Electronic Supplementary Information

Chemoselective Ullmann Coupling at Room Temperature: A Facile Access to 2-Aminobenzo[*b*]thiophenes

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Experimental Section:

General Considerations

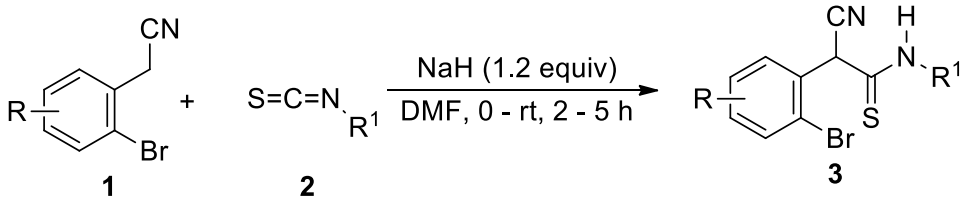
Reagents

All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. Toluene, CH_3CN, DMF, DMSO, Cs_2CO_3, KOH, K_2CO_3, DMAP, KO^tBu and Et_3N were purchased from Aldrich, Acros, Merck, Spectrochem or Alfa-Aesar and used as received. CuI, CuBr, CuCl and $Cu(OAc)_2$ were purchased from Aldrich. The isothiocyanates were purchased from Aldrich and noncommercial isothiocyanates were synthesized from the corresponding amines. Tetramethylethylenediamine, (*R*)-(+)-1,1'-Binaphthyl-2,2'-diamine, 2,2'-Bipyridine, L-Proline and 1,10-Phenanthroline were purchased from Aldrich. All other reagents were purchased from common suppliers and used without further purification. Flash chromatography was performed using Merck Silica gel (230-400 mesh). Fractions were monitored by thin-layer chromatography on precoated silica gel 60 F254 plates (Merck & co.) and were visualized by UV.

Analytical Methods

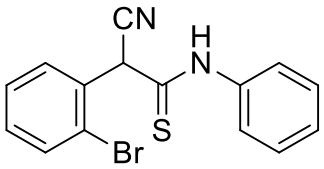
NMR data were recorded on Bruker ARX 400 & 700 spectrometers. ^{13}C and ^{1}H NMR Spectrum were recorded in $CDCl_3$, MeOH-d_4 and DMSO-d_6 referenced according to signals of deutero solvents. ESI HR-MS measurements were performed on Bruker micrOTOF-Q-II mass-spectrometer. The X-ray quality crystals for the compounds **4a** and **7j** were grown by slow diffusion of *n*-hexane over CH_2Cl_2 solution. Single-crystal X-ray diffraction data of **4a** and **7j were** collected in a Bruker KAPPA APEX-II, four angle rotation system, Mo-Kα radiation (0.71073 Å).

Scheme 1S: General Procedure for the Synthesis of Thioamides 3



To a stirring suspension of NaH (60% suspension in mineral oil) (3.6 mmol) in DMF (5.0 mL) at 0 ^{o}C was added drop wise the corresponding 2-bromobenzylnitrile (3 mmol) in DMF (3.0 mL). After being further stirred for 1 h at room temperature, a solution of isothiocyanate (3.3 mmol) in DMF (2.0 mL) was added to the reaction mixture at 0 ^{o}C and followed by further stirring for 2 h at room temperature. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layer washed with water (3 x 25 mL) & brine (25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by flash chromatography using EtOAc/hexanes as eluent.

2-(2-Bromophenyl)-2-cyano-*N*-phenylethanethioamide (3a)



Reaction time: 4 h

Yield: 70%, as a pale yellow colour viscous liquid.

R_f: 0.32 in 25% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3272, 3058, 2933, 2360, 2340, 2251, 2202, 1597, 1496, 1469, 1409, 1275, 1204, 1089, 1027, 763, 739.

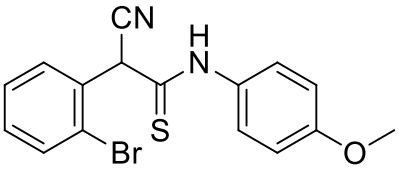
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.24 (s, 1H), 7.80 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66 – 7.61 (m, 3H), 7.47 – 7.43 (m, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.28 (m, 2H), 5.73 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.1, 138.0, 133.8, 132.0, 131.5, 130.9, 129.3, 129.1, 127.8, 123.9, 123.7, 116.7, 53.8.

HR-MS (ESI): Calcd. for $C_{15}H_{11}BrN_2S$ [M+H]: 330.9899, Found: 330.9896.

[M+H]: 332.9879, Found: 332.9885.

2-(2-Bromophenyl)-2-cyano-*N*-(4-methoxyphenyl)ethanethioamide (3b)



Reaction time: 4 h

Yield: 48%, as a yellow colour viscous liquid.

R_f: 0.40 in 33% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3274, 2923, 2365, 2340, 2247, 2190, 1605, 1509, 1467, 1439, 1405, 1300, 1249, 1027, 832, 752.

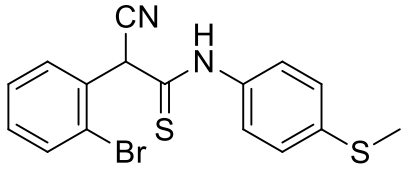
^{1}H NMR (700 MHz, DMSO-D_6) δ 12.18 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.67 (m, 3H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.36 (td, *J* = 7.8, 1.4 Hz, 1H), 7.03 – 6.98 (m, 2H), 3.77 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 189.5, 157.6, 133.1, 132.9, 131.9, 130.6, 130.5, 128.2, 124.6, 123.44, 117.0, 113.9, 55.3, 51.2.

HR-MS (ESI): Calcd. for $C_{16}H_{13}BrN_2OS$ [M+Na]: 382.9824, Found: 382.9842.

[M+Na]: 384.9804, Found: 384.9831.

2-(2-Bromophenyl)-2-cyano-*N*-(4-(methylthio)phenyl)ethanethioamide (3c)



Reaction time: 4 h

Yield: 80%, as a yellow colour viscous liquid.

R_f: 0.32 in 25% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3275, 2916, 2363, 2344, 2251, 1589, 1492, 1389, 1202, 1178, 1093, 1026, 815, 736.

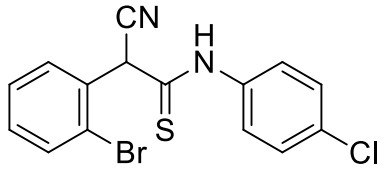
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.98 (s, 1H), 7.80 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.47 (td, *J* = 7.6, 1.2 Hz, 1H), 7.33 (td, *J* = 7.8, 1.6 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 5.70 (s, 1H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.8, 138.5, 135.0, 133.8, 131.9, 131.5, 130.9, 129.0, 126.8, 124.1, 123.9, 116.7, 53.6, 15.8.

HR-MS (ESI): Calcd. for $C_{16}H_{13}BrN_2S_2$ [M+H]: 376.9776, Found: 376.9782.

[M+H]: 378.9756, Found: 378.9759.

2-(2-Bromophenyl)-*N*-(4-chlorophenyl)-2-cyanoethanethioamide (3d)



Reaction time: 4 h

Yield: 48%, as a yellow colour viscous liquid.

R_f: 0.30 in 20% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3277, 2924, 2361, 2340, 2251, 2198, 1593, 1491, 1470, 1417, 1392, 1265, 1200, 1091, 1027, 1014, 830, 739, 703.

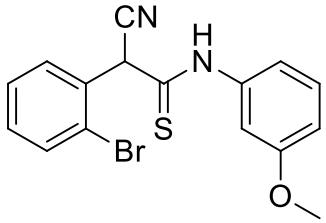
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.26 (s, 1H), 7.77 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.47 – 7.43 (m, 1H), 7.33 – 7.29 (m, 3H), 5.71 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.4, 136.4, 133.7, 132.8, 131.6, 131.4, 130.8, 129.2, 128.8, 125.0, 123.8, 116.8, 53.3.

HR-MS (ESI): Calcd. for $C_{15}H_{10}BrClN_2S$ [M+Na]: 386.9329, Found: 386.9312.

[M+Na]: 388.9308, Found: 388.9286.

2-(2-Bromophenyl)-2-cyano-*N*-(3-methoxyphenyl)ethanethioamide (3e)



Reaction time: 3.5 h

Yield: 45%, as a yellow colour viscous liquid.

R_f: 0.30 in 25% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3292, 2923, 2851, 2365, 2340, 2251, 2194, 1607, 1548, 1490, 1467, 1403, 1265, 1158, 1089, 850, 736.

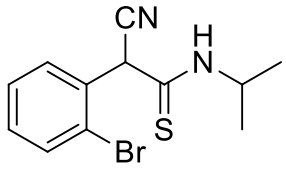
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.25 (s, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.33 – 7.27 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.73 (s, 1H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.8, 160.1, 139.1, 133.8, 132.0, 131.5, 130.8, 130.0, 129.0, 123.9, 116.7, 115.6, 113.4, 109.2, 55.6, 53.9.

HR-MS (ESI): Calcd. for $C_{16}H_{13}BrN_2OS$ [M+H]: 361.0005, Found: 361.0022.

[M+H]: 362.9984, Found: 363.0008.

2-(2-Bromophenyl)-2-cyano-*N*-isopropylethanethioamide (3f)



Reaction time: 3.5 h

Yield: 64%, as a brown colour viscous liquid.

R_f: 0.30 in 25% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3285, 3057, 2973, 2933, 2250, 2186, 1523, 1458, 1438, 1367, 1165, 1126, 1075, 1027, 751, 736.

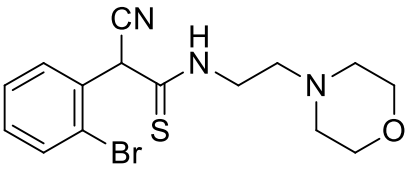
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.63 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.39 (s, 1H), 7.29 (td, *J* = 7.8, 1.6 Hz, 1H), 5.49 (s, 1H), 4.61 – 4.53 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.0, 133.6, 132.0, 131.2, 130.7, 128.8, 123.8, 116.7, 52.5, 48.6, 20.99, 20.98.

HR-MS (ESI): Calcd. for $C_{12}H_{13}BrN_2S$ [M+H]: 297.0056, Found: 297.0083.

[M+H]: 299.0035, Found: 299.0065.

2-(2-Bromophenyl)-2-cyano-*N*-(2-morpholinoethyl)ethanethioamide (3g)



Reaction time: 5 h.

Yield: 48%, as a yellow colour solid.

Melting point: 100 – 102 ^{o}C

R_f: 0.25 in 50% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3448, 3242, 2931, 2869, 2819, 2372, 2345, 2251, 1521, 1458, 1389, 1294, 1276, 1223, 1129, 1113, 1068, 1017, 852, 819, 800, 757.

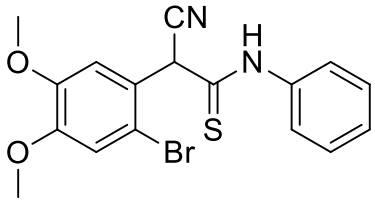
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (s, 1H), 7.75 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.47 (td, *J* = 7.6, 0.8 Hz, 1H), 7.33 (td, *J* = 7.6, 1.6 Hz, 1H), 5.60 (s, 1H), 3.67 – 3.59 (m, 2H), 3.54 (brs, 4H), 2.60 – 2.52 (m, 2H), 2.40 – 2.33 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.9, 133.8, 131.8, 131.3, 130.8, 128.9, 124.1, 116.8, 66.8, 54.7, 52.9, 52.6, 42.4.

HR-MS (ESI): Calcd. for $C_{15}H_{18}BrN_3OS$ [M+H]: 368.0427, Found: 368.0430.

[M+H]: 370.0406, Found: 370.0412.

2-(2-Bromo-4,5-dimethoxyphenyl)-2-cyano-*N*-phenylethanethioamide (3h)



Reaction time: 4 h

Yield: 51%, as a pale yellow colour solid.

Melting point: 161 – 163 °C

R_f: 0.40 in 20% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3270, 2962, 2914, 1592, 1504, 1458, 1401, 1377, 1329, 1267, 1204, 1184, 1162, 1083, 1020, 950, 871, 812, 748, 698.

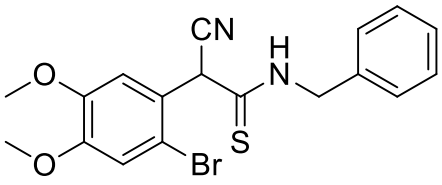
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.90 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.26 (s, 1H), 7.08 (s, 1H), 5.63 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.6, 150.9, 149.6, 138.0, 129.2, 127.7, 123.6, 123.4, 117.0, 115.7, 114.1, 112.3, 56.5 (2C), 53.7.

HR-MS (ESI): Calcd. for $C_{17}H_{15}BrN_2O_2S$ [M+H]: 391.0110, Found: 391.0149.

[M+H]: 393.0090, Found: 393.0129.

***N*-Benzyl-2-(2-bromo-4,5-dimethoxyphenyl)-2-cyanoethanethioamide (3i)**



Reaction time: 4 h

Yield: 50%, as a pale yellow colour solid.

Melting point: 116 – 118 °C

R_f: 0.32 in 33% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3306, 2935, 2843, 1600, 1505, 1455, 1379, 1340, 1265, 1227, 1166, 1028, 946, 860, 815, 737, 700.

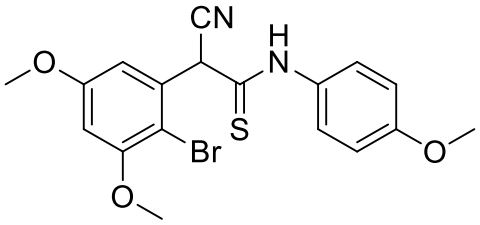
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (s, 1H), 7.36 – 7.29 (m, 3H), 7.25 – 7.23 (m, 2H), 7.15 (s, 1H), 7.02 (s, 1H), 5.52 (s, 1H), 4.87 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.75 (dd, *J* = 15.0, 5.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.2, 150.7, 149.5, 135.3, 129.1, 128.5, 128.1, 123.4, 117.0, 115.6, 114.1, 112.3, 56.45, 56.42, 52.1, 50.8.

HR-MS (ESI): Calcd. for $C_{18}H_{17}BrN_2O_2S$ [M+Na]: 427.0086, Found: 427.0092.

[M+Na]: 429.0066, Found: 429.0073.

2-(2-Bromo-3,5-dimethoxyphenyl)-2-cyano-*N*-(4 –methoxyphenyl)ethanethioamide (3j)



Reaction time: 4 h

Yield: 58%, as a yellow colour viscous liquid.

R_f: 0.32 in 33% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3282, 3007, 2938, 2839, 2360, 2340, 2250, 2198, 1589, 1510, 1455, 1331, 1300, 1251, 1205, 1167, 1085, 1026, 929, 832, 737,702.

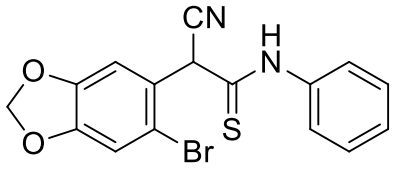
^{1}H NMR (700 MHz, DMSO-D_6) δ = 7.63 – 7.56 (m, 2H), 7.05 – 6.95 (m, 2H), 6.83 (d, *J* = 2.8 Hz, 1H), 6.77 (d, *J* = 2.8 Hz, 1H), 5.89 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ = 190.0, 159.9, 158.1, 157.2, 134.7, 132.3, 125.2, 117.4, 114.4, 108.2, 104.0, 100.0, 57.1, 56.1, 55.8, 52.0.

HR-MS (ESI): Calcd. for $C_{18}H_{17}BrN_2O_3S$ [M+H]: 421.0216, Found: 421.0250.

[M+H]: 423.0196, Found: 423.0229.

2-(2-Bromo-4,5-methylenedioxy-phenyl)-2-cyano-*N*-phenylethanethioamide (3k)



Reaction time: 4 h.

Yield: 53%, as a yellow colour solid.

Melting point: 58 – 60 ºC

R_f: 0.30 in 25% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3273, 2917, 2361, 2344, 2251, 2201, 1597, 1501, 1478, 1410, 1245, 1120, 1036, 930, 862, 757.

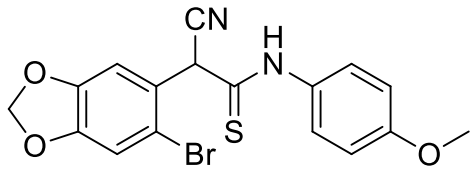
^{1}H NMR (700 MHz, DMSO-D_6) δ = 12.13 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.34 (s, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.15 (s, 1H), 6.15 (d, *J* = 2.1 Hz, 2H), 5.86 (s, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ = 190.3, 149.8, 148.6, 137.9, 129.2, 127.7, 124.7, 123.7, 116.8, 114.9, 113.2, 109.9, 102.8, 53.5.

HR-MS (ESI): Calcd. for $C_{16}H_{11}BrN_2O_2S$ [M+H]: 374.9797, Found: 374.9728.

[M+H]: 376.9777, Found: 376.9710.

2-(2-Bromo-4,5-methylenedioxy-phenyl)-2-cyano-*N*-(4-methoxyphenyl)ethanethioamide (3l)



Reaction time: 4 h

Yield: 53%, as a pale yellow colour viscous liquid.

R_f: 0.28 in 33% ethyl acetate in hexane

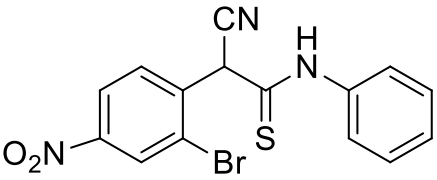
^{1}H NMR (700 MHz, DMSO-D_6) δ = 12.03 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 2H), 7.35 (s, 1H), 7.17 (s, 1H), 7.06 – 6.96 (m, 2H), 6.16 (d, *J* = 2.8 Hz, 2H), 5.85 (s, 1H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.3, 158.8, 149.8, 148.7, 130.9, 125.5, 124.8, 116.9, 115.0, 114.4, 113.2, 110.0, 102.8, 55.6, 53.2.

HR-MS (ESI): Calcd. for $C_{17}H_{13}BrN_2O_3S$ [M+H]: 404.9903, Found: 404.9866.

[M+H]: 406.9883, Found: 406.9848.

2-(2-Bromo-4-nitro-phenyl)-2-cyano-*N*-phenylethanethioamide (3m)

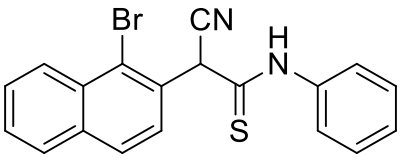


Reaction time: 3 h

R_f: 0.35 in 30% ethyl acetate in hexane

The compound **3m** was decomposed during flash chromatography. We proceeded next step without purification.

2-(1-Bromonaphthalen-2-yl)-2-cyano-*N*-phenylethanethioamide (3n)



Reaction time: 4 h

Yield: 49%, as a yellow colour solid.

Melting point: 101 – 103 ^{o}C

R_f: 0.30 in 20% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3448, 3306, 2924, 2370, 2345, 2243, 2186, 1544, 1492, 1399, 1283, 1196, 1113, 1026, 962, 813, 754.

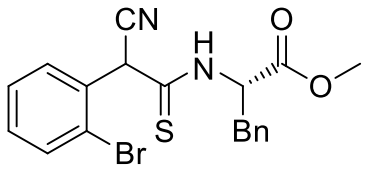
^{1}H NMR (700 MHz, DMSO-D_6) δ = 12.32 (s, 1H), 8.26 (d, *J* = 9.1 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.77 - 7.74 (m, 3H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 1H), 6.26 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.2, 138.0, 134.7, 132.4, 130.0, 129.7, 129.2, 128.8, 128.6, 128.2, 128.1, 127.7, 126.0, 125.2, 123.8, 116.9, 54.8.

HR-MS (ESI): Calcd. for $C_{19}H_{13}BrN_2S$ [M+H]: 381.0056, Found: 381.0060.

[M+H]: 383.0035, Found: 383.0041.

Methyl 2-(2-(2-bromophenyl)-2-cyanoethanethioamido)-3-phenylpropanoate (3o)



Reaction time: 4 h

Yield: 63%, as a yellow colour viscous liquid.

R_f: 0.30 in 20% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3326, 3058, 3030, 2952, 2362, 2336, 2250, 1741, 1513, 1470, 1438, 1409, 1349, 1218, 1084, 1027, 739, 702.

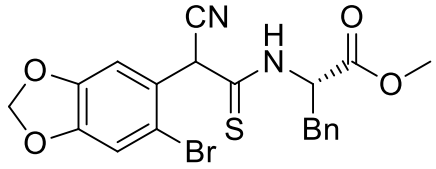
^1H NMR (400 MHz, $CDCl_3$ [*dr* (1 : 1.25)]) δ = 7.82 (brs, 2H), 7.71 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.64 – 7.59 (m, 3H), 7.44 – 7.38 (m, 2H), 7.33 – 7.28 (m, 3H), 7.254 – 7.249 (m, 1H), 7.18 – 7.12 (m, 4H), 7.02 – 7.00 (m, 2H), 6.78 – 6.76 (m, 2H), 5.62 (s, 1H), 5.57 (s, 1H), 5.28 – 5.22 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.40 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.37 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.19 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.11 (dd, *J* = 14.0, 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$ [*dr* (1 : 0.80)]) δ = 191.6, 191.4, 170.6, 170.5, 134.9, 134.6, 133.7, 131.7, 131.5, 131.3, 130.6, 130.4, 129.2, 129.1 (2C), 129.0, 128.95, 128.87, 128.85 (2C), 127.6, 127.5, 123.94, 123.92, 116.6, 116.5, 59.1, 59.0, 52.94, 52.88, 52.4, 52.3, 36.0, 35.6.

HR-MS (ESI): Calcd. for $C_{19}H_{17}BrN_2O_2S$ [M+H]: 417.0267, Found: 417.0251.

[M+H]: 419.0247, Found: 419.0235.

Methyl-2-(2-(2-bromo-4,5-methylenedioxy-phenyl)-2-cyanoethanethioamido)-3-phenyl propanoate (3p)



Reaction time: 5 h.

Yield: 43%, as a yellow colour viscous liquid.

R_f: 0.30 in 25% ethyl acetate in hexane

IR (as film in CCl_4): ν (cm^{-1}) = 3327, 3030, 2918, 2361, 2340, 2251, 2202, 1740, 1504, 1479, 1436, 1350, 1244, 1120, 1083, 1036, 929, 864, 737, 702.

HR-MS (ESI): Calcd. for $C_{20}H_{17}BrN_2O_4S$ [M+H]: 461.0165, Found: 461.0165.

The compound **3p** exists in diasteromers. NMR spectra of ^1H and ^{13}C are not clean. We proceed next step without further analysis.

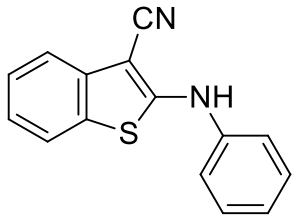
Procedure for the Optimization of the Ullmann Reaction of Thioamide 3a at Room Temperature

An oven-dried 8 mL reaction vial was charged with copper-salt (5 mol%), ligand (10 mol%) and base (0.75 mmol), thioamide **3a** (0.5 mmol) in solvent (2.0 mL) was stirred at room temperature for 2 h. After 2 h, the reaction mixture was purified by flash chromatography.

General Procedure for the Synthesis of 2-Aminobenzo[*b*]thiophenes at Room Temperature by Ullmann Coupling Reaction

An oven-dried 8 mL reaction vial was charged with CuBr (5 mol%), 1,10-phenanthroline (10 mol%) and Et_3N (0.75 mmol), respective thioamide (0.5 mmol) in DMF (2.0 mL) was stirred at room temperature for 1-3 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

3-Cyano-2-(phenylamino)benzo[*b*]thiophene (4a)



Reaction time: 2 h

Yield: 88% as a white colour solid.

Melting point: 134 – 136 ^oC

R_f: 0.42 in 20% ethyl acetate in hexane

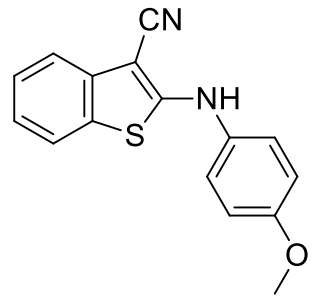
IR (KBr): ν (cm^{-1}) = 3436, 3263, 2211, 1602, 1561, 1426, 1081, 744.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.44 – 7.36 (m, 5H), 7.25 – 7.19 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.7, 140.1, 136.6, 129.9, 129.1, 126.2, 125.2, 123.8, 122.0, 120.3, 119.8, 115.4, 83.8.

HR-MS (ESI): Calcd. for $C_{15}H_{10}N_2S$ [M+H]: 251.0637, Found: 251.0655.

3-Cyano-2-[(4-methoxyphenyl)amino]benzo[*b*]thiophene (4b)



Reaction time: 2 h

Yield: 78%, as a pale yellow colour solid.

Melting point: 193 – 195 ^oC

R_f: 0.34 in 10% ethyl acetate in hexane

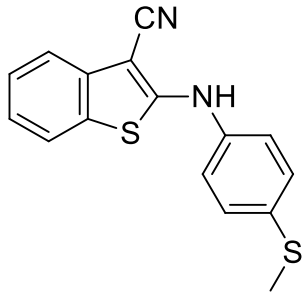
IR (KBr): ν (cm^{-1}) = 3440, 3261, 2210, 2202, 1598, 1566, 1513, 1466, 1438, 1247, 1027, 751.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.0, 158.1, 137.1, 132.9, 128.9, 126.2, 124.1, 123.4, 121.1, 119.7, 115.1 (2C), 81.8, 55.7.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2OS$ [M+H]: 281.0743, Found: 281.0778.

3-Cyano-2-[(4-(methylthio)phenyl)amino]benzo[*b*]thiophene (4c)



Reaction time: 2.5 h

Yield: 94%, as a white colour solid.

Melting point: 182 – 184 ^{o}C

R_f: 0.39 in 20% ethyl acetate in hexane

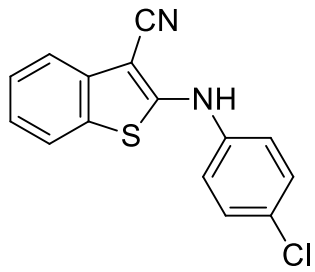
IR (KBr): ν (cm^{-1}) = 3432, 3254, 2914, 2207, 1602, 1555, 1497, 1465, 1435, 1319, 1096, 825, 748.

^{1}H NMR (400 MHz, DMSO) δ = 10.22 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, DMSO) δ = 160.8, 138.2, 137.0, 133.7, 128.5, 127.4, 126.1, 123.4, 122.5, 121.4, 118.6, 115.0, 82.0, 15.3.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2S_2$ [M+H]: 297.0515, Found: 297.0531.

3-Cyano-2-[(4-chlorophenyl)amino]benzo[*b*]thiophene (4d)



Reaction time: 2.5 h

Yield: 66%, as a pale yellow colour solid.

Melting point: 240 – 242 ^{o}C

R_f: 0.42 in 20% ethyl acetate in hexane

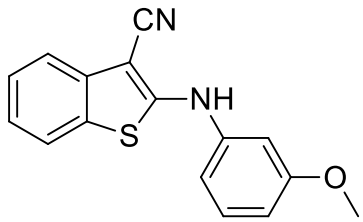
IR (KBr): ν (cm^{-1}) = 3449, 3246, 2213, 1565, 1439, 1088, 822, 743.

^{1}H NMR (400 MHz, DMSO) δ = 10.31 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.39 (m, 5H), 7.27 (t, *J* = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO) δ = 159.9, 139.9, 136.8, 129.4, 128.8, 127.9, 126.2, 123.8, 122.6, 121.7, 118.9, 114.8, 83.5.

HR-MS (ESI): Calcd. for $C_{15}H_9ClN_2S$ [M+H]: 285.0248, Found: 285.0209.

3-Cyano-2-[(3-methoxyphenyl)amino]benzo[*b*]thiophene (4e)



Reaction time: 2.5 h

Yield: 82%, as a yellow colour solid.

Melting point: 149 – 151 ºC

R_f: 0.40 in 20% ethyl acetate in hexane

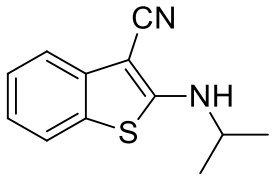
IR (KBr): ν (cm^{-1}) = 3428, 3282, 2953, 2197, 1596, 1558, 1292, 1163, 1053, 774, 751.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.59 – 7.53(m, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 6.95 (s, 1H), 6.93 (brs, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.9, 160.3, 141.3, 136.5, 130.7, 129.3, 126.2, 123.8, 122.0, 119.8, 115.4, 112.2, 110.6, 105.8, 84.0, 55.6.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2OS$ [M+H]: 281.0743, Found: 281.0770.

3-Cyano-2-(isopropylamino)benzo[*b*]thiophene (4f)



Reaction time: 1.5 h

Yield: 93%, as a white colour solid.

Melting point: 106 – 109 ºC

R_f: 0.43 in 20% ethyl acetate in hexane

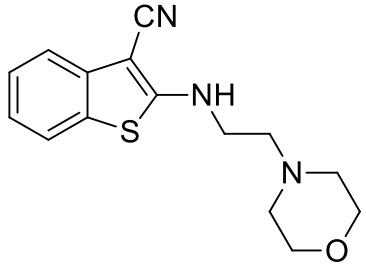
IR (KBr): ν (cm^{-1}) = 3446, 3323, 2973, 2372, 2346, 2194, 1560, 1451, 1169, 1075, 745.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* =8.0d Hz, 1H), 7.35 – 7.31 (m, 1H), 7.15 – 7.11 (m, 1H), 5.24 (s, 1H), 3.70 – 3.67 (m, 1H), 1.36 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.3, 137.8, 128.7, 126.0, 122.5, 121.9, 119.3, 116.2, 78.2, 50.3, 23.1.

HR-MS (ESI): Calcd. for $C_{12}H_{12}N_2S$ [M+H]: 217.0794, Found: 217.0821.

3-Cyano-2-[(2-morpholinoethyl)amino)benzo[*b*]thiophene (4g)



Reaction time: 2.5 h

Yield: 79%, as a brown colour viscous liquid.

R_f: 0.35 in 20% ethyl acetate in hexane

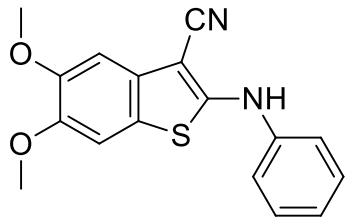
IR (as film in CCl_4): ν (cm^{-1}) = 3428, 3273, 2923, 2852, 2369, 2198, 1560, 1458, 1116, 864, 760.

^{1}H NMR (400 MHz, DMSO) δ = 8.24 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.32 (m, 2H), 7.15 – 7.11 (m, 1H), 3.63 (brs, 4H), 3.52 (brs, 2H), 2.67 – 2.59 (m, 6H).

^{13}C NMR (100 MHz, DMSO) δ = 164.9, 138.2, 127.8, 126.4, 126.0, 122.3, 122.2, 117.8, 116.2, 75.3, 65.7, 56.3, 52.9.

HR-MS (ESI): Calcd. for $C_{15}H_{17}N_3OS$ [M+H]: 288.1165, Found: 288.1129.

3-Cyano-5, 6-dimethoxy-2-(phenylamino)benzo[*b*]thiophene (4h)



Reaction time: 2 h

Yield: 77%, as a light brown colour solid.

Melting point: 180 – 182 ^{o}C

R_f: 0.32 in 25% ethyl acetate in hexane

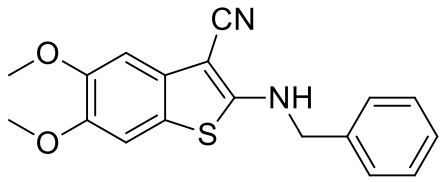
IR (KBr): ν (cm^{-1}) = 3272, 2993, 2963, 2199, 1601, 1562, 1491, 1474, 1461, 1435, 1402, 1298, 1246, 1208, 1173, 1083, 1033, 960, 836, 762, 700, 621.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.37 (m, 2H), 7.31 – 7.29 (m, 2H), 7.18 – 7.14 (m, 1H), 7.09 (s, 1H), 7.06 (s, 1H), 7.04 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.6, 149.5, 147.6, 140.4, 129.9, 129.8, 124.6, 121.1, 119.4, 115.5, 104.6, 102.4, 85.1, 56.5, 56.3.

HR-MS (ESI): Calcd. for $C_{17}H_{14}N_2O_2S$ [M+H]: 311.0849, Found: 311.0890.

2-(Benzylamino)-3-cyano-5,6-dimethoxybenzo[*b*]thiophene (4i)



Reaction time: 1 h

Yield: 97%, as a pale yellow colour solid.

Melting point: 168 – 170 ^{o}C

R_f: 0.32 in 33% ethyl acetate in hexane

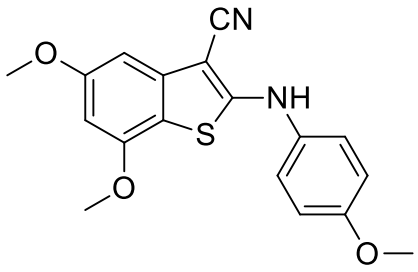
IR (KBr): ν (cm^{-1}) = 3304, 2923, 2193, 1570, 1489, 1401, 1292, 1241, 1204, 1169, 1038, 829.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.33 (m, 5H), 7.00 (s, 1H), 6.98 (s, 1H), 5.64 (brs, 1H), 4.50 (d, *J* = 5.2 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.2, 149.3, 146.6, 136.5, 130.9, 129.1, 128.4, 127.8, 120.1, 116.2, 104.9, 102.1, 79.2, 56.5, 56.3, 51.5.

HR-MS (ESI): Calcd. for $C_{18}H_{16}N_2O_2S$ [M+H]: 325.1005, Found: 325.1047.

3-Cyano-5,7-dimethoxy-2-[(4-methoxyphenyl)amino]benzo[*b*]thiophene (4j)



Reaction time: 2 h

Yield: 79%, as a pale brown colour solid.

Melting point: 188 – 189 ^{o}C

R_f: 0.36 in 25% ethyl acetate in hexane

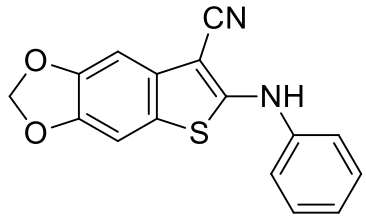
IR (KBr): ν (cm^{-1}) = 3448, 3254, 2926, 2373, 2208, 1577, 1549, 1513, 1437, 1297, 1248, 1203, 1148, 1105, 1027, 833, 804.

^{1}H NMR (400 MHz, DMSO) δ = 10.01 (s, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.54 (s, 1H), 6.44 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, DMSO) δ = 163.3, 160.2, 156.8, 154.0, 138.9, 133.8, 123.6, 115.3, 114.6, 107.2, 94.6, 94.4, 80.6, 55.9, 55.5, 55.3.

HR-MS (ESI): Calcd. for $C_{18}H_{16}N_2O_3S$ [M+H]: 341.0954, Found: 341.0964.

3-Cyano-5, 6-methylenedioxy-2-(phenylamino)benzo[*b*]thiophene (4k)[1]



Reaction time: 2.5 h

Yield: 68%, as a brown colour solid.

Melting point: 222 – 225 ^{o}C

R_f: 0.37 in 20% ethyl acetate in hexane

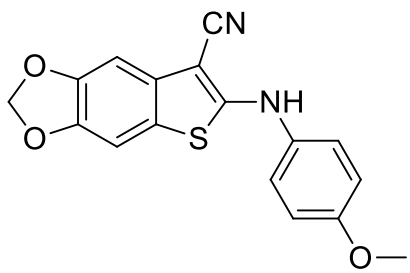
IR (KBr): ν (cm^{-1}) = 3441, 3255, 2371, 2345, 2204, 1561, 1474, 1295, 1052, 945, 823, 695.

^{1}H NMR (400 MHz, DMSO) δ = 9.97 (s, 1H), 7.41 (s, 1H), 7.39 – 7.34 (m, 4H), 7.10 (t, *J* = 5.6 Hz, 1H), 6.99 (s, 1H), 6.07 (s, 2H).

^{13}C NMR (100 MHz, DMSO) δ = 158.9, 147.3, 145.2, 141.4, 130.7, 129.4, 123.6, 121.2, 119.4, 114.9, 102.7, 101.4, 98.9, 84.3.

HR-MS (ESI): Calcd. for $C_{16}H_{10}N_2O_2S$ [M+H]: 295.0536, Found: 295.0565.

3-Cyano-5, 6-methylenedioxy-2-[(4-phenylamino)benzo[b]thiophene (4l)



Reaction time: 3 h

Yield: 53%, as a brown colour solid.

Melting point: 207 – 210 ^{o}C

R_f: 0.35 in 25% ethyl acetate in hexane

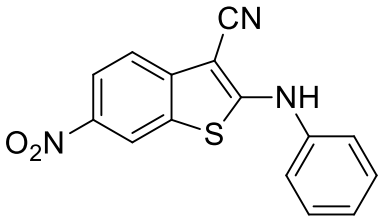
IR (KBr): ν (cm^{-1}) = 3408, 3293, 2371, 2345, 2197, 1597, 1406, 1291, 1257, 1036, 930, 831.

^{1}H NMR (400 MHz, DMSO) δ = 9.80 (s, 1H), 7.34 – 7.28 (m, 3H), 7.09 – 6.84 (m, 3H), 6.03 (s, 2H), 3.75 (s, 3H).

^{13}C NMR (100 MHz, DMSO) δ = 161.6, 156.6, 147.2, 144.7, 134.2, 131.3, 123.2, 120.4, 115.3, 114.7, 102.8, 101.4, 98.7, 81.0, 55.4.

HR-MS (ESI): Calcd. for $C_{17}H_{12}N_2O_3S$ [M+H]: 325.0641, Found: 325.0674.

6-Nitro-2-(phenylamino)benzo[*b*]thiophene-3-carbonitrile (4m)



Reaction time: 6 h

Yield: 66%, as a yellow colour solid.

Melting point: 257 - 258 ºC

R_f: 0.33 in 20% ethyl acetate in hexane

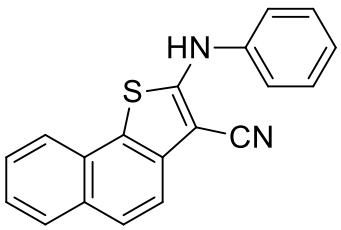
IR (KBr): ν (cm^{-1}) = 3255, 2211, 1595, 1594, 1557, 1468, 1411, 1328, 1124, 748, 695.

^{1}H NMR (700 MHz, DMSO-D_6) δ = 10.86 (s, 1H), 8.81 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 9.1 Hz, 1H), 7.48 - 7.43(m, 4H), 7.29 (s, 1H).

^{13}C NMR (175 MHz, DMSO-D_6) δ = 166.16, 143.44, 142.64, 139.99, 129.72, 128.15, 126.10, 122.15, 121.75, 119.28, 118.20, 114.25, 80.88.

HR-MS (ESI): Calcd. for $C_{15}H_9N_3O_2S$ [M+Na]: 318.0308, Found: 318.0312.

3-Cyano-2-(phenylamino)naphtha[1,2-*b*]thiophene (4n)



Reaction time: 2 h

Yield: 82%, as a brown colour solid.

Melting point: 204 – 207 ºC

R_f: 0.40 in 20% ethyl acetate in hexane

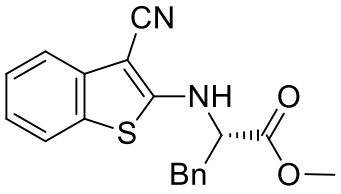
IR (KBr): ν (cm^{-1}) = 3432, 3261, 2927, 2209, 1560, 1086, 804, 695.

^{1}H NMR (400 MHz, DMSO) δ = 10.30 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.47 – 7.41 (m, 4H), 7.19 – 7.16 (m, 1H).

^{13}C NMR (100 MHz, DMSO) δ = 159.8, 141.2, 134.7, 130.0, 129.6, 129.1, 127.6, 127.6, 127.1, 125.2, 124.3, 123.6, 122.4, 120.0, 118.0, 114.9, 85.0.

HR-MS (ESI): Calcd. for $C_{19}H_{12}N_2S$ [M+H]: 301.0794, Found: 301.0810.

(*S*)-Methyl 2-[(3-cyanobenzo[*b*]thiophen-2-yl)amino]-3-phenylpropanoate (4o)



Reaction time: 3 h
Yield: 72%, >99% *ee* as a white colour solid.
$[\alpha]_D^{22.7}$ = -1.6 (*c* = 0.30, CH_2Cl_2)
Melting point: 110 – 112 ^oC

R_f: 0.37 in 20% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3428, 3316, 2927, 2200, 1725, 1559, 1384, 1288, 1175, 1115, 748.

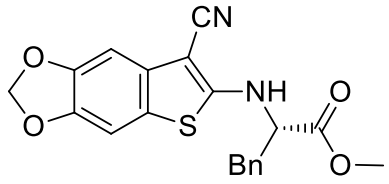
^1H NMR (400 MHz, $CDCl_3$) δ = 7.55 – 7.52 (m, 2H), 7.38 – 7.27 (m, 4H), 7.20 – 7.16 (m, 3H), 5.68 (d, *J* = 8.8 Hz, 1H), 4.52 – 4.47 (m, 1H), 3.77 (s, 3H), 3.31 (dd, *J* = 13.8, 5.6 Hz, 1H), 3.22 (dd, *J* = 13.8, 6.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9, 162.7, 137.7, 134.9, 129.4, 129.0, 128.9, 127.8, 126.3, 123.3, 121.9, 119.8, 115.2, 81.0, 60.9, 52.9, 38.8.

HR-MS (ESI): Calcd. for $C_{19}H_{16}N_2O_2S$ [M+H]: 337.1005, Found: 337.1029.

HPLC: Chiralcel OD-H column, hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}; Major enantiomer t_R = 6..45.

(*2*S)-Methyl 2-[(3-cyano-5,6-methylenedioxy-benzo[*b*]thiophen-2-yl)amino]-3-phenylpropanoate (4p)



Reaction time: 2.5 h.
Yield: 65%, 97% *ee* as a white colour solid.
$[\alpha]_D^{22.7}$ = -5.3 (*c* = 0.60, CH_2Cl_2)
Melting point: 148 – 150 ^oC

R_f: 0.38 in 20% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3441, 3311, 2953, 2373, 2346, 2202, 1727, 1555, 1485, 1283, 1220, 1082, 939, 841, 701.

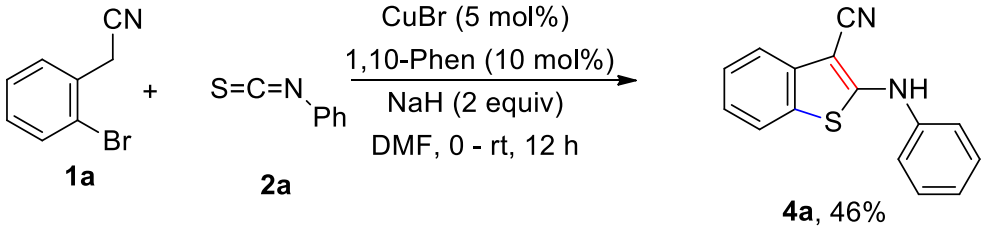
^1H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.27 (m, 3H), 7.17 – 7.15 (m, 2H), 6.99 (s, 1H), 6.95 (s, 1H), 5.98 (s, 2H), 5.49 (brs, 1H), 4.42 (brs, 1H), 3.76 (s, 3H), 3.27 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.19 (dd, *J* = 14.0, 6.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.1, 161.6, 147.8, 145.3, 135.0, 131.8, 129.4, 129.0, 127.7, 120.9, 115.2, 102.0, 101.5, 100.2, 81.7, 60.9, 52.9, 38.8.

HR-MS (ESI): Calcd. for $C_{20}H_{16}N_2O_4S$ [M+H]: 381.0904, Found: 381.0901.

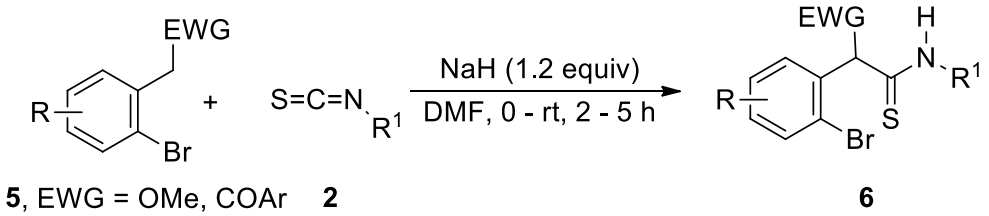
HPLC: Chiralcel OD-H column, hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL min^{-1}; t_R minor enantiomer (2*R*) t_R = 6.51; major enantiomer (2*S*) t_R = 7.82 min.

Scheme 2S: One-pot Procedure for the Synthesis of 2-Aminobenzo[*b*]thiophene 4a from 1a



To a stirring suspension of CuBr (5 mol%), 1,10-phenanthroline (10 mol%), and NaH (60% suspension in mineral oil) (4 mmol) in DMF (5.0 mL) at 0 °C was added drop wise 2-bromobenzylnitrile (2 mmol) in DMF (3.0 mL). After being further stirred for 1 h at room temperature, a solution of phenyl isothiocyanate (2.2 mmol) in DMF (2.0 mL) was added to the reaction mixture at 0 °C and followed by further stirring for 12 h at room temperature. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layer washed with water (3 x 25 mL) & brine (25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using EtOAc/hexanes as eluent. The 3-cyano-2-(phenylamino)benzo[*b*]thiophene was isolated as a white colour solid in 46% yield.

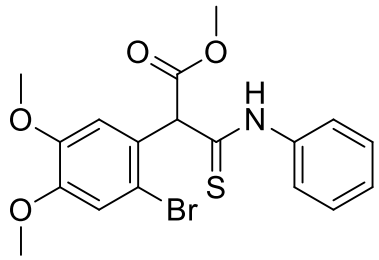
Scheme 3S: General Procedure for the Synthesis of *β*-Carboxyl and *β*-Carbonyl thioamides 6



To a stirring suspension of NaH (60% suspension in mineral oil) (3.6 mmol) in DMF (5.0 mL) at 0 °C was added drop wise the corresponding methyl-2-(2-bromoaryl)acetate/deoxybenzoin (3 mmol) in DMF (3.0 mL). After being further stirred for 1

h at room temperature, a solution of isothiocyanate (3.3 mmol) in DMF (2.0 mL) was added to the reaction mixture at 0 ^{o}C and followed by further stirring for 2 h at room temperature. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layer washed with water (3 x 25 mL) & brine (25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by flash chromatography using EtOAc/hexanes as eluent.

Methyl 2-(2-Bromo-4,5-dimethoxyphenyl)-3-(phenylamino)-3-thioxopropanoate (6a)



Reaction time: 3.5 h

Yield: 37%, as a white colour solid.

Melting point: 138 – 140 ^{o}C

R_f: 0.38 in 33% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3287, 2951, 2842, 2360, 2341, 1738, 1598, 1505, 1436, 1402, 1380, 1263, 1208, 1164, 1027, 860, 759, 700.

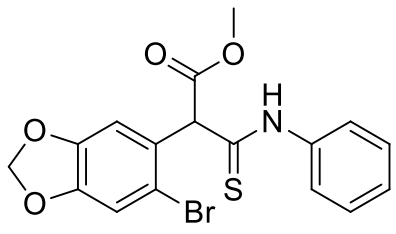
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.91 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.41 – 7.39 (m, 2H), 7.29 – 7.27 (m, 1H), 7.22 (s, 1H), 7.08 (s, 1H), 5.62 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.7, 171.0, 149.9, 149.0, 138.4, 129.8, 129.1, 127.3, 126.3, 125.4, 123.7, 115.9, 115.6, 112.0, 64.7, 56.34, 56.32, 53.2.

HR-MS (ESI): Calcd. for $C_{18}H_{18}BrNO_4S$ [M+H]: 424.0213, Found: 424.0243.

[M+H]: 426.0193, Found: 426.0221.

Methyl 2-(2-bromo-4,5-methylenedioxy-phenyl)-3-(phenylamino)-3-thioxopropanoate (6b)



Reaction Time: 4 h

Yield: 57%, as a yellow colour viscous liquid.

R_f: 0.28 in 20% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3348, 2912, 1724, 1599, 1556, 1499, 1479, 1405, 1286, 1261, 1240, 1110, 1033,`1016, 927, 763, 692.

