Double C-S Bonds Formation via Multiple Csp^3-H Bonds Cleavage: Synthesis of 4-Hydroxythiazoles from Amides and Elemental Sulfur under Metal-free Conditions

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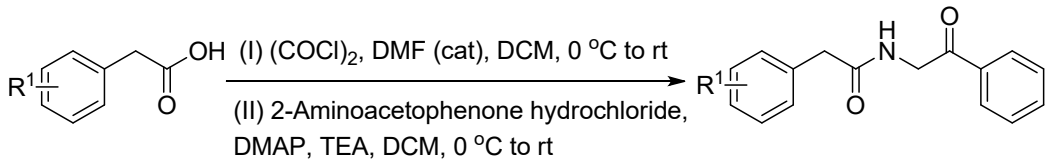
Supporting Information

1) General Information

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-500 instrument (500 MHz for ^{1}H; 125 MHz for ^{13}C) at room temperature, unless otherwise noted. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL mass spectrometer using ESI (electrospray ionization). Low-resolution mass spectra (LRMS) data were measured on GCMS-QP2010 Ultra. GC analyses were recorded on Hunan Huasi Instrument Co. Ltd GC 8010 gas chromstograph spectrometer using FID. Reactions were monitored by thin-layer chromatography. Column chromatography was performed on silica gel (200-300 mesh) using petroleum ether (PE)/ethyl acetate (EA).

2) Synthesis of Starting Materials [1, 2]

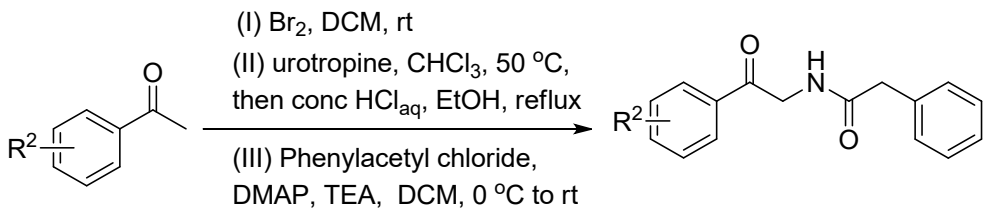
Method A:



Step I: Oxalyl chloride (2 equiv) was added to a solution of substituted phenylacetic acid (1.0 equiv)and DMF (4 drops) in CH_2Cl_2 at 0 °C drop-wise. The reaction was maintain at 0 °C for about 5 minutes and then allowed to warm to room temperature and was stirred for 3 h. The excess oxalyl chloride was removed under vacuum and the resulting crude acid chloride used in next step directly.

Step II: A solution of 2-Aminoacetophenone hydrochloride (1.0 equiv), DMAP (0.05 equiv) and TEA (2.0 equiv) was prepared in CH_2Cl_2 (10 mL) and cooled to 0 °C. The acyl chloride solution was added dropwise into the solution. After 5 minutes, the reaction was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford the pure product.

Method B:

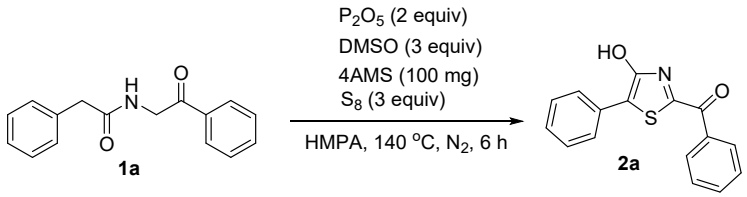


Step I: The appropriate ketone (1 eq.) was dissolved in dry DCM. Bromine (1 eq.) was added dropwise at room temperature under vigorous stirring. After complete addition, the mixture was stirred for additional 30 minutes at room temperature until decolorization. After addition of water and sodium sulfite the mixture was exracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed by rotary evaporation. The crude product was used directly in the next step without further purification.

Step II: substituted 2-Bromoacetophenone (1 equiv) and urotropine (1 equiv) were dissolved in 15 mL of dry chloroform. The reaction mixture was stirred at 50 °C for 2 h. A cloudy white precipitate was isolated by filtration and thoroughly washed with chloroform and ethanol to yield a white solid. This urotropinium salt was dissolved in 15 mL of absolute ethanol and concentrated hydrochloric acid. The mixture was heated to reflux for 2 h. The white solid was removed by filtration and washed with ethanol. The filtrate was evaporated under reduced pressure to yield substituted 2-Aminoacetophenone hydrochloride.

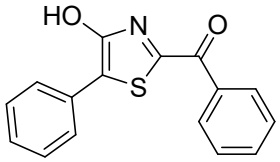
Step III: A solution of substituted 2-Aminoacetophenone hydrochloride (1.0 equiv), DMAP (0.05 equiv) and TEA (2.0 equiv) was prepared in CH_2Cl_2 (10 mL) and cooled to 0 °C. The Phenylacetyl chloride (1.0 equiv) solution was added dropwise into the solution. After 5 minutes, the reaction was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford the pure product.

3) Typical Procedures

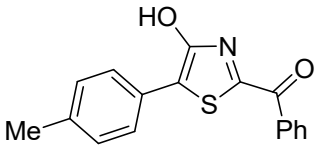


The sealed Schlenk tube was charged with (4-hydroxy-5-phenylthiazol-2-yl) (phenyl)methanone **1a** (0.2 mmol, 1 equiv), S_8 (0.075 mmol, 3 equiv), 4Å MS (100 mg), DMSO (0.6 mmol, 3 equiv), P_2O_5 (0.4 mmol, 2 equiv) and HMPA (2 mL). Then under the protection of nitrogen atmosphere, the mixture was stirred at 140 °C for 6 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, quenched by water and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford the pure product (**2a**).

4) Characterization Data of Products

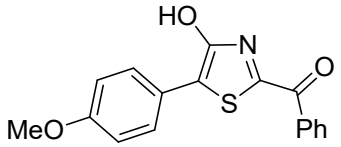


(4-Hydroxy-5-phenylthiazol-2-yl)(phenyl)methanone (2a): Yellow solid (43.3 mg, 77%); mp: 201-203 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.10 (s, 1H), 8.35 (d, *J* = 7.5 Hz, 2H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.3, 159.9, 157.9, 135.5, 134.1, 131.2, 131.1, 129.6, 129.0, 128.5, 127.5, 118.7; HRMS (ESI) m/z calcd for $C_{16}H_{12}NO_2S^+$ $(M+H)^+$ 282.0583, found 282.0591.

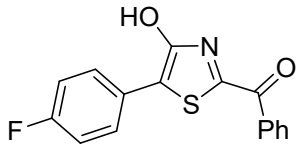


(4-Hydroxy-5-(p-tolyl)thiazol-2-yl)(phenyl)methanone (2b):Yellow solid (44.9 mg,

76%); mp: 169-171 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.96 (s, 1H), 8.34 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* =8.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.2, 159.5, 157.2, 138.1, 135.5, 134.0, 131.0, 130.1, 129.0, 128.4, 127.4, 119.2, 21.4; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_2S^+$ $(M+H)^+$ 296.0740, found 296.0742.

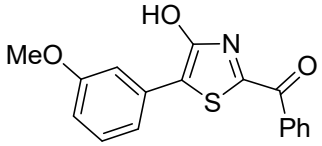


(4-Hydroxy-5-(4-methoxyphenyl)thiazol-2-yl)(phenyl)methanone (2c): Yellow solid (49.8 mg, 80%); mp: 196-198 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.88 (s, 1H), 8.33 (d, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.70 (t, *J* = 7.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.02 (d, *J* =8.5 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.1, 159.6, 159.0, 156.5, 135.6, 133.9, 131.0, 129.0, 129.0, 123.6, 119.5, 115.0, 55.8; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_3S^+$ $(M+H)^+$ 312.0689, found 312.0702.

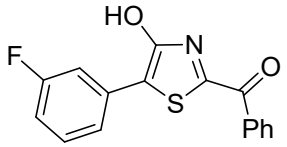


(5-(4-Fluorophenyl)-4-hydroxythiazol-2-yl)(phenyl)methanone (2d): Yellow solid (37.1 mg, 62%); mp: 174-176 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.10 (s, 1H), 8.34 (d, *J* = 7.5 Hz, 2H), 7.91-7.88 (m, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.2, 162.0 (d, *J* = 244.8), 159.6, 157.8, 135.4, 134.1, 131.0, 129.6 (d, *J* = 8.1 Hz), 129.0, 127.8 (d, *J* = 3.4 Hz), 117.6, 116.5 (d, *J* = 21.6 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{11}FNO_2S^+$

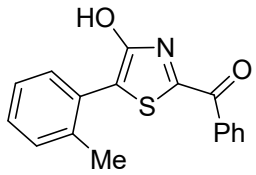
$(M+H)^+$ 300.0489, found 300.0503.



(4-Hydroxy-5-(3-methoxyphenyl)thiazol-2-yl)(phenyl)methanone (2e): Yellow solid (47.9 mg, 77%); mp: 195-196 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.08 (s, 1H), 8.34 (d, *J* = 6.0 Hz, 2H), 7.71-7.36 (m, 6H), 6.93 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.3, 160.0, 159.9, 157.9, 135.4, 134.0, 132.4, 131.1, 130.7, 129.0, 120.0, 118.4, 114.0, 112.8, 55.7; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_3S^+$ $(M+H)^+$ 312.0689, found 312.0704.

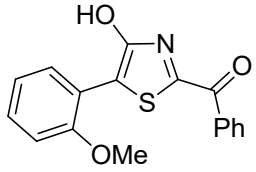


(5-(3-Fluorophenyl)-4-hydroxythiazol-2-yl)(phenyl)methanone (2f): Yellow solid (38.9 mg, 65%); mp: 204-206 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.31 (s, 1H), 8.34 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.49-7.44 (m, 1H), 7.15 (td, *J* = 8.5 Hz, *J* = 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.2, 162.8 (d, *J* = 241.9 Hz), 160.3, 158.7, 135.3, 134.1, 133.5 (d, *J* = 8.9 Hz), 131.5 (d, *J* = 8.6 Hz), 131.0, 129.0, 123.6 (d, *J* = 2.3 Hz), 116.9 (d, *J* = 3.6 Hz), 115.0 (d, *J* = 20.8), 113.7 (d, *J* = 23.8), HRMS (ESI) m/z calcd for $C_{16}H_{11}FNO_2S^+$ $(M+H)^+$ 300.0489, found 300.0504.

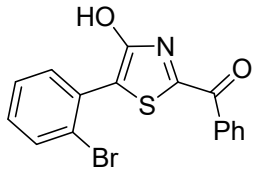


(4-Hydroxy-5-(o-tolyl)thiazol-2-yl)(phenyl)methanone (2g): Yellow solid (49.6 mg,

84%); mp: 130-132 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.52 (s, 1H), 8.37 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.32-7.25 (m, 3H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.3, 159.7, 159.6, 137.9, 135.5, 134.0, 131.6, 131.1, 129.5, 129.3, 129.0, 126.4, 117.8, 20.7; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_2S^+$ $(M+H)^+$ 296.0740, found 296.0745.

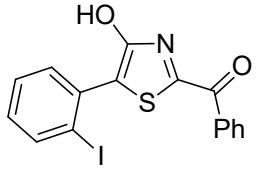


(4-Hydroxy-5-(2-methoxyphenyl)thiazol-2-yl)(phenyl)methanone (2h): Yellow solid (28.6 mg, 46%); mp: 153-155 °C;^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.93 (s, 1H), 8.34 (d, *J* = 7.5 Hz, 2H), 8.29 (d, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 184.2, 161.3, 158.2, 155.4, 136.0, 133.8, 130.9, 129.7, 128.9, 121.2, 120.1, 113.2, 112.1, 56.3; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_3S^+$$(M+H)^+$ 312.0689, found 312.0703.

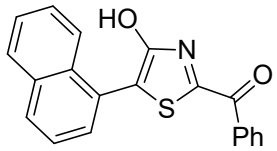


(5-(2-Bromophenyl)-4-hydroxythiazol-2-yl)(phenyl)methanone (2i): Yellow solid (31.7 mg, 44%); mp: 150-152 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.70 (s, 1H), 8.37 (d, *J* = 7.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.67 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.37 (td, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.5, 160.7, 160.0,

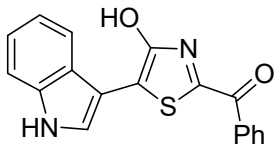
135.3, 134.2, 133.7, 133.3, 131.1, 131.0, 129.0, 128.4, 124.0, 115.9; HRMS (ESI) m/z calcd for $C_{16}H_{11}BrNO_2S^+$ $(M+H)^+$ 359.9688, found 359.9701.



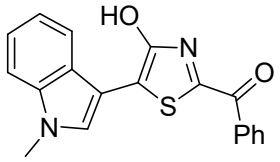
(4-Hydroxy-5-(2-iodophenyl)thiazol-2-yl)(phenyl)methanone (2j): Yellow solid (36.6 mg, 45%); mp: 108-110 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.59 (s, 1H), 8.38 (d, *J* = 7.5 Hz, 2H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 2H), 7.55-7.54 (m, 1H), 7,49 (t, *J* = 7.5 Hz, 1H), 7.17 (td, *J* = 8.0 Hz, J = 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.4, 160.2, 159.7, 139.9, 135.4, 135.0, 134.2, 132.7, 131.1, 131.1, 129.1, 128.9, 119.7, 101.8; HRMS (ESI) m/z calcd for $C_{16}H_{10}INO_2S^+$ $(M+H)^+$ 407.9550, found 407.9561.



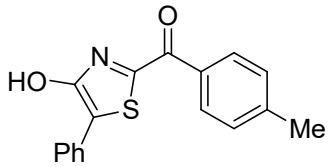
(4-Hydroxy-5-(naphthalen-1-yl)thiazol-2-yl)(phenyl)methanone (2k): Yellow solid (45.7 mg, 69%); mp: 82-84 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.54 (s, 1H), 8.42 (d, *J* = 8.0 Hz, 2H), 8.04-8.01 (m, 2H), 7.91 (dd, *J* =6 Hz, *J* = 3.5 Hz, 1H), 7.73 (t, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 7.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 2H), 7.61-7.57 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.4, 160.2, 160.2, 135.5, 134.1, 133.9, 131.6, 131.1, 130.1, 129.8, 129.0, 128.9, 127.4, 127.3, 126.8, 126.1, 126.0, 116.3; HRMS (ESI) m/z calcd for $C_{20}H_{13}NO_2S^+$ $(M+H)^+$ 332.0667, found 332.0679.



(4-Hydroxy-5-(1H-indol-3-yl)thiazol-2-yl)(phenyl)methanone (2l): Yellow solid (43.6 mg, 68%); mp: 91-93 ^{o}C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.82 (s, 1H), 11.77 (s, 1H), 8.37 (d, *J* = 6.5 Hz, 2H), 8.14 (s, 1H), 7.92 (d, *J* = 5.0 Hz, 1H), 7.68-7.53 (m, 4H), 7.26-7.22 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 182.7, 159.2, 153.4, 136.8, 136.2, 133.5, 130.8, 128.9, 127.0, 125.1, 122.9, 121.1, 119.7, 117.5, 113.0, 106.5; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_2O_2S^+$ $(M+H)^+$ 321.0692, found 321.0708.

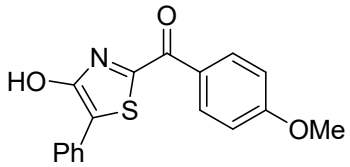


(4-Hydroxy-5-(1-methyl-1H-indol-3-yl)thiazol-2-yl)(phenyl)methanone (2m): Yellow solid (58.9 mg, 88%); mp: 84-86 ^{o}C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.86 (s, 1H), 8.36 (d, *J* = 6.5 Hz, 2H), 8.12 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.68-7.54 (m, 4H), 7.30-7.26 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 182.6, 159.1, 153.4, 137.2, 136.2, 133.4, 130.9, 130.8, 128.9, 125.4, 123.0, 121.2, 119.9, 117.1, 111.2, 105.6, 33.4; HRMS (ESI) m/z calcd for $C_{19}H_{14}N_2O_2S^+$ $(M+H)^+$ 335.0775, found 321.0787.

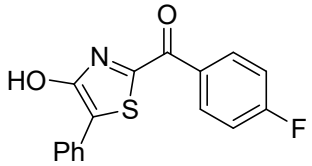


(4-Hydroxy-5-phenylthiazol-2-yl)(p-tolyl)methanone (2n) :Yellow solid (46.7 mg, 79%); mp: 221-223 ^{o}C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.01 (s, 1H), 8.31 (d, *J* =

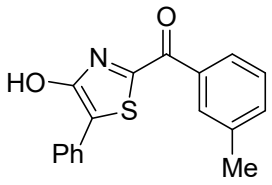
6.5 Hz, 2H), 7.86 (d, *J* = 6.5 Hz, 2H), 7.44 (t, *J* = 6.5 Hz, 2H), 7.38 (d, *J* = 6.5 Hz, 2H), 7.33 (t, *J* = 6.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 182.4, 159.7, 158.3, 144.8, 132.7, 131.3, 131.2, 129.6, 129.5, 128.3, 127.4, 118.3, 21.8; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_2S^+$ $(M+H)^+$ 296.0740, found 296.0748.



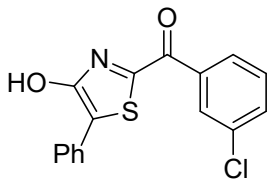
(4-Hydroxy-5-phenylthiazol-2-yl)(4-methoxyphenyl)methanone (2o): Yellow solid (53.5 mg, 86%); mp: 206-208 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.01 (s, 1H), 8.46 (d, *J* = 9.0 Hz, 2H), 7.86 (d, *J* = 7.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 181.1, 164.3, 159.6, 158.7, 133.7, 131.3, 129.5, 128.3, 127.8, 127.4, 117.9, 114.4, 56.2; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_3S^+$$(M+H)^+$ 312.0689, found 312.0701.



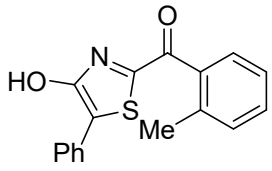
(4-Fluorophenyl)(4-hydroxy-5-phenylthiazol-2-yl)methanone (2p): Yellow solid (38.9 mg, 65%); mp: 225-227 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.10 (s, 1H), 8.50-8.47 (m, 2H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.47-7.42 (m, 4H), 7.34 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 181.5, 165.9 (d, *J* = 251.3 Hz), 159.8, 157.8, 134.2 (d, *J* = 9.4 Hz), 132.0 (d, *J* = 2.6 Hz), 131.2, 129.6, 128.5, 127.5, 118.8, 116.2 (d, *J* = 21.8 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{11}FNO_2S^+$ $(M+H)^+$ 300.0489, found 300.0502.



(4-Hydroxy-5-phenylthiazol-2-yl)(m-tolyl)methanone (2q): Yellow solid (40.7 mg, 69%); mp: 209-210 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.01(s, 1H), 8.18 (d, *J* = 6.5 Hz, 1H), 8.10 (s, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.52-7.42 (m, 4H), 7.34 (t, *J* = 6.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.4, 159.8, 157.9, 138.3, 135.5, 134.6, 131.2, 131.1, 129.5, 128.8, 128.4, 128.3, 127.4, 118.5, 21.4; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_2S^+$ $(M+H)^+$ 296.0740, found 296.0746.

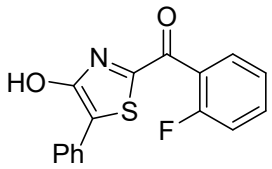


(3-Chlorophenyl)(4-hydroxy-5-phenylthiazol-2-yl)methanone (2r): Yellow solid (36.0 mg, 57%); mp: 219-220 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.14 (s, 1H), 8.39-8.38 (m, 1H), 8.25 (d, *J* = 7.5, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.80-7.78 (m, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 181.8, 159.9, 157.2, 137.3, 133.7, 133.7, 131.1, 131.0, 130.6, 129.5, 129.5, 128.5, 127.5, 119.4; HRMS (ESI) m/z calcd for $C_{16}H_{11}ClNO_2S^+$ $(M+H)^+$ 315.0121, found 315.0134.

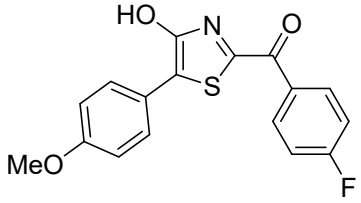


(4-Hydroxy-5-phenylthiazol-2-yl)(o-tolyl)methanone (2s): Yellow solid (44.3 mg, 75%); mp: 214-215 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.07 (s, 1H), 7.86 (d, *J*

= 7.5 Hz, 2H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.48-7.43 (m, 3H), 7.36-7.32 (m, 3H), 2.35 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 188.0, 160.1, 157.8, 137.1, 136.8, 131.5, 131.3, 131.2, 130.0, 129.5, 128.4, 127.4, 125.8, 119.0, 20.1; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_2S^+$ $(M+H)^+$ 296.0740, found 296.0747.

