Supporting Information

Discovery of Mercaptopropanamide-substituted Aryl Tetrazoles as New Broad-Spectrum Metallo-β-lactamase Inhibitors

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Contents

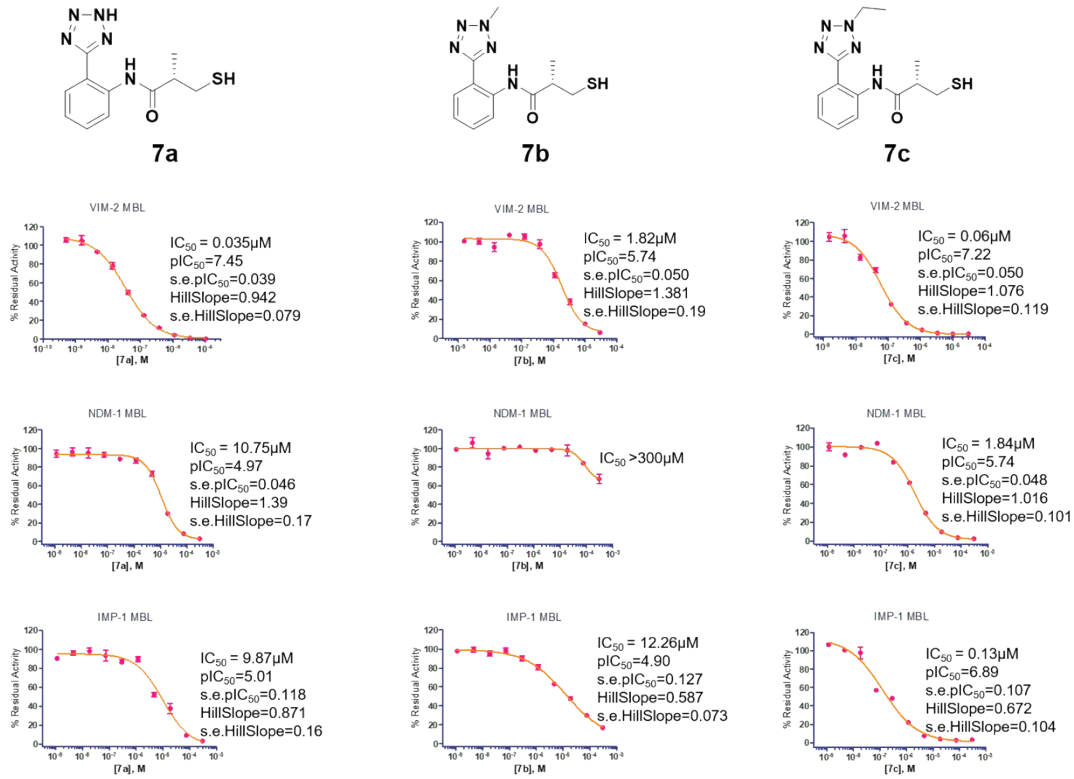
Table S1. Data collection and refinement statistics for VIM-2 PDB codes: 7CJL.

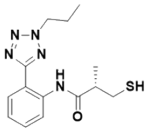
Structure	VIM-2: **13a**
PDB ID	7CJL
Radiation Source	SSRF Beamline BL19U1
Space Group	*P* 2 1 2 1 2 1
Unit Cell Dimensions a, b, c (Å)	45.356 90.132 125.849
Unit Cell Dimensions α, β, γ (˚)	90.00 90.00 90.00
*Mol/ASU	2
Resolution Range (outer shell) (Å)	45.066-1.789 (1.834-1.789)
Number of Unique Reflections	42398
Completeness (%)	85.48
$I/\sigma(I)$ (outer shell)	1.42
R_{merge} (outer shell)	0.158
Wilson B Factor (Å^2)	20.15
Overall B Factor (Å^2)	29.39
Protein B Factor (Å^2)	29.05
Ligand B Factor (Å^2) (occupancy)	46.17
Water B Factor (Å^2)	32.19
‡RMSD from Ideal Bond Length (Å)	0.019

RMSD from Ideal Angles (˚)	1.130
R_{work} (%)	20.53
R_{free} (%)	24.64

*Mol/ASU = molecules per asymmetric unit; ‡RMSD = root mean square deviation.

Figure S1. The dose–response curves of target compounds (in Table 1 and Table 2) inhibiting the representative MBL enzymes.





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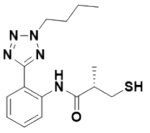

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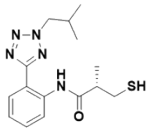

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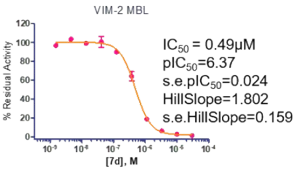

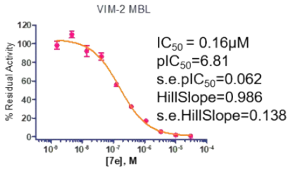

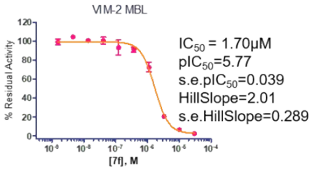

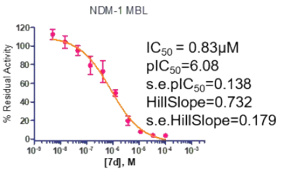

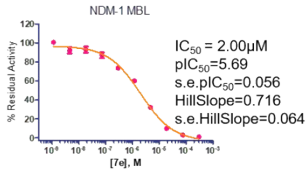

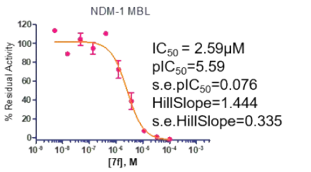

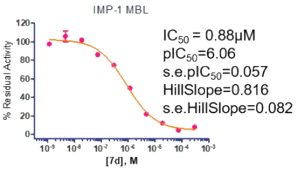

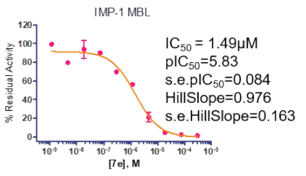

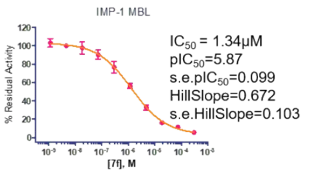

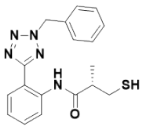

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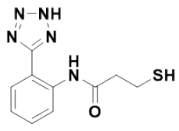

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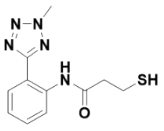

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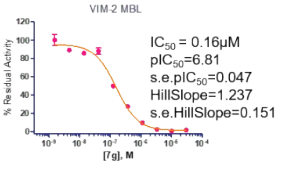

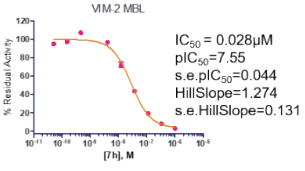

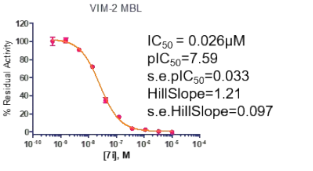

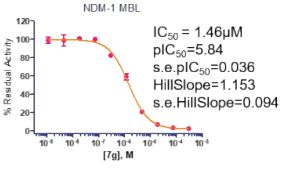

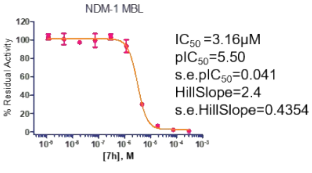

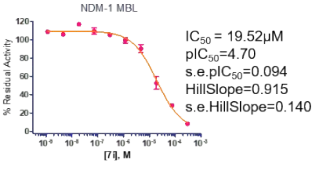

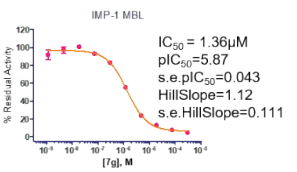

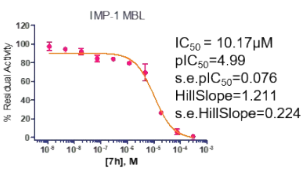

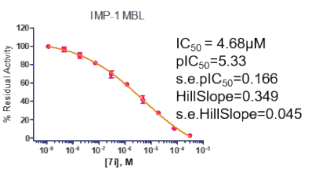

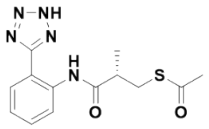

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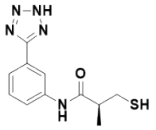

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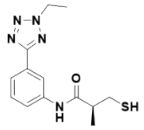

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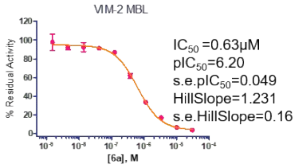

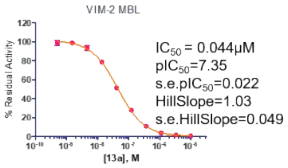

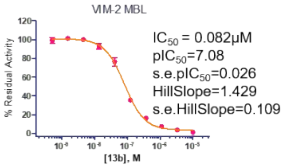

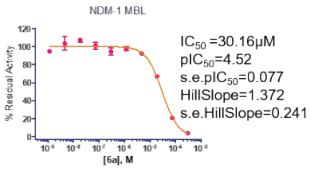

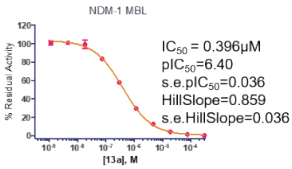

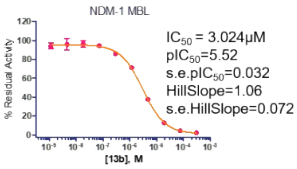

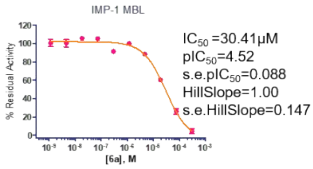

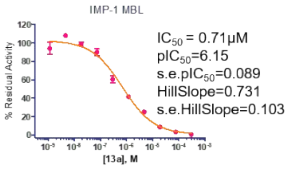

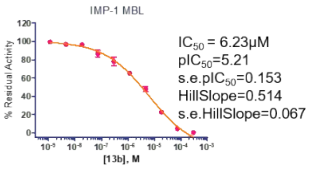

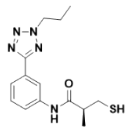

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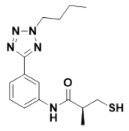

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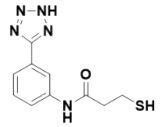

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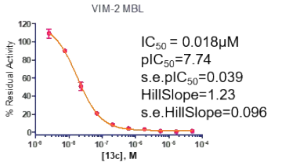

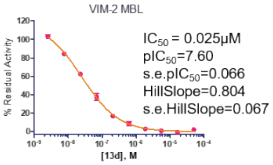

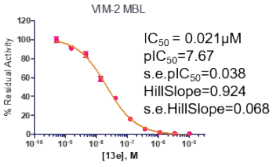

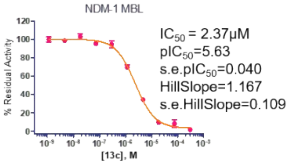

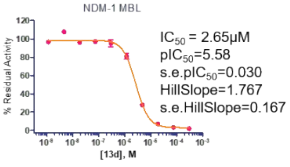

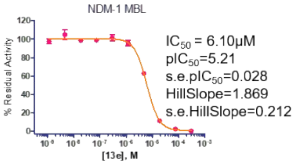

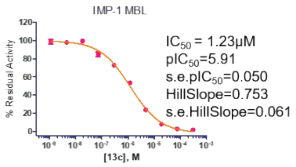

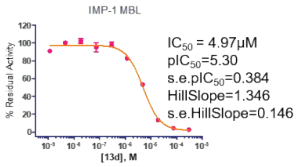

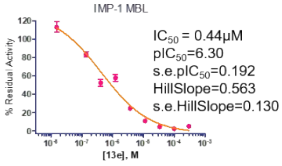

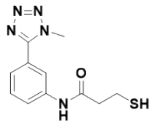

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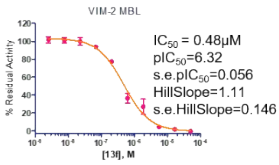

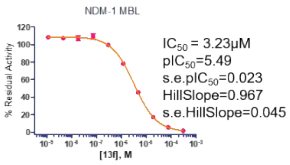

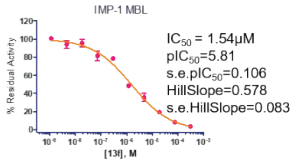

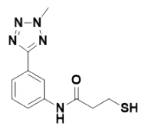

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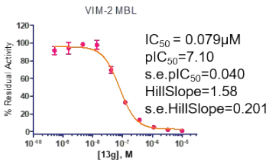
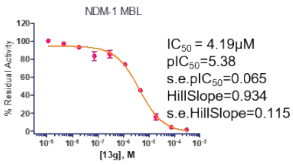
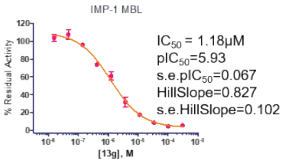
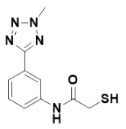
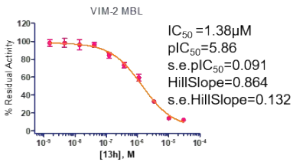


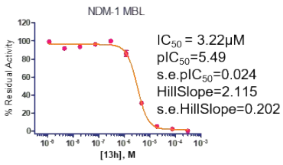


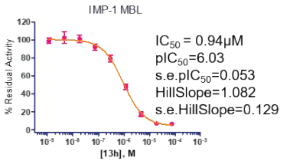


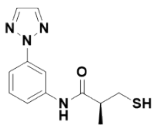


13h

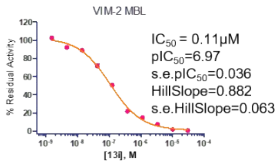


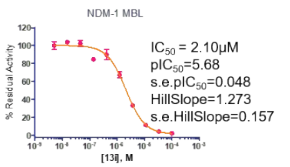


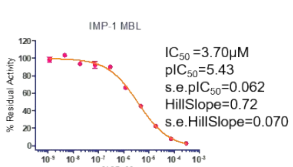


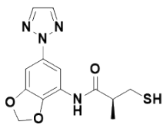


13i

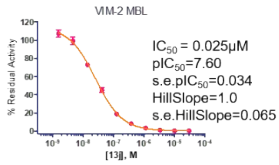


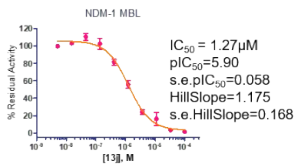


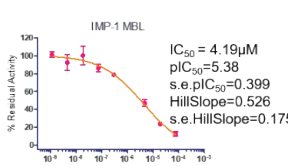


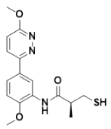


13j

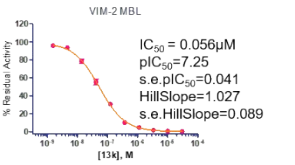


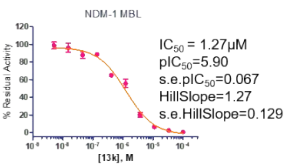






13k





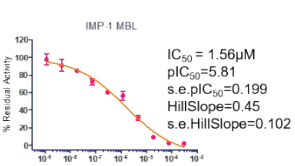


Table S2. MICs of meropenem (MEM) in the absence or presence of **13a** against VIM-2-producing *E. coli* strain.

Assay No.	Inhibitor 13a Concentration (μM)	Meropenem	MIC (μg/mL) *E. coli*-VIM-2	MIC (μg/mL) *E. coli*
1	200	+	4	<0.125
2	100	+	4	<0.125
3	50	+	8	<0.125
4	25	+	8	<0.125
5	200	_	>64	>64
6	100	_	>64	>64
7	50	_	>64	>64
8	25	_	>64	>64
9	_	+	8	<0.125

Chemical Synthesis of Target Compounds

Synthesis

All solvents were analytical reagent (AR) and commercially available and used without further

purification. All the reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. The product purification was done using silica gel column chromatography. Thin-layer chromatography (TLC) characterization was performed with precoated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100-200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. ^{1}H NMR spectra were recorded at 400 or 600 MHz (Varian) and ^{13}CNMR spectra were recorded at 100 or 150 MHz (Varian). Shifts are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) or DMSO-d_6 (δ = 2.50 ppm; H_2O signal was found at δ = 3.34 ppm) for ^{1}H NMR and chemical shifts for ^{13}C NMR spectra are reported in ppm relative to the central $CDCl_3$ (δ = 77.0 ppm) or DMSO-d_6 (δ = 39.6 ppm). Coupling constants were given in Hz. All target compounds were purified to >95% purity, as determined by the high-performance liquid chromatography (HPLC). The HPLC analysis was performed on Waters 2695 HPLC system equipped with a Kromasil C18 column (4.6 mm × 250 mm, 5 μm).

General procedure 1: Synthesis of 5-phenyl-2H-tetrazole (compound 2)

To a 250 mL round-bottomed flask was added benzonitrile (20 mmol), sodium azide (1.44 g, 22 mmol), zinc bromide (4.50 g, 20 mmol) and 40 mL of water. The reaction mixture was refluxed for 24 h with vigorous stirring. After cooled to rt, HCl (3 N, 30 mL) and ethyl acetate (100 mL) were added, and vigorous stirring was continued until no solid was present and the aqueous layer had a pH of 1. The organic layer was isolated and the aqueous layer extracted with ethyl acetate (100 ml × 3). The combined organic layers were evaporated, 200 mL of 0.25 N NaOH was added, and the mixture was stirred for 30 min until the original precipitate was dissolved and a suspension of zinc hydroxide was formed. The suspension was filtered, and the solid washed with 20 mL of 1 N NaOH. To the filtrate was added 40 mL of 3 N HCl with vigorous stirring causing 5-phenyltetrazole to precipitate. The tetrazole was filtered and washed with HCl (3 N, 3 × 20 mL) and dried in a drying oven to furnish the 5-phenyl-2H-tetrazole as a white powder (87%).

General procedure 2: Synthesis of compounds 3a-3h

To a stirred suspension of 5-phenyl-2H-tetrazole (1.0 equiv) in CH_3CN (2.5 ml/1 mmol) was added corresponding iodoalkanes (1.1 equiv) and K_2CO_3 (2.0 equiv), and the mixture was heated at reflux for 4 h. After cooling, the mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and distilled water. The organic layers were collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure and the residue was subjected to flash chromatography to give compounds **3a-3h** in 55%-83% yields.

