Supporting Information

Title: Design and synthesis of selective, small molecule inhibitors of coactivator-associated arginine methyltransferase 1 (CARM1)

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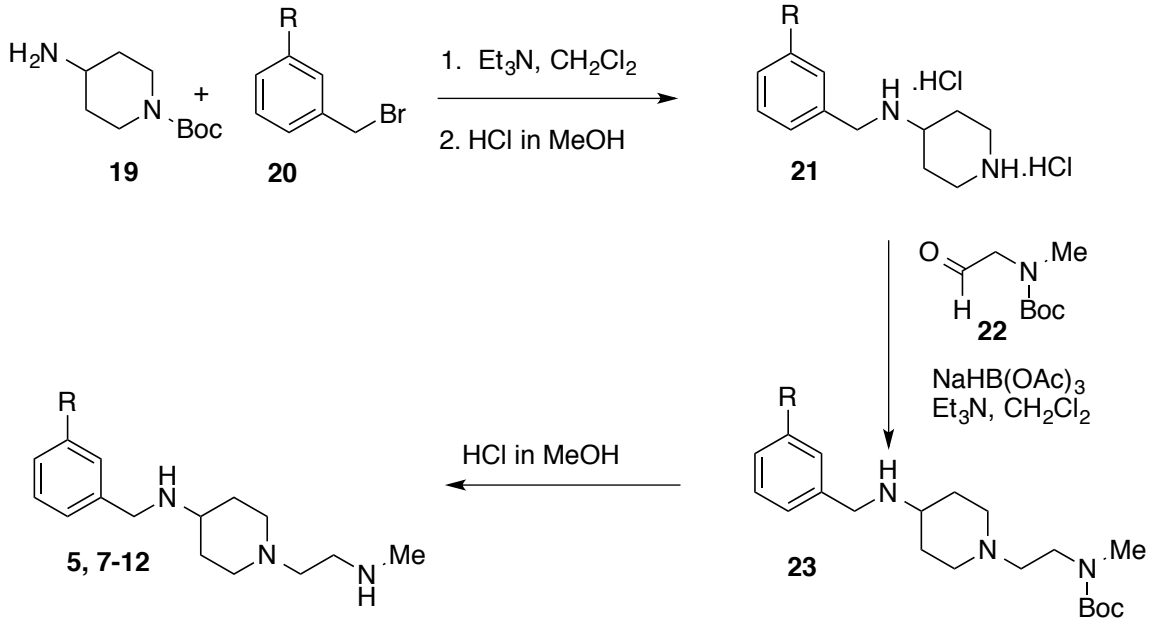
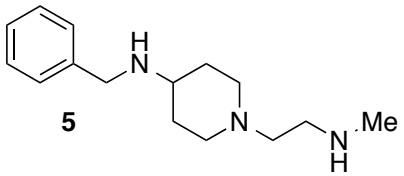
Chemistry General Procedures: Flash column chromatography was performed using a TeledyneISCO Rf+ system fitted with Redisep Rf normal phase silica gel columns. High-resolution mass spectra (HRMS) data were acquired in positive ion mode using an Agilent G1969A API-TOF with an electrospray ionization (ESI) source. Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker DRX-600 spectrometer with 600 MHz for proton (^{1}H NMR) and 151 MHz for carbon (^{13}C NMR); chemical shifts are reported in ppm (δ) referenced to the NMR solvent.[1] Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet); coupling constant(s) (*J*) in Hz; integration. Unless otherwise noted, NMR data were collected at 25 °C. All final compounds had > 95% purity either by ^{1}H-NMR or UV absorbance at 254 nm during tandem liquid chromatography/mass spectrometry (LCMS).



General procedure for the synthesis of compounds 5, 7-12 (Scheme 1):

To a stirring mixture of 4-amino-1-Boc-piperidine (**19**) (150 mg, 0.75 mmol, 1.0 eq.) in dichloromethane (DCM, 3 mL) was added triethylamine (Et_3N, 125 µL, 0.90 mmol, 1.2 eq.) followed by corresponding benzyl bromide **20** (0.90 mmol, 1.2 eq.) and the resulting clear solution was stirred at room temperature for 16 hours. The reaction mixture was then partitioned between water (10 mL) and DCM (10 mL) and extracted with DCM (3 x 15 mL). Combined organic layers were dried over anhydrous sodium sufate (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by flash column chromatography using 0-15% methanol/dichloromethane as the eluent to yield desired product. This product then was dissolved in methanolic HCl (3N, 0.5-1.0 mL) and allowed to stir at room temperature overnight. After evaporation of volatiles, the obtained solid (**21**) used for next step without further purification. Diamine **21**, was then dissolved in DCM (10 mL per mmol) and was added Et_3N (3.0 eq.) followed by N-Boc-(methylamino)acetaldehyde (**22**) (1.0 eq.) and sodium triacetoxyborohydride (1.5 eq) and resulting suspension was stirred at room temperature 24 hours. Water (10 mL) was added to the reaction and extracted with DCM (3 x 15 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure yielded the crude **23** that was purified by flash column chromatography using 0-10%

