Supplemental Information for

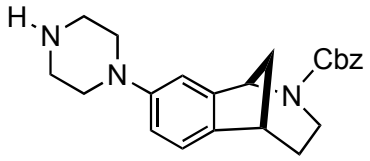
Norbenzomorphan Scaffold: Chemical Tool for Modulating Sigma Receptor-Subtype Selectivity

James J. Sahn, Timothy R. Hodges, Jessica Z. Chan, and Stephen F. Martin

General. Toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant[1] and was determined to have less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. Methanol (MeOH), methylene chloride (CH_2Cl_2), 1,2-dichloroethane (DCE), triethylamine (Et_3N) and diisopropylethylamine (*i*-Pr_2NEt) were used without further purification. All reagents were reagent grade and used without purification unless otherwise noted. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame or oven dried. Reaction temperatures refer to the temperature of the cooling/heating bath. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator at 20–30 °C (bath temperature). Thin layer chromatography was run on pre-coated plates of silica gel with a 0.25 mm thickness containing 60F-254 indicator (EMD Millipore). Chromatography was performed using forced flow (flash chromatography) and the indicated solvent system on 230-400 mesh silica gel (Silicycle flash F60) according to the method of Still,[2] unless otherwise noted. Radial Preparative Liquid Chromatography (radial plc) was performed on a Chromatotron® using glass plates coated with Merck, TLC grade 7749 silica gel with gypsum binder and fluorescent indicator.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent (*e.g.,* for $CDCl_3$, δ = 7.26 ppm and 77.0 ppm for ^{1}H and ^{13}C NMR, respectively) and are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent. Molecular mass was determined using an LCMS system comprised of an Agilent 1200 Series HPLC and an Agilent 6130 single quadrupole mass spectrometer. Samples were injected onto a Phenomenex Gemini C18 column (5 micron, 2.1 x 50 mm) and eluted at 0.7 ml/min using a gradient of 10-90% acetonitrile, 0.1% formic acid (11 minute linear ramp). Positive mode electrospray ionization ESI was used to verify the identity of the major component. All compounds submitted for testing at PDSP were >95% purity as determined by LC via AUC at 214- and 254 nm. Experimental and/or characterization data for **5**-**7**,[3] **35**, **36**, **22**,[4] **33**, **34**, and **38** have been reported previously.

General Procedure A: Cross coupling of piperazine with aryl chlorides 5 and 6:

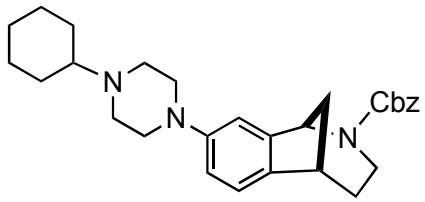


8

(±)-Benzyl-8-(piperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[*c*]azepine-2-carboxylate (**8**): A solution of **6** (208 mg, 0.63 mmol), NaO*t*Bu (85 mg, 0.88 mmol) and piperazine (3.18 mmol, 274 mg) in degassed toluene (1.7 mL) was stirred until the mixture became homogenous (ca. 5 min). A freshly prepared $Pd(OAc)_2$ (0.031 mmol, 7.0 mg) and JohnPhos® (di-*tert*-butylphosphine biphenyl) (0.031 mmol, 9.4 mg) solution in toluene (0.31 mL) that had been stirred for 20 min, was added to the reaction mixture via syringe. The reaction was heated at 100 °C for 1 ¾ h. The reaction was cooled to room temperature and poured into water (10 mL), and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried (K_2CO_3) and filtered through a pad of

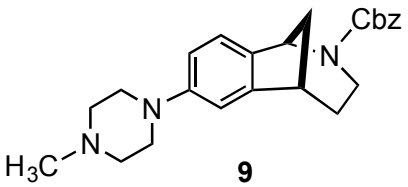
Celite® (filter cake was rinsed with EtOAc (2 x 10 mL). The combined filtrate and washings were concentrated under reduced pressure, and the residue was purified via radial plc (SiO_2), eluting with EtOAc/hexanes (5% v/v → 15% v/v → 30% v/v) to give 170 mg (72%) of **8** as a light yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.45-7.26 (comp, 5 H), 7.10 (d, *J* = 8.3 Hz, 1 H), 6.97 (br s, 0.6 H), 6.79 (app dd, *J* = 8.3, 2.0 Hz, 1.4 H), 5.45 (br s, 0.6 H), 5.34 (br s, 0.4 H), 5.26-5.06 (comp, 2 H), 3.86-3.74 (m, 1 H), 3.45 (br s, 1 H), 3.20-2.96 (comp, 8 H), 2.80-2.66 (m, 1 H), 2.52-2.37 (m, 1 H), 2.24-2.11 (m, 1 H), 2.02-1.88 (m, 1 H), 1.84 (d, *J* = 10.8 Hz, 1 H), 1.62-1.48 (m, 1 H); ^{13}C NMR (75 MHz) δ (rotamers) 155.3, 155.1, 151.9, 151.6, 142.4, 142.1, 137.8, 137.6, 137.4, 137.2, 128.7, 128.2, 128.1, 123.3, 116.4, 116.1, 112.6, 112.4, 78.8, 77.7, 67.1, 58.3, 58.0, 51.3, 50.4, 48.6, 46.5, 44.0, 39.2, 38.9, 30.7; IR (neat) 2942, 2825, 1692, 1417, 1231, 1101 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}N_3O_2$ $(M+H)^+$, 378.2176; found 378.2176.

General Procedure B: Reductive alkylation of arylpiperazines 7 and 8:



28

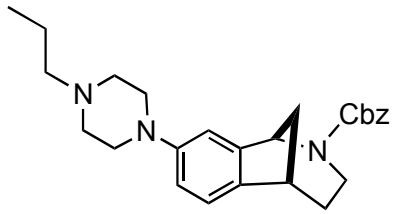
(±)-Benzyl-8-(4-cyclohexylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**28**). Cyclohexanone (23 mg, 25 µL, 0.237 mmol) was added to a stirred mixture of sodium triacetoxyborohydride (34 mg, 0.159 mmol) and **8** (30 mg, 0.079 mmol) in DCE (1 mL) at room temp. The mixture was stirred for 3 h and then poured into brine (10 mL). The mixture was extracted with Et_2O (3x10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified via flash column chromatography (SiO_2), eluting with MeOH/CH_2Cl_2 (2%), to afford 34 mg (94%) of **28** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.47-7.26 (comp, 5 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 6.97 (br s, 0.55 H), 6.81 (app dd, *J* = 8.2, 2.0 Hz, 1.45 H), 5.45 (br s, 0.55 H), 5.34 (br s, 0.45 H), 5.26-5.04 (comp, 2 H), 3.88-3.71 (m, 1 H), 3.28-3.12 (comp, 5 H), 2.80 (br s, 4 H), 2.52-2.35 (comp, 2 H), 2.25-2.10 (m, 1 H), 1.96 (br s, 3 H), 1.84 (app d, *J* = 7.8 Hz, 3 H), 1.66 (d, *J* = 12.0 Hz, 1 H), 1.63-1.48 (m, 1 H), 1.35-1.08 (comp, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.2, 154.9, 151.1, 142.3, 142.0, 137.8, 137.3, 137.0, 128.6, 128.6, 128.0, 127.9, 123.2, 123.1, 116.2, 115.8, 112.6, 112.4, 67.0, 63.8, 58.2, 57.9, 50.0, 49.1, 43.9, 39.1, 38.8, 30.6, 28.9, 26.3, 25.9; IR (neat): 2930, 2853, 1696, 1418, 1238 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{38}N_3O_2$ $(M+H)^+$, 460.2959; found 460.2960.