General procedure 3: *Ortho*-C-H amidation reactions of compounds 3a-3h

Compounds **3a-3h** (0.2 mmol), 3-phenyloxazolidinone (0.24 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol) and Ag_2SO_4 (0.02 mmol) were charged into a sealed tube, to which was added 1,2-dichloroethane (2.0 mL). The reaction mixture was stirred at 80°C for 24 h. After cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using petroleum ether/ethyl acetate as the eluent to afford the corresponding amides (**4a-4h**) in 54-85% yields.

General procedure 4: Synthesis of compounds 5a-5h

To a stirred solution of amides (**4a-4h**, 1.0 equiv) in ethanol was added sodium hydroxide. The reaction mixture was stirred at 80 °C for about 1 h. After cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using petroleum ether/ethyl acetate as the eluent to afford the corresponding amides (**5a-5h**) in 71-92% yields.

General procedure 5: Synthesis of compounds 6a-6i

To a stirred solution of different carboxylic acids (1.5 equiv) in DCM was added isobutyl chloroformate (1.0 equiv) and 4-methylmorpholine (1.0 equiv). The reaction mixture was stirred at -5 °C for 30 minutes to activate isobutyl chloroformate. After that, dichloromethane solution of corresponding amine was dropwise added into the reaction mixture, which was stirred at room temperature for 12 h. After completion (monitored by TLC), the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using petroleum ether/ethyl acetate to afford **6a-6i** in 72-83% yields.

General procedure 6: Synthesis of compounds 7a-7i

To a stirred solution of thioesters (**6a-6i,** 1.0 equiv) in methanol was added 1 N ammonium hydroxide solution and the resulting mixture was stirred for 2 h at room temperature under argon. After that, 1 N hydrochloric acid solution (15 ml/1 mmol) was added and the methanol was distilled off. The product was extracted with ethyl acetate and the organic phase was washed with water and saturated sodium chloride solution successively and then dried over Na_2SO_4. After distilling off the

ethyl acetate, the residue was purified by means of column chromatography on silica gel with petroleum ether/ethyl acetate as an eluent to furnish the target compounds **7a-7i** in 90%-95% yields.

General procedure 7: *Meta*-C-H nitration reactions of 9a-9j

Compound **9a-9j** (0.2 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (0.3 mmol), $Ru_3(CO)_{12}$ (0.15 mmol), PPh_3(0.06 mmol) and $PhI(TFA)_2$ (0.22 mmol) were charged into a sealed tube, to which was added HFIP (2.0 mL). The reaction mixture was stirred at 100 °C for 24 h. After cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using petroleum ether/ethyl acetate as the eluent to afford the corresponding *meta*-nitration products **10a-10j** in 81-90% yields.

General procedure 8: Synthesis of compounds 11a-11j

To a stirred solution of compounds **10a-10j (**1.0 equiv) in methanol was added palladium on charcoal (10 mol%, 2.0 equiv) under hydrogen atmosphere. The reaction mixture was stirred at room temperature for about 3 h. After removal of the catalyst by filtration through celite and evaporation of the solvent under reduced pressure, the organic solvent was removed and the residue was purified by column chromatography to give compounds **11a-11j** in 68-81% yields.

General procedure 9: Synthesis of compounds 12a-12k and 13a-13k

Compounds **12a-12k** were synthesized according to general procedure 5. Compounds **13a-13k** were synthesized according to general procedure 6.

The total yields and characterization data of all target compounds are as follows.

(S)-N-(2-(2H-tetrazol-5-yl)phenyl)-3-mercapto-2-methylpropanamide (7a) 34% yield, 96.5% HPLC purity. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 2.80-2.56 (m, 3H), 2.35 (t, J = 8.0 Hz, 1H), 1.22 (d, J = 4.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d6) δ 173.13, 154.40, 136.91, 131.75, 128.89, 124.27, 122.50, 114.13, 45.18, 27.27, 16.85 ppm. ESI-MS m/z: 264.1 [M + H]+.

(S)-3-mercapto-2-methyl-N-(2-(2-methyl-2H-tetrazol-5-yl)phenyl)propanamide (7b) 30% yield, 97.3% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.71 (d, J = 8.0 Hz, 1H),

8.19 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 4.46 (s, 3H), 3.01 – 2.94 (m, 1H), 2.78 – 2.64 (m, 2H), 1.57 (t, J = 8.0 Hz, 1H), 1.40 (d, J = 8.0 Hz, 3H) ppm. 13C NMR (100 MHz, $CDCl_3$) δ 173.90, 164.97, 137.61, 131.87, 128.78, 124.11, 121.61, 114.67, 47.37, 40.24, 28.57, 17.88 ppm. ESI-MS m/z: 278.1 [M + H]+.

(S)-N-(2-(2-ethyl-2H-tetrazol-5-yl)phenyl)-3-mercapto-2-methylpropanamide (7c) 32% yield, 96.9% HPLC purity. ^{1}H NMR (400 MHz, $CDCl^3$) δ 10.87 (s, 1H), 8.71 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 4.75 (q, J = 8.0 Hz, 2H), 3.01 – 2.93 (m, 1H), 2.80 – 2.62 (m, 2H), 1.72 (t, J = 8.0 Hz, 3H), 1.57 (t, J = 8.0 Hz, 1H), 1.40 (d, J = 8.0 Hz, 3H) ppm. ^{13}C NMR (150 MHz, Methanol-d4) δ 175.76, 164.94, 137.57, 131.97, 129.68, 125.55, 123.60, 117.85, 49.84, 47.77, 28.50, 17.53, 14.75 ppm. ESI-MS m/z: 292.1 [M + H]+.

(S)-3-mercapto-2-methyl-N-(2-(2-propyl-2H-tetrazol-5-yl)phenyl)propanamide (7d) 38% yield, 97.7% HPLC purity. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.72 (d, J = 6.0 Hz, 1H), 8.21 (d, J = 12.0 Hz, 1H), 7.48 (t, J = 12.0 Hz, 1H), 7.19 (t, J = 12.0 Hz, 1H), 4.67 (t, J = 6.0 Hz, 2H), 3.00 – 2.95 (m, 1H), 2.78 – 2.64 (m, 2H), 2.16 – 2.10 (m, 2H), 1.57 (t, J = 12.0 Hz, 1H), 1.40 (d, J = 6.0 Hz, 3H), 1.03 (t, J = 12.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-d) δ 173.50, 164.40, 137.32, 131.45, 128.47, 123.70, 121.21, 114.49, 55.21, 47.06, 28.25, 22.95, 17.53, 11.14 ppm. ESI-MS m/z: 306.1 [M + H]+.

(S)-N-(2-(2-butyl-2H-tetrazol-5-yl)phenyl)-3-mercapto-2-methylpropanamide (7e) 43% yield, 98.2% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.71 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 4.70 (t, J = 8.0 Hz, 2H), 3.01 – 2.94 (m, 1H), 2.79 – 2.63 (m, 2H), 2.07 (p, J = 8.0 Hz, 2H), 1.57 (t, J = 8.0 Hz, 1H), 1.45 – 1.43 (d, J = 8.0 Hz, 2H), 1.40 (d, J = 8.0 Hz, 3H), 0.99 (t, J = 8.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.49, 164.35, 137.30, 131.43, 128.46, 123.69, 121.19, 114.48, 53.36, 47.05, 31.33, 28.24, 19.73, 17.52, 13.47 ppm. ESI-MS m/z: 320.1 [M + H]+.

(S)-N-(2-(3-isobutyl-3H-1,2,4-triazol-5-yl)phenyl)-3-mercapto-2-methylpropanamide (7f) 42% yield, 98.5% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.72 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 4.52 (d, J = 8.0 Hz, 2H), 3.02 – 2.95 (m, 1H), 2.80 – 2.64 (m, 2H), 2.52 – 2.41 (m, 1H), 1.57 (t, J = 8.0 Hz, 1H), 1.41 (d, J = 4.0 Hz, 3H), 1.03 (d, J = 8.0 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.53, 164.38, 137.35, 131.49, 128.50, 123.73, 121.24, 114.50, 60.58, 47.10, 29.84, 29.40, 28.27, 19.95, 17.55 ppm. ESI-MS m/z: 320.1 [M + H]+.

(S)-N-(2-(2-benzyl-2H-tetrazol-5-yl)phenyl)-3-mercapto-2-methylpropanamide (7g) 37% yield, 96.4% HPLC purity. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.69 (s, 1H), 8.69 (d, J = 12.0 Hz, 1H), 8.22 (d, J = 6.0 Hz, 1H), 7.47 – 7.40 (m, 6H), 7.18 (t, J = 6.0 Hz, 1H), 5.85 (s, 2H), 2.96 – 2.90 (m, 1H), 2.65 – 2.61 (m, 2H), 1.52 (t, J = 6.0 Hz, 1H), 1.34 (d, J = 6.0 Hz, 3H) ppm. ^{13}C NMR (150

MHz, $CDCl_3$) δ 173.47, 164.70, 137.25, 132.86, 131.58, 129.43, 129.32, 128.73, 128.57, 123.71, 121.15, 114.32, 57.35, 47.04, 28.21, 17.51 ppm. ESI-MS m/z: 354.1 [M + H]+.

N-(2-(2H-tetrazol-5-yl)phenyl)-3-mercaptopropanamide (7h) 41% yield, 97.8% HPLC purity. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.17 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 2.68 – 2.62 (m, 2H), 2.59 – 2.57 (m, 2H) ppm. ^{13}C NMR (100 MHz, Methanol-d4) δ 180.16, 164.50, 146.07, 140.94, 137.39, 133.55, 131.57, 122.79, 50.66, 28.58 ppm. ESI-MS m/z: 250.0 [M + H]+.

N-(2-(2-methyl-2H-tetrazol-5-yl)phenyl)-3-mercaptopropanamide (7i) 35% yield, 96.9% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.67 (d, J = 8.0 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 4.45 (s, 3H), 2.94 (d, J = 8.0 Hz, 2H), 2.84 (t, J = 8.0 Hz, 2H), 1.71 (t, J = 8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, CDCl3) δ 169.55, 164.45, 137.07, 131.41, 128.33, 123.66, 121.05, 114.09, 42.22, 39.82, 20.21 ppm. ESI-MS m/z: 264.1 [M + H]+.

(S)-S-(3-((2-(2H-tetrazol-5-yl)phenyl)amino)-2-methyl-3-oxopropyl)ethanethioate (6a) 55% yield, 97.3% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.72 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 4.46 (s, 3H), 3.00 – 2.95 (m, 1H), 2.83 – 2.74 (m, 1H), 2.69 – 2.65 (m, 1H), 1.40 (d, J = 8.0 Hz, 3H) ppm.

N-(2-(2H-tetrazol-5-yl)phenyl)isobutyramide (8) 51% yield, 97.5% HPLC purity. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.45 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 2.67 – 2.60 (m, 1H), 1.13 (d, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d6) δ 175.55, 155.67, 140.27, 129.75, 124.63, 121.66, 121.39, 117.52, 34.96, 19.41 ppm. ESI-MS m/z: 232.1 [M + H]+.

(S)-N-(3-(2H-tetrazol-5-yl)phenyl)-3-mercapto-2-methylpropanamide (13a) 34% yield, 97.8% HPLC purity. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.46 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.71 – 2.64 (m, 1H), 2.61 – 2.55 (m, 1H), 2.32 (t, J = 8.0 Hz, 1H), 1.19 (d, J = 4.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.49, 140.04, 129.88, 124.73, 124.68, 121.73, 121.63, 117.55, 44.55, 27.19, 17.40 ppm. ESI-MS m/z: 264.1 [M + H]+.

(S)-N-(3-(2-ethyl-2H-tetrazol-5-yl)phenyl)-3-mercapto-2-methylpropanamide (13b) 40% yield, 98.2% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 8.0 Hz, 1H), 4.68 (q, J = 8.0 Hz, 2H), 2.98 – 2.85 (m, 1H), 2.64 – 2.57 (m, 2H), 1.67 (t, J = 8.0 Hz, 3H), 1.60 (t, J = 8.0 Hz, 1H), 1.31 (d, J = 4.0 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.05, 164.57, 138.27, 129.68, 128.15, 122.70, 121.83, 118.10, 48.46, 46.23, 28.07, 17.51, 14.57 ppm. ESI-MS m/z: 292.1 [M + H]+.

(S)-3-mercapto-2-methyl-N-(3-(2-propyl-2H-tetrazol-5-yl)phenyl)propanamide (13c) 42% yield, 98.6% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.44 (t, J = 8.0 Hz, 1H), 4.60 (t, J = 8.0 Hz, 2H), 2.97 – 2.88 (m, 1H), 2.64 – 2.58 (m, 2H), 2.12 – 2.03 (m, 3H), 1.60 (t, J = 8.0 Hz, 1H), 1.32 (d, J = 8.0 Hz, 3H), 0.98 (t, J = 8.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl3) δ 173.17, 164.69, 138.42, 129.86, 128.33, 122.86, 121.95, 118.22, 54.95, 46.43, 28.24, 23.01, 17.70, 11.12 ppm. ESI-MS m/z: 306.1 [M + H]+.

(S)-N-(3-(2-butyl-2H-tetrazol-5-yl)phenyl)-3-mercapto-2-methylpropanamide (13d) 38% yield, 96.6% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 1H), 4.45 (d, J = 4.0 Hz, 2H), 3.00 – 2.89 (m, 1H), 2.65 – 2.57 (m, 2H), 2.48 – 2.38 (m, 1H), 1.61 (t, J = 8.0 Hz, 1H), 1.33 (d, J = 8.0 Hz, 3H), 0.99 (d, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.12, 164.53, 138.34, 129.73, 128.17, 122.73, 121.86, 118.12, 60.20, 46.28, 30.98, 29.22, 28.11, 19.78, 17.57 ppm. ESI-MS m/z: 320.1 [M + H]+.

N-(3-(2H-tetrazol-5-yl)phenyl)-3-mercaptopropanamide (13e) 33% yield, 96.9% HPLC purity. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 2.78 – 2.70 (m, 4H), 2.51 – 2.46 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.06, 154.68, 137.22, 132.16, 129.42, 124.71, 123.03, 114.64, 41.45, 20.01 ppm. ESI-MS m/z: 250.0 [M + H]+.

N-(3-(1-methyl-1H-tetrazol-5-yl)phenyl)-3-mercaptopropanamide (13f) 45% yield, 97.4% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.12 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 4.20 (s, 3H), 2.89 (q, J = 8.0 Hz, 2H), 2.79 (t, J = 8.0 Hz, 2H), 1.69 (t, J = 8.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.01, 154.34, 139.16, 129.98, 123.79, 123.71, 122.56, 119.96, 41.12, 35.31, 20.18 ppm. ESI-MS m/z: 264.1 [M + H]+.

N-(3-(2-methyl-2H-tetrazol-5-yl)phenyl)-3-mercaptopropanamide (13g) 51% yield, 97.8% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.07 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 4.36 (s, 3H), 2.88 (q, J = 8.0, 2H), 2.71 (t, J = 8.0 Hz, 2H), 1.70 (t, J = 8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.61, 164.78, 138.37, 129.72, 127.94, 122.65, 121.95, 118.18, 41.25, 39.59, 20.29 ppm. ESI-MS m/z: 264.1 [M + H]+.

N-(3-(2-methyl-2H-tetrazol-5-yl)phenyl)-2-mercaptoacetamide (13h) 36% yield, 98.3% HPLC purity. ^{1}H NMR (600 MHz, Methanol-d4) δ 8.31 (s, 1H), 7.80 (d, J = 6.0 Hz, 1H), 7.68 (d, J = 6.0 Hz, 1H), 7.43 (t, J = 6.0 Hz, 1H), 4.38 (s, 3H), 3.33 (s, 2H) ppm. ^{13}C NMR (150 MHz, Methanol-d4) δ 171.70, 165.92, 140.49, 130.60, 129.22, 123.37, 122.80, 119.07, 39.95, 29.31 ppm. ESI-MS m/z: 250.0 [M + H]+.

(S)-N-(3-(2H-1,2,3-triazol-2-yl)phenyl)-3-mercapto-2-methylpropanamide (13i) 43% yield,

96.3% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.12 (s, 1H), 7.79 – 7.76 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 2.93 – 2.86 (m, 1H), 2.63 – 2.53 (m, 2H), 1.57 (t, J = 8.0 Hz, 1H), 1.27 (d, J = 8.0 Hz, 4H) ppm. 13C NMR (150 MHz, CDCl3) δ 173.30, 140.16, 138.66, 135.59, 129.88, 119.03, 114.69, 110.71, 46.17, 28.04, 17.51 ppm. ESI-MS m/z: 263.1 [M + H]+.

(S)-N-(6-(2H-1,2,3-triazol-2-yl)benzo[d][1,3]dioxol-4-yl)-3-mercapto-2-methyl propanamide (13j) 42% yield, 97.9% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.11 (s, 1H), 7.85 (s, 2H), 7.49 (s, 1H), 6.02 (s, 2H), 2.94 – 2.84 (m, 1H), 2.94 – 2.57 (m, 2H), 1.50 (t, J = 8.0 Hz, 1H), 1.31 (d, J = 8.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.89, 147.49, 144.14, 134.67, 124.77, 122.89, 103.52, 103.13, 102.18, 46.68, 29.82, 28.20, 17.24 ppm. ESI-MS m/z: 307.0 [M + H]+.