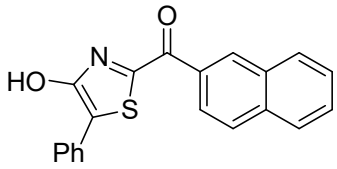


(2-Fluorophenyl)(4-hydroxy-5-phenylthiazol-2-yl)methanone (2t): Yellow solid (36.5 mg, 61%); mp: 171-173 °C;^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.10 (s, 1H), 7.87-7.82 (m, 3H), 7.69-7.65 (m, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.42-7.33 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.5, 160.2, 160.1 (d, *J* = 250.1 Hz), 156.7, 134.5 (d, *J* = 8.5 Hz), 131.6, 131.1, 129.5, 128.6, 127.5, 125.6 (d, *J* = 14.0 Hz), 124.9 (d, *J* = 3.3 Hz), 119.7, 116.8 (d, *J* = 21.0 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{11}FNO_2S^+$ $(M+H)^+$ 300.0489, found 300.0501.

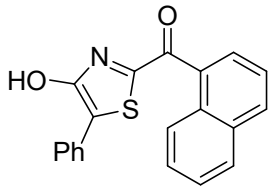


(4-Fluorophenyl)(4-hydroxy-5-(4-methoxyphenyl)thiazol-2-yl)methanone (2u): Yellow solid (43.5 mg, 66%); mp: 208-210 °C;^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.91 (s, 1H), 8.49-8.46 (m, 2H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.43 (t, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 181.3, 165.7 (d, *J* = 251.4 Hz), 159.6, 159.0, 156.3, 134.0 (d, *J* = 9.4 Hz), 132.1, 129.0, 123.6, 119.6, 116.1 (d, *J* = 21.6 Hz), 115.0, 55.8; HRMS (ESI) m/z calcd for

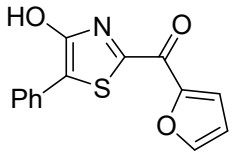
$C_{17}H_{13}FNO_3S^+$ $(M+H)^+$ 330.0595, found 330.0611.



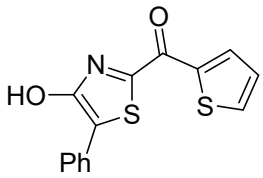
(4-Hydroxy-5-phenylthiazol-2-yl)(naphthalen-2-yl)methanone (2v): Yellow solid (44.4 mg, 67%); mp: 222-224 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.09 (s, 1H), 9.12 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 183.1, 159.8, 158.1, 135.6, 133.4, 132.8, 132.5, 132.3, 131.2, 130.2, 129.5, 128.6, 128.4, 128.3, 127.6, 127.5, 126.1, 118.6; HRMS (ESI) m/z calcd for $C_{20}H_{13}NO_2S^+$ $(M+H)^+$ 332.0667, found 332.0677.



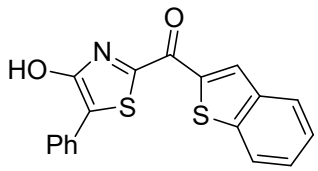
(4-Hydroxy-5-phenylthiazol-2-yl)(naphthalen-1-yl)methanone (2w)： Yellow solid (41.1 mg, 62%); mp: 135-137 °C;^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.08 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.14-8.04 (m, 3H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.62-7.60 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 187.1, 160.2, 158.2, 133.9, 133.7, 132.5, 131.2, 130.6, 129.9, 129.6, 129.1, 128.5, 128.2, 127.5, 127.1, 125.4, 125.2, 119.4; HRMS (ESI) m/z calcd for $C_{20}H_{13}NO_2S^+$ $(M+H)^+$ 332.0667, found 332.0675.



Furan-2-yl(4-hydroxy-5-phenylthiazol-2-yl)methanone (2x)： Yellow solid (30.9 mg, 57%); mp: 180-182 °C;^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.03 (s, 1H), 8.21 (s, 1H), 8.17 (d, *J* = 3.5 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 6.88 (dd, *J* = 3.5 Hz, *J* = 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 169.8, 159.7, 156.8, 150.2, 149.6, 131.2, 129.5, 128.3, 127.4, 124.4, 118.1, 113.6; HRMS (ESI) m/z calcd for $C_{14}H_{10}NO_3S^+$ $(M+H)^+$ 272.0376, found 272.0392.

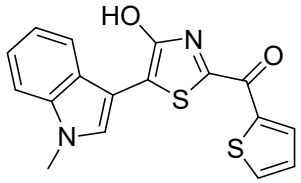


(4-Hydroxy-5-phenylthiazol-2-yl)(thiophen-2-yl)methanone (2y)： Yellow solid (31.6 mg, 55%); mp: 103-105 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.05 (s, 1H), 8.64 (d, *J* = 4.0 Hz, 1H), 8.19 (d, *J* = 4.5 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 4.0 Hz, 1H), 7.33 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 174.7, 159.6, 157.1, 140.0, 137.9, 137.3, 131.2, 129.5, 129.4, 128.4, 127.4, 118.6; HRMS (ESI) m/z calcd for $C_{14}H_{10}NO_2S_2^+$ $(M+H)^+$ 288.0147, found 288.0161.



Benzo[b]thiophen-2-yl(4-hydroxy-5-phenylthiazol-2-yl)methanone (2z)： Yellow solid (31.5 mg, 52%); mp: 210-212 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.16 (s,

1H), 9.04 (s, 1H), 8.10 (t, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 176.0, 159.9, 156.7, 142.8, 140.0, 139.5, 134.8, 131.1, 129.6, 128.8, 128.6, 127.5, 127.2, 126.0, 123.6, 119.2; HRMS (ESI) m/z calcd for $C_{18}H_{11}NO_2S_2^+$ $(M+H)^+$ 338.0231, found 338.0246.



(4-Hydroxy-5-(1-methyl-1H-indol-3-yl)thiazol-2-yl)(thiophen-2-yl)methanone(2aa)： Yellow solid (47.0 mg, 69%); mp: 87-89 ^{o}C;^{1}H NMR (DMSO-d_6, 500 MHz) δ = 11.84 (s, 1H), 8.63 (d, *J* = 3.0 Hz, 1H), 8.13 (d, *J* = 5.0 Hz, 1H), 8.12 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 4.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 174.2, 158.9, 152.5, 140.7, 137.2, 136.7, 136.3, 130.9, 129.2, 125.4, 123.0, 121.2, 119.9, 116.9, 111.2, 105.6, 33.4; HRMS (ESI) m/z calcd for $C_{17}H_{12}N_2O_2S_2^+$ $(M+H)^+$ 341.0341, found 341.0356.

5) References.

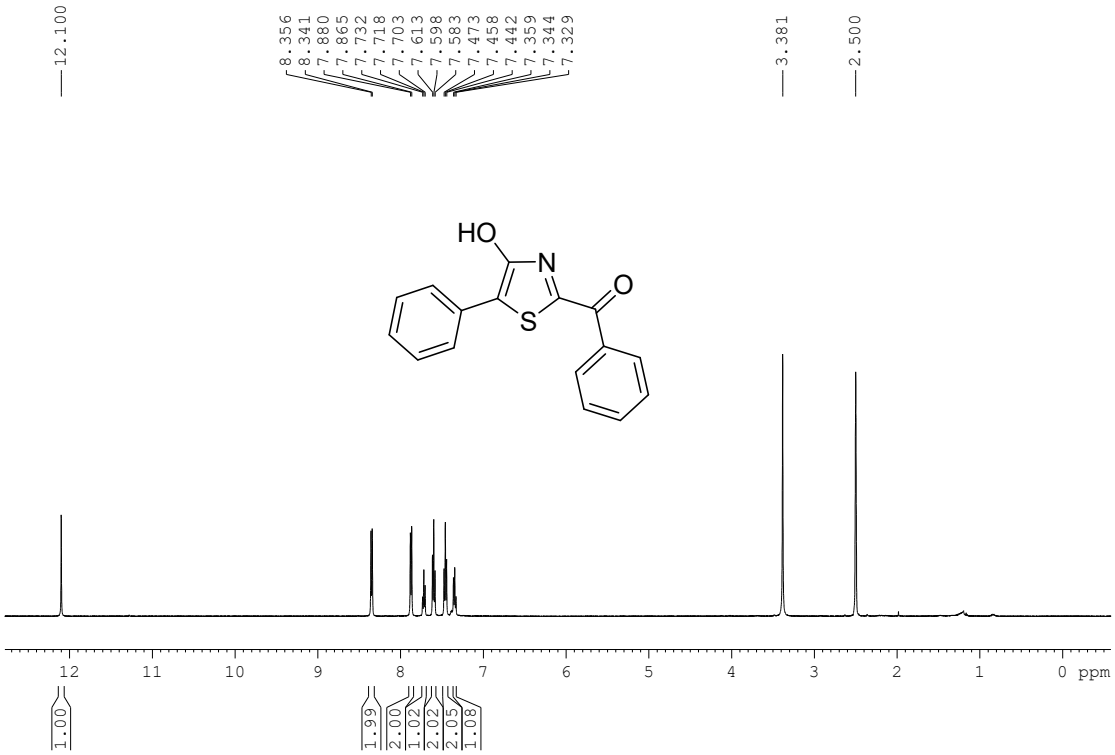
1. *(a)* T. Inoue, M. Morita, T. Tojo, A. Nagashima, A. Moritomo and H. Miyake, Novel 1H-imidazol-2-amine Derivatives as Potent and Orally Active Vascular Adhesion Protein-1 (VAP-1) Inhibitors for Diabetic Macular Edema Treatment, *Bioorg. Med. Chem*., 2013, **21**, 3873-3881; *(b)* X. Luo, Y. Xu, G. Xiao, W. Liu, C. Qian, G. Deng, J. Song, Y. Liang and C. Yang, Palladium-Catalyzed Tandem Reaction of Three Aryl Iodides Involving Triple C-H Activation, *Org. Lett*., 2018, **20**, 2997-3000.

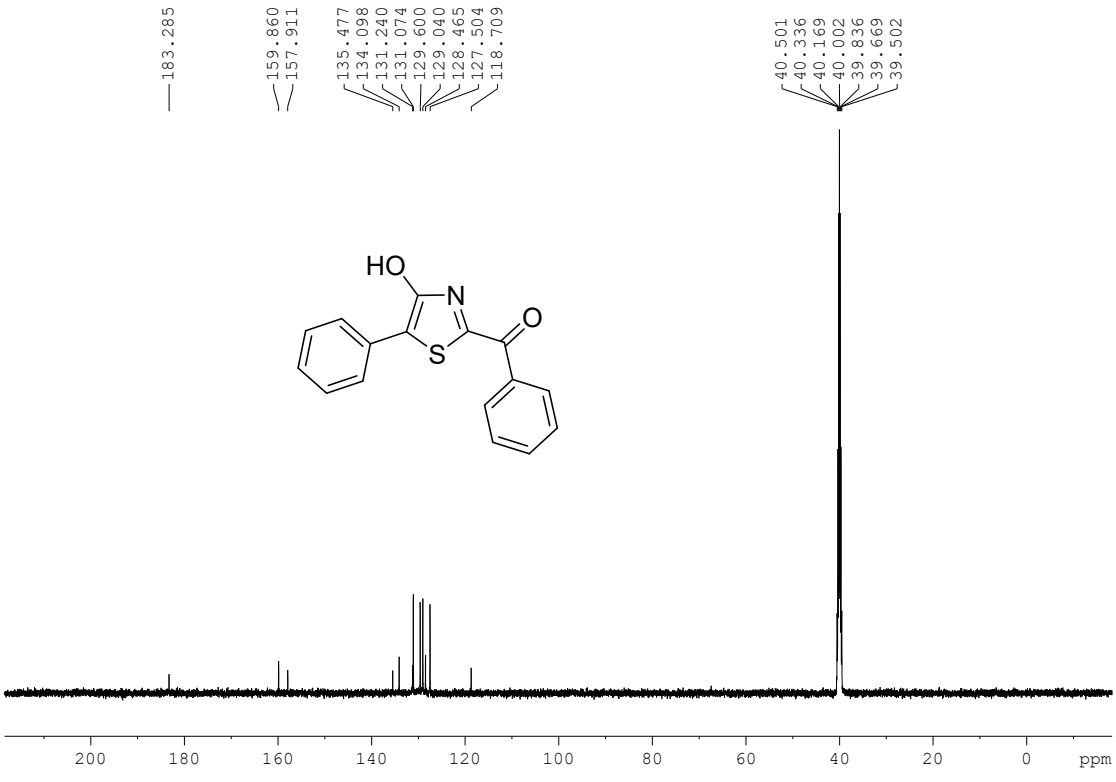
2. M. Günther, J. Lategahn, M. Juchum, E. Döring, M. Keul, J. Engel, H. Tumbrink,

D. Rauh and S. Laufer, Trisubstituted Pyridinylimidazoles as Potent Inhibitors of the Clinically Resistant L858R/T790M/C797S EGFR Mutant: Targeting of Both Hydrophobic Regions and the Phosphate Binding Site, *J. Med. Chem.,* 2017*,* **60***,* 5613-5637.

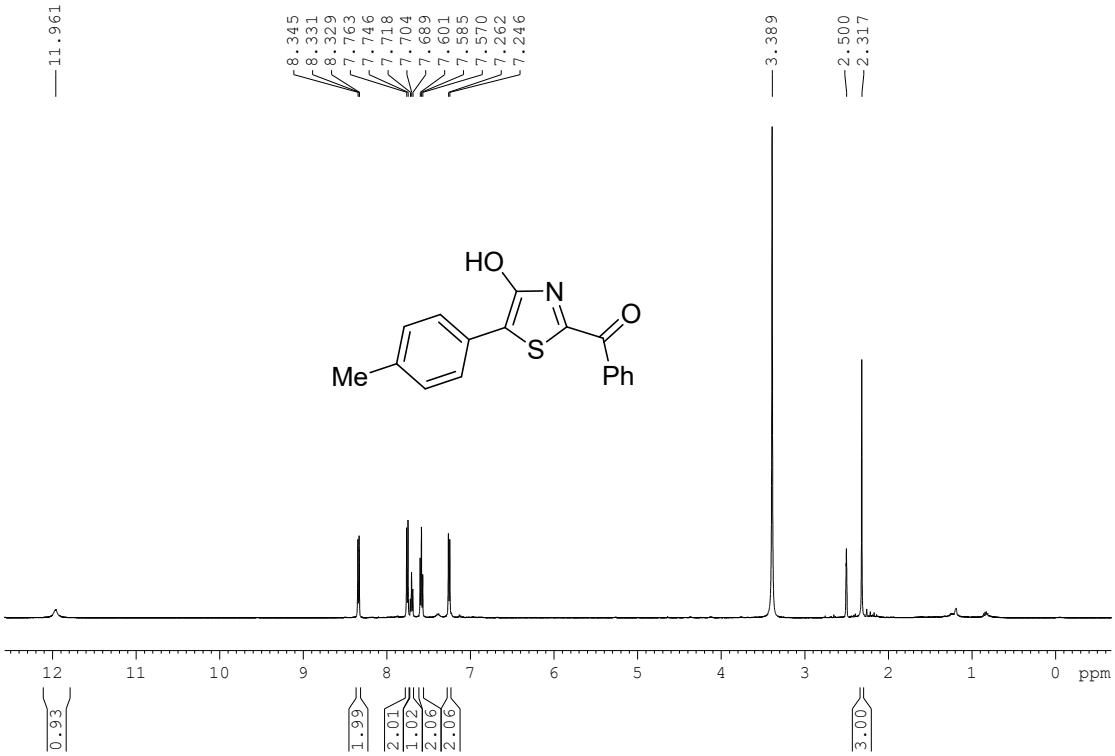
6) ^{1}H NMR and ^{13}C NMR Spectra of Products

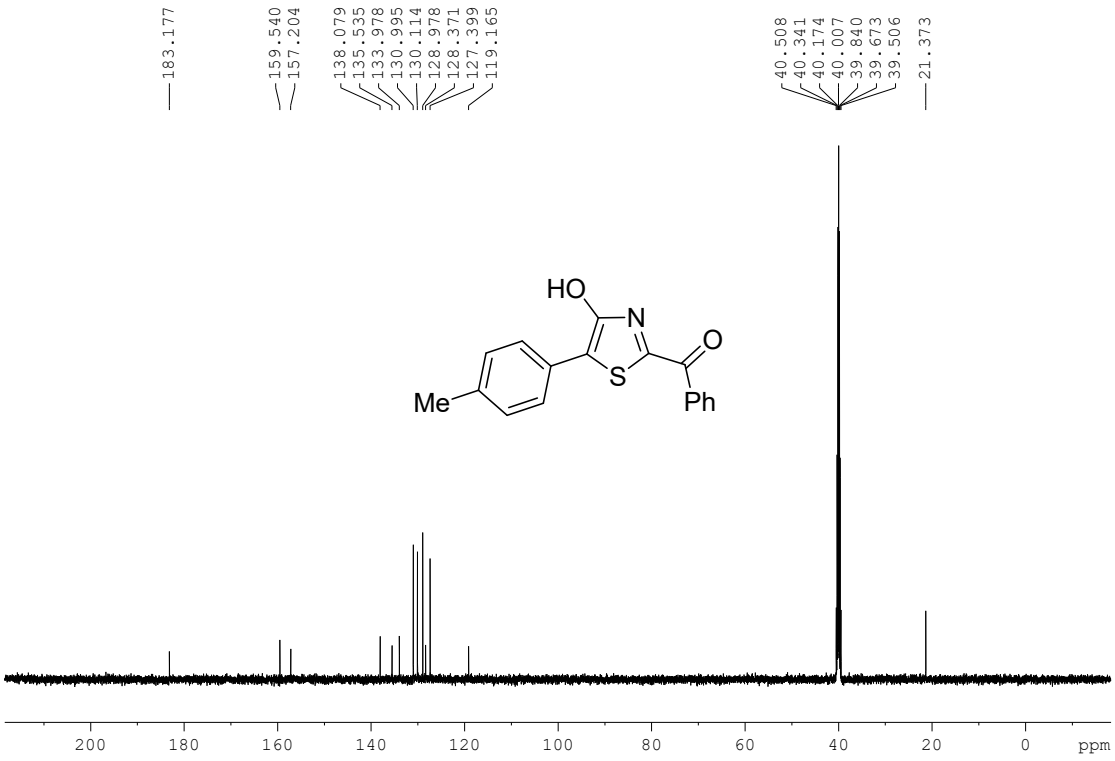
^{1}H and ^{13}C Spectrum of Compound **2a**



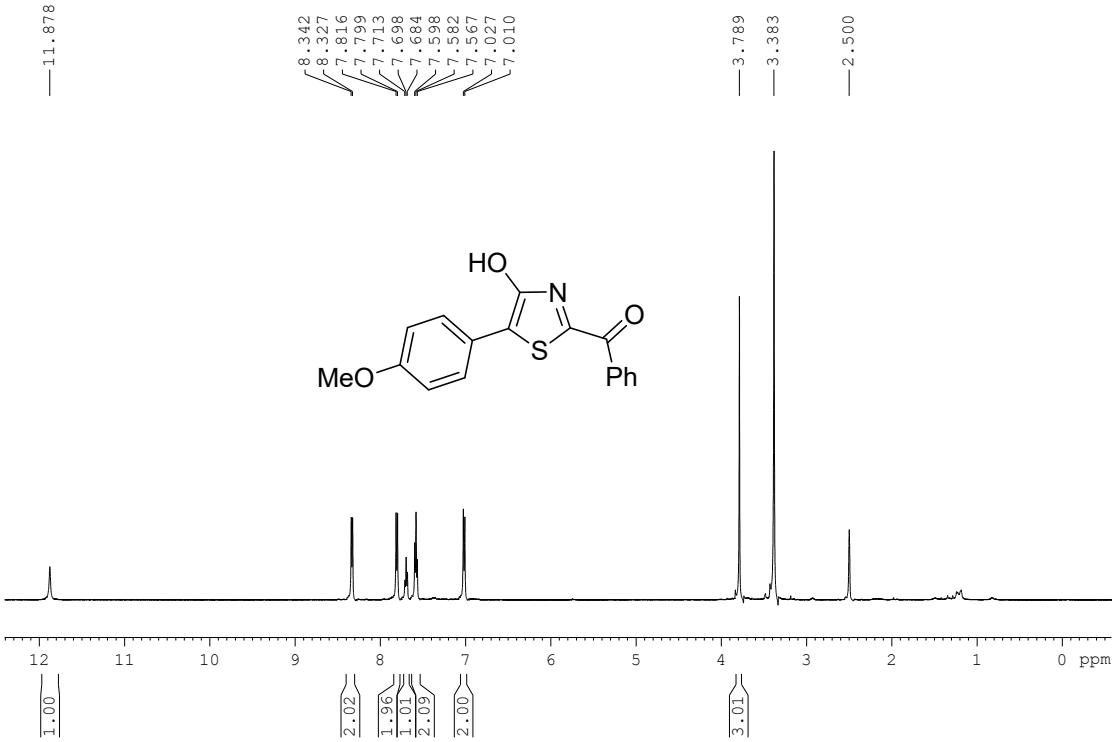


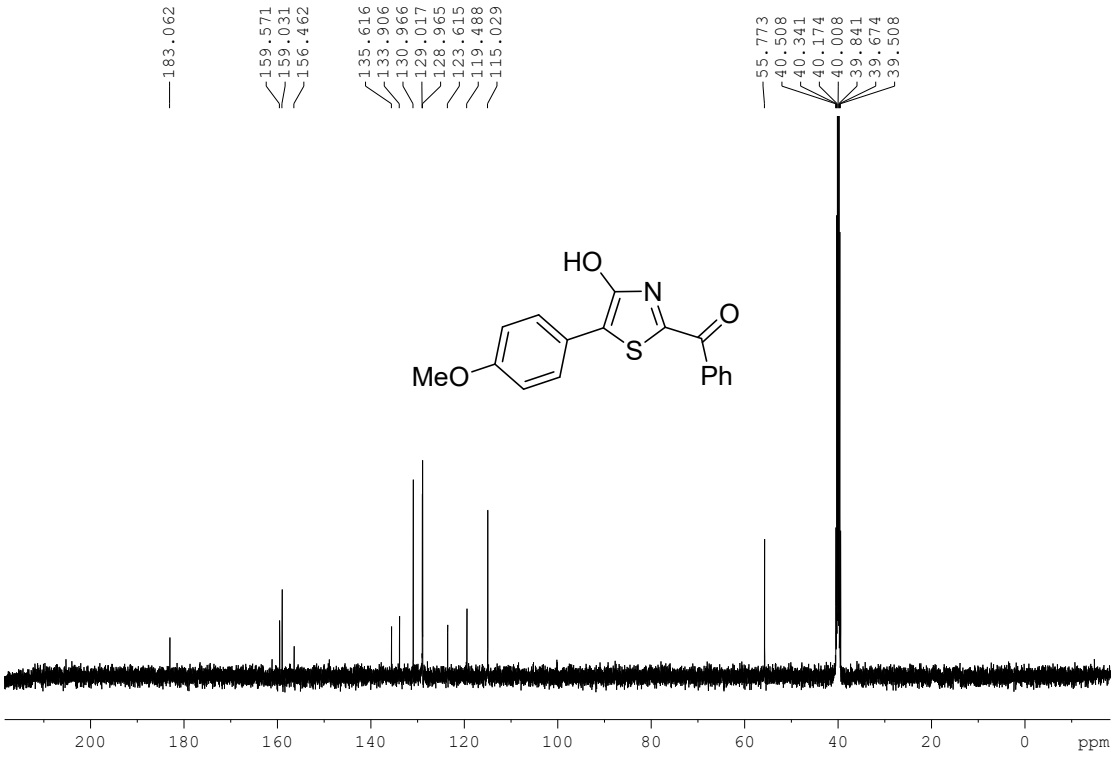
^{1}H and ^{13}C Spectrum of Compound **2b**



