Supplemental Materials

Chemistry Experimental Methods

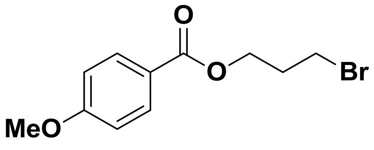
General details. All reactions were carried out under nitrogen (N_2) atmosphere. All reagents and solvents were purchased from commercial vendors and used as received. NMR spectra were recorded on a Bruker 300 (300 MHz ^{1}H, 75 MHz ^{13}C) spectrometer. Proton and carbon chemical shifts are reported in ppm (δ) referenced to the NMR solvent. Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz. Flash chromatography was performed using 40-60 µm Silica Gel (60 Å mesh) on a Teledyne Isco Combiflash R_f. Tandem Liquid Chromatography/Mass Spectrometry (LC/MS) was performed on a Waters 2795 separations module and 3100 mass detector. Analytical thin layer chromatography (TLC) was performed on EM Reagent 0.25 mm silica gel 60-F plates.

2-Bromoethyl 3,4,5-trimethoxybenzoate (2). To a solution of 3.5 g 3,4,5-trimethoxybenzoyl chloride (15.2 mmol) in 25 mL of CH_2Cl_2 is added 5 mL of triethylamine and 1.2 mL (16.7 mmol) 3-bromo-1-propanol and the mixture was stirred overnight. The reaction is rinsed with water, dried ($MgSO_4$), filtered and chromagraphed with 25% EtOAc in hexane to isolate 4.11 g of white solid (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 2H), 4.62 (t, *J* = 6.1, 2H), 3.92 (d, *J* = 1.1, 9H), 3.66 (t, *J* = 6.1, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.44, 152.77, 142.26, 124.36, 106.75, 64.05, 60.71, 56.04, 28.70.

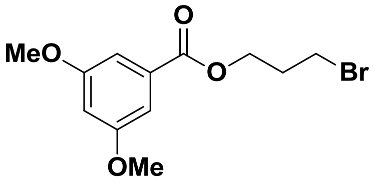
3-Bromopropyl 3,4,5-trimethoxybenzoate (1). To a solution of 3.5 g 3,4,5-trimethoxybenzoyl chloride (15.2 mmol) in 25 mL of CH_2Cl_2 was added 5 mL of triethylamine and 1.5 mL (16.7 mmol) 3-bromo-1-propanol and the mixture is stirred overnight. The reaction is rinsed with water, dried ($MgSO_4$), filtered and chromagraphed with 25% EtOAc in hexane to isolate 3.57 g of white solid (71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 4.48 (t, *J* = 6.1, 2H), 3.92 (s, 9H), 3.70 (t, *J* = 6.4, 2H), 2.25 (p, *J* = 6.2, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.87, 152.79, 142.15, 124.85, 106.65, 61.80, 60.75, 56.10, 41.20, 31.59.

2-Bromobutyl 3,4,5-trimethoxybenzoate (3). To a solution of 4.37 g 3,4,5-trimethoxybenzoyl chloride (19.0 mmol) in 25 mL of CH_2Cl_2 was added 5 mL of triethylamine and 2.90 gmL (19.0 mmol) 4-bromo-1-butanol and the mixture was stirred overnight. The reaction is rinsed with water, dried ($MgSO_4$), filtered and chromagraphed with 10-25% EtOAc in hexane to isolate 2.20 g of clear oil (33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 2H), 4.36 (t, *J* = 6.1, 2H), 3.92 (s, 6H), 3.91 (s, 3H), 3.50 (t, *J* = 6.3, 2H), 2.11 – 1.85 (m, 4H). ^{13}C NMR (75 MHz, MeOD) δ 167.15, 152.68, 141.82, 125.13, 106.80, 64.55, 60.43, 56.37, 55.84, 25.27, 20.48.

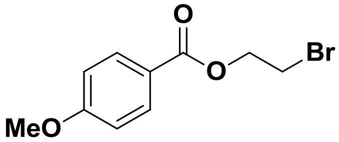
Other bromo-ester analogs were made similarly



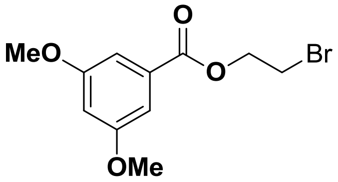
3-bromopropyl 4-methoxybenzoate (82%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.48 – 4.28 (m, 2H), 3.80 (s, 3H), 3.24 (t, *J* = 6.5 Hz, 1H), 2.27 (p, *J* = 6.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.88, 163.38, 131.50, 122.32, 113.59, 62.31, 55.35, 31.88, 29.70.



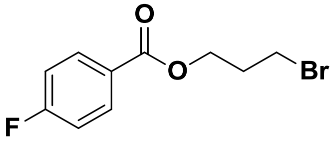
3-bromopropyl 3,5-dimethoxybenzoate (69%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 2H), 6.64 (s, 1H), 4.44 (t, *J* = 5.6 Hz, 2H), 3.82 (s, 6H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.31 (p, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.03, 160.62, 131.81, 107.18, 105.48, 62.84, 55.52, 31.78, 29.47.



2-bromoethyl 4-methoxybenzoate (87%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.56 (t, *J* = 6.1 Hz, 2H), 3.81 (s, 3H), 3.61 (t, *J* = 6.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.99, 161.94, 130.11, 120.30, 112.05, 62.29, 53.78, 27.53.



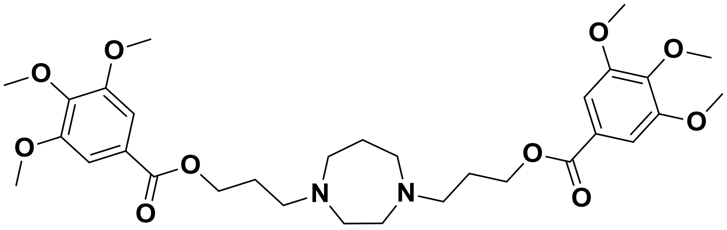
2-bromoethyl 3,5-dimethoxybenzoate (95%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 2H), 6.67 (s, 1H), 4.62 (t, *J* = 6.1 Hz, 2H), 3.84 (s, 6H), 3.64 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.82, 160.68, 131.44, 107.33, 105.95, 64.32, 55.59, 28.66.



3-bromopropyl 4-fluorobenzoate (80%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 – 7.89 (m, 2H), 7.14 (t, *J* = 8.6 Hz, 2H), 4.48 (t, *J* = 6.0 Hz, 2H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.34 (p, *J* = 6.3 Hz, 2H).

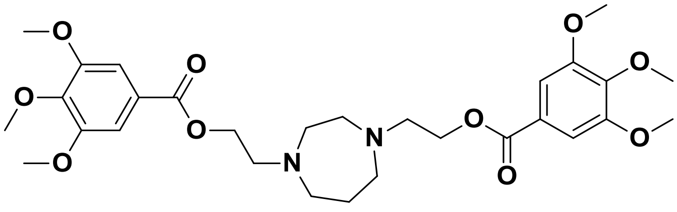
Bis-alkylation of diamine (general procedure)

Alkyl bromides (3 equivalents) were dissolved in 10 equivalents DMF (wt/v) and to this was added powdered K_2CO_3 (5 equivalents) and diamine. The mixture was stirred 2 d before addition of water which was rinsed several times with CH_2Cl_2, the combined CH_2Cl_2 was dried ($MgSO_4$), filtered and chromatographed with MeOH saturated with NH_3 in CH_2Cl_2 to isolate the product. Liquid products were dissolved in ether and precipitated out as white solids by the addition of 2M HCl/Ether.



