Supporting Information

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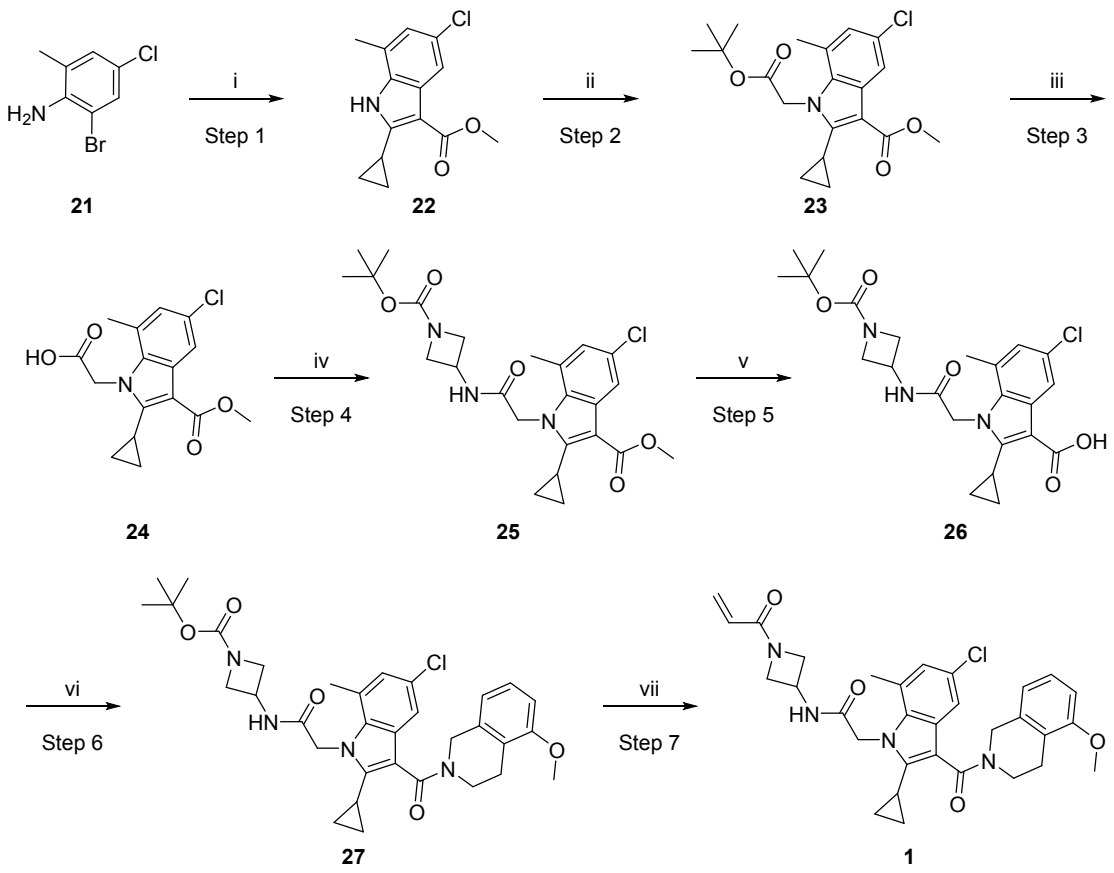
(i) Experimentals

General Chemistry. All solvents and chemicals used were reagent grade. Anhydrous solvents were purchased from Sigma-Aldrich and used as received. Analytical thin layer chromatography (TLC) and silica gel column chromatography were performed on Merck silica gel 60 (230-400 mesh). Removal of solvents was conducted using a rotary evaporator and residual solvents were removed from non-volatile compounds using a vacuum manifold maintained at approximately 1 Torr. All yields reported are isolated yields. Preparative reverse–phase high pressure liquid chromatography (RP–HPLC) was performed using an Agilent 1100 series HPLC and Phenomenex Gemini C18 column (5 μm, 100 mm × 30 mm i.d.), eluting with a binary solvent system, A and B, using a gradient elution [A, H_2O with 0.1% TFA, B, CH_3CN with 0.1% TFA] with UV detection at 220 nm. All final compounds were purified to ≥95% purity as determined by an Agilent 1100 series HPLC with UV detection at 220 nm using the following method: Zorbax SB-C8 column (3.5 μm, 150 mm × 4.6 mm i.d.), eluting with a binary solvent system, A and B, using a 5-95% B (0-15 min) gradient elution [A, H_2O with 0.1% TFA, B, CH_3CN with 0.1% TFA]; flow rate 1.5 mL/min. Mass spectral data was recorded on an Agilent 1100 series LC-MS with UV detection at 254 nm. NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as internal reference and coupling constants (*J*) are reported in hertz (Hz). Splitting patterns are indicated as follows: s = singlet; d = doublet; t = triplet; q = quartet; qn = quintet; dd = doublet of doublets; dt = doublet of triplets; tt = triplet of triplets; m = multiplet; br = broad peak.

Compound 1

2-(5-Chloro-2-cyclopropyl-3-((5-methoxy-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl)-7-methyl-1*H*-indol-1-yl)-*N*-(1-(2-propenoyl)-3-azetidinyl)acetamide



Reagents and conditions: (i) methyl 3-cyclopropyl-3-oxopropanoate, 2-(1*H*-tetrazol-1-yl)acetic acid, CuI/Cs_2CO_3, DMSO, 80 °C, 16 h, quantitative; (ii) *tert*-butyl 2-bromoacetate, NaH, DMF, 50 °C, 1.5 h, 77%; (iii) TFA, DCM, rt, 1.5 h, quantitative; (iv) *tert*-butyl 3-aminoazetidine-1-carboxylate, 1-propanephosphonic acid cyclic anhydride, 50 wt. % solution in EtOAc, DIPEA, DMF, rt, 1.5 h, 29%; (v) 5 N NaOH, MeOH-THF (2:1), 90 °C, 4.5 h, 77%; (vi) 5-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, HATU, DIPEA, DMF, rt, 2 h, 48%; (vii) (a) TFA, DCM, rt, 30 min (b) acryloyl chloride, DIPEA, DCM, 0 °C, 30 min, 63%.

