Supporting information

One-pot Synthesis of 4-Pyrimidone-2-Thioether through Base/Acid-Mediated Concentration of *S*-Alkylisothiourea and β-Ketoester

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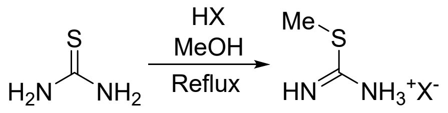
Contents

Section 1. General Experimental Details

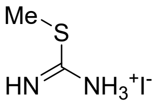
All reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz and 500 MHz Bruker Avance nuclear magnetic resonance (NMR) Spectrometer. Chemical shifts were reported in ppm relative to the residual 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. HRMS analysis was performed on an LCMS with Agilent 1260 HPLC+ 6530 (QTOF) instruments. Melting point was analyzed by DSC (TA DSC2500). Compound assay was determined by qNMR with 1,3,5-trimethoxybenzene as the internal standard.

Section 2. Synthesis of *S*-alkylisothiourea

2.1. Synthesis *S*-methylisothiouronium Salts with Different Counter Anion



X = Cl⁻, Br⁻, MsO⁻



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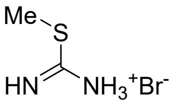
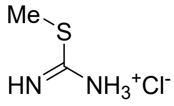
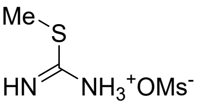


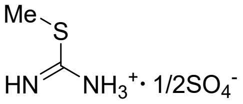
2.0 g
qNMR 96.6%
AIY 88.7%



4.7 g
qNMR 95.1%
AIY 74.0%



8.7 g
qNMR 99.6%
AIY 92.8%



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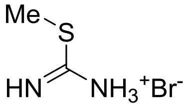
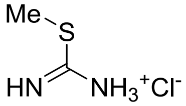
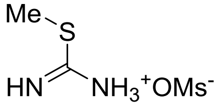


S-Methylisothiouronium Bromide A suspension of thiourea (990 mg, 13.0 mmol) in HBr/MeOH (18 mL, 5-10% HBr/MeOH form TCI) was refluxed for 3 h (70 °C external temp.), turning a clear solution. The subsequent solvent evaporation precipitated a solid, which was re-suspended with 2-MeTHF/MeOH (10:1. 5.5 mL). Vacuum filtration followed to afford the title compound as a white solid (2.00 g, 89.9% yield). **^{1}H NMR** (400 MHz, DMSO) δ 9.02 (d, *J* = 16.9 Hz, 4H), 2.62 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 172.4, 14.3. **HRMS** (ESI) calculated for $C_2H_7N_2S^+$: 91.0324 [M-Br]$^+$, found: 91.0326



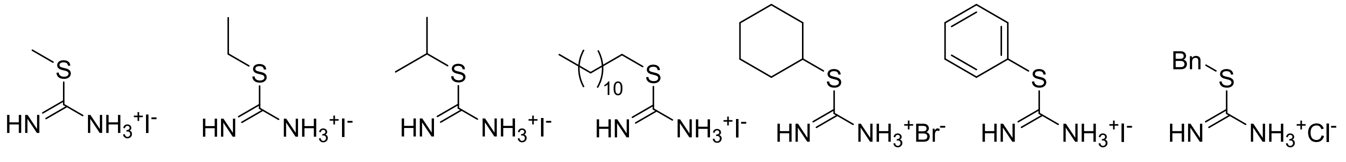
S-Methylisothiouronium Chloride To a suspension of thiourea (3.80 g, 50.0 mmol) in methanol was added 4N HCl/dioxane (16mL). The mixture was refluxed for 15 h, turning into a clear solution. The solvent was removed under reduced pressure. EtOAc (10 mL) was added to the crude and evaporated, twice. EtOAc (20mL) was added, and the suspension was cooled to 0 °C, a white solid precipitating out. Filtration followed to afford the title compound as a white solid (4.70 g, 74.0% yield). **^{1}H NMR** (400 MHz, DMSO) δ 9.29 (d, *J* = 23.3 Hz, 4H), 2.62 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 172.3, 14.4. **HRMS** (ESI) calculated for $C_2H_7N_2S^+$: 91.0324 [M-Cl]$^+$, found: 91.0324



S-Methylisothiouronium Mesylate: To a suspension of thiourea (3.80 g, 50.0 mmol) in MeOH (25mL) was added MsOH (3.7 mL, 57 mmol) dropwise at rt. The suspension was refluxed for 15 h, turning into a clear solution. The mixture was concentrated under reduced pressure, a pale-yellow solid crashing out. was added to Resuspension with 2-MeTHF (40 mL) and filtration yielded a white solid (8.68g, 92.9%). **^{1}H NMR** (400 MHz, DMSO) δ 9.17 (s, 2H), 9.05 (s, 2H), 2.60 (s, 3H), 2.47 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 172.3, 40.7, 14.2. **HRMS** (ESI) calculated for $C_2H_7N_2S^+$: 91.0324 [M-OMs]$^+$, found: 91.0324

2.2. Synthesis of *S*-alkylisothiouronium Iodide

The following *S*-alkylisothiourea was synthesized according to literature procedures[1]:



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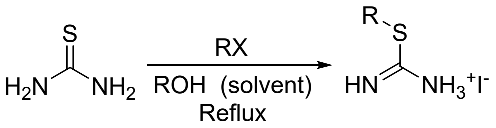
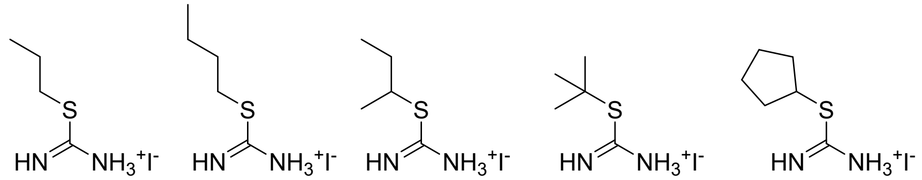
The following *S*-alkylisothiourea was synthesized with bellow procedure:





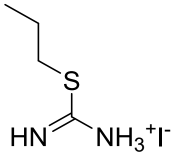
2.32 g
qNMR 97.5%
AIY 91.9%
Brown oil

2.23 g
qNMR 99.1%
AIY 84.2%
White solid

7.4 g
qNMR 95.6%
AIY 90.1%
Brown oil

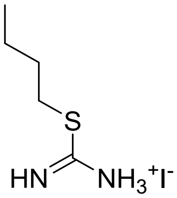
1.67 g
qNMR 98.3%
AIY 62.9%
white solid

7.58 g
qNMR 97.0%
AIY 95%
Brown oil



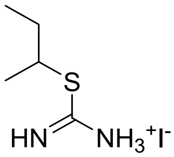
S-*n*-Propylisothiouronium iodide

To a suspension of thiourea (760 mg, 10.0 mmol) in *n*-propanol (5.0 mL) at rt was added 1-iodopropane (1.87 g, 1.10 equiv.). The mixture was refluxed for 15 h, turning to a clear brown solution. The solvent was removed under reduced pressure. By column chromatography (silica gel, DCM/MeOH 9/1 R_f 0.35 and 0.25, product and thiourea), the title compound was obtained as a brown oil (2.32 g, 94.3%). **^{1}H NMR** (400 MHz, DMSO) δ 8.95 (s, 4H), 3.21–3.11 (m, 2H), 1.71–1.58 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).**^{13}C NMR** (101 MHz, DMSO) δ 170.8, 49.5, 32.9, 22.9, 13.7. **HRMS** (ESI) calculated for $C_4H_{11}N_2S^+$:119.0638 [M-I]$^+$, found: 119.0634



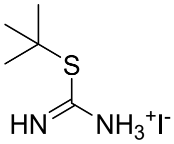
_S_-_n_-Butylisothiouronium iodide

To a suspension of thiourea (760mg, 10 mmol) in *n*-butanol (5.0 mL) was added 1-iodobutane (2.02g, 1.10 equiv.). The mixture was refluxed for 15 h, turning to a clear brown solution. A white solid crashed out as the solution cooled to 0 °C. Ensuing addition of *n*-Heptane (10 mL), 20-min sonication, and filtration yielded the title compound as a white solid (2.23 g, 85.7%). **^{1}H NMR** (400 MHz, DMSO) δ 8.95 (s, 4H), 3.17 (t, *J* = 7.4 Hz, 2H), 1.71–1.49 (m, 2H), 1.49–1.26 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 170.7, 31.2, 30.8, 21.9, 14.3. **HRMS** (ESI) calculated for $C_5H_{13}N_2S^+$: 133.0794 [M-I]$^+$, found: 133.0794



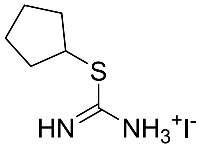
_S_-_sec_-Butylisothiouronium iodide

To a suspension of thiourea (2.28 g, 30.0 mmol) in *sec*-butanol (3.4 mL) at rt was added 2-iodobutane (5.63 g, 1.10 equiv.). The mixture was refluxed for 3 h, turning to a clear brown solution. Subsequent solvent removal and column chromatography (silica gel, DCM/MeOH 20/1) afforded the title compound as brown oil (7.40 g, 94.8%). **^{1}H NMR** (400 MHz, DMSO) δ 8.98 (s, 1H), 3.85–3.72 (m, 1H), 1.68–1.57 (m, 2H), 1.31 (d, *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 170.0, 43.6, 29.6, 21.1, 11.7. **HRMS** (ESI) calculated for $C_5H_{13}N_2S^+$: 133.0794 [M-I]$^+$, found: 133.0795.



_S_-_tert_-Butylisothiouronium iodide

To a suspension of thiourea (760 mg, 10.0 mmol) in *t*-butanol (5.0 mL) was added *t*-butyl iodide (2.5 g, 1.4 equiv.). The suspension was refluxed for 15 h, turning a brown solution. The solvent was removed under reduced pressure. A white solid crashed out upon addition of ethyl acetate (5 mL). The suspension was sonicated, reduced to 0°C, and stirred for 30 min. Filtration and cake washing with ethyl acetate (2 mL twice) afforded the title compound as a white solid (1.67 g, 64.1%). **^{1}H NMR** (400 MHz, DMSO) δ 9.12 (s, 4H), 1.52 (s, 9H). **^{13}C NMR** (101 MHz, DMSO) δ 166.8, 51.9, 31.9. **HRMS** (ESI) calculated for $C_5H_{13}N_2S^+$: 133.0794 [M-I]$^+$, found: 133.0792.

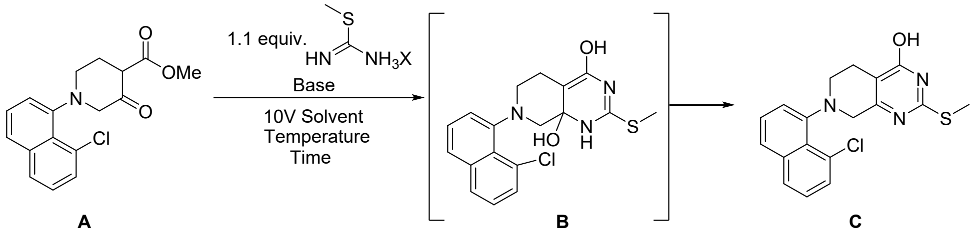


_S_-Cyclopentylisothiouronium iodide

To a suspension of thiourea (2.16 g, 28.4 mmol) in cyclopentanol (9.0 mL) was added iodocyclopentane (2.5 g, 1.1 equiv.). The suspension was refluxed for 4 h, turning a brown solution. The solvent was then azeotropically removed with toluene (3mL). By column chromatography (silica gel, DCM/MeOH 15/1), the title compound was obtained as a brown oil (7.58 g, 98.1%). **^{1}H NMR** (400 MHz, DMSO) δ 8.96 (d, *J* = 21.2 Hz, 4H), 4.03–3.94 (m, 1H), 2.21–2.11 (m, 2H), 1.79–1.68 (m, 2H), 1.68–1.60 (m, 2H), 1.60–1.49 (m, 2H). **^{13}C NMR** (101 MHz, DMSO) δ 170.6, 43.9, 33.6, 25.1. **HRMS** (ESI) calculated for $C_6H_{13}N_2S^+$: 145.0794 [M-I]$^+$, found: 145.0794.

Section 3. Reaction Condition Optimization

3.1. Counter Anion Effect and Base Effect at Stage 1



Entry	Counter Ion	Base	Solvents	Temp. (°C)	Time (h)	LCAP (%)		
						A	B	C
1	**I^-**	DIPEA	2-MeTHF	0	3	0.5	94.4	5.1
2	**Br^-**	DIPEA	2-MeTHF	0	3	71.2	25.2	3.6
3	**Cl^-**	DIPEA	2-MeTHF	0	3	94.3	5.6	0.0
4	**Mesylate**	DIPEA	2-MeTHF	0	3	100.0	0.0	0.0
5	**Semisulfate**	DIPEA	2-MeTHF	0	3	100.0	0.0	0.0
6	**I^- (1.5 equiv.)**	DIPEA	2-MeTHF	0	3	1.3	92.2	6.6
7	I^-	TEA	2-MeTHF	0	3	7.3	89.9	2.7
8	I^-	DIPEA	2-MeTHF	0	3	4.9	89.3	5.9
9	I^-	NMP	2-MeTHF	0	3	99.0	1.0	0.0
10	I^-	DBU	2-MeTHF	0	3	68.6	9.5	0.0
11	I^-	Pyridine	2-MeTHF	0	3	100.0	0.0	0.0
12	I^-	NaOEt	2-MeTHF	0	3	64.9	23.1	3.5
13	I^-	NaOt-Am	2-MeTHF	0	3	21.4	60.0	7.2
14	I^-	*t*BuONa	2-MeTHF	0	3	12.9	80.7	0.0
15	I^-	K_2CO_3	2-MeTHF	0	3	11.3	76.7	4.3
16	I^-	Cs_2CO_3	2-MeTHF	0	3	47.4	37.4	4.5
17	I^-	K_3PO_4	2-MeTHF	0	3	54.3	37.7	4.5
18	I^-	Na_2CO_3	2-MeTHF	0	3	98.4	1.6	0
19	I^-	DIPEA (2.0 equiv.)	2-MeTHF	0	3	7.6	87.0	5.4
20	I^-	DIPEA (3.0 equiv.)	2-MeTHF	0	3	27.7	65.6	6.7

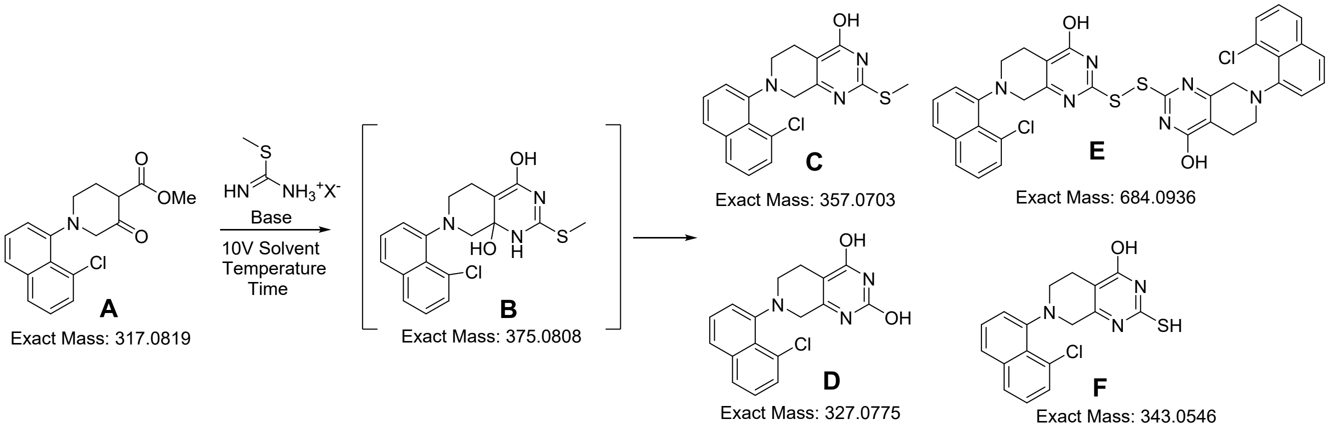
*Stage 1 condition: 0.5 mmol ketoester, 0.55 mmol *S*-methylisothiourea, and 0.55 mmol base in 1.5 mL solvent. Intra-entry comparison was based on area under peak (LCAP) at 220 nm.

Entry	**Counter Ion**	**Base**	**Solvents**	**Temp. (°C)**	**Time (h)**	**LCAP (%)**		
						A	**B**	**C**
21	I^-	DIPEA	THF	0	3	2.6	92.6	4.8
22	I^-	DIPEA	DMF	0	3	18.3	75.0	6.7
23	I^-	DIPEA	Dioxane	0	3	6.8	87.0	6.3
24	I^-	DIPEA	DMAc	0	3	36.0	58.6	5.4
25	I^-	DIPEA	NMP	0	3	36.0	58.6	5.3
26	I^-	DIPEA	DMSO	0	3	22.0	70.5	5.6
27	I^-	DIPEA	MTBE	0	3	73.7	20.9	5.4
28	I^-	DIPEA	*i*PrAc	0	3	7.9	86.0	7.1
29	I^-	DIPEA	ACN	0	3	2.0	90.5	7.3
30	I^-	DIPEA	Toluene	0	3	73.9	18.6	7.4
31	I^-	DIPEA	IPA	0	3	17.2	76.2	6.6
32	I^-	DIPEA	2-MeTHF	-10	3	6.2	86.5	7.3
33	I^-	DIPEA	2-MeTHF	25	3	3.6	88.1	7.3
34	I^-	DIPEA	2-MeTHF	0	0.5	45.0	49.9	5.0
35	I^-	DIPEA	2-MeTHF	0	1	24.2	69.9	5.0
36	I^-	DIPEA	2-MeTHF	0	2	5.1	88.2	6.7
37	I^-	DIPEA	2-MeTHF	0	3	2.3	90.9	6.8
38	I^-	DIPEA	2-MeTHF	0	5	1.6	93.9	4.7
39	I^-	DIPEA	2-MeTHF	0	18	0.3	96.7	3.0

3.2. Solvent Effect at Stage 1

*Stage 1 condition: 0.5 mmol ketoester, 0.55 mmol *S*-methylisothiourea, and 0.55 mmol base in 1.5 mL solvent. Intra-entry comparison was based on area under peak (LCAP) at 220 nm

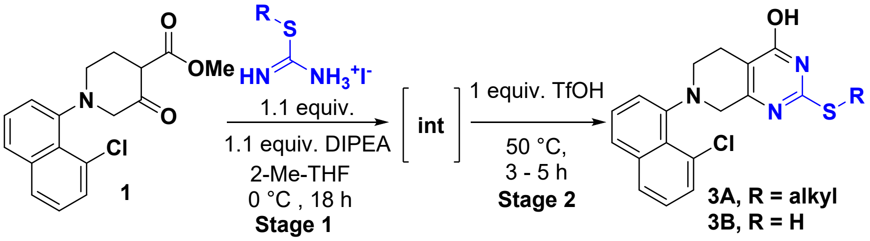
3.3. Acid Effect at Stage 2



Entry	Acid	Equiv.	Temp. (°C) stg2	Time (h) Stg1;Stg2	Stg2 LCAP (%)				
					A	B	C	D	E
1	AcOH	1.0	50	18;5	1.6	93.0	5.4	0	0
2	TFA	1.0	50	18;5	22.6	0	46.9	30.6	0
3	HCl	1.0	50	18;5	0	0	61.1	6.8	24.8
4	MsOH	1.0	50	18;5	8.2	0	65.5	14.9	11.5
5	TfOH	1.0	50	18;5	0	0	78.4	0	14.7
6	TfOH	0.1	50	18;2,27	0;0.9	93.6;76.1	6.4;23.0	0	0
7	TfOH	0.5	50	18;2,27	0;0	2.8;0	70.9;68.9	2.3;3.0	22.9;24.0
8	TfOH	1.5	50	18;2,27	0;0	0;0	74.0;77.1	0;0	16.4;13.0
8	TfOH	1.0	RT	18;1	1.9	88.1	10.0	0	0
9	TfOH	1.0	RT	18;2	1.8	80.6	17.6	0	0
10	TfOH	1.0	RT	18;27	4.8	26.6	58.0	0	10.6

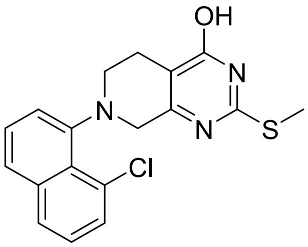
Section 4. Synthesis of 4-Pyrimidone-2-Thioether

4.1. With Different S-alkylisothiourea



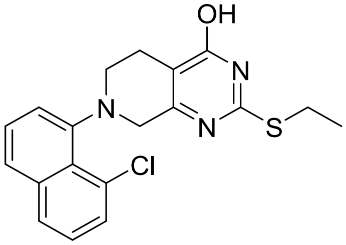
General Procedure:

Stage 1: To a solution of ketoester (3.0-6.0 mmol) and alkylisothiouronium iodide (1.1 equiv.) and in 2-MeTHF (0.33 M with respect to ketoester) at 0 °C under nitrogen was added DIPEA (1.1 equiv.) dropwise along the vial interior. The brown solution generally gradually turned into a white slurry over 2-72 h. The intermediate formation was monitored with UPLC-MS. **Stage 2**: To the slurry at 0 °C was added TfOH (1.0 equiv.) dropwise. The external temperature was elevated to 50 °C in 0.5 h. Upon the consumption of intermediate, distilled water (9.5-1.9 mL) and 20% $Na_2SO_{3(aq.)}$ was added to the reaction mixture at 50 °C. The organic layer was collected and concentrated. Solids were filtered and washed with mixed solvent ACN/2-MeTHF (v/v = 3/1, 2.0-4.0 mL twice, unless otherwise specified).



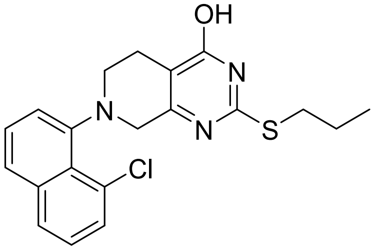
Washed with 2-MeTHF (3.0mL, twice), the title compound was obtained as a light brown solid (mp: 285.5 – 293.0 °C, 742 mg, 69%).

^{1}H NMR (400 MHz, DMSO) δ 12.73 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 4.00 (d, *J* = 17.2 Hz, 1H), 3.77 (d, *J* = 17.2 Hz, 1H), 3.49 (d, *J* = 11.3 Hz, 1H), 3.15–3.05 (m, 1H), 2.81–2.68 (m, 1H), 2.53–2.43 (m, 1H), 2.49 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ 162.1, 149.0, 138.0, 130.4, 129.8, 129.5, 127.7, 126.8, 125.9, 125.6, 119.7, 93.7, 57.8, 56.1, 50.6, 22.6, 13.6.
HRMS (ESI) calculated for $C_{18}H_{17}ClN_3OS^+$:358.0781 $[M+H]^+$, found: 358.0726



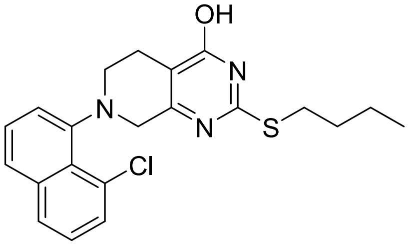
Additionally washed with ACN (3.0 mL, twice), the title compound was obtained as a Light brown solid (mp: 218.1 – 223.2 °C, 2.19 g, 84%)

^{1}H NMR (400 MHz, DMSO) δ 12.68 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.42–7.33 (m, 1H), 3.99 (d, *J* = 17.1 Hz, 1H), 3.76 (d, *J* = 17.2 Hz, 1H), 3.52–3.46 (m, 1H), 3.11 (q, *J* = 7.3 Hz, 2H), 3.09–3.03 (m, 1H), 2.83–2.65 (m, 1H), 2.53–2.44 (m, 1H), 1.30 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (101 MHz, DMSO) δ 162.9, 158.7, 149.0, 138.0, 130.4, 129.8, 129.5, 127.7, 126.8, 125.9, 125.6, 119.7, 115.4, 57.8, 50.6, 25.1, 22.7, 15.3.
HRMS (ESI) calculated for $C_{19}H_{19}ClN_3OS^+$: 372.0937 [M+H]$^+$, found: 372.0934



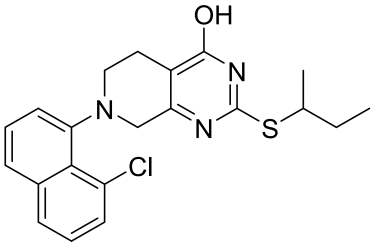
Additionally washed with ACN (2.0 mL, twice), the title compound was obtained as a light brown solid (mp: 193.1 – 195.4 °C, 1.02 g, 85%)

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.91 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.73 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.58 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.36 (dd, *J* = 7.5, 1.2 Hz, 1H), 3.95 (d, *J* = 17.1 Hz, 1H), 3.73 (dt, *J* = 17.2, 2.2 Hz, 1H), 3.44 (dd, *J* = 12.2, 5.7 Hz, 1H), 3.07 (t, *J* = 7.1 Hz, 2H), 2.72 (dt, *J* = 16.8, 7.7 Hz, 1H), 2.51–2.42 (m, 3H), 1.64 (h, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (101 MHz, DMSO) δ 158.6, 149.0, 138.0, 130.4, 129.8, 129.5, 127.7, 126.8, 125.9, 125.6, 119.7, 115.5, 57.8, 50.6, 32.4, 23.0, 22.7, 14.0.
HRMS (ESI) calculated for $C_{20}H_{21}ClN_3OS^+$: 386.1094 [M+H]$^+$, found: 386.1092



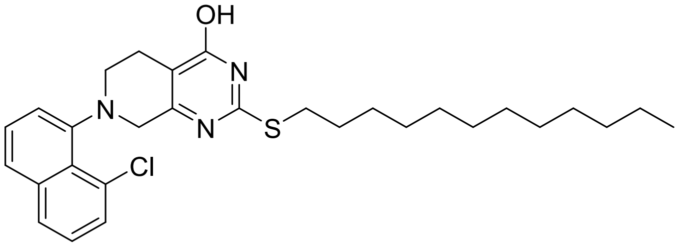
Additionally washed with ACN (3.0 mL, twice), the title compound was obtained as a light brown solid (mp: 174.7 – 180.2 °C, 1.51 g, 73%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.74 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.60 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.53 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.26 (dd, *J* = 7.5, 1.2 Hz, 1H), 4.19 (d, *J* = 17.7 Hz, 1H), 3.78 (d, *J* = 17.7 Hz, 1H), 3.62–3.50 (m, 1H), 3.17 (t, *J* = 7.3 Hz, 2H), 3.15–3.08 (m, 1H), 3.07–2.95 (m, 1H), 2.76–2.65 (m, 1H), 1.68 (tt, *J* = 7.6, 6.4 Hz, 2H), 1.43 (h, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 160.3, 158.2, 149.0, 137.7, 130.6, 129.9, 128.5, 126.7, 126.4, 125.9, 125.2, 118.9, 115.7, 57.9, 50.4, 31.4, 30.6, 22.3, 22.2, 13.9.
HRMS (ESI) calculated for $C_{21}H_{23}ClN_3OS^+$: 400.1250 [M+H]$^+$, found: 400.1248.



Additionally washed with ACN (4.0 mL, twice), the title compound was obtained as a white solid (mp: 211.8 – 215.8 °C, 2.20 g, 91%)

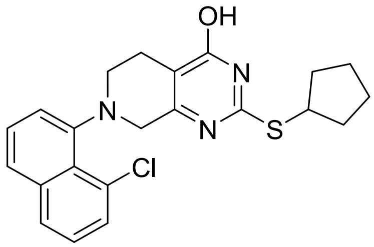
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 7.74 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.60 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.53 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.26 (dd, *J* = 7.5, 1.2 Hz, 1H), 4.20 (d, *J* = 17.6 Hz, 1H), 3.98–3.85 (m, 1H), 3.79 (d, *J* = 17.7 Hz, 1H), 3.22–3.08 (m, 1H), 3.08–2.96 (m, 1H), 2.81–2.64 (m, 1H), 1.82–1.62 (m, 1H), 1.40 (t, *J* = 6.5 Hz, 3H), 1.01 (td, *J* = 7.4, 4.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 160.3, 158.2, 149.0, 137.7, 130.6, 129.9, 128.5, 126.7, 126.4, 125.8, 125.2, 118.9, 115.6, 57.8, 50.4, 50.4, 43.2, 29.7, 29.7, 22.3, 22.3, 20.9, 11.7.
HRMS (ESI) calculated for $C_{21}H_{23}ClN_3OS^+$: 400.1250 [M+H]$^+$, found: 400.1251.



Additionally washed with ACN (3.0 mL, twice), the title compound was obtained as a white solid (mp: 113.9 – 121.9 °C, 2.22 g, 85%)

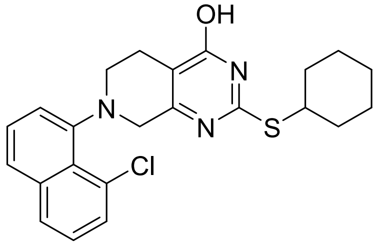
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.31 (s, 1H), 7.74 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.60 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.53 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.4 Hz, 1H), 4.19 (d, *J* =

17.6 Hz, 1H), 3.77 (d, *J* = 17.6 Hz, 1H), 3.69–3.47 (m, 1H), 3.25–3.07 (m, 3H), 3.07–2.92 (m, 1H), 2.81–2.59 (m, 1H), 1.78–1.61 (m, 2H), 1.47–1.33 (m, 2H), 1.33–1.11 (m, 16H), 0.86 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 160.3, 158.1, 149.0, 137.7, 130.6, 129.9, 128.5, 126.7, 126.4, 125.9, 125.2, 118.9, 115.7, 57.9, 50.4, 32.2, 31.0, 30.0, 29.9, 29.8, 29.7, 29.4, 29.4, 29.1, 23.0, 22.3, 14.5.
HRMS (ESI) calculated for $C_{29}H_{39}ClN_3OS^+$: 512.2502 [M+H]$^+$, found: 512.2497.



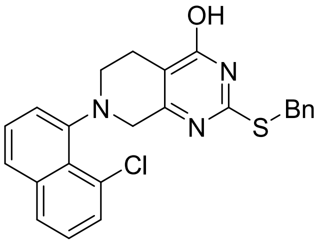
Additionally washed with ACN (3.0 mL, twice), the title compound was obtained as a white solid (mp: 203.1 – 208.5 °C, 1.84 g, 87%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.37 (s, 1H), 7.74 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.59 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.53 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 4.19 (d, *J* = 17.6 Hz, 1H), 4.13–3.98 (m, 1H), 3.78 (d, *J* = 17.6 Hz, 1H), 3.63–3.51 (m, 1H), 3.20–3.08 (m, 1H), 3.08–2.94 (m, 1H), 2.77–2.64 (m, 1H), 2.24–2.11 (m, 2H), 1.83–1.71 (m, 2H), 1.71–1.55 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.6, 160.4, 158.6, 149.0, 137.7, 130.6, 129.9, 128.5, 126.7, 126.4, 125.9, 125.2, 118.9, 115.6, 57.9, 50.4, 44.2, 33.6, 33.5, 25.1, 22.3.
HRMS (ESI) calculated for $C_{22}H_{23}ClN_3OS^+$: 412.1250 [M+H]$^+$, found: 412.1246



For this entry, cyclohexylisothiouronium bromide (1.5 equiv.) and NaI (1.5 equiv.) was used at stage 1. Additionally washed with ACN (4.0 mL, twice), the title compound was obtained as a white solid (mp: 196.8 – 202.0 °C, 1.65 g, 60%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.39 (s, 1H), 7.74 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.26 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.19 (d, *J* = 17.6 Hz, 1H), 3.95–3.83 (m, 1H), 3.79 (d, *J* = 17.6 Hz, 1H), 3.61–3.53 (m, 1H), 3.12 (ddd, *J* = 11.6, 9.9, 3.8 Hz, 1H), 3.08–2.93 (m, 1H), 2.76–2.64 (m, 1H), 2.13–1.99 (m, 2H), 1.81–1.68 (m, 2H), 1.62–1.46 (m, 3H), 1.46–1.33 (m, 2H), 1.33–1.22 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 160.4, 157.9, 149.0, 137.7, 130.6, 129.9, 128.5, 126.7, 126.4, 125.8, 125.2, 119.0, 115.7, 57.9, 50.4, 44.5, 33.3, 33.2, 26.2, 25.9, 22.3.
HRMS (ESI) calculated for $C_{23}H_{25}ClN_3OS^+$: 426.1407 [M+H]$^+$, Found: 426.1402



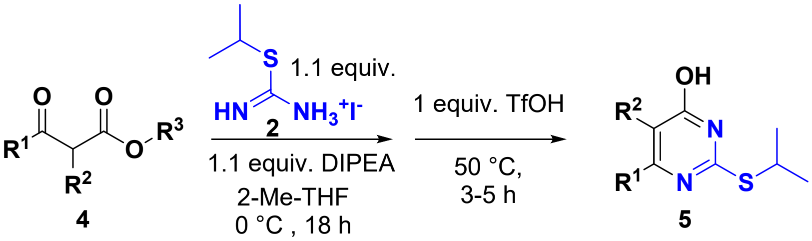
the title compound was obtained as a light brown solid (mp: 155.2 – 160.3 °C, 1.05 g, 75%)

^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.58 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.35 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.31 – 7.22 (m, 2H), 4.41 – 4.28 (m, 2H), 4.03 (d, *J* = 17.2 Hz, 1H), 3.74 (dt, *J* = 17.2, 2.2 Hz, 1H), 3.49 – 3.39 (m, 1H), 3.07 (ddd, *J* = 11.9, 10.0, 4.2 Hz, 1H), 2.77 – 2.64 (m, 1H), 2.44 (d, *J* = 3.3 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 160.5, 156.0, 155.9, 146.4, 135.8, 135.4, 127.8, 127.5, 127.3, 126.9, 126.7, 125.6, 125.1, 124.3, 123.3, 123.0, 117.1, 112.9, 55.2, 47.8, 31.8, 20.1.

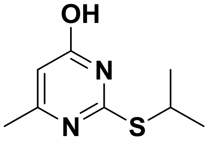
HRMS (ESI) calculated for $C_{24}H_{21}ClN_3OS^+$: 434.1094 $[M+H]^+$, Found: 434.1078.

4.2. With Different Ketoester



General Procedure (unless otherwise specified):

Stage 1: To a solution of ketoester (6.0 mmol) and alkylisothiouronium iodide (1.1 equiv.) and in 2-MeTHF (0.33 M with respect to ketoester) at 0 °C under nitrogen was added DIPEA (1.1 equiv.) dropwise along the vial interior. The brown solution generally gradually turned into a white slurry over 2-72 h. The intermediate formation was monitored with UPLC-MS. **Stage 2**: To the slurry at 0 °C was added TfOH (1.0 equiv.) dropwise. The external temperature was elevated to 50 °C in 0.5 h. Upon the consumption of intermediate, distilled water (9.5-1.9 mL) and 20% $Na_2SO_{3(aq.)}$ was added to the reaction mixture at 50 °C. The organic layer was collected and concentrated. Solids were filtered and washed with mixed solvent ACN/2-MeTHF (v/v = 3/1, 2.0-4.0 mL twice, unless otherwise specified).



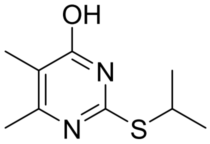
5a, R^3 = Me, 88%
5b, R^3 = Et, 84%
5c, R^3 = *i*-Pr, 78%
5d, R^3 = *t*-Bu, <5%

The title compound was obtained as a white solid (mp: 142.7 - 149.9 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, 1H), 4.04 (hept, *J* = 6.9 Hz, 1H), 2.24 (s, 3H), 1.40 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 165.9, 161.0, 108.4, 36.9, 24.5, 23.2.

HRMS (ESI) calculated for $C_8H_{13}N_2OS^+$: 185.0744 [M+H]$^+$, Found: 185.0743.

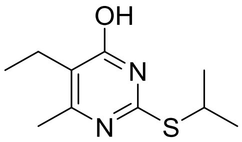


The title compound was obtained as a white solid (mp: 169.2 – 172.4 °C, 0.65 g, 55%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (hept, *J* = 6.9 Hz, 1H), 2.27 (s, 3H), 2.03 (s, 3H), 1.41 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 161.3, 156.4, 116.1, 36.9, 30.7, 24.1, 23.3, 22.3, 11.0.

HRMS (ESI) calculated for $C_9H_{15}N_2OS^+$: 199.0905 [M+H]$^+$, Found: 199.0904

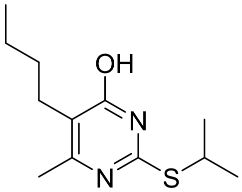


To a solution of ethyl 2-ethyl-3-oxobutanoate (500 mg, 3.16 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (855 mg, 3.47 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (381 mg, 2.95 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 48 hours and 10 °C for 24 hours. TfOH (521 mg, 3.47 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and the residue was purified by silica column (EtOAc/heptane, 0% to 60%), to afford the product as a white solid (mp: 140.2 - 141.9 °C, 297 mg, 1.39 mmol, 44%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.35 (br s, 1H), 3.87 (sep, *J* = 7.0 Hz, 1H), 2.35 (q, *J* = 7.5 Hz, 2H), 2.20 (s, 3H), 1.34 (d, *J* = 7.0 Hz, 6H), 0.97(t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 163.0, 159.2, 157.3, 120.8, 35.8, 23.1, 21.3, 18.5, 13.1.

HRMS (ESI) calculated for $C_{10}H_{17}N_2OS^+$: 213.1062 [M+H]$^+$, Found: 213.1055.



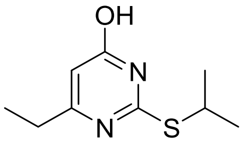
To a solution of ethyl 2-acetylhexanoate (500 mg, 2.68 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (726 mg, 2.95 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0

°C, DIPEA (381 mg, 2.95 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 48 hours and 10 °C for 24 hours. TfOH (443 mg, 2.95 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and the residue was purified by silica column (EtOAc/heptane, 0% to 60%), to afford the product as colorless oil (mp: 95.5 - 98.4 °C, 313 mg, 1.30 mmol, 49%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.34 (br s, 1H), 3.87 (sep, *J* = 7.0 Hz, 1H), 2.33 (t, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 1.34–1.30 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 163.2, 159.5, 157.0, 119.7, 35.7, 30.6, 24.9, 23.1, 22.6, 21.6, 14.2.

LCMS (ESI) calculated for $C_{12}H_{21}N_2OS^+$: 241.1375 [M+H]$^+$, Found: 241.1373.

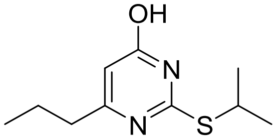


To a solution of ethyl 3-oxopentanoate (500 mg, 3.46 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (938 mg, 3.81 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (493 mg, 3.81 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 19 hours and TfOH (572 mg, 3.81 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and the residue was purified by silica column (EtOAc/heptane, 0% to 60%), to afford the product as an off-white solid (mp: 81.9 - 85.2 °C, 451 mg, 2.27 mmol, 65%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.40 (br s, 1H), 5.92 (br s, 1H), 3.88 (sep, *J* = 7.0 Hz, 1H), 2.43 (q, *J* = 7.5 Hz, 2H), 1.35 (d, *J* = 7.0 Hz, 6H), 1.13 (t, *J* = 7.5 Hz, 2H),

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 169.2, 163.6, 161.7, 106.3, 36.0, 30.2, 23.0, 12.5.

HRMS (ESI) calculated for $C_9H_{15}N_2OS^+$: 199.0905 [M+H]$^+$, Found: 199.0901.

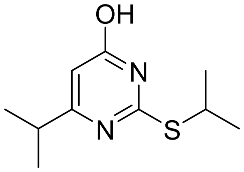


To a solution of ethyl 3-oxohexanoate (300 mg, 1.89 mmol) in 2-MeTHF (3.0 mL), isopropylisothiouronium iodide (513 mg, 2.08 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (269 mg, 2.08 mmol) was added dropwise, and the mixture was turned into a white slurry. The reaction mixture was stirred at 0 °C for 19 hours and TfOH (313 mg, 2.08 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (3.0 mL) was added, and the water layer was extracted with 2-MeTHF (1.5 mL). The combined organic layer was concentrated and triturated with CH_3CN/water (1:3, 1.2 mL). The solid was collected by filtration and washed with CH_3CN/water (1:3, 0.6 mL), to afford the product as a light-yellow solid (mp: 126.8 – 130.1 °C, 355 mg, 1.67 mmol, 88%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.41 (br s, 1H), 5.91 (br s, 1H), 3.88 (sep, *J* = 7.0 Hz, 1H), 2.39 (t, *J* = 7.5 Hz, 2H), 1.65–1.58 (m, 2H), 1.36 (d, *J* = 7.0 Hz, 6H), 0.88 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 167.8, 163.6, 161.8, 107.2, 38.9, 36.0, 23.0, 21.0, 13.8.

HRMS (ESI) calculated for $C_{10}H_{17}N_2OS^+$: 213.1062 [M+H]$^+$, Found: 213.1055.

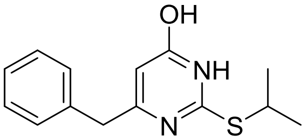


The title compound was obtained as a white solid (amorphous, no sharp mp, 0.78 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.37 (s, 1H), 5.97 (s, 1H), 4.08–3.77 (m, 1H), 2.75–2.53 (m, 1H), 1.32 (t, *J* = 5.8 Hz, 6H), 1.11 (d, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 166.2, 160.6, 105.4, 36.5, 35.6, 22.7, 22.7, 20.9, 20.9.

LCMS (ESI) calculated for $C_{10}H_{17}N_2OS^+$ [M+H]$^+$ 213.1057, Found: 213.1

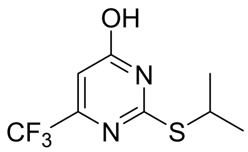


To a solution of ethyl 3-oxo-4-phenylbutanoate (500 mg, 2.42 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (656 mg, 2.66 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (344 mg, 2.66 mmol) was added dropwise and the mixture was turned into a white slurry. The reaction mixture was stirred at 0 °C for 19 hours and TfOH (400 mg, 2.66 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and triturated with CH_3CN/water (1:5, 2.0 mL). The solid was collected by filtration, to afford compound as a white solid (mp: 124.9 - 127.6 °C, 512 mg, 1.96 mmol, 81%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.50 (br s, 1H), 7.32–7.21 (m, 5H), 5.94 (br s, 1H), 3.84 (sep, *J* = 7.0 Hz, 1H), 3.75 (s, 2H), 1.29 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 166.8, 163.2, 161.5, 138.3, 129.6, 128.7, 126.9, 108.0, 43.2, 36.1, 22.9.

HRMS (ESI) calculated for $C_{14}H_{17}N_2OS^+$ [M+H]$^+$ 261.1062, Found: 261.1059.

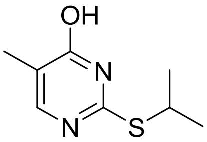


To a solution of ethyl 4,4,4-trifluoro-3-oxobutanoate (500 mg, 2.71 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (735 mg, 2.98 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (386 mg, 2.98 mmol) was added dropwise and the mixture was turned into a white slurry. The reaction mixture was stirred at 0 °C for 19 hours and TfOH (611 mg, 4.07 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and triturated with CH_3CN/water (1:5, 2.0 mL). The solid was collected by filtration, to afford compound as a white solid (mp: 130.0 - 133.0 °C, 489 mg, 2.05 mmol, 75%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 13.28 (br s, 1H), 6.58 (s, 1H), 3.82 (sep, *J* = 7.0 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 165.1, 162.1, 151.3, 124.2, 122.1, 119.9, 117.7, 108.8, 36.8, 22.7.

HRMS (ESI) calculated for $C_8H_{10}F_3N_2OS^+$ $[M+H]^+$ 239.0466, Found: 239.0460.

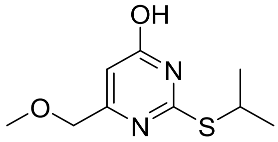


To a solution of ethyl 2-methyl-3-oxopropanoate (300 mg, 2.30 mmol) in 2-MeTHF (3.0 mL), isopropyl carbamimidothioate hydroiodide (624 mg, 2.53 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (327 mg, 2.53 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 48 hours and 10 °C for 24 hours. TfOH (380 mg, 2.53 mmol) was added dropwise at 0 °C and the reaction mixture was heated at 50 °C for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and triturated with CH_3CN (0.6 mL). The solid was collected by filtration, to afford the product as a white solid (185 mg, 1.00 mmol, 43%). The filtrate was concentrated, and the residue was purified by silica column (EtOAc/heptane, 0% to 60%), to afford additional compound as a white solid (mp: 140.6 - 143.4 °C, 139 mg, 0.754 mmol, 33%). Total 424 mg (1.75 mmol) of compound was obtained with 76% yield.

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.58 (br s, 1H), 7.73 (br s, 1H), 3.88 (sep, *J* = 7.0 Hz, 1H), 1.86 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 163.4, 159.0, 150.8, 119.5, 35.9, 23.1, 12.9.

HRMS (ESI) calculated for $C_8H_{13}N_2OS^+$ $[M+H]^+$ 185.0749, Found: 185.0745.

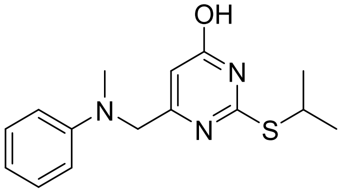


To a solution of methyl 4-methoxy-3-oxobutanoate (500 mg, 3.42 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (926 mg, 3.76 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (485 mg, 3.76 mmol) was added dropwise and the mixture was turned into a white slurry. The reaction mixture was stirred at 0 °C for 19 hours and TfOH (564 mg, 3.76 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and triturated with CH_3CN/water (1:3, 2.0 mL). The solid was collected by filtration and washed with CH_3CN/water (1:3, 1.0 mL), to afford the product as a light-yellow solid (mp: 123.1 - 126.4 °C, 577 mg, 2.69 mmol, 79%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.54 (br s, 1H), 6.00 (br s, 1H), 4.22 (s, 2H), 3.87 (sep, J = 7.0 Hz, 1H), 3.36 (s, 3H), 1.35 (d, J = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 164.6, 162.7, 161.6, 105.7, 73.4, 58.7, 36.0, 23.0.

HRMS (ESI) calculated for $C_9H_{15}N_2O_2S^+$ [M+H]$^+$ 215.0854, Found: 215.0851.

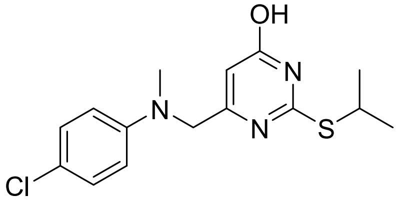


To a solution of 2-(isopropylthio)-6-((methyl(phenyl)amino)methyl)pyrimidin-4-ol (500 mg, 2.12 mmol) in 2-MeTHF (5.0 mL), isopropyl carbamimidothioate hydroiodide (784 mg, 3.18 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (411 mg, 3.18 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 48 hours and 10 °C for 24 hours. TfOH (956 mg, 6.37 mmol) was added dropwise at 0 °C and the reaction mixture was heated at 50 °C for 3 hours. Water (5.0 mL) and $NaHCO_3$ (714 mg, 8.50 mmol) were added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and triturated with CH_3CN (1.0 mL). The solid was collected by filtration, to afford the product as a white solid (325 mg, 1.12 mmol, 53%). The filtrate was concentrated and the residue was purified by silica column (EtOAc/heptane, 0% to 60%), to afford additional the product as a white solid (mp: 184.5 - 187.9 °C, 112 mg, 0.387 mmol, 18%). Total 437 mg (1.51 mmol) of the product was obtained with 71% yield.

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.53 (br s, 1H), 7.16–7.13 (m, 2H), 6.68–6.60 (m, 3H), 5.81 (br s, 1H), 4.34 (s, 2H), 3.82 (sep, J = 7.0 Hz, 1H), 3.04 (s, 3H), 1.30 (d, J = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 165.1, 162.9, 161.9, 149.0, 129.4, 116.4, 112.2, 106.6, 56.6, 36.1, 23.0.