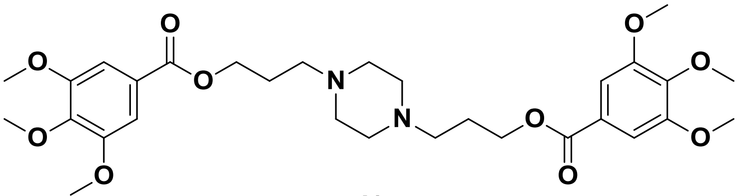
E19/G23

Dilazep (homopiperazine + **1**, bis HCl salt, 55% yield) was identical to commercially available material by NMR and LCMS analysis: ^{1}H NMR (300 MHz, D_2O) δ 7.14 (s, 4H), 4.30 (t, J = 5.86, 4H), 3.75 (s, 12 H), 3.70 (2, 6H), 3.65-3.75 (m, 4H), 3.45-3.65 (m, 4H), 3.35 (t, J= 7.89, 4H), 2.10-2.30 (m, 6H).



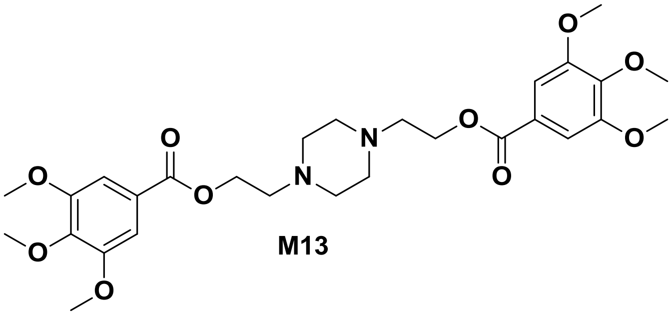
A11

homopiperazine + **2** (bis HCl salt, 55% yield) ^{1}H NMR (300 MHz, D_2O) δ 7.06 (s, 4H), 4.59-4.64 (m, 4H), 3.39 (s, 4H), 3.70 (s, 12 H), 3.68 (2, 6H), 3.60-3.66 (m, 8H), 2.10-2.30 (m, 2H). Mass 577 (M + 1).



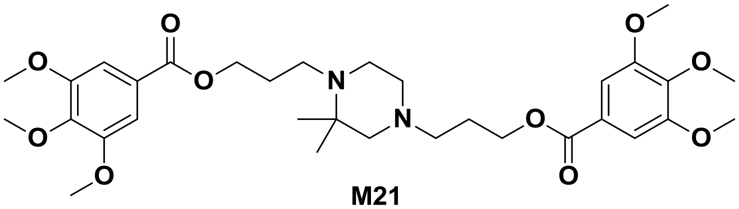
<u>I1</u>

Piperazine + **1** (free base, 46%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 4H), 4.37 (t, *J* = 6.4, 4H), 3.91 (s, 18H), 2.71 – 2.30 (m, 12H), 1.97 (dt, *J* = 6.5, 13.1, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.19, 152.94, 142.29, 125.37, 106.88, 63.59, 60.89, 56.26, 55.11, 53.23, 26.33. Mass 591 (M + 1).



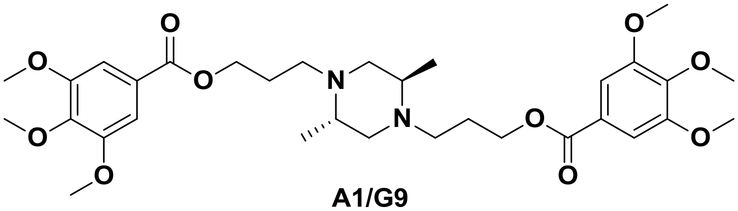
M13

Piperazine + **2** (free base, 32% yield) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29 (s, 4H), 4.45 (t, *J* = 5.9, 4H), 3.91 (s, 18H), 2.80 (t, *J* = 5.9, 4H), 2.64 (s, 8H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.04, 152.94, 142.35, 125.19, 106.93, 62.74, 60.89, 56.60, 56.23, 53.48. Mass 563 (M + 1).



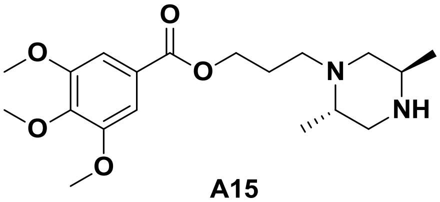
M21

M21 (**1** + 2,2-dimethylpiperazine, 69% free base). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.30 (s, 4H), 4.39 (t, J = 6.44 Hz, 4H), 3.91 (s, 18H), 2.35-2.65 (m, 8H), 2.12-2.25 (m, 2H), 1.84-1.96 (m, 2H), 1.05 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.07, 166.05, 152.78, 142.05, 141.99, 125.38, 125.33, 106.67, 106.60, 66.04, 63.51, 63.22, 60.75, 56.11, 56.05, 54.67, 54.39, 53.53, 46.80, 45.20, 27.48, 26.07. Mass 619 (M + 1).



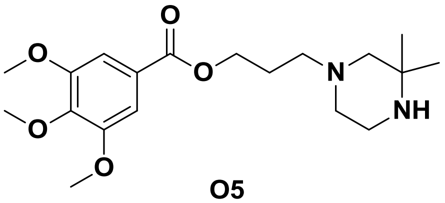
A1/G9

A1 (37%, free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.30 (s, 4H), 4.36 (dp, *J* = 10.9, 4.7 Hz, 4H), 3.91 (s, 17H), 2.95 (dt, *J* = 12.9, 7.9 Hz, 2H), 2.82 (dd, *J* = 11.2, 2.8 Hz, 2H), 2.39 (qt, *J* = 8.6, 3.9 Hz, 4H), 2.11 – 1.77 (m, 6H), 1.07 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.10, 152.89, 142.19, 125.32, 106.74, 63.52, 60.86, 59.84, 56.17, 55.46, 49.55, 25.08, 17.58. Mass 619 (M + 1).



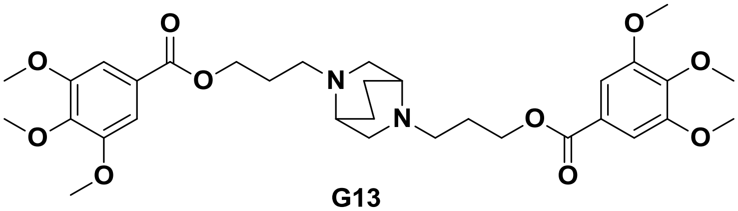
A15

A15 ^{1}H NMR (300 MHz, Deuterium Oxide) δ 7.16 (s, 2H), 4.30 (t, *J* = 6.0 Hz, 2H), 3.81 (dd, *J* = 13.2, 3.7 Hz, 1H), 3.75 (s, 6H), 3.69 (s, 3H), 3.68 – 3.47 (m, 4H), 3.30 – 3.01 (m, 3H), 2.32 – 1.95 (m, 2H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.28 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, D$_2$O) δ 167.50, 152.36, 141.48, 125.00, 107.22, 62.24, 60.96, 56.21, 55.62, 52.57, 49.22, 45.86, 22.58, 14.86, 13.36. Mass 367 (M + 1).



