SUPPORTING INFORMATION

Discovery of Potent and Orally Bioavailable Small Molecule Antagonists of Toll-like Receptors 7/8/9 (TLR7/8/9)

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EXPERIMENTAL SECTION

Chemical Methods. All commercially available chemicals and solvents were used without further purification. Reactions were performed under an atmosphere of nitrogen. All flash column chromatography was performed on EM Science silica gel 60 (particle size of 40 – 60 μm). All new compounds gave satisfactory ^{1}H NMR, LCMS, and mass spectrometry results. ^{1}H NMR spectra were obtained on a Bruker 400 MHz or a JEOL 500 MHz NMR spectrometer using the residual signal of deuterated NMR solvent as internal reference. Electrospray ionization (ESI) mass spectra were obtained on a Waters ZQ single quadrupole mass spectrometer. High-resolution mass spectral analysis was performed on an LTQ-FT mass spectrometer interfaced to a Waters Acquity ultraperformance liquid chromatography.

HPLC analyses were performed using the following conditions. All final compounds had an HPLC purity of ≥95% unless otherwise stated.

Analytical and Preparative HPLC conditions

Method A: (analytical) Waters Acquity UPLC, BEH C18 2.1 mm × 50 mm, 1.7 μm particles. Mobile phase A: 98:2 water:ACN with 0.05%TFA. Mobile phase B: acetonitrile with 0.05% TFA. Temperature: 50 °C; Gradient 2 − 98%B over 1 minute, then 0.5 min hold at 100%B. Flow 0.8 mL/min. Detection: UV 220 nm.

Method B: (analytical) Waters Acquity UPLC, BEH C18 2.1 mm × 50 mm, 1.7 μm particles. Mobile phase A: water:ACN with 0.05%TFA. Mobile phase B: acetonitrile 98-2% with 0.05% TFA. Temperature: 50 °C; Gradient 2% - 98%B (0 to 1 minute) 98%B (to 1.5 minute) 98% - 2% B (to 1.5 minute); Gradient Time: 1.8 min; Flow Rate: 0.8 mL/min; Detection: UV at 220 nm.

Method C: (analytical) Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate. Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

Method D: (analytical) Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

Method E: (analytical): Column: Waters Xbridge C18 4.6 x 50 mm 5 um particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate. Temperature: 50 °C; Gradient: 0-100% over 1 minute; Flow: 4 mL/min; Detection: UV at 220 nm.

Method F: (analytical): Column: 50 x 2.1mm, 2.7µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10 mM NH_4OAc; Mobile Phase B: 95:5 acetonitrile: water with 10 mM NH_4OAc; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes; Flow: 1.1ml/min; Detection: UV at 220 nm.

Method G: (preparative): Column: 19 x 150mm, 5µm particles; Mobile Phase A: 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; Mobile Phase B: 95: 5 acetonitrile: water with 0.1% trifluoroacetic acid; Temperature: 50 °C; Gradient: 10 - 45% B over 25 minutes, then a 10

minute hold at 45% B and 5 minute hold at 100% B; Flow: 15mL/min; Detection: UV at 220 nm.

Method H: (preparative): Column: 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile: water with 0.1% trifluoroacetic acid; Temperature: 25 °C; Gradient:5–100% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min; Detection: UV at 220 nm.

Method I: (preparative): Column: XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Temperature: 25 °C; Gradient: a 0-minute hold at 16% B, 16-56% B over 20 minutes, then a 4-minute hold at 100% B; Flow Rate: 20 mL/min; Detection: UV at 220 nm.

Method J: (preparative): Column: Waters XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% ammonium hydroxide; Mobile Phase B: 95:5 acetonitrile:water with 0.1% ammonium hydroxide; Temperature: 25 °C; Gradient: 15-100% B over 25 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min; Detection: UV at 220 nm.

5-Bromo-3-methyl-1H-indole (**9a**): A solution of 5-bromo-1H-indole-3-carbaldehyde (13.1 g, 58.6 mmol) in THF (100 mL) was added to a refluxing mixture of $LiAlH_4$ (4.9 g, 129 mmol) in THF (100 mL) (reflux condenser fitted to a two neck flask) over 30 min. The reaction mixture was refluxed for 8 hours, cooled to room temperature and treated with diethyl ether (~50 mL). The reaction mixture was acidified to ~pH 3 with 1N HCl, while cooling in an ice bath. The reaction mixture was diluted with ethyl acetate (125 mL), poured into a separatory funnel and washed with water (2 X 50 mL) and saturated aqueous sodium chloride solution (50 mL), dried

over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give crude product. The crude product was purified by silica gel chromatography to afford 5-bromo-3-methyl-1H-indole (5.5 g, 44% yield) as a brownish oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 - 10.73 (m, 1H), 7.64 (d, *J*=2.0 Hz, 1H), 7.29 (d, *J*=8.6 Hz, 1H), 7.20 - 7.12 (m, 2H), 2.22 (d, *J*=0.9 Hz, 3H). MS $(M+H)^+$ at *m/z* 210/212 HPLC tr 1.0 min (Method A).

tert-*Butyl 4-(3-methyl-1H-indol-5-yl)piperidine-1-carboxylate* (**10a**): Step 1. To a mixture of 5-bromo-3-methyl-1H-indole (0.42 g, 2.0 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.041 g, 0.050 mmol), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.67 g, 2.2 mmol) in a 40 mL reaction vial was added THF (10 mL) followed by a 3M aqueous solution of tripotassium phosphate (2 mL, 5.9 mmol). The vial was fitted with a Teflon-lined septum cap. The system was evacuated under vacuum (via a needle from a nitrogen/vacuum manifold line) and back-filled with nitrogen gas. The procedure was repeated three times. The needle was removed and the vial was heated at 75 °C for 18 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (125 mL). The mixture was poured into a separatory funnel and washed with water (2 X 50 mL) and saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give crude product. The crude product was purified by silica gel chromatography to afford *tert*-butyl 4-(3-methyl-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.51 g, 82 % yield) as a tan oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.02 - 7.92 (m, 1H), 7.59 (s, 1H), 7.34 (br d, *J*=0.7 Hz, 1H), 7.32 (d, *J*=0.7 Hz, 1H), 7.00 (dd, *J*=2.2, 1.1 Hz, 1H), 6.05 (br s, 1H), 4.20 - 4.08 (m, 2H), 3.71 (t, *J*=5.7 Hz, 2H), 2.67 (br d, *J*=1.1 Hz, 2H), 2.37 (d, *J*=1.1 Hz, 3H), 1.55 (s, 9H). MS $(M+H)^+$ at *m/z* 313 HPLC tr 1.10 min (Method A). Step 2. In a 250 mL round bottom flask was added *tert*-butyl 4-(3-methyl-1H-

indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.3 g, 4.2 mmol) and ethyl acetate (20 mL). The flask was purged with nitrogen gas and Pd/C (0.33 g, 0.31 mmol) was added. Following pump/purging with nitrogen gas three times, hydrogen gas was introduced via a balloon. The reaction mixture was stirred at room temperature overnight. The flask was evacuated and filled with nitrogen gas. The suspension was filtered through fluted filter paper and the filtrate was concentrated in vacuo. Collected *tert*-butyl 4-(3-methyl-1H-indol-5-yl)piperidine-1-carboxylate (1.1 g, 88% yield) as an off-white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.93 - 7.81 (m, 1H), 7.43 (d, *J*=0.9 Hz, 1H), 7.32 (d, *J*=8.4 Hz, 1H), 7.08 (dd, *J*=8.4, 1.8 Hz, 1H), 6.99 (dd, *J*=2.0, 1.1 Hz, 1H), 4.41 - 4.20 (m, 2H), 2.98 - 2.70 (m, 3H), 2.36 (d, *J*=0.9 Hz, 3H), 1.92 (br d, *J*=13.4 Hz, 2H), 1.75 (br dd, *J*=12.8, 4.2 Hz, 2H), 1.57 - 1.48 (m, 9H). MS $(M+H)^+$ at *m/z* 315 HPLC tr 1.15 min (Method A).

tert-*Butyl 4-(2-bromo-3-methyl-1H-indol-5-yl)piperidine-1-carboxylate* (**11a**): In a 100 mL round bottom flask was added *tert*-butyl 4-(3-methyl-1H-indol-5-yl) piperidine-1-carboxylate (1.1 g, 3.5 mmol) and DCE (20 mL). NBS (0.56 g, 3.1 mmol) was dissolved in 15 mL of DCE and added to the reaction dropwise, via an addition funnel over a 15 minute period. Following this addition, the reaction mixture was stirred at room temperature for 15 minutes, then quenched with a 10% aqueous sodium sulfite solution (1.0 mL). The mixture was diluted with DCM (100 mL), poured into a separatory funnel and washed with water (2 X 50 mL) and then, saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give crude product. The crude product was purified by silica gel chromatography to afford *tert*-butyl 4-(2-bromo-3-methyl-1H-indol-5-yl)piperidine-1-carboxylate (1.1 g, 76% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.33 (d, *J*=0.9 Hz, 1H), 7.24 (d, *J*=8.4 Hz, 1H), 7.06 (dd, *J*=8.4, 1.8 Hz, 1H), 4.42 - 4.18 (m, 2H), 2.98

- 2.64 (m, 3H), 2.28 (s, 3H), 2.00 - 1.84 (m, 2H), 1.82 - 1.64 (m, 2H), 1.53 (s, 9H). Indole NH not observed. MS $(M+H)^+$ at *m/z* 337/339 HPLC tr 1.16 min (Method A).

2-(3,4-Dimethoxyphenyl)-3-methyl-5-(piperidin-4-yl)-1H-indole hydrochloride (**6a**): Step 1. In a 40 mL reaction vial, tert-butyl 4-(2-bromo-3-methyl-1H-indol-5-yl)piperidine-1-carboxylate (1.1 g, 2.9 mmol) was taken in THF (10 mL) and (3,4-dimethoxyphenyl) boronic acid (0.59 g, 3.2 mmol, $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.16 g, 0.19 mmol), and a 3M dipotassium phosphate solution (2.9 mL, 8.8 mmol) were added and the mixture was sealed with a Teflon-lined cap and pump/purged with nitrogen gas three times. The reaction mixture was set to heat at 65 °C for 1 hour. The mixture was cooled to room temperature, diluted with EtOAc (100 mL), poured into a separatory funnel and washed with water (2 X 50 mL) and saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to give crude product. The crude product was purified by silica gel chromatography to afford *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidine-1-carboxylate (1.0 g, 75% yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.36 - 7.27 (m, 2H), 7.18 - 7.06 (m, 3H), 7.04 - 6.98 (m, 1H), 4.39 - 4.23 (m, 2H), 4.16 (d, *J*=7.3 Hz, 1H), 4.02 - 3.93 (m, 6H), 2.96 - 2.72 (m, 3H), 2.47 (s, 3H), 2.00 - 1.87 (m, 2H), 1.54 (s, 9H), 1.30 (s, 1H). Indole NH not observed. MS $(M+H)^+$ at *m/z* 451 HPLC tr 1.16 min (Method A). Step 2. In a 40 mL reaction vial was added *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidine-1-carboxylate (1.2 g, 2.7 mmol) followed by DCM (5 mL) and 4M HCl/dioxane (1.7 mL, 6.9 mmol). The reaction mixture was stirred at 25 °C for 60 minutes, then concentrated to dryness under a stream of nitrogen gas to give 2-(3,4-dimethoxyphenyl)-3-methyl-5-(piperidin-4-yl)-1H-indole, HCl (0.97 g, 91% yield). Further purification (10 mg) was performed using preparative LCMS (Method I) to afford 2-(3,4-dimethoxyphenyl)-3-methyl-5-

(piperidin-4-yl)-1H-indole (0.0057 g, 57% yield, purity = 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 - 10.92 (m, 1H), 7.96 (s, 1H), 7.34 - 7.27 (m, 2H), 7.24 - 7.15 (m, 2H), 7.09 (d, *J*=8.1 Hz, 1H), 3.99 - 3.78 (m, 7H), 2.90 (s, 3H), 2.74 (s, 2H), 2.40 (s, 3H), 1.94 (br s, 2H), 1.89 - 1.76 (m, 2H). MS $(M+H)^+$ at *m/z* 351 HPLC tr 0.71 min (Method A). HPLC tr 1.18 minutes (Method C).

2-(4-(2-(3,4-Dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5n**): In a 2 dram vial was added *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidine-1-carboxylate (0.27 g, 0.61 mmol), DCM (5 mL), TEA (0.42 mL, 3.0 mmol) and acetic acid (0.04 mL, 0.61 mmol). The mixture was stirred for 1 hour at 25 °C and then sodium triacetoxyborohydride (0.39 g, 1.8 mmol) was added. The reaction was set to stir at 25 °C overnight. The reaction was diluted with DCM and water and the layers were separated. The organic was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography to give a clear oil. This was treated with HCl in dioxane (0.019 mL, 0.61 mmol) in DCM (0.5 mL). The reaction was stirred at 25 °C for 30 minutes, then concentrated to afford 2-(4-(2-(3,4-dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (0.28 g, 97 % yield) as an oil. ^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.44 - 7.36 (m, 1H), 7.31 (d, *J*=8.4 Hz, 1H), 7.24 - 7.17 (m, 2H), 7.10 - 7.00 (m, 2H), 3.90 (d, *J*=12.3 Hz, 6H), 3.76 (br d, *J*=11.7 Hz, 2H), 3.57 (s, 4H), 3.28 - 3.16 (m, 2H), 3.06 - 2.91 (m, 1H), 2.84 (s, 3H), 2.43 (s, 3H), 2.24 - 2.14 (m, 4H). NH protons not observed. HPLC tr 1.36 minutes (Method C). MS $(M+H)^+$ at *m/z* 408; HPLC tr 1.05 minutes (Method D).

tert-*Butyl (2-(4-(2-bromo-3-methyl-1H-indol-5-yl)piperidin-1-yl) ethyl)(methyl)carbamate* (**13a**): In a 2 dram vial was added isopropyl 4-(2-bromo-3-methyl-1H-indol-5-yl)piperidine-1-carboxylate (0.11 g, 0.28 mmol) and DCM (2 mL). The reaction was placed under a nitrogen

atmosphere, cooled to 0 °C and hydrobromic acid in acetic acid (0.070 mL, 0.42 mmol) was added dropwise, via syringe. The reaction was stirred at 0 °C for 15 minutes and was quenched with TEA (0.19 mL, 1.38 mmol). To this was added *tert*-butyl methyl(2-oxoethyl)carbamate (0.053 g, 0.31 mmol) in DCM (1 mL). The reaction was stirred at 25 °C for 15 minutes and sodium triacetoxyborohydride (0.17 g, 0.83 mmol) was added and stirring was continued for an additional 1 hour. The mixture was diluted with water and DCM and the layers were separated. The organics were washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, were and concentrated to dryness. The residue was further purified by silica gel chromatography to afford 2-(4-(2-bromo-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.10 g, 85% yield) as a yellowish solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 - 11.28 (m, 1H), 7.27 (s, 1H), 7.18 (br d, *J*=8.4 Hz, 1H), 7.00 - 6.93 (m, 1H), 3.30 (s, 3H), 3.17 - 2.89 (m, 2H), 2.81 (br s, 3H), 2.18 - 2.11 (m, 2H), 1.90 (s, 2H), 1.74 (br s, 3H), 1.41 (s, 13H). MS $(M+H)^+$ at *m/z* 452 HPLC tr 0.84 min (Method B).