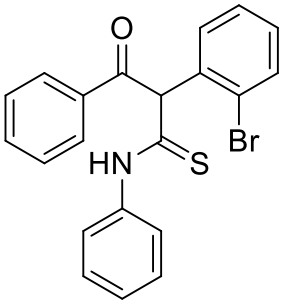
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.10 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.08 (s, 1H), 6.01 (s, 2H), 5.64 (s, 1H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.3, 171.1, 148.8, 148.1, 138.4, 129.1, 127.7, 127.3, 123.7, 116.2, 113.3, 109.1, 102.4, 64.5, 53.3.

HR-MS (ESI): Calcd. for $C_{17}H_{14}BrNO_4S$ [M+H]: 407.9900, Found: 407.9916.

[M+H]: 409.9880, Found: 409.9906.

2-(2-Bromophenyl)-3-oxo-*N*,3-diphenylpropanethioamide (6c)



Reaction Time: 4 h

Yield: 51%, as a yellow colour solid.

Melting point: 119 – 121 ^{o}C

R_f: 0.33 in 20% ethyl acetate in hexane

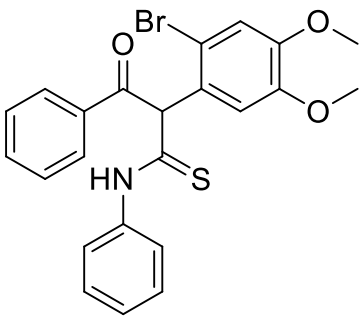
^{1}H NMR (400 MHz, $CDCl_3$) [enol : keto (1 : 1.5)] δ = 15.67 (s, 1H), 9.76 (s, 1H), 8.14 – 8.12 (m, 2H), 7.75 (s, 1H), 7.70 – 7.68 (m, 3H), 7.64 – 7.56 (m, 4H), 7.51 – 7.47 (m, 2H), 7.42 – 7.33 (m, 6H), 7.31 – 7.27 (m, 2H), 7.25 – 7.21 (m, 4H), 7.21 – 7.19 (m, 1H), 7.17 – 7.16 (m, 1H), 7.17 – 7.13 (m, 3H), 6.89 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) [enol : keto (1 : 1.5)] δ = 197.3, 195.2, 191.1, 172.4, 138.5, 137.7, 137.0, 136.8, 136.2, 135.2, 134.9, 134.4, 134.3, 133.7, 132.93, 132.92, 130.4, 130.3, 130.0, 129.5, 129.4, 129.3, 129.2, 129.1, 129.09, 129.08, 128.8, 128.6, 128.5, 128.2, 128.1, 127.8, 127.6, 127.3, 126.4, 126.2, 125.7, 125.5, 123.7, 119.1, 112.9, 68.3.

HR-MS (ESI): calcd. for $C_{21}H_{16}BrNOS$ [M+Na]: 432.0028, Found: 432.0041.

[M+Na]: 434.0008, Found: 434.0023.

2-(2-Bromo-4,5-dimethoxyphenyl)-3-oxo-*N*,3-diphenylpropanethioamide (6d)



Reaction time: 2.5 h

Yield: 91%, as a yellow colour solid.

Melting point: 154 – 156 ^{o}C

R_f: 0.28 in 25% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3448, 3277, 2931, 2367, 2345, 1684, 1579, 1501, 1460, 1445, 1376, 1319, 1259, 1204, 1167, 1027, 831, 781, 693.

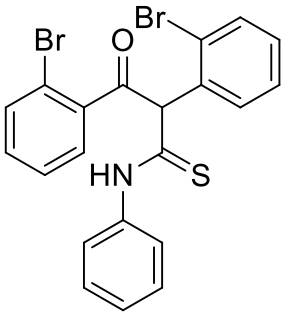
^{1}H NMR (400 MHz, $CDCl_3$) [keto : enol (1 : 0.93)] δ = 15.65 (s, 1H), 9.71 (s, 1H), 8.11 – 8.09 (m, 2H), 7.96 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.42 – 7.36 (m, 6H), 7.29 – 7.25 (m, 4H), 7.22 – 7.15 (m, 3H), 7.13 (s, 1H), 7.08 (s, 1H), 7.06 (s, 1H), 6.77 (s, 1H), 6.61 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.63 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) [keto : enol (1 : 1.06)] δ = 197.5, 196.2, 190.9, 172.5, 149.97, 149.93, 149.2, 149.1, 138.5, 137.7, 137.0, 136.3, 134.3, 129.3, 129.20 129.12, 129.10, 129.0, 128.5, 127.91, 127.87, 127.5, 127.3, 126.2, 126.0, 123.8, 118.2, 116.9, 116.6, 116.1, 115.7, 112.8, 111.7, 67.41, 56.4 (2C), 56.29, 56.26.

HR-MS (ESI): Calcd. for $C_{23}H_{20}BrNO_3S$ [M+H]: 470.0420, Found: 470.0422.

[M+H]: 472.0400, Found: 472.0405.

2,3-Bis(2-bromophenyl)-3-oxo-*N*-phenylpropanethioamide (6e)



Reaction time: 4.5 h

Yield: 77%, as a pale yellow colour solid.

Melting point: 168 – 170 ^{o}C

R_f: 0.35 in 20% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3444, 3322, 2370, 2345, 1572, 1498, 1466, 1309, 1229, 1190, 1087, 1024, 924, 797, 752, 695.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 15.56 (s, 1H), 7.76 (s, 1H), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.42 – 7.36 (m, 4H), 7.32 – 7.25 (m, 2H), 7.17 (td, *J* = 7.5, 1.2 Hz, 1H), 7.10 – 7.01 (m, 3H).

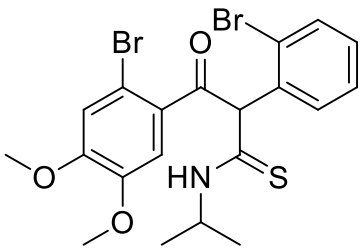
^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.2, 171.0, 137.8, 137.5, 136.2, 133.7, 133.4, 132.7, 130.6, 130.3, 129.1, 128.6, 127.7, 127.2, 127.0, 126.2, 126.1, 121.3, 113.8.

HR-MS (ESI): Calcd. for $C_{21}H_{15}Br_2NOS$ [M+H]: 487.9314, Found: 487.9297.

[M+H]: 489.9294, Found: 489.9285.

[M+H]: 491.9273, Found: 491.9258.

3-(2-Bromo-4,5-dimethoxyphenyl)-2-(2-bromophenyl)-*N*-isopropyl-3-oxopropane thioamide (6f)



Reaction time: 4 h

Yield: 72%, as a white colour solid.

Melting point: 141 – 143 ^{o}C

R_f: 0.32 in 25% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3345, 2971, 2835, 1601, 1585, 1381, 1252, 1160, 1020, 941, 888, 855, 792, 772.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 15.33 (s, 1H), 7.52 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.28 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.15 (td, *J* = 7.4, 1.2 Hz, 1H), 7.07 (td, *J* = 7.4, 1.6 Hz, 1H), 6.86 (s, 1H), 6.74 (s,

1H), 6.06 (d, *J* = 7.6 Hz, 1H), 4.70 – 4.61 (m, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H).

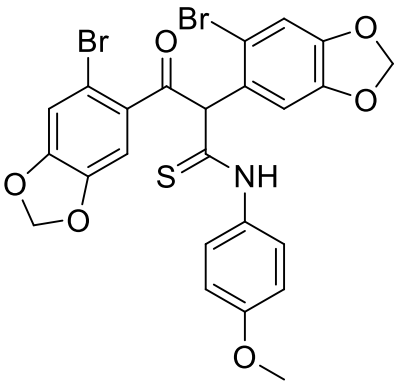
^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.8, 169.1, 149.4, 147.7, 136.6, 133.9, 133.0, 130.5, 130.2, 128.6, 126.9, 115.1, 113.2, 111.7, 111.3, 56.1, 56.0, 45.6, 21.6, 21.2.

HR-MS (ESI): Calcd. for $C_{20}H_{21}Br_2NO_3S$ [M+H]: 513.9682, Found: 513.9668.

[M+H]: 515.9662, Found: 515.9660.

[M+H]: 517.9641, Found: 517.9629.

2,3-Bis(2-bromo-4,5-methylenedioxy-phenyl)-*N*-(4-methoxyphenyl)-3-oxopropanethioamide (6g)



Reaction time: 4 h

Yield: 71%, as a yellow colour solid.

Melting point: 188 – 190 ºC

R_f: 0.37 in 33% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3452, 3346, 2895, 2366, 2345, 1596, 1511, 1500, 1474, 1329, 1249, 1169, 1117, 1028, 934, 835.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 15.46 (s, 1H), 7.79 (s, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 7.02 (s, 1H), 6.94 – 6.90 (m, 4H), 6.80 (s, 1H), 5.97 – 5.91(m, 4H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.4, 170.4, 158.8, 149.1, 148.7, 148.1, 146.9, 131.2, 130.2, 128.8, 127.7, 118.0, 114.3, 113.3, 113.1, 112.8, 112.5, 112.3, 108.1, 102.4, 102.1, 55.6.

HR-MS (ESI): Calcd. for $C_{24}H_{17}Br_2NO_6S$ [M+H]: 605.9216, Found: 605.9224.

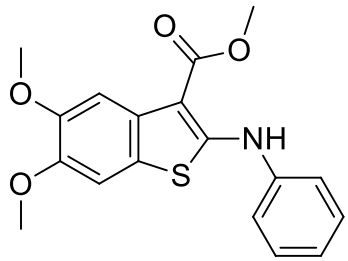
[M+H]: 607.9197, Found: 607.9215.

[M+H]: 609.9176, Found: 609.9193.

General Procedure for the Synthesis of Carbonyl Substituted 2-Aminobenzo[*b*]thiophenes 7 by Ullmann Reaction at Room Temperature

An oven-dried 8 mL reaction vial was charged with CuBr (5 mol%), 1,10-phenanthroline (10 mol%) and Et_3N (0.75 mmol), respective thioamide (0.5 mmol) in DMF (2.0 mL) was stirred at room temperature for 1-3 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

Methyl 5,6-dimethoxy-2-(phenylamino)benzo[*b*]thiophene-3-carboxylate (7a)



Reaction time: 3 h

Yield: 86%, as a pale yellow colour solid.

Melting point: 140 – 142 ^{o}C

R_f: 0.32 in 20% ethyl acetate in hexane

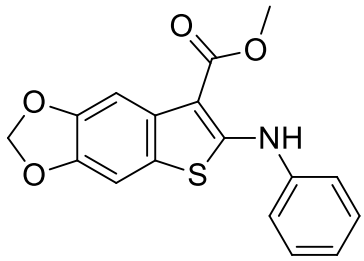
IR (KBr): ν (cm^{-1}) = 3432, 2953, 1654, 1594, 1559, 1496, 1388, 1291, 1253, 1202, 1075, 854, 751.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.37 (s, 1H), 7.70 (s, 1H), 7.41 – 7.36 (m, 4H), 7.16 – 7.13 (m, 1H), 7.02 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0, 160.9, 148.6, 146.5, 140.5, 130.0, 129.7, 124.3, 120.21, 120.20, 105.7, 104.1, 100.5, 56.3, 56.2, 51.4.

HR-MS (ESI): Calcd. for $C_{18}H_{17}NO_4S$ [M+H]: 344.0951, Found: 344.1007.

Methyl 5,6-methylenedioxy-2-(phenylamino)benzo[*b*]thiophene-3-carboxylate (7b)



Reaction time: 2 h

Yield: 88%, as a white colour solid.

Melting point: 134 – 136 ^{o}C

R_f: 0.43 in 20% ethyl acetate in hexane

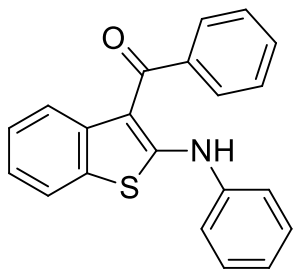
IR (KBr): ν (cm^{-1}) = 2949, 2920, 1658, 1593, 1569, 1500, 1433, 1393, 1287, 1251, 1225, 1206, 1032, 941, 917, 844, 826, 733.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.42 (s, 1H), 7.63 (s, 1H), 7.41 – 7.34 (m, 4H), 7.14 (t, *J* = 6.8 Hz, 1H), 6.95 (s, 1H), 5.97 (s, 2H), 3.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.1, 160.8, 147.3, 144.4, 140.5, 130.8, 129.7, 124.3, 120.6, 120.2, 103.0, 101.4, 101.2, 100.8, 51.3.

HR-MS (ESI): Calcd. for $C_{17}H_{13}NO_4S$ [M+H]: 328.0638, Found: 328.0597.

3-Benzoyl-2-(phenylamino)benzo[*b*]thiophene (7c)



Reaction time: 2 h

Yield: 87%, as a yellow colour solid.

Melting point: 93 – 95 ^{o}C

R_f: 0.32 in 5% ethyl acetate in hexane

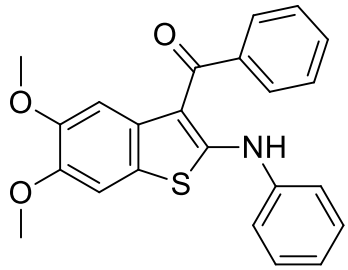
IR (KBr): ν (cm^{-1}) = 3057, 2354, 1586, 1538, 1455, 1351, 1255, 1232, 1197, 1174, 1054, 1022, 897, 849, 799, 752, 723, 696.7

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.08 (s, 1H), 7.65 – 7.63 (m, 2H), 7.58 – 7.53 (m, 2H), 7.50 – 7.43 (m, 6H), 7.25 – 7.21 (m, 1H), 7.09 (td, *J* = 7.2, 1.2 Hz, 1H), 7.03 – 6.99 (m, 1H), 6.72 – 6.70 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.2, 164.2, 141.4, 140.1, 136.9, 131.0, 129.8, 129.1, 128.7, 127.9, 125.3, 125.1, 122.7, 122.0, 121.7, 121.1, 110.2.

HR-MS (ESI): Calcd. for $C_{21}H_{15}NOS$ [M+H]: 330.0947, Found: 330.0913.

3-Benzoyl-5,6-dimethoxy-2-(phenylamino)benzo[*b*]thiophene (7d)



Reaction time: 2 h

Yield: 92%, as a yellow colour solid.

Melting point: 159 – 161 ^{o}C

R_f: 0.31 in 20% ethyl acetate in hexane

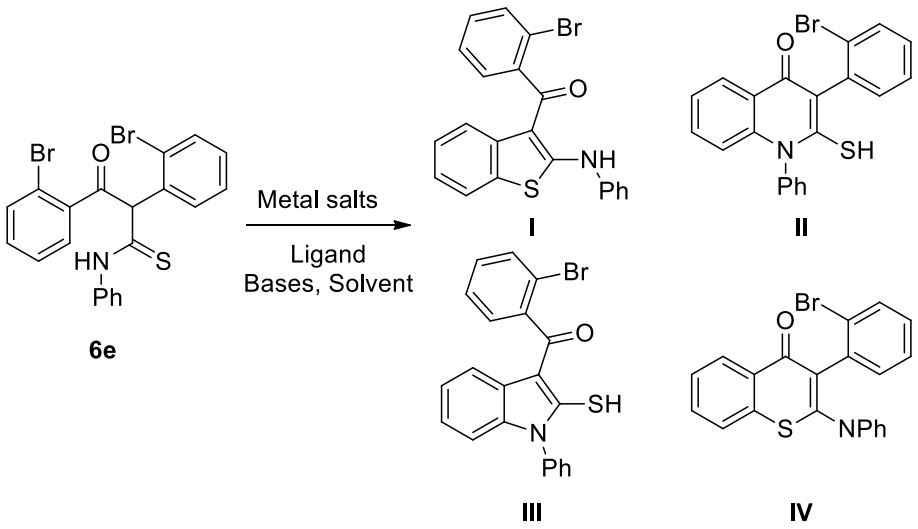
IR (KBr): ν (cm^{-1}) = 3448, 1595, 1582, 1555, 1496, 1404, 1265, 1207, 1050, 1028, 851, 793, 750.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.10 (s, 1H), 7.63 – 7.61 (m, 2H), 7.55 – 7.49 (m, 3H), 7.47 – 7.41 (m, 4H), 7.22 – 7.17 (m, 1H), 6.99 (s, 1H), 6.13 (s, 1H), 3.86 (s, 3H), 3.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.7, 163.3, 147.8, 146.4, 141.5, 140.2, 130.6, 130.1, 129.8, 128.7, 127.7, 124.9, 120.6, 120.4, 110.5, 105.2, 104.2, 56.3, 55.3.

HR-MS (ESI): Calcd. for $C_{23}H_{19}NO_3S$ [M+H]: 390.1158, Found: 390.1137.

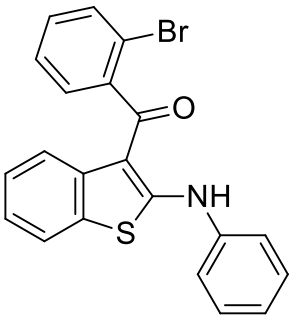
Scheme 4S: Possible Four Heterocyclic Compounds Via Ullmann Reaction



General Procedure for the Synthesis of 3-(2-Bromobenzoyl)-2-amino-benzo[b]thiophenes

An oven-dried 8 mL reaction vial was charged with CuBr (5 mol%), 1,10-phenanthroline (10 mol%) and Et_3N (0.75 mmol), respective thioamide (0.5 mmol) in DMF (2.0 mL) was stirred at room temperature for 1-3 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

3-(2-Bromobenzoyl)-2-(phenylamino)benzo[*b*]thiophene (7e)



Reaction time: 1 h

Yield: 83%, as a yellow colour solid.

Melting point: 126 – 128 ºC

R_f: 0.40 in 20% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3428, 2927, 2373, 1560, 1384, 1182, 1029, 760.

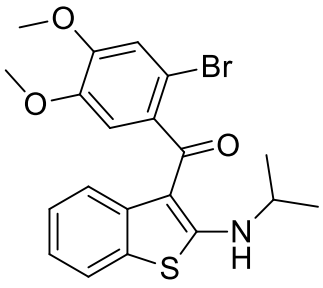
^1H NMR (400 MHz, $CDCl_3$) δ = 12.62 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.45 (m, 6H), 7.41 – 7.35 (m, 2H), 7.28 – 7.25 (m, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.4, 166.1, 142.9, 139.8, 136.2, 133.4, 130.8, 129.9, 129.0, 128.2, 128.0, 125.8 (2C), 123.1, 121.9, 121.5, 120.5, 119.2, 109.9.

HR-MS (ESI): Calcd. for $C_{21}H_{14}BrNOS$ [M+H]: 408.0052, Found: 408.0062.

[M+H]: 410.0032, Found: 410.0047.

3-(2-Bromo-4,5-dimethoxy-benzoyl)-2-(isopropylamino)benzo[*b*]thiophene (7f)



Reaction time: 2 h

Yield: 88%, as a yellow colour solid.

Melting point: 130 – 132 ºC

R_f: 0.30 in 25% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3422, 2971, 2932, 2840, 1577, 1538, 1506, 1466, 1408, 1332, 1254, 1209, 1162, 1098, 1032, 775, 751.

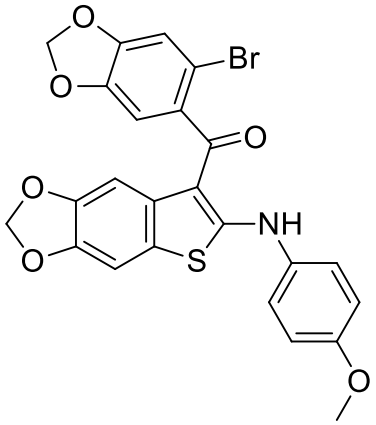
^1H NMR (400 MHz, $CDCl_3$) δ = 10.52 (d, *J* = 8.0 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.13 (s, 1H), 7.04 – 6.96 (m, 2H), 6.80 (s, 1H), 6.32 – 6.30 (m, 1H), 3.96 (s, 3H), 3.80 (s, 3H), 3.77 – 3.69 (m, 1H), 1.44 (d, *J* = 1.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.8, 169.6, 150.0, 149.0, 137.3, 135.3, 128.9, 125.7, 122.3, 121.8, 120.4, 115.8, 110.6, 109.6, 107.4, 56.4, 56.2, 50.5, 22.7.

HR-MS (ESI): Calcd. for $C_{20}H_{20}BrNO_3S$ [M+H]: 434.0420, Found: 434.0475.

[M+H]: 436.0400, Found: 436.0452.

3-(2-Bromo-4,5-methylenedioxy-benzoyl)-5,6-methylenedioxy-2-(phenylamino) benzo[*b*]thiophene (7g)



Reaction time: 2 h

Yield: 89%, as a yellow colour solid.

Melting point: 223 – 226 ^{o}C

R_f: 0.32 in 25% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3402, 3120, 2905, 1559, 1502, 1472, 1427, 1384, 1287, 1244, 1186, 1037, 936, 820.

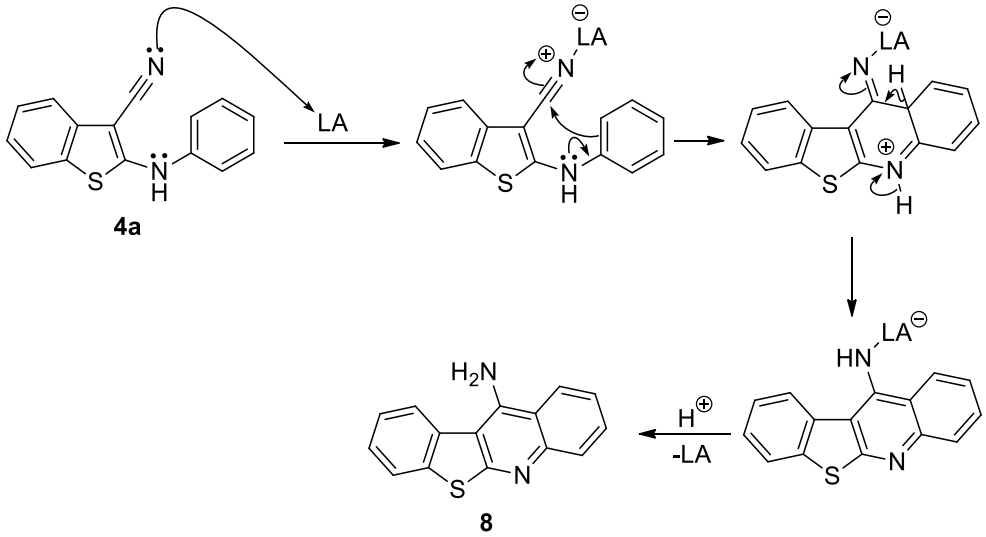
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.10 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.12 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.90 (s, 1H), 6.79 (s, 1H), 6.07 (s, 2H), 5.94 (s, 1H), 5.89 (s, 2H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.1, 167.2, 157.9, 149.3, 148.1, 147.1, 144.5, 136.0, 132.9, 130.7, 124.0, 120.7, 115.00, 113.5, 110.3, 109.6, 107.9, 102.3, 101.9, 101.3, 101.2, 55.7.

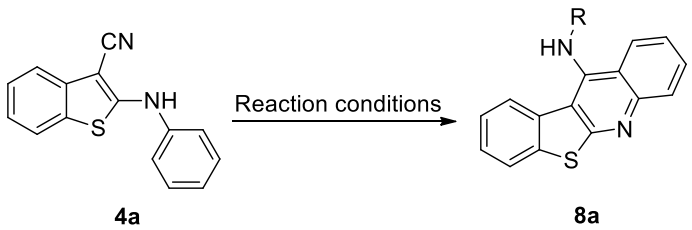
HR-MS (ESI): Calcd. for $C_{24}H_{16}BrNO_6S$ [M+H]: 525.9954, Found: 525.9976.

[M+H]: 527.9935, Found: 527.9958.

Scheme 5S: Proposed Strategy for Construction of 4-Aminoquinole over Benzo[*b*]thiophene



Optimization of Synthesis of 11-Amino-benzo[*b*]thieno[2,3-b]quinolines



4a **8a**

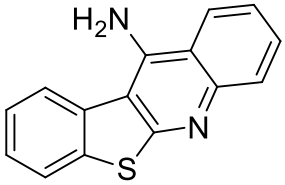
Entry	Acid	Solvent	Temp	Time	50a (% Yield)[a]
1.	$Cu(OTf)_2$ (10 mol%)	DCE	80 °C	15 h	No reaction
2.	$TiCl_4$ (10 equiv)	DCE	80 °C	15 h	No reaction
3.	TFA (10 equiv)	DCE	80 °C	40 h	24[b]
4.	TfOH (10 equiv)	DCE	80 °C	3 h	87
5.	TfOH (10 equiv)	DCE	rt	20 min	86

[a] *Isolated yield.* [b] ***8a*** *was isolated as -*$COCF_3$ *amide derivative*

Procedure for the Synthesis of 11-Amino-benzo[b]thieno[2,3-b]quinolines at Room Temperature

To an oven-dried 8 mL reaction vial was charged with respective 2-aminobenzo[*b*]thiophene (0.5 mmol) in dry DCE (2.0 mL) was added triflic acid (10 equiv) drop wise at room temperature. The reaction mixture was stirred at room temperature and monitored by TLC. After complete consumption of the starting material, the reaction mixture quenched with saturated $NaHCO_3$ solution and extracted with DCM. The combined organic layer washed with (3 x 5 mL) & brine (5 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by flash chromatography using EtOAc/hexanes as eluent.

Benzo[4,5]thieno[2,3-*b*]quinolin-11-amine (8a)



Reaction time: 20 min

Yield: 86%, as a white colour solid.

Melting point: 260 – 262 ºC

R_f: 0.30 in 33% ethyl acetate in hexane

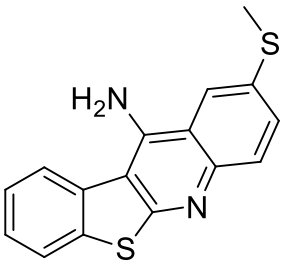
IR (KBr): ν (cm^{-1}) = 3495, 3307, 3146, 2372, 2345, 1648, 1578, 1560, 1429, 1264, 1068, 950.

^{1}H NMR (400 MHz, DMSO) δ = 8.55 (d, *J* = 8.4 Hz, 1H), 8.50 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.42 (s, 2H).

^{13}C NMR (100 MHz, DMSO) δ = 163.3, 147.8, 147.4, 134.7, 133.6, 129.8, 127.5, 125.7, 125.0, 123.5, 123.1, 123.0, 122.8, 116.2, 108.4.

HR-MS (ESI): Calcd. for $C_{15}H_{10}N_2S$ [M+H]: 251.0637, Found: 251.0663.

9-(Methylthio)benzo[4,5]thieno[2,3-*b*]quinolin-11-amine (8c)



Reaction time: 1.5 h

Yield: 54%, as a brown colour solid.

Melting point: 222 – 224 ºC

R_f: 0.30 in 33% ethyl acetate in hexane

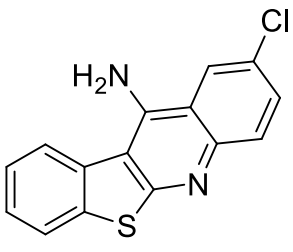
IR (KBr): ν (cm^{-1}) = 3448, 2921, 2372, 2345, 1640, 1554, 1423, 1257, 1133, 1020, 944, 815.

^{1}H NMR (400 MHz, DMSO) δ = 8.51 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 1.2 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.60 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.42 (s, 2H), 2.65 (s, 3H).

^{13}C NMR (100 MHz, DMSO) δ = 162.4, 146.8, 145.5, 134.7, 133.5, 132.9, 129.1, 128.0, 125.7, 124.9, 123.5, 122.7, 118.8, 116.6, 108.7, 15.5.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2S_2$ [M+H]: 297.0514, Found: 297.0534.

9-Chlorobenzo[4,5]thieno[2,3-*b*]quinolin-11-amine (8d)



Reaction time: 1.5 h

Yield: 70%, as a brown colour solid.

Melting point: 292 – 294 ºC

R_f: 0.37 in 33% ethyl acetate in hexane

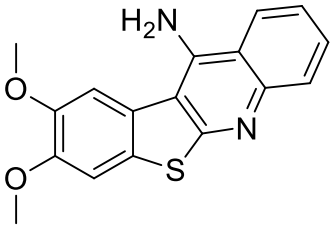
IR (KBr): ν (cm^{-1}) = 3468, 3308, 3191, 2920, 1633, 1573, 1494, 1434, 1257, 1091, 816, 718.

^{1}H NMR (400 MHz, DMSO) δ = 8.72 (s, 1H), 8.52 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.44 (m, 4H).

^{13}C NMR (100 MHz, DMSO) δ = 163.7, 147.0, 145.8, 134.7, 133.2, 130.0, 129.6, 127.5, 125.9, 125.0, 123.7, 122.8, 122.1, 116.9, 108.8.

HR-MS (ESI): Calcd. for $C_{15}H_9ClN_2S$ [M+H]: 285.0248, Found: 285.0250.

2,3-Dimethoxybenzo[4,5]thieno[2,3-*b*]quinolin-11-amine (8h)



Reaction time: 20 min

Yield: 63%, as a brown colour solid.

Melting point: 228 – 230 ^{o}C

R_f: 0.26 in 50% ethyl acetate in hexane

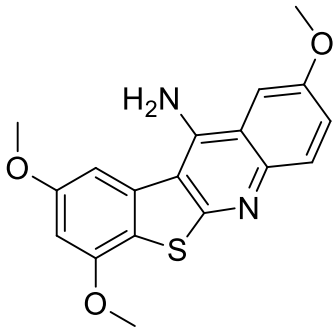
IR (KBr): ν (cm^{-1}) = 3364, 3226, 2919, 2347, 1634, 1576, 1403, 1308, 1272, 1210, 1079, 1038, 833, 803, 743.

^{1}H NMR (400 MHz, DMSO) δ = 8.53 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67(t, *J* = 7.2 Hz, 1H), 7.59 (s, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.21 (s, 2H), 3.98 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, DMSO) δ = 163.6, 148.3, 147.3, 146.7, 146.5, 129.1, 127.5, 126.9, 126.0, 122.8 (2C), 116.2, 109.5, 108.2, 106.0, 56.6, 55.8.

HR-MS (ESI): Calcd. for $C_{17}H_{14}N_2O_2S$ [M+H]: 311.0849, Found: 311.0862.

2,4,9-Trimethoxybenzo[4,5]thieno[2,3-*b*]quinolin-11-amine (8j)



Reaction time: 3 h

Yield: 59%, as a light brown colour solid.

Melting point: 190 – 193 ^{o}C

R_f: 0.41 in 33% hexane in ethylacetate.

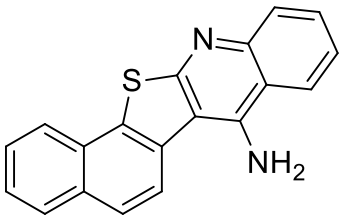
IR (KBr): ν (cm^{-1}) = 3446, 3324, 3197, 2998, 2931, 2833, 1646, 1575, 1505, 1450, 1419, 1357, 1328, 1282, 1236, 1206, 1165, 1140, 1108, 1033, 983, 940, 819, 729.

^{1}H NMR (400 MHz, DMSO) δ = 7.85 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.36 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.22 (s, 2H), 6.79 (d, *J* = 1.2 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H).

^{13}C NMR (100 MHz, DMSO) δ = 161.4, 159.2, 155.4, 153.8, 147.2, 143.2, 134.7, 129.0, 121.7, 116.4, 113.9, 109.2, 101.9, 101.7, 96.2, 56.0, 55.9, 55.8.

HR-MS (ESI): Calcd. for $C_{18}H_{16}N_2O_3S$ [M+H]: 341.0954, Found: 341.0966.

Naphtho[2′,1′:4,5]thieno[2,3-*b*]quinolin-7-amine (8n)



Reaction time: 20 min

Yield: 79%, as a brown colour solid.

Melting point: 284 – 286 ºC

R_f: 0.28 in 33% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3489, 3298, 3135, 2372, 2345, 1638, 1571, 1444, 1279, 1117, 1019, 952, 900, 795, 758.

^{1}H NMR (400 MHz, DMSO) δ = 8.67 (d, *J* = 8.8 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.08 – 8.04 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.64 – 7.61 (m, 1H), 7.51(s, 2H), 7.50 – 7.47 (m, 1H).

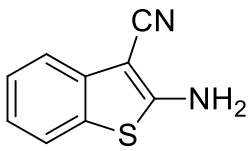
^{13}C NMR (100 MHz, DMSO) δ = 163.0, 148.0, 147.2, 131.4, 130.9, 130.8, 129.7, 128.7, 127.7, 127.6, 127.1, 126.2, 125.4, 124.1, 123.1, 123.0, 121.9, 116.1, 109.9.

HR-MS (ESI): Calcd. for $C_{19}H_{12}N_2S$ [M+H]: 301.0794, Found: 301.0813.

General Procedure for the Cleavage of *p*-Methoxyphenyl (PMP) group

To the solution of 2-((4-methoxyphenyl)amino)benzo[*b*]thiophene-3-carbonitrile 0.100g (0.35 mmol) in CH_3CN/H_2O (9 : 1) at 0 ºC was added portion wise of ceric ammonium nitrate (CAN) 0.767g (4 equiv) and the reaction mixture was stirred at 0 ºC for 3 h. The reaction mixture was monitored by TLC. After complete consumption of the starting material, the reaction mixture quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer washed with (3 x 5 mL) & brine (5 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by flash chromatography using EtOAc/hexanes as eluent.

2-Aminobenzo[*b*]thiophene-3-carbonitrile (9)[2]



Reaction time: 3 h.

Yield: 57%, as a brown colour solid.

Melting point: 150 – 154 ºC

R_f: 0.30 in 25% ethyl acetate in hexane

IR (KBr): ν (cm^{-1}) = 3415, 3325, 3220, 2371, 2345, 2210, 1633, 1544, 1457, 735, 716.

^{1}H NMR (400 MHz, MeOD) δ = 7.52 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.12 – 7.08 (m, 1H).

^{13}C NMR (100 MHz, MeOD) δ = 166.7, 139.4, 130.5, 126.7, 123.6, 122.8, 119.4, 116.5, 79.1.

HR-MS (ESI): Calcd. for $C_9H_6N_2S$ [M+H]: 175.0324, Found: 175.0317.

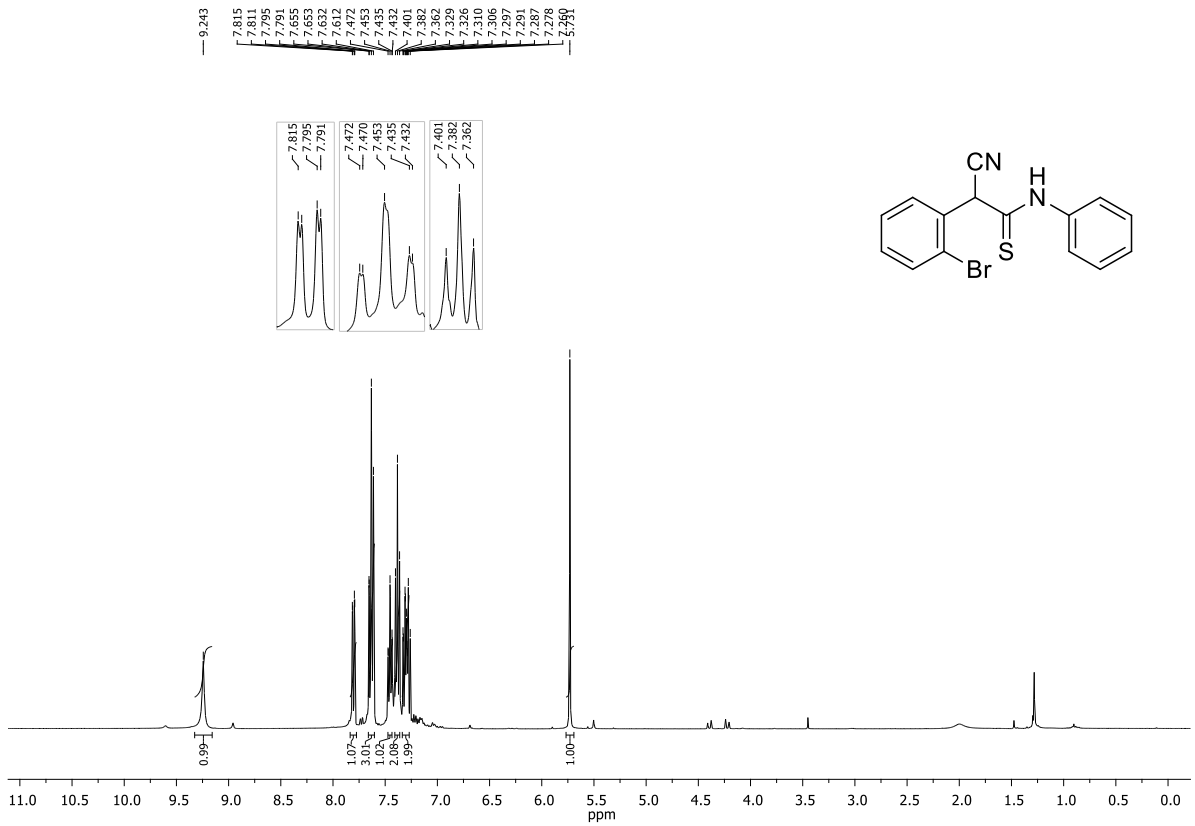
Crystal Data

Crystallographic data of **4a** in CH_2Cl_2/*n*-hexane: $C_{15}H_{10}N_2S$, Mw = 250.31, triclinic, space group P_1, a = 3.905 (5) Å, b = 12.317 (5) Å , c = 13.486 (5) Å , α = 74.773 (5) º, β = 83.574 (5) º, γ = 81.477 (5) º, *V* = 617.2 (9) Å, *Z* = 2, Dcalc = 1.347 mg/m^3, T = 293 K, R1 = 0.0448 {I > 2σ (I)}, wR2 = 0.1369, GOF = 1.072.

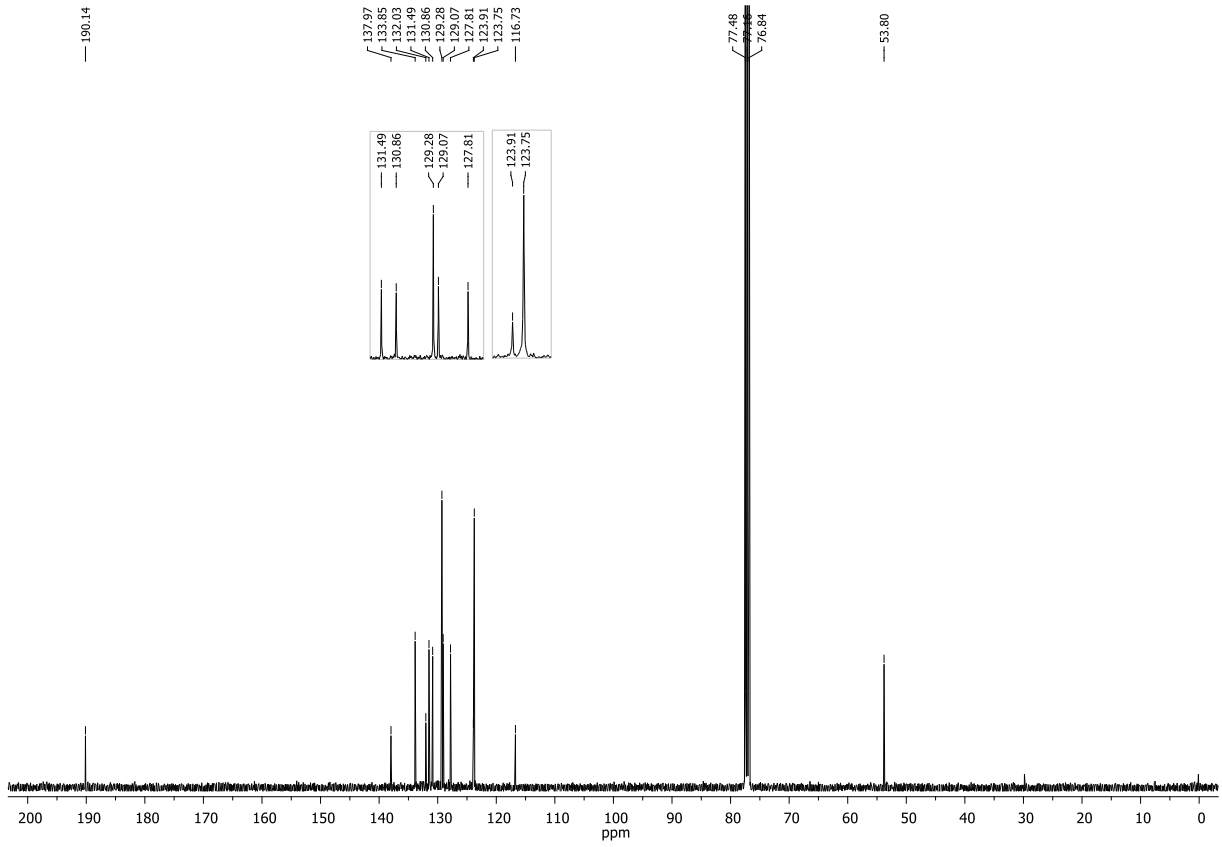
Crystallographic data of **7f** in CH_2Cl_2/*n*-hexane: $C_{20}H_{20}O_3SBrN$, Mw = 434.34, monoclinic, space group $P2_1/c$, a = 13.8970 (6) Å, b = 9.2923 (3) Å , c = 16.3213(7) Å , α = 90º, β = 110.260 (3) º, γ = 90 º, *V* = 1977.25(14) Å, *Z* = 4, Dcalc = 1.459 mg/m^3, T = 293 K, R1 = 0.0404{I > 2σ (I)}, wR2 = 0.1048, GOF = 1.023.

References:

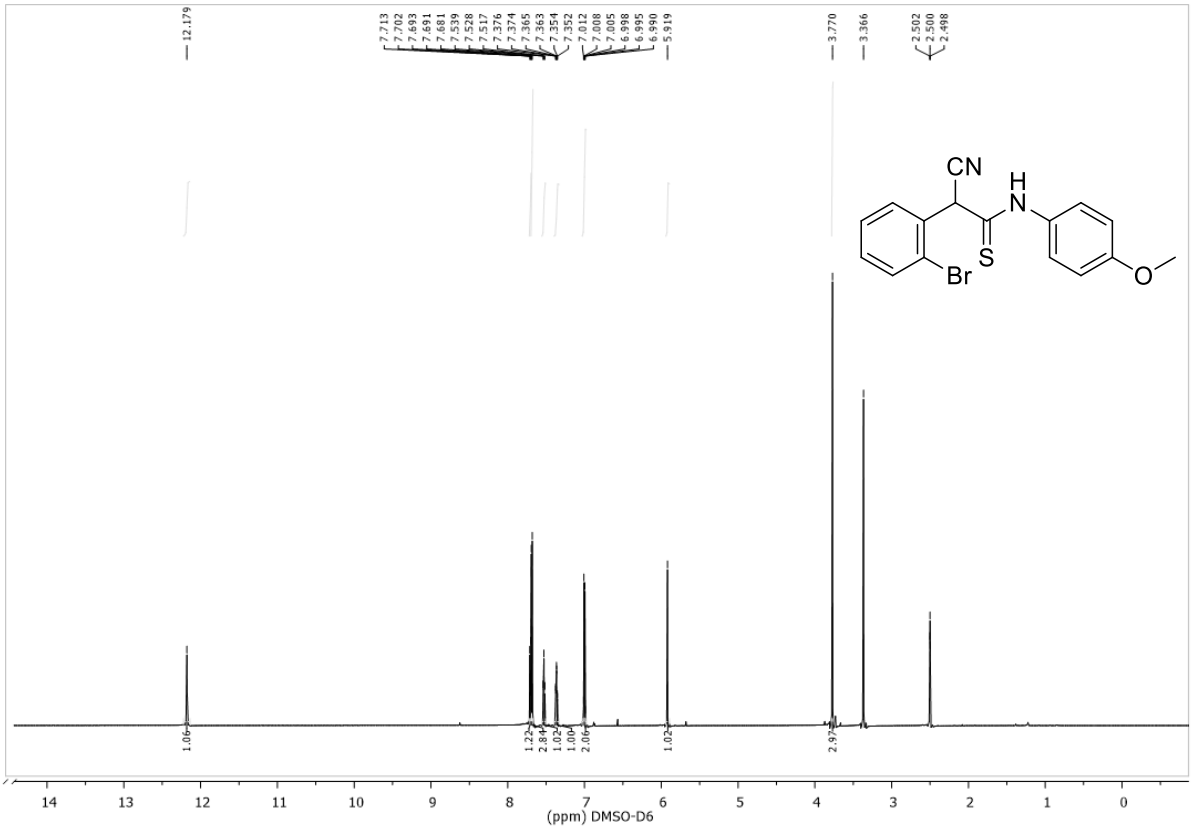
1. P. P. Singh, A. K. Yadav, H. Ila, H. Junjappa, *J. Org. Chem*. **2009,** *74*, 5496.
2. P. Selles, J. S. Wailes, W. G. Whittingham, E. D. Clarke, *PCT Int. Appl*., **2005**, 2005044008.