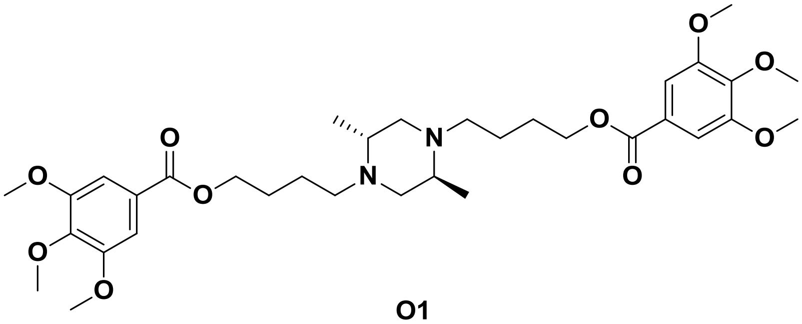
O5

O5 (HCl salt) ^{1}H NMR (300 MHz, Deuterium Oxide) δ 7.15 (s, 2H), 4.28 (t, *J* = 5.9 Hz, 2H), 3.75 (s, 6H), 3.69 (s, 3H), 3.56 – 3.32 (m, 6H), 3.32 – 3.12 (m, 2H), 2.14 (dq, *J* = 13.0, 6.9, 6.4 Hz, 2H), 1.41 (s, 6H). ^{13}C NMR (75 MHz, D$_2$O) δ 167.61, 152.35, 141.47, 125.05, 107.27, 62.47, 60.96, 57.71, 56.24, 55.34, 53.98, 48.18, 36.94, 23.02. Mass 367 (M + 1).



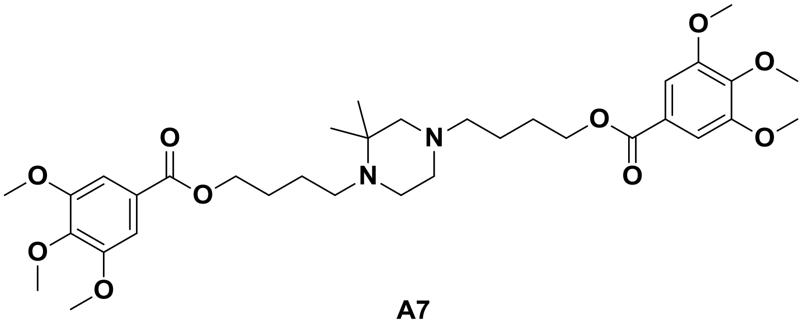
G13

G13 (free base, 20%) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.30 (s, 4H), 4.39 (t, *J* = 6.5 Hz, 4H), 3.91 (s 18H), 3.01 (dt, *J* = 10.2, 2.4 Hz, 2H), 2.79 – 2.53 (m, 8H), 2.04 – 1.83 (m, 8H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.23, 152.89, 142.08, 125.43, 106.74, 63.63, 60.91, 56.23, 53.81, 52.57, 50.81, 27.62, 24.30. Mass 617 (M + 1).



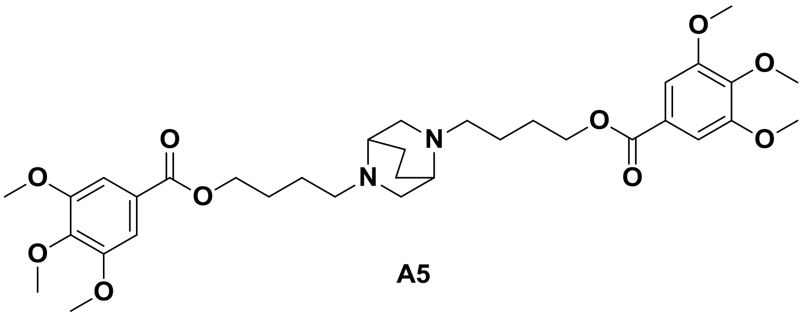
O1

O1 (44% free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.30 (s, 1H), 4.34 (t, *J* = 6.5 Hz, 1H), 3.92 (s, 4H), 2.88 – 2.70 (m, 1H), 2.45 – 2.13 (m, 1H), 2.00 (t, *J* = 10.7 Hz, 1H), 1.69 (ddd, *J* = 37.9, 15.0, 7.9 Hz, 2H), 1.05 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.14, 152.84, 142.07, 125.35, 106.69, 64.96, 60.86, 59.77, 56.18, 55.52, 52.84, 26.92, 22.06, 17.61. Mass 663 (M + 1).



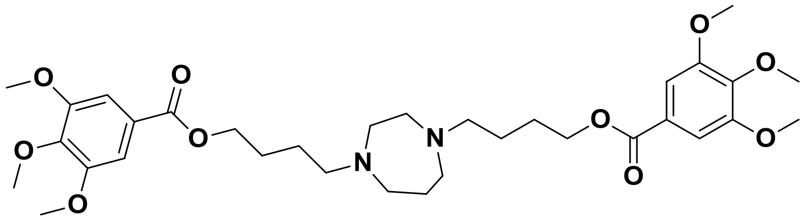
A7

A7 (27% HCl salt) ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.33 (s, 4H), 4.37 (t, *J* = 6.0 Hz, 4H), 3.89 (s, 12H), 3.82 (s, 6H), 3.78 – 3.41 (m, 10H), 2.14 – 1.72 (m, 8H), 1.63 (s, 6H). ^{13}C NMR (75 MHz, MeOD) δ 166.07, 152.97, 142.29, 125.06, 106.67, 106.65, 63.82, 63.74, 61.30, 59.69, 57.14, 55.41, 44.31, 25.67, 25.50, 21.32, 20.37. Mass 647 (M + 1)



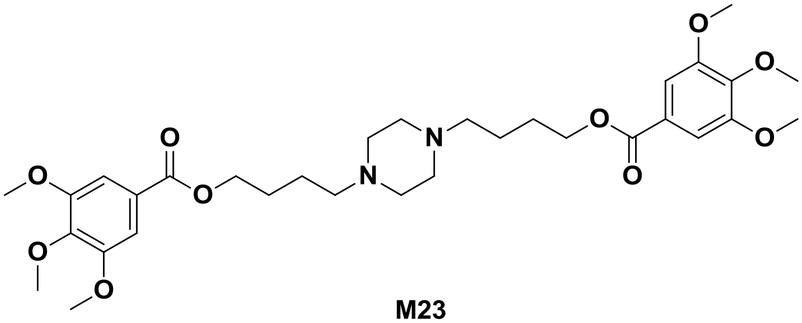
A5

A5 (10%, HCl salt) ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.33 (s, 4H), 4.39 (t, *J* = 6.6 Hz, 4H), 3.91-3.99 (m,, 4H), 3.89 (s, 12H), 3.82 (s, 6H), 3.73 – 3.37 (m, 5H), 2.60 – 2.30 (m, 2H), 2.22 – 1.66 (m, 12H). Mass 645 (M + 1)



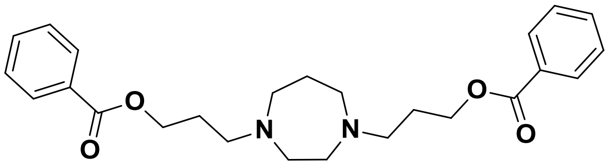
A3

A3 (HCl salt, 44%) ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.32 (s, 4H), 4.37 (t, *J* = 5.8 Hz, 4H), 3.88 (s, 12H), 3.82 (s, 6H), 3.42 – 3.22 (m, 12H), 2.24-2.38 (m, 2H), 1.78-1.98 (m, 8H). Mass 633 (M + 1).