Step 1: Methyl 5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate (22). A mixture of cesium carbonate (5.91 g, 18.14 mmol), 2-(1*H*-1,2,3,4-tetraazol-1-yl)acetic acid (0.23 g, 1.81 mmol), copper(I) iodide (0.17 g, 0.91 mmol) and 2-bromo-4-chloro-6-methylaniline **21** (2.00 g, 9.07 mmol) was treated with methyl 3-cyclopropyl-3-oxopropanoate (5.16 g, 36.3 mmol), and the mixture was stirred and heated at 80 °C overnight. The reaction mixture was treated with water and extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (eluent: 0-40% EtOAc/heptane) affording methyl 5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate **22** (2.39 g, 9.07 mmol, 100% yield) as viscous yellow-brown oil. ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.90 (d, *J*=1.7 Hz, 1 H), 7.76 (br s, 1 H), 6.98 (d, *J*=1.0 Hz, 1 H), 3.96 (s, 3 H), 3.04 (tt, *J*=8.7, 5.4 Hz, 1 H), 2.43 (s, 3 H), 1.20 - 1.28 (m, 2 H), 0.88 - 0.95 (m, 2 H). LCMS (ESI) *m/z* calculated for $C_{14}H_{14}ClNO_2$ $[M+H]^+$: 263.7, mass measured: 264.0.

Step 2: Methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate (23). A mixture of methyl 5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate **22** (2.39 g, 9.06 mmol) in THF (20 mL) was treated with sodium hydride, 60 wt% in mineral oil (1.16 g, 29.0 mmol) and allowed to stir at r.t. To the mixture was added *tert*-butylbromoacetate (2.95 mL, 18.13 mmol) and the reaction mixture allowed to stir at r.t. for 5 min and then the reaction mixture was carefully treated with DMF (10 mL) and stirred and heated at 50 °C for 1.5 h. The reaction mixture was treated with a saturated solution of $NaHCO_3$, extracted with EtOAc, washed with brine,

dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (eluent: 0-30% EtOAc/heptane) affording methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate **23** (2.65 g, 7.01 mmol, 77% yield) as light orange oil. LCMS (ESI) *m/z* calculated for $C_{20}H_{24}ClNO_4$ $[M+H]^+$: 377.9, mass measured: 378.2.

Step 3: 2-(5-Chloro-2-cyclopropyl-3-(methoxycarbonyl)-7-methyl-1*H*-indol-1-yl)acetic acid (24). A mixture of methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate **23** (2.65 g, 7.01 mmol) in DCM (10 mL) was treated with TFA (5.00 mL, 64.9 mmol) and stirred at r.t. for 1.5 h. The reaction mixture was concentrated in vacuo to afford 2-(5-chloro-2-cyclopropyl-3-(methoxycarbonyl)-7-methyl-1*H*-indol-1-yl)acetic acid **24** (2.26 g, 7.01 mmol, 100% yield). LCMS (ESI) *m/z* calculated for $C_{16}H_{16}ClNO_4$ $[M+H]^+$: 321.8, mass measured: 322.1.

Step 4: Methyl 1-(2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)amino)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate (25). 2-(5-Chloro-2-cyclopropyl-3-(methoxycarbonyl)-7-methyl-1*H*-indol-1-yl)acetic acid **24** (2.25 g, 6.99 mmol) in DMF (10 mL) was treated with DIPEA (4.89 mL, 28.0 mmol) and *tert*-butyl 3-aminoazetidine-1-carboxylate (1.20 mL, 6.99 mmol) and the solution was treated with 1-propanephosphonic acid cyclic anhydride, 50 wt. % solution in EtOAc (5.00 mL, 8.39 mmol). The reaction mixture was stirred at r.t. for 1.5 h. The reaction mixture was treated with brine and extracted with EtOAc and washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (eluent: 0-50% EtOAc/heptane) affording methyl 1-(2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)amino)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate **25** (0.96 g, 2.02 mmol, 29% yield) as white amorphous solid. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.94 (d, *J*=7.0 Hz, 1 H), 7.82 (d, *J*=1.8 Hz, 1 H), 6.99 (s, 1 H), 5.23 (s, 2 H), 4.27 - 4.49 (m, 2 H), 4.00 - 4.12 (m, 3 H), 3.83 (s, 3 H), 3.58 - 3.74 (m, 3 H), 1.81 - 1.91 (m, 1 H), 1.37 (s, 9 H), 1.08 - 1.15 (m, 2 H), 0.67 (br d, *J*=4.1 Hz, 2 H). LCMS (ESI) *m/z* calculated for $C_{24}H_{30}ClN_3O_5$ $[M+Na]^+$: 498.2, mass measured: 498.2.

Step 5: 1-(2-((1-(*tert*-Butoxycarbonyl)azetidin-3-yl)amino)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylic acid (26). To a solution of methyl 1-(2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)amino)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylate **25** (0.96 g, 2.02 mmol) in MeOH (20 mL) and THF (10 mL) was added sodium hydroxide, 5 N (6.05 mL, 30.3 mmol). The resulting mixture was stirred and heated at 90 °C for 4.5 h. The mixture was concentrated in vacuo and the reaction mixture was cooled to 0 °C in an ice bath and treated with hydrochloric acid, 2.5 N (12.9 mL, 32.3 mmol) slowly. The resulting white suspension was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The white solid was collected and dried to afford 1-(2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)amino)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylic acid **26** (0.72 g, 1.56 mmol, 77% yield) as off-white amorphous solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 8.94 (br d, *J*=7.7 Hz, 1 H), 7.88 (br s, 1 H), 6.93 - 6.97 (m, 1 H), 5.21 (s, 2 H), 4.03 - 4.53 (m, 5 H), 3.70 (br dd, *J*=7.5, 5.4 Hz, 3 H), 1.77 - 1.86 (m, 1 H), 1.37 (s, 9 H), 1.08 (br dd, *J*=8.8, 2.4 Hz, 2 H), 0.71 (br d, *J*=4.8 Hz, 2 H). LCMS (ESI) *m/z* calculated for $C_{23}H_{28}ClN_3O_5$ $[M+Na]^+$: 484.2, mass measured: 484.2.

