6.88 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.75 (s, 2H), 4.02 (s, 1H), 3.74 (ABq, $\Delta\nu_{AB}$ = 6.6 Hz, J_{AB}= 13.3 Hz, 2H), 2.99 (dd, *J* = 9.7, 7.0 Hz, 1H), 2.78 (td, *J* = 8.4, 6.1 Hz, 1H), 2.65 (dt, *J* = 8.5, 7.3 Hz, 1H), 2.53 (dd, *J* = 9.8, 4.7 Hz, 1H), 2.34 (m, 1H), 1.69 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{18}H_{20}FN_3O_3$ [M+1]: 346.2; found, 346.2. HRMS (EI): m/z calcd for $C_{18}H_{20}FN_3O_3$ [M+1]: 346.1561; found, 346.1571.

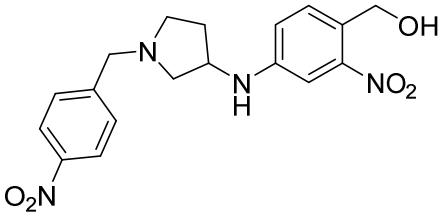


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-(trifluoromethyl)benzaldehyde* as the

aldehyde reagent. *(2-nitro-4-((1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-yl)amino)phenyl)methanol* ***(11c)***. Orange oil: 37.2 mg, 67%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.40 (t, *J* = 7.3 Hz 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.4 Hz, 1H), 4.75 (s, 2H) 4.04 (m, 1H), 3.82 (ABq, $\Delta\nu_{AB}$ = 14.6 Hz, J_{AB}= 13.0 Hz,f 2H), 2.93 (dd, *J* = 9.5, 6.7 Hz, 1H), 2.80 (td, *J* = 8.1, 5.5 Hz, 1H), 2.62 (td, *J* = 8.1, 5.5 Hz, 1H), 2.56 (dd, *J* = 9.5, 4.2 Hz, 1H), 2.35 (dtd, *J* = 13.5, 8.1, 5.7 Hz, 1H), 1.73 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{20}F_3N_3O_3$ [M+1]: 396.2; found, 396.2. HRMS (EI): m/z calcd for $C_{19}H_{20}F_3N_3O_3$ [M+1]: 396.1530; found, 396.1538.

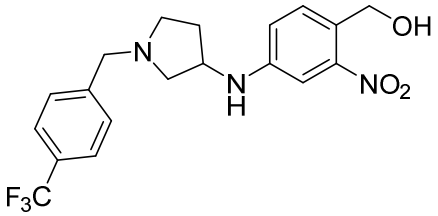


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(2-(trifluoromethoxy)benzyl)pyrrolidin-3-yl)amino)phenyl)methanol* ***(11d)***. Orange oil: 6.7 mg, 28%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (dd, *J* = 6.3, 2.1 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.36 (m, 2H), 7.30 (dd, *J* = 5.9, 1.6 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.76 (s, 2H), 4.04 (m, 1H), 3.78 (ABq, $\Delta\nu_{AB}$ = 13.6 Hz, J_{AB}= 10.5 Hz, 2H), 2.97 (dd, *J* = 9.5, 6.8 Hz, 1H), 2.79 (m, 1H), 2.64 (m, 1H), 2.55 (dd, *J* = 9.6, 4.6 Hz, 1H), 2.35 (m, 1H), 1.72 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{20}F_3N_3O_4$ [M+1]: 412.1; found, 412.2. HRMS (EI): m/z calcd for $C_{19}H_{20}F_3N_3O_4$ [M+1]: 412.1479; found, 412.1480.

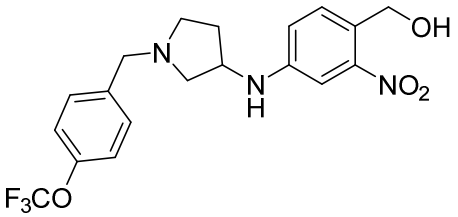


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *4-nitrobenzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(4-nitrobenzyl)pyrrolidin-3-yl)amino)phenyl)methanol* ***(11e)***. Orange oil: 4.6 mg,

5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.73 (s, 2H), 4.29 (d, *J* = 7.6 Hz, 1H), 4.05 (m, 1H), 3.73 (s, 2H) 2.86 (td, *J* = 9.0, 4.4 Hz 1H), 2.76 (dd, *J* = 9.6, 6.2 Hz, 1H), 2.63 (dd, *J* = 9.6, 3.1 Hz, 1H), 2.41 (m, 2H), 1.70 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{18}H_{20}N_4O_5$ [M+1]: 373.2; found, 373.2. HRMS (EI): m/z calcd for $C_{18}H_{20}N_4O_5$ [M+1]: 373.1506; found, 373.1517.

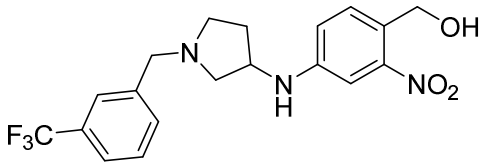


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *4-(trifluoromethyl)benzaldehyde* as the aldehyde reagent. *((2-nitro-4-((1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)amino)phenyl)methanol* ***(11f)***. Orange oil: 50.0 mg, 23%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, *J* = 8.1 Hz, 4H), 7.45 (d, *J* = 8.1 Hz, 4H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.64 (s, 2H), 3.94 (m, 1H), 3.64 (ABq, $\Delta\nu_{AB}$ = 11.6 Hz, J_{AB}= 13.1 Hz, 2H), 2.84 (dd, *J* = 9.7, 6.8 Hz, 1H), 2.67 (m, 1H), 2.60 (m, 1H), 2.52 (dd, *J* = 9.7, 4.5 Hz, 1H), 2.25 (m, 1H), 1.62 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{20}F_3N_3O_3$ [M+1]: 396.2; found, 396.2. HRMS (EI): m/z calcd for $C_{19}H_{20}F_3N_3O_3$ [M+1]: 396.1530; found, 396.1534.

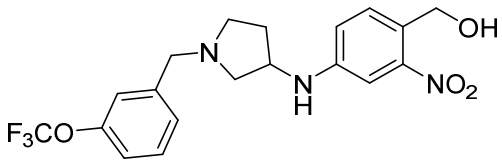


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *4-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(4-(trifluoromethoxy)benzyl)pyrrolidin-3-yl)amino)phenyl)methanol* ***(11g)***. Orange oil: 59.4 mg, 66%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.65 (s, 2H), 3.93 (m, 1H), 3.59 (ABq, $\Delta\nu_{AB}$ = 11.8 Hz, J_{AB}=

13.1 Hz, 2H), 2.85 (dd, *J* = 9.8, 6.9 Hz, 1H), 2.65 (m, 1H), 2.50 (m, 1H), 2.41 (dd, *J* = 9.8, 4.7 Hz, 1H), 2.24 (m, 1H), 1.61 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{20}F_3N_3O_4$ [M+1]: 412.1; found, 412.2. HRMS (EI): m/z calcd for $C_{19}H_{20}F_3N_3O_4$ [M+1]: 412.1479; found, 412.1487.

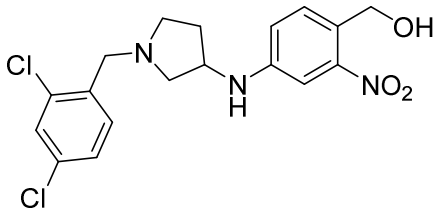


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *3-(trifluoromethyl)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)amino)phenyl)methanol (**11h**)*. Orange oil: 43.5 mg, 55%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (s, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 8.5, 2.5 Hz, 1H), 4.76 (s, 2H), 4.05 (ddt, J = 8.8, 7.1, 4.5 Hz, 1H), 3.76 (ABq, $\Delta\nu_{AB}$ = 8.3 Hz, J_{AB}= 13.1 Hz, 2H), 2.96 (dd, J = 9.8, 6.9 Hz, 1H), 2.79 (m, 1H), 2.61 (ddd, J = 9.3, 7.9, 6.4 Hz, 1H), 2.54 (dd, J = 9.8, 4.5 Hz, 1H), 2.36 (m, 1H), 1.72 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{20}F_3N_3O_3$ [M+1]: 396.2; found, 396.2. HRMS (EI): m/z calcd for $C_{19}H_{20}F_3N_3O_3$ [M+1]: 396.1530; found, 396.1540.

