Supporting Information

Structure-Activity Study of Bioisosteric Trifluoromethyl and Pentafluorosulfanyl Indole Inhibitors of the AAA ATPase p97

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General Methods

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware unless otherwise noted. Anhydrous tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl; anhydrous dichloromethane and toluene were distilled from CaH_2; alternatively, the same solvents were obtained from a solvent purification system using alumina columns. All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. Reactions were monitored via TLC using 250 μm pre-coated silica gel 60 F_{254} plates, which were visualized with 254 nm and/or 365 nm UV light and by staining with $KMnO_4$ (1.5 g $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10% NaOH in 200 mL water), cerium molybdate (0.5 g $Ce(NH_4)_2(NO_3)_6$, 12 g $(NH_4)_6Mo_7O_{24}•4H_2O$, and 28 mL conc. H_2SO_4 in 235 mL water), or vanillin (6 g vanillin and 1.5 mL conc. H_2SO_4 in 100 mL EtOH). Flash chromatography was performed with SiliCycle silica gel 60 (230-400 mesh) or with ISCO MPLC. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 300, 400, or 500 MHz spectrometers, using the residual solvent as an internal standard. IR spectra were obtained on a Smiths IdentifyIR or PerkinElmer Spectrum 100. HRMS data were obtained on a Thermo Scientific Exactive HRMS coupled to a Thermo Scientific Accela HPLC system using a 2.1 x 50 mm 3.5 μm Waters XTerra C_{18} column eluting with $MeCN/H_2O$ containing 0.1% formic acid. Purity of compounds was assessed using the same HPLC system with either the PDA or an Agilent 385 ELSD. All final screening samples passed QC based on >95% purity by LC/MS/ELSD analysis.

Experimental Procedures

tert-Butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(piperidin-4-yl)carbamate (17).

A solution of benzyl 4-oxopiperidine-1-carboxylate (1.54 g, 6.61 mmol), 2-(4-isopropylpiperazin-1-yl)ethan-1-amine[1] (1.03 g, 6.01 mmol), and AcOH (52.2 μL, 0.902 mmol) in anhydrous CH_2Cl_2 (100 mL) was treated with $NaBH(OAc)_3$ (1.94 g, 9.02 mmol). The reaction mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (100 mL), washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), and evaporated to give benzyl 4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidine-1-carboxylate (2.33 g, quant.) as a pale yellow oil that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5 H), 5.12 (s, 2 H), 4.11 (app d, *J* = 10.3 Hz, 2 H), 2.88 (app t, *J* = 11.8 Hz, 2 H), 2.74-2.47 (m, 14 H), 1.85 (d, *J* = 12.6 Hz, 2 H), 1.35-1.22 (m, 2 H), 1.06 (d, *J* = 6.5 Hz, 6 H).

A solution of benzyl 4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidine-1-carboxylate (8.34 g, 21.5 mmol) in anhydrous CH_2Cl_2 (350 mL) was treated with Boc_2O (8.43 g, 38.6 mmol). The reaction mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (350 mL), washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), evaporated, and purified by chromatography on SiO_2 (2% MeOH/CH_2Cl_2 with 1% TEA) followed by chromatography on basic Al_2O_3 (0 to 1% MeOH/CH_2Cl_2) to give benzyl 4-((*tert*-butoxycarbonyl)(2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidine-1-carboxylate (8.08 g, 77%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5 H), 5.11 (s, 2 H), 4.26 (bs, 2 H), 4.09 (bs, 1 H), 3.17 (bs, 2 H), 2.78 (bs, 2 H), 2.66-2.40 (m, 11 H), 1.65-1.56 (m, 4 H), 1.45 (s, 9 H), 1.03 (d, *J* = 6.5 Hz, 6 H).

A solution of benzyl 4-((*tert*-butoxycarbonyl)(2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidine-1-carboxylate (2.54 g, 5.20 mmol) in THF (120 mL) was treated with 10% Pd/C (0.512 g, 0.480 mmol). The reaction mixture was subjected to 3 cycles of vacuum/hydrogen backfill and stirred for 3 d under a hydrogen

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[1] Tapia, I.; Alonso-Cires, L.; Lopez-Tudanca, P. L.; Mosquera, R.; Labeaga, L.; Innerarity, A.; Orjales, A. *J. Med. Chem.* **1999**, *42*, 2870-2880.

atmosphere. The reaction mixture was filtered through a pad of Celite® and concentrated to give *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(piperidin-4-yl)carbamate (**17**, 1.80 g, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (bs, 1 H), 3.23 (app t, *J* = 5.4 Hz, 2 H), 3.11 (d, *J* = 11.8 Hz, 2 H), 2.68-2.43 (m, 13 H), 1.68-1.65 (m, 2 H), 1.60-1.52 (m, 2 H), 1.46 (s, 9 H), 1.04 (d, *J* = 6.5 Hz, 6 H); HRMS (ESI) *m/z* calcd for $C_{19}H_{39}O_2N_4$ $[M+H]^+$ 355.3068, found 355.3067.

***N*-(2-(4-Isopropylpiperazin-1-yl)ethyl)-1-(3-(5-(trifluoromethyl)-1*H*-indol-2-yl)phenyl)piperidin-4-amine (12)**.

A solution of 3-bromoiodobenzene (**32**, 0.284 g, 1.00 mmol), 5-trifluoromethylindole[2] (0.155 g, 0.840 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), bis(diphenylphosphino)methane (17 mg, 0.040 mmol), and KOAc (0.249 g, 2.51 mmol) in deoxygenated water (2 mL) was heated at 110 °C for 24 h, cooled to room temperature, diluted with EtOAc (10 mL) and 1 N HCl (5 mL), and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (10% EtOAc/petroleum ether). The residue was recrystallized (hexanes/CH_2Cl_2) to give 2-(3-bromophenyl)-5-(trifluoromethyl)-1*H*-indole (**16**, 139 mg, 49%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (bs, 1 H), 7.92 (s, 1 H), 7.79 (s, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.48 (d, *J* = 7.9 Hz, 1 H), 7.46–7.00 (m, 2 H), 7.36–7.27 (m, 1 H), 6.88 (d, *J* = 1.6 Hz, 1 H).

A solution of 2-(3-bromophenyl)-5-(trifluoromethyl)-1*H*-indole (**16**, 85 mg, 0.25 mmol), LiHMDS (0.10 g, 0.60 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol), and CyJohnPhos (7 mg, 0.02 mmol) in anhydrous THF was treated with *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(piperidin-4-yl)carbamate (**17**, 0.107 g, 0.300 mmol). The reaction mixture was heated at 55 °C overnight, cooled to room temperature, diluted with sat. $NaHCO_3$, and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (2% MeOH/CH_2Cl_2 with 0.1% TEA) followed by chromatography on basic Al_2O_3 (CH_2Cl_2) to give *tert*-butyl (2-(4-isopropylpiperazin-

[2] Walkington, A.; Gray, M.; Hossner, F.; Kitteringham, J.; Voyle, M. *Synth. Commun.* **2003**, *33*, 2229–2233.

1-yl)ethyl)(1-(3-(5-(trifluoromethyl)-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (35 mg, 0.057 mmol, 23%) as a foam: IR (ATR) 3234, 2963, 2930, 2812, 1685, 1601, 1465, 1330, 1151, 1110, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1 H), 7.89 (s, 1 H), 7.48 (d, *J* = 8.4 Hz, 1 H), 7.38 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.23 (bs, 1 H), 7.16 (bd, *J* = 7.6 Hz, 1 H), 6.90 (dd, *J* = 7.8, 1.0 Hz, 1 H), 6.84 (d, *J* = 1.2 Hz, 1 H), 4.12 (bs, 1 H), 3.79 (bd, *J* = 4.0 Hz, 2 H), 3.22 (bs, 2 H), 2.82–2.47 (m, 13 H), 1.76–1.75 (m, 3 H), 1.48 (s, 9 H), 1.25–1.22 (m, 1 H), 1.11 (d, *J* = 6.0 Hz, 6 H); HRMS (ESI) *m/z* calcd for $C_{34}H_{47}O_2N_5F_3$ $[M+H]^+$ 614.3676, found 614.3678.

