Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Thioamides Synthesis via Copper-Catalyzed C-H Activation of 1,2,3-Thiadiazoles Enabled by Slow Release and Capture of Thioketene

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I. General Information

Reagents

All compounds were used as received unless otherwise noted.

Metals and Ligand

All metal catalysts and ligands, unless otherwise noted, were stored and handled in a nitrogen-filled glovebox. $Cu(OAc)_2$ was purchased from *Energy Chemical* and used as received. Other catalyst in condition optimization table were $Cu(acac)_2$ (*Energy Chemical*), $CuSO_4$ (*Energy Chemical*), $CuCl_2$ (Innochem), CuCl (*Energy Chemical*), Cu(OAc) (*Energy Chemical*), $Pd(OAc)_2$ (*Energy Chemical*), $Ni(OAc)_2$ (*Bidepharm*), $Co(OAc)_2$ (Adamas) and Cu(OAc) (*Energy Chemical*). The ligands used were Xantphos (*Bidepharm*), DPPF (*Bidepharm*), PPh_3 (*Energy Chemical*), PCy_3 (*Energy Chemical*), bpy (Laajoo), 1,10-Phenanthroline (Accela), IPr-HCl (*Energy Chemical*), IMes-HCl (Innochem).

Solvents:

The solvent *N,N*-dimethylformamide (DMF) and CH_3CN were purchased from *Energy Chemical*. Tetrahydrofuran (THF) and 1,4-dioxane were distilled from sodium/benzophenone and stored under nitrogen before use.

Analytical Methods

^1H nuclear magnetic resonance (NMR) spectroscopy chemical shifts are reported in ppm and referenced to TMS (tetramethylsilane) in $CDCl_3$ (δ = 0 ppm) or the residual solvent peak for $CDCl_3$ (δ = 7.26 ppm). For ^{13}C NMR chemical shifts, the residual solvent peak ($CDCl_3$, δ = 77.00 ppm) were used as references. NMR spectra were recorded on Avance Bruker NMR spectrometers operating at either 400 MHz or 500 MHz and data analysis was performed using the MestReNova software. Chemical shifts are reported in parts per million (ppm), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (J)

are reported in Hertz. Melting points were measured using a melting point instrument. IR spectra were obtained with an infrared spectrometer on either potassium bromide pellets or liquid films between two potassium bromide pellets. GC analyses were performed on an Agilent 7890B GC equipped with HP-5 columns (30 m × 320 μm × 0.25 μm), FID detectors, and hydrogen as the carrier gas. A sample volume of 1 μL was injected at a temperature of 250 °C and a 15:1 split ratio. The initial inlet pressure was 2.7 psi but varied as the column flow was held constant at 1 mL/min for the duration of the run. The initial oven temperature of 60 °C was held for 0 min followed by a temperature ramp of 50 °C/min up to 300 °C. The temperature was held at 300 °C for 6 min. The total run time was ~10.8 min and the FID temperature was 300 °C. GC/MS analyses were performed on a Shimadzu GCMS-QP2010SE equipped with an RTX-5MS column (30 m × 0.25 mm × 0.25 μm) with a quadrupole mass analyzer using helium as the carrier gas. The analysis method used in all cases was 5 μL injection of sample, an injection temp of 250 ºC, and no split ratio. The initial inlet pressure was 7.8 psi, but varied as the column flow was held constant at 1.7 mL/min for the duration of the run. The interface temperature was held at 250 ºC, and the ion source (EI+, 30 eV) was held at 250 ºC. The initial oven temperature was held at 50 ºC for 1 min with the detector off, followed by a temperature ramp, with the detector on, to 250 ºC at 30 ° C/min. The temperature was held at 250 ºC for 0 min, then to 280 ºC and held for 7 min. Total run time was 16.2 min. High resolution mass spectra (HRMS) was carried out on a electrospray (ESI+) ionization methods (ESI-quadrupole). Thin layer chromatography was performed on TLC Silica Gel 60 F254 plates. Visualization was accomplished with potassium permanganate after inspection under UV light. Flash chromatography was performed using silica gel 60, particle size 0.040-0.063 mm using standard flash techniques.

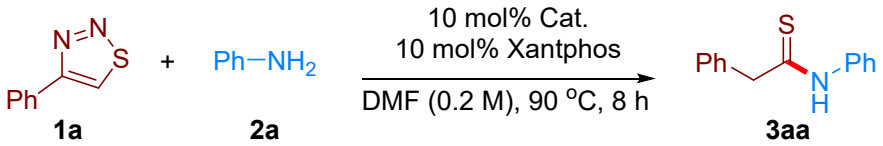
Procedure

All reactions were conducted in oven-dried Schlenk tubes. All the reaction temperatures reported are oil bath temperatures.

II. Optimization Study

General Procedure for the Optimization Reactions: To an oven-dried 20-mL Schlenk tube equipped with a magnetic stir bar were subsequently added with 1,2,3-thiadiazoles (0.1 mmol), catalyst (10 mol%), ligand (10 mol%) and amine (0.1 mmol) at room temperature, then solvent (0.5 mL) was added. The tube was placed under vacuum and backfilled with N_2 (3 times). The resulting mixture was maintained with stirring at the selected temperature for 8 h. After the reaction, the mixture was diluted with EtOAc (2 mL) and subjected to GC analysis with dodecane as the internal standard.

Table S1: Screening the metal catalysts.[a]

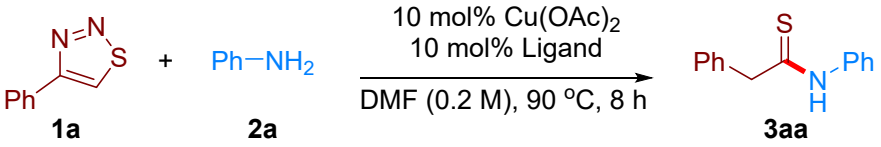


1a 0.1 mmol | **2a** 1 equiv | **3aa**

Entry	Cat.	Yield (%)
1	No Cat.	n.d.
2	$Cu(OAc)_2$	95
3	$Cu(acac)_2$, $CuSO_4$ or $CuCl_2$	trace
4	$Cu(acac)_2$ + 10 mol% NaOAc	22%
5	CuCl	n.d.
6	CuOAc	71%
7	$Pd(OAc)_2$, $Ni(OAc)_2$ or $Fe(OAc)_2$	trace
8	$Co(OAc)_2$	12
9	AgOAc	66
10	Ag_2CO_3	9

[a] All reactions were performed on a 0.1 mmol scale. Yield was determined by GC analysis with dodecane as an internal standard.

Table S2: Screening the ligands.[a]

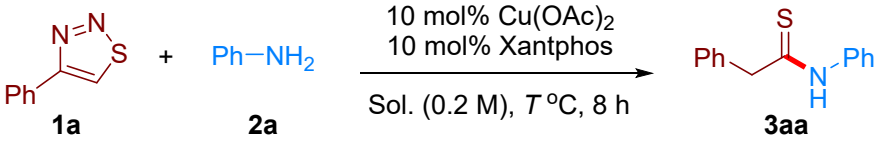


1a 0.1 mmol + **2a** 1 equiv → **3aa**

Entry	Ligand	Yield (%)
1	No ligand	trace
2	Xantphos	95
3	bpy	81
4	Phenanthrolline	85
5	IPr-HCl + 20 mol% Cs_2CO_3	51
6	IMes-HCl + 20 mol% LiOtBu	trace
7	PCy_3	74
8	PPh_3	47
9	DPPF	86

[a] All reactions were performed on a 0.1 mmol scale. Yield was determined by GC analysis with dodecane as an internal standard.

Table S3: Screening the solvents and temperature.[a]

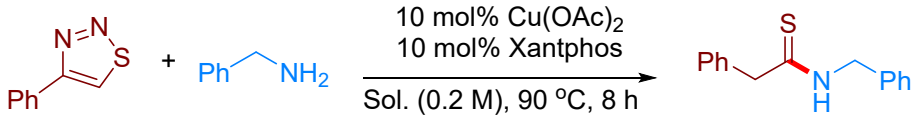


1a 0.1 mmol **2a** 1 equiv **3aa**

Entry	Solvent	Temperature (°C)	Yield (%)
1	THF	90	77
2	1,4-dioxane	90	53
3	benzene	90	45
4	DMF	90	95
5	CH_3CN	90	64
6	DCE	90	24
7	DMF	60	55
8	DMF	r.t.	n.d.

[a] All reactions were performed on a 0.1 mmol scale. Yield was determined by GC analysis with dodecane as an internal standard.

Table S4: Screening the solvents for benzylamine.[a]

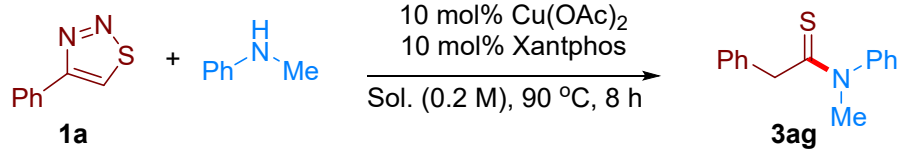


1a 0.1 mmol — 1 equiv — **3bb**

Entry	Solvent	Yield (%)
1	THF	97
2	1,4-dioxane	91
3	DMF	90
4	CH_3CN	76
5	benzene	92

[a] All reactions were performed on a 0.1 mmol scale. Yield was determined by GC analysis with dodecane as an internal standard.

Table S5: Screening the solvents and ligands for *N*-methylaniline.[a]



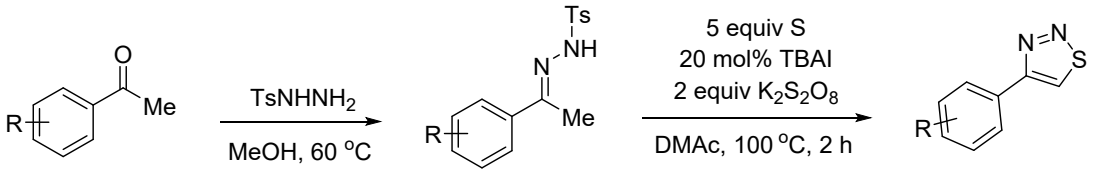
1a 0.1 mmol + 1 equiv → **3ag**

Entry	Solvent	Ligand	Yield (%)
1	THF	Xantphos	83
2	1,4-dioxane	Xantphos	78
3	DMF	Xantphos	90
4	CH_3CN	Xantphos	99
5	benzene	Xantphos	88
6	CH_3CN	PCy_3	86
7	CH_3CN	bpy	92
8	CH_3CN	No ligand	98

[a] All reactions were performed on a 0.1 mmol scale. [b] Yield was determined by GC analysis with dodecane as an internal standard.

III. Methods for the Synthesis of 1,2,3-Thiadiazole Derivatives

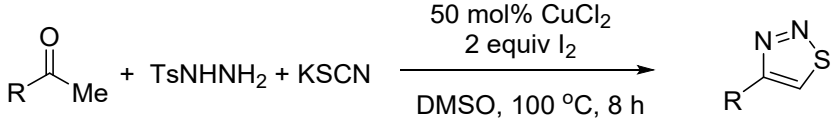
General procedure A:



p-toluenesulfonylhydrazide (1.86 g, 10 mmol) was placed in a round-bottom boiling flask equipped with a reflux condenser in 10 mL of dry methanol, the ketone (10 mmol) was added slowly and the mixture was heated in an oil bath at 60 °C Within 5−60 min, *N*-tosylhydrazone began to precipitate. The mixture was cooled to 0 °C, and the product was collected on a Büchner funnel, washed with petroleum ether, and then dried in vacuo to afford the pure product quantitatively.

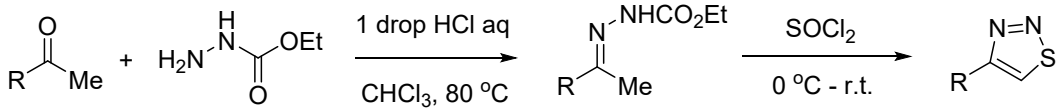
A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (15 mmol), TBAI (0.6 mmol), $K_2S_2O_8$ (6 mmol), and DMAC (30 mL). The mixture was stirring under air at 100 °C for 2 h. The mixture was washed with water and extracted by ethyl acetate and then concentrated in vacuum, and the residue was purified by preparative TLC (petroleum ether/ethyl acetate = 20:1) to afford the desired product.[1]

General procedure B:



A sealed tube was charged with ketone (1.0 mmol), *p*-toluenesulfonylhydrazide (1.0 mmol), and potassium thiocyanate (97.2 mg,1.0 mmol), iodine (507.6 mg,2.0 mmol) at room temperature, and DMSO (3mL) was added. The resulting mixture was stirred at 100 °C for 1 h. After the reaction completed, the mixture was quenched with saturation $Na_2S_2O_3$ solution (50mL), extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (petroleum ether/EtOAc = 20:1) to give the product. [2]

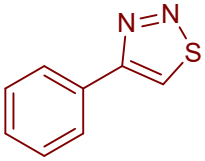
General procedure C:



1 equiv 1.2 equiv

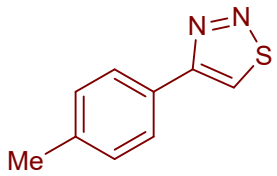
A mixture of acetophenone (1 equiv) and ethyl hydrazine carboxylate (1.2 equiv) was dissolved in chloroform. When the reaction mixture started refluxing, one drop of concentrated hydrochloric acid was added and the mixture was then refluxed overnight with continuous removal of the water generated. The solvent was removed under vacuum and the residue was washed several times with diethyl ether or chloroform to remove excess reactants. Next, an excess amount of thionyl chloride was stirred at 0 ºC and the hydrazones were added in several portions. The mixtures were stirred at room temperature overnight until no more hydrogen chloride was produced. The remaining thionyl chloride was evaporated under vacuum and the residue was washed with diethyl ether to give good yields of the corresponding 1,2,3-thiadiazoles as fine powders. A recrystallization from chloroform or dimethylsulfoxide was carried out when necessary.[3]

4-Phenyl-1,2,3-thiadiazole (1a)



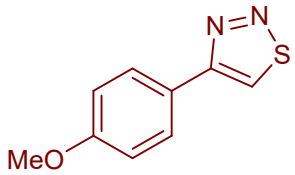
The general procedure C conducted with acetophenone (30 g, 250 mmol), ethyl hydrazinecarboxylate (31.2 g, 1.2 equiv), one drop of concentrated hydrochloric acid in dry $CHCl_3$ (100 mL) gave 54.6 g of ethyl (*E*)-2-(1-phenylethylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (80 mL) for 8 h to give 1,2,3-thiadiazoles as white solid after recrystalization (29.7 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.05 (dd, *J* = 5.3, 3.4 Hz, 2H), 7.51 (dd, *J* = 10.3, 4.7 Hz, 2H), 7.47 – 7.37 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 130.8, 130.0, 129.5, 129.2, 127.4. Spectroscopic data match those previously reported in the literature.[1]

4-(*p*-Tolyl)-1,2,3-thiadiazole (1ea)



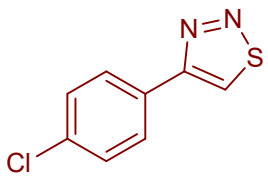
The general procedure A conducted with 1-(p-tolyl)ethan-1-one (1.34 g, 10 mmol), *p*-toluenesulfonylhydrazide (1.86 g, 10 mmol) in dry MeOH (50 mL) gave *N*-tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2 h gave 4-(p-tolyl)-1,2,3-thiadiazole as white solid (243 mg, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 139.5, 129.9, 129.3, 128.1, 127.3, 21.4. Spectroscopic data match those previously reported in the literature.[1]

(4-Methoxyphenyl)-1,2,3-thiadiazole (1eb)



The general procedure A conducted with 1-(4-methoxyphenyl)ethan-1-one (1.5 g, 10 mmol), *p*-toluenesulfonylhydrazide (1.86 g, 10 mmol) in dry MeOH (50 mL) gave *N*- tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2 h gave 4-(p-tolyl)-1,2,3-thiadiazole as white solid (409 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.98 (d, *J* = 6.3 Hz, 2H), 7.03 (d, *J* = 6.3 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 160.5, 128.8, 128.5, 123.6, 114.6, 55.4. Spectroscopic data match those previously reported in the literature.[1]

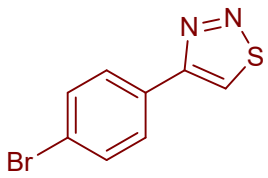
(4-Chlorophenyl)-1,2,3-thiadiazole (1ec)



The general procedure A conducted with 1-(4-chlorophenyl)ethan-1-one (1.54 g, 10 mmol), *p*-toluenesulfonylhydrazide (1.86 g, 10 mmol) in dry MeOH (50 mL) gave *N*- tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2

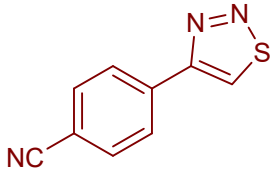
h gave 4-(4-chlorophenyl)-1,2,3-thiadiazole as pink solid (340 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 134.3, 129.1, 128.3, 128.2, 127.5. Spectroscopic data match those previously reported in the literature. [1]

(4-Bromophenyl)-1,2,3-thiadiazole (1ed)



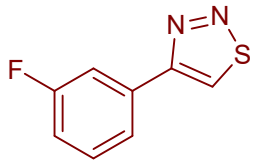
The general procedure A conducted with 1-(4-bromophenyl)ethan-1-one (1.97 g, 10 mmol), *p*-toluenesulfonylhydrazide (1.86 g, 10 mmol) in dry MeOH (50 mL) gave *N*- tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2 h gave 4-(4-chlorophenyl)-1,2,3-thiadiazole as pink solid (540 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 132.4, 130.3, 129.7, 128.9, 123.7. Spectroscopic data match those previously reported in the literature.[1]

4-(1,2,3-thiadiazol-4-yl)benzonitrile (1ee)



The general procedure A conducted with 4-acetylbenzonitrile (1.45 g, 10 mmol), *p*-toluenesulfonylhydrazide (1.86 g, 10 mmol) in dry MeOH (50 mL) gave *N*-tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2 h gave 4-(4-chlorophenyl)-1,2,3-thiadiazole as yellow solid (365 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 134.9, 133.0, 132.1, 127.9, 118.4, 113.0. Spectroscopic data match those previously reported in the literature.[1]

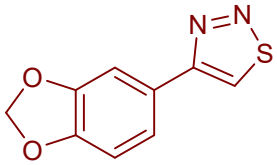
(3-Fluorophenyl)-1,2,3-thiadiazole (1ef)



The general procedure A conducted with 1-(3-

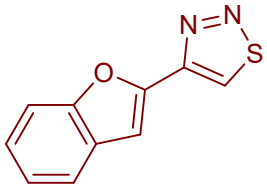
fluorophenyl)ethan-1-one (1.38 g, 10 mmol), *p*-toluenesulfonylhydrazide (1.86 g, 10 mmol) in dry MeOH (50 mL) gave *N*- tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2 h gave 4-(4-chlorophenyl)-1,2,3-thiadiazole as yellow solid (324 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.80 (dd, *J* = 17.8, 8.7 Hz, 2H), 7.47 (dd, *J* = 14.2, 7.4 Hz, 1H), 7.14 (t, *J* = 8.1 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.8 (dd, *J* = 15.0, 8.8 Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 162.2, 161.6 (d, *J* = 2.8 Hz), 132.8 (d, *J* = 8.3 Hz), 130.8 (d, *J* = 6.3 Hz), 123.0 (d, *J* = 2.9 Hz), 116.4 (d, *J* = 21.2 Hz), 114.4 (d, *J* = 23.3 Hz). Spectroscopic data match those previously reported in the literature.[5]

(Benzo[d][1,3]dioxol-5-yl)-1,2,3-thiadiazole (1eg)



The general procedure A conducted with 1-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-one (1.64 g, 10 mmol), *p*-toluenesulfonylhydrazide (1.86 g, 10 mmol) in dry MeOH (50 mL) gave *N*- tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2 h gave 4-(benzo[*d*][1,3]dioxol-5-yl)-1,2,3-thiadiazole as yellow solid (296 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.63 – 7.45 (m, 2H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.05 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6, 148.6, 148.4, 128.8, 125.0, 121.5, 108.9, 107.8, 101.5. Spectroscopic data match those previously reported in the literature. [1]

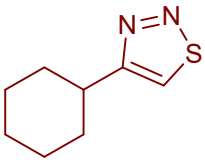
4-(Benzofuran-2-yl)-1,2,3-thiadiazole (1eh)



The general procedure C conducted the same as reported[6] with 1-(benzofuran-2-yl)ethan-1-one (1.6 g, 10 mmol), ethyl hydrazinecarboxylate (1.04 g, 1 equiv), one drop of HOAc in EtOH (20 mL) gave 2.44 g of ethyl (E)-2-(1-(benzofuran-2-

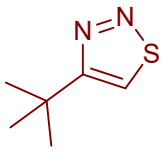
yl)ethylidene) hydrazine-1-carboxylate as a white solid. Dissolving 1.25g hydrazine in 0.4 mL $SOCl_2$ and 0.8 mL pyridine in 10 mL $CHCl_3$ at 55 °C for 5 min then add 0.6 mL $SOCl_2$ for 30 min to give the 1,2,3-thiadiazoles as yellow solid (751 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 154.6, 148.1, 130.5, 128.4, 125.5, 123.6, 122.0, 111.4, 105.8. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd. for $C_{10}H_7N_2OS$ 203.0274; found: 203.0275.

4-Cyclohexyl-1,2,3-thiadiazole (1ei)



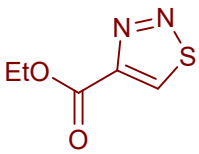
The general procedure B conducted with 1-cyclohexylethan-1-one (630 mg, 5 mmol), *p*-toluenesulfonylhydrazide (931 mg, 5 mmol) and potassiumthiocyanate (486 mg, 5 mmol), iodine (2.54 g, 10 mmol), $CuCl_2$ (335 mg, 2.5 mmol) in DMSO (15 mL) at 100 °C gave 4-cyclohexyl-1,2,3-thiadiazole as white solid (411 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 3.22 (t, *J* = 11.3 Hz, 1H), 2.17 (d, *J* = 12.4 Hz, 2H), 1.86 (d, *J* = 12.5 Hz, 2H), 1.77 (d, *J* = 12.5 Hz, 1H), 1.67 – 1.38 (m, 4H), 1.30 (dd, *J* = 25.0, 12.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 129.8, 38.0, 33.3, 26.2, 25.9. Spectroscopic data match those previously reported in the literature.[2]

4-(Tert-butyl)-1,2,3-thiadiazole (1ej)



The general procedure B conducted with 3,3-dimethylbutan-2-one (500 mg, 5 mmol), *p*-toluenesulfonylhydrazide (931 mg, 5 mmol) and potassiumthiocyanate (486 mg,5 mmol), iodine (2.54 g,10 mmol), $CuCl_2$ (335 mg, 2.5 mmol) in DMSO (15 mL) at 100 °C gave 4-(tert-butyl)-1,2,3-thiadiazole as yellow oil (390 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 129.1, 33.7, 30.6. Spectroscopic data match those previously reported in the literature.[2]

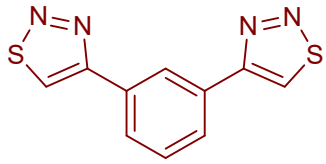
Ethyl 1,2,3-thiadiazole-4-carboxylate (1ek)



The general procedure C conducted the same as reported with

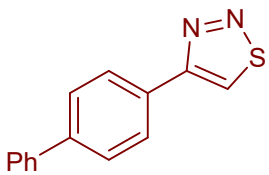
methyl hydrazinecarboxylate (0.9 g, 10 mmol, 1.0 equiv) ethyl pyruvate (1.1 mL, 10 mmol, 1.0 equiv) in ethanol (20 mL).[6] The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo. The crude hydrazone was washed with ethanol, dried in the air and used for the next step. Hydrazone (10 mmol) in CH_2Cl_2 (10 mL) was added $SOCl_2$ (3.6 mL, 50 mmol, 5.0 equiv) dropwise to afford 1,2,3-thiadiazole as white solid (751 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 4.52 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 154.9, 142.5, 62.3, 14.3. Spectroscopic data match those previously reported in the literature.[7]

1,3-Di(1,2,3-thiadiazol-4-yl)benzene (1el)



The general procedure B conducted with 1,1'-(1,3-phenylene)bis(ethan-1-one) (810 mg, 5 mmol), *p*-toluenesulfonylhydrazide (931 mg, 5 mmol) and potassiumthiocyanate (486 mg,5 mmol), iodine (2.54 g,10 mmol), $CuCl_2$ (335 mg, 2.5 mmol) in DMSO (15 mL) at 100 °C gave 1,3-di(1,2,3-thiadiazol-4-yl)benzene as white solid (265 mg, 22%). ^{1}H NMR (400 MHz, DMSO) δ 9.79 (s, 2H), 8.91 (s, 1H), 8.26 (d, J = 6.9 Hz, 2H), 7.75 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.8, 134.5, 132.1, 130.7, 128.4, 126.2. Spectroscopic data match those previously reported in the literature.[2]

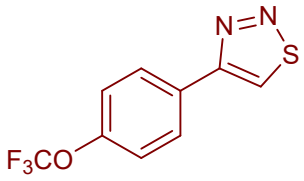
4-([1,1'-Biphenyl]-4-yl)-1,2,3-thiadiazole (1em)



The general procedure C conducted with 1-([1,1'-biphenyl]-4-yl)ethan-1-one (1.96 g, 10 mmol), ethyl hydrazinecarboxylate (1.25 g, 1.2 equiv), one drop of concentrated hydrochloric acid in dry $CHCl_3$ (20 mL) gave 2.77 g of ethyl (*E*)-2-(1-([1,1'-biphenyl]-4-yl)ethylidene) hydrazine-1-carboxylate. Dissolving in excess $SOCl_2$ (10 mL) for 8 h to give 1,2,3-thiadiazoles as yellow solid (1.79 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.13 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.70 – 7.63 (m, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz,

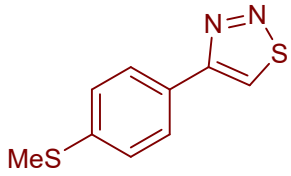
$CDCl_3$) δ 162.6, 142.2, 140.2, 129.9, 129.7, 128.9, 127.8, 127.8, 127.1. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{14}H_{11}N_2S$ 239.0637; found: 239.0637.

4-(4-(trifluoromethoxy)phenyl)-1,2,3-thiadiazole (1en)



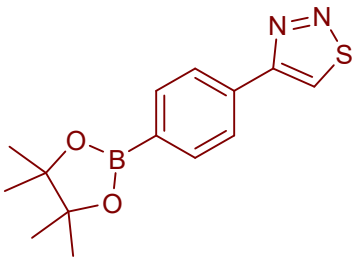
The general procedure C conducted with 1-(4-(trifluoromethoxy)phenyl)ethan-1-one (2.04 g, 10 mmol), ethyl hydrazinecarboxylate (1.25 g, 1.2 equiv), one drop of concentrated hydrochloric acid in dry $CHCl_3$ (20 mL) gave 2.74 g of ethyl (*E*)-2-(1-(4-(trifluoromethoxy)phenyl) ethylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (10 mL) for 8 h to give 1,2,3-thiadiazoles as yellow solid (2.02 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -57.78 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 149.9, 130.5, 129.5, 128.9, 121.6, 120.5 (q, *J* = 257.6 Hz). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_9H_6F_3N_2OS$ 247.0147; found: 247.0147.

4-(4-(methylthio)phenyl)-1,2,3-thiadiazole (1eo)



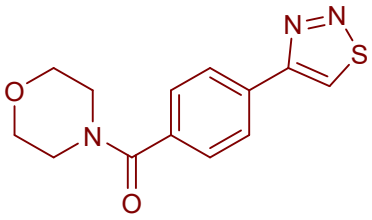
The general procedure A conducted with 1-(4-(methylthio)phenyl)ethan-1-one (0.83 g, 5 mmol), *p*-toluenesulfonylhydrazide (0.93 g, 5 mmol) in dry MeOH (10 mL) gave *N*-tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2 h gave 4-(4-(methylthio)phenyl)-1,2,3-thiadiazole as yellow solid (478 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5, 140.6, 129.3, 127.7, 127.4, 126.6, 15.4. Spectroscopic data match those previously reported in the literature. [4]

4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,2,3-thiadiazole (1ep)



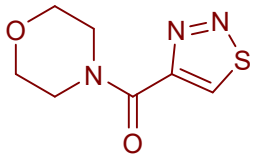
The general procedure C conducted with 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)ethan-1-one (2.46 g, 10 mmol), ethyl hydrazinecarboxylate (1.25 g, 1.2 equiv), one drop of concentrated hydrochloric acid in dry $CHCl_3$ (20 mL) gave 3.11 g of ethyl (*E*)-2-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (10 mL) for 8 h to give 1,2,3-thiadiazoles as yellow solid (1.47 g**,** 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.15 – 8.03 (m, 2H), 7.96 (d, *J* = 8.3 Hz, 2H), 1.39 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 135.6, 133.2, 130.6, 126.6, 84.1, 24.9. HRMS (ESI-quadrupole) *m/z*: $[M]^+$ Calcd. for $C_{14}H_{17}BN_2O_2S$ 288.1104; found: 288.1215.

(4-(1,2,3-Thiadiazol-4-yl)phenyl)(morpholino)methanone (1eq)



The general procedure C conducted with 1-(4-(morpholine-4-carbonyl)phenyl)ethan-1-one (2.33 g, 10 mmol), ethyl hydrazinecarboxylate (1.25 g, 1.2 equiv), one drop of concentrated hydrochloric acid in dry $CHCl_3$ (20 mL) gave 2.77 g of ethyl (*E*)-2-(1-(4-(morpholine-4-carbonyl) phenyl)ethylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (10 mL) for 8 h to give 1,2,3-thiadiazoles as yellow solid (1.62 g**,** 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 4.44 – 3.18 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 161.8, 136.1, 132.3, 131.0, 128.1, 127.6, 66.9. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{14}N_3O_2S$ 276.0801; found: 276.0803.

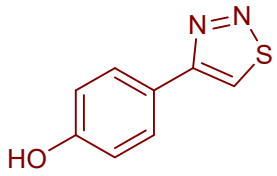
Morpholino(1,2,3-thiadiazol-4-yl)methanone (1er)



The general procedure C conducted with 1-morpholinopropane-1,2-dione (1.57 g, 10 mmol), ethyl hydrazinecarboxylate (1.25 g, 1.2 equiv), one drop of concentrated hydrochloric acid in dry

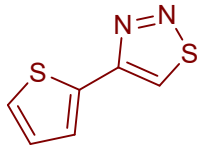
$CHCl_3$ (20 mL) gave 2.13 g of ethyl (*E*)-2-(1-morpholino-1-oxopropan-2-ylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (10 mL) for 8 h to give 1,2,3-thiadiazoles as yellow solid (1.25 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 4.13 – 4.01 (m, 2H), 3.98 – 3.73 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 158.1, 142.1, 67.1, 66.8, 48.0, 43.4. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_7H_{10}N_3O_2S$ 200.0488; found: 200.0486.

4-(1,2,3-Thiadiazol-4-yl)phenol (1et)



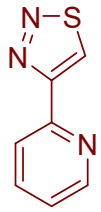
A modified procedure C conducted with 1-(4-hydroxyphenyl)ethan-1-one (2.05 g, 15 mmol), ethyl hydrazinecarboxylate (1.72 g, 1.1 equiv), *p*-TsOH (140 mg, 0.8 mmol) in dry toluene (50 mL) in dean-stark equipment gave 3.64 g of ethyl 2-(1-(4-hydroxyphenyl)ethylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (10 mL) for 8 h to give 1,2,3-thiadiazoles as yellow solid (2.16 g, 81%). ^{1}H NMR (500 MHz, DMSO) δ 9.88 (s, 1H), 9.37 (s, 1H), 7.98 – 7.93 (m, 2H), 6.95 – 6.91 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 162.7, 158.9, 131.1, 129.1, 122.3, 116.4. Spectroscopic data match those previously reported in the literature.[4]

4-(thiophen-2-yl)-1,2,3-thiadiazole (1eu)



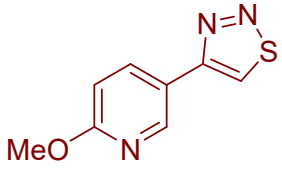
The general procedure A conducted with 1-(thiophen-2-yl)ethan-1-one (0.63 g, 5 mmol), *p*-toluenesulfonylhydrazide (0.93 g, 5 mmol) in dry MeOH (10 mL) gave *N*- tosylhydrazone as a white solid. A sealed tube was charged with *N*-tosylhydrazone (3 mmol), sulfur (480 mg, 15 mmol), TBAI (222 mg, 0.6 mmol), $K_2S_2O_8$ (1.62 g, 6 mmol) in DMAC (30 mL) under air at 100 °C for 2 h gave 4-(thiophen-2-yl)-1,2,3-thiadiazole as brown solid (470 mg, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.00–7.90 (m, 1H), 7.60 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.43 (dd, *J* = 4.9, 3.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 132.2, 129.5, 127.0, 126.5, 124.2. Spectroscopic data match those previously reported in the literature.[1]

4-(pyridin-2-yl)-1,2,3-thiadiazole (1ew)



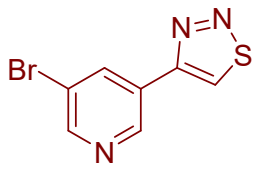
A modified procedure C conducted with 1-(pyridin-2-yl)ethan-1-one (1.21 g, 10 mmol), ethyl hydrazinecarboxylate (1.04 g, 1 equiv), CH_3COOH (four drop as catalyst) in MeOH (8 mL) to give ethyl (*E*)-2-(1-(pyridin-2-yl)ethylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (10 mL) at 0 °C and heated at 60 °C for 1 h. The remaining thionyl chloride was evaporated under vacuum. The mixture was washed with aq. Na_2CO_3 and extracted by ethyl acetate and then concentrated in vacuum, and the residue was purified by preparative TLC to afford the desired product as white solid (1.01 g**,** 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.60 (d, *J* = 4.5 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H), 7.79 (td, *J* = 7.7, 1.5 Hz, 1H), 7.26 (dd, *J* = 7.0, 5.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 149.9, 149.8, 137.3, 133.9, 123.9, 122.5. Spectroscopic data match those previously reported in the literature.[1]

4-(6-methoxypyridin-3-yl)-1,2,3-thiadiazole (1ex)



A modified procedure C conducted with 1-(6-methoxypyridin-3-yl)ethan-1-one (755 mg, 5 mmol), ethyl hydrazinecarboxylate (520 mg, 1 equiv), CH_3COOH (2 drop as catalyst) in MeOH (4 mL) to give 5-((1*E*)-1-(((ethylperoxy)-l3-methylene)hydrazineylidene)ethyl)-2-methoxypyridine as a white solid. Dissolving in excess $SOCl_2$ (5 mL) at 0 °C and heated at 60 °C for 1 h. The remaining thionyl chloride was evaporated under vacuum. The mixture was washed with aq. Na_2CO_3 and extracted by ethyl acetate and then concentrated in vacuum, and the residue was purified by preparative TLC to afford the desired product as white solid (714 mg**,** 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.1 Hz, 1H), 8.60 (s, 1H), 8.26 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 160.1, 145.9, 137.6, 129.0, 120.6, 111.4, 53.8. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_8H_8N_3OS$ 194.0382; found: 194.0383.

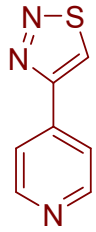
4-(5-bromopyridin-3-yl)-1,2,3-thiadiazole (1ey)



A modified procedure C conducted with 1-(5-bromopyridin-3-

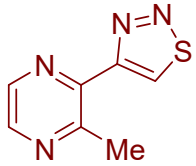
yl)ethan-1-one (1 g, 5 mmol), ethyl hydrazinecarboxylate (520 mg, 1 equiv), CH_3COOH (2 drop as catalyst) in MeOH (4 mL) to give 3-bromo-5-((1*E*)-1-(((ethylperoxy)-l3-methylene)hydrazineylidene)ethyl)pyridine as a white solid. Dissolving in excess $SOCl_2$ (5 mL) at 0 °C and heated at 60 °C for 1 h. The remaining thionyl chloride was evaporated under vacuum. The mixture was washed with aq. Na_2CO_3 and extracted by ethyl acetate and then concentrated in vacuum, and the residue was purified by preparative TLC to afford the desired product as yellow solid (971 mg**,** 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (d, *J* = 1.2 Hz, 1H), 8.81 (s, 1H), 8.74 (d, *J* = 1.8 Hz, 1H), 8.57 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 151.4, 146.3, 137.1, 131.8, 128.3, 121.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_7H_5N_3BrS$ 241.9382; found: 241.9381.

4-(pyridin-4-yl)-1,2,3-thiadiazole (1ez)



A modified procedure C conducted with 1-(pyridin-4-yl)ethan-1-one (1.21 g, 10 mmol), ethyl hydrazinecarboxylate (1.04 g, 1 equiv), CH_3COOH (four drop as catalyst) in MeOH (8 mL) to give ethyl (*E*)-2-(1-(pyridin-4-yl)ethylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (10 mL) at 0 °C and heated at 60 °C for 1 h. The remaining thionyl chloride was evaporated under vacuum. The mixture was washed with aq. Na_2CO_3 and extracted by ethyl acetate and then concentrated in vacuum, and the residue was purified by preparative TLC to afford the desired product as white solid (1.18 g**,** 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.78 (d, *J* = 5.9 Hz, 2H), 7.95 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 150.9, 137.8, 132.7, 121.4. Spectroscopic data match those previously reported in the literature.[1]

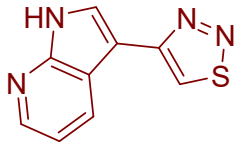
4-(3-methylpyrazin-2-yl)-1,2,3-thiadiazole (1eza)



A modified procedure C conducted with 1-(3-methylpyrazin-2-yl)ethan-1-one (0.68 g, 5 mmol), ethyl hydrazinecarboxylate (520 mg, 1 equiv), CH_3COOH (2 drop as catalyst) in MeOH (4 mL) to give 2-((1*E*)-1-(((ethylperoxy)-l3-methylene)hydrazineylidene)ethyl)-3-methylpyrazine as a white solid. Dissolving in excess $SOCl_2$ (5 mL) at 0 °C and

heated at 60 °C for 1 h. The remaining thionyl chloride was evaporated under vacuum. The mixture was washed with aq. Na_2CO_3 and extracted by ethyl acetate and then concentrated in vacuum, and the residue was purified by preparative TLC to afford the desired product as yellow solid (511 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.44 (d, *J* = 14.3 Hz, 2H), 2.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 153.2, 144.3, 143.5, 141.5, 137.5, 24.1. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_7H_7N_4S$ 179.0386; found: 179.0385.

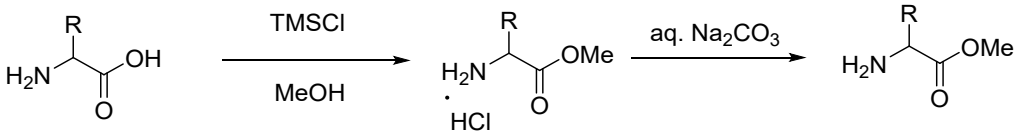
4-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-1,2,3-thiadiazole (1ezb)



A modified procedure C conducted with 1-(1H-pyrrolo[2,3-b]pyridin-3-yl)ethan-1-one (0.32 g, 2 mmol), ethyl hydrazinecarboxylate (208 mg, 1 equiv), CH_3COOH (2 drop as catalyst) in MeOH (4 mL) to give ethyl (*E*)-2-(1-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)ethylidene)hydrazine-1-carboxylate as a white solid. Dissolving in excess $SOCl_2$ (5 mL) at 0 °C and heated at 60 °C for 1 h. The remaining thionyl chloride was evaporated under vacuum. The mixture was washed with aq. Na_2CO_3 and extracted by ethyl acetate and then concentrated in vacuum, and the residue was purified by preparative TLC to afford the desired product as yellow solid (254 mg, 63%). ^{1}H NMR (500 MHz, DMSO) δ 12.19 (s, 1H), 9.41 (s, 1H), 8.57 (d, *J* = 7.6 Hz, 1H), 8.35 (d, *J* = 4.0 Hz, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 7.25 (dd, *J* = 7.9, 4.6 Hz, 1H).^{13}C NMR (126 MHz, DMSO) δ 158.1, 149.2, 144.1, 129.6, 129.0, 126.6, 117.5, 117.1, 106.1. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_9H_7N_4S$ 203.0386; found: 203.0385.

IV Methods for the Synthesis of Amine Substrates

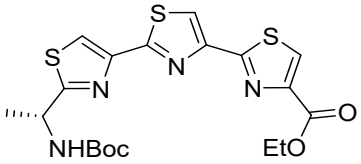
Methods for the Synthesis of Amino Acid Methyl Esters



Amino acid methyl esters were synthesized following the reported procedure.[8] Amino acid (10 mmol) was taken in a round bottom flask. Freshly distilled chlorotrimethylsilane (20 mmol) was added slowly and stirred with a magnetic stirrer. Then methanol (10 mL) was added and the resulting solution or suspension was stirred at room temperature. After the completion of reaction (as monitored by TLC), the reaction mixture was concentrated on a rotary evaporator to give the product amino acid ester hydrochloride.

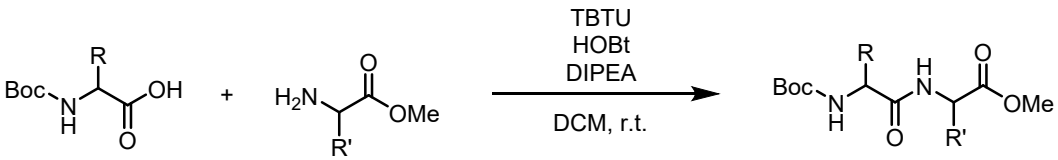
The amino acid ester hydrochloride salt (5 mmol) was introduced into a separatory funnel and mixed with CH_2Cl_2 (20 mL). An aqueous solution saturated with Na_2CO_3 was added and the solution was vigorously shaked for few minutes and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were collected, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to provide the pure amino acid ester amines in quantitative yields.

BocHN-D-Ala-Thiazole-Thiazole-Thiazole-OEt



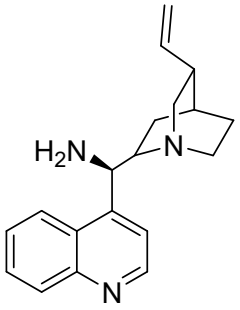
BocHN-*D*-Ala-Thiazole-Thiazole-Thiazole-OEt was supported by Dr. Y. Q. Zhang, which is synthesized following the reported procedure. [10]

Peptide coupling.



Peptides were synthesized according to the reported literature.[11] Boc-protected amino acid, TBTU, HOBt and DIPEA were added to DCM and stirred at room temperature. After 1 h, *N*-unprotected amino acid was added to the reaction mixture and stirring was continued overnight (approximately 15 h). The reaction mixture was then washed with $NaHCO_3$ (sat., aq.), citric acid (10 %, aq.) and NaCl (sat., aq.), dried over Na_2SO_4, filtered, evaporated in vacuum and purified by automated flash chromatography on a prepacked silica column.

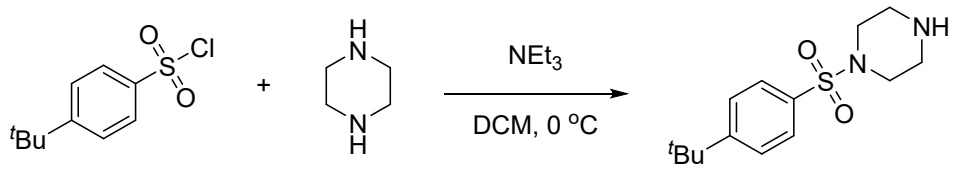
The synthesis of amino-*alkaloids* derivatives



Amino-alkaloids derivatives were synthesized according to the reported literature.[12] Cinchona alkaloid (1 mmol, 1.0 eq) and triphenylphosphine (1.2 mmol, 1.2 eq) were dissolved in dry THF (7 mL); then the resulting solution was cooled to 0 °C stirred for 10 min. Subsequently the Diisopropyl azodicarboxylate (DIAD) (1.2 mmol, 1.2 eq) was added dropwise, followed by the slow addition of the solution of $(PhO)_2P(O)N_3$ (1.2 mmol, 1.2 eq, 0.57 M solution in dry THF). Then the mixture was allowed to warm to room temperature and stirred for 8 h. The solution was then heated to 60 °C for 3 h; after this time, triphenylphosphine (1.2 mmol, 1.2 eq) was added as 0.46 M solution in dry THF. Then the reaction was stirred at 50 °C for 3 h, cooled to room temperature and 700 µL of distilled H_2O were added; finally, the reaction mixture was stirred for further 18 h. Then the solvent was removed under reduced pressure and 40 mL of CH_2Cl_2 and 40 mL of HCl 10% were added to the dried crude product. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The acqueous layer was then basified until pH = 12 with NH_4OH 30-33% and subsequently extracted with CH_2Cl_2 (3 x 30 mL). The

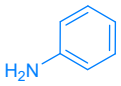
combined organic solution was dried over dry Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatographic purification.

The synthesis of 1-((4-(tert-butyl)phenyl)sulfonyl)piperazine



1-((4-(tert-butyl)phenyl)sulfonyl)piperazine was synthesized by adding triethylamine (31.5 mmol) slowly to a solution of piperazine in CH_2Cl_2 at 0 °C, and then commercially available 4-(tert-butyl)benzenesulfonyl chloride (11.4 mmol) was added and stirred for 30 min. After the completion of reaction, which was confirmed by TLC (petroleum ether and ethyl acetate (2:1)), the reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated on reduced pressure to give the desired product.[22]

Aromatic amine derivatives



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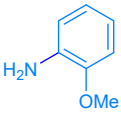

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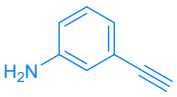

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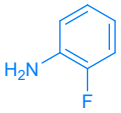
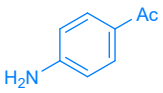


2ad



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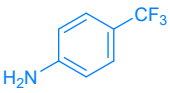

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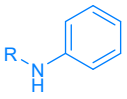
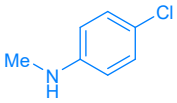
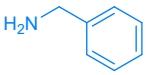


2ag, R = Me
2ah, R = Et
2ai, R = ^{i}Pr
2aj, R = Bn



2ak

Aliphatic amine derivatives



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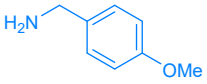

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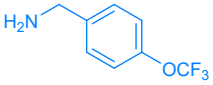

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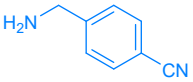

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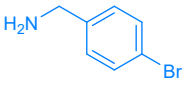

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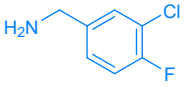

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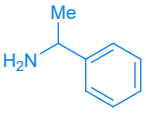

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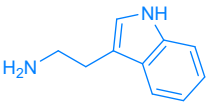

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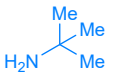

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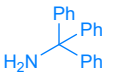

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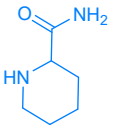

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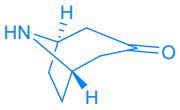

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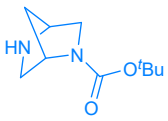

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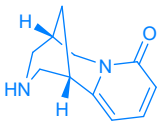
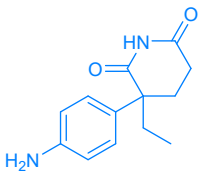
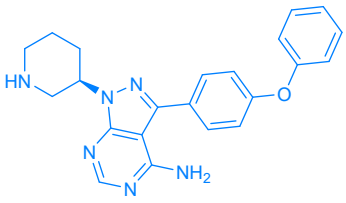


2bo

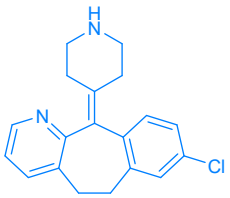
Late-stage modification of durgs and peptides



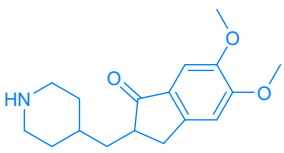
AMinoglutethiMide derivative



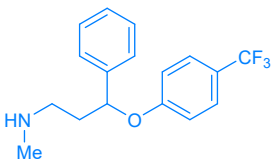
Ibrutinib intermediate



Desloratadine derivative



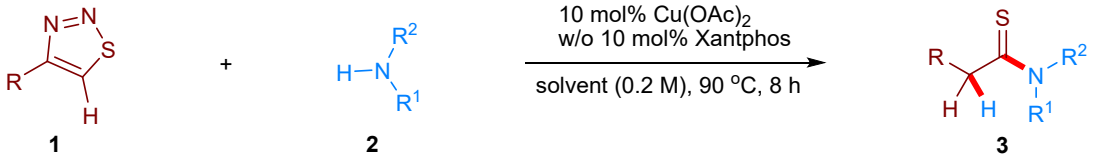
Donepezil analogue



Fluoxetine derivative

All the amines above were purchased and used directly.

V. General Procedures for $Cu(OAc)_2$-Catalysed Thioamidation of 5*H*-1,2,3-Thiadiazoles with Amines



1 2 3

R = (Het)Ar, alkyl, ester, amide

General procedure A for the synthesis of thioamides

A sealed tube was charged with 1,2,3-thiadiazoles **1** (0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and aniline derivatives **2** (0.5 mmol) at room temperature, then DMF (2.5 mL) was added. The resulting mixture was stirred at 90 °C for 8 h. After the reaction completed, the mixture was quenched with saturation NaCl solution (20 mL), extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20:1 - 5:1) to yield the desired thioamide product.

General procedure B for the synthesis of thioamides

A sealed tube was charged with 1,2,3-thiadiazoles (0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and primary alkylamine (0.5 mmol) at room temperature, then THF (2.5 mL) was added. The resulting mixture was stirred at 90 °C for 8 h. After the reaction completed, the mixture was quenched with saturation NaCl solution (20 mL), extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20:1 - 5:1) to yield the desired thioamide product.

General procedure C for the synthesis of thioamides

A sealed tube was charged with 1,2,3-thiadiazoles (0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and secondary alkylamine (0.5 mmol) at

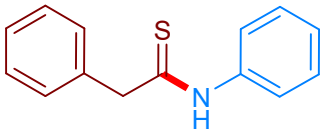
room temperature, then 1,4-dioxane (2.5 mL) was added. The resulting mixture was stirred at 90 °C for 8 h. After the reaction completed, the mixture was quenched with saturation NaCl solution (20 mL), extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20:1 - 5:1) to yield the desired thioamide product.

General procedure D for the synthesis of thioamides

A sealed tube was charged with 1,2,3-thiadiazoles (0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and N-alkylaniline (0.5 mmol) at room temperature, then CH_3CN (2.5 mL) was added. The resulting mixture was stirred at 90 °C for 8 h. After the reaction completed, the mixture was quenched with saturation NaCl solution (20 mL), extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20:1 - 5:1) to yield the desired thioamide product.

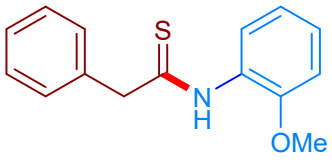
VI. Analysis Data for the Products

N,2-diphenylethanethioamide (3aa)



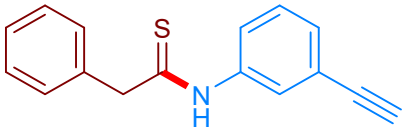
The general procedure A conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and aniline (47 mg, 0.5 mmol) in DMF (2.5 mL) at 90 °C for 8 h gave *N*,2-diphenylethanethioamide as yellow oil (102 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.54 (d, J = 7.9 Hz, 2H), 7.46 – 7.38 (m, 2H), 7.34 (dd, J = 13.0, 6.4 Hz, 5H), 7.22 (t, J = 7.4 Hz, 1H), 4.25 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.3, 138.5, 135.0, 129.6, 129.5, 128.9, 128.1, 127.1, 123.7, 54.9. Spectroscopic data match those previously reported in the litaerature.[13]

N-(2-methoxyphenyl)-2-phenylethanethioamide (3ab)



The general procedure A conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 2-methoxyaniline (62 mg, 0.5 mmol) in DMF (2.5 mL) at 90 °C for 8 h gave *N*-(2-methoxyphenyl)-2-phenylethanethioamide as yellow solid (110 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 9.03 (d, J = 8.1 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.36 (t, J = 6.9 Hz, 3H), 7.12 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 4.27 (s, 2H), 3.64 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 149.7, 134.9, 129.9, 129.2, 128.3, 127.9, 126.5, 121.4, 120.3, 110.4, 56.0, 55.8. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{16}NOS$ 258.0947; found: 258.0945.

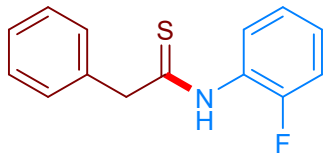
N-(3-ethynylphenyl)-2-phenylethanethioamide (3ac)



The general procedure A conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and

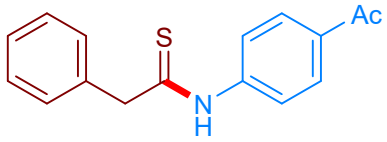
3-ethynylaniline (58 mg, 0.5 mmol) in DMF (2.5 mL) at 90 °C for 8 h gave *N*-(3-ethynylphenyl)-2-phenylethanethioamide as yellow solid (116 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.59 (d, *J* = 10.4 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 4H), 7.25 (t, *J* = 7.7 Hz, 1H), 4.20 (s, 2H), 3.07 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9, 138.5, 135.0, 130.6, 129.5, 129.5, 128.9, 128.1, 127.2, 124.4, 122.9, 82.7, 78.4, 54.8. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{14}NS$ 252.0841; found: 252.0839.

_N_-(2-fluorophenyl)-2-phenylethanethioamide (3ad)



The general procedure A conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 2-fluoroaniline (56 mg, 0.5 mmol) in DMF (2.5 mL) at 90 °C for 8 h gave *N*-(3-ethynylphenyl)-2-phenylethanethioamide as yellow solid (87 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.46 (t, *J* = 7.8 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.36 (d, *J* = 6.7 Hz, 3H), 7.15 (dt, *J* = 15.2, 7.0 Hz, 2H), 7.10 – 7.02 (m, 1H), 4.28 (s, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -126.72 (d, *J* = 12.9 Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 154.5 (d, *J* = 247.5 Hz), 134.7, 129.6, 129.5, 128.2, 127.7 (d, *J* = 8.1 Hz), 126.8 (d, *J* = 10.2 Hz), 124.8, 124.0 (d, *J* = 3.7 Hz), 115.4 (d, *J* = 19.3 Hz), 55.2. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{14}H_{13}NFS$ 246.0747; found: 246.0745.

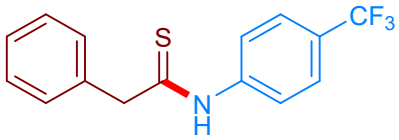
_N_-(4-acetylphenyl)-2-phenylethanethioamide (3ae)



The general procedure A conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 1-(4-aminophenyl)ethan-1-one (68 mg, 0.5 mmol) in DMF (2.5 mL) at 90 °C for 8 h gave *N*-(4-acetylphenyl)-2-phenylethanethioamide as yellow solid (78 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 6.9 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 3H), 4.27 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 197.0, 142.6, 134.9, 134.8, 129.5, 129.5, 129.3, 128.2,

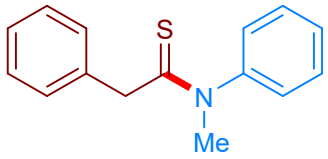
122.6, 55.5, 26.6. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{16}NOS$ 270.0947; found: 270.0944.

2-Phenyl-*N*-(4-(trifluoromethyl)phenyl)ethanethioamide (3af)



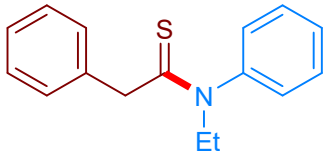
The general procedure A conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 4-Aminobenzotrifluoride (81 mg, 0.5 mmol) in DMF (2.5 mL) at 90 °C for 8 h gave 2-phenyl-*N*-(4-(trifluoromethyl) phenyl)ethanethioamide as yellow solid (96 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.44 (m, 2H), 7.40 (t, *J* = 9.0 Hz, 3H), 4.30 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ - 62.41 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1, 141.4, 134.7, 129.6, 128.7, 128.4, 128.3, 126.1 (dd, *J* = 7.4, 3.7 Hz), 123.8 (q, *J* = 271.8 Hz). 123.3, 55.2. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{13}NF_3S$ 296.0715; found: 296.0712.

***N*-methyl-*N*,2-diphenylethanethioamide (3ag)**



The modified procedure D conducted with 4-phenyl-1,2,3-thiadiazole (810 mg, 5 mmol), $Cu(OAc)_2$ (90 mg, 0.5 mmol) and *N*-methylaniline (540 mg, 5 mmol) in CH_3CN (25 mL) at 90 °C for 48 h gave *N*-methyl-*N*,2-diphenylethanethioamide as yellow oil (1.01 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 3H), 7.24 – 7.13 (m, 3H), 6.99 (dt, *J* = 5.4, 4.2 Hz, 4H), 4.02 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 145.4, 136.7, 129.7, 128.7, 128.5, 128.1, 126.7, 126.0, 50.8, 46.3. Spectroscopic data match those previously reported in the literature.[13]

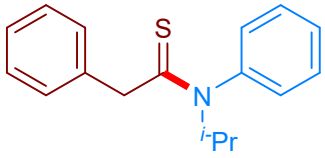
***N*-ethyl-*N*,2-diphenylethanethioamide (3ah)**



The general procedure D conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-ethylaniline (60 mg, 0.5 mmol) in CH_3CN

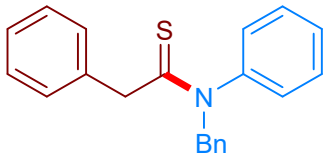
(2.5 mL) at 90 °C for 8 h gave *N*-ethyl-*N*,2-diphenylethanethioamide as yellow oil (80 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 4.9 Hz, 3H), 7.18 (s, 3H), 7.02 (s, 2H), 6.98 – 6.87 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 143.5, 136.8, 129.6, 128.6, 128.6, 128.2, 127.0, 126.6, 52.3, 51.3, 11.2. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{18}NS$ 256.1154; found: 256.1151.

_N_-isopropyl-_N_,2-diphenylethanethioamide (3ai)



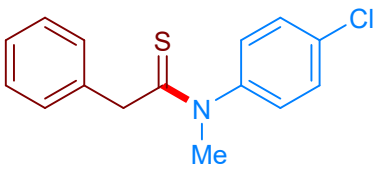
The general procedure D conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-isopropylaniline (68 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave *N*-isopropyl-*N*,2-diphenylethanethioamide as yellow solid (94 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dt, *J* = 23.0, 7.3 Hz, 3H), 7.17 (d, *J* = 1.8 Hz, 3H), 7.01 (s, 2H), 6.83 (d, *J* = 7.5 Hz, 2H), 6.02 (dt, *J* = 13.4, 6.7 Hz, 1H), 3.94 (s, 2H), 1.11 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 139.1, 136.9, 129.0, 128.8, 128.5, 128.1, 126.6, 53.6, 51.9, 20.2. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{17}H_{20}NS$ 270.1311; found: 270.1309.

_N_-benzyl-_N_,2-diphenylethanethioamide (3aj)



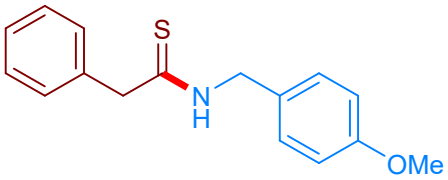
The general procedure D conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-benzylaniline (92 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave *N*-benzyl-*N*,2-diphenylethanethioamide as yellow solid (129 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 8H), 7.21 (dd, *J* = 9.3, 5.6 Hz, 3H), 7.06 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.85 – 6.57 (m, 2H), 5.62 (s, 2H), 4.08 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6, 143.3, 136.7, 135.6, 129.3, 128.9, 128.7, 128.5, 128.4, 128.2, 127.8, 127.2, 126.7, 60.4, 51.2. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{21}H_{20}NS$ 318.1311; found: 318.1309.

_N_-(4-chlorophenyl)-_N_-methyl-2-phenylethanethioamide (3ak)



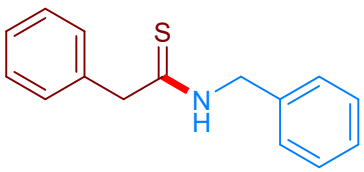
The general procedure D conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and 4-chloro-*N*-methylaniline (70 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave *N*-(4-chlorophenyl)-*N*-methyl-2-phenylethanethioamide as yellow oil (102 mg, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 7.25 – 7.14 (m, 3H), 7.11 – 6.99 (m, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.03 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0, 143.8, 136.5, 134.3, 129.8, 128.5, 128.3, 127.4, 126.8, 50.9, 46.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{15}NClS$ 276.0608; found: 276.0606.

_N_-(4-methoxybenzyl)-2-phenylethanethioamide (3ba)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (4-methoxyphenyl)methanamine (69 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(4-methoxybenzyl)-2-phenylethanethioamide as yellow oil (125 mg, 92%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.2 Hz, 2H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.16 (d, *J* = 7.3 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 4.64 (d, *J* = 5.2 Hz, 2H), 4.04 (s, 2H), 3.67 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9, 159.4, 135.0, 129.4, 129.3, 129.2, 128.0, 127.8, 114.3, 55.3, 53.1, 49.8. Spectroscopic data match those previously reported in the literature.[15]

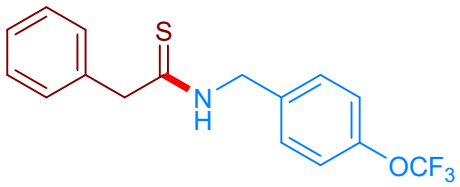
_N_-benzyl-2-phenylethanethioamide (3bb)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and phenylmethanamine (53 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-benzyl-2-phenylethanethioamide as yellow oil (110 mg, 91%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.31 – 7.22 (m, 6H), 7.15 (d, *J* = 6.6 Hz, 2H), 4.80 (d, *J* = 5.4

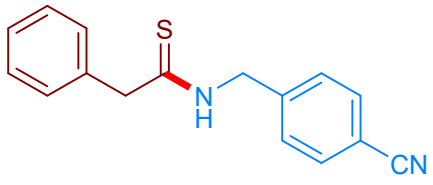
Hz, 2H), 4.14 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.3, 136.0, 134.9, 129.5, 129.3, 128.9, 128.0, 127.9, 127.8, 53.1, 50.2. Spectroscopic data match those previously reported in the literature.[14]

2-Phenyl-*N*-(4-(trifluoromethoxy)benzyl)ethanethioamide (3bc)



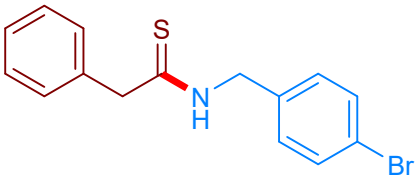
The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 4-(trifluoromethoxy)-benzylamnie (96 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave 2-phenyl-*N*-(4-(trifluoromethoxy)benzyl)ethanethioamide as yellow solid (145 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 4.82 (s, 2H), 4.15 (s, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -57.87 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 148.8, 134.8, 129.5, 129.3, 129.2, 128.0, 121.3, 120.4 (q, *J* = 259.35 Hz), 53.1, 49.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{15}NOF_3S$ 326.0821; found: 326.0819.

***N*-(4-Cyanobenzyl)-2-phenylethanethioamide (3bd)**



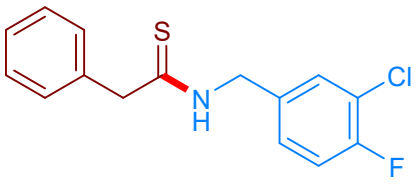
The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 4-(aminomethyl)benzonitrile (80 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave (4-cyanobenzyl)-2-phenylethanethioamide as yellow oil (113 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 6.9 Hz, 1H), 7.27 (dd, *J* = 12.4, 7.8 Hz, 4H), 4.90 (s, 2H), 4.17 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 141.7, 134.9, 132.5, 129. 5, 129. 3, 128.2, 128.0, 118.6, 111.5, 53.1, 48.9. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{15}N_2S$ 267.0950; found: 267.0947.

(4-bromobenzyl)-2-phenylethanethioamide (3be)



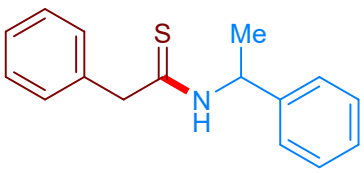
The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 4-bromobenzylamnie (92 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(4-bromobenzyl)-2-phenylethanethioamide as yellow solid (150 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 3H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H). 4.75 (s, 2H), 4.13 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.7, 135.1, 134.8, 131.9, 129.5, 129.5, 129.3, 128.0, 121.8, 53.1, 49.2. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{15}NBrS$ 320.0104; found: 320.0101.

(3-Chloro-4-fluorobenzyl)-2-phenylethanethioamide (3bf)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (3-chloro-4-fluorophenyl)methanamine (80 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(3-chloro-4-fluorobenzyl)-2-phenylethanethioamide as yellow solid (127 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.22 (d, *J* = 7.0 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 6.8 Hz, 1H), 6.99 – 6.89 (m, 2H), 4.67 (d, *J* = 5.3 Hz, 2H), 4.03 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.34 (d, *J* = 6.5 Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.0, 157.6 (d, *J* = 249.2 Hz), 134. 9, 133.3 (d, *J* = 3.8 Hz), 129.9, 129.4, 129.3, 128.0, 127.6 (d, *J* = 7.3 Hz), 121.2 (d, *J* = 18.1 Hz), 116.9 (d, *J* = 21.3 Hz), 53.0, 48.5. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{14}ClNFS$ 294.0514; found: 294.0512.

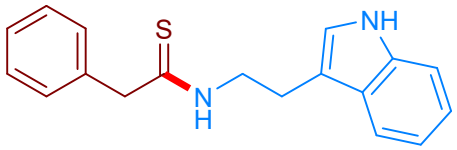
Phenyl-*N*-(1-phenylethyl)ethanethioamide (3bg)



The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 1-

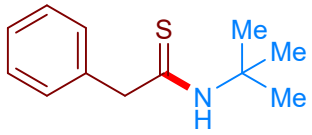
phenylethan-1-amine (66 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave phenyl-*N*-(1-phenylethyl)ethanethioamide as yellow oil (108 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (ddd, *J* = 23.6, 18.1, 12.8 Hz, 3H), 7.31 – 7.25 (m, 3H), 7.24 (dt, *J* = 11.7, 4.0 Hz, 3H), 7.18 – 7.12 (m, 2H), 5.80 – 5.65 (m, 1H), 4.08 (s, 2H), 1.46 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200. 9, 141.2, 135.1, 129.4, 129.2, 128.8, 127.9, 127.7, 126.3, 54.5, 53.2, 20.3. Spectroscopic data match those previously reported in the literature.[16]

_N_-(2-(1H-indol-3-yl)ethyl)-2-phenylethanethioamide (3bh)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 2-(1*H*-indol-3-yl)ethan-1-amine (80 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(2-(1*H*-indol-3-yl)ethyl)-2-phenylethanethioamide as yellow solid (101 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.21 (m, 4H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 4.6 Hz, 3H), 6.68 (s, 1H), 4.08 (s, 2H), 3.96 (q, *J* = 6.1 Hz, 2H), 3.03 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.6, 136.4, 134.7, 129.6, 129.1, 127.7, 127.0, 122.4, 122.1, 119.7, 118.6, 111.9, 111.3, 53.1, 46.0, 23.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{18}H_{19}N_2S$ 295.1263; found: 295.1262.

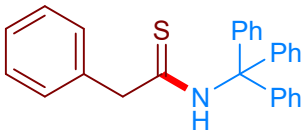
_N_-(tert-butyl)-2-phenylethanethioamide (3bi)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 2-methylpropan-2-amine (37 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(tert-butyl)-2-phenylethanethioamide as white solid (86 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 2H), 6.85 (s, 1H), 4.05 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, CDCl3) δ 200.7, 135.5, 129.4, 129.2, 127.8, 55.8, 55.7, 27.5. Spectroscopic data match those previously reported in the

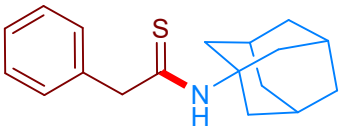
literature.[15]

2-Phenyl-*N*-tritylethanethioamide (3bj)



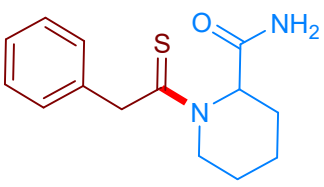
The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and triphenylmethanamine (130 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave 2-phenyl-*N*-tritylethanethioamide as white solid (83 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.45 – 7.28 (m, 6H), 7.27 – 7.16 (m, 8H), 7.08 (dd, *J* = 7.7, 1.8 Hz, 6H), 4.17 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.0, 142.8, 135.3, 129.5, 129.5, 128.9, 128.0, 127.9, 127.1, 74.0, 56.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{27}H_{24}NS$ 394.1551; found: 394.1546.

***N*-((3*S*,5*S*,7*S*)-adamantan-1-yl)-2-phenylethanethioamide (3bk)**



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (3*S*,5*S*,7*S*)-adamantan-1-amine (76 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-((3*S*,5*S*,7S)-adamantan-1-yl)-2-phenylethanethioamide as yellow solid (110 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 2H), 6.69 (s, 1H), 4.04 (s, 2H), 2.16 (d, *J* = 2.8 Hz, 6H), 2.07 (s, 3H), 1.65 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.1, 135.4, 129.4, 129.2, 127.8, 56.5, 56.1, 39.9, 36.2, 29.4. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{18}H_{24}NS$ 286.1624; found: 286.1623.

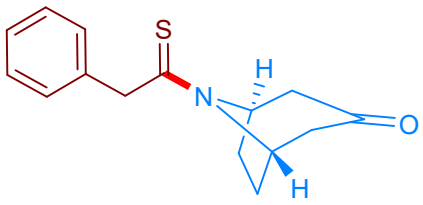
1-(2-Phenylethanethioyl)piperidine-2-carboxamide (3bl)



The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and piperidine-2-carboxamide (64 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL)

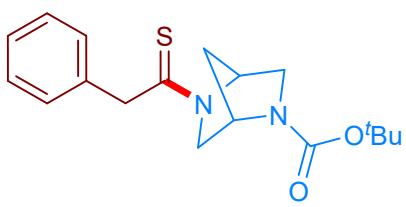
at 90 °C for 8 h gave (2-phenylethanethioyl)piperidine-2-carboxamide as yellow oil (86 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.07 (m, 5H), 6.46 (d, *J* = 1.9 Hz, 1H), 6.33 (s, 1H), 6.14 (d, *J* = 28.6 Hz, 1H), 4.46 (d, *J* = 15.2 Hz, 1H), 4.34 (d, *J* = 15.2 Hz, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 3.10 (td, *J* = 13.4, 2.6 Hz, 1H), 2.27 (d, *J* = 14.1 Hz, 1H), 1.91 – 1.43 (m, 4H), 1.14 – 0.91 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 171.7, 135.8, 129.0, 127.8, 127.2, 60.0, 50.7, 48.7, 25.6, 25.2, 19.7. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{14}H_{19}N_2OS$ 263.1213; found: 263.1210.

(1*R*,5*S*)-8-(2-Phenylethanethioyl)-8-azabicyclo[3.2.1]octan-3-one (3bm)



The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (1*R*,5*S*)-8-azabicyclo[3.2.1]octan-3-one (62.5 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave (1*R*,5*S*)-8-(2-phenylethanethioyl)-8-aza bicyclo[3.2.1]octan-3-one as yellow oil (95.8 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 5.60 (dd, *J* = 7.7, 3.7 Hz, 1H), 4.69 (dd, *J* = 6.5, 5.2 Hz, 1H), 4.38 (d, *J* = 14.7 Hz, 1H), 4.27 (d, *J* = 14.7 Hz, 1H), 2.96 (dd, *J* = 16.1, 3.6 Hz, 1H), 2.39 (d, *J* = 16.1 Hz, 1H), 2.25 – 2.11 (m, 2H), 2.11 – 1.98 (m, 1H), 1.92 (ddd, *J* = 16.3, 4.6, 1.7 Hz, 1H), 1.85 – 1.68 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.1, 196.0, 135.8, 129.1, 128.0, 127.4, 57.6, 57.2, 51.1, 48.3, 47.3, 29.5, 26.7. Optical Rotation: $[\alpha]^{25}_D$ = -2.26 (c 0.35, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{18}NOS$ 260.1104; found: 260.1106.

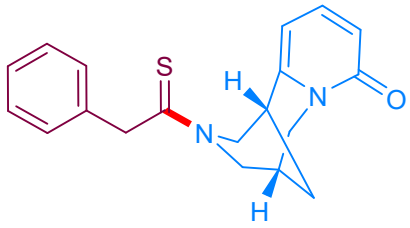
***tert*-Butyl-(1*S*,4*S*)-5-(2-phenylethanethioyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3bn)**



The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and tert-butyl (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-

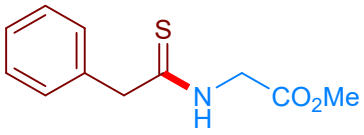
carboxylate (99 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave tert-butyl (1*S*,4*S*)-5-(2-phenylethanethioyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as yellow oil (97.9 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 6.98 (m, 5H), 4.80 – 4.42 (m, 2H), 4.25 (s, 1H), 4.17 – 3.98 (m, 1H), 3.92 – 3.68 (m, 1H), 3.49 (ddd, *J* = 42.3, 34.2, 10.1 Hz, 2H), 3.04 (ddd, *J* = 94.3, 57.7, 10.2 Hz, 1H), 2.15 – 1.75 (m, 2H), 1.41 (t, *J* = 17.1 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.99, 196.89, 153.95, 135.29, 128.86, 128.20, 127.17, 80.20, 67.03, 62.92, 61.58, 57.97, 56.56, 52.22, 51.79, 50.93, 50.50, 37.94, 36.22, 28.39. Optical Rotation: $[\alpha]^{25}_{D}$ = -175.4 (c 0.56, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{18}H_{25}N_2O_2S$ 333.1631; found: 333.1629.

(1*S*,5*R*)-3-(2-phenylethanethioyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3bo)



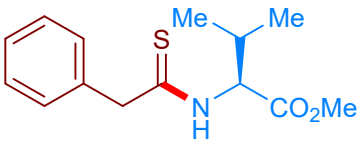
The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and CYTISINE (95 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave (1*S*,5*R*)-3-(2-phenylethanethioyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one as yellow oil (94 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 5.0 Hz, 2H), 7.19 – 6.92 (m, 5H), 6.37 (dd, *J* = 22.1, 9.1 Hz, 1H), 6.11 (d, *J* = 6.8 Hz, 0.5H), 5.87 (dd, *J* = 24.8, 13.4 Hz, 1H), 5.72 (d, *J* = 6.8 Hz, 0.5H), 4.42 – 3.88 (m, 4H), 3.69 (ddd, *J* = 76.4, 15.6, 6.4 Hz, 1H), 3.47 – 2.89 (m, 4H), 2.10 – 1.81 (m, 2.5H), 1.21 (dd, *J* = 7.8, 6.4 Hz, 0.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 202.4, 163.2, 163.0, 147.5, 147.1, 139.1, 138.9, 135.5, 135.5, 129.3, 129.0, 127.4, 127.2, 127.1, 126.8, 117.7, 117.5, 106.2, 105.2, 55.9, 55.8, 55.2, 55.1, 51.0, 50.5, 48.5, 48.4, 35.1, 34.8, 28.4, 28.0, 25.7, 25.5. Optical Rotation: $[\alpha]^{25}_{D}$ = -332.4 (c 0.47, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{19}H_{21}N_2OS$ 325.1369; found: 325.1366.

Methyl (2-phenylethanethioyl)glycinate (3ca)



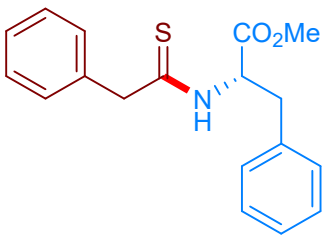
The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and methyl glycinate (45 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave methyl (2-phenylethanethioyl)glycinate as yellow oil (59 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.52 – 6.99 (m, 5H), 4.37 (d, *J* = 4.6 Hz, 2H), 4.18 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 169.2, 134.7, 129.5, 129.2, 127.9, 52.7, 52.7, 47.2. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{11}H_{14}NO_2S$ 224.0740; found: 224.0737.

Methyl (2-phenylethanethioyl)-*L*-valinate (3cb)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and methyl *L*-valinate (66 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave methyl (2-phenylethanethioyl)-*L*-valinate as yellow oil (76 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.32 (dd, *J* = 16.9, 6.9 Hz, 3H), 5.10 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.16 (q, *J* = 16.3 Hz, 2H), 3.72 (s, 3H), 2.27 (dq, *J* = 13.7, 6.8 Hz, 1H), 0.98 – 0.70 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 171.1, 134.9, 129.4, 129.2, 127.9, 62.6, 53.2, 52.3, 30.8, 18.4, 18.3. Optical Rotation: $[\alpha]^{25}_D$ = 5.75 (c 0.26, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{14}H_{20}NO_2S$ 266.1209; found: 266.1206.

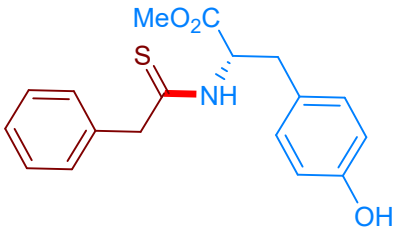
Methyl (2-phenylethanethioyl)-*L*-phenylalaninate (3cc)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and methyl *L*-phenylalaninate (90 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave methyl (2-phenylethanethioyl)-*L*-phenylalaninate as yellow solid (82 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.35 (dd, *J* = 5.9, 5.4 Hz, 3H),

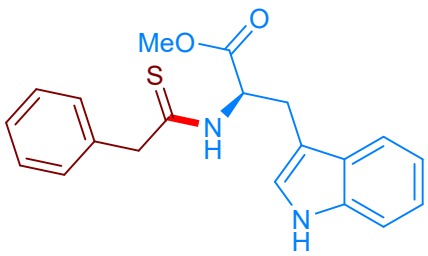
7.21 (dd, *J* = 10.3, 4.9 Hz, 5H), 6.96 – 6.55 (m, 2H), 5.40 (dt, *J* = 7.3, 5.4 Hz, 1H), 4.13 (dd, *J* = 38.0, 16.2 Hz, 2H), 3.74 (s, 3H), 3.34 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.11 (dd, *J* = 14.0, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 170.9, 135.1, 134.5, 129.5, 129.2, 129.1, 128.6, 127.9, 127.2, 58.3, 53.2, 52.5, 36.0. Optical Rotation: $[\alpha]^{25}_D$ = 43.1 (c 0.07, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{18}H_{20}NO_2S$ 314.1209; found: 314.1204.

Methyl (2-phenylethanethioyl)-*D*-tyrosinate (3cd)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and methyl *D*-tyrosinate (98 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave methyl (2-phenylethanethioyl)-*D*-tyrosinate as yellow solid (135 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 6.2 Hz, 1H), 7.43 – 7.28 (m, 3H), 7.20 (d, *J* = 7.5 Hz, 2H), 6.72 – 6.50 (m, 4H), 5.91 (s, 1H), 5.35 (dd, *J* = 12.7, 5.4 Hz, 1H), 4.11 (dd, *J* = 41.7, 16.2 Hz, 2H), 3.75 (d, *J* = 7.1 Hz, 3H), 3.23 (dd, *J* = 14.2, 5.5 Hz, 1H), 3.03 (dd, *J* = 14.2, 5.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3, 171.3, 155.1, 134.4, 130.2, 129.5, 129.2, 127.9, 126.7, 115.7, 58.6, 53.0, 52.6, 35.3. Optical Rotation: $[\alpha]^{25}_D$ = -95.2 (c 0.06, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{18}H_{20}NO_3S$ 330.1158; found: 330.1153.

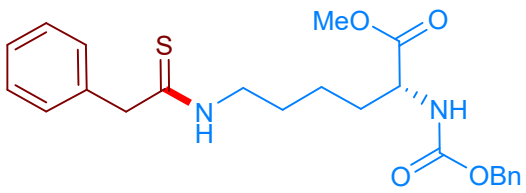
Methyl (2-phenylethanethioyl)-*L*-tryptophanate (3ce)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and methyl *L*-tryptophanate (109 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave methyl (2-phenylethanethioyl)-*L*-tryptophanate as yellow oil (110 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.54 (d, *J* = 6.4 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.18 (m, 4H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.10 –

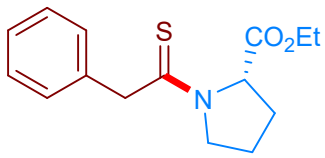
6.92 (m, 2H), 6.58 (d, J = 1.8 Hz, 1H), 5.44 (dd, J = 12.4, 5.2 Hz, 1H), 4.07 (s, 2H), 3.69 (d, J = 6.4 Hz, 3H), 3.64 – 3.48 (m, 1H), 3.34 (dd, J = 14.9, 4.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1, 171.4, 136.1, 134.6, 129.5, 129.0, 127.7, 127.5, 122.8, 122.3, 119.8, 118.5, 111.3, 109.1, 58.3, 53.1, 52.6, 25.9. Optical Rotation: $[\alpha]^{25}_D$ = 48.8 (c 0.16, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{20}H_{21}N_2O_2S$ 353.1318; found: 353.1312.

Methyl *N*2-((benzyloxy)carbonyl)-*N*6-(2-phenylethanethioyl)-*L*-lysinate (3cf)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and methyl ((benzyloxy)carbonyl)-*L*-lysinate (147 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave methyl *N*2-((benzyloxy)carbonyl)-*N*6-(2-phenylethanethioyl)-*L*-lysinate as yellow oil (155 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 6.84 (m, 10H), 5.43 (d, J = 8.0 Hz, 1H), 5.12 (d, J = 11.5 Hz, 2H), 4.34 (d, J = 4.8 Hz, 1H), 4.23 – 3.97 (m, 2H), 3.73 (s, 3H), 3.59 (d, J = 4.6 Hz, 2H), 1.81 (d, J = 7.3 Hz, 1H), 1.71 – 1.48 (m, 3H), 1.28 (dd, J = 19.6, 12.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1, 172.7, 156.1, 136.1, 135.3, 129.4, 129.2, 128.6, 128.3, 128.1, 127.7, 67.1, 53.5, 53.0, 52.5, 45.7, 32.4, 27.0, 22.5. Optical Rotation: $[\alpha]^{25}_D$ = 6.83 (c 0.28, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{23}H_{29}N_2O_4S$ 429.1843; found: 429.1838.

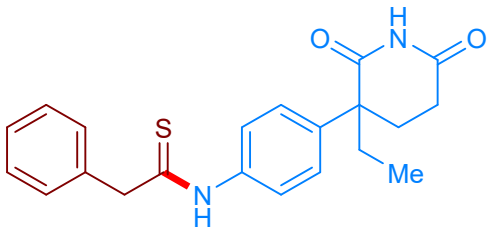
Ethyl (2-phenylethanethioyl)-*L*-prolinate (3cg)



The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and ethyl *L*-prolinate (72 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave ethyl (2-phenylethanethioyl)-*L*-prolinate as yellow oil (94 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 6.83 (m, 5H), 5.00 (dd, J = 9.0, 2.8 Hz, 1H), 4.42 – 4.02 (m, 4H), 3.81 – 3.45 (m, 2H), 2.49 – 2.13 (m, 1H), 2.13 – 1.84 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H).

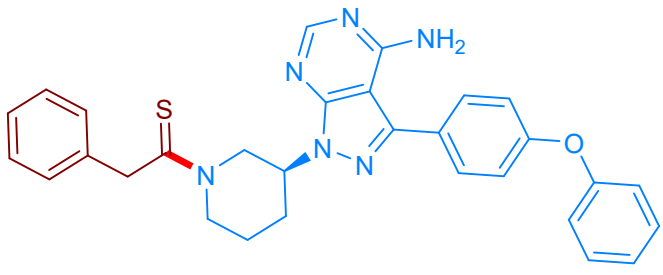
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 170.4, 135.4, 128.7, 128.4, 126.9, 65.8, 61.3, 51.5, 51.1, 29.4, 25.1, 14.2. Optical Rotation: $[\alpha]^{25}_D$ = -90.9 (c 0.36, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{20}NO_2S$ 278.1209; found: 278.1206.

AMinoglutethiMide derivative (3da)



The general procedure A conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and AMinoglutethiMide (116 mg, 0.5 mmol) in DMF (2.5 mL) at 90 °C for 8 h gave AMinoglutethiMide thioamide derivative as yellow oil (106.1 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.21 (s, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.52 – 7.38 (m, 2H), 7.38 – 7.30 (m,3H), 7.33 – 7.19 (m, 2H), 4.25 (s, 2H), 2.57 (dd, *J* = 18.1, 4.1 Hz, 1H), 2.35 (td, *J* = 13.1, 5.7 Hz, 2H), 2.21 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.01 (dd, *J* = 14.2, 7.3 Hz, 1H), 1.89 (s, 1H), 1.00 – 0.66 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.1, 174.9, 172.2, 138.0, 137.2, 135.0, 129.5, 129.4, 128.1, 126.7, 123.6, 55.2, 50.9, 32.8, 29.2, 27.0, 9.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{21}H_{23}N_2O_2S$ 367.1475; found: 367.1471.

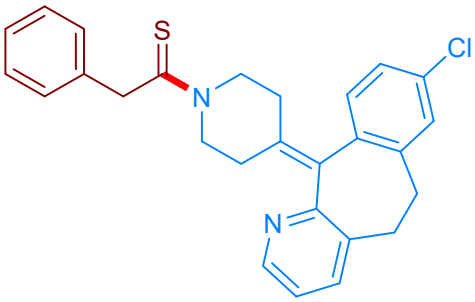
Ibrutinib intermediate (3db)



The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and Ibrutinib intermediate (193 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave Ibrutinib intermediate thioamide derivative as yellow oil (221 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 15.5 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 3H), 7.34 – 7.20 (m, 3H), 7.16 (t, *J* = 10.4 Hz, 3H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.74 – 5.41 (m, 2H), 5.20 – 4.58 (m, 1H), 4.57 – 4.06 (m, 4H), 3.76 (dt, *J* = 38.3,

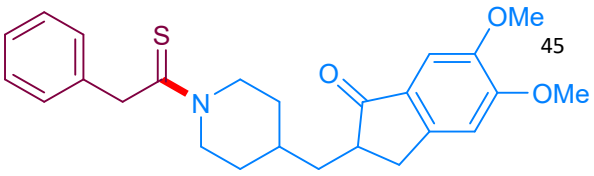
19.0 Hz, 1H), 3.23 (dt, *J* = 24.4, 11.8 Hz, 1H), 2.32 (dddd, *J* = 61.8, 53.9, 45.4, 40.9 Hz, 2H), 1.93 – 1.53 (m, 1H), 1.49 – 1.01 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.34, 158.62, 158.10, 156.28, 155.66, 154.13, 144.18, 135.90, 130.01, 129.93, 128.91, 127.86, 127.57, 127.02, 124.12, 119.60, 119.10, 98.57, 60.42, 55.84 – 52.57, 52.32 – 49.81, 29.53, 23.71, 21.08, 14.22. Optical Rotation: $[\alpha]^{25}_D$ = -211.9 (c 0.18, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{30}H_{29}N_6OS$ 521.2118; found: 521.2119.

1-(4-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidin-1-yl)-2-phenylethane-1-thione (3dc)



The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and Desloratadine (95 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave 1-(4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)- piperidin-1-yl)-2-phenylethane-1-thione as yellow oil (180 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.18 (m, 1H), 7.40 (t, *J* = 6.4 Hz, 1H), 7.36 – 7.22 (m, 4H), 7.21 – 6.87 (m, 5H), 5.19 – 4.63 (m, 1H), 4.61 – 4.19 (m, 2H), 3.80 (qdd, *J* = 13.7, 11.2, 4.5 Hz, 2H), 3.61 – 3.13 (m, 3H), 3.12 – 2.61 (m, 3H), 2.61 – 2.23 (m, 2H), 2.09 (dd, J = 13.5, 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 199.0, 156.5, 156.3, 146.7, 146.6, 139.7, 139.6, 137.8, 137.7, 137.5, 137.3, 136.0, 135.3, 135.2, 135.1, 133.4, 133.3, 133.1, 133.0, 130.4, 130.2, 129.1, 128.9, 127.8, 127.7, 127.0, 126.3, 126.2, 122.5, 122.5, 51.0, 50.3, 31.6, 31.5, 31.5, 30.5, 30.3, 29.7, 29.4. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{27}H_{26}N_2ClS$ 445.1500; found: 445.1495.