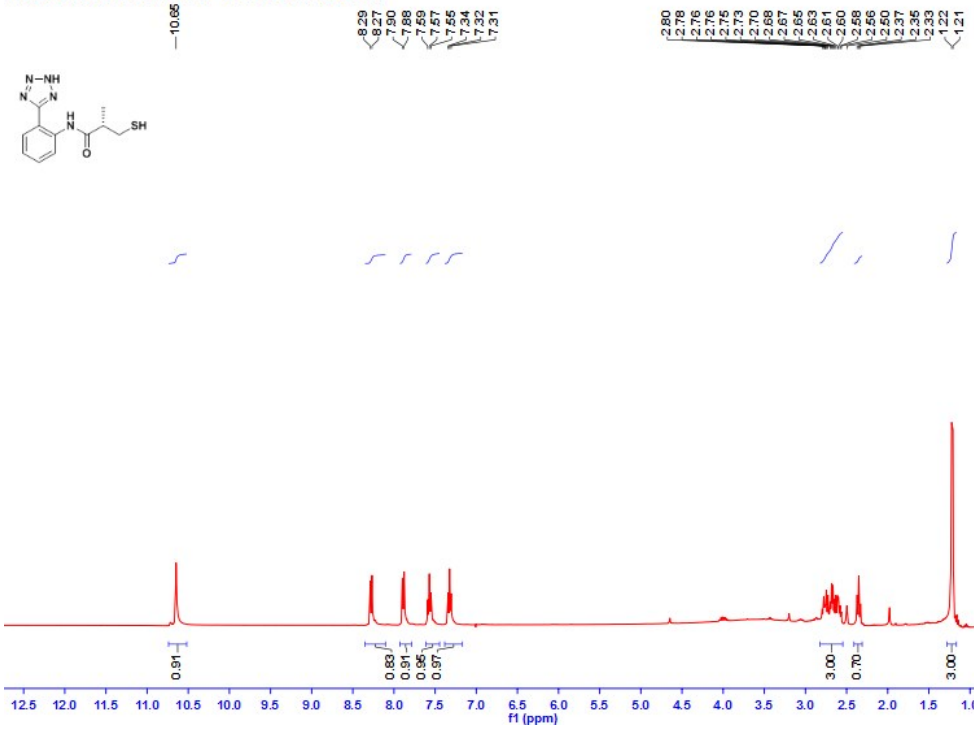
(S)-3-mercapto-N-(2-methoxy-5-(6-methoxypyridazin-3-yl)phenyl)-2-methylpropanamide (13k) 37% yield, 98.1% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 – 8.93 (m, 1H), 8.03 (dd, J = 8.0, 4.0 Hz, 1H), 7.97 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 4.16 (s, 3H), 3.96 (s, 3H), 2.99 – 2.90 (m, 1H), 2.66 – 2.60 (m, 2H), 1.60 (t, J = 8.0 Hz, 1H), 1.35 (d, J = 8.0 Hz, 3H) ppm. 13C NMR (150 MHz, CDCl3) δ 172.88, 164.12, 154.56, 149.12, 148.98, 127.79, 127.73, 123.03, 118.61, 117.86, 110.66, 56.03, 55.01, 46.60, 28.11, 17.62 ppm. ESI-MS m/z: 334.1 [M + H]+.

N-(3-(2H-tetrazol-5-yl)phenyl)isobutyramide (14) 52% yield, 98.5% HPLC purity. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 2.65 – 2.58 (m, 1H), 1.16 (d, J = 8.0 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d6) δ 175.18, 154.41, 137.25, 131.76, 128.73, 123.85, 121.96, 113.41, 36.02, 19.29 ppm. ESI-MS m/z: 232.1 [M + H]+.

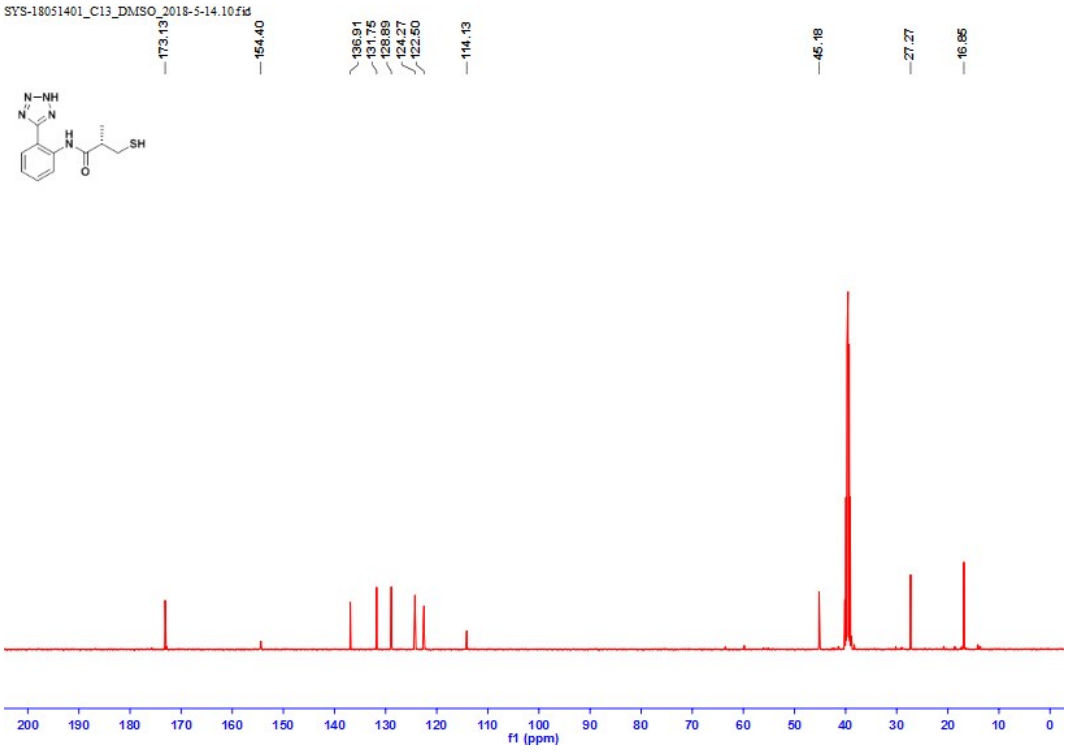
Spectral Data

^{1}H and ^{13}C NMR Spectra of Compound **7a**

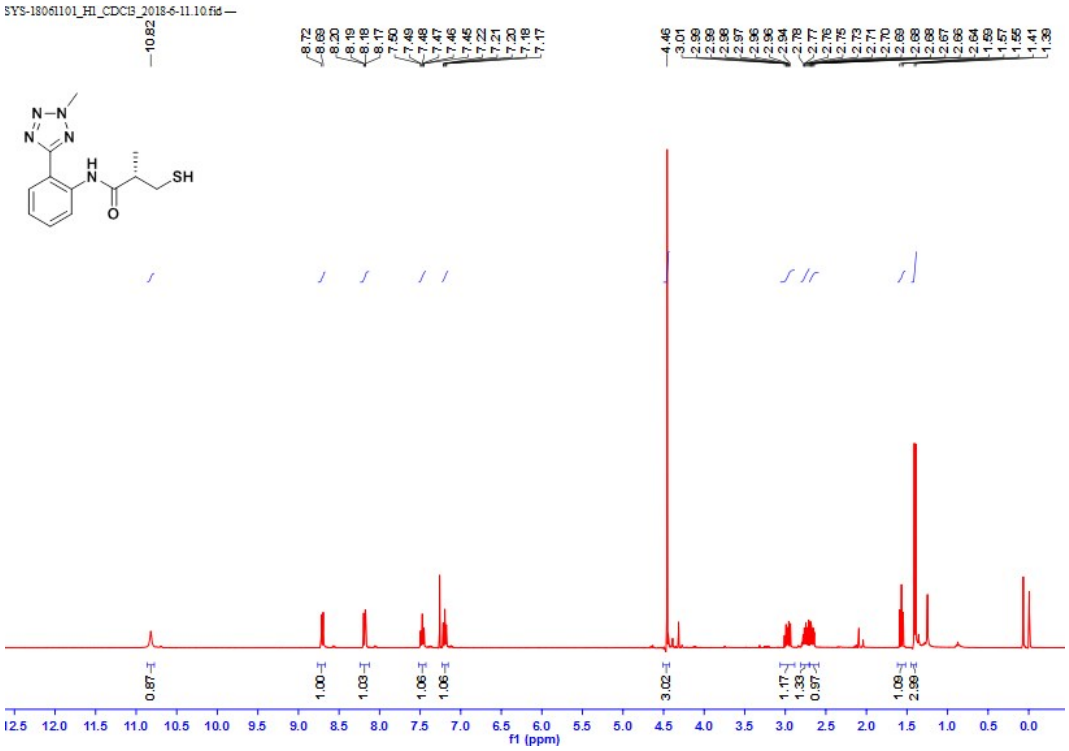
SYS-18051401-DMSO-H1-2018-5-14 — SYS-18051401-H1-2018-5-14 —

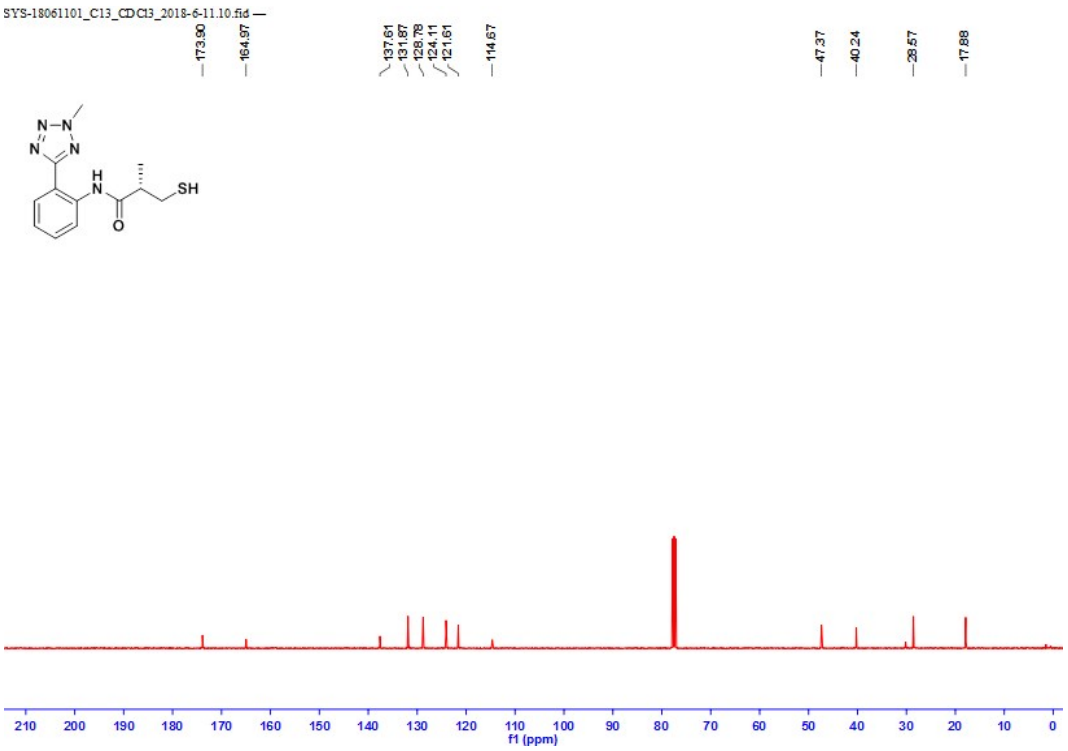


SYS-18051401_C13_DMSO_2018-5-14.10.fid

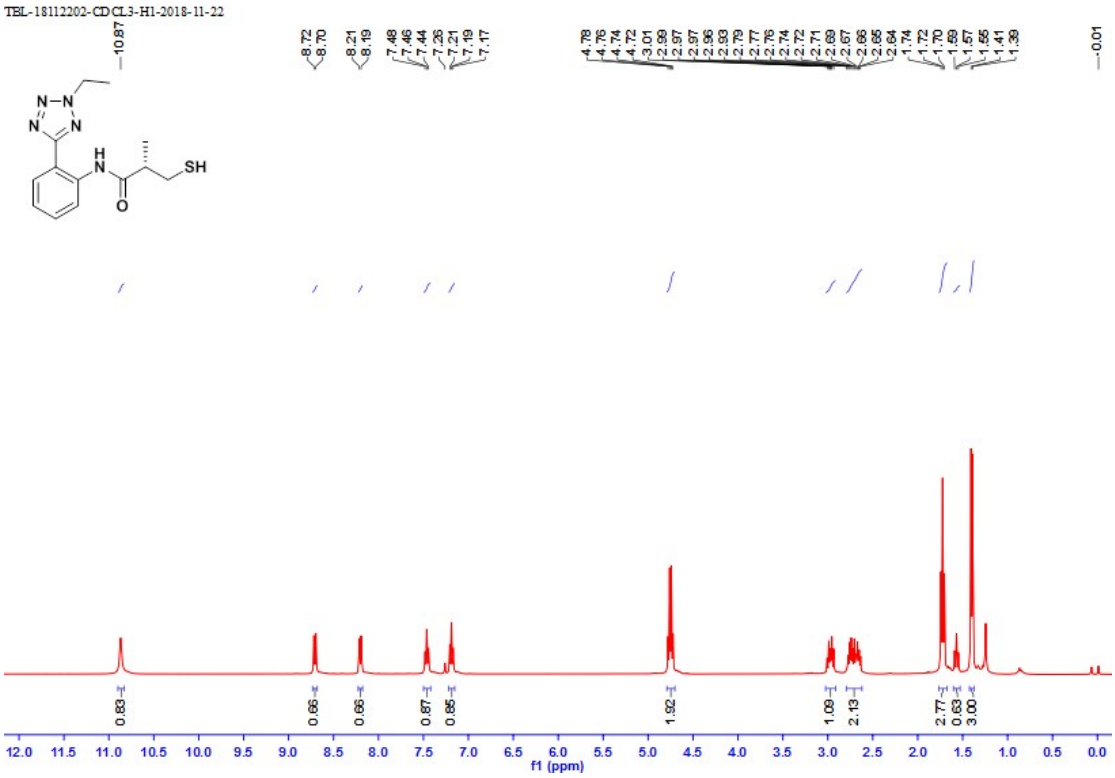


^{1}H and ^{13}C NMR Spectra of Compound **7b**

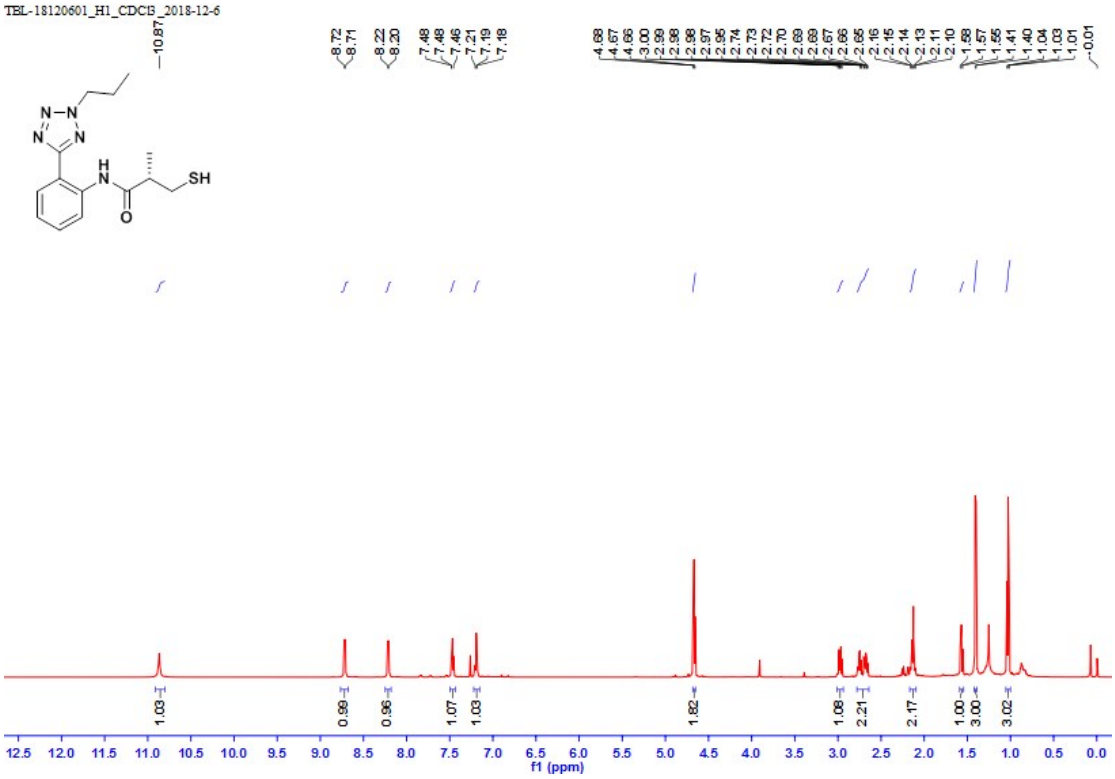


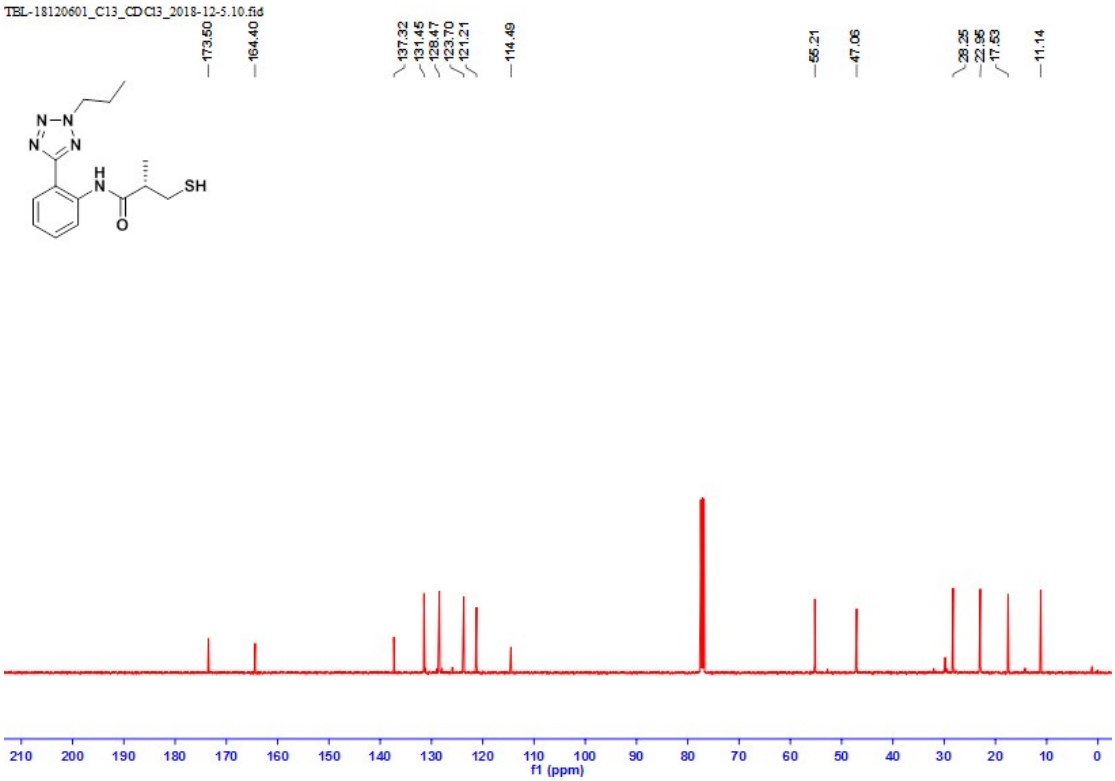


^{1}H Spectra of Compound **7c**


TBL-18112202-CDCL3-H1-2018-11-22
10.87
8.72
8.70
8.21
8.19
7.48
7.46
7.44
7.25
7.21
7.19
7.17
4.78
4.76
4.74
4.72
3.01
2.99
2.97
2.96
2.93
2.79
2.77
2.76
2.74
2.72
2.71
2.69
2.67
2.66
2.65
2.64
1.74
1.72
1.70
1.69
1.67
1.55
1.41
1.39
0.01
SH
0.83
0.66
0.66
0.87
0.85
1.92
1.09
2.13
2.77
0.63
3.00
f1 (ppm)

