Regioselective synthesis of 2,5- and 4,5- disubstituted thiazoles *via* cyclization of methyl-2-oxo-2-(amino)ethanedithioates with isocyanides

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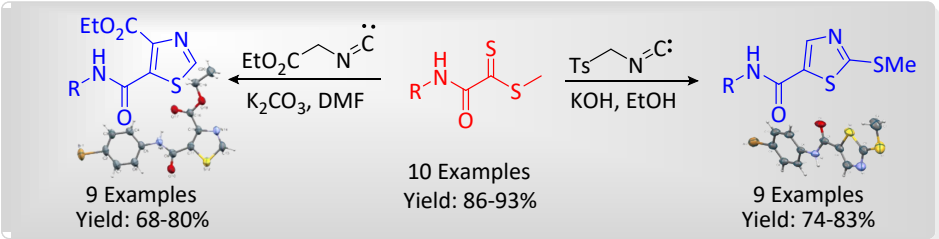
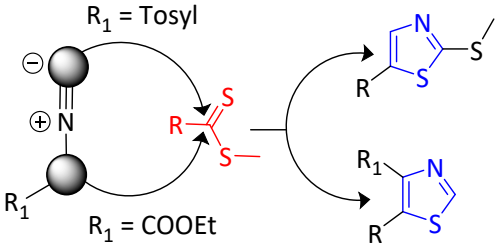
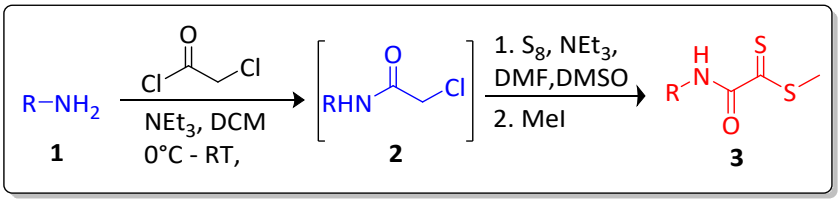




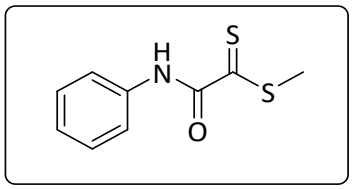
General Procedure for Synthesis of methyl-2-oxo-2-(amino)ethanedithioates 3(a-j):



A solution of anilines **1** (1.0 mmol) and triethylamine (2.0 mmol) in dichloromethane (DCM) (20 mL) was cooled at 0 °C and addition of chloroacetylchloride (1.1 mmol) dropwise over a period, the completion of reaction was monitored by TLC which leads for formation of 2-Chloro-*N*-phenylacetamide **2**, the excess DCM was removed under reduced pressure. The Chloro-*N*-phenylacetamide **2** and sulphur (0.25 mmol) were stirred in DMF:DMSO (15:5 mL), mixture was cooled to 0°C and triethylamine (2.0 mmol) was added slowly. The mixture was stirred at room temperature overnight, concentrated under vacuum to remove excess triethylamine, added dropwise methyl iodide (4 ml), and stirred again at room temperature and reaction was quenched with ice-cooled water. The product was extracted with ethylacetate (50 mL) and dried over Na_2SO_4. The solvent was evaporated and the product was purified by column chromatography (hexane/EtOAc).

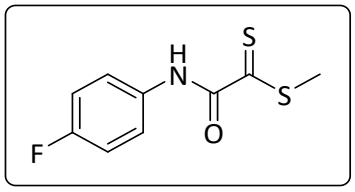
Characterisation Details of compounds 3(a-j)

Methyl 2-oxo-2-(phenylamino)ethanedithioate (3a):



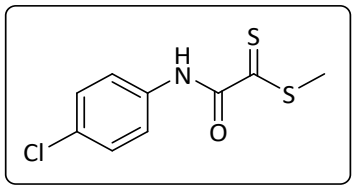
Yield: 93%; Red solid. ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H, NH), 7.74 (d, J = 7.9 Hz, 2H, Ar-H), 7.37 (t, J = 7.8 Hz, 2H, Ar-H), 7.16 (t, J = 7.4 Hz, 1H, Ar-H), 2.72 (s, 3H, SMe). ^{13}C NMR (100 MHz, DMSO) δ 226.55, 160.98, 137.60, 128.78, 124.68, 120.55, 19.24. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_{10}NOS_2$: 212.0204; found: 212.0210.

Methyl 2-((4-fluorophenyl)amino)-2-oxoethanedithioate (3b):



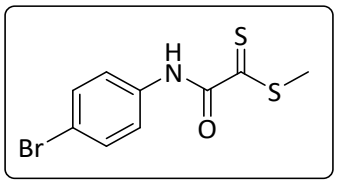
Yield: 90%; Red solid. ^{1}H NMR (400 MHz, DMSO) δ 10.51 (s, 1H, NH), 7.76 (dd, J = 9.2, 5.0 Hz, 2H, Ar-H), 7.21 (t, J = 8.9 Hz, 2H, Ar-H), 2.72 (s, 3H, SMe). ^{13}C NMR (100 MHz, DMSO) δ 226.35, 160.90, 160.05, 157.65, 134.01, 133.98, 122.62, 122.54, 115.55, 115.33, 19.26. HRMS (ESI): m/z $[M+H]^+$ calcd for 230.0110; found: 230.0092.

Methyl 2-((4-chlorophenyl)amino)-2-oxoethanedithioate (3c):



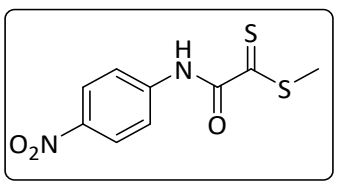
Yield: 90%; Red solid. ^{1}H NMR (400 MHz, DMSO) δ 10.59 (s, 1H, NH), 7.77 (d, J = 8.7 Hz, 2H, Ar-H), 7.43 (d, J = 8.7 Hz, 2H, Ar-H), 2.72 (s, 3H, SMe).^{13}C NMR (100 MHz, DMSO) δ 226.06, 161.10, 136.60, 128.73, 128.47, 122.18, 19.25. HRMS (ESI): m/z $[M+H]^+$calcd for $C_9H_9ClNOS_2$: 245.9814; found: 245.9821.

Methyl 2-((4-bromophenyl)amino)-2-oxoethanedithioate (3d):



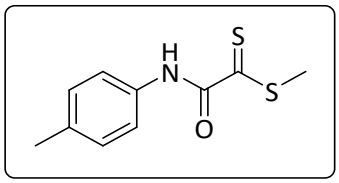
Yield: 92%; Red solid. ^{1}H NMR (400 MHz, DMSO) δ 10.58 (s, 1H, NH), 7.71 (d, J = 8.8 Hz, 2H, Ar-H), 7.55 (d, J = 8.8 Hz, 2H, Ar-H), 2.72 (s, 3H, SMe). ^{13}C NMR (100 MHz, DMSO) δ 226.03, 161.11, 137.02, 131.65, 122.53, 116.64, 19.25. HRMS (ESI): m/z $[M+H]^+$calcd for $C_9H_9BrNOS_2$: 289.9309; found: 289.9315.

Methyl 2-((4-nitrophenyl)amino)-2-oxoethanedithioate (3e):



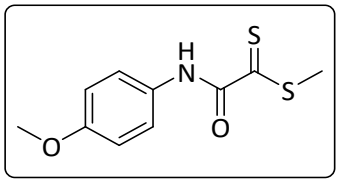
Yield: 86%; Red solid. ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H, NH), 8.27 (d, J = 8.3 Hz, 2H, Ar-H), 8.00 (d, J = 8.4 Hz, 2H, Ar-H), 2.75 (s, 3H, SMe). ^{13}C NMR (100 MHz, DMSO) δ 225.10, 161.76, 143.72, 143.28, 124.79, 120.47, 19.21. HRMS (ESI): m/z $[M+H]^+$calcd for $C_9H_9N_2O_3S_2$: 257.0055; found: 257.0056.

Methyl 2-oxo-2-(p-tolylamino)ethanedithioate (3f):



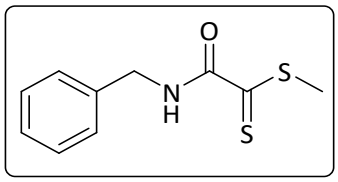
Yield: 89%; Red solid. ^{1}H NMR (400 MHz, DMSO) δ 10.35 (s, 1H, NH), 7.61 (d, J = 7.7 Hz, 2H, Ar-H), 7.17 (d, J = 8.3 Hz, 2H, Ar-H), 2.71 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 226.75, 160.75, 135.09, 133.84, 129.18, 120.51, 20.49, 19.25. HRMS (ESI): m/z $[M+H]^{+}$calcd for $C_{10}H_{12}NOS_2$: 226.0360; found: 226.0364.

Methyl 2-((4-methoxyphenyl)amino)-2-oxoethanedithioate (3g):



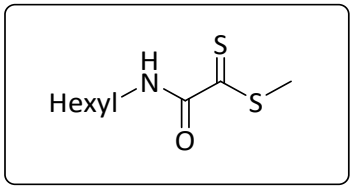
Yield: 92%; Red solid. ^{1}H NMR (400 MHz, DMSO) δ 10.31 (s, 1H, NH), 7.65 (d, J = 8.1 Hz, 2H, Ar-H), 6.94 (d, J = 8.1 Hz, 2H, Ar-H), 3.74 (s, 3H), 2.70 (s, 3H, SMe). ^{13}C NMR (100 MHz, DMSO) δ 226.86, 160.46, 156.27, 130.66, 122.17, 113.95, 55.23, 19.32. HRMS (ESI): m/z $[M+H]^{+}$calcd for $C_{10}H_{12}NO_2S_2$: 242.0309; found: 242.0303.

Methyl 2-(benzylamino)-2-oxoethanedithioate (3h):



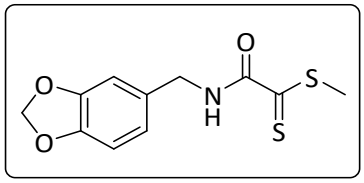
Yield: 88%; Red solid. ^{1}H NMR (400 MHz, DMSO) δ 9.17 (s, 1H, NH), 7.42 – 7.17 (m, 5H, Ar-H), 4.39 (d, J = 6.4 Hz, 2H), 2.65 (s, 3H, SMe).^{13}C NMR (100 MHz, DMSO) δ 227.17, 161.57, 138.51, 128.32, 127.22, 126.97, 43.09, 19.34. HRMS (ESI): m/z $[M+H]^{+}$calcd for $C_{10}H_{12}NOS_2$: 226.0360; found: 226.0365.

Methyl-2-(hexylamino)-2-oxoethanedithioate (3i):



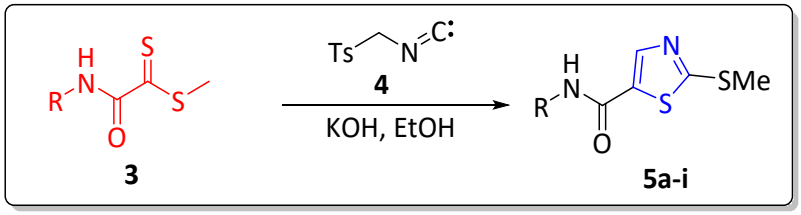
Yield: 92%; Red liquid. ^{1}H NMR (400 MHz, DMSO) δ 8.57 (t, J = 6.4 Hz, 1H), 3.16 (q, J = 6.7 Hz, 2H), 2.63 (s, 3H), 1.47 (p, J = 7.1 Hz, 2H), 1.26 (q, J = 4.7, 4.2 Hz, 6H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 227.73, 161.35, 39.64, 30.86, 28.53, 25.93, 21.98, 19.30, 13.84. HRMS (ESI): m/z $[M+H]^{+}$calcd for $C_9H_{18}NOS_2$: 220.0830; found: 220.0834.

Methyl-2-((benzo[d][1,3]dioxol-5-ylmethyl)amino)-2-oxoethanedithioate (3j):



Yield: 90%; Red solid.^{1}H NMR (400 MHz, DMSO) δ 9.09 (t, J = 6.5 Hz, 1H), 6.87 – 6.83 (m, 2H), 6.76 (dd, J = 8.0, 1.7 Hz, 1H), 5.98 (s, 2H), 4.28 (d, J = 6.4 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 227.20, 161.41, 147.21, 146.22, 132.32, 120.64, 108.02, 107.97, 100.85, 42.90, 19.33. HRMS (ESI): m/z $[M+H]^{+}$calcd for $C_{11}H_{12}NO_3S_2$: 270.0259; found: 270.0254.

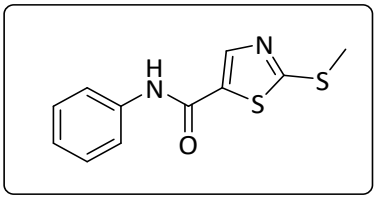
General Procedure for Synthesis of 2-(methylthio)-*N*-phenylthiazole-5-carboxamides 5(a-i)



A solution of KOH (1.0 mmol) in EtOH was placed in an ice bath. To the cooled solution a mixture of the methyl-2-oxo-2-(amino)ethane dithioates **3(a-j)** (0.5 mmol) and TosMIC **4** (0.5 mmol) in EtOH was added, and the reaction mixture was allowed to reach to r.t. The reaction was quenched with ice-cooled water and the mixture was extracted with EtOAc (3 × 25 mL), washed with brine solution, dried over Na_2SO_4 and evaporated. The crude material was subjected to column chromatography using hexane/EtOAc solvent system to give the desired compound.

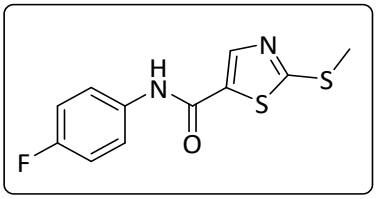
Characterisation Details of compounds 5(a-i)

2-(methylthio)-*N*-phenylthiazole-5-carboxamide (5a):



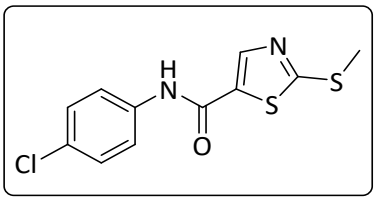
Yield: 83%; whiteoff solid.^{1}H NMR (400 MHz, DMSO) δ 10.32 (s, 1H), 8.48 (s, 1H), 7.68 (d, J = 7.5 Hz, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.87, 158.09, 143.94, 138.34, 134.66, 128.72, 123.98, 120.32, 16.19. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{11}N_2OS_2$: 251.0313; found: 251.0319.

***N*-(4-fluorophenyl)-2-(methylthio)thiazole-5-carboxamide (5b):**



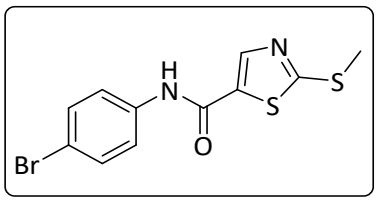
Yield: 78%; whiteoff solid.^{1}H NMR (400 MHz, DMSO) δ 10.38 (s, 1H), 8.45 (s, 1H), 7.69 (dd, J = 9.2, 5.0 Hz, 2H), 7.20 (t, J = 8.9 Hz, 2H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.94, 159.65, 158.04, 157.26, 143.98, 134.69, 134.66, 122.24, 122.17, 115.45, 115.23, 16.19. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{10}FN_2OS_2$: 269.0219; found: 269.0211.

***N*-(4-chlorophenyl)-2-(methylthio)thiazole-5-carboxamide (5c):**



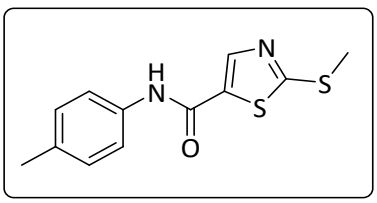
Yield: 80%; whiteoff solid. ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 8.46 (s, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 8.9 Hz, 2H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ = 172.20, 158.16, 144.17, 137.35, 134.30, 128.66, 127.62, 121.78, 16.20. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{10}ClN_2OS_2$: 284.9923; found: 284.9930.

***N*-(4-bromophenyl)-2-(methylthio)thiazole-5-carboxamide (5d):**



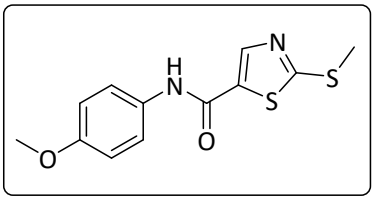
Yield: 82%; whiteoff solid. ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 8.47 (s, 1H), 7.67 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.9 Hz, 2H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.23, 158.16, 144.20, 137.78, 134.30, 131.57, 122.13, 115.70, 16.21. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{10}BrN_2OS_2$: 328.9418; found: 328.9424.

2-(methylthio)-*N*-(p-tolyl)thiazole-5-carboxamide (5e):



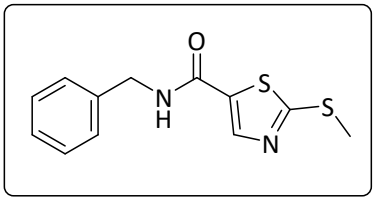
Yield: 80%; whiteoff solid.^{1}H NMR (400 MHz, DMSO) δ 10.25 (s, 1H), 8.45 (s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 2.73 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.69, 157.92, 143.76, 135.81, 134.81, 133.03, 129.13, 120.36, 20.47, 16.18. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N_2OS_2$ 265.0469; found: 265.0473.

***N*-(4-methoxyphenyl)-2-(methylthio)thiazole-5-carboxamide (5f):**



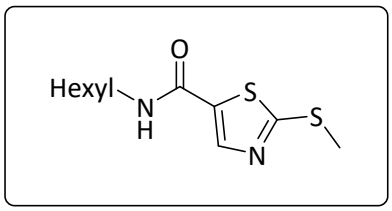
Yield: 74%; whiteoff solid.^{1}H NMR (400 MHz, DMSO) δ 10.22 (s, 1H), 8.43 (s, 1H), 7.58 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 3.74 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.49, 157.74, 155.79, 143.60, 134.82, 131.29, 121.99, 113.87, 55.17, 16.17. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N_2O_2S_2$ 281.0418; found: 281.0412.

***N*-benzyl-2-(methylthio)thiazole-5-carboxamide (5g):**



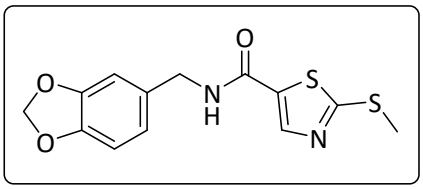
Yield: 76%; whiteoff solid. ^{1}H NMR (400 MHz, DMSO) δ 9.15 (s, 1H), 8.29 (s, 1H), 7.31 (h, J = 7.7 Hz, 5H), 4.44 (d, J = 6.2 Hz, 2H), 2.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 170.94, 159.44, 143.16, 139.05, 134.38, 128.36, 127.31, 126.93, 42.50, 16.14. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N_2OS_2$ 265.0469; found: 265.0472.

***N*-hexyl-2-(methylthio)thiazole-5-carboxamide (5h):**



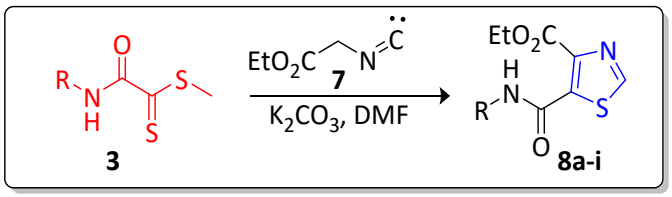
Yield: 78%; whiteoff solid. ^{1}H NMR (400 MHz, DMSO) δ 8.54 (t, *J* = 5.8 Hz, 1H), 8.20 (s, 1H), 3.20 (q, *J* = 7.0 Hz, 2H), 2.70 (s, 3H), 1.48 (p, *J* = 7.2 Hz, 2H), 1.28 (dd, *J* = 7.4, 3.9 Hz, 6H), 0.86 (t, *J* = 6.9 Hz, 3H).^{13}C NMR (100 MHz, DMSO) δ 170.44, 159.20, 142.72, 134.76, 39.07, 30.94, 28.98, 26.07, 22.01, 16.09, 13.86. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{19}N_2OS_2$ 259.0939; found: 259.0943.

***N*-(benzo[d][1,3]dioxol-5-ylmethyl)-2-(methylthio)thiazole-5-carboxamide (5i):**



Yield: 78%; whiteoff solid. ^{1}H NMR (400 MHz, DMSO) δ 9.06 (t, *J* = 6.0 Hz, 1H), 8.26 (s, 1H), 6.86 (d, *J* = 7.7 Hz, 2H), 6.78 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.98 (s, 2H), 4.33 (d, *J* = 6.0 Hz, 2H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 170.88, 159.33, 147.26, 146.19, 143.14, 134.38, 132.88, 120.62, 108.05, 108.02, 100.84, 42.34, 16.12. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{13}N_2O_3S_2$: 309.0368; found: 309.0364.

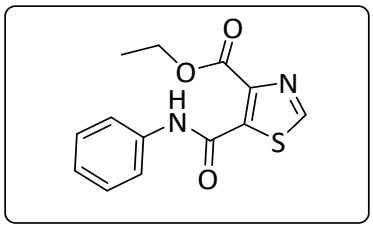
General Procedure for Synthesis of ethyl 5-(phenylcarbamoyl)thiazole-4-carboxylate 8(a-i):



A solution of K_2CO_3 (1.0 mmol) in DMF was placed in an ice bath for 10 minutes. To the cooled solution a mixture of the methyl-2-oxo-2-(amino)ethanedithioates **3(a-j)** (0.5 mmol) and ethyl isocyanoacetate **7** (0.5 mmol) was added in DMF, and the reaction mixture was allowed to reach to r.t. The reaction was quenched with ice-cooled water and the mixture was extracted with EtOAc (3 × 25 mL), washed with brine solution, dried over Na_2SO_4 and evaporated. The crude material was subjected to column chromatography using hexane/EtOAc solvent system to give the desired compound.

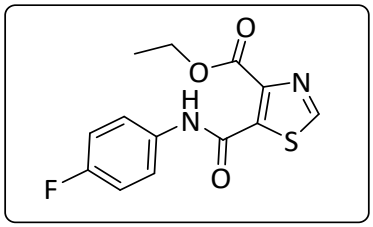
Characterisation Details of compounds 8(a-i)

Ethyl-5-(phenylcarbamoyl)thiazole-4-carboxylate (8a):



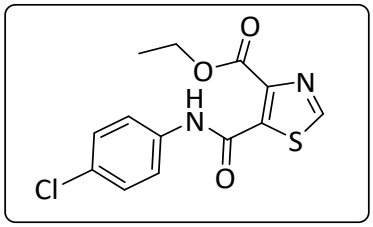
Yield: 80%; pale-orange solid.^{1}H NMR (400 MHz, DMSO) δ 10.90 (s, 1H), 9.22 (s, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 7.9 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 160.96, 158.54, 154.81, 143.19, 140.56, 138.47, 128.87, 124.17, 119.52, 61.23, 13.81. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{13}N_2O_3S$: 277.0647; found: 277.0653.

Ethyl-5-((4-fluorophenyl)carbamoyl)thiazole-4-carboxylate (8b):



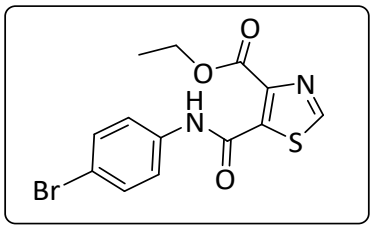
Yield: 80%; pale-orange solid.^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.22 (s, 1H), 7.68 (dd, J = 9.2, 5.0 Hz, 2H), 7.21 (t, J = 8.9 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 160.89, 159.68, 158.52, 157.29, 154.89, 143.32, 140.24, 134.91, 134.88, 121.39, 121.31, 115.62, 115.40, 61.22, 13.82. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}FN_2O_3S$: 295.0553; found: 295.0473.