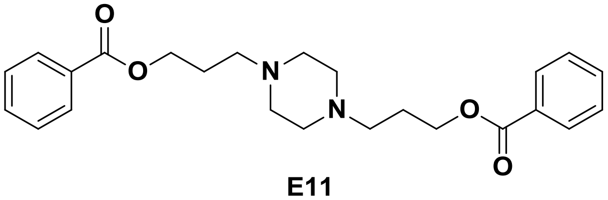
M23

M23 (HCl salt, 52%) ^{1}H NMR (300 MHz, Deuterium Oxide) δ 7.14 (s, 4H), 4.29 – 4.03 (m, 4H), 3.70 (s, 12H), 3.64 (s, 6H), 3.48 br (s, 8H), 3.27 – 2.96 (m, 4H), 1.71 (br s, 8H). ^{13}C NMR (75 MHz, MeOD) δ 166.06, 152.97, 142.30, 125.04, 106.66, 65.41, 63.73, 59.69, 55.40, 25.51, 20.94, 13.96. Mass 619 (M + 1). ^{13}C NMR (75 MHz, MeOD) δ 167.13, 152.67, 141.80, 125.12, 106.79, 64.55, 60.43, 56.37, 55.83, 48.76, 25.27, 20.47. Mass 619 (M + 1).



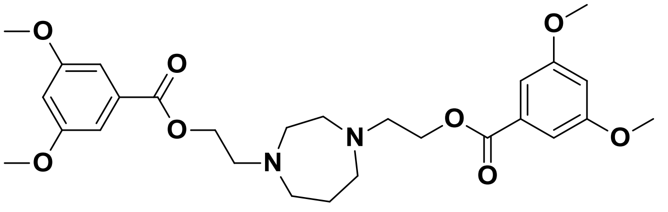
A13

A13 ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 7.1 Hz, 4H), 7.54 (t, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 4H), 4.37 (t, *J* = 6.5 Hz, 4H), 2.70 (m, 8H), 2.67 – 2.50 (t, *J* = 6.6 Hz,, 4H), 1.93 (p, *J* = 6.7 Hz, 4H), 1.80 (p, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.56, 132.81, 130.42, 129.51, 128.31, 63.49, 55.28, 54.91, 54.23, 27.71, 26.99.



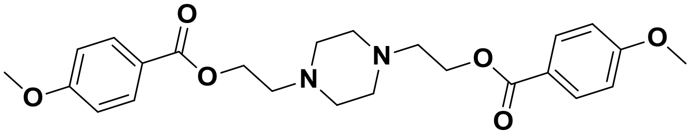
E11

E11 ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.4 Hz, 4H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 4H), 4.37 (t, *J* = 6.4 Hz, 4H), 2.71 – 2.30 (m, 12H), 1.96 (p, *J* = 6.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.53, 132.84, 130.36, 129.51, 128.31, 63.43, 55.13, 53.22, 26.30.



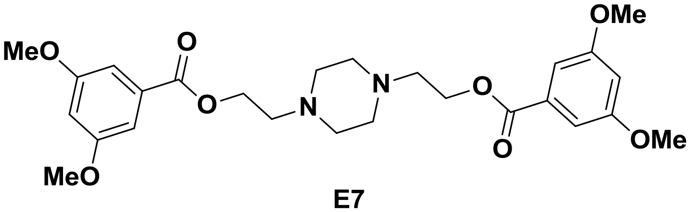
G7

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.17 (s, 4H), 6.64 (s, 2H), 4.40 (t, *J* = 6.1 Hz, 4H), 3.82 (s, 12H), 2.93 (t, *J* = 6.1 Hz, 4H), 2.88 – 2.75 (m, 8H), 1.80 (p, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.28, 160.60, 132.16, 107.18, 105.57, 77.44, 77.02, 76.60, 63.27, 56.17, 55.55, 54.35, 28.17.



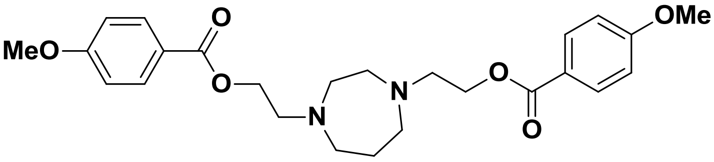
E23

E23 (free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.9 Hz, 4H), 6.91 (d, *J* = 8.9 Hz, 4H), 4.42 (t, *J* = 5.9 Hz, 4H), 3.85 (s, 6H), 2.78 (t, *J* = 5.9 Hz, 4H), 2.63 (br s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.17, 163.33, 131.71, 122.62, 113.59, 62.41, 56.69, 55.40, 53.43.



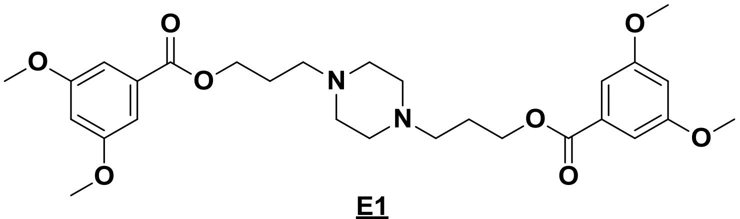
E7

E7 ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.17 (s, 4H), 6.64 (s, 2H), 4.44 (t, *J* = 5.9 Hz, 4H), 3.82 (s, 12H), 2.78 (t, *J* = 5.9 Hz, 4H), 2.62 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.51, 166.19, 160.60, 132.07, 107.19, 105.57, 77.47, 77.04, 76.62, 62.87, 56.57, 55.55, 53.45. Mass 503 (M + 1).



E5

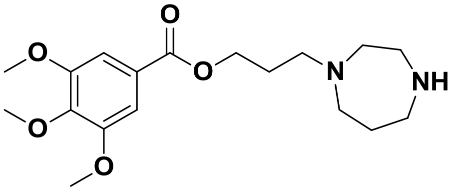
E5 (free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 9.0 Hz, 4H), 6.91 (d, *J* = 9.0 Hz, 4H), 4.38 (t, *J* = 6.1 Hz, 4H), 3.87 (s, 6H), 2.93 (t, *J* = 6.1 Hz, 4H), 2.82 (d, *J* = 7.2 Hz, 8H), 1.80 (p, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.29, 163.31, 131.58, 124.98, 113.59, 62.82, 56.29, 55.50, 55.42, 54.35, 28.05.