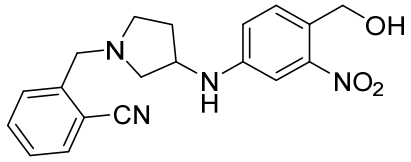


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *3-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(3-(trifluoromethoxy)benzyl)pyrrolidin-3-yl)amino)phenyl)methanol (**11i**)*. Orange oil: 35.0 mg, 46%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (m, 2H), 7.36 (d, J = 7.7 Hz, 1H), 7.30 (s, 1H), 7.19 (d, J = 2.5 Hz, 1H), 7.16 (m, 1H), 6.89 (dd, J = 8.5, 2.5 Hz, 1H), 4.75 (s, 2H), 4.04 (m, 1H), 3.71 (ABq, ΔV_{AB} =11.2 Hz, J_{AB}=13.0 Hz, 2H), 2.94 (dd, J = 9.7, 6.8 Hz, 2H), 2.76 (m, 1H), 2.60 (m, 1H), 2.52 (dd, J = 9.8, 4.5 Hz, 1H), 2.35 (dtd, J = 13.8, 8.0, 5.8 Hz, 1H), 1.72 (dddd, J = 12.9, 8.1, 6.3, 4.6 Hz, 1H). ESI-MS (m/z):

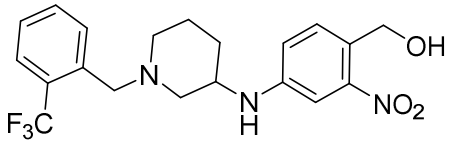
m/z calcd for $C_{19}H_{20}F_3N_3O_4$ [M+1]: 412.1; found, 412.2. HRMS (EI): m/z calcd for $C_{19}H_{20}F_3N_3O_4$ [M+1]: 412.1479; found, 412.1484.



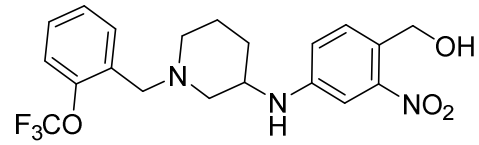
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *2,4-dichlorobenzaldehyde* as the aldehyde reagent. ***(4-((1-(2,4-dichlorobenzyl)pyrrolidin-3-yl)amino)-2-nitrophenyl)methanol (11j)***. Orange oil: 8.8 mg, 30%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (d, *J* = 8.3 Hz, 1H), 7.44 (s, 1H), 7.43 (d, *J* = 6.5 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.19 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.75 (s, 2H), 4.03 (s, 1H), 3.77 (s, 2H), 2.97 (m, 1H), 2.81 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.64 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.56 (dd, *J* = 9.5, 4.3 Hz, 1H), 2.34 (td, *J* = 13.8, 7.2 Hz, 1H), 1.71 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{18}H_{19}Cl_2N_3O_3$ [M+1]: 396.1; found, 396.1. HRMS (EI): m/z calcd for $C_{18}H_{19}Cl_2N_3O_3$ [M+1]: 396.0876; found, 396.0881.



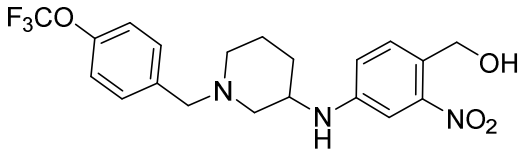
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(pyrrolidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-cyanobenzaldehyde* as the aldehyde reagent. ***2-((3-((4-(hydroxymethyl)-3-nitrophenyl)amino)pyrrolidin-1-yl)methyl)benzonitrile (11k)***. Orange oil: 16.3 mg, 21%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (ddd, *J* = 7.7, 1.2, 0.6 Hz, 1H), 7.53 (m, 2H), 7.34 (m, 2H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.65 (s, 2H), 3.94 (m, 1H), 3.77 (s, 2H), 2.86 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.72 (m, 1H), 2.49 (m, 2H), 2.24 (m, 1H), 1.62 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{20}N_4O_3$ [M+1]: 353.2; found, 353.2. HRMS (EI): m/z calcd for $C_{19}H_{20}N_4O_3$ [M+1]: 353.1608; found, 353.1617.



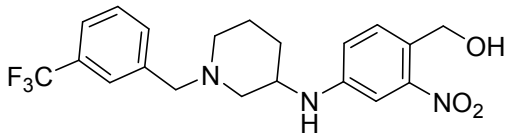
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-(trifluoromethyl)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(2-(trifluoromethyl)benzyl)piperidin-3-yl)amino)phenyl)methanol* ***(12a)***. Orange oil: 23.3 mg, 52%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.40 (d, J = 705 Hz, 1H) 7.39 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.6, 2.5 Hz, 1H), 4.72 (s, 1H), 3.67 (ABq, ΔV_{AB} =22.3 Hz, J_{AB}=14.4 Hz, 2H), 3.53 (m, 1H), 2.87 (d, J = 9.3 Hz, 1H), 2.66 (m, 1H), 2.28 (m, 1H), 2.05 (m, 1H), 1.92 (m, 1H), 1.78 (m, 1H), 1.68 (m, 1H), 1.43 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.04, 149.18, 138.99, 133.20, 131.69, 131.35, 129.58 (q, J = 30.4 Hz), 128.25, 127.42, 126.81 (q, J = 5.3 Hz), 124.79, 118.64, 108.34, 61.89, 59.55, 59.46, 55.08, 50.38, 30.76, 24.56. ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.2; found, 410.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.1686; found, 410.1686.



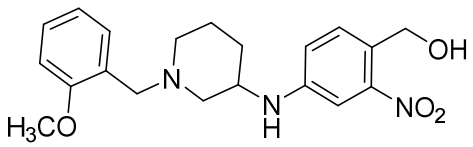
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(2-(trifluoromethoxy)benzyl)piperidin-3-yl)amino)phenyl)methanol* ***(12b)***. Orange oil: 45.2 mg, 67%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (dd, J = 6.3, 2.5 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.40 (m, 2H), 7.27 (dd, J = 7.5, 1.5 Hz, 1H), 7.17 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.62 (ABq, ΔV_{AB} =11.5 Hz, J_{AB}=13.8 Hz, 2H), 3.52 (m, 1H), 2.94 (d, J = 11.8 Hz, 1H), 2.70 (d, J = 9.3 Hz, 1H), 2.23 (t, J = 10.1 Hz, 1H), 2.01 (m, 1H), 1.92 (s, 1H), 1.78 (m, 1H), 1.67 (m, 1H), 1.39 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.2; found, 426.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.1635; found, 426.1637.



The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *4-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(4-(trifluoromethoxy)benzyl)piperidin-3-yl)amino)phenyl)methanol* ***(12c)***. Orange oil: 55.7 mg, 69 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.6 Hz, 4H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.80 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.72 (d, *J* = 6.3 Hz, 2H), 4.49 (s, 1H), 3.62 (m, 1H), 3.50 (ABq , ΔV_{AB} =11.8 Hz, J_{AB}=13.6 Hz, 2H), 2.60 (m, 2H), 2.49 (m, 2fH), 1.64 (s, 4H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.2; found, 426.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.1635; found, 426.1640.

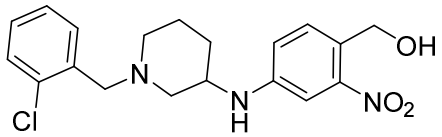


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *3-(trifluoromethyl)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(3-(trifluoromethyl)benzyl)piperidin-3-yl)amino)phenyl)methanol* ***(12d)***. Orange oil: 15.0 mg, 39%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (s, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.50 (dd,J = 7.6, 7.4 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.4 Hz, 1H), 4.73 (s, 2H), 3.62 (s, 2H), 3.52 (m, 1H), 2.95 (d, *J* = 10.5 Hz, 1H), 2.71 (d, *J* = 10.9 Hz, 1H), 2.19 (t, *J* = 9.9 Hz, 1H), 1.96 (m, 2H), 1.77 (m, 1H), 1.68 (m, 1H), 1.33 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.2; found, 410.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.1686; found, 410.1694.