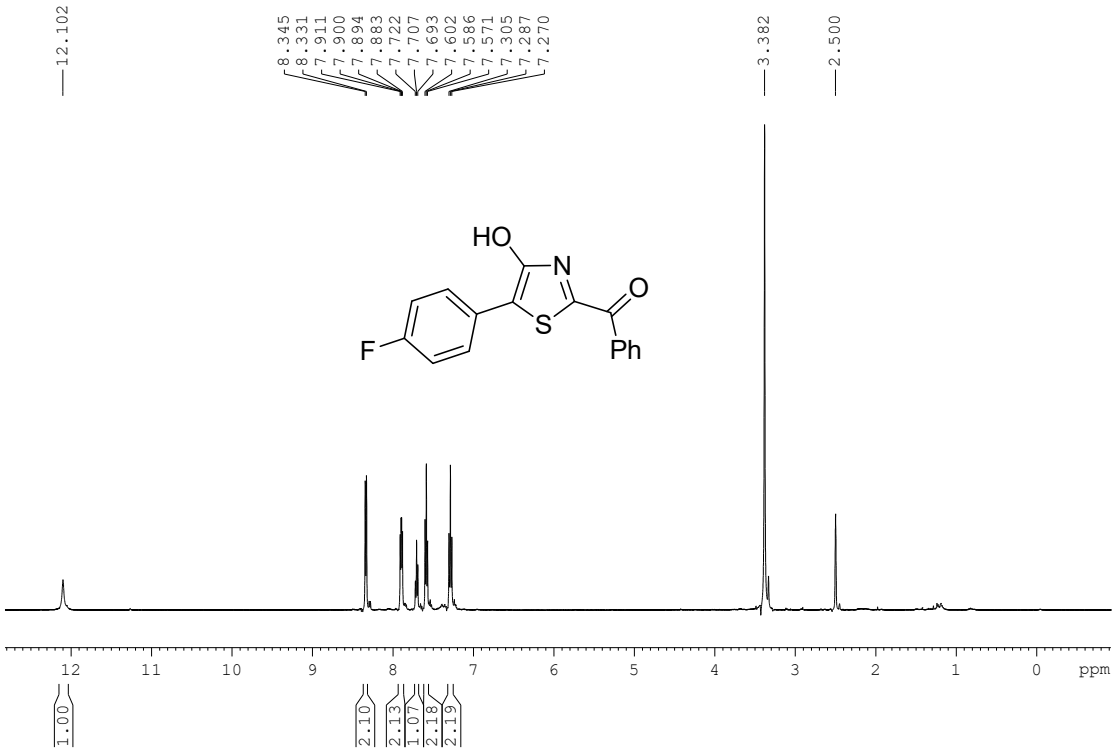


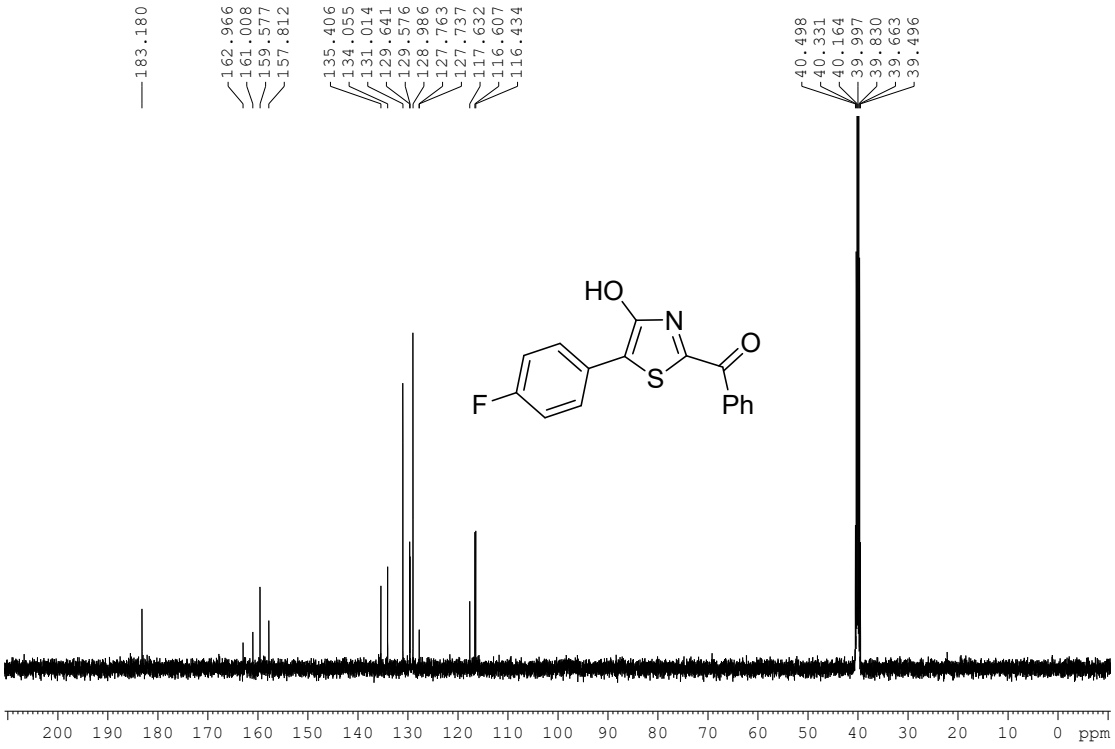
^{1}H and ^{13}C Spectrum of Compound **2c**



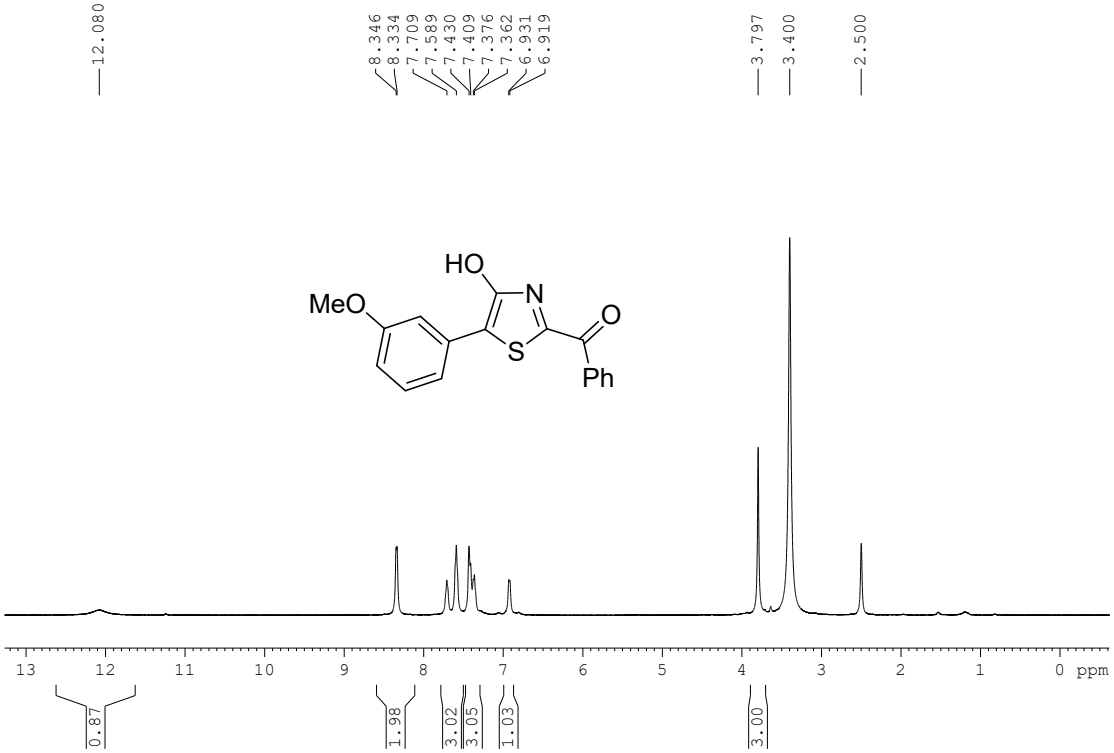


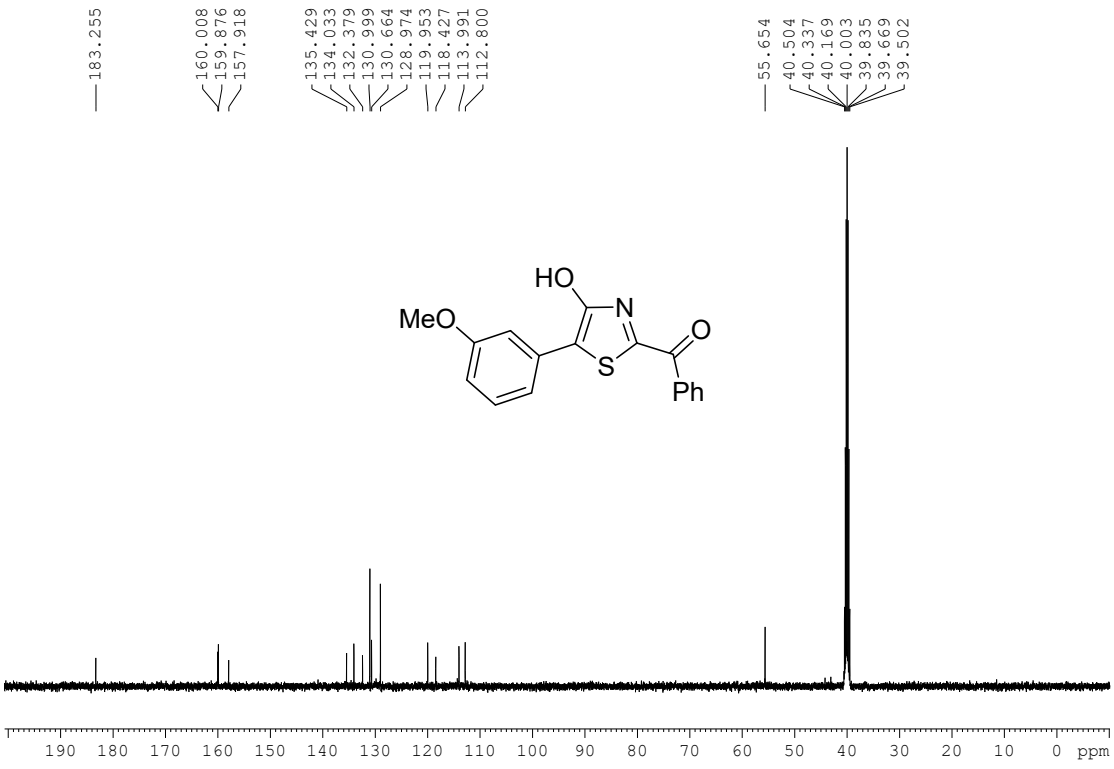
^{1}H and ^{13}C Spectrum of Compound **2d**



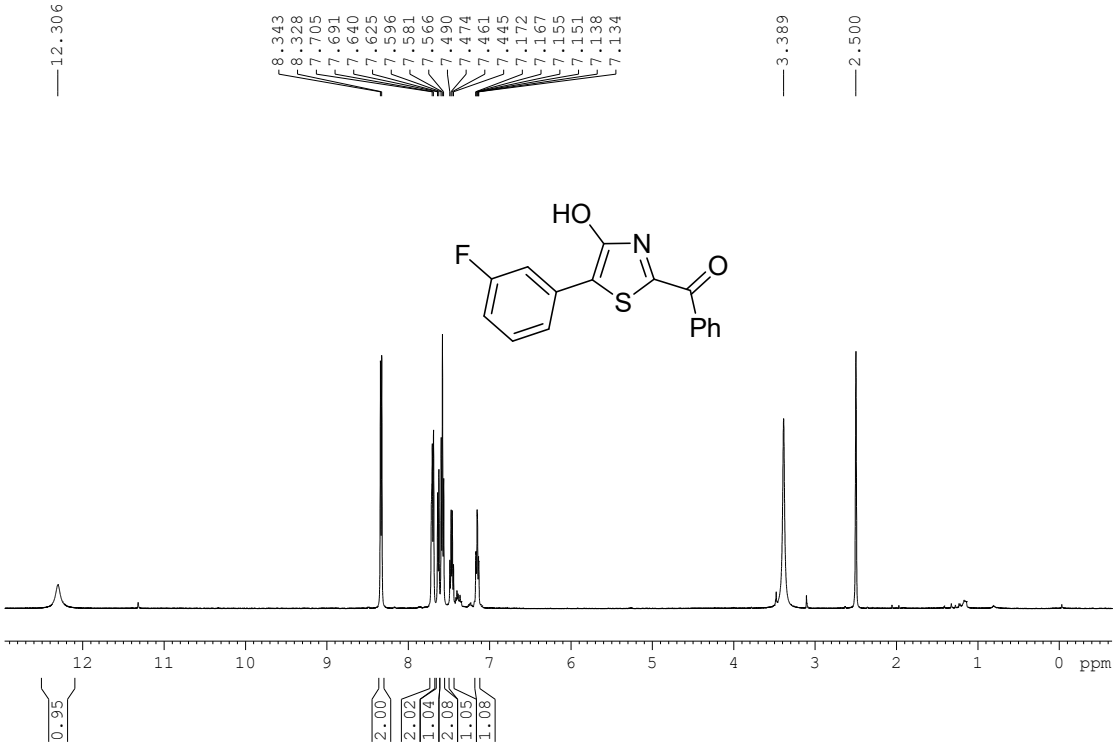


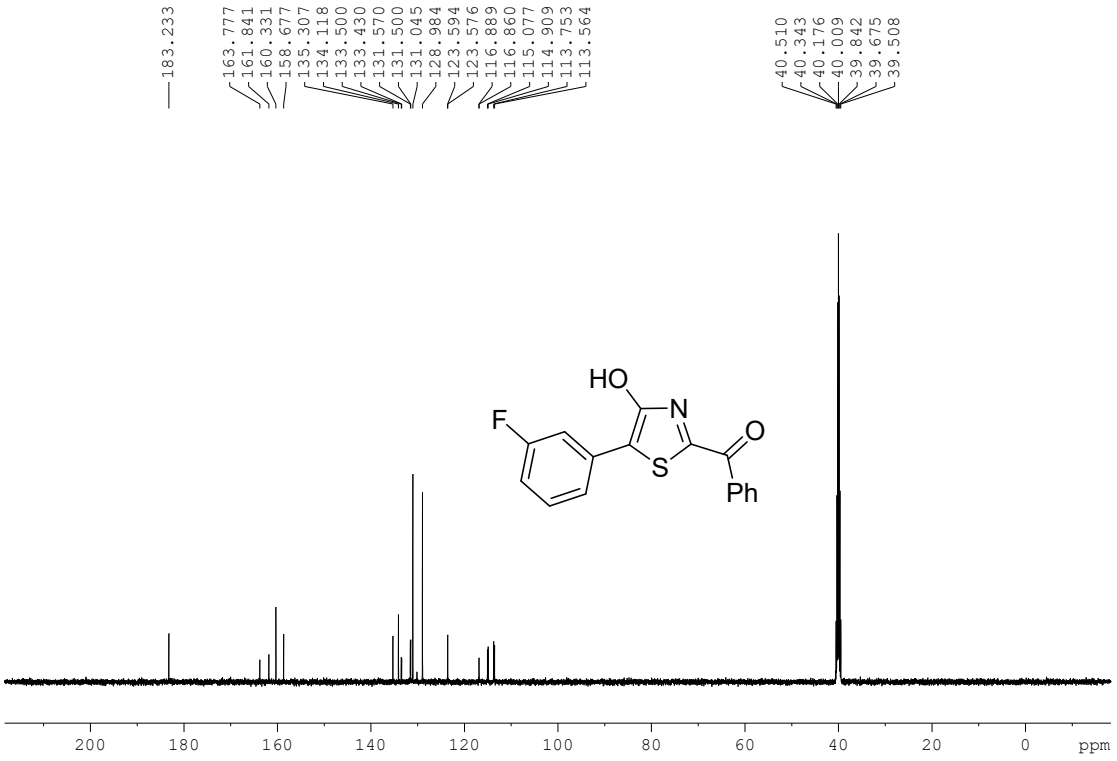
(4-hydroxy-5-(3-methoxyphenyl)thiazol-2-yl)(phenyl)methanone 2e



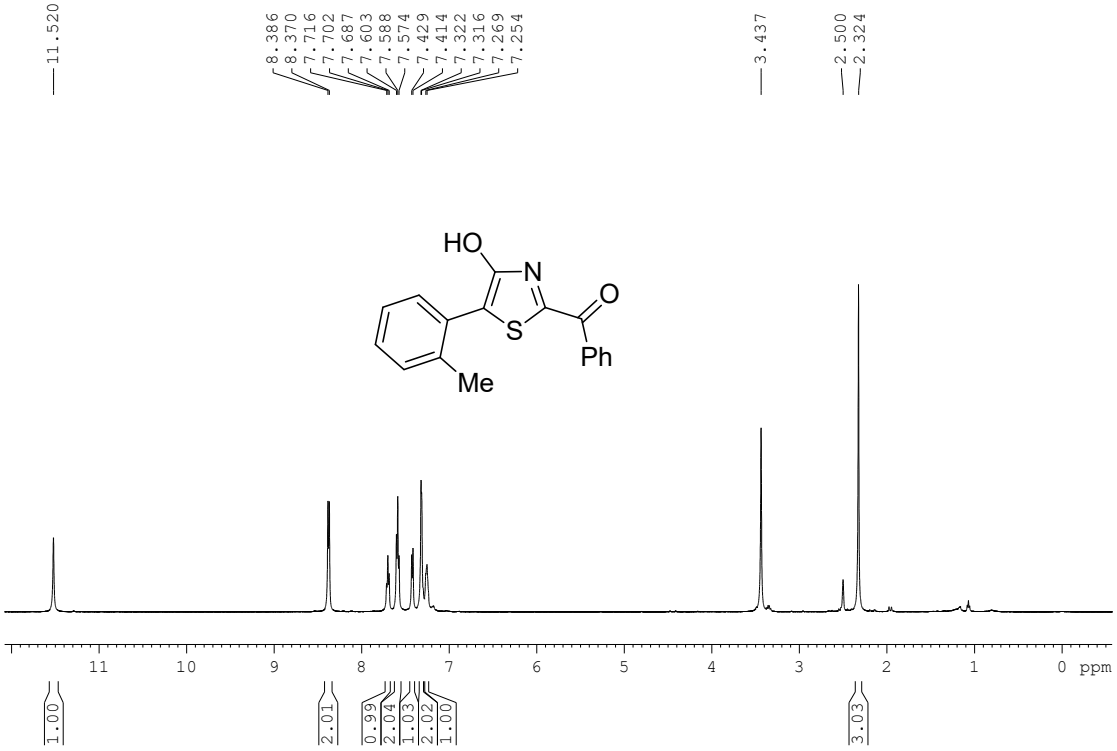


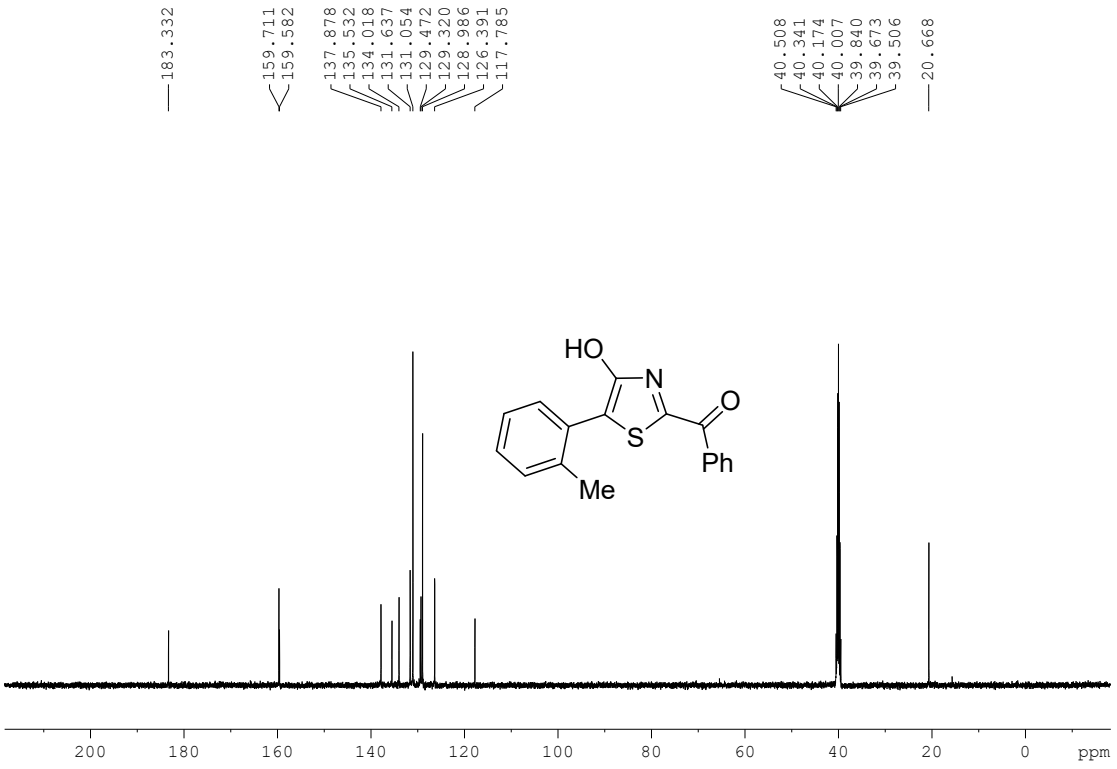
^{1}H and ^{13}C Spectrum of Compound **2f**