9

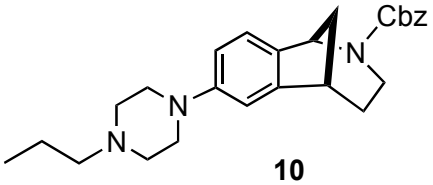
(±)-Benzyl-7-(4-methylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**9**): From **7** and paraformaldehyde following general procedure B, 99%, colorless oil: ^{1}H

NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.47-7.27 (comp, 5 H), 7.21 (d, *J* = 7.1 Hz, 0.5 H), 7.09 (d, *J* = 7.1 Hz, 0.5 H), 6.84 (d, *J* = 2.1 Hz, 1 H), 6.78-6.71 (m, 1 H), 5.43 (br s, 0.5 H), 5.33 (br s, 0.5 H), 5.24-5.05 (comp, 2 H), 3.87-3.72 (m, 1 H), 3.26-3.16 (comp, 5 H), 2.59 (t, *J* = 5.1 Hz, 4 H), 2.53-2.38 (m, 1 H), 2.36 (s, 3 H), 2.53-2.09 (m, 1 H), 2.04-1.87 (m, 1 H), 1.84 (d, *J* = 8.6 Hz, 1 H), 1.64-1.48 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.0, 154.8, 151.9, 147.7, 137.2, 137.0, 135.4, 132.5, 132.2, 128.6, 128.0, 127.9, 124.4, 124.3, 114.6, 111.0, 67.0, 57.2, 57.0, 55.2, 49.5, 46.1, 44.1, 40.3, 38.6, 30.5; IR (neat): 2936, 1694, 1418, 1238 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{24}H_{30}N_3O_2$ $(M+H)^+$, 392.2333; found 392.2333.



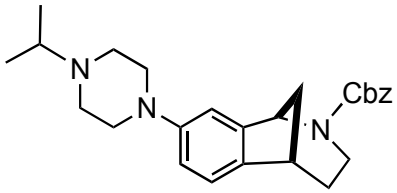
23

(±)-Benzyl-8-(4-propylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**23**): From **8** and propionaldehyde following general procedure B, 75%, colorless oil: ^1H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.47-7.26 (comp, 5 H), 7.10 (d, *J* = 8.3 Hz, 1 H), 6.98 (br s, 0.5 H), 6.85-6.77 (comp, 1.5 H), 5.45 (br s, 0.5 H), 5.34 (br s, 0.5 H), 5.27-5.03 (comp, 2 H), 3.88-3.70 (m, 1 H), 3.27-3.09 (comp, 5 H), 2.67-2.56 (m, 4 H), 2.52-2.34 (m, 1 H), 2.37 (t, *J* = 7.6 Hz, 2 H), 2.24 (m, 1 H), 2.02-1.87 (m, 1 H), 1.84 (d, *J* = 10.5 Hz, 1 H), 1.62-1.47 (m, 1 H), 1.56 (sext, 7.5 Hz, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.1, 154.8, 151.1, 142.1, 141.8, 137.5, 137.2, 136.9, 128.5, 127.9, 127.8, 123.1, 123.0, 116.0, 115.7, 112.4, 112.1, 66.9, 60.7, 58.0, 57.7, 53.3, 49.6, 43.8, 39.0, 38.7, 30.5, 20.0, 12.0; IR (neat): 2936, 1696, 1417, 1237 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_2$ $(M+H)^+$, 420.2646; found 420.2643.



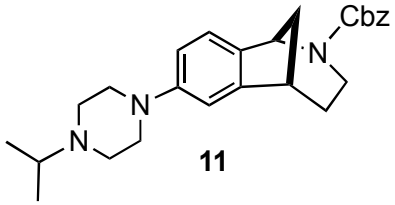
10

(±)-Benzyl-7-(4-propylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**10**)**.** From **7** and propionaldehyde following general procedure B, 99%, colorless oil: ^1H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.45-7.27 (comp, 5 H), 7.21 (d, *J* = 7.9 Hz, 0.5 H), 7.09 (d, *J* = 7.8 Hz, 0.5 H), 6.84 (d, *J* = 2.0 Hz, 1 H), 6.74 (br s, 1 H), 5.43 (brs, 0.5 H), 5.32 (br s, 0.5 H), 5.23-5.04 (comp, 2 H), 3.87-3.71 (m, 1 H), 3.28-3.13 (comp, 5 H), 2.62 (t, *J* = 4.9 Hz, 4 H), 2.53-2.40 (m, 1 H), 2.37 (t, *J* = 7.8 Hz, 2 H), 2.25-2.11 (m, 1 H), 2.05-1.88 (m, 1 H), 1.84 (d, *J* = 9.6 Hz, 1 H), 1.56 (sext, 7.5 Hz, 3 H), 0.93 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.0, 154.9, 152.1, 147.8, 137.3, 137.1, 132.4, 132.1, 128.6, 128.0, 127.9, 124.5, 124.3, 114.6, 111.0, 67.0, 60.8, 57.3, 57.0, 53.4, 49.6, 44.1, 40.4, 38.7, 30.5, 20.1, 12.1; IR (neat): 2937, 2816, 1696, 1417, 1235 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_2$ $(M+H)^+$, 420.2646; found 420.2646.



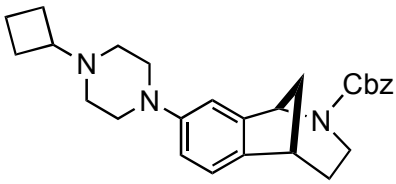
24

(±)-Benzyl-8-(4-isopropylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**24**). From **8** and acetone following general procedure B, 69%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.48-7.26 (comp, 5 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 6.97 (br s, 0.5 H), 6.805 (app dd, *J* = 8.2, 2.1 Hz, 1.5 H), 5.44 (br s, 0.5 H), 5.33 (br s, 0.5 H), 5.26-5.03 (comp, 2 H), 3.87-3.71 (m, 1 H), 3.27-3.11 (comp, 5 H), 2.80-2.66 (comp, 5 H), 2.52-2.34 (m, 1 H), 2.24-2.09 (m, 1 H), 2.03-1.86 (m, 1 H), 1.84 (d, *J* = 11.0 Hz, 1 H), 1.62-1.48 (m, 1 H), 1.12 ppm (s, 6 H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.2, 154.9, 151.2, 142.3, 142.0, 137.7, 137.3, 137.0, 128.6, 128.6, 128.0, 127.9, 123.2, 123.1, 116.2, 115.8, 112.6, 112.4, 67.0, 58.1, 57.8, 54.8, 50.0, 48.9, 43.9, 39.1, 38.8, 30.6, 18.6; IR (neat): 2936, 2820, 1696, 1417, 1238 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{34}N_3O_2$ $(M+H)^+$, 420.2646; found 420.2646.



11

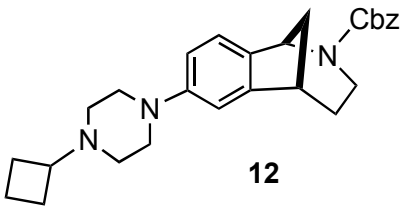
(±)-Benzyl-7-(4-isopropylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**11**)**.** From **7** and acetone following general procedure B, 65%, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.47-7.27 (comp, 5 H), 7.21 (d, *J* = 7.3 Hz, 0.5 H), 7.09 (d, *J* = 7.5 Hz, 0.5 H), 6.84 (d, *J* = 2.2 Hz, 1 H), 6.78-6.71 (m, 1 H), 5.43 (br s, 0.5 H), 5.33 (br s, 0.5 H), 5.23-5.05 (comp, 2 H), 3.86-3.73 (m, 1 H), 3.27-3.17 (comp, 5 H), 2.80-2.65 (comp, 5 H), 2.52-2.37 (m, 1 H), 2.25-2.11 (m, 1 H), 2.02-1.79 (comp, 2 H), 1.63-1.48 (m, 1 H), 1.11 (d, *J* = 6.6 Hz, 6 H); HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_2$ $(M+H)^+$, 420.2646; found 420.2656.



