Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.

Supporting Information

I. Supplemental tables

Table S1. Percentage of 249 kinases inhibited by greater than 50%, 75%, and 95% at a concentration of 1000 nM in the Nanosyn kinase profiling platform.

	1 (h1-t1)	**2** (h1-t2)	**3** (h2-t1)	**4** (h2-t2)	**5** (h3-t1)	**6** (h3-t2)
Inhibition levels	Percentage of kinases inhibited at a concentration of 1000 nM at the corresponding level					
>95%	14.9%	14.9%	15.7%	8%	3.6%	4.4%
>75%	28.5%	24.9%	30.5%	20.9%	12.4%	12%
>50%	35.7%	32.1%	38.2%	27.3%	20.1%	18.9%

Table S2. Comparison of the percentage of 249 kinases inhibited by compounds **1**, **3**, and ponatinib at a level greater than 50%, 75%, and 95% at a concentration of 100 nM

	1 (h1-t1)	**3** (h2-t1)	**Ponatinib**
Inhibition levels	Percentage of kinases inhibited at a concentration of 100 nM at the corresponding level		
>95%	7.2%	5.2%	16.5%
>75%	14.5%	14.9%	23.3%
>50%	21.3%	21.3%	26.9%

II. Supplemental figures

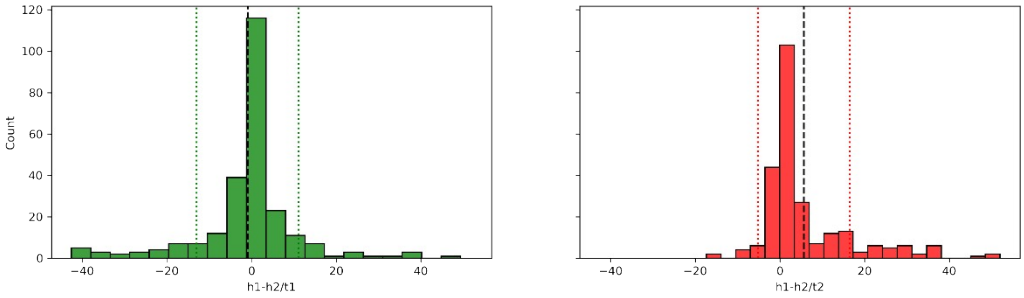


Figure S1. Differences in kinase inhibition values between h1 and h2 compounds for the two different tail groups. The dotted lines mark 1 standard deviation from the mean (dashed black line). 6 kinases are common in the area between the dotted lines. Compounds with an h1 group preferentially inhibit 4 additional kinases (beyond the dotted lines in the positive direction). Compounds with an h2 group do not preferentially inhibit any kinases >50%.

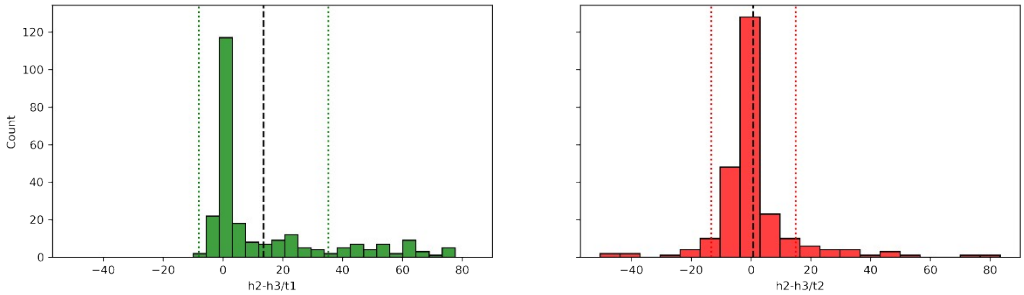
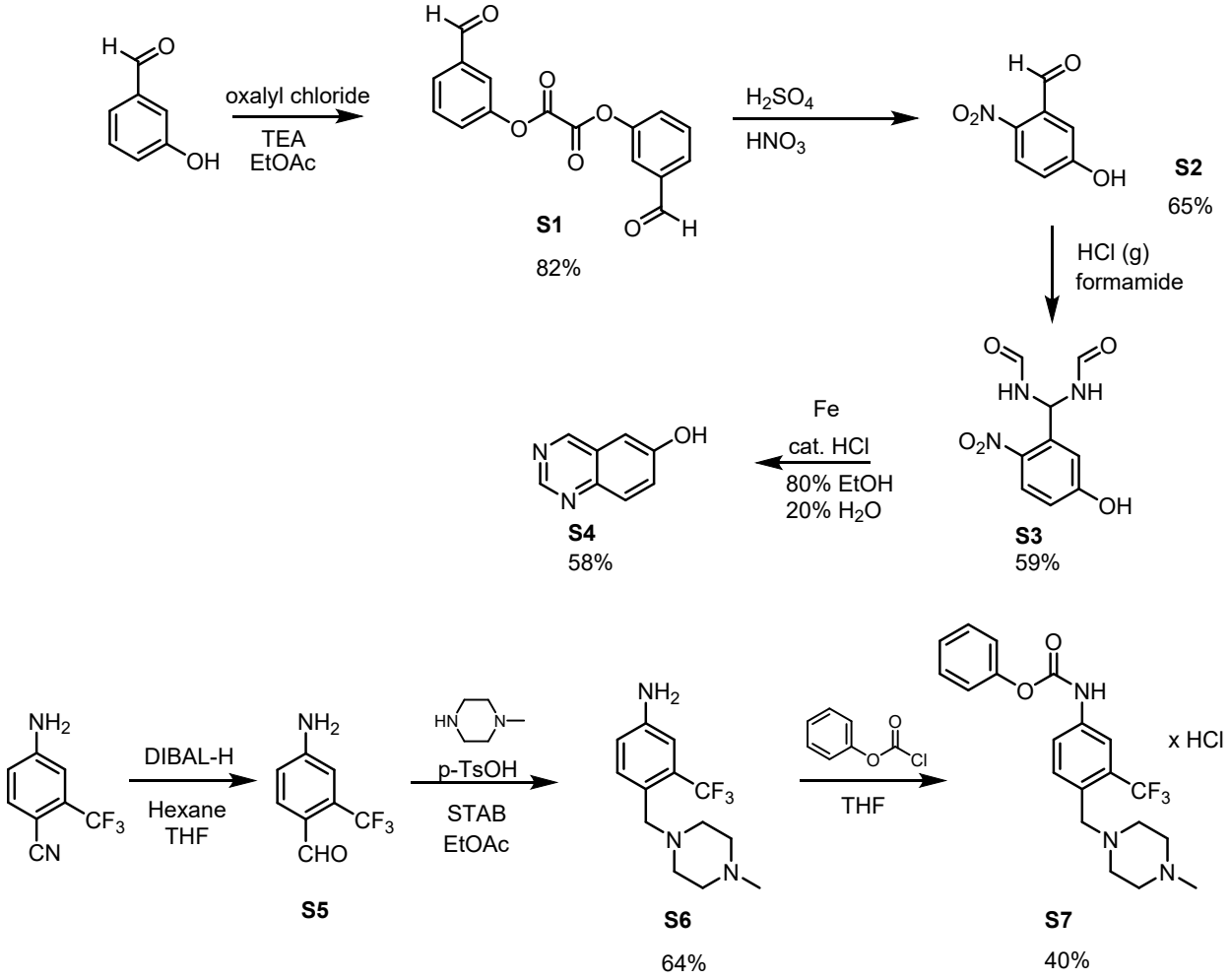


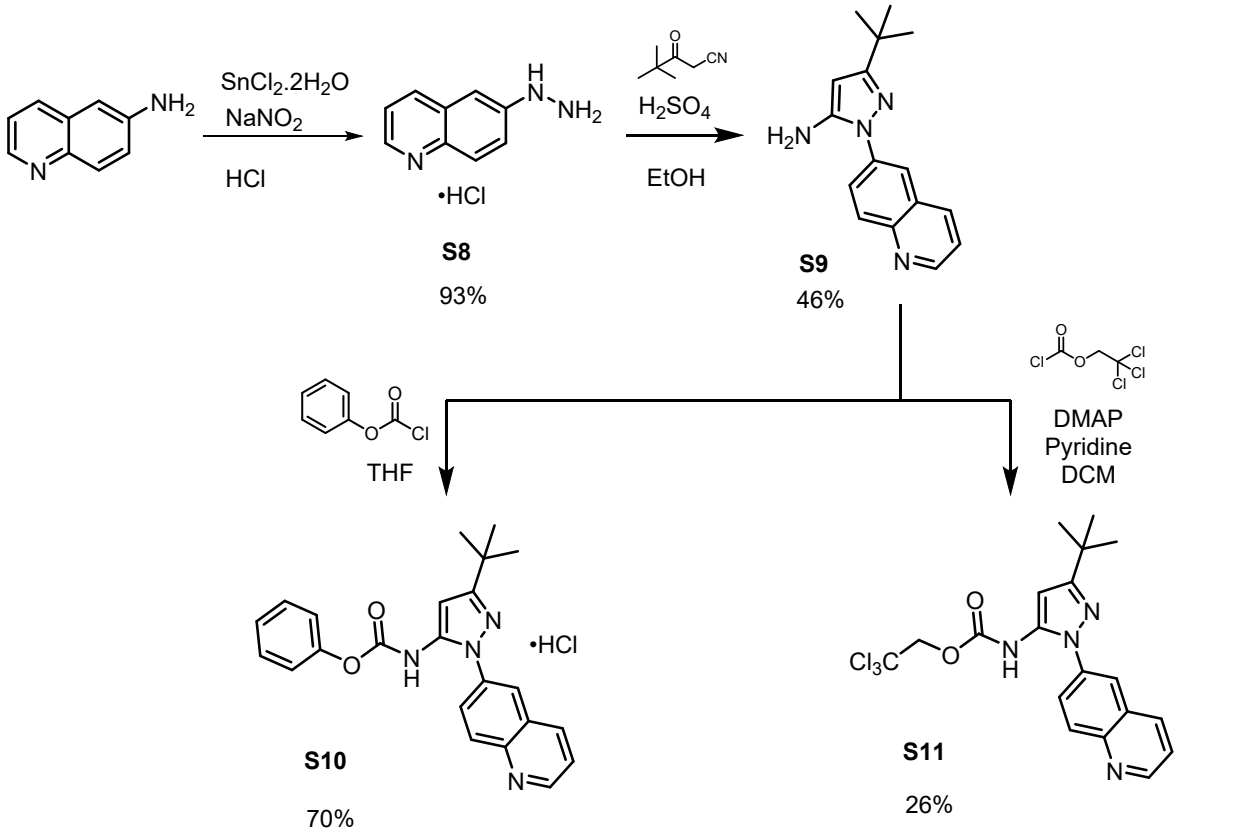
Figure S2. Differences in kinase inhibition values between h2 and h3 compounds for the two different tail groups. The dotted lines mark 1 standard deviation from the mean (dashed black line). 3 kinases are common in the area between the dotted lines. Compounds with an h2 group preferentially inhibit 6 additional kinases (beyond the dotted lines in the positive direction). Compounds with an h3 group do not preferentially inhibit any kinases >50%.

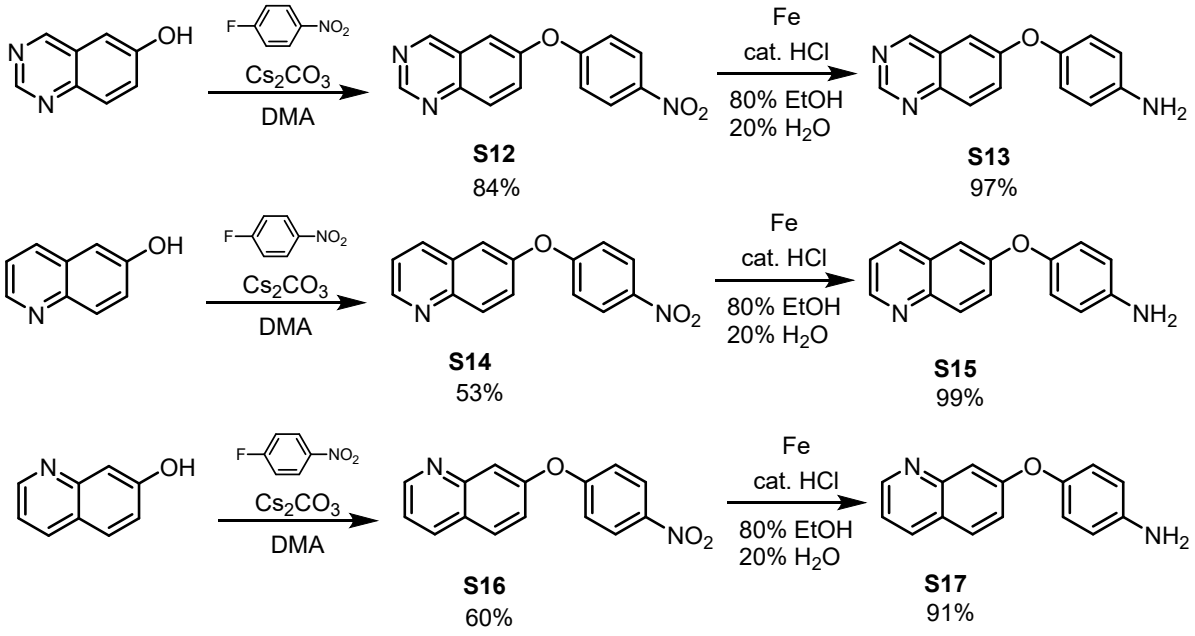
III. General synthetic methods

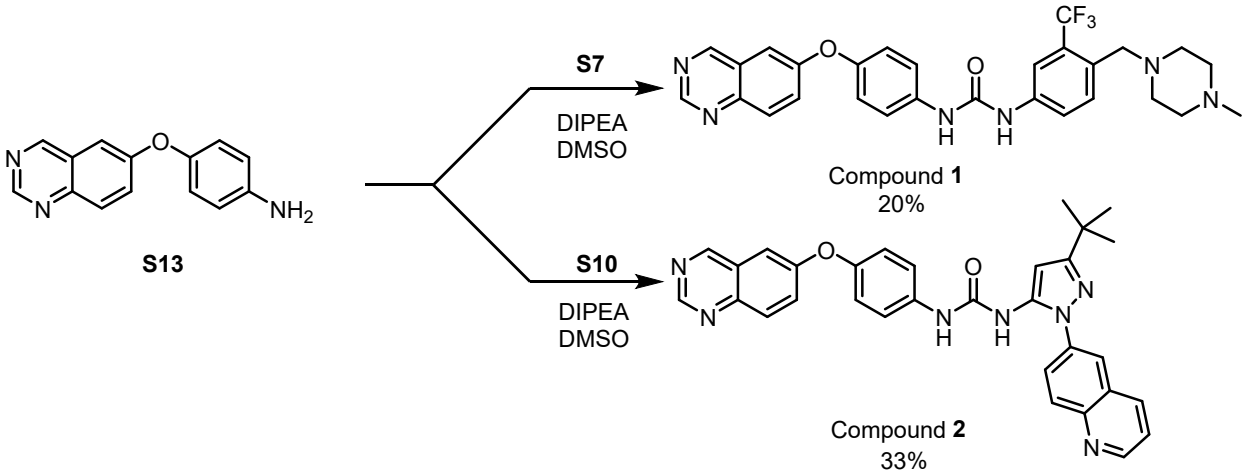
Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification. All ^{1}H, ^{19}F, and ^{13}C NMR spectra were measured with a Varian 400 or Inova 500 spectrometer. Mass Spectrometry (HRMS) was carried out on an Agilent 6230 TOF instrument.

