Supplementary Information

Supplementary Figures

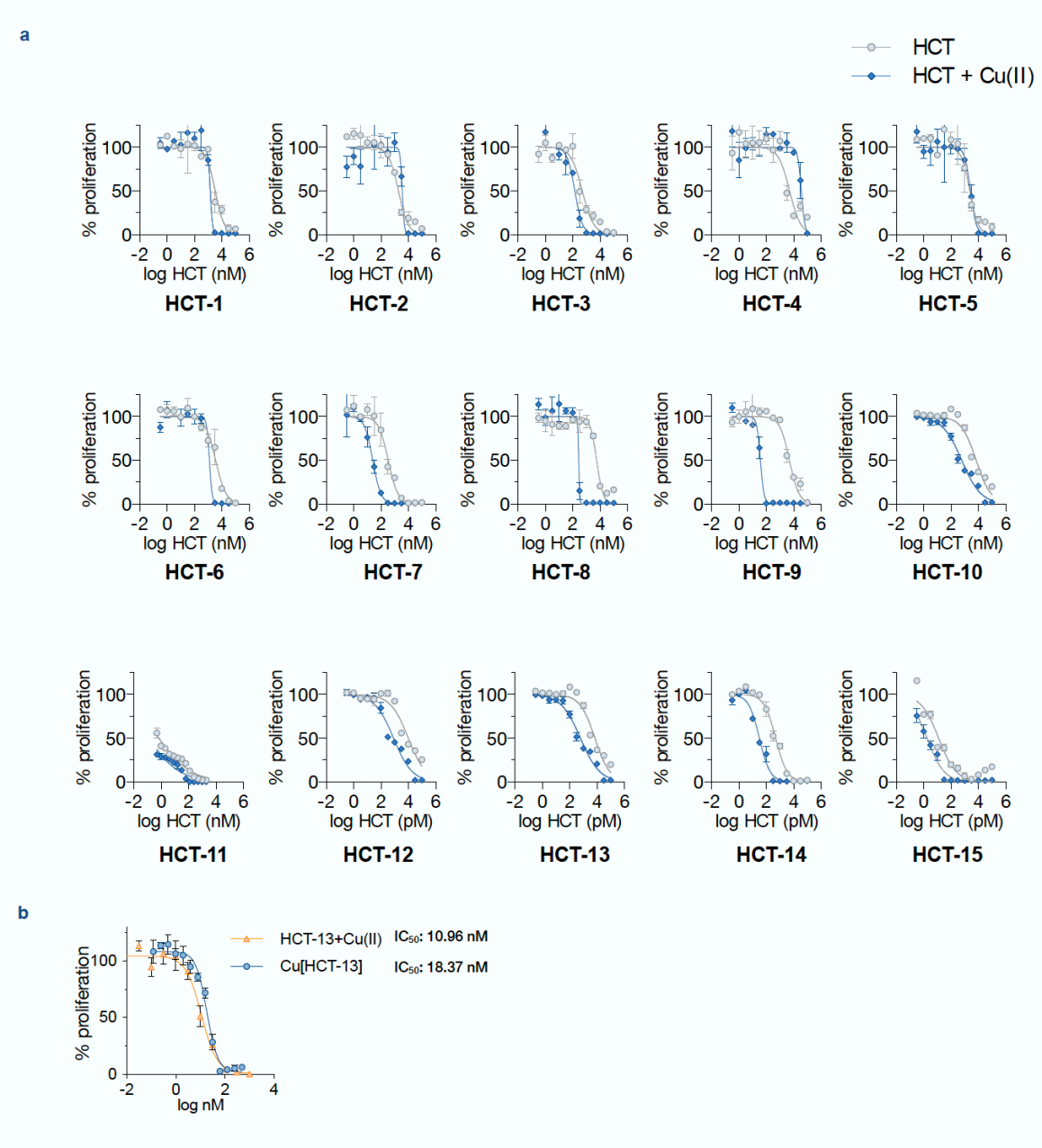


Figure S1 | Summary of HCT compound dose response curves. (a) CellTiterGlo assays of cell viability/proliferation in MIAPACA2 cells treated with each HCT (HCT1-15) compound ± Cu(II) (20 μM) for 72h. **(b)** CellTiterGlo assay of cell viability/proliferation in MIAPACA2 cells treated with Cu[HCT-13] for 72h.

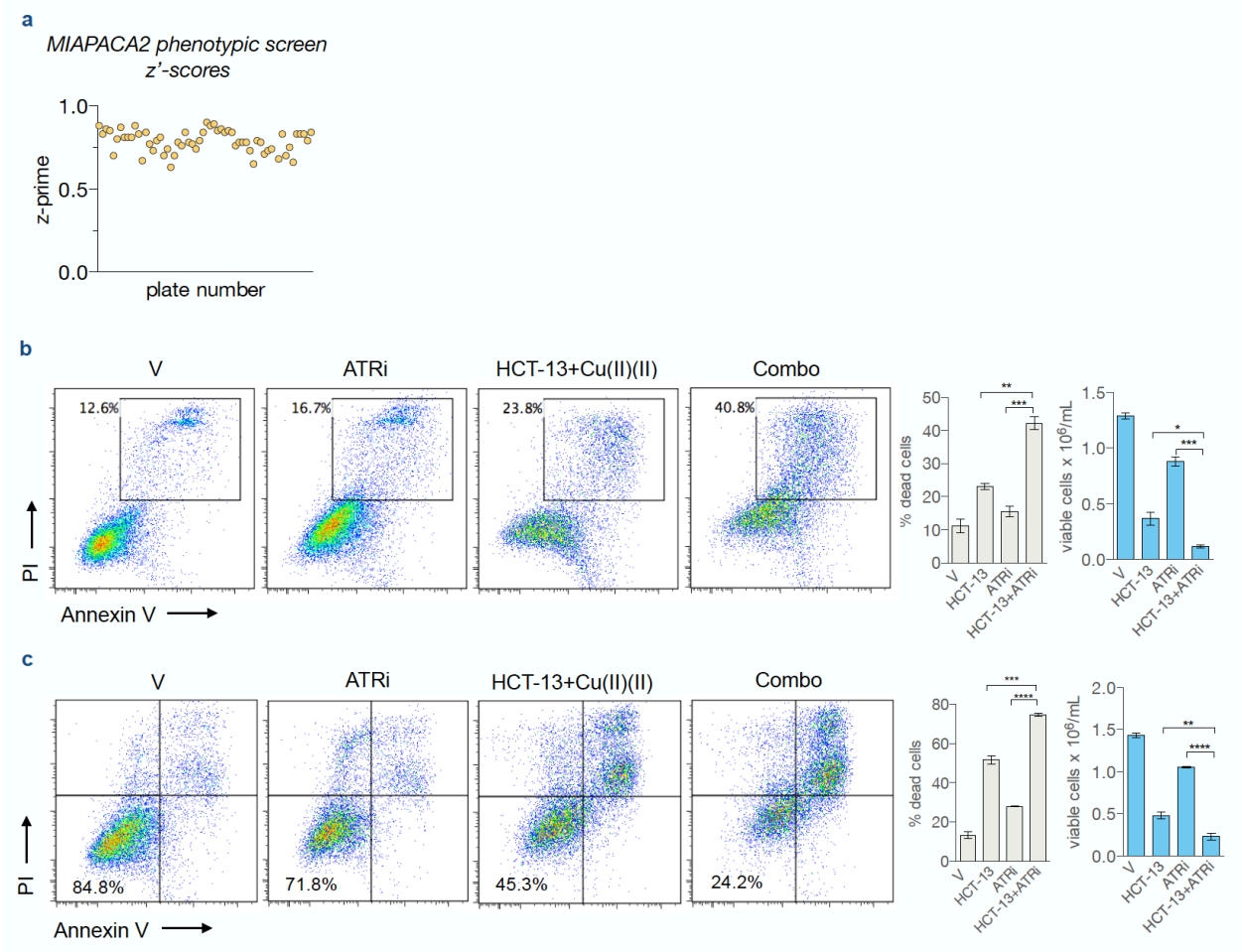


Figure S2 | Identification of metabolic vulnerabilities to HCT-13 using a chemical genomics screen (**a**) Assay quality, as measured by Z-factor (Z') scores (**b and c**) Annexin V/PI staining and Trypan Blue staining in CFPAC-1 PDAC cells and C4-2 PC cells to validate the synergistic interaction of HCT-13 with ATRi (250 nM VE-822) treated for 72h in presence of Cu(II) (20 μM); V: vehicle (mean ± s.d., n = 3, unpaired 2 tailed t-test, **** $P < 0.0001$).

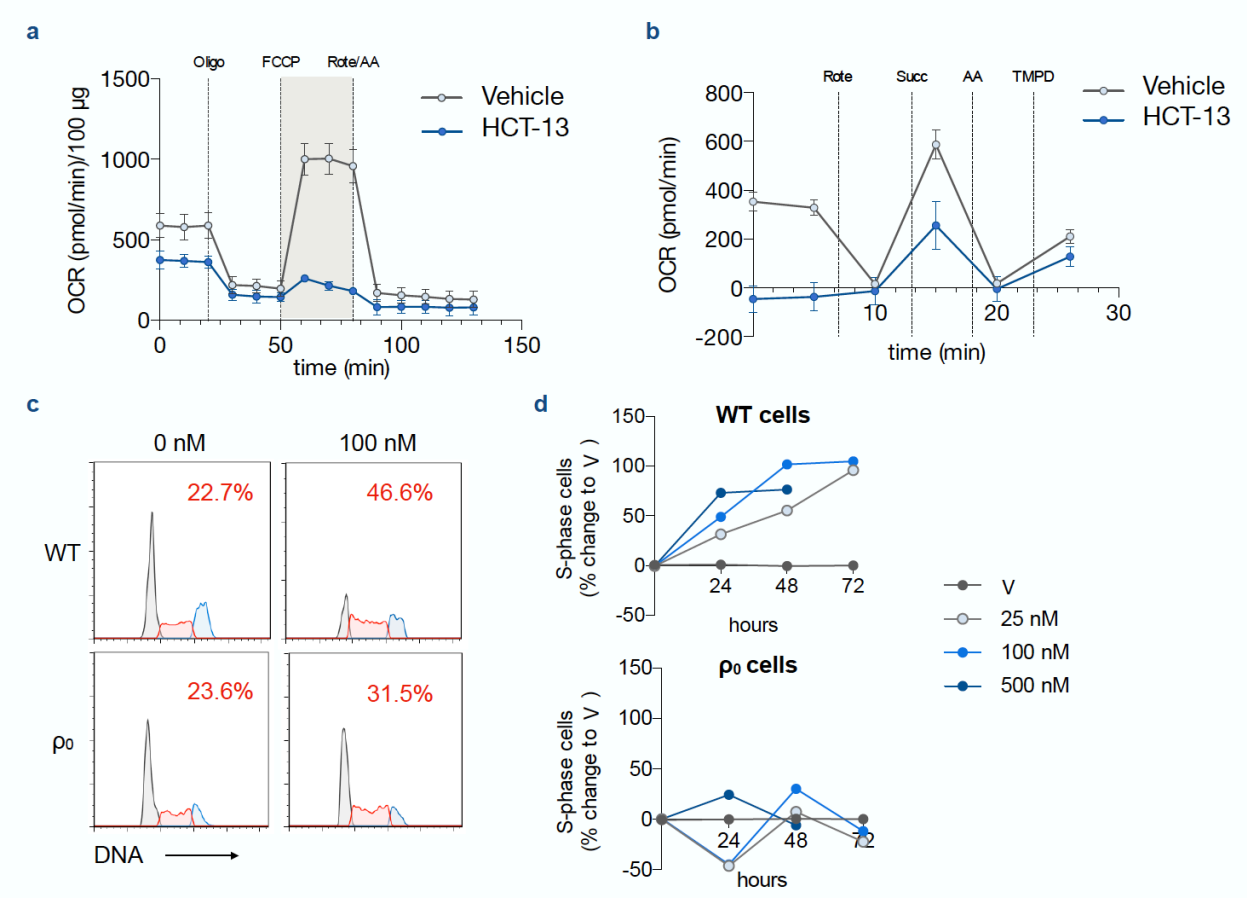


Fig. S3 | HCT-13 + Cu(II) reduces OXPHOS and has selective mitochondrial toxicity. (**a**) Mito Stress Test of MIAPACA2 PDAC cells treated with HCT-13 (25 nM) + Cu(II) (20 µM) for 24h. (**b**) Electron flow assay in isolated mitochondria treated with HCT-13 (100 nM) + Cu(II) (20 µM) for 1h. (**c & d**) Cell cycle histograms of 143 BTK WT and 143 BTK ρ_0 cells at 48h treated with 100 nM HCT-13 + 20 µM Cu(II) ; V: vehicle.

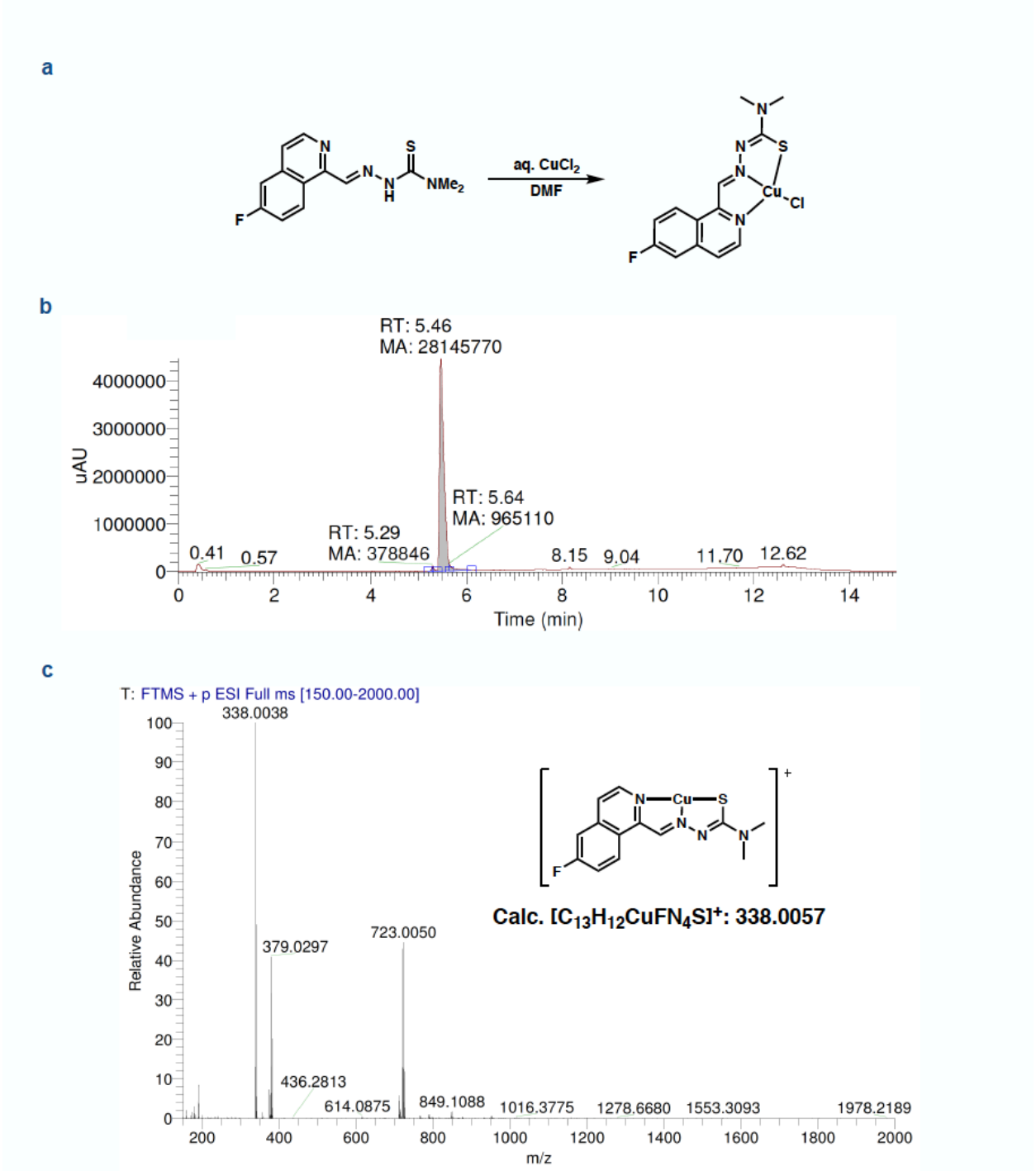


Figure S4 | Synthesis and characterization of Cu[HCT-13]. (**a**) Synthetic scheme (**b**) UV (254 nm) trace for synthesized Cu[HCT-13] (95% purity). Method: 0–95%B over 10 minutes using a ThermoFisher aquasil hypersil gold C18 column (1.9 μm, 2.1*100 mm). Mobile phase A: 0.1% FA in H_2O. Mobile phase B: 0.1% FA in MeCN. Flow rate: 400 μL/min. (Agilent 1100 HPLC) (**c**) HR-MS (ESI+) data: m/z calculated for $[C_{13}H_{12}CuFN_4S]^+$ = 338.0057; found 338.0038; m/z calculated for $[C_{13}H_{12}CuFN_4S + MeCN]^+$ = 379.0323; found 379.0297 (Thermo LTQ-Orbitrap XL). ESI analyses often displayed a variable occurrence of higher mass ions (e.g. m/z = 723.005) which appear to be mass multiples of HCT-13 plus iron or copper ions. The ions and their intensities changed dependent upon the specific instrument that was used, which was attributed to variable levels of metal ion contamination within the instruments.

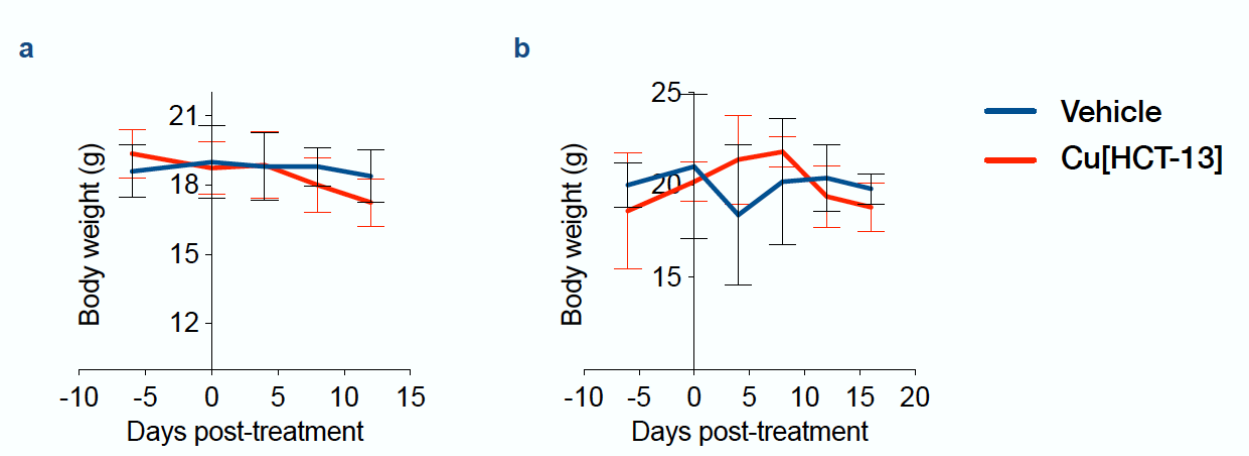


Figure S5 | Cu[HCT-13] is well tolerated *in vivo* as monitored by body weight. (**a & b**) Body weight measurements of (**a**) p185 pre-B ALL bearing mice and (**b**) MV4-11 AML bearing mice in treated and vehicle-treated groups.

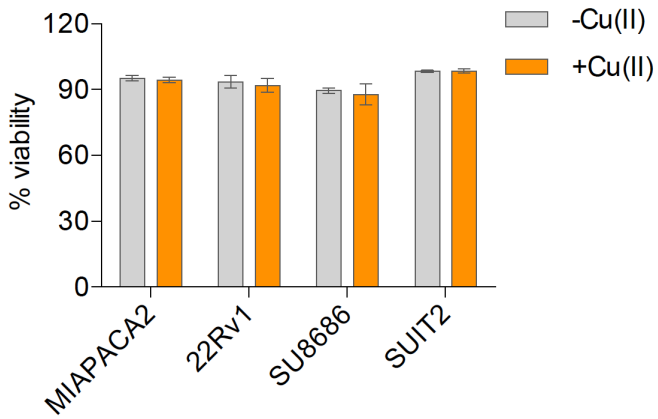
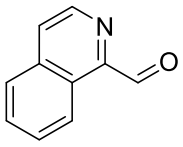
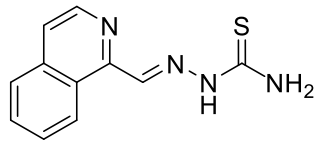


Figure S6 | 100 μM copper chloride supplementation has no effect on cell viability in PDAC and prostate cancer cell lines.

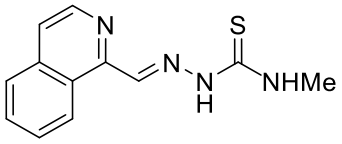
Synthesis of intermediates S1-S22 and final compounds HCT1-HCT15 and Cu[HCT-13]



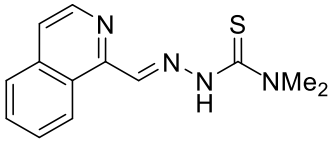
Isoquinoline-1-carboxaldehyde (S1). To a solution of 1-methylisoquinoline (1.0 g, 6.98 mmol) in 1,4-dioxane (10 mL) was added selenium dioxide (0.930 g, 8.38 mmol) and the mixture was heated at 60 °C overnight. The mixture was filtered, then concentrated in vacuo. The crude residue was purified by column chromatography (1:10 ethyl acetate: hex), and all fractions that were not pink were combined to give the product S1 as a taupe powder (0.840 g, 69% yield). 1H NMR (500 MHz, DMSO-d6) δ 10.28 (s, 1H), 9.15 (ddd, J = 7.7, 1.9, 0.8 Hz, 1H), 8.82 (d, J = 5.5 Hz, 1H), 8.21 (dd, J = 5.6, 0.9 Hz, 1H), 8.17–8.12 (m, 1H), 7.93–7.84 (m, 2H). 13C NMR (125 MHz, DMSO- d6) δ 195.64, 149.38, 142.47, 136.49, 131.00, 130.30, 127.45, 125.77, 125.41, 124.73. DART-MS: m/z calcd. for $C_{10}H_8NO$ $(M+H)^+$ 158.06004, found 158.05977.



(*E*)-2-(isoquinolin-1-ylmethylene)hydrazine-1-carbothioamide (HCT1). Synthesized from **S1** as previously reported.[3] ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.74 (s, 1H), 9.19 (d, J = 8.5 Hz, 1H), 8.60–8.54 (m, 2H) 8.49 (br s, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 5.6 Hz, 1H), 7.84–7.78 (m, 2H), 7.75 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.41, 150.78, 145.99, 142.13, 136.24, 130.47, 129.08, 127.22, 126.94, 125.58, 121.77. DART-MS: m/z calcd. for $C_{11}H_{10}N_4S$ $(M+H)^+$ 231.06989, found 231.06938.



(*E*)-2-(isoquinolin-1-ylmethylene)-*N*-methylhydrazine-1-carbothioamide (HCT6). To a solution of **S1** (0.060 g, 0.382 mmol) in ethanol (3 mL) was added 4-methyl-3-thiosemicarbazide (0.040g, 0.382 mmol) and HCl (0.318 mL, 12 M in H_2O). The mixture was refluxed for 4 h. The solid that formed was collected by filtration, washed with water, and recrystallized from EtOH to yield **HCT6** as a yellow powder (0.058 g, 62% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.78 (br s, 1H), 9.11 (br s, 1H), 8.61 (s, 1H), 8.56 (d, J = 5.6 Hz, 1H), 8.31 (br s, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.89–7.79 (m, 2H), 7.76 (t, J = 7.7 Hz, 1H), 3.07 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.36, 151.06, 144.76, 142.15, 136.25, 130.42, 128.86, 127.21, 126.82, 125.64, 121.48, 31.34. DART-MS: m/z calcd. for $C_{12}H_{13}N_4S$ $(M+H)^+$ 245.08554, found 245.08505.



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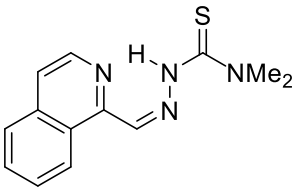
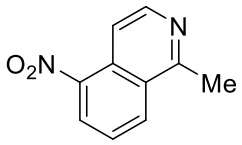
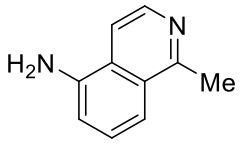


(*E*)-2-(Isoquinolin-1-ylmethylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide and (*Z*)-2-(Isoquinolin-1-ylmethylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide (HCT11). To a solution of **S1** (0.060 g, 0.382 mmol) in ethanol (3 mL) was added 4,4-dimethyl-3-thiosemicarbazide (0.046g, 0.382 mmol) and HCl (0.318 mL, 12 M in H2O). The mixture was refluxed for 30 min and let cool at RT until precipitates formed. The solid that formed was collected by filtration, washed with cold EtOH twice to give **HCT11** as a yellow powder (0.056 g, 57% yield) (mixture of E and Z isomers). ^{1}H NMR (500 MHz, DMSO-*d*6) δ 15.99 (s, 0.33H), 11.26 (br s, 1H), 9.77 (dd, *J* = 8.8, 5.1 Hz, 1H), 8.81 (d, *J* = 8.6 Hz, 0.33H), 8.70 (d, *J* = 1.7 Hz, 1H), 8.69 (d, *J* = 1.2 Hz, 0.33H), 8.63 (s, 0.33H), 8.55 (d, *J* = 5.5 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 0.33H), 8.01–7.96 (m, 1.33H), 7.92 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 0.33H), 7.88–7.76 (m, 2.33H), 7.72 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 3.43 (s, 1.98H), 3.35 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.88, 180.81, 151.94, 150.58, 147.81, 142.50, 140.45, 136.86, 136.82, 131.80, 130.77, 129.48, 129.16, 128.21, 128.17 (2C), 127.68, 126.83, 125.87, 124.60, 122.53, 121.93, 42.08 (4C). DART-MS: m/z calcd. for $C_{13}H_{15}N_4S$ $(M+H)^+$ 259.10119, found 259.10080.

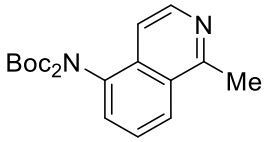


1-Methyl-5-nitroisoquinoline (S2). To a solution of 1-methylisoquinoline (28.80 g, 201.2 mmol) in sulfuric acid (92.4 mL) at 0℃ was added KNO_3 (20.4 g, 201.2 mmol) in sulfuric acid (78.0 mL). The mixture was heated at 60℃ for 2 h and then poured slowly over crushed ice. The solution was made alkaline with NH_4OH; the resulting tan precipitate was filtered, washed with water, and dried to afford **S2** as a tan solid (20.00 g, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 6.2 Hz, 1H), 8.47–8.50 (m, 2H), 8.28 (d, *J* = 6.3 Hz, 1H), 7.71 (t, *J* = 8.1 Hz, 1H), 3.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.53, 145.38, 132.53, 128.65, 128.23, 127.79, 125.58, 114.26 (2C), 23.38. DART-MS: *m/z* calcd. for $C_{10}H_9N_2O_2$ $(M+H)^+$ 189.06585, found 189.06544.

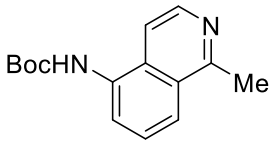


1-Methylisoquinolin-5-amine (S3). To a solution of **S2** (20.00 g, 106.28 mmol) in MeOH (530 mL) and iron powder (44.40 g, 795.05 mmol) was added concentrated HCl (1 mL, 12 M in H_2O). The mixture was refluxed for 2 h and then a solution of sodium hydroxide (6 mL, 2 M in H_2O) was added. The mixture was filtered, then concentrated *in vacuo*, and resuspended in EtOAc (200 mL) and water (200 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 200 mL). The organic

layers were combined and dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes). The isoquinoline **S3** was obtained as a brown solid (15.0 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 6.1 Hz, 1H), 7.55 (dt, J = 8.4, 1.0 Hz, 1H), 7.45 (d, J = 5.7 Hz, 1H), 7.39 (dd, J = 8.5, 7.4 Hz, 1H), 6.95 (dd, J = 7.5, 0.9 Hz, 1H), 4.18 (br s, 2H), 2.93 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.39, 159.15, 141.94, 128.35, 127.51, 126.16, 116.19, 113.09, 112.73, 23.06. DART-MS: *m/z* calcd. for $C_{10}H_{11}N_2$ $(M+H)^+$ 159.09167, found 159.09136.

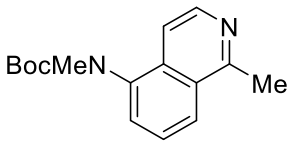


***tert*-Butyl (*tert*-butoxycarbonyl)(1-methylisoquinolin-5-yl)carbamate (S4).** To a solution of **S3** (360.0 mg, 2.28 mmol) in THF (10 mL) was added Boc_2O (1.68 g, 6.83 mmol), DMAP (28.0 mg, 0.23 mmol), and TEA (0.69 g, 3.65 mmol) and the mixture was stirred at 22 °C overnight. The reaction was quenched with water (10 mL) and the organic layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes). The isoquinoline **S4** was obtained as a brown solid (420.0 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 6.0 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.51 (dd, J = 7.3, 1.1 Hz, 1H), 7.46 (d, J = 5.9 Hz, 1H), 2.99 (s, 3H), 1.31 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.16, 151.59, 142.73, 135.74, 133.82, 129.64, 128.20, 126.55, 125.86, 113.74, 83.19 (2C), 27.90 (6C), 22.90. DART-MS: *m/z* calcd. for $C_{20}H_{27}N_2O_4$ $(M+H)^+$ 359.19653, found 359.19540.

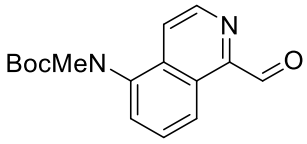


***tert*-Butyl (1-methylisoquinolin-5-yl)carbamate (S5).** To a solution of **S3** (10.00 g, 63.21 mmol) in THF (250 mL) was added Boc_2O (34.38 g, 158.0 mmol), DMAP (772.2 mg, 6.32 mmol), and TEA (15.96 g, 158.0 mmol) and the mixture was stirred at 22 °C overnight. After completion of the reaction as judged by TLC, $NaHCO_3$ (15.93 g, 189.6 mmol) and MeOH (100 mL) were added to the reaction mixture and it was refluxed overnight. After completion of the reaction (monitored by TLC), the mixture was concentrated *in vacuo* and then resuspended in EtOAc (200 mL) and water (200 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 200 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes). The isoquinoline **S5** was obtained as a brown oil (4.73 g, 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 6.1 Hz, 1H), 7.56 (dt, J = 8.3, 1.0 Hz, 1H), 7.46 (d, J = 6.7 Hz, 1H), 7.40 (dd, J = 8.5, 7.4 Hz, 1H), 6.95 (dd, J = 7.5, 0.9 Hz, 1H), 2.94 (s, 4H), 1.56 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.39, 159.15, 141.94, 128.35, 127.51, 126.16, 116.19, 113.09, 112.73, 76.91, 29.86 (3C), 23.06, one low-field carbon were either not observed or is overlapping

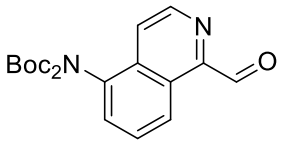
with another low- field carbon. DART-MS: *m/z* calcd. for $C_{15}H_{19}N_2O_2$ $(M+H)^+$ 259.14410, found 259.14349.



***tert*-Butyl methyl(1-methylisoquinolin-5-yl)carbamate (S6).** To a solution of **S5** (1.99 g, 7.68 mmol) in THF (50 mL) was added NaH 60% in mineral oil (399.6 mg, 9.99 mmol). After effervescence ceased, the resulting solution was refluxed for 30 min. To the reaction mixture was then added MeI (622 µL, 9.99 mmol) in THF (2 mL) and the solution was subsequently refluxed overnight. The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes). The isoquinoline **S6** was obtained as an amber oil (4.73 g, 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 6.0 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.46–7.61 (m, 3H), 3.31 (s, 3H), 3.01 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.01, 155.21, 140.21, 133.54, 128.35, 126.95, 124.96, 121.52, 114.65, 76.15, 29.71, 28.06 (3C), 22.51, one low-field carbon were either not observed or is overlapping with another low-field carbon. DART-MS: *m/z* calcd. for $C_{16}H_{21}N_2O_2$ $(M+H)^+$ 273.15975, found 273.15891.

