SUPPORTING INFORMATION

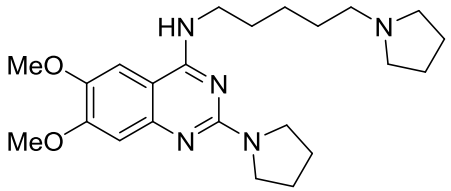
Structure-activity relationship studies of SETD8 inhibitors

Anqi Ma[a], Wenyu Yu[d], Yan Xiong[a], Kyle V. Butler[a], Peter J. Brown[d] and Jian Jin[*, a, b, c]*

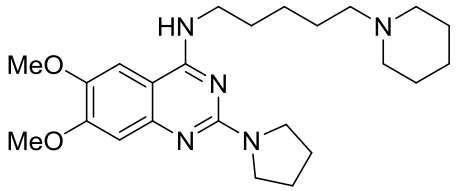
Table of Contents

Experimental Section

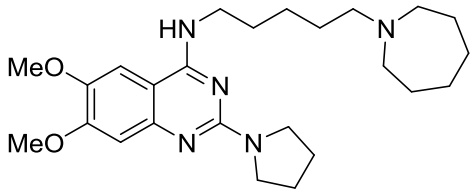
Chemistry General Procedures. HPLC spectra for all compounds were acquired using an Agilent 6110 Series system with UV detector set to 254 nm. Samples were injected (5.0 µL) onto an Agilent Eclipse Plus 4.6 x 50 mm, 1.8 µM, C18 column at room temperature. Method 1: A linear gradient from 10% to 100% B (MeOH + 0.1% acetic acid) in 5.0 min was followed by pumping 100% B for another 2 minutes with A being H_2O + 0.1% acetic acid. Method 2: A linear gradient from 10% to 50% B (MeOH + 0.1% acetic acid) in 5.0 min was followed by pumping 100% B for another 2 minutes with A being H_2O + 0.1% acetic acid. The flow rate was 1.0 mL/min. Mass spectra (MS) data were acquired in positive ion mode using an Agilent 6110 single quadrupole mass spectrometer with an electrospray ionization (ESI) source. Nuclear Magnetic Resonance (NMR) spectra were recorded at Varian Mercury spectrometer with 400 MHz for proton (^{1}H NMR) and 100 MHz for carbon (^{13}C NMR); chemical shifts are reported in ppm (δ). Preparative HPLC was performed on Agilent Prep 1200 series with UV detector set to 254 nm. Samples were injected onto a Phenomenex Luna 75 x 30 mm, 5 µM, C_{18} column at room temperature. The flow rate was 30 mL/min. A linear gradient was used with 10% (or 50%) of MeOH (A) in 0.1 % TFA in H_2O (B) to 100% of MeOH (A). HPLC was used to establish the purity of target compounds, all compounds had > 95% purity using the HPLC methods described above.



6,7-Dimethoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (1). This compound was synthesized according to the procedures reported previously.[1]

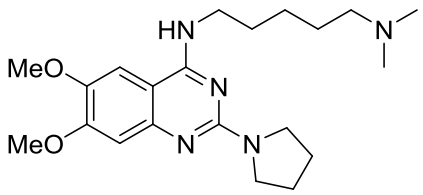


6,7-Dimethoxy-*N*-(5-(piperidin-1-yl)pentyl)-2-(pyrrolidin-1-yl)quinazolin-4-amine (2). This compound was synthesized according to the procedures reported previously.[1]

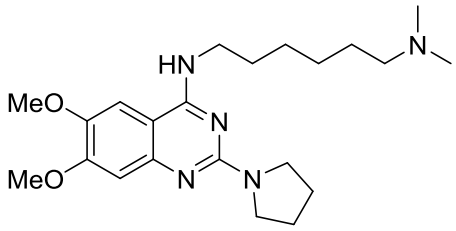


***N*-(5-(Azepan-1-yl)pentyl)-6,7-dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-amine (3).** To the solution of 2,4-dichloro-6,7-dimethoxyquinazoline (commercially available, 200 mg, 0.77 mmol) in THF (2.0 mL) was added 5-(azepan-1-yl)pentan-1-amine (commercially available, 157 mg, 0.85 mmol), followed by the addition of *N*,*N*-diisopropylethylamine (148 µL, 0.85 mmol). And the resulting mixture was stirred at room temperature for 6 hours until TLC showed that the starting material had disappeared. Water was added to the reaction mixture, and the resulting solution was extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give the crude product, which was purified by HPLC to give *N*-(5-(azepan-1-yl)pentyl)-2-chloro-6,7-dimethoxyquinazolin-4-amine (**S1**) as a TFA salt (183 mg, yield 38%). To the solution of *N*-(5-(azepan-1-yl)pentyl)-2-chloro-6,7-dimethoxyquinazolin-4-amine (**S1**, 60 mg, 0.09 mmol) and *n*-butanol (0.7 mL) were added pyrrolidine (commercially available, 31 µL, 0.37 mmol) and *N*,*N*-diisopropylethylamine (49 µL, 0.28 mmol). The resulting solution was stirred inside a microwave at 180 °C for 1 hour. After cooling, TLC indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was redissolved in CH_2Cl_2,

washed with brine. The organic layer was dried, concentrated and purified by HPLC to give the title compound **3** as a TFA salt, yellow solid (43 mg, yield 68%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.53 (s, 1H), 7.07 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.79 – 3.55 (m, 6H), 3.51 – 3.42 (m, 2H), 3.21 – 3.11 (m, 4H), 2.22 – 2.03 (m, 4H), 1.95 – 1.69 (m, 12H), 1.53 – 1.44 (m, 2H); ^{13}C NMR (100 MHz, d_4-MeOH) δ 160.33, 157.08, 151.47, 148.73, 136.91, 105.04, 103.58, 99.61, 58.63, 56.93 (two carbons), 56.80 (two carbons), 55.86 (two carbons), 42.50, 29.30, 27.36 (two carbons), 25.32 (two carbons), 25.27 (two carbons), 24.77 (two carbons). HPLC purity (method 1): >95%; t_R 3.56 min; MS (ESI): 442 $[M+H]^+$.

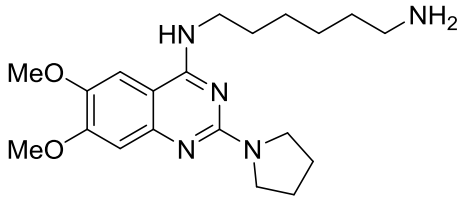


***N*^{1}-(6,7-Dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)-*N*^{5},*N*^{5}-dimethylpentane-1,5-diamine (4).** This compound was synthesized according to the procedures reported previously.[1]



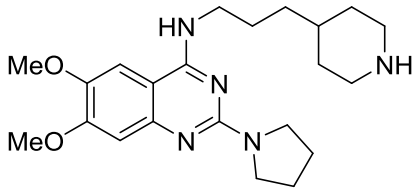
***N*^{1}-(6,7-Dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)-*N*^{6},*N*^{6}-dimethylhexane-1,6-diamine (5).** *N*^{1}-(2-Chloro-6,7-dimethoxyquinazolin-4-yl)-*N*^{6},*N*^{6}-dimethylhexane-1,6-diamine was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, *N*^{1},*N*^{1}-dimethylhexane-1,6-diamine (commercially available), *N*,*N*-diisopropylethylamine and THF. Compound **5** was prepared according to the procedures for

making **3** from N^1-(2-Chloro-6,7-dimethoxyquinazolin-4-yl)-N^6,N^6-dimethylhexane-1,6-diamine (110 mg, 0.30 mmol), pyrrolidine (99 µL, 1.2 mmol), *N*,*N*-diisopropylethylamine (105 µL, 0.60 mmol) and *n*-butanol (2.2 mL). The title compound **5** was obtained as a TFA salt, tan solid (106 mg, yield 56%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.56 (s, 1H), 7.10 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.80 – 3.57 (m, 6H), 3.15 – 3.08 (m, 2H), 2.87 (s, 6H), 2.22 – 2.02 (m, 4H), 1.83 – 1.69 (m, 4H), 1.56 – 1.39 (m, 4H). HPLC purity (method 1): >95%; t_R 3.42 min; MS (ESI): 402 $[M+H]^+$.

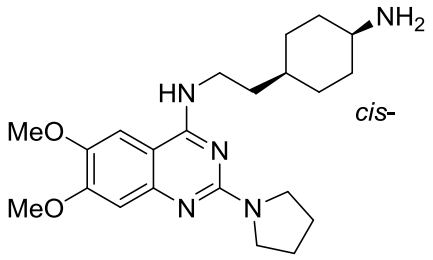


***N*^{1}-(6,7-Dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)hexane-1,6-diamine (6).** *tert*-Butyl (6-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)hexyl)carbamate was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, *N*-Boc-1,6-hexanediamine hydrochloride (commercially available), *N*,*N*-diisopropylethylamine and THF. Boc-protected compound **6** was prepared according to the procedures for making **3** from *tert*-butyl (6-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)hexyl)carbamate (131 mg, 0.30 mmol), pyrrolidine (99 µL, 1.2 mmol), *N*,*N*-diisopropylethylamine (105 µL, 0.60 mmol) and *n*-butanol (1.0 mL). To the resulting mixture was added TFA and stirred overnight at room temperature. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was purified by HPLC to give the title compound **6** as a TFA salt, white solid (115 mg, yield 64%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.55 (s, 1H), 7.09 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.78 – 3.55 (m, 6H), 2.98 – 2.87 (m, 2H), 2.23 – 2.00 (m, 4H), 1.85 – 1.73 (m, 2H),

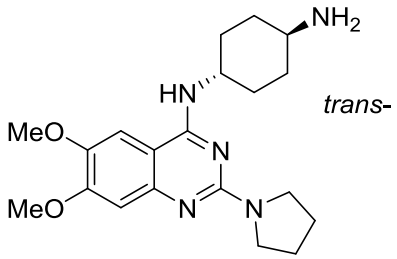
1.72 – 1.62 (m, 2H), 1.52 – 1.42 (m, 4H). HPLC purity (method 1): >95%; t_R 3.35 min; MS (ESI): 374 $[M+H]^+$.



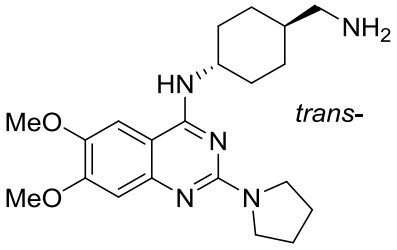
6,7-Dimethoxy-*N*-(3-(piperidin-4-yl)propyl)-2-(pyrrolidin-1-yl)quinazolin-4-amine (7). *tert*-Butyl 4-(3-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)propyl) piperidine-1-carboxylate was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, *tert*-butyl 4-(3-aminopropyl)piperidine-1-carboxylate (commercially available), *N*,*N*-diisopropylethylamine and THF. Boc-protected compound **7** was prepared according to the procedures for making **3** from *tert*-butyl 4-(3-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)propyl) piperidine-1-carboxylate (139 mg, 0.30 mmol), pyrrolidine (99 µL, 1.2 mmol), *N*,*N*-diisopropylethylamine (105 µL, 0.60 mmol) and *n*-butanol (1.0 mL). To the resulting mixture was added TFA and stirred overnight at room temperature. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was purified by HPLC to give the title compound **7** as a TFA salt, yellow solid (98 mg, yield 52%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.53 (s, 1H), 7.08 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.76 – 3.56 (m, 6H), 3.42 – 3.38 (m, 1H), 3.38 – 3.35 (m, 1H), 2.96 (td, J = 12.9, 2.7 Hz, 2H), 2.24 – 2.04 (m, 4H), 1.99 – 1.92 (m, 2H), 1.84 – 1.74 (m, 2H), 1.70 – 1.60 (m, 1H), 1.46 – 1.34 (m, 4H). HPLC purity (method 1): >95%; t_R 3.61 min; MS (ESI): 400 $[M+H]^+$.