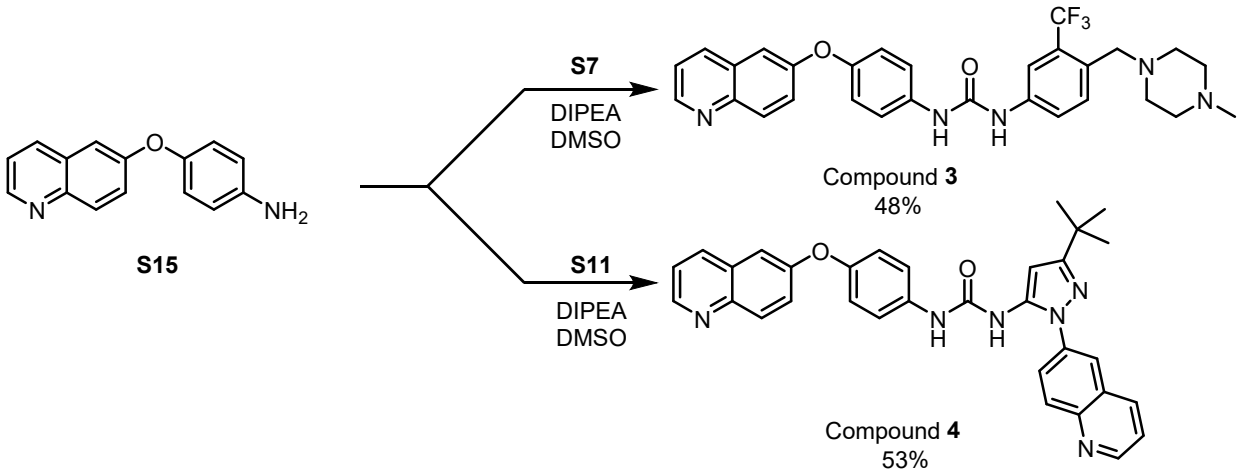
IV. Synthesis scheme

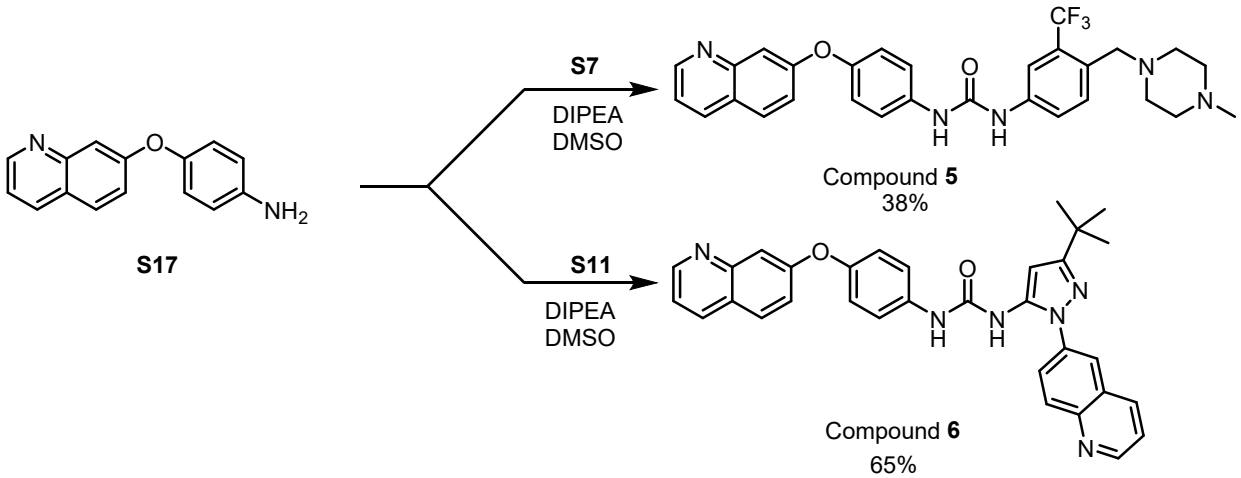



SnCl2.2H2O
NaNO2
HCl
•HCl
S8
93%
H2SO4
EtOH
S9
46%
THF
DMAP
Pyridine
DCM
S10
70%
S11
26%


Cs2CO3
DMA
S12
84%
Fe
cat. HCl
80% EtOH
20% H2O
S13
97%
S14
53%
S15
99%
S16
60%
S17
91%


S13
S7
DIPEA
DMSO
S10
DIPEA
DMSO
Compound 1
20%
Compound 2
33%


S15
S7
DIPEA
DMSO
S11
DIPEA
DMSO
Compound 3
48%
Compound 4
53%


S17
S7
DIPEA
DMSO
S11
DIPEA
DMSO
Compound 5
38%
Compound 6
65%

V. Synthesis of intermediate compounds S1-S17 and final compounds 1-6

S1.[1] TEA (19 mL, 2.3 Eq, 136 mmol) was added to a solution of 3-hydroxybenzaldehyde (11.9 g, 1.65 Eq, 97.5 mmol) in Ethyl acetate (54 mL). The solution was cooled on ice and degassed by bubbling nitrogen through it. To the reaction mixture was added a solution of oxalyl chloride (5 mL, 1 Eq, 59 mmol) in Ethyl acetate (6 mL) over 45 min. The reaction mixture was stirred overnight and the precipitate was filtered and washed with ethyl acetate. The precipitate was resuspended in water (50 mL), heated at 50 ºC for 30 min, filtered while hot, washed with water, and dried to give bis(3-formylphenyl) oxalate (**S1**) (11.84 g, 82%) as a cream solid that was used in the next step without further purification. ^{1}H NMR (500 MHz, dmso) δ 10.07 (s, 2H), 7.94 (dt, *J* = 7.7, 1.3 Hz, 2H), 7.84 (dd, *J* = 2.4, 1.5 Hz, 2H), 7.78 (t, *J* = 7.8 Hz, 2H), 7.66 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 2H); HRMS (TOF MS ES+) *m/z* calcd for $C_{16}H_{10}O_6$ $[M+H]^+$: 299.0550, found: 298.3252.

S2.[1] Nitric acid (35 g, 25 mL, 13 Eq, 0.56 mol) and sulfuric acid (92 g, 50 mL, 23 Eq, 0.94 mol) were added to a flask cooled at -10 °C to -20 °C. 1-2 g of bis(3-formylphenyl) oxalate (**S1**) (6.2 g, 0.5 Eq, 21 mmol) was added every 15 min. After the last addition, the reaction was poured over an ice/water mixture (500 mL), stirred for 30 min, and filtered. The precipitate was washed with water, suspended in methanol (125 mL) and stirred overnight. The solvent was evaporated *in vacuo*, and the residue suspended in water (90 mL) and stirred for 48 h. The pH was adjusted to 4 using 2N NaOH, cooled on ice, filtered, and washed with 1M citrate and water to give 5-hydroxy-2-nitrobenzaldehyde (**S2**) (4.532 g, 27.12 mmol, 65 %) as a yellow cream powder. ^{1}H NMR (400 MHz, $cdcl_3$) δ 10.47 (s, 1H), 8.16 (d, *J* = 8.9 Hz, 1H), 7.29 (d, *J* = 2.9 Hz, 1H), 7.13 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.72 (s, 1H).

S3.[2] 5-hydroxy-2-nitrobenzaldehyde (**S2**) (12.0 g, 1 Eq, 71.8 mmol) was added to formamide (67.8 g, 60.0 mL, 21.0 Eq, 1.51 mol) to form a suspension. HCl gas (generated by adding HCl over sulfuric acid) was added to the suspension until soluble (15-30 min). The solution was cooled on ice and the addition of HCl was continued until saturated (60 min). A precipitate was observed after 45 min. The suspension was poured onto ice (150 g), cooled, and the pH adjusted to 4 using 6N NaOH, filtered, and washed with water. The residue was suspended in water (75 mL), heated to boiling, stirred for 20 min, cooled and filtered to give N,N'-((5-hydroxy-2-nitrophenyl)methylene)diformamide (**S3**) (10.195 g, 42.623 mmol, 59.4 %) as a cream powder that contained impurities that were carried forward in the next step without further purification. ^{1}H NMR (400 MHz, dmso) δ 11.05 (s, 1H), 8.93 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.04 – 7.97 (m, 2H), 7.17 – 7.09 (m, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.91 (ddd, *J* = 9.1, 6.9, 2.6 Hz, 1H); HRMS (TOF MS ES+) *m/z* calcd for $C_9H_9N_3O_5$ $[M+Na]^+$: 262.0434, found: 262.0433.

S4. To a stirred suspension of N,N'-((5-hydroxy-2-nitrophenyl)methylene)diformamide (**S3**) (6.00 g, 1 Eq, 25.1 mmol) in Ethanol (100 mL) / Water (25.0 mL) was added iron (7.00 g, 5 Eq, 125 mmol) and a catalytic amount of concentrated HCl. The reaction mixture was refluxed at 80 °C for 3 h. The mixture was filtered over a pad of celite while hot and washed with boiling ethanol (3 x 75 mL). The filtrate was evaporated *in vacuo* to give a thick yellow slurry that was cooled on ice and the pH adjusted to 5. After 20 min, the precipitate was collected by filtration, washed with a small amount of water, and dried to give quinazolin-6-ol (**S4**) (2.124 g, 14.53 mmol, 57.9 %) as a light brown solid. ^{1}H NMR (400 MHz, dmso) δ 10.46 (s, 1H), 9.40 (s, 1H), 9.08 (s, 1H), 7.92 – 7.85 (m, 1H), 7.56 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.29 (d, *J* = 2.7 Hz, 1H); HRMS (TOF MS ES+) *m/z* calcd for $C_8H_6N_2O$ $[M+H]^+$: 147.0553, found: 147.0552.

S5.[3] 4-amino-2-(trifluoromethyl)benzonitrile (3.0 g, 1 Eq, 16 mmol) was dissolved in dry THF (9 mL) and a solution of DIBAL-H in Hexane (5.7 g, 40 mL, 1 molar, 2.5 Eq, 40 mmol) was added using a dropping funnel over 75 min keeping the temperature under 35 °C. The reaction mixture was stirred for another 10 min after complete addition and then carefully added to a mixture of methanol (4.5 mL) and a Rochelle salt solution (3M, 39 mL) over 1 h. The reaction mixture was then stirred at 50 °C for 10 min after which diethyl ether (18 mL) was added and stirring continued for another 10 min. The two layers were separated and the organic layer was washed with brine, dried, and evaporated *in vacuo* to give 4-amino-2-(trifluoromethyl)benzaldehyde containing oligomeric impurities that were used in the next step without further purification. ^{1}H NMR (500 MHz, dmso) δ 10.49 (s, 1H), 9.39 (s, 1H), 9.07 (s, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.56 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.28 (d, *J* = 2.7 Hz, 1H).

S6.[3] Immediately prior to carrying out the reaction, oligomeric 4-amino-2-(trifluoromethyl)benzaldehyde (6.1 g, 1 Eq, 32 mmol) was first converted to a monomer: 4-amino-2-(trifluoromethyl)benzaldehyde (6.1 g, 1 Eq, 32 mmol) was dissolved in Ethyl acetate (24 mL) and 1N HCl (31 mL) was added. The solution was stirred rapidly for 5 min and then a solution of 1N NaOH (24.6 mL) was added over 5 min and stirred for another 5 min. The mixture was poured into a serparatory funnel and the oprganic layer was separated and washed with 10% sodium chloride solution (15 mL). The organic layer was added to a 250 mL r.b. flask and diluted to ~48 mL. Separately, 1-methylpiperazine (16 g, 18 mL, 5 Eq, 0.16 mol) and pyridinium p-toluenesulfonate (0.81 g, 0.1 Eq, 3.2 mmol) were dissolved in 16 mL ethyl acetate and added to the first flask. The reaction mixture was heated to 78 °C and ethyl acetate was distilled off. After every 16 mL ethyl acetate that was distilled off, 16 mL fresh ethyl acetate was added to the flask. The distillation-addition process was continued about 10 times until 160 mL ethyl acetate was collected and re-added. The mixture was cooled to 50 °C and sodium triacetoxyborohydride (15 g, 2.15 Eq, 69 mmol) was added in portions over 1 h. After addition was complete, the reaction mixture was cooled to 10 °C and quenched with water (48 mL) over 1 h, keeping the temperature under 20 °C. The organic layer was separated, washed with water (2 x 50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to give 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (5.62 g, 20.6 mmol, 64 %) as an orange solid. ^{1}H NMR (400 MHz, dmso) δ 7.28 (d, *J* = 8.3 Hz, 1H), 6.92 – 6.82 (m, 1H), 6.74 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.44 (s, 2H), 3.38 (d, *J* = 1.9 Hz, 2H), 2.31 (s, 8H), 2.13 (s, 3H); HRMS (TOF MS ES+) *m/z* calcd for $C_{13}H_{18}F_3N_3$ $[M+H]^+$: 274.1526, found: 274.1523.

S7.[3] phenyl chloroformate (0.8 g, 0.6 mL, 1.35 Eq, 5 mmol) was added to THF (18 mL) in a 2-neck r.b. flask fitted with a reflux condenser and heated to 65 °C. A solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (1 g, 1 Eq, 4 mmol) dissolved in THF (14 mL) was added dropwise to the flask over 45 min. After complete addition, the mixture was stirred for 15 min and then cooled to room temperature over 45 min. The precipitate was collected by filtration and rinsed with THF. The precipitate was resuspended in THF (15 mL), stirred, and filtered (2x) to give phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate hydrochloride (652 mg, 1.52 mmol, 40 %) as a cream powder. ^{1}H NMR (400 MHz, dmso) δ 11.76 (s, 1H), 10.80 (s, 1H), 8.11 (s, 1H), 8.03 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.32 – 7.18 (m, 3H), 4.24 (s, 2H), 3.73 – 3.03 (m, 8H), 2.79 (s, 3H); HRMS (TOF MS ES+) *m/z* calcd for $C_{20}H_{22}F_3N_3O_2$ $[M+H]^+$: 394.1737, found: 394.1843.

S8.[4] quinolin-6-amine (10.0 g, 1 Eq, 69.4 mmol) was added to conc. HCl (30 mL) and cooled in an ice water bath. A solution of sodium nitrite (5.02 g, 1.05 Eq, 72.8 mmol) in water (8 mL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature, then cooled on ice, and a solution of tin(II) chloride dihydrate (32.9 g, 2.1 Eq, 146 mmol) in conc. HCl (30 mL) was added. The reaction was stirred at room temperature for 2 h after addition, then filtered and washed with ethanol and ether. The precipitate was suspended in ethanol (150 mL), stirred at boiling, and filtered while hot to give 6-hydrazineylquinoline hydrochloride (12.57 g, 64.25 mmol, 92.6 %) as an orange solid. ^{1}H NMR (400 MHz, dmso) δ 9.31 (s, 1H), 9.03 (dd, *J* = 5.1, 1.5 Hz, 1H), 8.85 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 9.2 Hz, 1H), 7.92 (dd, *J* = 8.4, 5.1 Hz, 1H), 7.84 – 7.70 (m, 1H), 7.48 (d, *J* = 2.6 Hz, 1H); HRMS (TOF MS ES+) *m/z* calcd for $C_{13}H_{18}F_3N_3$ $[M+H]^+$: 160.0869, $[M-NH_2+H]^+$:144.0677 found: 160.0870 and 144.0680, respectively.

S9.[4] To a mixture of 6-hydrazineylquinoline hydrochloride (5.0 g, 1 Eq, 26 mmol) and 4,4-dimethyl-3-oxopentanenitrile (3.2 g, 1 Eq, 26 mmol) in Ethanol (120 mL) was added sulfuric acid (13 g, 7.2 mL, 17.8 molar, 5 Eq, 0.13 mol) and heated to reflux. The reaction was monitored by TLC. After removal of solvent, water (100 mL) and DCM (120 mL) was added and the mixture stirred. The pH was adjusted to 6-7 using 6 N NaOH. The layers were separated and the aqueous layer was extracted with DCM (2x50 mL). The combined organics were washed with sat. NaHCO3 (1 x 100 mL), brine (1 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude residue. The reside was loaded onto silica and purified using a biotage isolera system (KP-SIL 100 g column, 30% then 60% EtOAc/Hex) to give 3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-amine (3.1023 g, 11.647 mmol, 46 %) as a red oil that solidifies on standing. ^{1}H NMR (500 MHz, dmso) δ 8.88 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.41 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.14 (d, *J* = 2.1 Hz, 1H), 8.12 – 8.04 (m, 2H), 7.55 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.46 (d, *J* = 10.8 Hz, 3H), 1.26 (s, 9H); HRMS (TOF MS ES+) *m/z* calcd for $C_{16}H_{18}N_4$ $[M+H]^+$: 267.1604, found: 267.1800.

S10. In a 2-neck round bottom flask, phenyl chloroformate (588 mg, 0.47 mL, 1.25 Eq, 3.75 mmol) was added to THF (15 mL) and heated to reflux at 65 °C. A solution of 3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-amine (800 mg, 1 Eq, 3 mmol) in THF (12 mL) was added dropwise over 45 min. After addition was complete, the reaction was stirred for 15 min, then cooled to room temperature over 45 min. The product precipitated and was collected by filtration and washed with a small amount of THF and ether. The precipitate was re-suspended in ether (10 mL), stirred for 15 min, collected by filtration, washed with ether and dried to give phenyl (3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-yl)carbamate hydrochloride (888 mg, 70 %) as a cream powder. ^{1}H NMR (500 MHz, dmso) δ 10.42 (s, 1H), 9.24 (dd, *J* = 5.0, 1.5 Hz, 1H), 9.09 (d, *J* = 8.4 Hz, 1H), 8.54 – 8.41 (m, 2H), 8.32 (dd, *J* = 9.1, 2.3 Hz, 1H), 8.02 (dd, *J* = 8.4, 4.9 Hz, 1H), 7.36 (s, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.10 (s, 2H), 6.48 (s, 1H), 1.33 (s, 9H); HRMS (TOF MS ES+) *m/z* calcd for $C_{23}H_{22}N_4O_2$ $[M+H]^+$: 387.1816 and $[M+Na]^+$: 409.1635, found: 387.1807 and 409.1635, respectively.

S11. 3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-amine (450 mg, 1 Eq, 1.69 mmol) was dissolved in DCM (6 mL) and cooled in an ice-brine bath. DMAP (10 mg, 0.048 Eq, 82 µmol) and pyridine (401 mg, 410 µL, 3 Eq, 5.07 mmol) were added followed by the dropwise addition of a solution of 2,2,2-trichloroethyl carbonochloridate (501 mg, 326 µL, 1.4 Eq, 2.37 mmol) in DCM (2 mL) over 15 min. The reaction was stirred for 1 h, DCM (20 mL) and water (20 mL) were added and stirring continued for 10 min. The two layers were separated and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The crude material was loaded onto silica and purified on a Biotage isolera system (25% EtOAc/Hex → 55% EtOAc/Hex)

to give 2,2,2-trichloroethyl (3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-yl)carbamate (196 mg, 444 µmol, 26.3 %) as a glassy white solid on extensive drying. ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.89 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.5, 4.4 Hz, 2H), 7.95 – 7.78 (m, 2H), 7.46 (dd, *J* = 8.3, 4.3 Hz, 2H), 6.48 (s, 1H), 4.82 (s, 2H), 1.36 (d, *J* = 10.3 Hz, 9H), NMR contains other unknown impurities; HRMS (TOF MS ES+) *m/z* calcd for $C_{19}H_{19}Cl_3N_4O_2$ [M+H]$^+$: 441.0647, found: 441.0635.

S12. quinazolin-6-ol (4.02 g, 1 Eq, 27.5 mmol) and cesium carbonate (10.8 g, 1.2 Eq, 33.0 mmol) were added to DMF (140 mL) followed by 1-fluoro-4-nitrobenzene (4.66 g, 3.50 mL, 1.2 Eq, 33.0 mmol). The reaction was stirred at 70 °C for 1 h. The reaction was cooled to room temperature, poured into 550 mL water, and the product was extracted with ethyl acetate (3 x 120 mL). The combined organics were washed with brine (1 x 250 mL), dried over anhydrous sodium sulfate, and evaporated. The crude material was loaded onto silica and purified on a Biotage isolera system (purified in 2 batches, each on a 100 g KP-SIL column, step gradient 40% EtOAc/Hex, then 90% EtOAc/Hex) to give 6-(4-nitrophenoxy)quinazoline (**S12**) (6.15 g, 23.0 mmol, 83.7 %) as a yellow solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 9.39 – 9.33 (m, 2H), 8.33 – 8.24 (m, 2H), 8.16 (dt, *J* = 9.1, 0.7 Hz, 1H), 7.73 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.52 (dd, *J* = 2.7, 0.5 Hz, 1H), 7.20 – 7.11 (m, 2H); HRMS (TOF MS ES+) *m/z* calcd for $C_{14}H_9N_3O_3$ [M+H]$^+$: 268.0717, found: 268.0726.