2-(4-(2-(4-Methoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (**5g**): In a 2 dram vial was added *tert*-butyl (2-(4-(2-bromo-3-methyl-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate (0.018 g, 0.040 mmol), (4-methoxyphenyl)boronic acid (6 mg, 0.040 mmol), $PdCl_2$(dppf)-CH_2Cl_2Adduct (0.033 g, 0.040 mmol). To this was added THF (1 mL) and a tribasic potassium phosphate solution (0.040 mL, 0.12 mmol). The mixture was capped and pump/purged with nitrogen gas three times and was set to heat at 70 °C for 14 hour. Upon cooling to 25 °C, the mixture was concentrated and the crude residue was diluted with DCM (0.5 mL) and to this was added TFA (0.1 mL). The reaction was stirred at 25 °C for 30 minutes, then concentrated to dryness under a stream of nitrogen gas. The residue was diluted with 1 mL of DMSO. The solids were filtered off and the crude material was purified via preparative LCMS

(Method H) to afford 2-(4-(2-(4-methoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (0.0048 g, 29% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.07 - 10.94 (m, 1H), 9.21 - 8.72 (m, 1H), 7.95 (s, 1H), 7.58 (br d, *J*=8.5 Hz, 2H), 7.38 - 7.23 (m, 2H), 7.15 - 6.91 (m, 3H), 3.81 (s, 3H), 3.62 (br s, 3H), 3.17 (s, 2H), 2.88 (s, 3H), 2.73 (s, 2H), 2.66 (s, 3H), 2.36 (s, 3H), 2.02 (br d, *J*=18.9 Hz, 4H). HPLC tr 1.50 minutes (Method C). MS $(M+H)^+$ at *m/z* 378; HPLC tr 1.13 minutes (Method D).

5-bromo-3-ethyl-1H-indole (**9b**): 5-bromo-1H-indole (2.8 g, 14.2 mmol), Shvo's Catalyst (0.15 g, 0.14 mmol), potassium carbonate (0.1 g, 0.71 mmol) and diethylamine (2.1 g, 28.6 mmol) were added to a 30 mL pressure tube. The reaction mixture was purged with nitrogen and heated to 155 °C for 20 hours. The reaction mixture was diluted with dichloromethane and washed with 1N HCl. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified using silica gel chromatography to afford 5-bromo-3-ethyl-1H-indole (2.1 g, 65% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 - 10.82 (m, 1H), 7.65 (d, *J*=2.0 Hz, 1H), 7.30 (d, *J*=8.6 Hz, 1H), 7.23 - 7.09 (m, 2H), 2.74 - 2.58 (m, 2H), 1.24 (t, *J*=7.5 Hz, 3H). MS $(M+H)^+$ at *m/z* 224/226 HPLC tr 1.06 min (Method A).

tert-*Butyl 4-(3-ethyl-1H-indol-5-yl)piperidine-1-carboxylate* (**10b**): Step 1. THF (35 mL) was added to a mixture of 5-bromo-3-ethyl-1H-indole (1.9 g, 8.70 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.18 g, 0.22 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.8 g, 9.14 mmol) in a 100 mL round bottom flask. An aqueous solution of 3M tripotassium phosphate (8.7 mL, 26.1 mmol) was added to the reaction mixture. The vial was fitted with a Teflon lined septum cap. The system was evacuated under vacuum (via a needle from a nitrogen/vacuum manifold line) and backfilled with nitrogen gas. The procedure was repeated three times. The needle was removed and the vial was heated at 75

°C for 18 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and poured into a separatory funnel. The mixture was washed with water (2 X 50 mL) and saturated aqueous NaCl solution (50 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to give crude product. The crude product was purified with silica gel chromatography to afford *tert*-butyl 4-(3-ethyl-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.3 g, 81% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.78 - 10.68 (m, 1H), 7.51 (d, *J*=1.4 Hz, 1H), 7.27 (d, *J*=8.5 Hz, 1H), 7.19 (dd, *J*=8.5, 1.7 Hz, 1H), 7.11 - 7.04 (m, 1H), 6.03 (br s, 1H), 4.00 (br s, 2H), 3.56 (br s, 2H), 2.70 (dd, *J*=7.5, 0.9 Hz, 2H), 2.53 (br d, *J*=1.7 Hz, 2H), 1.43 (s, 9H), 1.25 (t, *J*=7.5 Hz, 3H). MS $(M+H)^+$ at *m/z* 327 HPLC tr 1.12 min (Method A). Step 2. Tert-butyl 4-(3-ethyl-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.1 g, 6.43 mmol) and ethyl acetate (20 mL) were added to a 250 mL round-bottom flask. The flask was purged with nitrogen gas. Pd/C (0.48 g, 0.45 mmol) was added to the reaction flask, followed by pump/purging with nitrogen gas, three times. Hydrogen gas was introduced via a balloon. The reaction mixture was stirred at room temperature overnight. The flask was evacuated and back-filled with nitrogen gas. The suspension was filtered through fluted filter paper and the filtrate was concentrated. The residue was purified by flash chromatography to afford *tert*-butyl 4-(3-ethyl-1H-indol-5-yl)piperidine-1-carboxylate (1.2 g, 54% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 - 10.46 (m, 1H), 7.31 (s, 1H), 7.24 (d, *J*=8.4 Hz, 1H), 7.08 - 7.02 (m, 1H), 6.94 (dd, *J*=8.4, 1.5 Hz, 1H), 4.16 - 4.02 (m, 2H), 2.93 - 2.59 (m, 5H), 1.85 - 1.71 (m, 2H), 1.61 - 1.48 (m, 2H), 1.42 (s, 9H), 1.25 (t, *J*=7.5 Hz, 3H). MS $(M+H)^+$ at *m/z* 329 HPLC tr 1.13 min (Method A).

tert-*Butyl 4-(2-bromo-3-ethyl-1H-indol-5-yl)piperidine-1-carboxylate* (**11b**): Tert-butyl 4-(3-ethyl-1H-indol-5-yl)piperidine-1-carboxylate (1.8 g, 5.54 mmol) and 1,2-dichloroethane (DCE, 10 mL) were added to a 100 mL round-bottom flask. N-bromosuccinimide (0.98 g, 5.54 mmol)

was dissolved in 10 mL of DCE. The solution of NBS was added to the reaction mixture dropwise via an addition funnel over 15 minutes. The reaction was quenched with 5 mL of a 10% sodium sulfite solution and the volatiles were removed. The residue was taken up in dichloromethane (5 mL), filtered and loaded onto a silica gel column. The column was purified by silica gel chromatography to afford *tert*-butyl 4-(2-bromo-3-ethyl-1H-indol-5-yl)piperidine-1-carboxylate (1.9 g, 86% yield) as a white foam. ^{1}H NMR (300MHz, CHLOROFORM-d) d = 7.92 (br s, 1H), 7.36 (d, *J*=0.8 Hz, 1H), 7.24 (d, *J*=8.3 Hz, 1H), 7.04 (dd, *J*=1.9, 8.3 Hz, 1H), 4.37 - 4.20 (m, 2H), 2.93 - 2.69 (m, 5H), 1.94 - 1.84 (m, 2H), 1.80 - 1.66 (m, 2H), 1.51 (s, 9H), 1.25 (t, *J*=7.6 Hz, 3H). MS $(M+H)^{+}$ at *m/z* 408 HPLC tr 1.20 min (Method A).

tert-*Butyl (2-(4-(2-bromo-3-ethyl-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate* (**13b**): To a 2 dram vial was added *tert*-butyl 4-(2-bromo-3-ethyl-1H-indol-5-yl) piperidine-1-carboxylate (0.32 g, 0.79 mmol) and DCM (5 mL). The reaction mixture was placed under a nitrogen atmosphere, cooled to 0 °C and 48% hydrobromic acid in acetic acid (0.19 mL, 1.18 mmol) was added dropwise via syringe. The reaction mixture was stirred at 0 °C for 15 minutes. While maintaining the temperature at 0 °C, the reaction was quenched with TEA (0.55 mL, 3.96 mmol). Next, *tert*-butyl methyl(2-oxoethyl)carbamate (0.15 g, 0.87 mmol) in 1 mL of DCM was added. The bath was removed and the reaction mixture was allowed to stir at room temperature for 15 minutes and then sodium triacetoxyborohydride (0.50 g, 2.38 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and DCM and the contents added to a separatory funnel. The layers were separated and the combined organics were washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography

to afford *tert*-butyl (2-(4-(2-bromo-3-ethyl-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate (0.29 g, 79 % yield) as a yellow solid. MS $(M+H)^+$ at *m/z* 464/466 HPLC tr 0.87 min (Method A).

2-(4-(2-(3,4-Dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (**7d**): To a 2 dram vial was added *tert*-butyl (2-(4-(2-bromo-3-ethyl-1H-indol-5-yl) piperidin-1-yl)ethyl)(methyl)carbamate (0.022 g, 0.047 mmol), THF (1 mL), (3,4-dimethoxyphenyl)boronic acid (10.3 mg, 0.057 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (1.5 mg, 2.36 μmol) and a 3M tripotassium phosphate solution (0.047 mL, 0.14 mmol). The vessel was capped with a Teflon-lined cap and the mixture was pump/purged with nitrogen gas three times. The vial was set to heat at 70 °C for 1 hour, cooled to room temperature and the mixture was concentrated. The crude residue was diluted with DCM and to this was added 0.1 mL of TFA. The reaction mixture was stirred at room temperature for 30 minutes, then concentrated to dryness under a stream of nitrogen gas. The residue was diluted with 1 mL of DMF, the solids were filtered off and the crude material was purified via preparative LCMS (Method J) to afford 2-(4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (0.014 g, 68% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 7.42 - 7.19 (m, 2H), 7.18 - 6.90 (m, 4H), 3.82 (br d, *J*=16.2 Hz, 6H), 2.97 (br d, *J*=9.8 Hz, 2H), 2.91 - 2.78 (m, 3H), 2.72 (br s, 3H), 2.38 (br s, 3H), 2.05 (br t, *J*=9.4 Hz, 2H), 1.88 - 1.64 (m, 6H), 1.25 (br t, *J*=6.9 Hz, 3H) . HPLC tr 1.53 minutes (Method C). MS $(M+H)^+$ at *m/z* 422; HPLC tr 1.23 minutes (Method D).

5-Bromo-3-isopropyl-1H-indole (**9c**): A 250 mL round bottom flask was charged with triethylsilane (8.9 g, 77.0 mmol), trichloroacetic acid (6.2 g, 38.3 mmol) and toluene (50 mL). The solution was heated to 70 °C, then a solution of 5-bromo-1H-indole (5.0 g, 25.5 mmol) and acetone (2.2 mL, 30.6 mmol) in toluene (30 mL) was added drop wise via an addition funnel. The resulting brown solution was heated at 70 °C for 1.5 hours. The solution was cooled to 10

°C, quenched with 10% sodium bicarbonate and diluted with diethyl ether. The organic layer was separated, dried and concentrated under vacuum to get crude compound. The crude was purified using silica gel chromatography to afford 5-bromo-3-isopropyl-1H-indole (5.5 g, 95% yield) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 - 10.83 (m, 1H), 7.68 (d, *J*=2.0 Hz, 1H), 7.29 (d, *J*=8.6 Hz, 1H), 7.20 - 7.12 (m, 2H), 3.10 (td, *J*=6.8, 0.7 Hz, 1H), 1.32 - 1.24 (m, 6H). MS $(M+H)^+$ at *m/z* 238 HPLC tr 1.42 min (Method A).

tert-*Butyl 4-(3-isopropyl-1H-indol-5-yl)piperidine-1-carboxylate* (**10c**): Step 1. To a mixture of 5-bromo-3-isopropyl-1H-indole (5.5 g, 23.10 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (7.50 g, 24.25 mmol) in a 250 mL round bottom flask was added THF (50 mL) followed by aqueous solution of potassium phosphate, dibasic (12.0 g, 69.3 mmol, 20 mL). The resulting reaction mixture was degassed for 10 minutes with nitrogen gas, then $PdCl_2$(dppf)-CH_2Cl_2 adduct, (0.47 g, 0.57 mmol) was added. The mixture was degassed again for 5 min. The resulting reaction mixture was heated at 75 °C for 18 hours. The reaction mixture was diluted with ethyl acetate (100 mL), poured into a separatory funnel and was washed with water (2 X 50 mL), brine (50 mL), dried over sodium sulfate, and concentrated to give crude product. The crude material was purified using silica gel chromatography to afford *tert*-butyl 4-(3-isopropyl-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (6.5 g, 83% yield) as an oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.00 - 7.90 (m, 1H), 7.65 (d, *J*=0.7 Hz, 1H), 7.36 - 7.31 (m, 1H), 7.29 - 7.25 (m, 1H), 6.99 (dd, *J*=2.3, 0.7 Hz, 1H), 6.03 (br s, 1H), 4.20 - 4.08 (m, 2H), 3.71 (t, *J*=5.7 Hz, 2H), 3.25 (did, *J*=13.8, 6.8, 0.7 Hz, 1H), 2.67 (br s, 2H), 1.54 (s, 9H), 1.40 (d, *J*=6.8 Hz, 6H). MS $(M+H)^+$ at *m/z* 339 HPLC tr 1.21 min (Method A). Step 2. To a solution of *tert*-butyl 4-(3-isopropyl-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (7.9 g, 23.20 mmol) in ethyl acetate (150 mL), under a

nitrogen atmosphere, was added palladium on carbon (0.61 g, 0.58 mmol). The vessel was pump/purged three times with nitrogen gas then evacuated. Hydrogen gas was introduced via balloon and the mixture was stirred at 25 ^{o}C for 5 hours. The suspension was filtered through Celite and the filtrate was concentrated. The crude residue was purified by silica gel chromatography to afford *tert*-butyl 4-(3-isopropyl-1H-indol-5-yl)piperidine-1-carboxylate (6.5 g, 82% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.96 - 7.83 (m, 1H), 7.49 (d, *J*=0.9 Hz, 1H), 7.32 (d, *J*=8.3 Hz, 1H), 7.08 (dd, *J*=8.4, 1.7 Hz, 1H), 6.98 (dd, *J*=2.3, 0.7 Hz, 1H), 3.23 (td, *J*=6.8, 0.7 Hz, 1H), 2.95 - 2.71 (m, 3H), 1.92 (br d, *J*=13.1 Hz, 2H), 1.82 - 1.68 (m, 2H), 1.61 (s, 2H), 1.53 (s, 9H), 1.40 (d, *J*=6.8 Hz, 6H) MS $(M+H)^{+}$ at *m/z* 341 HPLC tr 2.48 min (Method A).

tert-*Butyl 4-(2-bromo-3-isopropyl-1H-indol-5-yl)piperidine-1-carboxylate* (**11c**): To a solution of *tert*-butyl 4-(3-isopropyl-1H-indol-5-yl)piperidine-1-carboxylate (6.3 g, 18.4 mmol) in DCE (60 mL) at 0 °C, was added NBS (3.3 g, 18.4 mmol) in DCE (50 mL) dropwise via an addition funnel over 10 minutes. The resulting brown solution was stirred at room temperature for 20 minutes. The reaction was quenched with a 10% sodium sulfite solution (15 mL) and the volatiles were removed. The residue was taken up in DCM (50 mL) and the mixture was poured into a separatory funnel and the aqueous layer was separated. The organic layer was dried over Na_2SO_4 and concentrated to give crude compound. The crude material was purified by silica gel chromatography to afford *tert*-butyl 4-(2-bromo-3-isopropyl-1H-indol-5-yl)piperidine-1-carboxylate (6.4 g, 83% yield) as a white solid. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.89 - 7.84 (m, 1H), 7.51 (d, *J*=0.9 Hz, 1H), 7.25 (d, *J*=8.4 Hz, 1H), 7.04 (dd, *J*=8.4, 1.5 Hz, 1H), 3.32 - 3.18 (m, 1H), 2.93 - 2.82 (m, 2H), 2.75 (s, 1H), 1.90 (br d, *J*=13.1 Hz, 2H), 1.81 - 1.66 (m, 2H),

1.53 (s, 9H), 1.45 (d, *J*=7.2 Hz, 6H), 1.27 (s, 2H). MS $(M+H)^+$ at *m/z* 421 HPLC tr 3.94 min (Method A).