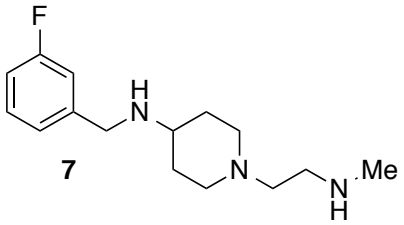
methanol/dichloromethane as the eluent. This reductive amination product (**23**) was then treated again with Methanolic HCl (3N, 1-2 mL) at room temperature for 12 hours to yield desired products as 3xHCl salts after removal of volatiles under vacuo. The NMR data reported for free amine products of **5, 7-12** after the HCl salts basified and extracted to DCM that was dried over sodium sulfate and concentrated under reduced pressure.



5

***N*-benzyl-1-(2-(methylamino)ethyl)piperidin-4-amine (5)**

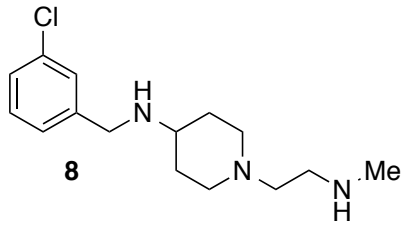
Benzyl bromide (154 mg, 107 μL) is used. Yield (3x HCl salt): 8% (22 mg) over 4 steps. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.36-7.30 (m, 4H), 7.25 (t, J = 7.0 Hz, 1H), 3.77 (s, 2H), 2.93 (d, J = 11.6 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 2.52-2.47 (m, 3H), 2.42 (s, 3H), 2.02 (t, J = 11.9 Hz, 2H), 1.93 (d, J = 12.7 Hz, 2H), 1.49-1.42 (m, 2H). LRMS (ESI) for $C_{15}H_{26}N_3^+$ [M + H]$^+$: calculated 248.4, found 248.2.



7

***N*-(3-fluorobenzyl)-1-(2-(methylamino)ethyl)piperidin-4-amine (7)**

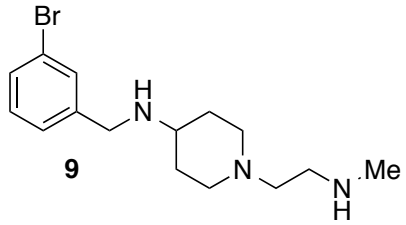
3-Fluorobenzyl bromide (170 mg, 111 μL) is used. Yield (3x HCl salt): 23% (71 mg) over 4 steps. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.35-731 (m, 1H), 7.16-712 (m, 2H), 6.98 (td, J = 8.8, 2.7 Hz, 1H), 3.79 (s, 2H), 2.93 (d, J = 11.7 Hz, 2H), 2.71 (t, J = 6.7 Hz, 2H), 2.50-2.46 (m, 3H), 2.42 (s, 3H), 2.03 (t, J = 11.9 Hz, 2H), 1.92 (d, J = 12.7 Hz, 2H), 1.45 (td, J = 12.8, 6.9 Hz, 2H). LRMS (ESI) for $C_{15}H_{25}FN_3^+$ [M + H]$^+$: calculated 266.2, found 266.2.



8

***N*-(3-chlorobenzyl)-1-(2-(methylamino)ethyl)piperidin-4-amine (8)**

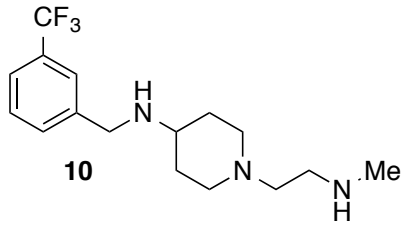
3-Chlorobenzyl bromide (185 mg, 117 μL) is used. Yield (3x HCl salt): 20% (61 mg) over 4 steps.[1]H NMR (600 MHz, Deuterium Oxide) δ 7.37 (s, 1H), 7.33-7.29 (m, 2H), 7.26-7.21 (m, 1H), 3.72 (s, 2H), 2.88 (d, *J* = 11.6 Hz, 2H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.50-244 (m, 3H), 2.33 (s, 3H), 2.03 (t, *J* = 11.9 Hz, 2H), 1.87 (d, *J* = 12.8 Hz, 2H), 1.34-1.28 (m, 2H). LRMS (ESI) for $C_{15}H_{25}ClN_3^+$ [M + H]$^+$: calculated 282.2, found 282.2.