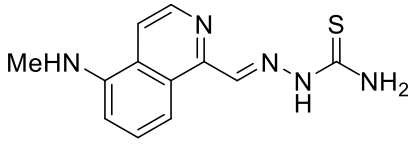


***tert*-Butyl (1-formylisoquinolin-5-yl)(methyl)carbamate (S7).** To a solution of **S6** (1.50 g, 5.51 mmol) in 1,4-dioxane (60 mL) was added SeO_2 (1.22 g, 11.0 mmol). The mixture was stirred at 60 °C overnight then cooled to 22 °C. The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 5–25% EtOAc:hexanes). The isoquinoline **S7** was obtained as a white solid (711.9 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39, 9.28 (d, J = 8.6 Hz, 1H), 8.80 (d, J = 5.7 Hz, 1H), 7.88 (d, J = 5.1 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.61 (m, 1H), 3.33 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.44, 155.05, 150.18, 142.85, 139.95, 134.55, 129.90, 128.96, 127.08, 124.99, 120.65, 80.72, 37.85, 28.08 (3C). DART-MS: *m/z* calcd. for $C_{16}H_{19}N_2O_3$ $(M+H)^+$ 287.13902, found 287.13812.

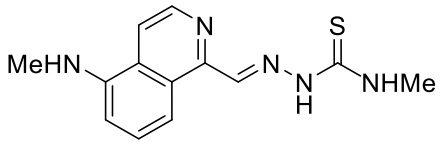


***tert*-Butyl (*tert*-butoxycarbonyl)(1-formylisoquinolin-5-yl)carbamate (S8).** To a solution of **S4** (200.0 mg, 0.558 mmol) in 1,4-dioxane (5.5 mL) was added SeO_2 (123.8 mg, 1.12 mmol). The mixture was

stirred at 60 °C overnight then cooled to 22 °C. The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 5–25% EtOAc:hexanes). The isoquinoline **S8** was obtained as a white solid (63.2 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.34 (dt, *J* = 8.7, 1.0 Hz, 1H), 8.81 (d, *J* = 5.7 Hz, 1H), 7.89 (dd, *J* = 5.7, 1.0 Hz, 1H), 7.76 (dd, *J* = 8.7, 7.4 Hz, 1H), 7.61 (dd, *J* = 7.3, 1.1 Hz, 1H), 1.32 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.59, 151.36, 150.23, 143.31, 134.94, 130.49, 129.74, 126.88, 126.00, 119.90, 83.60 (2C), 27.91 (6C), two low-field carbon were either not observed or is overlapping with another low-field carbon . DART-MS: *m/z* calcd. for $C_{20}H_{25}N_2O_5$ $(M+H)^+$ 373.17580, found 373.17496.



(*E*)-2-((5-(Methylamino)isoquinolin-1-yl)methylene)hydrazine-1-carbothioamide (HCT4). To a solution of **S7** (100.0 mg, 0.3492 mmol) in EtOH (1.75 mL) was added thiosemicarbazide (31.8 mg, 0.3492 mmol) and HCl (350 µL, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h and then cooled to 22 °C. The hydrochloride salt that formed was neutralized with 1.4 mL of a saturated aqueous $NaHCO_3$ solution. The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT4** as a black solid (622.4 mg, 97%). ^{1}H NMR (500 MHz, DMSO- d_6) δ 12.32 (s, 1H), 9.07 (br s, 1H), 8.92 (s, 1H), 8.90 (s, 1H), 8.57 (d, *J* = 6.6 Hz, 1H), 8.52 (d, *J* = 6.7 Hz, 1H), 7.85 (t, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.30 (br s, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 2.91 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.40, 146.25, 146.00, 133.09, 130.09, 128.72, 126.75 (2C), 119.38, 111.17, 110.66, 30.39. DART-MS: *m/z* calcd. for $C_{12}H_{14}N_5S$ $(M+H)^+$ 260.09644, found 260.09501.



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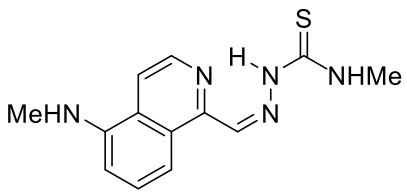
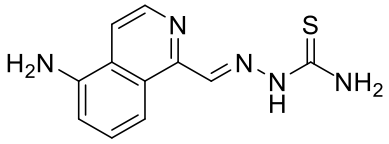
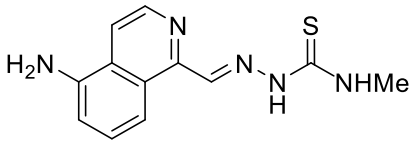


(*E*)-*N*-Methyl-2-((5-(methylamino)isoquinolin-1-yl)methylene)hydrazine-1-carbothioamide and (*Z*)-*N*-Methyl-2-((5-(methylamino)isoquinolin-1-yl)methylene)hydrazine-1-carbothioamide (HCT9). To a solution of **S7** (51.4 mg, 0.18 mmol) in EtOH (0.88 mL) was added 4-methyl-3-thiosemicarbazide (18.9 mg, 0.18 mmol) and HCl (0.18 mL, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was neutralized with saturated aqueous $NaHCO_3$ solution (0.88 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT9** as a black solid (49.0 mg, 94%) (mixture of *E* and *Z* isomers). ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.74 (s, 0.15H), 12.22 (s, 1H), 9.39 (br s, 1H), 8.93 (q, *J* = 4.7 Hz, 0.15H), 8.78 (s, 1H), 8.54 (d, *J* = 5.9 Hz, 0.15H), 8.50 (d, *J* = 6.5 Hz, 1H), 8.38 (s, 1H), 8.17 (s, 0.15H), 8.12 (d, *J* = 5.9 Hz, 0.15H), 7.82 (d, *J* = 8.6 Hz, 0.15H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.69 (s, 1H), 7.56 (t, *J* = 8.1 Hz, 0.15H), 7.08 (br s, 1H), 6.92 (d, *J* = 7.7 Hz, 1.15H), 6.72 (d, *J* = 7.8 Hz, 0.15H), 3.07 (d, *J* = 4.6 Hz, 3H), 3.02 (d, *J* = 4.6 Hz, 0.45 H), 2.88 (s, 3H), 2.86 (s, 0.45H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.84, 178.38, 150.11, 147.37, 145.83 (2C), 145.56, 138.94, 132.45, 130.58, 129.19,

128.23, 128.22, 126.87 (2C), 126.80, 118.47, 117.04, 111.57, 110.13, 109.63, 106.57, 31.59, 31.42, 30.42 (2C). DART- MS: *m/z* calcd. for $C_{13}H_{16}N_5S$ $(M+H)^+$ 274.11209, found 274.11104.



(*E*)-2-((5-Aminoisoquinolin-1-yl)methylene)hydrazine-1-carbothioamide (HCT5). To a solution of **S8** (30.0 mg, 0.081 mmol) in EtOH (0.39 mL) was added thiosemicarbazide (7.3 mg, 0.802 mmol) and HCl (80.6 μL, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was neutralized with saturated aqueous $NaHCO_3$ solution (0.39 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT5** as a green solid (19.6 mg, 99%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.66 (br s, 1H), 8.57 (s, 1H), 8.42 (d, J = 5.8 Hz, 1H), 8.31 (br s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 5.8 Hz, 1H), 7.60 (br s, 1H), 7.42 (t, J = 8.1 Hz, 1H), 6.89 (d, J = 7.1 Hz, 1H), 6.02 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.46, 150.36, 145.86, 144.62, 140.01, 129.74, 126.78. 125.83. 116.50, 113.12, 110.74. DART-MS: *m/z* calcd. for $C_{11}H_{11}N_5S$ $(M+H)^+$ 246.08079, found 246.08020.



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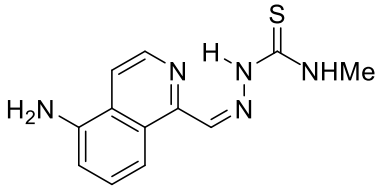
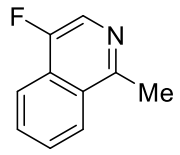
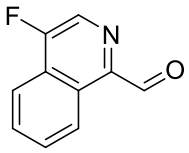


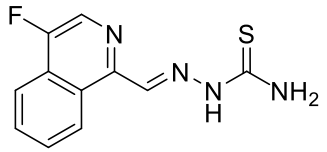
(*E*)-2-((5-Aminoisoquinolin-1-yl)methylene)-*N*-methylhydrazine-1-carbothioamide and (*Z*)- 2-((5-Aminoisoquinolin-1-yl)methylene)-*N*-methylhydrazine-1-carbothioamide (HCT10). To a solution of **S8** (27.1 mg, 0.0728 mmol) in EtOH (0.73 mL) was added 4-methyl-3-thiosemicarbazide (7.7 mg, 0.0732 mmol) and HCl (72.8 μL, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was neutralized with saturated aqueous $NaHCO_3$ solution (0.73 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT10** as a yellow solid (5.1 mg, 27%) (mixture of *E* and *Z* isomers). ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.80 (s, 0.08H), 11.66 (br s, 1H), 8.95 (d, J = 4.9 Hz, 0.08H), 8.62 (s, 1H), 8.52 (d, J = 5.9 Hz, 0.8H), 8.42 (d, J = 5.8 Hz, 1H), 8.25 (d, J = 3.3 Hz, 1H), 8.18 (s, 0.08H), 8.11–8.15 (m, 1.08H), 7.99 (d, J = 5.9 Hz, 1H), 7.83 (d, J = 8.4 Hz, 0.08H), 7.48 (t, J = 7.9 Hz, 0.08H), 7.43 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 7.6 Hz, 0.08H), 6.91 (dd, J = 7.6, 0.9 Hz, 1H), 6.21 (s, 0.16H), 6.04 (s, 2H), 3.05– 3.07 (m, 3.24H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.85, 178.52, 150.83, 150.19, 145.53, 145.20, 145.10, 140.49, 138.40, 130.28, 130.10, 129.16, 128.41, 127.36, 126.27, 126.16, 117.81, 116.96, 113.24, 111.66, 111.18, 110.61, 31.74, 31.59. DART-MS: *m/z* calcd. for $C_{12}H_{14}N_5S$ $(M+H)^+$ 260.09644, found 260.09563.



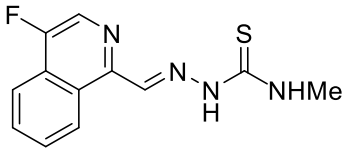
4-Fluoro-1-methylisoquinoline (S9). To a solution of 4-fluoroisoquinoline (1.50 g, 10.19 mmol) in THF (102 mL) was added allyl chloroformate (2.17 mL, 20.38 mmol). MeMgBr (10.19 mL, 2 M in diethyl ether) was then added dropwise to the reaction mixture at 0 °C with stirring. The reaction mixture was gradually warmed to 22 °C over a period of 2 h. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and water (100 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue in EtOAc was filtered through a silica plug, concentrated *in vacuo* and the residue was subjected to the next reaction without further purification. To a solution of the crude residue and $Pd(PPh_3)_4$ (70.1 mg, 0.061 mmol) in DCM (60 mL) at 0 °C was added morpholine (523.1 uL, 6.07 mmol). The reaction mixture was stirred and slowly warmed to 22 °C over a period of 3 h. The mixture was cooled to 0 °C and DDQ (1.38 g, 6.07 mmol) was added in portions. After the reaction mixture stirred at 0 °C for 30 min, the reaction was slowly poured into a solution of saturated $NaHCO_3$ solution (60 mL) and extracted with DCM (3 × 60). The combined extracts are washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 5–25% EtOAc:hexanes). The isoquinoline **S9** was obtained as a brown oil (241.9 mg, 15% over three steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 1.7 Hz, 1H), 8.06–8.09 (m, 2H), 7.73-7.76 (m, 1H), 7.64-7.67 (m, 1H), 2.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.48 (d, $^1J_{C\text{-}F}$ = 257.5 Hz), 154.24 (d, $^3J_{C\text{-}F}$ = 4.9 Hz), 130.14 (d, $^4J_{C\text{-}F}$ = 1.6 Hz), 128.35 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 127.83, 126.64 (d, $^2J_{C\text{-}F}$ = 15.3 Hz), 126.57 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 125.60 (d, $^4J_{C\text{-}F}$ = 2.1 Hz), 120.09 (d, $^3J_{C\text{-}F}$ = 4.5 Hz), 22.10. ^{19}F NMR (376 MHz, $CDCl_3$) δ –143.11, extraneous peak found at –139.82. DART-MS: *m/z* calcd. for $C_{10}H_9FN$ $(M+H)^+$ 162.07135, found 162.07092.



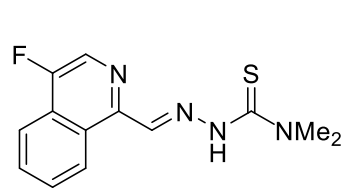
4-Fluoroisoquinoline-1-carboxaldehyde (S10). To a solution of **S9** (40.0 mg, 0.248 mmol) in 1,4-dioxane (2.5 mL) was added SeO_2 (55.1 mg, 0.496 mmol). The mixture was stirred at 60 °C overnight then cooled to 22 °C. The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 5–25% EtOAc:hexanes). The isoquinoline **S10** was obtained as a white solid (27.3 mg, 63%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.37–9.41 (m, 1H), 8.59 (d, J = 1.5 Hz, 1H), 8.16–8.20 (m, 1H), 7.82-7.87 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 194.23, 157.16 (d, $^1J_{C\text{-}F}$ = 270.3 Hz), 146.44 (d, $^3J_{C\text{-}F}$ = 5.6 Hz), 131.07 (d, $^4J_{C\text{-}F}$ = 2.2 Hz), 130.95 128.48 (d, $^2J_{C\text{-}F}$ = 24.6 Hz), 128.14 (d, $^4J_{C\text{-}F}$ = 4.1 Hz), 126.85 (d, $^2J_{C\text{-}F}$ = 14.4 Hz), 125.64 (d, $^4J_{C\text{-}F}$ = 1.8 Hz), 119.85 (d, $^3J_{C\text{-}F}$ = 4.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –129.02. DART-MS: *m/z* calcd. for $C_{10}H_6FNO$ $(M+H)^+$ 176.05062, found 176.05012.



(*E*)-2-((4-Fluoroisoquinolin-1-yl)methylene)hydrazine-1-carbothioamide (HCT2). To a solution of **S10** (6.0 mg, 0.0343 mmol) in EtOH (0.5 mL) was added thiosemicarbazide (3.3 mg, 0.0343 mmol) and HCl (34 μL, 0.206 mmol, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was then neutralized with saturated aqueous $NaHCO_3$ solution (0.5 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT2** as a pale-yellow solid (3.0 mg, 35%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.70 (s, 1H), 9.28 (d, J = 8.5 Hz, 1H), 8.56 (d, J = 1.5 Hz, 1H), 8.53 (s, 1H), 8.48 (s, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.94 (ddd, J = 8.2, 7.0, 0.9 Hz, 1H), 7.85 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.84, 154.73 (d, $^1J_{C\text{-}F}$ = 262.2 Hz), 148.03 (d, $^3J_{C\text{-}F}$ = 5.2 Hz), 145.84, 131.75, 130.69, 128.10 (d, $^2J_{C\text{-}F}$ = 23.3 Hz), 127.75, 127.35 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 126.51 (d, $^2J_{C\text{-}F}$ = 14.9 Hz), 119.79 (d, $^3J_{C\text{-}F}$ = 4.6 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ –137.31. DART-MS: *m/z* calcd. for $C_{11}H_9FN_4S$ $(M+H)^+$ 249.06047, found 249.05042.



(*E*)-2-((4-Fluoroisoquinolin-1-yl)methylene)-*N*-methylhydrazine-1-carbothioamide (HCT7). To a solution of **S10** (6.0 mg, 0.0343 mmol) in EtOH (0.5 mL) was added 4-methyl-3-thiosemicarbazide (3.6 mg, 0.0343 mmol) and HCl (34 μL, 0.206 mmol, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was then neutralized with saturated aqueous $NaHCO_3$ solution (0.5 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT7** as a pale-yellow solid (2.6 mg, 29%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.76 (s, 1H), 9.19 (d, J = 8.6 Hz, 1H), 8.56 (d, J = 1.4 Hz, 1H), 8.56 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.94–7.97 (m, 1H), 7.85–7.89 (m, 1H), 3.06 (d, J = 4.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.84, 154.73 (d, $^1J_{C\text{-}F}$ = 262.2 Hz), 148.03 (d, $^3J_{C\text{-}F}$ = 5.2 Hz), 145.84, 131.75, 130.69, 128.10 (d, $^2J_{C\text{-}F}$ = 23.3 Hz), 127.75, 127.35 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 126.51 (d, $^2J_{C\text{-}F}$ = 14.9 Hz), 119.79 (d, $^3J_{C\text{-}F}$ = 4.6 Hz), 31.86. ^{19}F NMR (376 MHz, DMSO-d_6) δ –137.53, extraneous peak found at –134.32. DART-MS: *m/z* calcd. for $C_{12}H_{12}FN_4S$ $(M+H)^+$ 263.07612, found 263.07520.



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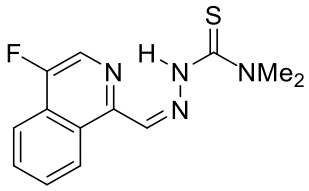
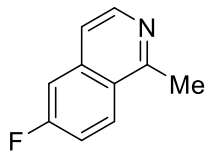
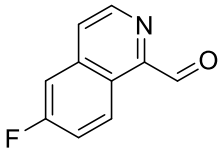


(*E*)-2-((4-Fluoroisoquinolin-1-yl)methylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide and (*Z*)-2-((4-Fluoroisoquinolin-1-yl)methylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide (HCT12). To a solution of **S10** (17.8 mg, 0.102 mmol) in MeOH (1.0 mL) was added 4,4-dimethyl-3-thiosemicarbazide (12.0 mg, 0.102 mmol) and HCl (101 μL, 0.610 mmol, 6 M in H_2O). The mixture was microwaved at 300 W and 50 °C for 1.0 h. The hydrochloride salt that formed was then neutralized with saturated aqueous $NaHCO_3$ solution (1.0 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT12** as a pale-yellow solid (16.0 mg, 57%) (mixture of *E* and *Z* isomers). ^{1}H NMR (500 MHz, DMSO-d_6) δ 15.52 (s, 0.15H), 11.28 (s, 1H), 9.87 (d, J = 8.7 Hz, 1H), 8.87 (d, J = 9.0 Hz, 0.15H), 8.77 (d, J = 1.9 Hz, 0.15H), 8.69 (s, 1H), 8.57 (d, J = 1.6 Hz, 1.15H), 8.23 (d, J = 8.2 Hz, 0.15H), 8.15 (d, J = 8.2 Hz, 1H), 8.02–8.05 (m, 0.15H), 7.92–7.97 (m, 1.15H), 7.86 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 3.42 (s, 0.90H), 3.36 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.79, 180.73, 154.60 (d, $^1J_{C\text{-}F}$ = 261.7 Hz), 154.13 (d, $^1J_{C\text{-}F}$ = 261.8 Hz), 148.75 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 147.76 (d, $^3J_{C\text{-}F}$ = 5.7 Hz), 147.05, 132.52, 131.59 (d, $^4J_{C\text{-}F}$ = 5.1 Hz), 131.10, 130.49, 130.30, 128.60 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 128.41 (d, $^4J_{C\text{-}F}$ = 1.0 Hz), 127.90 (d, $^2J_{C\text{-}F}$ = 23.3 Hz), 127.19 (d, $^4J_{C\text{-}F}$ = 2.6 Hz), 126.88 (d, $^2J_{C\text{-}F}$ = 14.8 Hz), 126.71 (d, $^2J_{C\text{-}F}$ = 14.7 Hz), 126.35 (d, $^2J_{C\text{-}F}$ = 25.2 Hz),124.98, 120.23 (d, $^3J_{C\text{-}F}$ = 4.3 Hz), 119.79 (d, $^3J_{C\text{-}F}$ = 4.7 Hz), 42.04 (4C). ^{19}F NMR (376 MHz, DMSO-d_6) δ –134.93, –138.02. DART-MS: *m/z* calcd. for $C_{13}H_{14}FN_4S$ $(M+H)^+$ 277.09177, found 277.09096.

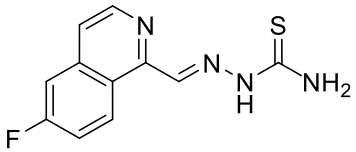


6-Fluoro-1-methylisoquinoline (S11). To a solution of 6-fluoroisoquinoline (1.00 g, 6.80 mmol) in THF (120 mL) was added allyl chloroformate (1.64 mL, 13.59 mmol). MeMgBr (6.98 mL, 13.59 mmol, 2 M in diethyl ether) was then added dropwise to the reaction mixture at 0 °C while stirring and the mixture was gradually warmed to 22 °C over a period of 2 h. The reaction was quenched with saturated aqueous NH_4Cl (12 mL) and water (120 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 120 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue in EtOAc was filtered through a silica plug, concentrated *in vacuo* and the crude residue was subjected to the next reaction without further purification. To a solution of the crude residue and $Pd(PPh_3)_4$ (293.4 mg, 0.254 mmol) in DCM (50 mL) at 0 °C was added morpholine (437.9 uL, 5.08 mmol). The reaction was stirred and slowly warmed to 22 °C over a period of 3 h. The mixture was cooled to 0 °C and DDQ (1.15 g, 5.08 mmol) was added portionwise. After the reaction mixture stirred at 0 °C for 30 min, the reaction was slowly poured into a solution of saturated $NaHCO_3$ solution (50 mL) and extracted with DCM (3 × 50). The combined extracts are washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 5–25% EtOAc:hexanes). The isoquinoline **S11** was obtained as a brown oil (583.9 mg, 53% over three steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (d, J = 5.8 Hz,

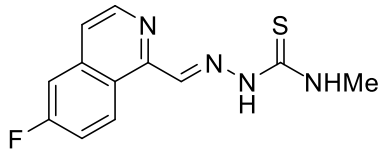
1H), 8.13 (dd, J = 9.2, 5.5 Hz, 1H), 7.46 (d, J = 5.8 Hz, 1H), 7.40 (dd, J = 9.3, 2.6 Hz, 1H), 7.34 (td, J = 8.8, 2.6 Hz, 1H), 2.95 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.94 (d, $^{1}J_{C\text{-}F}$ = 252.2 Hz), 158.53 (d, $^{5}J_{C\text{-}F}$ = 1.0 Hz), 142.77, 137.58 (d, $^{3}J_{C\text{-}F}$ = 10.4 Hz), 128.79 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz), 124.72 (d, $^{4}J_{C\text{-}F}$ = 1.0 Hz), 119.01 (d, $^{4}J_{C\text{-}F}$ = 5.0 Hz), 117.31 (d, $^{2}J_{C\text{-}F}$ = 25.0 Hz), 110.44 (d, $^{2}J_{C\text{-}F}$ = 20.6 Hz), 22.53. ^{19}F NMR (376 MHz, $CDCl_3$) δ –108.23. DART-MS: *m/z* calcd. for $C_{10}H_9FN$ $(M+H)^+$ 162.07135, found 162.07096.



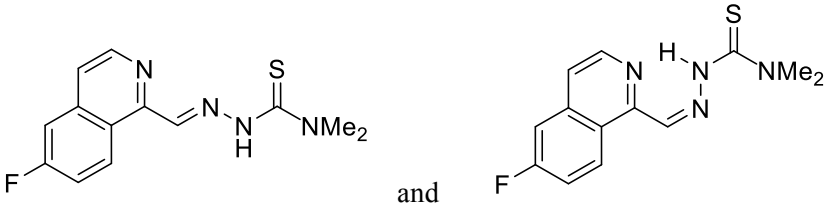
6-Fluoroisoquinoline-1-carboxaldehyde (S12). To a solution of **S11** (500.0 mg, 3.10 mmol) in 1,4-dioxane (19.0 mL) was added SeO_2 (688.4 mg, 6.20 mmol). The mixture was stirred at 60 °C overnight then cooled to 22 °C. The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 5–25% EtOAc:hexanes). The isoquinoline **S12** was obtained as a white solid (200.9 mg, 37%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.39 (ddd, J = 10.1, 5.6, 0.9 Hz, 1H), 8.75 (dd, J = 5.6, 0.4 Hz, 1H), 7.85 (d, J = 5.5 Hz, 1H), 7.50–7.54 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 195.51, 163.18 (d, $^{1}J_{C\text{-}F}$ = 255.1 Hz), 149.71 (d, $^{4}J_{C\text{-}F}$ = 1.8 Hz), 143.34 (d, $^{5}J_{C\text{-}F}$ = 1.0 Hz), 138.70 (d, $^{3}J_{C\text{-}F}$ = 10.4 Hz), 129.24 (d, $^{3}J_{C\text{-}F}$ = 9.2 Hz), 124.90 (d, $^{4}J_{C\text{-}F}$ = 5.4 Hz), 123.49 (d, $^{5}J_{C\text{-}F}$ = 1.0 Hz), 120.53 (d, $^{2}J_{C\text{-}F}$ = 24.8 Hz), 110.23 (d, $^{2}J_{C\text{-}F}$ = 20.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.46. DART- MS: *m/z* calcd. for $C_{10}H_7FNO$ $(M+H)^+$ 176.05062, found 176.05015.



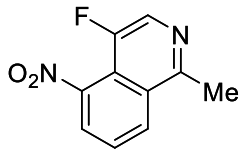
(*E*)-2-((6-Fluoroisoquinolin-1-yl)methylene)hydrazine-1-carbothioamide (HCT3). To a solution of **S12** (10.2 mg, 0.0582 mmol) in EtOH (0.5 mL) was added thiosemicarbazide (5.3 mg, 0.0582 mmol) and HCl (58 µL, 0.349 mmol, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was then neutralized with saturated aqueous $NaHCO_3$ solution (0.5 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT3** as a pale-yellow solid (13.4 mg, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.74 (s, 1H), 9.30 (dd, J = 9.4, 5.8 Hz, 1H), 8.55 (d, J = 5.6 Hz, 1H), 8.51 (s, 2H), 7.80–7.85 (m, 3H), 7.57 (td, J = 9.0, 2.8 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.88, 162.70 (d, $^{1}J_{C\text{-}F}$ = 250.4 Hz), 151.35, 146.33, 143.50, 138.62 (d, $^{3}J_{C\text{-}F}$ = 10.7 Hz), 131.52 (d, $^{3}J_{C\text{-}F}$ = 9.5 Hz), 123.24, 121.79 (d, $^{4}J_{C\text{-}F}$ = 5.0 Hz), 119.36 (d, $^{2}J_{C\text{-}F}$ = 24.5 Hz), 110.86 (d, $^{2}J_{C\text{-}F}$ = 20.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ – 107.79, extraneous peak found at –106.49. DART-MS: *m/z* calcd. for $C_{11}H_{10}FN_4S$ $(M+H)^+$ 249.06047, found 249.05984.



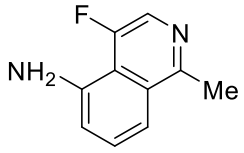
(*E*)-2-((6-Fluoroisoquinolin-1-yl)methylene)-*N*-methylhydrazine-1-carbothioamide (HCT8). To a solution of **S12** (8.8 mg, 0.0502 mmol) in EtOH (0.5 mL) was added 4-methyl-3-thiosemicarbazide (5.3 mg, 0.0502 mmol) and HCl (50 µL, 0.300 mmol, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was then neutralized with saturated aqueous $NaHCO_3$ solution (0.5 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT8** as a pale-yellow solid (10.8 mg, 82%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.80 (s, 1H), 9.20 (dd, J = 9.4, 5.7 Hz, 1H), 8.55 (d, J = 5.6 Hz, 1H), 8.54 (s, 1H), 8.35 (d, J = 4.7 Hz, 1H), 7.83 (dd, J = 9.2, 3.9 Hz, 2H) 7.60 (td, J = 9.0, 2.7 Hz, 1H), 3.06 (d, J = 4.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.56, 162.71 (d, $^1J_{C\text{-}F}$ = 250.4 Hz), 151.55, 145.22, 143.53, 138.62 (d, $^3J_{C\text{-}F}$ = 10.6 Hz), 131.28 (d, $^3J_{C\text{-}F}$ = 9.5 Hz), 123.29, 121.67 (d, $^4J_{C\text{-}F}$ = 5.1 Hz), 119.23 (d, $^2J_{C\text{-}F}$ = 24.8 Hz), 110.89 (d, $^2J_{C\text{-}F}$ = 20.8 Hz), 31.85. ^{19}F NMR (376 MHz, DMSO-d_6) δ –106.55, extraneous peak found at –107.74. DART-MS: *m/z* calcd. for $C_{12}H_{12}FN_4S$ $(M+H)^+$ 263.07612, found 263.07538.



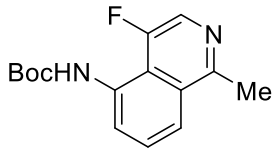
(*E*)-2-((6-Fluoroisoquinolin-1-yl)methylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide and (*Z*)-2-((6-Fluoroisoquinolin-1-yl)methylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide (HCT13). To a solution of **S12** (8.6 mg, 0.0491 mmol) in EtOH (0.5 mL) was added 4,4-dimethyl-3-thiosemicarbazide (5.9 mg, 0.0491 mmol) and HCl (49 µL, 0.294 mmol, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was then neutralized with saturated aqueous $NaHCO_3$ solution (0.5 mL). the precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT13** as a pale-yellow solid containing a mixture of E and Z isomers (7.4 mg, 55%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 15.90 (s, 0.21H), 11.30 (s, 1H), 9.87 (dd, J = 9.5, 5.9 Hz, 1H), 8.91 (dd, J = 9.4, 5.4 Hz, 0.21H), 8.66 (m, 1.21H), 8.59 (s, 0.21H), 8.55 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 5.6 Hz, 0.21H), 7.91 (dd, J = 9.6, 2.7 Hz, 0.21H), 7.79–7.82 (m, 2H), 7.73 (td, J = 9.1, 2.7 Hz, 0.21H), 7.62 (ddd, J = 9.6, 8.6, 2.8 Hz, 1H), 3.40 (s, 1.26H), 3.33 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.78 (2C), 163.19 (d, $^1J_{C\text{-}F}$ = 251.7 Hz), 162.66 (d, $^1J_{C\text{-}F}$ = 250.6 Hz), 151.99 (d, $^5J_{C\text{-}F}$ = 1.2 Hz), 150.63 (d, $^5J_{C\text{-}F}$ = 0.9 Hz), 147.57, 143.42, 141.42, 138.83 (d, $^3J_{C\text{-}F}$ = 15.5 Hz), 138.76 (d, $^4J_{C\text{-}F}$ = 10.7 Hz), 132.08 (d, $^3J_{C\text{-}F}$ = 9.3 Hz), 131.62, 128.64 (d, $^3J_{C\text{-}F}$ = 9.9 Hz), 124.14, 123.10, 122.12 (d, $^4J_{C\text{-}F}$ = 5.2 Hz), 121.56 (d, $^4J_{C\text{-}F}$ = 5.1 Hz), 119.54 (d, $^2J_{C\text{-}F}$ = 25.6 Hz), 119.14 (d, $^2J_{C\text{-}F}$ = 24.4 Hz), 111.48 (d, $^2J_{C\text{-}F}$ = 20.8 Hz), 110.90 (d, $^2J_{C\text{-}F}$ = 20.7 Hz), 42.04 (4C). ^{19}F NMR (376 MHz, DMSO-d_6) δ –106.34, –107.95. DART-MS: *m/z* calcd. for $C_{13}H_{14}FN_4S$ $(M+H)^+$ 277.09232, found 277.0905



4-Fluoro-1-methyl-5-nitroisoquinoline (S13). To a solution of **S11** (0.376 g, 2.333 mmol) in sulfuric acid (0.4 mL) at 0 ℃ was added KNO_3 (0.234 g, 2.333 mmol) in sulfuric acid (0.6 mL). The mixture was heated at 60 ℃ for 2 h and then poured slowly over crushed ice. The solution was made alkaline with NH_4OH; the resulting tan precipitate was filtered, washed with water, and dried to afford **S13** as a tan solid (0.210 g, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 2.9 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 7.4 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 3.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.10 (d, $^4J_{C\text{-}F}$ = 5.2 Hz), 151.08 (d, $^1J_{C\text{-}F}$ = 262.1 Hz), 144.92, 130.04 (d, $^2J_{C\text{-}F}$ = 25.2 Hz), 129.62, 128.88, 127.24, 125.53, 118.43 (d, $^3J_{C\text{-}F}$ = 12.1 Hz), 22.66. ^{19}F NMR (376 MHz, $CDCl_3$) δ -133.19. DART-MS: *m/z* calcd. for $C_{10}H_8FN_2O_2$ $(M+H)^+$ 207.05643, found 207.05705.