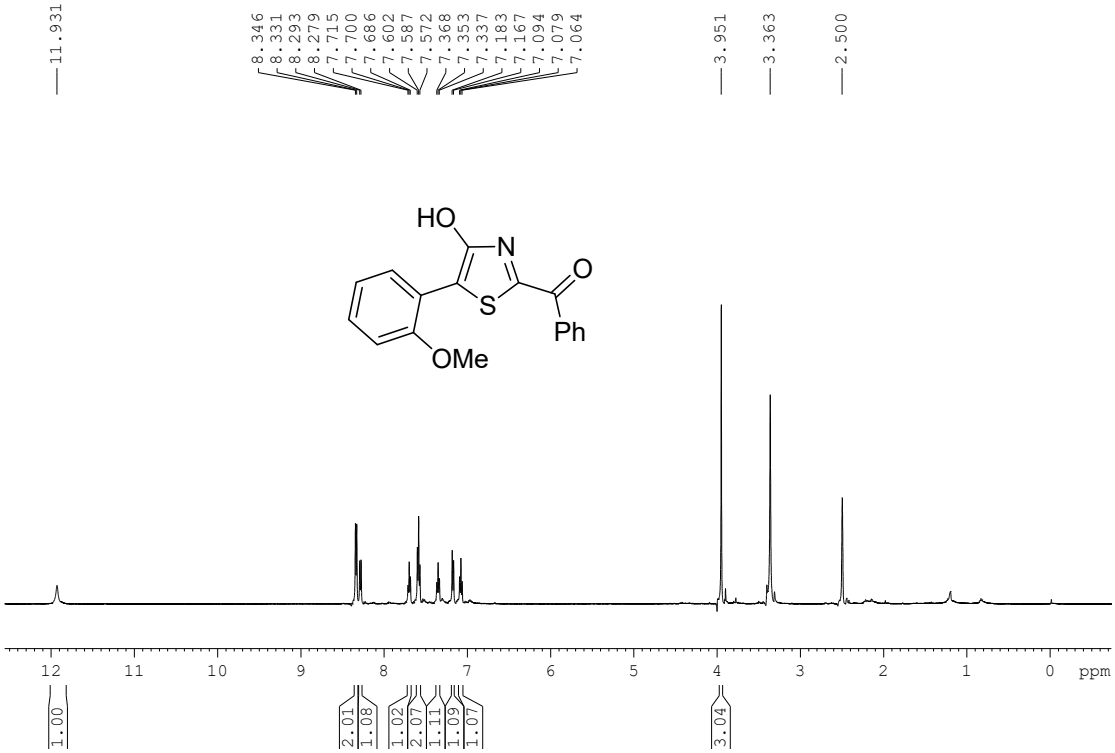


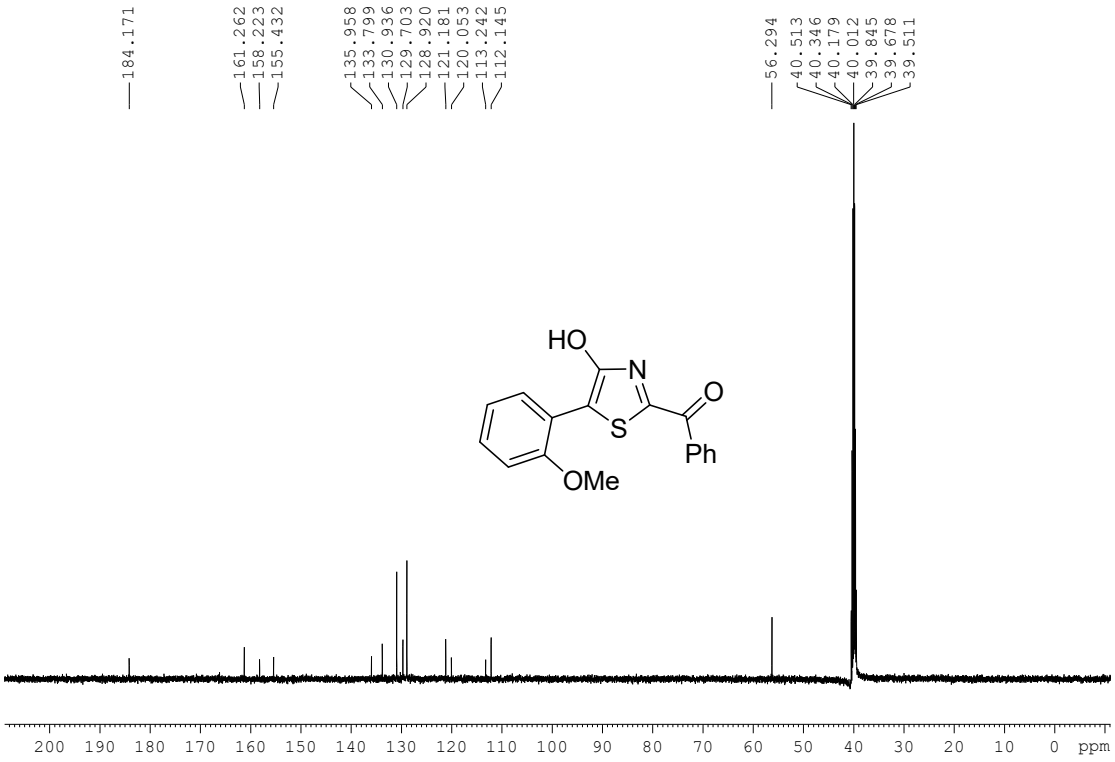
^{1}H and ^{13}C Spectrum of Compound **2g**



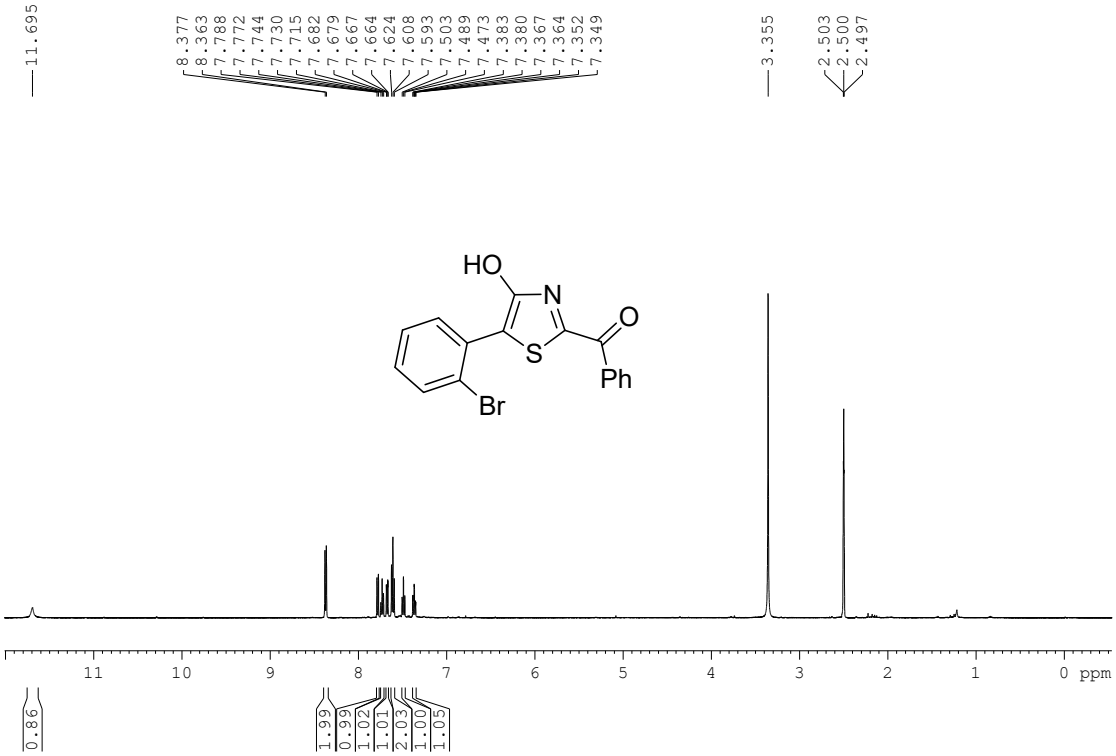


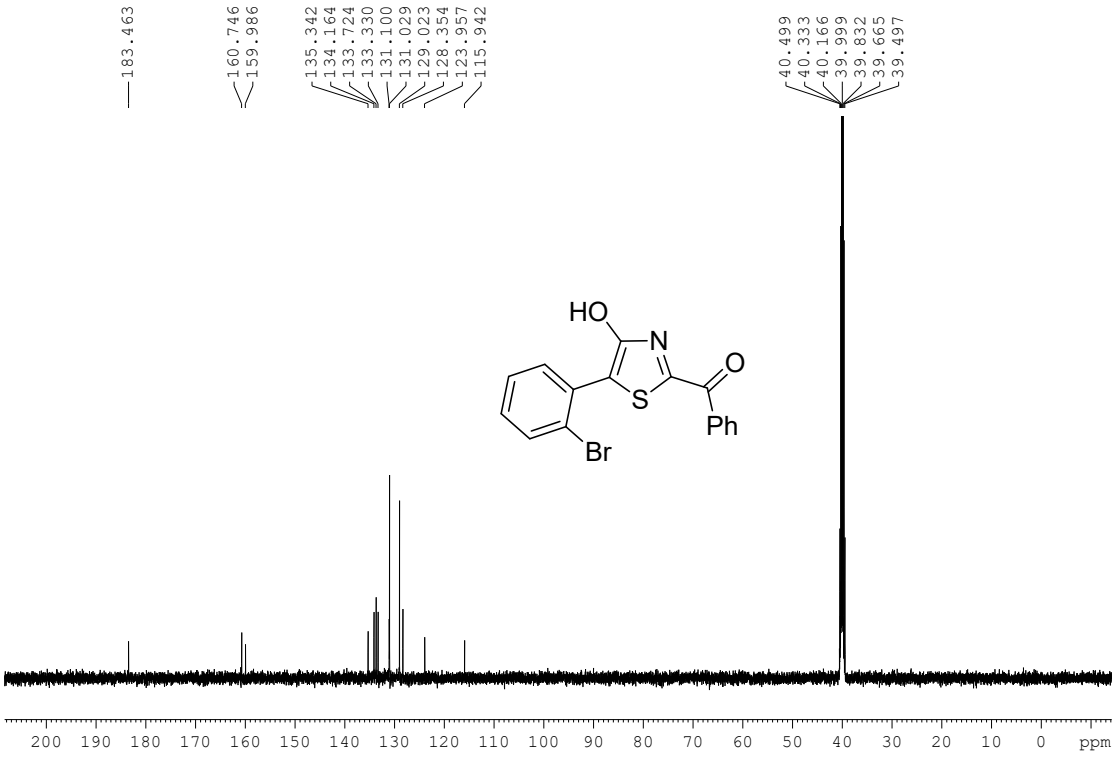
^{1}H and ^{13}C Spectrum of Compound **2h**



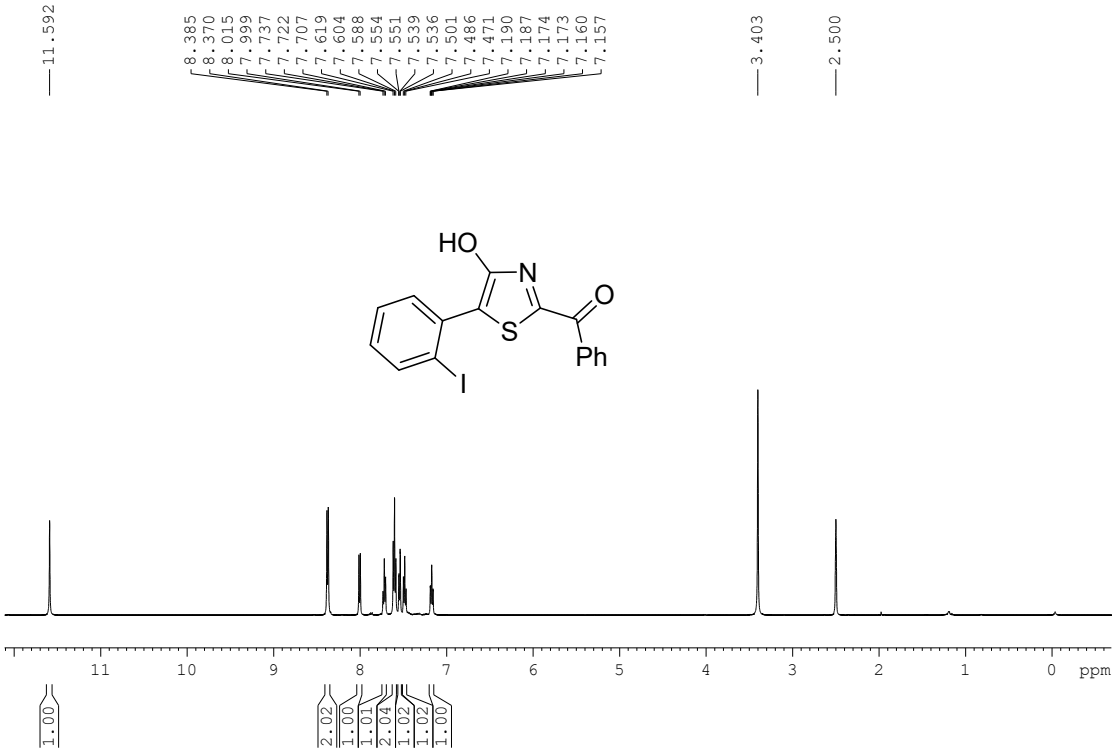


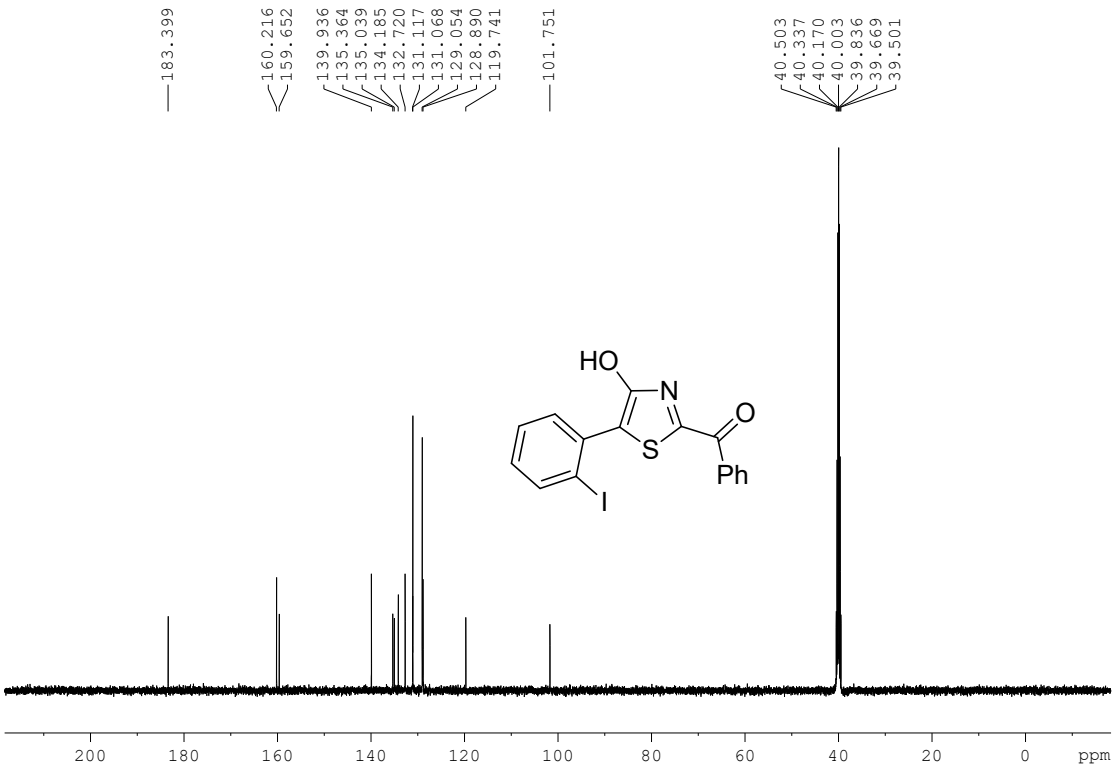
^{1}H and ^{13}C Spectrum of Compound **2i**