9

***N*-(3-bromobenzyl)-1-(2-(methylamino)ethyl)piperidin-4-amine (9)**

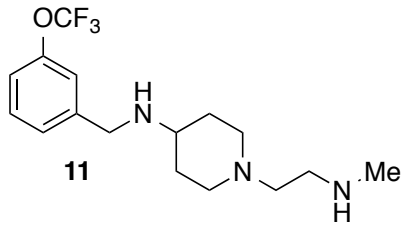
3-Bromobenzyl bromide (225 mg) is used. Yield (3x HCl salt): 23% (71 mg) over 4 steps. [1]H NMR (600 MHz, Methanol-d_4) δ 7.56 (s, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 3.76 (s, 2H), 2.93 (d, *J* = 11.6 Hz, 2H), 2.71 (t, *J* = 6.7 Hz, 2H), 2.50-245 (m, 3H), 2.41 (s, 3H), 2.03 (t, *J* = 11.5 Hz, 2H), 1.92 (d, *J* = 12.8 Hz, 2H), 1.52-1.38 (m, 2H). [13]C NMR (151 MHz, Methanol-d_4) δ 143.7, 132.5, 131.2, 131.2, 128.3, 123.4, 57.8, 55.2, 53.8 (2 carbons), 50.6, 49.1, 35.8, 32.6 (2 carbons). HRMS (m/z) for $C_{15}H_{25}BrN_3^+$ [M + H]$^+$: calculated 326.1226 found 326.1222.



10

1-(2-(methylamino)ethyl)-*N*-(3-(trifluoromethyl)benzyl)piperidin-4-amine (10)

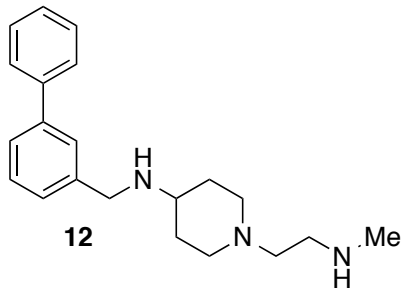
3-(trifluoromethyl)benzyl bromide (215 mg, 137 μL) is used. Yield (3x HCl salt): 24% (73 mg) over 4 steps. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.70 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.57-7.51 (m, 2H), 3.86 (s, 2H), 2.93 (d, J = 11.8 Hz, 2H), 2.71 (t, J = 6.7 Hz, 2H), 2.52-248 (m, 3H), 2.42 (s, 3H), 2.04 (t, J = 11.9 Hz, 2H), 1.94 (d, J = 12.8 Hz, 2H), 1.49-143 (m, 2H). LRMS (ESI) for $C_{16}H_{25}F_3N_3^+$ [M + H]$^+$: calculated 316.2, found 316.2.



11

1-(2-(methylamino)ethyl)-*N*-(3-(trifluoromethoxy)benzyl)piperidin-4-amine (11)

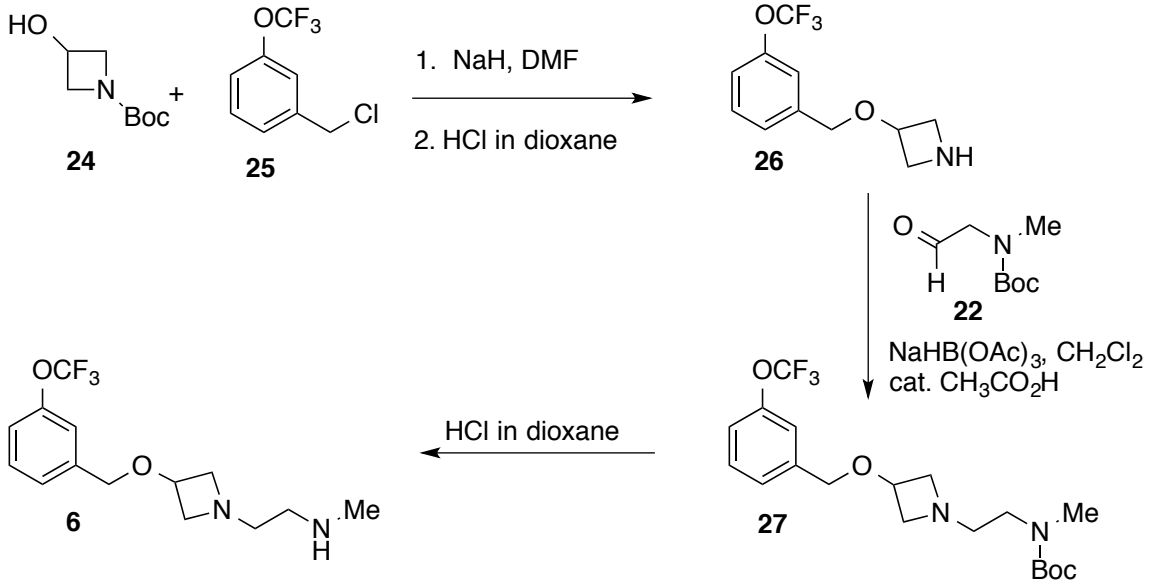
3-(trifluoromethoxy)benzyl bromide (229 mg, 146 μL) is used. Yield (3x HCl salt): 17% (55 mg) over 4 steps.^{1}H NMR (600 MHz, Methanol-d_4) δ 7.42 (t, J = 7.9 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.31 (s, 1H), 7.17 (d, J = 7.3 Hz, 1H), 3.82 (s, 2H), 2.93 (d, J = 11.6 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 2.50-2.46 (m, 3H), 2.42 (s, 3H), 2.03 (t, J = 11.8 Hz, 2H), 1.92 (d, J = 12.7 Hz, 2H), 1.49-142 (m, 2H). LRMS (ESI) for $C_{16}H_{25}F_3N_3O^+$ [M + H]$^+$: calculated 332.2, found 332.2.