HRMS (ESI) calculated for $C_{15}H_{20}N_3OS^+$ $[M+H]^+$ 290.1327, Found: 290.1322.

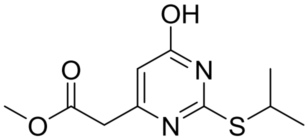


To a solution of ethyl 4-((4-chlorophenyl)(methyl)amino)-3-oxobutanoate (500 mg, 1.85 mmol) in 2-MeTHF (5.0 mL), isopropyl carbamimidothioate hydroiodide (501 mg, 2.03 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (263 mg, 2.03 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 24 hours and 10 °C for 16 hours. TfOH (612 mg, 4.07 mmol) was added dropwise at 0 °C and the reaction mixture was heated at 50 °C for 3 hours. Water (5.0 mL) and $NaHCO_3$ (621 mg, 6.52 mmol) were added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and triturated with CH_3CN (1.0 mL). The solid was collected by filtration, to afford the product as a white solid (284 mg, 0.876 mmol, 47%). The filtrate was concentrated and the residue was purified by silica column (EtOAc/heptane, 0% to 60%), to afford additional the product as a white solid (mp: 170.4 - 176.9 °C, 82 mg, 0.253 mmol, 14%). Total 366 mg (1.13 mmol) of the product was obtained with 61% yield.

^{1}H NMR (500.1 MHz, DMSO-*d*$_6$) δ 12.57 (br s, 1H), 7.16 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 5.82 (br s, 1H), 4.35 (s, 2H), 3.78 (sep, *J* = 7.0 Hz, 1H), 3.02 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-*d*$_6$) δ 164.6, 162.6, 161.8, 148.0, 128.9, 120.1, 113.8, 107.1, 56.5, 39.5, 36.1, 23.0.

HRMS (ESI) calculated for $C_{15}H_{19}ClN_3OS^+$ $[M+H]^+$ 324.0937, Found: 324.0933.

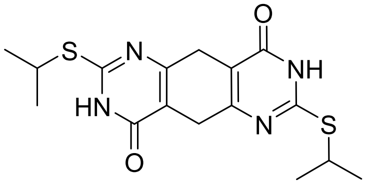


To a solution of dimethyl 3-oxopentanedioate (500 mg, 2.87 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (777 mg, 3.15 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (407 mg, 3.15 mmol) was added dropwise and the mixture was turned into a white slurry. The reaction mixture was stirred at 0 °C for 19 hours and TfOH (472 mg, 3.15 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and the residue was purified by silica column (EtOAc/heptane, 0% to 60%), to afford the product as a white solid (mp: 120.7 - 124.0 °C, 507 mg, 2.09 mmol, 73%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.59 (br s, 1H), 6.08 (br s, 1H), 3.82 (sep, *J* = 7.0 Hz, 1H), 3.63 (s, 3H), 3.57 (s, 2H), 1.32 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 170.1, 163.1, 161.8,161.0, 109.5, 52.2, 42.5, 36.2, 22.8.

HRMS (ESI) calculated for $C_{10}H_{15}N_2O_3S^+$ [M+H]$^+$ 243.0803, Found: 243.0799.

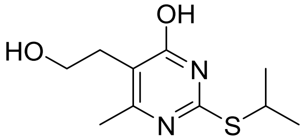


The title compound was obtained as a white solid (amorphous, no sharp mp, 1.34 g, 61%)

^{1}H NMR (400 MHz, D_2O) δ 3.60 (p, *J* = 6.7 Hz, 1H), 3.34 (s, 2H), 1.18 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, D_2O) δ 173.1, 166.8, 158.4, 110.8, 35.1, 29.3, 22.3.

HRMS (ESI) calculated for $C_{16}H_{21}N_4O_2S_2^+$: 365.1106 [M+H]$^+$, Found: 365.1105.

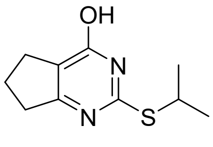


To a solution of ethyl 3-acetyldihydrofuran-2(3H)-one (500 mg, 3.90 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (1.05 g, 4.29 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (554 mg, 4.29 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 48 hours and 10 °C for 24 hours. TfOH (644 mg, 4.29 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and the residue was purified by reverse phase column (CH_3CN/water, 5% to 60%), to afford the product as an off-white solid (mp: 160.9 - 164.3 °C, 467 mg, 2.04 mmol, 52%).

^{1}H NMR (500.1 MHz, DMSO-d_6) δ 12.38 (br s, 1H), 4.58 (t, *J* = 5.0 Hz, 1H), 3.88 (sep, *J* = 7.0 Hz, 1H), 4.58 (t, *J* = 5.0 Hz, 1H), 3.43 (dt, *J* = 5.0 Hz, 7.0 Hz, 2H), 2.53 (t, *J* = 7.0 Hz, 2H), 2.26 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-d_6) δ 163.3, 160.8, 157.1, 116.6, 59.7, 35.8, 29.4, 23.1, 22.0.

HRMS (ESI) calculated for $C_{10}H_{17}N_2O_2S^+$ [M+H]$^+$ 229.1011, Found: 229.1009.

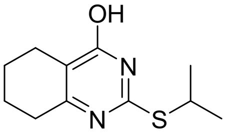


The title compound was synthesized with general procedure as a white solid (mp: 204.3 – 208.9 °C, 0.87 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (hept, *J* = 6.8 Hz, 1H), 2.84 – 2.73 (m, 4H), 2.01 (p, *J* = 7.7 Hz, 2H), 1.37 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 163.1, 160.4, 120.1, 36.5, 35.1, 27.1, 22.9, 21.2.

HRMS (ESI) calculated for $C_{10}H_{15}N_2OS^+$: 211.0905 [M+H]$^+$, Found:211.0903

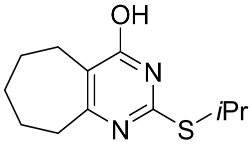


To a solution of ethyl 2-oxocyclohexane-1-carboxylate (200 mg, 1.17 mmol) in 2-MeTHF (2.0 mL), isopropylisothiouronium iodide (318 mg, 1.29 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (167 mg, 1.29 mmol) was added dropwise and the mixture was turned into a white slurry. The reaction mixture was stirred at 0 °C for 19 hours and TfOH (193 mg, 1.29 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 3 hours. Water (2.0 mL) was added, and the water layer was extracted with 2-MeTHF (1.0 mL). The combined organic layer was concentrated and triturated with CH_3CN/water (V/V = 1:3, 0.8 mL). The solid was collected by filtration and washed with CH_3CN/water (1:3, 0.4 mL), to afford the product as a light-yellow solid (mp: 200.1 – 200.7 °C, 229 mg, 1.02 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (p, *J* = 6.9 Hz, 1H), 2.54 (t, *J* = 6.1 Hz, 2H), 2.46 (t, *J* = 6.1 Hz, 2H), 1.80 – 1.62 (m, 4H), 1.35 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 161.9, 156.7, 117.3, 36.3, 31.8, 22.9, 22.3, 21.8, 21.7.

HRMS (ESI) calculated for $C_{11}H_{17}N_2OS^+$: 225.1062 [M+H]$^+$, Found:225.1058.

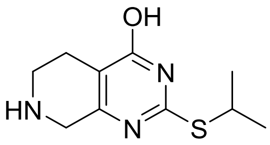


The title compound was obtained as a white solid (mp: 185.6 – 188.6 °C, 0.94 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 4.03 (hept, *J* = 6.9 Hz, 1H), 2.76 (t, *J* = 5.4 Hz, 2H), 2.71 (d, *J* = 5.5 Hz, 2H), 1.92–1.73 (m, 2H), 1.73–1.50 (m, 4H), 1.41 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 165.0, 156.7, 122.1, 38.8, 36.7, 32.6, 26.9, 25.7, 23.9, 23.2.

HRMS (ESI) calculated for $C_{12}H_{19}N_2OS^+$: 239.1218 [M+H]$^+$, Found:239.1218

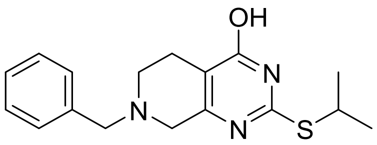


To a solution of ethyl 3-oxopiperidine-4-carboxylate hydrochloride (500 mg, 2.40 mmol) in CH_3CN (5.0 mL), isopropylisothiouronium iodide (651 mg, 2.64 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (684 mg, 5.29 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 19 hours and 10 °C for 6 hours. TfOH (794 mg, 5.29 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 10 hours. Solid precipitation was observed and the stirring became difficult. CH_3CN (2.5 mL) and 2-MeTHF (2.5 mL) was added to aid the stirring. The reaction mixture was heated at 60 °C for 24 h and the volume was reduced to 5 mL by concentration. The solid was collected by filtration and washed with water (1.0 mL), to afford the product as a white solid (mp: 248.8 - 268.9 °C, 672 mg, 1.79 mmol, 74%).

^{1}H NMR (500.1 MHz, DMSO-*d*$_6$) δ 12.85 (br s, 1H), 9.00 (br s, 2H), 4.00 (s, 2H), 3.87 (sep, *J* = 7.0 Hz, 1H), 3.35–3.30 (m, 2H), 2.55–2.49 (m, 2H), 1.36 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-*d*$_6$) δ 161.4, 159.4, 152.7, 124.9, 122.4, 119.8, 117.3, 114.2, 45.0, 36.2, 23.0, 18.7.

HRMS (ESI) calculated for $C_{10}H_{16}N_3OS^+$: 226.1014 [M+H]$^+$, Found: 226.1008.

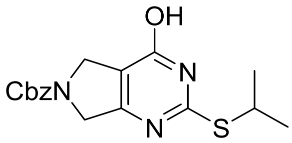


To a solution of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride (500 mg, 1.67 mmol) in 2-MeTHF (2.5 mL) and CH_3CN (2.5 mL), isopropylisothiouronium iodide (454 mg, 1.84 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (477 mg, 3.69 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 19 hours and then 10 °C for 24 hours. After reaction mixture was cooled to 0 °C, TfOH (554 mg, 3.69 mmol) was added dropwise. The reaction mixture was heated to 50 °C and kept stirred at the same temperature for 9 hours. Water (5.0 mL) and $NaHCO_3$ (282 mg, 3.35 mmol) were added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and triturated with CH_3CN/water (1:5, 2.0 mL). The solid was collected by filtration, to afford the product as a white solid (mp: 172.3 - 175.0 °C, 409 mg, 1.29 mmol, 77%).

^{1}H NMR (500.1 MHz, DMSO-*d*$_6$) δ 12.48 (br s, 1H), 7.34–7.26 (m, 5H), 3.84 (sep, *J* = 7.0 Hz, 1H), 3.64 (s, 2H), 3.14 (s, 2H), 2.66 (t, *J* = 5.5 Hz, 2H), 2.59 (t, *J* = 5.5 Hz, 2H), 1.33 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-*d*$_6$) δ 161.4, 158.9, 158.0, 138.7, 129.2, 128.7, 127.5, 115.2, 62.0, 49.7, 49.1, 35.9, 31.8, 23.1.

HRMS (ESI) calculated for $C_{17}H_{22}N_3OS^+$: 316.1484 [M+H]$^+$, Found: 316.1480.

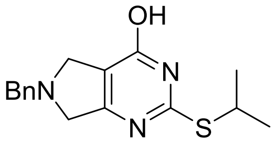


To a solution of 1-benzyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (500 mg, 1.71 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (464 mg, 1.88 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (244 mg, 1.88 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 24 hours, 10 °C for 24 hours and 20 °C for 6 hours. TfOH (283 mg, 1.88 mmol) was added dropwise at 0 °C. The reaction mixture was heated at 50 °C for 6 hours and 60 °C for 4 hours. Water (5.0 mL) was added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and triturated with CH_3CN/water (1:1, 1.0 mL). The solid was collected by filtration, to afford the product as a white solid (mp: 217.9 - 221.4 °C, 406 mg, 1.17 mmol, 68%).

^{1}H NMR (500.1 MHz, DMSO-*d*$_6$) δ 12.83 (br s, 1H), 7.42–7.31 (m, 5H), 5.13 (s, 2H), 4.51–4.35 (m, 4H), 3.90 (sep, *J* = 7.0 Hz, 1H), 1.36–1.34 (m, 6H).

^{13}C NMR (125.7 MHz, DMSO-*d*$_6$) δ 163.0, 159.2, 157.3, 120.8, 35.8, 23.1, 21.3, 18.5, 13.1.

HRMS (ESI) calculated for $C_{17}H_{20}N_3O_3S^+$: 346.1225 [M+H]$^+$, Found: 346.1223.

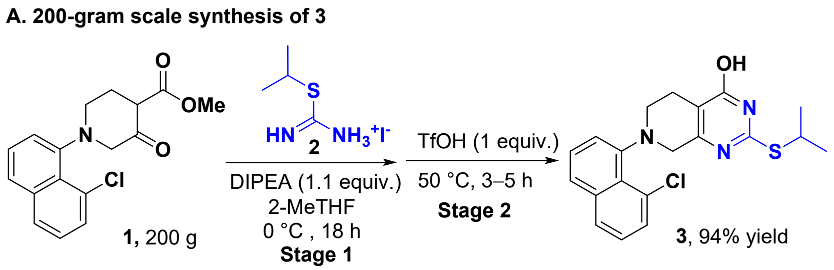


To a solution of ethyl 1-benzyl-4-oxopyrrolidine-3-carboxylate (500 mg, 2.02 mmol) in 2-MeTHF (5.0 mL), isopropylisothiouronium iodide (547 mg, 2.22 mmol) was added at 20 °C. The reaction mixture was stirred at 20 °C for 5 mins until a clear yellow solution was observed. After the solution was cooled to 0 °C, DIPEA (287 mg, 2.22 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 24 hours and 10 °C for 16 hours. TfOH (667 mg, 4.44 mmol) was added dropwise at 0 °C and the reaction mixture was heated at 50 °C for 6 hours. Water (5.0 mL) and $NaHCO_3$ (678 mg, 8.08 mmol) were added, and the water layer was extracted with 2-MeTHF (2.5 mL). The combined organic layer was concentrated and the residue was purified by silica column (EtOAc/heptane, 0% to 80%), to afford the product as a white solid (mp: 162.1 - 165.1 °C, 355 mg, 1.17 mmol, 58%).

^{1}H NMR (500.1 MHz, DMSO-*d*$_6$) δ 12.61 (br s, 1H), 7.35–7.25 (m, 5H), 3.90 (sep, *J* = 7.0 Hz, 1H), 3.83 (s, 2H), 3.74–3.66 (m, 4H), 1.33 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (125.7 MHz, DMSO-*d*$_6$) δ 165.7, 162.3, 159.3, 139.2, 128.9, 128.7, 127.4, 116.8, 59.8, 59.4, 54.6, 36.1, 23.0.

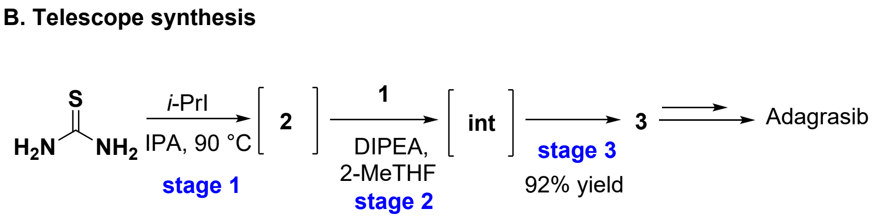
HRMS (ESI) calculated for $C_{16}H_{20}N_3OS^+$: 302.1327 [M+H]$^+$, Found: 302.1325.



Section 5. 200-gram Demo and Telescope Synthesis

Stage 1: To a solution of ketoester **1** (200 g, 613 mmol) and isopropylisothiouronium iodide (1.1 equiv., 168 g) in 2-MeTHF (2 L) at 0 °C in a 5-L reactor was added DIPEA (1.1 equiv., 117 mL) dropwise over 30 min. The brown solution was stirred at 0 °C for 18 h to reach completion and give a white slurry.

Stage 2: TfOH (1.0 equiv., 54 mL) was added dropwise to the slurry at 0 °C in 10 min. The resulting mixture was then heated to 50 °C in 0.5 h and then stirred for 5 hours. Upon the consumption of intermediate, 1.2 L Na_2SO_3(aq., 7 wt%) was added and the reaction mixture stirred at 50 °C for 10 min. The layers were separated and the organic layer was collected and concentrated to give a 600 mL slurry. The slurry was filtered and the remanent was washed with mixed solvent ACN/2-MeTHF (v/v = 3/1, 400 mL twice). The solid was dried under vacuum at 35 °C for 18 h to afford compound **3** as a light-yellow solid (mp: 225.8 – 225.9 °C, 223 g, 94% yield).



Stage 1: To a 100-mL easymax reactor was charged with isopropanol (16 mL) and thiourea (2.4 g, 31 mmol). The mixture was cooled to 0 °C and then added with *i*-PrI (1.1 equiv., 5.7 g) dropwise. The reaction was heated to reflux (~90 °C) for 18 hours and then concentrated to 7 mL crude. 10 mL 2-MeTHF was added and then concentrated to give a 10 mL crude. This solvent swap process was repeated 3 times and the resulting crude was added with 90 mL 2-MeTHF.

Stage 2: To the above mixture was added ketoester **1** (10 g, 31 mmol). The mixture was cooled to 0 °C and then was added with DIPEA (1.1 equiv., 5.9 mL) dropwise over 10 min. The brown solution was stirred at 0 °C for 18 h to reach completion and give a white slurry.

Stage 3: TfOH (1.0 equiv., 2.7 mL) was added dropwise to the slurry at 0 °C in 10 min. The resulting mixture was then heated to 50 °C in 0.5 h and then stirred for 5 hours. Upon the consumption of intermediate, 60 mL Na_2SO_3(aq., 7 wt%) was added and the reaction mixture stirred at 50 °C for 10 min. The layers were separated and the organic layer was collected and concentrated to give a 30 mL slurry.

The slurry was filtered and the remanent was washed with mixed solvent ACN/2-MeTHF (v/v = 3/1, 20 mL twice). The solid was dried under vacuum at 35 °C for 18 h to afford compound **3** as a light-yellow solid (11.1 g, 92% yield)

Section 6. RC1 Calorimetric Data for TfOH Addition:

Triflic Acid Casting		
Data	**Securities**	**Feedback**
Tp (Process Temperature)	0°C	
Integral of qr-hf heat reaction	16.8kJ 107kJ /mol d' Uop 29.8kJ/kg final reaction mass	$q_r = q_{flow+} q_{accu+} q_{dos}$
Integral of qr-hf heat removal ***(energy to be evacuated including both the reaction energy and the energy provided by the added reactant in the case of a "hot" reagent on a "cold" medium***	17.7kJ 112kJ /mol d' Uop 31.4kJ/kg final reaction mass	Sum of the reaction energy and the energy provided by the addition of reactant: casting of triflic acid at 19°C on the reaction medium at 0°C
Cp (specific heat of the reaction medium at the end of the reaction)	1.82kJ/(kg*K)	Cp measured after heating and holding at 45°C
Final Reaction Mass	563.3g	
Thermal build-up at the end of casting	11.5%	At the end of the triflic acid pour
Accumulation at the equivalency point	N/A	Non-linear casting
Qmax (to be recorded on Heat removal if hot on cold)	25W 47W/Kg reaction mass before casting	Qmax observed at the beginning of the reagent pour (non-linear casting) Before casting m_{MR}= 538.4g
ΔTad	17°C	ΔTad=Integral Heat removal/(mr $_{finalexCprfinal}$) to be used in the case of reactive casting hotter than the reaction mass

Heating and holding at 45°C		
Data	**Securities**	**Feedback**
Tp (Process Temperature)	0°C to 45°C	
Integral of qr-hf heat reaction	4.0kJ 25,4kJ /mol d' Uop 7.1kJ/kg final reaction mass	$q_r = q_{flow+} q_{accu+} q_{dos+} q_{loss}$ (cases where the process temperature is higher than the ambient temperature to account for lid losses)
Cp (specific heat of the reaction medium at the end of the reaction)	1.82kJ/(kg*K)	
Final Reaction Mass	563.3g	
Accumulation at the equivalency point	N/A	N/A
Qmax	N/A	N/A
ΔTad	4°C	ΔTad=Intégrale qr_hf/(mr $_{\text{finalexCprfinal}}$)

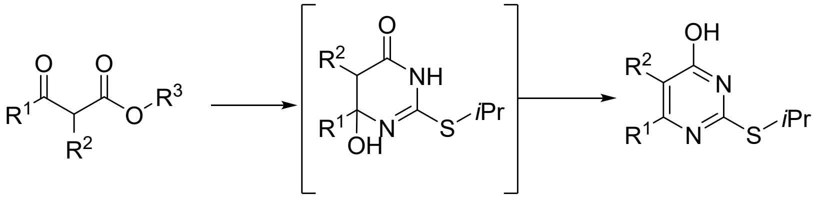
The formation energy of reaction is therefore equal to heat removal (triflic acid casting) + Q (heating and maintaining at 45°C) **i.e. 21.7kJ** (i.e. 138.0kJ /mol Uop – 38.5kJ /kg final reaction mass.

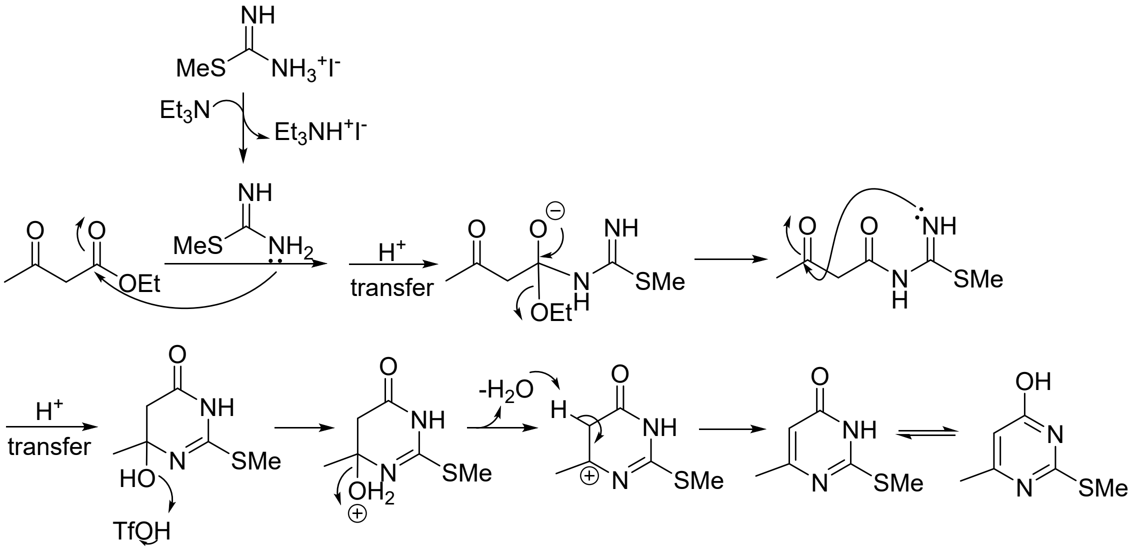
The Tad of this reaction is **21 °C** according to the equation ΔTad=Integral qr_hf/(mr $_{\text{finale}}$xCpr$_{\text{final}}$)

Reaction Rating, Criticality Index		
Data	**Securities**	**Feedback**
Tp Process Temperature	**55°C**	Triflic acid is poured over the medium at 0°C. Then the reaction medium is heated to 50/55°C mass.
Batch or semi-batch process	Batch/Semi-batch	
ΔTad	**21°C**	
MTSR Maximum Synthesis Temperature ($T_{process} + x_{accumulation} * \Delta Tad$)	**76°C**	We calculate the worst-case case for which the accumulation is 100% and the entire reaction energy would be released once the medium is at 55°C.

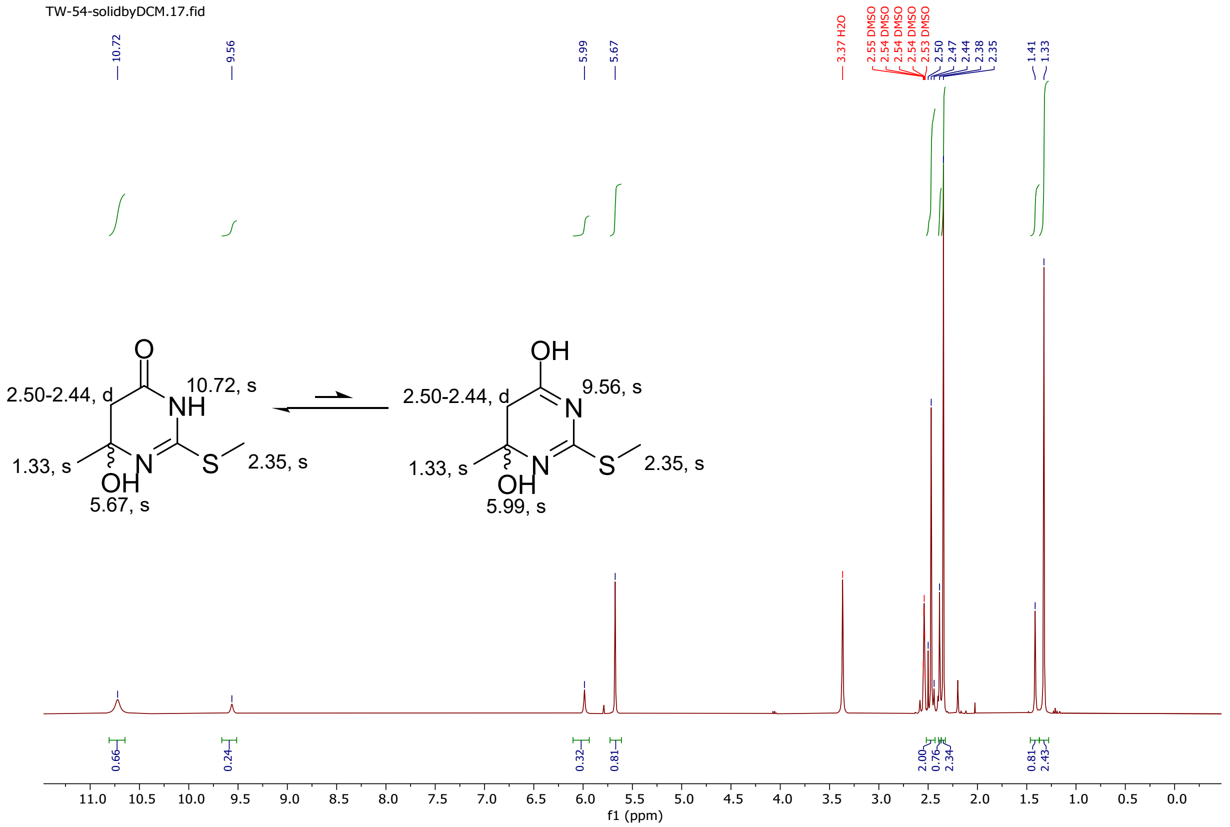
Bp Boiling point	**78°C**	=T°eb 2-MeTHF
Texo Texo=Tstart-100°C ou TD24-10°C	**>200°C**	In DSC, no energy degradation greater than 100J/g up to 300°C.
Criticality Index	**1b**	**Thermally safe reaction** Note: The MTSR is very close to Bp because we consider the maximum temperature of the process (55°C). In the process, part of the reaction takes place at 0°C and during the temperature rise

Section 7. Mechanism Study





Substrate scope investigation showed that the amount of intermediate (semi-quantitatively by UV absorption on TLC plate) varying with R^1: Me > iPr > *t*Bu, Aryl. The reactivity difference prompted speculation that the intermediate adopted a cyclic form at stage 1, where the bulkiness of proximate R^1 dictates its formation. To probe the structure, a prototypical reaction was performed with ethyl acetoacetate, triethylamine, and *S*-methylisothiouronium iodide. Though an initial attempt to directly interpret NMR spectra of the reaction mixture failed for their complexity, we managed to isolate the intermediate by column chromatography. The *m/z* suggested an adduct absent from the ethoxy fragment. NMR further proved it to be a cyclic hemiaminal-containing configuration, of which the ketone carbon and α-H shifted upfield (δ 200 to 80 ppm, remaining quaternary; δ 2.27 to 1.33 ppm). Given to the presence of -OH at stage 1, events at stage 2 are analogous to acid-catalyzed dehydration of alkyl alcohol to alkene. Acids with p*K*a several magnitudes higher than those of alkyloxoniums facilitate the protonation, the trend aligning with the conversion at stage 2: TfOH > HCl > TFA> AcOH. An E1 elimination assumedly ensues, where the leaving water serves as a base to abstract the acidic proton at α-C to tertiary carbocation and carbonyl, affording a 4-pyrimidone that tautomerizes to aromatic 4-pyrimidinol.


TW-54-solidbyDCM.17.fid
10.72
9.56
5.99
5.67
3.37 H2O
2.55 DMSO
2.54 DMSO
2.54 DMSO
2.54 DMSO
2.53 DMSO
2.50
2.47
2.44
2.38
2.35
1.41
1.33
O
NH
10.72, s
2.50-2.44, d
1.33, s
N
S
2.35, s
OH
5.67, s
OH
N
9.56, s
2.50-2.44, d
1.33, s
N
S
2.35, s
OH
5.99, s
0.66
0.24
0.32
0.81
2.00
0.76
2.34
0.81
2.43
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)

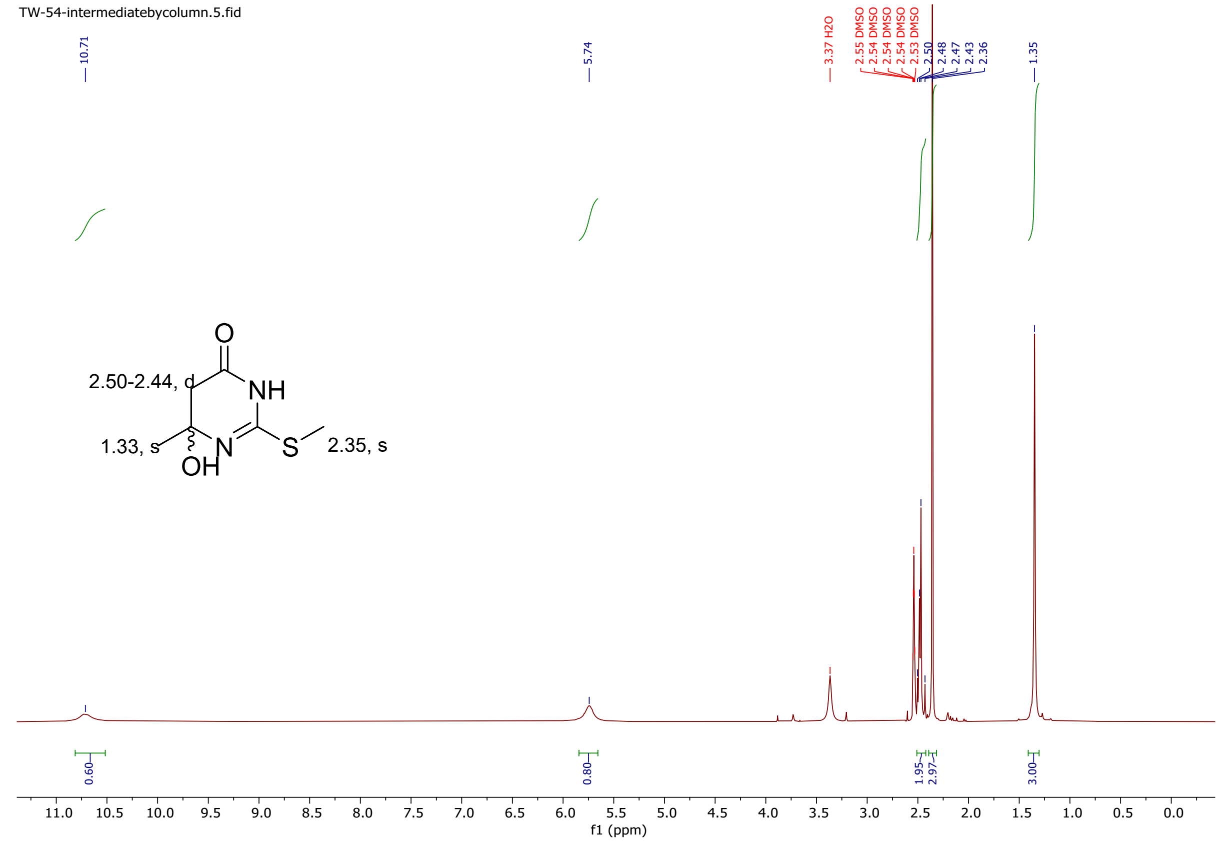

TW-54-intermediatebycolumn.5.fid
10.71
5.74
3.37 H2O
2.55 DMSO
2.54 DMSO
2.54 DMSO
2.54 DMSO
2.53 DMSO
2.50
2.48
2.47
2.43
2.36
1.35
O
NH
2.50-2.44, d
1.33, s
N
S
2.35, s
OH
0.60
0.80
1.95
2.97
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

Figure 1. (a) ^{1}H spectrum of intermediate # precipitated out as a pair of tautomers by dichloromethane (b) ^{1}H spectrum of int B obtained by column chromatography