***N*-(2-(*cis*-4-Aminocyclohexyl)ethyl)-6,7-dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-amine (8).** *tert*-Butyl (*cis*-4-(2-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)ethyl) cyclohexyl)carbamate was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, *tert*-butyl *cis*-4-(2-aminoethyl)cyclohexylcarbamate (commercially available), *N*,*N*-diisopropylethylamine and THF. Boc-protected compound **8** was prepared according to the procedures for making **3** from *tert*-butyl (*cis*-4-(2-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)ethyl) cyclohexyl)carbamate (139 mg, 0.30 mmol), pyrrolidine (99 µL, 1.2 mmol), *N*,*N*-diisopropylethylamine (105 µL, 0.60 mmol) and *n*-butanol (1.0 mL). To the resulting mixture was added TFA and stirred overnight at room temperature. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was purified by HPLC to give the title compound **8** as a TFA salt, tan solid (105 mg, yield 56%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.55 (s, 1H), 7.10 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.80 – 3.57 (m, 6H), 3.30 – 3.25 (m, 1H), 2.25 – 2.00 (m, 4H), 1.85 – 1.66 (m, 9H), 1.63 – 1.51 (m, 2H). HPLC purity (method 1): >95%; t_R 3.55 min; MS (ESI): 400 $[M+H]^+$.

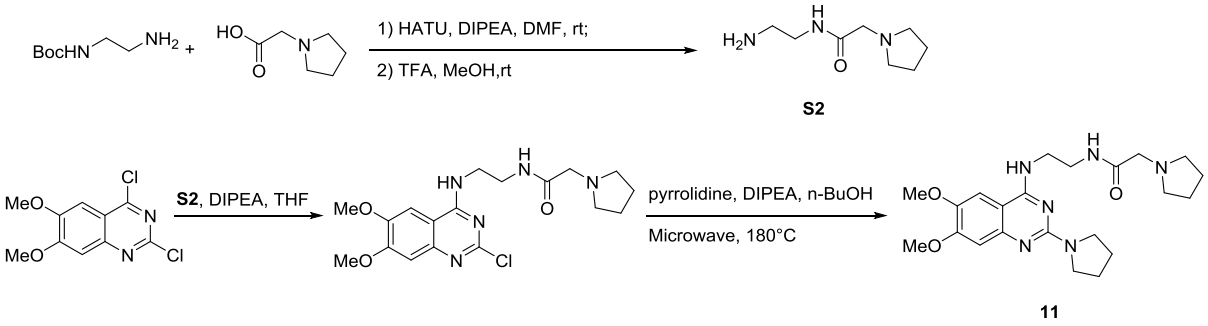


***trans*-N^1-(6,7-Dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)cyclohexane-1,4-diamine (9).** *tert*-Butyl (*trans*-4-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)cyclohexyl)carbamate was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, *trans*-*N*-Boc-1,4-cyclohexanediamine (commercially available), *N*,*N*-diisopropylethylamine and THF. Boc-protected compound **9** was prepared according to the procedures for making **3** from *tert*-butyl (*trans*-4-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)cyclohexyl) carbamate (506 mg, 1.2 mmol), pyrrolidine (383 µL, 4.7 mmol), *N*,*N*-diisopropylethylamine (610 µL, 3.5 mmol) and *n*-butanol (8.0 mL). To the resulting mixture was added HCl in dioxane (4.0 M) and stirred overnight at 70ºC. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was purified by HPLC to give the title compound **9** as a TFA salt, white solid (180 mg, yield 26%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.65 (s, 1H), 7.11 (s, 1H), 4.34 – 4.25 (m, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.82 – 3.56 (m, 4H), 3.24 – 3.14 (m, 1H), 2.32 – 2.22 (m, 2H), 2.22 – 1.99 (m, 6H), 1.72 – 1.54 (m, 4H). HPLC purity (method 2): >95%; t_R 3.92 min; MS (ESI): 372 $[M+H]^+$.



***N*-(*trans*-4-(Aminomethyl)cyclohexyl)-6,7-dimethoxy-2-(pyrrolidin-1-yl) quinazolin-4-amine (10).** *tert*-Butyl ((*trans*-4-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)cyclohexyl)methyl)carbamate was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, *tert*-butyl *trans*-4-aminocyclohexyl-methylcarbamate (commercially available), *N*,*N*-diisopropylethylamine and THF. Boc-protected

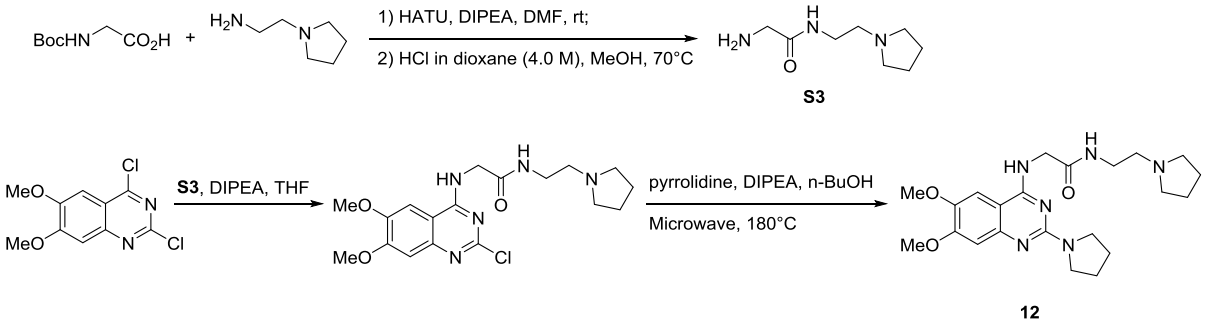
compound **10** was prepared according to the procedures for making **3** from *tert*-butyl (*trans*-4-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)cyclohexyl) carbamate (405 mg, 0.9 mmol), pyrrolidine (296 µL, 3.6 mmol), *N*,*N*-diisopropylethylamine (470 µL, 2.7 mmol) and *n*-butanol (6.7 mL). To the resulting mixture was added HCl in dioxane (4.0 M) and stirred overnight at 70ºC. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was purified by HPLC to give the title compound **10** as a TFA salt, white solid (115 mg, yield 21%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.66 (s, 1H), 7.11 (s, 1H), 4.29 (tt, J = 11.9, 4.0 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.85 – 3.55 (m, 4H), 2.87 (d, J = 7.0 Hz, 2H), 2.26 – 2.03 (m, 6H), 2.02 – 1.93 (m, 2H), 1.80 – 1.66 (m, 1H), 1.65 – 1.51 (m, 2H), 1.33 – 1.19 (m, 2H).



***N*-(2-((6,7-Dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)ethyl)-2-(pyrrolidin-1-yl)acetamide (11).** *N*-Boc-Ethylenediamine (commercially available, 590 mg, 3.6 mmol) and pyrrolidin-1-yl-acetic acid hydrochloride (commercially available, 609 mg, 3.6 mmol) were dissolved in DMF (12 mL). To this solution were added *N*,*N*-diisopropylethylamine (1.4 mL, 8.1 mmol) and HATU (1.5 g, 4.0 mmol). The resulting solution was stirred at room temperature overnight. TLC indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was redissolved in CH_2Cl_2, washed with brine. The organic layer was dried, concentrated and purified by ISCO to give *tert*-butyl (2-(2-(pyrrolidin-1-yl)acetamido)ethyl)carbamate (748 mg, yield 75%). To the solution of *tert*-butyl (2-(2-

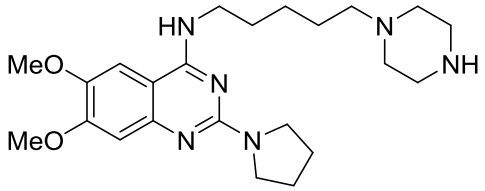
(pyrrolidin-1-yl)acetamido)ethyl)carbamate in MeOH was added TFA at room temperature and stirred overnight at room temperature. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the product *N*-(2-aminoethyl)-2-(pyrrolidin-1-yl)acetamide (**S2**) obtained was used for next step without further purification.

N-(2-((2-Chloro-6,7-dimethoxyquinazolin-4-yl)amino)ethyl)-2-(pyrrolidin-1-yl) acetamide was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, *N*-(2-aminoethyl)-2-(pyrrolidin-1-yl)acetamide (**S2**), *N*,*N*-diisopropylethylamine and THF. Compound **11** was prepared according to the procedures for making **3** from *N*-(2-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)ethyl)-2-(pyrrolidin-1-yl)acetamide (88 mg, 0.14 mmol), pyrrolidine (47 µL, 0.57 mmol), *N*,*N*-diisopropylethylamine (75 µL, 0.43 mmol) and *n*-butanol (1.0 mL). The title compound **11** was obtained as a TFA salt, brown solid (42 mg, yield 46%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.53 (s, 1H), 7.11 (s, 1H), 4.03 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.86 – 3.54 (m, 10H), 3.18 – 3.01 (m, 2H), 2.23 – 1.95 (m, 8H); ^{13}C NMR (100 MHz, d_4-MeOH) δ 166.52, 160.80, 157.43, 151.55, 148.90, 137.14, 105.13, 103.65, 99.59, 57.02, 56.94 (two carbons), 56.83 (two carbons), 55.93 (two carbons), 42.19, 39.00, 24.08 (four carbons). HPLC purity (method 1): >95%; t_R 3.02 min; MS (ESI): 429 $[M+H]^+$.

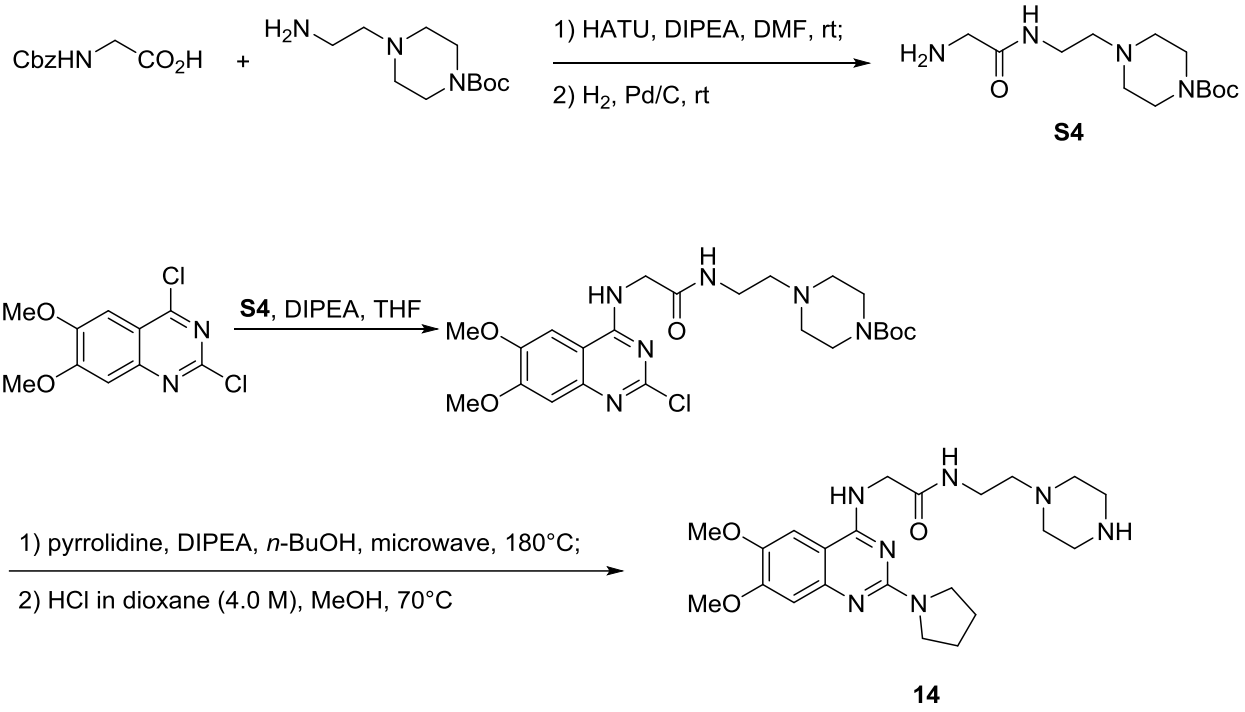


2-((6,7-Dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)-*N*-(2-(pyrrolidin-1-yl)ethyl)acetamide (12). Boc-Glycine (commercially available, 645 mg, 3.6 mmol) and 1-(2-aminoethyl)pyrrolidine (commercially available, 466 µL, 3.6 mmol) were dissolved in DMF (12 mL). To this solution were added *N*,*N*-diisopropylethylamine (770 µL, 4.4 mmol) and HATU (1.5 g, 4.0 mmol). The resulting solution was stirred at room temperature overnight. TLC indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was redissolved in CH_2Cl_2, washed with brine. The organic layer was dried, concentrated and purified by ISCO to give *tert*-butyl (2-oxo-2-((2-(pyrrolidin-1-yl)ethyl)amino)ethyl)carbamate (679 mg, yield 68%). To the solution of *tert*-butyl (2-oxo-2-((2-(pyrrolidin-1-yl)ethyl)amino)ethyl)carbamate in MeOH was added TFA and stirred overnight at room temperature. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the product 2-amino-*N*-(2-(pyrrolidin-1-yl)ethyl)acetamide (**S3**) obtained was used for next step without further purification.