S13. To a suspension of 6-(4-nitrophenoxy)quinazoline (**S12**) (4.61 g, 1 Eq, 17.3 mmol) in Ethanol (72.0 mL) / Water (18.0 mL) was added iron (4.82 g, 5 Eq, 86.3 mmol) and a catalytic amount of conc. HCl. The reaction was heated at 80 °C for 1.5 h. The reaction mixture was filtered while hot over a pad of celite, and washed with EtOAc (2 x 100 mL). The filtrate was evaporated, the residue dissolved in EtOAc (250 mL), and washed with sat. NaHCO3 (2 x 125 mL), brine (1 x 125 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to give 4-(quinazolin-6-yloxy)aniline (**S13**) (3.9625 g, 16.701 mmol, 96.8 %) as a red oil that formed a yellow solid after extensive drying and trituration with DCM/Hexanes. ^{1}H NMR (400 MHz, cdcl$_3$) δ 9.21 (d, *J* = 10.9 Hz, 2H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.69 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.13 – 7.06 (m, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 3.74 (s, 2H); HRMS (TOF MS ES+) *m/z* calcd for $C_{14}H_{11}N_3O$ [M+H]$^+$: 238.0975, found: 238.1089.

S14. quinolin-6-ol (1.52 g, 1 Eq, 10.5 mmol) and cesium carbonate (3.75 g, 1.1 Eq, 11.5 mmol) were added to DMF (52 mL). 1-fluoro-4-nitrobenzene (1.55 g, 1.2 mL, 1.05 Eq, 11.0 mmol) was added and the reaction stirred at 70 °C overnight. The reaction mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to give a residue that was purified on a Biotage isolera system (100% Hexane and then 50% EtOAc/Hex → 100% EtOAc) to give 6-(4-nitrophenoxy)quinoline (1.47 g, 5.52 mmol, 52.7 %). ^{1}H NMR (500 MHz, cdcl$_3$) δ 8.90 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.22 (s, 1H), 8.21 – 8.13 (m, 2H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.11 – 7.05 (m, 2H); HRMS (TOF MS ES+) *m/z* calcd for $C_{15}H_{10}N_2O_3$ [M+H]$^+$: 267.0764, found: 267.0806.

S15. To a suspension of 6-(4-nitrophenoxy)quinoline (1000.0 mg, 1 Eq, 3.7557 mmol) in Ethanol (16 mL) / Water (4.0 mL) was added iron (1.049 g, 5 Eq, 18.779 mmol) and a catalytic amount of conc. HCl. The reaction was heated at 70 °C for 1.5 h. The reaction mixture was filtered while hot over a pad of celite, and washed with EtOAc. The filtrate was evaporated and 10% potassium carbonate solution was added. The suspension was extracted with EtOAc, and the organic layer washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give 4-(quinolin-6-yloxy)aniline (876 mg, 3.71 mmol, 98.7 %) as a tan powder. ^{1}H NMR (500 MHz, cdcl$_3$) δ 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.94 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.47 (dd,

J = 9.3, 2.7 Hz, 1H), 7.31 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.06 (d, *J* = 2.7 Hz, 1H), 6.97 – 6.91 (m, 2H), 6.76 – 6.69 (m, 2H), 3.68 (s, 2H); HRMS (TOF MS ES+) *m/z* calcd for $C_{15}H_{12}N_2O$ $[M+H]^+$: 237.1022, found: 237.1066.

S16. quinolin-7-ol (82 mg, 1 Eq, 0.5649 mmol) and cesium carbonate (221 mg, 1.2 Eq, 0.6779 mmol) were added to DMF (3 mL). 1-fluoro-4-nitrobenzene (0.072 mL, 1.2 Eq, 0.6779 mmol) was added and the reaction stirred at 70 °C for 2 h. The reaction mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate (3x). The organic layer was washed with 10% potassium carbonate solution, brine, dried over anhydrous sodium sulfate, and evaporated to give a residue that was purified on a Biotage isolera system (20% EtOAc/Hex → 40% EtOAc/Hex) to give 7-(4-nitrophenoxy)quinoline (90 mg, 60 %) as a light-yellow solid.^{1}H NMR (500 MHz, $cdcl_3$) δ 8.92 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.27 – 8.22 (m, 2H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.35 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.18 – 7.11 (m, 2H); HRMS (TOF MS ES+) *m/z* calcd for $C_{15}H_{10}N_2O_3$ $[M+H]^+$: 267.0764, found: 267.0780.

S17. To a suspension of 7-(4-nitrophenoxy)quinoline (95.0 mg, 1 Eq, 357 µmol) in Ethanol (1.6 mL) / Water (0.40 mL) was added iron (99.6 mg, 5 Eq, 1.78 mmol) and a catalytic amount of conc. HCl. The reaction was heated at 70 °C for 1.5 h. The reaction mixture was filtered while hot over a pad of celite, and washed with EtOAc. The filtrate was evaporated and 10% potassium carbonate solution was added. The suspension was extracted with EtOAc, and the organic layer washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give 4-(quinolin-7-yloxy)aniline (77 mg, 0.33 mmol, 91 %). ^{1}H NMR (500 MHz, $cdcl_3$) δ 8.80 (d, *J* = 4.3 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.29 – 7.23 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 3.60 (s, 2H); HRMS (TOF MS ES+) *m/z* calcd for $C_{15}H_{12}N_2O$ $[M+H]^+$: 237.1022, found: 237.1094.

Compound **1**. 4-(quinazolin-6-yloxy)aniline (260 mg, 1 Eq, 1.10 mmol), phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate hydrochloride (471 mg, 1 Eq, 1.10 mmol), and DIPEA (153 mg, 206 µL, 1.08 Eq, 1.18 mmol) were added to DMSO (1.5 mL) and the mixture heated at 70 °C for 2 h. The reaction mixture was cooled to 50 °C and KOH (80 mg in 1 mL water) was added. The resultant mixture was transferred to water (25 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give a residue that was loaded onto C-18 silica gel and purified using a Biotage Isolera system (C-18 Ultra 30 g column, 30% Acetonitrile/Water → 100% Acetonitrile) to give 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(quinazolin-6-yloxy)phenyl)urea (117.8 mg, 219.5 µmol, 20.0 %). ^{1}H NMR (400 MHz, dmso) δ 9.50 (s, 1H), 9.21 (s, 1H), 9.05 (s, 1H), 8.90 (s, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.98 (d, *J* = 2.2 Hz, 1H), 7.82 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.66 – 7.55 (m, 4H), 7.42 (d, *J* = 2.8 Hz, 1H), 7.20 – 7.14 (m, 2H), 3.53 (s, 2H), 2.37 (s, 8H), 2.17 (s, 3H); ^{19}F NMR (376 MHz, dmso) δ -58.01; HRMS (TOF MS ES+) *m/z* calcd for $C_{28}H_{27}F_3N_6O_2$ $[M+H]^+$: 537.2221, found: 537.2489.

Compound **2**. 4-(quinazolin-6-yloxy)aniline (**S13**) (272.5 mg, 1 Eq, 1.149 mmol) and phenyl (3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-yl)carbamate hydrochloride (**S10**) (485.7 mg, 1 Eq, 1.149 mmol) were added to DMSO (1.9 mL) followed by DIPEA (160.3 mg, 0.22 mL, 1.08 Eq, 1.240 mmol) . The reaction mixture was heated at 70 °C under nitrogen for 3.5 h. The solution was cooled to 50 °C and KOH (*~1.3 Eq = 64 mg in 2 mL*) was added, followed by 2 mL ethyl acetate. After stirring for 5 min a cream precipitate formed that was collected by vacuum filtration, washed with water (3 x 3 mL), ethyl acetate (3 x 3 mL), and dried. The precipitate was loaded

onto C-18 silica gel and purified using a Biotage Isolera system (C-18 Ultra 30 g column, 75% Acetonitrile/Water → 100% Acetonitrile) to give 1-(3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(quinazolin-6-yloxy)phenyl)urea (compound **2**) (203.7 mg, 384.6 µmol, 33.49 %) as a white solid. ^{1}H NMR (400 MHz, dmso) δ 9.48 (s, 1H), 9.20 (s, 1H), 9.11 (s, 1H), 8.96 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.60 (s, 1H), 8.52 – 8.45 (m, 1H), 8.17 (dd, *J* = 5.8, 3.3 Hz, 2H), 8.04 (d, *J* = 9.1 Hz, 1H), 7.97 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.80 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.62 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.39 (d, *J* = 2.8 Hz, 1H), 7.17 – 7.09 (m, 2H), 6.46 (s, 1H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, dmso) δ 161.42, 159.66, 156.87, 153.80, 151.68, 151.04, 149.60, 146.38, 145.88, 137.76, 136.41, 136.28, 130.18, 130.10, 127.99, 127.50, 126.53, 125.55, 122.24, 122.08, 120.79, 120.08, 110.25, 110.15, 95.79, 32.16, 30.23; HRMS (TOF MS ES+) *m/z* calcd for $C_{31}H_{27}N_7O_2$ $[M+H]^+$: 530.2291, found: 530.2287.

Compound **3**. 4-(quinolin-6-yloxy)aniline (**S15**) (1121 mg, 1.2 Eq, 4.745 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate hydrochloride (**S7**) (1700 mg, 1.000 Eq, 3.955 mmol) were added to DMSO (6 mL) in a r.b. flask. DIPEA (536.6 mg, 723 µL, 1.05 Eq, 4.152 mmol) was then added and the reaction mixture was stirred at 70 °C for 3 h. The reaction mixture was cooled to 50 °C and a KOH (4Eq in ~ 2mL) solution and water (17 mL) was added. The product was extracted with EtOAc (2x), washed with brine, dried over anhydrous sulfate and evaporated. The crude residues was purified using a Biotage Isolera system (KP-SIL, 10% Hexane/DCM → 6% Ammonia in methanol (7N)/10% Hexane/DCM) to give 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(quinolin-6-yloxy)phenyl)urea (1014.9 mg, 1.8950 mmol, 47.93 %) (compound **3**) as a white solid. ^{1}H NMR (500 MHz, cdcl$_3$) δ 8.84 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 8.01 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.47 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.21 (d, *J* = 2.7 Hz, 1H), 7.10 – 7.03 (m, 3H), 6.93 (s, 1H), 3.58 (s, 2H), 2.44 (d, *J* = 29.5 Hz, 8H), 2.28 (s, 3H); ^{19}F NMR (376 MHz, dmso) δ -58.06; HRMS (TOF MS ES+) *m/z* calcd for $C_{29}H_{28}F_3N_5O_2$ $[M+H]^+$: 536.2268, found: 536.2256.

Compound **4**. 4-(quinolin-6-yloxy)aniline (**S15**) (48.0 mg, 1 Eq, 0.203 mmol) and 2,2,2-trichloroethyl (3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-yl)carbamate (**S11**) (89.7 mg, 1.00 Eq, 0.203 mmol) were added to DMSO (1 mL) in a vial. DIPEA (52.5 mg, 70.7 µL, 2 Eq, 406 µmol) was then added and the reaction mixture was stirred at 70 °C overnight. The reaction was cooled, poured into EtOAc (30 mL) and washed with 10% K_2CO_3 (2 x 20 mL), brine (1 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a crude residue that was laded onto a KP-SIL silica gel column and purified using a Biotage Isolera system (70% EtOAc/Hex → 100% EtOAc → 5% MeOH/EtOAc) to give 1-(3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(quinolin-6-yloxy)phenyl)urea (compound **4**) (57.0 mg, 108 µmol, 53.1 %). ^{1}H NMR (400 MHz, dmso) δ 9.07 (s, 1H), 8.96 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.58 (s, 1H), 8.48 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.28 – 8.21 (m, 1H), 8.17 (dd, *J* = 5.8, 3.3 Hz, 2H), 8.02 (d, *J* = 9.1 Hz, 1H), 7.97 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.62 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.58 – 7.43 (m, 4H), 7.29 (d, *J* = 2.8 Hz, 1H), 7.11 – 7.03 (m, 2H), 6.46 (s, 1H), 1.32 (s, 9H); HRMS (TOF MS ES+) *m/z* calcd for $C_{32}H_{28}N_6O_2$ $[M+H]^+$: 529.2347, found: 529.2342.

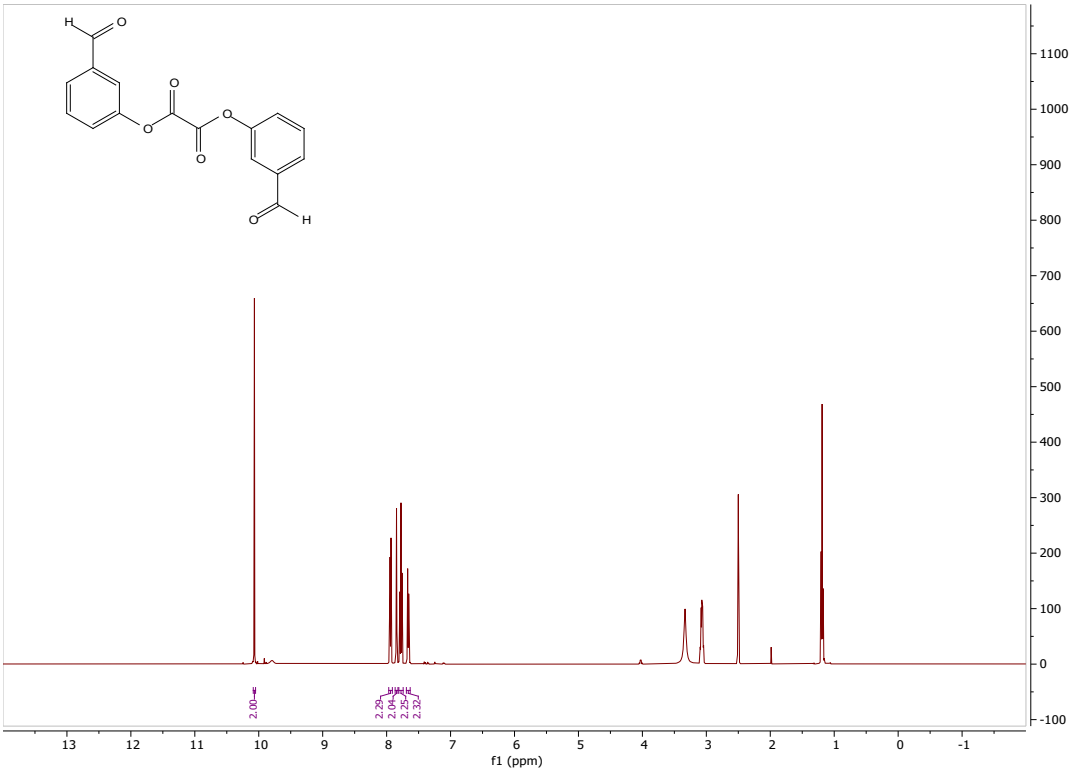
Compound **5**. 4-(quinolin-7-yloxy)aniline (**S17**) (23.6 mg, 1 Eq, 99.9 µmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate hydrochloride (**S7**) (42.9 mg, 1 Eq, 99.9 µmol) were added to DMSO (1 mL) in a vial. DIPEA (13.9 mg, 18.8 µL, 1.08 Eq, 108 µmol) was then added and the reaction mixture was stirred at 60 °C overnight. The reaction was cooled to r.t. and directly purified using a Biotage Isolera system (C-18 Ultra column, 40%

Acetonitrile/Water → 75% Acetonitrile/Water) to give 1-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(quinolin-7-yloxy)phenyl)urea (compound **5**) (20.4 mg, 38.1 µmol, 38.1 %) as a white solid. ^{1}H NMR (500 MHz, dmso) δ 9.05 (s, 1H), 8.88 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.34 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.01 (d, *J* = 8.9 Hz, 1H), 7.98 (d, *J* = 2.2 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.60 – 7.53 (m, 3H), 7.42 (ddd, *J* = 13.1, 8.6, 3.4 Hz, 2H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.18 – 7.11 (m, 2H), 3.53 (s, 2H), 2.37 (s, 8H), 2.15 (s, 3H); ^{19}F NMR (376 MHz, dmso) δ -58.00; HRMS (TOF MS ES+) *m/z* calcd for $C_{29}H_{28}F_3N_5O_2$ $[M+H]^+$: 536.2268, found: 536.2263.

Compound **6**. 4-(quinolin-7-yloxy)aniline (**S17**) (24.0 mg, 1 Eq, 102 µmol) and 2,2,2-trichloroethyl (3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-yl)carbamate (**S11**) (44.9 mg, 1 Eq, 102 µmol) were added to DMSO (0.5 mL) in a vial. DIPEA (26.3 mg, 35.4 µL, 2 Eq, 203 µmol) was then added and the reaction mixture was stirred at 70 °C overnight. The reaction was cooled, poured into EtOAc (20 mL) and washed with 10% K_2CO_3 (2 x 20 mL), brine (1 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a crude residue that was laded onto a KP-SIL silica gel column and purified using a Biotage Isolera system (70% EtOAc/Hex → 100% EtOAc → 5% MeOH/EtOAc) to give 1-(3-(tert-butyl)-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(quinolin-7-yloxy)phenyl)urea (compound **6**) (34.8 mg, 65.8 µmol, 64.8 %). ^{1}H NMR (400 MHz, dmso) δ 9.09 (s, 1H), 8.96 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.82 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.60 (s, 1H), 8.49 (d, *J* = 8.3 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.17 (dd, *J* = 5.8, 3.2 Hz, 2H), 8.04 – 7.93 (m, 2H), 7.62 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.41 (ddd, *J* = 17.0, 8.6, 3.4 Hz, 2H), 7.20 (d, *J* = 2.5 Hz, 1H), 7.14 – 7.08 (m, 2H), 6.46 (s, 1H), 1.32 (s, 9H); HRMS (TOF MS ES+) *m/z* calcd for $C_{32}H_{28}N_6O_2$ $[M+H]^+$: 529.2347, found: 529.2339.