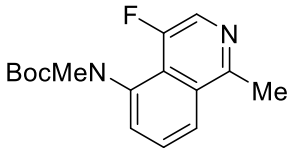


4-Fluoro-1-methylisoquinolin-5-amine (S14). To a solution of **S13** (0.210 g, 1.02 mmol) in MeOH (50 mL) iron powder (0.171 g, 3.06 mmol and HCl (1 mL, 12 M in H_2O). The mixture was refluxed for 2 h and then a solution of sodium hydroxide (2 mL, 6 M in H_2O) was added. The mixture was filtered and extracted with diethyl ether (200 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes). The isoquinoline **S14** was obtained as a brown solid (0.173 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 5.1 Hz, 1H), 7.46–7.39 (m, 2H), 6.88 (dd, J = 6.9, 1.8 Hz, 1H), 4.83 (br s, 2H), 2.87 (d, J = 1.3, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.92 (d, $^1J_{C\text{-}F}$ = 253.3 Hz), 154.74 (d, $^4J_{C\text{-}F}$ = 4.9 Hz), 142.23 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 129.19, 115.79 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 114.77, 114.76, 113.81 (2C), 22.61. ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.45. DART-MS: *m/z* calcd. for $C_{10}H_{10}FN_2$ $(M+H)^+$ 177.08225, found 177.08220.

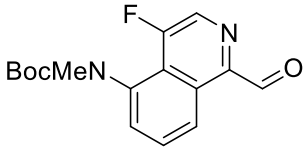


***tert*-butyl (4-fluoro-1-methylisoquinolin-5-yl)carbamate (S15).** To a solution of **S14** (1.14 g, 6.49 mmol) in THF (15 mL) was added DMAP (79.3 mg, 0.65 mmol) then Boc_2O (3.54 g, 16.23 mmol) and the mixture was stirred at 22 °C overnight. After completion of the reaction as judged by TLC, K_2CO_3 (2.69 g, 19.47 mmol) and MeOH (10 mL) were added to the reaction mixture and then refluxed overnight.

The mixture was then concentrated *in vacuo* and resuspended in EtOAc (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 5–20% EtOAc:hexanes). The isoquinoline **S15** was obtained as a brown oil (0.572 g, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (dd, J = 7.9, 1.0 Hz, 1H), 8.17 (d, J = 5.7 Hz, 1H), 8.05 (d, J = 17.8 Hz, 1H), 7.73 (ddd, J = 8.4, 3.0, 1.0 Hz, 1H), 7.60 (t, J = 8.2 Hz, 1H), 2.88 (d, J = 1.3 Hz, 3H), 1.55 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.37 (d, $^1J_{C\text{-}F}$ = 296.5 Hz), 153.19, 137.68, 131.10, 128.23 (d, $^3J_{C\text{-}F}$ = 10.7 Hz), 124.83, 124.45, 121.14 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 119.58, 82.72, 28.15 (3C), 17.84, one low-field carbon were either not observed or is overlapping with another low-field carbon. ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.85. DART-MS: *m/z* calcd. for $C_{15}H_{18}FN_2O_2$ $(M+H)^+$ 277.13468, found 277.13425.

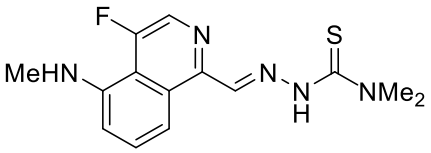


***tert*-Butyl methyl(4-fluoro-1-methylisoquinolin-5-yl)carbamate (S16).** To a solution of **S15** (0.524 g, 1.90 mmol) in THF (10 mL) was added NaH 60% in mineral oil (59.2 mg, 2.49 mmol). After effervescence ceased, the resulting solution was refluxed for 30 min. To the reaction mixture was then added MeI (0.350 g, 4.49 mmol) in THF (2 mL) and the solution refluxed overnight. The mixture was concentrated and passed through a silica plug (1:10-2:1 EtOAc:hexanes). The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes). The isoquinoline **S16** was obtained as an amber oil containing a mixture of rotamers (0.456 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25–8.22 (m, 1.5H), 8.11–8.02 (m, 1.5H), 7.71–7.61 (m, 2H), 7.55 (dd, J = 7.3, 1.3 Hz, 1H), 3.28 (s, 3H), 3.27 (s, 1.5H), 2.96 (s, 3H), 2.95 (s, 1.5H), 1.53 (s, 4.5H), 1.21 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.41, 154.92 (d, $^4J_{C\text{-}F}$ = 5.7 Hz), 154.90 (d, $^4J_{C\text{-}F}$ = 5.4 Hz), 154.63, 154.51, 153.54 (d, $^1J_{C\text{-}F}$ = 259.3 Hz), 137.94, 131.60, 130.52, 130.05, 129.74, 128.44, 128.19, 127.82 (d, $^2J_{C\text{-}F}$ = 27.6 Hz), 125.49, 125.08, 124.53, 124.34 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 80.79, 80.23, 38.52 (d, $^5J_{C\text{-}F}$ = 3.82 Hz), 37.81 (d, $^5J_{C\text{-}F}$ = 3.07 Hz), 28.38 (3C), 28.05 (3C), 22.46, 22.26, two low-field carbons were either not observed or is overlapping with another low-field carbon. ^{19}F NMR (376 MHz, $CDCl_3$) δ -140.37, -141.22. DART-MS: *m/z* calcd. for $C_{16}H_{20}FN_2O_2$ $(M+H)^+$ 291.15033, found 291.14981.



***tert*-Butyl methyl(4-fluoro-1-formylisoquinolin-5-yl)carbamate (S17).** To a solution of **S16** (0.40 g, 1.38 mmol) in 1,4-dioxane (10 mL) was added SeO_2 (0.183 g, 1.65 mmol). The mixture was stirred at 60 °C overnight then cooled to 22 °C. The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 5–25% EtOAc:hexanes). The isoquinoline **S17** was obtained as an off-white solid containing a mixture of rotamers (0.152 g, 36%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (d, J = 1.5 Hz, 1H), 10.29 (d, J = 1.6 Hz, 0.5H), 9.38 (tdd, J = 7.5, 2.7, 1.4 Hz, 1.5H),

8.58 (dd, J = 3.9, 1.1 Hz, 1H), 8.56 (dd, J = 4.0, 1.3 Hz, 0.5H), 7.80 (tt, J = 7.3, 1.4 Hz, 1.5H), 7.68 (dt, J = 7.5, 0.5Hz, 0.5H), 7.62 (dt, J = 7.4, 1.0 Hz, 1H), 3.31 (d, J = 1.1 Hz, 3H), 3.30 (d, J = 0.9 Hz, 1.5H), 1.54 (s, 4.5H), 1.21 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) 194.12, 194.09, 156.39 (d, $^1J_{C\text{-}F}$ = 272.5 Hz), 156.35 (d, $^1J_{C\text{-}F}$ = 255.9 Hz), 155.21, 154.41, 146.67 (d, $^3J_{C\text{-}F}$ = 6.1 Hz), 137.64 (d, $^4J_{C\text{-}F}$ = 1.7 Hz), 131.73 (d, $^4J_{C\text{-}F}$ = 1.9 Hz), 131.12 (d, $^4J_{C\text{-}F}$ = 1.9 Hz), 131.05, 130.95 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 130.85, 130.57 (d, $^2J_{C\text{-}F}$ = 28.5 Hz), 130.25 (d, $^2J_{C\text{-}F}$ = 28.2 Hz), 129.83 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 129.49 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 125.05, 124.68 (d, $^4J_{C\text{-}F}$ = 1.7 Hz), 124.56 ($^3J_{C\text{-}F}$, J = 7.4 Hz), 124.44 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 81.01, 80.49, 38.56 (d, $^5J_{C\text{-}F}$ = 3.3 Hz), 37.83 (d, $^5J_{C\text{-}F}$ = 2.6 Hz), 28.36 (3C), 28.03 (3C), one low-field carbon were either not observed or is overlapping with another low-field carbon. ^{19}F NMR (376 MHz, $CDCl_3$) δ -133.9. DART-MS: *m/z* calcd. for $C_{16}H_{18}FN_2O_3$ $(M+H)^+$ 305.12960, found 305.12824.



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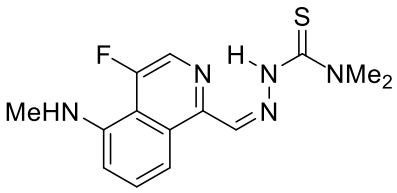
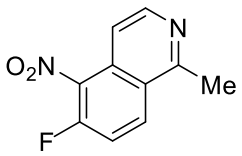
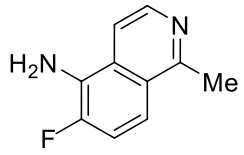


(*E*)-2-((4-Fluoro-5-(methylamino)isoquinolin-1-yl)methylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide and (*Z*)-2-((4-Fluoro-5-(methylamino)isoquinolin-1-yl)methylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide (HCT15). To a solution of **S17** (30.0 mg, 0.099 mmol) in MeOH (3.0 mL) was added 4,4-dimethyl-3-thiosemicarbazide (11.7 mg, 0.985 mmol) and HCl (98 µL, 0.59 mmol, 6 M in H_2O). The mixture was microwaved at 300 W and 50 °C for 1.0 h. The hydrochloride salt that formed was then neutralized with saturated aqueous $NaHCO_3$ solution (1.5 mL). The precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT15** as a pale-yellow solid containing a mixture of *E*- and *Z*-isomers (12.2 mg, 41%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 15.46 (s, 0.33H), 11.13 (br s, 1H), 8.91 (dd, J = 8.4, 2.9 Hz, 1H), 8.62 (s, 1H), 8.50 (d, J = 5.1 Hz, 0.33H), 8.39 (s, 0.33H), 8.32 (d, J = 4.8 Hz, 1H), 7.89 (dd, J = 8.5, 2.9 Hz, 0.33H), 7.65 (t, J = 8.2 Hz, 0.33H), 7.57 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 8.0 Hz, 0.33H), 6.73 (d, J = 7.9 Hz, 1H), 6.55 (dd, J = 11.9, 5.2 Hz, 0.33H), 6.39 (dd, J = 12.4, 5.0 Hz, 1H), 3.37 (s, 1.98H), 3.31 (s, 6H), 2.86–2.84 (m, 3.99H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.95, 180.72, 156.41 (d, J = 260.4 Hz), 147.99 (d, $^4J_{C\text{-}F}$ = 4.3 Hz), 147.41, 147.16, 144.92, 144.61 (d, $^4J_{C\text{-}F}$ = 3.7 Hz), 131.90, 131.69, 130.83, 130.78, 129.29 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 127.41 (d, $^2J_{C\text{-}F}$ = 28.8 Hz), 125.43 (d, $^2J_{C\text{-}F}$ = 30.5 Hz), 115.98 (d, $^2J_{C\text{-}F}$ = 7.6 Hz), 113.89, 113.84, 110.26, 108.50, 107.78, 42.15 (4C), 30.95 (2C), one low-field carbon were either not observed or is overlapping with another low-field carbon. ^{19}F NMR (376 MHz, DMSO-d_6) δ -125.86, -129.02. DART- MS: *m/z* calcd. for $C_{14}H_{17}FN_5S$ $(M+H)^+$ 306.11832, found 306.11716.

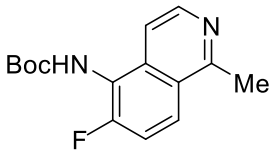


6-Fluoro-1-methyl-5-nitroisoquinoline (S18). To a solution of **S11** (0.584 g, 3.623 mmol) in sulfuric acid (0.8 mL) at 0℃ was added KNO_3 (0.366 g, 3.623 mmol) in sulfuric acid (1.2 mL). The mixture was heated at 60℃ for 2 h and then poured slowly over crushed ice. The solution was made alkaline with

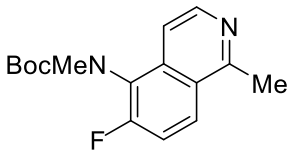
NH_4OH; the resulting tan precipitate was filtered, washed with water, and dried to afford **S18** as a tan solid (0.264 g, 35%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 6.1 Hz, 1H), 8.41 (dd, J = 9.4, 4.9 Hz, 1H), 7.70 (d, J = 6.0 Hz, 1H), 7.55 (t, J = 9.2 Hz, 1H), 3.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.08, 155.06 (d, $^1J_{C\text{-}F}$ = 266.6 Hz), 144.50, 132.29 (d, $^3J_{C\text{-}F}$ = 10.0 Hz), 129.83 (2C), 124.19, 117.40 (d, $^2J_{C\text{-}F}$ = 23.5 Hz), 113.60, 22.41. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.01. DART-MS: *m/z* calcd. for $C_{10}H_8FN_2O_2$ $(M+H)^+$ 207.05643, found 207.05690.



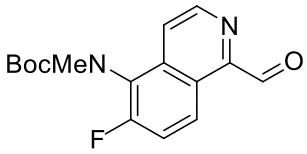
6-Fluoro-1-methylisoquinolin-5-amine (S19). To a solution of **S18** (0.264 g, 1.28 mmol) in MeOH (60 mL) iron powder (0.214 g, 3.83 mmol) and HCl (1 mL, 12 M in H_2O). The mixture was refluxed for 2 h and then a solution of sodium hydroxide (2 mL, 6 M in H_2O) was added. The mixture was filtered and extracted with diethyl ether (200 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes). The isoquinoline **S19** was obtained as a brown solid (145.8 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 6.2 Hz, 1H), 7.62 (dd, J = 9.1, 4.8 Hz, 2H), 7.44 (d, J = 9.9 Hz, 1H), 4.27 (br s, 2H), 3.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.80, 159.77 (d, $^1J_{C\text{-}F}$ = 263.7 Hz), 150.34, 139.41 (d, $^3J_{C\text{-}F}$ = 10.8 Hz), 137.94, 133.78, 128.91, 122.74 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 118.04 (d, $^4J_{C\text{-}F}$ = 5.2 Hz), 27.69. ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.82. DART-MS: *m/z* calcd. for $C_{10}H_{10}FN_2$ $(M+H)^+$ 177.08225, found 177.08291.



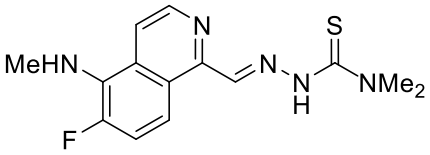
***tert*-Butyl (6-fluoro-1-methylisoquinolin-5-yl)carbamate (S20).** To a solution of **S19** (0.715 g, 4.06 mmol) in THF (15 mL) was added DMAP (49.5 mg, 0.41 mmol) then Boc_2O (2.21 g, 10.14 mmol) and the mixture was stirred at 22 °C overnight. After completion of the reaction as attested by TLC, K_2CO_3 (1.68 g, 12.17 mmol) and MeOH (10 mL) were added to the reaction mixture and was refluxed overnight. The mixture was then concentrated *in vacuo* and resuspended in EtOAc (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 5–20% EtOAc:hexanes). The isoquinoline **S20** was obtained as a brown oil (0.303 g, 27%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 6.0 Hz, 1H), 8.06 (dd, J = 9.3, 5.0 Hz, 1H), 7.65 (d, J = 6.0 Hz, 1H), 7.39 (t, J = 9.3 Hz, 1H), 6.59 (br s, 1H), 2.95 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.58 (d, $^1J_{C\text{-}F}$ = 260.2 Hz), 157.19, 153.19, 137.68, 131.09 (d, $^4J_{C\text{-}F}$ = 4.9 Hz), 128.23 (d, $^3J_{C\text{-}F}$ = 10.7 Hz), 124.83, 124.45, 121.14 (d, $^2J_{C\text{-}F}$ = 22.1 Hz), 119.60, 82.72, 28.15 (3C), 17.84. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.86. DART-MS: *m/z* calcd. for $C_{15}H_{18}FN_2O_2$ $(M+H)^+$ 277.13468, found 277.13425.



***tert*-Butyl methyl(6-fluoro-1-methylisoquinolin-5-yl)carbamate (S21).** To a solution of **S20** (0.150 g, 0.543 mmol) in THF (4 mL) was added NaH 60% in mineral oil (28.0 mg, 0.706 mmol). After effervescence ceased, the resulting solution was refluxed for 30 min. To the reaction mixture was added the MeI (0.10 g, 0.706 mmol) in THF (0.5 mL) and the solution refluxed overnight. The mixture was concentrated and passed through a silica plug (1:10-2:1 EtOAc:hexanes). The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes). The isoquinoline **S21** was obtained as a mixture of rotational isomers as an amber oil (0.120 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 5.8 Hz, 1.27H), 8.16–8.02 (m, 1.27H), 7.51 (d, J = 6.0 Hz, 1H), 7.49 (d, J = 6.3 Hz, 0.27H), 7.39 (t, J = 9.3 Hz, 1.27H), 3.26 (s, 0.81H), 3.25 (s, 3H), 2.98 (s, 3H), 2.96 (s, 0.81H), 1.56 (s, 2.43H), 1.26 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.89, 158.88, 158.09 (d, $^{1}J_{C\text{-}F}$ = 254.3 Hz), 154.97, 154.78, 143.18 (2C), 135.55, 135.36 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 127.66 (d, $^{3}J_{C\text{-}F}$ = 9.7 Hz), 127.38 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz), 125.25, 125.06 (2C), 124.88, 124.78, 117.42 (d, $^{2}J_{C\text{-}F}$ = 24.0 Hz), 117.12 (d, $^{2}J_{C\text{-}F}$ = 24.1 Hz), 114.35 (d, $^{3}J_{C\text{-}F}$ = 5.8 Hz), 81.18, 80.61, 37.43, 36.39, 28.35 (3C), 27.99 (3C), 22.62, 22.56, one low-field carbon were either not observed or is overlapping with another low-field carbon. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.54, -115.33. DART-MS: *m/z* calcd. for $C_{16}H_{20}FN_2O_2$ $(M+H)^+$ 291.15033, found 291.15011.



***tert*-Butyl methyl(6-fluoro-1-formylisoquinolin-5-yl)carbamate (S22).** To a solution of **S21** (0.1000 g, 0.344 mmol) in 1,4-dioxane (2 mL) was added SeO_2 (38.2 mg, 0.344 mmol). The mixture was stirred at 60 °C overnight then cooled to 22 °C. The mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (gradient, 5–25% EtOAc:hexanes). The isoquinoline **S22** was obtained as an off-white solid containing a mixture of rotamers (45.3 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 10.35 (s, 0.3H), 9.35 (dd, J = 9.4, 5.1 Hz, 1.3H), 8.82 (d, J = 5.8 Hz, 1.3H), 7.92 (d, J = 5.7 Hz, 1H), 7.88 (d, J = 5.8 Hz, 0.3H), 7.56 (t, J = 9.4 Hz, 1.3H), 3.29 (s, 0.9H), 3.28 (s, 3H), 1.57 (s, 2.7H), 1.25 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.40 (2C), 158.41 (d, $^{1}J_{C\text{-}F}$ = 257.6 Hz), 154.77 (2C), 149.92, 143.81, 143.72 (2C), 136.73 (d, $^{4}J_{C\text{-}F}$ = 4.6 Hz), 136.59 (d, $^{4}J_{C\text{-}F}$ = 3.8 Hz), 128.17 (d, $^{3}J_{C\text{-}F}$ = 10.7 Hz), 127.91 (d, $^{3}J_{C\text{-}F}$ = 9.3 Hz), 124.72 (d, $^{3}J_{C\text{-}F}$ = 13.3 Hz), 124.00, 123.80, 120.68 (d, $^{2}J_{C\text{-}F}$ = 24.7 Hz), 120.44 (d, $^{2}J_{C\text{-}F}$ = 24.1 Hz), 120.31, 120.22 (d, $^{3}J_{C\text{-}F}$ = 6.3 Hz), 81.55, 81.00, 37.58, 36.53, 28.32 (3C), 27.97 (3C), two low-field carbon were either not observed or is overlapping with another low-field carbon. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.18, -112.95. DART-MS: *m/z* calcd. for $C_{16}H_{18}FN_2O_3$ $(M+H)^+$ 305.1296, found 305.12819.



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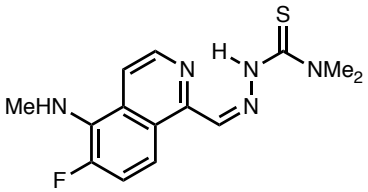
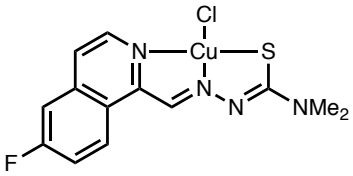
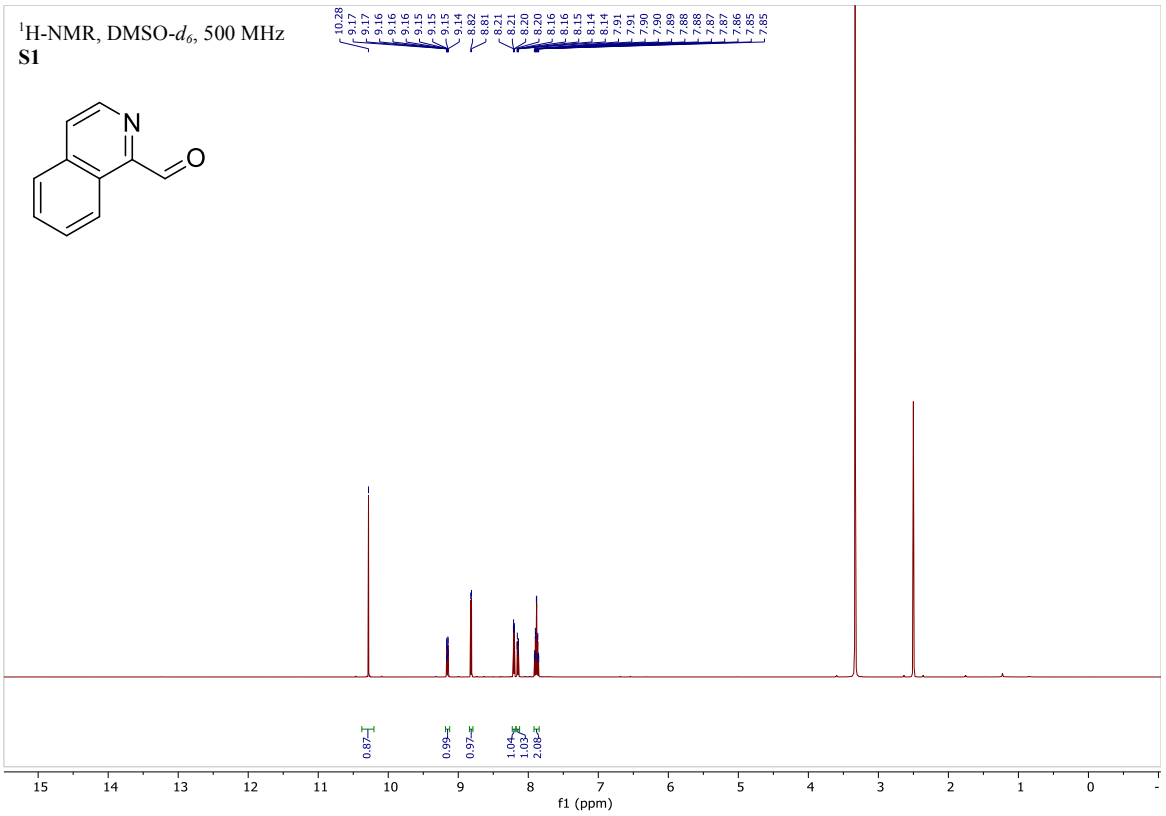


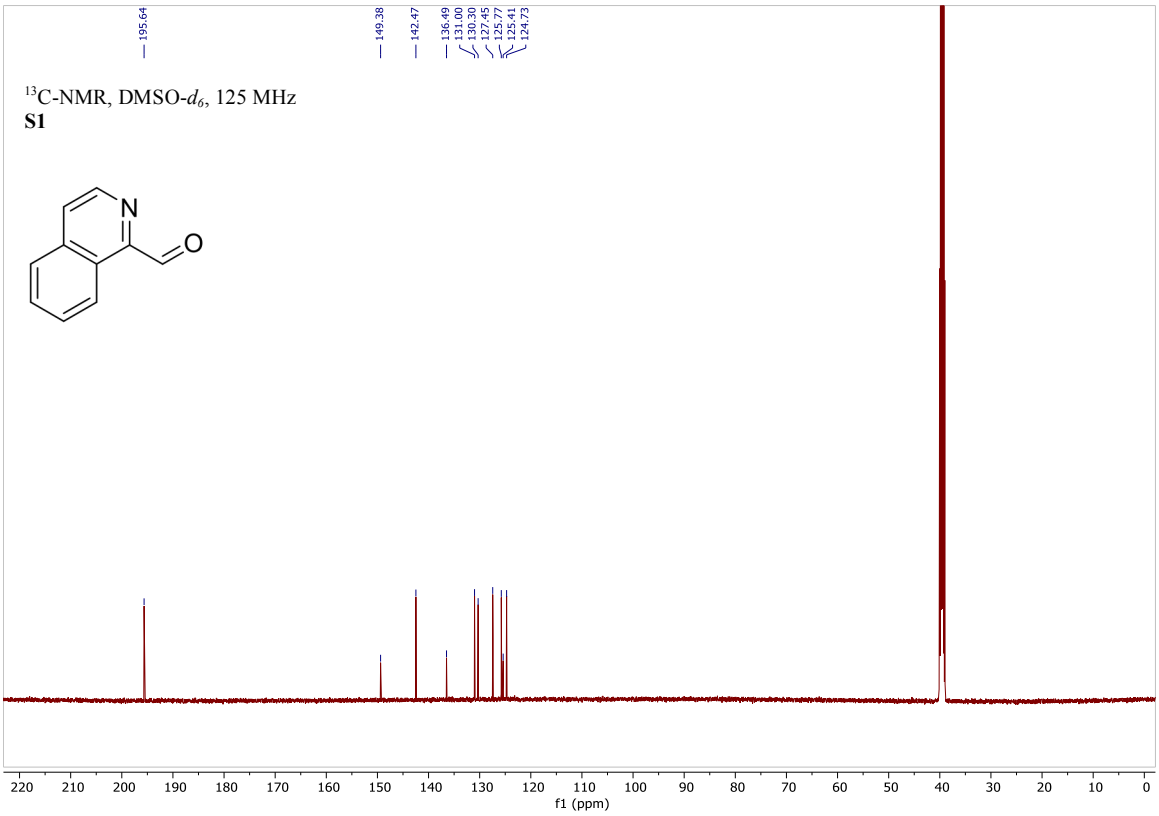
(*E*)-2-((6-Fluoro-5-(methylamino)isoquinolin-1-yl)methylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide and (*Z*)-2-((6-Fluoro-5-(methylamino)isoquinolin-1-yl)methylene)-*N*,*N*-dimethylhydrazine-1-carbothioamide (HCT14). To a solution of **S22** (10.0 mg, 0.033 mmol) in EtOH (0.5 mL) was added 4,4-dimethyl-3-thiosemicarbazide (3.9 mg, 0.033 mmol) and HCl (33 µL, 0.197 mmol, 6 M in H_2O). The mixture was stirred and refluxed for 1.5 h then cooled to 22 °C. The hydrochloride salt that formed was then neutralized with saturated aqueous $NaHCO_3$ solution (0.5 mL). the precipitate of the desired compound was collected by filtration, washed with water, EtOH and then dried to yield the isoquinoline **HCT14** as a pale-yellow solid (6.7 mg, 67%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 15.96 (s, 0.17H), 11.22 (Br s, 1H), 9.20 (s, 1H), 8.62–8.54 (m, 1.17H), 8.52 (s, 0.17H), 8.34 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 6.2 Hz, 0.17H), 8.07 (dd, J = 9.3, 4.2 Hz, 0.17H), 7.87 (br s, 1H), 7.56 (dd, J = 13.6, 9.2 Hz, 0.17H), 7.33 (dd, J = 13.4, 9.5 Hz, 1H), 6.10 (br s, 0.17H), 5.69 (br s, 1H), 3.41 (s, 1.02H), 3.27 (s, 6H), 3.10 (t, J = 5.5 Hz, 0.51H), 3.05 (t, J = 5.2 Hz, 3H). A ^{13}C NMR was not obtained. ^{19}F NMR (376 MHz, $CDCl_3$) δ - 129.05, -129.53. DART-MS: *m/z* calcd. for $C_{14}H_{17}FN_5S$ $(M+H)^+$ 306.11832, found 306.11719.

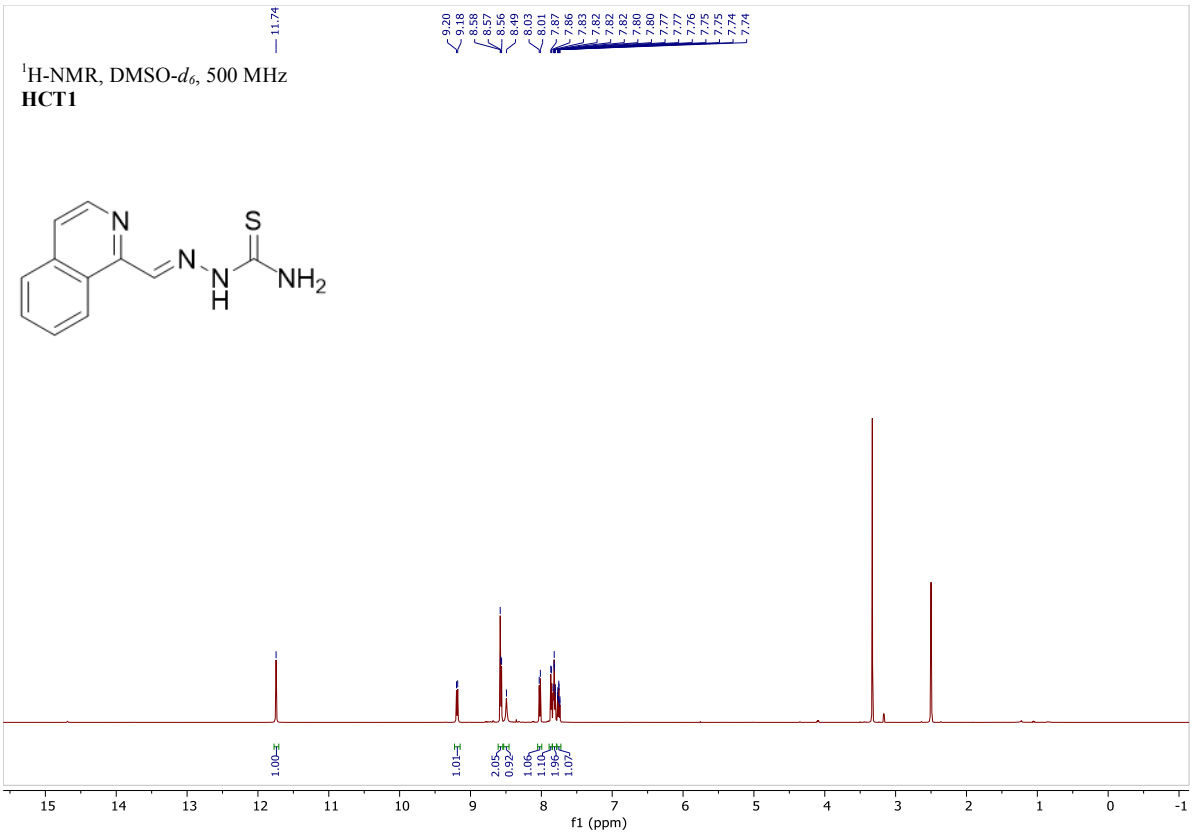


Cu[HCT13]. HCT-13 (100.0 mg, 0.362 mmol) was dissolved in DMF (8 mL). A solution of $CuCl_2$ (48.7 mg, 0.362 mmol) in water (8 mL) was added dropwise with stirring, and the solution immediately turned dark brown and a tan color solid formed upon further addition of the copper(II) chloride solution. The solid was filtered, washed with EtOH three times then dried through suction to obtain a brown solid (94.8 mg, 70%). HR-MS (ESI+) data; m/z calcd for $[C_{13}H_{12}FCuN_4S + MeCN]^+$ = 379.0323; found 379.0297. M/z calcd for $[C_{13}H_{12}FCuN_4S]^+$ = 338.00572; found 338.0038 (Thermo LTQ-Orbitrap XL). Refer to Figure S4 for HPLC trace and ESI mass spectrum.