12

***N*-([1,1'-biphenyl]-3-ylmethyl)-1-(2-(methylamino)ethyl)piperidin-4-amine (12)**

3-Phenylbenzyl bromide (223 mg) is used. Yield (3x HCl salt): 7% (20 mg) over 4 steps. ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.65-7.64 (m, 3H), 7.54 (d, J = 7.7 Hz, 1H), 7.44-7.39 (m, 3H), 7.38-7.32 (m, 2H), 3.87 (s, 2H), 2.96 (d, J = 11.6 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.60-2.53 (m, 1H), 2.51 (t, J = 6.7 Hz, 2H), 2.44 (s, 3H), 2.06 (t, J = 11.9 Hz, 2H), 1.98 (d, J = 12.7 Hz, 2H), 1.56-1.45 (m, 2H). LRMS (ESI) for $C_{21}H_{30}N_3^+$ [M + H]$^+$: calculated 324.2, found 324.2.

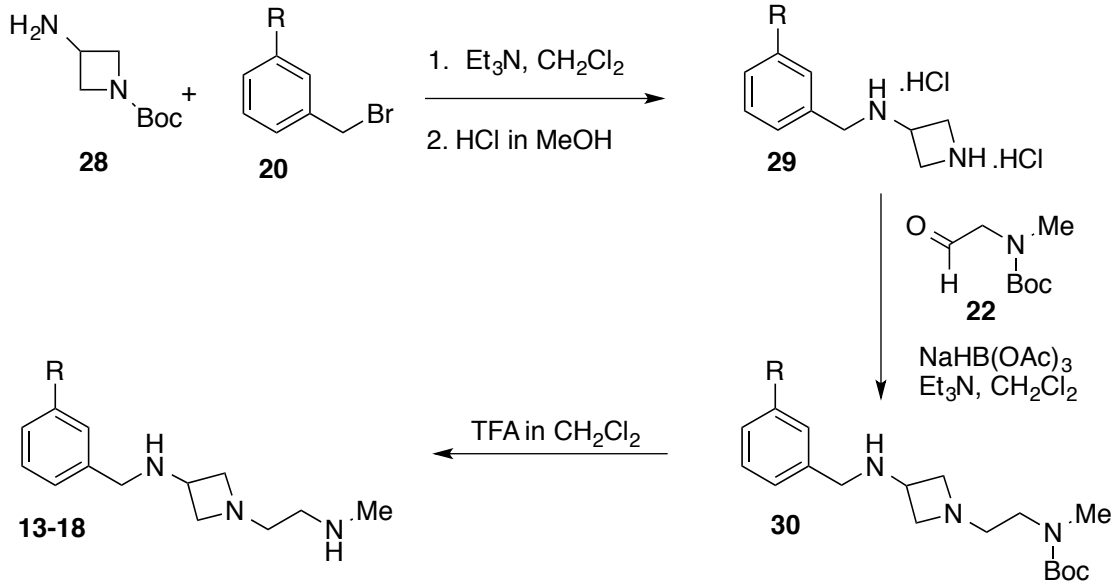


***N*-methyl-2-(3-((3-(trifluoromethoxy)benzyl)oxy)azetidin-1-yl)ethanamine (6)**

To a solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (**24**) (150 mg, 0.866 mmol, 1.0 eq.) and 1-(chloromethyl)-3-(trifluoromethoxy)benzene (**25**) (365 mg, 1.73 mmol, 2.0 eq.) in DMF (10 mL) at room temperature was added sodium hydride (60% dispersion in