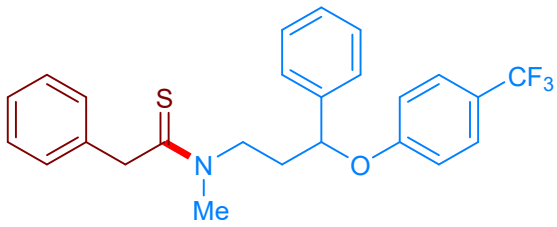
5,6-Dimethoxy-2-((1-(2-phenylethanethioyl)piperidin-4-yl)methyl)-2,3-dihydro-1*H*-inden-1-one (3dd)



The general procedure C conducted

with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 5,6-Dimethoxy-2-(4-piperidinylmethyl)-1-indanone (145 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave 5,6-dimethoxy-2-((1-(2-phenylethanethioyl)piperidin-4-yl)methyl)-2,3-dihydro-1*H*-inden-1-one as yellow oil (160 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 5H), 7.12 (s, 1H), 6.83 (s, 1H), 5.87 – 5.35 (m, 1H), 4.33 (dd, *J* = 35.7, 15.2 Hz, 2H), 4.22 – 4.04 (m, 1H), 3.94 (d, *J* = 7.0 Hz, 3H), 3.88 (d, *J* = 6.9 Hz, 3H), 3.54 – 3.14 (m, 1H), 3.02 (ddd, *J* = 21.7, 21.1, 11.4 Hz, 2H), 2.62 (ddd, *J* = 19.3, 12.2, 7.5 Hz, 2H), 1.92 – 1.71 (m, 3H), 1.62 (s, 1H), 1.43 – 1.17 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1, 198.6, 155.6, 149.5, 148.6 (d, *J* = 2.9 Hz), 136.1, 129.1 (d, *J* = 5.3 Hz), 128.8 (d, *J* = 1.0 Hz), 127.8 (d, *J* = 1.1 Hz), 126.9 (d, *J* = 3.5 Hz), 107.4, 104.4, 56.2 (d, *J* = 13.8 Hz), 50.8 (d, *J* = 37.3 Hz), 44.9 (d, *J* = 26.5 Hz), 38.0 (d, *J* = 16.3 Hz), 33.8 (d, *J* = 38.3 Hz), 33.3 (d, *J* = 22.6 Hz), 32.8, 32.0 (d, *J* = 16.8 Hz), 31.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{25}H_{30}NO_3S$ 424.1941; found: 424.1935.

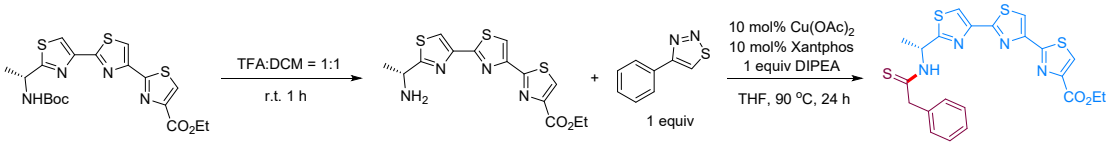
N-Methyl-2-phenyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)ethanethioamide (3de)



The general procedure C conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and Fluoxetine (155 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave N-methyl-2-phenyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)ethanethioamide as yellow oil (171 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 13.1, 8.7 Hz, 2H), 7.41 – 7.19 (m, 10H), 6.89 (t, *J* = 8.2 Hz, 2H), 5.17 (ddd, *J* = 11.9, 8.6, 3.7 Hz, 1H), 4.53 – 4.07 (m, 3H), 3.93 – 3.65 (m, 1H), 3.31 (d, *J* = 126.3 Hz, 3H), 2.65 – 2.26 (m, 1H), 2.10 – 1.96 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.49 (d, *J* = 23.6 Hz, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 160.1, 139.9, 135.9, 129.1, 129.0 – 128.8, 128.4, 128.1, 127.1, 127.0 – 126.7, 125.6, 115.8, 53.5, 51.3, 50.6, 41.8, 35.5, 29.7. HRMS (ESI-quadrupole) *m/z*: [M+H]+ Calcd. for $C_{25}H_{25}NF_3OS$ 444.1603; found:

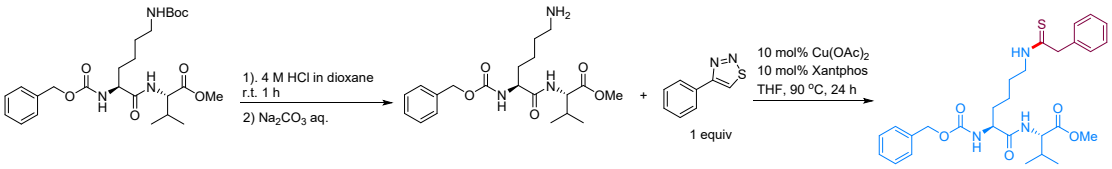
444.1599.

Ethyl-(*R*)-2''-(1-(2-phenylethanethioamido)ethyl)-[2,4':2',4''-terthiazole]-4-carboxylate (3df)



The modified procedure B conducted with ethyl (*R*)-2''-(1-((tert-butoxycarbonyl)amino)ethyl)-[2,4':2',4''-terthiazole]-4-carboxylate (60 mg, 0.13 mmol) in TFA/DCM (1 mL:1 mL) at r.t. for 1 h. TLC monitored until quant. transformation. Removing the excess TFA and DCM, concentrated in vacuo, after which, 4-phenyl-1,2,3-thiadiazole (21 mg, 0.13 mmol), $Cu(OAc)_2$ (2 mg, 0.013 mmol), Xantphos (6 mg, 0.013 mmol) and DIPEA (17 mg, 0.13 mmol) in THF (0.5 mL) at 90 °C for 8 h gave ethyl-(*R*)-2''-(1-(2-phenylethanethioamido)ethyl) -[2,4':2',4''-terthiazole]-4-carboxylate as yellow solid (40 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.09 (s, 2H), 7.94 (s, 1H), 7.35 (dd, *J* = 19.3, 6.2 Hz, 5H), 6.39 – 5.56 (m, 1H), 4.44 (dd, *J* = 13.6, 6.6 Hz, 2H), 4.20 (s, 2H), 1.66 (d, *J* = 6.5 Hz, 3H), 1.42 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 170.7, 163.2, 162.6, 161.4, 149.1, 147.9, 147.8, 134.8, 129.5, 129.3, 127.9, 118.0, 117.1, 61.6, 53.1, 52.7, 20.5, 14.4. Optical Rotation: $[\alpha]^{25}_D$ = -31.5 (c 0.11, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{22}H_{21}N_4O_2S_4$ 501.0542; found: 501.0539.

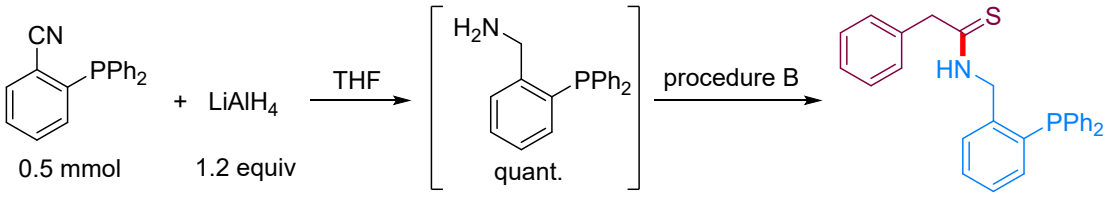
Methyl *N*2-((benzyloxy)carbonyl)-*N*6-(2-phenylethanethioyl)-*L*-lysyl-*L*-valinate (3dg)



The modified procedure B conducted with methyl *N*2-((benzyloxy)carbonyl)-*N*6-(tert-butoxycarbonyl)-*L*-lysyl-*L*-valinate (124 mg, 0.25 mmol) in 4M HCl in dioxane (2 mL) at r.t. for 1 h. TLC monitored until quant. transformation. Removing the excess

HCl under reduced pressure and free amine was obtained by neutralization of sodium carbonate aqueous solutionand, extracted by DCM, concentrated in vacuo. 4-phenyl-1,2,3-thiadiazole (32 mg, 0.19 mmol), $Cu(OAc)_2$ (3.6 mg, 0.019 mmol), Xantphos (10 mg, 0.019 mmol) and methyl ((benzyloxy)carbonyl)-*L*-lysyl-*L*-valinate (75 mg, 0.19 mmol) was added in THF (1 mL) at 90 °C for 8 h gave methyl *N*2-((benzyloxy)carbonyl)-*N*6-(2-phenylethan e-thioyl)-*L*-lysyl-*L*-valinate as yellow oil (62.5 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 6.7 Hz, 1H), 7.31 (dd, *J* = 15.7, 8.1 Hz, 10H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.38 – 4.83 (m, 3H), 4.46 (dd, *J* = 8.6, 4.9 Hz, 1H), 4.10 (dt, *J* = 30.8, 9.4 Hz, 2H), 3.82 – 3.50 (m, 3H), 3.37 – 2.93 (m, 1H), 2.14 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.88 – 1.70 (m, 1H), 1.47 (d, *J* = 5.7 Hz, 2H), 1.36 – 1.09 (m, 4H), 1.09 – 0.66 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.56, 172.08, 170.35, 156.63, 136.56, 135.30, 129.20, 129.07, 128.52, 128.10, 127.71, 66.68, 58.42, 57.48, 52.92, 52.25, 40.26, 30.76, 30.31, 29.69, 29.30, 21.90, 18.98, 17.72. Optical Rotation: $[\alpha]^{25}_D$ = -112.4 (c 0.11, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{28}H_{38}N_3O_5S$ 528.2527; found: 528.2521.

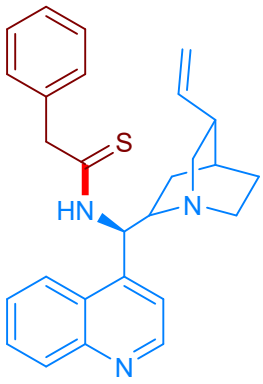
_N_-(2-(Diphenylphosphaneyl)benzyl)-2-phenylethanethioamide (3dh)



The modified procedure B was conducted. Degassed and dry THF was added under nitrogen to a round-bottomed flask equipped with a magnetic stirring bar and containing pre-weighted $LiAlH_4$ (1.2 eq.). The suspention was cooled down to 0 °C and 2-(diphenylphosphino)benzonitrile (287 mg, 0.5 mmol) was added portion-wise. After 2 additional hours at 0 °C it was stirred at room temperature overnight. It was then cooled down back to 0 °C and slowly quenched with aqueous sodium hydroxide. After THF removal, the remaining residue was dissolved in DCM, passed through a celite plug. The DCM solution was washed with water, dried other sodium sulfate and concentrated to dryness and further dried under high vacuum to afford crude product

next, which mixed with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(2-(diphenylphosphaneyl)benzyl)-2-phenylethanethioamide as yellow oil (93.5 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 7H), 7.30 – 7.22 (m, 5H), 7.21 – 7.15 (m, 5H), 7.12 – 7.01 (m, 2H), 6.98 – 6.73 (m, 1H), 5.01 (d, *J* = 5.7 Hz, 2H), 3.84 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.6, 140.5 (d, *J* = 25.4 Hz, 1C), 136.2 (d, *J* = 14.1 Hz, 1C), 135.8 (d, *J* = 8.8 Hz, 1C), 135.1, 134.0, 133.9, 133.8, 132.0 (d, *J* = 10.0 Hz, 1C), 130.3 (d, *J* = 5.6 Hz, 1C), 129.4, 129.1, 129.1, 128.8, 128.8, 128.4, 127.6, 125.9, 53.0, 49.0 (d, *J* = 19.3 Hz, 1C). ^{31}P NMR (202 MHz, $CDCl_3$) δ -15.5. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{27}H_{25}NPS$ 426.1440; found: 426.1443.

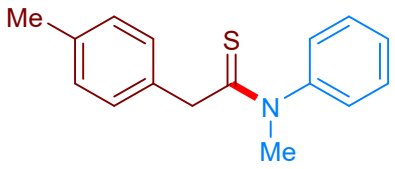
2-Phenyl-N-((*R*)-quinolin-4-yl((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ethanethioamide (3di)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (R)-quinolin-4-yl((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine (147 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave 2-phenyl-*N*-((*R*)-quinolin-4-yl((1*S*,2*R*,4*S*,5*R*)-5-vinyl -quinuclidin-2-yl)methyl)ethanethioamide as yellow oil (100.3 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.79 (d, *J* = 4.4 Hz, 1H), 8.21 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.29 (dd, *J* = 14.7, 7.3 Hz, 3H), 7.20 (d, *J* = 3.4 Hz, 1H), 5.89 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H), 5.57 (s, 1H), 5.14 (dd, *J* = 34.4, 13.9 Hz, 2H), 4.09 (q, *J* = 15.6 Hz, 2H), 2.93 (dd, *J* = 17.7, 8.6 Hz, 1H), 2.77 (dd, *J* = 16.2, 7.7 Hz, 3H), 2.63 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.26 (dd, *J* = 15.9, 7.7 Hz, 1H), 1.49 (dd, *J* = 9.9, 7.4 Hz, 1H), 1.37 (ddd, *J* = 14.5, 9.1, 4.4 Hz, 2H), 0.96 – 0.85 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9, 149.9, 148.4, 139.8, 135.7, 130.3, 129.3, 129.1, 128.9, 127.5,

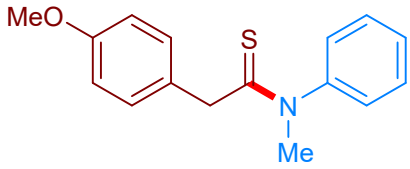
126.5, 123.7, 115.2, 53.1, 48.8, 46.8, 39.0, 27.2, 26.4, 25.4. Optical Rotation: $[\alpha]^{25}_{D}$ = 412.3 (c 0.27, CH_2Cl_2). HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{27}H_{30}N_3S$ 428.2155; found: 428.2156.

_N_-methyl-_N_-phenyl-2-(p-tolyl)ethanethioamide (3ea)



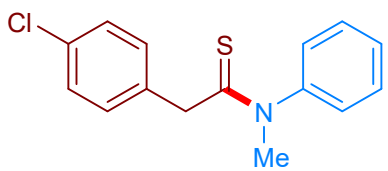
The general procedure D conducted with 4-(*p*-tolyl)-1,2,3-thiadiazole (88 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave *N*-methyl-*N*-phenyl-2-(*p*-tolyl)ethanethioamide as yellow oil (110 mg, 86%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 3H), 7.10 – 6.93 (m, 4H), 6.89 (d, *J* = 7.6 Hz, 2H), 3.95 (s, 2H), 3.70 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1, 145.4, 136.2, 133.8, 129.7, 128.9, 128.6, 128.5, 126.0, 50.3, 46.3, 21.1. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{18}NS$ 256.1154; found: 256.1152.

2-(4-Methoxyphenyl)-_N_-methyl-_N_-phenylethanethioamide (3eb)



The general procedure D conducted with 4-(4-methoxyphenyl)-1,2,3-thiadiazole (96 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave 2-(4-methoxyphenyl)-*N*-methyl- *N*-phenylethanethioamide as yellow oil (114 mg, 84%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 4.8 Hz, 3H), 7.00 (d, *J* = 6.9 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 7.9 Hz, 2H), 3.94 (s, 2H), 3.74 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 158.4, 145.4, 129.7, 129.7, 128.8, 128.5, 126.0, 113.5, 55.2, 49.8, 46.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{18}NOS$ 272.1104; found: 272.1099.

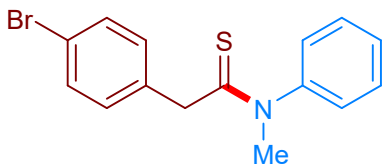
2-(4-Chlorophenyl)-_N_-methyl-_N_-phenylethanethioamide (3ec)



The general procedure D conducted with 4-(4-chlorophenyl)-1,2,3-thiadiazole (98 mg, 0.5 mmol),

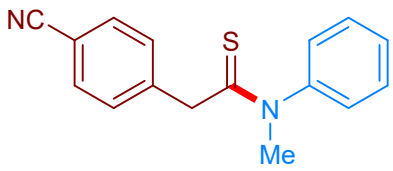
$Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave 2-(4-chlorophenyl)-*N*-methyl-*N*-phenylethanethioamide as yellow oil (122 mg, 89%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 4.6 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 19.1 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.42 (s, 1H), 5.12 (q, *J* = 7.8 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.3, 143.7, 138.9, 134.0, 129.9, 129.1, 128.7, 128.4, 126.8, 73.4, 46.9. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{15}NClS$ 276.0608; found: 276.0254.

2-(4-Bromophenyl)-*N*-methyl-*N*-phenylethanethioamide (3ed)



The general procedure D conducted with 4-(4-bromophenyl)-1,2,3-thiadiazole (120 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave 2-(4-bromophenyl)-*N*-methyl-*N*-phenylethanethioamide as yellow oil (120 mg, 75%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 4.5 Hz, 3H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.12 – 6.95 (m, 2H), 6.88 (d, *J* = 7.9 Hz, 2H), 3.94 (s, 2H), 3.71 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9, 145.3, 135.7, 131.2, 130.5, 129.9, 128.7, 125.9, 120.7, 50.0, 46.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{15}NBrS$ 320.0103; found: 320.0099.

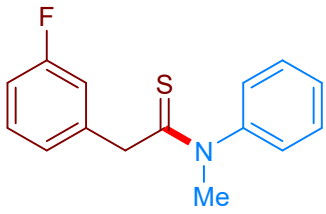
2-(4-cyanophenyl)-*N*-methyl-*N*-phenylethanethioamide (3ee)



The general procedure D conducted with 4-(1,2,3-thiadiazol-4-yl)benzonitrile (94 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave 2-(4-cyanophenyl)-*N*-methyl-*N*-phenylethanethioamide as yellow solid (89 mg, 67%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 6.9 Hz, 1H), 7.27 (dd, *J* = 12.4, 7.8 Hz, 4H), 4.90 (s, 2H), 4.17 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 141.7, 134.9, 132.5, 129.5, 129.3, 128.2, 128.0, 118.6, 111.5, 53.1, 48.9. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{15}N_2S$ 267.0950;

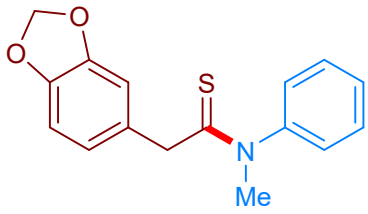
found: 267.0949.

2-(3-Fluorophenyl)-*N*-methyl-*N*-phenylethanethioamide (3ef)



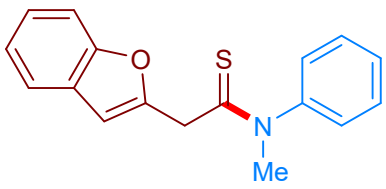
The general procedure D conducted with 4-(3-fluorophenyl)-1,2,3-thiadiazole (90 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave 2-(3-fluorophenyl)-*N*-methyl-*N*-phenylethanethioamide as yellow oil (105 mg, 81%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 1.5 Hz, 3H), 7.11 (dd, *J* = 14.5, 7.1 Hz, 1H), 7.00 (s, 2H), 6.85 (t, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 2H), 4.00 (s, 2H), 3.72 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -113.42 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7, 162.5 (d, *J* = 245.4 Hz), 145.2, 139.1 (d, *J* = 7.5 Hz), 129.8, 129.5 (d, *J* = 8.3 Hz), 128.7, 125.9, 124.4 (d, *J* = 2.7 Hz), 115.6 (d, *J* = 22.0 Hz), 113.6 (d, *J* = 21.0 Hz), 50.3 (d, *J* = 1.3 Hz), 46.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{15}NFS$ 260.0904; found: 260.0900.

(Benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-*N*-phenylethanethioamide (3eg)



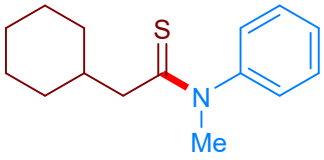
The general procedure D conducted with 4-(benzo[*d*][1,3]dioxol-5-yl)-1,2,3-thiadiazole (103 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave 2-(benzo[*d*][1,3]dioxol-5-yl) -*N*-methyl-*N*-phenylethanethioamide as yellow solid (80 mg, 56%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 5.6 Hz, 3H), 6.95 (d, *J* = 7.1 Hz, 2H), 6.55 (s, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 6.25 (d, *J* = 7.9 Hz, 1H), 5.82 (s, 2H), 3.84 (s, 2H), 3.64 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.9, 147.4, 146.3, 145.4, 130.4, 129.7, 128.6, 126.0, 121.9, 109.2, 107.9, 100.9, 50.2, 46.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{16}H_{16}NO_2S$ 286.0896; found: 286.0891.

1-(Benzofuran-2-yl)-*N*-methyl-*N*-phenylethanethioamide (3eh)



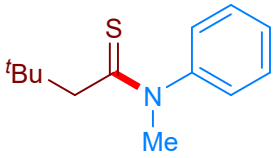
The general procedure D conducted with 4-(benzofuran-2-yl)-1,2,3-thiadiazole (101 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave 1-(benzofuran-2-yl)-*N*-methyl- *N*-phenylethanethioamide as yellow oil (98 mg, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 9.8, 2.8 Hz, 1H), 7.42 (ddd, *J* = 8.8, 6.1, 3.9 Hz, 4H), 7.31 – 7.12 (m, 4H), 6.50 (s, 1H), 4.13 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 154.7, 153.6, 145.3, 130.0, 128.8, 128.6, 125.6, 123.7, 122.6, 120.7, 111.0, 104.7, 46.3, 44.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{17}H_{16}NOS$ 282.0947; found: 282.0944.

Cyclohexyl-*N*-methyl-*N*-phenylethanethioamide (3ei)



The general procedure D conducted with 4-cyclohexyl-1,2,3-thiadiazole (84 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave cyclohexyl-*N*-methyl-*N*-phenylethanethioamide as yellow oil (90 mg, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (dt, *J* = 27.6, 7.4 Hz, 3H), 7.10 (d, *J* = 7.6 Hz, 2H), 3.70 (s, 3H), 2.35 (d, *J* = 7.0 Hz, 2H), 2.12 – 1.92 (m, 1H), 1.59 (dd, *J* = 31.5, 11.0 Hz, 5H), 1.16 (d, *J* = 12.7 Hz, 2H), 1.08 – 0.87 (m, 1H), 0.65 (d, *J* = 12.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3, 145.7, 129.9, 128.4, 126.0, 50.7, 46.0, 39.5, 32.7, 26.2, 26.1. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{22}NS$ 248.1467; found: 248.1465.

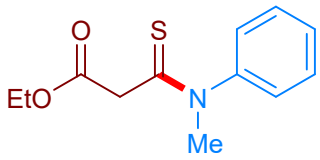
***N*,3,3-Trimethyl-*N*-phenylbutanethioamide (3ej)**



The general procedure D conducted with 4-(tert-butyl)-1,2,3-thiadiazole (71 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave *N*,3,3-trimethyl-*N*-phenylbutanethioamide as yellow oil (78 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 24.4, 6.7 Hz, 3H), 7.17 (d, *J* = 7.0 Hz, 2H), 3.75 (s, 3H), 2.73 (s, 2H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.4,

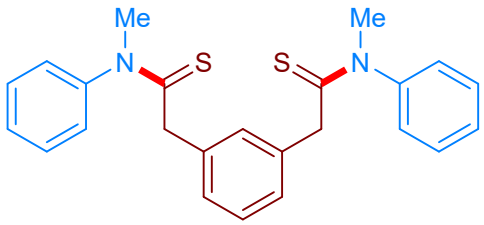
146.6, 129.7, 128.1, 126.4, 54.8, 46.6, 33.0, 30.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{20}NS$ 222.1311; found: 222.1309.

Ethyl 3-(methyl(phenyl)amino)-3-thioxopropanoate (3ek)



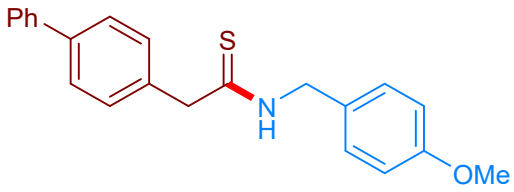
The general procedure D conducted with ethyl 1,2,3-thiadiazole-4-carboxylate (79 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and N-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave ethyl 3-(methyl(phenyl)amino)-3-thioxopropanoate as yellow oil (78 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dq, *J* = 14.5, 7.2 Hz, 3H), 7.25 (d, *J* = 7.0 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 2H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 168.0, 145.3, 130.0, 128.9, 125.6, 61.3, 50.4, 45.8, 14.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{12}H_{16}NO_2S$ 238.0896; found: 238.0894.

2,2'-(1,3-Bhenylene)bis(*N*-methyl-*N*-phenylethanethioamide) (3el)



The general procedure D conducted with 1,3-di(1,2,3-thiadiazol-4-yl)benzene (123 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave 2,2'-(1,3-phenylene)bis(*N*-methyl-*N*-phenylethanethioamide) as yellow oil (109 mg, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 6H), 7.02 (d, *J* = 18.4 Hz, 5H), 6.82 (d, *J* = 7.4 Hz, 2H), 6.71 (s, 1H), 3.92 (s, 4H), 3.74 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 145.4, 136.8, 129.7, 128.8, 128.5, 127.9, 127.0, 126.0, 50.4, 46.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{24}H_{25}N_2S_2$ 405.1454; found: 405.1450.

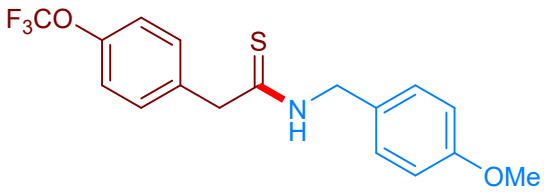
2-([1,1'-Biphenyl]-4-yl)-*N*-(4-methoxybenzyl)ethanethioamide (3em)



The general procedure B conducted with 4-([1,1'-biphenyl]-4-yl)-1,2,3-thiadiazole (119 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05

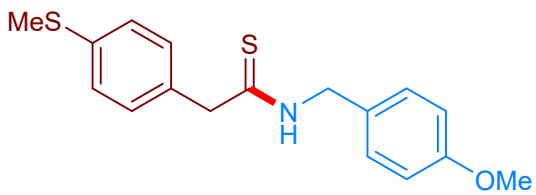
mmol), Xantphos (28 mg, 0.05 mmol) and (4-methoxyphenyl)methanamine (69 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave 2-([1,1'-biphenyl]-4-yl)-*N*-(4-methoxybenzyl)ethanethioamide as yellow oil (91.9 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.53 (m, 4H), 7.43 (t, *J* = 7.6 Hz, 3H), 7.33 (dt, *J* = 7.7, 7.1 Hz, 3H), 7.13 (t, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.76 (d, *J* = 5.2 Hz, 1.18H), 4.34 (d, *J* = 5.7 Hz, 0.67H), 4.18 (s, 1.22H), 3.77 (d, *J* = 11.1 Hz, 3H), 3.62 (s, 0.73H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9, 159.4, 159.0, 140.7, 140.4, 134.0, 132.1, 129.9, 129.3, 129.0, 128.9, 127.8, 127.7, 127.5, 127.4, 127.0, 114.3, 114.1, 55.3, 52.7, 49.8, 43.4, 43.2, 29.7. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{22}H_{22}NOS$ 348.1417; found: 348.1419.

_N_-(4-Methoxybenzyl)-2-(4-(trifluoromethoxy)phenyl)ethanethioamide (3en)



The general procedure B conducted with 4-(4-(trifluoromethoxy)phenyl)-1,2,3-thiadiazole (123 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (4-methoxyphenyl)methanamine (69 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(4-methoxybenzyl)-2-(4-(trifluoromethoxy)phenyl) ethanethioamide as yellow oil (150.1 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.14 (dd, *J* = 17.8, 8.4 Hz, 4H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 5.2 Hz, 2H), 4.04 (s, 2H), 3.75 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -57.84 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.3, 159.4, 148.6, 134.3, 130.7, 129.4, 127.9, 121.4, 120.5 (q, *J* = 257.5 Hz), 114.3, 55.3, 52.1, 49.9. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{17}H_{17}F_3NO_2S$ 356.0927; found: 356.0930.

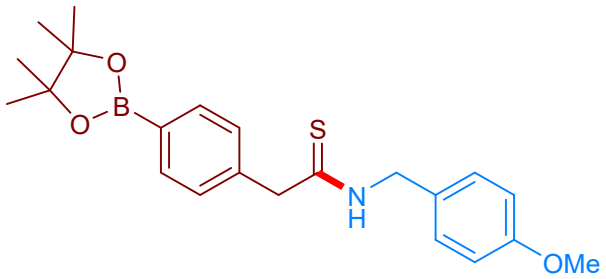
_N_-(4-methoxybenzyl)-2-(4-(methylthio)phenyl)ethanethioamide (3eo)



The general procedure B conducted with 4-(4-(methylthio)phenyl)-1,2,3-thiadiazole (104 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol)

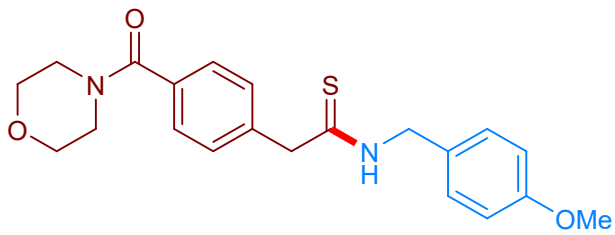
and (4-methoxyphenyl)methanamine (69 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(4-methoxybenzyl)-2-(4-(methylthio)phenyl)ethanethioamide as yellow oil (129 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.24 – 7.07 (m, 6H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.72 (d, *J* = 5.2 Hz, 2H), 4.06 (s, 2H), 3.76 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 159.4, 138.3, 131.6, 129.9, 129.4, 128.0, 127.0, 114.3, 55.3, 52.5, 49.8, 15.7. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{17}H_{20}NOS_2$ 318.0981; found: 318.0978.

_N_-(4-methoxybenzyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanethioamide (3ep)



The general procedure B conducted with (4-(1,2,3-thiadiazol-4-yl)phenyl)(morpholino)methanone (144 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (4-methoxyphenyl)methanamine (69 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(4-methoxybenzyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanethioamide as yellow oil (79.4 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 6.1 Hz, 2H), 7.18 (d, *J* = 5.5 Hz, 3H), 7.03 (d, *J* = 6.7 Hz, 2H), 6.74 (d, *J* = 6.6 Hz, 2H), 4.64 (s, 2H), 4.07 (s, 2H), 3.69 (s, 3H), 1.26 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.6, 159.3, 138.1, 135.6, 129.3, 128.8, 128.0, 114.3, 84.0, 55.3, 53.2, 49.8, 24.9. HRMS (ESI-quadrupole) *m/z*: $[M]^+$ Calcd. for $C_{22}H_{28}BNO_3S$ 397.1883; found: 397.1996.

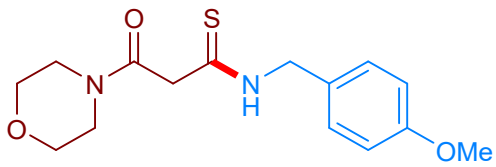
_N_-(4-methoxybenzyl)-2-(4-(morpholine-4-carbonyl)phenyl)ethanethioamide (3eq)



The general procedure B conducted with (4-(1,2,3-thiadiazol-4-yl) -phenyl)(morpholino)methanone (138 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (4-methoxyphenyl)methanamine

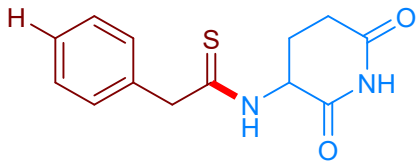
(69 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(4-methoxybenzyl)-2-(4-(morpholine-4-carbonyl)phenyl)ethanethioamide as yellow oil (147.8 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.21 (d, *J* = 5.8 Hz, 4H), 7.19 – 7.04 (m, 2H), 6.81 (dd, *J* = 9.2, 2.5 Hz, 2H), 4.69 (d, *J* = 5.2 Hz, 2H), 4.05 – 3.90 (m, 2H), 3.86 – 3.72 (m, 3H), 3.69 – 3.28 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.0, 170.2, 159.2, 138.5, 133.7, 129.6, 129.2, 128.3, 127.4, 114.1, 66.8, 55.3, 52.1, 49.7. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{21}H_{25}N_2O_3S$ 385.1580; found: 385.1581.

_N_-(4-Methoxybenzyl)-3-morpholino-3-oxopropanethioamide (3er)



The general procedure B conducted with morpholino(1,2,3-thiadiazol-4-yl)methanone (100 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and (4-methoxyphenyl)methanamine (69 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(4-methoxybenzyl)-2-(4-(trifluoromethoxy)phenyl)ethanethioamide as yellow oil (72.4 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.79 – 7.03 (m, 2H), 6.80 (d, *J* = 8.2 Hz, 2H), 4.69 (d, *J* = 5.2 Hz, 2H), 3.78 (s, 2H), 3.72 (d, *J* = 0.6 Hz, 3H), 3.67 – 3.53 (m, 6H), 3.53 – 3.46 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9, 167.1, 159.3, 129.5, 128.1, 114.2, 66.6, 66.5, 55.3, 49.7, 47.8, 46.7, 42.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{21}N_2O_3S$ 309.1267; found: 309.1263.

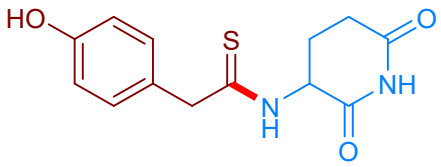
_N_-(2,6-Dioxopiperidin-3-yl)-2-phenylethanethioamide (3es)



The general procedure B conducted with 4-phenyl-1,2,3-thiadiazole (81 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 3-aminopiperidine-2,6-dione (64 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(2,6-dioxopiperidin-3-yl)-2-phenylethanethioamide as yellow oil (103.5 mg, 79%). ^{1}H NMR (500 MHz, DMSO) δ 11.00 (s, 1H), 10.51 (s, 1H), 8.27 – 6.55 (m, 5H), 5.37 (d, *J* = 7.2 Hz, 1H), 4.26 – 3.77 (m, 2H), 3.03 – 2.32 (m, 2H), 2.32 – 1.76 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 202.8, 173.1, 171.4, 137.8, 129.2, 128.7,

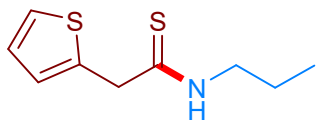
127.1, 55.2, 51.6, 31.0, 23.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{15}N_2O_2S$ 263.0849; found: 263.0853.

_N_-(2,6-Dioxopiperidin-3-yl)-2-(4-hydroxyphenyl)ethanethioamide (3et)



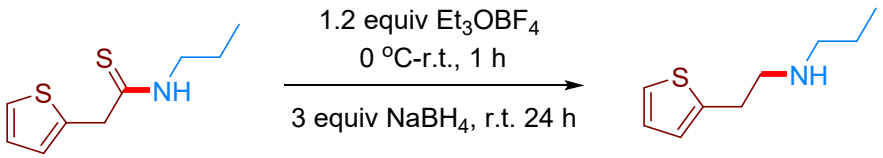
The general procedure B conducted with 4-(1,2,3-thiadiazol-4-yl)phenol (89 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 3-aminopiperidine-2,6-dione (64 mg, 0.5 mmol) in THF (2.5 mL) at 90 °C for 8 h gave *N*-(2,6-dioxopiperidin-3-yl)-2-(4-hydroxyphenyl)- ethanethioamide as pale yellow solid (89 mg, 64%). ^{1}H NMR (500 MHz, DMSO) δ 10.96 (d, *J* = 18.5 Hz, 1H), 10.34 (d, *J* = 10.2 Hz, 1H), 9.75 – 8.51 (m, 1H), 7.12 (dd, *J* = 11.6, 6.7 Hz, 2H), 6.92 – 6.50 (m, 2H), 5.35 (s, 1H), 3.83 (dd, *J* = 12.1, 6.6 Hz, 2H), 2.62 (d, *J* = 102.4 Hz, 2H), 2.00 (d, *J* = 83.1 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 203.5, 173.1, 171.4, 156.6, 130.2, 127.9, 115.4, 55.2, 50.9, 31.0, 23.3. Spectroscopic data match those previously reported in the literature.[19]

_N_-Propyl-2-(thiophen-2-yl)ethanethioamide (3eu)



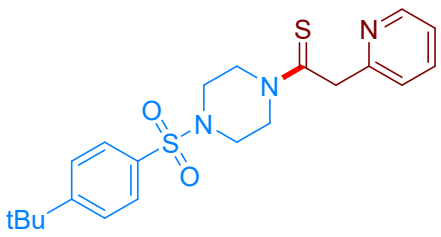
The general procedure B conducted with 4-(thiophen-2-yl)-1,2,3-thiadiazole (672 mg, 4 mmol), $Cu(OAc)_2$ (72 mg, 0.4 mmol), Xantphos (224 mg, 0.4 mmol) and propan-1-amine (236 mg, 4 mmol) in THF (20 mL) at 90 °C for 8 h gave *N*-propyl-2-(thiophen-2-yl)ethanethioamideas yellow oil (700 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.30 (d, *J* = 5.2 Hz, 1H), 7.03 (dd, *J* = 4.8, 3.7 Hz, 1H), 6.97 (d, *J* = 2.9 Hz, 1H), 4.32 (s, 2H), 3.59 (dd, *J* = 13.0, 6.8 Hz, 2H), 1.91 – 1.38 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.2, 136.1, 128.1, 127.6, 126.4, 47.8, 46.7, 21.1, 11.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_9H_{14}NS_2$ 200.0562; found: 200.0560.

_N_-(2-(Thiophen-2-yl)ethyl)propan-1-amine (3ev)



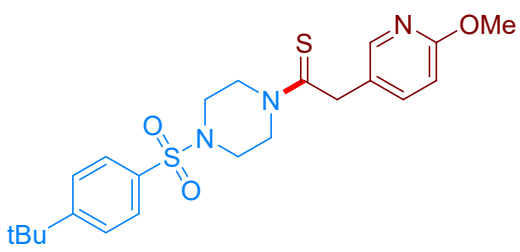
The general procedure conducted as reported[18]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 5.2 Hz, 1H), 7.02 – 6.89 (m, 1H), 6.84 (d, *J* = 3.0 Hz, 1H), 3.03 (t, *J* = 6.9 Hz, 2H), 2.91 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 1.50 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 126.9, 125.0, 123.5, 51.6, 51.1, 30.4, 23.1, 11.8. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_9H_{16}NS$ 170.0998; found: 170.0996.

1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(pyridin-2-yl)ethane-1-thione (3ew)



The general procedure C conducted with 4-(pyridin-2-yl)-1,2,3-thiadiazole (82 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 1-((4-(tert-butyl)phenyl)sulfonyl)piperazine (141 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave 1-(4-((4-(tert-butyl)phenyl)sulfinyl)piperazin-1-yl)-2-(pyridin-2-yl)ethane-1-thione as yellow solid (153 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 4.2 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.57 – 7.50 (m, 3H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.12 (dd, *J* = 6.7, 5.1 Hz, 1H), 4.71 – 4.29 (m, 4H), 4.15 – 3.84 (m, 2H), 3.24 – 3.01 (m, 2H), 2.97 – 2.79 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5, 157.1, 156.1, 149.2, 136.8, 132.0, 127.6, 126.2, 123.4, 122.2, 53.1, 50.0, 49.0, 45.9, 45.3, 35.2, 31.1. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{21}H_{28}N_3O_2S_2$ 418.1617; found: 418.1618.

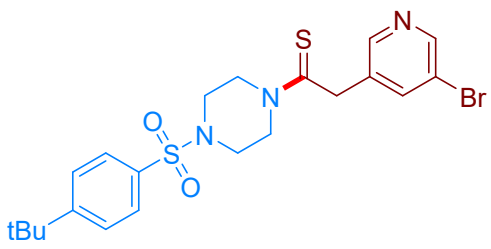
1-(4-((4-(tert-butyl)phenyl)sulfinyl)piperazin-1-yl)-2-(6-methoxypyridin-3-yl)ethane-1-thione (3ex)



The general procedure C conducted with 4-(6-methoxypyridin-2-yl)-1,2,3-thiadiazole (97 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and

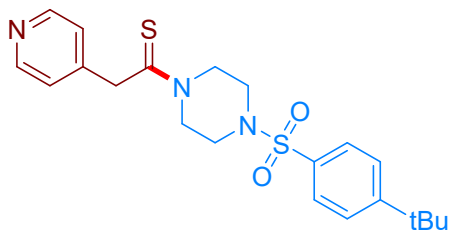
1-((4-(tert-butyl)phenyl)sulfonyl) -piperazine (141 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave 1-(4-((4-(tert-butyl)phenyl)sulfinyl)piperazin-1-yl)-2-(6-methoxypyridin-3-yl)ethane-1-thione as white solid (169 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$)δ 7.95 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 3H), 6.59 (d, *J* = 8.5 Hz, 1H), 4.41 (s, 2H), 4.15 (s, 2H), 3.91 (s, 3H), 3.77 (s, 2H), 3.08 (d, *J* = 4.4 Hz, 2H), 2.83 (s, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.4, 163.4, 157.3, 145.9, 138.4, 131.9, 127.6, 126.3, 123.9, 111.1, 53.4, 49.3, 49.0, 46.7, 45.8, 45.3, 35.2, 31.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{22}H_{30}N_3O_3S_2$ 448.1723; found: 448.1724.

2-(5-bromopyridin-3-yl)-1-(4-((4-(tert-butyl)phenyl)sulfinyl)piperazin-1-yl)ethane-1-thione (3ey)



The general procedure C conducted with 4-(5-bromopyridin-3-yl)-1,2,3-thiadiazole (121 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 1-((4-(tert-butyl)phenyl)sulfonyl) -piperazine (141 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave 2-(5-bromopyridin-3-yl)-1-(4-((4-(tert-butyl)phenyl) -sulfinyl)piperazin-1-yl)ethane -1-thione as yellow solid (191 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 1.6 Hz, 1H), 8.36 (s, 1H), 7.79 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 4.61 – 4.34 (m, 2H), 4.19 (s, 2H), 3.95 – 3.60 (m, 2H), 3.32 – 3.06 (m, 2H), 3.04 – 2.87 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 157.4, 149.8, 147.6, 138.3, 133.2, 132.0, 127.6, 126.4, 120.9, 49.4, 49.0, 46.5, 45.8, 45.3, 35.3, 31.1. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{21}H_{27}N_3O_2S_2Br$ 496.0723; found: 496.0722.

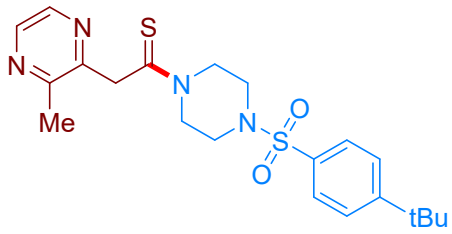
1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(pyridin-4-yl)ethane-1-thione (3ez)



The general procedure C conducted with 4-(pyridin-4-yl)-1,2,3-thiadiazole (82 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 1-((4-(tert-

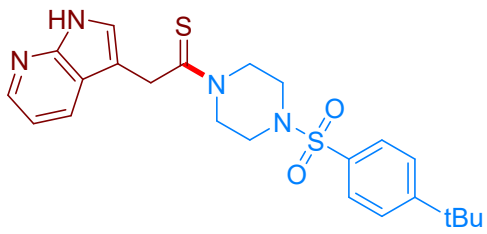
butyl)phenyl)sulfonyl)piperazine (141 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave 1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(pyridin-4-yl)ethane-1-thione as yellow solid (172 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.5 Hz, 2H), 7.57 (q, *J* = 8.6 Hz, 4H), 7.15 (d, *J* = 5.5 Hz, 2H), 4.58 – 4.33 (m, 2H), 4.25 (s, 2H), 3.88 – 3.56 (m, 2H), 3.14 – 2.97 (m, 2H), 2.90 – 2.67 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5, 157.3, 150.2, 144.6, 131.8, 127.5, 126.4, 123.1, 49.6, 49.5, 48.8, 45.6, 45.2, 35.2, 31.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{21}H_{28}N_3O_2S_2$ 418.1617; found: 418.1617.

1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(3-methylpyrazin-2-yl)ethane-1-thione (3eza)



The general procedure C conducted with 4-(3-methylpyrazin-2-yl)-1,2,3-thiadiazole (89 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 1-((4-(tert-butyl)phenyl)sulfonyl)piperazine (141 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave 1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(3-methylpyrazin-2-yl)ethane-1-thione as brown solid (172 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.09 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 4.49 (s, 2H), 4.38 (s, 2H), 4.07 – 3.83 (m, 2H), 3.27 – 3.14 (m, 2H), 3.14 – 3.02 (m, 2H), 2.60 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 157.3, 153.4, 150.8, 142.3, 141.1, 132.0, 127.7, 126.3, 50.0, 48.8, 48.6, 46.0, 45.4, 35.3, 31.1, 22.0. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{21}H_{29}N_4O_2S_2$ 433.1726; found: 433.1722.

1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1-thione (3ezb)

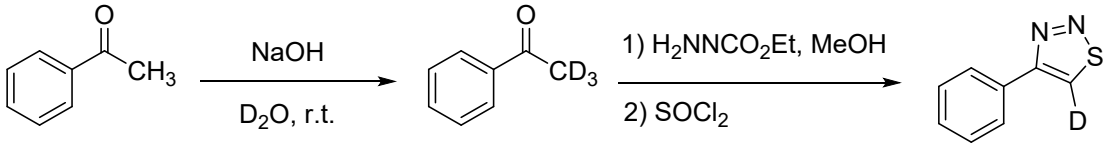


The general procedure C conducted with 4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1,2,3-thiadiazole (101 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), Xantphos (28 mg, 0.05 mmol) and 1-((4-(tert-butyl)phenyl)sulfonyl) -

piperazine (141 mg, 0.5 mmol) in 1,4-dioxane (2.5 mL) at 90 °C for 8 h gave 1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1-thione as yellow solid (164 mg, 72%). ^{1}H NMR (500 MHz, DMSO) δ 11.50 (s, 1H), 8.17 (d, *J* = 4.0 Hz, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.79 – 7.51 (m, 4H), 7.30 (s, 1H), 6.97 (dd, *J* = 7.8, 4.7 Hz, 1H), 4.33 (s, 4H), 3.91 (s, 2H), 2.98 (d, *J* = 4.7 Hz, 2H), 2.82 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 200.7, 157.0, 148.9, 143.1, 132.3, 127.9, 127.8, 126.8, 124.3, 119.4, 115.4, 108.0, 60.2, 49.3, 48.9, 46.2, 45.8, 35.4, 31.2. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{23}H_{29}N_4O_2S_2$ 457.1726; found: 457.1722.

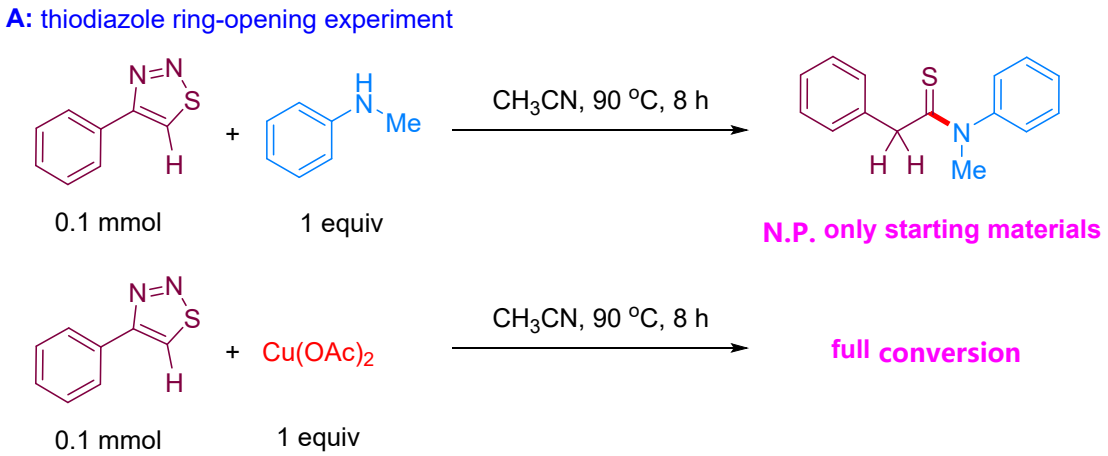
VII. Mechanism Studies

1. Synthesis of 5-*D*-4-phenyl-1,2,3-thiadiazole



5-*D*-4-phenyl-1,2,3-thiadiazole Dissolving NaOH (10 mmol, 400 mg) in D_2O (8 mL), acetophenone (1.45 g, 12 mmol) was added dropwise to the above mixture at room temperature. After stirring for 8 h, the mixture was extracted with diethyl ether (50 mL x 2). The organic layer was dried with $MgSO_4$, and concentrated in *vacuo* to give the product as yellow oil (1.14 g, 77%). The general procedure C conducted with acetophenone-d_3 (1 g, 8.1 mmol), ethyl hydrazinecarboxylate (1.04 g, 10 mmol), one drop of concentrated hydrochloric acid gave hydrazone as white solid. Dissolving hydrazone intermediate (1.05 g, 5 mmol) in excess $SOCl_2$ (10 mL) at 0 °C, stired at r.t. for 8 h to give 5-*D*-4-phenyl-1,2,3-thiadiazole as yellow solid (688 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 2H), 7.51 (t, J = 7.3 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 130.8, 130.1 (m), 129.5, 129.2, 127.4. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_8H_6DN_2S$ 164.0387; found: 164.0384.

2. Thiodiazole ring-opening experiment

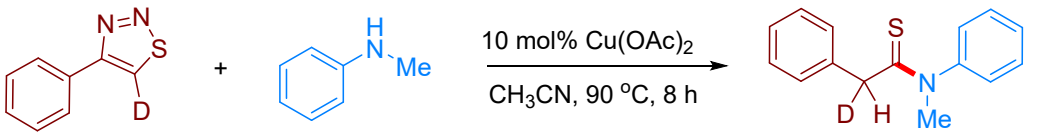


Under N_2 atmosphere, 5-*H*-4-phenyl-1,2,3-thiadiazole (16.2 mg, 0.1 mmol) with 1 equivalent amount of *N*-methylaniline (11 mg, 0.1 mmol) (experiment A-1) or with

$Cu(OAc)_2$ (18 mg, 0.1 mmol) (experiment A-2) were introduced in a Schlenk tube followed with 0.5 mL CH_3CN. Then, the Schlenk tube was closed and the resulting mixture was stirred at 90 °C (oil bath temperature) for 8 h. After the reaction, dodecane was added as internal standard for GC-testing. GC and TLC both indicated that 5-*H*-4-phenyl-1,2,3-thiadiazole didn't react with *N*-methylaniline, only starting material left. However, $Cu(OAc)_2$ can react with 5-*H*-4-phenyl-1,2,3-thiadiazole with almost full conversion.

3. D-labelling experiment

A: D-labeling experiment

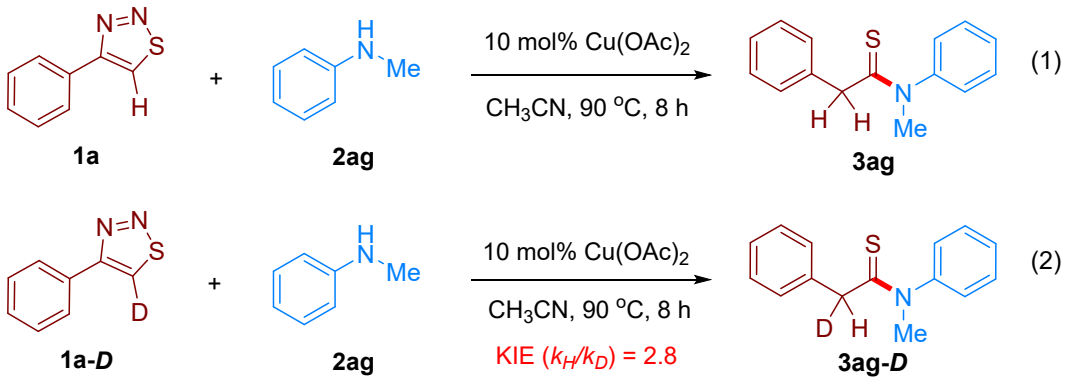


1a-*D* (90% D) **2ag** **3ag-*1D***, 75% yield, 70% D

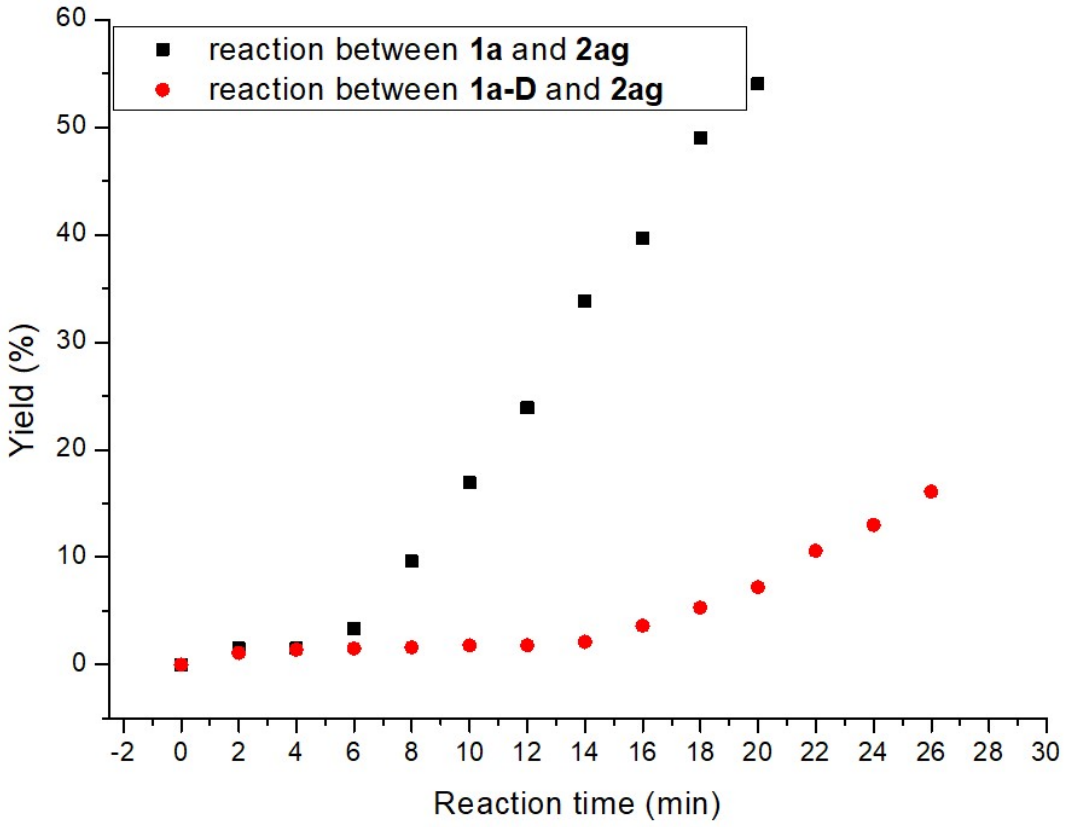
The general procedure D conducted with 5-*D*-4-phenyl-1,2,3-thiadiazole (82 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol) and *N*-methylaniline (54 mg, 0.5 mmol) in CH_3CN (2.5 mL) at 90 °C for 8 h gave *N*-methyl-*N*,2-diphenylethanethioamide-2-d compound as yellow oil (91 mg, 75%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.27 (m, 3H), 7.19 – 7.07 (m, 3H), 7.05 – 6.87 (m, 4H), 4.02 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 145.4, 136.8, 129.7, 128.7, 128.5, 128.2, 126.7, 126.0, 50.8, 46.3. HRMS (ESI-quadrupole) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{15}DNS$ 243.1061; found: 243.1058.

4. KIE experiments

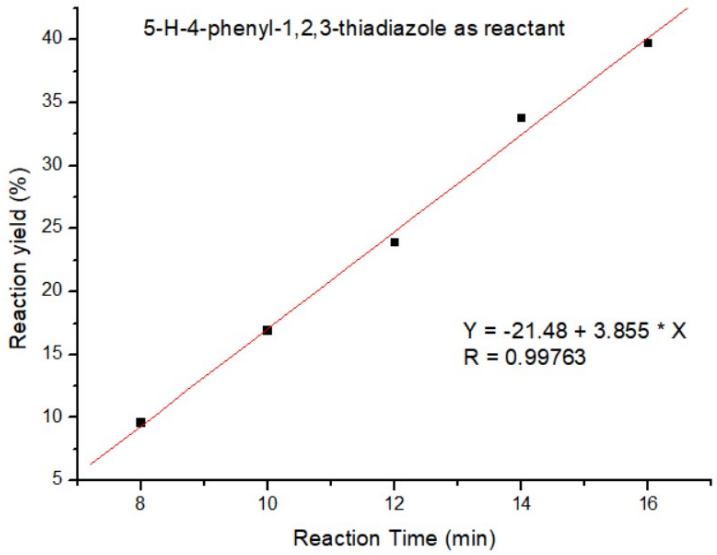
B: KIE experiment



The initial rate of the reaction was determined by measuremnt experiment yields after 2 minutes, 4 minutes, 6 minutes, 8 minutes, 10 minutes, 12 minutes, 14 minutes, 16 minutes, 18 minutes, 20 minutes, 24 minutes, 26 minutes respectively by GC: To a dried 15 mL Schleck tube, 5-(*H/D*)-4-phenyl-1,2,3-thiadiazole (0.5 mmol, 81 mg), PhNHMe (0.5 mmol, 54 mg), $Cu(OAc)_2$ (0.05 mmol, 9 mg) were dissolved in dry CH_3CN (5 mL) under N_2 atmosphere. n-dodecane (17 mg) was used as internal standard. The sealed tube was subsequently inmmersed in a preheated oil bath at 90 °C. Every two minutes, microinjector was used to take 20 μL samples for GC testing. During this period of time, the colour of reaction solution changed from blue to green, yellow and finally brown. The results were shown in below.



From the figure we can see that there is an obvious induction period of approximately 6 min in the reaction procedure. After 6 min, the reaction go as first order reaction. Select the 8, 10, 12, 14, 16 min to calculate the initial rate. For 5-D-4-phenyl-1,2,3-thiadiazole, the results were obtained with the same procedure as above with 5-H-4-phenyl-1,2,3-thiadiazole. From the figure we can see that there is an obvious induction period of approximately 14 min in the reaction procedure. After 14 min, the reaction go as first order reaction. Select the 18, 20, 22, 24, 26 min to calculate the initial rate.

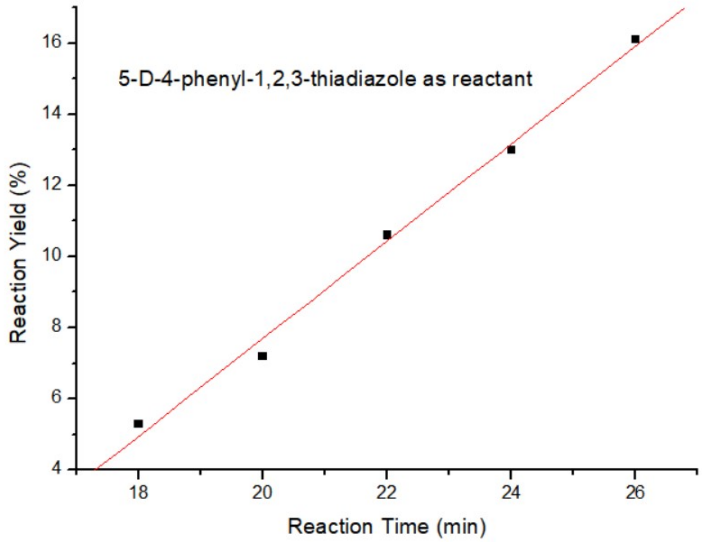


Linear Regression for Data1_B:

Y = A + B * X

Parameter	Value	Error
A	-21.48	1.89232
B	3.855	0.15349

R	SD	N	P
0.99763	0.97074	5	1.38402E-4



Linear Regression for Data1_B:
Y = A + B * X

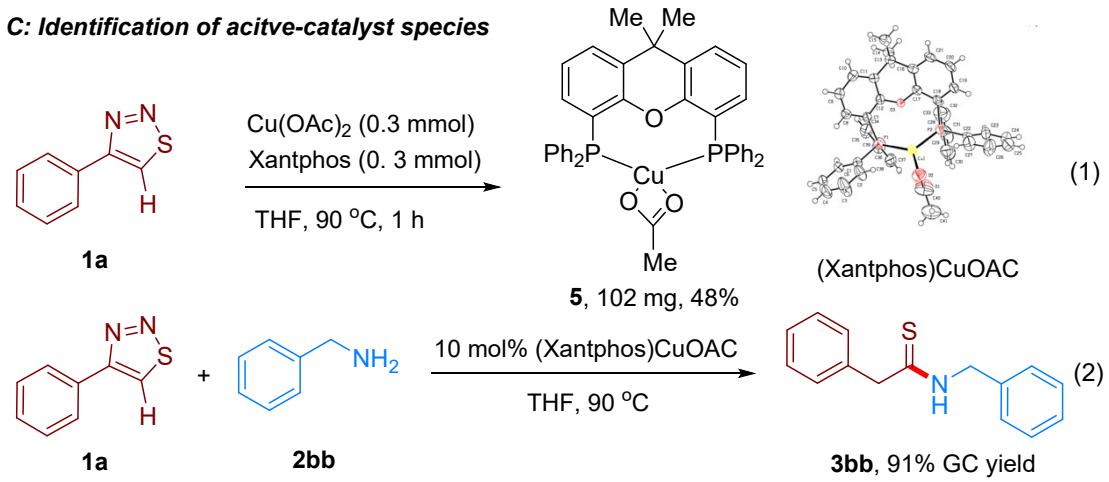
Parameter	Value	Error
A	-19.7	1.36733
B	1.37	0.06164

R	SD	N	P
0.99698	0.38987	5	1.99447E-4

So, the KIE of K(*H/D*) = 3.855/1.37 = 2.8.

5. Intermediate identification

C: Identification of acitve-catalyst species



Under N_2 atmosphere, 5-*H*-4-phenyl-1,2,3-thiadiazole (48.6 mg, 0.3 mmol) with 1 equivalent amount of $Cu(OAc)_2$ (54 mg, 0.3 mmol) and Xantphos (173 mg, 0.3 mmol) were introduced in a Schlenk tube followed with 1 mL THF. Then, the Schlenk tube was closed and the resulting mixture was stirred at 90 °C (oil bath temperature) for 1 h. After the reaction, the mixture was taken into the glovebox again, then filtrated through a short plug of celite. The mixture was dropped into the pentane (10 mL) to produce red solid (102 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 2H), 7.37 (s, 7H), 7.32 – 7.16 (m, 15H), 7.14 – 7.00 (m, 2H), 6.58 (s, 2H), 2.01 (s, 3H), 1.65 (s, 6H).

k_0m_sq

Table S6 Crystal data and structure refinement for k_0m_sq.

Identification code	k_0m_sq
Empirical formula	$C_{41}H_{35}CuO_3P_2$
Formula weight	701.17
Temperature/K	170.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.0488(11)
b/Å	19.0703(19)
c/Å	20.399(3)
α/°	90
β/°	93.731(4)
γ/°	90
Volume/Å^3	3900.8(8)
Z	4
ρ_{calc}g/cm^3	1.194
μ/mm^{-1}	0.676
F(000)	1456.0
Crystal size/mm^3	0.15 × 0.05 × 0.03
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/	4.002 to 50.052
Index ranges	-11 ≤ h ≤ 11, -21 ≤ k ≤ 22, -24 ≤ l ≤ 19
Reflections collected	24115
Independent reflections	6766 [R_{int} = 0.1124, R_{sigma} = 0.1108]
Data/restraints/parameters	6766/0/427
Goodness-of-fit on F^2	1.036
Final R indexes [I>=2σ (I)]	R_1 = 0.0829, wR_2 = 0.2054
Final R indexes [all data]	R_1 = 0.1653, wR_2 = 0.2571
Largest diff. peak/hole / e Å^{-3}	1.32/-0.78

Table S7 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for k_0m_sq. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cu1	7506.7(9)	3550.6(4)	1736.5(5)	50.7(3)
P1	6574.1(17)	2557.9(9)	2038.7(9)	34.3(5)
P2	6583.2(17)	4573.3(9)	1978.5(10)	37.6(5)
O3	5669(4)	3583(2)	2937(2)	33.2(1

				0)
O2	9243(6)	3558(3)	1253(3)	69.8(16)
O1	7463(6)	3609(4)	554(3)	82(2)
C39	4837(6)	2514(3)	1713(4)	37.5(17)
C17	6031(6)	4201(3)	3258(3)	35.5(16)
C18	6446(6)	4747(3)	2851(4)	38.1(17)
C1	7322(7)	1744(4)	1778(4)	40.5(17)
C12	6039(6)	2981(3)	3285(3)	36.4(16)
C7	6443(6)	2422(3)	2923(3)	35.8(16)
C28	4894(7)	4640(4)	1604(4)	41.8(18)
C8	6793(7)	1804(4)	3255(4)	43.4(18)
C16	6015(6)	4256(4)	3930(4)	41.7(17)
C6	6650(7)	1121(4)	1683(3)	43.1(18)
C19	6807(7)	5370(4)	3164(4)	44.8(19)
C21	6442(7)	4885(4)	4211(4)	49(2)
C34	3826(7)	2261(4)	2082(4)	52(2)
C13	5529(7)	3626(4)	4305(4)	44.9(18)
C10	6361(7)	2341(4)	4282(4)	48.6(19)
C22	7387(7)	5376(3)	1703(3)	40.9(18)
C37	4526(7)	2776(4)	1093(4)	48.1(19)
C11	5997(7)	2969(4)	3968(4)	42.1(18)
C9	6741(8)	1772(4)	3921(4)	52(2)
C23	6693(8)	5965(4)	1504(4)	55(2)
C5	7286(8)	516(4)	1511(4)	51(2)
C20	6801(8)	5442(4)	3832(4)	52(2)

C14	3990(7)	3629(4)	4246(4)	52(2)	
C29	4696(8)	4592(4)	938(4)	60(2)	
C38	3216(8)	2774(4)	836(4)	60(2)	
C40	8703(8)	3584(5)	661(5)	74(3)	
C33	3797(8)	4720(5)	1969(5)	63(2)	
C15	5993(9)	3642(4)	5032(4)	62(2)	
C35	2521(7)	2275(4)	1811(5)	63(2)	
C36	2206(9)	2530(5)	1198(5)	72(3)	
C2	8689(7)	1750(4)	1707(5)	68(3)	
C24	7355(11)	6557(4)	1312(5)	74(3)	
C27	8749(8)	5376(5)	1710(5)	71(3)	
C25	8724(11)	6570(5)	1348(5)	87(4)	
C4	8617(10)	531(4)	1435(5)	80(3)	
C30	3423(10)	4644(5)	625(5)	72(3)	
C32	2522(9)	4764(6)	1657(6)	83(3)	
C31	2345(9)	4721(5)	1000(6)	81(3)	
C41	9597(10)	3625(6)	114(6)	103(4)	
C26	9410(10)	5973(5)	1543(5)	88(3)	
C3	9330(9)	1156(5)	1530(6)	100(4)	

Table S8 Anisotropic Displacement Parameters ($Å^2×10^3$) for k_0m_sq. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cu1	46.9(6)	33.8(5)	74.1(8)	0.0(5)	24.8(5)	1.3(4)
P1	38.2(10)	29.3(9)	35.7(11)	-2.3(8)	6.2(8)	1.0(8)
P2	39.5(10)	31.1(9)	43.3(12)	-1.2(8)	11.3(8)	-0.9(8)
O3	44(2)	26(2)	30(3)	0(2)	6(2)	0(2)
O2	63(4)	77(4)	70(4)	2(4)	9(3)	2(3)
O1	62(4)	112(6)	73(5)	-17(4)	8(3)	3(4)
C39	35(4)	29(3)	49(5)	-5(3)	8(3)	-4(3)
C17	32(3)	32(4)	43(5)	-7(3)	2(3)	-1(3)
C18	33(4)	30(4)	54(5)	-2(3)	14(3)	3(3)
C1	44(4)	32(4)	45(5)	0(3)	0(3)	-2(3)
C12	38(4)	30(4)	42(5)	2(3)	3(3)	2(3)
C7	35(4)	31(4)	41(4)	1(3)	6(3)	1(3)
C28	41(4)	36(4)	49(5)	-3(3)	9(4)	1(3)
C8	51(4)	40(4)	39(5)	-1(3)	6(3)	9(3)
C16	39(4)	45(4)	41(5)	-7(4)	7(3)	5(3)
C6	56(4)	34(4)	40(5)	-6(3)	9(4)	-2(4)
C19	48(4)	31(4)	56(6)	-8(3)	16(4)	-5(3)

C21	62(5)	44(4)	41(5)	-17(4)	1(4)	2(4)
C34	42(4)	52(5)	64(6)	10(4)	16(4)	9(4)
C13	59(5)	42(4)	35(4)	-7(3)	10(3)	-4(4)
C10	58(5)	49(5)	39(5)	9(4)	3(4)	2(4)
C22	57(5)	36(4)	32(4)	-9(3)	19(3)	0(4)
C37	52(5)	53(5)	40(5)	3(4)	10(4)	1(4)
C11	53(4)	41(4)	33(5)	-1(3)	8(3)	2(4)
C9	72(5)	39(4)	45(5)	4(4)	6(4)	6(4)
C23	66(5)	32(4)	67(6)	4(4)	15(4)	0(4)
C5	72(6)	29(4)	51(5)	0(3)	5(4)	-2(4)
C20	64(5)	36(4)	58(6)	-20(4)	10(4)	-5(4)
C14	60(5)	46(5)	54(5)	-4(4)	21(4)	1(4)
C29	60(5)	60(5)	60(6)	-4(4)	5(4)	-8(4)
C38	62(5)	58(5)	59(6)	11(4)	-9(5)	7(4)
C40	42(5)	125(9)	52(6)	-33(6)	-7(4)	11(5)
C33	50(5)	72(6)	69(6)	-1(5)	6(4)	7(4)
C15	95(6)	50(5)	40(5)	-9(4)	1(4)	2(5)
C35	35(4)	65(6)	89(7)	14(5)	8(4)	-4(4)
C36	55(5)	70(6)	87(8)	10(6)	-15(5)	1(5)
C2	39(5)	46(5)	122(9)	-21(5)	16(5)	2(4)
C24	115(8)	43(5)	66(7)	10(4)	29(6)	-1(5)
C27	45(5)	59(5)	111(8)	3(5)	28(5)	-3(4)
C25	97(8)	58(6)	115(9)	-8(6)	68(7)	-23(6)
C4	89(7)	44(5)	109(9)	-16(5)	27(6)	17(5)
C30	87(7)	63(6)	63(7)	3(5)	-24(6)	-3(5)
C32	56(6)	98(8)	94(9)	3(7)	-2(6)	8(5)
C31	54(6)	63(6)	122(10)	-6(6)	-13(6)	11(5)
C41	71(7)	139(11)	99(9)	-17(8)	18(6)	13(7)
C26	65(6)	71(7)	130(10)	21(6)	35(6)	-4(5)
C3	52(5)	56(6)	194(13)	-25(7)	35(7)	12(5)

Table S9 Bond Lengths for k_0m_sq.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cu1	P1	2.2174(19)	C16	C13	1.521(10)
Cu1	P2	2.2290(19)	C6	C5	1.375(9)
Cu1	O2	2.059(6)	C19	C20	1.369(10)
Cu1	O1	2.412(7)	C21	C20	1.376(10)
P1	C39	1.828(7)	C34	C35	1.389(10)
P1	C1	1.820(7)	C13	C11	1.518(9)
P1	C7	1.835(7)	C13	C14	1.544(10)

P2	C18	1.824(7)	C13	C15	1.526(10)
P2	C28	1.820(7)	C10	C11	1.395(9)
P2	C22	1.836(7)	C10	C9	1.379(10)
O3	C17	1.386(7)	C22	C23	1.370(10)
O3	C12	1.388(7)	C22	C27	1.368(10)
O2	C40	1.292(10)	C37	C38	1.386(10)
O1	C40	1.251(9)	C23	C24	1.380(11)
C39	C34	1.389(9)	C5	C4	1.357(11)
C39	C37	1.377(10)	C29	C30	1.395(11)
C17	C18	1.412(9)	C38	C36	1.374(11)
C17	C16	1.376(9)	C40	C41	1.479(13)
C18	C19	1.387(9)	C33	C32	1.395(11)
C1	C6	1.374(9)	C35	C36	1.360(12)
C1	C2	1.390(10)	C2	C3	1.364(11)
C12	C7	1.373(9)	C24	C25	1.373(13)
C12	C11	1.397(10)	C27	C26	1.373(12)
C7	C8	1.394(9)	C25	C26	1.376(13)
C28	C29	1.364(10)	C4	C3	1.397(12)
C28	C33	1.378(10)	C30	C31	1.374(13)
C8	C9	1.364(10)	C32	C31	1.343(13)
C16	C21	1.387(9)			

Table S10 Bond Angles for k_0m_sq.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
P1	Cu1	P2	119.73(7)	C17	C16	C21	117.0(7)
P1	Cu1	O1	109.70(17)	C17	C16	C13	117.8(6)
P2	Cu1	O1	101.54(17)	C21	C16	C13	125.2(7)
O2	Cu1	P1	121.68(17)	C1	C6	C5	121.9(7)
O2	Cu1	P2	118.57(17)	C20	C19	C18	121.7(7)
O2	Cu1	O1	58.8(2)	C20	C21	C16	121.4(7)
C39	P1	Cu1	110.4(2)	C35	C34	C39	118.9(8)
C39	P1	C7	102.8(3)	C16	C13	C14	108.1(6)
C1	P1	Cu1	117.2(2)	C16	C13	C15	112.7(6)
C1	P1	C39	104.9(3)	C11	C13	C16	107.7(6)
C1	P1	C7	103.0(3)	C11	C13	C14	107.8(6)
C7	P1	Cu1	116.9(2)	C11	C13	C15	111.9(6)
C18	P2	Cu1	115.7(2)	C15	C13	C14	108.5(6)
C18	P2	C22	102.1(3)	C9	C10	C11	120.3(7)
C28	P2	Cu1	111.0(2)	C23	C22	P2	123.3(6)
C28	P2	C18	105.6(3)	C27	C22	P2	117.1(6)

C28	P2	C22	103.3(3)	C27	C22	C23	119.6(7)
C22	P2	Cu1	117.6(2)	C39	C37	C38	120.0(7)
C17	O3	C12	114.1(5)	C12	C11	C13	118.0(6)
C40	O2	Cu1	97.5(5)	C10	C11	C12	116.6(6)
C40	O1	Cu1	82.6(5)	C10	C11	C13	125.4(7)
C34	C39	P1	122.3(6)	C8	C9	C10	121.8(7)
C37	C39	P1	118.1(5)	C22	C23	C24	120.6(8)
C37	C39	C34	119.5(7)	C4	C5	C6	119.3(7)
O3	C17	C18	115.3(6)	C19	C20	C21	120.1(7)
C16	C17	O3	121.1(6)	C28	C29	C30	121.4(8)
C16	C17	C18	123.6(6)	C36	C38	C37	121.0(8)
C17	C18	P2	119.0(5)	O2	C40	C41	117.9(8)
C19	C18	P2	124.8(5)	O1	C40	O2	121.1(8)
C19	C18	C17	116.1(7)	O1	C40	C41	120.9(9)
C6	C1	P1	124.7(5)	C28	C33	C32	120.3(9)
C6	C1	C2	118.2(7)	C36	C35	C34	122.0(8)
C2	C1	P1	116.9(5)	C35	C36	C38	118.6(8)
O3	C12	C11	119.9(6)	C3	C2	C1	120.5(8)
C7	C12	O3	116.4(6)	C25	C24	C23	119.9(9)
C7	C12	C11	123.6(6)	C22	C27	C26	119.8(8)
C12	C7	P1	117.6(5)	C24	C25	C26	118.8(8)
C12	C7	C8	117.9(6)	C5	C4	C3	120.2(8)
C8	C7	P1	124.4(5)	C31	C30	C29	119.1(9)
C29	C28	P2	119.0(6)	C31	C32	C33	120.6(10)
C29	C28	C33	118.4(7)	C32	C31	C30	120.3(9)
C33	C28	P2	122.6(6)	C27	C26	C25	121.2(9)
C9	C8	C7	119.8(7)	C2	C3	C4	119.9(8)

Table S11 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for k_0m_sq.

Atom	*x*	*y*	*z*	U(eq)
H8	7067.85	1405.8	3019.07	52
H6	5719.3	1107.7	1738.36	52
H19	7064.32	5758.08	2908.67	54
H21	6488.09	4933.43	4675.71	59
H34	4022.28	2081.17	2511.57	62
H10	6345.65	2305.78	4745.69	58
H37	5210.55	2959.05	842.23	58
H9	6973.47	1347.09	4142.28	62
H23	5747.1	5966.48	1498.75	65

H5	6798.62	92.18	1446.83	61
H20	7044.51	5876.93	4032.81	63
H14A	3660.96	4050.61	4457.76	79
H14B	3655	3211.45	4461.87	79
H14C	3675.72	3627.02	3781.04	79
H29	5439.58	4520.49	680.92	72
H38	3012.76	2943.23	402.94	72
H33	3909.61	4745.35	2434.06	76
H15A	6969.74	3654.99	5077.76	93
H15B	5673.69	3221.25	5248.68	93
H15C	5634.04	4060.09	5237.25	93
H35	1828.33	2101.25	2061.54	75
H36	1305.93	2540.14	1023.56	86
H2	9179.81	2171.4	1782.69	82
H24	6864.03	6955.55	1154.67	88
H27	9236.35	4963.24	1830.97	85
H25	9189.63	6983.29	1239.63	105
H4	9065.37	116.29	1315.71	96
H30	3302.77	4627.58	159.56	87
H32	1772.38	4823.93	1912.56	100
H31	1470.64	4744.31	794.09	97
H41A	10524.9	3655.03	292.54	154
H41B	9376.69	4042.49	-151.32	154
H41C	9482.57	3205.27	-160.57	154
H26	10357.02	5974.4	1562.94	105
H3	10260.23	1166.38	1471.74	120

Table S12 Solvent masks information for k_0m_sq.

Number	X	Y	Z	Volume	Electron count Content
1	0.000	0.000	0.000	334	107
2	0.000	0.500	0.500	334	107

Experimental

Single crystals of $C_{41}H_{35}CuO_3P_2$ **[k_0m_sq]** were **[]**. A suitable crystal was selected and **[]** on a **'D8 VENTURE '** diffractometer. The crystal was kept at 170.0 K during data collection. Using Olex2 [1], the structure was solved with the ShelXT [2] structure solution program using Intrinsic Phasing and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal structure determination of [k_0m_sq]

Crystal Data for $C_{41}H_{35}CuO_3P_2$ (M =701.17 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 10.0488(11) Å, b = 19.0703(19) Å, c = 20.399(3) Å, β = 93.731(4), V = 3900.8(8) Å^3, Z = 4, T = 170.0 K, μ(MoKα) = 0.676 mm^{-1}, *Dcalc* = 1.194 g/cm^3, 24115 reflections measured (4.002° ≤ 2Θ ≤ 50.052), 6766 unique (R_{int} = 0.1124, R_{sigma} = 0.1108) which were used in all calculations. The final R_1 was 0.0829 (I > 2σ(I)) and wR_2 was 0.2571 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1. Fixed Uiso

 At 1.2 times of:

  All C(H) groups

 At 1.5 times of:

  All C(H,H,H) groups

2.a Aromatic/amide H refined with riding coordinates:

 C8(H8), C6(H6), C19(H19), C21(H21), C34(H34), C10(H10), C37(H37), C9(H9), C23(H23), C5(H5), C20(H20), C29(H29), C38(H38), C33(H33), C35(H35), C36(H36), C2(H2), C24(H24), C27(H27), C25(H25), C4(H4), C30(H30), C32(H32), C31(H31), C26(H26), C3(H3)

2.b Idealised Me refined as rotating group:

 C14(H14A,H14B,H14C), C15(H15A,H15B,H15C), C41(H41A,H41B,H41C)

This report has been created with Olex2, compiled on 2018.05.29 svn.r3508 for OlexSys. Please **let us know** if there are any errors or if you would like to have additional features.

Datablock: k_0m_sq

Bond precision: C-C = 0.0117 A Wavelength=0.71073

Cell: a=10.0488(11) b=19.0703(19) c=20.399(3)

alpha=90 beta=93.731(4) gamma=90

Temperature: 170 K

	Calculated	Reported
Volume	3900.9(8)	3900.8(8)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C41 H35 Cu O3 P2 [+ solvent]	C41 H35 Cu O3 P2
Sum formula	C41 H35 Cu O3 P2 [+ solvent]	C41 H35 Cu O3 P2
Mr	701.18	701.17
Dx,g cm-3	1.194	1.194
Z	4	4
Mu (mm-1)	0.676	0.676
F000	1456.0	1456.0
F000’	1458.57	
h,k,lmax	11,22,24	11,22,24
Nref	6874	6766
Tmin,Tmax	0.960,0.980	0.117,0.149

Tmin’ 0.904

Correction method= # Reported T Limits: Tmin=0.117 Tmax=0.149

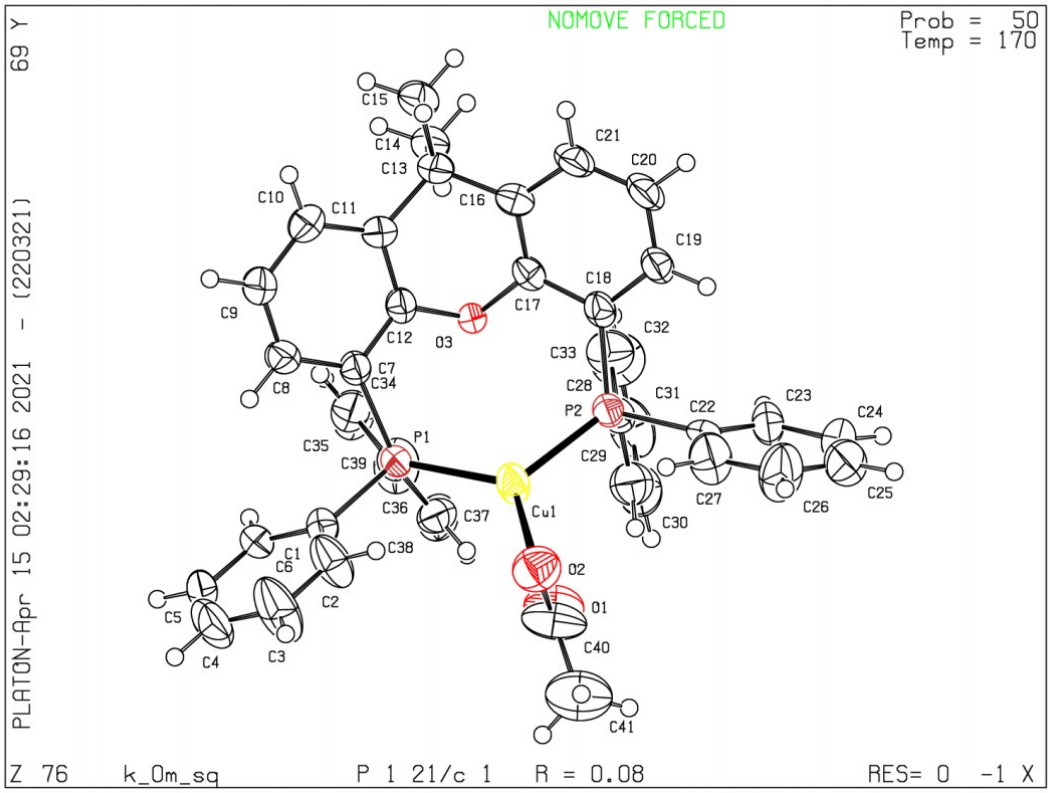
AbsCorr = MULTI-SCAN

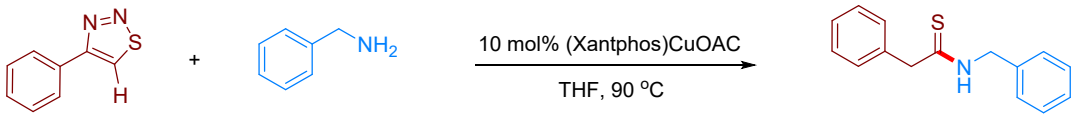
Data completeness= 0.984 Theta(max)= 25.026

R(reflections)= 0.0829(3343) wR2(reflections)= 0.2571(6766)

S = 1.036 Npar= 427

Datablock k_0m_sq - ellipsoid plot

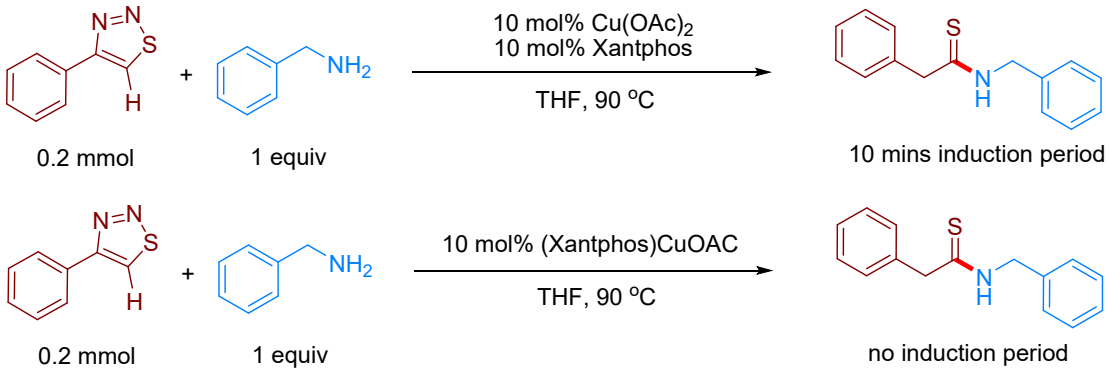




1a **2bb** **3bb**, 91% GC yield

In order to test whether the (Xantphos)Cu(OAc) is the active catalyst species, we conducted the reaction using (Xantphos)Cu(OAc) as catalyst. To a dried 15 mL Schleck tube, 5-H-4-phenyl-1,2,3-thiadiazole (0.1 mmol, 16 mg), PhNHMe (0.1 mmol, 11 mg), (XantPhos)Cu(OAc) (0.01 mmol, 7 mg) were dissolved in dry THF (1 mL) under N_2 atmosphere. n-dodecane (17 mg) was used as internal standard. The sealed tube was subsequently inmmersed in a preheated oil bath at 90 °C for 8 h. GC tested for the reaction yield (91% GC yield)

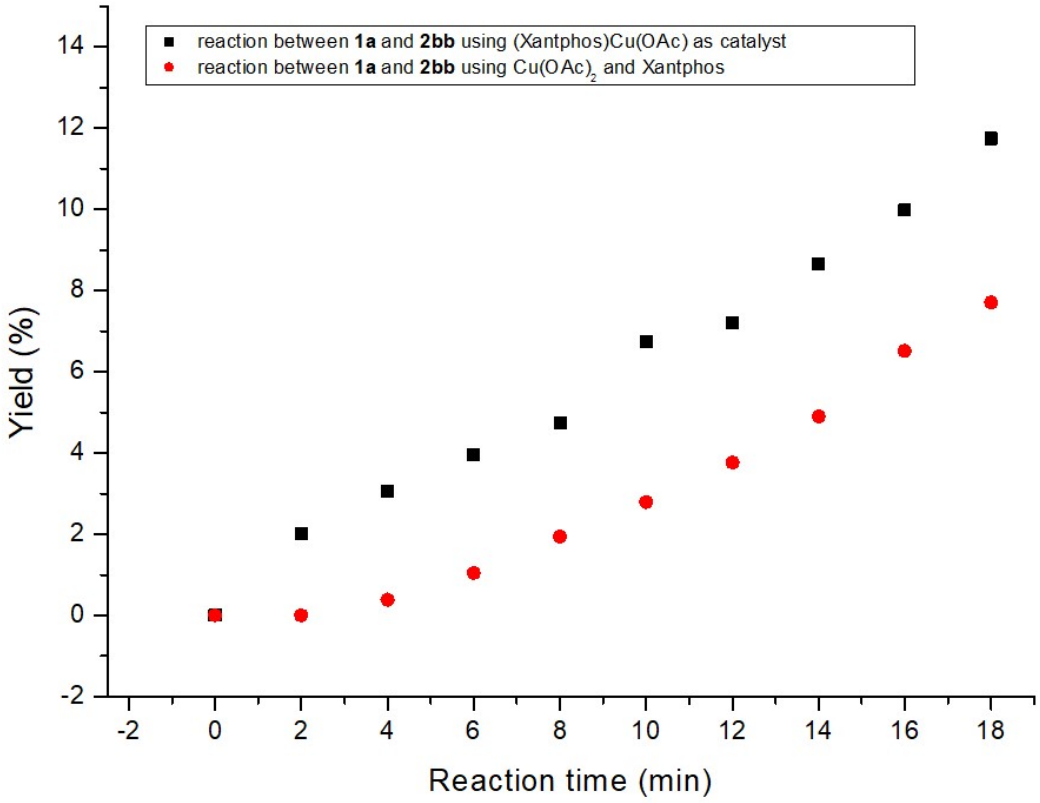
6. Comparing the initial rate of $Cu(OAc)_2$/Xantphos system and (Xantphos)Cu(OAc).