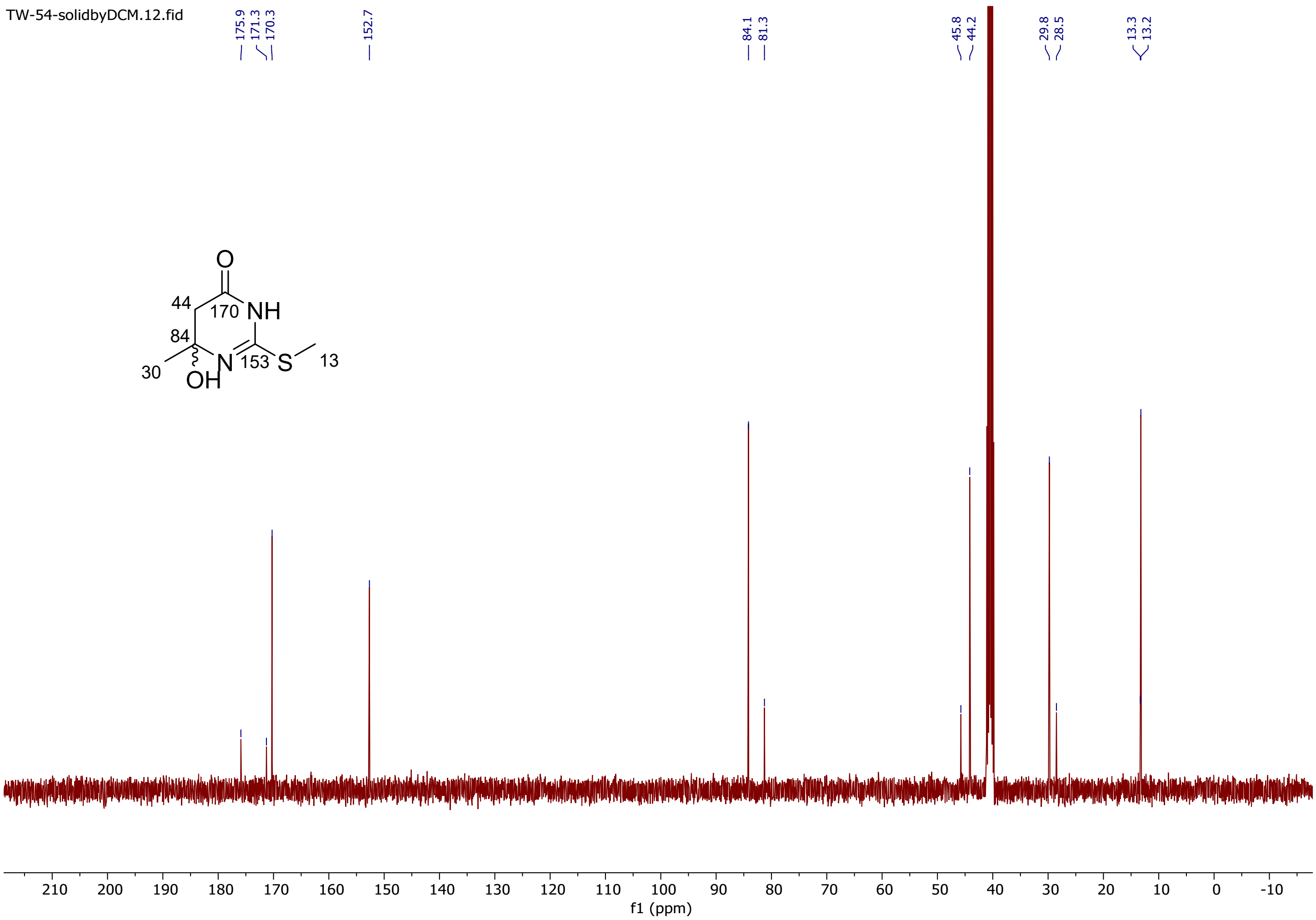


Figure 2. ^{13}C-NMR Spectrum of int B

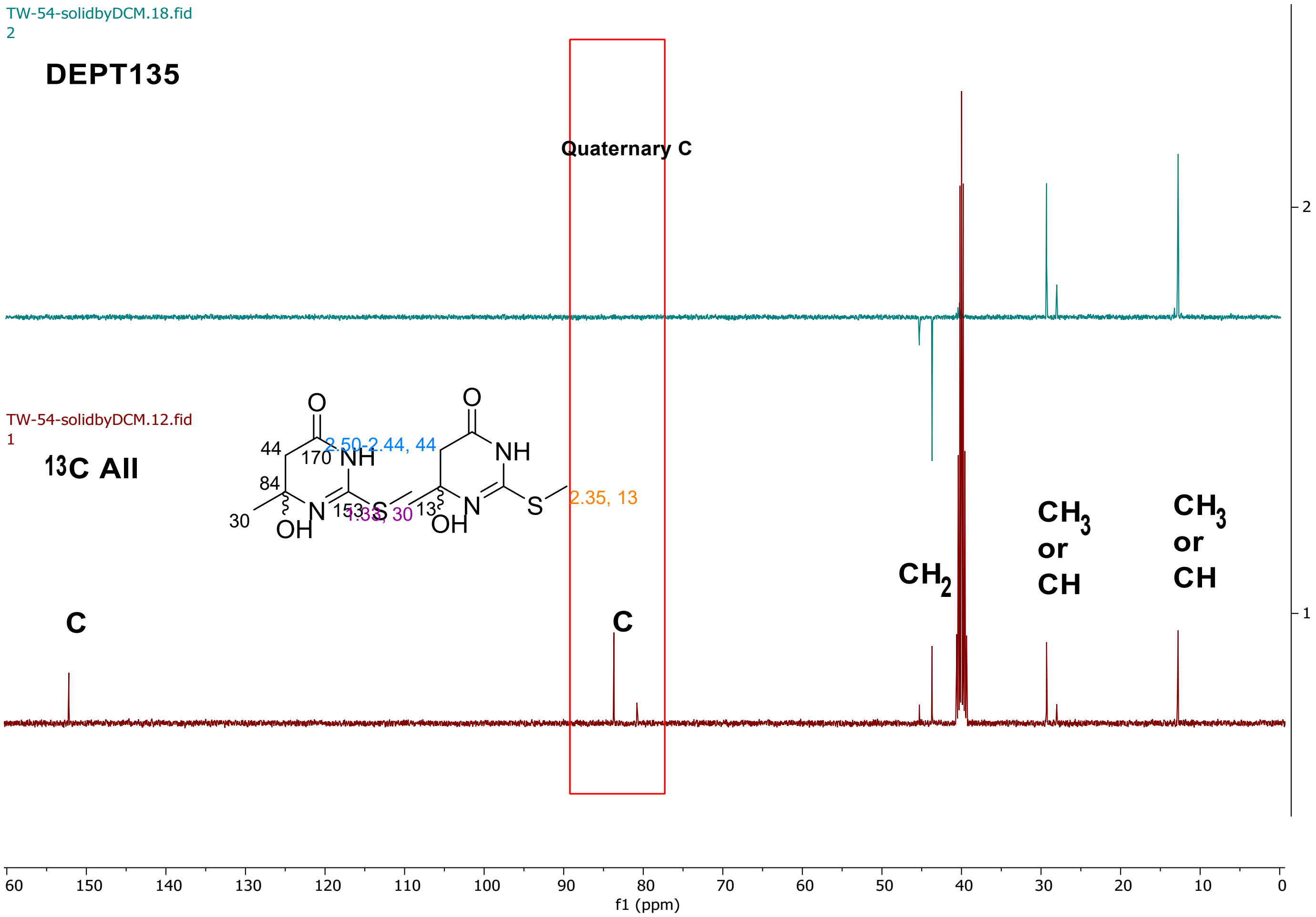


Figure 3. DEPT-135 and ^{13}C-NMR spectra of int B

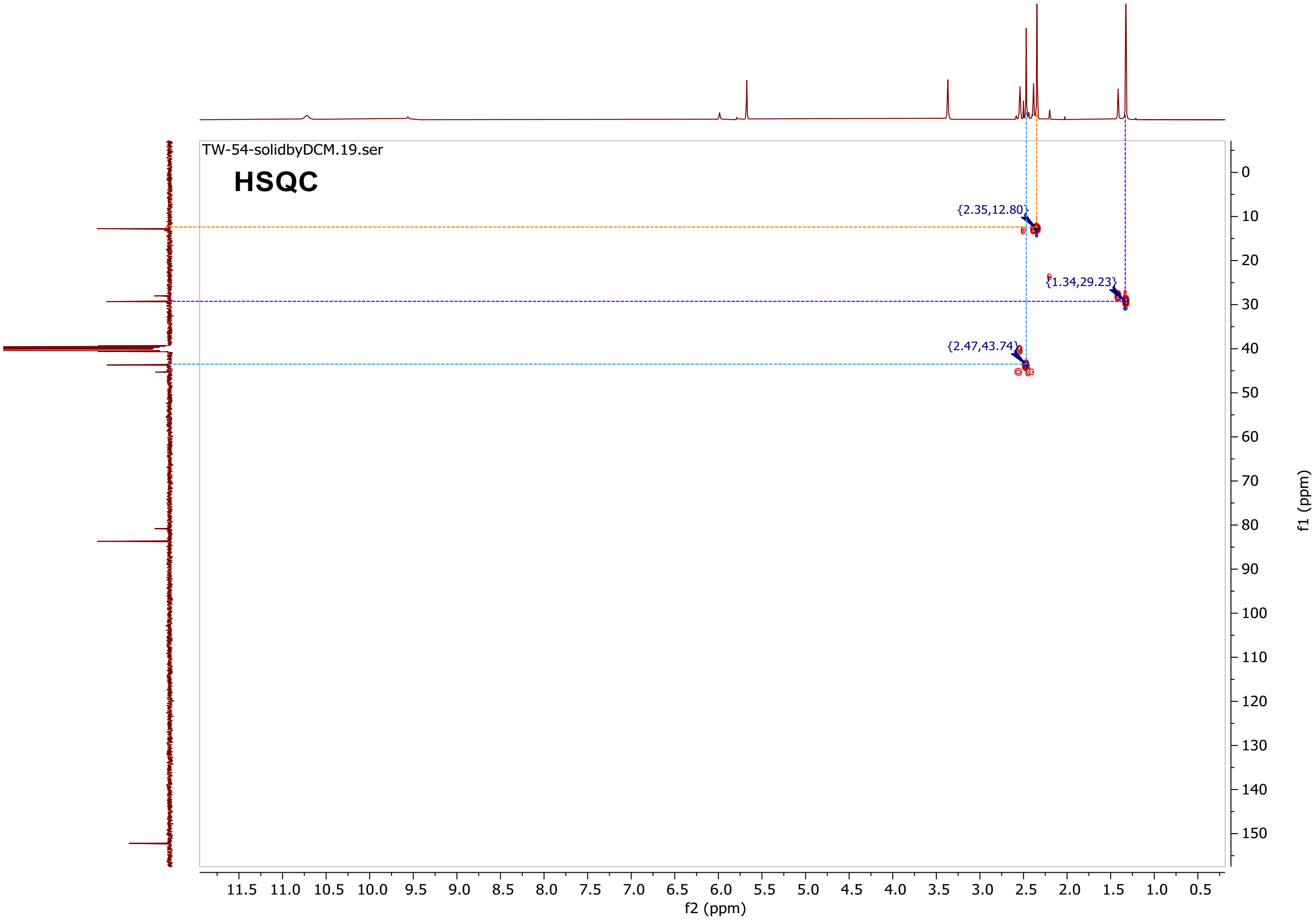


Figure 4. HSQC spectrum of int B

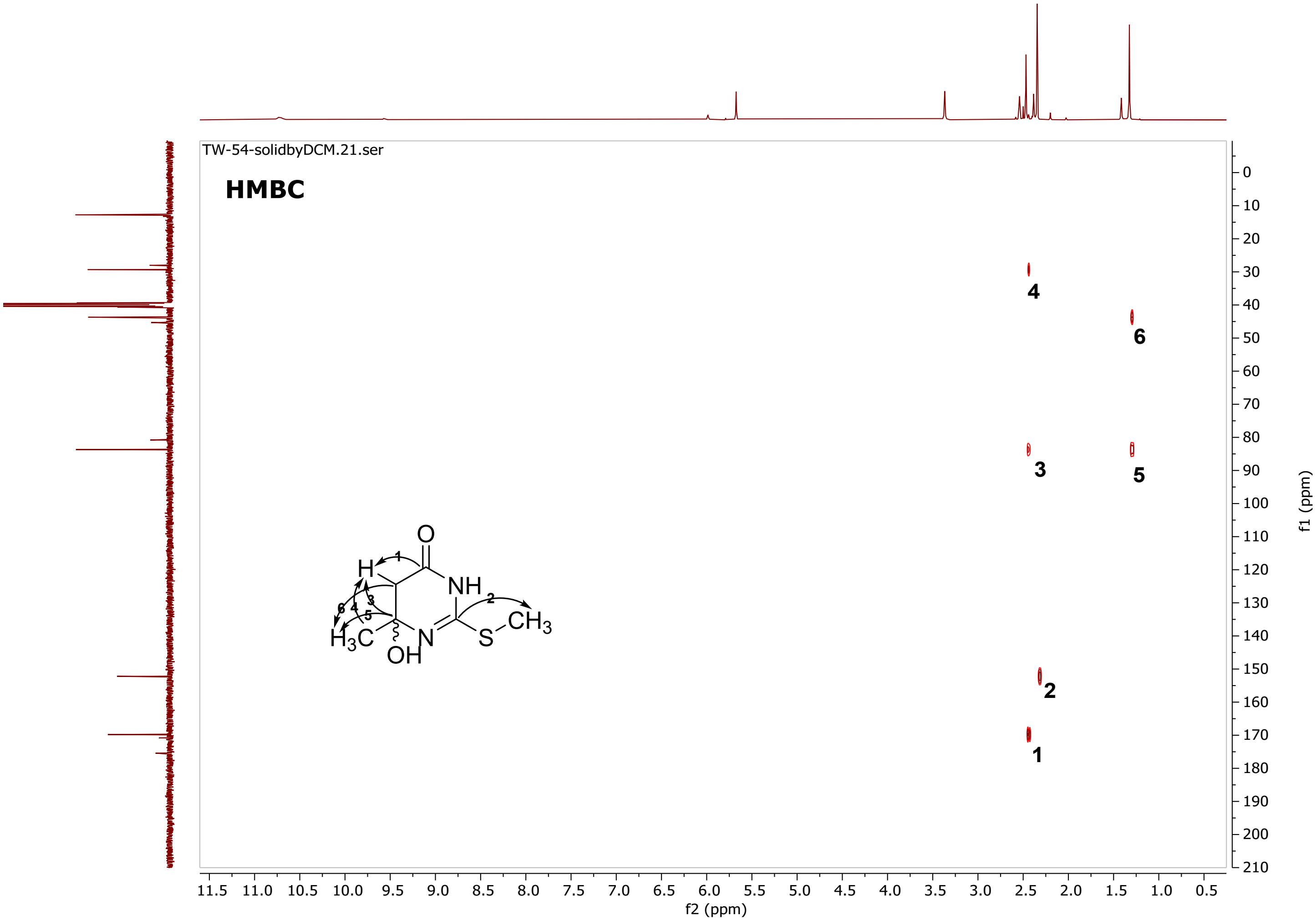
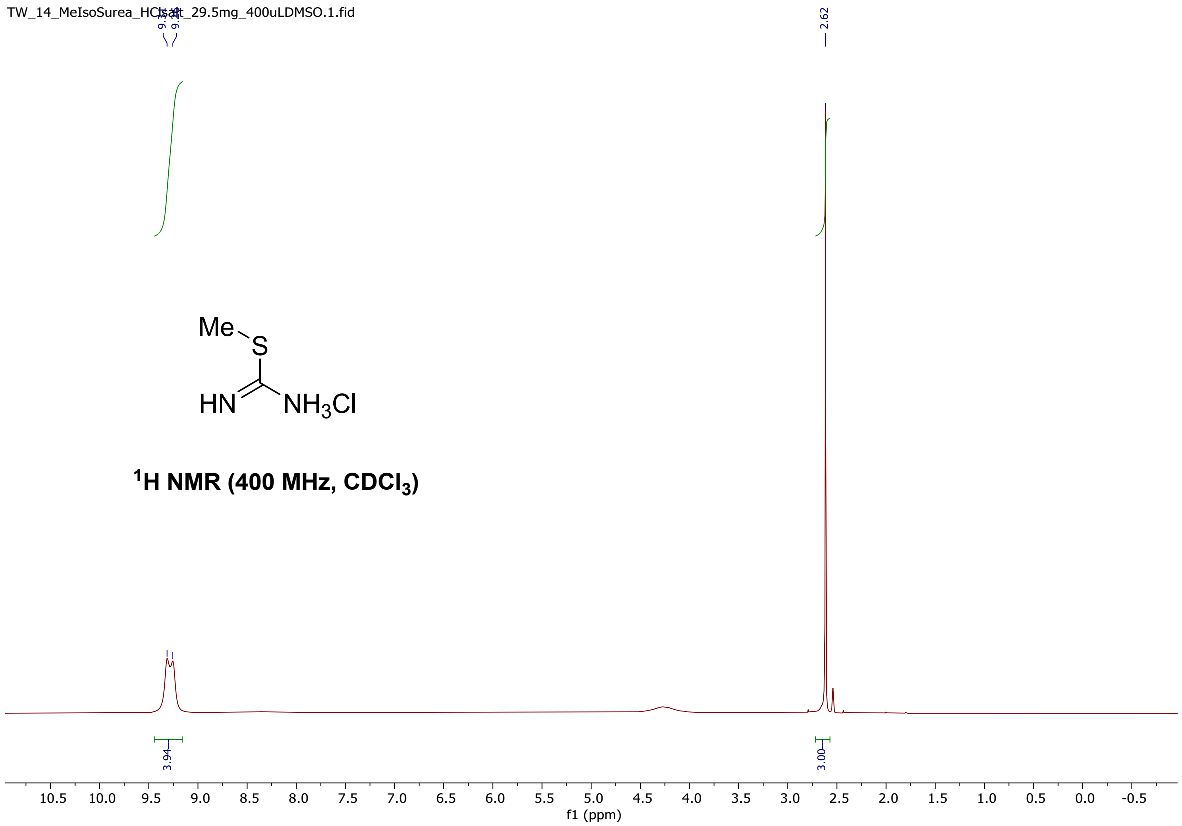
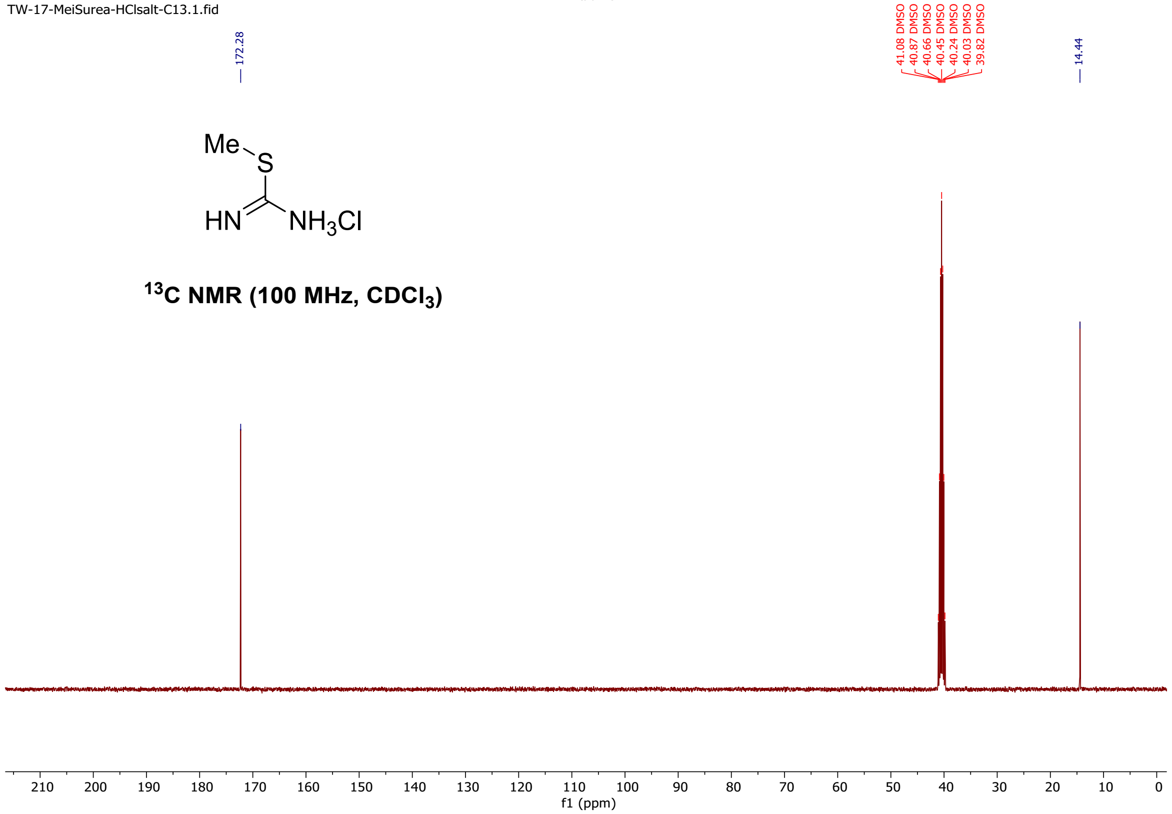
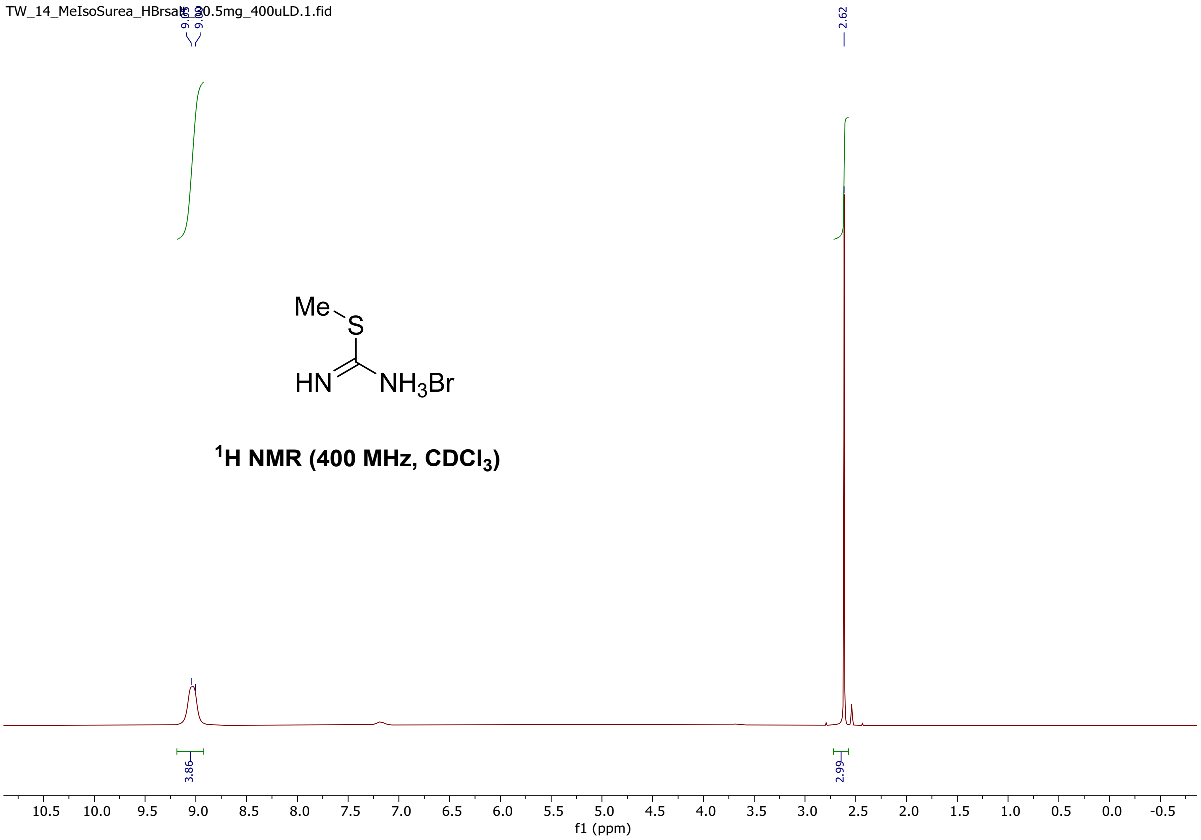


Figure 5. HMBC spectrum of int 5

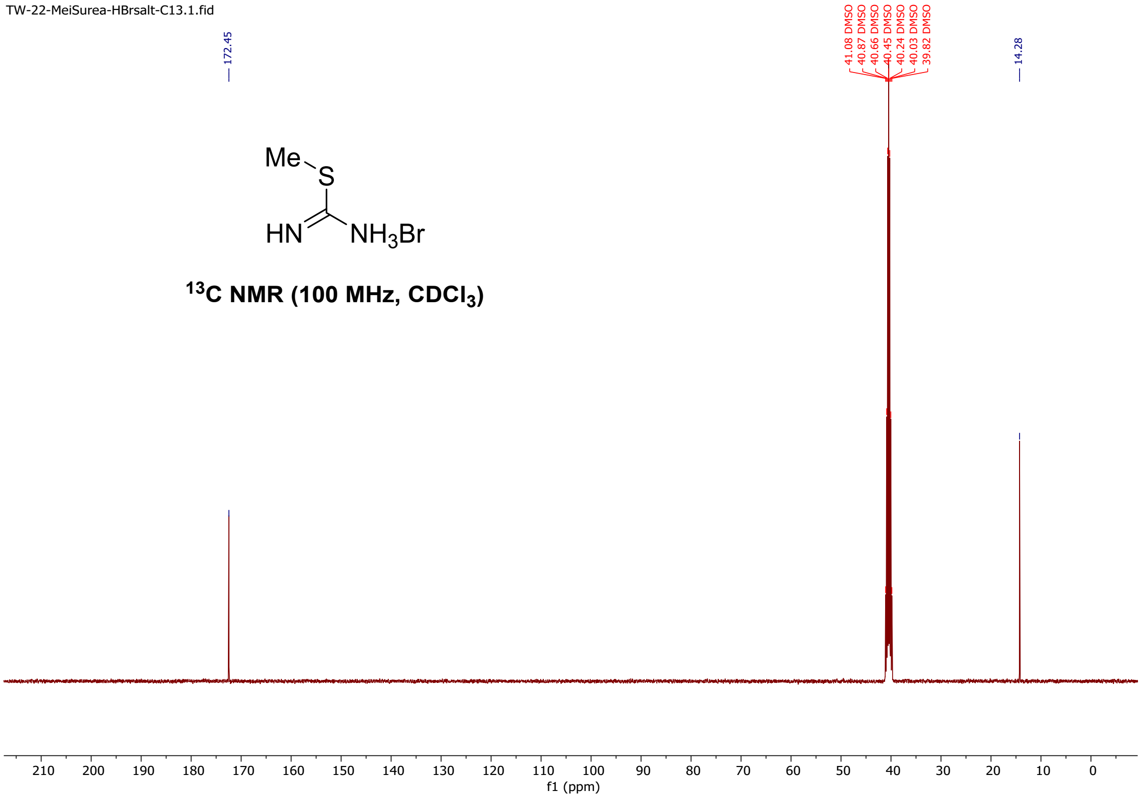
Section 8. 1H, 13C NMR spectra



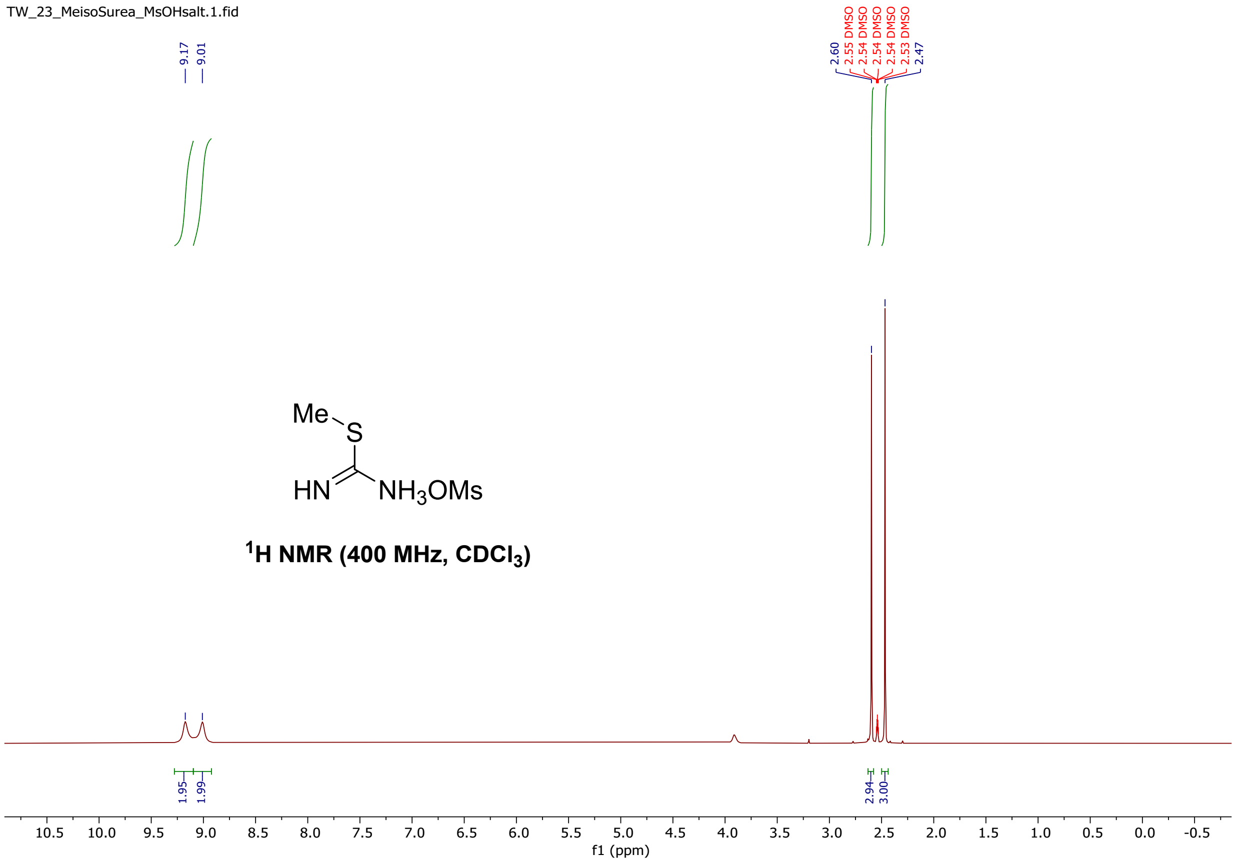


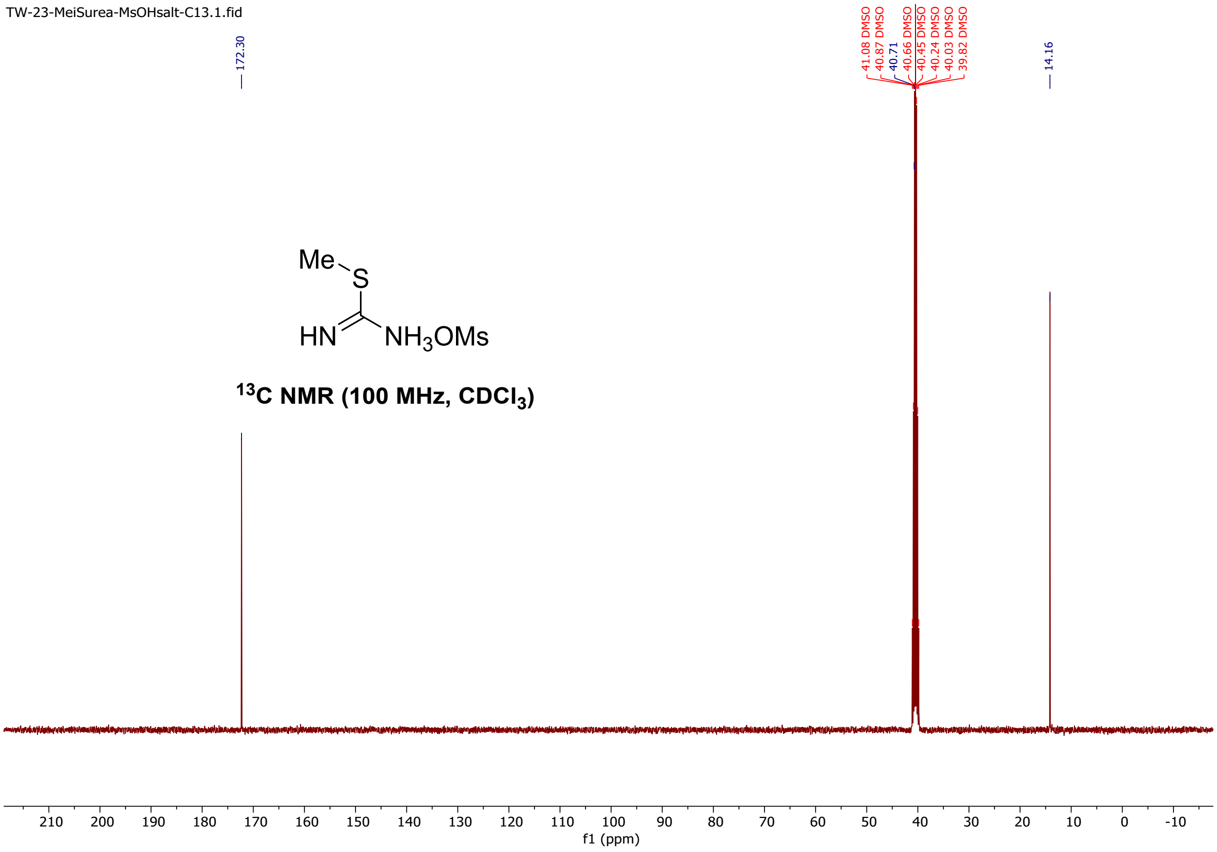


^{1}H NMR (400 MHz, CDCl$_3$)



^{13}C NMR (100 MHz, CDCl$_3$)


TW_23_MeisoSurea_MsOHsalt.1.fid
9.17
9.01
2.60
2.55 DMSO
2.54 DMSO
2.54 DMSO
2.54 DMSO
2.53 DMSO
2.47
Me
S
HN
NH3OMs
1H NMR (400 MHz, CDCl3)
1.95
1.99
2.94
3.00
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 -0.5
f1 (ppm)


TW-23-MeiSurea-MsOHsalt-C13.1.fid
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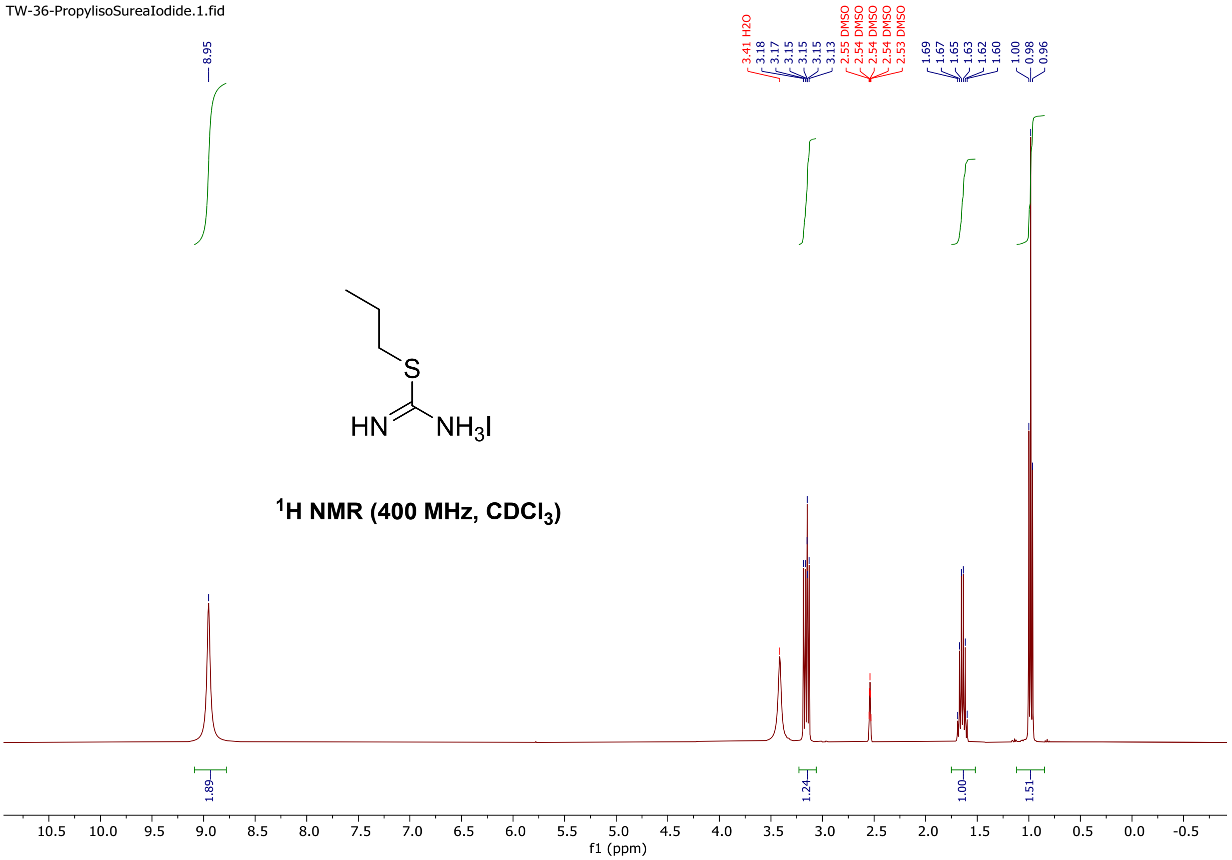
41.08 DMSO
40.87 DMSO
40.71
40.66 DMSO
40.45 DMSO
40.24 DMSO
40.03 DMSO
39.82 DMSO
14.16
Me
S
HN
NH3OMs
13C NMR (100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


TW-36-PropylisoSureaIodide.1.fid
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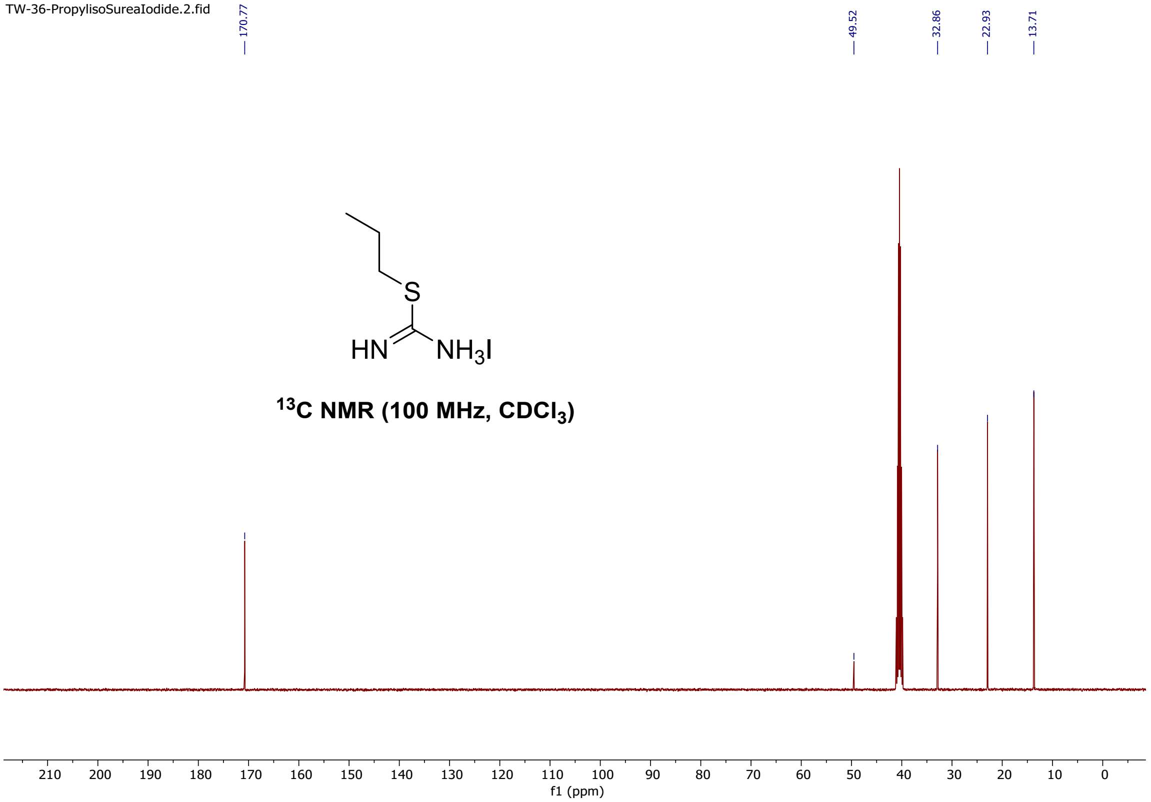
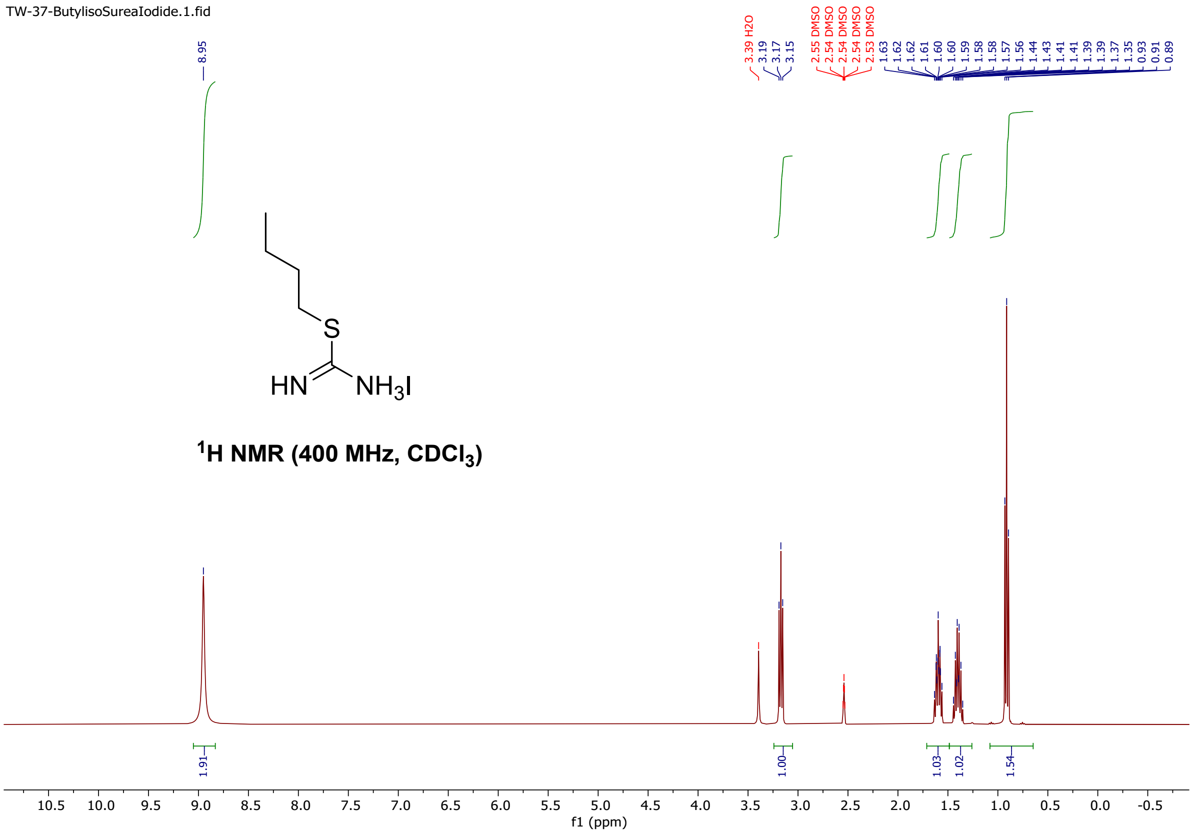
3.41 H2O
3.18
3.17
3.15
3.15
3.15
3.13
2.55 DMSO
2.54 DMSO
2.54 DMSO
2.54 DMSO
2.53 DMSO
1.69
1.67
1.65
1.63
1.62
1.60
1.00
0.98
0.96
S
HN
NH3I
¹H NMR (400 MHz, CDCl3)
1.89
1.24
1.00
1.51
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


TW-36-PropylisoSureaIodide.2.fid
170.77
49.52
32.86
22.93
13.71
S
HN
NH3I
¹³C NMR (100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


TW-37-ButylisoSureaIodide.1.fid
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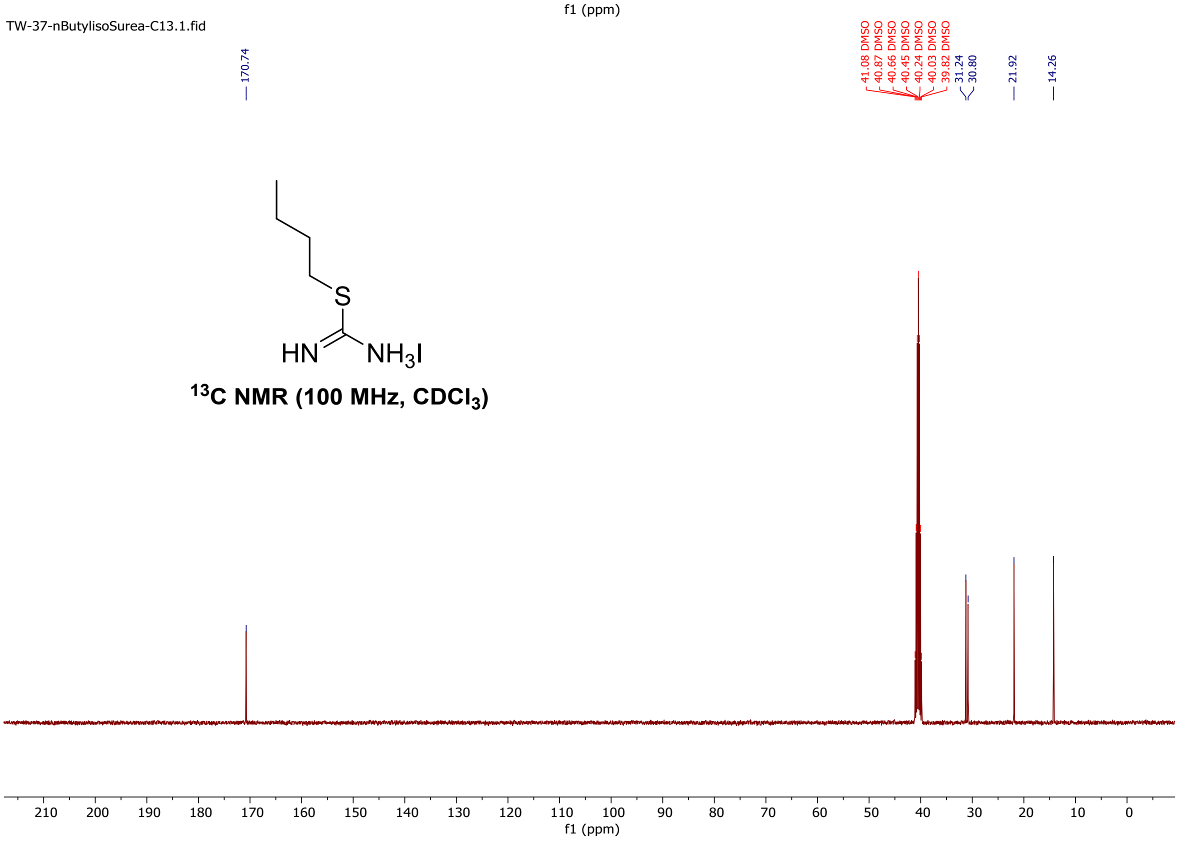
3.19
3.17
3.15
2.55 DMSO
2.54 DMSO
2.54 DMSO
2.54 DMSO
2.53 DMSO
1.63
1.62
1.62
1.61
1.60
1.60
1.59
1.58
1.58
1.57
1.56
1.44
1.43
1.41
1.41
1.39
1.39
1.37
1.35
0.93
0.91
0.89
S
HN
NH3I
1H NMR (400 MHz, CDCl3)
1.91
1.00
1.03
1.02
1.54
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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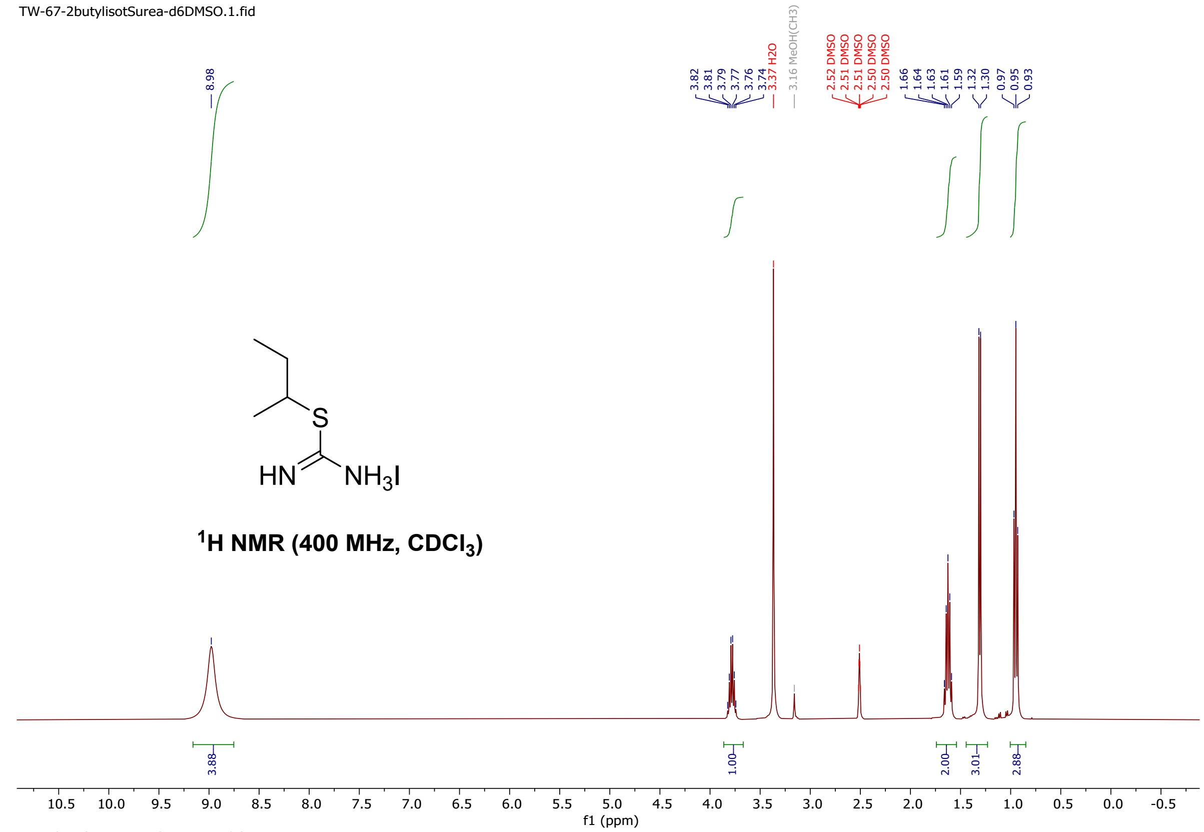
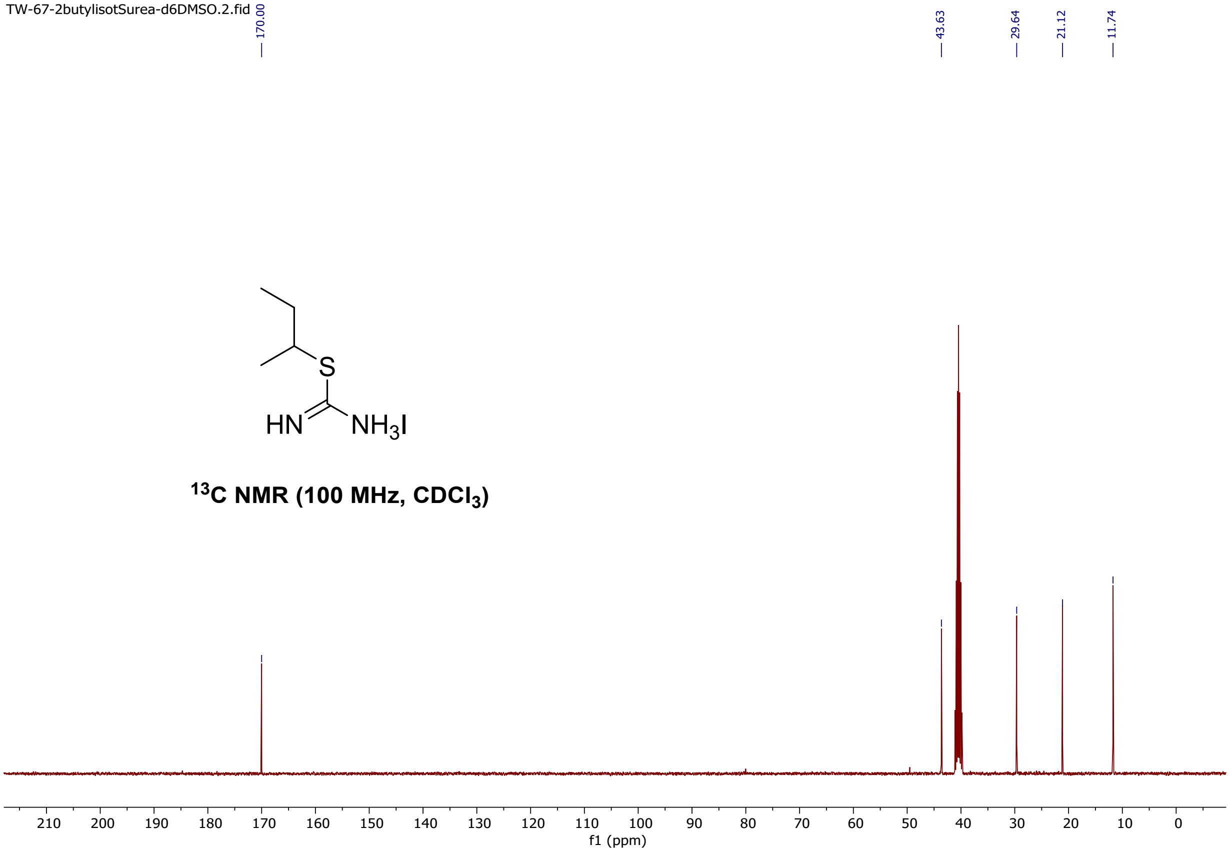
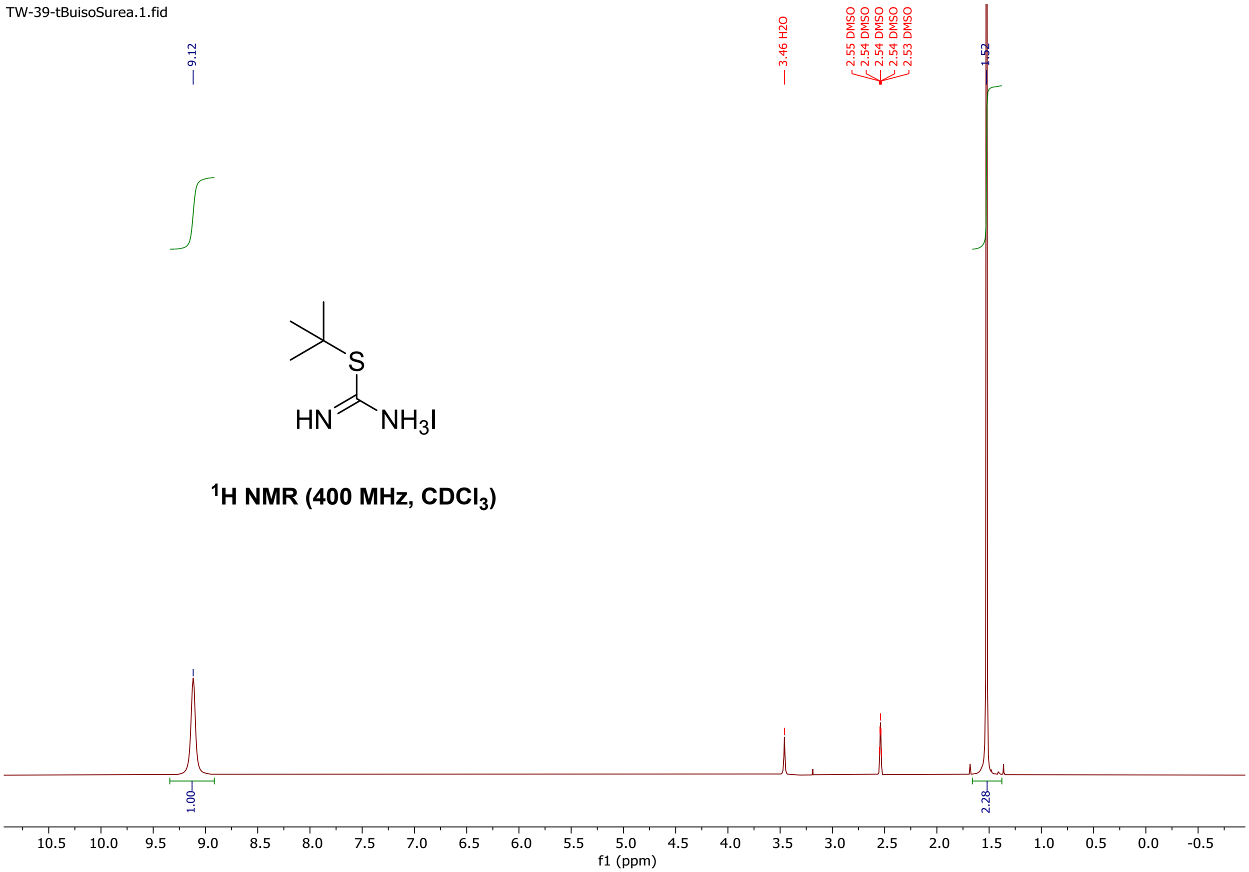
170.74
41.08 DMSO
40.87 DMSO
40.66 DMSO
40.45 DMSO
40.24 DMSO
40.03 DMSO
39.82 DMSO
31.24
30.80
21.92
14.26
S
HN
NH3I
13C NMR (100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



^{1}H NMR (400 MHz, CDCl$_3$)