25

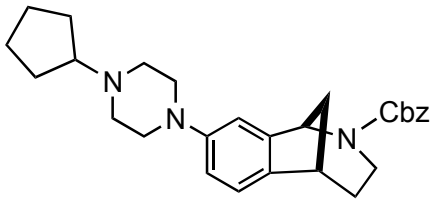
(±)-Benzyl-8-(4-cyclobutylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**25**). From **8** and cyclobutanone following general procedure B, 75%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.46-7.27 (comp, 5 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 6.97 (br s, 0.5 H), 6.80 (app dd, *J* = 8.2, 2.4 Hz, 1.5 H), 5.45 (br s, 0.5 H), 5.33 (br s, 0.5 H), 5.26-5.03 (comp, 2 H), 3.87-3.71 (m, 1 H), 3.24-3.07 (comp, 5 H), 2.79 (quint, *J* = 7.9 Hz, 1 H), 2.49 (t, *J* = 4.8 Hz, 4 H), 2.47-2.35 (m, 1 H), 2.25-2.02 (comp, 3 H), 2.02-1.48 (comp, 7 H); ^{13}C NMR (150 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.2, 154.9, 151.3, 142.3, 142.0, 137.7, 137.0, 128.6, 128.6, 128.0, 127.9, 123.2, 123.1, 116.2, 115.9, 112.7, 112.4, 67.1, 60.5, 58.2, 57.9, 49.7, 49.6,

43.9, 39.1, 38.8, 30.6, 27.1, 14.5. IR (neat) 2939, 2818, 1696, 1418, 1239 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_3O_2$ $(M+H)^+$, 432.2646; found 432.2651.



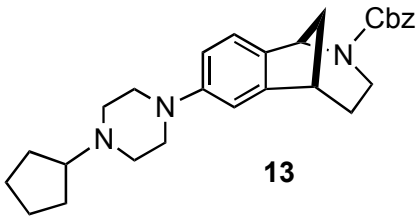
12

(±)-Benzyl-7-(4-cyclobutylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**12**). From **7** and cyclobutanone following general procedure B, 92%, colorless oil: ^1H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.46-7.27 (comp, 5 H), 7.20 (d, *J* = 7.2 Hz, 0.5 H), 7.09 (d, *J* = 7.2 Hz, 0.5 H), 6.84 (d, *J* = 2.0 Hz, 1 H), 6.78-6.68 (m, 1 H), 5.43 (br s, 0.5 H), 5.32 (br s, 0.5 H), 5.24-5.04 (comp, 2 H), 3.88-3.70 (m, 1 H), 3.26-3.14 (comp, 5 H), 2.79 (quin, *J* = 7.9 Hz, 1 H), 2.50 (t, *J* = 4.8 Hz, 5 H), 2.25-2.12 (m, 1 H), 2.11-1.65 (comp, 8 H), 1.65-1.48 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.0, 154.9, 152.1, 147.8, 137.3, 137.1, 132.6, 132.2, 128.6, 128.0, 127.9, 124.5, 124.3, 114.7, 111.1, 67.0, 60.4, 57.3, 57.0, 49.6, 49.3, 44.1, 40.3, 38.6, 30.5, 27.1; IR (neat) 2938, 2816, 1659, 1417, 1237, 1199, 1095 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_3O_2$ $(M+H)^+$, 432.2646; found 432.2646.



26

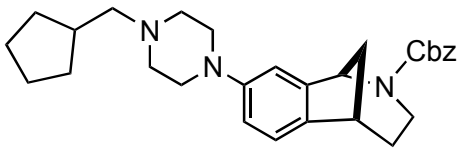
(±)-Benzyl-8-(4-cyclopentylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**26**). From **8** and cyclopentanone following general procedure B, 94%, colorless oil: ^1H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.44-7.26 (comp, 5 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 6.97 (br s, 0.55 H), 6.82-6.77 (comp, 1.45 H), 5.44 (d, *J* = 2.7 Hz, 0.55 H), 5.33 (d, *J* = 2.7 Hz, 0.45 H), 5.26-5.03 (comp, 2 H), 3.86-3.70 (m, 1 H), 3.24-3.12 (comp, 5 H), 2.68 (t, *J* = 4.8 Hz, 4 H), 2.61-2.35 (comp, 2 H), 2.25-2.10 (m, 1 H), 2.01-1.40 (comp, 11 H); ^{13}C NMR (100 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.2, 151.1, 142.2, 142.0, 137.7, 137.3, 137.0, 128.6, 128.0, 127.9, 123.2, 123.1, 116.1, 115.8, 112.6, 112.3, 67.7, 67.0, 58.1, 57.8, 52.5, 49.7, 43.9, 39.1, 38.8, 30.6, 30.5, 24.3; IR (neat): 2953, 1696, 1417, 1238 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}N_3O_2$ $(M+H)^+$, 446.2802; found 446.2808.



13

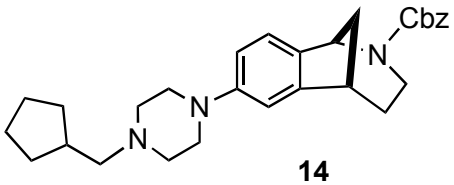
(±)-Benzyl-7-(4-cyclopentylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**13**). From **7** and cyclopentanone following general procedure B, 99%, colorless oil: ^1H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.46-7.27

(comp, 5 H), 7.21 (d, J = 7.9 Hz, 0.5 H), 7.09 (d, J = 7.9 Hz, 0.5 H), 6.84 (d, J = 1.9 Hz, 1 H), 6.78-6.70 (m, 1 H), 5.43 (br s, 0.5 H), 5.32 (br s, 0.5 H), 5.23-5.04 (comp, 2 H), 3.88-3.72 (m, 1 H), 3.30-3.13 (comp, 5 H), 2.68 (t, J = 4.8 Hz, 4 H), 2.60-2.35 (comp, 2 H), 2.26-2.10 (m, 1 H), 2.04-1.79 (comp, 4 H), 1.75-1.66 (comp, 2 H), 1.64-1.39 (comp, 5 H); ^{13}C NMR (150 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.0, 154.9, 152.0, 147.8, 137.3, 137.1, 132.4, 132.1, 128.6, 128.0, 127.9, 124.5, 124.3, 114.5, 111.0, 67.7, 67.0, 57.3, 57.0, 52.5, 49.6, 44.1, 40.3, 38.7, 30.5, 30.54, 30.51, 24.3; IR (neat) 2953, 2817, 1696, 1417, 1237, 1096 cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{36}N_3O_2$ $(M+H)^+$, 446.2802; found 446.2806.



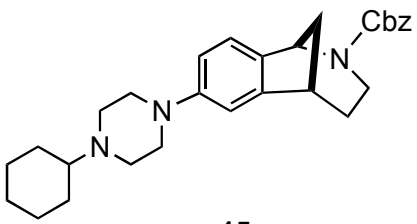
27

(±)-Benzyl-8-(4-(cyclopentylmethyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**27**). From **8** and cyclopentanecarboxaldehyde following general procedure B, 46%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.46-7.27 (comp, 5 H), 7.09 (d, *J* = 8.2 Hz, 1 H), 6.97 (br s, 0.55 H), 6.83-6.76 (comp, 1.45 H), 5.45 (d, *J* = 2.8 Hz, 0.55 H), 5.33 (d, *J* = 2.8 Hz, 0.45 H), 5.26-5.04 (comp, 2 H), 3.86-3.70 (m, 1 H), 3.25-3.09 (comp, 5 H), 2.60 (t, *J* = 4.8 Hz, 4 H), 2.53-2.37 (m, 1 H), 2.34 (d, *J* = 7.5 Hz, 2 H), 2.24-2.11 (m, 1 H), 2.10 (sept, *J* = 7.5 Hz, 1 H), 2.03-1.87 (m, 1 H), 1.84 (d, *J* = 3.0 Hz, 1 H), 1.82-1.74 (comp, 2 H), 1.65-1.48 (comp, 5 H), 1.30-1.16 (comp, 2 H); IR (neat): 2944, 1697, 1417, 1237 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{38}N_3O_2$ $(M+H)^+$, 460.2959; found 460.2963.