2-((2-Chloro-6,7-dimethoxyquinazolin-4-yl)amino)-*N*-(2-(pyrrolidin-1-yl)ethyl) acetamide was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, 2-amino-*N*-(2-pyrrolidin-1-ylethyl)acetamide (**S3**), *N*,*N*-diisopropylethylamine and THF. Compound **12** was prepared according to the procedures for making **3** from 2-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)-*N*-(2-(pyrrolidin-1-yl)ethyl) acetamide (208 mg, 0.33 mmol), pyrrolidine (55 µL, 0.67 mmol), *N*,*N*-diisopropylethylamine (174 µL, 1.0 mmol) and *n*-butanol (1.5 mL). The title compound **12** was obtained as a TFA salt, gray solid (83 mg, yield 38%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.58 (s, 1H), 7.11 (s, 1H), 4.30 (s, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 3.78 – 3.53 (m, 8H), 3.35 (t, J = 6.1 Hz, 2H), 3.20 – 3.01 (m, 2H), 2.23 – 1.97 (m, 8H). HPLC purity (method 1): >95%; t_R 2.92 min; MS (ESI): 429 $[M+H]^+$.



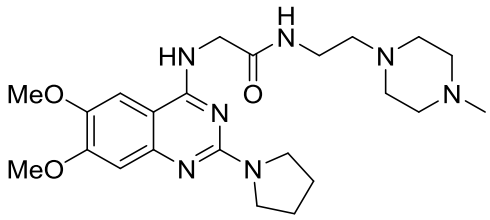
6,7-Dimethoxy-*N*-(5-(piperazin-1-yl)pentyl)-2-(pyrrolidin-1-yl)quinazolin-4-amine (13). This compound was synthesized according to the procedures reported previously.[1]



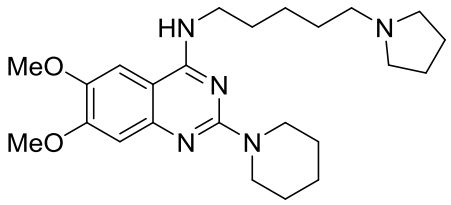
2-((6,7-Dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)-*N*-(2-(piperazin-1-yl)ethyl)acetamide (14). *N*-Carbobenzyloxyglycine (commercially available, 770 mg, 3.6 mmol) and 4-(2-aminoethyl)-1-Boc-piperazine (commercially available, 844 mg, 3.6 mmol) were dissolved in DMF (12 mL). To this solution were added *N*,*N*-diisopropylethylamine (770 µL, 4.4 mmol) and HATU (1.5 g, 4.0 mmol). The resulting solution was stirred at room temperature overnight. TLC indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was redissolved in CH_2Cl_2, washed with brine. The organic layer was dried,

concentrated and purified by ISCO to give *tert*-butyl 4-(2-(2-(((benzyloxy) carbonyl)amino)acetamido)ethyl)piperazine-1-carboxylate. A stirred suspension of the intermediate and Pd/C in methanol (20 mL) was treated with hydrogen at 1 atm overnight at room temperature. The product *tert*-butyl 4-(2-(2-aminoacetamido)ethyl)piperazine-1-carboxylate (**S4**) was obtained after filtration and concentration. It was used for next step without further purification.

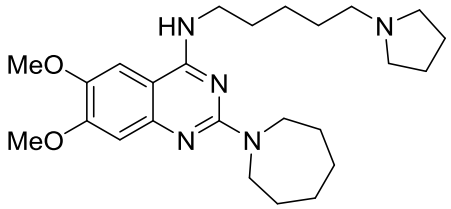
tert-Butyl 4-(2-(2-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)acetamido)ethyl) piperazine-1-carboxylate was prepared according to the procedures for making **S1** from 2,4-dichloro-6,7-dimethoxylquinazoline, *tert*-butyl 4-(2-(2-aminoacetamido)ethyl)piperazine-1-carboxylate (**S4**), *N*,*N*-diisopropylethylamine and THF. Boc-protected compound **14** was prepared according to the procedures for making **3** from *tert*-butyl 4-(2-(2-((2-chloro-6,7-dimethoxyquinazolin-4-yl)amino)acetamido)ethyl) piperazine-1-carboxylate (356 mg, 0.70 mmol), pyrrolidine (229 µL, 2.8 mmol), *N*,*N*-diisopropylethylamine (365 µL, 2.0 mmol) and *n*-butanol (4.0 mL). To the resulting mixture was added HCl in dioxane (4.0 M) and stirred overnight at 70ºC. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was purified by HPLC to give the title compound **14** as a TFA salt, tan solid (164 mg, yield 35%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.58 (s, 1H), 7.13 (s, 1H), 4.27 (s, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 3.77 – 3.54 (m, 4H), 3.42 (t, J = 6.6 Hz, 2H), 3.27 – 3.21 (m, 4H), 2.87 – 2.78 (m, 4H), 2.65 (t, J = 6.7 Hz, 2H), 2.22 – 1.94 (m, 4H). HPLC purity (method 1): >95%; t_R 2.91 min; MS (ESI): 444 $[M+H]^+$.



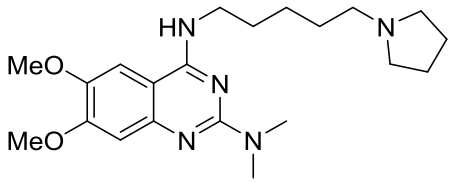
2-((6,7-Dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)acetamide (15). To the solution of 2-((6,7-dimethoxy-2-(pyrrolidin-1-yl)quinazolin-4-yl)amino)-*N*-(2-(piperazin-1-yl)ethyl)acetamide (**14**, 40 mg, 0.06 mmol) in MeOH (1.0 mL) were added formaldehyde (commercially available, 57 µL, 0.72 mmol), acetic acid (42 µL, 0.72 mmol) and sodium cyanoborohydride (23 mg, 0.36 mmol) at 0°C. The resulting mixture was warmed to room temperature and stirred overnight. LC-MS indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was purified by HPLC to give the title compound **15** as a TFA salt, white solid (33 mg, yield 80%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.56 (s, 1H), 7.11 (s, 1H), 4.27 (s, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 3.73 – 3.57 (m, 4H), 3.47 (t, J = 6.5 Hz, 2H), 3.42 – 3.32 (m, 4H), 3.15 – 2.98 (m, 4H), 2.90 (s, 3H), 2.83 (t, J = 6.5 Hz, 2H), 2.20 – 1.99 (m, 4H). HPLC purity (method 1): >95%; t_R 2.79 min; MS (ESI): 458 $[M+H]^+$.



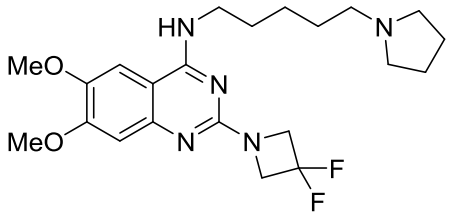
6,7-Dimethoxy-2-(piperidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (16). This compound was synthesized according to the procedures reported previously.[1]



2-(Azepan-1-yl)-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (17). This compound was synthesized according to the procedures reported previously.[1]

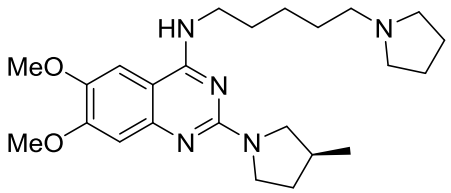


6,7-Dimethoxy-N^2,N^2-dimethyl-N^4-(5-(pyrrolidin-1-yl)pentyl)quinazoline-2,4-diamine (18). This compound was synthesized according to the procedures reported previously.[1]

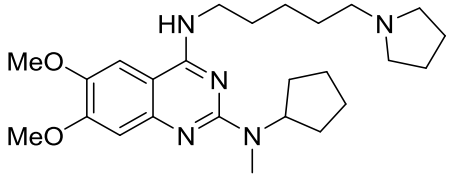


2-(3,3-Difluoroazetidin-1-yl)-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (19). The intermediate 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**) was synthesized according to the procedures reported previously.[1] To the solution of $Pd(OAc)_2$ (2 mg, 0.01 mmol), (+)-BINAP (6 mg, 0.01 mmol) and THF (0.50 mL) were added 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 46 mg, 0.10 mmol), 3,3-difluoroazetidine hydrochloride (commercially available, 15 mg, 0.12 mmol) and Cs_2CO_3 (73 mg, 0.24 mmol). The resulting solution was stirred inside a microwave at 140 °C for 30 min. After cooling, TLC indicated the completion of the reaction. After removal of the

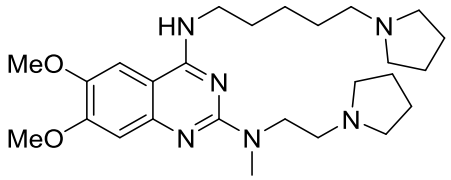
solvent *in vacuo*, the residue was redissolved in CH_2Cl_2, washed with brine. The organic layer was dried, concentrated and purified by HPLC to give the title compound **19** as a TFA salt, white solid (44 mg, yield 71%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.60 (s, 1H), 6.99 (s, 1H), 4.70 (t, *J* = 11.8 Hz, 4H), 3.96 (s, 3H), 3.92 (s, 3H), 3.72 – 3.61 (m, 4H), 3.23 – 3.16 (m, 2H), 3.12 – 3.00 (m, 2H), 2.21 – 2.08 (m, 2H), 2.08 – 1.95 (m, 2H), 1.87 – 1.74 (m, 4H), 1.55 – 1.45 (m, 2H). HPLC purity (method 1): >95%; t_R 2.91 min; MS (ESI): 436 $[M+H]^+$.



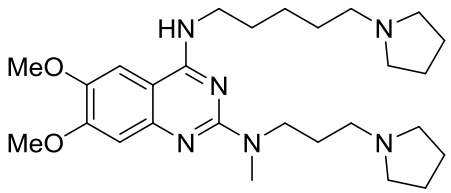
(*S*)-6,7-Dimethoxy-2-(3-methylpyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl) quinazolin-4-amine (20). Compound **20** was prepared according to the procedures for making **3** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 68 mg, 0.14 mmol), (*S*)-3-methyl-pyrrolidine hydrochloride (commercially available, 34 mg, 0.27 mmol), *N*,*N*-diisopropylethylamine (120 μL, 0.69 mmol) and *n*-butanol (1.5 mL). The title compound **20** was obtained as a TFA salt, off white solid (58 mg, yield 64%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.54 (s, 1H), 7.08 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.89 – 3.40 (m, 7H), 3.29 – 2.92 (m, 5H), 2.56 – 2.39 (m, 1H), 2.31 – 2.21 (m, 1H), 2.21 – 2.09 (m, 2H), 2.07 – 1.94 (m, 2H), 1.90 – 1.65 (m, 5H), 1.57 – 1.44 (m, 2H), 1.19 (d, *J* = 6.5 Hz, 3H). HPLC purity (method 1): >95%; t_R 3.57 min; MS (ESI): 428 $[M+H]^+$.