VI. NMR Spectra for intermediate compounds S1-S17 and final compounds 1-6

S1



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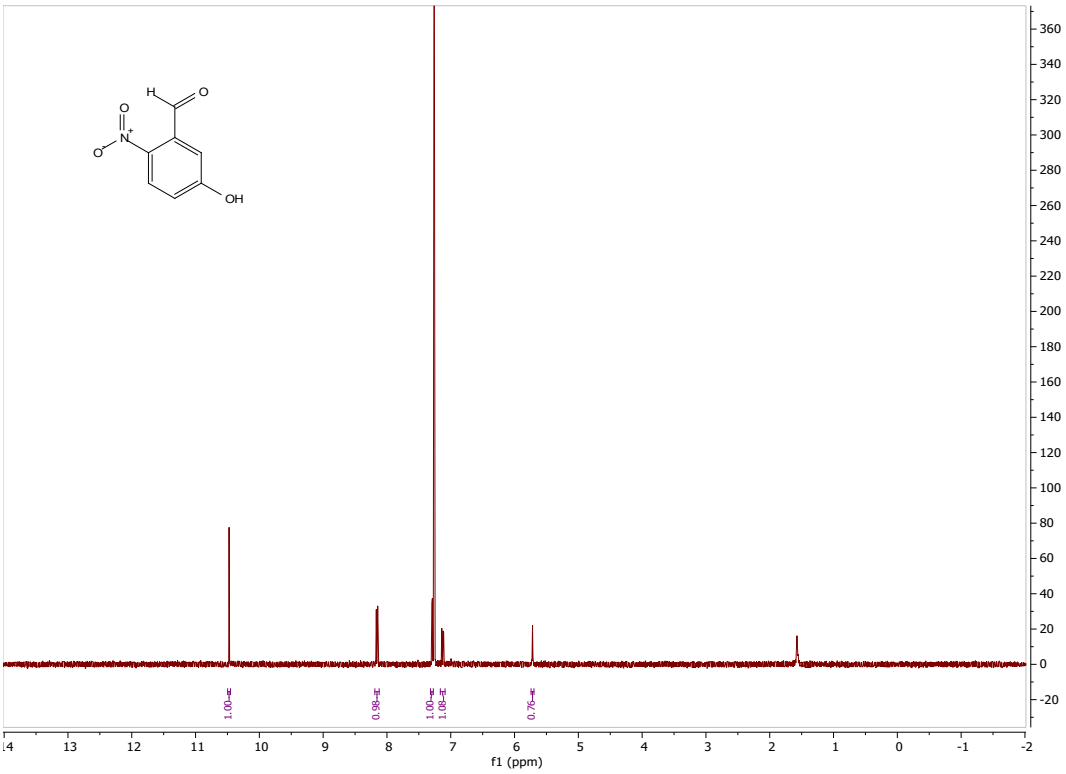
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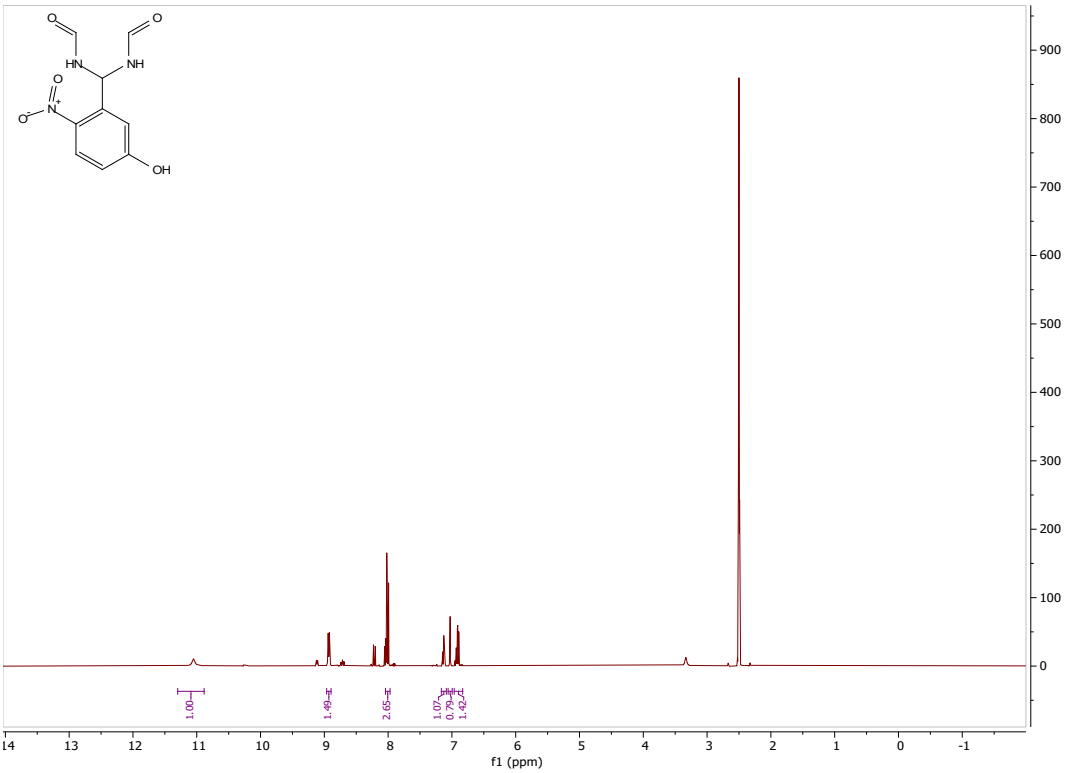
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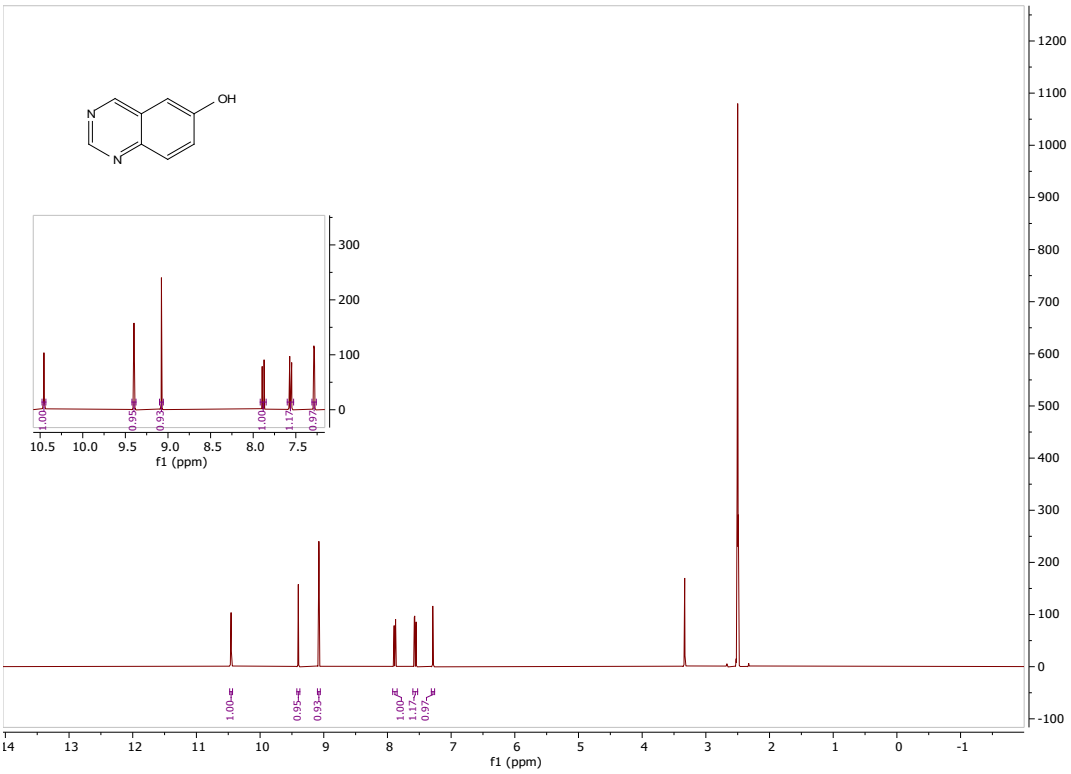
S4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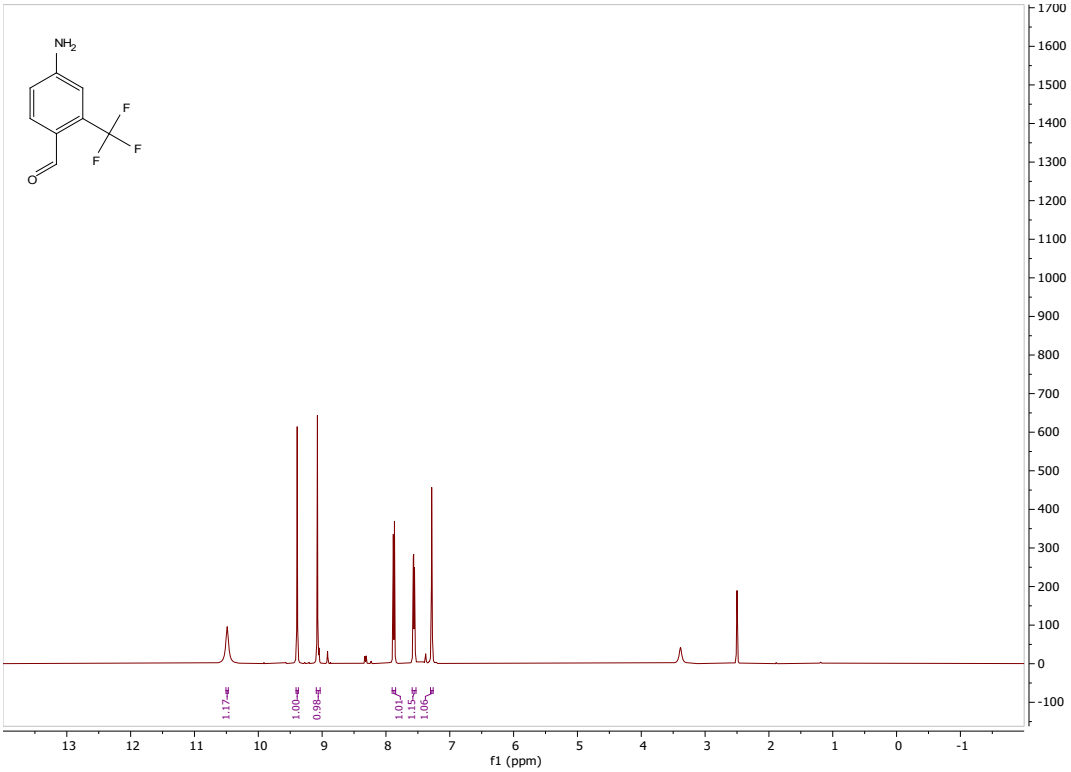
f1 (ppm)

S5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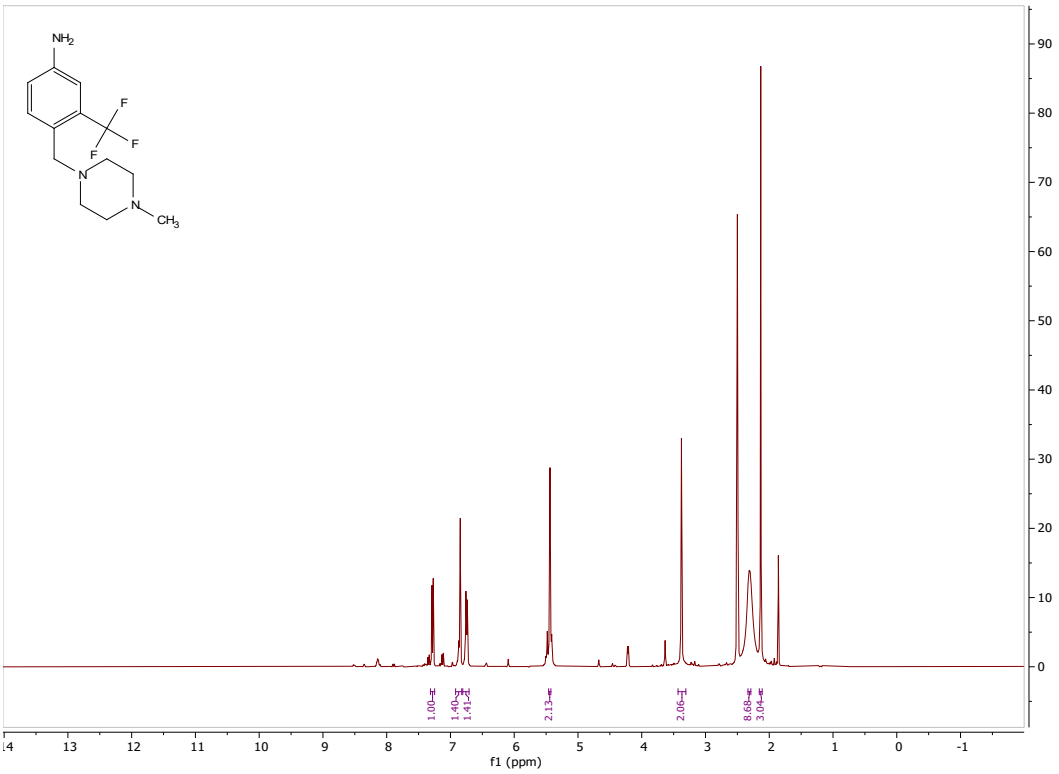
S6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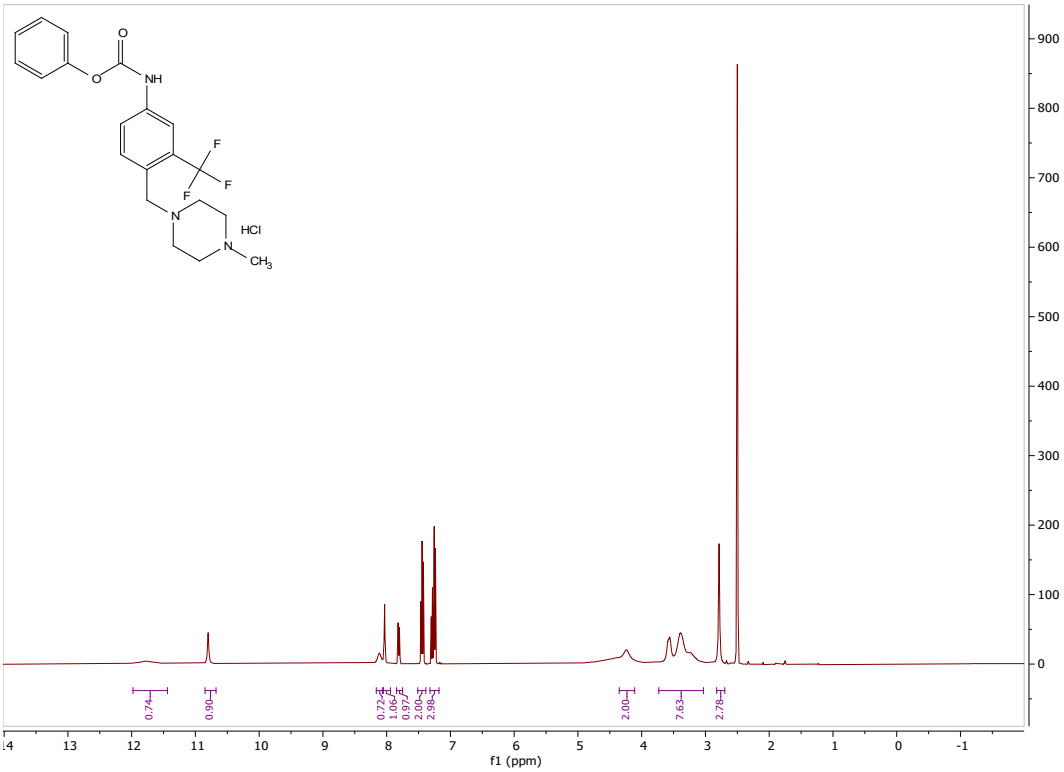
S7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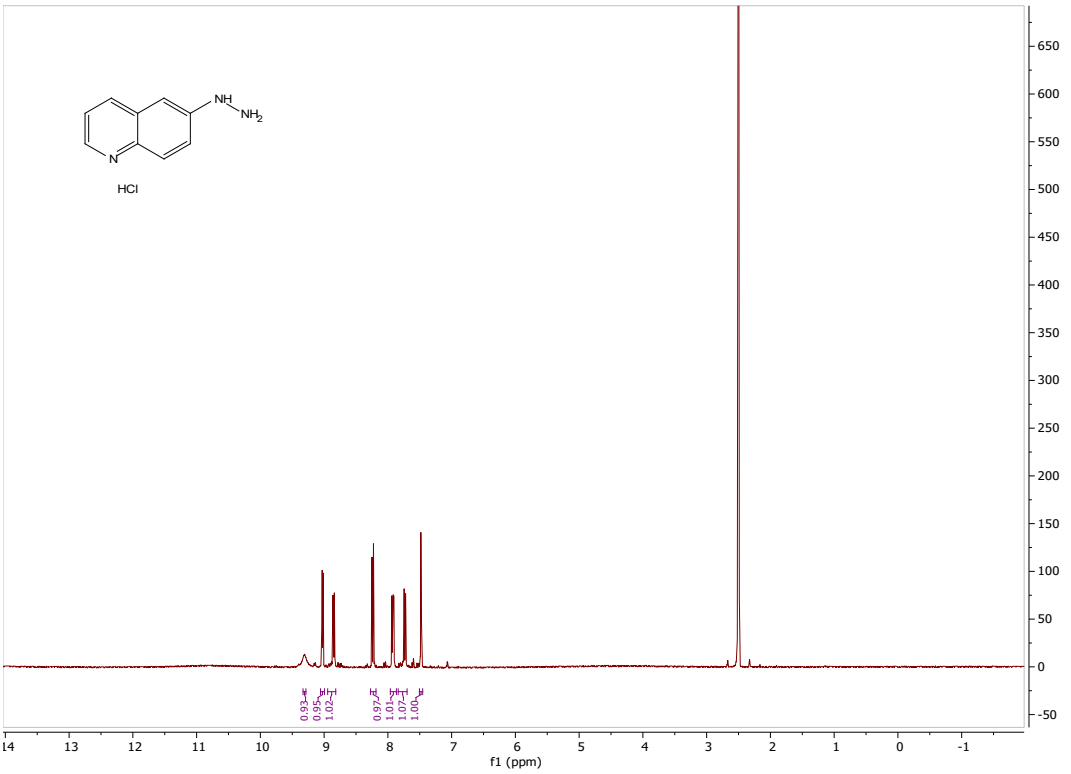
S8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400
350
300
250
200
150
100
50
0
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7
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4
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2
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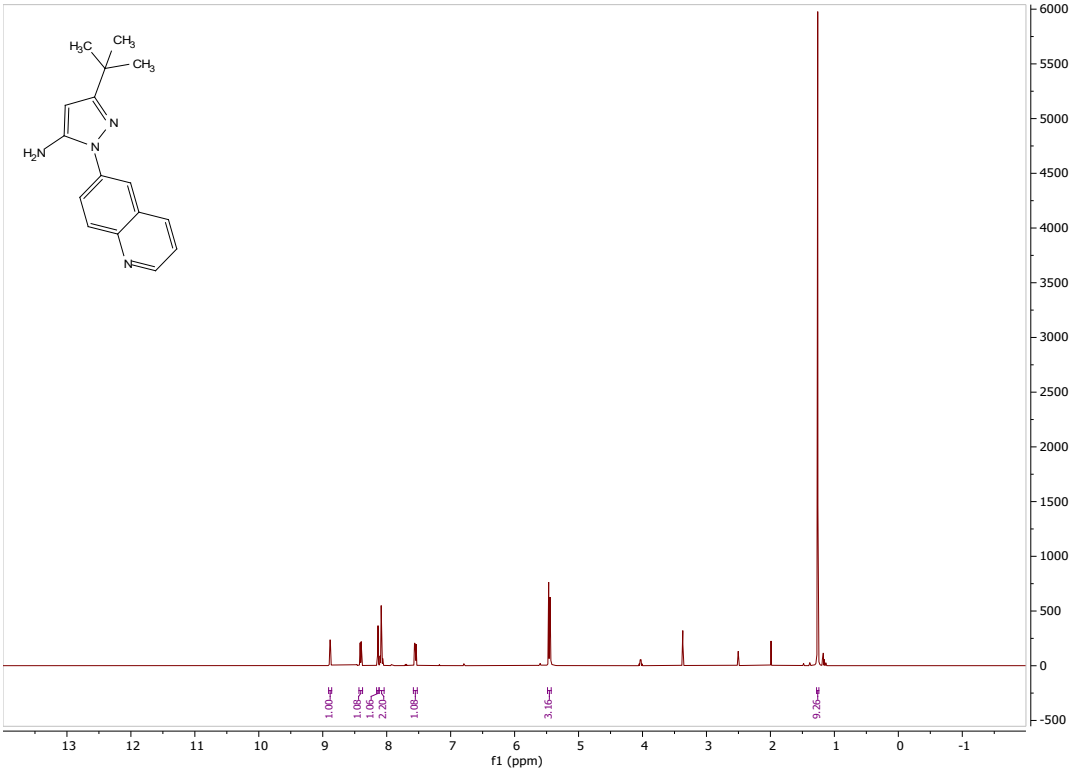
f1 (ppm)

