Supporting information

Synthesis of *Adagrasib* (MRTX849), a Covalent KRAS^{G12C} Inhibitor Drug for the Treatment of Cancer

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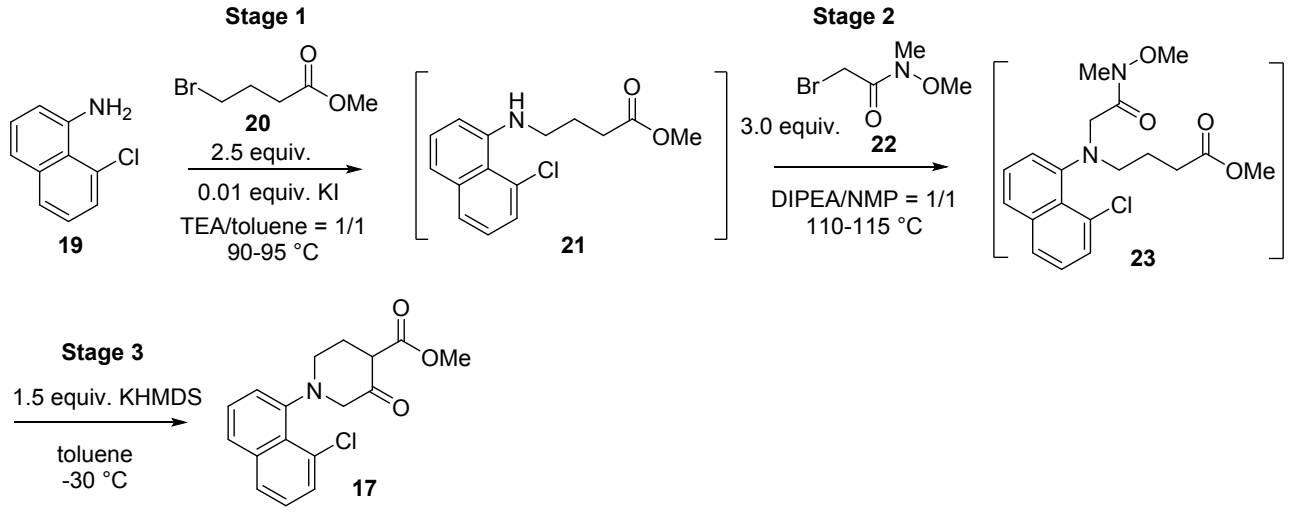
Section 1. General experimental details

All reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Avance nuclear magnetic resonance (NMR) Spectrometer. Chemical shifts were reported in ppm relative to the residual deuterated solvent for ^{1}H and ^{13}C, and *J* values were expressed in hertz. The following abbreviations were used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; dddt = doublet of doublet of doublet of triplets; dq= doublet of quartets; qd= quartet of doublets. HRMS analysis was performed on an LCMS with Agilent 1260 HPLC+ 6530 (QTOF) instruments. Compound assay was determined by qNMR with 1,3,5-trimethoxybenzene as the internal standard. All reactions were performed with jacketed reactor and temperature was controlled by a heating or cooling jacket circulated with oil. Otherwise, the reaction was conducted with EasyMax which has a built-in solid-state thermostat covering the entire temperature range without an additional cryostat.

Section 2. Synthesis of Ketoester

2.1 Reaction Procedure:

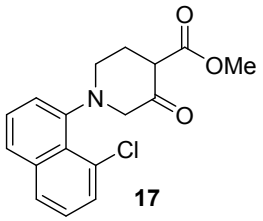


Stage 1: To a 100-L glass jacketed reactor was charged with amine **19** (2 kg, 11.3 mol), KI (20 g, 0.12 mol), PhMe (8 L), methyl-4-bromobutyrate (5.68 kg, 28.1 mol), and TEA (8 L) sequentially. The reaction was heated to 90 °C under a heating jacket and stirred for 17 h. The reaction mixture was cooled to room temperature, followed by the addition of toluene (8 L) and H_2O (8 L). After stirring for 1 hour and then stopped to allow phase separation, the bottom aqueous layer was drained and the organic layer was concentrated to give crude **21**.

Stage 2: To a 100-L jacketed reactor was charged with the stage 1 crude **21**, NMP (7.5 L), Weinreb fragment **22** (7.0 kg, 30.8 mol, 80.0% w/w), DIPEA (6 L). The mixture was heated to 100 - 110 °C under a heating jacket and stirred for 19 h. The mixture was then cooled to room temperature and 20% citric acid aqueous solution (8 L) was added. After stirring for 30 min at room temperature and phase separation, the bottom aqueous layer was transferred to a 50-L jacketed reactor which was extracted with toluene (8 L). The result organic layer was transferred back to the 100-L jacketed reactor. The combined layer was washed with 5% aq. sodium bicarbonate solution (8 L) and 10% brine (8 L) sequentially. The organic layer was separated and concentrated to give crude **23**.

Stage 3: To a 50-L jacketed reactor was charged with crude **23** and toluene (4 L). The mixture was cooled to -35 °C and KHMDS (15% w/w, 22.4 kg, 16.8 mol) in toluene was added in 3 h, during which the temperature was maintained at -33 to -28 °C. Another portion of KHMDS (15% w/w, 3.3 kg, 2.5 mol) in toluene was added and the result reaction was stirred for 14 h at -33 °C. The reaction mixture was charged to 20% cirtric acid aqueous solution (8 L) at 0 - 5 °C in 100-L reactor. The biphasic mixture was armed to 25 °C and layers were separated. The aqueous layer extracted with toluene (4 L). The organic layers were combined and washed with 20% aq. citric acid (4.0 L) solution and water

(4.0 L) sequentially. The layers were separated and the organic layer was washed with 5% aq. sodium bicarbonate (8.0 L) and 10% brine (8.0 L) sequentially, and filtered through a bed of charcoal/celite. The filtrate was concentrated followed by addition of isopropanol (4 L) and heptane (8.5 L). The result mixture was warmed to 60-65°C under a heating jacket to dissolve solids and cooled down to 44 °C in 1 h. Ketoester **17** seed (50 g, 0.16 mol) and heptane (4 L) were added sequentially to form a slurry. This slurry was slowly to -10 °C in 15 h and filtered. The wet cake was washed with a premixed solution of heptane (4 L) and isopropanol (0.5 L). The product was dried at 60 °C in a drying oven for 48 h to afford ketoester **17** (2.56 kg, 89.2% assay) as a pale brown powder (60% overall yield in 3 steps)

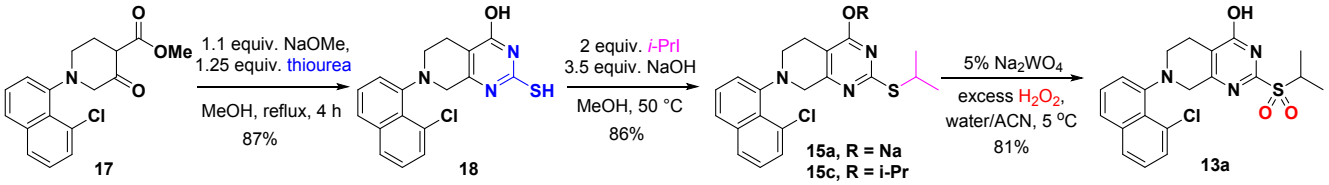


17

17: Pale brown powder (2.56 kg, 89.2% assay, 60% yield). R_f = 0.76 (heptane/ethyl acetate =1/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.03 (s, 1H), 7.75 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.61 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.92 (dd, *J* = 17.4, 1.5 Hz, 1H), 3.84 (s, 3H), 3.52 (dt, *J* = 17.4, 2.0 Hz, 1H), 3.44 (dddd, *J* = 11.9, 5.1, 3.3, 1.4 Hz, 1H), 3.07 (ddd, *J* = 11.9, 9.8, 4.1 Hz, 1H), 2.73 (dddt, *J* = 13.6, 9.6, 5.6, 1.9 Hz, 1H), 2.41 – 2.31 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 169.1, 148.2, 137.4, 130.1, 129.7, 128.2, 126.4, 126.0, 125.6, 125.0, 118.5, 96.4, 54.8, 51.6, 50.5, 22.4. **HRMS: (ESI)** m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}O_3ClN$ 318.0892, Found: 318.0884.

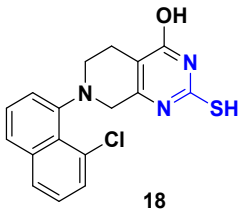
Section 3. Synthesis of 11 Through Cyclization/alkylation/oxidation

3.1 Reaction Procedure:



Synthesis of 18:

To a mixture of ketoester **17** (100 g, 95% assay, 0.3 mol) and thiourea (64 g, 0.38 mol) in MeOH (1 L) in a 2-L jacketed reactor was added sodium methoxide solution (25wt%, 192 mL, 0.84 mol) slowly. The reaction was heated under a heating jacket under reflux for 4 h and cooled to 0-5 °C. Conc. HCl was charged slowly to the reaction mixture until pH to 3-4, during which the product precipitated out to give a slurry. The slurry was filtered, the cake was washed with MeOH (0.5 L) and triturated with water (1 L) at 60 °C under a heating jacket for 1 h. The slurry was filtered and the cake was washed with water (0.5 L). The product was dried under vacuum at 60 °C in a drying oven for 18 h until thermogravimetric analysis (TGA) showed < 0.2% weight loss to afford thiol **18** as a pale-yellow solid (95 g, 94% assay, 87% yield).



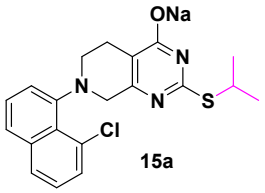
18

18: Pale yellow solid (95 g, 94% assay, 87% yield). R_f = 0.67 (dichloromethane/methanol =10/1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 12.32 (s, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 3.96 (d, *J* = 17.4 Hz, 1H), 3.57 (d, *J* = 17.4 Hz, 1H), 3.38 (m, 1H), 3.09 (td, *J* = 11.0, 4.2 Hz, 1H), 2.61 – 2.50 (m, 2H), 2.35 (d, *J* = 16.6 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 174.2, 160.9, 147.53, 147.50, 137.0, 129.7, 128.72, 128.66, 126.8, 126.0, 125.2, 125.0, 119.4, 109.8, 52.0, 48.9, 21.0. **HRMS** (ESI) calculated for $C_{17}H_{15}ClN_3OS$: 344.0624 $[M+H]^+$, Found: 344.0620.

Synthesis of 15a:

To a 2-L jacketed reactor was charged with sulfide **18** (65 g, 94% assay, 0.18 mol), MeOH (195 mL), and 3M NaOH (0.2 L, 0.62 mol) and the mixture was stirred to a solution. Isopropyl iodide (60 g, 0.35 mol) was added to the solution in one portion. The resulting mixture was heated to 50 °C under a heating jacket and tirred at this temperature for

2 h. 2-MeTHF (650 mL) and water (260 mL) were added to the reaction. The mixture was cooled to 17-20 °C and layers were separated. The bottom aqueous layer was discarded and the top organic layer was washed with 325 mL NaOH (0.5M) three times. The resulting organic layer was concentrate to ~ 100 mL and added slowly to a mixture of 650 mL DCM and 325 mL aqueous NaOH (0.5 M). After stirring for 17 h, the slurry was filtered and washed with 325 mL aq. Na_2CO_3 (0.15 M). The wet cake was dried under vacuum at 40 °C in a drying oven for 22 h to afford sulfide **15a** as a pale-yellow solid (66 g, 94% assay, 86% yield).

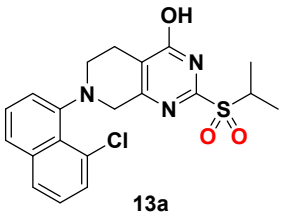


15a

15a: light yellow solid (66 g, 94% assay, 86% yield). R_f = 0.69 (dichloromethane/methanol =10/1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ δ 7.87 (dd, J = 8.2, 1.1 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.54 (dd, J = 7.4, 1.2 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.28 (dd, J = 7.6, 0.8 Hz, 1H), 3.84 (d, J = 15.9 Hz, 1H), 3.74 (p, J = 6.8 Hz, 1H), 3.56 (d, J = 15.9 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.00 (ddd, J = 11.7, 9.9, 4.3 Hz, 1H), 2.63 (ddd, J = 15.9, 9.9, 5.8 Hz, 1H), 2.37 (d, J = 16.4 Hz, 1H), 1.27 (dd, J = 6.8, 1.7 Hz, 1H).**^{13}C NMR** (101 MHz, DMSO- d_6) δ 172.3, 165.5, 156.4, 149.1, 137.1, 129.2, 129.1, 128.4, 126.8, 125.7, 124.9, 123.8, 118.0, 110.3, 57.2, 51.3, 33.5, 23.5, 22.8. **HRMS** (ESI) calculated for $C_{20}H_{21}ClN_3OS$: 386.1089$[M-Na+2H]^+$, Found: 386.1081.

Synthesis of 13a:

To a 100-mL reactor was charged with sulfide **15a** (5 g, 94% assay, 11.5 mmol), $Na_2WO_4 \bullet 2\ H_2O$ (0.19 g, 0.58 mmol), H_2O (25 mL), and CH_3CN (50 mL). The mixture was stirred to give a solution and cooled to 5 °C. H_2O_2 (30wt%, 34.5 mmol, 3.52 mL) was added over 5 h and the mixture was stirred at 5 °C for 12 h. The reaction was quenched with aq. $NaHSO_3$ (11.5 mmol, 1.2 g $NaHSO_3$ in 20 mL Water) to pH ~7. CH_3CN was removed *via* distillation at approx. 40 °C followed by slow addition of AcOH (1.5 equiv., 0.98 mL) at room temperature during which a precipitate forms. The slurry was filtered and washed with 2X25 mL water. The cake was dried at 40 °C overnight in a drying oven to give yellow solid (3.89 g, 97% assay, 81% yield). (Caution: H_2O_2 is unstable, can decompose and may release oxygen slowly at room temperature! It is recommended to do electrostatic discharge and nitrogen protection during feeding, reaction and post-treatment).[1]



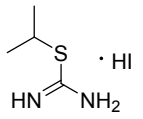
13a

13a: light yellow solid (3.89 g, 97% assay, 81% yield). R_f = 0.47 (dichloromethane/methanol =10/1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.65 (s, 1H), 7.92 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.75 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.57 (d, *J* = 6.1 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.20 (d, *J* = 17.2 Hz, 1H), 4.00 (dt, *J* = 17.4, 1.8 Hz, 1H), 3.82 (hept, *J* = 6.8 Hz, 1H), 3.60 – 3.50 (m, 1H), 3.20 (ddd, *J* = 12.0, 10.1, 4.1 Hz, 1H), 3.05 – 2.92 (m, 1H), 2.72 – 2.65 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.0, 163.5, 160.0, 147.7, 137.0, 129.6, 128.8, 128.6, 126.8, 125.9, 125.0, 124.9, 119.0, 117.3, 57.1, 50.6, 49.2, 22.3, 14.6 (d, *J* = 8.4 Hz). **HRMS** (ESI) calculated for $C_{20}H_{21}ClN_3O_3S$: 418.0992$[M+H]^+$, Found: 418.0987.

Section 4. Synthesis of 11 Through Pre-Alkylated Isothiourea

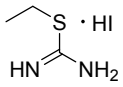
4.1 Synthesis of Pre-Alkylated Isothiourea:

The following pre-alkylated isothiourea was synthesized according to literature procedures: **16a** (1.3 kg, 89% yield),[2] **16b** (27.6 g, 90% yield),[2] **16c** (32.5 g, 89% yield),[3] **16e** (32.5 g, 51% yield),[4] **16f** (19.3 g, 66.7% yield),[4] **16g** (50.4 g, 94% yield)[5]. **16d** is commercially available.



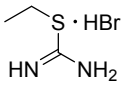
16a

1.3 kg, 89% yield
yellow solid



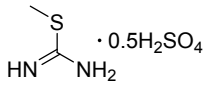
16b

27.6 g, 90% yield
orange solid



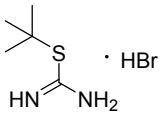
16c

32.5 g, 89% yield
off-white solid



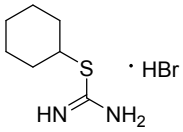
16d

comercially available
white solid



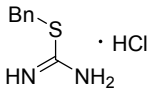
16e

32.5 g, 51% yield
white solid



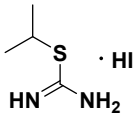
16f

19.3 g, 66.7% yield
off-white solid



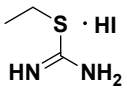
16g

50.4 g, 94% yield
white solid



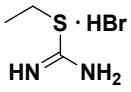
16a

16a: yellow solid (1.3 kg, 89% yield). **^{1}HNMR** (400 MHz, DMSO-d_6) δ = δ 9.14 – 8.63 (m, 4H), 3.91 (dt, *J* = 13.1, 6.5 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 6H).



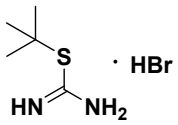
16b

16b: orange solid (27.6 g, 90% yield). **^{1}HNMR** (400 MHz, DMSO-d_6) δ = 8.92 (s, 4H), 3.15 (q, *J* = 8.0 Hz, 2H), 1.25(t, *J* = 8.0 Hz, 3H).



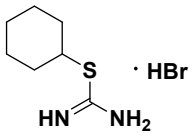
16c

16c: off-white solid (32.5 g, 89% yield). **^{1}HNMR** (400 MHz, DMSO-d_6) δ = 8.92 (s, 4H), 3.13-3.18 (m, 2H), 1.23-1.27 (m, 3H).



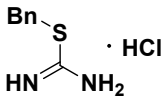
16e

16e: white solid (32.5 g, 51% yield). **^{1}HNMR** (400 MHz, DMSO-d_6) δ = 9.19 (s, 4H), 1.50 (s, 9H).



16f

16f: off-white solid (19.3 g, 66.7% yield). **^{1}HNMR** (400 MHz, DMSO-d_6) δ = 8.98-9.14 (m, 4H), 1.92-1.98 (m, 2H), 1.64-1.72 (m, 2H), 1.53-1.59 (m, 1H), 1.34-1.45 (m, 4H), 1.20-1.28 (m, 1H).