E1

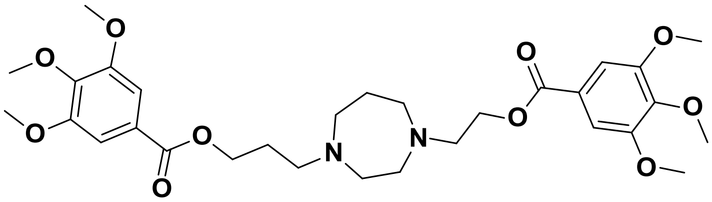
E1 (free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.17 (s, 4H), 6.64 (s, 2H), 4.36 (t, *J* = 6.4 Hz, 4H), 3.82 (s, 12H), 2.65 – 2.27 (m, 12H), 1.96 (p, *J* = 6.7 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.25, 160.57, 132.20, 107.10, 105.42, 63.59, 55.50, 55.08, 53.20, 26.24. Mass 531 (M + 1).

Unsymmetrical diamines via tBOC



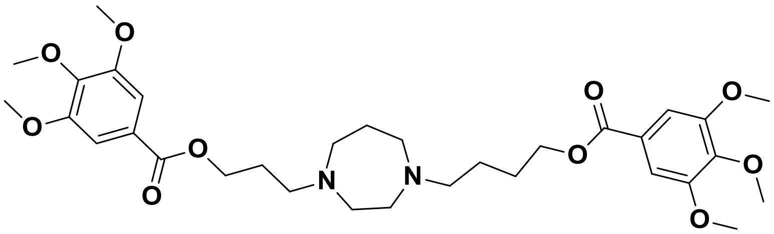
To 200 mg of **1** (0.72 mmol) dissolved in 2 mL DMF was added 290 mg (1.40 mmol) of tBOC homopiperazine and 500 mg (6.60 mmol) of K_2CO_3 and the mixture was stirred 2 d. Ethyl acetate and water were added, the EtOAc was dried, concentrated and chromatographed with 0-25% EtOAc in hexane to yield 302 mg of product (93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 2H), 4.37 (t, *J* = 6.5, 2H), 3.91 (s, 9H), 3.56 – 3.36 (m, 4H), 2.73 – 2.55 (m, 6H), 1.99 – 1.89 (m, 2H), 1.89 – 1.76 (m, 2H), 1.46 (s, 9H). The material was dissolved in 5 mL CH_2Cl_2, cooled in an ice bath and to it was added 5 mL TFA. The solution stirred overnight, warming to room temperature before concentration to an oil. This was dissolved in MeOH and 2 N HCl in ether solution was added before concentrating and repeating. The product HCl salt was isolated as a white solid, 242 mg (93%). ^{1}H NMR (300 MHz, D_2O) δ 6.98 (s, 2H), 4.26 (t, *J* = 6.0, 2H), 3.71 (s, 6H), 3.67 (s, 3H), 3.63 (br s, 4H), 3.54 (m, 2H), 3.47 – 3.27 (m, 4H), 2.35 – 2.04 (m, 4H). ^{13}C NMR (75 MHz, D_2O) δ 167.32, 152.20, 141.43, 124.74, 107.08, 62.42, 60.92, 56.18, 54.87, 54.07, 50.31, 44.76, 40.80, 23.69, 20.78. Mass 353 (M + 1).

This amine was treated as above with bromides **2** and **3** to produce M19 and A9 respectively.



M19

M19 (54% 2 HCl salt). ^{1}H NMR (300 MHz, D_2O) δ 7.05 (s, 2H), 6.95 (s, 2H), 4.58 (br s, 2H), 4.26 (t, *J* = 5.8, 2H), 3.93 – 3.75 (m, 4H), 3.70 (s, 6H), 3.68 (s, 6H), 3.65 (s, 6H), 3.52-3.62 (m, 4H), 3.44 – 3.30 (m, 2H), 2.24-2.36 (m, 2H), 2.10-2.24 (m, 2H). ^{13}C NMR (75 MHz, D2O) δ 167.28, 166.77, 152.25, 152.17, 141.72, 141.43, 124.65, 124.10, 107.37, 107.02, 62.36, 60.88, 59.41, 56.24, 56.15, 55.86, 54.83, 53.89, 53.59, 48.93, 48.66, 38.80, 23.68, 20.29. Mass 591 (M + 1).

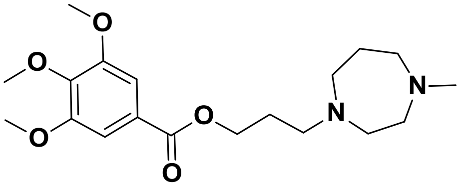


A9

A9 (50% yield, 2 HCl salt). ^1H NMR (300 MHz, D_2O) δ 7.06 (s, 2H), 7.05 (s, 2H), 4.33 – 4.10 (m, 4H), 3.70 (s, 12H), 3.65 (s, 3H), 3.64 (s, 3H), 3.54 – 3.37 (m, 6H), 3.34 – 3.11 (m, 6H), 2.08-2.19 (m, 2H), 1.82 – 1.59 (m, 4H), 1.25 – 1.12 (m, 2H), 1.11 – 0.96 (m, 2H). Mass 619 (M + 1).

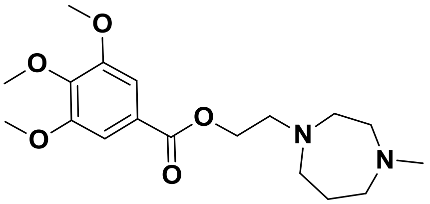
Alkylation of amine (general procedure)

Alkyl bromide was dissolved in 10 equivalents of THF (wt/v) before addition of 10 equivalents of amine and stirring overnight. EtOAc and sat'd NaHCO3 solution were added and separated, the water was rinsed several times with EtOAc. The combined EtOAc layers were dried and chromatographed with MeOH saturated with NH_3 in CH_2Cl_2 to isolate the product. Liquid products were dissolved in ether and precipitated out as white solids by the addition of 2M HCl/Ether.



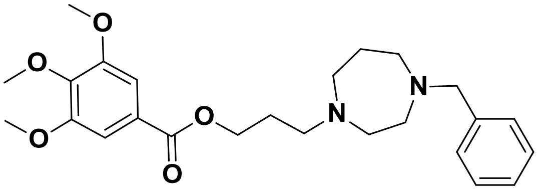
C19

N-Methylhomopiperazine + **1** C19 (HCl salt, 78%) ^1H NMR (300 MHz, D_2O) δ 7.25 (s, 2H), 4.33 (t, J = 6.15, 2H), 3.80 (s, 6H), 3.74 (s, 3H), 3.72 (s, 4H), 3.42-3.58 (m, 4H), 3.35 (t, J = 8.07, 4H), 2.89 (s, 3H), 2.15-2.26 (m, 4H). ^{13}C NMR (75 MHz, D_2O) δ 167.46, 152.29, 141.50, 124.88, 107.21, 66.00, 62.39, 60.96, 56.25, 55.55, 54.90, 53.46, 48.91, 44.10, 23.69, 20.39. Mass 367 (M + 1).