oil, 70 mg, 1.73 mmol, 2.0 eq.). The resulting solution was stirred for 4 h prior to dilution with water (10 mL) and extraction with EtOAc (3 x 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 10-100% EtOAc/hexanes as the eluent to afford *tert*-butyl 3-((3-(trifluoromethoxy)benzyl)oxy)azetidine-1-carboxylate (226 mg, 75%), which was taken directly to next step. To a solution of *tert*-butyl 3-((3-(trifluoromethoxy)benzyl)oxy)azetidine-1-carboxylate (226 mg, 0.651 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at room temperature was added HCl/dioxane (4.0 M solution, 5 mL). The resulting solution was stirred for 1 hr prior to removal of all solvents under reduced pressure, and dissolution of the residue in water (10 mL). Following basification of the aqueous solution to pH = 12 with aqueous sodium hydroxide solution (1.0 N), the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 3-((3-(trifluoromethoxy)benzyl)oxy)azetidine (**26**) (159 mg, 99%), which was used in the subsequent reaction without further purification. To a solution of **26** (159 mg, 0.642 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) at room temperature was added *tert*-butyl methyl(2-oxoethyl)carbamate (**22**) (133 mg, 0.770 mmol, 1.2 eq.) and glacial acetic acid (2 drops). The resulting solution was stirred for 10 mins prior to the addition of sodium triacetoxyborohydride (191 mg, 0.899 mmol, 1.4 eq.), after which the solution was stirred an additional 16 hrs. Following dilution with water (10 mL) and extraction with EtOAc (3 x 10 mL), the combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 10-100% EtOAc/hexanes as the eluent to afford *tert*-butyl methyl(2-(3-((3-(trifluoromethoxy)benzyl)oxy)azetidin-1-yl)ethyl)carbamate (**27**) (161 mg, 62%), which was taken directly to next step. To a solution **27** (161 mg, 0.398 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at room temperature was added HCl/dioxane (4.0 M solution, 4 mL). The resulting solution was stirred for 1 h prior to removal of all solvents under reduced pressure, and dissolution of the residue in water (10 mL). Following basification of the aqueous solution to pH = 12 with aqueous sodium hydroxide solution (1.0 N), the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts

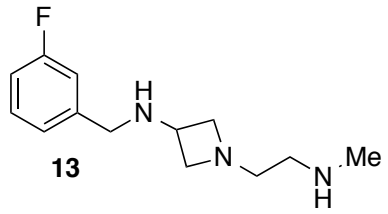
were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *N*-methyl-2-(3-((3-(trifluoromethoxy)benzyl)oxy)azetidin-1-yl)ethanamine (**6**) (120 mg, 99%), which was not subject to further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 (t, J = 8.0 Hz, 1H), 7.39-7.34 (m, 1H), 7.32-7.26 (m, 2H), 4.44 (s, 2H), 4.16-4.09 (m, 1H), 3.50-3.44 (m, 2H), 2.82-2.76 (m, 2H), 2.44 (t, J = 6.2 Hz, 2H), 2.38 (t, J = 6.0 Hz, 2H), 2.24 (s, 3H). LRMS (ESI) for $C_{14}H_{20}F_3N_2O_2^+$ $[M + H]^+$: calculated 304.3, found 304.9.



General procedure for the synthesis of compounds 13-18 (Scheme 3):

To a stirring mixture of 1-Boc-3-(Amino)azetidine (**28**) (387 mg, 2.25 mmol, 1.0 eq.) in dichloromethane (DCM, 9 mL) was added triethylamine (Et_3N, 375 µL, 2.70 mmol, 1.2 eq.) followed by corresponding benzyl bromide **20** (2.70 mmol, 1.2 eq) and the resulting clear solution was stirred at room temperature 16 hrs. The reaction mixture was then partitioned between water (10 mL) and DCM (20 mL) and extracted with DCM (3 x 20 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography using 0-15% methanol/dichloromethane as the eluent to yield desired amine. This amine then dissolved in methanolic HCl (3N, 1.5-2.0 mL) and allowed to stir at room temperature 12 hrs. After evaporation of volatiles, the obtained solid (**29**) used for next step without any further purification. Diamine **29**, was dissolved in DCM (10 mL

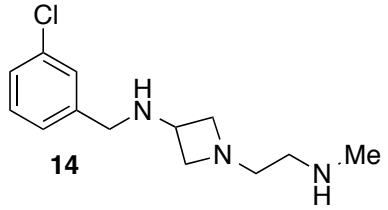
per mmol) and was added Et_3N (3.0 eq.) followed by N-Boc-(methylamino)acetaldehyde (1.0 eq.) and sodium triacetoxyborohydride (1.5 eq.) and resulting suspension was stirred at room temperature 24 hrs. Water (10 mL) was added to the reaction and extracted with DCM (3 x 15 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure yielded the crude **30** that was purified by flash column chromatography using 0-10% methanol/dichloromethane as the eluent. This reductive amination product (**30**) was then treated with TFA in DCM (1 in 4 mL) at room temperature to yield desired products (**13-18**) as 3xTFA salts after removal of volatiles under vacuo. The NMR data reported are for TFA salts in D_2O.