^{13}C NMR (100 MHz, CDCl$_3$)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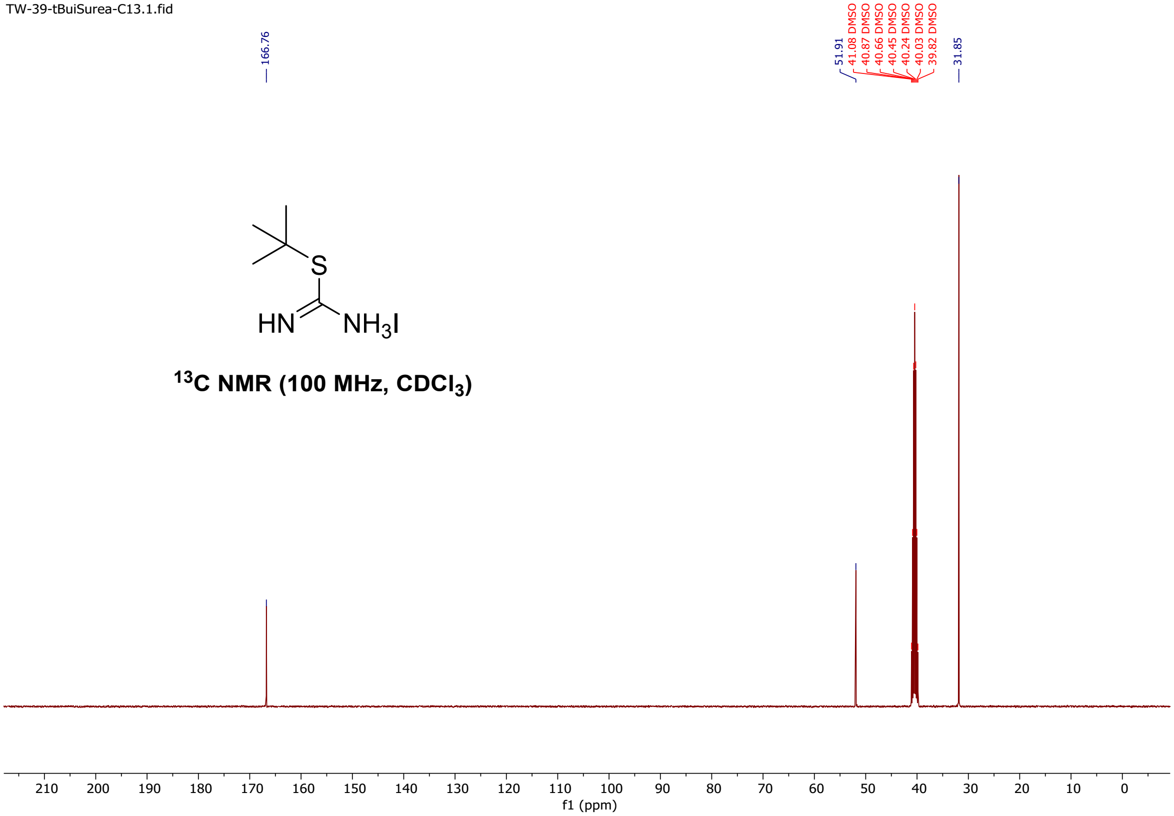
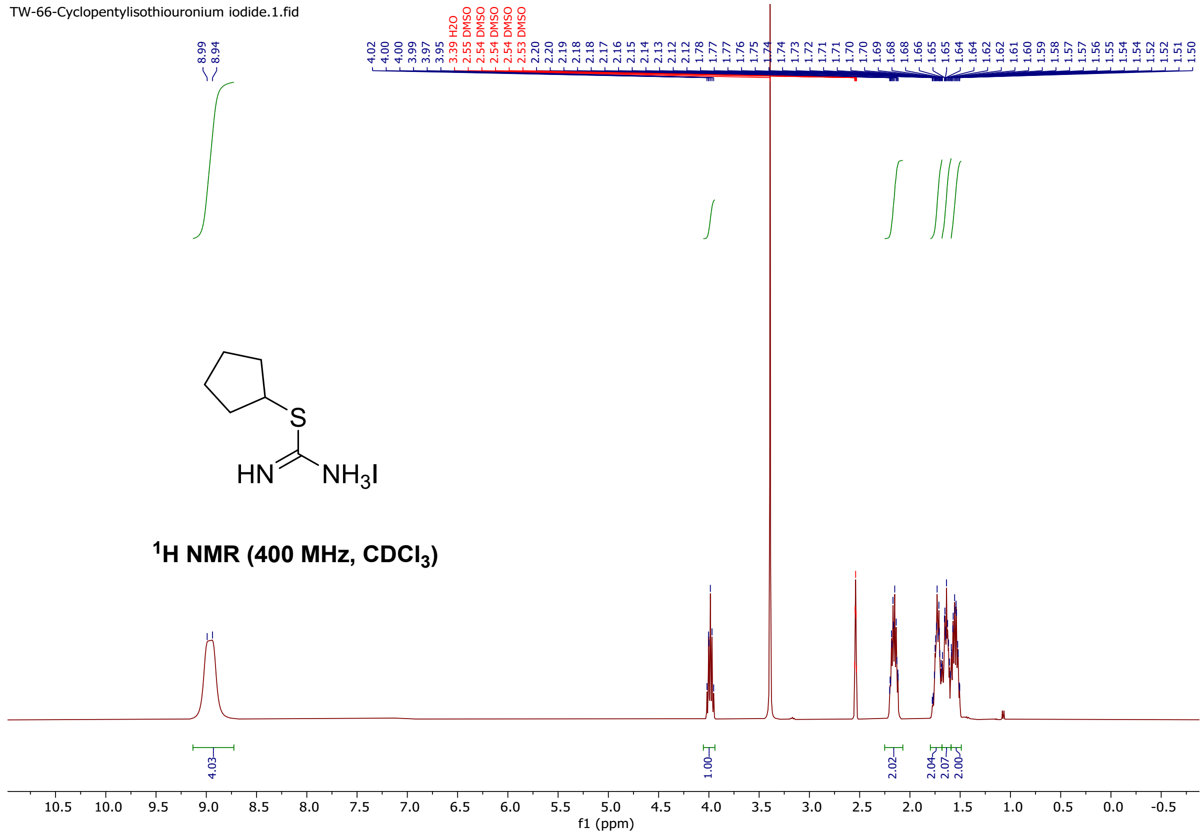
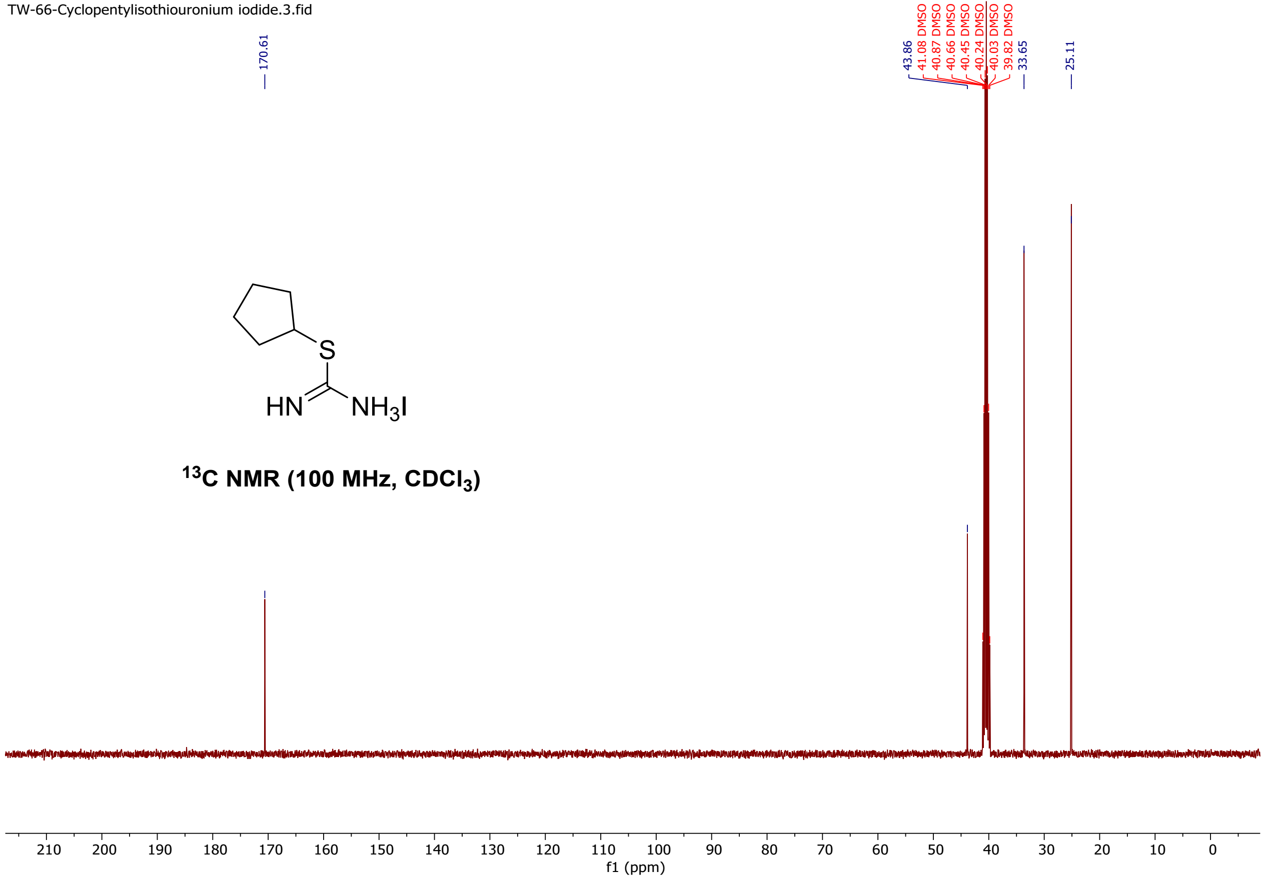
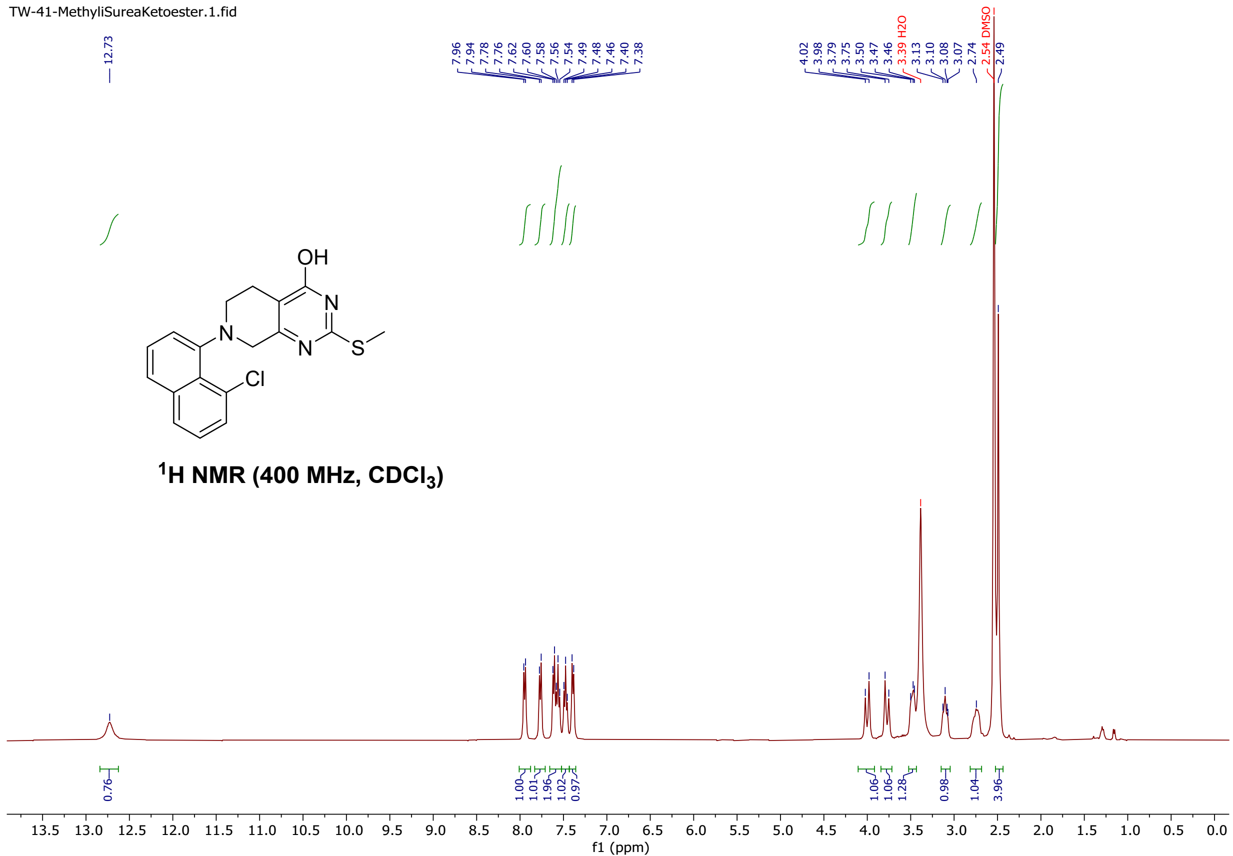
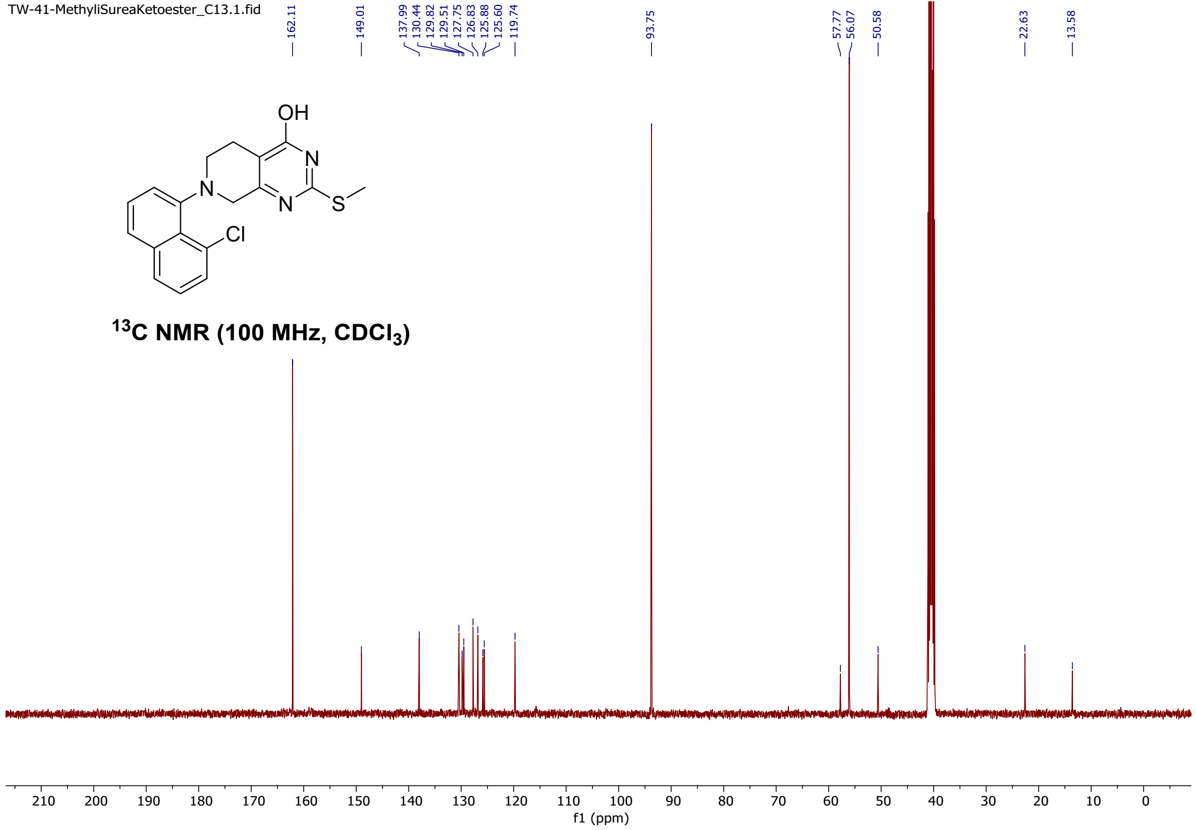
2.55 DMSO
2.54 DMSO
2.54 DMSO
2.54 DMSO
2.53 DMSO
1.52
S
HN
NH3I
1H NMR (400 MHz, CDCl3)
1.00
2.28
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

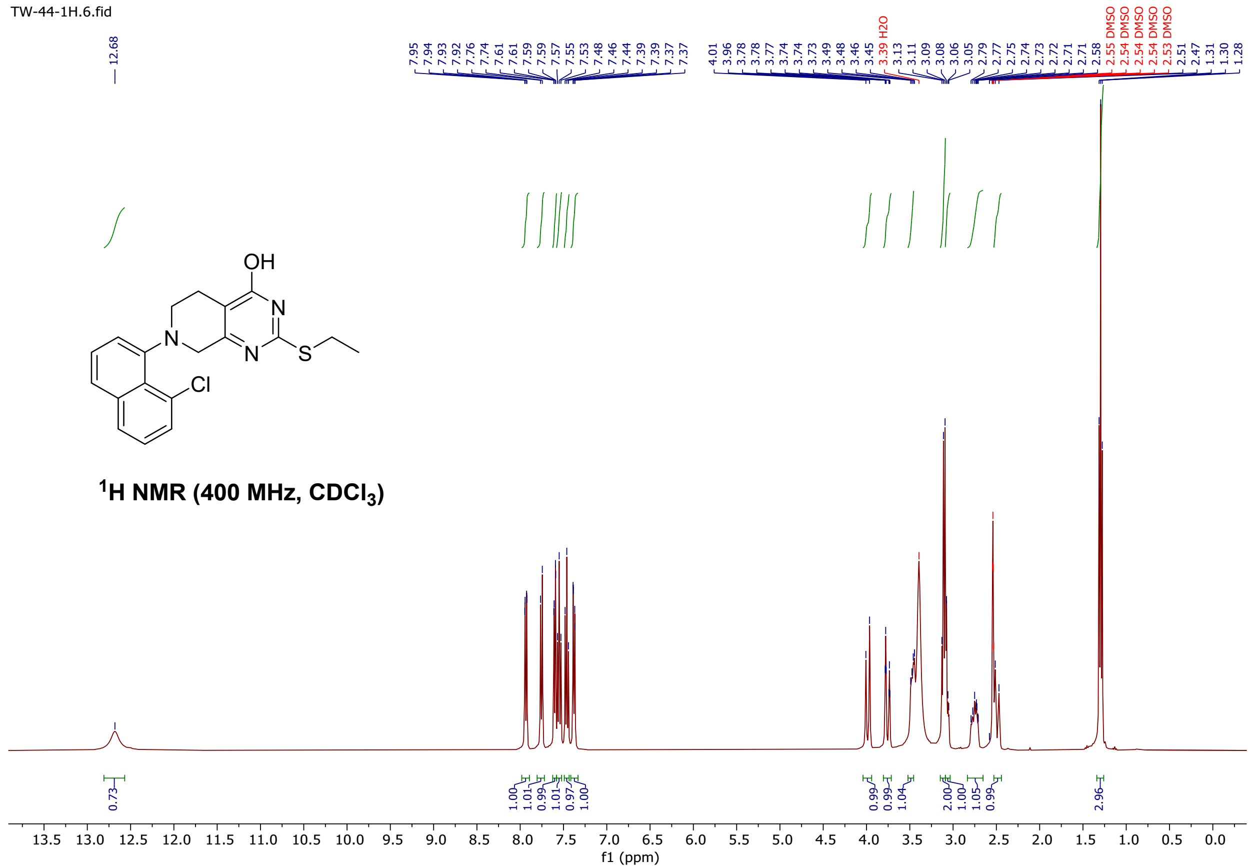

TW-39-tBuiSurea-C13.1.fid
166.76
51.91
41.08 DMSO
40.87 DMSO
40.66 DMSO
40.45 DMSO
40.24 DMSO
40.03 DMSO
39.82 DMSO
31.85
S
HN
NH3I
13C NMR (100 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

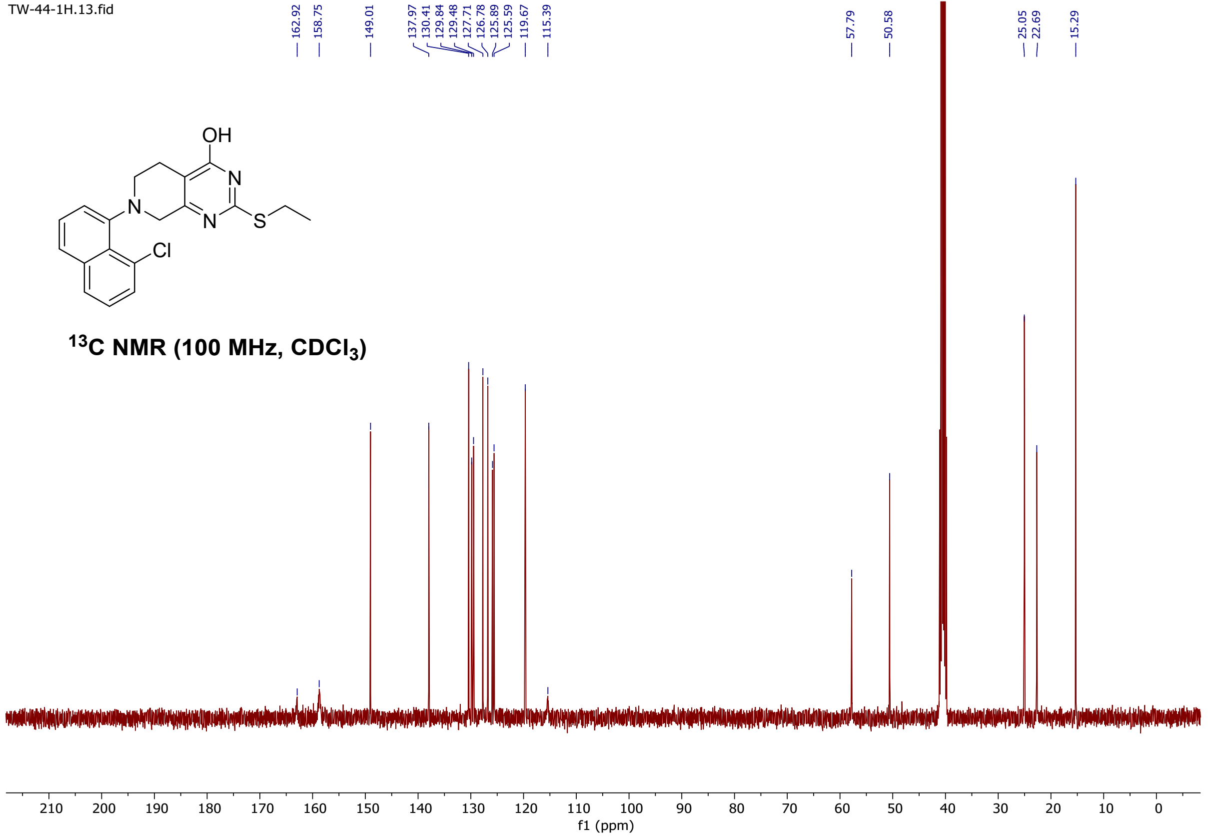

TW-66-Cyclopentylisothiouronium iodide.1.fid
8.99
8.94
4.02
4.00
4.00
3.99
3.97
3.95
3.39 H2O
2.55 DMSO
2.54 DMSO
2.54 DMSO
2.54 DMSO
2.53 DMSO
2.20
2.20
2.19
2.18
2.18
2.17
2.16
2.15
2.14
2.13
2.12
2.12
1.78
1.77
1.77
1.76
1.75
1.74
1.74
1.73
1.72
1.71
1.71
1.70
1.70
1.69
1.68
1.68
1.66
1.65
1.65
1.64
1.64
1.62
1.62
1.61
1.60
1.59
1.58
1.57
1.57
1.56
1.55
1.54
1.54
1.52
1.52
1.51
1.50
S
HN
NH3I
1H NMR (400 MHz, CDCl3)
4.03
1.00
2.02
2.04
2.07
2.00
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
-0.5
f1 (ppm)

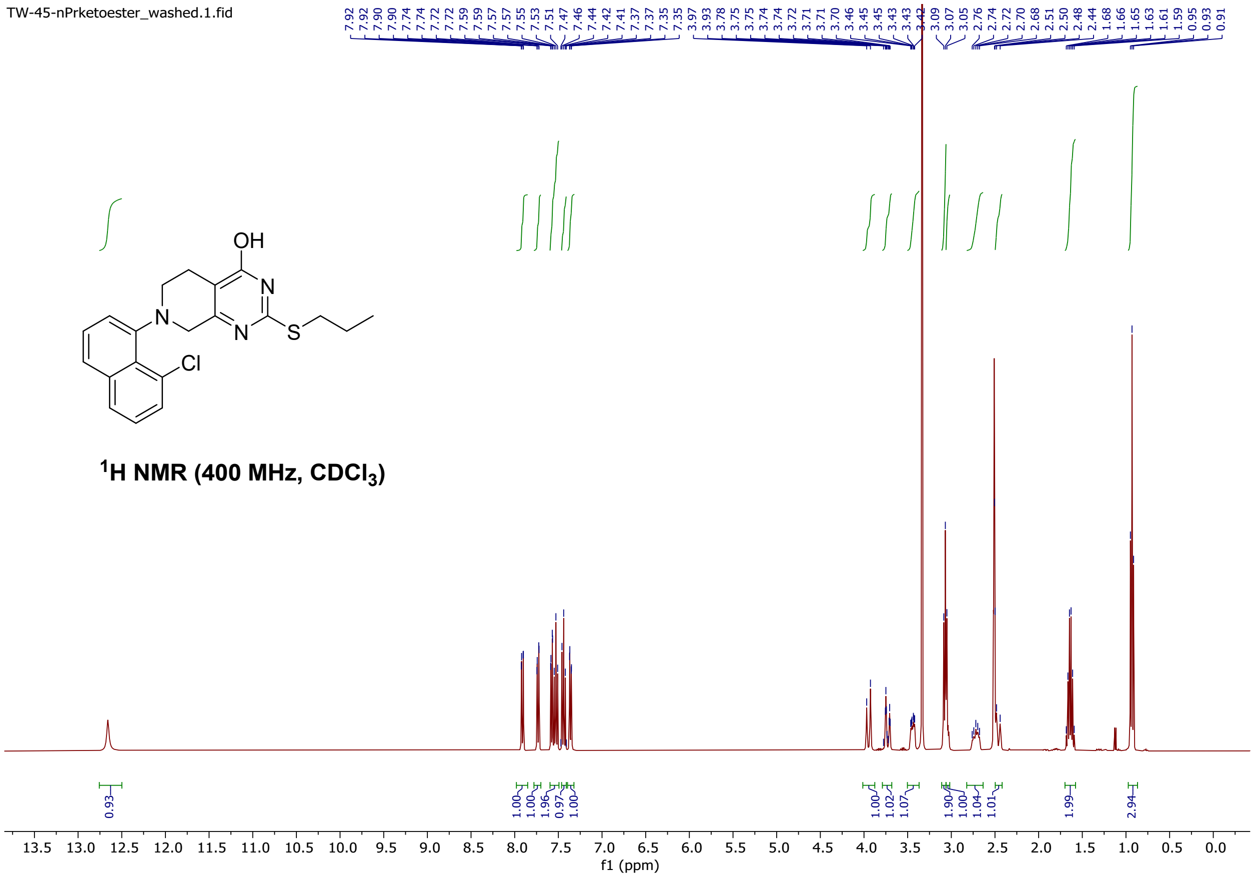

TW-66-Cyclopentylisothiouronium iodide.3.fid
170.61
43.86
41.08 DMSO
40.87 DMSO
40.66 DMSO
40.45 DMSO
40.24 DMSO
40.03 DMSO
39.82 DMSO
33.65
25.11
S
HN
NH3I
13C NMR (100 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


TW-41-MethyliSureaKetoester.1.fid
12.73
7.96
7.94
7.78
7.76
7.62
7.60
7.58
7.56
7.54
7.49
7.48
7.46
7.40
7.38
4.02
3.98
3.79
3.75
3.50
3.47
3.46
3.39 H2O
3.13
3.10
3.08
3.07
2.74
2.54 DMSO
2.49
OH
N
N
N
S
Cl
^{1}H NMR (400 MHz, CDCl$_3$)
0.76
1.00
1.01
1.96
1.02
0.97
1.06
1.06
1.28
0.98
1.04
3.96
13.5
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)

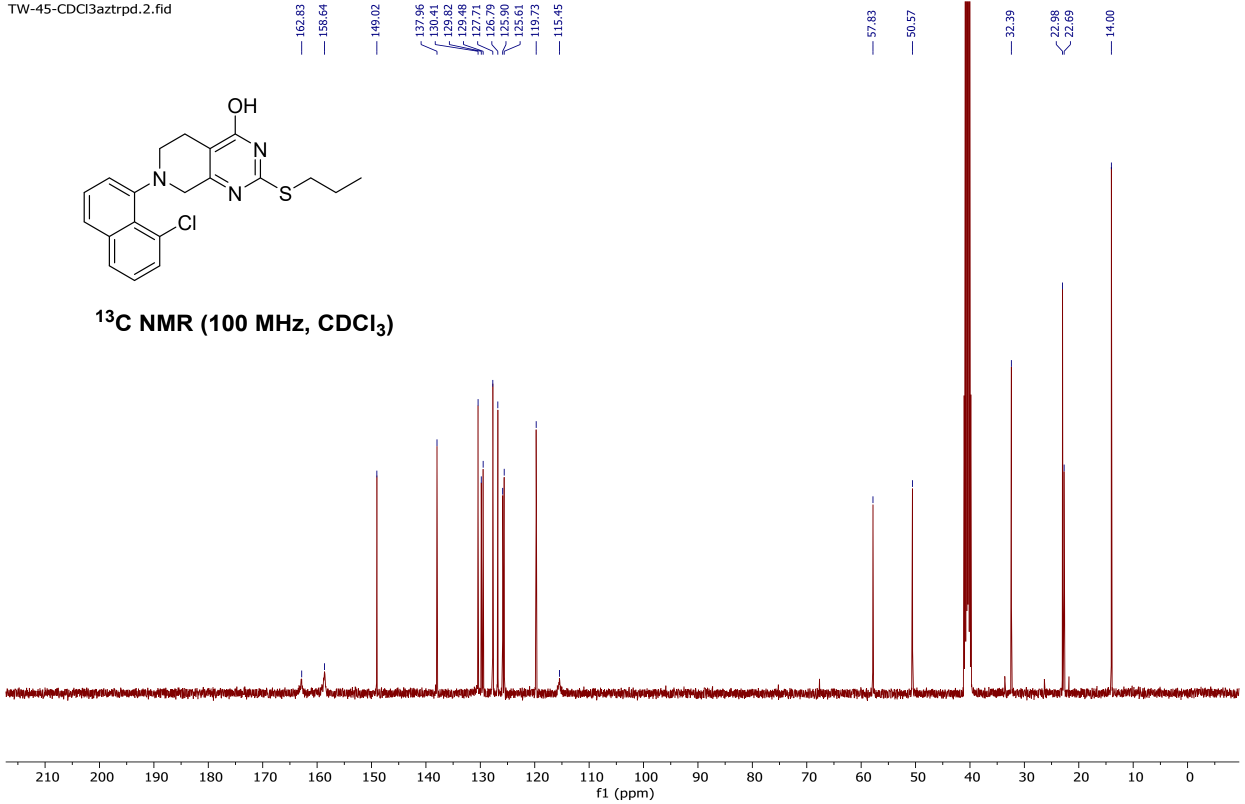

TW-41-MethyliSureaKetoester_C13.1.fid
162.11
149.01
137.99
130.44
129.82
129.51
127.75
126.83
125.88
125.60
119.74
93.75
57.77
56.07
50.58
22.63
13.58
OH
N
N
N
S
Cl
^{13}C NMR (100 MHz, CDCl$_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


TW-44-1H.6.fid
12.68
7.95
7.94
7.93
7.92
7.76
7.74
7.61
7.61
7.59
7.59
7.57
7.55
7.53
7.48
7.46
7.44
7.39
7.39
7.37
7.37
4.01
3.96
3.78
3.78
3.77
3.74
3.74
3.73
3.49
3.48
3.46
3.45
3.39 H2O
3.13
3.11
3.09
3.08
3.06
3.05
2.79
2.77
2.75
2.74
2.73
2.72
2.71
2.71
2.58
2.55 DMSO
2.54 DMSO
2.54 DMSO
2.54 DMSO
2.53 DMSO
2.51
2.47
1.31
1.30
1.28
OH
N
N
N
S
Cl
^{1}H NMR (400 MHz, CDCl$_3$)
0.73
1.00
1.01
0.99
1.01
0.97
1.00
0.99
0.99
1.04
2.00
1.00
1.05
0.99
2.96
13.5
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)

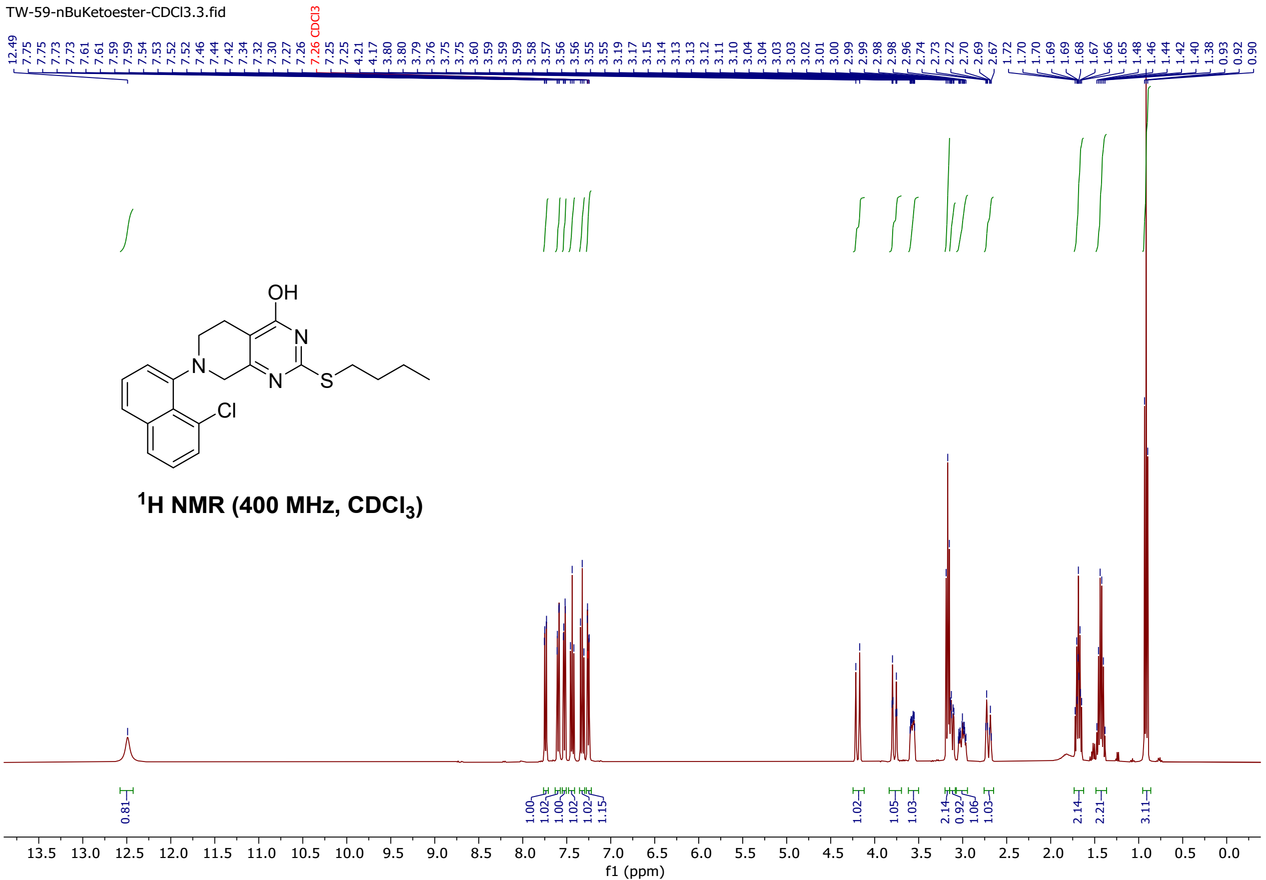

TW-44-1H.13.fid
162.92
158.75
149.01
137.97
130.41
129.84
129.48
127.71
126.78
125.89
125.59
119.67
115.39
57.79
50.58
25.05
22.69
15.29
OH
N
N
N
S
Cl
^{13}C NMR (100 MHz, CDCl$_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

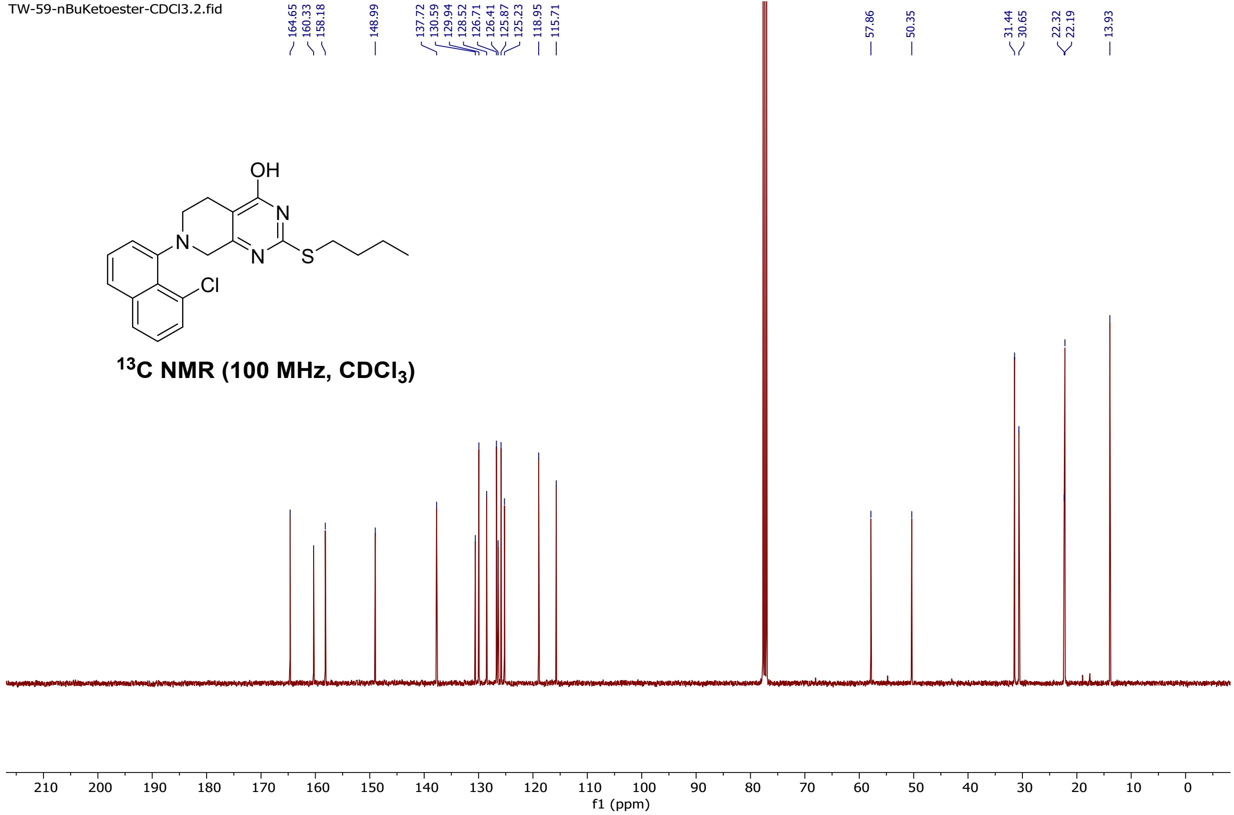


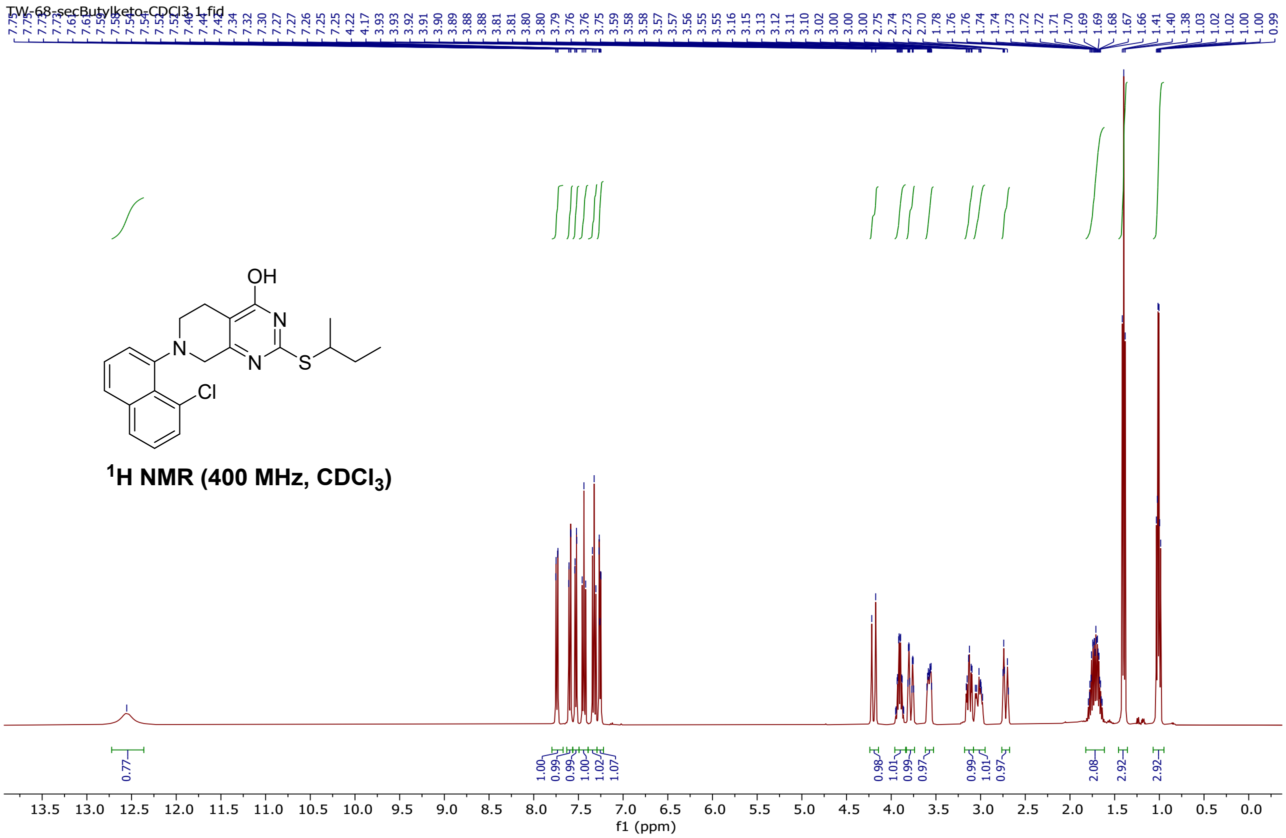
^{1}H NMR (400 MHz, CDCl$_3$)

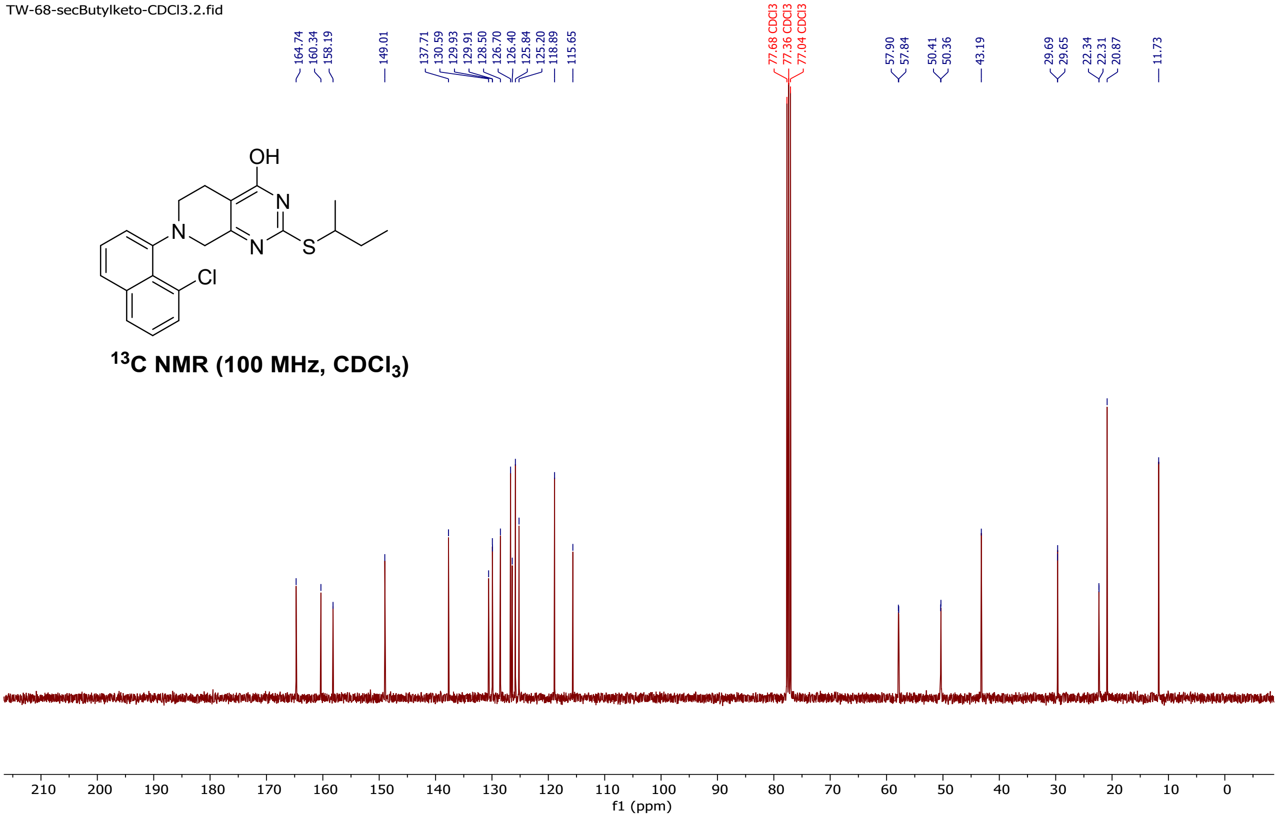


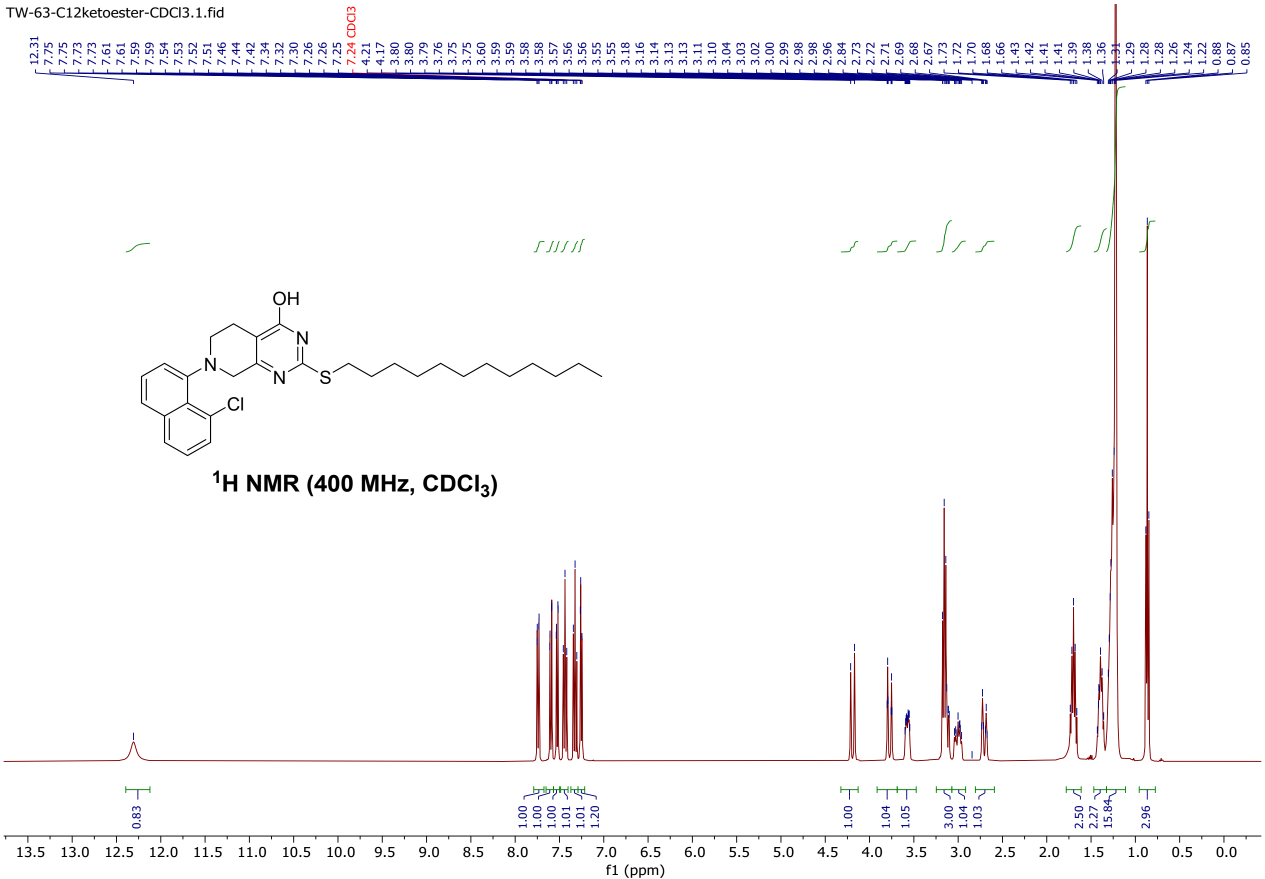
^{13}C NMR (100 MHz, CDCl$_3$)


TW-59-nBuKetoester-CDCl3.3.fid
12.49
7.75
7.75
7.73
7.73
7.61
7.61
7.59
7.59
7.54
7.53
7.52
7.52
7.46
7.44
7.42
7.34
7.32
7.30
7.27
7.26 CDCl3
7.25
7.25
4.21
4.17
3.80
3.80
3.79
3.76
3.75
3.75
3.60
3.59
3.59
3.58
3.57
3.56
3.56
3.55
3.55
3.19
3.17
3.15
3.14
3.13
3.13
3.12
3.11
3.10
3.04
3.04
3.03
3.03
3.02
3.01
3.00
2.99
2.99
2.98
2.98
2.96
2.74
2.73
2.72
2.70
2.69
2.67
1.72
1.70
1.70
1.69
1.69
1.68
1.67
1.66
1.65
1.48
1.46
1.44
1.42
1.40
1.38
0.93
0.92
0.90
OH
N
N
N
S
Cl
^{1}H NMR (400 MHz, CDCl$_3$)
0.81
1.00
1.02
1.00
1.02
1.02
1.15
1.02
1.05
1.03
2.14
0.92
1.06
1.03
2.14
2.21
3.11
13.5
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)