Ethyl-5-((4-chlorophenyl)carbamoyl)thiazole-4-carboxylate (8c):



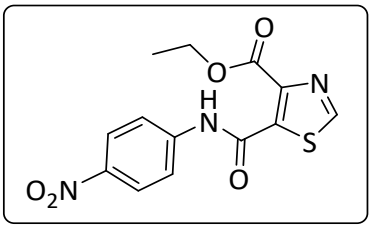
Yield: 76%; organe gummy solid.^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 9.23 (s, 1H), 7.69 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 160.82, 158.74, 154.98, 143.38, 140.07, 137.43, 128.82, 127.79, 121.06, 61.22, 13.82. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}ClN_2O_3S$: 311.0257; found: 311.0264.

Ethyl5-((4-bromophenyl)carbamoyl)thiazole-4-carboxylate (8d):



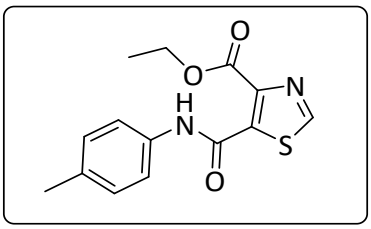
Yield: 70%; pale-brown solid. ^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 9.23 (s, 1H), 7.64 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 160.81, 158.76, 155.00, 143.38, 140.07, 137.84, 131.74, 121.42, 115.87, 61.23, 13.83. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}BrN_2O_3S$: 354.9752; found: 354.9760.

Ethyl-5-((4-nitrophenyl)carbamoyl)thiazole-4-carboxylate (8e):



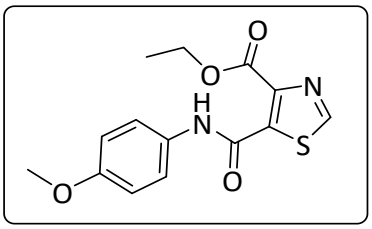
Yield: 68%; pale-yellow solid.^{1}H NMR (400 MHz, DMSO) δ 11.43 (s, 1H), 9.26 (s, 1H), 8.29 (d, J = 9.2 Hz, 2H), 7.91 (d, J = 9.2 Hz, 2H), 4.26 (q, J = 7.0 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H).^{13}C NMR (100 MHz, DMSO) δ 160.66, 159.60, 155.40i, 144.44, 143.76, 142.91, 139.40, 125.06, 119.37, 61.29, 13.81. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_3O_5S$: 322.0498; found: 322.0499.

Ethyl-5-(p-tolylcarbamoyl)thiazole-4-carboxylate (8f):



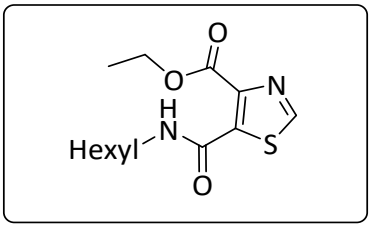
Yield: 78%; pale-yellow solid.^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.22 (d, J = 3.5 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 161.02, 158.24, 154.75, 143.08, 140.75, 135.99, 133.21, 129.24, 119.70, 119.51, 61.23, 20.48, 13.83. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_3S$: 291.0803; found: 291.0807.

Ethyl-5-((4-methoxyphenyl)carbamoyl)thiazole-4-carboxylate (8g):



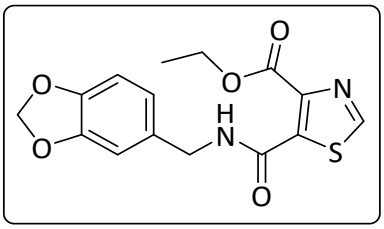
Yield: 72%; pale-yellow solid.^{1}H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 9.21 (s, 1H), 7.58 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 9.1 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 161.06, 157.96, 155.83, 154.70, 143.06, 140.79, 131.61, 121.05, 113.99, 61.22, 55.18, 13.84. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_4S$: 307.0753; found: 307.0747.

Ethyl-5-(hexylcarbamoyl)thiazole-4-carboxylate (8h):

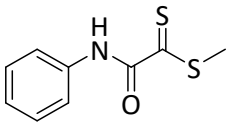


Yield: 76%; orange liquid.^{1}H NMR (400 MHz, DMSO) δ 9.13 (s, 1H), 8.96 (t, J = 5.9 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.22 (q, J = 6.7 Hz, 2H), 1.49 (q, J = 7.1 Hz, 2H), 1.28 (dd, J = 7.1 Hz, 9H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 161.58, 159.49, 154.50, 142.71, 140.97, 61.28, 39.47,30.89, 28.55, 26.01, 21.99, 13.88, 13.83. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{21}N_2O_3S$: 285.1273; found: 285.1277.

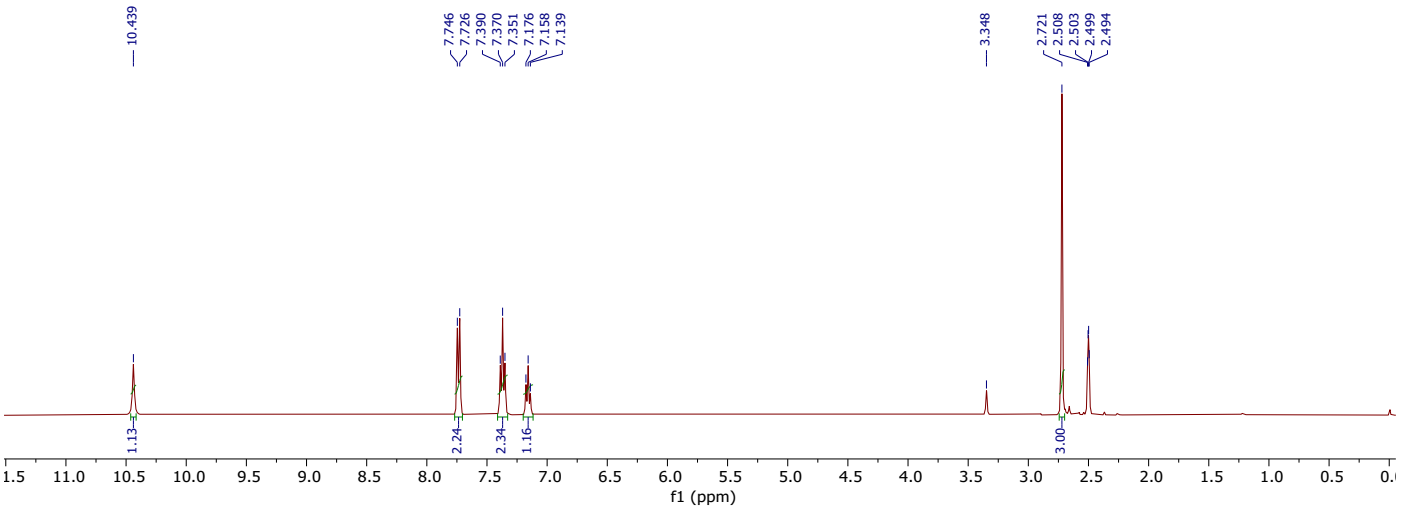
Ethyl-5-((benzo[d][1,3]dioxol-5-ylmethyl)carbamoyl)thiazole-4-carboxylate (8i):



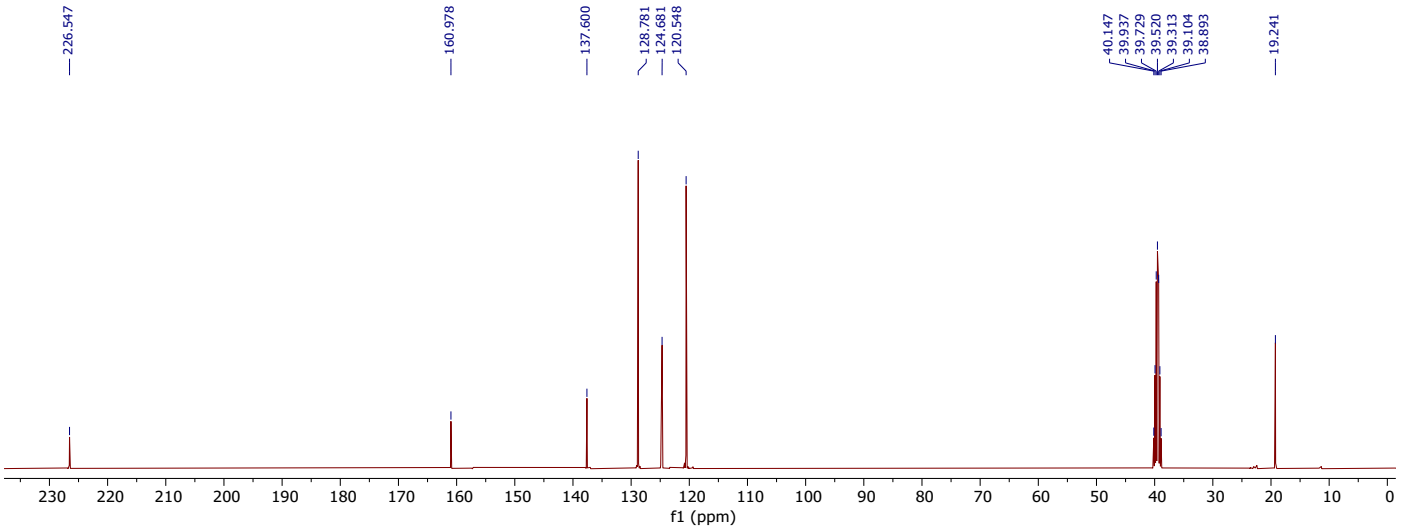
Yield: 72%; yellow gummy solid.^{1}H NMR (400 MHz, DMSO) δ 9.43 (t, J = 5.9 Hz, 1H), 9.15 (s, 1H), 6.93 (d, J = 1.7 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.82 (dd, J = 7.9, 1.7 Hz, 1H), 5.99 (s, 2H), 4.38 (d, J = 5.9 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 161.60, 159.71, 154.74, 147.30, 146.27, 143.05, 140.47, 132.26, 120.74, 108.10, 108.04, 100.88, 61.37, 42.86, 13.84. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_5S$: 337.0858; found: 337.0854.



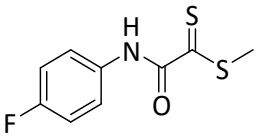
Methyl-2-oxo-2-(phenylamino)ethanedithioate (3a)



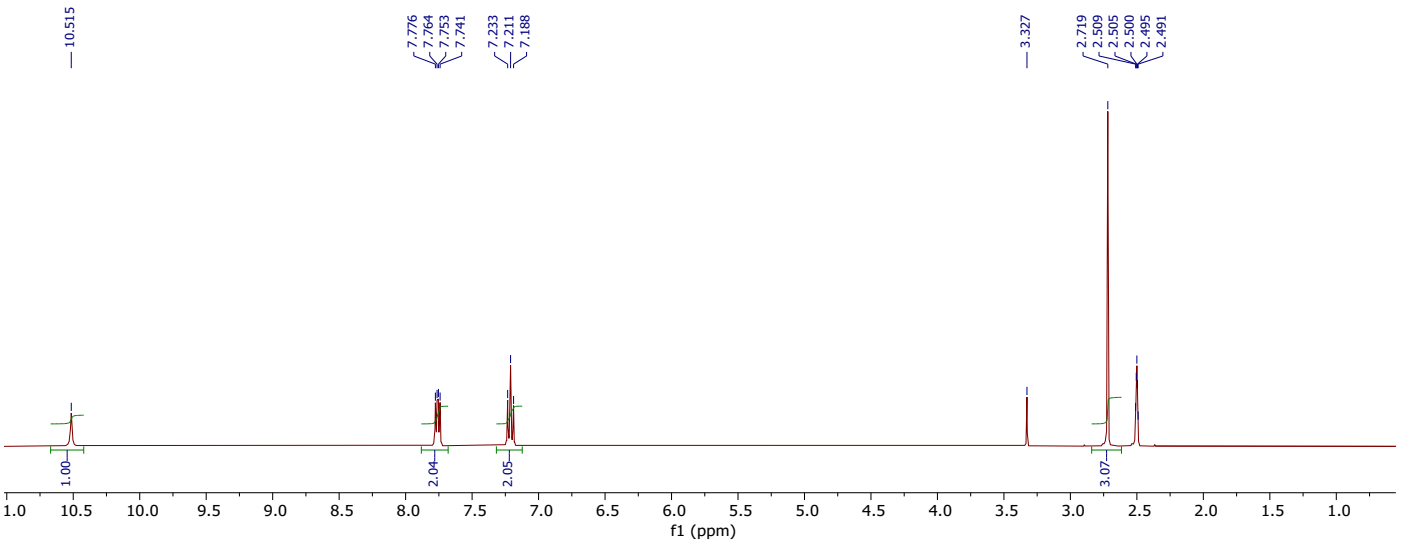
^{1}H NMR Spectra of Methyl-2-oxo-2-(phenylamino)ethanedithioate (3a)



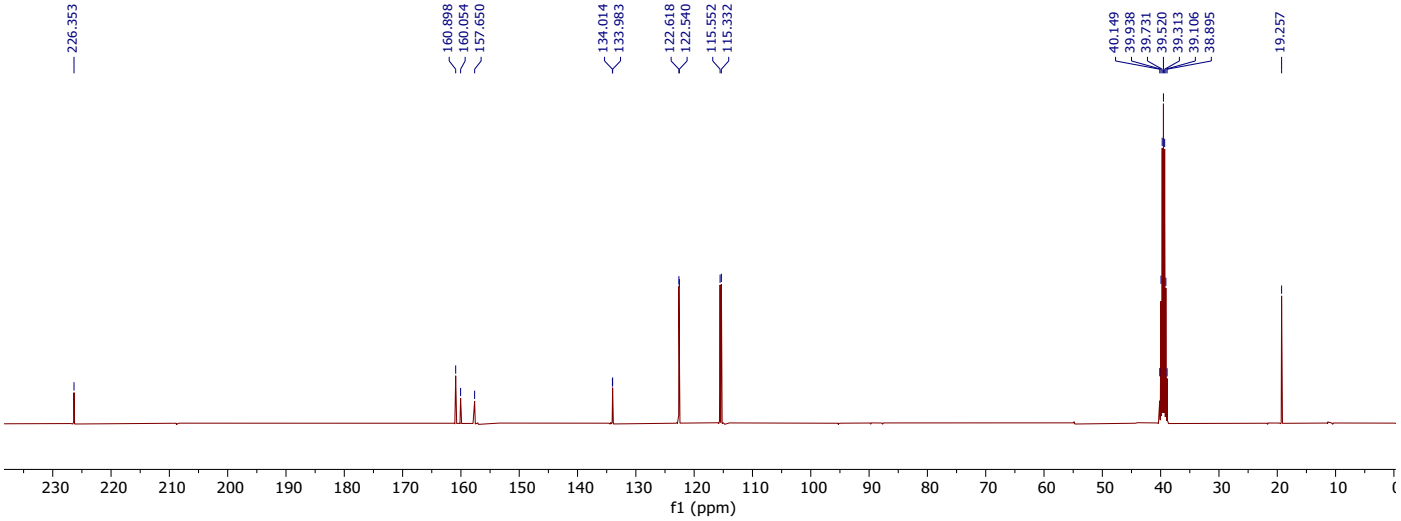
^{13}C NMR Spectra of Methyl-2-oxo-2-(phenylamino)ethanedithioate (3a)



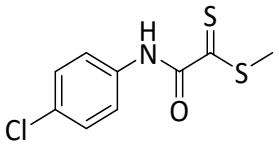
Methyl-2-((4-fluorophenyl)amino)-2-oxoethanedithioate (3b)



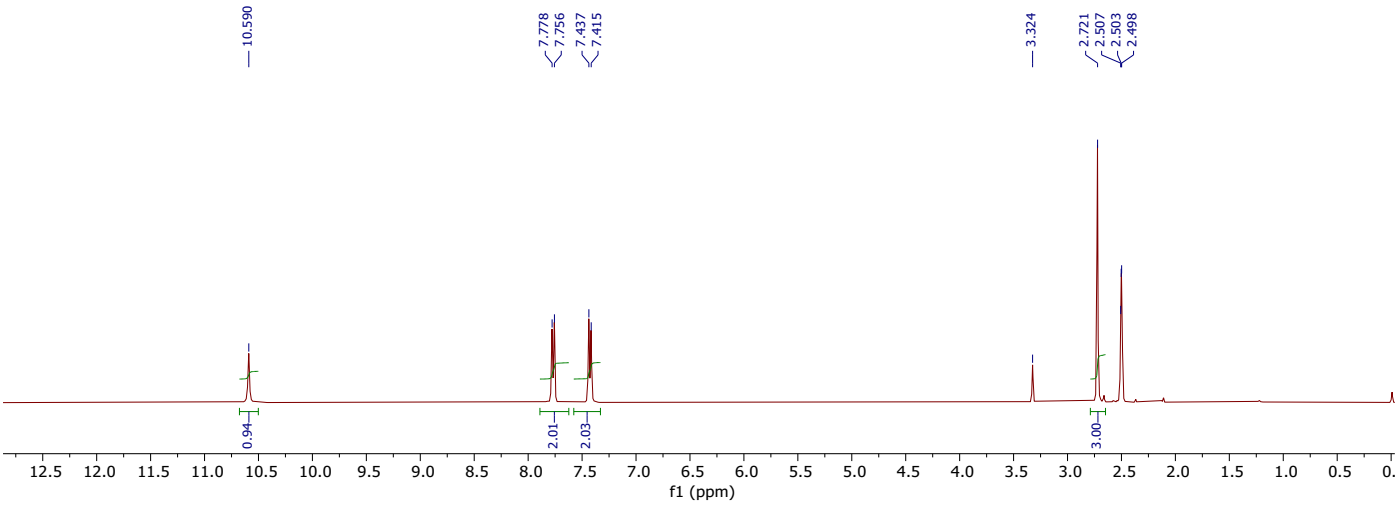
^{1}H NMR Spectra of Methyl-2-((4-fluorophenyl)amino)-2-oxoethanedithioate (3b)



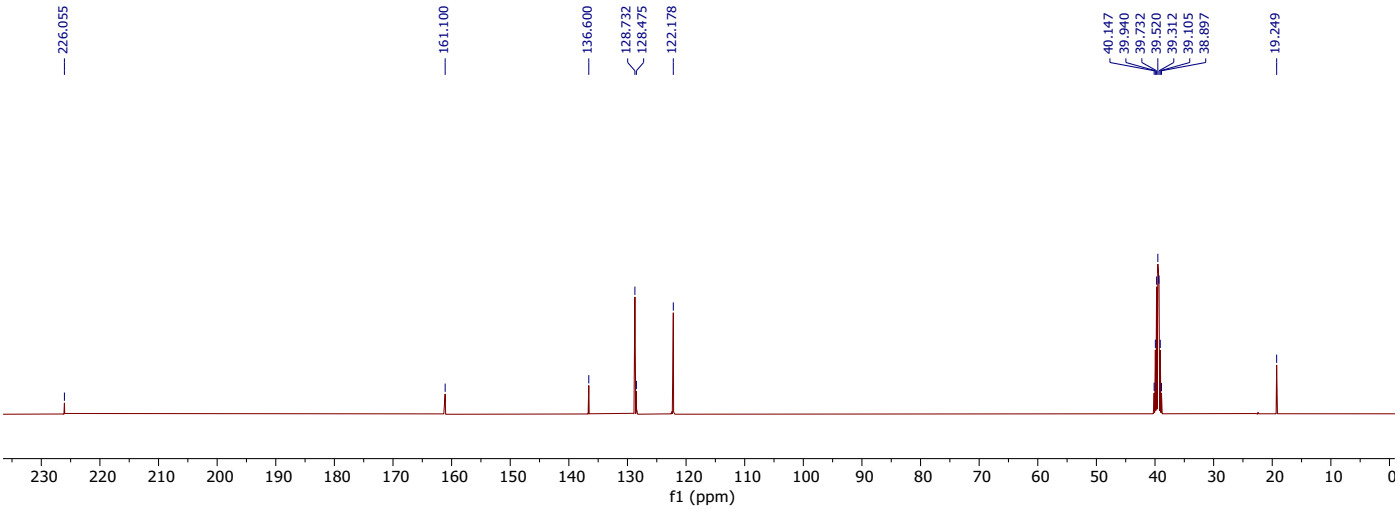
^{13}C NMR Spectra of Methyl-2-((4-fluorophenyl)amino)-2-oxoethanedithioate (3b)



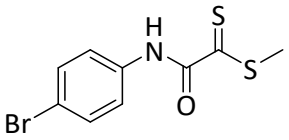
Methyl-2-((4-chlorophenyl)amino)-2-oxoethanedithioate (3c)



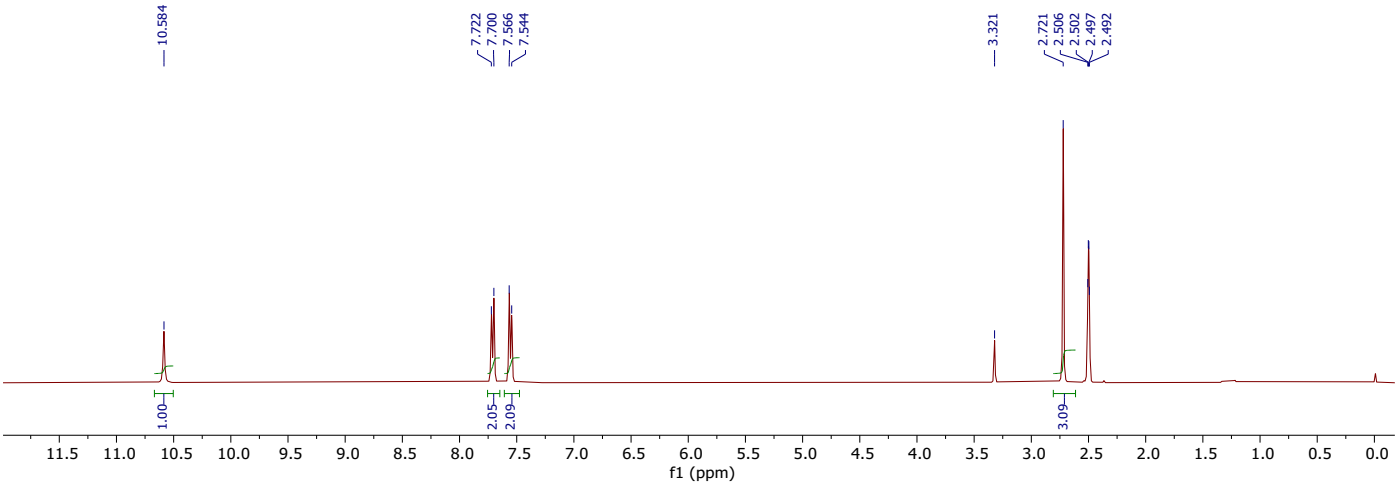
^{1}H NMR Spectra of Methyl-2-((4-chlorophenyl)amino)-2-oxoethanedithioate (3c)