Step 6: *tert*-Butyl 3-(2-(5-chloro-2-cyclopropyl-3-(5-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-7-methyl-1*H*-indol-1-yl)acetamido)azetidine-1-carboxylate (27). A mixture of 1-(2-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)amino)-2-oxoethyl)-5-chloro-2-cyclopropyl-7-methyl-1*H*-indole-3-carboxylic acid **26** (0.39 g, 0.84 mmol), 5-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.19 g, 0.93 mmol) in DMF (5 mL) and DIPEA (0.74 mL, 4.22 mmol) was treated wtih HATU (0.40 g, 1.06 mmol) and the reaction mixture was stirred at r.t. for 2 h. The reaction mixture was treated with a saturated solution of $NaHCO_3$, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo affording *tert*-butyl 3-(2-(5-chloro-2-cyclopropyl-3-(5-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-7-methyl-1*H*-indol-1-yl)acetamido)azetidine-1-carboxylate **27** (0.25 mg, 0.41 mmol, 48% yield) as light yellow film. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.92 (br dd, *J*=12.0, 6.2 Hz, 1 H), 7.04 - 7.26 (m, 2 H), 6.48 - 6.96 (m, 3 H), 5.14 (br s, 2 H), 4.40 - 4.88 (m, 3 H), 3.84 - 4.16

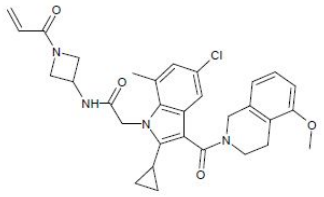
(m, 4 H), 3.50 - 3.83 (m, 6 H), 2.72 - 2.79 (m, 1 H), 2.56 (s, 3 H), 1.71 - 1.89 (m, 1 H), 1.38 (s, 9 H), 0.29 - 0.92 (m, 4 H). LCMS (ESI) *m/z* calculated for $C_{33}H_{39}ClN_4O_5$ [M-Boc]: 507.2, mass measured: 507.2.

