Electronic Supplementary Information (ESI)

Green Synthesis of Thioamide Derivatives in Environmentally Benign Deep Eutectic Solvent (DES)

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Table of contents:

1. Experimental Section

1a. General Information

All the reactions were performed in open air using dry glassware. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded by using Bruker advance III-400 spectrometer. Mass spectrometry data of the corresponding thioamide derivatives were collected on ESI-HRMS mass spectrometer (Model: 1260 Infinity II, make: Agilent) and ESI-LCMS mass spectrometer. The NMR solvent $CDCl_3$ and all other reagents were purchased from Sigma Aldrich and were used without any further purification.

1b. General procedure for synthesis of DES

DES was prepared according to the previously reported procedure in the literature.[1] In a dry 50 mL round bottom flask, Choline chloride (ChCl) (0.028 mol, 4 g) and urea (0.057 mol, 3.4 g) were mixed in a 1:2 ratio and then heated at 80 °C for 30 min. A colorless liquid was produced. This liquid eutectic mixture is used for catalytic experiments without any kind of purification. The DES is characterized by ^{1}H and ^{13}C NMR spectroscopy.

1c. General procedure for thioamidation reaction.

In a 25 mL dry sealed tube, the corresponding aldehyde or ketone (1.56 mmol), secondary amine (1.56 mmol), elemental sulfur powder (0.195 mmol) and 25 mol% of DES [Choline chloride:urea (1:2)] (0.4 mmol, 101 mg) were added. Then this whole reaction mixture was heated at 45 °C for five hours in an oil bath. After completion of the reaction as monitored by TLC plate, the reaction mixture was cooled to room temperature, diluted with water (10 mL), and then extracted with ethyl acetate (3 x 5 mL). The reaction mixture was then quenched with saturated $NaHCO_3$ solution (2 x 5 mL) and dried over anhydrous sodium sulfate. The organic layer collected was evaporated under reduced pressure and the resulted crude was purified using silica gel column chromatography with hexane: EtOAc (100:5). The corresponding thioamide derivatives obtained were characterised by ^{1}H, ^{13}C NMR spectroscopy, and mass-spectrometry analysis. The aqueous layer was utilized for the recovery of DES.

1d. Recyclability Test

The reusability test was performed using the reaction between *p*-tolulaldehyde, diethylamine, and the elemental sulfur powder in DES (25 mol%) in 1:1:0.125 molar ratio under optimized conditions (at 45 °C temperature for five hours) as the multicomponent model reaction. After completion of the reaction, DES was recovered from water phase by evaporation at 85 °C under reduced pressure. The remainder of the viscous DES was further dried at 70 °C for three hours under reduced pressure to remove any traces of water and then subjected to the next run with the same reactants without further addition of DES in the cycle.

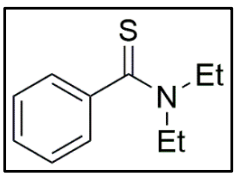
1e. Gram scale Thioamidation reaction.

In a 50 mL dry Schlenk tube, diethylamine amine (0.03 mol, 2.3 g), elemental sulfur powder (0.004 mol, 1 g), *p*-tolulaldehyde (0.03 mol, 3.7 g), and 25 mol% of DES (7.8 mmol, 2 g) were added. Then this whole reaction mixture was heated at 45 °C for five hours in an oil bath. After completion of the reaction as monitored by TLC plate, the reaction mixture was cooled to room temperature, diluted with water (30 mL) and extracted with ethylacetate (3 x 15 mL). The combined ethyl acetate extracts were washed with saturated aq. sodium bicarbonate solution (2 x 5 mL) and dried over anhydrous sodium sulfate. The combined ethyl acetate extracts were concentrated in *vacuo* and the resulting product was directly charged on a small silica gel column and eluted with a mixture of hexane: ethyl acetate (EtOAc) (3:2) to afford the pure thioamide derivative in each case. Each derivative was characterised by ^{1}H, ^{13}C NMR spectroscopy (and by MS analysis wherever required).

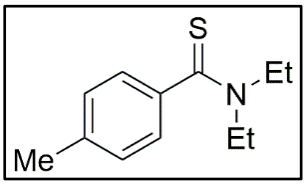
Characterization data of DES[1]

^{1}H NMR (600 MHz, D_2O, 25 ºC): δ_H 5.94 (s, 1H), 4.79 (s, 8H), 4.15 - 4.10 (m, 2H), 3.63 - 3.58 (m, 2H), 3.28 (s, 9H) ppm. $^{13}C\{^{1}H\}$ NMR (150 MHz, D_2O, 25 ºC): δ_C 162.42, 67.56, 55.79, 54.04 ppm.

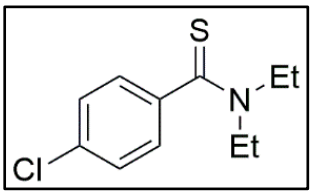
Characterisation data of thioamides (3a-3n) from aliphatic secondary amine:



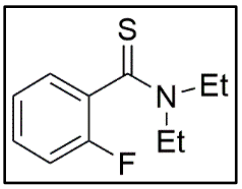
N,N-diethylbenzothioamide **(3a)**.[2] Yield: 272 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.38 - 7.19 (m, 5H, Ar*H*), 4.12 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 3.43 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 1.38 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.13 (t, *J* = 7.1 Hz, 3H, CH_2CH_3) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 200.2, 143.8, 128.3, 128.0, 124.9, 47.8, 46.1, 13.8, 11.3 ppm.



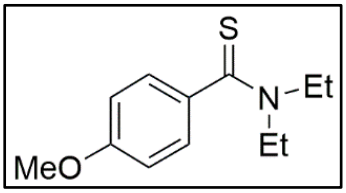
N,N-diethyl-4-methylbenzothioamide **(3b)**.[2] Yield: 301 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.16 - 7.10 (m, 4H, Ar*H*), 4.12 (q, J = 7.1Hz, 2H, CH_2CH$_3$), 3.46 (q, J = 7.1 Hz, 2H, CH_2CH$_3$) 2.34 (s, 3H, CH_3), 1.39 (t, J = 7.1 Hz, 3H, CH$_2$CH_3), 1.15 (t, J = 7.2 Hz, 3H, CH$_2$CH_3,) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 200.8, 141.3, 138.1, 129.1, 125.1, 47.9, 46.2, 21.3, 14.0, 11.4 ppm.



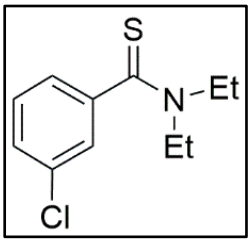
4-chloro-N,N-diethylbenzothioamide **(3c)**.[2] Yield: 323 mg, 91%. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ_H 7.34 - 7.29 (m, 2H, Ar*H*), 7.21 - 7.15 (m, 2H, Ar*H*), 4.10 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 3.43 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 1.37 (t, J = 7.1 Hz, 3H, CH$_2$CH_3), 1.14 (t, J = 7.2 Hz, 3H, CH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 25 °C): δ_C 198.6, 142.1, 133.8, 128.5, 126.4, 47.8, 46.1, 13.8, 11.2 ppm.



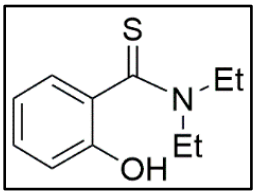
N,N-diethyl-2-fluorobenzothioamide **(3d)**.[3] Yield: 287 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.35 - 7.27 (m, 2H, Ar*H*), 7.17 - 7.13 (m, 1H, Ar*H*), 7.07 - 7.03 (m, 1H, Ar*H*), 4.31 (dq, J = 14.2 Hz, 7.1 Hz, 1H, CH_2CH$_3$), 3.98 (dq, J = 14.2 Hz, 7.1 Hz, 1H, CH_2CH$_3$), 3.44 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 1.39 (t, J = 7.1 Hz, 3H, CH$_2$CH_3), 1.14 (t, J = 7.2 Hz, 3H, CH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 193.2, 155.5 (d, J = 245 Hz), 131.4 (d, J = 17 Hz), 130.0 (d, J = 8 Hz), 128.3 (d, J = 3 Hz) 124.6 (d, J = 4 Hz), 115.9 (d, J = 21 Hz), 48.1, 46.1, 13.5, 11.3 ppm. ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, 25 °C): δ_F -116.9 ppm.



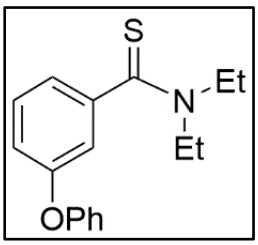
N,N-diethyl-4-methoxybenzothioamide **(3e)**.[4] Yield: 321 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.23 - 7.17 (m, 2H, Ar*H*), 6.88 - 6.83 (m, 2H, Ar*H*), 4.11 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 3.80 (s, 3H, OCH_3), 3.48 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 1.38 (t, J = 7.1 Hz, 3H, CH$_2$CH_3), 1.15 (t, J = 7.1 Hz, 3H, CH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 200.3, 159.4, 136.5, 126.7, 113.6, 55.3, 47.8, 46.2, 13.9, 11.2 ppm.



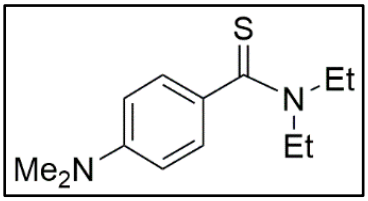
3-chloro-N,N-diethylbenzothioamide **(3f)**.[5] Yield: 331 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.23 - 7.17 (m, 2H, Ar*H*), 7.16 - 7.14 (m, 1H, Ar*H*), 7.06 - 7.01 (m, 1H, Ar*H*), 4.02 (q, J = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.35 (q, J = 7.2 Hz, 2H, C*H*$_2$CH$_3$), 1.30 (t, J = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.07 (t, J = 7.2 Hz, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 197.9, 145.1, 134.2, 129.7, 128.1, 125.1, 123.1, 47.9, 46.1, 13.8, 11.2 ppm.



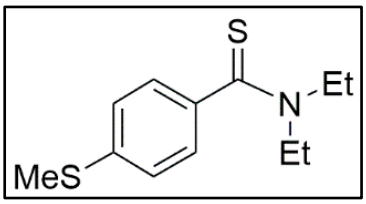
N,N-diethyl-2-hydroxybenzothioamide **(3g)**.[6] Yield: 294 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.46 (s, 1H, O*H*), 7.20 - 7.15 (m, 1H, Ar*H*), 6.99 - 6.91 (m, 2H, ArH), 6.86 (t, J = 7.5 Hz, 1H, Ar*H*), 4.11 (s, 2H, C*H*$_2$CH$_3$), 3.51 (s, 2H, C*H*$_2$CH$_3$), 1.36 (s, 3H, CH$_2$C*H*$_3$), 1.16 (s, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 196.0, 152.5, 130.2, 128.8, 125.2, 119.9, 118.0, 48.5, 46.3, 13.7, 11.4 ppm.



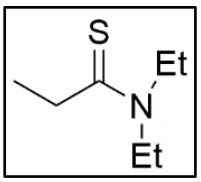
N,N-diethyl-3-phenoxybenzothioamide **(3h)**. Yield: 397 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.38 - 7.24 (m, 3H, Ar*H*), 7.14 - 7.09 (m, 1H, Ar*H*), 7.05 - 7.00 (m, 2H, Ar*H*), 6.96 - 6.90 (m, 2H, Ar*H*), 6.87 - 6.84 (m, 1H, Ar*H*), 4.08 (q, J = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.43 (q, J = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 1.35 (t, J = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.12 (t, J = 7.2 Hz, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 199.0, 157.3, 156.4, 145.2, 129.8, 123.7, 119.7, 119.3, 117.8, 115.0, 47.8, 46.0, 13.8, 11.2 ppm. HRMS (ESI) m/z: [(M+H)$^{+}$] calcd for $C_{17}H_{19}NOS$ 286.1187, found 286.1265.



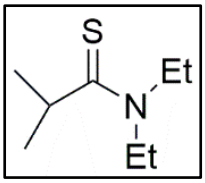
4-(dimethylamino)-N,N-diethylbenzothioamide **(3i)**. Yield: 317 mg, 86%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.76 (d, J = 9.0 Hz, 2H, Ar*H*), 6.63 (d, J = 9.0 Hz, 2H, Ar*H*), 3.87 (q, J = 7.3 Hz, 2H, C*H*$_2$CH$_3$), 3.08 (q, J = 7.3 Hz, 2H, C*H*$_2$CH$_3$), 3.02 (s, 6H, N(C*H*$_3$)$_2$), 1.36 (t, J = 7.3 Hz, 3H, CH$_2$C*H*$_3$), 1.25 (t, J = 7.4 Hz, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 201.6, 190.4, 150.6, 132.1, 127.1, 111.5, 111.1, 47.9, 46.4, 40.4, 40.2, 14.1, 11.5 ppm. HRMS (ESI) m/z: [(M+H)$^{+}$] calcd for $C_{13}H_{20}N_2S$ 237.1347, found 237.1409.



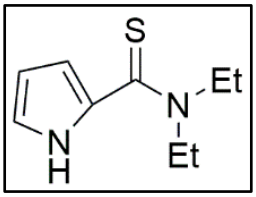
N,N-diethyl-4-(methylthio)benzothioamide **(3j)**. Yield: 329 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.31 - 7.09 (m, 4H, Ar*H*), 4.11 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 3.46 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 2.48 (s, 3H, SCH_3,), 1.37 (t, J = 7.1 Hz, 3H, CH$_2$CH_3), 1.14 (t, J = 7.1 Hz, 3H, CH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 199.7, 140.5, 138.8, 126.0, 125.6, 47.8, 46.2, 15.6, 13.9, 11.3 ppm. HRMS (ESI) m/z: [(M+H) $^{+}$] calcd for $C_{12}H_{17}NS_2$ 240.0802, found 240.0876.



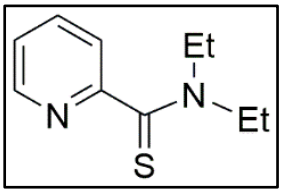
N,N-diethylpropanethioamide **(3k)**.[7] Yield: 181 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 4.02 - 3.98 (m, 2H, Alkyl-CH_2), 3.56 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 2.77 (q, J = 7.5 Hz, 2H, CH_2CH$_3$), 1.39 - 1.27 (m, 9H, CH$_2$CH_3, Alkyl-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C 127.4, 48.0, 47.9, 45.9, 44.6, 36.1, 23.9, 15.3, 14.3, 13.8, 11.3, 11.2 ppm.



N,N-diethyl-2-methylpropanethioamide **(3l)**.[8] Yield: 219 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 3.97 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 3.56 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 3.07 (hept, J = 6.5 Hz, 1H, Alkyl-C*H*), 1.25 - 1.17 (m, 12H, CH$_2$CH_3, Alkyl-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 209.7, 48.2, 45.4, 36.2, 23.5, 14.2, 11.2 ppm.

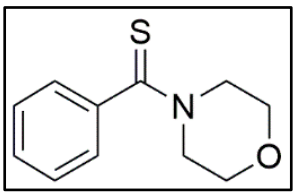


N,N-diethyl-1H-pyrrole-2-carbothioamide **(3m)**. Yield: 248 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 10.01 (s, 1H, N*H*), 6.98 - 6.93 (m, 1H, Ar*H*), 6.51 - 6.45 (m, 1H, Ar*H*), 6.30 - 6.24 (m, 1H, Ar*H*), 4.01 (s, 4H, CH_2CH$_3$), 1.39 (t, J = 6.7 Hz, 6H, CH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C (100 MHz, $CDCl_3$, 25 °C) 185.5, 129.8, 122.9, 110.7, 110.2, 48.2 ppm. HRMS (ESI) m/z: [(M+H) $^{+}$] calcd for $C_9H_{14}N_2S$ 183.0878, found 183.0953.

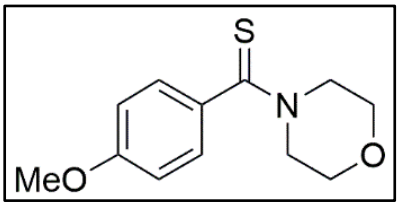


N,N-diethylpyridine-2-carbothioamide **(3n)**.[9] Yield: 282 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.45 - 8.35 (m, 1H, Ar*H*), 7.65 - 7.63 (m, 1H, Ar*H*), 7.37 - 7.32 (m, 1H, Ar*H*), 7.15 - 7.09 (m, 1H, Ar*H*), 4.00 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 3.33 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 1.30 (t, J = 7.1 Hz, 3H, CH$_2$CH_3), 1.04 (t, J = 7.1 Hz, 3H, CH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 196.9, 159.5, 148.0, 136.6, 122.7, 122.0, 47.7, 46.3, 13.6, 11.0 ppm.

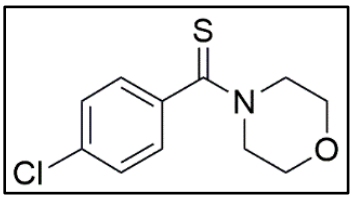
Characterisation data of thioamides (4a-4p) from cyclic secondary amines:



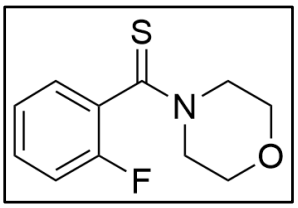
Morpholino(phenyl)methanethione **(4a)**.[4] Yield: 294 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.40 - 7.26 (m, 5H, Ar*H*), 4.48 - 4.43 (m, 2H), 3.93 - 3.87 (m, 2H), 3.66 - 3.58 (m, 4H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 201.1, 142.6, 129.0, 128.6, 126.0, 66.8, 66.6, 52.6, 49.6 ppm.



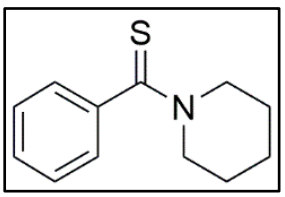
(4-methoxyphenyl)(morpholino)methanethione **(4b)**.[10] Yield: 356 mg, 96%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.31 - 7.26 (m, 2H, Ar*H*), 6.90 - 6.84 (m, 2H, Ar*H*), 4.43 (s, 3H, OCH_3), 3.88 (s, 2H), 3.82 (s, 2H), 3.65 (s, 4H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 201.4, 160.4, 135.0, 128.2, 113.9, 66.9, 66.7, 55.5, 52.9, 50.1 ppm.



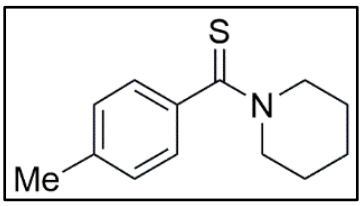
(4-chlorophenyl)(morpholino)methanethione **(4c)**.[10] Yield: 351 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.36 - 7.33 (m, 2H, Ar*H*), 7.27 - 7.22 (m, 2H, Ar*H*), 4.44 - 4.39 (m, 2H), 3.90 - 3.86 (m, 2H), 3.66 - 3.58 (m, 4H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 199.7, 140.8, 135.0, 128.9, 127.5, 66.8, 66.6, 52.7, 49.7 ppm.



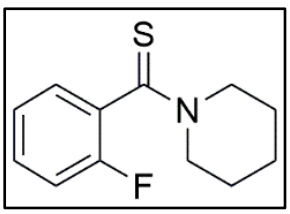
(2-fluorophenyl)(morpholino)methanethione **(4d)**.[11] Yield: 302 mg, 86%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.39 - 7.26 (m, 2H, Ar*H*), 7.16 - 7.11 (m, 1H, Ar*H*), 7.04 - 6.96 (m, 1H, Ar*H*), 4.46 - 4.34 (m, 2H), 3.86 - 3.80 (m, 2H), 3.72 - 3.58 (m, 2H), 3.57 - 3.43 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 193.3, 155.3 (d, J = 246 Hz), 130.7 (d, J = 8 Hz), 129.9 (d, J = 17 Hz), 129.4 (d, J = 2 Hz), 124.7 (d, J = 4 Hz), 115.5 (d, J = 22 Hz), 66.4, 66.3, 52.1, 49.2 ppm. ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, 25 °C): δ_F -116.2 ppm.



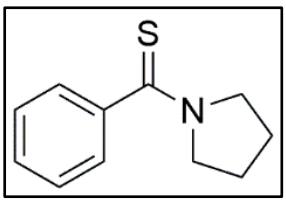
Phenyl(piperidin-1-yl)methanethione **(4e)**.[11] Yield: 295 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.36 - 7.23 (m, 5H, Ar*H*), 4.37 - 4.30 (m, 2H), 3.52 - 3.47 (m, 2H), 1.85 - 1.50 (m, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 199.2, 143.3, 128.3, 128.2, 125.3, 53.0, 50.5, 26.8, 25.4, 24.0 ppm.



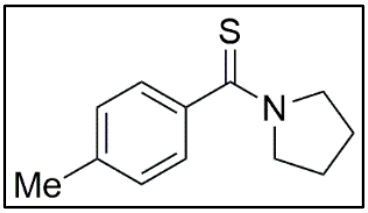
Piperidin-1-yl(p-tolyl)methanethione **(4f).**[4] Yield: 322 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.19 - 7.11 (m, 4H, Ar*H*), 4.37 - 4.32 (m, 2H), 3.57 - 3.49 (m, 2H), 2.34 (s, 3H, CH_3), 1.84 - 1.71 (m, 4H), 1.58 - 1.54 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 200.1, 140.7, 138.6, 129.1, 125.7, 53.3, 50.9, 27.0, 25.6, 24.3, 21.4 ppm.



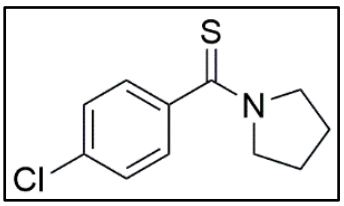
(2-fluorophenyl)(piperidin-1-yl)methanethione **(4g)**.[13] Yield: 314 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.36 - 7.26 (m, 2H, Ar*H*), 7.17 - 7.12 (m, 1H, Ar*H*), 7.05 - 6.99 (m, 1H, Ar*H*), 4.44 - 4.26 (m, 2H), 3.54 - 3.44 (m, 2H), 1.80 - 1.50 (m, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 191.7, 155.2 (d, J = 246 Hz), 130.6 (d, J = 17 Hz), 129.9 (d, J = 8 Hz), 128.4 (d, J = 2 Hz), 124.3 (d, J = 3 Hz), 115.3 (d, J = 21 Hz), 52.7, 49.9, 26.3, 25.2, 23.7 ppm. ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, 25 ºC): δ_F -116.5 ppm.



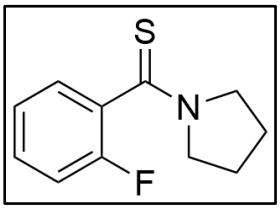
Phenyl(pyrrolidin-1-yl)methanethione **(4h)**.[14] Yield: 266 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.39 - 7.25 (m, 5H, Ar*H*), 3.98 (t, J = 7.1 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 2.12 - 1.92 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 197.4, 144.1, 128.8, 128.4, 125.8, 53.9, 53.5, 26.6, 24.8 ppm.



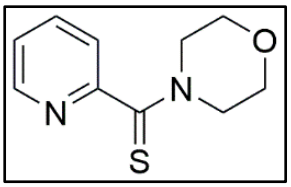
Pyrrolidin-1-yl(p-tolyl)methanethione **(4i)**.[12] Yield: 292 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.18 - 7.13 (m, 2H, Ar*H*), 7.02 (d, J = 7.2 Hz, 2H, Ar*H*), 3.82 (t, J = 6.7 Hz, 2H), 3.36 (t, J = 6.4 Hz, 2H), 2.22 (s, 3H), 1.95 - 1.78 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 196.6, 140.7, 138.2, 128.3, 125.3, 53.4, 53.0, 26.0, 24.2, 20.8 ppm.



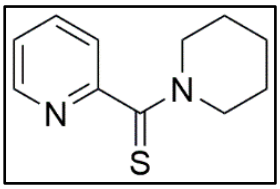
(4-chlorophenyl)(pyrrolidin-1-yl)methanethione **(4j)**.[12] Yield: 310 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.23 (s, 4H, Ar*H*), 3.85 (t, J = 7.1 Hz, 2H), 3.37 (t, J = 6.7 Hz, 2H), 2.03 - 1.85 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 195.4, 142.1, 134.4, 128.3, 127.1, 53.7, 53.4, 26.4, 24.5 ppm.



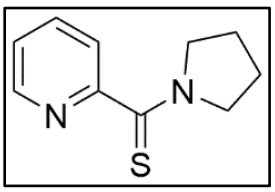
(2-fluorophenyl)(pyrrolidin-1-yl)methanethione **(4k)**. Yield: 278 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.33 - 7.17 (m, 2H), 7.10 - 6.90 (m, 2H), 3.84 (s, 2H), 3.33 (t, J = 7.2 Hz, 2H), 2.05 - 1.83 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 190.0, 155.5 (d, J = 245 Hz), 131.3 (d, J = 16 Hz), 130.1 (d, J = 7 Hz), 128.5 (d, J = 2 Hz), 124.2 (d, J = 4 Hz), 115.4 (d, J = 21 Hz), 52.8, 52.3, 25.9, 24.3 ppm. $^{19}F\{^{1}H\}$ NMR (565 MHz, $CDCl_3$, 25 ºC): δ_F -116.4 ppm. HRMS (ESI) m/z: [$(M+H)^+$] calcd for $C_{11}H_{12}FNS$ 210.0674, found 210.0748.



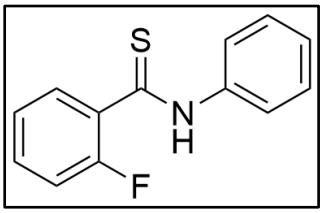
Morpholino(pyridin-2-yl)methanethione **(4l)**.[10] Yield: 296 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 8.50 (d, J = 4.8 Hz, 1H, Ar*H*), 7.76 - 7.70 (m, 1H, Ar*H*), 7.59 (d, J = 7.9 Hz, 1H, Ar*H*), 7.25 - 7.22 (m, 1H, Ar*H*), 4.44 - 4.41 (m, 2H), 3.91 - 3.88 (m, 2H), 3.72 - 3.68 (m, 2H), 3.60 - 3.57 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 197.7, 158.8, 148.3, 137.1, 123.9, 123.6, 66.8, 66.5, 52.5, 49.6 ppm.



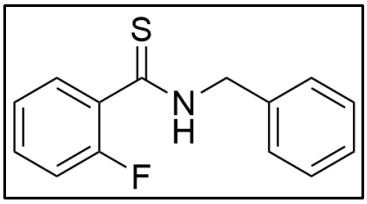
Piperidin-1-yl(pyridin-2-yl)methanethione **(4m).**[9] Yield: 287 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 8.51 (d, J = 4.8 Hz, 1H, Ar*H*), 7.77 - 7.70 (m, 1H, Ar*H*), 7.48 (d, J = 7.9 Hz, 1H, Ar*H*), 7.27 - 7.23 (m, 1H, Ar*H*), 4.37 - 4.31 (m, 2H), 3.50 - 3.43 (m, 2H), 1.85 - 1.73 (m, 4H), 1.65 - 1.59 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 195.5, 159.0, 147.8, 136.5, 122.5, 121.9, 52.6, 49.8, 26.2, 24.9, 23.5 ppm.



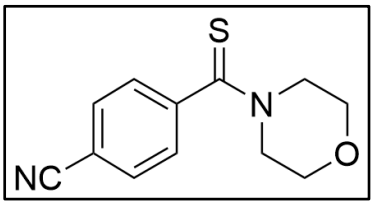
Pyridin-2-yl(pyrrolidin-1-yl)methanethione **(4n)**.[9] Yield: 282 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 8.36 (d, J = 0.7 Hz, 1H, Ar*H*), 7.65 - 7.53 (m, 2H, Ar*H*), 7.17 - 7.11 (m, 1H, Ar*H*), 3.87 - 3.80 (m, 2H), 3.52 - 3.45 (m, 2H), 1.95 - 1.83 (m, 4H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 193.2, 159.3, 147.5, 136.6, 123.3, 123.0, 53.4, 52.9, 26.3, 24.0 ppm.



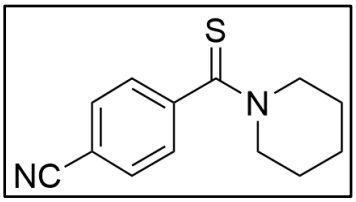
2-fluoro-N-phenylbenzothioamide **(4o)**.[11] Yield: 282 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 8.81 (s, 1H, N*H*), 7.97 - 7.93 (m, 2H, Ar*H*), 7.87 - 7.83 (m, 2H, Ar*H*), 7.44 - 7.39 (m, 2H, Ar*H*), 7.35 - 7.30 (m, 3H, Ar*H*) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 192.7, 157.3 (d, J = 247 Hz), 138.8, 133.4, 132.60 (d, J = 8 Hz), 129.2 (d, J = 10 Hz), 128.0 (d, J = 4 Hz), 127.3, 124.8 (d, J = 4 Hz), 124.1, 116.1 (d, J = 24 Hz) ppm. ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, 25 ºC): δ_F -116.2 ppm.



N-benzyl-2-fluorobenzothioamide **(4p)**.[11] Yield: 291 mg, 76%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.91 (s, 1H, N*H*), 7.69 - 7.64 (m, 2H, Ar*H*), 7.35 - 7.25 (m, 7H, Ar*H*), 4.90 (d, *J* = 5.3 Hz, 2H, CH_2NH) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 193.4, 157.8 (d, *J* = 248 Hz), 136.0, 133.5, 132.5 (d, *J* = 9 Hz), 129.1, 128.3 (d, *J* = 5 Hz), 128.1 (d, *J* = 11 Hz), 124.7 (d, *J* = 3 Hz), 116.0 (d, *J* = 24 Hz), 51.32 ppm. ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$, 25 ºC): δ_F -116.4 ppm.

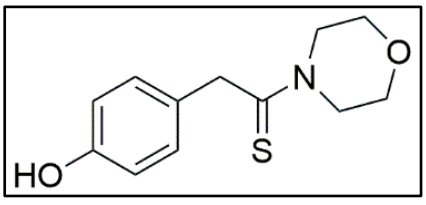


4-(morpholine-4-carbonothioyl)benzonitrile **(4q)**.[14] Yield: 311 mg, 86%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.65 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.36 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.41 - 4.37 (m, 2H), 3.89 - 3.84 (m, 2H), 3.66 - 3.61 (m, 2H), 3.55 - 3.50 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 197.9, 146.3, 132.6, 126.5, 118.2, 112.4, 66.6, 66.5, 52.6, 49.3 ppm.

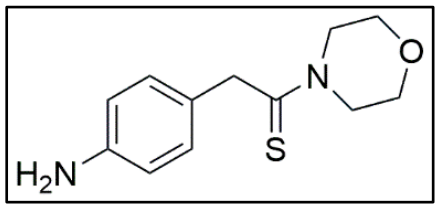


4-(piperidine-1-carbonothioyl)benzonitrile **(4r)**.[14] Yield: 323 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.60 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.32 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.31 - 4.26 (m, 2H), 3.44 - 3.40 (m, 2H), 1.80 - 1.70 (m, 4H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 196.2, 147.1, 132.4, 126.0, 118.3, 111.7, 53.2, 50.3, 26.8, 25.3, 23.9 ppm.

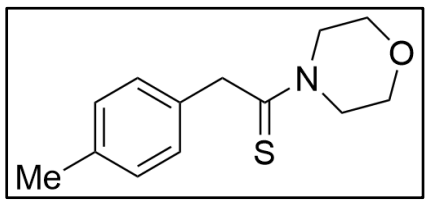
Characterisation data of thioamides (5a-5g) from ketones and different amines:



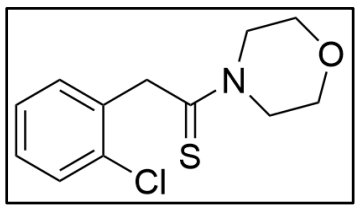
2-(4-hydroxyphenyl)-1-morpholinoethane-1-thione **(5a)**.[15] Yield: 259 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.12 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.77 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.35 - 4.31 (m, 2H), 4.24 (s, 2H, CH_2CS), 3.74 - 3.71 (m, 2H), 3.64 - 3.61 (m, 2H), 3.42 - 3.37 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 200.6, 155.0, 132.8, 129.0, 127.5, 116.2, 116.0, 66.4, 66.2, 50.9, 50.4, 49.7 ppm.



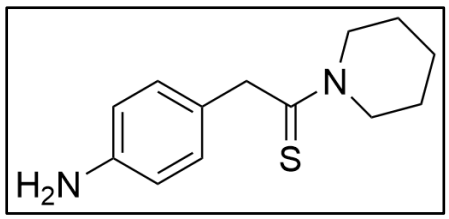
2-(4-aminophenyl)-1-morpholinoethane-1-thione **(5b)**.[16] Yield: 251 mg, 68%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.05 (d, J = 8.3 Hz, 2H, Ar*H*), 6.60 (d, J = 8.2 Hz, 2H, Ar*H*), 4.31 – 4.28 (m, 2H), 4.19 (s, 2H, CH_2CS), 3.70 - 3.67 (m, 2H), 3.62 - 3.59 (m, 2H), 3.39 - 3.33 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 200.8, 152.8, 145.4, 132.6, 128.7, 125.3, 115.5, 113.9, 66.5, 66.3, 66.3, 66.2, 50.7, 50.2, 49.8, 47.1 ppm.



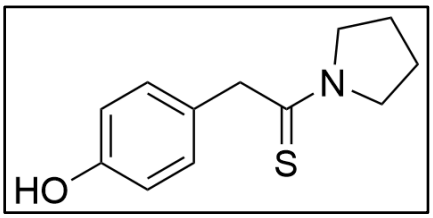
1-morpholino-2-(p-tolyl)ethane-1-thione **(5c)**.[17] Yield: 261 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.88 (d, J = 8.2 Hz, 1H, Ar*H*), 7.30 - 7.18 (m, 3H), 4.36 - 4.30 (m, 4H), 3.92 - 3.87 (m, 2H), 3.75 - 3.71 (m, 2H), 2.43 (s, 2H, CH_2CS), 2.32 (s, 3H, CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 200.4, 145.8, 136.8, 132.8, 130.1, 129.8, 129.7, 127.7, 126.8, 66.6, 66.2, 52.0, 50.9, 50.3, 50.3, 47.2, 22.0, 21.2 ppm.



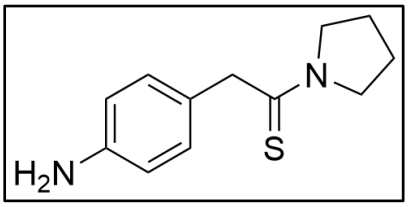
2-(2-chlorophenyl)-1-morpholinoethane-1-thione **(5d)**.[17] Yield: 291 mg, 73%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.45 - 7.36 (m, 2H, Ar*H*), 7.28 - 7.20 (m, 2H, Ar*H*), 4.40 - 4.35 (m, 4H), 3.79 - 3.75 (m, 2H), 3.57 - 3.53 (m, 2H), 3.49 - 3.45 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 199.5, 133.8, 133.2, 129.7, 129.1, 128.6, 127.4, 66.4, 66.2, 50.8, 50.1, 47.2 ppm.



2-(4-aminophenyl)-1-(piperidin-1-yl)ethane-1-thione **(5e)**. Yield: 238 mg, 65%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.12 (d, J = 8.5 Hz, 2H, Ar*H*), 6.65 - 6.60 (m, 2H, Ar*H*), 4.27 - 4.21 (m, 4H), 3.64 - 3.53 (m, 3H), 1.64 - 1.55 (m, 3H), 1.35 - 1.27 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 199.3, 145.2, 128.9, 126.1, 115.6, 51.8, 51.6, 50.4, 26.4, 25.4, 24.0 ppm. HRMS (ESI) m/z: [(M+H) $^{+}$] calcd for $C_{13}H_{18}N_2S$ 235.1191, found 235.1263.

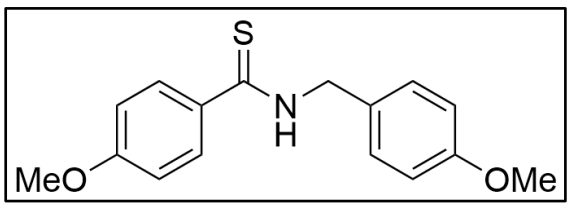


2-(4-hydroxyphenyl)-1-(pyrrolidin-1-yl)ethane-1-thione **(5f)**. Yield: 228 mg, 66%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.13 (d, J = 8.4 Hz, 2H, Ar*H*), 6.78 - 6.74 (m, 2H, Ar*H*), 4.07 (s, 2H, CH_2CS), 3.83 (t, J = 6.8 Hz, 2H), 3.51 (m, 3H), 1.97 - 1.91 (m, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 197.5, 155.0, 132.9, 129.7, 127.0, 116.2, 115.9, 54.4, 51.2, 50.3, 26.5, 24.4 ppm. HRMS (ESI) m/z: [(M+H)$^{+}$] calcd for $C_{12}H_{15}NOS$ 222.0874, found 222.0948.

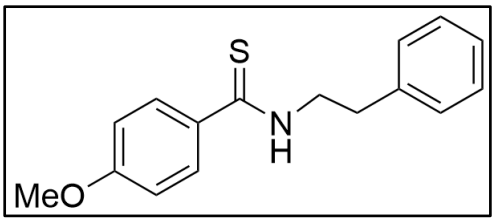


2-(4-aminophenyl)-1-(pyrrolidin-1-yl)ethane-1-thione **(5g)**. Yield: 230 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.80 - 7.76 (m, 2H, Ar*H*), 6.62 - 6.59 (m, 2H, Ar*H*), 4.35 (s, 2H, CH_2CS), 3.94 - 3.88 (m, 3H), 3.86 - 3.82 (m, 1H), 3.54 - 3.50 (m, 4H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 194.0, 152.5, 132.9, 129.5, 115.5, 114.0, 54.3, 51.3, 51.2, 51.0, 50.7, 26.6, 26.2, 24.4, 24.0 ppm. HRMS (ESI) m/z: [(M+H)$^{+}$] calcd for $C_{12}H_{16}N_2S$ 221.1034, found 221.1106.

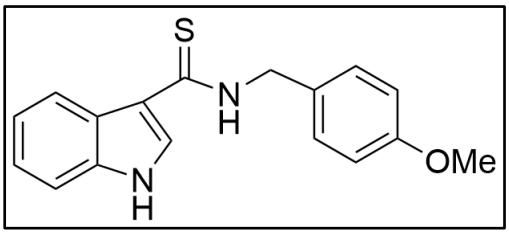
Characterisation data of thioamides (6a-6c) from acid and different amines:



4-methoxy-N-(4-methoxybenzyl)benzothioamide **(6a)**.[18] Yield: 399 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.76 - 7.71 (m, 2H, Ar*H*), 7.69 (s, 1H, N*H*), 7.32 - 7.28 (m, 2H, Ar*H*), 6.91 - 6.87 (m, 2H, Ar*H*), 6.85 - 6.80 (m, 2H, Ar*H*), 4.88 (d, J = 5.1 Hz, 2H, CH_2NH), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 197.7, 162.2, 159.5, 133.9, 129.8, 128.6, 128.5, 114.4, 113.7, 55.5, 55.4, 50.6 ppm.

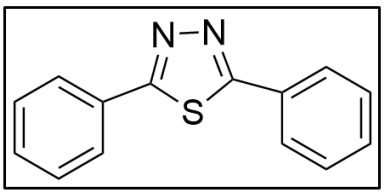


4-methoxy-N-phenethylbenzothioamide **(6b)**.[18] Yield: 364 mg, 86%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.68 - 7.63 (m, 2H, Ar*H*), 7.48 (s, 1H, N*H*), 7.37 - 7.25 (m, 5H, Ar*H*), 6.86 - 6.80 (m, 2H, Ar*H*), 4.13 - 4.07 (m, 2H, CH_2CH_2NH), 3.82 (s, 3H, OCH_3), 3.07 (t, J = 6.9 Hz, 2H, CH_2CH_2NH) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 198.2, 162.3, 138.5, 134.3, 129.0, 128.9, 128.5, 127.0, 113.8, 55.6, 47.5, 34.1 ppm.

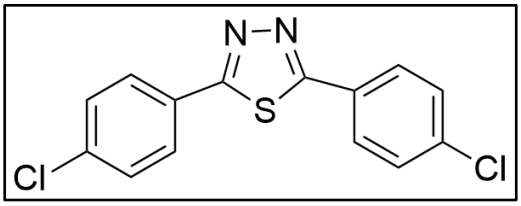


N-(4-methoxybenzyl)-1H-indole-3-carbothioamide **(6c)**. Yield: 393 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.79 - 7.75 (m, 2H, Ar*H*), 7.56 (s, 1H, N*H*), 7.35 - 7.31 (m, 2H, Ar*H*), 6.95 - 6.80 (m, 5H, Ar*H*), 4.92 (d, J = 4.9 Hz, 2H, CH_2NH), 3.83 (s, 3H, OCH_3) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 197.8, 162.4, 159.7, 130.0, 128.7, 114.5, 113.8, 55.6, 55.5, 50.8 ppm. LCMS (ESI) m/z: [(M+H) $^{+}$] calcd for $C_{17}H_{16}N_2OS$ 296.10, found 297.1.

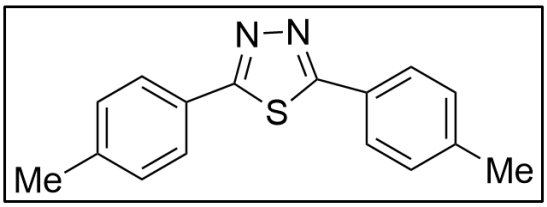
Characterisation data of thiazole products (7a-7d) obtained from thioamides:



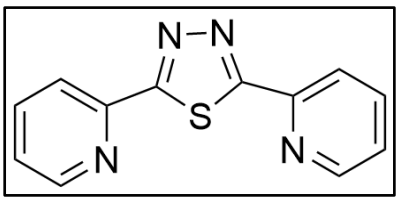
2,5-diphenyl-1,3,4-thiadiazole **(6a)**.[19] Yield: 113 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.71 - 7.65 (m, 4H, Ar*H*), 7.50 - 7.39 (m, 6H, Ar*H*) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 148.8, 130.9, 130.2, 129.0, 126.2 ppm.