***N*²-Cyclopentyl-6,7-dimethoxy-*N*²-methyl-*N*⁴-(5-(pyrrolidin-1-yl)pentyl) quinazoline-2,4-diamine (21).** This compound was synthesized according to the procedures reported previously.[1]

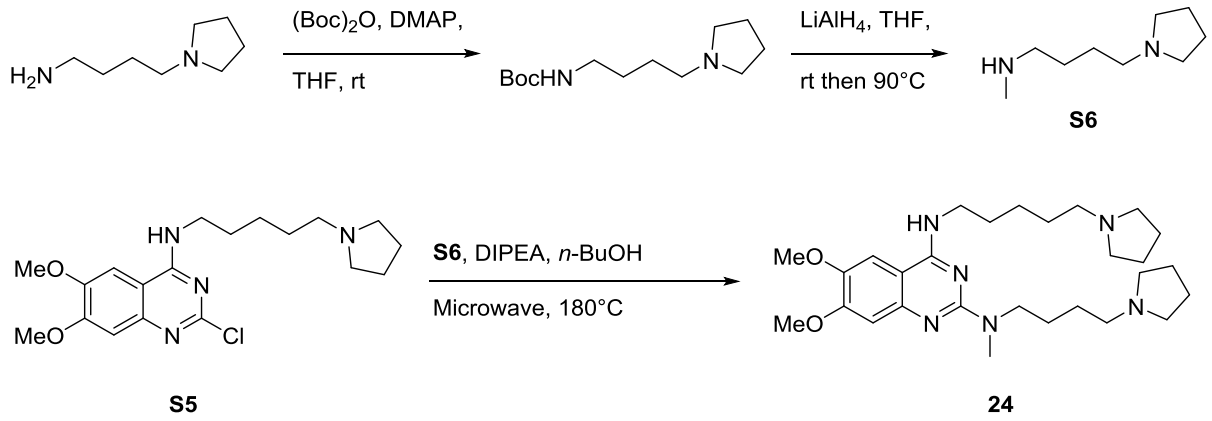


6,7-Dimethoxy-*N*²-methyl-*N*²-(2-(pyrrolidin-1-yl)ethyl)-*N*⁴-(5-(pyrrolidin-1-yl)pentyl)quinazoline-2,4-diamine (22). Compound **22** was prepared according to the procedures for making **3** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 46 mg, 0.10 mmol), *N*-methyl-2-pyrrolidin-1-yl-ethanamine (commercially available, 15 mg, 0.11 mmol), *N*,*N*-diisopropylethylamine (49 µL, 0.28 mmol) and *n*-butanol (1.0 mL). The title compound **22** was obtained as a TFA salt, yellow liquid (39 mg, yield 56%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.62 (s, 1H), 7.25 (s, 1H), 4.21 (t, *J* = 6.6 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.87 – 3.70 (m, 4H), 3.69 – 3.62 (m, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.34 (s, 3H), 3.29 – 3.12 (m, 4H), 3.11 – 3.00 (m, 2H), 2.29 – 1.94 (m, 8H), 1.89 – 1.73 (m, 4H), 1.61 – 1.45 (m, 2H). HPLC purity (method 1): >95%; t_R 2.17 min; MS (ESI): 471 $[M+H]^+$.



6,7-Dimethoxy-*N*²-methyl-*N*⁴-(5-(pyrrolidin-1-yl)pentyl)-*N*²-(3-(pyrrolidin-1-yl)propyl)quinazoline-2,4-diamine (23). Compound **23** was prepared according to the procedures for making **3** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-

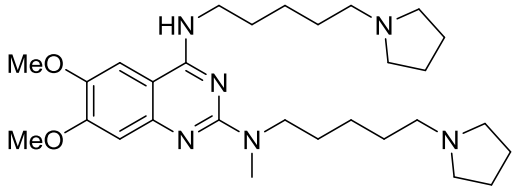
4-amine (**S5**, 46 mg, 0.10 mmol), *N*-methyl-3-(1-pyrrolidinyl)-1-propanamine (commercially available, 16 mg, 0.11 mmol), *N*,*N*-diisopropylethylamine (49 µL, 0.28 mmol) and *n*-butanol (1.0 mL). The title compound **23** was obtained as a TFA salt, yellow liquid (41 mg, yield 63%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.59 (s, 1H), 7.21 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.86 (t, *J* = 7.0 Hz, 2H), 3.74 – 3.59 (m, 6H), 3.31 – 3.26 (m, 5H), 3.23 – 3.16 (m, 2H), 3.13 – 3.01 (m, 4H), 2.26 – 2.08 (m, 6H), 2.07 – 1.94 (m, 4H), 1.88 – 1.74 (m, 4H), 1.59 – 1.47 (m, 2H). HPLC purity (method 1): >95%; t_R 2.33 min; MS (ESI): 485 $[M+H]^+$.



6,7-Dimethoxy-*N*^{2}-methyl-*N*^{2}-(4-(pyrrolidin-1-yl)butyl)-*N*^{4}-(5-(pyrrolidin-1-yl)pentyl)quinazoline-2,4-diamine (24). 4-(1-Pyrrolidinyl)-1-butylamine (commercially available, 2.0 g, 14 mmol) and di-*tert*-butyl dicarbonate (3.4 g, 15 mmol) were dissolved in THF (42 mL). To this solution was added 4-dimethylaminopyridine (172 mg, 1.4 mmol) and the resulting solution was stirred at room temperature for 2 hours. TLC indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was used for next step without further purification. To a stirred suspension of $LiAlH_4$ (1.87 g, 49 mmol) in anhydrous THF (73 mL) was added the THF (11 mL) solution of *tert*-butyl (4-(pyrrolidin-1-yl)butyl)carbamate dropwise at room temperature. The resulting mixture was stirred at room temperature overnight and then heated at 90ºC for 1 hour to ensure full conversion of starting material. After cooling,

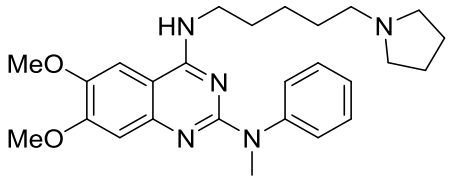
TLC indicated the completion of the reaction. To the mixture were added H_2O (2 mL), NaOH solution (15%, 2 mL) and H_2O (6 mL) successively. The filtrate was concentrated *in vacuo* to give the product *N*-methyl-4-(pyrrolidin-1-yl)butan-1-amine (**S6**), which was used for next step without further purification.

Compound **24** was prepared according to the procedures for making **3** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 68 mg, 0.14 mmol), *N*-methyl-4-(pyrrolidin-1-yl)butan-1-amine (**S6**, 26 mg, 0.17 mmol), *N*,*N*-diisopropylethylamine (72 µL, 0.41 mmol) and *n*-butanol (1.5 mL). The title compound **21** was obtained as a TFA salt, brown liquid (71 mg, yield 71%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.58 (s, 1H), 7.19 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.84 – 3.75 (m, 2H), 3.72 – 3.60 (m, 6H), 3.30 (s, 3H), 3.27 – 3.15 (m, 4H), 3.14 – 2.98 (m, 4H), 2.22 – 2.09 (m, 4H), 2.07 – 1.95 (m, 4H), 1.89 – 1.74 (m, 8H), 1.56 – 1.47 (m, 2H). HPLC purity (method 1): >95%; t_R 2.48 min; MS (ESI): 499 $[M+H]^+$.

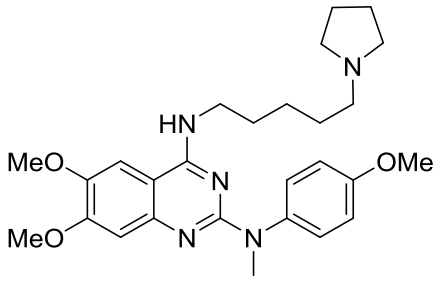


6,7-Dimethoxy-N^2-methyl-N^2,N^4-bis(5-(pyrrolidin-1-yl)pentyl)quinazoline-2,4-diamine (25). *N*-Methyl-5-(pyrrolidin-1-yl)pentan-1-amine was prepared according to the procedures for making *N*-methyl-4-(pyrrolidin-1-yl)butan-1-amine (**S6**). Compound **25** was prepared according to the procedures for making **3** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 68 mg, 0.14 mmol), *N*-methyl-5-(pyrrolidin-1-yl)pentan-1-amine (47 mg, 0.27 mmol), *N*,*N*-diisopropylethylamine (72 µL, 0.41 mmol) and *n*-butanol (1.5 mL). The title compound **25** was obtained as a TFA salt, tan liquid (44 mg, yield

43%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.57 (s, 1H), 7.19 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.81 – 3.45 (m, 8H), 3.28 (s, 3H), 3.25 – 2.91 (m, 8H), 2.20 – 1.94 (m, 8H), 1.88 – 1.72 (m, 8H), 1.55 – 1.42 (m, 4H). HPLC purity (method 1): >95%; t_R 2.77 min; MS (ESI): 513 $[M+H]^+$.

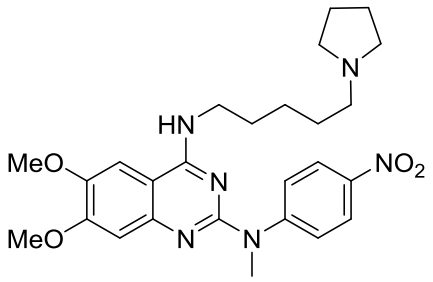


6,7-Dimethoxy-*N*^{2}-methyl-*N*^{2}-phenyl-*N*^{4}-(5-(pyrrolidin-1-yl)pentyl)quinazoline-2,4-diamine (26). Compound **26** was prepared according to the procedures for making **19** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 46 mg, 0.09 mmol), *N*-methylaniline (commercially available, 13 µL, 0.11 mmol), $Pd(OAc)_2$ (1 mg, 0.01 mmol), (+)-BINAP (6 mg, 0.01 mmol), Cs_2CO_3 (43 mg, 0.13 mmol) and THF (0.80 mL). The title compound **26** was obtained as a TFA salt, brown solid (42 mg, yield 68%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.63 – 7.56 (m, 3H), 7.53 – 7.48 (m, 1H), 7.47 – 7.43 (m, 2H), 7.13 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.72 – 3.62 (m, 4H), 3.62 (s, 3H), 3.22 – 3.15 (m, 2H), 3.12 – 3.01 (m, 2H), 2.21 – 2.10 (m, 2H), 2.07 – 1.96 (m, 2H), 1.81 – 1.71 (m, 4H), 1.49 – 1.40 (m, 2H). HPLC purity (method 1): >95%; t_R 3.61 min; MS (ESI): 450 $[M+H]^+$.

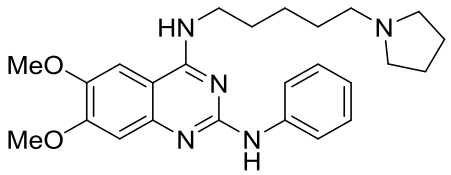


6,7-Dimethoxy-*N*^{2}-(4-methoxyphenyl)-*N*^{2}-methyl-*N*^{4}-(5-(pyrrolidin-1-yl)pentyl) quinazoline-2,4-diamine (27). Compound **27** was prepared according to the procedures for

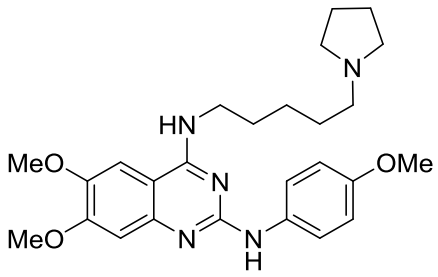
making **19** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 68 mg, 0.14 mmol), 4-methoxy-*N*-methylaniline (commercially available, 23 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), (+)-BINAP (9 mg, 0.01 mmol), Cs_2CO_3 (63 mg, 0.19 mmol) and THF (1.2 mL). The title compound **27** was obtained as a TFA salt, brown liquid (70 mg, yield 72%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.58 (s, 1H), 7.39 – 7.31 (m, 2H), 7.16 – 7.07 (m, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.88 (s, 3H), 3.73 – 3.61 (m, 4H), 3.58 (s, 3H), 3.24 – 3.15 (m, 2H), 3.11 – 3.02 (m, 2H), 2.21 – 2.10 (m, 2H), 2.07 – 1.97 (m, 2H), 1.85 – 1.71 (m, 4H), 1.52 – 1.42 (m, 2H). HPLC purity (method 1): >95%; t_R 3.60 min; MS (ESI): 480 $[M+H]^+$.



6,7-Dimethoxy-N^2-methyl-N^2-(4-nitrophenyl)-N^4-(5-(pyrrolidin-1-yl)pentyl) quinazoline-2,4-diamine (28). Compound **28** was prepared according to the procedures for making **19** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 68 mg, 0.14 mmol), *N*-methyl-4-nitroaniline (commercially available, 25 mg, 0.17 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), (+)-BINAP (9 mg, 0.01 mmol), Cs_2CO_3 (63 mg, 0.19 mmol) and THF (1.2 mL). The title compound **28** was obtained as a TFA salt, brown liquid (56 mg, yield 57%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.43 – 8.38 (m, 2H), 7.77 – 7.71 (m, 2H), 7.60 (s, 1H), 7.16 (s, 1H), 3.93 (s, 6H), 3.70 (s, 3H), 3.68 – 3.59 (m, 2H), 3.53 (t, J = 7.2 Hz, 2H), 3.21 – 3.11 (m, 2H), 3.11 – 3.00 (m, 2H), 2.23 – 2.10 (m, 2H), 2.09 – 1.94 (m, 2H), 1.79 – 1.64 (m, 4H), 1.42 – 1.29 (m, 2H). HPLC purity (method 1): >95%; t_R 3.53 min; MS (ESI): 495 $[M+H]^+$.