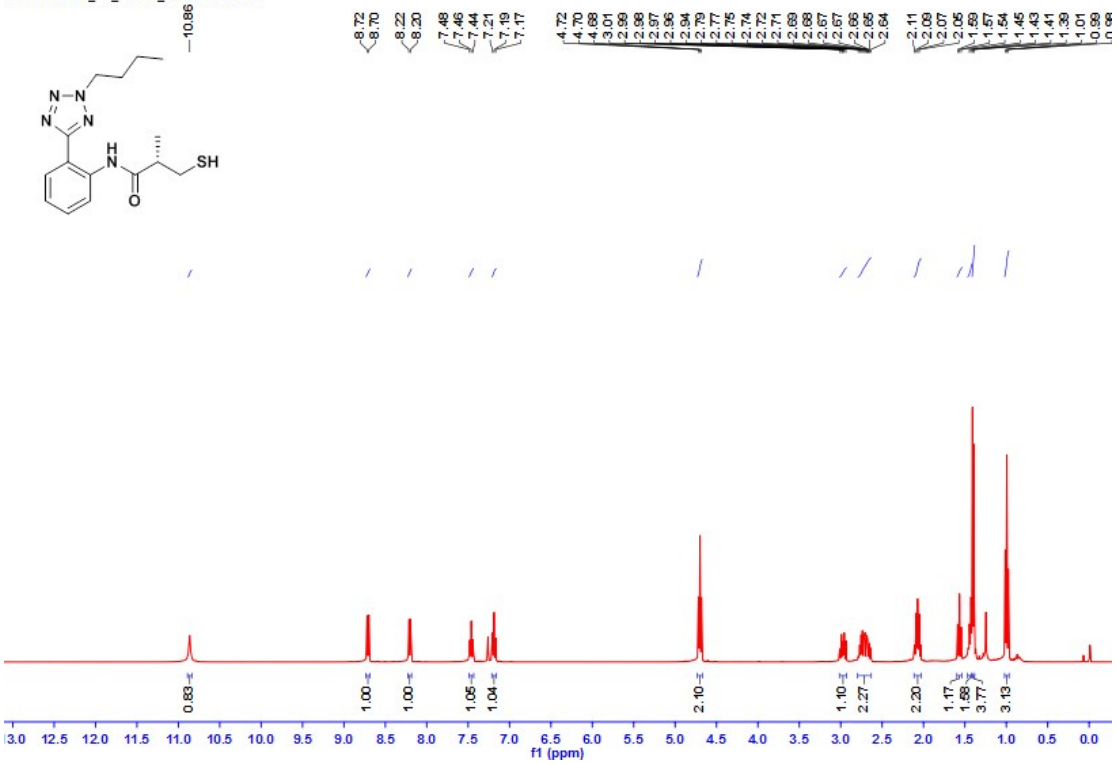
^{1}H and ^{13}C NMR Spectra of Compound **7d**



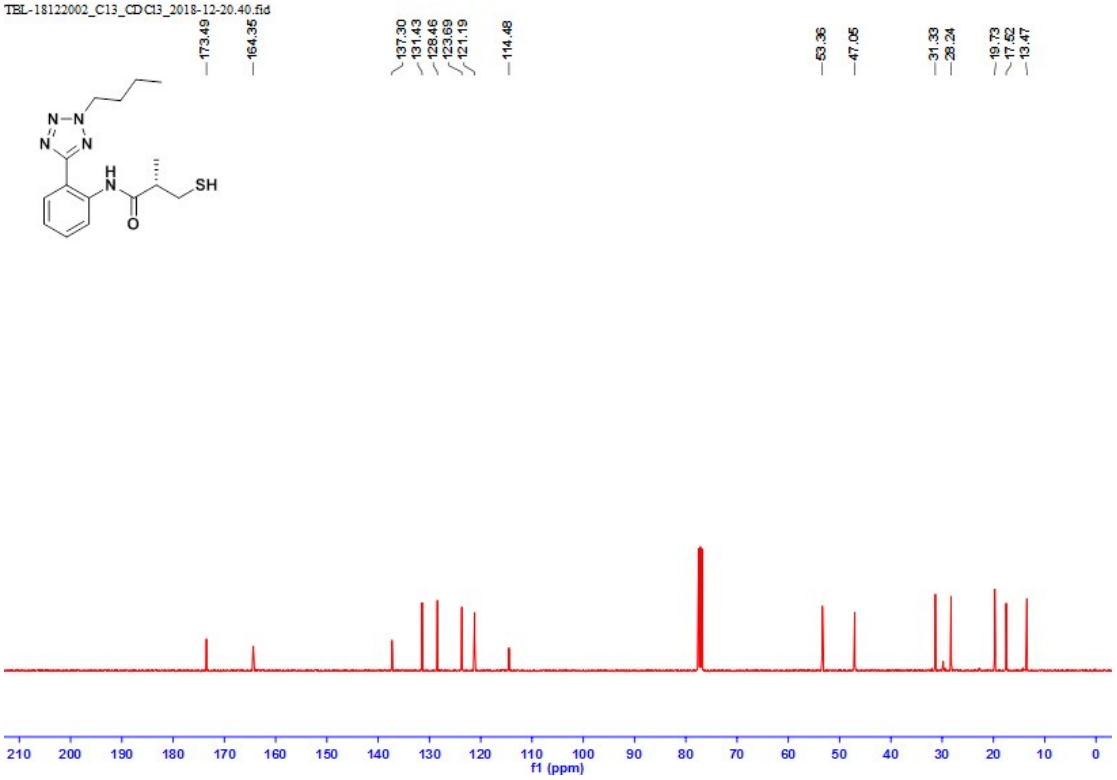


^{1}H and ^{13}C NMR Spectra of Compound **7e**

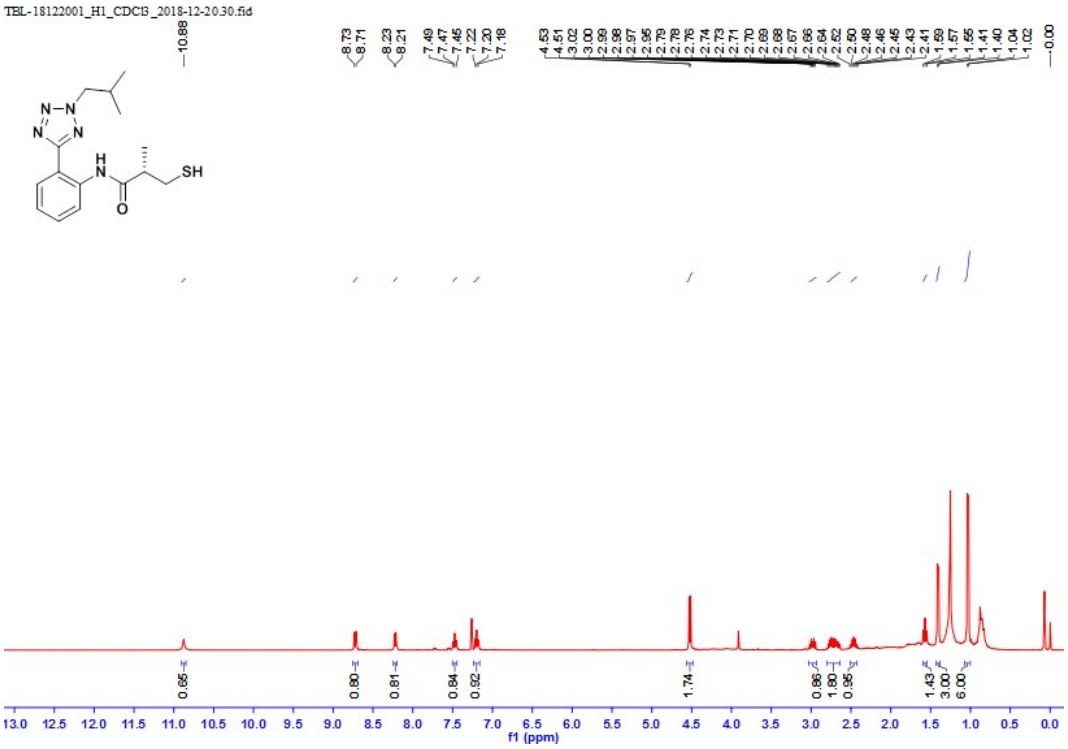
TBL-18122002_H1_CDCl3_2018-12-20.40.fid

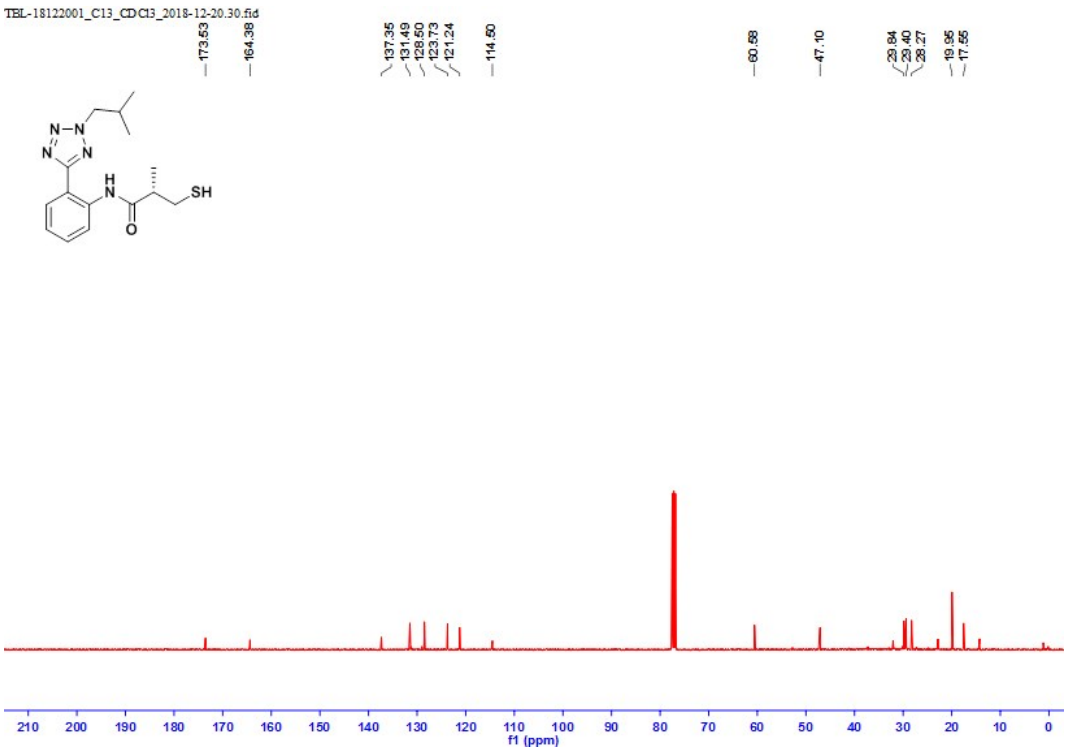


TBL-18122002_C13_CDCl3_2018-12-20.40.fid

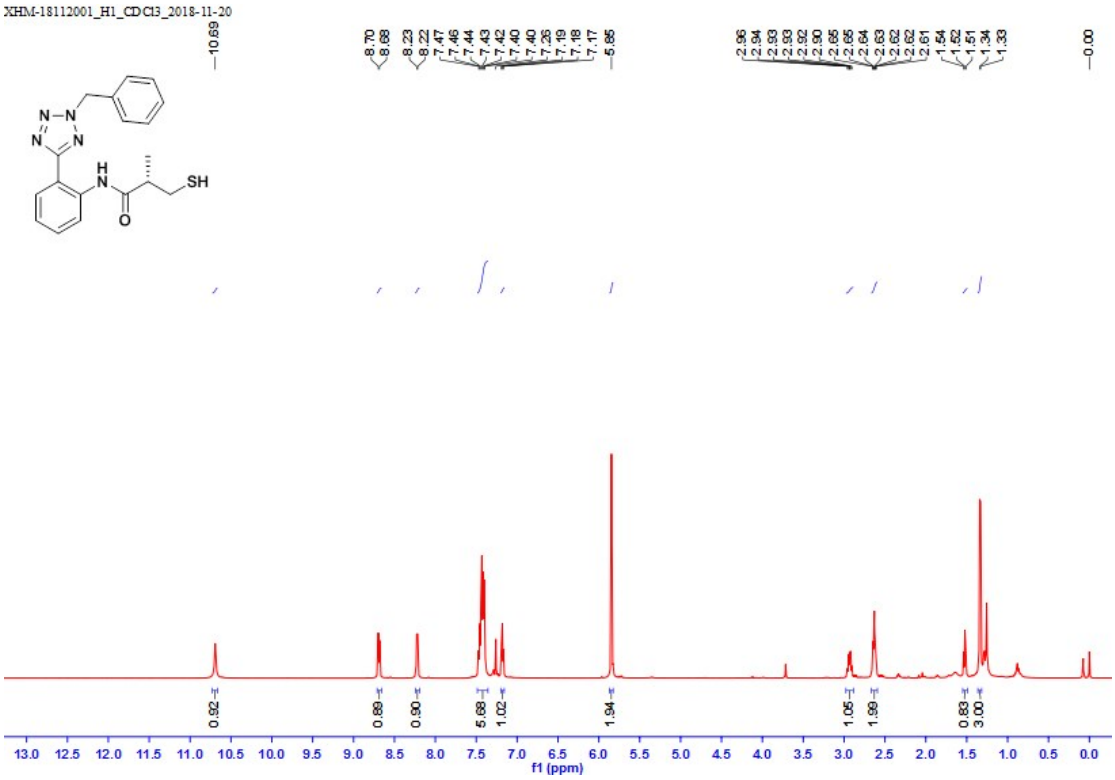


^{1}H and ^{13}C NMR Spectra of Compound **7f**





^{1}H and ^{13}C NMR Spectra of Compound **7g**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8.68
8.23
8.22
7.47
7.46
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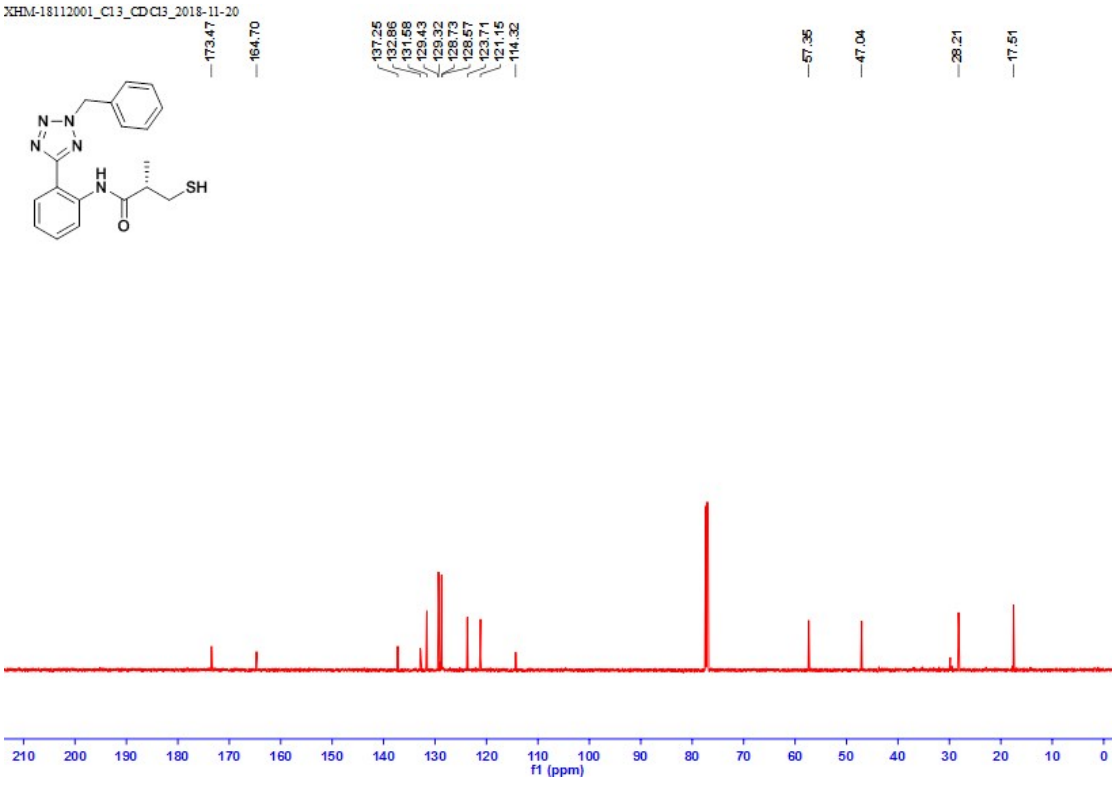
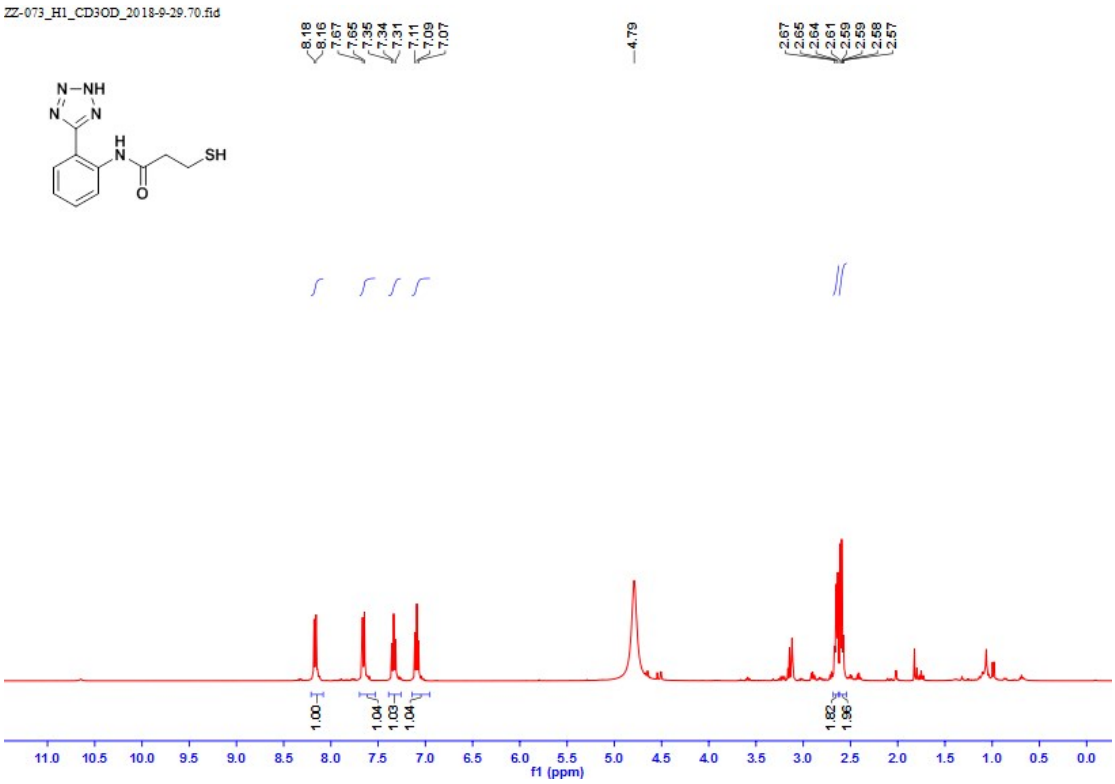
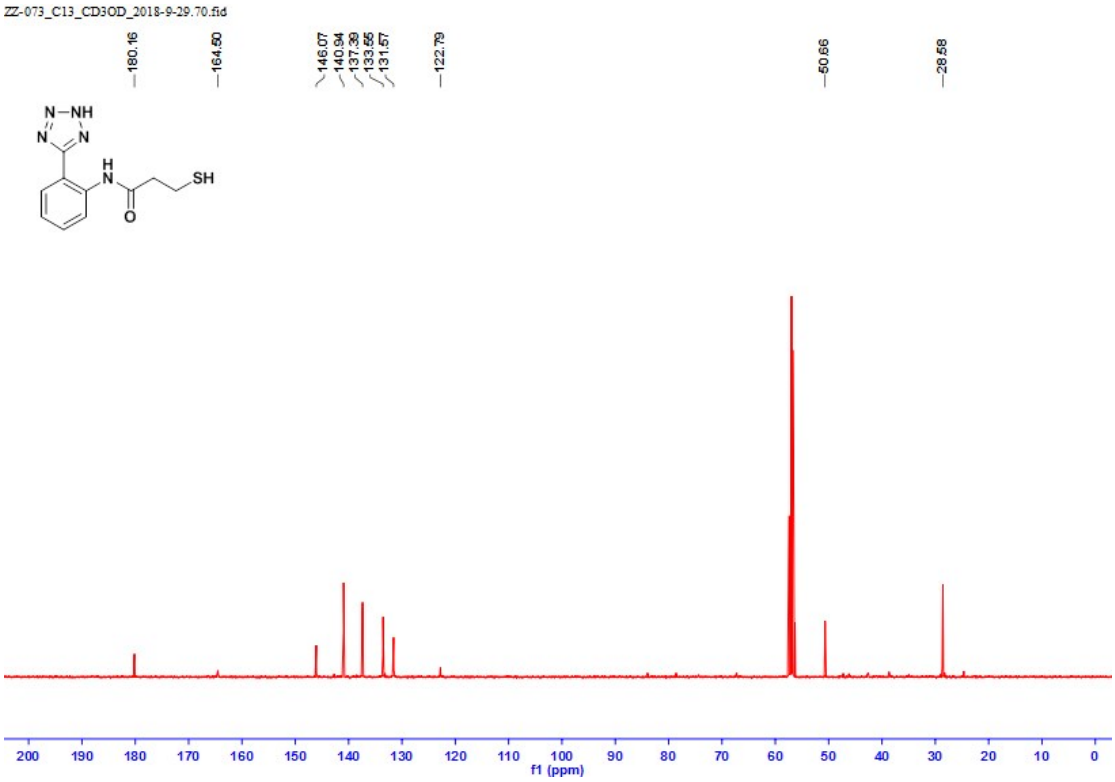
7.42
7.40
7.26
7.19
7.18
7.17
5.86
2.96
2.94
2.93
2.93
2.92
2.90
2.65
2.64
2.63
2.62
2.62
2.61
1.54
1.52
1.51
1.34
1.33
0.00
SH
0.92
0.89
0.90
5.68
1.02
1.94
1.05
1.99
0.83
3.00
f1 (ppm)