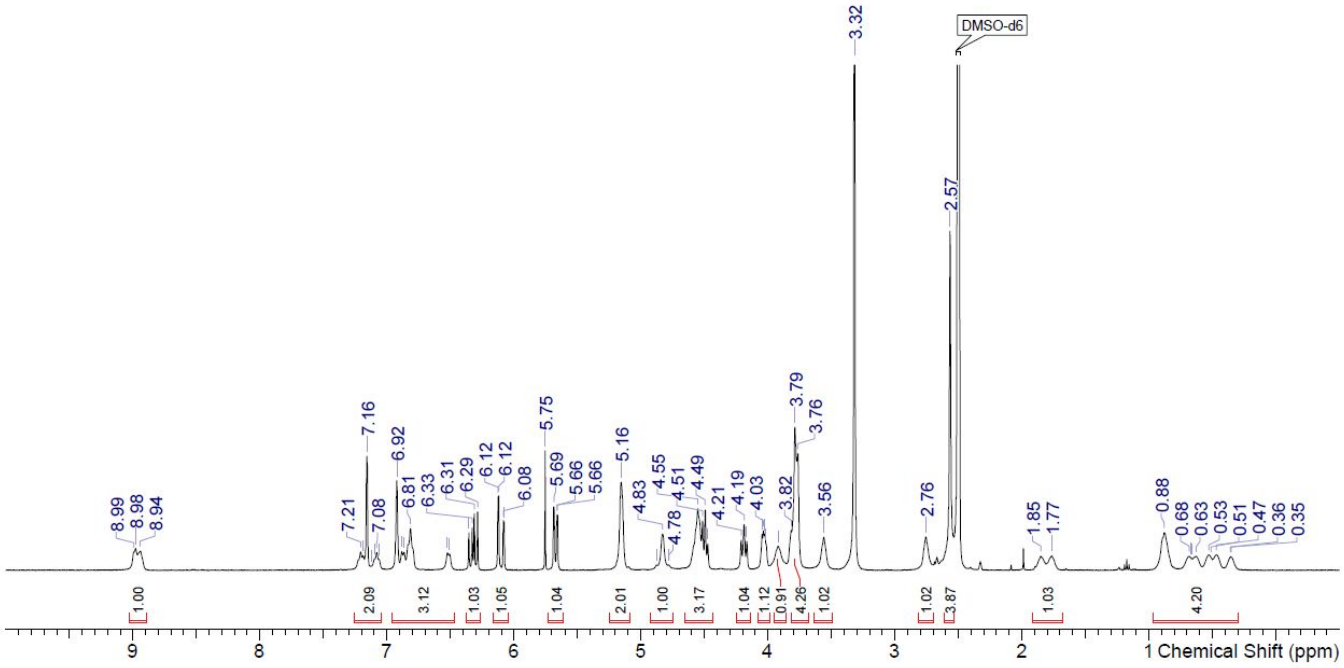
Step 7: 2-(5-Chloro-2-cyclopropyl-3-((5-methoxy-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl)-7-methyl-1*H*-indol-1-yl)-*N*-(1-(2-propenoyl)-3-azetidinyl)acetamide (1). A mixture of *tert*-butyl 3-(2-(5-chloro-2-cyclopropyl-3-(5-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-7-methyl-1*H*-indol-1-yl)acetamido)azetidine-1-carboxylate **27** (0.25 g, 0.41 mmol) in DCM (5 mL) was treated with TFA (2.0 mL, 26.0 mmol) was stirred at r.t. for 30 min. The reaction mixture was concentrated in vacuo to afford *N*-(azetidin-3-yl)-2-(5-chloro-2-cyclopropyl-3-(5-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-7-methyl-1*H*-indol-1-yl)acetamide. The crude product was treated with DCM (5 mL) in an ice bath and treated with DIPEA (0.21 mL, 1.23 mmol) and acryloyl chloride (37 uL, 0.45 mmol). The mixture was stirred at 0 °C for 30 min. The reaction mixture was treated with a saturated $NaHCO_3$, extracted with DCM, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (eluent: 0-30% DCM-MeOH (4:1)/DCM) affording 2-(5-chloro-2-cyclopropyl-3-((5-methoxy-3,4-dihydro-2(1*H*)-isoquinolinyl)carbonyl)-7-methyl-1*H*-indol-1-yl)-*N*-(1-(2-propenoyl)-3-azetidinyl)acetamide **1** (0.14 g, 0.26 mmol, 63% yield) as white amorphous solid. ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 8.89 - 9.03 (m, 1 H), 7.04 - 7.25 (m, 2 H), 6.47 - 6.96 (m, 3 H), 6.32 (dd, *J*=17.0, 10.4 Hz, 1 H), 6.10 (dd, *J*=17.0, 1.9 Hz, 1 H), 5.61 - 5.73 (m, 1 H), 5.16 (br s, 2 H), 4.74 - 4.92 (m, 1 H), 4.43 - 4.66 (m, 3 H), 4.19 (br t, *J*=8.8 Hz, 1 H), 4.03 (br dd, *J*=8.3, 4.6 Hz, 1 H), 3.92 (br s, 1 H), 3.72 - 3.85 (m, 4 H), 3.56 (br s, 1 H), 2.76 (br s, 1 H), 2.57 (s, 4 H), 1.68 - 1.92 (m, 1 H), 0.30 - 0.96 (m, 4 H). ^{13}C NMR (at 300 K, 151 MHz, DMSO-d6) ppm 6.77 (dd, J=257.67, 21.85 Hz, 1 C), 19.15 (s, 1 C), 22.77 (br s, 1 C), 39.43 (br s, 1 C), 44.05 (br d, J=16.65 Hz, 1 C), 47.83 - 48.37 (m, 1 C), 48.83 (br s, 1 C), 54.67 (s, 1 C), 55.74 (s, 1 C), 57.34 (s, 1 C), 108.05 - 108.73 (m, 1 C), 108.96 - 109.60 (m, 1 C), 115.60 - 116.74 (m, 1 C), 119.10 (br s, 1 C), 124.69 (s, 1 C), 127.11 (s, 1 C), 127.21 (br s, 1 C), 133.89 (s, 1 C), 135.09 (br d, J=53.41 Hz, 1 C), 141.20 - 142.89 (m, 1 C), 157.15 - 157.29 (m, 1 C), 165.09 (s, 1 C), 168.76 (s, 1 C). HRMS (ESI) *m/z* calculated for $C_{31}H_{33}ClN_4O_4$ $[M+H]^+$: 561.2269; mass measured, 561.2272.

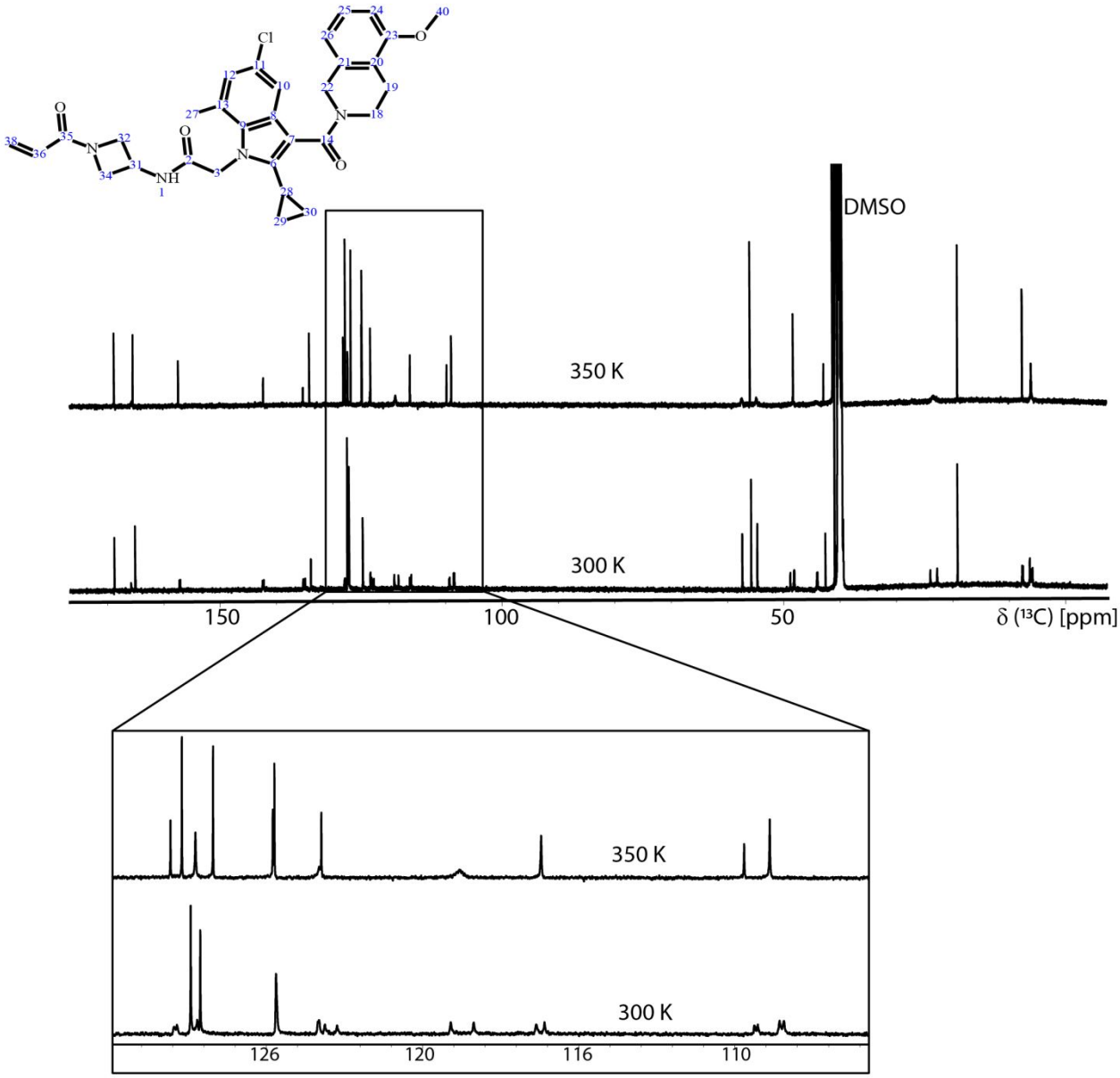
.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 - 9.03 (m, 1 H), 7.04 - 7.25 (m, 2 H), 6.47 - 6.96 (m, 3 H), 6.32 (dd, *J*=17.0, 10.4 Hz, 1 H), 6.10 (dd, *J*=17.0, 1.9 Hz, 1 H), 5.61 - 5.73 (m, 1 H), 5.16 (br s, 2 H), 4.74 - 4.92 (m, 1 H), 4.43 - 4.66 (m, 3 H), 4.19 (br t, *J*=8.8 Hz, 1 H), 4.03 (br dd, *J*=8.3, 4.6 Hz, 1 H), 3.92 (br s, 1 H), 3.72 - 3.85 (m, 4 H), 3.56 (br s, 1 H), 2.76 (br s, 1 H), 2.57 (s, 4 H), 1.68 - 1.92 (m, 1 H), 0.30 - 0.96 (m, 4 H)