2,5-bis(4-chlorophenyl)-1,3,4-thiadiazole **(6b)**.[19] Yield: 119 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.64 - 7.58 (m, 4H, Ar*H*), 7.44 - 7.36 (m, 4H, Ar*H*) ppm. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 147.7, 137.1, 129.4, 128.5, 127.4 ppm.



2,5-di-p-tolyl-1,3,4-thiadiazole **(6c)**.[19] Yield: 112 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 7.57 (d, J = 8.2 Hz, 4H, Ar*H*), 7.24 (d, J = 8.0 Hz, 4H, Ar*H*), 2.39 (s, 6H, CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 149.0, 141.2, 129.7, 127.3, 126.1, 21.6 ppm.



2,5-di(pyridin-2-yl)-1,3,4-thiadiazole **(6d)**.[20] Yield: 105 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ_H 8.58 - 8.55 (m, 2H, Ar*H*), 8.07 - 8.02 (m, 2H, Ar*H*), 7.78 - 7.71 (m, 2H, Ar*H*), 7.37 - 7.30 (m, 2H, Ar*H*) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25 ºC): δ_C 148.5, 147.6, 146.8, 136.8, 125.0, 121.4 ppm.

NMR spectra of DES:

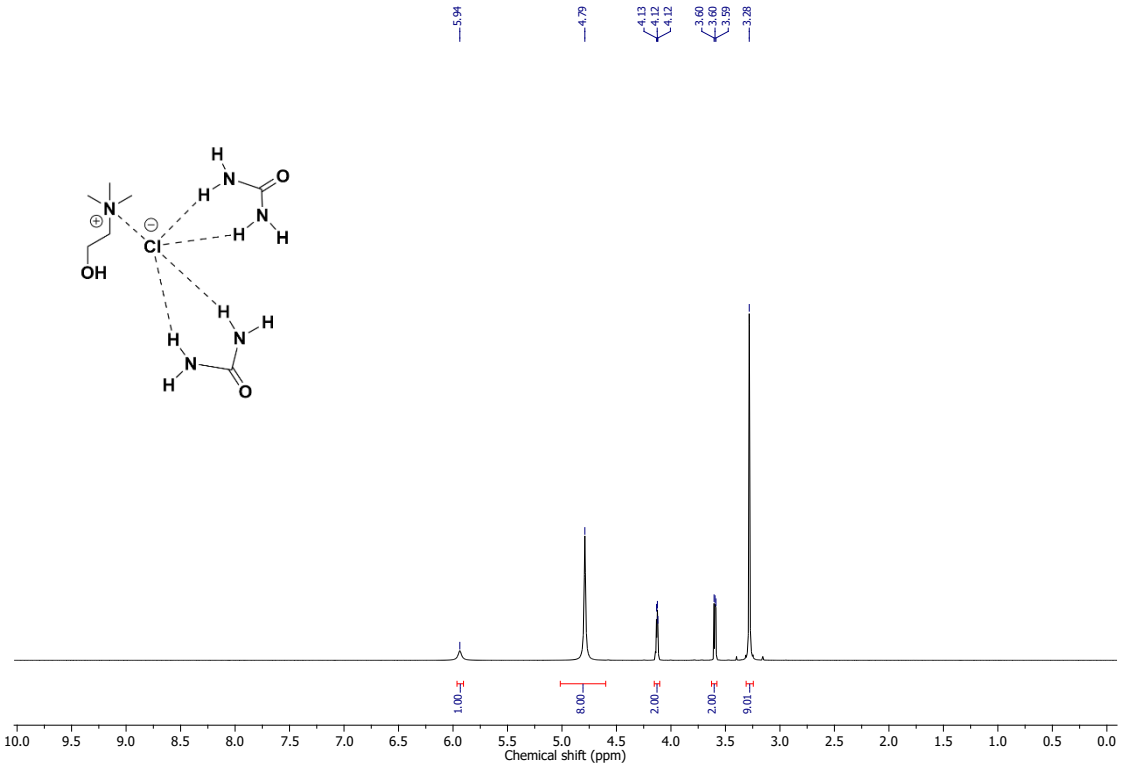


Fig S1. ^{1}H NMR spectra of (ChCl-urea) **DES** (D_2O, 600 MHz).

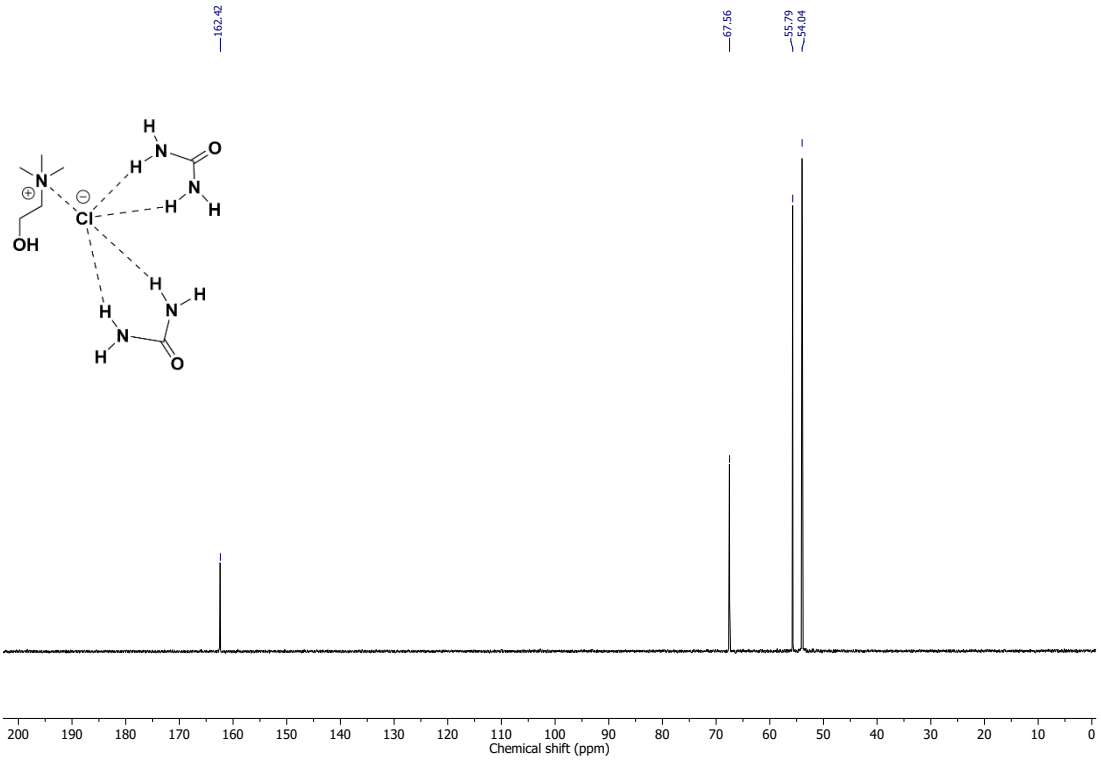


Fig S2. ^{13}C NMR spectra of (ChCl-urea) **DES** (D_2O, 150 MHz).

NMR spectra of thioamide compounds (3a-3n):

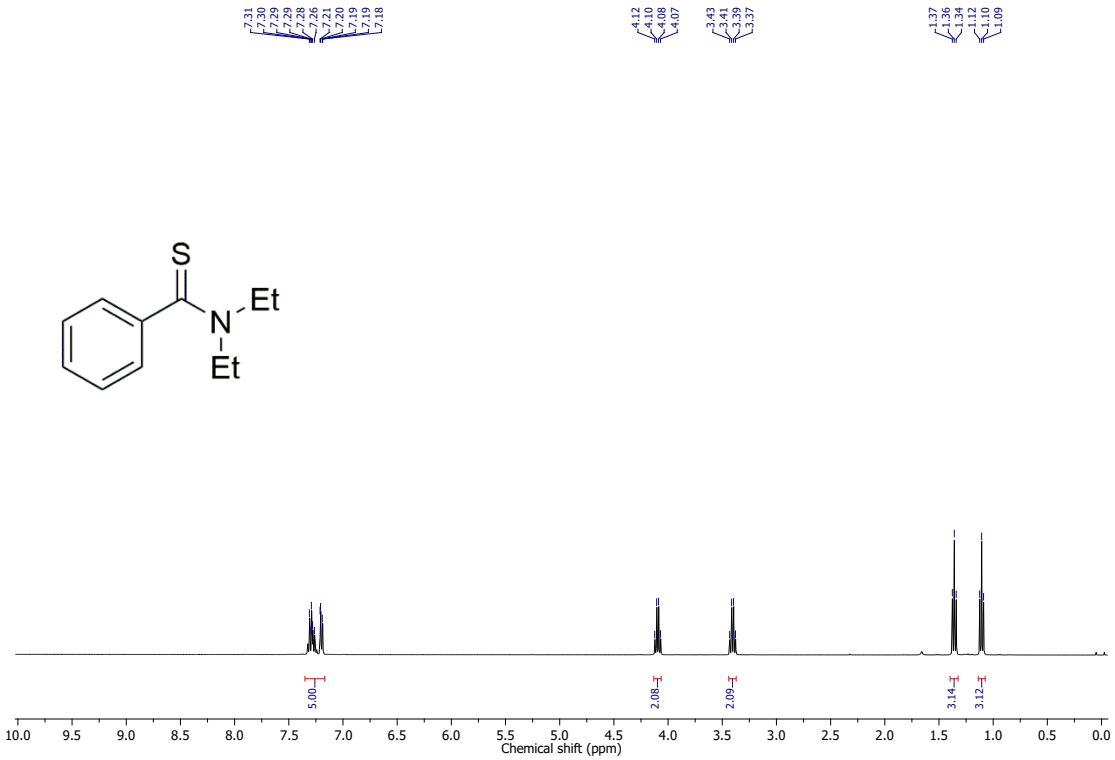


Fig S3. ^{1}H NMR spectra of **3a** ($CDCl_3$, 400 MHz).

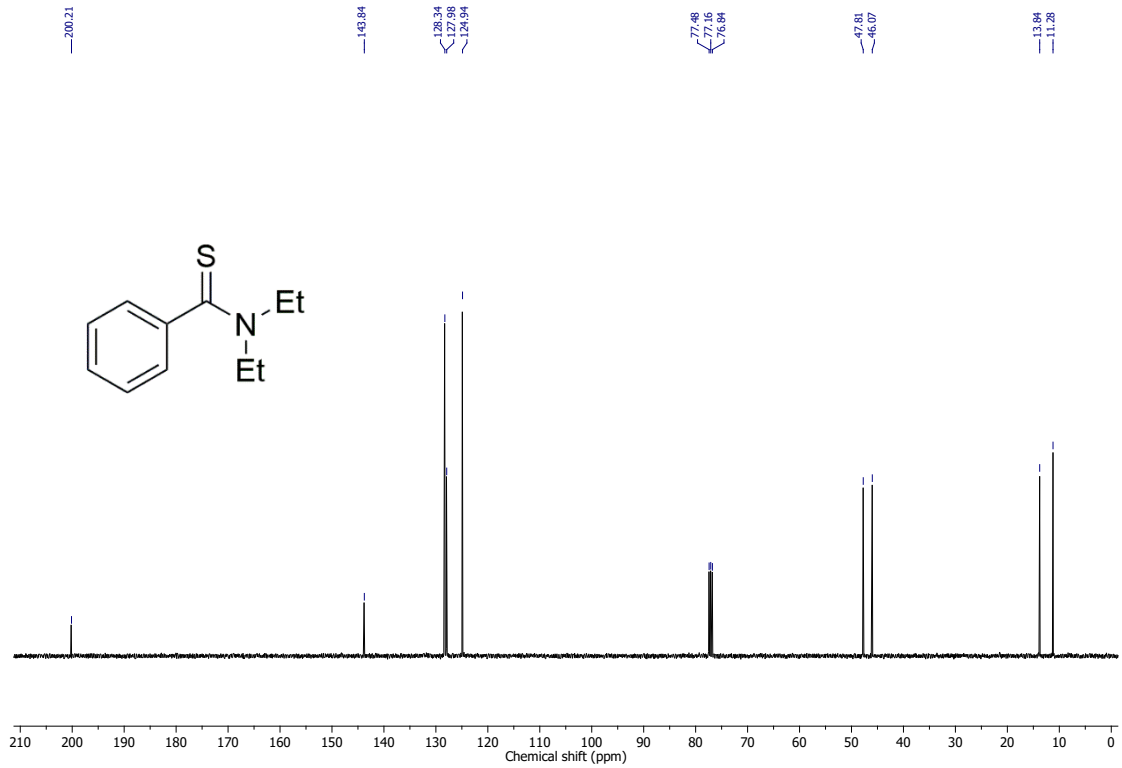


Fig S4. ^{13}C NMR spectra of **3a** ($CDCl_3$, 100 MHz).

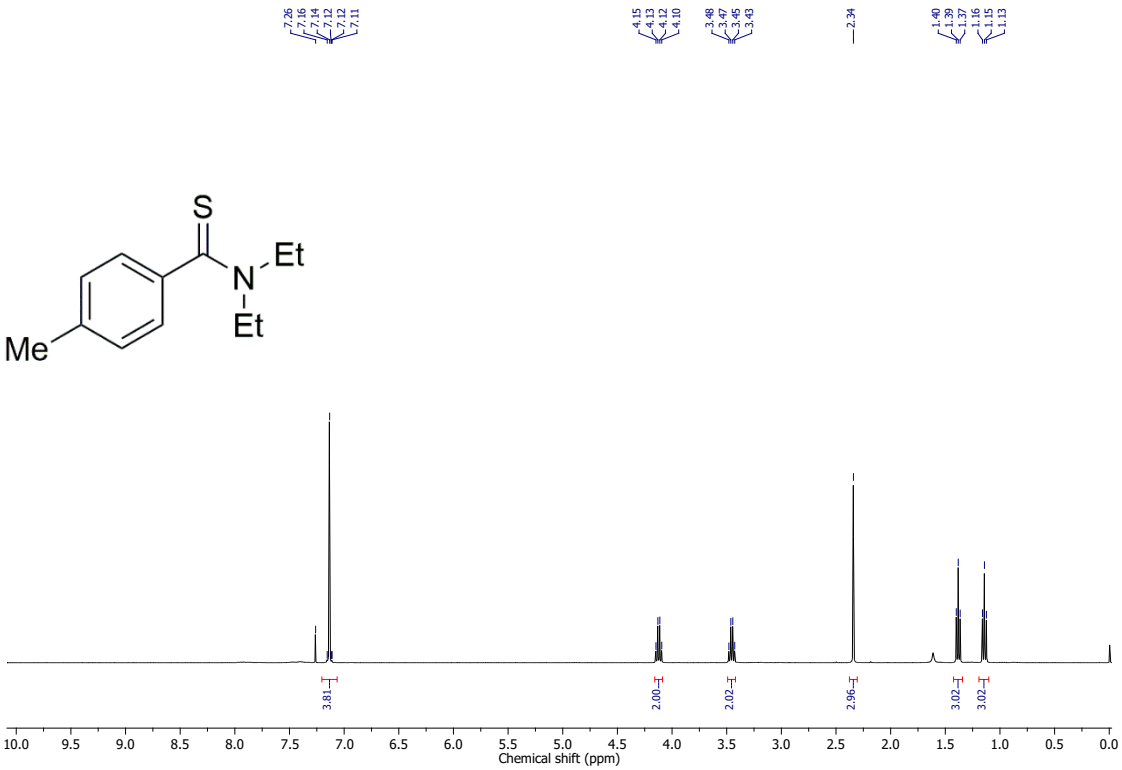


Fig S5. ^{1}H NMR spectra of **3b** ($CDCl_3$, 400 MHz)

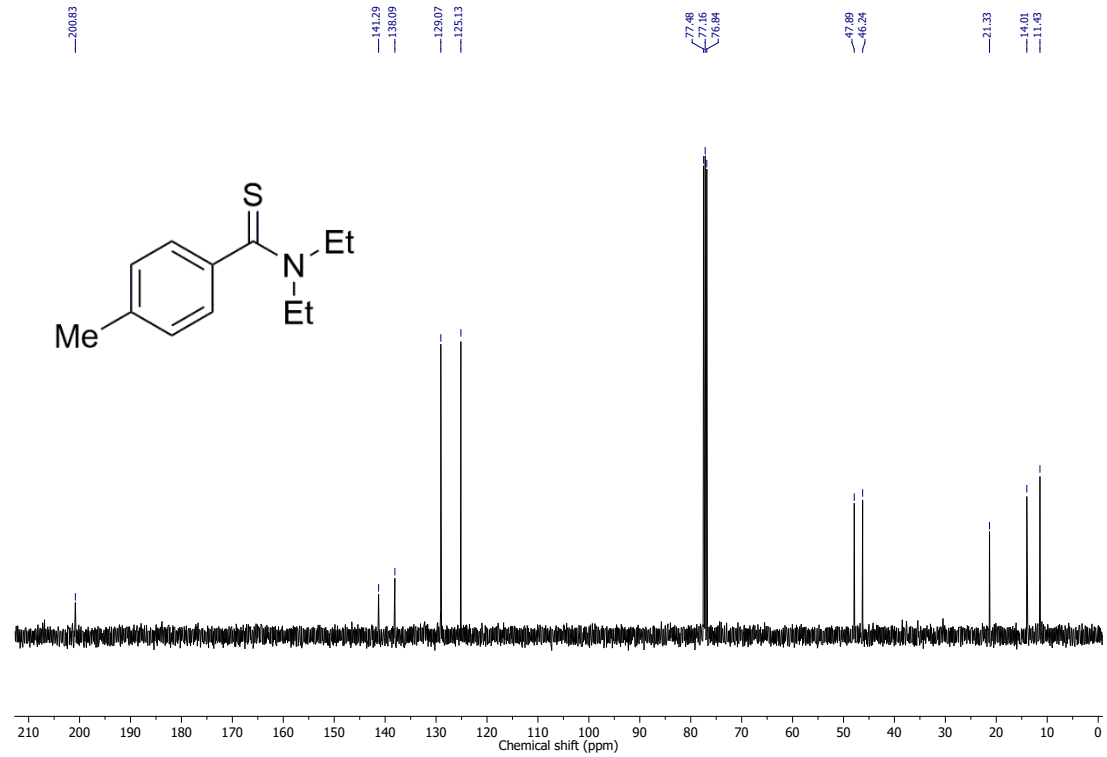


Fig S6. ^{13}C NMR spectra of **3b** ($CDCl_3$, 100 MHz).

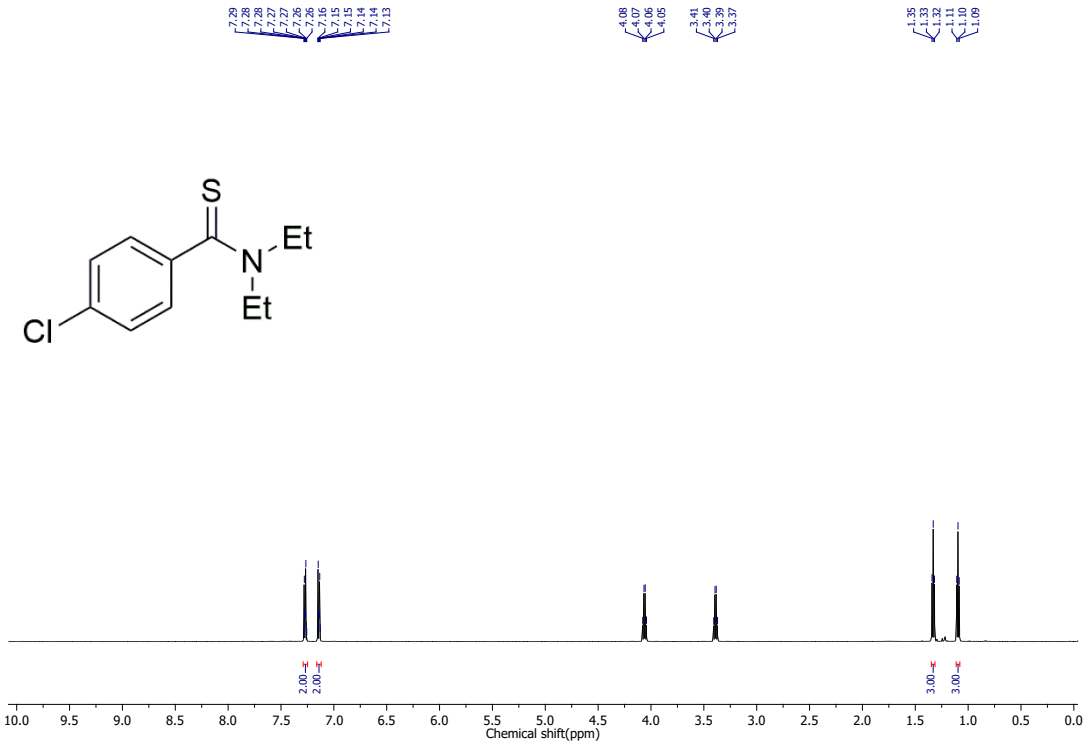


Fig S7. ^{1}H NMR spectra of **3c** ($CDCl_3$, 600 MHz).

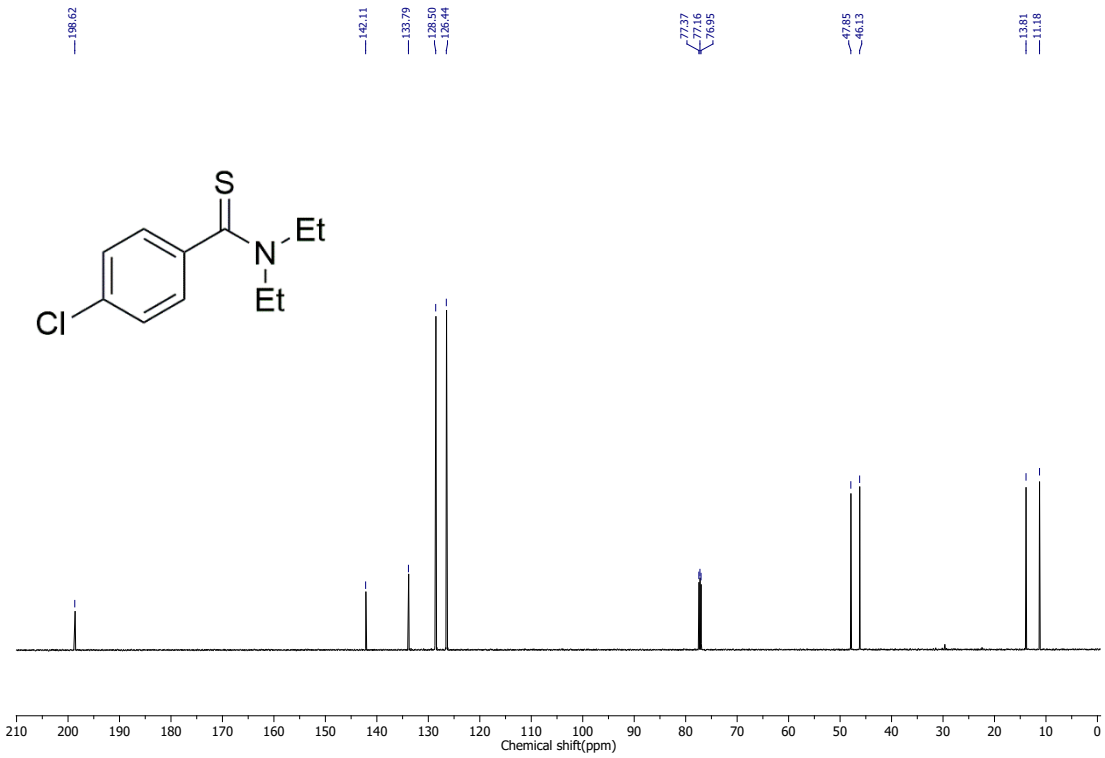


Fig S8. ^{13}C NMR spectra of **3c** ($CDCl_3$, 150 MHz).

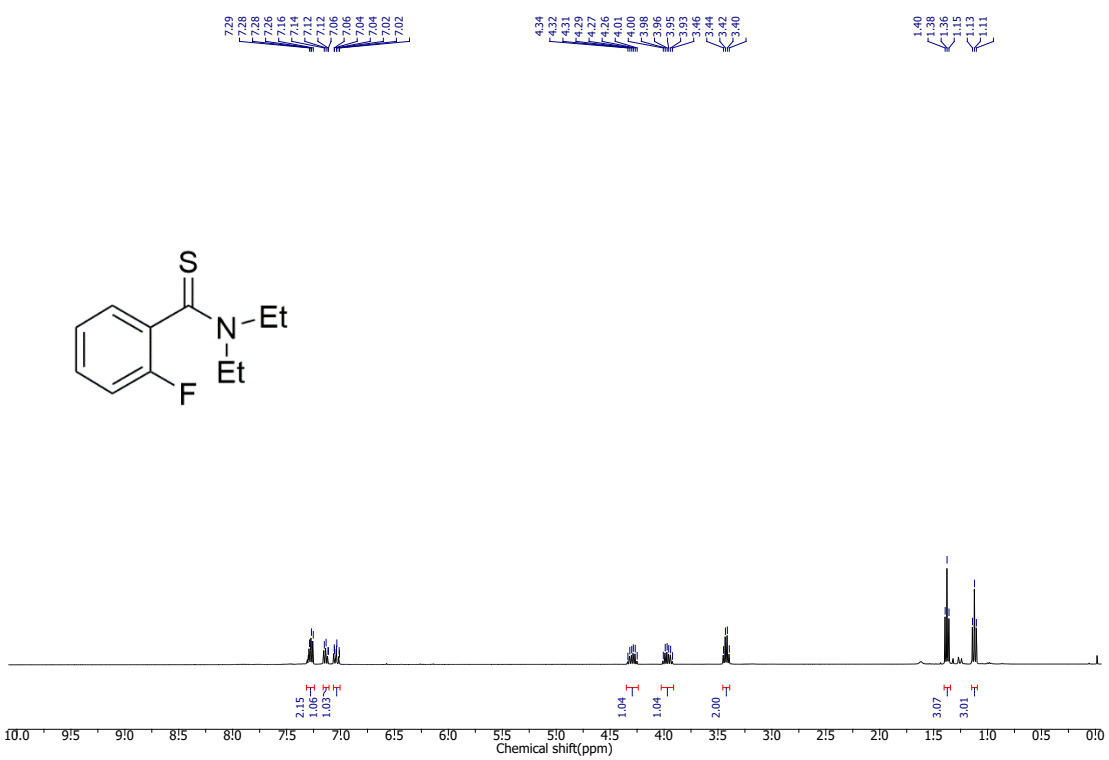


Fig S9. ^{1}H NMR spectra of **3d** ($CDCl_3$, 400 MHz).

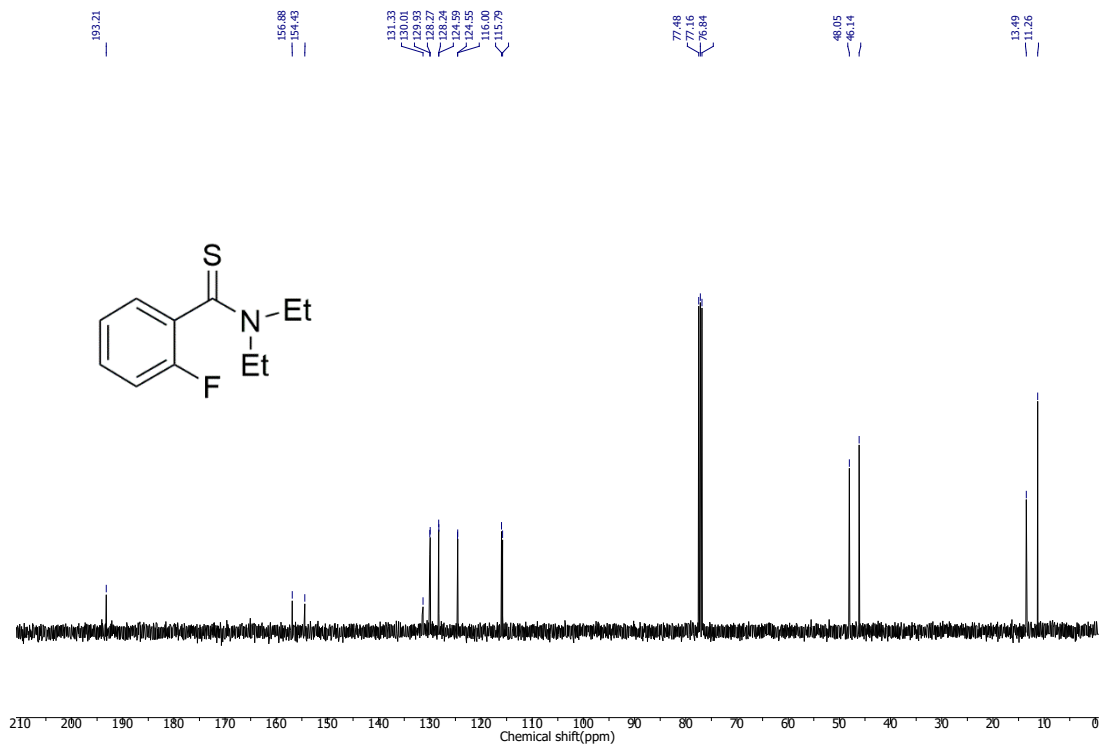


Fig S10. ^{13}C NMR spectra of **3d** ($CDCl_3$, 100 MHz).

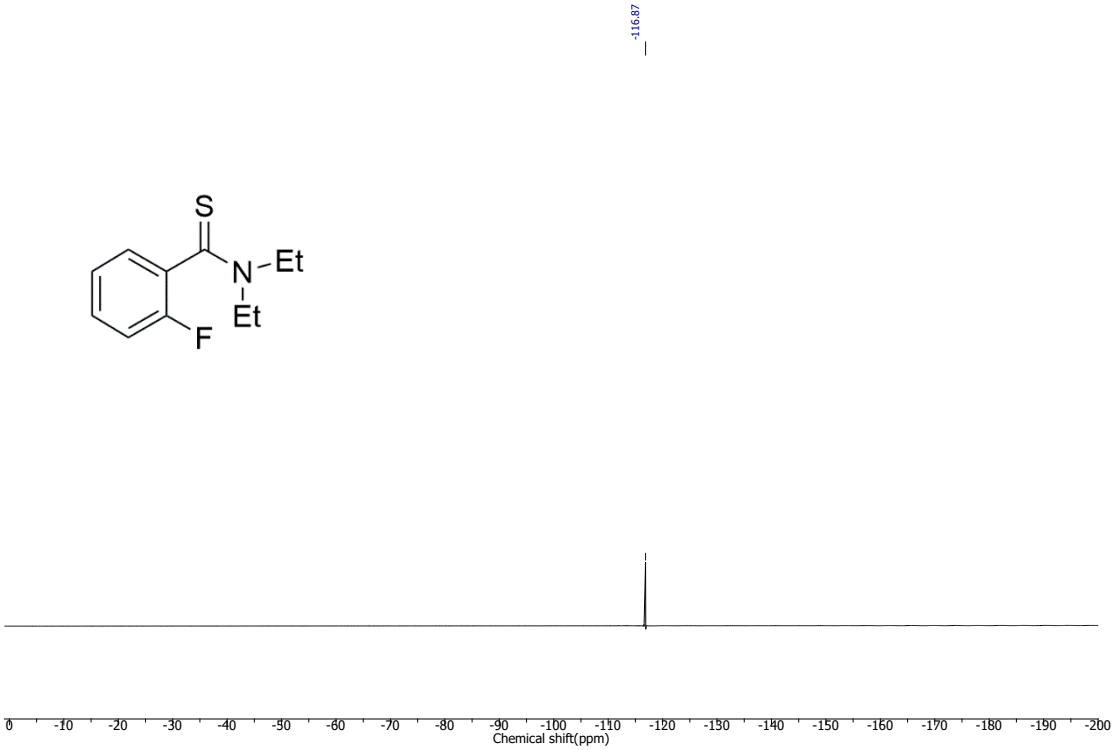


Fig S11. $^{19}F\{^{1}H\}$ NMR spectra of **3d** ($CDCl_3$, 565 MHz).

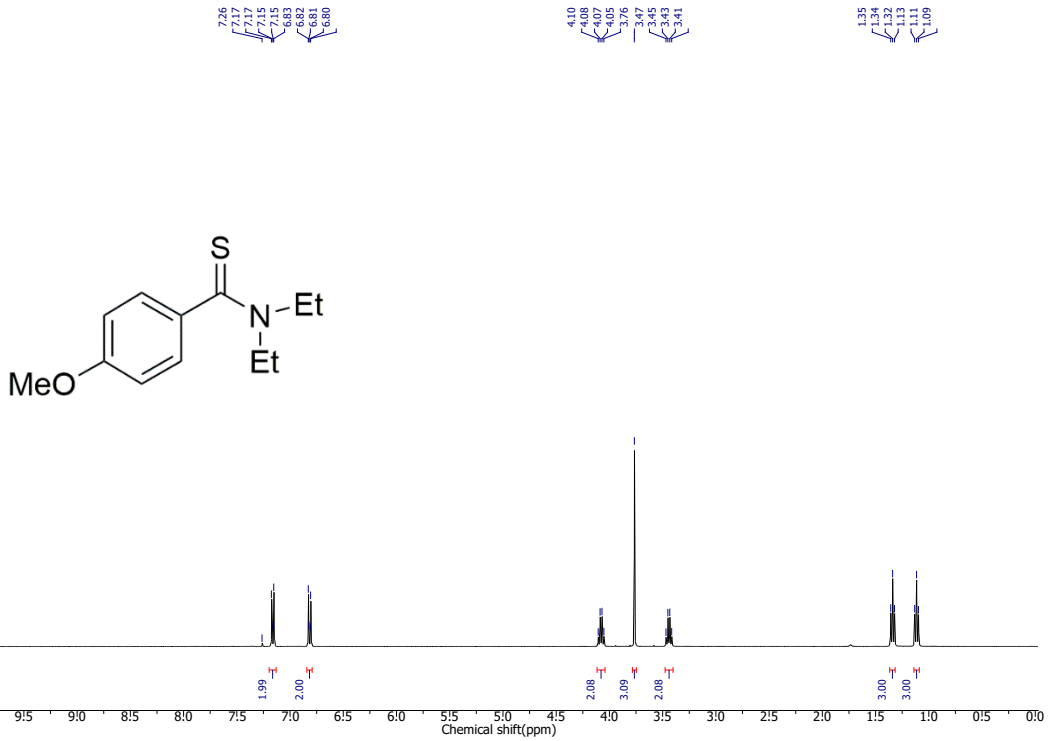


Fig S12. ^{1}H NMR spectra of **3e** ($CDCl_3$, 400 MHz).

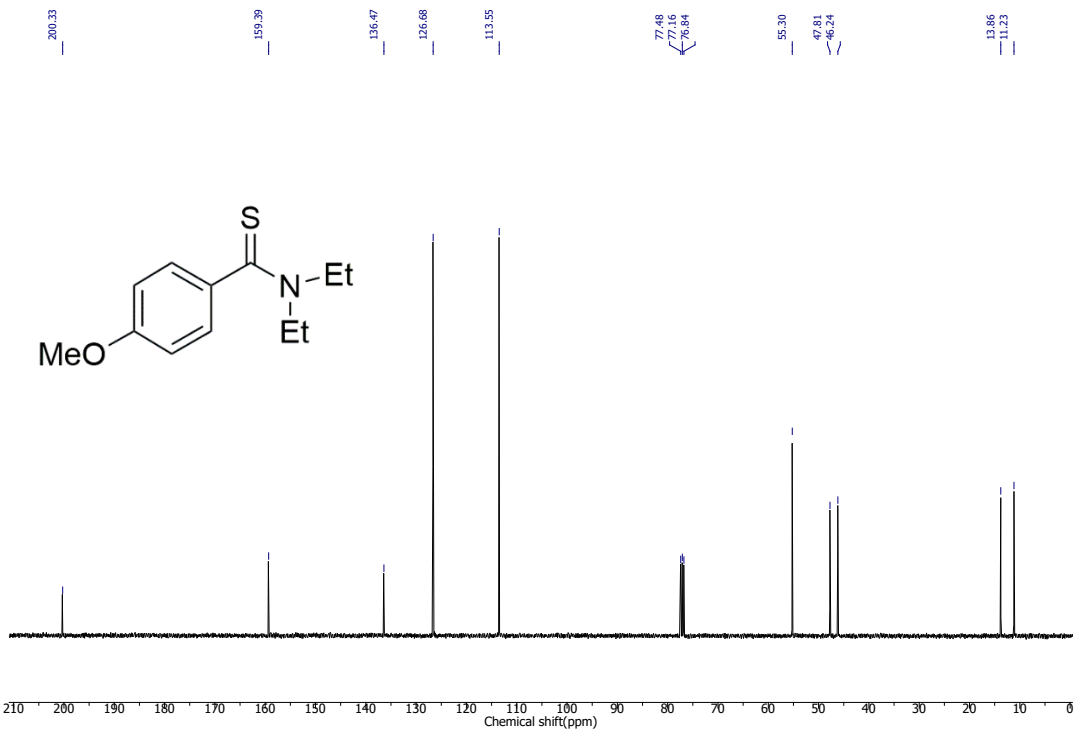


Fig S13. ^{13}C NMR spectra of **3e** ($CDCl_3$, 100 MHz).

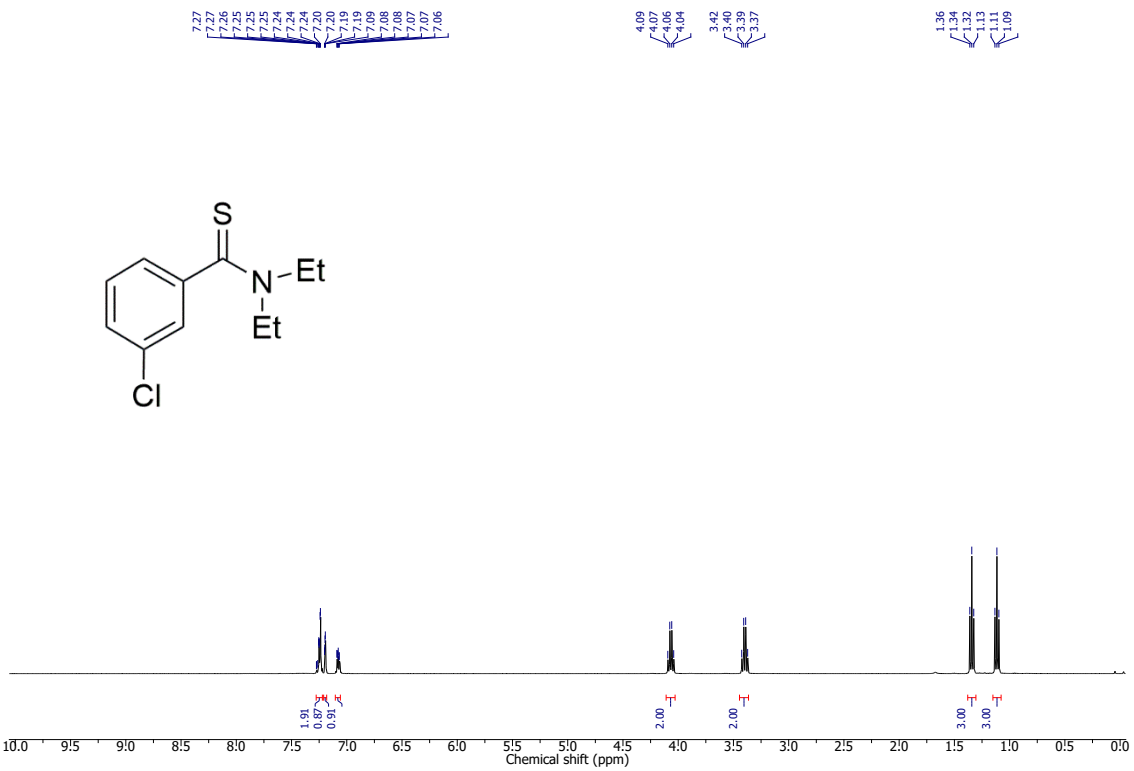


Fig S14. ^{1}H NMR spectra of **3f** ($CDCl_3$, 400 MHz).

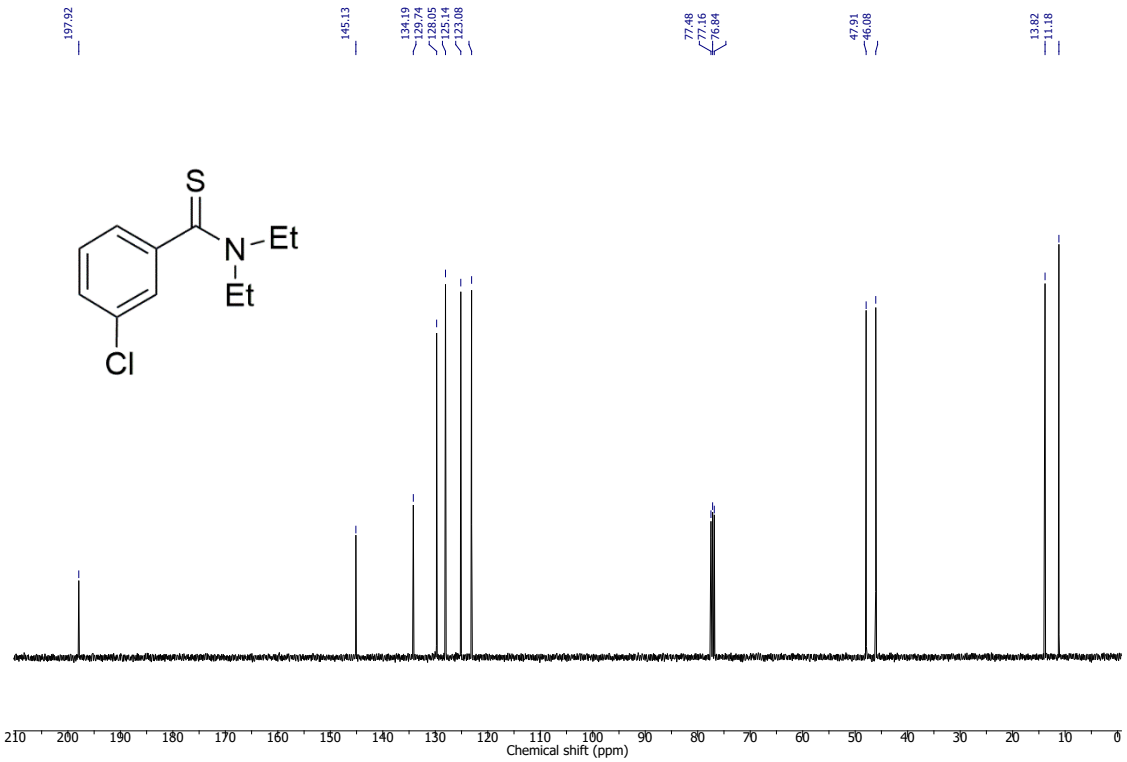


Fig S15. ^{13}C NMR spectra of **3f** ($CDCl_3$, 100 MHz).