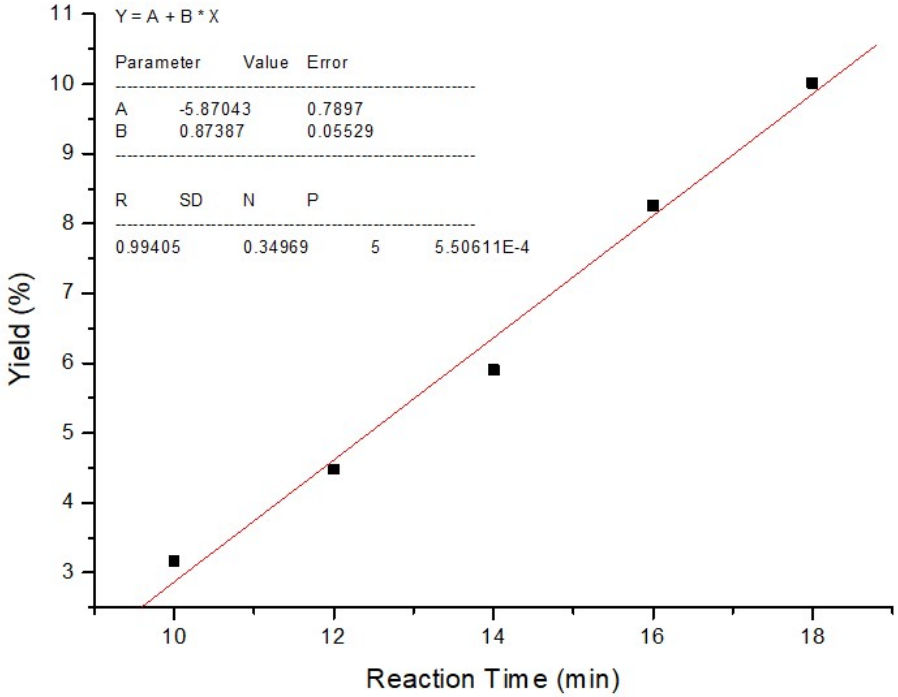


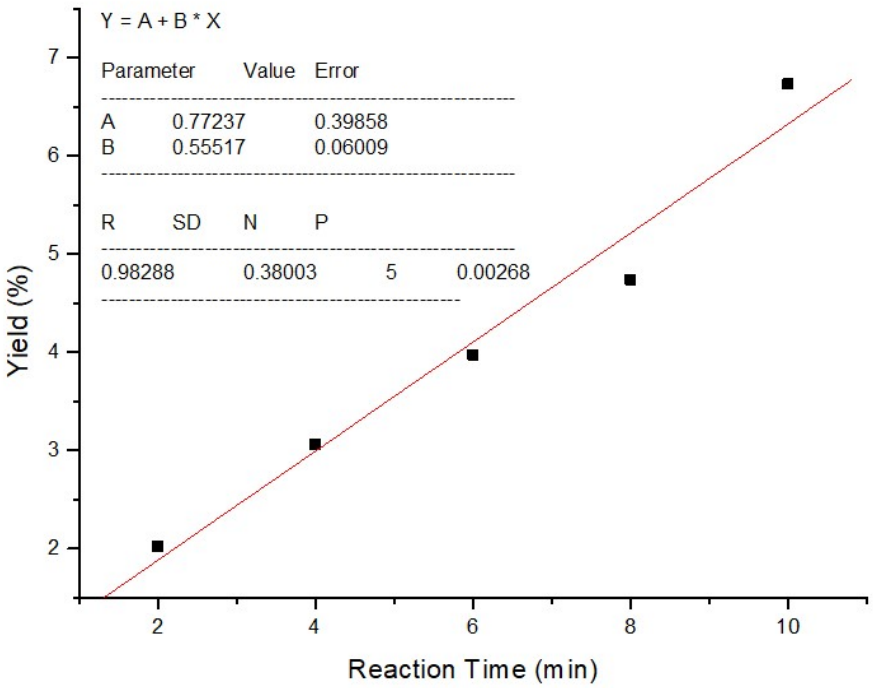
(Reaction A) To a dried 15 mL Schleck tube, 5-H-4-phenyl-1,2,3-thiadiazole (0.2 mmol, 32.4 mg), phenylmethanamine (0.2 mmol, 21.4 mg), $Cu(OAc)_2$ (0.02 mmol, 3.6 mg), Xantphos (0.02 mmol, 11.5 mg) were dissolved in dry THF (5 mL) under N_2 atmosphere. n-dodecane (13 mg) was used as internal standard. The sealed tube was subsequently inmmersed in a preheated oil bath at 90 °C. Every two minutes, microinjector was used to take 20 μL samples for GC testing. During this period of time, the colour of reaction solution changed from blue to green, yellow and finally brown.

(Reaction B) To a dried 15 mL Schleck tube, 5-H-4-phenyl-1,2,3-thiadiazole (0.2 mmol, 32.4 mg), phenylmethanamine (0.2 mmol, 21.4 mg), (Xantphos)Cu(OAc) (0.02 mmol, 14 mg) were dissolved in dry THF (5 mL) under N_2 atmosphere. n-dodecane (12.5 mg) was used as internal standard. The sealed tube was subsequently inmmersed in a preheated oil bath at 90 °C. Every two minutes, microinjector was used to take 20 μL samples for GC testing. During this period of time, the colour of reaction solution changed from blue to green, yellow and finally brown. The results were shown in below.

From the figure we can see that there is an obvious induction period of approximately 10 min in the $Cu(OAc)_2$/Xantphos system. After 10 min, the reaction go as first order reaction. Select the 10, 12, 14, 16, 18 min to calculate the initial rate. For (Xantphos)Cu(OAc) catalyst system, there is almost no induction period. The reaction go as first order immediately. Select the 2, 4, 6, 8, 10 min to calculate the initial rate.

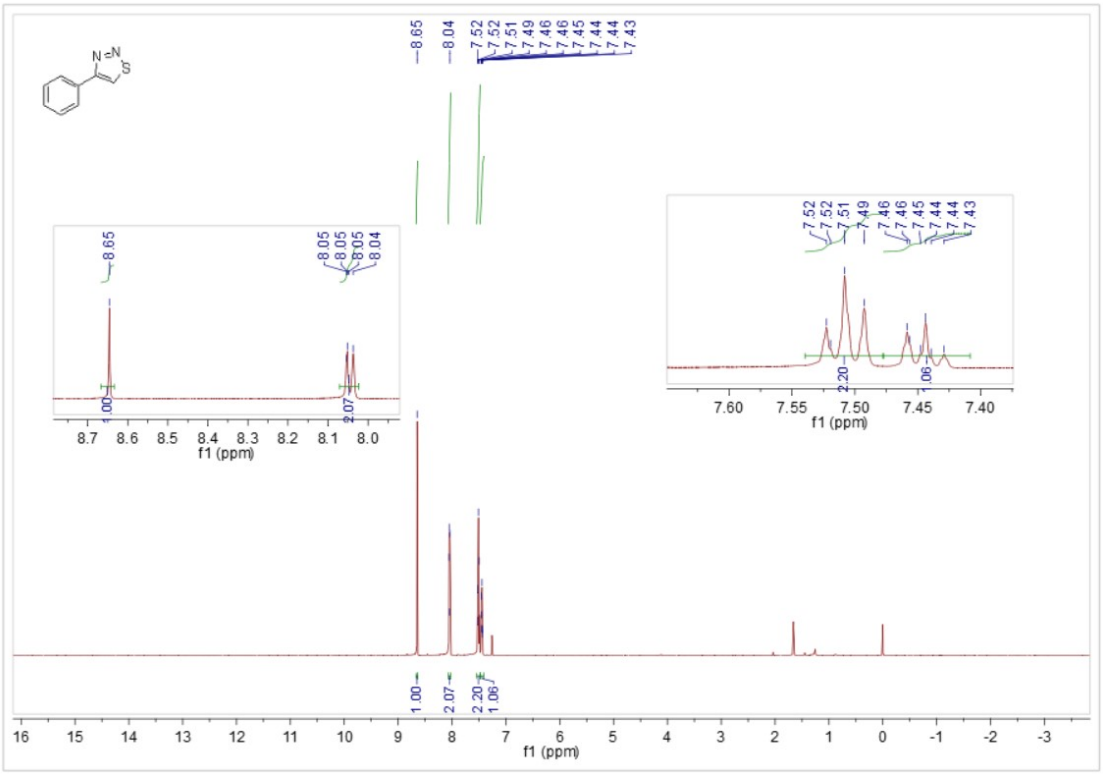

reaction between 1a and 2bb using (Xantphos)Cu(OAc) as catalyst
reaction between 1a and 2bb using Cu(OAc)2 and Xantphos
Yield (%)
Reaction time (min)

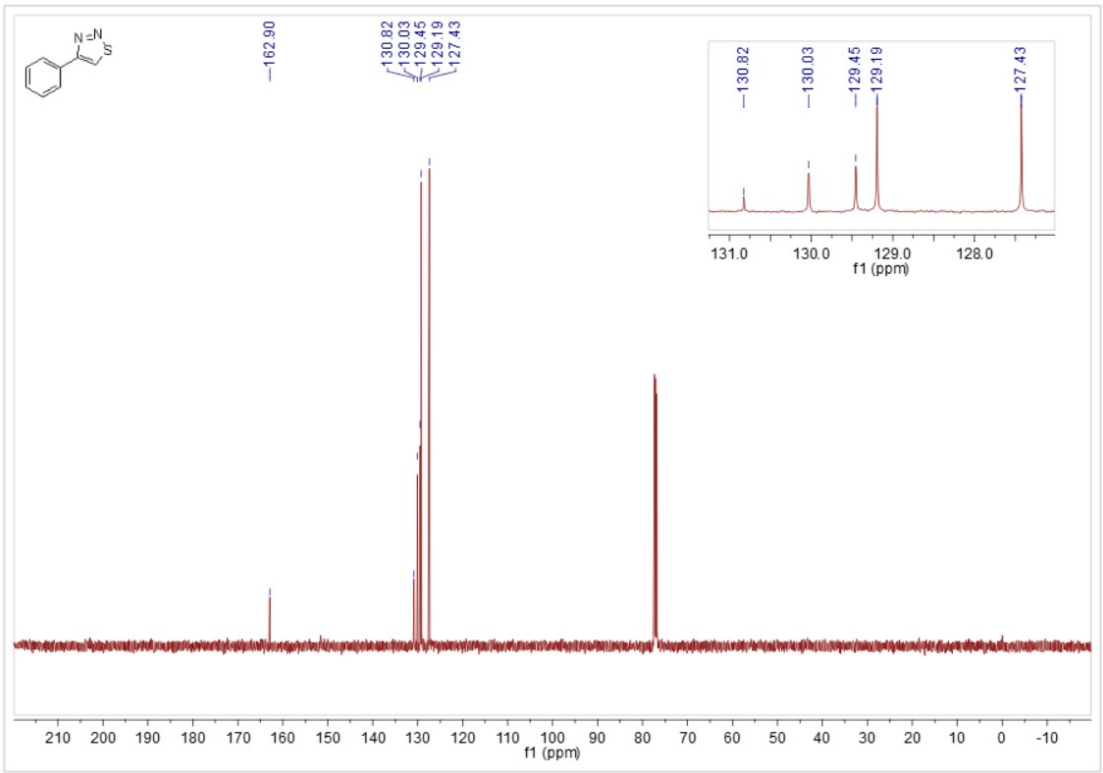

Y = A + B * X
Parameter Value Error
A -5.87043 0.7897
B 0.87387 0.05529
R SD N P
0.99405 0.34969 5 5.50611E-4
Yield (%)
Reaction Time (min)


Y = A + B * X
Parameter Value Error
A 0.77237 0.39858
B 0.55517 0.06009
R SD N P
0.98288 0.38003 5 0.00268
Yield (%)
Reaction Time (min)
2
3
4
5
6
7
2
4
6
8
10

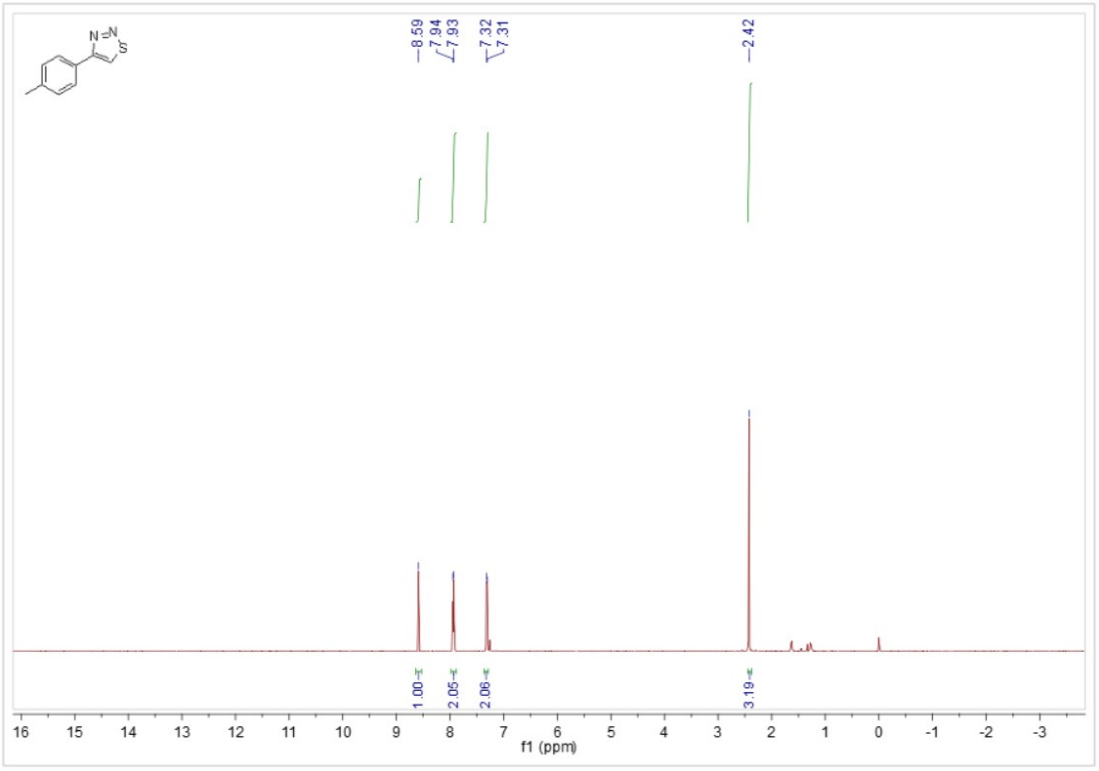
VIII. NMR Spectra of Compounds

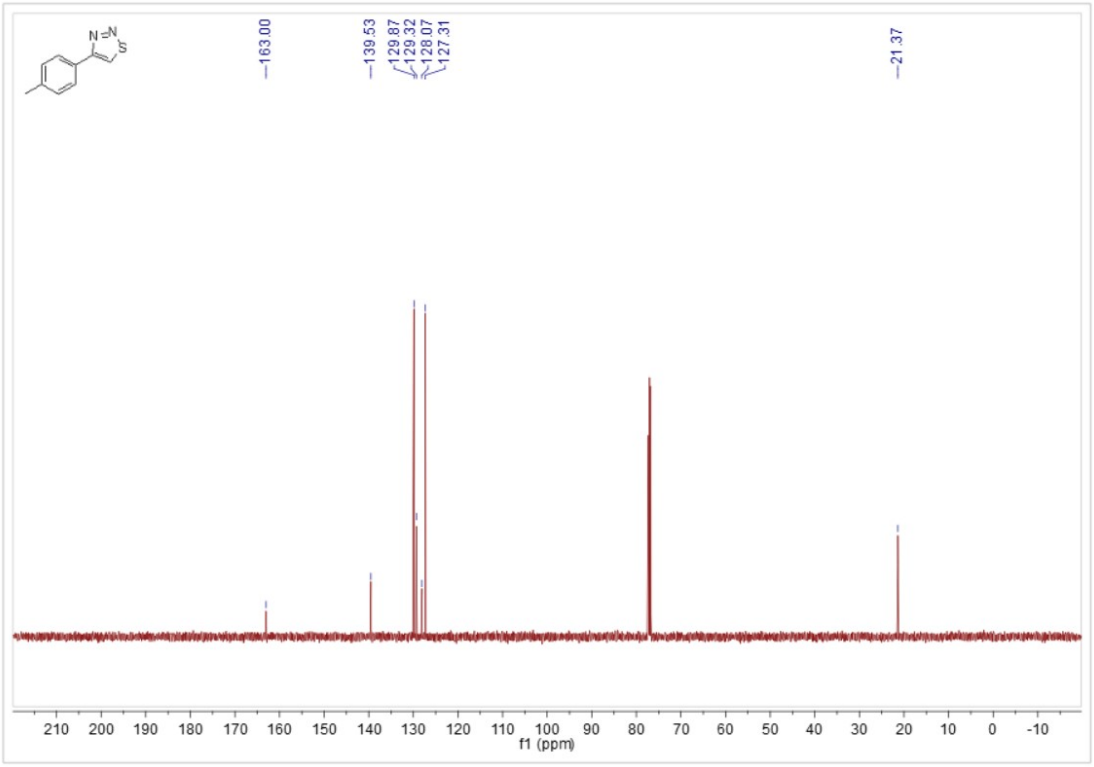
4-Phenyl-1,2,3-thiadiazole (1a)



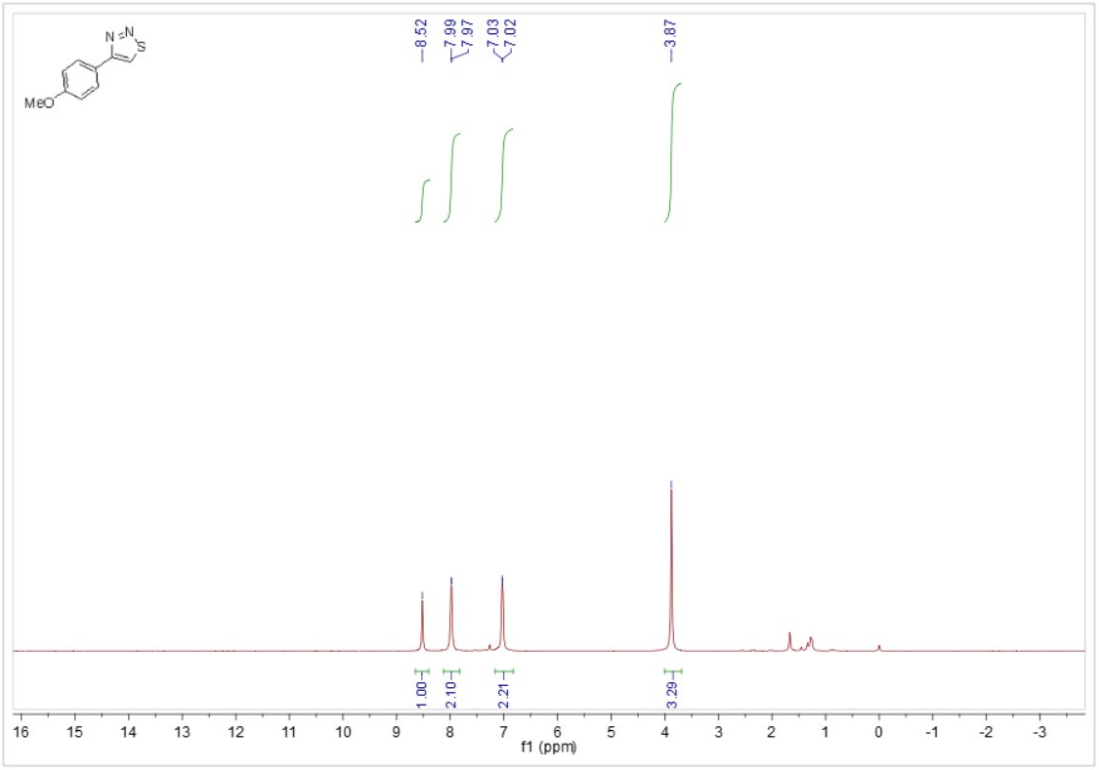


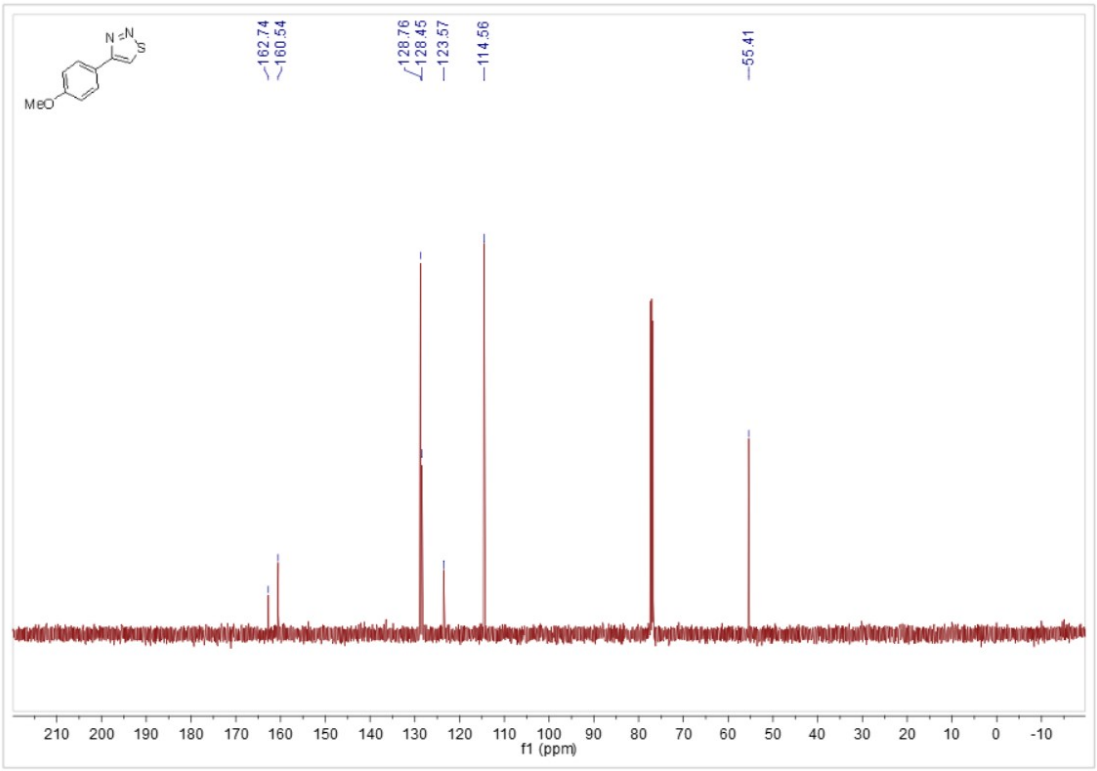
4-(*p*-Tolyl)-1,2,3-thiadiazole (1ea)



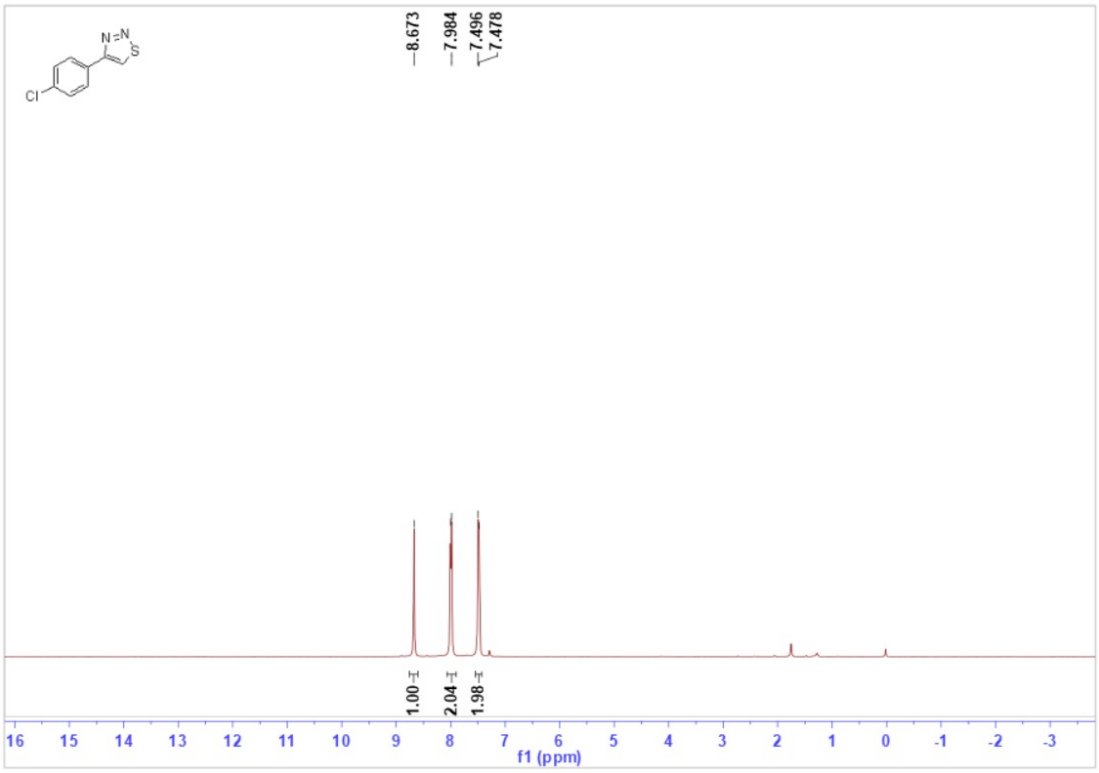


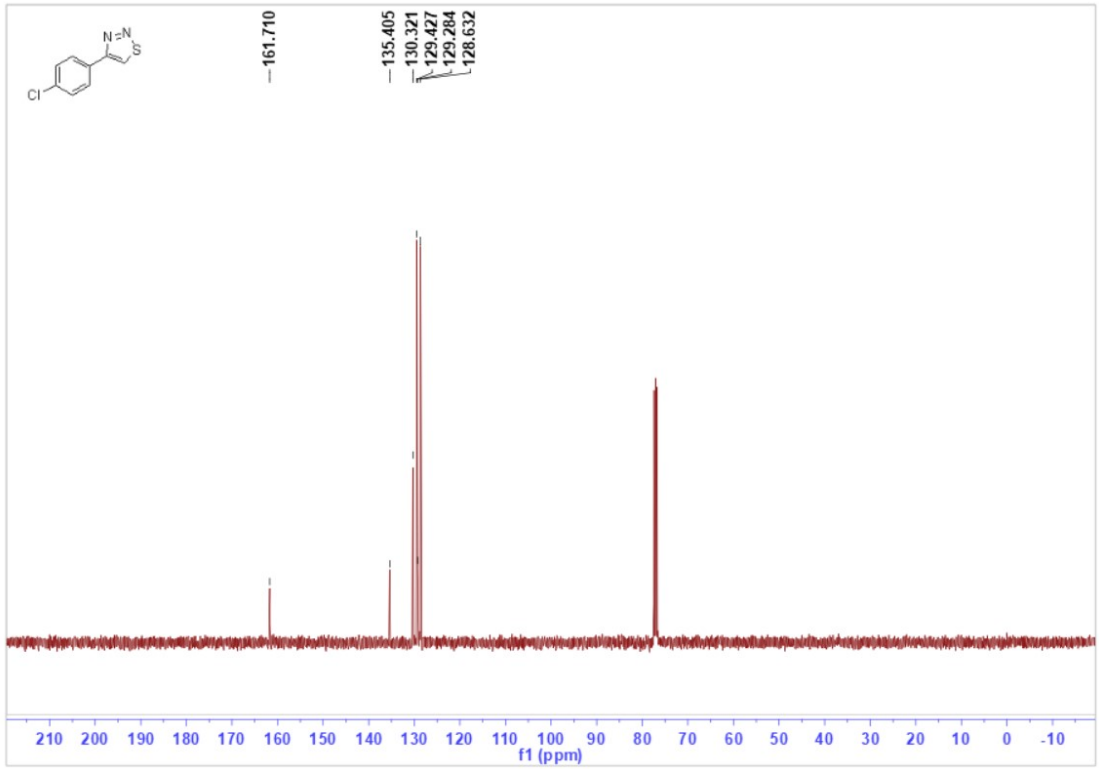
(4-Methoxyphenyl)-1,2,3-thiadiazole (1eb)



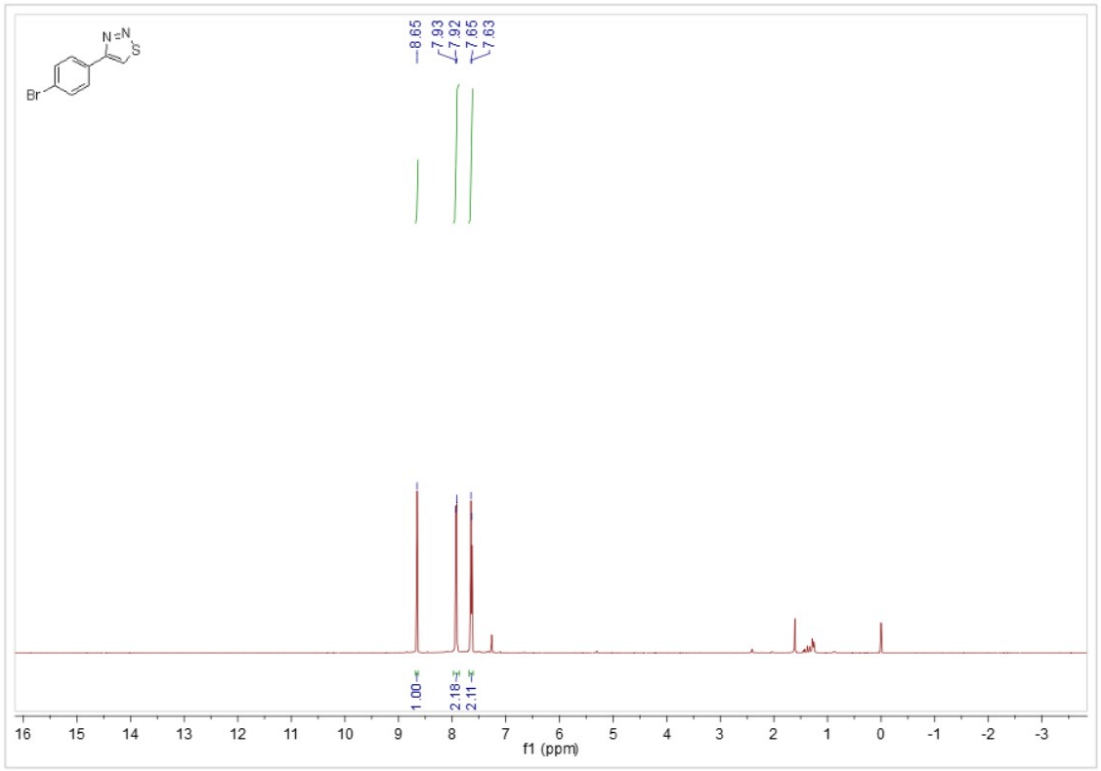


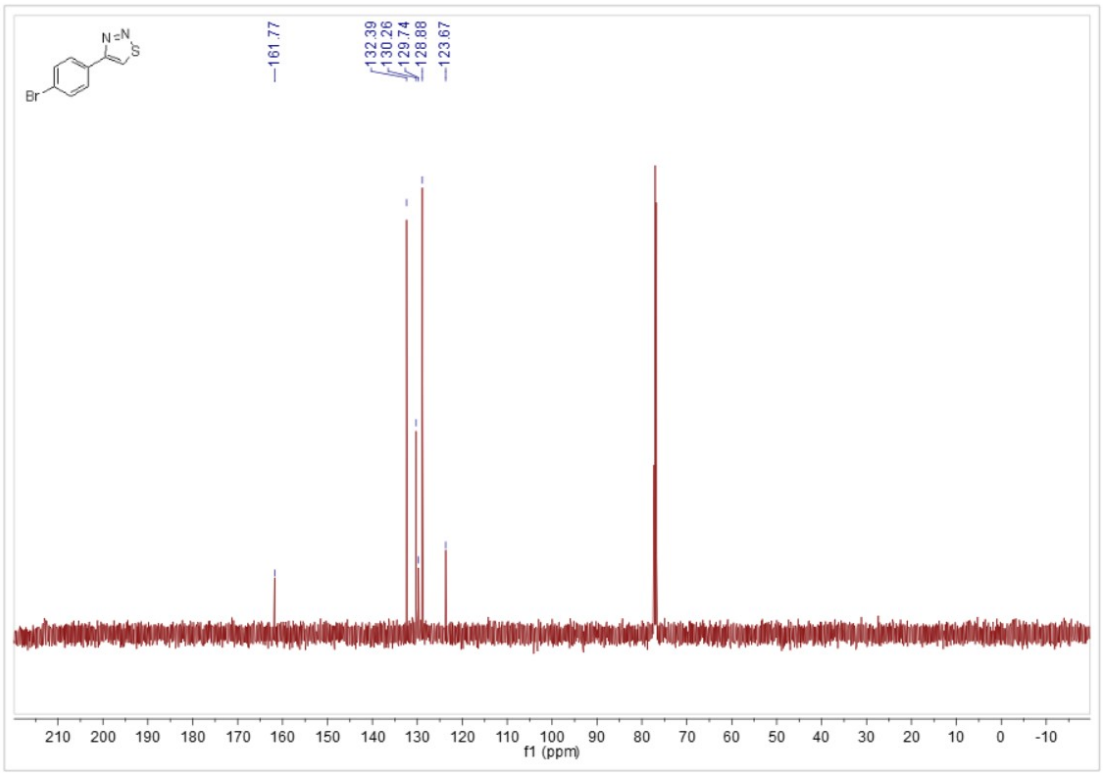
(4-Chlorophenyl)-1,2,3-thiadiazole (1ec)



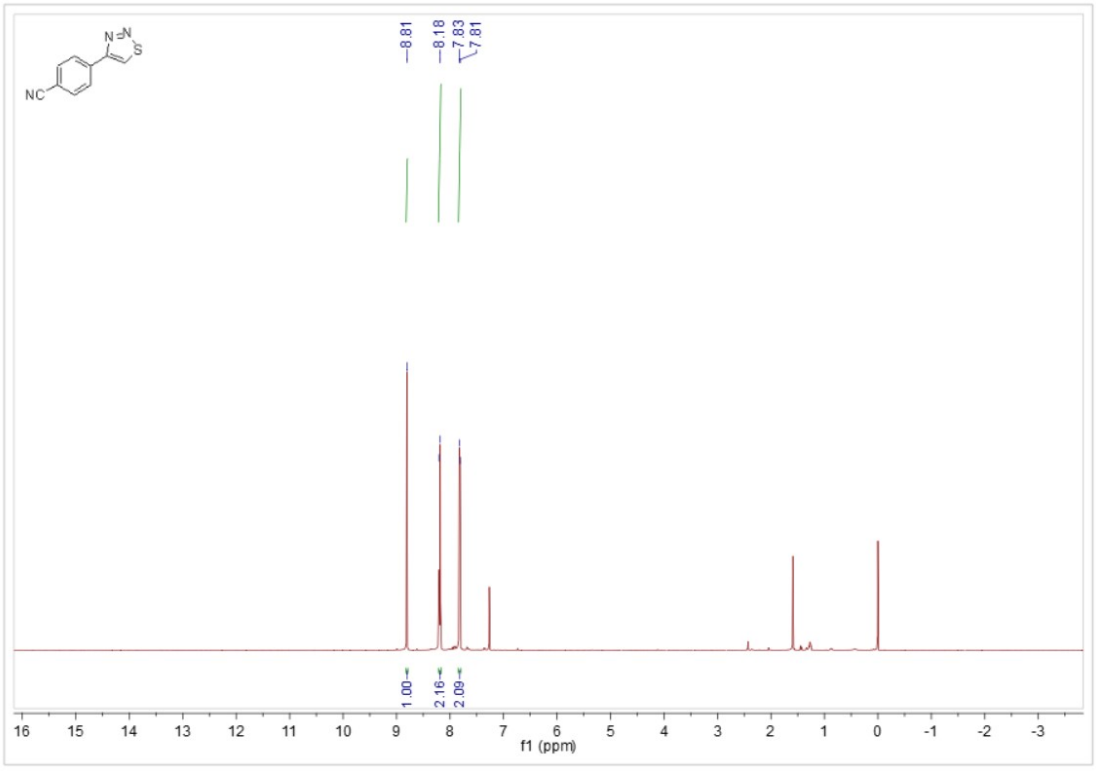


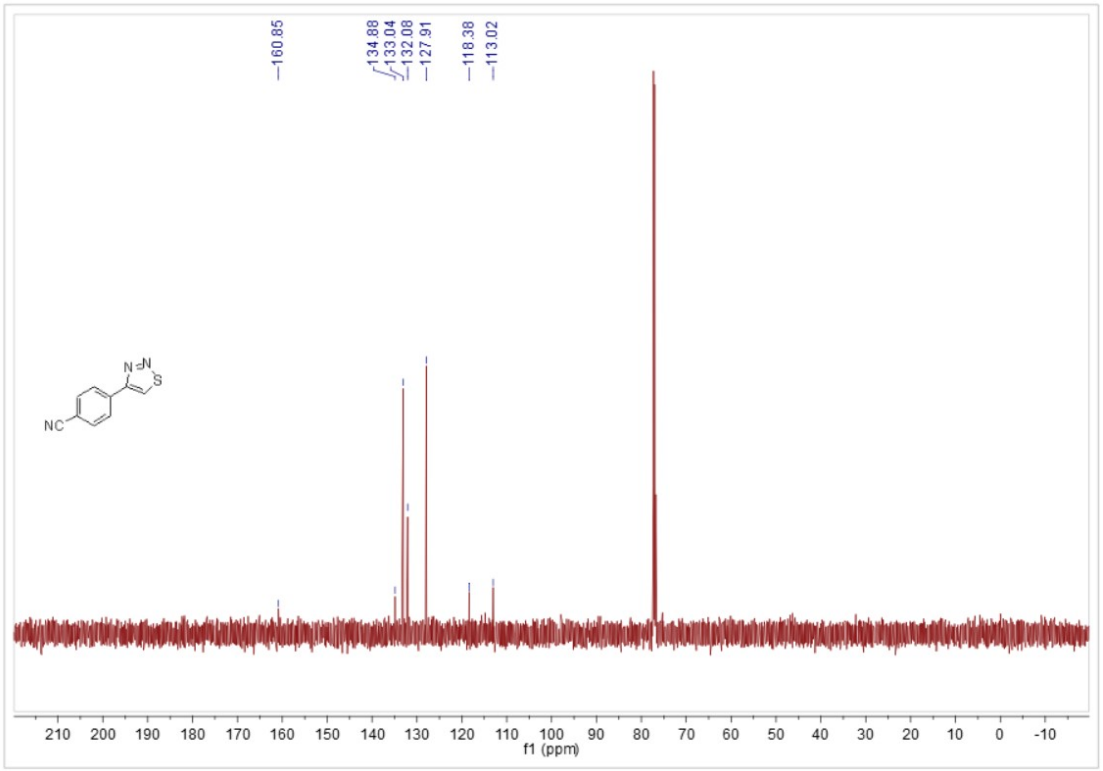
(4-Bromophenyl)-1,2,3-thiadiazole (1ed)



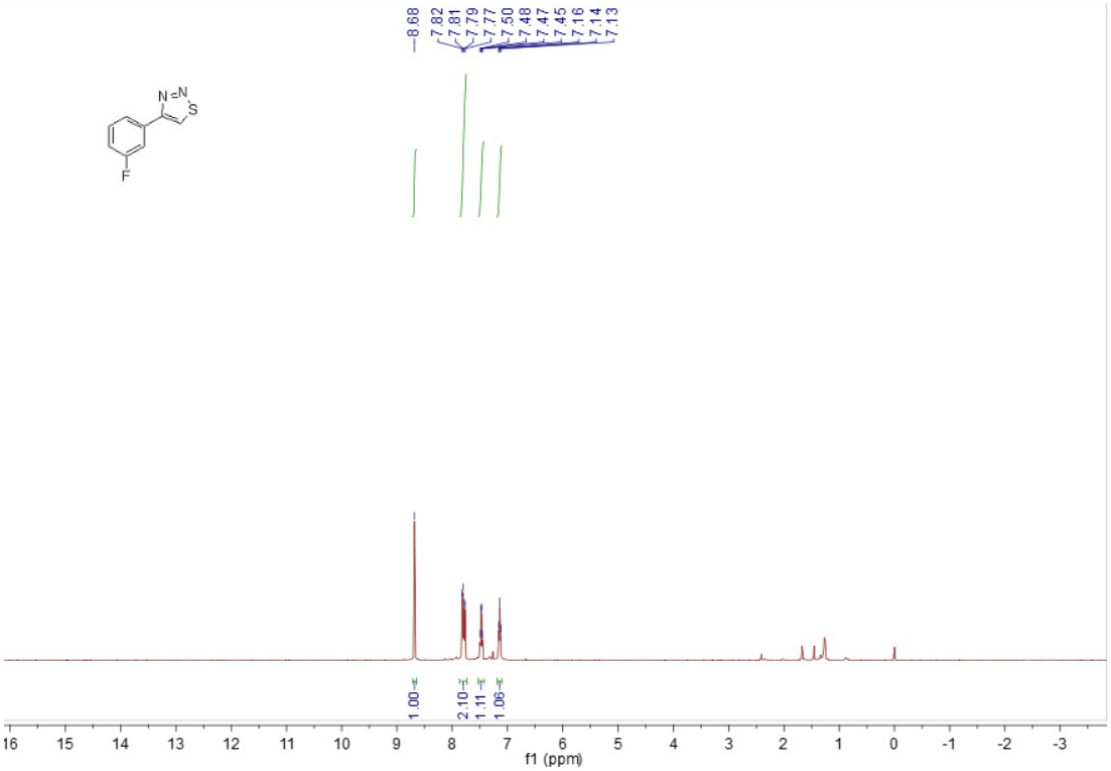


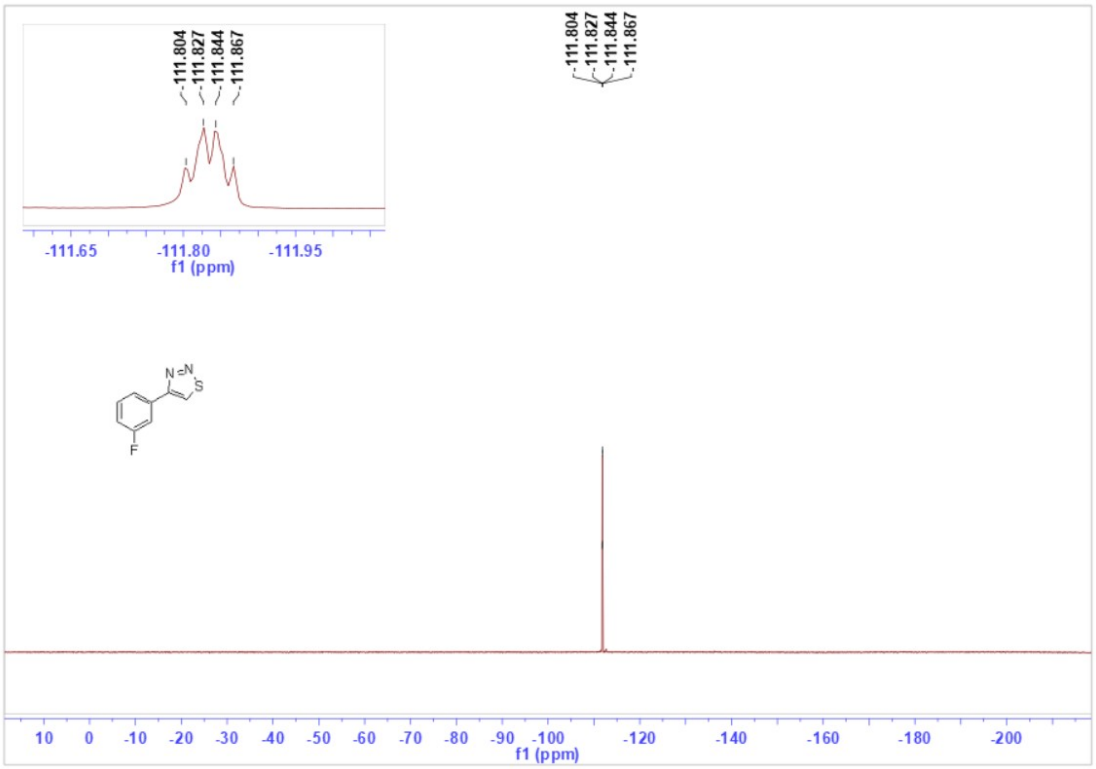
4-(1,2,3-Thiadiazol-4-yl)benzonitrile (1ee)

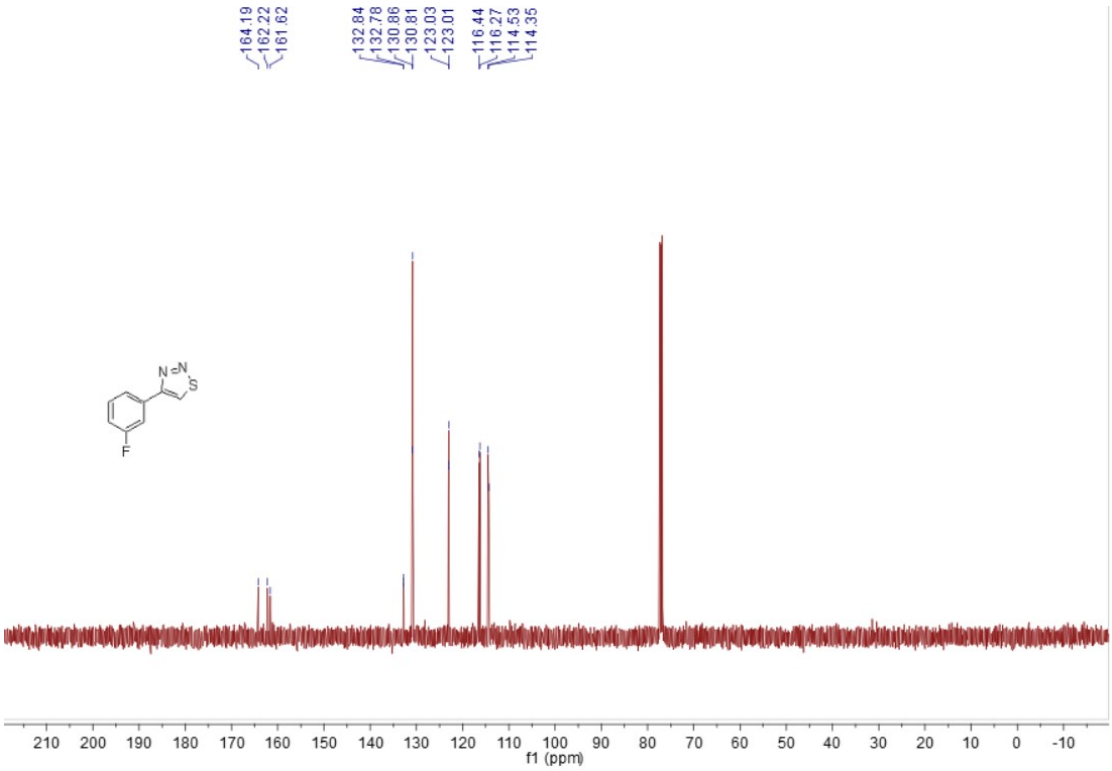




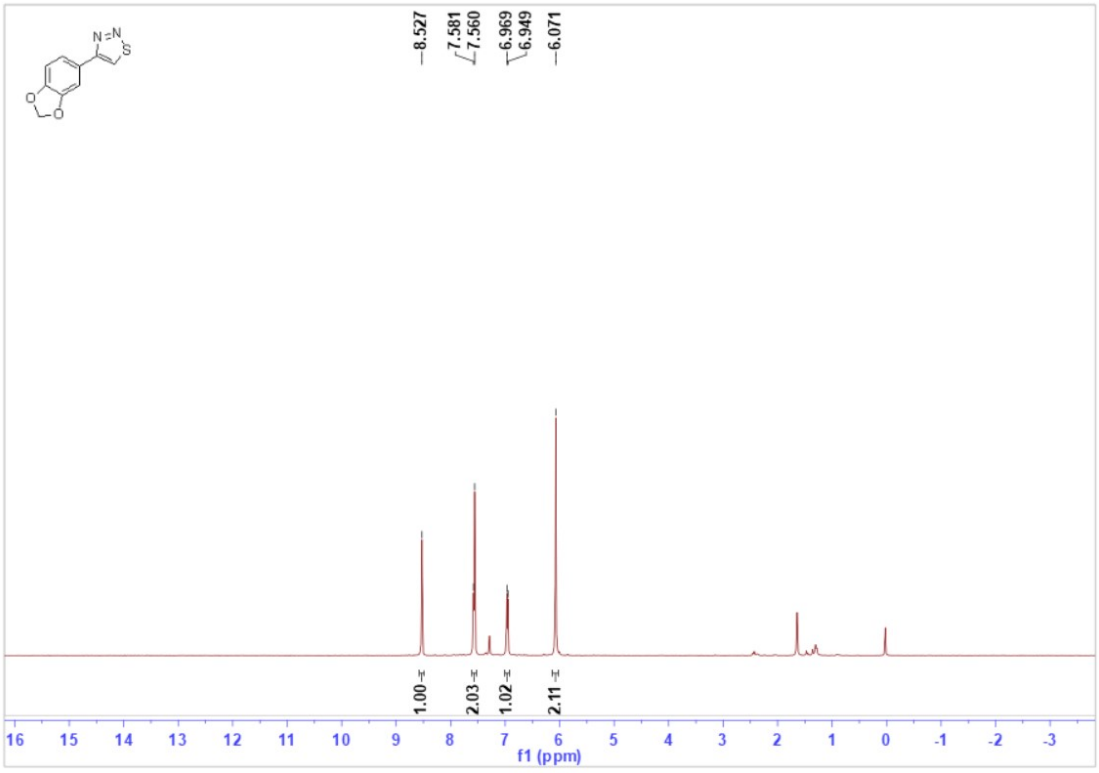
(3-Fluorophenyl)-1,2,3-thiadiazole (1ef)

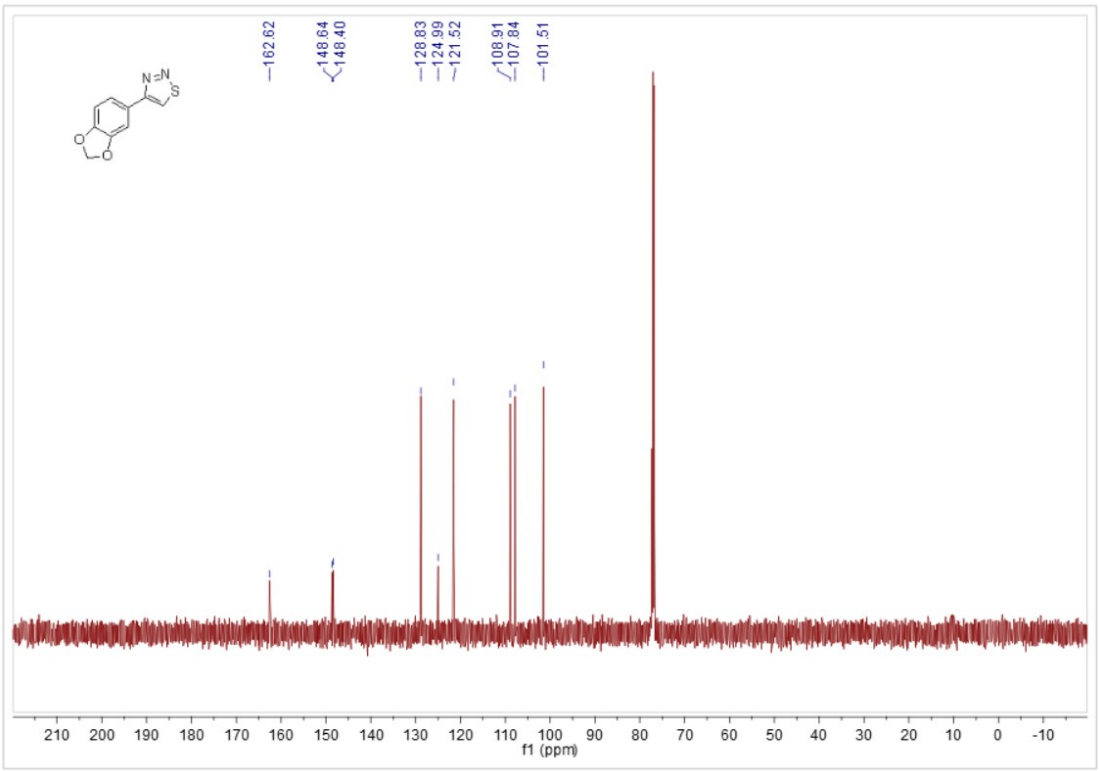




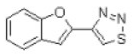

164.19
162.22
161.62
132.84
132.78
130.86
130.81
123.03
123.01
116.44
116.27
114.53
114.35
N
N
S
F
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

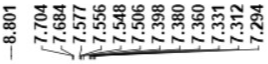
(Benzo[*d*][1,3]dioxol-5-yl)-1,2,3-thiadiazole (1eg)

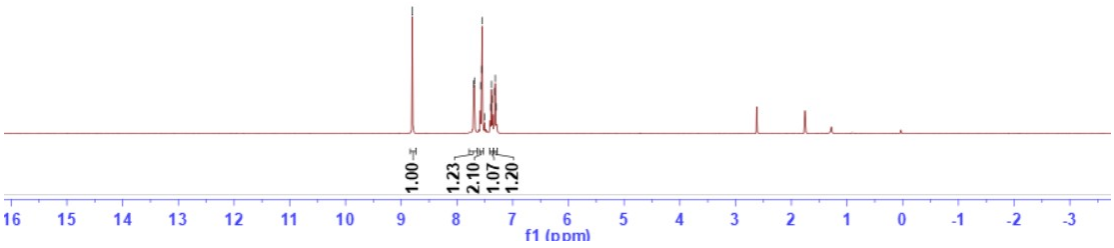


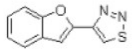


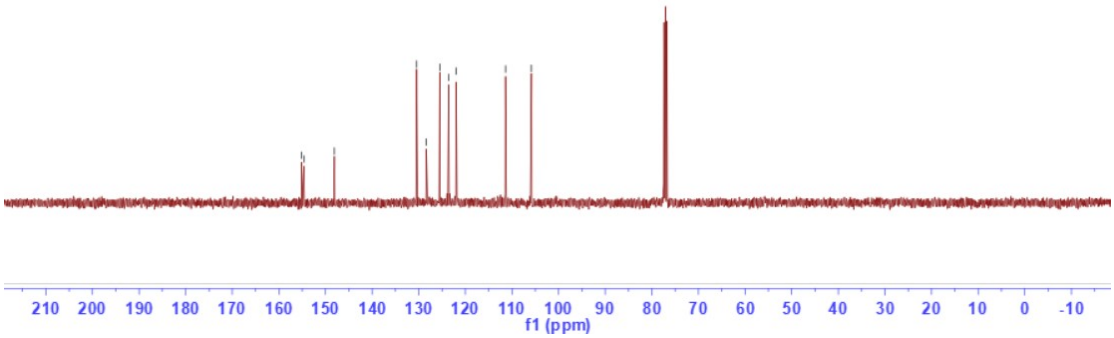
4-(Benzofuran-2-yl)-1,2,3-thiadiazole (1eh)



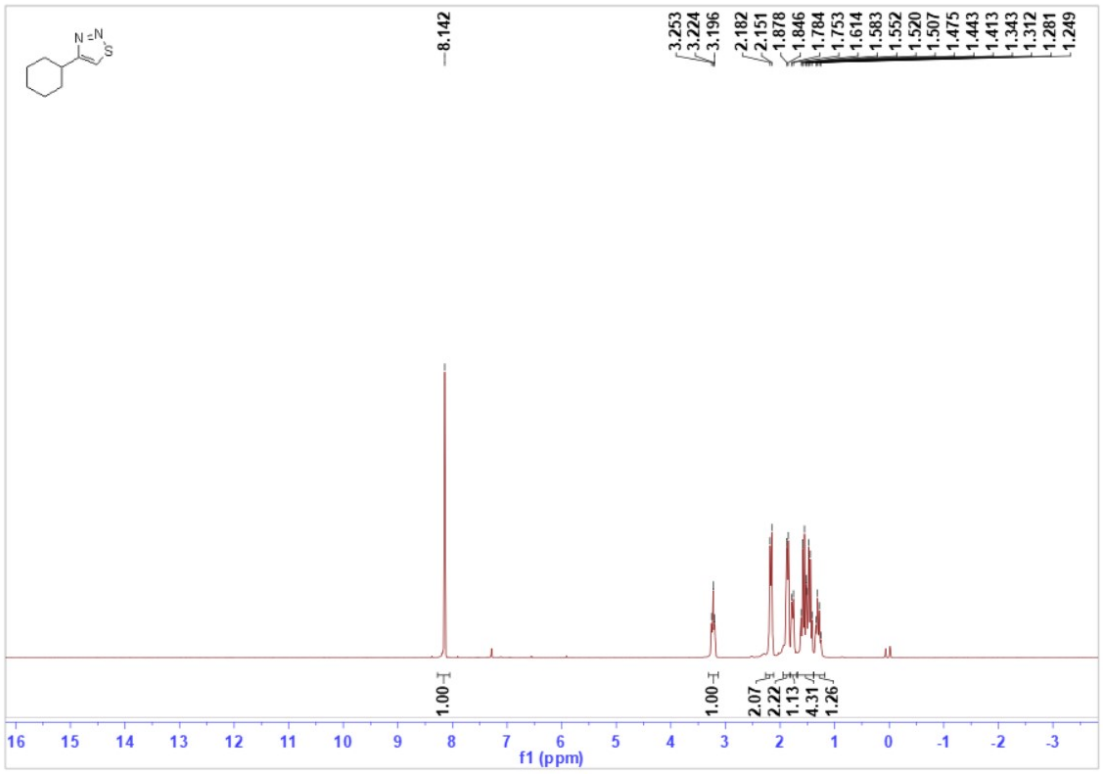


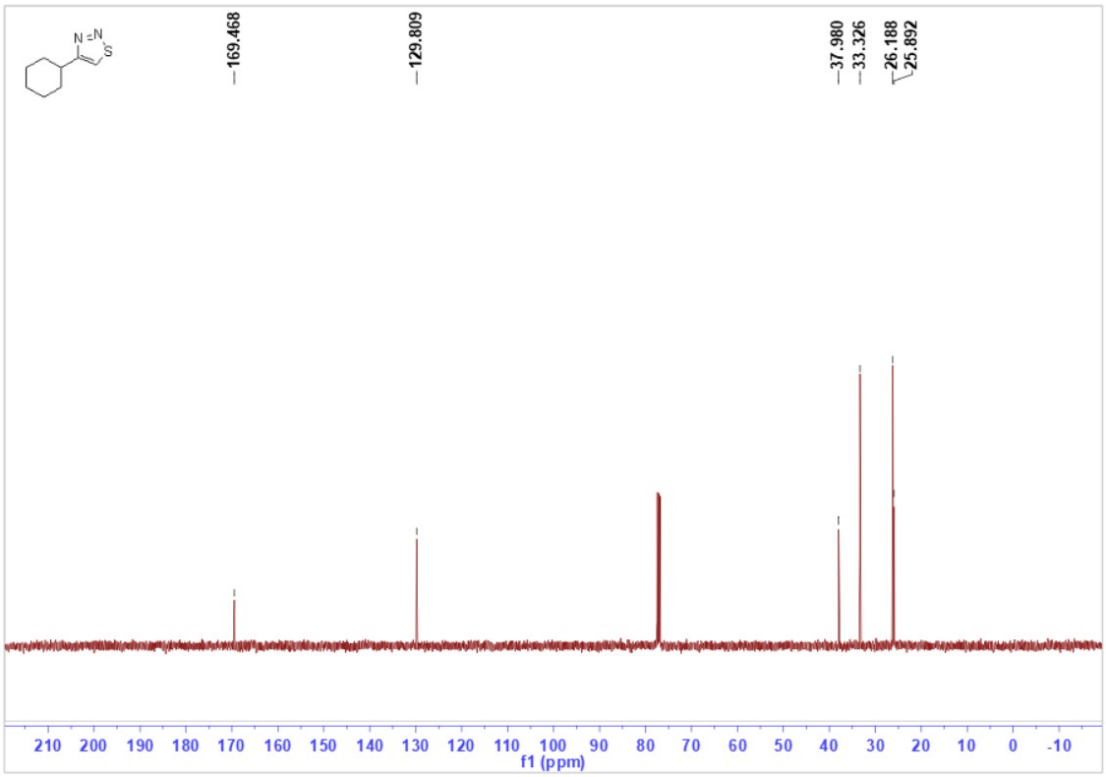




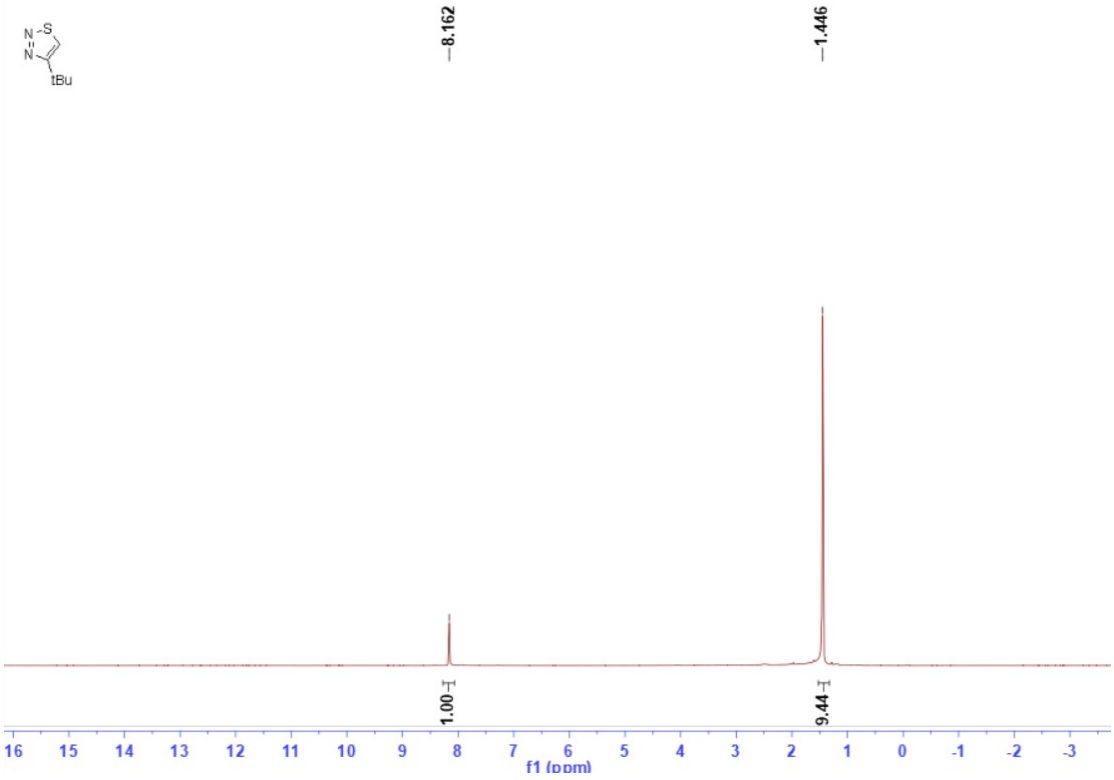


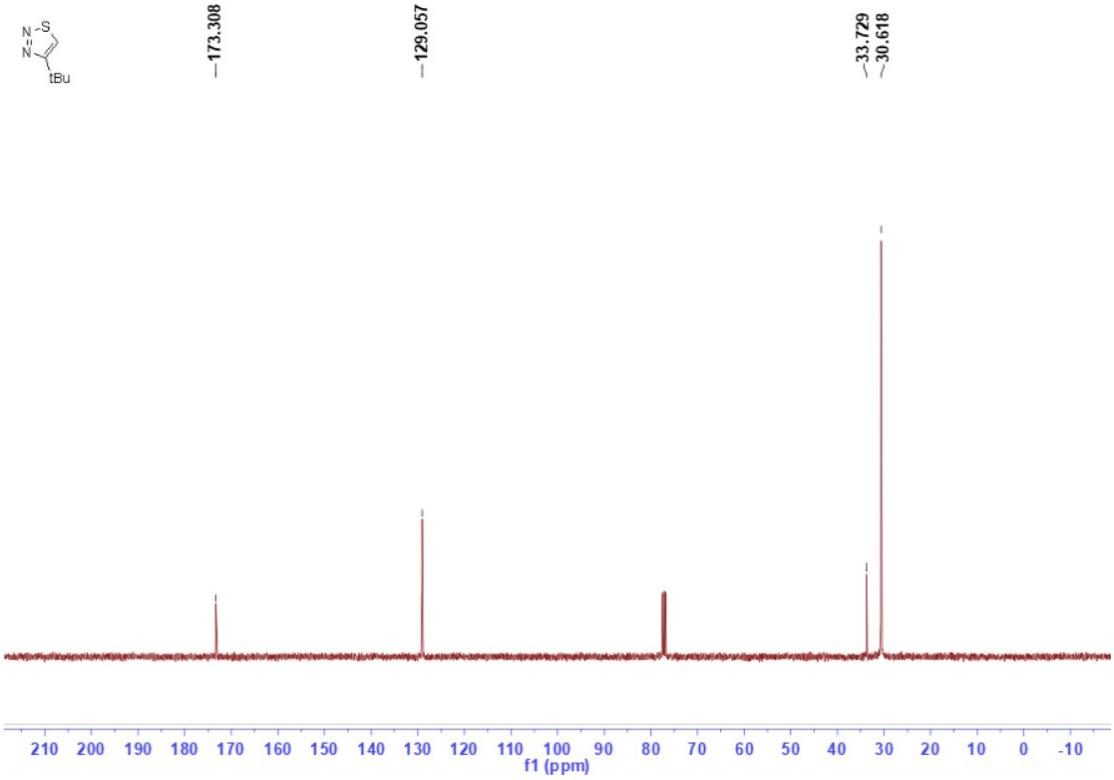
4-Cyclohexyl-1,2,3-thiadiazole (1ei)



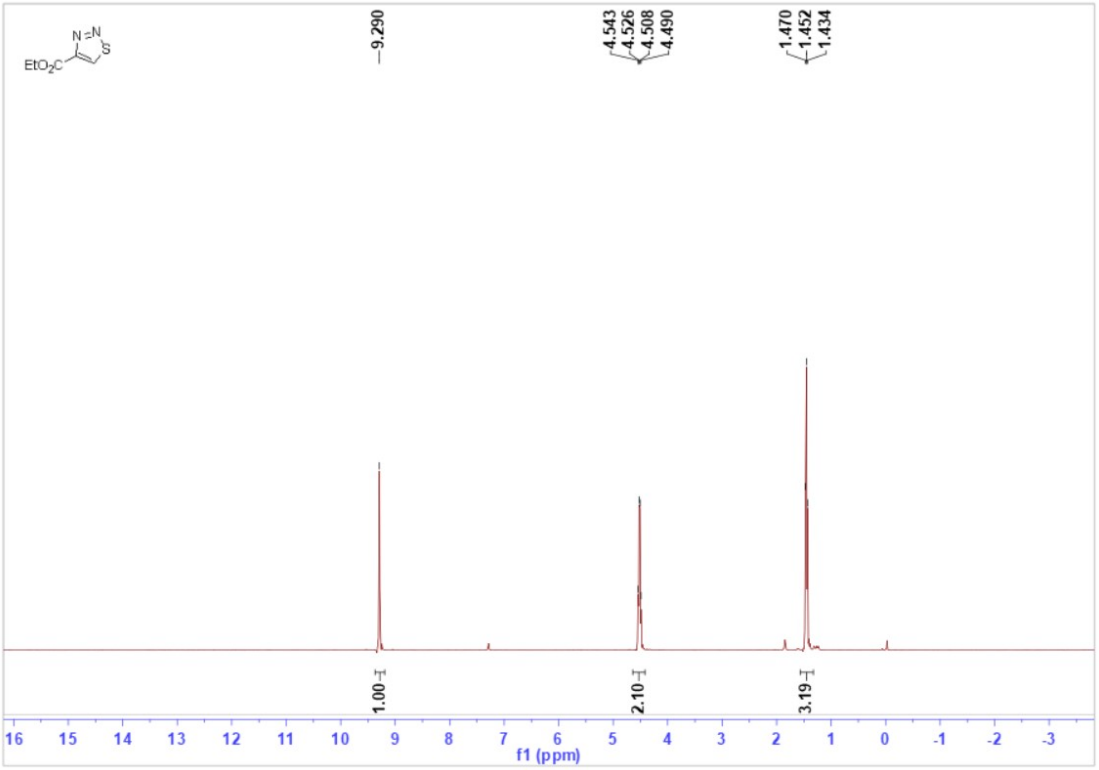


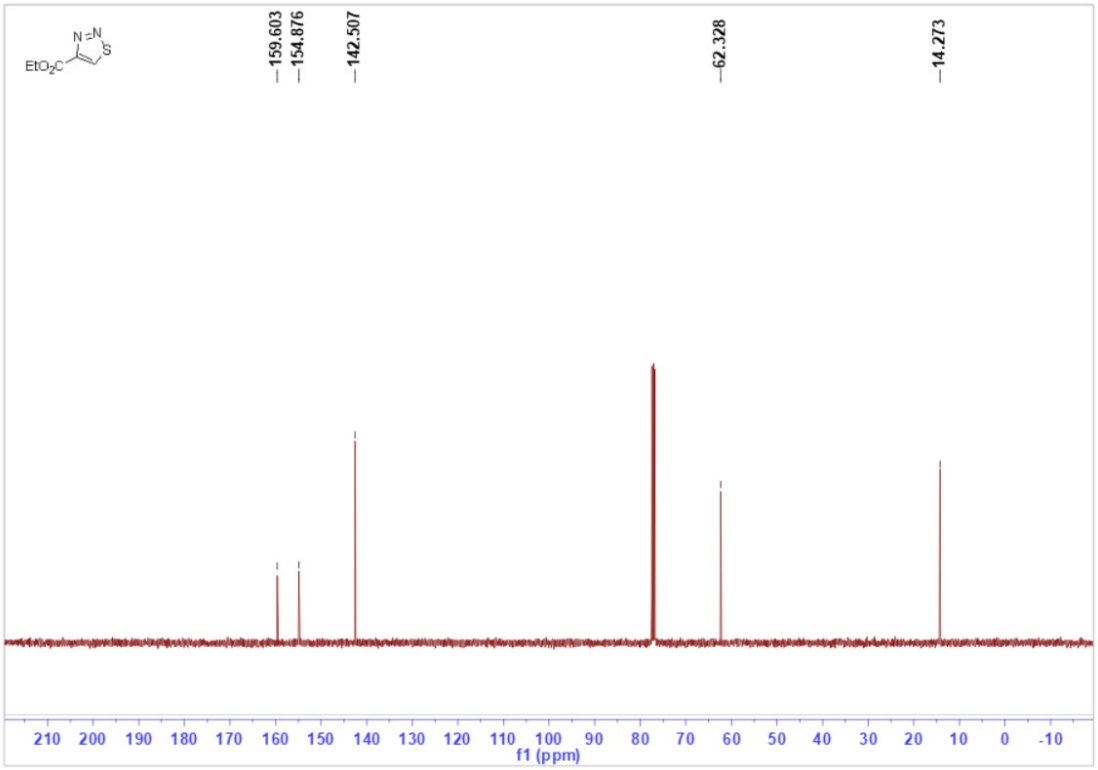
4-(Tert-butyl)-1,2,3-thiadiazole (1ej)



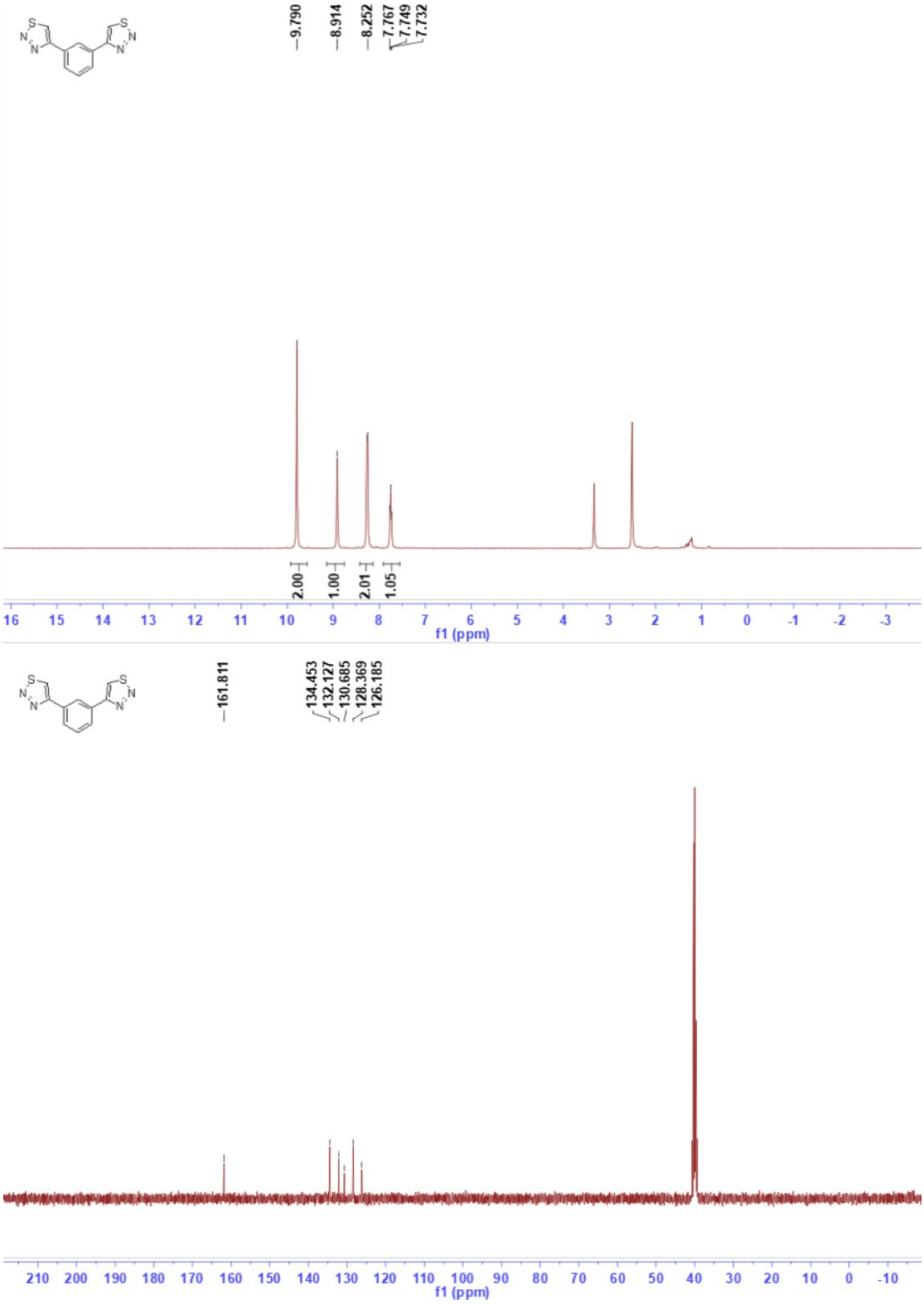


Ethyl 1,2,3-thiadiazole-4-carboxylate (1ek)

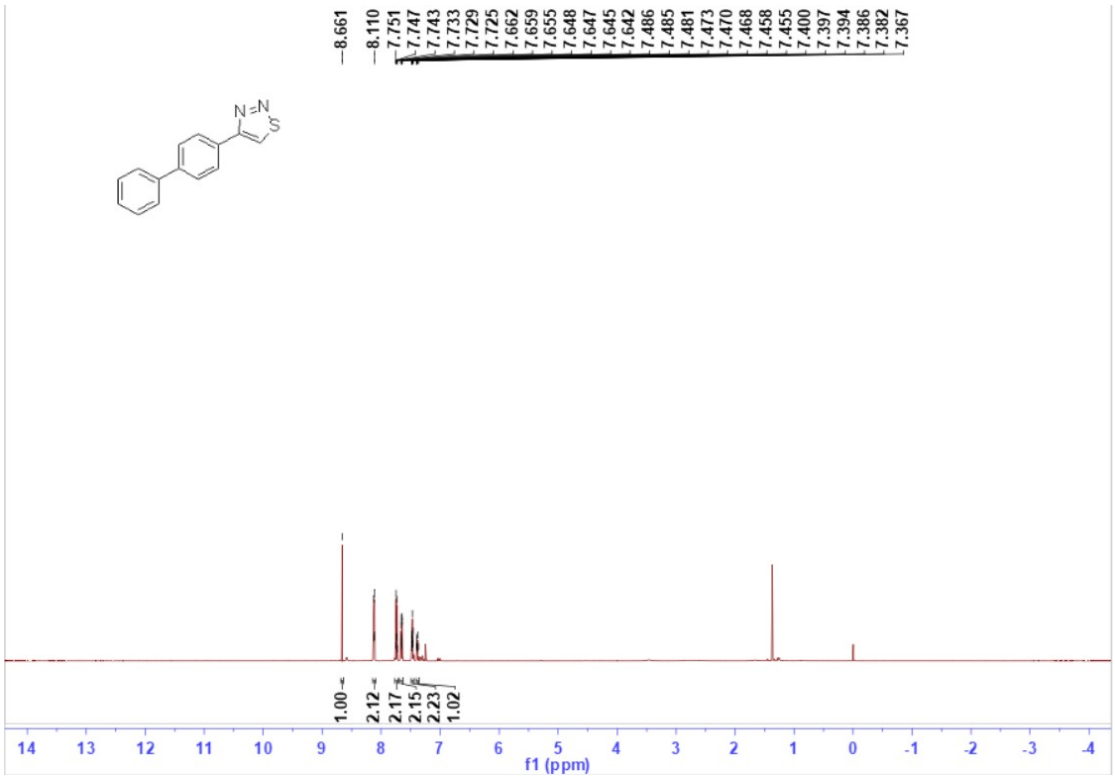


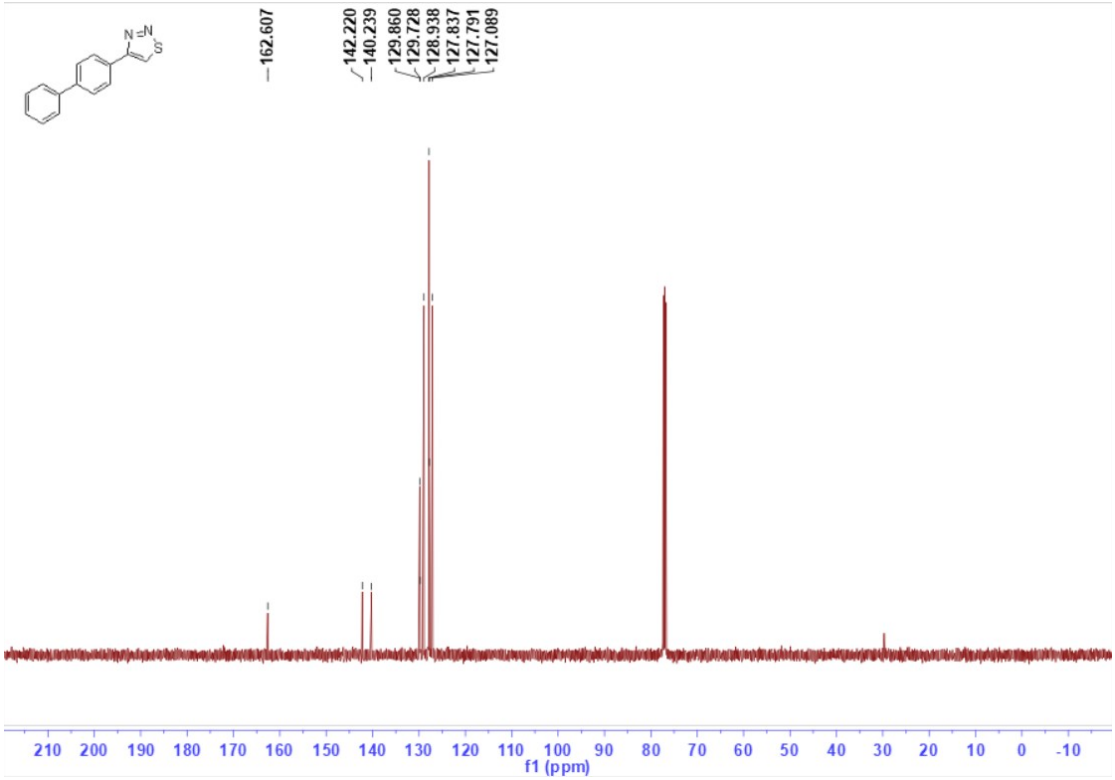


1,3-Di(1,2,3-thiadiazol-4-yl)benzene (1el)

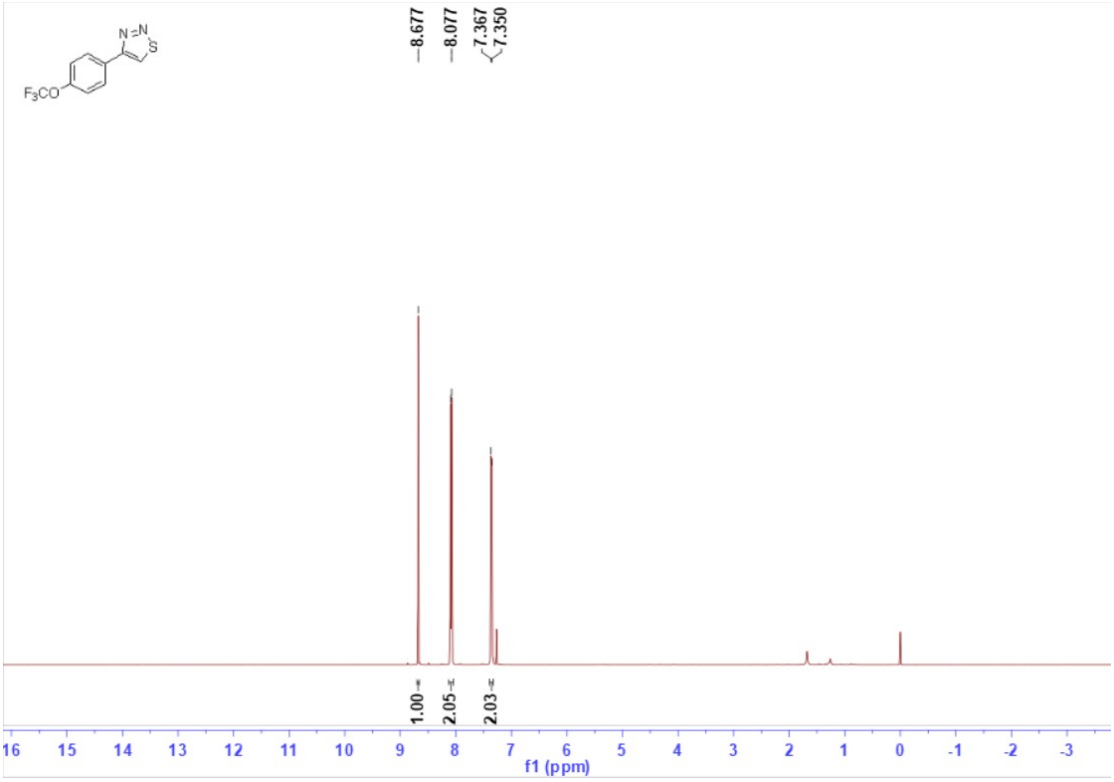


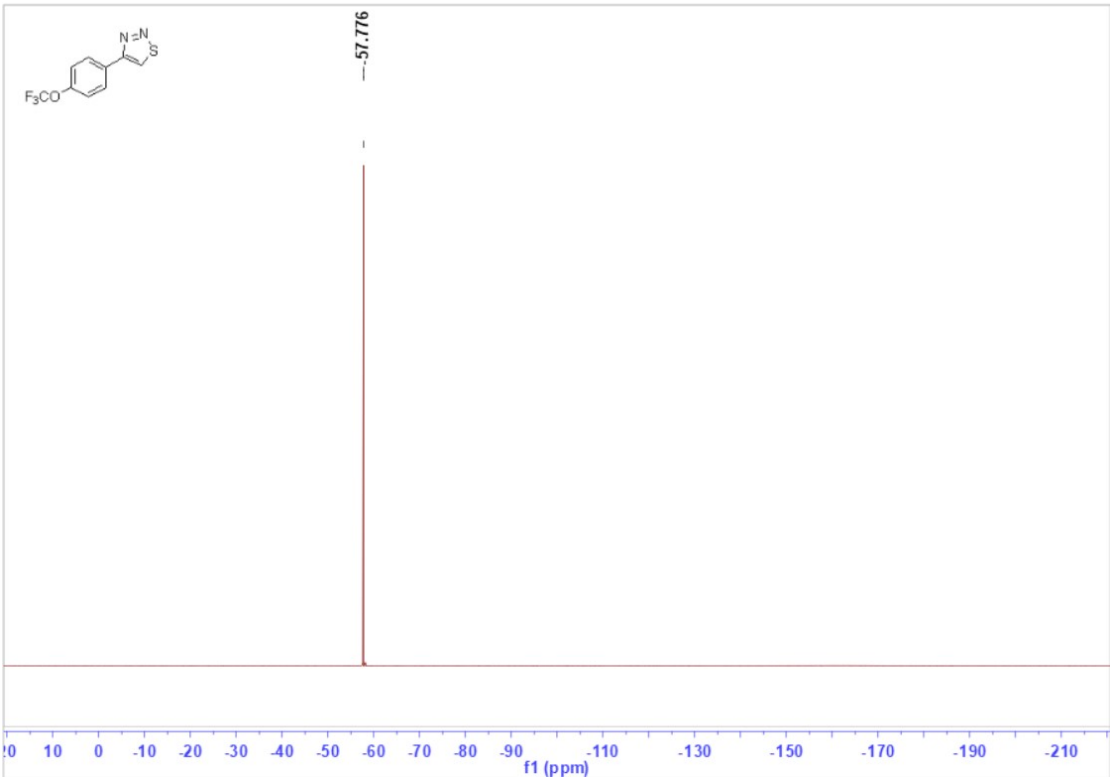
4-([1,1'-Biphenyl]-4-yl)-1,2,3-thiadiazole (1em)

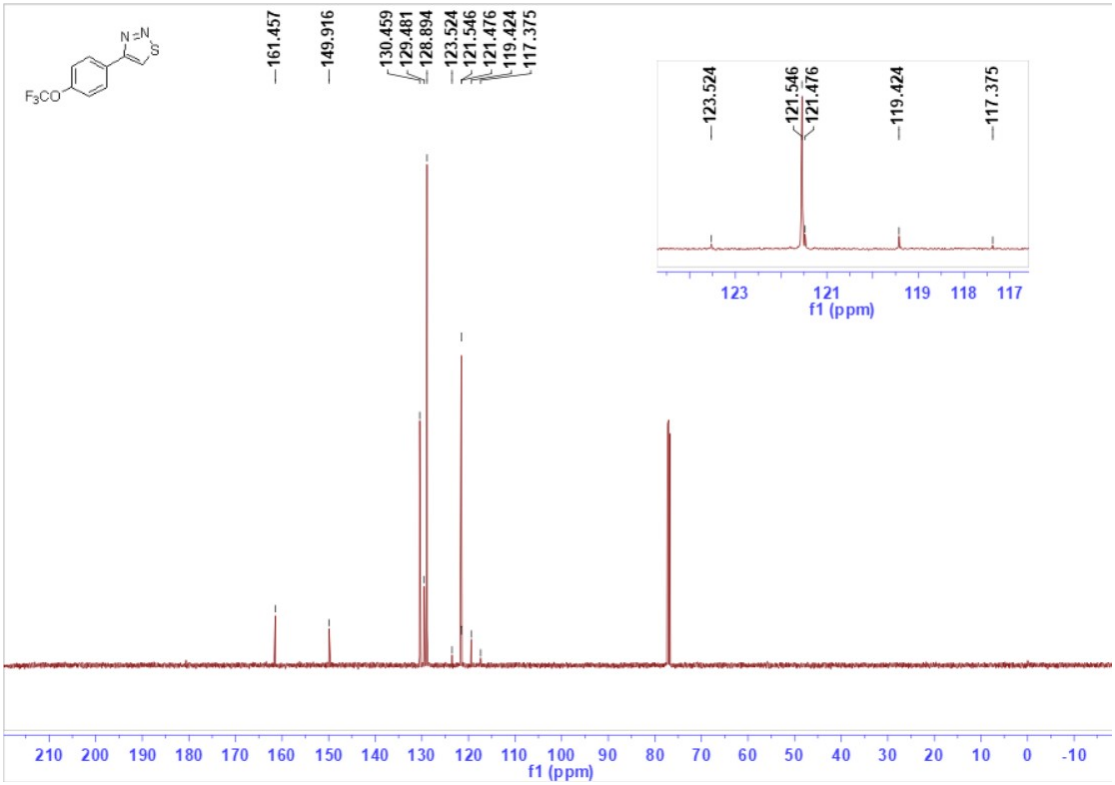




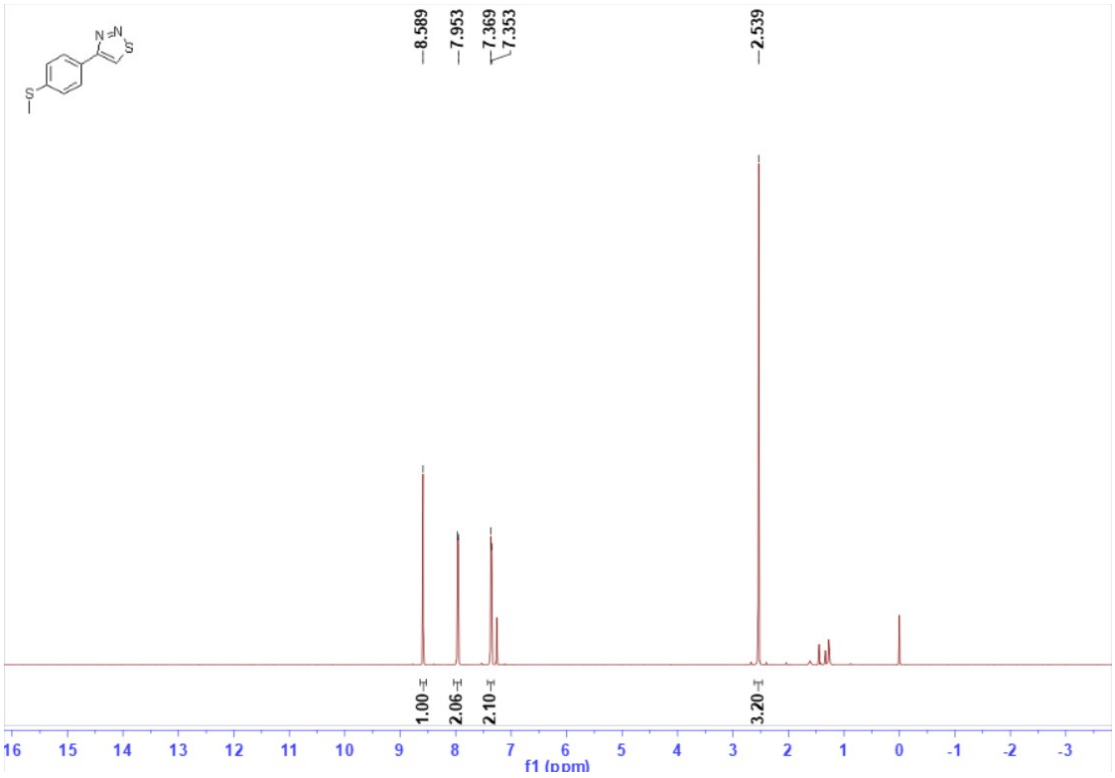
4-(4-(Trifluoromethoxy)phenyl)-1,2,3-thiadiazole (1en)