A solution of TFA (0.43 mL, 5.7 mmol) and triethylsilane (92 μL, 0.57 mmol) in CH_2Cl_2 (1 mL) was added to a solution of *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-(trifluoromethyl)-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (35 mg, 0.057 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred under an atmosphere of N_2 at room temperature for 1 h, concentrated, diluted with sat. $NaHCO_3$, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (7 to 9% MeOH/CH_2Cl_2 with 0.1% TEA) followed by chromatography on basic Al_2O_3 (0 to 9% MeOH/CH_2Cl_2) to give *N*-(2-(4-isopropylpiperazin-1-yl)ethyl)-1-(3-(5-(trifluoromethyl)-1*H*-indol-2-yl)phenyl)piperidin-4-amine (**12**, 17 mg, 0.033 mmol, 58%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1 H), 7.89 (s, 1 H), 7.44 (d, *J* = 8.5 Hz, 1 H), 7.40 (dd, *J* = 8.5, 1.0 Hz, 1 H), 7.33–7.30 (m, 1 H), 7.22 (app s, 1 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 6.93 (dd, *J* = 8.3, 2.3 Hz, 1 H), 6.84 (d, *J* = 1.5 Hz, 1 H), 3.74 (app d, *J* = 12.5 Hz, 2 H), 2.85 (td, *J* = 12.0, 1.8 Hz, 2 H), 2.78 (t, *J* = 6.3 Hz, 2 H), 2.68–2.49 (m, 13 H), 2.01 (bd, *J* = 12.0 Hz, 2 H), 1.54 (qd, *J* = 11.6, 3.1 Hz, 2 H), 1.05 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 140.6, 138.1, 132.7, 129.9, 129.3, 128.7, 125.5 (q, J_{CF} = 271.0 Hz), 122.7 (q, J_{CF} = 31.6 Hz), 118.9 (q, J_{CF} = 3.4 Hz), 118.3 (q, J_{CF} = 4.2 Hz), 116.5, 113.6, 111.2, 100.5, 58.1, 55.2, 54.6, 53.7, 48.9, 48.6, 43.6, 32.7, 18.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.4; HRMS (ESI) *m/z* calcd for $C_{29}H_{39}N_5F_3$ $[M+H]^+$ 514.3152, found 514.3154.

N-(2-(4-isopropylpiperazin-1-yl)ethyl)-1-(3-(5-(pentafluoro-λ⁶-sulfanyl)-1H-indol-2-yl)phenyl)piperidin-4-amine (13).

A suspension of 1-bromo-3-(dimethoxymethyl)benzene[3] (**18**, 0.19 g, 0.82 mmol), **17** (0.32 g, 0.90 mmol) and K_3PO_4 (0.27 g, 1.2 mmol) in dry dioxane (2.5 mL) was degassed for 40 min by bubbling argon, then $Pd_2(dba)_3$ (8 mg, 0.008 mmol) and CyJohnPhos (12 mg, 0.032 mmol) were added. The flask was sealed and the reaction mixture was heated at 110 °C for 10 h, diluted with sat. $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in acetone (27 mL) and H_2O (3 mL) and treated with TsOH•H_2O (0.48 g, 2.5 mmol) at rt for 3 h, then diluted with sat. Na_2CO_3 and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on SiO_2 (95:5 to 85:15 CH_2Cl_2/MeOH) to give *tert*-butyl (1-(3-formylphenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (**19**, 0.32 g, 0.70 mmol, 85% for two steps) as a pale yellow viscous oil: IR (ATR) 2961, 2931, 2808, 1685, 1595, 1450, 1365, 1175, 1145, 776 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 9.97 (s, 1 H), 7.44 (t, J = 7.9 Hz, 2 H), 7.32 (d, J = 7.4 Hz, 1 H), 7.23 (dd, J = 8.2, 2.4 Hz, 1 H), 4.09 (t, J = 1.9 Hz, 1 H), 3.87 (d, J = 12.5 Hz, 2 H), 3.23 (s, 2 H), 2.88 (t, J = 11.6 Hz, 2 H), 2.70-2.45 (m, 11 H), 1.90-1.80 (m, 4 H), 1.48 (s, 9 H), 1.06 (d, J = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 192.6, 155.1, 151.7, 137.5, 129.7, 122.0, 120.9, 115.4, 79.3, 58.3, 54.5, 49.1, 48.5, 40.6, 29.9, 28.2, 18.2; HRMS (ESI) m/z calcd for $C_{26}H_{43}O_3N_4$ $[M+H]^+$ 459.3330, found 459.3329.

A solution of 1-nitro-4-(pentafluoro- λ⁶-sulfanyl)benzene (**20**, 1.0 g, 4.0 mmol) and ((chloromethyl)sulfonyl)benzene (**21**, 0.77 g, 4.0 mmol) in DMF (4.0 mL) was added dropwise to a solution of *t*-BuOK (1.6 g, 14 mmol) in DMF (10 mL) at -30 °C. The reaction mixture was stirred for 30 min at -30 °C, quenched by addition of aq HCl (30 mL, 1 M), and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by chromatography on SiO_2 (75:25 hexanes/EtOAc) to afford

[3] Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2005**, *46*, 8319-8323.

pentafluoro(4-nitro-3-((phenylsulfonyl)methyl)phenyl)-λ⁶-sulfane[4] (1.4 g, 3.4 mmol, 86%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.9 Hz, 1 H), 7.95 (dd, J = 8.9, 2.3 Hz, 1 H), 7.74-7.69 (m, 4 H), 7.56 (t, J = 7.8 Hz, 2 H), 4.98 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (quintuplet, J_{CF} = 19.7), 150.6, 137.4, 134.6, 131.91, 131.86, 131.82, 129.6, 128.4, 127.97, 127.93, 127.88, 126.1, 124.5, 58.4.

A suspension of pentafluoro(4-nitro-3-((phenylsulfonyl)methyl)phenyl)-λ⁶-sulfane (1.4 g, 3.5 mmol) and 10% Pd/C (0.11 g, 0.10 mmol) in EtOH (100 mL) was treated with H_2 (balloon, 1 atm) at room temperature for 4 h. The mixture was filtered on Celite® and concentrated to afford a pale yellow solid. The solid was suspended in Et_2O and filtered. The residue was washed with cold Et_2O to give 4-(pentafluoro-λ⁶-sulfanyl)-2-((phenylsulfonyl)methyl)aniline (**22**, 0.5 g) as a white-pale yellow solid. More material was collected from concentration of the mother liquor as a pale yellow solid (0.7 g). The solids were combined to give 4-(pentafluoro-λ⁶-sulfanyl)-2-((phenylsulfonyl)methyl)aniline (**22**, 1.2 g, 3.5 mmol, quant) that was used in the next step without further purification: ^{1}H NMR (400 MHz, MeOD) δ 7.79-7.71 (m, 3 H), 7.68 (dd, J = 9.1, 2.6 Hz, 1 H), 7.59 (t, J = 7.8 Hz, 2 H), 7.39 (d, J = 9.1 Hz, 1 H), 7.06 (d, J = 2.5 Hz, 1 H), 4.58 (s, 2 H).