13

***N*-(3-fluorobenzyl)-1-(2-(methylamino)ethyl)azetidin-3-amine (13):**

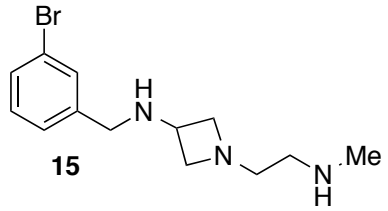
3-Fluorobenzyl bromide (510 mg, 331 μL) is used**.** Yield (3x TFA salt): 42% (96 mg) over 4 steps. ^{1}H NMR (600 MHz, Deuterium Oxide) δ 7.50-7.46 (m, 1H), 7.26-7.21(m, 3H), 4.55-4.54 (m, 3H), 4.43-4.41 (m, 2H), 4.27 (s, 2H), 3.68 (t, *J* = 7.4 Hz, 2H), 3.28 (t, *J* = 7.4 Hz, 2H), 2.72 (s, 3H). LRMS (ESI) for $C_{13}H_{21}FN_3^+[M + H]^+$: calculated 238.2, found 238.2.



14

***N*-(3-chlorobenzyl)-1-(2-(methylamino)ethyl)azetidin-3-amine (14):** 1-Boc-3-(Amino)azetidine (**28**) (258 mg, 1.5 mmol, 1.0 eq.) 3-Chlorobenzyl bromide (340.2 mg, 220 μL) is used**.** Yield (3x TFA salt): 23% (69 mg) over 4 steps.^{1}H NMR (600 MHz, Deuterium Oxide) δ 7.53-7.47 (m, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 4.46-4.43 (m, 3H), 4.34-4.29 (m, 2H), 4.24 (s, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 3.29-3.22

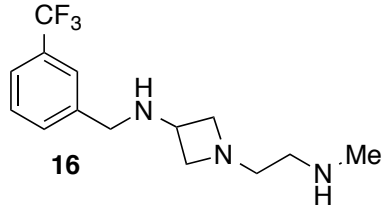
(m, 2H), 2.72 (s, 3H). LRMS (ESI) for $C_{13}H_{21}ClN_3^+$[M + H]$^+$: calculated 254.1, found 254.1, found 254.1.



15

***N*-(3-bromobenzyl)-1-(2-(methylamino)ethyl)azetidin-3-amine (15):**

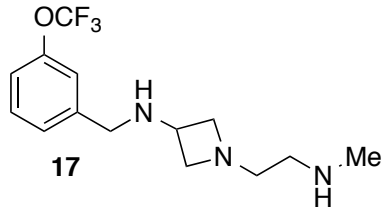
3-Bromobenzyl bromide (675 mg) is used**.** Yield (3x TFA salt): 30% (91 mg) over 4 steps.^{1}H NMR (600 MHz, Deuterium Oxide) δ 7.67-7.64 (m, 2H), 7.42-7.36 (m, 2H), 4.56-4.52 (m, 3H), 4.46-4.38 (m, 2H), 4.24 (s, 2H), 3.68 (t, *J* = 7.3 Hz, 2H), 3.28 (t, *J* = 7.3 Hz, 2H), 2.73 (s, 3H). LRMS (ESI) for $C_{13}H_{21}BrN_3^+$[M + H]$^+$: calculated 298.1, found 298.1.



16

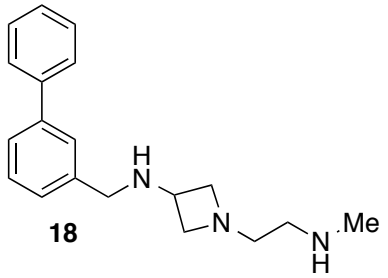
1-(2-(methylamino)ethyl)-*N*-(3-(trifluoromethyl)benzyl)azetidin-3-amine (16):

3-(Trifluoromethyl)benzyl bromide (645 mg, 412 μL) is used**.** Yield (3x TFA salt): 33% (102 mg) over 4 steps.^{1}H NMR (600 MHz, Deuterium Oxide) δ 7.83-7.77 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 4.56-4.54 (m, 3H), 4.44-4.42 (m, 2H), 4.33 (s, 2H), 3.67 (t, *J* = 7.3 Hz, 2H), 3.28 (t, *J* = 7.3 Hz, 2H), 2.73 (s, 3H). LRMS (ESI) for $C_{14}H_{21}F_3N_3^+$ [M + H]$^+$: calculated 288.2, found 288.2.