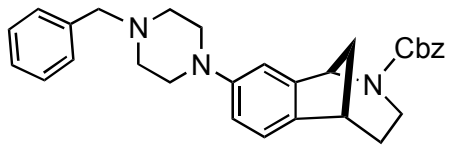
14

(±)-Benzyl-7-(4-(cyclopentylmethyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**14**). From **7** and cyclopentanecarboxaldehyde following general procedure B, 54%, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.46-7.27 (comp, 5 H), 7.20 (d, J = 7.3 Hz, 0.5 H), 7.12 (d, J = 7.3 Hz, 0.5 H), 6.84 (d, J = 2.0 Hz, 1 H), 6.77-6.71 (m, 1 H), 5.43 (br s, 0.5 H), 5.33 (br s, 0.5 H), 5.22-5.06 (comp, 2 H), 3.87-3.74 (m, 1 H), 3.24-3.16 (comp, 5 H), 2.61 (t, J = 5.1 Hz, 4 H), 2.52-2.37 (m, 1 H), 2.33 (2 H), 2.24-2.14 (m, 1 H), 2.10 (sept, J = 6.4 Hz, 1 H), 2.03-1.89 (m, 1 H), 1.88-1.17 (comp, 10 H); IR (neat): 2945, 2867, 1696, 1418, 1236 cm^{-1}; HRMS (ESI) m/z calcd for $C_{29}H_{38}N_3O_2$ $(M+H)^+$, 460.2959; found 460.2962.



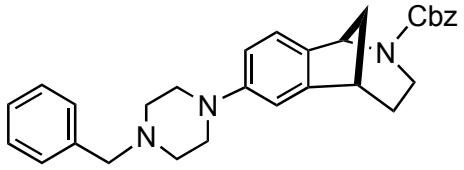
15

(±)-Benzyl-7-(4-cyclohexylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**15**): From **7** and cyclohexanone following general procedure B, 47%, colorless oil: ^{1}H NMR (400 MHz, CD_3OD, as a mixture of rotamers) δ 7.45-7.24 (comp, 5 H), 7.10 (dd, J = 12.2, 7.5 Hz, 1 H), 6.92 (d, J = 2.0 Hz, 1 H), 6.85-6.77 (m, 1 H), 5.31 (brs, 1 H), 5.21-5.04 (comp, 2 H), 3.81-3.69 (m, 1 H), 3.24-3.11 (comp, 5 H), 2.79 (t, J = 5.0 Hz, 4 H), 2.46-2.27 (comp, 2 H), 2.21-2.10 (m, 1 H), 2.04-1.92 (comp, 3 H), 1.84 (app d, J = 11.0 Hz, 3 H), 1.70-1.51 (comp, 2 H), 1.37-1.09 (comp, 5 H); ^{13}C NMR (150 MHz, CD_3OD, as a mixture of rotamers) δ 156.7, 156.5, 153.6, 148.8, 138.4, 138.2, 133.3, 129.5, 129.1, 128.9, 128.8, 124.9, 116.0, 112.1, 68.2, 65.0, 58.8, 58.5, 50.6, 50.1, 44.9, 41.4, 39.7, 31.4, 29.7, 27.3, 26.9; IR (neat) 2929, 2853, 1696, 1417, 1235 cm^{-1}; HRMS (ESI) m/z calcd for $C_{29}H_{38}N_3O_2$ $(M+H)^+$, 460.2959; found 460.2958.



29

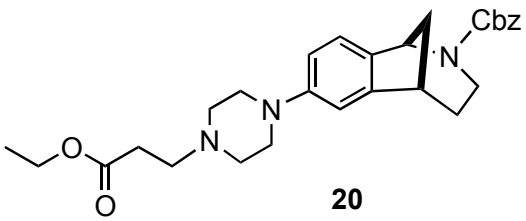
(±)-Benzyl-8-(4-benzylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**29**)**.** From **8** and benzaldehyde following general procedure B, 65%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.46-7.24 (comp, 10 H), 7.12 (d, *J* = 8.2 Hz, 1 H), 6.95-6.71 (comp, 2 H), 5.33 (d, *J* = 4.2 Hz, 1 H), 5.28-5.04 (comp, 2 H), 3.80-3.66 (m, 1 H), 3.60 (s, 2 H), 3.21-3.05 (comp, 5 H), 2.63 (br s, 4 H), 2.46-2.26 (m, 1 H), 2.21-2.09 (m, 1 H), 2.03-1.89 (m, 1 H), 1.83 (d, *J* = 11.0 Hz, 1 H), 1.64-1.47 (m, 1 H); HRMS (ESI) *m/z* calcd for $C_{30}H_{34}N_3O_2$ $(M+H)^+$, 468.2646; found 468.2644.



16

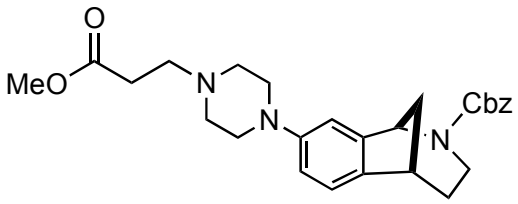
(±)-Benzyl-7-(4-benzylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**16**). From **7** and benzaldehyde following general procedure B, 74%, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.44-7.26 (comp, 10 H), 7.20 (br d, *J* = 7.8 Hz, 0.5 H), 7.08 (br d, *J* = 7.8 Hz, 0.5 H), 6.82 (d, *J* = 2.2 Hz, 1 H), 6.76-6.70 (m, 1 H), 5.43 (br s, 0.5 H), 5.32 (br s, 0.5 H), 5.23-5.06 (comp, 2 H), 3.86-3.73 (m, 1 H), 3.57 (s, 2 H), 3.25-3.15 (comp, 5 H), 2.65-2.57 (m, 4 H), 2.53-2.38 (m, 1 H), 2.24-2.12 (m, 1 H), 2.03-1.88 (m, 1 H), 1.87-1.80 (m, 1 H), 1.63-1.51 (m, 1 H, behind water peak); HRMS (ESI) m/z calcd for $C_{30}H_{34}N_3O_2$ $(M+H)^+$, 468.2646; found 468.2644.