A suspension of 4-(pentafluoro-λ⁶-sulfanyl)-2-[(phenylsulfonyl)methyl]aniline (**22**, 0.20 g, 0.54 mmol), aldehyde **19** (0.49 g, 1.1 mmol), and $MgSO_4$ (0.32 g, 2.7 mmol) in acetic acid (2 mL) was heated at 75 °C for 14 h, concentrated, basified with $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry DMSO (4 mL) and added to a suspension of powdered KOH (0.15 g, 2.7 mmol) in dry DMSO (2 mL). The reaction mixture was stirred at rt for 90 min, then acidified to pH 8 with sat. NH_4Cl, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography on SiO_2 (7:3, EtOAc/MeOH) to provide *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-(pentafluoro-λ⁶-sulfanyl)-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (0.030 g, 0.045 mmol, 8%) as a pale yellow

[4] Iakobson, G.; Pošta, M.; Beier, P. *Synlett* **2013**; *24*, 855-859.

foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1 H), 8.07 (d, *J* = 1.8 Hz, 1 H), 7.59 (dd, *J* = 9.0, 2.1 Hz, 1 H), 7.41 (d, *J* = 8.9 Hz, 1 H), 7.35 (t, *J* = 7.9 Hz, 1 H), 7.23 (s, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 6.88 (d, *J* = 0.7 Hz, 1 H), 3.82-3.79 (m, 2 H), 3.26 (t, *J* = 1.1 Hz, 2 H), 2.79-2.51 (m, 13 H), 1.79 (s, 4 H), 1.51 (s, 9 H), 1.08 (d, *J* = 6.5 Hz, 6 H).

A solution of trifluoroacetic acid (1 mL) in CH_2Cl_2 (1 mL) was added to a solution of *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-(pentafluoro-λ^6-sulfanyl)-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (0.025 g, 0.037 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred under N_2 at room temperature for 1 h, concentrated, diluted with $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography on SiO_2 (100:8:1 to 100:15:1, CH_2Cl_2/MeOH/NEt_3). Purified fractions were concentrated and subsequently filtered through basic Al_2O_3 (100:0 then 100:10, CH_2Cl_2/MeOH) to provide *N*-(2-(4-isopropylpiperazin-1-yl)ethyl)-1-(3-(5-(pentafluoro-λ^6-sulfanyl)-1*H*-indol-2-yl)phenyl)piperidin-4-amine (**13**, 0.013 g, 0.023 mmol, 61%) as a white foam: IR (ATR) 3147, 2923, 2852, 2815, 1603, 1458, 1383, 1148, 839, 809 cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ 8.05 (d, *J* = 2.0 Hz, 1 H), 7.55 (dd, *J* = 9.0, 2.1 Hz, 1 H), 7.48 (d, *J* = 9.0 Hz, 1 H), 7.43 (s, 1 H), 7.34-7.29 (m, 2 H), 6.99-6.96 (m, 2 H), 3.82 (d, *J* = 12.6 Hz, 2 H), 2.85-2.76 (m, 4 H), 2.67-2.51 (m, 13 H), 2.03 (d, *J* = 11.7 Hz, 2 H), 1.54 (dq, *J* = 11.8, 3.2 Hz, 2 H), 1.09 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, MeOD) δ 152.0, 146.8, 146.7, 146.5, 141.5, 137.8, 132.5, 129.3, 127.9, 118.5, 118.4, 118.3, 118.2, 116.6, 116.3, 113.3, 110.1, 99.6, 57.0, 54.8, 54.5, 52.7, 42.4, 31.4, 17.3; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{39}N_5F_5S$ $[M+H]^+$ 572.2841, found 572.2836.

***N*-(2-(4-Isopropylpiperazin-1-yl)ethyl)-1-(3-(5-nitro-1H-indol-2-yl)phenyl)piperidin-4-amine (23).**

A solution of phenylhydrazine (**27**, 1.80 g, 16.6 mmol) and 3'-bromoacetophenone (**15**, 3.31 g, 16.6 mmol) in EtOH (100 mL) was treated with AcOH (0.050 mL, 0.86 mmol). The mixture was heated at reflux for 2 h under nitrogen, and then concentrated. The residue was recrystallized from hexanes/EtOAc (4:1) and filtered

to afford (*E*)-1-(1-(3-bromophenyl)ethylidene)-2-phenylhydrazine as a pale yellow solid (4.30 g, 14.9 mmol, 90%). This compound was quite unstable and was used immediately for the next conversion.

A suspension of P_2O_5 (12.8 g, 45.1 mmol) and concentrated H_3PO_4 (8 mL) was heated at 100 °C under nitrogen until it formed a clear solution. The temperature was increased to 120 °C and (*E*)-1-(1-(3-bromophenyl)ethylidene)-2-phenylhydrazine (2.00 g, 6.90 mmol) was added in one portion. The reaction mixture was stirred for 1 h at 120 °C, cooled to room temperature, and quenched with crushed ice and water to obtain a white suspension. The solid was filtered, dried on the filter for 15 min, dissolved in Et_2O, dried (Na_2SO_4) and concentrated to afford 2-(3-bromophenyl)-1*H*-indole (**28**, 1.70 g, 6.25 mmol, 90%) as a pale yellow solid: Mp 153-154 °C; IR (ATR) 3430, 1562, 1439, 1420, 1346, 1230, 1073, 1051, 776, 712, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (bs, 1 H), 7.80 (t, *J* = 2.0 Hz, 1 H), 7.65 (dd, *J* = 8.0, 0.5 Hz, 1 H), 7.57 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1 H), 7.45 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1 H), 7.40 (dd, *J* = 8.0, 0.5 Hz, 1 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.23 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1 H), 7.15 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1 H), 6.84 (dd, *J* = 2.0, 1.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 136.2, 134.4, 130.52, 130.49, 129.1, 128.1, 123.7, 123.2, 122.9, 120.9, 120.5, 111.0, 101.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}NBr$ $[M+H]^+$ 272.0069, found 272.0069.

A suspension of 2-(3-bromophenyl)-1H-indole (**28**, 5.49 g, 20.2 mmol) in concentrated sulfuric acid (120 mL) at 5 °C was treated dropwise over 30 min with a cold (5 °C) solution of sodium nitrate (1.82 g, 21.4 mmol) in concentrated sulfuric acid (60 mL). The mixture was stirred for 15 min, and then poured onto crushed ice. The yellow precipitate was filtered, dissolved in EtOAc (400 mL), washed with H_2O(3 x 100 mL), sat. $NaHCO_3$ (2 x 50 mL) and brine, dried (Na_2SO_4), filtered and concentrated. The give crude product (5.53 g) was suspended in MeOH (350 mL), stirred overnight and filtered to afford 2-(3-bromophenyl)-5-nitro-1*H*-indole (4.18 g, 13.2 mmol, 65%) as a bright yellow solid: ^1H NMR (300 MHz, DMSO-d_6) δ 12.37 (s, 1 H), 8.55 (d, *J* = 2.1 Hz, 1 H), 8.14 (t, *J* = 1.8 Hz, 1 H), 8.03 (dd, *J* = 8.9, 2.3 Hz, 1 H), 7.93 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1 H), 7.61-7.56 (m, 2 H), 7.47 (t, *J* = 7.8 Hz, 1 H), 7.30

(d, *J* = 1.5 Hz, 1 H); HRMS (ESI) *m/z* calcd for $C_{14}H_{10}O_2N_2Br$ $[M+H]^+$ 316.9920, found 316.9918.