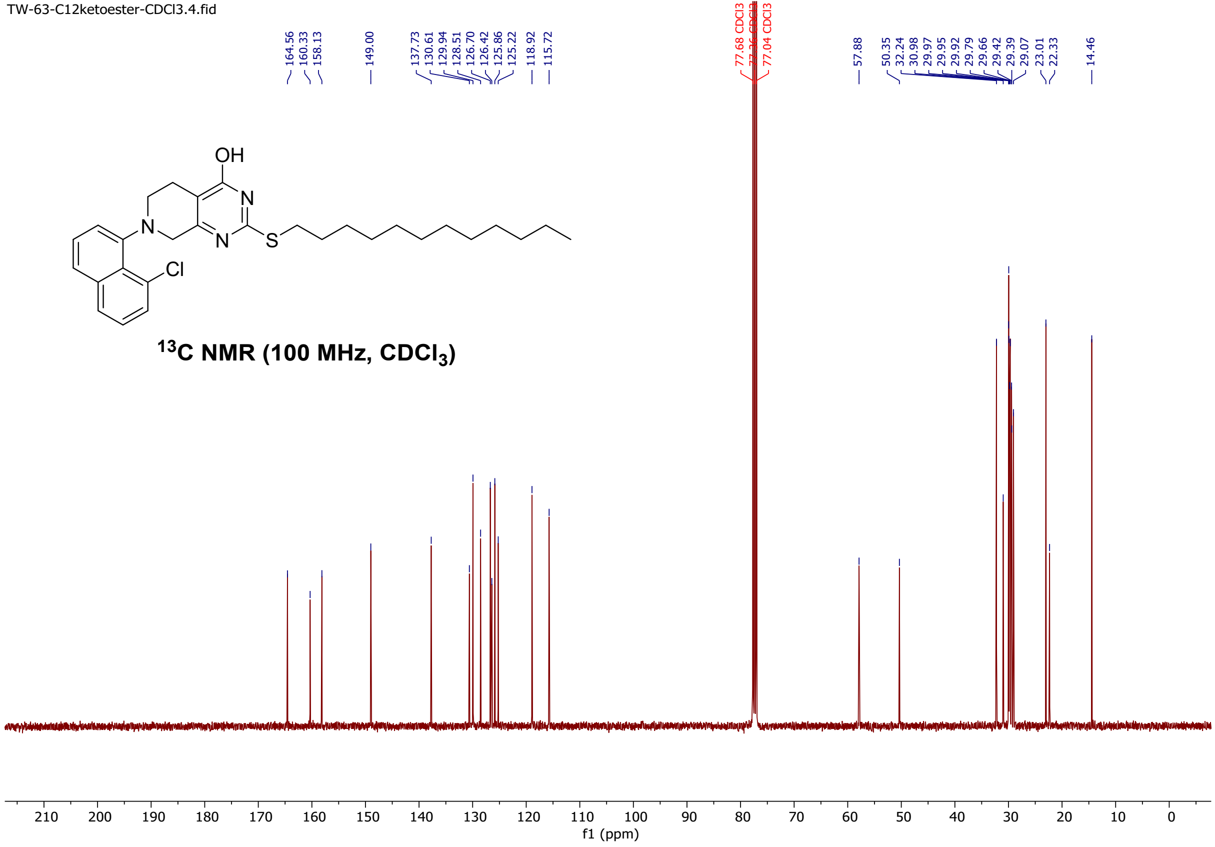

TW-59-nBuKetoester-CDCl3.2.fid
164.65
160.33
158.18
148.99
137.72
130.59
129.94
128.52
126.71
126.41
125.87
125.23
118.95
115.71
57.86
50.35
31.44
30.65
22.32
22.19
13.93
OH
N
N
N
S
Cl
^{13}C NMR (100 MHz, CDCl$_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


TW-68-secButylketo-CDCl3.1.fid
7.75 7.75 7.73 7.73 7.61 7.61 7.59 7.58 7.54 7.54 7.52 7.51 7.46 7.44 7.42 7.34 7.32 7.30 7.27 7.27 7.26 7.25 7.25 4.22 4.17 3.93 3.93 3.92 3.91 3.90 3.89 3.88 3.88 3.81 3.81 3.80 3.80 3.79 3.76 3.76 3.75 3.59 3.58 3.58 3.57 3.57 3.56 3.55 3.55 3.16 3.15 3.13 3.12 3.11 3.10 3.02 3.00 3.00 3.00 2.75 2.74 2.73 2.70 1.78 1.76 1.76 1.74 1.74 1.73 1.72 1.72 1.71 1.70 1.69 1.69 1.68 1.67 1.66 1.41 1.40 1.38 1.03 1.02 1.02 1.00 1.00 0.99
OH
N
N
N
S
Cl
^{1}H NMR (400 MHz, CDCl$_3$)
0.77
1.00 0.99 0.99 1.00 1.02 1.07
0.98 1.01 0.99 0.97
0.99 1.01 0.97
2.08 2.92 2.92
13.5 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)

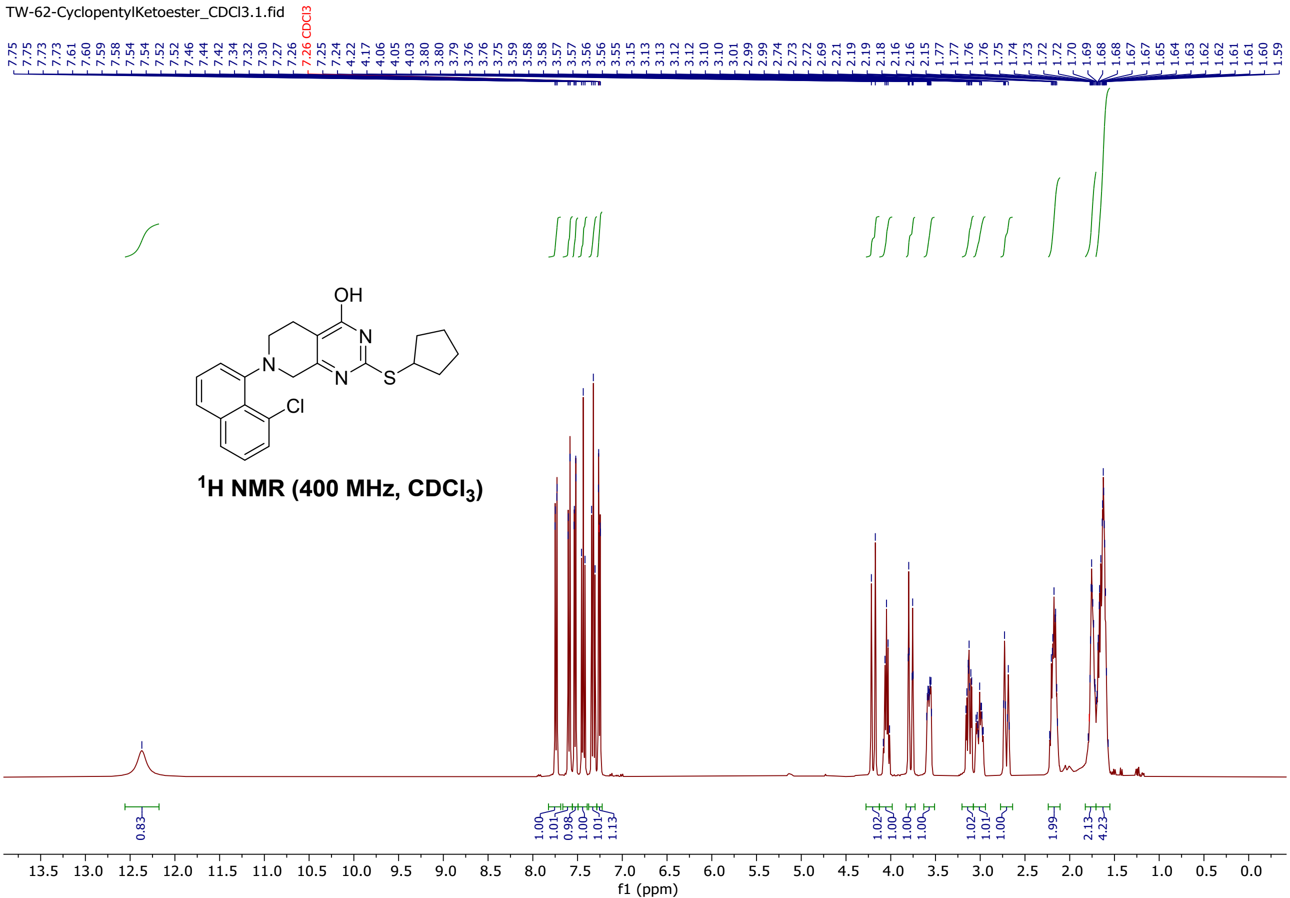

TW-68-secButylketo-CDCl3.2.fid
164.74 160.34 158.19
149.01
137.71 130.59 129.93 129.91 128.50 126.70 126.40 125.84 125.20 118.89 115.65
77.68 CDCl3 77.36 CDCl3 77.04 CDCl3
57.90 57.84
50.41 50.36
43.19
29.69 29.65
22.34 22.31 20.87
11.73
OH
N
N
N
S
Cl
^{13}C NMR (100 MHz, CDCl$_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



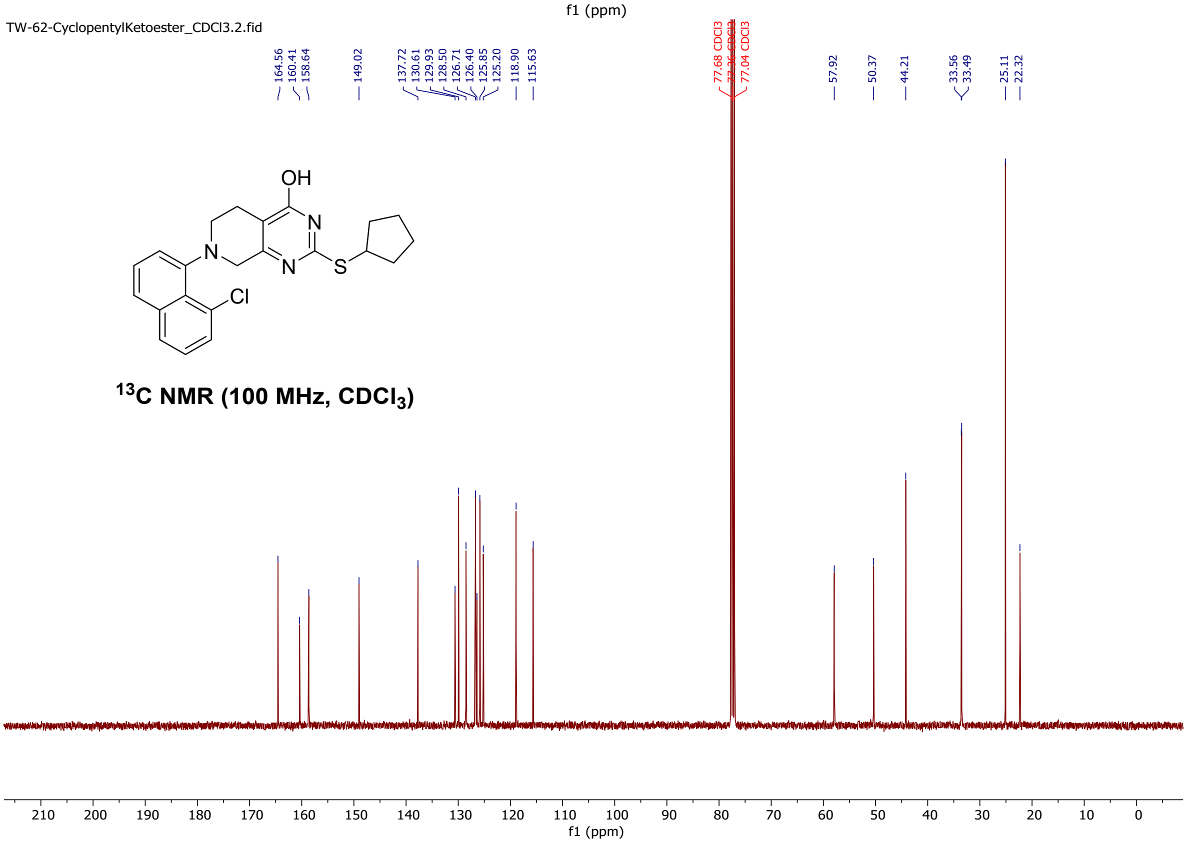
^{1}H NMR (400 MHz, CDCl$_3$)



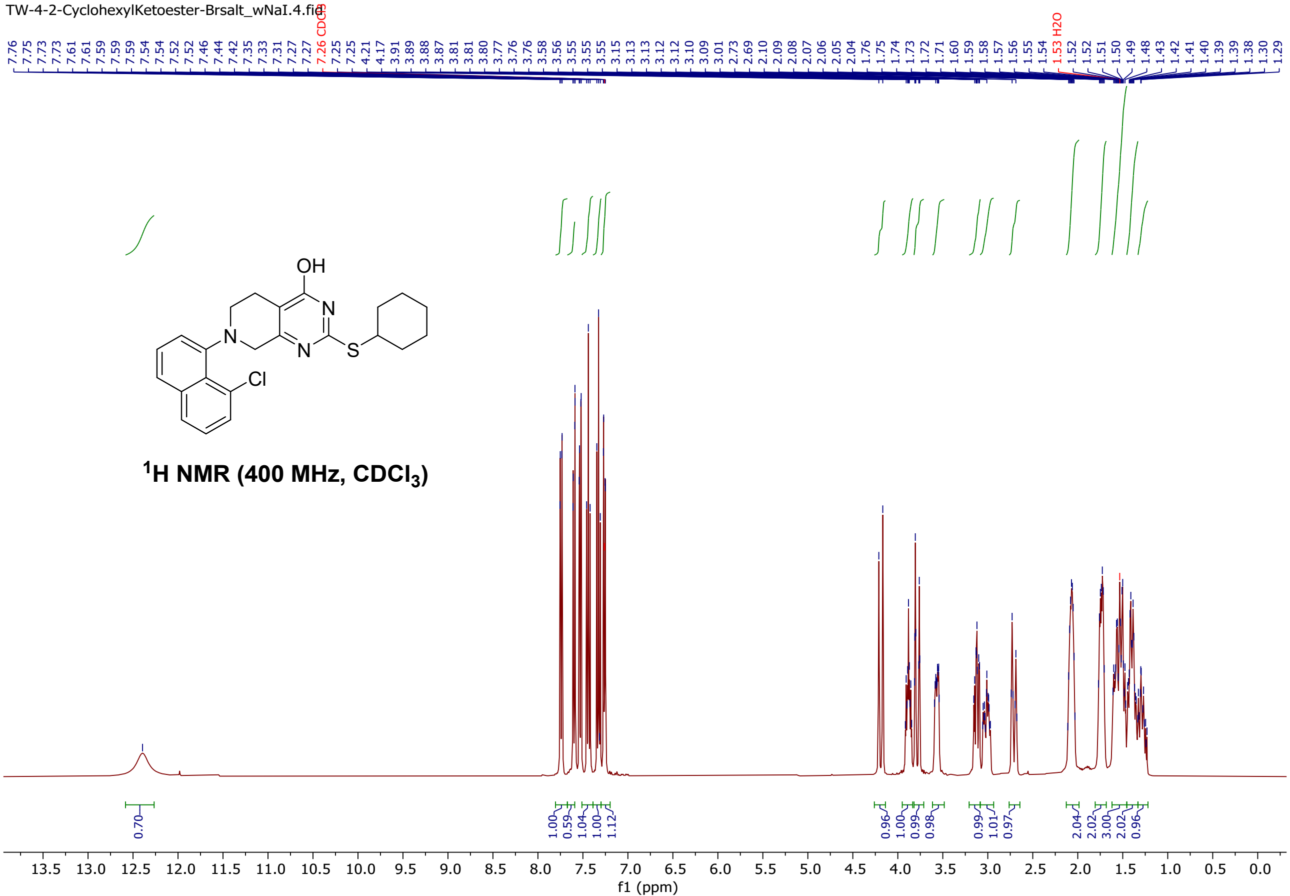
^{13}C NMR (100 MHz, CDCl$_3$)



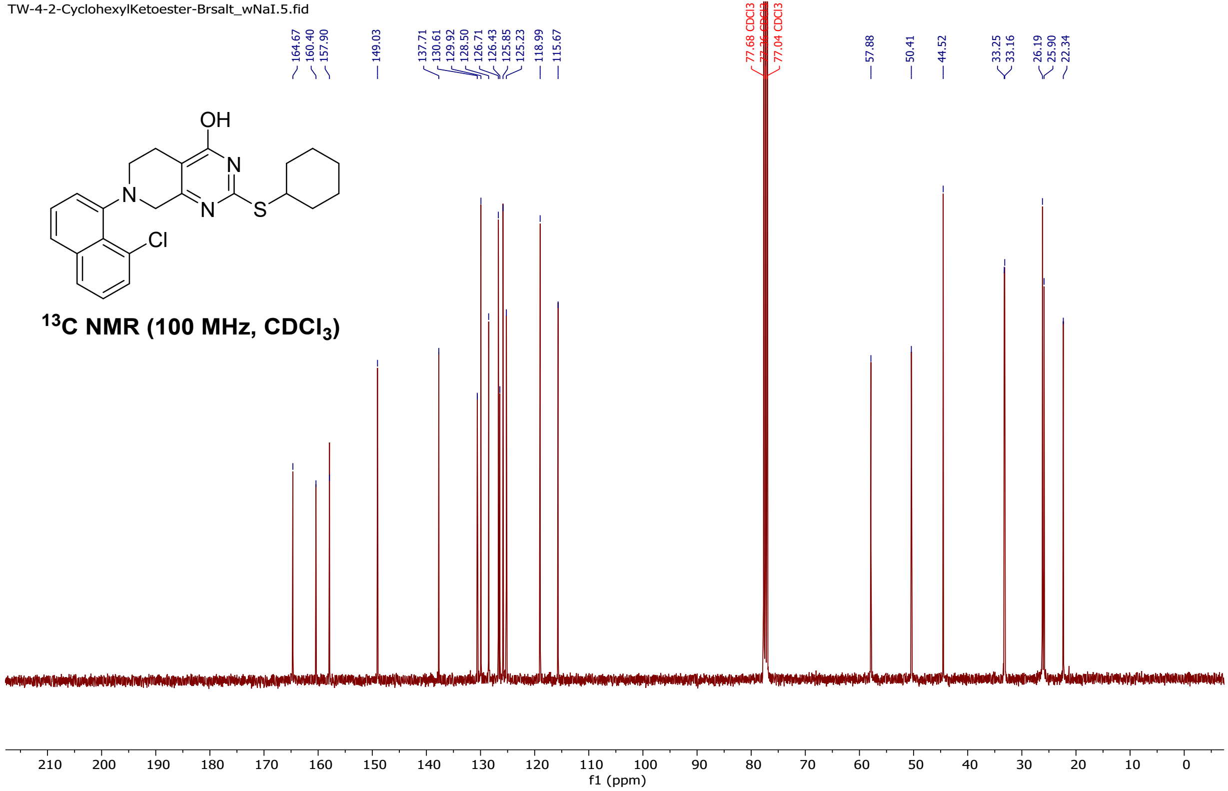
^{1}H NMR (400 MHz, CDCl$_3$)



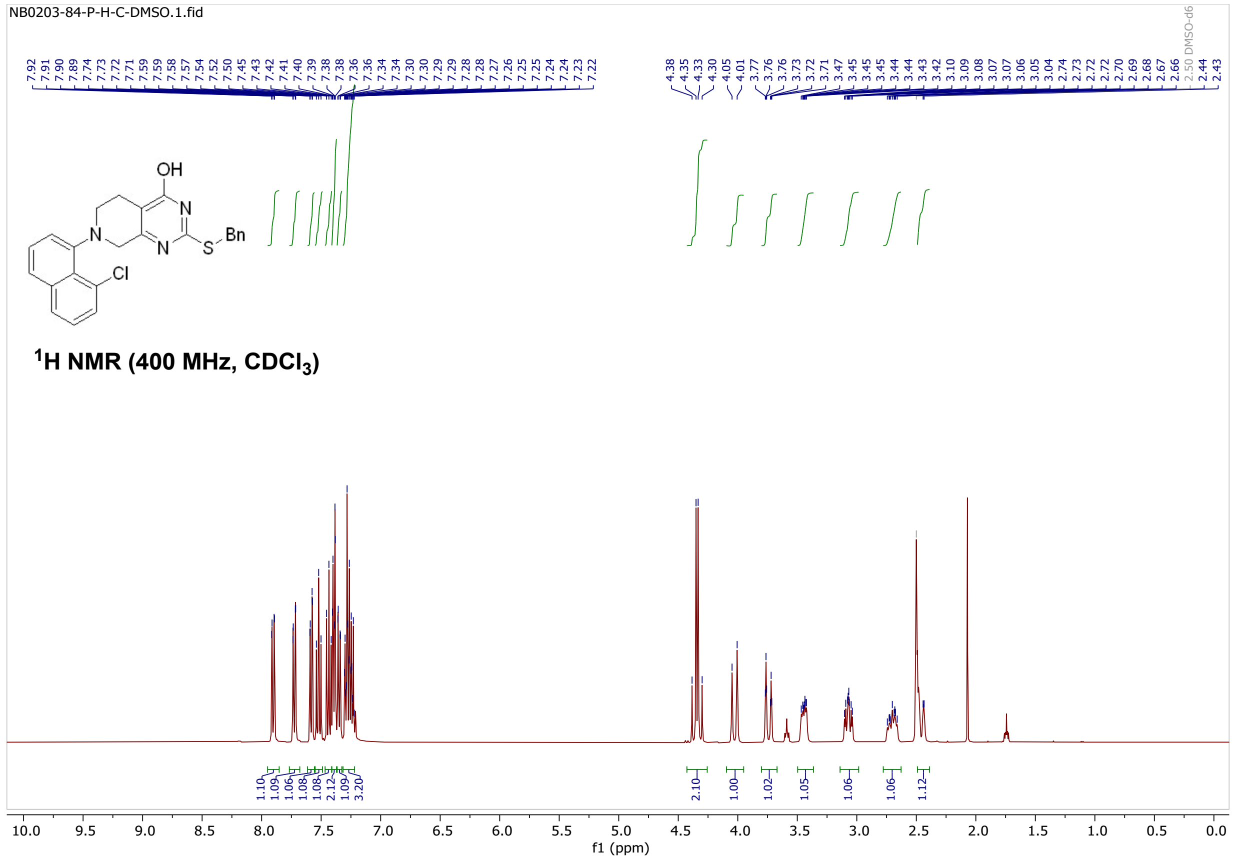
^{13}C NMR (100 MHz, CDCl$_3$)

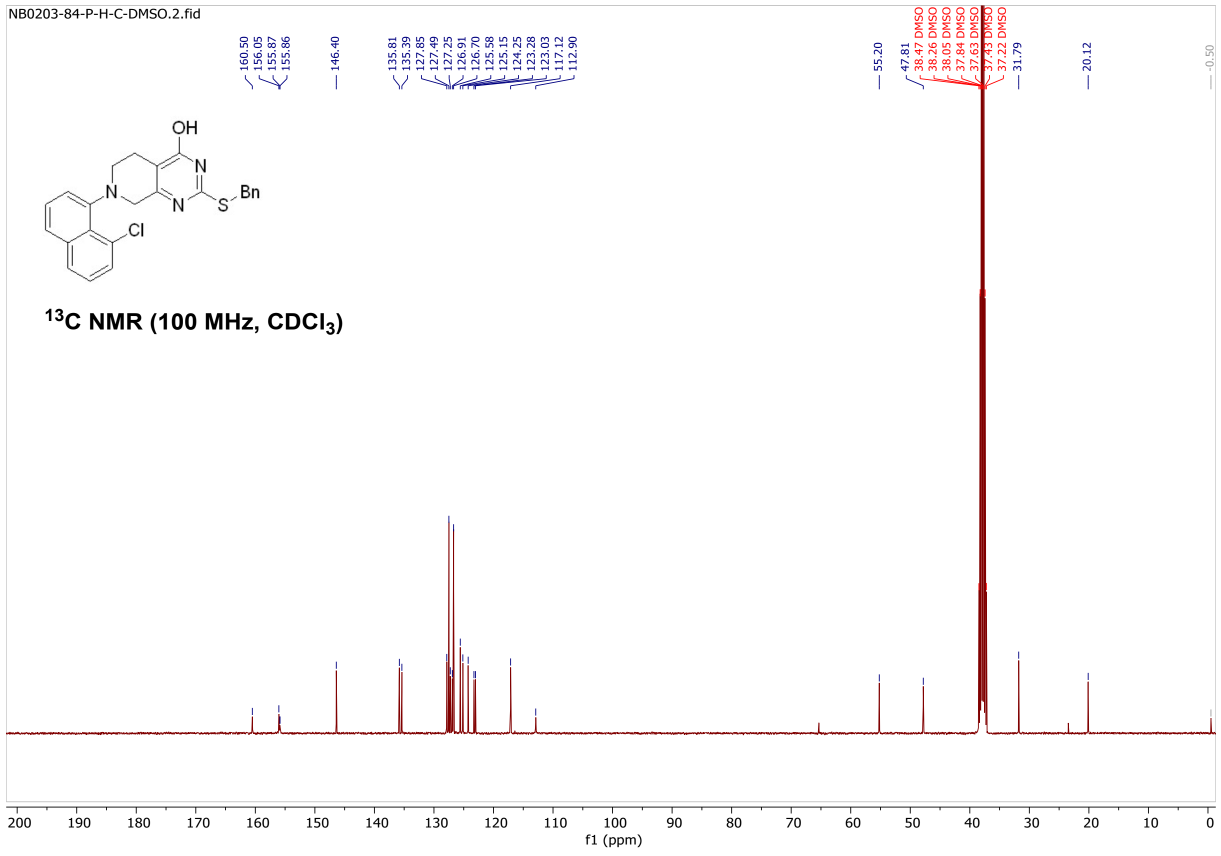


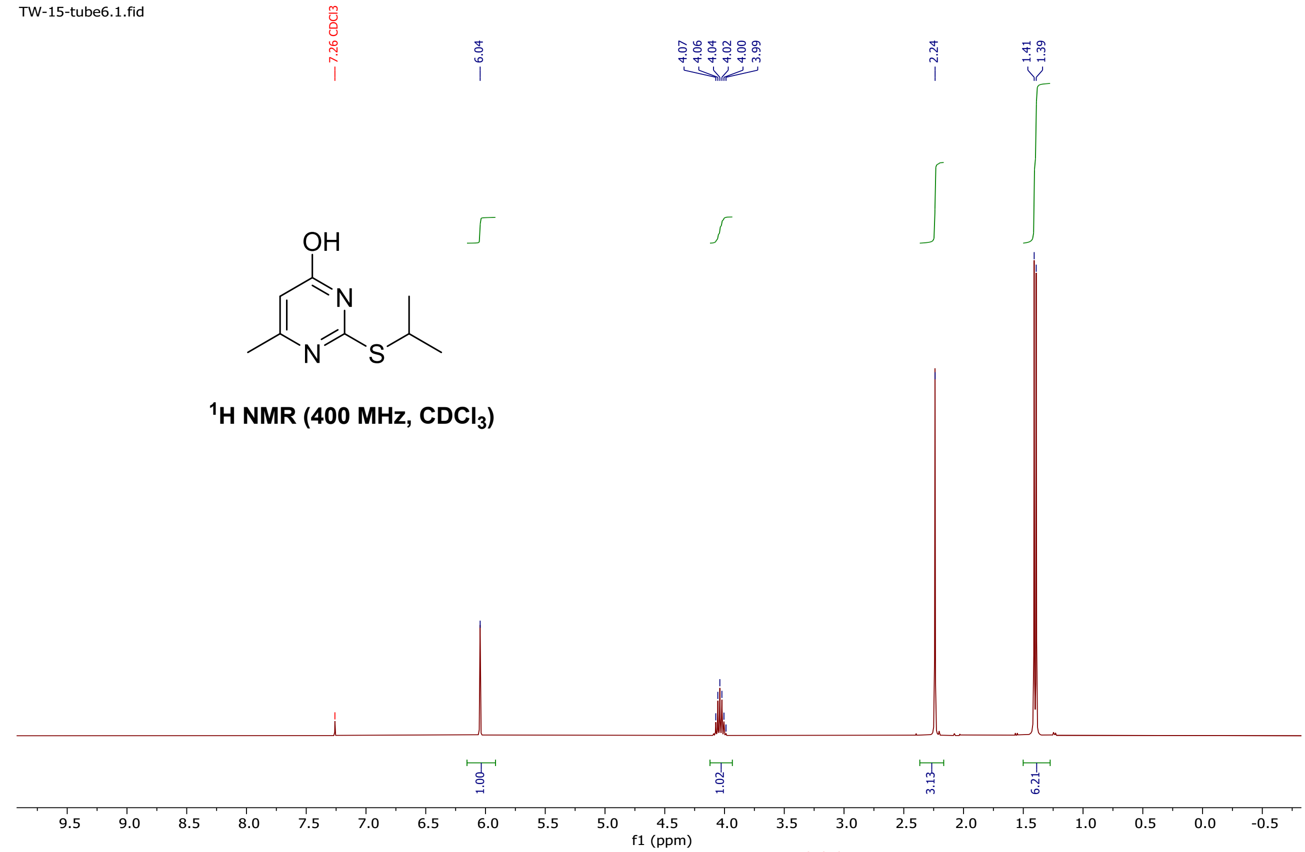
^{1}H NMR (400 MHz, $CDCl_3$)

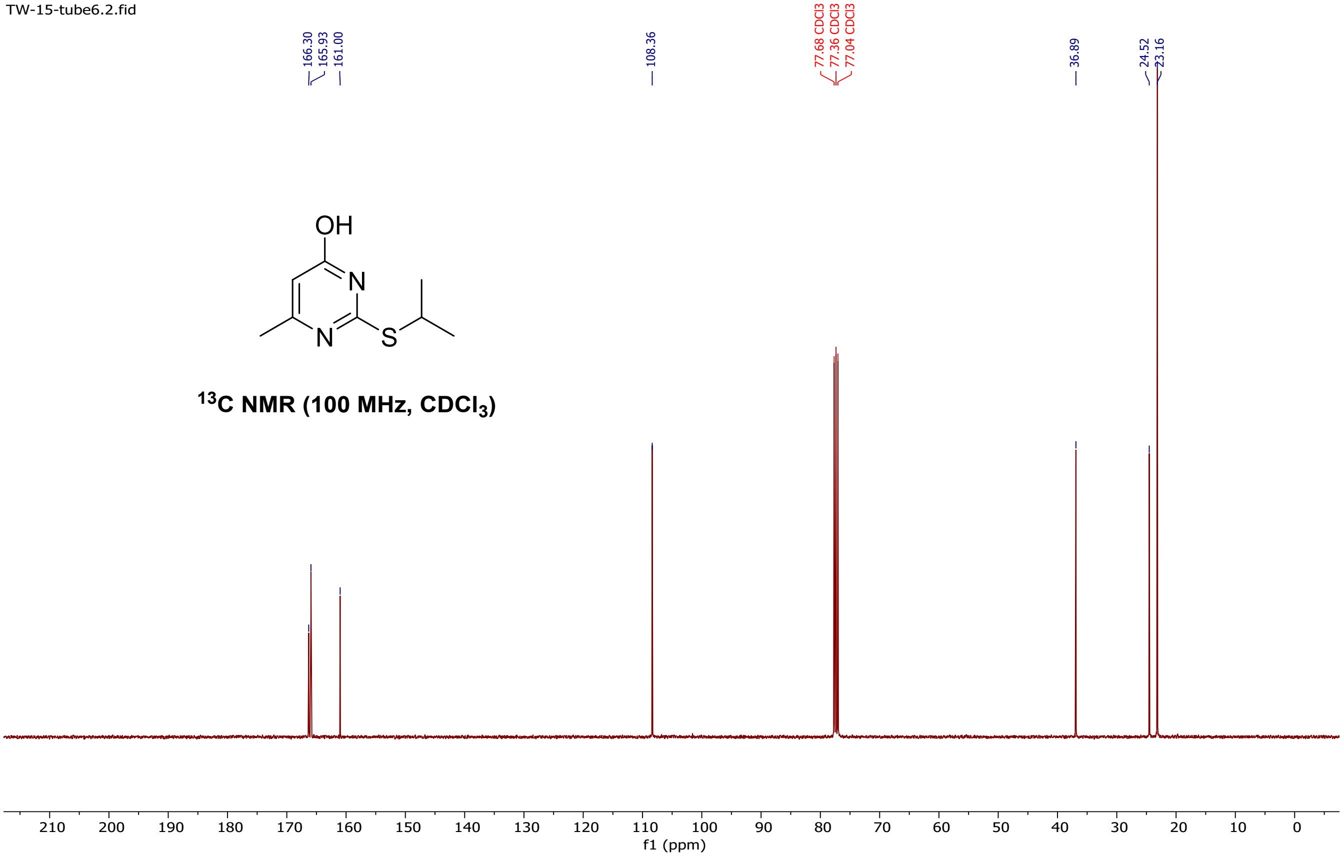


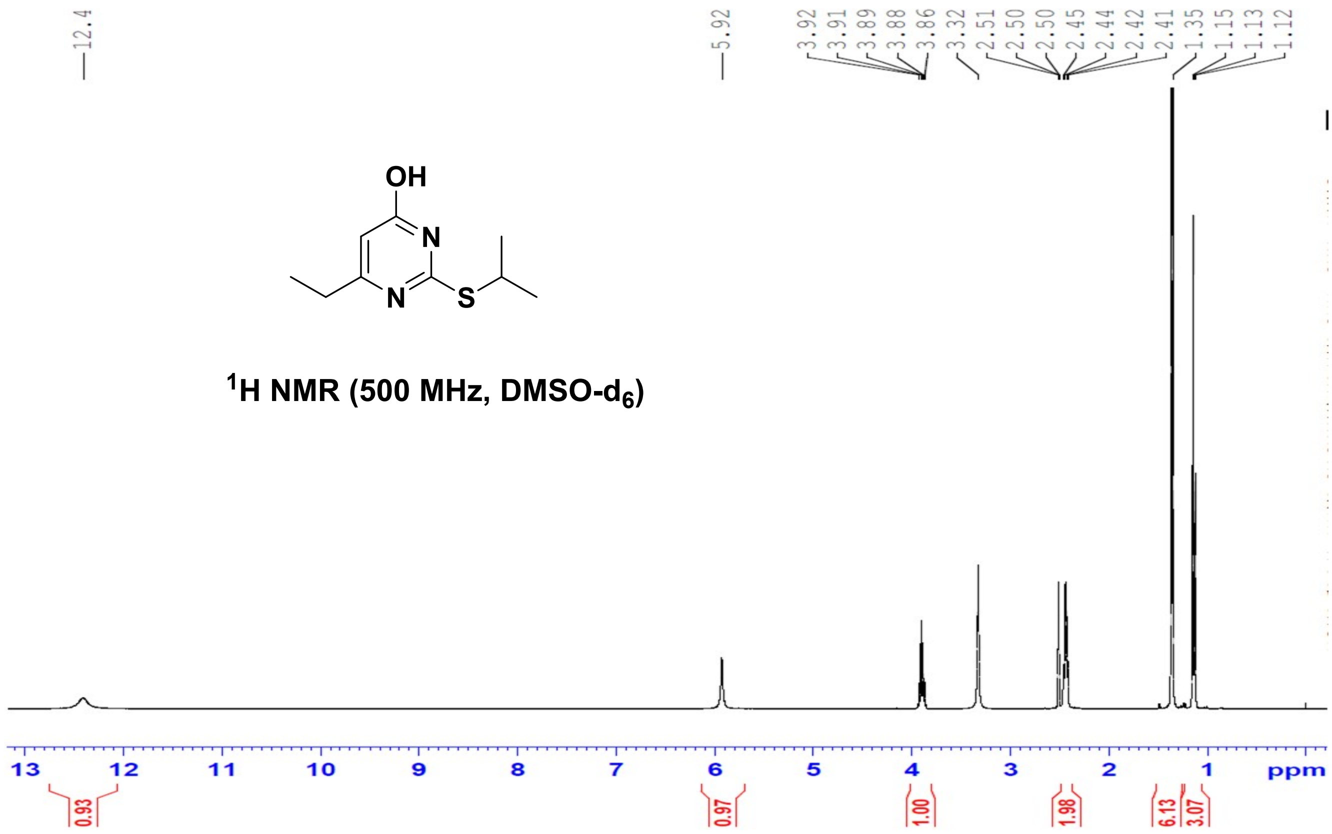
^{13}C NMR (100 MHz, $CDCl_3$)


NB0203-84-P-H-C-DMSO.1.fid
7.92 7.91 7.90 7.89 7.74 7.73 7.72 7.71 7.59 7.59 7.58 7.57 7.54 7.52 7.50 7.45 7.43 7.42 7.41 7.40 7.39 7.38 7.38 7.36 7.36 7.34 7.34 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.26 7.25 7.25 7.24 7.24 7.23 7.22
4.38 4.35 4.33 4.30 4.05 4.01 3.77 3.76 3.76 3.73 3.72 3.71 3.47 3.45 3.45 3.45 3.44 3.44 3.43 3.42 3.10 3.09 3.08 3.07 3.07 3.06 3.05 3.04 2.74 2.73 2.72 2.72 2.70 2.69 2.68 2.67 2.66 2.50 DMSO-d6 2.44 2.43
OH
N
N
N
S
Bn
Cl
^{1}H NMR (400 MHz, CDCl$_3$)
1.10 1.09 1.06 1.08 1.08 2.12 1.09 3.20
2.10 1.00 1.02 1.05 1.06 1.06 1.12
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)

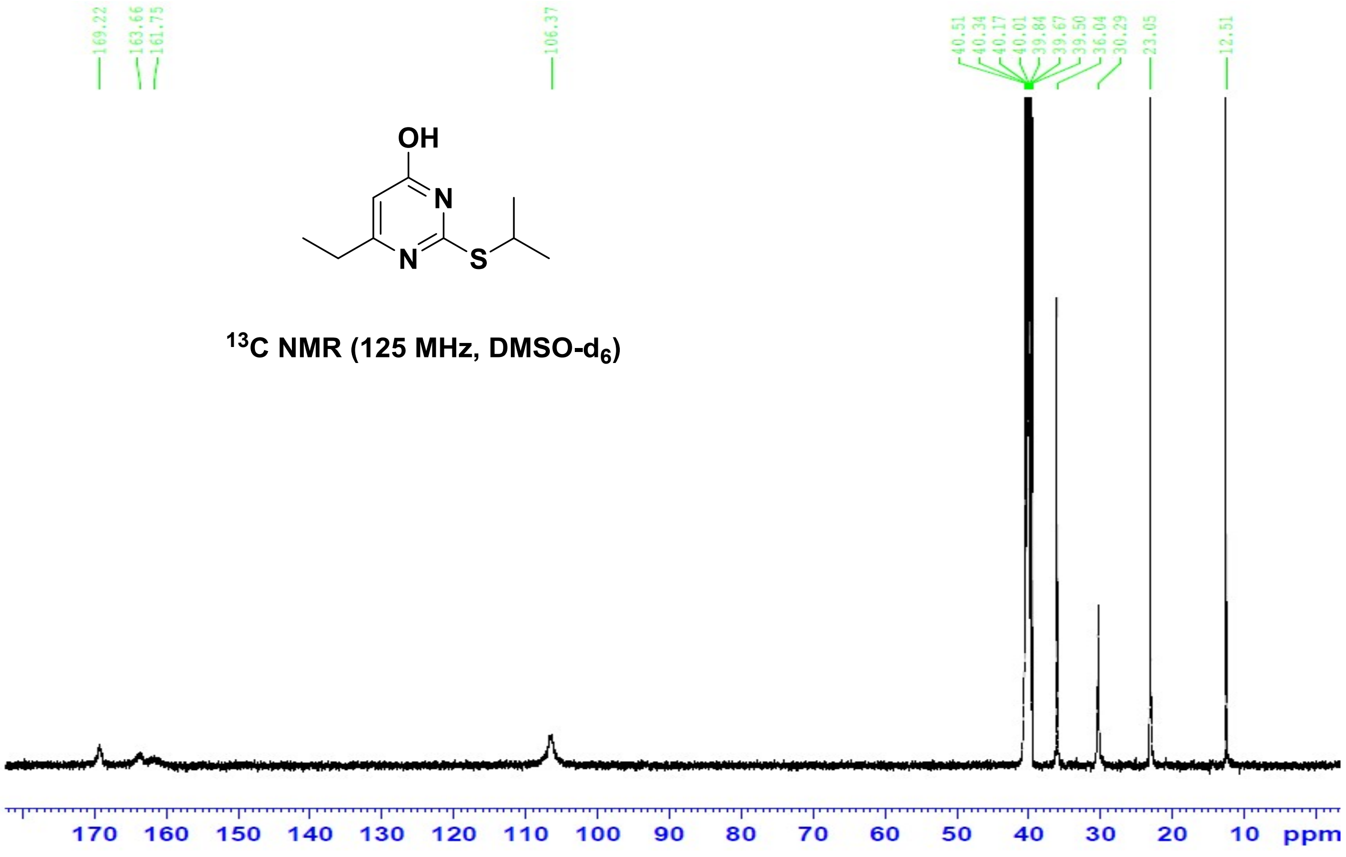

NB0203-84-P-H-C-DMSO.2.fid
160.50 156.05 155.87 155.86 146.40 135.81 135.39 127.85 127.49 127.25 126.91 126.70 125.58 125.15 124.25 123.28 123.03 117.12 112.90
55.20 47.81 38.47 DMSO 38.26 DMSO 38.05 DMSO 37.84 DMSO 37.63 DMSO 37.43 DMSO 37.22 DMSO 31.79 20.12 -0.50
OH
N
N
N
S
Bn
Cl
^{13}C NMR (100 MHz, CDCl$_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


TW-15-tube6.1.fid
7.26 CDCl3
6.04
4.07
4.06
4.04
4.02
4.00
3.99
2.24
1.41
1.39
OH
N
N
S
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
1.02
3.13
6.21
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
-0.5
f1 (ppm)

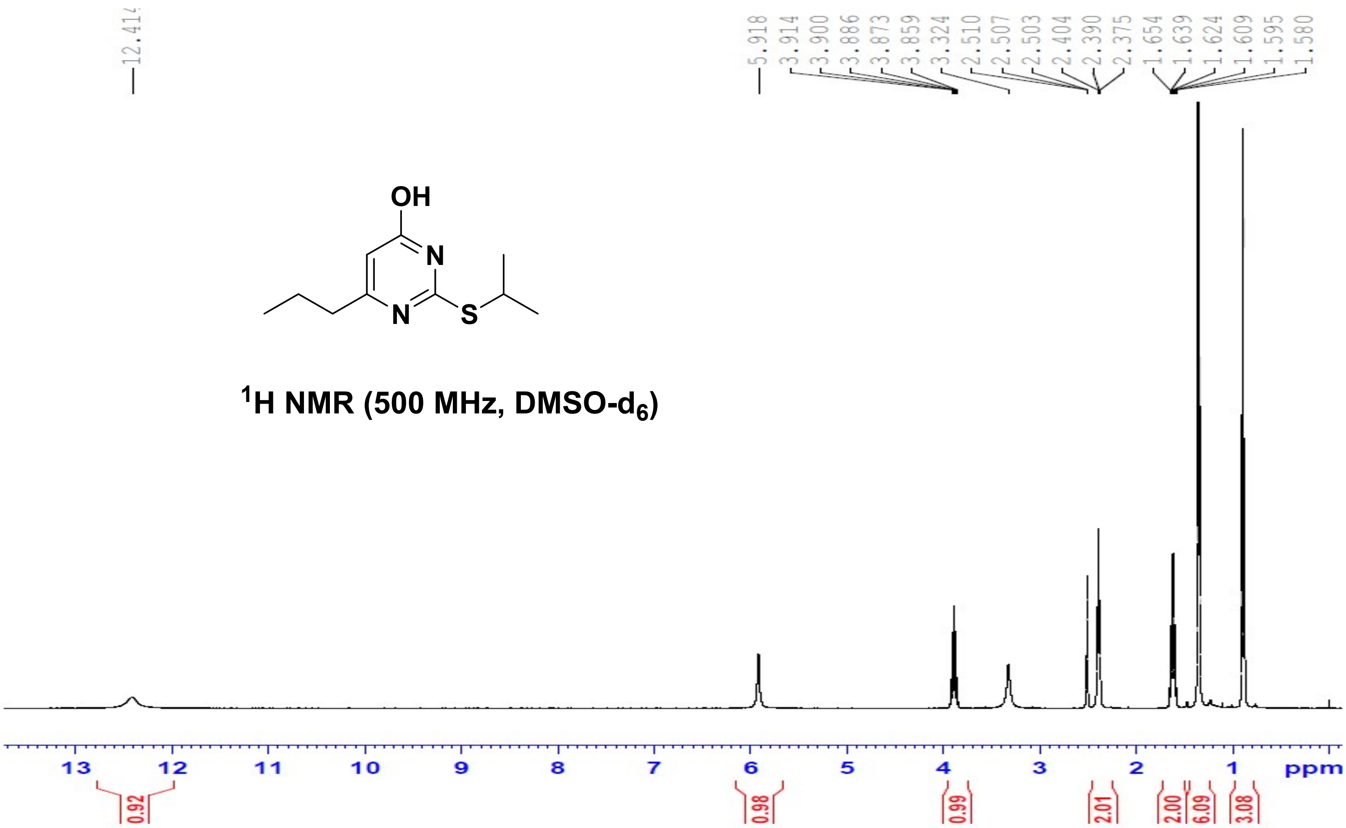

TW-15-tube6.2.fid
166.30
165.93
161.00
108.36
77.68 CDCl3
77.36 CDCl3
77.04 CDCl3
36.89
24.52
23.16
OH
N
N
S
^{13}C NMR (100 MHz, CDCl$_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



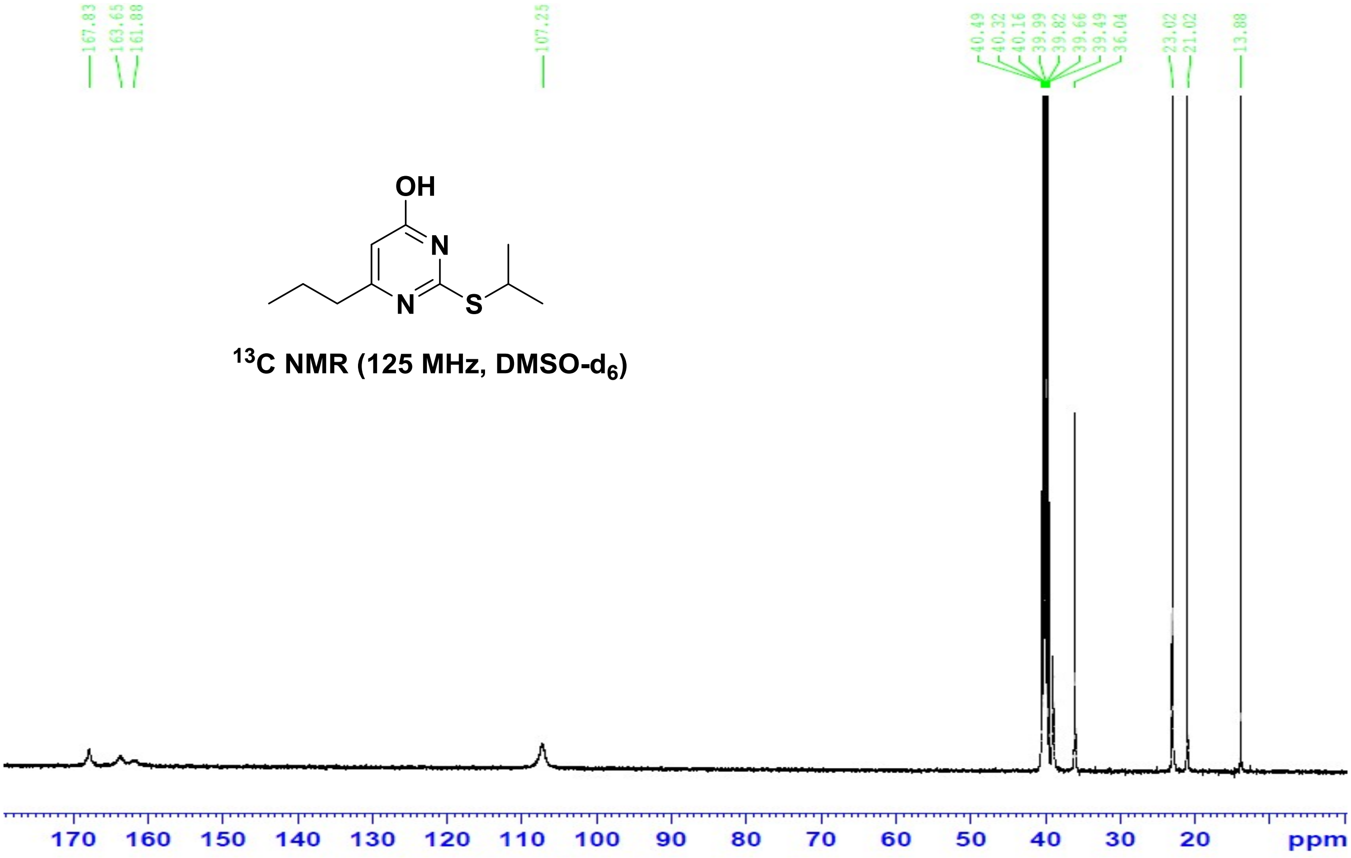
^{1}H NMR (500 MHz, DMSO-d_6)