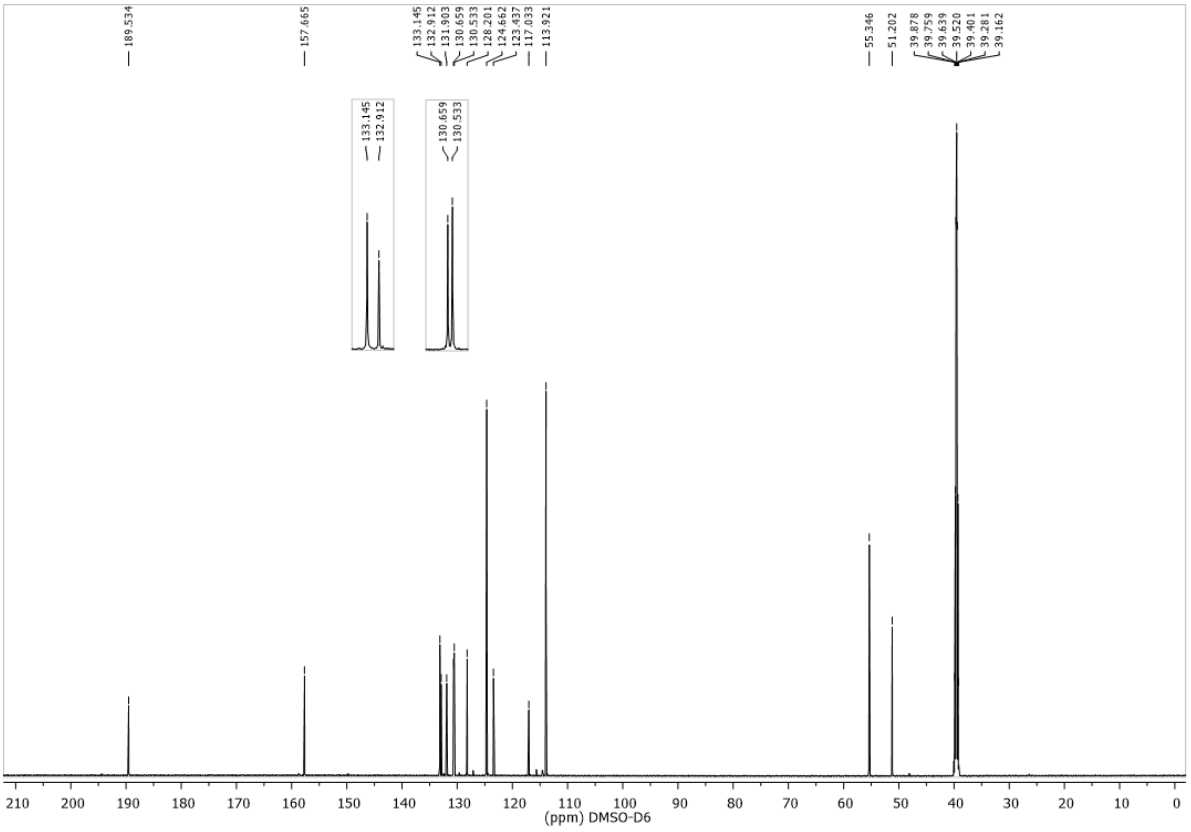
^{1}H NMR Spectrum of **3a**



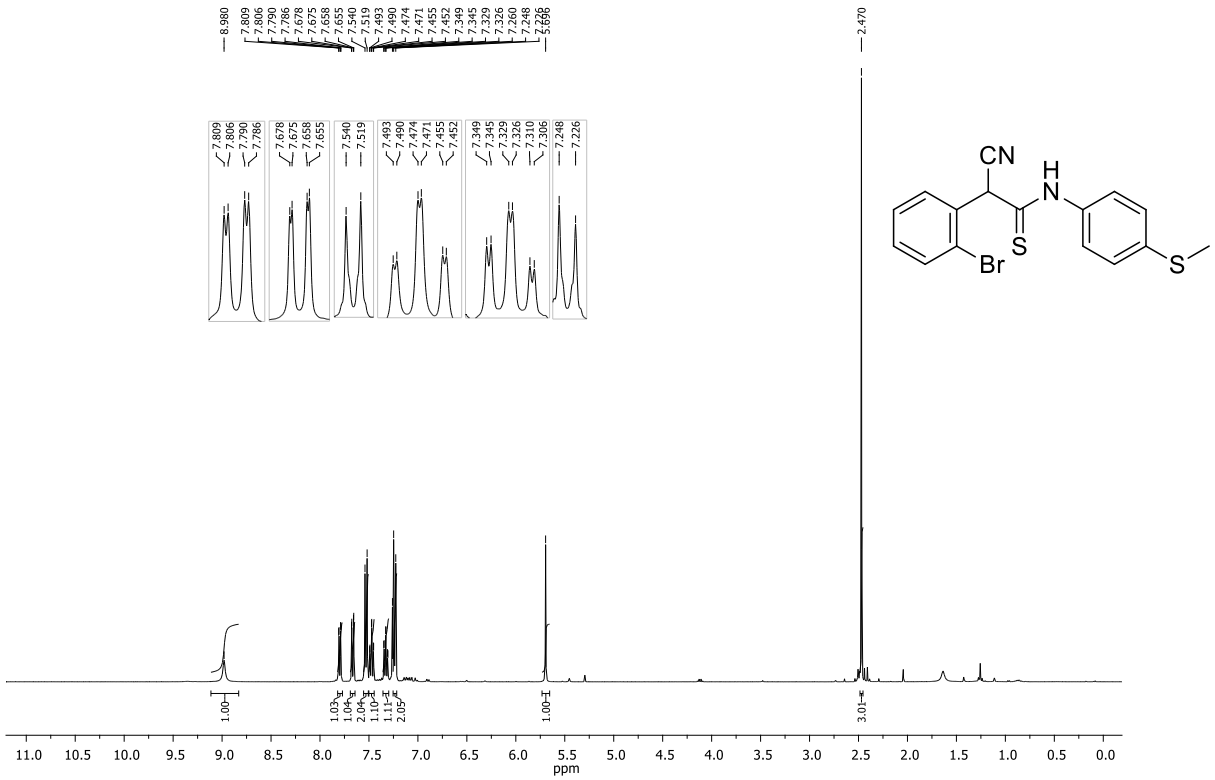
^{13}C NMR Spectrum of **3a**



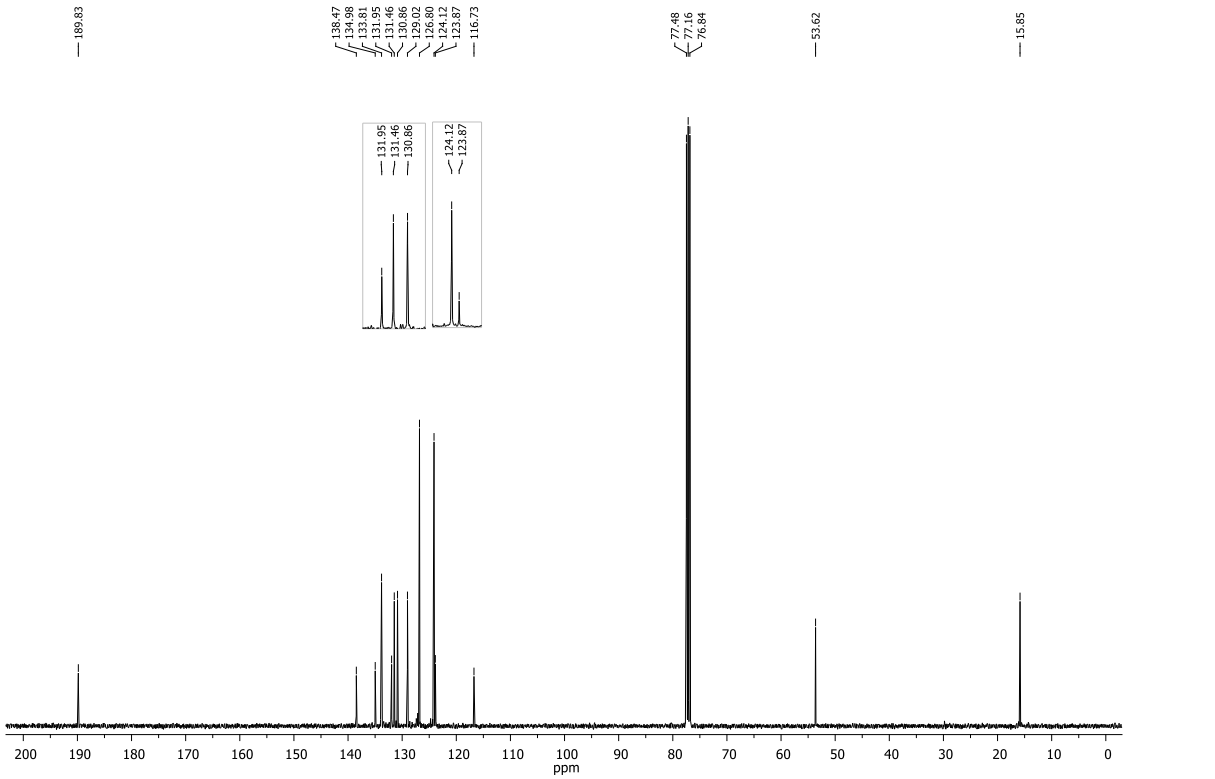
^{1}H NMR Spectrum of **3b**



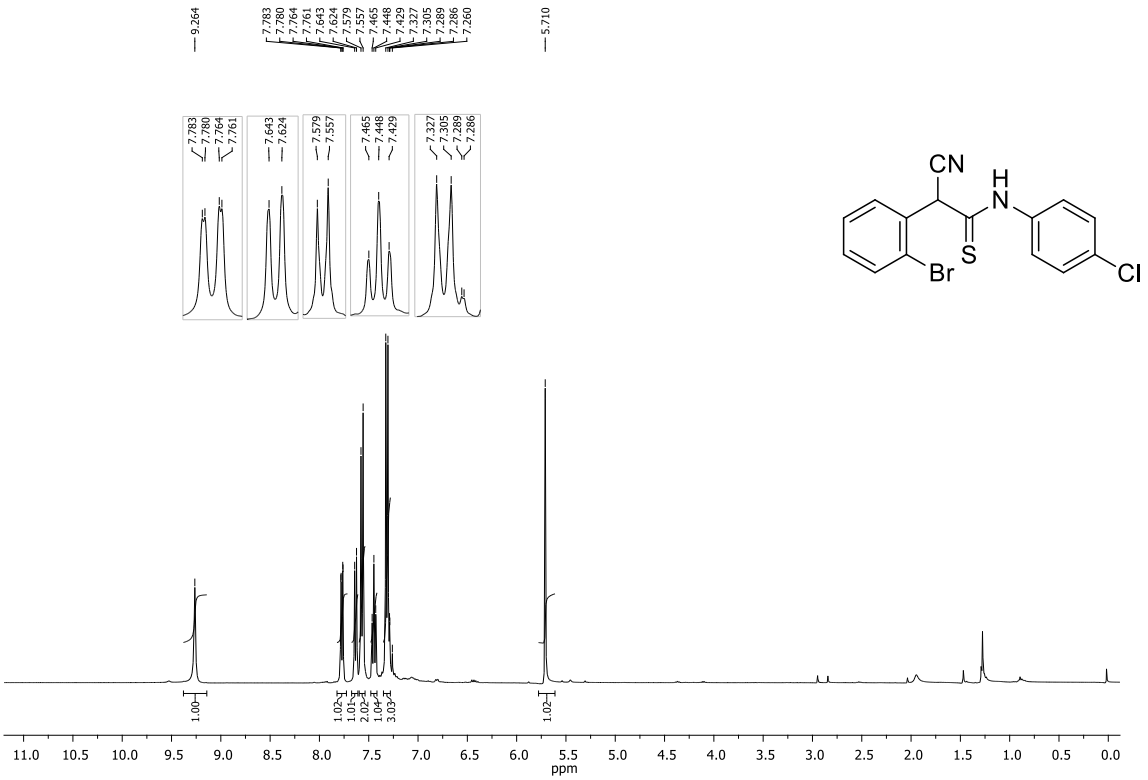
^{13}C NMR Spectrum of **3b**



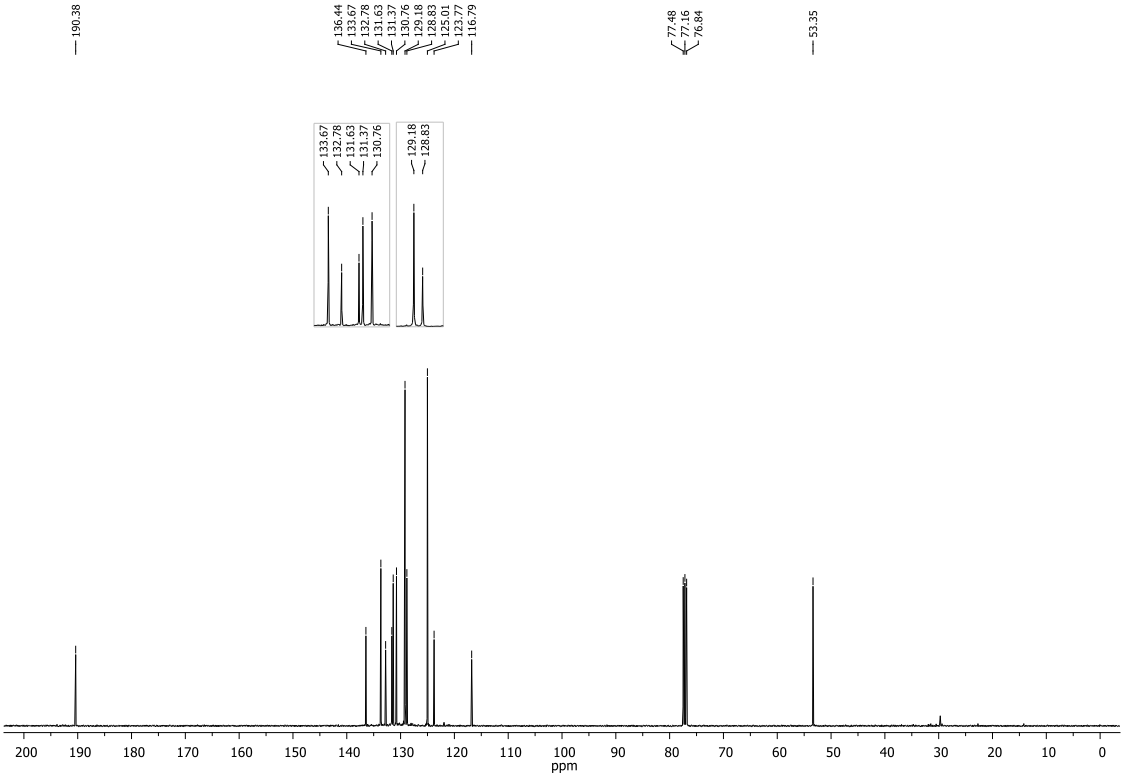
^{1}H NMR Spectrum of **3c**



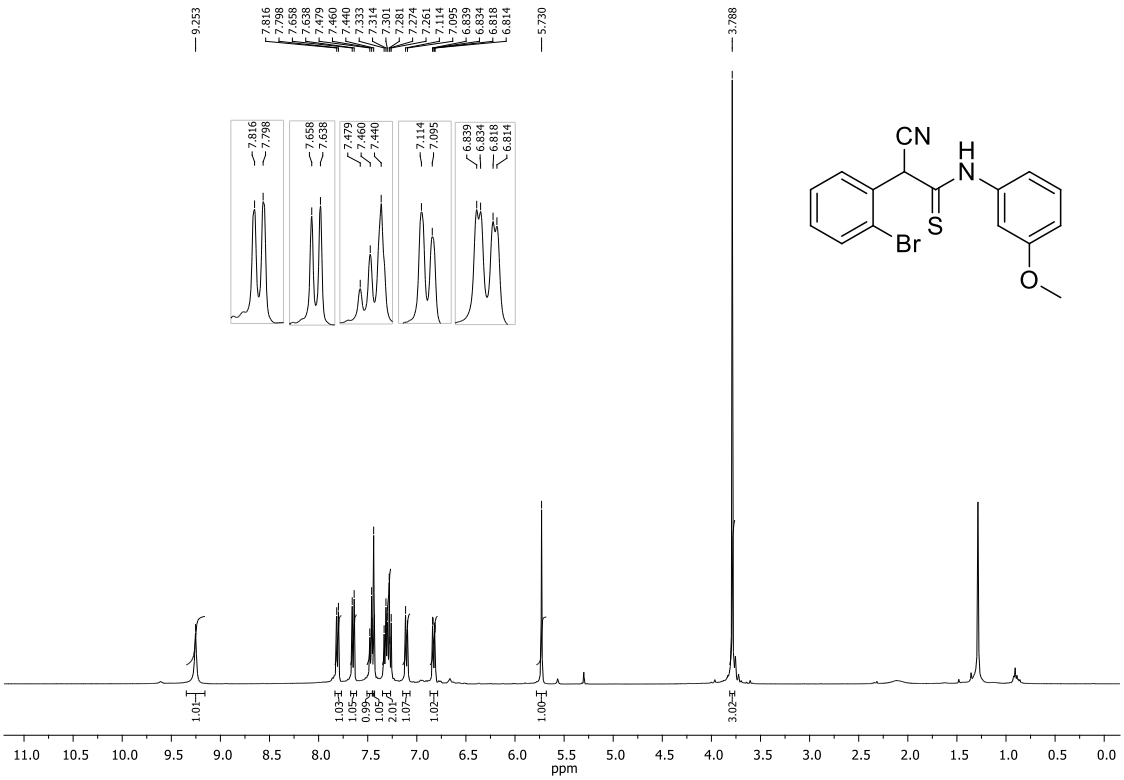
^{13}C NMR Spectrum of **3c**



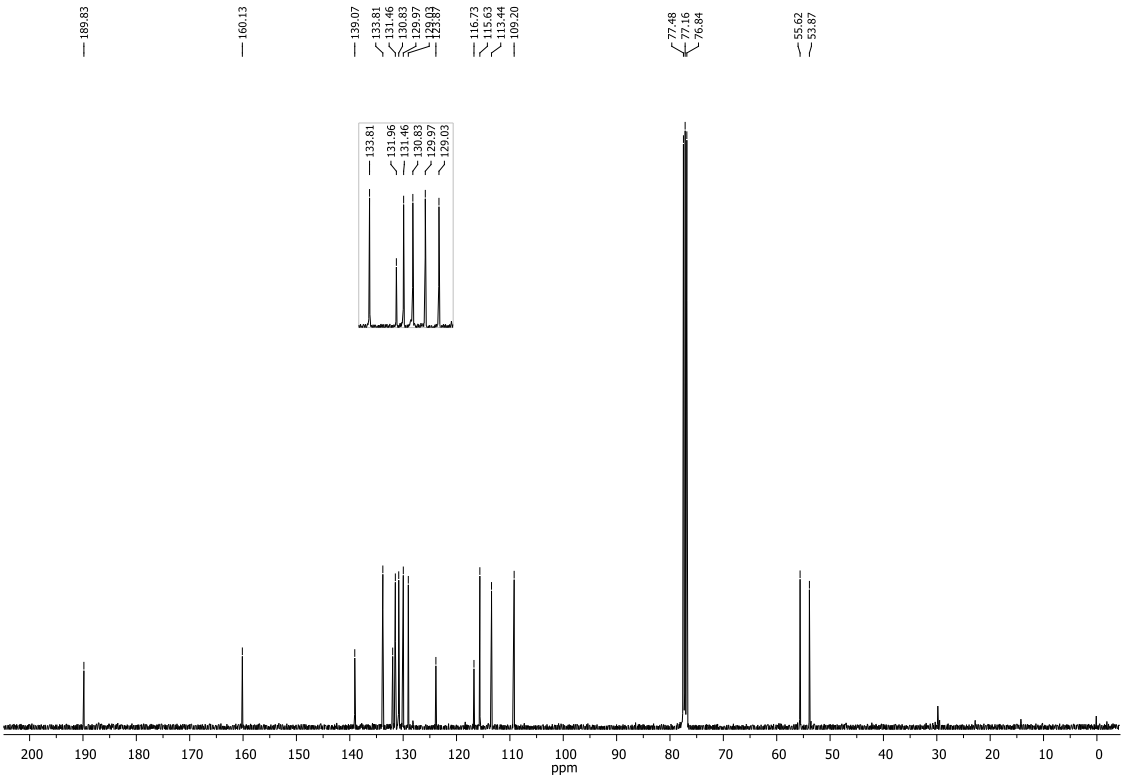
^{1}H NMR Spectrum of **3d**



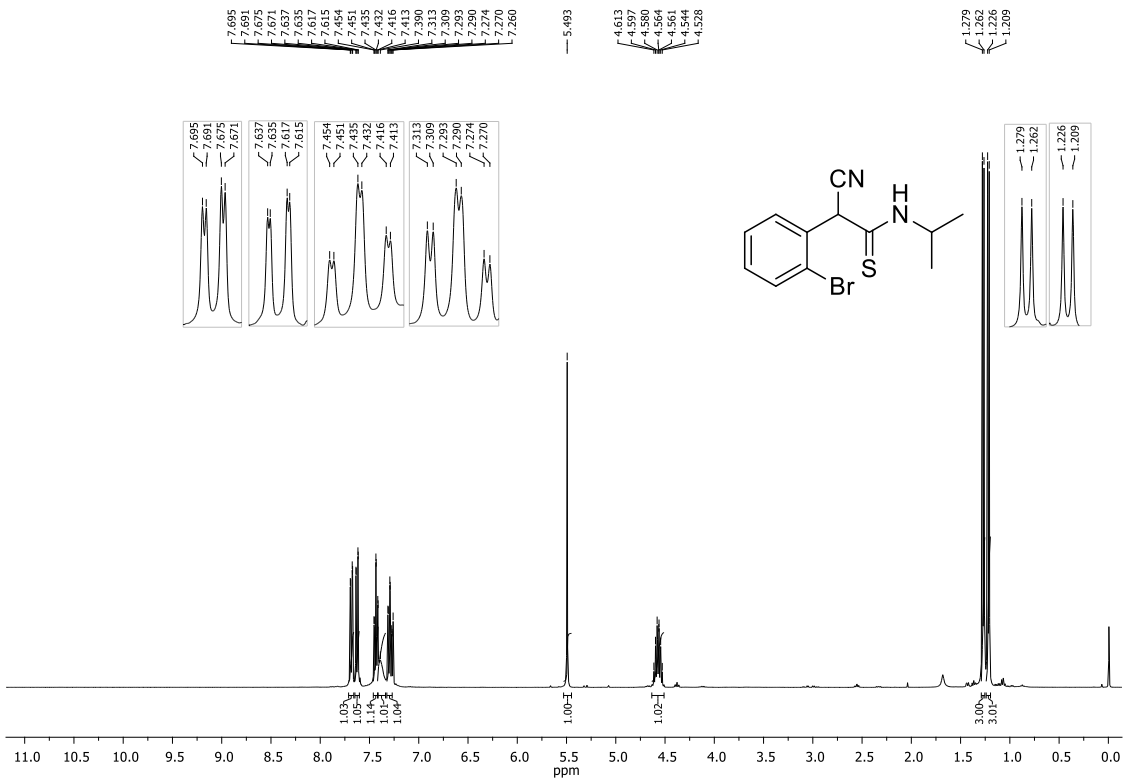
^{13}C NMR Spectrum of **3d**



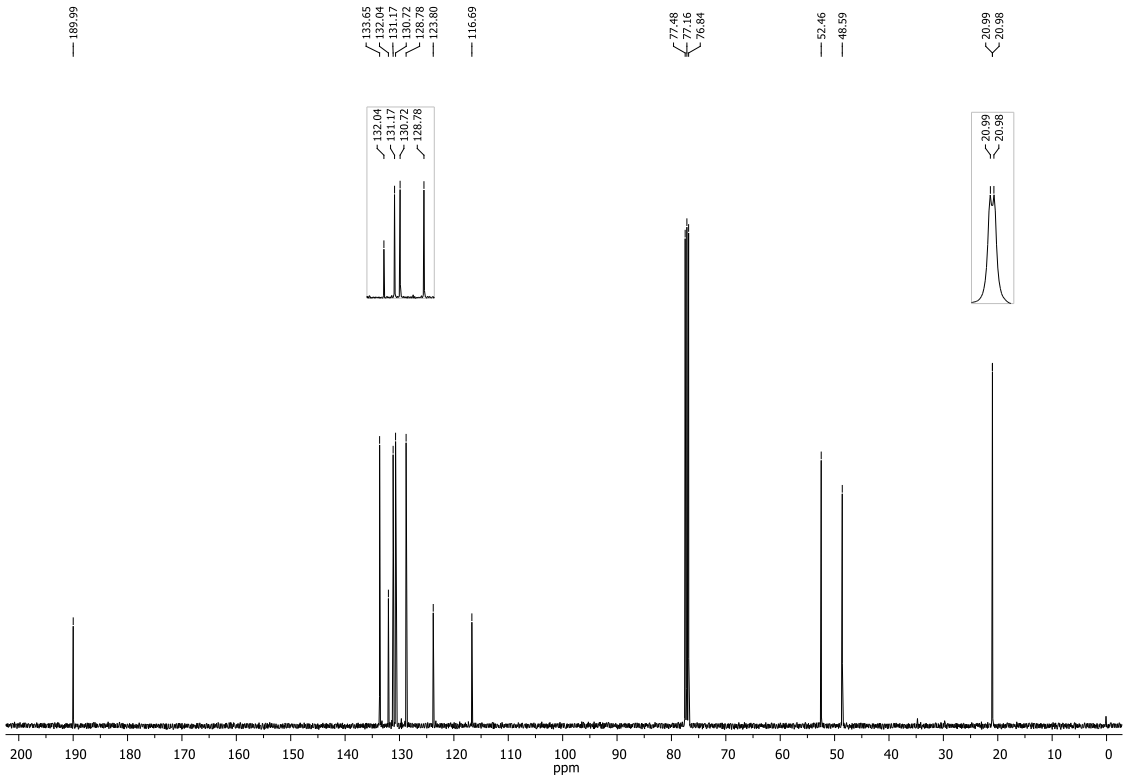
^{1}H NMR Spectrum of **3e**



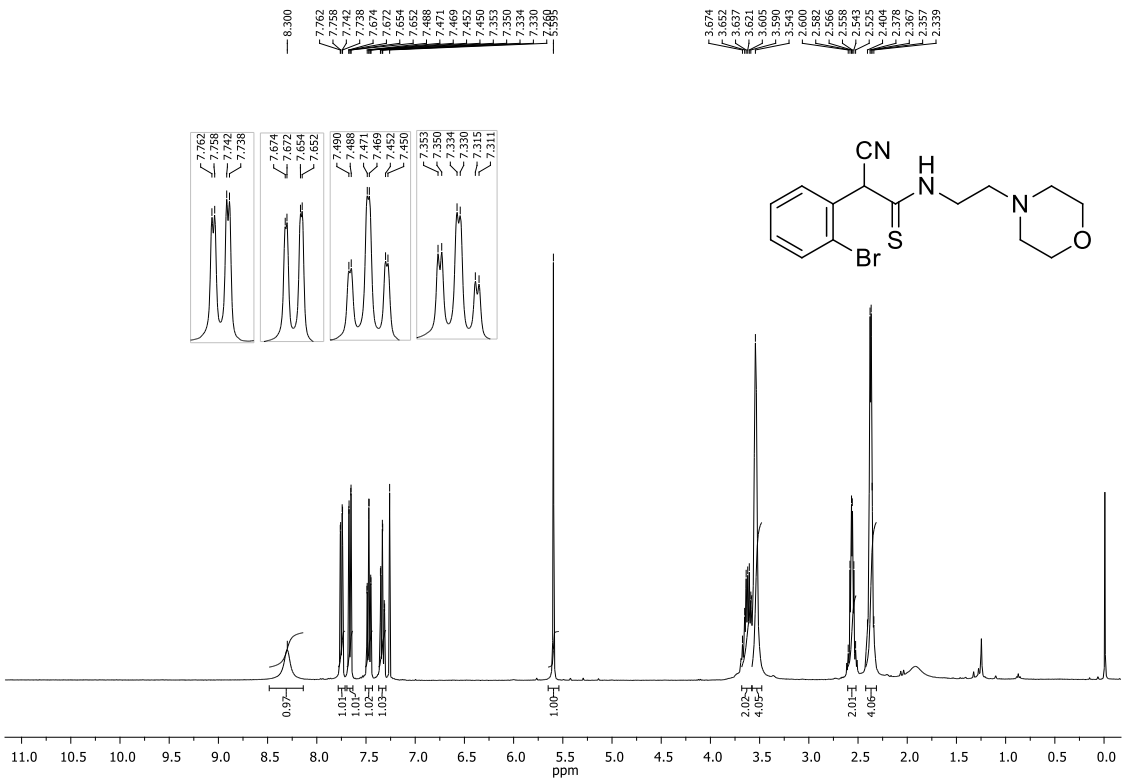
^{13}C NMR Spectrum of **3e**



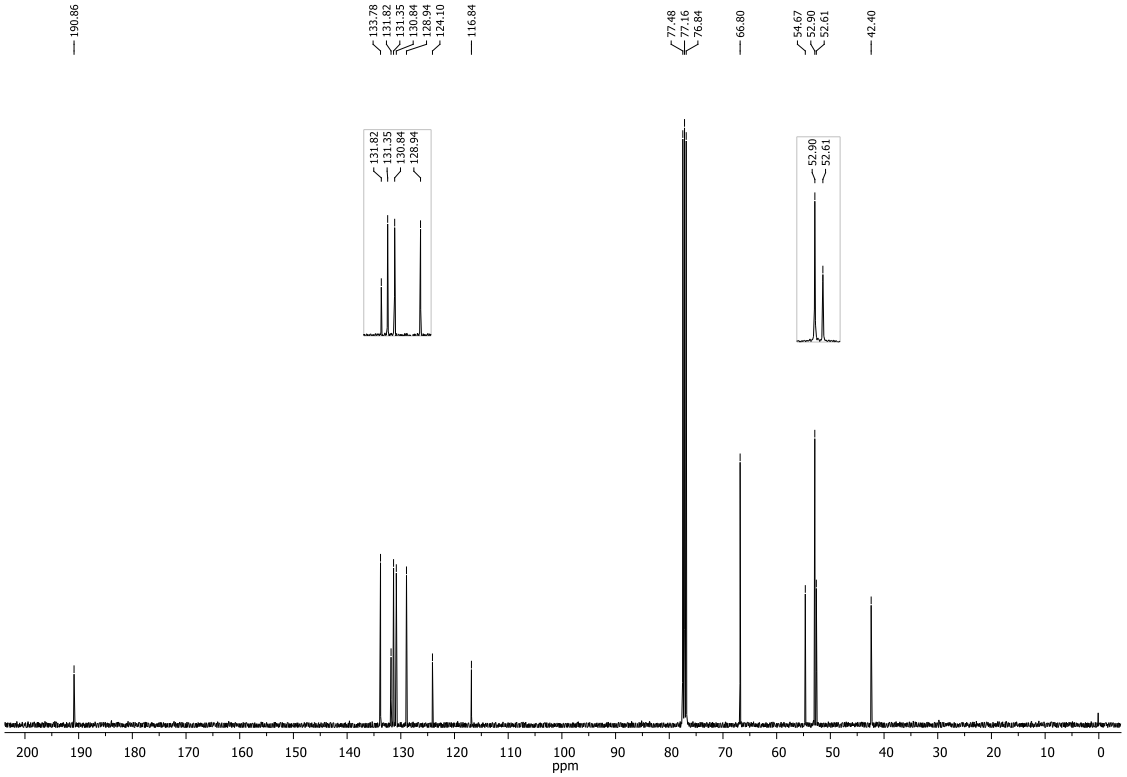
^{1}H NMR Spectrum of **3f**



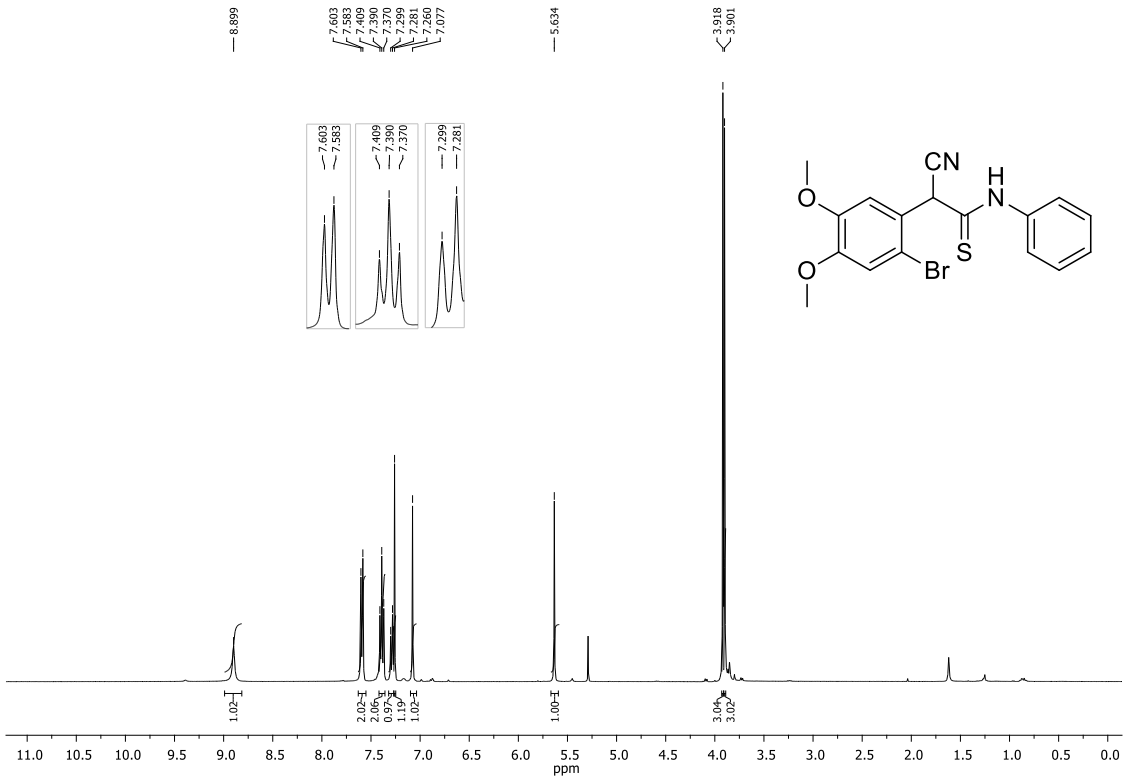
^{13}C NMR Spectrum of **3f**



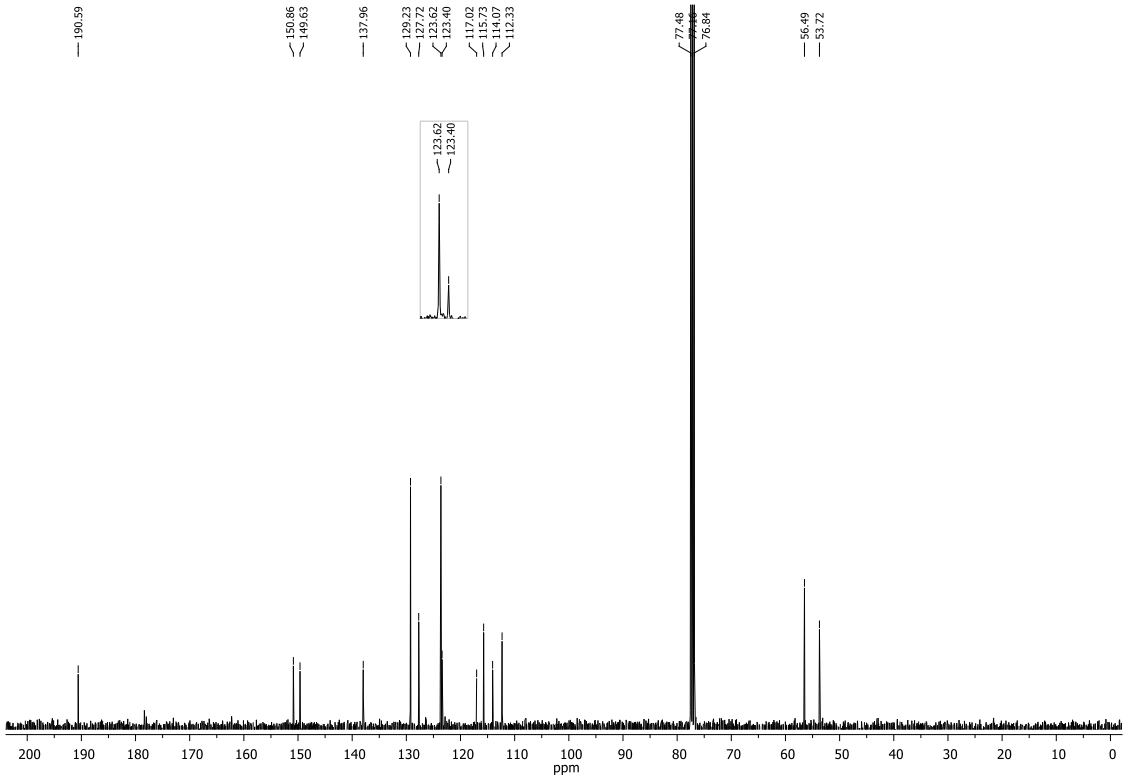
^{1}H NMR Spectrum of **3g**



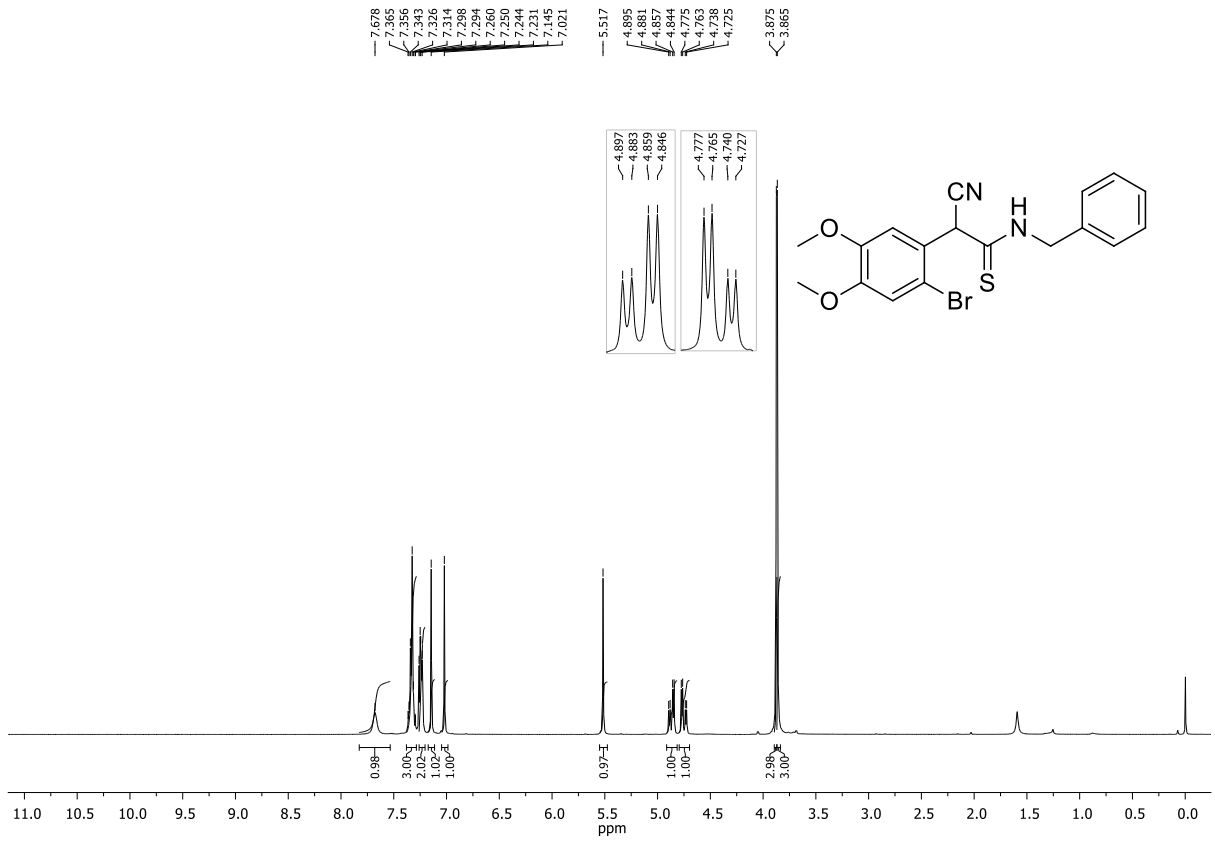
^{13}C NMR Spectrum of **3g**



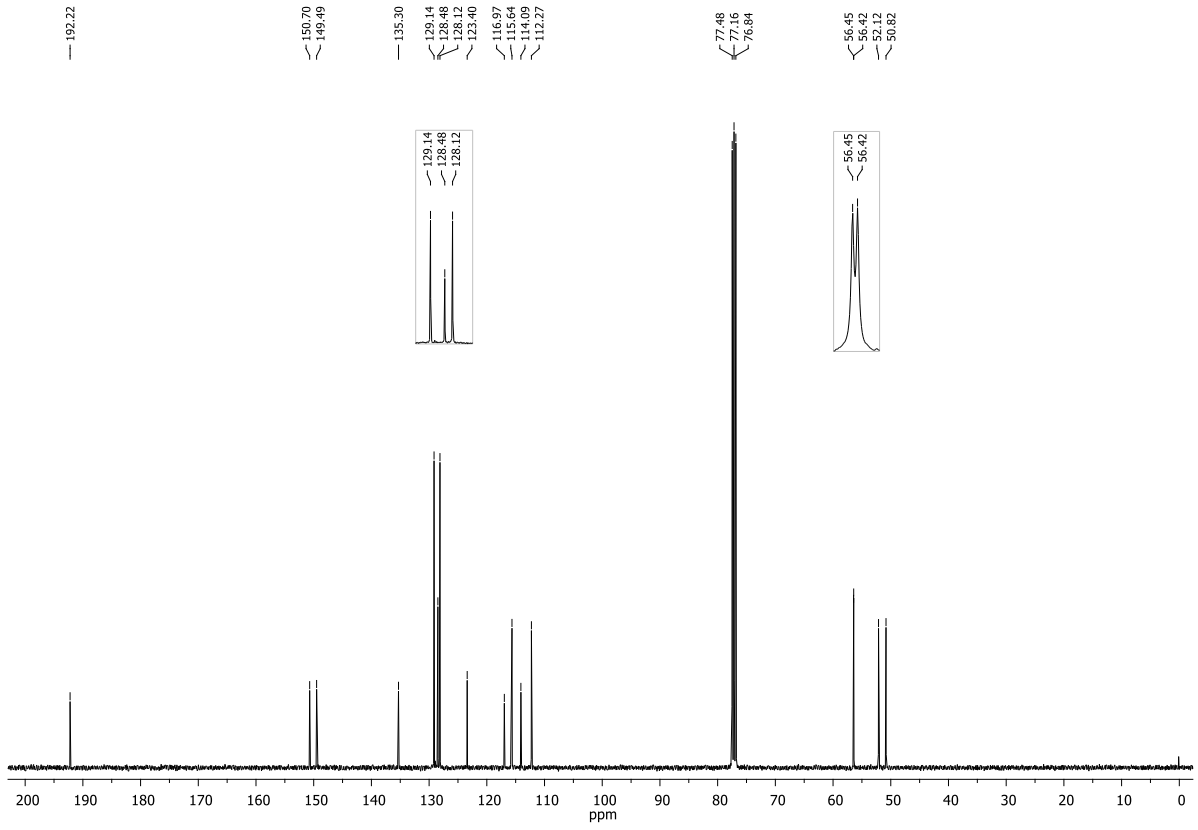
^{1}H NMR Spectrum of **3h**



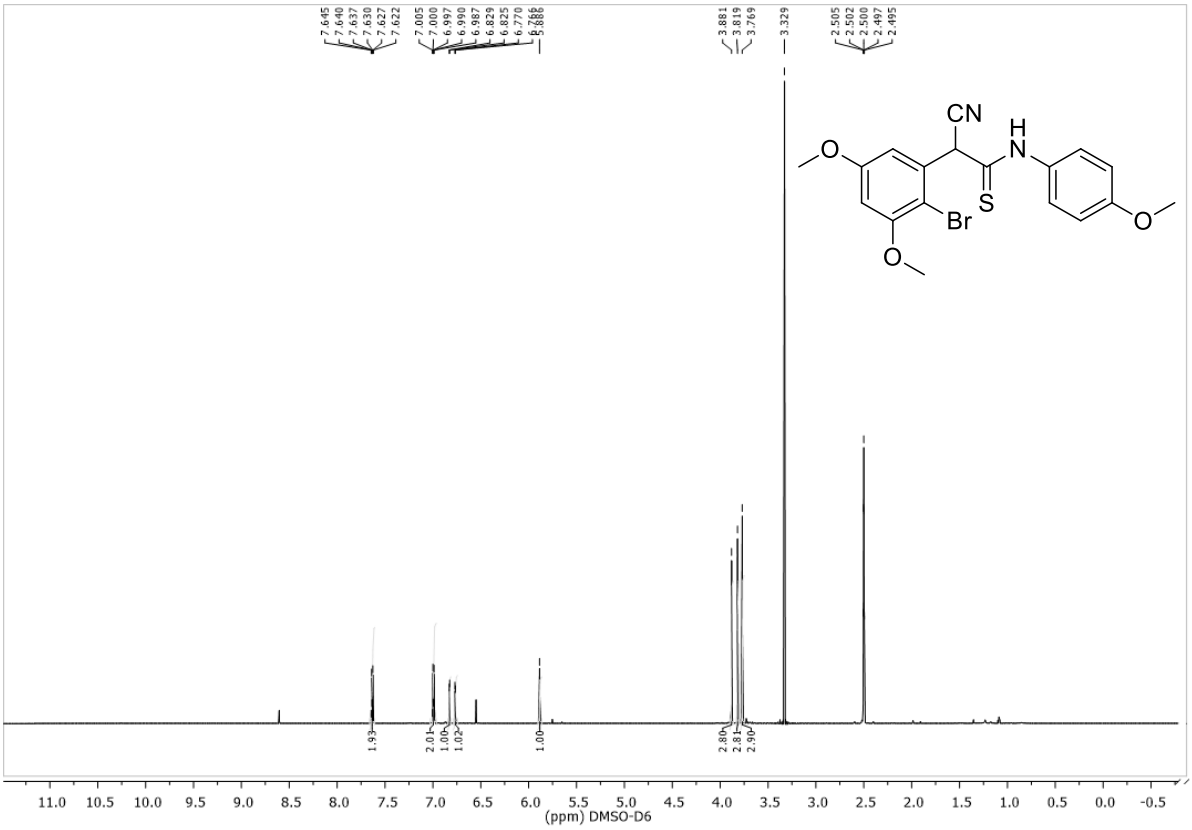
^{13}C NMR Spectrum of **3h**



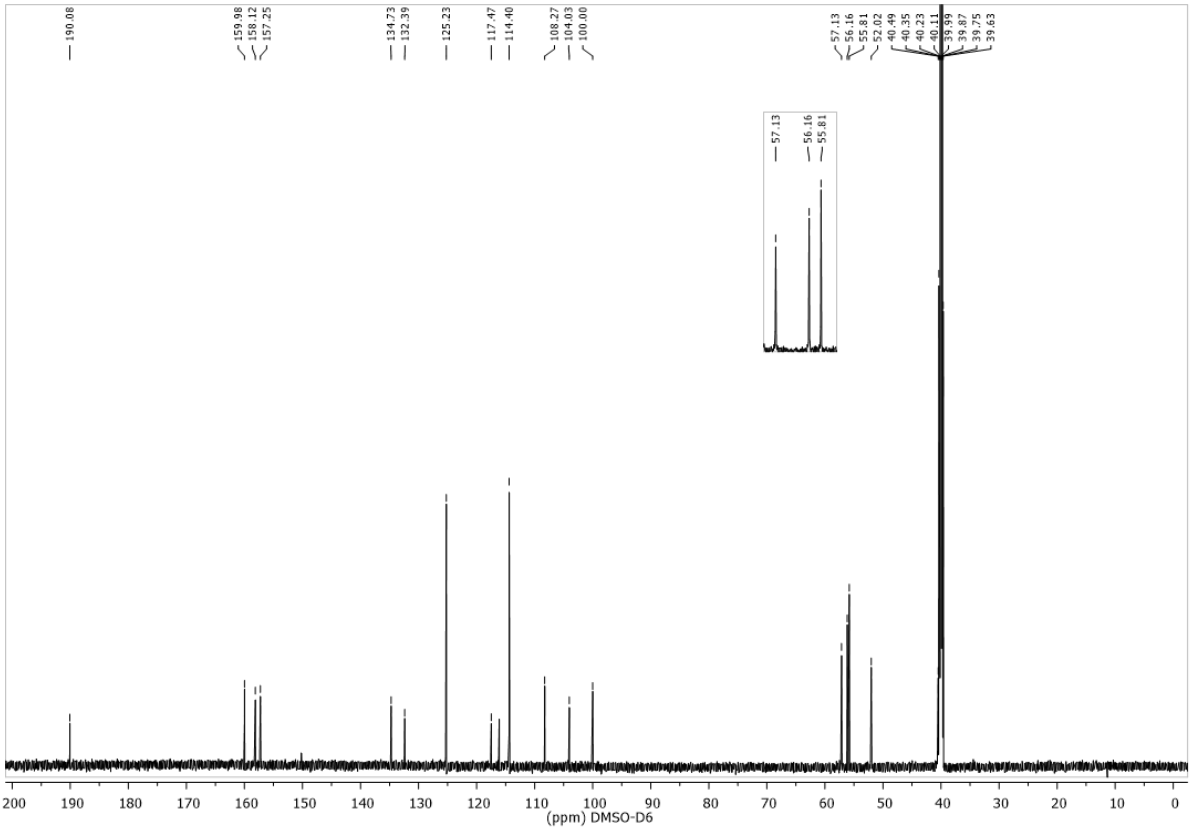
^{1}H NMR Spectrum of **3i**