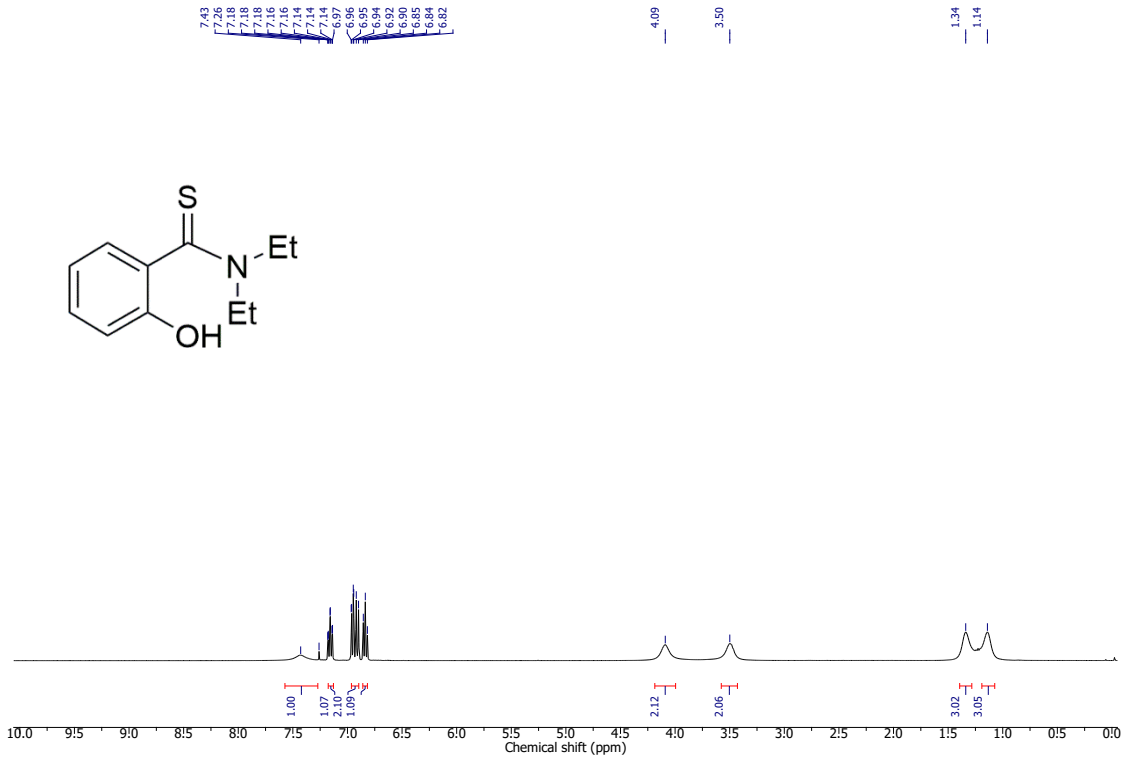


Fig S16. ^{1}H NMR spectra of **3g** ($CDCl_3$, 400 MHz).

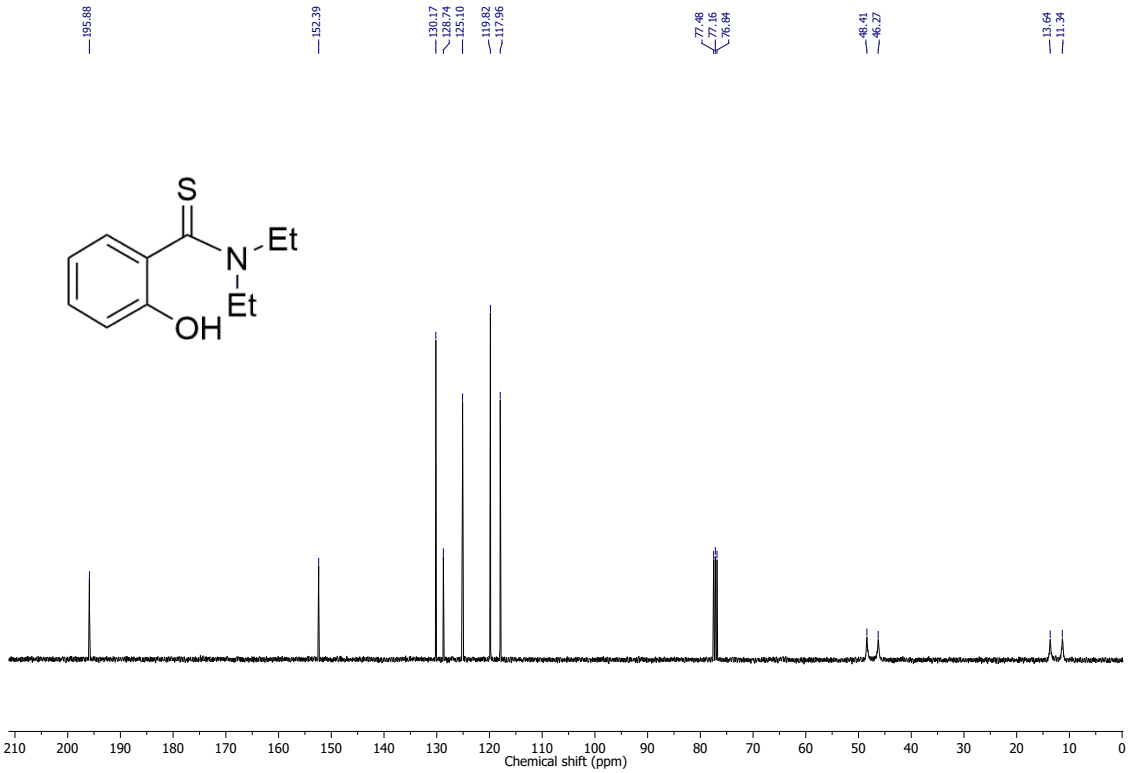


Fig S17. ^{13}C NMR spectra of **3g** ($CDCl_3$, 100 MHz).

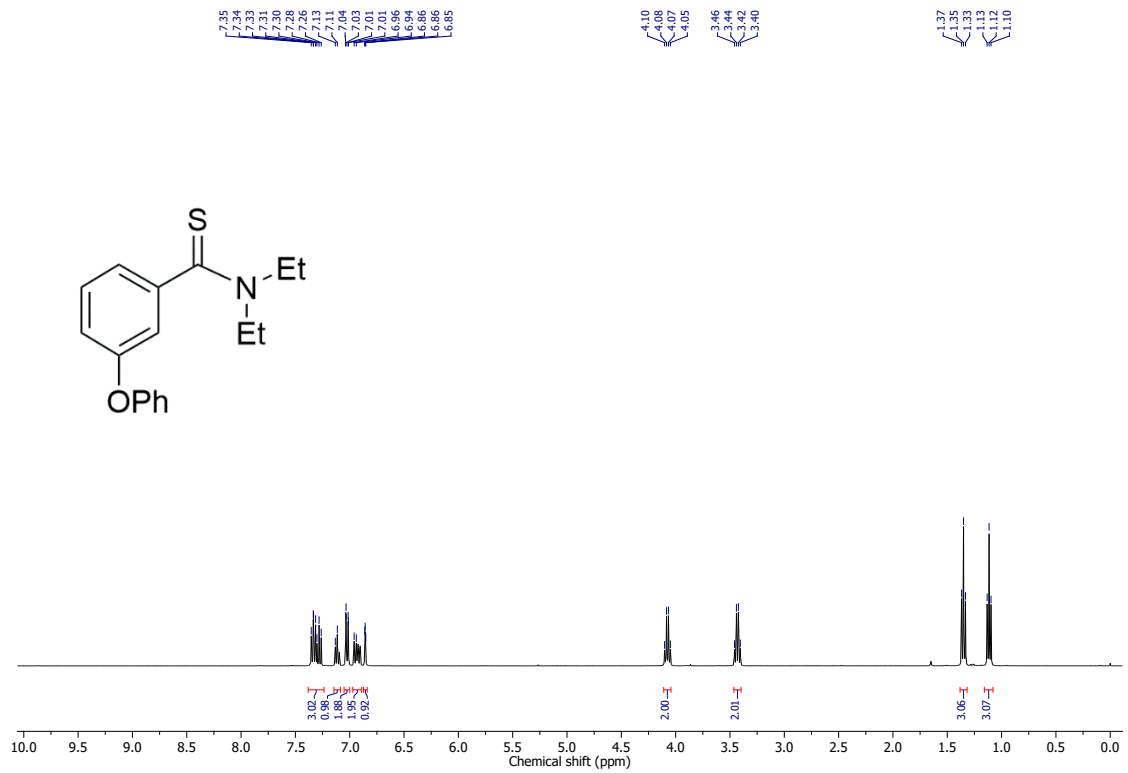


Fig S18. ^{1}H NMR spectra of **3h** ($CDCl_3$, 400 MHz).

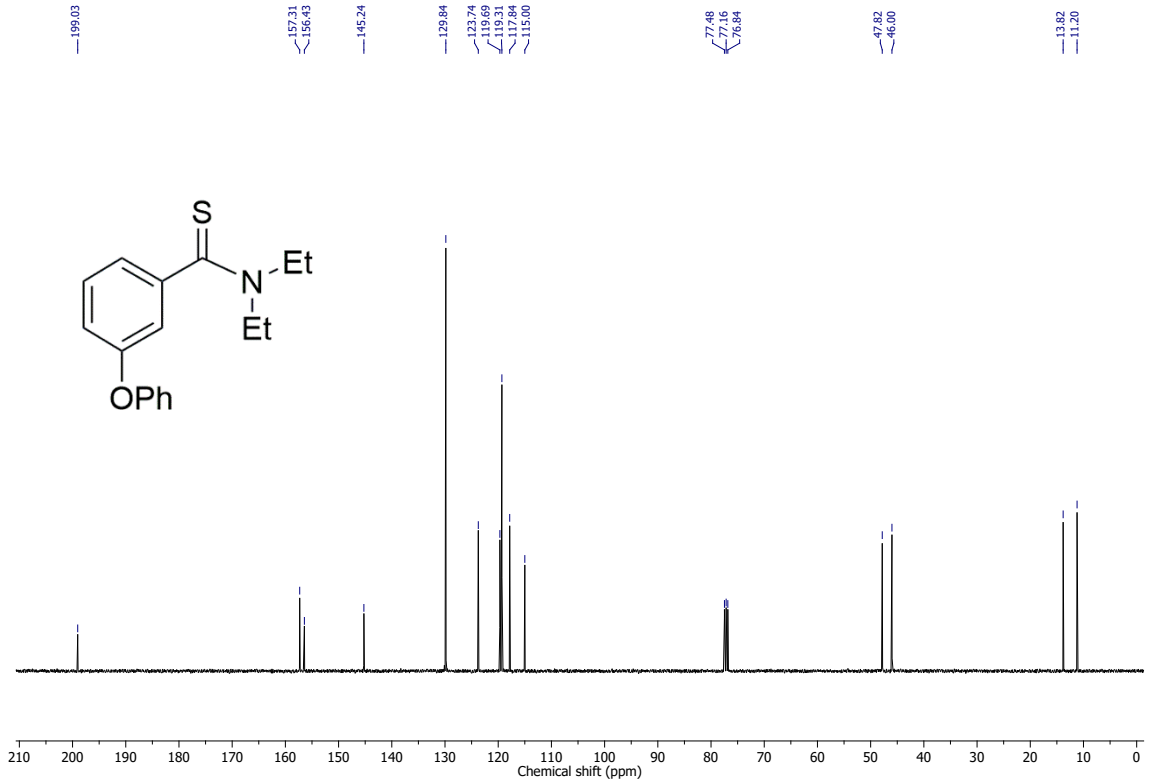


Fig S19. ^{13}C NMR spectra of **3h** ($CDCl_3$, 100 MHz).

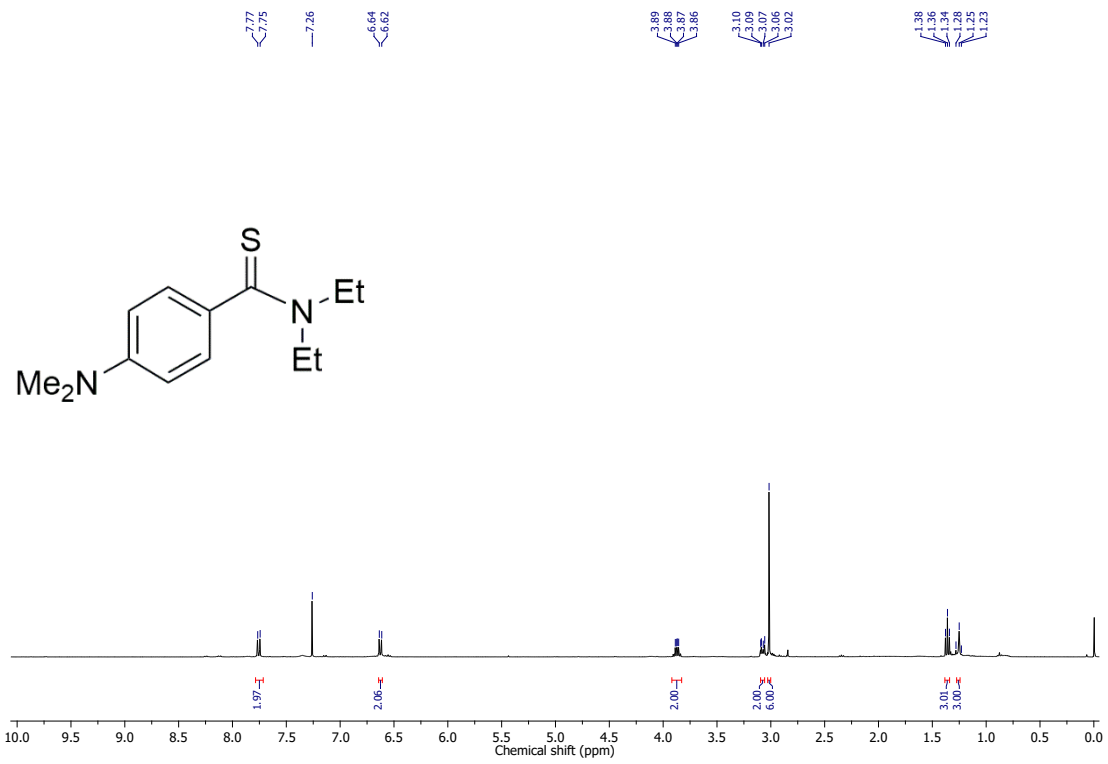


Fig S20. ^{1}H NMR spectra of **3i** ($CDCl_3$, 400 MHz).

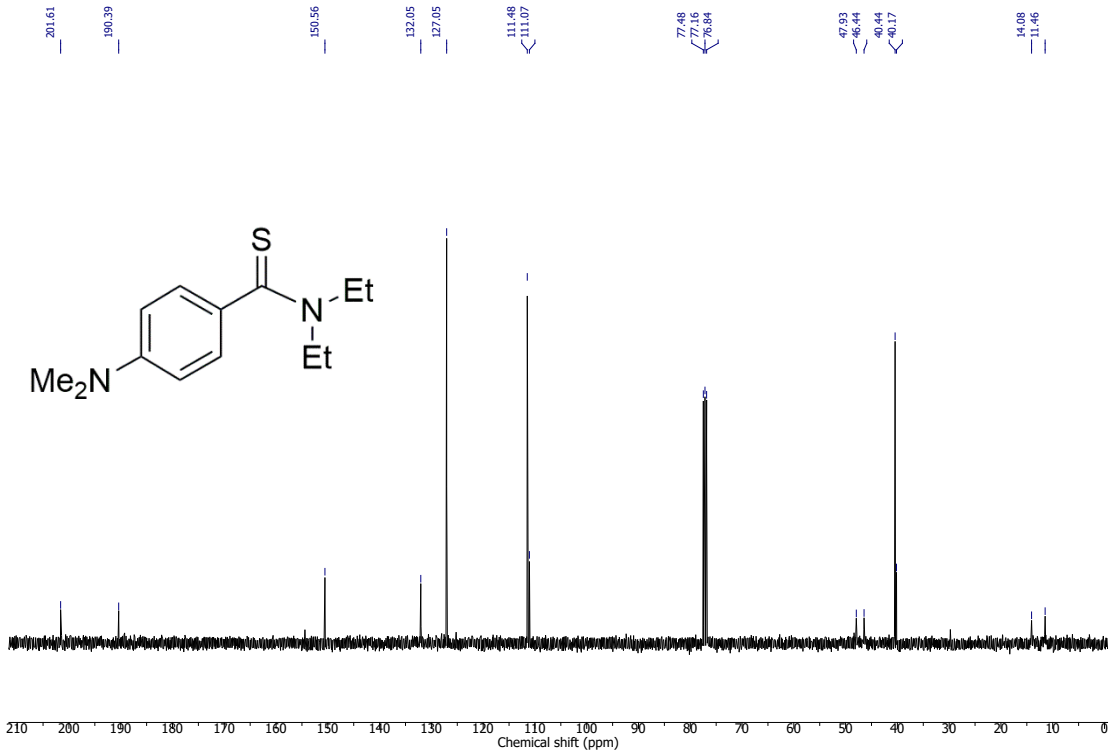


Fig S21. ^{13}C NMR spectra of **3i** ($CDCl_3$, 100 MHz).

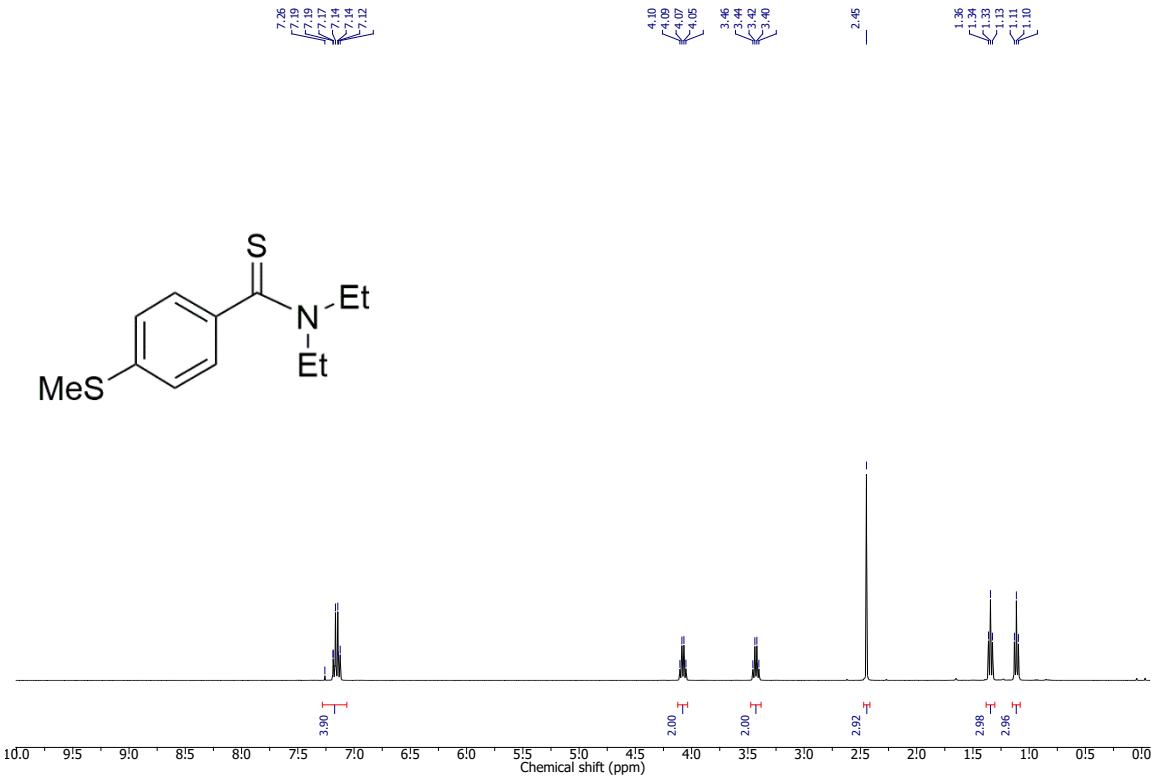


Fig S22. ^{1}H NMR spectra of **3j** ($CDCl_3$, 400 MHz).

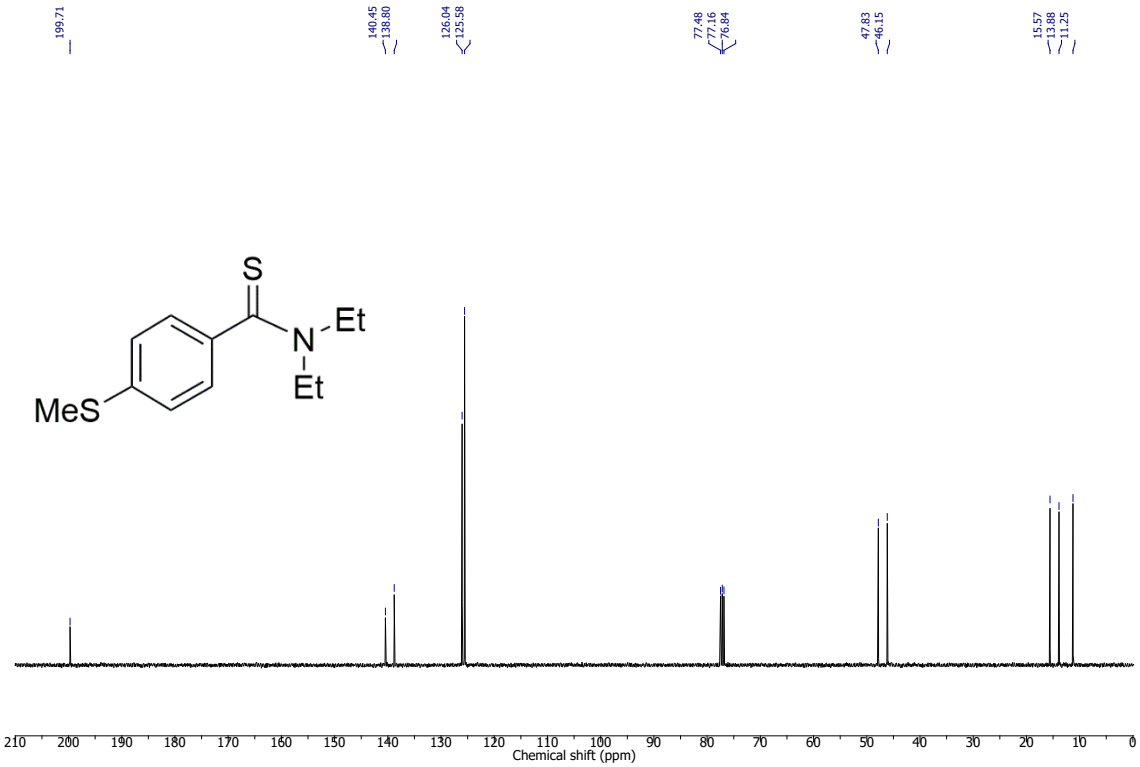


Fig S23. ^{13}C NMR spectra of **3j** ($CDCl_3$, 100 MHz).

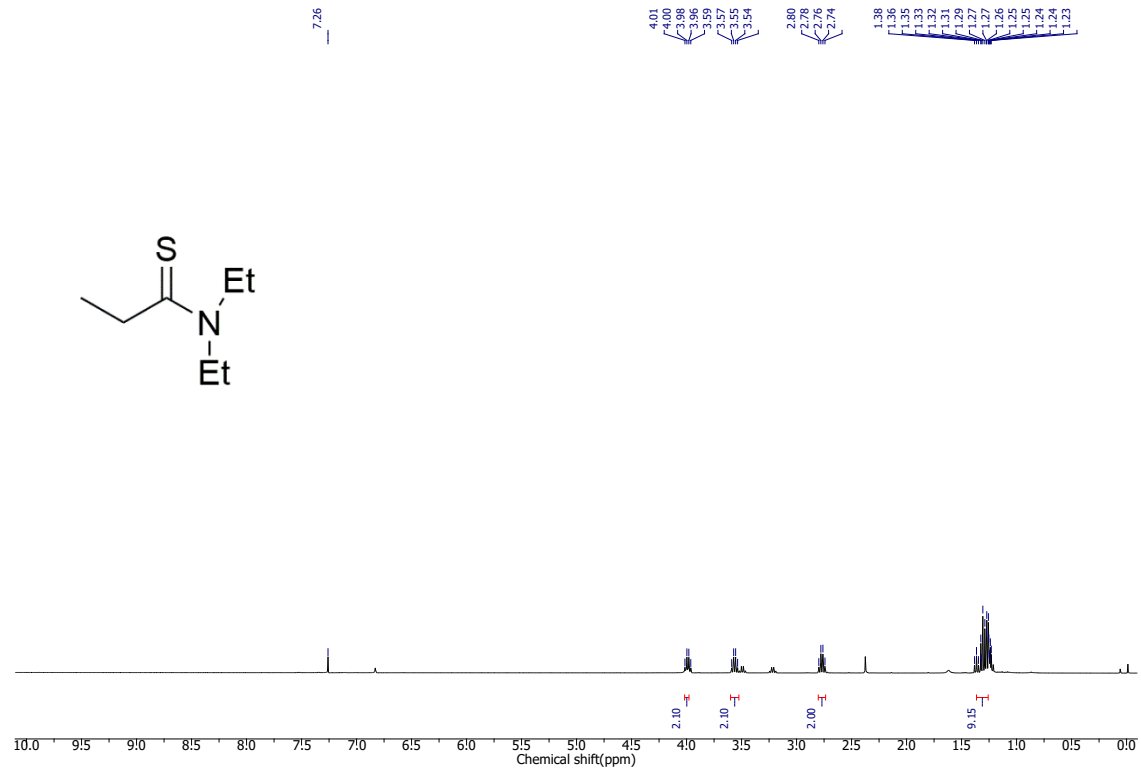


Fig S24. ^{1}H NMR spectra of **3k** ($CDCl_3$, 400 MHz).

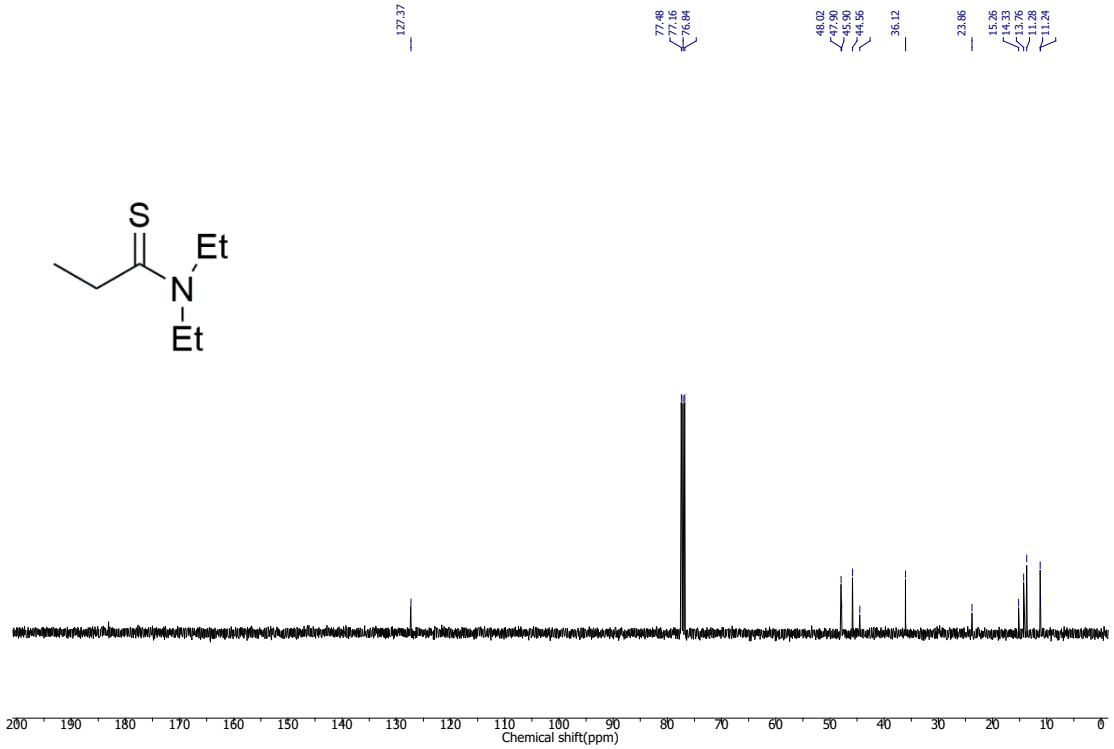


Fig S25. ^{13}C NMR spectra of **3k** ($CDCl_3$, 100 MHz).

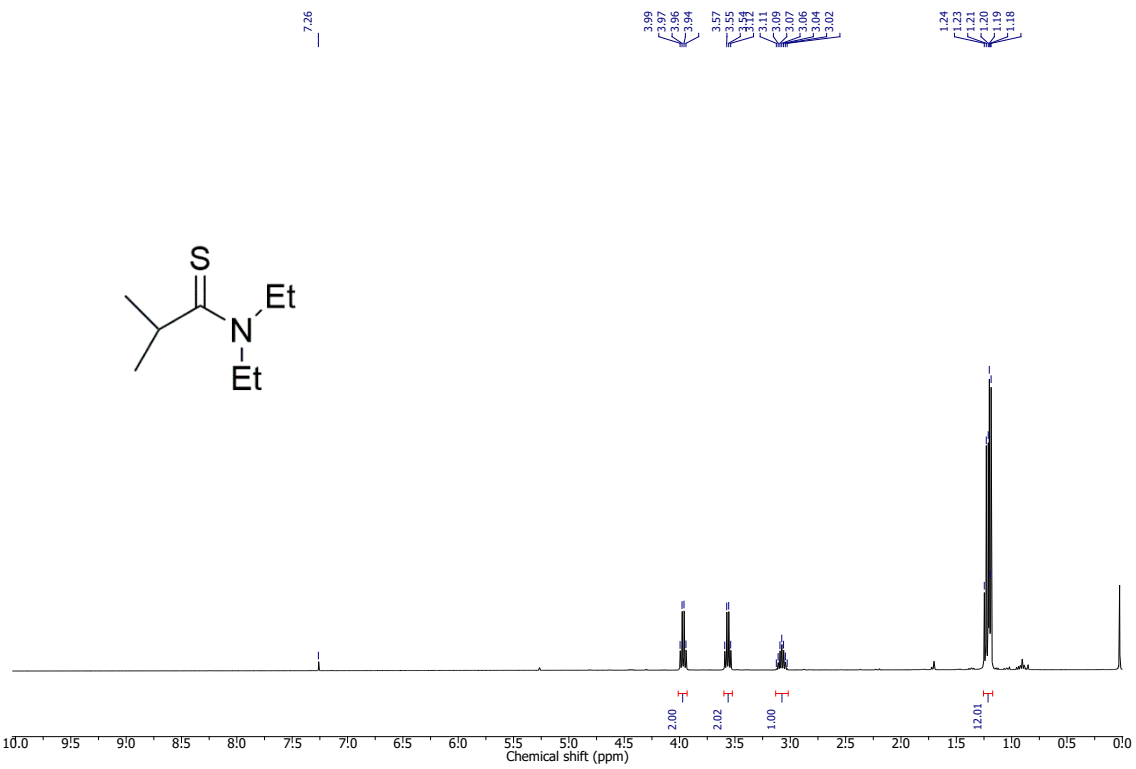


Fig S26. ^{1}H NMR spectra of **3l** ($CDCl_3$, 400 MHz).

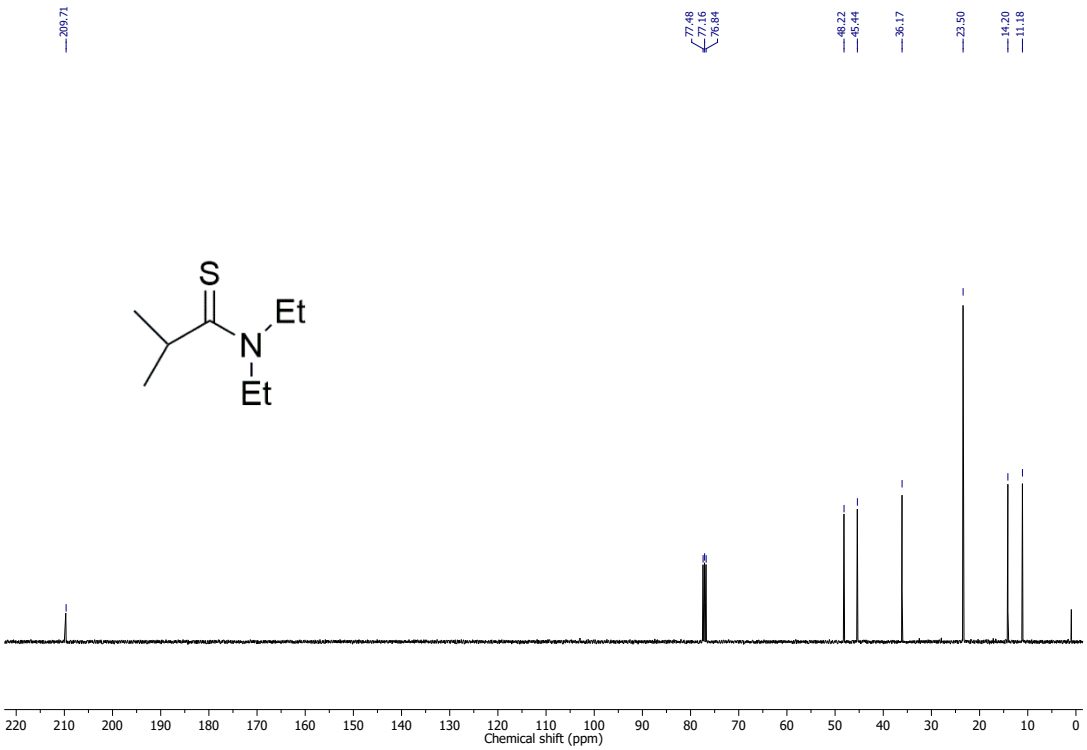


Fig S27. ^{13}C NMR spectra of **3l** ($CDCl_3$, 100 MHz).

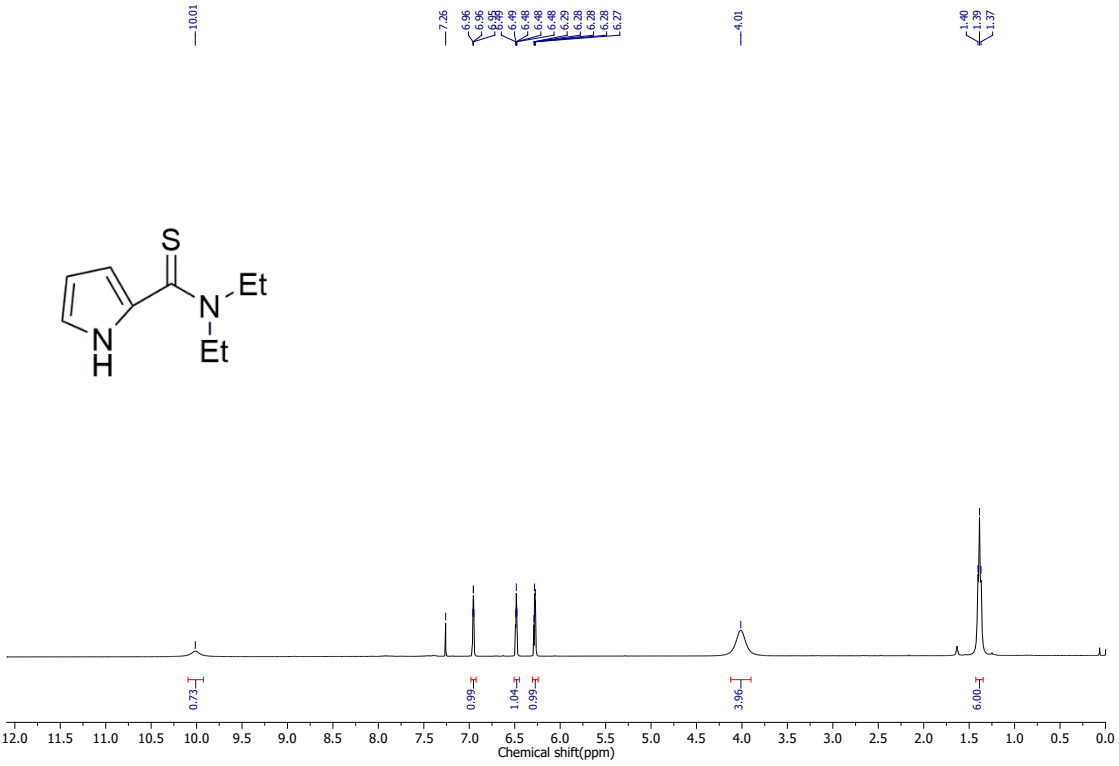


Fig S28. ^{1}H NMR spectra of **3m** ($CDCl_3$, 400 MHz).

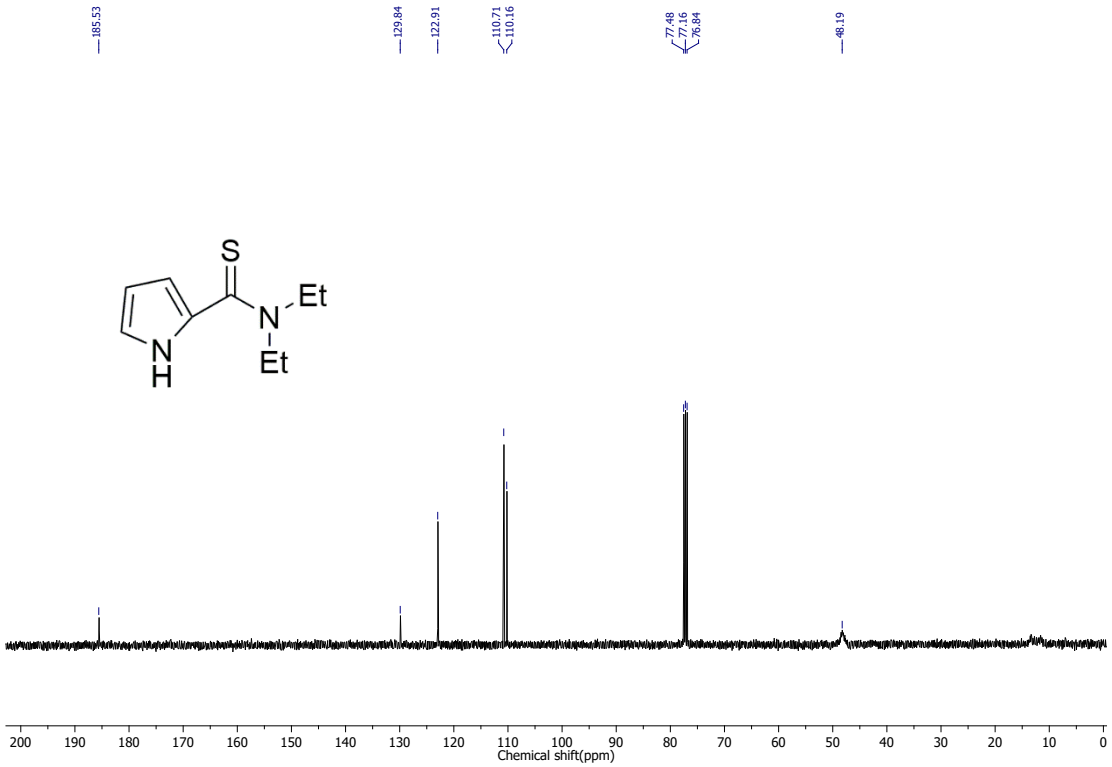


Fig S29. ^{13}C NMR spectra of **3m** ($CDCl_3$, 100 MHz).

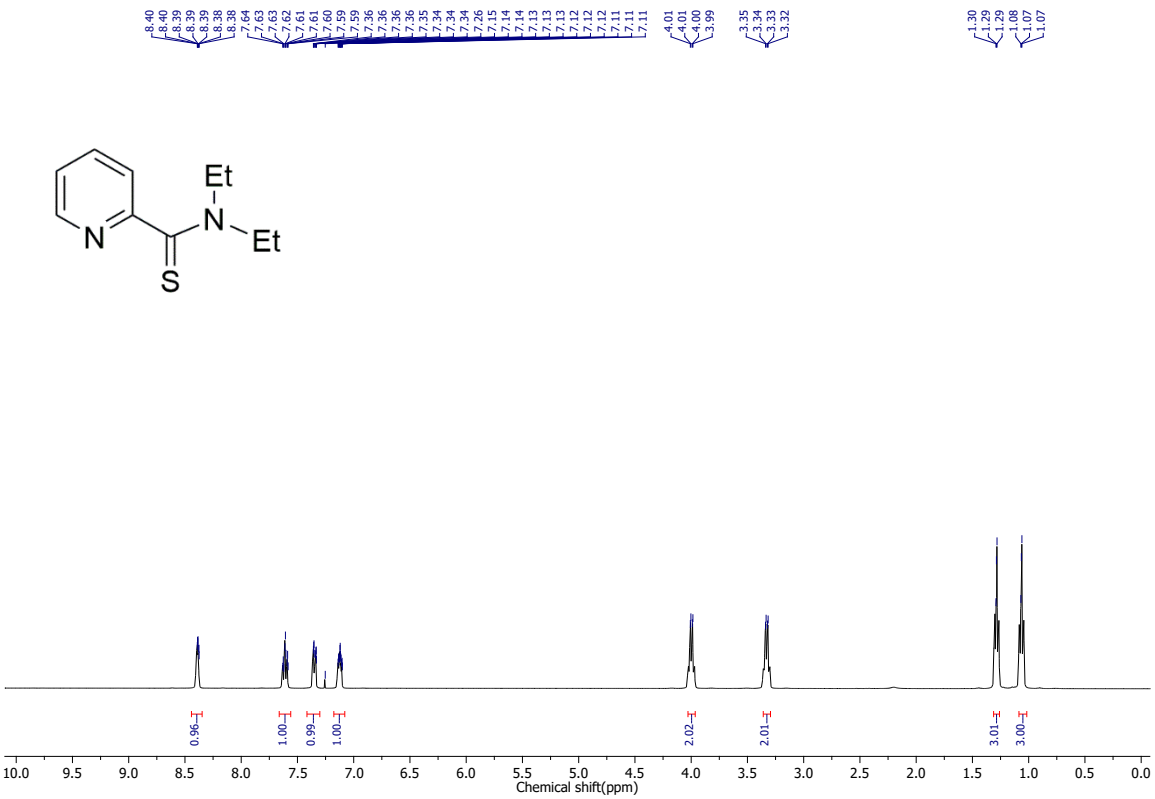


Fig S30. ^{1}H NMR spectra of **3n** ($CDCl_3$, 400 MHz).