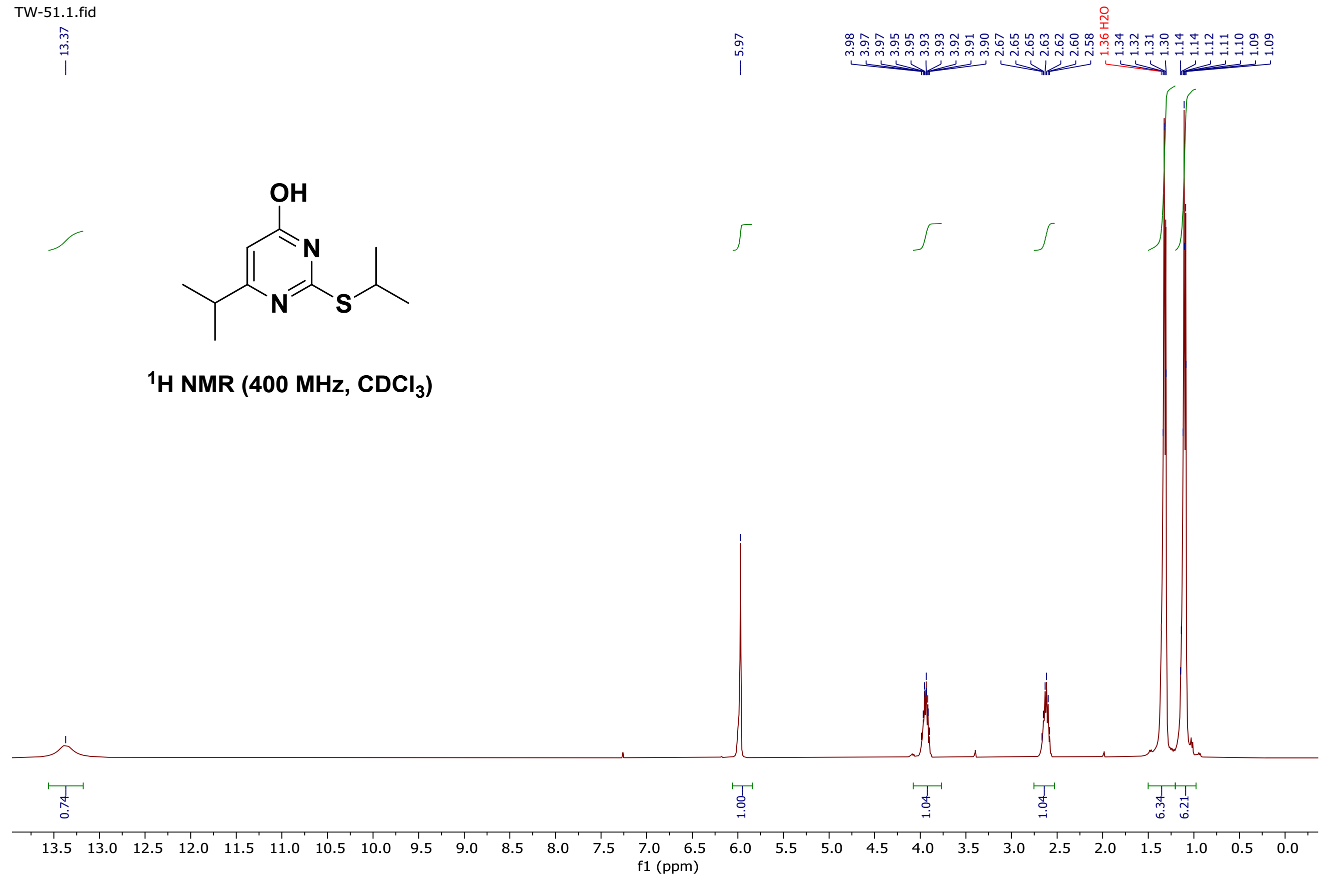
^{13}C NMR (125 MHz, DMSO-d_6)

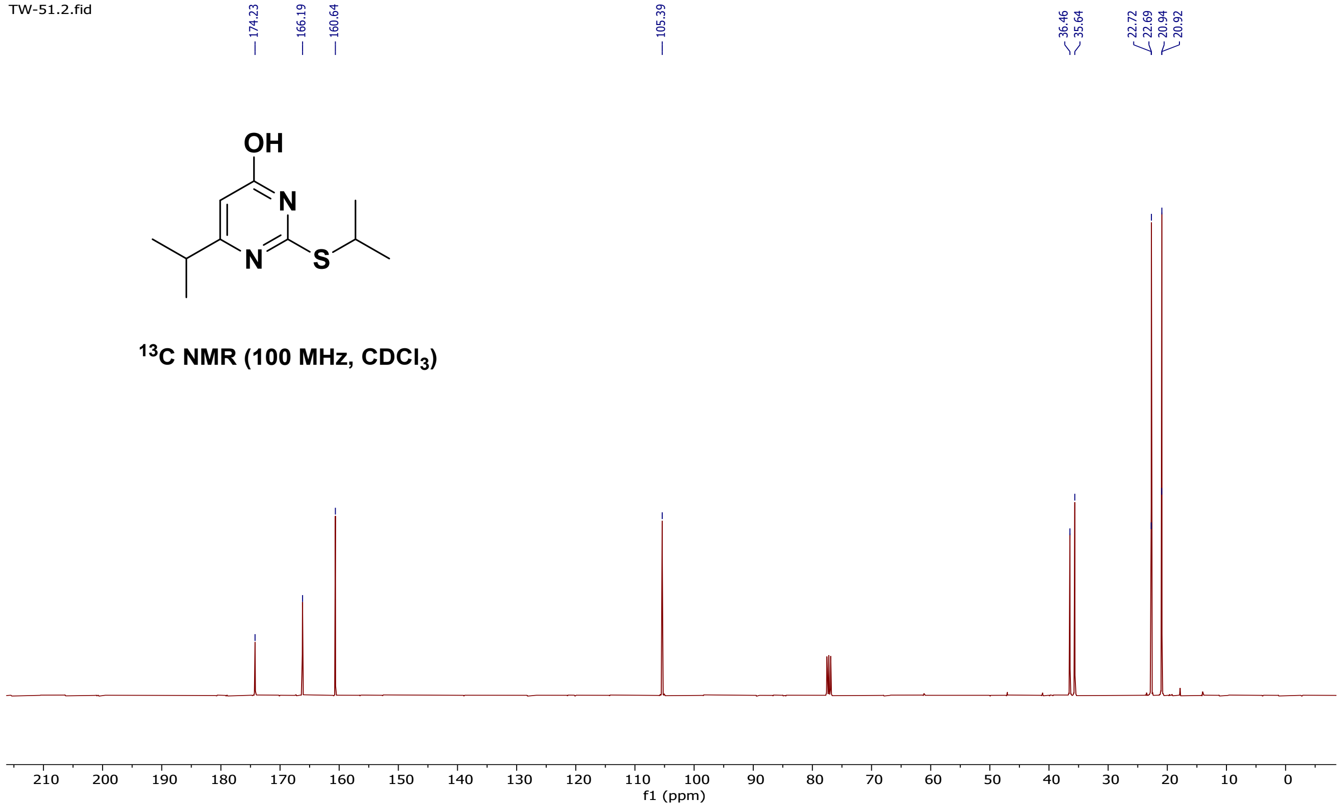


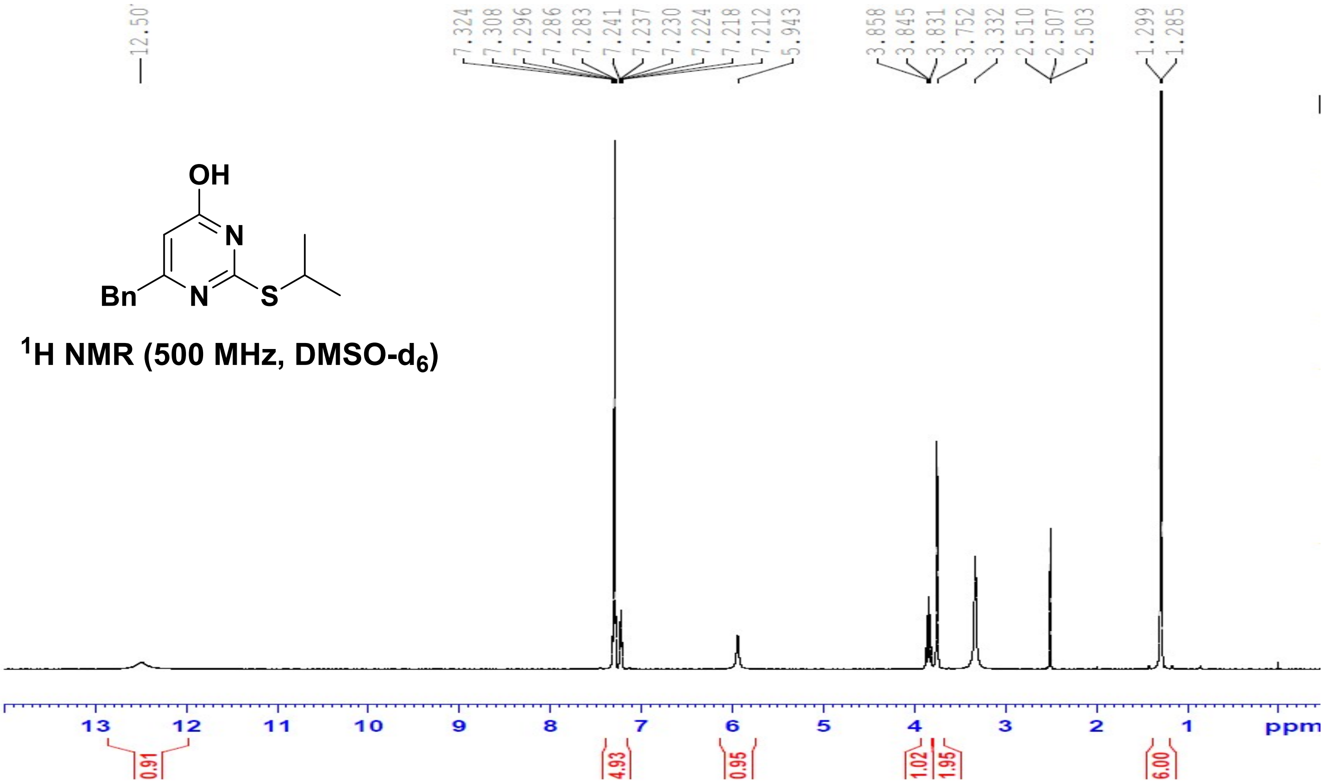
^{1}H NMR (500 MHz, DMSO-d_6)



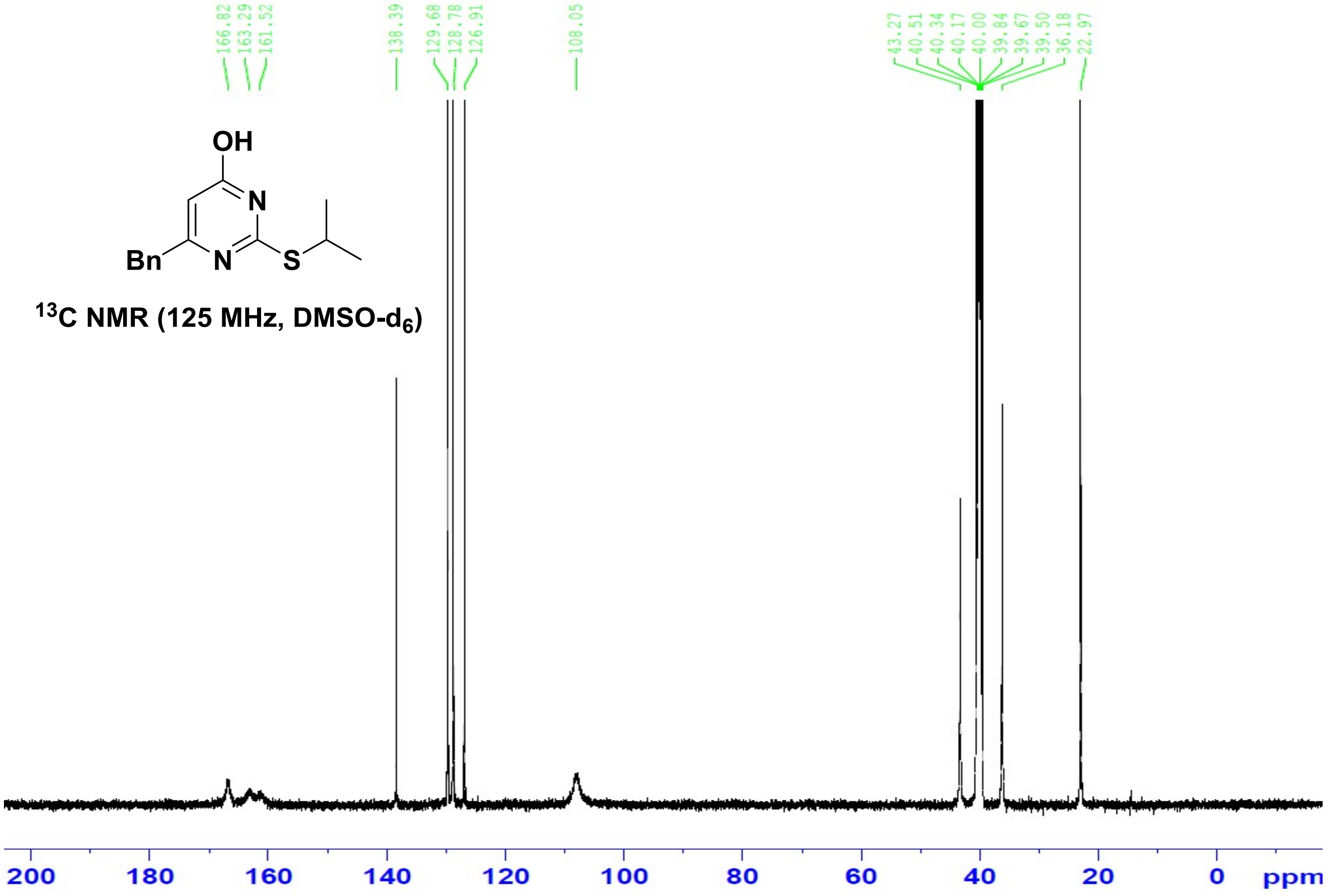
^{13}C NMR (125 MHz, DMSO-d_6)


TW-51.1.fid
13.37
5.97
3.98 3.97 3.97 3.95 3.95 3.93 3.93 3.92 3.91 3.90
2.67 2.65 2.65 2.63 2.62 2.60 2.58
1.36 H2O
1.34 1.32 1.31 1.30 1.14 1.14 1.12 1.11 1.10 1.09 1.09
OH
N
N
S
^{1}H NMR (400 MHz, CDCl$_3$)
0.74
1.00
1.04
1.04
6.34
6.21
13.5 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)

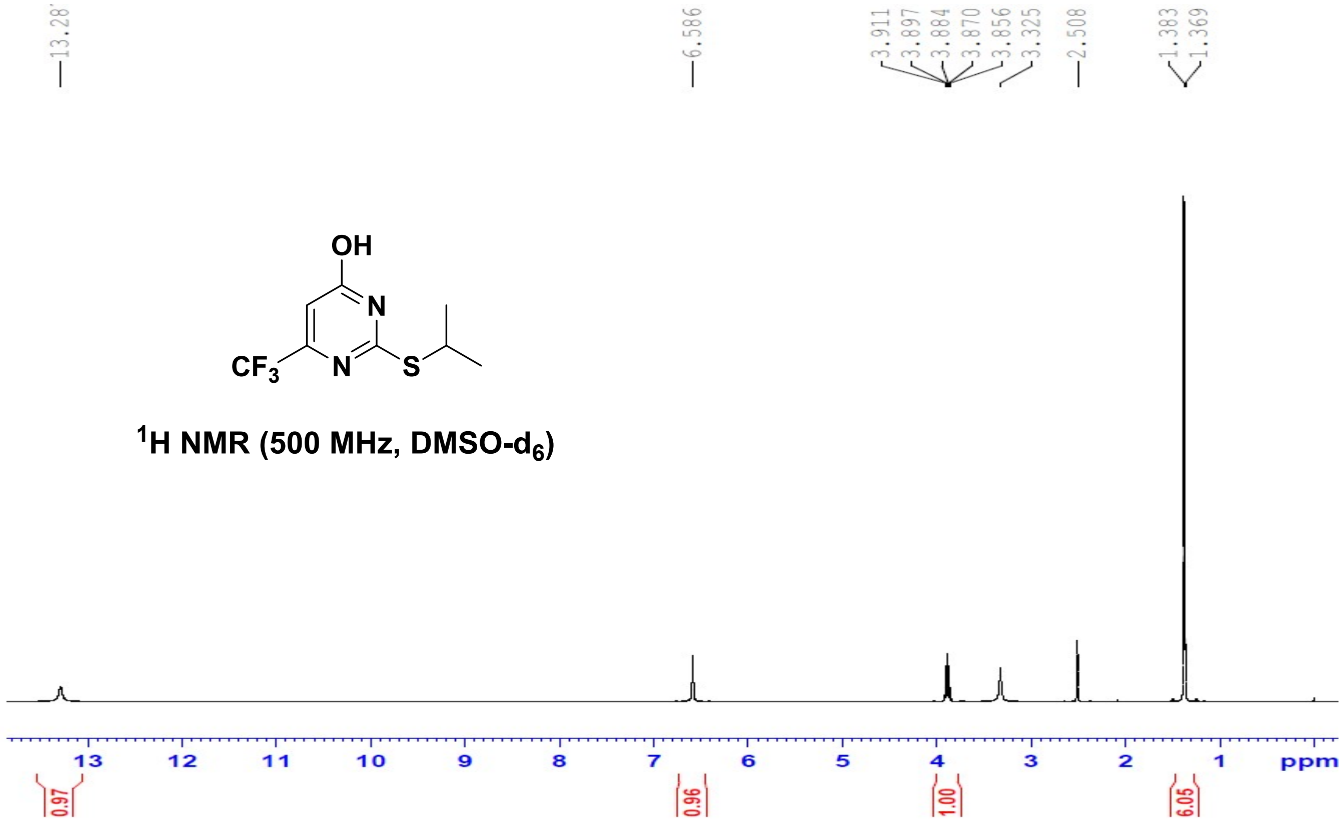

TW-51.2.fid
174.23
166.19
160.64
105.39
36.46
35.64
22.72
22.69
20.94
20.92
OH
N
N
S
^{13}C NMR (100 MHz, CDCl$_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



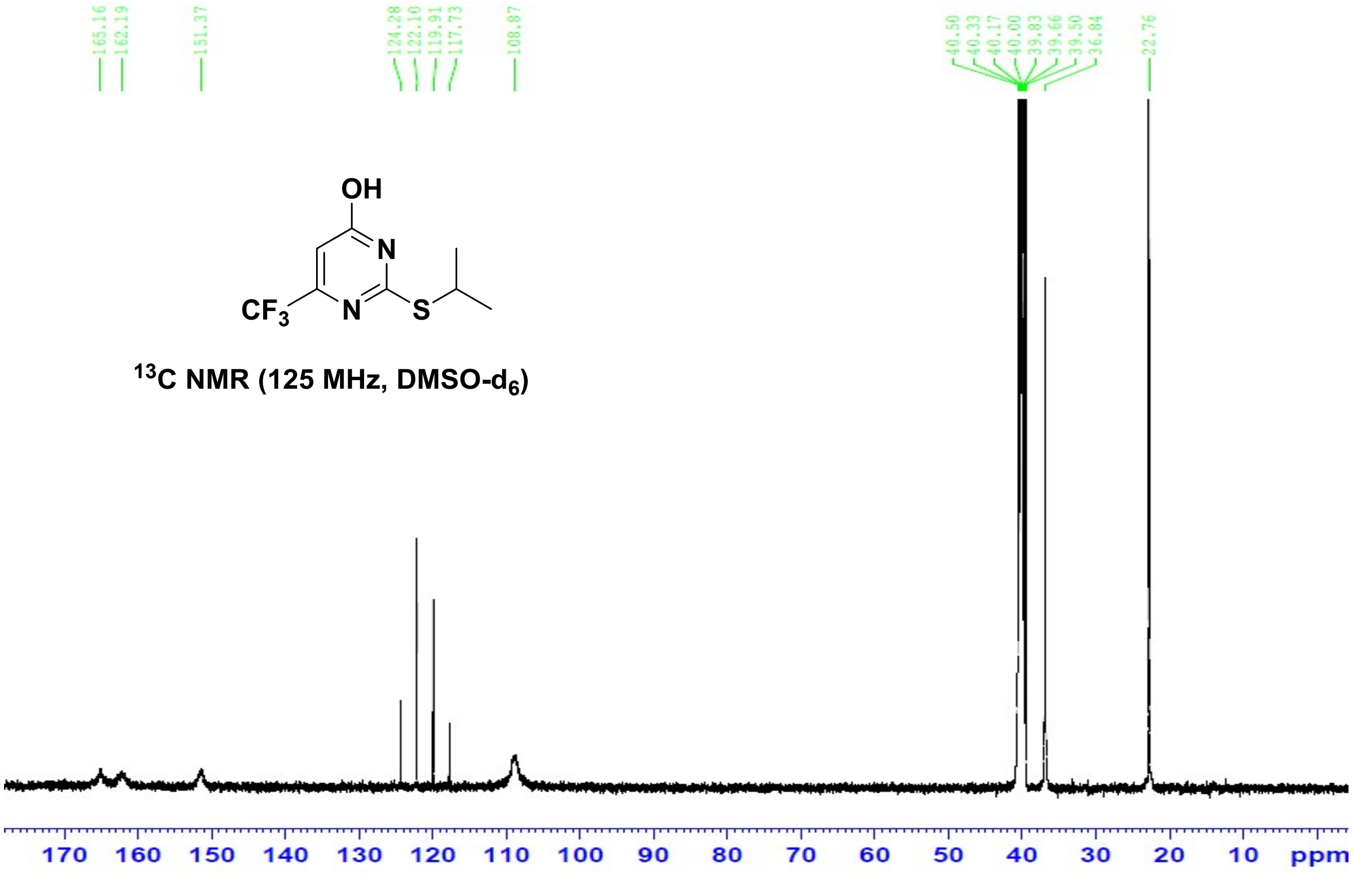
^{1}H NMR (500 MHz, DMSO-d$_6$)



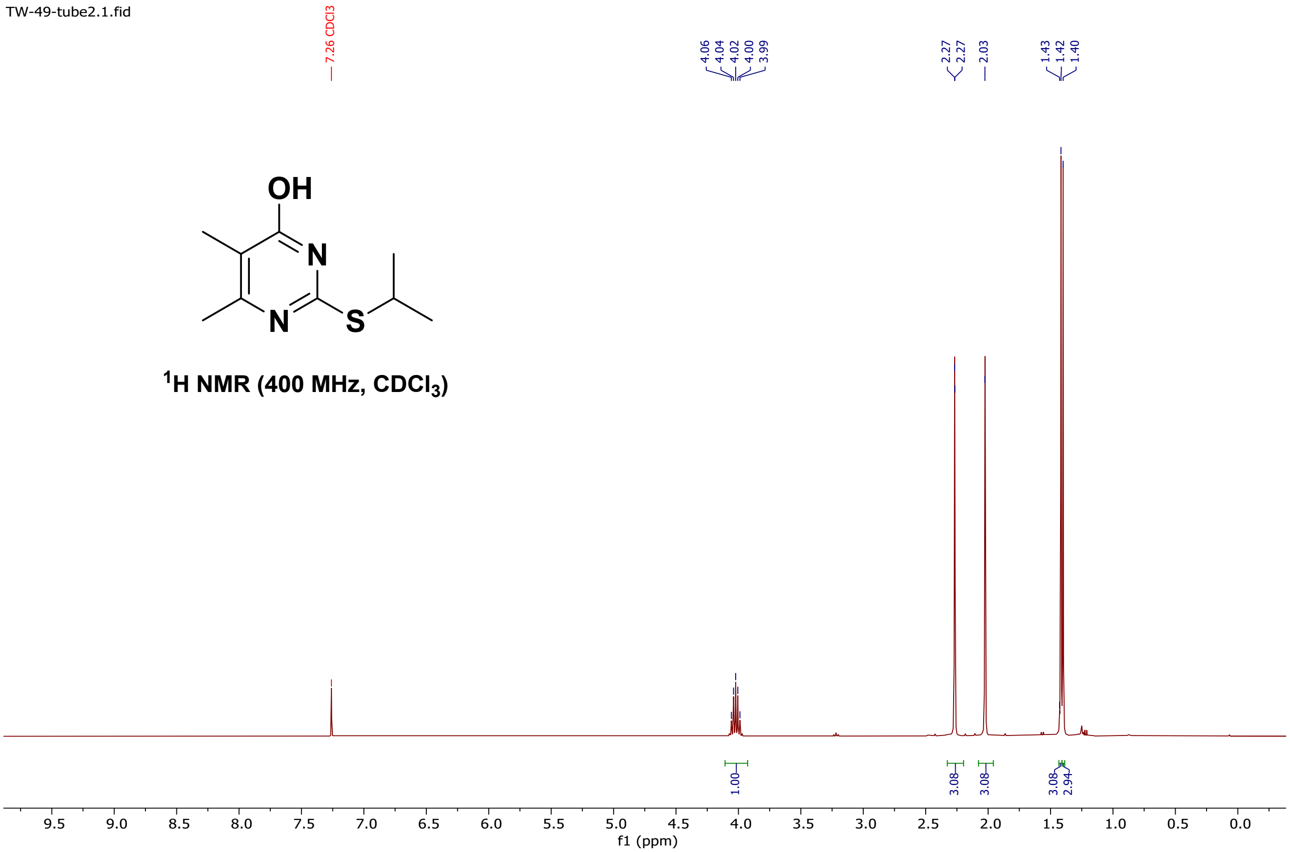
^{13}C NMR (125 MHz, DMSO-d$_6$)

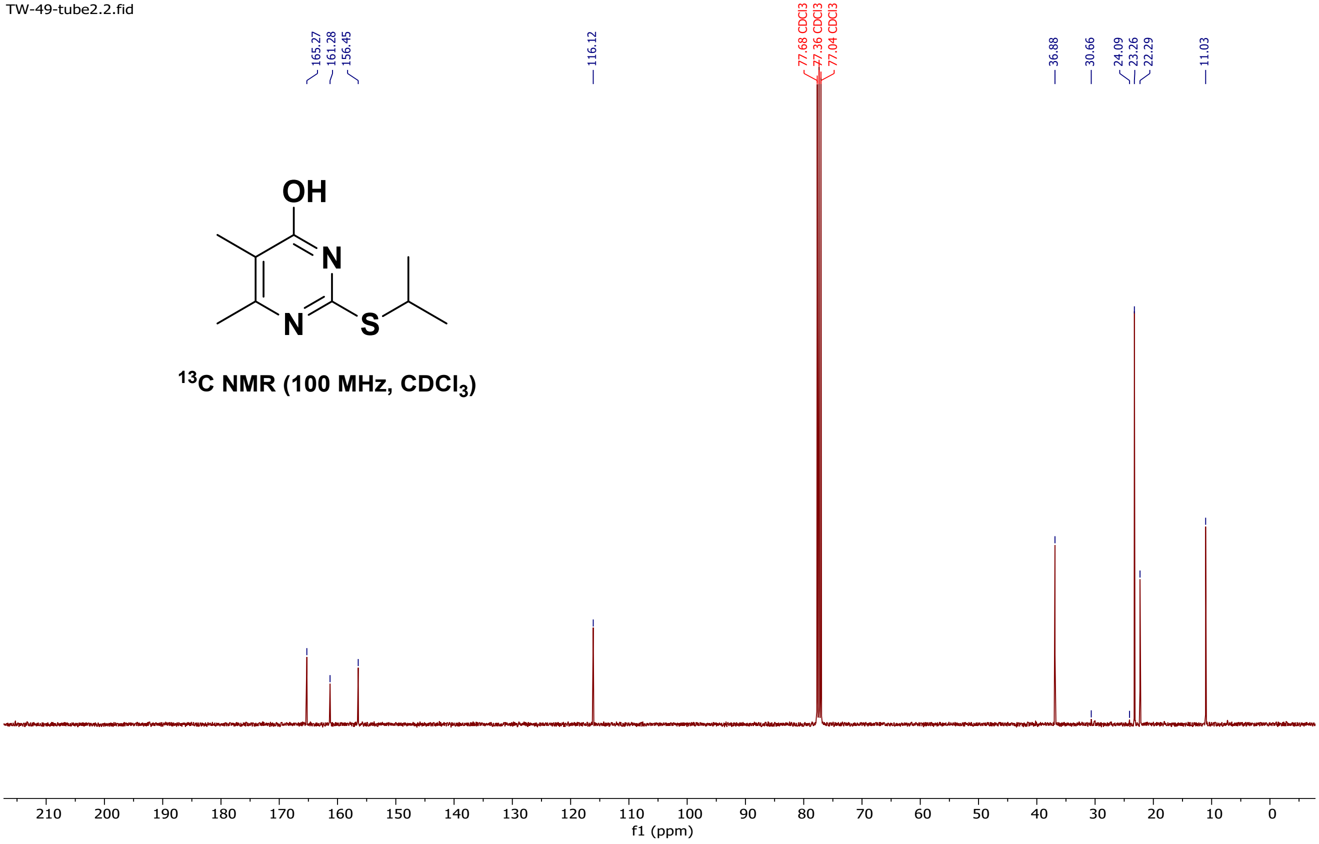


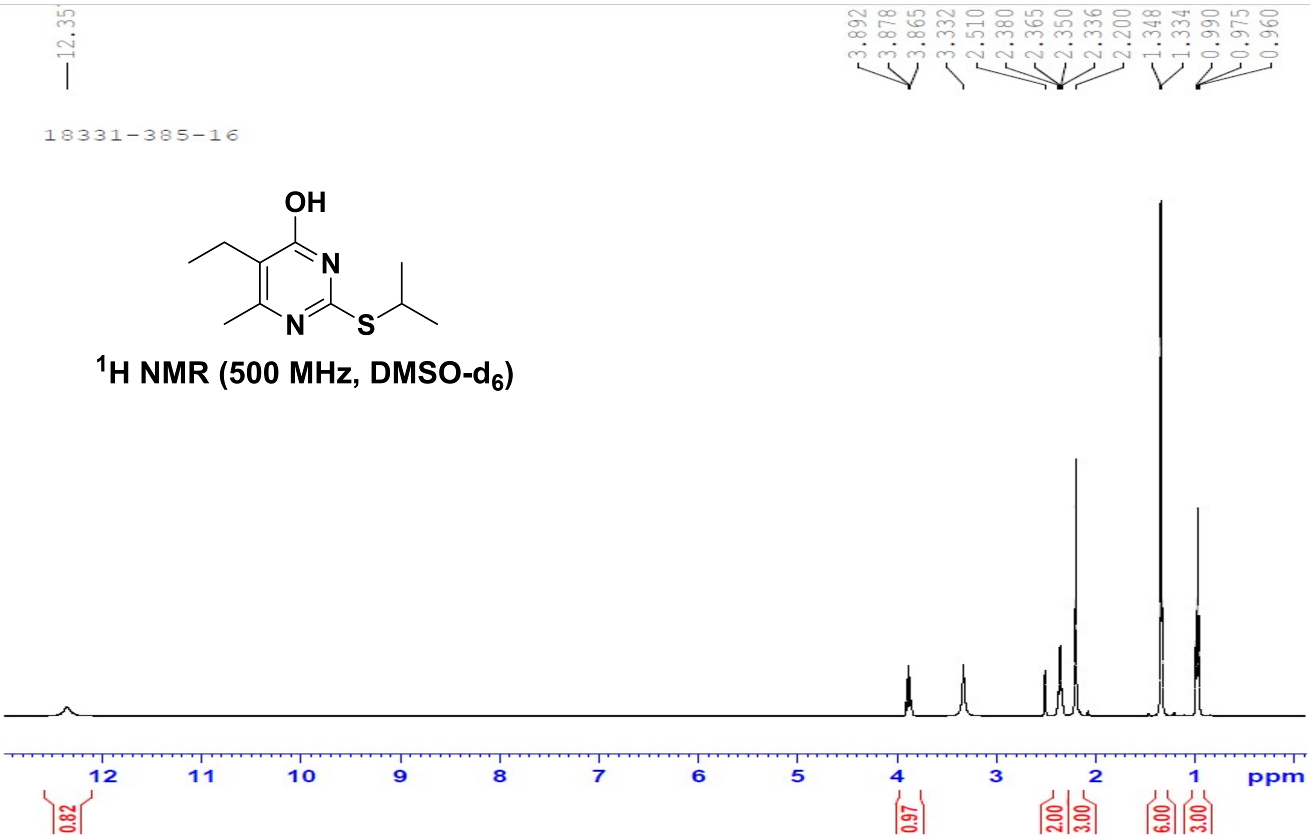
^{1}H NMR (500 MHz, DMSO-d_6)

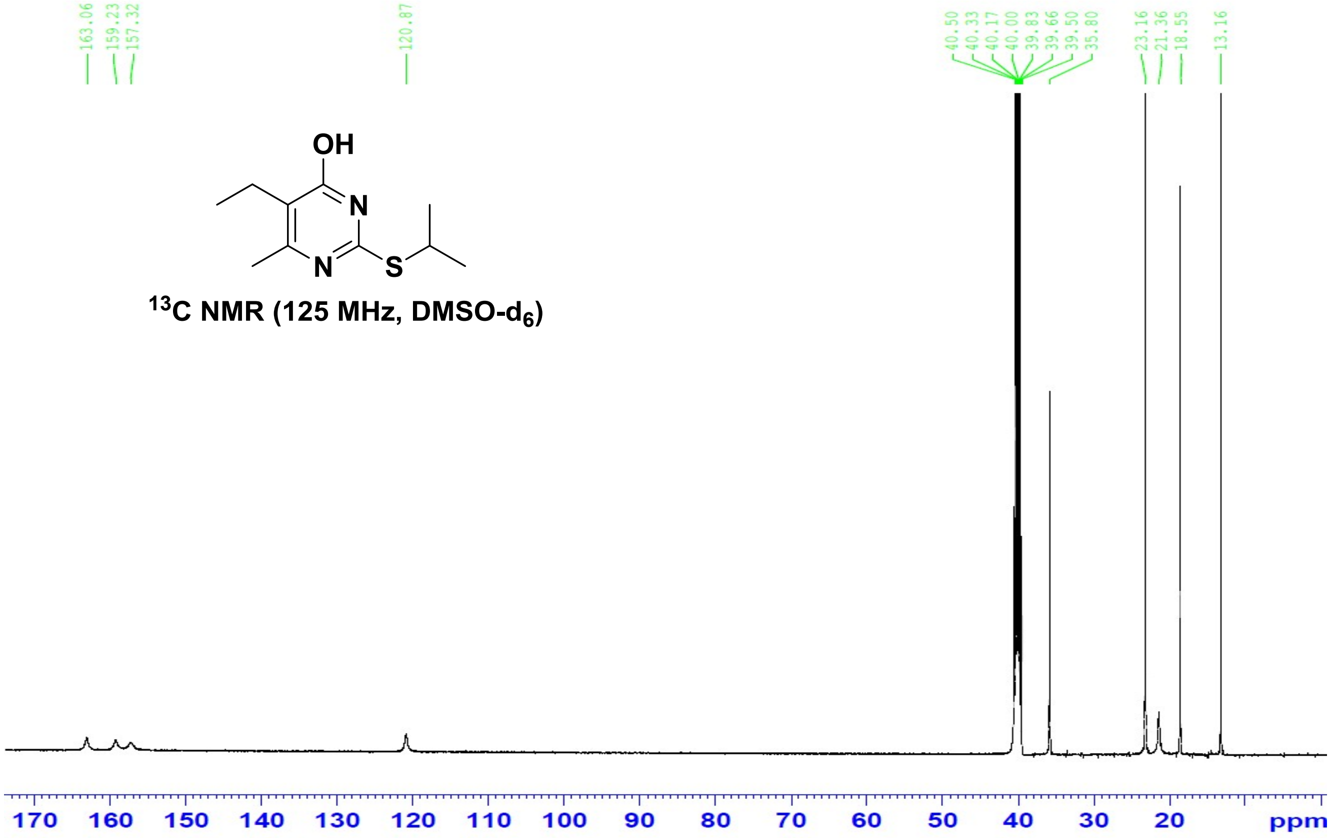


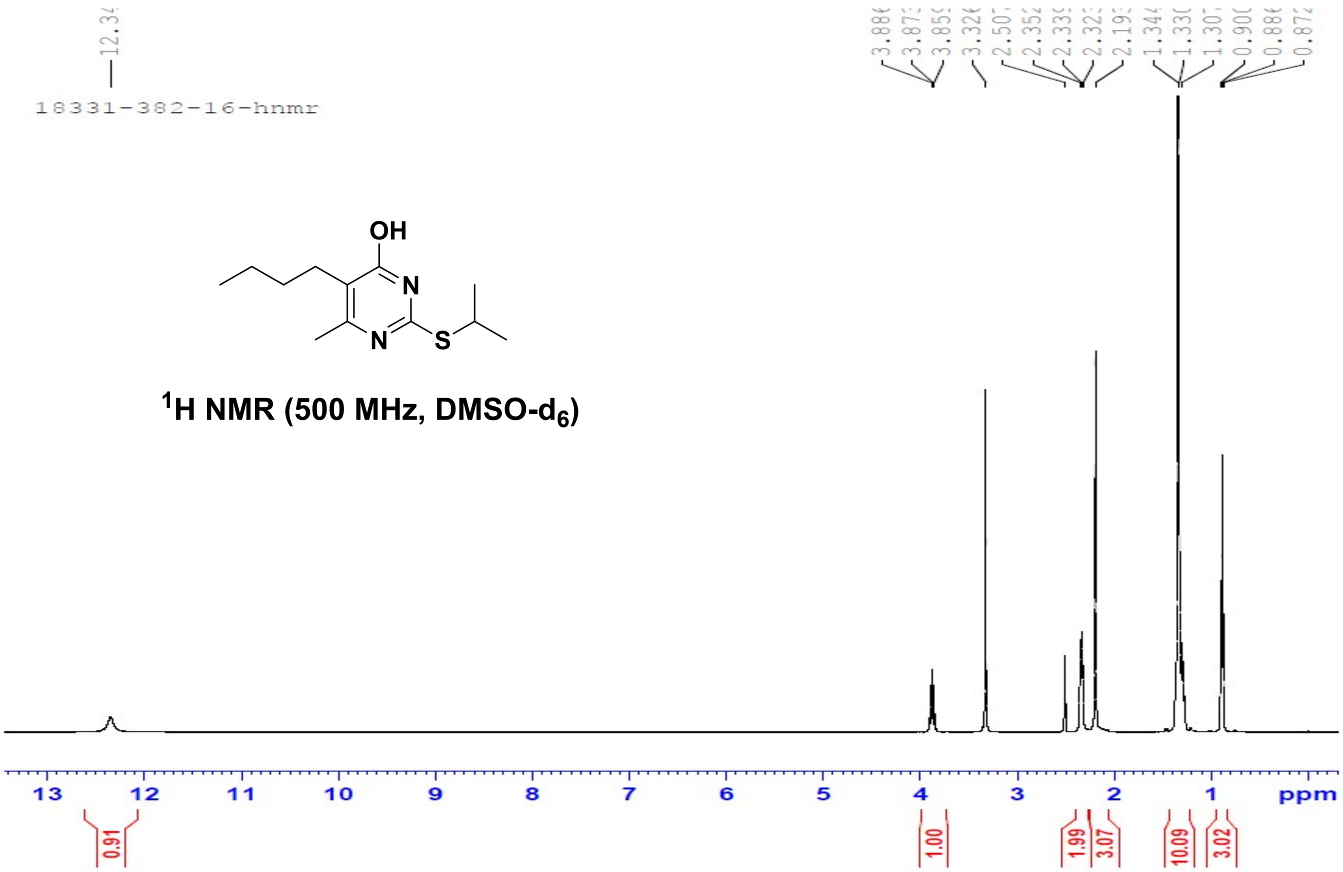
^{13}C NMR (125 MHz, DMSO-d_6)


TW-49-tube2.1.fid
7.26 CDCl3
4.06
4.04
4.02
4.00
3.99
2.27
2.27
2.03
1.43
1.42
1.40
OH
N
N
S
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
3.08
3.08
3.08
2.94
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)

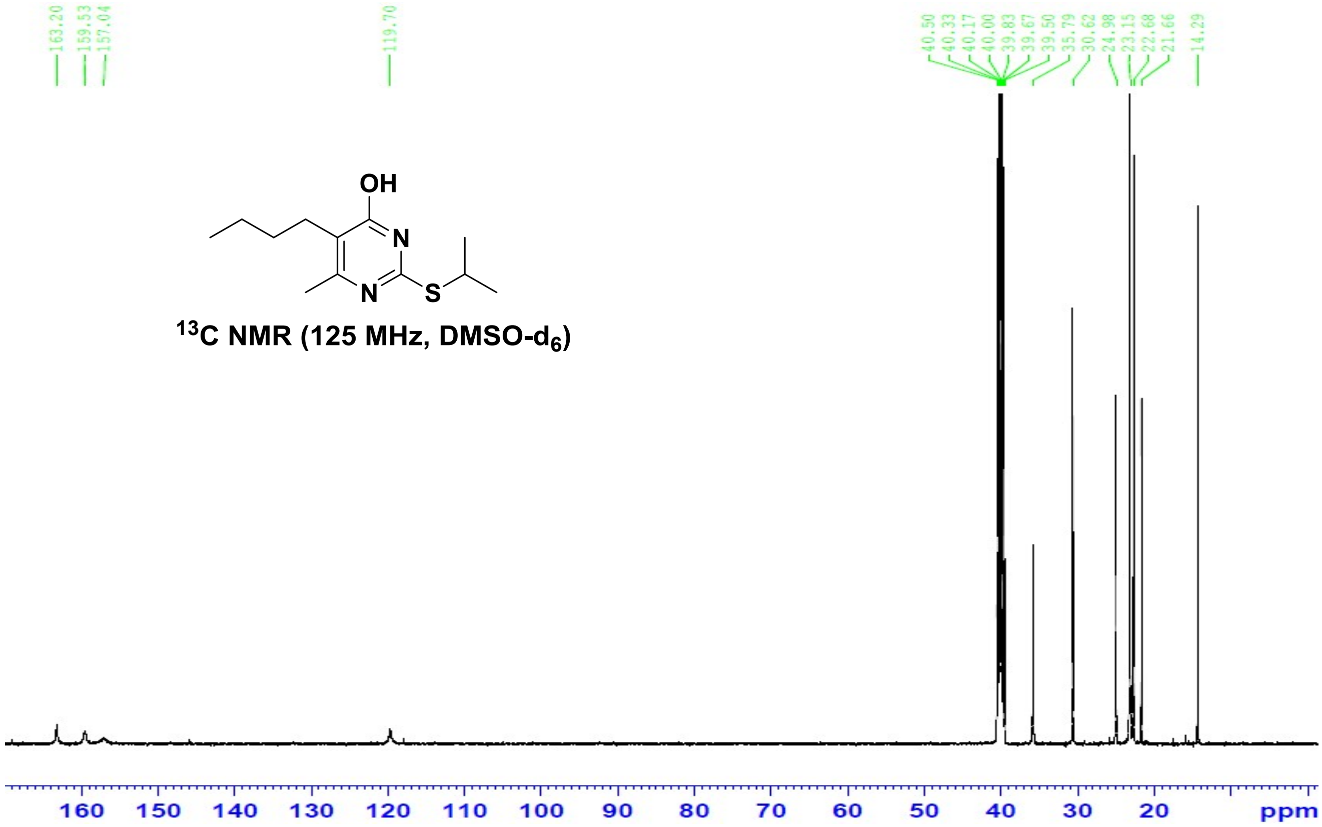

TW-49-tube2.2.fid
165.27
161.28
156.45
116.12
77.68 CDCl3
77.36 CDCl3
77.04 CDCl3
36.88
30.66
24.09
23.26
22.29
11.03
OH
N
N
S
^{13}C NMR (100 MHz, CDCl$_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


12.357
3.892
3.878
3.865
3.332
2.510
2.380
2.365
2.350
2.336
2.200
1.348
1.334
0.990
0.975
0.960
18331-385-16
OH
N
N
S
^{1}H NMR (500 MHz, DMSO-d$_6$)
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.82
0.97
2.00
3.00
6.00
3.00

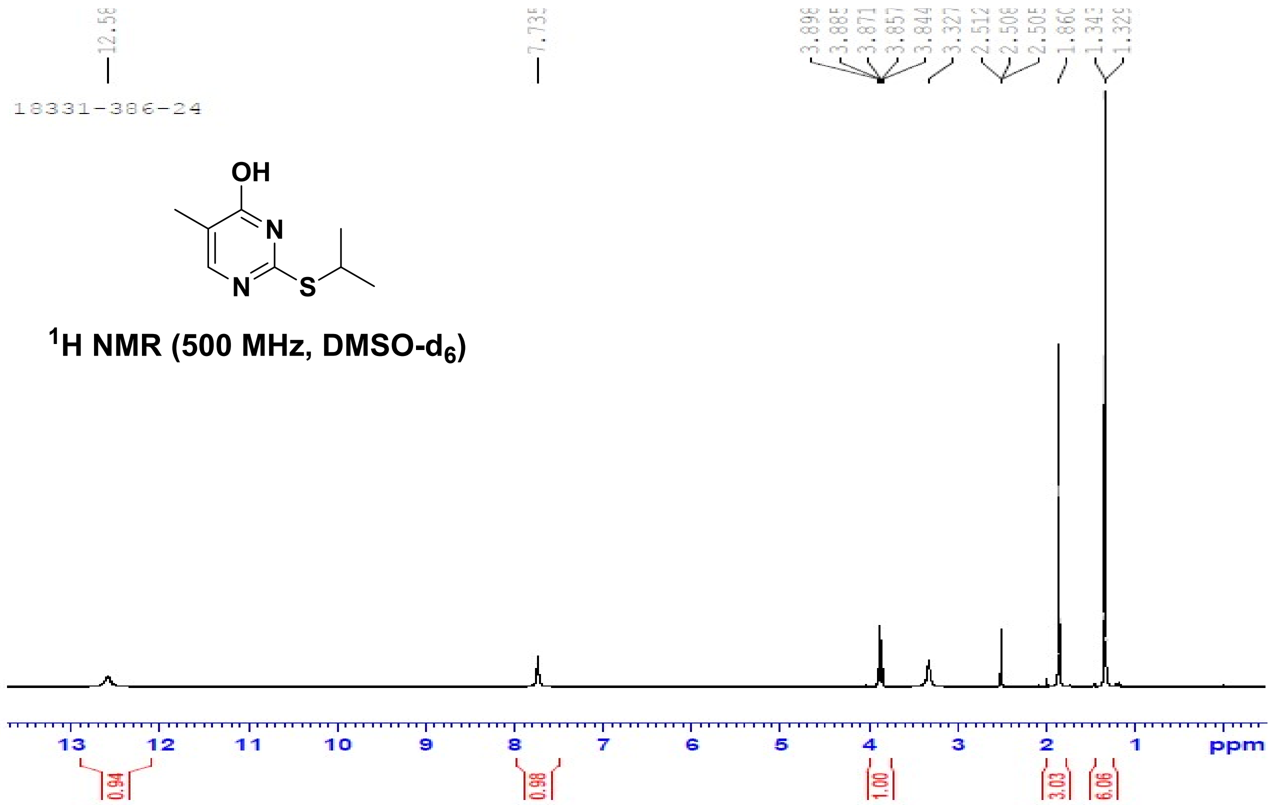

163.06
159.23
157.32
120.87
40.50
40.33
40.17
40.00
39.83
39.66
39.50
35.80
23.16
21.36
18.55
13.16
OH
N
N
S
^{13}C NMR (125 MHz, DMSO-d$_6$)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