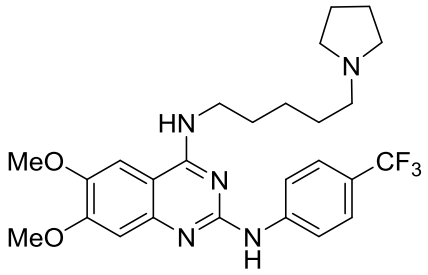


6,7-Dimethoxy-N^2-phenyl-N^4-(5-(pyrrolidin-1-yl)pentyl)quinazoline-2,4-diamine (29). Compound **29** was prepared according to the procedures for making **19** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 46 mg, 0.09 mmol), aniline (commercially available, 11 μL, 0.11 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), (+)-BINAP (6 mg, 0.01 mmol), Cs_2CO_3 (73 mg, 0.22 mmol) and THF (0.5 mL). The title compound **29** was obtained as a TFA salt, white solid (46 mg, yield 75%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.66 – 7.58 (m, 2H), 7.45 (s, 1H), 7.41 – 7.34 (m, 2H), 7.22 – 7.15 (m, 1H), 6.87 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.63 – 3.53 (m, 4H), 3.14 – 3.07 (m, 2H), 3.04 – 2.94 (m, 2H), 2.19 – 2.06 (m, 2H), 2.05 – 1.93 (m, 2H), 1.78 – 1.65 (m, 4H), 1.47 – 1.36 (m, 2H); ^{13}C NMR (100 MHz, d_4-MeOH) δ 161.19, 157.59, 152.16, 149.20, 138.70, 136.67, 130.01 (two carbons), 125.94, 123.10 (two carbons), 104.59, 103.90, 99.44, 56.93, 56.82, 56.01, 55.05 (two carbons), 42.99, 29.24, 26.73, 25.08, 23.92 (two carbons). HPLC purity (method 1): >95%; t_R 3.50 min; MS (ESI): 436 $[M+H]^+$.



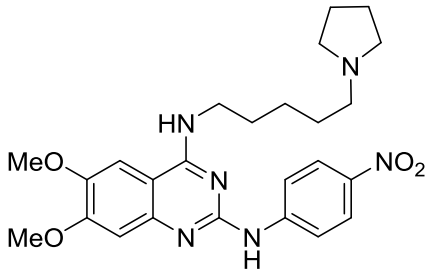
6,7-Dimethoxy-N^2-(4-methoxyphenyl)-N^4-(5-(pyrrolidin-1-yl)pentyl)quinazoline-2,4-diamine (30). Compound **30** was prepared according to the procedures for making **19** from 2-

chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 46 mg, 0.09 mmol), *p*-anisidine (commercially available, 13 µL, 0.11 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), (+)-BINAP (6 mg, 0.01 mmol), Cs_2CO_3 (73 mg, 0.22 mmol) and THF (0.50 mL). The title compound **30** was obtained as a TFA salt, off white solid (37 mg, yield 57%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.52 – 7.41 (m, 3H), 7.00 – 6.86 (m, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 3.64 – 3.54 (m, 4H), 3.18 – 3.08 (m, 2H), 3.07 – 2.94 (m, 2H), 2.18 – 2.07 (m, 2H), 2.05 – 1.94 (m, 2H), 1.78 – 1.66 (m, 4H), 1.46 – 1.37 (m, 2H); ^{13}C NMR (100 MHz, d_4-MeOH) δ 161.19 (two carbons), 157.47 (two carbons), 149.04 (two carbons), 136.68, 115.26 (two carbons), 104.71 (two carbons), 103.92 (two carbons), 99.50, 56.90, 56.84, 56.05, 55.99, 55.07 (two carbons), 42.79, 29.26, 26.73, 25.07, 23.93 (two carbons). HPLC purity (method 1): >95%; t_R 3.55 min; MS (ESI): 466 $[M+H]^+$.

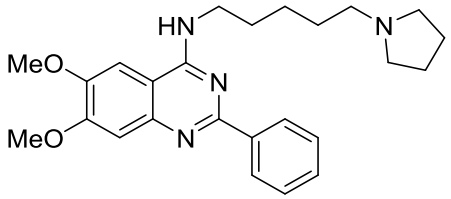


6,7-Dimethoxy-N^4-(5-(pyrrolidin-1-yl)pentyl)-N^2-(4-(trifluoromethyl)phenyl) quinazoline-2,4-diamine (31). Compound **31** was prepared according to the procedures for making **19** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 46 mg, 0.09 mmol), 4-(trifluoromethyl)aniline (commercially available, 14 µL, 0.11 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), (+)-BINAP (6 mg, 0.01 mmol), Cs_2CO_3 (73 mg, 0.22 mmol) and THF (0.50 mL). The title compound **31** was obtained as a TFA salt, white solid (21 mg, yield 31%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.86 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 7.62 (s, 1H), 7.06 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.73 (t, J = 7.2 Hz, 2H), 3.65 – 3.55 (m, 2H),

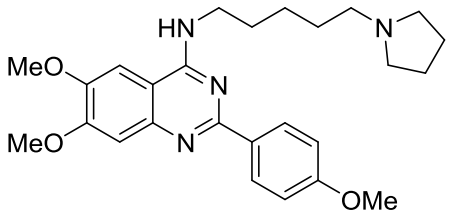
3.19 – 3.12 (m, 2H), 3.08 – 2.96 (m, 2H), 2.20 – 2.07 (m, 2H), 2.06 – 1.93 (m, 2H), 1.87 – 1.79 (m, 2H), 1.78 – 1.70 (m, 2H), 1.54 – 1.44 (m, 2H). HPLC purity (method 1): >95%; t_R 3.87 min; MS (ESI): 504 $[M+H]^+$.



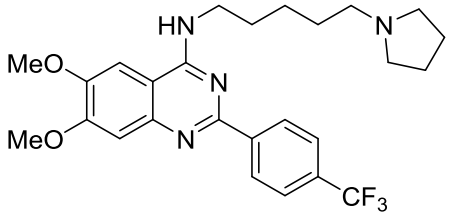
6,7-Dimethoxy-N^2-(4-nitrophenyl)-N^4-(5-(pyrrolidin-1-yl)pentyl)quinazoline-2,4-diamine (32). Compound **32** was prepared according to the procedures for making **19** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 46 mg, 0.09 mmol), 4-nitroaniline (commercially available, 16 mg, 0.11 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), (+)-BINAP (6 mg, 0.01 mmol), Cs_2CO_3 (73 mg, 0.22 mmol) and THF (0.50 mL). The title compound **32** was obtained as a TFA salt, yellow solid (26 mg, yield 40%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.25 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.04 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.78 – 3.70 (m, 2H), 3.65 – 3.57 (m, 2H), 3.21 – 3.13 (m, 2H), 3.08 – 2.99 (m, 2H), 2.19 – 2.08 (m, 2H), 2.05 – 1.95 (m, 2H), 1.89 – 1.81 (m, 2H), 1.79 – 1.69 (m, 2H), 1.58 – 1.49 (m, 2H); ^{13}C NMR (100 MHz, d_4-MeOH) δ 161.48, 158.15, 151.70, 149.98, 145.30, 144.85, 136.73, 125.71 (two carbons), 121.92 (two carbons), 104.66, 104.54, 99.77, 57.13, 56.98, 56.11, 55.17 (two carbons), 43.37, 29.33, 26.88, 25.28, 23.95 (two carbons). HPLC purity (method 1): >95%; t_R 3.75 min; MS (ESI): 481 $[M+H]^+$.



6,7-Dimethoxy-2-phenyl-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (33). To the solution of 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 70 mg, 0.18 mmol), phenylboronic acid (commercially available, 34 mg, 0.27 mmol), dioxane (1.6 mL) and H_2O (0.40 mL) were added $Pd(PPh_3)_4$ (21 mg, 0.02 mmol) and K_2CO_3 (77 mg, 0.56 mmol). The resulting solution was stirred inside a microwave at 150 °C for 15 min. After cooling, TLC indicated the completion of the reaction. After removal of the solvent *in vacuo*, the residue was redissolved in CH_2Cl_2, washed with brine. The organic layer was dried, concentrated and purified by HPLC to give the title compound **33** as a TFA salt, yellow solid (95 mg, yield 96%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.31 – 8.24 (m, 2H), 7.75 – 7.67 (m, 2H), 7.66 – 7.59 (m, 2H), 7.31 (s, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.86 (t, J = 7.1 Hz, 2H), 3.66 – 3.57 (m, 2H), 3.22 – 3.13 (m, 2H), 3.08 – 2.95 (m, 2H), 2.17 – 2.05 (m, 2H), 2.05 – 1.93 (m, 2H), 1.92 – 1.75 (m, 4H), 1.60 – 1.47 (m, 2H); ^{13}C NMR (100 MHz, d_4-MeOH) δ 160.69, 158.13, 157.03, 151.98, 136.62, 134.39, 132.57, 130.33 (two carbons), 129.50 (two carbons), 106.98, 103.80, 100.63, 57.10, 57.05, 56.04, 55.04 (two carbons), 42.85, 29.42, 26.74, 24.97, 23.92 (two carbons). HPLC purity (method 1): >95%; t_R 3.46 min; MS (ESI): 421 $[M+H]^+$.

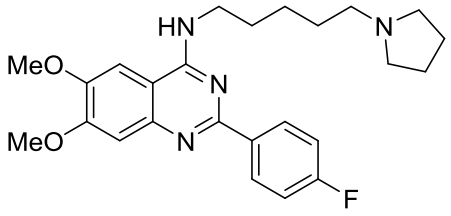


6,7-Dimethoxy-2-(4-methoxyphenyl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (34). Compound **34** was prepared according to the procedures for making **33** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 35 mg, 0.09 mmol), 4-methoxyphenylboronic acid (21 mg, 0.14 mmol), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol), K_2CO_3 (39 mg, 0.28 mmol), dioxane (0.80 mL) and H_2O (0.20 mL). The title compound **34** was obtained as a TFA salt, white solid (33 mg, yield 63%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.30 – 8.24 (m, 2H), 7.69 (s, 1H), 7.31 (s, 1H), 7.18 – 7.11 (m, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.92 (s, 3H), 3.91 – 3.84 (m, 2H), 3.67 – 3.56 (m, 2H), 3.22 – 3.13 (m, 2H), 3.08 – 2.96 (m, 2H), 2.16 – 2.06 (m, 2H), 2.04 – 1.93 (m, 2H), 1.92 – 1.74 (m, 4H), 1.61 – 1.49 (m, 2H); ^{13}C NMR (100 MHz, d_4-MeOH) δ 165.51, 160.69, 158.12, 156.75, 151.75, 136.72, 131.49 (two carbons), 124.48, 115.71 (two carbons), 106.77, 103.88, 100.55, 57.09, 57.03, 56.26, 56.07, 55.08 (two carbons), 42.76, 29.54, 26.81, 25.01, 23.93 (two carbons). HPLC purity (method 1): >95%; t_R 3.34 min; MS (ESI): 451 $[M+H]^+$.

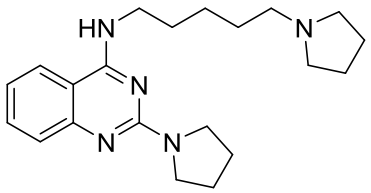


6,7-Dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)-2-(4-(trifluoromethyl)phenyl) quinazolin-4-amine (35). Compound **35** was prepared according to the procedures for making **33** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 35 mg, 0.09 mmol), 4-(trifluoromethyl)phenylboronic acid (27 mg, 0.14 mmol), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol), K_2CO_3 (39 mg, 0.28 mmol), dioxane (0.80 mL) and H_2O (0.20 mL). The title compound **35** was obtained as a TFA salt, yellow solid (40 mg, yield 71%). ^{1}H NMR (400 MHz, d_4-MeOH)

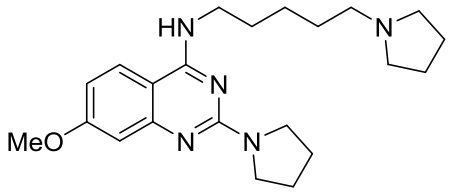
δ 8.47 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.76 (s, 1H), 7.37 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 3.93 (t, *J* = 7.1 Hz, 2H), 3.67 – 3.55 (m, 2H), 3.24 – 3.13 (m, 2H), 3.09 – 2.96 (m, 2H), 2.16 – 2.06 (m, 2H), 2.04 – 1.95 (m, 2H), 1.94 – 1.86 (m, 2H), 1.85 – 1.74 (m, 2H), 1.63 – 1.50 (m, 2H). HPLC purity (method 1): >95%; t_R 4.18 min; MS (ESI): 489 $[M+H]^+$.