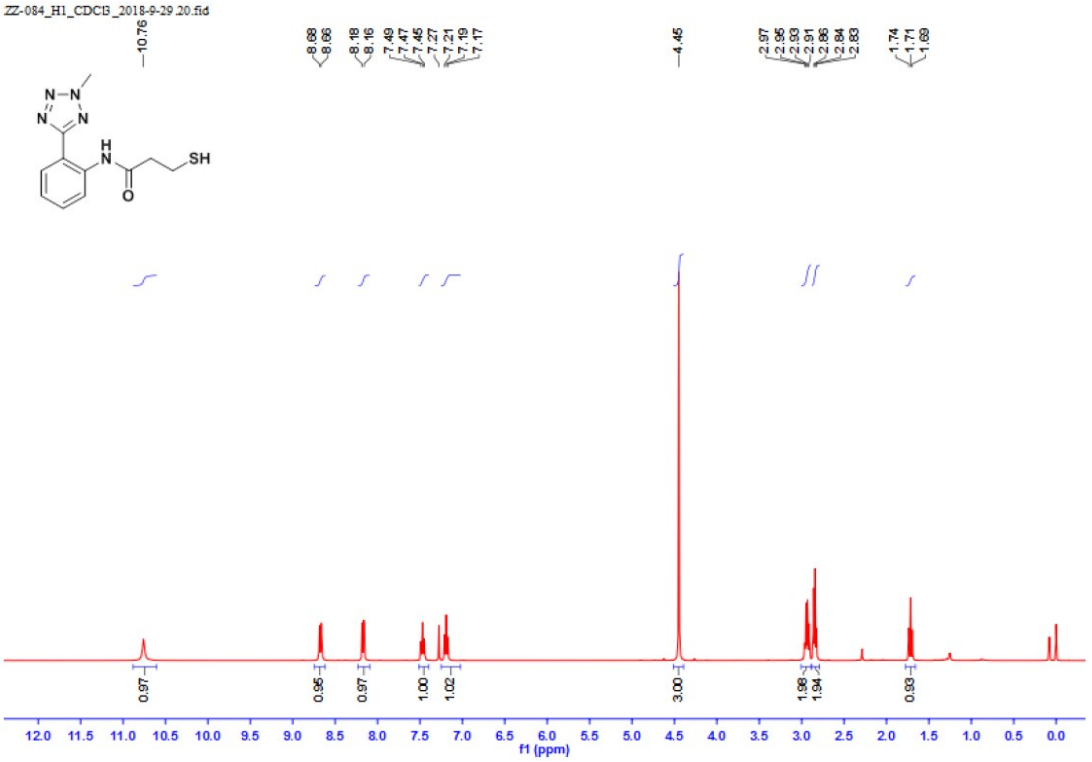

XHM-18112001_C13_CDCl3_2018-11-20
173.47
164.70
137.25
132.86
131.58
129.43
129.32
128.73
128.57
123.71
121.15
114.32
57.35
47.04
28.21
17.51
SH
f1 (ppm)

^{1}H and ^{13}C NMR Spectra of Compound **7h**





^{1}H and ^{13}C NMR Spectra of Compound **7i**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10.76
8.68
8.66
8.18
8.16
7.49
7.47
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7.19
7.17
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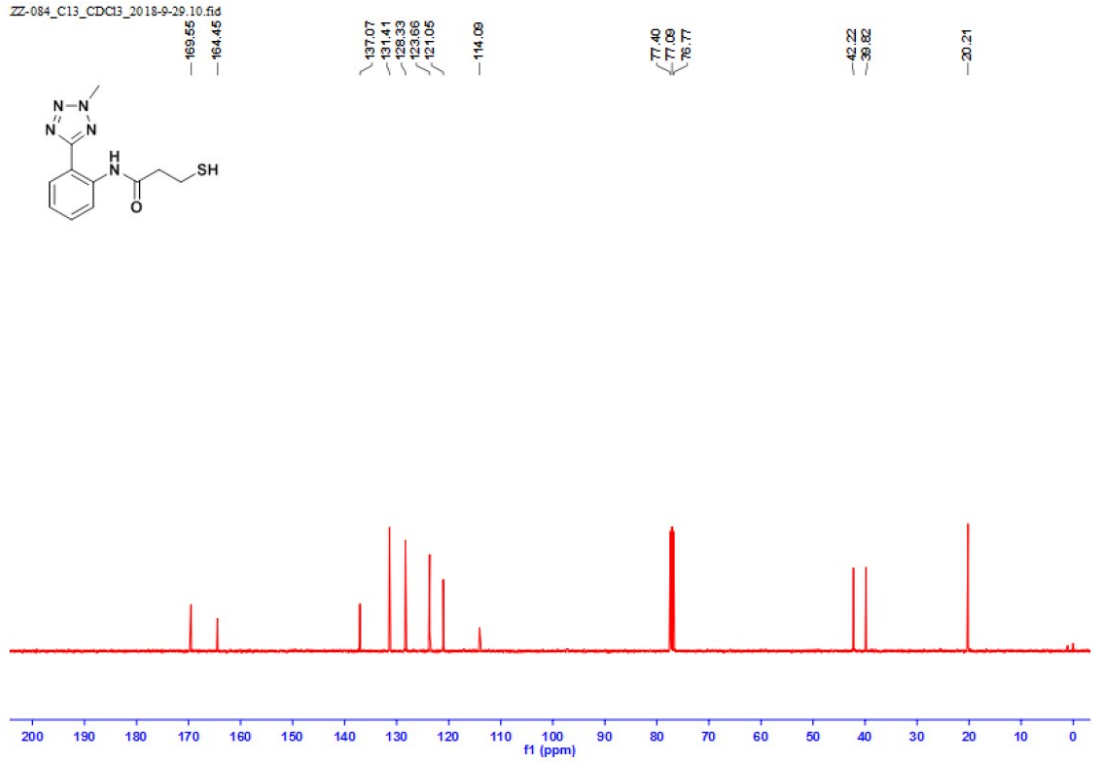
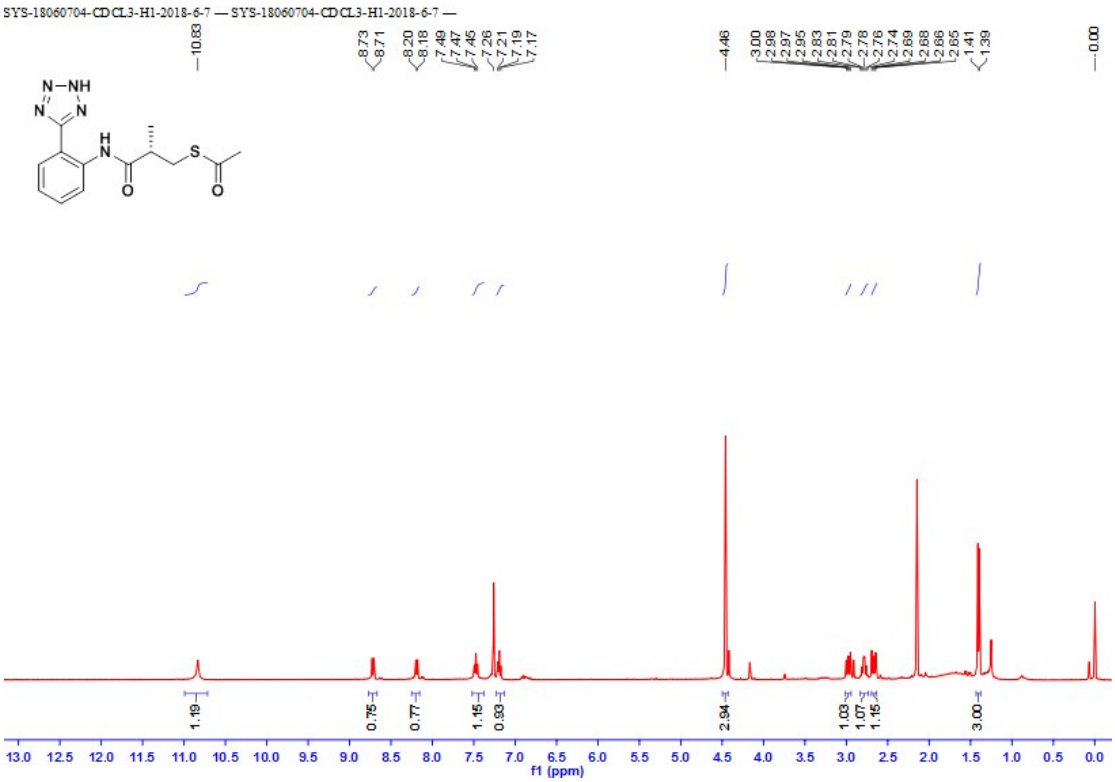
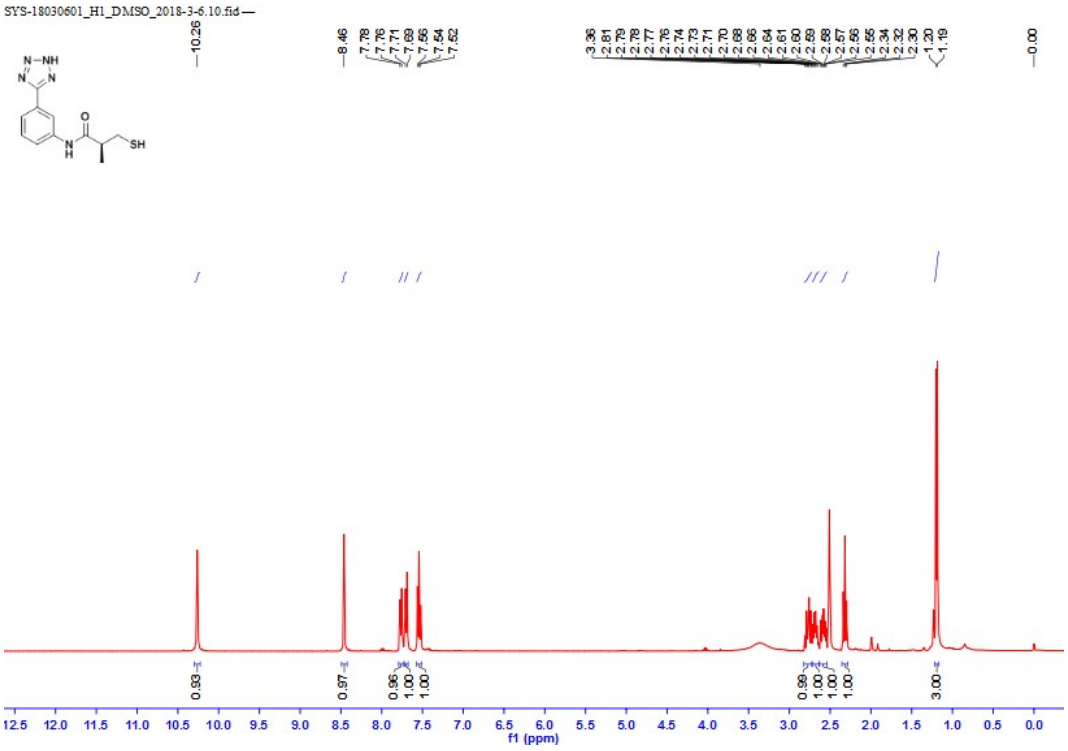
2.97
2.95
2.93
2.91
2.86
2.84
2.83
1.74
1.71
1.69
SH
0.97
0.95
0.97
1.00
1.02
3.00
1.98
1.94
0.93
f1 (ppm)

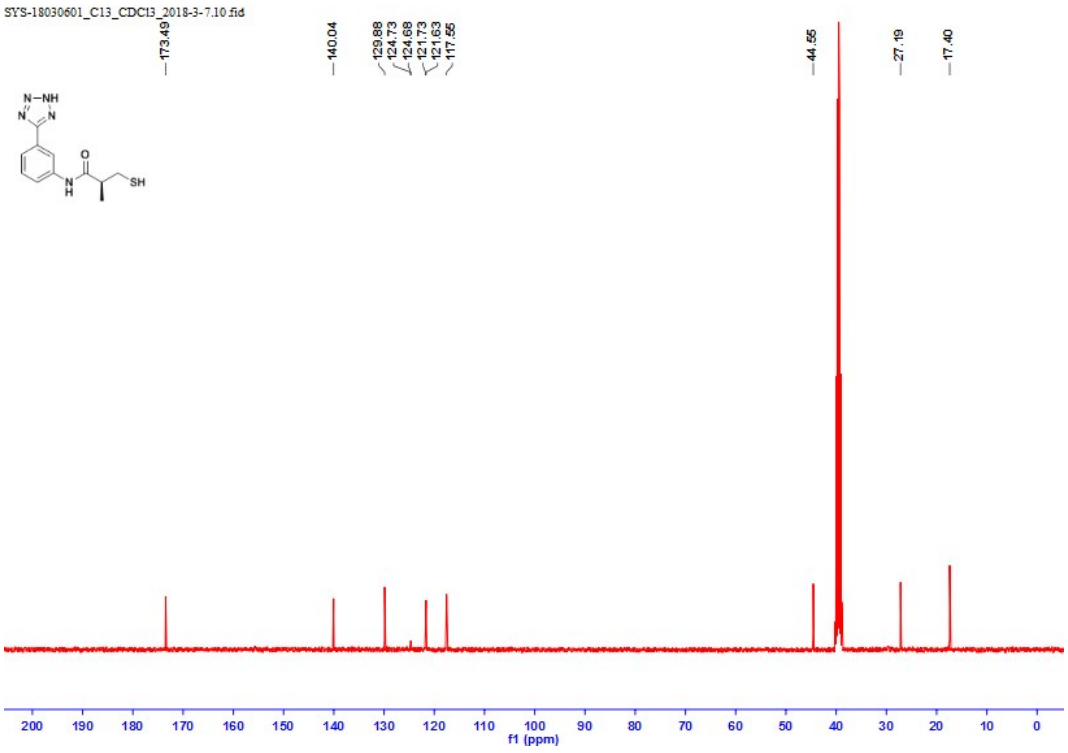

ZZ-084_C13_CDCl3_2018-9-29 10.fid
169.55
164.45
137.07
131.41
128.33
123.66
121.05
114.09
77.40
77.09
76.77
42.22
39.82
20.21
SH
f1 (ppm)