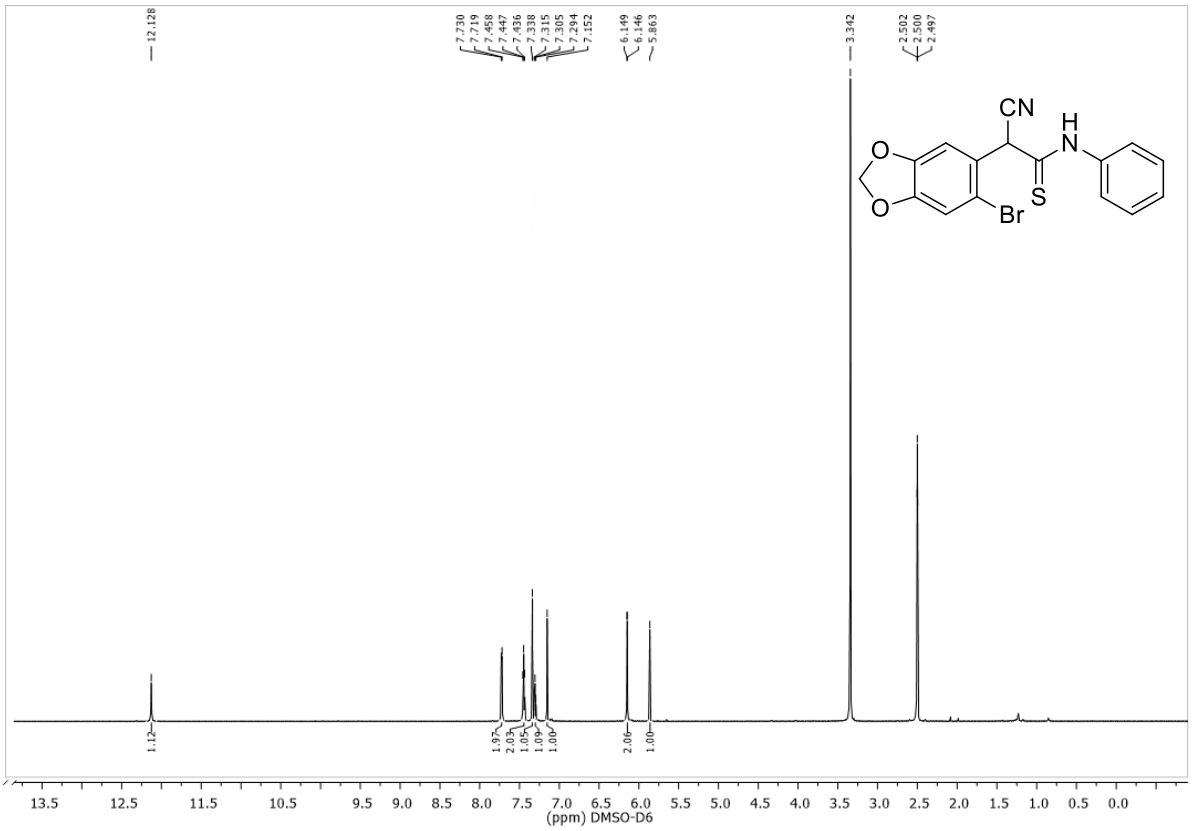
^{13}C NMR Spectrum of **3i**



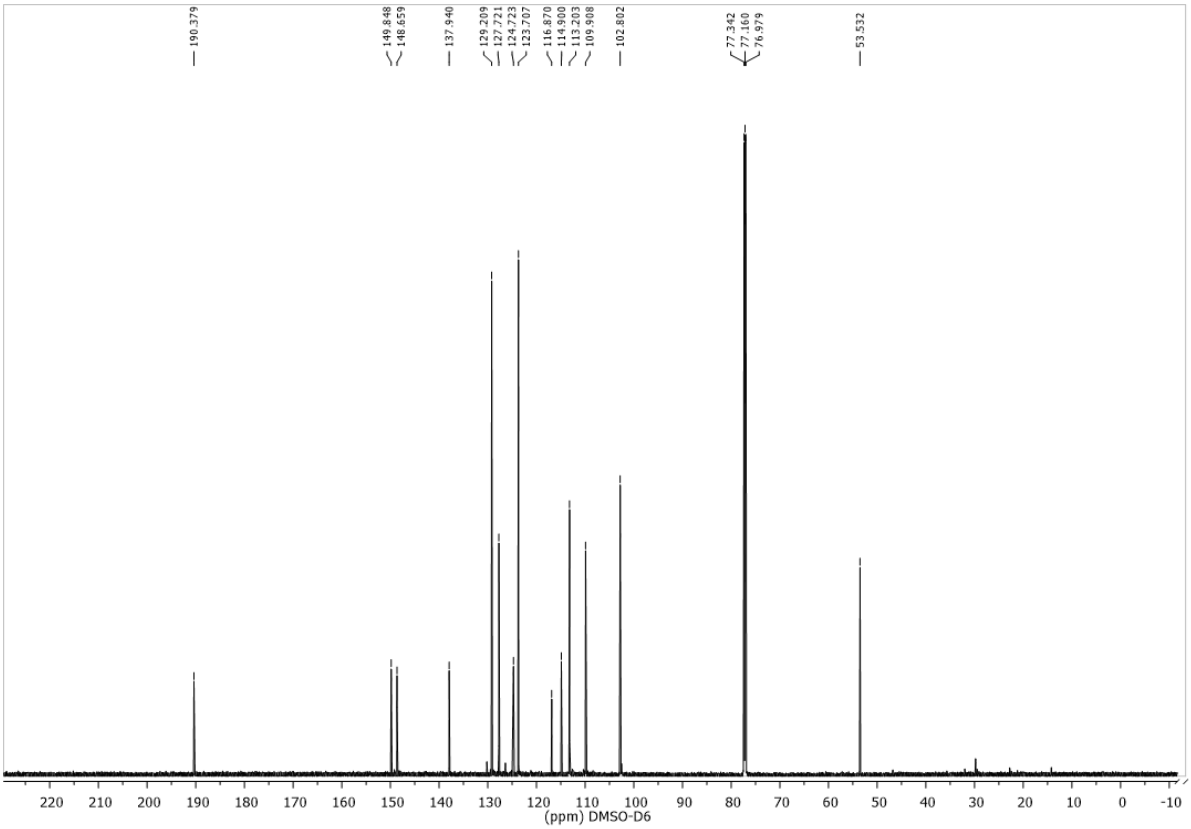
^{1}H NMR Spectrum of **3j**



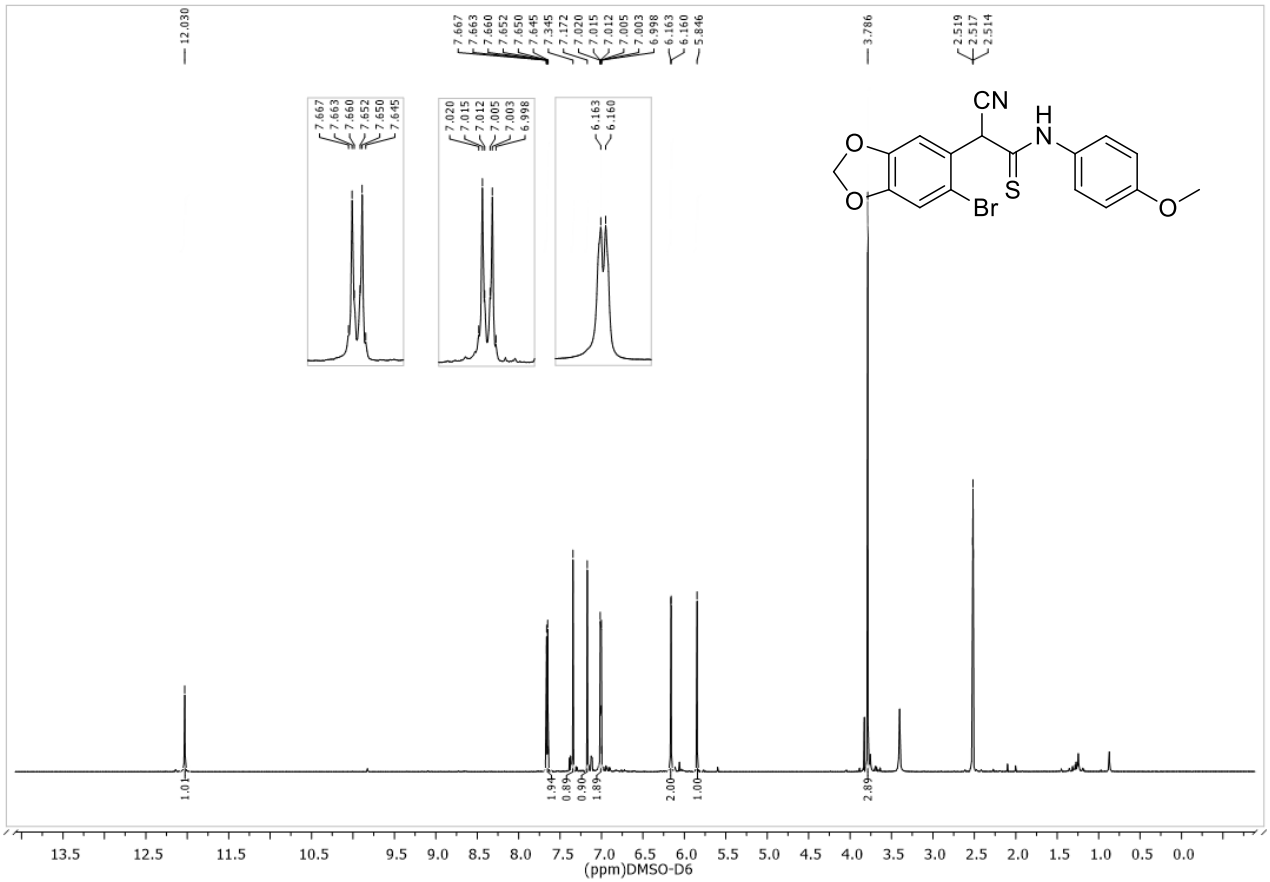
^{13}C NMR Spectrum of **3j**



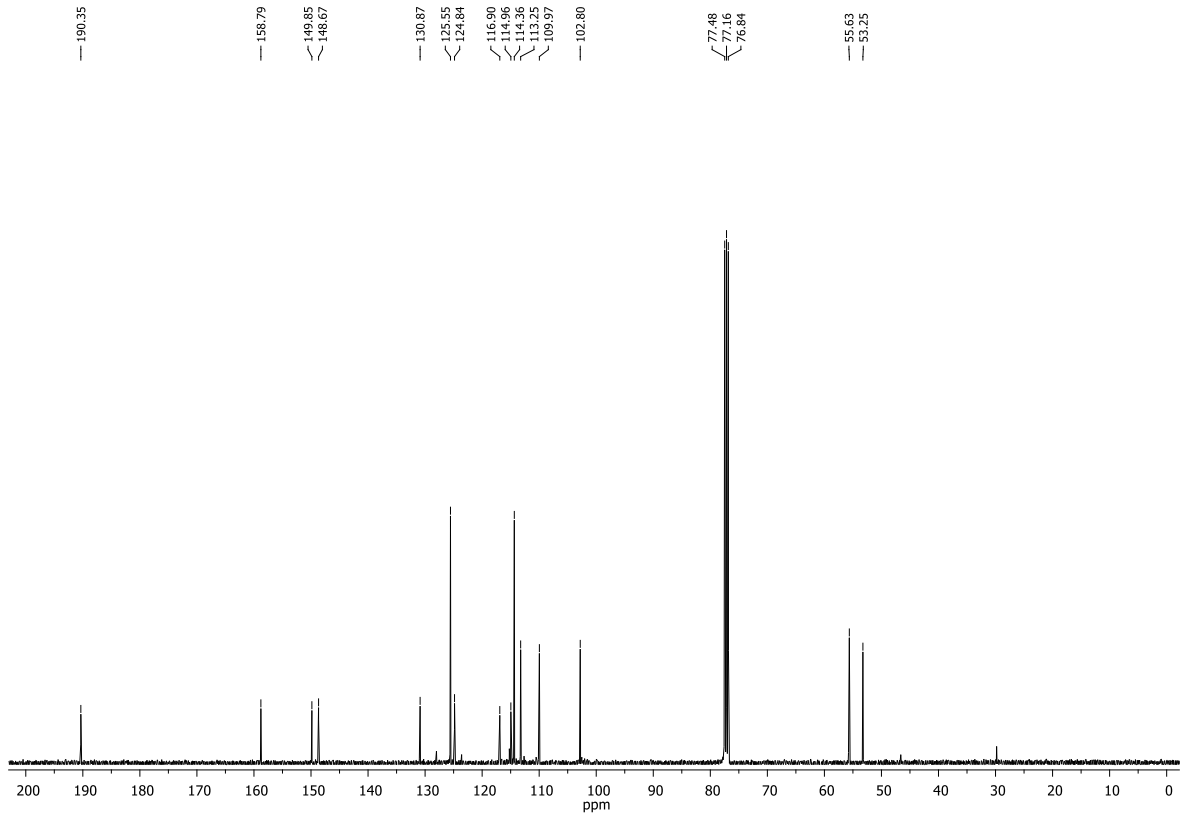
^{1}H NMR Spectrum of **3k**



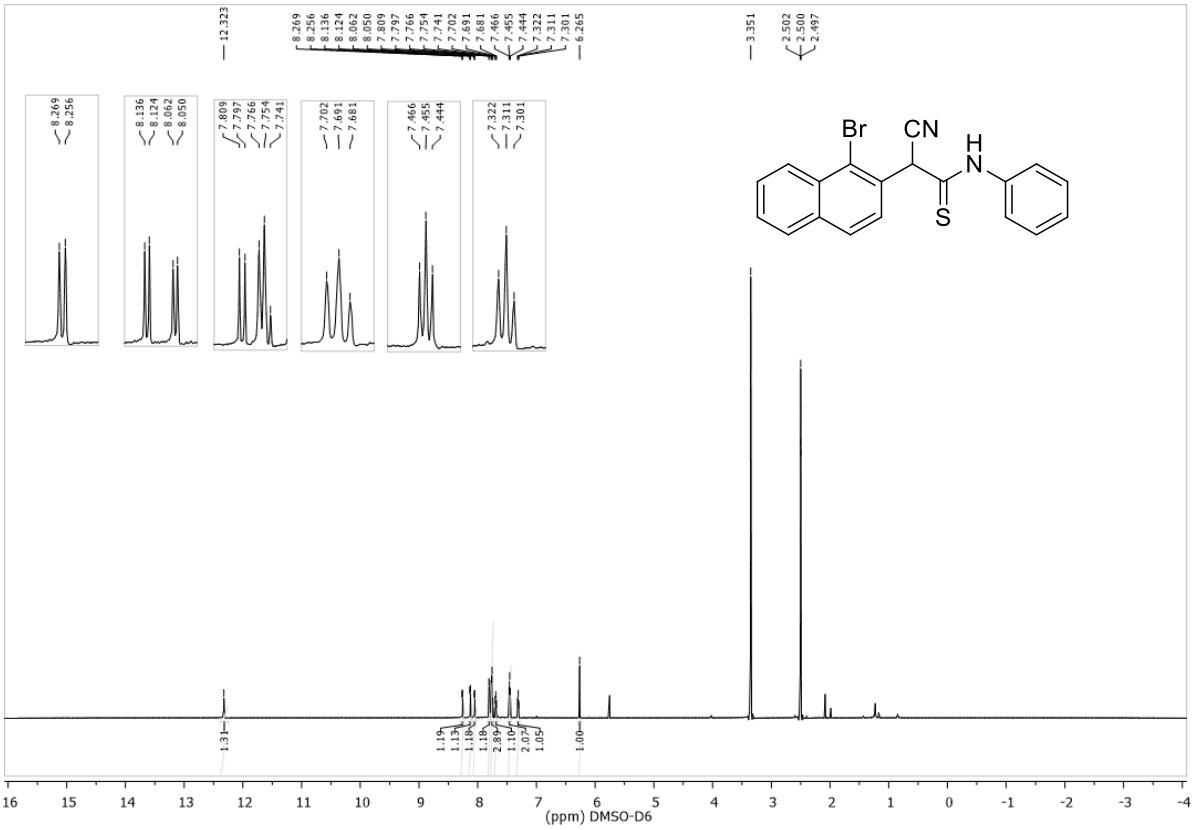
^{13}C NMR Spectrum of **3k**



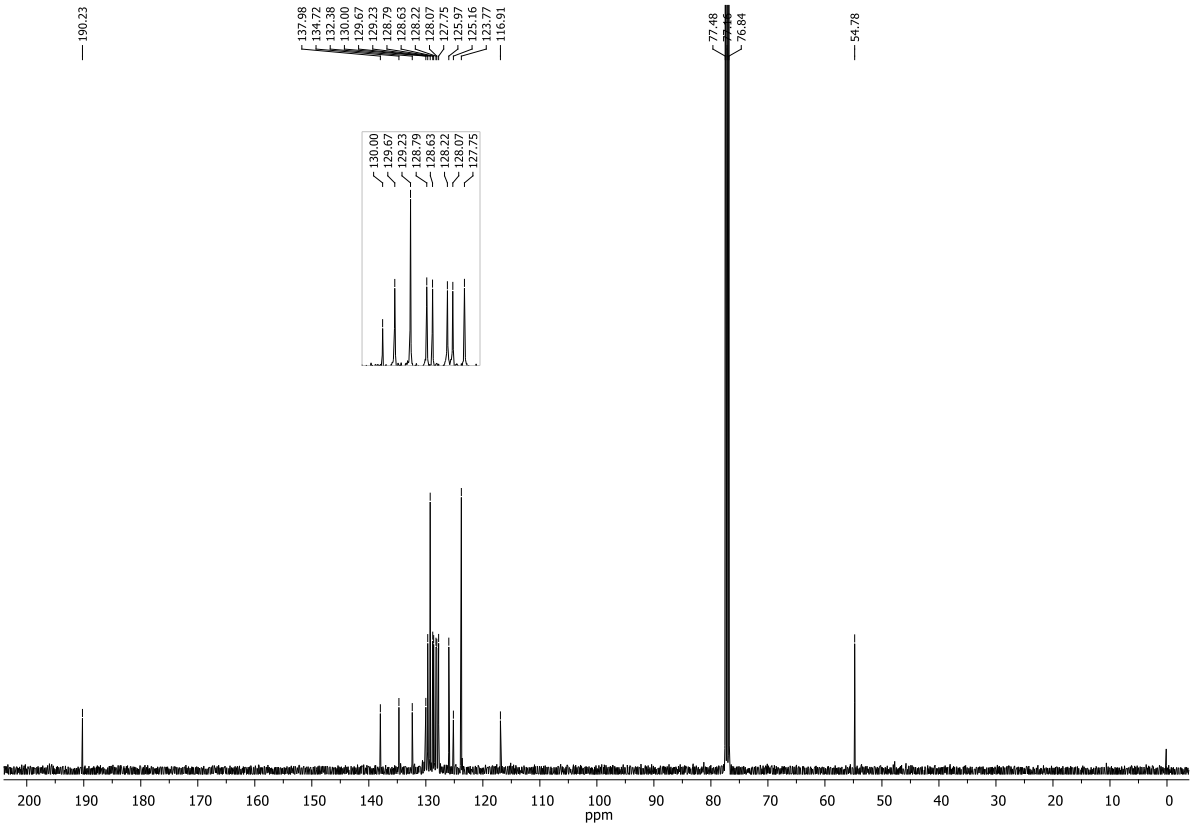
^{1}H NMR Spectrum of **3l**



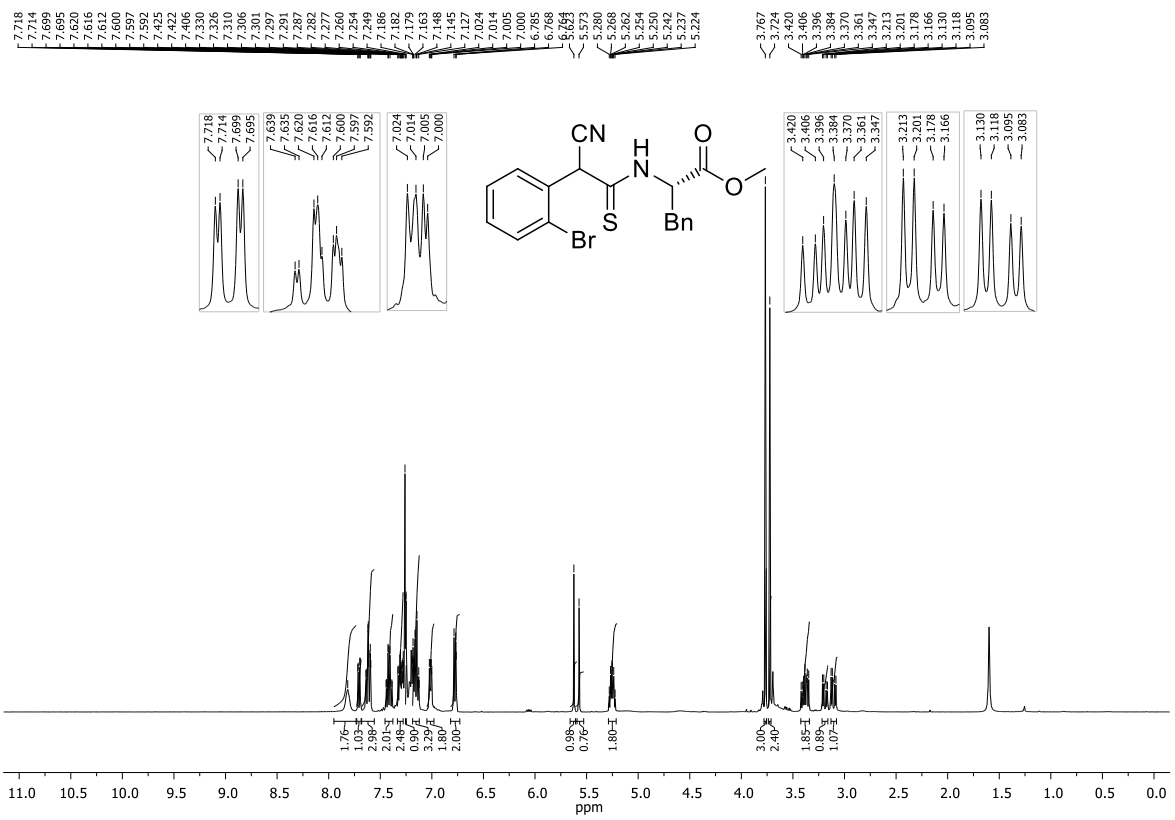
^{13}C NMR Spectrum of **3l**



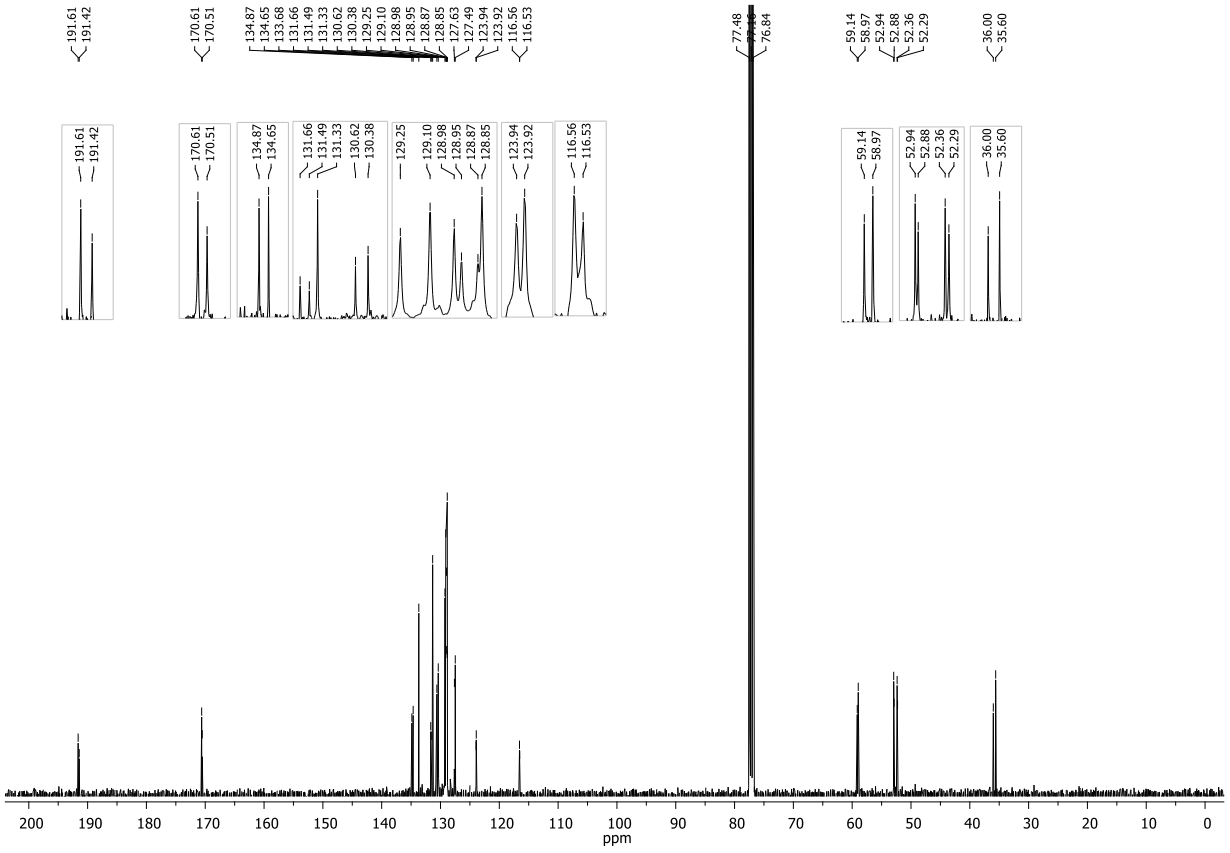
^{1}H NMR Spectrum of **3n**



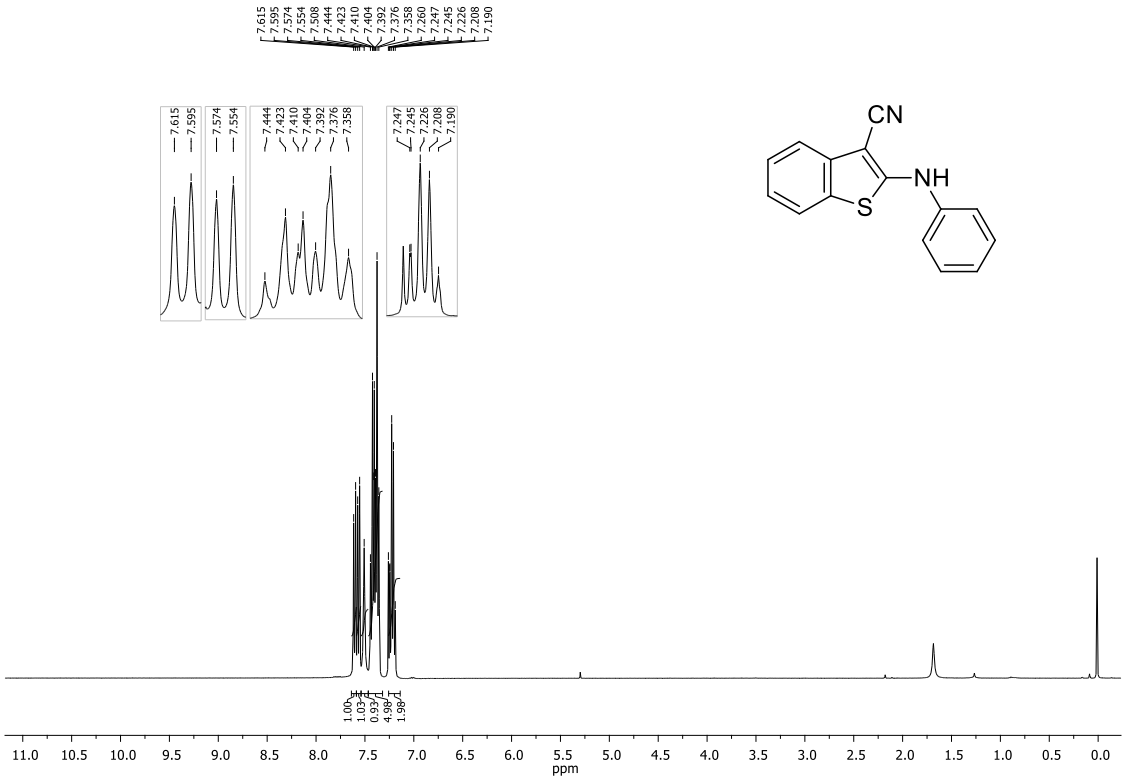
^{13}C NMR Spectrum of **3n**



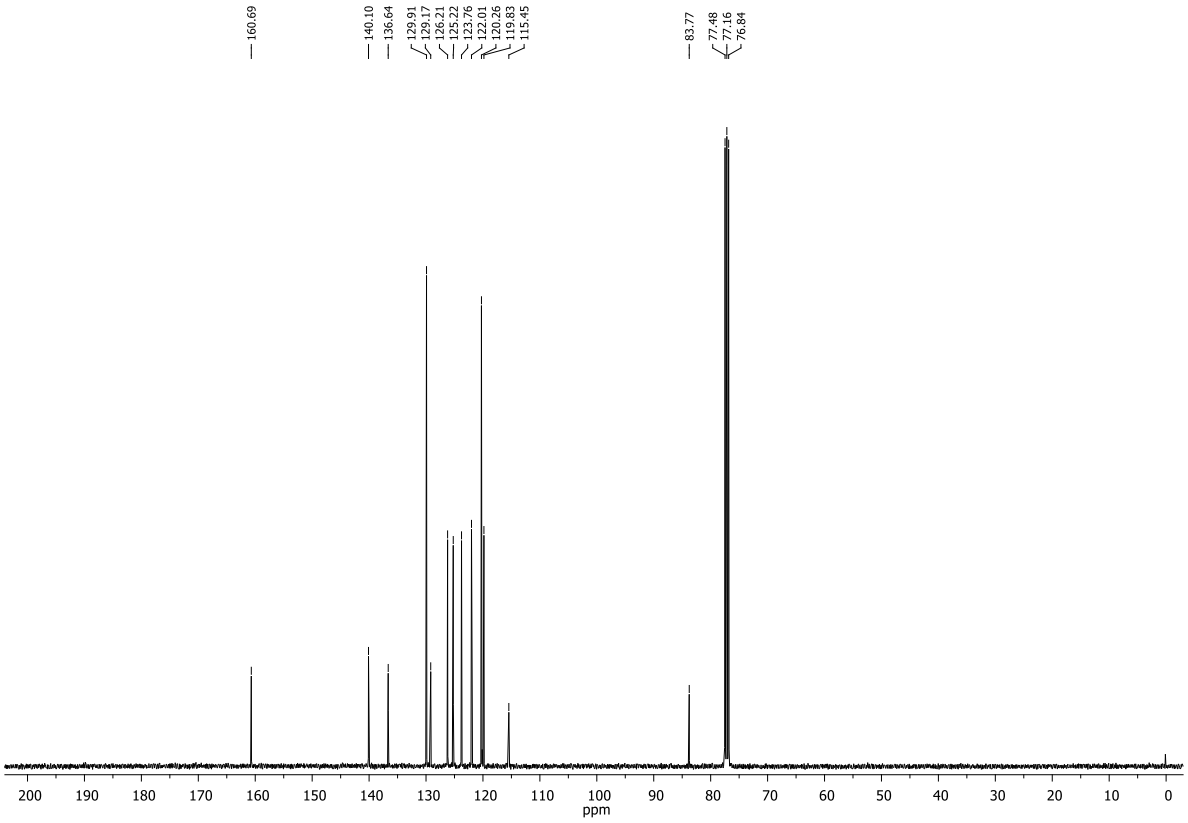
^{1}H NMR Spectrum of **3o**



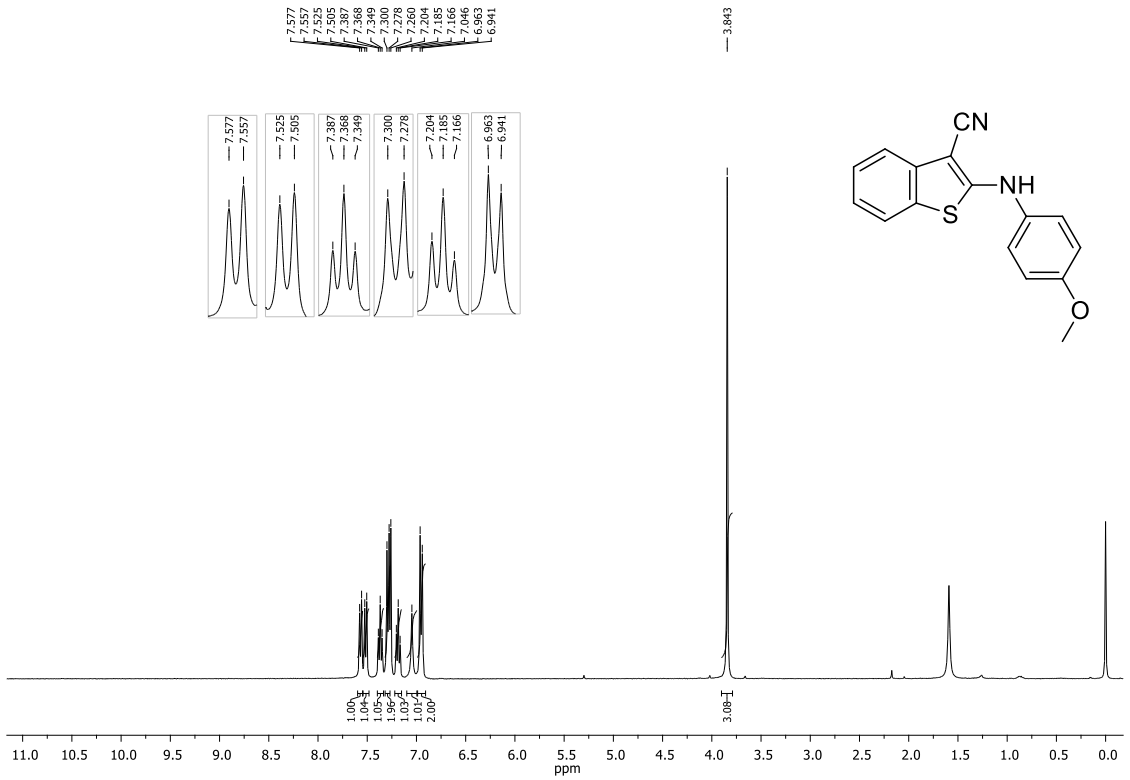
^{13}C NMR Spectrum of **3o**



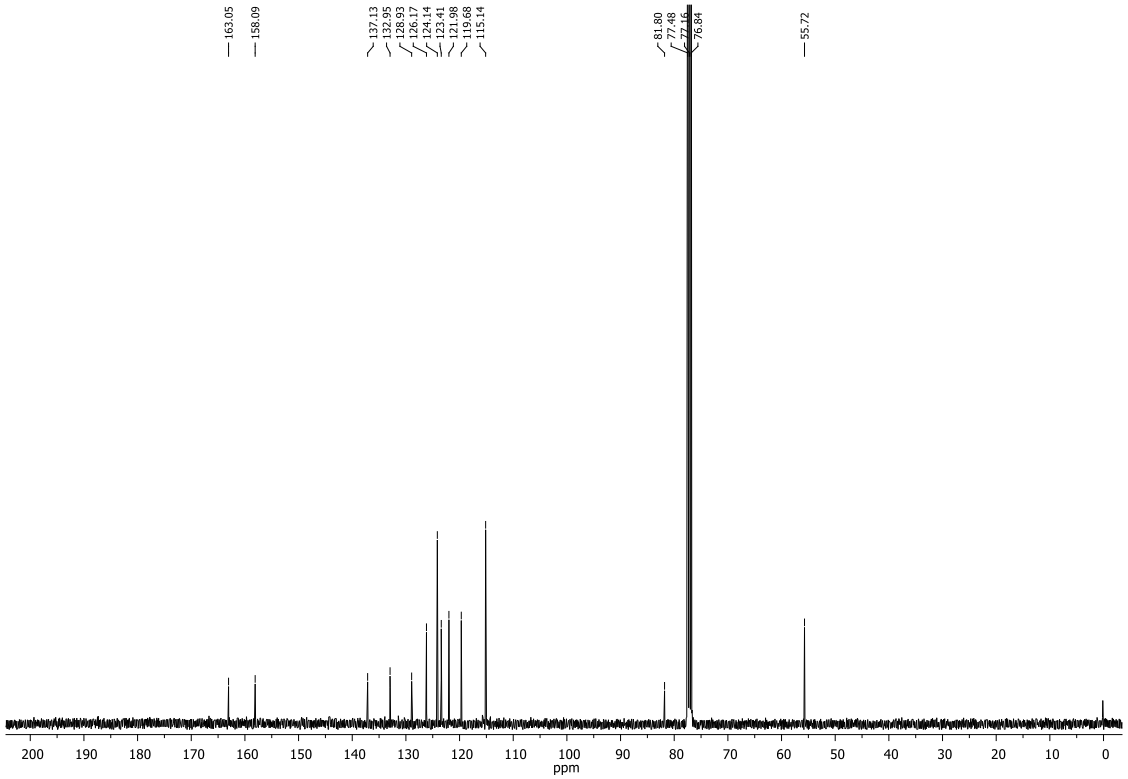
^{1}H NMR Spectrum of **4a**



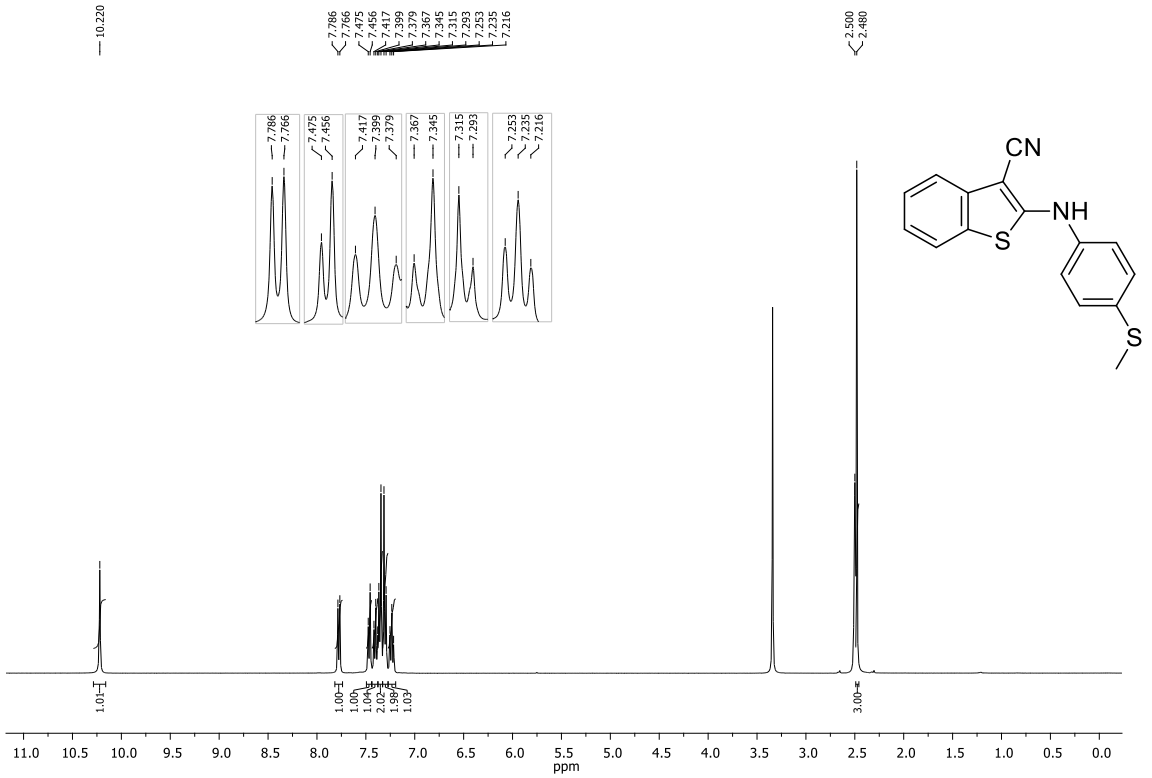
^{13}C NMR Spectrum of **4a**



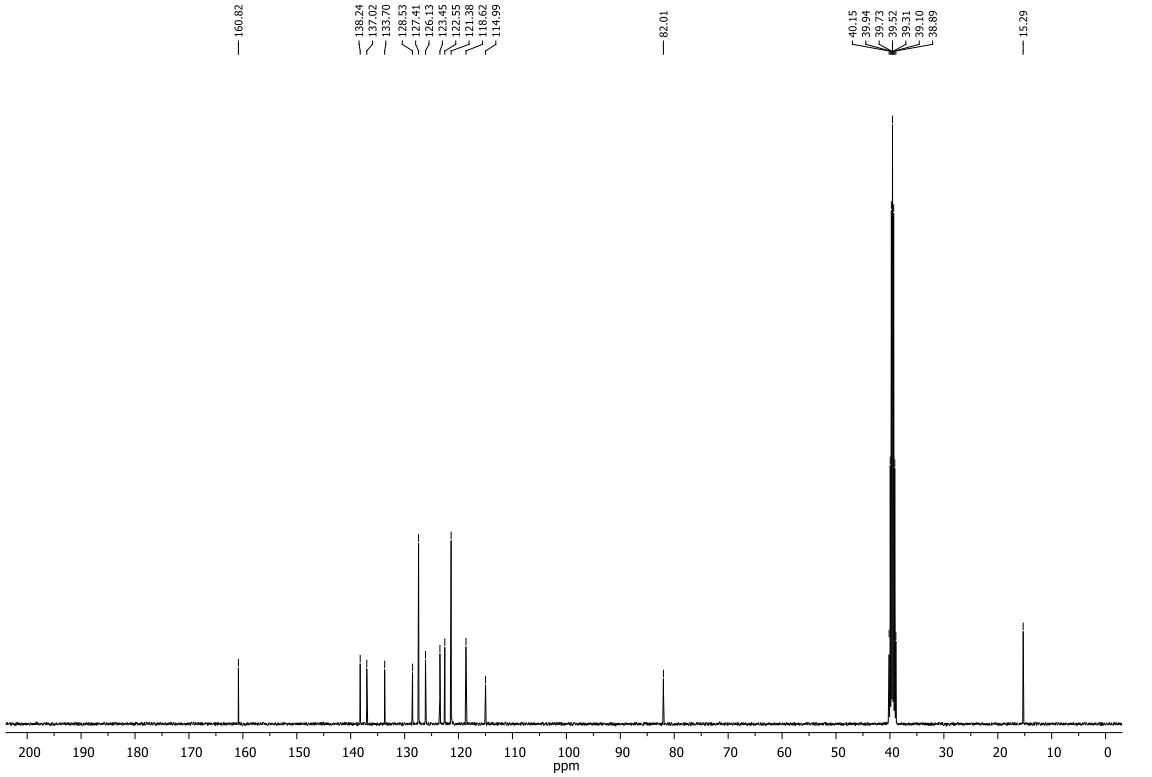
^{1}H NMR Spectrum of **4b**



^{13}C NMR Spectrum of **4b**



^{1}H NMR Spectrum of **4c**



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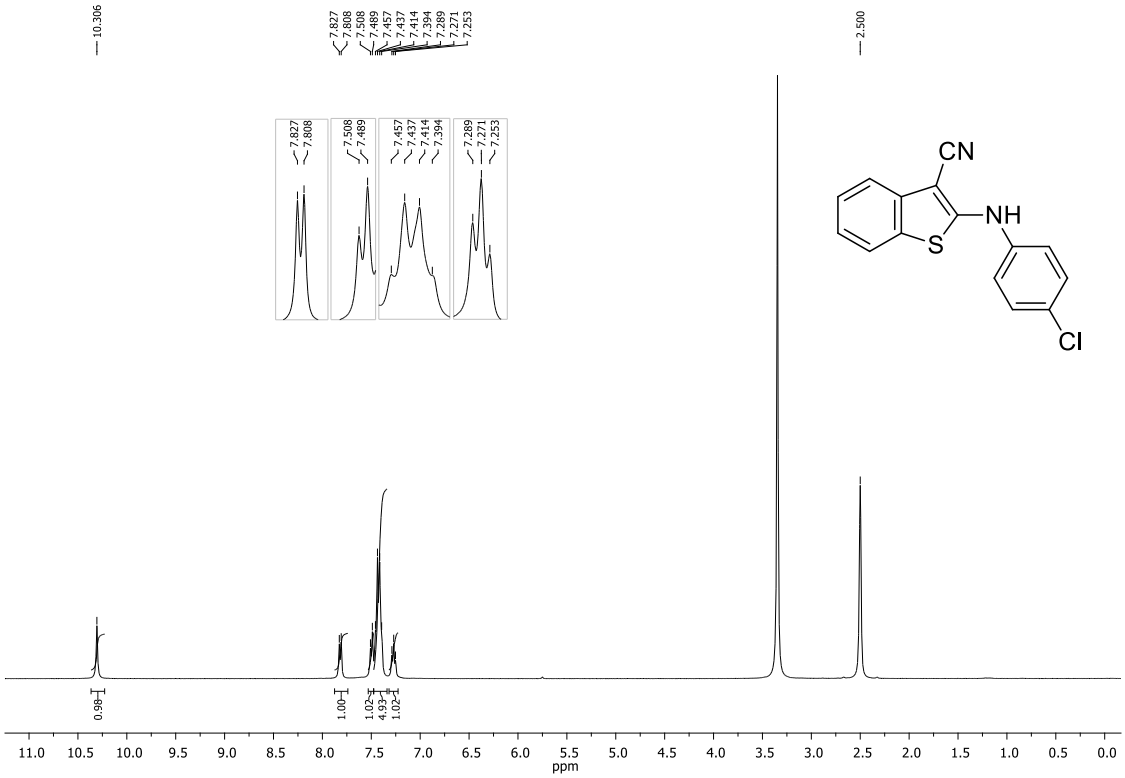
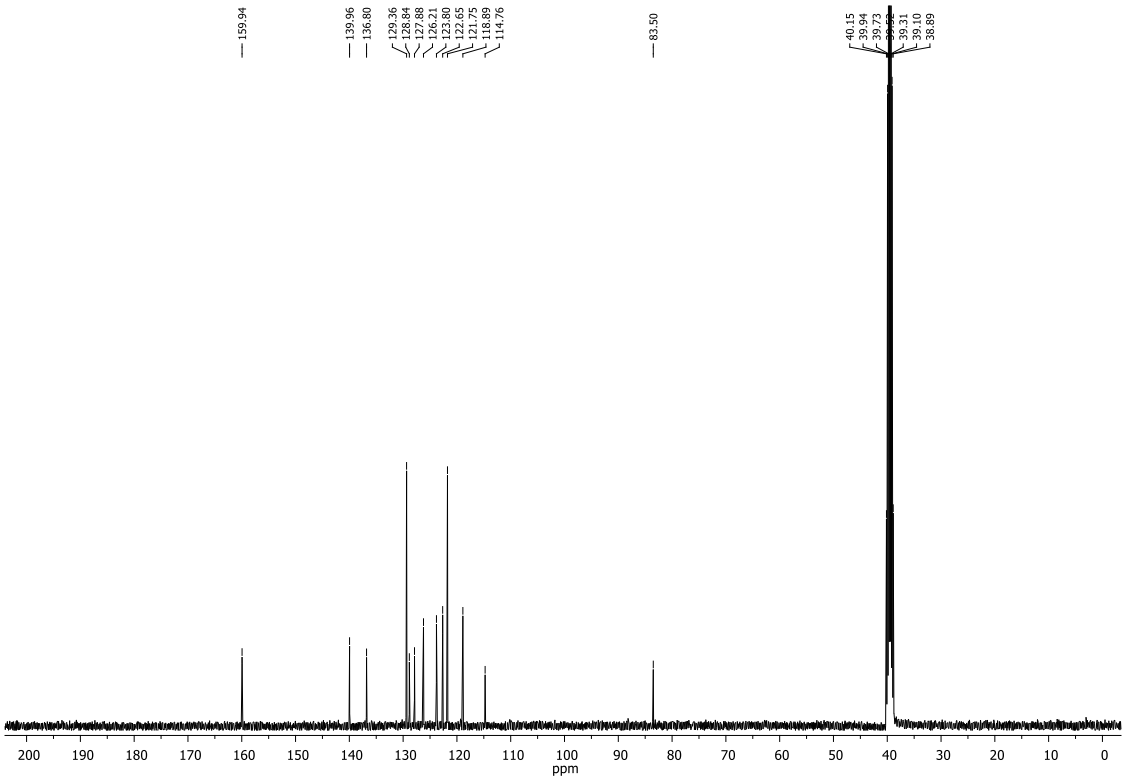
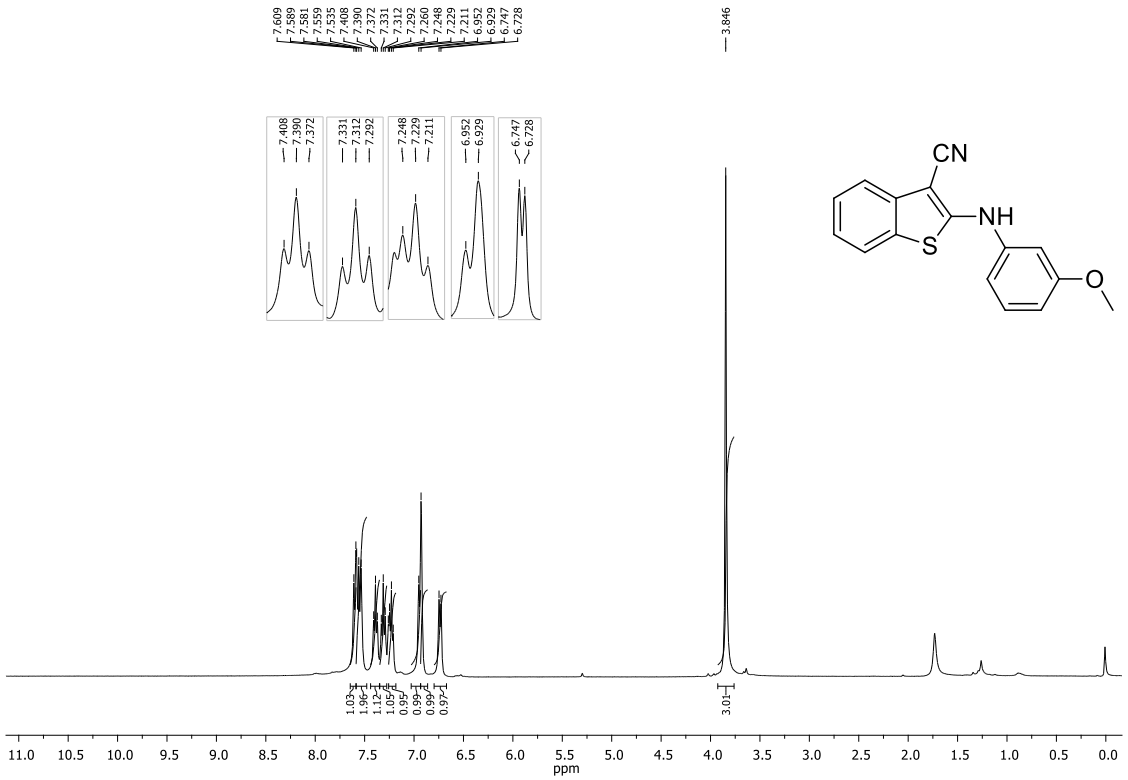