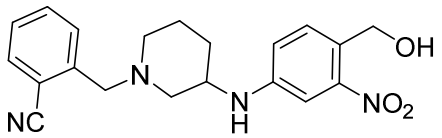


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-methoxybenzaldehyde* as the aldehyde

reagent. *(4-((1-(2-methoxybenzyl)piperidin-3-yl)amino)-2-nitrophenyl)methanol* ***(12e)***. Orange oil: 34.0 mg, 67%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, J = 8.5 Hz, 1H), 7.30 (dd, J = 7.4, 1.7 Hz, 1H), 7.25 (ddd, J = 8.2, 7.6, 1.7 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 6.96 (dd, J = 8.2, 1.0Hz, 1H), 6.92 (dd, J = 7.4, 1.0 Hz, 1H), 6.89 (dd, J = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.81 (s, 3H), 3.61 (s, 2H), 3.52 (m, 1H), 3.05 (d, J = 10.6 Hz, 1H), 2.80 (d, J = 9.4 Hz, 1H), 2.19 (t, J = 10.0 Hz, 1H), 1.97 (m, 2H), 1.71 (m, 2H), 1.30 (m, 2H). ESI-MS (m/z): m/z calcd for $C_{20}H_{25}N_3O_4$ [M+1]: 372.2; found, 372.2. HRMS (EI): m/z calcd for $C_{20}H_{25}N_3O_4$ [M+1]: 372.1918; found, 372.1925.

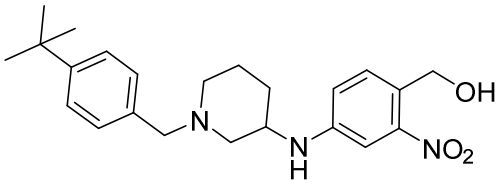


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-chlorobenzaldehyde* as the aldehyde reagent. *(4-((1-(2-chlorobenzyl)piperidin-3-yl)amino)-2-nitrophenyl)methanol* ***(12f)***. Orange oil: 22.8 mg, 44%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (td, J = 7.6, 1.6 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.30 (m, 1H), 7.19 (d, J = 2.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 8.4 Hz, 1H), 6.89 (dd, J = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.65 (s, 2H), 3.52 (m, 1H), 3.00 (d, J = 12.7 Hz, 1H), 2.77 (d, J = 10.2 Hz, 1H), 2.20 (t, J = 10.5 Hz, 1H), 2.01 (d, J = 7.5 Hz, 1H), 1.94 (m, 1H), 1.78 (m, 1H), 1.68 (m, 1H), 1.32 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{22}ClN_3O_3$ [M+1]: 376.1; found, 376.2. HRMS (EI): m/z calcd for $C_{19}H_{22}ClN_3O_3$ [M+1]: 376.1422; found, 376.1427.

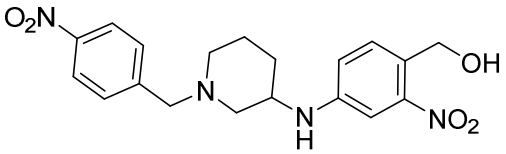


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-cyanobenzaldehyde* as the aldehyde reagent. *2-((3-((4-(hydroxymethyl)-3-nitrophenyl)amino)piperidin-1-yl)methyl)benzonitrile* ***(12g)***. Orange oil: 32.0 mg, 48%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (dd, J = 7.9, 1.0 Hz, 1H), 7.61 (ddd, J = 7.7, 7.4, 1.4 Hz, 1H), 7.56 (ddd, J = 7.8, 1.4, 0.5 Hz, 1H), 7.42 (td, J = 7.5, 1.4 1H), 7.39 (dt, J = 8.5, 0.6 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 6.89 (dd, J = 8.5, 2.5 Hz, 1H), 4.72 (s, 2H), 3.70 (ABq, ΔV_{AB} =37.3 Hz, J_{AB}=13.9 Hz, 2H), 3.56 (m, 1H), 2.87 (d, J = 11.4 Hz, 1H) 2.57 (m, 1H), 2.35 (m, 1H), 2.25 (s, 1H), 1.79 (m, 2H), 1.62 (m, 1H), 1.50 (m, 1H). ESI-MS

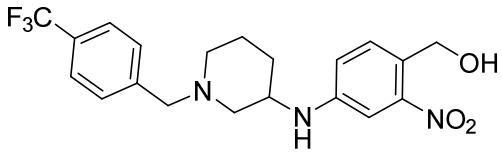
(m/z): m/z calcd for $C_{20}H_{22}N_4O_3$ [M+1]: 367.2; found, 367.2. HRMS (EI): m/z calcd for $C_{20}H_{22}N_4O_3$ [M+1]: 367.1765; found, 367.1770.



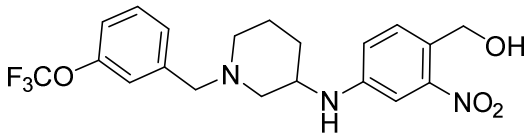
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *4-tertbutylbenzaldehyde* as the aldehyde reagent. ***(4-((1-(4-(tert-butyl)benzyl)piperidin-3-yl)amino)-2-nitrophenyl)methanol (12h)***. Orange oil: 16.2 mg, 52%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 2.1 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.0 Hz,1H), 4.68 (s, 2H), 3.48 (s, 2H), 3.45 (m, 4H), 2.94 (d, *J* = 11.1 Hz, 2H), 2.70 (m, 1H), 2.10 (d, *J* = 9.4 Hz, 1H), 1.88 (m, 2H), 1.73 (m, 1H), 1.63 (m, 1H), 1.25 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{23}H_{32}N_3O_3$ [M+1]: 398.2; found, 398.2.



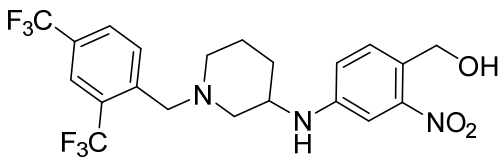
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *4-nitrobenzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(4-nitrobenzyl)piperidin-3-yl)amino)phenyl)methanol* ***(12i)***. Orange oil: 13.5 mg, 18%. ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 2.5 Hz, 1H), 6.89 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.73 (s, 2H), 3.67 (ABq, ΔV_{AB} =8.6 Hz, J_{AB}=14.0 Hz, 2H), 3.54 (m, 1H), 2.93 (d, *J* = 11.7 Hz, 1H), 2.71 (d, *J* = 10.1 Hz, 1H), 2.24 (m, 1H), 2.02 (m, 1H), 1.94 (m, 1H), 1.81 (m, 1H), 1.69 (m, 1H), 1.38 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{19}H_{22}N_4O_5$ [M+1]: 387.2; found, 387.2. HRMS (EI): m/z calcd for $C_{19}H_{22}N_4O_5$ [M+1]: 387.1663; found, 387.1663.



The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *4-(trifluoromethyl)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(4-(trifluoromethyl)benzyl)piperidin-3-yl)amino)phenyl)methanol* ***(12j)***. Orange oil: 52.3 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 2.5 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.72 (s, 2H), 4.51 (s, 1H), 3.63 (s, 1H), 3.56 (ABq, ΔV_{AB} =11.8 Hz, J_{AB}=13.6 Hz, 2H), 2.64 (d, *J* = 10.5 Hz, 1H), 2.49 (m, 1H), 2.39 (d, *J* = 17.7 Hz, 2H), 1.72 (m, 2H), 1.60 (m, 2H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.2; found, 410.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.1686; found, 410.1687.

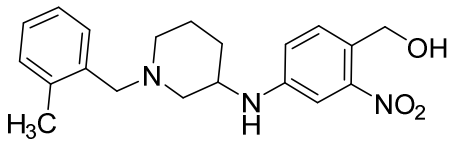


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *3-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(3-(trifluoromethoxy)benzyl)piperidin-3-yl)amino)phenyl)methanol* ***(12k)***. Orange oil: 35.6 mg, 66%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (t, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.29 (s, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.73 (s, 2H), 3.59 (s, 2H), 3.52 (m, 1H), 2.95 (d, *J* = 10.7 Hz, 1H), 2.71 (d, *J* = 11.0 Hz, 1H), 2.18 (t, *J* = 9.9 Hz, 1H), 1.96 (m, 2H), 1.78 (m, 1H), 1.67 (m, 1H), 1.35 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.2; found, 426.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.1635; found, 426.1639.