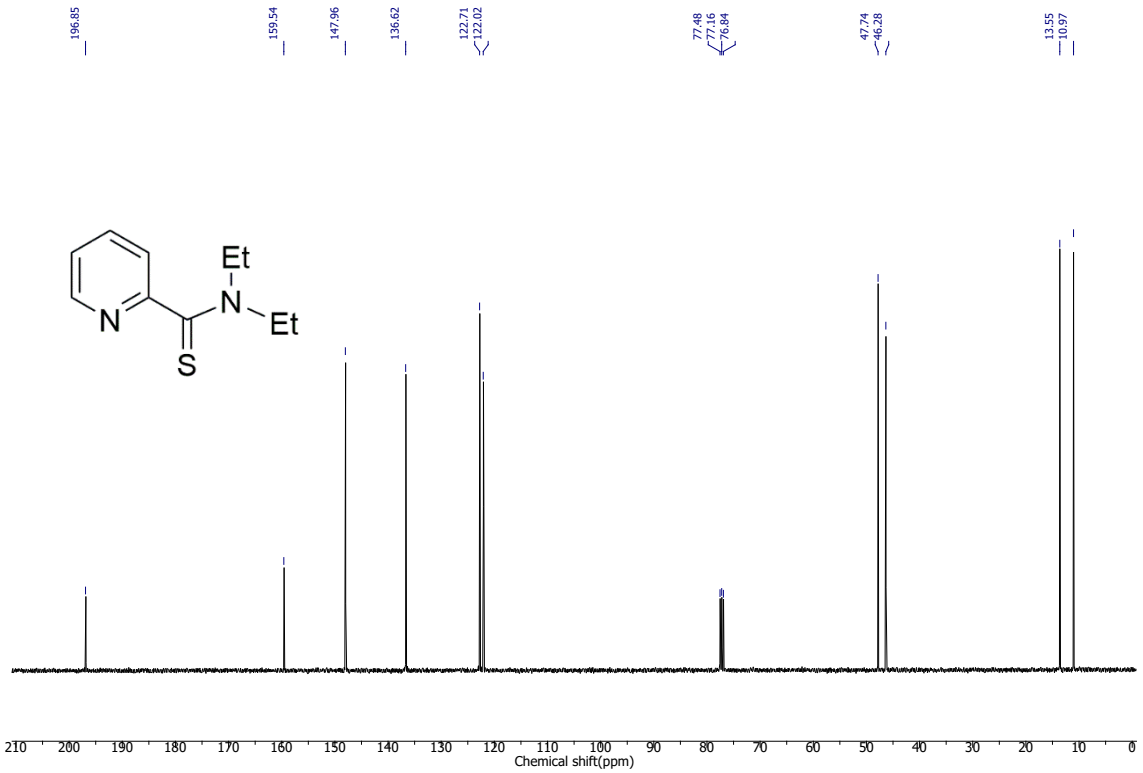


Fig S31. ^{13}C NMR spectra of **3n** ($CDCl_3$, 100 MHz)

NMR spectra of thioamides (4a-4p) from cyclic secondary amines:

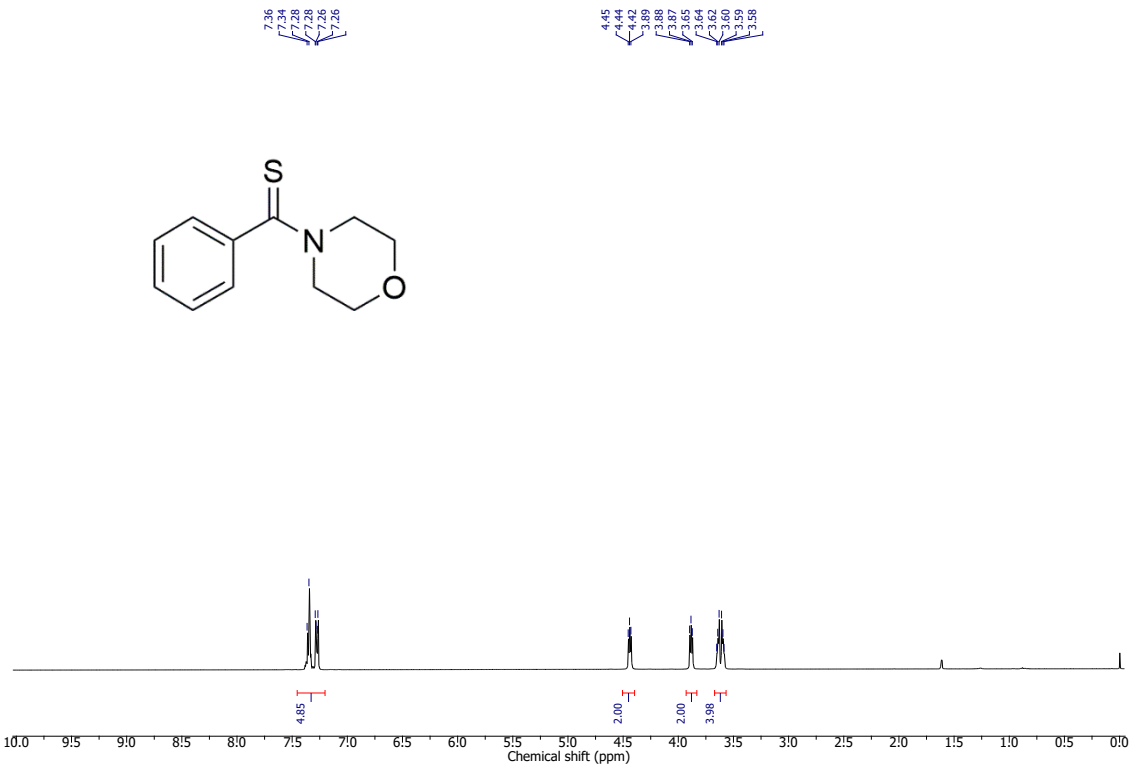


Fig S32. ^{1}H NMR spectra of **4a** ($CDCl_3$, 400 MHz).

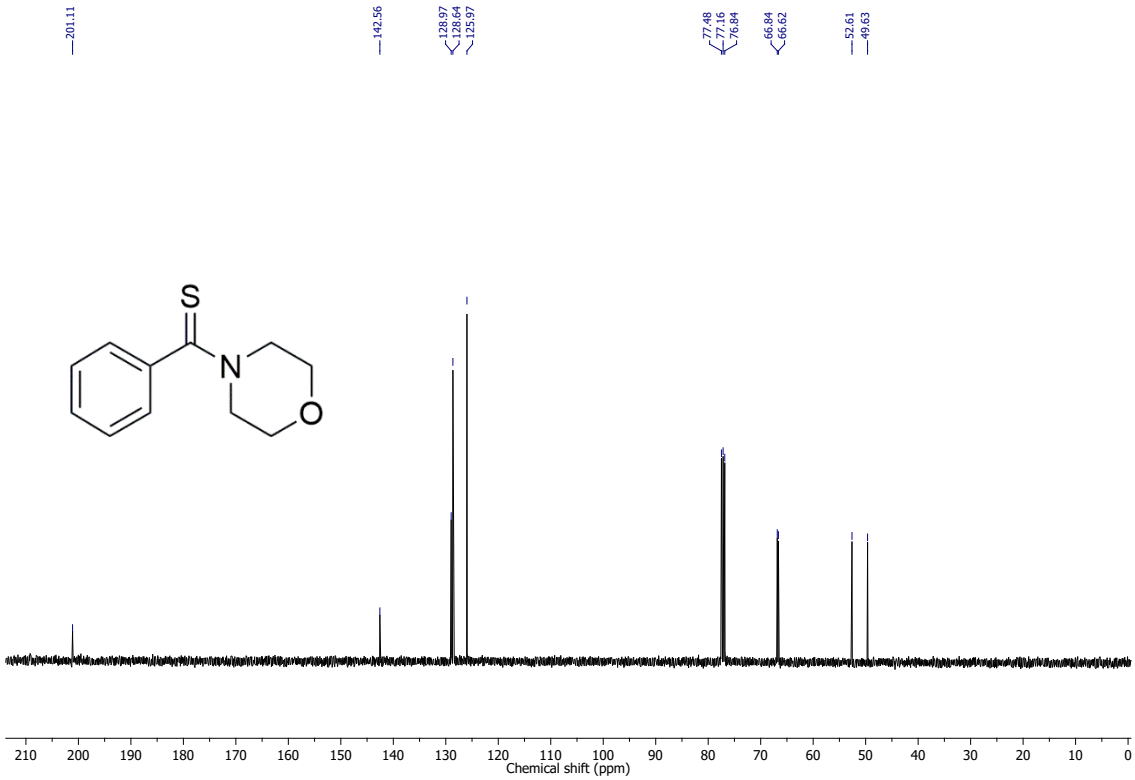


Fig S33. ^{13}C NMR spectra of **4a** ($CDCl_3$, 100 MHz).

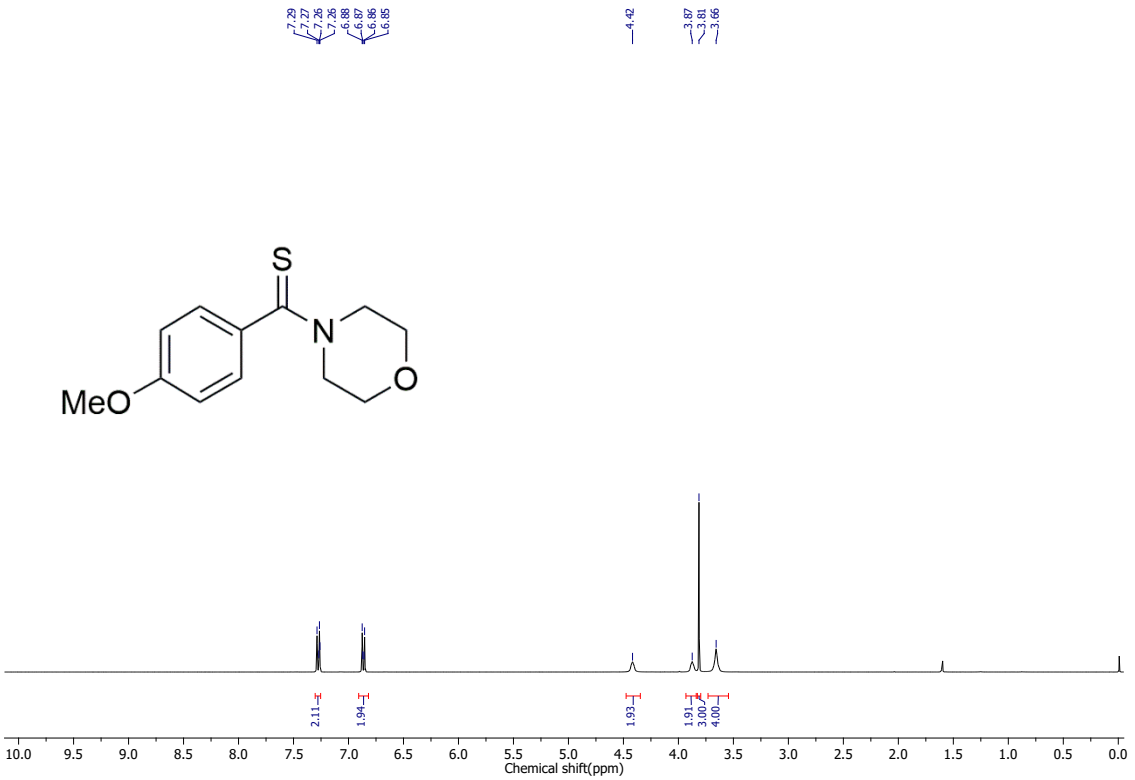


Fig S34. ^{1}H NMR spectra of **4b** ($CDCl_3$, 400 MHz).

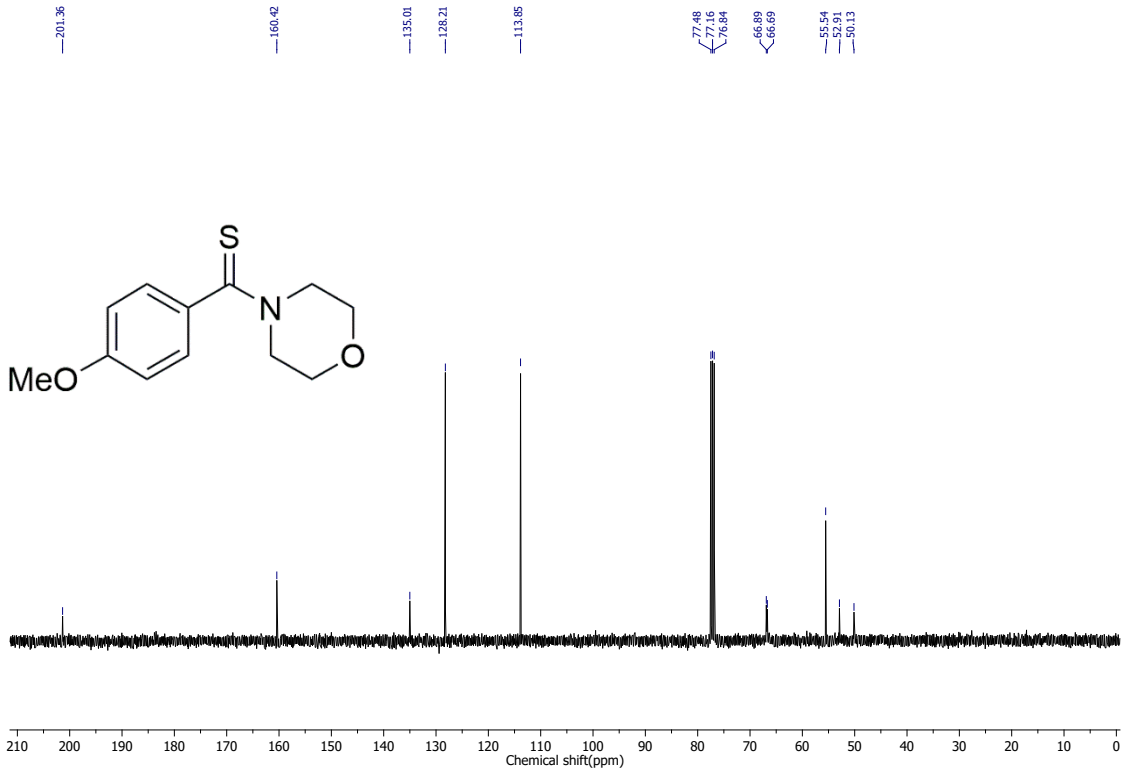


Fig S35. ^{13}C NMR spectra of **4b** ($CDCl_3$, 100 MHz).

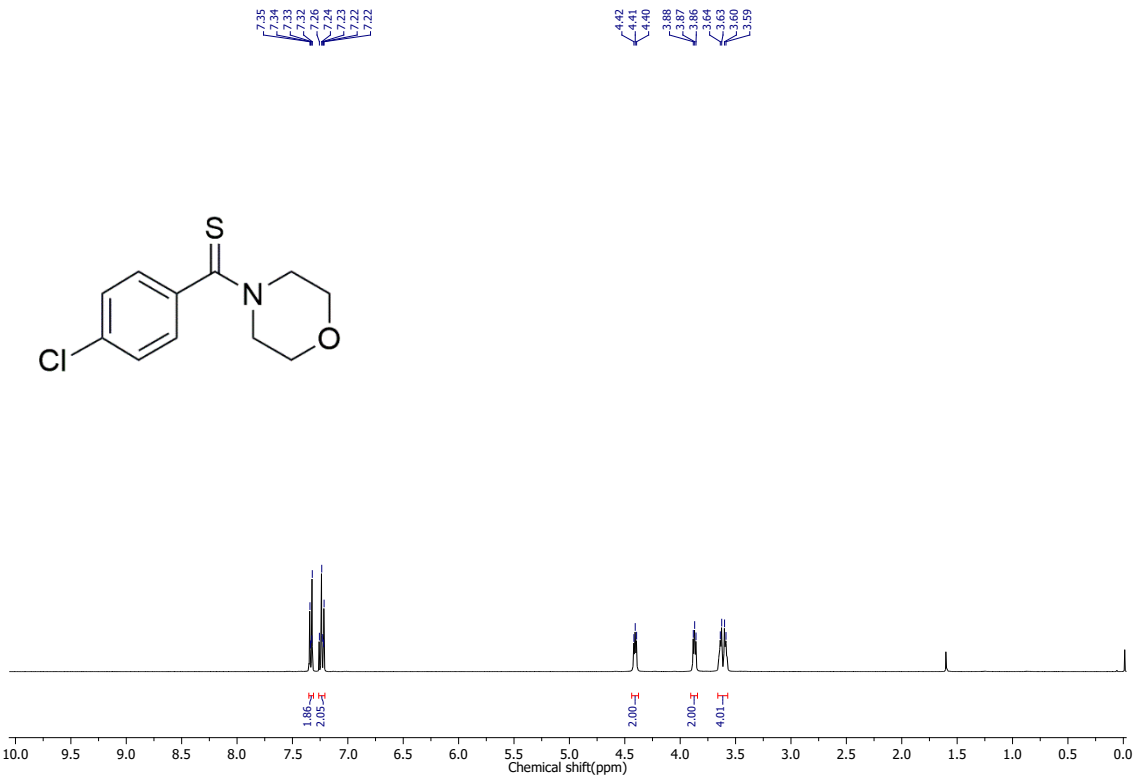


Fig S36. ^{1}H NMR spectra of **4c** ($CDCl_3$, 400 MHz).

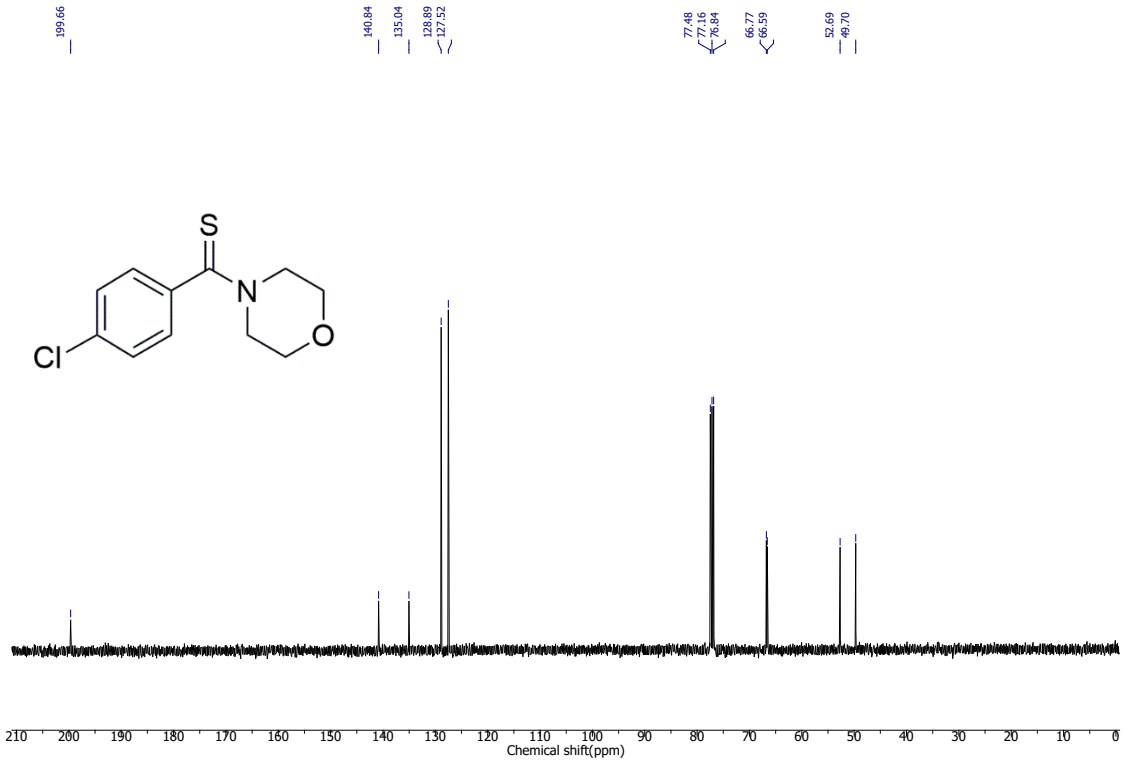


Fig S37. ^{13}C NMR spectra of **4c** ($CDCl_3$, 100 MHz).

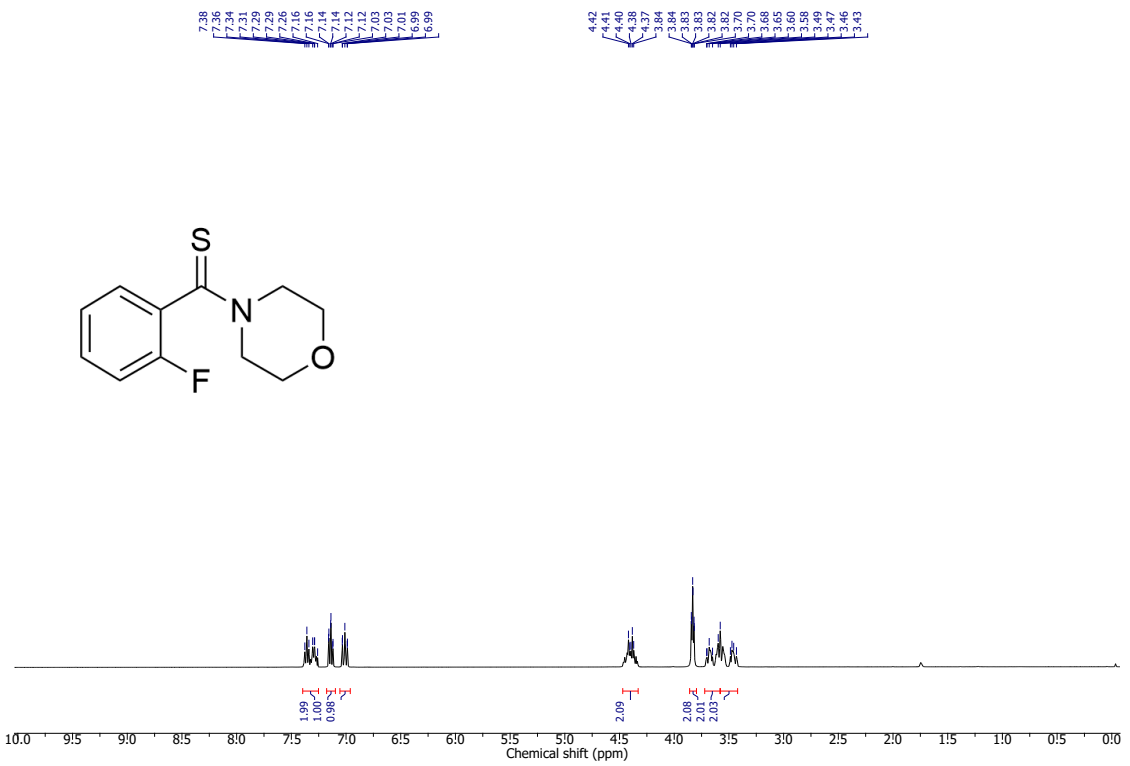


Fig S38. ^{1}H NMR spectra of **4d** ($CDCl_3$, 400 MHz).

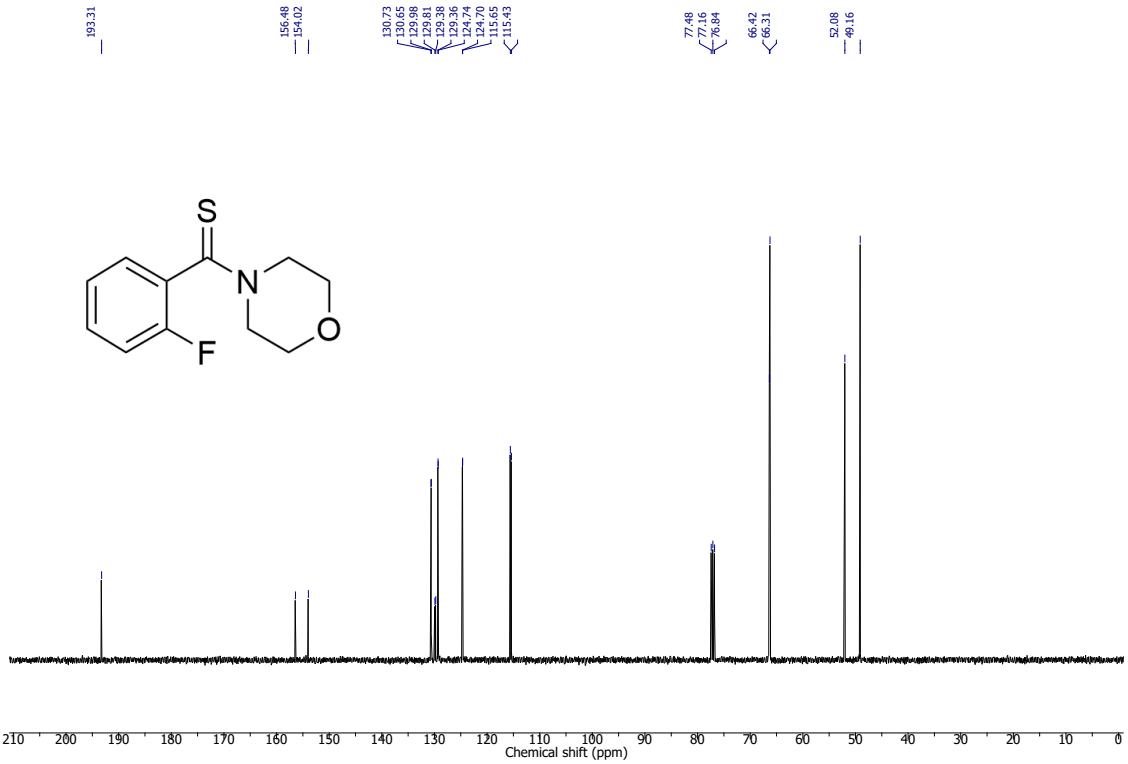


Fig S39. ^{13}C NMR spectra of **4d** ($CDCl_3$, 100 MHz).

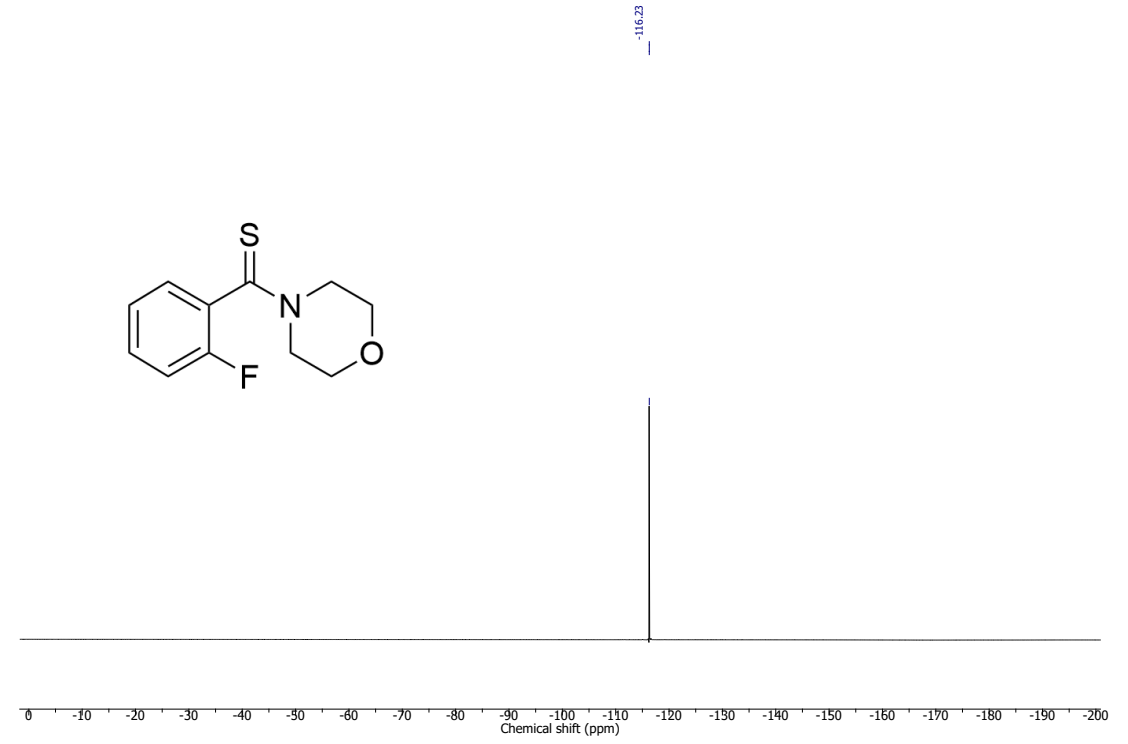


Fig S40. $^{19}F\{^1H\}$ NMR spectra of **4d** ($CDCl_3$, 565 MHz).

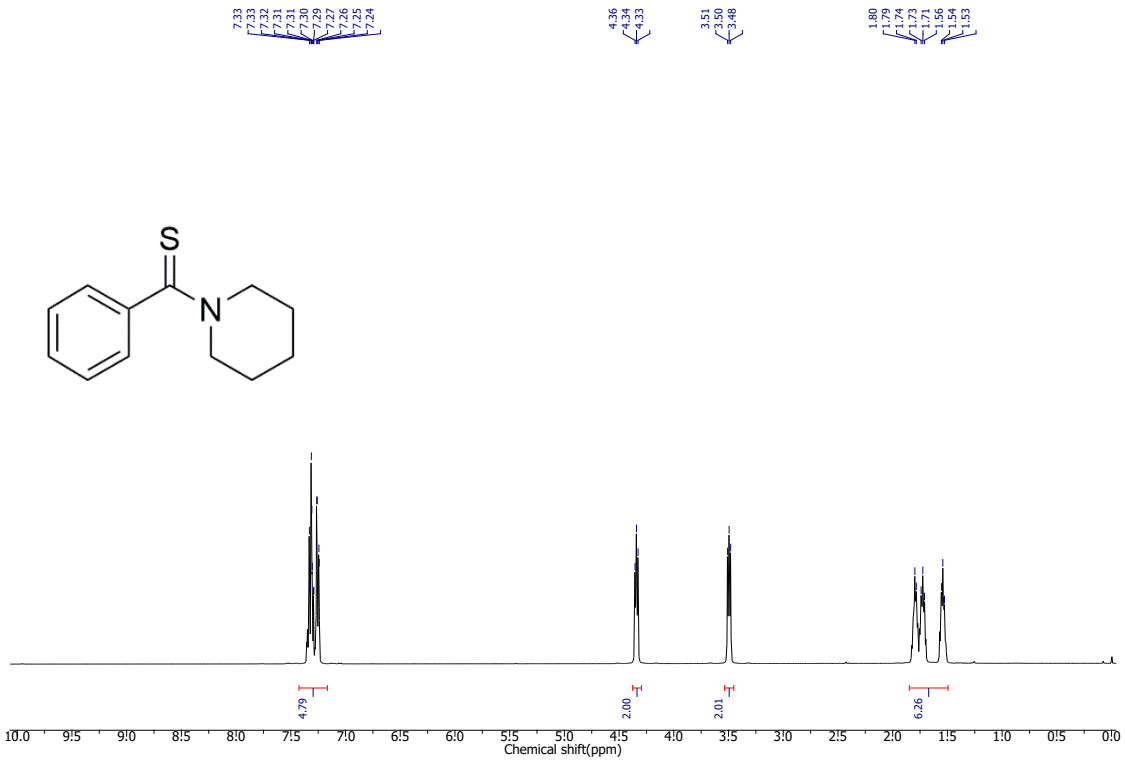


Fig S41. ^{1}H NMR spectra of **4e** ($CDCl_3$, 400 MHz).

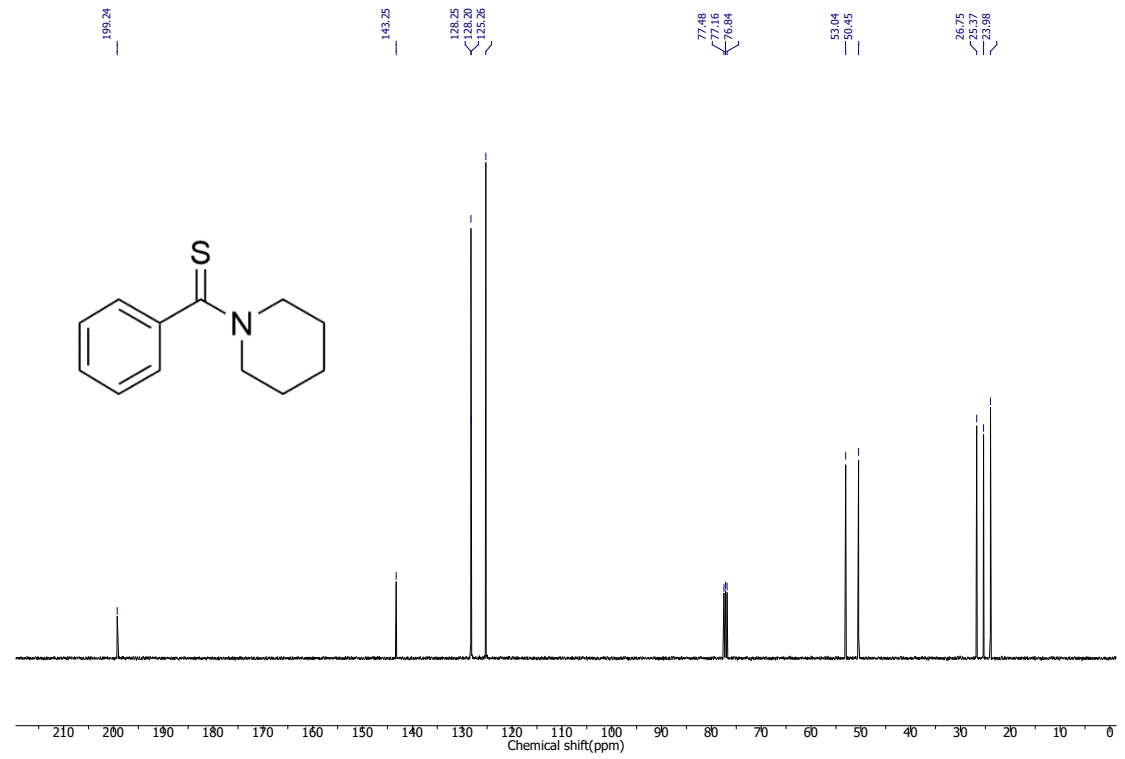


Fig S42. ^{13}C NMR spectra of **4e** ($CDCl_3$, 100 MHz).

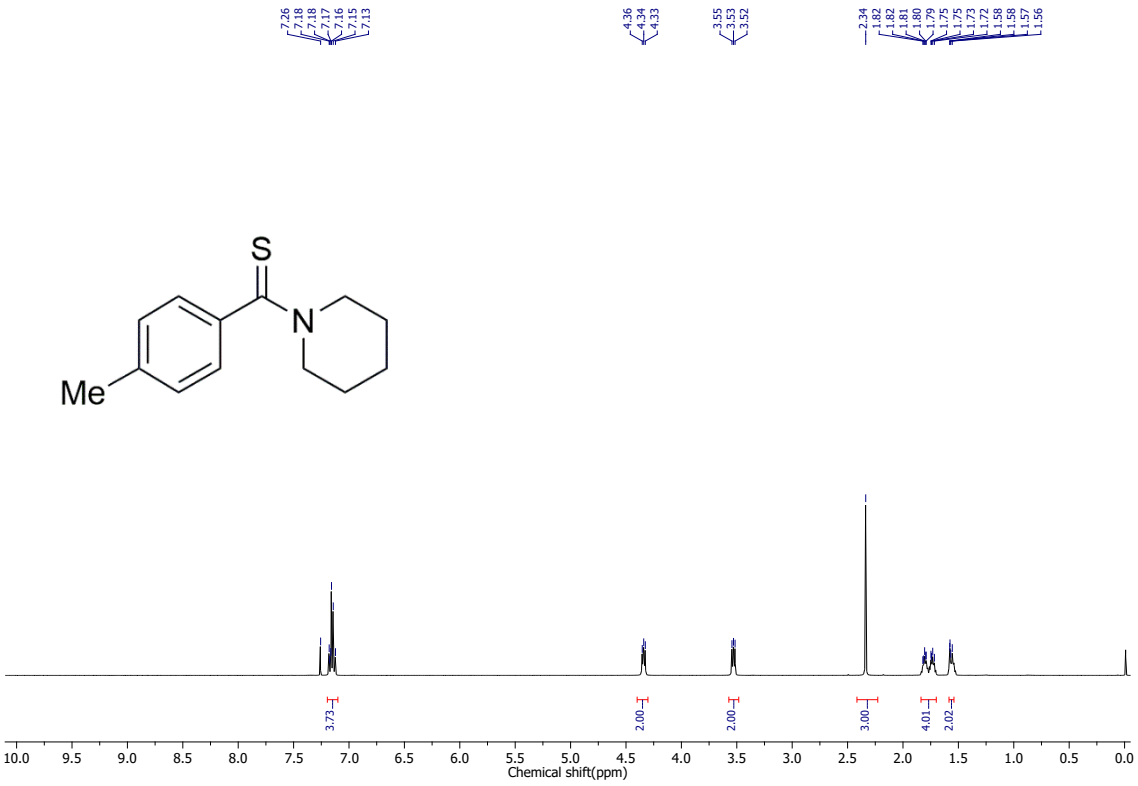


Fig S43. ^{1}H NMR spectra of **4f** ($CDCl_3$, 400 MHz).

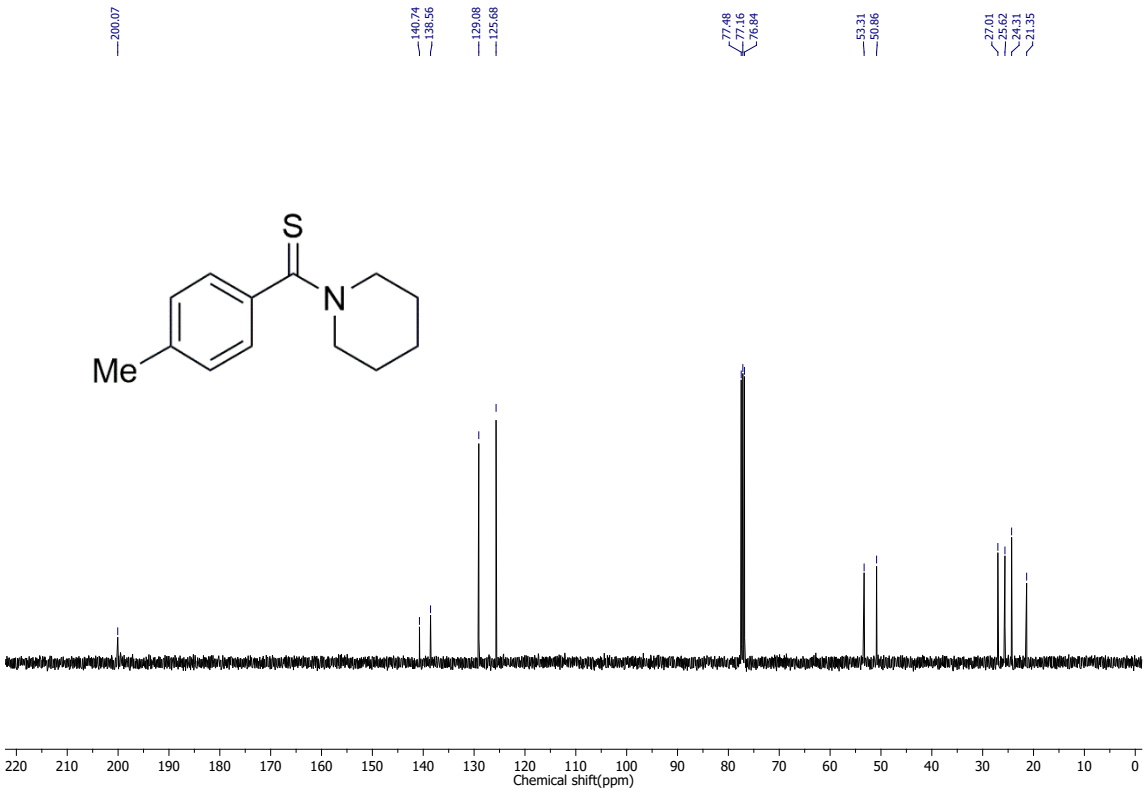


Fig S44. ^{13}C NMR spectra of **4f** ($CDCl_3$, 100 MHz).