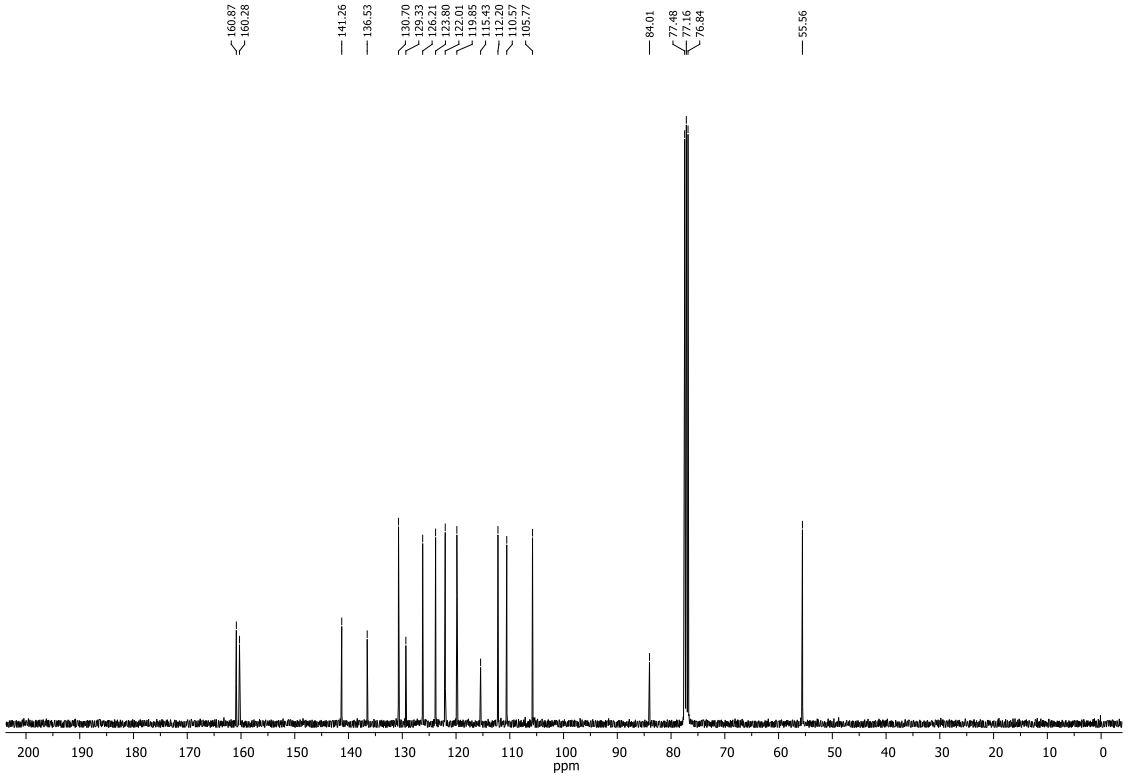
^{1}H NMR Spectrum of **4d**



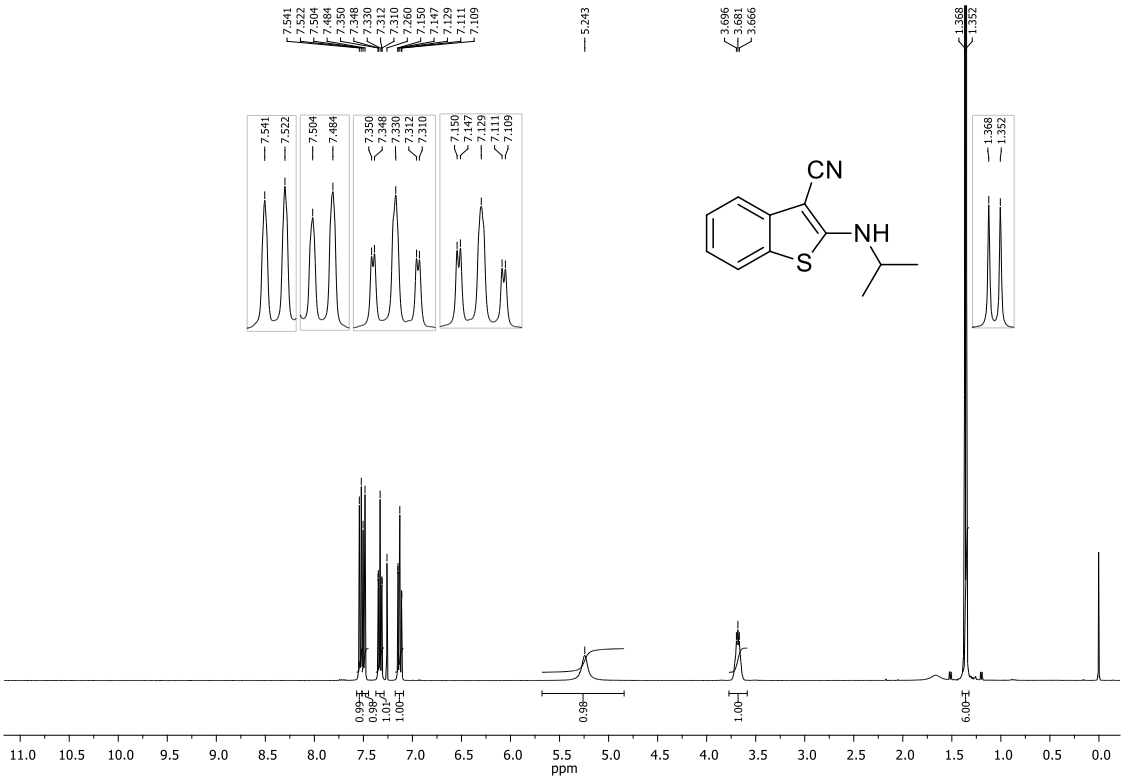
^{13}C NMR Spectrum of **4d**



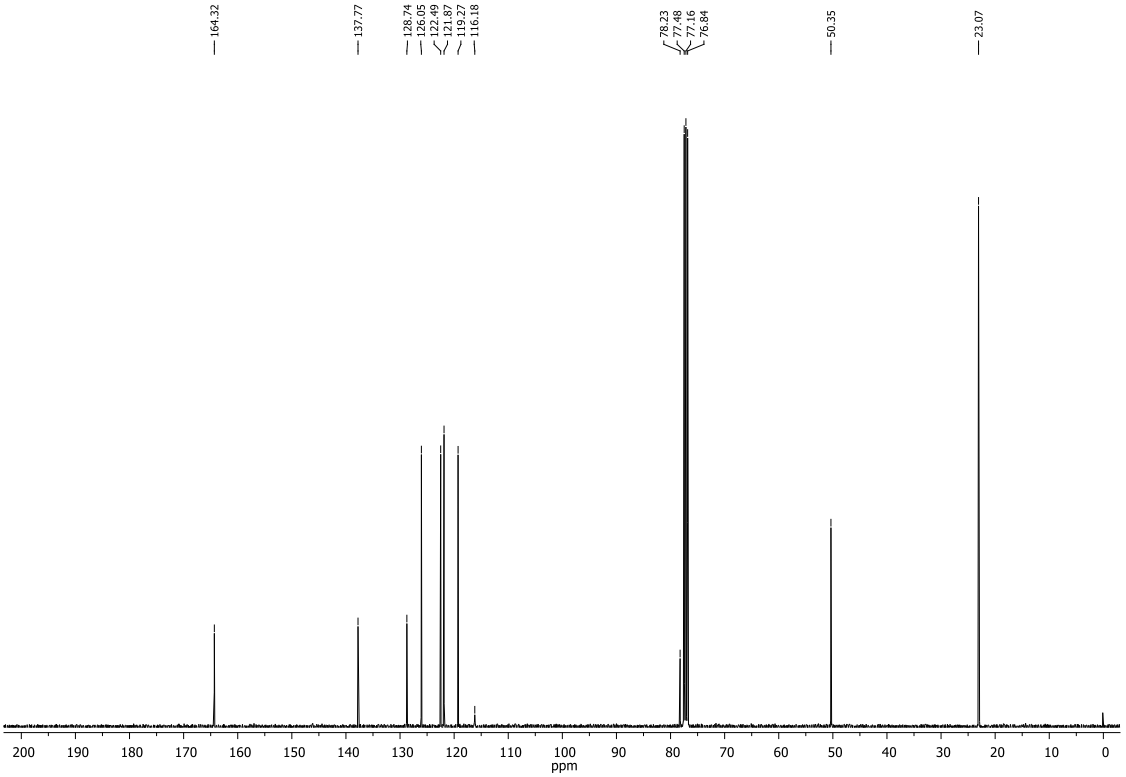
^{1}H NMR Spectrum of **4e**



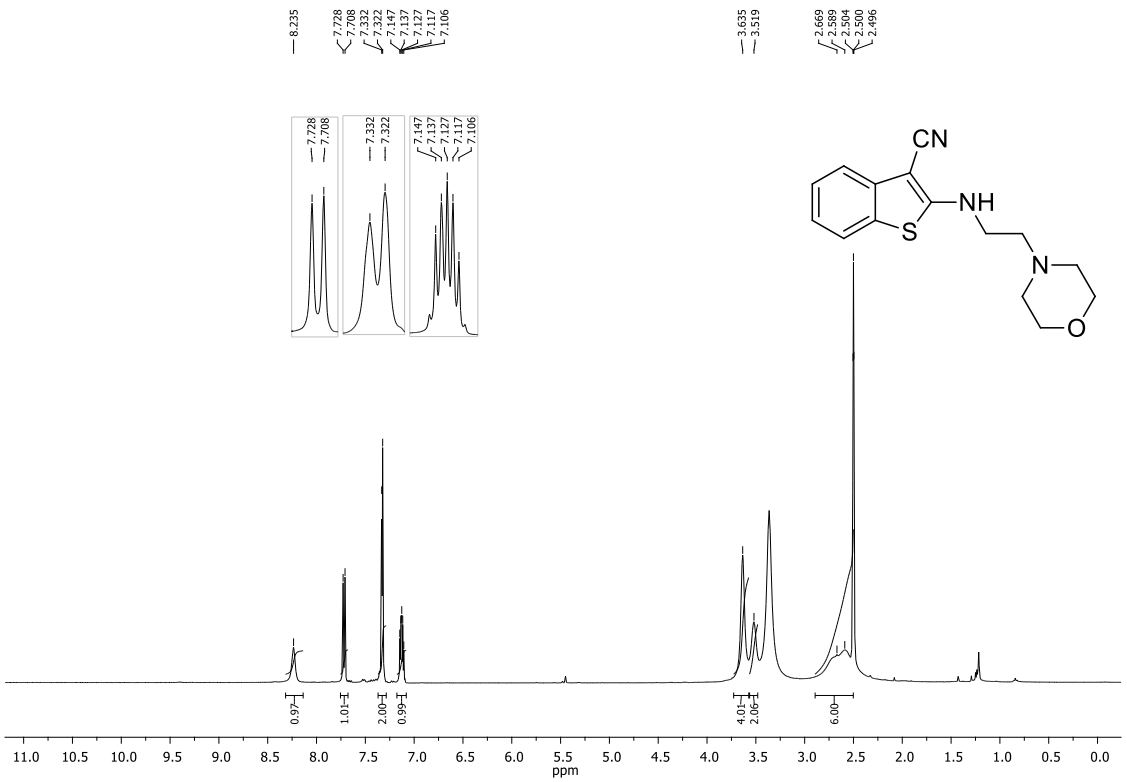
^{13}C NMR Spectrum of **4e**



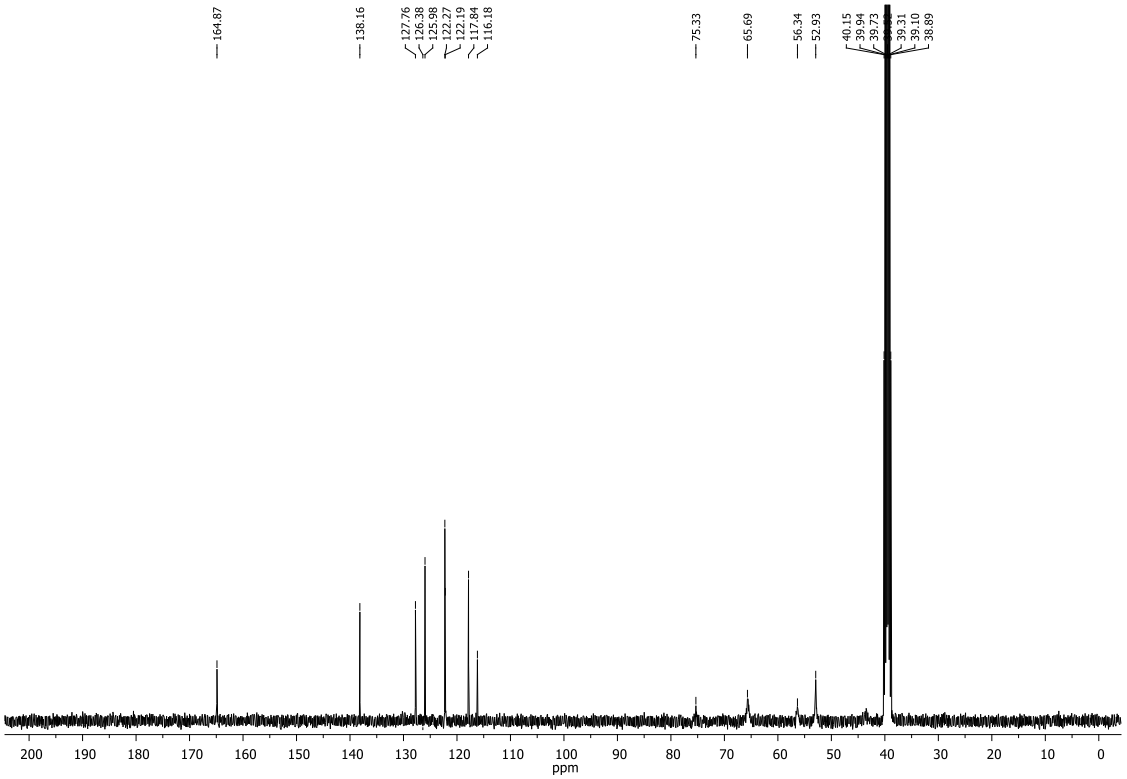
^{1}H NMR Spectrum of **4f**



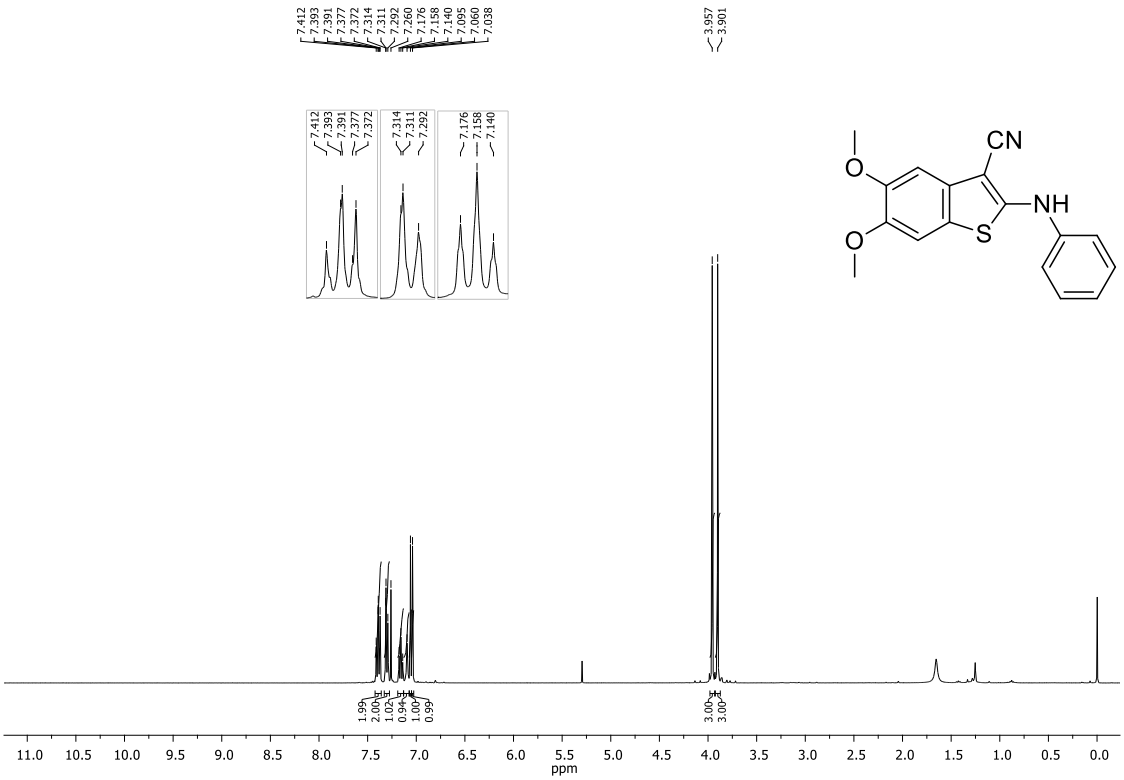
^{13}C NMR Spectrum of **4f**



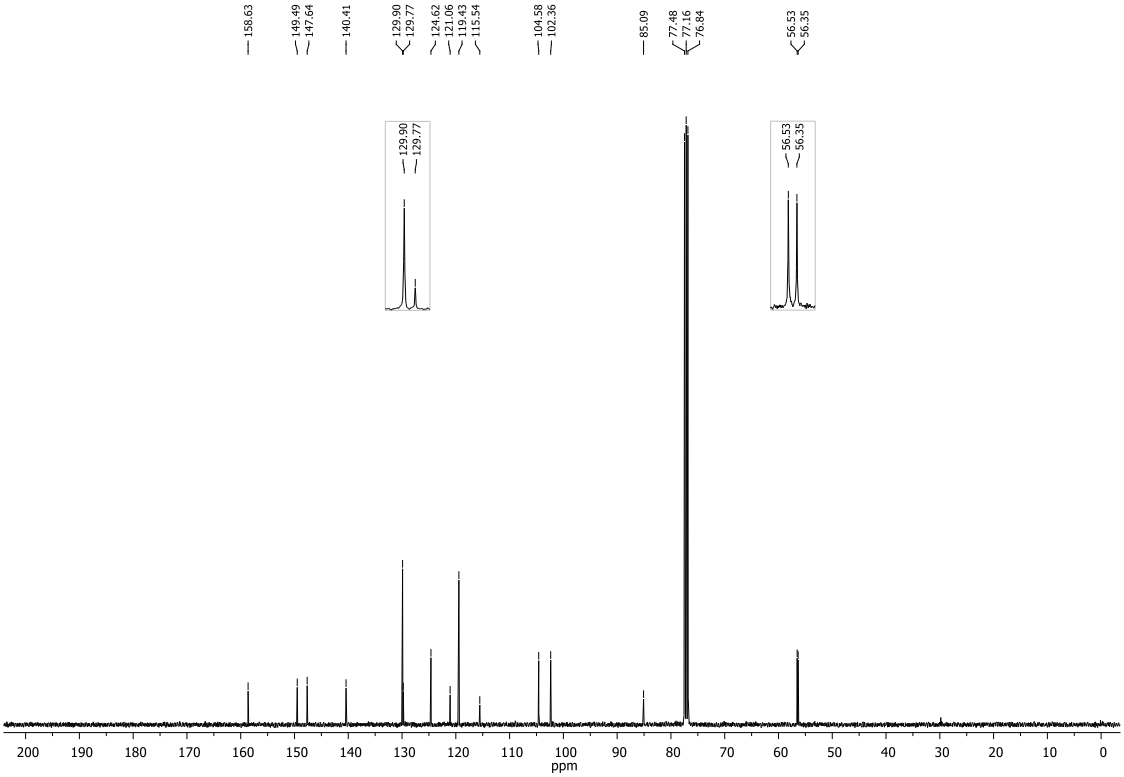
^{1}H NMR Spectrum of **4g**



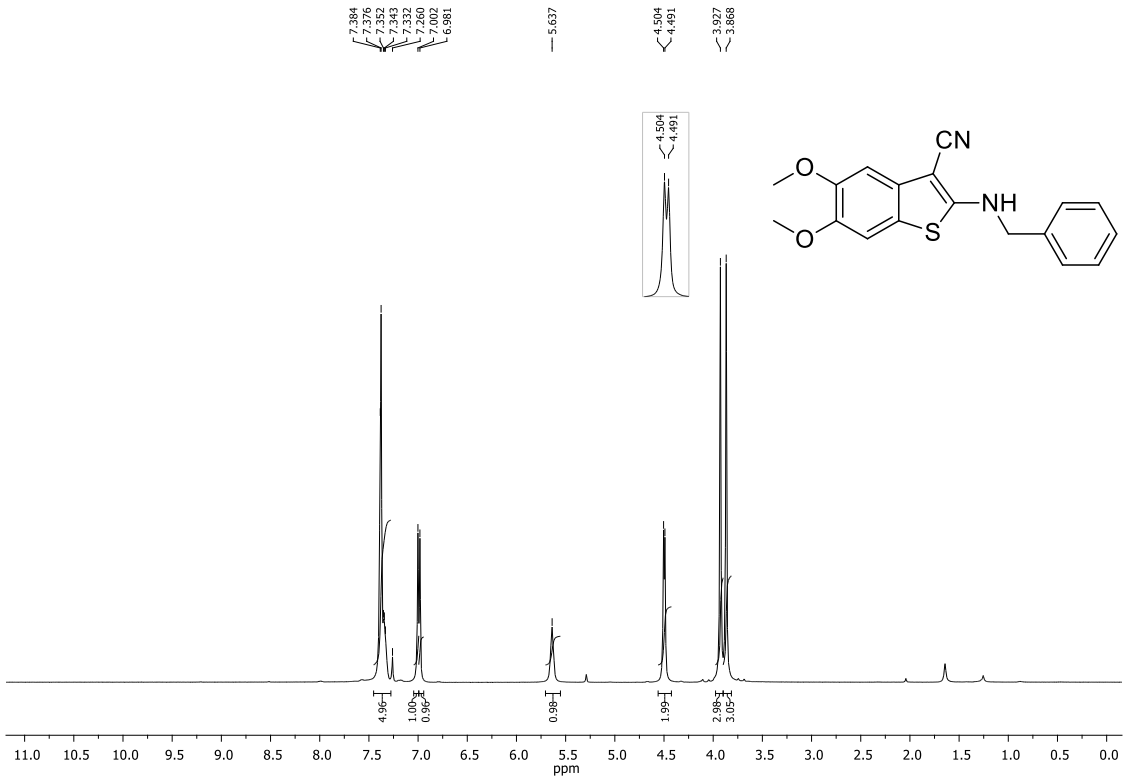
^{13}C NMR Spectrum of **4g**



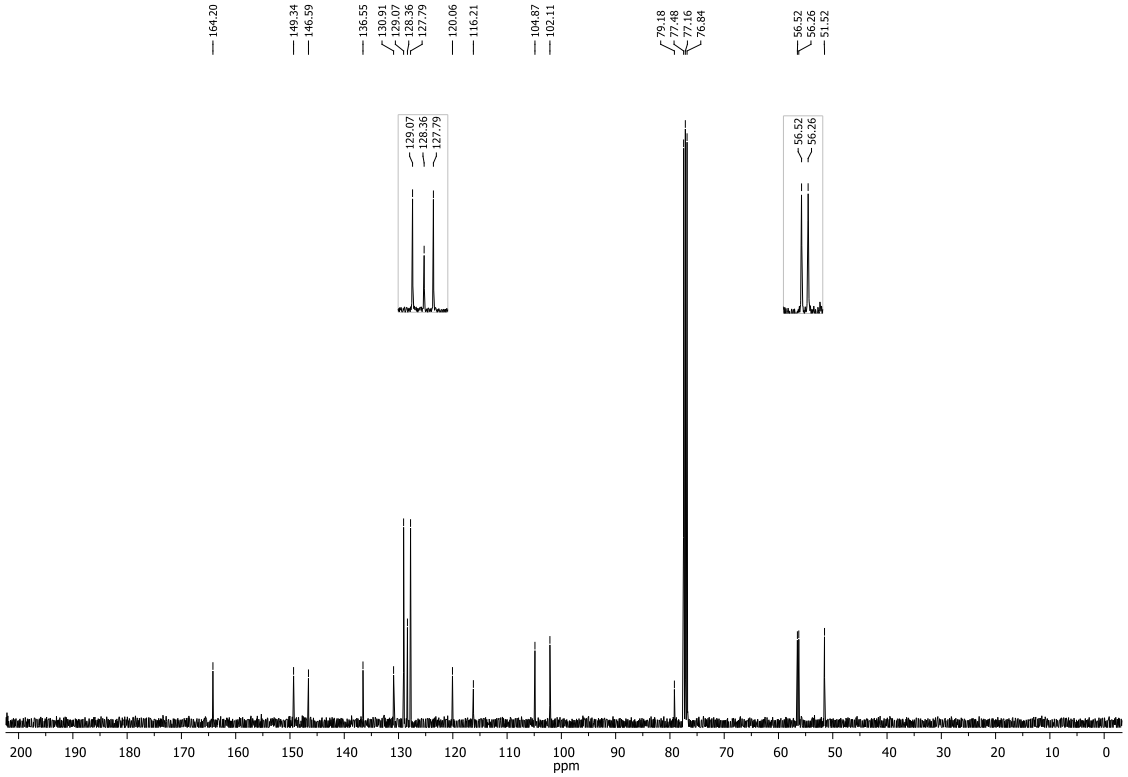
^{1}H NMR Spectrum of **4h**



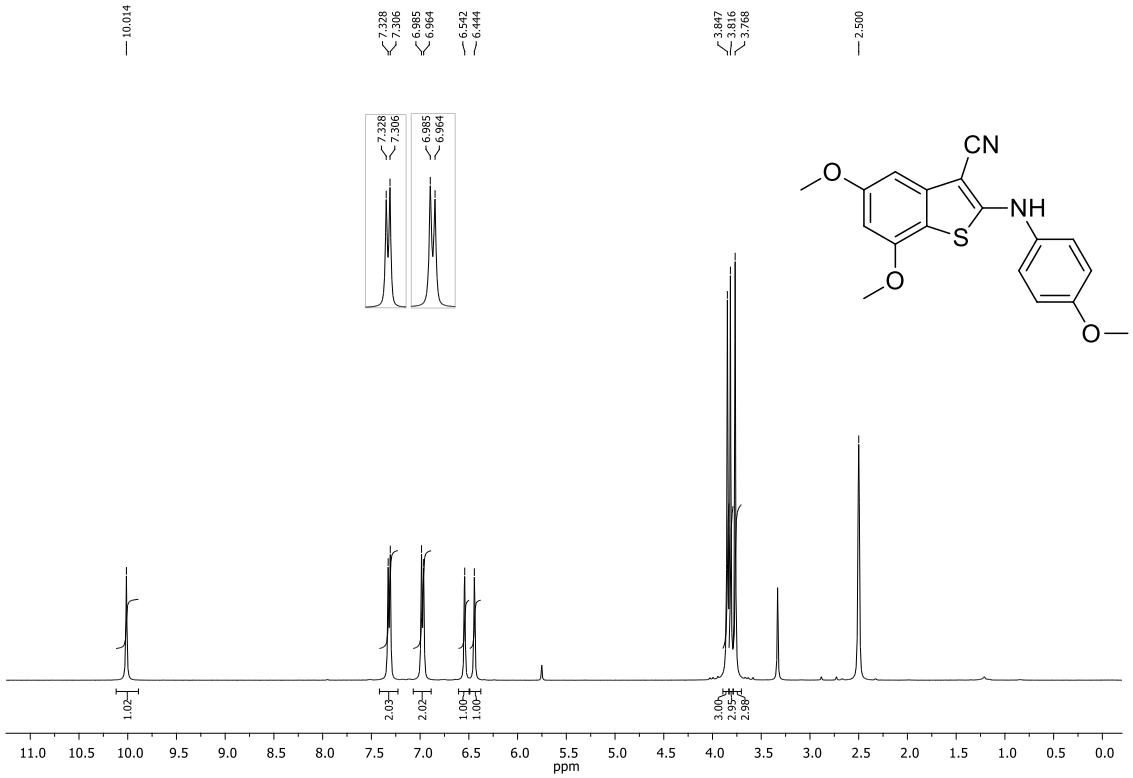
^{13}C NMR Spectrum of **4h**



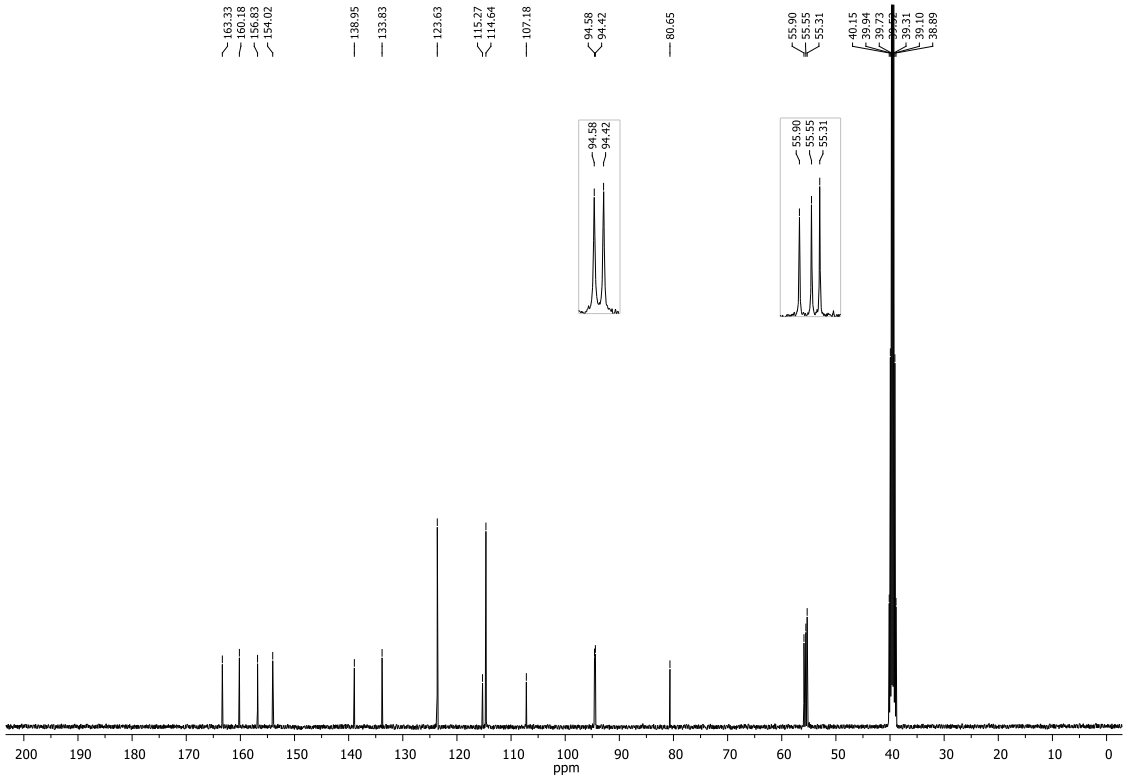
^{1}H NMR Spectrum of **4i**



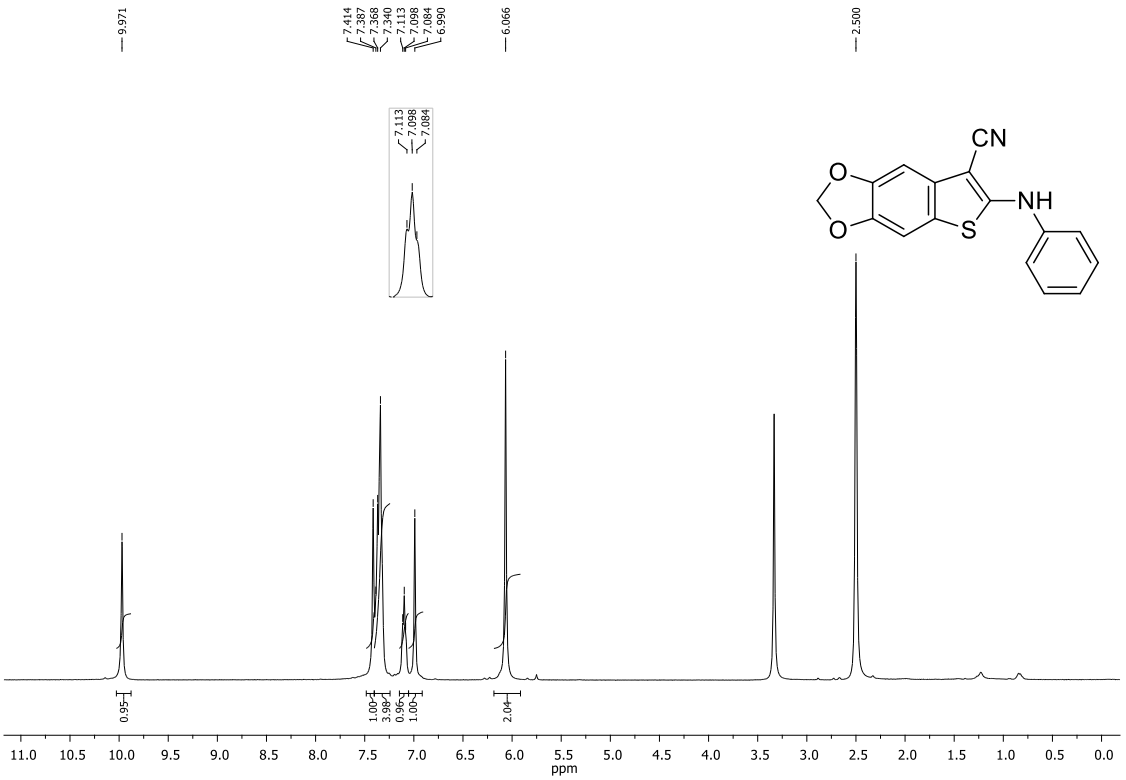
^{13}C NMR Spectrum of **4i**



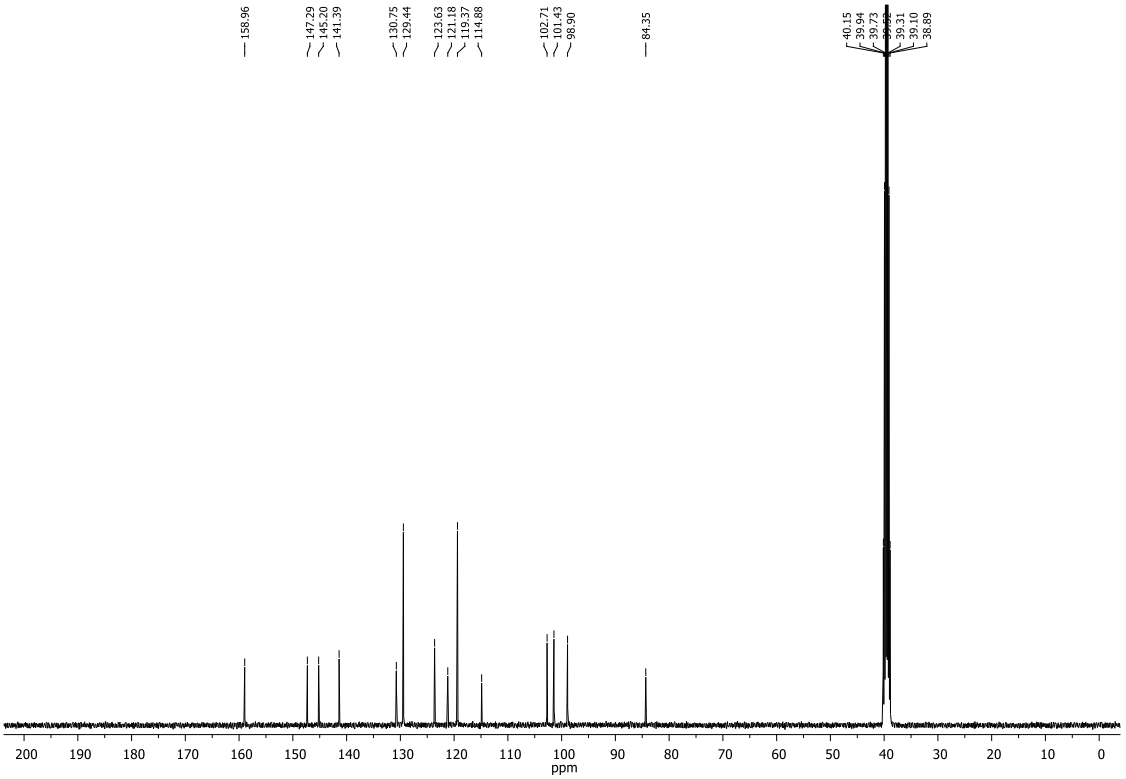
^{1}H NMR Spectrum of **4j**



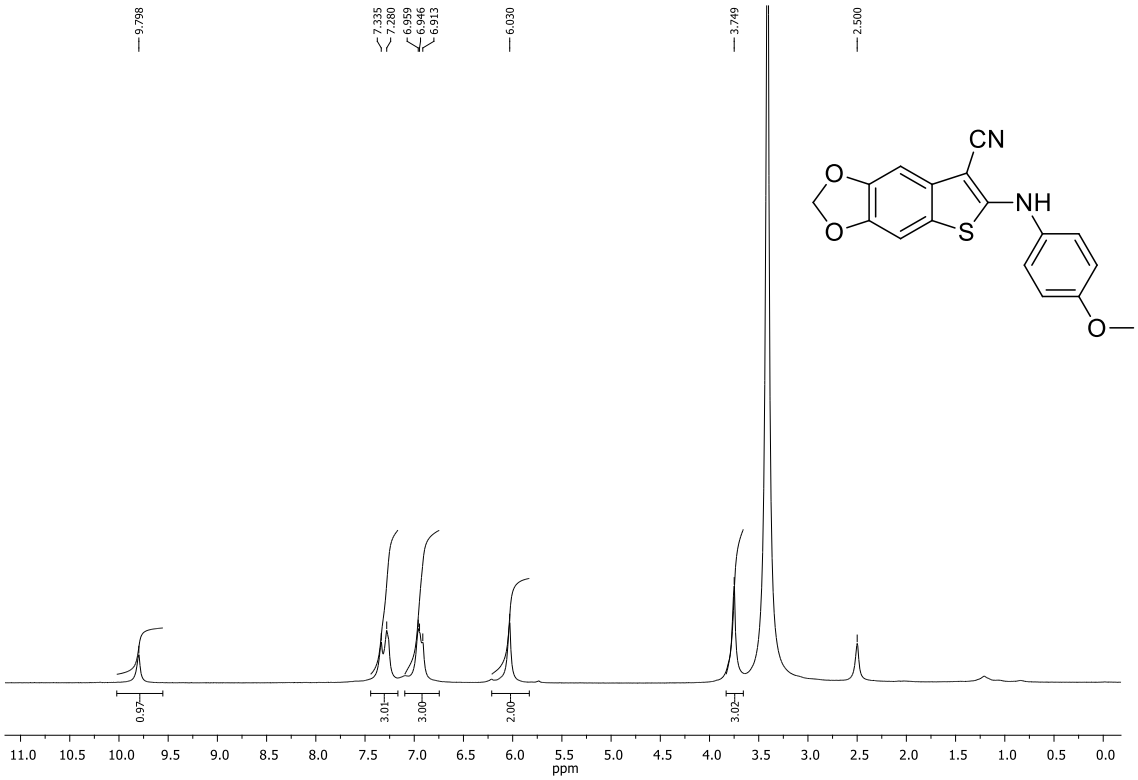
^{13}C NMR Spectrum of **4j**



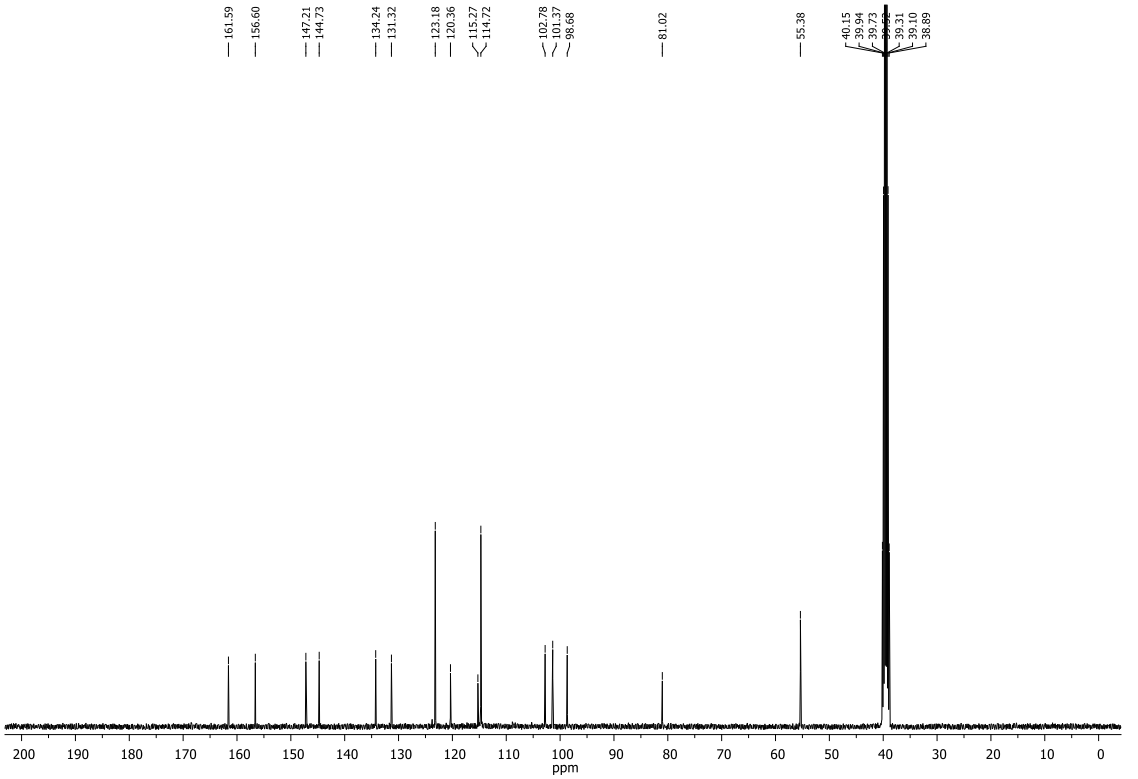
^{1}H NMR Spectrum of **4k**



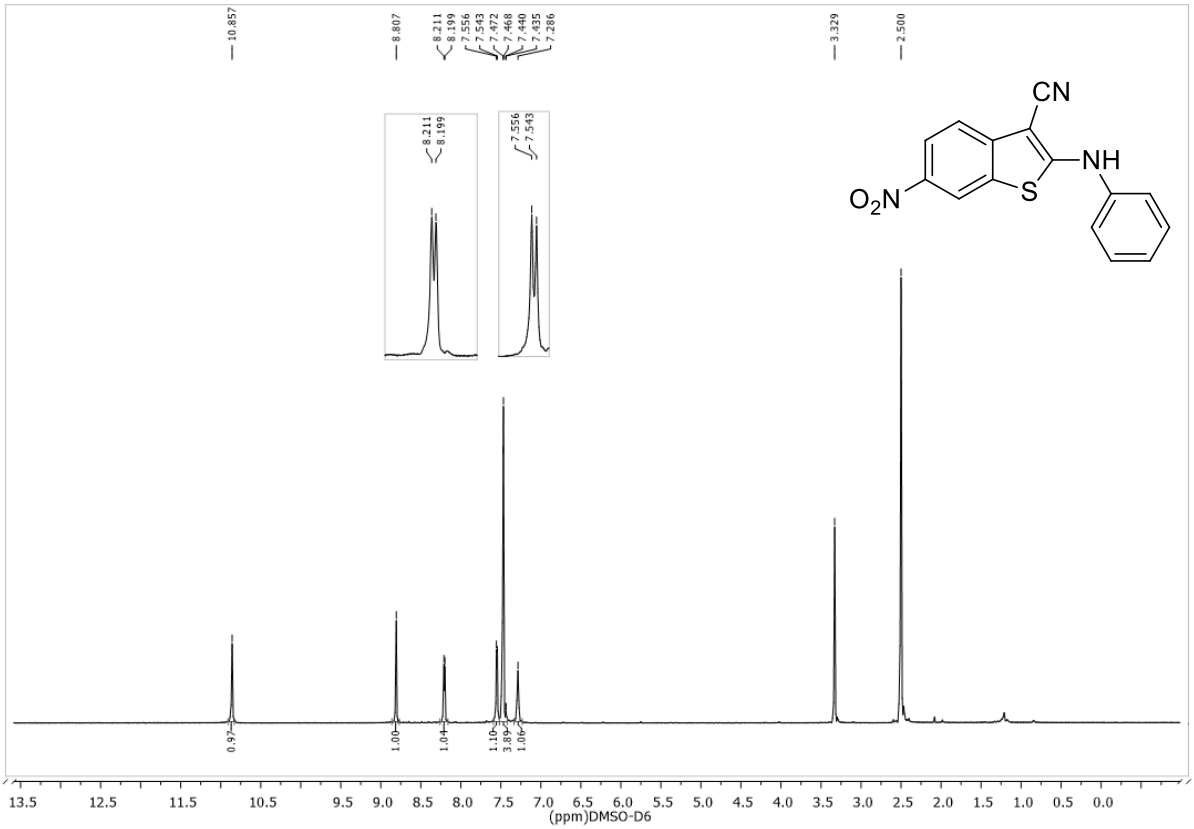
^{13}C NMR Spectrum of **4k**



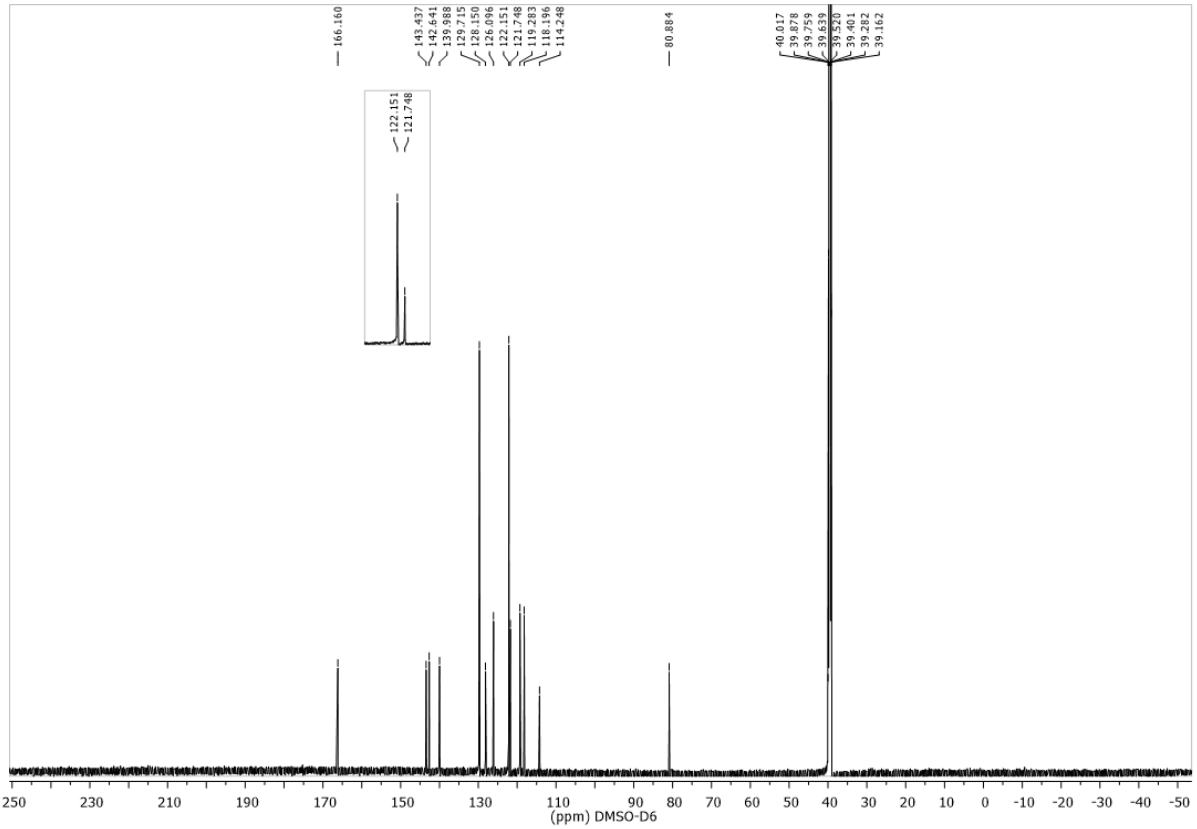
^{1}H NMR Spectrum of **4l**



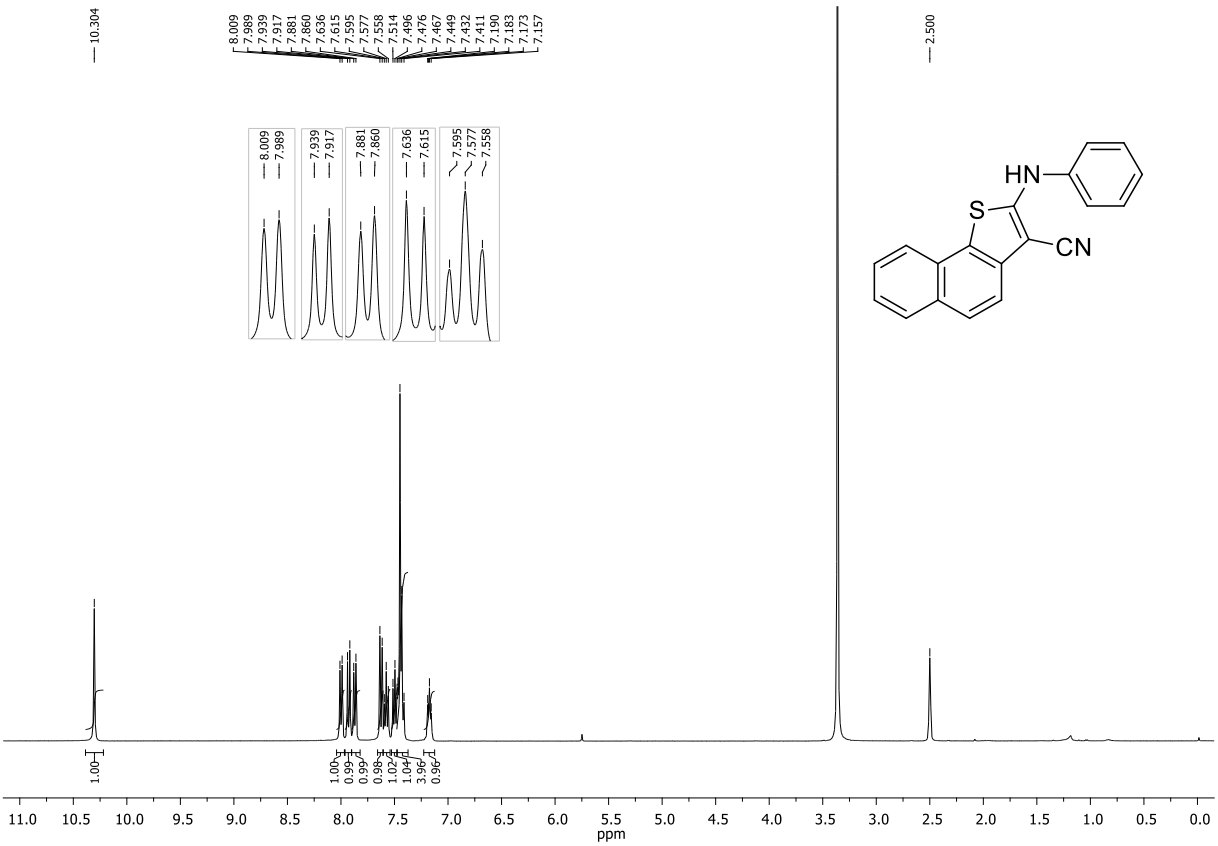
^{13}C NMR Spectrum of **4l**



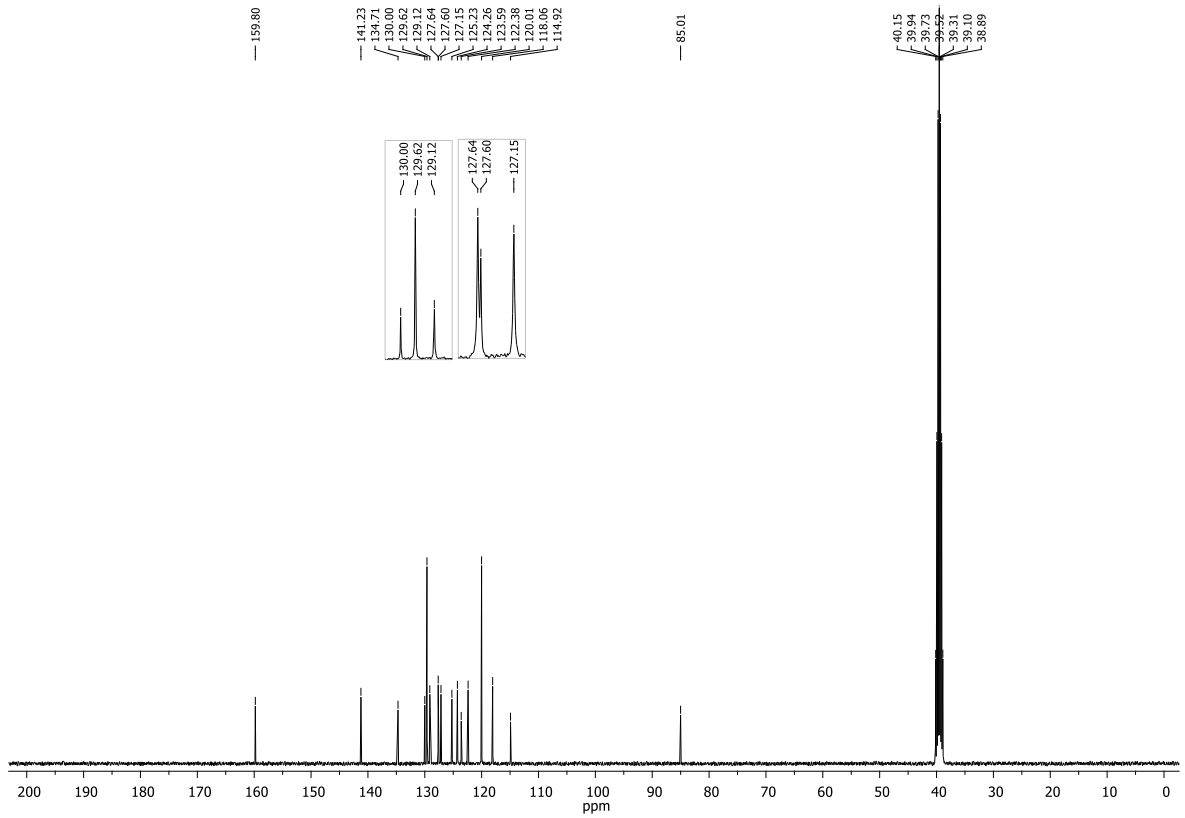
^{1}H NMR Spectrum of **4m**