^{1}H Spectra of Compound **6a**

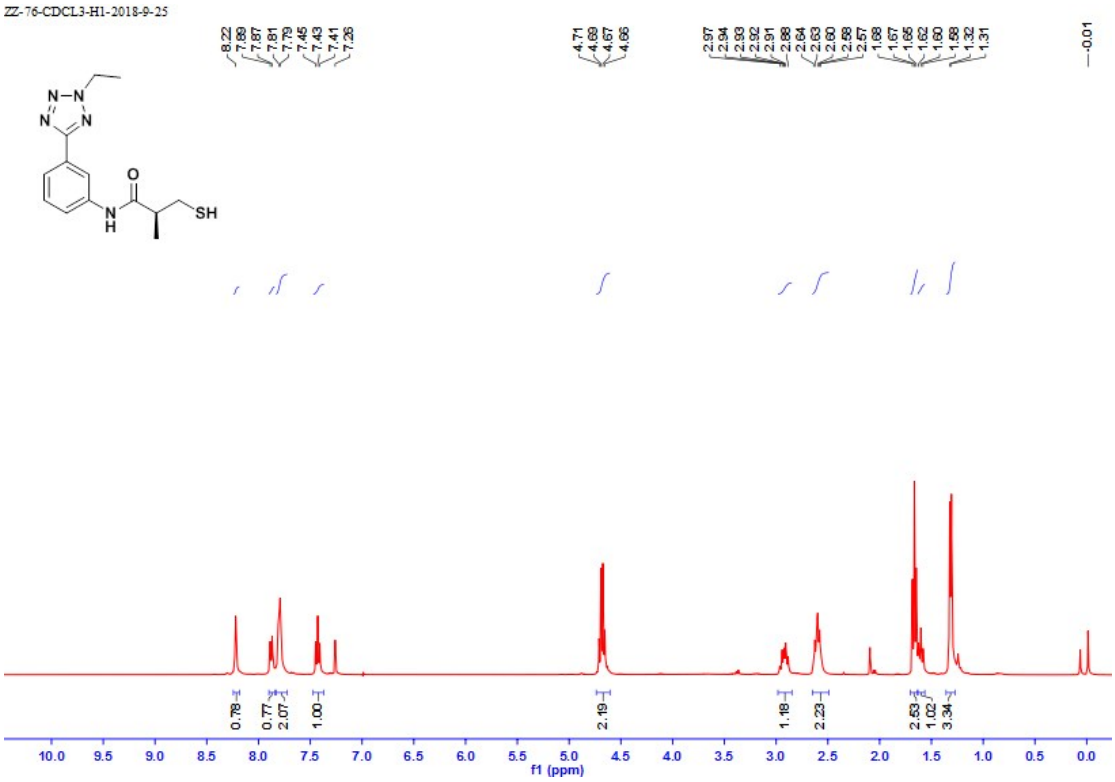


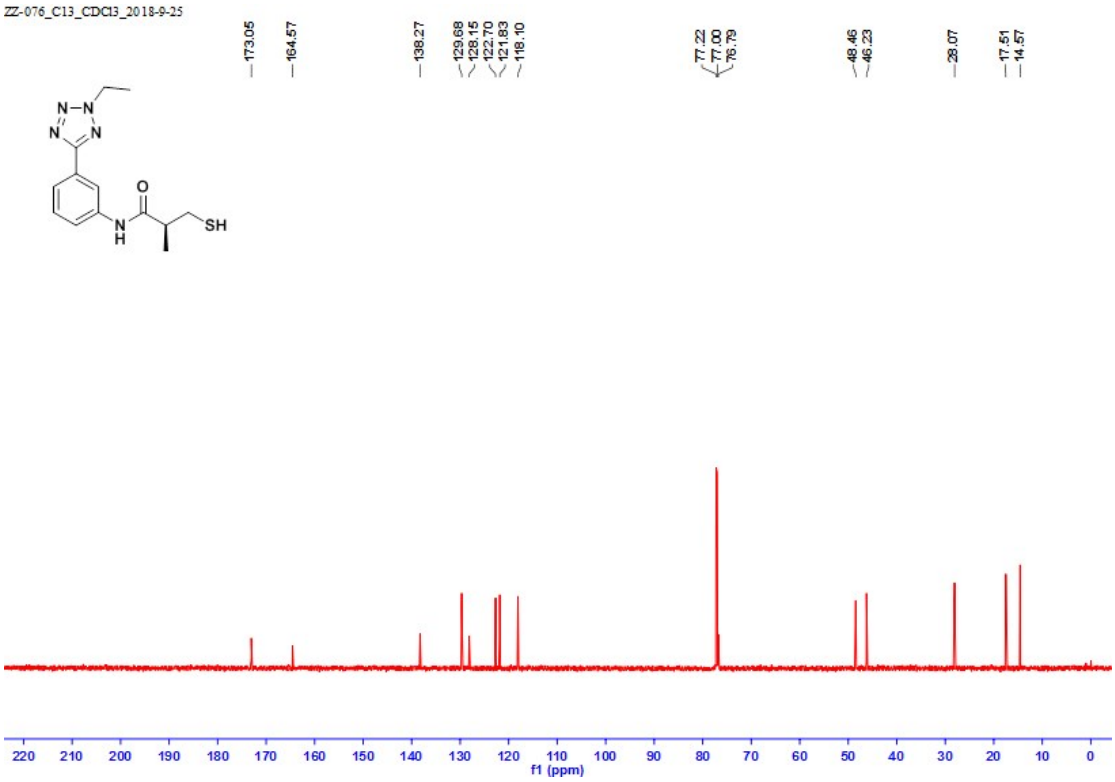
^{1}H and ^{13}C NMR Spectra of Compound **13a**





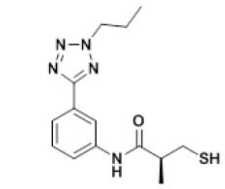
^{1}H and ^{13}C NMR Spectra of Compound **13b**



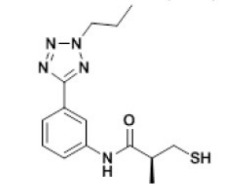


^{1}H and ^{13}C NMR Spectra of Compound **13c**

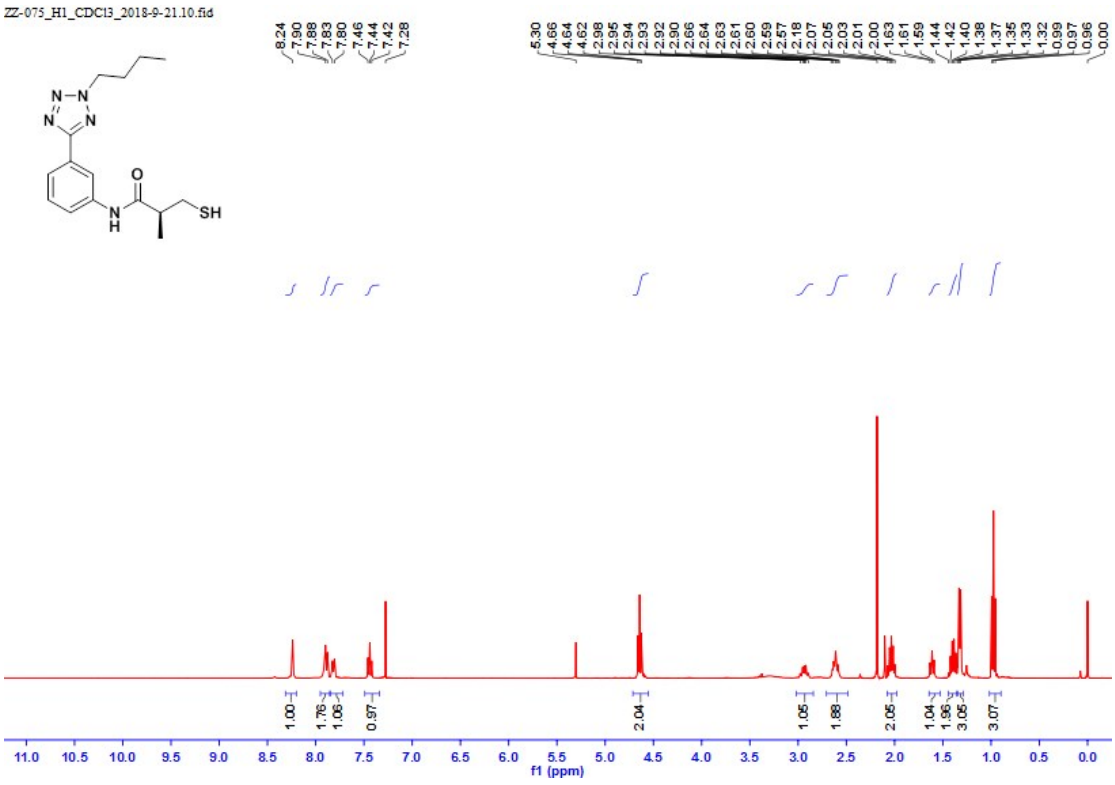
ZZ-077-CDCL3-H1-2018-9-20

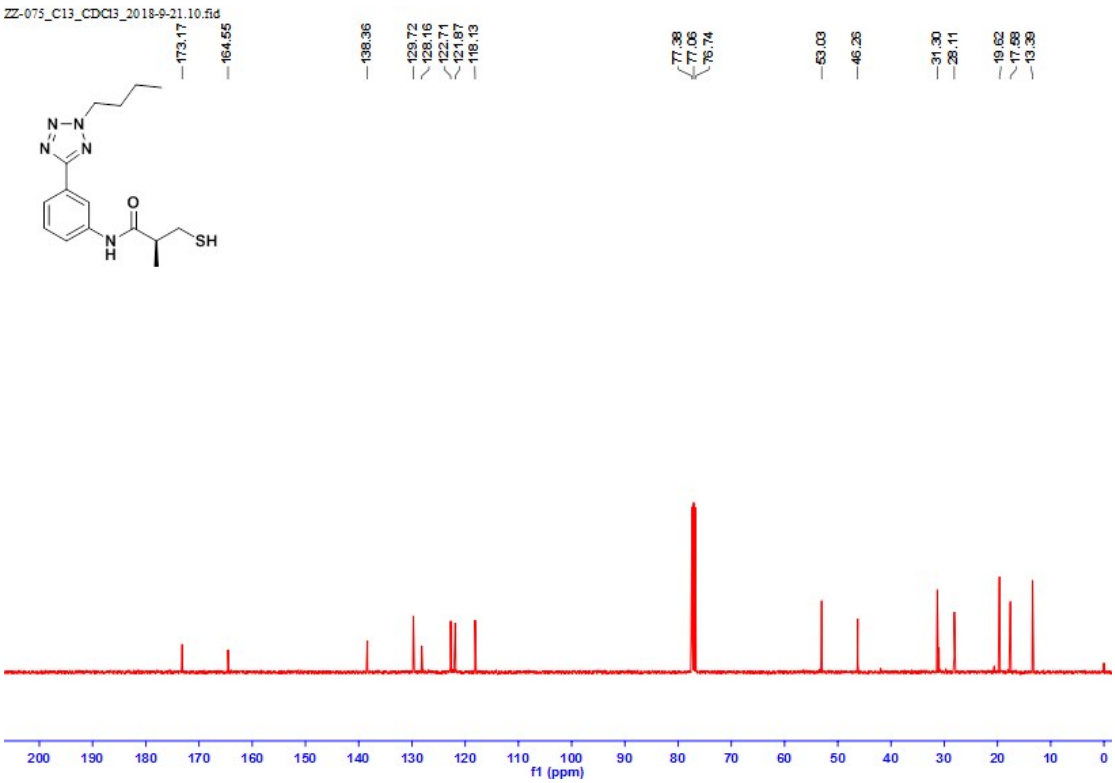


ZZ-077-CDCL3-C13-2018-9-21.10.fid

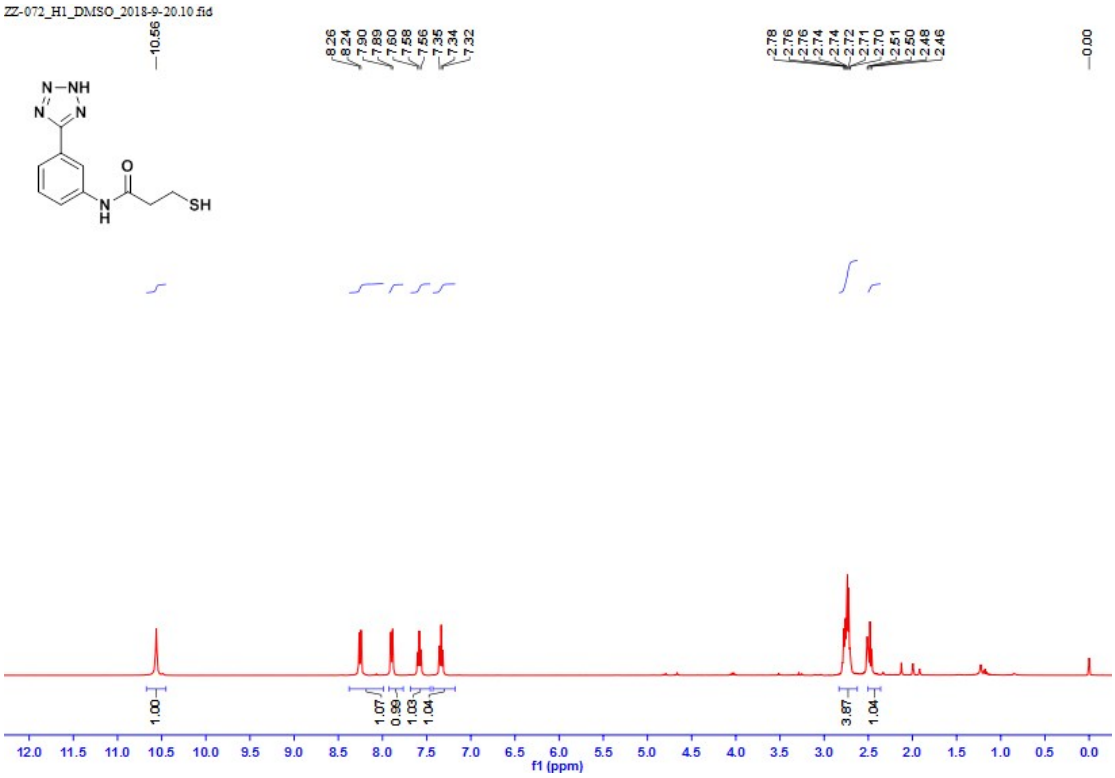


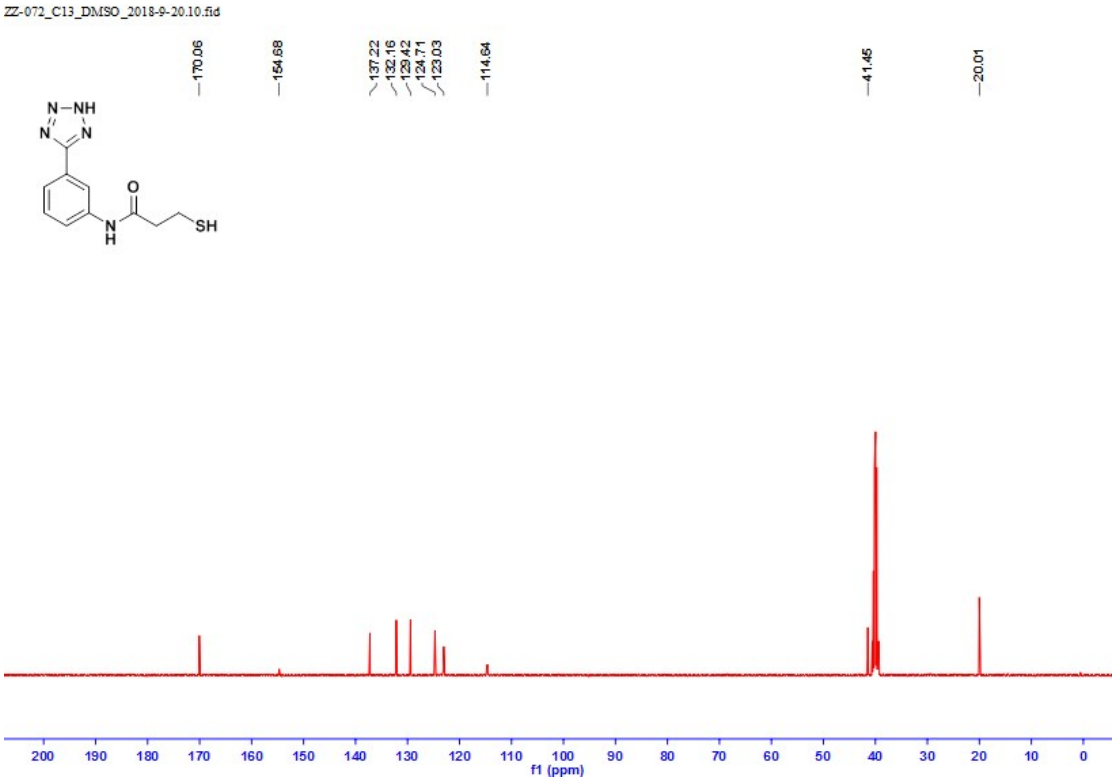
^{1}H and ^{13}C NMR Spectra of Compound **13d**