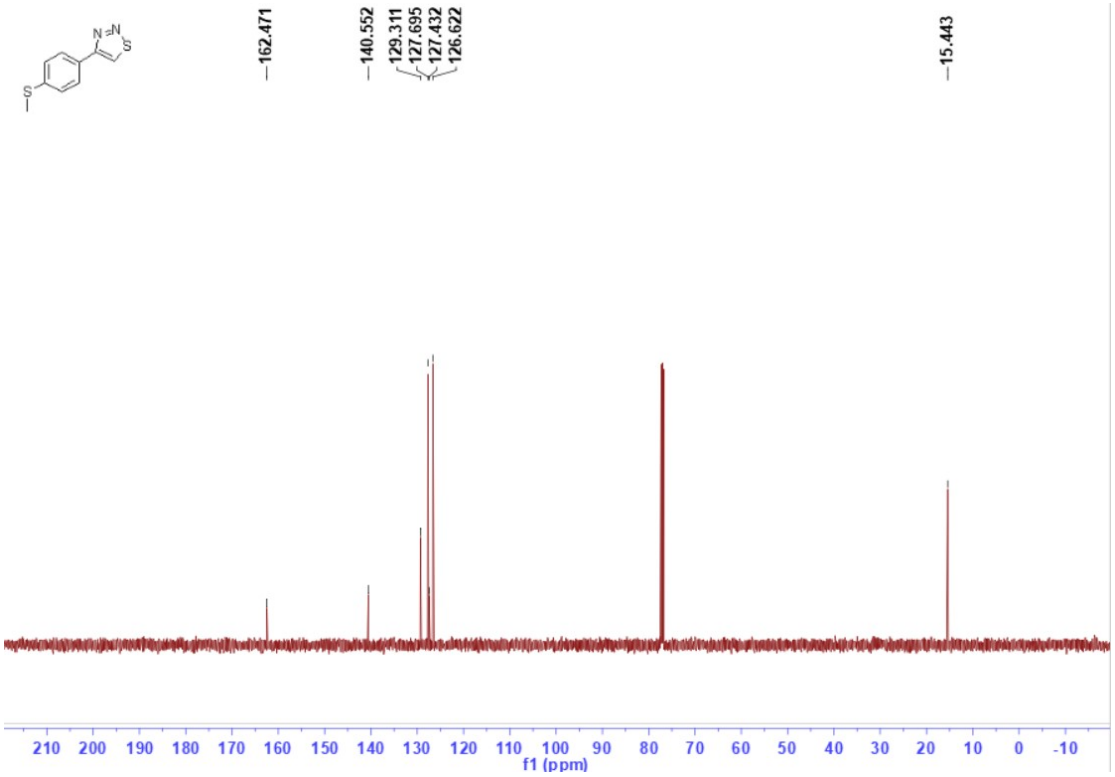




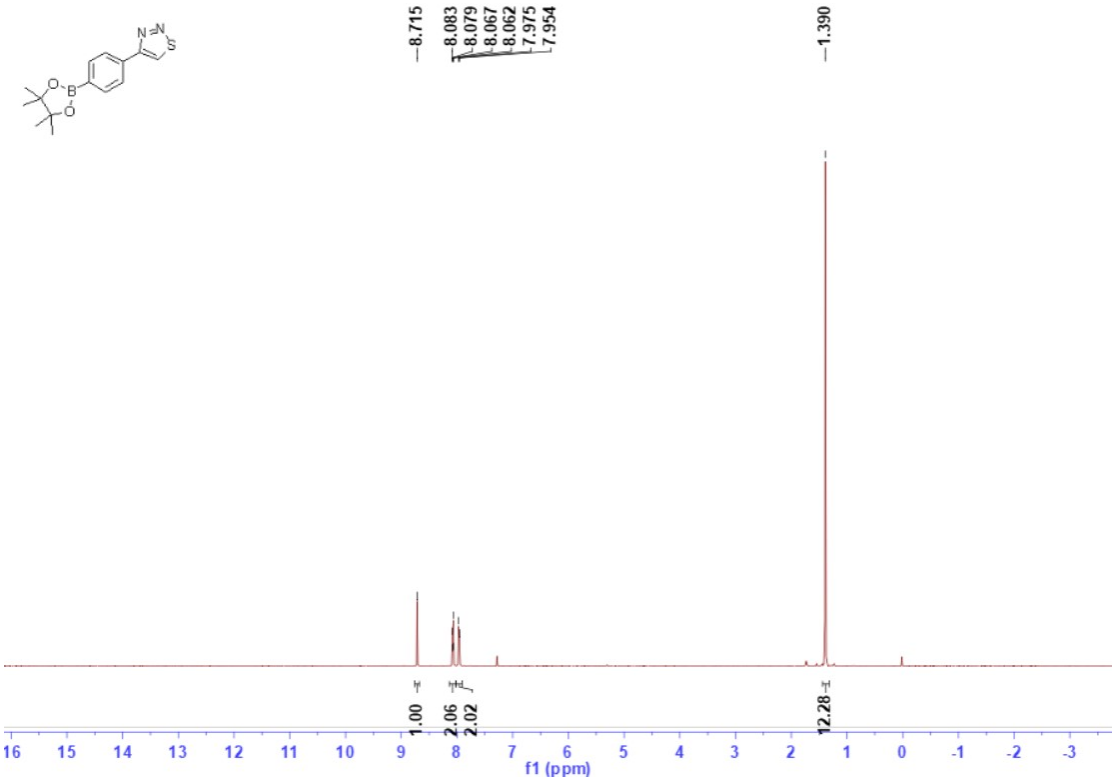

F3CO
N
S
161.457
149.916
130.459
129.481
128.894
123.524
121.546
121.476
119.424
117.375
123.524
121.546
121.476
119.424
117.375
123
121
119
118
117
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

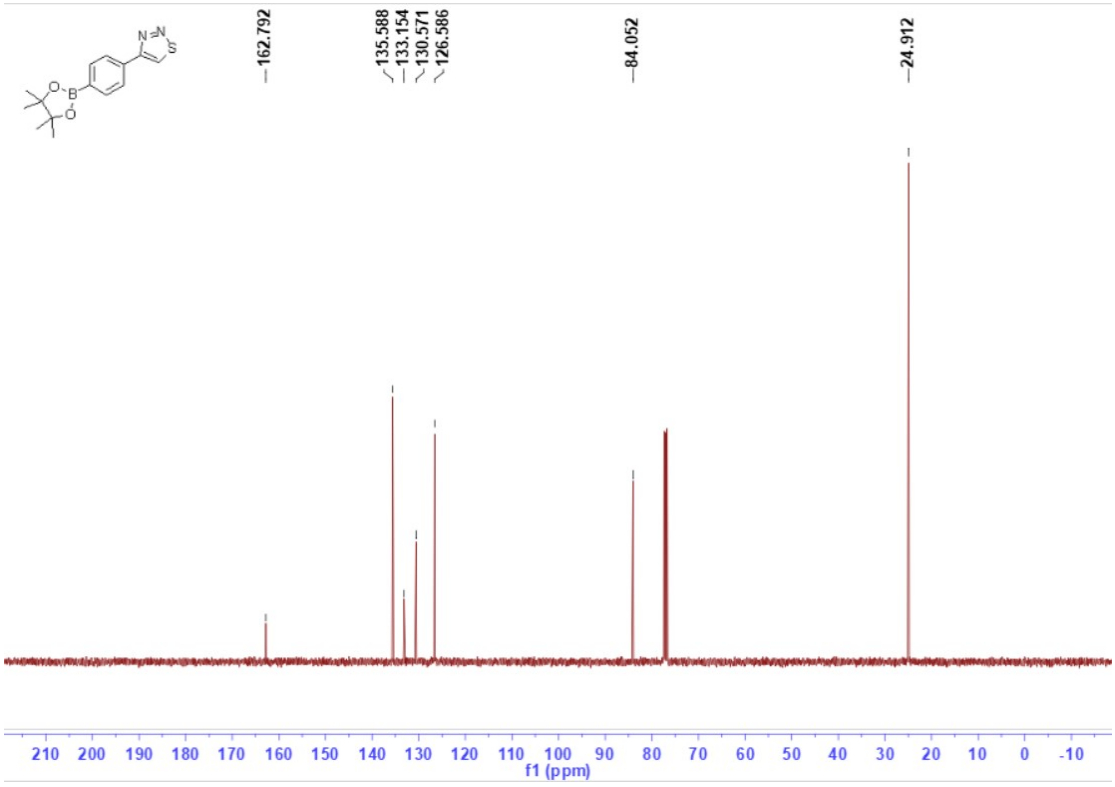
4-(4-(Methylthio)phenyl)-1,2,3-thiadiazole (1eo)



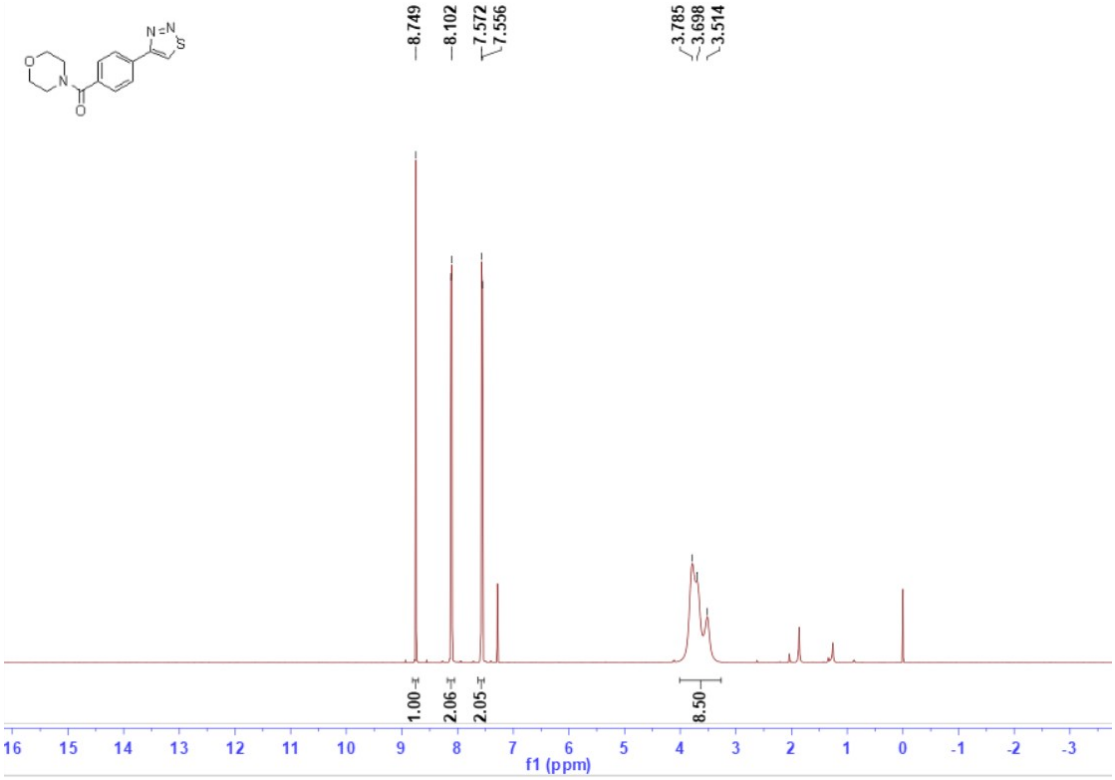


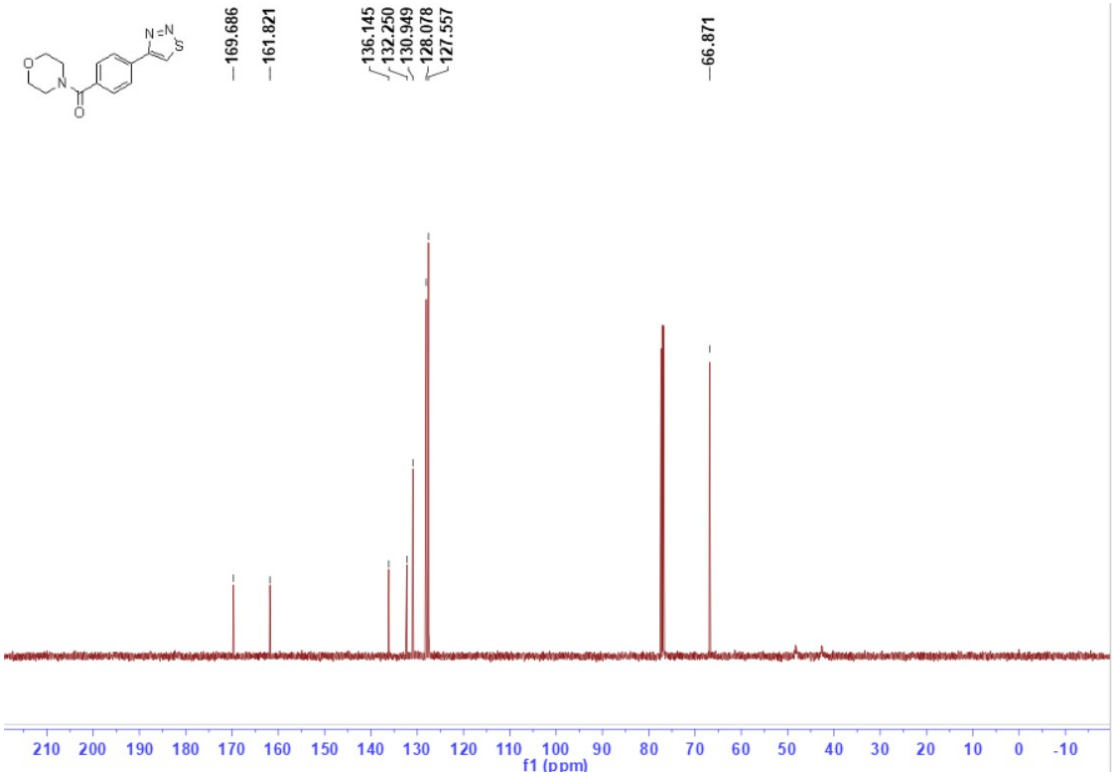
4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,2,3-thiadiazole (1ep)



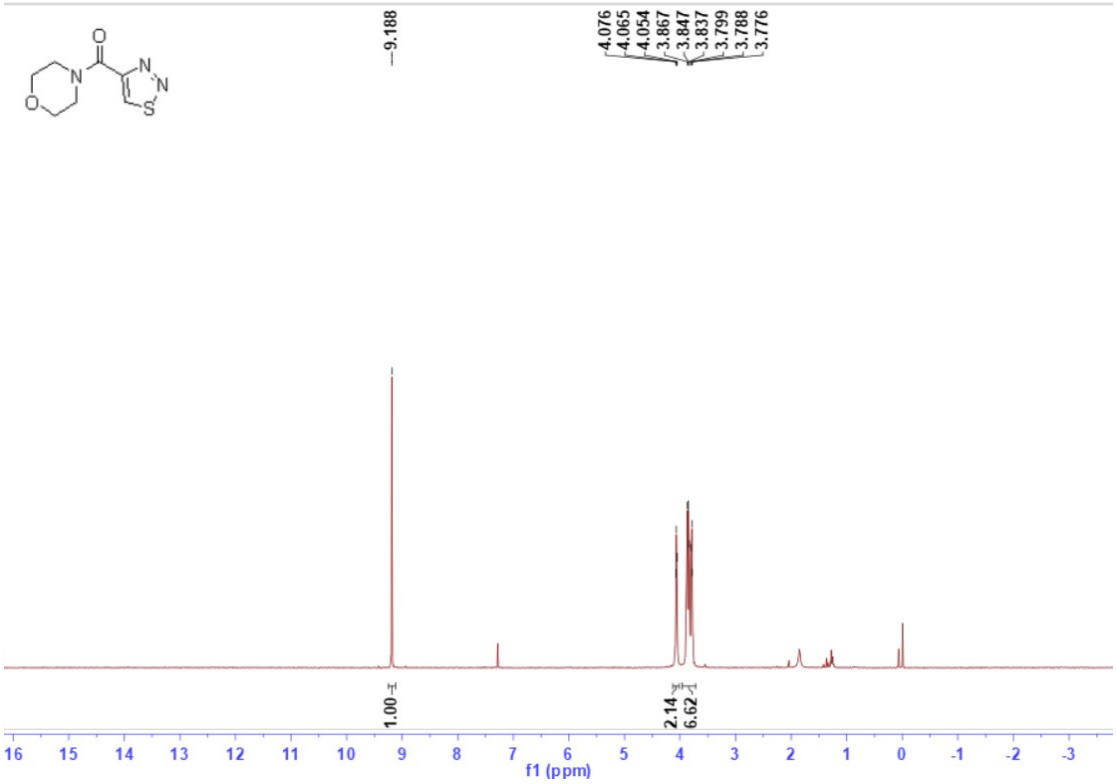


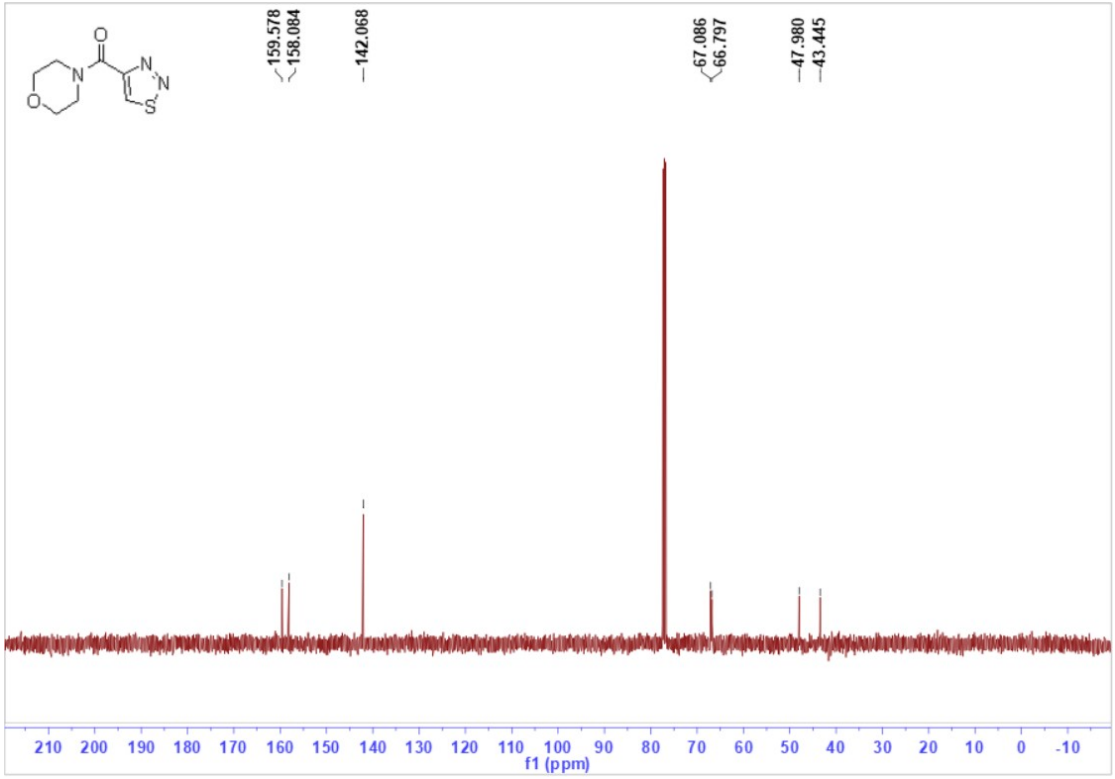
(4-(1,2,3-Thiadiazol-4-yl)phenyl)(morpholino)methanone (1eq)



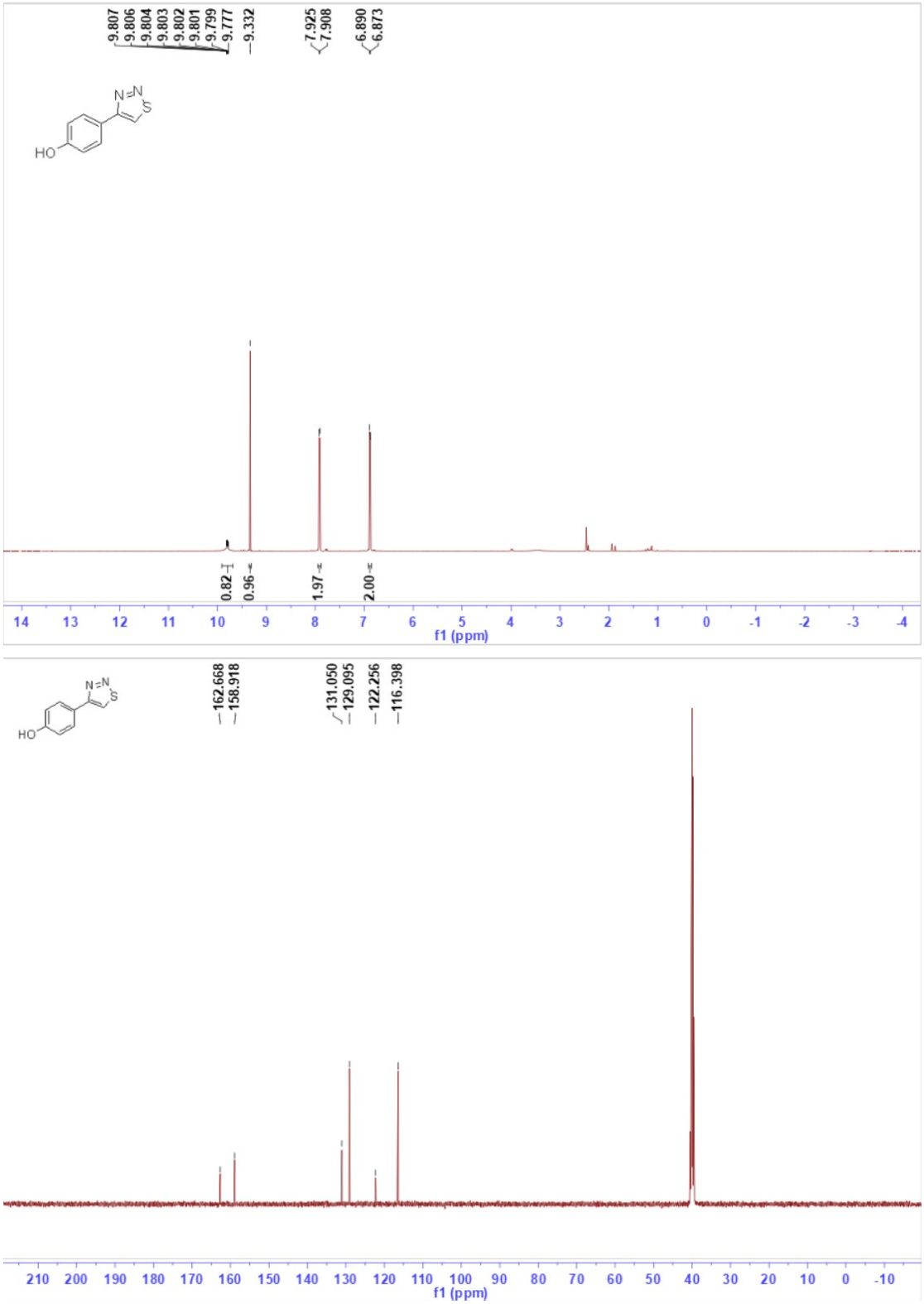


Morpholino(1,2,3-thiadiazol-4-yl)methanone (1er)

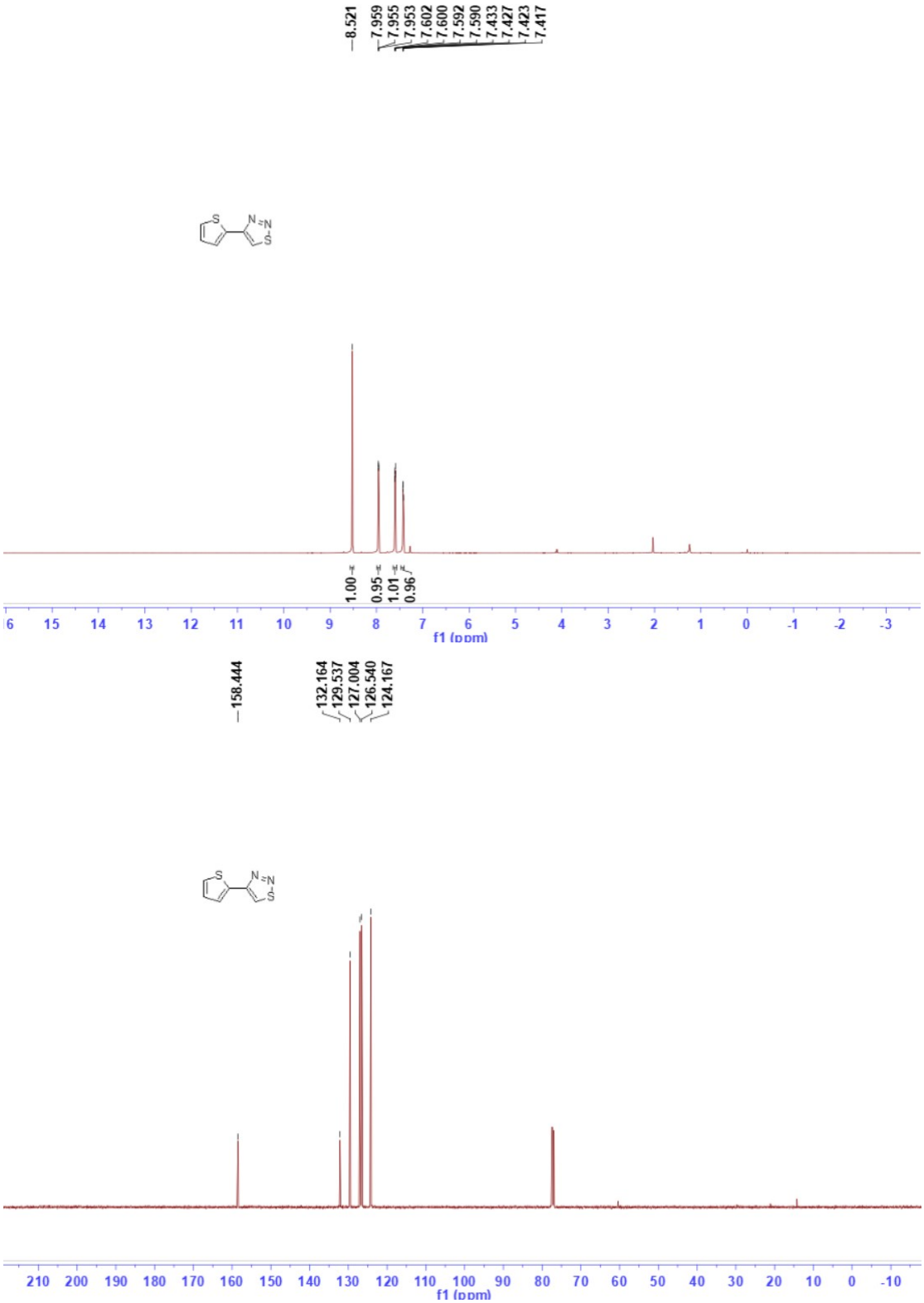




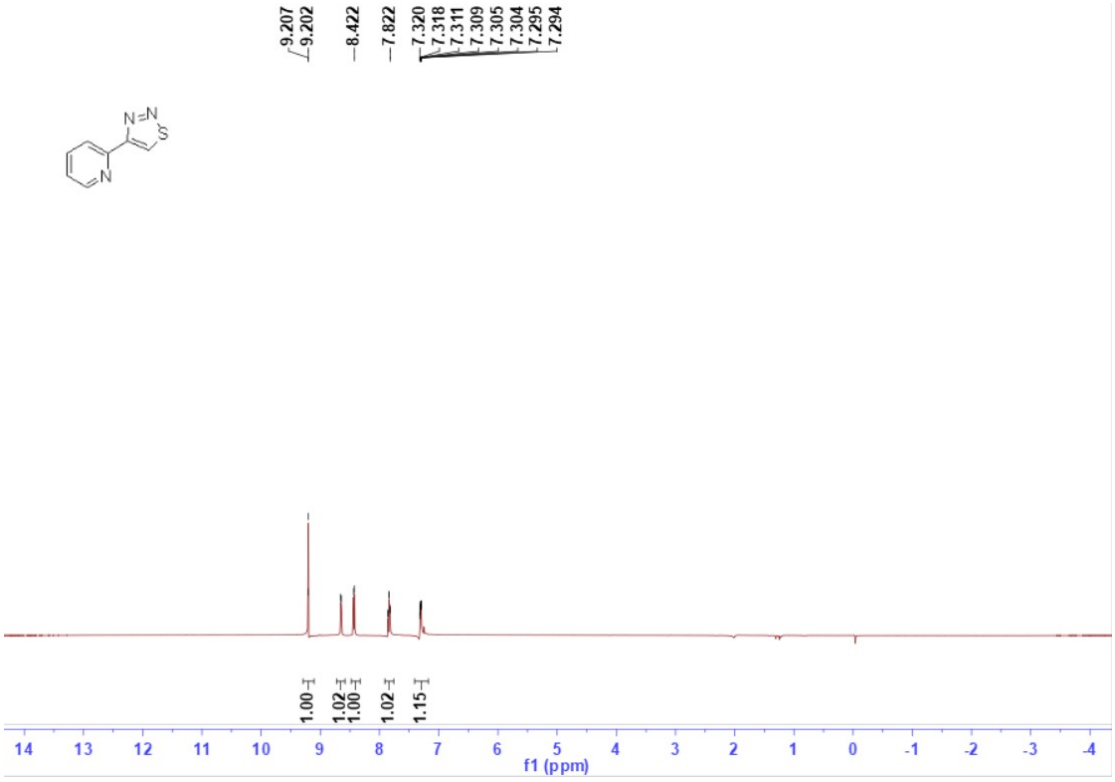
4-(1,2,3-Thiadiazol-4-yl)phenol (1et)

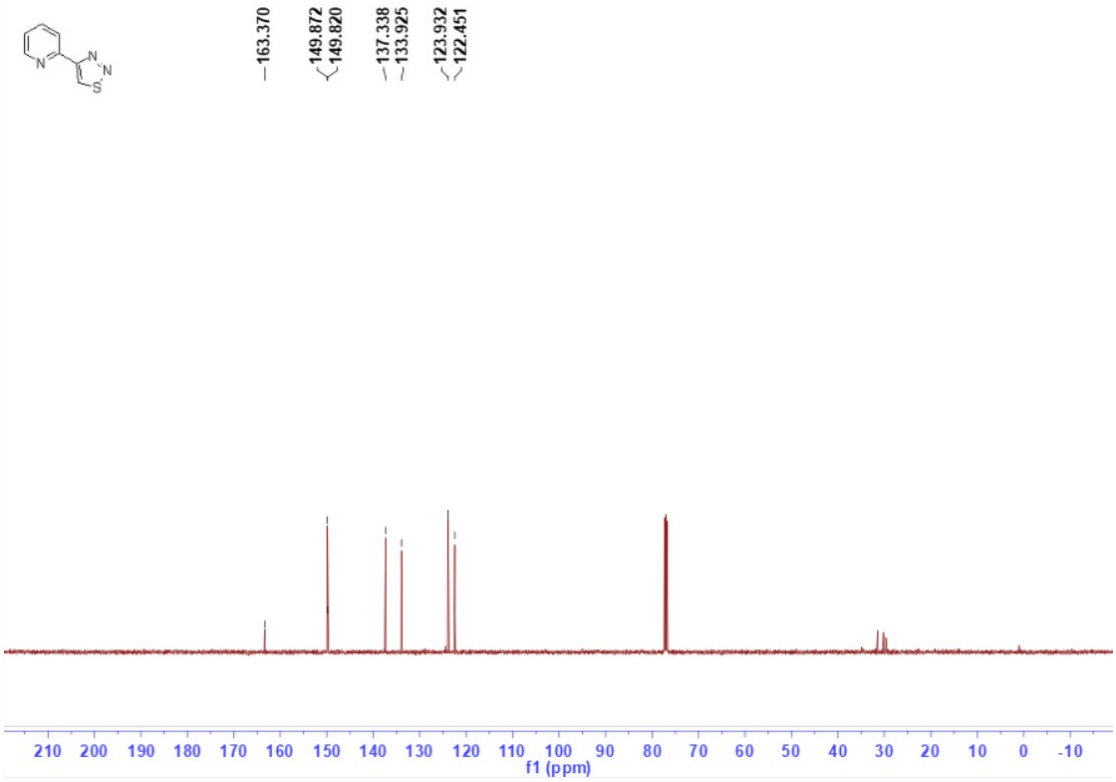


4-(Thiophen-2-yl)-1,2,3-thiadiazole (1eu)

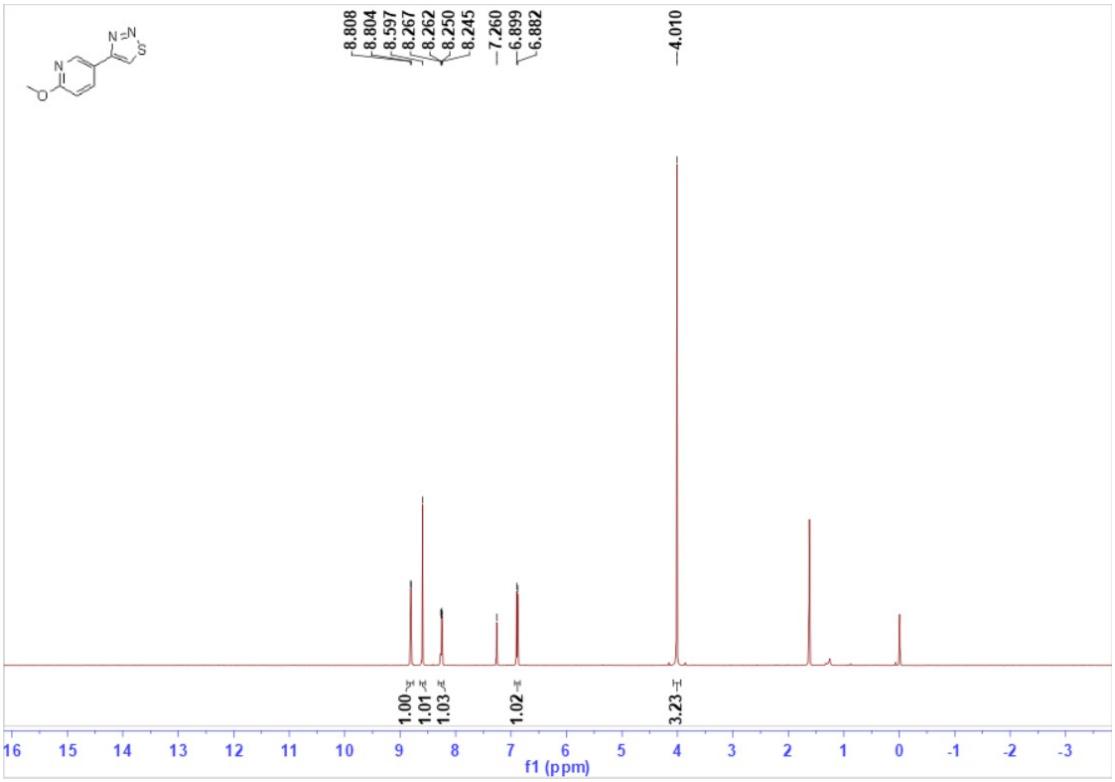


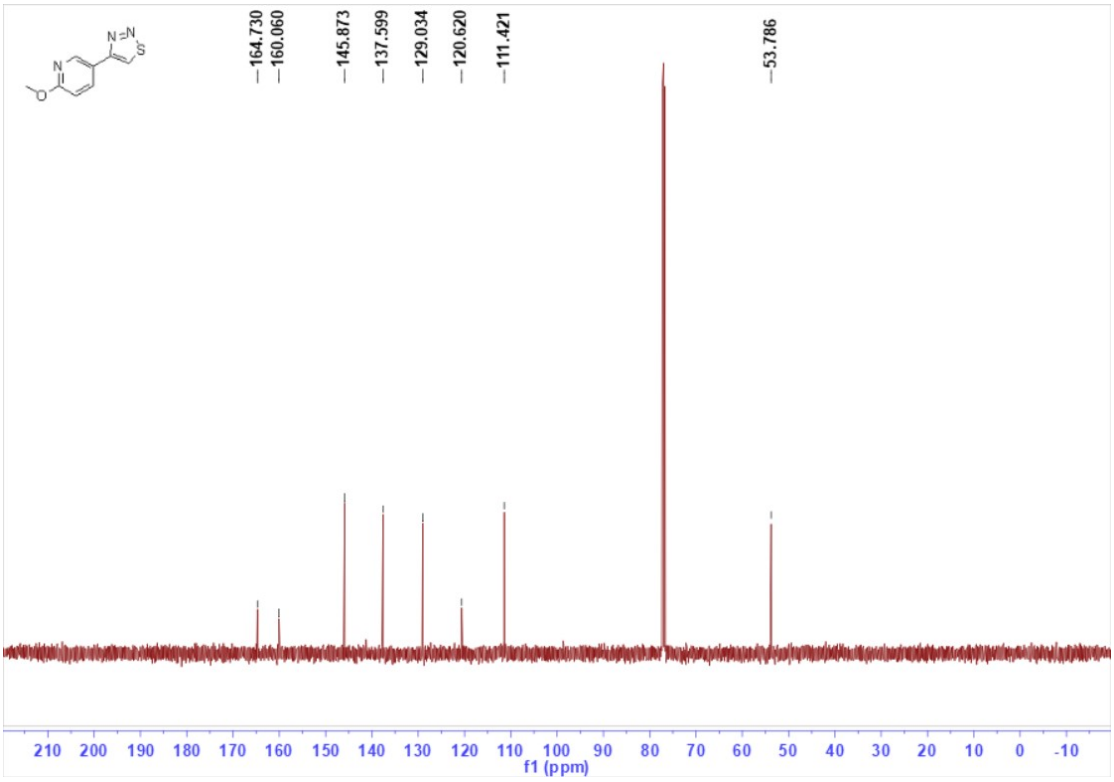
4-(pyridin-2-yl)-1,2,3-thiadiazole (1ew)



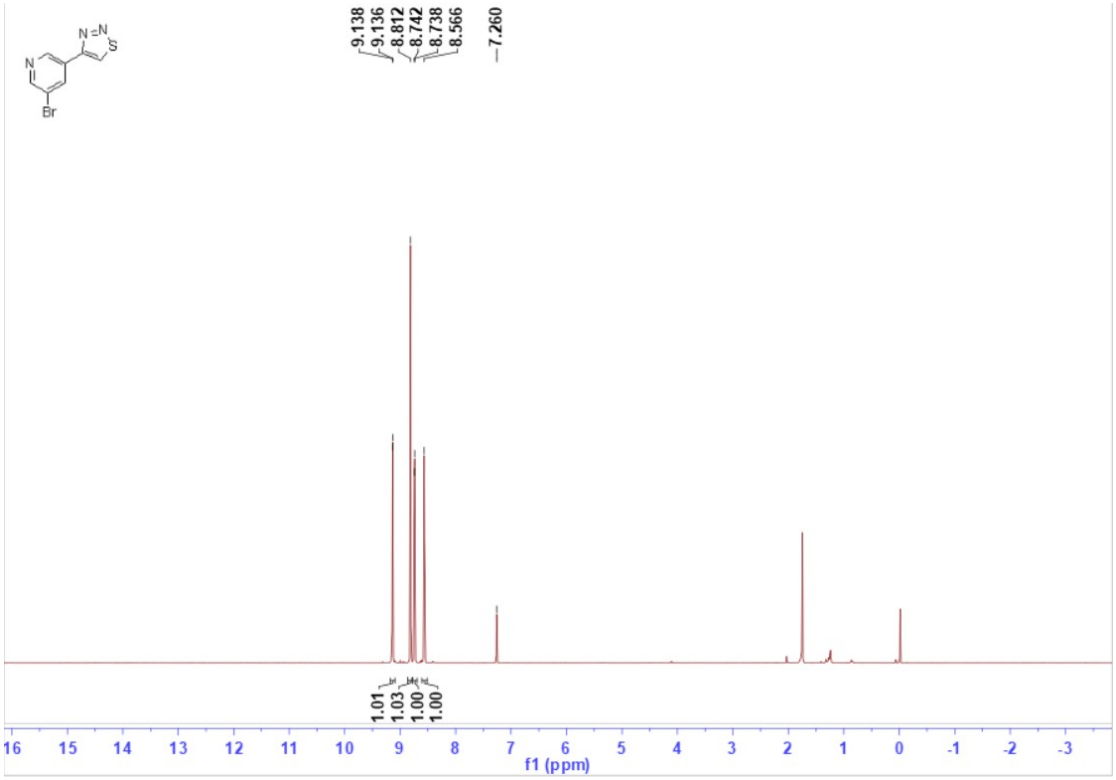


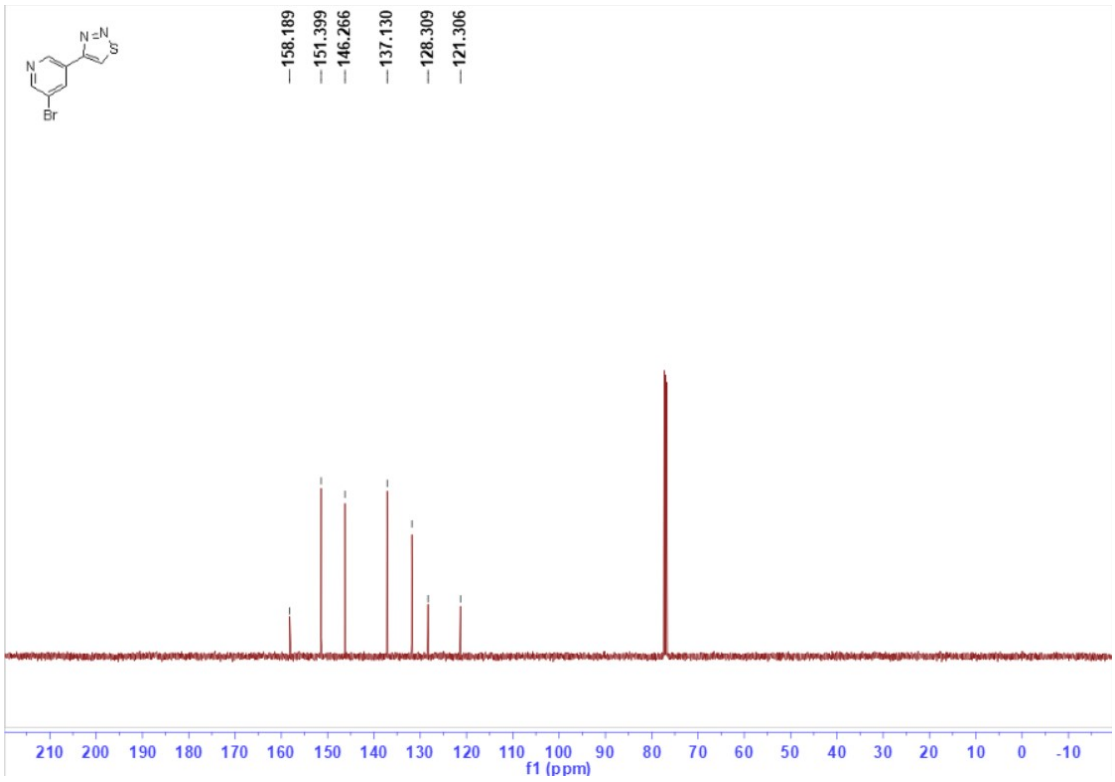
4-(6-methoxypyridin-3-yl)-1,2,3-thiadiazole (1ex)



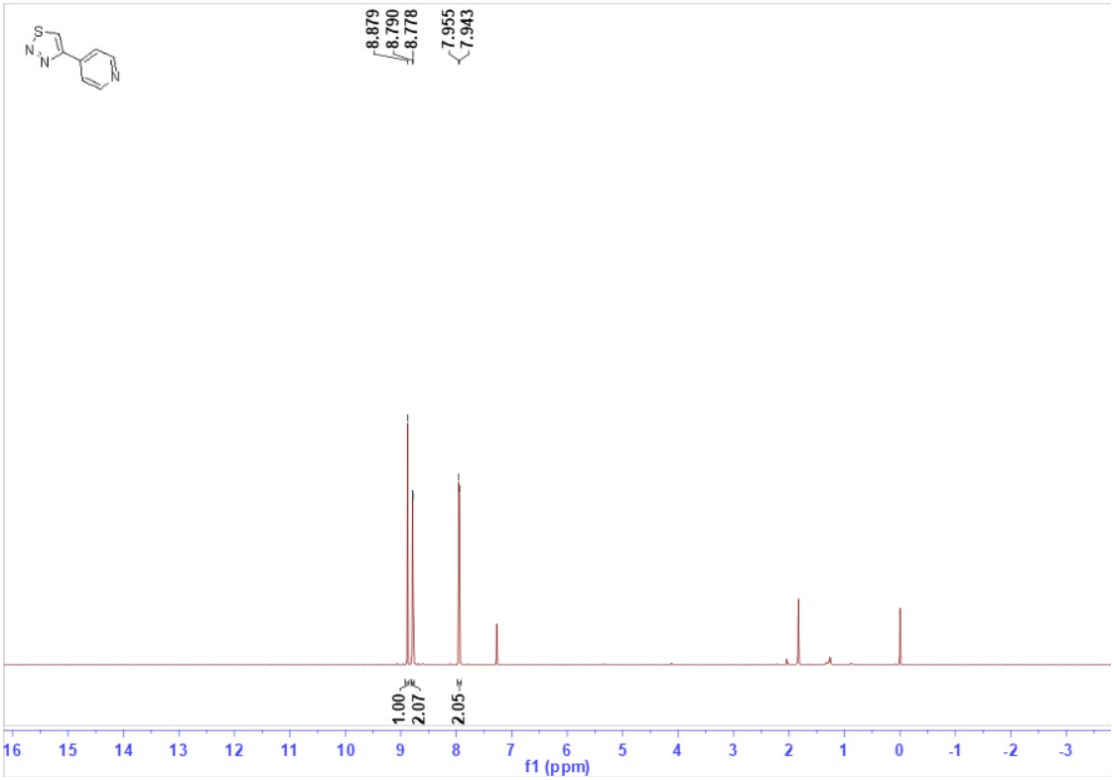


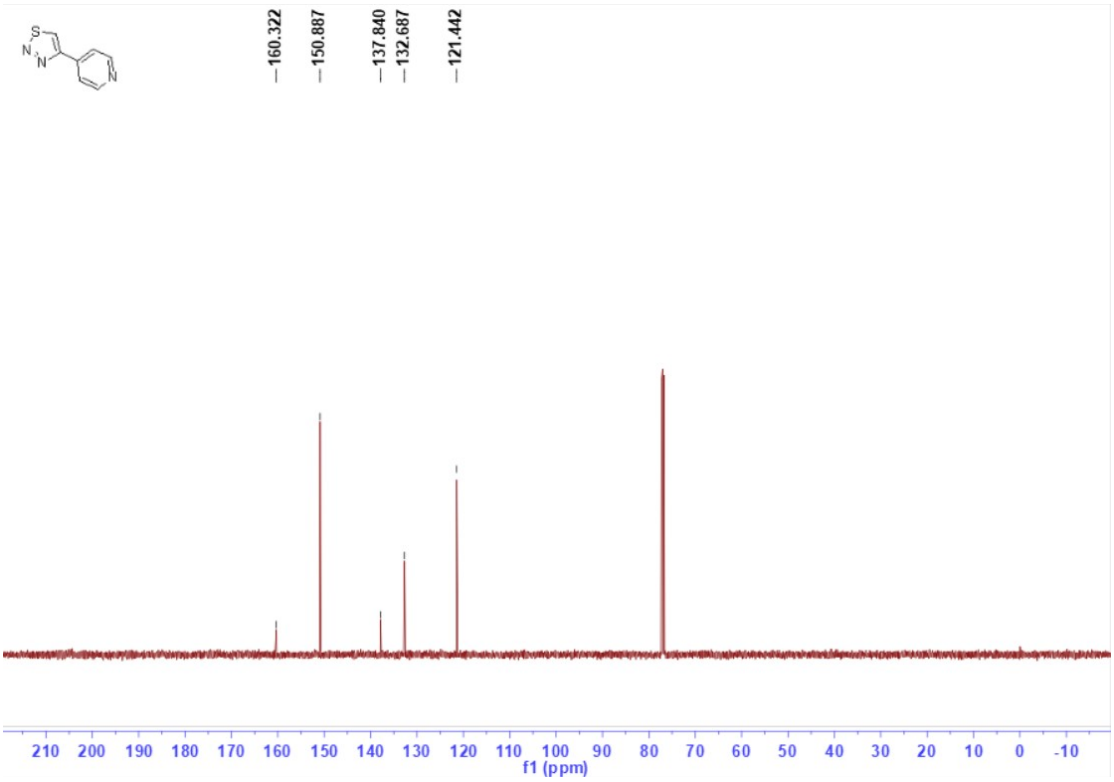
4-(5-bromopyridin-3-yl)-1,2,3-thiadiazole (1ey)



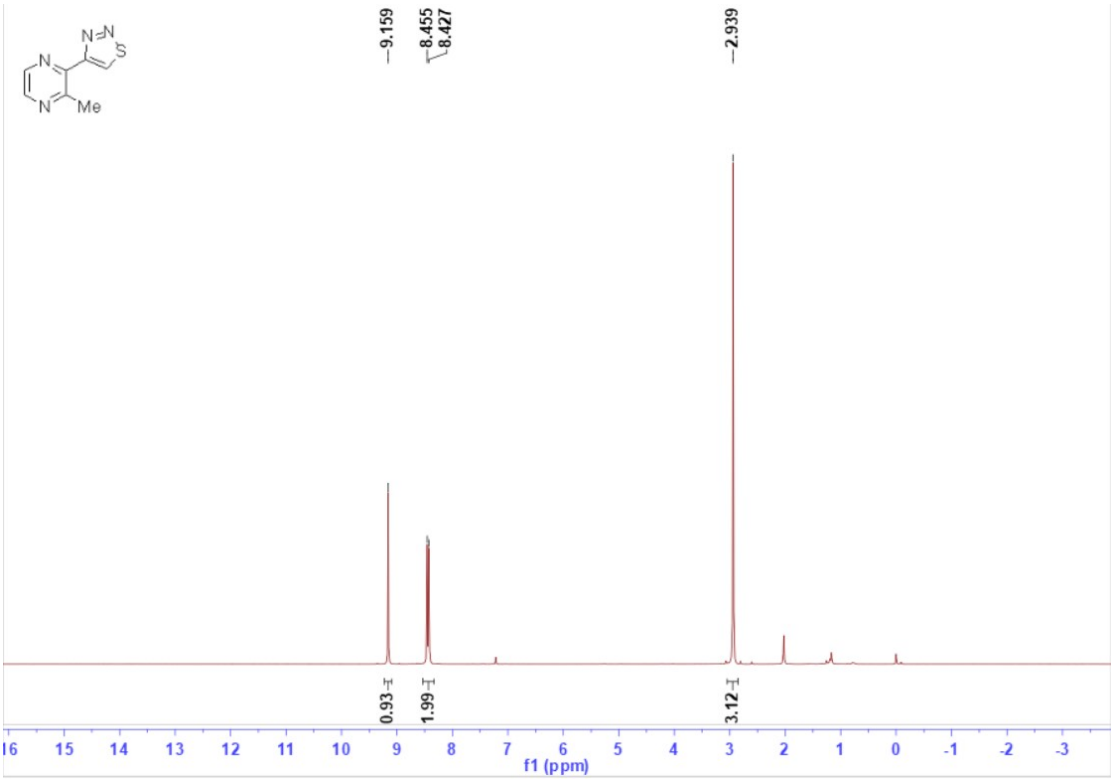


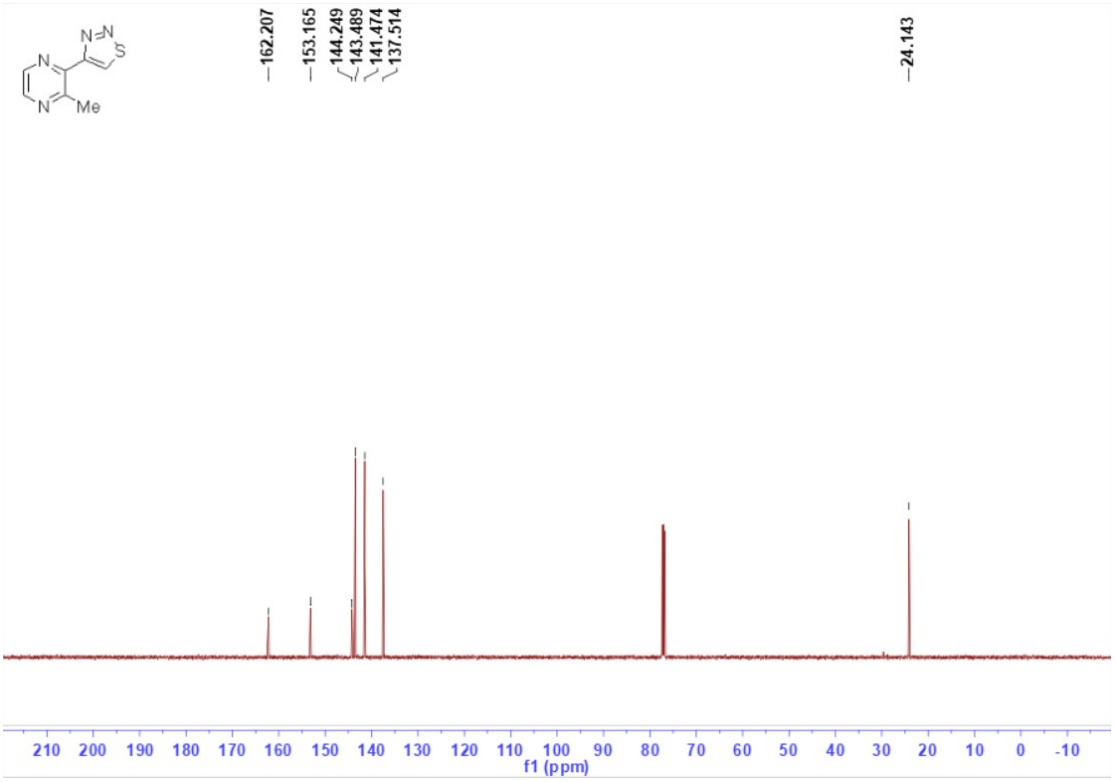
4-(pyridin-4-yl)-1,2,3-thiadiazole (1ez)



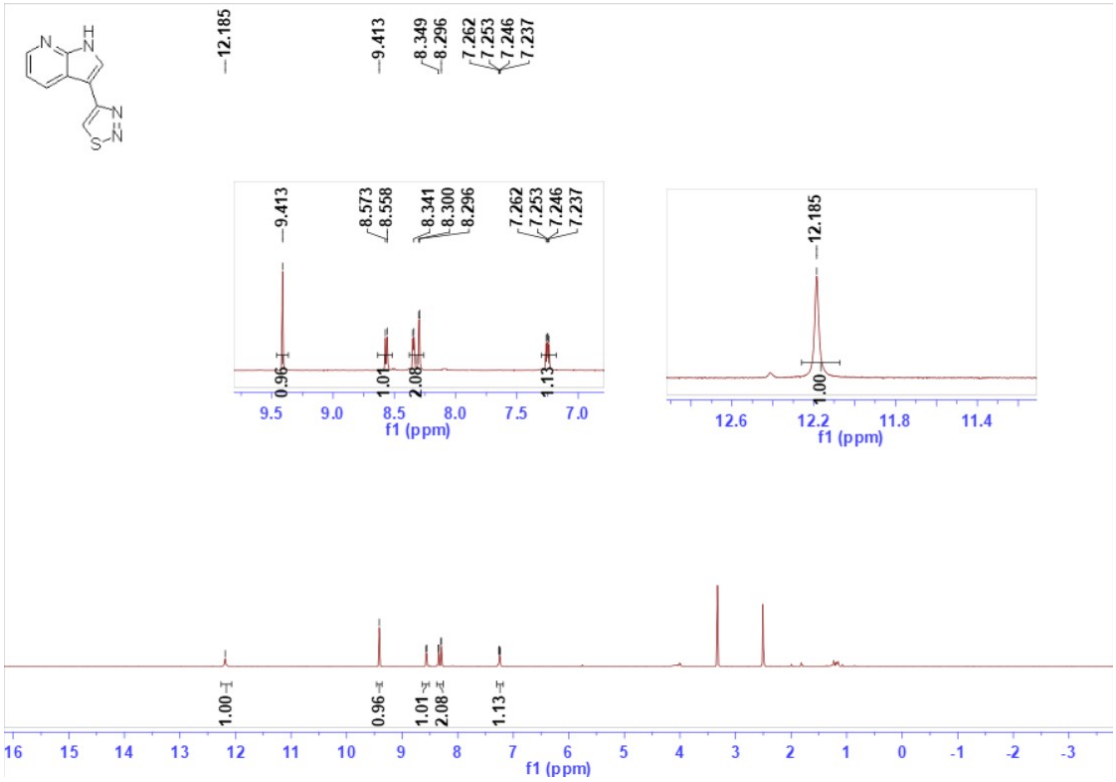


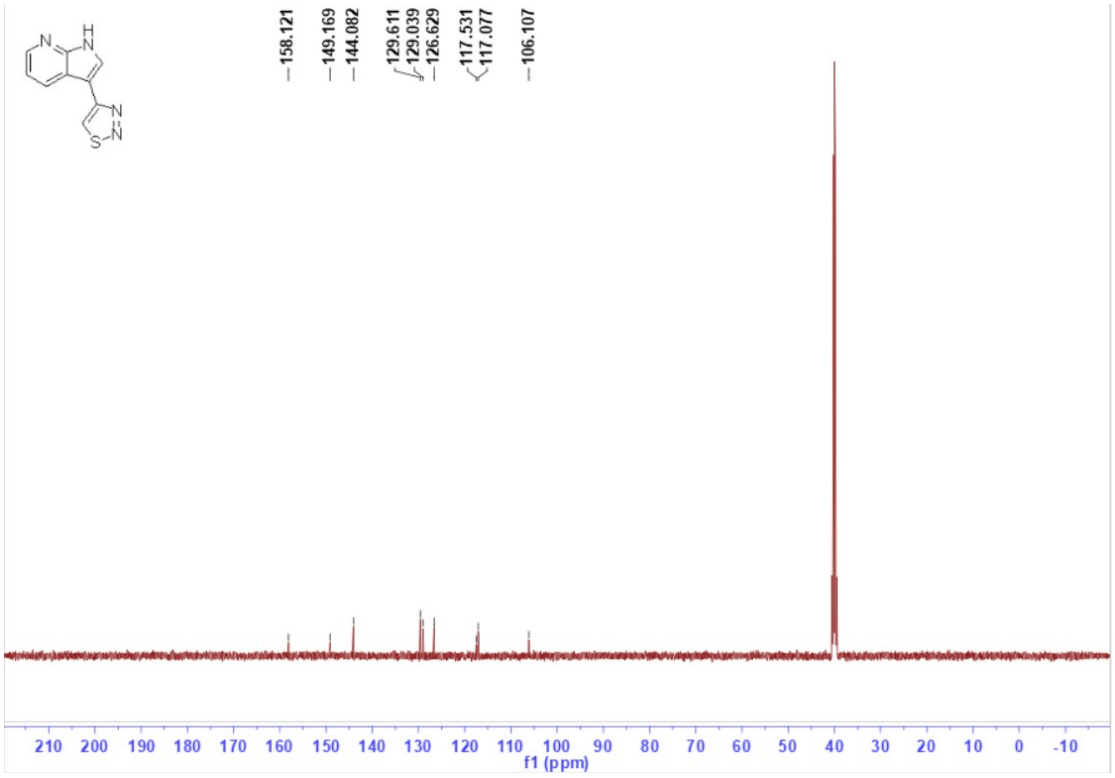
4-(3-methylpyrazin-2-yl)-1,2,3-thiadiazole (1eza)



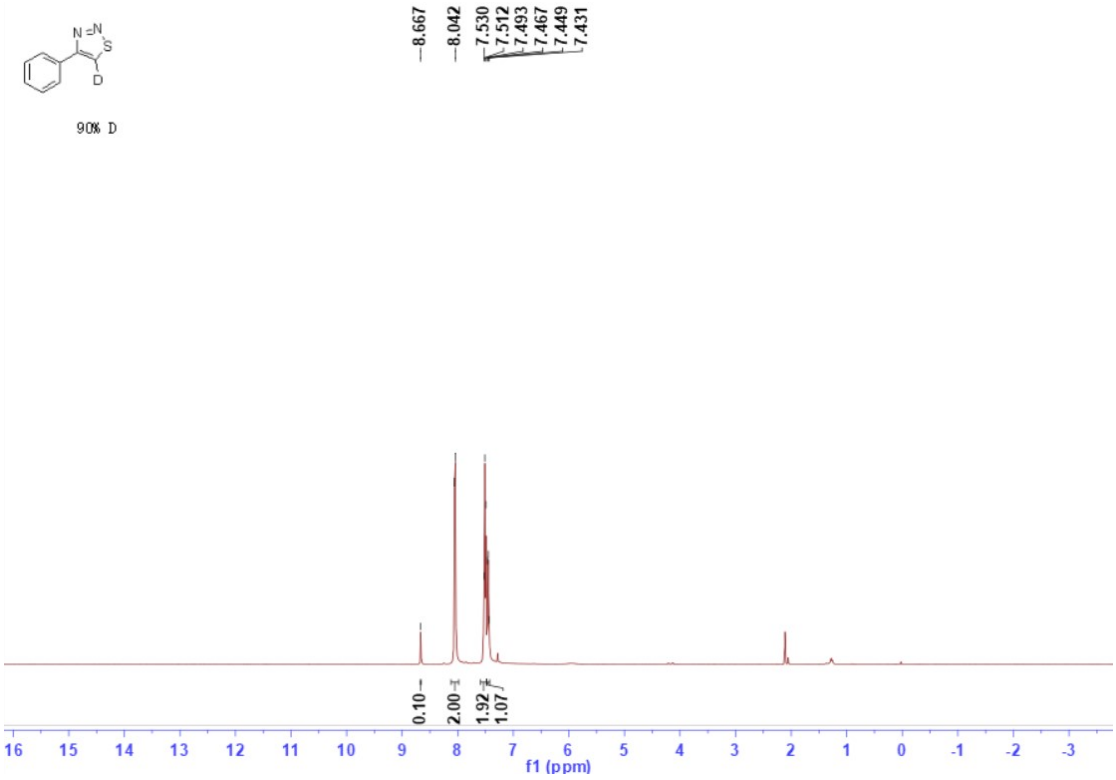


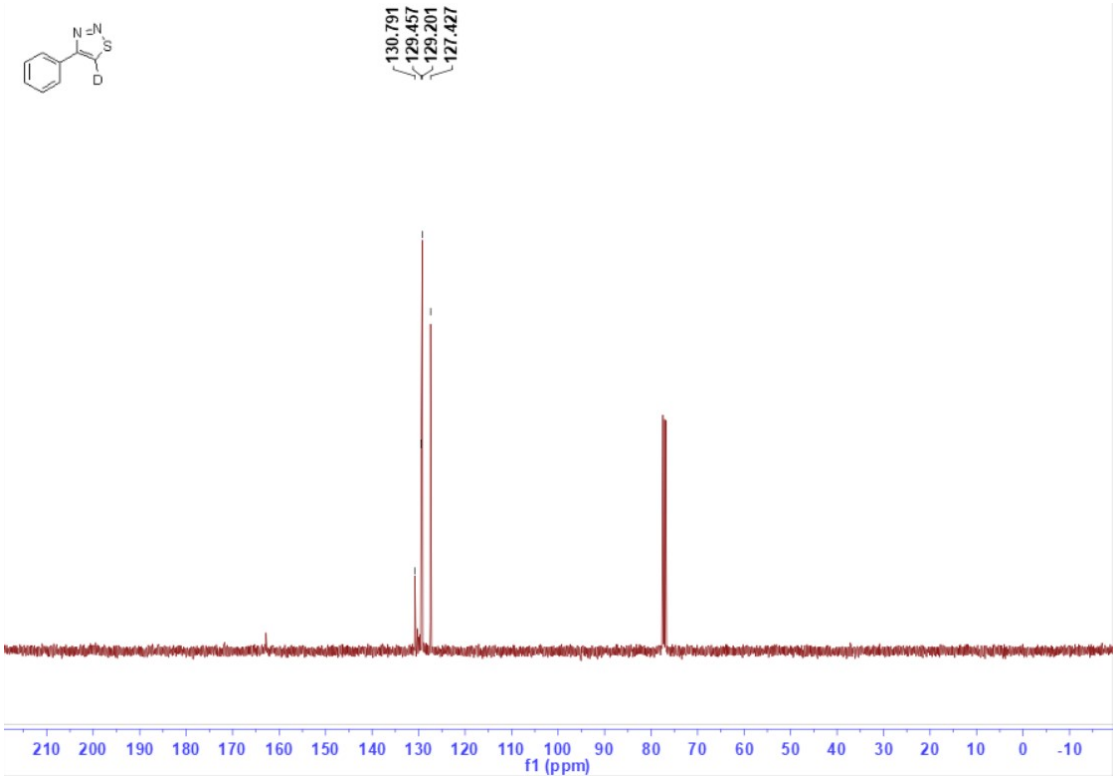
4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1,2,3-thiadiazole (1ezb)



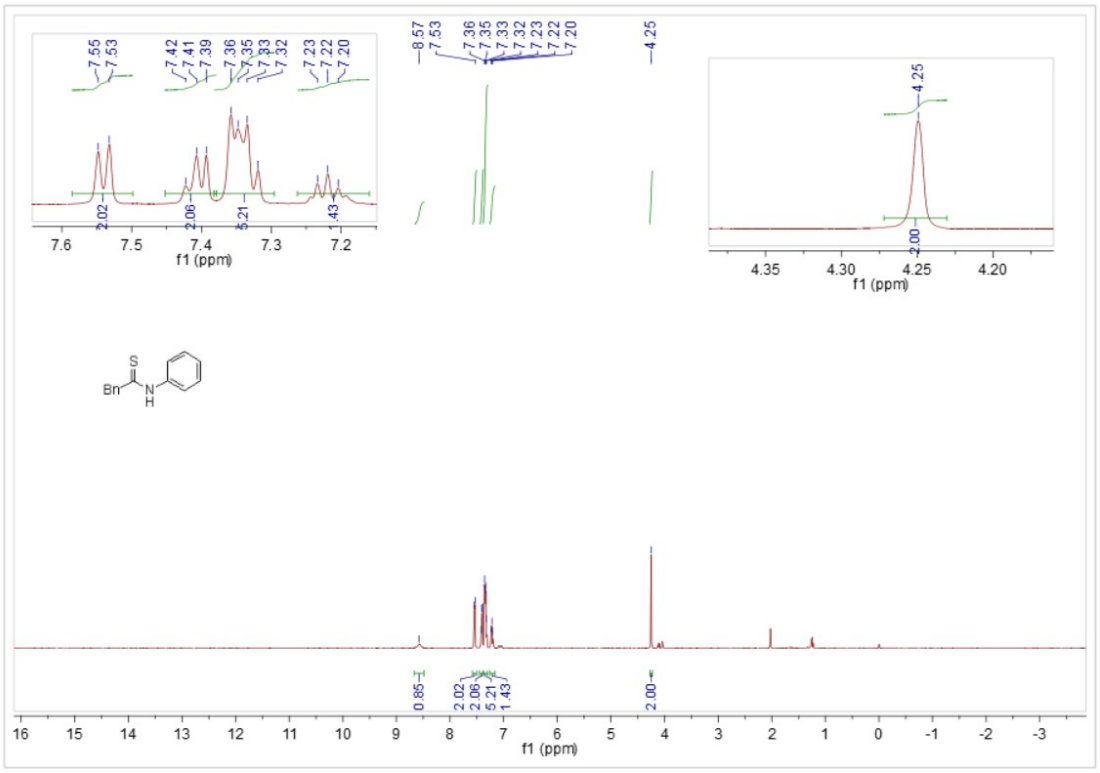


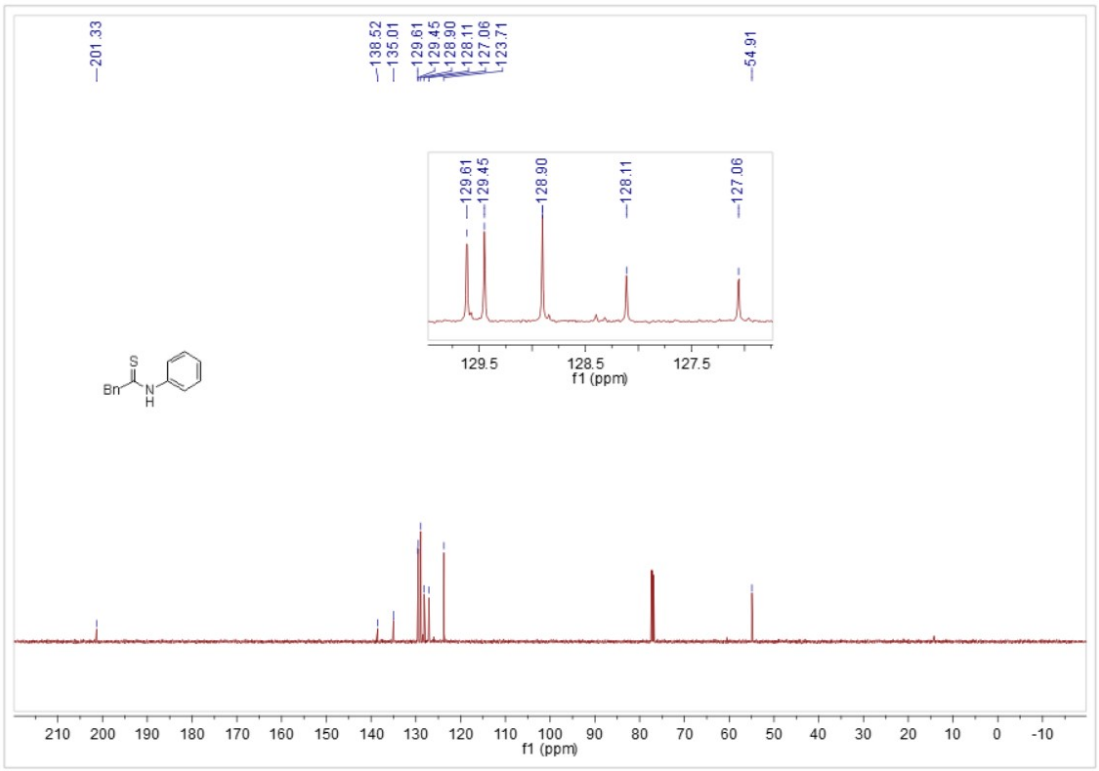
4-Phenyl-1,2,3-thiadiazole-5-d (1a-d)



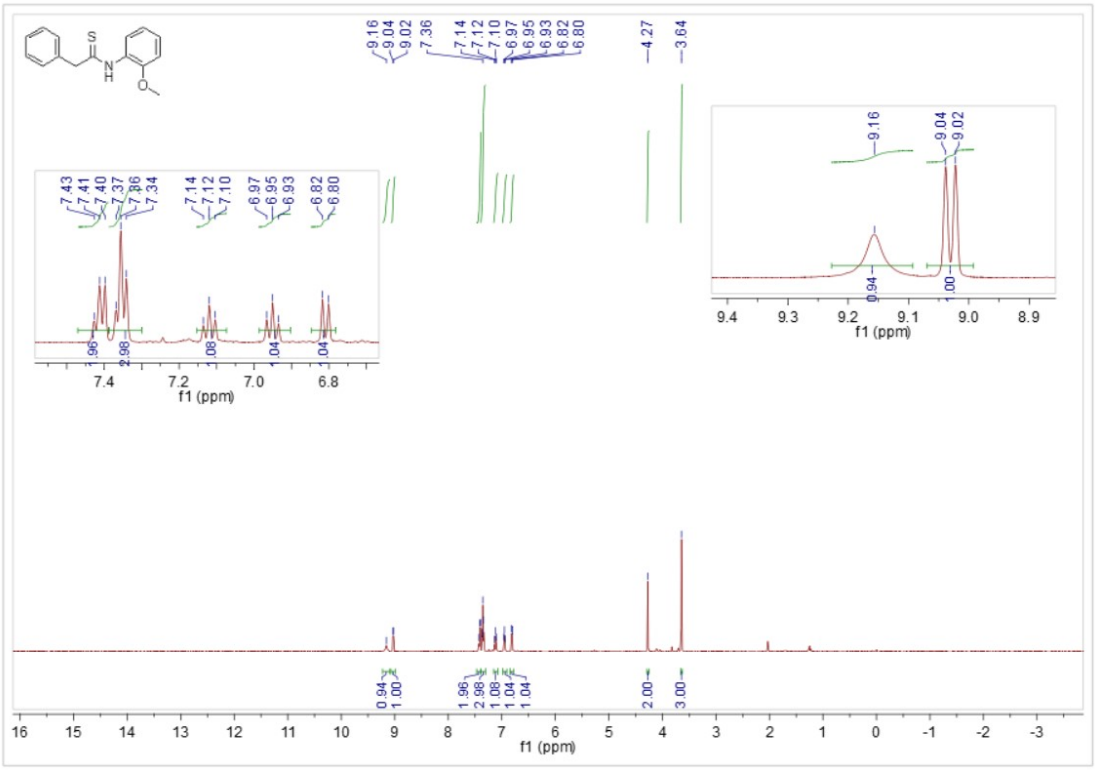


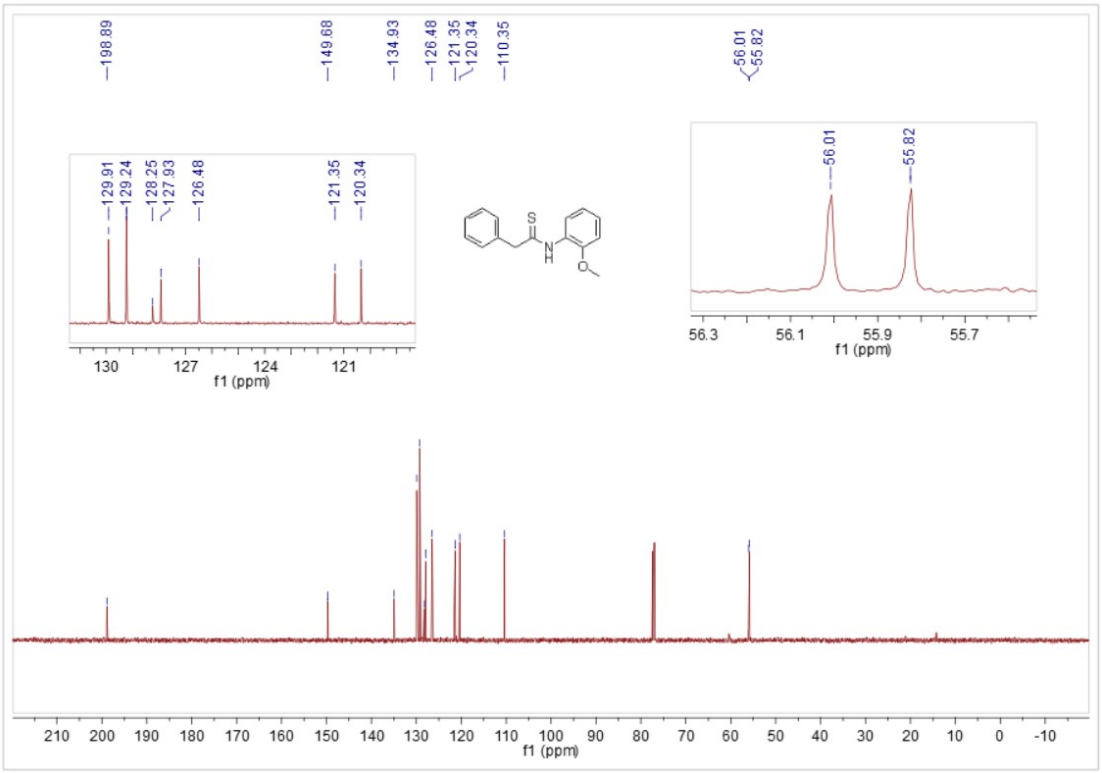
N,2-diphenylethanethioamide (3aa)



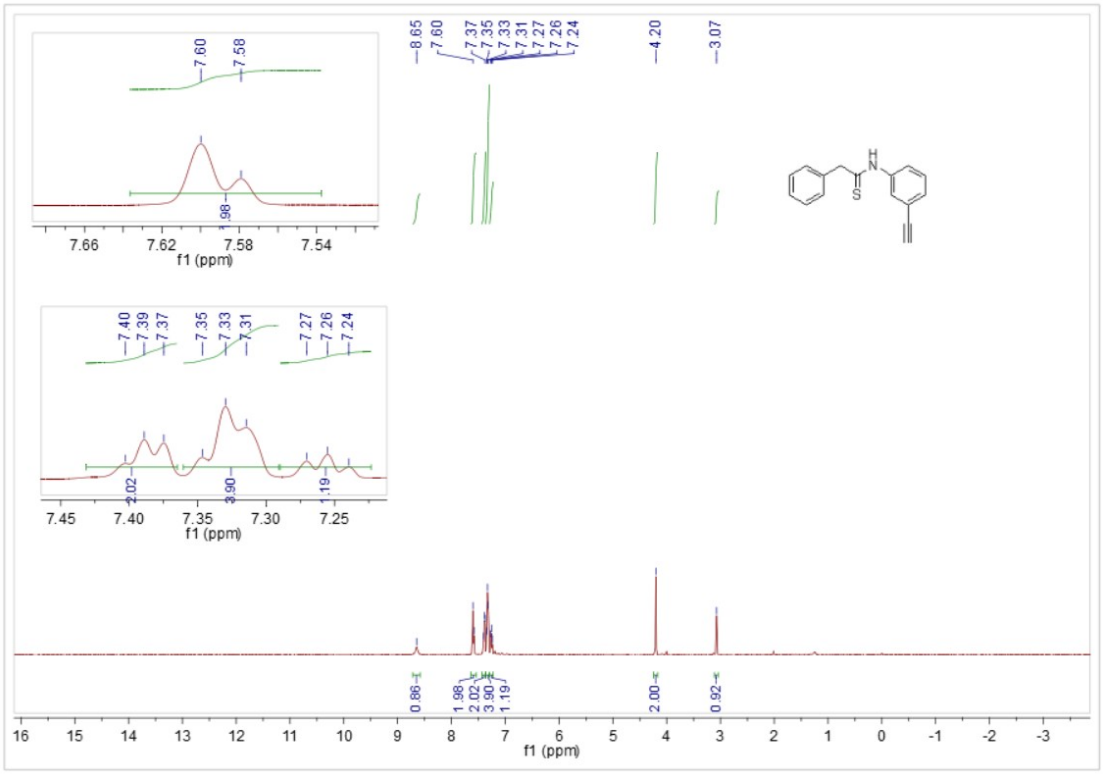


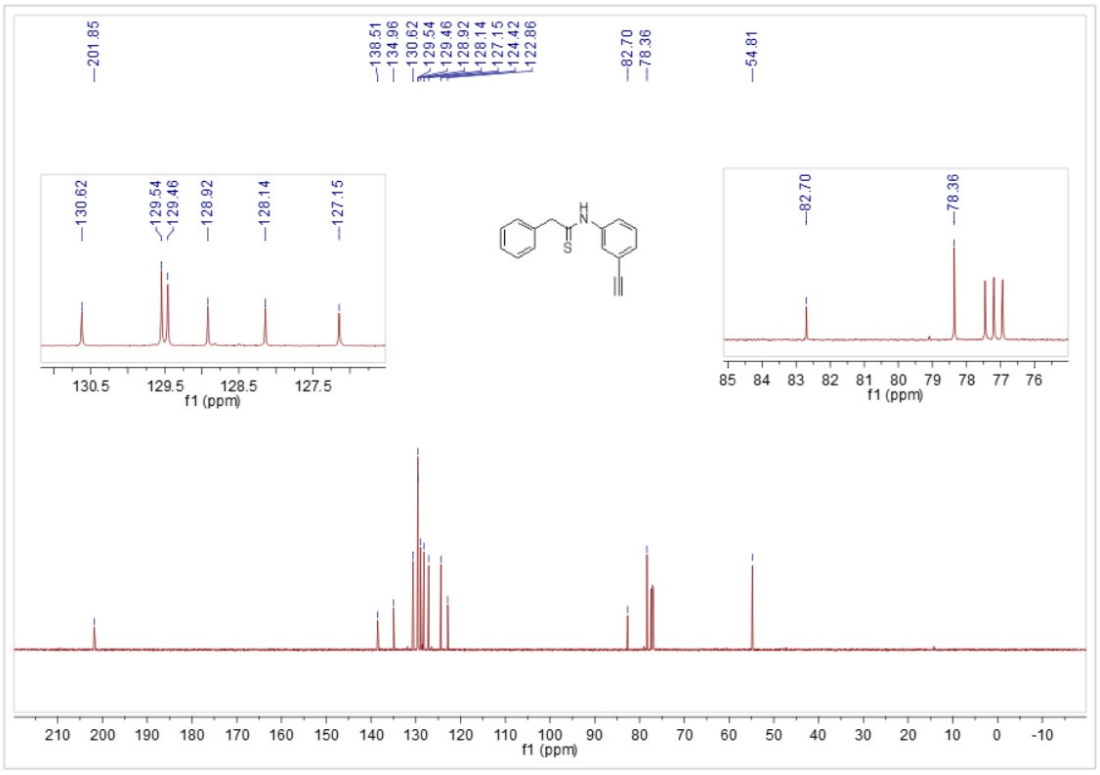
N-(2-methoxyphenyl)-2-phenylethanethioamide (3ab)



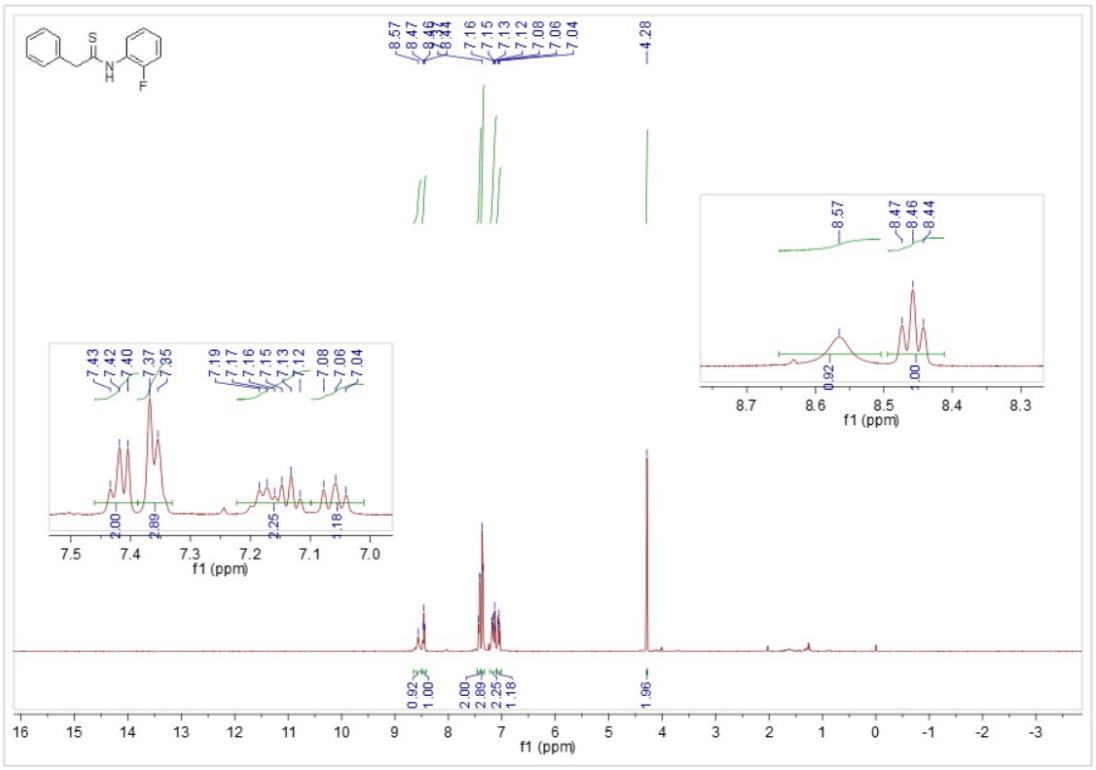


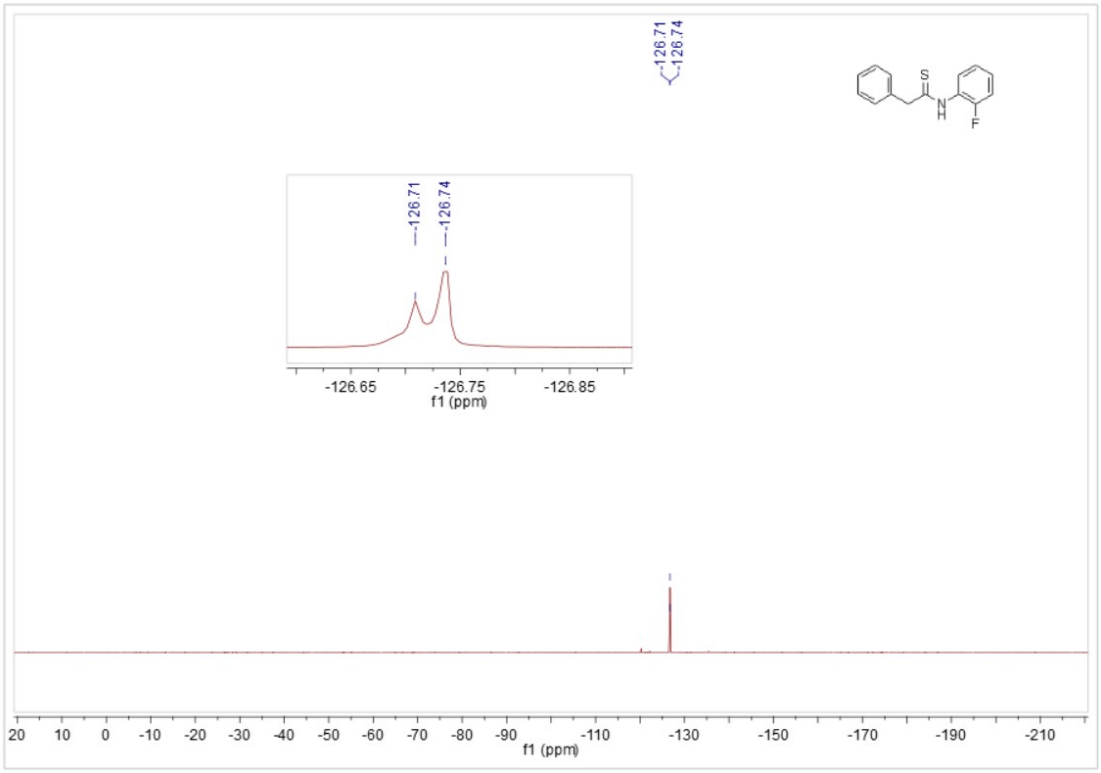
N-(3-ethynylphenyl)-2-phenylethanethioamide (3ac)

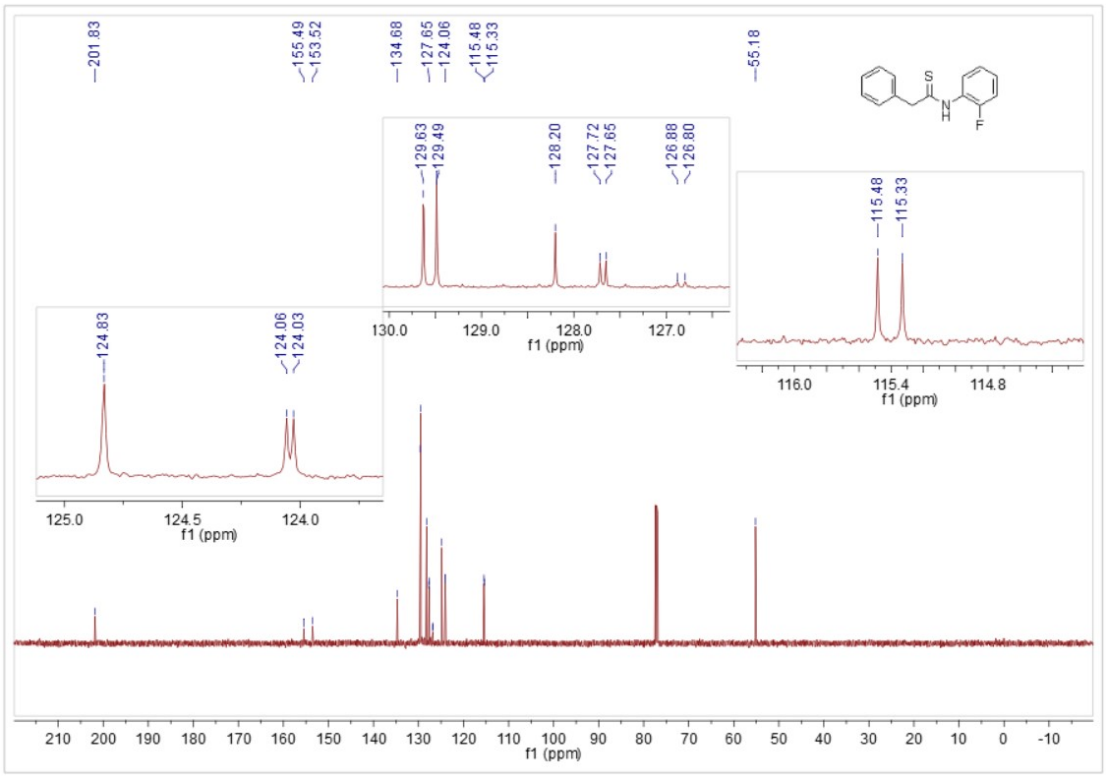




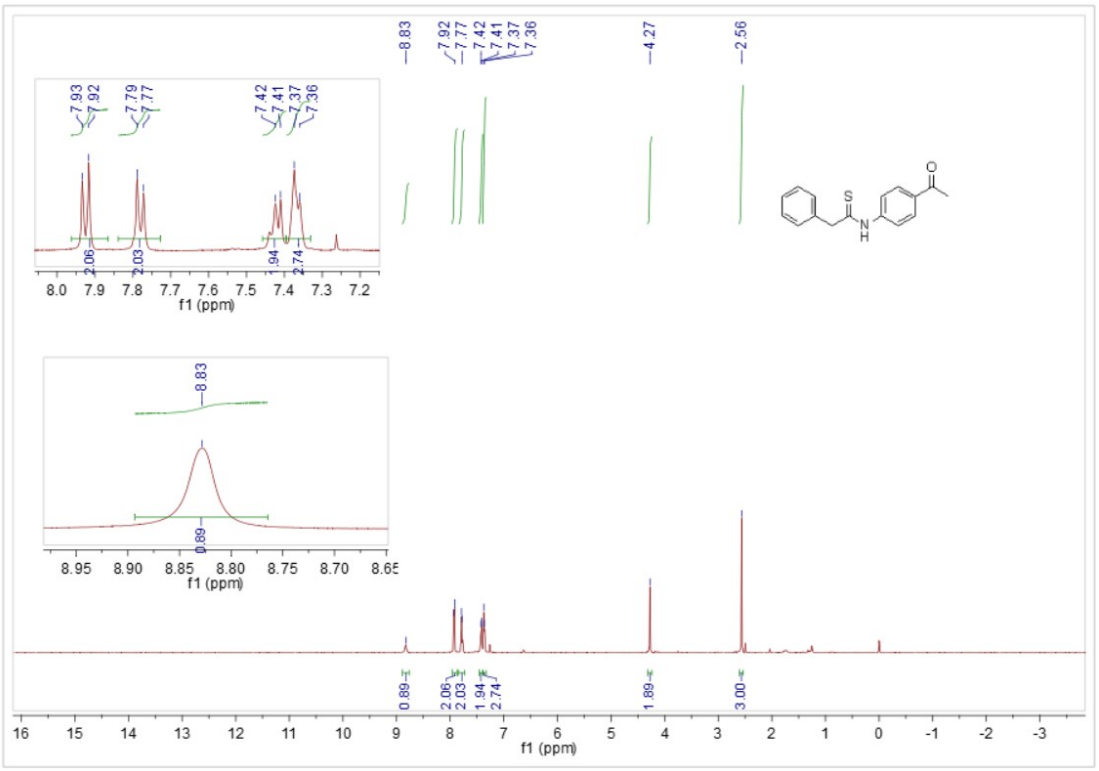
N-(2-fluorophenyl)-2-phenylethanethioamide (3ad)