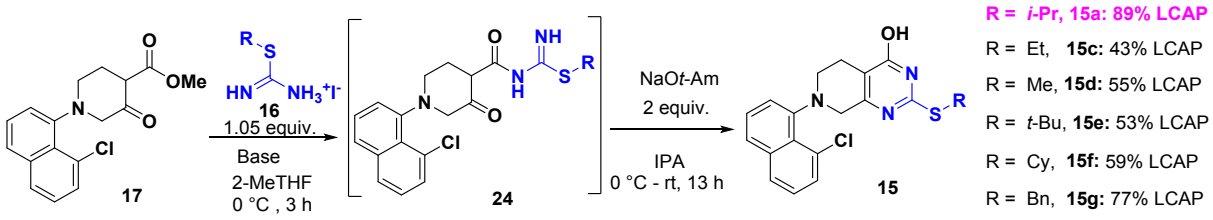


16g

16g: white solid (50.4 g, 94% yield). **^{1}HNMR** (400 MHz, DMSO-d_6) δ = 9.88 (s, 4H), 7.44-7.46 (m, 2H), 7.30-7.43 (m, 3H), 4.56 (s, 2H).

4.2 Screening of Pre-Alkylated Isothiourea:

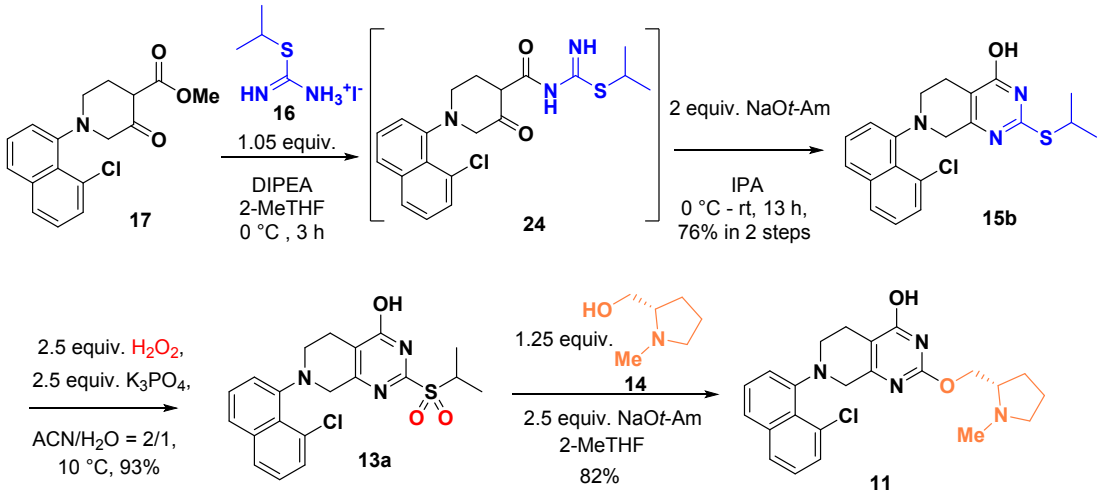
General Reaction Procedure:



Stage 1: Under nitrogen, to isothiourea (1.05 equiv., 5 g) in 2-MeTHF (75 mL) at 0-5 °C was added base (1.5 equiv.) dropwise, keeping the reaction temperature at 0-5 °C. The mixture was stirred at 0 °C for 10 min followed by addition of ketoester **17** (1.0 equiv.). The resulting slurry was stirred at 0 °C for 3 h or until the completion of the reaction.

Stage 2: The above crude mixture was dissolved in anhydrous IPA (50 mL) to give a slurry and cooled to 0 °C. Sodium tert-pentoxide (2 equiv.) was added slowly, keeping the reaction temperature <5 °C. The reaction was warmed to room temperature and stirred at this temperature for 13 h or until the completion of the reaction. H_2O (20 mL) was added to give a hazy solution which was polish filtered through celite to give a clear solution. HOAc/IPA (1/1) was added dropwise until the reaction solution became hazy. A fine slurry was obtained upon seeding and continuous stirring. Filtration of the slurry and cake wash with IPA/H_2O = 3/7 (10 mL) afforded the desired sulfide products: **15c**, **15d**, **15e**, **15f**, **15g**. These products were used directly except **15g** was further purified by chromatography.

4.3 Reaction Procedure:

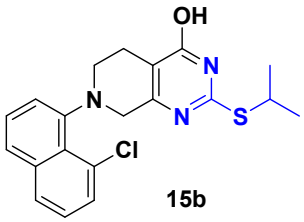


Synthesis of 15b:

Stage 1: To a solution of **16** (154 g, 0.625 mol) in 1000 mL 2-MeTHF at 0 °C in 5-L jacketed reactor was added 1.5 equiv. of DIPEA (117 g, 0.895 mol) dropwise over 1 h to give a white slurry. Ketoester **17** (200 g, 95% assay, 0.597 mol) was added slowly in 15 min followed by rinse with 600 mL 2Me-THF. The resulting slurry was stirred at 0 °C for 20 h. 400 mL water was added followed by addition of aqueous HCl (1M, 360 mL) dropwise in 20 min to afford a white slurry (pH = 3). The slurry was warmed to 20 °C to give a clear biphasic mixture. The aqueous solution (1.2 L) was discarded. The organic layer (1600 mL) was concentrated to 500 mL and azeotropically exchanged with 2X400 mL IPA to give a yellow slurry (~500 mL in volume).

Stage 2: 2 L isopropanol was added to the above slurry and the mixture was cooled to 0 °C. NaO*t*-Am (138 g, 1.19 mol) was added slowly to the mixture and rinsed with 200 mL isopropanol. The reaction mixtured was stirred at 0°C for 0.5 h and then warmed to 25 °C over 0.5 h. The yellow slurry was stirred for 15 h followed by addition of 800 mL H_2O at 20 °C to give a hazy solution. This solution was polish filtered through celite to give a clear solution. The

solution was quenched by addition of 150 mL HOAc/ isopropanol (1/1) in 20 min. The solution (pH =7.02) turned to hazy and upon seeding (2 g seed) formed a thick slurry after 3 h. The slurry was filtered and the cake was washed with 2X200 mL isopropanol /H_2O (V/V=1/1), and 200 mL isopropanol sequentially, dried at 45 °C in a dring oven for 15 h to afford sulfide **15b** as a free-flow pale yellow solid (182.8 g, 93.7% assay, 76% yield).

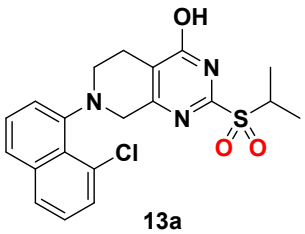


15b

15b: light yellow solid (182.8 g, 93.7% assay, 76% yield). R_f = 0.69 (dichloromethane/methanol =10/1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 7.88 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.70 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.95 (d, *J* = 17.1 Hz, 1H), 3.84 (p, *J* = 6.9 Hz, 1H), 3.69 (dt, *J* = 17.2, 2.2 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.02 (ddd, *J* = 11.8, 10.0, 4.1 Hz, 1H), 2.78 – 2.65 (m, 1H), 2.49 – 2.42 (m, 1H), 1.31 (dd, *J* = 6.9, 5.1 Hz, 6H). **^{13}C NMR** (101 MHz, DMSO- d_6) δ 162.0, 157.85, 157.77, 148.1, 137.0, 129.5, 128.9, 128.5, 126.7, 125.8, 124.9, 124.6, 118.7, 114.5, 56.9, 49.6, 35.5, 22.5 (d, *J* = 1.6 Hz), 21.8. **HRMS** (ESI) calculated for $C_{20}H_{21}ClN_3OS$: 386.1089$[M+H]^+$, Found: 386.1081.

Synthesis of 13a:

To a 5-L jacketed reactor was added sequentially with H_2O (560 mL), K_3PO_4 (191 g, 0.883 mol), sulfide **15** (140 g, 97% assay, 0.353 mol), and ACN (1.12 L). The mixture was heated to 35 °C under a heating jacket for 15 min to dissolve sulfide and resulted in a biphasic mixture. Phase cut to discard the bottom layer (370 mL) and the result organic layer was polish filtered. To the filtrate (pH = 12.2) cooled at 10 °C was added 30 wt % H_2O_2 (90.2 mL, 0.883 mol) in 1 h, keeping the reaction temperature between 8 - 11°C. The mixture was stirred at 10 °C for 25 h followed by addition of aq. HCl (220 mL, 1M) dropwise over 15 min. The reaction temperature was raised to 20 °C to give a hazy solution (pH = 5.3). Seeding with 1 g sulfone and stirring for 2 h afforded a slurry. To the slurry was sequentially added 150 mL aqueous HCl (1 M) dropwise over 10 min (reaction mixture at pH = 1.7) and 720 mL water over 20 min. The slurry was filtered and cake was washed with 2X140 mL ACN/H_2O=3/7 mixture. The product was dried under vacuum at ambient temperature in a drying oven for 48 h to give sulfone **13a** as a light-yellow solid (142 g, 98.6% assay, 94% yield). (Caution: H_2O_2 is unstable, can decompose and may release oxygen slowly at room temperature! It is recommended to do electrostatic discharge and nitrogen protection during feeding, reaction and post-treatment).[1]

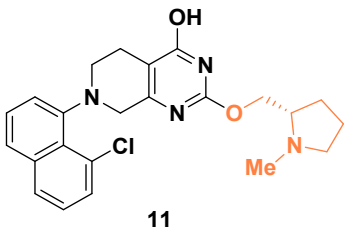


13a

13a: light yellow solid (142 g, 98.6% assay, 94% yield). R_f = 0.47 (dichloromethane/methanol =10/1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.65 (s, 1H), 7.92 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.75 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.57 (d, *J* = 6.1 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.20 (d, *J* = 17.2 Hz, 1H), 4.00 (dt, *J* = 17.4, 1.8 Hz, 1H), 3.82 (hept, *J* = 6.8 Hz, 1H), 3.60 – 3.50 (m, 1H), 3.20 (ddd, *J* = 12.0, 10.1, 4.1 Hz, 1H), 3.05 – 2.92 (m, 1H), 2.72 – 2.65 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.0, 163.5, 160.0, 147.7, 137.0, 129.6, 128.8, 128.6, 126.8, 125.9, 125.0, 124.9, 119.0, 117.3, 57.1, 50.6, 49.2, 22.3, 14.6 (d, *J* = 8.4 Hz). **HRMS** (ESI) calculated for $C_{20}H_{21}ClN_3O_3S$: 418.0992$[M+H]^+$, Found: 418.0987.

Synthesis of 11:

To a cooled solution of sulfone **13a** (140 g, 98.6% assay, 0.33 mol) and prolinol **14** (46.6 g, 0.41 mol) in 2-MeTHF (1.4 L) at 0 °C in a 5-L jacketed reactor was added Na*t*-Amylate solution (30 wt%, 0.33 L, 0.81 mol) in 2-MeTHF slowly in 1h. The reaction mixture was warmed to room temperature and stirred at this temperature for 15 h. The reaction mixture was then cooled to 0 °C and followed by sequential addition of H_2O (1.4 L) and aq. HCl (2 M, 0.64 L) slowly in 15 min. The mixture was warmed to room temperature and layers were separated. The aq layer was extracted with 2-MeTHF (1.2 L). To the combined organic layers was added 10 M NaOH (140 mL) to adjust pH to 8 during which period a precipitation initiated. H_2O (0.42 L) was added to afford a thick slurry. 2-MeTHF (2.1 L) was added to the slurry and the mixture was heated to 60 °C under a heating jacket and stirred at this temperature for 1 h. The aqueous layer was discarded and the organic layer was polish filtered. The filtrate was concentrated to 1.2 L and then diluted with 1.2 L acetonitrile. The mixture was charged with 3 wt% seeds and heated to 40 °C under jacketed reactor. After 3 hours stirring, the mixture was concentrated to 1.2 L. Another 1.2 L acetionitrile was added concentraton again to 1.2 L to give a thick slurry. The slurry was filtered and washed with 2X 0.28 L ACN. The product was dried under vacuum in a drying oven at room temperature for 18 h to give **11** as a light-yellow solid (113 g, 97.1% assay, 82 % yield).



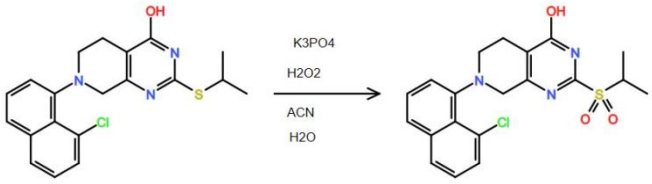
11

11: gray solid (113 g, 97.1% assay, 82% yield). R_f = 0.13 (dichloromethane/methanol =10/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.51 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.22 (dt, *J* = 7.6, 1.2 Hz, 1H), 4.34 (t, *J* = 4.7 Hz, 2H), 4.11 (d, *J* = 17.5 Hz, 1H), 3.71 (dq, *J* = 17.5, 2.0 Hz, 1H), 3.59 – 3.49 (m, 1H), 3.11 (tt, *J* = 11.2, 4.0 Hz, 2H), 2.98 – 2.85 (m, 1H), 2.70 – 2.57 (m, 2H), 2.46 (d, *J* = 1.7 Hz, 3H), 2.34 – 2.23 (m, 1H), 2.05 – 1.91 (m, 1H), 1.89 – 1.78 (m, 1H), 1.78 – 1.64 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 (d, *J* = 1.9 Hz), 159.9, 155.2, 148.8, 137.5, 130.4, 129.7, 128.3, 126.5, 126.2, 125.6, 124.9, 118.6, 113.0, 77.4, 69.9 (d, *J* = 18.2 Hz), 63.9 (d, *J* = 3.9 Hz), 57.6 (d, *J* = 1.8 Hz), 50.3 (d, *J* = 2.7 Hz), 41.7 (d, *J* = 8.9 Hz), 28.3 (d, *J* = 2.3 Hz), 23.1 (d, *J* = 4.0 Hz), 21.9. **HRMS** (ESI) calculated for $C_{23}H_{26}ClN_4O_2$: 425.1739 $[M+H]^+$, Found: 425.1740.

4.4 Safety Evaluation for 13a Synthesis

Scheme Information

Scheme Name: PB9999-MR-ST2-Initial version
Category: Oxidation reaction
Production Information: PharmaBlock Nanjing 20 L



Name	CAS	Mol. W. (g/mol)	Stoic. Ratio	Design Ratio	Design Amount	Conc.	Comments
PCS1861	-	385.91	1	1.0 Eq.	20.00 g	100%	-
K_3PO_4	7778-53-2	212.27	-	2.5 Eq.	27.50 g	100%	-
H_2O_2	7722-84-1	34.02	2	2.5 Eq.	14.70 g	30%	-
ACN	75-05-8	41.05	-	8.0 mL/g	160.0 mL	100%	-
H_2O	7732-18-5	18.01	-	4.0 mL/g	80.0 mL	100%	-

Reaction Procedure

1. 4 V H_2O, 2.5 eq K_3PO_4 were added to the reactor. Sulfide and 8 V ACN were then added;
2. The mixture was heated to 40 °C for 10 min to afford a clear biphasic solution;
3. Phase settle and discard the bottom layer (≈ 2.5 V), and the top organic layer was set to 10 °C;
4. 2.5 eq H_2O_2 (30 wt.%) is added dropwise and the resulting mixture was stirred at 10 °C;
5. The reaction reached completion in 18 hours (sulfide + sulfoxide <1%);
6. Aqueous HCl (1 M) was added dropwise to give a hazy solution (pH = 5.2);
7. Seeding (1% seeds) and stirring for 2 hours to afford a nice slurry;
8. More aqueous HCl (1 M) was added dropwise until pH ≈ 2;
9. 8 V water was added dropwise to push more product out of the mother liquor;
10. Filtration and cake wash with 1.5 V ACN/H_2O = 3/7 mixed solution twice;
11. Vacuum dry the product at rt for 15 hours to give a light brown solid.

Process Risk Level

Risk Level:	**Level 3（Level 5 was reduced to level 3）**		
Assessment Criteria:	T_{D24}:	5.83 °C	refer to T_{safe} of PB9999-MR-ST2-RC1-03(DSC)
	T_p:	10 °C	
	MTSR:	40.52 °C	
	MTT:	81 °C	refer to boiling point of ACN

Process Hazard Assessment Conclusions

Material Hazards:

1. Hydrogen peroxide (30% H_2O_2): May intensify fire, oxidizer. May be harmful if swallowed or if inhaled. Causes serious eye damage. Toxic to aquatic life. Harmful to aquatic life with long lasting effects. Incompatible materials: zinc, powdered metals, iron, copper, nickel, brass, iron and iron salts. Unstable, can decompose and release oxygen slowly at room temperature.
2. Potassium phosphate tribasic (K_3PO_4): Causes serious eye damage. May cause respiratory irritation. Incompatible materials: strong oxidizing agents.
3. Acetonitrile (ACN): Highly flammable liquid and vapor. Upper/lower flammability or explosive limits: Upper explosion limit: 16% (V), Lower explosion limits: 4.4% (V). Flash point is 2.0 °C. Then concentration of ACN in gas phase in reactor is 5.74% (10 °C) and 22.73% (40 °C) respectively, pay attention to electrostatic protection and nitrogen is recommended for protection. Harmful if swallowed. Harmful if inhaled. Harmful in contact with skin. Causes serious eye irritation. Incompatible materials: rubber, various plastics, strong oxidizing agents.