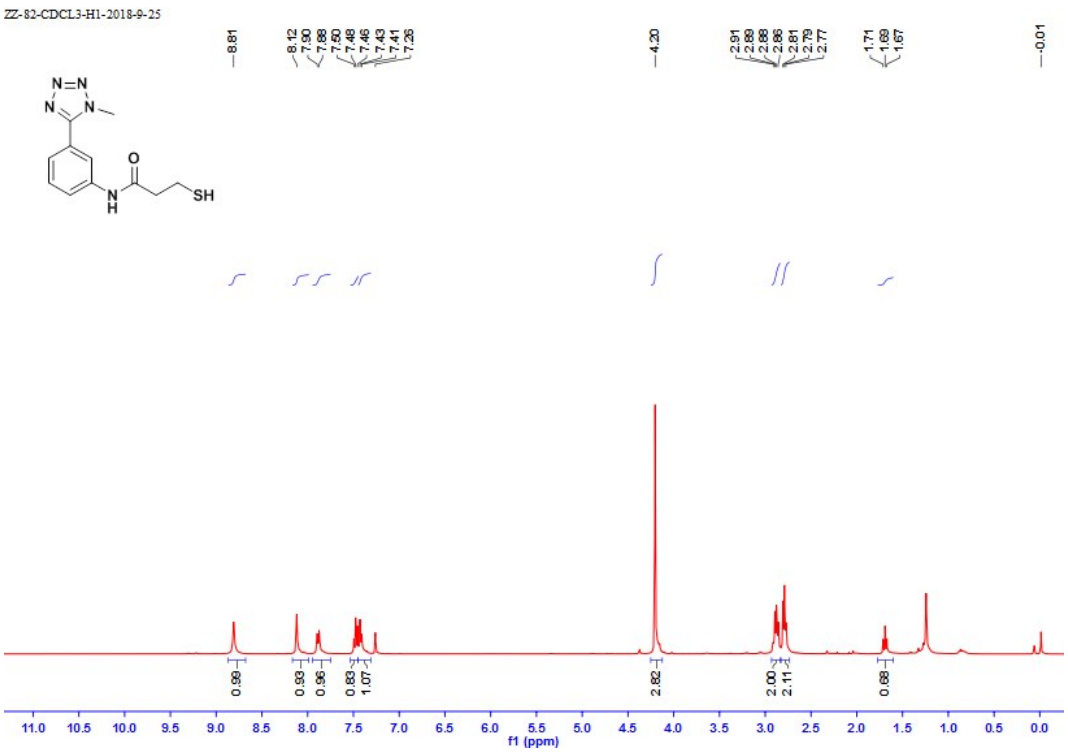


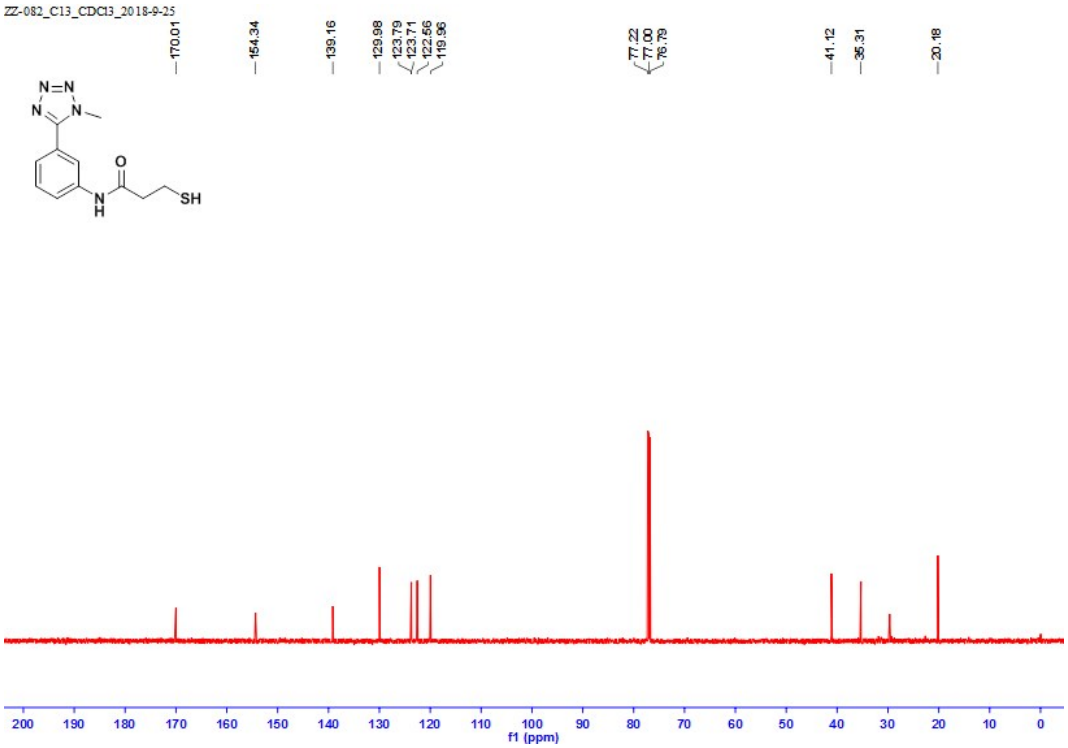
^{1}H and ^{13}C NMR Spectra of Compound **13e**


ZZ-072_H1_DMSO_2018-9-20.10.fid
10.56
8.26
8.24
7.90
7.89
7.60
7.58
7.56
7.35
7.34
7.32
2.78
2.76
2.76
2.74
2.74
2.72
2.71
2.70
2.51
2.50
2.48
2.46
0.00
N–NH
N
N
O
N
H
SH
1.00
1.07
0.99
1.03
1.04
3.87
1.04
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)

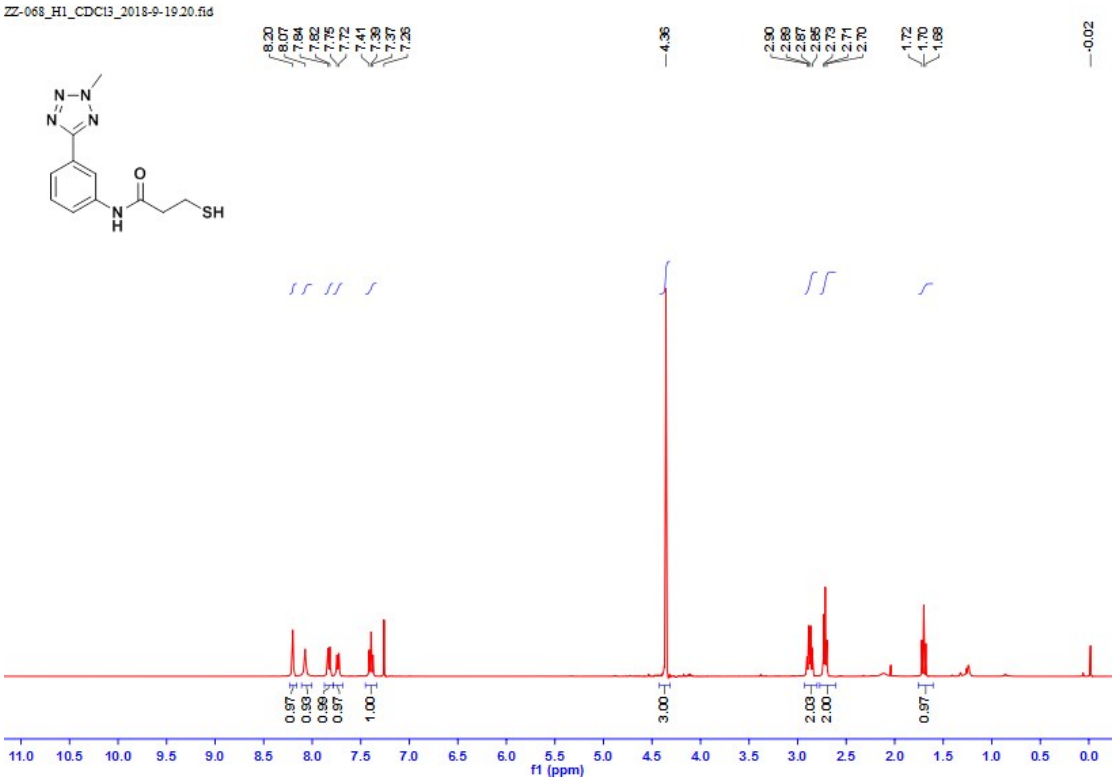


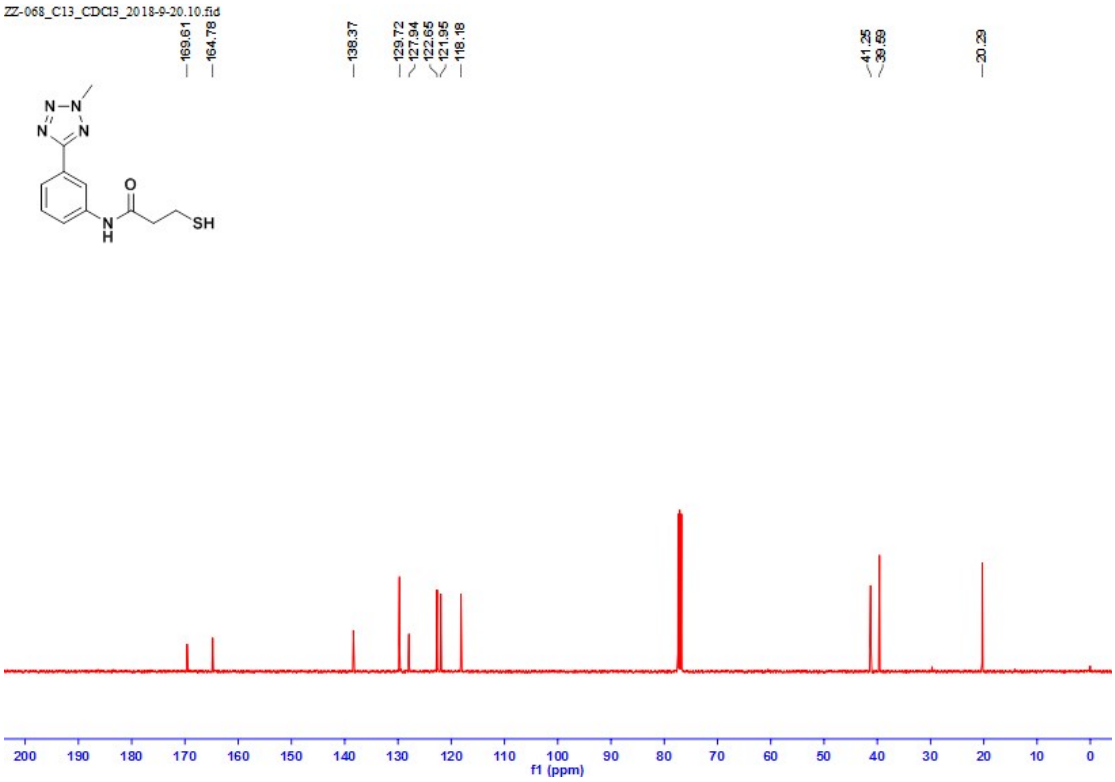
^{1}H and ^{13}C NMR Spectra of Compound **13f**



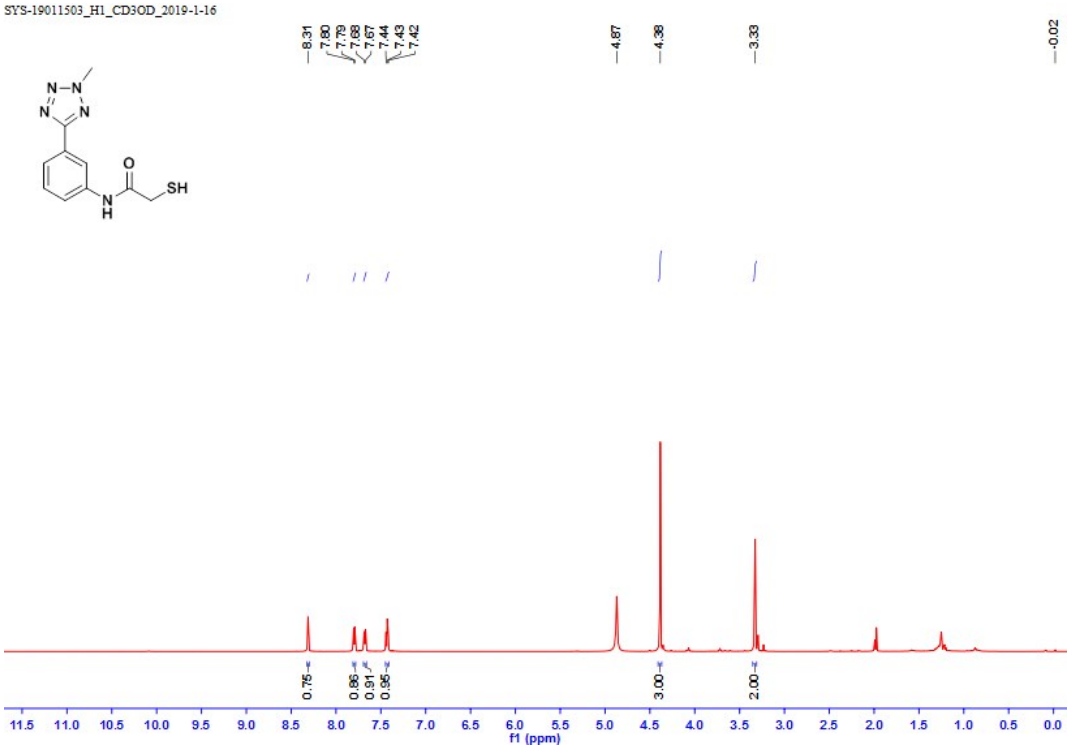


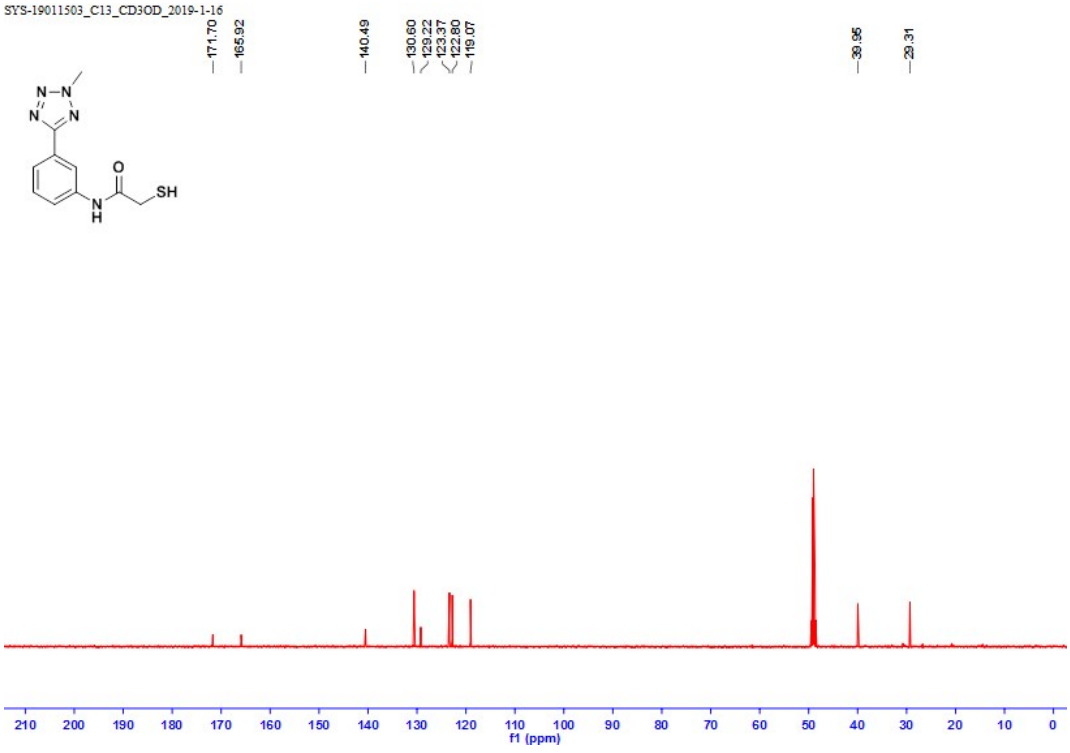
^{1}H and ^{13}C NMR Spectra of Compound **13g**


ZZ-068_H1_CDCl3_2018-9-19.20.fid
8.20
8.07
7.84
7.82
7.75
7.72
7.41
7.39
7.37
7.26
4.36
2.90
2.89
2.87
2.86
2.73
2.71
2.70
1.72
1.70
1.68
-0.02
0.97
0.93
0.98
0.97
1.00
3.00
2.03
2.00
0.97
f1 (ppm)


ZZ-068_C13_CDCl3_2018-9-20.10.fid
169.61
164.78
138.37
129.72
127.94
122.65
121.95
118.18
41.25
39.69
20.29
f1 (ppm)

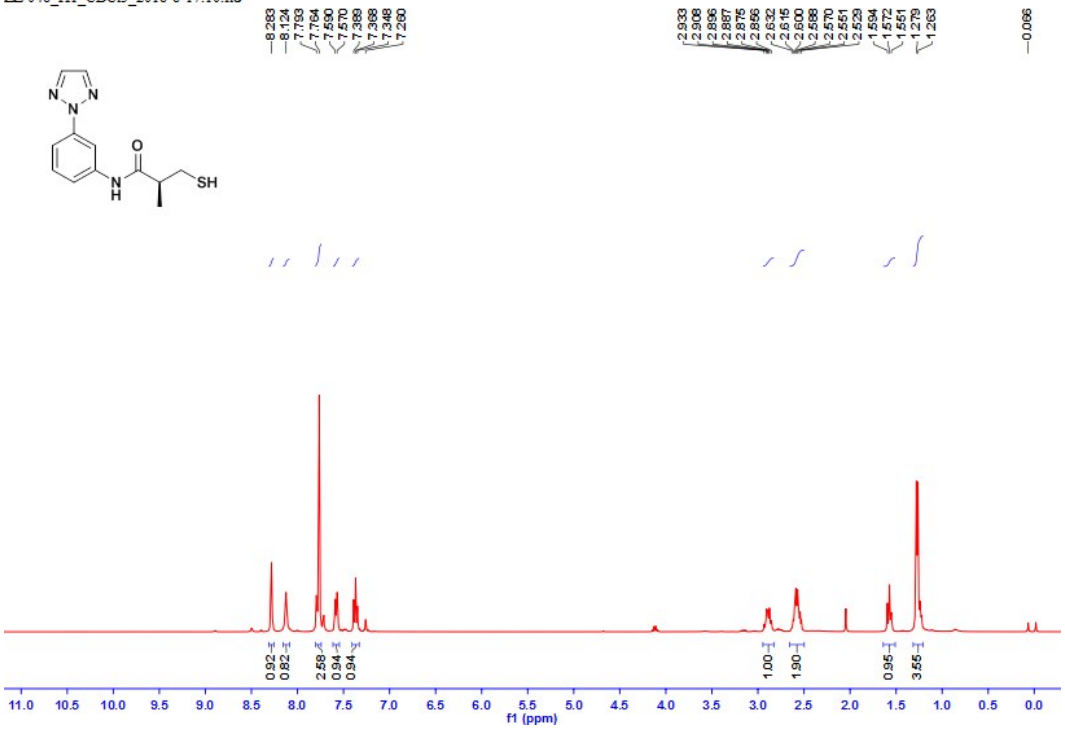
^{1}H and ^{13}C NMR Spectra of Compound **13h**