2-(3,4-Dimethoxyphenyl)-3-isopropyl-5-(piperidin-4-yl)-1H-indole hydrochloride (**17c**): Step 1. To a degassed solution (nitrogen gas, 10 minutes) of *tert*-butyl 4-(2-bromo-3-isopropyl-1H-indol-5-yl)piperidine-1-carboxylate (2.0 g, 4.75 mmol), (3,4-dimethoxyphenyl)boronic acid (0.95 g, 5.22 mmol) and potassium carbonate (1.9 g, 14.24 mmol) in THF (40 mL) and water (10 mL), was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.194 g, 0.237 mmol). The reaction mixture was degassed for an additional 5 minutes and then heated at 70 °C for 5 hours. The reaction mixture was concentrated. The residue was dissolved in ethyl acetate and the solution was washed with water. The organic layer was collected, dried over Na_2SO_4 and concentrated to dryness. The crude material was purified by silica gel chromatography to afford *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl) piperidine-1-carboxylate (1.4 g, 61% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.91 - 7.81 (m, 1H), 7.63 (s, 1H), 7.34 (d, *J*=8.4 Hz, 1H), 7.10 - 7.02 (m, 3H), 7.02 - 6.97 (m, 1H), 4.43 - 4.23 (m, 2H), 3.96 (d, *J*=6.8 Hz, 5H), 3.48 - 3.30 (m, 1H), 2.98 - 2.73 (m, 3H), 1.92 (br s, 2H), 1.84 - 1.68 (m, 3H), 1.57 - 1.47 (m, 15H). MS $(M+H)^+$ at *m/z* 479 HPLC tr 3.87 min (Method A). Step 2. To a solution of *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)piperidine-1-carboxylate (1.4 g, 2.93 mmol) in DCM (5 mL) was added 4M HCl in dioxane (3.6 mL, 14.63 mmol). The mixture was stirred at room temperature for 1 hour. The resulting slurry was concentrated and the residue was triturated with diethyl ether (2 X 10 mL) to afford 2-(3,4-dimethoxyphenyl)-3-isopropyl-5-(piperidin-4-yl)-1H-indole hydrochloride (1.1 g, 99% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 - 10.84 (m, 1H), 7.52 (s, 1H), 7.30 (d, *J*=8.4 Hz, 1H), 7.12 - 6.99 (m, 3H), 6.95 (br d, *J*=8.1 Hz, 1H), 3.82 (d, *J*=9.4 Hz, 6H), 3.54 - 3.38 (m, 1H), 3.37

- 3.29 (m, 1H), 3.18 (d, *J*=4.7 Hz, 1H), 3.10 - 2.98 (m, 2H), 2.90 (br d, *J*=4.4 Hz, 1H), 2.02 - 1.80 (m, 4H), 1.42 (br d, *J*=7.1 Hz, 6H), 1.29 - 1.21 (m, 1H). MS $(M+H)^+$ at *m/z* 379 HPLC tr 1.41 min (Method A).

2-(4-(2-(3,4-Dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**7f**): Step 1: To a solution of 2-(3,4-dimethoxyphenyl)-3-isopropyl-5-(piperidin-4-yl)-1H-indole hydrochloride (**17c**) (1.0 g, 2.6 mmol) and *tert*-butyl methyl(2-oxoethyl)carbamate (**12**) (0.82 g, 4.7 mmol) in DCM (25 mL) was added TEA (1.8 mL, 13.2 mmol) and acetic acid (0.6 mL, 10.6 mmol). The solution was stirred for 2 hours at 25 ^oC, then sodium triacetoxyborohydride (2.8 g, 13.2 mmol) was added and the reaction was stirred at 25 ^oC for 1 hour. The reaction was diluted with water and extracted with DCM. The organics were washed with saturated NaCl, dried over anhydrous sodium sulfate, filtered and concentrated. Further purification was done by silica gel chromatography to afford *tert*-butyl (2-(4-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate (1.4 g, 99% yield) as a yellowish solid. Step 2: To a solution of *tert*-butyl (2-(4-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate (0.24 g, 0.45 mmol) in DCM (1.0 mL) was added 4M HCl in dioxane (1.1 mL, 4.5 mmol). The reaction was stirred for 1 hour, then was concentrated under a stream of nitrogen gas. The residue was diluted with a saturated sodium bicarbonate solution and extracted with DCM. The organics were washed with water followed by saturated NaCl, dried over anhydrous sodium sulfate, filtered and concentrated. Further purification was done by silica gel chromatography to afford 2-(4-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (0.086 g, 65% yield) as an off-white solid MS $(M+H)^+$ at *m/z* 436 HPLC tr 0.69 min (Method B). ^1H NMR (500 MHz, DMSO-d6) δ 10.81 (s, 1H), 7.50 (s, 1H), 7.25 (d, J=8.34 Hz, 1H), 7.01-7.10 (m, 3H), 6.96 (dd, J=1.43, 8.34 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.32

(m, 2H), 2.98 (br d, J=10.85 Hz, 2H), 2.65 (br t, J=6.32 Hz, 2H), 2.52-2.59 (m, 1H), 2.40-2.49 (m, 2H), 2.35 (s, 3H), 2.06 (br t, J=10.67 Hz, 2H), 1.67-1.87 (m, 4H), 1.42 (d, J=7.15 Hz, 6H)

5-Bromo-3-isobutyl-1H-indole (**9d**): To a 2 dram vial was added 5-bromo-1H-indole (0.26 g, 1.31 mmol), Shvo's Catalyst (0.014 g, 0.013 mmol), potassium carbonate (9.0 mg, 0.066 mmol) and diisobutylamine (0.46 mL, 2.62 mmol). The reaction mixture was purged with nitrogen gas and heated to 155 °C for 48 hours. The reaction mixture was concentrated under a stream of nitrogen gas. The resulting residue was purified by silica gel chromatography to afford 5-bromo-3-isobutyl-1H-indole (0.068 g, 21% yield).as a yellowish oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 - 11.13 (m, 1H), 7.72 (d, *J*=2.0 Hz, 1H), 7.39 (t, *J*=2.8 Hz, 1H), 7.21 - 7.13 (m, 2H), 6.41 (ddd, *J*=3.0, 2.0, 0.9 Hz, 1H), 2.38 (br d, *J*=6.6 Hz, 1H), 1.97 - 1.80 (m, 1H), 1.82 - 1.56 (m, 1H), 0.94 - 0.79 (m, 6H). MS $(M+H)^+$ at *m/z* 253 HPLC tr 1.15 min (Method A).

tert-*Butyl 4-(3-isobutyl-1H-indol-5-yl)piperidine-1-carboxylate* (**10d**): Step 1. To a mixture of 5-bromo-3-isobutyl-1H-indole (0.068 g, 0.27 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (5.5 mg, 6.74 µmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.092 g, 0.29 mmol) was added THF (10 mL) followed by an aqueous solution of tripotassium phosphate (0.27 mL, 0.81 mmol). The system was evacuated under vacuum (via a needle from a nitrogen/vacuum manifold line) and back-filled with nitrogen gas. The procedure was repeated three times. The vial was heated at 75 °C for 18 hours, cooled to room temperature then was diluted with EtOAc (100 mL). The contents was poured into a separatory funnel and washed with water (2 X 50 mL) and saturated aqueous NaCl solution (50 mL) dried over anhydrous sodium sulfate and filtered. The filtrate concentrated in vacuo to afford *tert*-butyl 4-(3-isobutyl-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.080 g, 84% yield). MS $(M+H)^+$ at *m/z* 355 HPLC tr 1.19 min (Method A). Step 2. In a 250 mL round bottom flask was

added *tert*-butyl 4-(3-isobutyl-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.080 g, 0.22 mmol) and ethyl acetate (20 mL). The flask was purged with nitrogen gas and 10% Pd/C (0.017 g, 0.016 mmol) was added. Following pump/purging with nitrogen gas three times, hydrogen gas was introduced via a balloon. The reaction was stirred at 25 ^{o}C overnight. The suspension was filtered through fluted filter paper and the filtrate was concentrated to afford *tert*-butyl 4-(3-isobutyl-1H-indol-5-yl)piperidine-1-carboxylate (0.072 g, 97% yield) as a yellowish oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.69 - 10.56 (m, 1H), 7.31 (s, 1H), 7.24 (d, J=8.4 Hz, 1H), 7.04 (d, J=2.2 Hz, 1H), 6.94 (dd, J=8.4, 1.5 Hz, 1H), 4.20 - 4.05 (m, 2H), 2.93 - 2.65 (m, 4H), 1.98 - 1.85 (m, 1H), 1.83 - 1.72 (m, 2H), 1.59 - 1.55 (m, 1H), 1.63 - 1.49 (m, 1H), 1.55 - 1.40 (m, 9H), 1.21 - 1.21 (m, 1H), 0.91 (d, J=6.6 Hz, 6H). MS $(M+H)^{+}$ at *m/z* 357 HPLC tr 1.20 min (Method A).

tert-*Butyl 4-(2-bromo-3-isobutyl-1H-indol-5-yl)piperidine-1-carboxylate* (**11d**): In a 100 mL round bottom flask was added *tert*-butyl 4-(3-isobutyl-1H-indol-5-yl)piperidine-1-carboxylate (0.089 g, 0.25 mmol) and DCE (50 mL). NBS (0.044 g, 0.25 mmol) was dissolved in DCE (25 mL) and added to the reaction, dropwise, via an addition funnel over 15 minutes. The reaction was stirred for an additional 16 minutes at 25 ^{o}C, then quenched with a 10% sodium sulfite solution. The volatiles were removed and the resulting residue was purified by silica gel chromatography to afford *tert*-butyl 4-(2-bromo-3-isobutyl-1H-indol-5-yl)piperidine-1-carboxylate (0.020 g, 20% yield) as a white foam. MS $(M+H)^{+}$ at *m/z* 435/437 HPLC tr 1.26 min (Method A).

2-(3,4-Dimethoxyphenyl)-3-isobutyl-5-(piperidin-4-yl)-1H-indole hydrochloride (**17d**): Step 1. To a mixture of *tert*-butyl 4-(2-bromo-3-isobutyl-1H-indol-5-yl)piperidine-1-carboxylate (18 mg, 0.041 mmol), (3,4-dimethoxyphenyl)boronic acid (10 mg, 0.058 mmol) and $PdCl_2$(dppf)-CH_2Cl_2

adduct (2 mg, 2.12 μmol) in a screw cap vial was added THF (2 mL) and an aqueous solution of tripotassium phosphate (0.041 mL, 0.12 mmol). The vial was fitted with a Teflon-lined septum cap and the system was evacuated under vacuum (via a needle from a nitrogen/vacuum manifold line) and backfilled with nitrogen gas. The procedure was repeated three times. The reaction was heated at 65 °C for 3 hours, then was diluted with EtOAc (25 mL) and poured into a separatory funnel and washed with water (2 X 5 mL), then saturated aqueous NaCl solution (5 mL). The organics were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The crude product was purified by silica gel chromatography to afford *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-isobutyl-1H-indol-5-yl) piperidine-1-carboxylate. MS $(M+H)^+$ at *m/z* 493 HPLC tr 1.24 min (Method A). Step 2. *tert*-Butyl 4-(2-(3,4-dimethoxyphenyl)-3-isobutyl-1H-indol-5-yl) piperidine-1-carboxylate was treated with hydrogen chloride (0.026 mL, 0.10 mmol) in DCM (0.5 mL) for 20 minutes. The reaction was concentrated to afford 2-(3,4-dimethoxyphenyl)-3-isobutyl-5-(piperidin-4-yl)-1H-indole, HCl (0.031 g, 100% yield, 2 steps) as an off-white solid. MS $(M+H)^+$ at *m/z* 393 HPLC tr 0.9 min (Method A).