General Procedure C: Alkylation of piperazines 7 and 8 with acrylates:



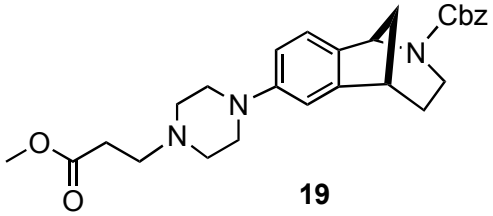
20

(±)-Benzyl-7-(4-(3-ethoxy-3-oxopropyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**20**). A solution of **7** (20 mg, 0.053) and ethyl acrylate (53 mg, 58μL, 0.53 mmol) in ethanol (1 mL) was stirred for 2.5 h at room temperature. The mixture was concentrated under reduced pressure and the residue was purified via flash column chromatography (SiO_2), eluting with MeOH/CH_2Cl_2 (2% v/v), to afford 25 mg (99%) of **20** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.45-7.27 (comp, 5 H), 7.21 (d, *J* = 7.8 Hz, 0.5 H), 7.09 (d, *J* = 7.8 Hz, 0.5 H, 6.83 (d, *J* = 2.2 Hz, 1 H), 6.73 (br s, 1 H), 5.43 (br s, 0.5 H), 5.32 (br s, 0.5 H), 5.22-5.05 (comp, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.87-3.71 (m, 1 H), 3.25-3.13 (comp, 5 H), 2.76 (t, *J* = 7.2 Hz, 2 H), 2.63 (t, *J* = 5.0 Hz, 4 H), 2.54 (t, *J* = 7.3 Hz, 2 H), 2.50-2.36 (m, 1 H), 2.24-2.10 (m, 1 H), 2.03-1.88 (m, 1 H), 1.84 (d, *J* = 7.9 Hz, 1 H), 1.64-1.49 (m, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, as a mixture of rotamers) δ 172.6, 155.0, 154.9, 152.0, 147.8, 137.3, 137.1, 132.5, 132.2, 128.6, 128.0, 127.9, 124.5, 124.3, 114.6, 111.0, 67.0, 60.6, 57.3, 57.0, 53.7, 53.1, 49.6, 44.1, 40.3, 38.6, 32.5, 30.5; IR (neat) 2940, 2821, 1733, 1695, 1418, 1237, 1200 cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{36}N_3O_4$ $(M+H)^+$, 478.2700; found 478.2700.



32

(±)-Benzyl-8-(4-(3-methoxy-3-oxopropyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**32**). From **8** and methyl acrylate following general procedure C, 99%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.47-7.27 (comp, 5 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 6.96 (br s, 0.55 H), 6.79 (app dd, *J* = 8.2, 2.4 Hz, 1.45 H), 5.45 (d, *J* = 2.5 Hz, 0.55 H), 5.33 (d, *J* = 2.5 Hz, 0.45 H), 5.26-5.04 (comp, 2 H), 3.86-3.72 (m, 1 H), 3.69 (s, 3 H), 3.22-3.06 (comp, 5 H), 2.76 (t, *J* = 7.4 Hz, 2 H), 2.62 (t, *J* = 4.9 Hz, 4 H), 2.56 (t, *J* = 7.4 Hz, 2 H), 2.52-2.34 (m, 1 H), 2.24-2.09 (m, 1 H), 2.01-1.87 (m, 1 H), 1.84 (d, *J* = 11.0 Hz, 1 H), 1.62-1.48 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, as a mixture of rotamers) δ 172.8, 155.1, 154.8, 151.0, 142.2, 141.9, 137.7, 137.2, 136.9, 128.5, 127.9, 127.8, 123.1, 116.2, 115.9, 112.4, 112.2, 66.9, 58.1, 57.8, 53.5, 53.0, 51.8, 49.6, 43.8, 39.0, 38.7, 32.0, 30.5. IR (neat): 2945, 2821, 1738, 1695, 1418, 1239, 1200, 1097 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_3O_4$ $(M+H)^+$, 464.2544; found 464.2546.

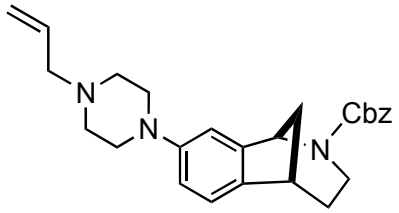


19

(±)-Benzyl-7-(4-(3-methoxy-3-oxopropyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**19**). From **7** and methyl acrylate following general procedure C, 81%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.46-7.27 (comp, 5 H), 7.21 (d, *J* = 7.0 Hz, 0.5 H), 7.09 (d, *J* = 7.0 Hz, 0.5 H), 6.83 (d, *J* = 2.1 Hz, 1 H), 6.73 (br s, 1 H), 5.43 (br s, 0.5 H), 5.33 (br s, 0.5 H), 5.24-5.03 (comp, 2 H), 3.88-3.73 (m, 1 H), 3.69 (s, 3 H), 3.24-3.15 (comp, 5 H), 2.76 (t, *J* = 7.3 Hz, 2 H), 2.63 (t, *J* = 5.0 Hz, 4 H), 2.55 (t, *J* = 7.2 Hz, 2 H), 2.51-2.36 (m, 1 H), 2.24-2.11 (m, 1 H), 2.04-1.88 (m, 1 H), 1.84 (d, *J* = 10.7 Hz, 1 H), 1.66-1.49 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, as a mixture of rotamers) δ 172.9, 155.0, 154.9, 152.0, 147.8, 137.3, 137.1, 132.6, 132.4, 128.6, 128.0, 127.9, 124.5, 124.3, 114.7, 111.1, 67.0, 57.3, 57.1, 53.1, 51.9, 49.5, 44.1,

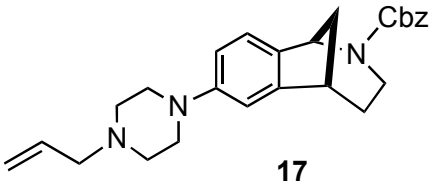
40.4, 38.7, 32.2, 30.5; IR (neat): 2945, 2821, 1738, 1694, 1418, 1237, 1200 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{34}N_3O_4$ $(M+H)^+$, 464.2544; found 464.2544.

General Procedure D: Alkylation of piperazines 7 and 8 with alkyl bromides:



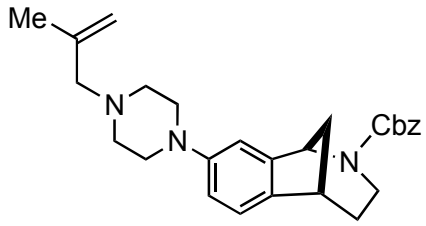
30

(±)-Benzyl-8-(4-allylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo-[c]azepine-2-carboxylate (**30**). A mixture of K_2CO_3 (17 mg, 0.12 mmol), **8** (15 mg, 0.04 mmol), and allyl bromide (5 mg, 3.6 µL, 0.05 mmol) in acetone was stirred at room temperature for 24 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified via flash column chromatography (SiO_2), eluting with $MeOH/CH_2Cl_2$ (2% v/v), to afford 14 mg (86%) of **30** as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.49-7.26 (comp, 5 H), 7.11 (d, *J* = 8.3 Hz, 1 H), 6.97 (br s, 0.6 H), 6.84-6.75 (comp, 1.4 H), 6.02-5.86 (m, 1 H), 5.50-5.01 (comp, 5 H), 3.89-3.71 (m, 1 H), 3.32-3.02 (comp, 7 H), 2.66 (br s, 4 H), 2.52-2.34 (m, 1 H), 2.24-2.09 (m, 1 H), 2.03-1.87 (m, 1 H), 1.84 (d, *J* = 10.2 Hz, 1 H), 1.64-1.48 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.2, 154.9, 151.2, 142.3, 142.0, 137.6, 137.3, 137.0, 135.0, 128.6, 128.0, 127.9, 123.19, 123.12, 118.3, 116.2, 115.8, 112.5, 112.3, 67.0, 61.9, 58.2, 57.9, 53.3, 49.8, 43.9, 39.1, 38.8, 30.6; IR (neat) 2938, 2818, 1696, 1419, 1236 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{32}N_3O_2$ $(M+H)^+$, 418.2489; found 418.2486.