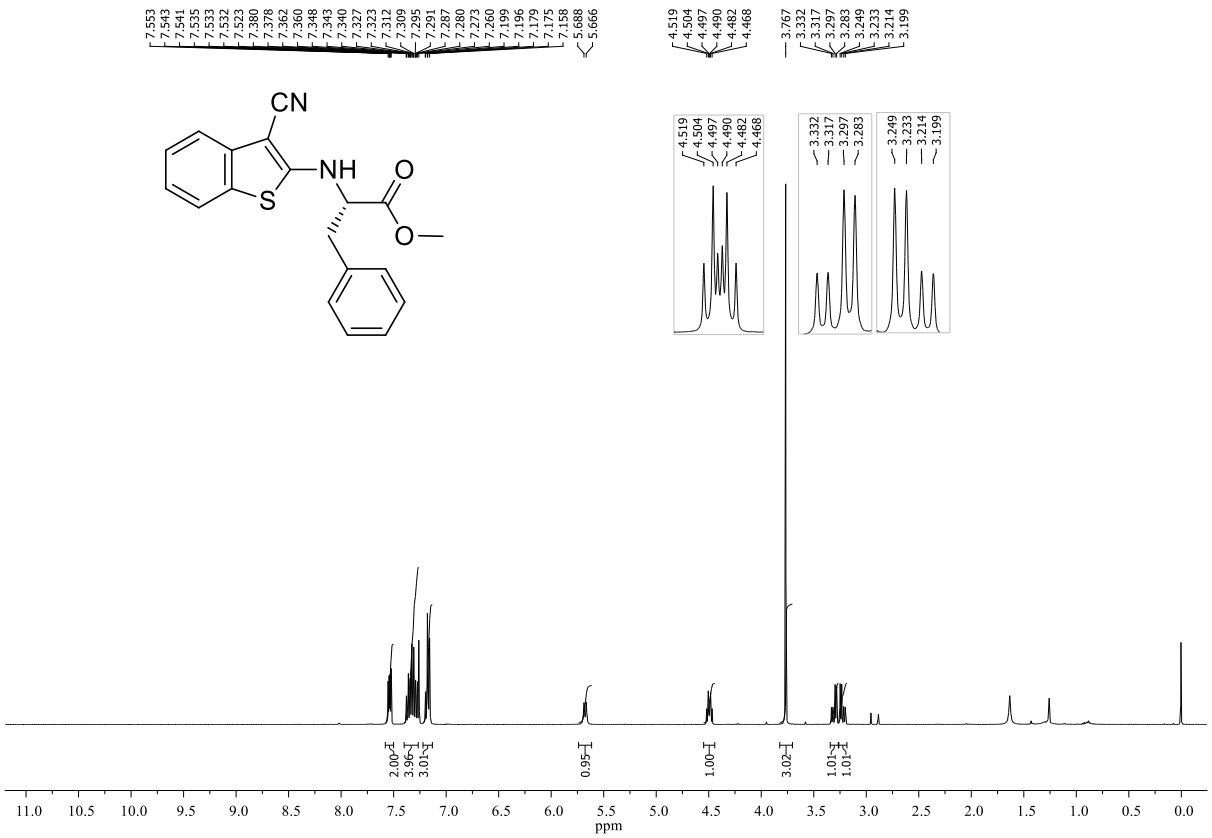
^{13}C NMR Spectrum of **4m**



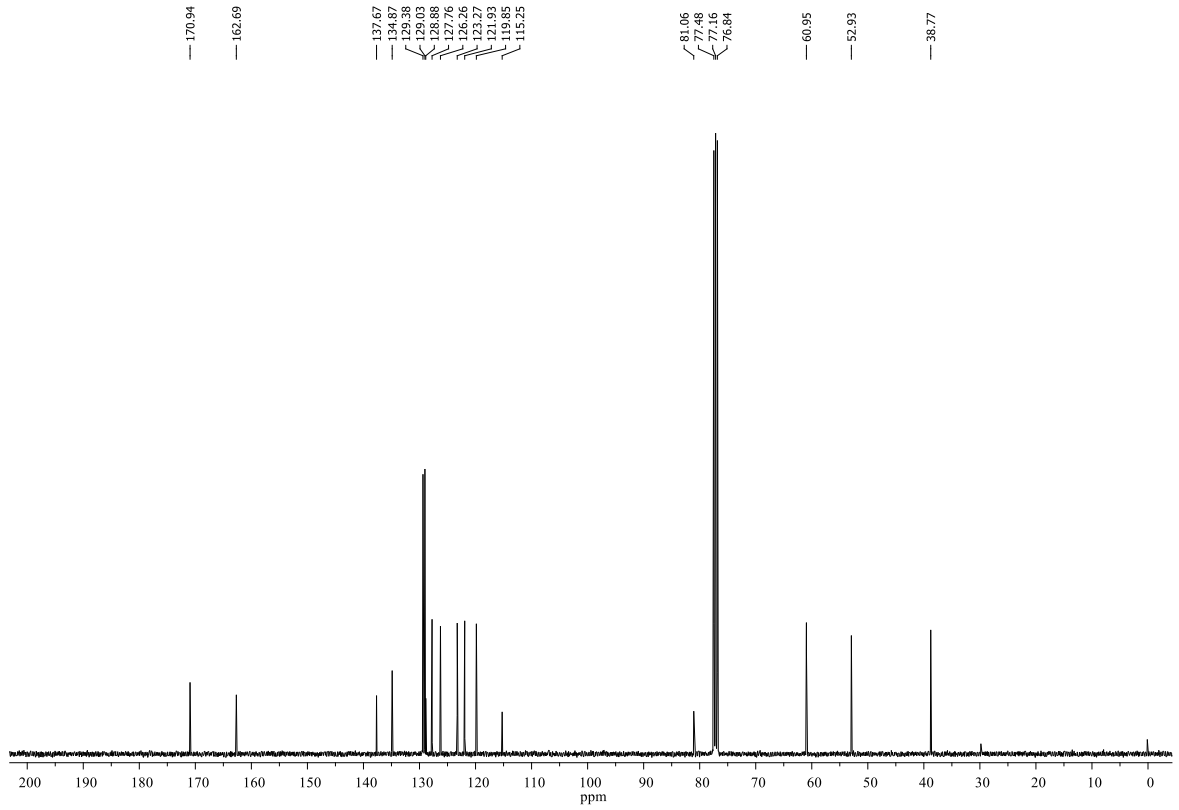
^{1}H NMR Spectrum of **4n**



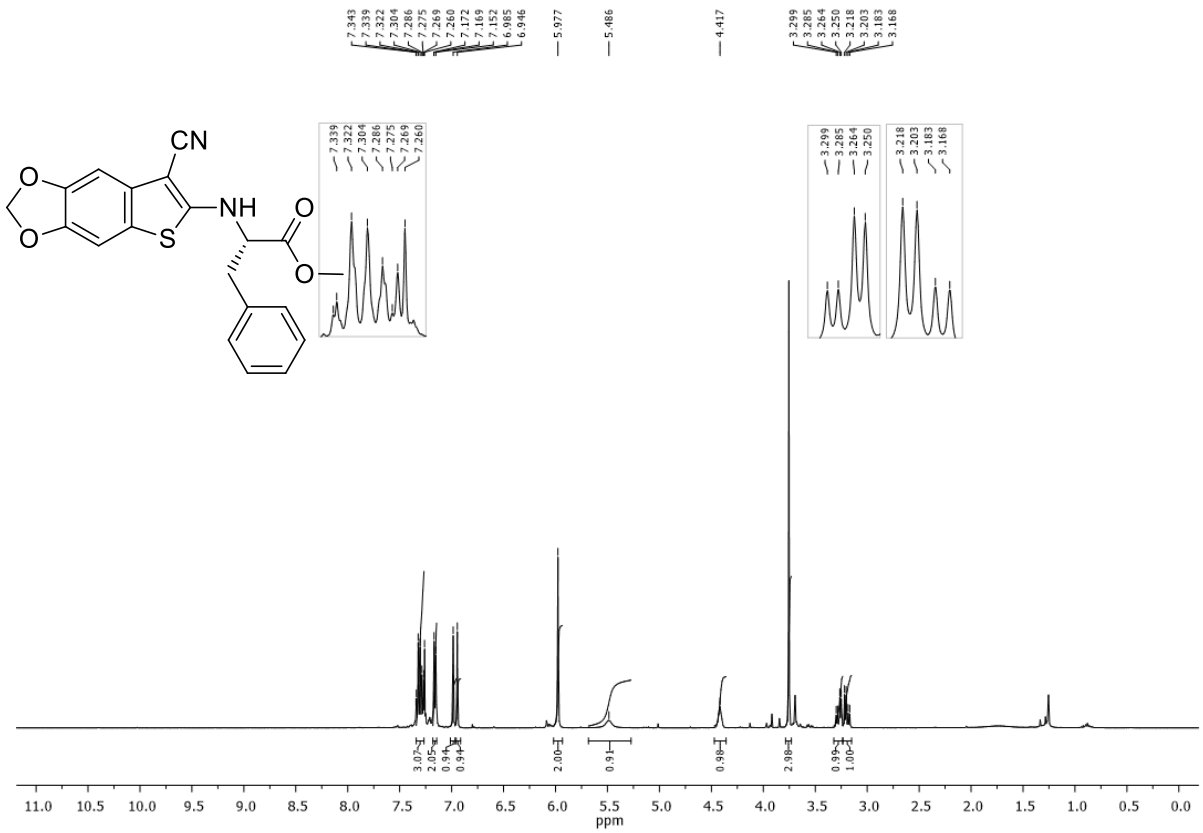
^{13}C NMR Spectrum of **4n**



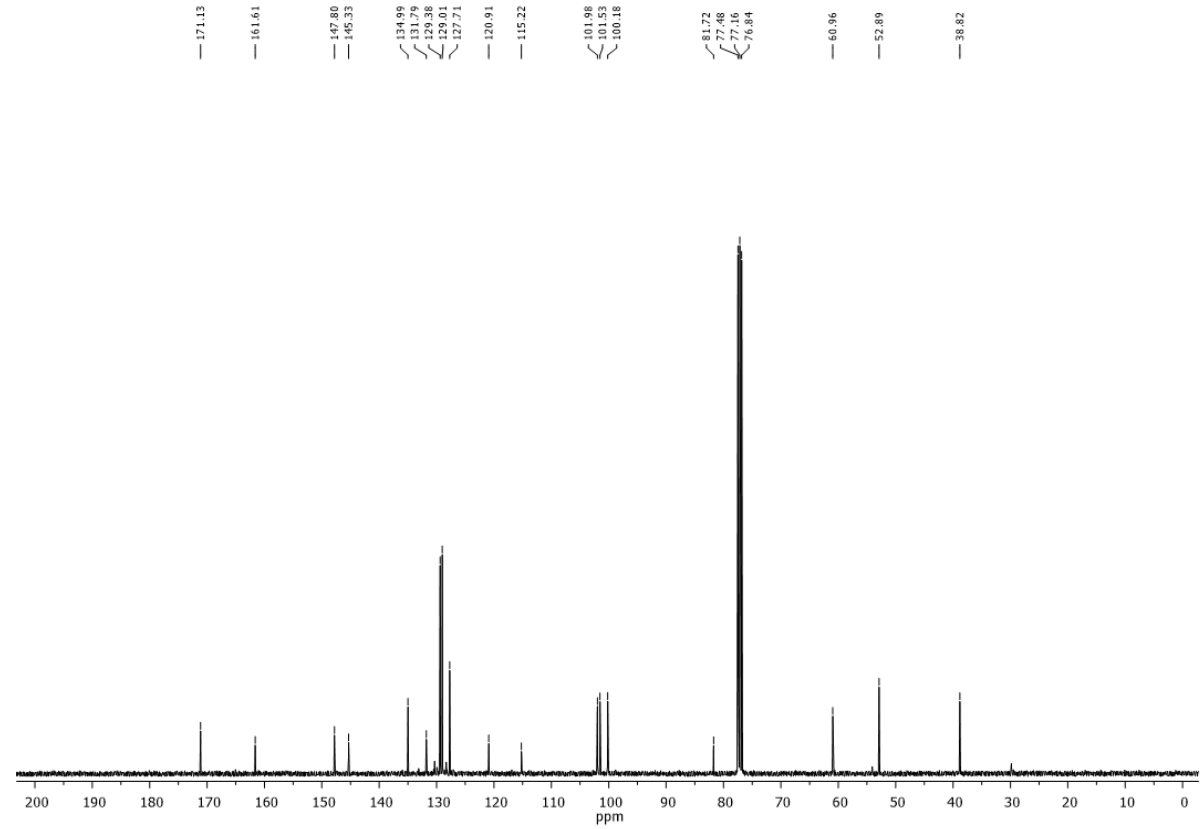
^{1}H NMR Spectrum of **4o**



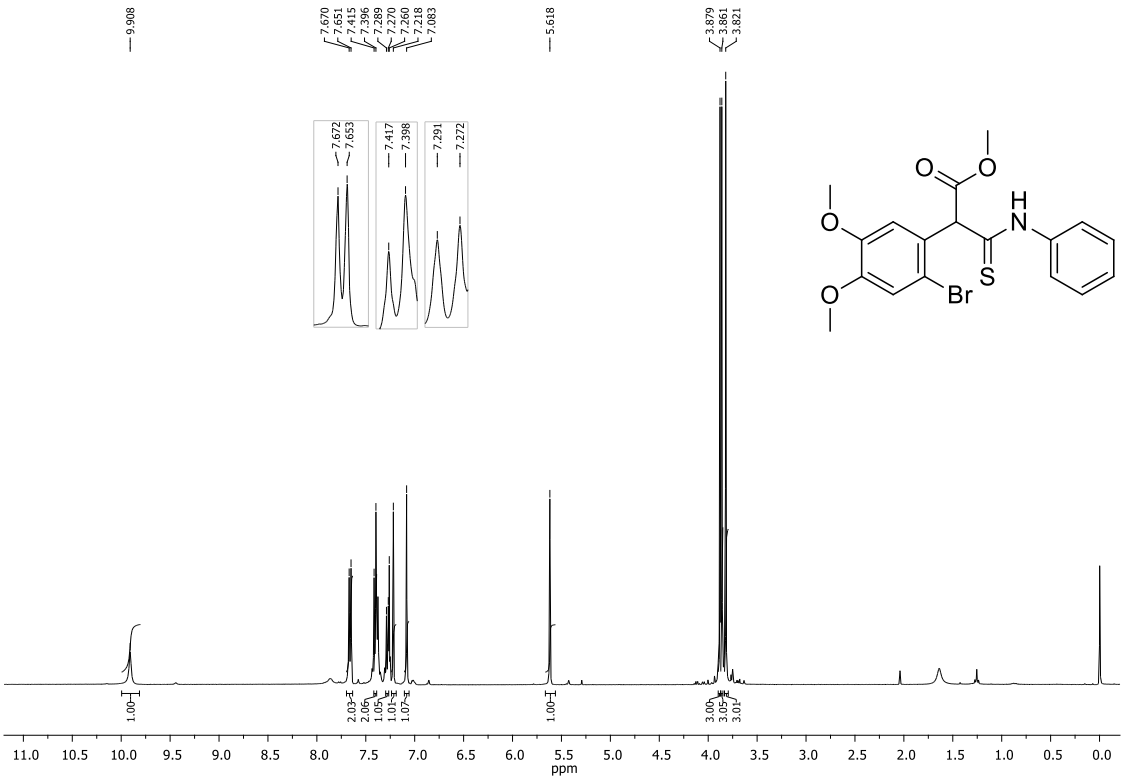
^{13}C NMR Spectrum of **4o**



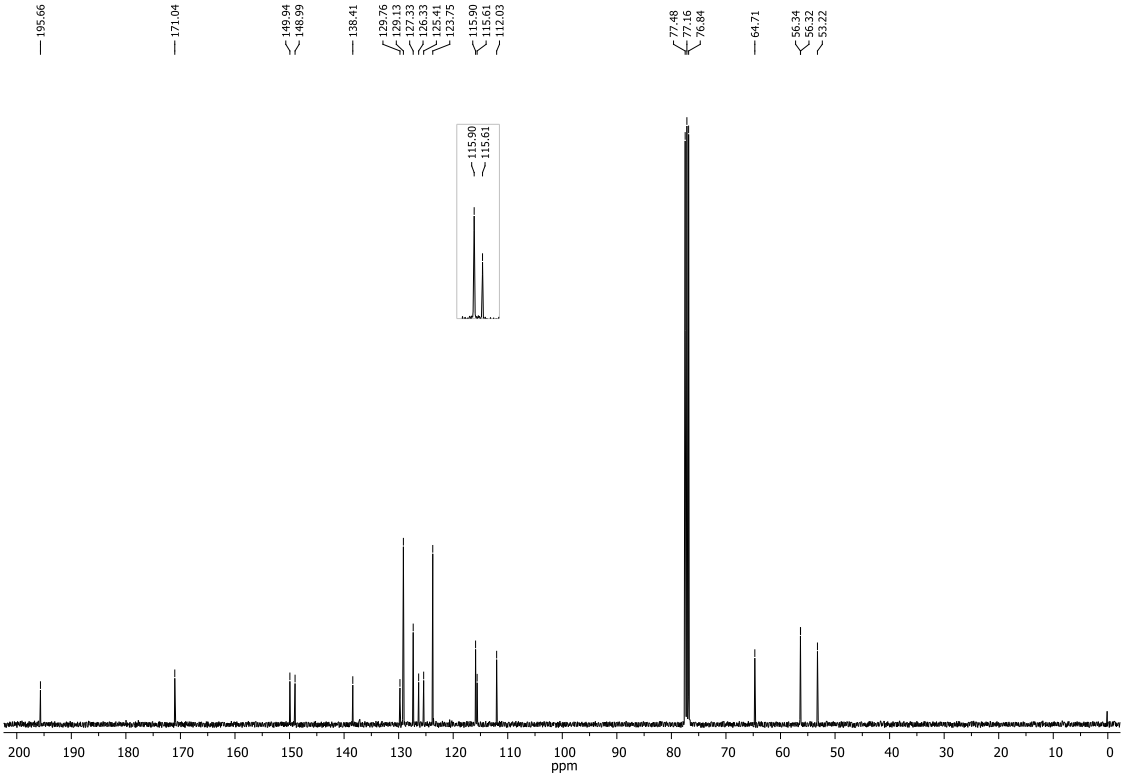
^{1}H NMR Spectrum of **4p**



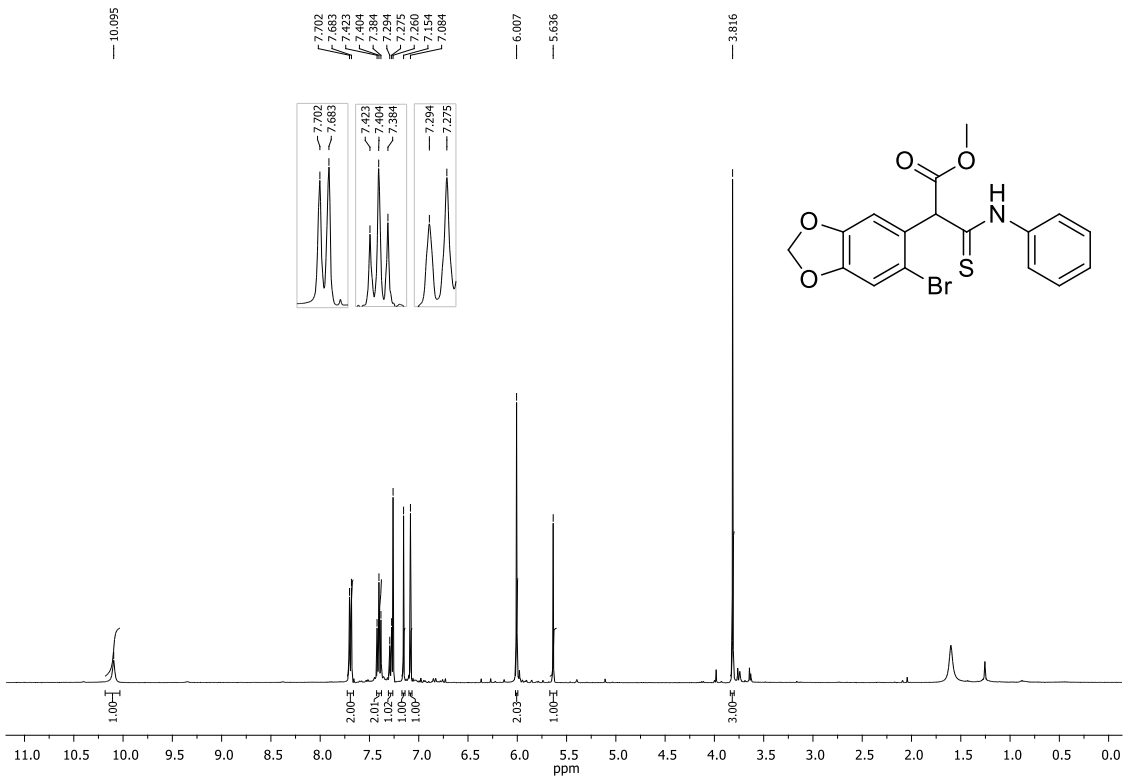
^{13}C NMR Spectrum of **4p**



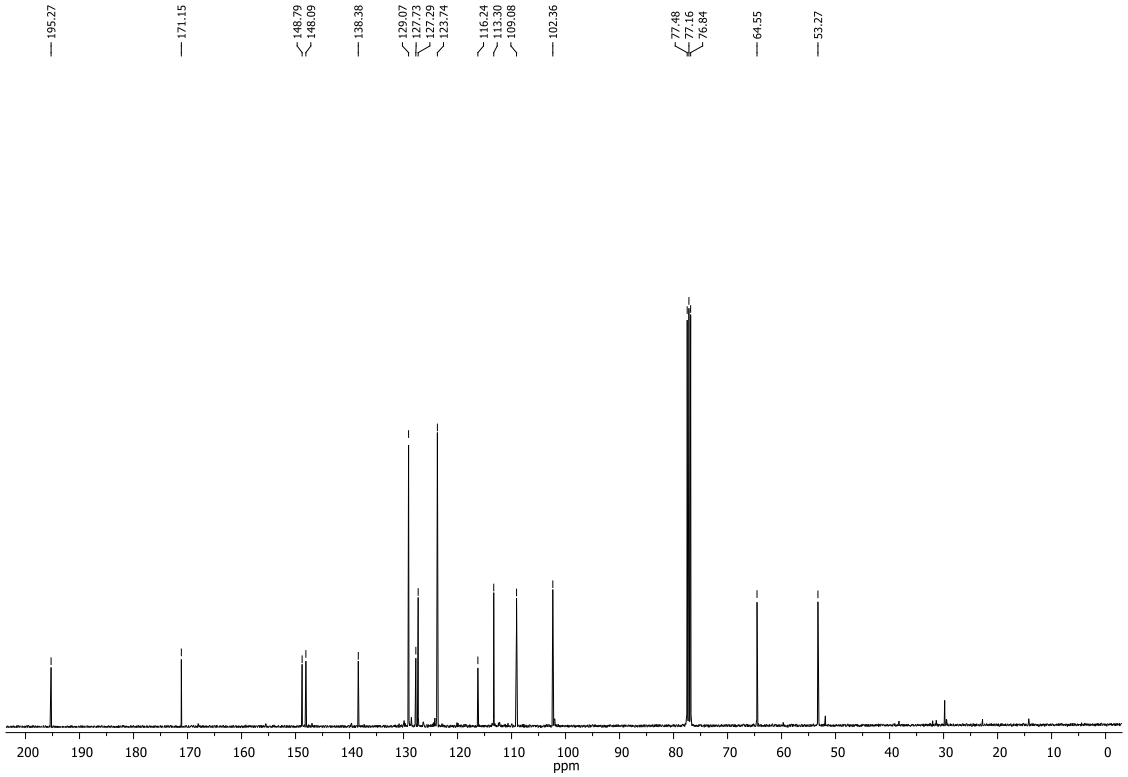
^{1}H NMR Spectrum of **6a**



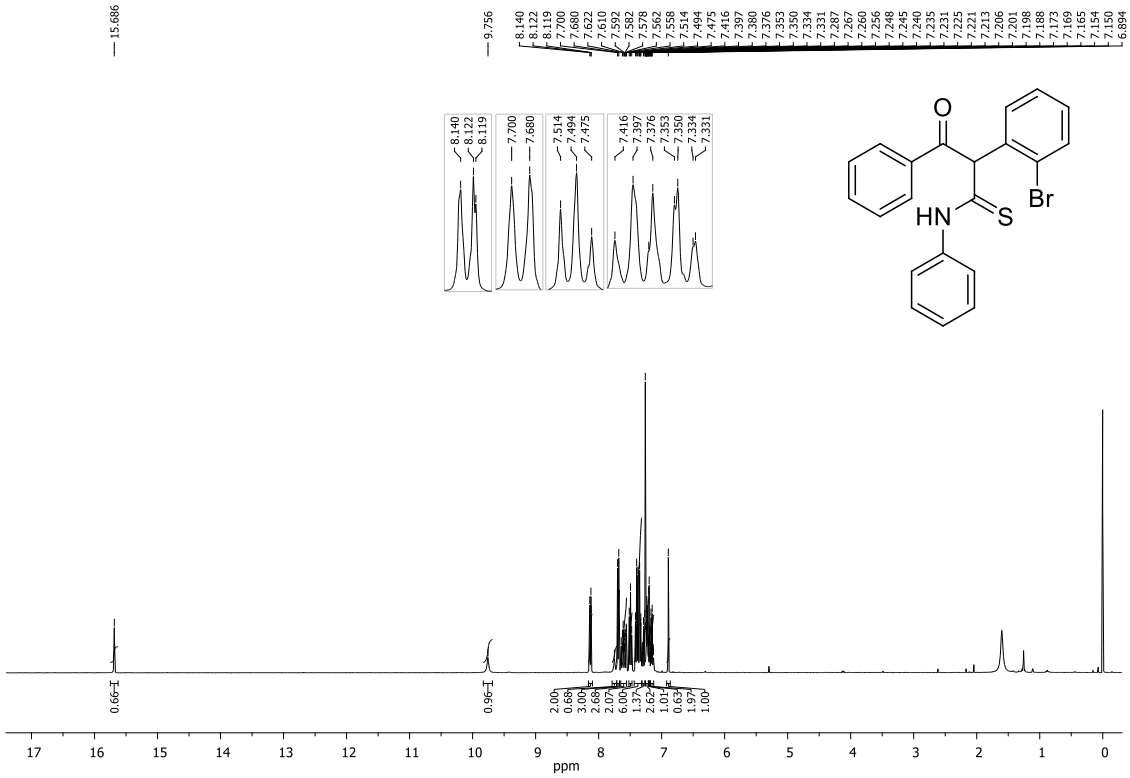
^{13}C NMR Spectrum of **6a**



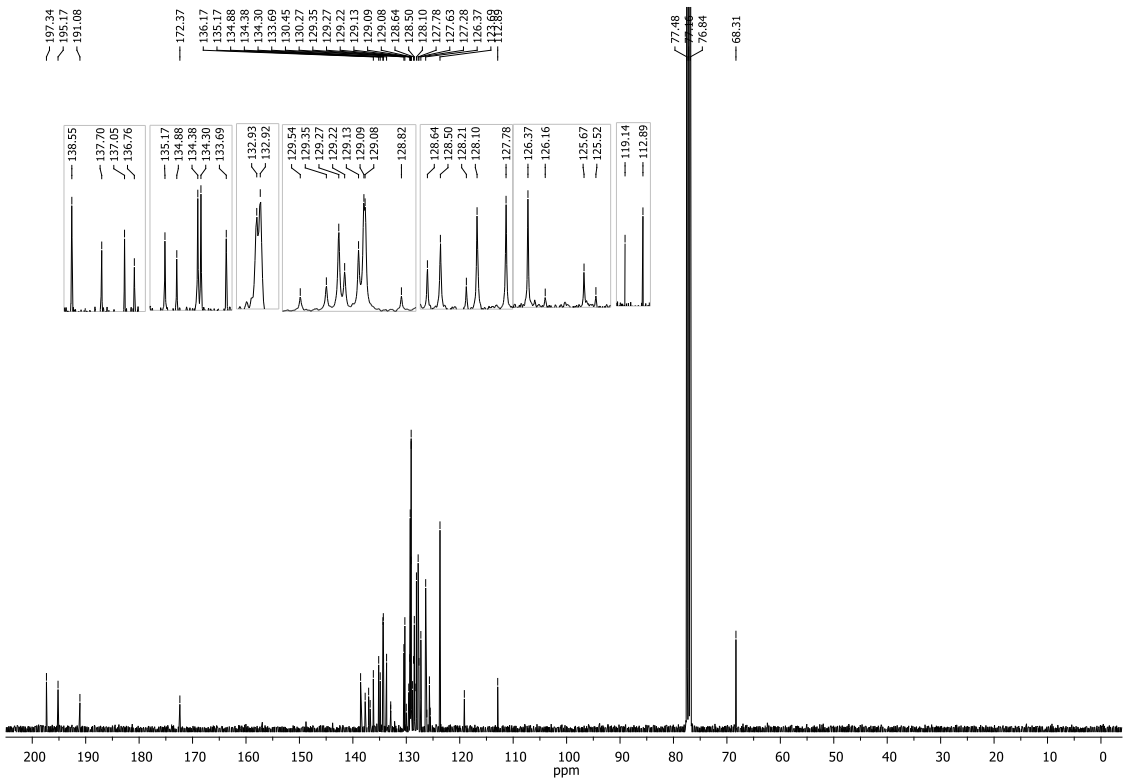
^{1}H NMR Spectrum of **6b**



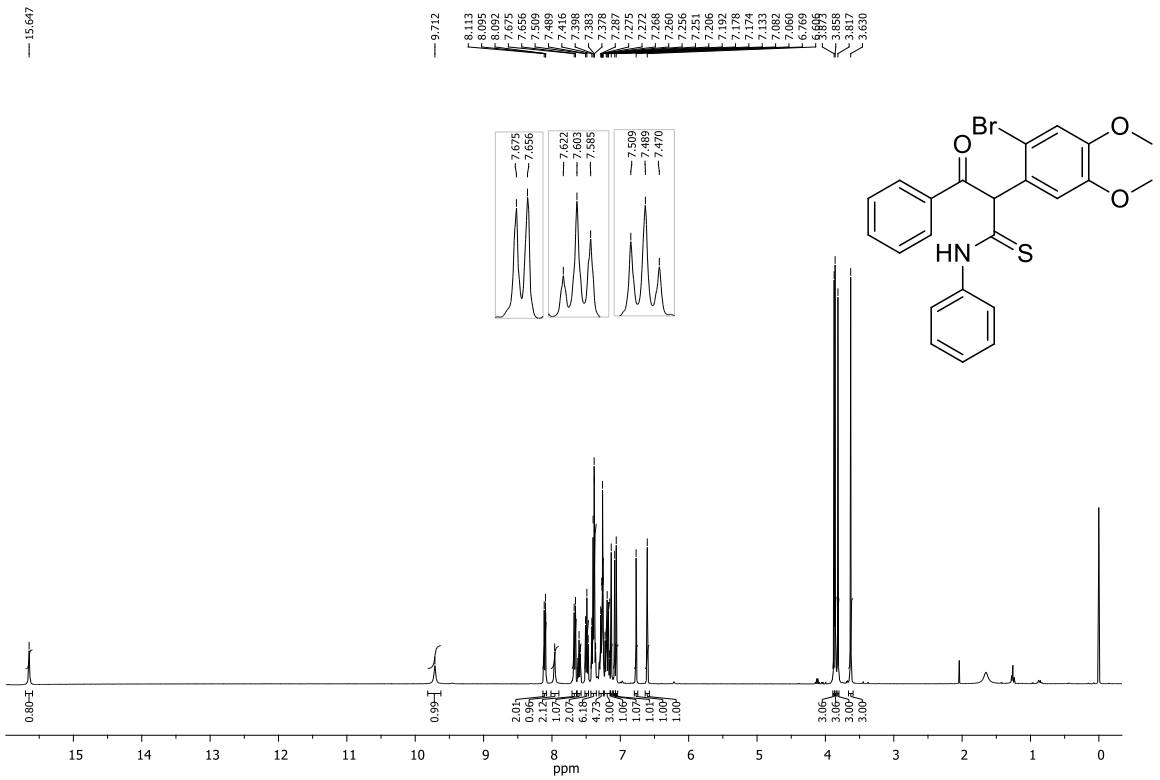
^{13}C NMR Spectrum of **6b**



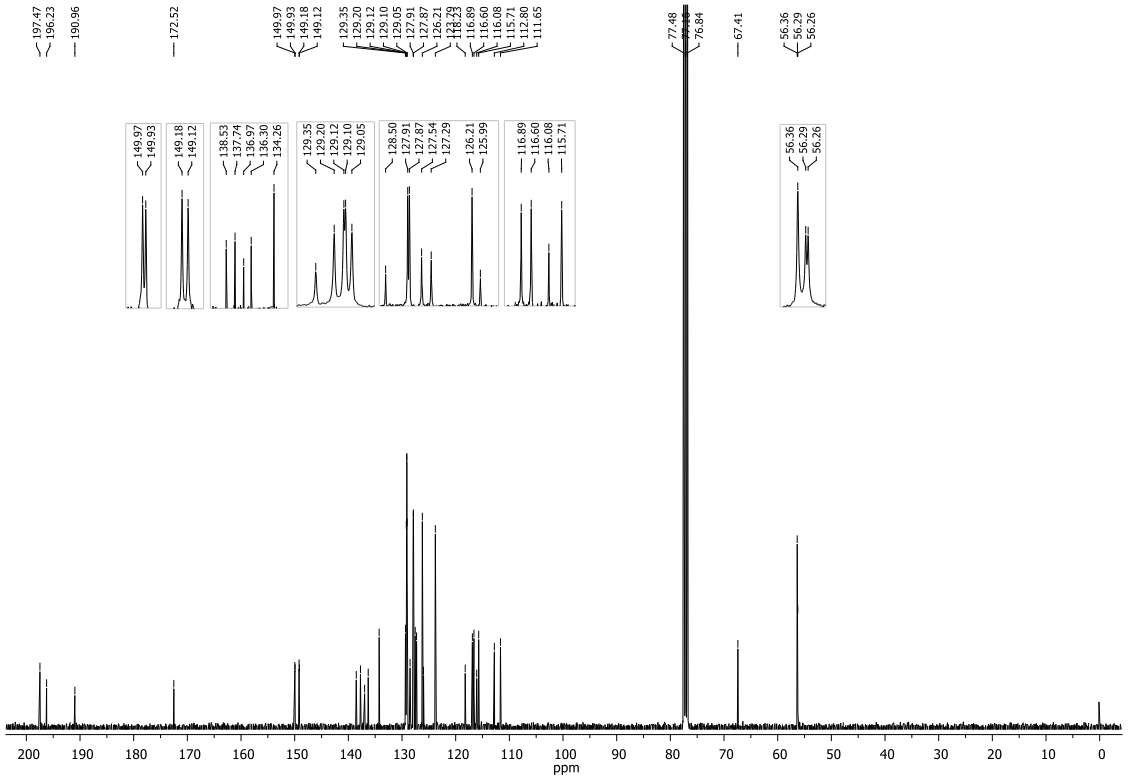
^{1}H NMR Spectrum of **6c**



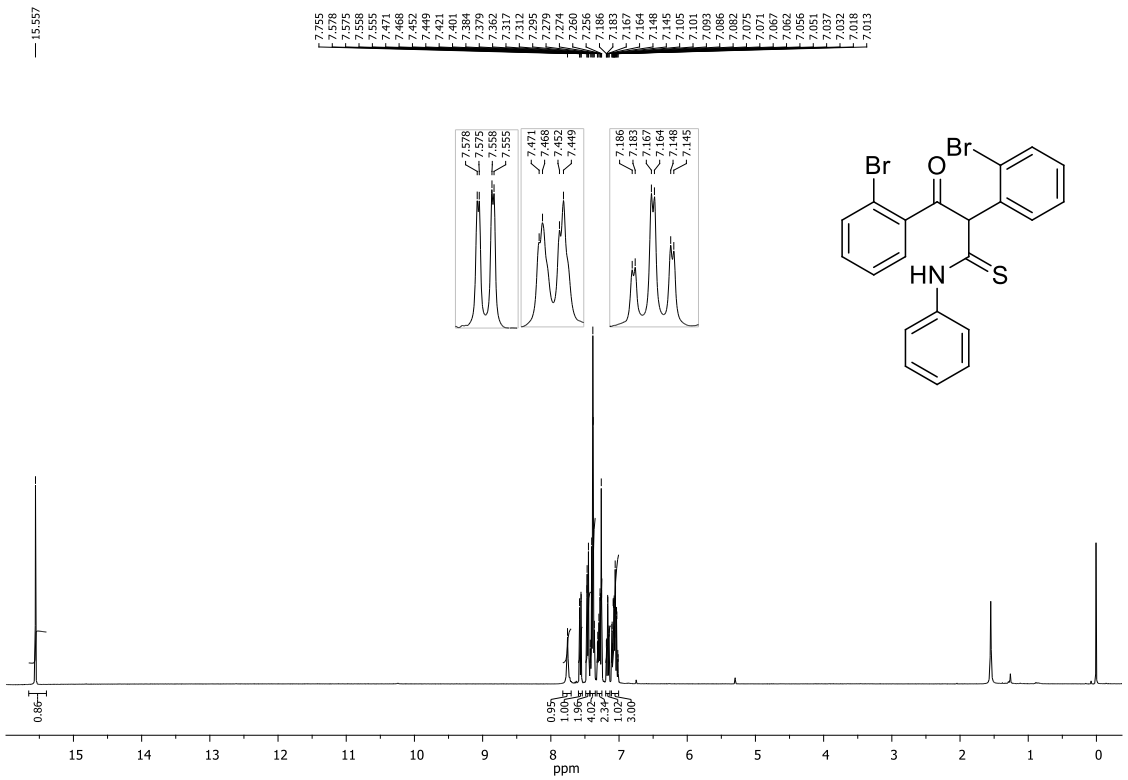
^{13}C NMR Spectrum of **6c**



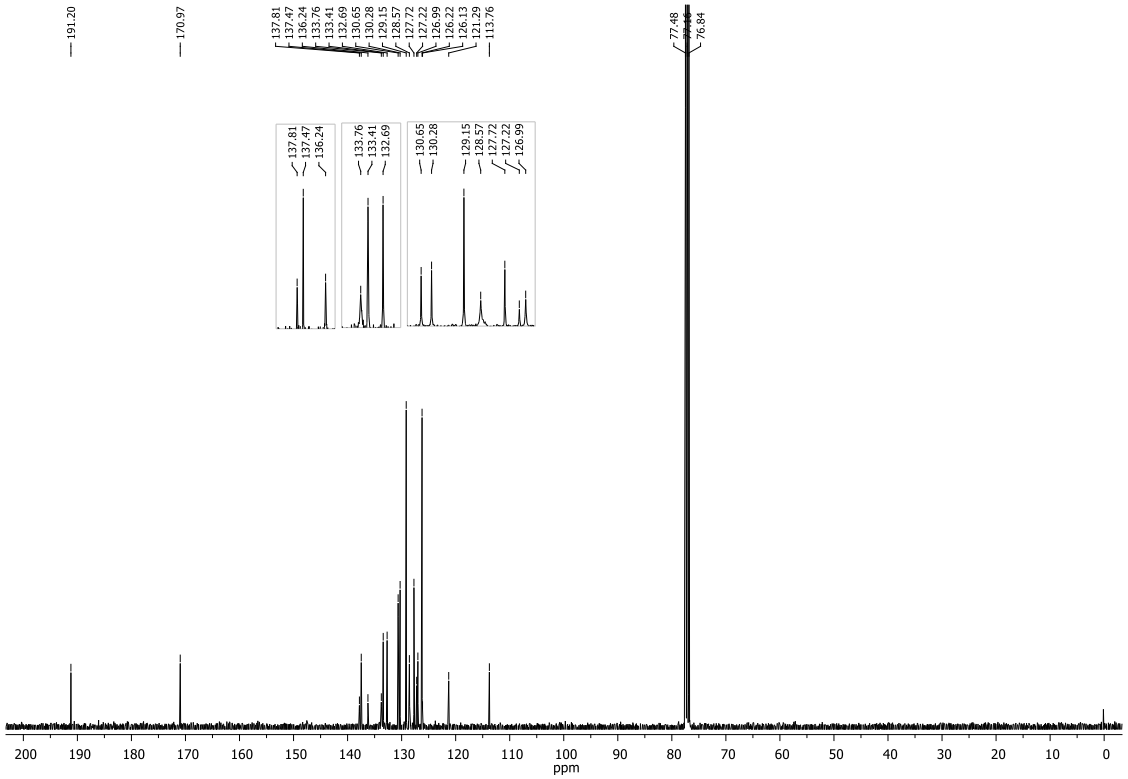
^{1}H NMR Spectrum of **6d**



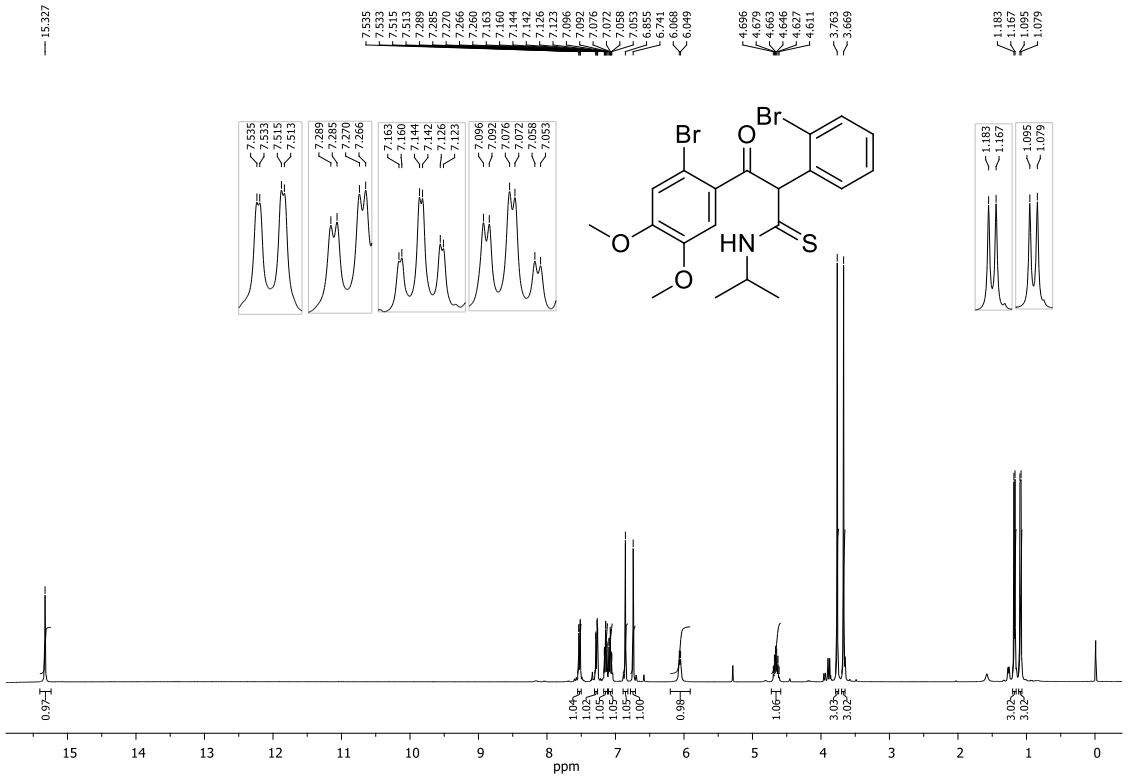
^{13}C NMR Spectrum of **6d**



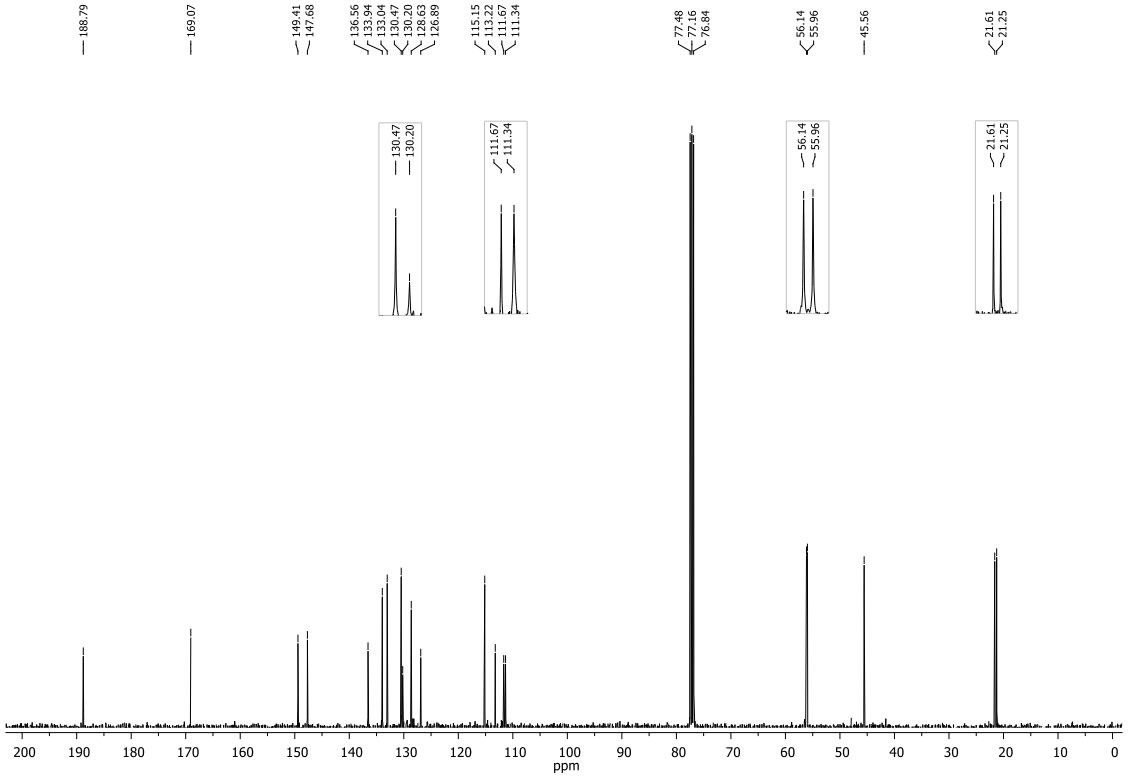
^{1}H NMR Spectrum of **6e**



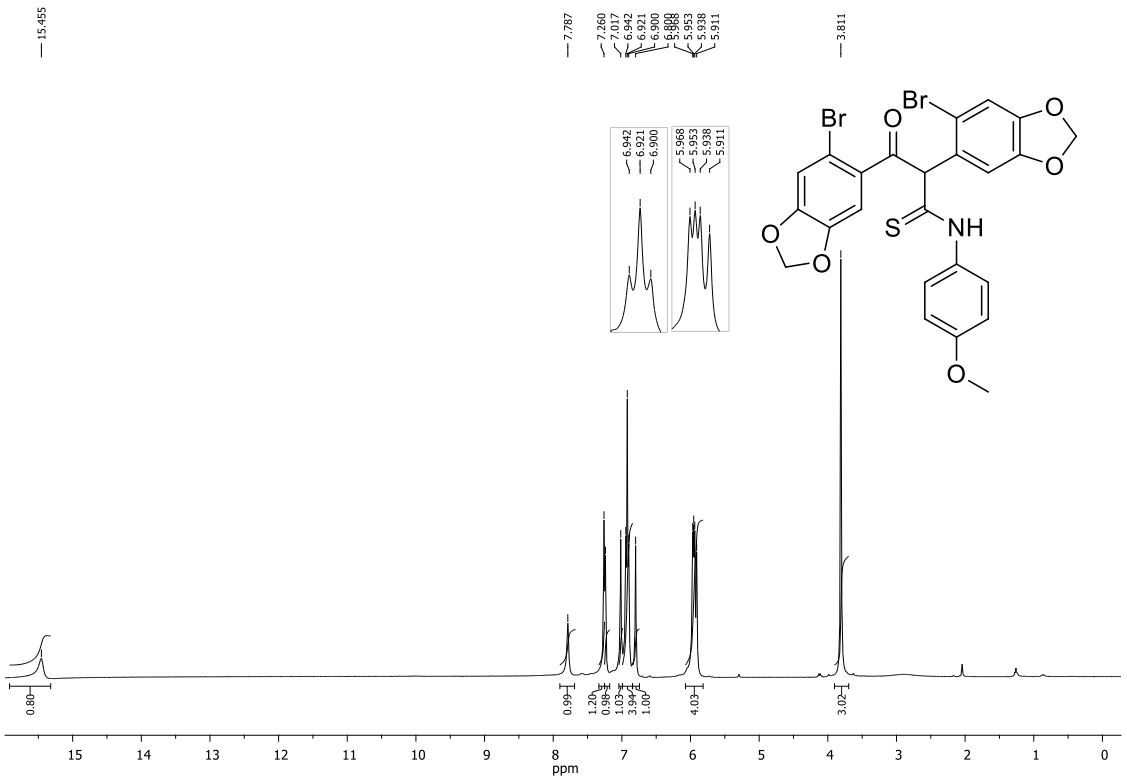
^{13}C NMR Spectrum of **6e**



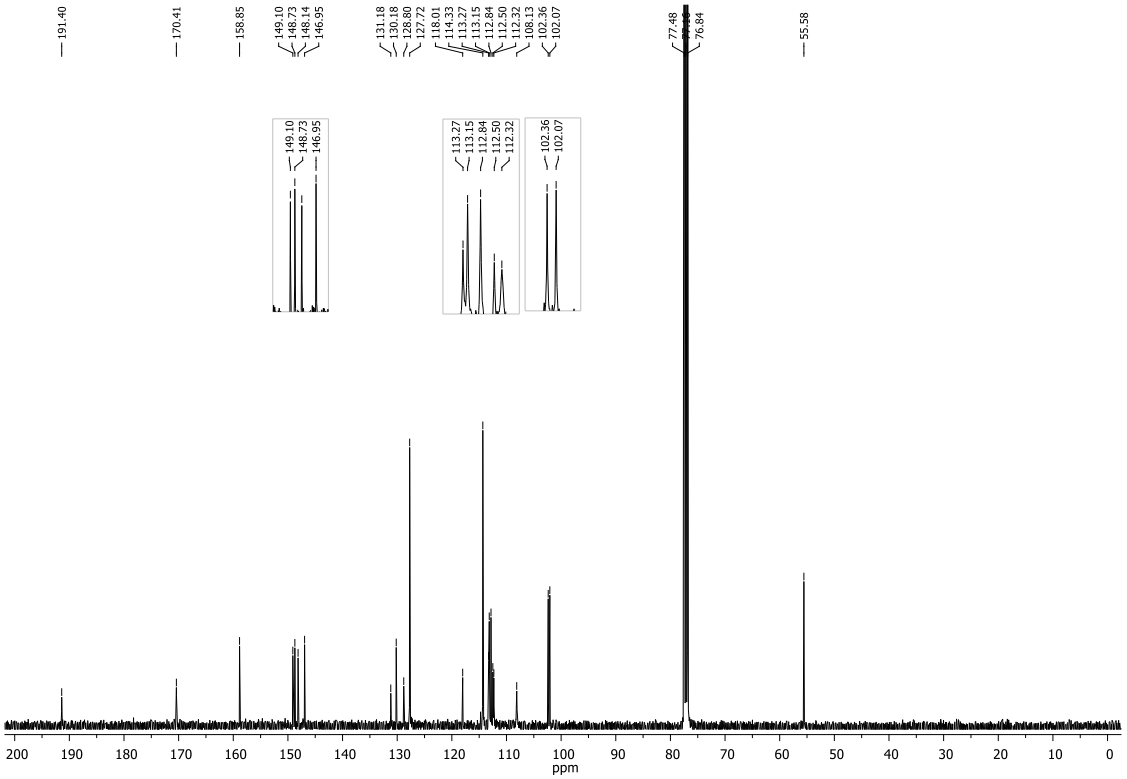
^{1}H NMR Spectrum of **6f**



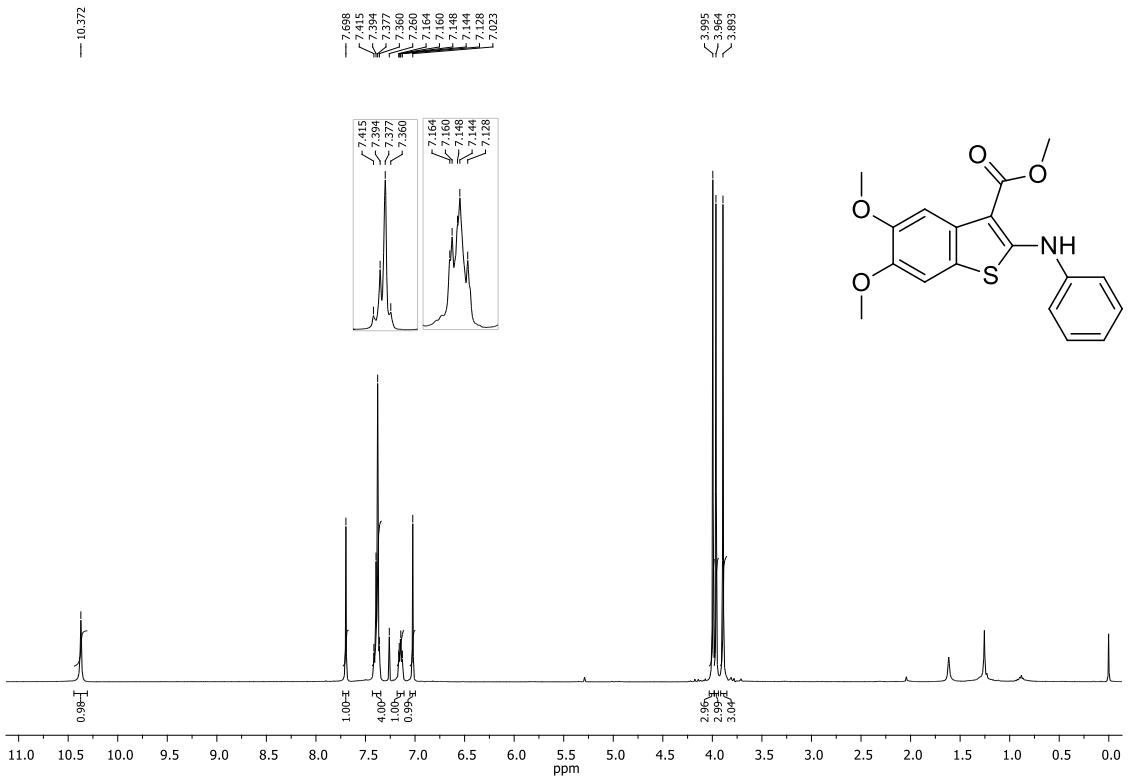