2-(4-(2-(3,4-Dimethoxyphenyl)-3-isobutyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (**7g**): In a 2 dram vial was added 2-(3,4-dimethoxyphenyl)-3-isobutyl-5-(piperidin-4-yl)-1H-indole hydrochloride (0.019 g, 0.044 mmol), DCM (1 mL), TEA (0.031 mL, 0.22 mmol), *tert*-butyl (2-oxoethyl)carbamate (10.58 mg, 0.066 mmol) and acetic acid (2.54 μl, 0.044 mmol). The reaction was stirred at 25 ^oC for 30 minutes and sodium triacetoxyborohydride (0.028 g, 0.133 mmol) was added in one portion. The reaction was stirred for 2 hours, then water and DCM were added. The mixture was separated and the combined organics were washed with brine and dried over anhydrous sodium sulfate. The solids were filtered off and the filtrate was concentrated. To this was added DCM (1 mL) followed by HCl in dioxane (0.055 mL, 0.22

mmol). The reaction was stirred at 25 °C for 30 minutes, then concentrated to dryness. The crude material was purified via preparative LCMS (Method H) to afford 1-(4-(2-(3,4-dimethoxyphenyl)-3-isobutyl-1H-indol-5-yl)piperidin-1-yl)-2-(ethylamino)ethanone (0.0024 g, 12% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.07 - 10.83 (m, 1H), 7.32 (s, 1H), 7.25 (br d, *J*=8.4 Hz, 1H), 7.20 - 7.13 (m, 2H), 7.08 (br d, *J*=8.1 Hz, 1H), 6.97 (br d, *J*=8.1 Hz, 1H), 3.82 (br d, *J*=13.8 Hz, 4H), 2.98 (br d, *J*=10.8 Hz, 1H), 2.80 - 2.67 (m, 4H), 2.59 - 2.44 (m, 3H), 2.39 (s, 3H), 2.06 (br t, *J*=9.8 Hz, 2H), 1.96 (br s, 1H), 1.87 - 1.67 (m, 8H), 0.89 (br d, *J*=6.4 Hz, 6H). HPLC tr 1.38 minutes (Method C). MS $(M+H)^+$ at *m/z* 450; HPLC tr 1.21 minutes (Method D).

tert-*Butyl 4-(3-cyano-1H-indol-5-yl)piperidine-1-carboxylate* (**10e**): In a 2 dram vial, 5-bromo-1H-indole-3-carbonitrile (0.50 g, 2.26 mmol) was taken in THF (2 mL) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.19 g, 0.614 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.023 g, 0.028 mmol), and 3M tripotassium phosphate solution (0.5 mL, 1.67 mmol) were added. The vial was capped and pump/purged with nitrogen gas three times. The reaction mixture was set to heat at 50 °C for 1 hour. The mixture was cooled to room temperature and concentrated under a stream of nitrogen gas. The crude residue was purified by silica gel chromatography to afford *tert*-butyl 4-(3-cyano-1H-indol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate as a clear oil. The oil was transferred to a 100 mL round bottom flask with EtOAc and purged with nitrogen gas. 10% Pd/C (0.059 g, 0.56 mmol) was introduced and the vessel was pump/purged with nitrogen gas, then back-filled with hydrogen gas, via balloon. The reaction mixture was allowed to stir at atmospheric pressure overnight. The suspension was filtered and the cake was rinsed with MeOH. The material was concentrated to dryness via rotary-evaporation to afford *tert*-butyl 4-(3-cyano-1H-indol-5-yl)piperidine-1-carboxylate (0.14 g, 80% yield), which was used as such in the next step. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 8.18 (s, 1H), 7.46 (d, *J*=8.4 Hz, 1H), 7.44 (d, *J*=0.9 Hz, 1H), 7.17 (dd, *J*=8.4, 1.5 Hz, 1H), 4.25 - 3.96 (m, 2H), 3.90 (s, 1H), 2.92 - 2.70 (m, 2H), 1.87 - 1.72 (m, 2H), 1.62 - 1.48 (m, 2H), 1.42 (s, 9H). Indole NH not observed. MS $(M+H)^+$ at *m/z* 326 HPLC tr 0.98 min (Method B).

Isopropyl 4-(2-bromo-3-cyano-1H-indol-5-yl)piperidine-1-carboxylate (**11e**): To a 100 mL round bottom flask was added *tert*-butyl 4-(3-cyano-1H-indol-5-yl) piperidine-1-carboxylate (0.55 g, 1.69 mmol) and DCE (7 mL). NBS (0.28 g, 1.60 mmol) was added to DCE (2 mL) and the suspension was added to the reaction mixture, dropwise via a pipet over 15 minutes. The reaction mixture was allowed to heat at 50 °C for 1 hour. The reaction was quenched with a 10% sodium sulfite solution (5 mL) and the volatiles were removed in vacuo. DCM was added and the suspension was filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography to afford isopropyl 4-(2-bromo-3-cyano-1H-indol-5-yl)piperidine-1-carboxylate (0.24 g, 36% yield) as a white foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 - 8.18 (m, 1H), 7.80 (s, 1H), 7.56 (s, 1H), 4.21 - 4.08 (m, 2H), 3.21 - 3.05 (m, 1H), 2.98 - 2.73 (m, 1H), 1.89 - 1.75 (m, 2H), 1.67 - 1.52 (m, 1H), 1.43 (s, 9H). Indole NH and one aliphatic proton not distinguishable. MS $(M+H)^+$ at *m/z* 405/407 HPLC tr 1.04 min (Method B).

2-(3,4-Dimethoxyphenyl)-5-(piperidin-4-yl)-1H-indole-3-carbonitrile hydrochloride (**17e**): Step 1. To a 40 mL reaction vial was added *ter*t-butyl 4-(2-bromo-3-cyano-1H-indol-5-yl)piperidine-1-carboxylate (0.040 g, 0.099 mmol), (3,4-dimethoxyphenyl)boronic acid (0.020 g, 0.11 mmol), THF (15 mL), $PdCl_2$(dppf)-CH_2Cl_2 adduct (4.04 mg, 4.95 μmol) and 3M tripotassium phosphate solution (0.099 mL, 0.29 mmol). The vial was capped with a Teflon-lined cap and flushed with nitrogen for 1 minute. The reaction mixture was set to heat at 50 °C for 1 hour. The mixture was cooled to 25 °C and concentrated. The crude residue was purified by silica gel

chromatography to afford *tert*-butyl 4-(3-cyano-2-(3,4-dimethoxyphenyl)-1H-indol-5-yl)piperidine-1-carboxylate (0.0030 g, 66% yield) as a clear oil. Step 2. To *tert*-butyl 4-(3-cyano-2-(3,4-dimethoxyphenyl)-1H-indol-5-yl)piperidine-1-carboxylate (0.0030 g, 0.065 mmol) was added DCM (0.5 mL) and 4M HCl in dioxane (0.5 mL). The reaction mixture was stirred at 25 ^{o}C for 30 minutes, then concentrated to dryness under a stream of nitrogen gas to give 2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1H-indole-3-carbonitrile hydrochloride (0.022 g, 60% yield). MS $(M+H)^+$ at *m/z* 362 HPLC tr 0.67 min (Method B).

2-(3,4-Dimethoxyphenyl)-5-(1-(2-(methylamino)ethyl)piperidin-4-yl)-1H-indole-3-carbonitrile (**7c**): To a 40 mL reaction vial was added 2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1H-indole-3-carbonitrile hydrochloride (10 mg, 0.025 mmol) and DCM (1 mL). To this was added TEA (0.018 mL, 0.12 mmol) followed by *tert*-butyl(2-oxoethyl) carbamate (4.8 mg, 0.030 mmol) and acetic acid (1 µl, 0.025 mmol). The mixture was stirred at room temperature for 15 minutes and sodium triacetoxyborohydride (0.016 g, 0.075 mmol) was added. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water and ethyl acetate and the layers were separated. The organics were combined and washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was diluted with 1 mL of DCM and 1 mL of TFA and stirred for 25 minutes at room temperature, then concentrated to a viscous oil. The crude material was purified via preparative LCMS (Method I) to afford 2-(3,4-dimethoxyphenyl)-5-(1-(2-(methylamino)ethyl)piperidin-4-yl)-1H-indole-3-carbonitrile (0.0052 g, 47% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.58 (br d, *J*=8.4 Hz, 1H), 7.55 (s, 1H), 7.45 (br d, *J*=8.4 Hz, 1H), 7.40 (s, 1H), 7.18 (br d, *J*=8.4 Hz, 2H), 3.85 (d, *J*=12.8 Hz, 4H), 3.64 - 3.44 (m, 2H), 2.97 (br d, *J*=10.4 Hz, 2H), 2.73 (br d, *J*=7.1 Hz, 2H), 2.66 - 2.56 (m, 1H), 2.38 (br s,

3H), 2.06 (br t, *J*=10.8 Hz, 2H), 1.84 - 1.65 (m, 7H). Indole NH not observed. HPLC tr 1.33 minutes (Method C). MS $(M+H)^+$ at *m/z* 419; HPLC tr 0.95 minutes (Method D).

tert-*Butyl 4-(3-chloro-1H-indol-5-yl)piperidine-1-carboxylate* (**10f**): Step 1. To a mixture of 5-bromo-1H-indole (1.1 g, 5.41 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.11 g, 0.13 mmol), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.8 g, 5.95 mmol) in a screw cap vial was added THF (13 mL) followed by an aqueous solution of 3M tripotassium phosphate (5.4 mL, 16.22 mmol). The vial was fitted with a Teflon-lined septum cap. The system was evacuated under vacuum (via a needle from a nitrogen/vacuum manifold line) and back-filled with nitrogen gas. The procedure was repeated three times. The needle was removed and the vial was heated at 70 °C for 18 hours. The reaction mixture was diluted with EtOAc (100 mL), poured into a separatory funnel and washed with water (2 X 50 mL) and saturated aqueous NaCl solution (50 mL), dried over anhydrous sodium sulfate, was filtered and concentrated. The crude product was purified by silica gel chromatography to afford *tert*-butyl 4-(1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.4 g, 88% yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.33 - 8.16 (m, 1H), 7.66 (s, 1H), 7.44 - 7.35 (m, 1H), 7.31 (d, *J*=1.7 Hz, 1H), 7.26 - 7.18 (m, 1H), 6.58 (ddd, *J*=3.1, 2.1, 0.9 Hz, 1H), 6.03 (br s, 1H), 4.19 - 4.07 (m, 2H), 3.77 - 3.65 (m, 2H), 2.65 (br s, 2H), 1.57 - 1.48 (m, 9H). MS $(M+H)^+$ at *m/z* 299 HPLC tr 1.03 min (Method A). Step 2. To a 250 mL round bottom flask was added tert-butyl 4-(1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.3 g, 4.36 mmol) and ethyl acetate (20 mL). The flask was purged with nitrogen gas and 10% Pd/C (0.32 g, 0.30 mmol) was added. Following pump/purging with nitrogen gas three times, hydrogen gas was introduced via a balloon. The reaction mixture was stirred at 25 ^{o}C for 18 hours. The flask was evacuated and filled with nitrogen gas. The suspension was filtered through fluted filter paper and the filtrate

was concentrated in vacuo to afford *tert*-butyl 4-(1H-indol-5-yl)piperidine-1-carboxylate (1.2 g, 88% yield) as an off-white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 - 8.10 (m, 1H), 7.50 (d, *J*=0.7 Hz, 1H), 7.37 (d, *J*=8.4 Hz, 1H), 7.26 - 7.20 (m, 1H), 7.09 (dd, *J*=8.4, 1.7 Hz, 1H), 6.54 (ddd, *J*=3.1, 2.0, 0.9 Hz, 1H), 4.29 (br d, *J*=2.3 Hz, 2H), 2.96 - 2.69 (m, 2H), 1.91 (br d, *J*=13.1 Hz, 2H), 1.99 - 1.85 (m, 1H), 1.73 (qd, *J*=12.5, 4.6 Hz, 2H), 1.58 - 1.47 (m, 9H). MS $(M+H)^+$ at *m/z* 301 HPLC tr 1.04 min (Method A). Step 3. To a 100 mL round bottom flask was added *tert*-butyl 4-(1H-indol-5-yl)piperidine-1-carboxylate (0.21 g, 0.70 mmol) and DCM (6 mL). NCS (0.093 g, 0.70 mmol) was added to DCE (2 mL) and added to the reaction mixture dropwise, via a pipet over 5 minutes. The reaction was quenched with a 10% sodium sulfite solution (5 mL) and concentrated under a stream of nitrogen gas. The residue was taken up in DCM, filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography to afford *tert*-butyl 4-(3-chloro-1H-indol-5-yl)piperidine-1-carboxylate (0.20 g, 86% yield) as a white foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 - 11.16 (m, 1H), 7.45 (d, *J*=2.6 Hz, 1H), 7.33 (d, *J*=8.4 Hz, 1H), 7.27 (s, 1H), 7.06 (dd, *J*=8.5, 1.7 Hz, 1H), 4.14 - 4.03 (m, 2H), 2.90 - 2.68 (m, 3H), 1.77 (br s, 2H), 1.59 - 1.45 (m, 2H), 1.41 (s, 9H). MS $(M+H)^+$ at *m/z* 335 HPLC tr 1.10 min (Method A).

tert-*Butyl-4-(2-bromo-3-chloro-1H-indol-5-yl)piperidine-1-carboxylate* (**11f**): To a 100 mL round bottom flask was added *tert*-butyl 4-(3-chloro-1H-indol-5-yl) piperidine-1-carboxylate (0.13 g, 0.39 mmol) and DCE (6 mL). NBS (0.066 g, 0.37 mmol) was added to DCE (2 mL) and the suspension was added to the reaction mixture via pipet over 5 minutes at 25 ^{o}C. The reaction was quenched with a 10% sodium sulfite solution (5 mL). DCM was added and the layers were separated. The organics were washed with brine, dried over anhydrous sodium sulfate, were filtered and concentrated. The crude product was purified by silica gel chromatography to afford

tert-butyl-4-(2-bromo-3-chloro-1H-indol-5-yl)piperidine-1-carboxylate (0.060 g, 37% yield) as a white foam. MS $(M+H)^+$ at *m/z* 414/416 HPLC tr 1.17 min (Method A).

3-Chloro-2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1H-indole hydrochloride (**17f**): Step 1. To a 2 dram vial was added *tert*-butyl 4-(2-bromo-3-chloro-1H-indol-5-yl) piperidine-1-carboxylate (0.075 g, 0.18 mmol), (3,4-dimethoxyphenyl)boronic acid (0.040 g, 0.22 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (7 mg, 9.0 µmol). To this mixture and under a nitrogen gas atmosphere was added THF (1 mL) and a 3M potassium phosphate solution (0.18 mL, 0.54 mmol). The vial was capped and pump/purged with nitrogen gas three times. The reaction mixture was set to heat at 50 °C for 1 hour. Upon cooling, the mixture was concentrated under a stream of nitrogen gas and the crude residue was purified by silica gel chromatography to afford *tert*-butyl 4-(3-chloro-2-(3,4-dimethoxyphenyl)-1H-indol-5-yl)piperidine-1-carboxylate (0.072 g, 84% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 7.52 - 7.47 (m, 1H), 7.46 (d, *J*=2.2 Hz, 1H), 7.34 (d, *J*=8.4 Hz, 1H), 7.29 (s, 1H), 7.15 - 7.06 (m, 2H), 4.18 - 4.02 (m, 2H), 3.84 (d, *J*=13.4 Hz, 6H), 2.91 - 2.72 (m, 3H), 1.90 - 1.75 (m, 2H), 1.64 - 1.48 (m, 2H), 1.43 (s, 9H). MS $(M+H)^+$ at *m/z* 471 HPLC tr 1.17 min (Method A). Step 2. To a 40 mL reaction vial was added *tert*-butyl 4-(3-chloro-2-(3,4-dimethoxyphenyl)-1H-indol-5-yl)piperidine-1-carboxylate (0.027 g, 0.057 mmol), DCM (0.5 mL) and TFA (0.5 mL). The reaction mixture was stirred for 15 minutes, then concentrated to dryness under a stream of nitrogen gas to afford 3-chloro-2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1H-indole hydrochloride (0.023 g, 100% yield), which was carried forward to the next step.