33 H's / 33 H's (spectrum / structure)







13C NMR (at 350 K, 151 MHz, DMSO-d6) δ ppm 6.05 (br s, 1 C) 7.61 (s, 1 C) 19.09 (s, 1 C) 21.77 - 24.82 (m, 1 C) 39.81 (s, 1 C) 48.26 (s, 1 C) 54.26 - 55.02 (m, 1 C) 55.91 (s, 1 C) 56.62 - 57.75 (m, 1 C) 108.88 (s, 1 C) 109.70 (s, 1 C) 116.20 (s, 1 C) 118.05 - 119.55 (m, 1 C) 123.24 (s, 1 C) 124.74 (s, 1 C) 124.79 (s, 1 C) 126.70 (s, 1 C) 127.26 (s, 1 C) 127.70 (s, 1 C) 128.06 (s, 1 C) 134.10 (s, 1 C) 135.21 (br s, 1 C) 142.26 (s, 1 C) 157.34 (s, 1 C) 165.38 (s, 1 C) 168.75 (s, 1 C)

13C NMR (at 300 K, 151 MHz, DMSO-d6) δ ppm 6.77 (dd, J=257.67, 21.85 Hz, 1 C) 19.15 (s, 1 C) 22.77 (br s, 1 C) 39.43 (br s, 1 C) 44.05 (br d, J=16.65 Hz, 1 C) 47.83 - 48.37 (m, 1 C) 48.83 (br s, 1 C) 54.67 (s, 1 C) 55.74 (s, 1 C) 57.34 (s, 1 C) 108.05 - 108.73 (m, 1 C) 108.96 - 109.60 (m, 1 C) 115.60 - 116.74 (m, 1 C) 119.10 (br s, 1 C) 124.69 (s, 1 C) 127.11 (s, 1 C) 127.21 (br s, 1 C) 133.89 (s, 1 C) 135.09 (br d, J=53.41 Hz, 1 C) 141.20 - 142.89 (m, 1 C) 157.15 - 157.29 (m, 1 C) 165.09 (s, 1 C) 168.76 (s, 1 C)

(ii) KRAS LCMS Assay Procedure:

Mass Spectrometry Assay Conditions

MS assays were performed in the following buffer: 25 mM HEPES pH 7.4, 20 mM $MgCl_2$, 10 mM NaCl, 3% DMSO, 0.0005% CHAPS with 100 μM GDP made fresh and added to the assay buffer. The final concentration of $KRAS^{G12C}$ was 2 μM. Assay incubation times were 1 min, 10 min, 2 h, or 20 h and the inhibitor concentration was 10 μM. Greiner polypropylene clear V-bottom plates were used for the mass spectrometry assays. Typically, the reaction was initiated by addition of $KRAS^{G12C}$ to a well containing inhibitor followed by Rapidfire MS analysis. Relative % bound values at the various incubation times were used to estimate a k_{obs} value at 10 μM inhibitor

Instrumentation

RapidFire Sample Liquid handling System

The RapidFire liquid handling unit used was the RF 360 model. Solvents were delivered by Agilent 1260 Infinity pumps. The instrument control software was the Agilent RapidFire High Throughput MS-system software (v4.0.12333.14274). A single C4 Type A (Agilent technologies, G9203) SPE-cartridge was used for these experiments. A volume of 10 μL (sample loop determined) was removed from each well of a 384-well plate by using an aspiration time of 300 ms. The sample load/wash time was 6000 ms at a flow rate of 1.25 mL/min (H_2O, 0.1% v/v formic acid, 0.05% v/v trifluoroacetic acid); elution time was 7000 ms (acetonitrile, 0.1% v/v formic acid, 0.05% v/v trifluoroacetic acid); re-equilibration time was 700 ms at a flow rate of 1.25 mL/min (H_2O, 0.1% v/v formic acid, 0.05% v/v trifluoroacetic acid).