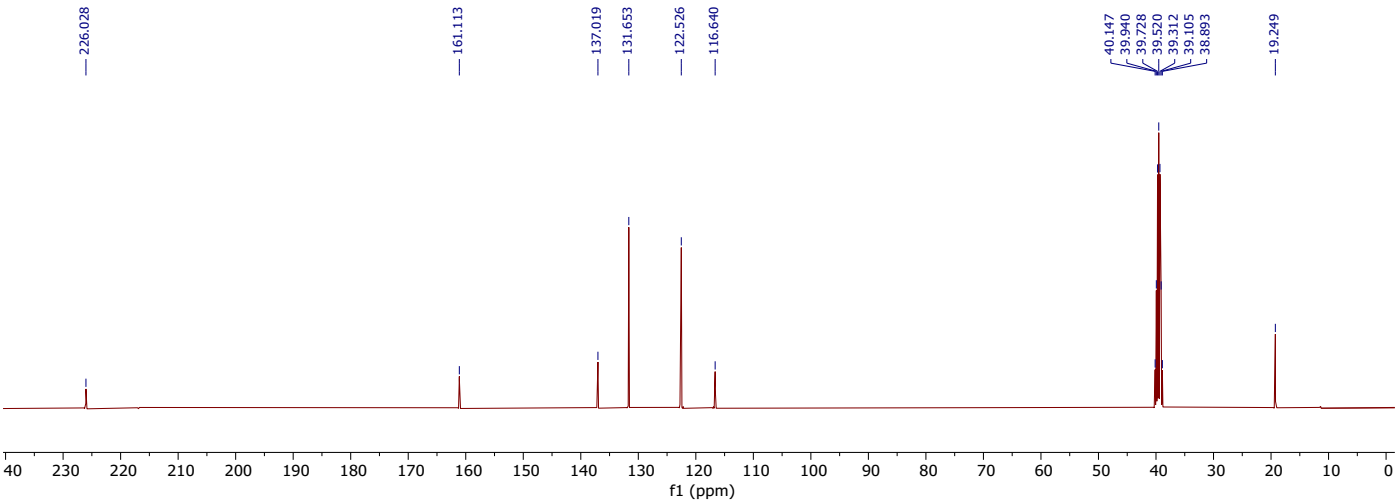
^{13}C NMR Spectra of Methyl-2-((4-chlorophenyl)amino)-2-oxoethanedithioate (3c)



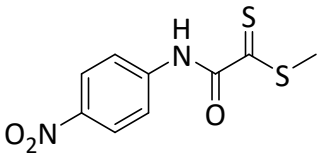
Methyl-2-((4-bromophenyl)amino)-2-oxoethanedithioate (3d)



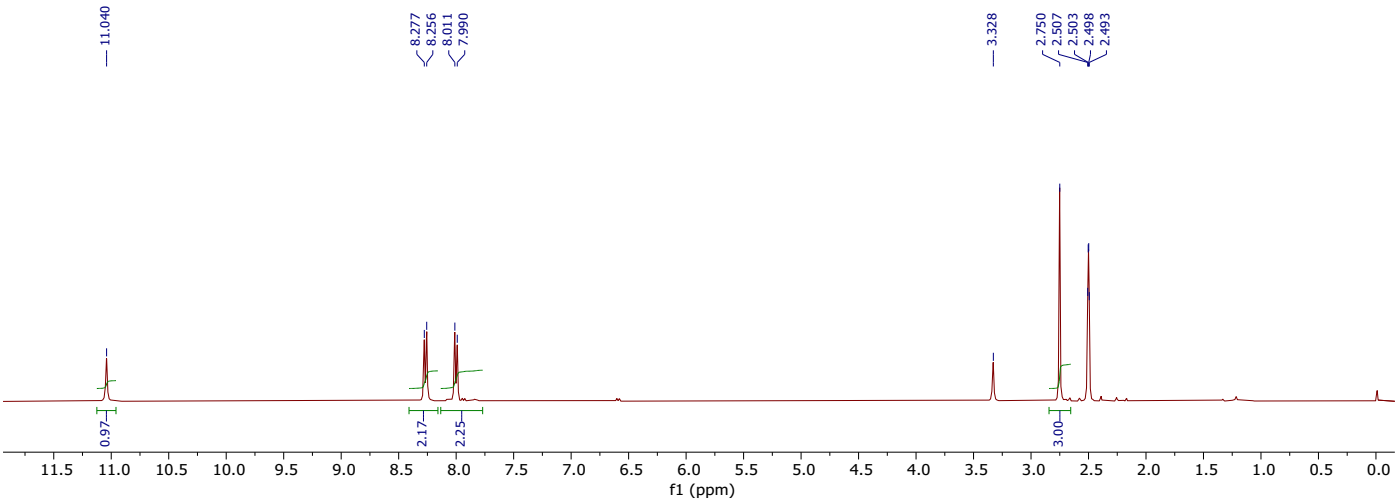
^{1}H NMR Spectra of Methyl-2-((4-bromophenyl)amino)-2-oxoethanedithioate (3d)



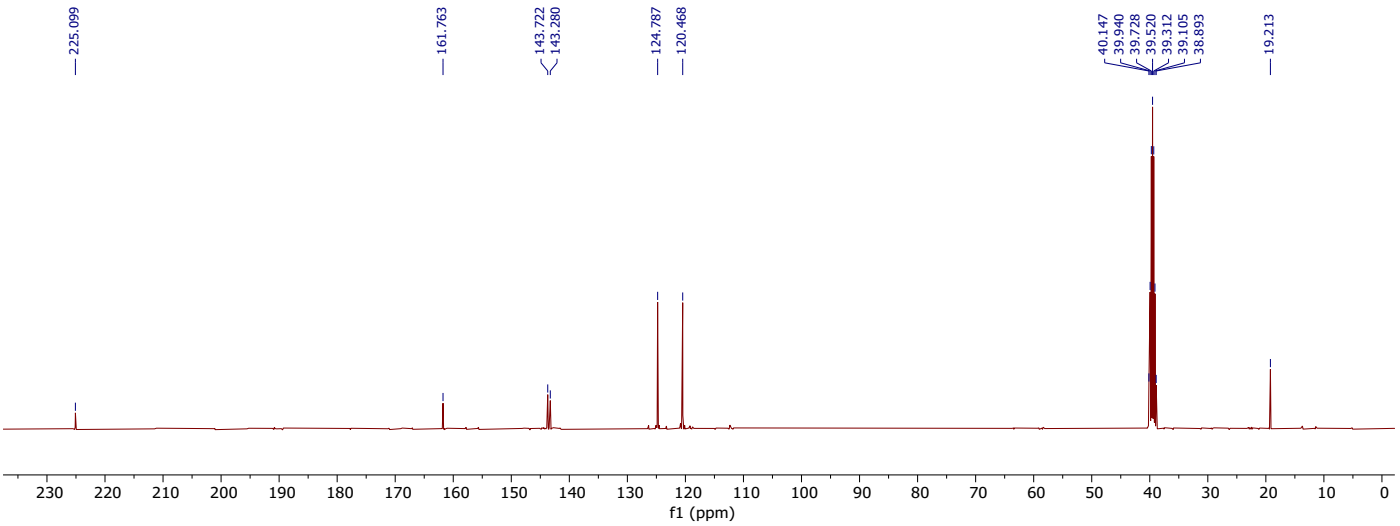
^{13}C NMR Spectra of Methyl-2-((4-bromophenyl)amino)-2-oxoethanedithioate (3d)



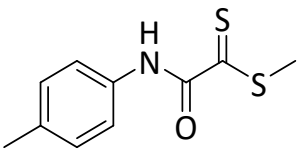
Methyl-2-((4-nitrophenyl)amino)-2-oxoethanedithioate (3e)



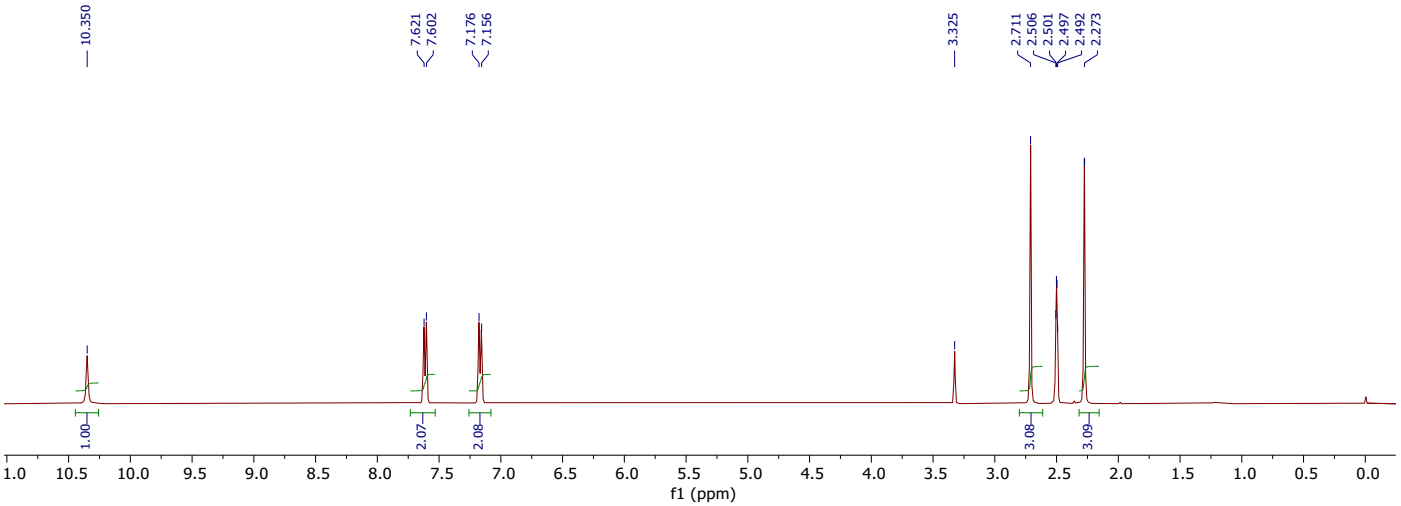
^{1}H NMR Spectra of Methyl-2-((4-nitrophenyl)amino)-2-oxoethanedithioate (3e)



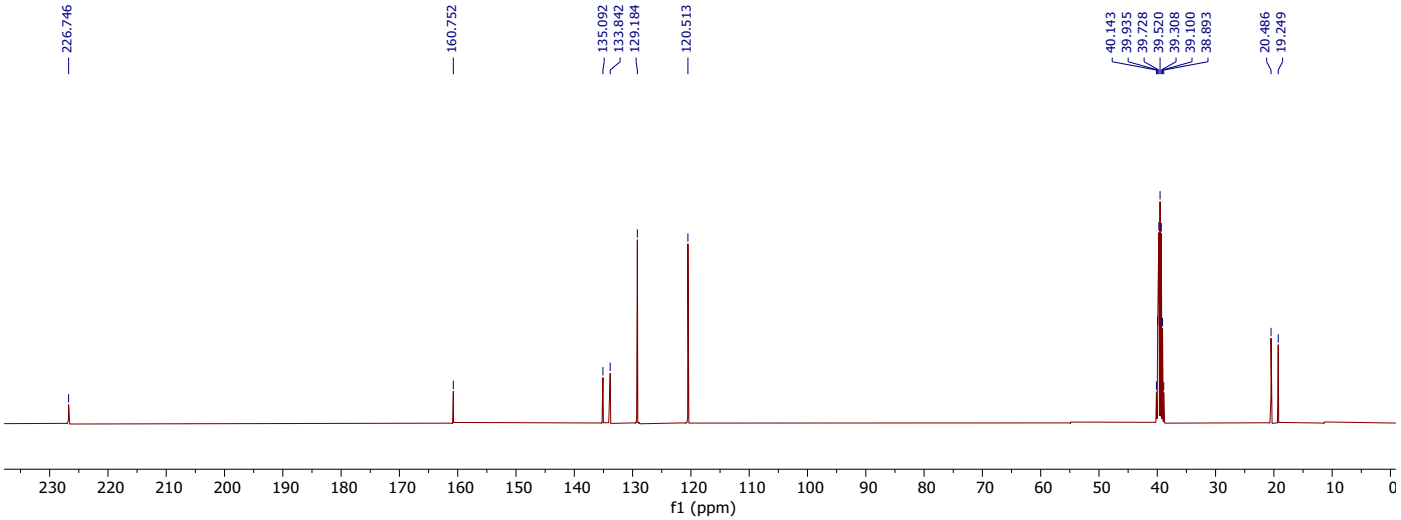
^{13}C NMR Spectra of Methyl-2-((4-nitrophenyl)amino)-2-oxoethanedithioate (3e)



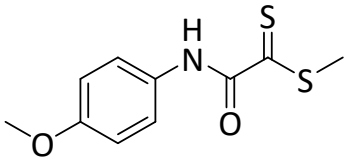
Methyl-2-oxo-2-(p-tolylamino)ethanedithioate (3f)



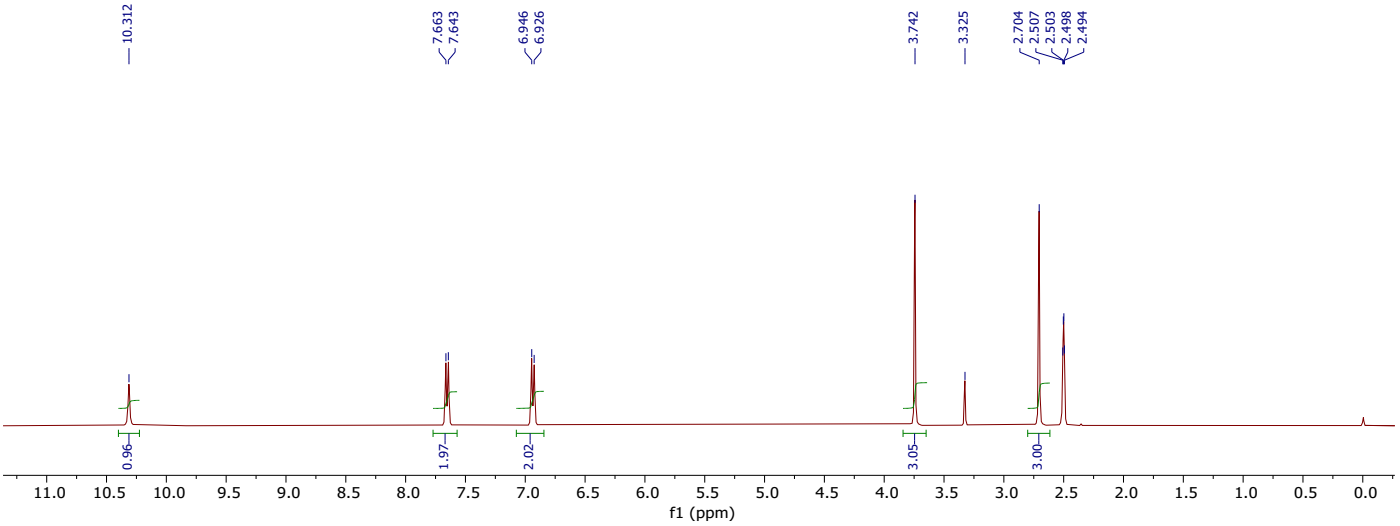
^{1}H NMR Spectra of Methyl-2-oxo-2-(p-tolylamino)ethanedithioate (3f)



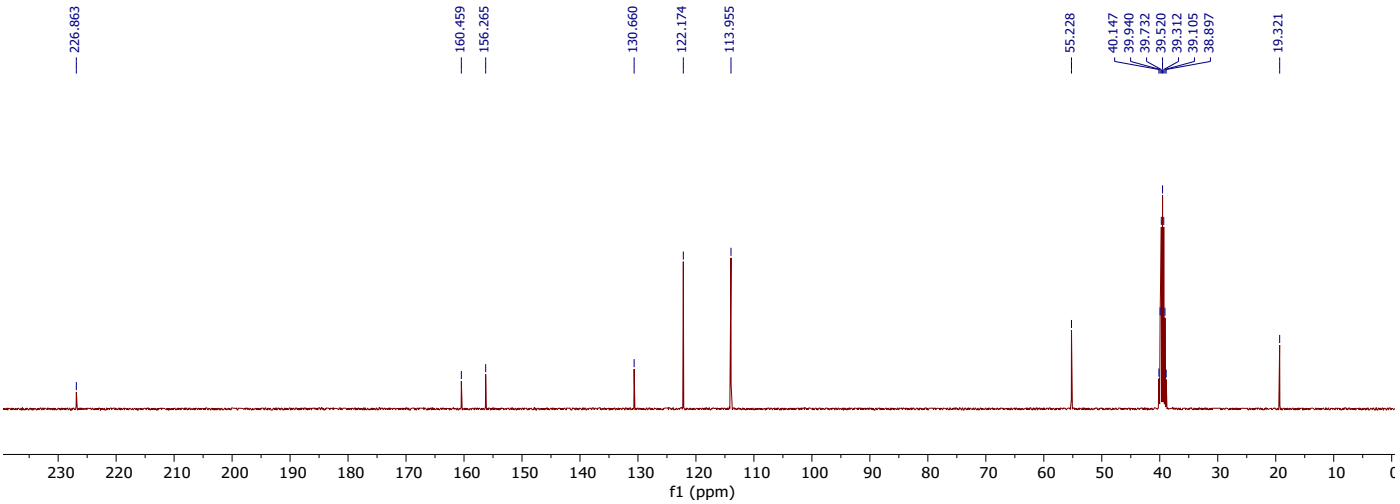
^{13}C NMR Spectra of Methyl-2-oxo-2-(p-tolylamino)ethanedithioate (3f)



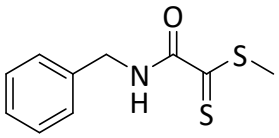
Methyl-2-((4-methoxyphenyl)amino)-2-oxoethanedithioate (3g)



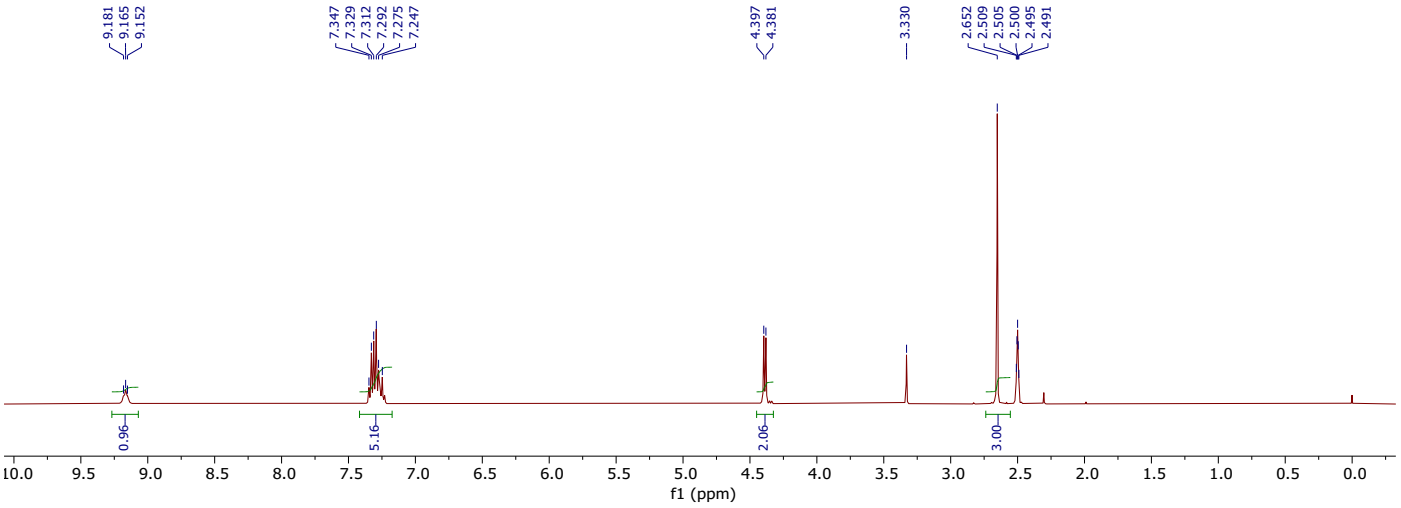
^{1}H NMR Spectra of Methyl-2-((4-methoxyphenyl)amino)-2-oxoethanedithioate (3g)



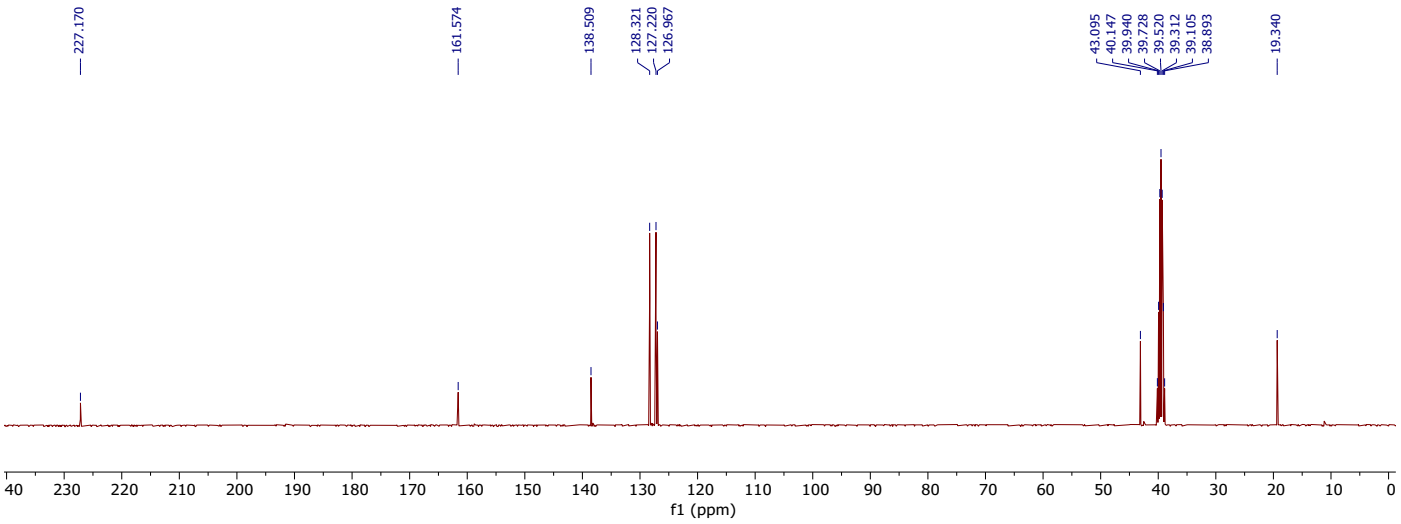
^{13}C NMR Spectra of Methyl-2-((4-methoxyphenyl)amino)-2-oxoethanedithioate (3g)



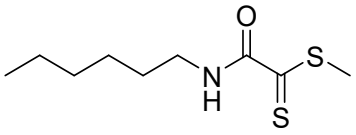
Methyl-2-(benzylamino)-2-oxoethanedithioate (3h)



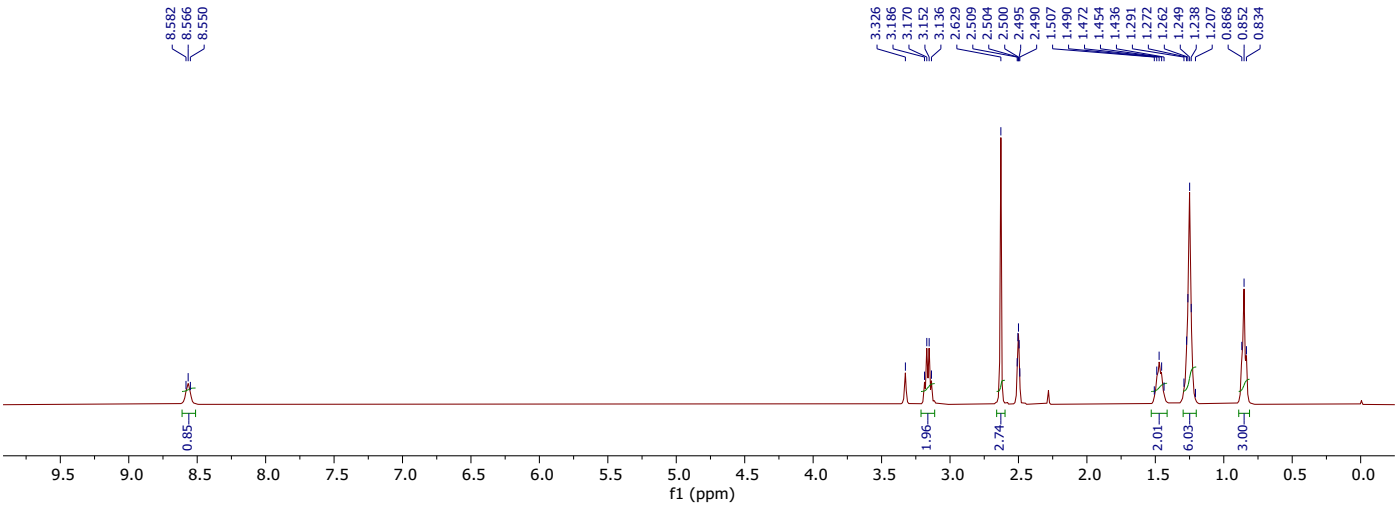
^{1}H NMR Spectra of Methyl-2-(benzylamino)-2-oxoethanedithioate (3h)