A suspension of 2-(3-bromophenyl)-5-nitro-1*H*-indole (0.15 g, 0.47 mmol), and LiHMDS (0.061 mg, 1.4 mmol) in dry deoxygenated THF (1.5 mL) was treated with **17** (0.20 g, 0.57 mmol). The solution was purged with argon for 20 min and treated with $Pd_2(dba)_3$ (0.009 g, 0.01 mmol) and CyJohnPhos (0.013 g, 0.038 mmol). The reaction mixture was heated at 70-75 °C for 24 h in a sealed tube, quenched with sat. $NaHCO_3$ (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on SiO_2, (10 to 20% MeOH/CH_2Cl_2) to give *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-nitro-1H-indol-2-yl)phenyl)piperidin-4-yl)carbamate (0.13 g, 0.31 mmol, 45%) as a yellowish foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (bs, 1 H), 8.54 (d, *J* = 2.0 Hz, 1 H), 8.05 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.42 (d, *J* = 8.8 Hz, 1 H), 7.30 (t, *J* = 7.8 Hz, 1 H), 7.20-7.16 (m, 2 H), 6.94-6.83 (m, 2 H), 4.06 (bs, 1 H), 3.80-3.60 (m, 2 H), 3.22 (bs, 2 H), 2.70-2.44 (m, 14 H), 1.82-1.61 (m, 4 H), 1.49 (s, 9 H), 1.04 (d, *J* = 6.4 Hz, 6 H); HRMS (ESI) *m/z* calcd for $C_{33}H_{47}O_4N_6$ $[M+H]^+$ 591.3653, found 591.3654.

A solution of TFA (0.14 mL, 1.9 mmol) in CH_2Cl_2 (0.5 mL) was treated with *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-nitro-1H-indol-2-yl)phenyl)piperidin-4-yl)carbamate (0.020 g, 0.033 mmol) in CH_2Cl_2 (0.5 mL) and stirred for 1.5 h. The reaction mixture was concentrated, diluted with sat. $NaHCO_3$, and extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by chromatography on SiO_2, (5 to 10% MeOH/CH_2Cl_2 with 0.1% Et_3N) followed by filtration through a plug of basic Al_2O_3 (0 to 10% MeOH/CH_2Cl_2) to give *N*-(2-(4-isopropylpiperazin-1-yl)ethyl)-1-(3-(5-nitro-1*H*-indol-2-yl)phenyl)piperidin-4-amine (**23**, 0.006 g, 0.01 mmol, 36%) as a yellow foam: IR (ATR, neat) 2932, 2823, 2106, 1660, 1601, 1508, 1472, 1465, 1457, 1327, 1294, 1178, 1070, 753 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.55 (d, *J* = 2.5 Hz, 1 H), 8.03 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.56 (d, *J* = 9.0 Hz, 1 H), 7.48 (t, *J* = 1.8 Hz, 1 H), 7.35-7.29 (m, 2 H), 7.16 (d, *J* = 1.0 Hz, 1 H), 7.00 (ddd, *J* = 7.8, 2.5, 1.4 Hz, 1 H), 3.79-3.75 (m, 2 H), 2.90 (td, *J* = 11.9, 2.1 Hz, 2 H), 2.78-2.71 (m, 6 H),

2.67-2.57 (m, 3 H), 2.48-2.41 (m, 10 H), 1.99-1.95 (m, 2 H), 1.50-1.43 (m, 2 H), 0.98 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 152.3, 142.4, 141.8, 140.1, 132.0, 129.7, 128.5, 116.84, 116.77, 116.1, 115.9, 112.8, 111.2, 100.7, 58.2, 54.6, 54.0, 53.7, 48.5, 47.6, 43.5, 32.4, 17.9; HRMS (ESI) *m/z* calcd for $C_{28}H_{39}O_2N_6$ $[M+H]^+$ 491.3129, found 491.3126.

***N*-(2-(4-Isopropylpiperazin-1-yl)ethyl)-1-(3-(5-methyl-1H-indol-2-yl)phenyl)piperidin-4-amine (24)**.

A solution of 3-bromoacetophenone (2.00 g, 10.0 mmol), p-toluidine (1.29 g, 12.1 mmol), and TsOH•H_2O (17 mg, 0.10 mmol) in toluene (50 mL) was heated overnight under Dean-Stark conditions. The reaction mixture was cooled to room temperature, concentrated, and purified by chromatography on SiO_2 (0 to 5% EtOAc/hexanes) to provide (*E*)-1-(3-bromophenyl)-*N*-(p-tolyl)ethan-1-imine as a yellow oil (1.10 g, 3.82 mmol, 38%) that was used without further purification.

A solution of (*E*)-1-(3-bromophenyl)-*N*-(p-tolyl)ethan-1-imine (0.246 g, 0.854 mmol), $Pd(OAc)_2$ (18 mg, 0.080 mmol), and $Cu(OAc)_2$•H_2O (514 mg, 2.57 mmol) in DMSO (3.0 mL) was heated at 90 °C for 5 h, cooled to room temperature, and diluted with EtOAc and H_2O. The layers were separated and the aqueous layer was back-extracted with EtOAc. The combined organic layers were dried ($NaSO_4$) and concentrated. The residue was absorbed onto SiO_2 and purified by chromatography on SiO_2 (ISCO-Rf, 0 to 20% EtOAc/hexanes) followed by trituration with Et_2O/hexanes (1/1) to give 2-(3-bromophenyl)-5-methyl-1*H*-indole (**30**, 0.156 g, 0.545 mmol, 64%) as an off white solid: Mp 189-190 °C; IR (ATR) 3428, 1575, 1450, 1420, 1215, 1077, 798, 767, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (bs, 1 H), 7.79 (t, *J* = 2.0 Hz, 1 H), 7.56 (d, *J* = 7.5 Hz, 1 H), 7.43-7.41 (m, 2 H), 7.31-7.27 (m, 2 H), 7.04 (dd, *J* = 1.0, 8.0 Hz, 1 H), 6.75 (d, *J* = 1.0 Hz, 1 H), 2.45 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 135.3, 134.6, 130.5, 130.3, 129.7, 129.3, 127.9, 124.5, 123.5, 123.1, 120.5, 110.6 (2C), 21.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}NBr$ $[M+H]^+$ 286.0226, found 286.0224.

A solution of 2-(3-bromophenyl)-5-methyl-1*H*-indole (**30**, 0.143 g, 0.501 mmol), LiHMDS (0.201 g, 1.20 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), and CyJohnPhos (14

mg, 0.040 mmol) in anhydrous THF was treated with *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(piperidin-4-yl)carbamate (**17**, 0.213 g, 0.601 mmol). The reaction mixture was heated at 75 °C overnight, cooled to room temperature, diluted with sat. $NaHCO_3$, and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), evaporated, and purified by chromatography on SiO_2 (2 to 7% MeOH/CH_2Cl_2) to provide *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-methyl-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (0.124 g, 0.222 mmol, 44%) as a foam: IR (ATR) 3303, 2963, 2930, 2809, 1685, 1663, 1599, 1465, 1450, 1174, 1146, 1010, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1 H), 7.39 (s, 1 H), 7.27-7.24 (m, 2 H), 7.20 (bs, 1 H), 7.13 (d, *J* = 7.2 Hz, 1 H), 6.99 (dd, *J* = 8.0, 0.8 Hz, 1 H), 6.82 (bd, *J* = 7.2 Hz, 1 H), 6.70 (s, 1 H), 4.10 (bs, 1 H), 3.70 (m, 2 H), 3.23 (bs, 2 H), 2.68-2.44 (m, 16 H), 1.72 (bs, 4 H), 1.51 (s, 9 H), 1.04 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 151.7, 138.6, 135.2, 133.5, 129.6, 129.5, 129.1, 123.6, 120.1, 116.7, 116.0, 113.6, 110.6, 99.2, 79.9, 54.5, 53.8, 49.6, 49.5, 48.6, 39.8, 30.0, 28.5, 21.5, 18.5; HRMS (ESI) *m/z* calcd for $C_{34}H_{50}O_2N_5$ $[M+H]^+$ 560.3959, found 560.3932.