Hazards of Target Reaction: (DSC, RSC, RC)

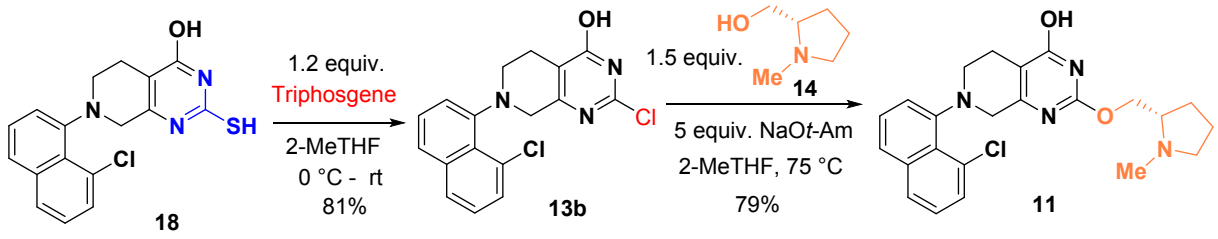
1. T_{D24}(5.83 °C) < T_p(10 °C) < MTSR(40.52 °C) < MTT(81 °C), process hazard level is 5, high explosion risk, but according to the test results of DSC and RSC, the process hazard level is reduced to level 3 according to the regulation in appendix 3.1(Decomposition heat is lower than 100 J/g (DSC data), and the decomposition gas release(RSC data) level (Table 5) is lower than 3);
2. According to the RC results of target reaction, the heat release is slowly and the heat accumulation is large (88.69%) during the reaction, there is a risk of temperature rise, it is recommended to decrease feeding rate and pay attention to temperature control system in scale-up production.
3. The reaction uses flammable liquid (ACN), and it is recommended to do ESD and nitrogen protection during feeding, reaction and post-treatment.

Hazards of Concentration and Drying: (DSC)

1. H_2O_2 solution is very unstable and oxidative. Make sure no H_2O_2 remains after the reaction.
2. Filtration can generated large amount of static electricity, which could be a potential ignition energy, pay attention to electrostatic protection.
3. T_{safe} of PCS1862 (product) is about 88.93 °C (DSC, Extra-100K), the drying process (room temperature) has a low thermal runaway risk.

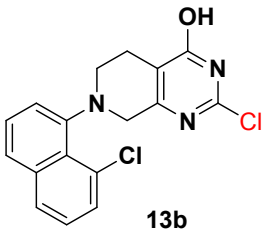
Section 5. Synthesis of 11 Through Triphosgene Route

5.1 Reaction Procedure:



Synthesis of 13b:

To a solution of thiol **18** (15 g, 44 mmol) in 2-MeTHF (300 mL) at 0-5 °C was added 10.1 mL HCl (4 M in dioxane) solution slowly and followed with the addition of triphosgene (14.5 g, 52 mmol). The reaction mixture was warmed to 25 °C and stirred at this temperature for 15 h, wh to afford a slurry. The slurry was filtered and the cake was rinsed with 75 mL ACN, followed by 75 mL MTBE. The product was dried under vacuum at room temperature in a drying oven for 18 h to afford chloride **13b** as a pale-yellow solid (13.5 g, 93.4% assay, 81% yield).



13b

13b: white solid (13.5 g, 93.4% assay, 81% yield). R_f = 0.58 (dichloromethane/methanol =10/1). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.89 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.55 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.00 (d, *J* = 17.4 Hz, 1H), 3.78 (dt, *J* = 17.4, 2.1 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.14 – 3.04 (m, 1H), 2.83 – 2.70 (m, 1H), 2.56 – 2.46 (m, 1H). 13C NMR (101 MHz, DMSO-d_6) δ 165.0, 160.8, 148.9, 147.9, 137.1, 129.7, 129.0, 128.7, 126.8, 126.0, 125.1, 125.0, 119.1, 116.2, 56.7, 49.4, 21.9. **HRMS (ESI)** calculated for $C_{17}H_{14}Cl_2N_3O$: 346.0509 $[M+H]^+$, Found: 346.0491.

Synthesis of 11:

To chloride **13b** (41 g, 93% assay, 0.11 mol) in 2-Me THF (205 mL) at 0 °C was added prolinol **5** (17.8 g, 0.165 mol) and NaO*t*-Am (56.7 g, 0.55 mol) sequentially and the reactor was rinsed with 2-Me THF (205 mL). The mixture was heated to 75 °C under a heating jacket and stirred at this temperature for 48 h. The reaction mixture was cooled to 0 °C followed by addition of H_2O (0.41 L) and aq. HCl (2M, 0.24 L). The bottom aqueous layer was separated and

extracted with 2-MeTHF (0.41 L). To the combined organic layers was added NaOH aqueous solution (10M , 140 mL). Precipitation initiated at pH 8. 2-MeTHF (0.41 L) was added to the mixture which was heated to 55 °C under a heating jacket and stirred at this temperature for 1 h. The biphasic mixture was separated and the bottom aqueous layer was extracted by 2-MeTHF (0.41 L). The two organic layers were combined and concentrated to 0.41 L followed by addition of 0.2 L acetonitrile. The mixture was seeded with 4 wt% seeds and stirred at room temperature for 15 h. The resulting slurry was filtered and washed with 2x 0.2L ACN. The product was dried under vacuum at room temperature for 18 h to give **11** as a light-yellow solid (41.9 g, 94.8% assay, 79% yield).

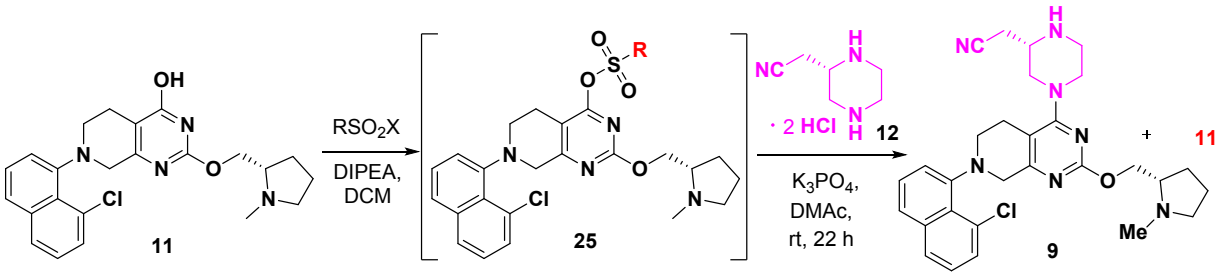
The product NMR data is in accordance with the aforementioned **11** NMR data.

Section 6. Synthesis of 9 through Activation/S_NAr Sequence

6.1 General Reaction Procedure:

Stage 1: To a mixture of **11** (1 g, 97.1% assay, 2.3 mmol) and DIPEA (1 mL, 5.7 mmol) in DCM (7 mL) at 0 °C was added 1.1 equiv. activation reagent ($ArSO_2Cl$ / Tf_2O / MsCl) and DMAP (14 mg, 0.12 mmol) sequentially. The reaction mixture was stirred at 0 °C for 15 min and warmed to room temperature. H_2O (3 mL) was added to the reaction mixture and the bottom organic layer was seperated. The top organic layer was dried (over $MgSO_4$) and concentrated to afford crude intermediate **25** which is used directly in the next stage.

Stage 2: A mixture of crude intermediate **25**, piperazine (1.5 equiv.), K_3PO_4(3 equiv.) in DMAc (3 mL) was stirred at room temperature for 2 h.

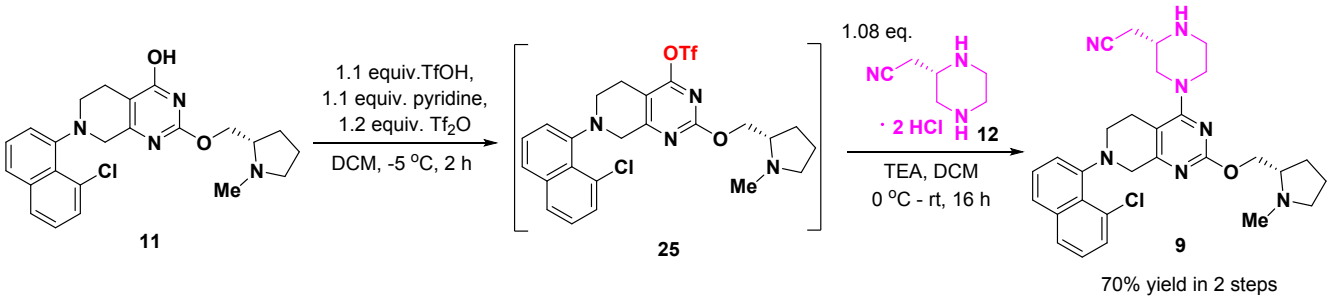


25a, R = **CF_3**, **9** / **11** = 99% / 0.4%

25b, R = **Tol**, **9** / **11** = 92% / 6%

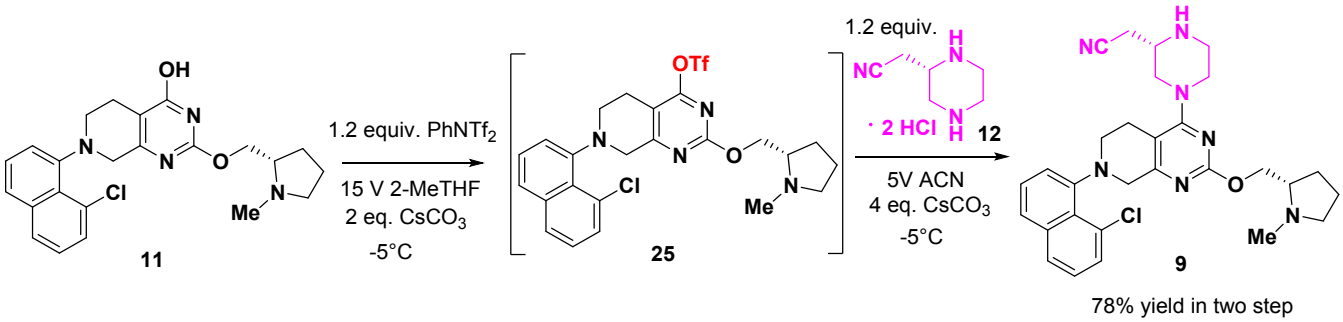
25c, R = **Me**, **9** / **11** = 65% / 29%

6.2 Synthesis of 9 through Triflate:



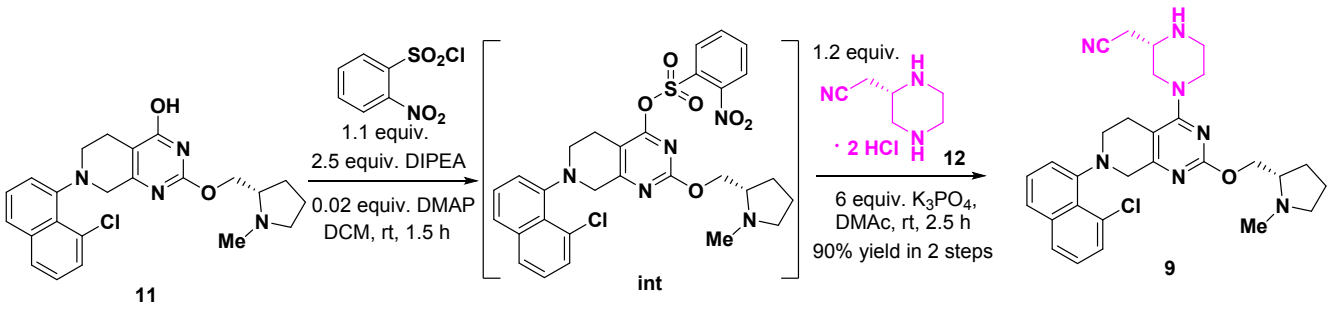
A 100-mL flask was charged with **11** (4 g, 97.1% assay, 9 mmol), DCM (40 mL) and the resultant solution was cooled to -5 °C. Pyridine (0.8 mL, 10 mmol) was added and then followed by slow addition of TfOH (0.9 mL, 10 mmol, exotherm). Tf_2O (1.83 mL, 10.8 mmol) was added slowly to the resultant mixture (exotherm!). The reaction was stirred at -5 °C for 2 h and quenched with 20 mL 5% aq. $NaHCO_3$ solution. The organic layer was drained into a second reactor and cooled to 5 °C. Piperazine side chain (2 g, 9.7 mmol) was added followed by addition of triethylamine (4.5 mL, 32 mmol). The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was washed

with 30 mL 15% aq. Na_2CO_3 solution and the aq layer (pH = 9.8) was discarded. Solvent switch from DCM to 8 mL of DMAc was carried out by distillation at 40 °C. To the resultant solution in DMAc was added 6 mL water to afford a hazy mixture. The mixture was seeded and the product precipitated. The remaining 4 mL water was added to precipitate out the remaining product. The slurry was stirred for 1 h, filtered, washed with 6 mL water/DMAc (V/V = 60/40), 20 mL of water sequentially. The product was dried at 40 °C in the vacuum oven to afford **9** as yellow solid (3.7 g, 92% assay, 70% yield).



To a 500-mL flask was charged with **11** (20 g, 97.1% assay, 45.7 mmol), 2-MeTHF (300 mL) and the resultant solution was cooled to -5 °C. Cs_2CO_3(30 g, 91 mmol) and $PhNTf_2$ (19.6 g, 55 mmol) were added sequentially and the reaction was kept at approx. -5 °C under stirring for 2 h. Once the **11** was consumed, acetonitrile (100 mL) was added, followed by the addition of **12** (10.8 g, 55 mmol) and Cs_2CO_3 (60 g, 183 mmol). The reaction was stirred at -5 °C for 15 h and then H_2O (100 mL) was added to give a biphasic mixture. The aq. layer was separated and extracted with 2-MeTHF (100 mL). The combined organic layers were washed with brine (200 mL) and concentrated. To the resultant crude mixture in 2-MeTHF (200 mL) was added 2M HCl (114 mL, 229 mmol) and H_2O (100 mL) sequentially. The organic layer was separated and treated with 2M HCl (23 mL, 45.7 mmol) and H_2O (20 mL). Two aqueous layers were combined and the solution pH was adjusted to 10-12 with NaOH (10 M). The aq solution was extracted with 2-MeTHF (200 mL). The organic solution was washed by brine (200 mL) and solvent switched to acetonitrille and concentrated to a final volume of ~80 mL in acetonitrile. H_2O (100 mL) was added to afford a cloudy solution followed by seeding with 1 wt% seed. The slurry was stirred at room temperature for 15 h followed by addition of H_2O (40 mL) dropwise. The resultant slurry was filitered and the filter cake was washed with 2X40 mL ACN/H_2O= 1/4 mixed solvents. The product was dried in the vacuum oven to afford **9** as a white solid (20.8 g, 91% assay, 78% yield).

6.3 Synthesis of 9 through 2-Nosylate:



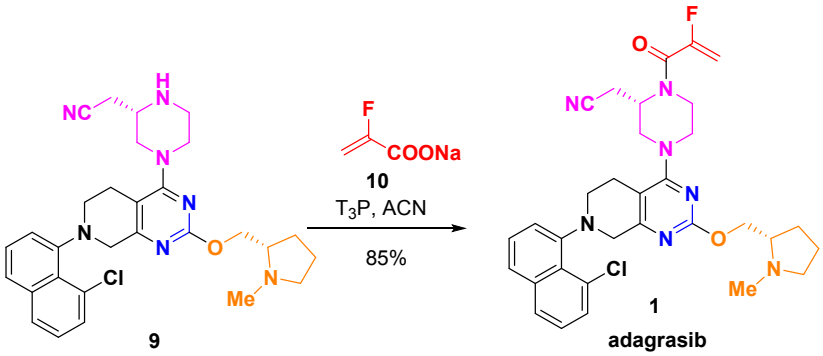
Stage 1: To a mixture of **11** (50 g, 97.1% assay, 114 mmol) and DIPEA (50 mL, 285 mmol) in DCM (350 mL) at 0 °C was added 2-NO_2PhSO_2Cl (27.8 g, 137 mmol) and DMAP (0.28 g, 2.3 mmol) sequentially. The reaction mixture was stirred at 0 °C for 15 min, warmed to room temperature and stirred at this temperature for 1.5 h. H_2O (150 mL) was added to the reaction mixture and layers were separated. The bottom organic layer was seperated and dried ($MgSO_4$) and concentrated to afford crude intermediate **25**, which was used directly in the next stage.

Stage 2: To a mixture of piperazine side chain (27.0 g, 137 mmol) and crude intermediate **25** DMAc (150 mL) at 10 °C was added K_3PO_4 (145 g, 685 mmol). The mixture was stirred at room temperature for 2.5 h. To the resultant slurry was added DMAc (250 mL) and H_2O (400 mL) sequentially, keeping the reaction temperature around 40 °C under EasyMax until a clear biphasic solution formed. The top organic layer was separated followed by addition of H_2O until the mixture turned hazy. 2 wt% seeds was added and the mixture was stirred at room temperature for 15 h. H_2O (640 mL) was added slowly over 6 h to afford a white slurry. The slurry was filtered and the cake was washed with 100 mL DMAc/H_2O = 1/2 (V/V) mixture and 100 mL H_2O sequentially. The product was dried under vacuum at room temperature for 18 h to give **9** as a white solid (60 g, 90.1% assay, 90% yield).

9: white solid (60 g, 90.1% assay, 90% yield). R_f = 0.15 (dichloromethane/methanol = 5/1). **^{1}H NMR** (400 MHz, DMSO-d6) δ 7.88 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.55 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.29 (ddd, *J* = 7.6, 2.9, 1.2 Hz, 1H), 4.24 (dd, *J* = 10.8, 4.8 Hz, 1H), 4.17 (dd, *J* = 17.2, 2.9 Hz, 1H), 4.06 – 3.94 (m, 1H), 3.89 – 3.81 (m, 1H), 3.73 – 3.64 (m, 2H), 3.45 (s, 1H), 3.16 – 2.97 (m, 3H), 2.97 – 2.85 (m, 3H), 2.85 – 2.53 (m, 6H), 2.52 – 2.42 (m, 1H), 2.31 (d, *J* = 1.5 Hz, 3H), 2.12 (q, *J* = 8.5 Hz, 1H), 1.94 – 1.81 (m, 1H), 1.71 – 1.50 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d6) δ 165.9 (d, *J* = 14.7 Hz), 164.1 (d, *J* = 8.0 Hz), 162.3 (d, *J* = 2.5 Hz), 148.3 (d, *J* = 2.2 Hz), 137.2, 129.7, 129.1, 128.8, 127.1, 126.1, 125.2, 124.9 (d, *J* = 2.0 Hz), 119.0 (d, *J* = 1.6 Hz), 118.9 (d, *J* = 1.9 Hz), 108.5 (d, *J* = 20.0 Hz), 69.0 (d, *J* = 4.0 Hz), 63.7, 58.9 (d, *J* = 6.9 Hz), 57.2 (d, *J* = 3.8 Hz), 51.9 (d, *J* = 8.4 Hz), 51.1 (d, *J* = 41.1 Hz), 50.3 (d, *J* = 5.7 Hz), 47.9 (d, *J* = 25.3 Hz), 44.9 (d, *J* = 2.5 Hz), 41.4 (d, *J* = 1.7 Hz), 28.8 (d, *J* = 4.6 Hz), 25.9 (d, *J* = 8.4 Hz), 22.7, 21.4 (d, *J* = 19.9 Hz). **HRMS** (ESI) calculated for $C_{29}H_{35}ClN_7O$: 532.2592 $[M+H]^+$, Found: 532.2593.