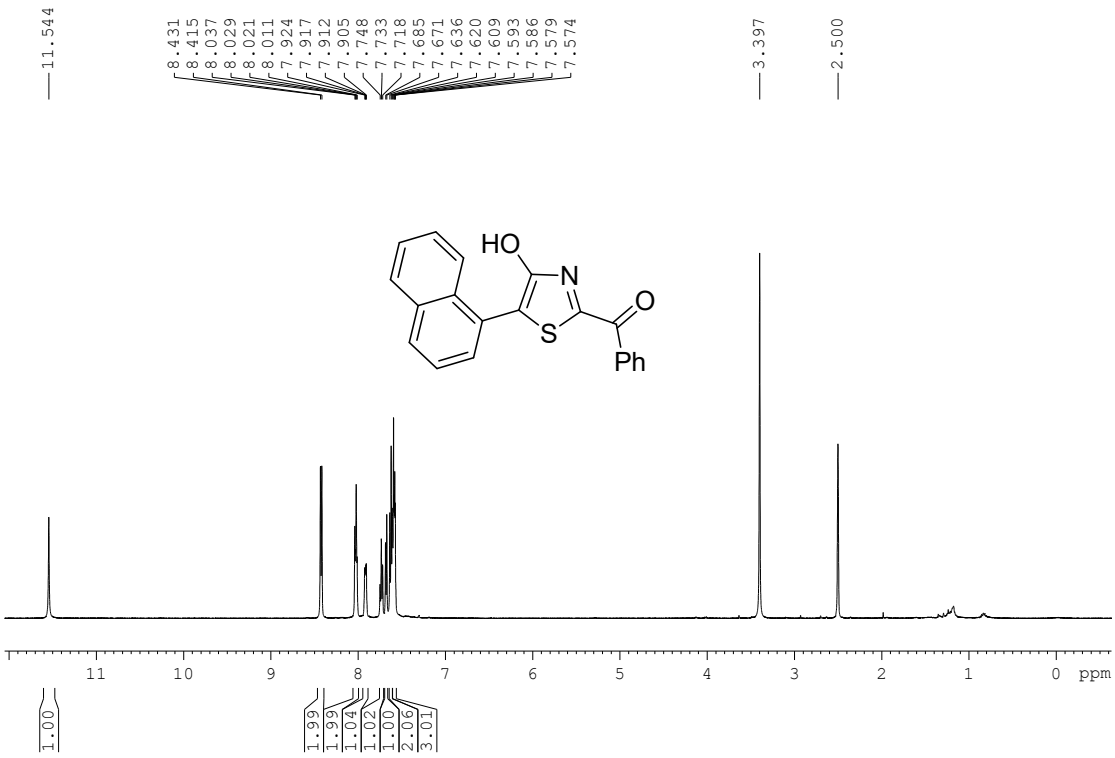


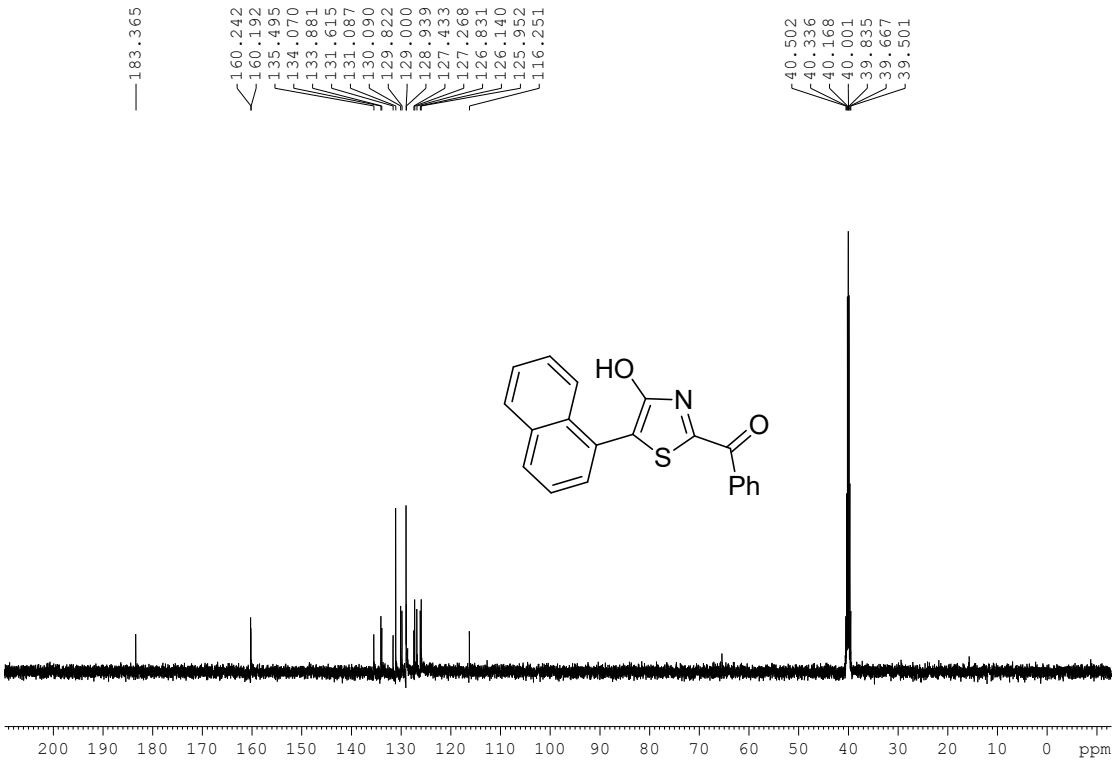
^{1}H and ^{13}C Spectrum of Compound **2j**



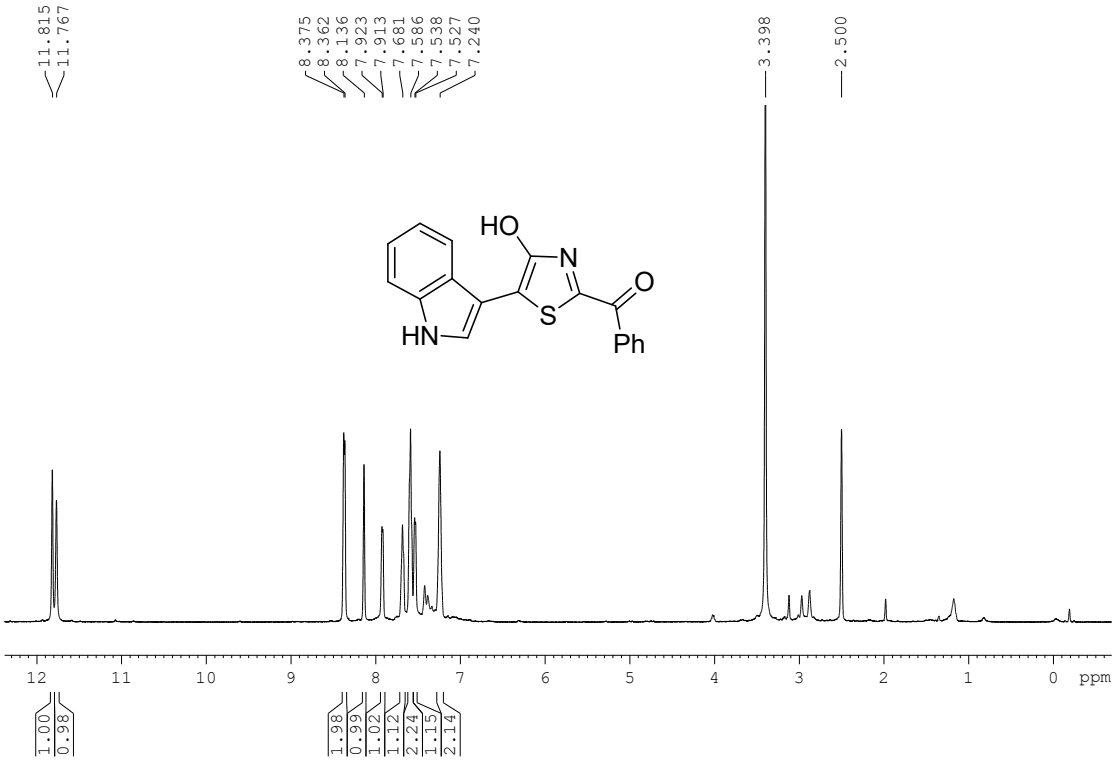


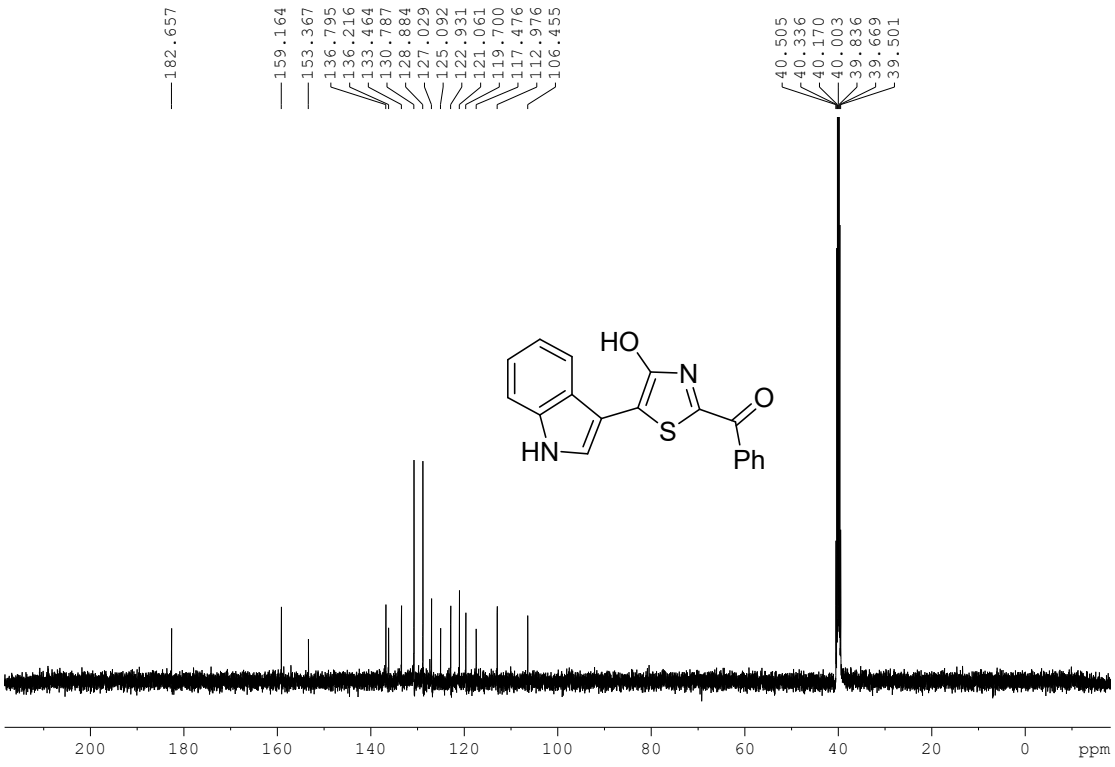
^{1}H and ^{13}C Spectrum of Compound **2k**



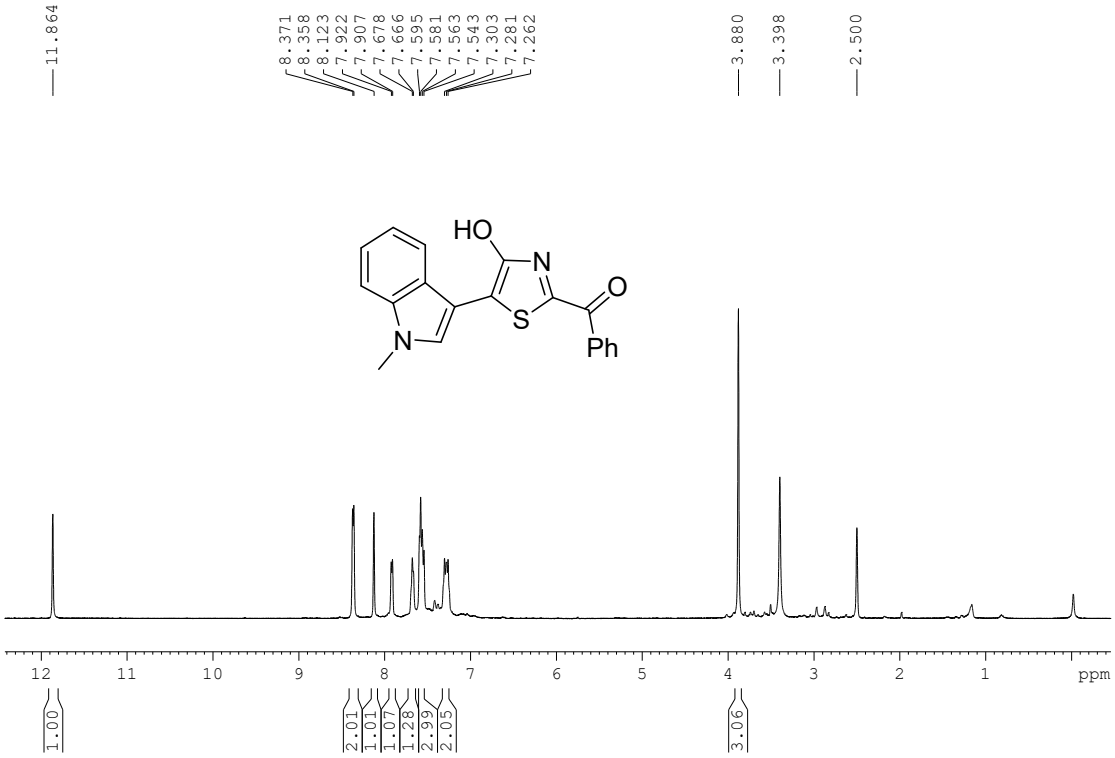


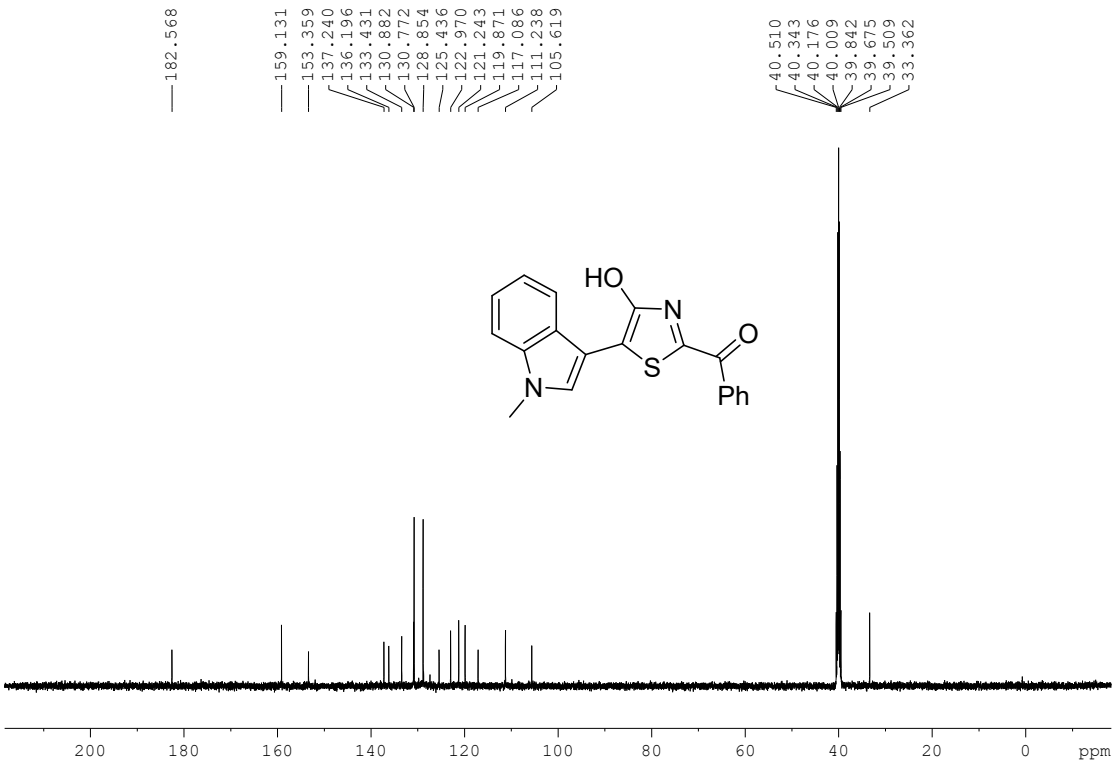
^{1}H and ^{13}C Spectrum of Compound **2l**



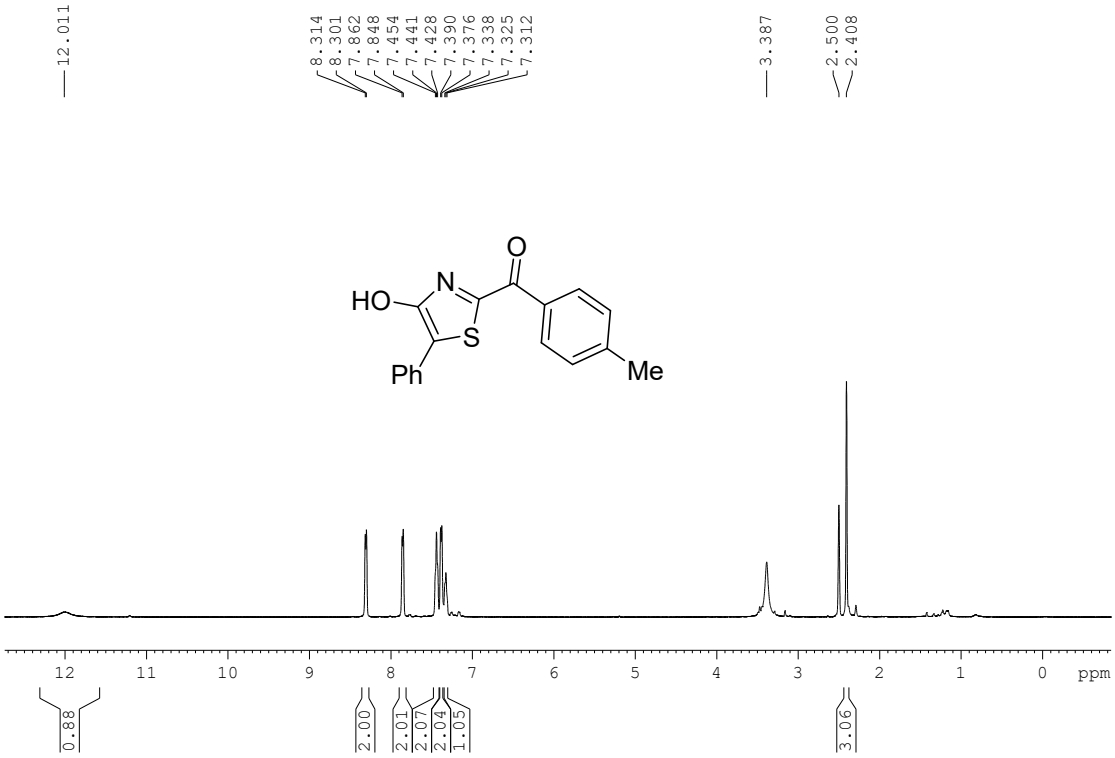


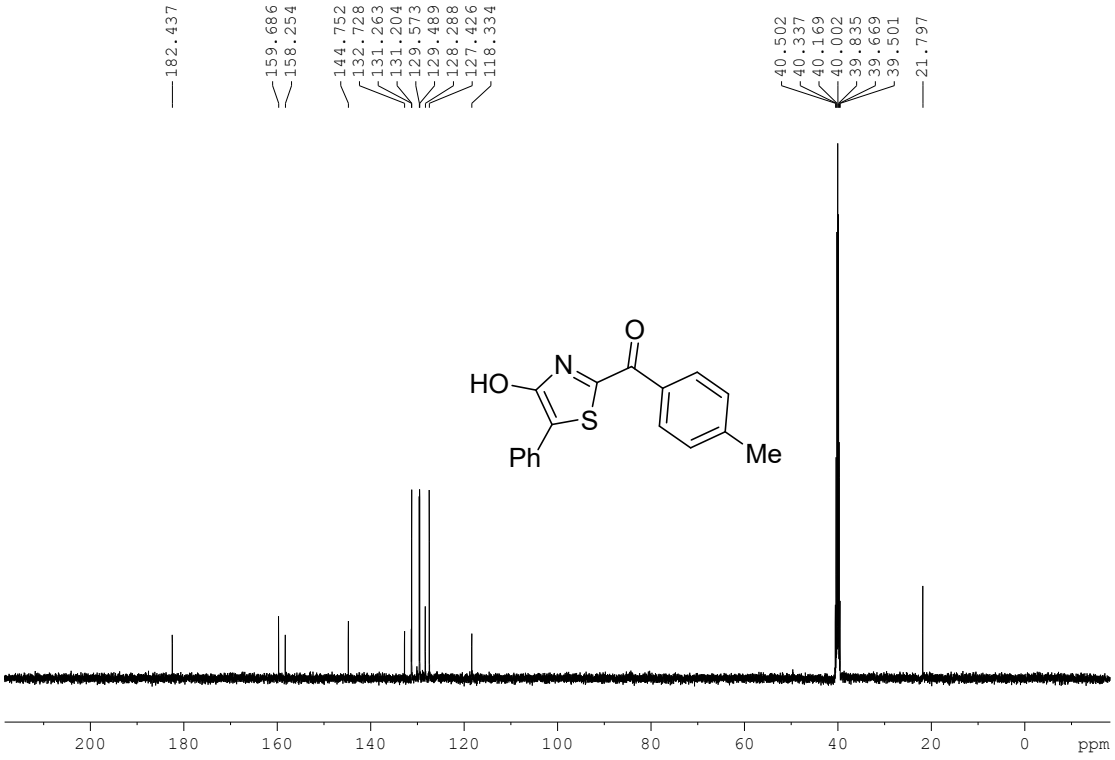
^{1}H and ^{13}C Spectrum of Compound **2m**