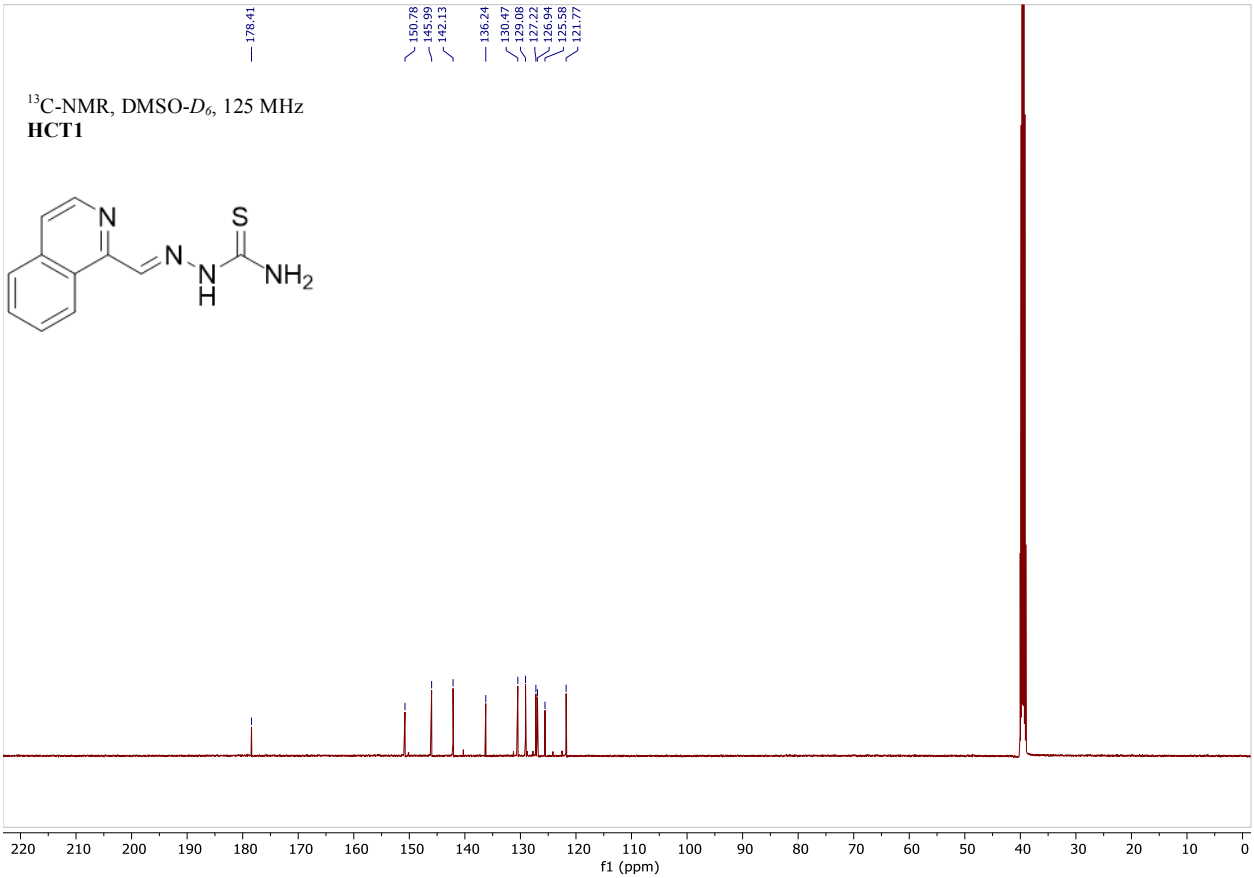
^{1}HNMR and ^{13}CNMR of compounds **S1-S22** and **HCT1-15**



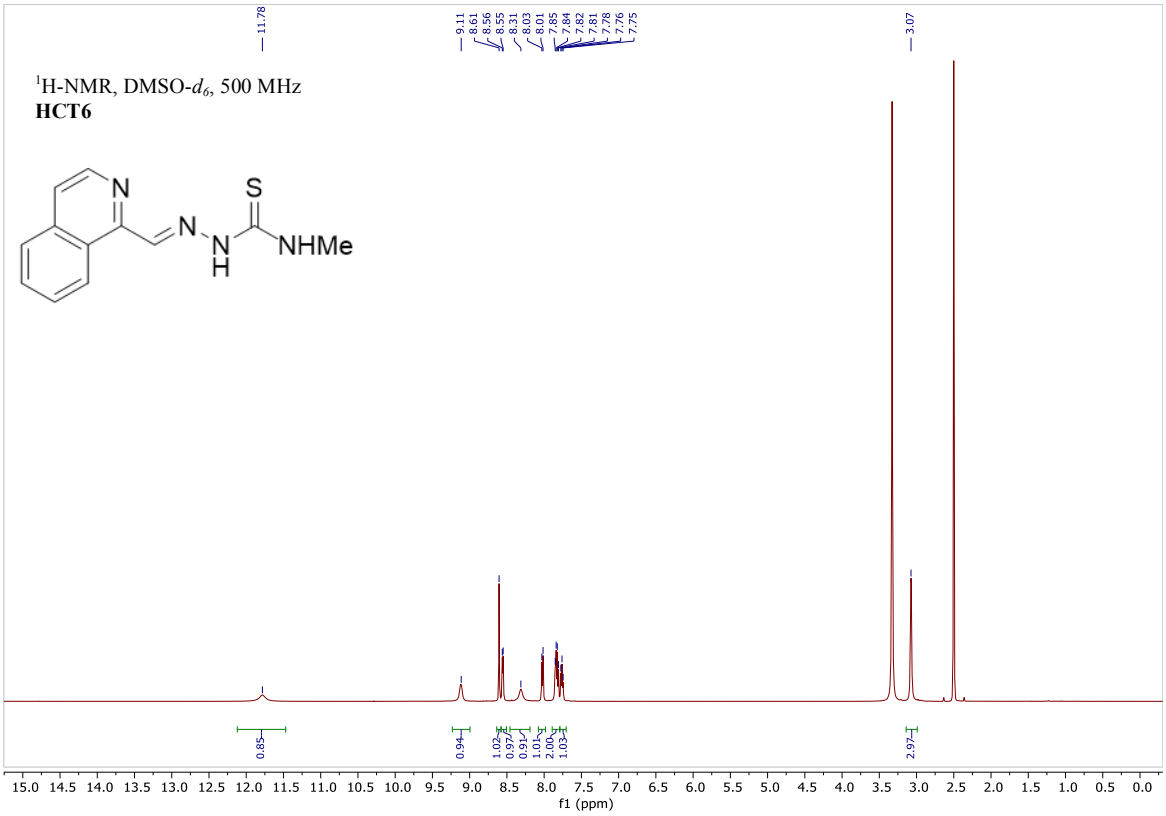




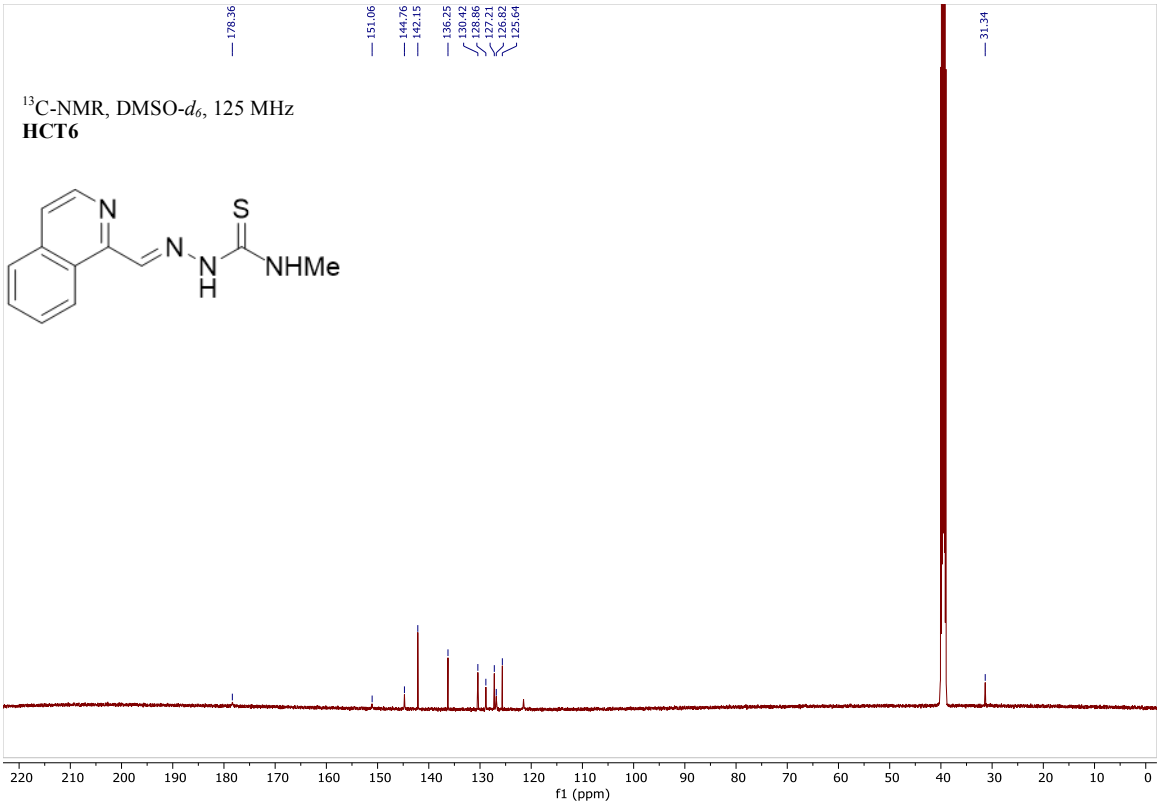
^{1}H-NMR, DMSO-d_6, 500 MHz
HCT1



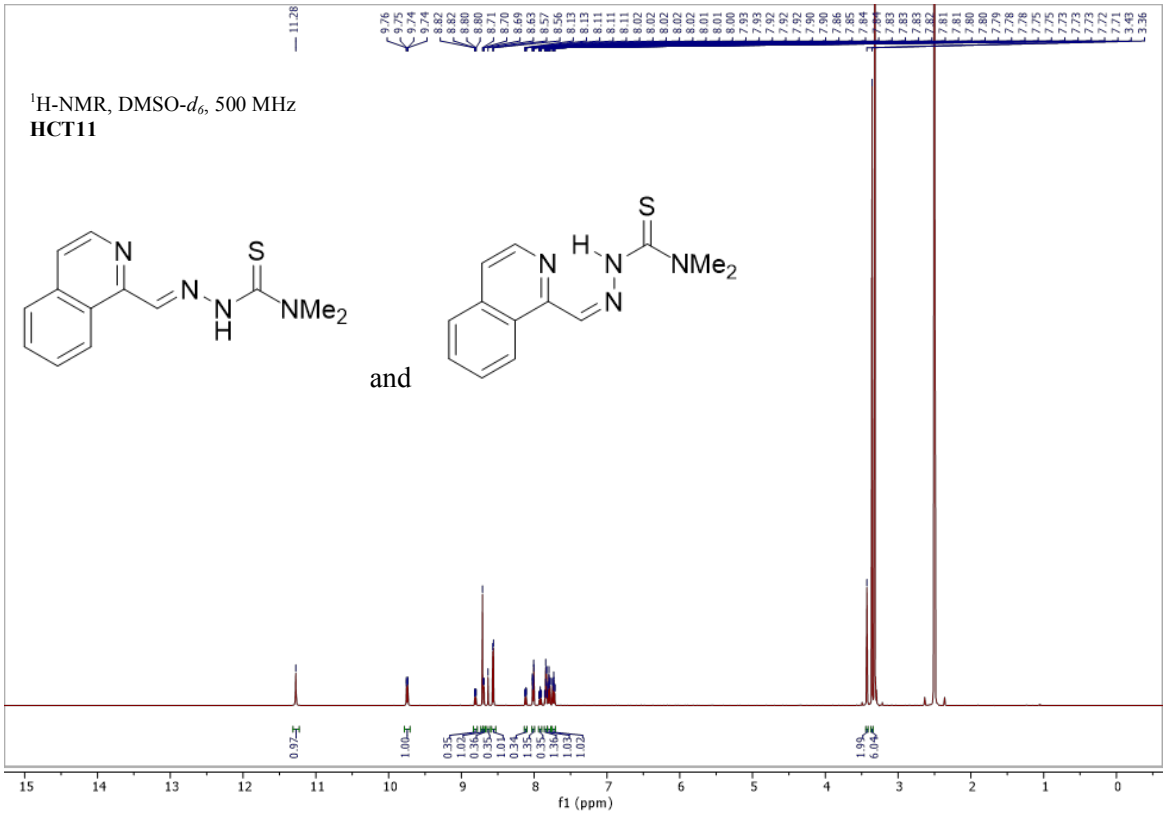
^{13}C-NMR, DMSO-D_6, 125 MHz
HCT1

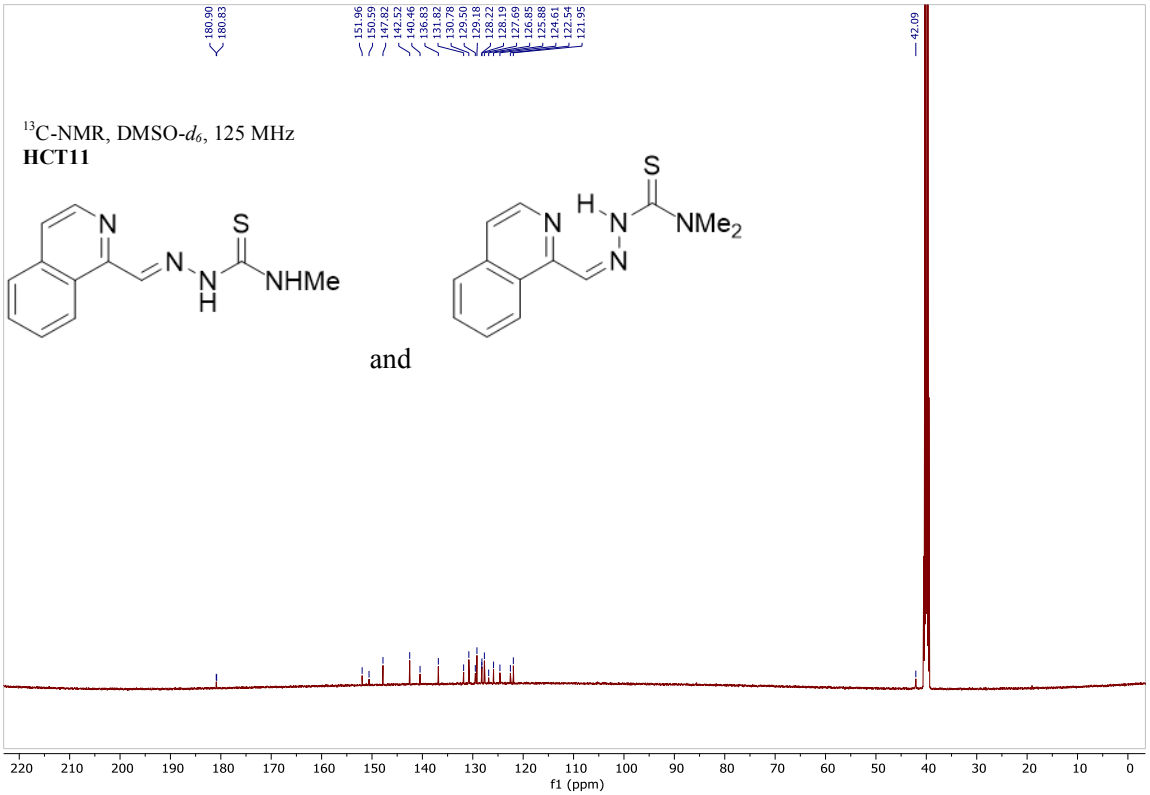


^{1}H-NMR, DMSO-d_6, 500 MHz
HCT6

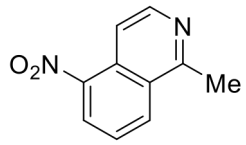


^{13}C-NMR, DMSO-d_6, 125 MHz
HCT6

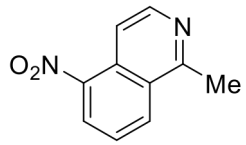

[1]H-NMR, DMSO-d6, 500 MHz
HCT11
and
f1 (ppm)


[13]C-NMR, DMSO-d6, 125 MHz
HCT11
and
f1 (ppm)