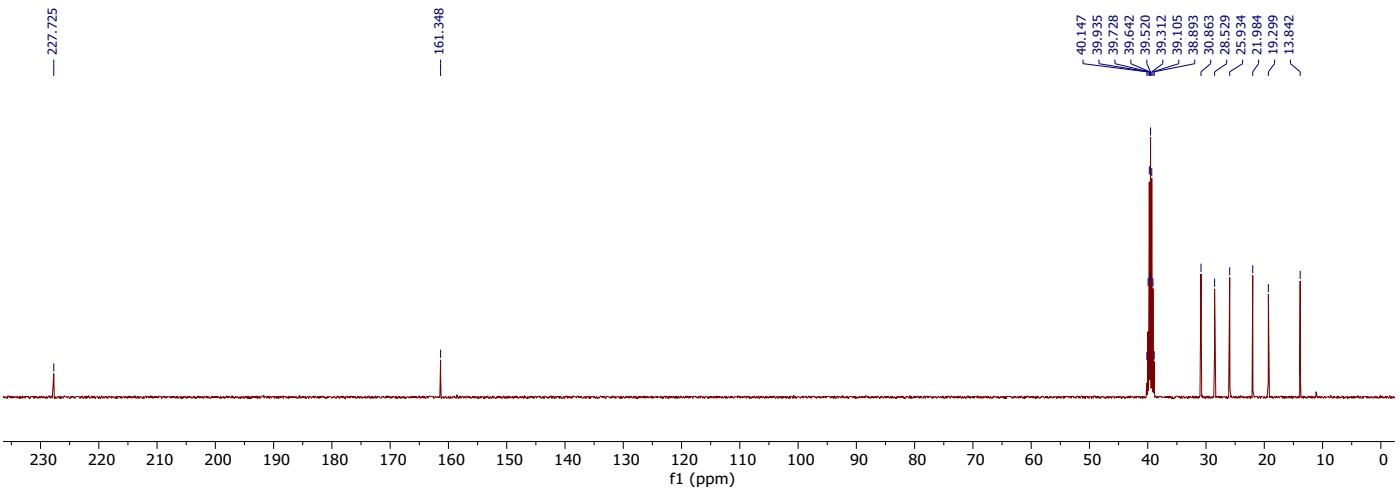
^{13}C NMR Spectra of Methyl-2-(benzylamino)-2-oxoethanedithioate (3h)



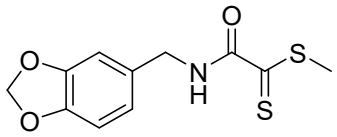
Methyl-2-(hexylamino)-2-oxoethanedithioate (3i)



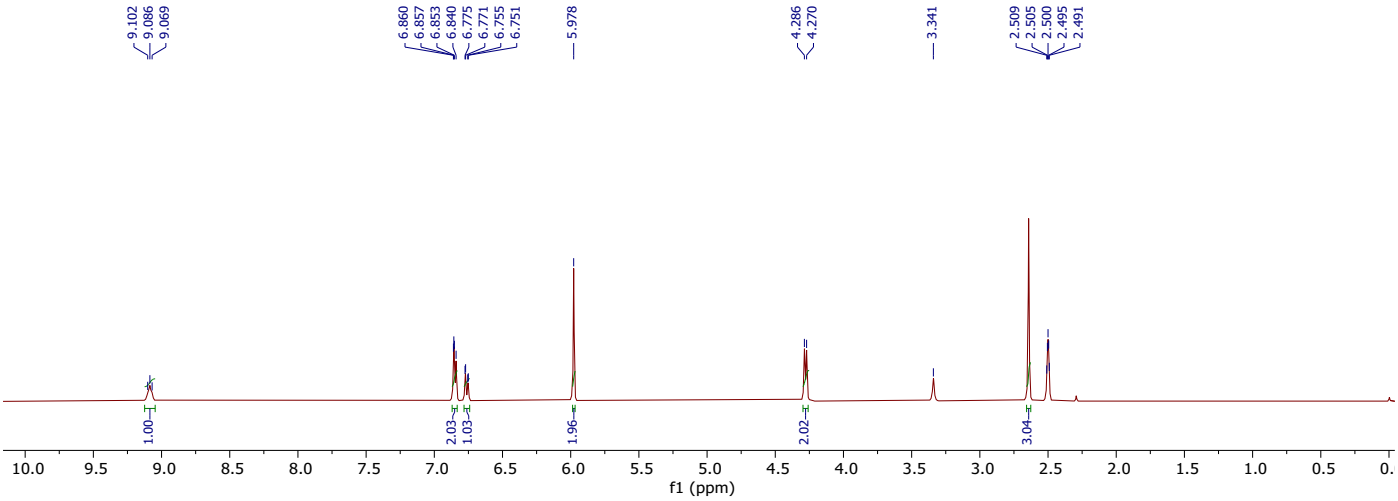
^{1}H NMR Spectra of Methyl-2-(hexylamino)-2-oxoethanedithioate (3i)



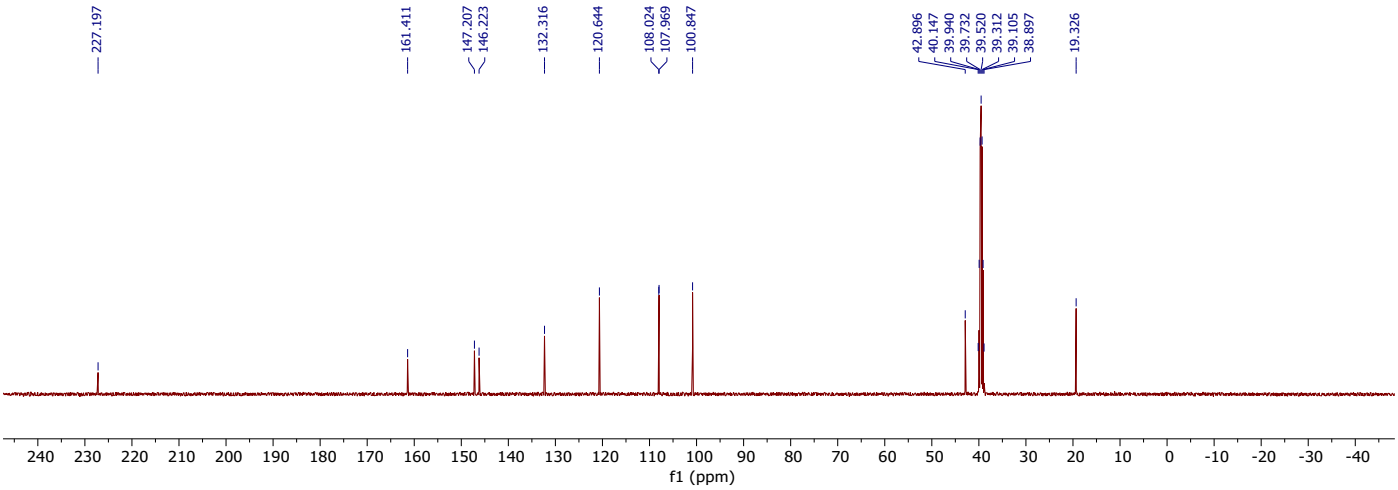
^{13}C NMR Spectra of Methyl-2-(hexylamino)-2-oxoethanedithioate (3i)



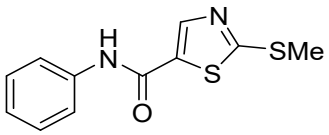
Methyl-2-((benzo[d][1,3]dioxol-5-ylmethyl)amino)-2-oxoethanedithioate (3j)



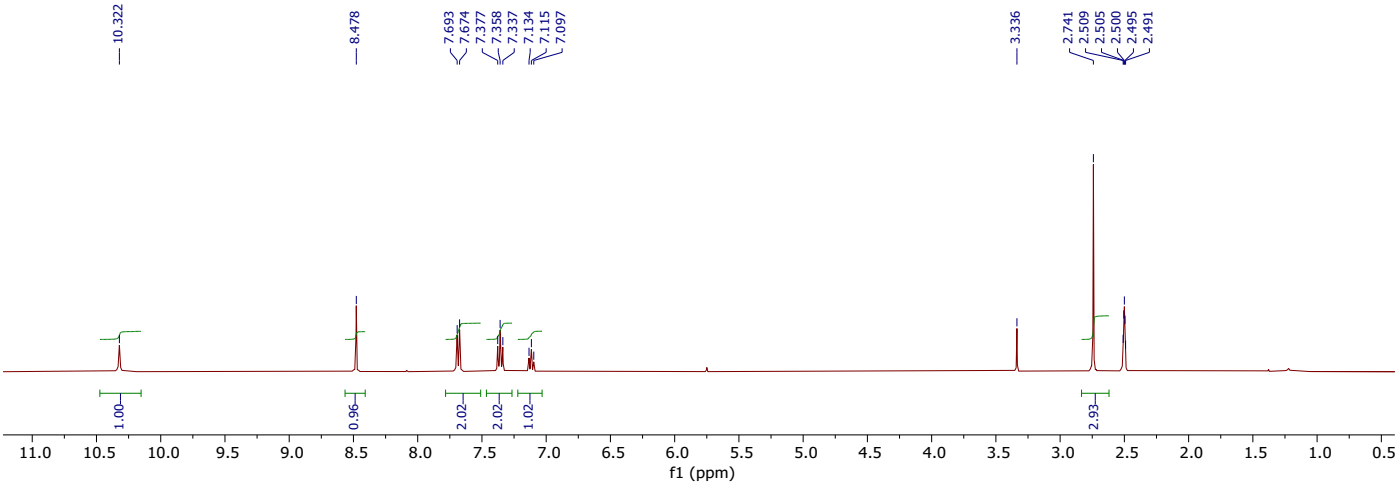
^{1}H NMR Spectra of Methyl-2-((benzo[d][1,3]dioxol-5-ylmethyl)amino)-2-oxoethanedithioate (3j)



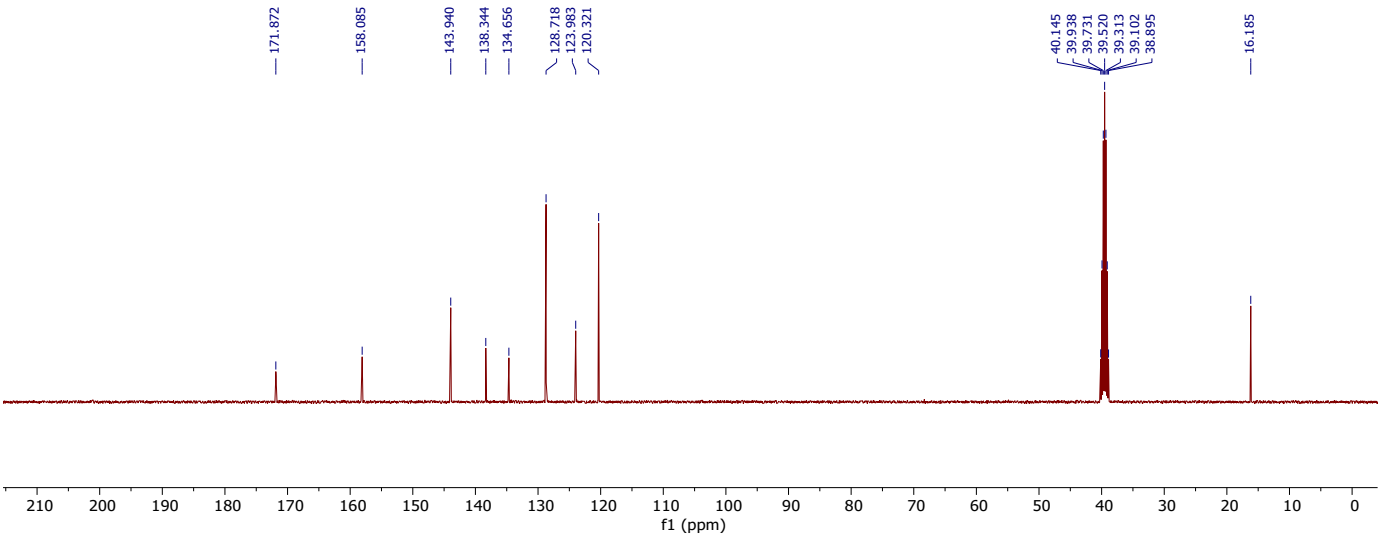
^{13}C NMR Spectra of Methyl-2-((benzo[d][1,3]dioxol-5-ylmethyl)amino)-2-oxoethanedithioate (3j)



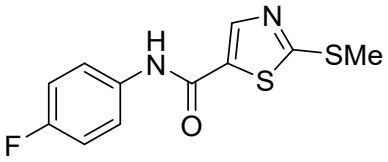
2-(methylthio)-*N*-phenylthiazole-5-carboxamide (5a)



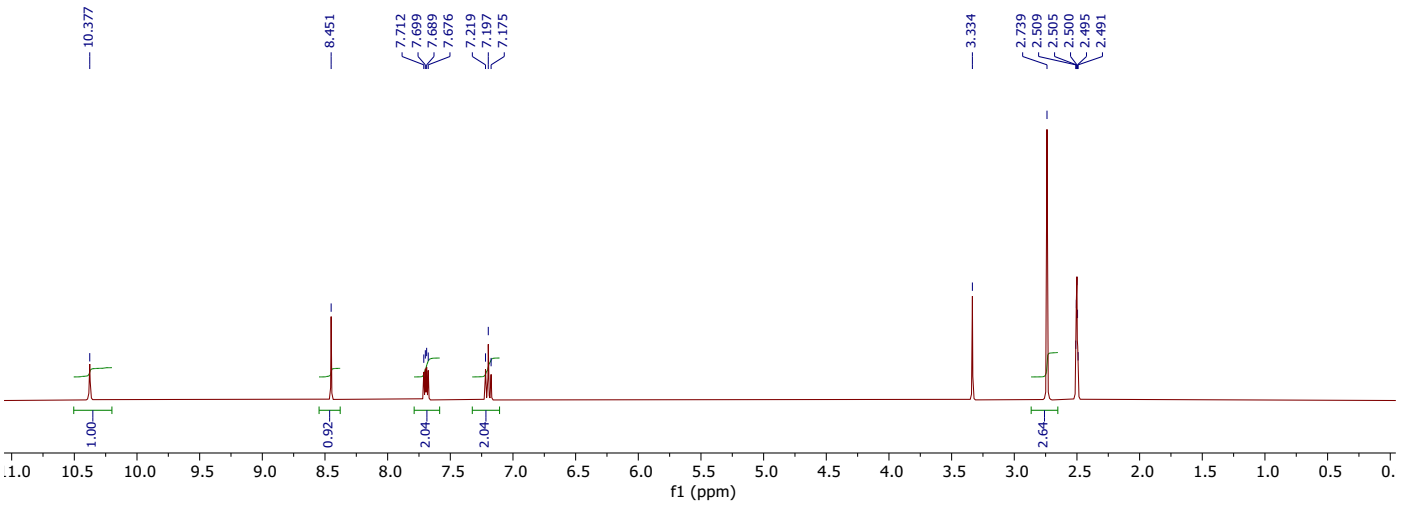
^{1}H NMR Spectra of 2-(methylthio)-*N*-phenylthiazole-5-carboxamide (5a)



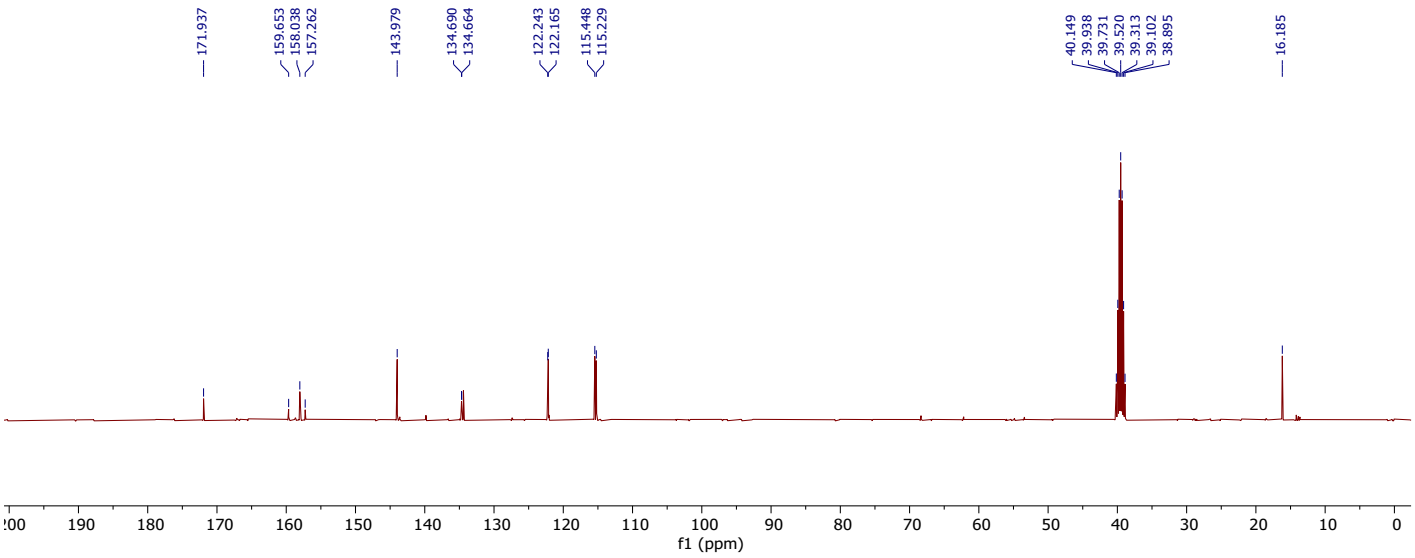
^{13}C NMR Spectra of 2-(methylthio)-*N*-phenylthiazole-5-carboxamide (5a)



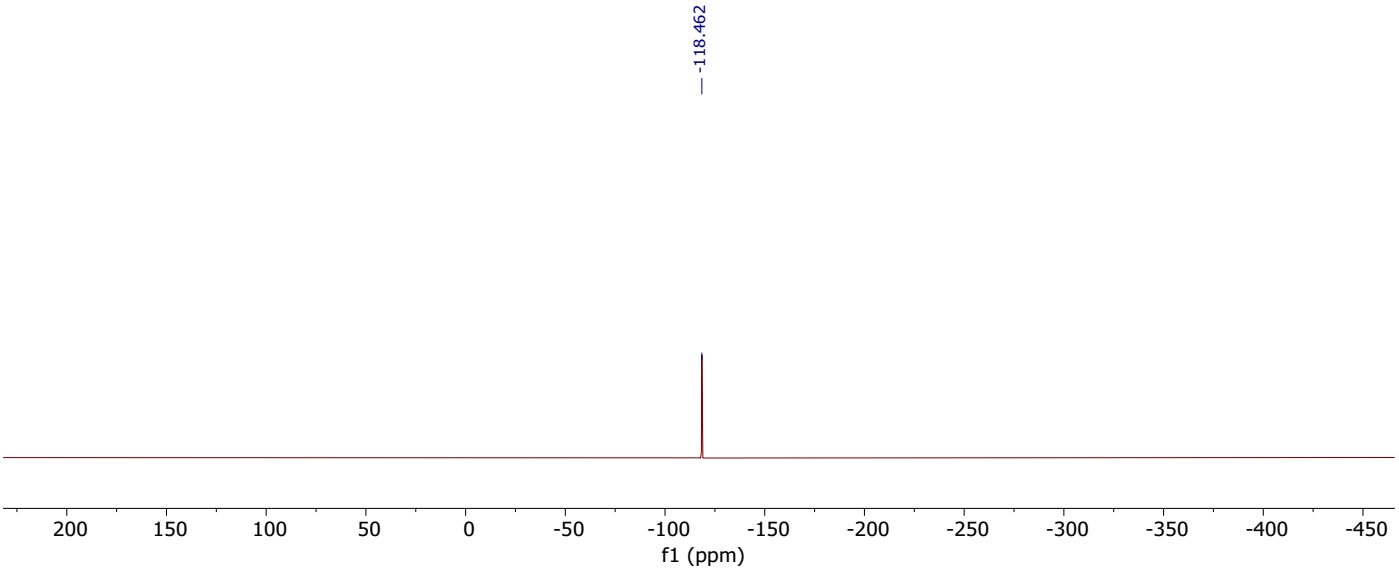
***N*-(4-fluorophenyl)-2-(methylthio)thiazole-5-carboxamide (5b)**



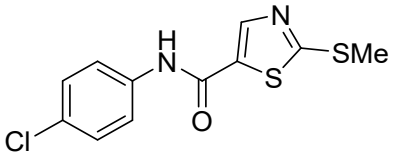
^{1}H NMR Spectra of *N*-(4-fluorophenyl)-2-(methylthio)thiazole-5-carboxamide (5b)



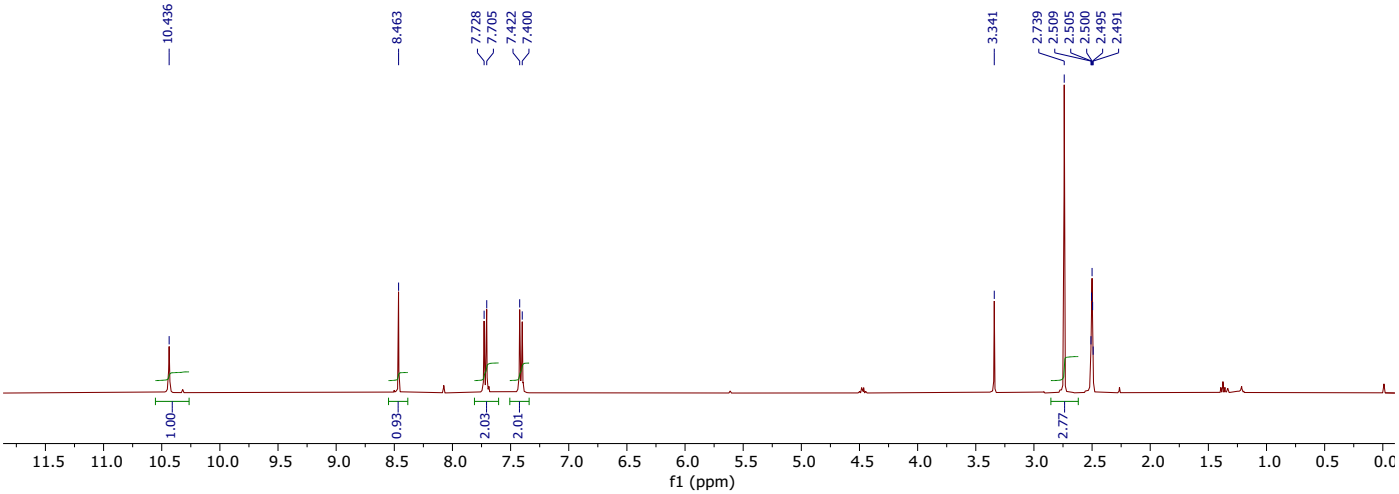
^{13}C NMR Spectra of *N*-(4-fluorophenyl)-2-(methylthio)thiazole-5-carboxamide (5b)