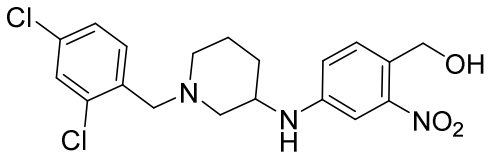


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2,4-bis(trifluoromethyl)benzaldehyde* as the

aldehyde reagent. *(4-((1-(2,4-bis(trifluoromethyl)benzyl)piperidin-3-yl)amino)-2-nitrophenyl)methanol* ***(12l)***. Orange oil: 30.4 mg, 64%. ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.90 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.89 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.73 (s, 2H), 3.75 (ABq, ΔV_{AB} =16.9 Hz, J_{AB}=15.5 Hz, 2H), 3.57 (m, 1H), 2.87 (d, J = 12.1 Hz, 1H), 2.67 (m, 1H), 2.32 (t, J = 9.6 Hz, 1H), 2.10 (m, 1H), 1.94 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.44 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{21}H_{21}F_6N_3O_3$ [M+1]: 478.2; found, 478.2. HRMS (EI): m/z calcd for $C_{21}H_{21}F_6N_3O_3$ [M+1]: 478.1560; found, 478.1569.

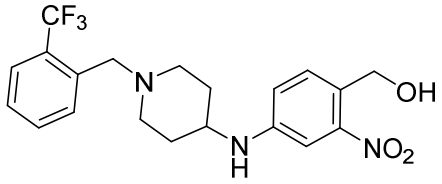


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2-methylbenzaldehyde* as the aldehyde reagent. *(4-((1-(2-methylbenzyl)piperidin-3-yl)amino)-2-nitrophenyl)methanol* ***(12m)***. Orange oil: 20.1 mg, 53%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (d, *J* = 8.2 Hz, 1H), 7.32 (m, 1H), 7.25 (d, *J* = 6.5 Hz, 1H), 7.14 (m, 3H), 6.85 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.73 (s, 2H), 3.49 (ABq, , ΔV_{AB} =16.9 Hz, J_{AB}=15.5 Hz, 2H), 2.95 (d, *J* = 11.0 Hz, 1H), 3.48 (m, 1H), 2.71 (m, 1H), 2.37 (s, 3H), 2.20 (m, 1H), 1.96 (m, 2H), 1.74 (m, 1H), 1.64 (m, 1H), 1.37 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{20}H_{25}N_3O_3$ [M+1]: 356.2; found, 356.2. HRMS (EI): m/z calcd for $C_{20}H_{25}N_3O_3$ [M+1]: 356.1969; found, 356.1977.

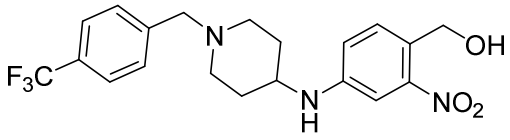


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-3-ylamino)phenyl)methanol* as the amine reagent and *2,4-dichlorobenzaldehyde* as the aldehyde reagent. *(4-((1-(2,4-dichlorobenzyl)piperidin-3-yl)amino)-2-nitrophenyl)methanol* ***(12n)***. Orange oil: 10.3 mg, 19%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.40 (s, 1H), 7.31 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.74 (s, 2H), 3.62 (s, 2H), 3.54 (m, 1H), 2.94 (d, *J* = 9.7 Hz, 1H), 2.72 (m, 1H), 2.30 (t, *J* = 10.7 Hz, 1H), 2.10 (m, 1H), 1.92 (m, 1H), 1.78 (m, 1H), 1.67 (m, 1H), 1.40 (m, 1H).

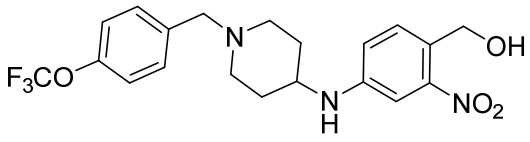
ESI-MS (m/z): m/z calcd for $C_{19}H_{21}Cl_2N_3O_3$ [M+1]: 410.1; found, 410.1. HRMS (EI): m/z calcd for $C_{19}H_{21}Cl_2N_3O_3$ [M+1]: 410.1033; found, 410.1037.



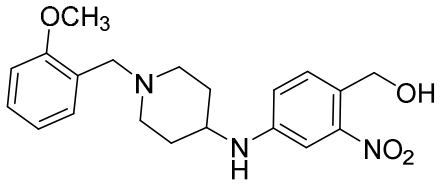
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *2-(trifluoromethyl)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(2-(trifluoromethyl)benzyl)piperidin-4-yl)amino)phenyl)methanol* ***(13a)***. Orange oil: 22.1 mg, 50%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (d, *J* = 7.4 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 8.6, 2.5 Hz, 1H), 4.74 (s, 2H), 3.69 (s, 2H), 3.35 (m, 2H), 2.86 (d, *J* = 11.8 Hz, 2H), 2.26 (td, *J* = 11.7, 2.2 Hz, 2H), 2.01 (dd, *J* = 12.7, 2.6 Hz, 2H), 1.54 (ddd, *J* = 24.3, 10.7, 3.2 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.2; found, 410.2.



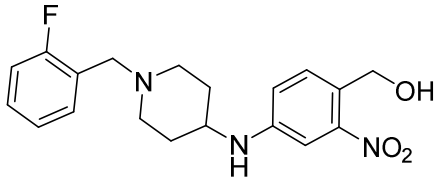
The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *4-(trifluoromethyl)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)amino)phenyl)methanol* ***(13b)***. Orange oil: 26.2 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 2.5 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.73 (s, 2H), 3.90 (d, *J* = 7.9 Hz, 1H), 3.58 (s, 2H), 3.35 (m, 1H), 2.84 (d, *J* = 8.6 Hz, 2H), 2.60 (bs, 1H), 2.20 (t, *J* = 13.3 Hz, 2H), 2.04 (d, *J* = 16.4 Hz, 2H), 1.52 (m, 2H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.2; found, 410.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.1686; found, 410.1689.



The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *4-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)amino)phenyl)methanol* ***(13c)***. Orange oil: 36.1mg, 85.3%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 2.5 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.58 (s, 2H), 3.34 (m, 1H), 2.89 (d, *J* = 12.1 Hz, 2H), 2.24 (td, *J* = 11.7, 2.2 Hz, 2H), 2.02 (d, *J* = 13.3 Hz, 2H), 1.53 (ddd, *J* = 14.0, 11.3, 3.6 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.2; found, 426.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.1635; found, 426.1639.

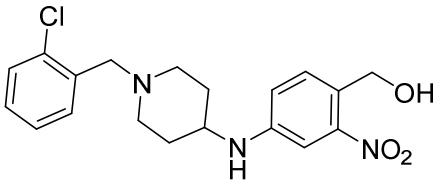


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *2-methoxybenzaldehyde* as the aldehyde reagent. *(4-((1-(2-methoxybenzyl)piperidin-4-yl)amino)-2-nitrophenyl)methanol* ***(13d)***. Orange oil: 28.3 mg, 78%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.29 (td, *J* = 7.8, 1.9 Hz, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.94 (td, *J* = 7.4, 1.0 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.85 (s, 3H), 3.73 (s, 2H), 3.36 (m, 1H), 3.03 (d, *J* = 12.0 Hz, 2H), 2.44 (t, *J* = 11.3 Hz, 2H), 2.03 (d, *J* = 11.0 Hz, 2H), 1.57 (dd, *J* = 21.1, 10.1 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_{20}H_{25}N_3O_4$ [M+1]: 372.2; found, 372.2. HRMS (EI): m/z calcd for $C_{20}H_{25}N_3O_4$ [M+1]: 372.1918; found, 372.1923.

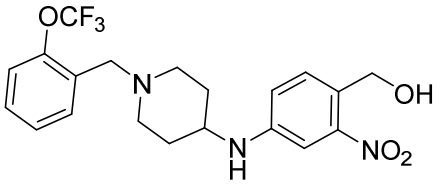


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *2-fluorobenzaldehyde* as the aldehyde

reagent. *(4-((1-(2-fluorobenzyl)piperidin-4-yl)amino)-2-nitrophenyl)methanol* ***(13e)***. Orange oil: 27.4 mg, 79%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (m, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.31 (tdd, *J* = 7.3, 5.3, 1.8 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 7.15 (td, *J* = 7.5, 1.1 Hz, 1H), 7.09 (ddd, J = 9.9, 8.4, 1.1 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.64 (s, 2H), 2.93 (d, *J* = 12.1 Hz, 2H), 2.29 (t, *J* = 12.2 Hz, 2H), 2.01 (d, *J* = 11.3 Hz, 2H), 1.53 (m, 2H). ESI-MS (m/z): m/z calcd for $C_{19}H_{22}FN_3O_3$ [M+1]: 360.2; found, 360.2. HRMS (EI): m/z calcd for $C_{19}H_{22}FN_3O_3$ [M+1]: 360.1718; found, 360.1725.