Section 7. Final Step of Adagrasib Synthesis

7.1 Reaction Procedure:

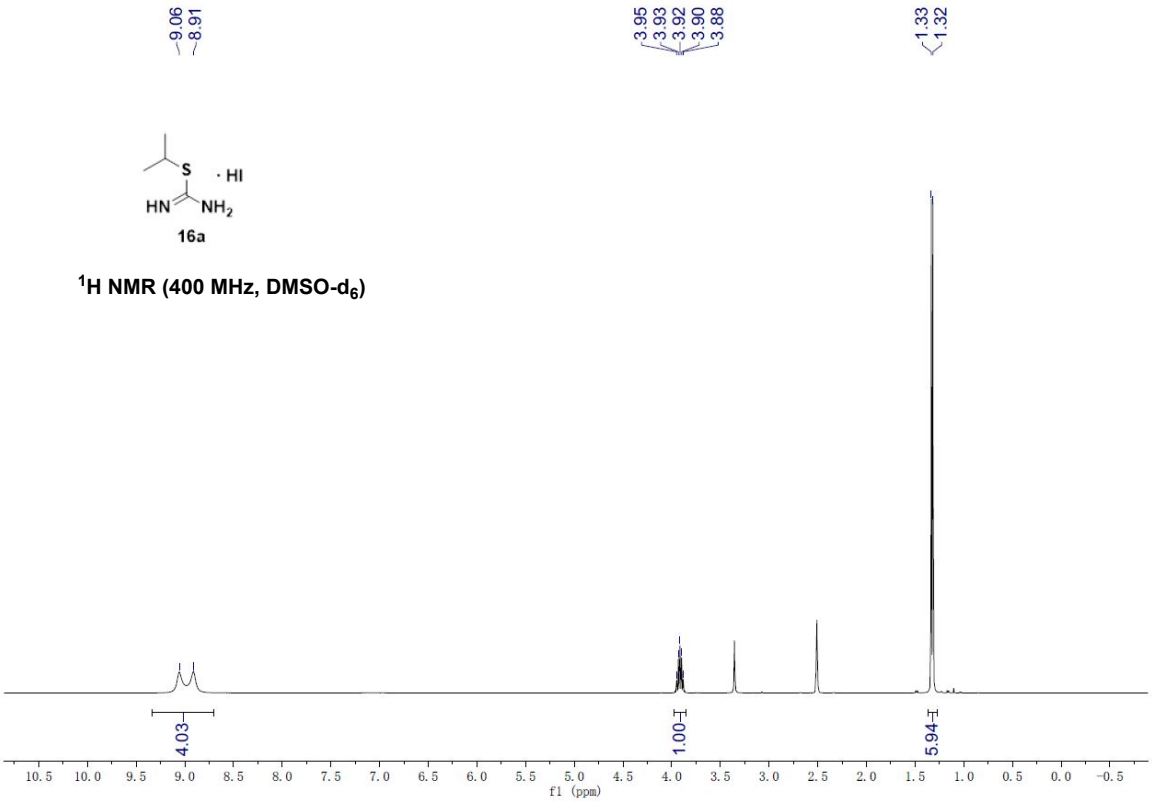


To **9** (5 g, 90.1% assay, 8.5 mmol) in dry MeCN (75 mL) at 10-20 °C was added compound **10** (1.61 g, 14 mmol) and 50% T_3P in ethyl acetate solution (7.5 mL, 12.8 mmol) sequentially. The mixure was stirred at 10-20 °C for 2 h. 12 wt% aqueous K_2CO_3 solution was added to the reaction mixture until pH of the mixture reached to 8-9. The resultant biphasic solution was separated and the organic layer was washed with 20 wt% aq. K_3PO_4 solution. The combined aqueous phases were back extracted with 2-MeTHF (15 mL). The two organic layers were combined and solvent switched to isoproapanol. The resultant mixture (40 mL) was heated to 60 °C under EasyMax followed by addition of *n*-heptane (10 mL) to afford a clear solution. Subsequently cooling of this solution to room temperature afforded a slurry. The slurry was filtered and the cake was washed with 10 mL IPA/H_2O = 1/6 (V/V) and 10 mL H_2O sequentially. The product was dried under vacuum at 35 °C for 18 h to give *adagrasib* (**1**) as a white solid (4.3 g, 99% assay, 85% yield)

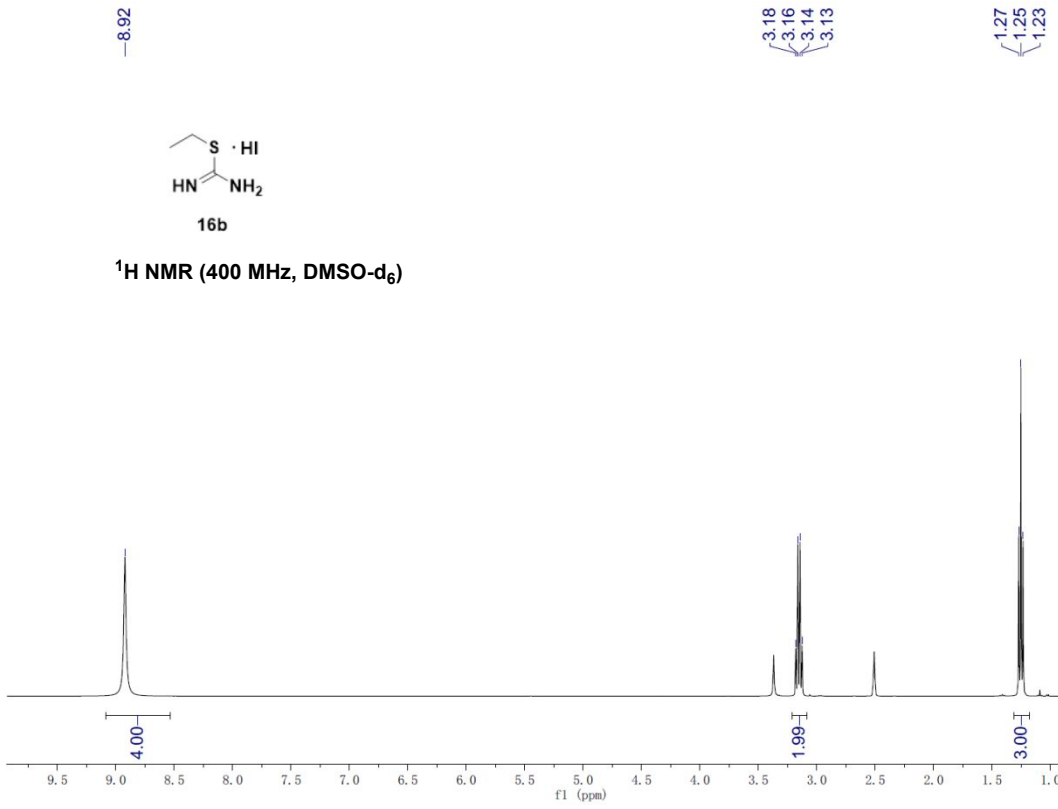
Adagrasib (**1**): white solid (4.3 g, 99% assay, 85% yield). R_f = 0.18 (dichloromethane/methanol =10/1). **^{1}H NMR** (400 MHz, DMSO-d6) δ 7.91 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.57 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.52 (q, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.33 (ddd, *J* = 15.9, 7.6, 1.2 Hz, 1H), 5.38 (dd, *J* = 18.0, 4.1 Hz, 1H), 5.36 – 5.18 (m, 1H), 4.84 (s, 1H), 4.26 – 4.21 (m, 1H), 4.18 (dd, *J* = 16.1, 9.5 Hz, 1H), 4.08 – 3.94 (m, 2H), 3.91 – 3.86 (m, 1H), 3.75 (dd, *J* = 20.2, 17.4 Hz, 1H), 3.47 (q, *J* = 7.3 Hz, 1H), 3.23 (dd, *J* = 13.7, 3.7 Hz, 1H), 3.18 – 2.99 (m, 3H), 2.98 – 2.88 (m, 2H), 2.70 – 2.52 (m, 1H), 2.48 – 2.46 (m, 1H), 2.32 (d, *J* = 3.5 Hz, 3H), 2.14 (qd, *J* = 8.7, 2.2 Hz, 1H), 1.90 (dq, *J* = 12.1, 8.2 Hz, 1H), 1.71 – 1.50 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d6) δ 165.9, 164.3 (d, *J* = 14.5 Hz), 162.1 (d, *J* = 2.1 Hz), 160.8 (dd, *J* = 31.7, 12.2 Hz), 155.6 (d, *J* = 266.7 Hz), 148.0 (d, *J* = 20.4 Hz), 137.0 (d, *J* = 2.9 Hz), 129.4 (d, *J* = 2.1 Hz), 128.9 (d, *J* = 4.3 Hz), 128.5, 126.8 (d, *J* = 2.6 Hz), 125.8, 125.0 (d, *J* = 5.6 Hz), 124.7 (d, *J* = 6.1 Hz), 118.7 (d, *J* = 2.6 Hz), 118.1 (d, *J* = 3.9 Hz), 108.7 (d, *J* = 20.7 Hz), 99.9 (d, *J* = 14.3 Hz), 68.9 (d, *J* = 7.0 Hz), 63.4 (d, *J* = 2.7 Hz), 58.5 (d, *J* = 25.8 Hz), 57.0 (d, *J* = 4.0 Hz), 50.0, 49.0, 48.2, 47.3 (d, *J* = 36.2 Hz), 46.4, 41.2 (d, *J* = 2.9 Hz), 28.5 (d, *J* = 7.1 Hz), 25.2 (d, *J* = 35.0 Hz), 22.5, 18.1. ^{19}F **NMR** (101 MHz, DMSO-d6) δ -105.18 (d, *J* = 334.7 Hz). **HRMS** (ESI) calcd for $C_{32}H_{36}ClFN_7O_2$: 604.2598 $[M+H]^+$, found 604.2607.

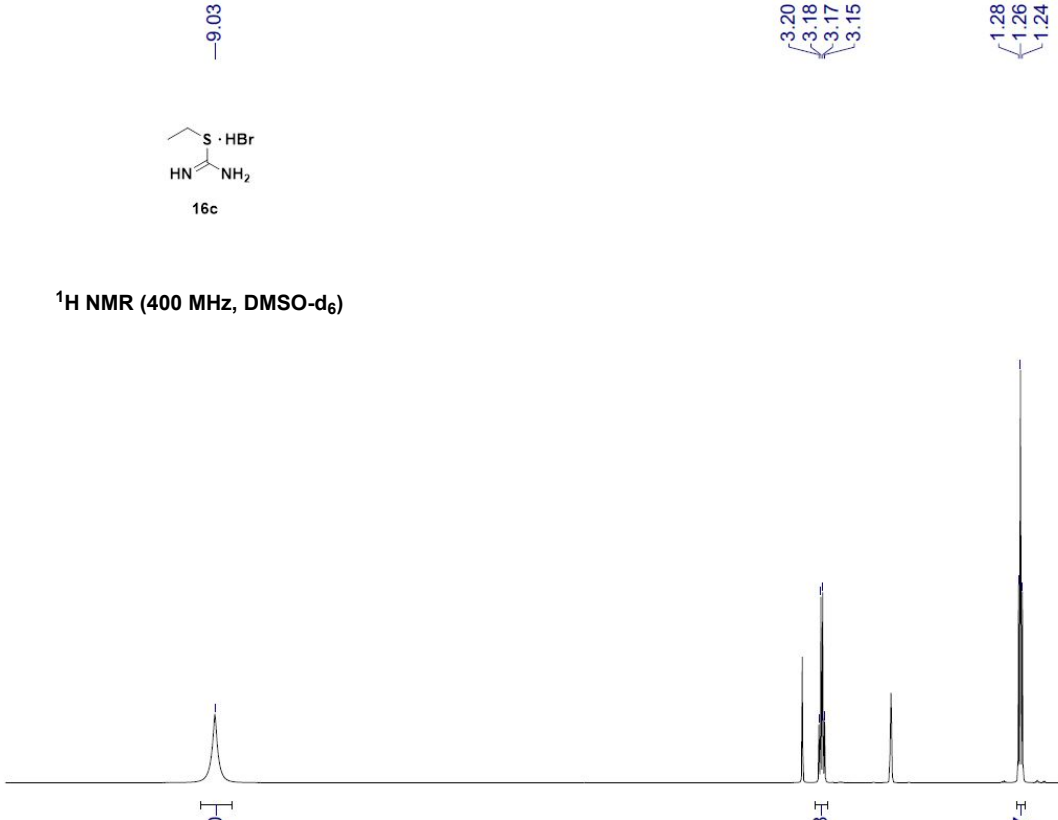
Section 8. ^{1}H, ^{13}C, and ^{19}F NMR spectra

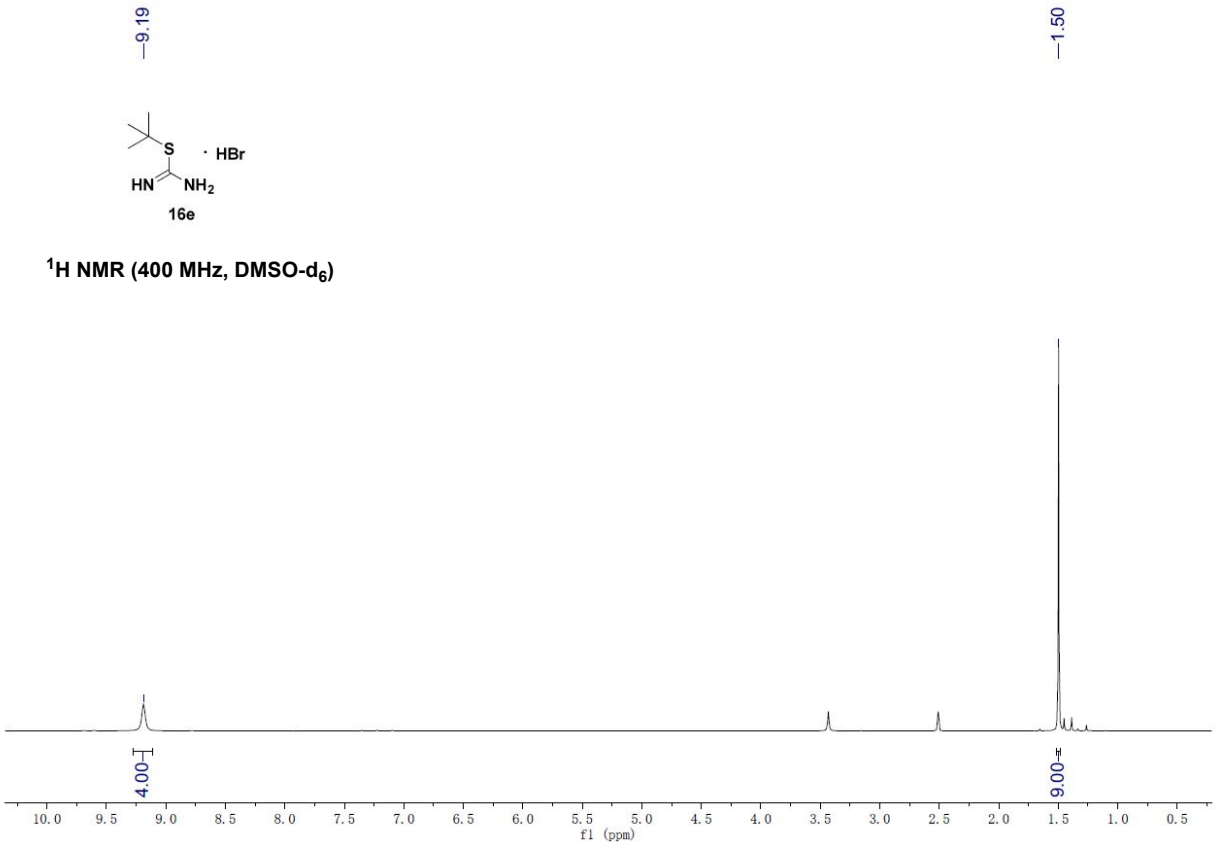
8.1 S-Alkyl Isothiourea



^{1}H NMR (400 MHz, DMSO-d_6)

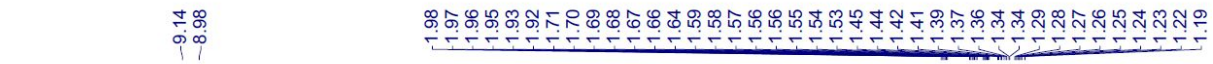

8.92
3.18
3.16
3.14
3.13
1.27
1.25
1.23
S · HI
HN
NH2
16b
1H NMR (400 MHz, DMSO-d6)
4.00
1.99
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

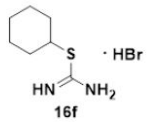

9.03
3.20
3.18
3.17
3.15
1.28
1.26
1.24
S · HBr
HN
NH2
16c
1H NMR (400 MHz, DMSO-d6)
4.00
2.08
3.07
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