17

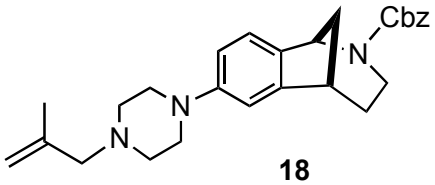
(±)-Benzyl-7-(4-allylpiperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo-[c]azepine-2-carboxylate (**17**). From **7** and allyl bromide following general procedure D, 84%, colorless oil: ^1H NMR (400 MHz, CD_3OD, as a mixture of rotamers) δ 7.45-7.25 (comp, 5 H), 7.14 (d, *J* = 8.2 Hz, 0.5 H), 7.06 (d, *J* = 8.2 Hz, 0.5 H), 6.93 (d, *J* = 2.3 Hz, 1 H), 6.85-6.77 (m, 1 H), 5.92 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1 H), 5.35-5.04 (comp, 5 H), 3.81-3.69 (m, 1 H), 3.27-3.18 (comp, 5 H), 3.09 (d, *J* = 6.7 Hz, 2 H), 2.69-2.61 (m, 4 H), 2.48-2.27 (m, 1 H), 2.24-2.11 (m, 1 H), 2.04-1.92 (m, 1 H), 1.85 (d, *J* = 10.8 Hz, 1 H), 1.67-1.52 (m, 1 H); HRMS (ESI) m/z calcd for $C_{26}H_{32}N_3O_2$ $(M+H)^+$, 418.2489; found 418.2492.



31

(±)-Benzyl-8-(4-(2-methylallyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[*c*]azepine-2-carboxylate (**31**): From **8** and 3-bromo-2-methylpropene following

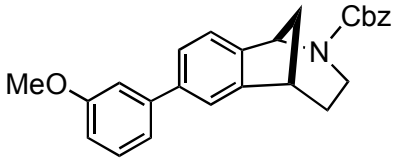
general procedure D, 97%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.45-7.28 (comp, 5 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 6.97 (br s, 0.6 H), 6.81 (d, *J* = 8.2 Hz, 1.4 H), 5.47-5.43 (m, 0.6 H), 5.36-5.31 (m, 0.4 H), 5.26-5.05 (comp, 2 H), 4.91 (d, *J* = 10.4 Hz, 2 H), 3.87-3.72 (m, 1 H), 3.26-3.08 (comp, 5 H), 2.94 (s, 2 H), 2.64-2.48 (comp, 4 H), 2.48-2.36 (m, 1 H), 2.24-2.10 (m, 1 H), 2.02-1.88 (m, 1 H), 1.84 (d, *J* = 10.4 Hz, 1 H), 1.79 (s, 3 H), 1.70-1.48 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.0, 154.8, 151.2, 142.1, 141.8, 137.2, 136.9, 128.5, 128.4, 127.9, 127.8, 123.1, 123.0, 116.0, 115.7, 112.3, 66.9, 65.3, 58.0, 57.7, 53.1, 49.7, 43.8, 39.0, 38.6, 30.5, 29.7, 21.0; IR (neat) 2935, 2804, 1692 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_3O_2$ $(M+H)^+$, 432.2646; found 432.2650.



18

(±)-Benzyl-7-(4-(2-methylallyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[c]azepine-2-carboxylate (**18**). From **7** and 3-bromo-2-methylpropene following general procedure D, 47%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.45-7.16 (comp, 5 H), 7.21 (d, *J* = 7.9 Hz, 0.5 H), 7.10 (d, *J* = 7.5 Hz, 0.5 H), 6.85 (d, *J* = 2.4 Hz, 1 H), 6.78-6.72 (m, 1 H), 5.44 (br s, 0.5 H), 5.34 (br s, 0.5 H), 5.24-5.06 (comp, 2 H) 4.90 (d, *J* = 15.1 Hz, 2 H), 3.91-3.74 (m, 1 H), 3.26-3.14 (comp, 5 H), 2.94 (s, 2 H), 2.60-2.38 (comp, 5 H), 2.25-2.10 (m, 1 H), 2.03-1.89 (m, 1 H), 1.88-1.81 (m, 1 H), 1.77 (s, 3 H), 1.66-1.50 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$, as a mixture of rotamers) δ 155.0, 154.9, 152.2, 147.8, 142.7, 137.3, 137.1, 132.3, 132.0, 128.6, 128.0, 127.9, 124.5, 124.3, 114.5, 113.2, 110.9, 67.0, 65.5, 57.3, 57.1, 53.3, 49.7, 44.2, 40.4, 38.7, 30.5, 21.1; IR (neat) 2939, 2816, 1696, 1418 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{34}N_3O_2$ $(M+H)^+$, 432.2646; found 432.2653.

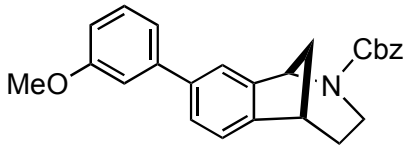
General Procedure E: Suzuki cross coupling of aryl chlorides 5 and 6:



39

(±)-Benzyl-7-(3-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[*c*]azepine-2-carboxylate (39): A solution of carbamate **5** (122 mg, 0.37 mmol), 3-methoxyphenylboronic acid (114 mg, 0.74 mmol), Cs_2CO_3 (243 mg, 0.75 mmol), Pd[(^{t}-butyl)$_3$]$_2$ phosphine (9.5 mg, 0.02 mmol) in degassed 1,4-dioxane (1.5 mL) was stirred for 5 h at 100 ^{o}C. The reaction was cooled to room temp and diluted with CH_2Cl_2 (3 mL) and filtered through Celite. The filter cake was rinsed with CH_2Cl_2 (10 mL) and the mixture was concentrated under reduced pressure to provide the crude product, which was purified via radial plc (SiO_2) eluting with ethyl acetate/hexanes (5% v/v) to give 110 mg (74%) of **39** as a white foam: ^{1}H NMR (600 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.48-7.38 (comp, 5 H), 7.37-7.36 (m, 1 H), 7.36-7.33 (comp, 3 H), 7.18 (d, *J* = 6.0 Hz, 1 H), 7.13-7.11 (m, 1 H), 6.90 (d, *J* = 12 Hz, 1 H), 5.56 (br s, 0.6 H), 5.45 (br s, 0.4 H), 5.26-5.06 (comp, 2 H), 3.88-3.34 (m, 1 H), 3.87 (s, 3 H), 3.38-3.30 (m, 1 H), 2.59-2.43 (m, 1 H), 2.25 (br d, *J* = 30 Hz, 1 H), 2.09-1.97 (m, 1 H), 1.95-1.85 (m, 1 H), 1.92 (d, *J* = 10 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$, as a mixture of rotamers) δ 159.9, 155.0, 154.8, 147.1, 142.8, 141.6, 140.2, 140.0, 137.0, 136.8, 129.7, 128.5, 127.9, 127.8, 126.4, 124.1, 123.8, 121.6, 119.7,

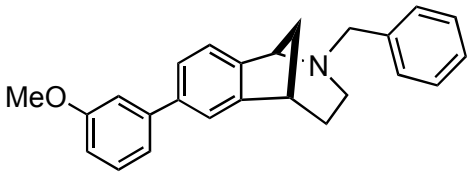
112.9, 112.7, 67.0, 57.3, 57.1, 55.3, 43.7, 39.9, 38.6, 30.3, 29.7; IR (neat) 2941, 1699, 1421, 1302 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{25}NO_3Na$ $(M+Na)^+$, 422.1727, found 422.1734.