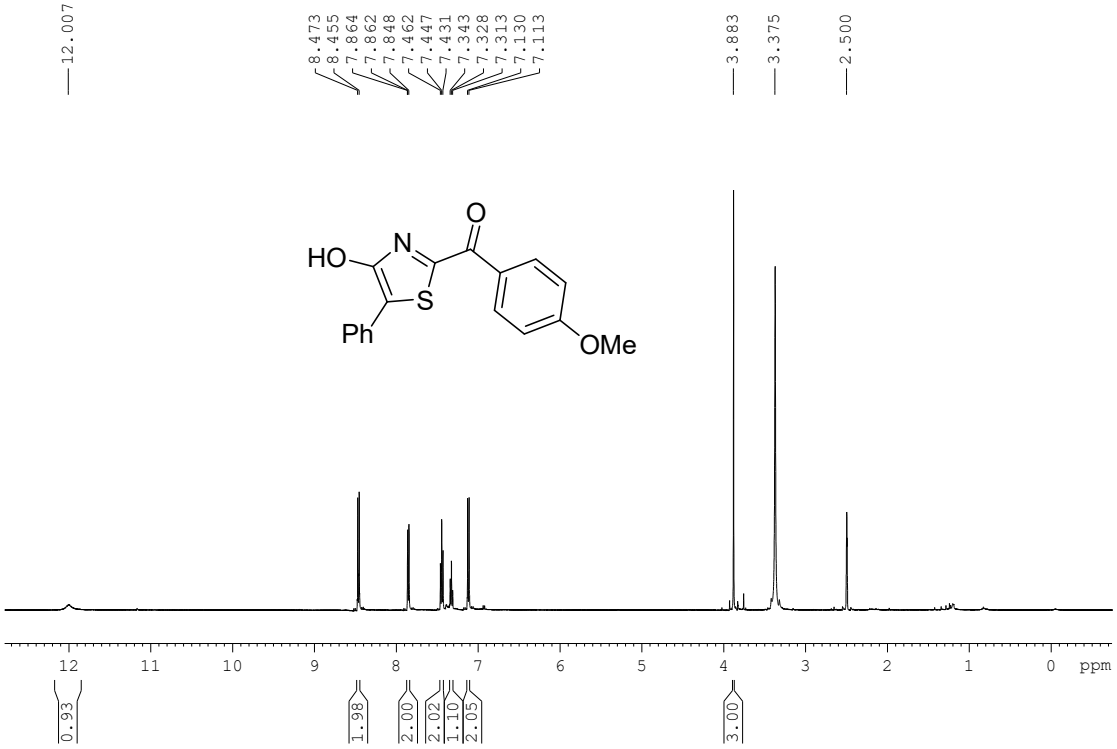


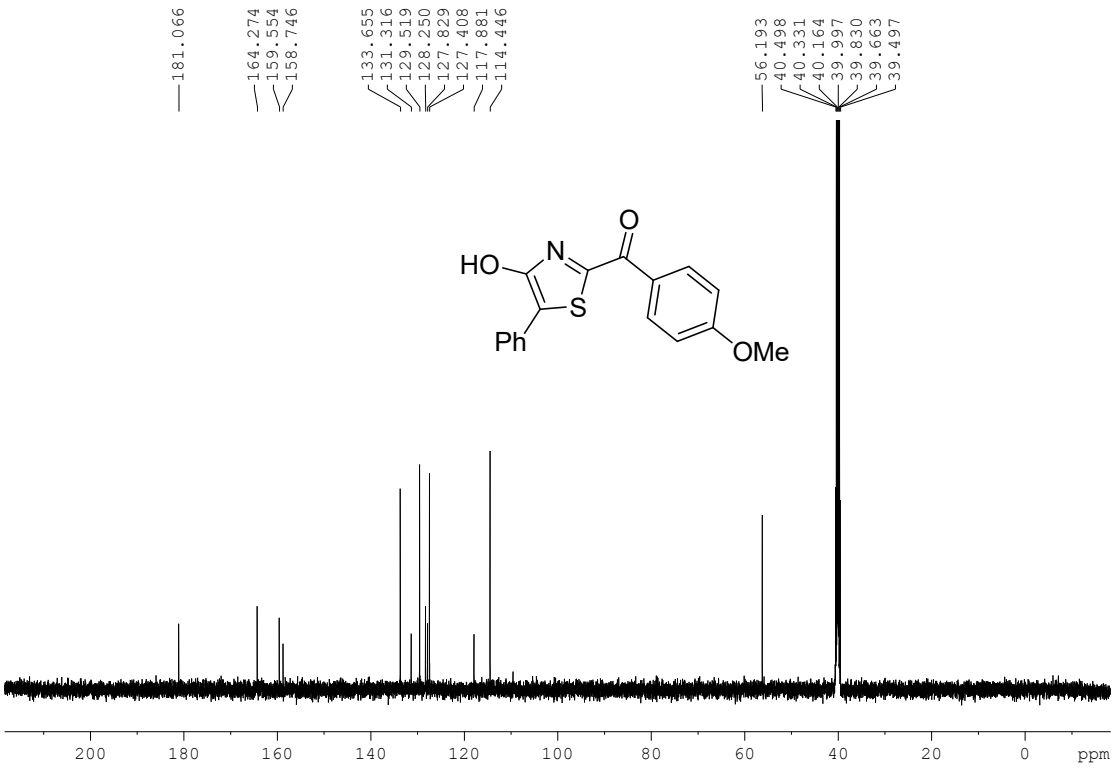
^{1}H and ^{13}C Spectrum of Compound **2n**



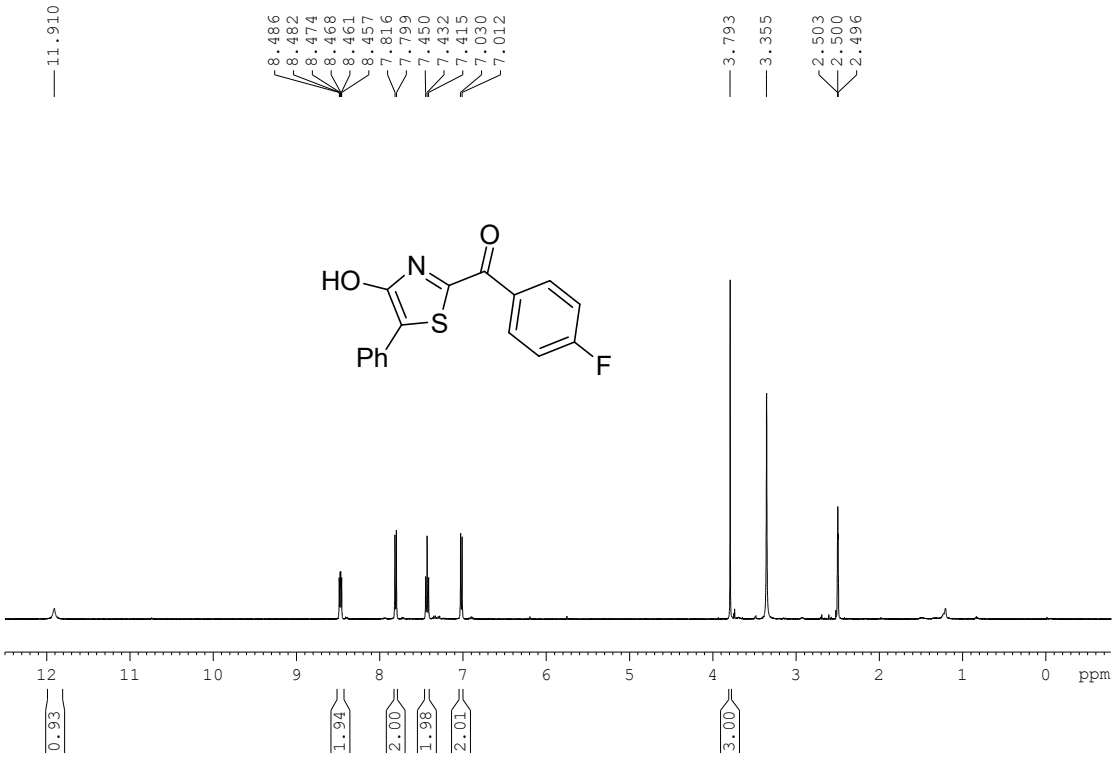


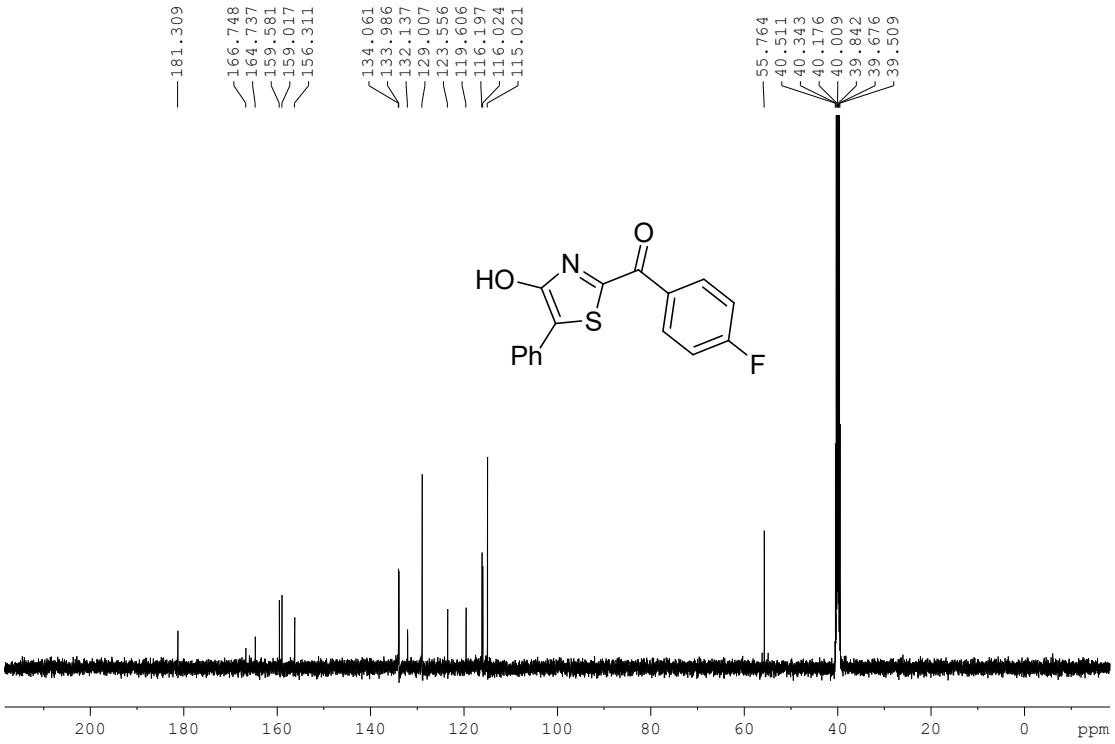
^{1}H and ^{13}C Spectrum of Compound **2o**



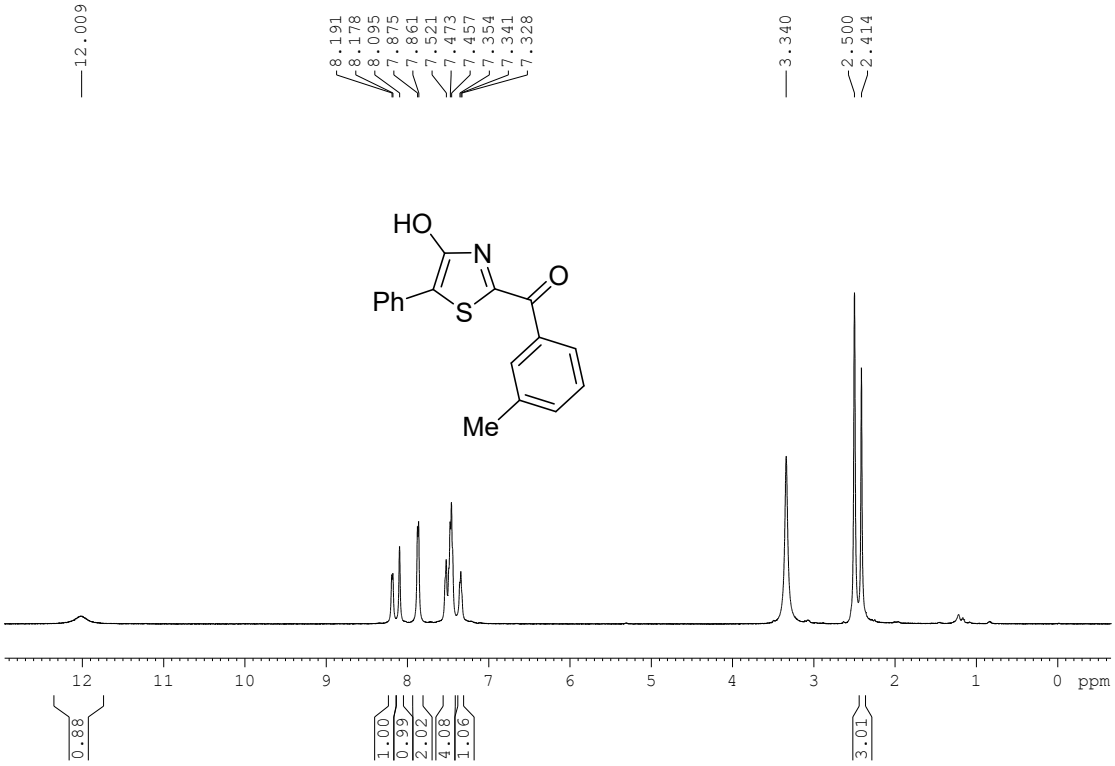


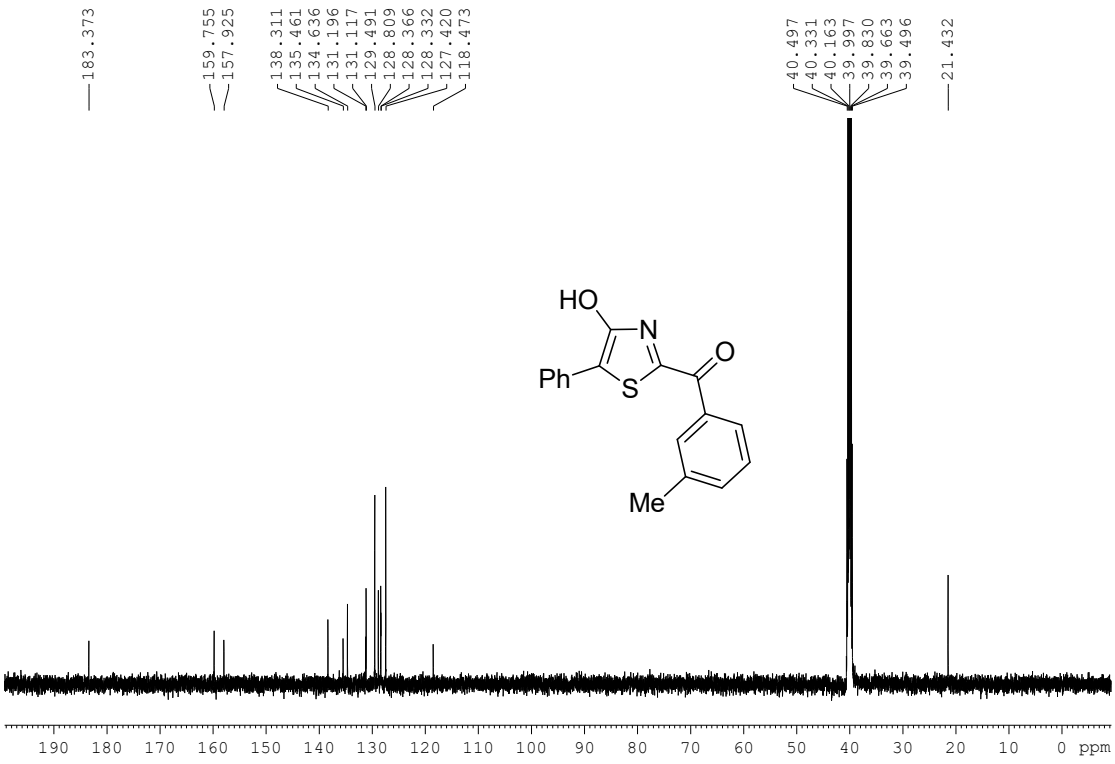
^{1}H and ^{13}C Spectrum of Compound **2p**



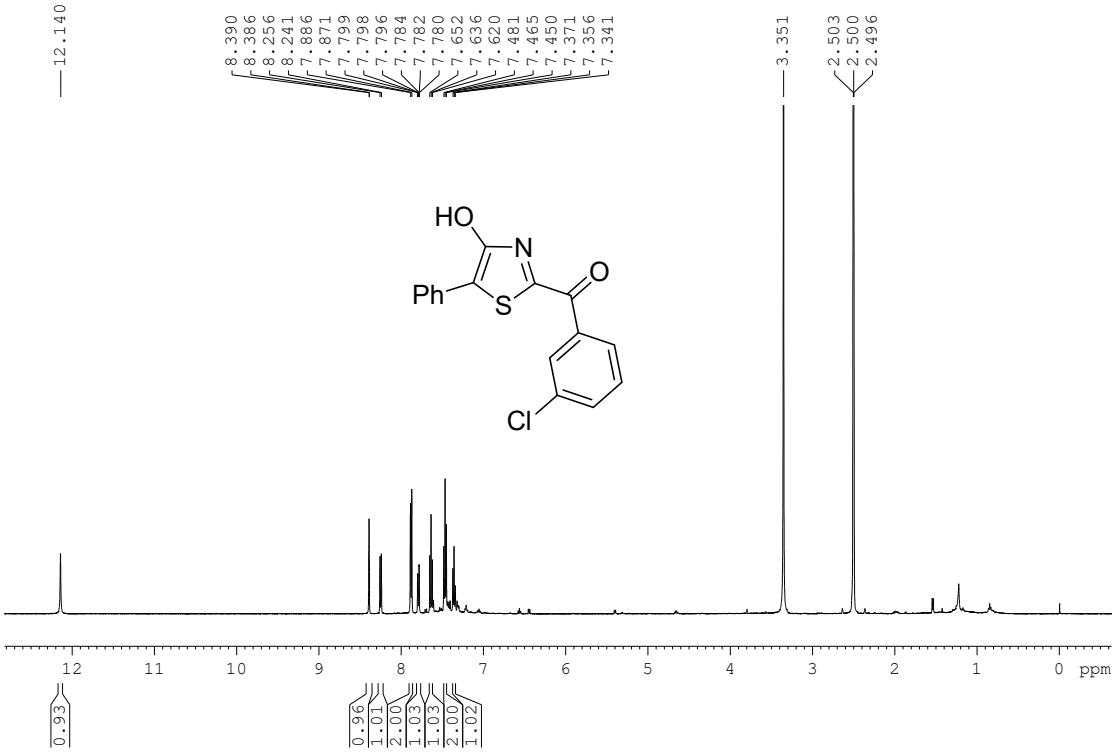


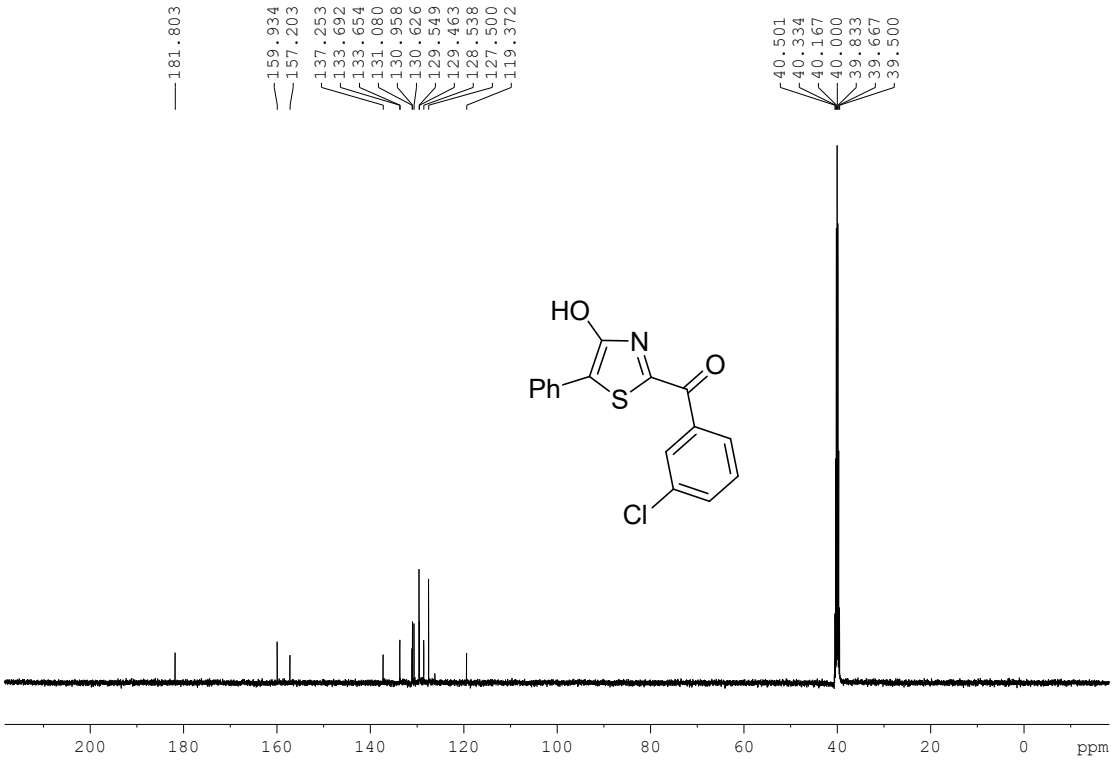
^{1}H and ^{13}C Spectrum of Compound **2q**