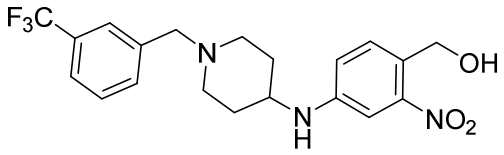


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *2-chlorobenzaldehyde* as the aldehyde reagent. *(4-((1-(2-chlorobenzyl)piperidin-4-yl)amino)-2-nitrophenyl)methanol* ***(13f)***. Orange oil: 33.3 mg, 84.3%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.29 (td, *J* = 7.4, 1.6 Hz, 1H), 7.24 (td, J = 7.5, 1.9 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.68 (s, 2H), 3.36 (m, 1H), 2.93 (d, *J* = 12.2 Hz, 2H), 2.32 (t, *J* = 12.7 Hz, 2H), 2.01 (d, *J* = 11.6 Hz, 2H), 1.53 (ddd, *J* = 14.5, 11.2, 3.7 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_{19}H_{22}ClN_3O_3$ [M+1]: 376.1; found, 376.1. HRMS (EI): m/z calcd for $C_{19}H_{22}ClN_3O_3$ [M+1]: 376.1422; found, 376.1427.

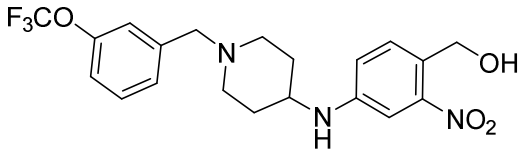


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *2-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(2-(trifluoromethoxy)benzyl)piperidin-4-yl)amino)phenyl)methanol* ***(13g)***. Orange oil: 21.5 mg, 55%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (dd, *J* = 6.9, 2.5 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.35 (m, 2H), 7.29 (m, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.63 (s, 2H), 3.33 (s, 1H), 2.89 (d, *J* = 11.9 Hz, 2H), 2.27 (t, *J* = 10.5 Hz, 2H), 2.00 (d, *J* = 12.8 Hz, 2H), 1.53 (m, 2H). ESI-MS (m/z):

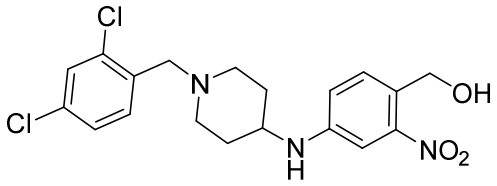
m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.2; found, 426.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.1635; found, 426.1639.



The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *3-(trifluoromethyl)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(3-(trifluoromethyl)benzyl)piperidin-4-yl)amino)phenyl)methanol* ***(13h)***. Orange oil: 29.8 mg, 73%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (d, *J* = 7.4 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H) 7.40 (s, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.74 (s, 2H), 3.69 (s, 2H), 3.37 (m, 1H), 2.86 (d, *J* = 11.8 Hz, 2H), 2.26 (td, *J* = 11.8, 2.5 Hz, 2H), 2.01 (d, *J* = 11.8 Hz, 2H), 1.54 (ddd, *J* = 23.9, 10.7, 3.3 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.2; found, 410.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_3$ [M+1]: 410.1686; found, 410.1688.

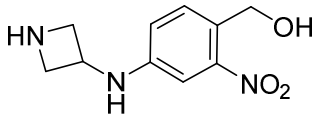


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *3-(trifluoromethoxy)benzaldehyde* as the aldehyde reagent. *(2-nitro-4-((1-(3-(trifluoromethoxy)benzyl)piperidin-4-yl)amino)phenyl)methanol* ***(13i)***. Orange oil: 24.7 mg, 65%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, *J* = 8.5, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.30 (s, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.74 (s, 2H), 3.59 (s, 2H), 3.34 (m, 1H), 2.88 (d, *J* = 12.2 Hz, 2H), 2.24 (td, *J* = 11.8, 2.1 Hz, 2H), 2.02 (d, *J* = 12.0 Hz, 2H), 1.53 (ddd, *J* = 13.9, 11.5, 3.6 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.2; found, 426.2. HRMS (EI): m/z calcd for $C_{20}H_{22}F_3N_3O_4$ [M+1]: 426.1635; found, 426.1635.

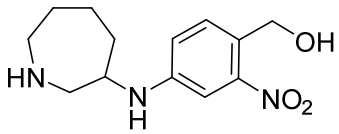


The following compound was prepared using the general reductive amination procedure described above, employing *(2-nitro-4-(piperidin-4-ylamino)phenyl)methanol* as the amine reagent and *2,4-dichlorobenzaldehyde* as the aldehyde reagent. *(4-((1-(2,4-dichlorobenzyl)piperidin-4-yl)amino)-2-nitrophenyl)methanol* ***(13j)***. Orange oil: 28.0 mg, 69%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 6.91 (dd, *J* = 8.6, 2.1 Hz, 1H), 4.74 (s, 2H), 3.65 (s, 2H), 3.37 (s, 1H), 2.91 (d, *J* = 11.8 Hz, 2H), 2.32 (t, *J* = 11.1 Hz, 2H), 2.02 (d, *J* = 11.7 Hz, 2H), 1.54 (ddd, *J* = 15.7, 12.6, 4.0 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_{19}H_{21}Cl_2N_3O_3$ [M+1]: 410.1; found, 410.1. HRMS (EI): m/z calcd for $C_{19}H_{21}Cl_2N_3O_3$ [M+1]: 410.1033; found, 410.1044.

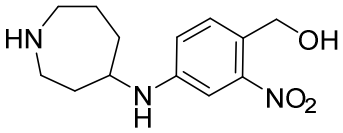
The following compounds were prepared using the general procedure described above for tertbutylcarbamate deprotection.



(4-(azetidin-3-ylamino)-2-nitrophenyl)methanol ***(14)***. Orange oil: 18.2 mg, 34.6%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.76 (s, 2H), 4.40 (t, *J* = 8 Hz, 1H), 3.94 (m, *J* = 8 Hz, 2H), 3.57 (m, *J* = 8 Hz, 2H). ESI-MS (m/z): m/z calcd for $C_{10}H_{13}N_3O_3$ [M+1]: 224.1; found, 224.1. HRMS (EI): m/z calcd for $C_{10}H_{13}N_3O_3$ [M+1]: 224.1030; found, 224.1033.



(4-(azepan-3-ylamino)-2-nitrophenyl)methanol ***(15)***. Orange oil: 250.5 mg, 79.1%.^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.75 (s, 2H), 3.68 (m, 1H), 3.23 (m, 2H), 3.11 (m, 2H), 2.17 (m, 2H), 1.97 (m, 1H), 1.84 (m, 2H), 1.67 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{13}H_{19}N_3O_3$ [M+1]: 266.1; found, 266.1. HRMS (EI): m/z calcd for $C_{13}H_{19}N_3O_3$ [M+1]: 266.1499; found, 266.1505.



*(4-(azepan-4-ylamino)-2-nitrophenyl)methanol (**16**).* Orange oil: 240.5 mg, 81.4%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (d, *J* = 8.5 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.73 (s, 2H), 3.66 (m, 1H), 3.15 (m, 4H), 2.16 (m, 2H), 1.95 (m, 1H), 1.80 (m, 2H), 1.65 (m, 1H). ESI-MS (m/z): m/z calcd for $C_{13}H_{19}N_3O_3$ [M+1]: 266.1; found, 266.1. HRMS (EI): m/z calcd for $C_{13}H_{19}N_3O_3$ [M+1]: 266.1499; found, 266.1504.