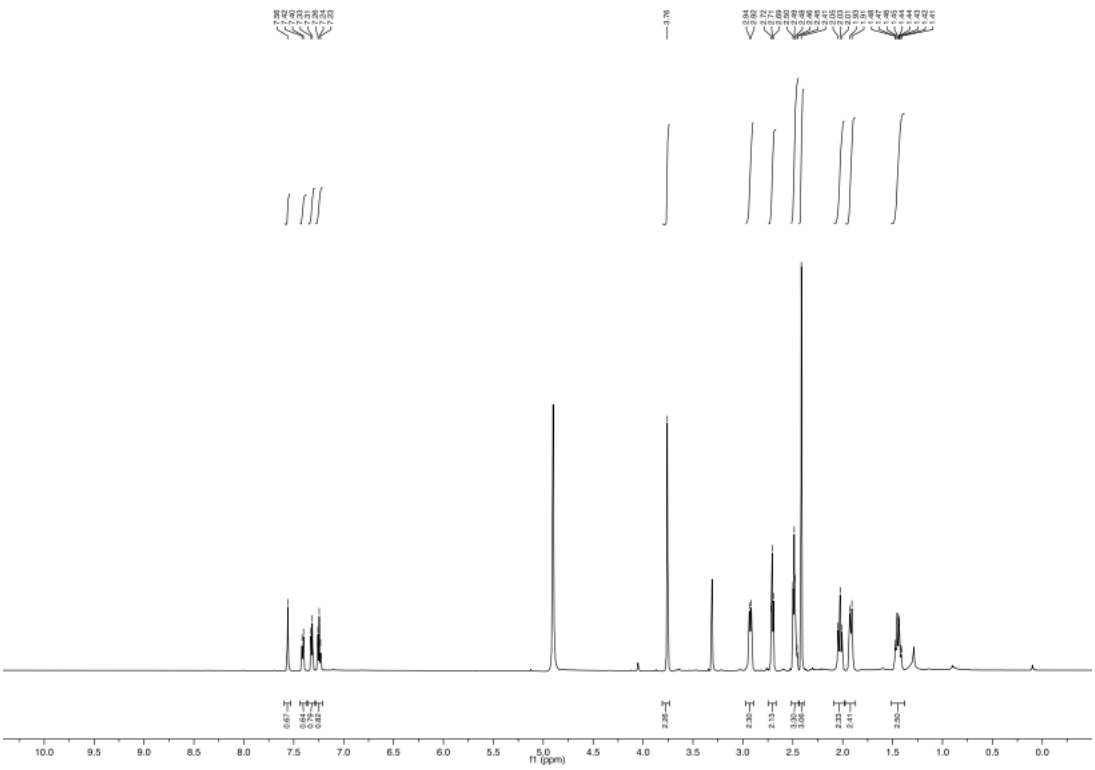
17

1-(2-(methylamino)ethyl)-*N*-(3-(trifluoromethoxy)benzyl)azetidin-3-amine (17): 3-(Trifluoromethoxy)benzyl bromide (645 mg, 412 μL) is used**.** Yield (3x TFA salt): 9% (61 mg) over 4 steps.^{1}H NMR (600 MHz, Deuterium Oxide) δ 7.57-7.54 (m, 1H), 7.47-7.39 (m, 3H), 4.53-4.45 (m, 3H), 4.39-4.32 (m, 2H), 4.28 (s, 2H), 3.62 (t, *J* = 7.3 Hz, 2H), 3.26 (t, *J* = 7.3 Hz, 2H), 2.72 (s, 3H). LRMS (ESI) for $C_{14}H_{21}F_3N_3O^+$ $[M + H]^+$: calculated 304.2, found 304.2.