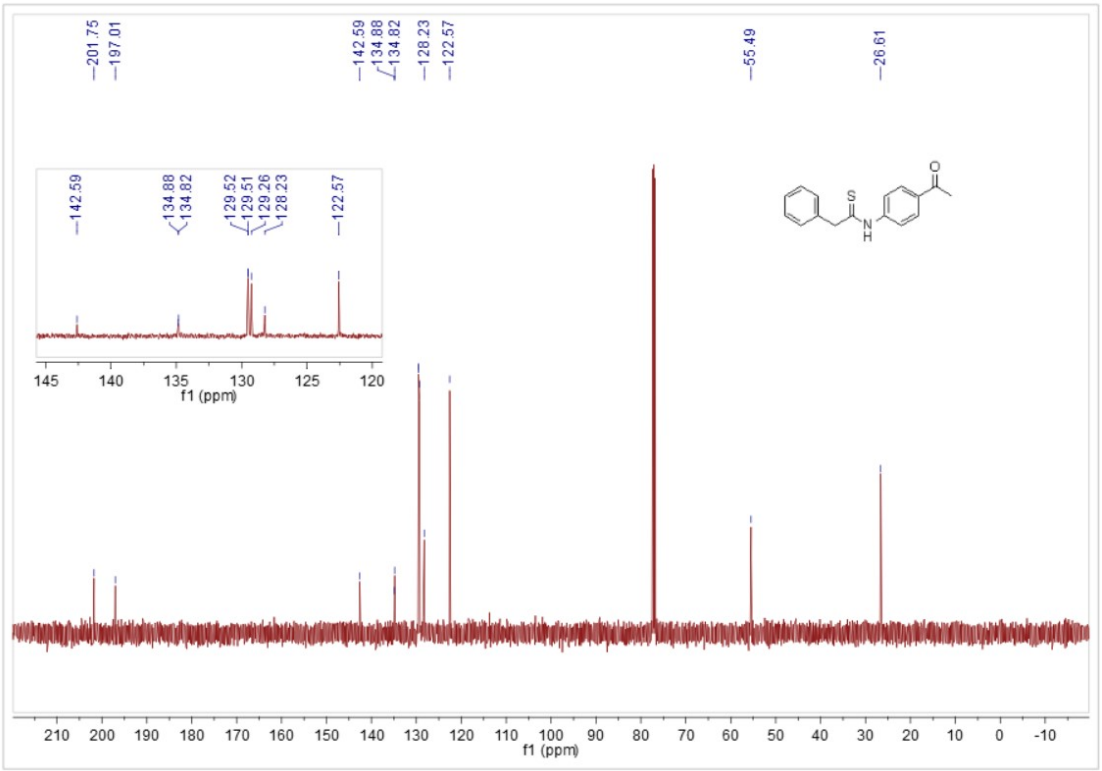




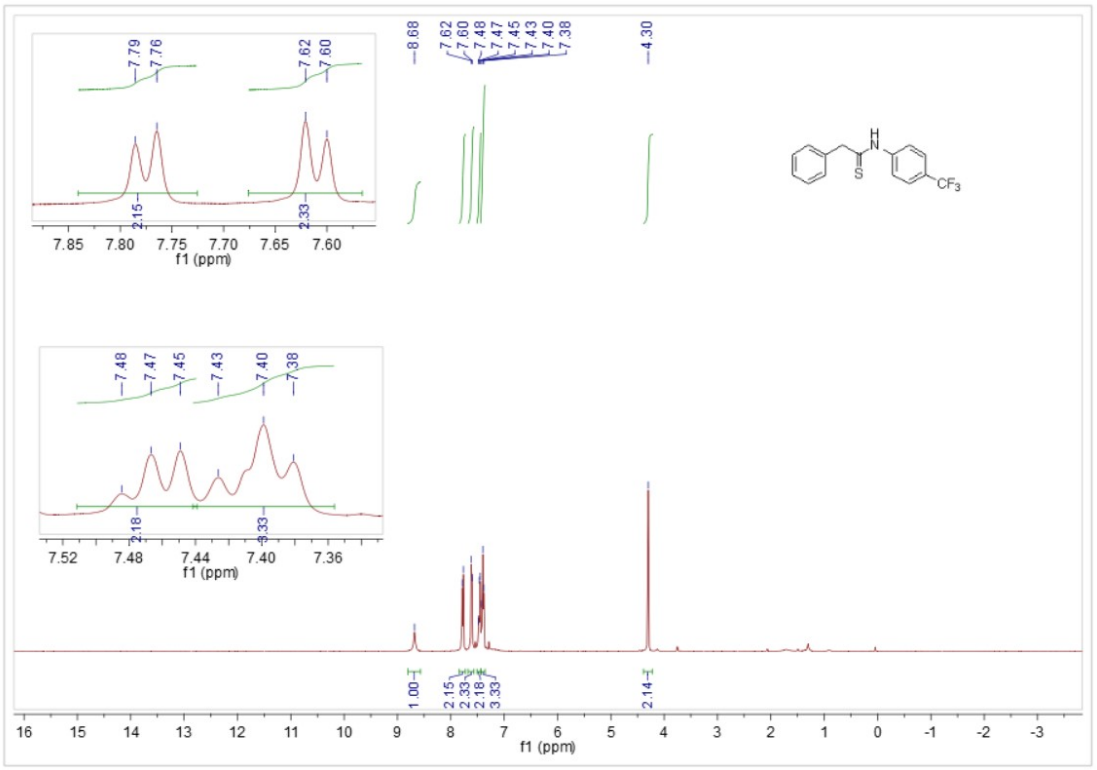

201.83
155.49
153.52
134.68
127.65
124.06
115.48
115.33
55.18
129.63
129.49
128.20
127.72
127.65
126.88
126.80
124.83
124.06
124.03
f1 (ppm)

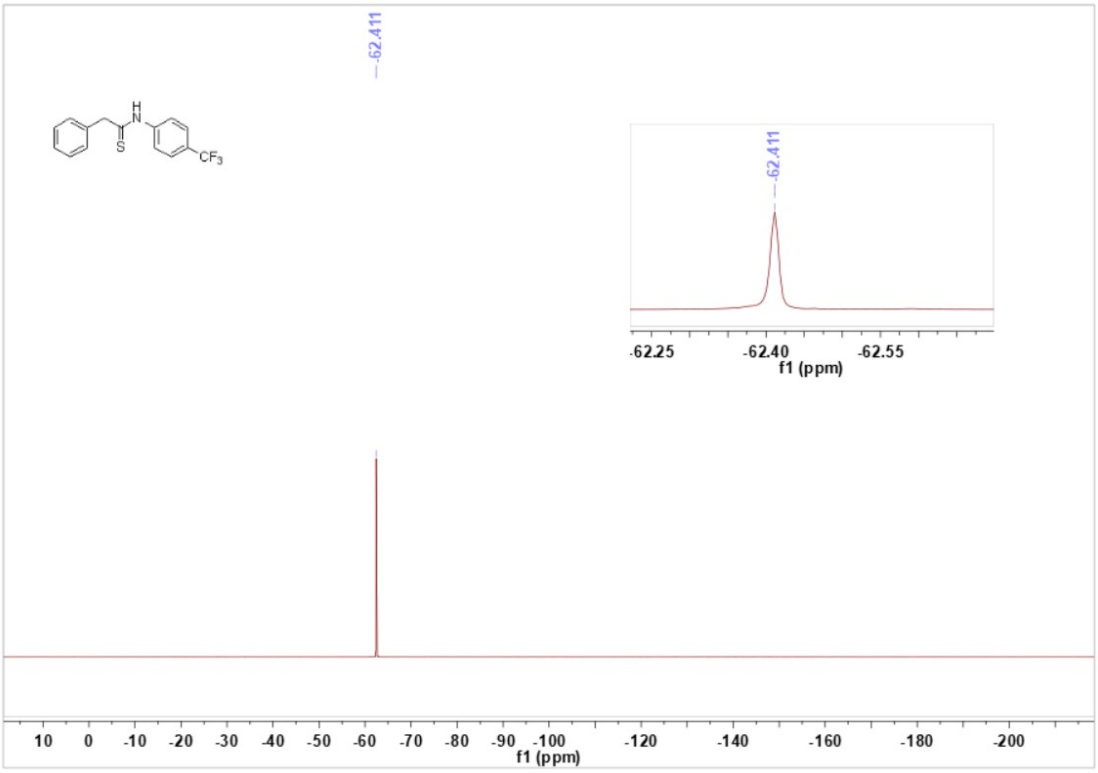
N-(4-acetylphenyl)-2-phenylethanethioamide (3ae)

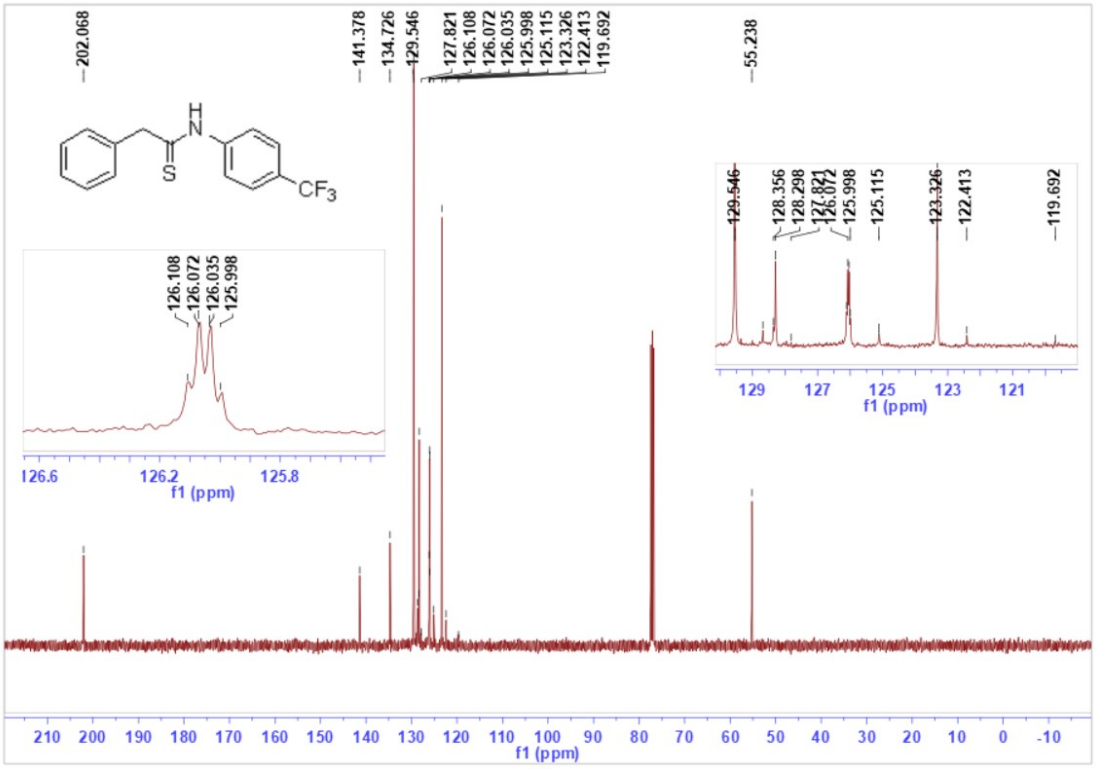




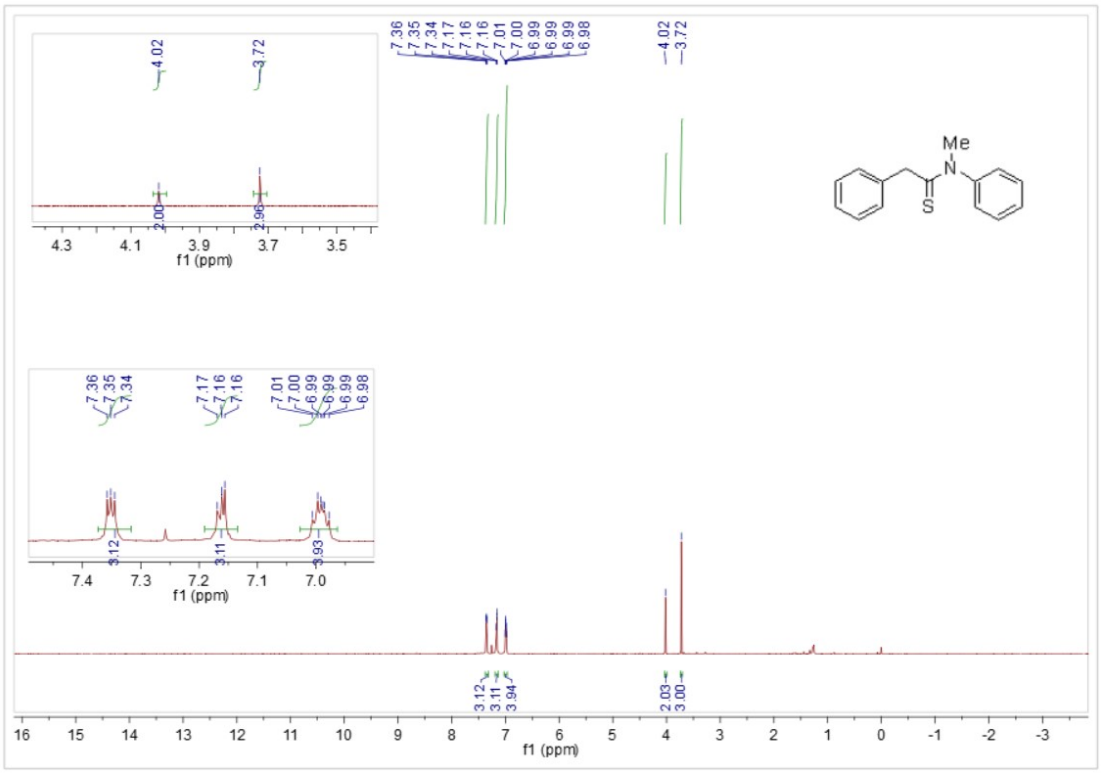
2-Phenyl-*N*-(4-(trifluoromethyl)phenyl)ethanethioamide (3af)

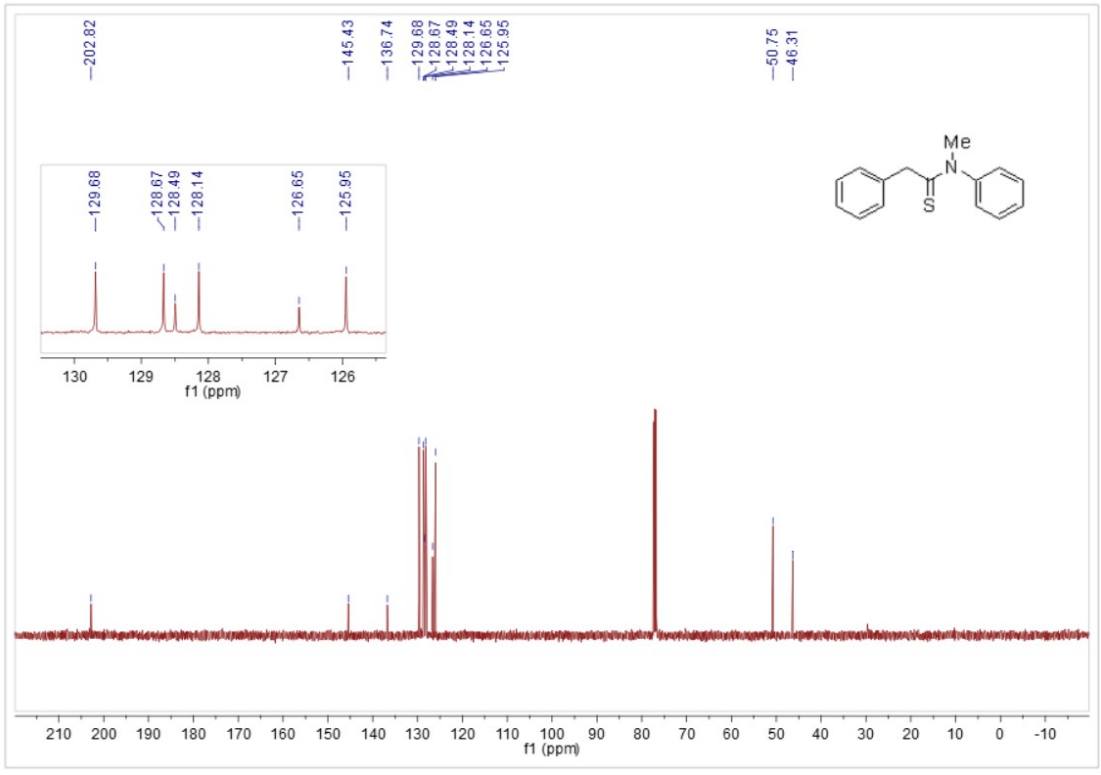




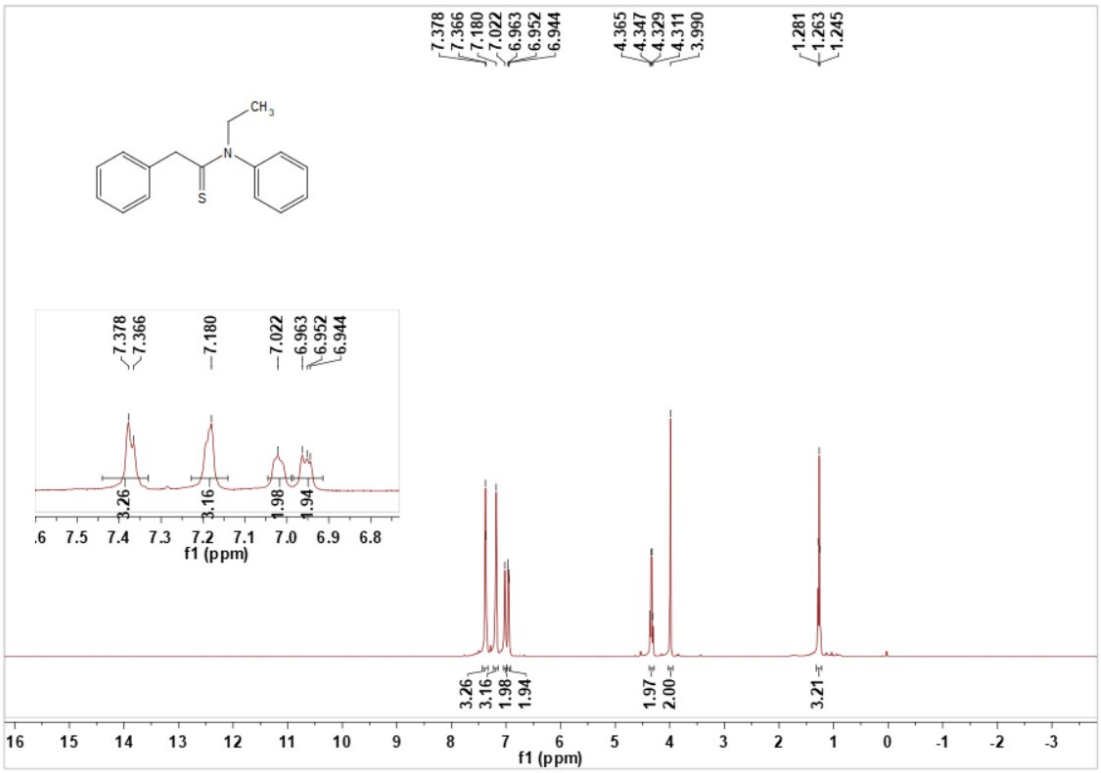

202.068
141.378
134.726
129.546
127.821
126.108
126.072
126.035
125.998
125.115
123.326
122.413
119.692
55.238
S
H
N
CF3
126.108
126.072
126.035
125.998
126.6
126.2
125.8
f1 (ppm)
129.546
128.356
128.298
127.821
126.072
125.998
125.115
123.326
122.413
119.692
129
127
125
123
121
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

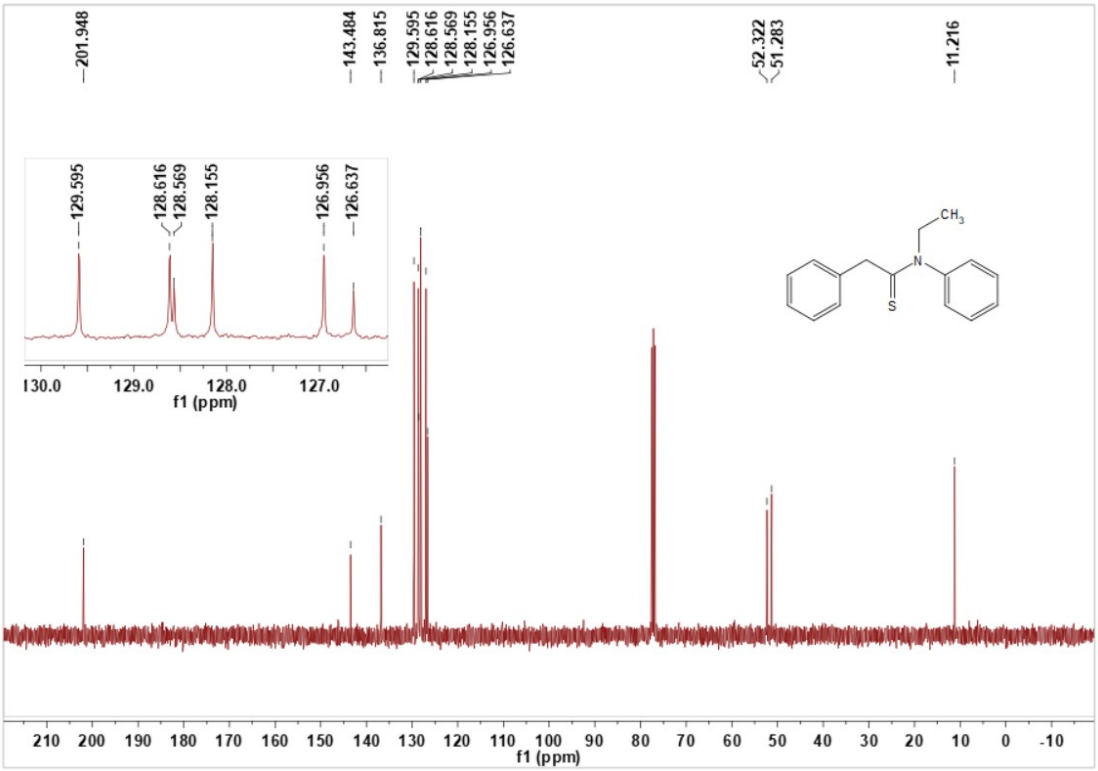
N-methyl-*N*,2-diphenylethanethioamide (3ag)



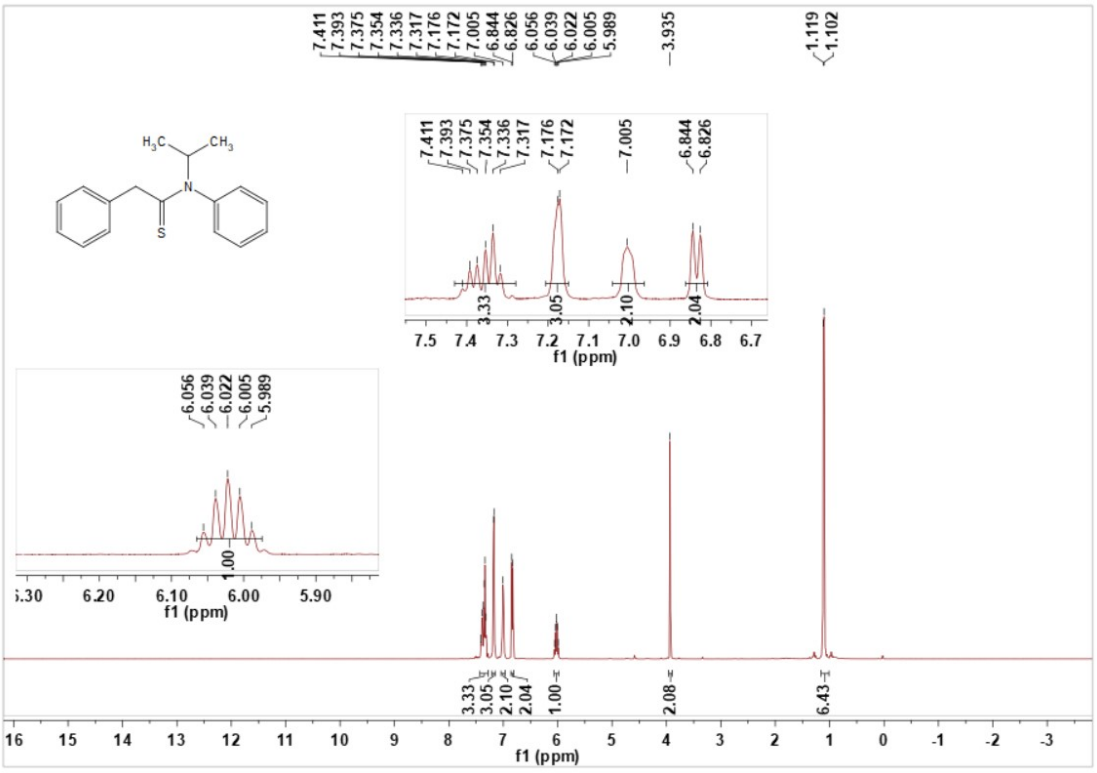


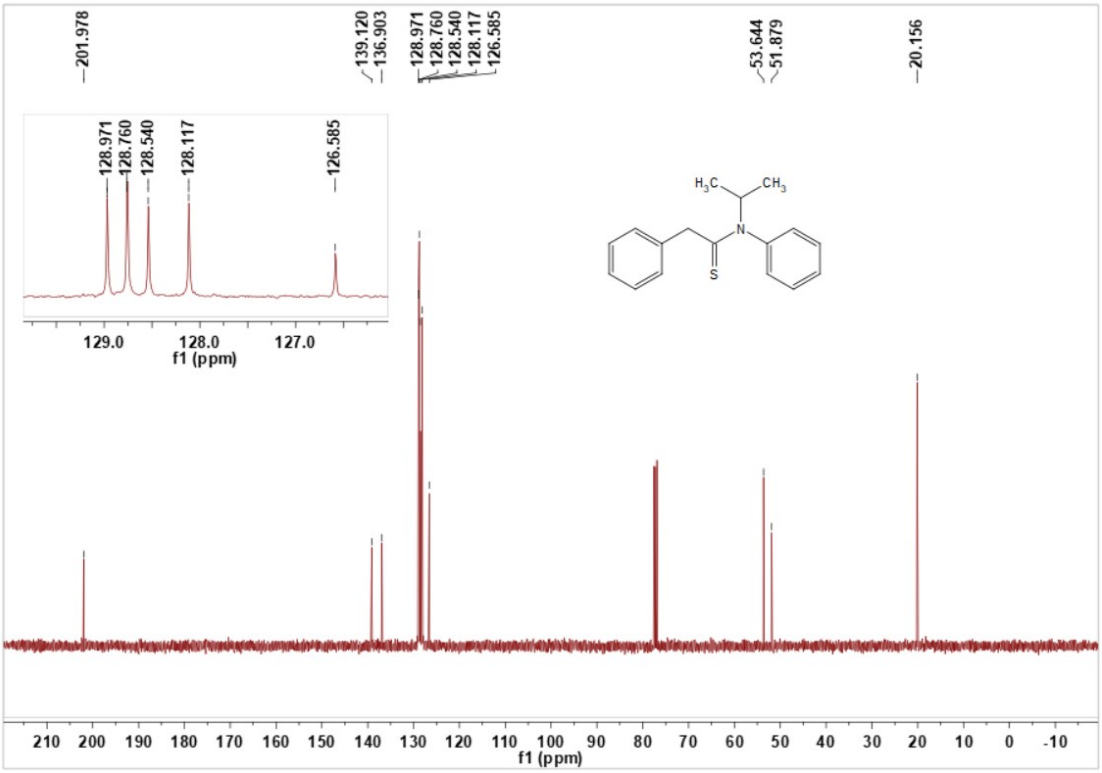
N-ethyl-*N*,2-diphenylethanethioamide (3ah)



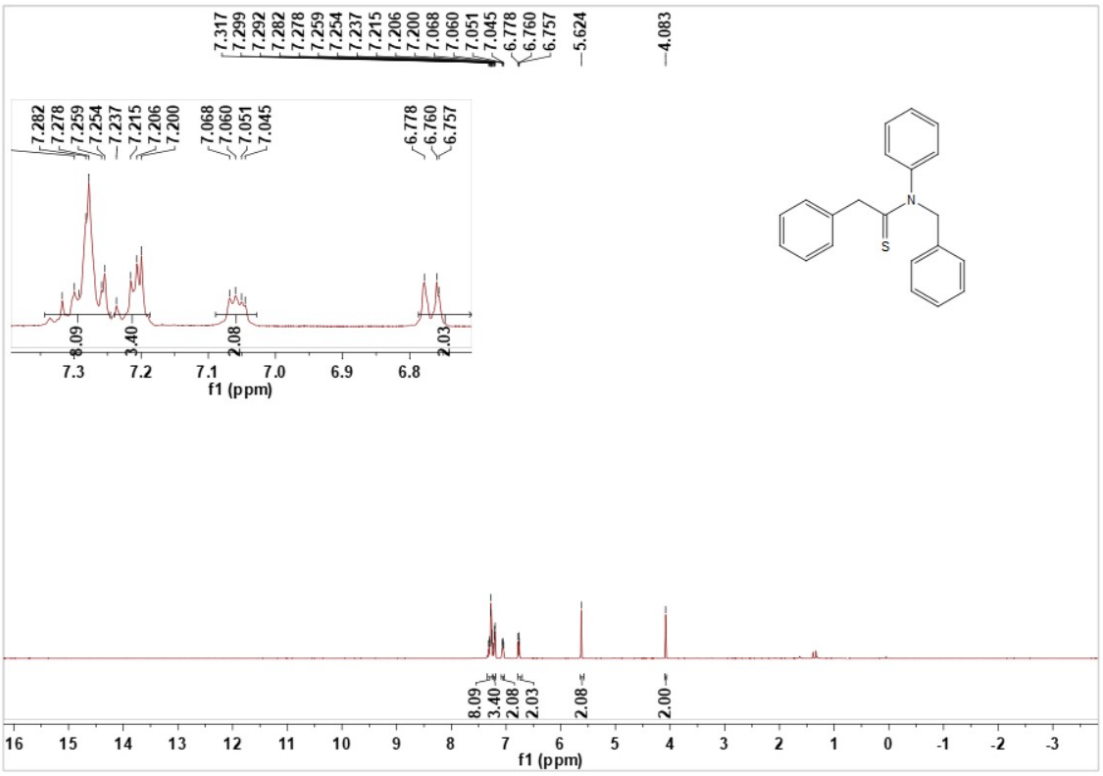


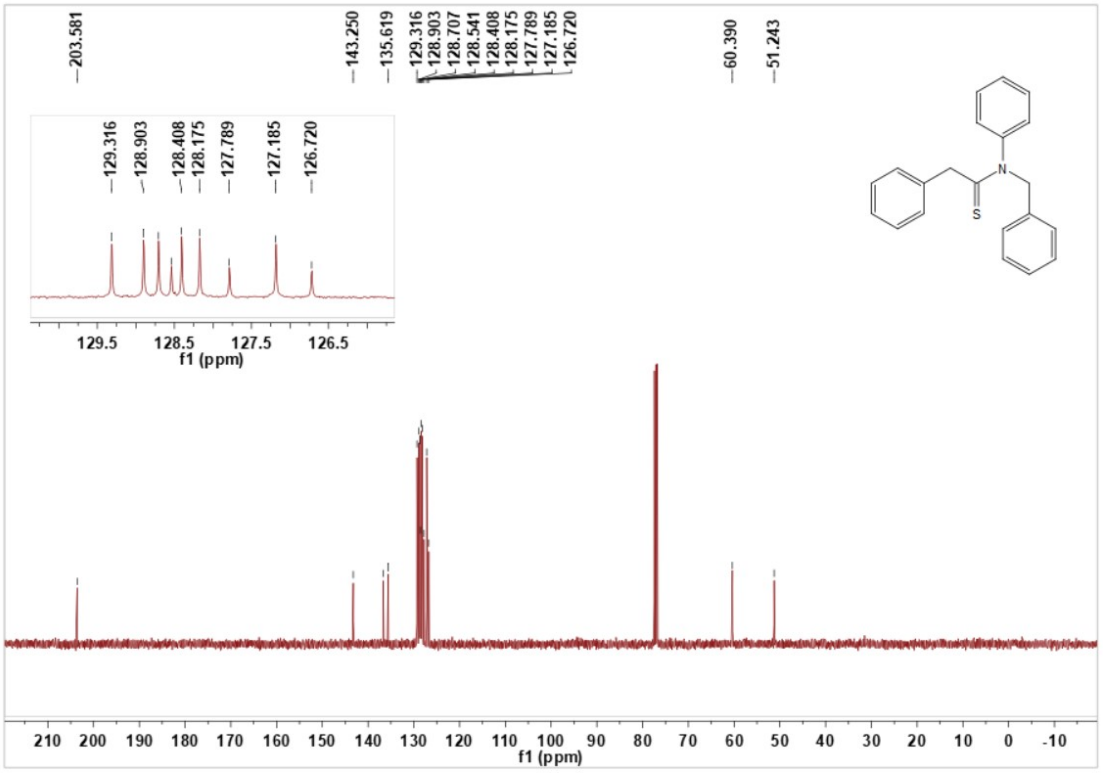
N-isopropyl-*N*,2-diphenylethanethioamide (3ai)



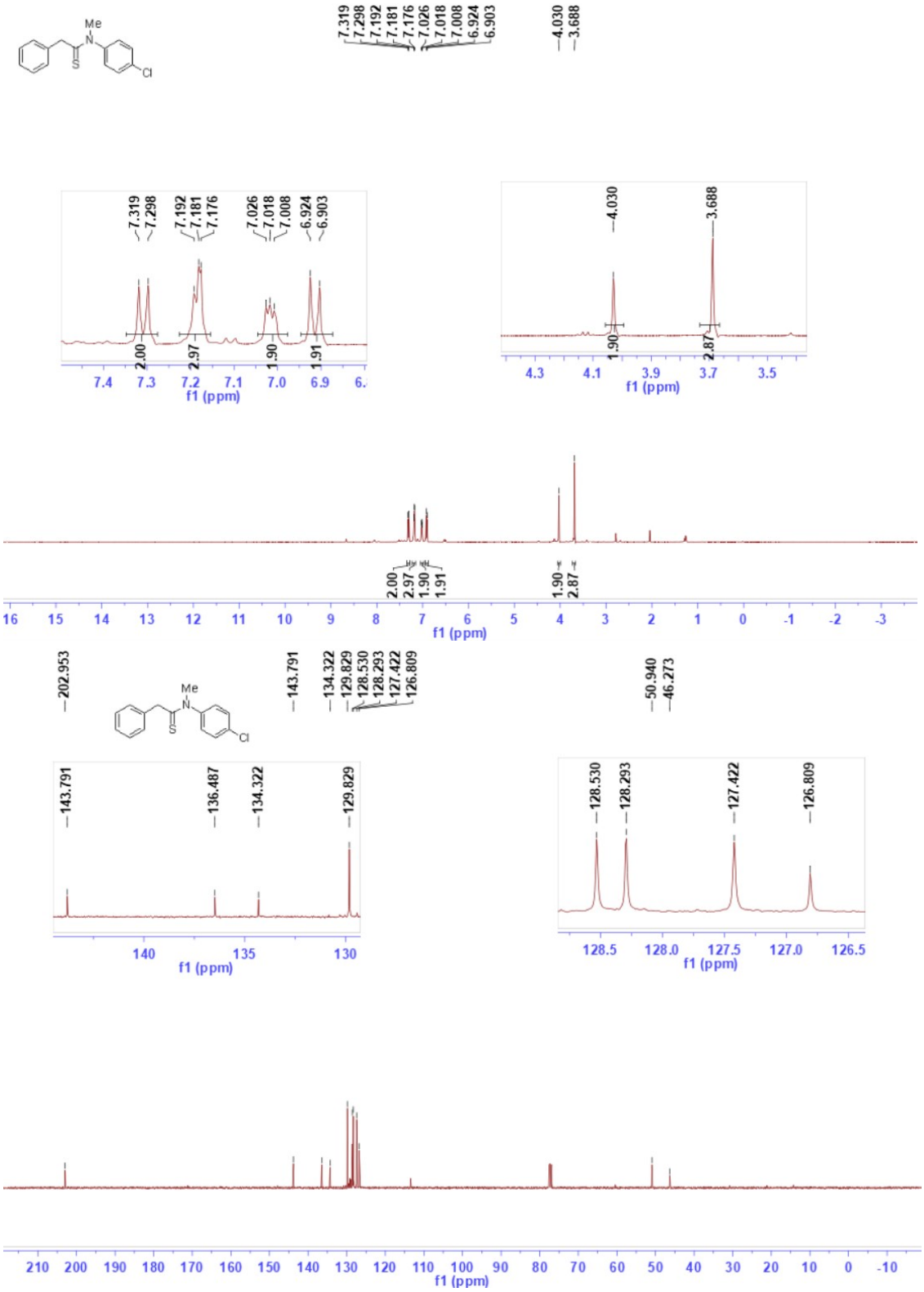


N-benzyl-*N*,2-diphenylethanethioamide (3aj)

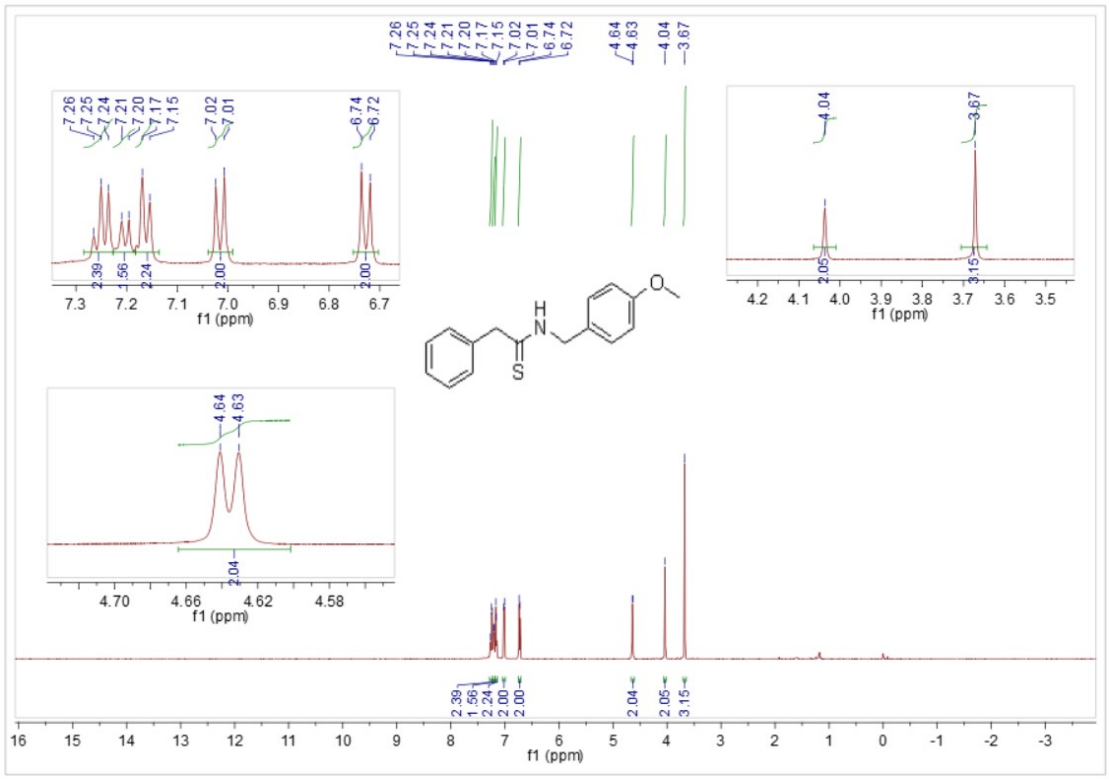


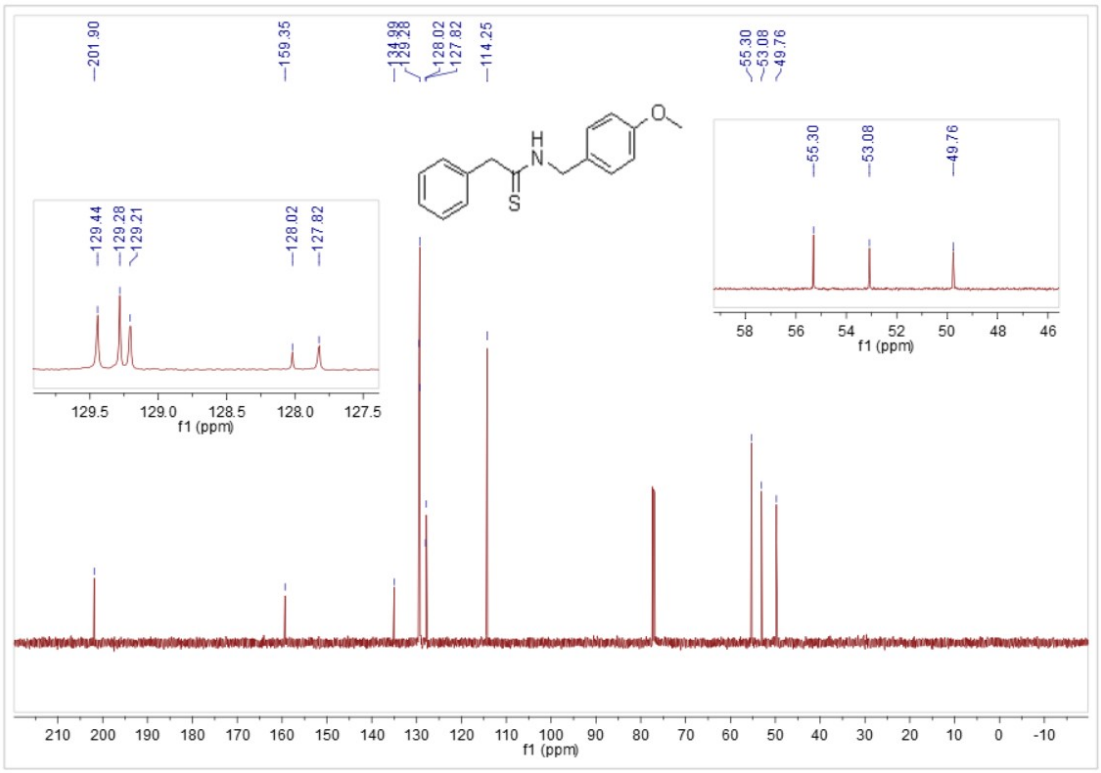


N-(4-chlorophenyl)-*N*-methyl-2-phenylethanethioamide (3ak)

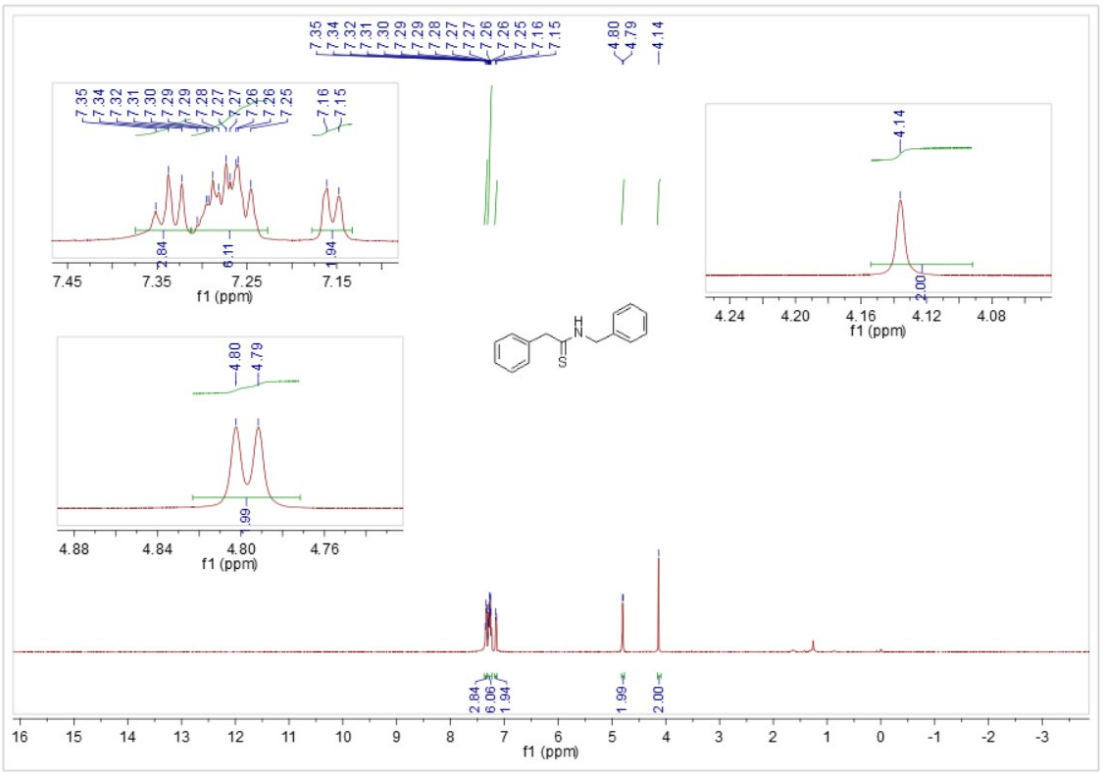


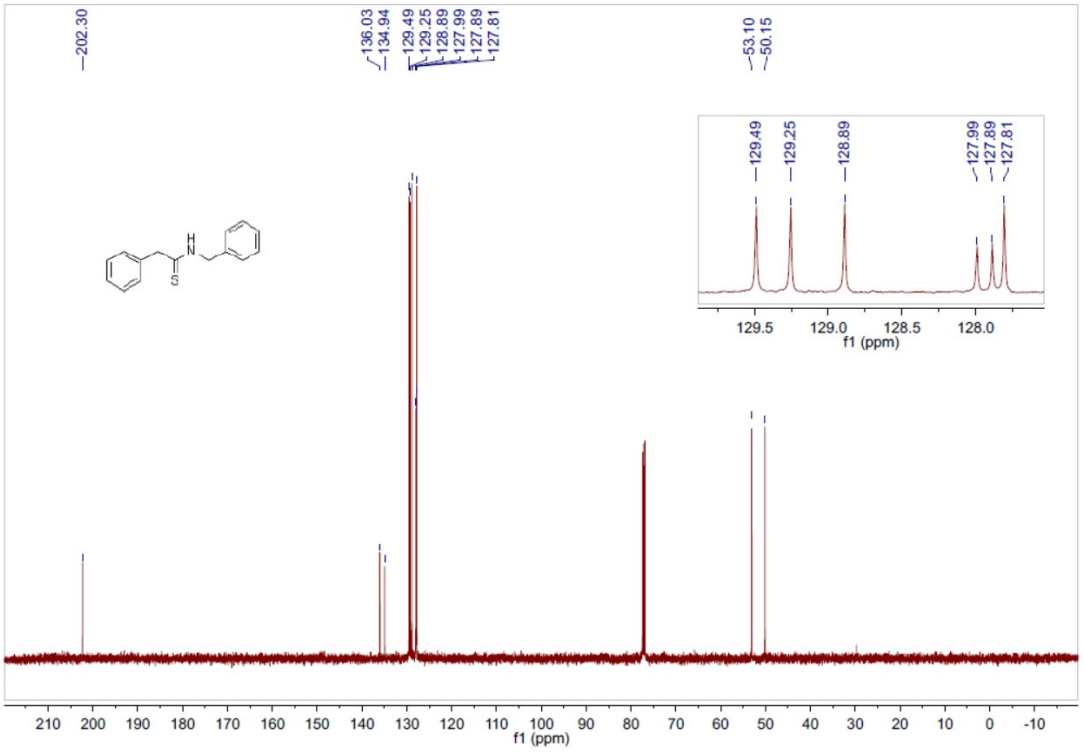
N-(4-methoxybenzyl)-2-phenylethanethioamide (3ba)



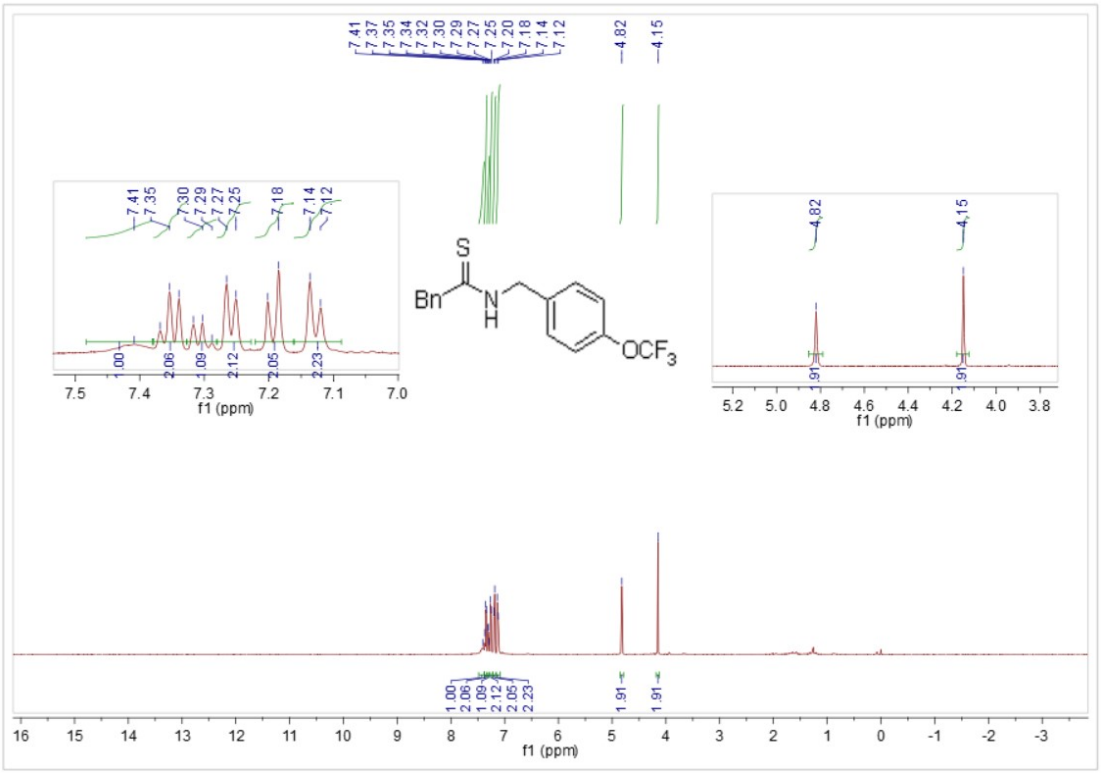


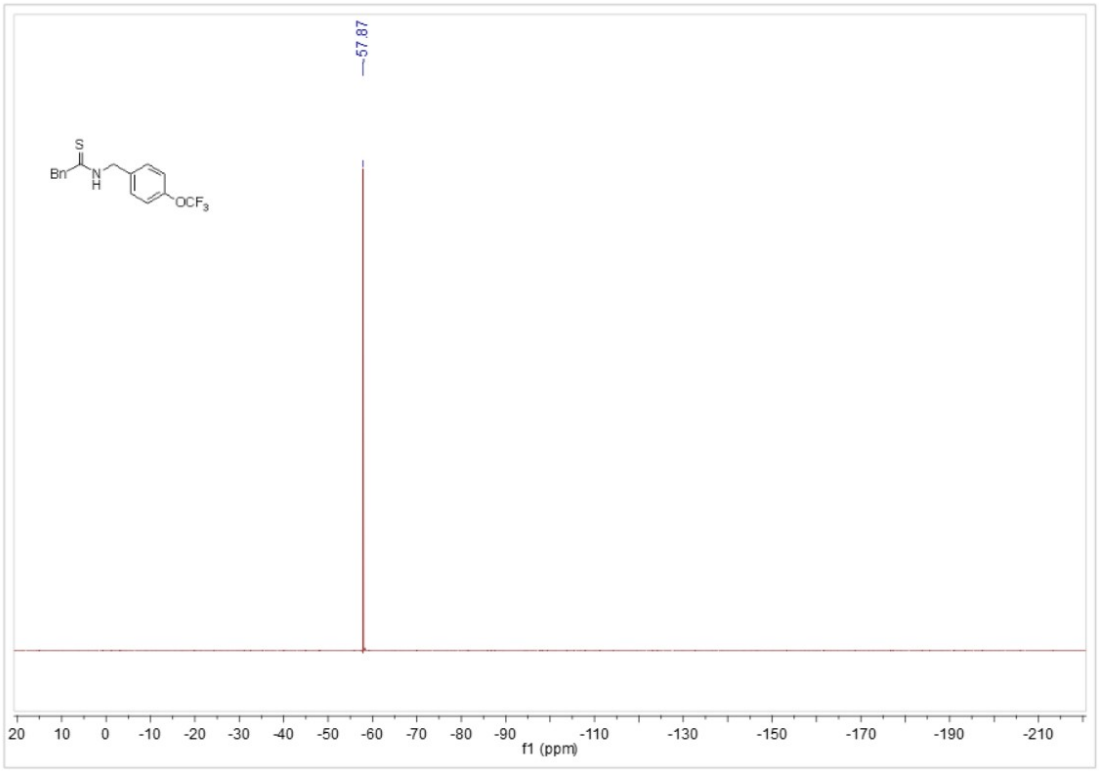
N-benzyl-2-phenylethanethioamide (3bb)

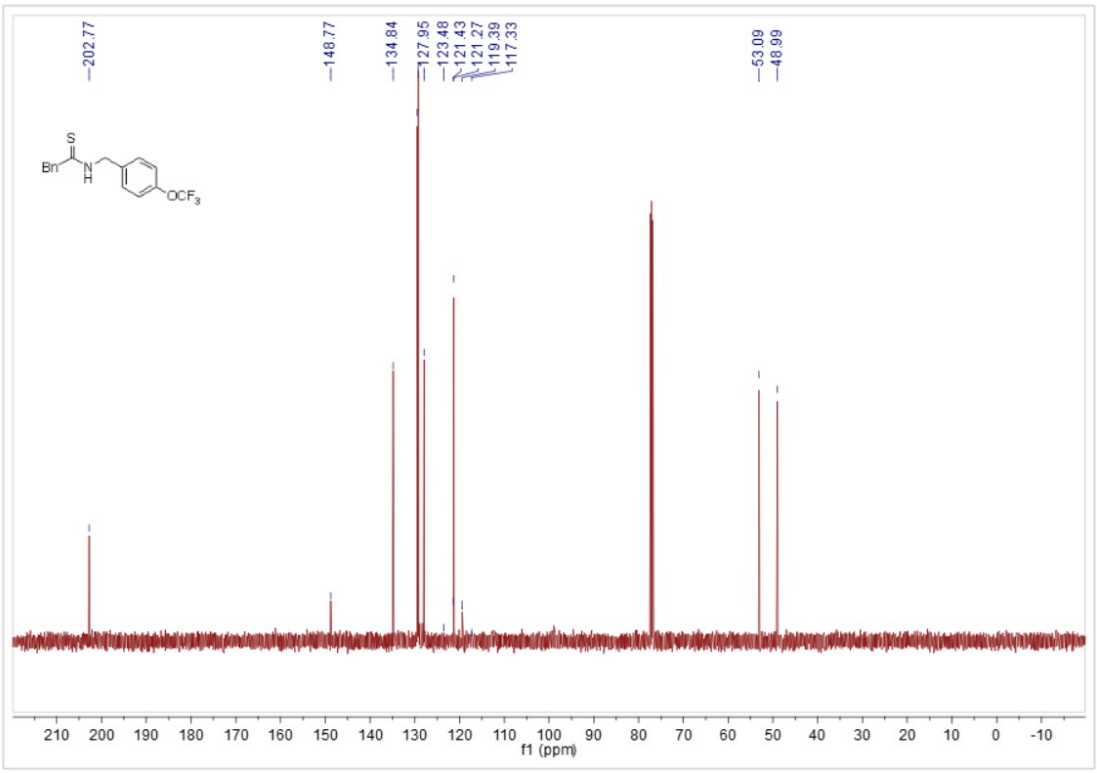




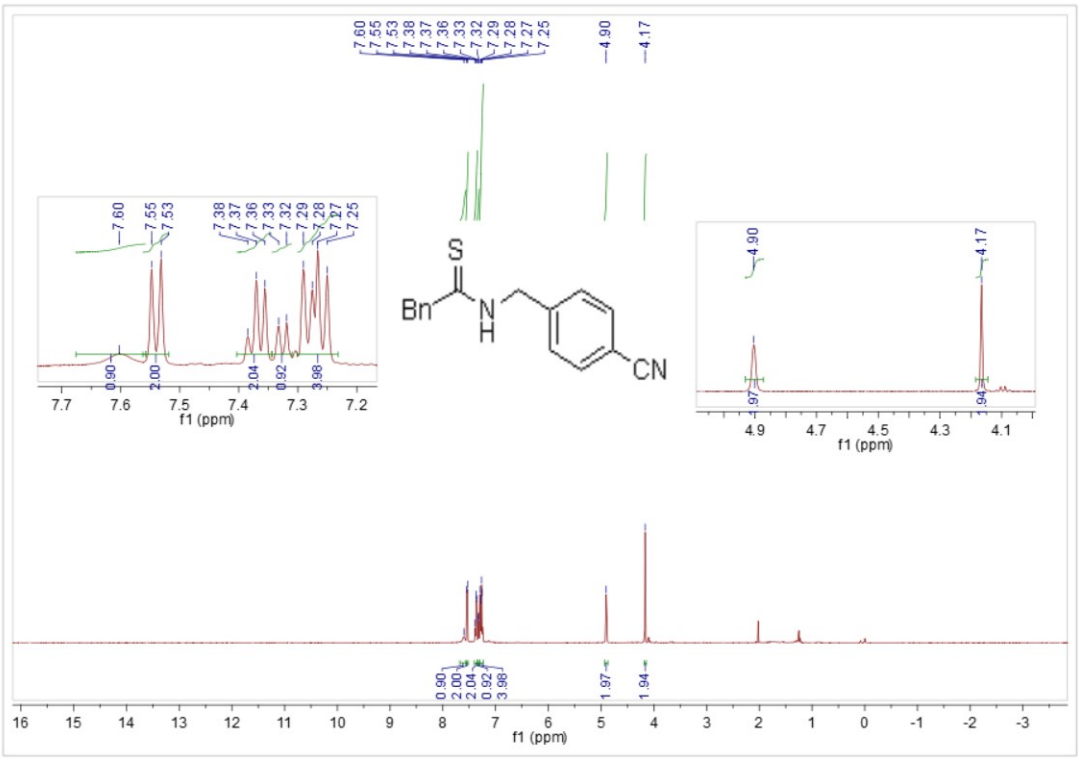
2-Phenyl-*N*-(4-(trifluoromethoxy)benzyl)ethanethioamide (3bc)

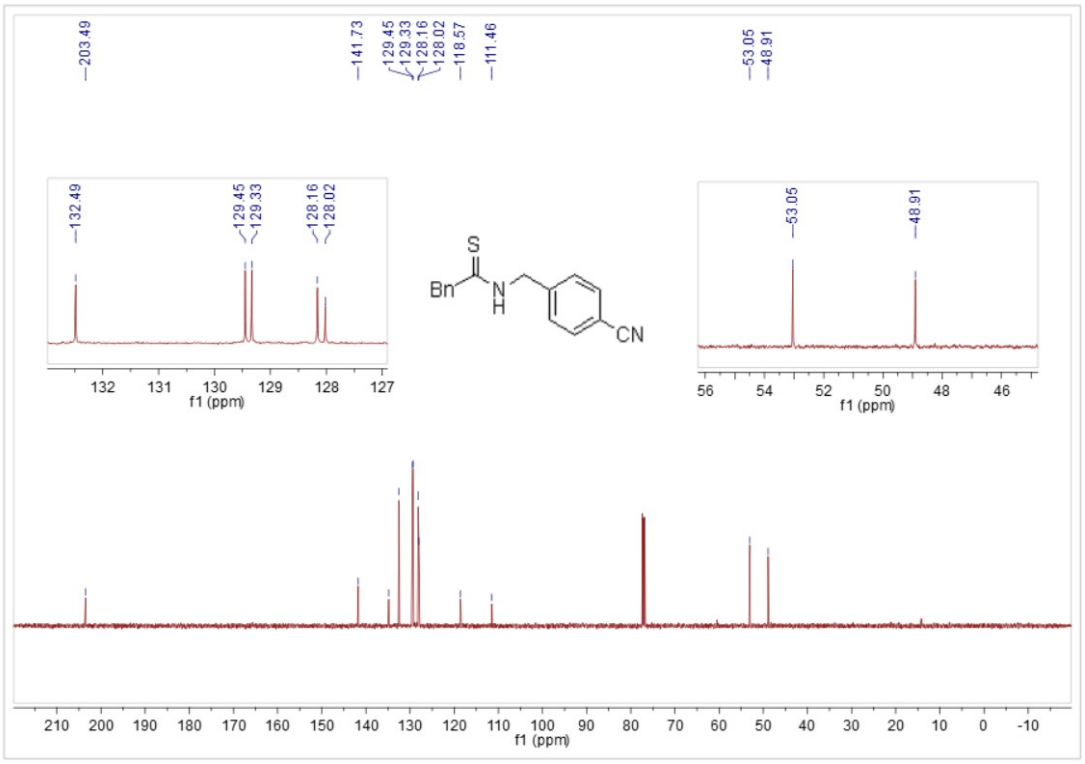




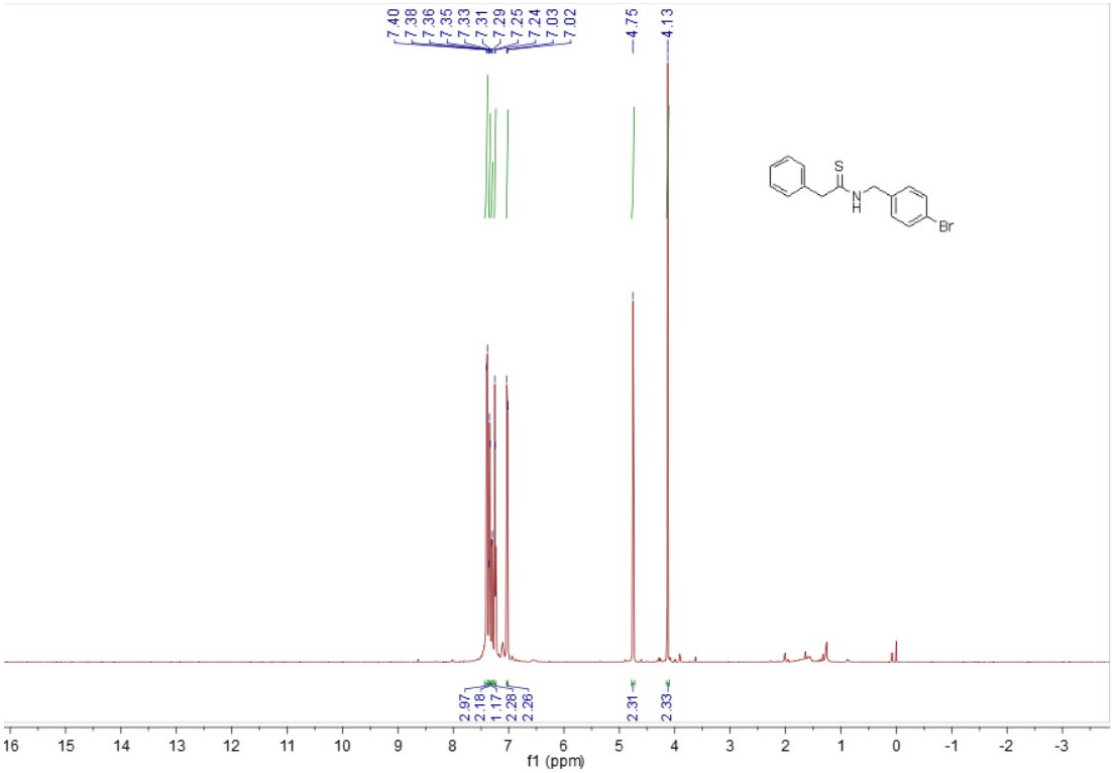

202.77
148.77
134.84
127.95
123.48
121.43
121.27
119.39
117.33
53.09
48.99
Bn
S
N
H
OCF3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

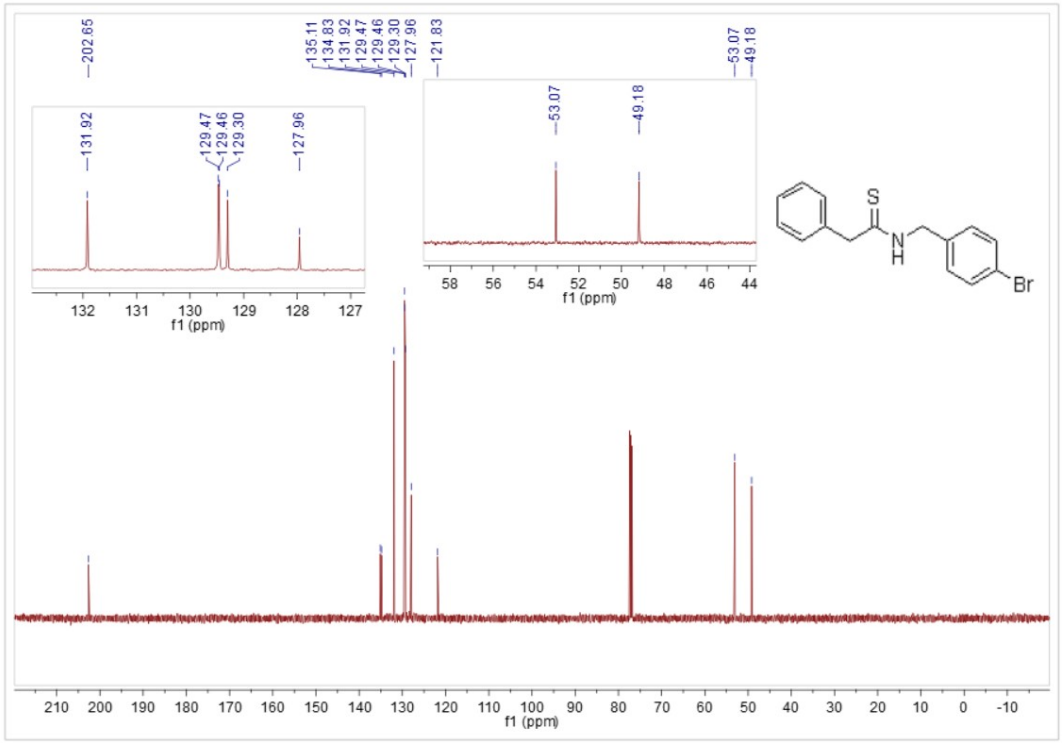
N-(4-cyanobenzyl)-2-phenylethanethioamide (3bd)



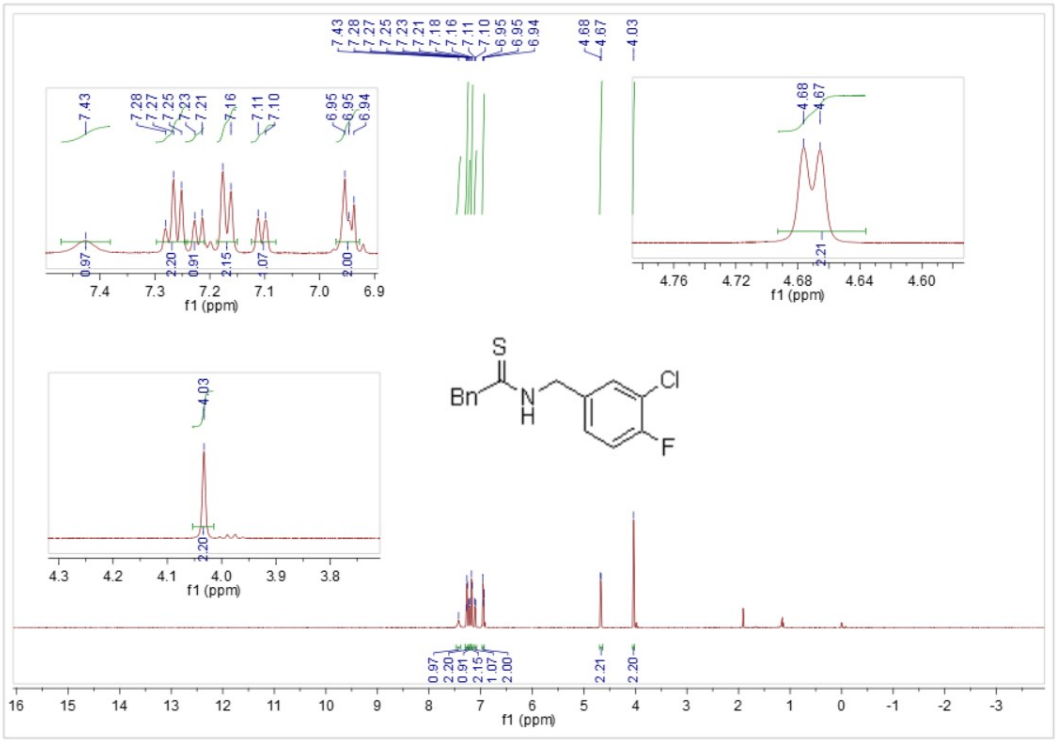


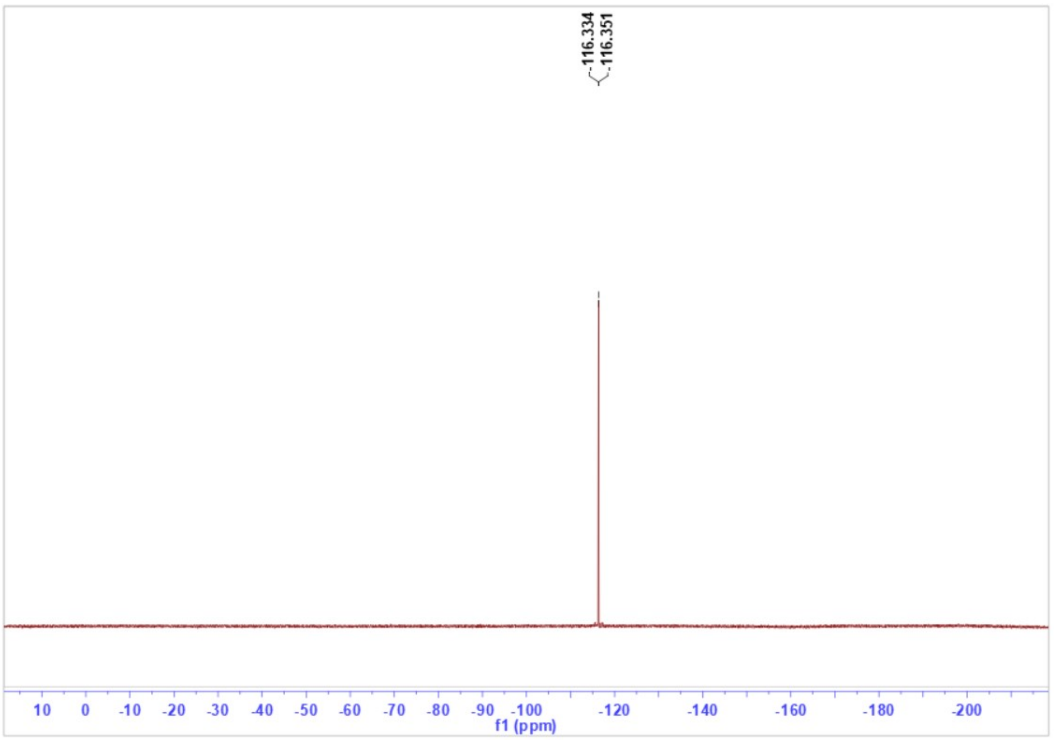
N-(4-bromobenzyl)-2-phenylethanethioamide (3be)

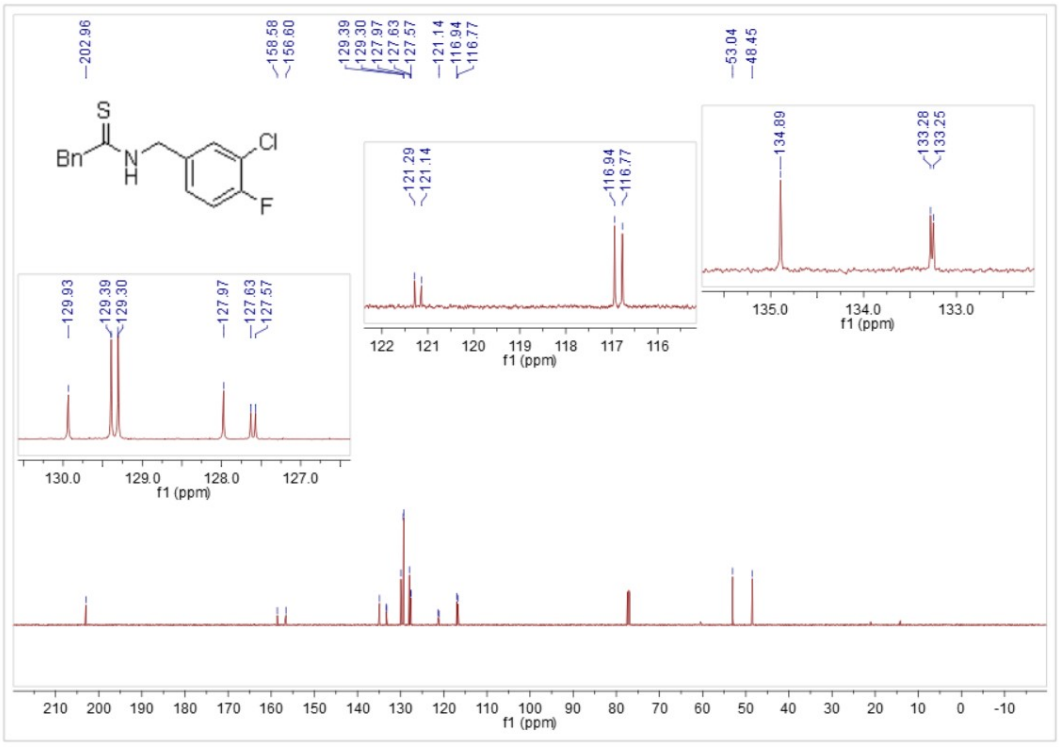




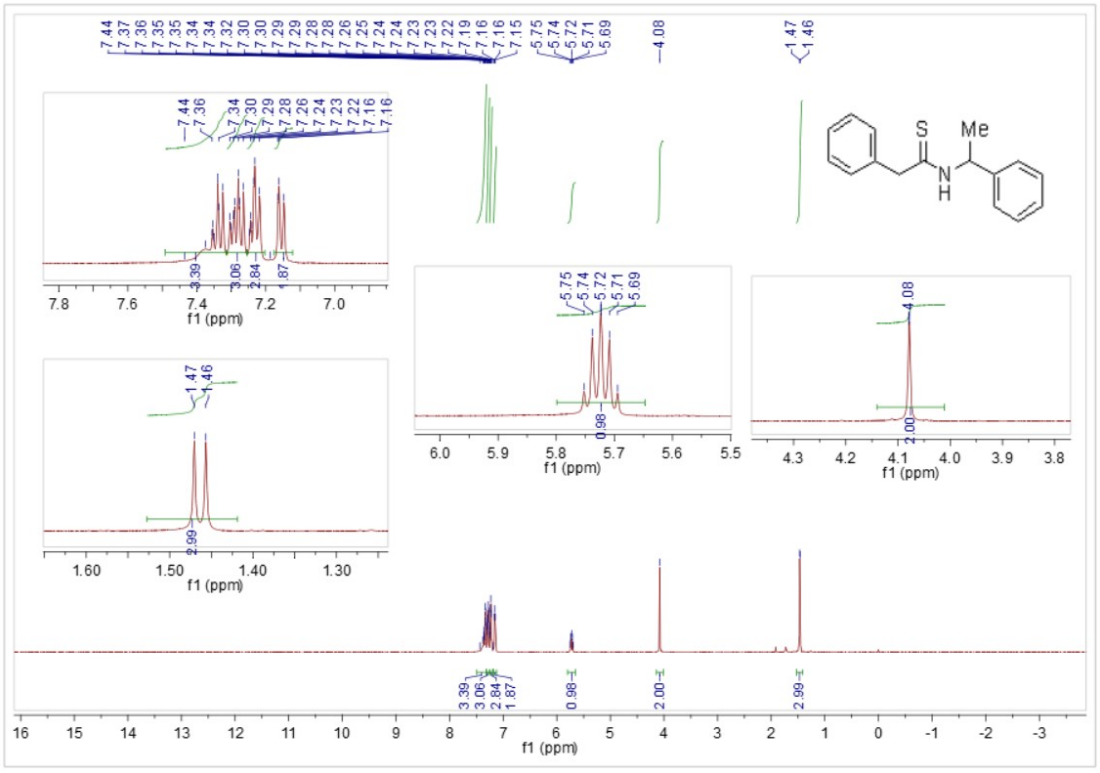
N-(3-chloro-4-fluorobenzyl)-2-phenylethanethioamide (3bf)

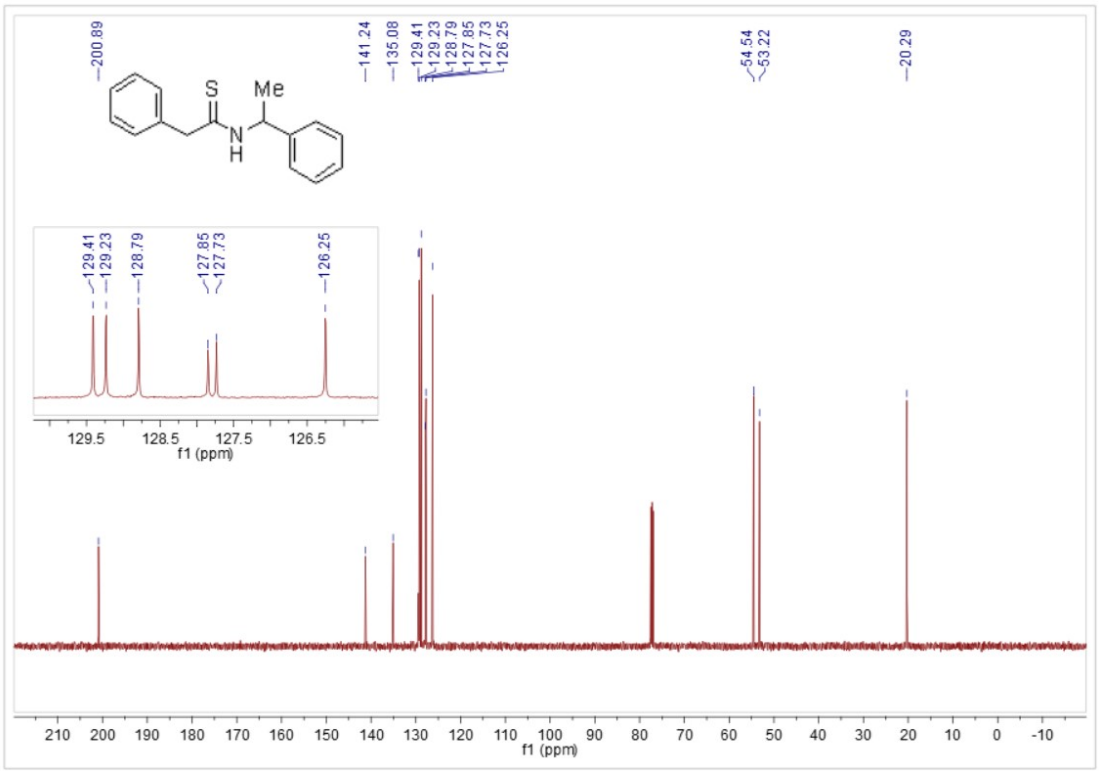




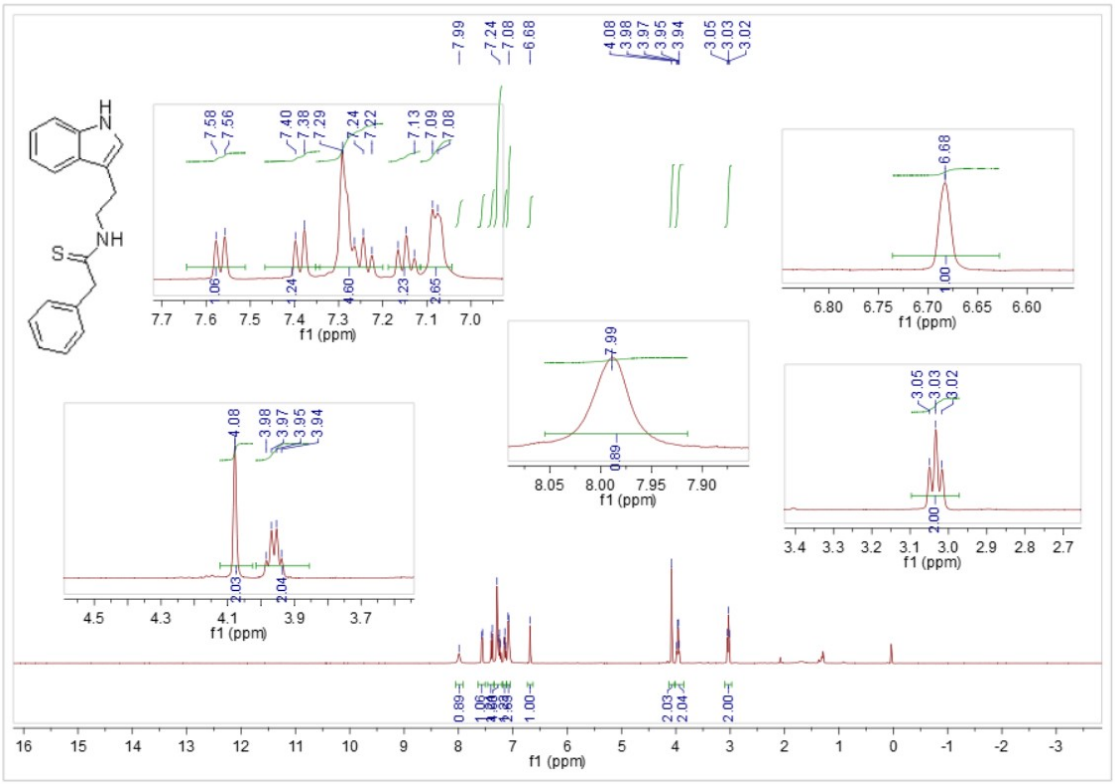

202.96
158.58
156.60
129.39
129.30
127.97
127.63
127.57
121.14
116.94
116.77
53.04
48.45
S
Bn
N
H
Cl
F
121.29
121.14
116.94
116.77
134.89
133.28
133.25
129.93
129.39
129.30
127.97
127.63
127.57
f1 (ppm)

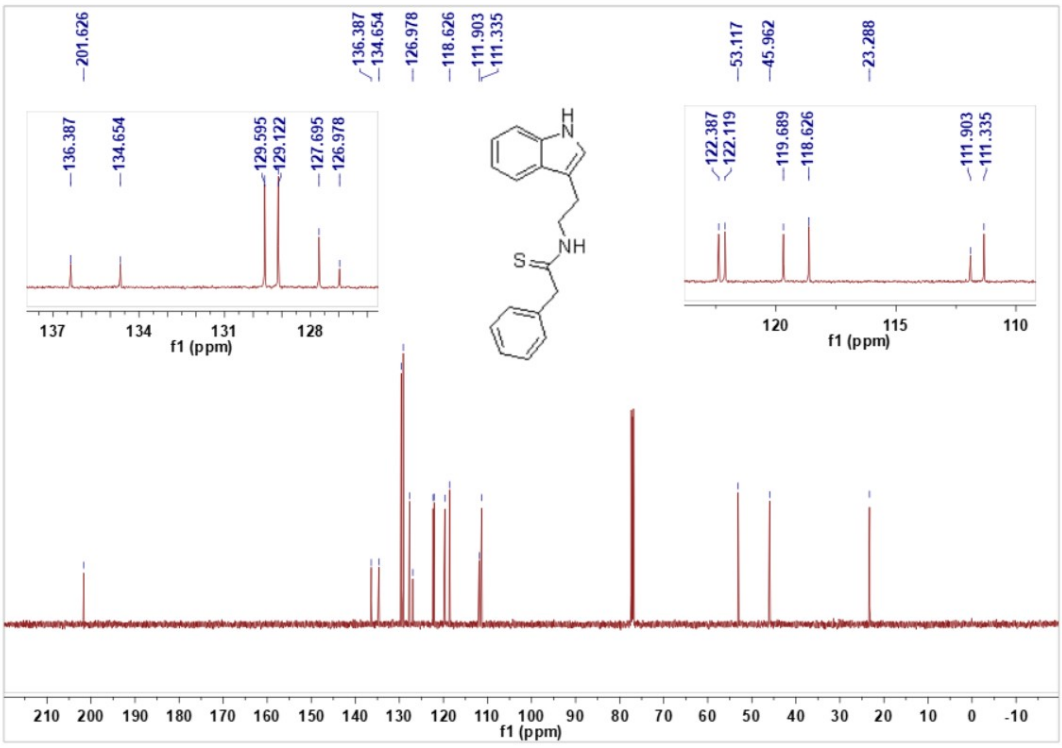
Phenyl-*N*-(1-phenylethyl)ethanethioamide (3bg)



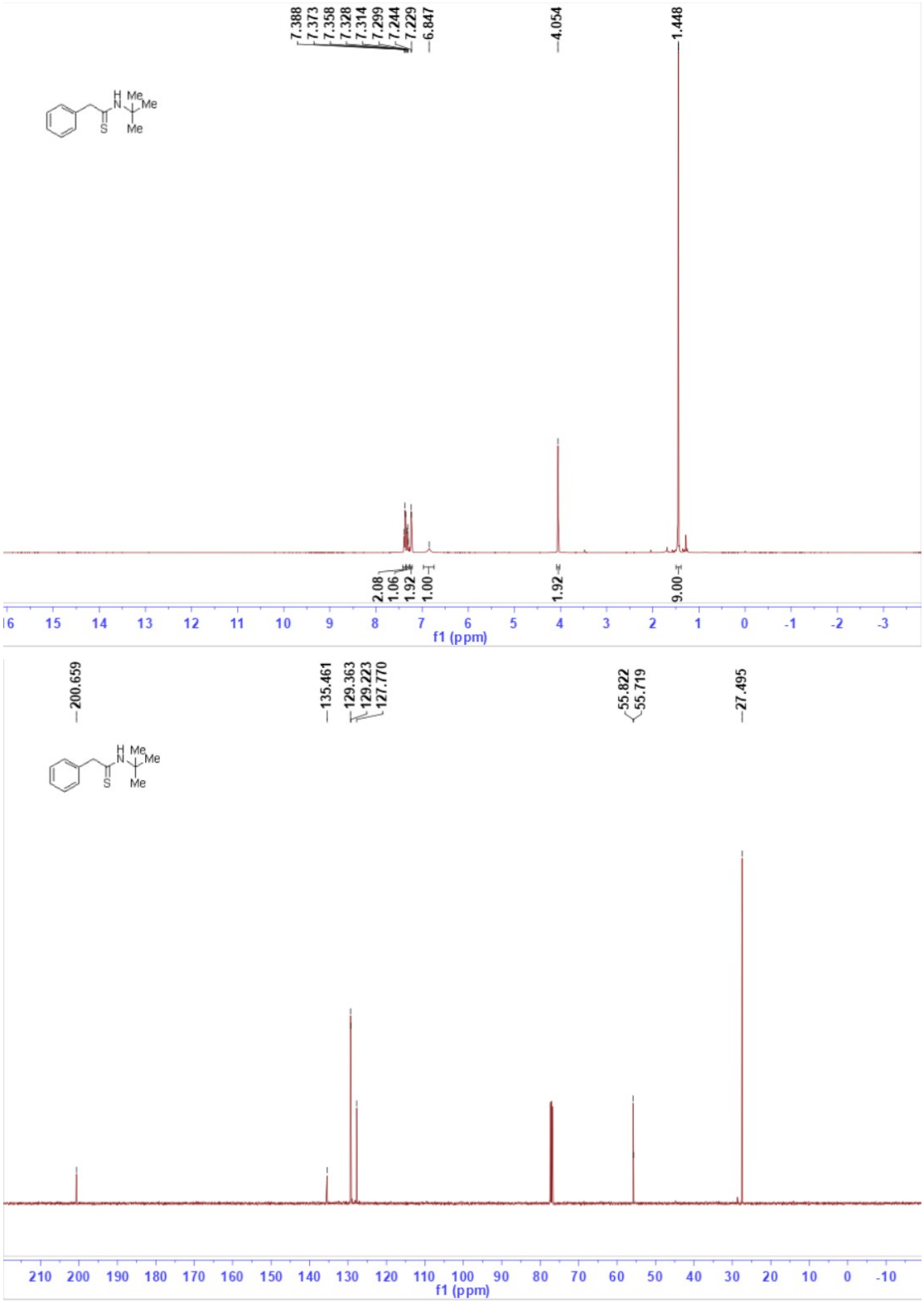


N-(2-(1*H*-indol-3-yl)ethyl)-2-phenylethanethioamide (3bh)