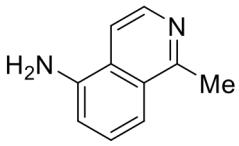
^{1}H-NMR, $CDCl_3$, 500 MHz
S2

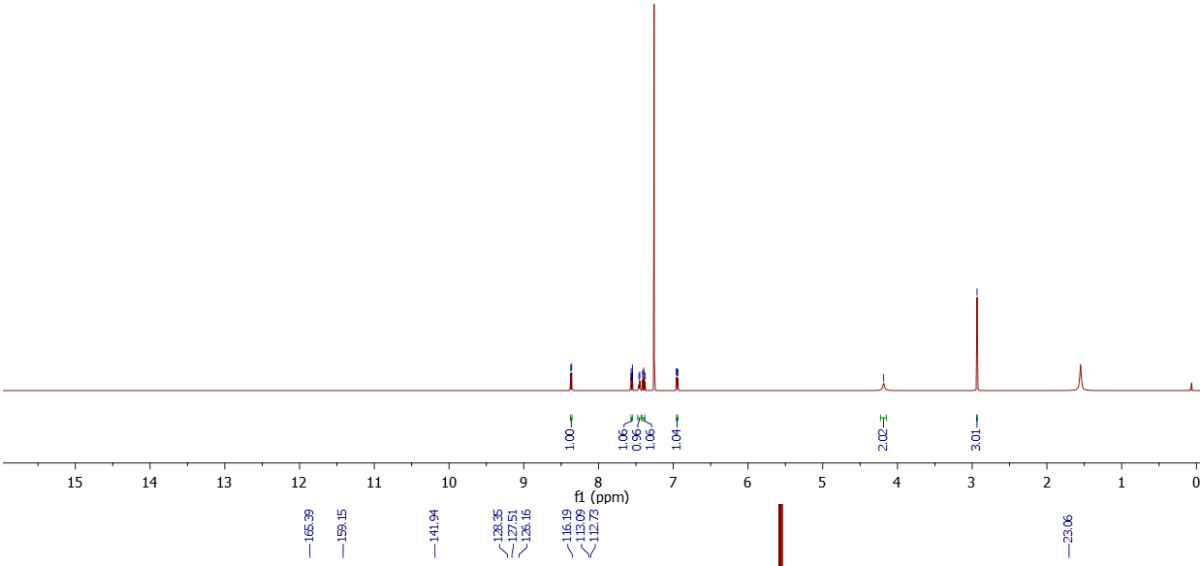


^{13}C-NMR, $CDCl_3$, 125 MHz
S2

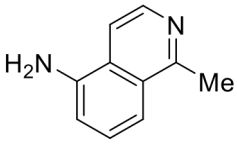


^{1}H-NMR, $CDCl_3$, 500 MHz
S3

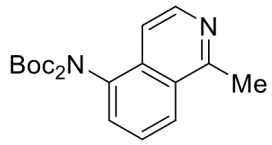




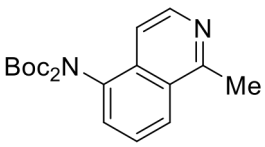
^{13}C-NMR, $CDCl_3$, 125 MHz
S3

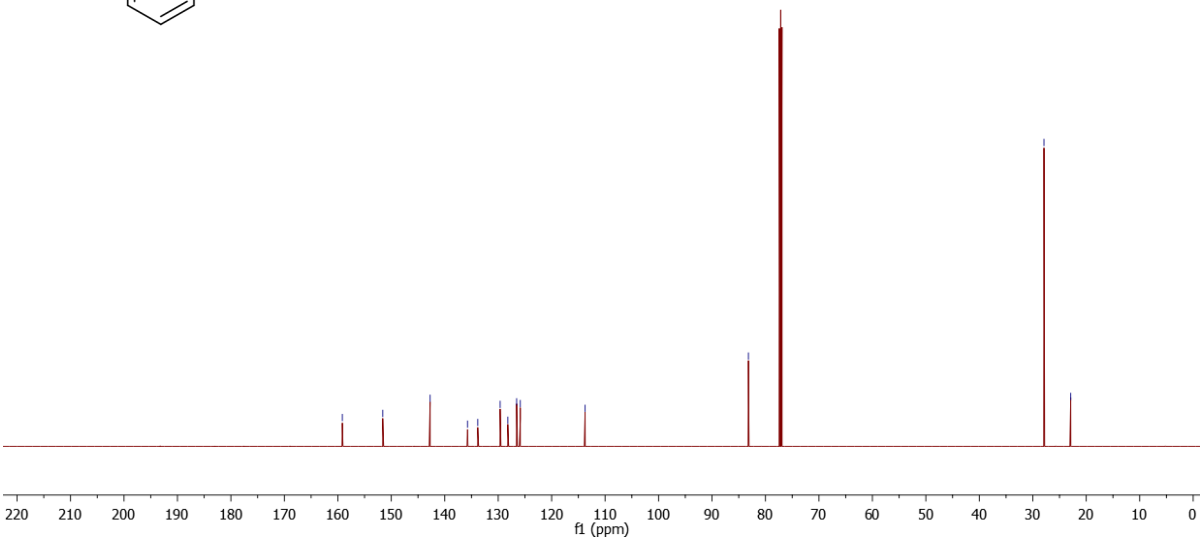


^{1}H-NMR, $CDCl_3$, 500 MHz
S4

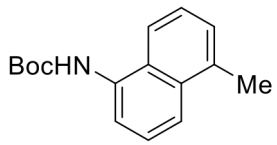


^{13}C-NMR, $CDCl_3$, 125 MHz
S4

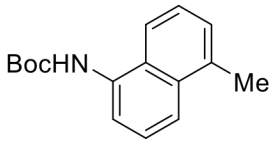




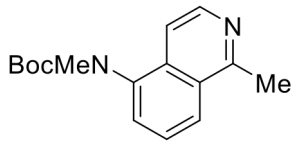
^{1}H-NMR, $CDCl_3$, 500 MHz
S5



^{13}C-NMR, $CDCl_3$, 125 MHz
S5

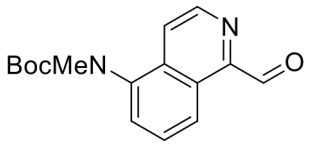


^{1}H-NMR, $CDCl_3$, 500 MHz
S6

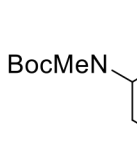


^{1}3C-NMR, $CDCl_3$, 125 MHz
S6

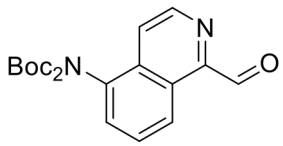
^{1}H-NMR, $CDCl_3$, 500 MHz
S7



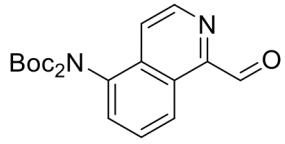
^{13}C-NMR, $CDCl_3$, 125 MHz
S7

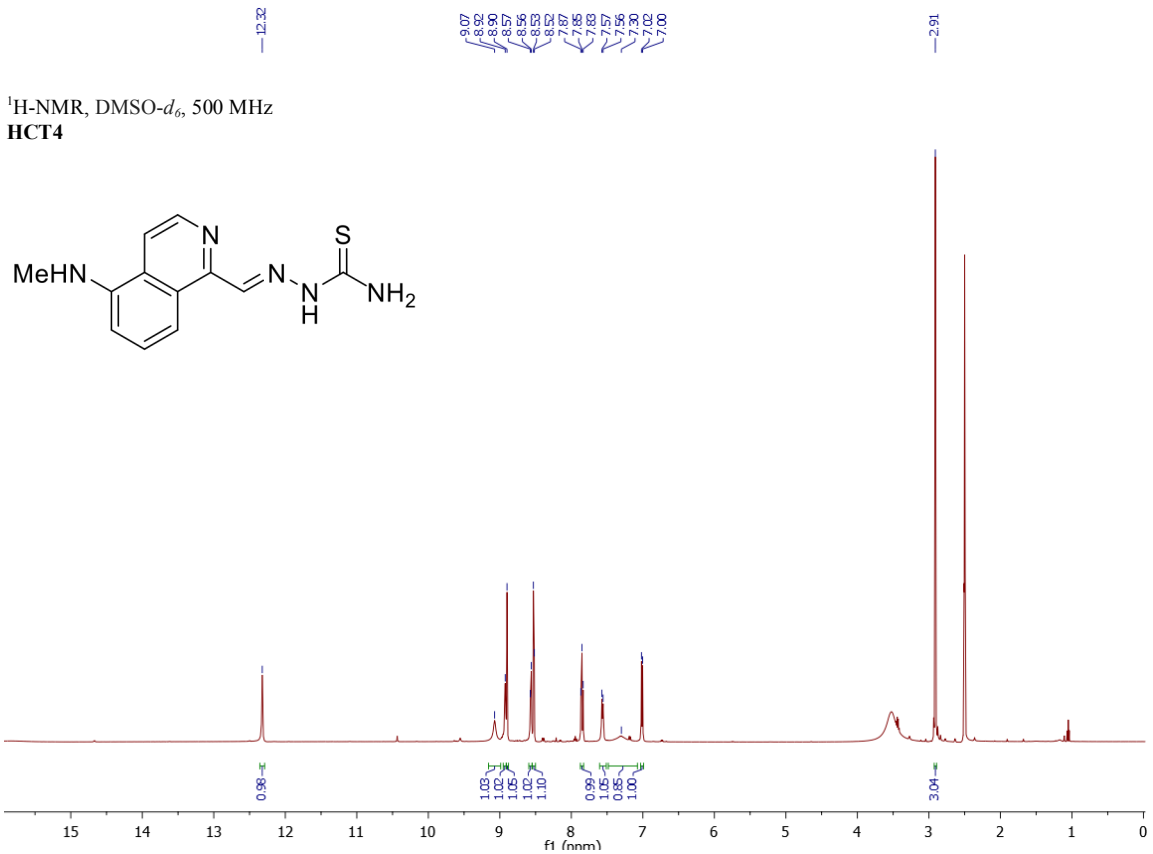


^{1}H-NMR, $CDCl_3$, 500 MHz
S8

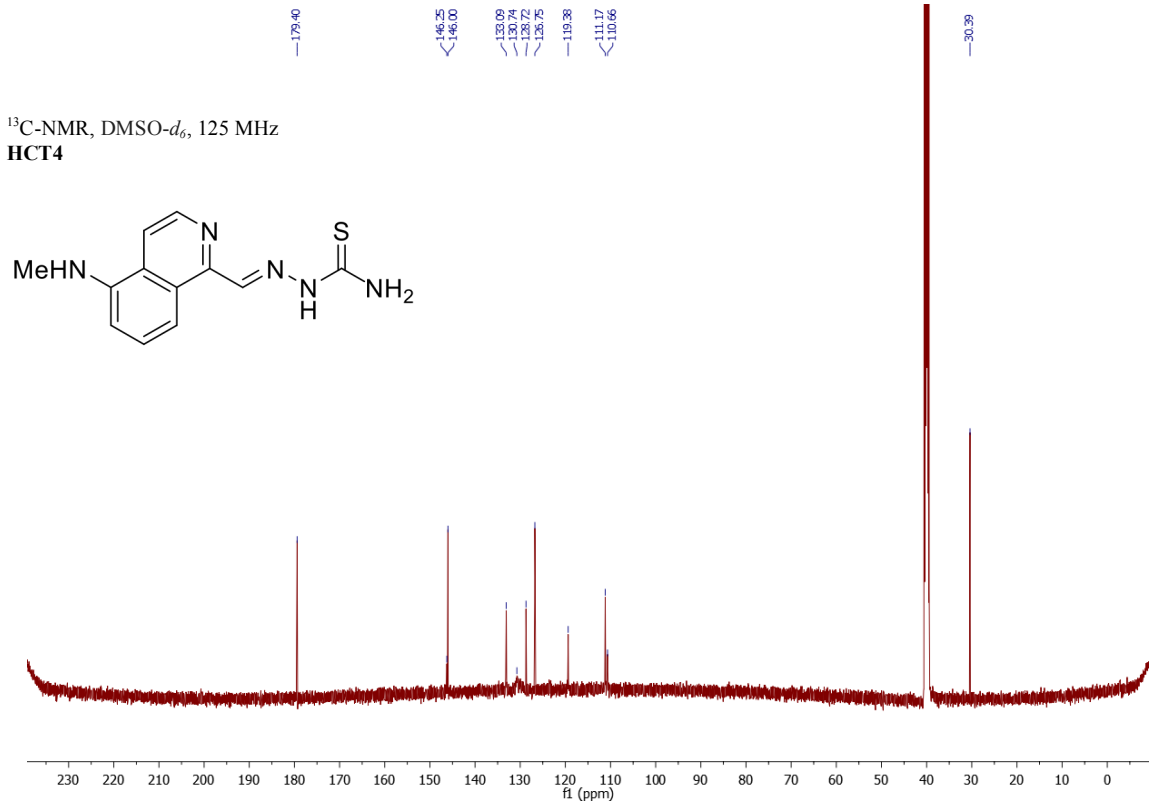


^{13}C-NMR, $CDCl_3$, 125 MHz
S8

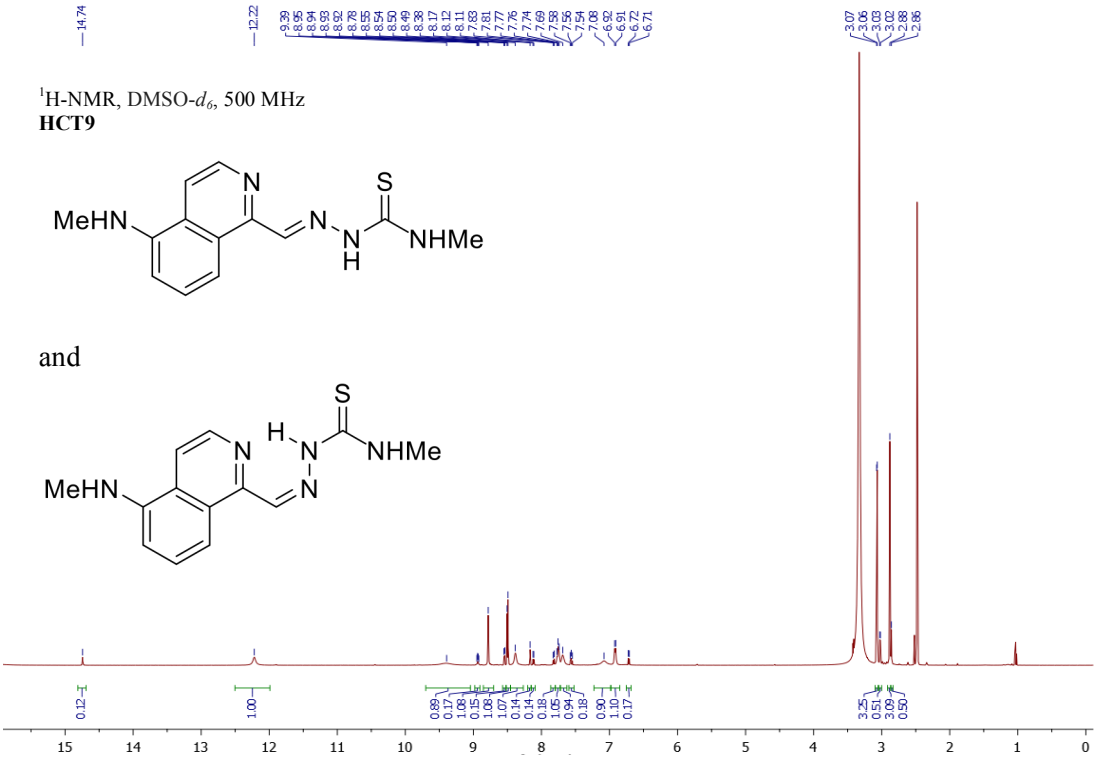




^{1}H-NMR, DMSO-d_6, 500 MHz
HCT4

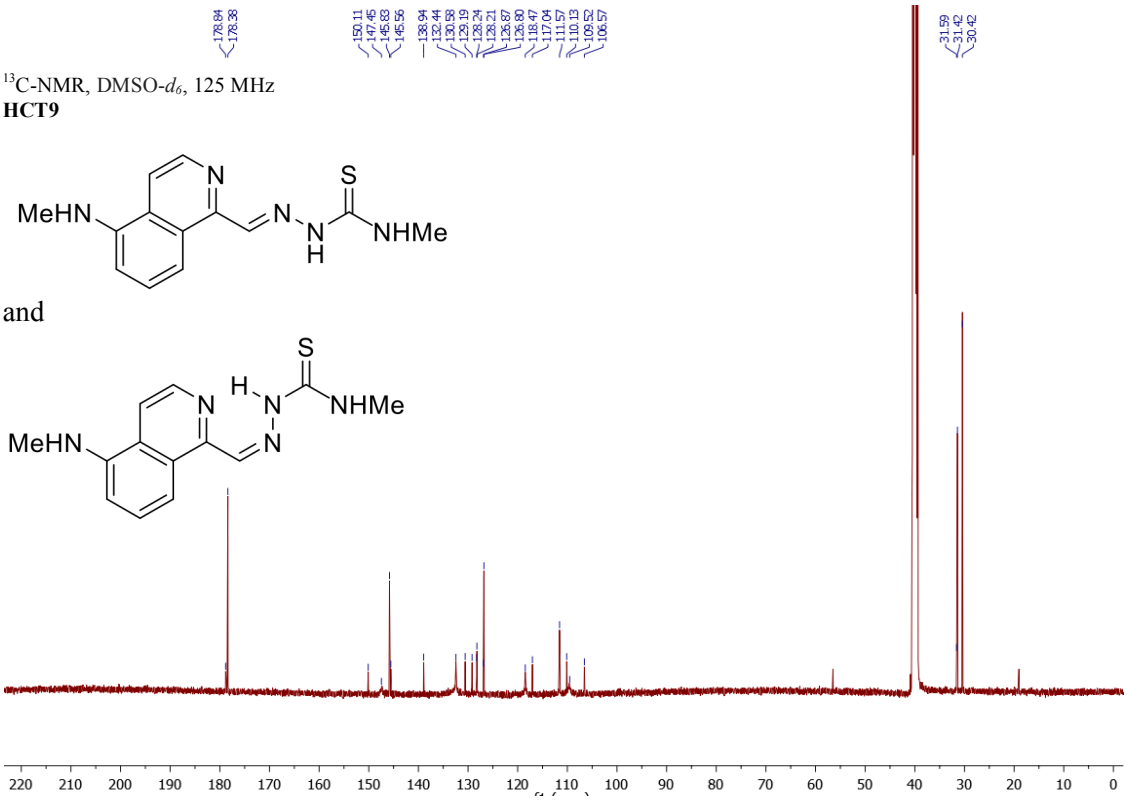


^{13}C-NMR, DMSO-d_6, 125 MHz
HCT4



^{1}H-NMR, DMSO-d_6, 500 MHz
HCT9

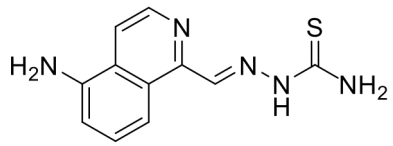
and



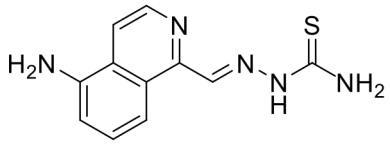
^{13}C-NMR, DMSO-d_6, 125 MHz
HCT9

and

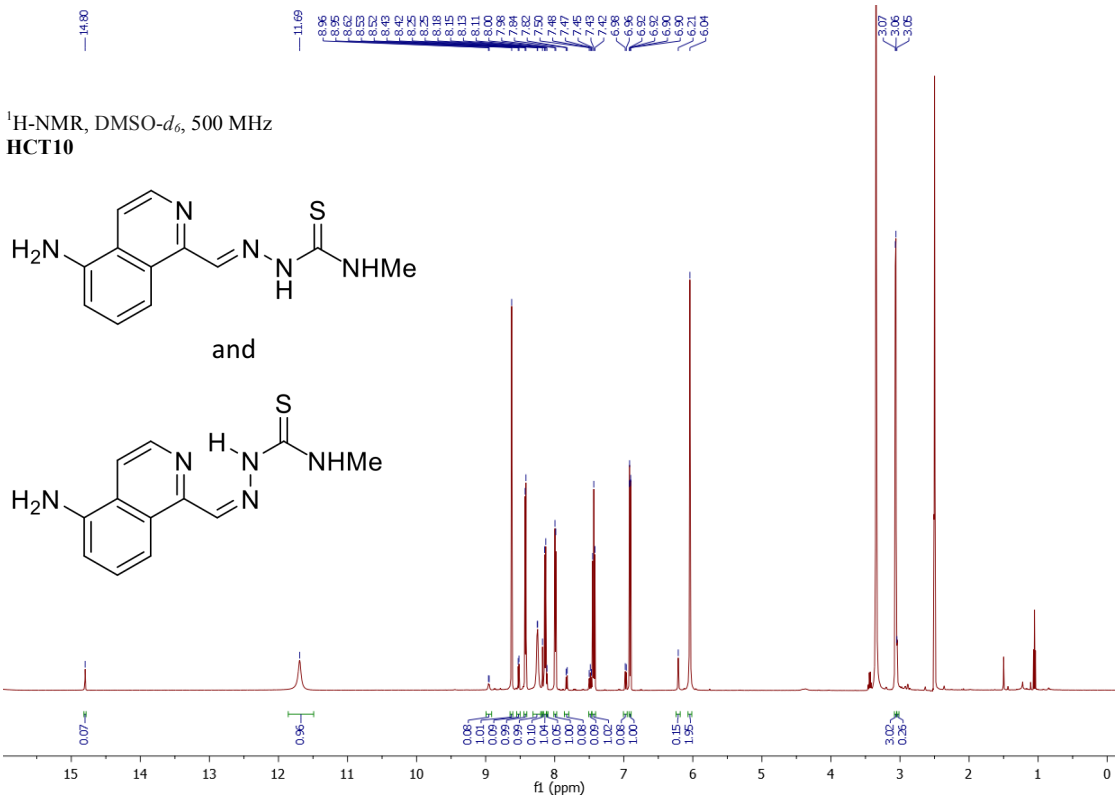
^{1}H-NMR, DMSO-d_6, 500 MHz
HCT5



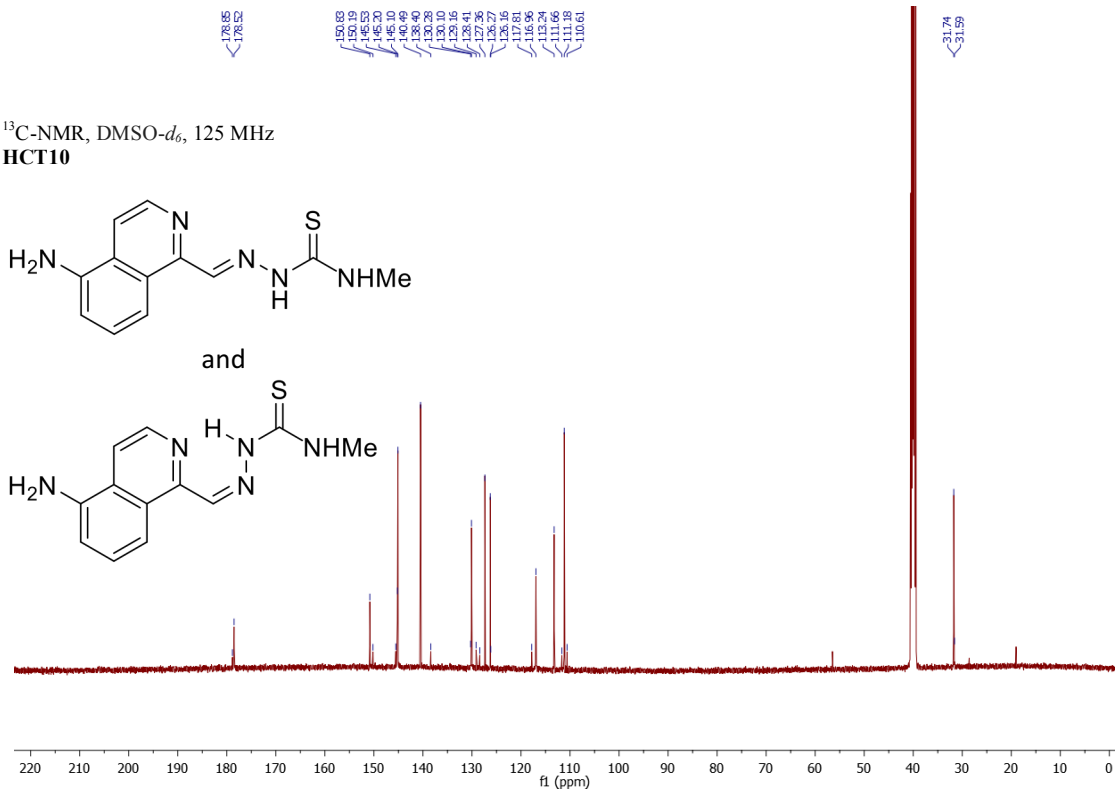
^{13}C-NMR, DMSO-d_6, 125 MHz
HCT5



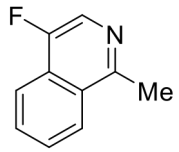
^{1}H-NMR, DMSO-d_6, 500 MHz
HCT10



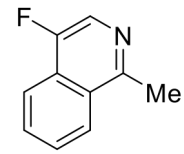
^{13}C-NMR, DMSO-d_6, 125 MHz
HCT10



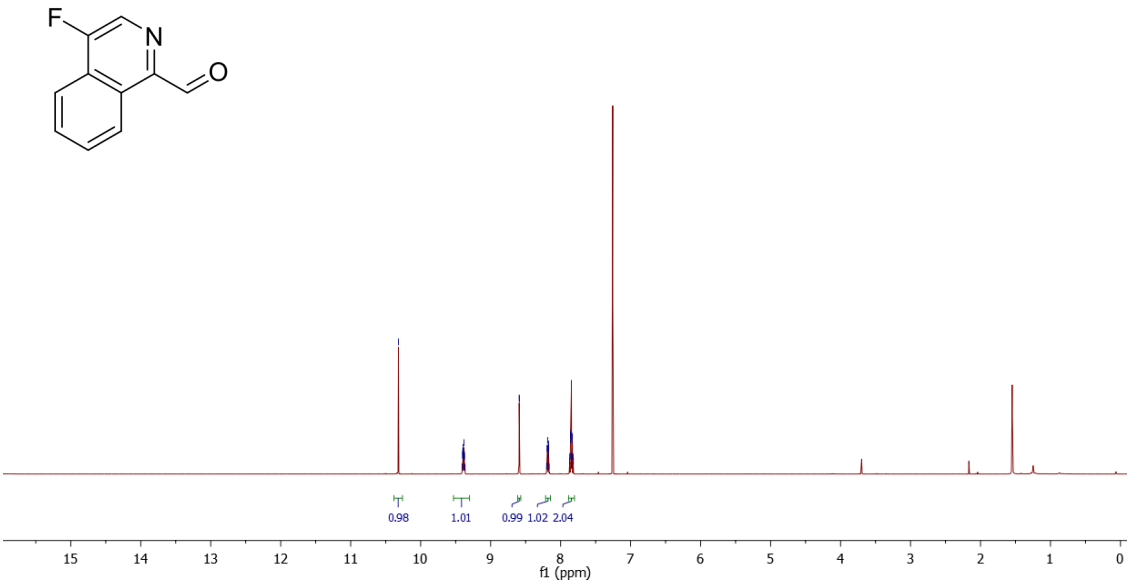
^{1}H-NMR, DMSO-d_6, 500 MHz
S9

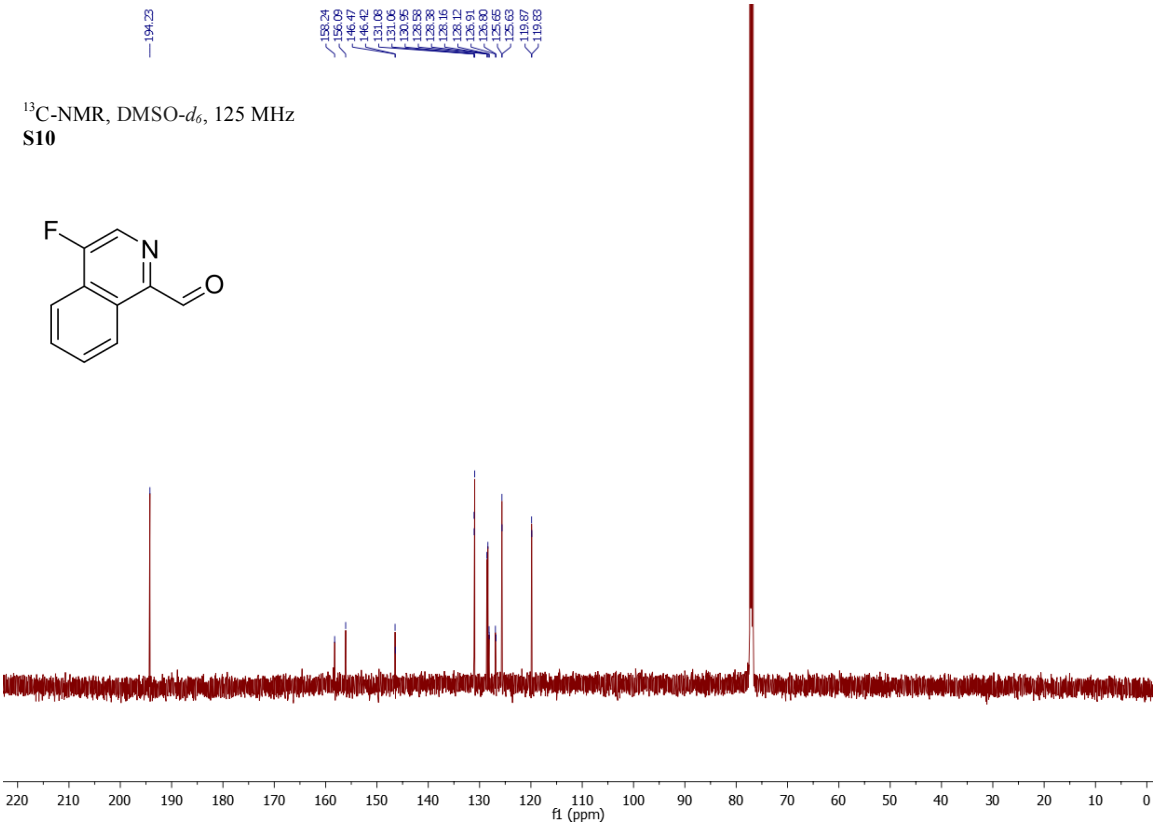


^{13}C-NMR, DMSO-d_6, 125 MHz
S9

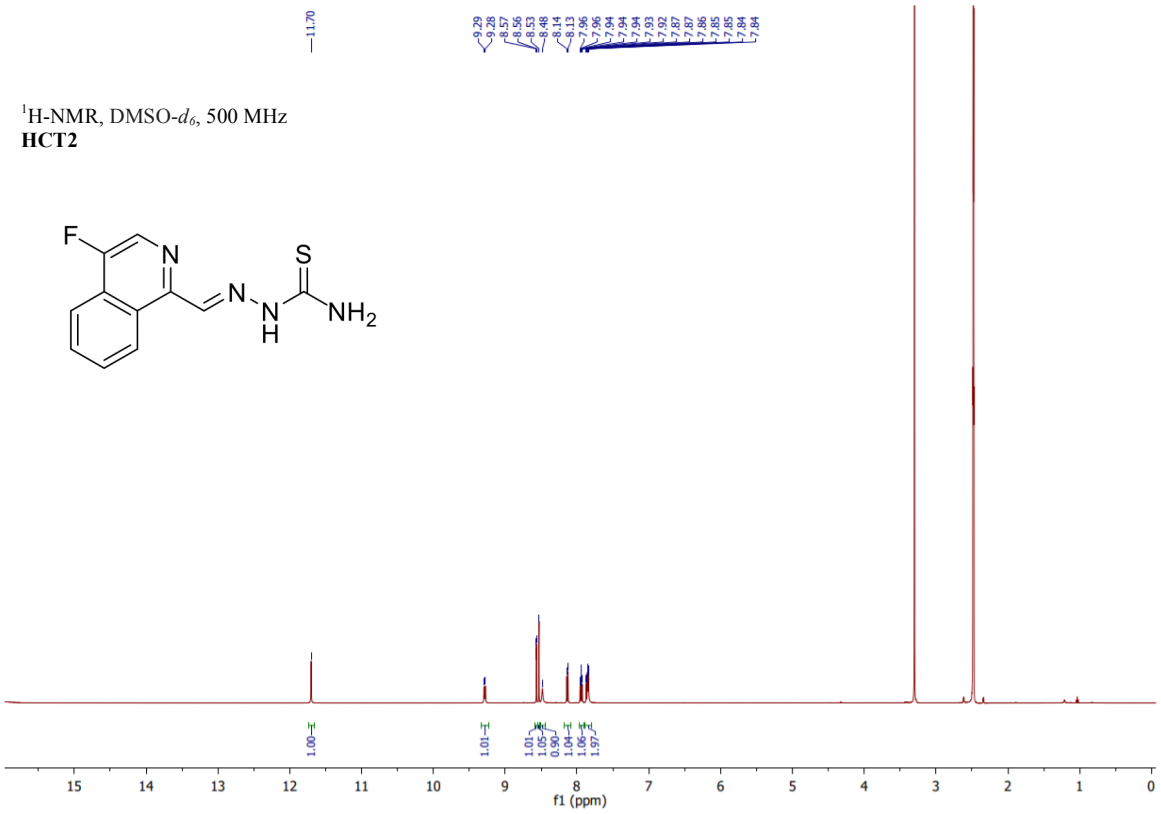


^{1}H-NMR, DMSO-d_6, 500 MHz
S10

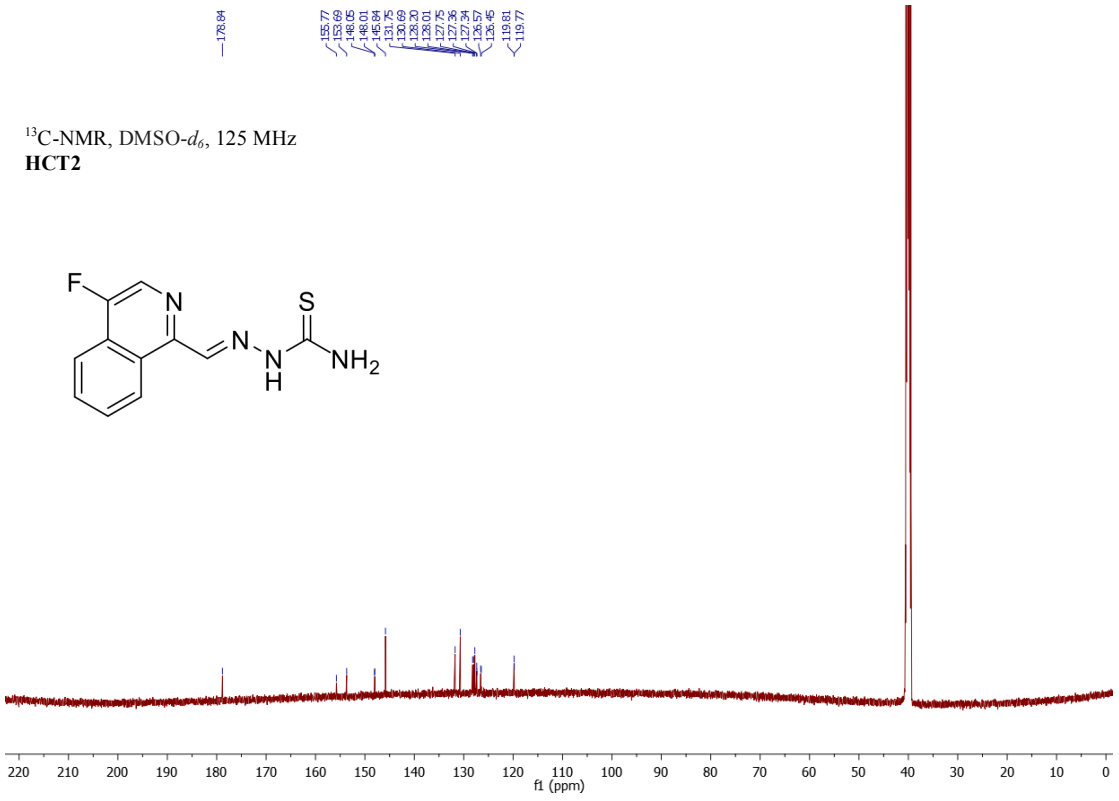