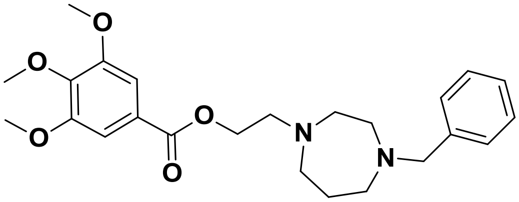
A23

N-Methylhomopiperazine + **2** A23 (HCl salt, 63%) ^1H NMR (300 MHz, D_2O) δ 7.16 (s, 2H), 4.60 (br s, 2H), 3.76 (s, 6H), 3.71 (s, 3H), 3.60-3.90 (m, 8H), 2.91 (s, 3H), 2.25-2.34 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 166.93, 152.36, 141.78, 124.32, 107.58, 66.00, 61.00, 59.32, 56.35, 55.96, 53.70, 50.30, 49.23, 44.11, 20.28. Mass 353 (M + 1).



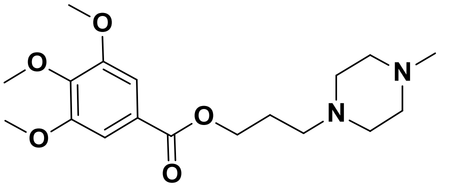
K3

K3 (N-Benzylhomopiperazine + **1**, HCl salt, 75%) ^{1}H NMR (300 MHz, D_2O) δ 7.40 (s, 5H), 7.20 (s, 2H), 4.35 (s, 2H), 4.31 (t, *J* = 6.0, 2H), 3.78 (s, 6H), 3.72 (s, 3H), 3.68 (s, 4H), 3.41-3.55 (m, 4H), 3.38 – 3.22 (m, 2H), 2.19-2.27 (m, 4H). Mass 443 (M + 1).



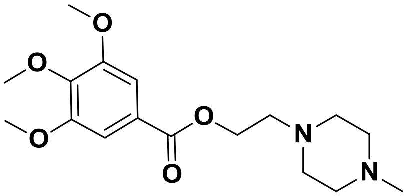
M7

M7 (N-Benzylhomopiperazine + **2**, HCl salt, 34%) ^{1}H NMR (300 MHz, D_2O) δ 7.39 (s, 5H), 7.20 (s, 2H), 4.56-4.63 (m, 2H), 4.36 (s, 2H), 3.78 (s, 6H), 3.74 (s, 3H), 3.64-3.74 (m, 4H), 3.55-3.63 (m, 2H), 3.45 – 3.49 (m, 2H), 2.18-2.28 (m, 2H). Mass 429 (M + 1).



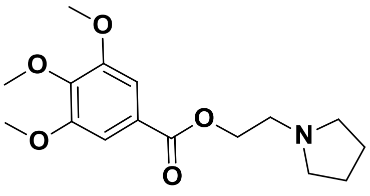
M9

M9 (N-Methylpiperazine + **1**, HCl salt, 78%) ^{1}H NMR (300 MHz, D_2O) δ 7.22 (s, 2H), 4.33 (t, *J* = 6.1, 2H), 3.79 (s, 6H), 3.73 (s, 3H), 3.57 (br s, 6H), 3.41 – 3.26 (m, 2H), 2.92 (s, 3H), 2.14-2.19 (m, 2H). ^{13}C NMR (75 MHz, D_2O) δ 167.69, 152.44, 141.57, 125.14, 107.39, 62.39, 61.01, 56.31, 54.10, 50.38, 48.85, 42.87, 23.29. Mass 353 (M + 1).



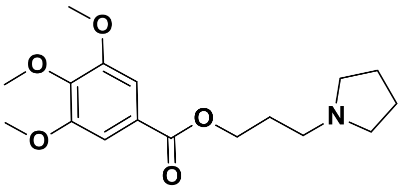
M11

M11 (N-Methylpiperazine + **2**, HCl salt, 75%) ^{1}H NMR (300 MHz, D_2O) δ 7.26 (s, 2H), 4.60 (t, J = 4.61, 2H), 3.79 (s, 6H), 3.73 (s, 3H), 3.51-3.66 (m, 8H), 2.92 (s, 3H). ^{13}C NMR (75 MHz, D_2O) δ 152.45, 141.78, 124.55, 114.49, 107.62, 61.01, 59.38, 56.35, 55.38, 50.46, 49.12, 42.88. Mass 339 (M + 1).



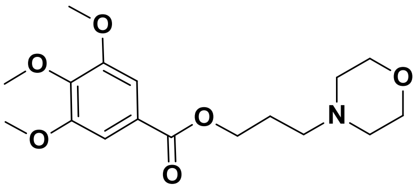
C9

C9 (69% free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22 (s, 2H), 4.37 (t, *J* = 6.0 Hz, 2H), 3.81 (s, 6H), 3.80 (s, 3H), 2.79 (t, *J* = 6.0 Hz, 2H), 2.55 (br s, 4H), 1.70 (br s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.92, 152.79, 142.08, 125.16, 106.78, 64.26, 60.75, 56.09, 54.65, 54.37, 23.48.



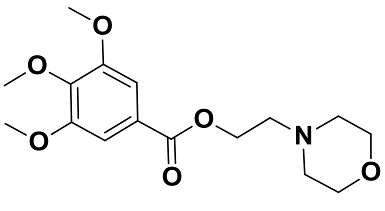
E15

E15 (83%, free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.13 (s, 2H), 4.21 (t, *J* = 6.4 Hz, 2H), 3.74 (s, 6H), 3.72 (s, 3H), 2.40-2.58 (m, 6H), 1.87 (p, *J* = 6.6 Hz, 2H), 1.64 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.90, 152.73, 142.00, 125.17, 106.63, 63.28, 60.64, 56.04, 53.97, 52.79, 27.94, 23.29.



C1

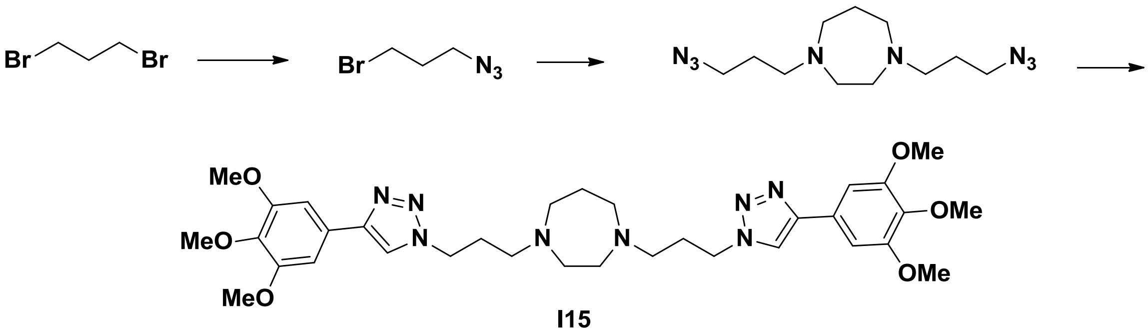
C1 (98%, free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.21 (s, 2H), 4.30 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 6H), 3.82 (s, 3H), 3.69 – 3.59 (m, 4H), 2.49 – 2.25 (m, 6H), 1.89 (p, *J* = 6.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.99, 152.81, 142.08, 125.23, 106.69, 66.82, 63.34, 60.74, 56.11, 55.37, 53.61, 25.85.