A solution of TFA (2.35 g, 20.4 mmol) in CH_2Cl_2 (1 mL) was added to a solution of *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-methyl-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (0.114 g, 0.204 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred under an atmosphere of N_2 at room temperature for 1 h, concentrated, diluted with sat. $NaHCO_3$, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (7 to 9% MeOH/CH_2Cl_2 with 0.1% TEA) followed by filtration on basic Al_2O_3 (CH_2Cl_2/MeOH, 100:0 to 100:10) to provide *N*-(2-(4-isopropylpiperazin-1-yl)ethyl)-1-(3-(5-methyl-1H-indol-2-yl)phenyl)piperidin-4-amine (**24**, 68 mg, 0.15 mmol, 73%) as a yellow foam: IR (ATR) 2930, 2924, 2811, 1599, 1457, 1448, 1379, 1344, 1189, 1176, 1144, 1117, 982, 775, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1 H), 7.39 (d, *J* = 0.7 Hz, 1 H), 7.30-7.26 (m, 2 H), 7.21 (t, *J* = 1.9 Hz, 1 H), 7.10 (ddd, *J* = 7.6, 1.4, 0.8 Hz, 1 H), 7.01-6.98 (ddd, *J* = 8.0, 1.6, 0.4 Hz, 1 H), 6.88 (dd, *J* = 8.0, 2.1 Hz, 1 H), 6.70 (dd, *J* = 2.1, 0.8 Hz, 1 H), 3.73 (app d, *J* = 12.6 Hz, 2 H), 2.86-2.76 (m, 4 H), 2.68-2.48 (m, 12 H), 2.44

(s, 3 H), 2.00 (dd, *J* = 12.6, 2.2 Hz, 2 H), 1.53 (dq, *J* = 11.5, 3.0 Hz, 2 H), 1.05 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 138.8, 135.2, 133.5, 129.7, 129.6, 129.3, 123.8, 120.3, 116.4, 115.9, 113.5, 110.6, 99.4, 58.1, 55.2, 54.6, 53.6, 48.8, 48.7, 43.5, 32.7, 21.6, 18.8; HRMS (ESI) *m/z* calcd for $C_{29}H_{42}N_5$ $[M+H]^+$ 460.3435, found 460.3434.

N-(2-(4-Isopropylpiperazin-1-yl)ethyl)-1-(3-(5-methoxy-1H-indol-2-yl)phenyl)piperidin-4-amine (25).

A solution of 3-bromoiodobenzene (**32**, 0.283 g, 1.00 mmol), 5-methoxyindole (**31**, 0.147 g, 1.00 mmol), $Pd(OAc)_2$ (12 mg, 0.050 mmol), bis(diphenylphosphino)methane (20 mg, 0.05 mmol), and KOAc (0.297 g, 3.00 mmol) in deoxygenated water (2 mL) was heated at 110 °C for 24 h, cooled to room temperature, diluted with ethyl acetate (10 mL) and 1 N HCl (5 mL), and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and purified by chromatography on SiO_2 (10% EtOAc/hexanes) followed by recrystallization from hexanes and CH_2Cl_2 to give 2-(3-bromophenyl)-5-methoxy-1*H*-indole (**33**, 0.133 g, 0.440 mmol, 44%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (bs, 1 H), 7.77 (s, 1 H), 7.55 (app d, *J* = 7.7 Hz, 1 H), 7.43 (app d, *J* = 8.1 Hz, 1 H), 7.30 (m, 2 H), 7.08 (d, *J* = 2.3 Hz, 1 H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.76 (d, *J* = 1.5 Hz, 1 H), 3.87 (s, 3 H); HRMS (ESI) *m/z* calcd for $C_{15}H_{13}ONBr$ $[M+H]^+$ 302.0175, found 302.0174.

A solution of **33** (76 mg, 0.25 mmol), K_3PO_4 (82 mg, 0.38 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol), CyJohnPhos (7 mg, 0.02 mmol) in anhydrous and deoxygenated dioxane (1 mL) in a 2-5 mL conical sealed vessel was degassed by bubbling argon for 5 min. The reaction mixture was treated with *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(piperidin-4-yl)carbamate (**17**, 0.106 g, 0.300 mmol) in dry dioxane (1.5 mL) and degassed for 15 min. The vessel was sealed and heated at 110 °C for 11 h in a Biotage Initiator microwave reactor, cooled to room temperature, diluted with sat. $NaHCO_3$, and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), evaporated, and purified by chromatography on SiO_2 (2% MeOH/CH_2Cl_2 and 0.1% TEA) followed by

chromatography on basic Al_2O_3 (CH_2Cl_2) to give *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-methoxy-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (46 mg, 0.080 mmol, 32%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1 H), 7.28-7.25 (m, 2 H), 7.18 (br s, 1 H), 7.12 (d, *J* = 7.6 Hz, 1 H), 7.07 (d, *J* = 2.2 Hz, 1 H), 6.85-6.81 (m,, 2 H), 6.71 (d, *J* = 1.2 Hz, 1 H), 4.11 (br s, 1 H), 3.85 (s, 3 H), 3.74-3.72 (m, 2 H), 3.29-3.19 (m, 2 H), 2.71-2.45 (m, 13 H), 1.76-1.72 (m, 3 H), 1.48 (s, 9 H), 1.05 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 154.4, 151.8, 139.3, 133.5, 132.1, 129.7, 116.7, 116.1, 113.6, 112.4, 111.8, 102.2, 99.6, 80.0, 55.9, 49.6, 48.6, 30.11, 30.09, 28.6, 18.6.

A solution of TFA (0.599 mL, 7.99 mmol) and triethylsilane (0.129 mL, 0.799 mmol) in CH_2Cl_2 (1 mL) was added to a solution of *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-methoxy-1H-indol-2-yl)phenyl)piperidin-4-yl)carbamate (46 mg, 0.080 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred under an atmosphere of N_2 at room temperature for 2 h, evaporated, diluted with sat. $NaHCO_3$, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), evaporated, and purified by chromatography on SiO_2 (7 to 9% MeOH/CH_2Cl_2 with 0.1% TEA) followed by chromatography on basic Al_2O_3 (0 to 9% MeOH/CH_2Cl_2) to give *N*-(2-(4-isopropylpiperazin-1-yl)ethyl)-1-(3-(5-methoxy-1*H*-indol-2-yl)phenyl)piperidin-4-amine (**25**, 20 mg, 0.041 mmol, 51%) as a yellow oil: IR (ATR) 3221, 2924, 2818, 1577, 1452, 1881, 1381, 1204, 1176, 1146, 1114, 839, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (bs, 1 H), 7.29 (m, 2 H), 7.21 (app t, *J* = 1.9 Hz, 1 H), 7.11 (app d, *J* = 7.8 Hz, 1 H), 7.07 (d, *J* = 2.3 Hz, 1 H), 6.87 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.83 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.71 (app d, *J* = 1.0 Hz, 1 H), 4.01 (bs, 2 H), 3.85 (s, 3 H), 3.72 (app d, *J* = 12.6 Hz, 2 H), 2.84-2.51 (m, 16 H), 2.00 (m, 3 H), 1.56 (qd, *J* = 11.6, 3.0 Hz, 2 H), 1.06 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 152.0, 139.5, 133.5, 132.2, 129.8, 116.6, 116.0, 113.5, 112.4, 111.8, 102.3, 99.7, 57.4, 56.0, 55.0, 54.7, 53.1, 48.67, 48.54, 43.0, 32.1, 18.5; HRMS (ESI) *m/z* calcd for $C_{29}H_{42}ON_5$ $[M+H]^+$ 476.3384, found 476.3383.

N-(2-(4-Isopropylpiperazin-1-yl)ethyl)-1-(3-(5-(trifluoromethoxy)-1H-indol-2-yl)phenyl)piperidin-4-amine (26).