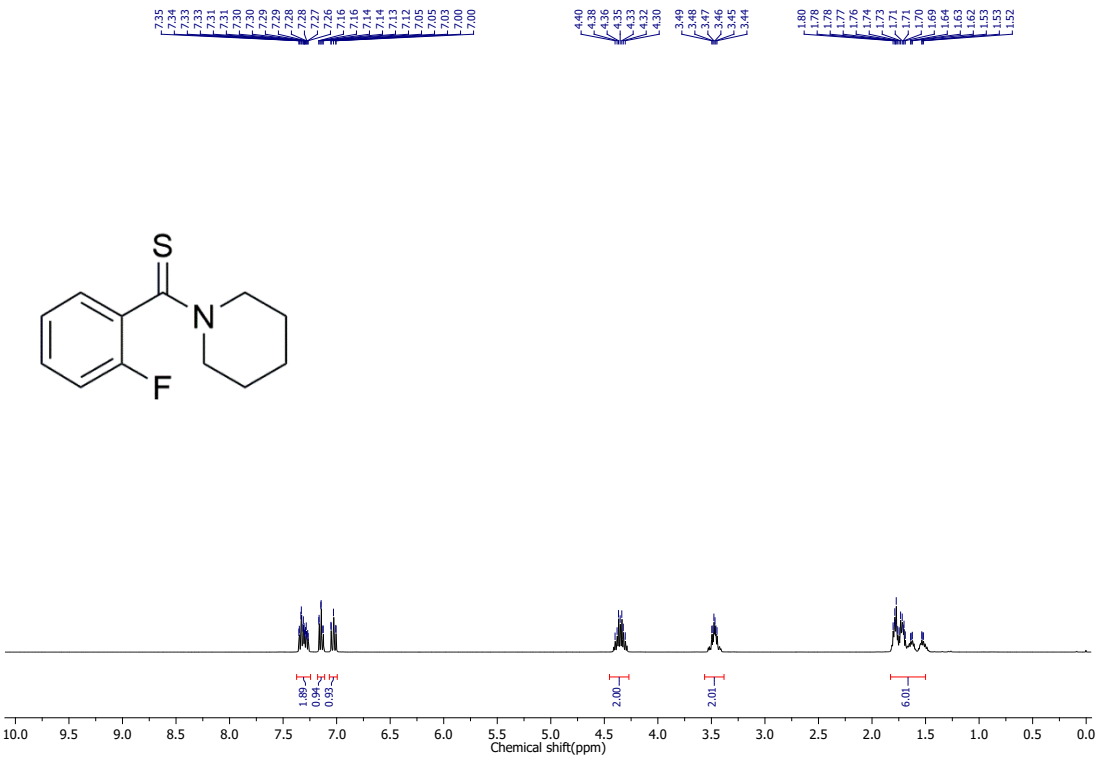


Fig S45. ^{1}H NMR spectra of **4g** ($CDCl_3$, 400 MHz).

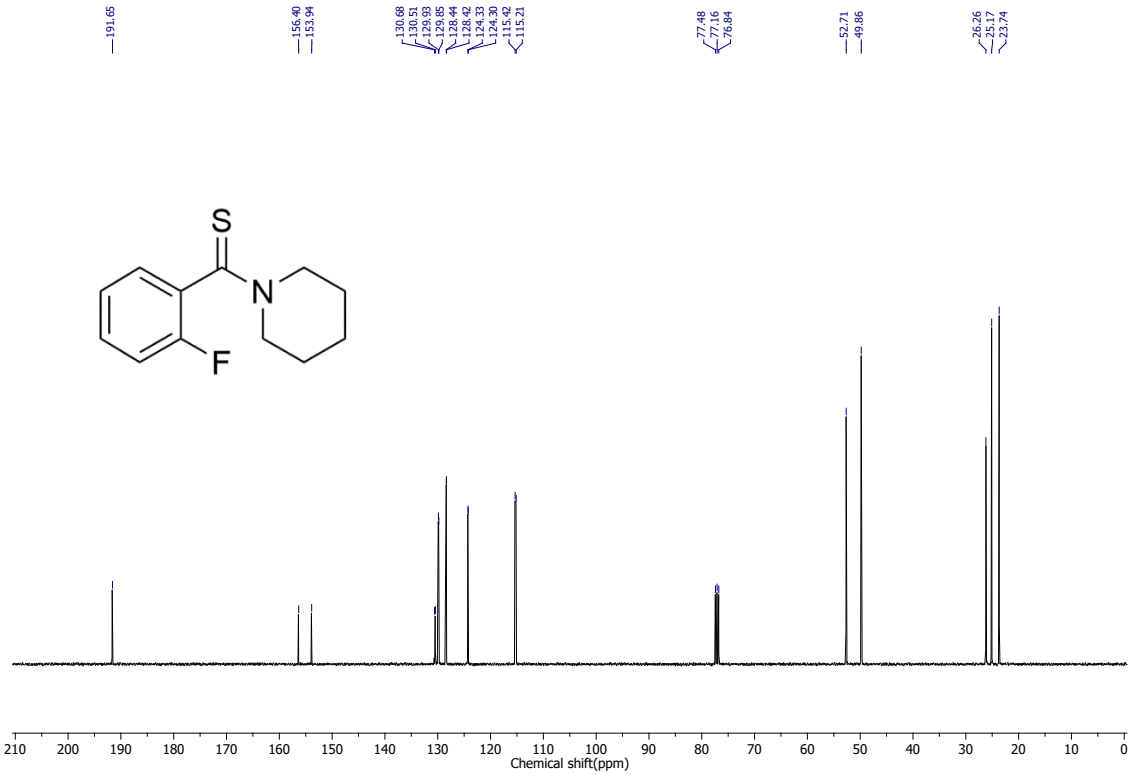


Fig S46. ^{13}C NMR spectra of **4g** ($CDCl_3$, 100 MHz).

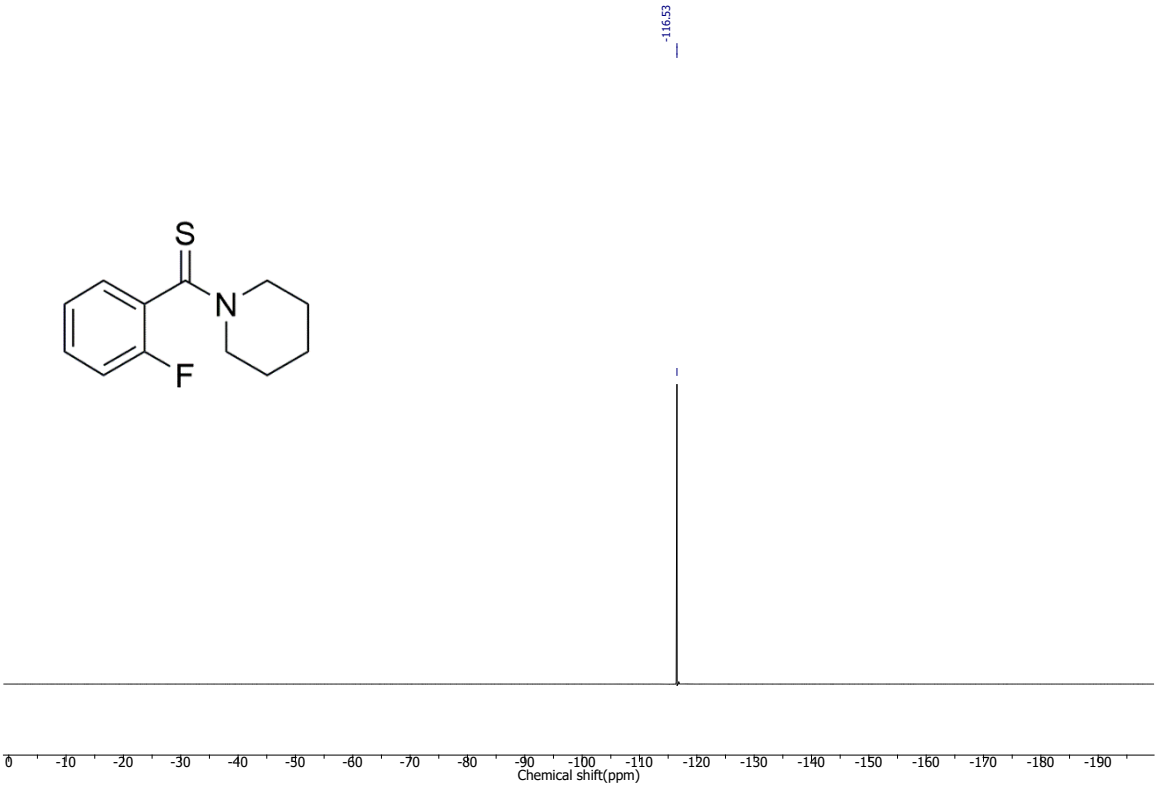


Fig S47. $^{19}F\{^{1}H\}$ NMR spectra of **4g** ($CDCl_3$, 565 MHz).

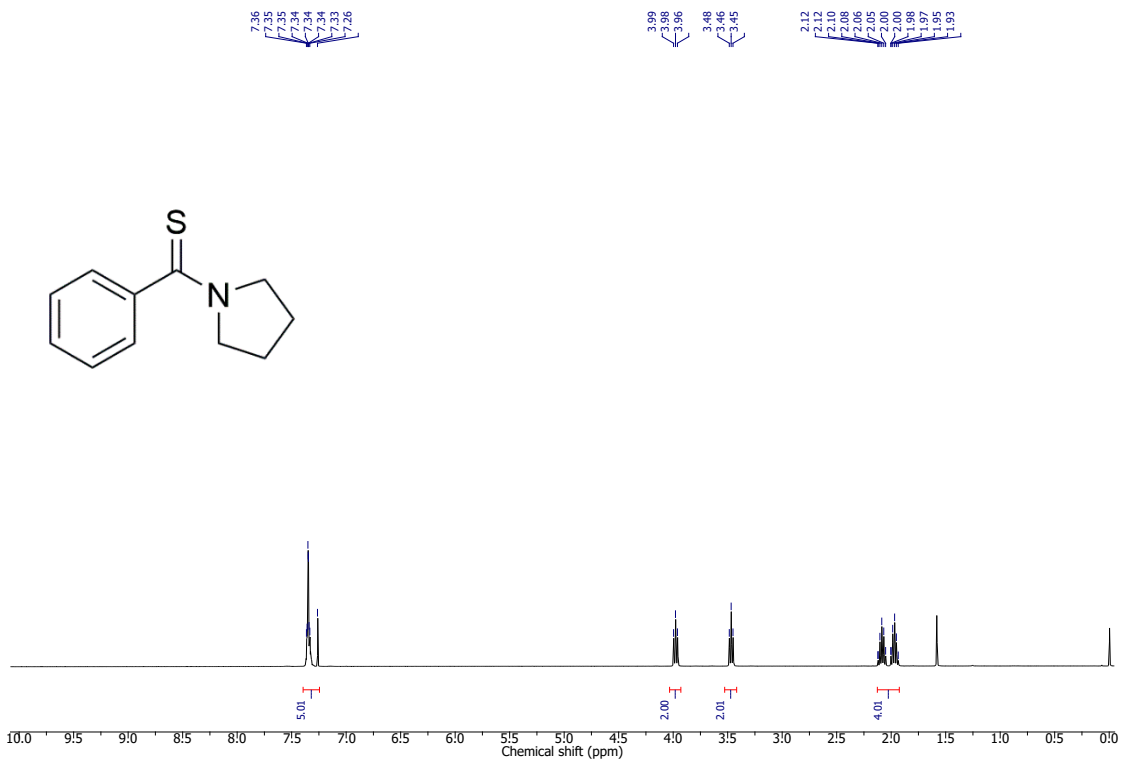


Fig S48. ^{1}H NMR spectra of **4h** ($CDCl_3$, 400 MHz).

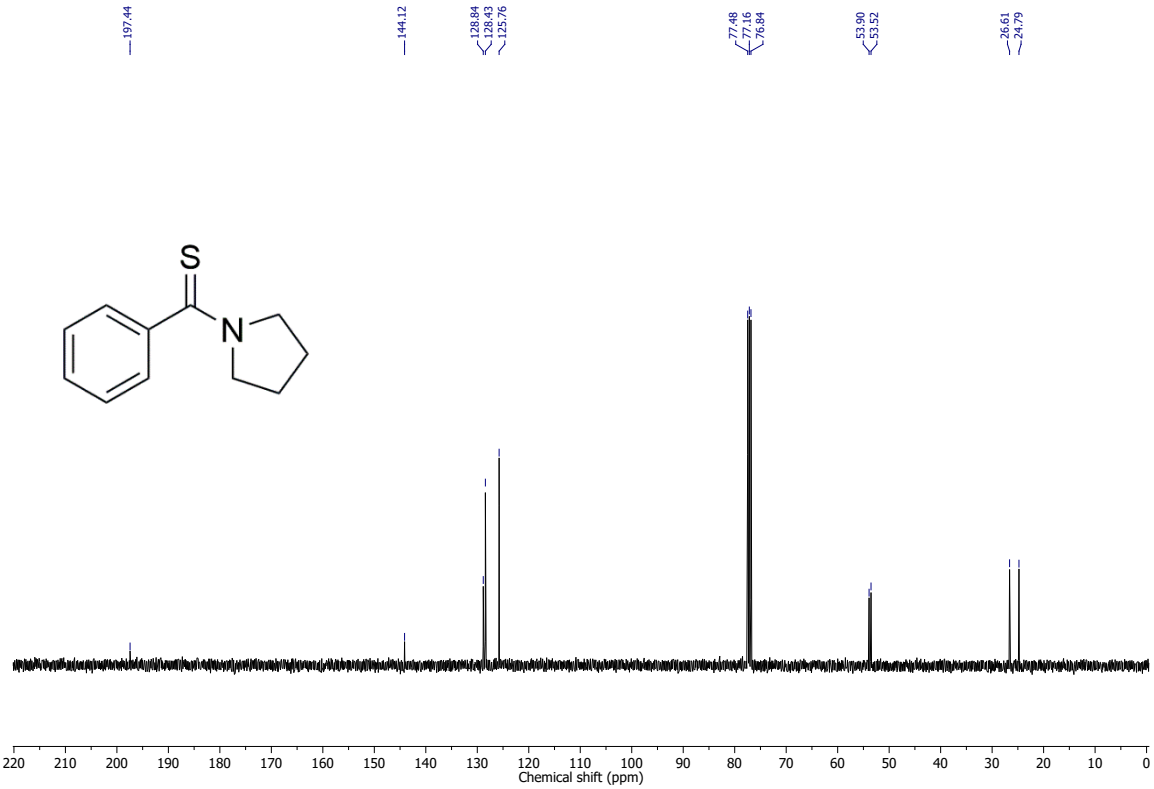


Fig S49. ^{13}C NMR spectra of **4h** ($CDCl_3$, 100 MHz).

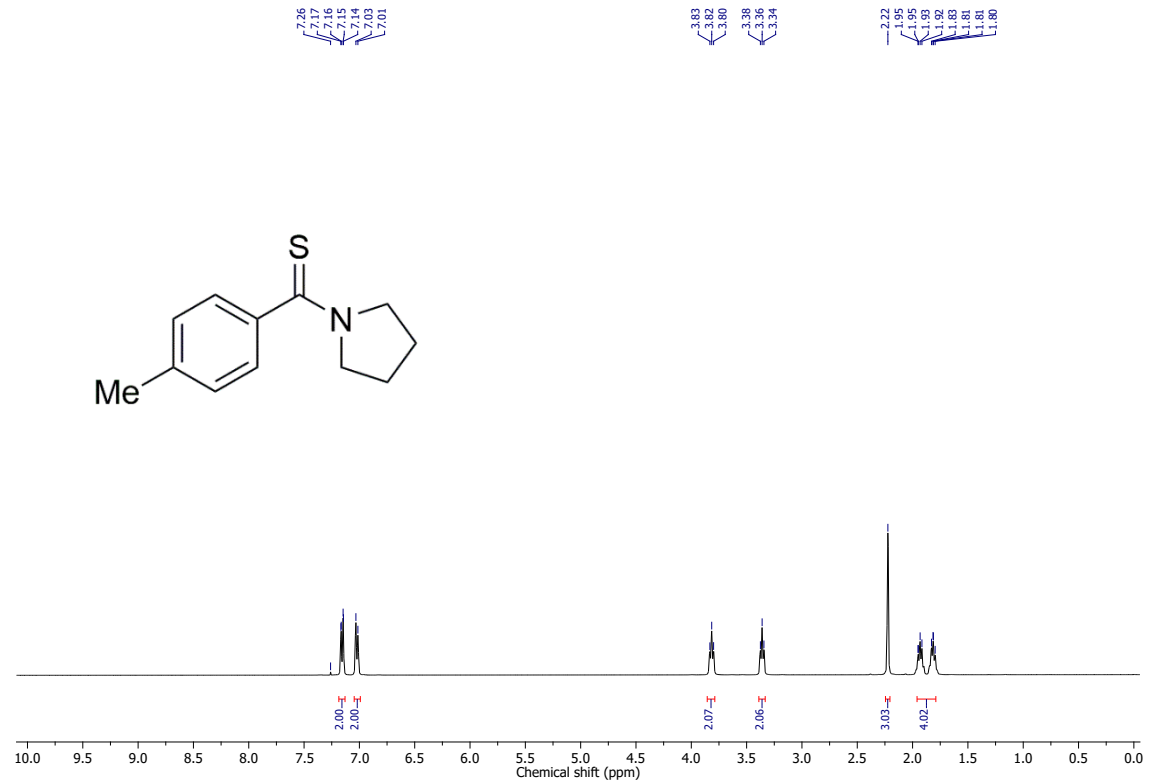


Fig S50. ^{1}H NMR spectra of **4i** ($CDCl_3$, 400 MHz).

Fig S51. ^{13}C NMR spectra of **4i** ($CDCl_3$, 100 MHz).

Fig S52. ^{1}H NMR spectra of **4j** ($CDCl_3$, 400 MHz).

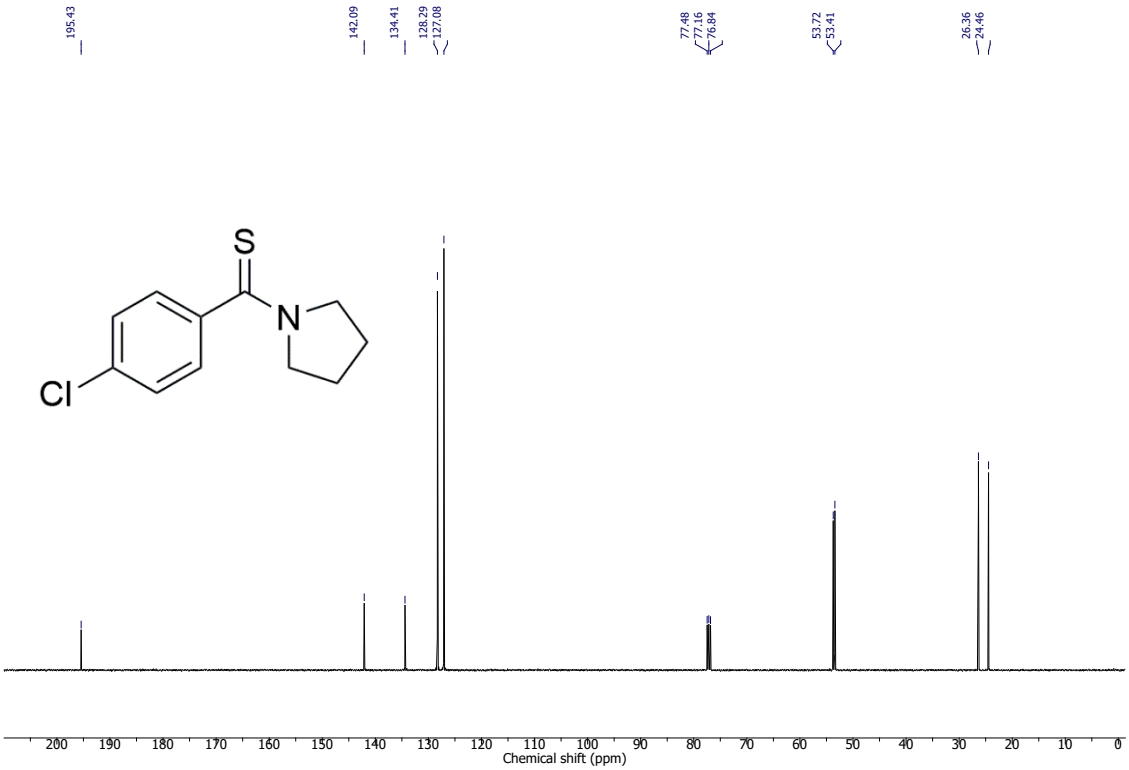


Fig S53. ^{13}C NMR spectra of **4j** ($CDCl_3$, 100 MHz).

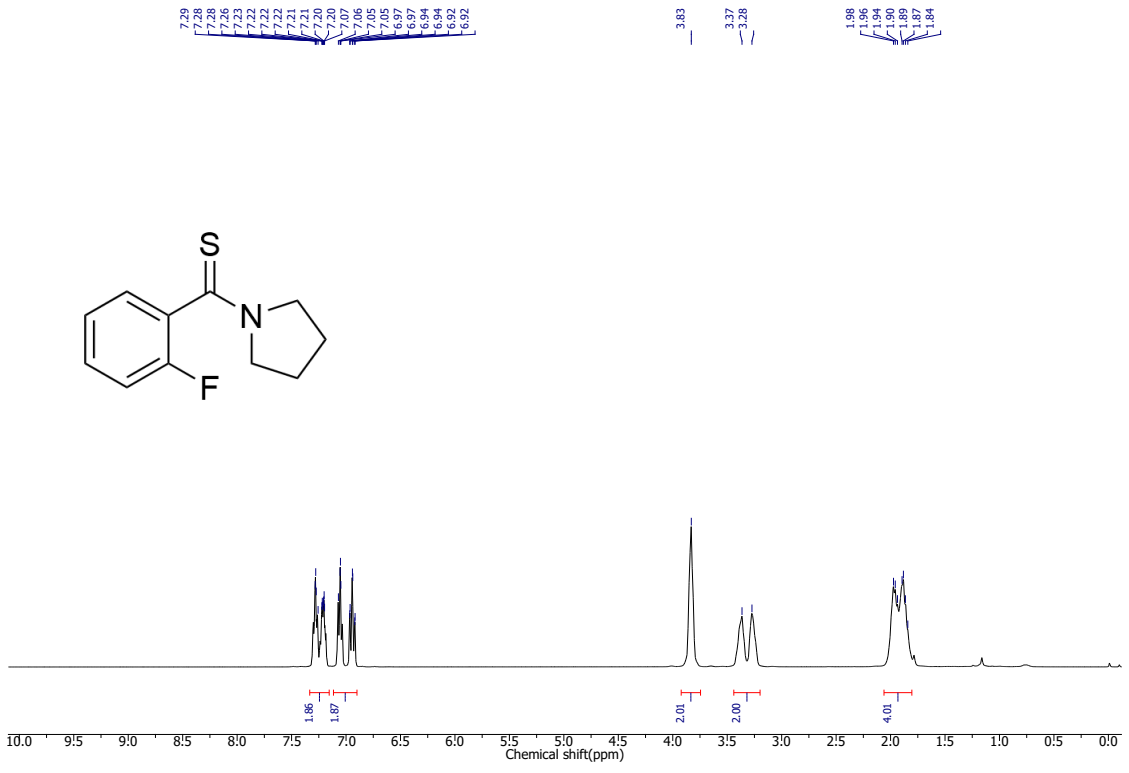


Fig S54. ^{1}H NMR spectra of **4k** ($CDCl_3$, 400 MHz).

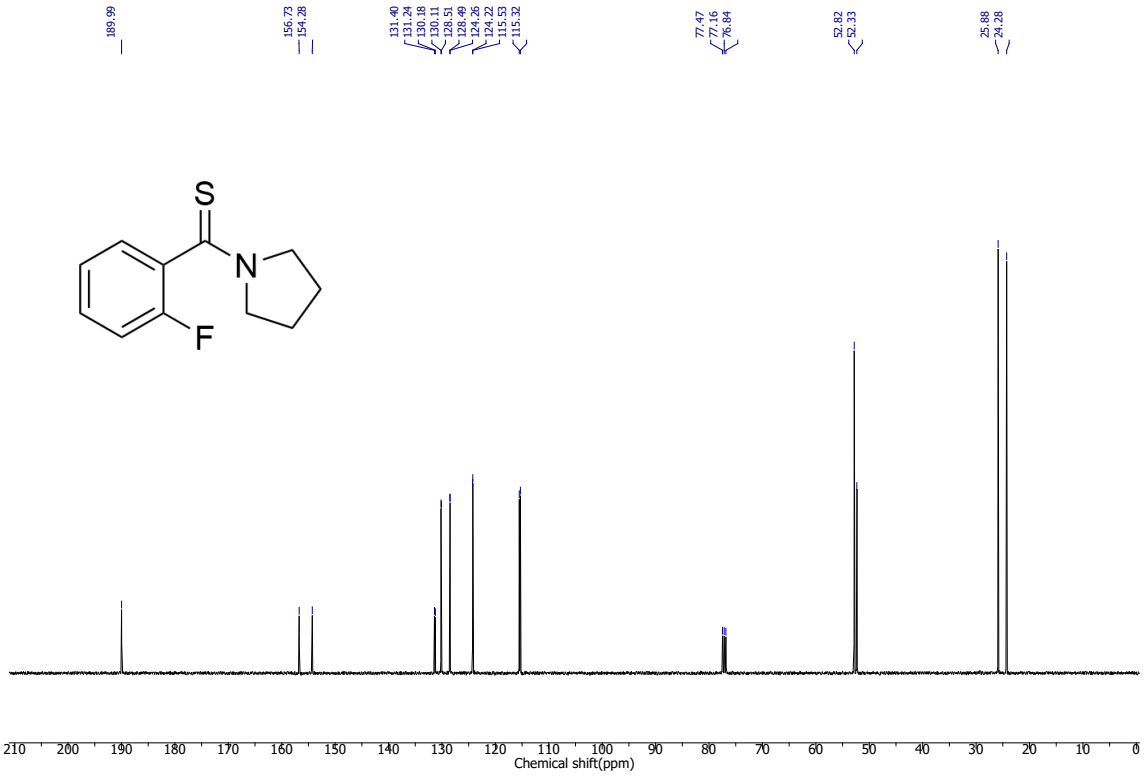


Fig S55. ^{13}C NMR spectra of **4k** ($CDCl_3$, 100 MHz).

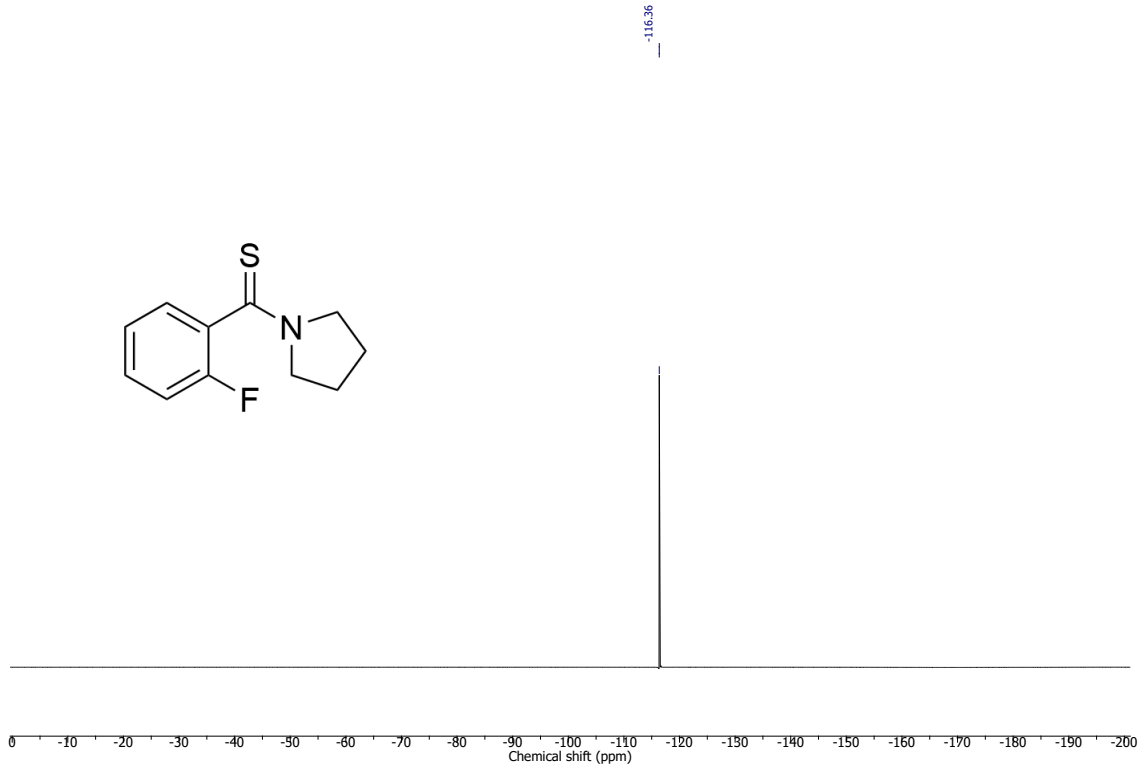


Fig S56. $^{19}F\{^1H\}$ NMR spectra of **4k** ($CDCl_3$, 565 MHz).

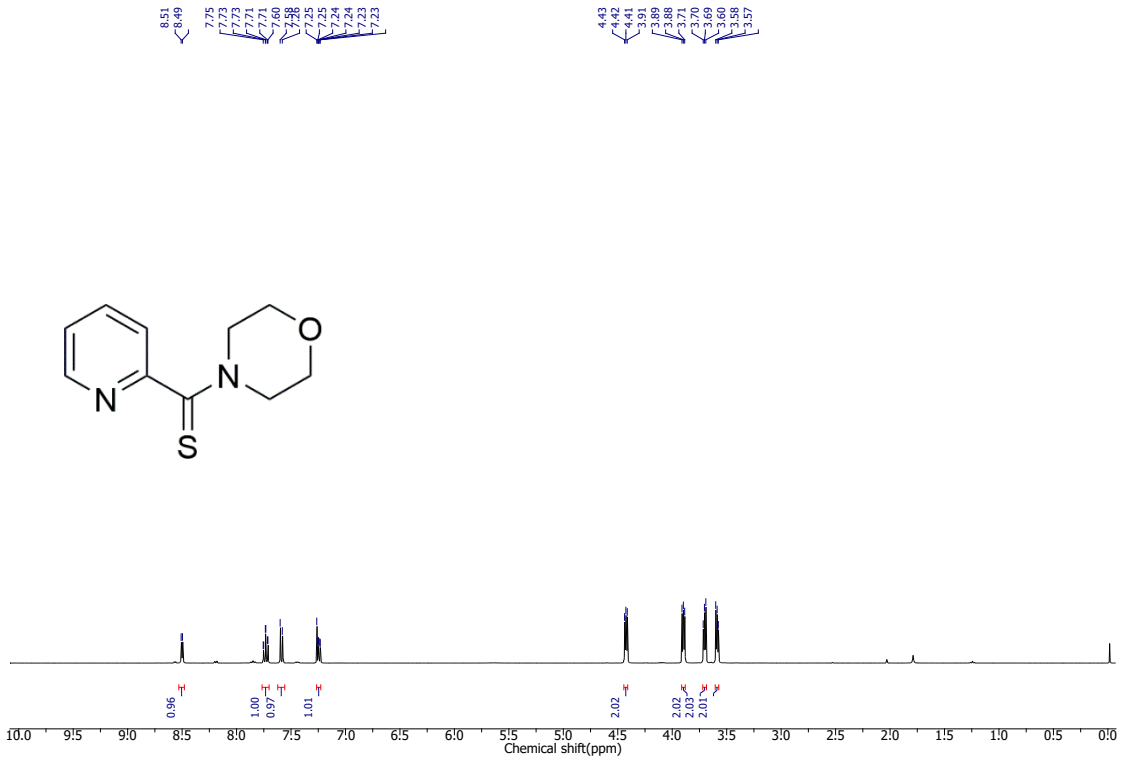


Fig S57. ^{1}H NMR spectra of **4l** ($CDCl_3$, 400 MHz).

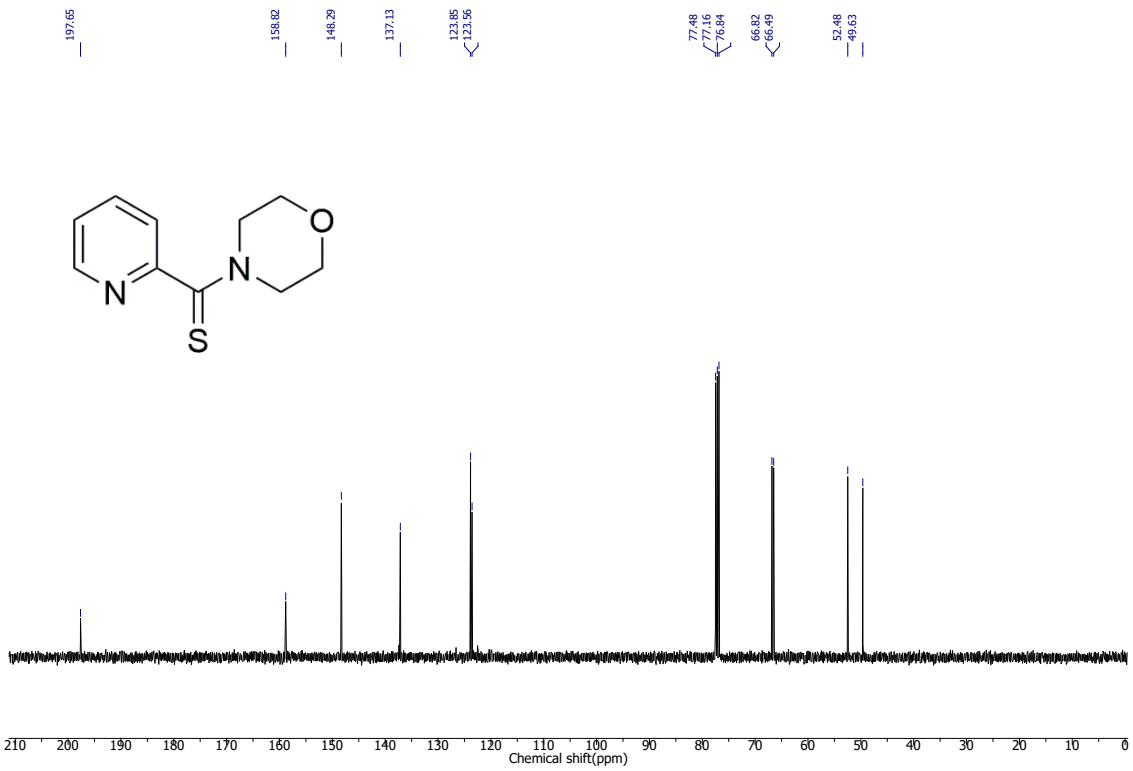


Fig S58. ^{13}C NMR spectra of **4l** ($CDCl_3$, 100 MHz).

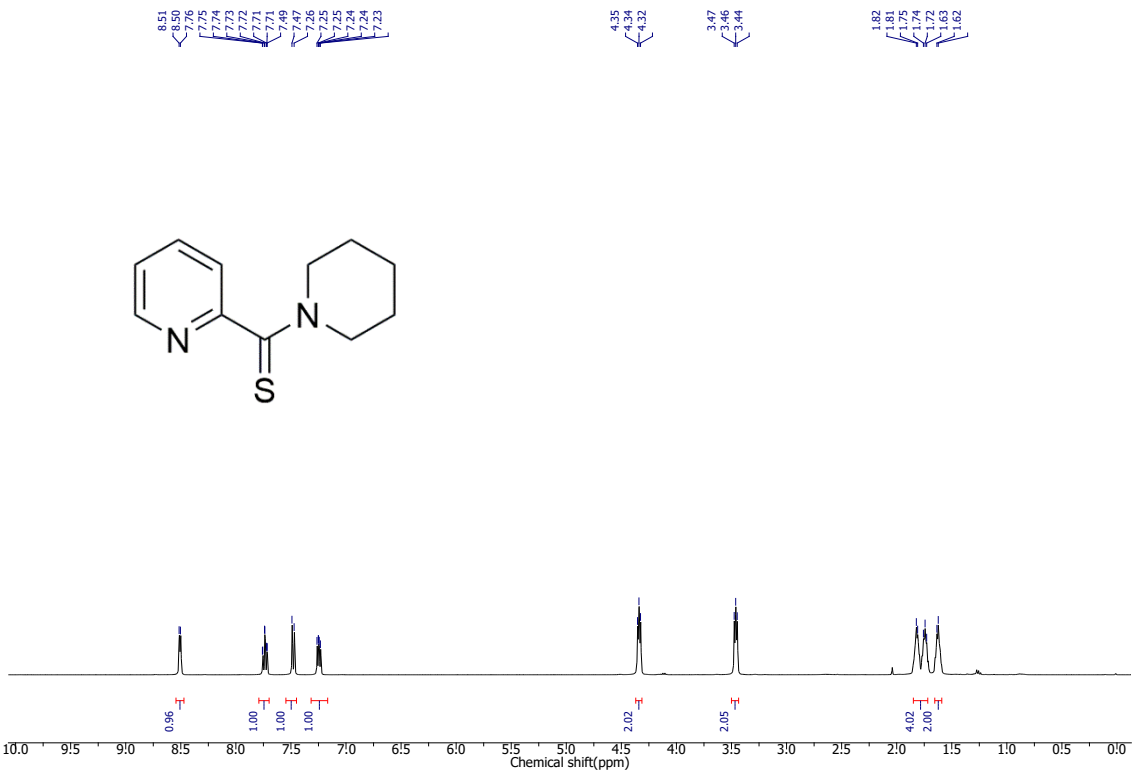


Fig S59. ^{1}H NMR spectra of **4m** ($CDCl_3$, 400 MHz).

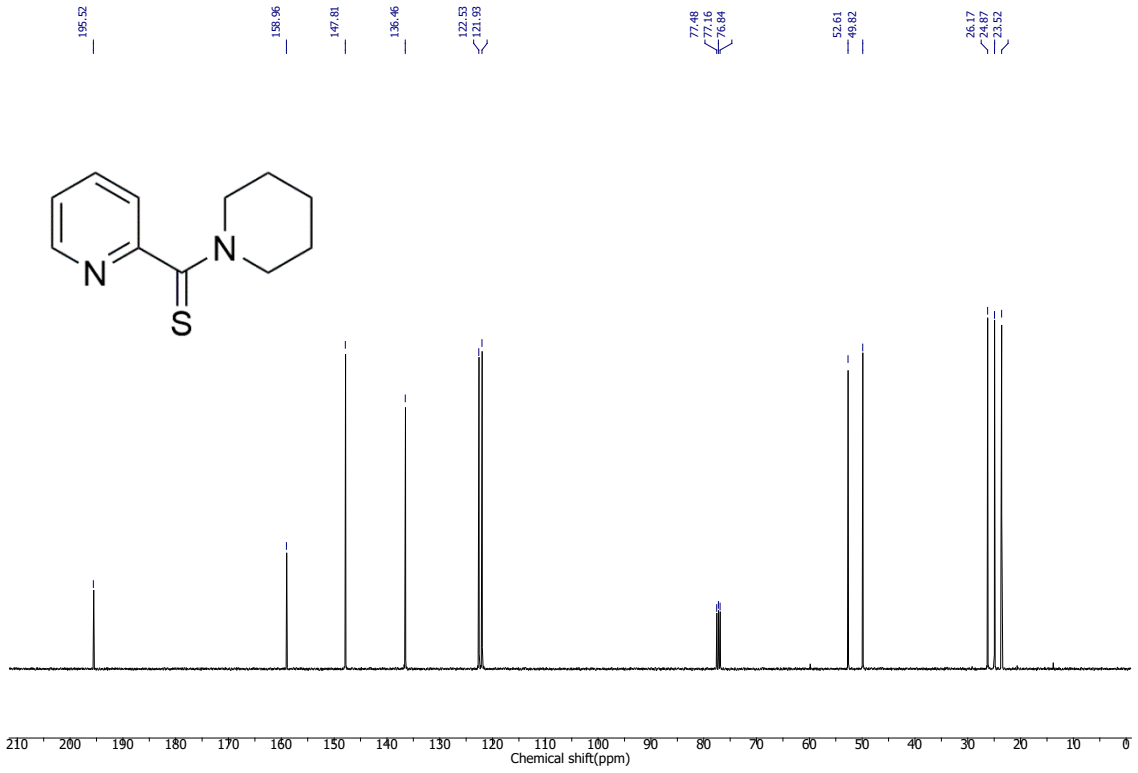


Fig S60. ^{13}C NMR spectra of **4m** ($CDCl_3$, 100 MHz).

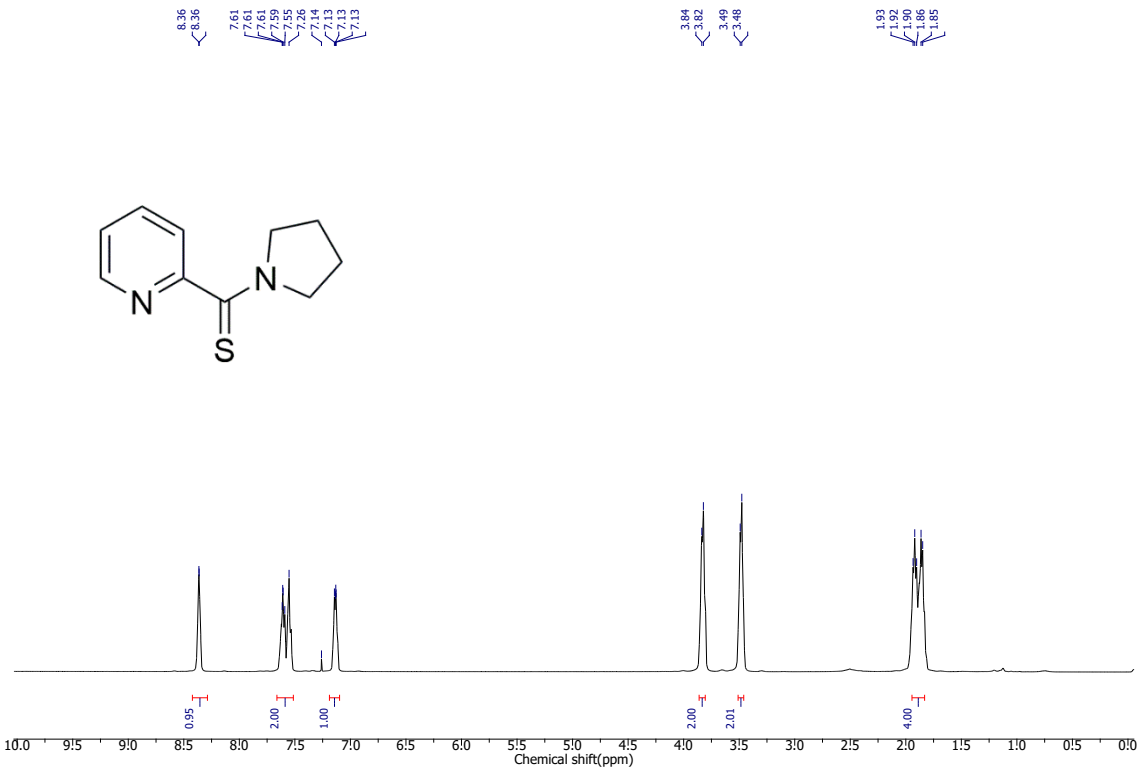


Fig S61. ^{1}H NMR spectra of **4n** ($CDCl_3$, 400 MHz).