2-(3,4-2-(4-(3-Chloro-2-(3,4-dimethoxyphenyl)-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (**7b**): To 3-chloro-2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1H-indole hydrochloride (0.023 g, 0.057 mmol) was added DCM (1 mL), TEA (0.051 mL, 0.36 mmol) and

tert-butyl (2-oxoethyl)carbamate (0.014 g, 0.087 mmol). Acetic acid (4 µl, 0.073 µmol) was added and the mixture was stirred at 25 °C for 15 minutes and then sodium triacetoxyborohydride (0.046 g, 0.22 mmol) was added. The reaction mixture was stirred at 25 °C for 4 hours, then was diluted with MeOH and concentrated to dryness. The residue was diluted with DCM (1 mL) and to this was added TFA (0.5 mL). The mixture was stirred for 15 minutes and concentrated under a stream of nitrogen gas. The residue was diluted with 2 mL of DMSO and filtered through a 0.45 micron syringe filter. The crude material was purified via preparative LCMS (Method J) to afford 2-(3,4-2-(4-(3-chloro-2-(3,4-dimethoxyphenyl)-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (0.026 g, 70% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.51 - 7.26 (m, 4H), 7.10 (br d, *J*=8.4 Hz, 2H), 3.90 - 3.71 (m, 4H), 3.67 - 3.53 (m, 2H), 3.46 - 3.29 (m, 4H), 3.15 (s, 2H), 2.96 (br s, 1H), 2.87 (s, 1H), 2.71 (s, 2H), 2.64 (s, 3H), 2.07 (br d, *J*=12.8 Hz, 2H), 1.93 (br d, *J*=12.1 Hz, 2H). HPLC tr 1.41 minutes (Method C). MS $(M+H)^+$ at *m/z* 428; HPLC tr 1.10 minutes (Method D).

5-Bromo-2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole (**16**):

Step 1: *1-(3,4-Dimethoxyphenyl)-4,4,4-trifluorobutan-1-one*: To a solution of 4,4,4-trifluorobutanoic acid (10 g, 70 mmol) in toluene (100 mL) at 0 °C was added 1,2-dimethoxybenzene (9 mL, 70 mmol) in a portion wise manner. The suspension was stirred for 10 minutes at 0 °C, then polyphosphoric acid (141 mmol) was added. The reaction mixture was heated at 75 °C for 16 hours and then, was quenched with water (50 mL) and extracted with ethyl acetate (3 X 100 mL). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure to yield a colorless liquid. The crude compound purified by silica gel chromatography to afford 1-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutan-1-one (8 g, 43% yield) as an oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.60 (dd, *J*=2.0, 8.3 Hz, 1H),

7.53 (d, *J*=2.0 Hz, 1H), 6.91 (d, *J*=8.5 Hz, 1H), 3.95 (d, *J*=6.3 Hz, 6H), 3.27 - 3.17 (m, 2H), 2.68 - 2.49 (m, 2H). MS $(M+H)^+$ at *m/z* 263 HPLC tr 2.30 min (Method F).

Step 2: To a mixture of (4-bromophenyl)hydrazine (1.070 g, 5.72 mmol), 1-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutan-1-one (1.5 g, 5.72 mmol) and (4-bromophenyl) hydrazine (1.070 g, 5.72 mmol) at 25 ^oC was added polyphosphoric acid (3.40 mL, 5.72 mmol) in a portion-wise manner. The suspension was stirred for 10 minutes at 25 ^oC, then stirred at 155 °C for 10-20 minutes. The reaction was quenched with water (20 mL), and the mixture was extracted with ethyl acetate (3 X 50 mL). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography to afford 5-bromo-2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole (0.900 g, 38% yield) as a brown solid. ^1H NMR (300MHz, CHLOROFORM-d) δ = 8.22 (br s, 1H), 7.79 (s, 1H), 7.38 - 7.31 (m, 1H), 7.30 (s, 1H), 7.16 - 6.99 (m, 3H), 3.96 (d, *J*=7.2 Hz, 6H), 3.63 - 3.48 (m, 2H). MS $(M+H)^+$ at *m/z* 413 HPLC tr 3.40 min (Method F).

2-(3,4-Dimethoxyphenyl)-5-(piperidin-4-yl)-3-(2,2,2- trifluoroethyl)-1H-indole, hydrochloride (**17g**): Step 1. A mixture of 5-bromo-2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole (0.90 g, 2.17 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.3 g, 4.35 mmol), and K_2CO_3 (0.90 g, 6.52 mmol) in 1,4-dioxane (50 mL) and water (10 mL) was purged under nitrogen for 10 minutes. Next, 1,1'-($PdCl_2$(dppf)-CH_2Cl_2 (0.18 g, 0.22 mmol) was added to the reaction mixture, then the mixture was stirred at 90 °C for 20–30 minutes. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude compound was

purified by silica gel chromatography to afford *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.90 g, 80% yield) as a light yellow solid. MS $(M+H)^+$ at *m/z* 515 HPLC tr 2.12 min (Method F). Step 2. To a solution of *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.0 g, 1.93 mmol) in ethyl acetate (50 mL) and methanol (50 mL) was added 10% Pd/C (0.30 g, 2.82 mmol). The reaction mixture was stirred at 25 ^oC under a hydrogen bladder for 16 hours. The mixture was filtered through a Celite pad, washed with methanol (20 mL) and the filtrates were collected and concentrated under reduced pressure to afford *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)piperidine-1-carboxylate (0.90 g, 90% yield) as a light yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.32 (s, 1H), 7.44 (s, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.20 - 7.09 (m, 3H), 7.04 (dd, *J*=1.8, 8.3 Hz, 1H), 4.11 (br d, *J*=10.5 Hz, 2H), 3.84 (d, *J*=3.5 Hz, 6H), 3.81 - 3.71 (m, 2H), 2.96 - 2.64 (m, 3H), 1.80 (br d, *J*=11.0 Hz, 2H), 1.64 - 1.50 (m, 2H), 1.47 - 1.42 (m, 9H). MS $(M+H)^+$ at *m/z* 413 HPLC tr 2.21 min (Method F). Step 3. To a solution of *tert*-butyl 4-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)piperidine-1-carboxylate (0.90 g, 1.73 mmol) in DCM (10 mL) was added 4M HCl in dioxane (2 mL, 8.0 mmol). The mixture was stirred at 25 ^oC for 1 hour. The reaction mixture was concentrated under reduced pressure and the crude mixture was washed with diethyl ether (3 X 10 mL) and dried under vacuum to afford 2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-3-(2,2,2- trifluoroethyl)-1H-indole, hydrochloride (0.70 g, 81% yield) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ = 11.43 (s, 1H), 9.13 - 8.46 (m, 2H), 7.52 - 7.29 (m, 2H), 7.21 - 7.09 (m, 3H), 7.03 (dd, *J*=1.5, 8.3 Hz, 1H), 3.83 (d, *J*=3.0 Hz, 8H), 3.55 - 3.38 (m, 3H), 3.20 - 2.79 (m, 3H), 2.11 - 1.74 (m, 4H). MS $(M+H)^+$ at *m/z* 418 HPLC tr 1.84 min (Method F).

2-(4-(2-(3,4-Dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (**7e**)**:** Step 1. To a 40 mL reaction vial was added 2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1H-indole-3-carbonitrile hydrochloride (0.040 g, 0.088 mmol) and MeOH (2 mL). To this was added *tert*-butyl(2-oxoethyl)carbamate (4.8 mg, 0.030 mmol) and titanium(iv)isopropoxide (0.064 mL, 0.22 mmol) and the reaction was set to heat at 50 ^{o}C for 5 hours. The reaction temperature was then brought to 25 ^{o}C and sodium cyanoborohydride (0.011 g, 0.17 mmol) was added. The reaction mixture was stirred at 25 ^{o}C for 18 hours. The reaction mass was diluted with water and extracted with DCM. The combined organics were concentrated and purified by silica gel chromatography to afford *tert*-butyl (2-(4-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate (0.040 g, 44% yield). MS $(M+H)^+$ at *m/z* 576 HPLC tr 2.14 min (Method F). Step 2. In a 25 mL two-necked flask was added *tert*-butyl (2-(4-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate (0.040 mg, 0.069 mmol), DCM (1 mL) and TFA (0.5 mL, 6.49 mmol). The reaction was stirred at 25 ^{o}C overnight. The crude mixture was concerted through rotary-evaporation, then water (5 mL) and ethyl acetate were added. The contents of the flask were transferred to a separatory funnel and the layers were separated. The combined organics were dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified via preparative LCMS (Method G) to afford 2-(4-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (0.007 g, 21% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.48 - 11.35 (m, 1H), 8.81 - 8.52 (m, 1H), 7.46 - 7.32 (m, 2H), 7.25 - 7.02 (m, 4H), 3.84 (d, *J*=3.0 Hz, 6H), 3.81 - 3.62 (m, 4H), 3.20 - 2.83 (m, 5H), 2.70 - 2.64 (m, 4H), 2.17 - 1.65 (m, 5H). HPLC tr 1.05 minutes (Method F). MS $(M+H)^+$ at *m/z* 476.

2-(4-(2-(3,4-Dimethoxyphenyl)-1,3-dimethyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**7a**)**:** To a 2 dram vial was added *tert*-butyl (2-(4-(2-(3,4-dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate (0.055 g, 0.11 mmol), DMF (1 ml) and at 0 °C, NaH (6.5 mg, 0.27 mmol). Under a nitrogen atmosphere, the mixture was allowed to stir for 20 minutes at 0 °C. To this was added methyl iodide (0.020 ml, 0.32 mmol) and the reaction mixture was allowed to warm to 25 °C and stirred for 1 hour. The reaction was quenched with water and the mixture was concentrated to dryness under a stream of nitrogen gas. To the residue was added DCM (1 mL) and TFA (0.5 mL) and the reaction mixture was stirred for 30 minutes at 25 °C. The volatiles were removed under a stream of nitrogen gas and the crude material was purified via preparative LCMS (Method I) to afford 2-(4-(2-(3,4-dimethoxyphenyl)-1,3-dimethyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (0.025 g, 52% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 - 7.27 (m, 2H), 7.13 - 7.01 (m, 2H), 6.98 - 6.91 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.56 (s, 1H), 2.97 (br d, *J*=10.8 Hz, 2H), 2.70 (br t, *J*=6.4 Hz, 2H), 2.56 (br dd, *J*=9.9, 4.5 Hz, 1H), 2.46 (br t, *J*=6.2 Hz, 2H), 2.37 (s, 3H), 2.18 (s, 3H), 2.09 - 2.00 (m, 2H), 1.84 (s, 3H), 1.81 - 1.70 (m, 4H). HPLC tr 1.57 minutes (Method C). MS $(M+H)^+$ at *m/z* 422; HPLC tr 1.24 minutes (Method D).

The following compounds were prepared through the route described for **5g**:

2-(4-(2-(Phenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5a**): Purification conditions: (Method H). Obtained 2-(4-(2-(phenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.016 g, 66% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.12 (s, 1H), 7.65 (br d, *J*=7.4 Hz, 2H), 7.50 (t, *J*=7.7 Hz, 2H), 7.39 - 7.29 (m, 3H), 7.01 (br d, *J*=8.1 Hz, 1H), 2.98 - 2.84 (m, 1H), 2.66 (s, 3H), 2.54 (br t, *J*=4.9 Hz, 1H), 2.39 (s, 3H),

2.16 - 1.85 (m, 4H), 8 aliphatic protons not distinguishable. HPLC tr 1.52 minutes (Method C). MS $(M+H)^+$ at *m/z* 348; HPLC tr 1.16 minutes (Method D).

2-(4-(2-(2-Methylphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5b**): Purification conditions: (Method H). Obtained 2-(4-(2-(2-methylphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.0007 g, 2% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.42 - 7.21 (m, 6H), 7.00 (br d, *J*=8.3 Hz, 1H), 3.84 - 3.44 (m, 3H), 2.73 - 2.62 (m, 5H), 2.55 (s, 3H), 2.23 (s, 3H), 2.11 (s, 3H), 2.06 - 1.81 (m, 6H). HPLC tr 1.88 minutes (Method C). MS $(M+H)^+$ at *m/z* 362; HPLC tr 1.25 minutes (Method D).

2-(4-(2-(3-Methylphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1 (**5c**): Purification conditions: (Method H). Obtained 2-(4-(2-(3-methylphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.008 g, 38% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.27 - 10.83 (m, 1H), 7.49 - 7.41 (m, 2H), 7.41 - 7.32 (m, 2H), 7.30 (d, *J*=8.4 Hz, 1H), 7.17 (br d, *J*=7.4 Hz, 1H), 7.00 (br d, *J*=8.1 Hz, 1H), 2.66 (s, 4H), 2.39 (s, 7H), 2.13 - 1.86 (m, 4H) 8 aliphatic protons not distinguishable. HPLC tr 1.62 minutes (Method C). MS $(M+H)^+$ at *m/z* 362; HPLC tr 1.31 minutes (Method D).

2-(4-(2-(4-Methylphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5d**): Purification conditions: (Method H). Obtained 2-(4-(2-(4-Methylphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.004 g, 22% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.22 - 10.88 (m, 1H), 7.73 - 7.62 (m, 2H), 7.41 - 7.31 (m, 3H), 7.28 (d, *J*=8.3 Hz, 1H), 7.01 (br d, *J*=8.1 Hz, 1H), 3.63 - 3.47 (m, 2H), 3.01 (br d, *J*=6.7 Hz, 3H), 2.60 - 2.53 (m, 8H), 2.37 (s, 3H), 2.17 - 2.05 (m, 2H), 1.91 (s, 2H), 1.84 - 1.73 (m, 3H). HPLC tr 1.60 minutes (Method C). MS $(M+H)^+$ at *m/z* 362; HPLC tr 1.19 minutes (Method D).

2-(4-(2-(2-Methoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5e**): Purification conditions: (Method I). Obtained 2-(4-(2-(2-methoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.0009 g, 4% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.05 - 10.97 (m, 1H), 7.46 - 7.20 (m, 6H), 6.98 (br s, 1H), 3.76 - 3.33 (m, 4H), 2.69 - 2.61 (m, 4H), 2.57 - 2.53 (m, 2H), 2.41 - 2.33 (m, 3H), 2.28 (br d, *J*=15.5 Hz, 6H), 2.13 - 1.80 (m, 4H). HPLC tr 1.74 minutes (Method C). MS $(M+H)^+$ at *m/z* 378; HPLC tr 1.30 minutes (Method D).

2-(4-(2-(3-Methoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5f**): Purification conditions: (Method H). Obtained 2-(4-(2-(3-methoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.007 g, 49% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.21 - 11.04 (m, 1H), 7.42 (br t, *J*=7.7 Hz, 1H), 7.37 (br s, 1H), 7.32 (br d, *J*=8.1 Hz, 1H), 7.25 (br d, *J*=7.1 Hz, 1H), 7.20 (br s, 1H), 7.02 (br d, *J*=7.1 Hz, 1H), 6.94 (br d, *J*=7.4 Hz, 1H), 3.84 (s, 2H), 2.89 (s, 1H), 2.67 (br s, 3H), 2.41 (br s, 3H), 2.16 - 1.83 (m, 4H), 1.15 (br dd, *J*=13.5, 5.0 Hz, 2H). 7 aliphatic protons and NH not observed. HPLC tr 1.51 minutes (Method C). MS $(M+H)^+$ at *m/z* 378; HPLC tr 1.24 minutes (Method D).