^{13}C NMR Spectrum of **6f**



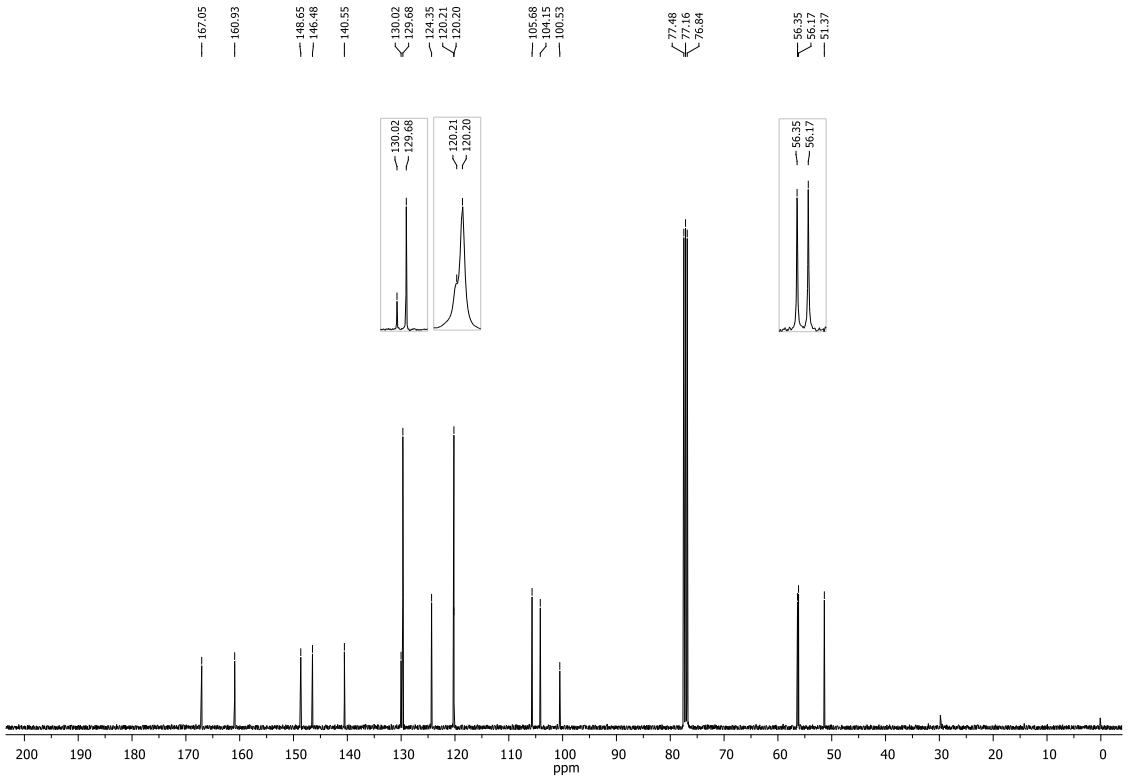
^{1}H NMR Spectrum of **6g**



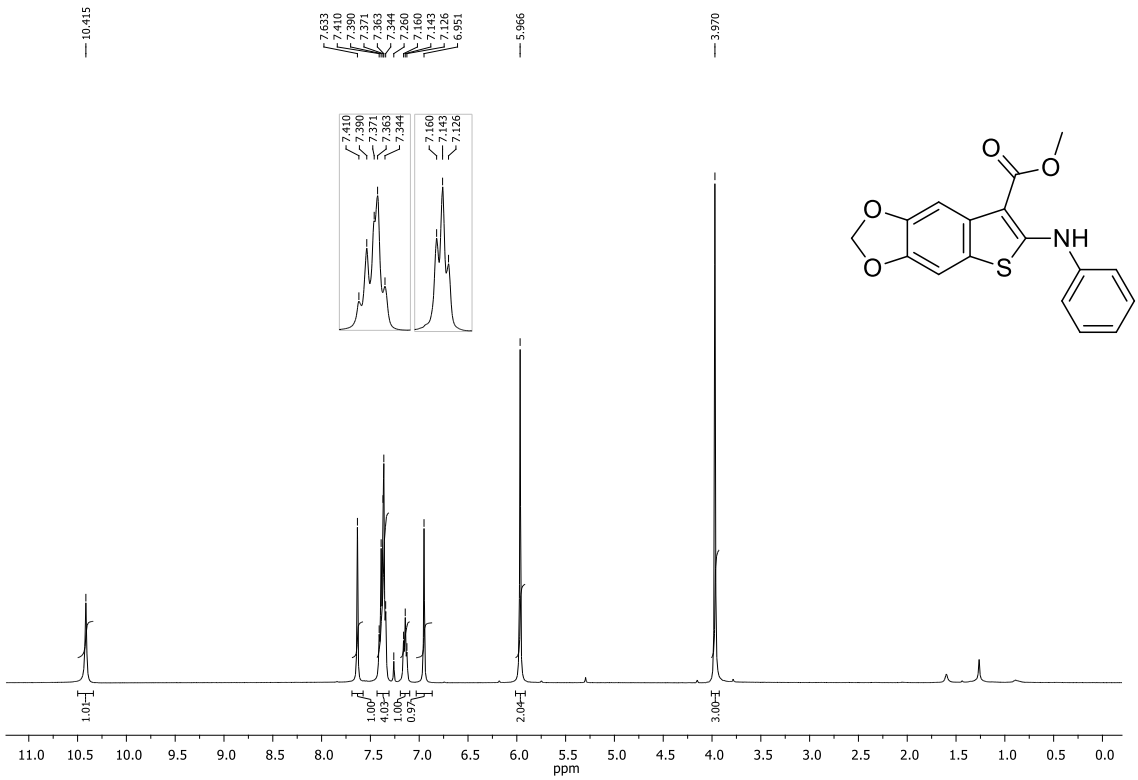
^{13}C NMR Spectrum of **6g**



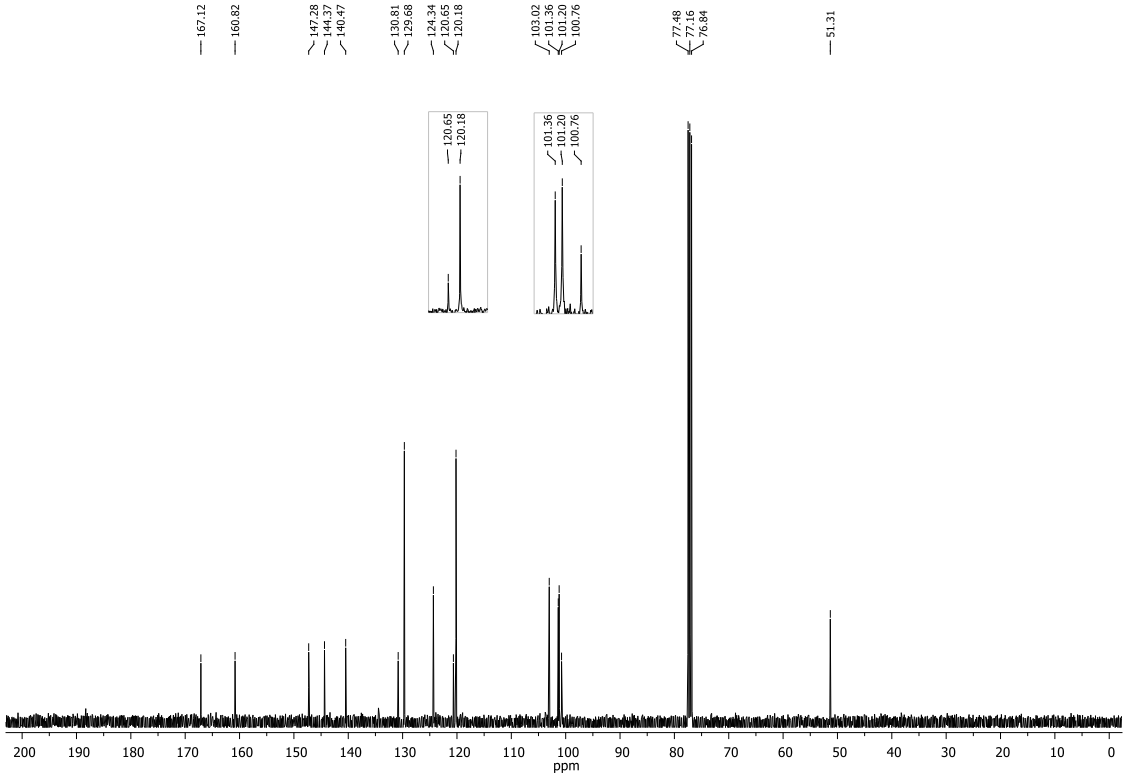
^{1}H NMR Spectrum of **7a**



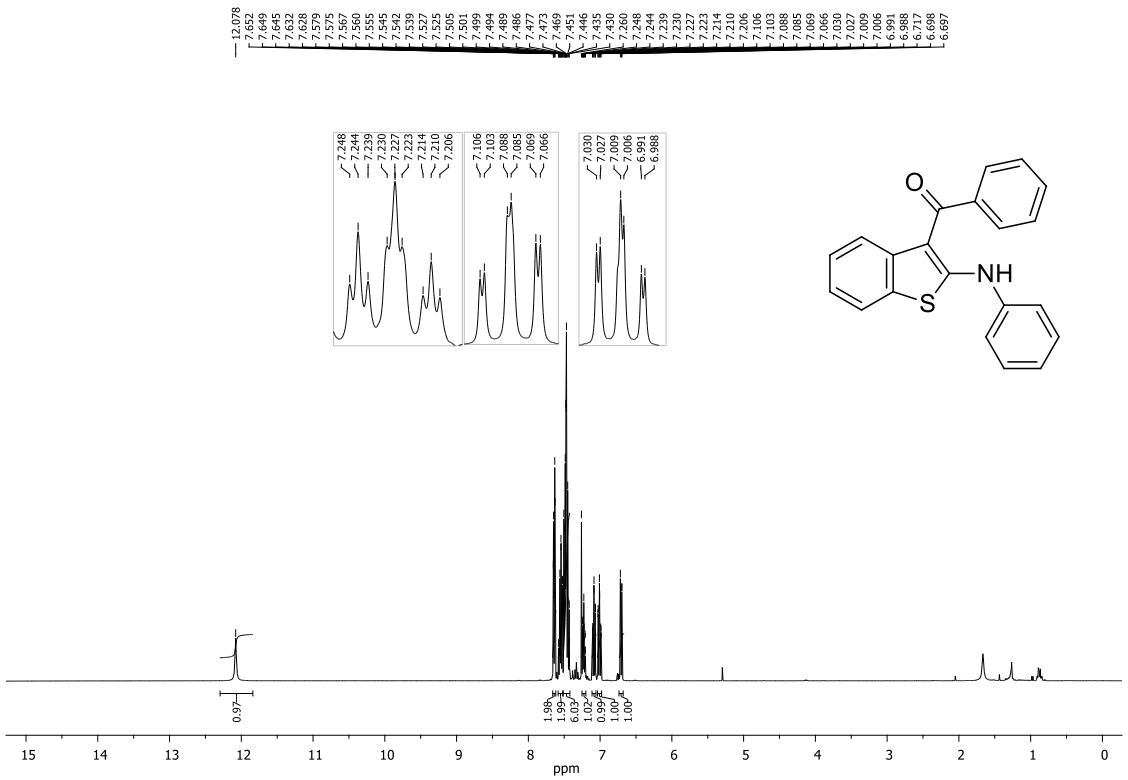
^{13}C NMR Spectrum of **7a**



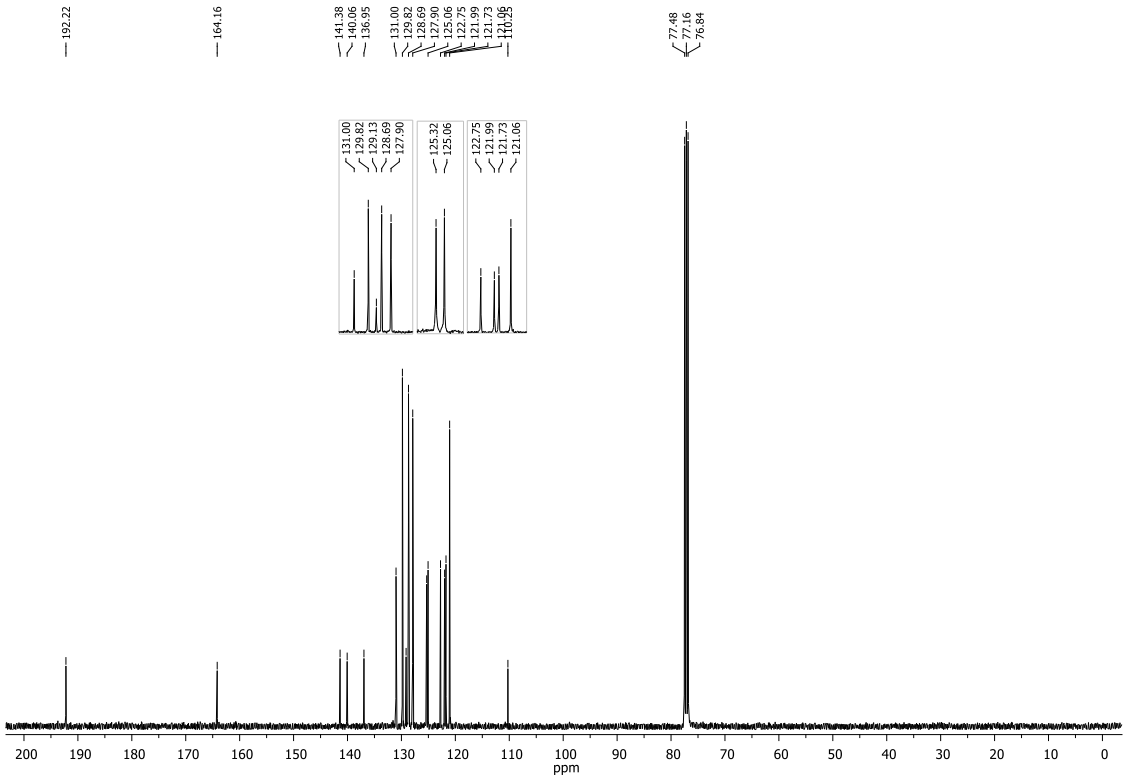
^{1}H NMR Spectrum of **7b**



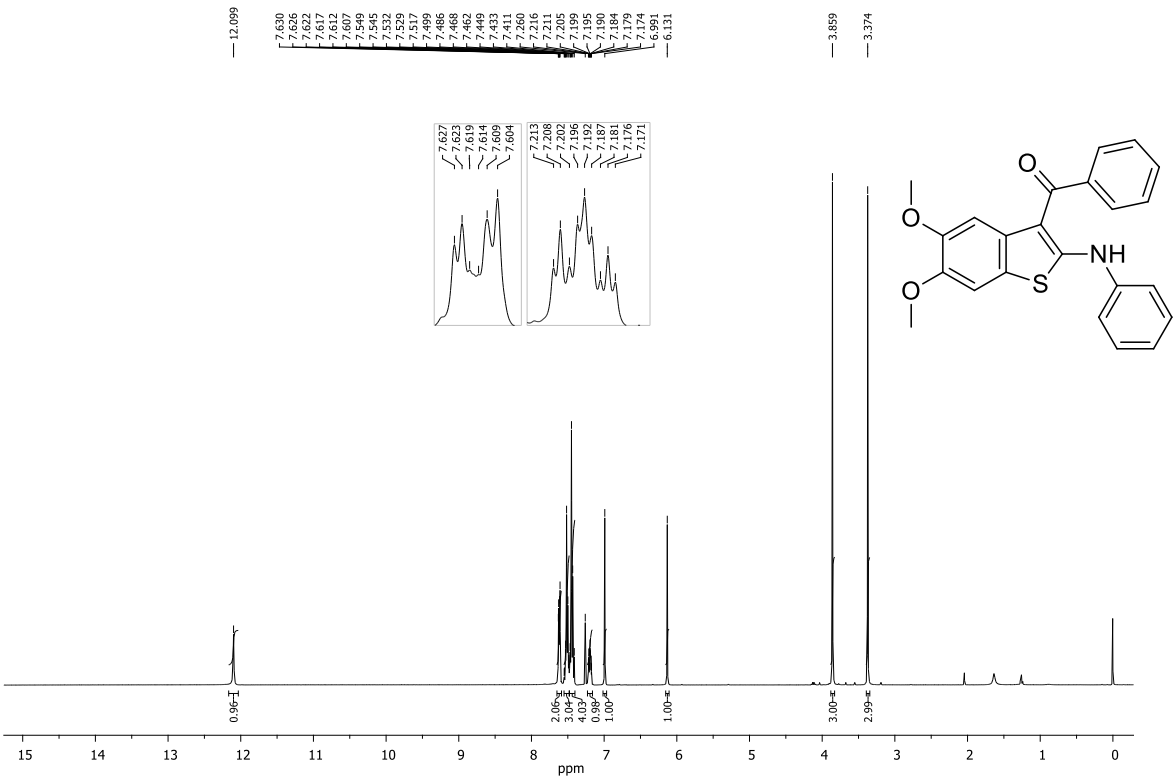
^{13}C NMR Spectrum of **7b**



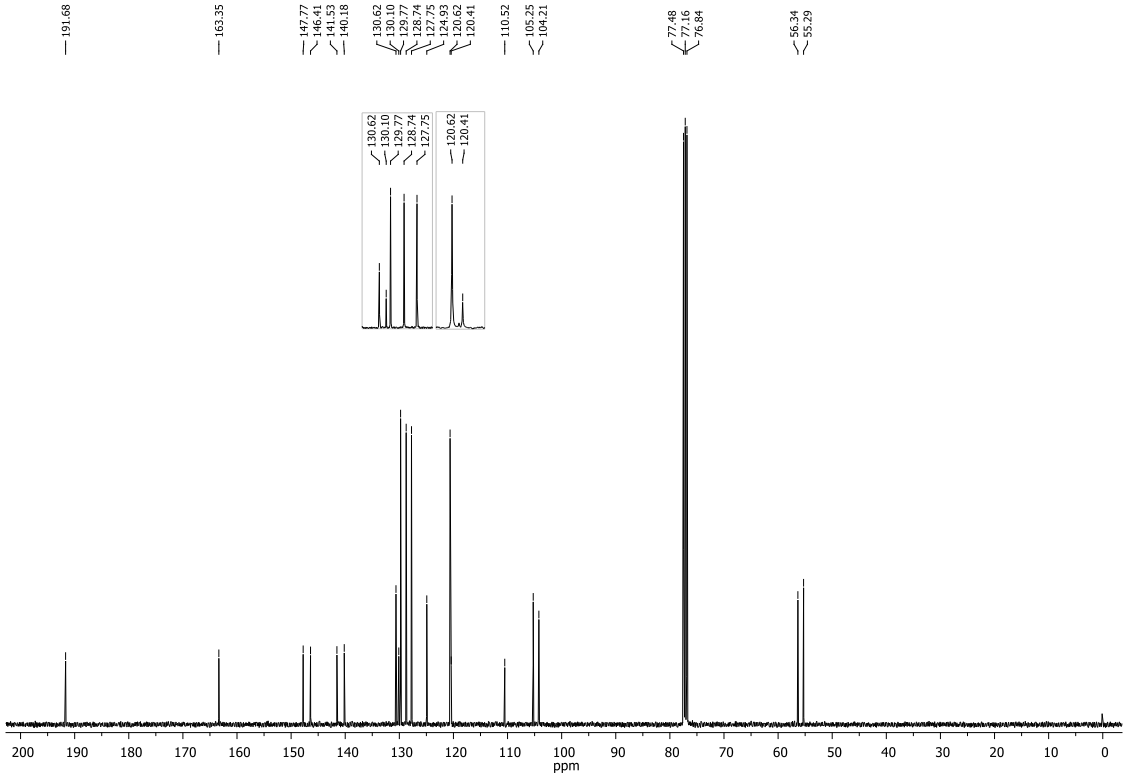
^{1}H NMR Spectrum of **7c**



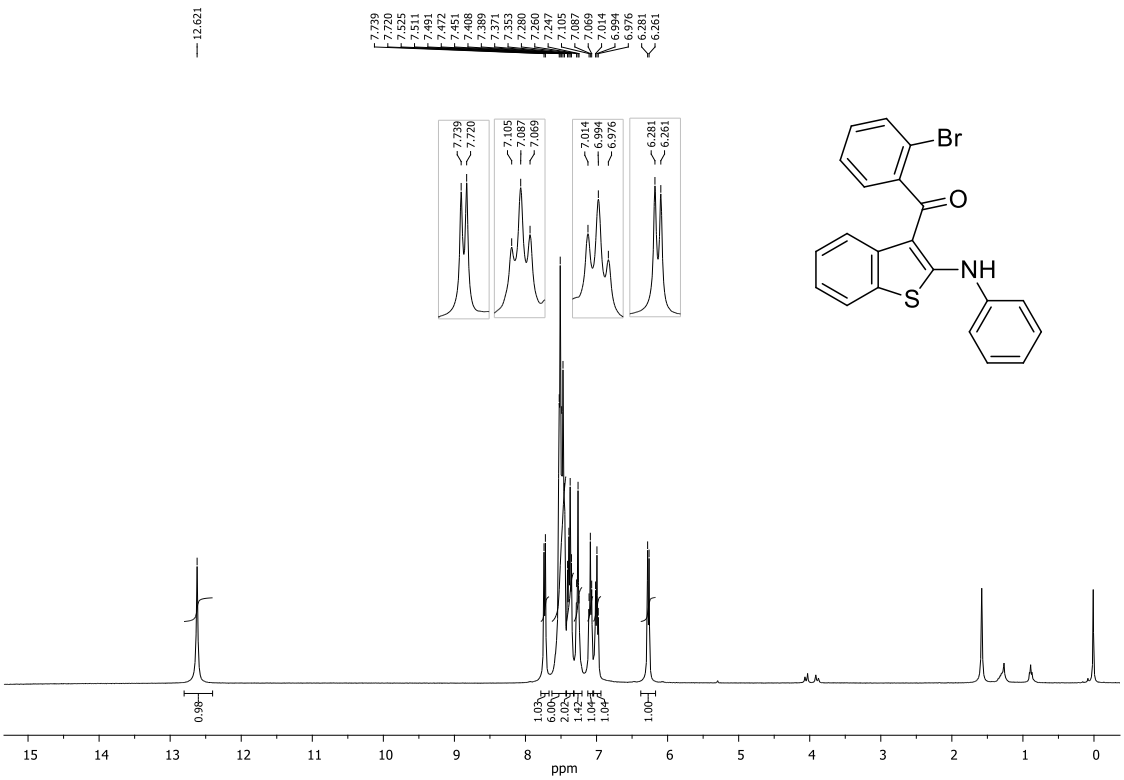
^{13}C NMR Spectrum of **7c**



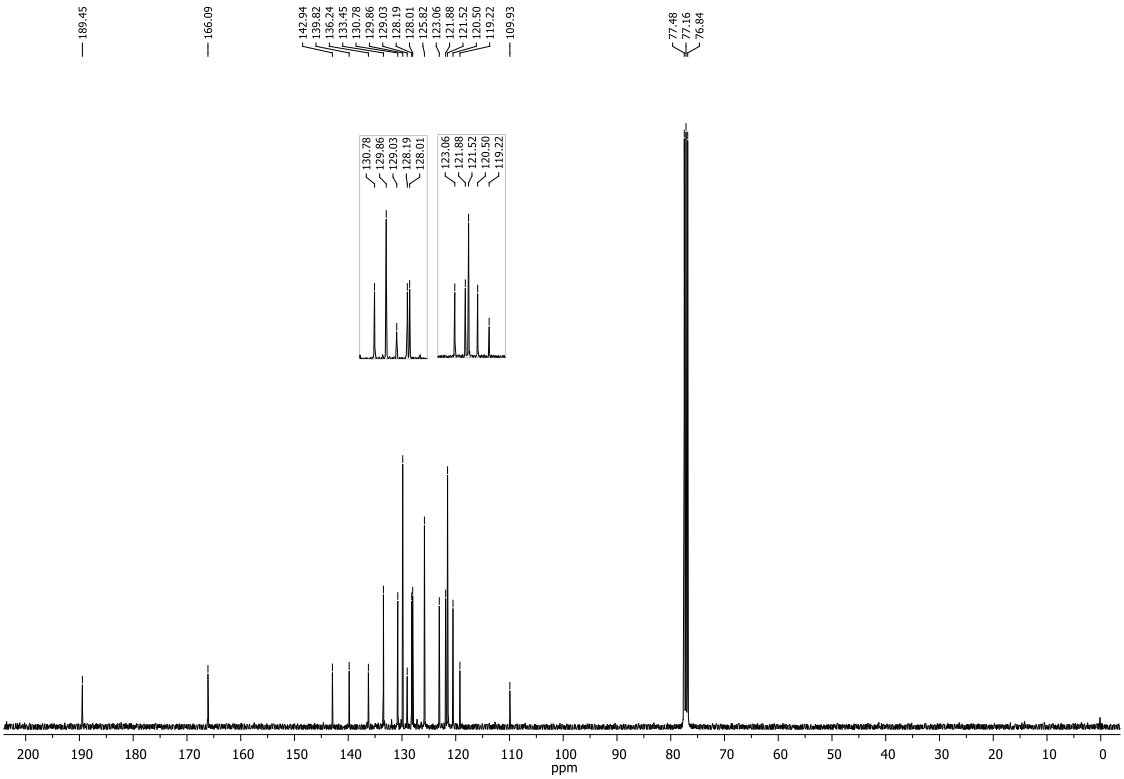
^{1}H NMR Spectrum of **7d**



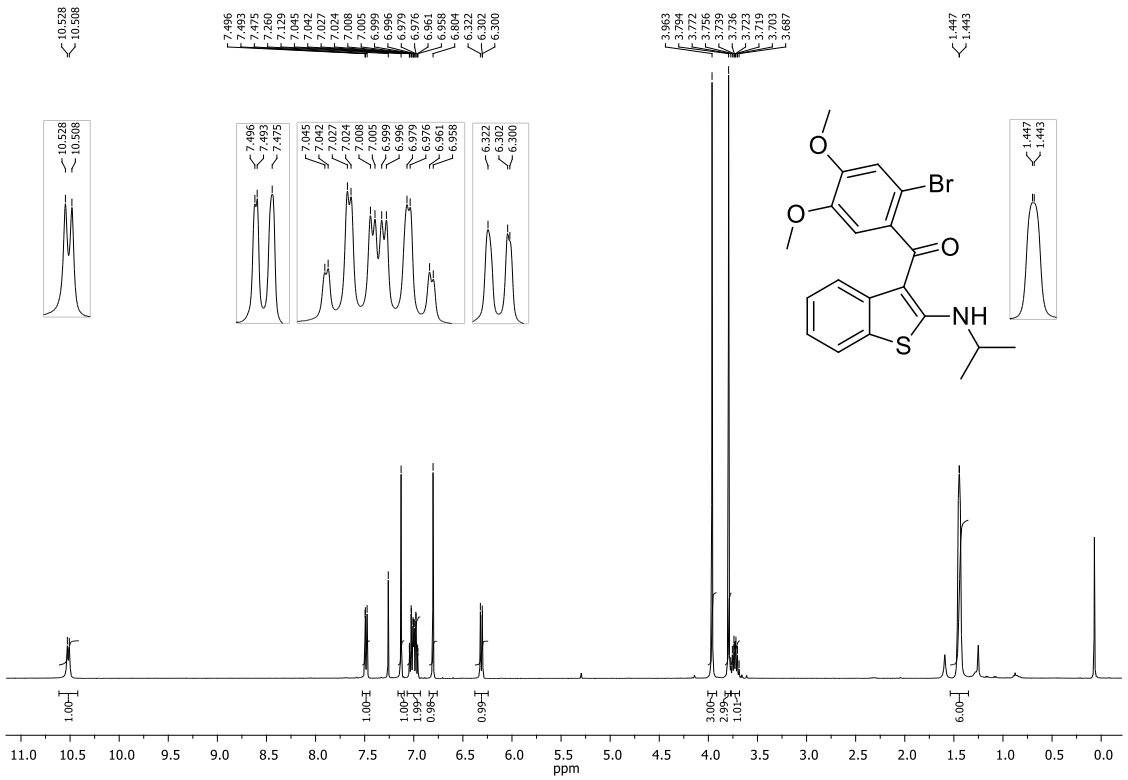
^{13}C NMR Spectrum of **7d**



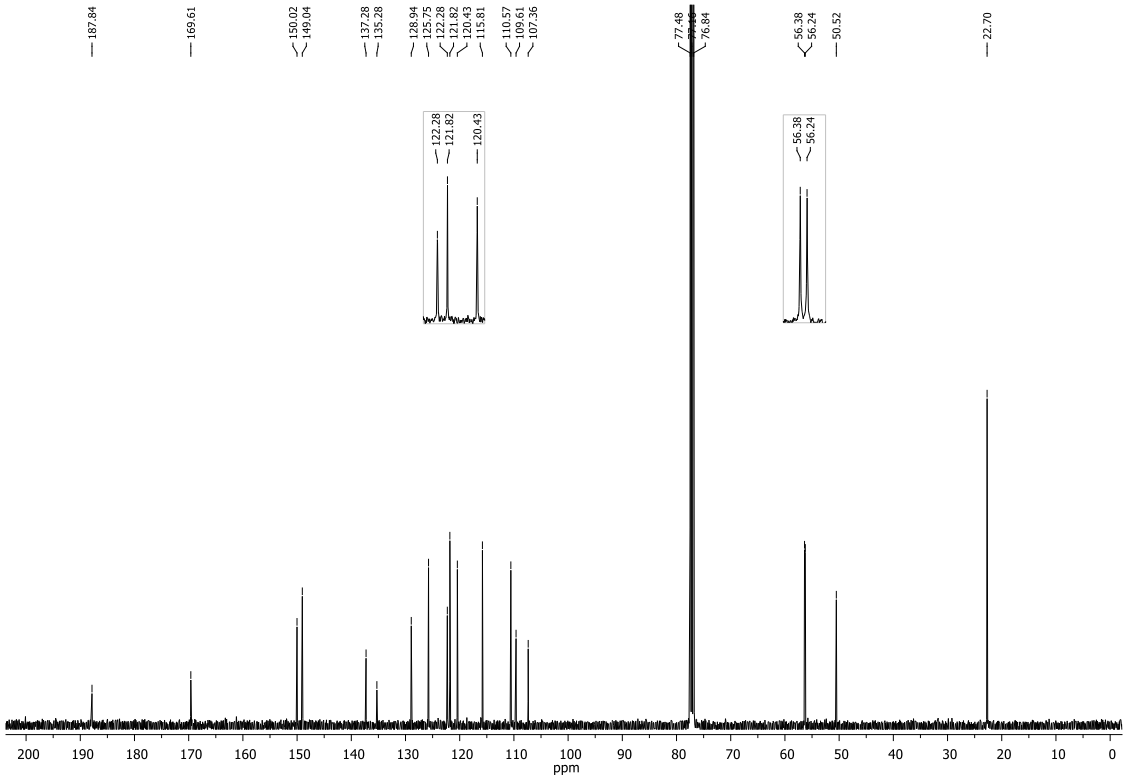
^{1}H NMR Spectrum of **7e**



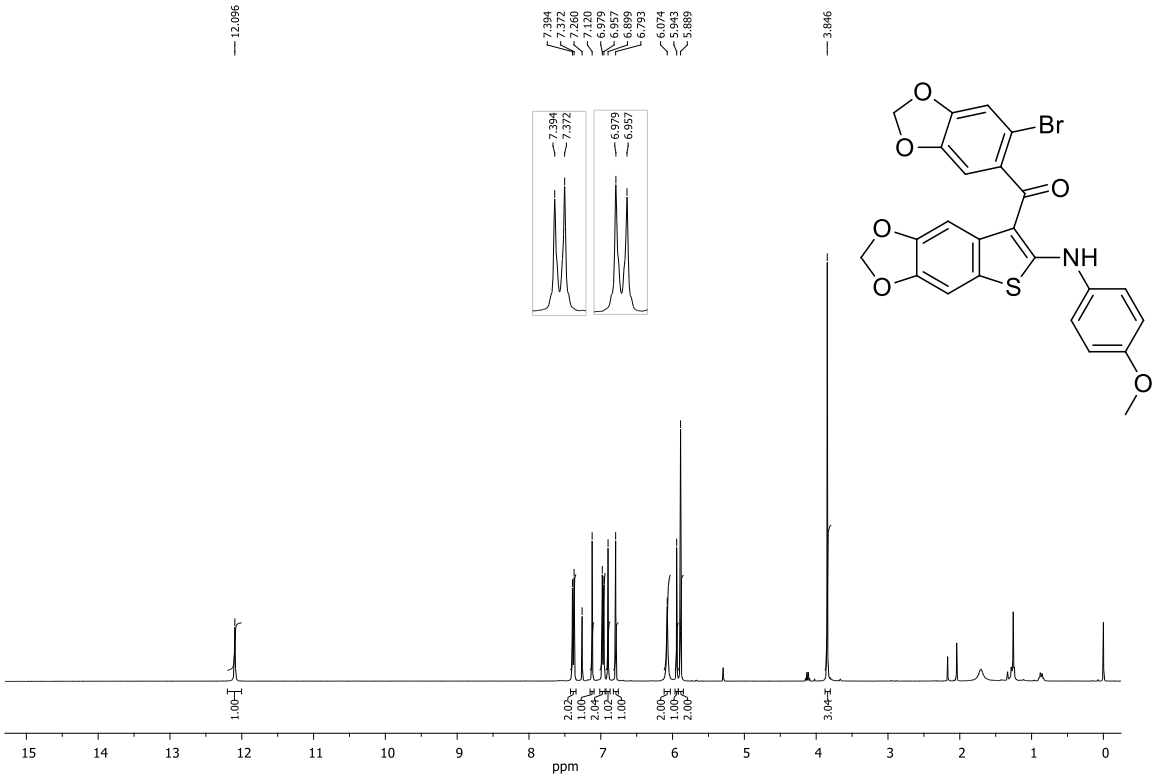
^{13}C NMR Spectrum of **7e**



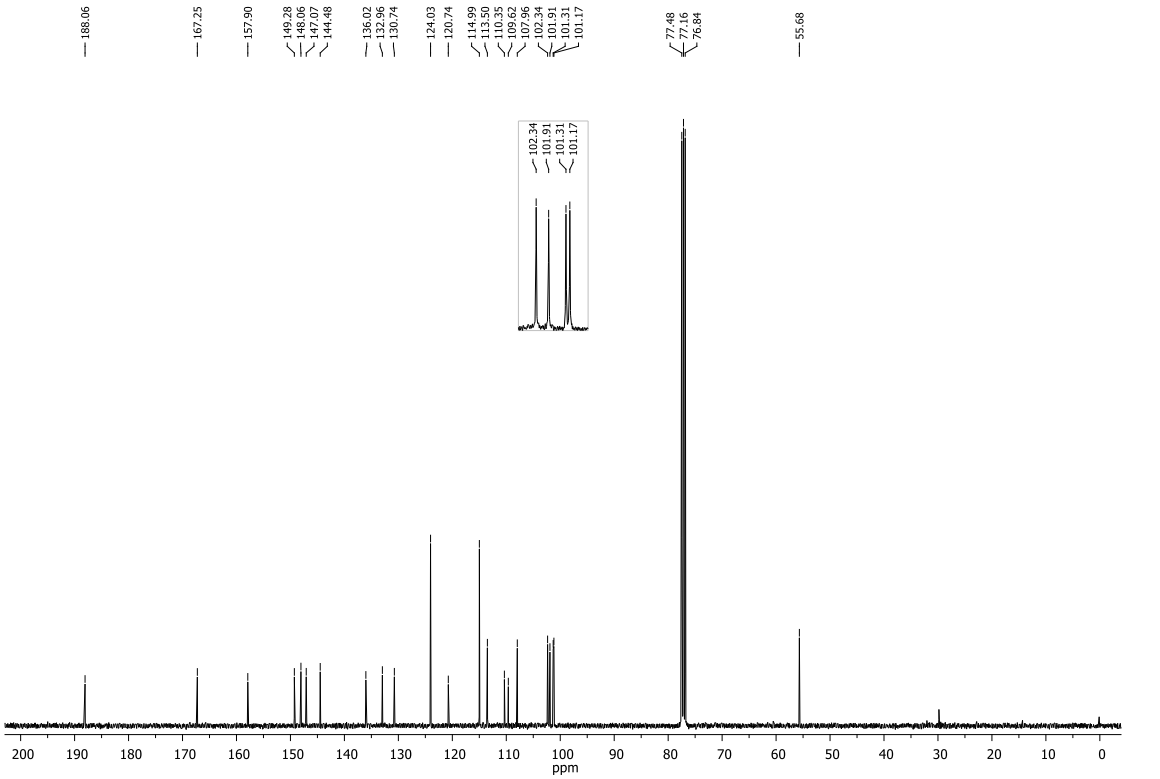
^{1}H NMR Spectrum of **7f**



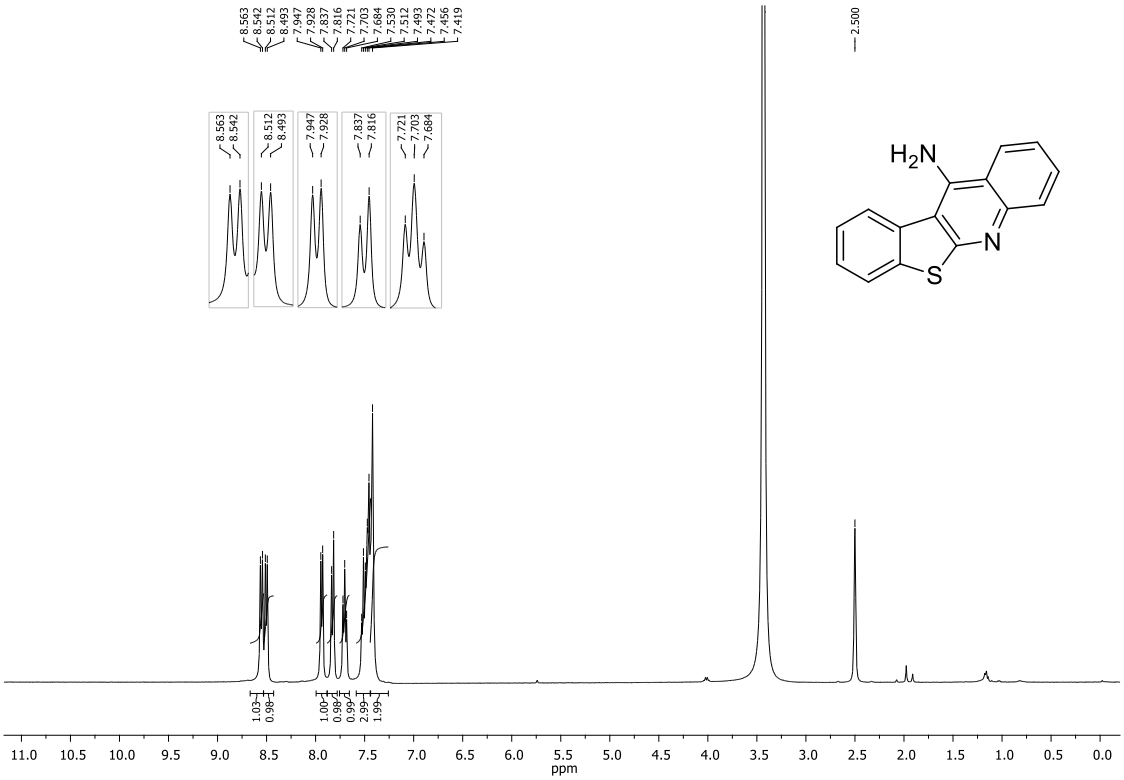
^{13}C NMR Spectrum of **7f**



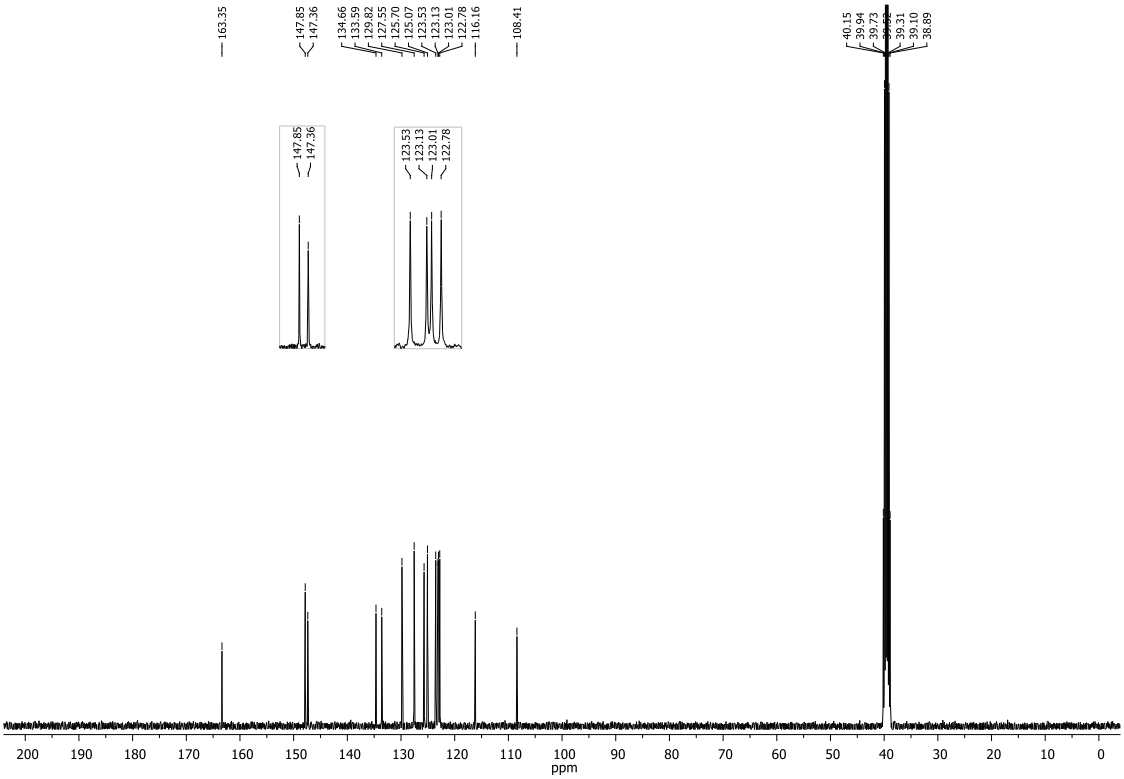
^{1}H NMR Spectrum of **7g**



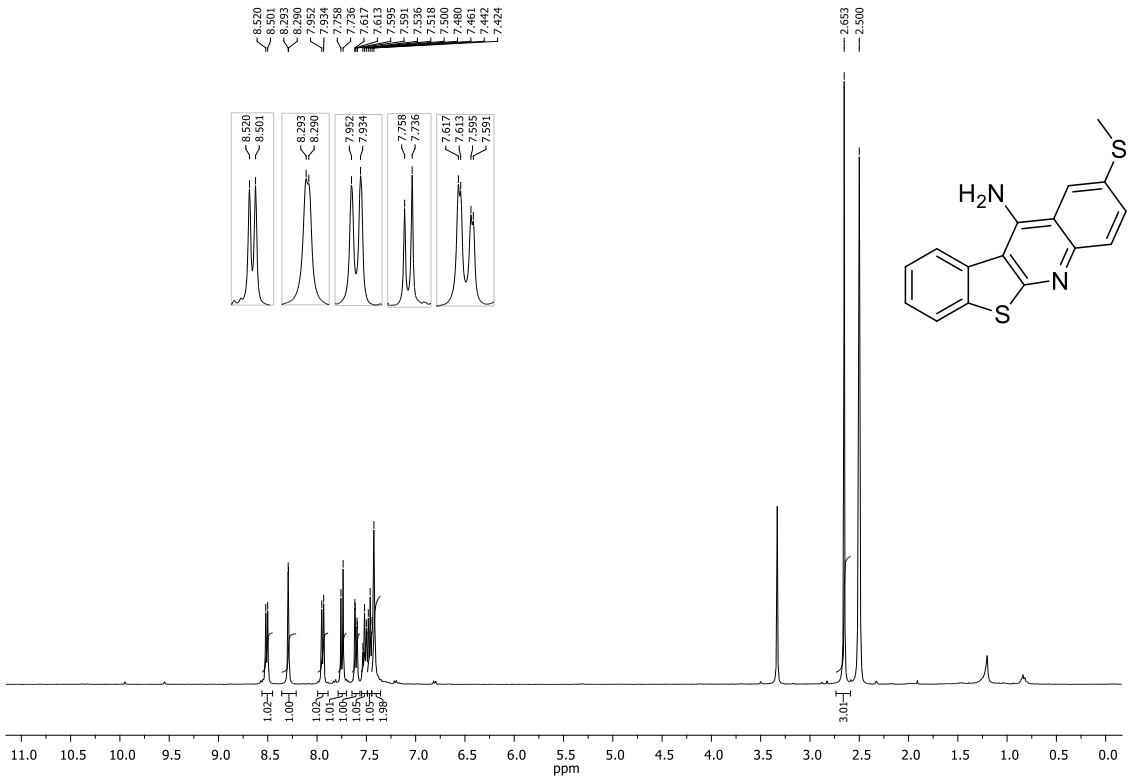
^{13}C NMR Spectrum of **7g**



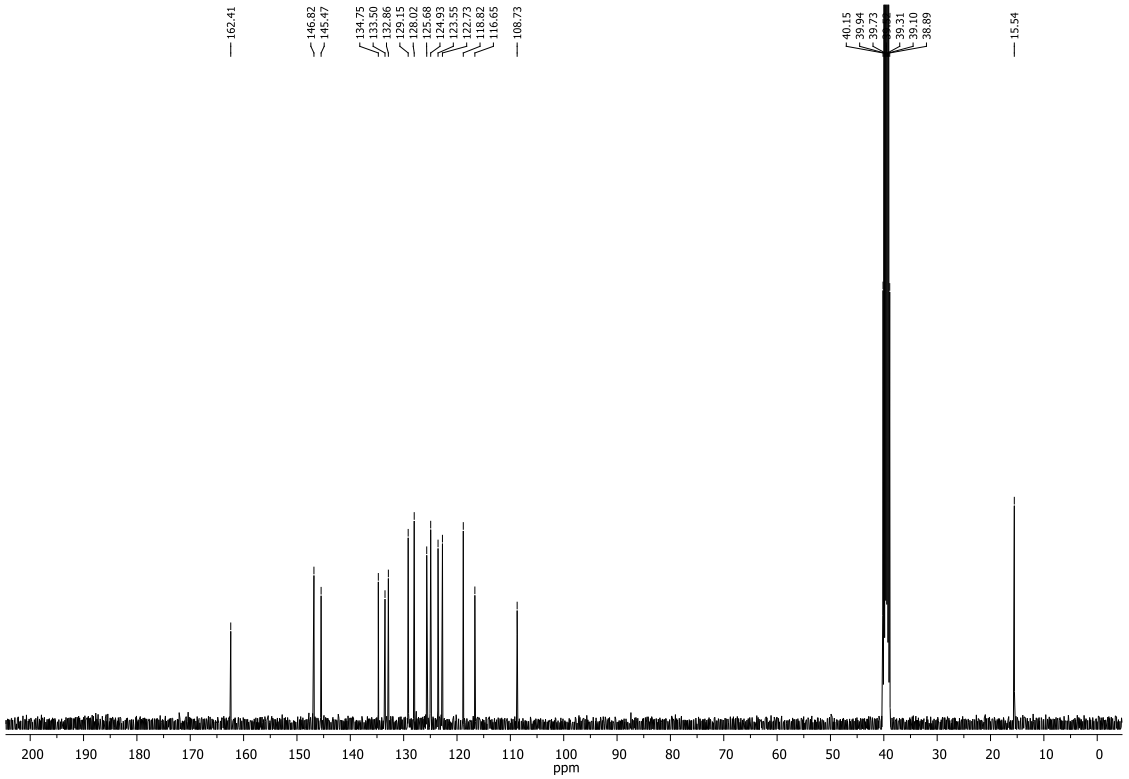
^{1}H NMR Spectrum of **8a**



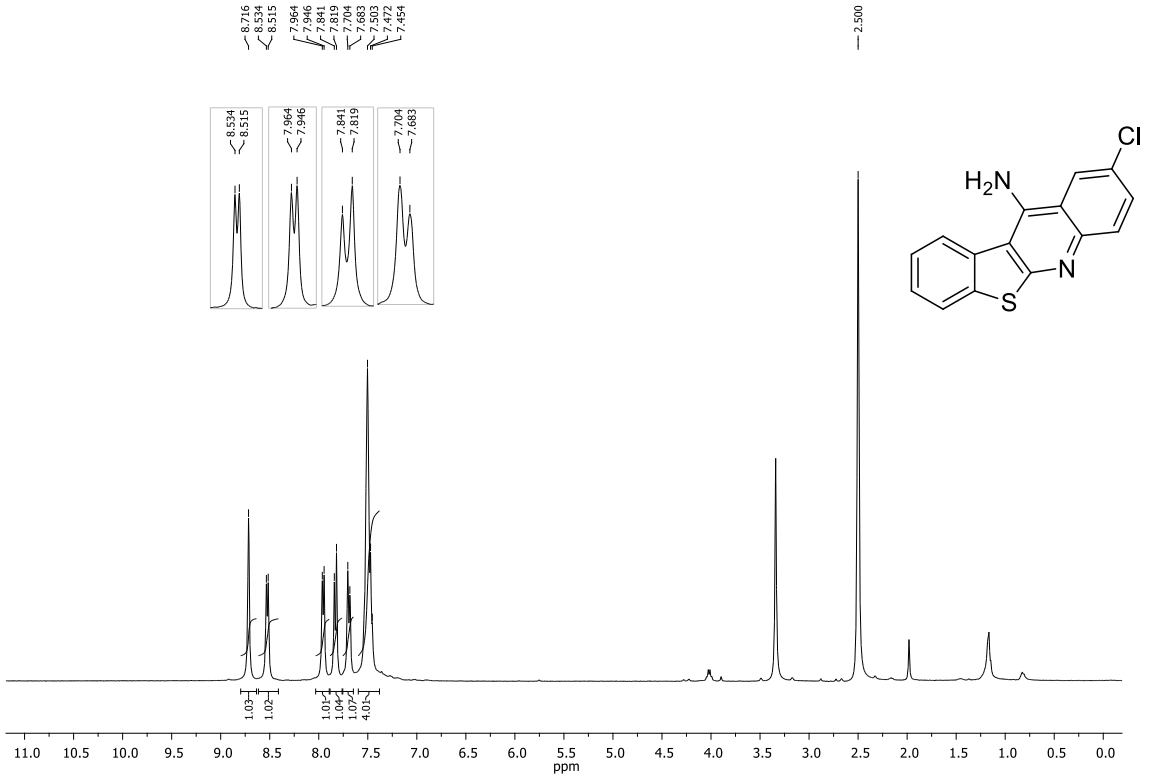
^{13}C NMR Spectrum of **8a**



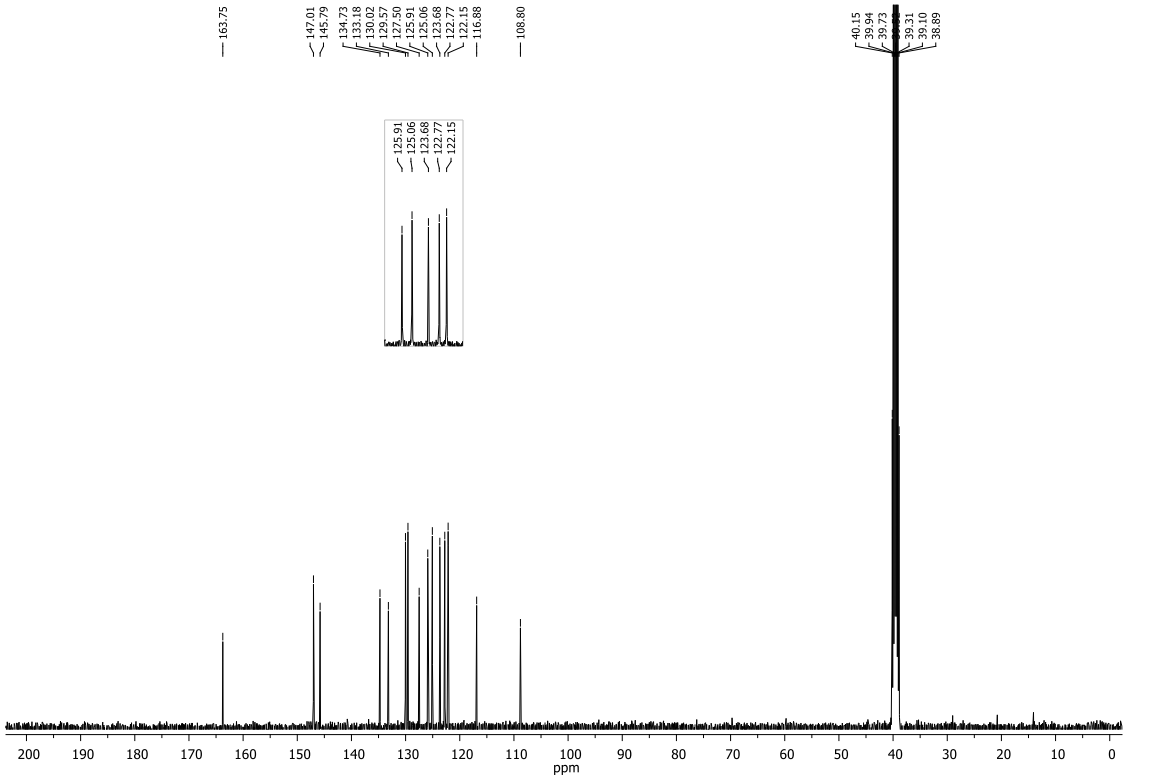