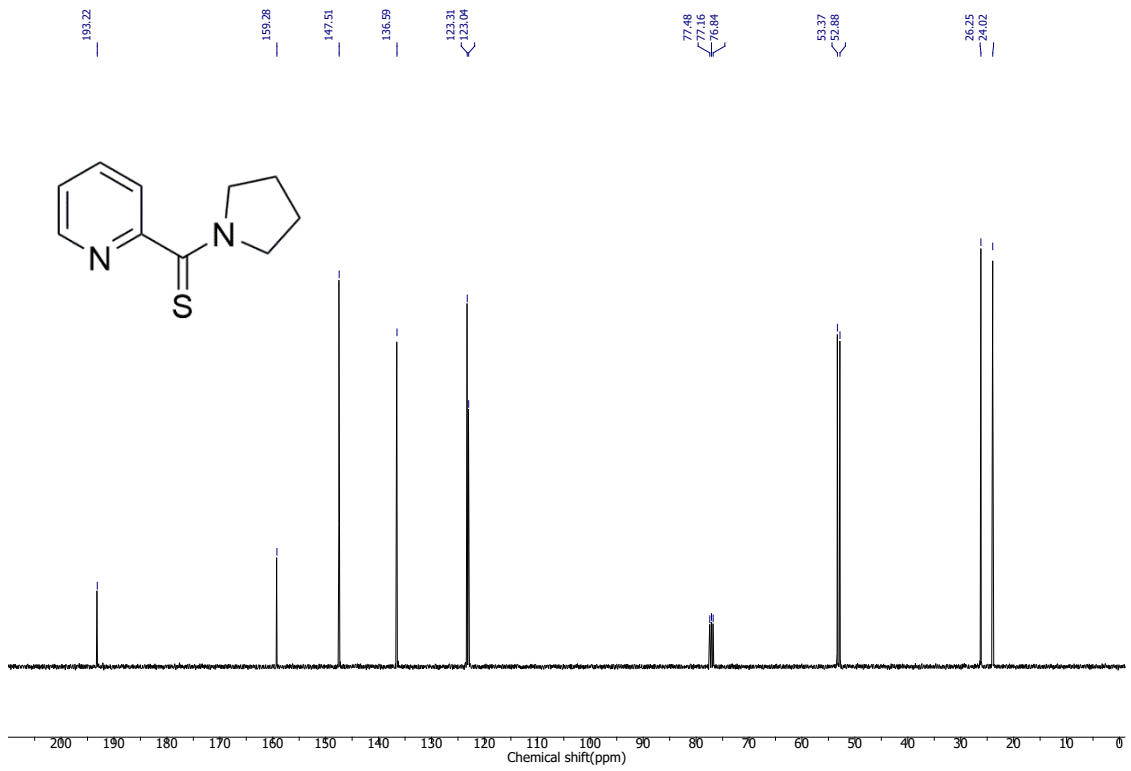


Fig S62. ^{13}C NMR spectra of **4n** ($CDCl_3$, 100 MHz).

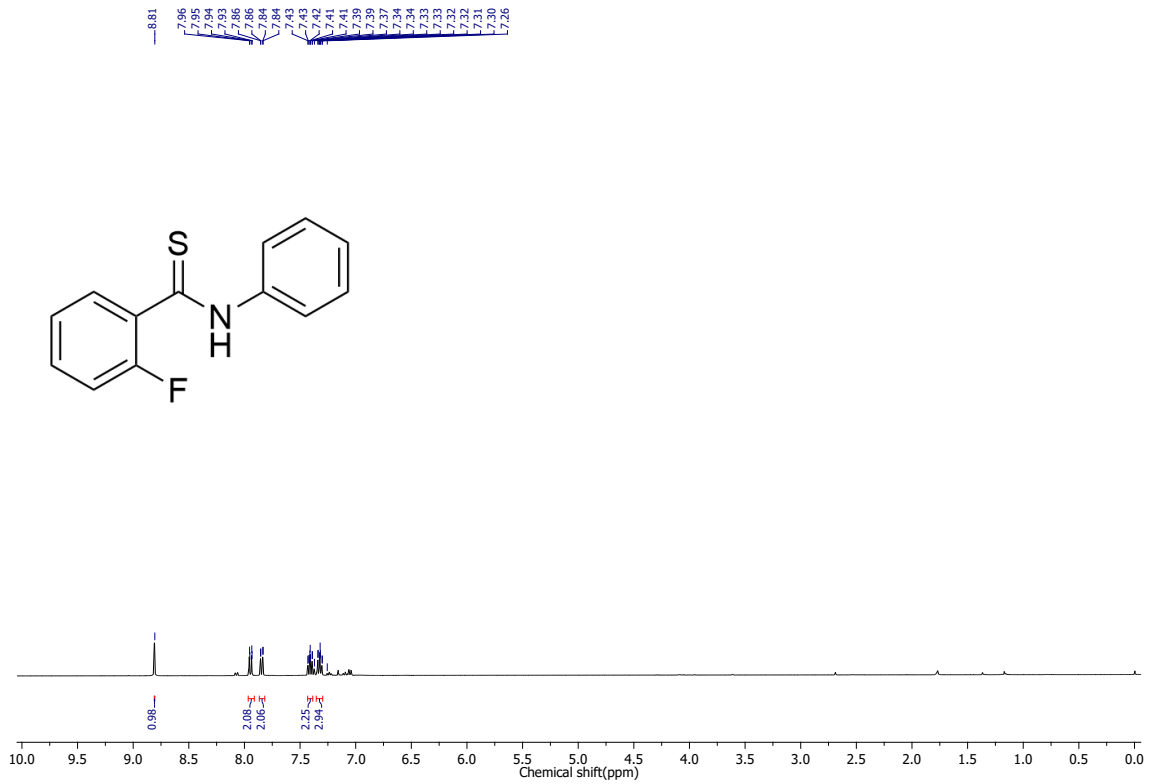


Fig S63. ^{1}H NMR spectra of **4o** ($CDCl_3$, 400 MHz).

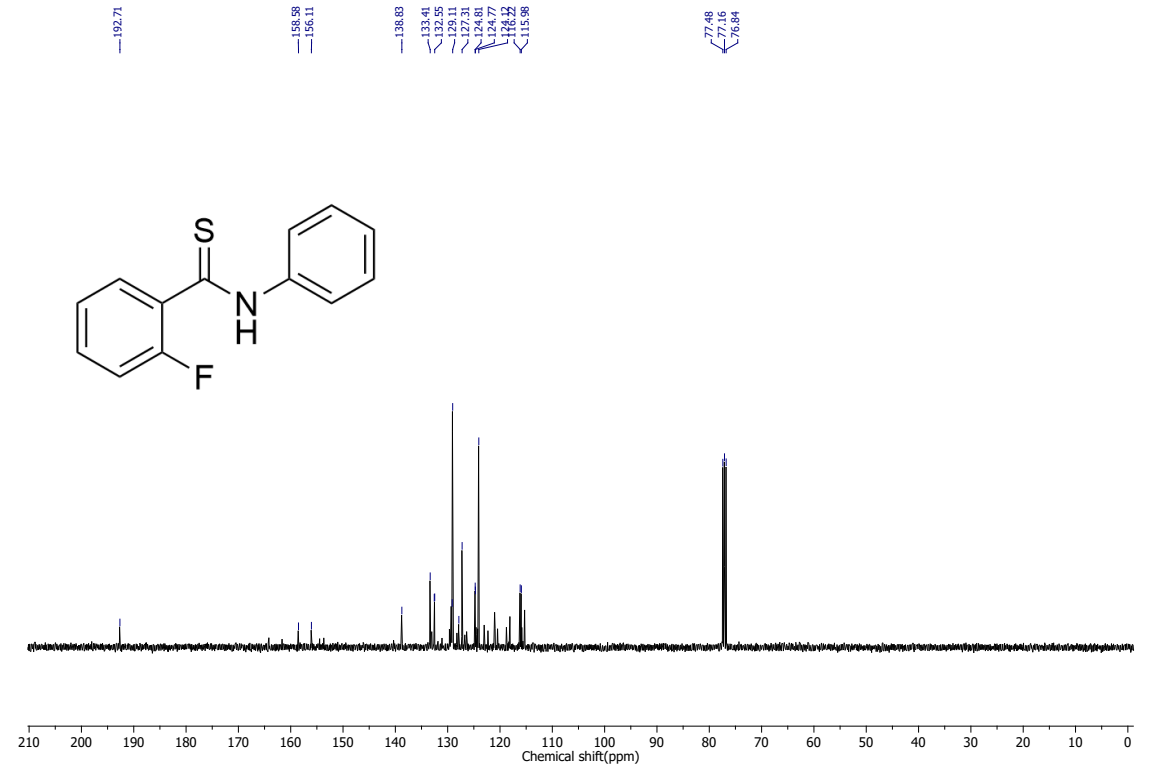


Fig S64. ^{13}C NMR spectra of **4o** ($CDCl_3$, 100 MHz).

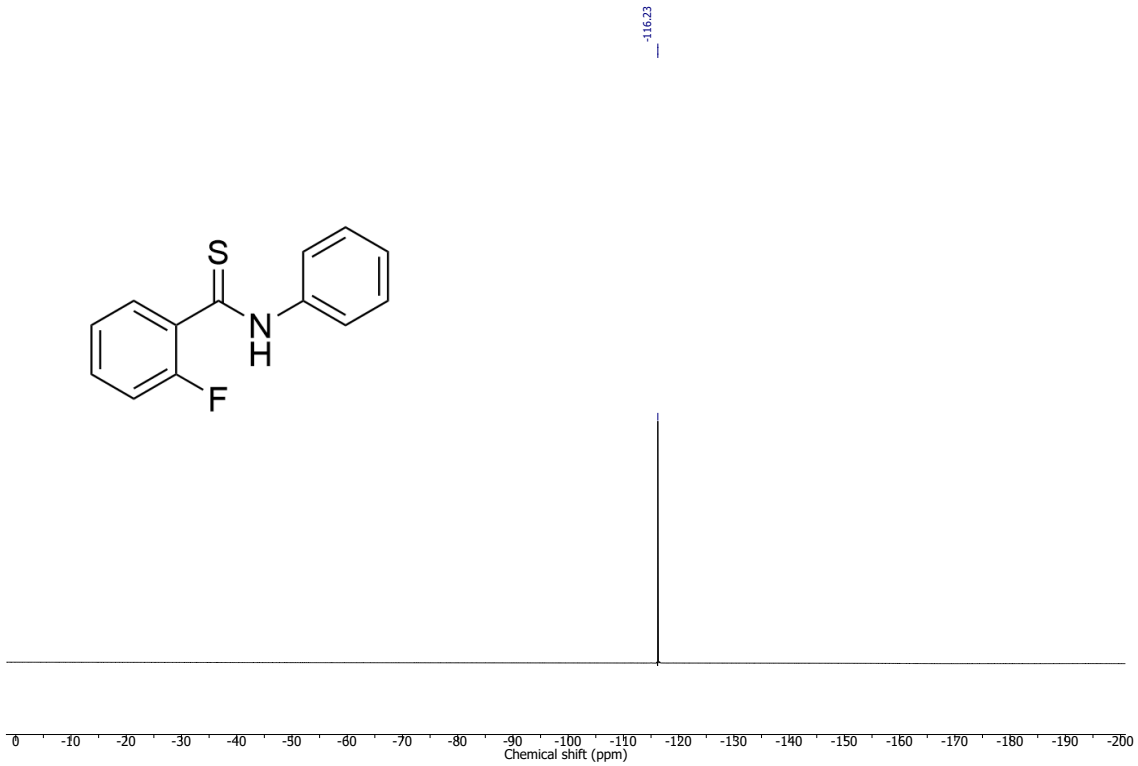


Fig S65. $^{19}F\{^{1}H\}$ NMR spectra of **4o** ($CDCl_3$, 565 MHz).

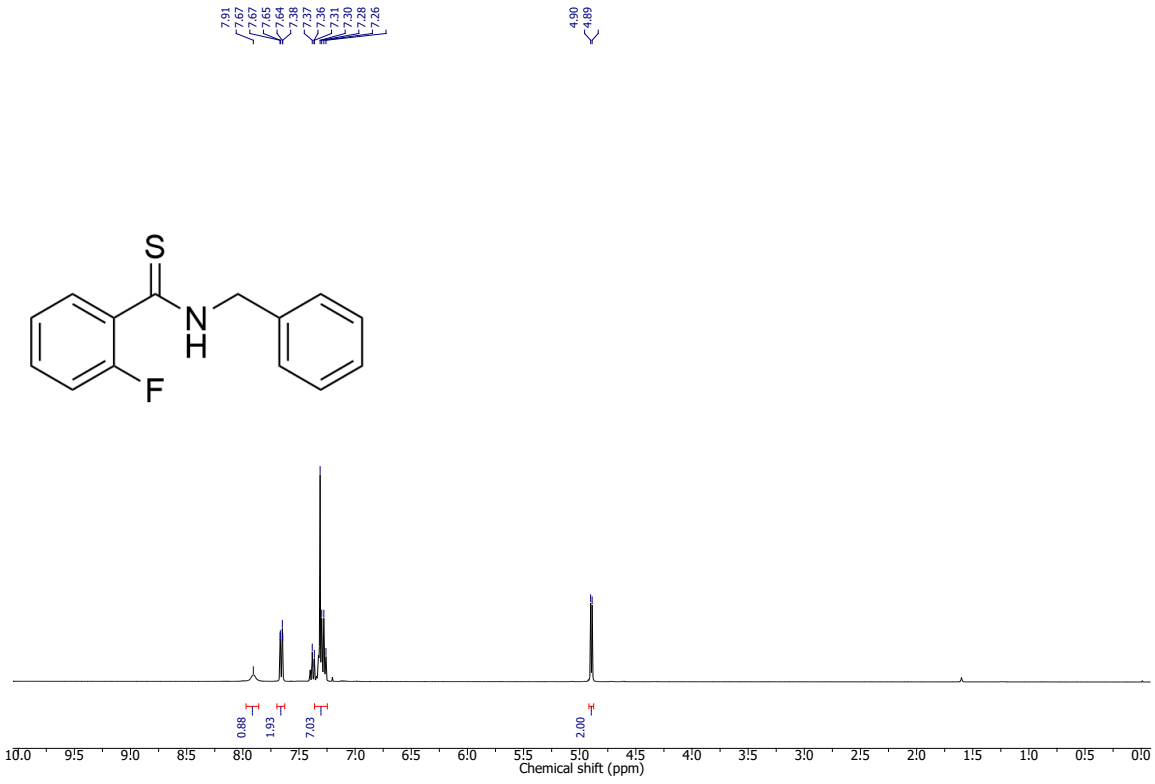


Fig S66. ^{1}H NMR spectra of **4p** ($CDCl_3$, 400 MHz).

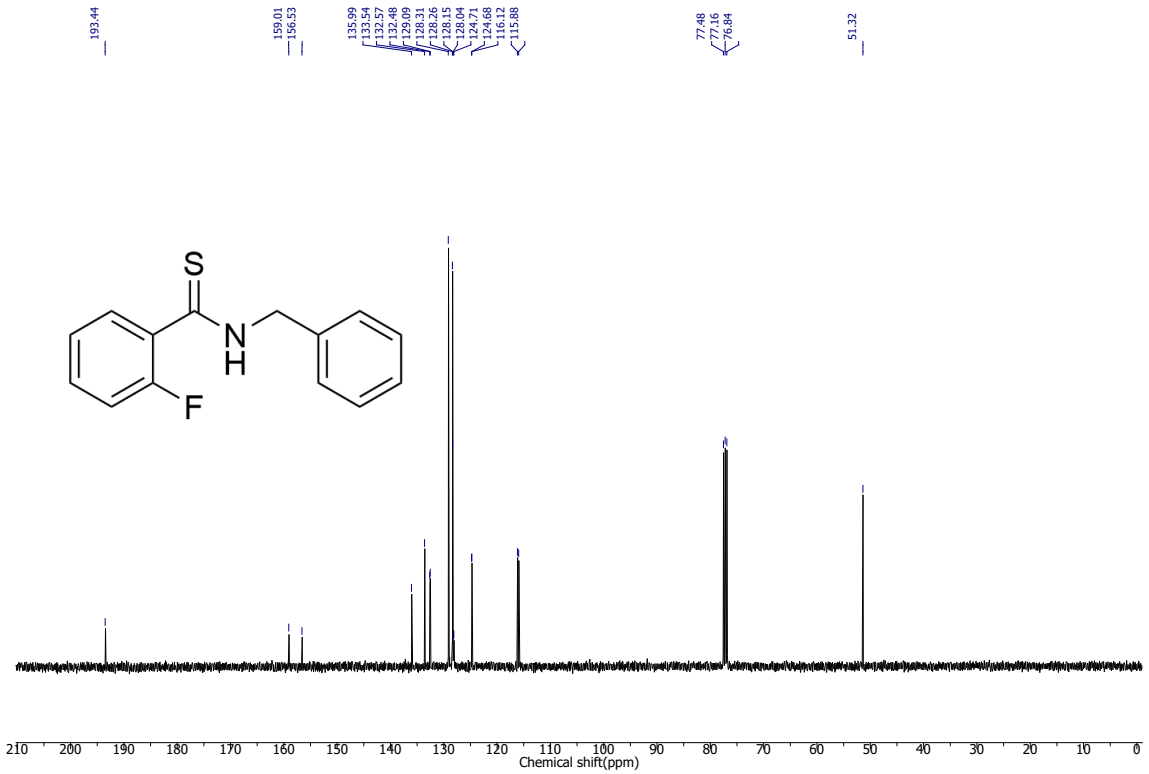


Fig S67. ^{13}C NMR spectra of **4p** ($CDCl_3$, 100 MHz).

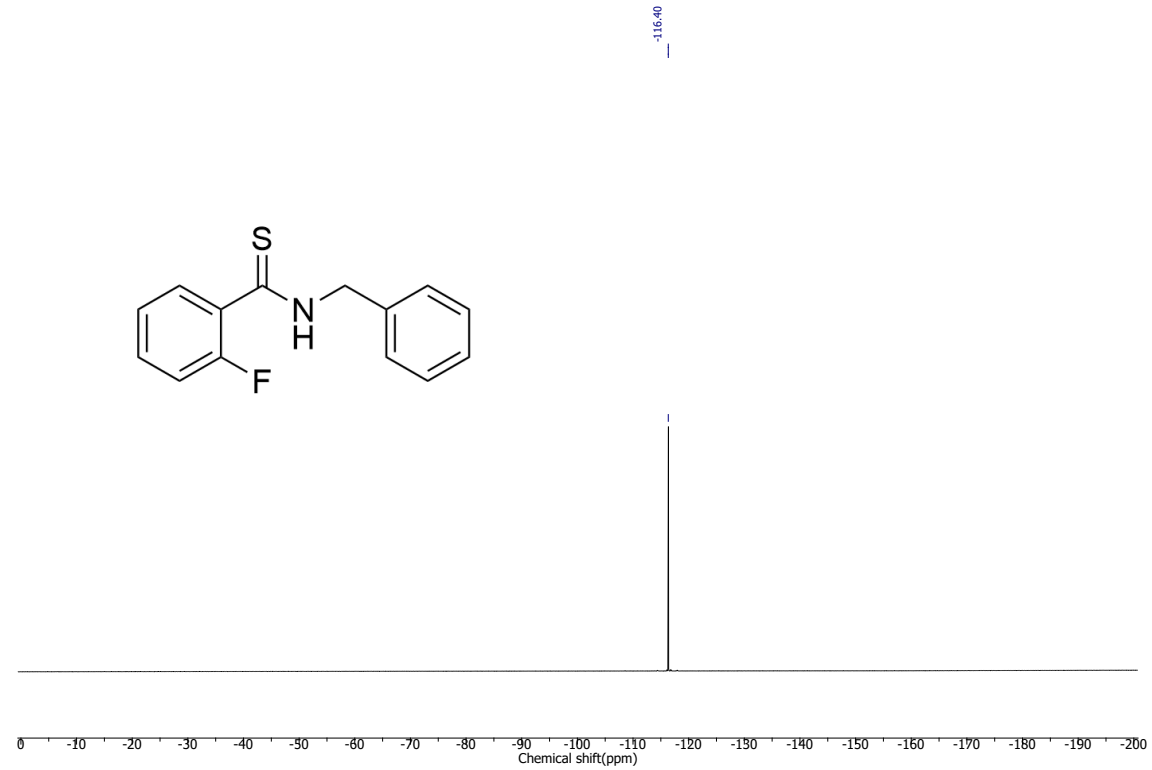


Fig S68. $^{19}F\{^1H\}$ NMR spectra of **4p** ($CDCl_3$, 565 MHz).

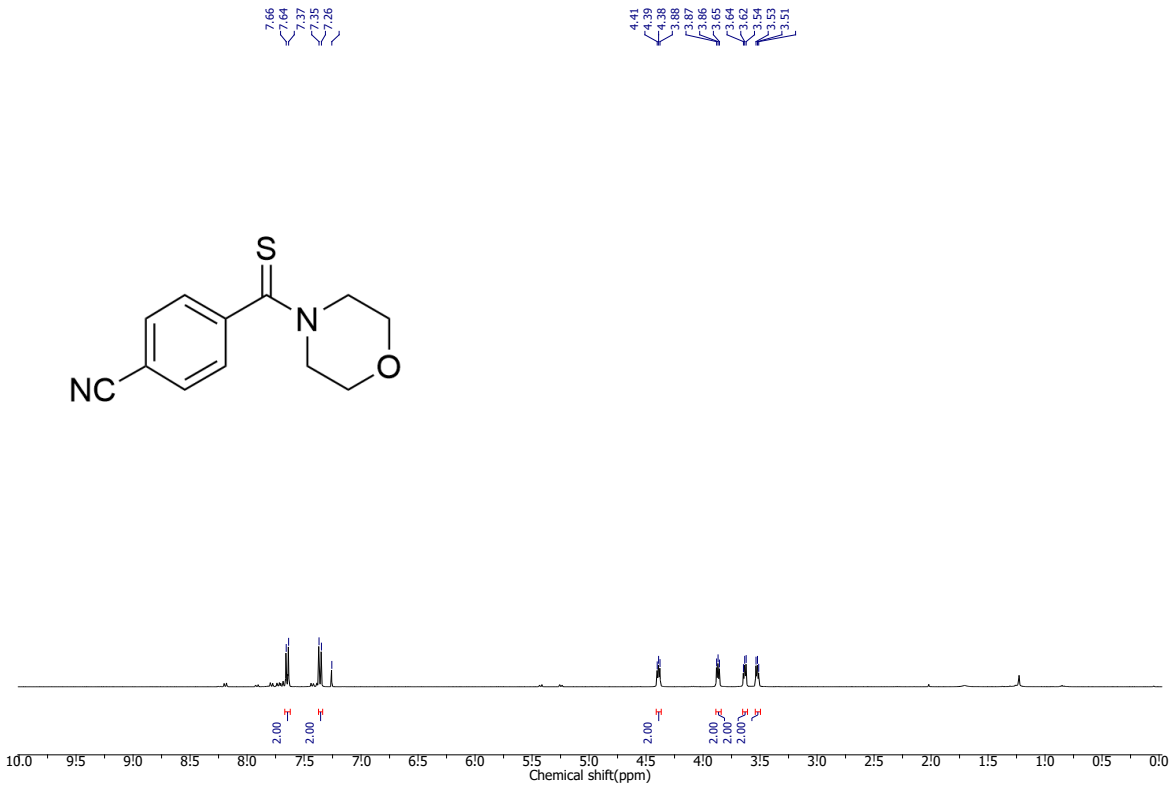


Fig S69. ^{1}H NMR spectra of **4q** ($CDCl_3$, 400 MHz).

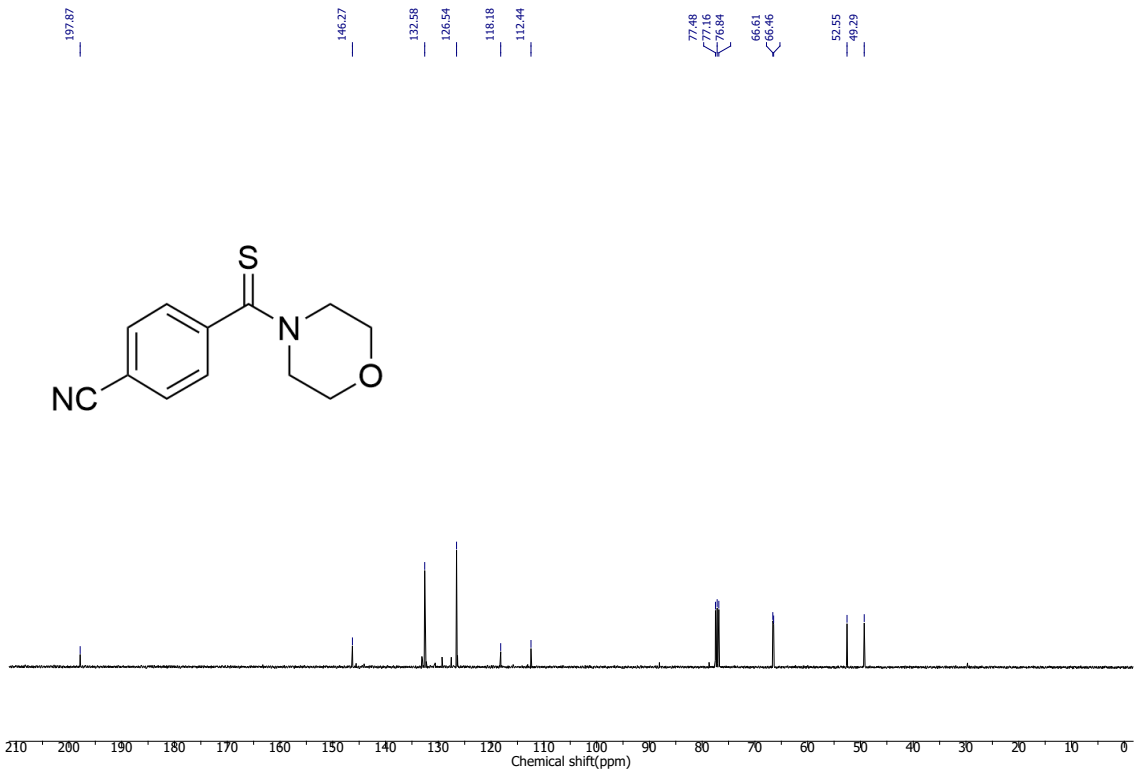


Fig S70. ^{13}C NMR spectra of **4q** ($CDCl_3$, 100 MHz).

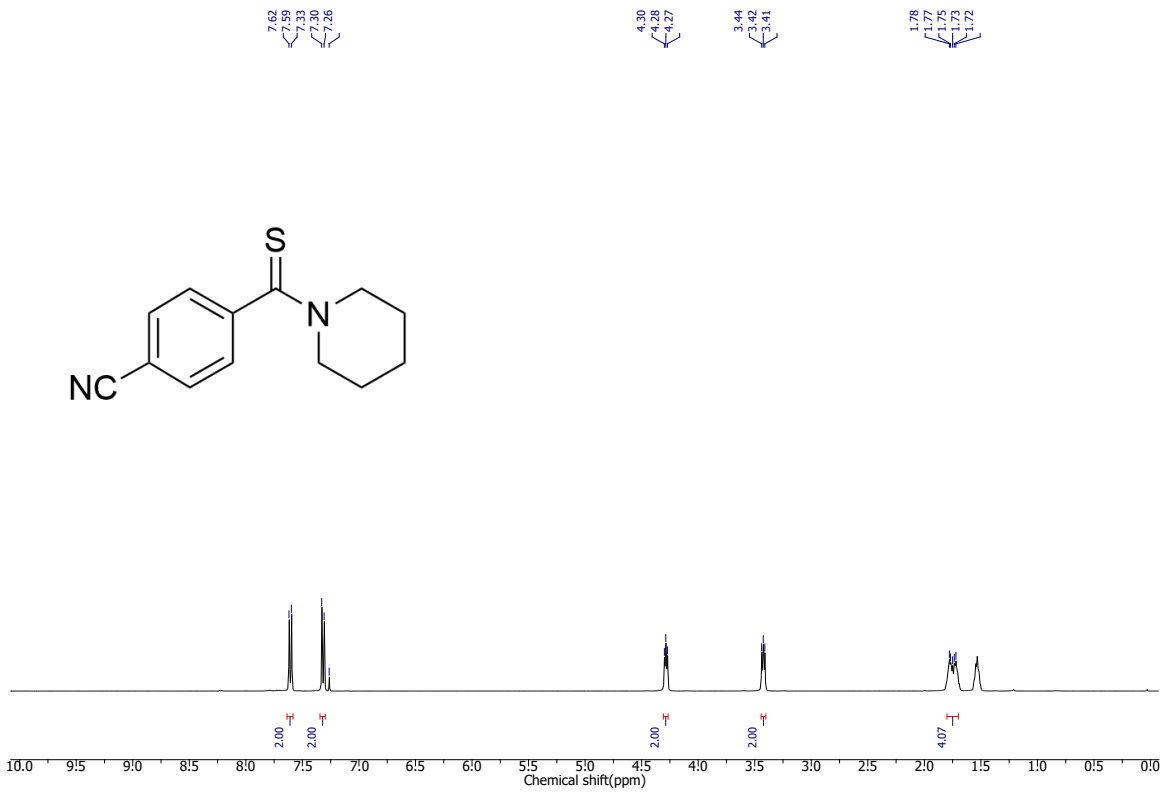


Fig S71. ^{1}H NMR spectra of **4r** ($CDCl_3$, 400 MHz).

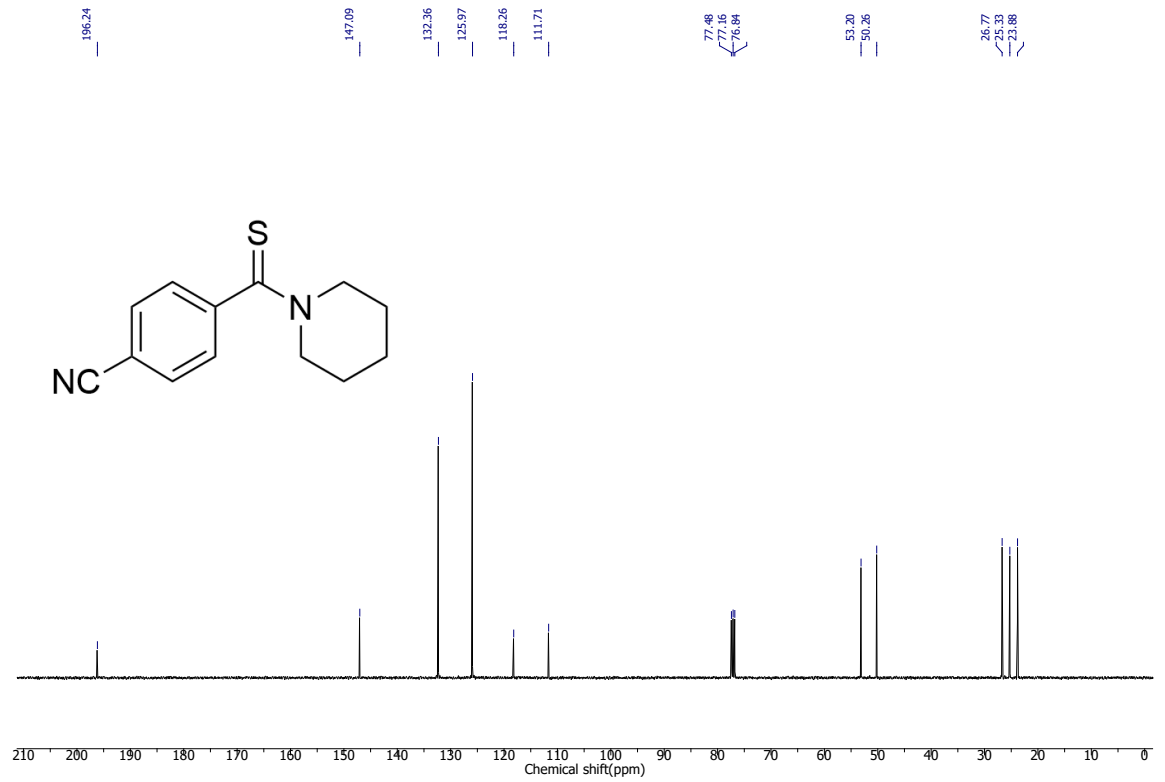


Fig S72. ^{13}C NMR spectra of **4r** ($CDCl_3$, 100 MHz).

NMR spectra of thioamide compounds (5a-5g) from ketone and different amine:

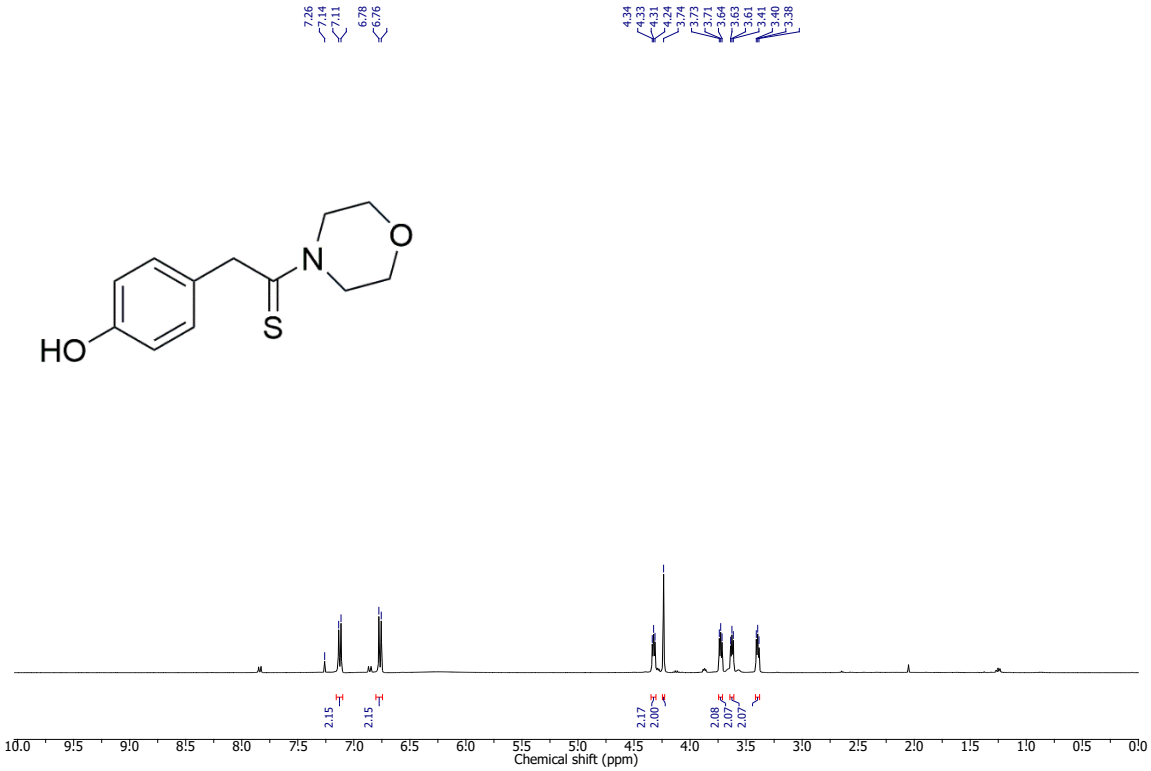


Fig S73. ^{1}H NMR spectra of **5a** ($CDCl_3$, 400 MHz)

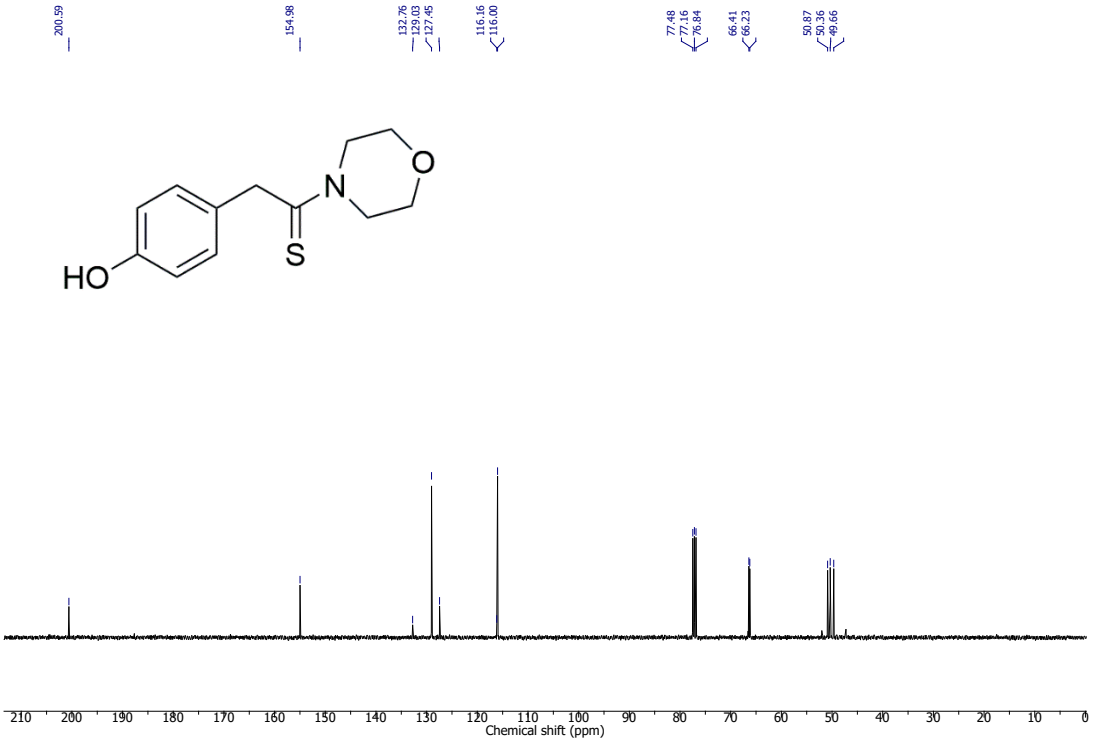


Fig S74. ^{13}C NMR spectra of **5a** ($CDCl_3$, 100 MHz)

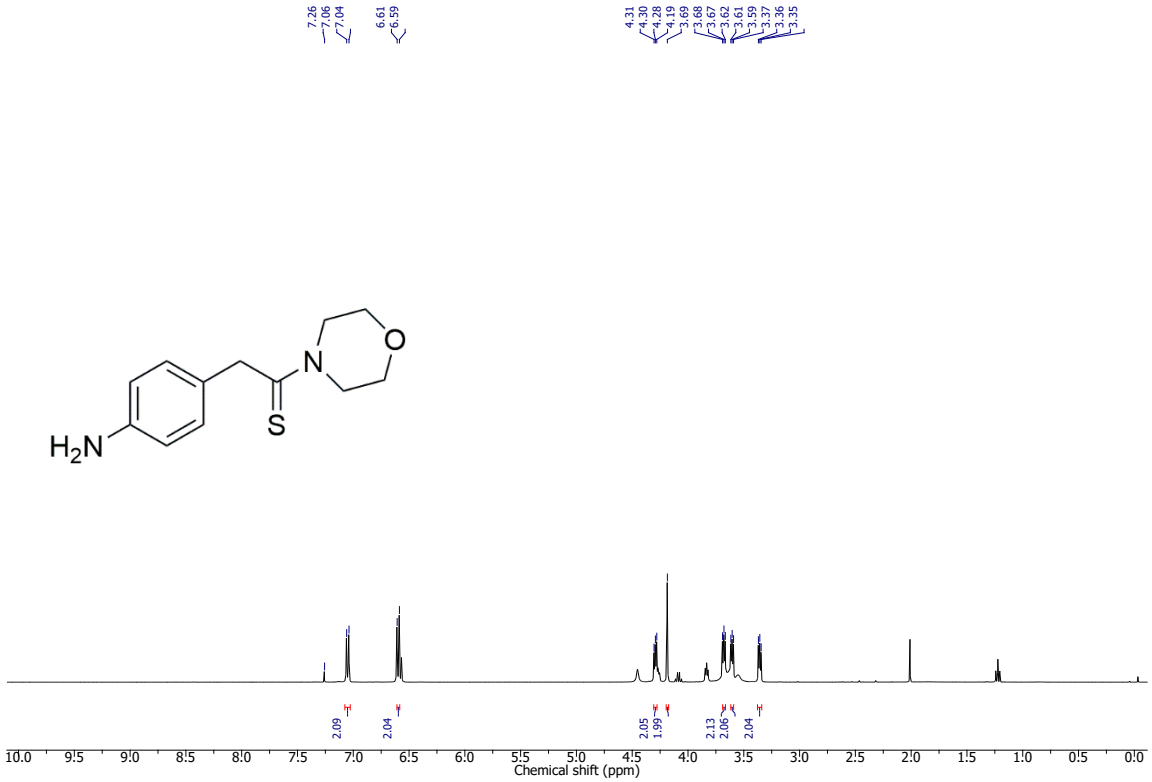


Fig S75. ^{1}H NMR spectra of **5b** ($CDCl_3$, 400 MHz)