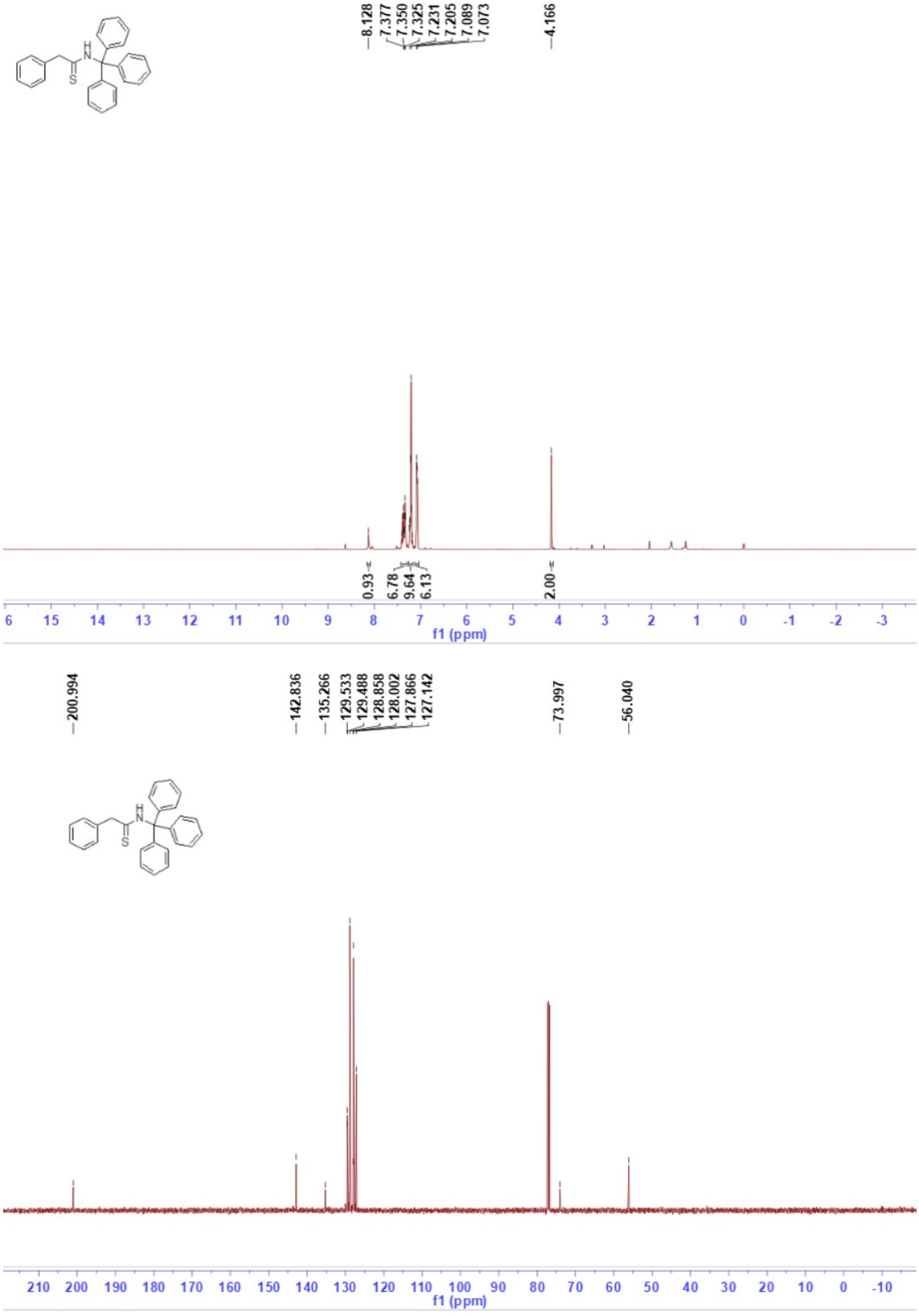




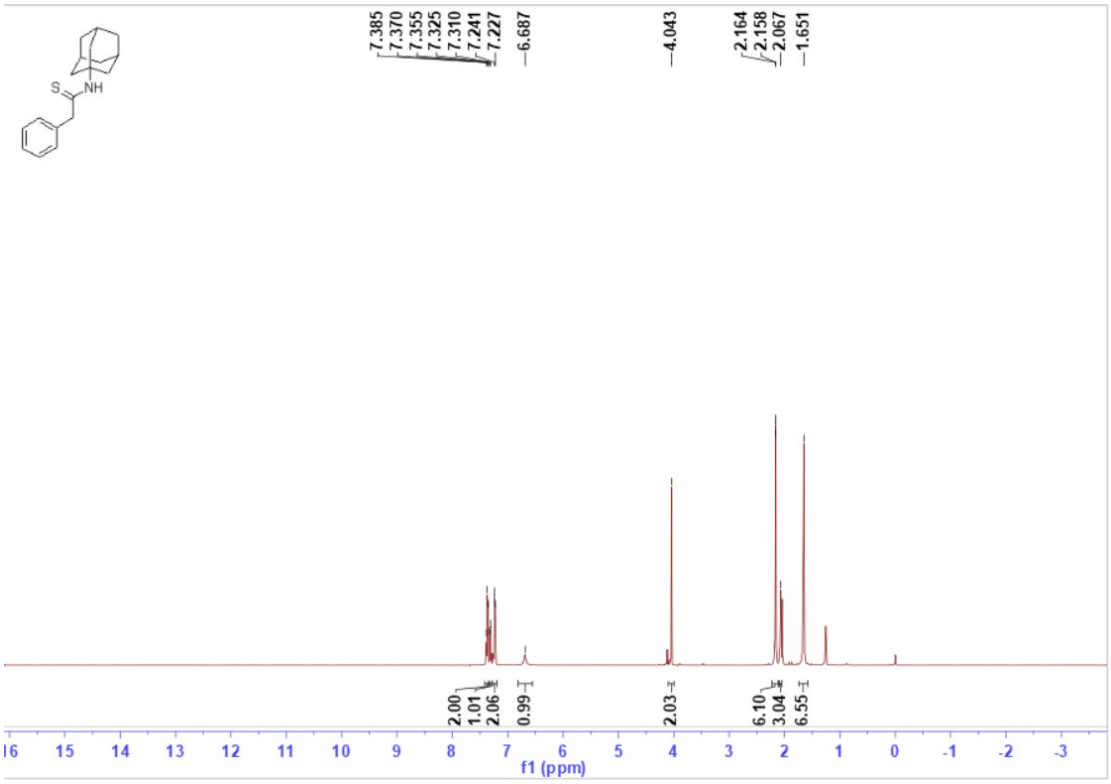
N-(tert-butyl)-2-phenylethanethioamide (3bi)

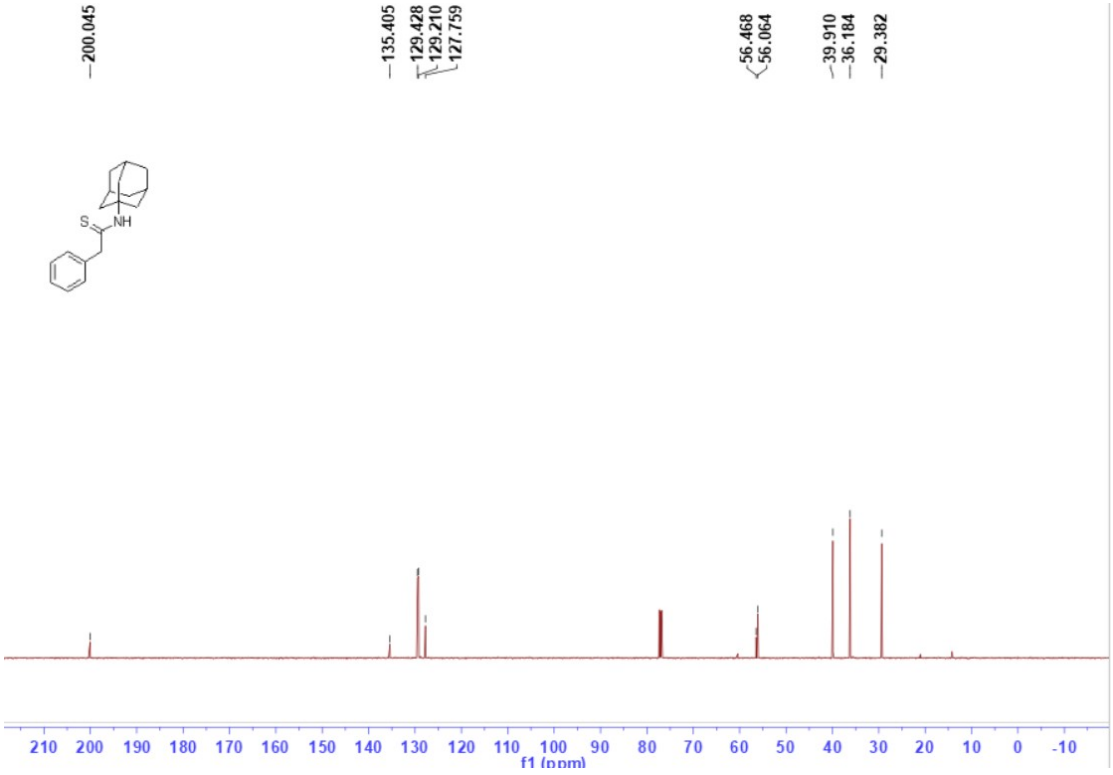


2-Phenyl-*N*-tritylethanethioamide (3bj)

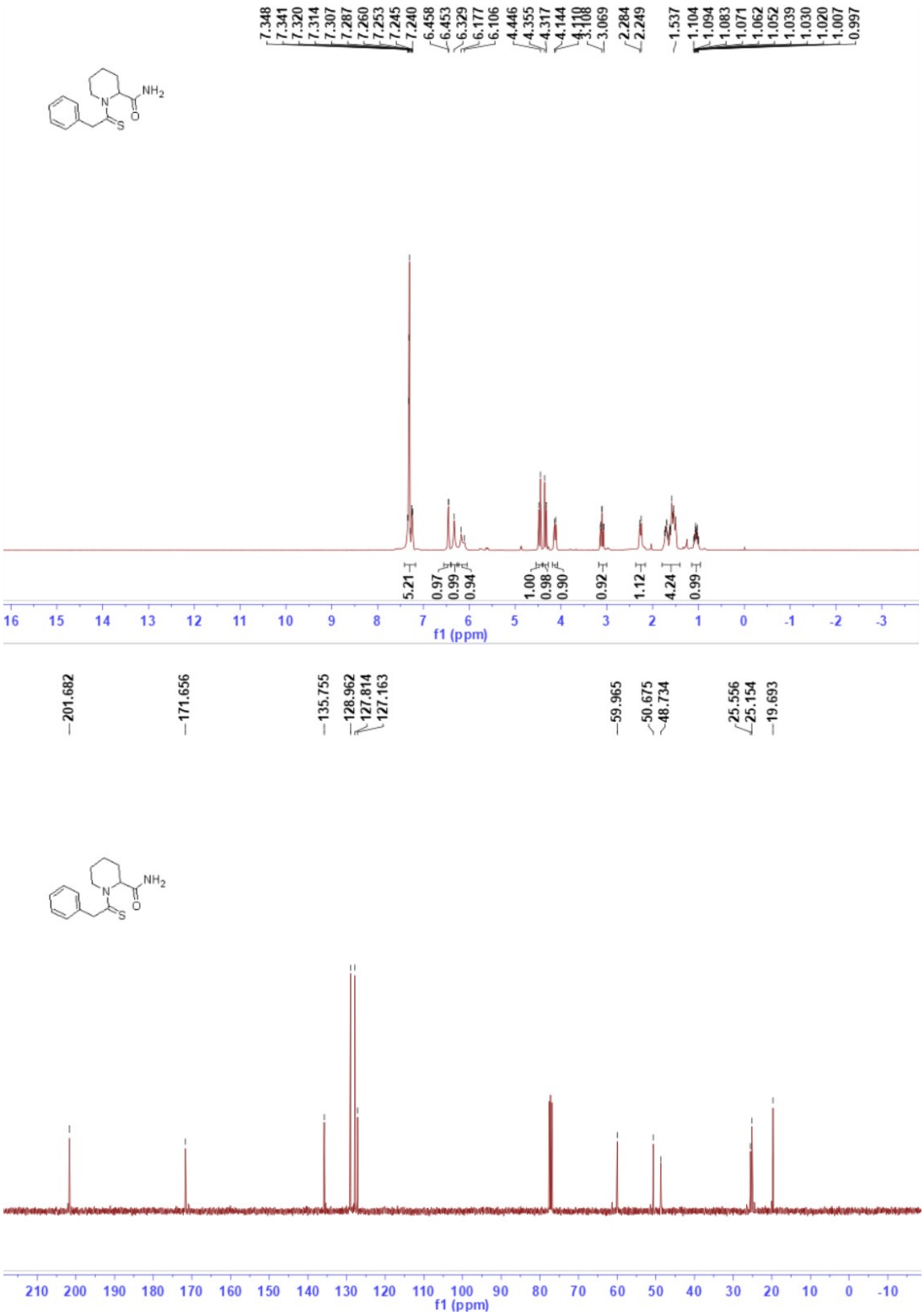


N-((3s,5s,7s)-adamantan-1-yl)-2-phenylethanethioamide (3bk)

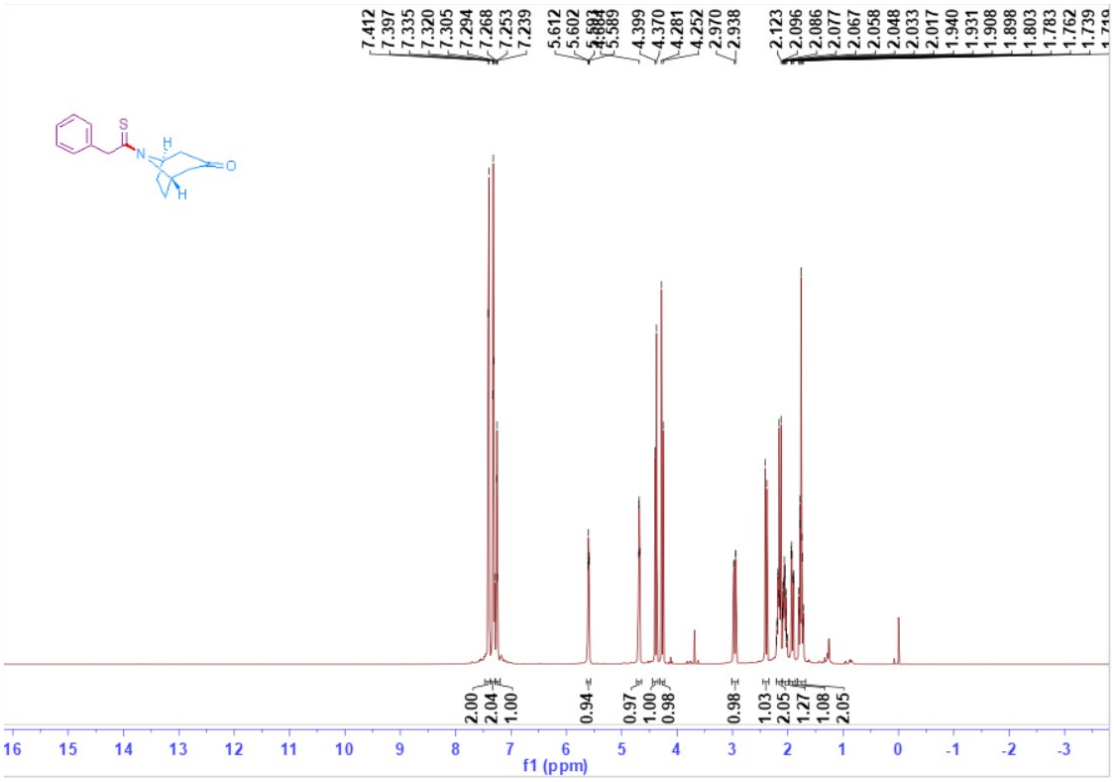


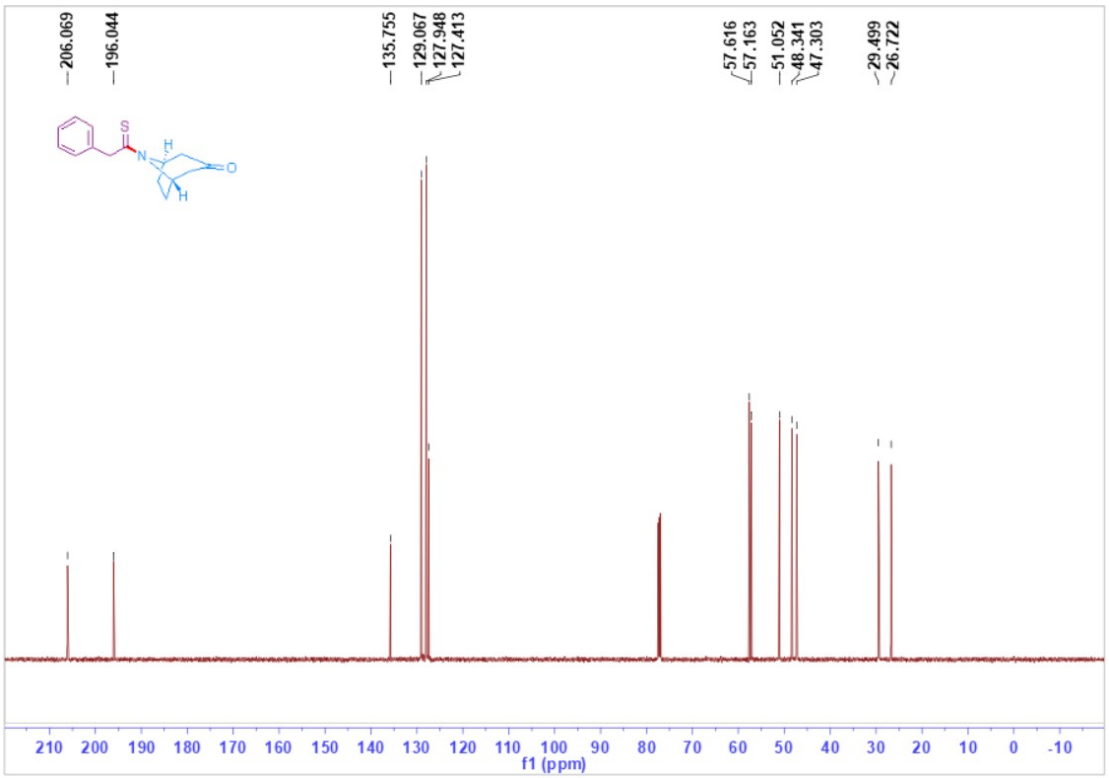


1-(2-Phenylethanethioyl)piperidine-2-carboxamide (3bl)

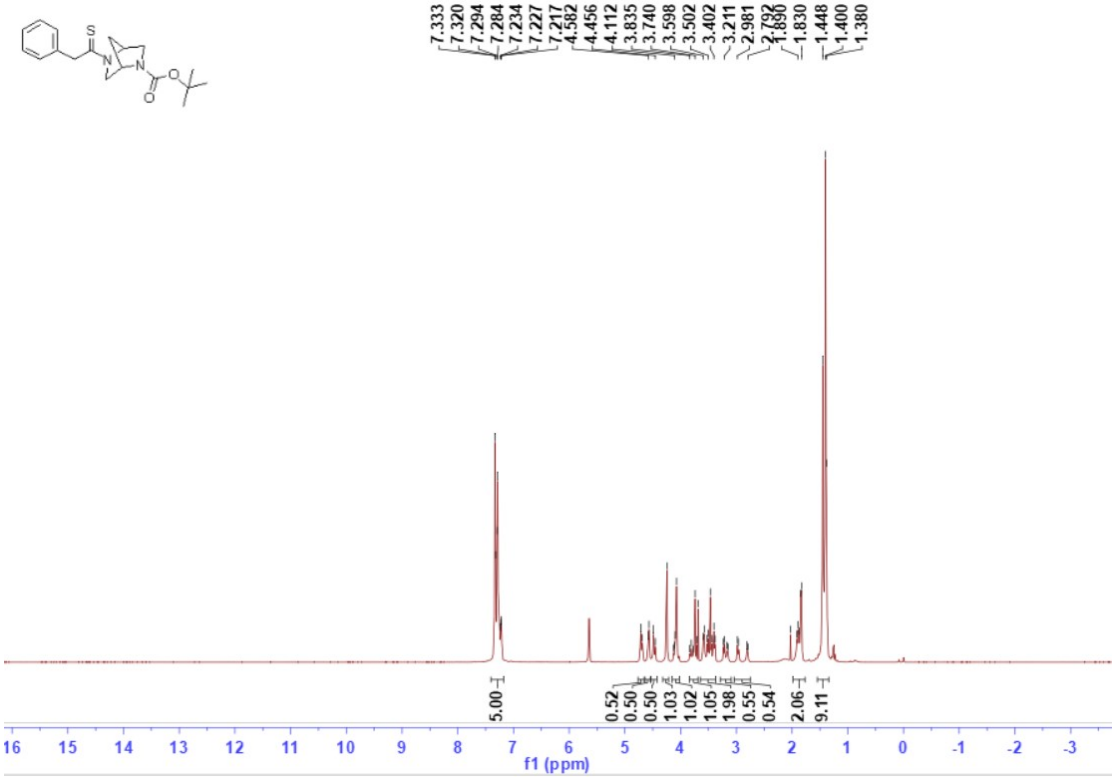


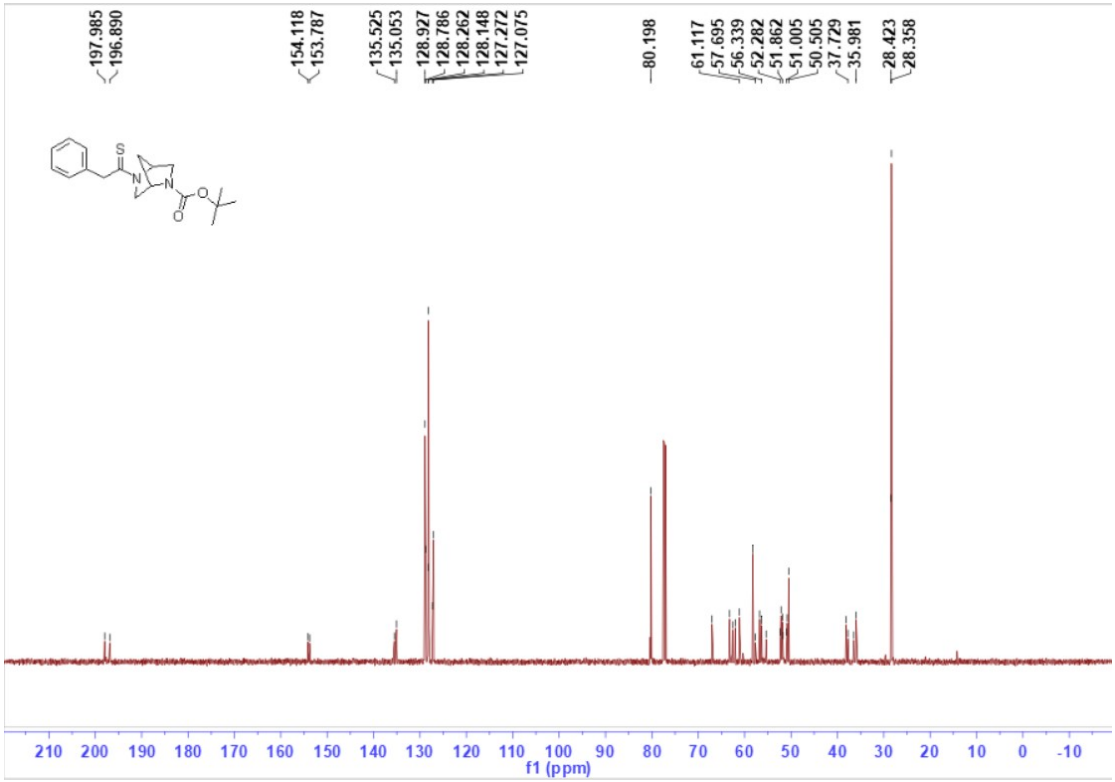
(1*R*,5*S*)-8-(2-Phenylethanethioyl)-8-azabicyclo[3.2.1]octan-3-one (3bm)



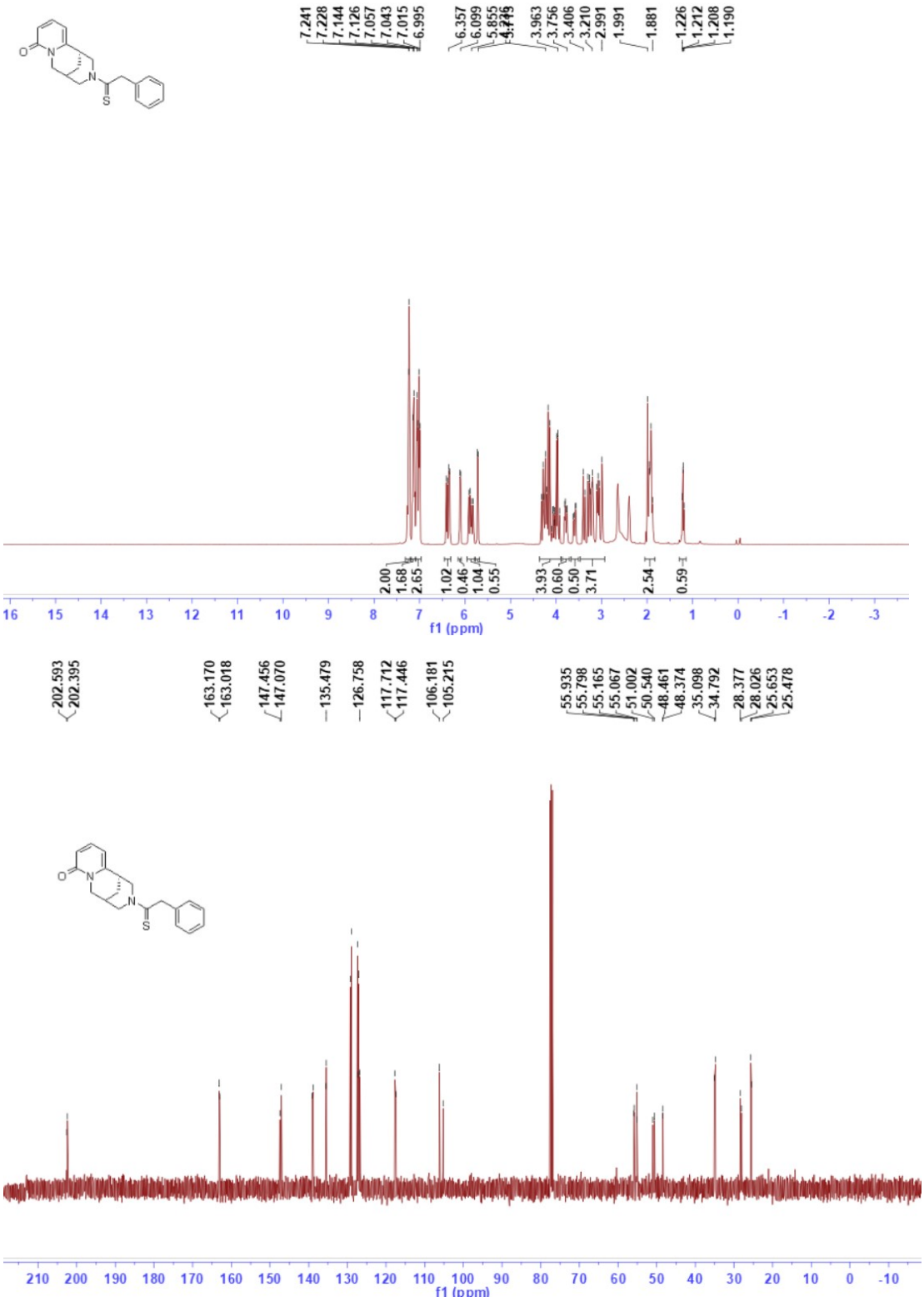


Tert-butyl (1*S*,4*S*)-5-(2-phenylethanethioyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3bn)

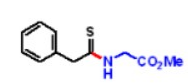


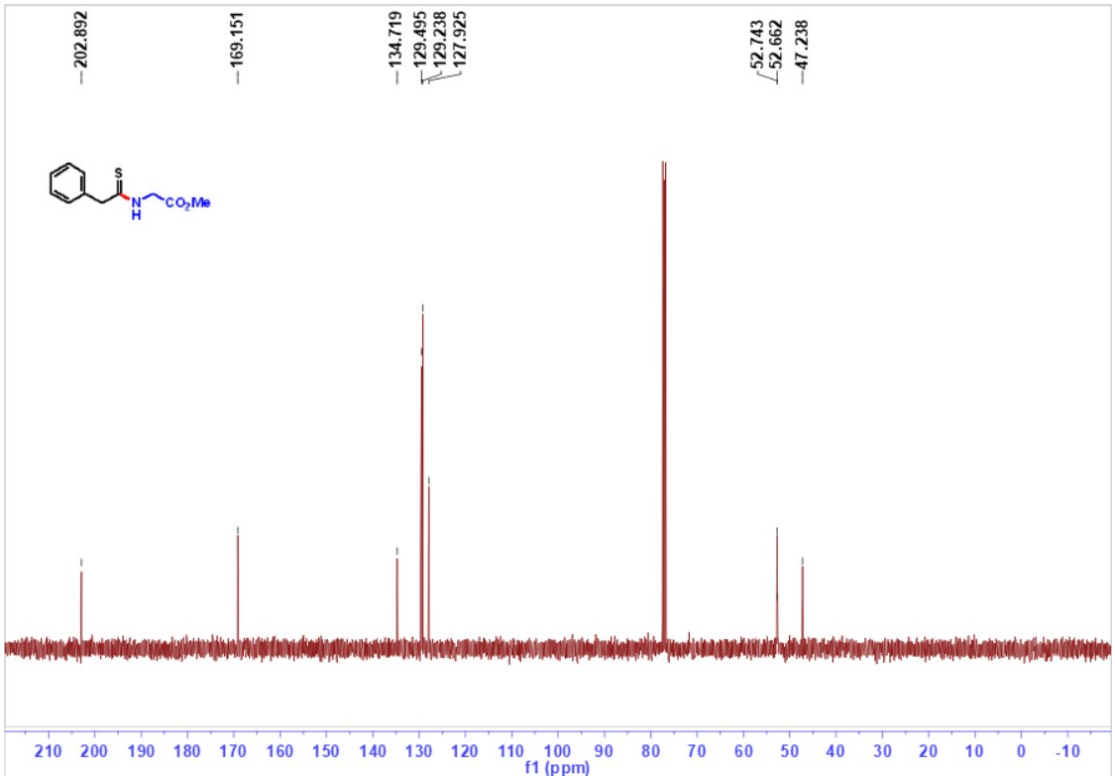


(1*S*,5*R*)-3-(2-Phenylethanethioyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3bo)

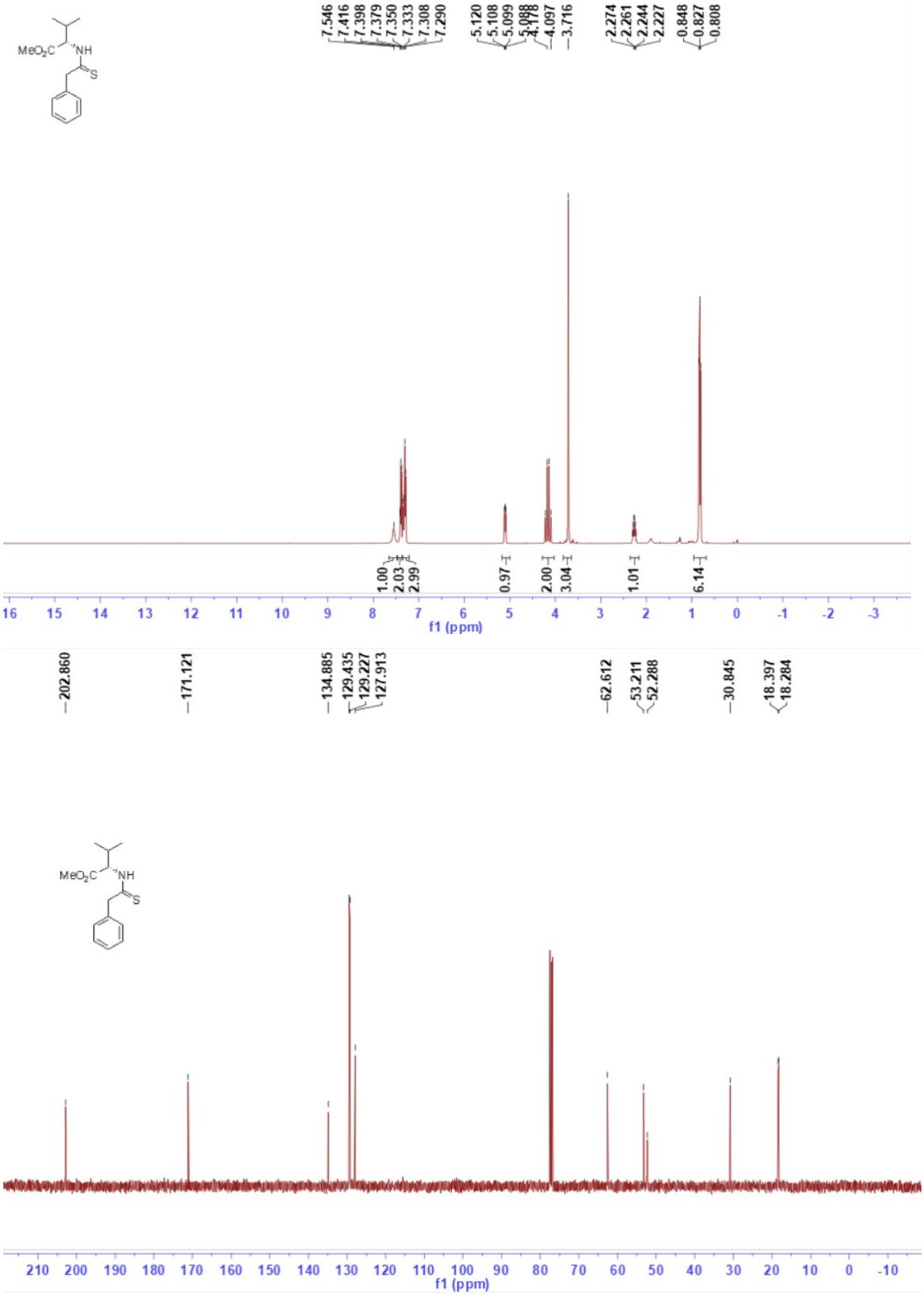


Methyl (2-phenylethanethioyl)glycinate (3ca)

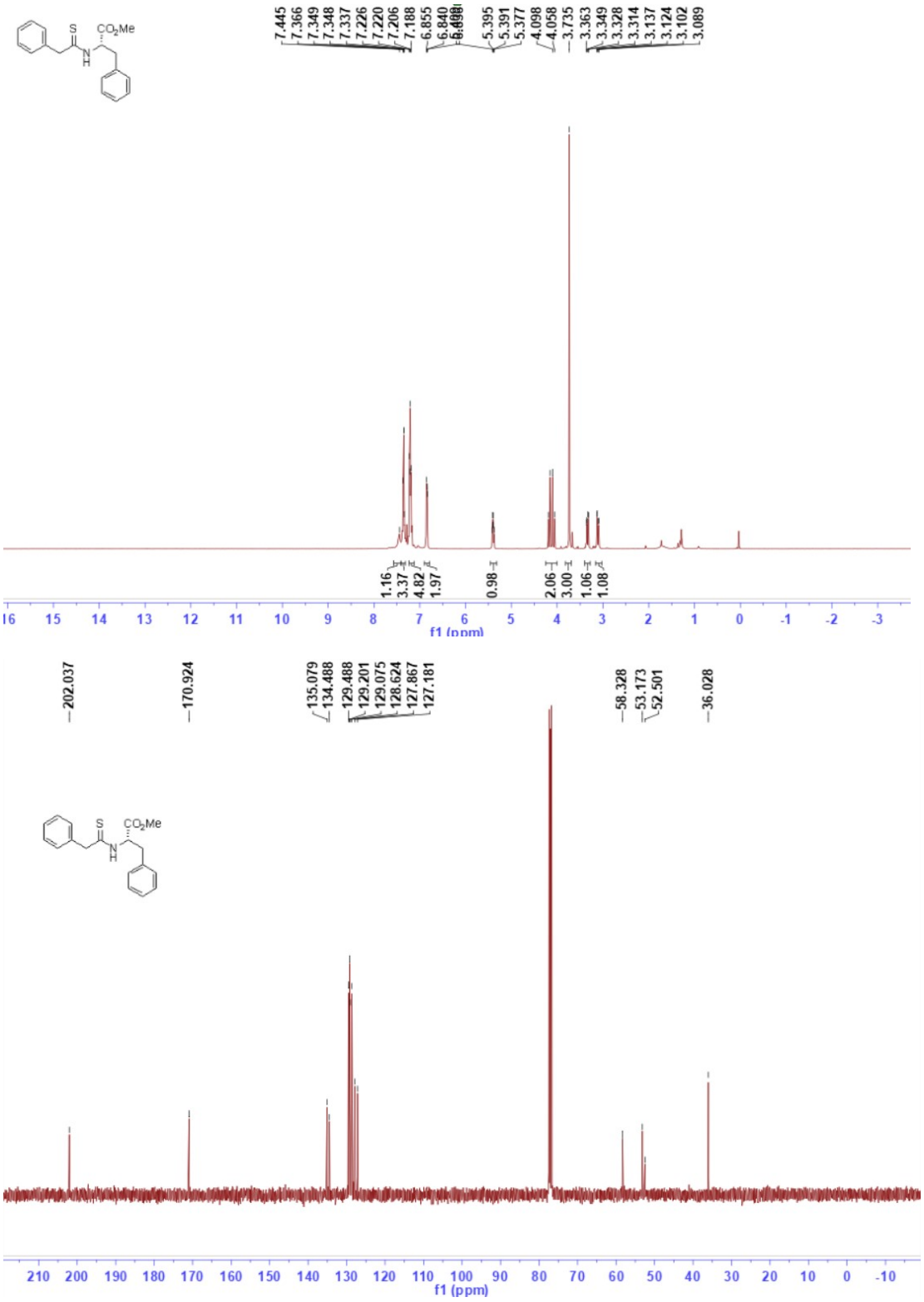




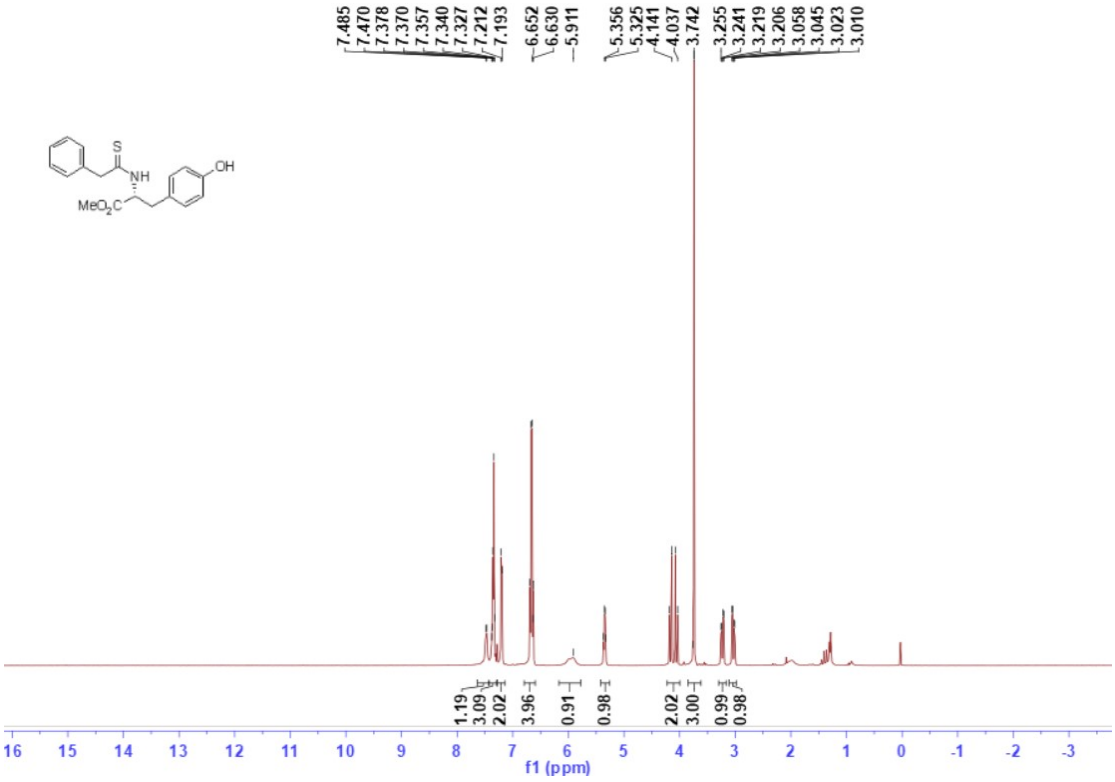
Methyl (2-phenylethanethioyl)-*L*-valinate (3cb)

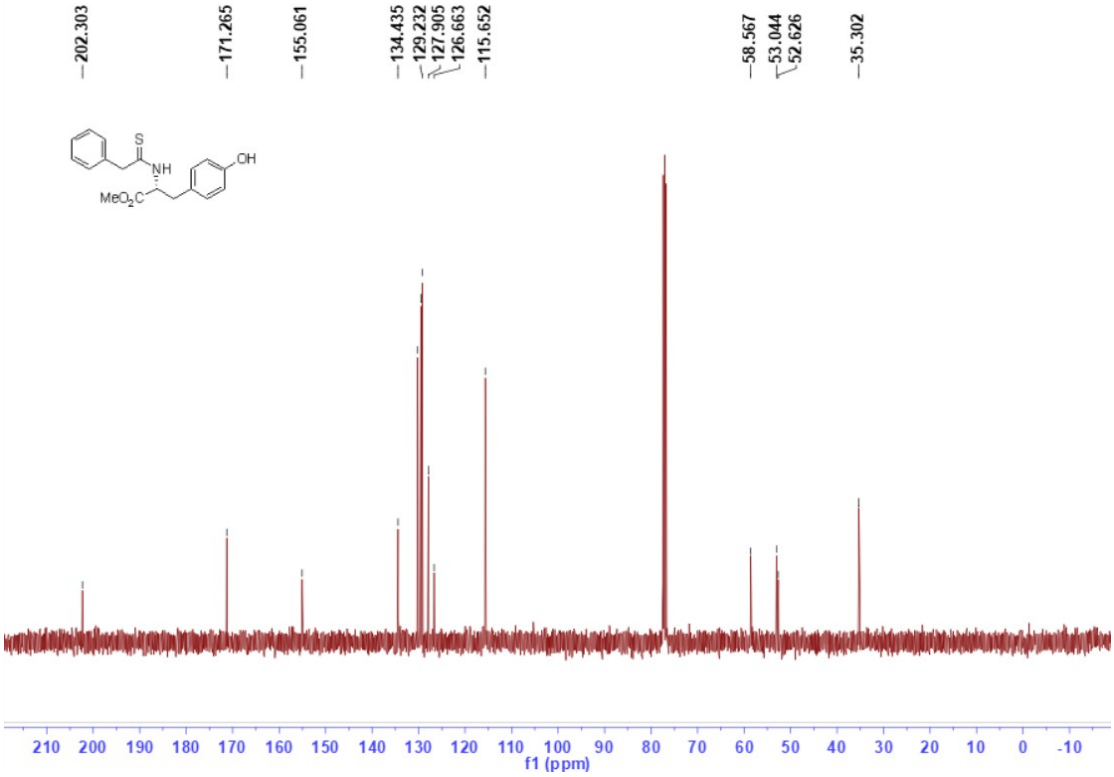


Methyl (2-phenylethanethioyl)-*L*-phenylalaninate (3cc)

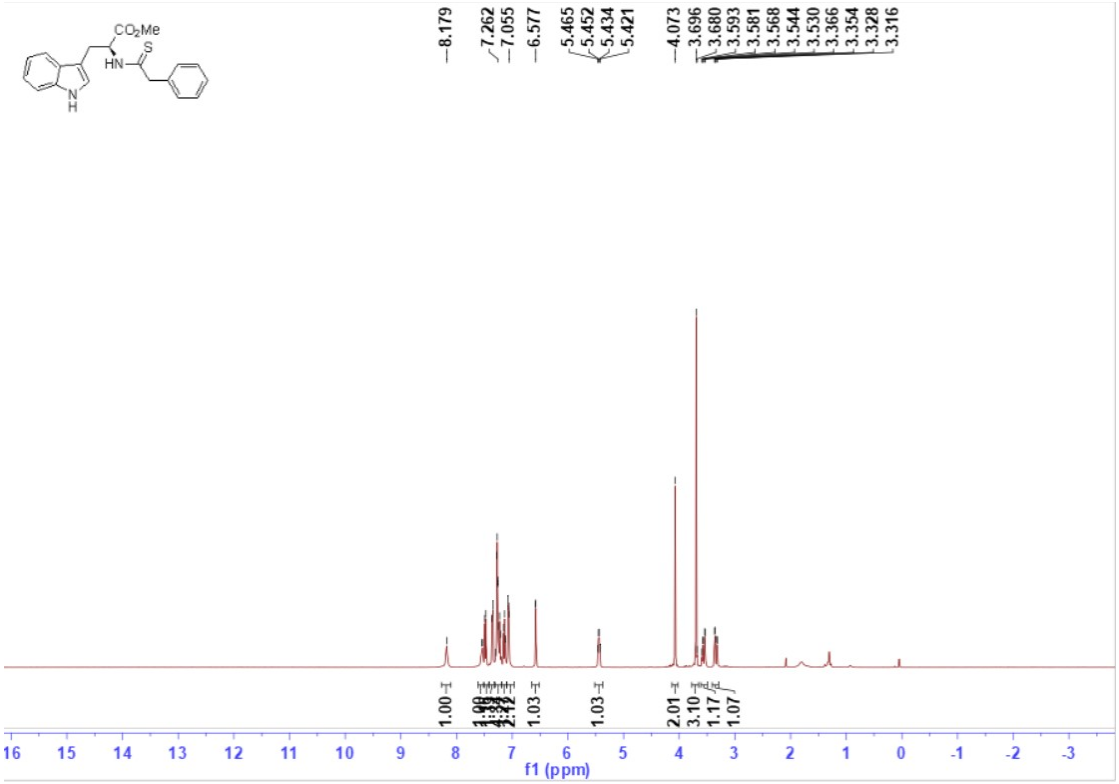


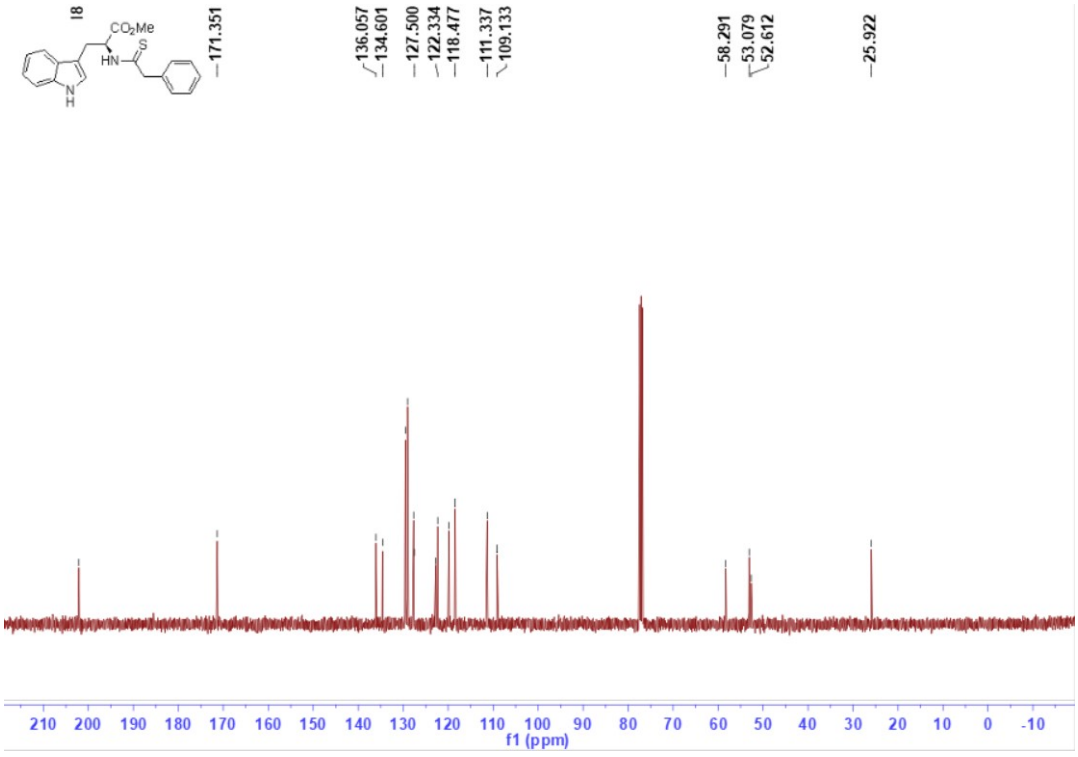
Methyl (2-phenylethanethioyl)-*D*-tyrosinate (3cd)



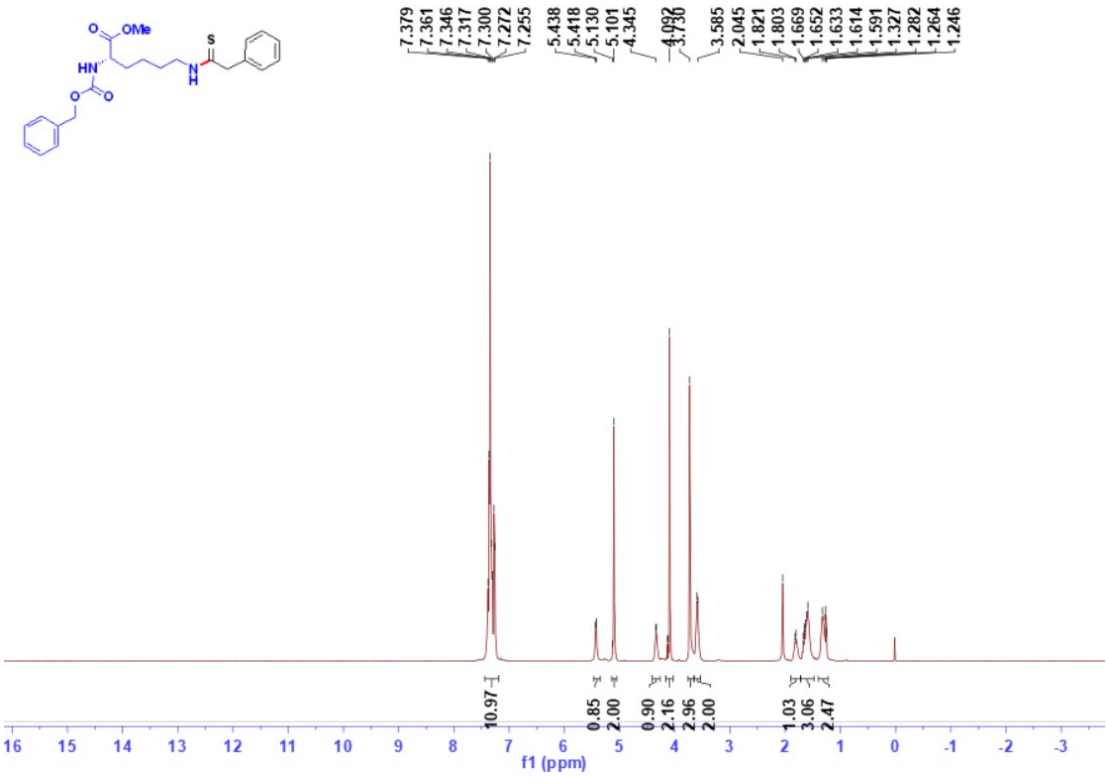


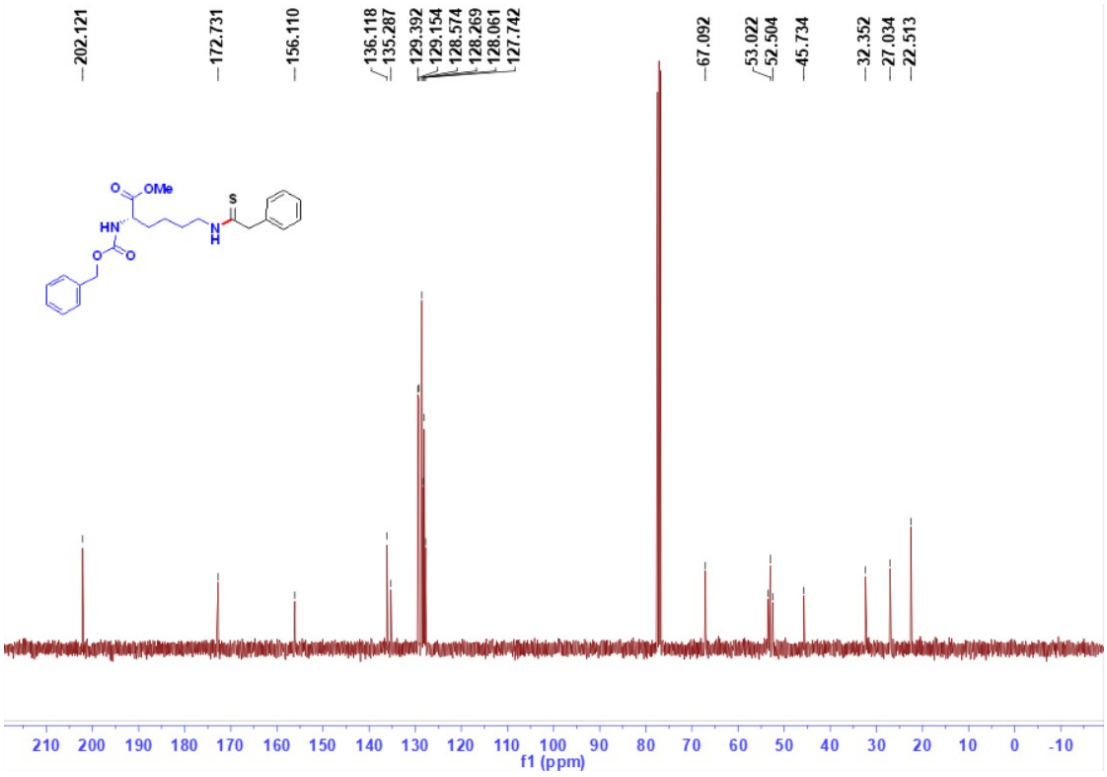
Methyl (2-phenylethanethioyl)-*L*-tryptophanate (3ce)



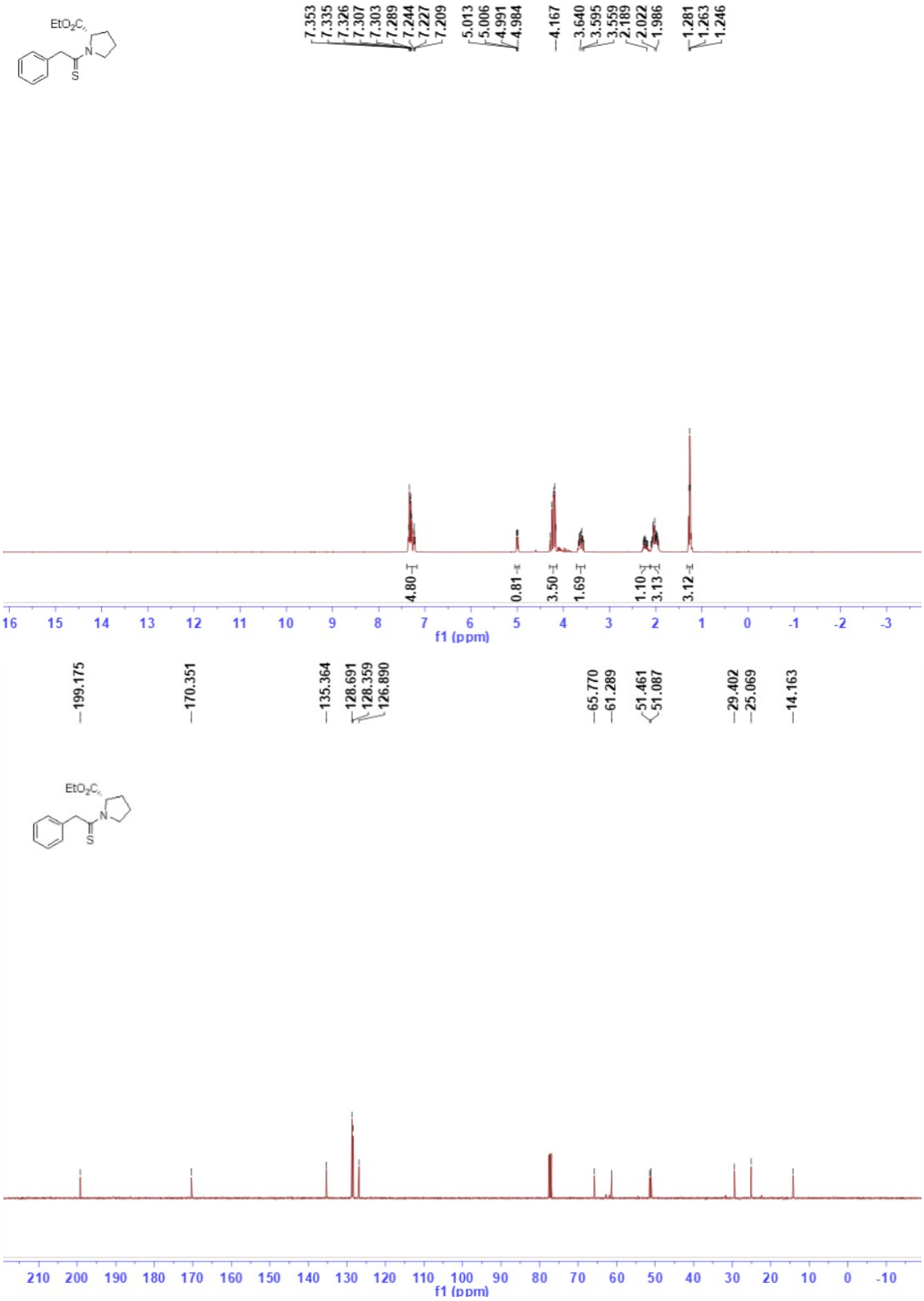


Methyl *N*2-((benzyloxy)carbonyl)-*N*6-(2-phenylethanethioyl)-*L*-lysinate (3cf)

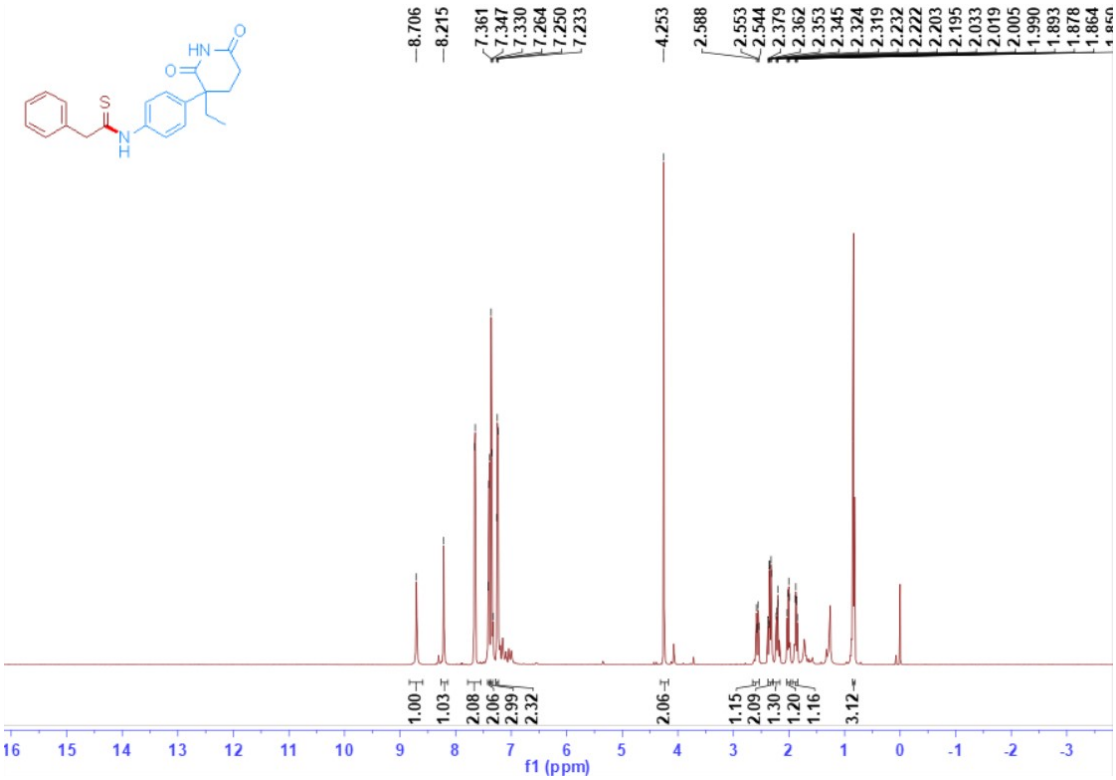


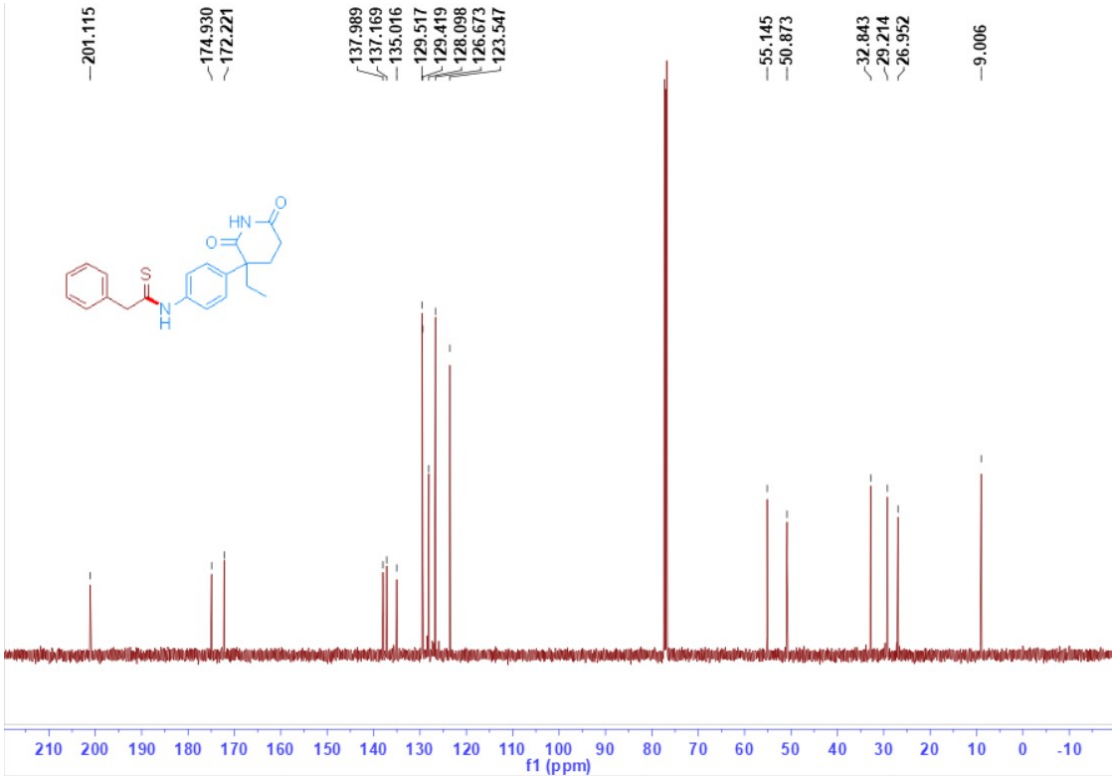


Ethyl (2-phenylethanethioyl)-*L*-prolinate (3cg)

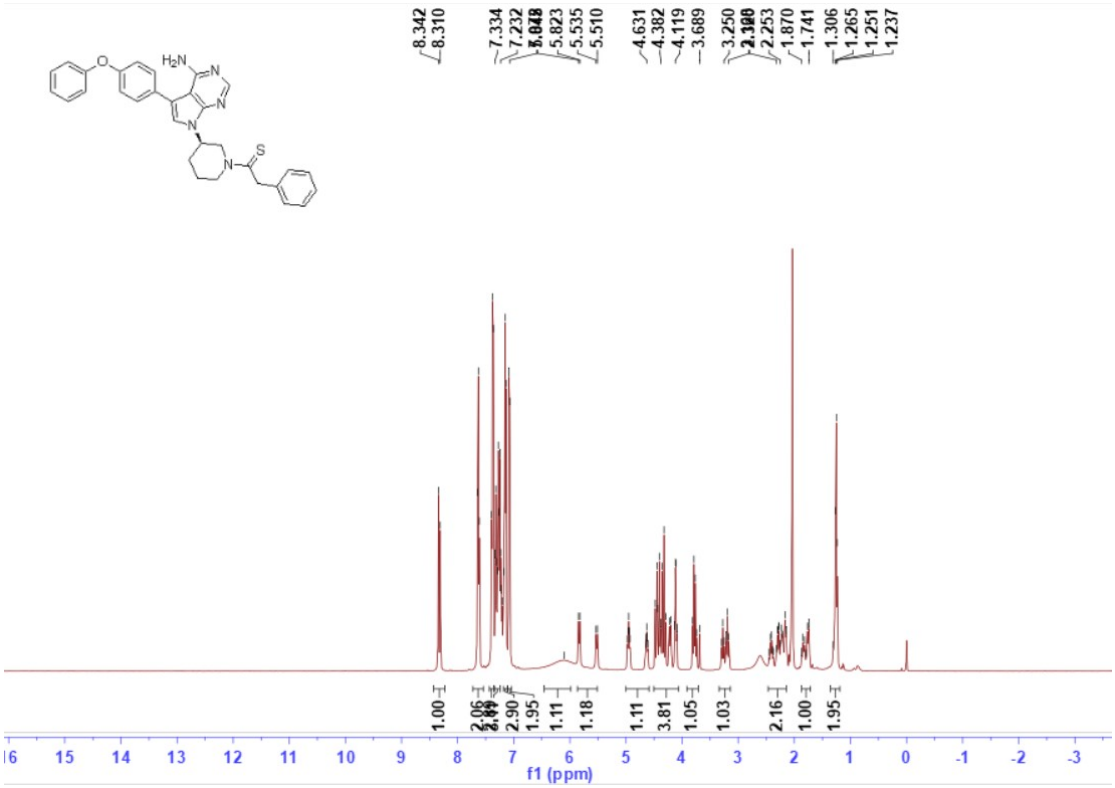


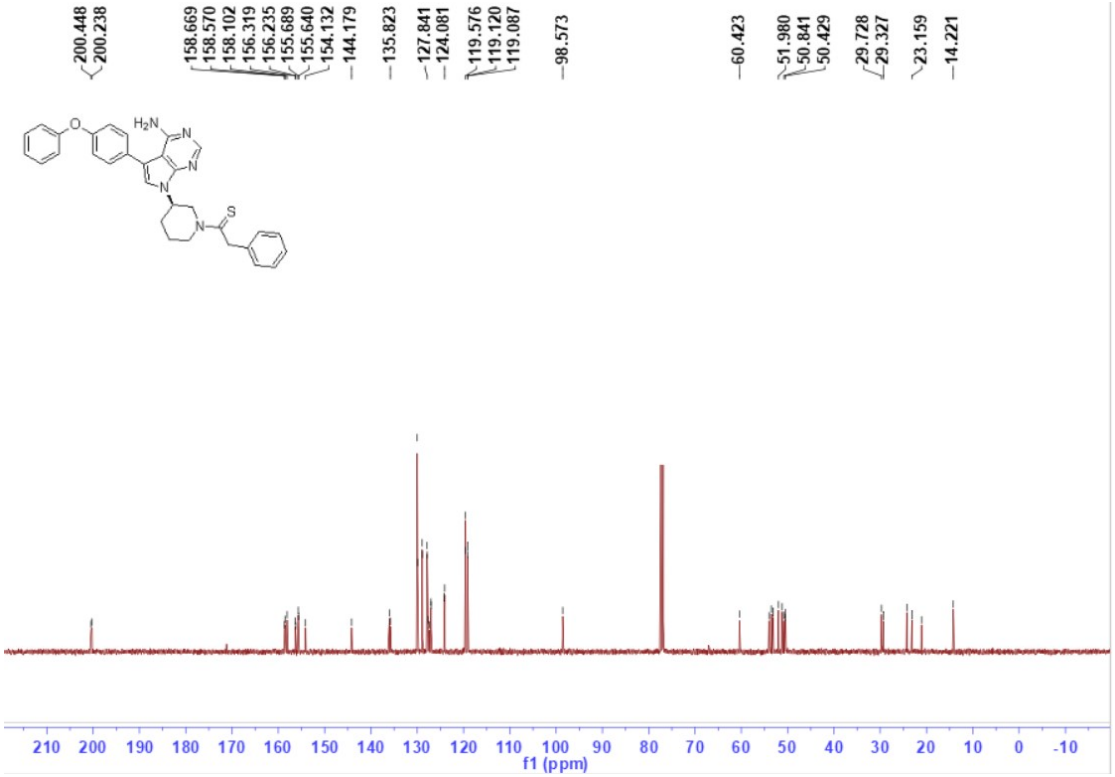
AminoglutethiMide tihoamidation derivative (3da)



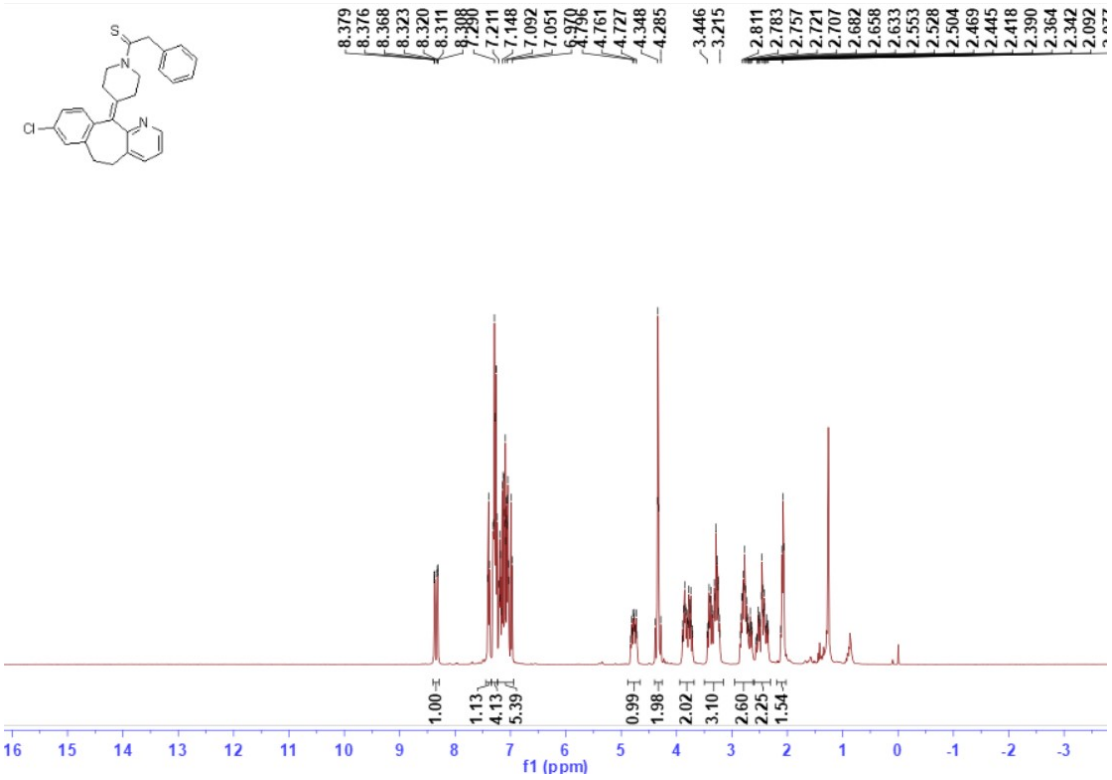


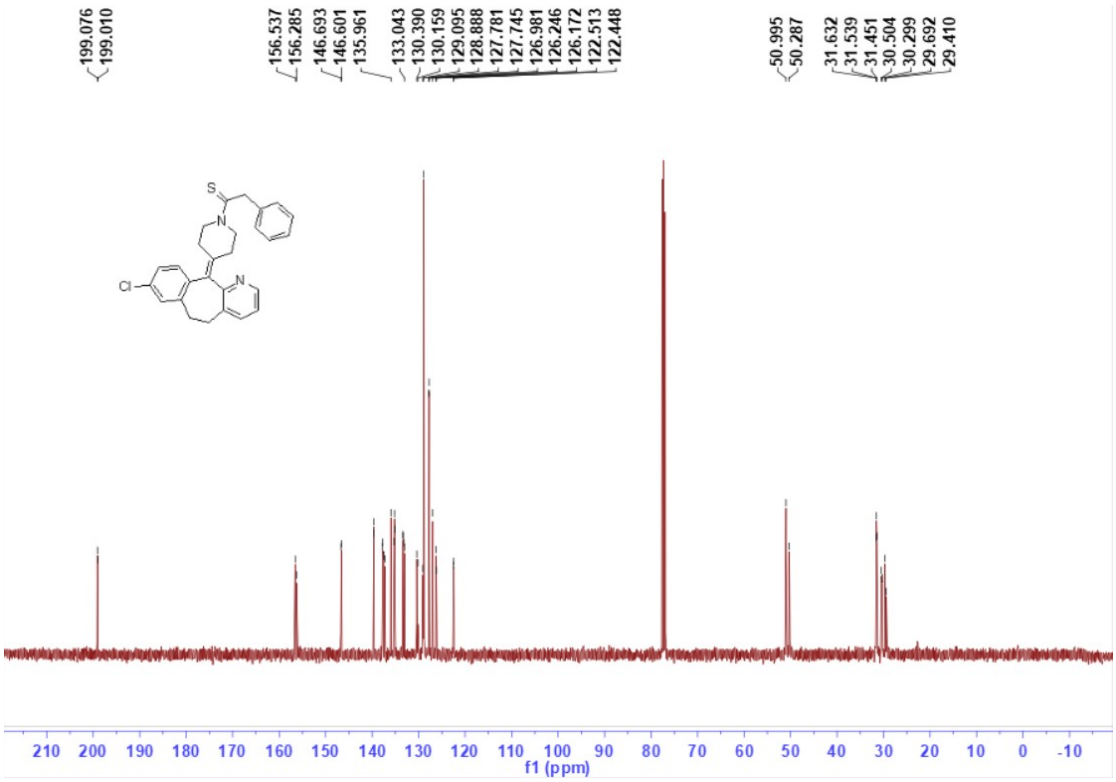
Ibrutinib intermediate thioamidation (3db)



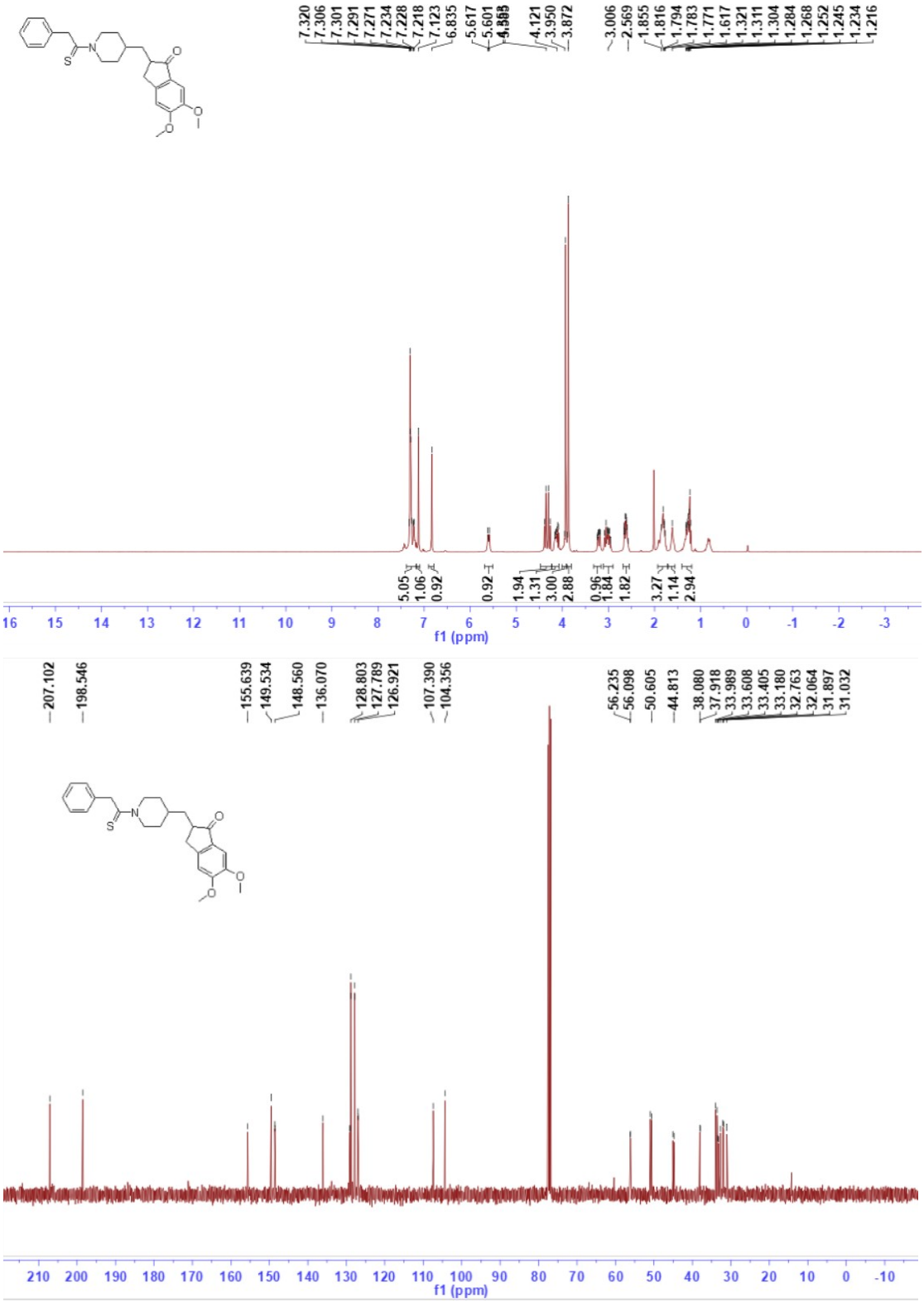


1-(4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidin-1-yl)-2-phenylethane-1-thione (3dc)

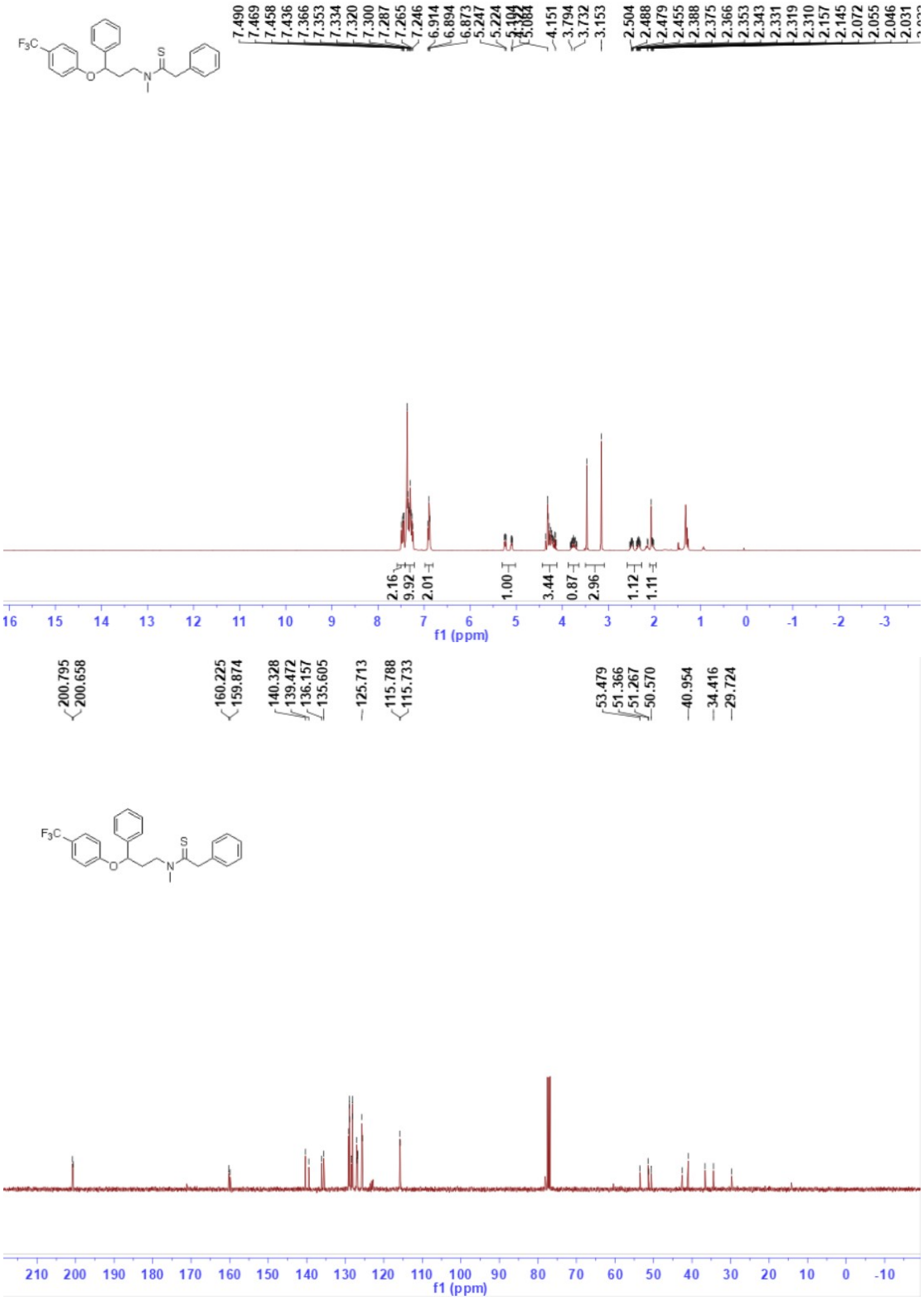


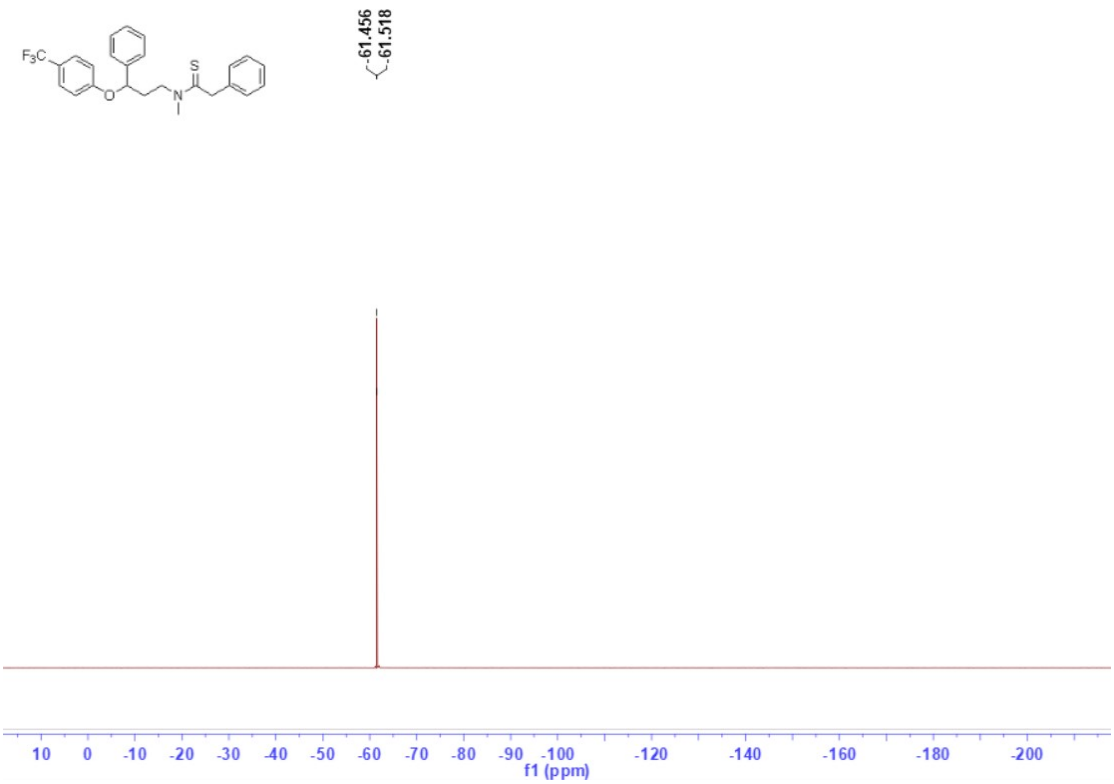


5,6-Dimethoxy-2-((1-(2-phenylethanethioyl)piperidin-4-yl)methyl)-2,3-dihydro-1*H*-inden-1-one (3dd)

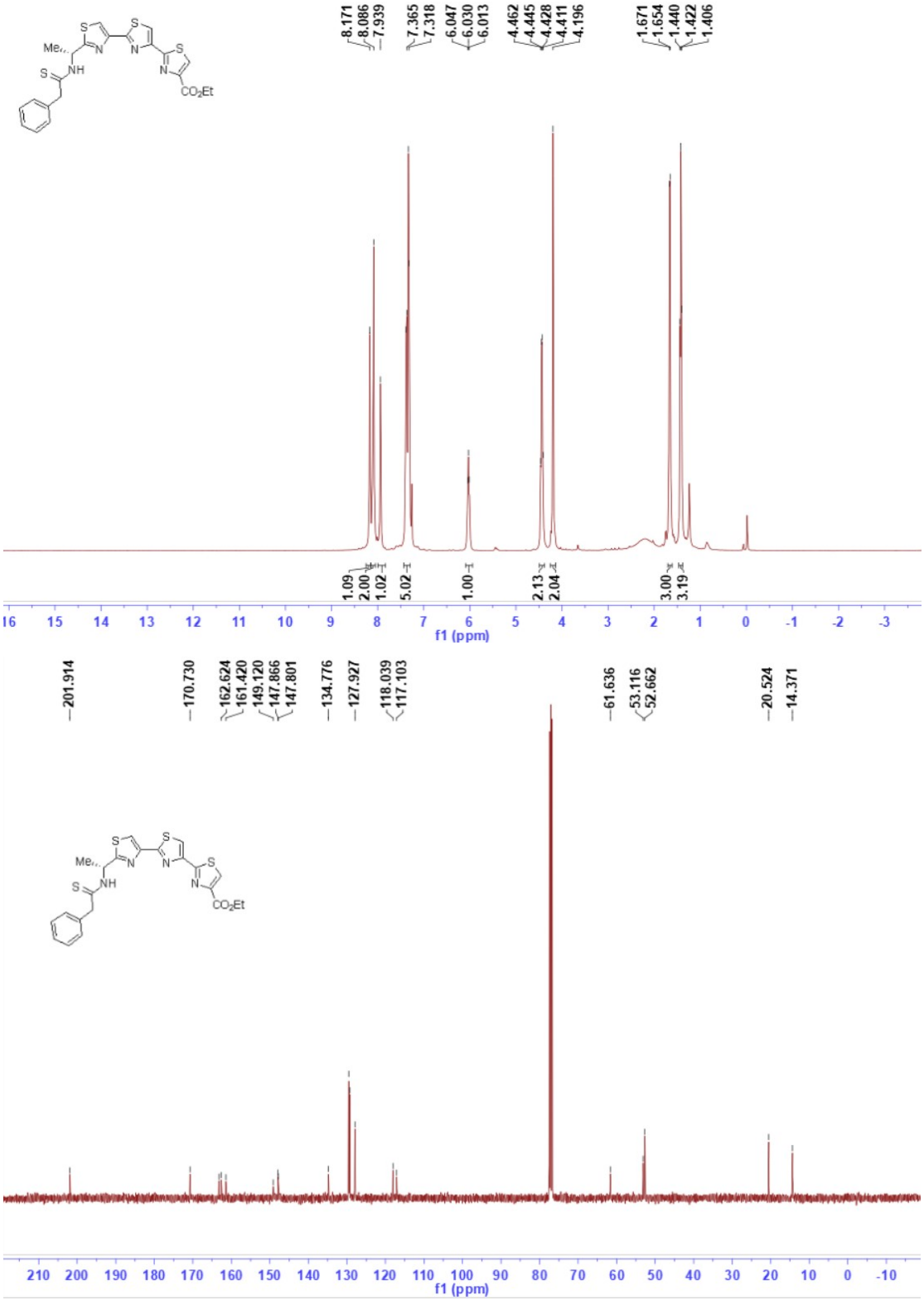


_N_-methyl-2-phenyl-_N_-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)ethanethioamide (3de)