^{13}C-NMR, DMSO-d_6, 125 MHz
S10

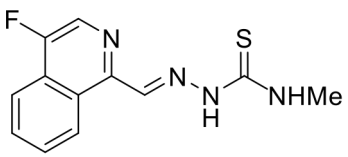


^{1}H-NMR, DMSO-d_6, 500 MHz
HCT2

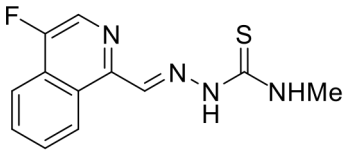


^{13}C-NMR, DMSO-d_6, 125 MHz
HCT2

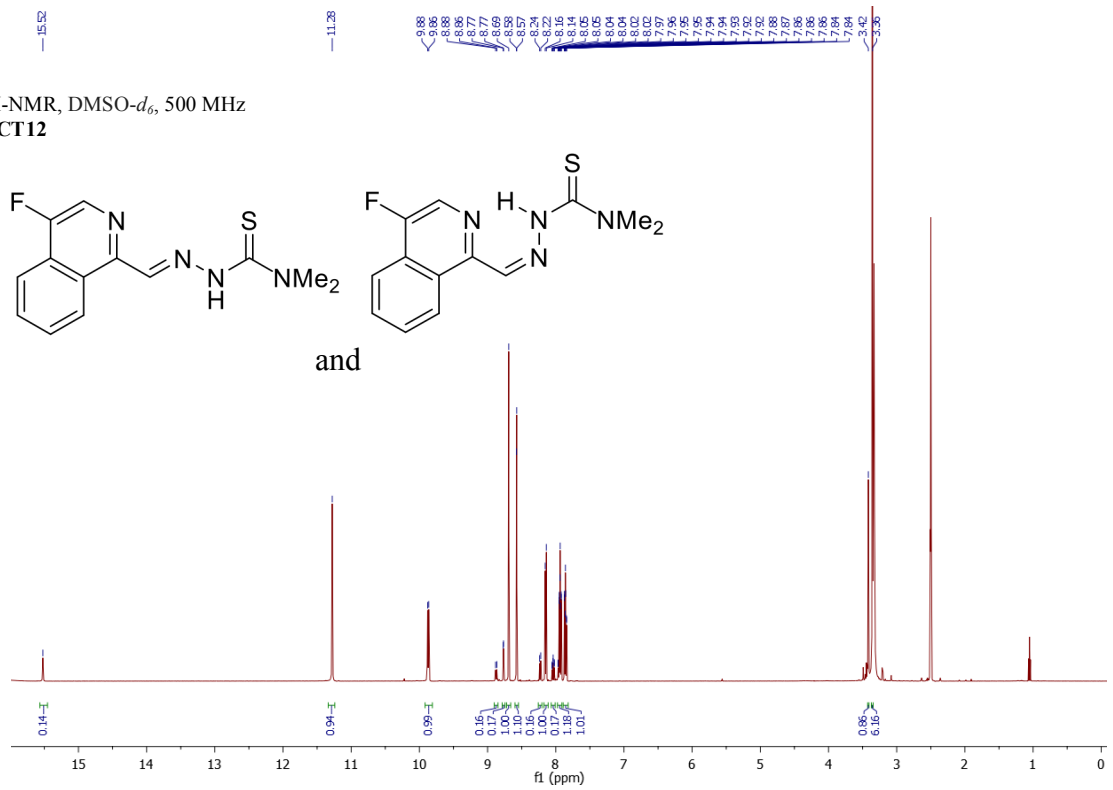
^{1}H-NMR, DMSO-d_6, 500 MHz
HCT7



^{13}C-NMR, DMSO-d_6, 125 MHz
HCT7



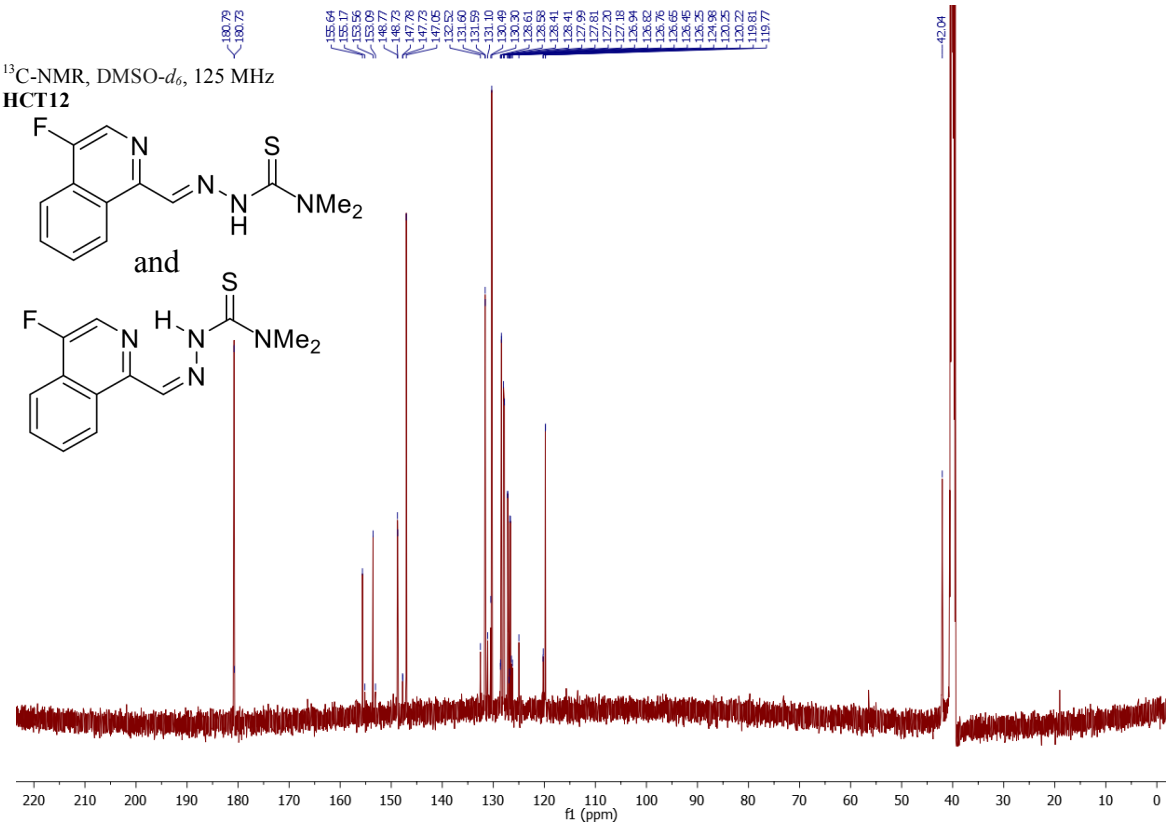
^{1}H-NMR, DMSO-d_6, 500 MHz
HCT12



and

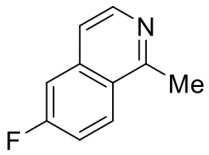
r

^{13}C-NMR, DMSO-d_6, 125 MHz
HCT12

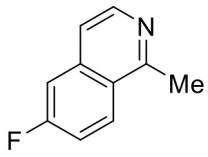


and

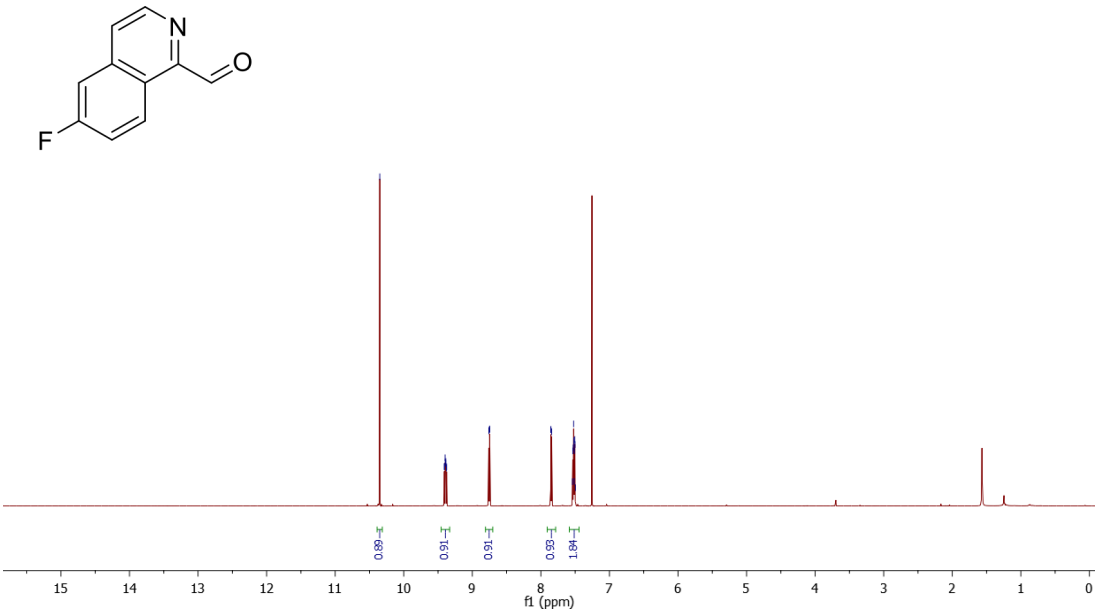
^{1}H-NMR, DMSO-d_6, 500 MHz
S11



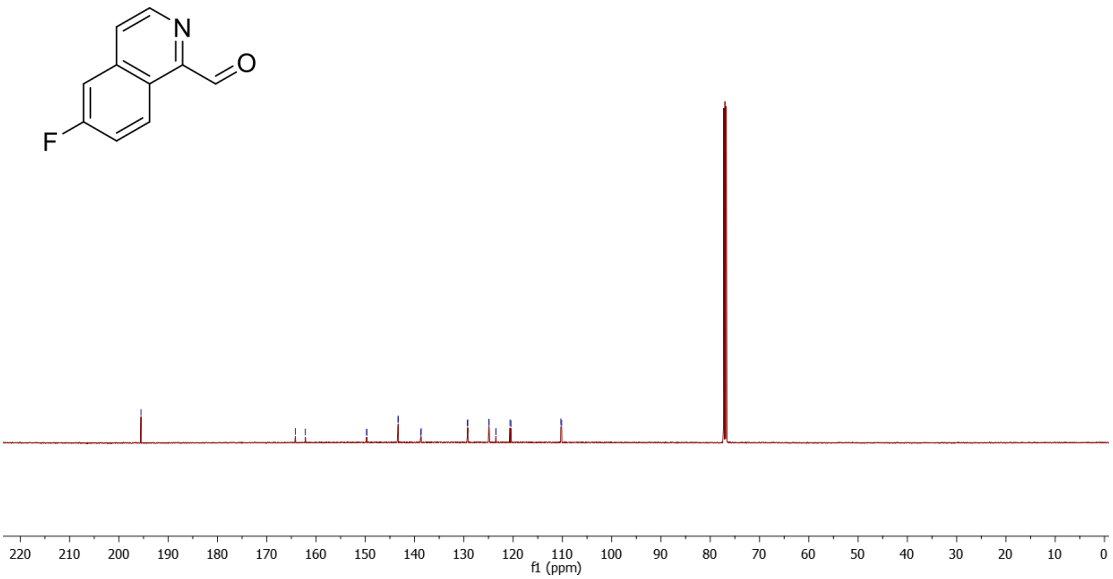
^{13}C-NMR, DMSO-d_6, 125 MHz
S11

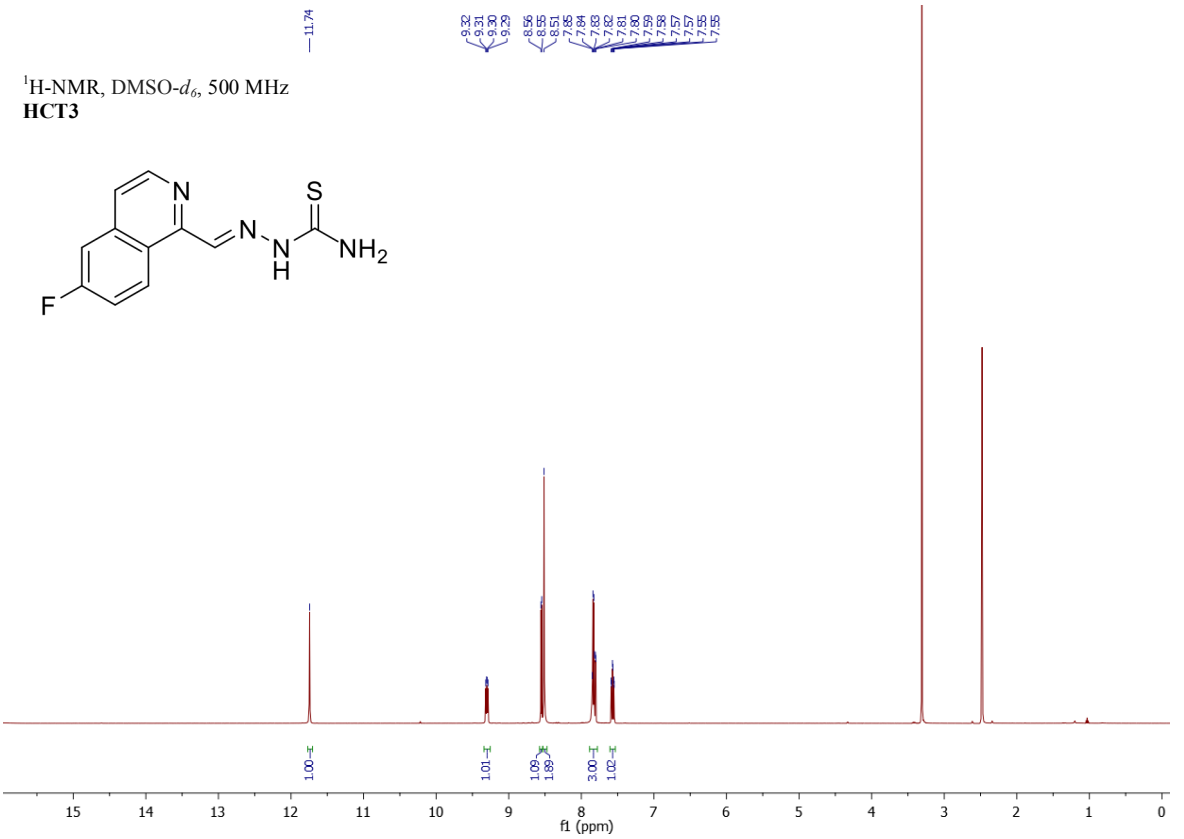


^{1}H-NMR, DMSO-d_6, 500 MHz
S12

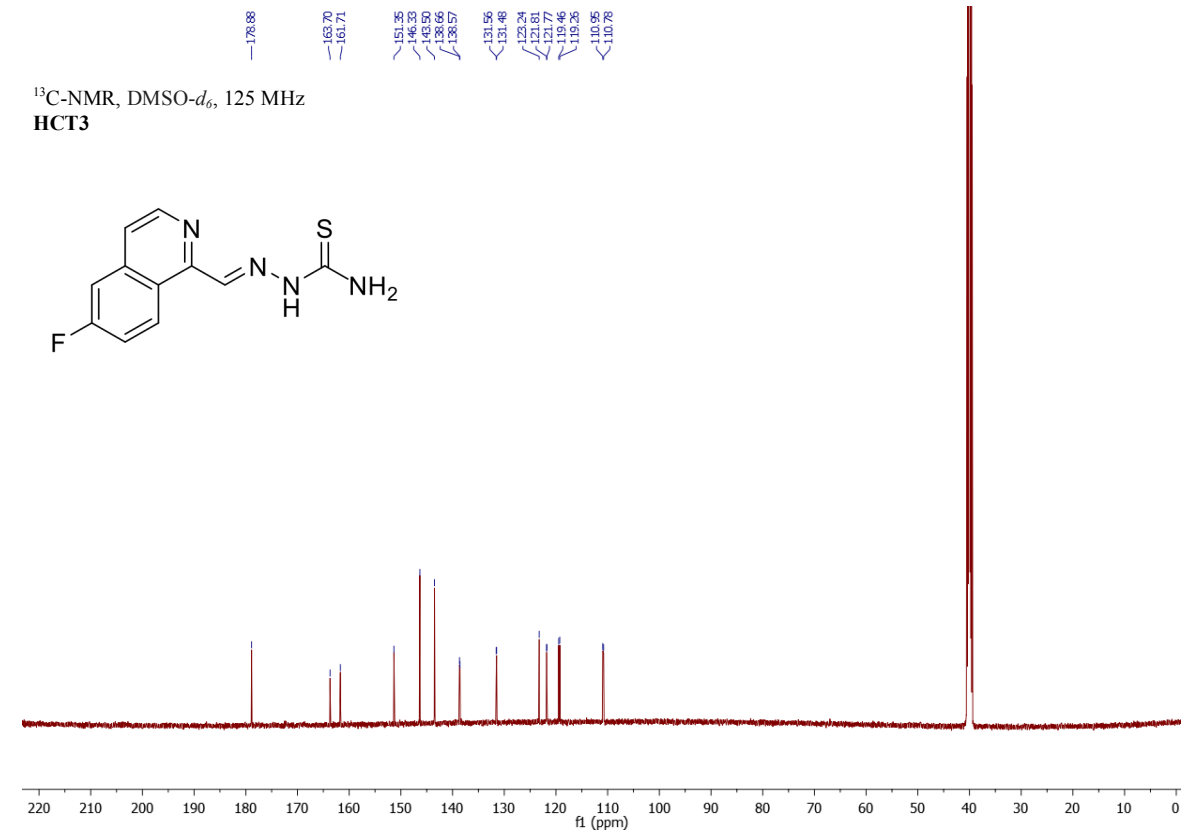


^{13}C-NMR, DMSO-d_6, 125 MHz
S12



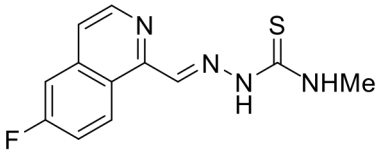


^{1}H-NMR, DMSO-d_6, 500 MHz
HCT3

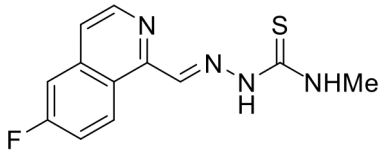


^{13}C-NMR, DMSO-d_6, 125 MHz
HCT3

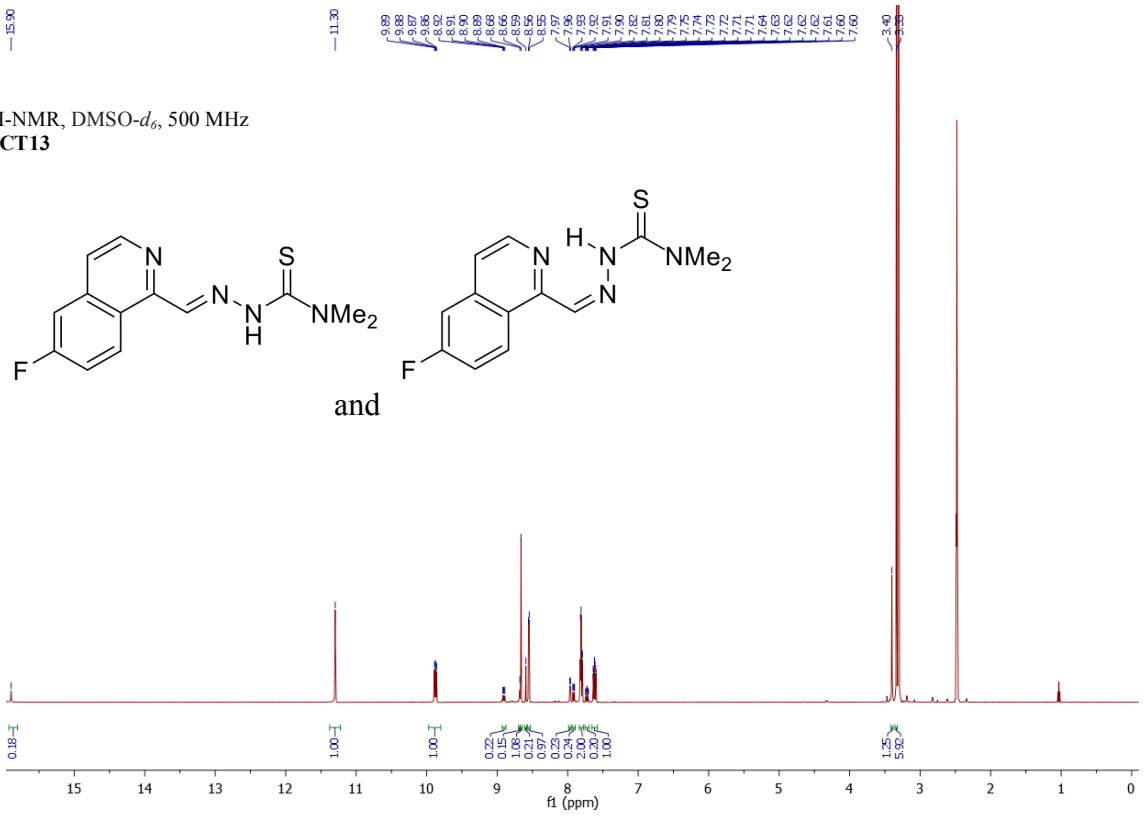
[1]H-NMR, DMSO-d_6, 500 MHz
HCT8



[13]C-NMR, DMSO-d_6, 125 MHz
HCT8

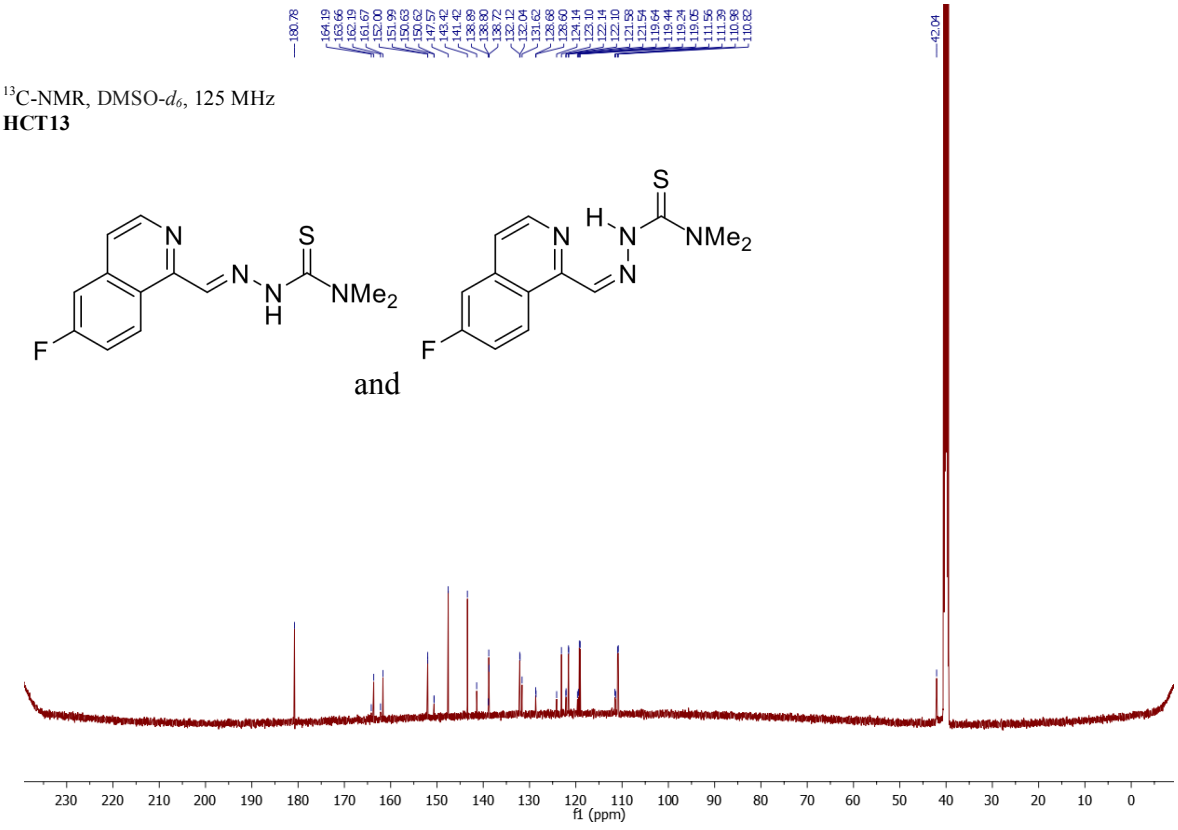


^{1}H-NMR, DMSO-d_6, 500 MHz
HCT13



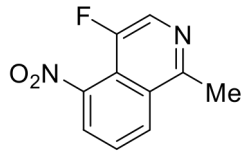
and

^{13}C-NMR, DMSO-d_6, 125 MHz
HCT13

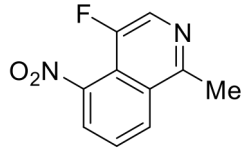


and

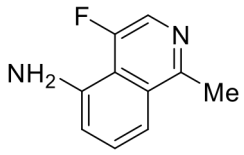
^{1}H-NMR, $CDCl_3$, 500 MHz
S13



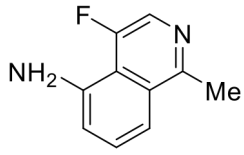
^{1}3C-NMR, $CDCl_3$, 500 MHz
S13



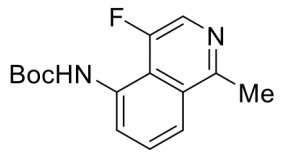
^{1}H-NMR, $CDCl_3$, 400 MHz
S14



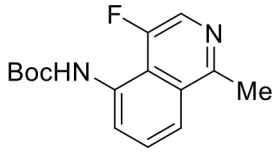
^{13}C-NMR, $CDCl_3$, 125 MHz
S14

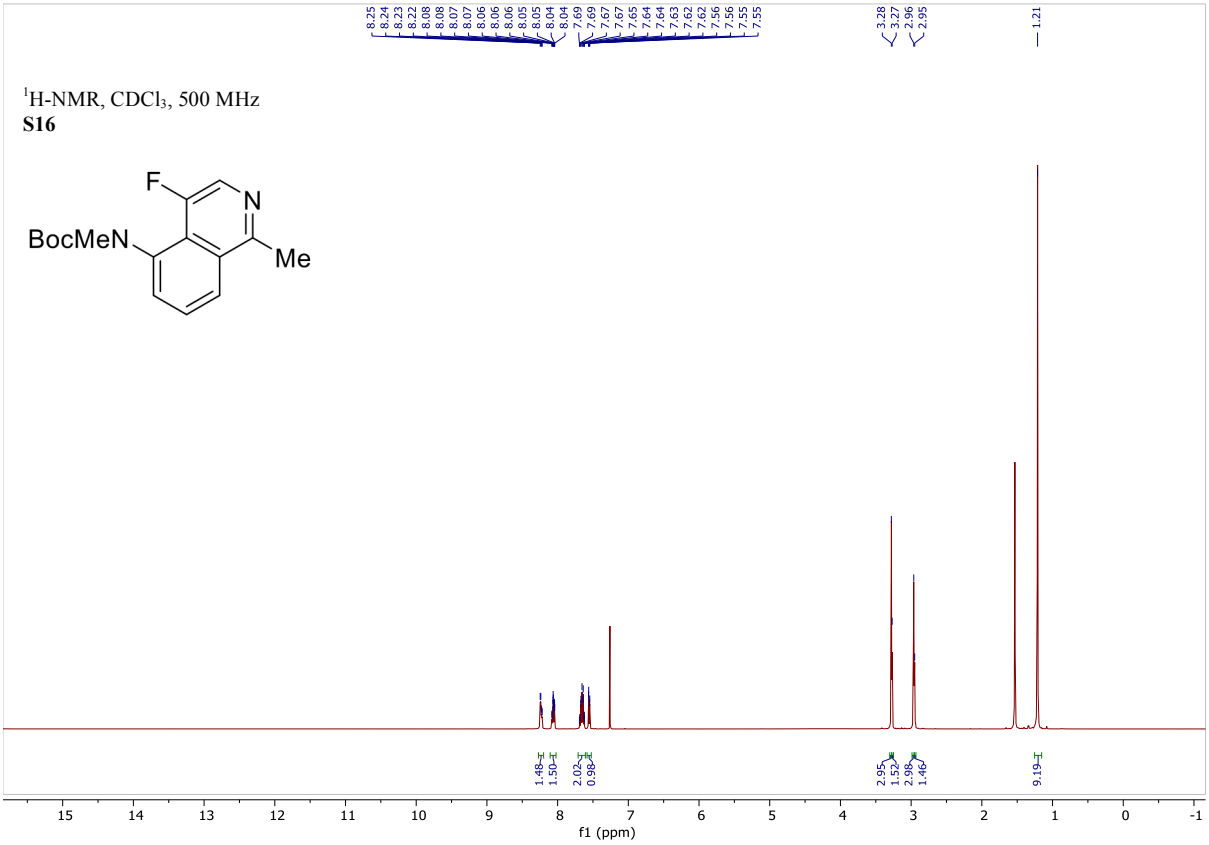


^{1}H-NMR, $CDCl_3$, 400 MHz
S15

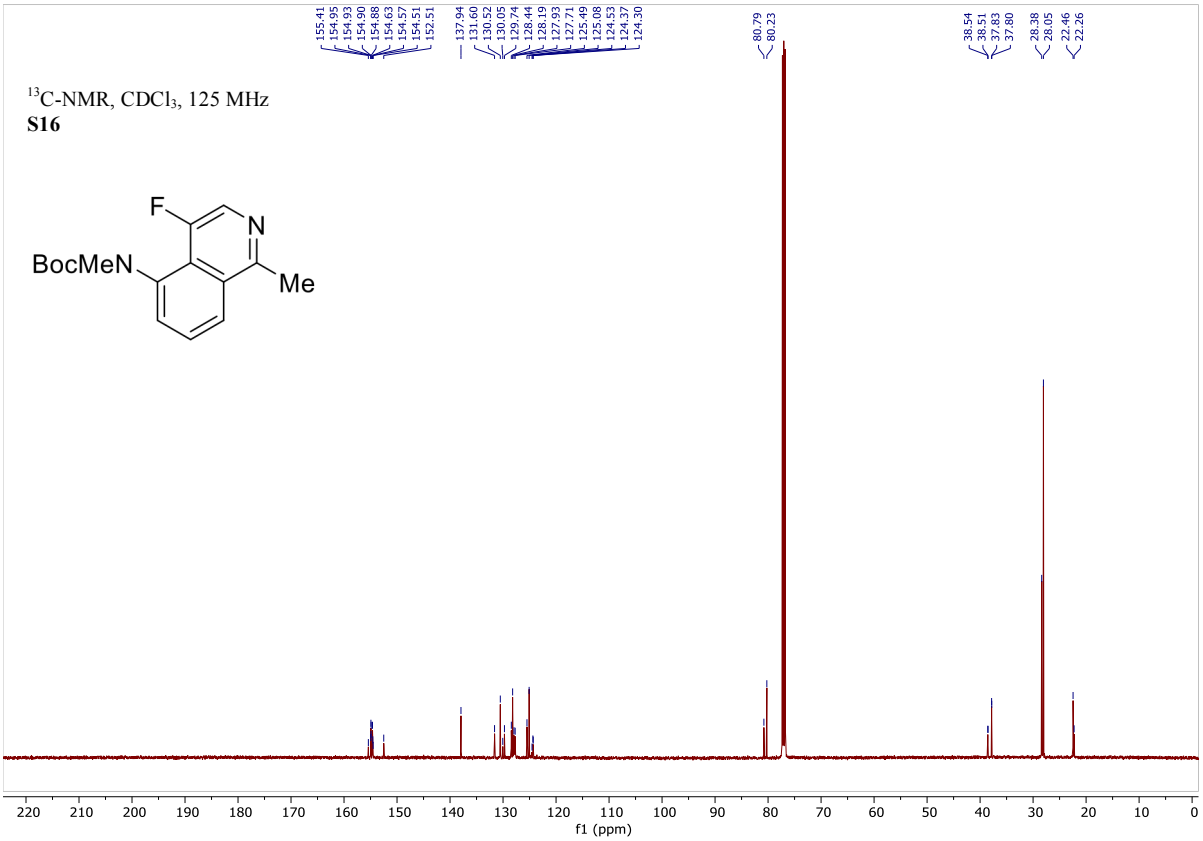


^{13}C-NMR, $CDCl_3$, 125 MHz
S15

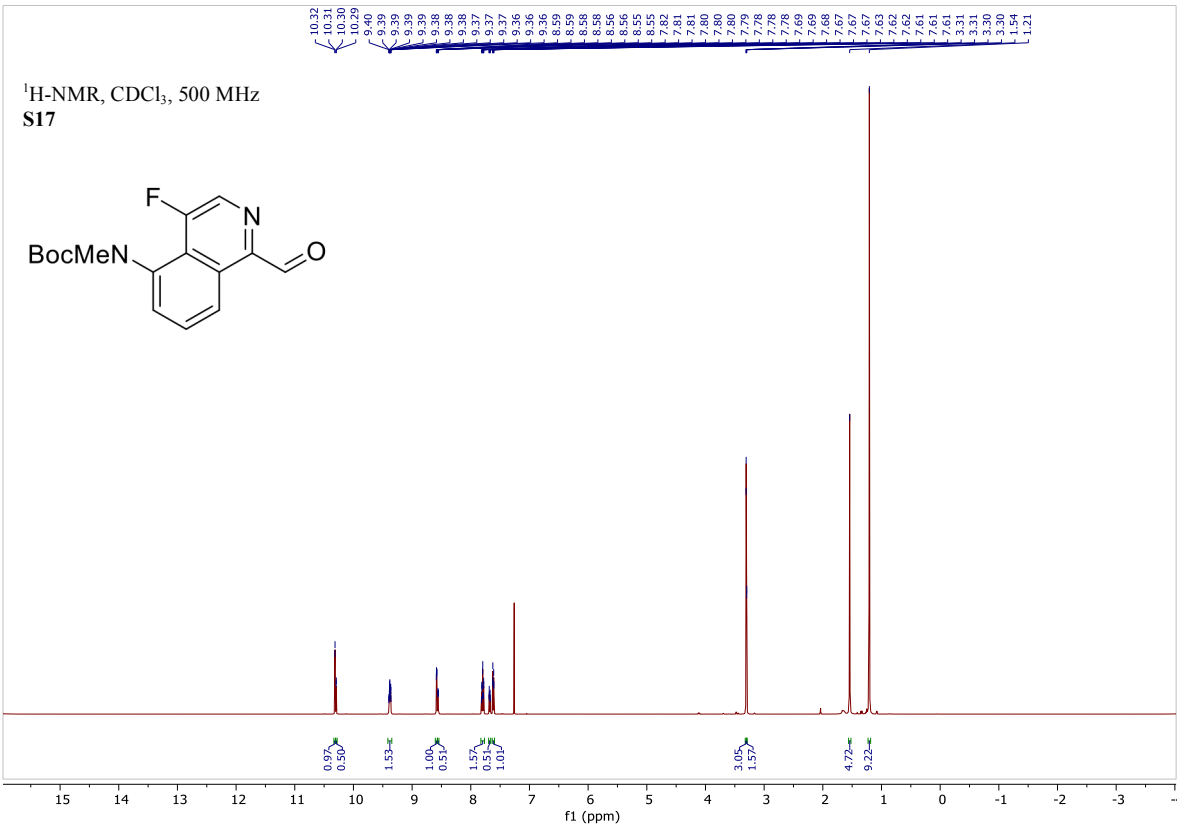




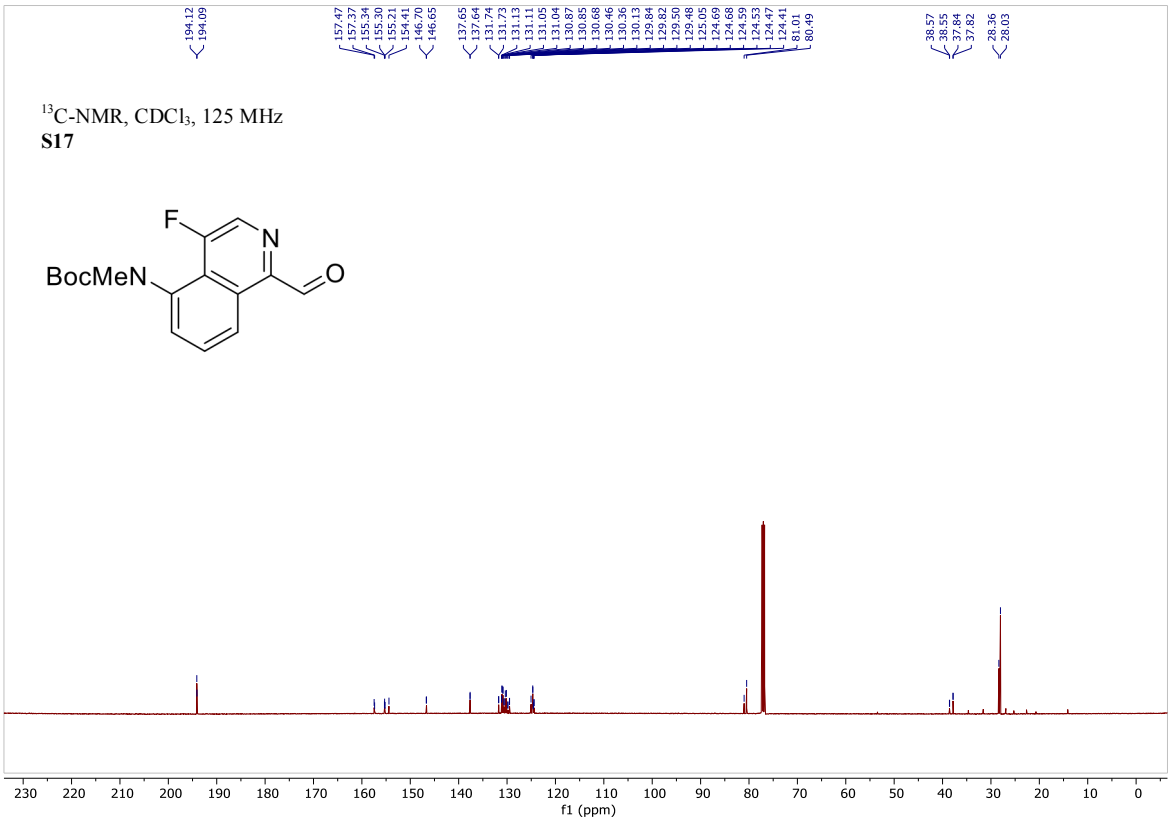
^{1}H-NMR, $CDCl_3$, 500 MHz
S16



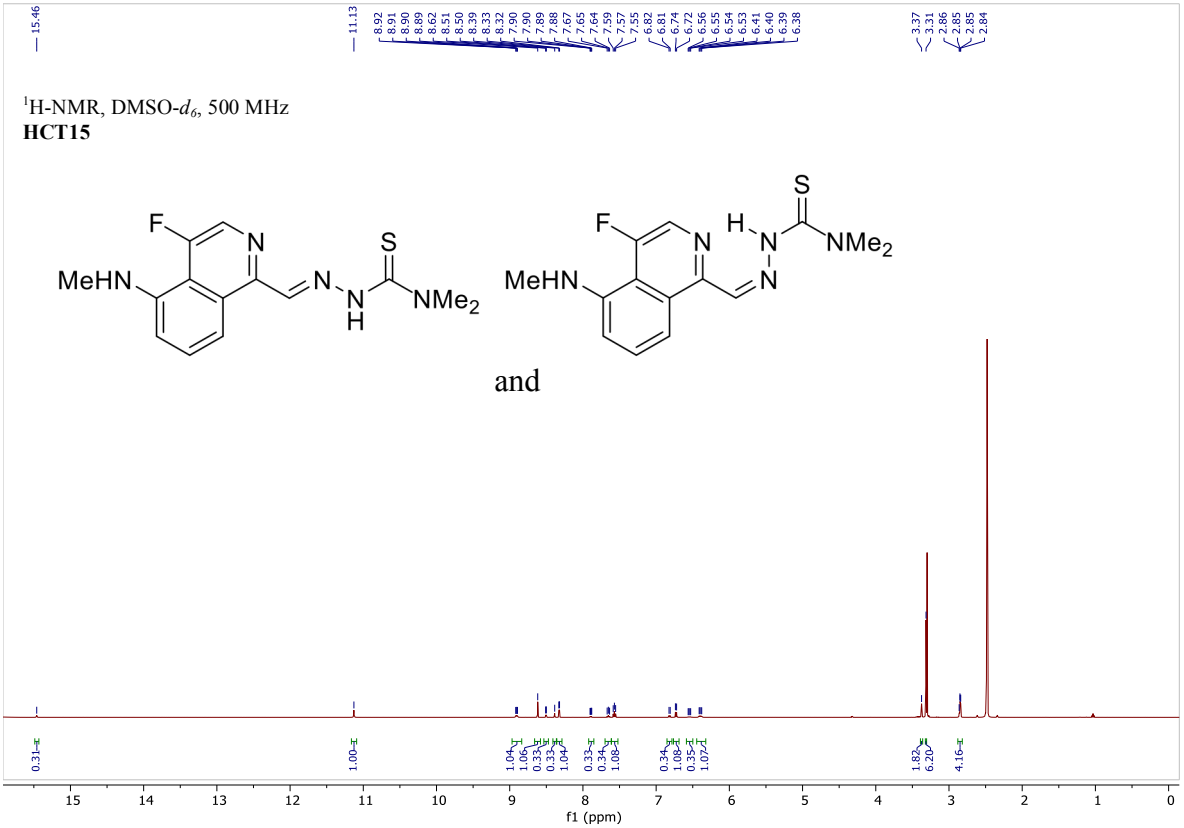
^{13}C-NMR, $CDCl_3$, 125 MHz
S16



^{1}H-NMR, $CDCl_3$, 500 MHz
S17