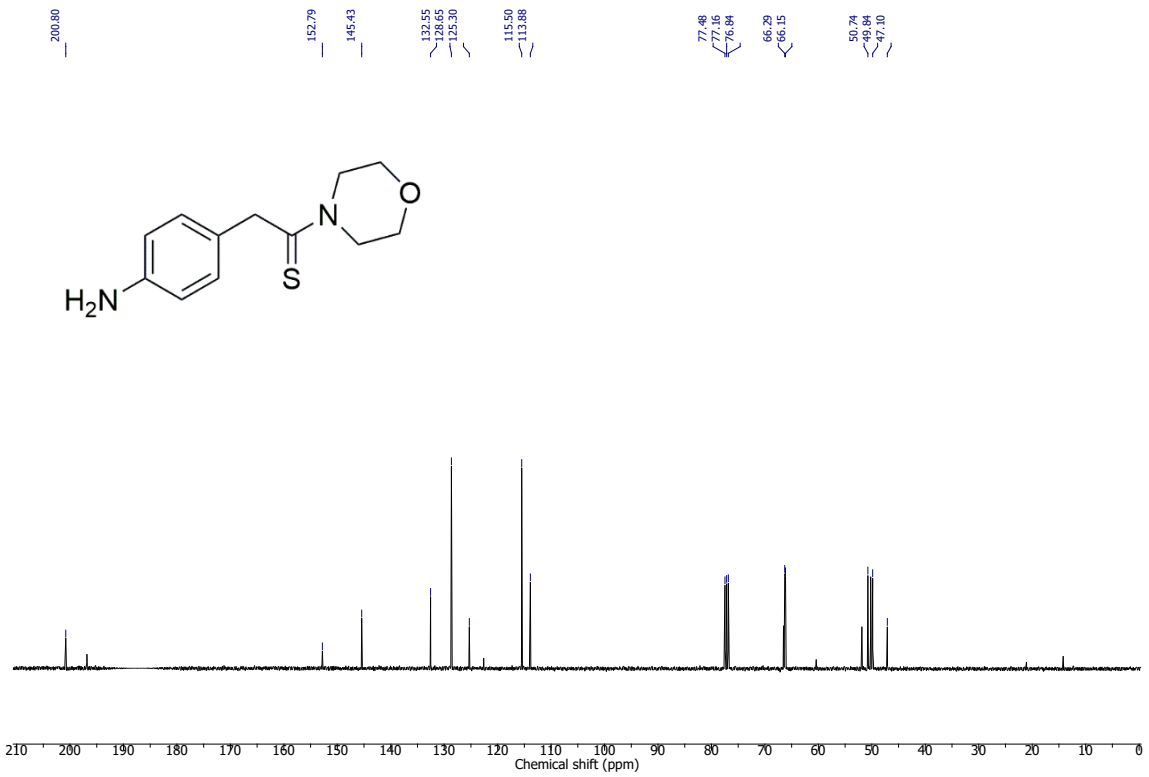


Fig S76. ^{13}C NMR spectra of **5b** ($CDCl_3$, 100 MHz)

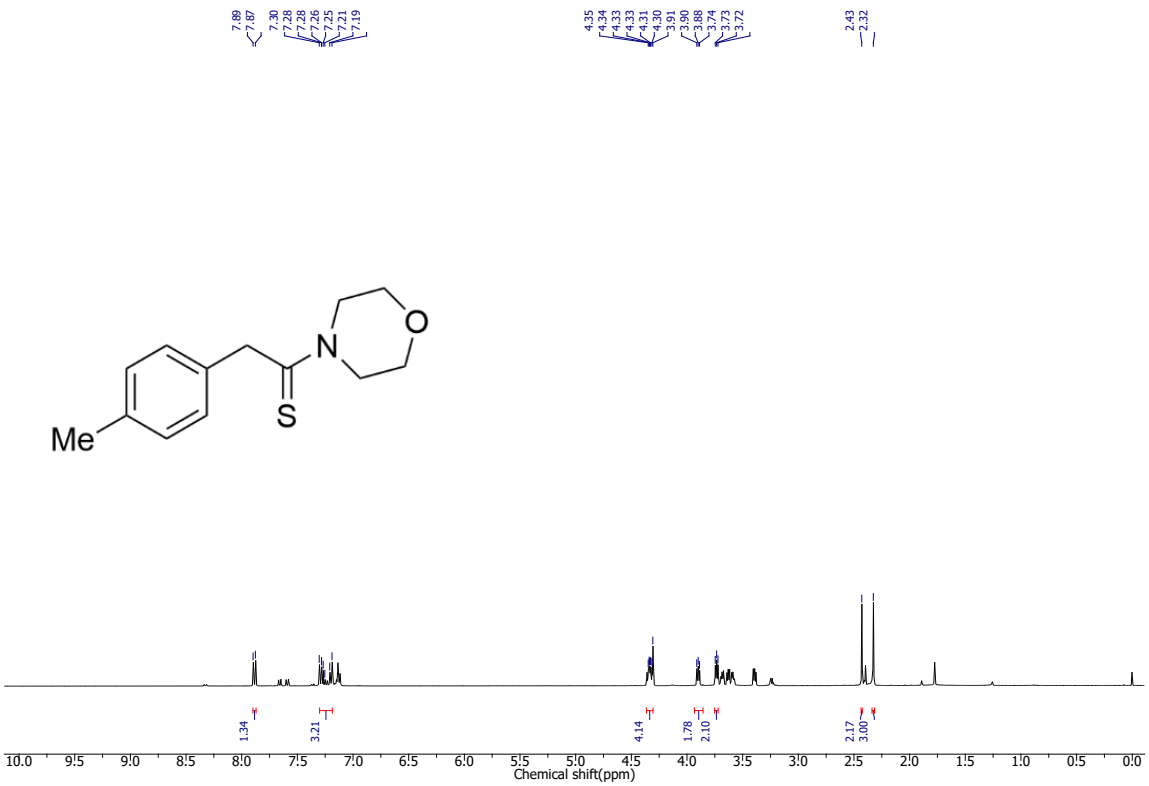


Fig S77. ^{1}H NMR spectra of **5c** ($CDCl_3$, 400 MHz)

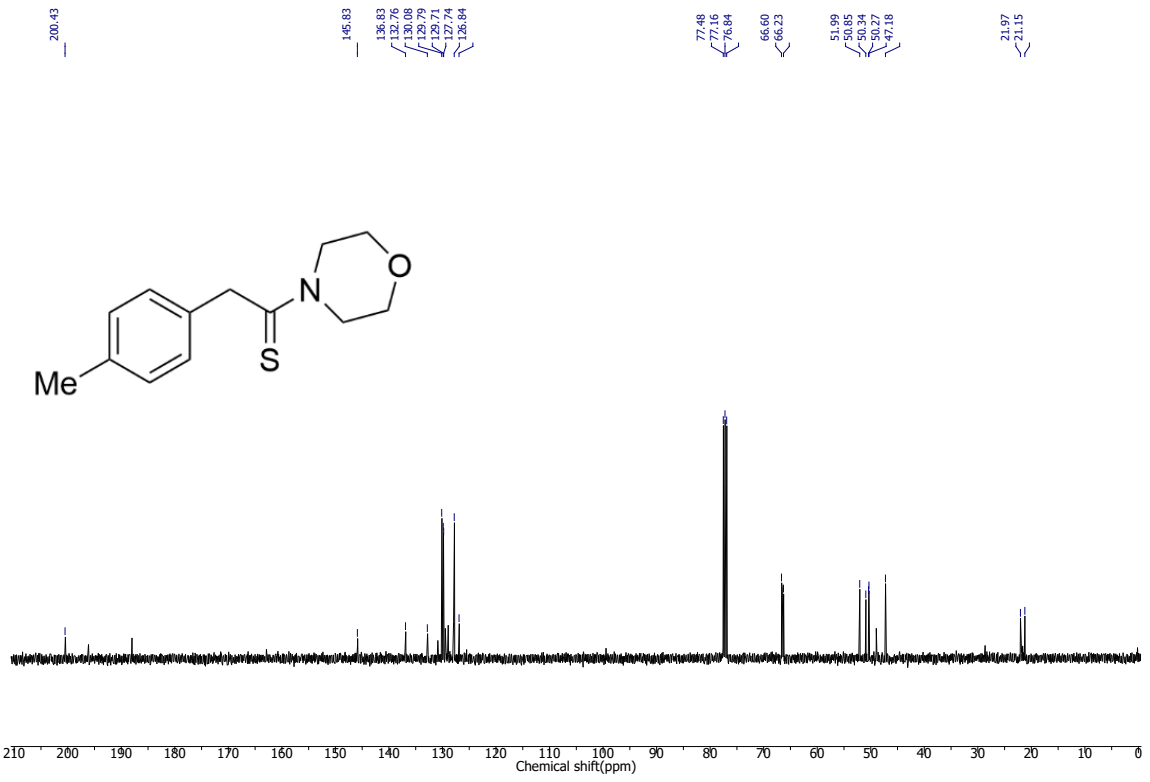


Fig S78. ^{13}C NMR spectra of **5c** ($CDCl_3$, 100 MHz)

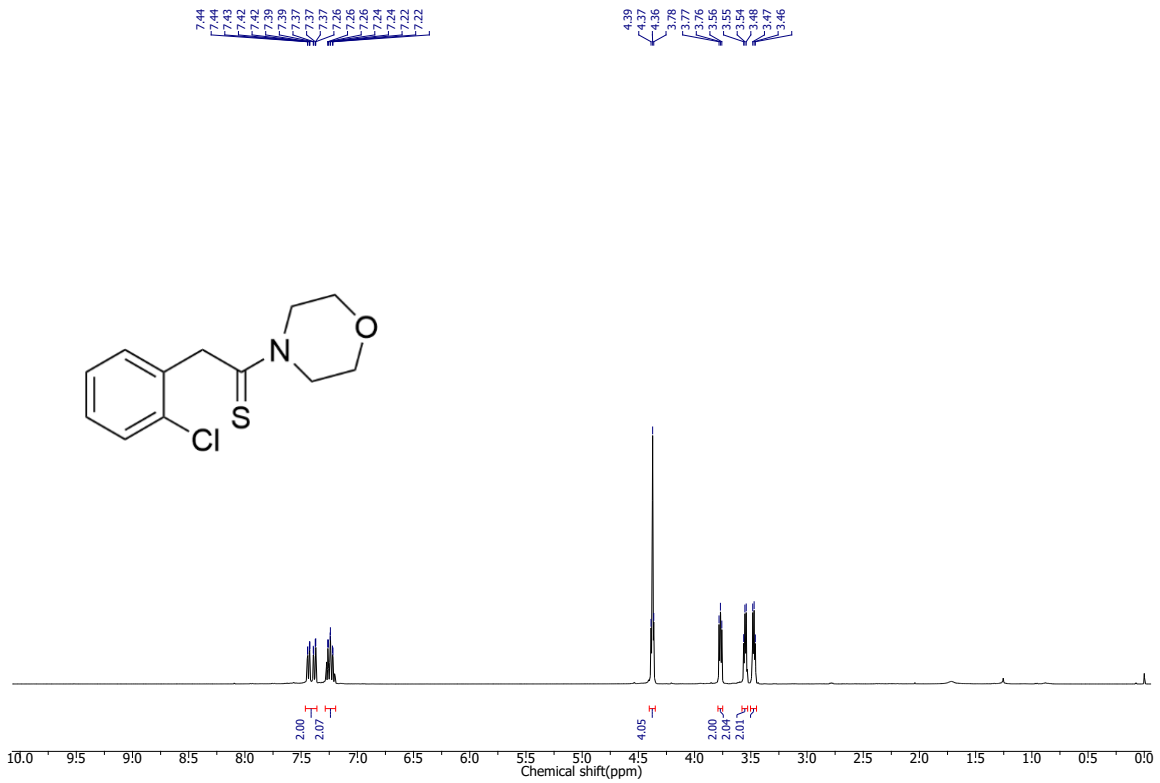


Fig S79. ^{1}H NMR spectra of **5d** ($CDCl_3$, 400 MHz)

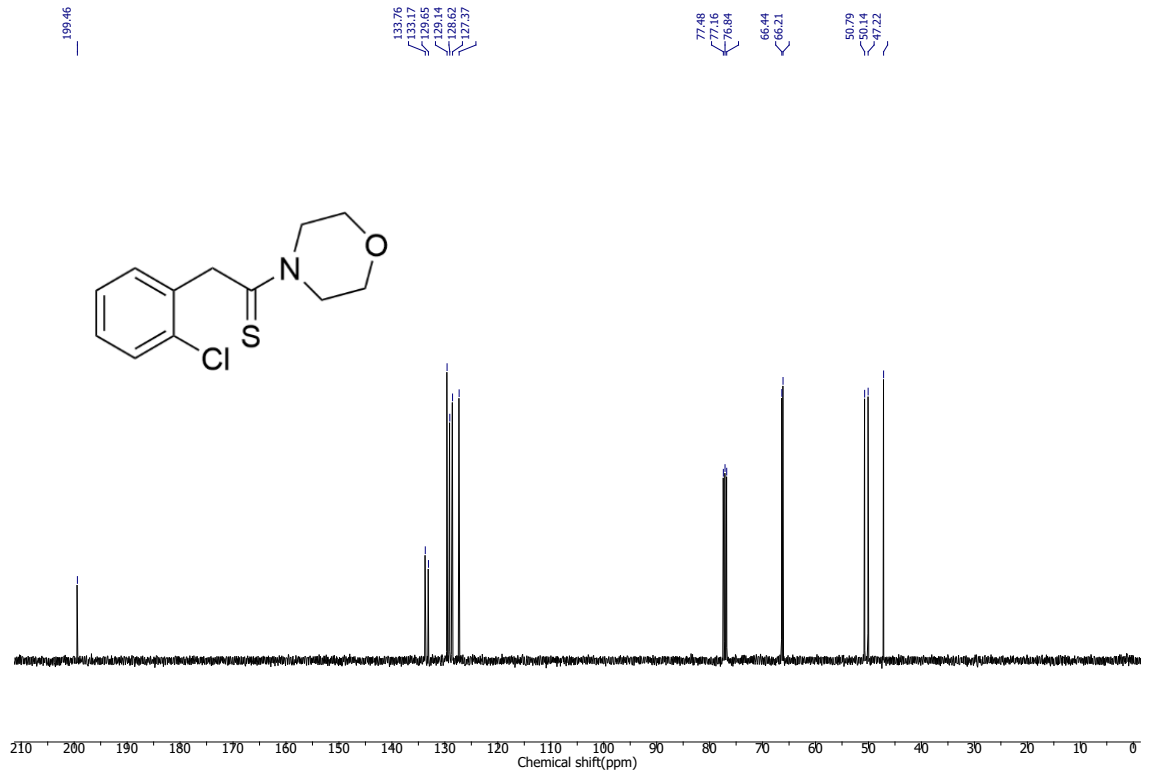


Fig S80. ^{13}C NMR spectra of **5d** ($CDCl_3$, 100 MHz)

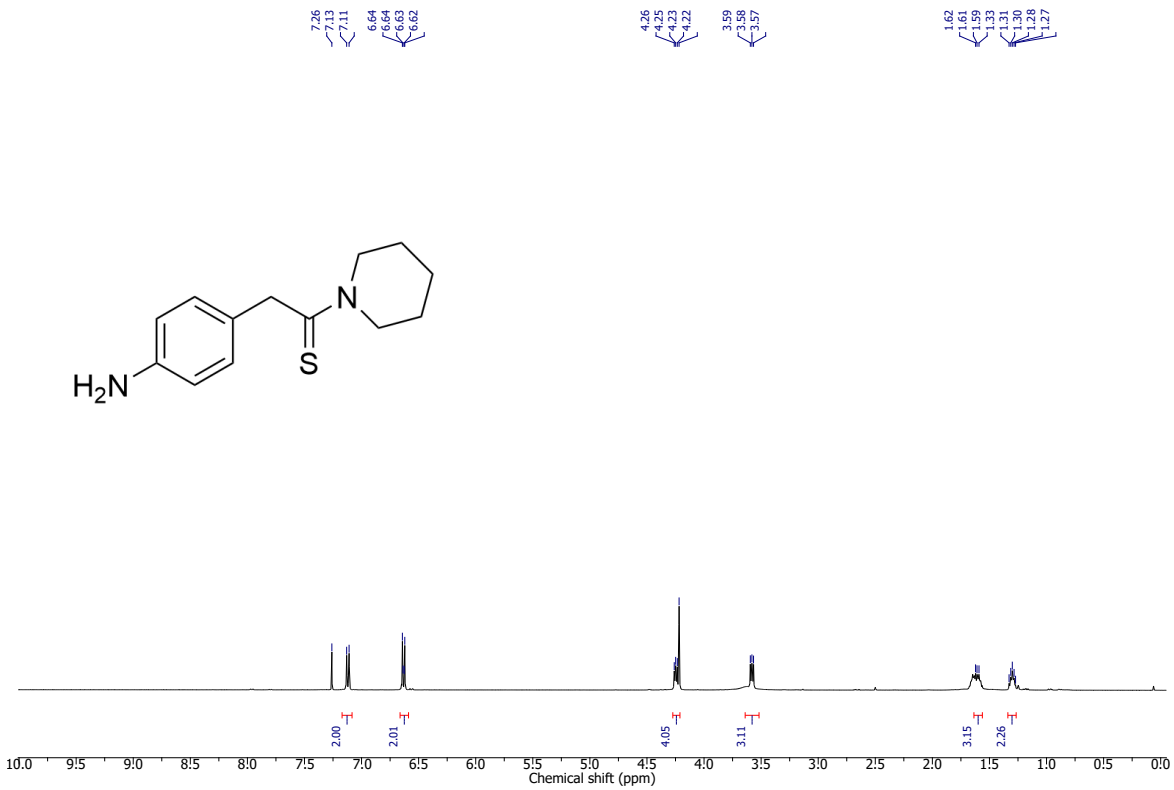


Fig S81. ^{1}H NMR spectra of **5e** ($CDCl_3$, 400 MHz)

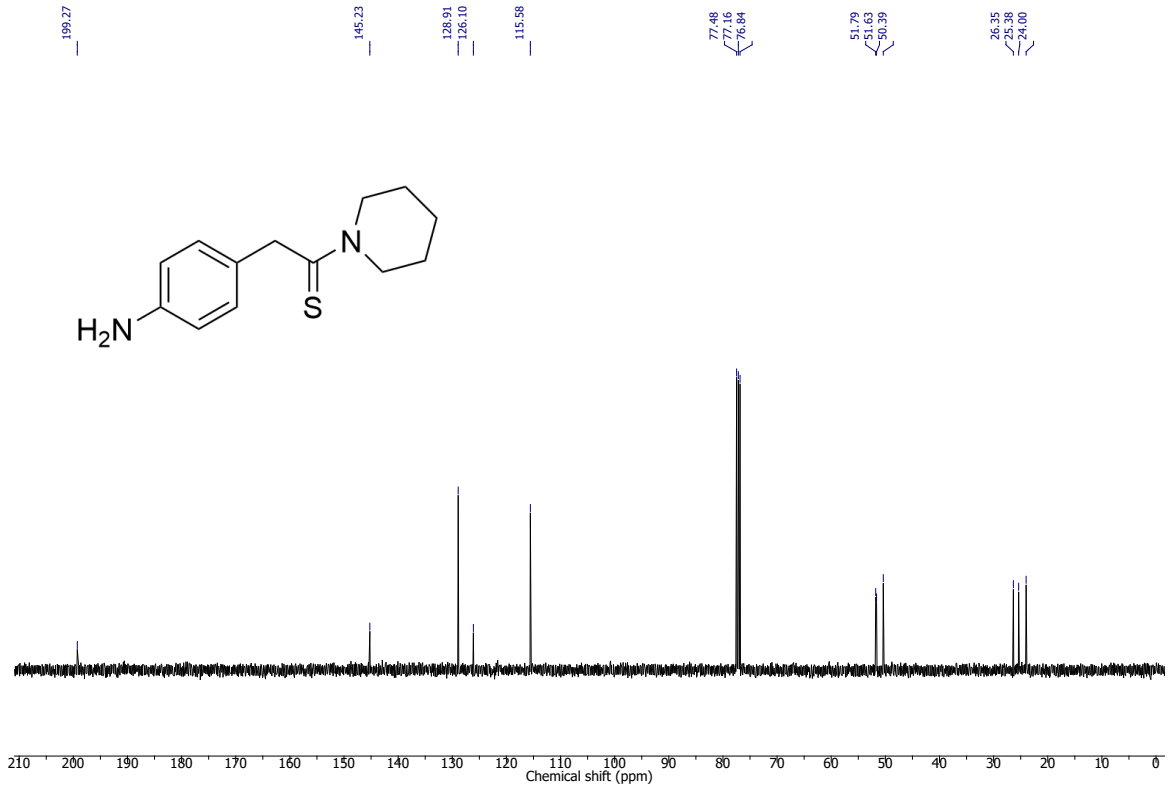


Fig S82. ^{13}C NMR spectra of **5e** ($CDCl_3$, 100 MHz)

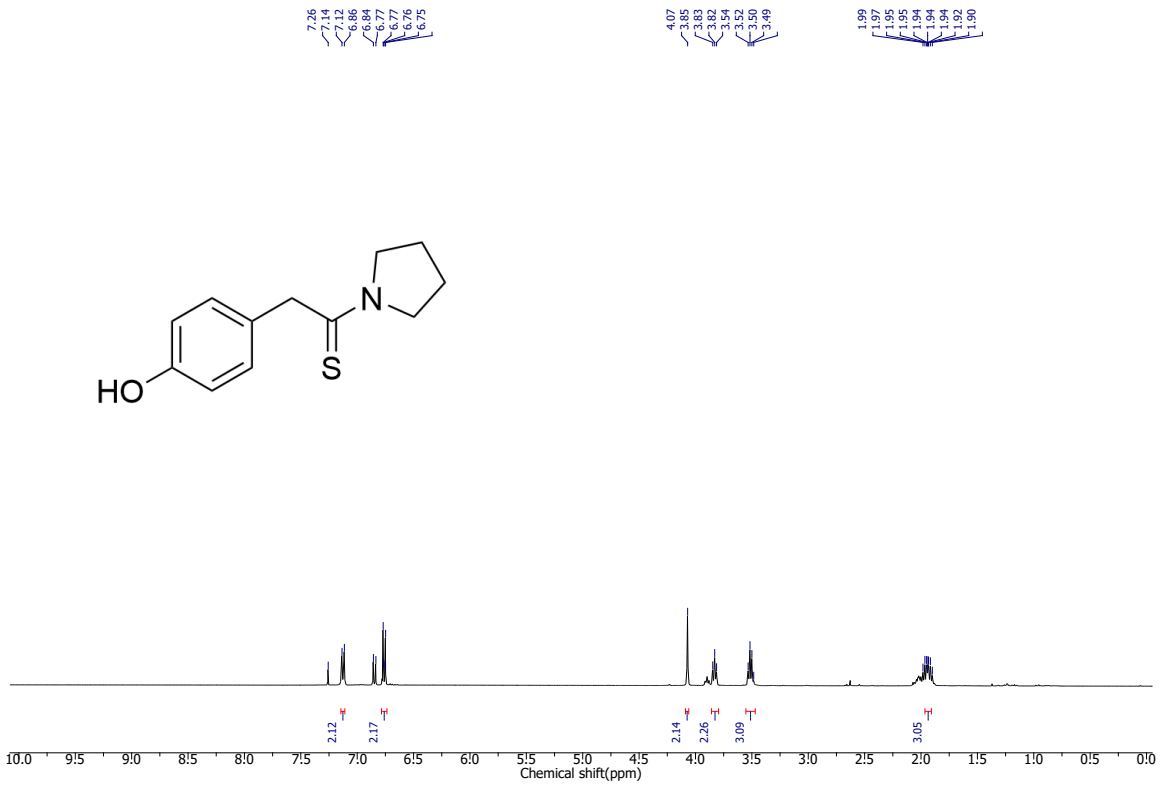


Fig S83. ^{1}H NMR spectra of **5f** ($CDCl_3$, 400 MHz)

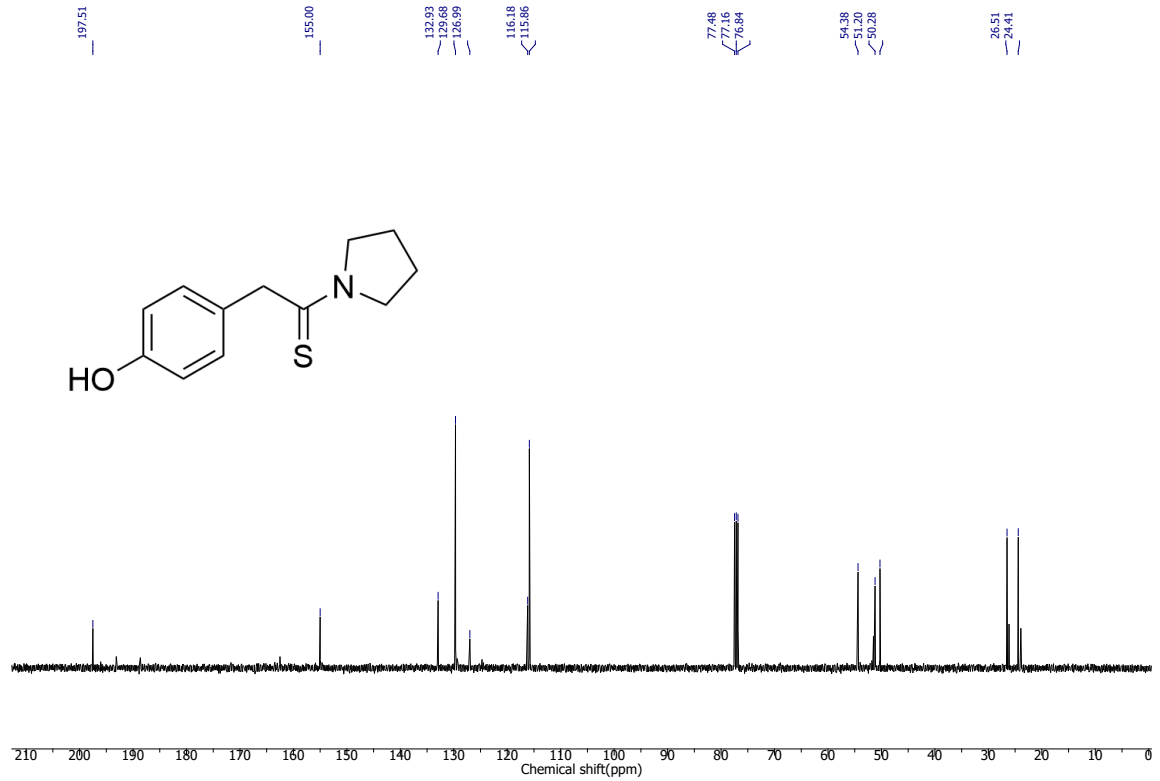


Fig S84. ^{13}C NMR spectra of **5f** ($CDCl_3$, 100 MHz)

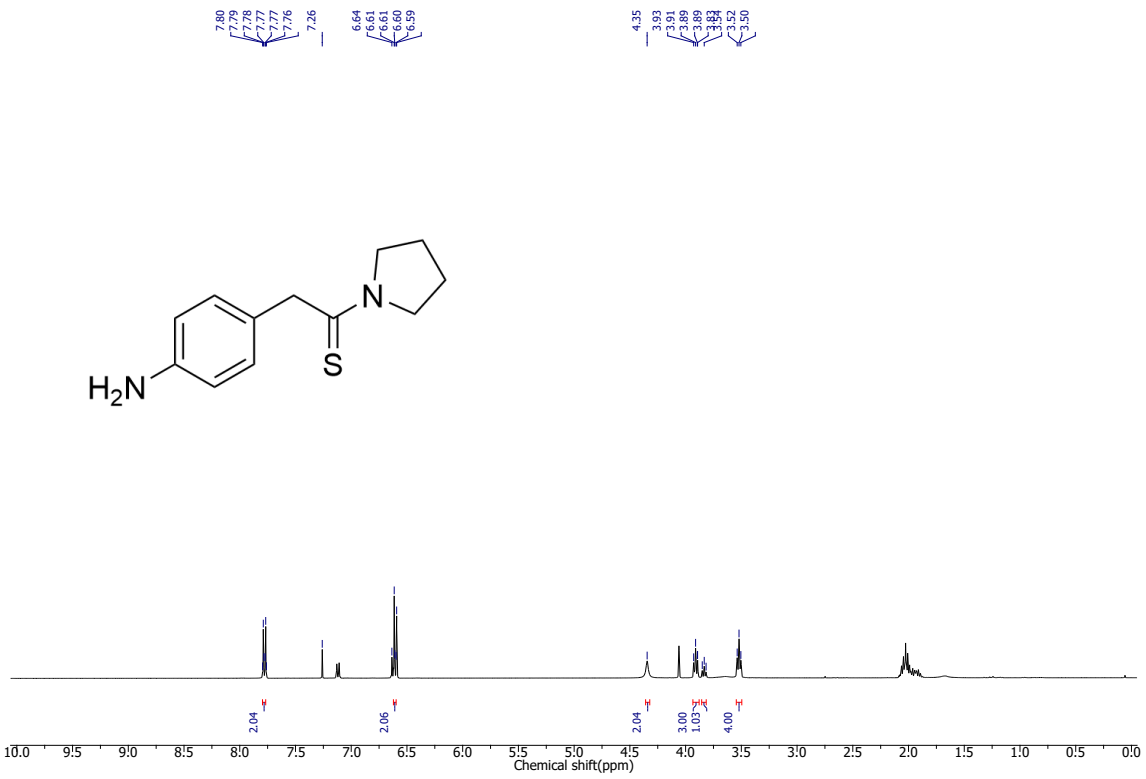


Fig S85. ^{1}H NMR spectra of **5g** ($CDCl_3$, 400 MHz)

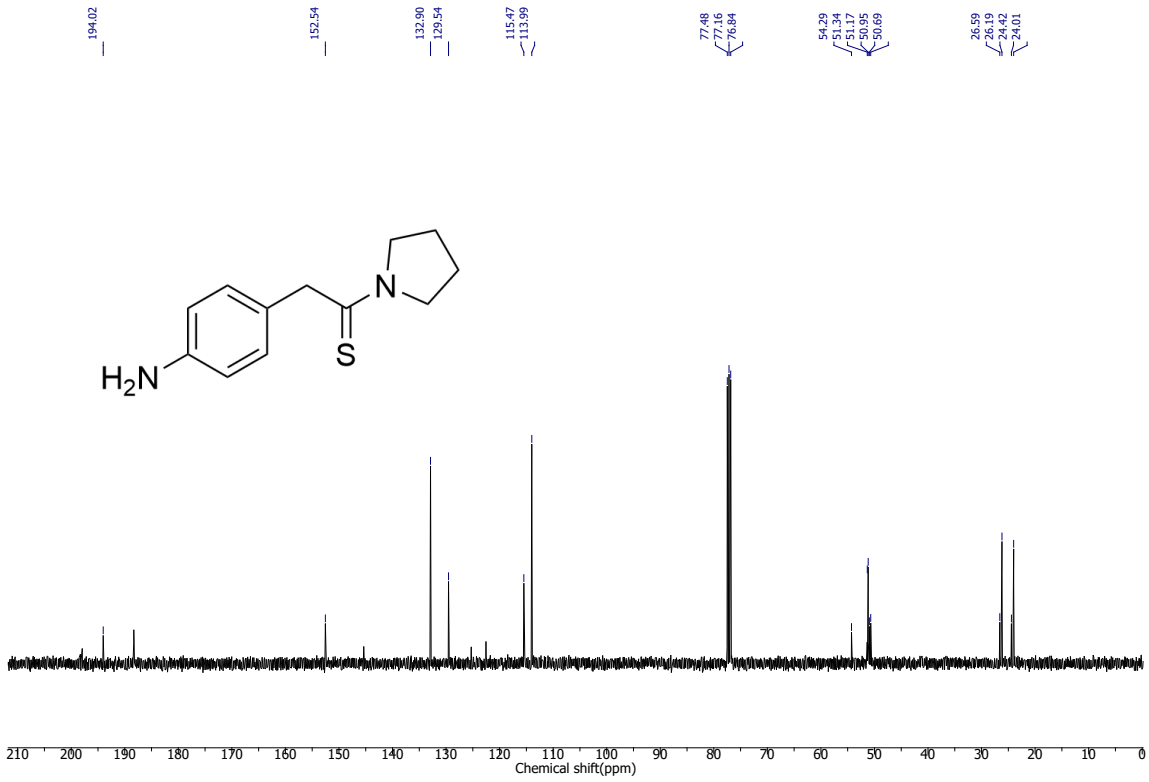


Fig S86. ^{13}C NMR spectra of **5g** ($CDCl_3$, 100 MHz)

NMR spectra of thioamide compounds (6a-6c) from acid and different amines:

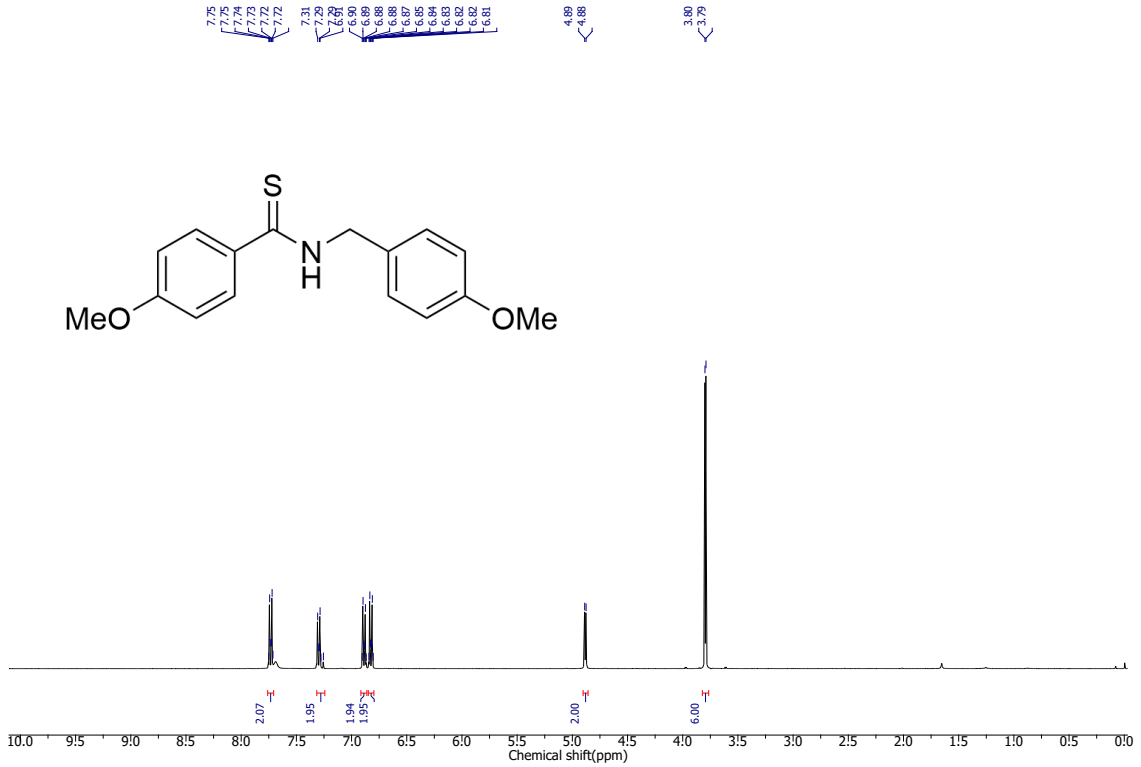


Fig S87. ^{1}H NMR spectra of **6a** ($CDCl_3$, 400 MHz)

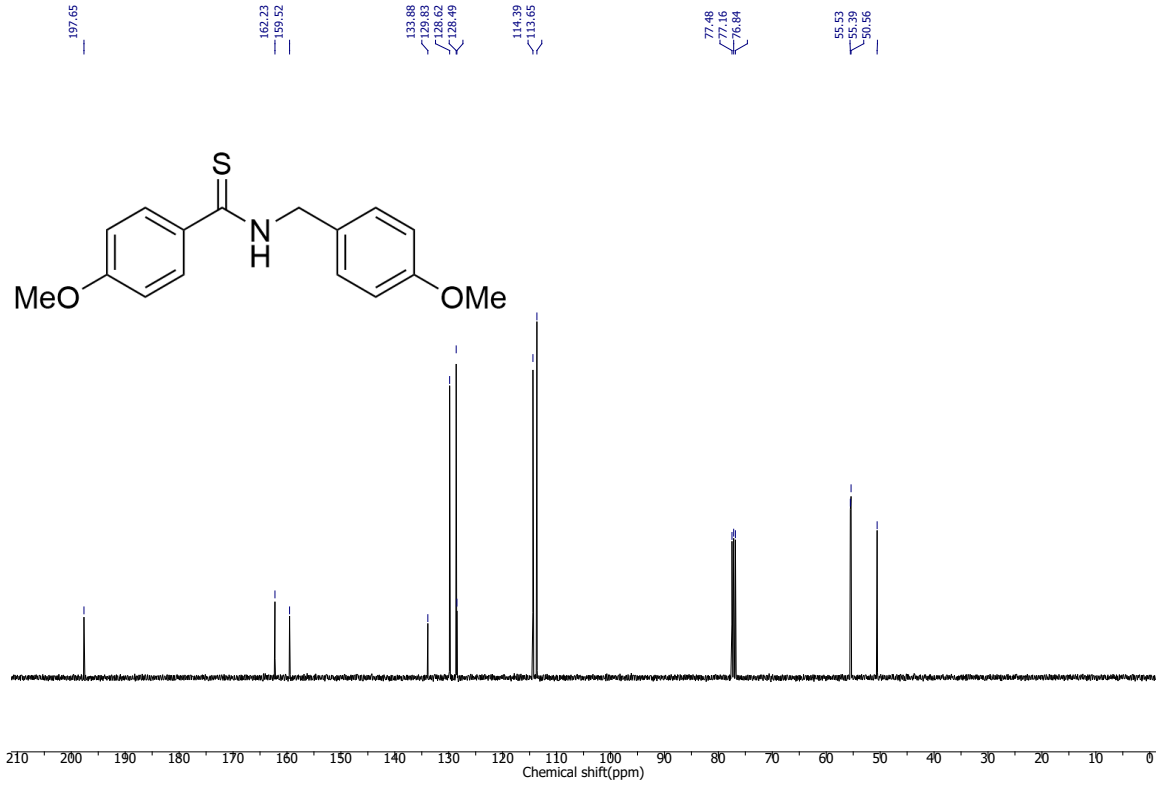


Fig S88. ^{13}C NMR spectra of **6a** ($CDCl_3$, 100 MHz)

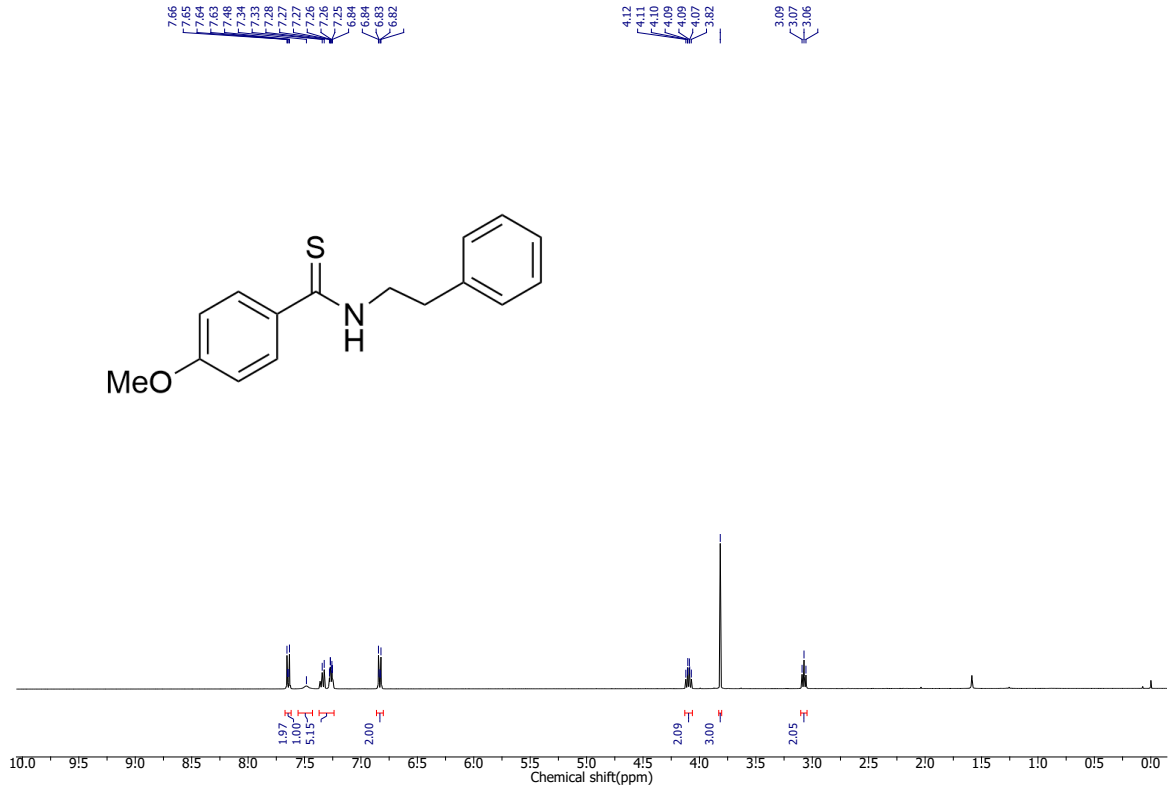


Fig S89. ^{1}H NMR spectra of **6b** ($CDCl_3$, 400 MHz)