Mass Spectrometry

Mass spectrometric data was acquired on an Agilent 6530 quadrupole time-of-flight (ToF) MS system, operated with a dual Agilent Jet Spray (AJS) ion source, in positive ionization mode. The instrument parameters were as follows: gas temperature 350 °C; drying gas 5 L/min; nebulizer 60 psi; sheath gas 350 °C; sheath gas flow 11 L/min; capillary 3.5 kV (0.037 μA); nozzle 1.75 kV; fragmentor 200 V; skimmer 75 V; octapole RF 800 V peak-to-peak. Data was acquired at the rate of 5 spectra/s. The mass scale was calibrated using the Agilent positive ion tune mix, over the *m/z* range 300-3200. The instrument control software was Agilent MassHunter Workstation Data Acquisition (vB.05.01).

Mass Spectrometry Data Processing and Informatics

All data processing was performed using a HP Z620, 64-bit, 12-processor, Windows 7 PC, using a combination of Agilent MassHunter Qualitative Analysis (B.05.00) Agilent RapidFire control software (v4.0.12333.14070) and the Agilent DA Reprocessor Offline Utilities B.05.00, Build 162. The SPE-MS data acquired from the RapidFire-MS system is typically a single SPE-MS data file composed of multiple injection events. For effective charge state extraction, SPE-peak integration and subsequent MS-spectral deconvolution, the single SPE-MS data file is split into single injection events. This is typically performed off-line and achieved through the RapidFire User Interface software, using the Agilent RapidFire control software (v4.0.12333.14070) using the Convert MS Data option. Once the individual injection-event MS-data files have been produced, they are all batch processed using the DA Reprocessor Offline Utilities (B.05.00, Build 162, Agilent). For batch processing a method file was created using Agilent MassHunter Qualitative Analysis B.05.00. The details of this method file are contained within the BioConfirm Workflow and are as follows: Integrate (MS), Integrator Selection: General, smooth option selected; detector point sampling 1; start threshold 5.0; stop threshold 0.0; filtering 5 point; peak location, top. Extract (MS): Peak Spectrum Extraction (MS) within *m/z* 800-1400. Deconvolute (MS) Maximum Entropy: mass range 19,000-21,000 Daltons; Mass step 1.0 Da; S/N threshold 20.0; Use limited *m/z* range 800-1400; adduct proton; isotope peak width automatic; minimum consecutive charge states 5.

Once the individual injection event MS-files are processed using the method file described above, a single report file is generated for each injection event MS-file, in the form of an Excel spreadsheet. Relevant protein molecular weight and intensity values, contained within specific cells in the spread sheet are extracted from the Excel report/results file using a custom routine written within Pipeline Pilot (BIOVIA) and used to calculate percent-of-control (POC) and percent-bound (% -Bound) values in the form of a concatenated output file (text, tab delimited in format; Figure S4a). POC = (Unmodified Protein Peak Intensity/ Control Protein Peak Intensity) x100 and % Bound = (Expected Protein Adduct Peak Intensity/ Control Protein Peak Intensity) x100. Relative % Bound = % Bound/(POC + % Bound) x100 is a normalized measure of covalent binding that accounts for sample variability or compound effects on ionization or detection efficiencies. These values are then input into Amgen's data analysis suite (Genedata) for further data analysis and then finally loaded into Amgen's central database. The specific input files for the Pipeline Pilot script are the Excel report/result file directory; the compound molecular weight file (Amgen registry compound number and expected covalent modification) and the Injection Sequence File (RFTIME file; not shown), which is produced during the RapidFire-MS acquisition and contains the injection sequence, injection position and the plate bar code (which corresponds with the 384-well plate map dispensed by the Amgen Sample Bank). Additional information that is manually input to the Pipeline Pilot routine via a user interface are the protein's molecular weight (average molecular weight in Da) and the molecular weight variance, typically 0.01% (± 2 Da for a 19.5 kDa protein).

(iii) Noncovalent Binding to KRAS^{G12} by ^{1}H-ddNMR:

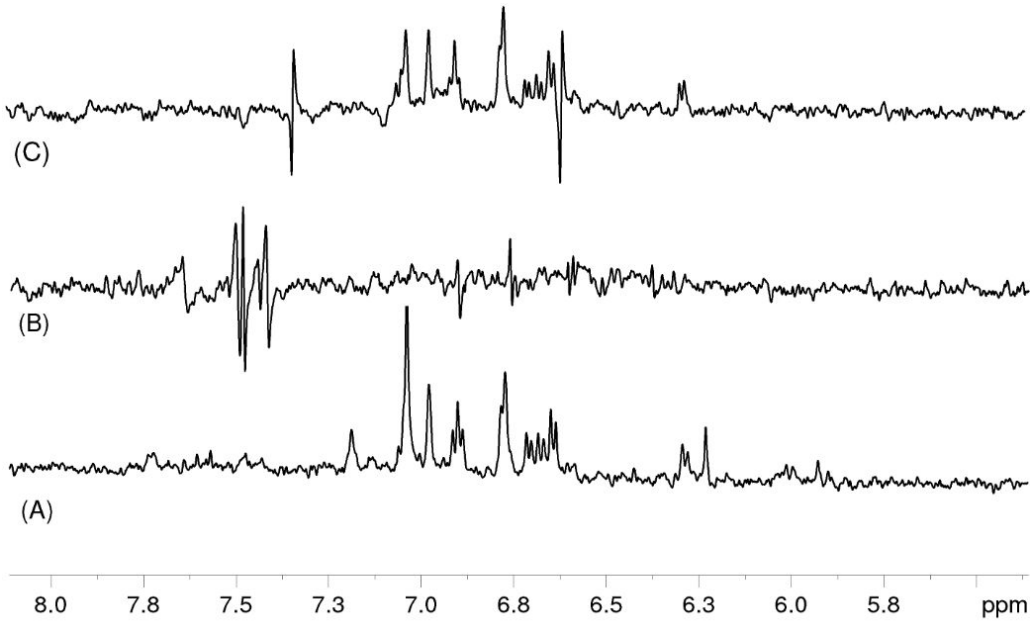


Figure S1. Binding of Compound **1** to KRAS^{G12} as determined by ^{1}H-ddNMR (proton direct deconvolution NMR) using split samples with the protein and the compound plus protein, followed by subtraction of the corresponding spectra. The spectra were recorded with excitation sculpting[1] pulse sequence for the suppression of water signal and only aromatic expansions are shown (**A**) 10 μM of Compound **1** in protein buffer. (**B**) Deconvoluted spectrum obtained for 10 μM of Compound **1** plus 15 μM of KRAS^{G12}. Based on the free fraction of the ^{1}H NMR signals at 6.32 and 6.70 ppm, which are in slow exchange limit, the estimated K_D < 20 μM. (**C**) The same control experiment with 10 μM of Compound **1** and 100 μM of ubiquitin. The deconvoluted spectrum shows no binding. As determined by ^{1}H NMR Compound **1** is readily soluble in the protein buffer up to 20 μM and starts to aggregate above this concentration.

1. T-L. Hwang, A.J. Shaka *J. Am. Chem. Soc*. **1992**, *114*, 3157-3159

(iv) Coupled Nucleotide Exchange Assay: Purified GDP-bound KRAS protein (aa 1-169), containing both G12C and C118A amino acid substitutions and an *N*-terminal His-tag, was pre-incubated in assay buffer (25 mM HEPES pH 7.4, 10 mM $MgCl_2$, and 0.01% Triton X-100) with a compound dose-response titration for either 2 hours. Following compound pre-incubation, purified SOS protein (aa 564-1049) and GTP (Roche 10106399001) were added to the assay wells and incubated for an additional hour. To determine the extent of inhibition of SOS-mediated nucleotide exchange, purified GST-tagged cRAF (aa 1-149), nickel chelate AlphaLISA acceptor beads (PerkinElmer AL108R), and AlphaScreen glutathione donor beads (PerkinElmer 6765302) were added to the assay wells and incubated for 10 minutes. The assay plates were then read on a PerkinElmer EnVision® Multilabel Reader, using AlphaScreen® technology, and data were analyzed using a 4-parameter logistic model to calculate IC_{50} values.

(v) Phospho-ERK1/2 MSD Assay: MIA PaCa-2 (ATCC® CRL-1420™) or A549® (CCL-185™) cells were cultured in RPMI 1640 Medium (ThermoFisher Scientific 11875093) containing 10% fetal bovine serum (ThermoFisher Scientific 16000044) and 1x penicillin-streptomycin-glutamine (ThermoFisher Scientific 10378016). Sixteen hours prior to compound treatment, MIA PaCa-2 or A549 cells were seeded in 96-well cell culture plates at a density of 25,000 cells/well and incubated at 37 °C, 5% CO_2. A compound titration was diluted in growth media, added to appropriate wells of a cell culture plate, and then incubated at 37 °C, 5% CO_2 for 4 hours. Following compound treatment, cells were stimulated with 10 ng/mL EGF (Roche 11376454001) for 10 min, washed with ice-cold Dulbecco's phosphate-buffered saline, no Ca^{2+} or Mg^{2+} (ThermoFisher Scientific 14190144), and then lysed in RIPA buffer (50 mM Tris-HCl pH 7.5, 1% Igepal, 0.5% sodium deoxycholate, 150 mM NaCl, and 0.5% sodium dodecyl sulfate) containing protease inhibitors (Roche 4693132001) and phosphatase inhibitors (Roche 4906837001). Phosphorylation of ERK1/2 in compound-treated lysates was assayed using Phospho-ERK1/2 Whole Cell Lysate kits (Meso Scale Discovery K151DWD) according to the manufacturer's protocol. Assay plates were read on a Meso Scale Discovery Sector Imager 6000. The luminescence signal of treated samples was normalized to DMSO control, and data were analyzed using a 4-parameter logistic model to calculate IC_{50} values.

(vi) Cell Viability Assay: MIA PaCa-2 or A549 cells were cultured as described above. Sixteen hours prior to compound treatment, MIA PaCa-2 or A549 cells were seeded in 384-well cell culture plates at a density of 500 cells/well and incubated at 37 °C, 5% CO_2. A compound titration was diluted in growth media, added to appropriate wells of a cell culture plate, then incubated at 37 °C, 5% CO_2 for 72 hours. Cell viability was measured using a CellTiter-Glo® Luminescent Cell Viability Assay kit (Promega G7571) according to the manufacturer's protocol. Assay plates were read on a Perkin Elmer EnVision® Multilabel Reader. The luminescence signal of treated samples was normalized to DMSO control, and data were analyzed using a 4-parameter logistic model to calculate IC_{50} values.