^{1}H NMR (400 MHz, DMSO-d_6)

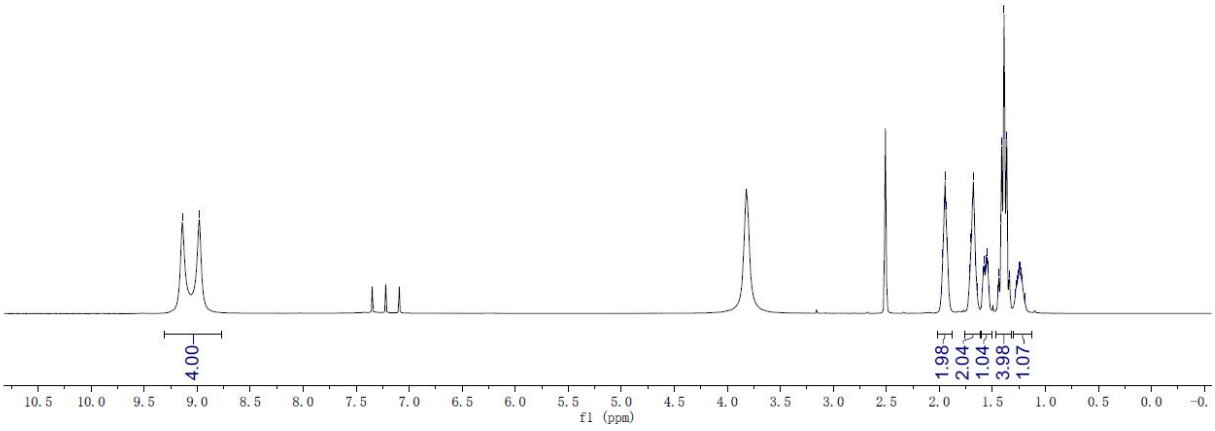
^{1}H NMR (400 MHz, DMSO-d_6)

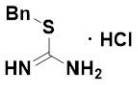




16f

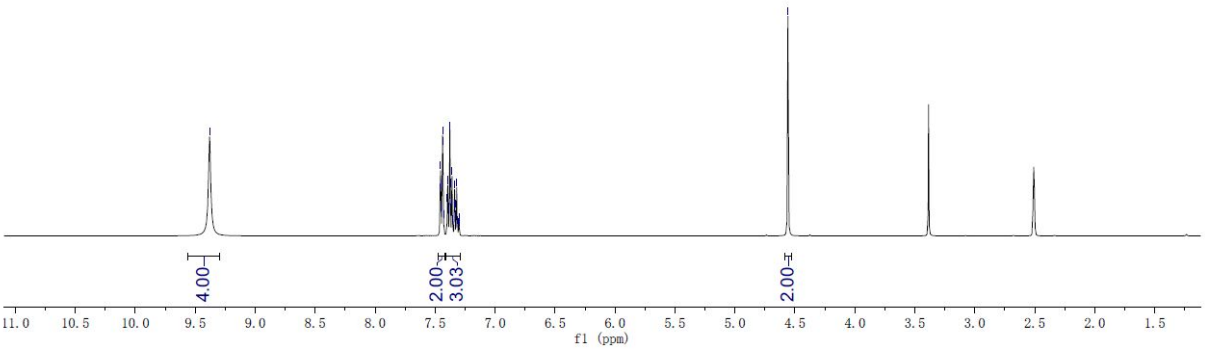
^{1}H NMR (400 MHz, DMSO-d_6)



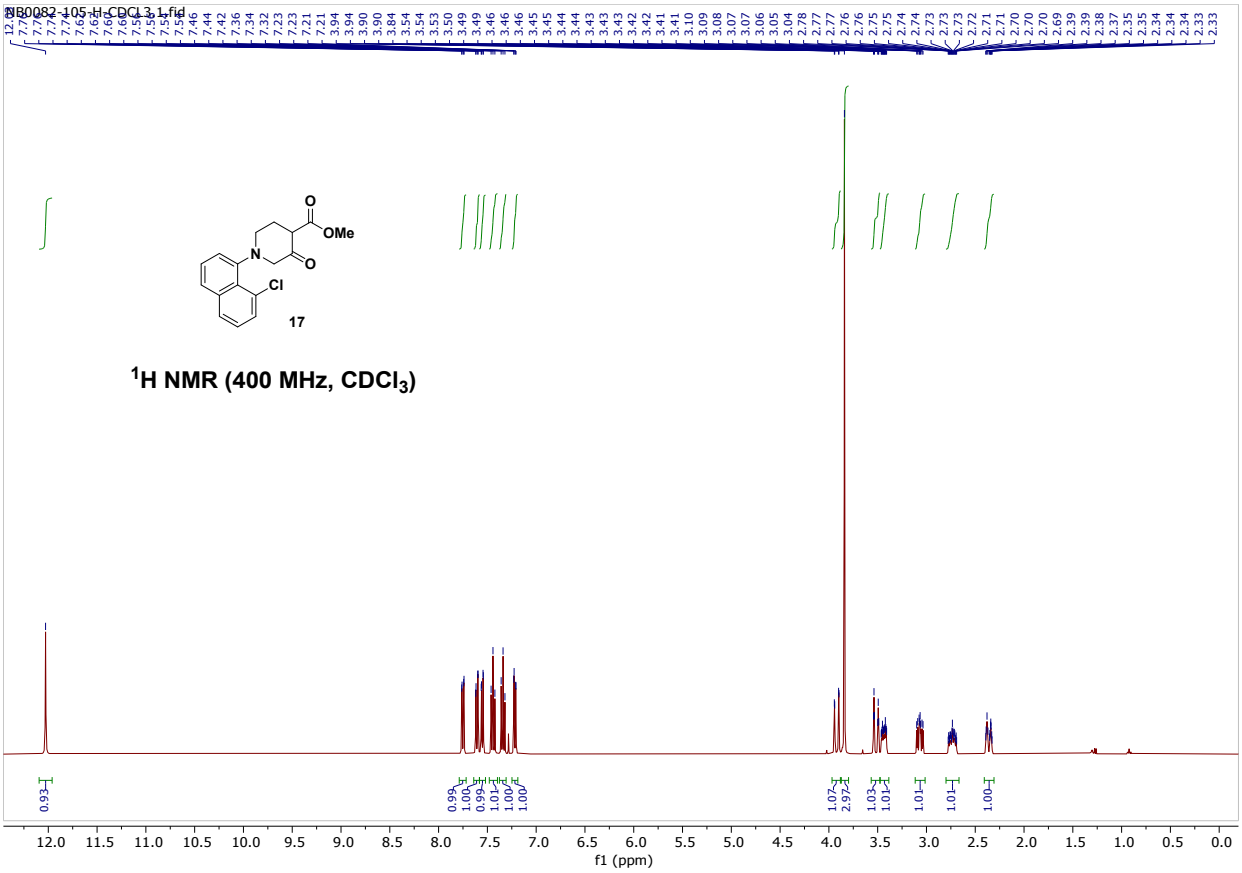


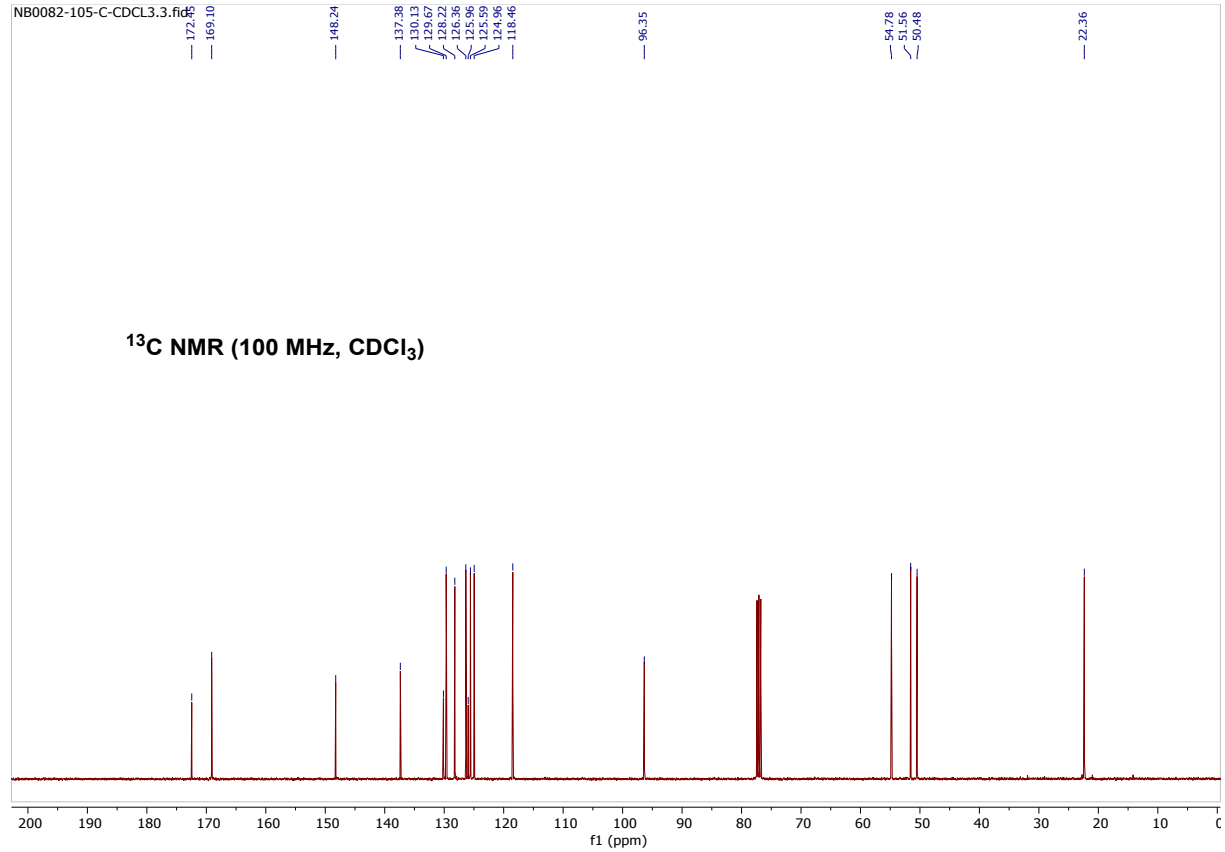
16g

^{1}H NMR (400 MHz, DMSO-d_6)

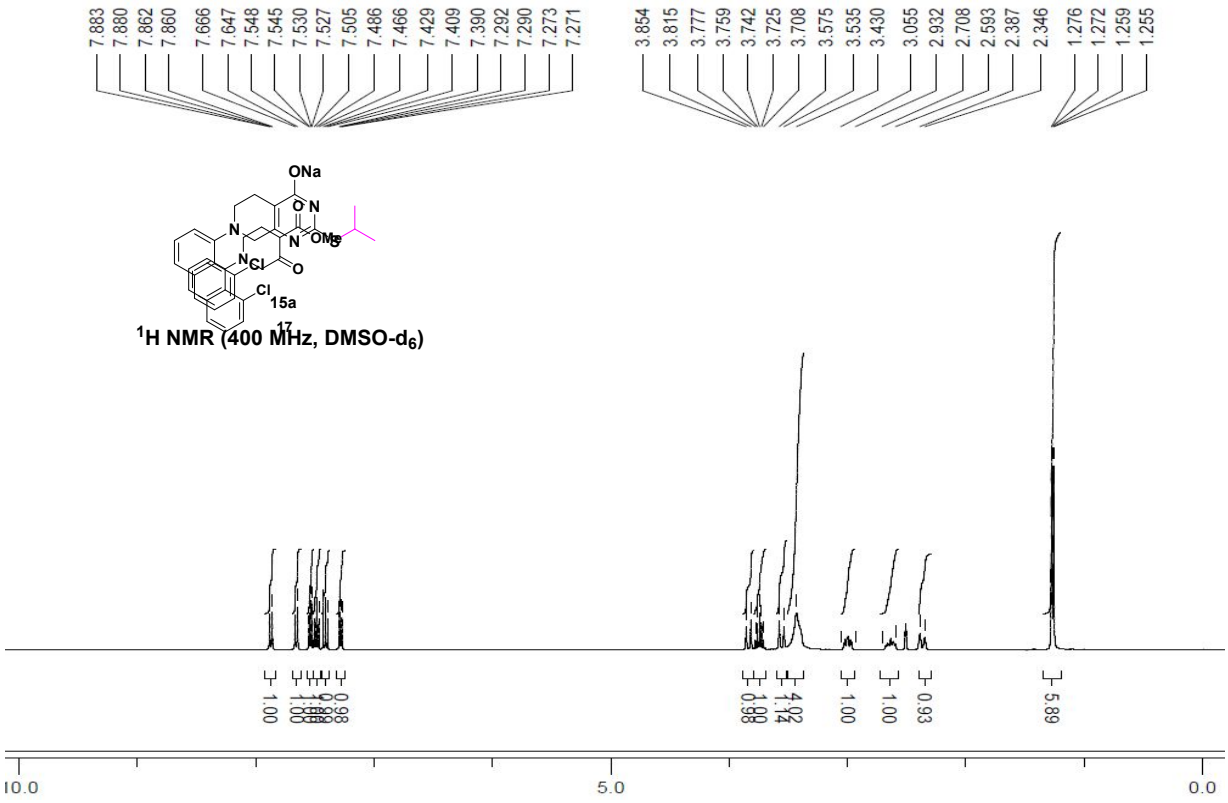


8.2 Intermediates and Product

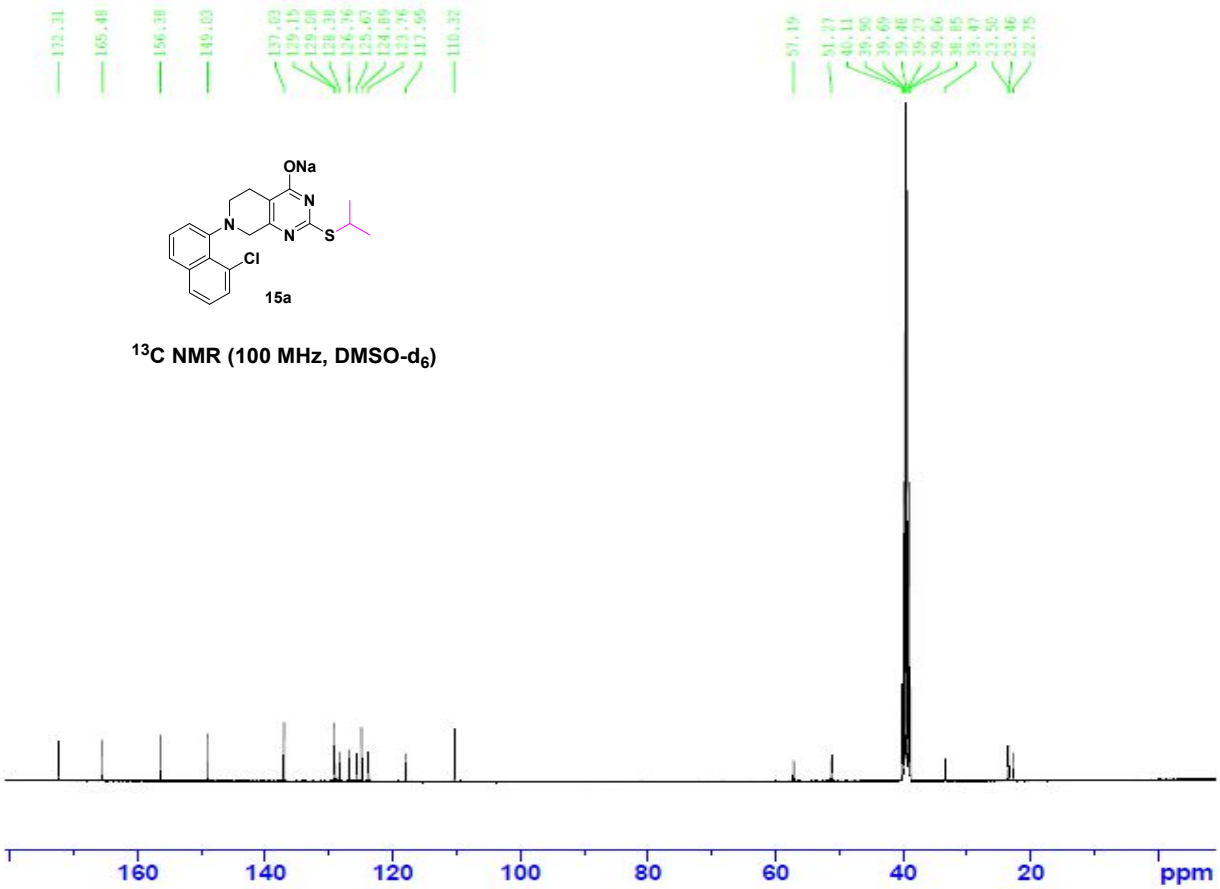




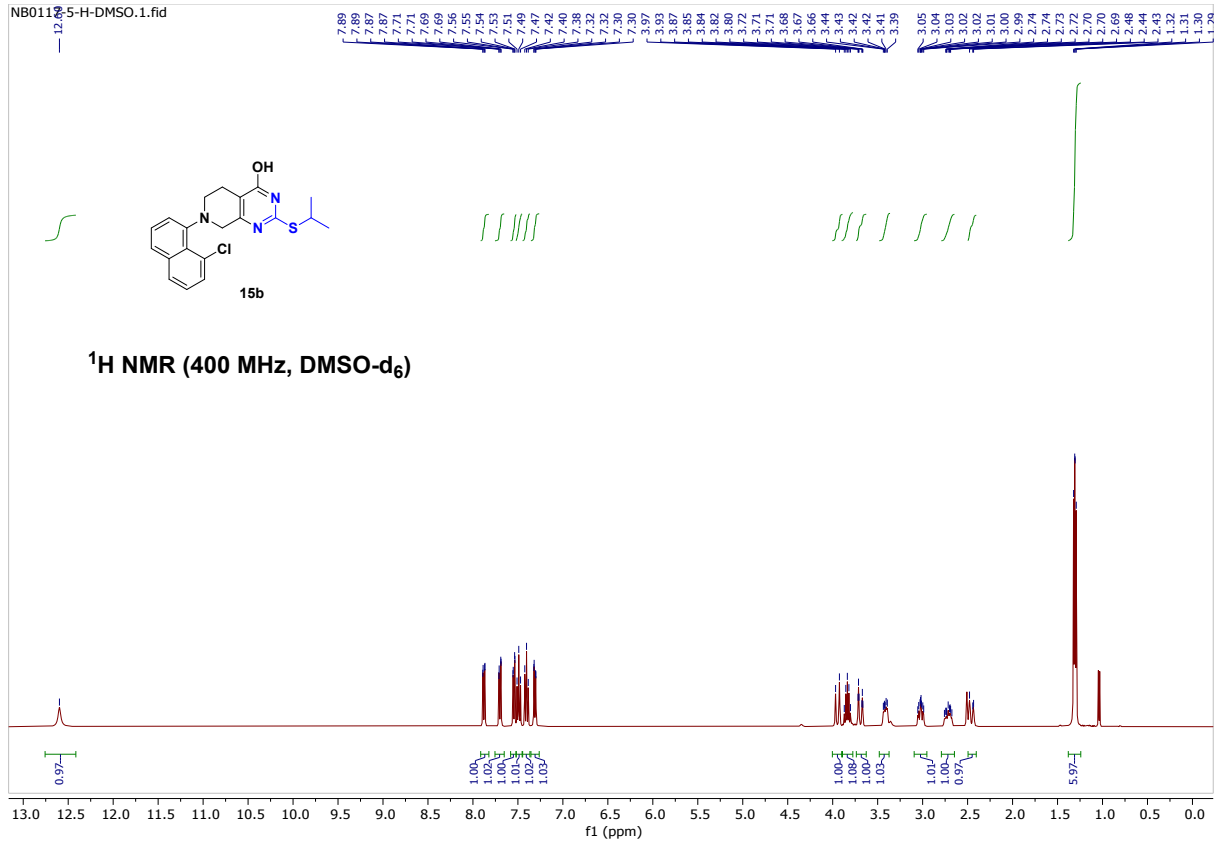
^{13}C NMR (100 MHz, $CDCl_3$)