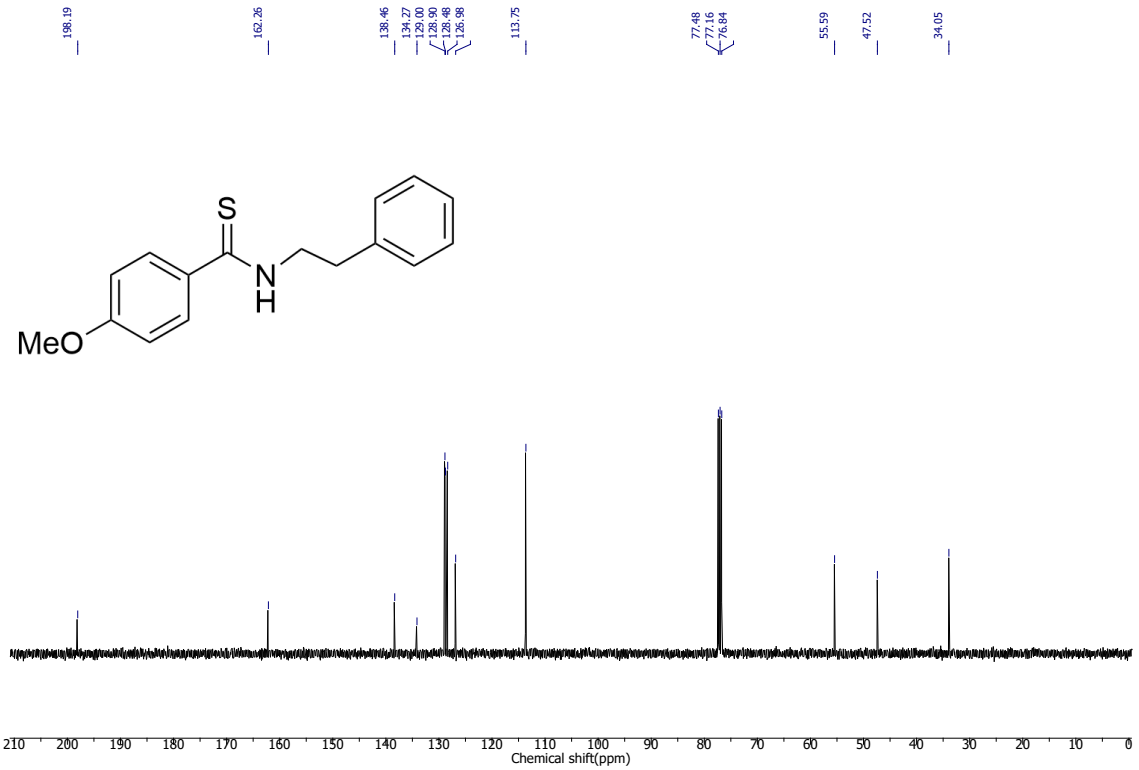


Fig S90. ^{13}C NMR spectra of **6b** ($CDCl_3$, 100 MHz)

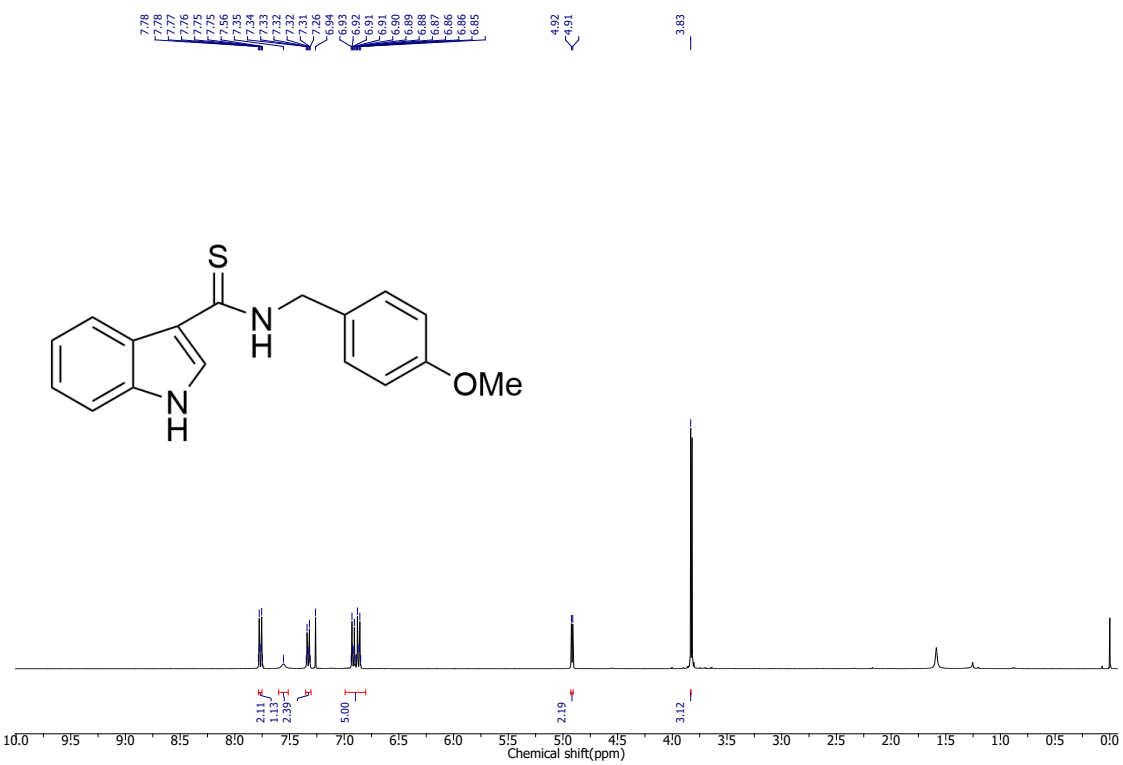


Fig S91. ^{1}H NMR spectra of **6c** ($CDCl_3$, 400 MHz)

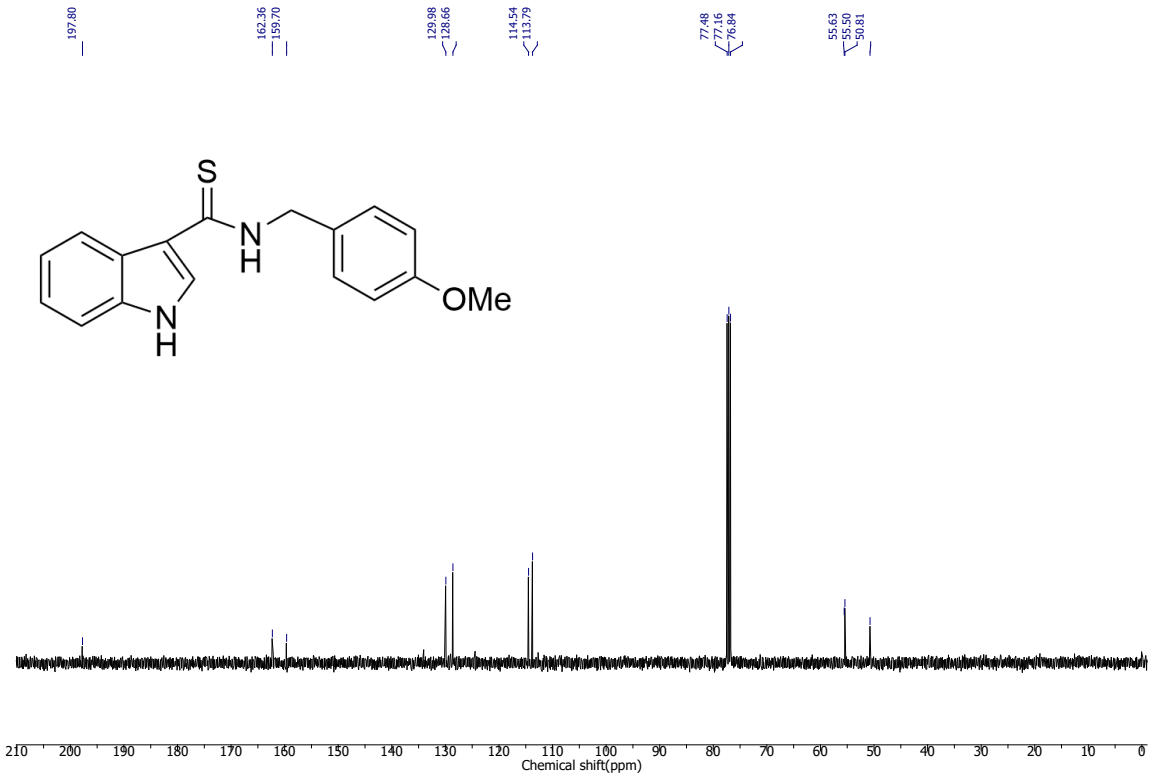


Fig S92. ^{13}C NMR spectra of **6c** ($CDCl_3$, 100 MHz)

NMR spectra of 1,3,4 thiadiazole compounds (7a-7d) obtained from thioamide:

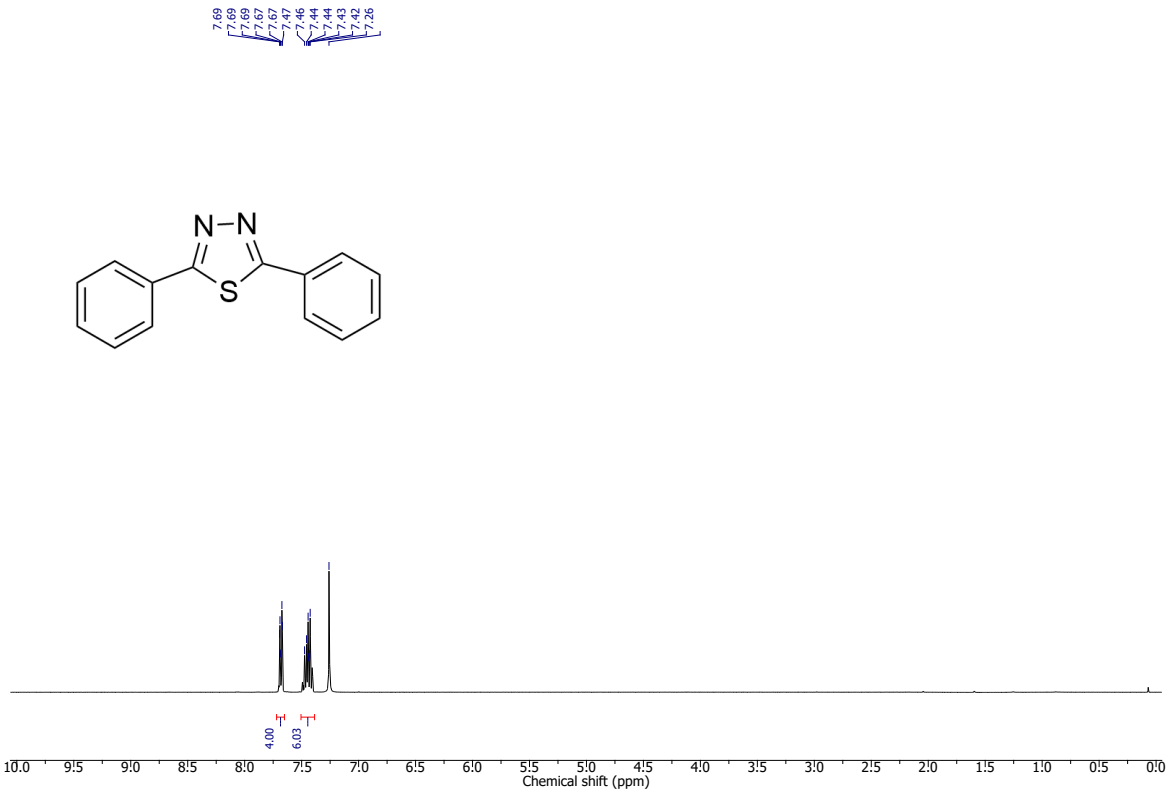


Fig S93. ^{1}H NMR spectra of **7a** ($CDCl_3$, 400 MHz)

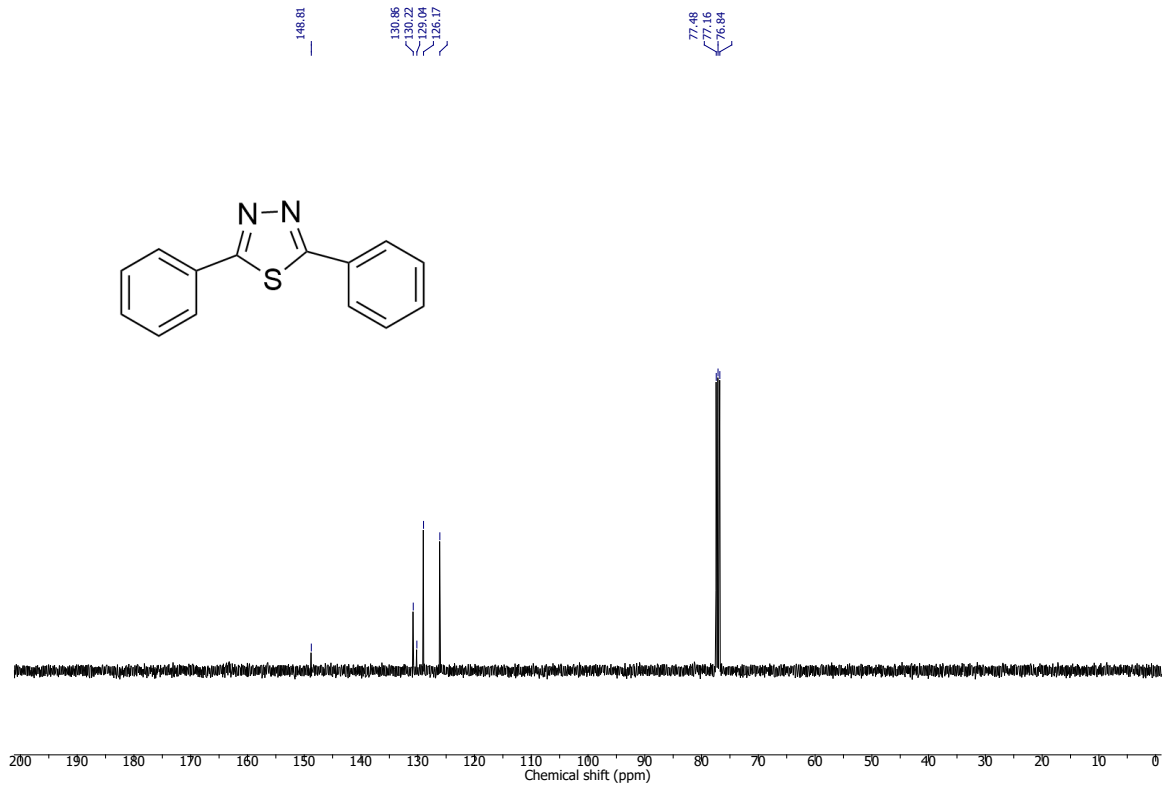


Fig S94. ^{13}C NMR spectra of **7a** ($CDCl_3$, 100 MHz)

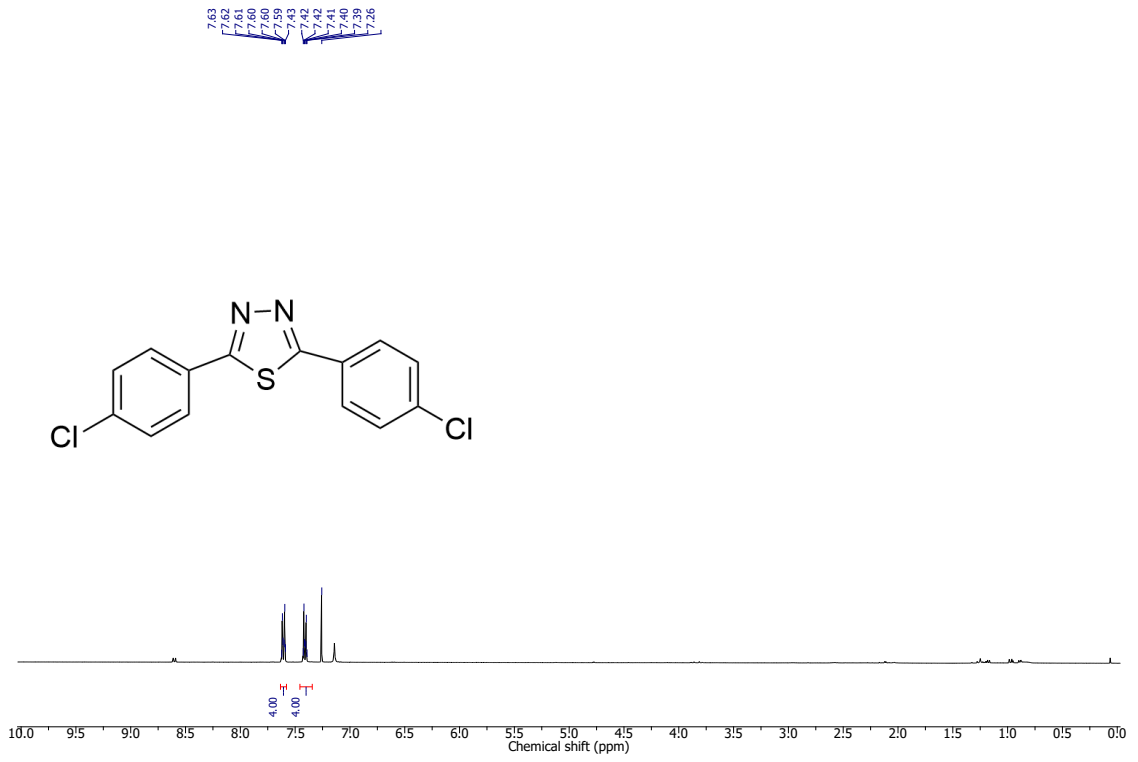


Fig S95. ^{1}H NMR spectra of **7b** ($CDCl_3$, 400 MHz)

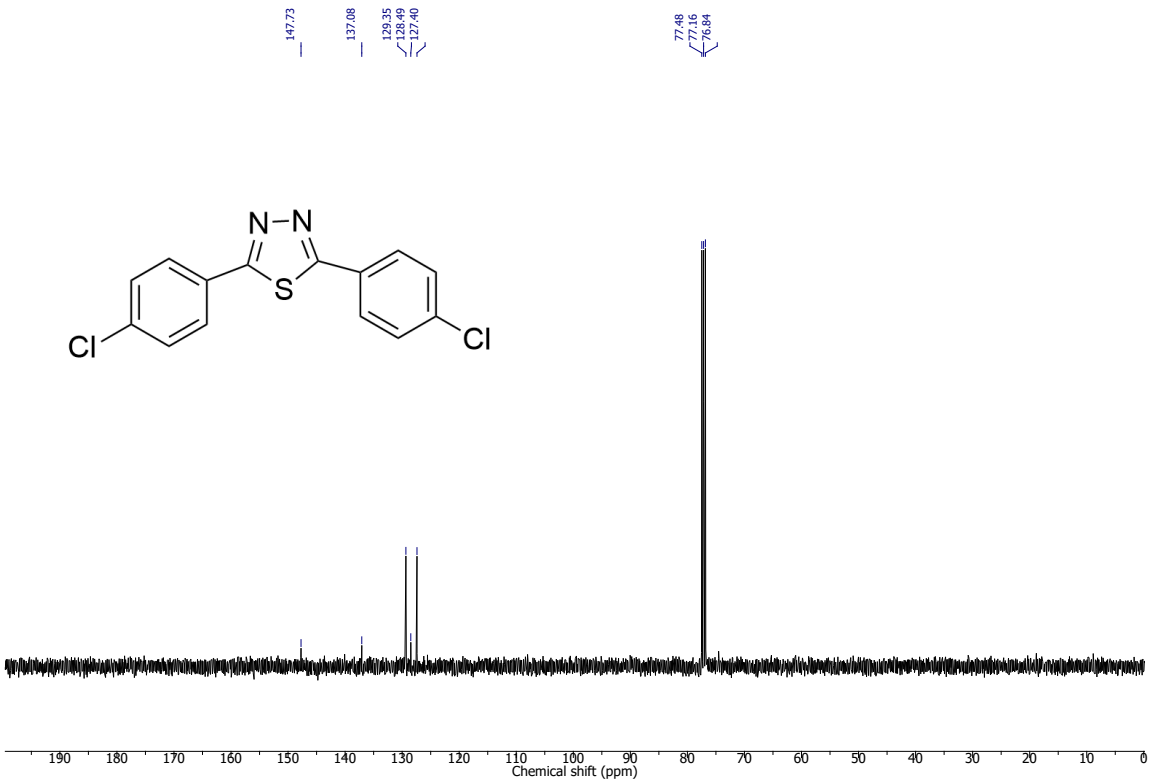


Fig S96. ^{13}C NMR spectra of **7b** ($CDCl_3$, 100 MHz)

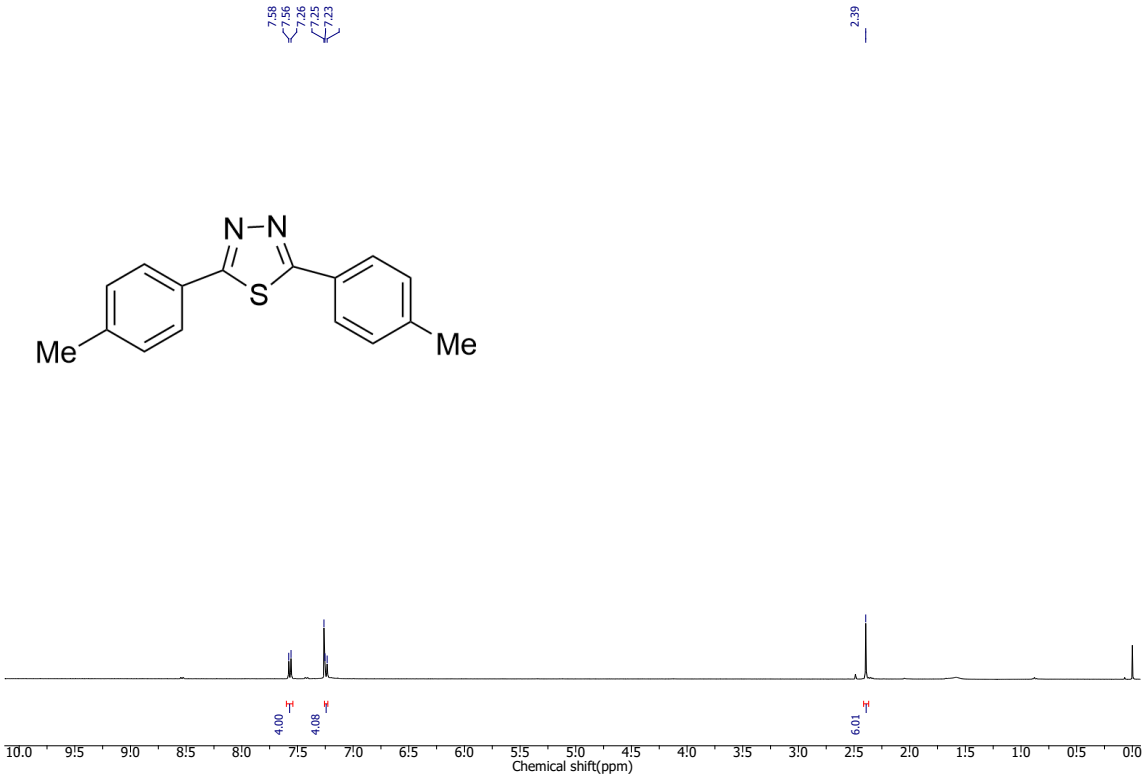


Fig S97. ^{1}H NMR spectra of **7c** ($CDCl_3$, 400 MHz)

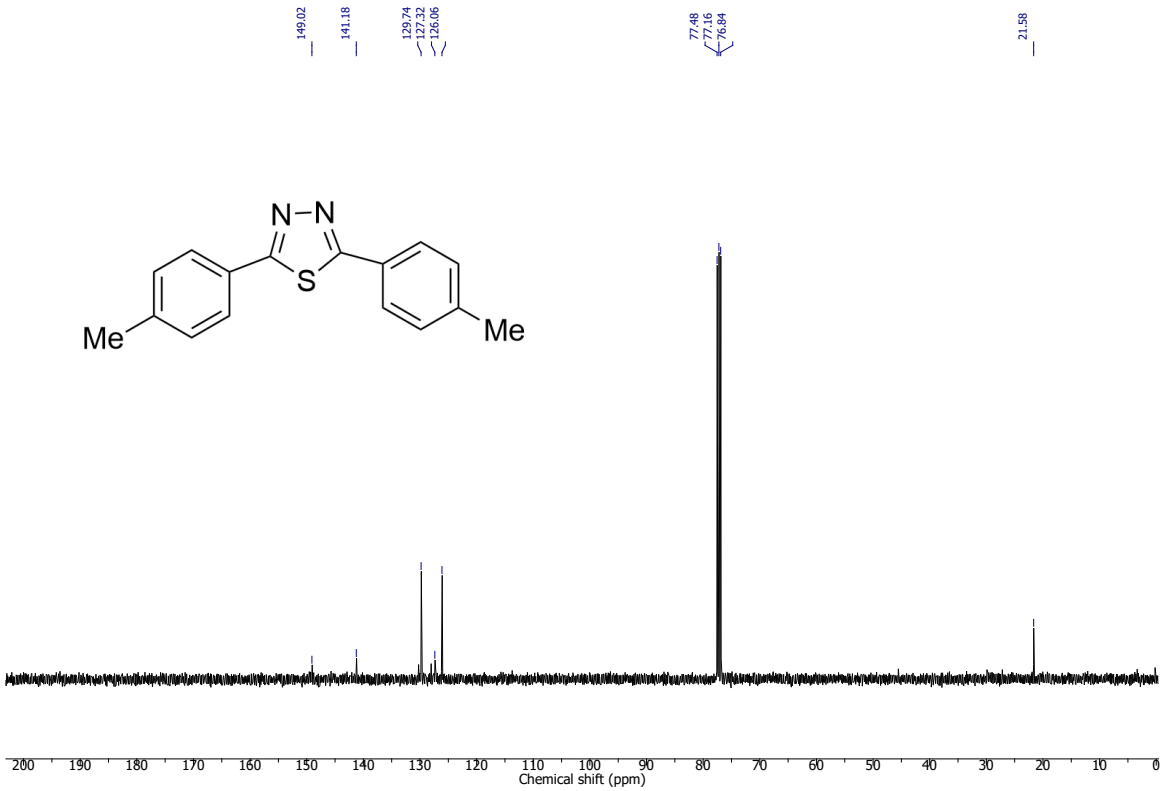


Fig S98. ^{13}C NMR spectra of **7c** ($CDCl_3$, 100 MHz)

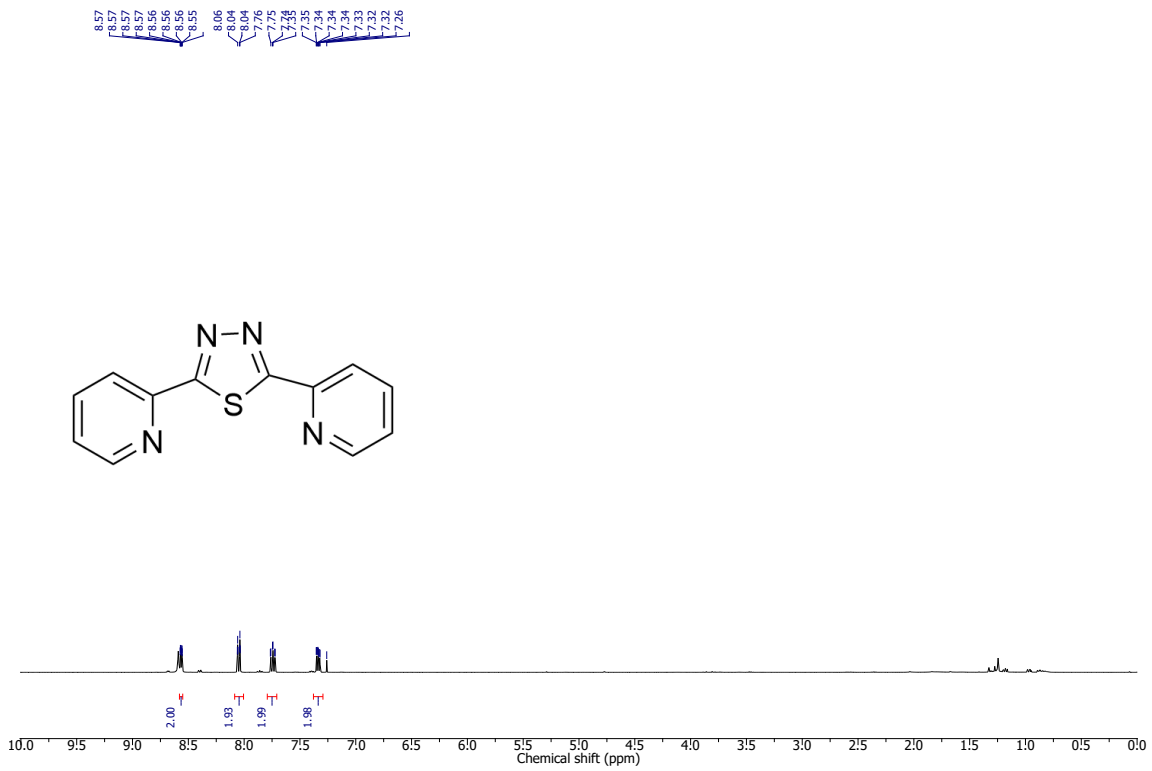


Fig S99. ^{1}H NMR spectra of **7d** ($CDCl_3$, 400 MHz)

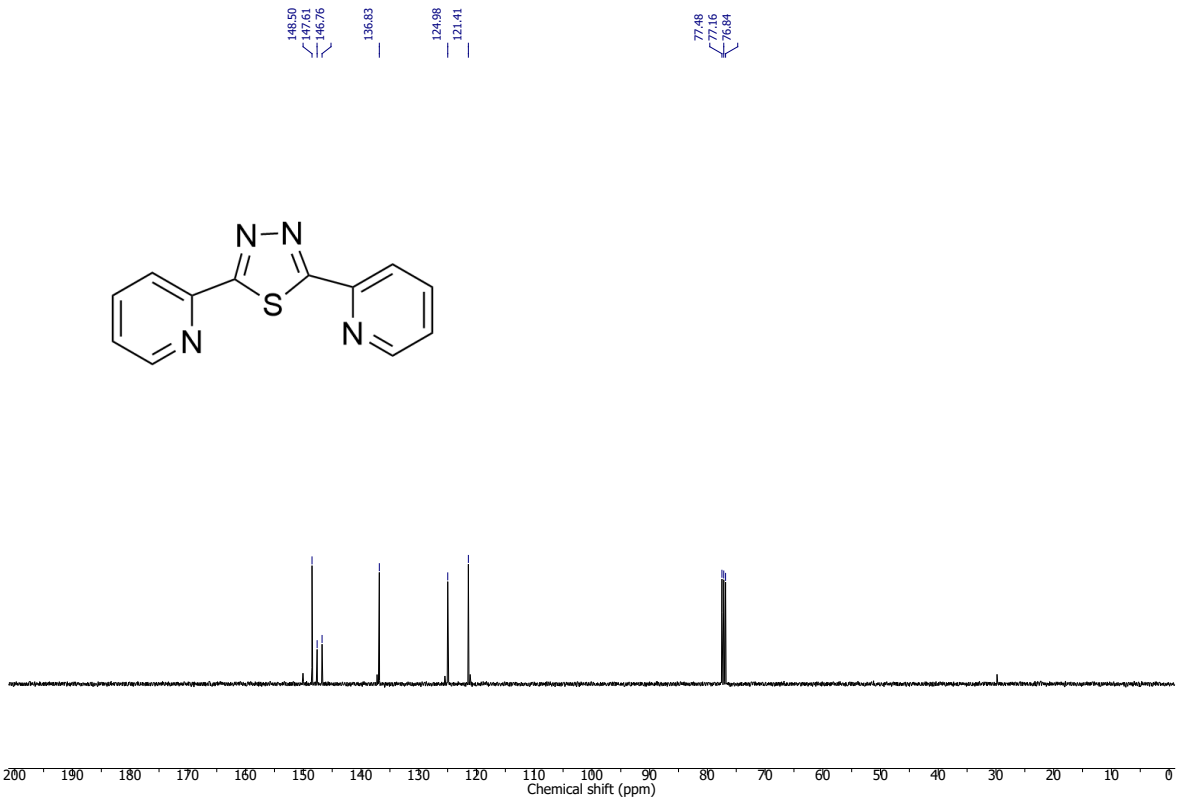


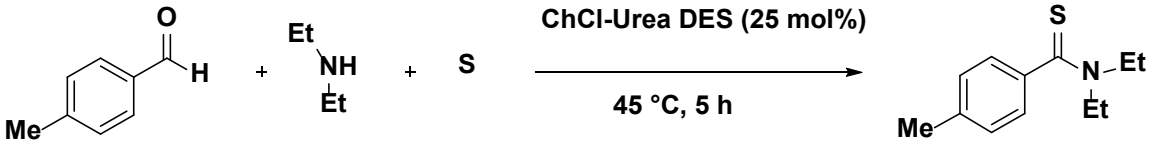
Fig S100. ^{13}C NMR spectra of **7d** ($CDCl_3$, 100 MHz)

Calculations of Green chemistry metrics for thioamidation reaction:

There are different parameters for green chemistry metric like

1. E-factor or environmental factor
2. Atom economy (AE)
3. Atom efficiency
4. Carbon efficiency
5. Product mass intensity (PMI)
6. Reaction mass efficiency (RME)

Here we have calculated different green chemistry metric parameter[21],[22] for our optimized reaction.



Yield = 93%

	Name	Chemical formula	Molecular weight	millimole	mg
Reactant 1	4-methylbenzaldehyde	C_8H_8O	120.15	1.5625	187.7
Reactant 2	Diethylamine	$C_4H_{11}N$	73.14	1.5625	114.3
Reactant 3	Sulfur powder	S	32	1.5625	50
Solvent	DES (ChCl: Urea = 1:2)	-	259.5	0.3906	101
Product	N,N-diethyl-4-methylbenzothioami-de	$C_{12}H_{17}NS$	207.34	-	301

1. **E - factor or environmental factor**

$$\textbf{E factor} = \frac{\text{Total mass of the waste}}{\text{Mass of the product}}$$

$$\text{E} - \text{factor} = \frac{\{(120.15 \times 1.5625) + (73.14 \times 1.5625) + (32 \times 1.5625) - 301\}\ \text{mg}}{301\ \text{mg}}$$

$$\textbf{E} - \textbf{factor} = \mathbf{0.17}$$

2. Atom economy (AE)

$$\text{Atom economy} = \frac{\text{MW of product}}{\Sigma\ (\text{MW of reactants})} \times 100$$

$$= \frac{207.34}{(120.15\ + 73.14 + 32)} \times 100$$

$$= \mathbf{92}\%$$

3. Atom efficiency

$$\textbf{Atom efficiency} = \frac{\%\ \text{yield of product}\ \times \%\ \text{atom economy}}{100}$$

$$= \frac{93\%\ \times 92\%}{100}$$

$$\textbf{Atom efficiency} = \mathbf{85.6}\%$$

4. Carbon efficiency (CE)

$$\textbf{Carbon efficiency} = \frac{\text{No of carbon atoms in product}}{\Sigma\ (\text{No of carbon atoms in reactants})} \times 100$$

$$\text{Carbon efficiency (CE)} = \frac{12}{(8 + 4)} \times 100$$

$$\textbf{Carbon efficiency (CE)} = \mathbf{100}\%$$

5. Product mass intensity (PMI)

$$\text{PMI} = \frac{\Sigma\ (\text{Mass of reactants including solvent})}{\text{Mass of the product}}$$

$$\text{PMI} = \frac{(120.15\ \times 1.5625) + (73.14\ \times 1.5625) + (32\ \times 1.5625)}{301}$$

= 1.17 (Ideal value of PMI = E – factor + 1)

6. **Reaction mass efficiency (RME)**

$$\text{RME} = \frac{\text{Mass of product}}{\Sigma\ (\text{mass of reactants})} \times 100$$

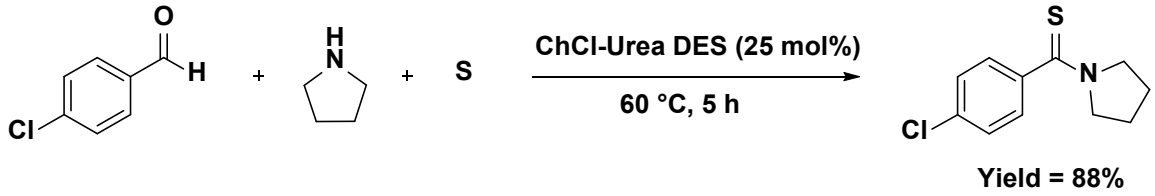
$$= \frac{301}{(120.15\ \times 1.5625) + (73.14\ \times 1.5625) + (32\ \times 1.5625)} \times 100$$

$$\mathbf{RME = 85.5\%}$$

E- factor	0.17
Atom economy (AE)	92 %
Atom efficiency	85.6%
Carbon efficiency	100%
PMI	1.17
RME	85.5%

Later we have calculated the green chemistry metrics for another four thioamide compounds.

Example 2:

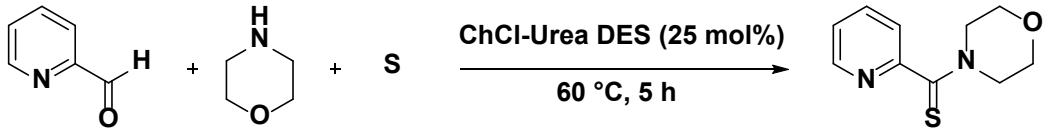


Yield = 88%

	Name	**Chemical formula**	**Molecular weight**	**millimole**	**mg**
Reactant 1	4-chlorobenzaldehyde	C_7H_5ClO	140.57	1.5625	219.6
Reactant 2	pyrrolidine	C_4H_9N	71.11	1.5625	111.1
Reactant 3	Sulfur powder	S	32	1.5625	50
Solvent	DES (ChCl: Urea = 1:2)	-	259.5	0.3906	101
Product	(4-chlorophenyl) (pyrrolidin-1-yl) methanethione	$C_{11}H_{12}ClNS$	225.73	-	310

E- factor	0.23
Atom economy (AE)	92.6 %
Atom efficiency	81.5%
Carbon efficiency	100%
PMI	1.23
RME	81.4%

Example 3:

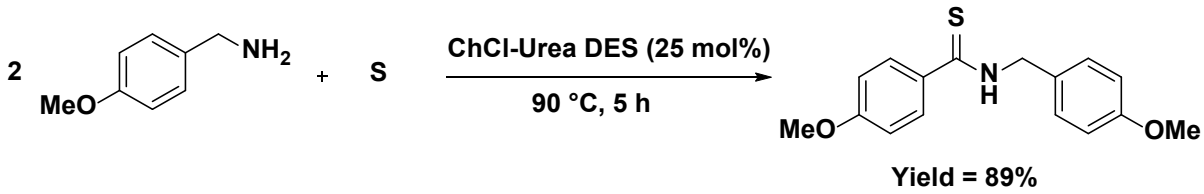


Yield = 91%

	Name	**Chemical formula**	**Molecular weight**	**millimole**	**mg**
Reactant 1	2-Pyridine carboxaldehyde	C_6H_5NO	107.11	1.5625	167.3
Reactant 2	morpholine	C_4H_9NO	87.12	1.5625	136.1
Reactant 3	Sulfur powder	S	32	1.5625	50
Solvent	DES (ChCl: Urea = 1:2)	-	259.5	0.3906	101
Product	morpholino(pyridin-2-yl)methanethione	$C_{10}H_{12}N_2OS$	208.28	-	296

E- factor	0.19
Atom economy (AE)	92 %
Atom efficiency	83.7%
Carbon efficiency	100%
PMI	1.19
RME	83.7%

Example 4:



	Name	Chemical formula	Molecular weight	millimole	mg
Reactant 1	4-Methoxybenzylamine	$C_8H_{11}NO$	137.18	1.5625	214.3
Reactant 2	Sulfur powder	S	32	1.5625	50
Solvent	DES (ChCl: Urea = 1:2)	-	259.5	0.3906	101
Product	4-methoxy-N-(4-methoxybenzyl)benzo thioamide	$C_{16}H_{17}NO_2S$	287.38	-	399

E- factor	0.20
Atom economy (AE)	93.8 %
Atom efficiency	83.5%
Carbon efficiency	100%
PMI	1.2
RME	83.3%

References:

1. A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed, V. Tambyrajah, *Chem. Commun.* **2003**, 70–71.
2. B. Kaboudin, V. Yarahmadi, J. Y. Kato, T. Yokomatsu, *RSC Adv.* **2013**, *3*, 6435–6441.
3. J. Baudoux, D. Cahard, *Org. React.* **2008**, *69*, 1–326.
4. A. D. Kale, D. S. Dalal, *ChemistrySelect* **2022**, *7*, DOI 10.1002/slct.202203497.
5. M. Lai, Z. Wu, Y. Wang, Y. Zheng, M. Zhao, *Org. Chem. Front.* **2019**, *6*, 506–511.
6. A. Blade-Font, S. Aguila, T. De Mas, J. M. Torres, *J. Chem. Research (S)* **1981**.
7. R. S. Sukhai, R. De Jong, L. Brandsma, *Synthesis* **1977**.
8. C. Spanka, E. Schaumann, *Sci. Synth.* **2006**, *23* 735-780.
9. A. Gupta, J. K. Vankar, J. P. Jadav, G. N. Gururaja, *J. Org. Chem.* **2022**, *87*, 2410–2420.

10. J. Li, X. Ren, G. Li, H. Liang, Y. Zhao, Z. Wang, H. Li, B. Yuan, *J. Sulfur Chem.* **2020**, *41*, 229–237.
11. M. J. Burke, B. M. Trantow, *Tetrahedron Lett.* **2008**, *49*, 4579–4581.
12. J. Zhang, Y. Liu, Q. Jia, Y. Wang, Y. Ma, M. Szostak, *Org. Lett.* **2020**, *22*, 6884–6890.
13. S. Mai, W. Li, X. Li, Y. Zhao, Q. Song, *Nat. Commun.* **2019**, *10*, 1–12.
14. Y. A. Tayade, A. D. Jangale, D. S. Dalal, *ChemistrySelect* **2018**, *3*, 8895–8900.
15. M. M. Mojtahedi, T. Alishiri, M. S. Abaee, *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, *186*, 1910–1915.
16. S. D. Salim, S. P. Pathare, K. G. Akamanchi, *Catal. Commun.* **2011**, *13*, 78–81.
17. W. Lin, M. H. Hu, X. Feng, L. Fu, C. P. Cao, Z. Bin Huang, D. Q. Shi, *Tetrahedron Lett.* **2014**, *55*, 2238–2242.
18. P. Gisbert, I. M. Pastor, *Synth.* **2018**, *50*, 3031–3040.
19. Kemparajegowda, H. A. Swarup, S. Chandrasekhar, B. K. Jayanna, K. Kumara, N. K. Lokanath, S. B. Thimmaiah, K. Mantelingu, *J. Mol. Struct.* **2022**, *1251*, 131970.
20. M. Lebrini, F. Bentiss, M. Lagrenée, *J. Heterocycl. Chem.* **2005**, *42*, 991–994.
21. V. P. Charpe, A. A. Hande, A. Sagadevan, K. C. Hwang, *Green Chem.* **2018**, *20*, 4859–4864.
22. S. Mathavan, K. Kannan, R. B. R. D. Yamajala, *Org. Biomol. Chem.* **2019**, *17*, 9620–9626.