2-(4-(2-(2-Cyanophenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5h**): Purification conditions: (Method H). Obtained 2-(4-(2-(2-Cyanophenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.003 g, 20% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.41 - 10.99 (m, 1H), 7.99 (d, *J*=7.7 Hz, 1H), 7.88 - 7.79 (m, 1H), 7.71 - 7.58 (m, 3H), 7.40 (s, 1H), 7.31 (d, *J*=8.4 Hz, 1H), 3.00 (br d, *J*=10.4 Hz, 2H), 2.80 - 2.70 (m, 2H), 2.64 - 2.55 (m, 2H), 2.40 (s, 4H), 2.14 - 2.01 (m, 2H), 1.87 (br s, 3H), 1.83 - 1.71 (m, 5H). HPLC tr 1.72 minutes (Method C). MS $(M+H)^+$ at *m/z* 373; HPLC tr 0.97 minutes (Method D).

2-(4-(2-(3-Cyanophenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine **(5i)**: Purification conditions: (Method H). Obtained 2-(4-(2-(3-Cyanophenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.004 g, 4% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.47 - 11.11 (m, 1H), 8.07 (s, 1H), 8.00 (br d, *J*=8.1 Hz, 1H), 7.81 (br d, *J*=7.7 Hz, 1H), 7.76 - 7.68 (m, 1H), 7.40 (br s, 1H), 7.35 (d, *J*=8.4 Hz, 1H), 7.07 (br d, *J*=8.1 Hz, 1H), 2.89 (s, 2H), 2.73 (s, 1H), 2.67 (s, 4H), 2.51 (br s, 4H), 2.43 (s, 4H), 2.11 - 1.91 (m, 5H). HPLC tr 1.65 minutes (Method C). MS $(M+H)^+$ at *m/z* 373; HPLC tr 1.12 minutes (Method D).

2-(4-(2-(4-cyanophenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5j**): Purification conditions: (Method H). Obtained 2-(4-(2-(4-cyanophenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.011 g, 17% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.47 - 11.19 (m, 1H), 7.95 (br d, *J*=8.2 Hz, 2H), 7.85 (br d, *J*=8.3 Hz, 2H), 7.42 (s, 1H), 7.36 (d, *J*=8.3 Hz, 1H), 7.14 - 7.05 (m, 1H), 2.66 (s, 3H), 2.55 (s, 6H), 2.52 (br s, 4H), 2.45 (s, 3H), 2.10 - 1.89 (m, 5H). HPLC tr 1.62 minutes (Method C). MS $(M+H)^+$ at *m/z* 373; HPLC tr 1.24 minutes (Method D).

4-(3-Methyl-5-(1-(2-(methylamino)ethyl)piperidin-4-yl)-1H-indol-2-yl)benzamide (**5k**): Purification conditions: (Method H). Obtained 4-(3-Methyl-5-(1-(2-(methylamino)ethyl)piperidin-4-yl)-1H-indol-2-yl)benzamide (0.013 g, 86% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 - 11.09 (m, 1H), 8.06 (br s, 1H), 8.00 (br d, *J*=8.4 Hz, 2H), 7.74 (br d, *J*=8.1 Hz, 2H), 7.48 - 7.30 (m, 3H), 7.05 (br d, *J*=8.1 Hz, 1H), 2.90 (s, 2H), 2.74 (s, 2H), 2.67 (s, 3H), 2.51 (br s, 4H), 2.44 (s, 4H), 2.14 - 1.90 (m, 5H). HPLC tr 1.02 minutes (Method C). MS $(M+H)^+$ at *m/z* 391; HPLC tr 0.69 minutes (Method D).

2-(4-(2-(2,4-Dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5l**): Purification conditions: (Method H). 2-(4-(2-(2,4-Dimethoxyphenyl)-3-methyl-1H-indol-

5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.005 g, 5% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.34 - 7.23 (m, 3H), 6.96 (br d, *J*=7.9 Hz, 1H), 6.70 (d, *J*=2.1 Hz, 1H), 6.66 (dd, *J*=8.4, 2.3 Hz, 1H), 3.83 (s, 1H), 3.79 (s, 1H), 2.95 - 2.88 (m, 1H), 2.84 (q, *J*=7.2 Hz, 6H), 2.70 - 2.64 (m, 2H), 2.56 (s, 1H), 2.15 (s, 1H), 2.09 - 1.91 (m, 5H), 1.12 (t, *J*=7.2 Hz, 8H). HPLC tr 1.72 minutes (Method C). MS $(M+H)^+$ at *m/z* 408; HPLC tr 1.35 minutes (Method D).

2-(4-(2-(2,3-Dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (**5m**): Purification conditions: (Method H). Obtained 2-(4-(2-(2,3-Dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.005 g, 25% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.91 - 10.66 (m, 1H), 7.37 - 7.28 (m, 2H), 7.21 - 7.14 (m, 1H), 7.13 - 7.07 (m, 1H), 7.03 - 6.92 (m, 2H), 2.99 (br d, *J*=2.3 Hz, 1H), 2.95 - 2.82 (m, 2H), 2.66 (s, 2H), 2.55 (s, 3H), 2.18 (s, 3H), 2.08 - 1.88 (m, 5H). 10 aliphatic protons obscured by solvent (2.50 ppm 4H) and residual water (3.65 - 3.75 ppm 6H). HPLC tr 1.55 minutes (Method C). MS $(M+H)^+$ at *m/z* 408; HPLC tr 1.13 minutes (Method D).

2-(4-(2-(3-Ethoxy-4-isopropoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine **(5o)**: Purification conditions: (Method H). Obtained 2-(4-(2-(3-Ethoxy-4-isopropoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.014 g, 63% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 - 10.95 (m, 1H), 7.94 (s, 1H), 7.36 - 7.26 (m, 2H), 7.20 (s, 1H), 7.16 (br d, *J*=8.4 Hz, 1H), 7.07 (br d, *J*=8.4 Hz, 1H), 6.99 (br d, *J*=8.4 Hz, 1H), 4.11 (q, *J*=6.7 Hz, 2H), 2.89 (s, 3H), 2.73 (s, 3H), 2.66 (s, 3H), 2.38 (s, 3H), 2.12 - 1.84 (m, 5H), 1.37 (t, *J*=6.9 Hz, 4H), 1.33 - 1.23 (m, 9H) HPLC tr 1.66 minutes (Method C). MS $(M+H)^+$ at *m/z* 450; HPLC tr 1.50 minutes (Method D).

2-(4-(2-(Benzo[d][1,3]dioxol-5-yl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine **(5p)**: Purification conditions: (Method I). Obtained 2-(4-(2-(Benzo[d][1,3]dioxol-5-yl)-

3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethan-1-amine (0.009 g, 70% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 - 10.77 (m, 1H), 7.95 (s, 1H), 7.37 - 6.88 (m, 5H), 6.08 (s, 2H), 2.98 (br d, *J*=9.4 Hz, 2H), 2.90 (s, 2H), 2.74 (s, 3H), 2.43 - 2.27 (m, 5H), 2.05 (br d, *J*=7.1 Hz, 2H), 1.93 - 1.64 (m, 6H). HPLC tr 1.56 minutes (Method C). MS $(M+H)^+$ at *m/z* 392; HPLC tr 1.22 minutes (Method D).

1-(4-(2-(3,4-Dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)ethan-1-one (**6b**): In a 2 dram reaction vial was added 2-(3,4-dimethoxyphenyl)-3-methyl-5-(piperidin-4-yl)-1H-indole hydrochloride (0.015 g, 0.039 mmol), DCM (0.5 mL), TEA, (0.027 mL, 0.194 mmol) and acetyl chloride (0.007 g, 0.078 mmol). The reaction was stirred for 1 hour at 25 °C, then diluted with water (0.050 mL). The volatiles were removed under a stream of nitrogen gas, then diluted with DMF and filtered. The crude material was purified via preparative LC/MS (Method I) to afford *1-(4-(2-(3,4-dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)ethan-1-one (0.006 g, 36% yield)*. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.35 - 7.29 (m, 1H), 7.25 (d, *J*=8.2 Hz, 1H), 7.22 - 7.15 (m, 2H), 7.07 (d, *J*=8.2 Hz, 1H), 6.97 (br d, *J*=8.2 Hz, 1H), 4.62 - 4.45 (m, 1H), 3.98 - 3.88 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.14 (br s, 1H), 2.87 - 2.76 (m, 1H), 2.66 - 2.57 (m, 1H), 2.37 (s, 3H), 2.04 (s, 3H), 1.89 - 1.74 (m, 2H), 1.74 - 1.60 (m, 1H), 1.57 - 1.41 (m, 1H). HPLC tr 1.66 minutes (Method C). MS $(M+H)^+$ at *m/z* 393; HPLC tr 1.70 minutes (Method D).

The following compounds were prepared through the route described for **5n**:

3-(4-(2-(3,4-Dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylpropan-1-amine (**6c**): Purification conditions: (Method I). Obtained 3-(4-(2-(3,4-dimethoxyphenyl)-3-methyl-1H-indol-5-yl)piperidin-1-yl)-N-methylpropan-1-amine (0.005 g, 31% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 - 10.88 (m, 1H), 7.34 - 7.28 (m, 1H), 7.24 (br d, *J*=8.4 Hz, 1H), 7.22 - 7.15 (m, 2H), 7.07 (br d, *J*=8.4 Hz, 1H), 6.97 (br d, *J*=7.7 Hz, 1H), 3.89 (s, 1H), 3.84 (s, 3H),

3.80 (s, 3H), 2.99 (br d, *J*=10.1 Hz, 2H), 2.78 (br s, 1H), 2.38 (s, 6H), 1.99 (br t, *J*=10.4 Hz, 2H), 1.82 (s, 4H), 1.77 (br s, 6H). HPLC tr 1.24 minutes (Method C). MS $(M+H)^+$ at *m/z* 422; HPLC tr 1.12 minutes (Method D).

5-(1-(Azetidin-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-3-methyl-1H-indole (**6f**): Purification conditions: (Method I). Obtained 5-(1-(azetidin-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-3-methyl-1H-indole (0.013 g, 88% yield, purity = 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.30 (s, 1H), 7.25 (br d, *J*=8.1 Hz, 1H), 7.21 - 7.13 (m, 2H), 7.07 (br d, *J*=8.1 Hz, 1H), 6.96 (br d, *J*=8.1 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.69 - 3.51 (m, 3H), 2.82 (br t, *J*=7.4 Hz, 3H), 2.37 (s, 2H), 1.88 (br t, *J*=10.9 Hz, 2H), 1.81 (s, 3H), 1.74 - 1.63 (m, 2H), 1.10 (t, *J*=7.2 Hz, 2H). MS $(M+H)^+$ at *m/z* 406; HPLC tr 1.15 minutes (Method D).

The following compounds were prepared through the route described for **5n** with omission of HCl treatment:

2-(3,4-Dimethoxyphenyl)-3-methyl-5-(1'-methyl-[1,4'-bipiperidin]-4-yl)-1H-indole (**6d**): Purification conditions: (Method H). Obtained 2-(3,4-dimethoxyphenyl)-3-methyl-5-(1'-methyl-[1,4'-bipiperidin]-4-yl)-1H-indole (0.004 g, 24% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.34 - 7.26 (m, 2H), 7.24 - 7.15 (m, 2H), 7.08 (br d, *J*=8.4 Hz, 1H), 6.97 (br d, *J*=7.4 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.60 (br s, 2H), 3.45 (br d, *J*=6.7 Hz, 2H), 3.16 (br d, *J*=7.4 Hz, 2H), 3.02 (br s, 2H), 2.93 (br s, 2H), 2.79 (br s, 3H), 2.42 - 2.27 (m, 5H), 2.12 - 1.86 (m, 6H). HPLC tr 1.34 minutes (Method C). MS $(M+H)^+$ at *m/z* 448; HPLC tr 1.12 minutes (Method D).

2-(3,4-Dimethoxyphenyl)-3-methyl-5-(1-((1-methylpiperidin-2-yl)methyl)piperidin-4-yl)-1H-indole (**6e**): Purification conditions: (Method I). Obtained 2-(3,4-dimethoxyphenyl)-3-methyl-5-(1-((1-methylpiperidin-2-yl)methyl)piperidin-4-yl)-1H-indole (0.014 g, 58% yield). ^{1}H NMR

(500 MHz, DMSO-d_6) δ 10.91 (s, 1H), 7.30 (s, 1H), 7.24 (d, *J*=8.1 Hz, 1H), 7.21 - 7.14 (m, 2H), 7.07 (d, *J*=8.4 Hz, 1H), 6.96 (br d, *J*=8.1 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.95 (br s, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.19 - 1.92 (m, 5H), 1.89 (s, 3H), 1.81 - 1.59 (m, 6H), 1.50 (br s, 2H), 1.19 (br d, *J*=10.1 Hz, 2H). HPLC tr 1.60 minutes (Method C). MS $(M+H)^+$ at *m/z* 462; HPLC tr 1.03 minutes (Method D).

2-(3,4-Dimethoxyphenyl)-3-methyl-5-(1-((1-methyl-1H-imidazol-5-yl)methyl)piperidin-4-yl)-1H-indole (**6g**): Purification conditions: (Method I). Obtained 2-(3,4-dimethoxyphenyl)-3-methyl-5-(1-((1-methyl-1H-imidazol-5-yl)methyl)piperidin-4-yl)-1H-indole (0.002 g, 11% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.61 (br s, 1H), 7.60 (br s, 1H), 7.33 - 7.26 (m, 2H), 7.18 (br s, 2H), 7.08 (s, 1H), 6.97 (br d, *J*=7.9 Hz, 1H), 4.41 (br s, 2H), 3.83 (d, *J*=5.2 Hz, 6H), 3.79 (s, 3H), 3.64 - 3.42 (m, 4H), 2.88 (s, 1H), 2.37 (s, 3H), 2.00 (br s, 4H). HPLC tr 1.72 minutes (Method C). MS $(M+H)^+$ at *m/z* 445; HPLC tr 0.98 minutes (Method D).

2-(3,4-Dimethoxyphenyl)-3-methyl-5-(1-((2-methyl-1H-imidazol-5-yl)methyl)piperidin-4-yl)-1H-indole (**6h**): Purification conditions: (Method H). Obtained 2-(3,4-dimethoxyphenyl)-3-methyl-5-(1-((2-methyl-1H-imidazol-5-yl)methyl)piperidin-4-yl)-1H-indole (0.008 g, 47% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.62 (br s, 1H), 7.33 - 7.25 (m, 2H), 7.23 - 7.15 (m, 2H), 7.08 (br d, *J*=8.4 Hz, 1H), 6.96 (br d, *J*=8.4 Hz, 1H), 4.40 (br s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.63 - 3.38 (m, 1H), 3.17 - 3.05 (m, 2H), 2.92 - 2.83 (m, 2H), 2.54 (br s, 3H), 2.38 (s, 3H), 2.09 - 1.91 (m, 4H). HPLC tr 1.29 minutes (Method C) MS $(M+H)^+$ at *m/z* 445; HPLC tr 1.17 minutes (Method D).