S9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5000
4500
4000
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3000
2500
2000
1500
1000
500
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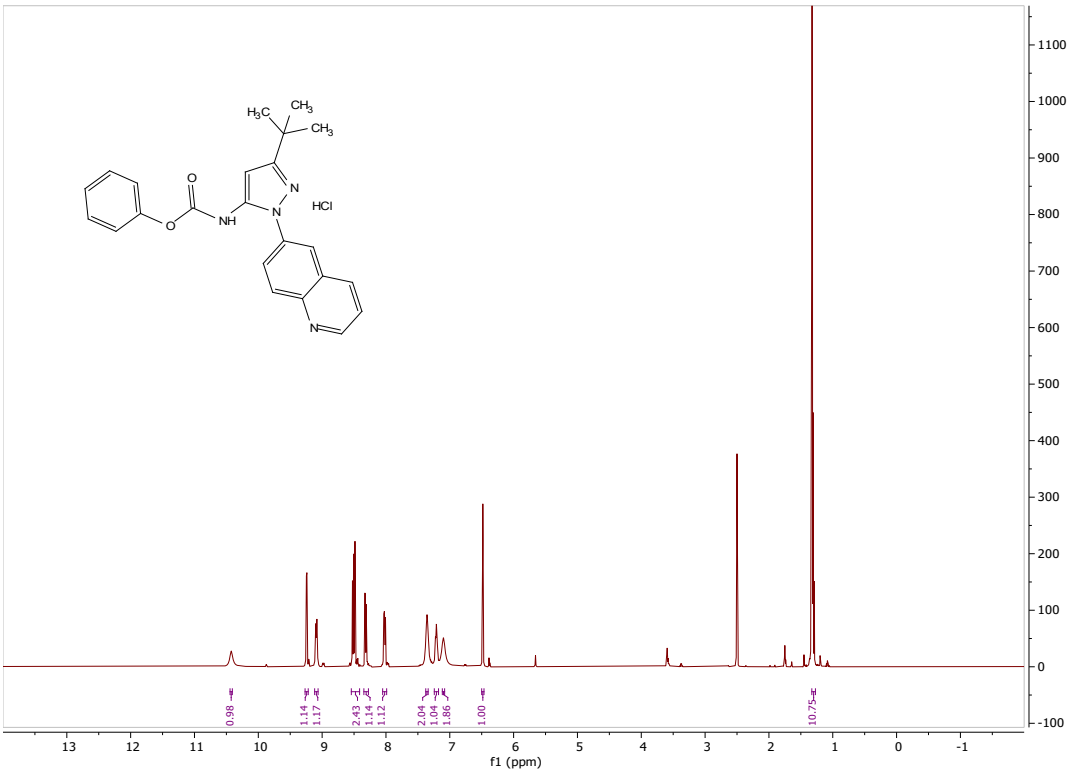
f1 (ppm)

S10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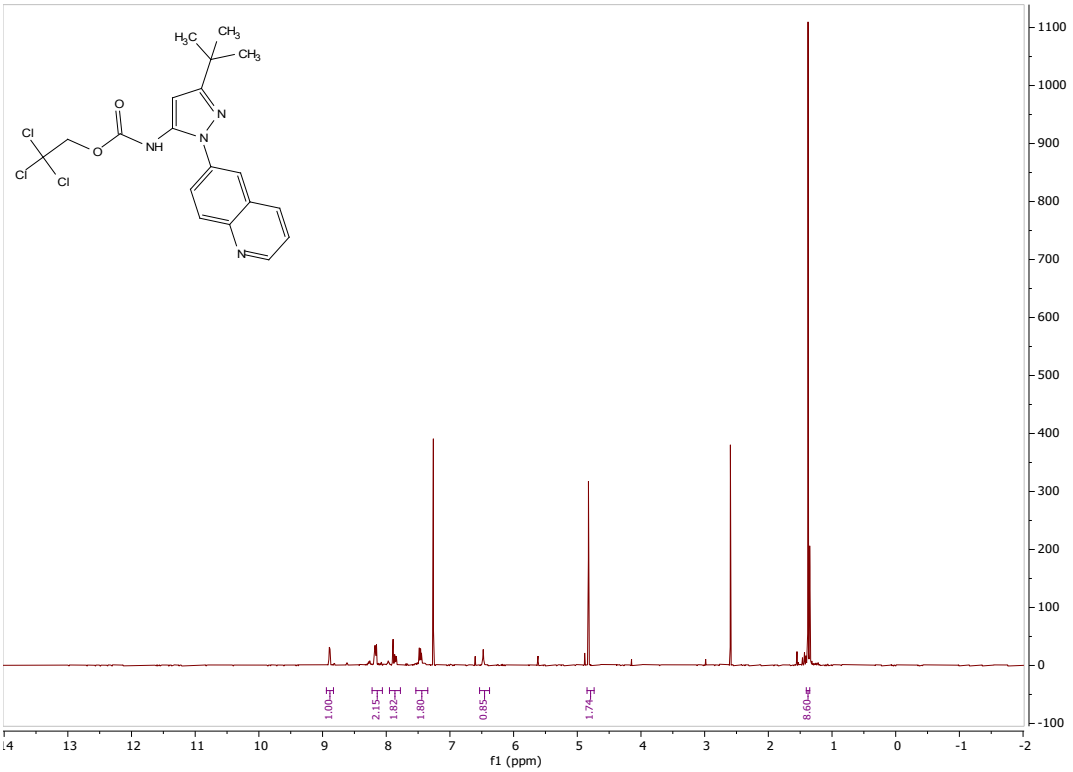
S11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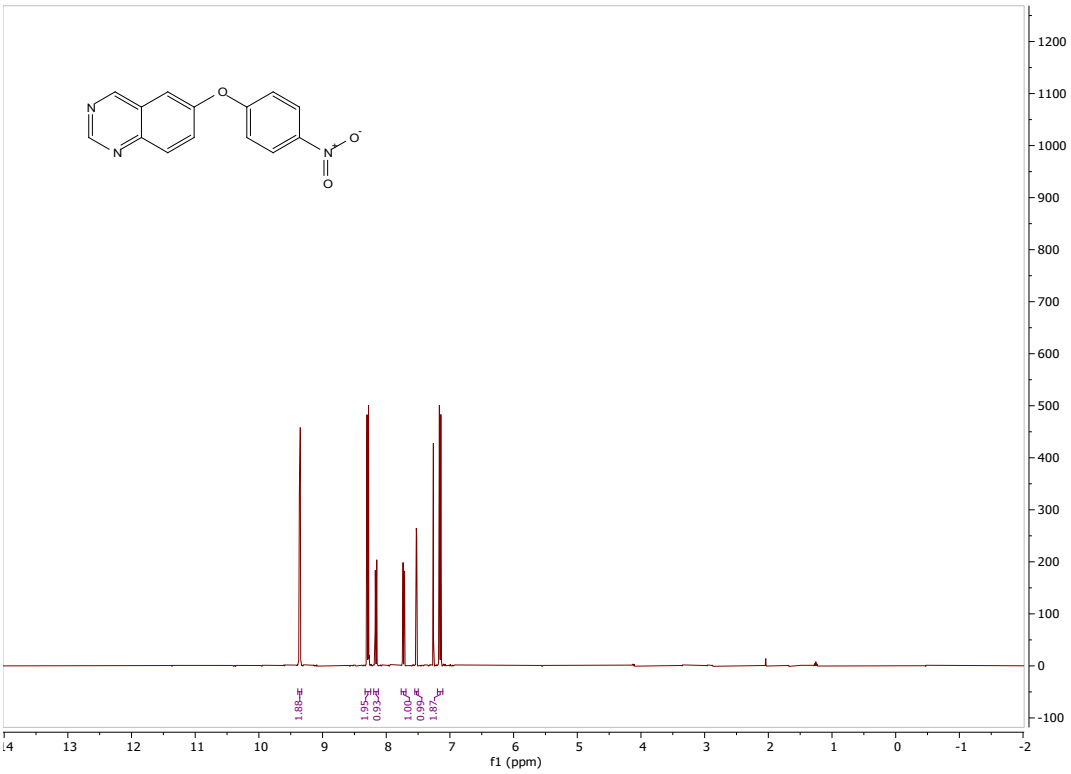
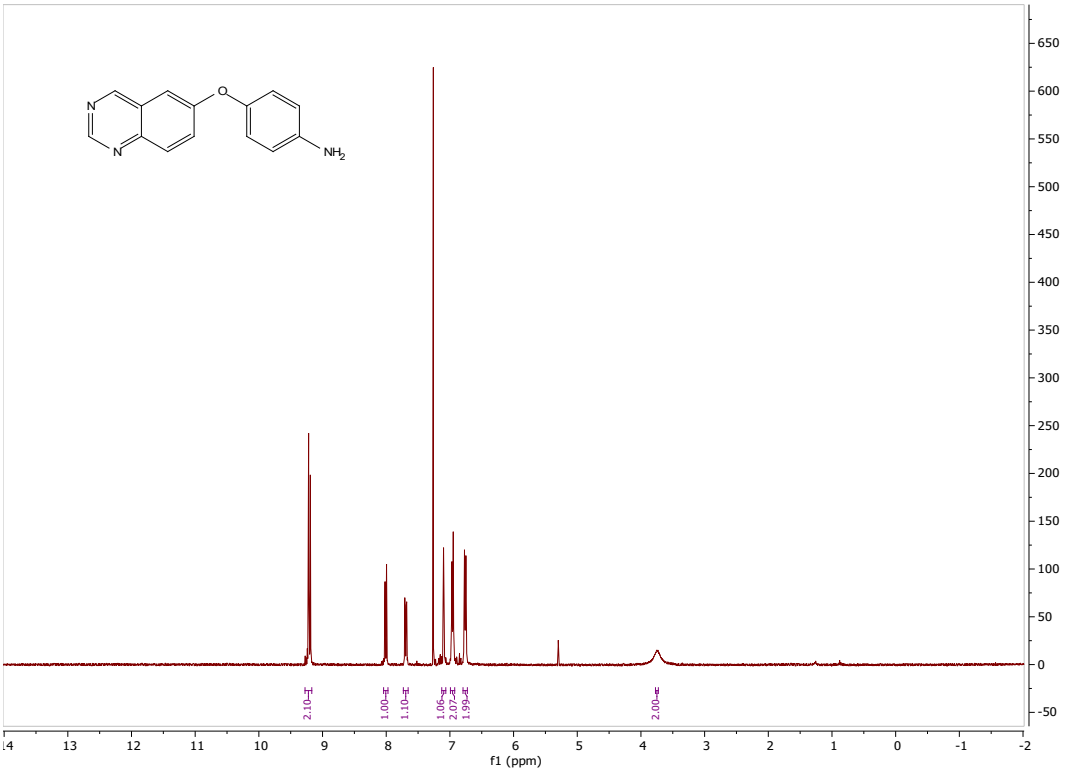
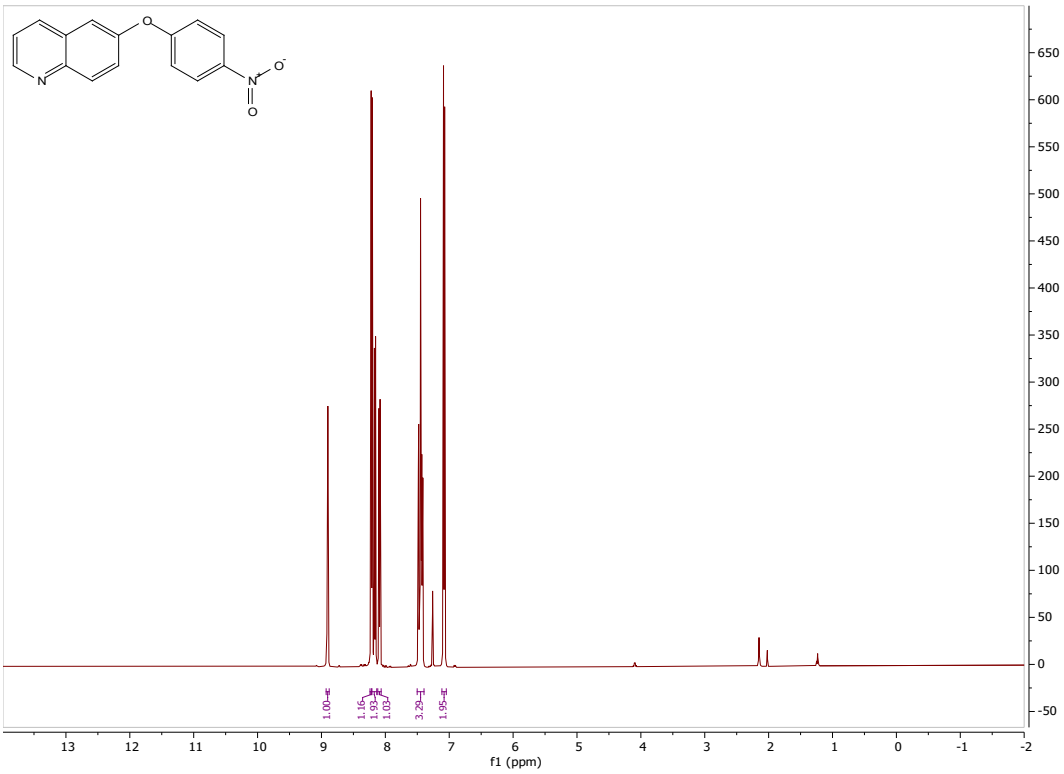
S12