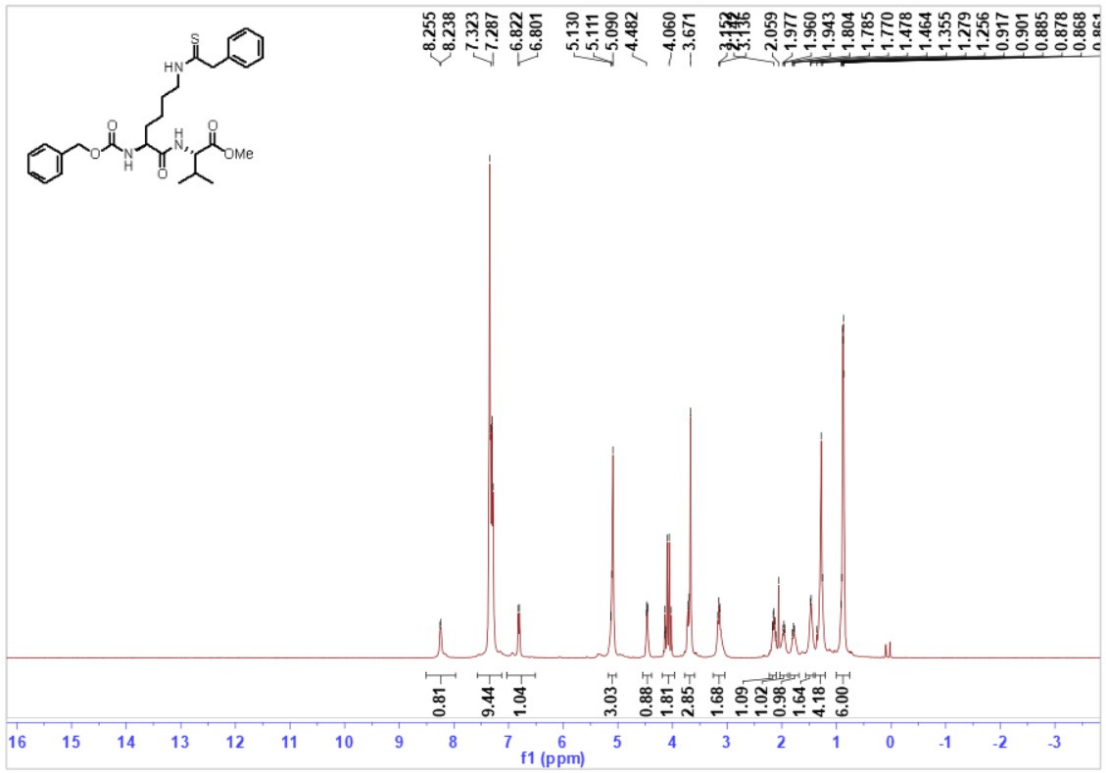


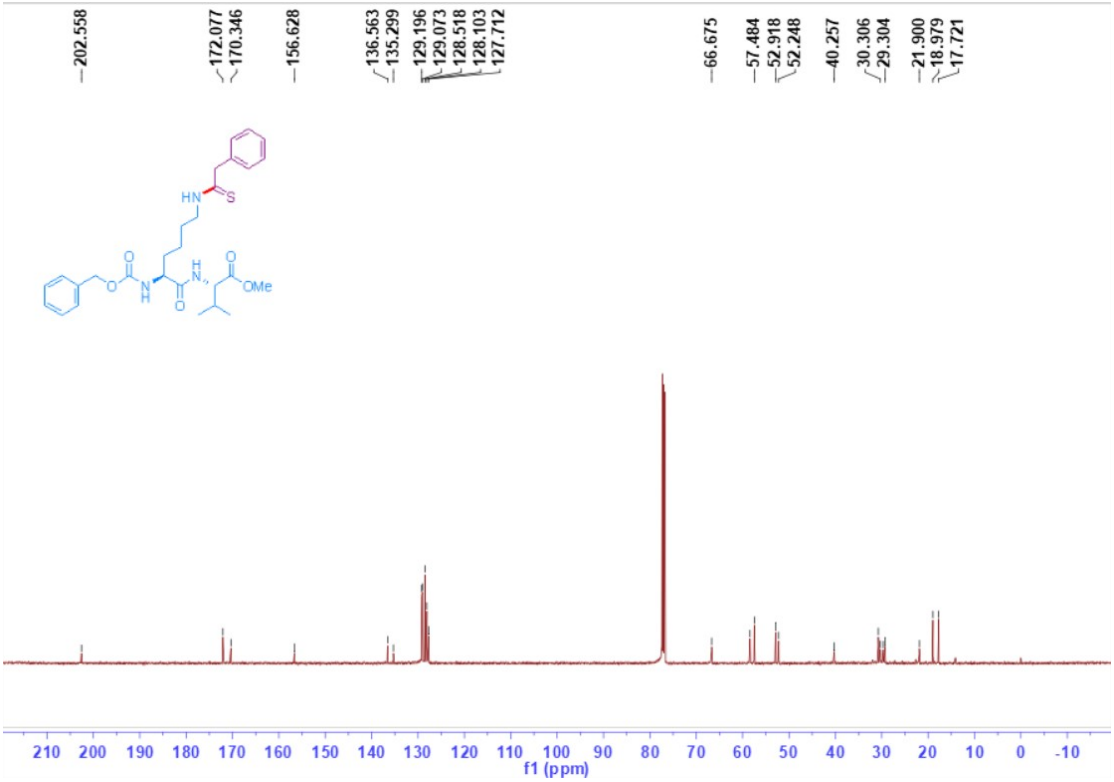

F3C
O
N
S
-61.456
-61.518
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

Ethyl-(*R*)-2''-(1-(2-phenylethanethioamido)ethyl)-[2,4':2',4''-terthiazole]-4-carboxylate (3df)

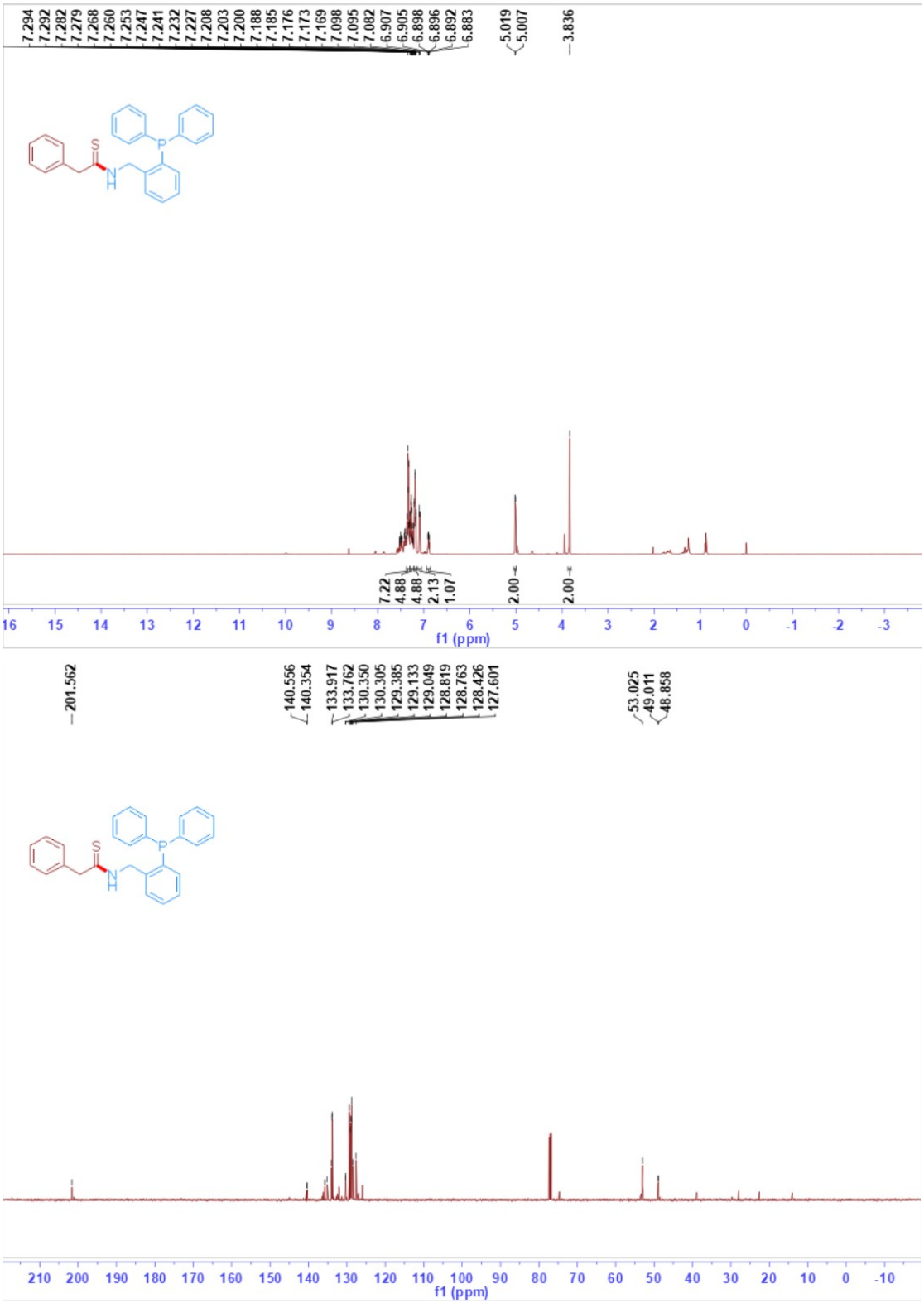


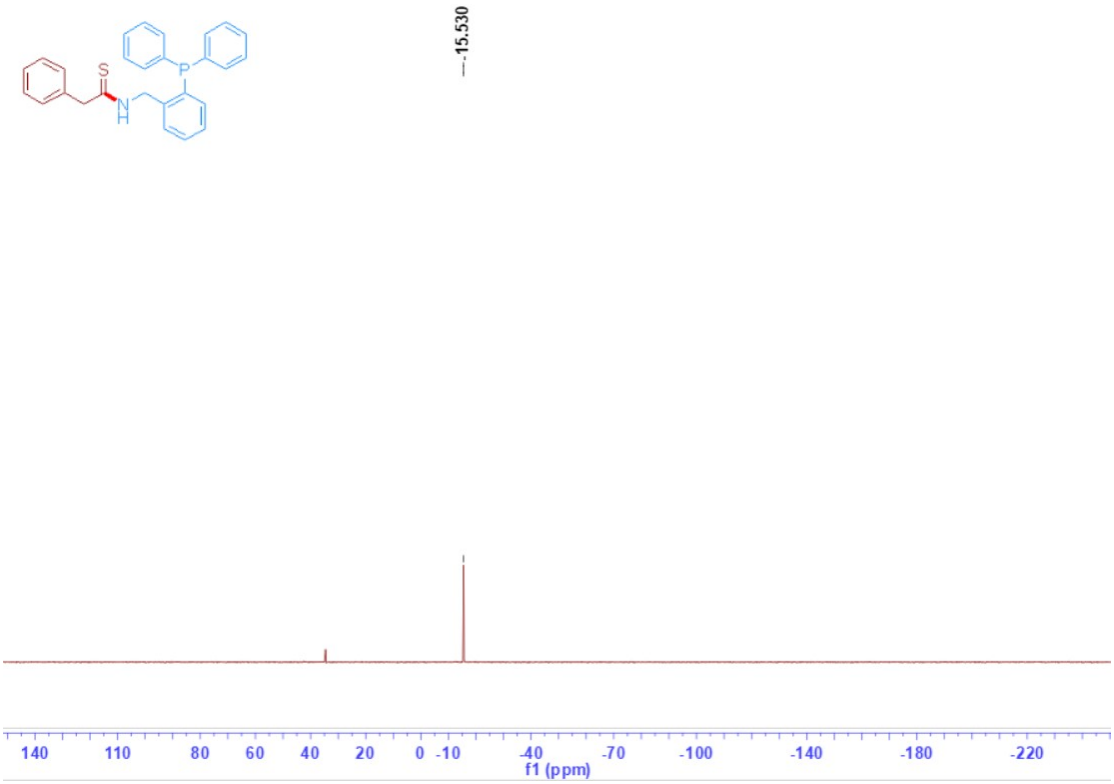
CbzHN-Lys-Val-OMe thioamide derivatives (3dg)



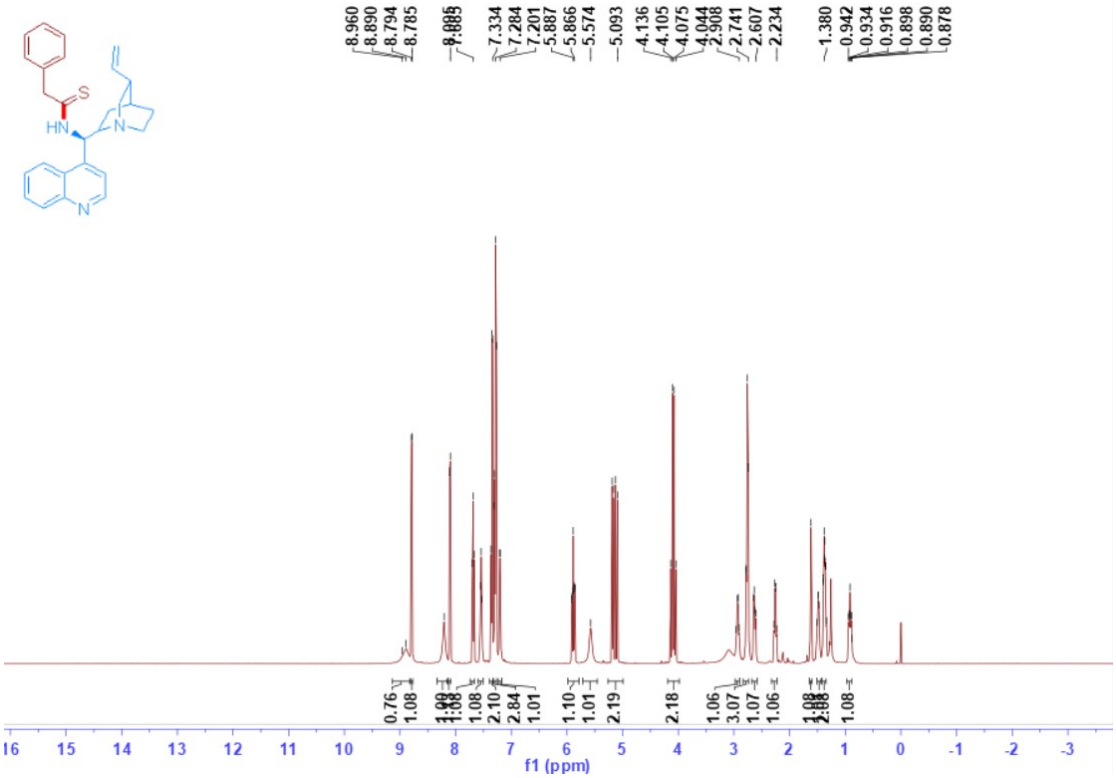


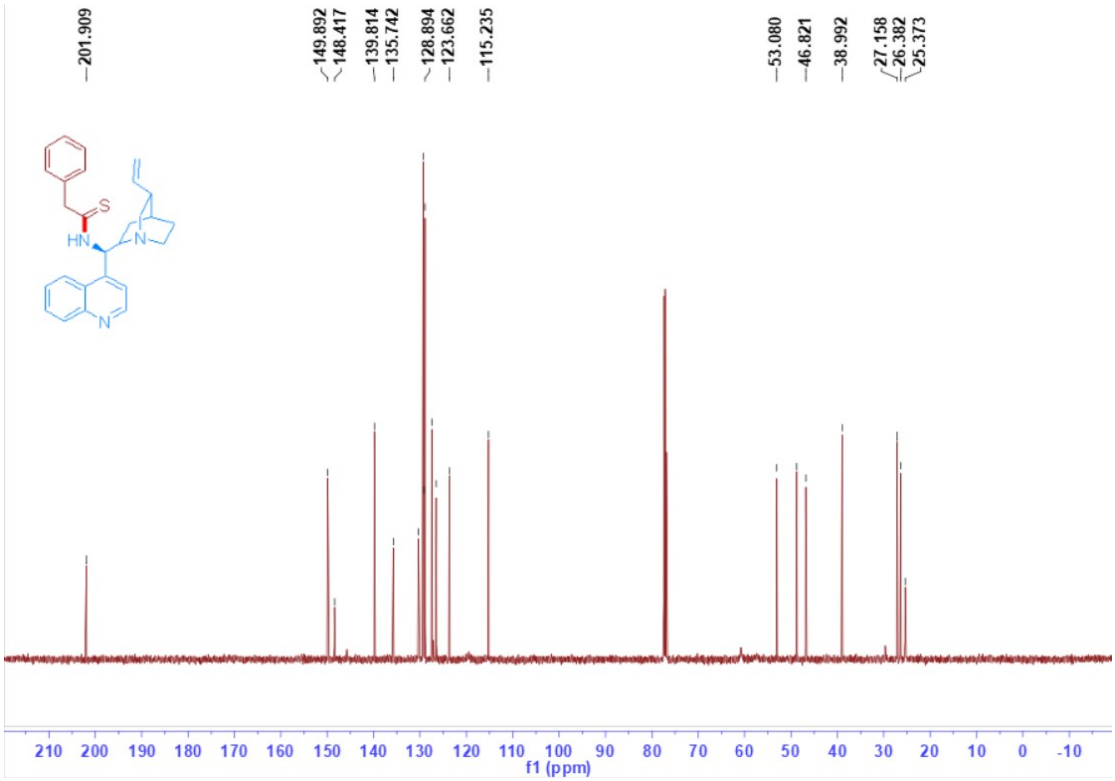
N-(2-(diphenylphosphaneyl)benzyl)-2-phenylethanethioamide (3dh)



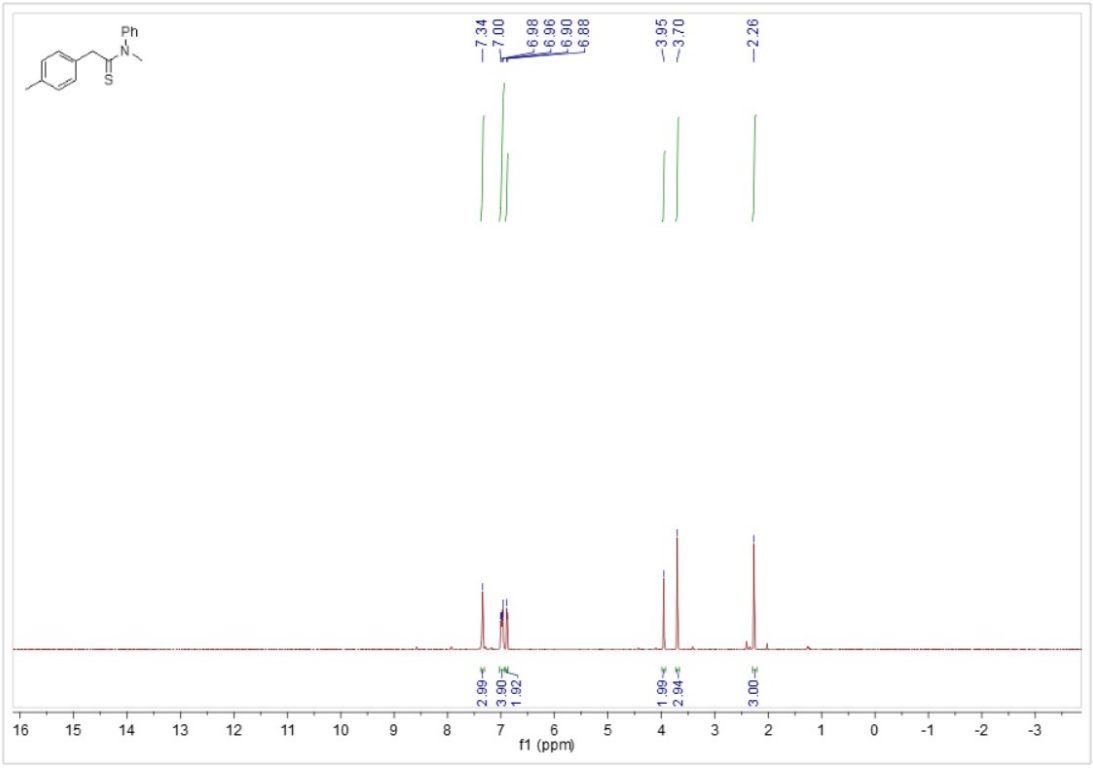

-15.530
S
P
N
H
140
110
80
60
40
20
0
-10
-40
-70
-100
-140
-180
-220
f1 (ppm)

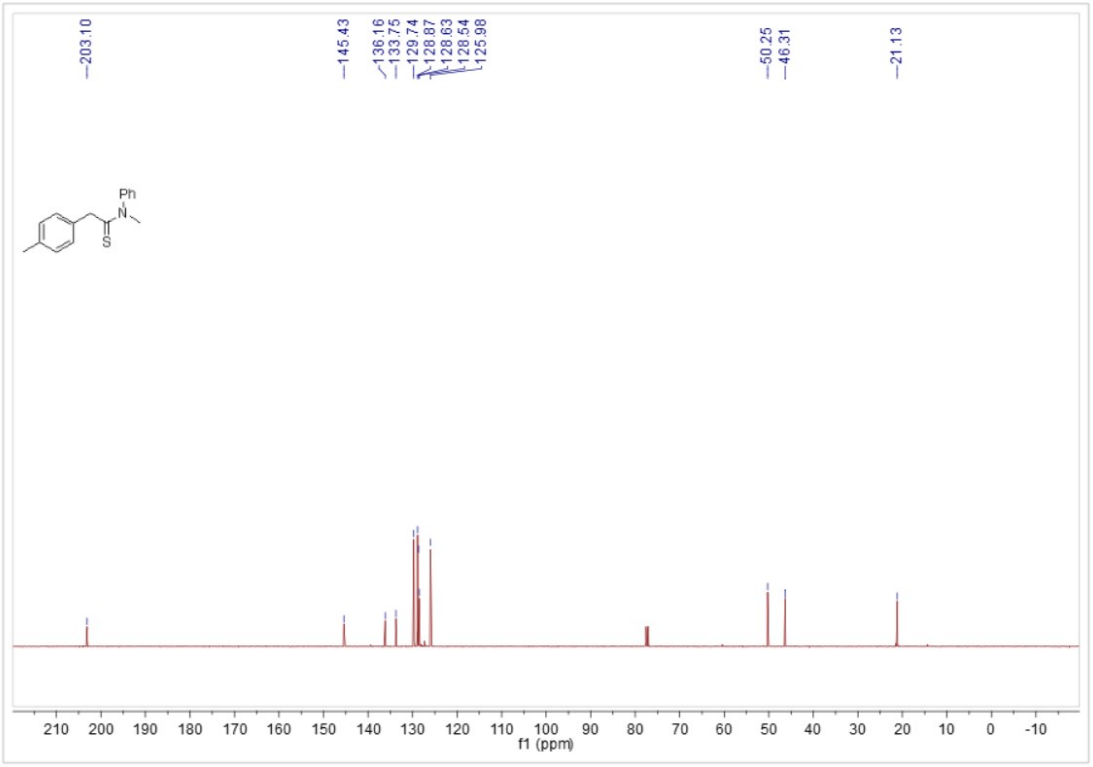
2-Phenyl-N-((*R*)-quinolin-4-yl((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ethanethioamide (3di)



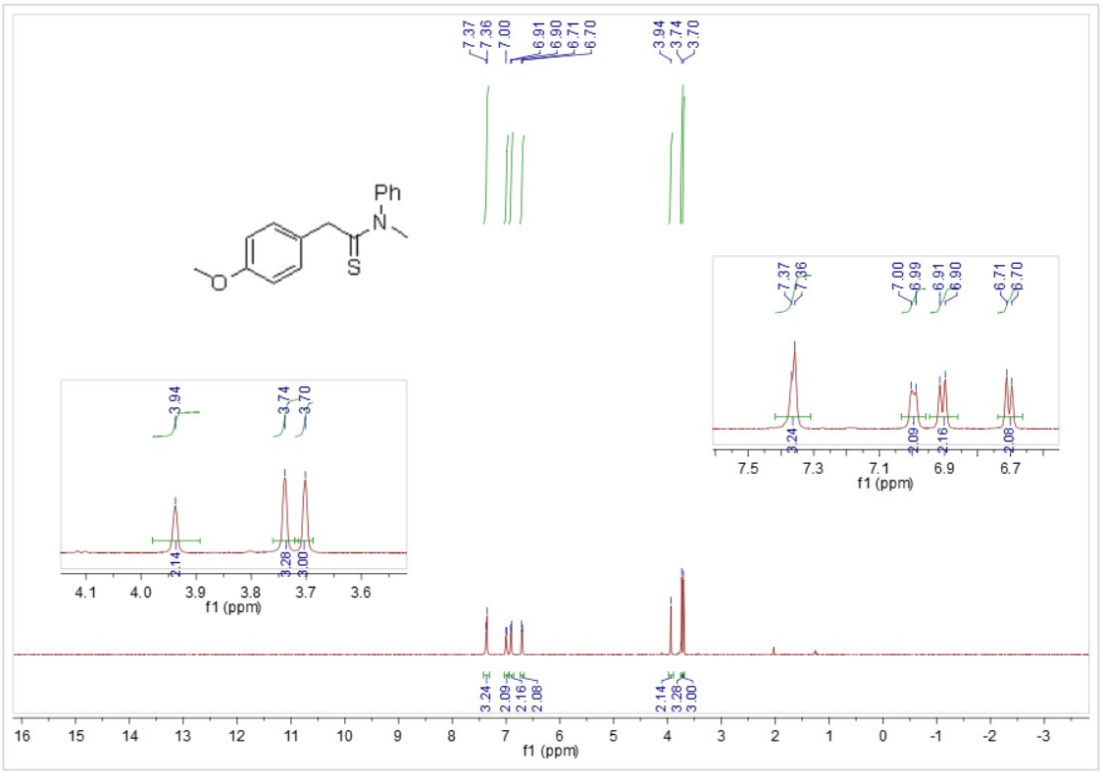


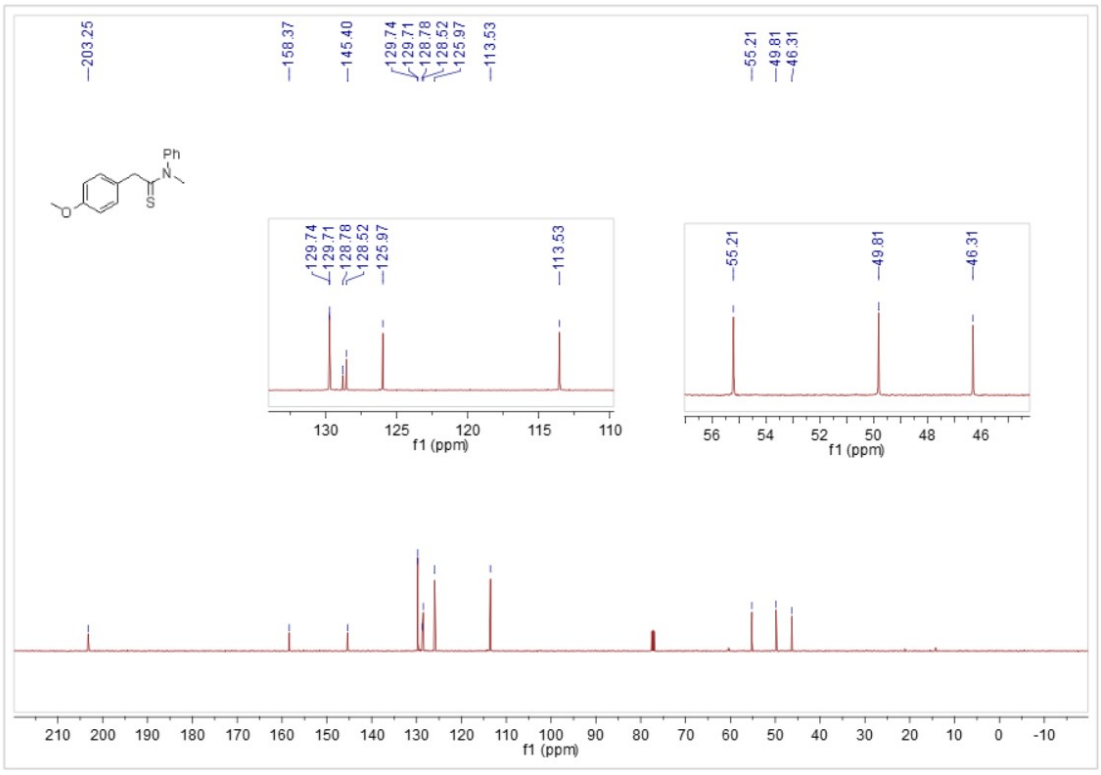
N-methyl-*N*-phenyl-2-(p-tolyl)ethanethioamide (3ea)



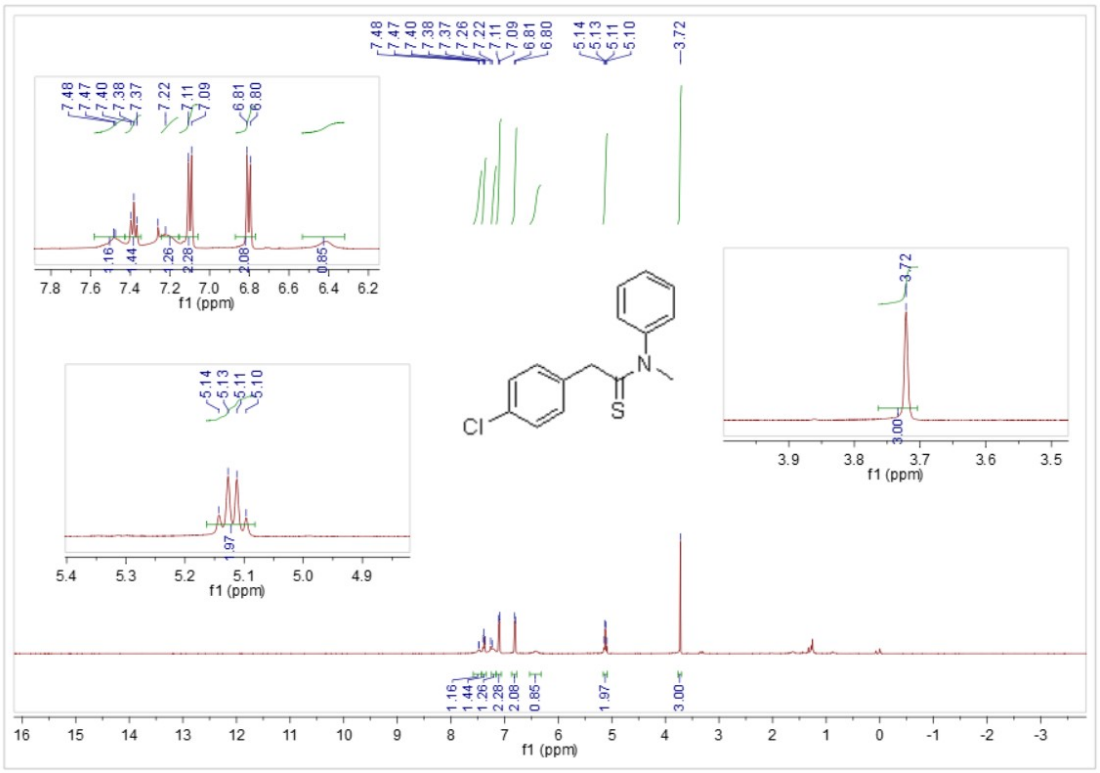


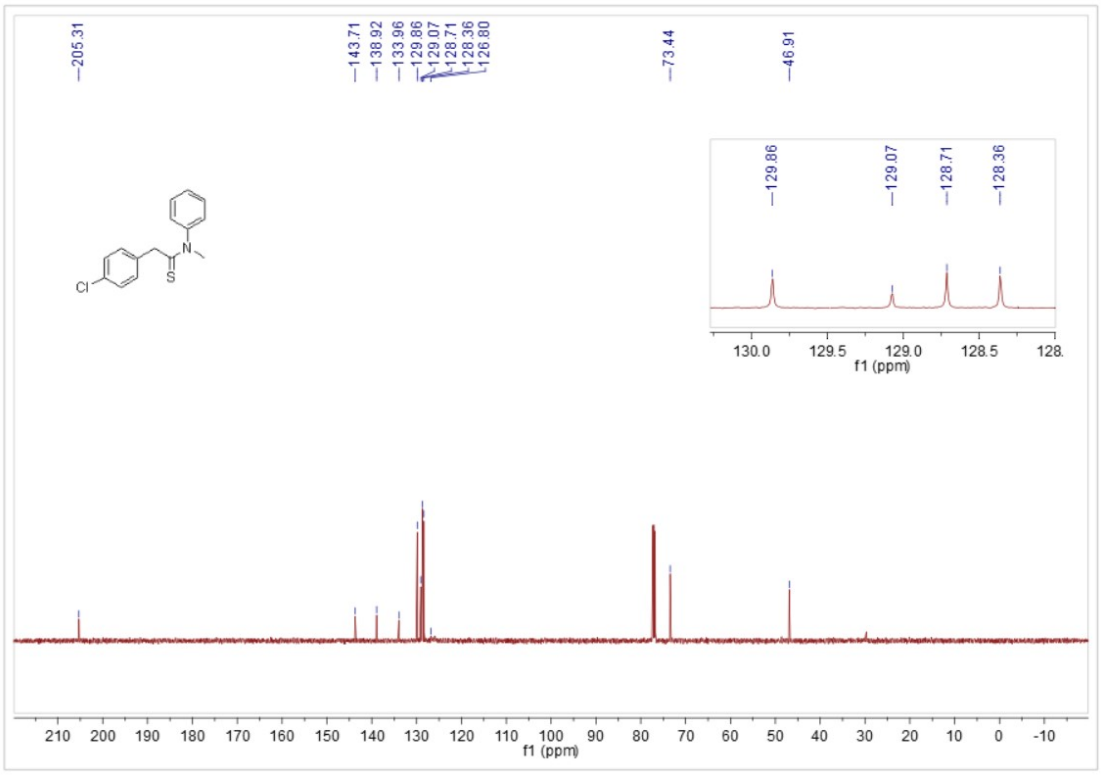
2-(4-Methoxyphenyl)-*N*-methyl-*N*-phenylethanethioamide (3eb)



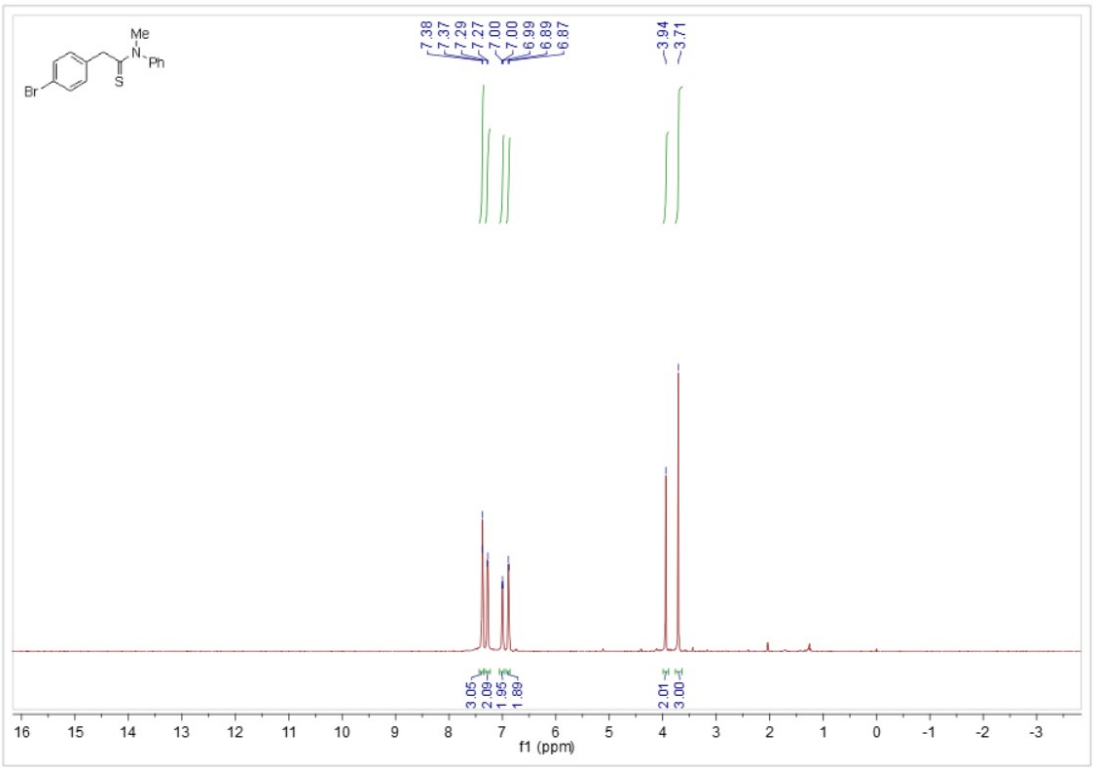


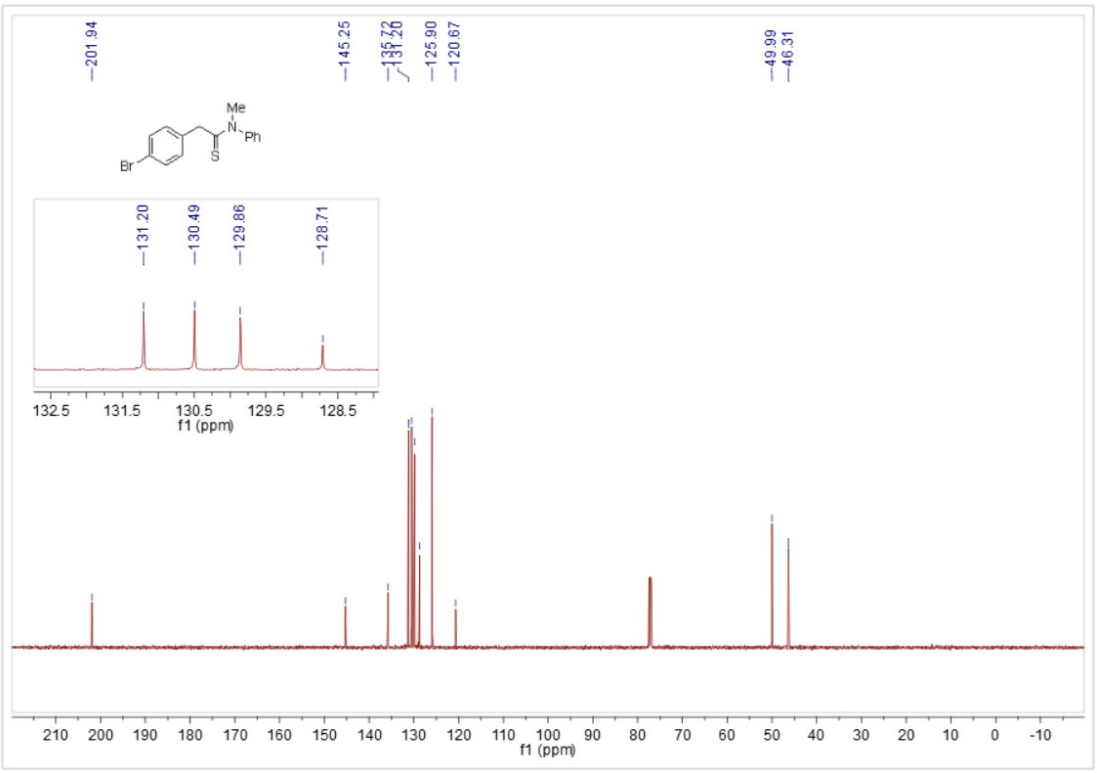
2-(4-Chlorophenyl)-*N*-methyl-*N*-phenylethanethioamide (3ec)



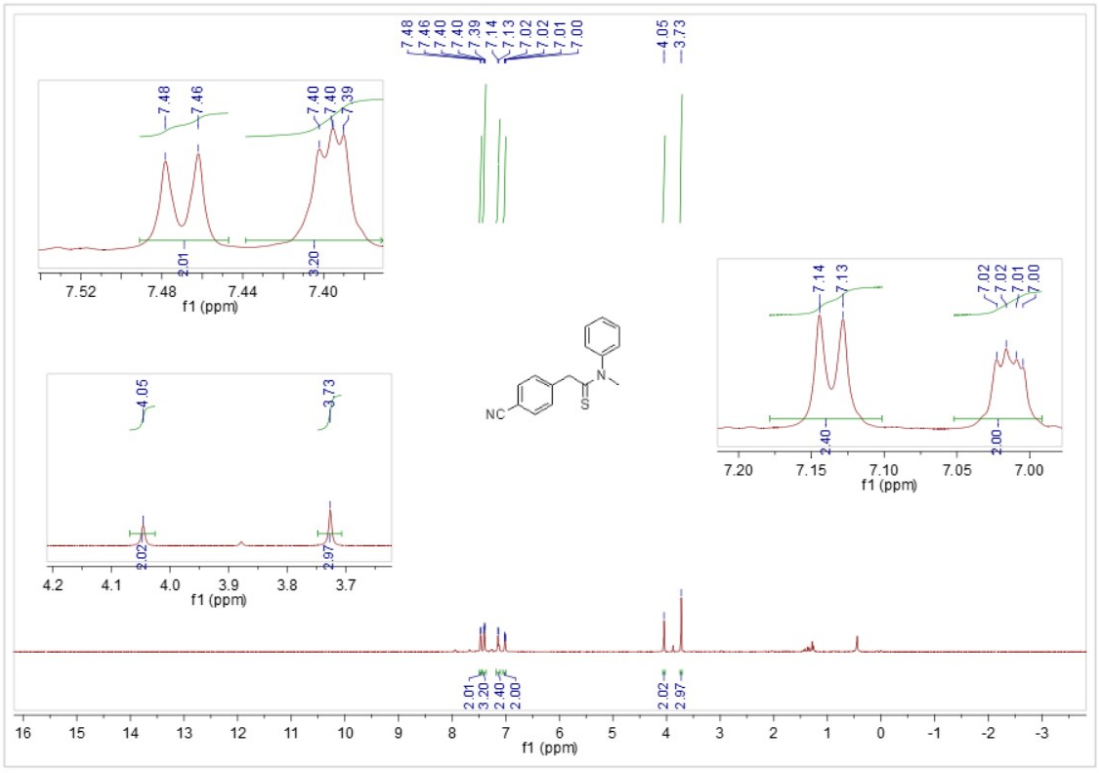


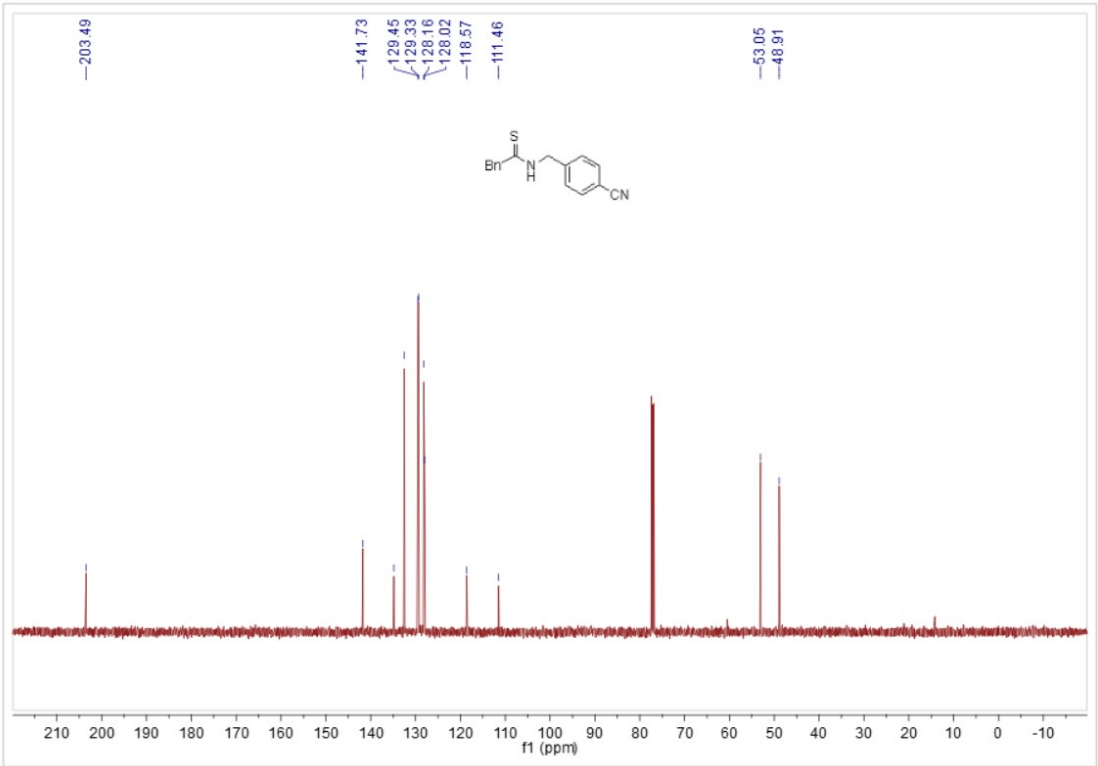
2-(4-Bromophenyl)-*N*-methyl-*N*-phenylethanethioamide (3ed)



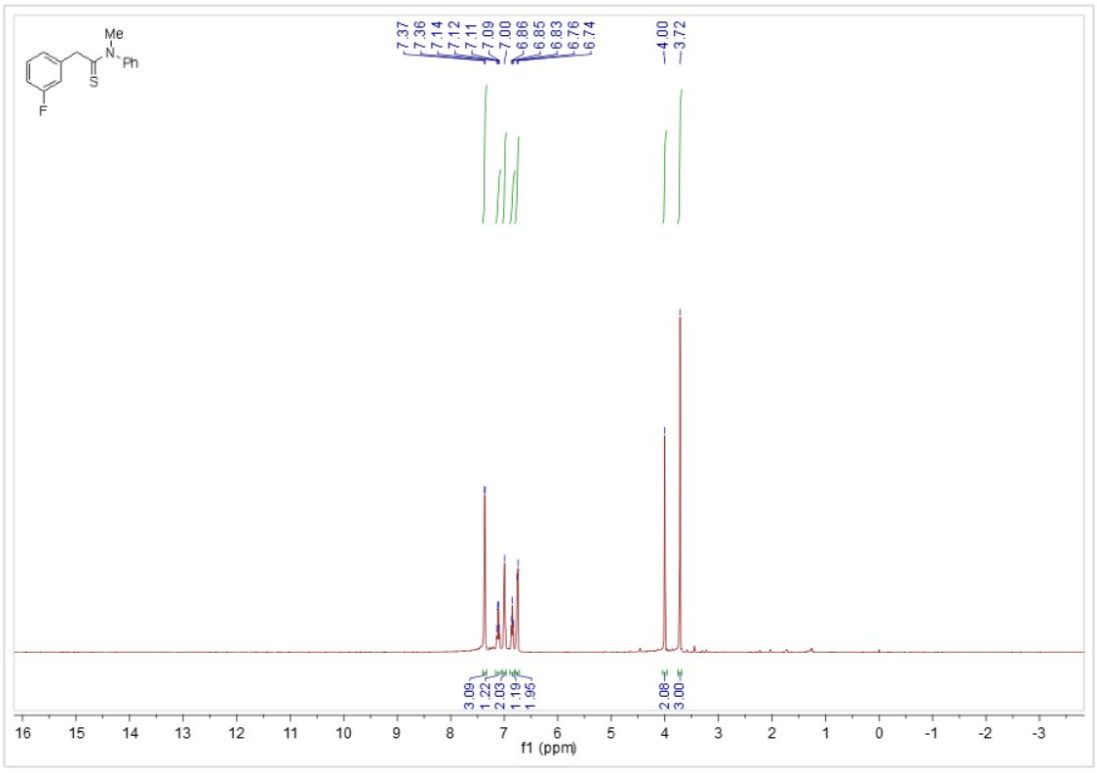


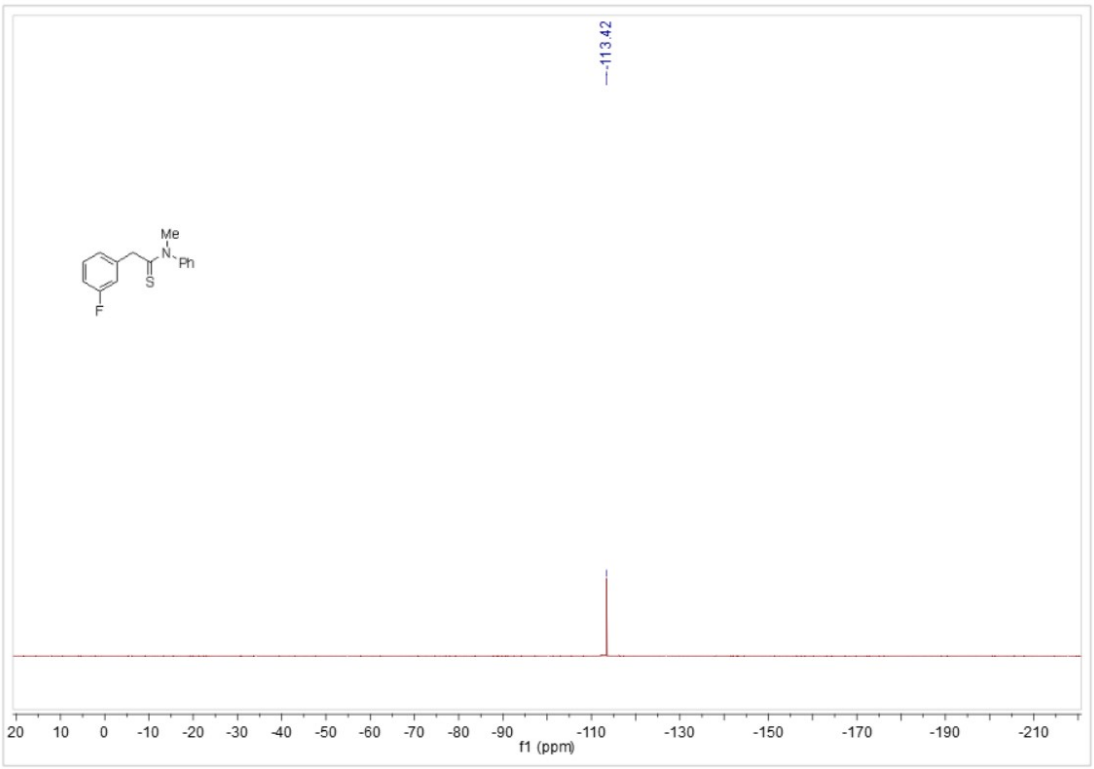
2-(4-Cyanophenyl)-*N*-methyl-*N*-phenylethanethioamide (3ee)

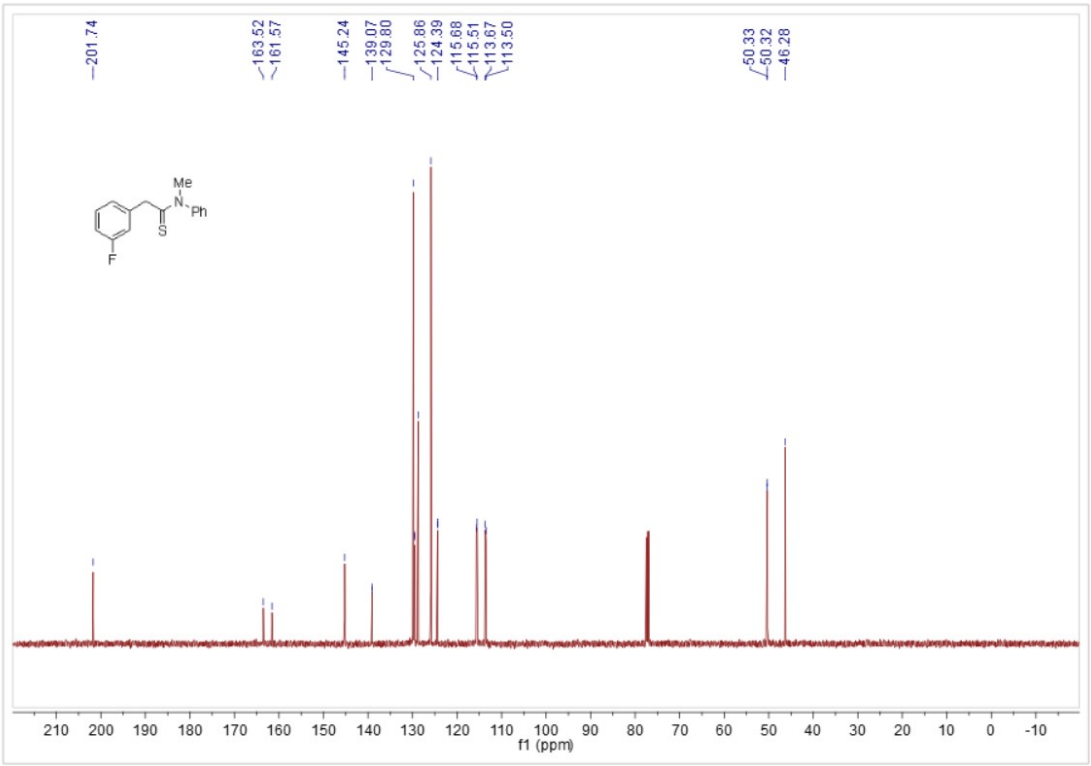




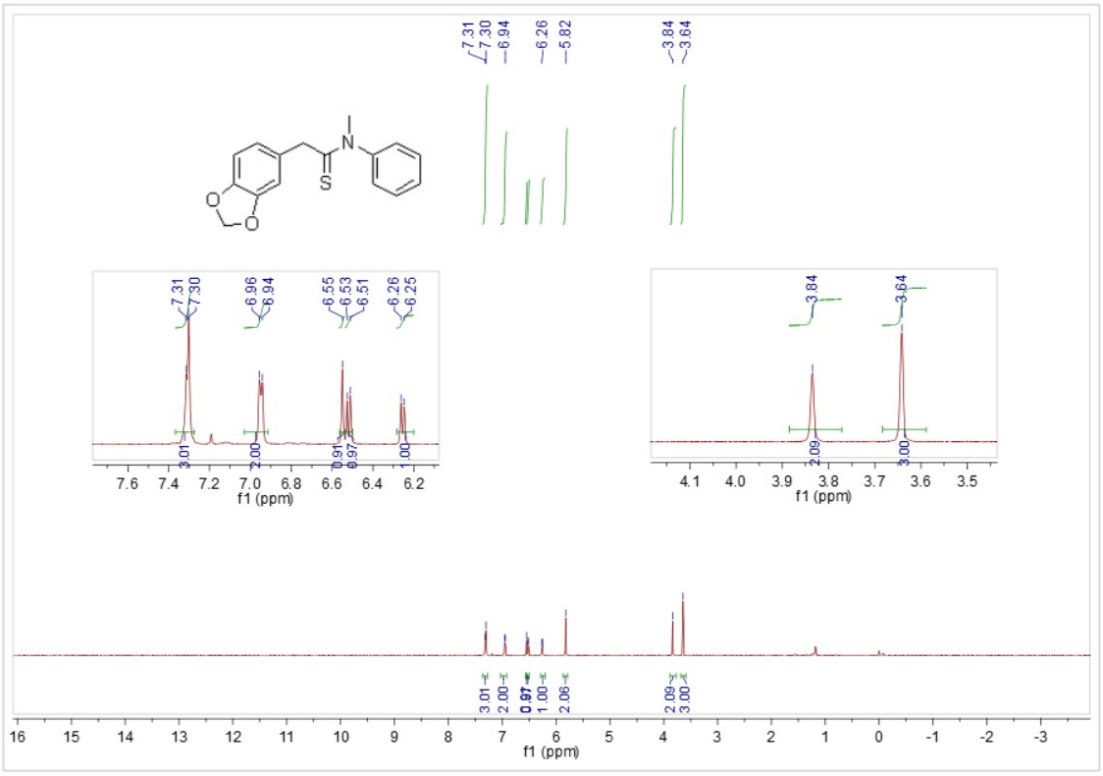
2-(3-Fluorophenyl)-*N*-methyl-*N*-phenylethanethioamide (3ef)

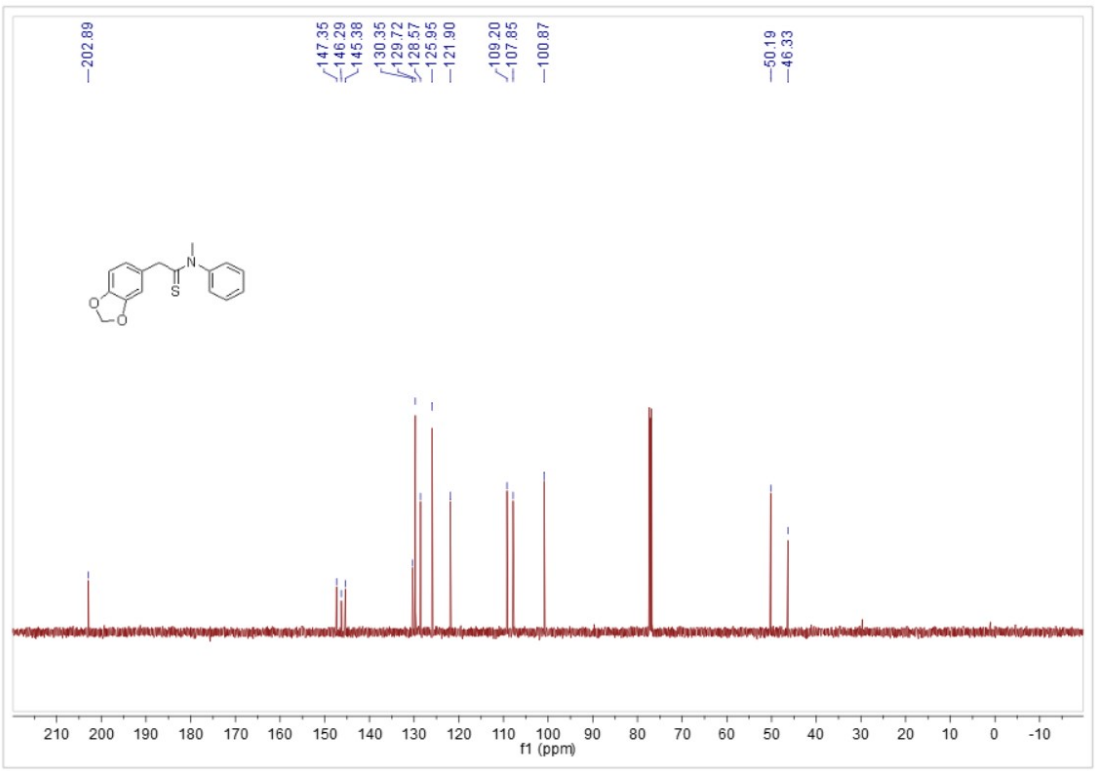




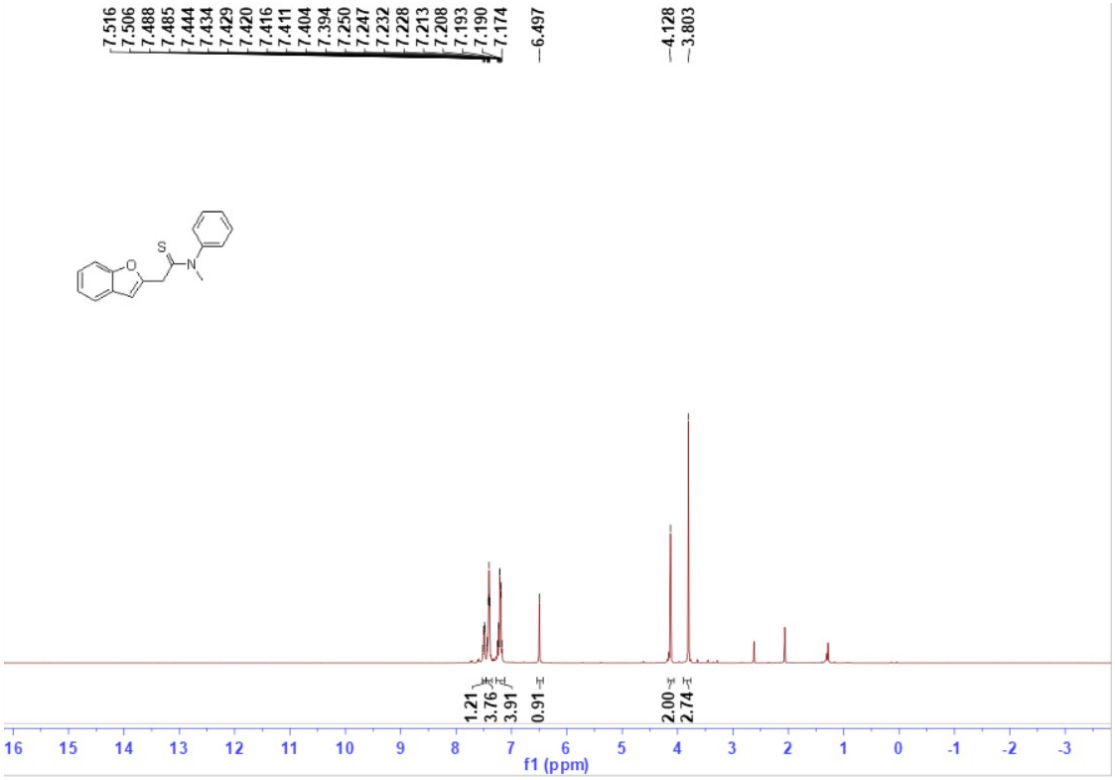

201.74
163.52
161.57
145.24
139.07
129.80
125.86
124.39
115.68
115.51
113.67
113.50
50.33
50.32
46.28
Me
N
Ph
S
F
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

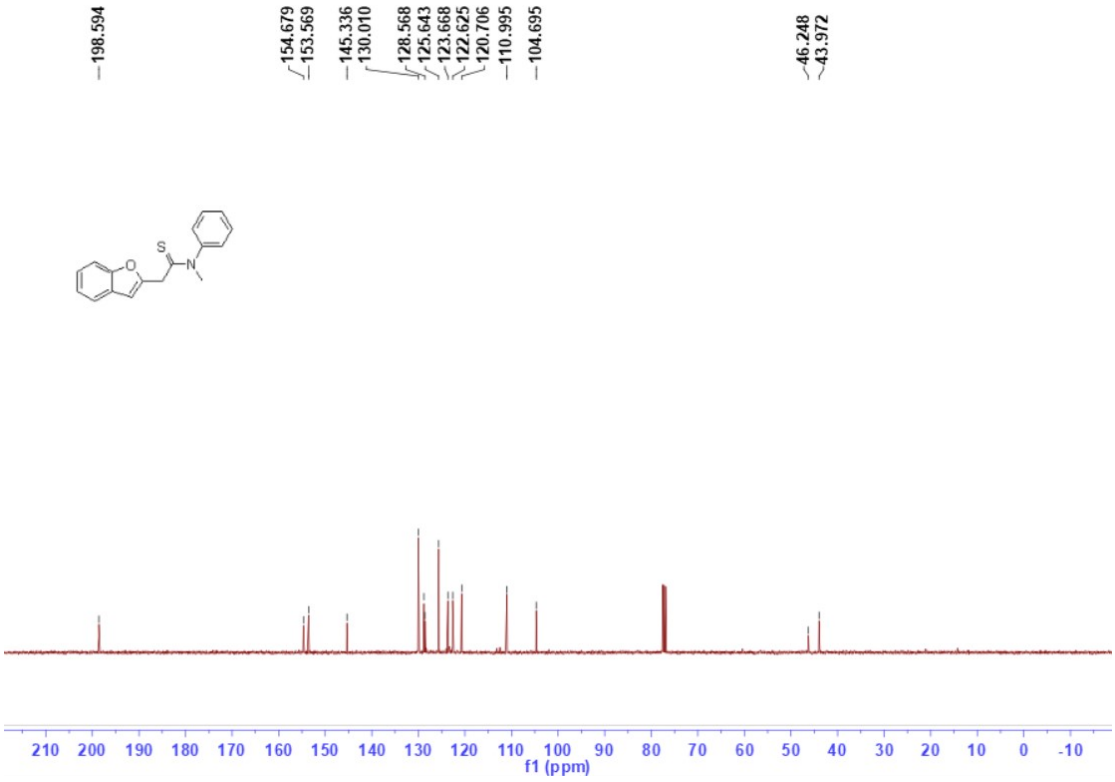
2-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-methyl-*N*-phenylethanethioamide (3eg)



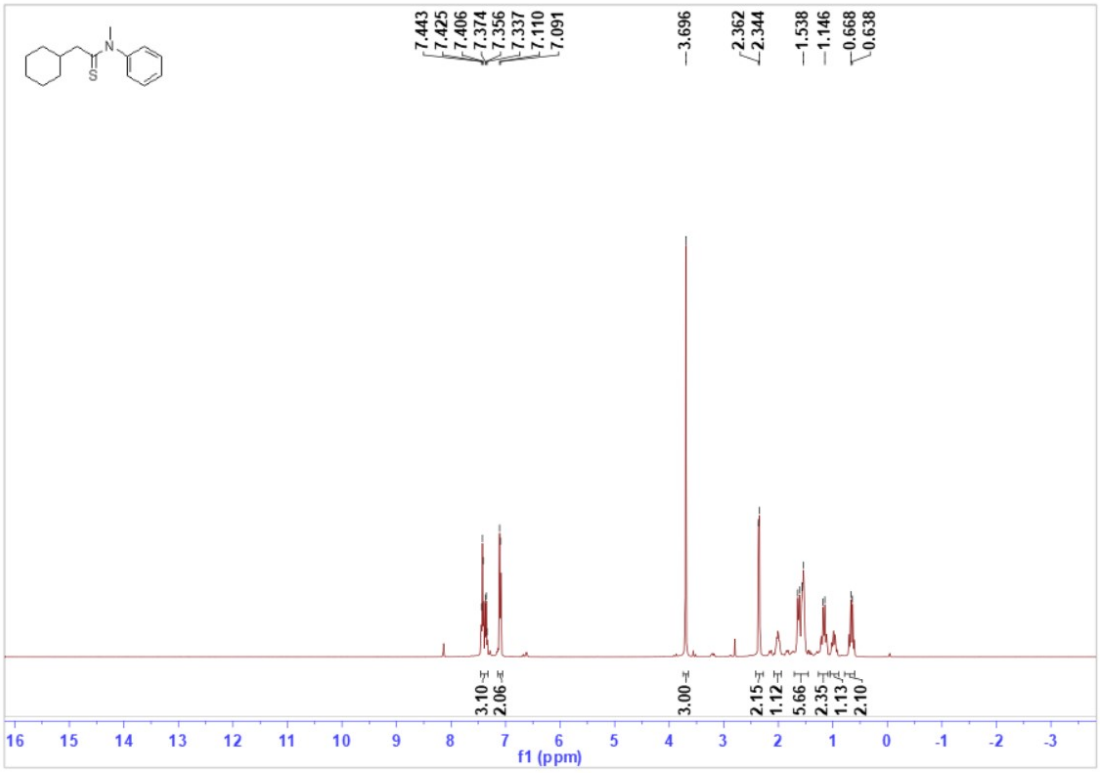


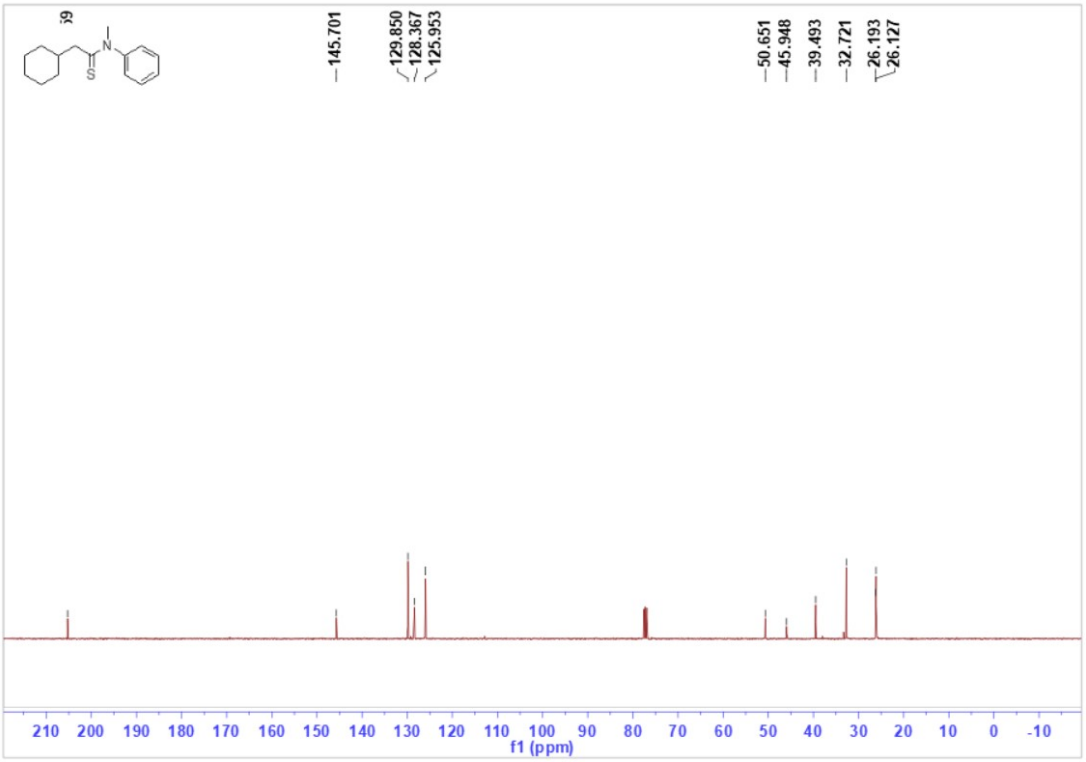
1-(Benzofuran-2-yl)-*N*-methyl-*N*-phenylethanethioamide (3eh)



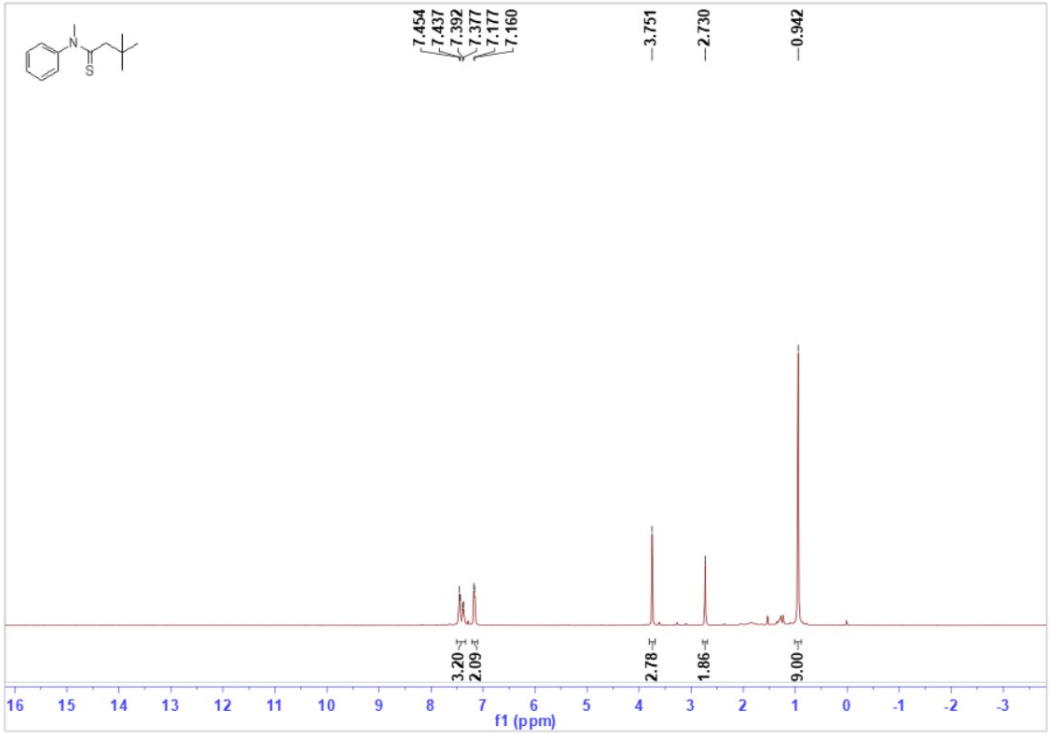


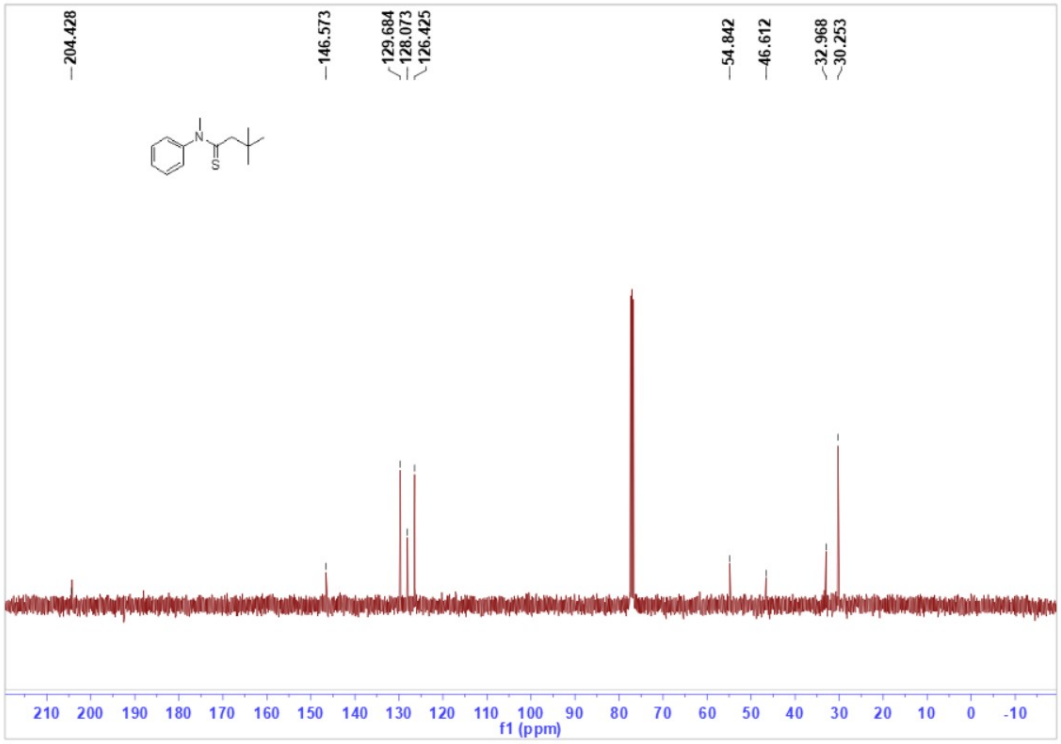
Cyclohexyl-*N*-methyl-*N*-phenylethanethioamide (3ei)



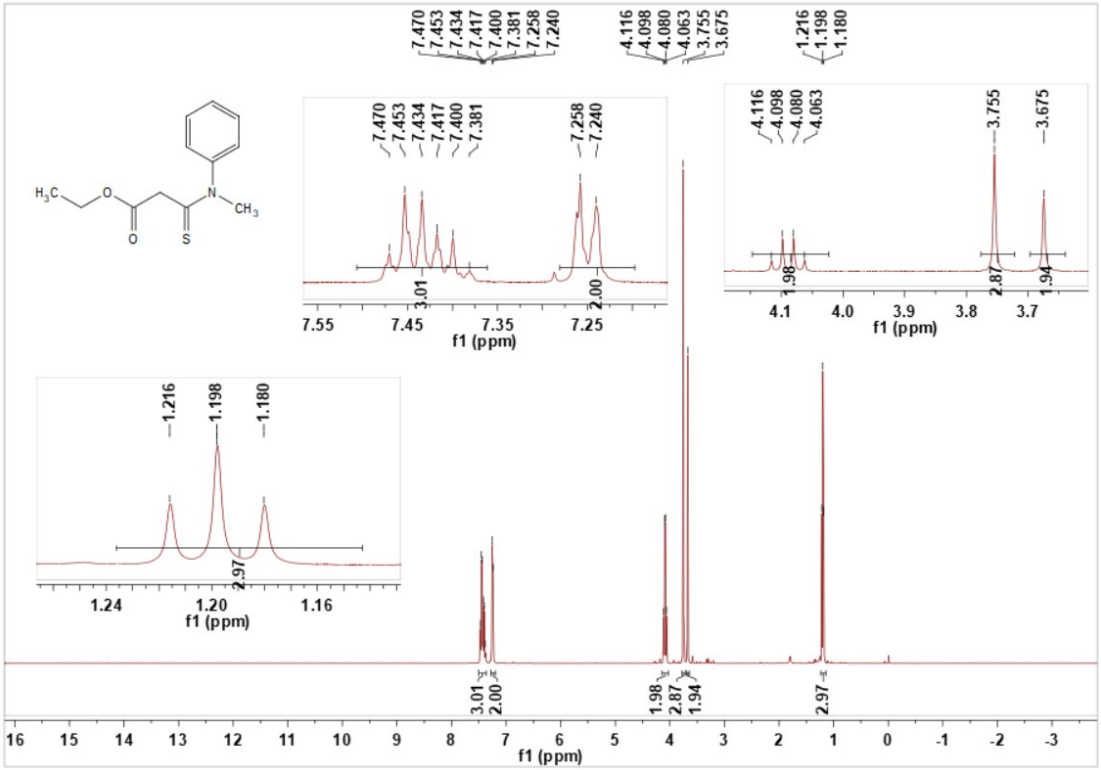


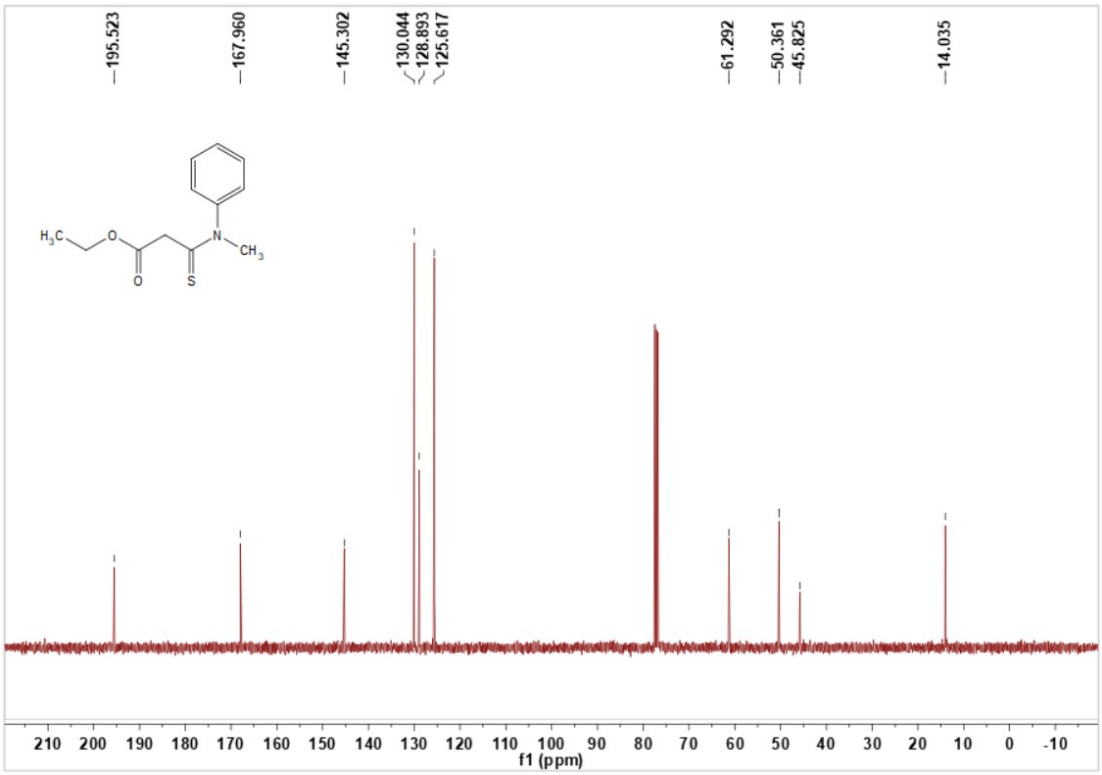
N,3,3-trimethyl-*N*-phenylbutanethioamide (3ej)



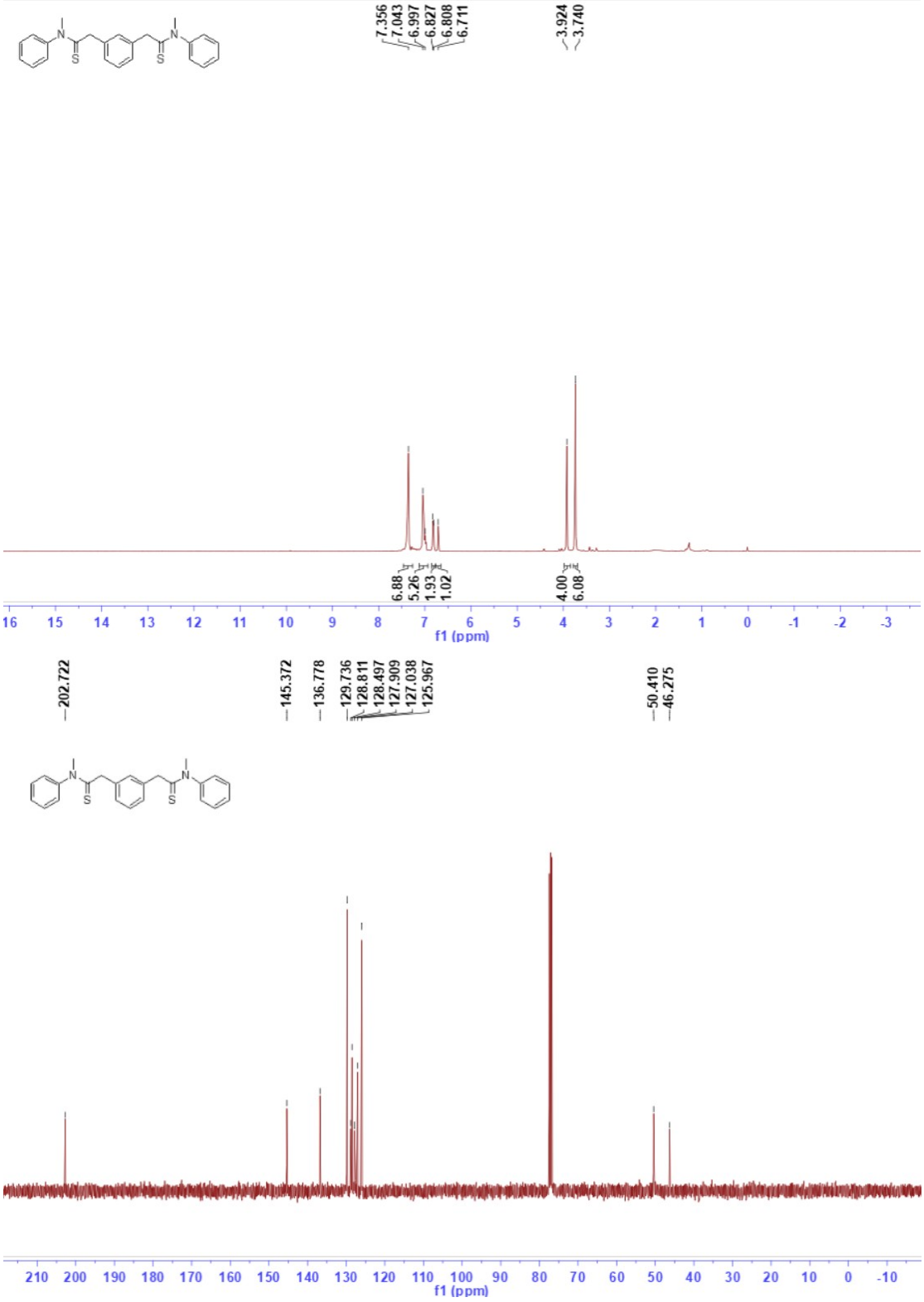


Ethyl 3-(methyl(phenyl)amino)-3-thioxopropanoate (3ek)

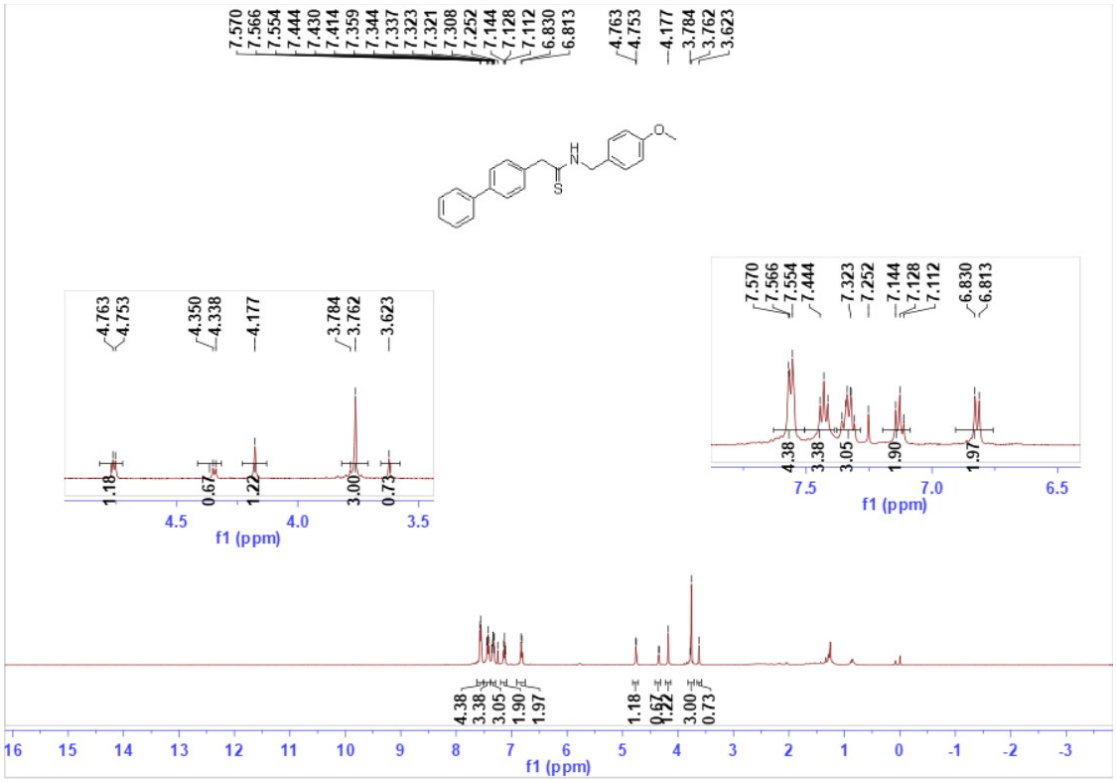


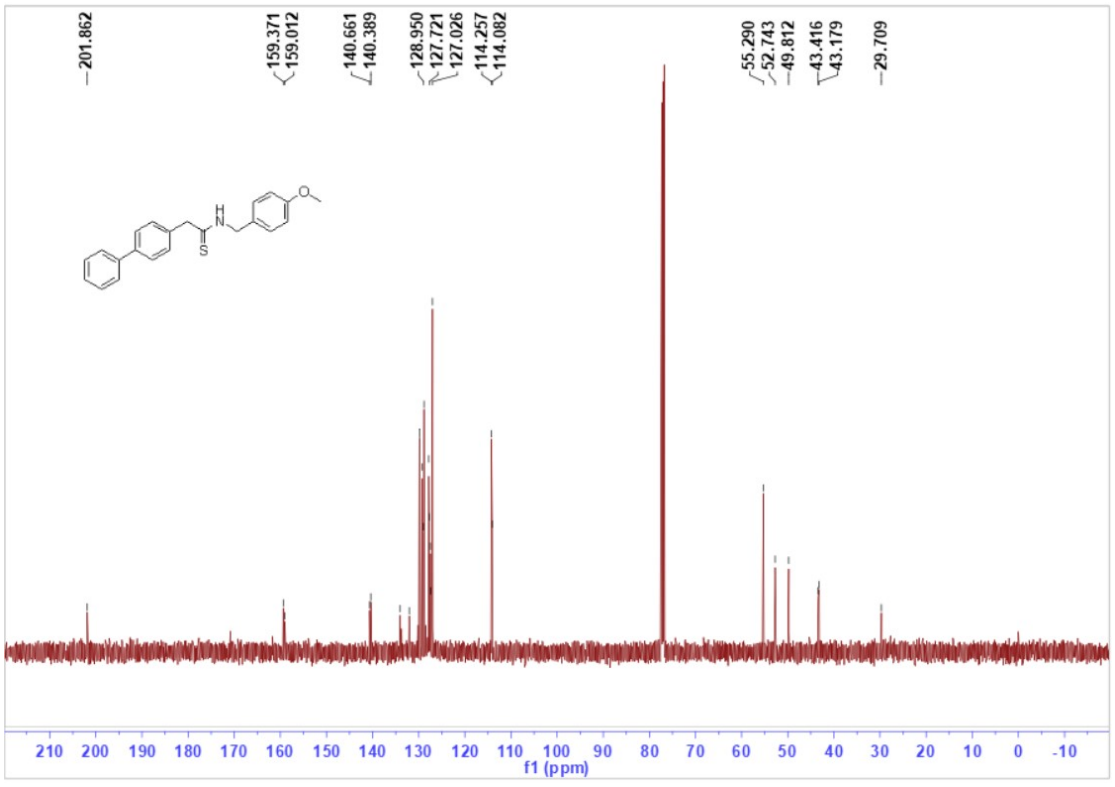


2,2'-(1,3-Phenylene)bis(*N*-methyl-*N*-phenylethanethioamide) (3el)