40

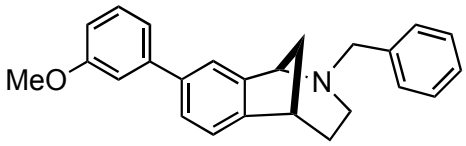
(±)-Benzyl-8-(3-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-1,5-methanobenzo[*c*]azepine-2-carboxylate (**40**): From **6** and (3-methoxyphenyl)boronic acid following general procedure E, 57%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers) δ 7.61 (br s, 0.4 H), 7.54-7.32 (comp, 7.6 H), 7.30 (dd, *J* = 7.4, 2.2 Hz, 1 H), 7.22-7.08 (comp, 2 H), 6.90 (dd, *J* = 8.4, 2.4 Hz, 1 H), 5.61 (br s, 0.6 H), 5.49 (br s, 0.4 H), 5.30-5.09 (comp, 2 H), 3.95-3.80 (m, 1 H), 3.88 (s, 3 H), 3.36-3.31 (m, 1 H), 2.62-2.46 (m, 1 H), 2.36-2.20 (m, 1 H), 2.12-1.97 (m, 1 H), 1.93 (d, *J* = 10.8 Hz, 1 H), 1.72-1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, as a mixture of rotamers) δ 160.9, 159.9, 157.6, 155.0, 154.8, 145.5, 142.5, 141.7, 141.4, 140.4, 129.9, 129.7, 128.4, 127.8, 127.3, 122.9, 122.6, 119.6, 112.8, 112.6, 107.8, 105.8, 101.5, 67.0, 57.6, 57.3, 55.3, 55.1, 43.7, 39.4, 38.5, 34.6, 32.1, 32.0, 31.5, 30.9, 30.2; IR (neat) 2941, 1698, 1432 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{25}NO_3Na$ $(M+Na)^+$, 422.1727, found 422.1733.

General Procedure F: Deprotection/N-benzylation of carbamates 35, 36, 39 and 40:



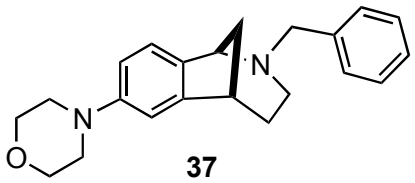
41

(±)-2-Benzyl-7-(3-methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[*c*]azepine (**41**): Iodotrimethylsilane (52 mg, 37 µL, 0.26 mmol) was added to a solution of carbamate **39** (52 mg, 0.13 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C in the dark. After stirring for 5 min at 0 °C and 4 h at room temp, in the dark, MeOH (3 mL) and a saturated aqueous $NaHCO_3$ solution (3 mL) were added, and the mixture was stirred for 10 min at room temp. The MeOH was removed under reduced pressure, and the aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the residue was purified via flash column chromatography (SiO_2), eluting with EtOAc/hexanes (10% v/v) → EtOAc/hexanes (20% v/v) to give 40 mg (87 %) of benzylamine **41** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.43 (comp, 4 H), 7.40-7.34 (comp, 3 H), 7.31-7.25 (comp, 2 H), 7.23-7.20 (m, 1 H), 7.17 (t, *J* = 2.0 Hz, 1 H), 6.91 (dd, *J* = 8.4, 2.4 Hz, 1 H), 4.00-3.96 (m, 1 H), 3.89 (s, 3 H), 3.50 (d, *J* = 13.0 Hz, 1 H), 3.38 (d, *J* = 13.0 Hz, 1 H), 3.24-3.19 (m, 1 H), 2.70-2.60 (m, 1 H), 2.27-2.20 (m, 1 H), 2.14-2.0 (comp, 2 H), 1.66-1.55 (comp, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 147.8, 143.3, 141.2, 130.0, 129.6, 128.7, 127.4, 125.6, 124.7, 121.8, 120.0, 113.1, 112.9, 62.6, 60.4, 55.6, 47.4, 44.6, 40.1, 30.3; IR (neat): 2939, 1608, 1472, 1227, 1065 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{26}NO$ $(M+H)^+$, 356.2009; found 356.2010.



42

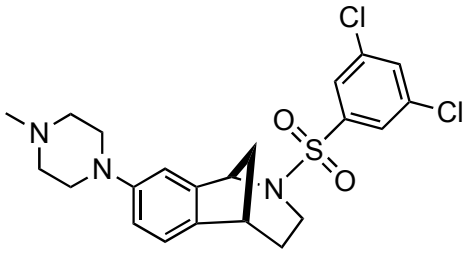
(±)-2-Benzyl-8-(3-methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[*c*]azepine (**42**)**:** From **40**, following general procedure F, 75%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.6, 1.8 Hz, 1 H), 7.46-7.21 (comp, 9 H), 7.17 (t, *J* = 2.0 Hz, 1 H), 6.92 (dd, *J* = 8.4, 2.4 Hz, 1 H), 3.99 (d, *J* = 4.0 Hz, 1 H), 3.90 (s, 3 H), 3.52 (d, *J* = 13.4 Hz, 1 H), 3.35 (d, *J* = 13.4 Hz, 1 H), 3.22-3.17 (m, 1 H), 2.68-2.58 (m, 1 H), 2.27-2.19 (m, 1 H), 2.13-2.03 (comp, 2 H), 1.64-1.53 (comp, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 146.1, 143.2, 139.4, 129.7, 129.2, 128.3, 127.0, 126.8, 123.0, 122.7, 119.7, 113.1, 112.3, 62.8, 60.2, 55.3, 47.1, 44.5, 39.6, 29.7; IR (neat): 2928, 2853, 1609, 1472 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{26}NO$ $(M+H)^+$, 356.2009; found 356.2012.



37

(±)-2-Benzyl-2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[*c*]azepin-7-yl)morpholine (**37**): From **35**, following general procedure F, 58%, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.8 Hz, 2 H), 7.33 (t, *J* = 7.2 Hz, 2 H), 7.26-7.24 (m, 1 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 6.85 (d, *J* = 2.0 Hz, 1 H), 6.75 (dd, *J* = 8.2, 2.2 Hz, 1 H), 3.88 (t, *J* = 4.8, 4 H), 3.83 (d, *J* = 4.8 Hz, 1 H), 3.7 (d, *J* = 13.2 Hz, 1 H), 3.27 (d, *J* = 13.2 Hz, 1 H), 3.18 (t, *J* = 5.0 Hz, 4 H), 3.09-3.05 (m, 1 H), 2.57-2.51 (m, 1 H), 2.18-2.12 (m, 1 H), 2.02-1.92 (m, 1 H), 1.92 (d, *J* = 10.4 Hz, 1 H), 1.55-1.45 (comp, 2 H); ^{13}C NMR (mono-HCl salt) (125 MHz, DMSO-d_6) δ 151.3, 148.7, 131.3, 131.2, 130.0, 129.2, 128.7, 126.8, 114.28, 111.0, 65.6, 63.1, 57.3, 49.1, 46.6, 39.8, 38.0, 26.8; IR (mono HCl salt) (neat): 2964, 1628, 1432 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{27}N_2O$ $(M+H)^+$, 335.2118; found 335.2128.

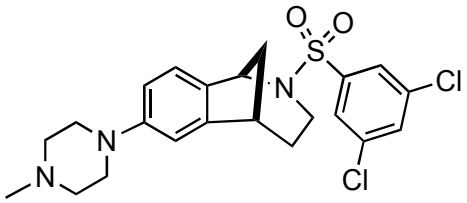
General Procedure G: Deprotection/sulfonylation of arylpiperazines 9 and 22:



34

(±)-2-((3,5-Dichlorophenyl)sulfonyl)-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[*c*]azepine (**34**): Iodotrimethylsilane (613 mg, 0.436 mL 3.06 mmol) was added in one portion to a solution of carbamate **22** (300 mg, 0.766 mmol) in CH_2Cl_2 at 0 °C in flask wrapped in foil. The mixture was stirred for 75 min, and it was then canulated into $HCl_{(aq)}$ (3 M, 20 mL) at ~5 °C, using CH_2Cl_2 (15 mL) to ensure complete transfer. The biphasic mixture was concentrated under reduced pressure to remove CH_2Cl_2, and the aqueous layer was washed with Et_2O (3x10 mL) to remove benzyl iodide. The pH of the aqueous layer was adjusted to ~8 by the slow addition of solid NaOH, and was subsequently extracted with Et_2O (3x20 mL). The combined organic extracts were dried (Na_2SO_4) and

concentrated under reduced pressure to afford 161 mg (82%) of the secondary amine intermediate, which was of sufficient purity (>95% LC and ^{1}H NMR) to be used in subsequent reactions without purification. 3,5-Dichlorosulfonyl chloride (35 mg, 0.143 mmol) was added to a stirred solution of secondary amine (28 mg, 0.109 mmol) and Et_3N (33 mg, 46 µL) in DCE (1 mL) at room temp. After 15 min, the mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified via flash column chromatography (SiO_2), eluting with MeOH/CH_2Cl_2 (0% → 2% v/v gradient), to afford 35 mg (70%) of **34** as a colorless foam. The characterization data for **34** have been previously reported.[3]