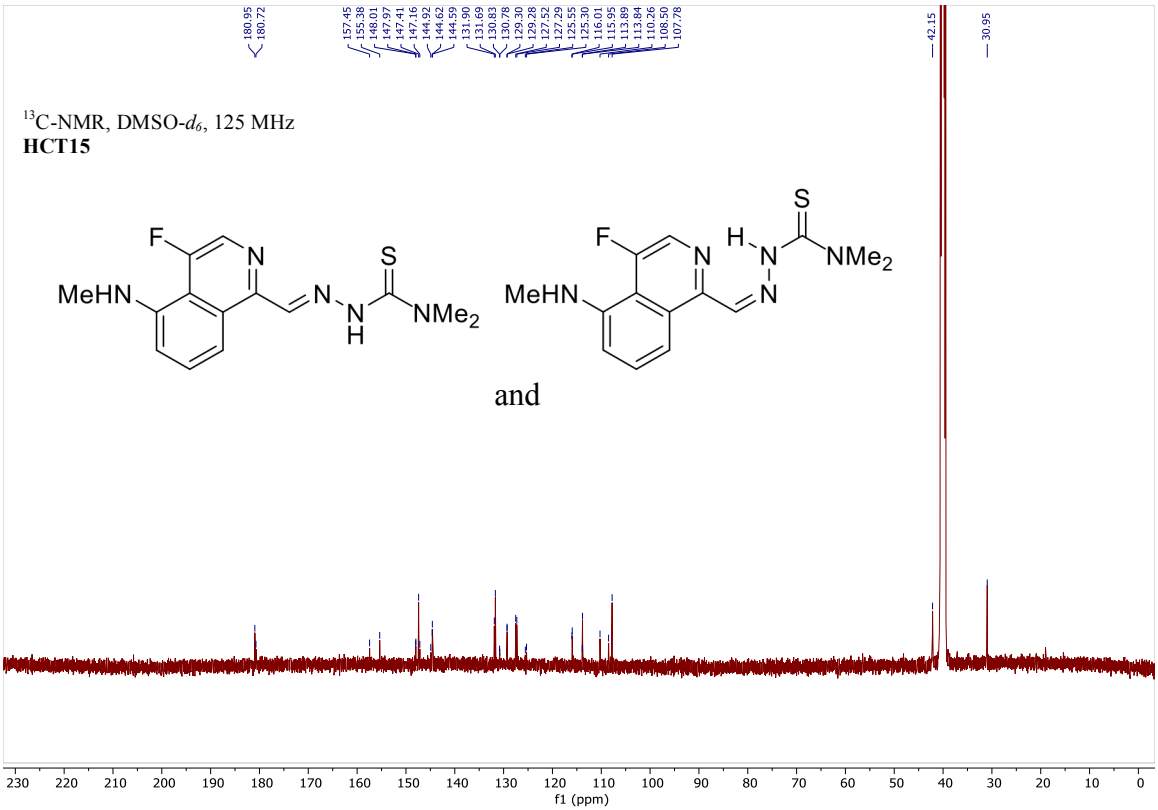


^{13}C-NMR, $CDCl_3$, 125 MHz
S17



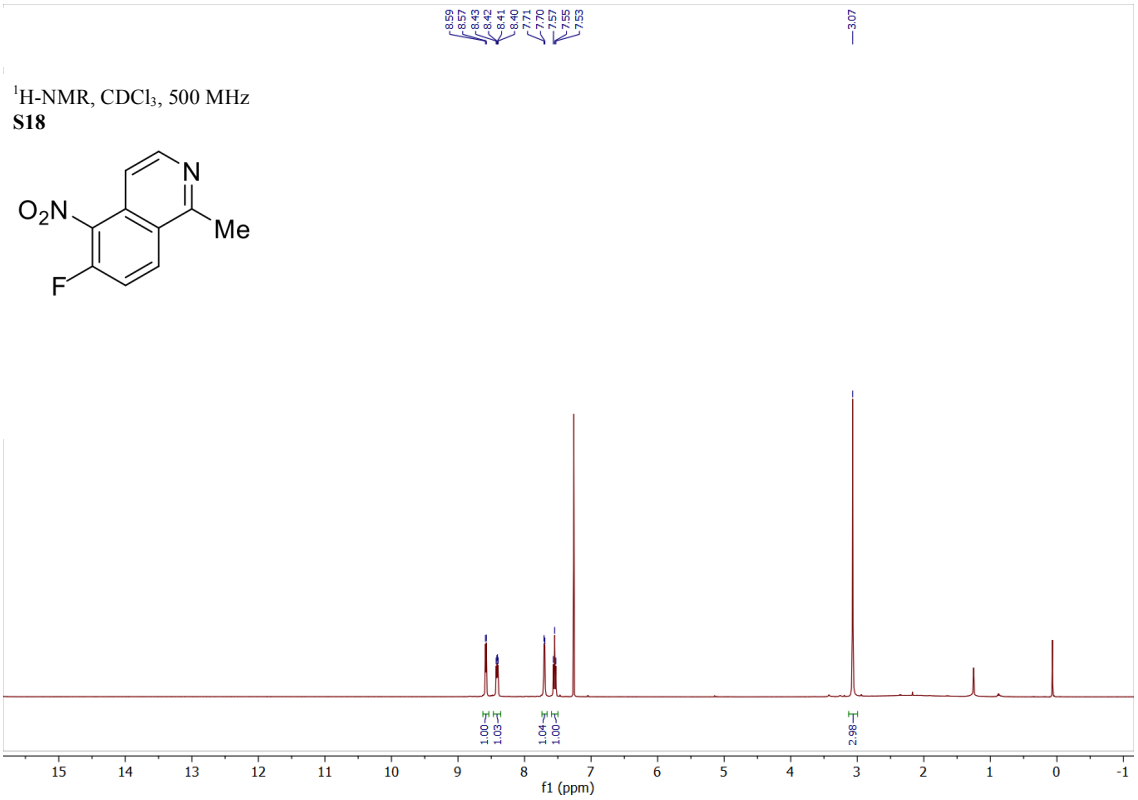
^{1}H-NMR, DMSO-d_6, 500 MHz
HCT15

and

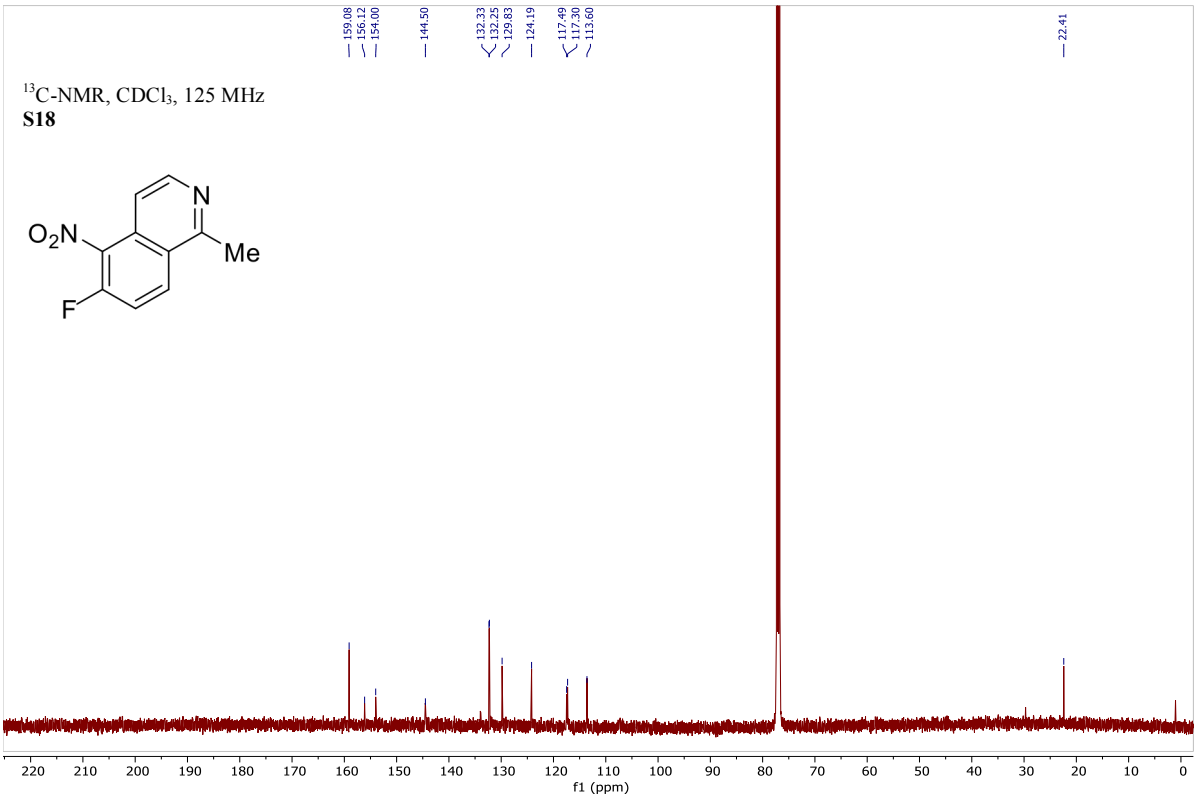


^{13}C-NMR, DMSO-d_6, 125 MHz
HCT15

and

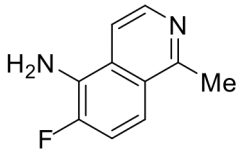


^{1}H-NMR, $CDCl_3$, 500 MHz
S18

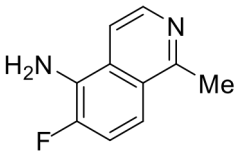


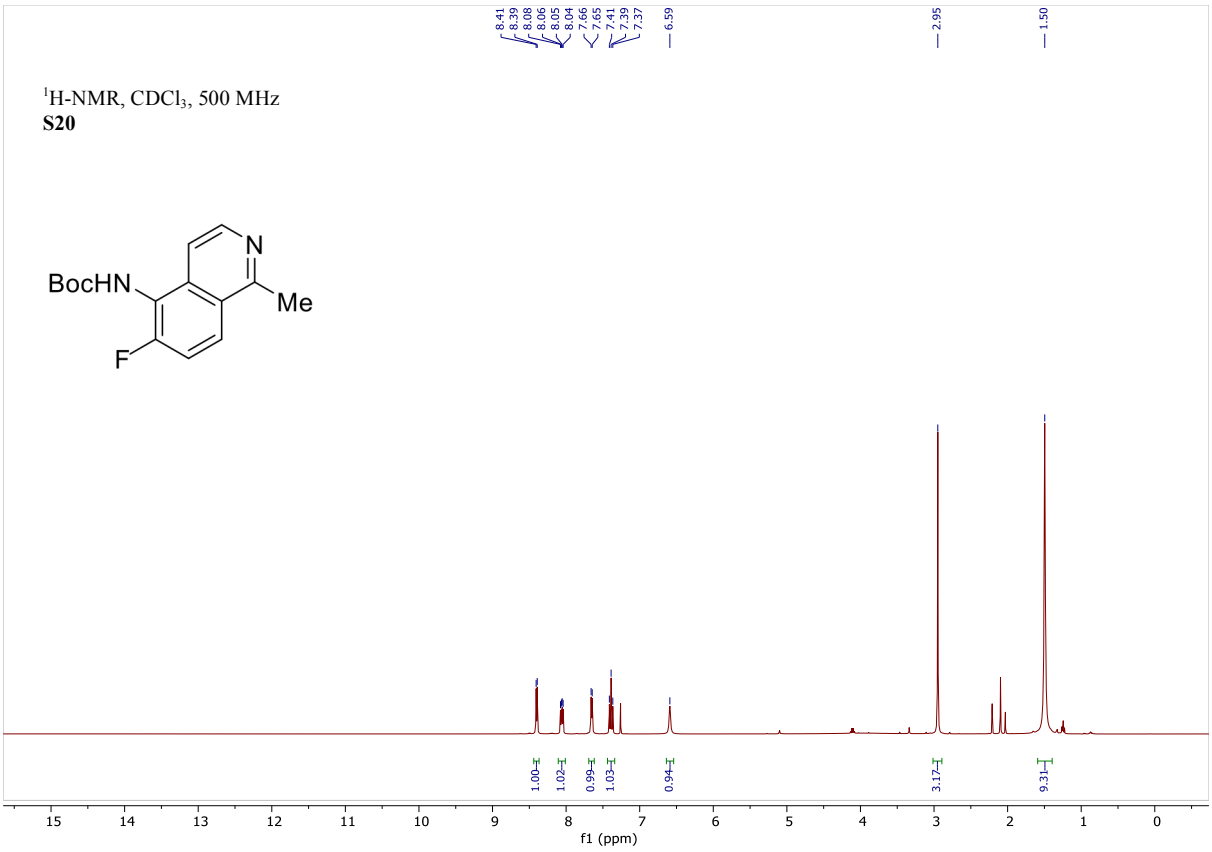
^{13}C-NMR, $CDCl_3$, 125 MHz
S18

^{1}H-NMR, $CDCl_3$, 500 MHz
S19

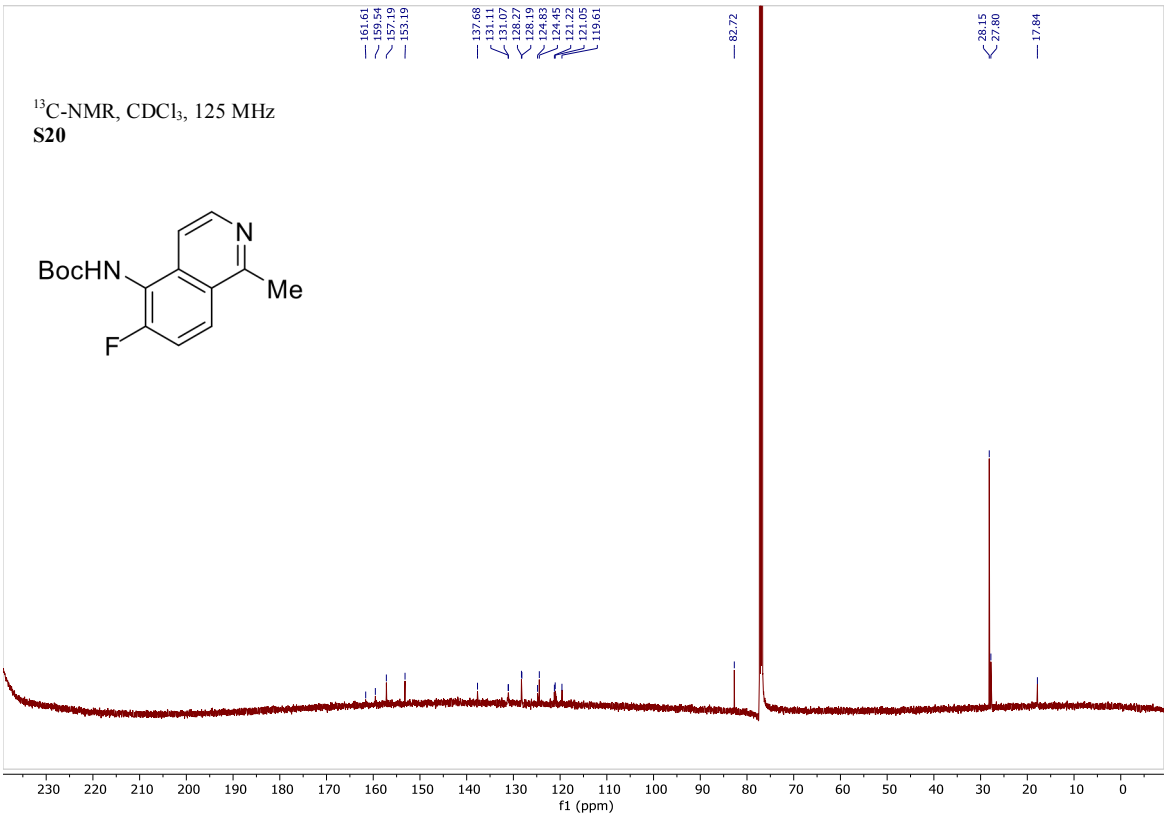


^{13}C-NMR, $CDCl_3$, 125 MHz
S19

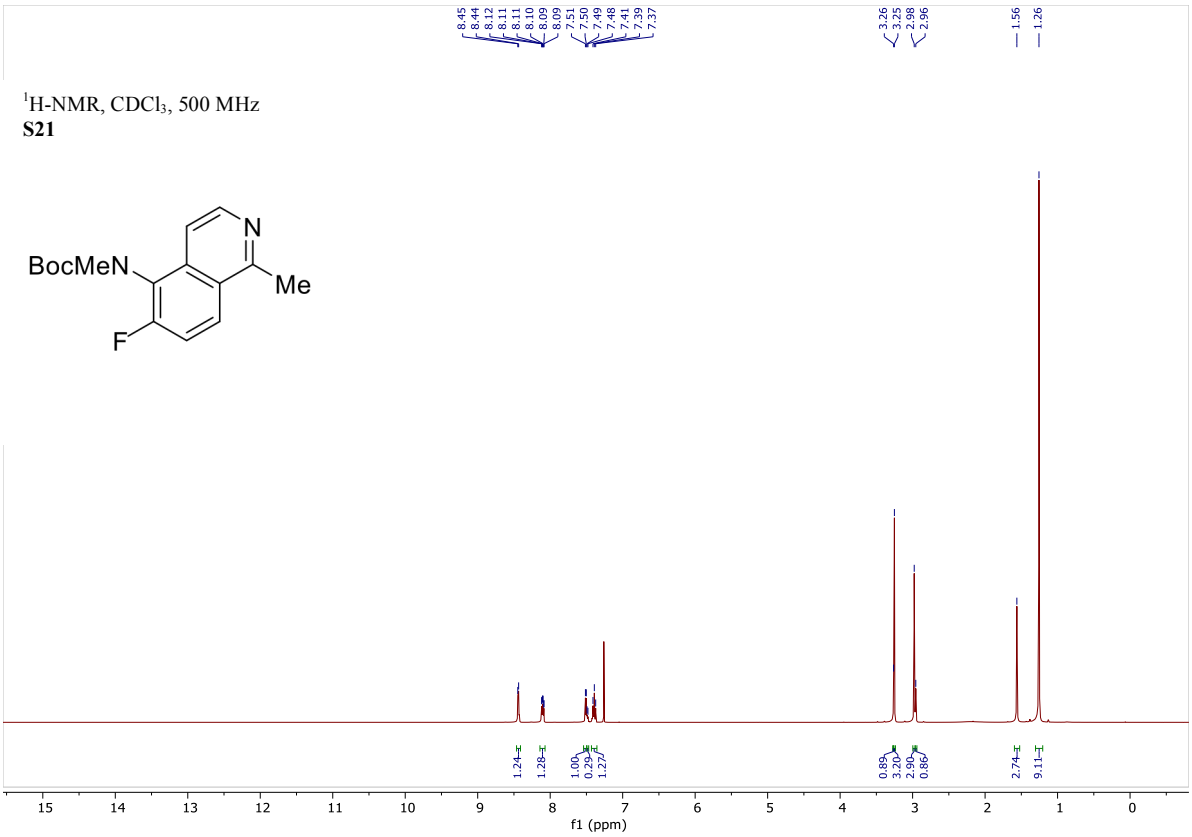




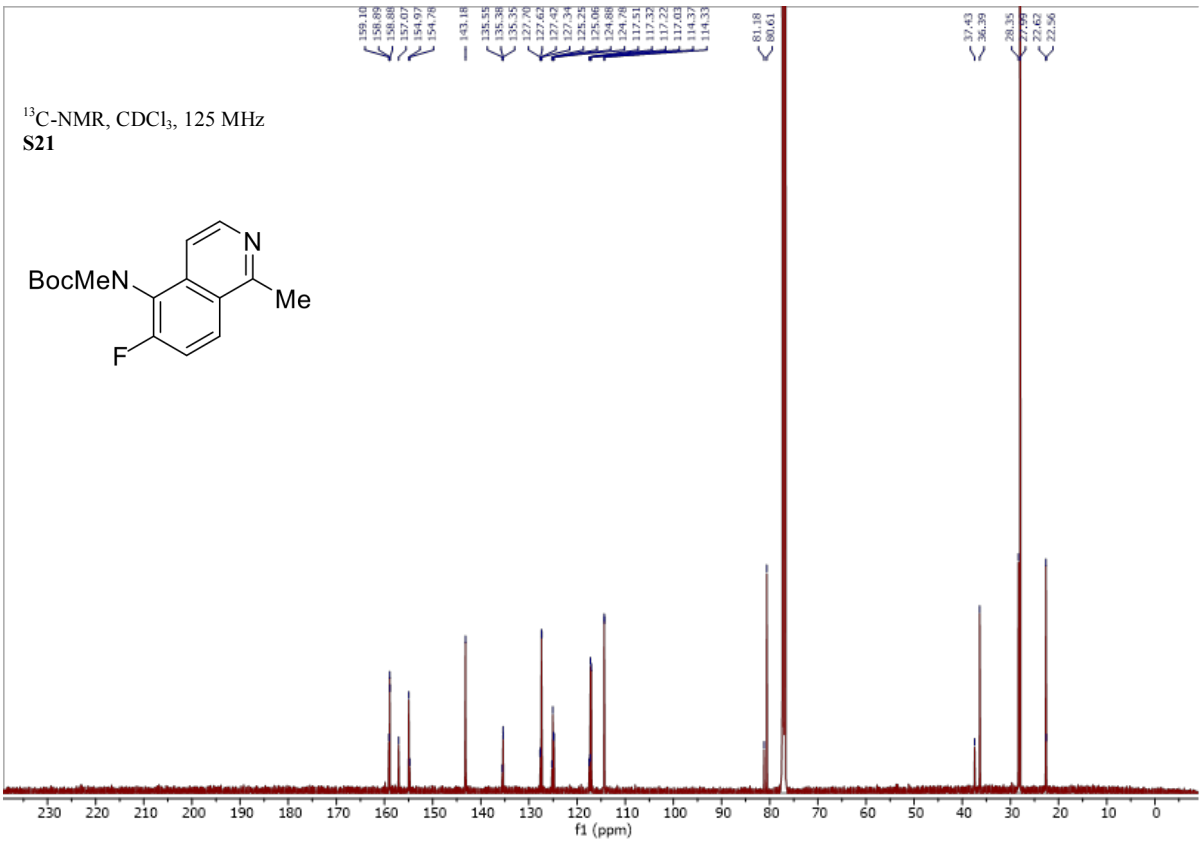
^{1}H-NMR, $CDCl_3$, 500 MHz
S20



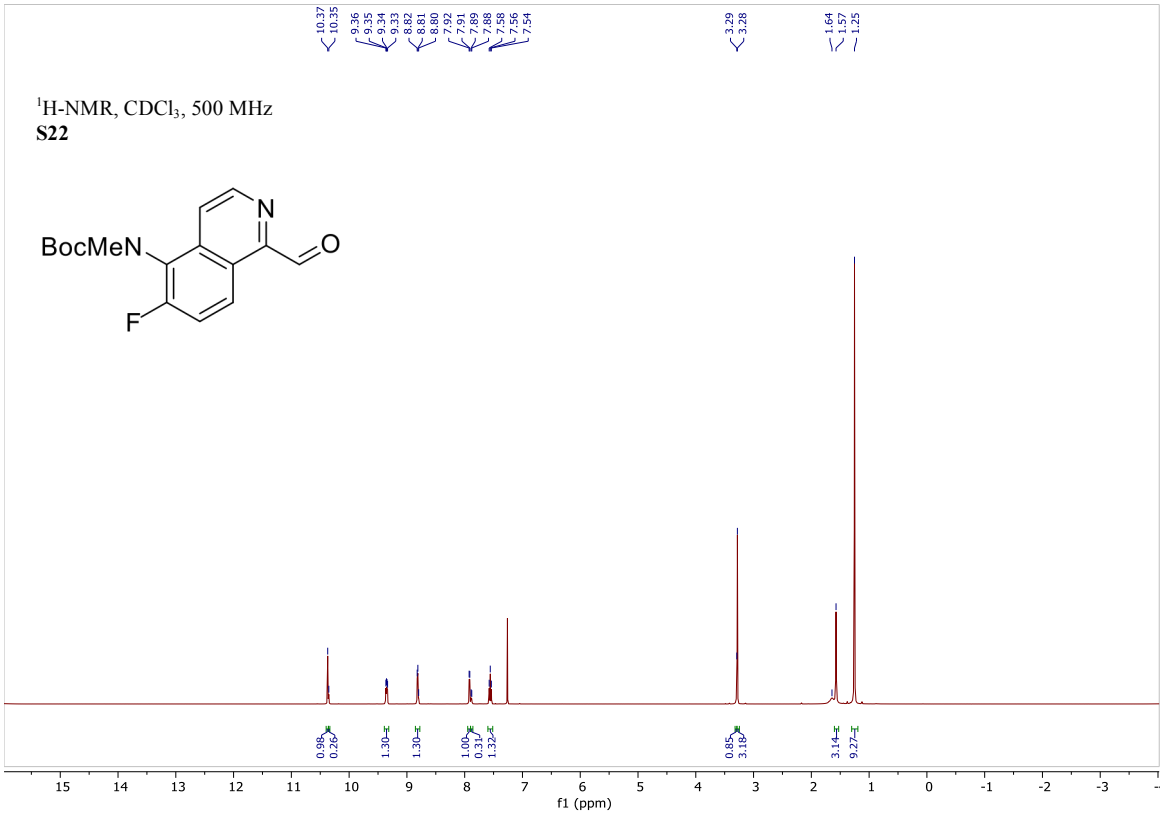
^{13}C-NMR, $CDCl_3$, 125 MHz
S20



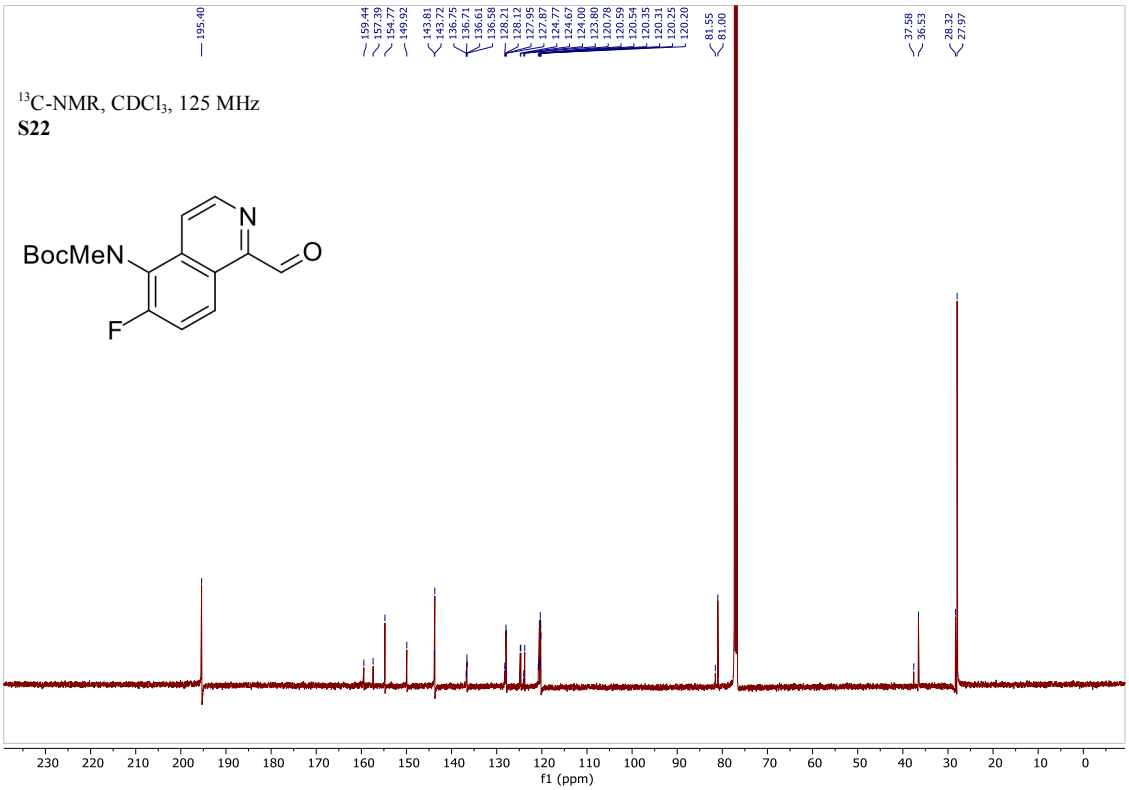
^{1}H-NMR, $CDCl_3$, 500 MHz
S21



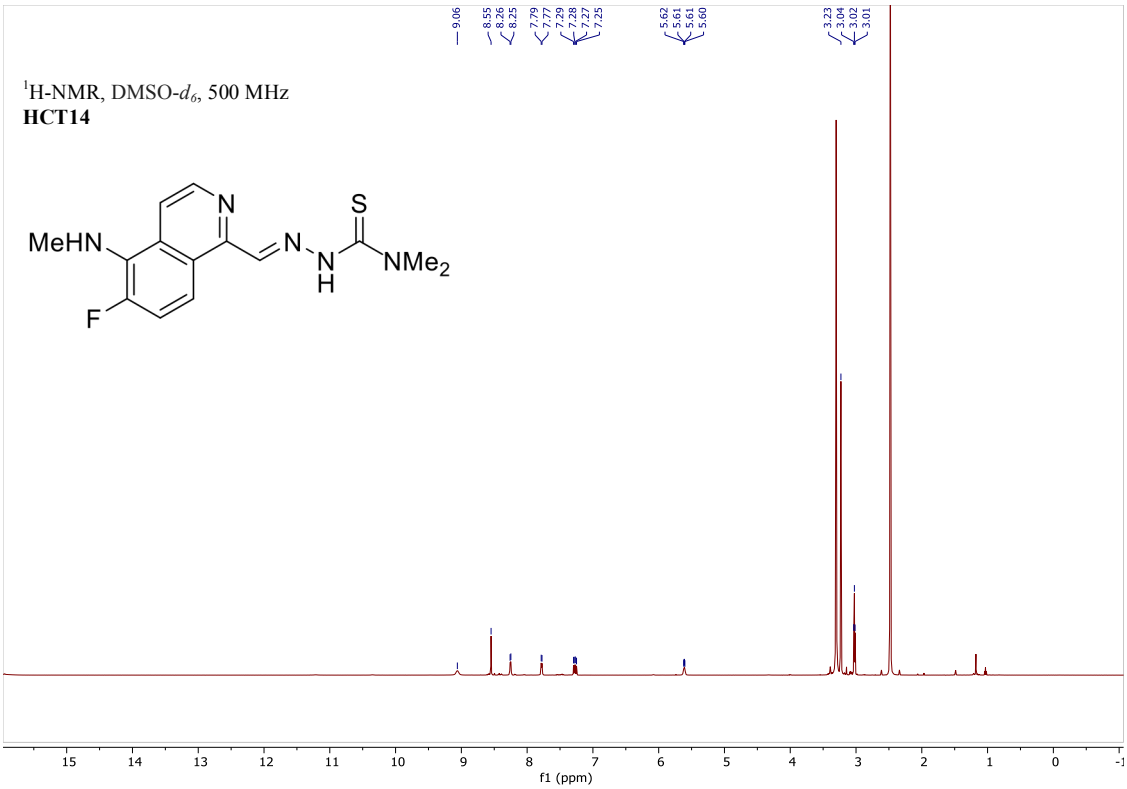
^{13}C-NMR, $CDCl_3$, 125 MHz
S21

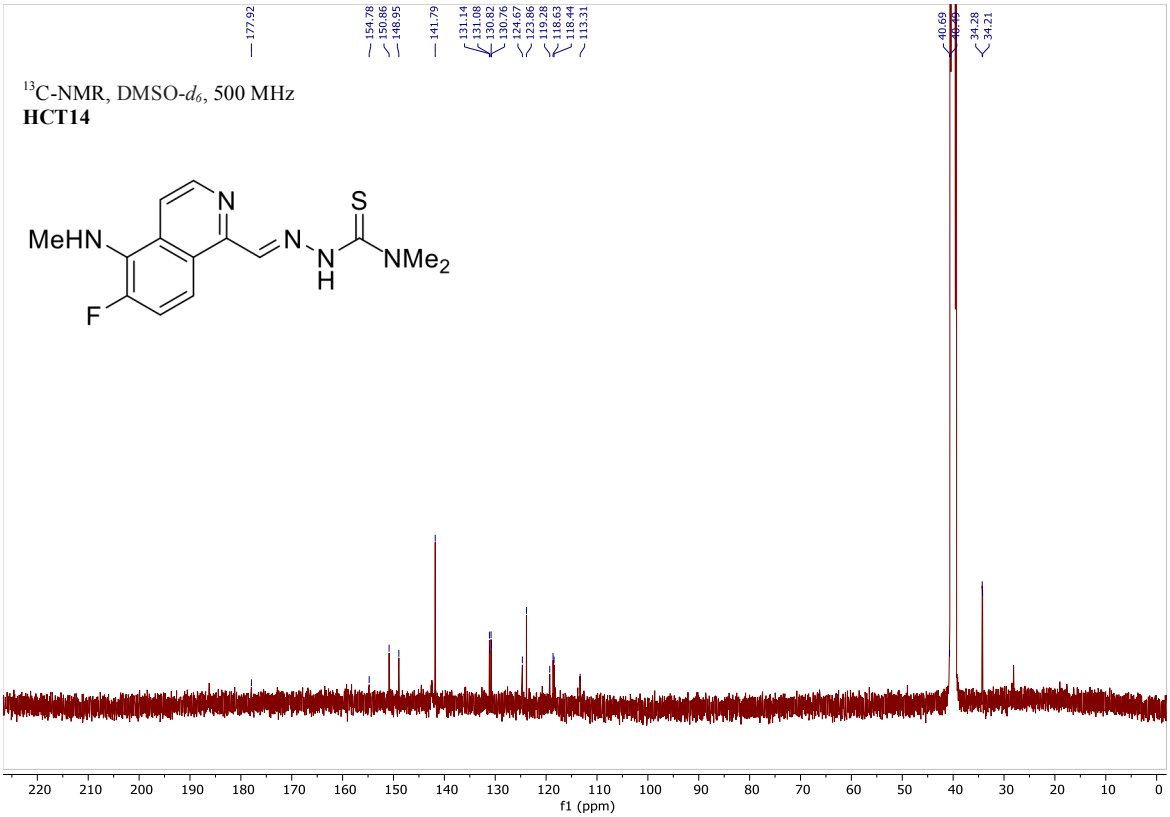


^{1}H-NMR, $CDCl_3$, 500 MHz
S22



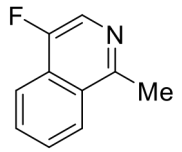
^{13}C-NMR, $CDCl_3$, 125 MHz
S22


9.06
8.55
8.26
8.25
7.79
7.77
7.29
7.28
7.27
7.25
5.62
5.61
5.61
5.60
3.23
3.04
3.02
3.01
^{1}H-NMR, DMSO-d_6, 500 MHz
HCT14
MeHN
N
S
N
N
H
NMe$_2$
F
f1 (ppm)

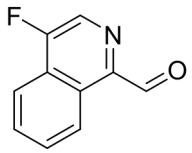

177.92
154.78
150.86
148.95
141.79
131.14
131.08
130.82
130.76
124.67
123.86
119.28
118.63
118.44
113.31
40.69
40.28
34.28
34.21
^{13}C-NMR, DMSO-d_6, 500 MHz
HCT14
MeHN
N
S
N
N
H
NMe$_2$
F
f1 (ppm)

Supplementary Figure 3: ^{19}FNMR of compounds **S9-S22** and **HCT2, 3, 7, 8, and 12 – 15**

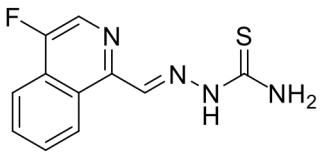
^{19}F-NMR, $CDCl_3$, 376 MHz
S9



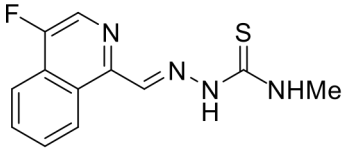
^{19}F-NMR, $CDCl_3$, 376 MHz
S10



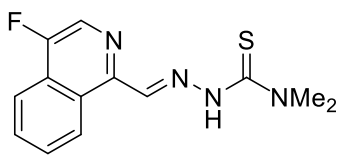
^{19}F-NMR, $CDCl_3$, 376 MHz
HCT2



^{19}F-NMR, $CDCl_3$, 376 MHz
HCT7



^{19}F-NMR, $CDCl_3$, 376 MHz
HCT12



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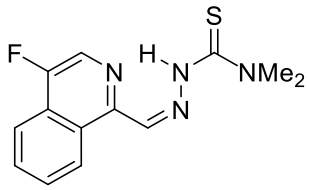
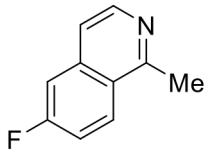
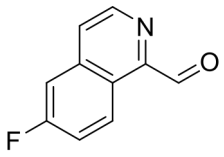