2-(3,4-Dimethoxyphenyl)-3-methyl-5-(1-((1-methyl-1H-imidazol-2-yl)methyl)piperidin-4-yl)-1H-indole (**6i**): Purification conditions: (Method H). Obtained 2-(3,4-dimethoxyphenyl)-3-methyl-5-(1-((1-methyl-1H-imidazol-2-yl)methyl)piperidin-4-yl)-1H-indole (0.004 g, 20%

yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.49 (s, 1H), 7.32 (br s, 2H), 7.28 (d, *J*=8.1 Hz, 1H), 7.22 - 7.15 (m, 2H), 7.08 (d, *J*=8.1 Hz, 1H), 6.97 (br d, *J*=8.1 Hz, 1H), 4.39 (br s, 2H), 3.84 (s, 3H), 3.81 (d, *J*=5.4 Hz, 6H), 3.56 - 3.38 (m, 1H), 3.06 - 2.94 (m, 2H), 2.86 - 2.76 (m, 1H), 2.38 (s, 3H), 2.05 - 1.86 (m, 5H). HPLC tr 1.63 minutes (Method C). MS $(M+H)^+$ at *m/z* 445; HPLC tr 1.20 minutes (Method D).

2-(3,4-Dimethoxyphenyl)-3-methyl-5-(1-(pyridin-4-ylmethyl)piperidin-4-yl)-1H-indole (**6j**): Purification conditions: (Method I). Obtained 2-(3,4-dimethoxyphenyl)-3-methyl-5-(1-(pyridin-4-ylmethyl)piperidin-4-yl)-1H-indole (0.006 g, 32% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.49 (br d, *J*=3.7 Hz, 2H), 7.37 (br d, *J*=4.6 Hz, 2H), 7.31 (s, 1H), 7.25 (br d, *J*=8.2 Hz, 1H), 7.20 - 7.14 (m, 2H), 7.06 (br d, *J*=8.2 Hz, 1H), 6.97 (br d, *J*=8.2 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.66 - 3.50 (m, 4H), 2.95 - 2.83 (m, 2H), 2.36 (s, 1H), 2.17 - 2.05 (m, 2H), 1.89 (s, 1H), 1.76 (br s, 4H). HPLC tr 1.72 minutes (Method C). MS $(M+H)^+$ at *m/z* 442; HPLC tr 1.15 minutes (Method D).

Compound **7f** was prepared in an alternative route starting from compound **11c** in the following manner:

tert-*Butyl (2-(4-(2-bromo-3-isopropyl-1H-indol-5-yl)piperidin-yl)ethyl)(methyl)carbamate* (**13c**): In a 2 dram vial was added tert-butyl 4-(2-bromo-3-isopropyl-1H-indol-5-yl)piperidine-1-carboxylate (0.1 g, 0.24 mmol) and DCM (5 mL). The reaction was placed under a nitrogen atmosphere and cooled to 0 ^{o}C and hydrobromic acid in acetic acid (0.06 mL, 0.36 mmol) was added dropwise via syringe. The reaction was stirred at 0 ^{o}C for 15 minutes, then was quenched with TEA (0.1 mL, 1.18 mmol). To this was added *tert*-butyl methyl(2-oxoethyl)carbamate (0.045 g, 0.26 mmol) in DCM (1.0 mL). The reaction was stirred at 25 ^{o}C for 15 minutes and sodium triacetoxyborohydride (0.15 g, 0.71 mmol) was added and the reaction was stirred for an additional

60 minutes at 25 °C. The mixture was diluted with water and DCM and the layers were separated. The combined organics were washed with a saturated NaCl solution, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography to afford *tert*-butyl (2-(4-(2-bromo-3-isopropyl-1H-indol-5-yl)piperidin-yl)ethyl)(methyl)carbamate (0.053 g, 47% yield) as a yellowish solid. MS $(M+H)^+$ at *m/z* 480 HPLC tr 0.91 min (Method A).

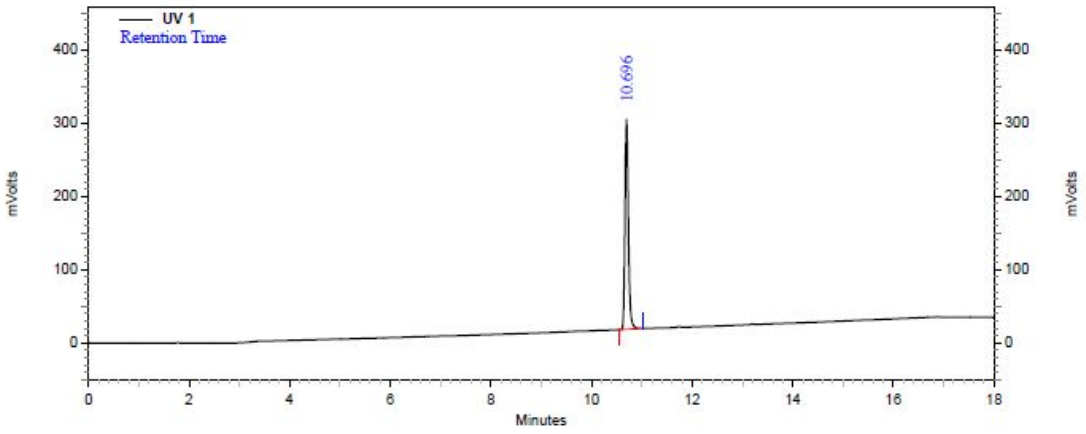
2-(4-(2-(3,4-Dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (**7f**): In a 2 dram vial was added *tert*-butyl (2-(4-(2-bromo-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)ethyl)(methyl)carbamate (0.025 g, 0.052 mmol), 2-(3,4-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.017 g, 0.063 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.47 g, 0.58 mmol) and THF (1 mL). The mixture was degassed for 1 minute and an aqueous solution of potassium phosphate, tribasic (0.052 mL, 0.16 mmol) was added and the mixture was again degassed with nitrogen gas. The reaction was heated at 75 °C for 18 hours. The mixture was diluted with ethyl acetate (10 mL), poured into a separatory funnel and was washed with water (2 X 5 mL), then brine (1 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was diluted with DCM (0.5 mL) and to this was added TFA (0.1 mL). The reaction was stirred at 25 °C for 30 minutes, then concentrated to dryness. The crude material was purified via preparative LCMS (Method I) to afford 2-(4-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)-N-methylethanamine (0.0048 g, 20% yield).

Additional characterization information for compound **7f**:

HRMS (ESI) for $C_{27}H_{38}N_3O_2$[M+H]+, calc. 436.2959; found, 436.2957

```
Inj. Vol. = 10 uL
Start % B = 0
Final % B = 100
Gradient Time = 15 min
Flow Rate = 1 ml/min
```

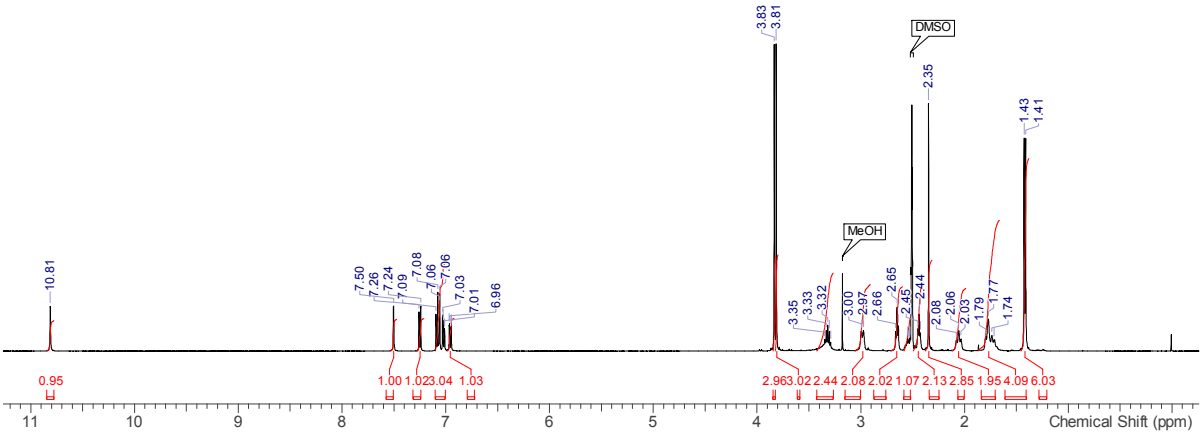
```
Wavelength1 = 254
Solvent Pair = MEOH/H2O/TFA
Solvent A = 10% MeOH - 90% H20 - 0.1% TFA
Solvent B = 90% MeOH - 10% H20 - 0.1% TFA
Column 5 = XBridge C18 3.5um 4.6 x 150mm
Oven Temp. = 40
```



UV 1 Results

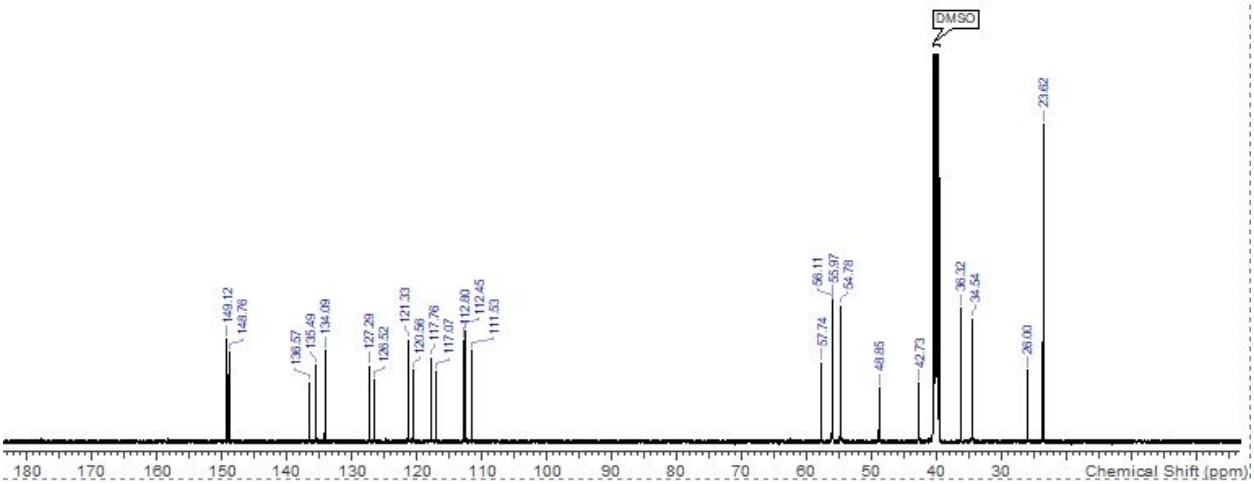
Pk #	RT	Area	Area %	Height (uV)	Plates
1	10.696	1341092	100.000	286135	133154
Totals		1341092	100.000	286135	

Figure S1: HPLC Analysis of Compound **7f**



^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 7.50 (s, 1H), 7.25 (d, *J*=8.34 Hz, 1H), 7.01-7.10 (m, 3H), 6.96 (dd, *J*=1.43, 8.34 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.32 (m, 2H), 2.98 (br d, *J*=10.85 Hz, 2H), 2.65 (br t, *J*=6.32 Hz, 2H), 2.52-2.59 (m, 1H), 2.40-2.49 (m, 2H), 2.35 (s, 3H), 2.06 (br t, *J*=10.67 Hz, 2H), 1.67-1.87 (m, 4H), 1.42 (d, *J*=7.15 Hz, 6H)

Figure S2: [1]HNMR of Compound **7f** (free-base).



^{13}C NMR (126 MHz, DMSO-d_6) δ 149.1, 148.8, 136.6, 135.5, 134.1, 127.3, 126.5, 121.3, 120.6, 117.8, 117.1, 112.8, 112.4, 111.5, 57.7, 56.1, 56.0, 54.8, 48.8, 42.7, 36.3, 34.5, 26.0, 23.6

Figure S3: [13]CNMR of Compound **7f** (free-base).

Summary of molecular formula, mass and observed ion for compounds **5—7.**

Compound	Molecular Formula	Observed	Exact Mass
5a	C23 H29 N3	348	347.2
5b	C24 H31 N3	362	361.3
5c	C24 H31 N3	362	361.3
5d	C24 H31 N3	362	361.3
5e	C24 H31 N3 O	378	377.3
5f	C24 H31 N3 O	378	377.3
5g	C24 H31 N3 O	378	377.3
5h	C24 H28 N4	373	372.2
5i	C24 H28 N4	373	372.2
5j	C24 H28 N4	373	372.2
5k	C24 H30 N4 O	391	390.2
5l	C25 H33 N3 O2	408	407.3
5m	C25 H33 N3 O2	408	407.3
5n	C25 H33 N3 O2	408	407.3
5o	C28 H39 N3 O2	450	449.3
5p	C24 H29 N3 O2	392	391.2

6a	C22 H26 N2 O2	351	350.2
6b	C24 H28 N2 O3	393	392.2
6c	C26 H35 N3 O2	422	421.3
6d	C28 H37 N3 O2	448	447.3
6e	C29 H39 N3 O2	462	461.3
6f	C25 H31 N3 O2	406	405.2
6g	C27 H32 N4 O2	445	444.3
6h	C27 H32 N4 O2	445	444.3
6i	C27 H32 N4 O2	445	444.3
6j	C28 H31 N3 O2	442	441.2
7a	C26 H35 N3 O2	422	421.3
7b	C24 H30 Cl N3 O2	428	427.2
7c	C25 H30 N4 O2	419	418.2
7d	C26 H35 N3 O2	422	421.3
7e	C26 H32 F3 N3 O2	476	475.2
7f	C27 H37 N3 O2	436	435.3
7g	C28 H39 N3 O2	450	449.3

Biological Assays.

Animal care use statement:

All experimental procedures with animals followed National Institutes of Health guidelines and were authorized by and in compliance with policies of the Bristol-Myers Squibb Animal Use and Care Committee

TLR3/4/7/8/9 Reporter Assays:

HEK-Blue™-cells (Invivogen) overexpressing human TLR3, TLR4, TLR7, TLR8 or TLR9 were used for evaluating inhibitors of these receptors using an inducible SEAP (secreted embryonic alkaline phosphatase) reporter gene under the control of the IFN-β minimal promoter fused to five NF-κB and AP-1-binding sites. Briefly, cells are seeded into Greiner 384 well plates (10,000 cells per well for TLR3, 25,000 cells for TLR4, 15,000 cells TLR7, 20,000 cells for TLR8 and 25,000 cells for TLR9) and then treated with test compounds in DMSO to yield a final

dose response concentration range of 0.05 nM–50 μM. After a 30 minute compound pre-treatment at room temperature, the cells are then stimulated with a TLR3 ligand (Poly IC, 5 migrogram/mL), TLR4 ligand (LPD-RK, 25 ng/mL), TLR7 ligand (gardiquimod at a final concentration of 7.5 μM), TLR8 ligand (R848 at a final concentration of 15.9 μM) or TLR9 ligand (ODN2006 at a final concentration of 5 nM) to activate NF-κB and AP-1 which induce the production of SEAP. After a 22 hour incubation at 37 °C, 5% CO_2, SEAP levels are determined with the addition of HEK-Blue™ Detection reagent (Invivogen), a cell culture medium that allows for detection of SEAP, according to manufacturer's specifications. The percent inhibition is determined as the % reduction in the HEK-Blue™ signal present in wells treated with agonist plus DMSO alone compared to wells treated with a known inhibitor.