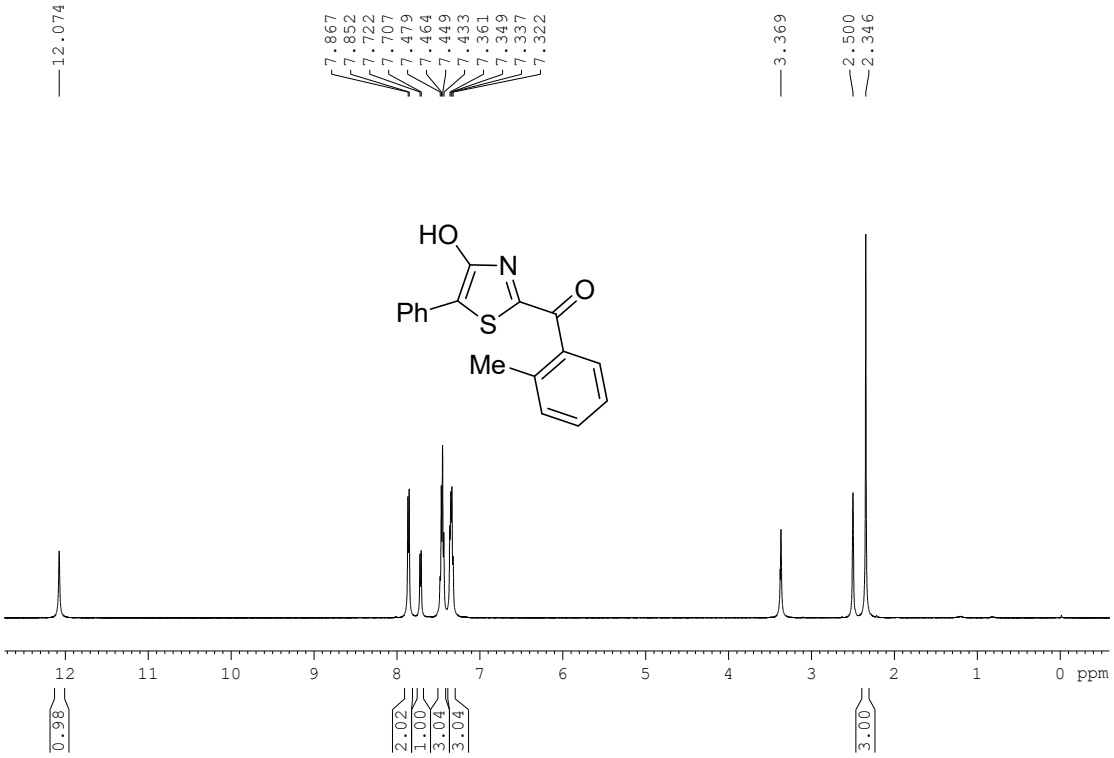


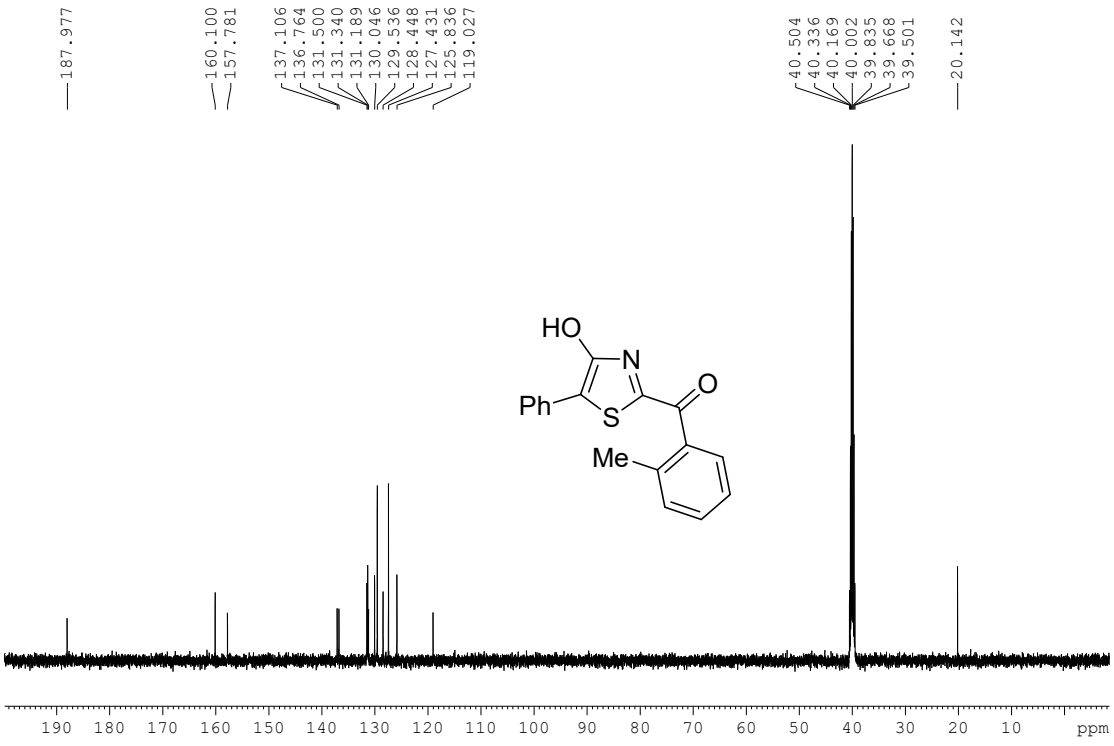
^{1}H and ^{13}C Spectrum of Compound **2r**



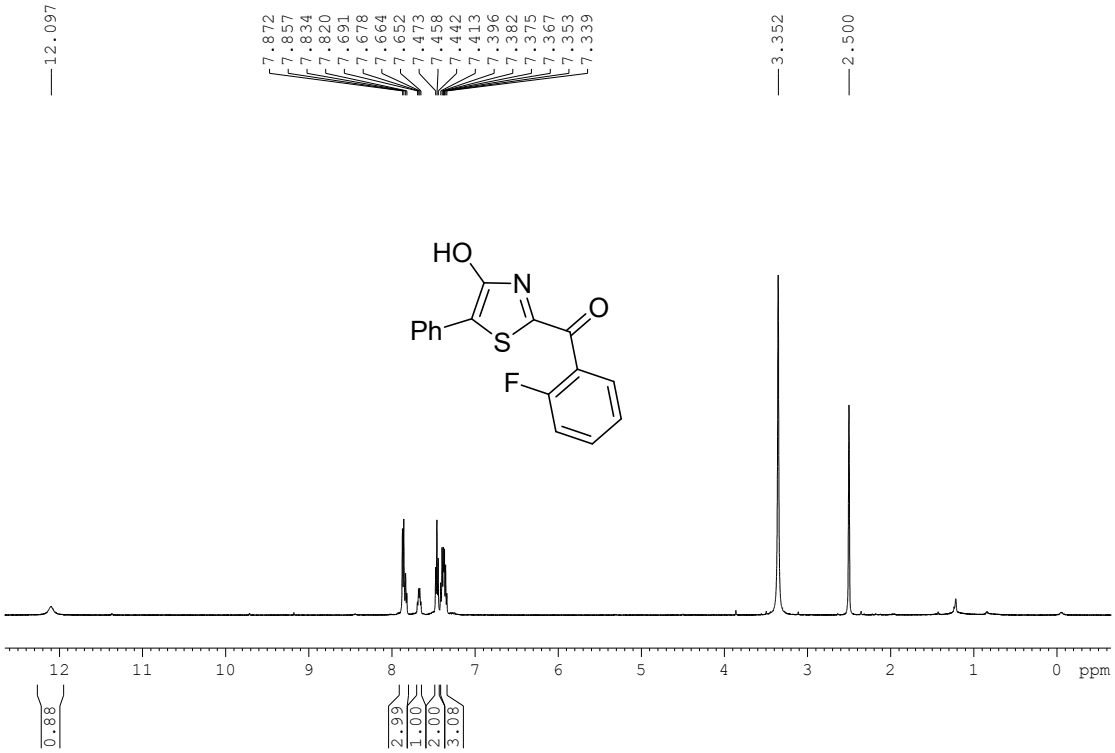


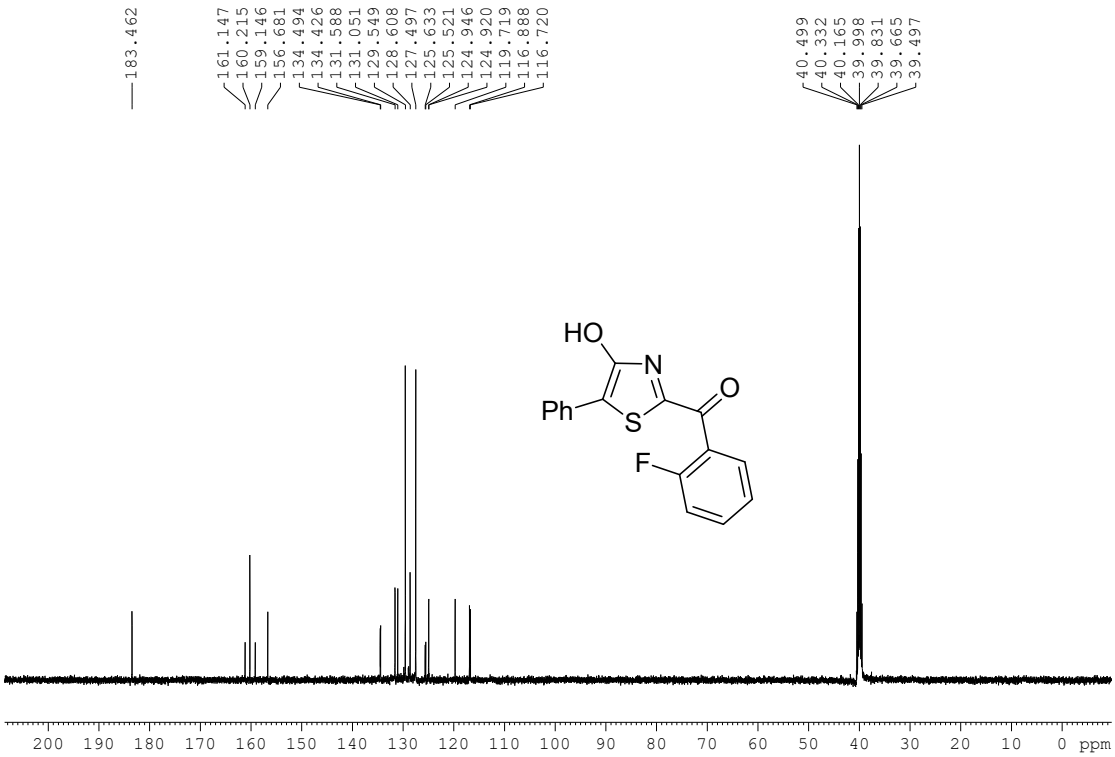
^{1}H and ^{13}C Spectrum of Compound **2s**



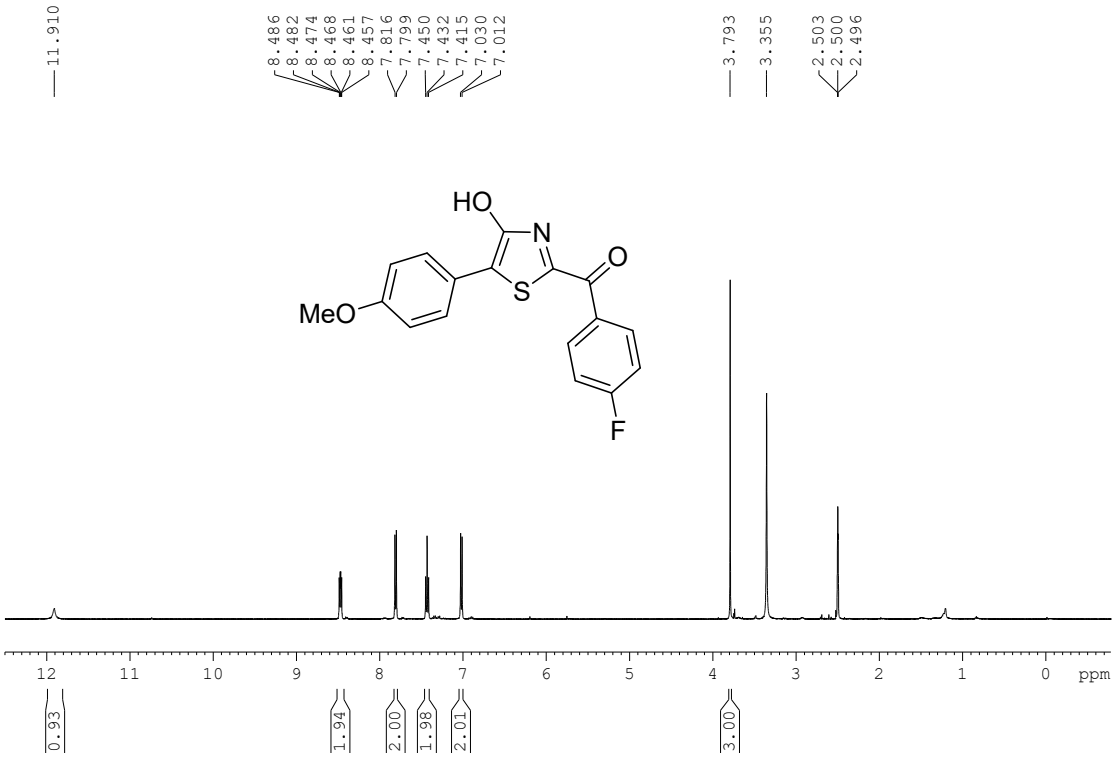


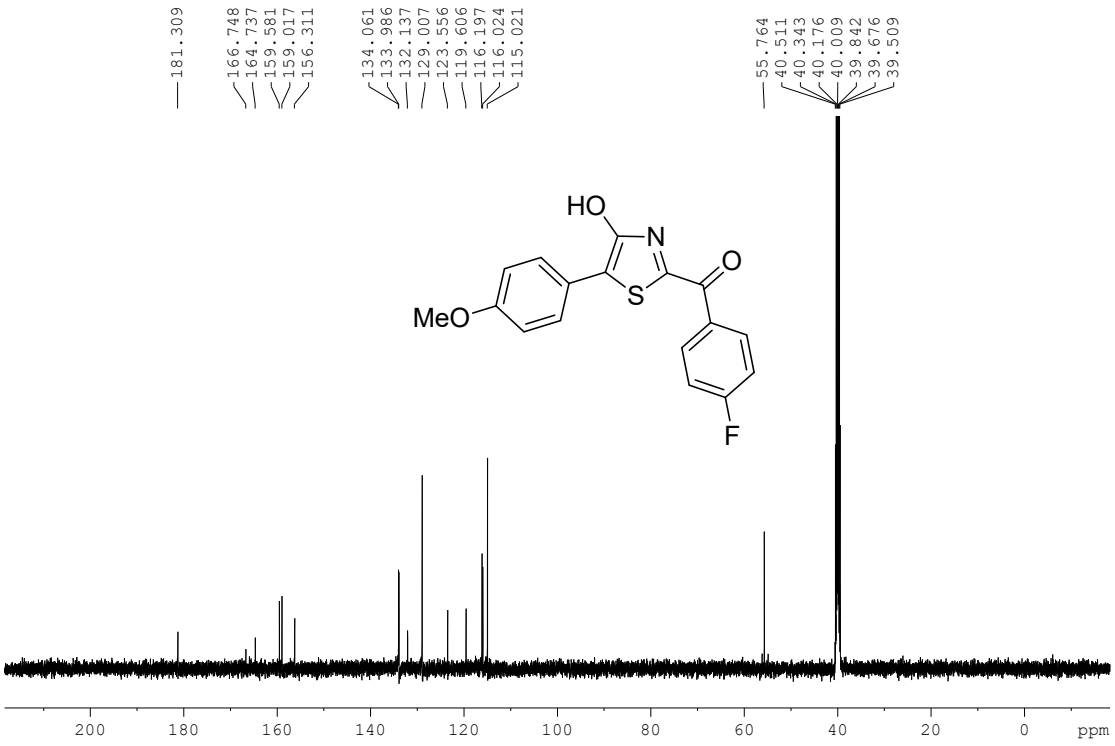
^{1}H and ^{13}C Spectrum of Compound **2t**



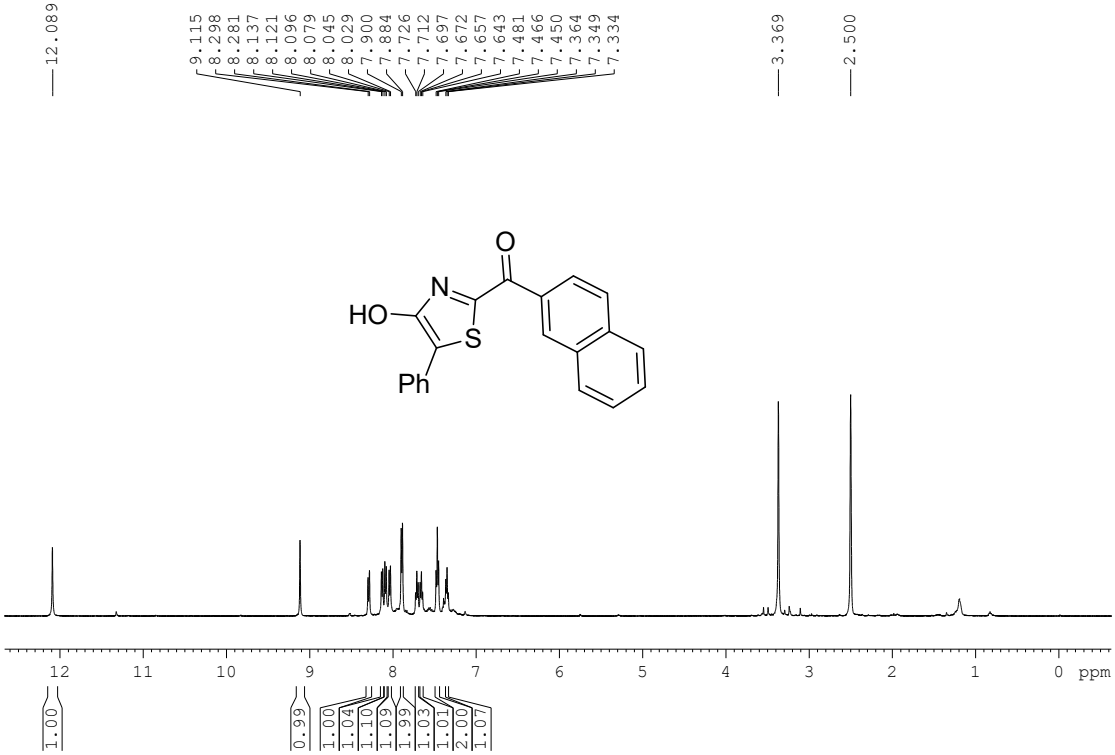


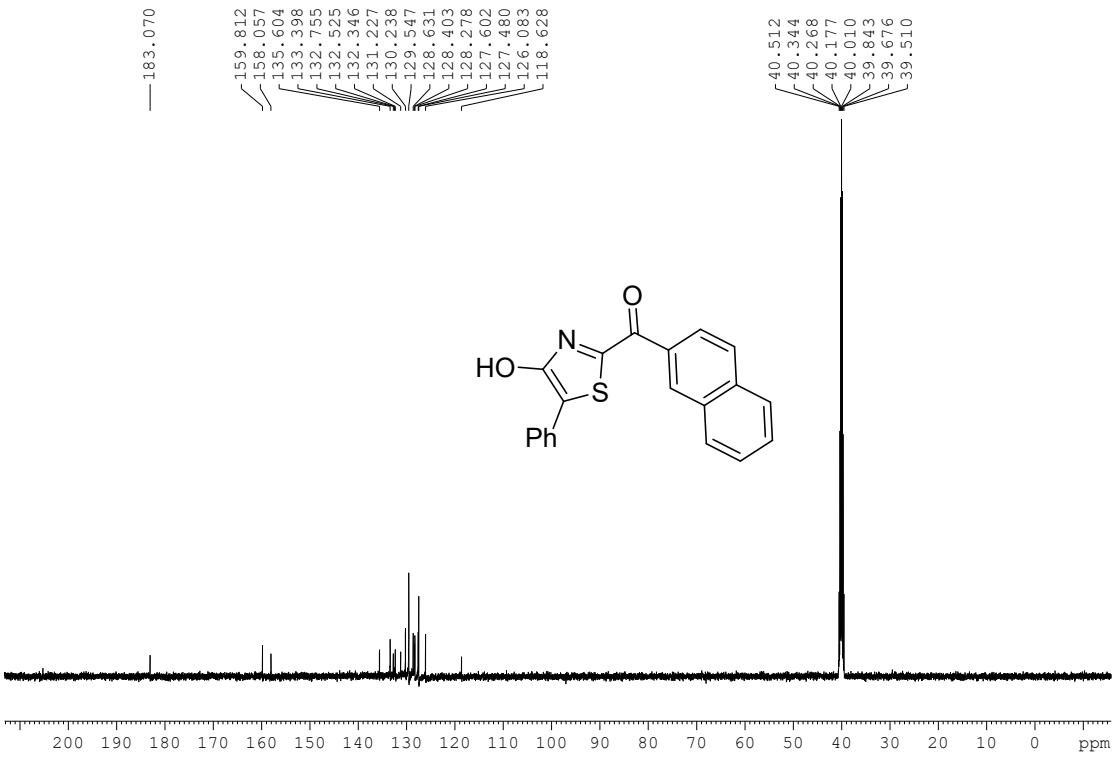
^{1}H and ^{13}C Spectrum of Compound **2u**