2-(4-Fluorophenyl)-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (36). Compound **36** was prepared according to the procedures for making **33** from 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S5**, 35 mg, 0.09 mmol), 4-fluorophenylboronic acid (20 mg, 0.14 mmol), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol), K_2CO_3 (39 mg, 0.28 mmol), dioxane (0.80 mL) and H_2O (0.20 mL). The title compound **36** was obtained as a TFA salt, white solid (33 mg, yield 65%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.40 – 8.33 (m, 2H), 7.73 (s, 1H), 7.42 – 7.35 (m, 2H), 7.34 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.90 (t, *J* = 7.1 Hz, 2H), 3.67 – 3.56 (m, 2H), 3.22 – 3.14 (m, 2H), 3.09 – 2.96 (m, 2H), 2.17 – 2.06 (m, 2H), 2.05 – 1.95 (m, 2H), 1.93 – 1.85 (m, 2H), 1.84 – 1.76 (m, 2H), 1.60 – 1.51 (m, 2H); ^{13}C NMR (100 MHz, d_4-MeOH) δ 167.24 (d, *J* = 252 Hz, one carbon), 160.76, 158.24, 156.21, 152.07, 136.76, 132.35, 132.25, 129.16, 117.50, 117.28, 107.01, 103.83, 100.71, 57.14, 57.07, 56.06, 55.07 (two carbons), 42.90, 29.49, 26.80, 25.02, 23.94 (two carbons). HPLC purity (method 1): >95%; t_R 3.41 min; MS (ESI): 439 $[M+H]^+$.

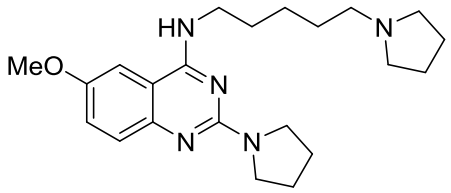


2-(Pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (37). 2-Chloro-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine was prepared according to the procedures for making **S5** from 2,4-dichloroquinazoline (commercially available), 5-(pyrrolidin-1-yl)pentan-1-amine (commercially available), *N*,*N*-diisopropylethylamine and THF. Compound **37** was prepared according to the procedures for making **3** from 2-chloro-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (111 mg, 0.35 mmol), pyrrolidine (115 µL, 1.4 mmol), *N*,*N*-diisopropylethylamine (183 µL, 1.1 mmol) and *n*-butanol (2.0 mL). The title compound **37** was obtained as a TFA salt, tan solid (158 mg, yield 78%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.09 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.78 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.61 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.42 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 3.87 – 3.75 (m, 2H), 3.74 – 3.70 (m, 2H), 3.69 – 3.59 (m, 4H), 3.22 – 3.16 (m, 2H), 3.10 – 3.00 (m, 2H), 2.23 – 1.97 (m, 8H), 1.88 – 1.75 (m, 4H), 1.56 – 1.46 (m, 2H). HPLC purity (method 1): >95%; t_R 3.06 min; MS (ESI): 354 $[M+H]^+$.

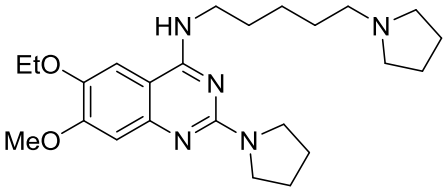


7-Methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (38). 2-Chloro-7-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine was prepared according to the procedures for making **S5** from 2,4-dichloro-7-methoxyquinazoline (synthesized according to the procedures reported previously[2]), 5-(pyrrolidin-1-yl)pentan-1-amine, *N*,*N*-

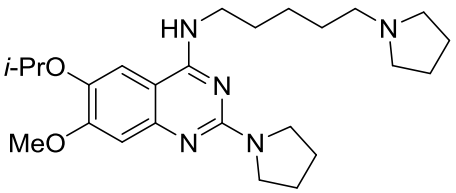
diisopropylethylamine, MeOH and THF. Compound **38** was prepared according to the procedures for making **3** from 2-chloro-7-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (1.5 g, 4.4 mmol), pyrrolidine (1.4 mL, 17 mmol), *N*,*N*-diisopropylethylamine (1.5 mL, 8.6 mmol) and *n*-butanol (8.0 mL). The title compound **38** was obtained as a TFA salt, clear oil (1.18 g, yield 54%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.02 (d, *J* = 9.1 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.00 (dd, *J* = 9.1, 2.5 Hz, 1H), 4.57 (s, 1H), 3.94 (s, 3H), 3.89 – 3.51 (m, 8H), 3.27 – 3.21 (m, 2H), 3.20 – 3.15 (m, 2H), 2.15 – 1.98 (m, 8H), 1.85 – 1.76 (m, 4H), 1.57 – 1.47 (m, 2H). HPLC purity (method 1): >95%; t_R 3.32 min; MS (ESI): 384 $[M+H]^+$.



6-Methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (39). 2-Chloro-6-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine was prepared according to the procedures for making **S5** from 2,4-dichloro-6-methoxyquinazoline (commercially available), 5-(pyrrolidin-1-yl)pentan-1-amine, *N*,*N*-diisopropylethylamine and THF. Compound **39** was prepared according to the procedures for making **3** from 2-chloro-6-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (70 mg, 0.20 mmol), pyrrolidine (66 μL, 0.81 mmol), *N*,*N*-diisopropylethylamine (70 μL, 0.40 mmol) and *n*-butanol (2.0 mL). The title compound **39** was obtained as a TFA salt, white solid (68 mg, yield 68%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.59 (d, *J* = 2.6 Hz, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.36 (dd, *J* = 9.1, 2.6 Hz, 1H), 3.88 (s, 3H), 3.81 – 3.53 (m, 8H), 3.24 – 3.14 (m, 2H), 3.12 – 2.98 (m, 2H), 2.19 – 1.96 (m, 8H), 1.87 – 1.75 (m, 4H), 1.56 – 1.46 (m, 2H). HPLC purity (method 1): >95%; t_R 3.27 min; MS (ESI): 384 $[M+H]^+$.

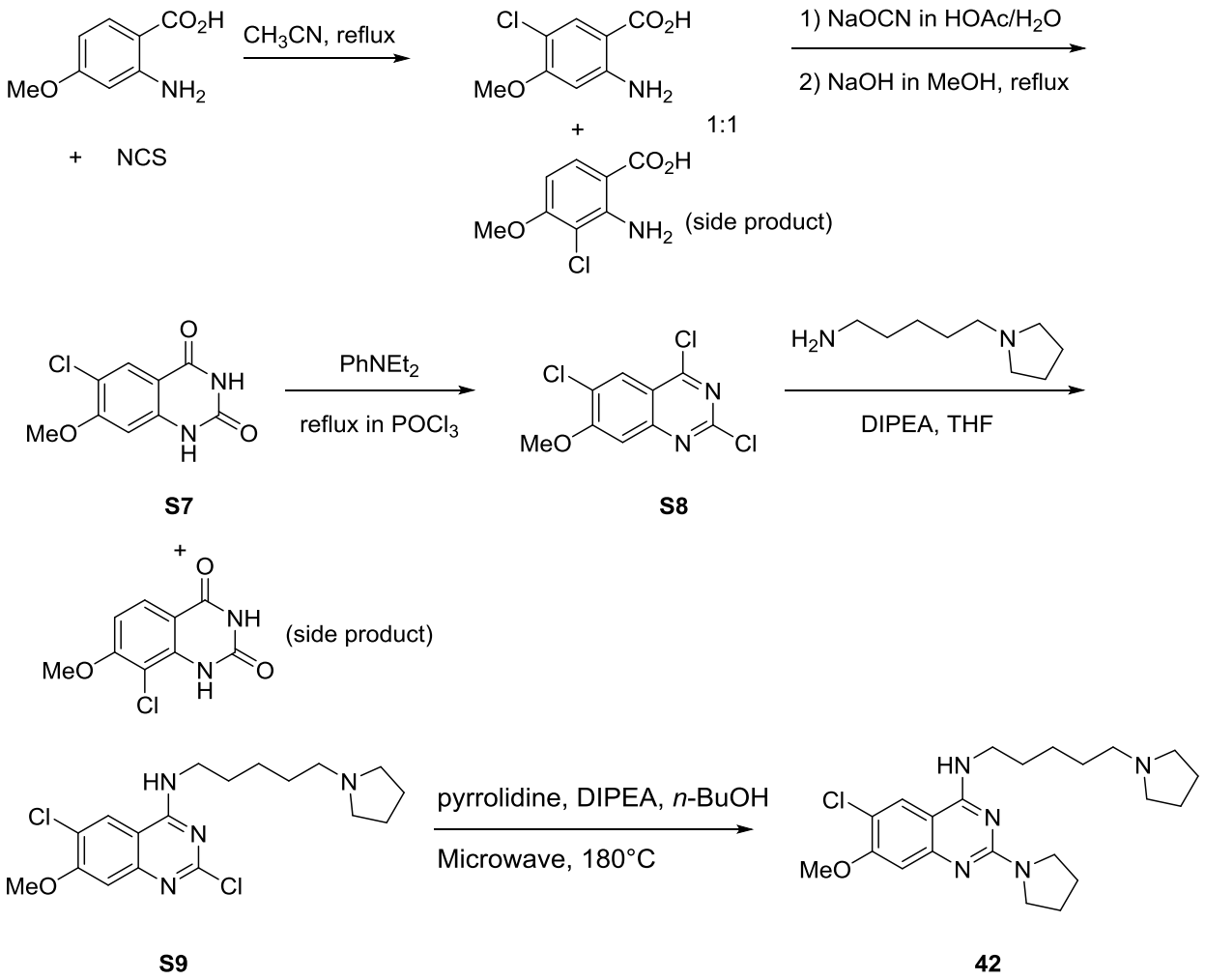


6-Ethoxy-7-methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (40). 2,4-Dichloro-6-ethoxy-7-methoxyquinazoline was prepared according to the procedures for making **S13** (see page S34) from 3-hydroxy-4-methoxybenzonitrile (commercially available). 2-Chloro-6-ethoxy-7-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine was prepared according to the procedures for making **S5** from 2,4-dichloro-6-ethoxy-7-methoxyquinazoline, 5-(pyrrolidin-1-yl)pentan-1-amine, *N*,*N*-diisopropylethylamine and THF. Compound **40** was prepared according to the procedures for making **3** from 2-chloro-6-ethoxy-7-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (109 mg, 0.28 mmol), pyrrolidine (91 µL, 1.1 mmol), *N*,*N*-diisopropylethylamine (98 µL, 0.56 mmol) and *n*-butanol (2.0 mL). The title compound **40** was obtained as a TFA salt, white solid (105 mg, yield 70%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.48 (s, 1H), 7.03 (s, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.92 (s, 3H), 3.76 – 3.51 (m, 8H), 3.22 – 3.14 (m, 2H), 3.11 – 2.99 (m, 2H), 2.21 – 1.95 (m, 8H), 1.88 – 1.70 (m, 4H), 1.54 – 1.46 (m, 2H), 1.44 (t, *J* = 7.0 Hz, 3H). HPLC purity (method 1): >95%; t_R 3.44 min; MS (ESI): 428 $[M+H]^+$.