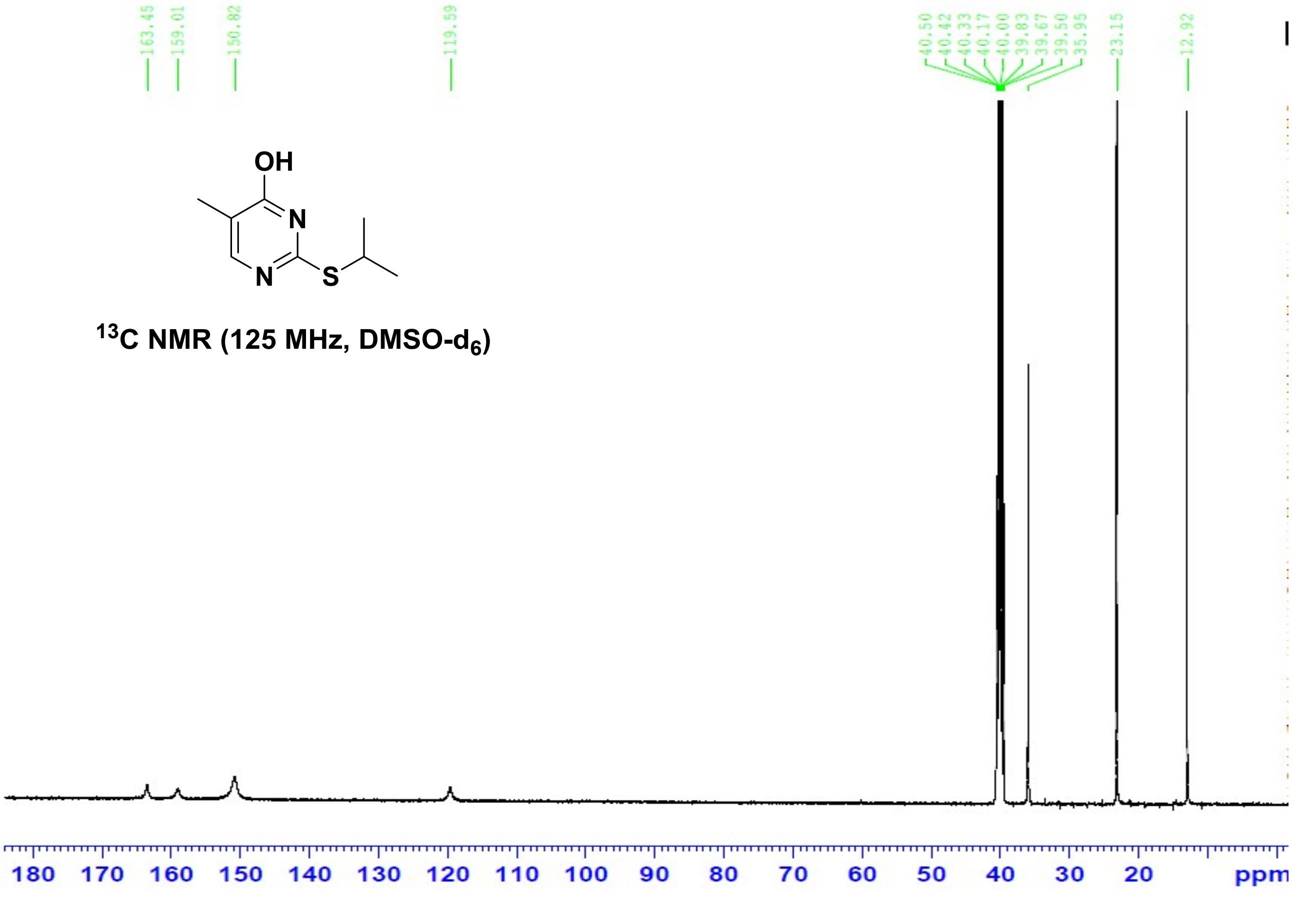
^{1}H NMR (500 MHz, DMSO-d$_6$)



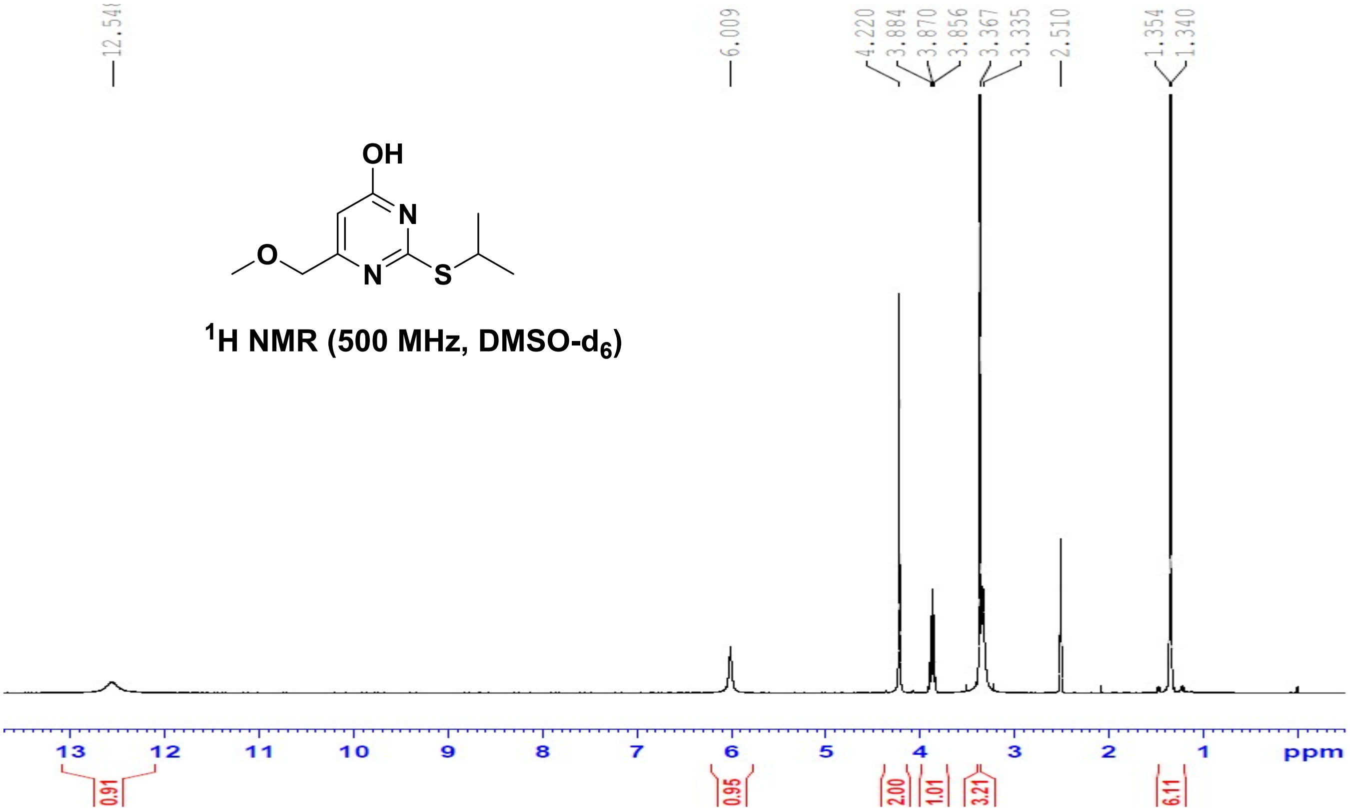
^{13}C NMR (125 MHz, DMSO-d$_6$)

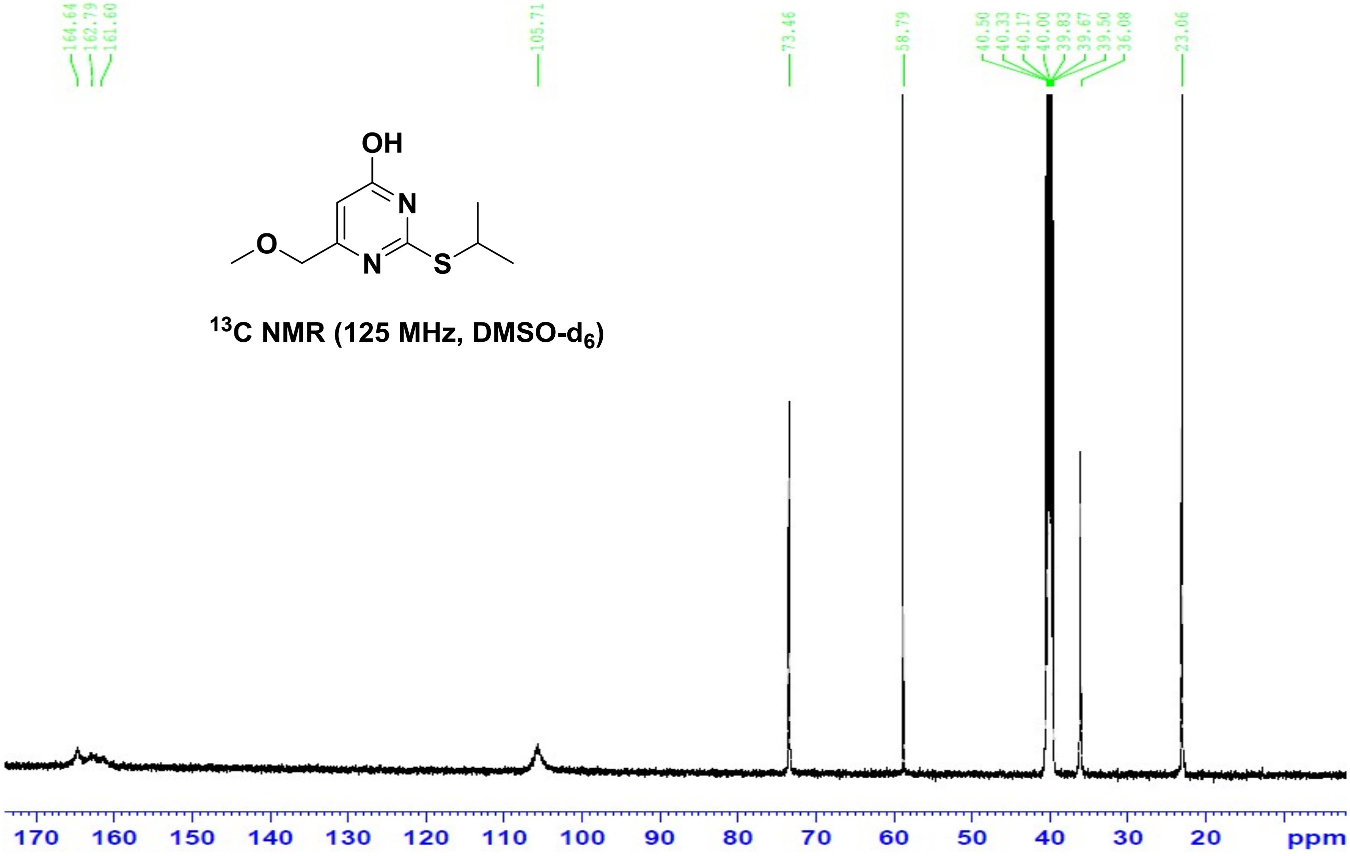


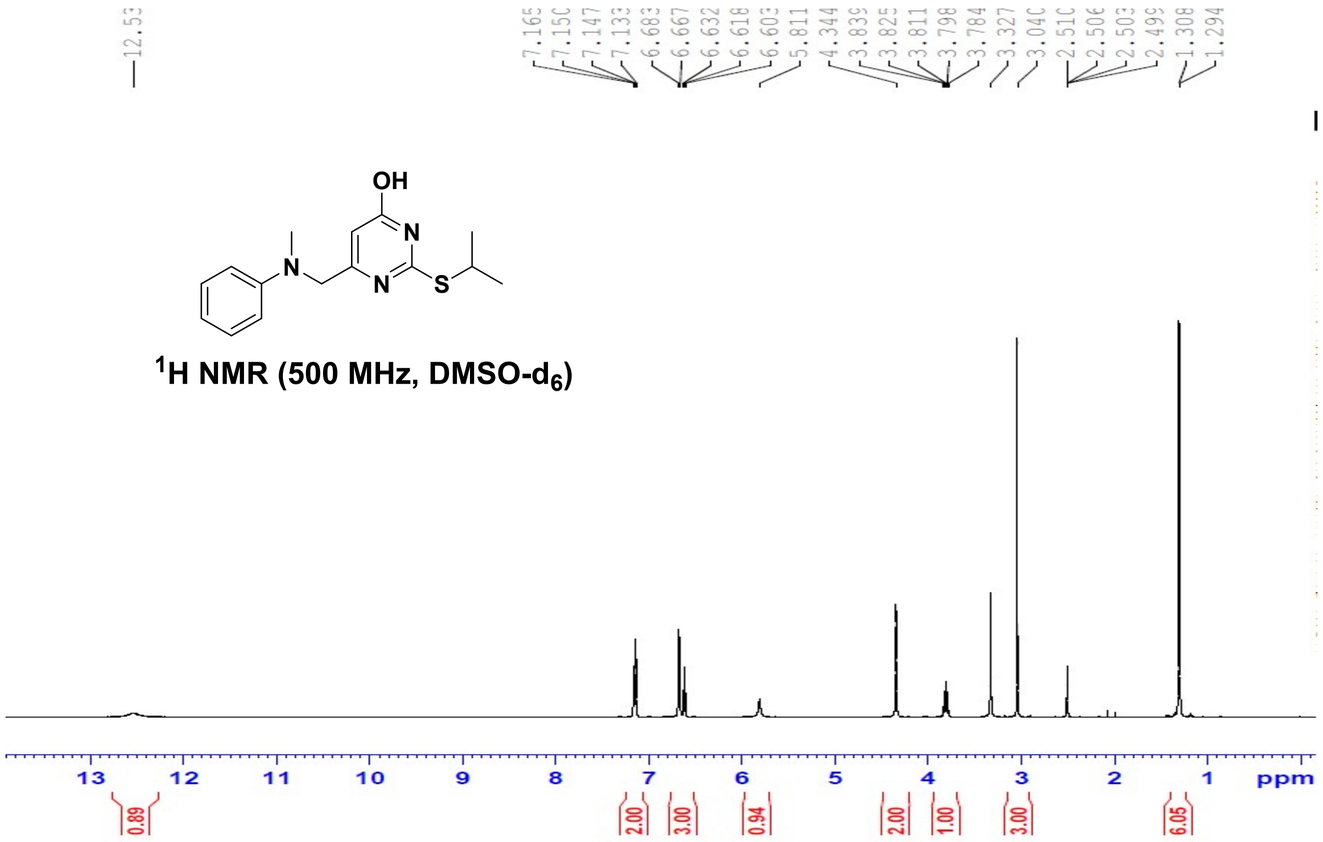
^{1}H NMR (500 MHz, DMSO-d$_6$)



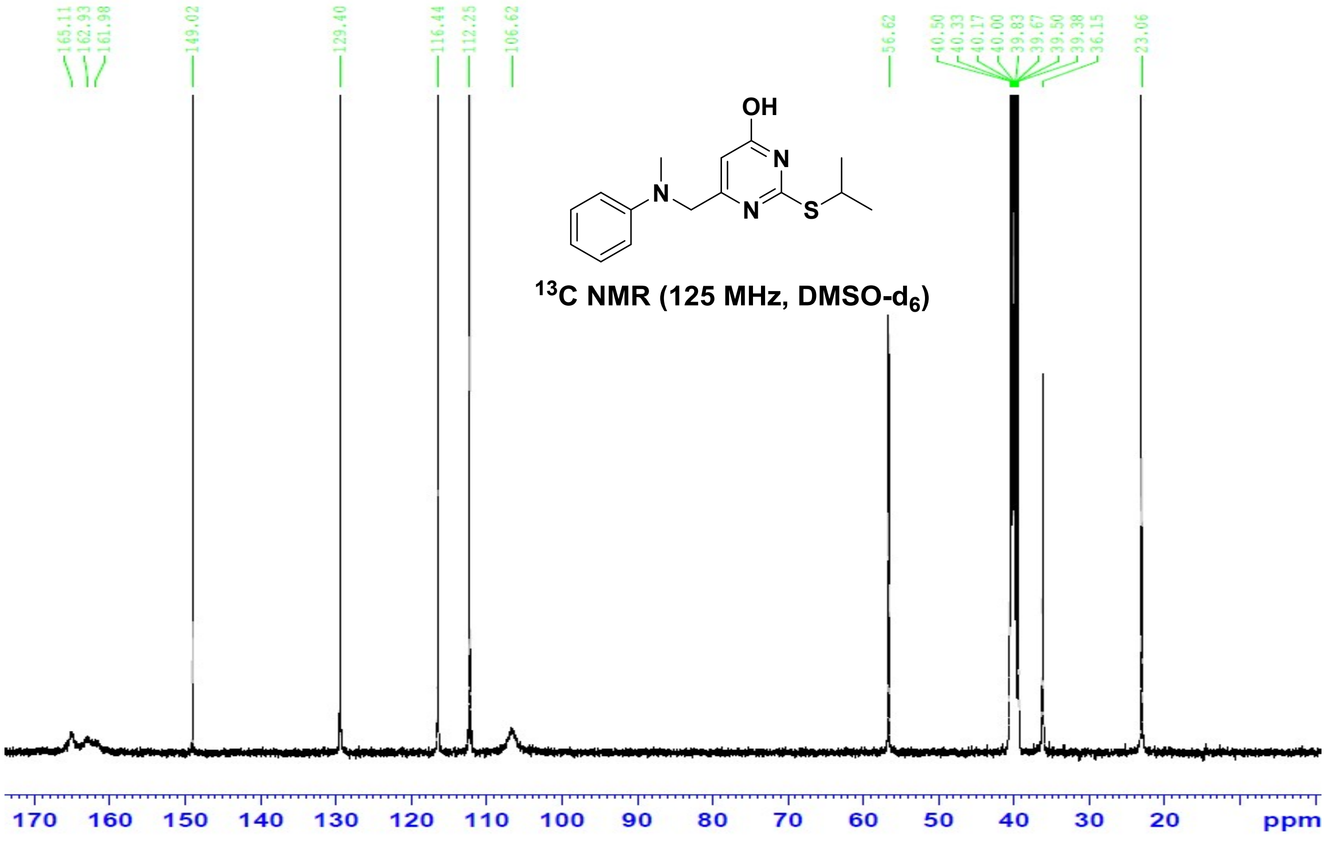
^{13}C NMR (125 MHz, DMSO-d$_6$)


12.54
6.009
4.220
3.884
3.870
3.856
3.367
3.335
2.510
1.354
1.340
OH
N
O
N
S
^{1}H NMR (500 MHz, DMSO-d$_6$)
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.91
0.95
2.00
1.01
3.21
6.11

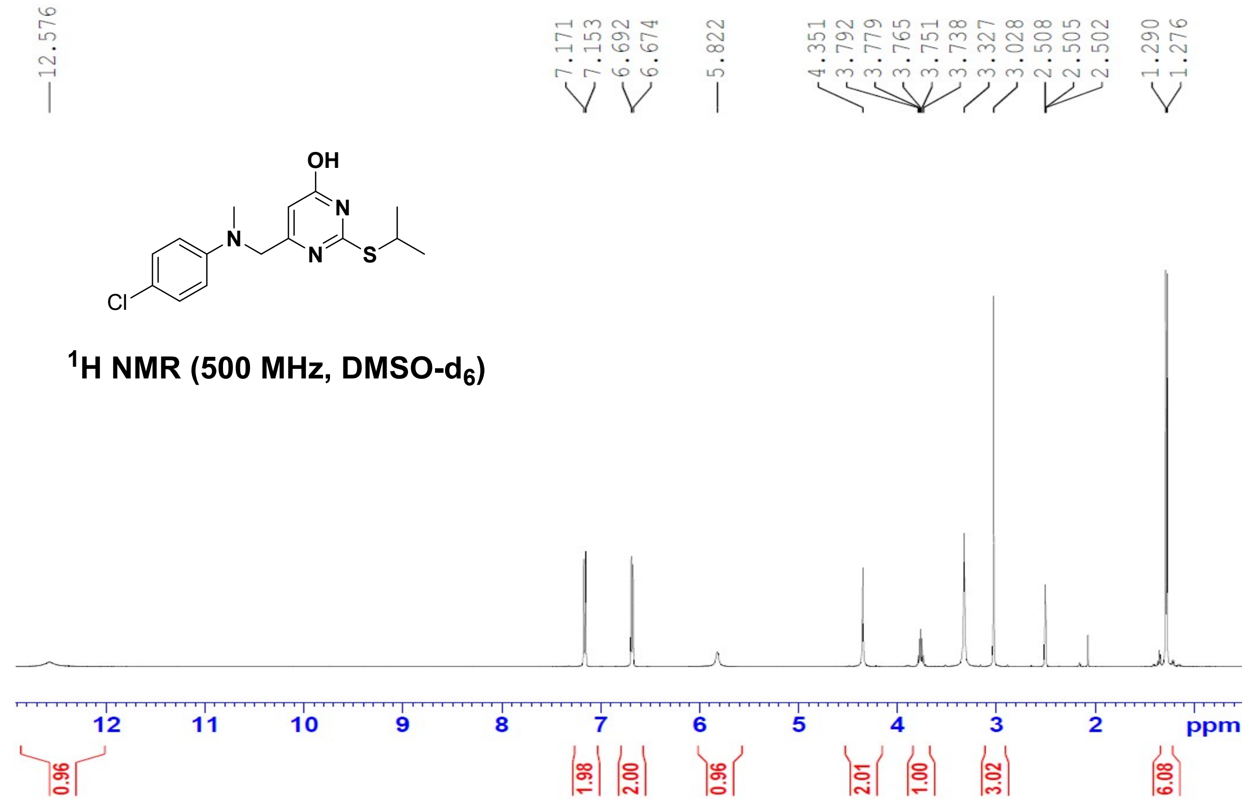

164.64
162.79
161.60
105.71
73.46
58.79
40.50
40.33
40.17
40.00
39.83
39.67
39.50
36.08
23.06
OH
N
O
N
S
^{13}C NMR (125 MHz, DMSO-d$_6$)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



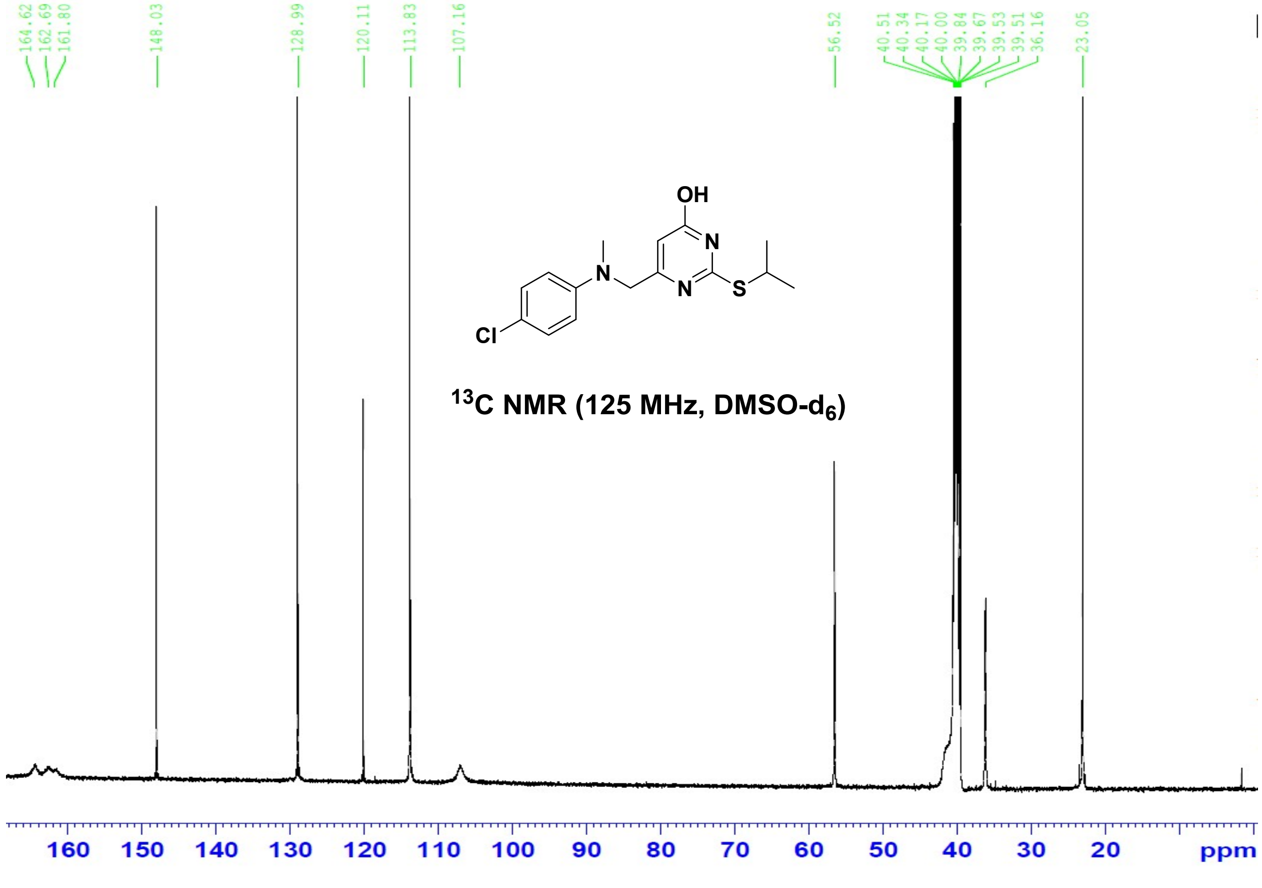
^{1}H NMR (500 MHz, DMSO-d$_6$)



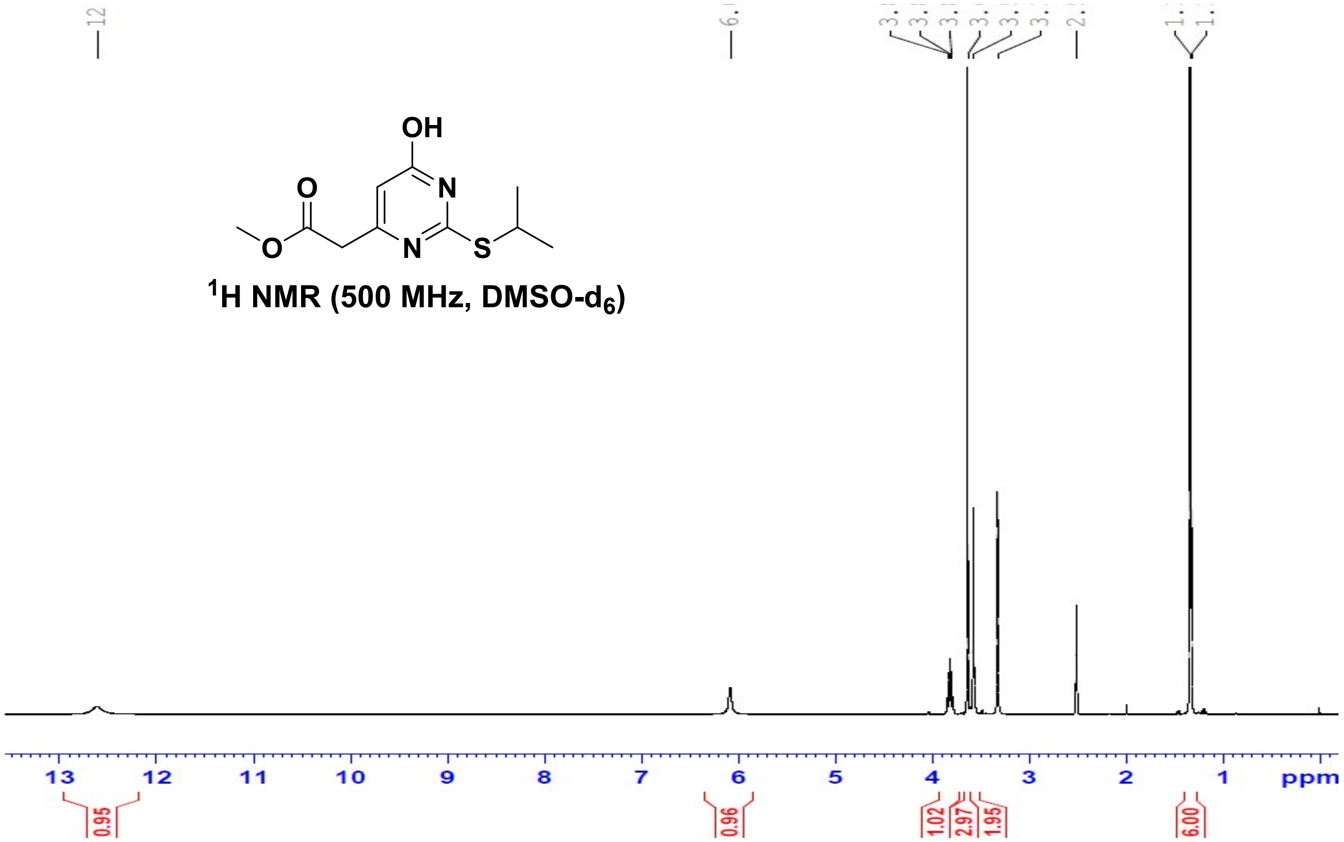
^{13}C NMR (125 MHz, DMSO-d$_6$)

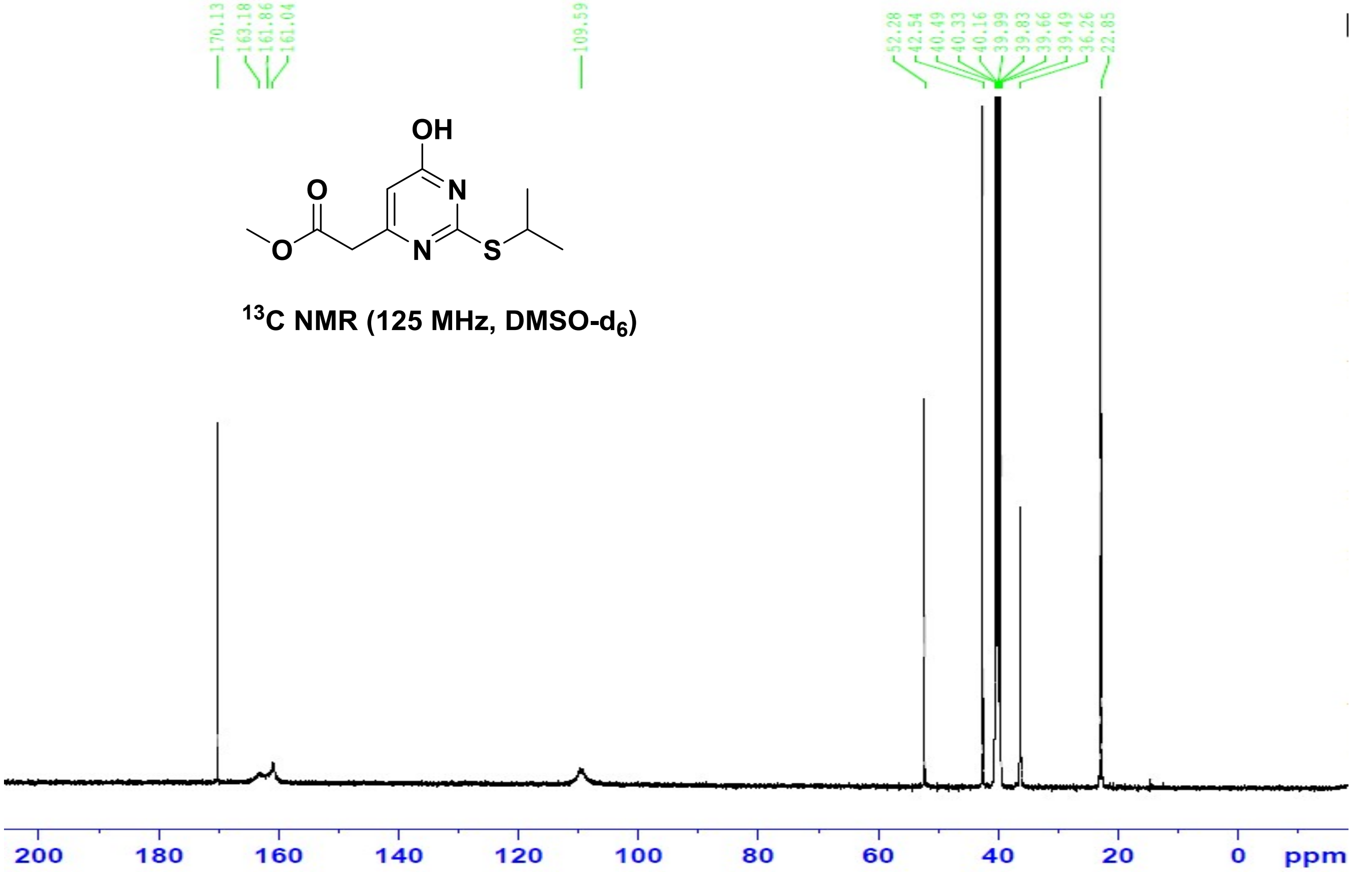


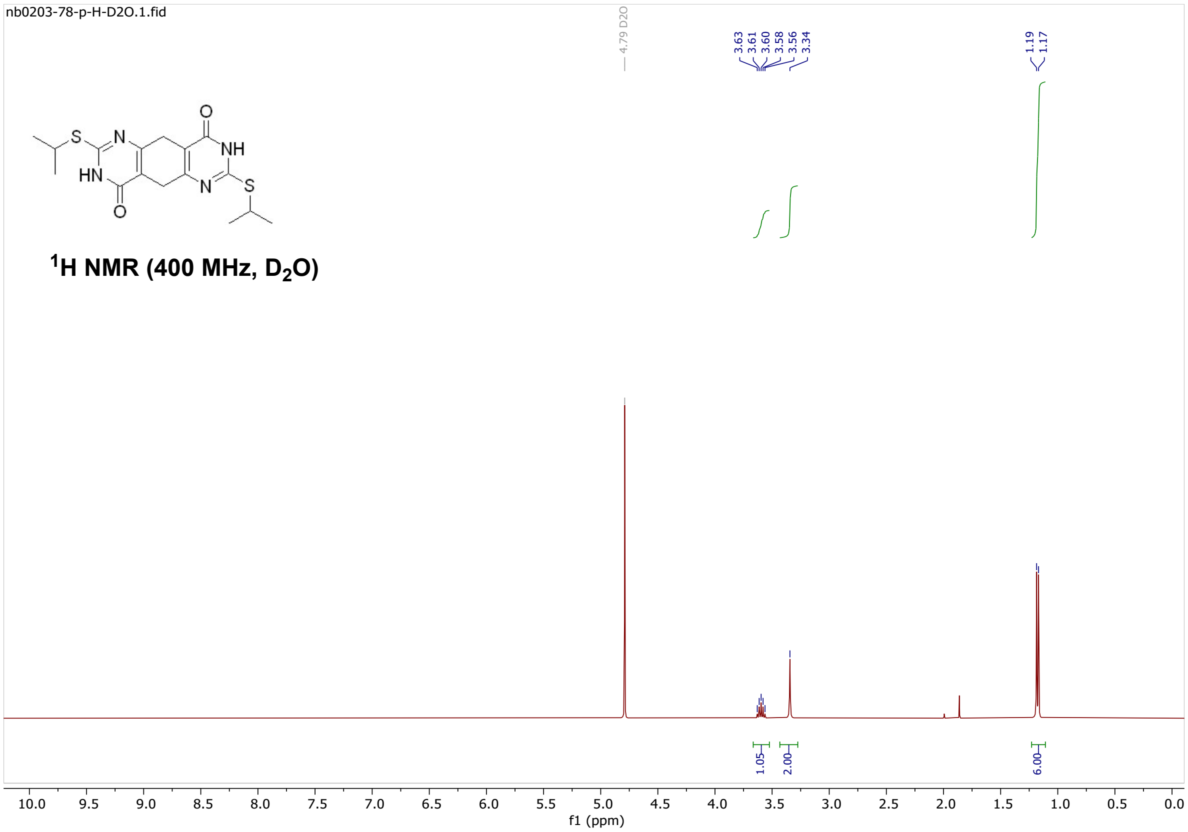
^{1}H NMR (500 MHz, DMSO-d$_6$)

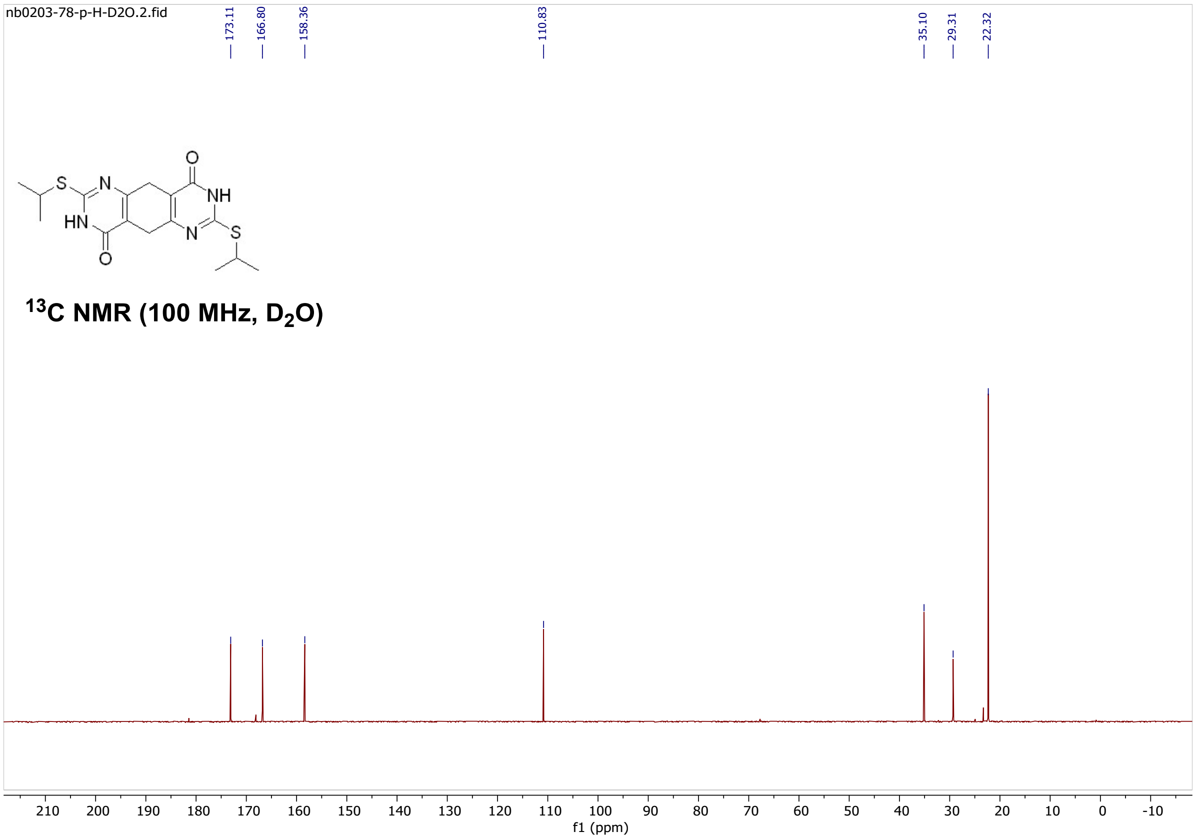


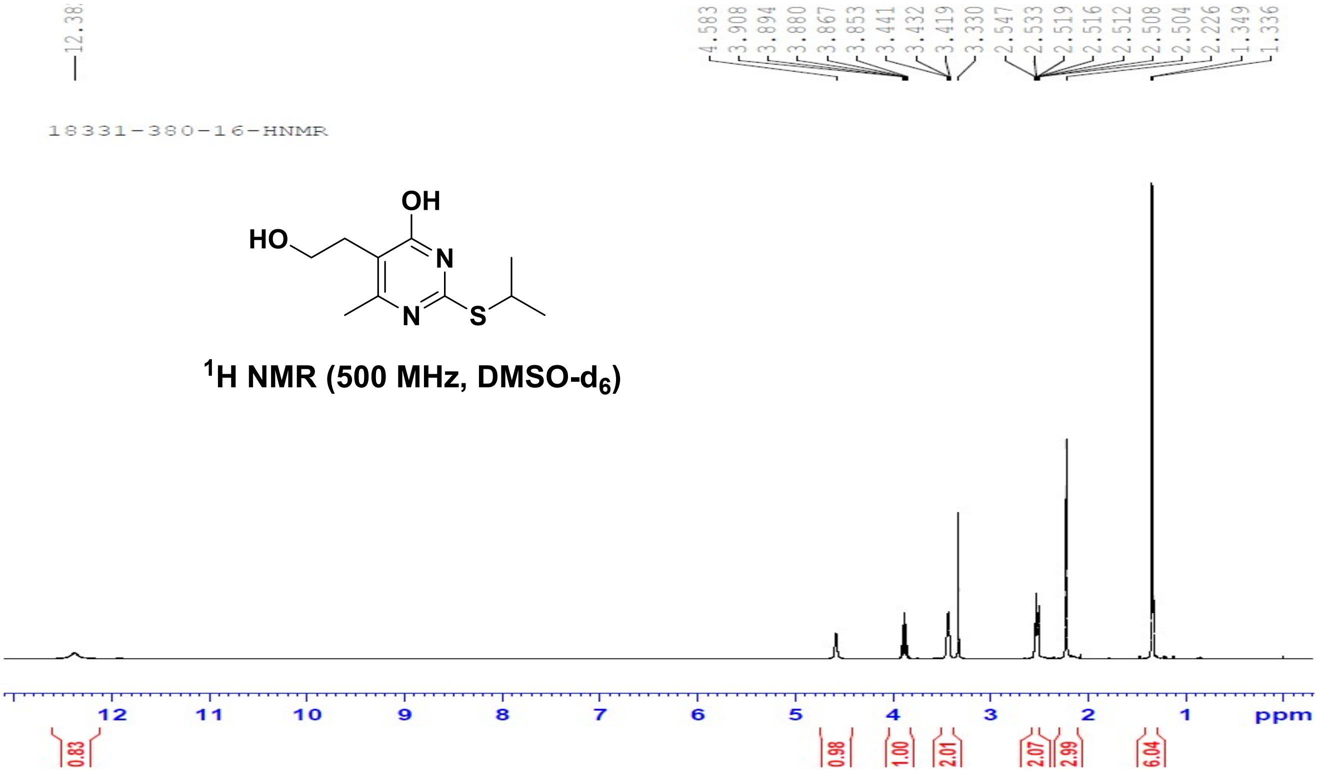
^{13}C NMR (125 MHz, DMSO-d$_6$)


^{1}H NMR (500 MHz, DMSO-d$_6$)

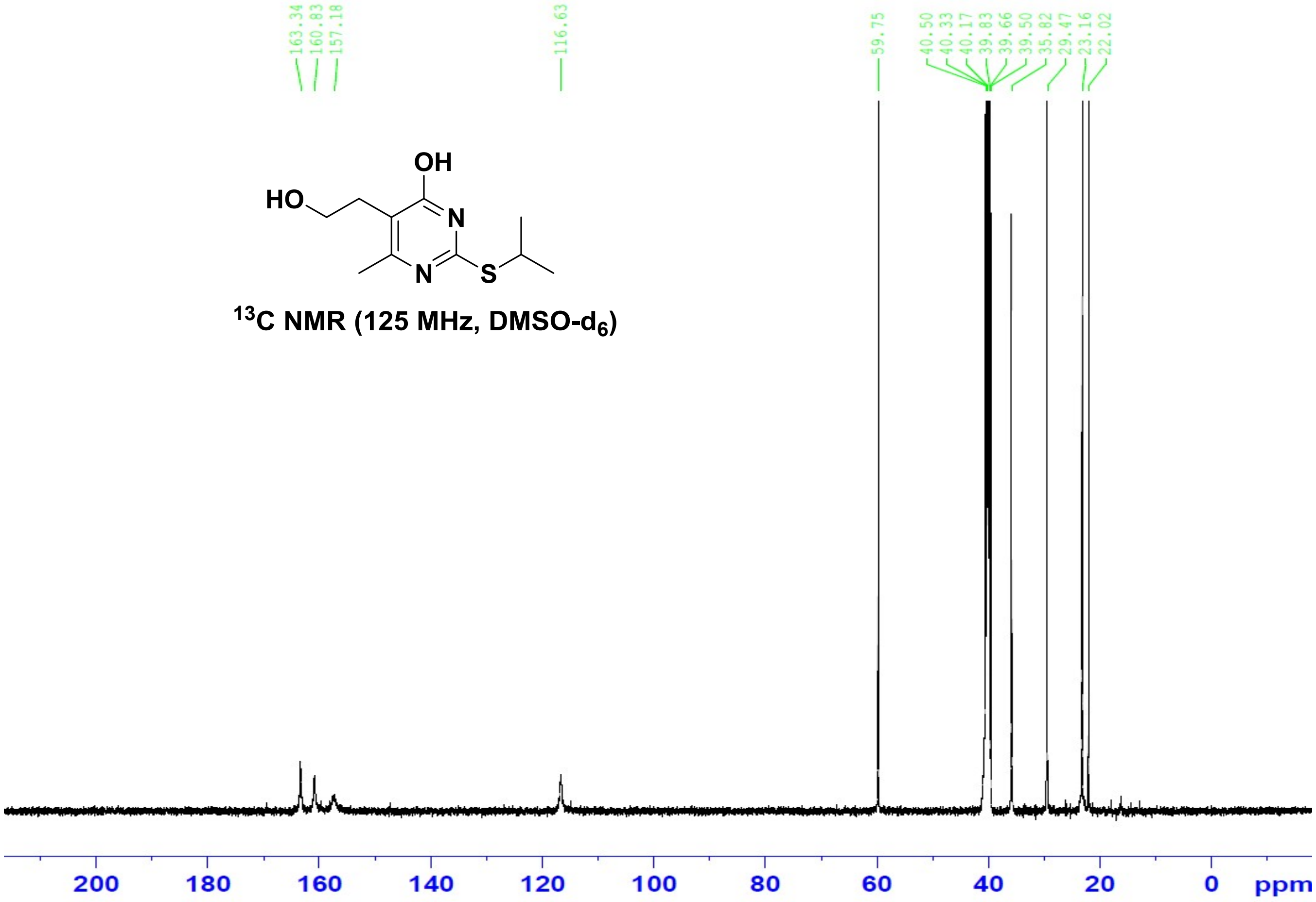

^{13}C NMR (125 MHz, DMSO-d$_6$)


nb0203-78-p-H-D2O.1.fid
4.79 D2O
3.63
3.61
3.60
3.58
3.56
3.34
1.19
1.17
S
N
O
NH
HN
N
S
O
^{1}H NMR (400 MHz, D$_2$O)
1.05
2.00
6.00
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)

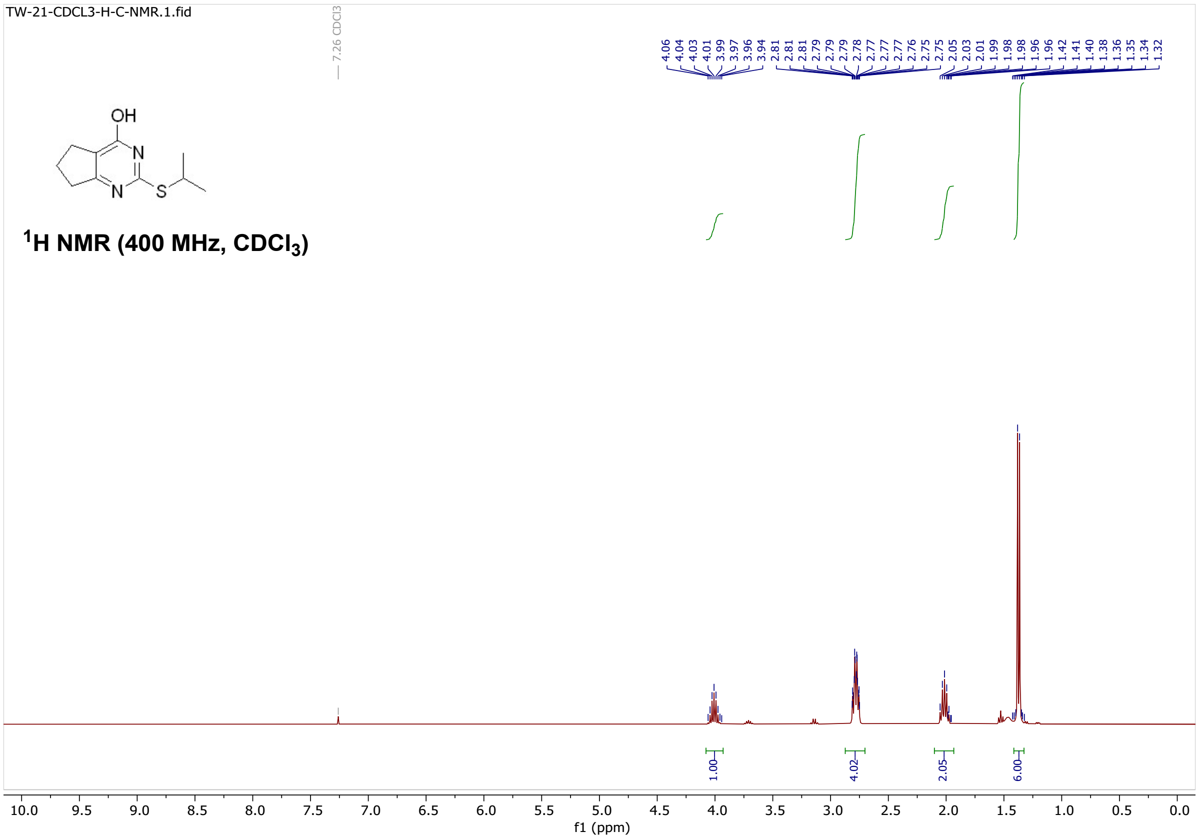

nb0203-78-p-H-D2O.2.fid
173.11
166.80
158.36
110.83
35.10
29.31
22.32
S
N
O
NH
HN
N
S
O
^{13}C NMR (100 MHz, D$_2$O)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