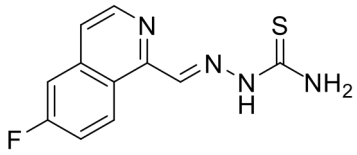
^{19}F-NMR, $CDCl_3$, 376 MHz
S11



^{19}F-NMR, $CDCl_3$, 376 MHz
S12

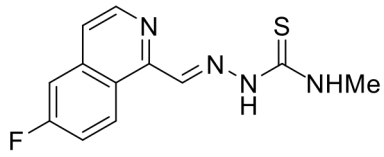


^{19}F-NMR, $CDCl_3$, 376 MHz
HCT3



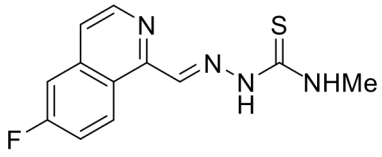
^{19}F-NMR, $CDCl_3$, 376 MHz

HCT8

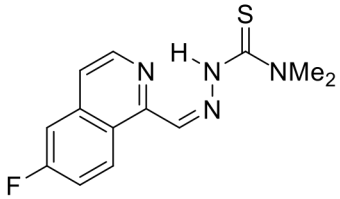


^{19}F-NMR, $CDCl_3$, 376 MHz

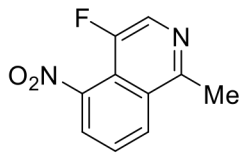
HCT13



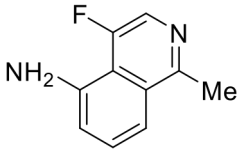
and



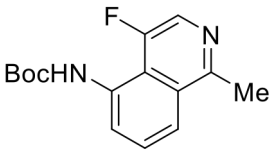
^{19}F-NMR, $CDCl_3$, 376 MHz
S13



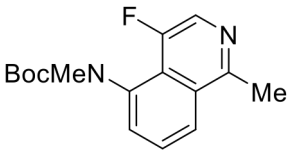
^{19}F-NMR, $CDCl_3$, 376 MHz
S14



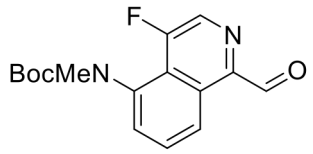
^{19}F-NMR, $CDCl_3$, 376 MHz
S15



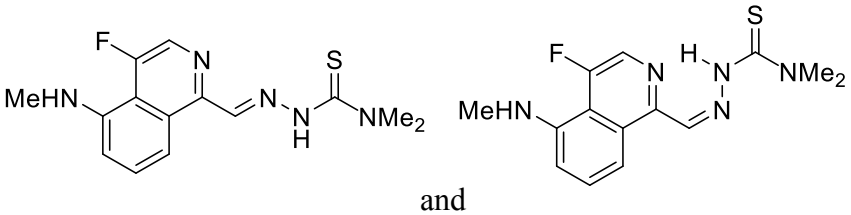
^{19}F-NMR, $CDCl_3$, 376 MHz
S16



^{19}F-NMR, $CDCl_3$, 376 MHz
S17

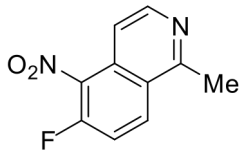


^{19}F-NMR, DMSO-d_6, 376 MHz
HCT15

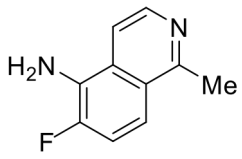


and

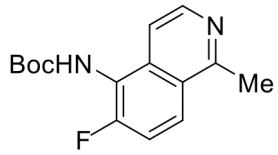
^{19}F-NMR, $CDCl_3$, 376 MHz
S18



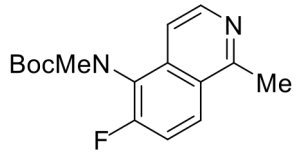
^{19}F-NMR, $CDCl_3$, 376 MHz
S19



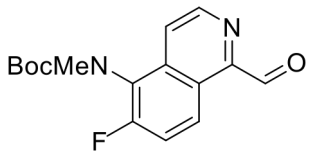
^{19}F-NMR, $CDCl_3$, 376 MHz
S20



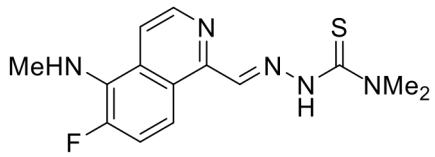
^{19}F-NMR, $CDCl_3$, 376 MHz
S21



^{19}F-NMR, $CDCl_3$, 376 MHz
S22



^{19}F-NMR, DMSO-d_6, 376 MHz
HCT14



Computation results

Compound **HCT 5**:

C	-3.616266	1.995109	0.074056
C	-2.246860	1.847170	0.057438
C	-1.675417	0.548405	0.017260
C	-2.540970	-0.594514	0.006757
C	-3.965248	-0.407748	-0.026209
C	-4.474297	0.880306	0.018638
H	-4.050148	2.990438	0.111332
H	-1.620795	2.729523	0.088371
C	-0.252062	0.296185	-0.001722
C	-1.951458	-1.882038	0.046379
C	-0.581464	-2.000814	0.054521
H	-0.101379	-2.974924	0.095020
C	0.706948	1.404333	-0.046096
H	0.315838	2.413736	-0.090023
N	0.251819	-0.940361	0.014922
H	-2.563600	-2.775089	0.109945
H	-5.551249	1.031300	0.002758
N	2.005736	1.375882	-0.051458
N	2.671162	0.209094	-0.009805
H	2.143717	-0.669313	0.016296
C	4.048883	0.194136	-0.013030
S	4.875678	-1.265130	0.031847
N	4.634334	1.406221	-0.053303
N	-4.808174	-1.521627	-0.040451
H	-5.779711	-1.299923	-0.222294
H	-4.502173	-2.288875	-0.626460
H	4.063646	2.241296	-0.081765
H	5.640146	1.456264	-0.060013

Compound **HCT 11**:

C	4.482243	-1.822334	0.314330
C	3.118354	-1.629852	0.273406
C	2.569461	-0.336466	0.061806
C	3.472208	0.761761	-0.112241
C	4.872586	0.532549	-0.064259
C	5.368819	-0.733100	0.145499
H	4.881038	-2.819553	0.477019
H	2.467063	-2.486125	0.402255
C	1.153890	-0.048698	0.005912
C	2.930382	2.053928	-0.330072
C	1.566515	2.210357	-0.370328
H	1.114257	3.184668	-0.535938
C	0.159434	-1.108222	0.197195
H	0.520278	-2.105530	0.421963
N	0.696973	1.187036	-0.209138
H	5.543881	1.377073	-0.197181
H	3.591535	2.905256	-0.464316
H	6.441595	-0.900955	0.181072
N	-1.138619	-1.050760	0.164317
N	-1.762546	0.112071	-0.097542
H	-1.192887	0.964361	-0.138076
C	-3.134287	0.264259	0.055029
S	-3.707935	1.810902	0.397673
N	-3.914251	-0.833736	-0.096719
C	-3.539108	-1.999789	-0.903060
H	-4.405172	-2.284400	-1.510928
H	-2.713861	-1.758187	-1.570982
H	-3.242227	-2.846274	-0.276164
C	-5.321836	-0.777712	0.286891
H	-5.935576	-0.335213	-0.508454
H	-5.664179	-1.798397	0.483579
H	-5.441648	-0.173497	1.186308

Compound **HCT 12**:

C	4.138288	-2.271306	0.307209
C	2.788377	-1.994502	0.262845
C	2.320594	-0.664910	0.088440
C	3.301673	0.368676	-0.042177
C	4.684968	0.065000	0.006280
C	5.094429	-1.237179	0.179371
H	4.471809	-3.296267	0.441397
H	2.083728	-2.811564	0.360525
C	0.926586	-0.281973	0.030570
C	2.827599	1.688780	-0.220546
C	1.486299	1.962590	-0.268646
H	1.130434	2.979132	-0.406324
C	-0.136434	-1.279162	0.177365
H	0.158452	-2.304957	0.368379
N	0.558810	0.988631	-0.146403
H	5.401094	0.872988	-0.095376
H	6.153595	-1.474993	0.217369
N	-1.427252	-1.137403	0.137202
N	-1.974277	0.071584	-0.087764
H	-1.356374	0.888986	-0.090055
C	-3.335102	0.305222	0.064847
S	-3.811143	1.871110	0.463473
N	-4.181428	-0.734582	-0.132187
C	-3.874605	-1.890490	-0.981034
H	-4.752182	-2.096115	-1.603968
H	-3.030703	-1.676244	-1.634871
H	-3.636651	-2.777333	-0.385658
C	-5.585614	-0.603389	0.245991
H	-6.163275	-0.090460	-0.533842
H	-5.994224	-1.606946	0.399165
H	-5.673404	-0.029544	1.168728

F	3.725852	2.684869	-0.346675

Compound **HCT 13**:

C	4.157669	-1.658457	0.280051
C	2.791201	-1.496478	0.244102
C	2.205391	-0.217506	0.038185
C	3.077390	0.906929	-0.135936
C	4.483116	0.724805	-0.095809
C	4.987267	-0.532961	0.108710
H	4.614862	-2.629612	0.436100
H	2.166606	-2.371790	0.373589
C	0.782640	0.027482	-0.011213
C	2.496501	2.183462	-0.346859
C	1.128370	2.297705	-0.380130
H	0.648036	3.259481	-0.539956
C	-0.179407	-1.061268	0.179706
H	0.209739	-2.049453	0.397425
N	0.288317	1.250139	-0.219640
H	5.155621	1.566329	-0.225179
H	3.130826	3.054544	-0.480992
N	-1.478950	-1.039865	0.153251
N	-2.137943	0.103925	-0.099370
H	-1.594655	0.973234	-0.139438
C	-3.513579	0.214816	0.063846
S	-4.128014	1.741395	0.422143
N	-4.261643	-0.904288	-0.090452
C	-3.857306	-2.054024	-0.906408
H	-4.718455	-2.360587	-1.510376
H	-3.044141	-1.783951	-1.578291
H	-3.531408	-2.894845	-0.286438
C	-5.668133	-0.891044	0.301913
H	-6.298091	-0.455881	-0.484616
H	-5.981314	-1.922803	0.488500

H	-5.798731	-0.300902	1.209195
F	6.319350	-0.719580	0.148747

Deprotonated Compound **HCT 5**:

C	3.091563	-2.309202	-0.106423
C	1.824367	-1.765817	-0.108906
C	1.636090	-0.359896	-0.045146
C	2.791179	0.485704	-0.009821
C	4.096511	-0.106633	0.039499
C	4.229500	-1.482839	-0.012650
H	3.220845	-3.387789	-0.159366
H	0.966673	-2.423354	-0.173664
C	0.319423	0.275035	-0.023867
C	2.596131	1.890169	-0.026530
C	1.300934	2.369761	-0.053668
H	1.125380	3.446700	-0.088291
C	-0.877338	-0.531686	0.022920
H	-0.788368	-1.617036	0.109808
N	0.194994	1.613159	-0.033946
H	3.433986	2.578711	-0.074910
N	-2.082867	-0.016138	-0.019191
N	-3.046446	-0.934739	0.055256
C	-4.315539	-0.458297	0.026188
N	-5.217705	-1.518735	0.044744
S	-4.943745	1.128243	-0.042575
H	5.223388	-1.927983	0.021664
H	-6.140465	-1.276419	0.377496
H	-4.822861	-2.383254	0.400486
N	5.231969	0.733605	0.092514
H	5.098999	1.531012	0.706602
H	6.065795	0.229666	0.376143

Deprotonated Compound **HCT 11**:

C	-3.944429	-2.292727	-0.371567
C	-2.720343	-1.658771	-0.269739
C	-2.620791	-0.265521	-0.026004
C	-3.838859	0.481031	0.094491
C	-5.084089	-0.195604	-0.010753
C	-5.139691	-1.553595	-0.236313
H	-3.986239	-3.363042	-0.559616
H	-1.816873	-2.245695	-0.387746
C	-1.353672	0.453974	0.100345
C	-3.752678	1.879121	0.307143
C	-2.498111	2.449932	0.382657
H	-2.401640	3.526708	0.534892
C	-0.102160	-0.258630	0.030707
H	-0.110714	-1.350527	-0.018341
N	-1.335609	1.784123	0.293171
H	-5.998892	0.386308	0.087330
H	-4.655339	2.478324	0.401154
N	1.062561	0.348624	0.035245
N	2.092277	-0.490441	0.020819
C	3.321060	0.072724	-0.124126
S	3.697125	1.689888	-0.541701
N	4.339078	-0.869115	0.051075
C	5.735372	-0.491436	0.025958
H	6.095671	-0.163279	1.016723
H	6.334667	-1.358839	-0.284705
H	5.878233	0.334702	-0.670603
C	4.075907	-2.151591	0.683670
H	4.308902	-2.127955	1.763236
H	3.023426	-2.396187	0.556677
H	4.703089	-2.928108	0.222806
H	-6.101527	-2.056398	-0.315594

Deprotonated Compound **HCT 12**:

C	3.525369	2.659035	-0.356856
C	2.337428	1.958126	-0.259897
C	2.314822	0.556073	-0.053038
C	3.580698	-0.111018	0.034528
C	4.791119	0.622114	-0.064509
C	4.762548	1.986354	-0.254475
H	3.505641	3.734481	-0.516110
H	1.401765	2.496964	-0.351751
C	1.094867	-0.241956	0.066377
C	3.552962	-1.509172	0.211787
C	2.358300	-2.180496	0.291372
H	2.359105	-3.262927	0.420158
C	-0.197934	0.396037	0.021188
H	-0.252899	1.487646	-0.002936
N	1.161459	-1.574191	0.228493
H	5.730501	0.083314	0.009530
N	-1.323409	-0.279564	0.018634
N	-2.402587	0.495451	0.029604
C	-3.595316	-0.139162	-0.120797
S	-3.873264	-1.767995	-0.568758
N	-4.668175	0.734357	0.078450
C	-6.038717	0.271568	0.053574
H	-6.371442	-0.096918	1.039756
H	-6.692405	1.105978	-0.237015
H	-6.134947	-0.548402	-0.658094
C	-4.480558	2.017983	0.735213
H	-4.702907	1.958355	1.815616
H	-3.446567	2.330787	0.606215
H	-5.158773	2.762566	0.294454
H	5.692374	2.545986	-0.330755
F	4.737583	-2.183911	0.299775

Deprotonated Compound **HCT 13**:

C	-3.715872	-1.960146	-0.304914
C	-2.457984	-1.392745	-0.220322
C	-2.272091	-0.006699	0.009286
C	-3.442069	0.815677	0.134279
C	-4.730011	0.220924	0.049389
C	-4.837959	-1.128913	-0.161691
H	-3.857429	-3.021448	-0.481904
H	-1.594317	-2.035389	-0.342485
C	-0.961105	0.632687	0.116258
C	-3.266958	2.206307	0.330687
C	-1.976572	2.697399	0.386107
H	-1.813618	3.768027	0.524512
C	0.241397	-0.155937	0.045557
H	0.166920	-1.245879	0.009426
N	-0.858687	1.962519	0.292965
H	-5.625080	0.828366	0.145654
H	-4.128410	2.862269	0.427388
N	1.442118	0.379772	0.034507
F	-6.070508	-1.696641	-0.243758
N	2.417770	-0.518233	0.022584
C	3.678449	-0.029691	-0.137807
S	4.142792	1.551768	-0.594987
N	4.640239	-1.022970	0.056958
C	6.055771	-0.726263	0.007288
H	6.439477	-0.364381	0.976835
H	6.602195	-1.642190	-0.257033
H	6.242166	0.050859	-0.734053
C	4.309273	-2.270213	0.727886
H	4.556875	-2.230772	1.803487
H	3.242640	-2.454800	0.618838
H	4.882787	-3.095123	0.281852

Copper(II)-complex **HCT 5**:

C	4.247554	2.249825	0.277392
C	2.879370	2.090894	0.216320
C	2.340682	0.794130	0.028866
C	3.222268	-0.338791	-0.092974
C	4.645199	-0.130155	-0.080918
C	5.123005	1.159225	0.120958
H	4.667642	3.239484	0.428810
H	2.234276	2.954087	0.322706
C	0.936588	0.535879	-0.032659
C	2.649019	-1.627419	-0.199486
C	1.280372	-1.775342	-0.223429
H	0.797800	-2.742056	-0.310123
C	-0.073121	1.588088	0.015018
H	0.174634	2.642632	0.072276
N	0.448986	-0.711796	-0.151355
H	3.270443	-2.514753	-0.231394
N	-1.319789	1.225431	-0.044389
N	-2.314632	2.117231	-0.036133
Cu	-1.582911	-0.758432	-0.146524
O	-1.762563	-2.797632	-0.582577
H	-2.073981	-3.163298	0.267901
H	-2.428906	-3.031997	-1.251719
O	-1.964021	-1.766350	1.946100
H	-1.333987	-1.632819	2.672307
H	-2.791629	-1.332921	2.219417
C	-3.514375	1.552252	-0.150051
N	-4.570820	2.379277	-0.153321
S	-3.841242	-0.182895	-0.290073
H	6.195819	1.330719	0.146621
H	-5.508712	2.030772	-0.283979
H	-4.417228	3.378810	-0.113609
N	5.505295	-1.210451	-0.200187
H	5.241714	-1.940344	-0.849303

H	6.486438	-0.974964	-0.284268

Copper(II)-complex **HCT 11**:

C	4.725455	2.467471	-0.161740
C	3.384925	2.155036	-0.139898
C	2.964333	0.805129	0.004605
C	3.960009	-0.223192	0.125477
C	5.332773	0.134293	0.099497
C	5.706290	1.451558	-0.040813
H	5.036794	3.501518	-0.271981
H	2.654286	2.950246	-0.234775
C	1.593267	0.403672	0.037977
C	3.534098	-1.567639	0.271265
C	2.190798	-1.856371	0.288039
H	1.809304	-2.863869	0.409933
C	0.479930	1.337405	-0.048871
H	0.613184	2.410838	-0.130806
N	1.247758	-0.890604	0.168184
H	6.080776	-0.647628	0.192967
H	4.265042	-2.363156	0.373599
N	-0.725405	0.843372	0.002172
N	-1.803367	1.617532	-0.040915
C	-2.955770	0.936366	0.064834
S	-3.068793	-0.829249	0.236897
N	-4.085613	1.659958	0.040769
C	-5.399975	1.029634	0.202429
H	-5.482129	0.539560	1.178086
H	-6.166781	1.800210	0.128277
H	-5.572488	0.284250	-0.579881
C	-3.989382	3.125137	-0.067957
H	-3.500203	3.544929	0.816287
H	-3.405175	3.401855	-0.948543
H	-4.995049	3.535124	-0.155967

Cu	-0.765383	-1.155090	0.143657
O	-0.995029	-2.277227	-1.911015
H	-0.363462	-2.099179	-2.626204
H	-1.855603	-1.940293	-2.216164
O	-0.730822	-3.188451	0.661970
H	-0.989390	-3.621392	-0.174155
H	-1.377906	-3.464213	1.334065
H	6.758304	1.719430	-0.059330

Copper(II)-complex **HCT 12**:

C	4.376459	2.854438	-0.169958
C	3.055860	2.461950	-0.145164
C	2.716265	1.088975	-0.017911
C	3.781563	0.133772	0.081049
C	5.131344	0.559981	0.053637
C	5.419262	1.901160	-0.069780
H	4.622451	3.907242	-0.266898
H	2.277767	3.212490	-0.224116
C	1.371577	0.599290	0.017935
C	3.423553	-1.229291	0.208979
C	2.109830	-1.626093	0.233232
H	1.822822	-2.664450	0.346456
C	0.199468	1.459151	-0.050089
H	0.263921	2.539967	-0.118946
N	1.114283	-0.715123	0.133593
H	5.918914	-0.180910	0.131791
N	-0.971315	0.888765	0.001438
N	-2.097315	1.593848	-0.026263
C	-3.202525	0.840537	0.082033
S	-3.201139	-0.931283	0.239782
N	-4.377184	1.489439	0.073641
C	-5.646758	0.774181	0.239956
H	-5.692253	0.277407	1.214683

H	-6.462581	1.493215	0.171385
H	-5.774280	0.021335	-0.543796
C	-4.376050	2.958792	-0.019285
H	-3.905577	3.399532	0.864931
H	-3.819880	3.281774	-0.902323
H	-5.406714	3.304475	-0.092880
Cu	-0.885322	-1.109135	0.118716
O	-1.063367	-2.222660	-1.944379
H	-0.458382	-2.008811	-2.672626
H	-1.949604	-1.943773	-2.234488
O	-0.700193	-3.138883	0.610645
H	-0.943170	-3.582540	-0.224577
H	-1.306809	-3.471777	1.294501
H	6.452282	2.234245	-0.090612
F	4.391528	-2.146800	0.310384

Copper(II)-complex **HCT 13**:

C	-4.564179	-2.131724	-0.148005
C	-3.211555	-1.891482	-0.127752
C	-2.711202	-0.566634	0.013127
C	-3.646360	0.519034	0.133542
C	-5.035633	0.251628	0.110920
C	-5.461524	-1.046698	-0.026855
H	-4.966477	-3.133187	-0.253998
H	-2.531178	-2.729702	-0.221921
C	-1.319974	-0.249930	0.042659
C	-3.138840	1.836521	0.276121
C	-1.780996	2.041274	0.289631
H	-1.340237	3.024695	0.408851
C	-0.265511	-1.249450	-0.044740
H	-0.462064	-2.313265	-0.124657
N	-0.895953	1.021838	0.169597
H	-5.760289	1.053449	0.201465

H	-3.819504	2.675083	0.378482
N	0.967627	-0.828308	0.003703
F	-6.768927	-1.314557	-0.050091
N	1.996045	-1.665648	-0.039841
C	3.188489	-1.054899	0.064011
S	3.407966	0.700275	0.234406
N	4.271630	-1.845817	0.039513
C	5.622323	-1.295972	0.197418
H	5.734423	-0.806892	1.170528
H	6.340658	-2.112205	0.127131
H	5.839205	-0.566458	-0.588818
C	4.087065	-3.302787	-0.068957
H	3.574568	-3.691931	0.816023
H	3.486425	-3.543803	-0.948931
H	5.066116	-3.772528	-0.157900
Cu	1.128714	1.165201	0.141601
O	1.425136	2.272446	-1.911239
H	0.784430	2.139743	-2.628152
H	2.264124	1.887526	-2.219598
O	1.215587	3.196152	0.660633
H	1.502436	3.614499	-0.173696
H	1.873703	3.434266	1.336421

Copper(I)-complex **HCT 5**:

C	4.197007	2.221939	0.554757
C	2.845074	2.018536	0.384489
C	2.369030	0.735626	0.008291
C	3.296849	-0.342256	-0.157692
C	4.702984	-0.088657	-0.022036
C	5.124014	1.183126	0.337195
H	4.564401	3.202239	0.845069
H	2.150723	2.832770	0.553280
C	0.975037	0.455683	-0.197545

C	2.776060	-1.634802	-0.421364
C	1.419320	-1.804608	-0.558749
H	0.983555	-2.781251	-0.740451
C	-0.048328	1.496584	-0.125362
H	0.194167	2.548605	-0.263488
N	0.534269	-0.780559	-0.495698
H	3.427389	-2.499671	-0.480450
N	-1.275516	1.101370	0.020359
N	-2.284479	1.992963	-0.043549
Cu	-1.554258	-0.980516	-0.363661
O	-1.642884	-2.684083	1.036990
H	-2.039259	-2.119423	1.751678
H	-2.369808	-3.261046	0.752987
O	-2.839743	-0.668276	2.426363
H	-2.185151	0.024832	2.230955
H	-3.469745	-0.562314	1.682308
C	-3.456290	1.421097	-0.307554
N	-4.541230	2.243065	-0.210266
S	-3.767222	-0.251635	-0.778791
H	6.187541	1.381220	0.450263
H	-5.386652	1.973441	-0.690331
H	-4.351157	3.233078	-0.118841
N	5.612833	-1.136413	-0.192028
H	5.398930	-1.772155	-0.951154
H	6.579443	-0.836893	-0.240149

Copper(I)-complex **HCT 11**:

C	-4.719668	2.401454	0.413521
C	-3.391938	2.060077	0.269164
C	-3.015474	0.728942	-0.051471
C	-4.041020	-0.259097	-0.193983
C	-5.399302	0.122807	-0.041969
C	-5.732432	1.426441	0.251846

H	-4.991787	3.424710	0.655906
H	-2.629316	2.818007	0.409929
C	-1.649438	0.316390	-0.227520
C	-3.651605	-1.596911	-0.464359
C	-2.317773	-1.894961	-0.590986
H	-1.976242	-2.906257	-0.785515
C	-0.533433	1.250194	-0.144823
H	-0.669903	2.321654	-0.278187
N	-1.334058	-0.963267	-0.507655
H	-6.171005	-0.633935	-0.157315
H	-4.403018	-2.373480	-0.570643
N	0.653060	0.737460	0.004354
N	1.735998	1.524551	-0.036405
C	2.870678	0.859441	-0.293674
S	2.988546	-0.845882	-0.764711
N	4.012801	1.602691	-0.220805
C	5.330352	1.009792	-0.407675
H	5.323635	0.330924	-1.262239
H	6.049791	1.811747	-0.593552
H	5.655234	0.441826	0.475215
C	3.950272	2.950672	0.342291
H	3.067543	3.466586	-0.036171
H	3.888046	2.927917	1.439381
H	4.850558	3.497422	0.050842
Cu	0.718220	-1.358793	-0.349299
O	2.067452	-1.090901	2.432419
H	1.471994	-0.352415	2.214520
H	2.680033	-1.081331	1.665783
O	0.665616	-3.018546	1.104572
H	1.119503	-2.478992	1.803791
H	1.330334	-3.671090	0.831982
H	-6.774979	1.709894	0.366796

Copper(I)-complex **HCT 12**:

C	-4.368944	2.786466	0.421535
C	-3.064055	2.367986	0.265577
C	-2.766570	1.010622	-0.024042
C	-3.857836	0.091892	-0.122223
C	-5.191412	0.540175	0.040614
C	-5.439854	1.869291	0.304234
H	-4.577490	3.829840	0.639716
H	-2.257687	3.084855	0.372121
C	-1.430459	0.509480	-0.208605
C	-3.533697	-1.263664	-0.365677
C	-2.234974	-1.669677	-0.513454
H	-1.990590	-2.710079	-0.693923
C	-0.256968	1.372070	-0.155551
H	-0.327783	2.447139	-0.310113
N	-1.201589	-0.792777	-0.463970
H	-5.999029	-0.178846	-0.042912
N	0.895733	0.789012	-0.004304
N	2.026139	1.505985	-0.068713
C	3.114398	0.766538	-0.322337
S	3.122649	-0.952695	-0.757552
N	4.300562	1.439082	-0.275054
C	5.577338	0.762116	-0.460655
H	5.521484	0.070070	-1.302821
H	6.343569	1.514186	-0.666452
H	5.873690	0.190571	0.429866
C	4.323182	2.801980	0.254460
H	3.485112	3.369303	-0.151716
H	4.241045	2.811452	1.350276
H	5.264067	3.277048	-0.033728
Cu	0.832228	-1.312152	-0.299358
O	2.244036	-1.082054	2.453568
H	1.707130	-0.300156	2.235394

H	2.841339	-1.133122	1.676280
O	0.663317	-2.913693	1.197670
H	1.176625	-2.399293	1.874894
H	1.256523	-3.637053	0.939231
H	-6.461427	2.216881	0.429024
F	-4.535469	-2.161340	-0.461309

Copper(I)-complex **HCT 13**:

C	-4.552761	2.082974	0.332221
C	-3.209572	1.807610	0.204225
C	-2.755825	0.496206	-0.100193
C	-3.724230	-0.549600	-0.243920
C	-5.103258	-0.250394	-0.111671
C	-5.483746	1.038501	0.164982
H	-4.915043	3.079237	0.561509
H	-2.493883	2.609156	0.346676
C	-1.367160	0.162164	-0.257833
C	-3.255959	-1.865613	-0.495930
C	-1.905374	-2.086065	-0.603428
H	-1.505619	-3.078873	-0.781875
C	-0.308291	1.159221	-0.175376
H	-0.504359	2.220171	-0.318206
N	-0.976174	-1.100813	-0.520207
H	-5.853590	-1.026416	-0.220839
H	-3.959699	-2.685189	-0.602166
N	0.905269	0.716511	-0.014583
F	-6.790893	1.333196	0.292633
N	1.940059	1.563421	-0.053539
C	3.115521	0.961564	-0.289405
S	3.335667	-0.737687	-0.741224
N	4.212033	1.769000	-0.210656
C	5.562966	1.250282	-0.380945
H	5.604637	0.570948	-1.234203

H	6.238347	2.091204	-0.559431
H	5.907893	0.702721	0.507027
C	4.071167	3.116709	0.339064
H	3.147551	3.566313	-0.025138
H	4.035937	3.102678	1.437583
H	4.925738	3.719484	0.021269
Cu	1.095251	-1.377571	-0.339477
O	2.404710	-1.015812	2.450610
H	1.772705	-0.310283	2.227000
H	3.021337	-0.976557	1.688203
O	1.113958	-3.022288	1.128014
H	1.535206	-2.456034	1.826533
H	1.809397	-3.648165	0.869938

Energy Table:

Compound	**H (Hartree)**	**G (Hartree)**
Compound **HCT 5**	-1097.528531	-1097.585273
Compound **HCT 11**	-1120.750223	-1120.810657
Compound **HCT 12**	-1219.983719	-1220.045525
Compound **HCT 13**	-1219.985892	-1220.047679
Deprotonated Compound **HCT 5**	-1096.967387	-1097.024858
Deprotonated Compound **HCT 11**	-1120.195734	-1120.257637
Deprotonated Compound **HCT 12**	-1219.436872	-1219.500779
Deprotonated Compound **HCT 13**	-1219.440279	-1219.504105
Copper (II)-complex **HCT 5**	-1445.741952	-1445.812126
Copper (II)-complex **HCT 11**	-1468.969499	-1469.043895
Copper (II)-complex **HCT 12**	-1568.204824	-1568.281123
Copper (II)-complex **HCT 13**	-1568.208061	-1568.284321
Copper (II)-complex **HCT 5**	-1445.948025	-1446.018006
Copper (II)-complex **HCT 11**	-1469.174027	-1469.248335
Copper (II)-complex **HCT 12**	-1568.411747	-1568.487949
Copper (II)-complex **HCT 13**	-1568.414849	-1568.491171
Copper (II)-$(H_2O)_2$	-348.17626	-348.211596

SMILES codes for HCT compounds synthesized and tested *in vitro*

Compound	SMILES	IC_{90} (nM) in MIA-PACA2 cells	Cu-supplemented (20 μM) IC_{90} (nM) in MIA-PACA2 cells
HCT1	NC(N/N=C/C1=NC=CC2=C1C=CC=C2)=S	18100	2210
HCT2	NC(N/N=C/C1=NC=C(F)C2=C1C=CC=C2)=S	24600	2060
HCT3	NC(N/N=C/C1=NC=CC2=C1C=CC(F)=C2)=S	5440	2040
HCT4	NC(N/N=C/C1=NC=CC2=C1C=CC=C2NC)=S	11500	5330
HCT5	NC(N/N=C/C1=NC=CC2=C1C=CC=C2N)=S	40500	71100
HCT6	S=C(NC)N/N=C/C1=NC=CC2=C1C=CC=C2	18700	311
HCT7	S=C(NC)N/N=C/C1=NC=C(F)C2=C1C=CC=C2	2080	114
HCT8	S=C(NC)N/N=C/C1=NC=CC2=C1C=CC(F)=C2	4080	233
HCT9	S=C(NC)N/N=C/C1=NC=CC2=C1C=CC=C2NC	4240	607
HCT10	S=C(NC)N/N=C/C1=NC=CC2=C1C=CC=C2N	11200	7870
HCT11	S=C(N(C)C)N/N=C/C1=NC=CC2=C1C=CC=C2	29600	73.7
HCT12	S=C(N(C)C)N/N=C/C1=NC=C(F)C2=C1C=CC=C2	274	26.6
HCT13	S=C(N(C)C)N/N=C/C1=NC=CC2=C1C=CC(F)=C2	111	21.6
HCT14	S=C(N(C)C)N/N=C/C1=NC=CC2=C1C=CC(F)=C2NC	272	38.4
HCT15	S=C(N(C)C)N/N=C/C1=NC=C(F)C2=C1C=CC=C2NC	327	42.3

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