A solution of 3-bromoacetophenone (**15**, 1.00 g, 5.02 mmol), 4-(trifluoromethoxy)aniline (1.07 g, 6.04 mmol), and TsOH•H_2O (8.7 mg, 0.046 mmol) in toluene (50 mL) was heated under Dean-Stark conditions overnight. The reaction mixture was cooled to room temperature, concentrated, and purified by chromatography on SiO_2 (0 to 5% EtOAc/hexanes) to give (*E*)-1-(3-bromophenyl)-N-(4-(trifluoromethoxy)phenyl)ethan-1-imine as a yellow oil (0.91 g, 2.5 mmol, 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1 H), 7.88-7.86 (m, 1 H), 7.62-7.59 (m, 1 H), 7.32 (td, *J* = 7.6, 0.4 Hz, 1 H), 7.21 (app d, *J* = 8.8 Hz, 2 H), 6.81-6.77 (m, 2 H), 2.22 (s, 3 H).

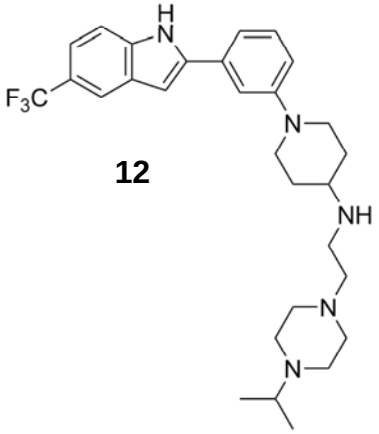
A solution of (*E*)-1-(3-bromophenyl)-N-(4-(trifluoromethoxy)phenyl)ethan-1-imine (75 mg, 0.21 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), and TBAB (0.13 g, 0.40 mmol) in DMSO (1 mL) in a Schlenk tube was purged, filled with oxygen and heated at 60 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (5 mL), and filtered through SiO_2. The filtrate was washed with 1 M $NaHSO_3$, concentrated and purified by chromatography on SiO_2 (30% CH_2Cl_2/hexanes) to give 2-(3-bromophenyl)-5-(trifluoromethoxy)-1*H*-indole (**35**, 62 mg, 0.17 mmol, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (bs, 1 H), 7.78 (s, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.48-7.46 (m, 2 H), 7.35 (d, *J* = 8.8 Hz, 1 H), 7.31 (app t, *J* = 8.0 Hz, 1 H), 7.09 (d, *J* = 8.8 Hz, 1 H), 6.81 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 138.2, 135.3, 134.0, 131.1, 130.7, 129.3, 128.3, 123.9, 123.4, 120.9 (q, J_{CF} = 255.3 Hz), 116.9, 113.3, 111.7, 101.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{10}ONBrF_3$ $[M+H]^+$ 355.9892, found 355.9891.

A solution of **35** (89.1 mg, 0.250 mmol), K_3PO_4 (82 mg, 0.39 mmol), $Pd_2(dba)_3$ (4.70 mg, 0.005 mmol), and CyJohnPhos (7.20 mg, 0.020 mmol) in anhydrous and deoxygenated dioxane (1 mL) in a 2-5 mL conical sealed vial was degassed by bubbling argon for 5 min. The reaction mixture was treated with a solution of *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(piperidin-4-yl)carbamate (**17**, 0.106 g, 0.299 mmol) in dry dioxane (1.5 mL) and degassed for 15 min. The vial was sealed and heated at 110 °C for 11 h in a Biotage Initiator microwave reactor, cooled to room temperature, diluted with sat. $NaHCO_3$, and extracted with CH_2Cl_2 (3x). The organic layers were combined, washed with brine, dried (Na_2SO_4), evaporated, and purified by chromatography on SiO_2 (2% MeOH/CH_2Cl_2 with 0.1% TEA) followed by

chromatography on basic Al_2O_3 (CH_2Cl_2) to give *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-(trifluoromethoxy)-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (46 mg, 0.073 mmol, 29%) as a light yellow oil: IR (ATR) 3266, 2969, 2961, 2952, 2933, 2928, 2818, 2810, 1681, 1664, 1601, 1478, 1465, 1450, 1413, 1383, 1366, 1346, 1329, 1301, 1253, 1217, 1152, 1010, 1003, 995, 973, 895, 867 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 10.47 (s, 1 H), 6.97-6.93 (m, 3 H), 6.80-6.76 (m, 2 H), 6.52 (d, *J* = 8.8 Hz, 1 H), 6.45-6.43 (m, 2 H), 3.40 (d, *J* = 12.0 Hz, 2 H), 2.72 (bs, 2 H), 2.48 (bs, 2 H), 2.29 (app t, *J* = 11.6 Hz, 2 H), 1.93-1.89 (m, 9 H), 1.52 (app s, 1 H), 1.42 (bs, 2 H), 1.24 (bs, 2 H), 0.93 (s, 9 H), 0.43 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 155.6, 152.8, 143.7, 141.9, 136.6, 133.6, 130.5, 130.3, 129.1, 128.4, 121.8 (q, J_{CF} = 253.2 Hz), 117.0, 116.7, 116.0, 113.8, 113.1, 112.8, 100.1, 79.5, 54.9, 54.8, 50.0, 49.3, 28.7, 18.7; HRMS [ESI] *m/z* calcd for $C_{34}H_{47}O_3N_5F_3$ $[M+H]^+$ 630.3626, found 630.3628.

A solution of TFA (0.50 mL) and triethylsilane (0.10 mL, 0.64 mmol) in CH_2Cl_2 (1 mL) was added to a solution of *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(1-(3-(5-(trifluoromethoxy)-1*H*-indol-2-yl)phenyl)piperidin-4-yl)carbamate (40 mg, 0.064 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred under an atmosphere of N_2 at room temperature for 1 h, concentrated, diluted with sat. $NaHCO_3$, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (7 to 9% MeOH/CH_2Cl_2 with 0.1% TEA) followed by chromatography on basic Al_2O_3 (0 to 9% MeOH/CH_2Cl_2) to give *N*-(2-(4-isopropylpiperazin-1-yl)ethyl)-1-(3-(5-(trifluoromethoxy)-1*H*-indol-2-yl)phenyl)piperidin-4-amine (**26**, 15 mg, 0.028 mmol, 45%) as a light yellow foam: IR (ATR) 2975, 2818, 1670, 1458, 1254, 1199, 1174, 1130, 829, 800, 783, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1 H), 7.45 (d, *J* = 1.2 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 1 H), 7.30 (app t, *J* = 7.6 Hz, 1 H), 7.24 (app t, *J* = 1.6 Hz, 1 H), 7.14-7.11 (m, 1 H), 7.03 (ddd, *J* = 8.8, 2.4, 0.8 Hz, 1 H), 6.90 (ddd, *J* = 8.4, 2.4, 0.8 Hz, 1 H), 6.77 (app d, *J* = 1.2 Hz, 1 H), 3.74 (app d, *J* = 12.8 Hz, 2 H), 2.86-2.52 (m, 16 H), 2.01 (dd, *J* = 12.7, 2.3 Hz, 2 H), 1.59 (qd, *J* = 12.8, 4.0 Hz, 2 H), 1.08 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 143.4, 140.7, 135.2, 133.0, 129.9, 129.5, 121.0 (q, J_{CF} = 255.2 Hz), 116.7, 116.4, 116.1, 113.7, 112.9, 111.6, 100.1, 57.1,

55.2, 55.0, 52.9, 48.5, 43.0, 31.9, 18.4; HRMS [ESI] *m/z* calcd for $C_{29}H_{39}ON_5F_3$ $[M+H]^+$ 530.3101, found 530.3100.