^{1}H NMR Spectrum of **8c**



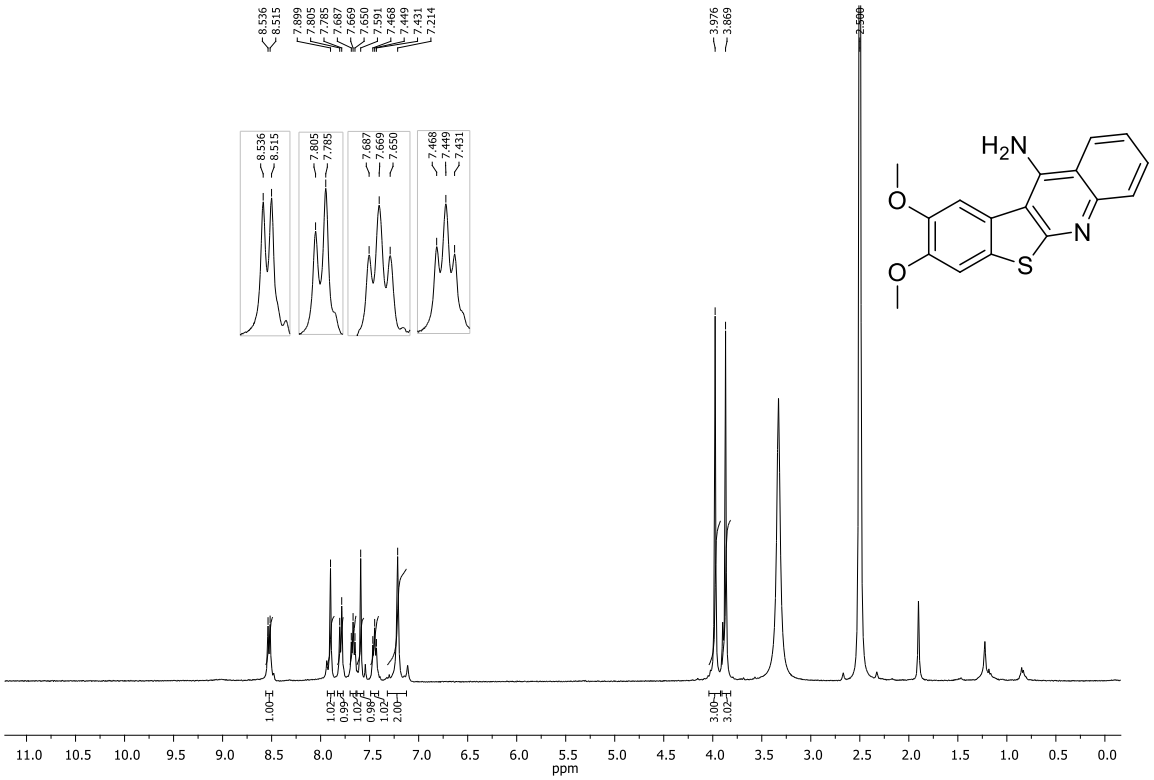
^{13}C NMR Spectrum of **8c**



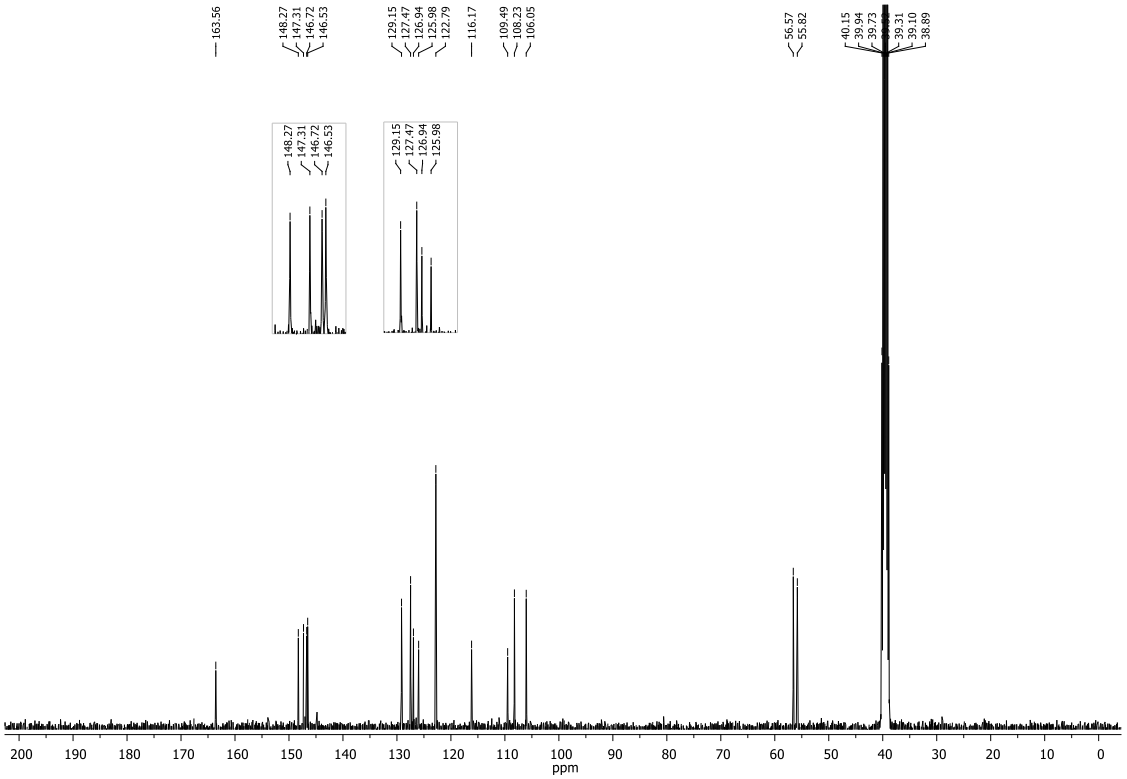
^{1}H NMR Spectrum of **8d**



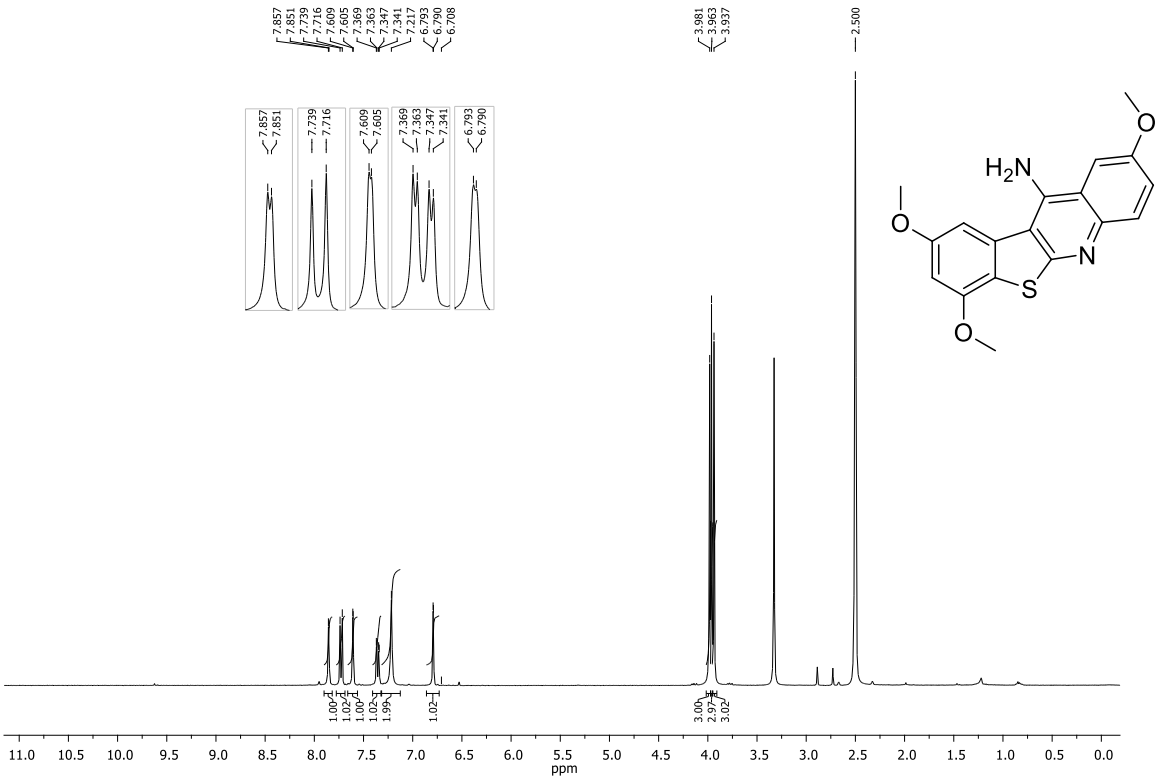
^{13}C NMR Spectrum of **8d**



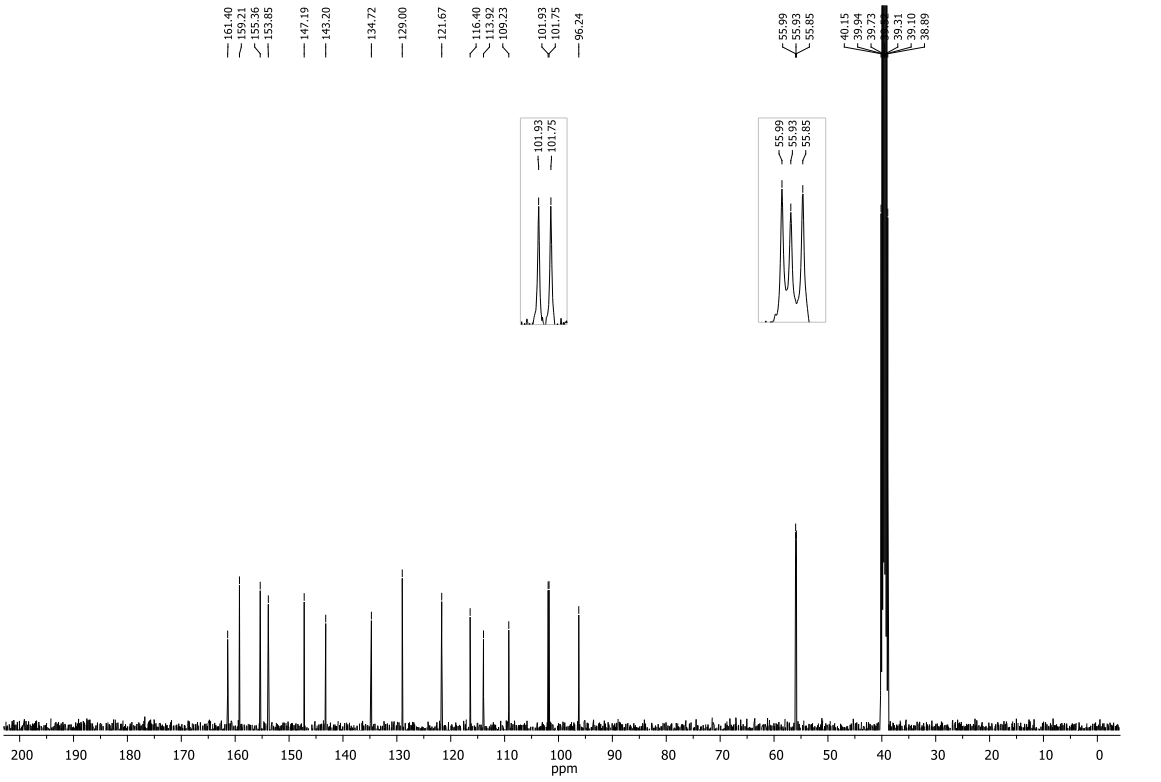
^{1}H NMR Spectrum of **8h**



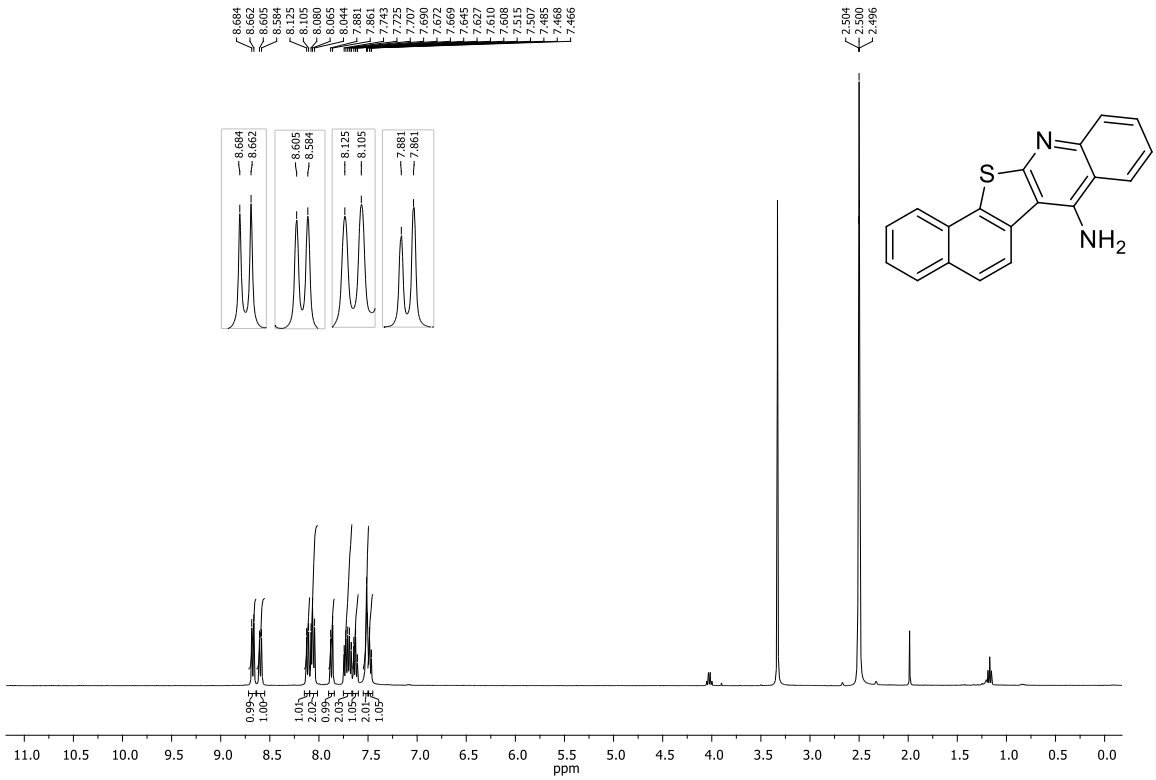
^{13}C NMR Spectrum of **8h**



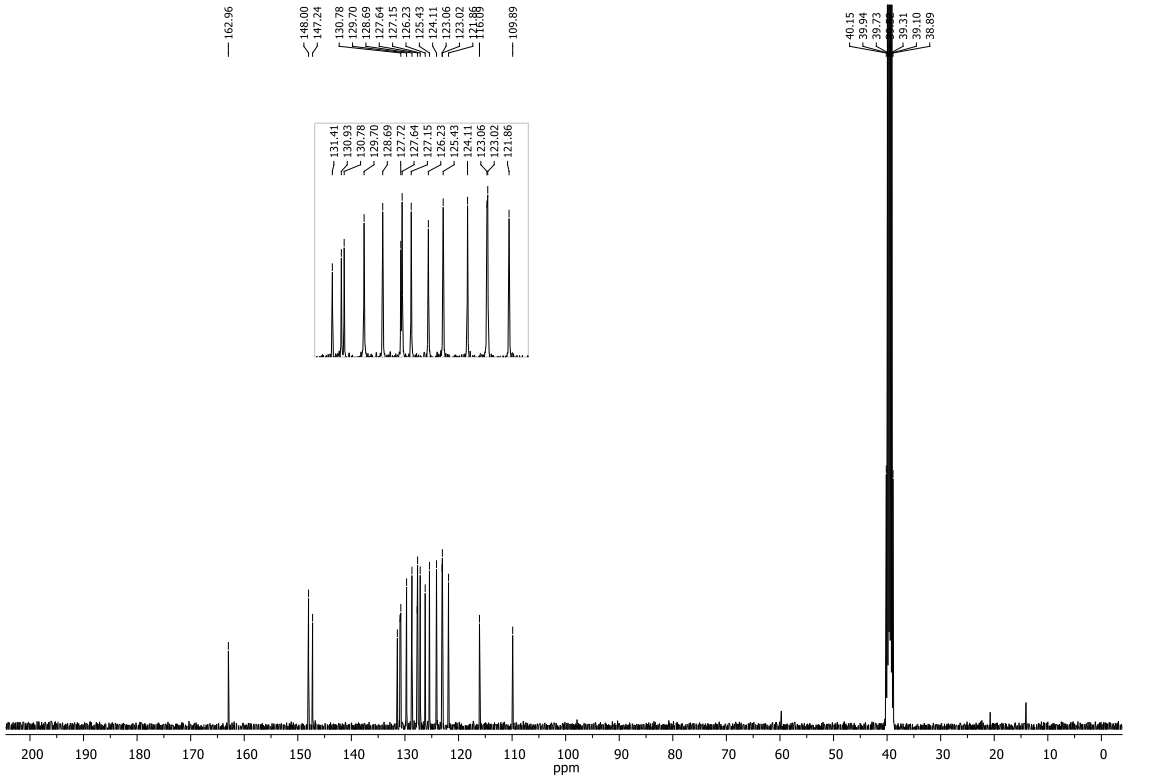
^{1}H NMR Spectrum of 8**j**



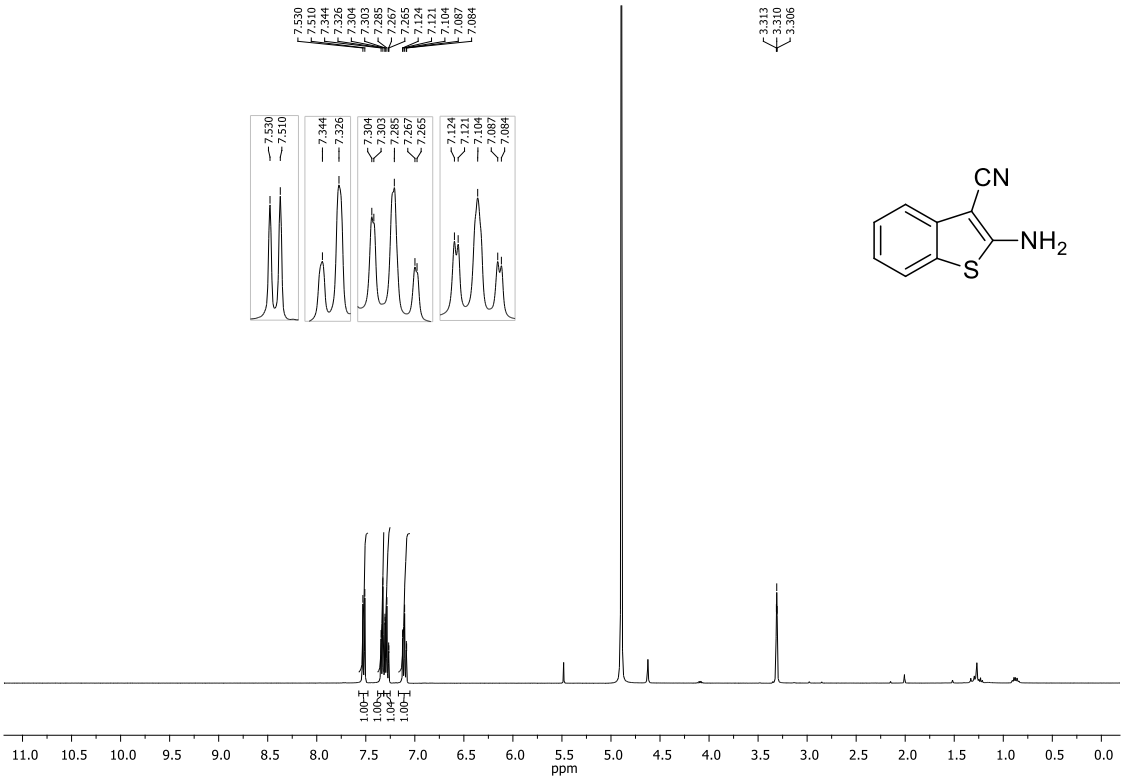
^{13}C NMR Spectrum of **8j**



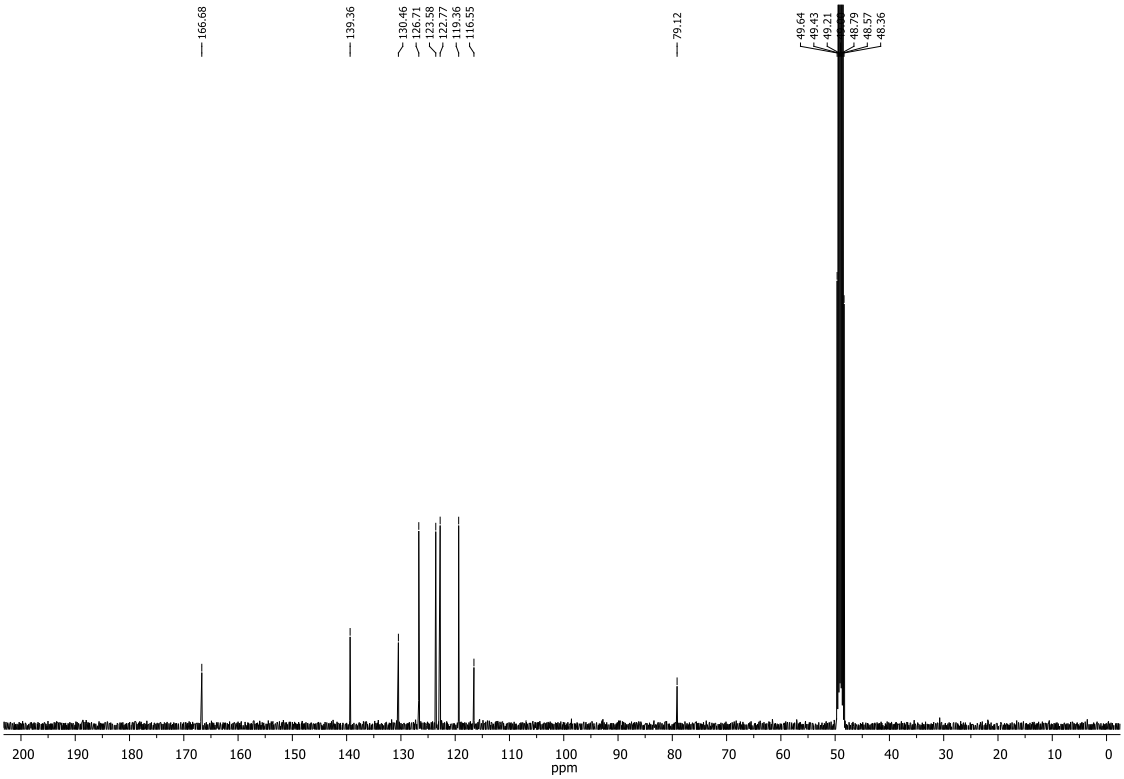
^{1}H NMR Spectrum of **8n**



^{13}C NMR Spectrum of 8**n**



^{1}H NMR Spectrum of **9**



^{13}C NMR Spectrum of **9**

MJ_0330 MJ 650 22/04/2017 23:34:35

HPLC Chromatogram

Chromatogram Information	
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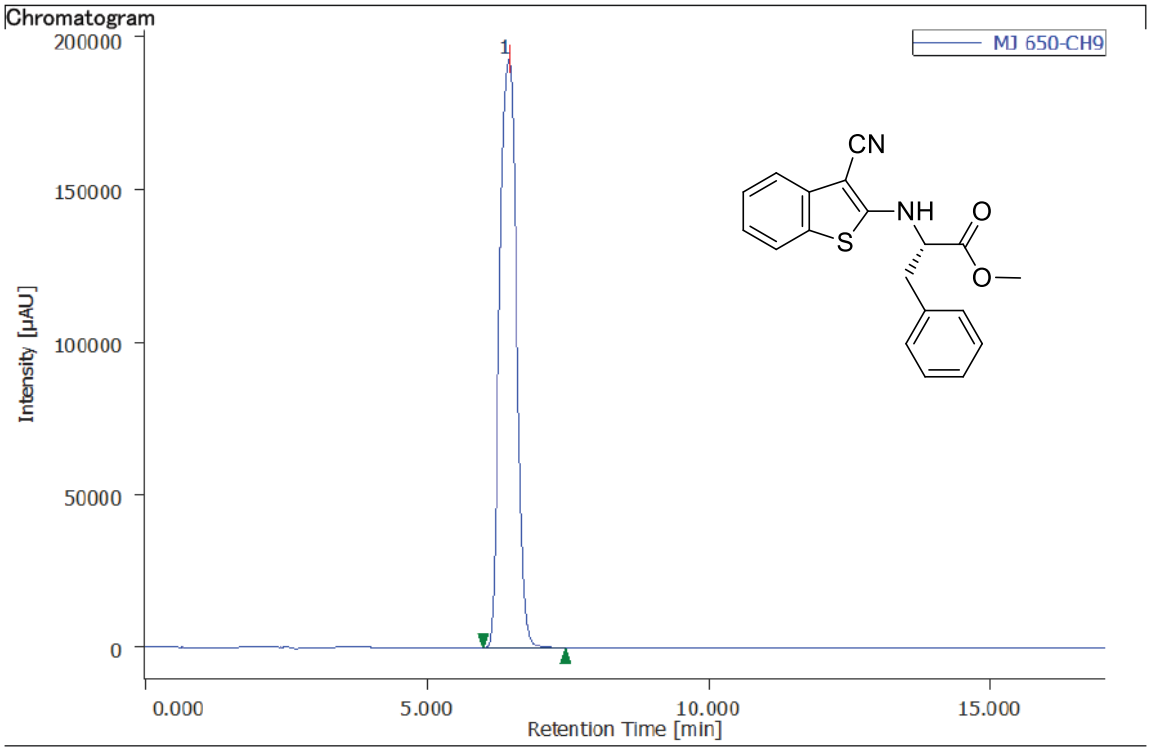
Chromatogram Name	MJ 650
Control Method	Hex_IPA 90_10_1mL
Channel Name	304.0nm



Peak Information

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BMS_0421 MJ 659_008 22/04/2017 22:55:27

HPLC Chromatogram

Chromatogram Information

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Injection Date	21/04/2017 14:24:52
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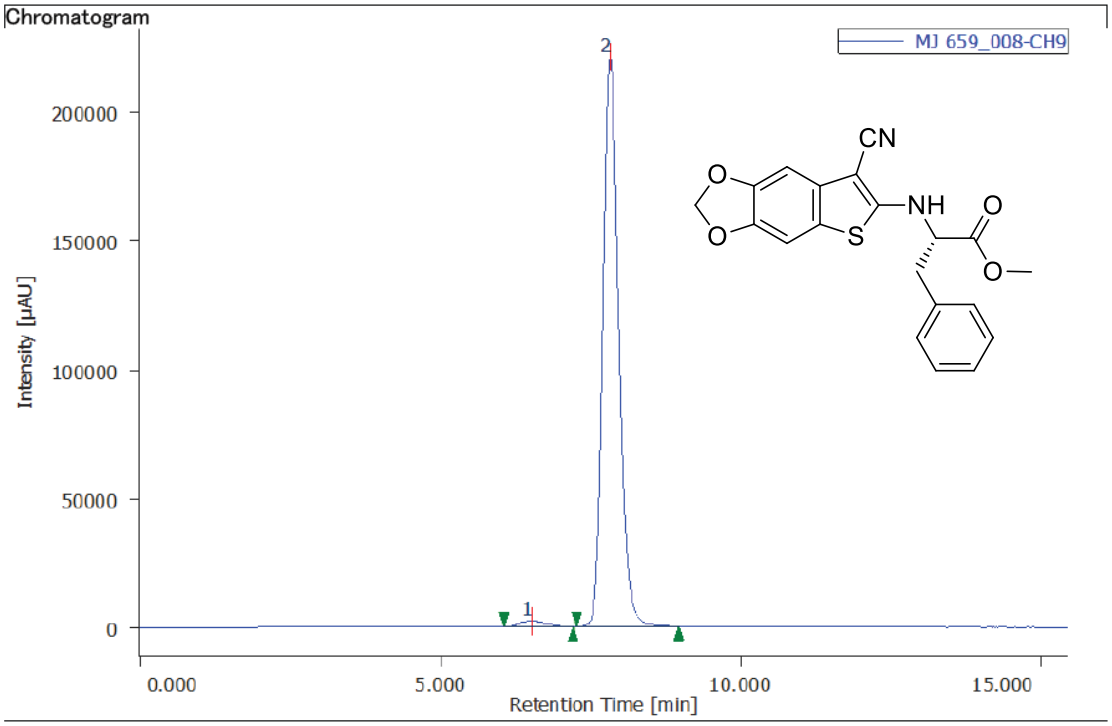

Peak Information

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