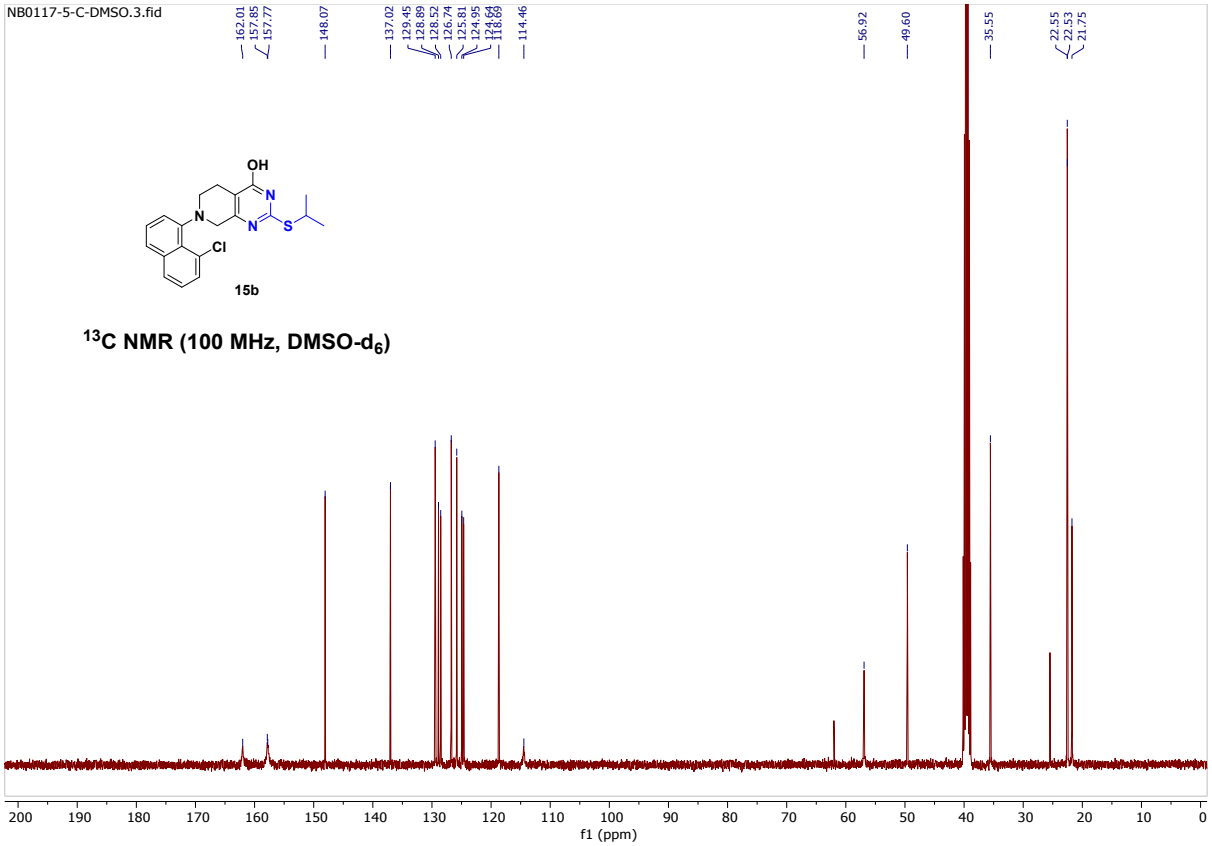
^{1}H NMR (400 MHz, DMSO-d_6)



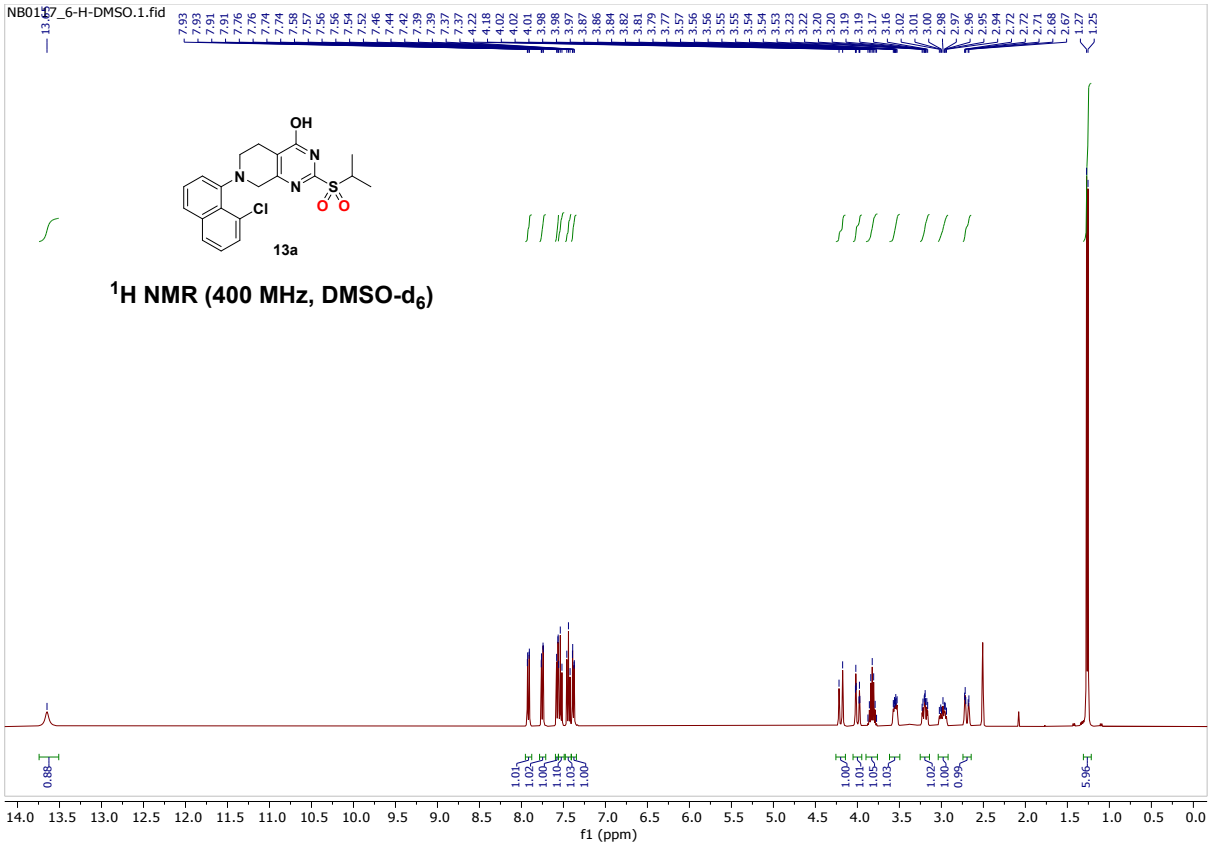
^{13}C NMR (100 MHz, DMSO-d_6)

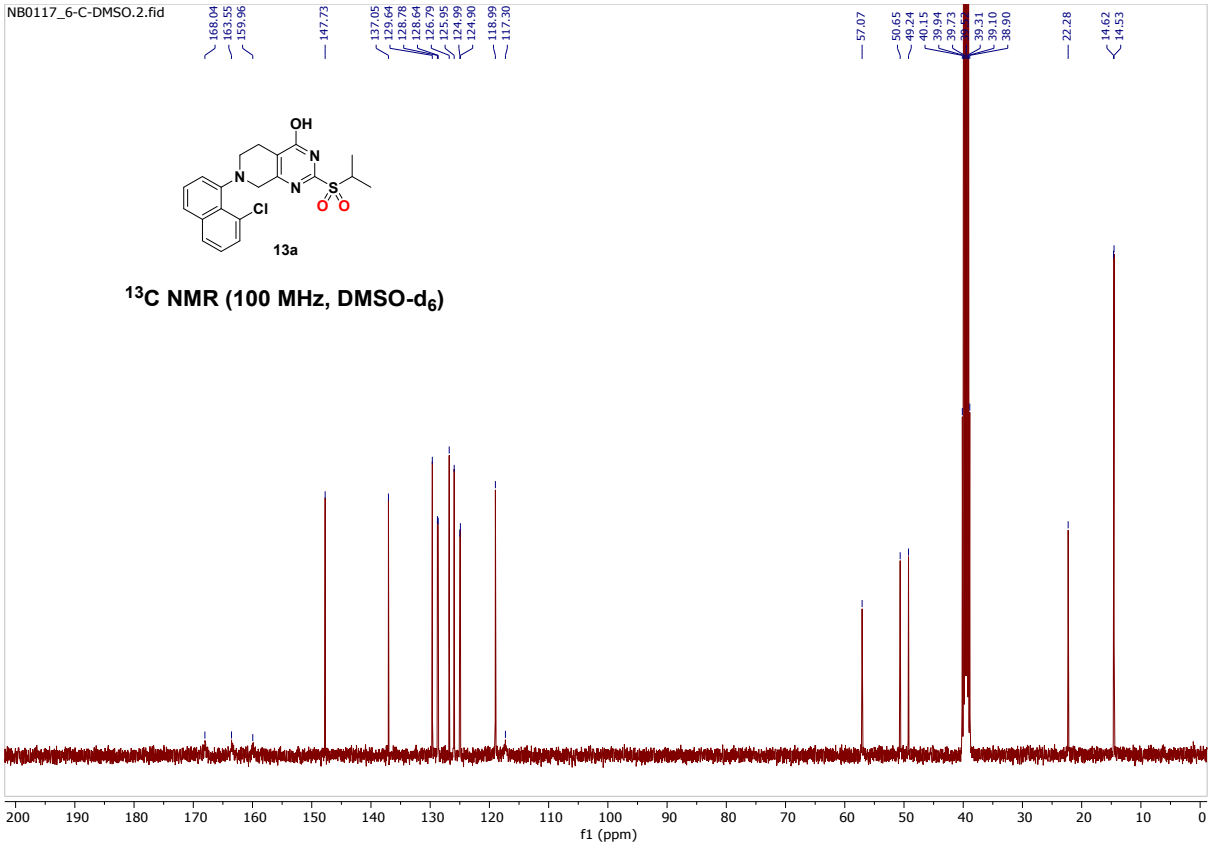


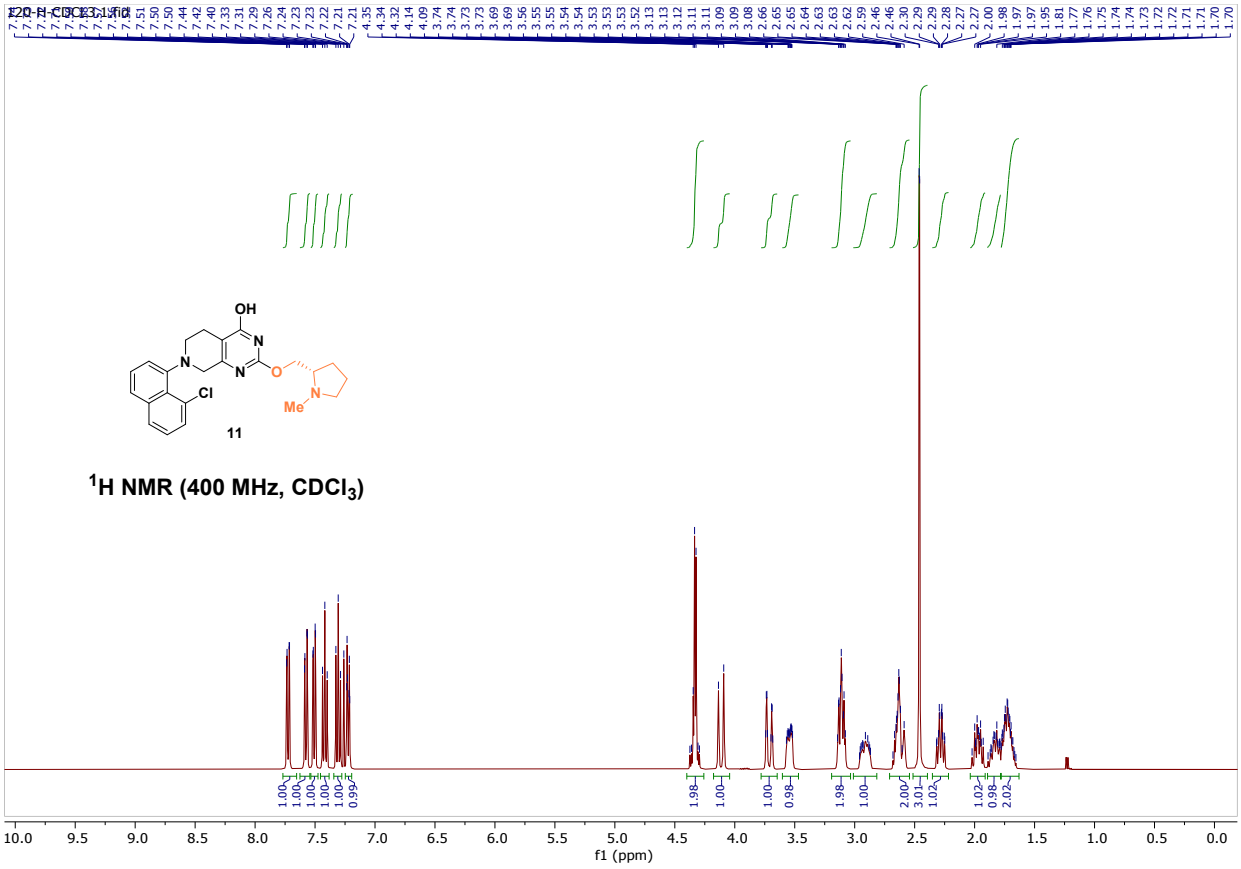
^{1}H NMR (400 MHz, DMSO-d_6)

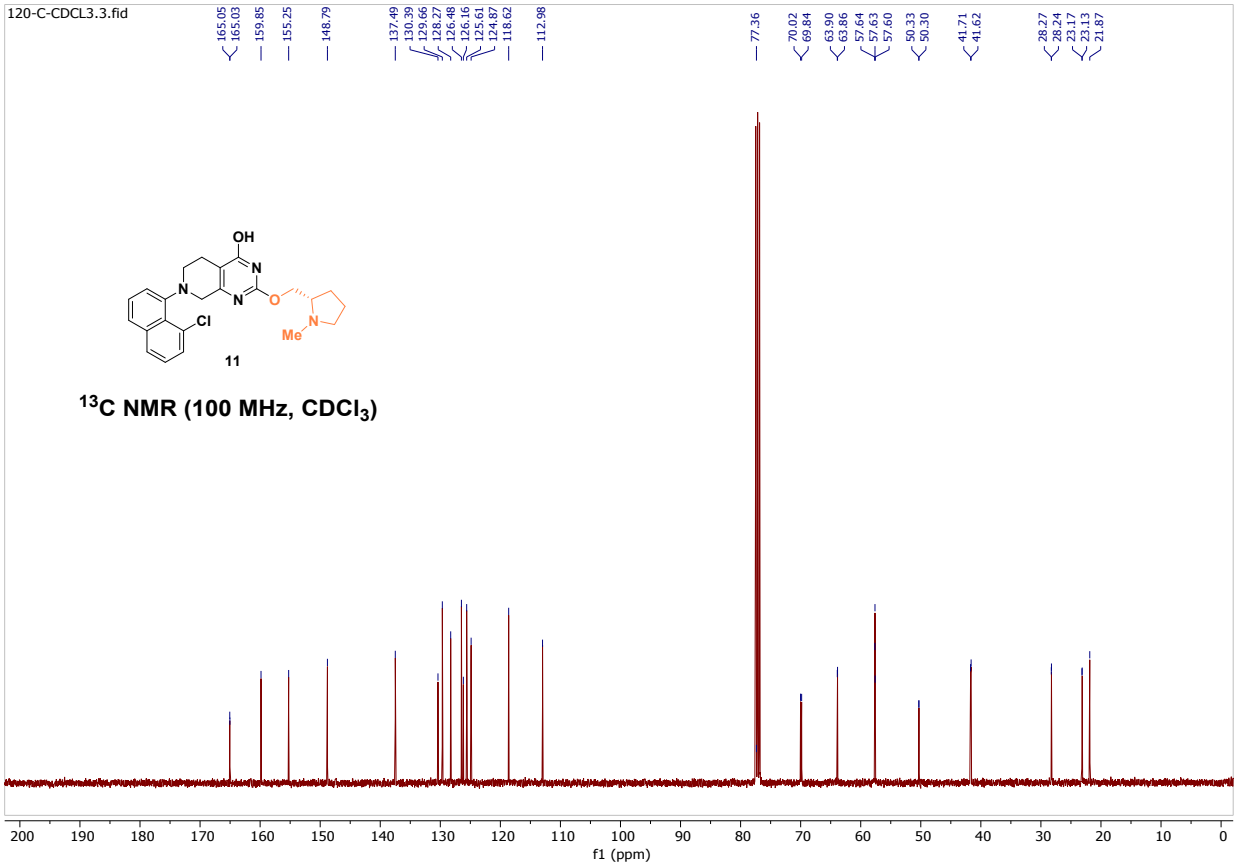


^{13}C NMR (100 MHz, DMSO-d_6)