S13



S14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O-
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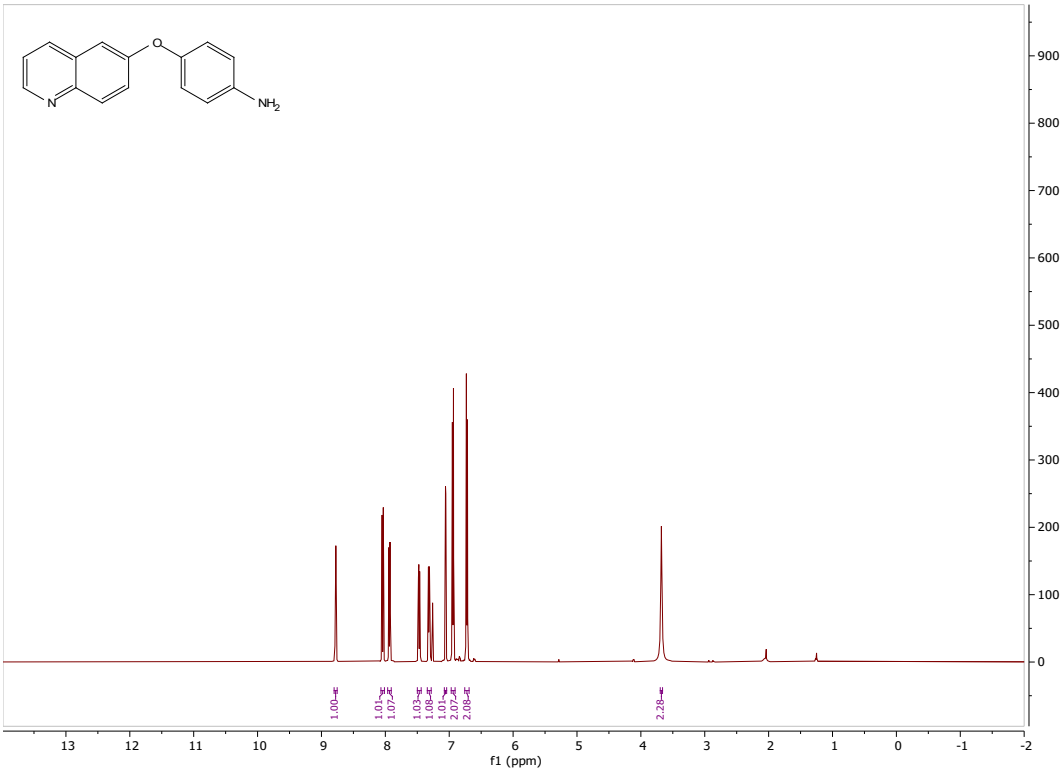
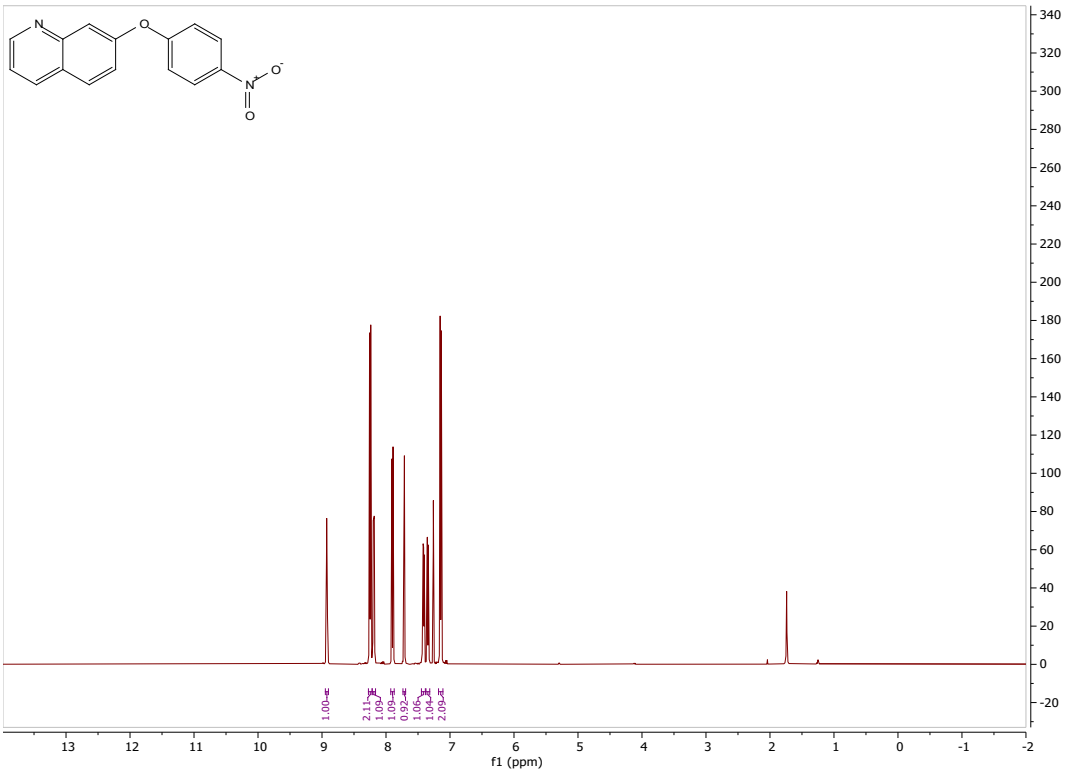
-50
1.00
1.16
1.93
1.03
3.29
1.95
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

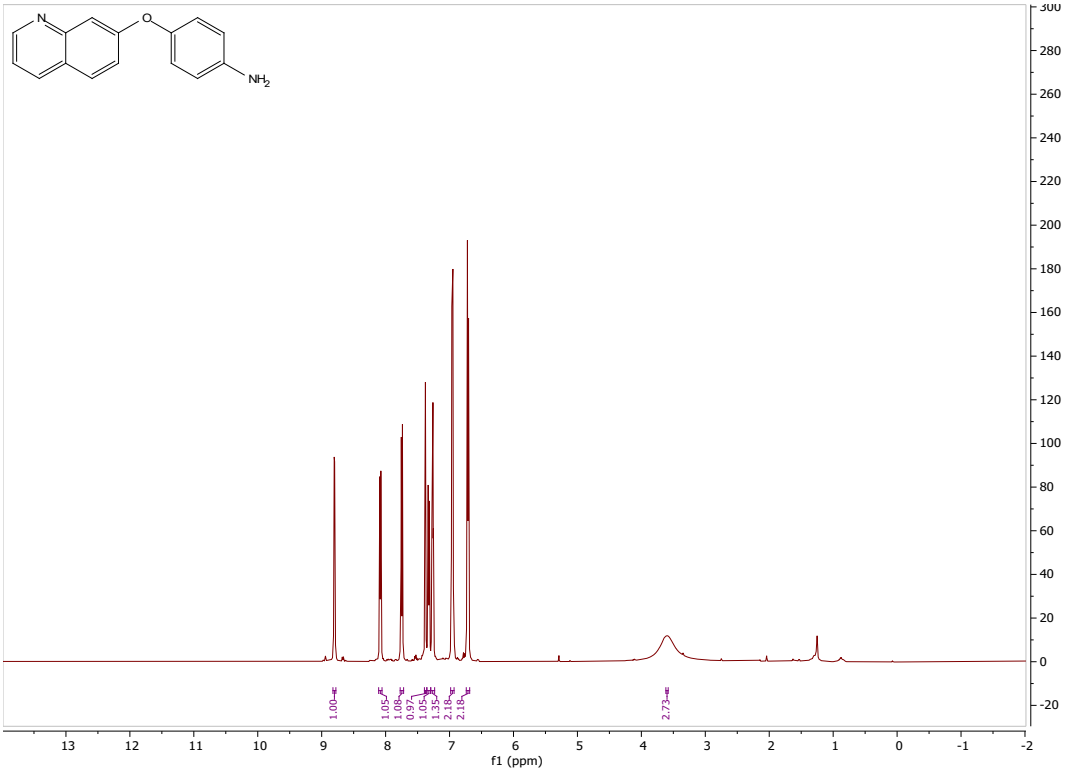
S15


O
N
NH2
900
800
700
600
500
400
300
200
100
0
1.00
1.01
1.07
1.03
1.08
1.01
2.03
2.08
2.28
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

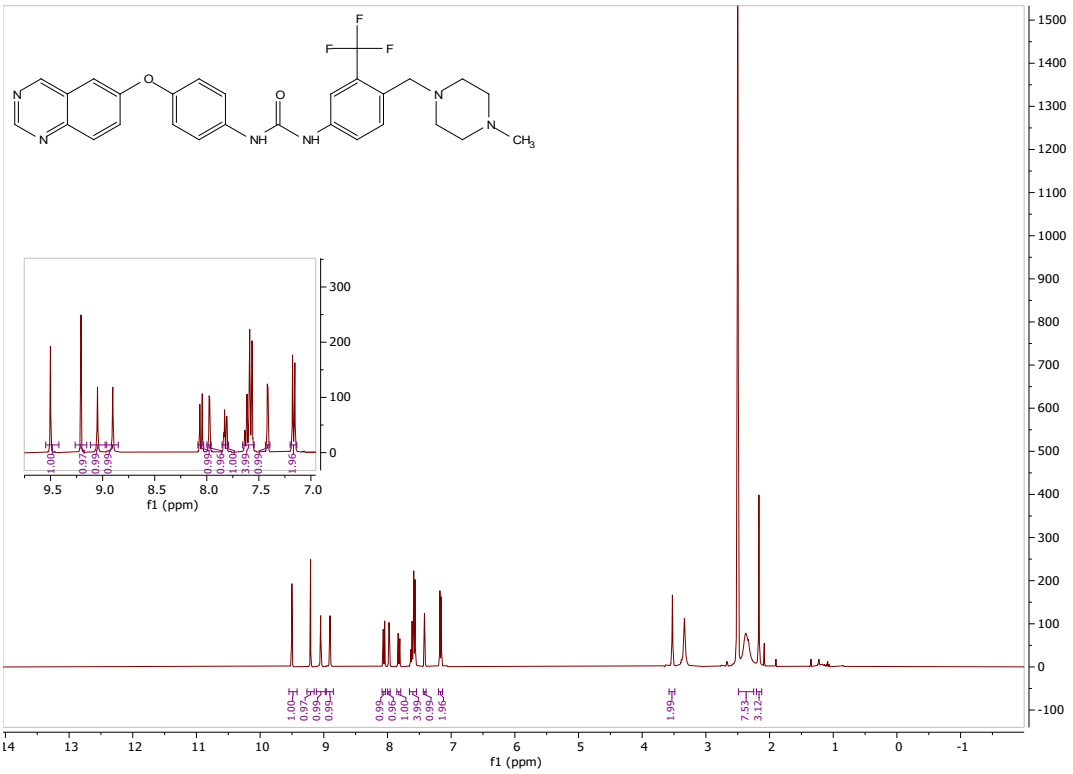
S16

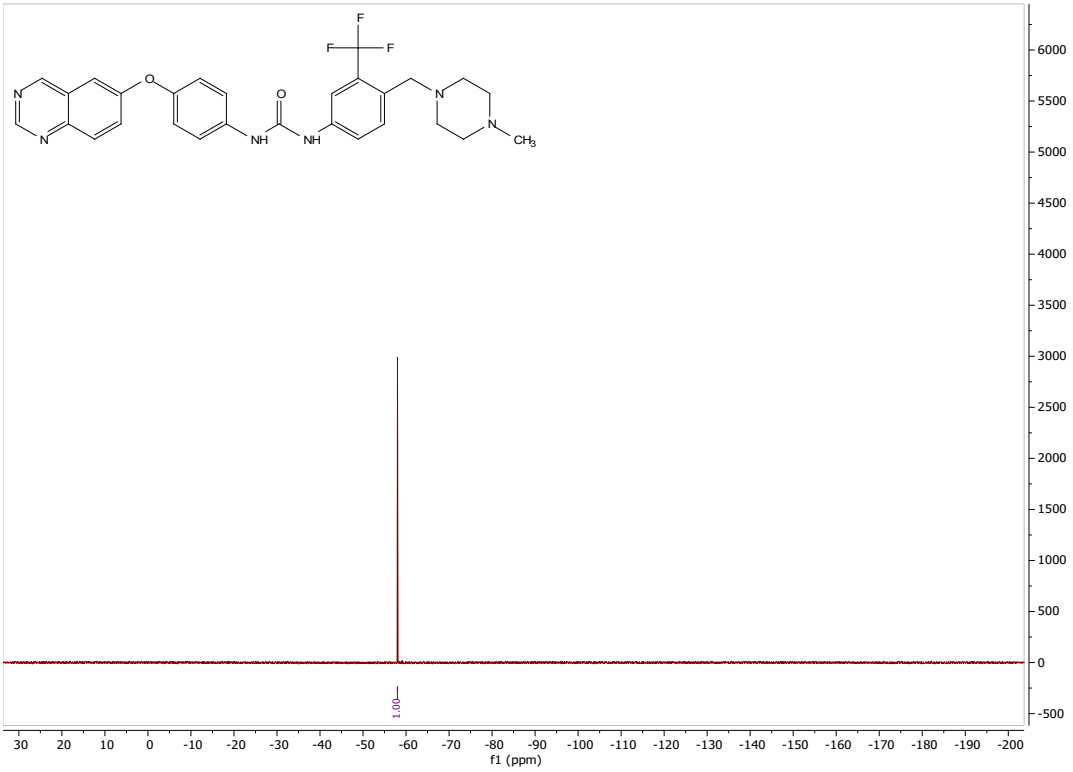

1.00
2.11
1.09
1.09
0.92
1.06
1.04
2.09
f1 (ppm)

S17

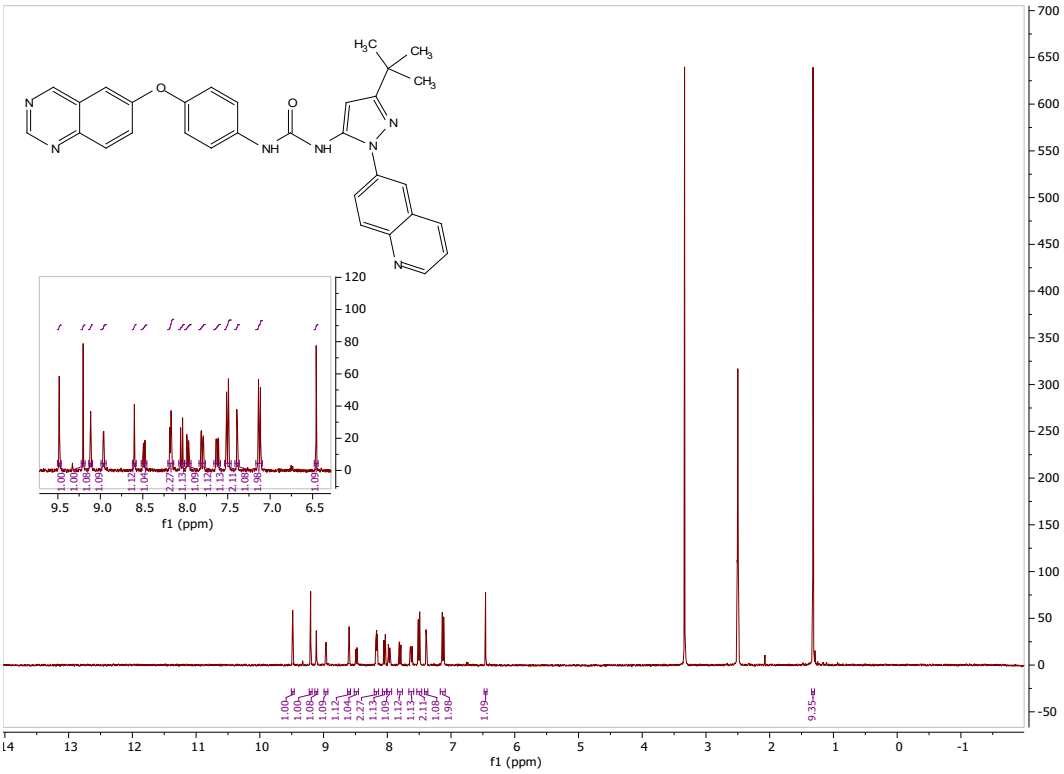

NH2
1.00
1.05
1.08
0.97
1.05
1.35
2.18
2.18
2.73
f1 (ppm)