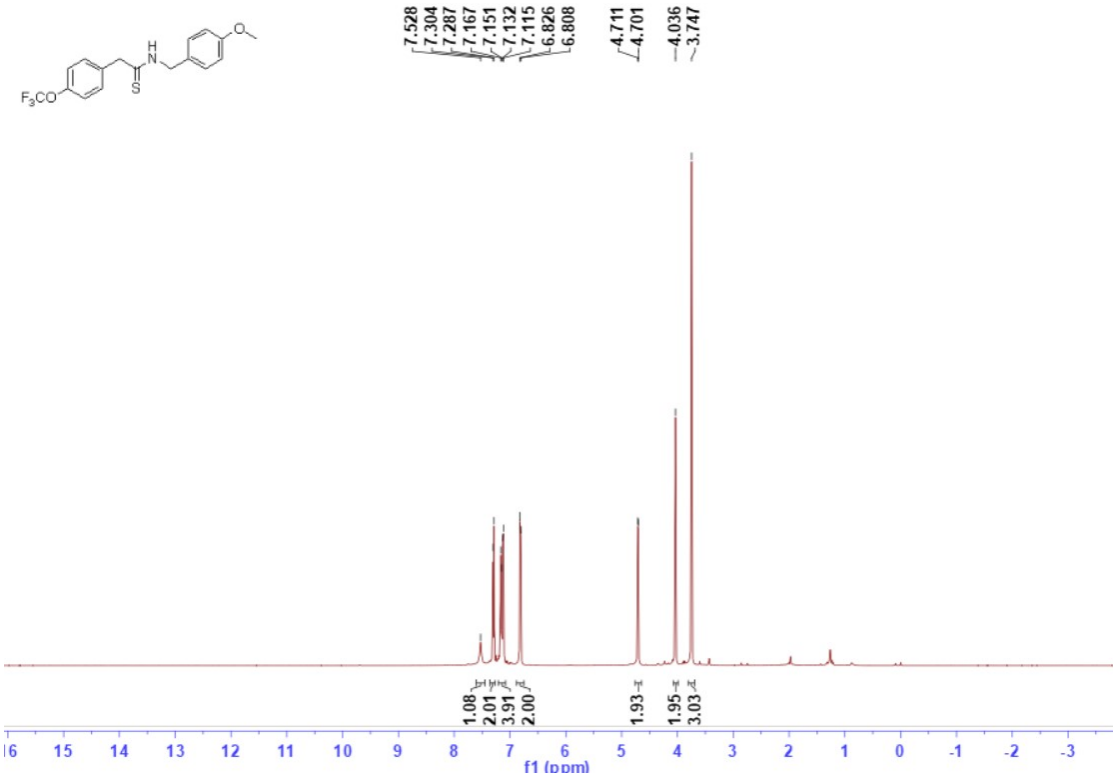


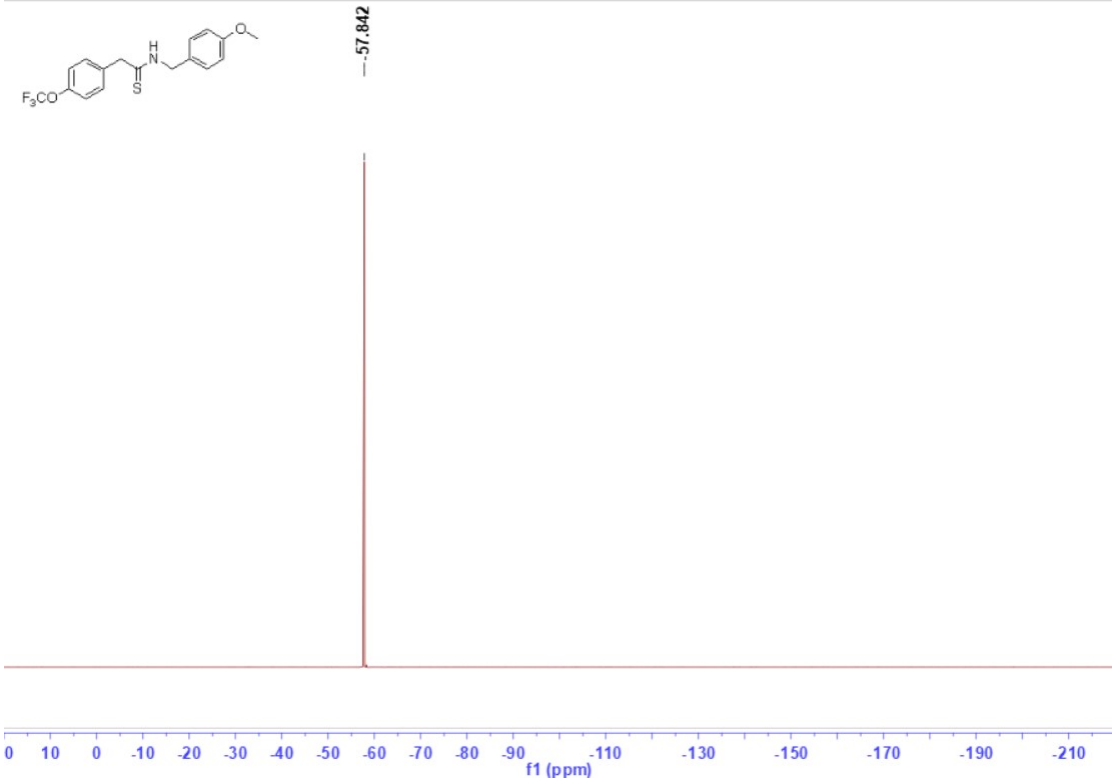
2-([1,1'-Biphenyl]-4-yl)-*N*-(4-methoxybenzyl)ethanethioamide (3em)

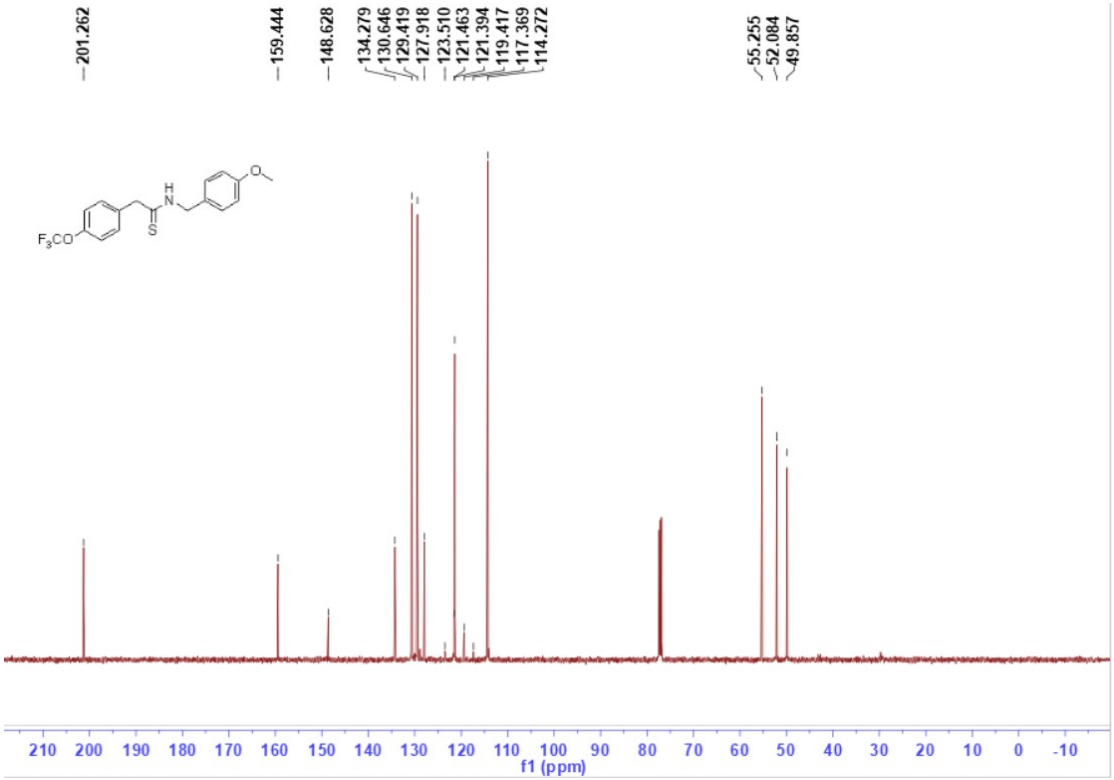




N-(4-methoxybenzyl)-2-(4-(trifluoromethoxy)phenyl)ethanethioamide (3en)



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123.510
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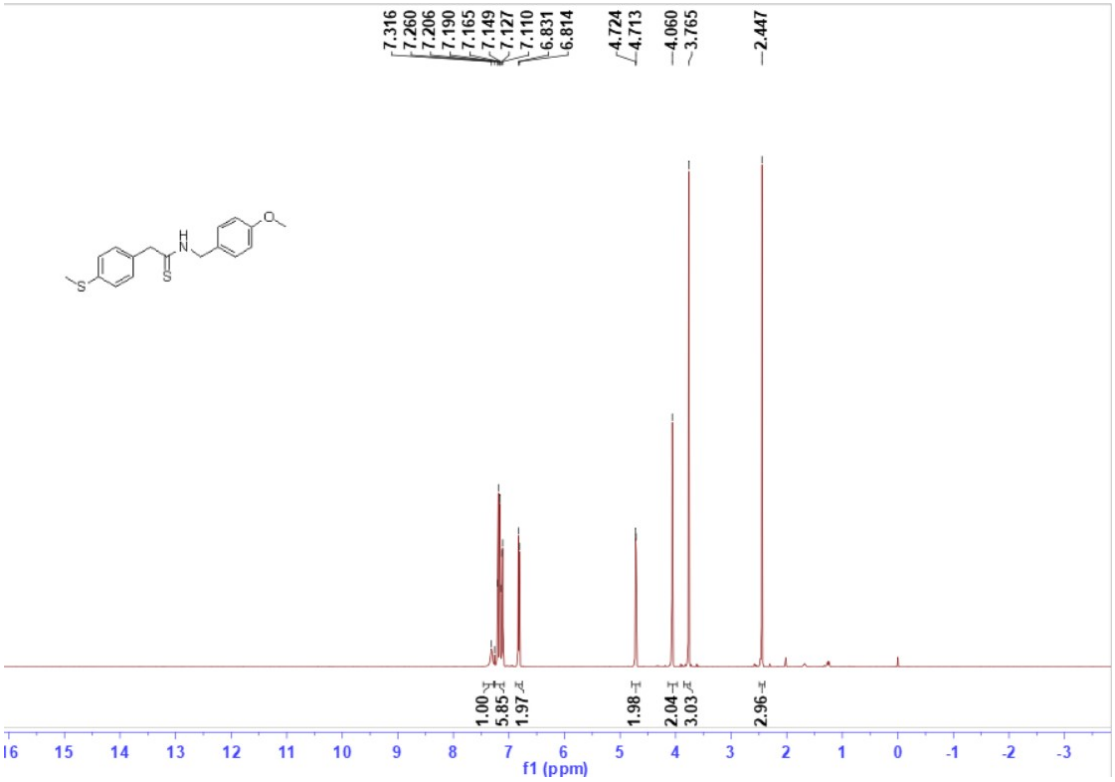
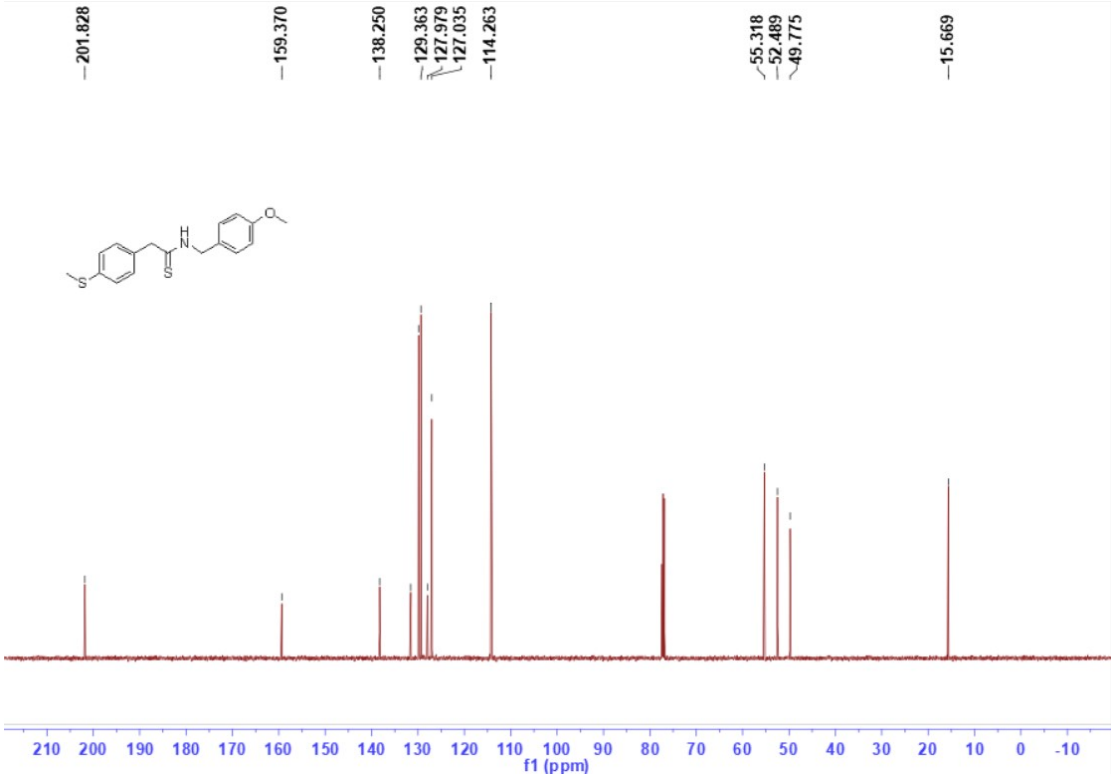
117.369
114.272
55.255
52.084
49.857
F3CO
H
N
S
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

N-(4-methoxybenzyl)-2-(4-(methylthio)phenyl)ethanethioamide (3eo)





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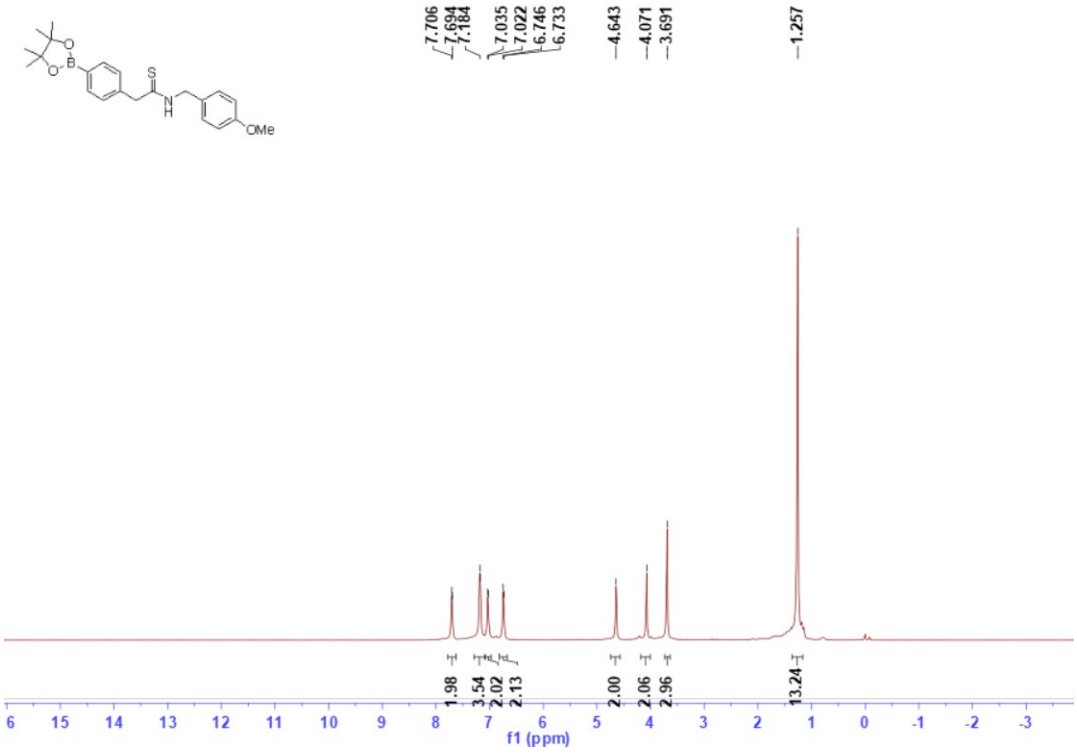
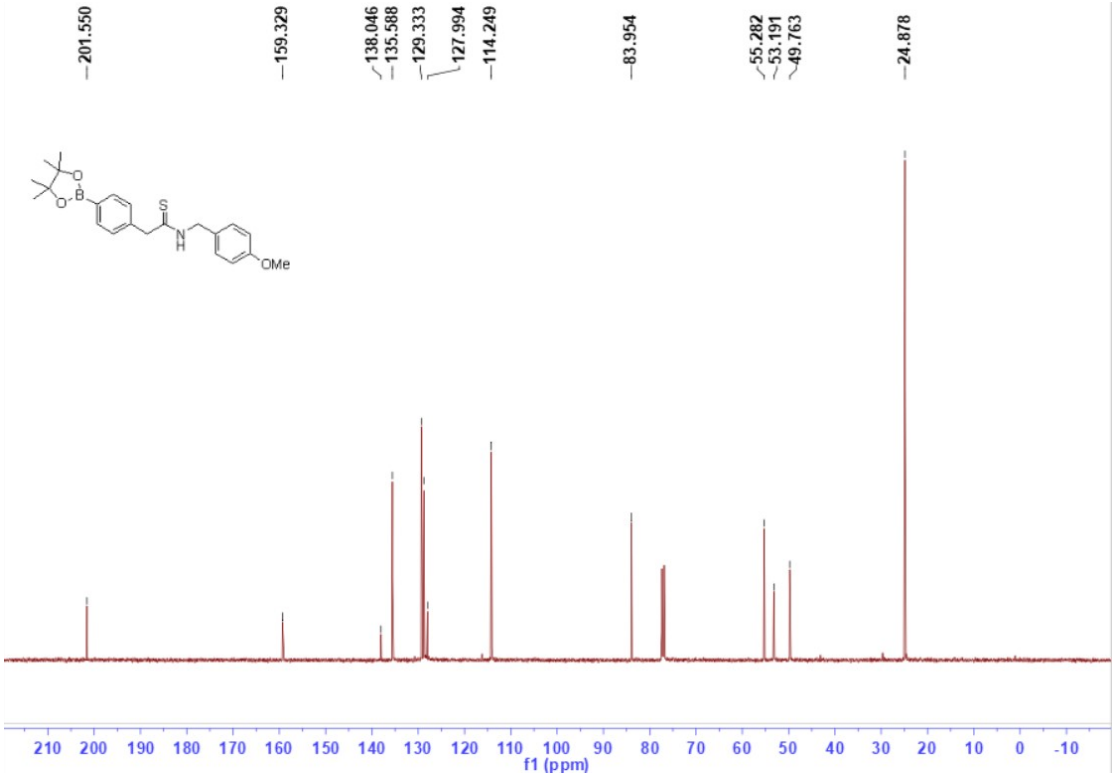
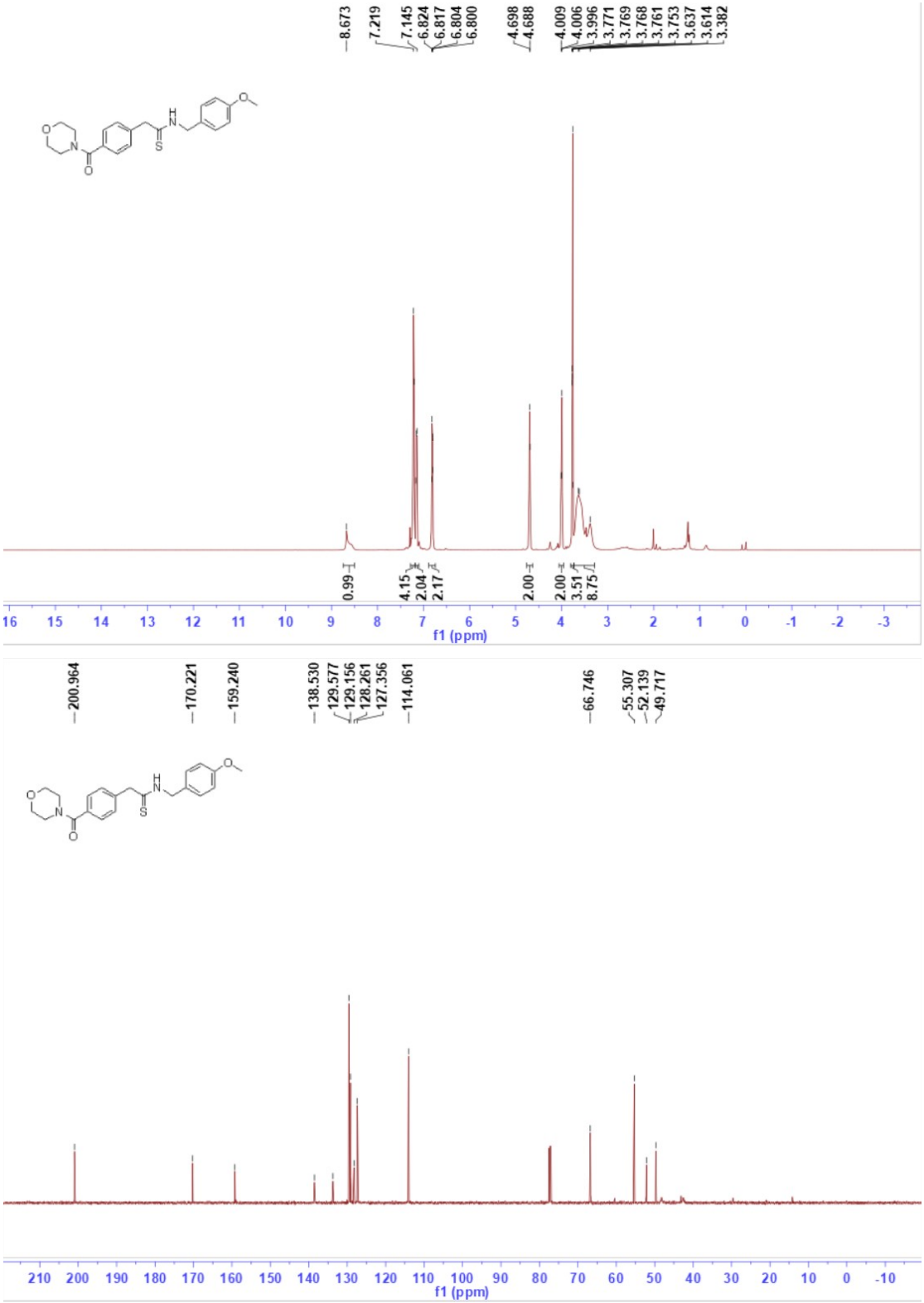




N-(4-methoxybenzyl)-2-(4-(morpholine-4-carbonyl)phenyl)ethanethioamide (3eq)



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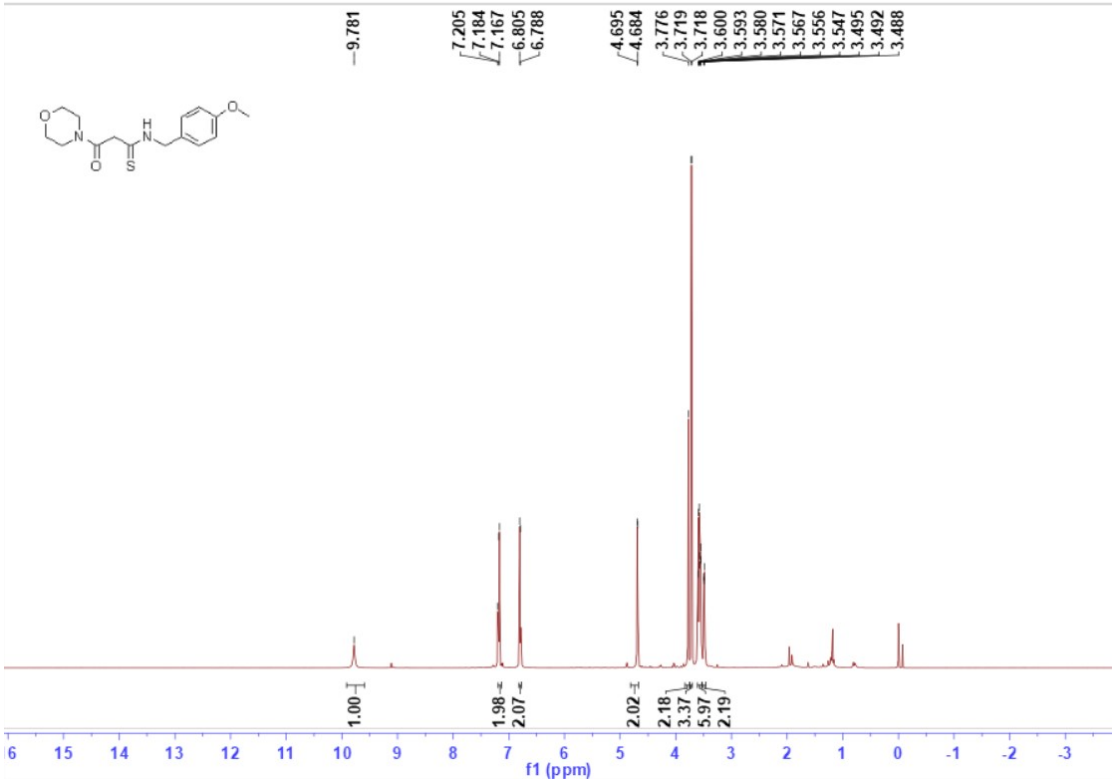
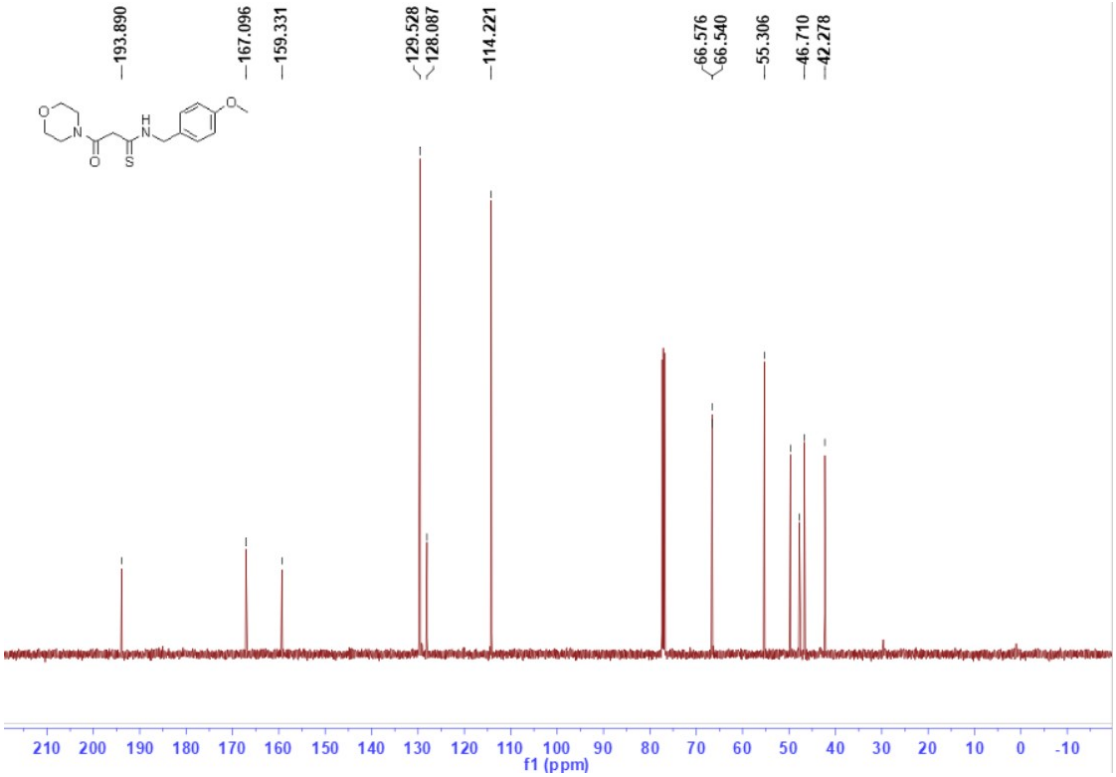
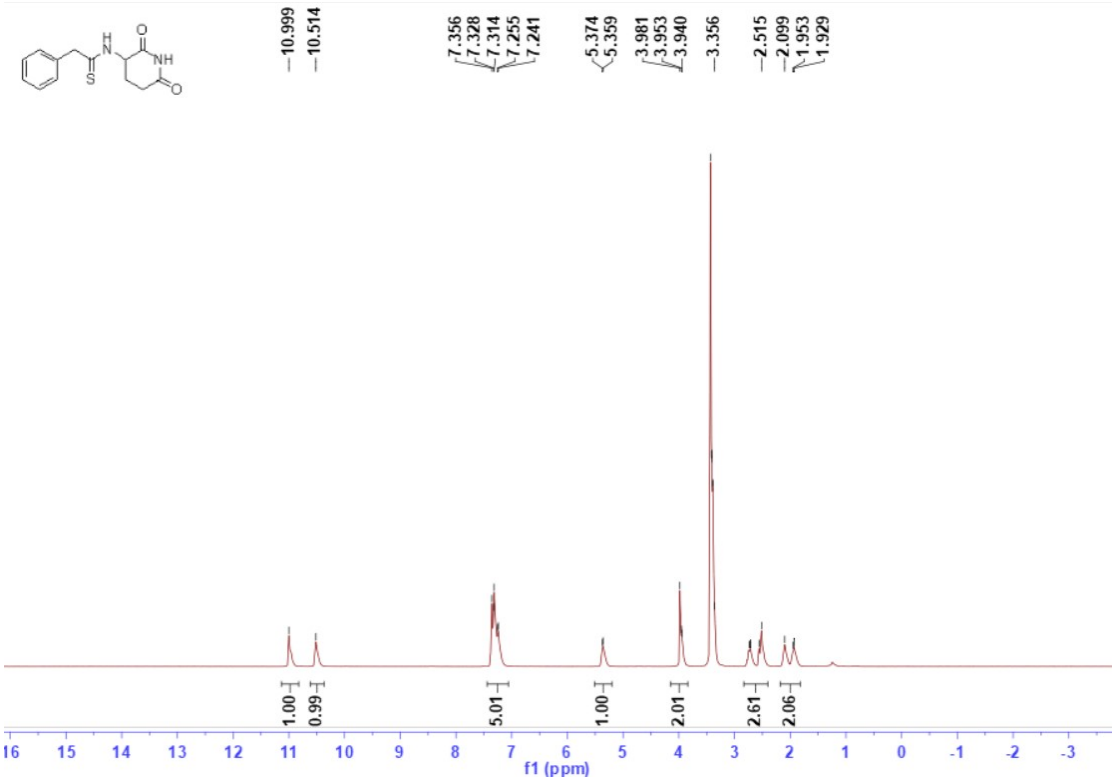
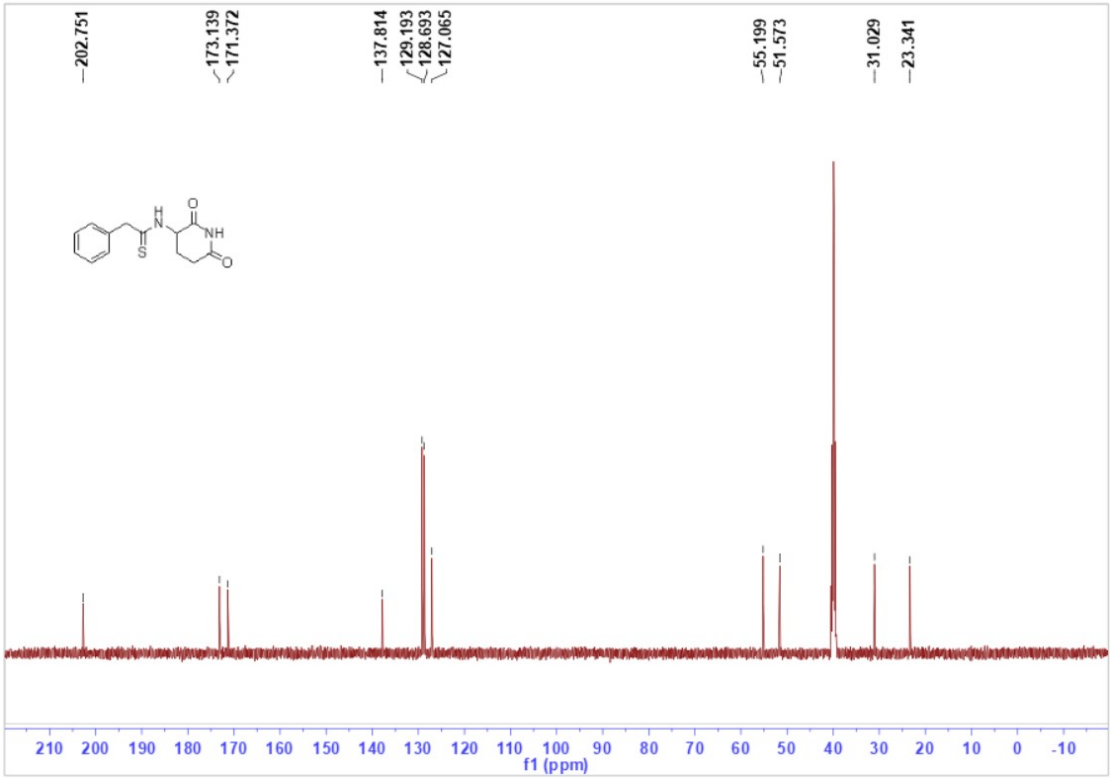




N-(2,6-dioxopiperidin-3-yl)-2-phenylethanethioamide (3es)





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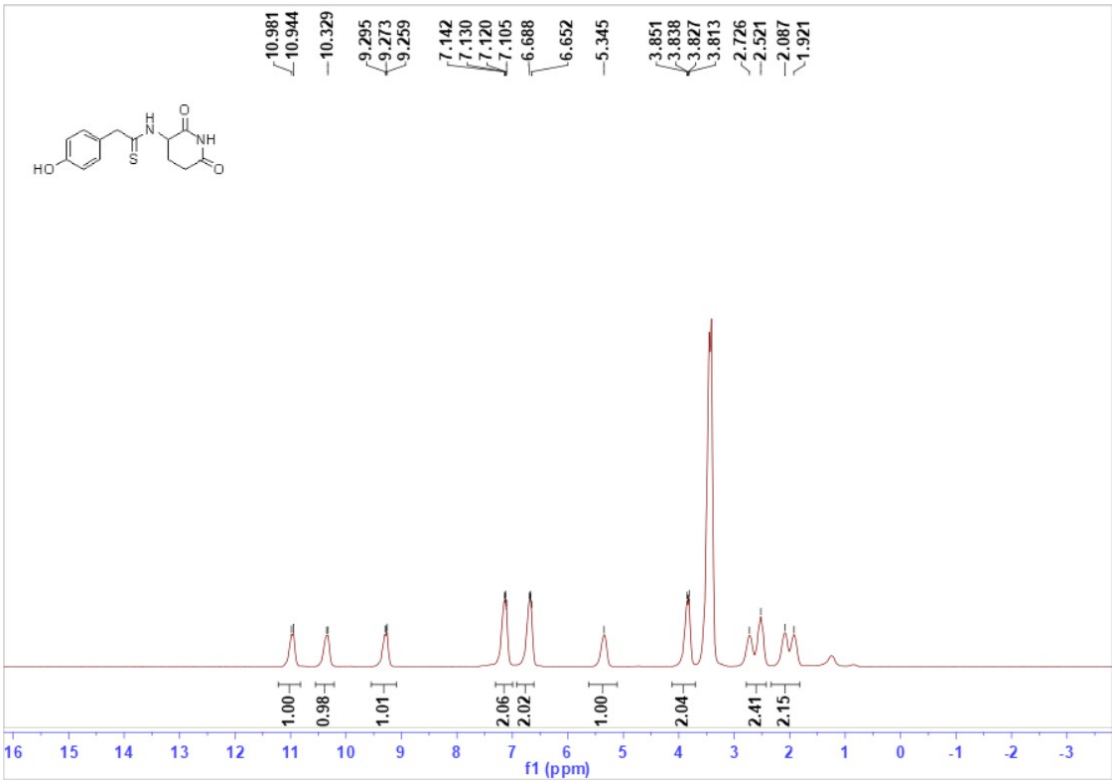

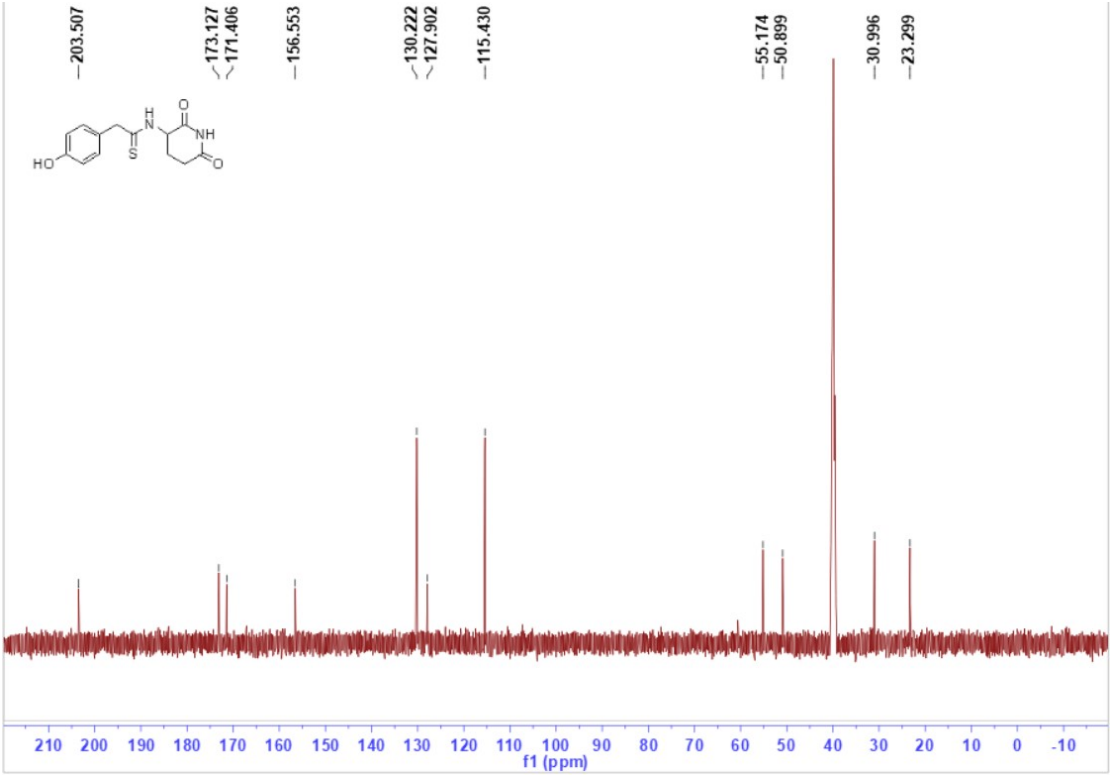

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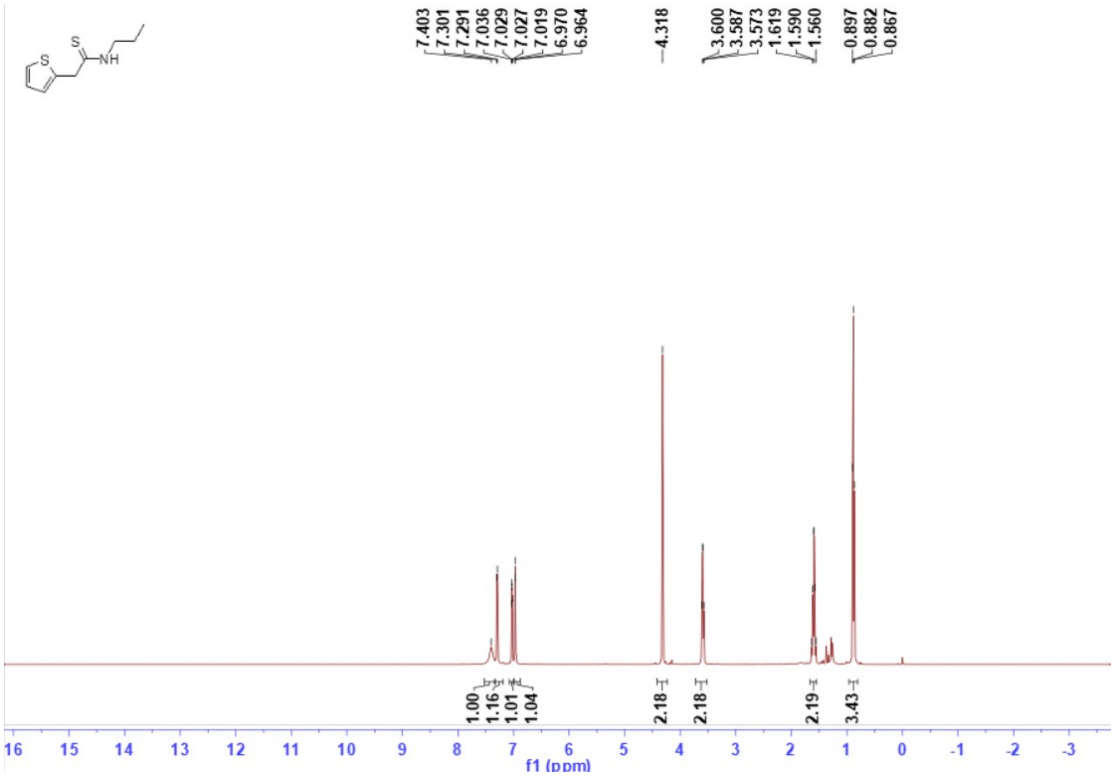
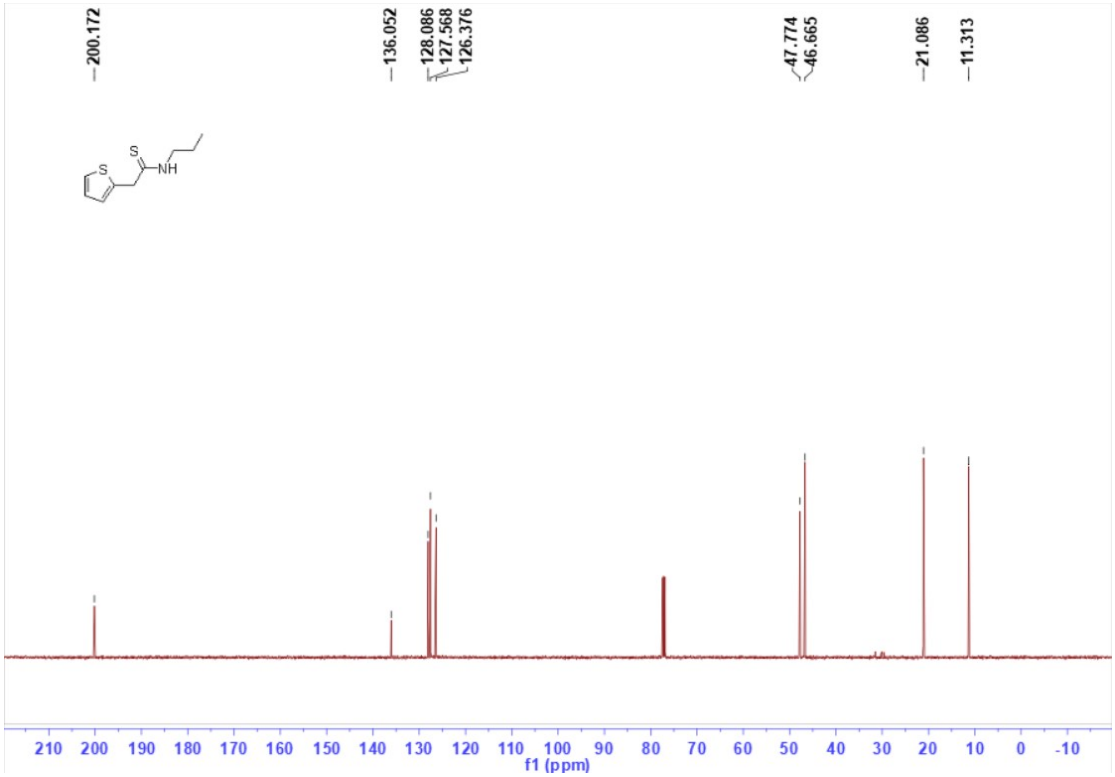
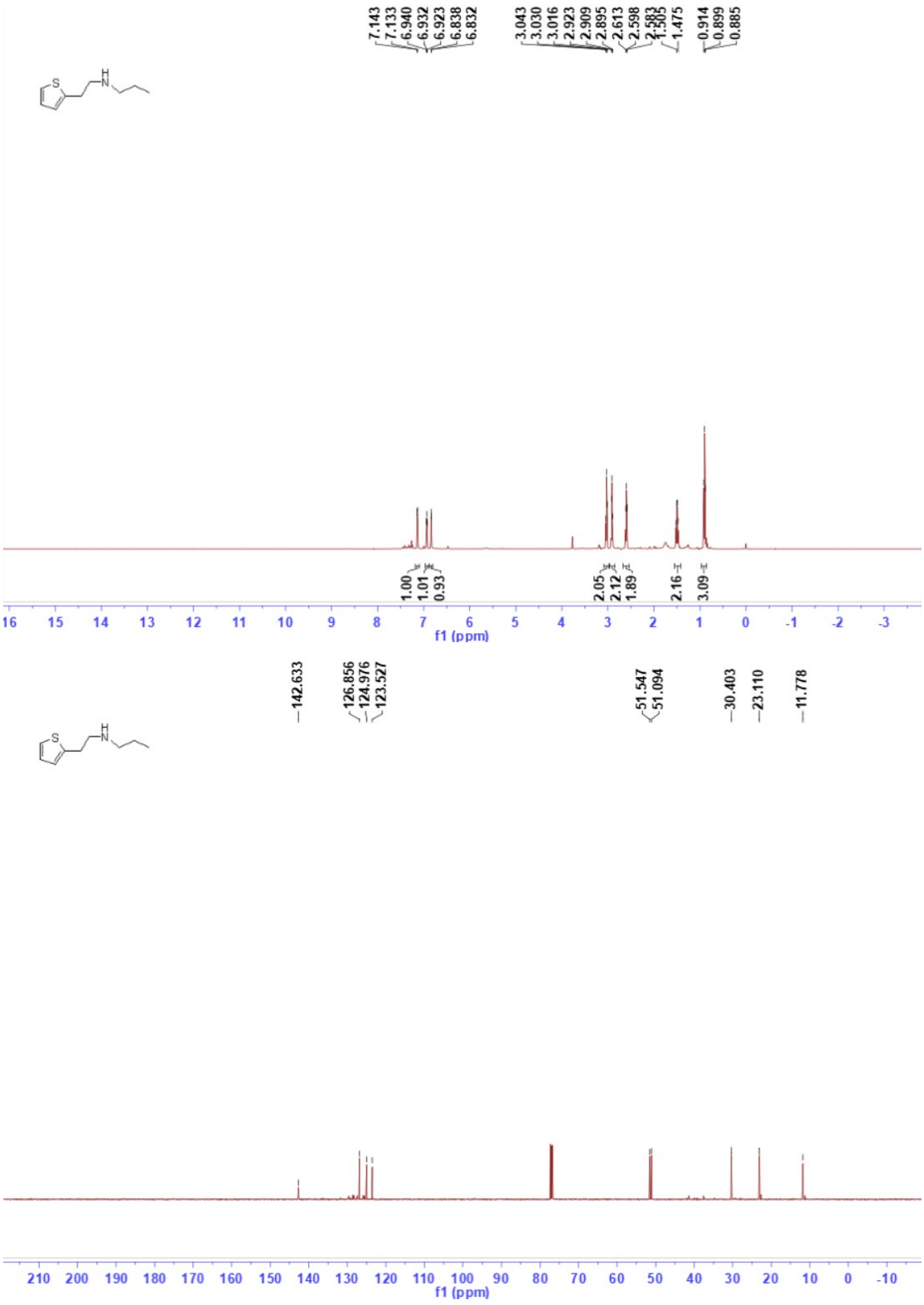
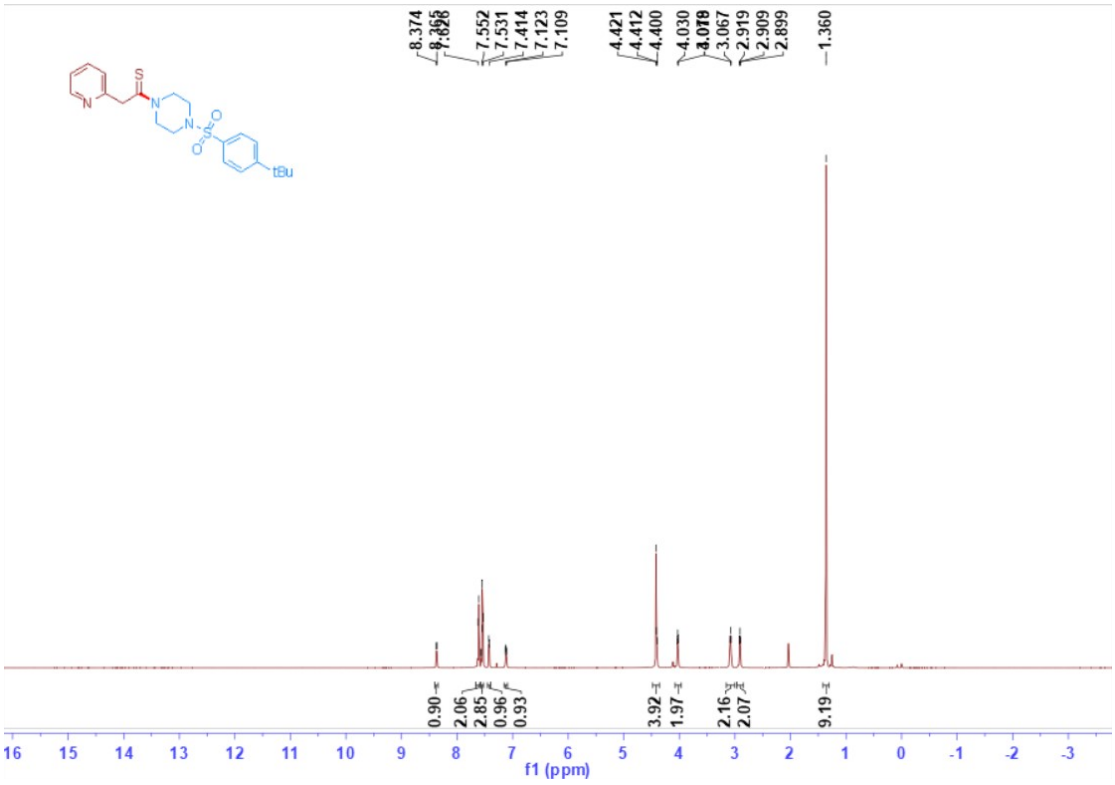


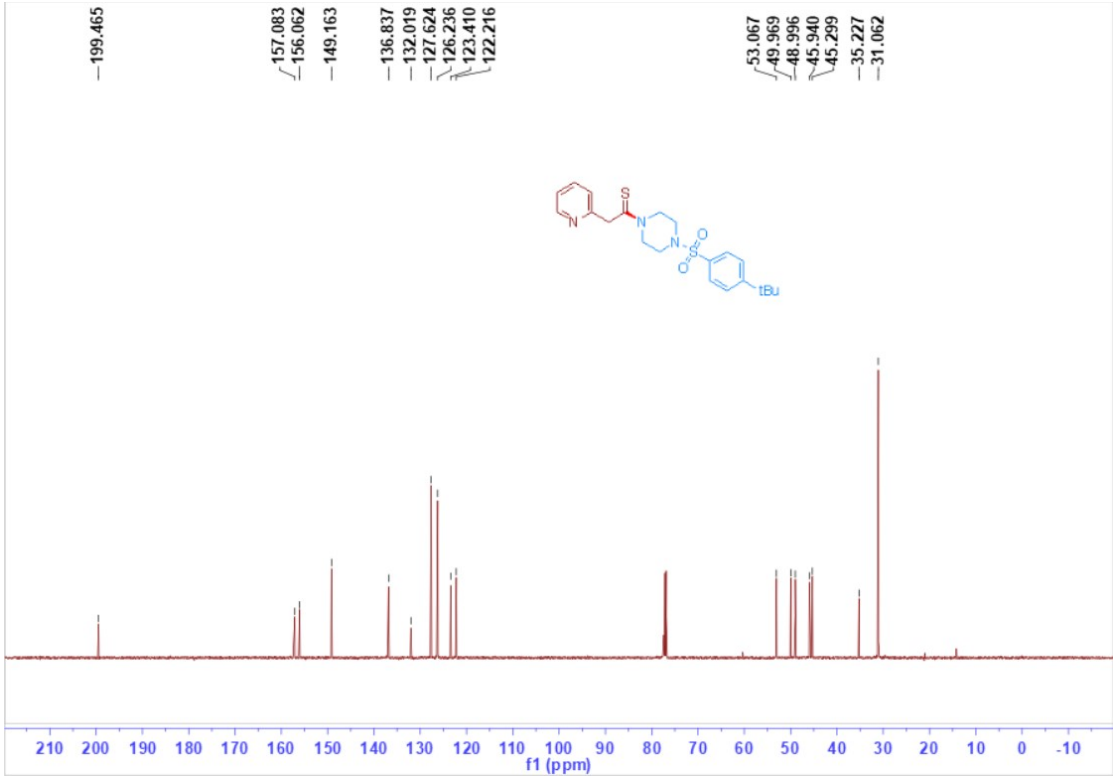


(2-(Thiophen-2-yl)ethyl)propan-1-amine (3ev)

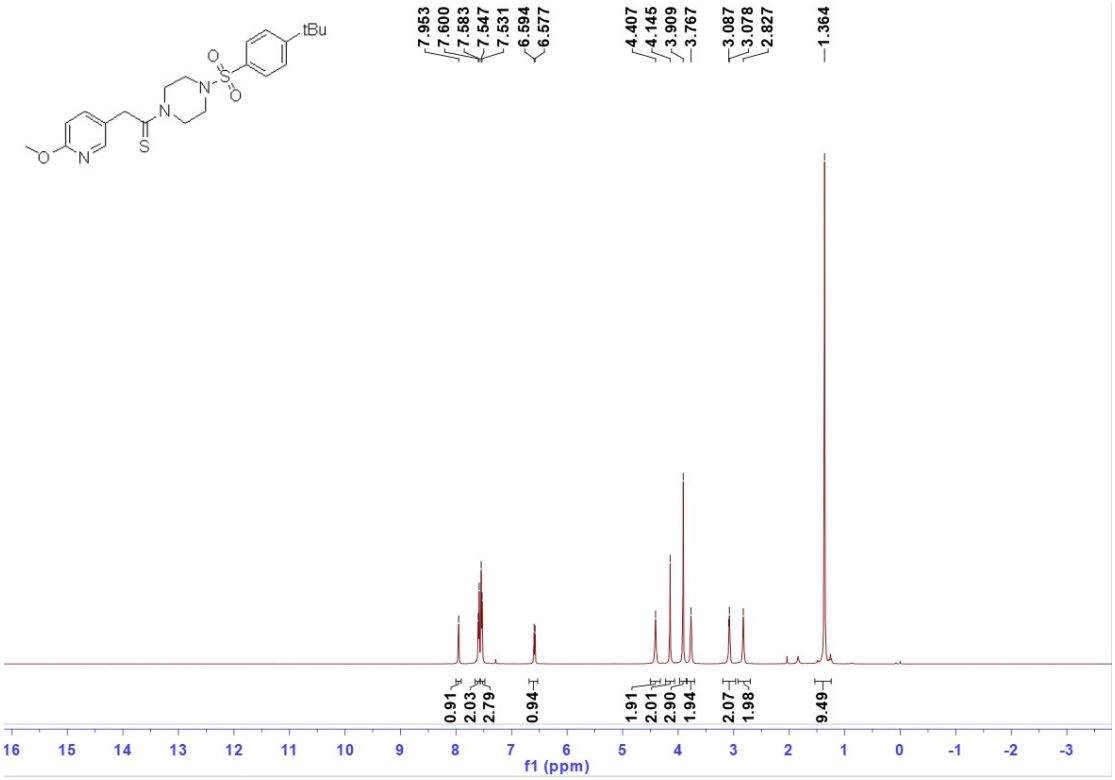


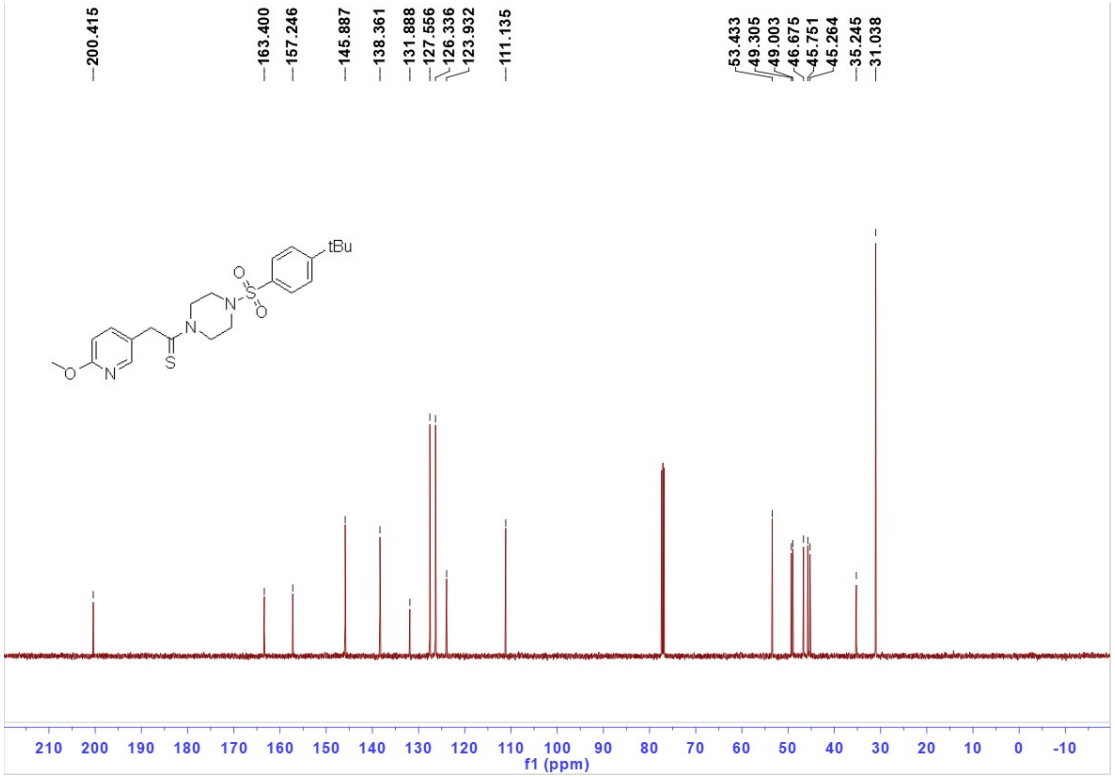
1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(pyridin-2-yl)ethane-1-thione (3ew)





1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(6-methoxypyridin-3-yl)ethane-1-thione (3ex)





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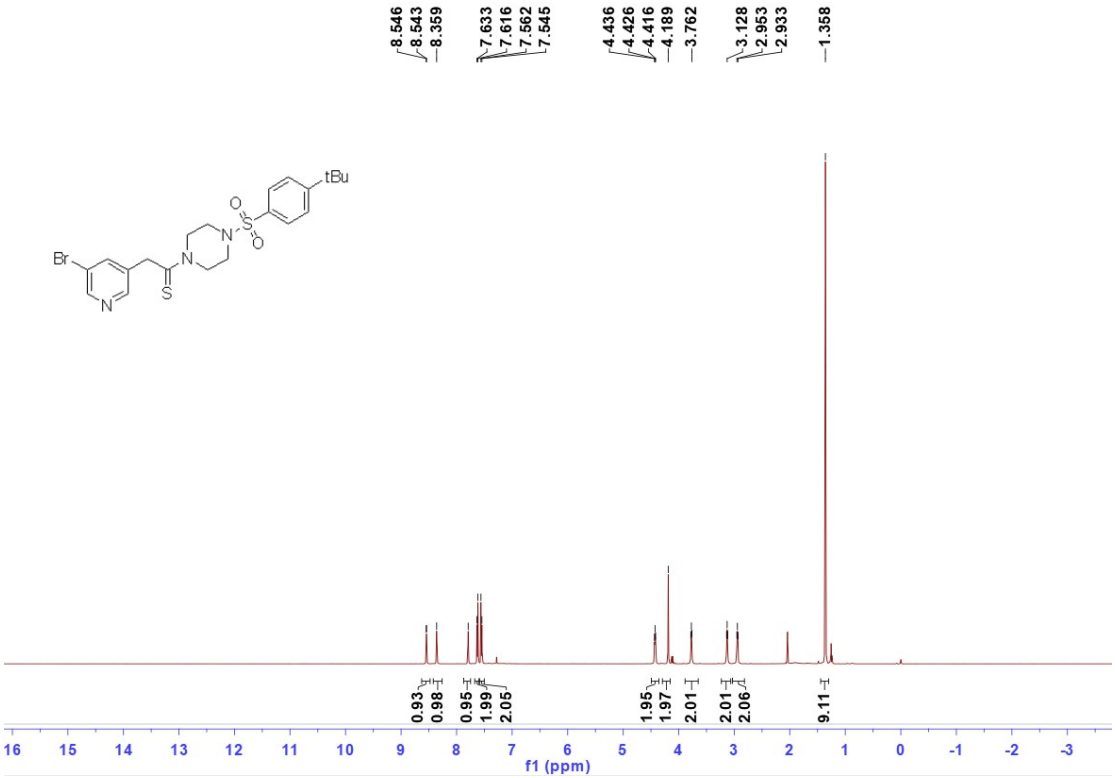
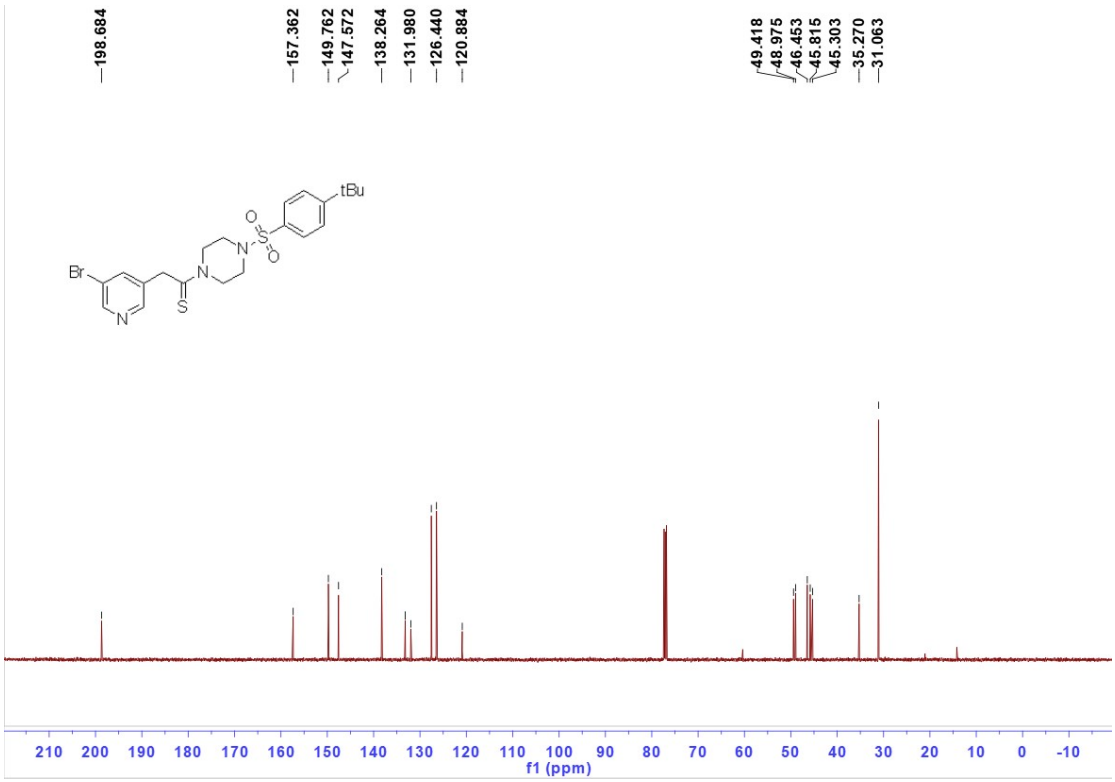
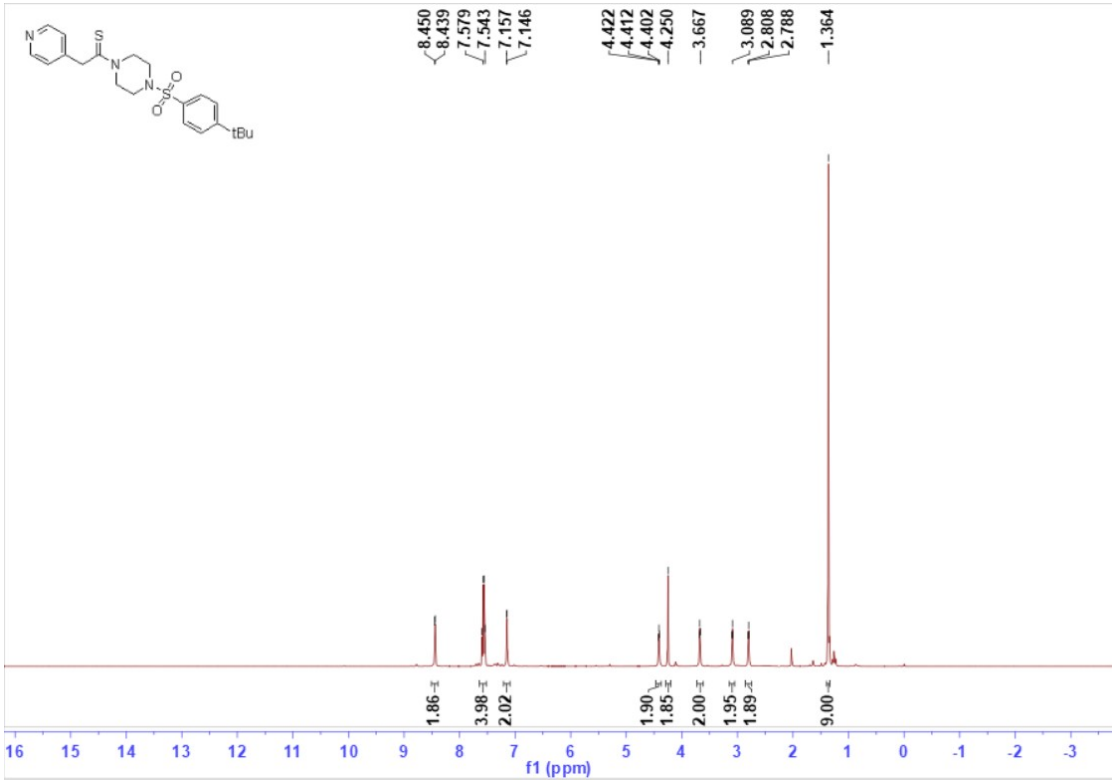
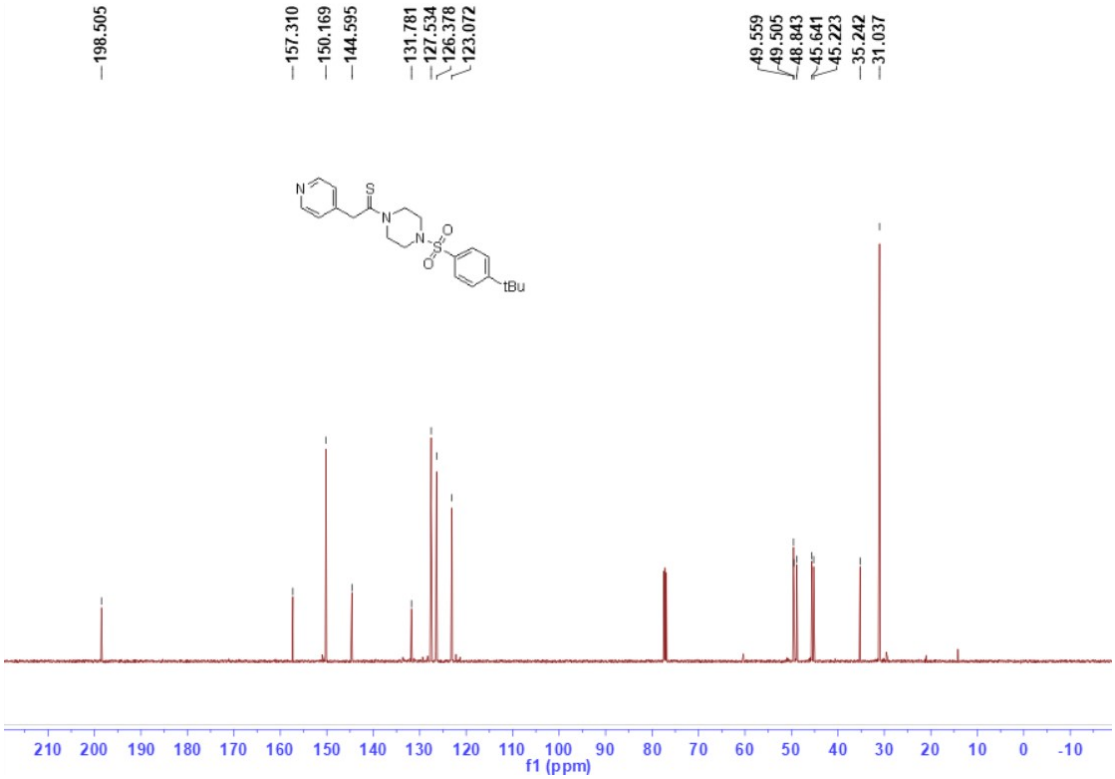




1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(pyridin-4-yl)ethane-1-thione (3ez)





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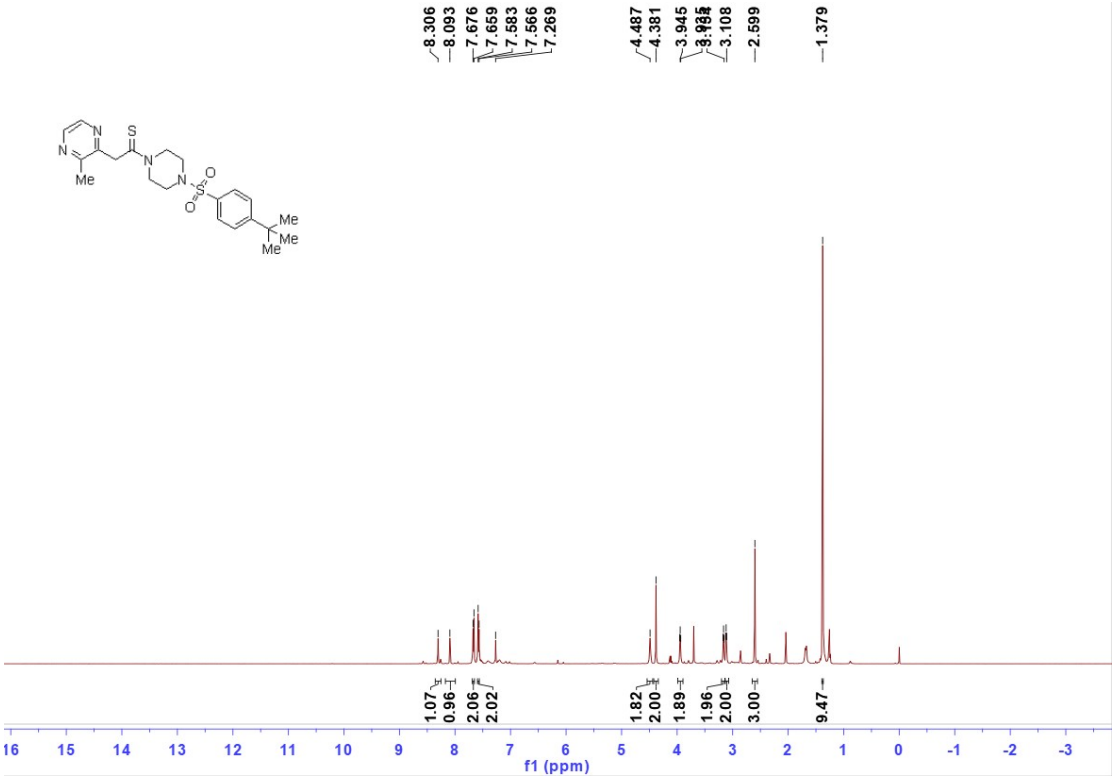
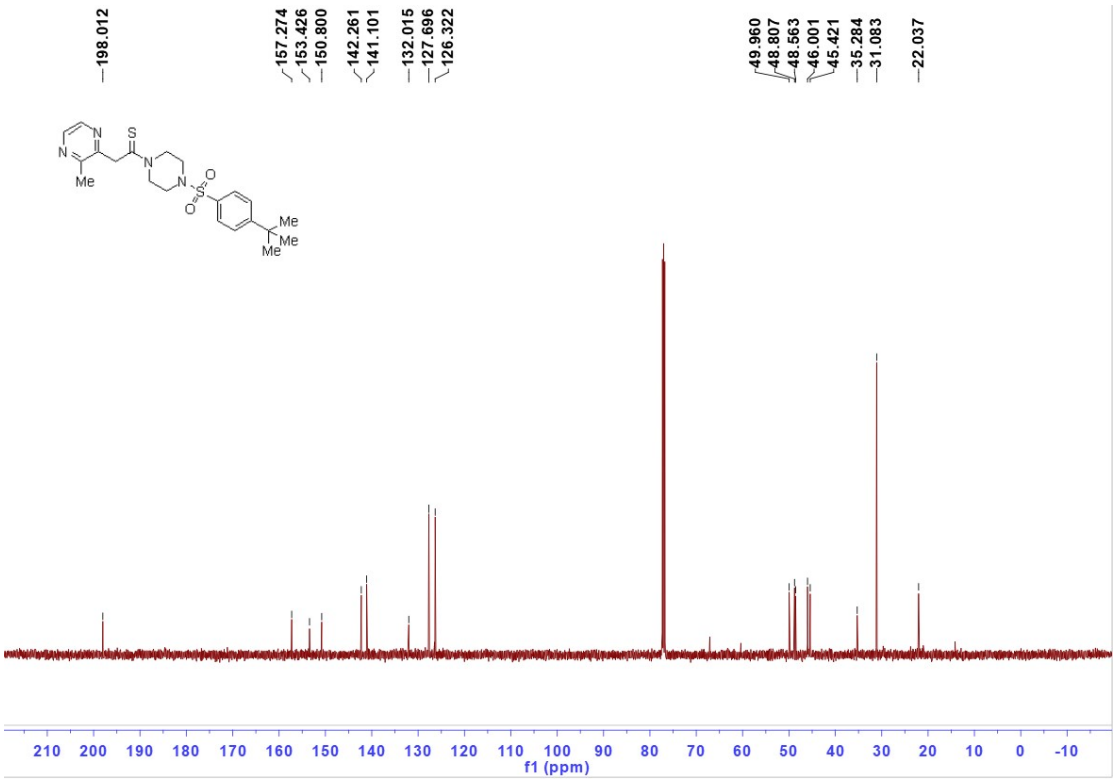
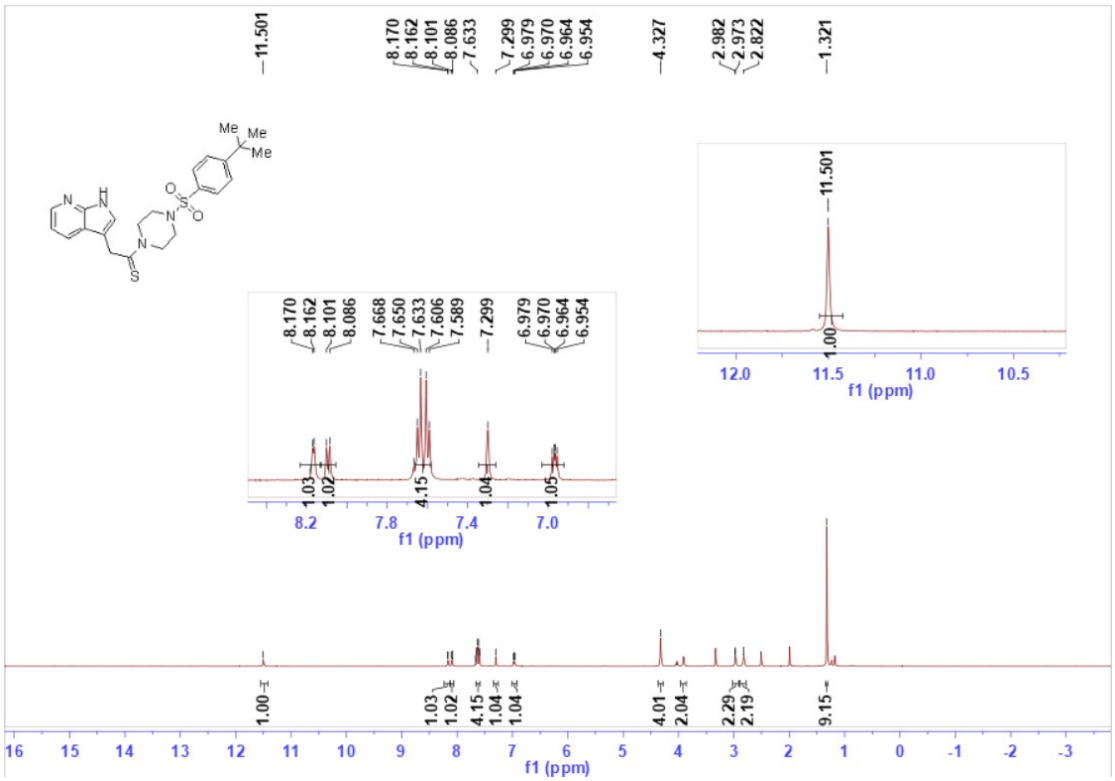
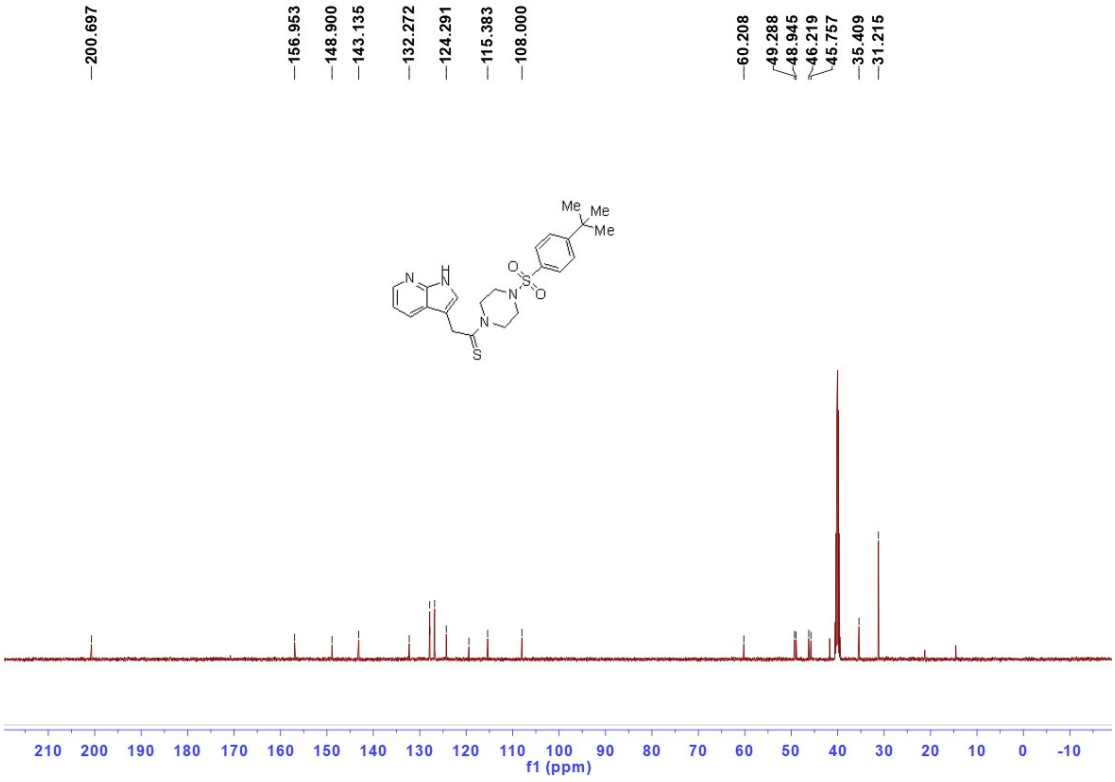


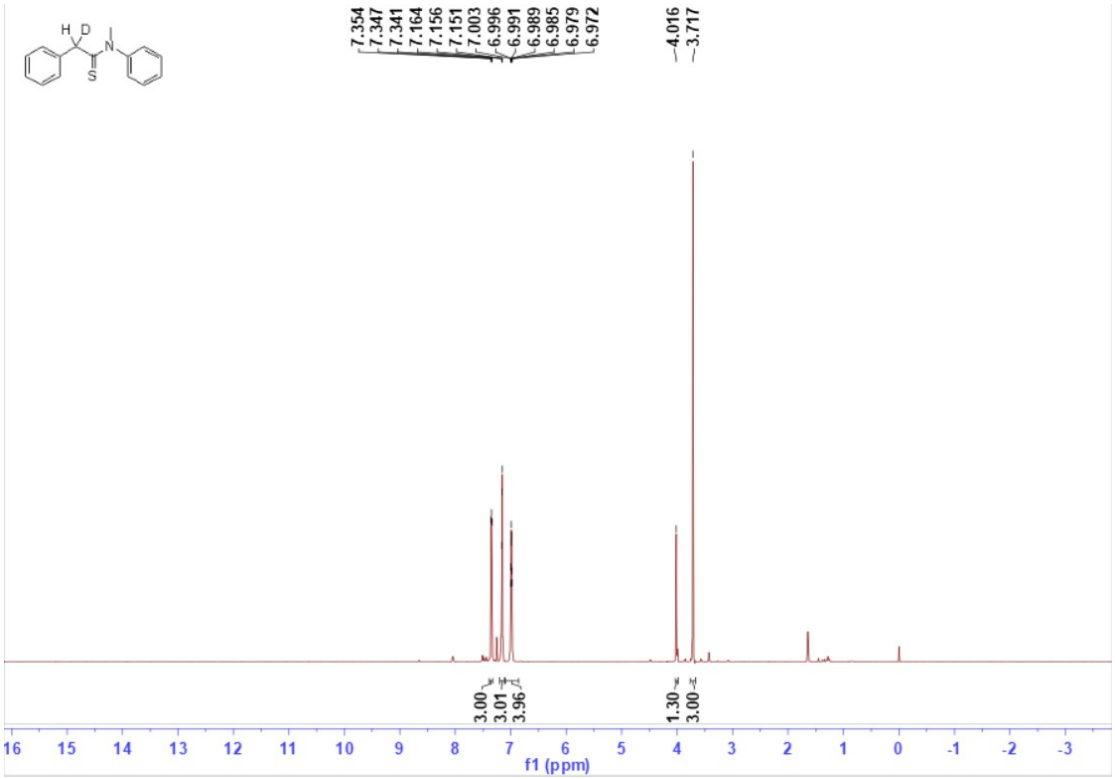


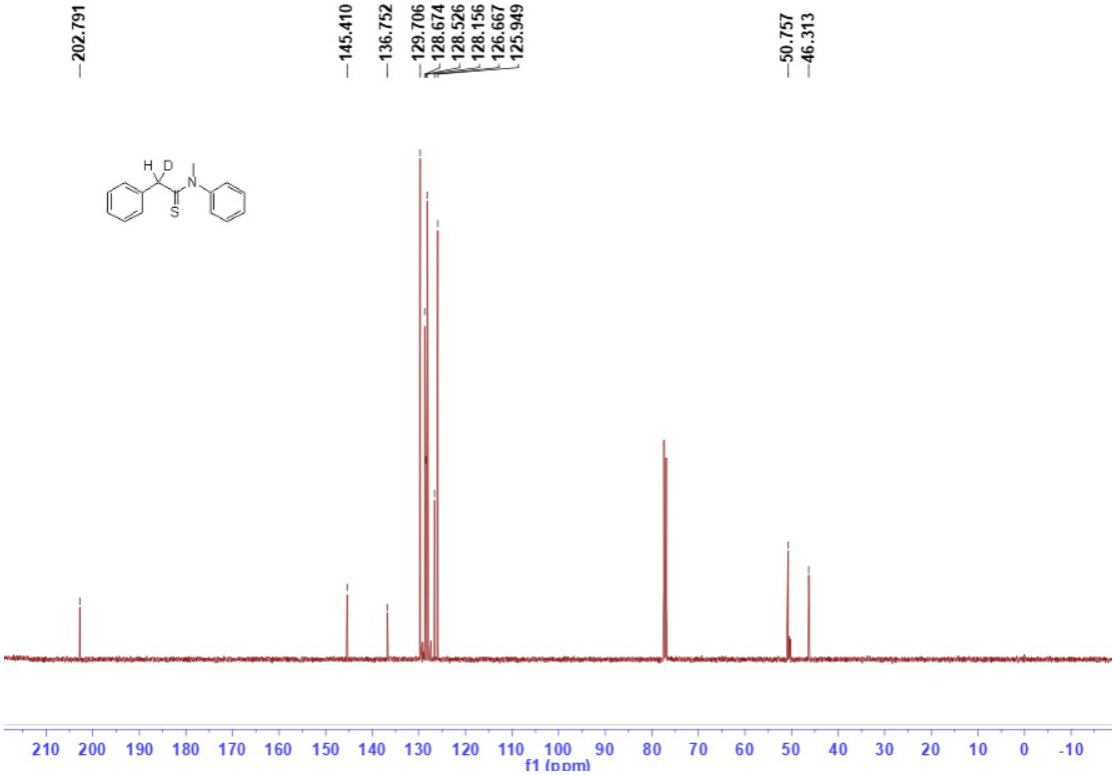
1-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1-thione (3ezb)



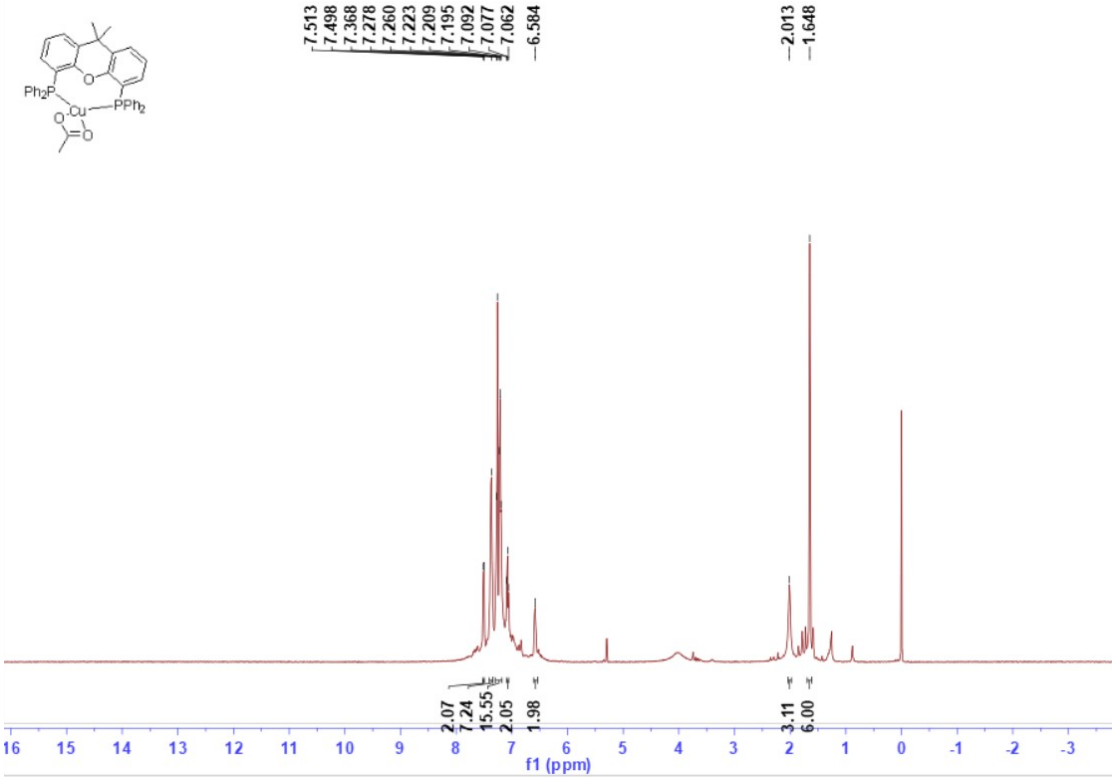


N-methyl-*N*,2-diphenylethanethioamide-2-d





(Xantphos)Cu(OAc)



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