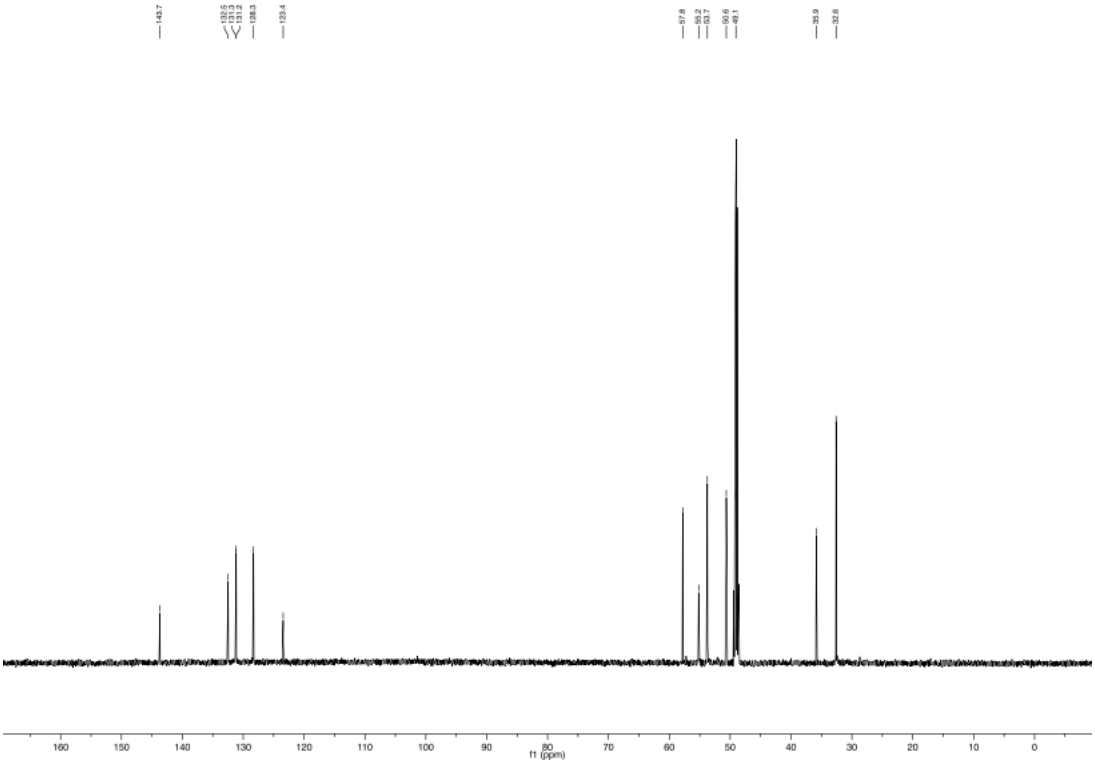


18

***N*-([1,1'-biphenyl]-3-ylmethyl)-1-(2-(methylamino)ethyl)azetidin-3-amine (18):**Yield (3x TFA salt): 7% (14 mg) over 4 steps. ^{1}H NMR (600 MHz, Deuterium Oxide) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.74-7.66 (m, 3H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.53-7.50 (m, 2H), 7.44-7.42 (m, 2H), 4.49 (p, *J* = 7.0 Hz, 1H), 4.43-4.40 (m, 2H), 4.32 (s, 2H), 4.31-4.25 (m, 2H), 3.56 (t, *J* = 7.3 Hz, 2H), 3.23 (t, *J* = 7.2 Hz, 2H), 2.71 (s, 3H). LRMS (ESI) for $C_{19}H_{26}N_3^+$ $[M + H]^+$: calculated 296.2, found 296.2.



^{1}H-NMR spectrum of compound **9**



^{13}C-NMR spectrum of compound **9**

PRMT Biochemical Assays.
A scintillation proximity assay (SPA) was used for assessing the selectivity as well as the effect of compounds on inhibiting the methyl transfer activity of PRMTs as described elswhere.[2] The tritiated S-adenosyl-L-methionine (^{3}H-SAM, specific activity range of 1.8-0.06 Ci/mmol, PerkinElmer Life Sciences) was used as the donor of methyl group. The (^{3}H) methylated biotin labeled peptide substrate was captured in a FlashPlates Plus (Perkin-Elmer, Waltham MA) and quantified using a TopCount NXT plate reader (Perkin Elmer, Waltham MA). When necessary, nontritiated SAM was used to supplement the reactions. The IC_{50} values were determined under balanced conditions at K_m concentrations of both substrate and cofactor by titration of test compounds in the reaction mixture.

MOA studies. The above mentioned radioactivity assay was used to determine the MOA of compound **9** against CARM1 by assessing the competition of the compound with SAM and peptide independently as described previously.[2] To assess the competition of compound 9 with SAM, peptide concentration was kept at saturation (3 μM) and IC_{50} values were determined at various SAM concentrations (0.5, 1, 4, 8, 12, 16, 20, and 25×K_m). To determine the competition with peptide, the SAM concentration was kept at saturation (12 μM) and the compound potency was determined at various peptide concentrations (0.5, 1, 2, 4, 8, 12, 16, and 20 × K_m).

1. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010,** 29, 2176-2179.
2. Kaniskan, H. U.; Szewczyk, M. M.; Yu, Z.; Eram, M. S.; Yang, X.; Schmidt, K.; Luo, X.; Dai, M.; He, F.; Zang, I.; Lin, Y.; Kennedy, S.; Li, F.; Dobrovetsky, E.; Dong, A.; Smil, D.; Min, S. J.; Landon, M.; Lin-Jones, J.; Huang, X. P.; Roth, B. L.; Schapira, M.; Atadja, P.; Barsyte-Lovejoy, D.; Arrowsmith, C. H.; Brown, P. J.; Zhao, K.; Jin, J.; Vedadi, M. A potent, selective and cell-active allosteric inhibitor of protein arginine methyltransferase 3 (PRMT3). *Angew Chem Int Ed Engl* **2015,** 54, 5166-5170.