6-Isopropoxy-7-methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl) quinazolin-4-amine (41). 2,4-Dichloro-6-isopropoxy-7-methoxyquinazoline was prepared

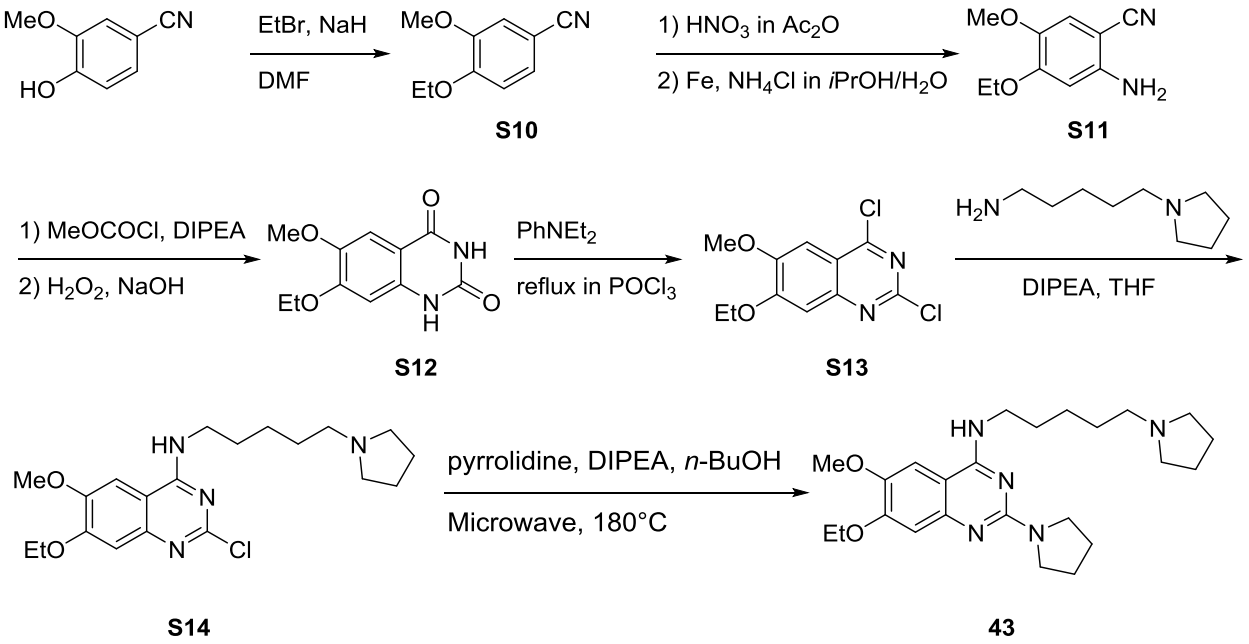
according to the procedures for making **S13** (see page S34) from 3-hydroxy-4-methoxybenzonitrile. 2-Chloro-6-isopropoxy-7-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine was prepared according to the procedures for making **S5** from 2,4-dichloro-6-isopropoxy-7-methoxyquinazoline, 5-(pyrrolidin-1-yl)pentan-1-amine, *N*,*N*-diisopropylethylamine and THF. Compound **41** was prepared according to the procedures for making **3** from 2-chloro-6-isopropoxy-7-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (100 mg, 0.25 mmol), pyrrolidine (78 µL, 0.96 mmol), *N*,*N*-diisopropylethylamine (87 µL, 0.50 mmol) and *n*-butanol (2.0 mL). The title compound **41** was obtained as a TFA salt, white solid (89 mg, yield 65%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.60 (s, 1H), 7.12 (s, 1H), 4.69 – 4.60 (m, 1H), 3.95 (s, 3H), 3.82 – 3.49 (m, 8H), 3.23 – 3.14 (m, 2H), 3.11 – 2.98 (m, 2H), 2.24 – 1.91 (m, 8H), 1.88 – 1.70 (m, 4H), 1.57 – 1.43 (m, 2H), 1.35 (d, J = 6.1 Hz, 6H). HPLC purity (method 1): >95%; t_R 3.63 min; MS (ESI): 442 $[M+H]^+$.



6-Chloro-7-methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (42). To the solution of 2-amino-4-methoxybenzoic acid (commercially available, 0.61 g, 3.7 mmol) in CH_3CN (12 mL) was added the CH_3CN (3.0 mL) solution of NCS (0.50 g, 3.7 mmol) at room temperature. The resulting mixture was heated at 75ºC for 1 hour. TLC indicated the completion of the reaction. 2-Amino-5-chloro-4-methoxybenzoic acid was obtained after filtration as a solid, together with the side product 2-amino-3-chloro-4-methoxybenzoic acid (1:1). The mixture was used for next step without further purification.

To the solution of the solid obtained in HOAc (5.0 mL) and H_2O (2.5 mL) was added sodium cyanate (0.60 g, 9.0 mmol) at room temperature and the mixture was stirred overnight. After removal of the solvent *in vacuo*, the gray solid obtained was redissolved in MeOH (5.0 mL). 10% NaOH aqueous solution was added to neutralize the solution. Additional 10% NaOH aqueous solution (3.0 mL) was added. The suspension was heated under reflux for 5 hours, then neutralized with conc. HCl. 6-Chloro-7-methoxyquinazoline-2,4(1*H*,3*H*)-dione (**S7**) was obtained after filtration as a gray solid, together with the side product 8-chloro-7-methoxyquinazoline-2,4(1*H*,3*H*)-dione (1:1), which was used for next step without further purification.

2,4,6-Trichloro-7-methoxyquinazoline (**S8**) was prepared according to the procedures for making **S13** (see page S34) from **S7**. 2,6-Dichloro-7-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S9**) was prepared according to the procedures for making **S5** from **S8**, 5-(pyrrolidin-1-yl)pentan-1-amine, *N*,*N*-diisopropylethylamine and THF. Compound **42** was prepared according to the procedures for making **3** from 2,6-dichloro-7-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S9**, 65 mg, 0.17 mmol), pyrrolidine (56 µL, 0.69 mmol), *N*,*N*-diisopropylethylamine (61 µL, 0.35 mmol) and *n*-butanol (2.0 mL). The title compound **42** was obtained as a TFA salt, white solid (60 mg, yield 66%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.14 (s, 1H), 7.17 (s, 1H), 3.99 (s, 3H), 3.78 – 3.59 (m, 8H), 3.24 – 3.14 (m, 2H), 3.11 – 2.99 (m, 2H), 2.22 – 1.98 (m, 8H), 1.84 – 1.73 (m, 4H), 1.55 – 1.42 (m, 2H). HPLC purity (method 1): >95%; t_R 3.41 min; MS (ESI): 418 $[M+H]^+$.



7-Ethoxy-6-methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (43). To a suspension of 60% sodium hydride (0.48 g, 12 mmol) in DMF (25 mL) was added the DMF (15 mL) solution of 4-hydroxy-3-methoxy-benzonitrile (commercially available, 1.48 g, 9.9 mmol) over 5 min at 0ºC. The resulting mixture was stirred at 0ºC for 30 min. Then ethyl bromide (1.4 mL, 18 mmol) was slowly added into the reaction mixture at 0ºC. The resulting mixture was warmed to room temperature and stirred overnight. TLC indicated the completion of the reaction. Brine (60 mL) was added into the reaction mixture and the product precipitated out. 4-Ethoxy-3-methoxybenzonitrile (**S10**) was obtained after filtration as a white solid (1.8 g, yield 100%).

To the solution of 4-ethoxy-3-methoxybenzonitrile (**S10**, 1.8 g, 10 mmol) in acetic anhydride (15 mL) was slowly added 69 wt% nitric acid (3.6 mL, 40 mmol) at 0ºC. The reaction mixture was stirred overnight at room temperature, and then poured into ice-water. The resulting precipitate was collected, washed with water and dried to provide 4-ethoxy-5-methoxy-2-

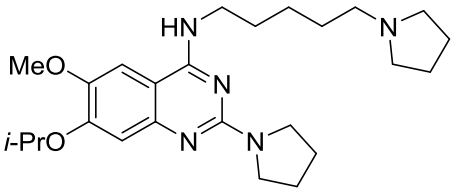
nitrobenzonitrile. A mixture of crude 4-ethoxy-5-methoxy-2-nitrobenzonitrile, iron powder (2.2 g, 40 mmol) and ammonium chloride (3.0 g, 56 mmol) in isopropanol-water was heated under reflux for 4 hours. The filtrate was concentrated and purified by ISCO to give 2-amino-4-ethoxy-5-methoxybenzonitrile (**S11**, 1.7 g, yield 77% over 2 steps).

To the solution of 2-amino-4-ethoxy-5-methoxybenzonitrile (**S11**, 1.7 g, 7.7 mmol), *N*,*N*-diisopropylethylamine (2.4 mL, 14 mmol), DMF (20 mL) and DCM (10 mL) was added methyl chloroformate (0.92 mL, 12 mmol) at 0ºC. The resulting mixture was stirred overnight at room temperature. TLC indicated the completion of the reaction. Water (60 mL) was added into the reaction mixture and the product precipitated out, which was used for next step after filtration without further purification. The ethanol (50 mL) solution of the product, 30 wt% H_2O_2 (20 ml) and NaOH (0.31 g, 7.8 mmol) was heated under reflux for 2 hours. After cooling, water (50 mL) was added into the reaction mixture and the product precipitated out, which was filtered and washed to give 7-ethoxy-6-methoxyquinazoline-2,4(1*H*,3*H*)-dione (**S12**, 0.99 g, 4.2 mmol, yield 55% over 2 steps).

The solution of 7-ethoxy-6-methoxyquinazoline-2,4(1*H*,3*H*)-dione (**S12**, 0.99 g, 4.2 mmol) and *N*,*N*-diethylaniline (0.72 mL, 4.5 mmol) in $POCl_3$ (8.0 mL) was heated under reflux for 7 hours. After removal of the solvent *in vacuo*, saturated $NaHCO_3$ solution was added. The resulting mixture was extracted with chloroform. The organic layer was washed with brine, dried and concentrated to give the crude product, which was purified by ISCO to give 2,4-dichloro-7-ethoxy-6-methoxyquinazoline (**S13**, 0.57 g, 2.1 mmol, yield 50%).

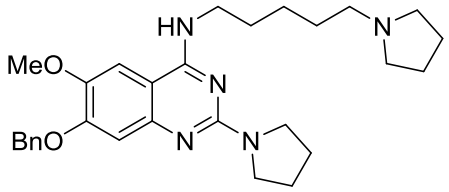
2-Chloro-7-ethoxy-6-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S14**) was prepared according to the procedures for making **S5** from 2,4-dichloro-7-ethoxy-6-

methoxyquinazoline (**S13**), 5-(pyrrolidin-1-yl)pentan-1-amine, *N*,*N*-diisopropylethylamine and THF. Compound **43** was prepared according to the procedures for making **3** from 2-chloro-7-ethoxy-6-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (**S14**, 101 mg, 0.26 mmol), pyrrolidine (82 µL, 1.0 mmol), *N*,*N*-diisopropylethylamine (87 µL, 0.50 mmol) and *n*-butanol (2.0 mL). The title compound **43** was obtained as a TFA salt, white solid (102 mg, yield 73%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.55 (s, 1H), 7.07 (s, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 3.80 – 3.47 (m, 8H), 3.22 – 3.15 (m, 2H), 3.11 – 3.00 (m, 2H), 2.18 – 1.93 (m, 8H), 1.87 – 1.73 (m, 4H), 1.56 – 1.49 (m, 2H), 1.48 (t, J = 7.2 Hz, 3H). HPLC purity (method 1): >95%; t_R 3.44 min; MS (ESI): 428 $[M+H]^+$.

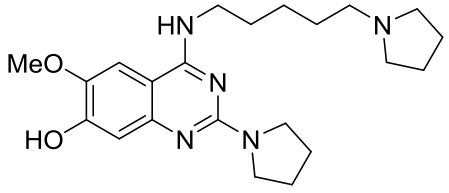


7-Isopropoxy-6-methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl) quinazolin-4-amine (44). 2,4-Dichloro-7-isopropoxy-6-methoxyquinazoline was prepared according to the procedures for making **S13** from 4-hydroxy-3-methoxy-benzonitrile. 2-Chloro-7-isopropoxy-6-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine was prepared according to the procedures for making **S5** from 2,4-dichloro-7-isopropoxy-6-methoxyquinazoline, 5-(pyrrolidin-1-yl)pentan-1-amine, *N*,*N*-diisopropylethylamine and THF. Compound **44** was prepared according to the procedures for making **3** from 2-chloro-7-isopropoxy-6-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (133 mg, 0.33 mmol), pyrrolidine (110 µL, 1.4 mmol), *N*,*N*-diisopropylethylamine (124 µL, 0.71 mmol) and *n*-butanol (2.0 mL). The title compound **44** was obtained as a TFA salt, white solid (136 mg, yield 75%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.56 (s, 1H), 7.12 (s, 1H), 4.79 – 4.64 (m, 1H), 3.91 (s, 3H),

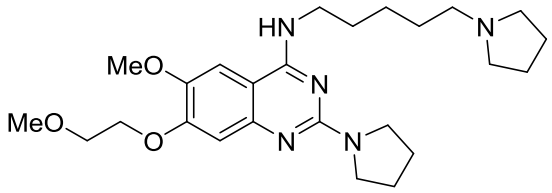
3.76 – 3.59 (m, 8H), 3.25 – 3.13 (m, 2H), 3.11 – 2.98 (m, 2H), 2.18 – 1.97 (m, 8H), 1.85 – 1.76 (m, 4H), 1.61 – 1.43 (m, 2H), 1.41 (d, *J* = 6.0 Hz, 6H). HPLC purity (method 1): >95%; t_R 3.57 min; MS (ESI): 442 $[M+H]^+$.