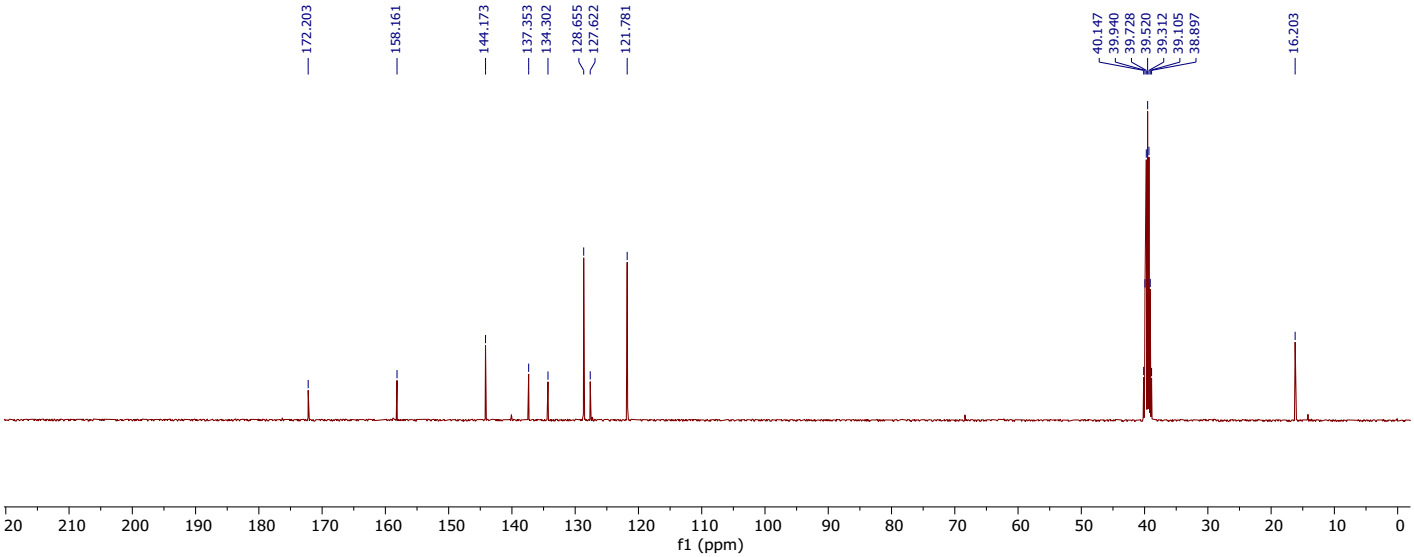
^{19}F NMR Spectra of *N*-(4-fluorophenyl)-2-(methylthio)thiazole-5-carboxamide (5b)



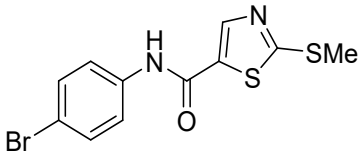
***N*-(4-chlorophenyl)-2-(methylthio)thiazole-5-carboxamide (5c)**



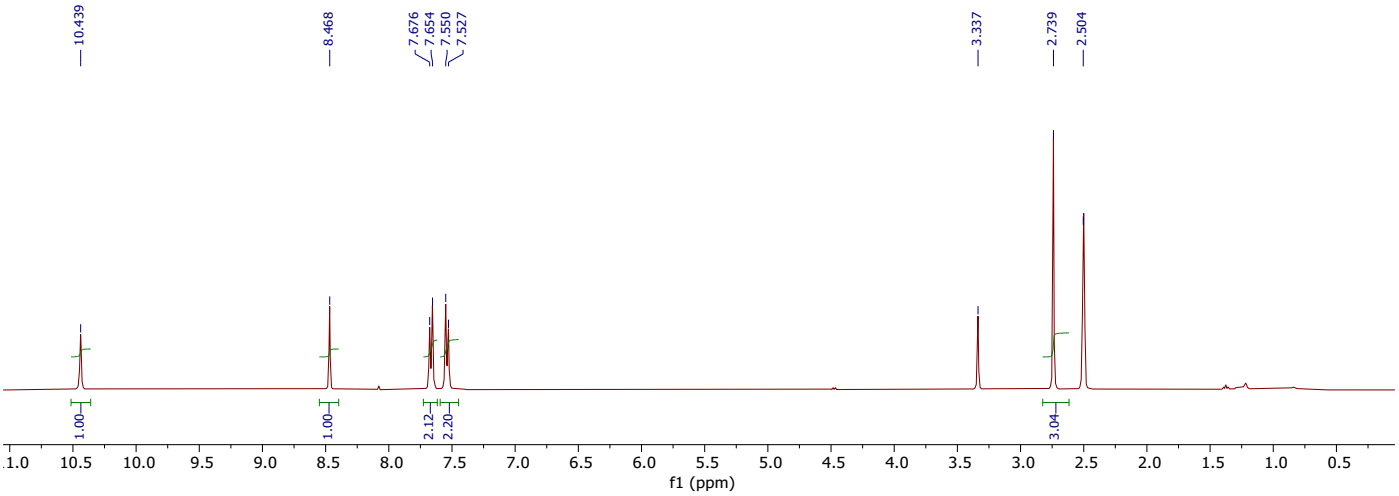
^{1}H NMR Spectra of *N*-(4-chlorophenyl)-2-(methylthio)thiazole-5-carboxamide (5c)



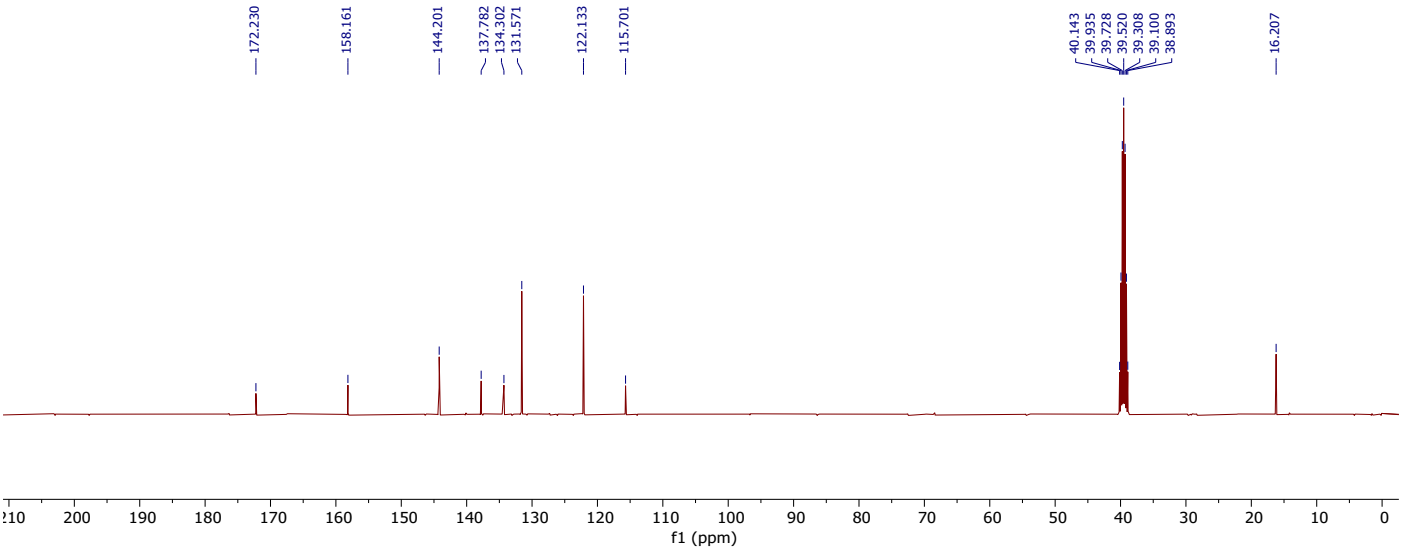
^{13}C NMR Spectra of *N*-(4-chlorophenyl)-2-(methylthio)thiazole-5-carboxamide (5c)



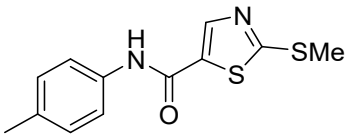
***N*-(4-bromophenyl)-2-(methylthio)thiazole-5-carboxamide (5d)**



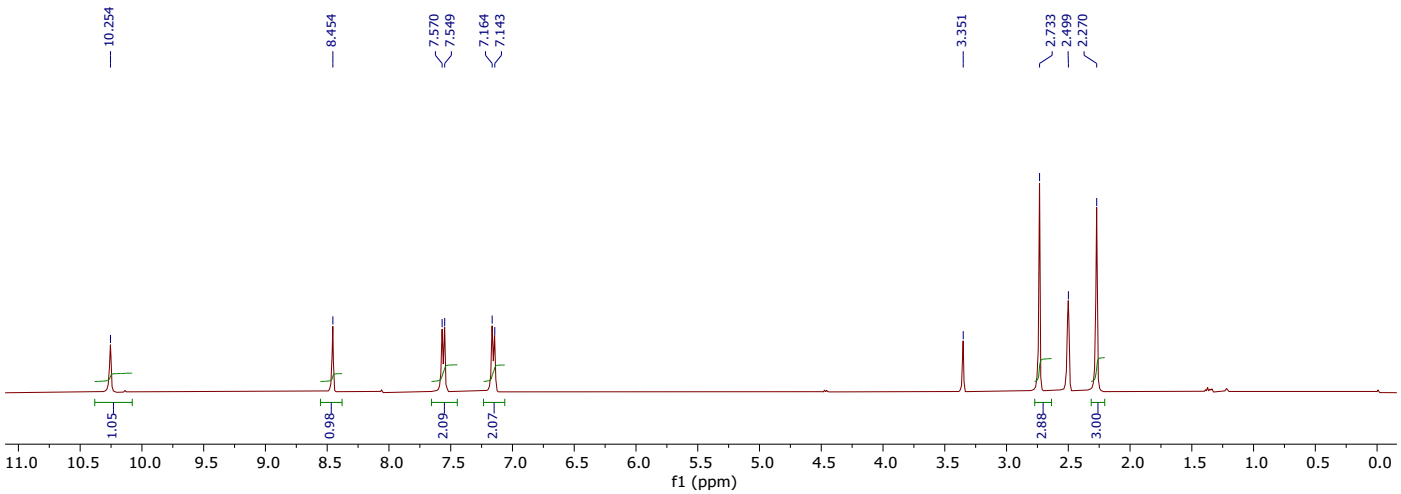
^{1}H NMR Spectra of *N*-(4-bromophenyl)-2-(methylthio)thiazole-5-carboxamide (5d)



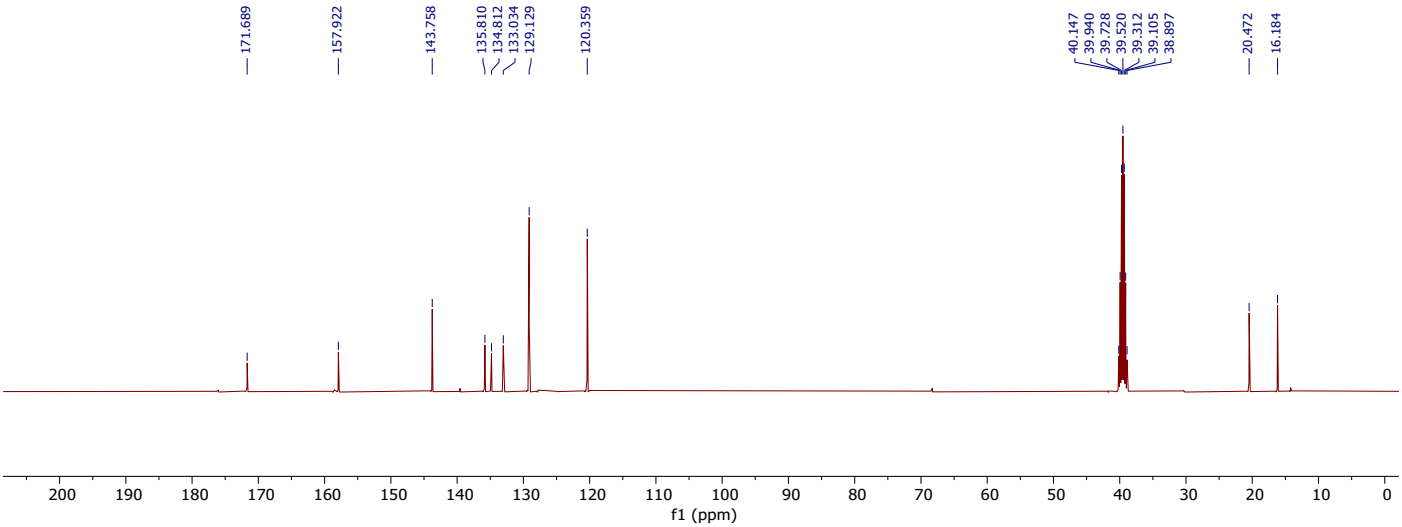
^{13}C NMR Spectra of *N*-(4-bromophenyl)-2-(methylthio)thiazole-5-carboxamide (5d)



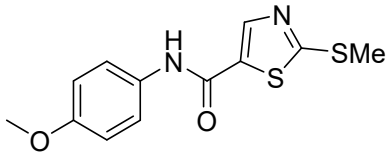
2-(methylthio)-*N*-(p-tolyl)thiazole-5-carboxamide (5e)



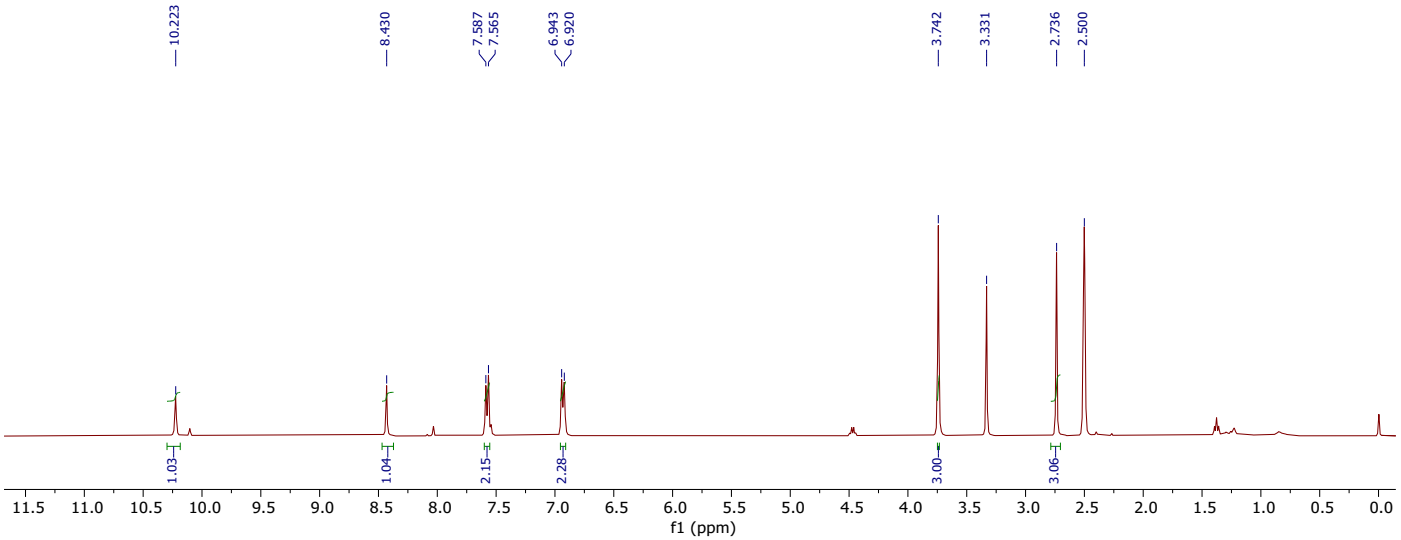
^{1}H NMR Spectra of 2-(methylthio)-*N*-(p-tolyl)thiazole-5-carboxamide (5e)



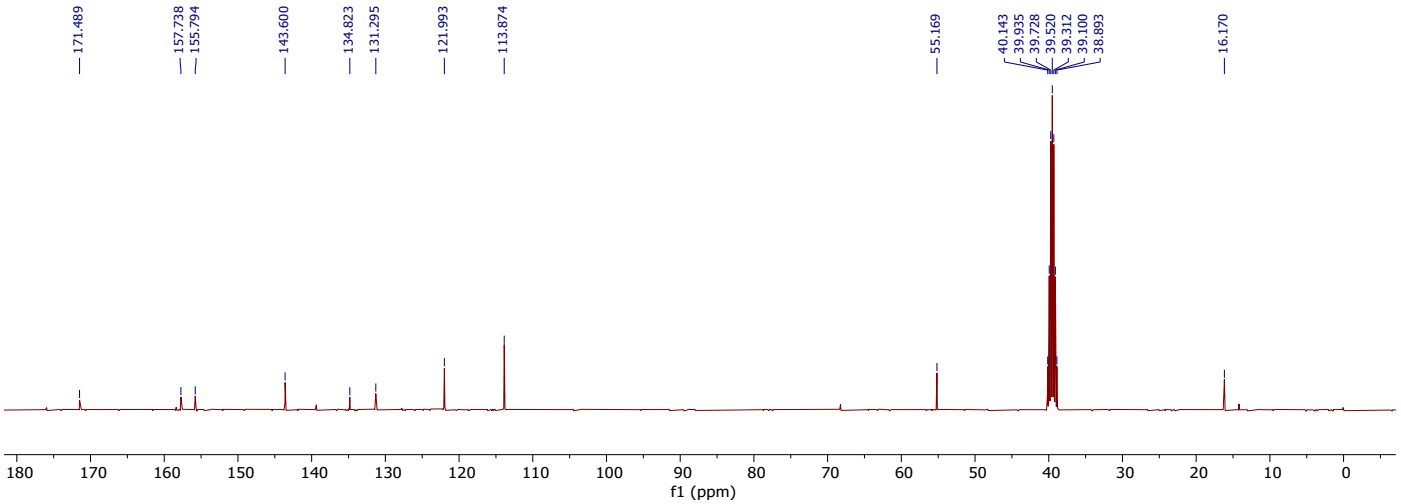
^{13}C NMR Spectra of 2-(methylthio)-*N*-(p-tolyl)thiazole-5-carboxamide (5e)



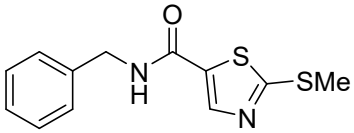
***N*-(4-methoxyphenyl)-2-(methylthio)thiazole-5-carboxamide (5f)**



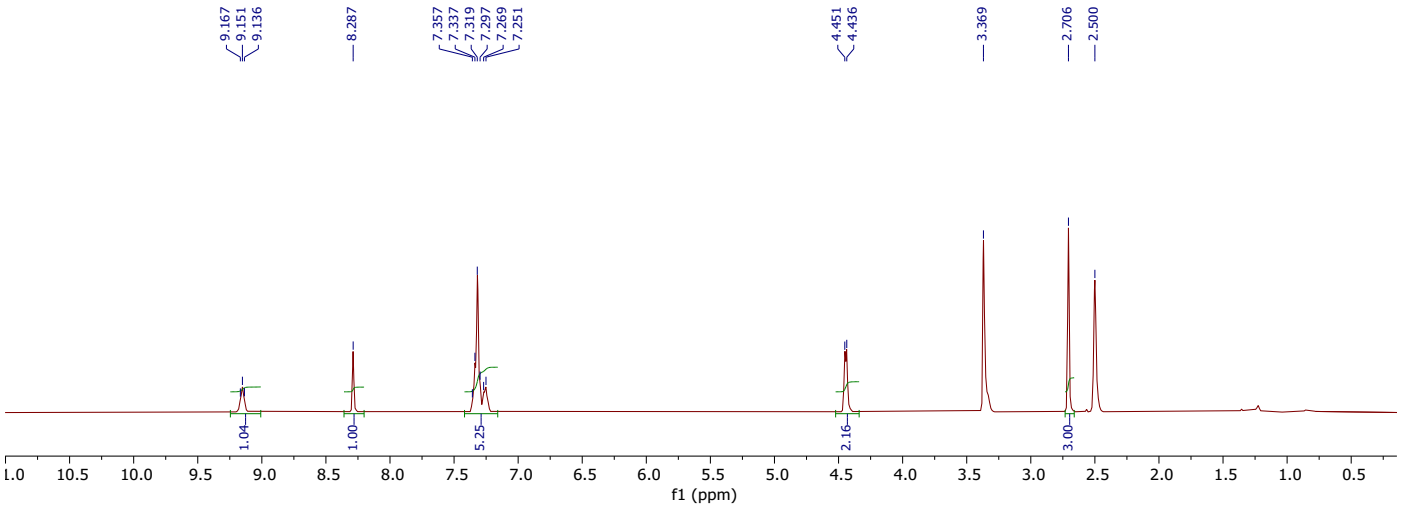
^{1}H NMR Spectra of *N*-(4-methoxyphenyl)-2-(methylthio)thiazole-5-carboxamide (5f)



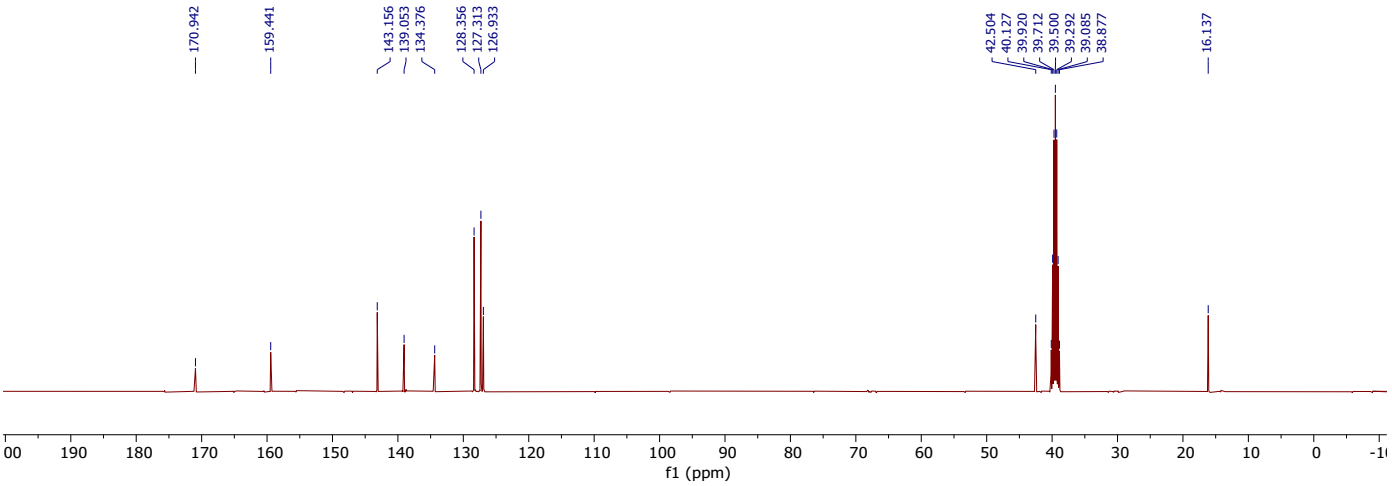
^{13}C NMR Spectra of *N*-(4-methoxyphenyl)-2-(methylthio)thiazole-5-carboxamide (5f)



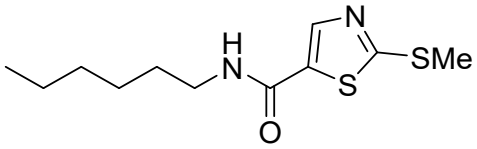
***N*-benzyl-2-(methylthio)thiazole-5-carboxamide (5g)**