M15

M15 (79%, free base) ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.23 (s, 2H), 4.38 (t, *J* = 6.0 Hz, 2H), 3.84 (s, 9H), 3.72 – 3.59 (m, 4H), 2.71 (t, *J* = 6.0 Hz, 2H), 2.57 – 2.44 (m, 4H).

Scheme 5

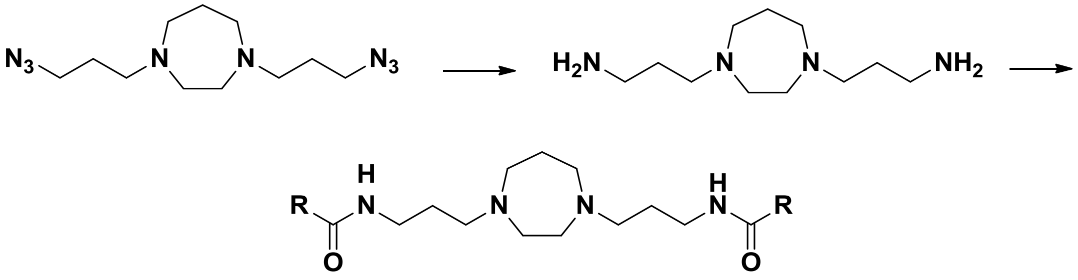


I15

Azido-1-bromopropane. To 80 mL of DMF was added 4.00 g of sodium azide (61.5 mmol) and 24.8 g of 1,3-dibromopropane (123 mmol) and the solution was stirred 2 d before the addition of 160 mL of water. The water was rinsed several times with hexane, the combined hexane rinses were washed with brine, dried, and concentrated to 16 g of clear oil which was chromatographed with 10% EtOAc in hexane to yield 3.10 g of product as a clear oil (31%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.47-3.53 (m, 4H), 2.05-2.14 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 49.38, 31.69, 29.92. (Based upon Agnew, H. et al. *Angew. Chem., Int. Ed.* **2009,** *48,* 4944-4948).

N, N'-Bis(3-azidopropyl)homopiperazine. To 950 mg of homopiperazine (9.5 mmol) dissolved in 15 mL of DMF was added 3.27 g of anhydrous K2CO3 (24 mmol) and 3.10 g of 3-azido-1-bromopropane (19 mmol) and the mixture was stirred overnight. Water was added and the solution was rinsed several times with EtOAc, the combined EtOAc was rinsed with brine, dried, concentrated and chromatographed with 5% NH3 saturated MeOH in DCM to isolate 1.38 g of product as a clear oil (55%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.34 (t, *J* = 6.7, 4H), 2.65-2.69 (m, 8H), 2.55 (t, *J* = 7.0, 4H), 1.83 – 1.66 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 55.23, 55.00, 54.13, 49.53, 27.69, 27.01.

I15. To 44 mg of N, N'-Bis(3-azidopropyl)homopiperazine (0.17 mmol) in 0.5 mL water was added 79 mg (0.41 mmol) of (3,4,5-trimethoxyphenyl)acetylene (*J. Med. Chem*. **2007**, *50*, 1001-1006) and 25 mg of Cu powder (39 mmol) and the mixture was stirred overnight before filtering adding to a 2 g SCX (acidic) solid phase extraction column. The column was first rinsed with MeOH and then 1 M NH$_3$ in MeOH, the basic fraction was concentrated to 104 mg of product as a white solid (97%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.75 (s, 2H), 7.06 (s, 4H), 4.48 (t, *J* = 6.7, 2H), 3.93 (s, 12H), 3.88 (s, 6H), 2.67 (s, 8H), 2.51 (t, *J* = 6.6, 4H), 2.19 – 1.99 (m, 4H), 1.90 – 1.72 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 153.33, 147.11, 137.67, 126.22, 119.64, 102.50, 60.63, 55.91, 54.88, 54.06, 53.81, 47.94, 27.98, 27.49. Mass 651 (M + 1).



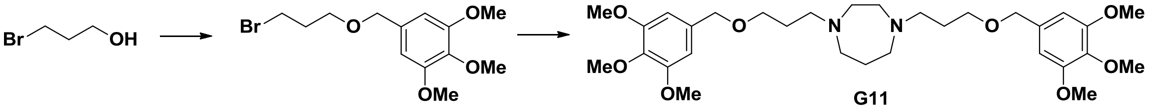
I5 R = 3,4,5-(OMe)$_3$Ph
G17 R = CH$_3$

N, N'-Bis(3-aminopropyl)homopiperazine. To 1.26 g of N, N'-Bis(3-azidopropyl) homopiperazine (4.73 mmol) in 10 mL of THF was added a solution of 2.48 g of triphenylphosphine (9.46 mmol) in 5 mL of THF and then 1 mL of water was added and the solution was stirred overnight. The THF was removed and the mixture partitioned between EtOAc and acidic water, the water was removed to give 1.81 g of the 4 HCl salt of the product as a white solid (63%). ^{1}H NMR (300 MHz, D$_2$O) δ 3.79 (s, 4H), 3.55 (s, 4H), 3.38 – 3.26 (m, 4H), 3.02 (t, *J* = 7.6, 4H), 2.26-2.29 (m, 2H), 2.06-2.13 (m, 15.9, 4H); ^{13}C NMR (75 MHz, D$_2$O) δ 54.35, 53.45, 48.92, 36.42, 22.24, 20.29.

I5. N, N'-Bis(3-(3,4,5-trimethoxybenzoyl)aminopropyl)homopiperazine. To 10 mL of pyridine was added 3.20 g (0.89 mmol) of N, N'-Bis(3-aminopropyl) homopiperazine (4 HCl salt) and 689 mg (2.99 mmol) of 3,4,5-trimethoxybenzoyl chloride and the mixture was stirred overnight. The solvent was removed and the reaction mixture partitioned between 10 % NaOH solution and EtOAc. The EtOAc was dried, filtered, concentrated, and chromatographed with 5% NH3 saturated MeOH in DCM to isolate 265 mg of product as a white solid (50%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 (s, 2H), 7.03 (s, 4H), 3.88 (s, 9H), 3.86 (s, 6H), 3.49 (d, *J* = 5.4, 4H), 2.71 – 2.62 (m, 4H), 2.61 (s, 4H), 2.55 (t, *J* = 6.0, 4H), 1.63-1.69 (m, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.22, 152.95, 140.52, 130.65, 104.48, 60.76, 57.20, 56.22, 54.87, 54.41, 40.01, 27.30, 25.94.