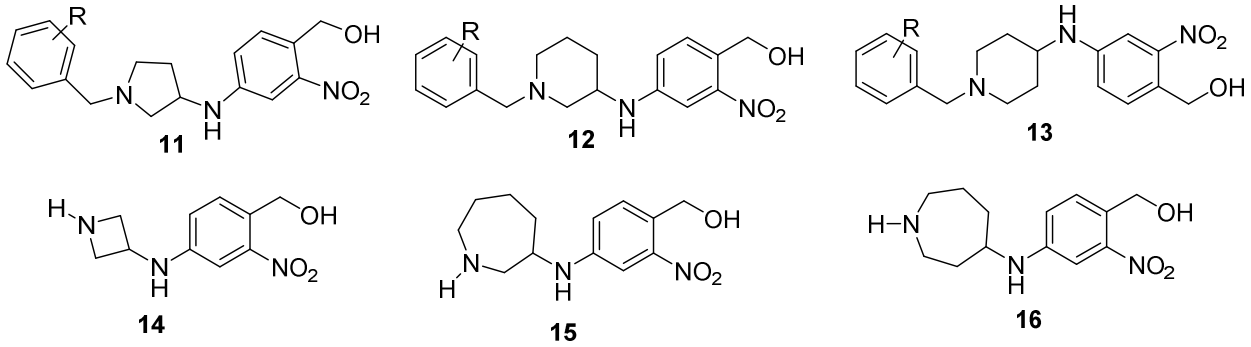
Screening in Schistosoma

Strains of *S. mansoni, S. haematobium,* and *S. japonicum* were maintained by passage through species-specific snail intermediate hosts (*Biomphlaria glabrata, Bulinus truncatus,* and *Oncomelania hupensis*, respectively) and Golden Syrian hamsters as a definitive host. Definitive host animals were sacrificed in accordance with IACUC protocol (UTHSCSA IACUC Protocol #08039) by intraperitoneal injection using Fatal-Plus (Butler Animal Health, Ohio), a sodium pentobarbital solution, with 10% heparin added. The adult parasites were obtained by perfusion as previously described using 0.9% saline containing EDTA.[1] Derivatives were solubilized in DMSO and diluted to working concentration of 50 mM and added directly to each well of a 24-well plate within 2-24 hours after harvesting adult schistosomes from the hamsters at a final concentration of 143 μM. Each analog was tested in triplicate. DMSO, oxamniquine, or hycanthone were used as controls as needed. Drugs were incubated with the worms at 37 °C, 5% CO_2 for 45 minutes, mimicking physiological conditions.[2, 3] The worms were washed with plain media 3 times to remove any residual derivatives. Worms were then incubated in culture media as previously described for a period of 10-14 days. On day 14, the assay gives % worms alive as an efficacy data point. For comparison, compound **3** scores 50% alive in this assay. The compounds were first tested on *S. mansoni*, and a few of the more active analogs were tested on *S. haematobium* and *S. japonicum.*

Additional Structural Analogs Screened for *S. mansoni*

Compounds highlighted below in table S1 showed no significant killing activity (<40%) in *S. mansoni.*

[a]**Table S1**. SAR data on worm killing of *S. mansoni.*



Entry	R=	% Killing (*S. m.*)	% Killing (*S. h.*)	% Killing (*S. j.*)
11k	2-CN	0	ND	ND
12e	2-OMe	10	ND	ND
12f	2-Cl	10	ND	ND
12g	2-CN	3	ND	ND
12h	4-tBu	<40	ND	ND
12i	4-NO_2	0	ND	ND
12j	4-CF_3	3	ND	ND
12k	3-OCF_3	37	ND	ND
12l	2,4-CF_3	<40	ND	ND
12m	2- Me	<40	ND	ND
12n	2,4-diCl	<40	ND	ND
13d	2-OMe	7	ND	ND
13e	2-F	0	ND	ND
13f	2- Cl	0	ND	ND
13g	2-OCF_3	20	ND	ND
13h	3-CF_3	17	ND	ND
13i	3-OCF_3	30	ND	ND
13j	2,4-diCl	37	ND	ND
14	NA	20	ND	ND
15	NA	12	ND	ND
16	NA	12	ND	ND

[a]*Compounds were tested against adult male S. mansoni (S. m.) worms in vitro. All compounds were tested at a final concentration of 143 µM. All screens were performed in experimental and*

*biological triplicate. Positive control, compound **3** kills 85% ± 15 of S. mansoni parasites in vitro.*

X-Ray Structure determination

Crystals of *S. mansoni* sulfotransferase:compound complexes were prepared and X-ray crystal structures were determined as previously described.[3,4] Briefly, crystals of the sulfotransferase containing the sulfate-depleted co-substrate adenosine-3'-5'-diphosphate (PAP) were soaked overnight in mother liquor saturated with CIDD compounds. Data were acquired at the UTHSCSA X-ray Crystallography Core Laboratory or at the Advanced Photon Source Northeastern Collaborative Access Team (NE-CAT) beamline 24-ID-E and integrated and scaled using XDS.[5] Coordinates and restraints for CIDD compounds were generated using JLigand.[6] Models were manually rebuilt using COOT[7] and refined using PHENIX[8]. Data collection and refinement statistics are provided in Table S2. Figures were generated using PyMOL (Schrödinger, LLC).

Table S2. Data collection and refinement statistics.

	***(R)*-9c** CIDD-0000071	***(S)*-10a** CIDD-0000074	***(R)*-9f** CIDD-0000206	***(S)*-11f** CIDD-0000204	***(S)*-11g** CIDD-0000773
PDB code	6BDP	6BDQ	6BDR	6BDS	6MFE
Data collection					
Space group	$P2_12_12$	$P2_12_12$	$P2_12_12$	$P2_12_12$	$P2_12_12$
Cell dimensions					
a, *b*, *c* (Å)	140.9, 39.5, 53.8	139.5, 38.7, 54.1	141.3, 39.4, 53.6	140.8, 39.5, 53.6	140.6, 39.6, 53.7
α, β, γ, (°)	90, 90, 90	90, 90, 90	90, 90, 90	90, 90, 90	90, 90, 90
Wavelength (Å)	1.54178	1.54178	0.97918	0.97918	1.54178
Resolution (Å)	42.73-1.43 (1.51-1.43)	46.48-1.83 (1.93-1.83)	141.27-1.66 (1.75-1.66)	140.78-1.53 (1.61-1.53)	42.66-1.44 (1.52-1.44)
R_{sym}	0.066 (0.784)	0.076 (0.829)	0.090 (1.065)	0.074 (0.958)	0.067 (0.818)
R_{pim}	0.030 (0.368)	0.039 (0.426)	0.040 (0.456)	0.033 (0.432)	0.027 (0.351)
Mean $I/\sigma I$	16.7 (2.1)	14.6 (2.0)	20.6 (2.0)	16.4 (2.0)	17.2 (2.1)
Completeness (%)	99.5 (99.3)	99.5 (99.7)	99.7 (100)	99.5 (100)	95.7 (86.2)
Redundancy	4.5 (4.2)	4.5 (4.5)	6.1 (6.2)	5.8 (5.8)	6.7 (5.9)
Wilson value (Å^2)	13.5	23.6	20.2	16.6	15.1
Refinement					
Resolution (Å)	26.41-1.43	42.76-1.83	37.92-1.66	38.07-1.53	42.66-1.44
No. reflections	56,031	26,505	36,092	45,784	52,225
R_{work}/ R_{free}	0.170/0.207	0.184/0.216	0.147/0.198	0.151/0.202	0.165/0.211
No. atoms					
Protein	2,060	2,116	2,111	2,099	2,102
Ligand	51 (1 PAP, 1 Compound 9c)	45 (1 PAP, 1 Compound 10a)	67 (1 PAP, 2 Compound 9f)	72 (1 PAP, 2 Compound 11f)	65 (1 PAP, 1 Compound 11g)
Water	342	127	236	350	339
B-factors (Å^2)					
Protein	18.6	27.1	26.1	21.9	21.7
Ligand	19.7	21.2	37.9	32.0	33.1
Water	31.6	32.0	37.1	35.1	34.0
R.m.s deviations					
Bond lengths (Å)	0.008	0.006	0.010	0.010	0.010
Bond angles (°)	1.128	0.967	1.340	1.232	1.353
Ramachandran plot (%)					
Favored, allowed, outliers	98.4, 1.6, 0.0	97.6, 2.4, 0.0	97.2, 2.8, 0.0	98.8, 1.2, 0.0	98.0, 2.0, 0.0

*Highest resolution shell is shown in parentheses.

Molecular Modeling and Docking Studies

Materials and Methods

Molecular modeling was performed with Schrodinger suite (2018-2). Compound structures were handled by Chemaxon InstantJchem suite (18.11). Protonation states of the 3-aminopyrrolidine and 3-aminopiperidine nitrogens were calculated with Jaguar-pKa module using 11g and 12a as corresponding series representatives. Five conformers were initially generated for both protonated and deprotonated states with conformational energy window 12 kcal/mol. The lowest energy conformers were used for geometry optimization and single point calculations.