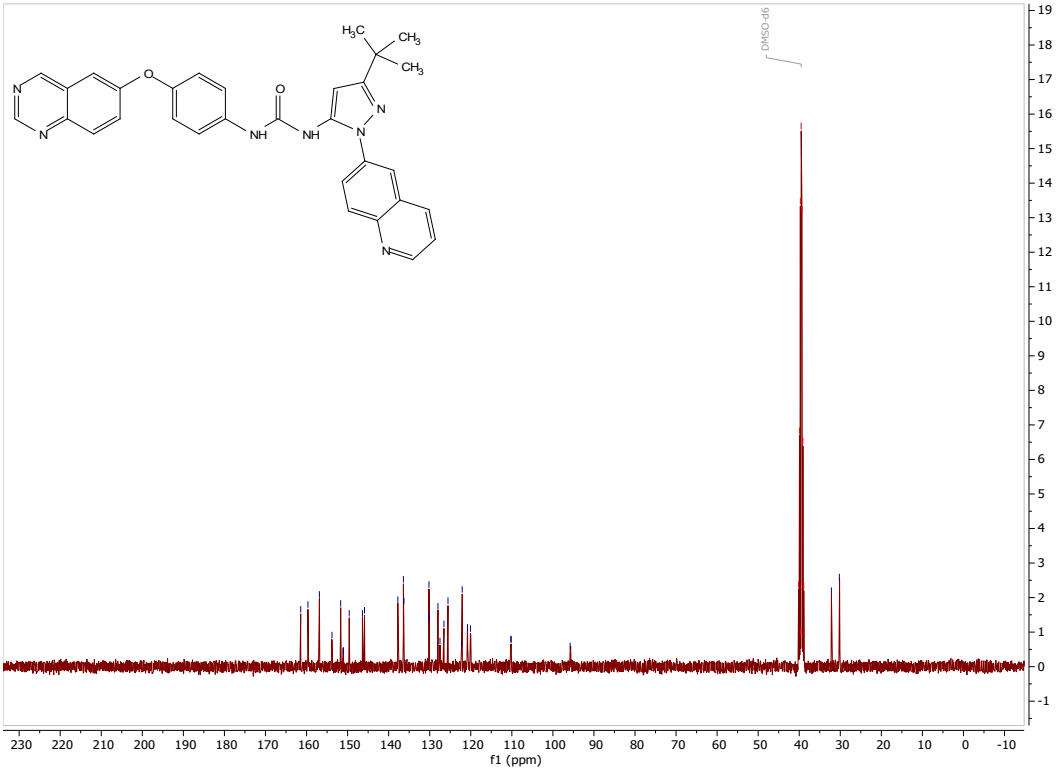
Compound **1**



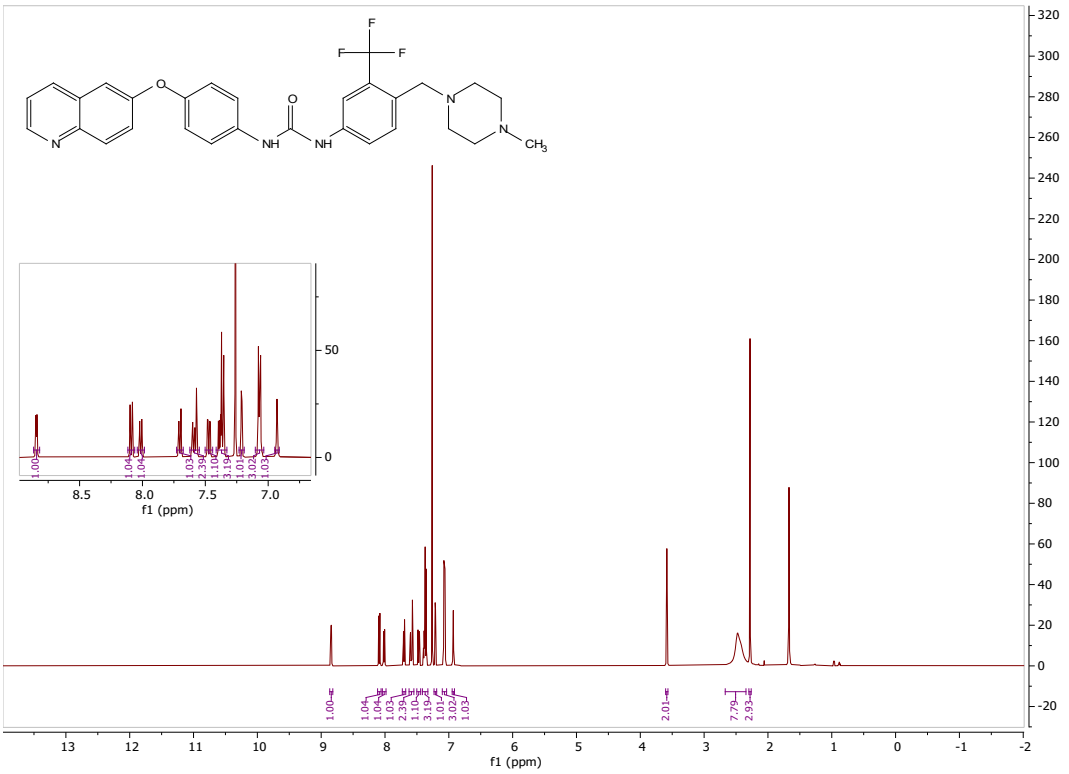


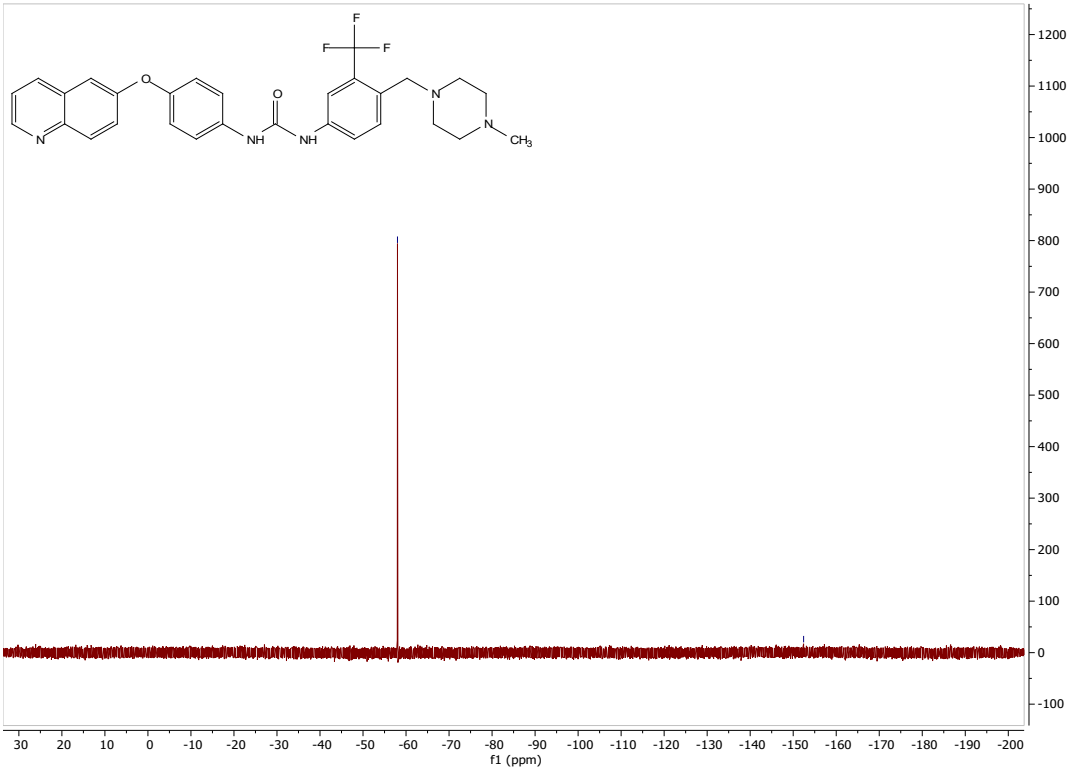
Compound **2**



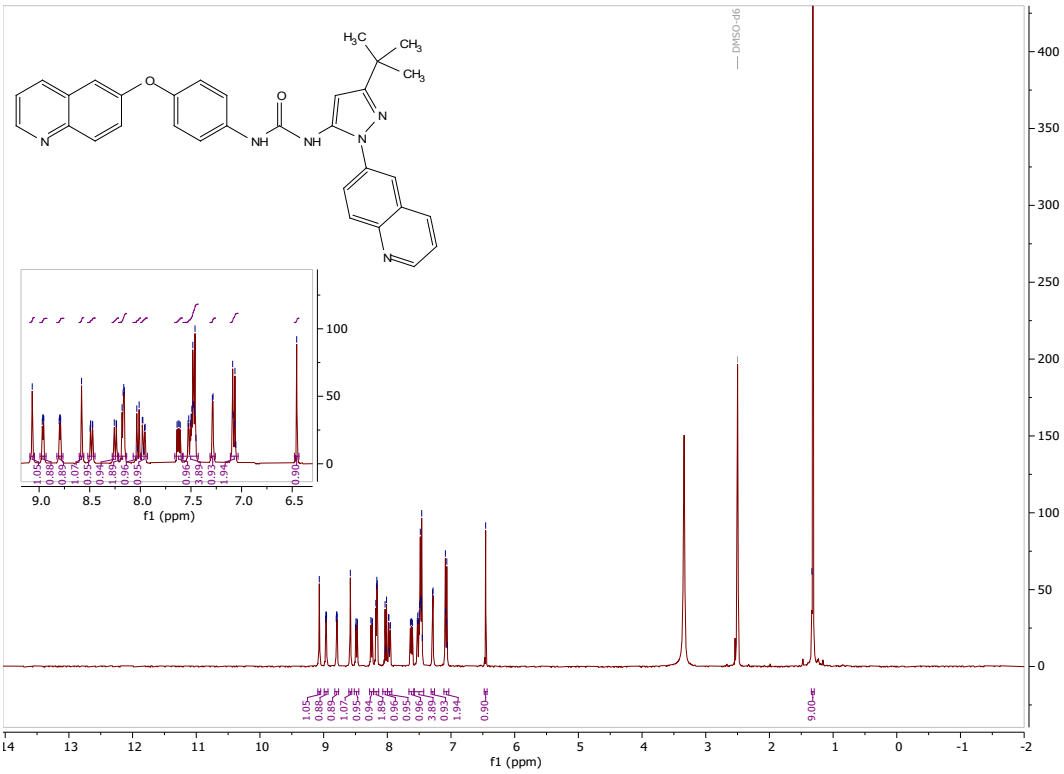


Compound **3**

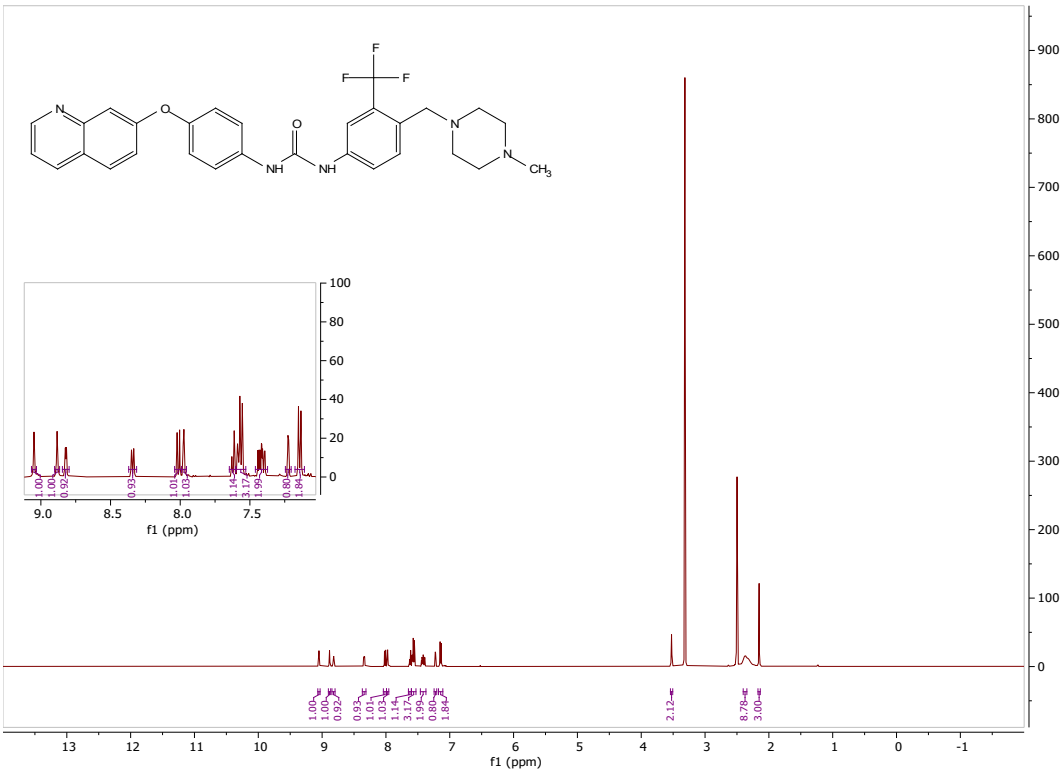


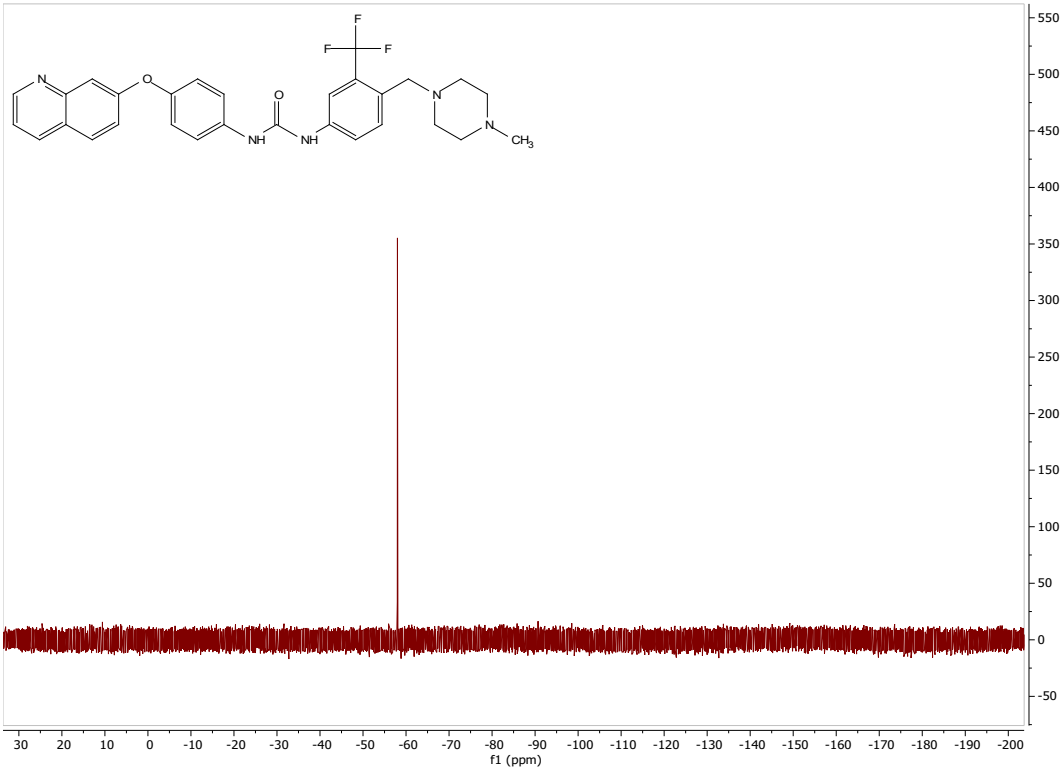


Compound **4**

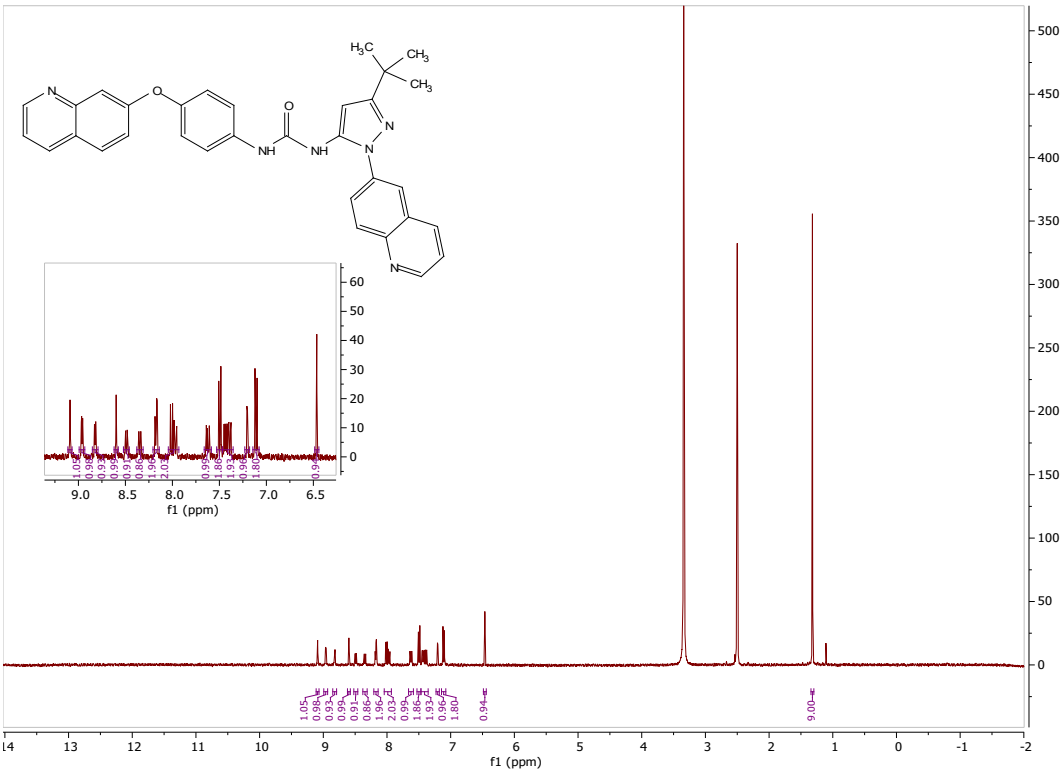


Compound **5**

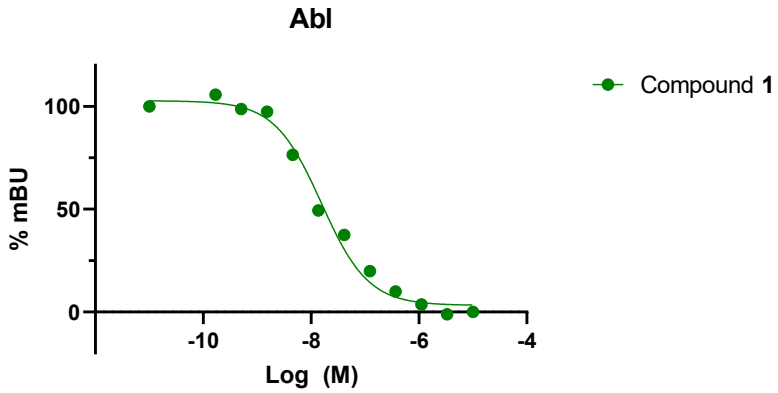




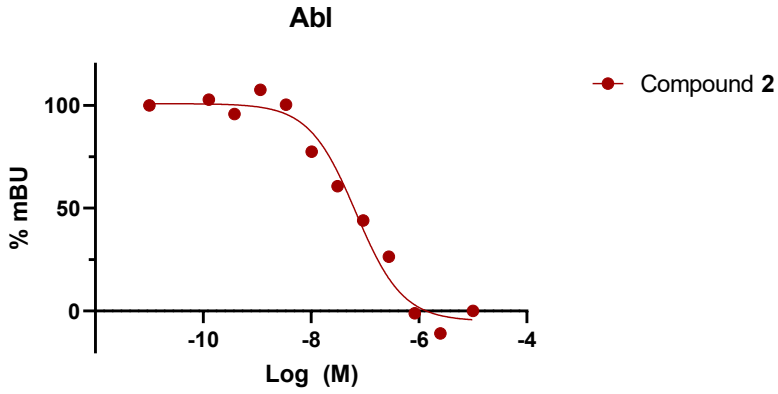
Compound **6**



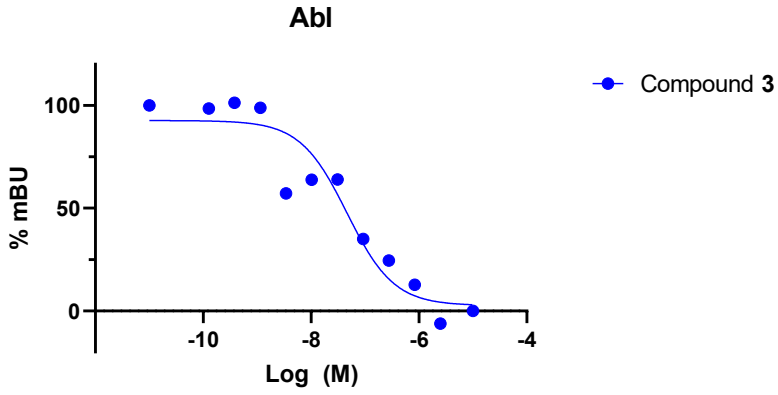
VII. Representative NanoBRET IC_{50} curves