NB0117_6-H-DMSO.1.fid
13a
^{1}H NMR (400 MHz, DMSO-d$_6$)
f1 (ppm)


NB0117_6-C-DMSO.2.fid
13a
^{13}C NMR (100 MHz, DMSO-d$_6$)
f1 (ppm)


120-H-CDCL3.1.fid
OH
N
N
N
O
N
Me
Cl
11
1H NMR (400 MHz, CDCl3)
f1 (ppm)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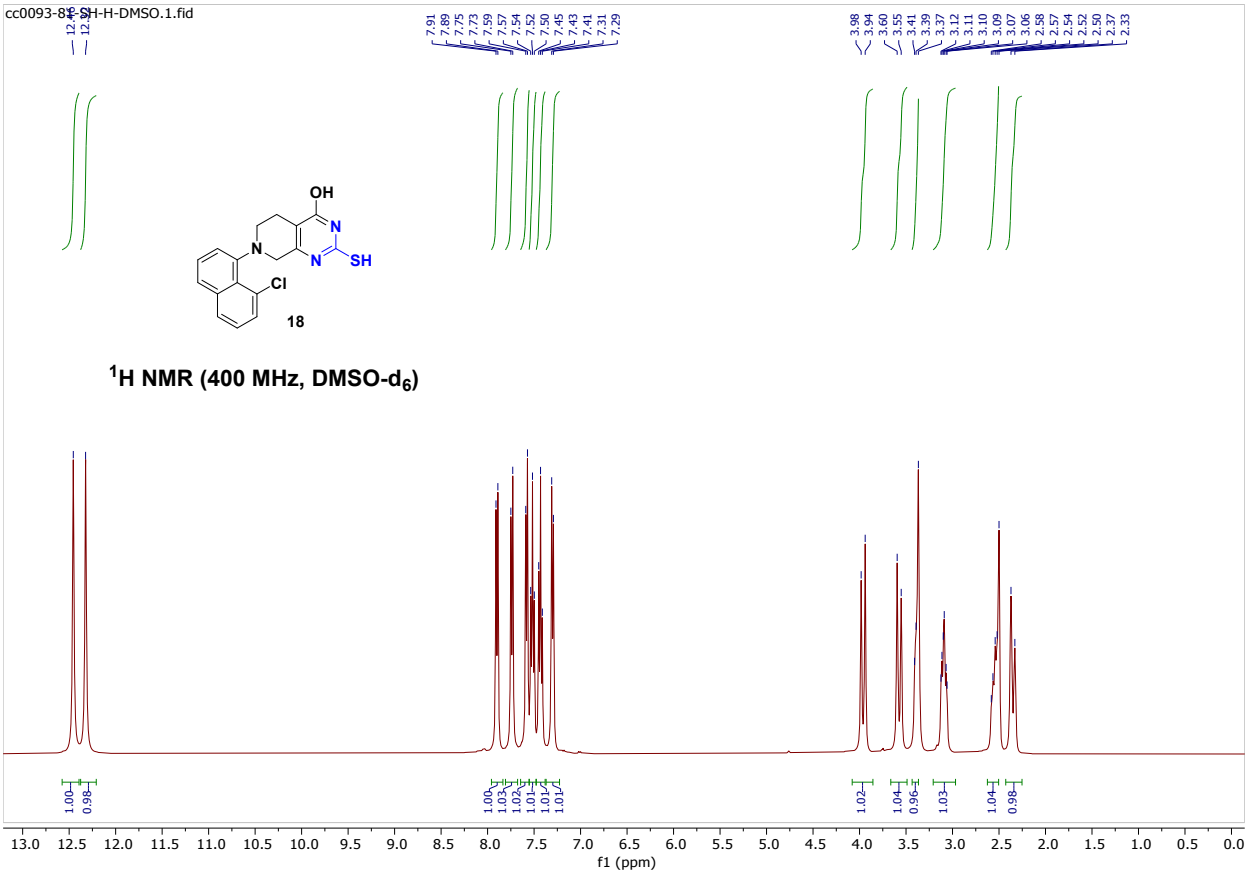
N
N
N
O
N
Me
Cl
11
13C NMR (100 MHz, CDCl3)
f1 (ppm)


cc0093-8-SH-H-DMSO.1.fid
12.49
12.47
7.91
7.89
7.75
7.73
7.59
7.57
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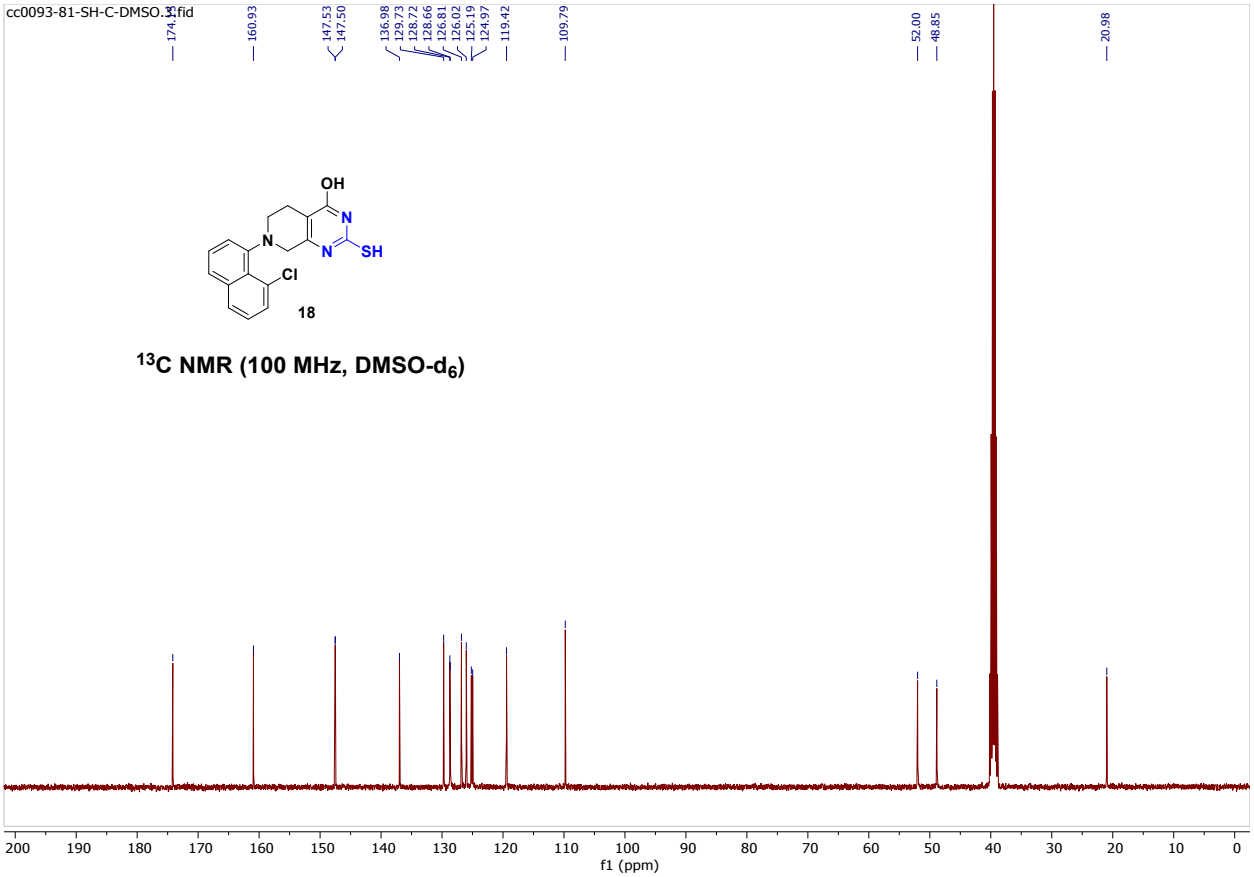
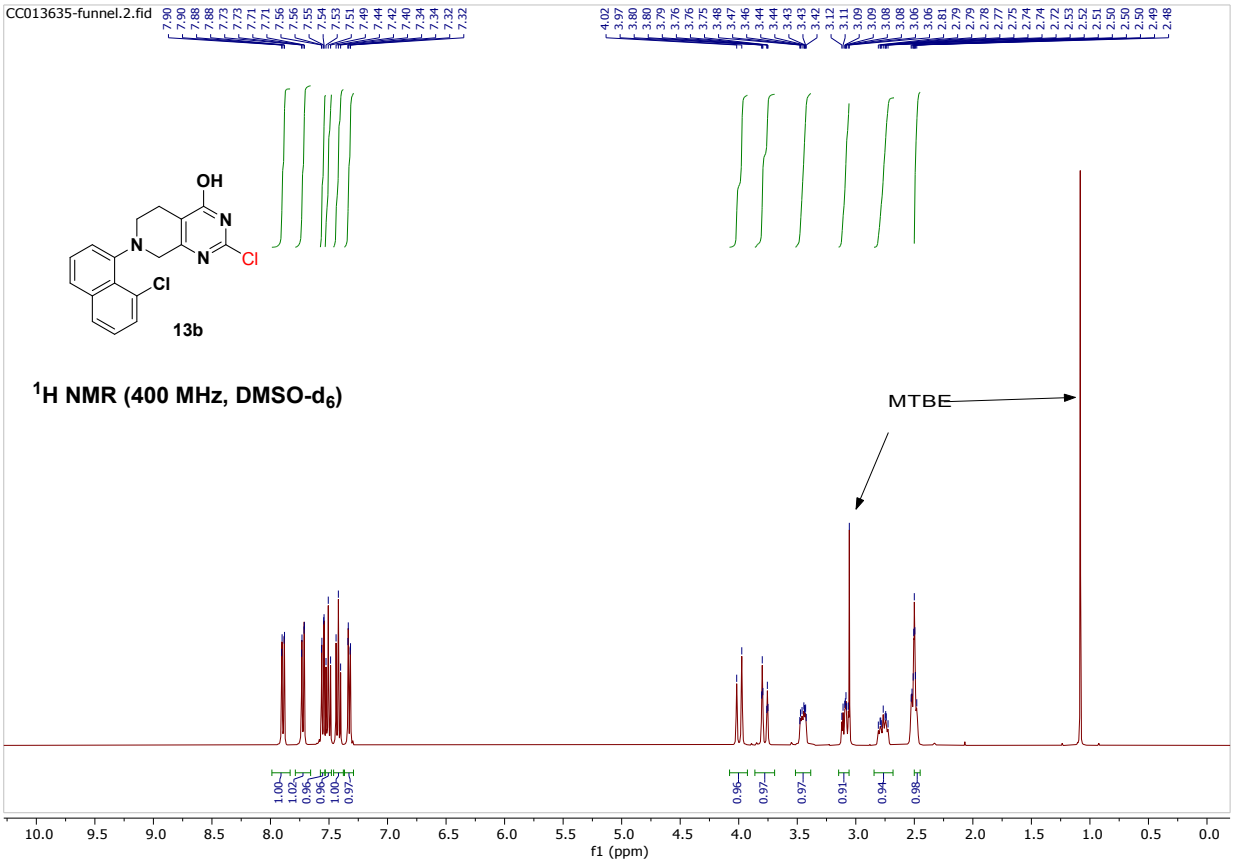
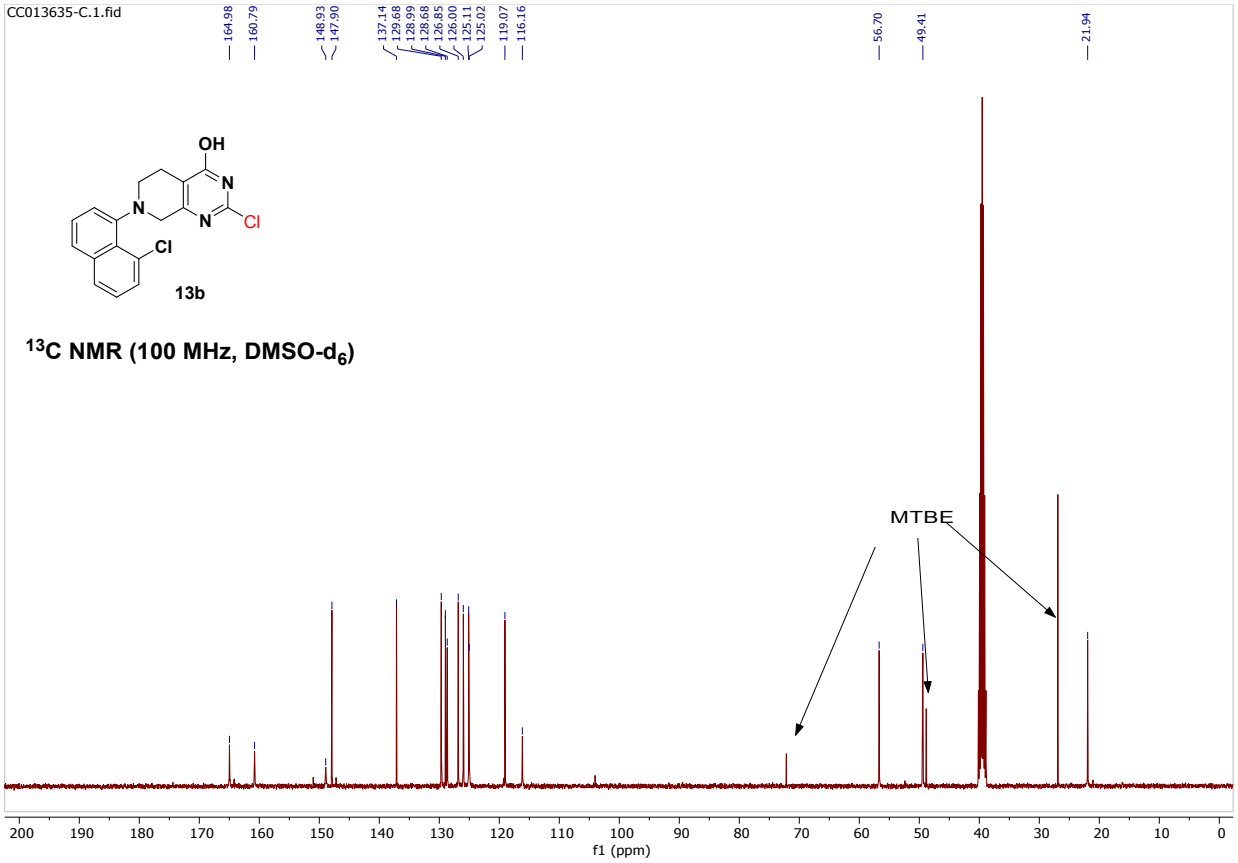
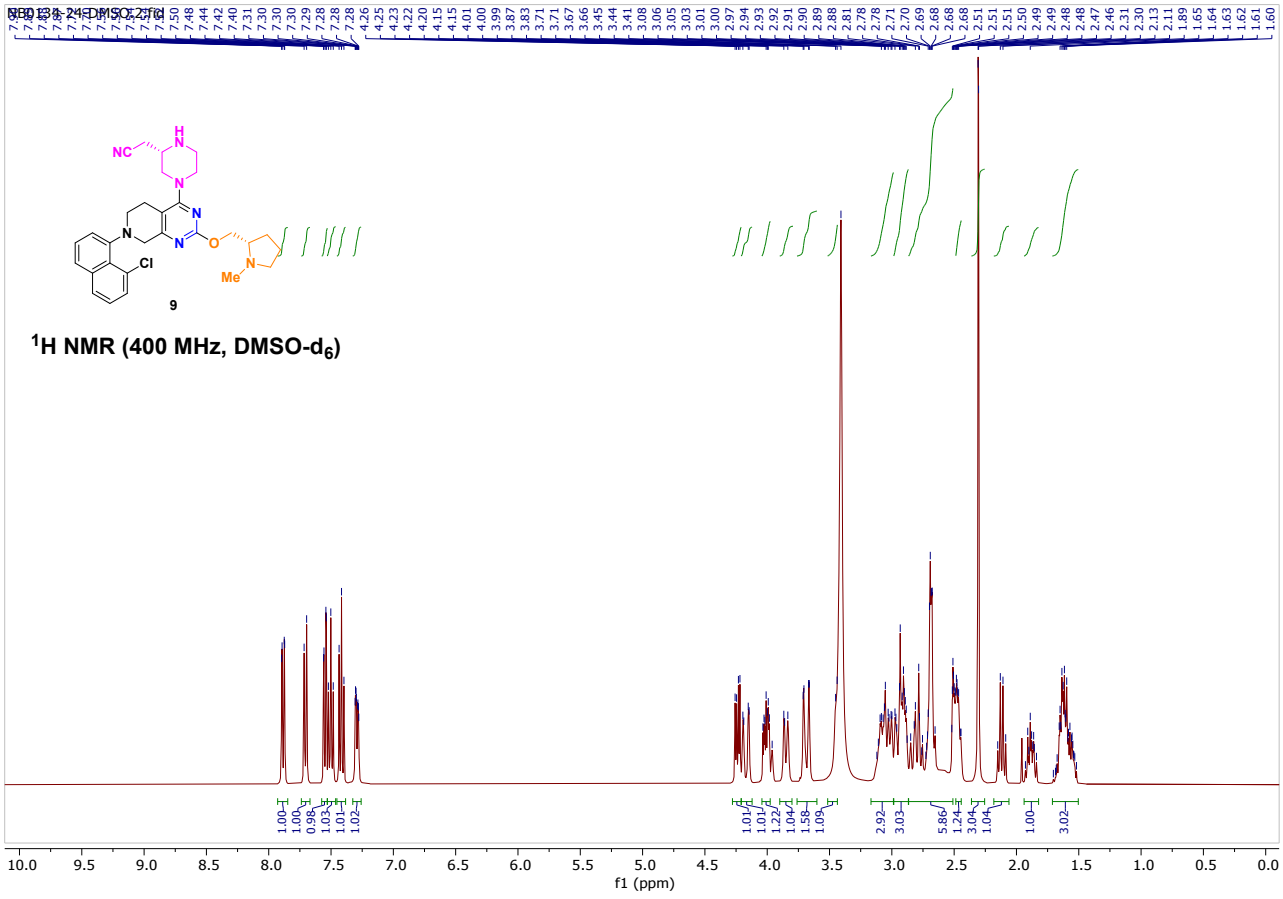
7.52
7.50
7.45
7.43
7.41
7.31
7.29
3.98
3.94
3.60
3.55
3.41
3.39
3.37
3.12
3.11
3.10
3.09
3.07
3.06
2.58
2.57
2.54
2.52
2.50
2.37
2.33
OH
N
N
SH
N
Cl
18
1H NMR (400 MHz, DMSO-d6)
1.00
0.98
1.00
1.03
1.02
1.01
1.01
1.01
1.02
1.04
0.96
1.03
1.04
0.98
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


cc0093-81-SH-C-DMSO.3.fid
174.34
160.93
147.53
147.50
136.98
129.73
128.72
128.66
126.81
126.02
125.19
124.97
119.42
109.79
52.00
48.85
20.98
OH
N
N
SH
N
Cl
18
13C NMR (100 MHz, DMSO-d6)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