7-(Benzyloxy)-6-methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl) quinazolin-4-amine (45). 7-(Benzyloxy)-2-chloro-6-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl) quinazolin-4-amine was prepared according to the procedures for making **S5** from 7-(benzyloxy)-2,4-dichloro-6-methoxyquinazoline (synthesized according to the procedures reported previously[3]), 5-(pyrrolidin-1-yl)pentan-1-amine, *N*,*N*-diisopropylethylamine and THF. Compound **45** was prepared according to the procedures for making **3** from 7-(benzyloxy)-2-chloro-6-methoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine (1.2 g, 2.6 mmol), pyrrolidine (866 µL, 11 mmol), *N*,*N*-diisopropylethylamine (1.3 mL, 7.9 mmol) and *n*-butanol (15 mL). The title compound **45** was obtained as a white solid (919 mg, yield 82%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.51 – 7.44 (m, 2H), 7.40 – 7.28 (m, 4H), 6.98 (s, 1H), 5.19 (s, 2H), 3.90 (s, 3H), 3.66 – 3.54 (m, 6H), 2.61 – 2.51 (m, 4H), 2.50 – 2.41 (m, 2H), 2.02 – 1.93 (m, 4H), 1.85 – 1.71 (m, 6H), 1.65 – 1.56 (m, 2H), 1.48 – 1.38 (m, 2H). HPLC purity (method 1): >95%; t_R 3.97 min; MS (ESI): 490 $[M+H]^+$.

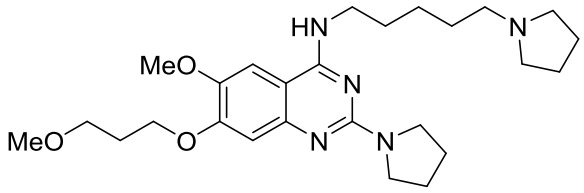


6-Methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino)quinazolin-7-ol (46). A stirred suspension of 7-(benzyloxy)-6-methoxy-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl) quinazolin-4-amine (**45**, 600 mg, 1.2 mmol) and Pd/C in ethanol (75 mL) was treated with hydrogen at 1 atm for 3 days at room temperature until TLC showed that the starting material had disappeared. The title compound **46** was obtained after filtration and concentration without further purification as a white solid (475 mg, yield 96%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.17 (s, 1H), 6.55 (s, 1H), 3.84 (s, 3H), 3.67 – 3.55 (m, 6H), 2.64 – 2.55 (m, 4H), 2.54 – 2.47 (m, 2H), 2.11 – 2.00 (m, 4H), 1.85 – 1.77 (m, 4H), 1.77 – 1.70 (m, 2H), 1.67 – 1.56 (m, 2H), 1.47 – 1.39 (m, 2H). HPLC purity (method 1): >95%; t_R 3.43 min; MS (ESI): 400 $[M+H]^+$.

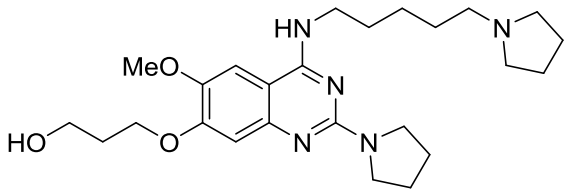


6-Methoxy-7-(2-methoxyethoxy)-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl)pentyl) quinazolin-4-amine (47). To a suspension of 6-methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino)quinazolin-7-ol (**46**, 62 mg, 0.15 mmol), K_2CO_3 (23 mg, 0.17 mmol), NaI (3 mg, 0.20 mmol) and DMF (0.8 mL) was added 2-bromoethyl methyl ether (15 µL, 0.15 mmol). The resulting suspension was stirred for 3 days at room temperature until TLC showed that the starting material had disappeared. After removal of the solvent *in vacuo*, the residue was redissolved in CH_2Cl_2, washed with brine. The organic layer was dried, concentrated and purified by ISCO to give the title compound **47** as a tan semi-solid (25 mg, yield 35%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.28 (s, 1H), 6.89 (s, 1H), 4.21 – 4.14 (m, 2H), 3.85 (s, 3H), 3.80 – 3.75 (m, 2H), 3.61 – 3.52 (m, 6H), 3.41 (s, 3H), 2.54 – 2.46 (m, 4H), 2.46 – 2.39 (m, 2H), 2.00 – 1.90

(m, 4H), 1.81 – 1.68 (m, 6H), 1.62 – 1.52 (m, 2H), 1.45 – 1.36 (m, 2H). HPLC purity (method 1): >95%; t_R 3.54 min; MS (ESI): 458 $[M+H]^+$.

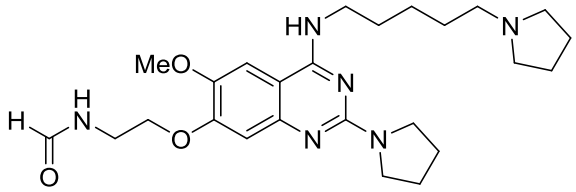


6-Methoxy-7-(3-methoxypropoxy)-2-(pyrrolidin-1-yl)-*N*-(5-(pyrrolidin-1-yl) pentyl)quinazolin-4-amine (48). Compound **48** was prepared according to the procedures for making **47** from 6-methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino) quinazolin-7-ol (**46**, 50 mg, 0.13 mmol), 1-bromo-3-methoxypropane (commercially available, 19 mg, 0.13 mmol), K_2CO_3 (26 mg, 0.19 mmol) and DMF (1.0 mL). The title compound **48** was obtained as a TFA salt, clear oil (26 mg, yield 37%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.56 (s, 1H), 7.10 (s, 1H), 4.19 (t, J = 6.3 Hz, 2H), 3.93 (s, 3H), 3.81 – 3.45 (m, 11H), 3.35 (s, 3H), 3.22 – 2.99 (m, 3H), 2.22 – 1.96 (m, 10H), 1.90 – 1.74 (m, 4H), 1.57 – 1.45 (m, 2H). HPLC purity (method 1): >95%; t_R 3.87 min; MS (ESI): 472 $[M+H]^+$.



3-((6-Methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino) quinazolin-7-yl)oxy)propan-1-ol (49). Compound **49** was prepared according to the procedures for making **47** from 6-methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino) quinazolin-7-ol (**46**, 60 mg, 0.15 mmol), 3-bromo-1-propanol (commercially available, 14 µL, 0.15 mmol), K_2CO_3 (31 mg, 0.23 mmol) and DMF (1.0 mL). The title compound **49** was obtained as a TFA salt, clear oil

(24 mg, yield 30%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.56 (s, 1H), 7.11 (s, 1H), 5.49 (s, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.92 (s, 3H), 3.80 – 3.61 (m, 10H), 3.23 – 3.15 (m, 2H), 3.11 – 3.00 (m, 2H), 2.21 – 1.99 (m, 10H), 1.86 – 1.77 (m, 4H), 1.58 – 1.46 (m, 2H). HPLC purity (method 1): 95%; t_R 3.58 min; MS (ESI): 458 $[M+H]^+$.



***N*-(2-((6-Methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino) quinazolin-7-yl)oxy)ethyl)formamide (50).** To a suspension of 6-methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino)quinazolin-7-ol (**46**, 133 mg, 0.33 mmol), K_2CO_3 (115 mg, 0.83 mmol) and acetone (8.0 mL) was added 2-(Boc-amino)ethyl bromide (commercially available, 75 mg, 0.33 mmol). The resulting suspension was stirred for 3 days at 70ºC until TLC showed that most of the starting material had disappeared. After removal of the solvent *in vacuo*, the residue was redissolved in CH_2Cl_2, washed with brine. The organic layer was dried, concentrated and purified by HPLC to give *tert*-butyl (2-((6-methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino)quinazolin-7-yl)oxy)ethyl)carbamate as a TFA salt (157 mg, yield 61%). To a stirred suspension of $LiAlH_4$ (20 mg, 0.54 mmol) in anhydrous THF (3.0 mL) was added the THF (2.0 mL) solution of *tert*-butyl (2-((6-methoxy-2-(pyrrolidin-1-yl)-4-((5-(pyrrolidin-1-yl)pentyl)amino)quinazolin-7-yl)oxy)ethyl)carbamate (51 mg, 0.06 mmol) dropwise at 0ºC. The resulting mixture was stirred at 60ºC over night to ensure full conversion of starting material. After cooling, TLC indicated the completion of the reaction. To the mixture were added H_2O (2.0 mL), NaOH solution (15%, 2.0 mL) and H_2O (6.0 mL) successively. After filtration, the organic layer was washed with brine, dried and concentrated to give the crude

product, which was purified by HPLC to give title compound **50** as a TFA salt, clear oil (15 mg, yield 32%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.12 (s, 1H), 7.58 (s, 1H), 7.09 (s, 1H), 4.21 (t, *J* = 5.4 Hz, 2H), 3.94 (s, 3H), 3.78 – 3.59 (m, 10H), 3.23 – 3.16 (m, 2H), 3.11 – 3.00 (m, 2H), 2.19 – 1.96 (m, 8H), 1.87 – 1.75 (m, 4H), 1.55 – 1.48 (m, 2H). HPLC purity (method 1): 95%; t_R 3.30 min; MS (ESI): 471 $[M+H]^+$.

Radioactive Assay (also known as Scintillation Proximity Assay). The assay was conducted according to the procedures reported previously.[1] Methylation (10 μL) reactions were carried out in a buffer containing 50 mM Tris-HCl (pH 8.0), 10 mM GSH, 0.1%Triton X-100, at room temperature using 50 nM SETD8, 1.5 μM tritium labelled SAM (Cat #: NET155V250UC; PerkinElmer), and 5 μM biotinylated H4 (1-24) peptide substrate (SGRGKGGKGLGKGGAKRHRKVLRDK-biotin) in 384-well plates in the presence of 50 μM compounds. The reactions were then quenched by addition of equal volume of 7.5 M guanidine hydrochloride after 1 hour incubation. 40 μL of buffer (20 mM Tris-HCl, pH 8.0) was added into the quenched samples, and all samples were then transferred into a streptavidin/scintillant-coated microplate (Cat #: SMP410; PerkinElmer). The amount of methylated peptide was quantified by tracing the radioactivity (counts per minute) as measured after 1 hour using a TopCount plate reader (PerkinElmer). For IC_{50} values determination, the compounds were serially diluted 2-fold in DMSO for a total of eleven concentrations, beginning at 0.25 mM and tested in the same condition.

References

1. A. Ma, W. Yu, F. Li, R. M. Bleich, J. M. Herold, K. V. Butler, J. L. Norris, V. Korboukh, A. Tripathy, W. P. Janzen, C. H. Arrowsmith, S. V. Frye, M. Vedadi, P. J. Brown and J. Jin, *Journal of medicinal chemistry*, 2014, 57, 6822-6833.
2. S. M. Chichetti, S. P. Ahearn and A. Rivkin, *Tetrahedron Letters*, 2008, 49, 6081-6083.

3. F. Liu, X. Chen, A. Allali-Hassani, A. M. Quinn, T. J. Wigle, G. A. Wasney, A. Dong, G. Senisterra, I. Chau, A. Siarheyeva, J. L. Norris, D. B. Kireev, A. Jadhav, J. M. Herold, W. P. Janzen, C. H. Arrowsmith, S. V. Frye, P. J. Brown, A. Simeonov, M. Vedadi and J. Jin, *Journal of medicinal chemistry*, 2010, 53, 5844-5857.