21

(±)-2-((3,5-Dichlorophenyl)sulfonyl)-7-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-methanobenzo[c]azepine (**21**): From **9,** via TMSI and 3,5-dichlorophenylsulfonyl chloride, following general procedure G, 78%, colorless foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 2.0 Hz, 2 H), 7.52 (t, *J* = 2.0 Hz, 1 H), 6.76 (br s, 1 H), 6.55 (app d, *J* = 1.4 Hz, 2 H), 5.04 (d, *J* = 4.3 Hz, 1 H), 3.56 (dd, *J* = 11.9, 5.9 Hz, 1 H), 3.23 (dd, *J* = 5.5, 4.5 Hz, 4 H), 3.20-3.15 (m, 1 H), 2.65 (t, *J* = 5.0 Hz, 4 H), 2.40 (s, 3 H), 2.29-2.16 (comp, 2 H), 2.10-2.00 (m, 1 H), 1.97 (d, *J* = 10.9 Hz, 1 H), 1.60 (d, *J* = 12.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 147.6, 142.7, 136.0, 132.3, 129.4, 125.8, 124.4, 114.4, 110.8, 59.7, 55.0, 48.9, 45.9, 44.8, 40.5, 39.9, 30.0; IR (neat): 2938, 1614, 1568, 1350, 1167, 936 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{26}Cl_2N_3O_2S$ $(M+H)^+$, 466.1117; found 466.1117.

References

1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and convenient procedure for solvent purification. *Organometallics* **1996**, *15*, 1518-1520.
2. Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.
3. Sahn, J. J.; Martin, S. F. Expedient synthesis of norbenzomorphan library via multicomponent assembly process coupled with ring-closing reactions. *ACS Combi. Sci.* **2012**, *14*, 496-502.
4. Sahn, J. J.; Hodges, T. R.; Martin, S. F. Norbenzomorphan framework as a novel scaffold for generating sigma 2 subtype selective ligands. *ChemMedChem* **2016**, *11*, 556-561.

Sigma Receptor Binding Assay Protocol:

Receptor binding assays were performed by the Psychoactive Drug Screening Program (PDSP) at Chapel Hill, North Carolina. The assay protocol book can be accessed free of charge at: **https://pdspdb.unc.edu/pdspWeb/content/PDSP%20Protocols%20II%202013-03-28.pdf**. Briefly, σ1 receptors were sourced from Guinea pig brain and Sig1R binding affinity (K_i) was determined through competition binding assays with [^{3}H]-(+)-pentazocine. σ2 receptors were obtained from rat PC12 cells and the Sig2R ligand binding affinity (K_i) was determined through competition binding assays using the radioligand [^{3}H]-ditolylguanidine in the presence of (+)-pentazocine to block σ1 receptor binding sites. K_i values are calculated from best-fit IC_{50} determinations and are the average of 2 or more independent runs performed in triplicate.

Table S1. Binding affinity (K_i, nM) of representative compounds at non-σ1 receptor targets.

ID	$5HT_{1A}$	$5HT_{1B}$	$5HT_{1D}$	$5HT_{2A}$	$5HT_{2B}$	$5HT_{2C}$	$5HT_3$	$5HT_6$	$5HT_7$	α_{1A}
9	2,777	1,562	1,101	127	531	52	7,475	300	>10,000	>10,000
22	158	1,504	2,007	610	483	245	*	278	742	*
17	5,341	2,157	1,172	420	568	842	>10,000	1,810	>10,000	4,485
30	1,771	1,523	813	2,159	1,656	*	*	1,351	1,875	*
15	4,036	5,235	2,998	2,097	439	3,939	4,866	4,522	2,764	7,293
28	1,438	>10,000	8,660	1,123	609	6,186	>10,000	2,031	795	2,620
16	4,303	>10,000	3,049	>10,000	994	6,527	7,595	>10,000	>10,000	>10,000
29	2,634	3,307	4,380	2,200	1,446	5,198	>10,000	1,735	2,639	3,298
41	*	*	*	*	771	861	6,041	*	*	>10,000
42	*	*	*	*	567.5[a]	*	3,330	*	*	*
37	*	*	*	*	*	3,840[b]	*	*	*	*
38	*	*	*	*	*	*	1,800	*	*	*

ID	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{2C}	β_1	β_2	β_3	δ	κ	μ
9	>10,000	>10,000	30	1,049	707	5,353	>10,000	>10,000	>10,000	>10,000	6,937
22	*	*	281	*	683	*	*	*	*	*	*
17	>10,000	3,976	231	2,304	751	5,022	>10,000	>10,000	>10,000	>10,000	4,468
30	*	*	621	*	1,697	*	*	*	*	5,366.5[b]	*
15	>10,000	1,793	526	961	345	7,574	>10,000	>10,000	>10,000	6,077	819
28	2,136	3,505	1,152	>10,000	305	>10,000	>10,000	5,068	3,556	4,291	3,657
16	7,349	>10,000	346	1,346	580	>10,000	>10,000	>10,000	>10,000	>10,000	5,346
29	>10,000	4,442	1,633	2,519	856	>10,000	>10,000	3,956	>10,000	>10,000	5,379
41	>10,000	*	1,571	2,787	82	*	*	*	*	>10,000	*
42	*	*	2,627	1,048	473	*	*	*	*	2,031	*
37	*	>10,000	1,243	1,043	178	*	*	*	*	*	*
38	*	*	*	2,453	>10,000	*	*	*	*	>10,000	*

ID	DAT	NET	SERT	D_1	D_2	D_3	D_4	D_5	H_1	H_2	H_3

9	990	5,424	6,042	*	*	1,515	1,205	*	*	1,830	*
22	1,102	*	*	3,075	3,979	756	*	*	*	1,052	1,582
17	1,581	3,291	2,570	>10,000	8,519	*	*	*	*	*	*
30	1,470	1,375	*	2,175	*	*	*	*	*	*	*
15	2,541	3,107	2,755	7,978	4,345	444	>10,000	7,951	465	7,630	902
28	1,354	1,418	4,017	2,307	6,249	1,671	>10,000	2,853	2,737	>10,000	616
16	5,729	1,479	2,480	6,534	8,316	>10,000	>10,000	6,093	1,278	2,107	5,516
29	3,182	881	1,387	>10,000	6,866	2,535	2,875	7,023	777	1,831	3,172
41	*	*	49	*	8,732	*	227	*	5,188	423	*
42	2,345	232	*	*	*	*	*	*	*	*	*
37	*	*	471	*	*	*	*	*	*	5,112	*
38	*	*	*	*	*	*	*	*	*	*	*

ID	H_4	M_1	M_2	M_3	M_4	M_5
9	85	*	*	*	*	*
22	707	3,536	*	*	3,908	4,444
17	>10,000	*	*	*	*	*
30	*	>10,000	*	*	*	*
15	>10,000	1,623	1,920	1,912	1,160	1,061
28	5,232	>10,000	1,500	1,598	970	853
16	>10,000	5,698	>10,000	4,557	5,014	5,792
29	>10,000	>10,000	>10,000	1,562	3,139	1,366
41	*ND*	*	*	>10,000	*	*
42	*	*	*	*	*	*
37	*ND*	1,274	*	*	*	*
38	*ND*	*	*	*	5,581	*

* < 50% inhibition of radioligand binding at 10 μM.

[a] Average of 2 or more K_i determinations

ND Not determined