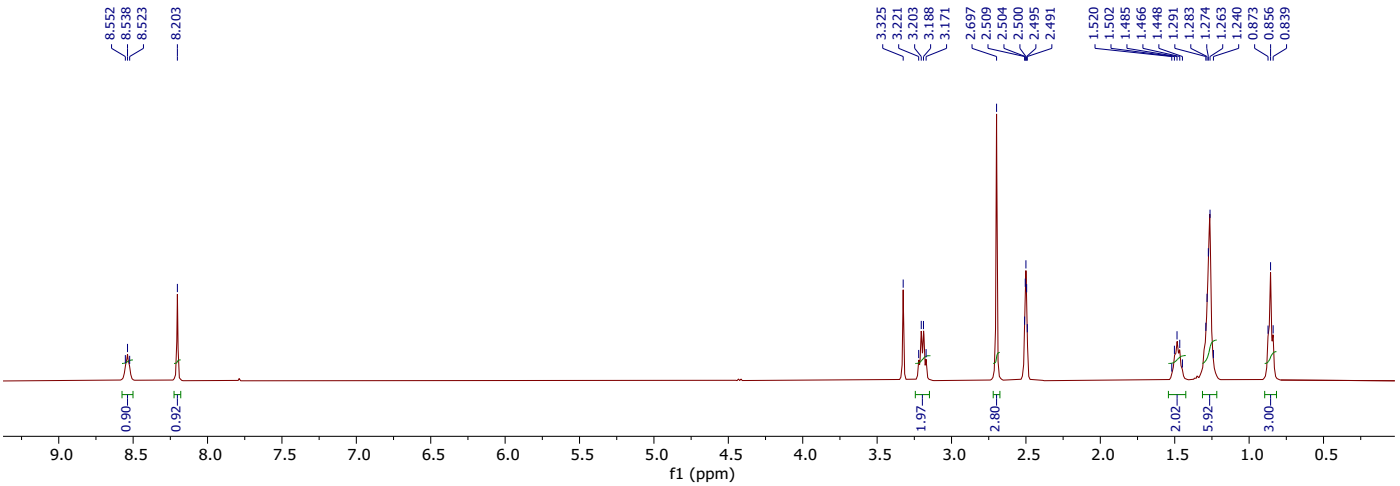
^{1}H NMR Spectra of *N*-benzyl-2-(methylthio)thiazole-5-carboxamide (5g)



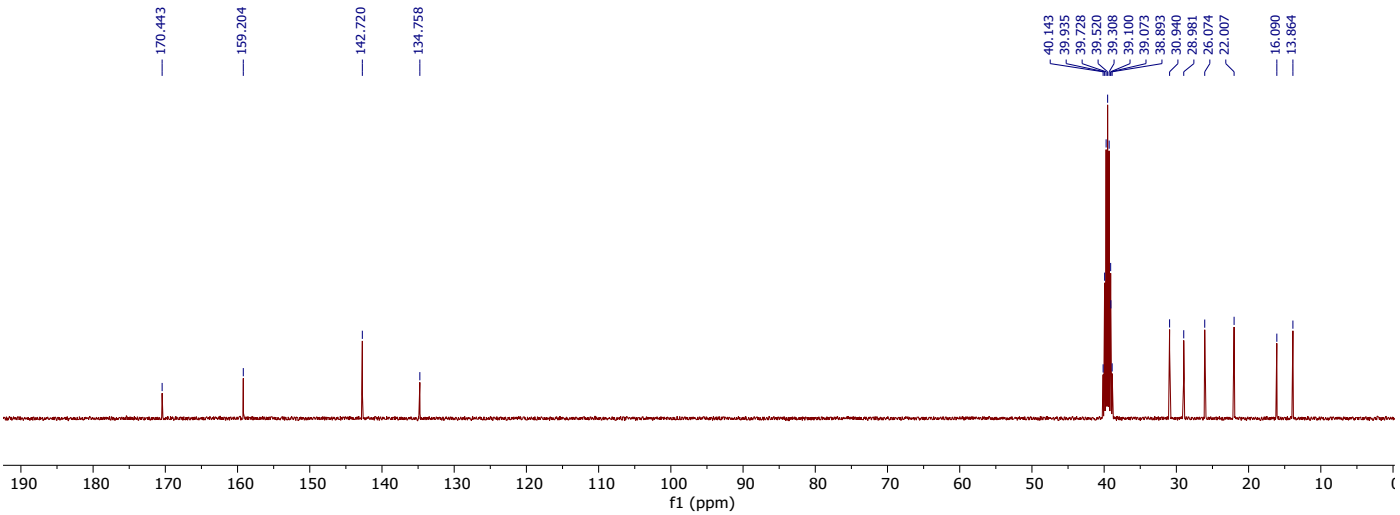
^{13}C NMR Spectra of *N*-benzyl-2-(methylthio)thiazole-5-carboxamide (5g)



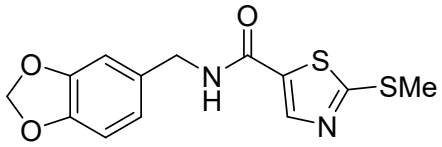
***N*-hexyl-2-(methylthio)thiazole-5-carboxamide (5h)**



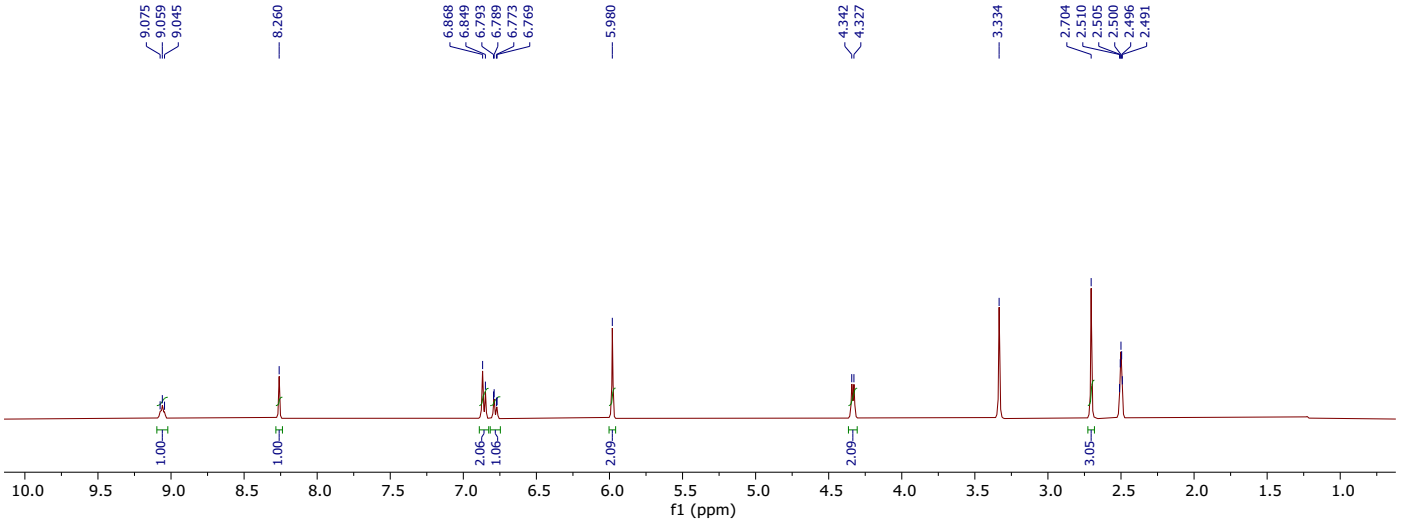
^{1}H NMR Spectra of *N*-hexyl-2-(methylthio)thiazole-5-carboxamide (5h)



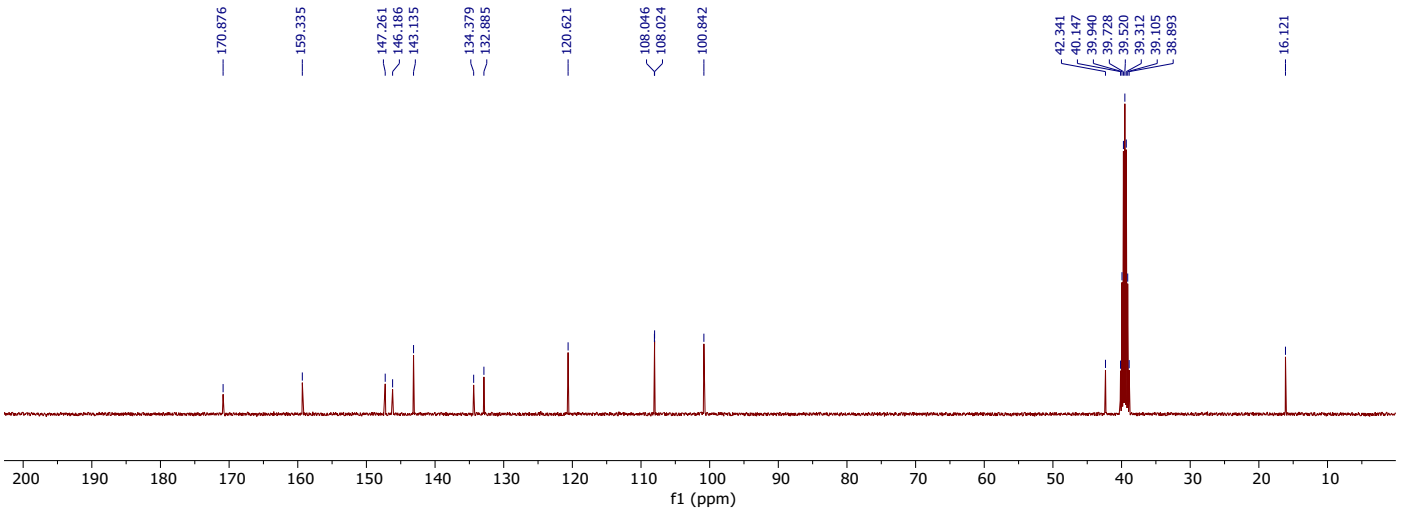
^{13}C NMR Spectra of *N*-hexyl-2-(methylthio)thiazole-5-carboxamide (5h)



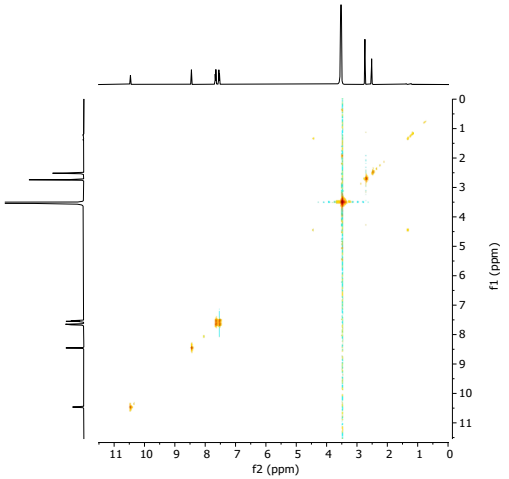
***N*-(benzo[d][1,3]dioxol-5-ylmethyl)-2-(methylthio)thiazole-5-carboxamide (5i)**



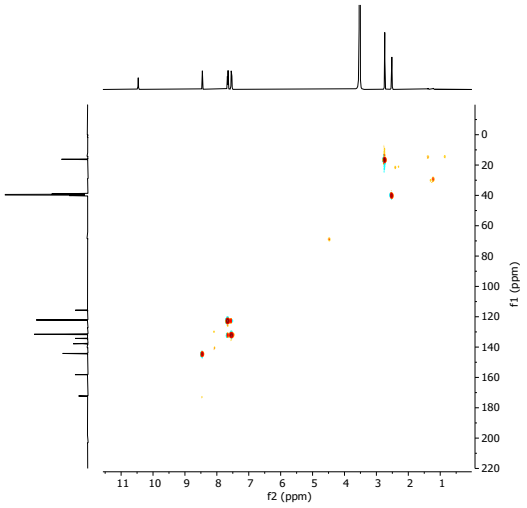
^{1}H NMR Spectra of *N*-(benzo[d][1,3]dioxol-5-ylmethyl)-2-(methylthio)thiazole-5-carboxamide (5i)



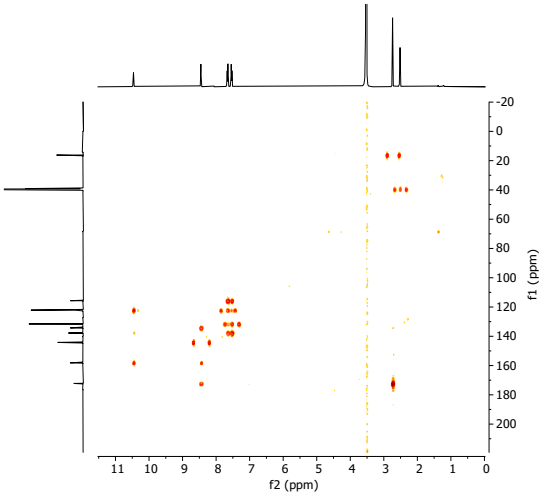
^{13}C NMR Spectra of *N*-(benzo[d][1,3]dioxol-5-ylmethyl)-2-(methylthio)thiazole-5-carboxamide (5i)



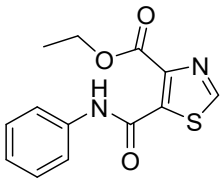
COSY Spectra of *N*-(4-bromophenyl)-2-(methylthio)thiazole-5-carboxamide (5d)



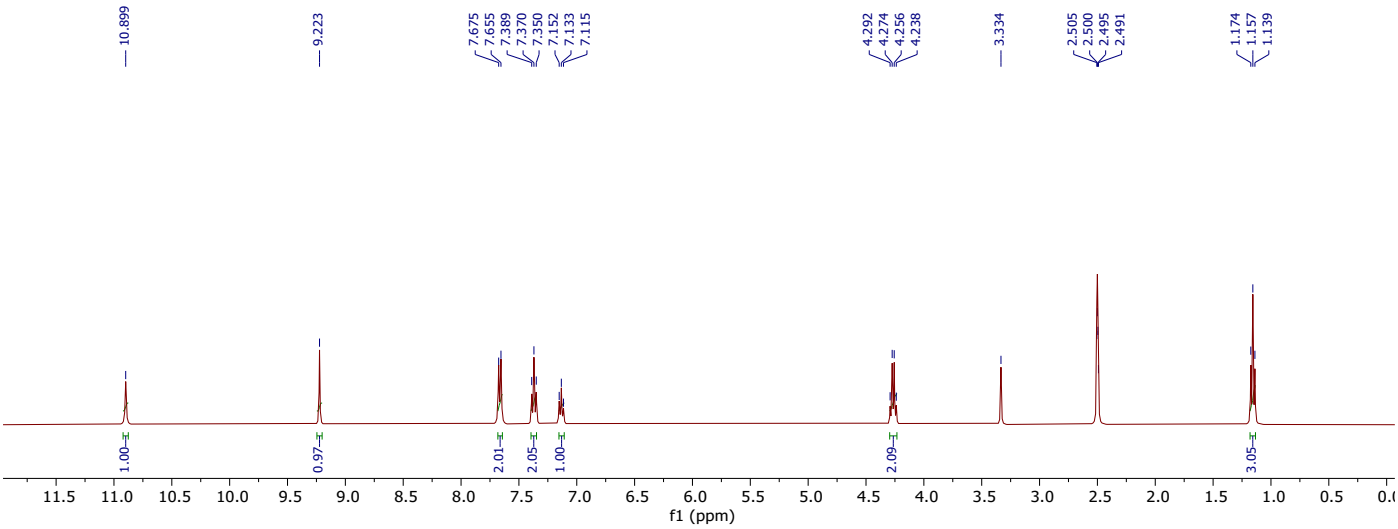
HSQC Spectra of *N*-(4-bromophenyl)-2-(methylthio)thiazole-5-carboxamide (5d)



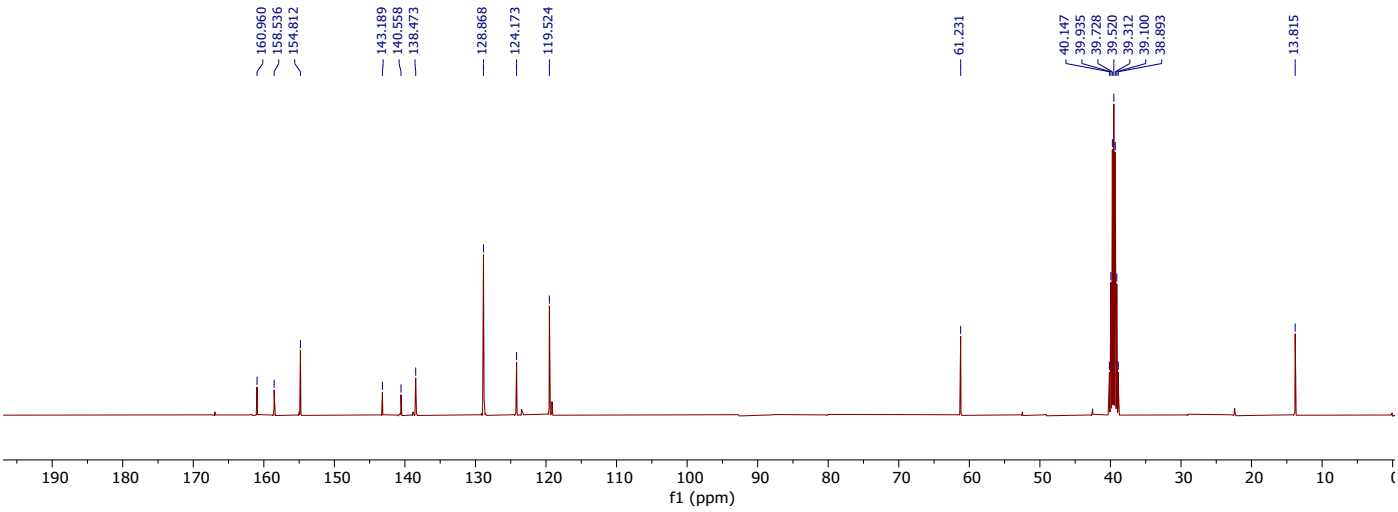
HMBC Spectra of *N*-(4-bromophenyl)-2-(methylthio)thiazole-5-carboxamide (5d)



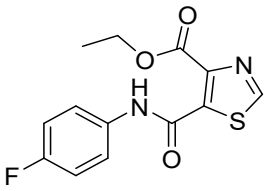
Ethyl-5-(phenylcarbamoyl)thiazole-4-carboxylate (8a)



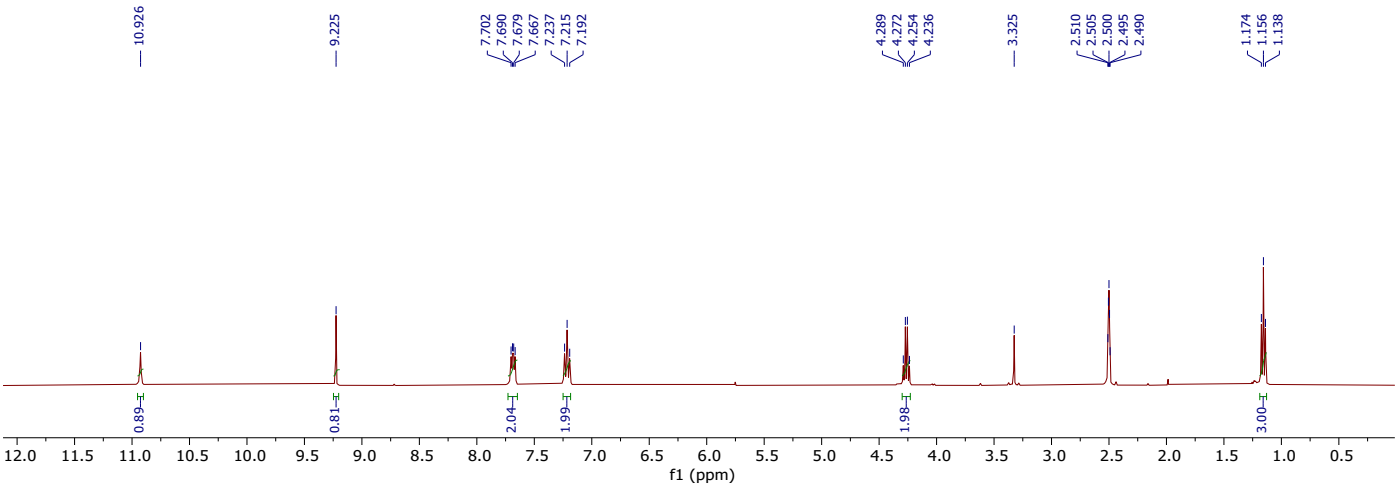
^{1}H NMR Spectra of Ethyl-5-(phenylcarbamoyl)thiazole-4-carboxylate (8a)



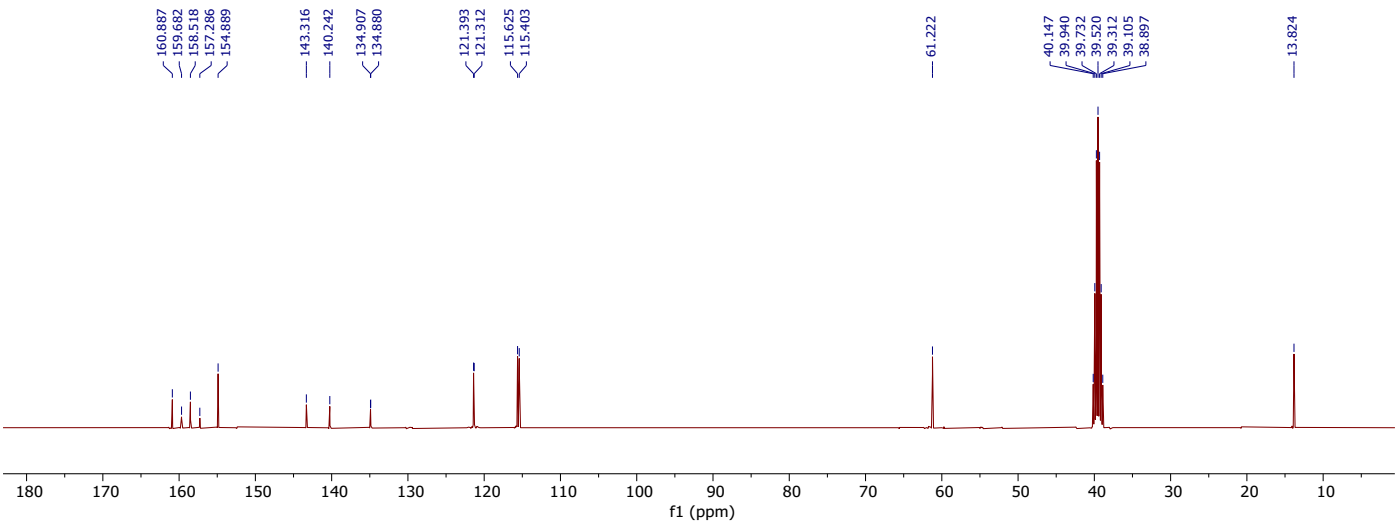
^{13}C NMR Spectra of Ethyl-5-(phenylcarbamoyl)thiazole-4-carboxylate (8a)