TLR Whole Blood IL-6 Assays (Human and Mouse):

Human or mouse whole blood was stimulated with a TLR7 agonist (gardiquimod; final conc. 3 μM for human and 20 μM for mouse) or a TLR9 agonist (ODN-2216; final conc. 1 μM for human blood assay or ODN-1585; final conc. 10 μM for mouse blood assay). The inhibition of IL-6 production by the test compound relative to control was evaluated through ELISA analysis of IL-6. Total assay volume is 200 μl (5 μl compound in RPMI-1640 MEDIUM, 180 μl of human whole blood, 15 μl of agonist in working media) (Final DMSO conc. 0.2%).

Plasmacytoid Dendritic Cell (pDC) IFN-α production assay:

Whole blood was collected in 3.2% sodium citrate as an anticoagulant from healthy volunteers who found to be negative upon testing, for ongoing viral infections (HIV, HCV and HBV). Blood was diluted ~3x using sterile PBS and carefully layered on 15ml of histopaque in a conical

tube. Following centrifugation for 25 min\400 g\20° without brake, the mononuclear cell interphase was transferred to a new 50 ml conical tube. Following a wash with sterile PBS, cells were treated with ACK lysis buffer to get rid of RBC contamination, and washed again with sterile PBS. After taking a count on hemocytometer, cell count was adjusted to 5x107 cells per ml and used to isolate plasmacytoid dendritic cells (pDCs) by using pDC Enrichment Kit (CAT# 19062) from Easy Sep Stemcell Technologies as per manufacturer's instructions. Briefly, fresh PBMCs were subjected to immunomagnetic negative selection by targeting non-pDCs including myeloid dendritic cells (mDCs) for removal with antibodies (provided in the kit) recognizing specific cell surface markers. Unwanted cells are labeled with antibodies and magnetic particles are separated without columns using an EasySep™ magnet. Desired pDCs are then simply poured off into a new tube and used immediately to check the purity of population and to evaluate the effect of test compounds on IFN-alpha production. Purity of pDCs was checked by staining cells for CD304 and CD123 markers with respective antibodies conjugated with fluorochrome. Stained cells were then acquired on flow cytometer to estimate the purity of population. To understand the effect of test compound on TLR7 dependent IFN-α production, enriched pDCs were first incubated with different concentrations of test compounds in the presence or absence of UV inactivated flu virus for 24h. Similarly, compounds were evaluated upon incubation for 24h, in the presence or absence of ODN2216 to understand the impact on TLR9 dependent IFN-α production. Following incubation, supernatant was collected from each well and subjected for IFN-α Elisa as per manufacturer's instructions (Cat#41100-2, PBL Interferon Source). Percent suppression in IFN-α was calculated at each concentration of test compound with reference to DMSO control and IC50 was calculated by using GraphPad Prism software.

Mouse TLR7 and TLR9 Pharmacodynamic (PD) Model:

Adult male C57BL/6 mice were used for the experiments. Mice (7 to 10 per group) were randomized into different treatment groups based on body weight. Mice from the respective treatment groups were orally administered vehicle or test compound in vehicle. Thirty minutes after the oral administration of vehicle or test compound, mice were challenged with intraperitoneal injection of gardiquimod for TLR7 PD model or CpG-ODN-1585 for TLR9 PD model. Ninety minutes after gardiquimod injection or 120 minutes after CpG-ODN-1565 injection, mice were bled under isoflurane anesthesia and plasma IL-6 level was estimated by using commercially available ELISA kit (BD Biosciences). At the end of experiment, mean cytokine data was plotted and one way ANOVA with Dunnett's test was performed to calculate the significance of test compound treated group vs. vehicle control group. Percent inhibition of cytokine induction was calculated for test compound treated group vs vehicle control group.

Imiquimod-Induced Psoriasis:

Male C57BL/6 mice of 8–9 week age were used to evaluate the impact of TLR inhibition on imiquimod-induced psoriasis-like skin changes. Mice (7 to 10 per group) were randomized into different treatment groups based on body weight. Mice from the respective treatment groups were treated orally, once daily for 6 days with vehicle (40% 20 mM Citrate Buffer, 45% PEG-300, 10% Ethanol, 5% Pluronic F-68) or test compound. Psoriasis was induced by application of imiquimod cream on the shaved back region of the mice each day for 6 days. Disease severity was monitored daily by recording of skin thickness, erythema and scaling. At the end of experiment, one way ANOVA with Dunnett's test was performed to calculate the significance of test compound treated

group vs. vehicle control group. Overall percent reduction in imiquimod-induced psoriasis was calculated for test compound treated group vs vehicle control group.

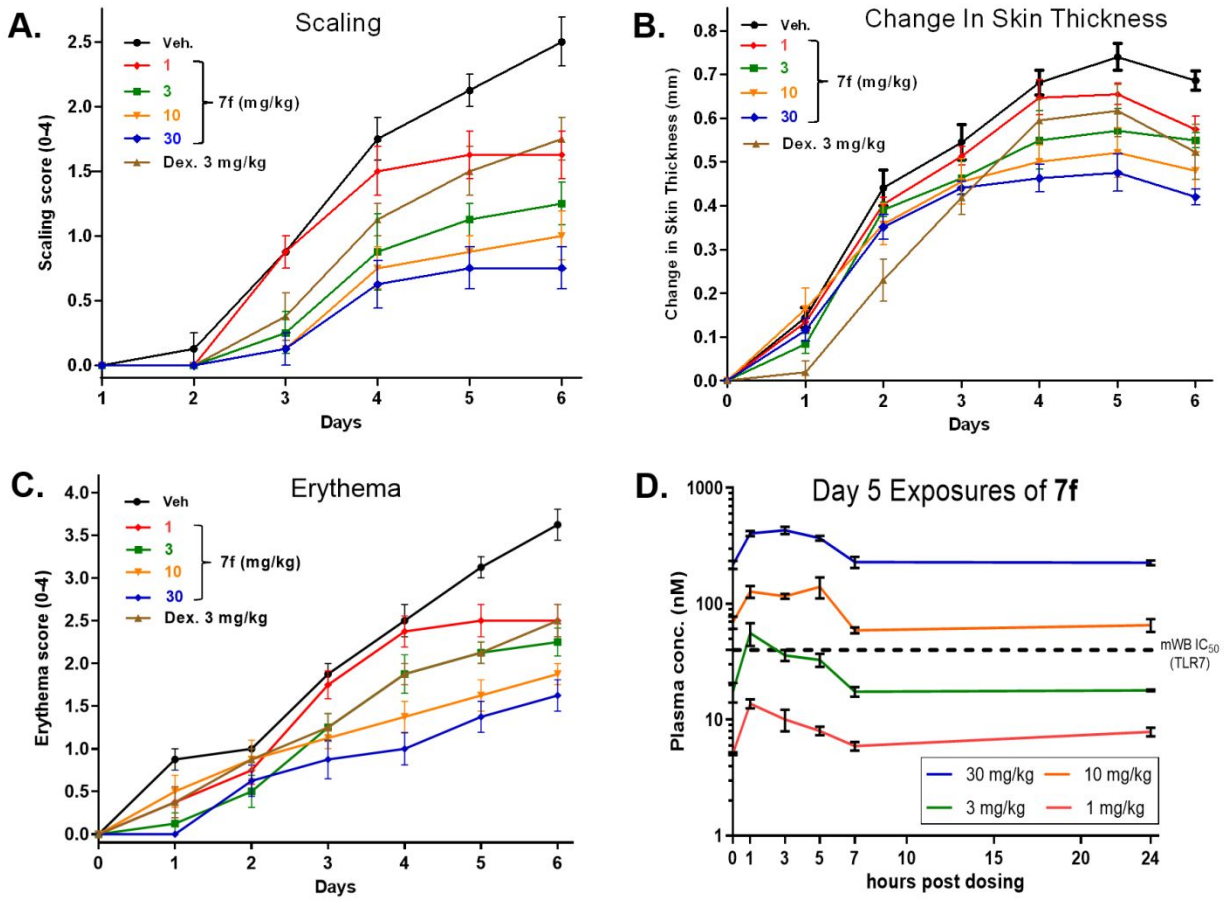


Figure S4: Efficacy of **7f** (1, 3, 10, 30 mg/kg) or dexamethasone (3 mg/kg) *vs.* vehicle in imiquimod-induced mouse model of psoriasis. N = 7–10 mice per group.

MRL/lpr Model of Lupus (SLE):

Male MRL/lpr mice of 12–14 weeks of age were screened and randomized based on the titers of anti-dsDNA antibodies and urinary NGAL (Neutrophil Gelatinase Associated Lipocalin). Mice were treated orally, once daily for 8 weeks with vehicle or test compound. The effect of test compound on disease severity was assessed by measuring endpoints including proteinuria, urinary-

NGAL (Neutrophil Gelatinase Associated Lipocalin), anti-dsDNA Antibody titer, plasma levels of IL10 and IL12p40, relative spleen weights and lymphadenopathy. At the end of experiment, one way ANOVA with Dunnett's test was performed to calculate the significance of test compound treated groups vs. vehicle control group. Percent reduction in disease severity was calculated for each parameter, for test compound treated groups vs vehicle control group.

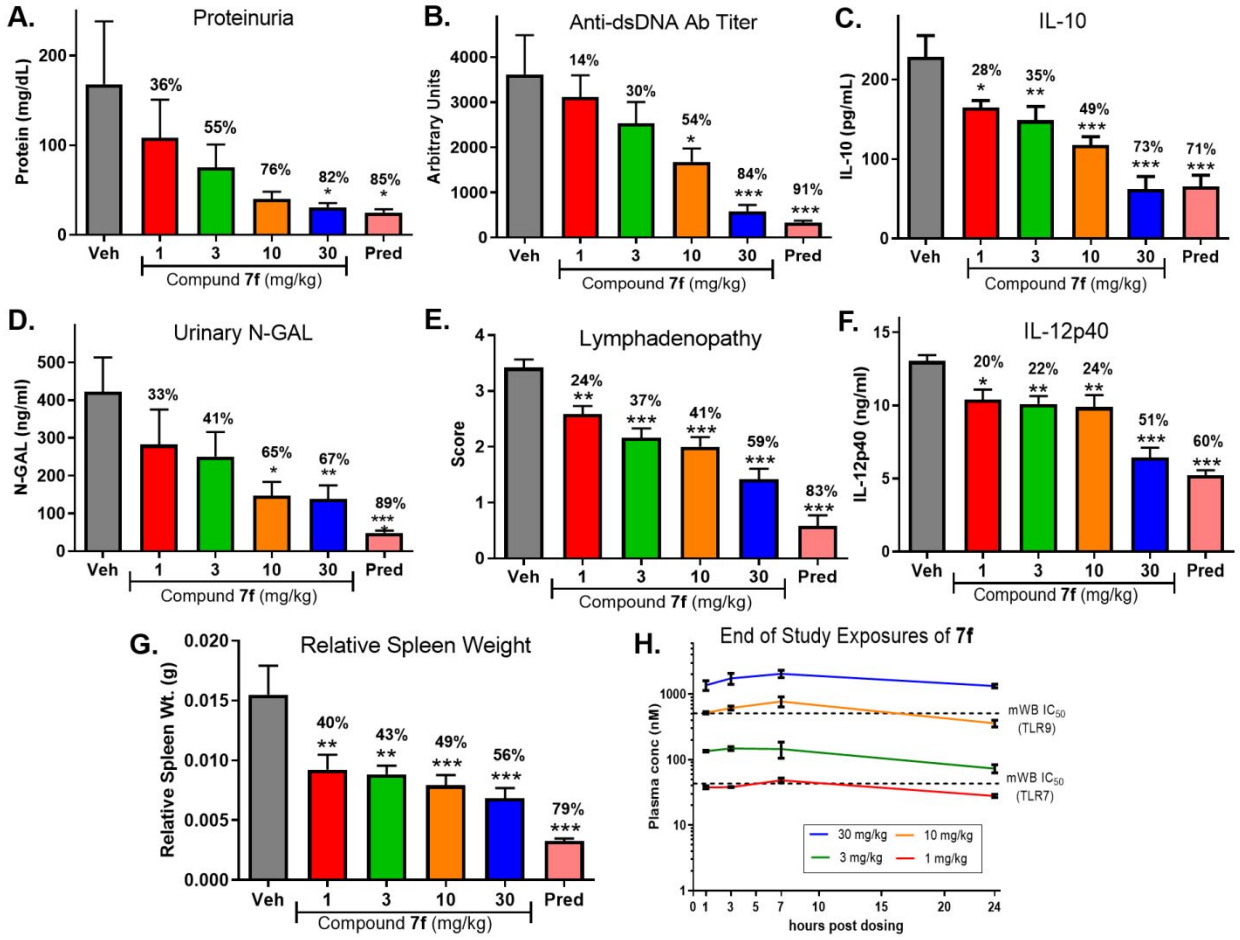


Figure S5: Efficacy of **7f** (1, 3, 10, 30 mg/kg) or prednisolone (10 mg/kg) *vs.* vehicle MRL/lpr mouse model of lupus. N = 12 mice per group.

X-ray Crystallographic Data and Refinement Statistics. Structure determination statistics for TLR8 in complex with compound **17c**. (PDB ID **6V9U**)

	TLR8+17c
Crystal parameters	
Space group	*C*2
Cell dimensions	*a* = 163.6 Å, *b* = 86.8 Å, *c* = 151.4 Å, *β* = 119.8 °
Molecules per AU[a]	2
Data Collection	
Beamline	APS, IMCA 17ID
Wavelength (Å)	1.0
Resolution range (Å)[b]	131.37–2.65 (2.79–2.65)
Observed / unique[c] reflections	180140 / 53326 (25949 / 7762)
Completeness (%)[b]	99.3 (99.9)
R_{merge} (%)[b,d]	5.9 (48.3)
$I/\sigma(I)$[b]	11.8 (2.3)
Refinement	
Resolution (Å)	131.37–2.65
R_{work}/R_{free}[e]	29.6 / 30.6
No. atoms	
Protein	11360
Ligand	665
Water	40
B-factors	
Protein	101.9
Ligand	47.4
Water	51.0
r.m.s.d.[f]	
Bond lengths (Å)	0.008
Bond angles (°)	0.97
Ramachandran (%)[g]	91.2 / 8.0 / 0.8

[a]Asymmetric unit. [b]Values in parentheses for resolution range, completeness, R_{merge}, and $I/\sigma(I)$ correspond to the last resolution shell. [c]Friedel pairs were treated as identical reflections. [d]$R_{merge}(I) = \sum_{hkl}\sum_j|[I(hkl)_j - I(hkl)]|/\sum_{hkl}I_{hkl}$, where $I(hkl)_j$ is the measurement of the intensity of reflection *hkl* and $\langle I(hkl)\rangle$ is the average intensity. [e]$R = \sum_{hkl}||F_{obs}| - |F_{calc}||/\sum_{hkl}|F_{obs}|$, where R_{free} is calculated without a σ cutoff for a randomly chosen 5% of reflections, which were not used for structure refinement, and R_{work} is calculated for the remaining reflections. [f]Root mean square deviations from ideal bond lengths/angles. [g]Number of residues in favored region/allowed region/outlier region.