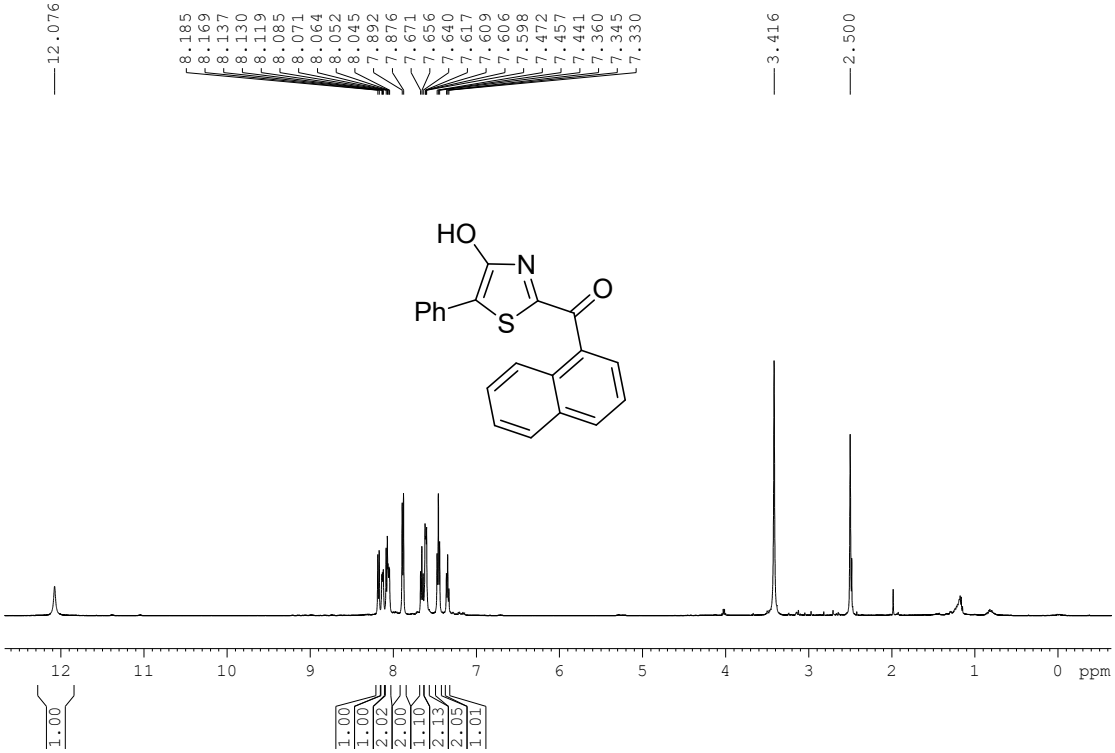


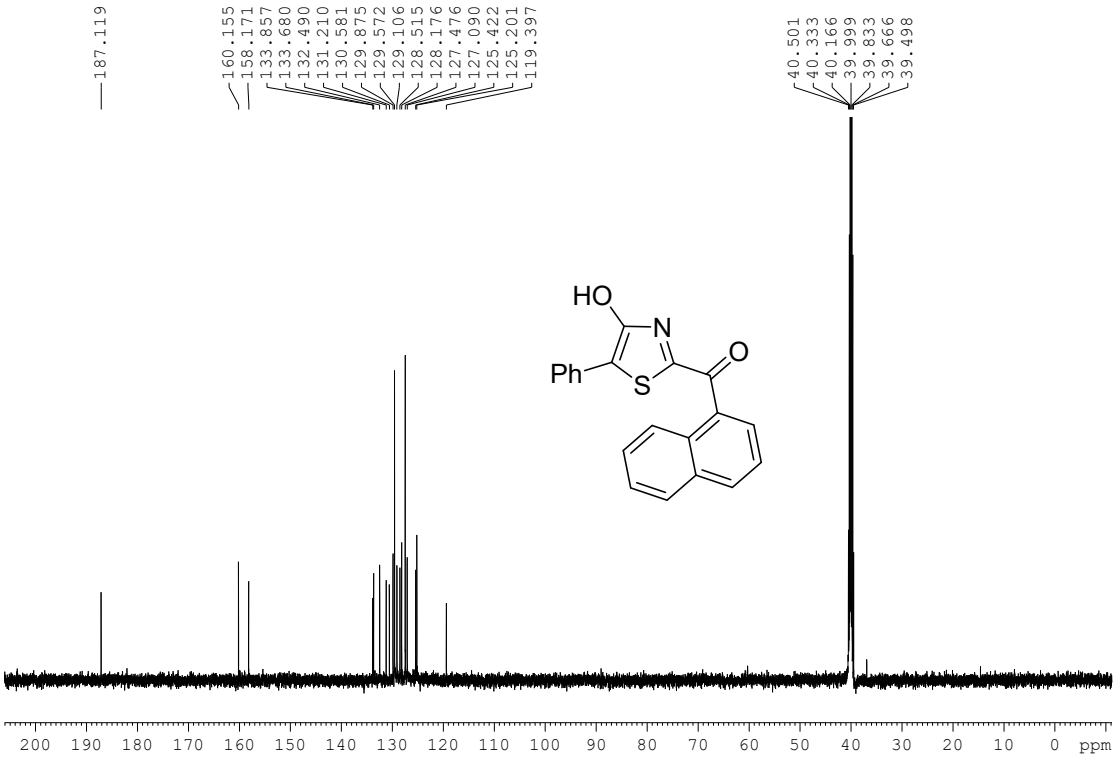
^{1}H and ^{13}C Spectrum of Compound **2v**



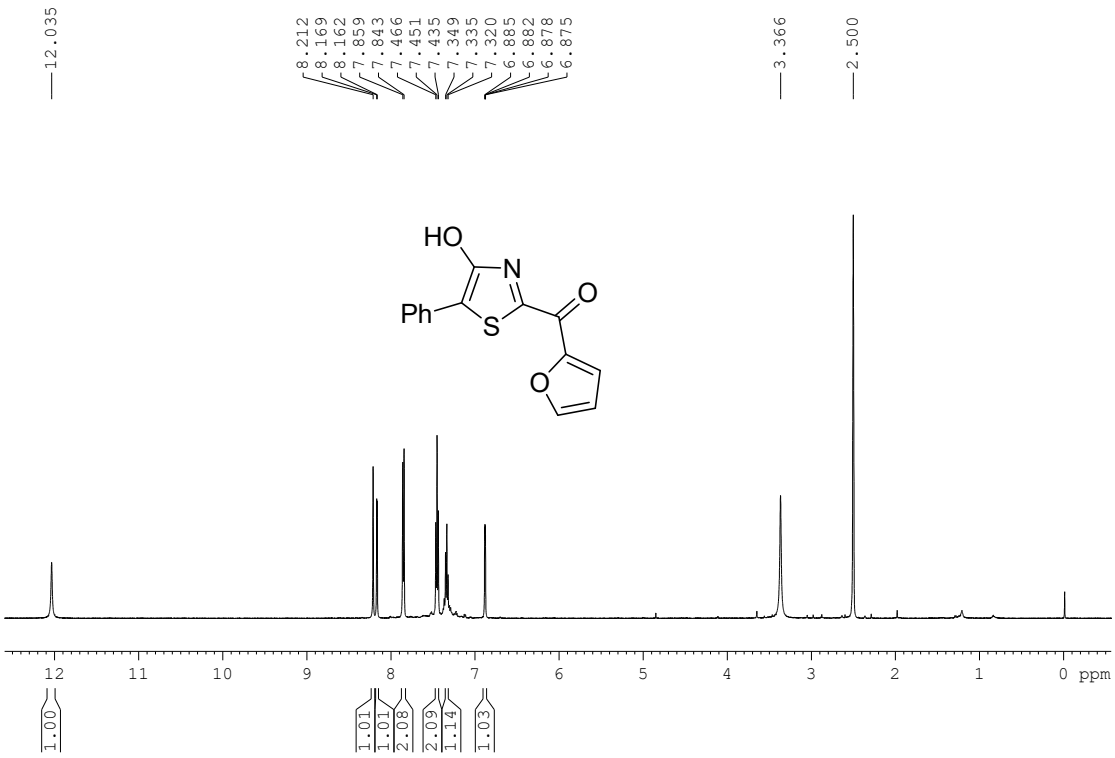


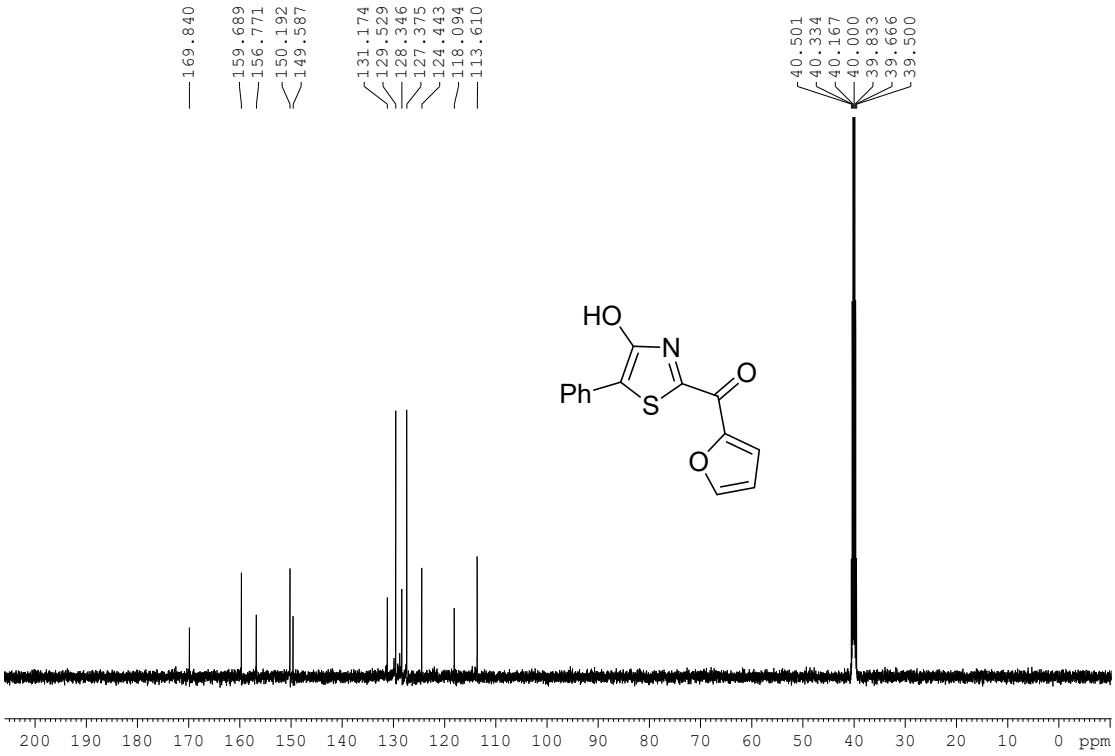
^{1}H and ^{13}C Spectrum of Compound **2w**



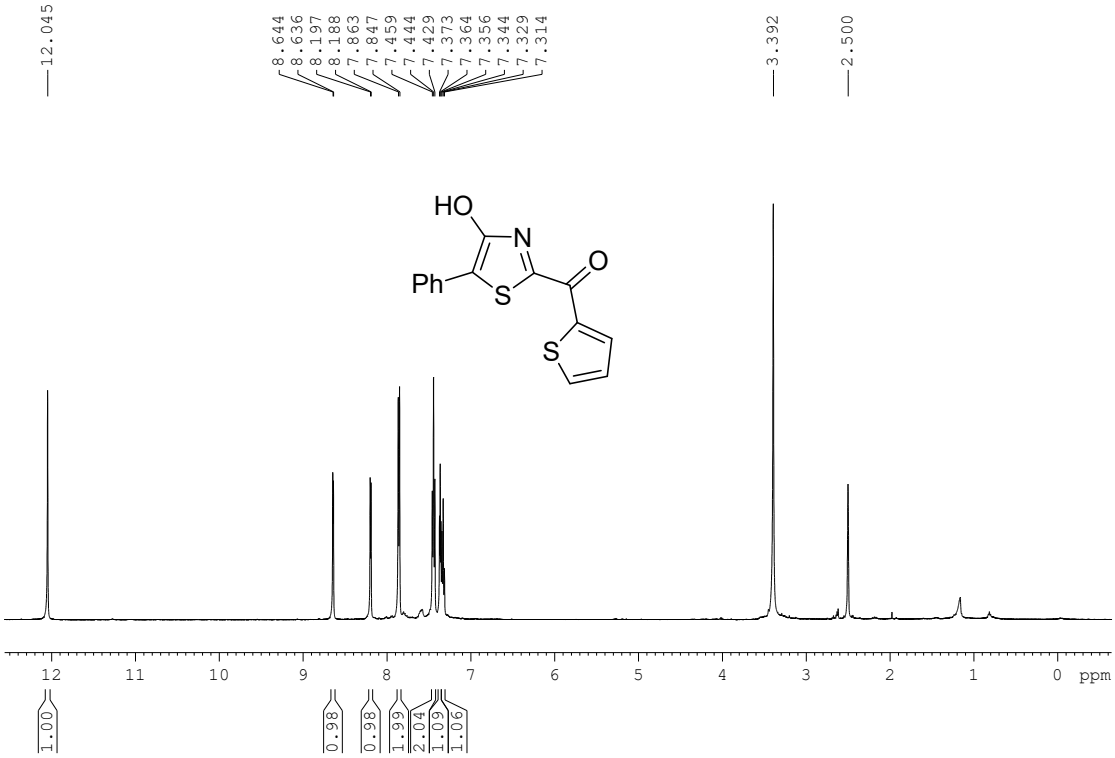


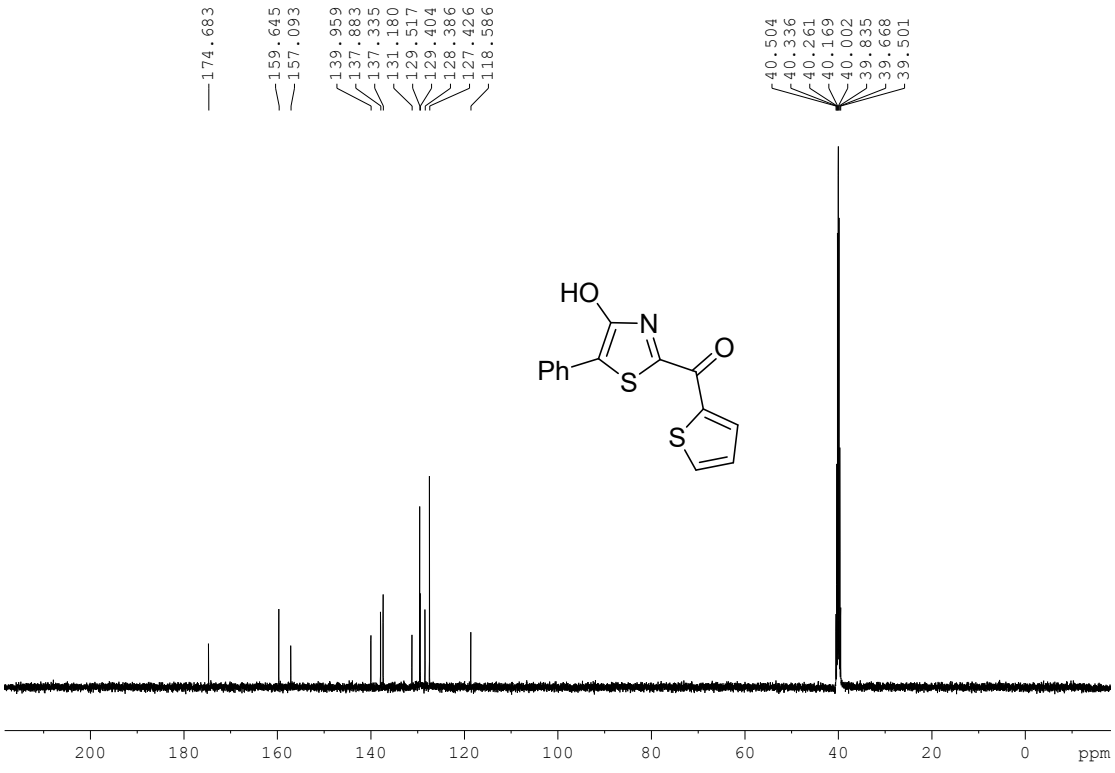
^{1}H and ^{13}C Spectrum of Compound **2x**



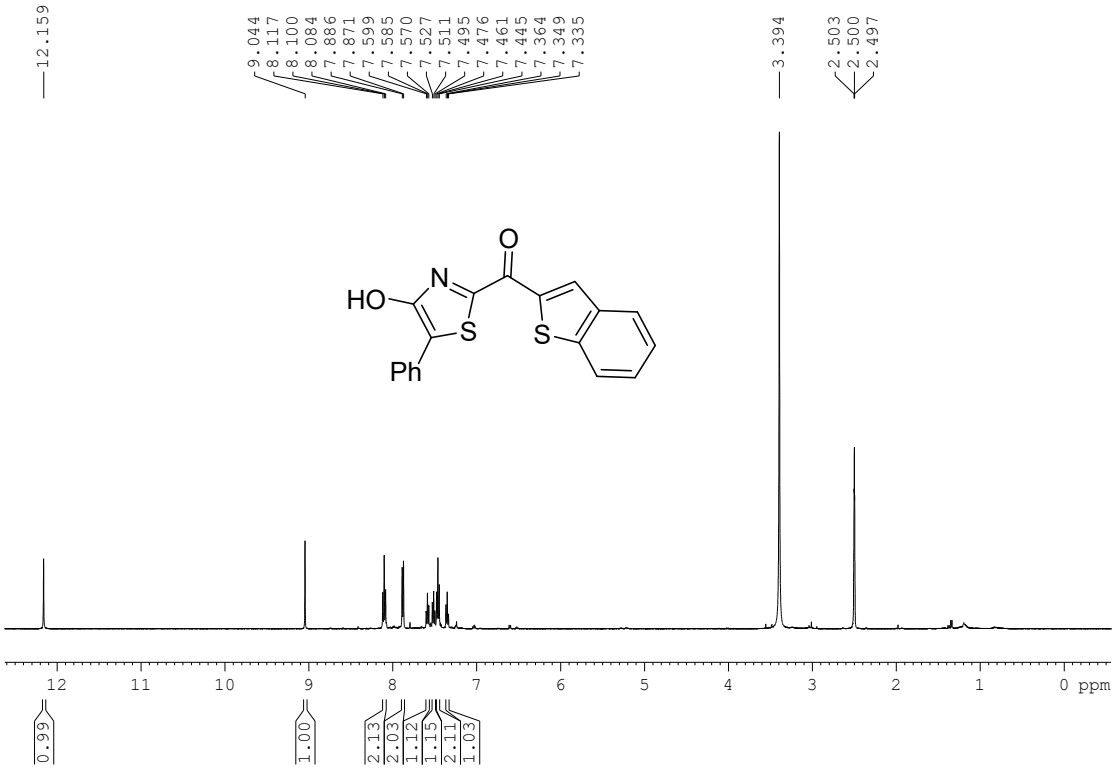


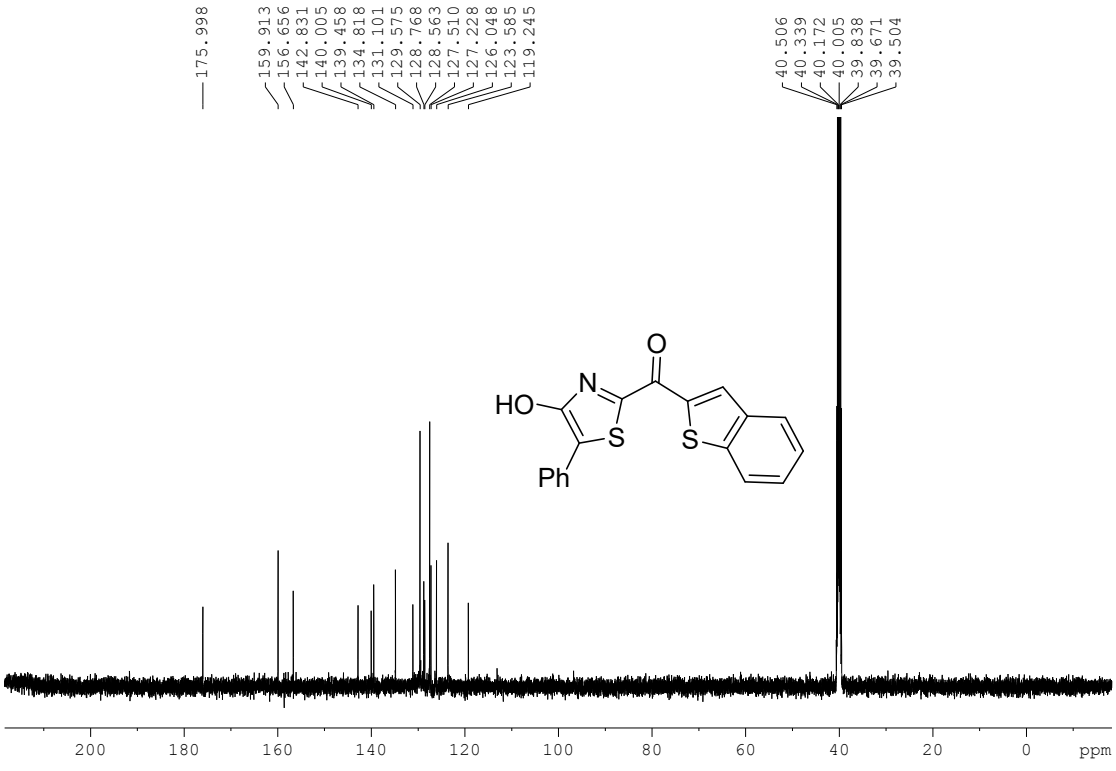
^{1}H and ^{13}C Spectrum of Compound **2y**





^{1}H and ^{13}C Spectrum of Compound **2z**





^{1}H and ^{13}C Spectrum of Compound **2aa**