(vii) Crystallography Table of Statistics

Data collection and refinement statistics

	6P8W (Compound 2)	6P8X (Compound 5)	6P8Y (Compound 6)	6P8Z (Compound 1)
Data collection				
Wavelength (Å)	1.5418	1.0000	1.0000	0.97741
Space group	P 1	P 1	P 1 21 1	P 1 21 1
Cell dimensions				
a, *b*, *c* (Å)	32.85, 39.08, 61.85	33.33, 66.15, 78.63	33.76, 106.05, 39.90	39.76, 65.39, 62.60
α, β, γ (°)	78.30, 81.43, 77.30	66.48, 78.75, 89.47	90.00, 93.90, 90.00	90.00, 105.09, 90.00
Resolution (Å)	30.0 - 2.10 (2.18 - 2.10)	30.0 - 2.10 (2.18 - 2.10)	30.0 - 2.30 (2.38 - 2.30)	30.0 – 1.65 (1.71 – 1.65)
Unique reflections	17067	34585	12295	37138
R_{sym}	0.068 (0.246)	0.152 (0.533)	0.190 (0.511)	0.108 (0.613)
$I / \sigma I$	10.2 (3.05)	3.9 (1.86)	5.9 (3.07)	7.1 (1.55)
Completeness (%)	93.9 (78.5)	97.5 (93.4)	96.9 (97.9)	98.7 (99.8)
Redundancy	1.9 (1.8)	3.4 (3.1)	5.8 (4.8)	3.4 (3.5)
Refinement				

Resolution (Å)	30.00 - 2.10	29.86 - 2.11	30.00 - 2.31	30.00 – 1.65
Completeness (%)	93.78	96.74	96.59	98.11
No. reflections	15252	32118	11311	34850
R_{work} / R_{free}	0.2299 / 0.2769	0.2653 / 0.3129	0.2374 / 0.2690	0.2293 / 0.2693
No. atoms	2950	5781	2731	3036
Protein	2689	5334	2571	2641
Ligand/ion	118	254	130	140
Water	143	193	30	255
Average B overall (Å^2)	30.21	32.24	51.32	32.30
R.m.s. deviations				
Bond lengths (Å)	0.005	0.010	0.005	0.005
Bond angles (°)	0.966	1.481	1.038	1.128
Ramachandran ^				
Favored (%)	96.7	94.5	96.5	97.8
Allowed (%)	3.3	5.5	3.5	2.2
Outliers (%)	0	0	0	0

One crystal data set was collected for each of these structures
*Values in parentheses are for highest-resolution shell.
^ MolProbity Ramachandran *Lovell, Davis, et al. Proteins 50:437 (2003)*

6P8W data set was collected using a Saturn92 CCD detector on a home source Rigaku FR-E Superbright rotating anode generator.

6P8X data set was collected on a Pilatus3 6M silicon pixel detector at the Advanced Light Source Beamline 5.0.2

6P8Y data set was collected on a Rayonix MX300HS CCD detector at the Advanced Photon Source SER-CAT Beamline 22-ID.

6P8Z data set was collected on an ADSC Q315R CCD detector at the Advanced Light Source Beamline 5.0.1

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(viii) Mean, Standard Deviation, 'n' for biological replicates:

Compound	Nucleotide Exchange KRAS G12C IC50 (µM)	4 h pERK MiaPaCa-2 IC50 IP (µM)	4 h pERK A549 IC50 IP (µM)	72 h MiaPaCa-2 G12C KRAS CTG IC50 IP (µM)	72 h A549 G12S KRAS CTG IC50 IC50 IP (µM)
1	0.115 +/- 0.002 (n=2)	0.219 +/- 0.084 (n=4)	60.4 +/- 9.8 (n=3)	0.067 +/- 0.013 (n=5)	9.33 +/- 1.57 (n=4)
2	>250				
3	>250				
4	>250				
5	2.78 +/- 0.58 (n=2)	11.3 +/- 1.5 (n=3)			
6	0.638 (n=1)	11.4 +/- 13.6 (n=2)			
7	14.2 (n=1)	>100			
8	4.26 (n=1)	41.2 (n=1)			
9	6.63 (n=1)	52.7 (n=1)			
10	1.27 (n=1)	36.5 (n=1)			
11	1.37 (n=1)	28.0 (n=1)			
12	2.12 (n=1)	30.0 (n=1)			
13	2.00 (n=1)	17.9 (n=1)			
14	1.29 (n=1)	23.9 (n=1)			
15	0.299 +/- 0.017 (n=3)	1.68 +/- 0.99 (n=5)			
16	0.139 (n=1)	0.604 +/- 0.617 (n=2)			
17	0.174 (n=1)	12.8 (n=1)			
18	0.109 (n=1)	0.299 +/- 0.093 (n=3)			
19	0.369 (n=1)	3.55 (n=1)			
20	0.150 (n=1)	0.683 +/- 0.220 (n=2)			

(viv) HPLC Purity and LRMS data for compounds 2-20:

Cmpd	MW	Molecular_Formula	Purity (%)	LRMS: m/z (ESI, +ve ion): (M+H)+
2	463.3	C19 H19 Br N4 O5	98	463.0/465.0
3	339.2	C14 H15 Br N2 O3	>99	339.0/341.0
4	362.2	C16 H16 Br N3 O2	95	362.0/364.0
5	510.4	C25 H24 Br N3 O4	98	510.1
6	551.4	C27 H27 Br N4 O4	97	551.2
7	495.4	C24 H23 Br N4 O3	98	495.0
8	509.4	C25 H25 Br N4 O3	98	509.1
9	509.4	C25 H25 Br N4 O3	98	509.1
10	521.4	C26 H25 Br N4 O3	97	521.1/523.1
11	539.4	C26 H24 Br F N4 O3	97	539.2/541.2
12	539.4	C26 H24 Br F N4 O3	97	539.1/541.1
13	555.9	C26 H24 Br Cl N4 O3	98	555.0/557.0
14	555.9	C26 H24 Br Cl N4 O3	95	555.0
15	565.5	C28 H29 Br N4 O4	>99	565.0/567.2
16	591.5	C30 H31 Br N4 O4	97	591.2/593.3
17	565.5	C28 H29 Br N4 O4	95	565.1
18	579.5	C29 H31 Br N4 O4	>99	579.1/581.2
19	521.0	C28 H29 Cl N4 O4	>99	521.2
20	535.0	C29 H31 Cl N4 O4	>99	535.3