12

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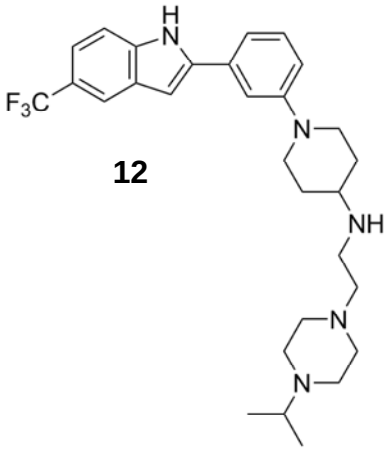
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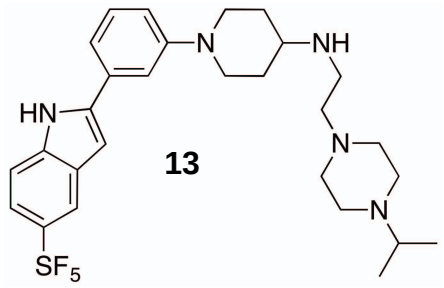

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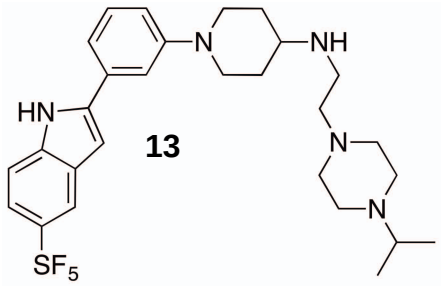
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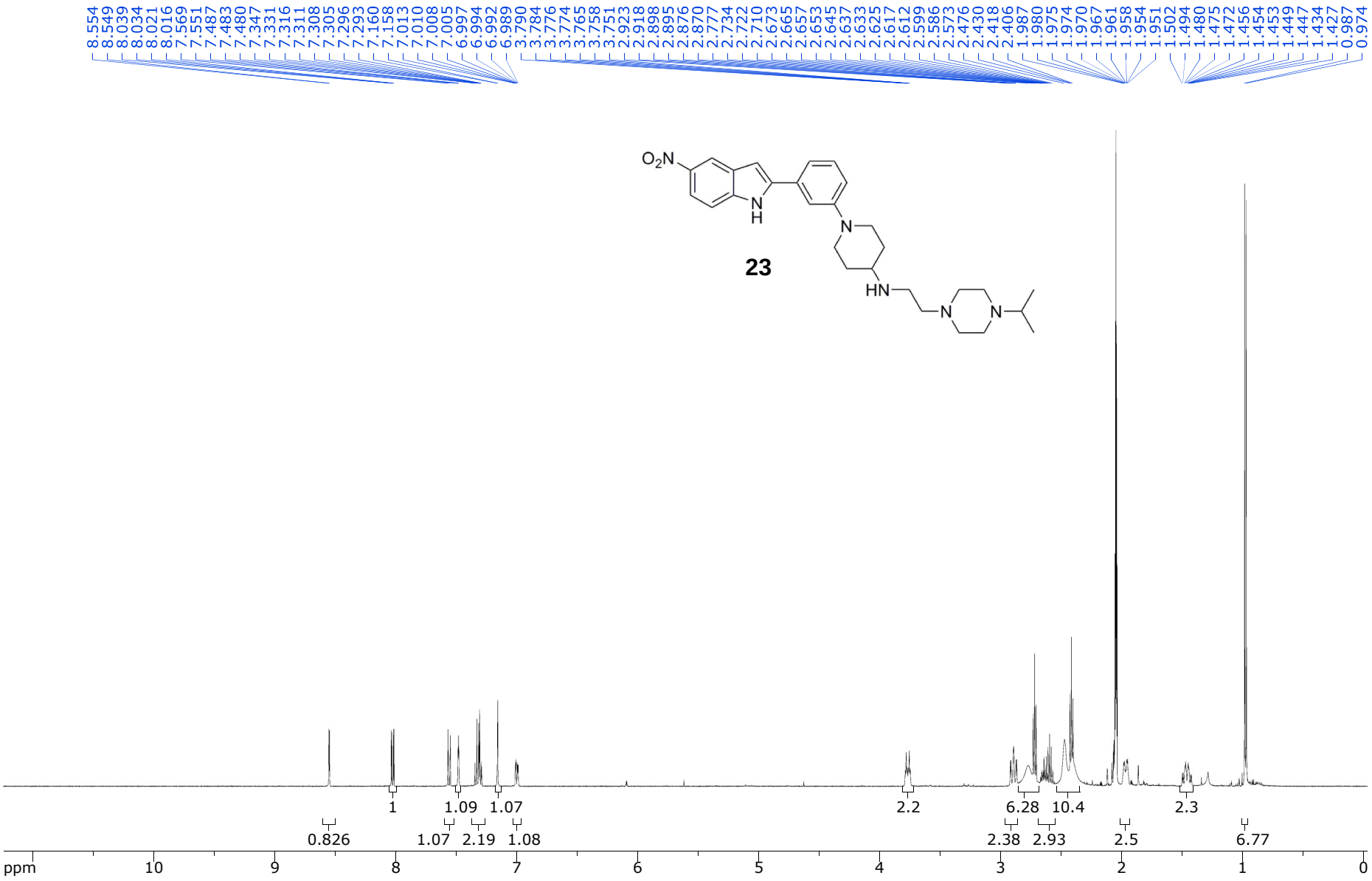
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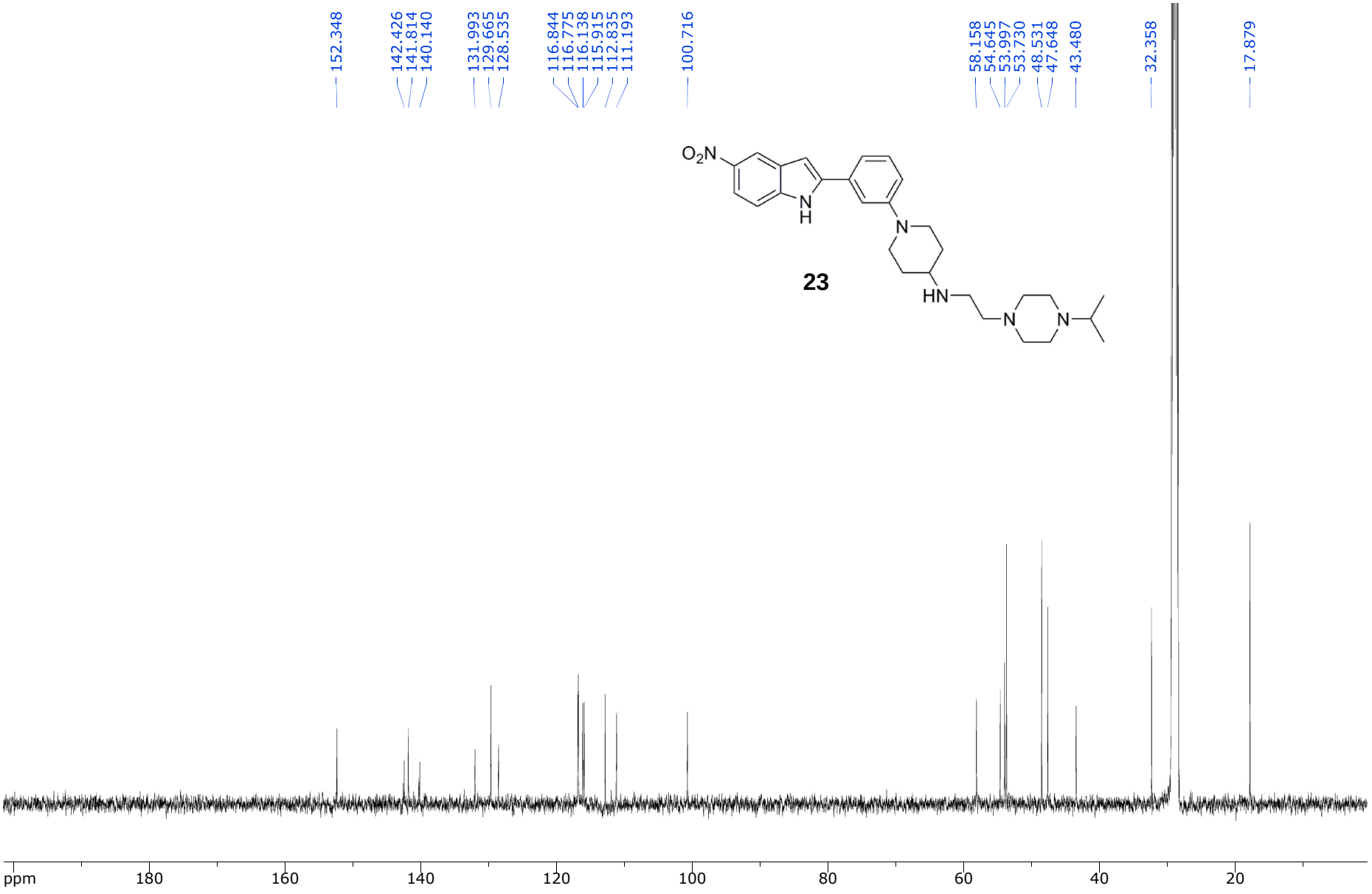
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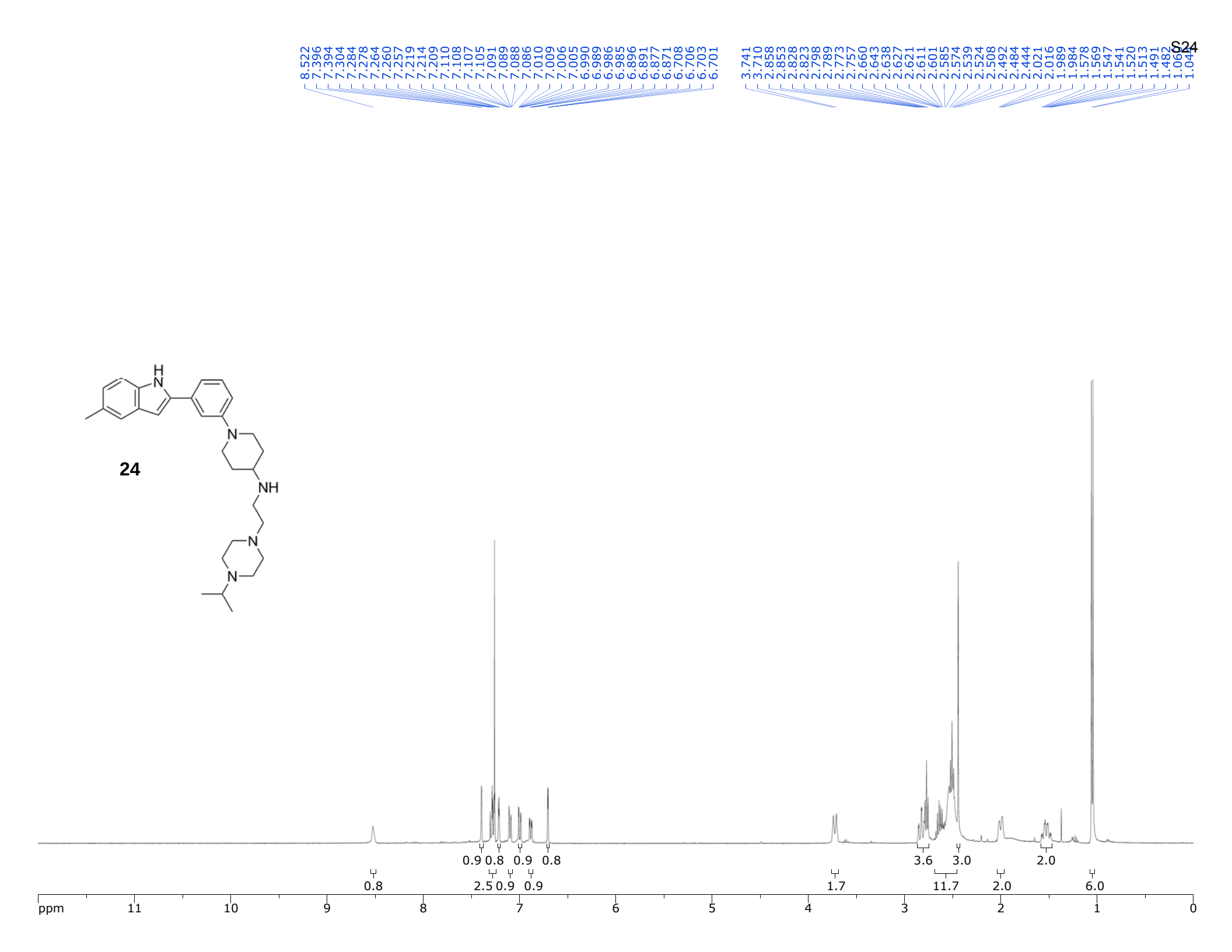
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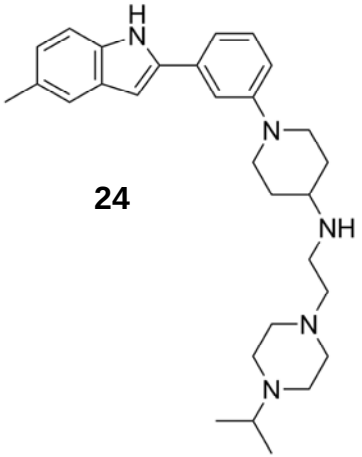