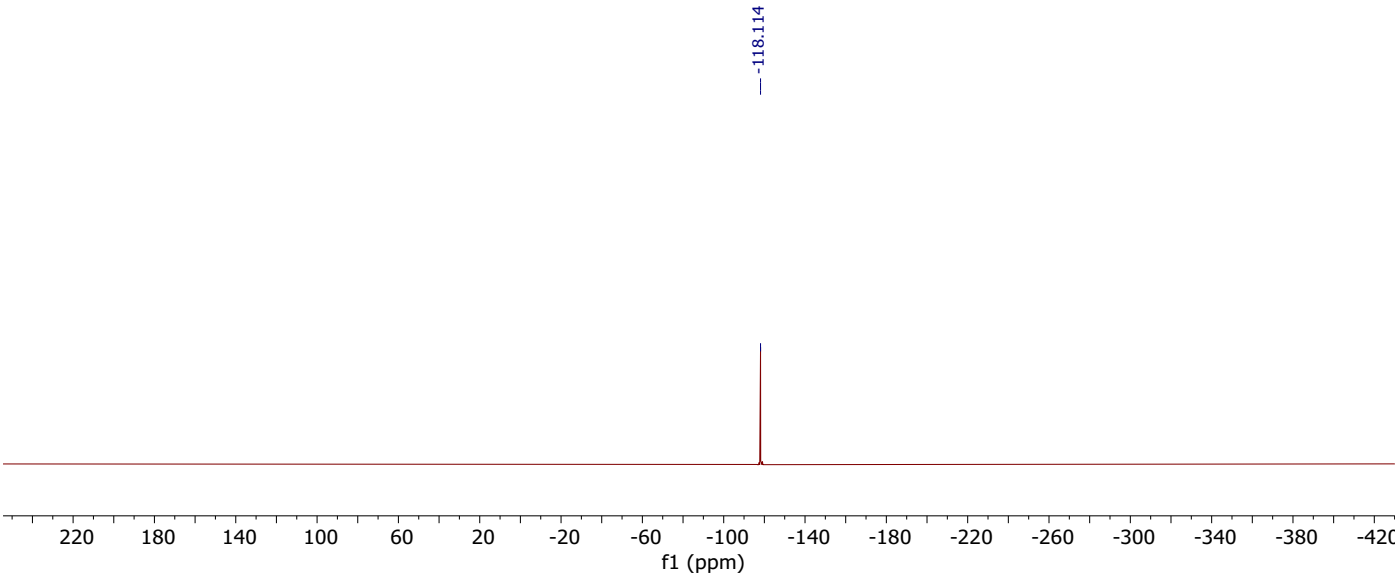
Ethyl-5-((4-fluorophenyl)carbamoyl)thiazole-4-carboxylate (8b)



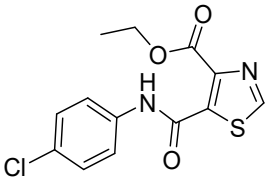
^{1}H NMR Spectra of Ethyl-5-((4-fluorophenyl)carbamoyl)thiazole-4-carboxylate (8b)



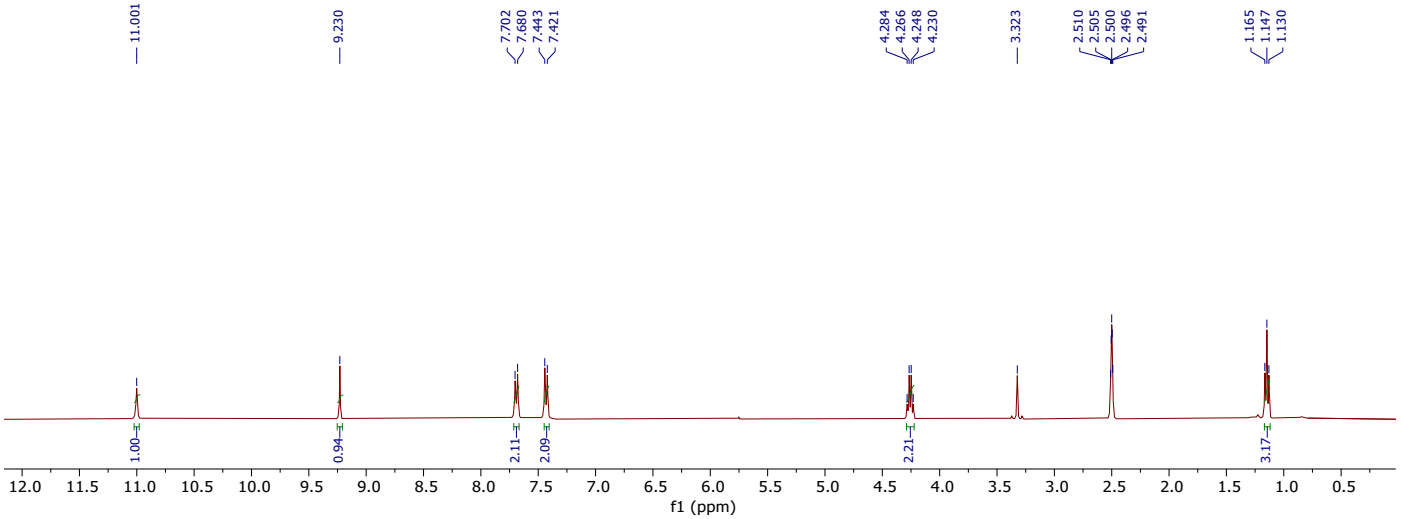
^{13}C NMR Spectra of Ethyl-5-((4-fluorophenyl)carbamoyl)thiazole-4-carboxylate (8b)



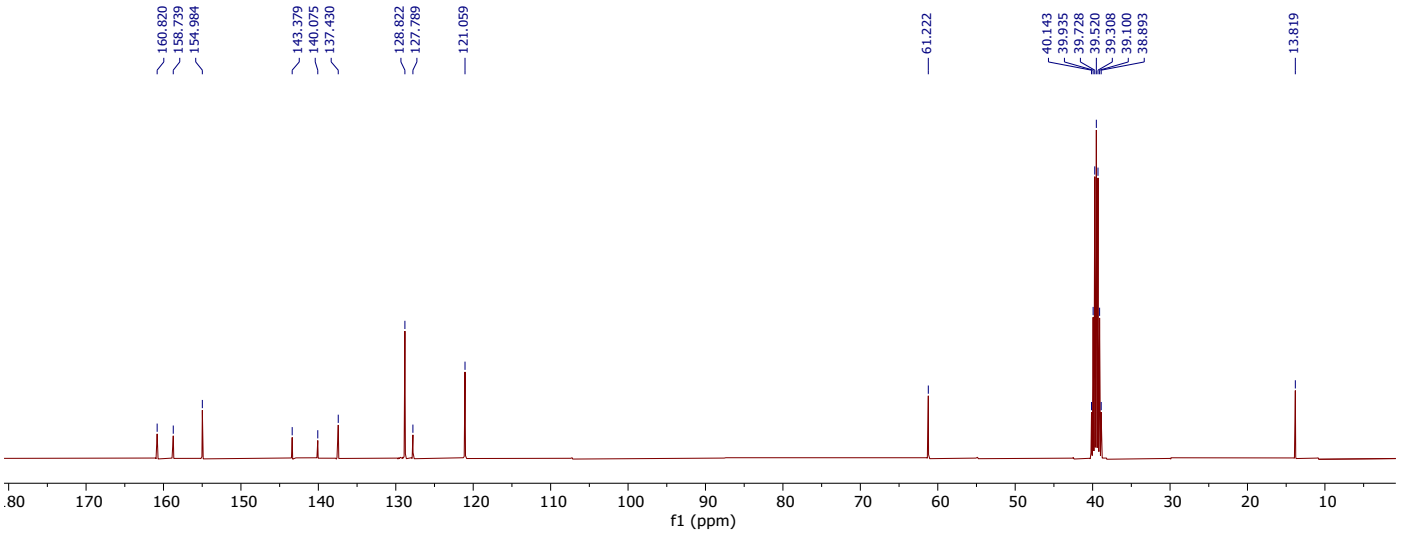
^{19}F NMR Spectra of Ethyl-5-((4-fluorophenyl)carbamoyl)thiazole-4-carboxylate (8b)



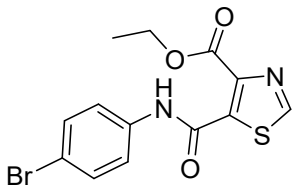
Ethyl-5-((4-chlorophenyl)carbamoyl)thiazole-4-carboxylate (8c)



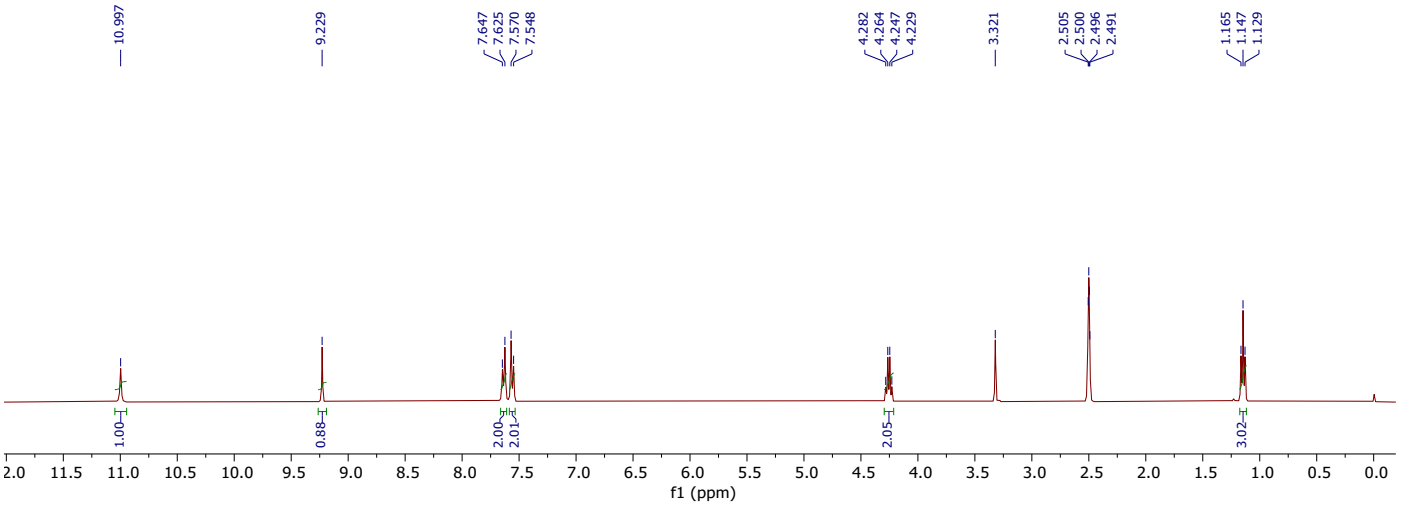
^{1}H NMR Spectra of Ethyl-5-((4-chlorophenyl)carbamoyl)thiazole-4-carboxylate (8c)



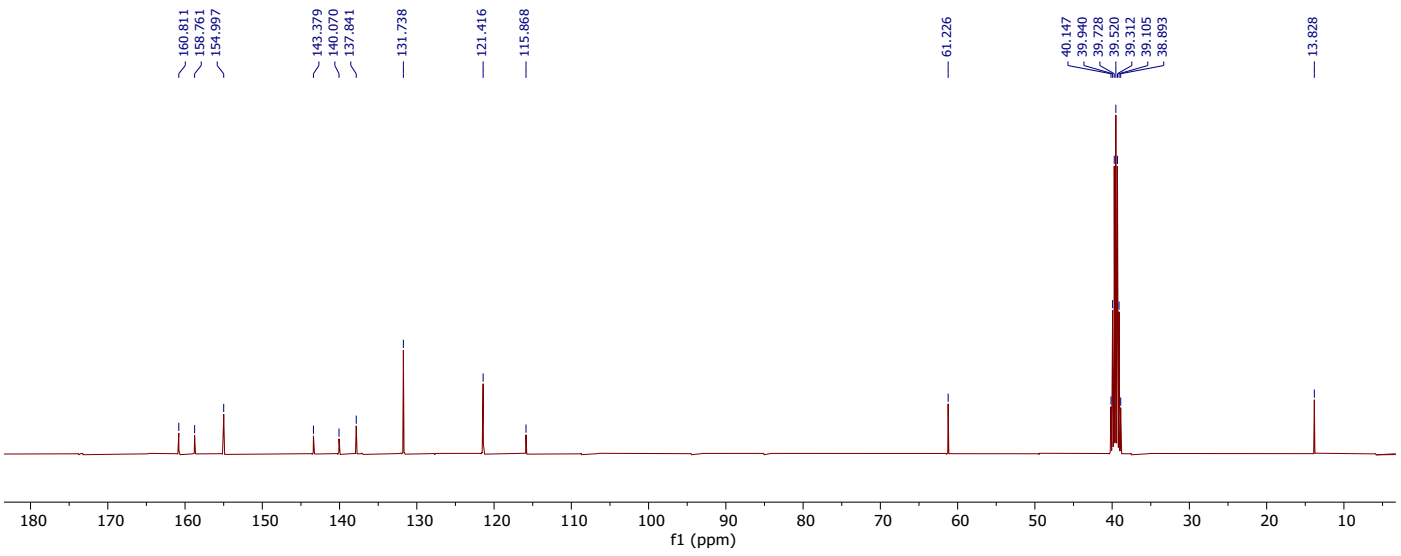
^{13}C NMR Spectra of Ethyl-5-((4-chlorophenyl)carbamoyl)thiazole-4-carboxylate (8c)



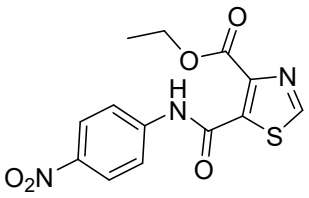
Ethyl5-((4-bromophenyl)carbamoyl)thiazole-4-carboxylate (8d)



^{1}H NMR Spectra of Ethyl5-((4-bromophenyl)carbamoyl)thiazole-4-carboxylate (8d)



^{13}C NMR Spectra of Ethyl5-((4-bromophenyl)carbamoyl)thiazole-4-carboxylate (8d)



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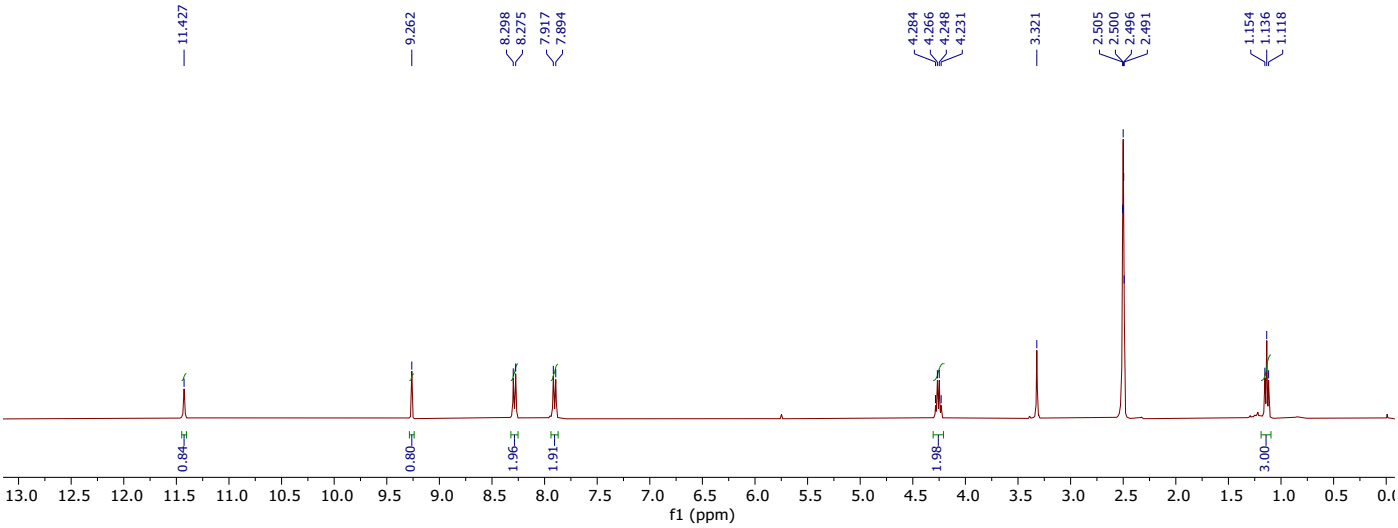

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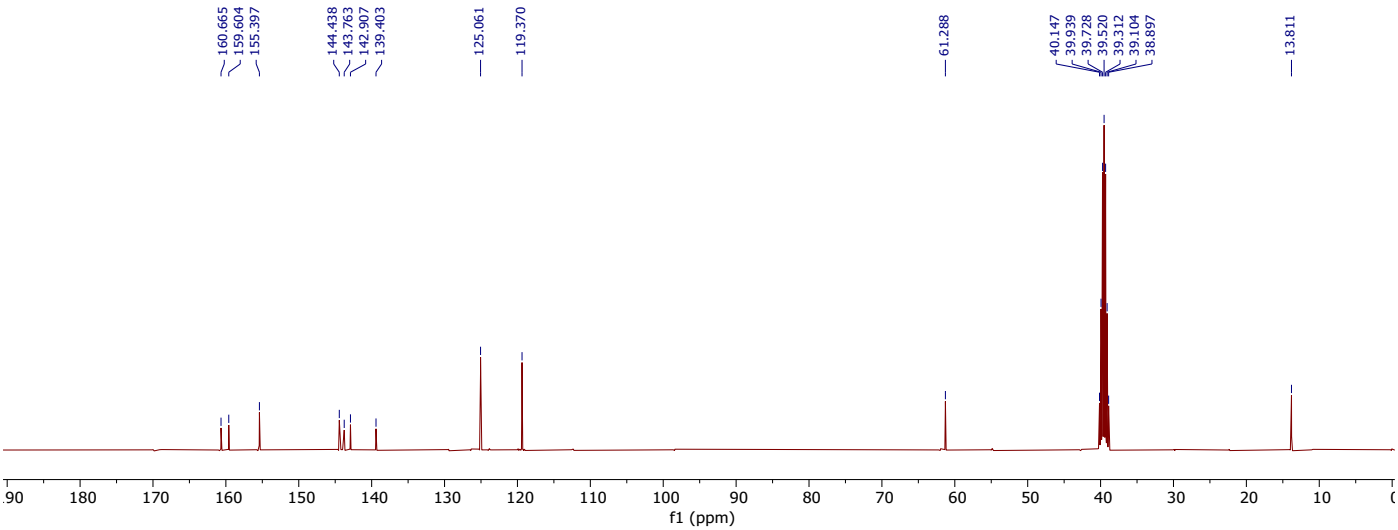

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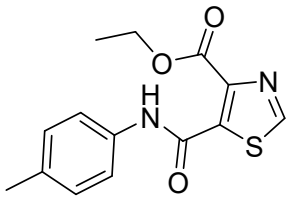

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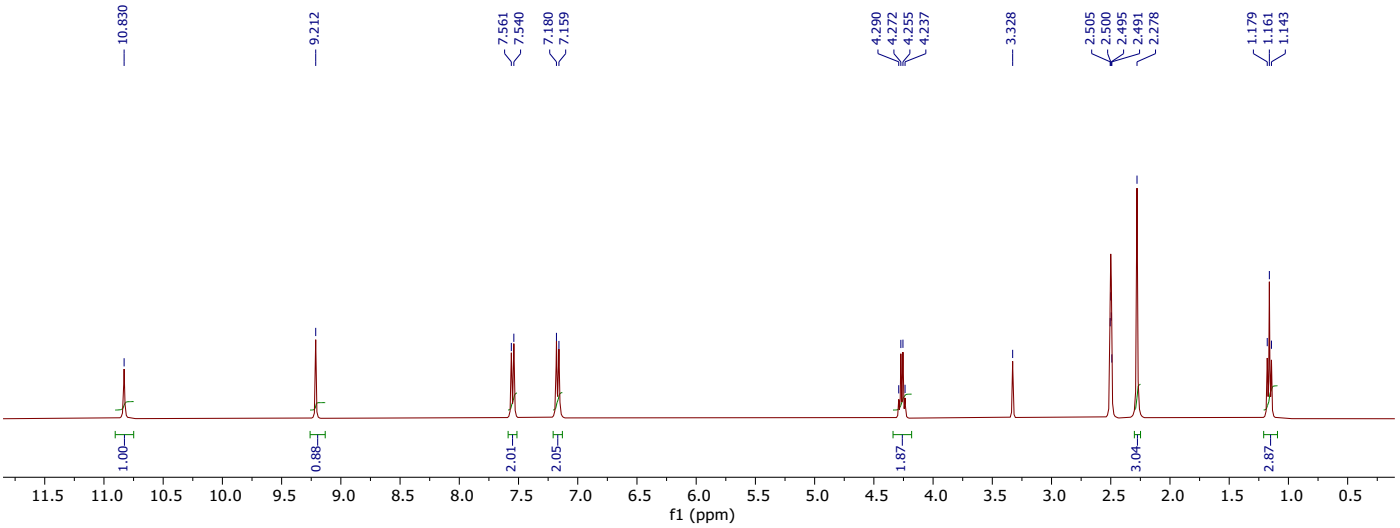

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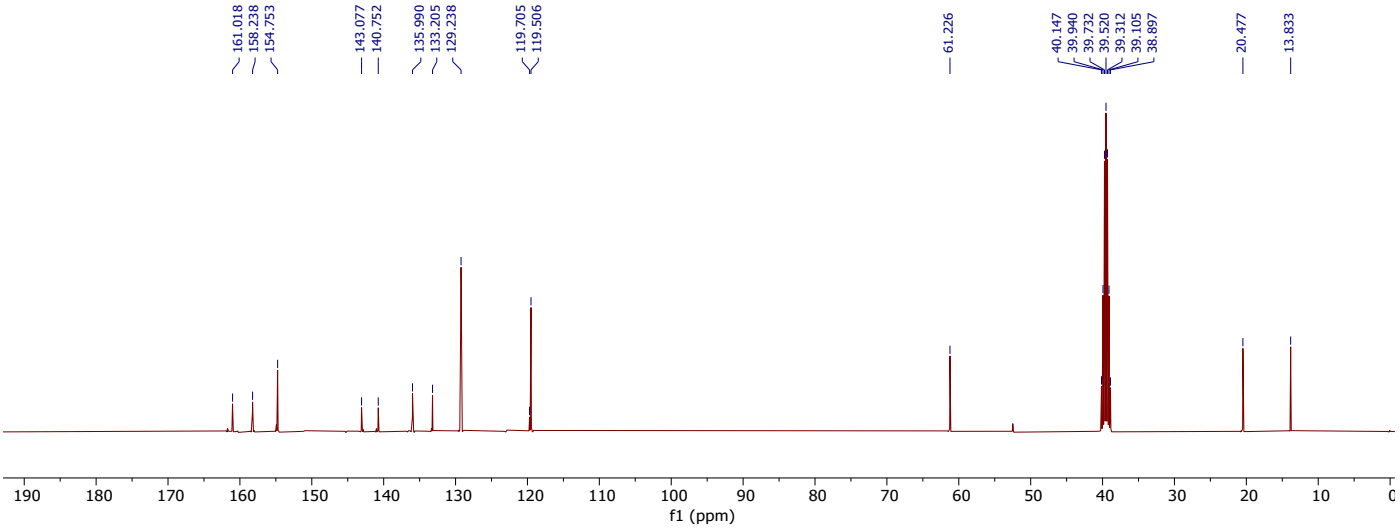

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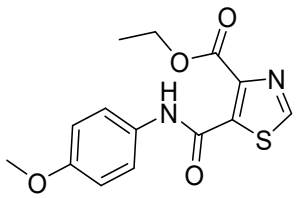
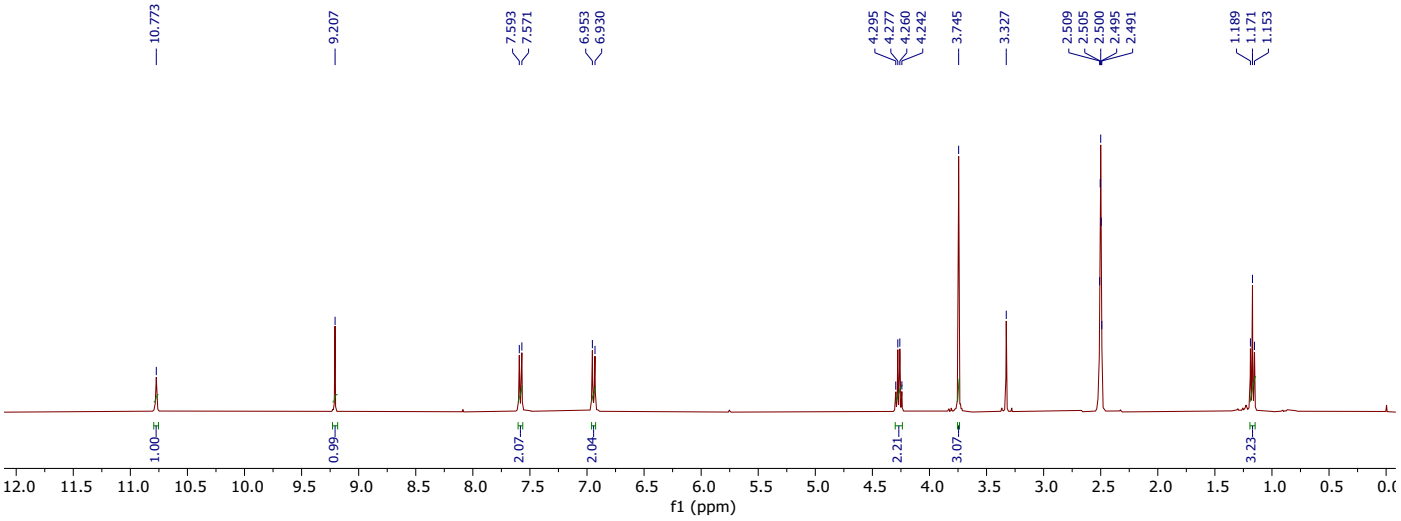