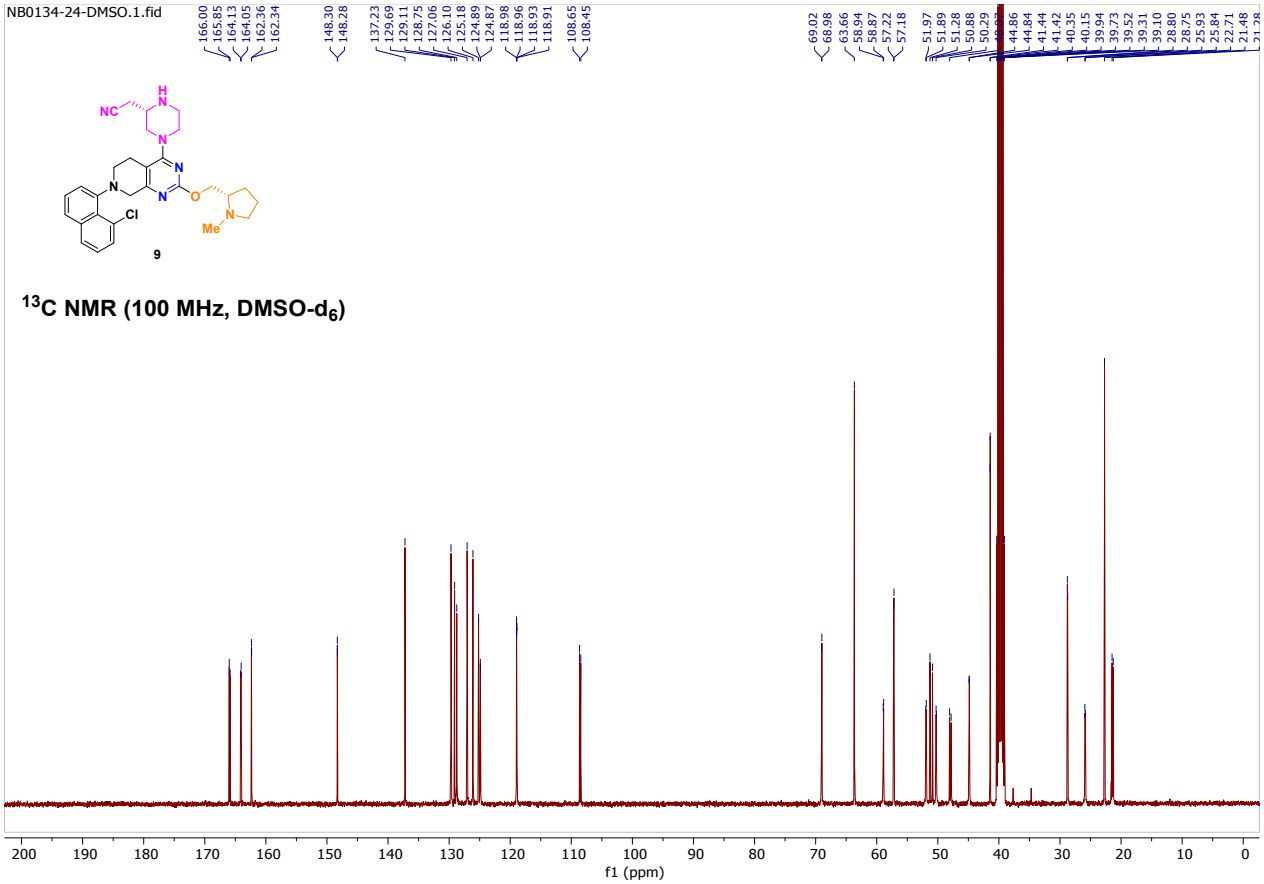

CC013635-funnel.2.fid
7.90
7.90
7.88
7.88
7.73
7.73
7.71
7.71
7.56
7.56
7.55
7.54
7.53
7.51
7.49
7.44
7.42
7.40
7.34
7.32
7.32
4.02
3.97
3.80
3.80
3.79
3.76
3.76
3.75
3.48
3.47
3.46
3.44
3.44
3.43
3.43
3.42
3.12
3.11
3.09
3.09
3.08
3.08
3.06
3.06
2.81
2.79
2.79
2.78
2.77
2.75
2.74
2.74
2.72
2.53
2.52
2.51
2.50
2.50
2.50
2.49
2.48
OH
N
N
N
Cl
Cl
13b
1H NMR (400 MHz, DMSO-d6)
MTBE
1.00
1.02
0.96
0.96
1.00
0.97
0.96
0.97
0.97
0.91
0.94
0.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

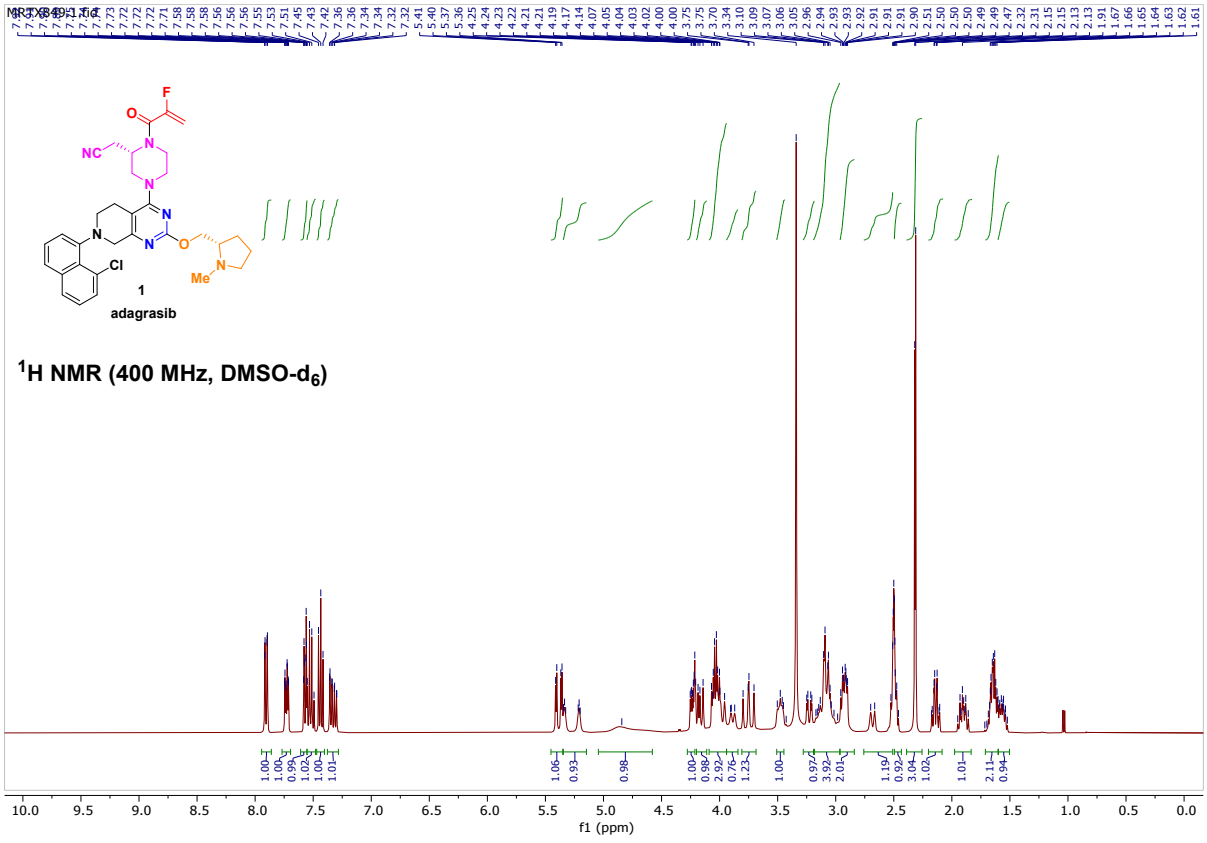


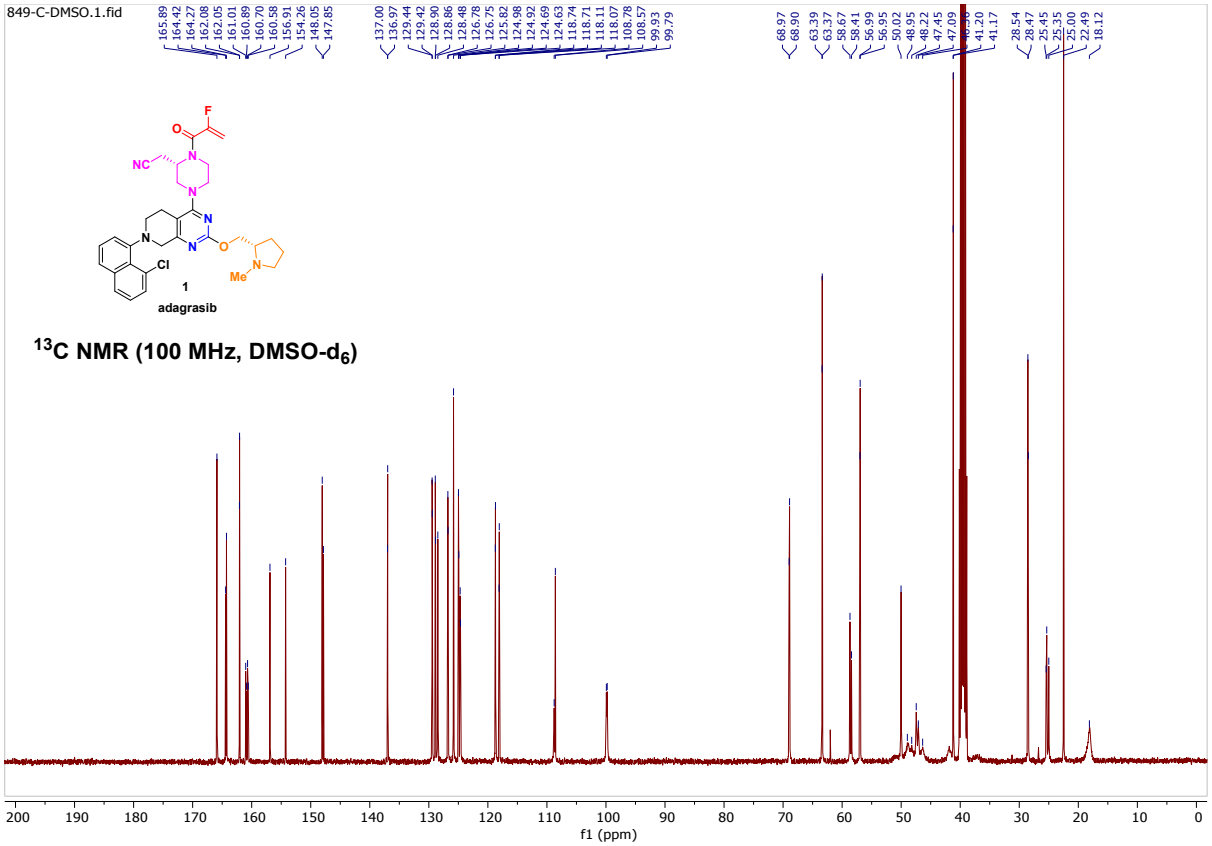
^{13}C NMR (100 MHz, DMSO-d_6)

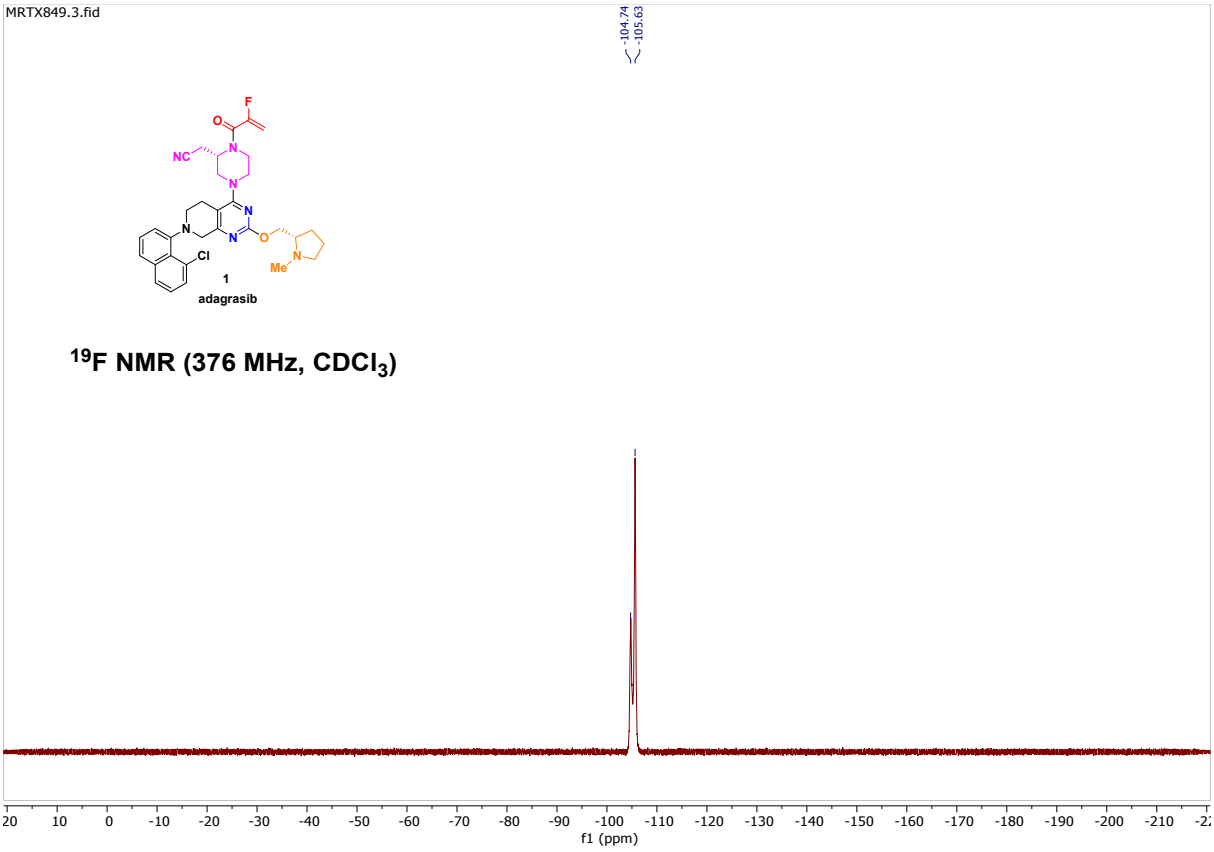


^{1}H NMR (400 MHz, DMSO-d_6)


NB0134-24-DMSO.1.fid
9
13C NMR (100 MHz, DMSO-d6)
f1 (ppm)


1
adagrasib
1H NMR (400 MHz, DMSO-d6)
f1 (ppm)


849-C-DMSO.1.fid
165.89
164.42
164.27
162.08
162.05
161.01
160.89
160.70
160.58
156.91
154.26
148.05
147.85
137.00
136.97
129.44
129.42
128.90
128.86
128.48
126.78
126.75
125.82
124.98
124.92
124.69
124.63
118.74
118.71
118.11
118.07
108.78
108.57
99.93
99.79
68.97
68.90
63.39
63.37
58.67
58.41
56.99
56.95
50.02
48.95
48.22
47.45
47.09
41.20
41.17
28.54
28.47
25.45
25.35
25.00
22.49
18.12
F
O
NC
N
N
N
N
N
O
N
Me
Cl
1
adagrasib
13C NMR (100 MHz, DMSO-d6)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MRTX849.3.fid
-104.74
-105.63
F
O
NC
N
N
N
N
O
N
Me
Cl
1
adagrasib
19F NMR (376 MHz, CDCl3)
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

Section 9. References

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