24

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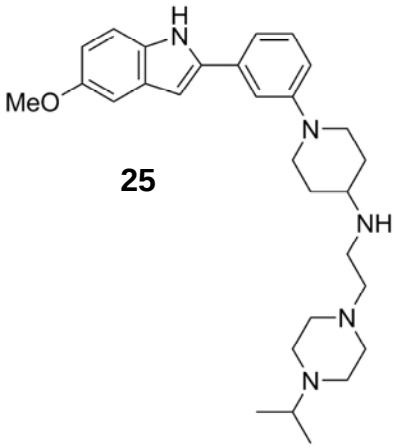
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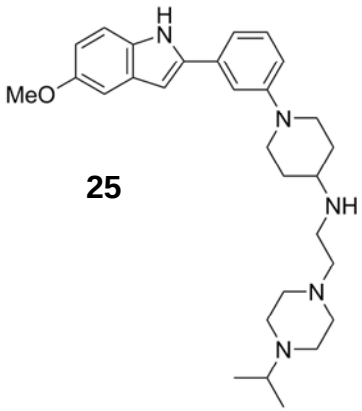

25

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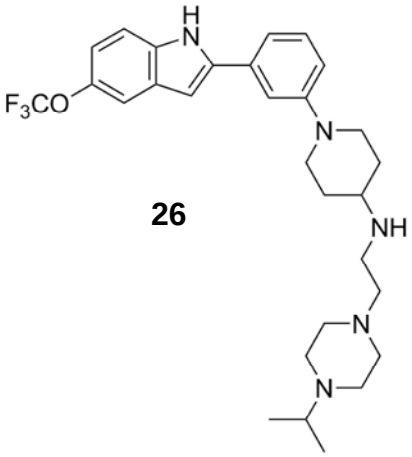
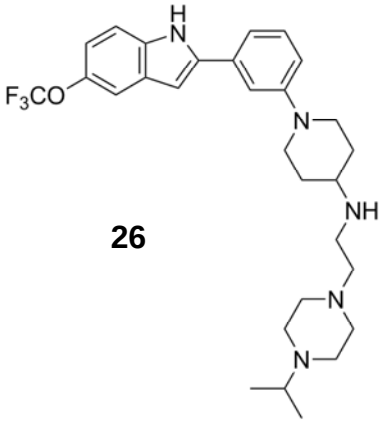


26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26

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