Ethyl-5-((4-methoxyphenyl)carbamoyl)thiazole-4-carboxylate (8g)



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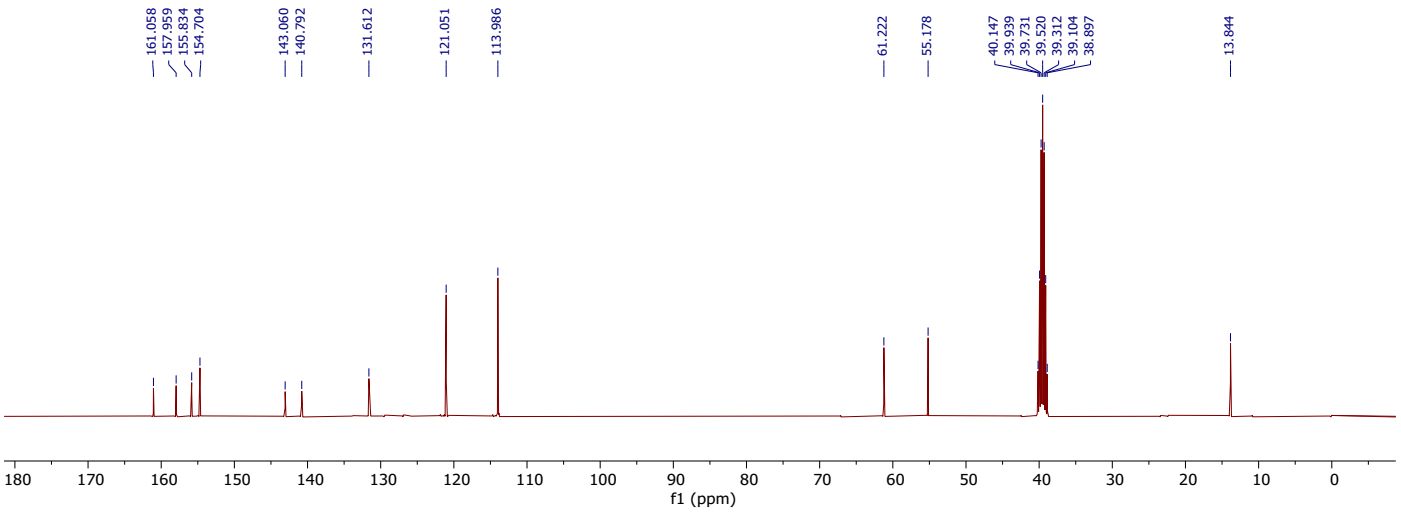

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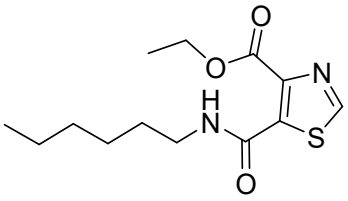
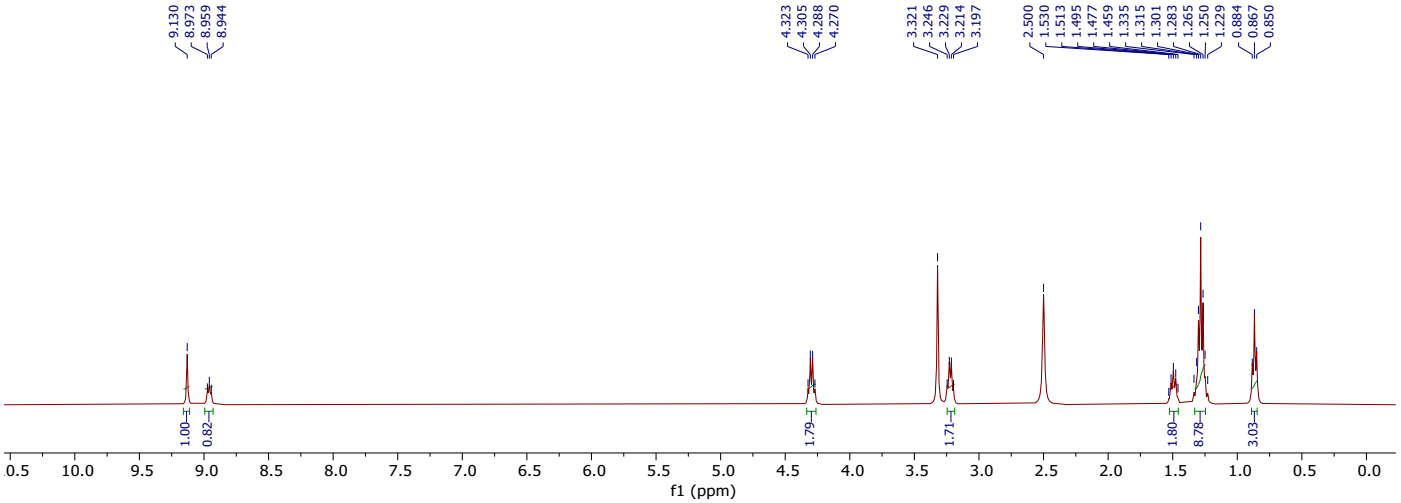


Ethyl-5-(hexylcarbamoyl)thiazole-4-carboxylate (8h)



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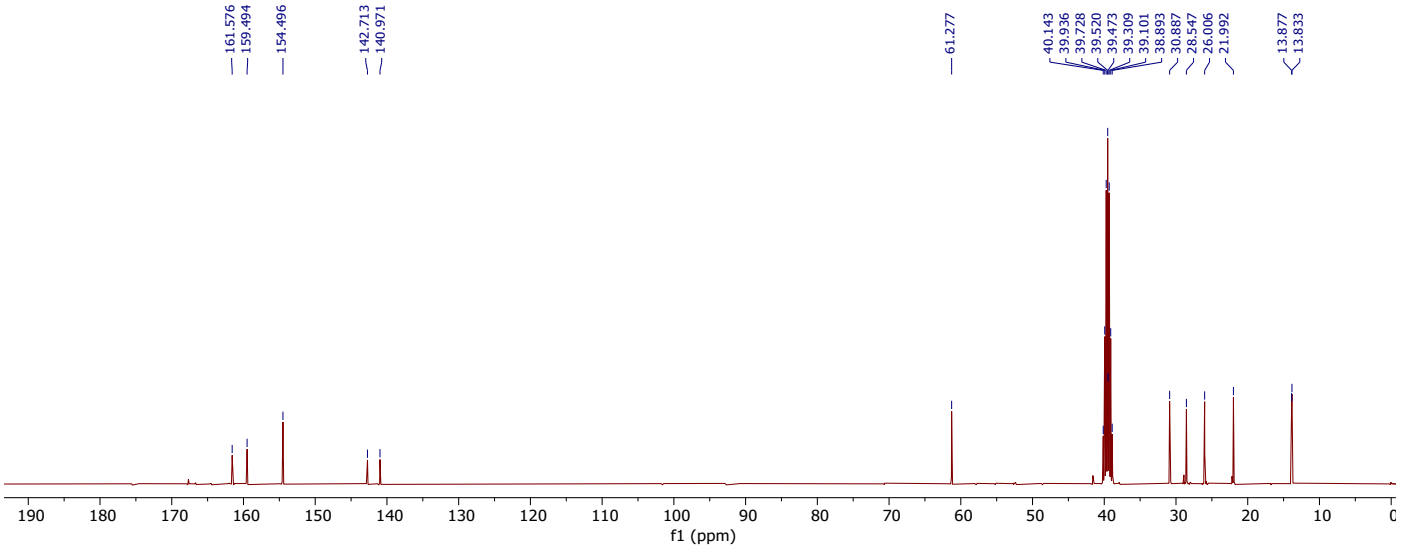

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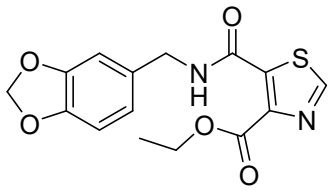
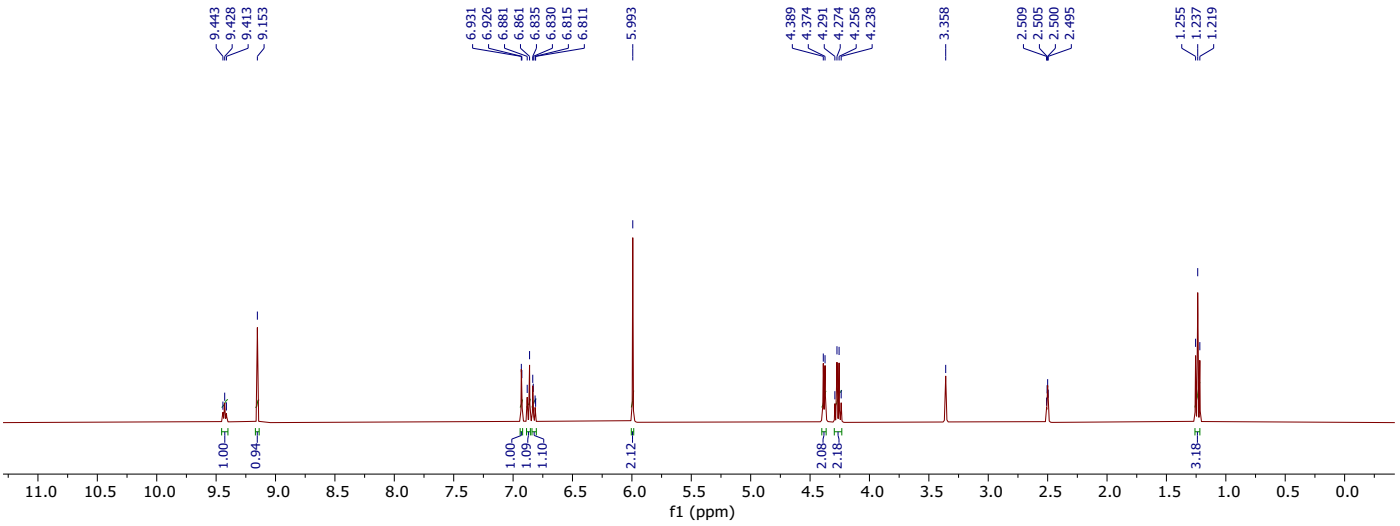
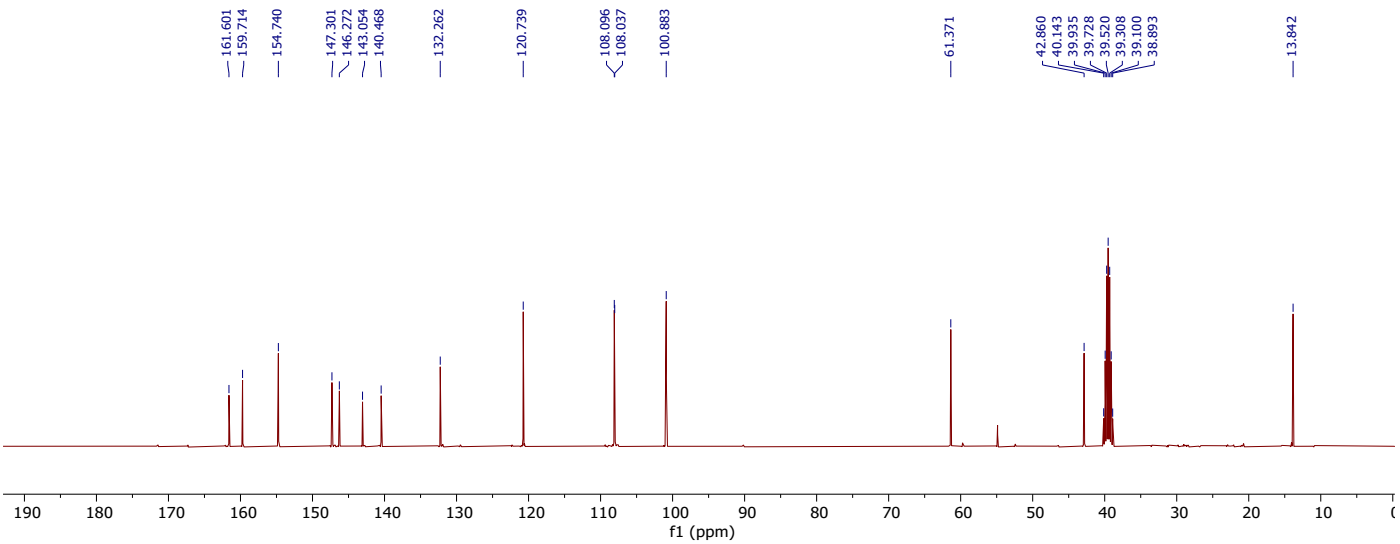


Ethyl-5-((benzo[d][1,3]dioxol-5-ylmethyl)carbamoyl)thiazoles-4-carboxylate (8i)



^{1}H NMR Spectra of Ethyl-5-((benzo[d][1,3]dioxol-5-ylmethyl)carbamoyl)thiazoles-4-carboxylate (8i)



^{13}C NMR Spectra of Ethyl-5-((benzo[d][1,3]dioxol-5-ylmethyl)carbamoyl)thiazoles-4-carboxylate (8i)

Materials and Methods

A single crystals **(5d & 8d)** with approximate dimensions 0.25mm × 0.22mm × 0.18mm and 0.23mm × 0.20mm × 0.15mm were selected for the X-ray diffraction study. The X-ray intensity data were collected on a Bruker Kappa Apex-II diffractometer having an X-rays tube containing Mo and Cu as a target. The graphite monochromator and CCD were used for recording the intensity peaks. APEX-II and SAINT software were used to carry-out for data collection and data reduction [1]. SHELXS97 was employed for structure solution [2] and SHELXL2018/3 was used for the structure refinement [3]. Anisotropic refinement was done for all the non-hydrogen atoms. A total of 309 parameters were refined with 6367 unique reflections for the molecule **5d** and 182 parameters were refined with 2689 unique reflections. The final residual factor, *R* converged to 0.0402 and 0.0686 and the goodness of fit were 1.016 and 1.330 for the molecules **5d** and **8d** respectively. The standard geometrical calculations were done using the program PLATON [4] and the thermal ellipsoidal plot was generated using the software Mercury4.0 [5].

References

1. Bruker APEX2 (Version 1.22) and SAINT-Plus (Version 7.06a), 2009.
2. Sheldrick, G. M. A short history of SHELX. Acta Crystallogr., Sect. A: Found. Crystallogr. 2008, 64, 112−122.
3. Sheldrick, G. M. Crystal structure refinement with SHELXL. Acta Crystallogr., Sect. C: Struct. Chem. 2015, 71, 3−8.
4. Spek, A. L. Single-crystal structure validation with the program PLATON. J. Appl. Crystallogr. 2003, 36, 7−13.
5. Macrae, C. F.; Sovago, I.; Cottrell, S. J.; Galek, P. T.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M. Mercury 4.0: from visualization to analysis, design and prediction. J. Appl. Crystallogr 2020, 53, 226.

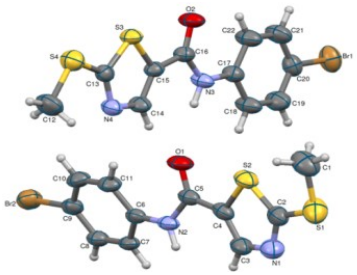


Figure 3. Single crystal structure of *N*-(4-bromophenyl)-2-(methyl-thio)thiazole-5-carboxamide (5d): CCDC Number-2119472

The structure of ***N*-(4-bromophenyl)-2-(methylthio)thiazole-5-carboxamide 5d** was confirmed by single-crystal X-ray diffraction studies (CCDC reference number 2119472), and its ORTEP diagram is depicted in Fig. 3. Crystal data of compound **5d** having molecular formula $C_{11}H_9BrN_2OS_2$ (M= 329.24g/mol), crystal system= Triclinic, space group P – 1, a = 10:6549(6) Å, b = 11:8312(6) Å, c = 12:7053(7) Å, α = 62.656(2)° β = 78.805(2)° γ = 65.198(2)°, V = 1291.45(12) $Å^3$, Z = 4, T = 296 K, μ(MoKα) = 3.490 mm^{-1}, *Dcalc* = 1.693g/cm^3, 46752 reflections measured (3.29° to 28.27°), R_{int} = 0.0507 which were used in all calculations. The final R_1 was 0.0402 (>2sigma(I)) and ωR2 was 0.1014.

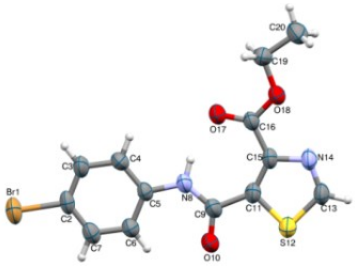


Figure 4. Single crystal structure Ethyl 5-((4-bromophenyl) carbamoyl)thiazole-4-carboxylate (8d): CCDC Number-2119473

The structure of **Ethyl 5-((4-bromophenyl)carbamoyl)thiazole-4-carboxylate 8d** was also confirmed by single-crystal X-ray diffraction studies (CCDC reference number 2119473), and its ORTEP diagram is depicted in Fig. 4. Crystal data of compound **8d** having molecular formula $C_{13}H_{11}BrN_2O_3S$ (M= 355.21/mol), crystal system= monoclinic, space group = P21/c, a = 6.5681(4) Å, b = 14.0924(9) Å, c = 15.4674(10) Å, α = 90° β = 94.190° γ = 90°, V = 1427.84(16) $Å^3$, Z = 4, T = 297 K, μ(CuKα) = 5.380 mm^{-1}, *Dcalc* = 1.652g/cm^3, 23502 reflections measured (4.25° to 70:44°) which were used in all calculations. The final R_1 was 0.0686 (>2sigma(I)) and ωR_2 was 0.1440.

Computational details on proposed reaction mechanism

The quantum chemical computations have been carried out at B3LYP methods with 6-31G(d,p) basis set in ethanol (PCM) model using Gaussian 09W software and the obtained results are visualized using GaussView 5.0 software. The geometry optimization and vibrational frequencies of reactants, intermediates and final product were calculated at 298.15 K. The optimized geometries of reactants, intermediates, and the product of the proposed mechanism are depicted in Figure 5. The reaction of tosylmethyl isocyanide **4** with methyl-2-oxo-2-(amino)ethanedithioates **3** was chosen for the calculations, forming the intermediates **10-14**, the most significant step is the formation **13** could be stable with –29.82 Kcal/mol, where methane thiolate attacks **13** at more electrophilic site of thiazole ring, to afford intermediate **14** with –6.79 Kcal/mol, after tosyl group elimination, the formation of product **5** with energy of –85.94 Kcal/mol was observed. However the energy of the product **5** is lower by –56.12 Kcal/mol compared to tosyl group situated at 2nd position of thiazole ring **13**.

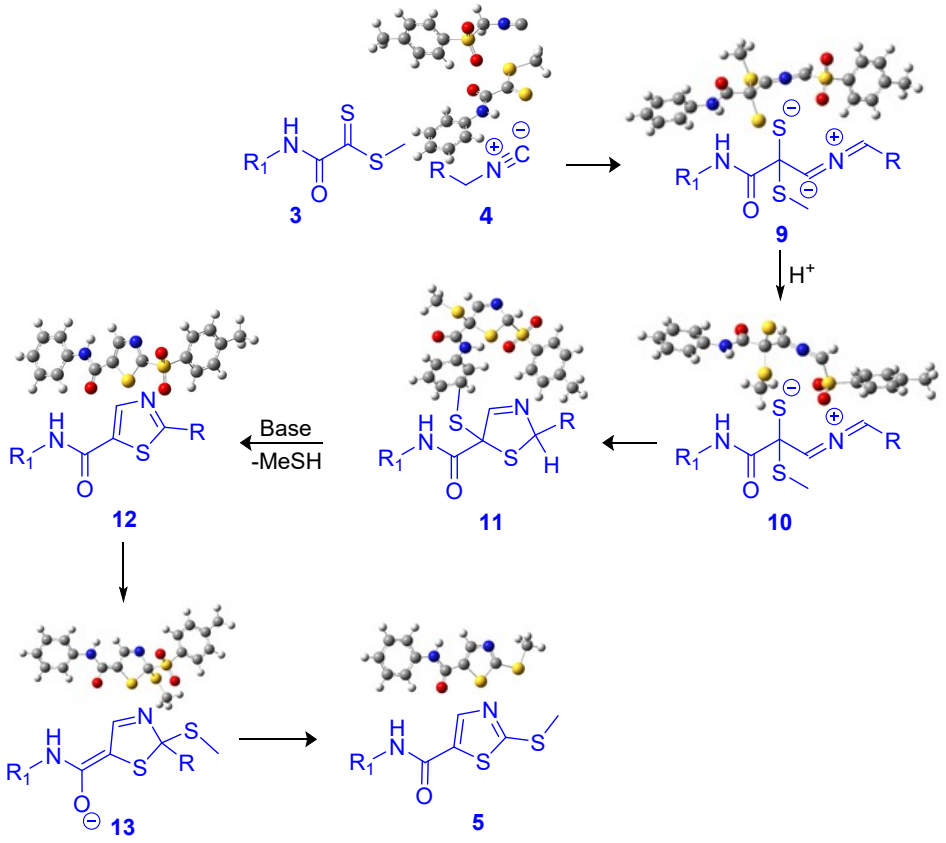


Figure 5. Optimized geometries of the reactants, intermediates and product of the proposed reaction mechanism, determined at the B3LYP/6-31G(d,p) level of theory in Ethanol (PCM).

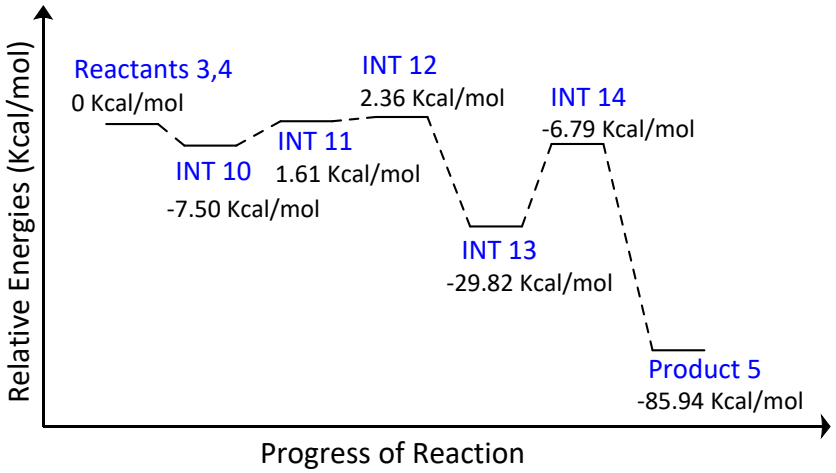


Figure 6. Relative energies of the reactants, intermediates (Int10–Int14) and product of the plausible reaction mechanism (Scheme 4), computed at the B3LYP/6-31G(d,p) level of theory in EtOH.