For the docking studies, the crystal structure of smSULT with **11g** was used. The structure was processed with protein preparation wizard. Water molecules HOH199, HOH200 and HOH307 were removed. A grid box with a side of 20 Å and centered at geometric center of **11g** was generated. The sulfate-depleted PAP molecule was retained in the system during grid generation. Docking was performed at standard precision level with two poses saved. Intramolecular strain was calculated with Epik. No additional constraints were imposed on docking routine. Table S3 below shows the binding energies calculated across the **9-13** analogs included in the SAR studies.

[a]**Table S3.** Calculated docking scores in *S. mansoni*

Compound	***S. mansoni*** **docking score Kcal/mol**	Compound	***S. mansoni*** **docking score Kcal/mol**
11c (S)	-9.917	9d (S)	-8.087
11f (R)	-9.846	11i (R)	-8.024
10f (S)	-9.54	11i (S)	-7.985
11j (S)	-9.486	10c (R)	-7.979
11f (S)	-9.417	12c (R)	-7.908
11d (S)	-9.417	11b (R)	-7.906
9f (S)	-9.41	12d (S)	-7.834
12d (S)	-9.378	11a (R)	-7.813
10g (S)	-9.361	9c (R)	-7.794
11b (S)	-9.164	9d (R)	-7.785
13b	-9.147	10e (R)	-7.746
11e (S)	-8.886	11g (R)	-7.706
11h (R)	-8.821	13c	-7.622
10f (R)	-8.787	10b (S)	-7.62
9g (R)	-8.751	9e (S)	-7.618
12c (S)	-8.75	9e (R)	-7.588
12a (S)	-8.644	12a (R)	-7.586
9f (R)	-8.582	12b (R)	-7.579
11a (S)	-8.516	9a (S)	-7.485
11c (R)	-8.483	13a	-7.387
9c (S)	-8.469	10d (R)	-7.371
10c (S)	-8.423	9b (R)	-7.366
10d (S)	-8.398	11h (S)	-7.333
11g (S)	-8.371	10g (R)	-7.272
10e (S)	-8.298	10a (R)	-7.249
11e (R)	-8.294	12b (S)	-7.248
11d (R)	-8.278	10a (S)	-7.232
11j (R)	-8.215	10b (R)	-7.214
12d (R)	-8.156	9a (R)	-7.168
9g (S)	-8.114	9b (S)	-6.941

[a]Docking studies of analogs **9-13** on *S. mansoni.* Molecular modeling was performed with Schrodinger suite (2018-2). Compound structures were handled by Chemaxon InstantJchem suite (18.11).