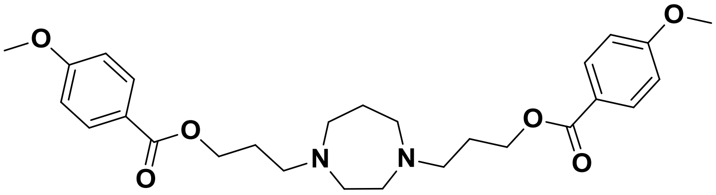
G17. To 5 mL of pyridine was added 200 mg (0.56 mmol) of N, N'-Bis(3-aminopropyl) homopiperazine (4 HCl salt) and 200 uL acetic anhydride (2.0 mmol) and the reaction was stirred 4 d. The solvent was removed by rotary evaporation and the residue partitioned between CH$_2$Cl$_2$ and water. The layers were separated and the water was rinsed several times with CH$_2$Cl$_2$, the combined CH$_2$Cl$_2$ layers were dried, concentrated, dissolved in MeOH and added to an acidic SCX resin column with was eluted first with MeOH and then with ca. 1 N NH3/MeOH to isolate the product which was converted to its 2 HCl salt by addition of HCl after dissolving in ether, 22 mg (9%). ^{13}C NMR (75 MHz, D$_2$O) δ 174.68, 55.30, 53.40, 48.98, 36.14, 23.98, 21.87, 20.47. Mass 299 (M + 1).

Scheme 4



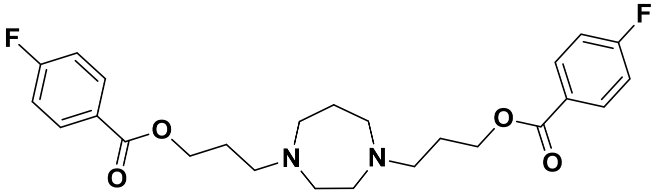
A mixture of 4 mL of 3-bromo-1-ol (24 mmol), 2.0 g of 3,4,5-trimethoxybenzyl chloride (9.2 mmol) and 3 g of K$_2$CO$_3$ was heated in 20 mL of THF overnight at 60 C. After cooling and filtering, water was added and rinsed with EtOAc several times, the EtOAc layers were dried, chromatographed and columned with 10% EtOAc in hexane to yield 450 mg of product as an oil (15%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.57 (s, 2H), 4.46 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 3.62 (t, *J* = 5.8 Hz, 2H), 3.55 (t, *J* = 6.5 Hz, 2H), 2.15 (p, *J* = 6.2 Hz, 2H).

G11. A mixture of 240 mg (0.76 mmol) of this bromide was stirred with 38 mg of homopiperazine (0.38 mmol) and 260 mg of K2CO3 in 2 mL of DMF for 3 d. Water was added and rinsed several times with EtOAc, the combined EtOAc layers were rinsed with brine, dried, concentrated and chromatographed with 5-10% NH3 saturated MeOH in DCM to isolate the product which was converted to the HCl salt by treatment with 2 N HCl in ether (11%). ^{1}H NMR (300 MHz, D_2O) δ 6.64 (s, 4H), 4.35 (s, 4H), 3.73 (s, 12H), 3.64 (s, 6H), 3.41-3.58 (m, 12H), 3.19 (t, J = 7.8 Hz, 4H), 2.13 (d, J = 6.5 Hz, 2H), 2.02 – 1.80 (m, 4H). ^{13}C NMR (75 MHz, D_2O) δ 152.58, 136.57, 134.12, 106.14, 72.88, 66.98, 60.93, 56.18, 55.71, 53.50, 48.66, 24.17, 20.24.



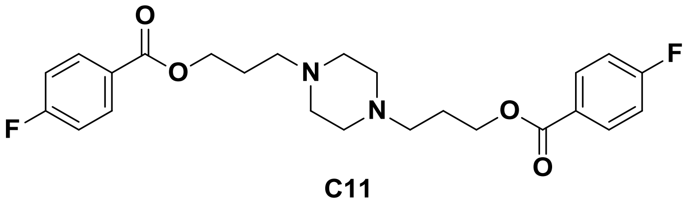
AT 007/ C5

AT-HSV-007 (13%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.9 Hz, 4H), 6.91 (d, J = 8.9 Hz, 4H), 4.33 (t, J = 6.5 Hz, 4H), 3.85 (s, 6H), 2.72 (d, J = 8.3 Hz, 8H), 2.67 – 2.58 (m, 4H), 1.92 (p, J = 6.8 Hz, 4H), 1.80 (p, J = 5.9 Hz, 2H). Mass 485 (M + 1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.34, 163.25, 131.52, 122.84, 113.55, 63.19, 55.40, 55.26, 54.97, 54.24, 27.67, 27.03.



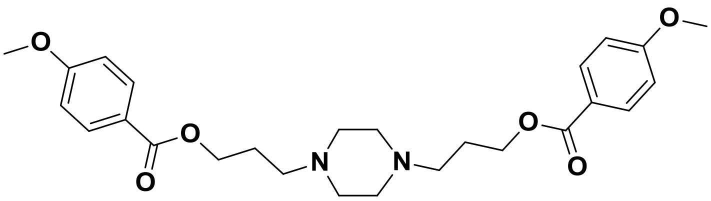
E17

E17 (44% free base). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.02 (dd, J = 8.8, 5.5 Hz, 4H), 7.08 (t, J = 8.7 Hz, 4H), 4.35 (t, J = 6.4 Hz, 4H), 2.74 (t, J = 6.2 Hz, 8H), 2.69 – 2.60 (m, 4H), 1.80-2.00 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.67 ($J_{C\text{-}F}$ = 254 Hz) , 165.55, 132.03 ($J_{C\text{-}F}$ = 9 Hz), 126.54, 115.45 ($J_{C\text{-}F}$ = 22 Hz), 63.42, 54.86, 54.82, 53.99, 27.07, 26.71.



C11

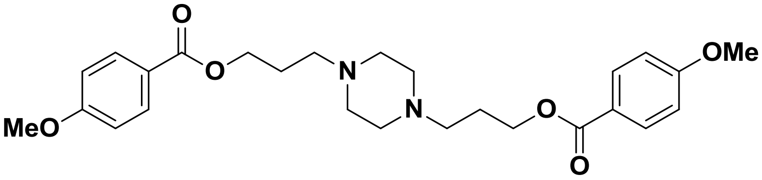
C11 (45%, free base). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 (dd, J = 8.5, 5.4 Hz, 4H), 7.09 (t, J = 8.4 Hz, 4H), 4.36 (t, J = 6.5 Hz, 4H), 2.64 – 2.28 (m, 12H), 1.95 (p, J = 6.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.68 ($J_{C\text{-}F}$ = 254 Hz) , 165.57, 132.04 ($J_{C\text{-}F}$ = 9 Hz), 126.59, 115.45 ($J_{C\text{-}F}$ = 22 Hz), 63.54, 55.07, 53.18, 26.25.



AT 009/G3

AT-HSV-009/G3 ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, 4H), 6.83 (d, *J* = 8.8 Hz, 4H), 4.25 (t, *J* = 6.4 Hz, 4H), 3.77 (s, 6H), 2.61 – 2.20 (m, 12H), 1.96 – 1.74 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.32, 163.28, 131.52, 122.75, 113.56, 63.10, 55.39, 55.17, 53.18, 26.32. Mass 471 (M + 1).

AT-HSV-016 4-MeO ester two carbon piperazine



G3

G3 ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.9 Hz, 4H), 6.83 (d, *J* = 8.9 Hz, 4H), 4.26 (t, *J* = 6.4 Hz, 4H), 3.77 (s, 6H), 2.60 – 2.30 (m, 12H), 1.87 (p, *J* = 6.6 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.32, 163.28, 131.52, 122.75, 113.56, 63.10, 55.39, 55.17, 53.18, 26.32. Mass 471 (M + 1)