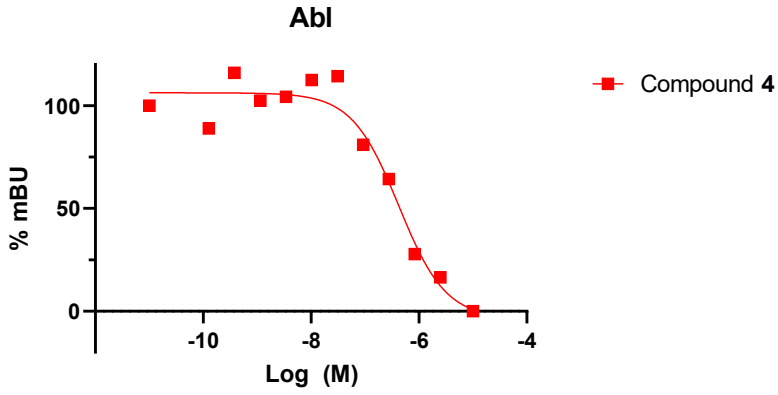
	Compound **1**
EC50	1.553e-008



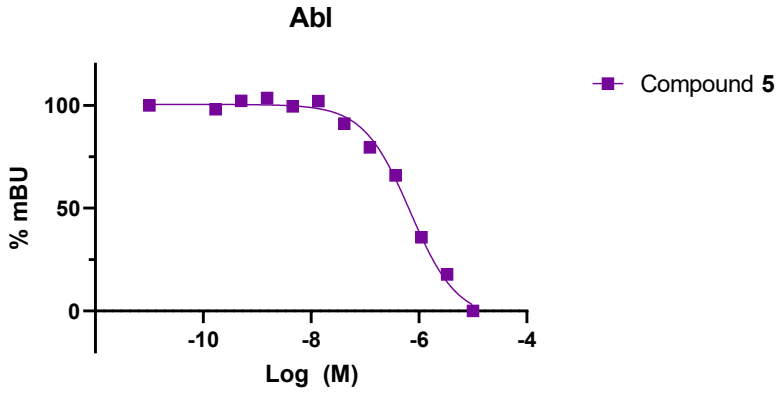
	Compound **2**
EC50	6.769e-008



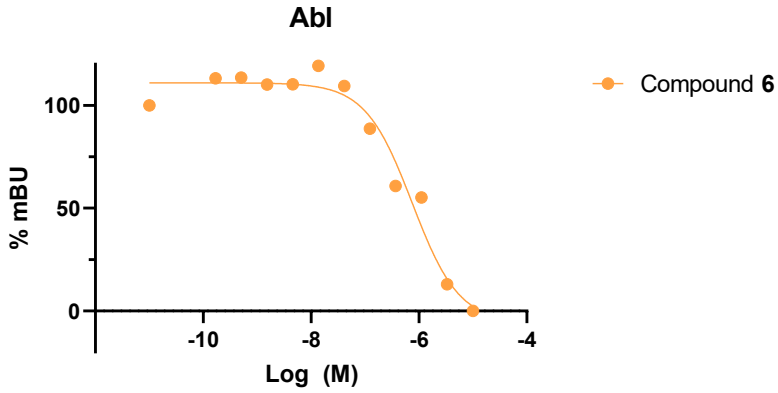
	Compound **3**
EC50	4.643e-008



	Compound **4**
EC50	4.222e-007

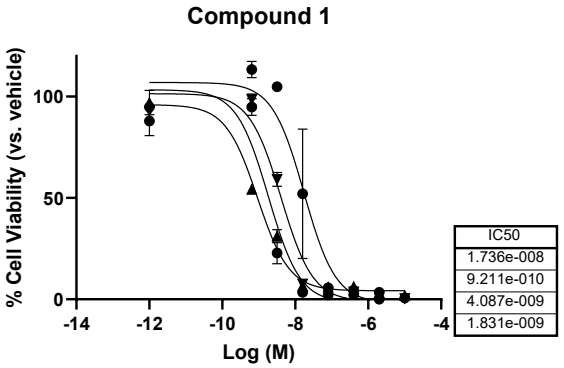


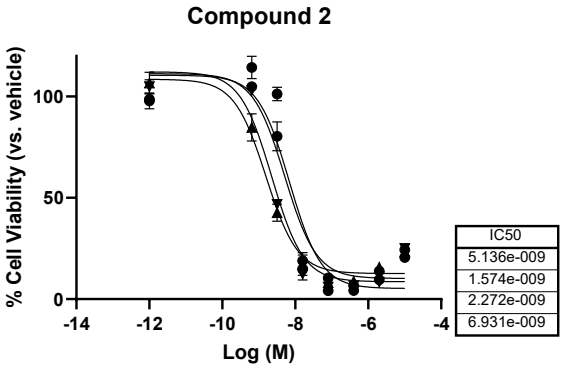
	Compound **5**
EC50	6.871e-007

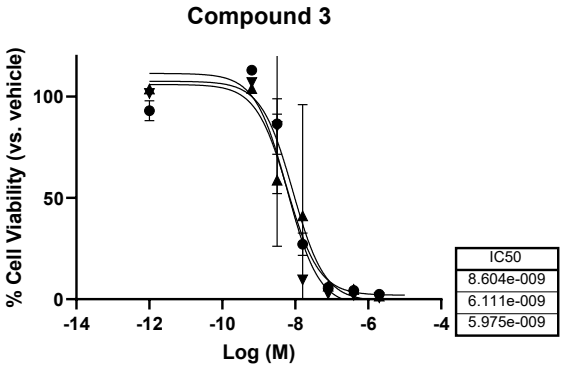


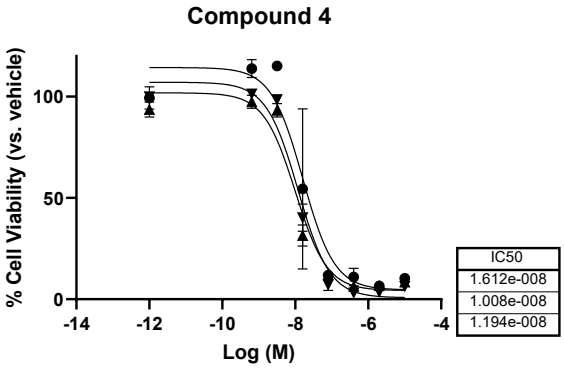
	Compound **6**
EC50	7.497e-007

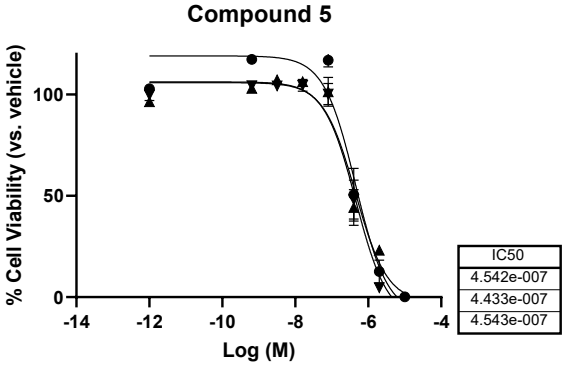
VIII. K562 GI_{50} curves

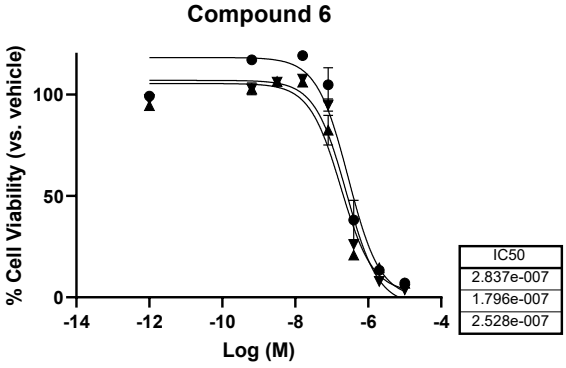




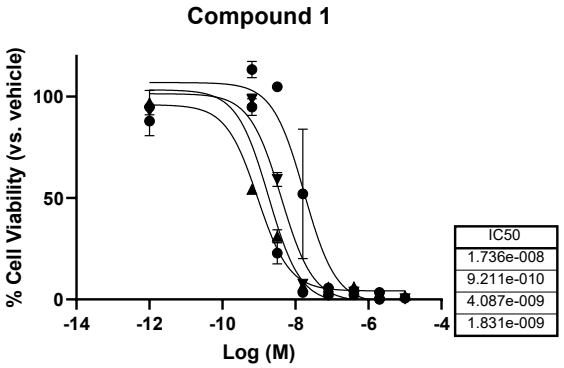


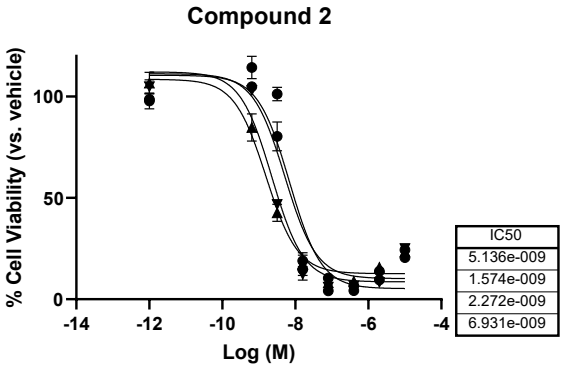


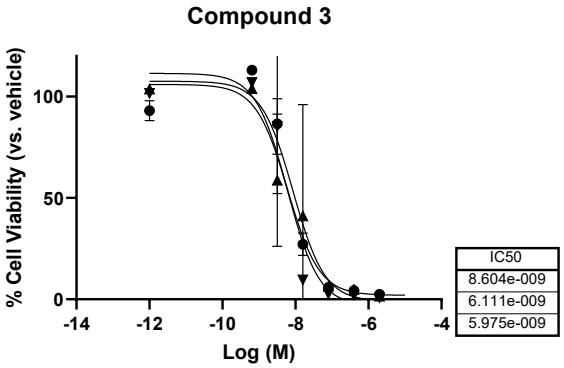


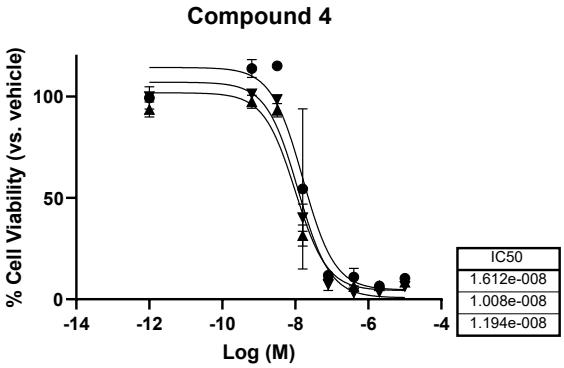


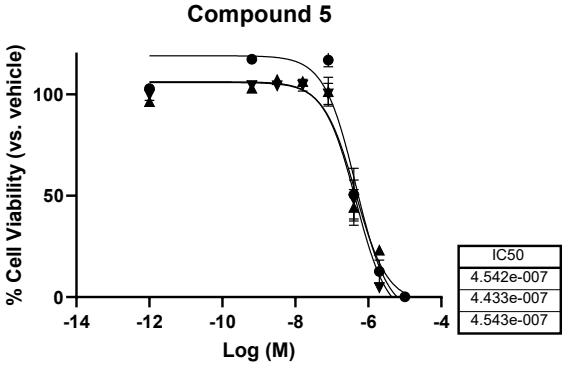
IX. Ba/F3 WT ABL GI_{50} curves

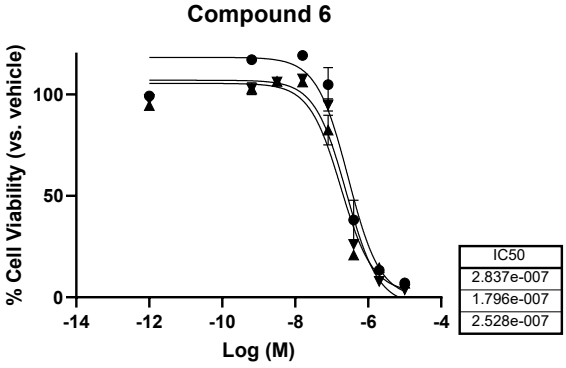




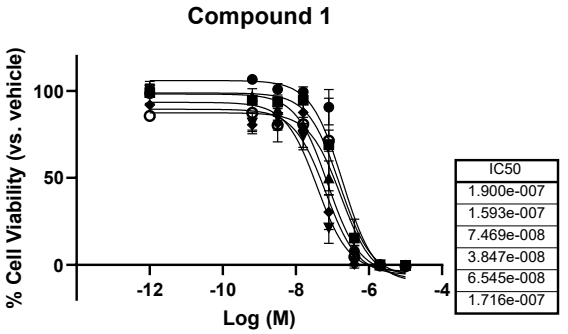


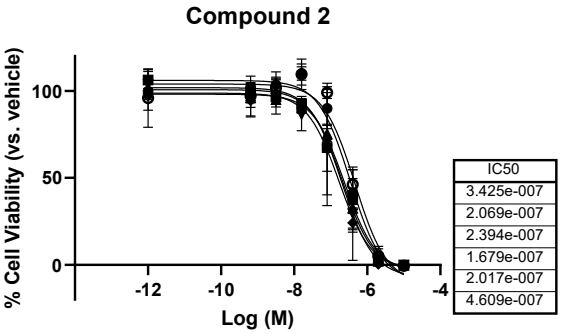


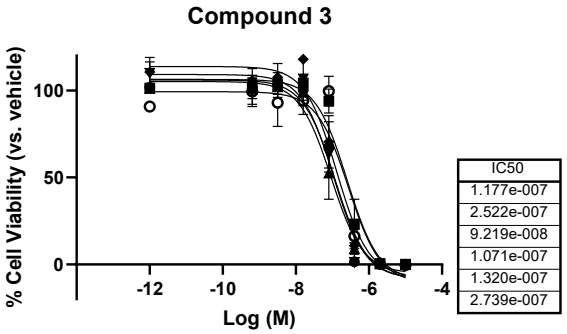


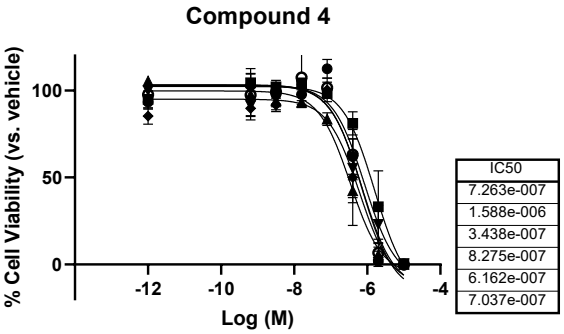


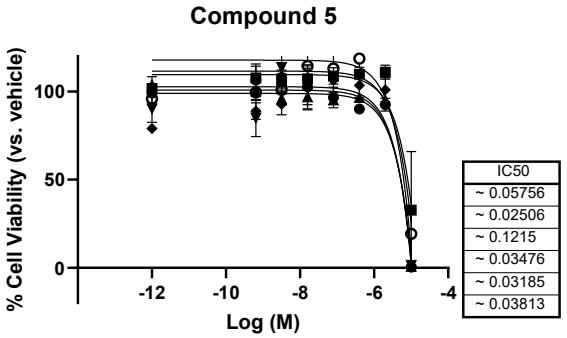
X. Ba/F3 T315I ABL GI_{50} curves

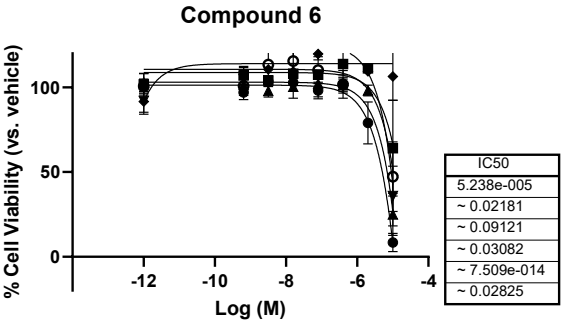












XI. References

1. Griffin, D. R.; Kasko, A. M., Photodegradable macromers and hydrogels for live cell encapsulation and release. *J Am Chem Soc* **2012,** *134* (31), 13103-7.
2. Albert, A.; Hampton, A., Analogues of 8-Hydroxyquinoline Having Additional Cyclic Nitrogen Atoms .1. Preparative. *J Chem Soc* **1952,** (Dec), 4985-4993.
3. Shieh, W.-C.; McKenna, J.; Sclafani, J. A.; Xue, S.; Girgis, M.; Vivelo, J.; Radetich, B.; Prasad, K., Syntheses of a Triad of Flt3 Kinase Inhibitors: From Bench to Pilot Plant. *Organic Process Research & Development* **2008,** *12* (6), 1146-1155.
4. Deciphera WO2006/71940 A2, 2006.