Figure S.1 Full COSY compound **12a**

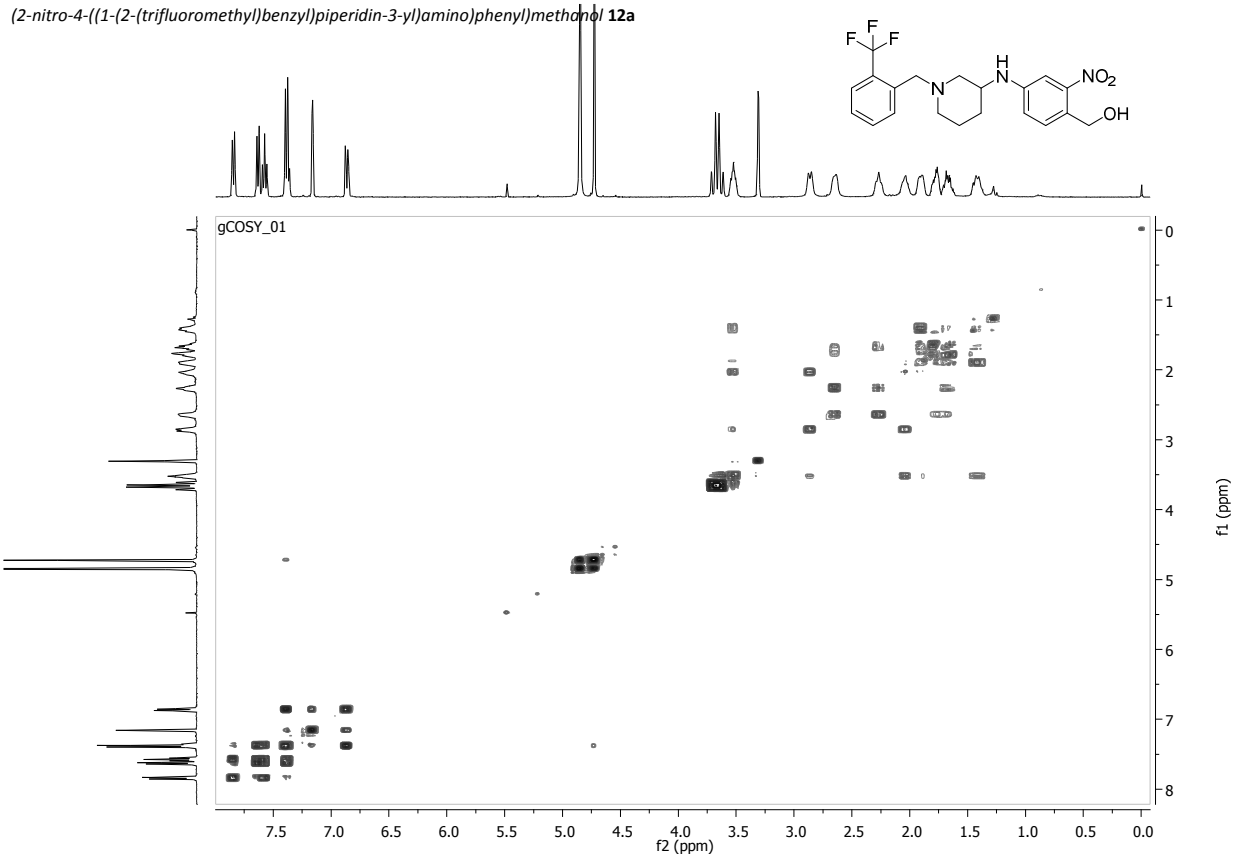


Figure S.2 Aromatic region expanded COSY compound **12a**

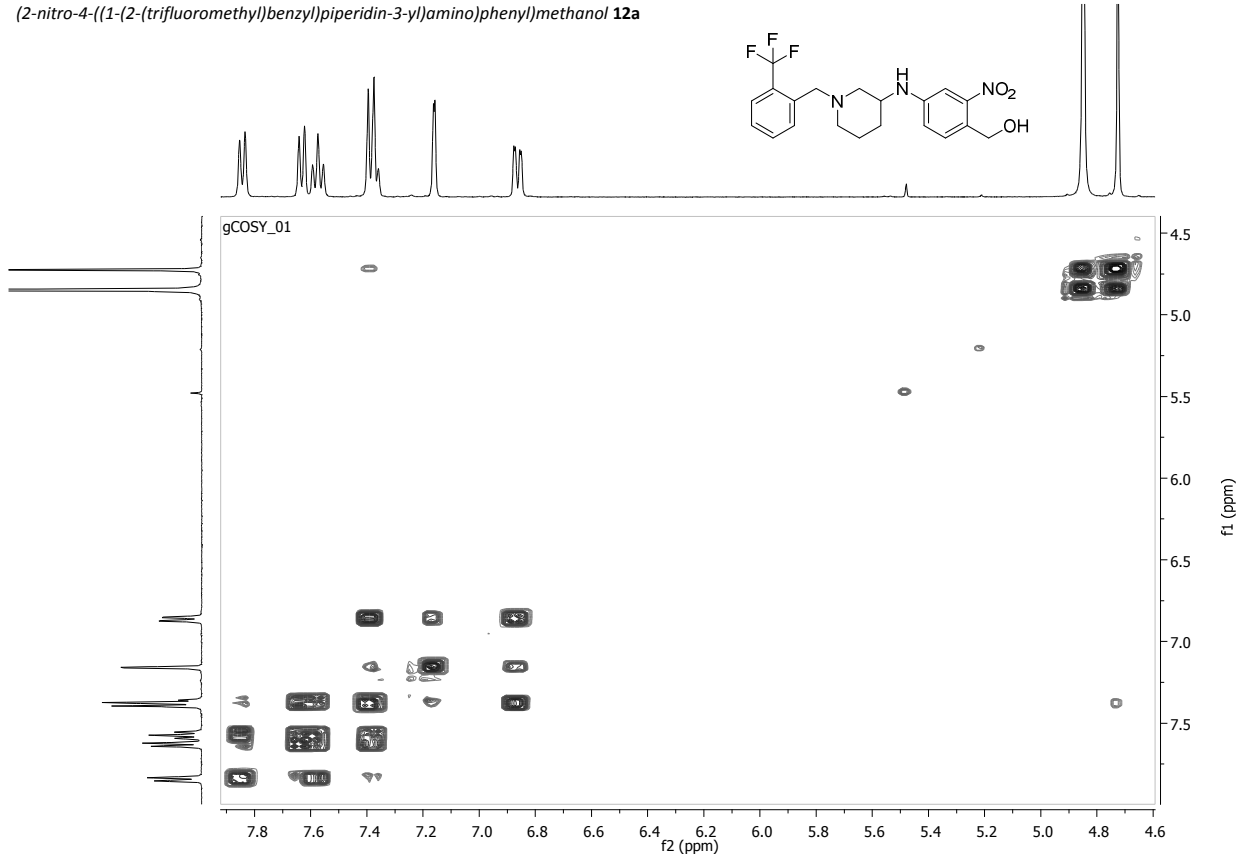


Figure S.3 Aliphatic region expanded COSY compound **12a**

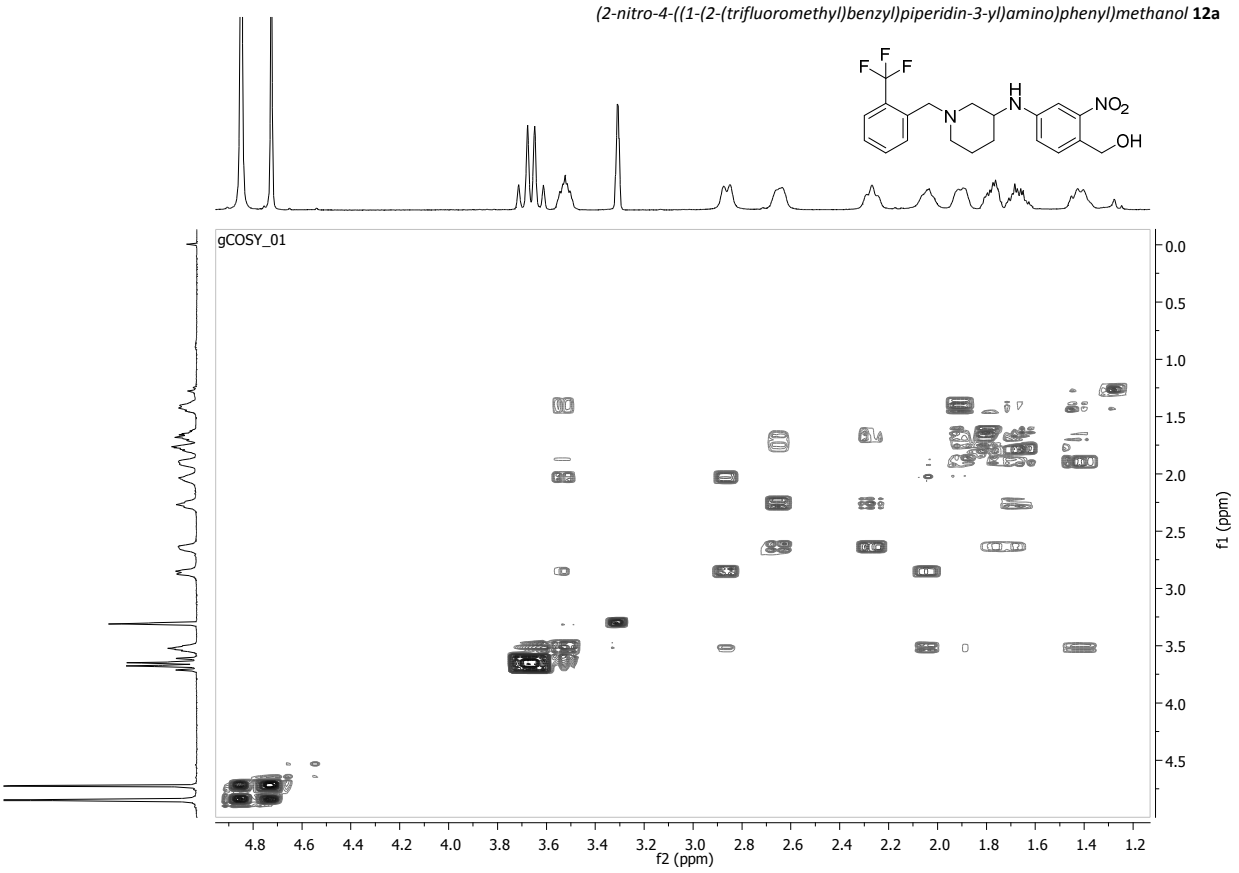
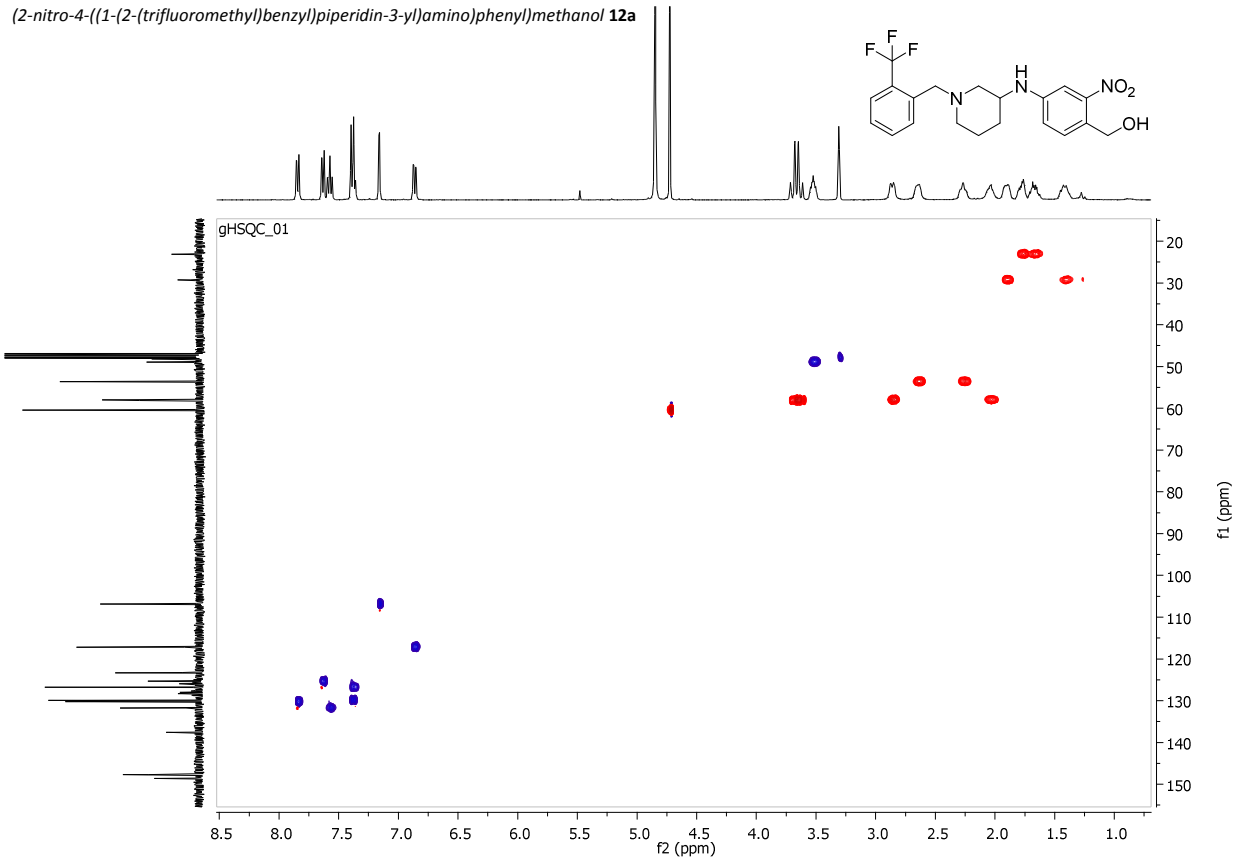


Figure S.4 Full HSQC compound **12a**



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