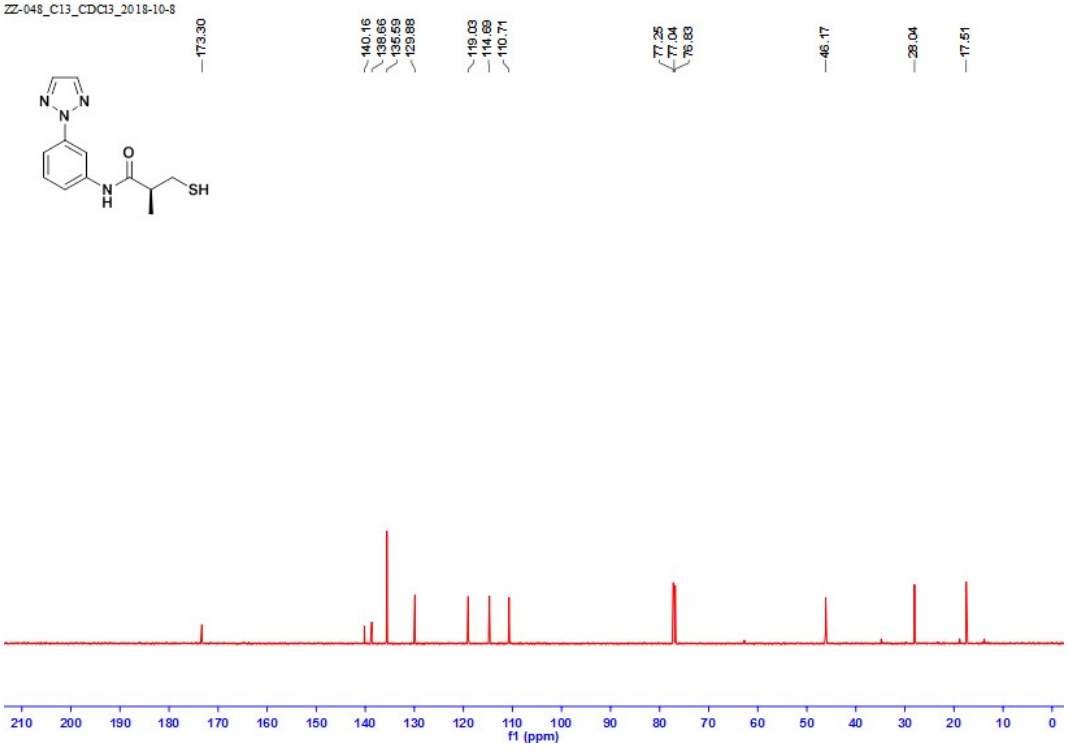


^{1}H and ^{13}C NMR Spectra of Compound **13i**

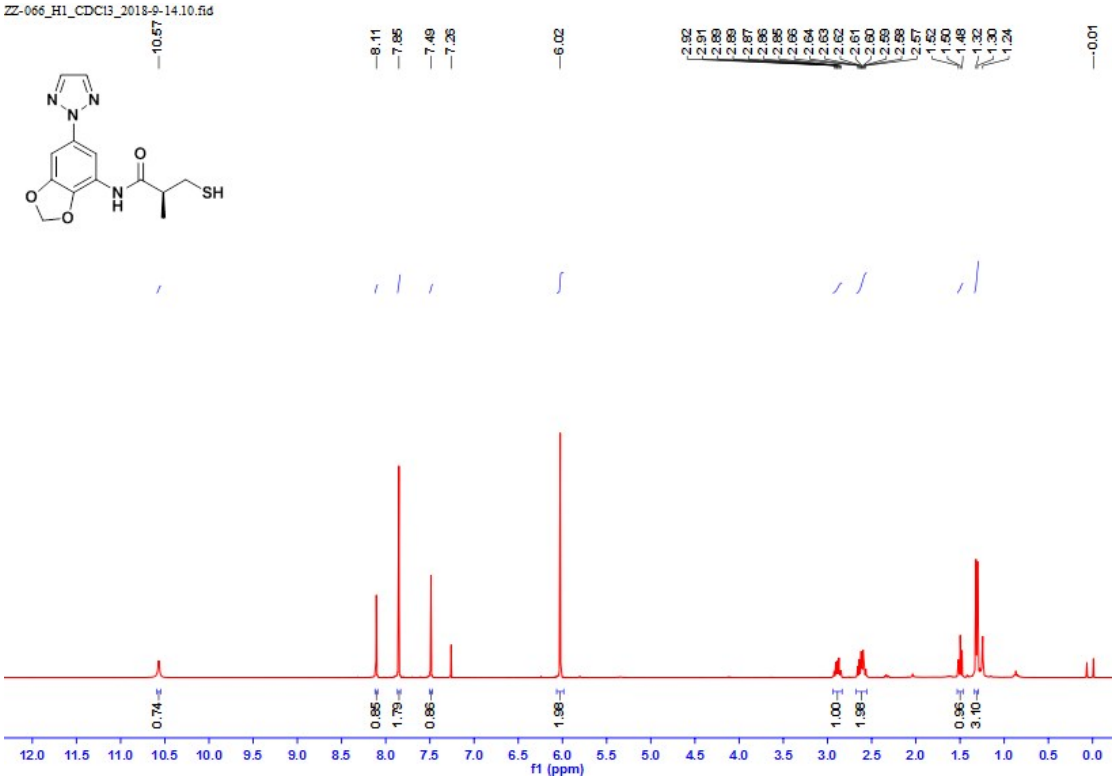
ZZ-048_H1_CDCl3_2018-8-17.10.fid

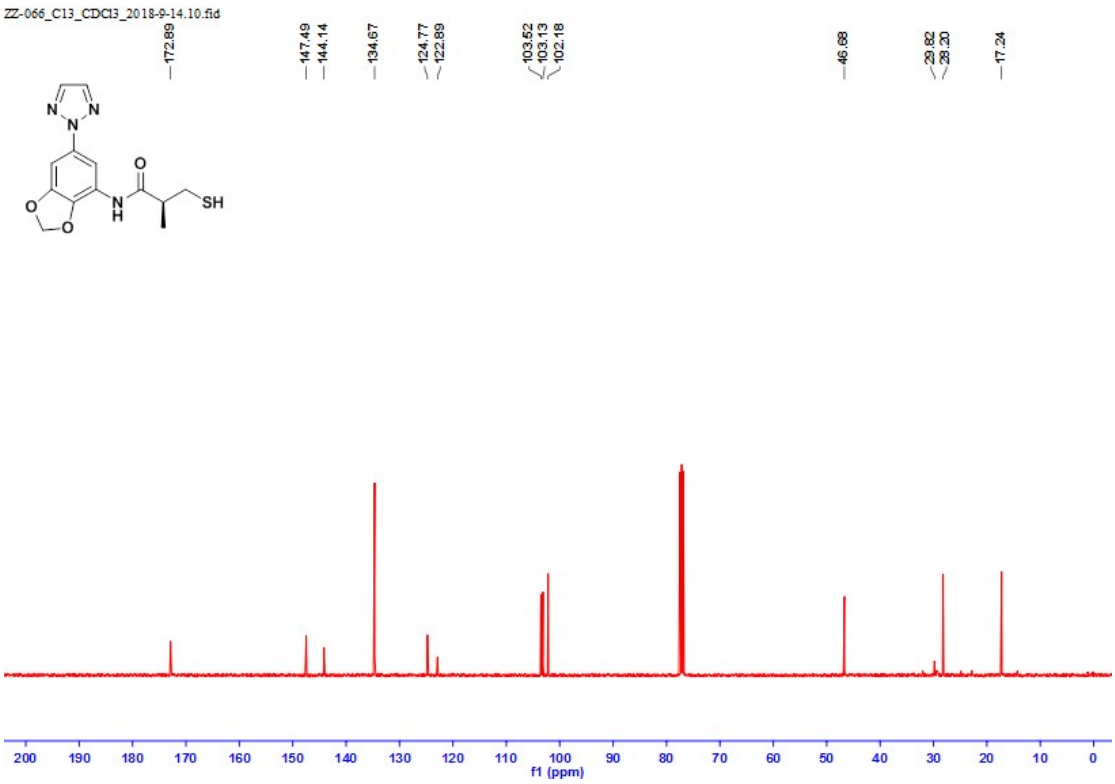


ZZ-048_C13_CDCl3_2018-10-8

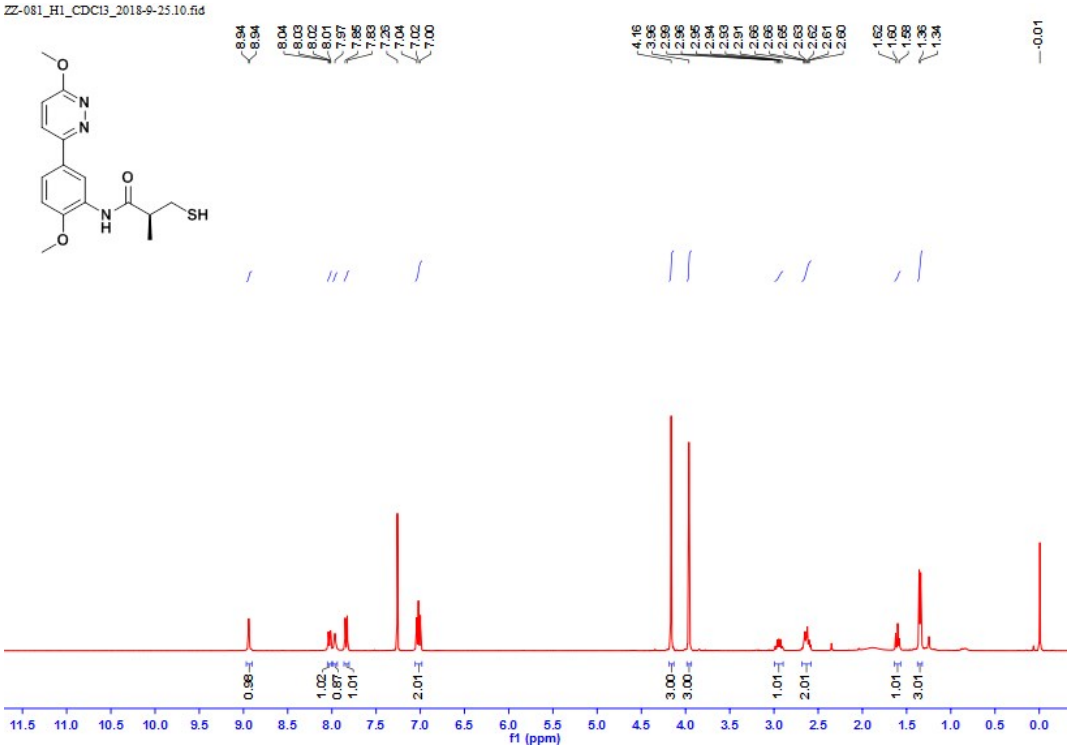


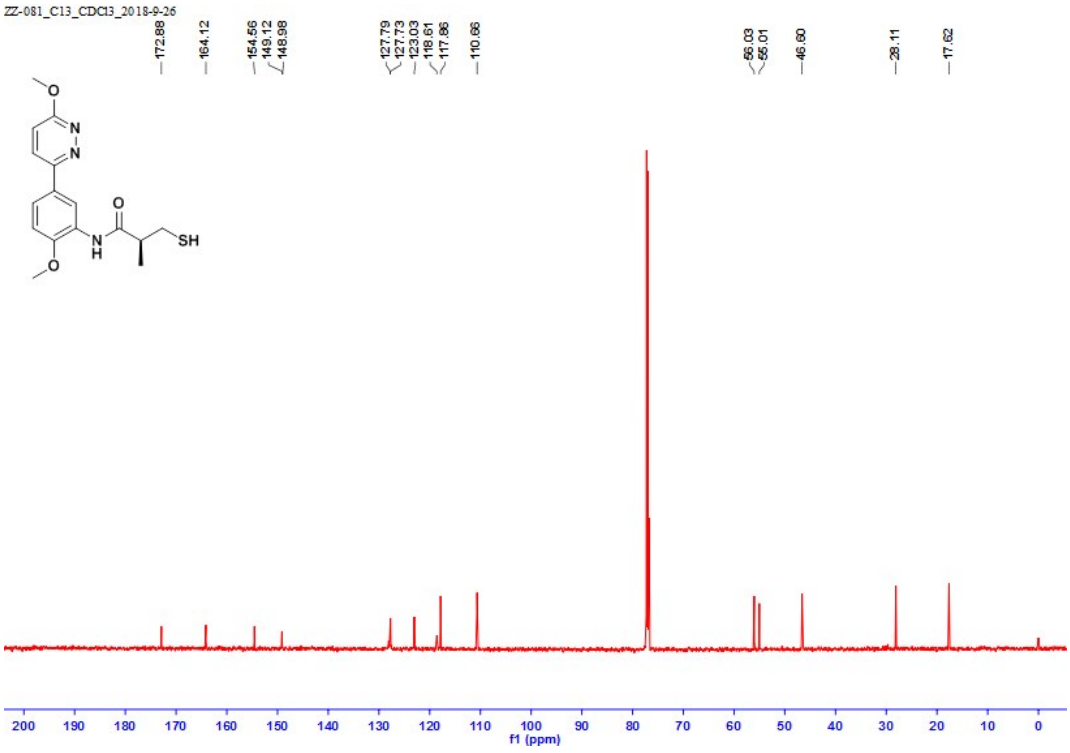
^{1}H and ^{13}C NMR Spectra of Compound **13j**



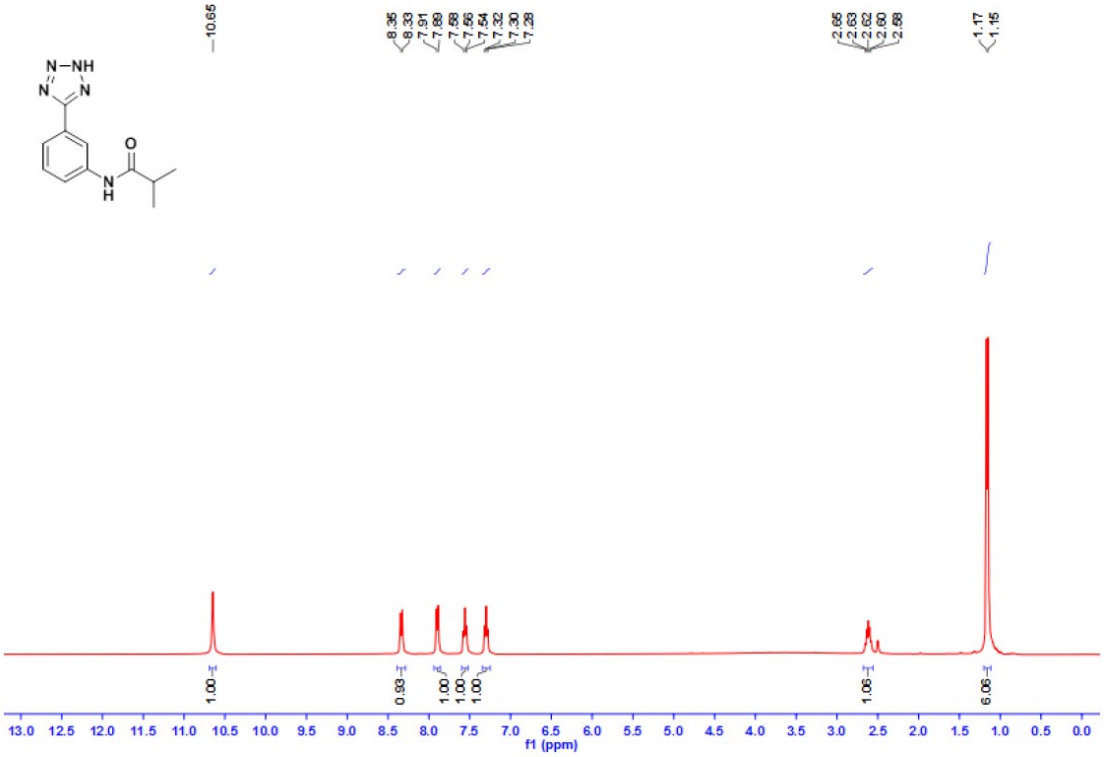


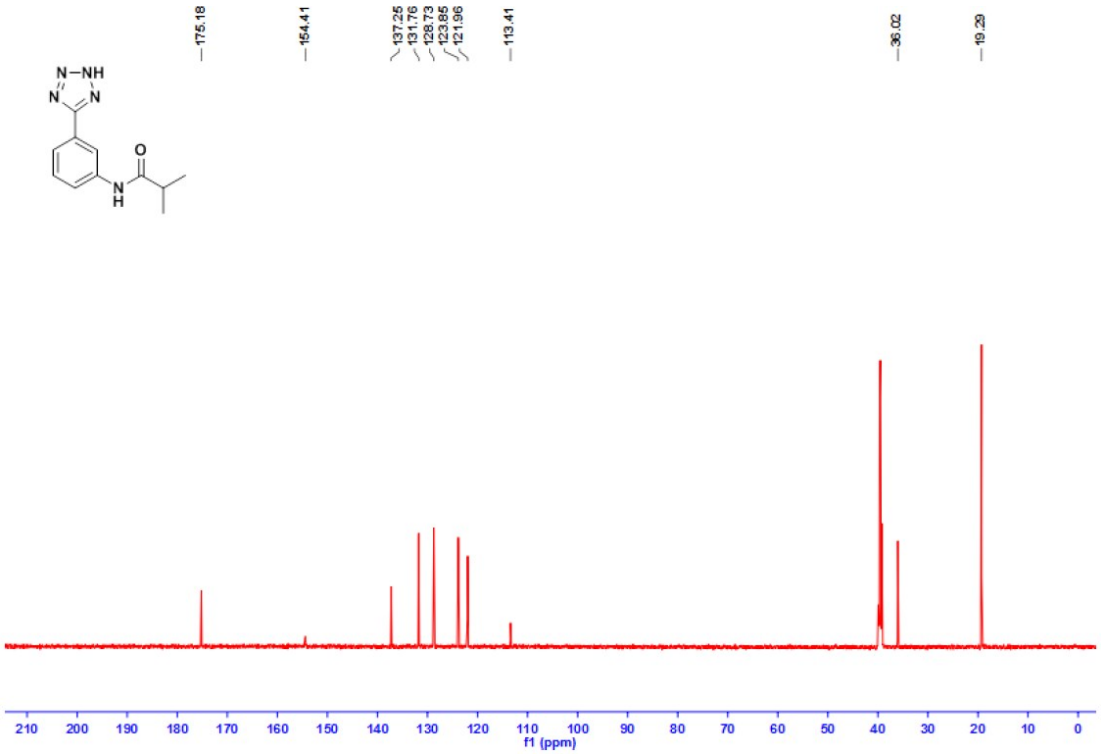
^{1}H and ^{13}C NMR Spectra of Compound **13k**


ZZ-081_H1_CDCl3_2018-9-25.10.fid
f1 (ppm)


ZZ-081_C13_CDCl3_2018-9-26
f1 (ppm)

^{1}H and ^{13}C NMR Spectra of Compound **14**




175.18
154.41
137.25
131.76
128.73
123.85
121.96
113.41
36.02
19.29
N–NH
N
N
O
N
H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)