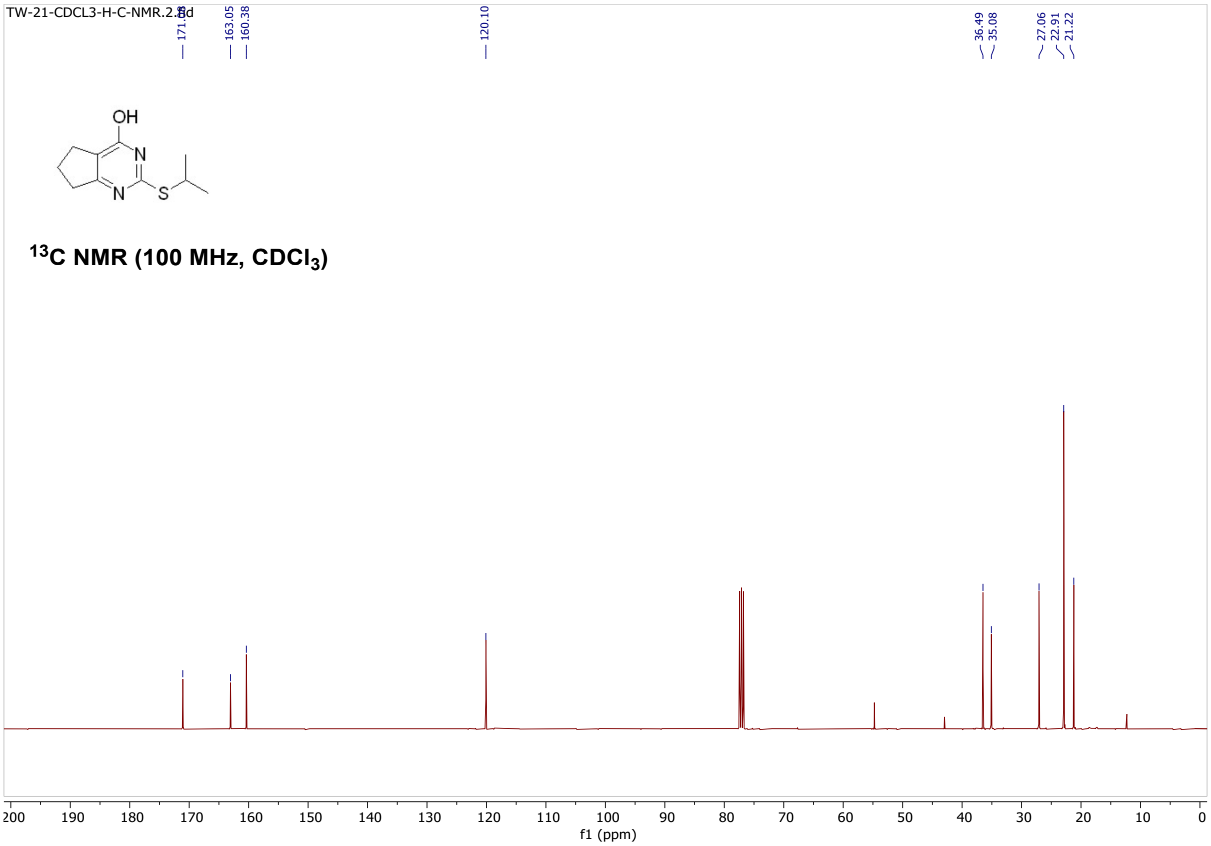
^{1}H NMR (500 MHz, DMSO-d$_6$)



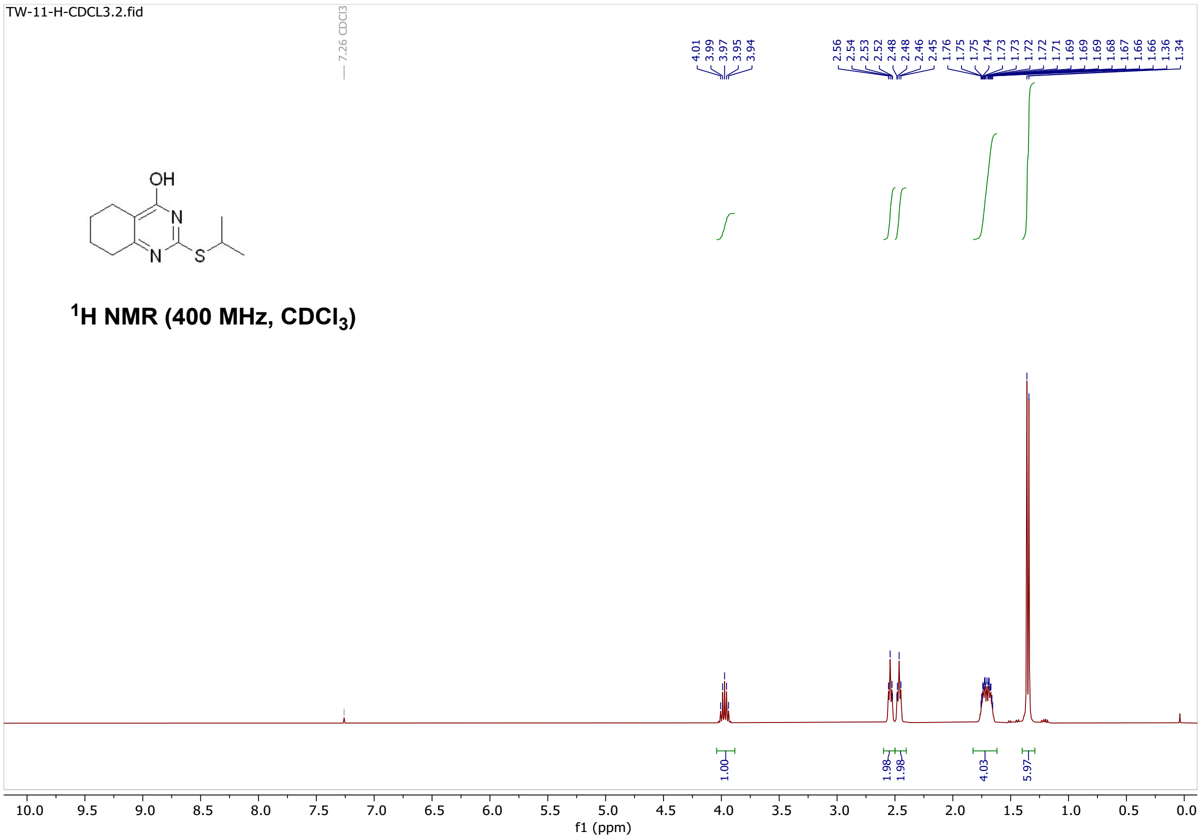
^{13}C NMR (125 MHz, DMSO-d$_6$)

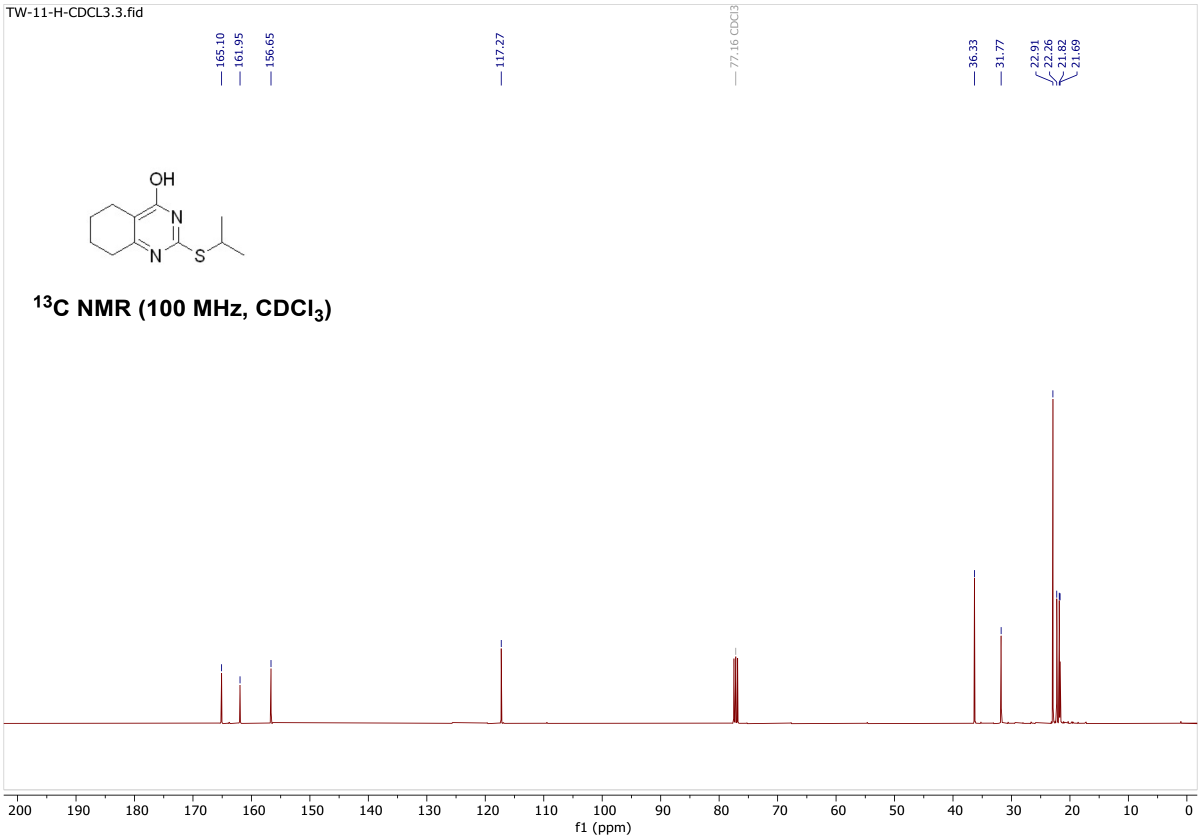


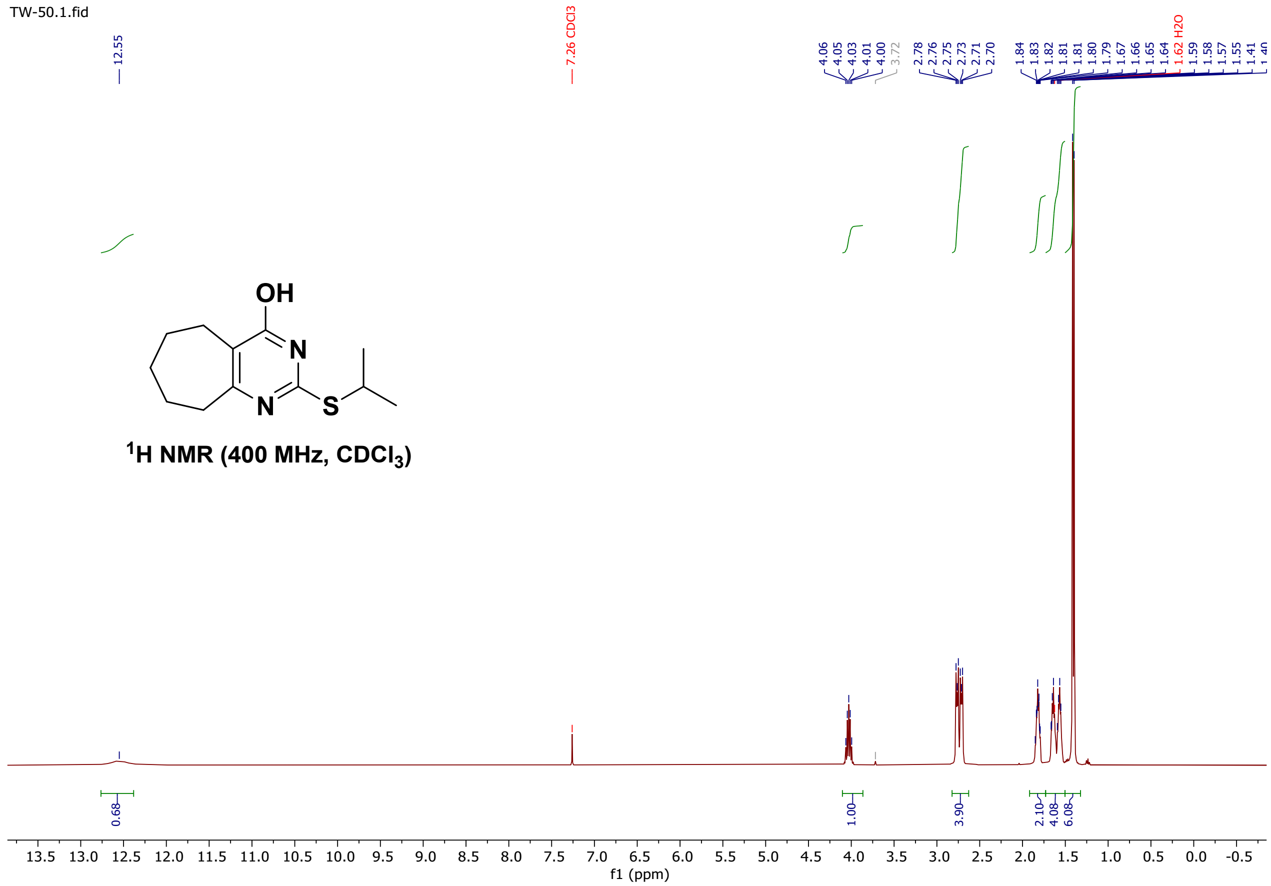
^{1}H NMR (400 MHz, CDCl$_3$)

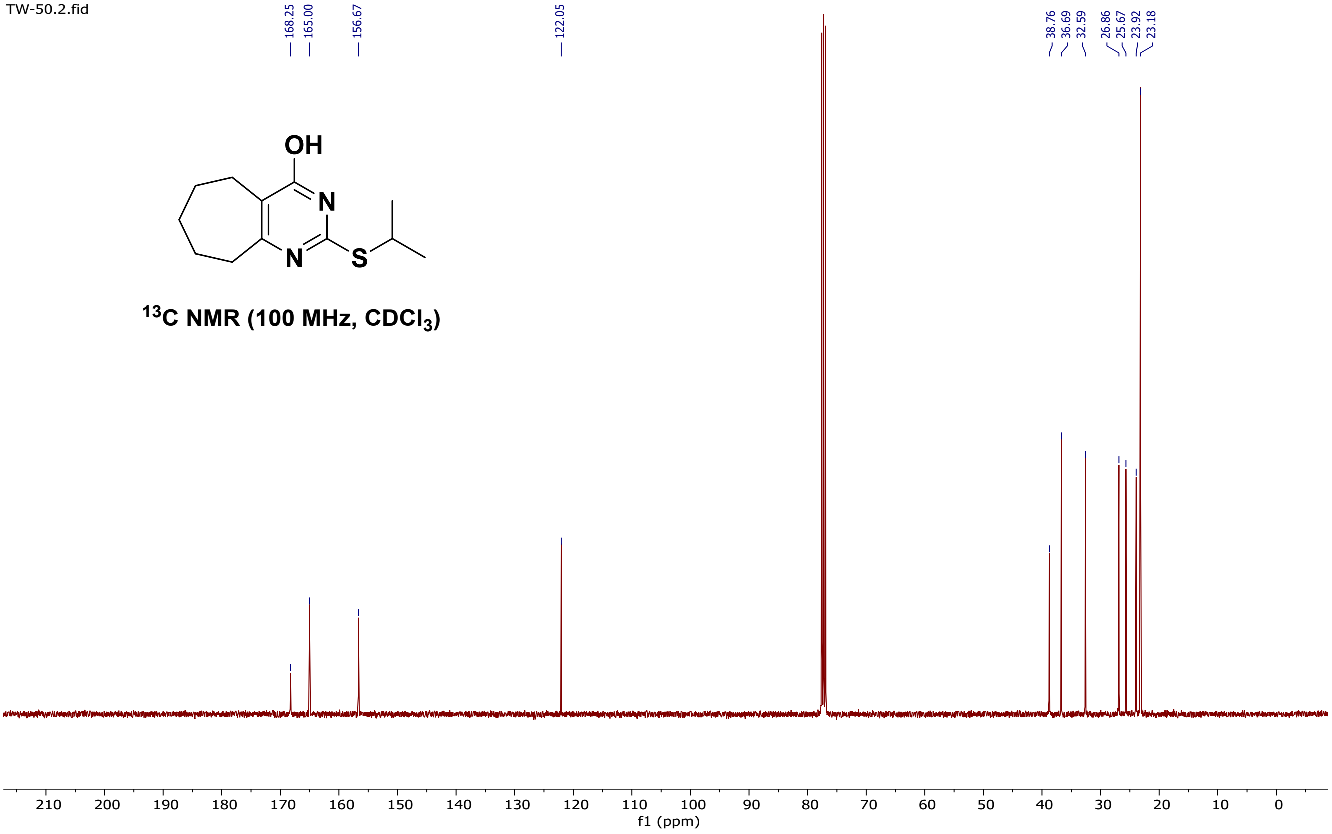


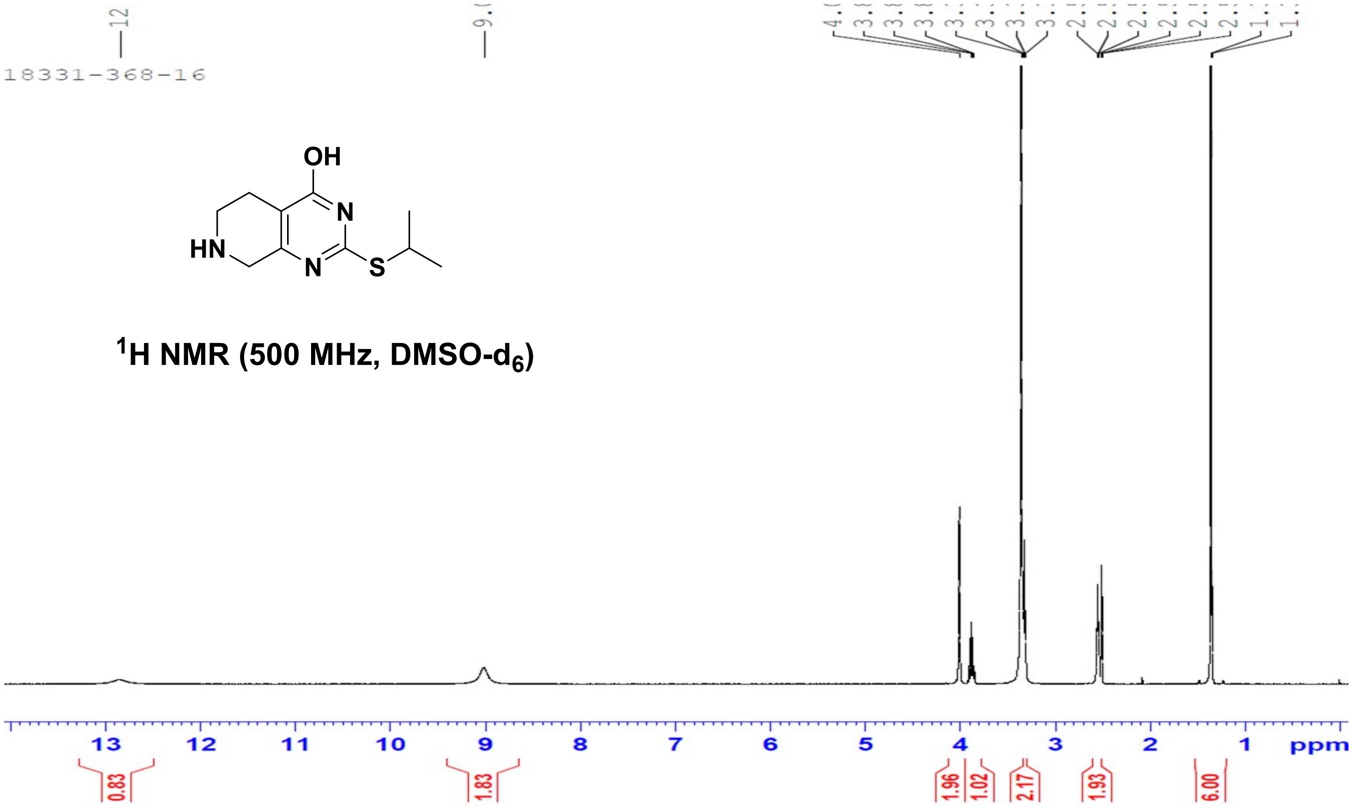
^{13}C NMR (100 MHz, CDCl$_3$)


TW-11-H-CDCL3.2.fid
7.26 CDCl3
4.01
3.99
3.97
3.95
3.94
2.56
2.54
2.53
2.52
2.48
2.48
2.46
2.45
1.76
1.75
1.75
1.74
1.73
1.73
1.72
1.72
1.71
1.69
1.69
1.69
1.68
1.67
1.66
1.66
1.36
1.34
OH
N
N
S
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
1.98
1.98
4.03
5.97
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)

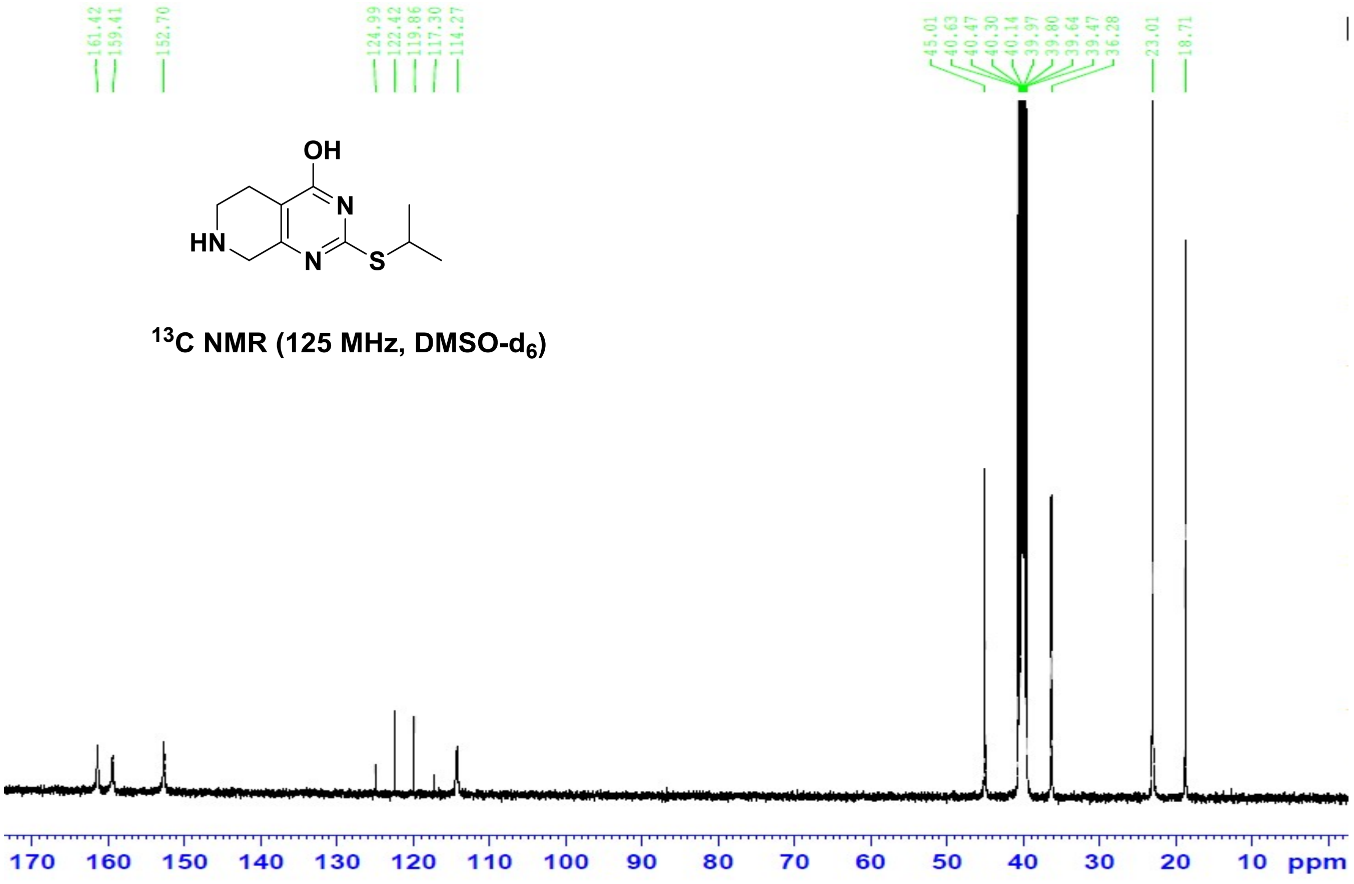

TW-11-H-CDCL3.3.fid
165.10
161.95
156.65
117.27
77.16 CDCl3
36.33
31.77
22.91
22.26
21.82
21.69
OH
N
N
S
^{13}C NMR (100 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


TW-50.1.fid
12.55
7.26 CDCl3
4.06
4.05
4.03
4.01
4.00
3.72
2.78
2.76
2.75
2.73
2.71
2.70
1.84
1.83
1.82
1.81
1.81
1.80
1.79
1.67
1.66
1.65
1.64
1.62 H2O
1.59
1.58
1.57
1.55
1.41
1.40
OH
N
N
S
^{1}H NMR (400 MHz, CDCl$_3$)
0.68
1.00
3.90
2.10
4.08
6.08
13.5 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 -0.5
f1 (ppm)

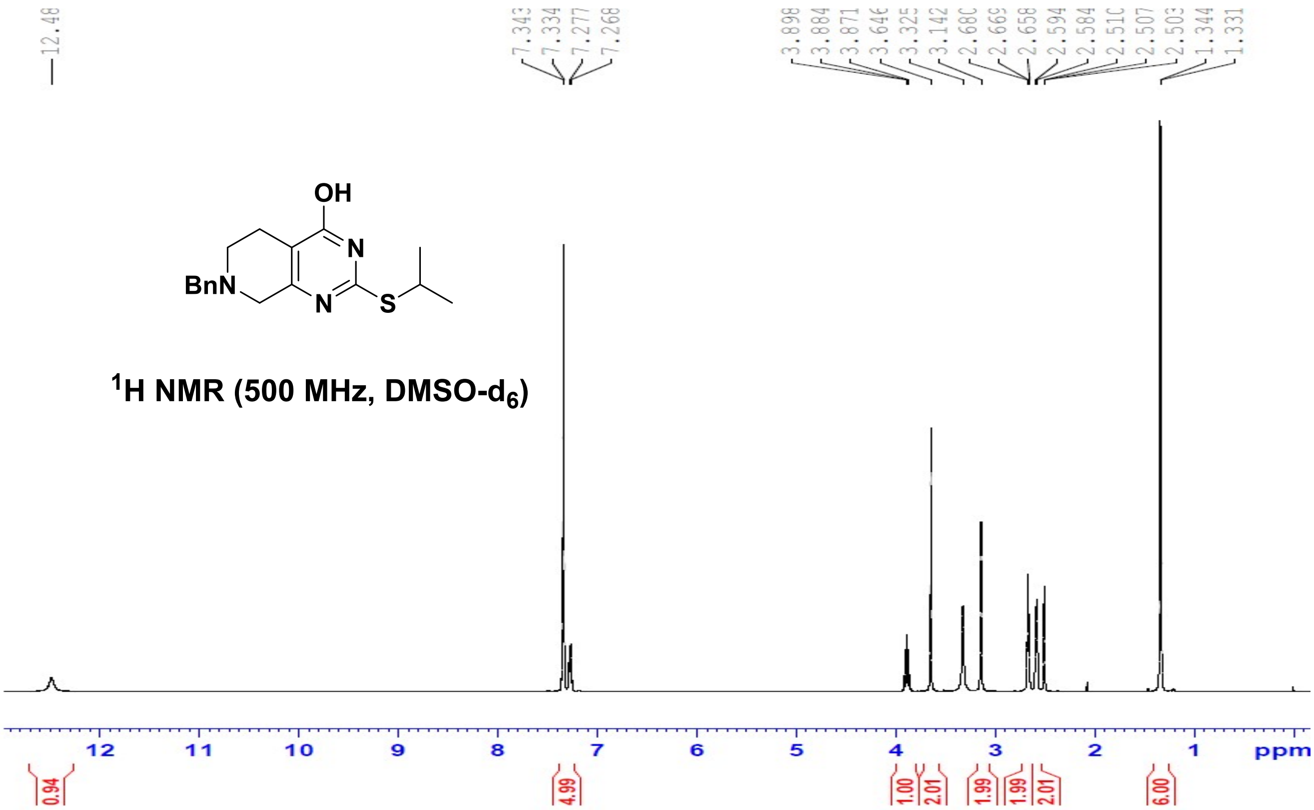

TW-50.2.fid
168.25
165.00
156.67
122.05
38.76
36.69
32.59
26.86
25.67
23.92
23.18
OH
N
N
S
^{13}C NMR (100 MHz, CDCl$_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



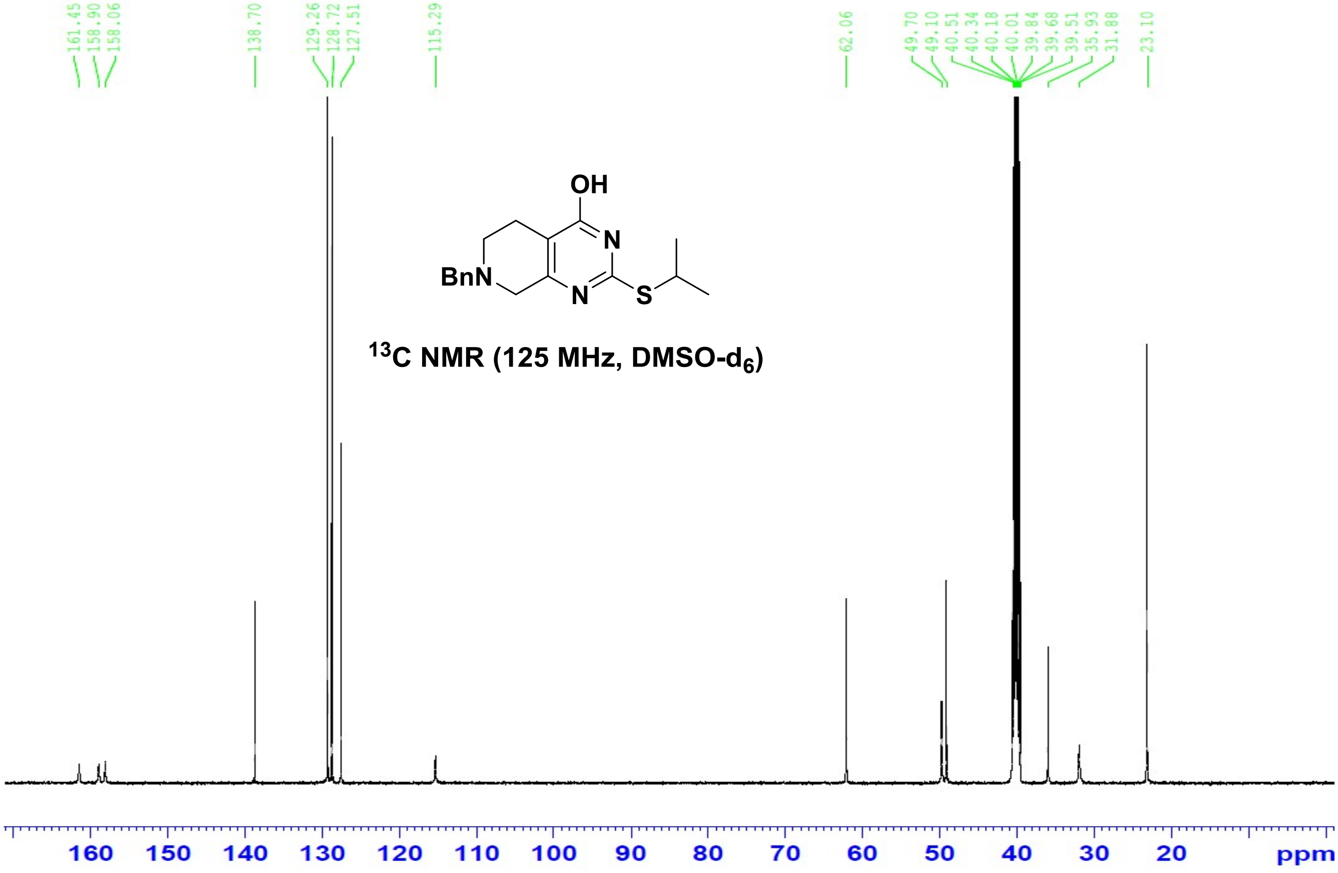
^{1}H NMR (500 MHz, DMSO-d$_6$)



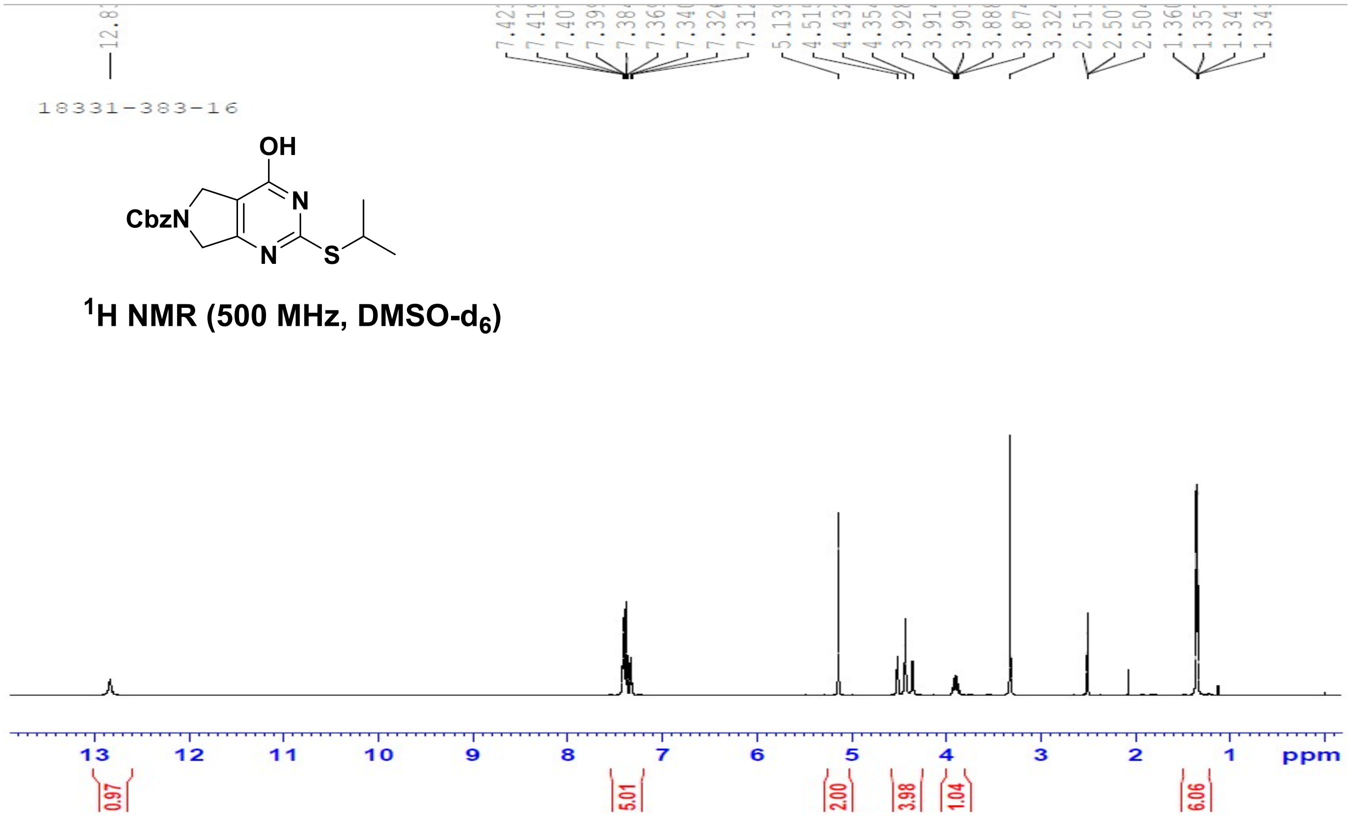
^{13}C NMR (125 MHz, DMSO-d$_6$)



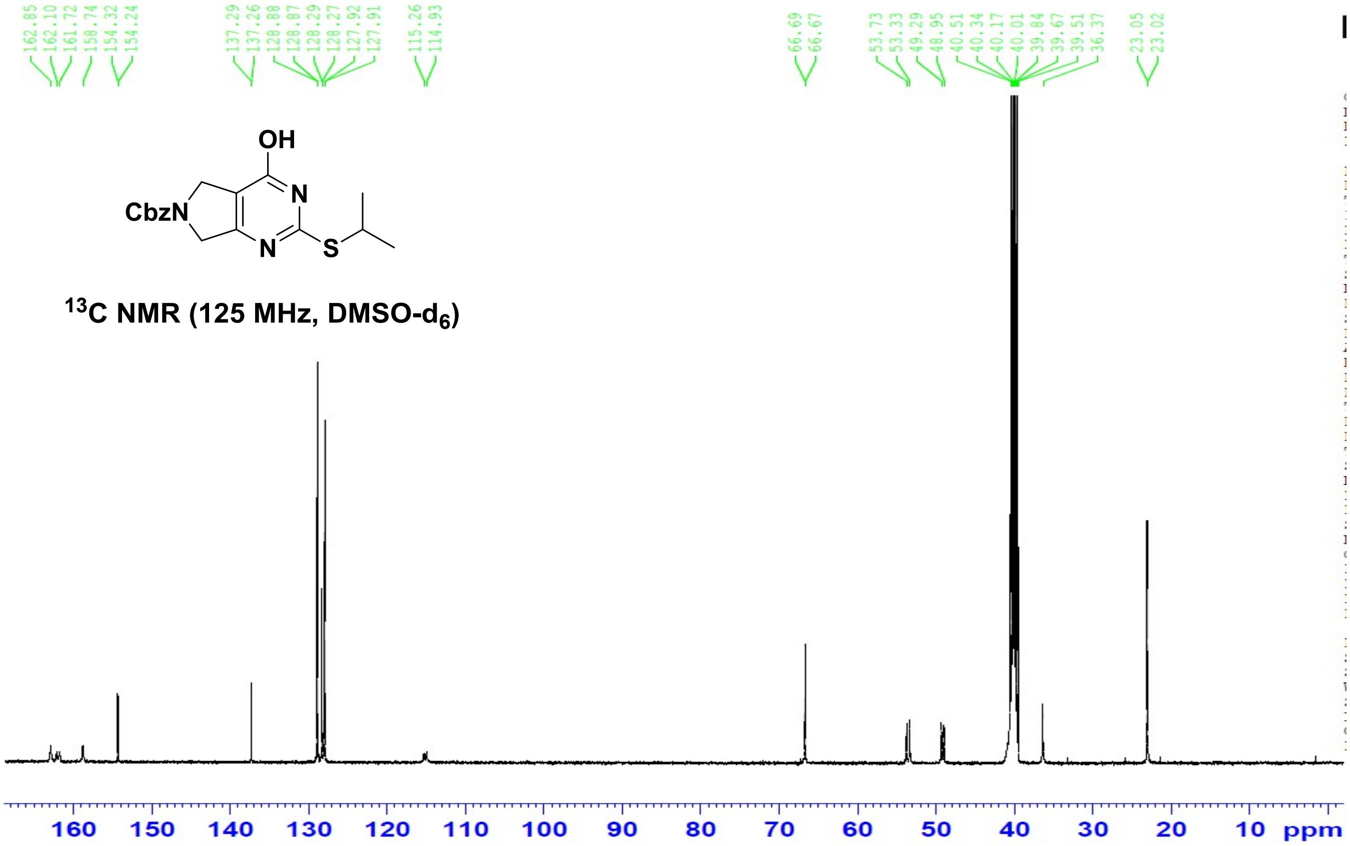
^{1}H NMR (500 MHz, DMSO-d$_6$)



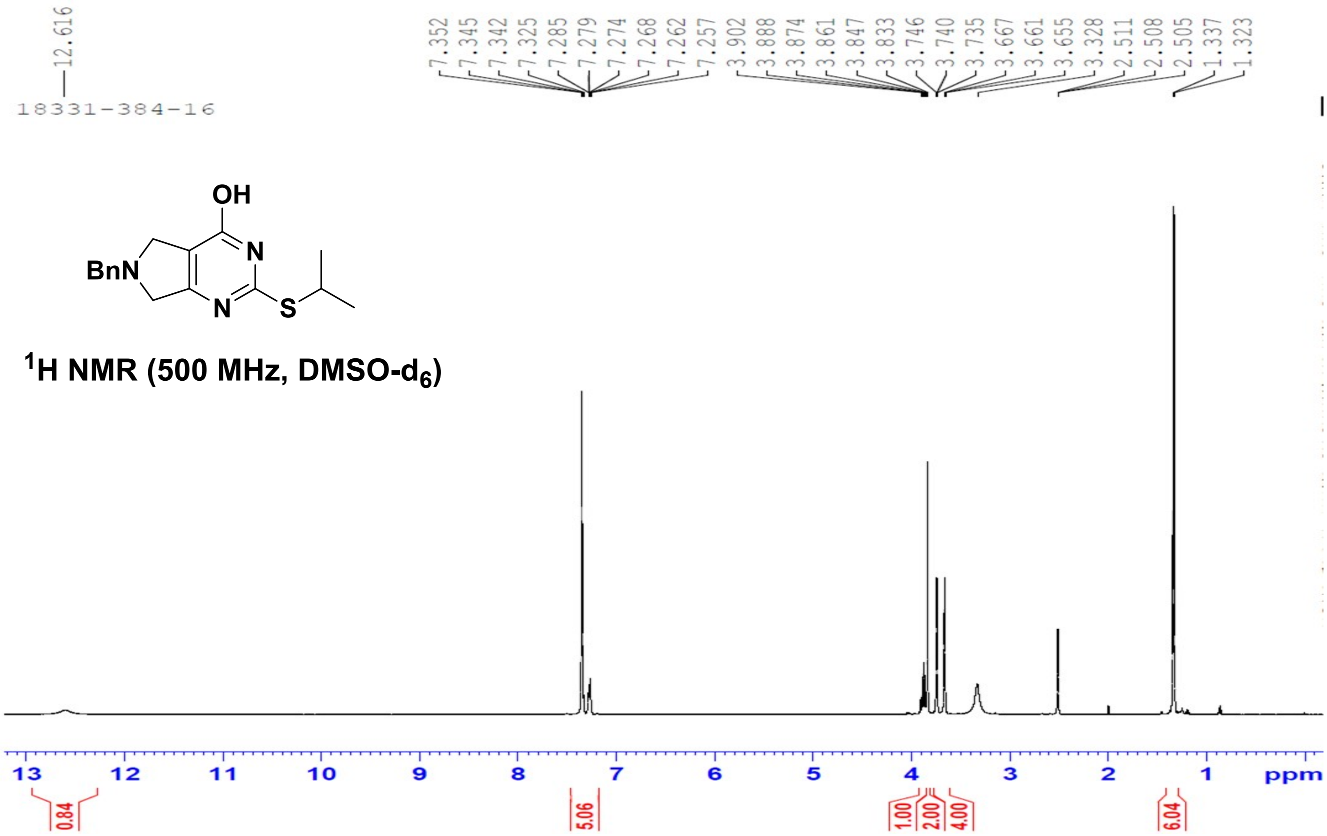
^{13}C NMR (125 MHz, DMSO-d$_6$)



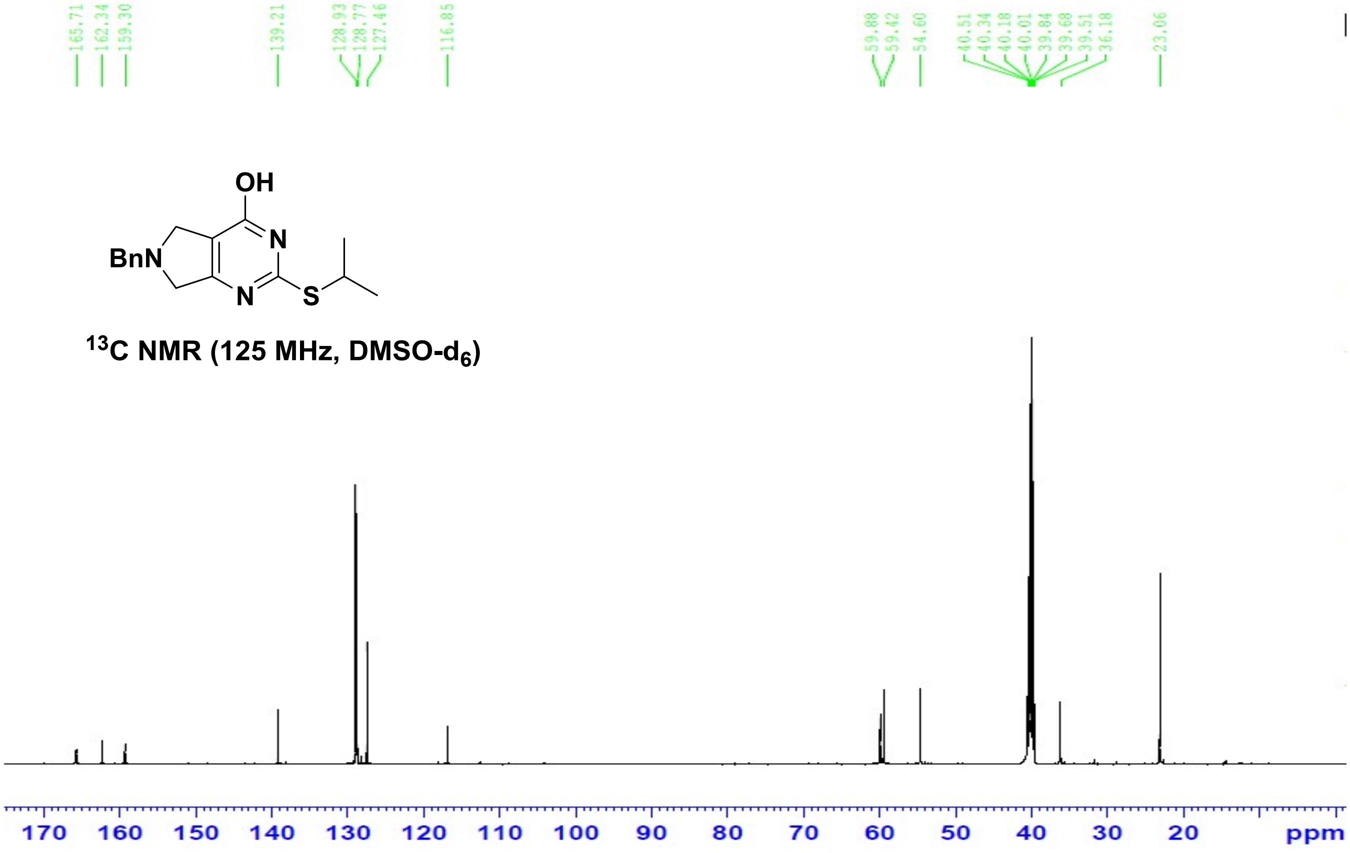
^{1}H NMR (500 MHz, DMSO-d$_6$)



^{13}C NMR (125 MHz, DMSO-d$_6$)



^{1}H NMR (500 MHz, DMSO-d$_6$)



^{13}C NMR (125 MHz, DMSO-d$_6$)

Section 9. References

1. C.-y. Chen, Z. Lu, T. Scattolin, C. Chen, Y. Gan and M. McLaughlin, *Org. Lett.*, 2023, **25**, 944-949.