Supporting information

Antimycobacterial activity of spirooxindolo-pyrrolidine, pyrrolizine and pyrrolothiazole hybrids obtained by a three-component regio- and stereoselective 1,3-dipolar cycloaddition

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Experimental Section

General

The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H, ^{13}C and the 2D NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 ^{o}C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Crystals suitable for X-ray crystallographic studies were obtained by crystallisation from methanol. Ten fold serial dilutions of each test compound/drug were prepared and incorporated into Middlebrook 7H11 agar medium with OADC Growth Supplement. Inoculum of *Mycobacterium tuberculosis* H37Rv were prepared from fresh Middlebrook 7H11 agar slants with OADC Growth Supplement adjusted to 1mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a

concentration of approximately 10^7 cfu/mL. A 5 µL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37˚C, and final readings were recorded after 28 days. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to completely inhibit the bacterial growth.

Structural assignment of 4 and 5 using NMR spectroscopic data:

The ^{1}H and ^{13}C NMR chemical shifts of 2'-(aryl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'- pyrrolizin]-2-one (**4**) and 6'-(aryl)-7'-nitro-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-*c*]thiazol]-2-one (**5**) have also been done by the straightforward considerations as done′ for 3 -(aryl)-4′-nitro-5′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (**3**)**.** As representative examples ortep diagram for **3f** (**Figure 1**), ^{1}H and ^{13}C NMR chemical shifts and HMB correlations of **4i (Figure 2** & **3),** ortep diagram for **4i (Figure 4),** and **5a** (**Figure 5** & **6**) are shown below.

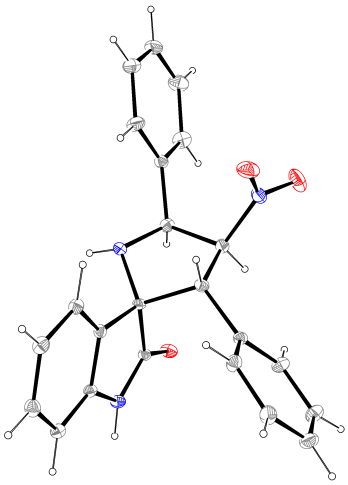


Figure 1. Ortep diagram for **3f**

Figure 2. Selected ^{1}H and ^{13}C NMR chemical shifts of **4i**

Figure 3. Selected HMBCs of **4i**

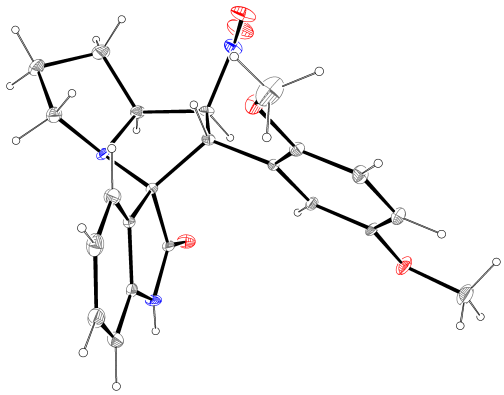


Figure 4. Selected HMBCs of **4i**

Figure 5. Selected ^{1}H and ^{13}C NMR chemical shifts of **5a**

Figure 6. Selected HMBCs of **5a**

General procedure for the synthesis of 3′-(aryl)-4′-nitro-5′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (**3**):

A mixture of β-nitrostyrene **1** (1 mmol), isatin **2** (1 mmol) and phenylglycine (1 mmol) dissolved in methanol (10 mL) was heated to reflux for 40 min. After completion of the reaction (TLC), the mixture was poured into crushed ice, the precipitated solid filtered and washed with water (100 mL) to obtain pure **3** as pale yellow solid.

3'-(4-Methoxyphenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3a)

Obtained as yellow solid. Yield: 86%; m.p. = 231 ^{o}C. IR (KBr): 1359, 1548, 1704, 3185, 3205 cm^{-1}; (300 MHz, DMSO-d_6) δ_H 2.75 (d, 1H, *J*=5.7 Hz, 1′-NH), 3.69 (s, 3H), 4.52 (d, 1H, *J*=10.1 Hz), 5.86 (dd, 1H, *J*=10.0, 5.7 Hz), 6.36 (t, 1H, *J*=10.1 Hz), 6.65-6.69 (m, 2H), 6.97 (d, 2H, *J*=8.7 Hz), 7.16-7.22 (m, 2H), 7.31-7.39 (m, 4H), 7.59 (d, 2H, *J*=6.6 Hz), 7.72-7.75 (d, 1H, *J*=7.2 Hz), 9.94 (br s, 1H, 1-NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 53.5, 53.6, 59.1, 70.2,

89.8, 108.5, 112.3, 120.8, 122.5, 122.9, 126.5, 126.6, 126.7, 127.0, 127.6, 127.9, 137.7, 141.0, 157.6, 178.6. Anal. Calcd for $C_{24}H_{21}N_3O_4$: C, 69.39; H, 5.10; N, 10.11%. Found C, 69.30; H, 5.18; N, 10.17%.

3'-(4-Chlorophenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3b)

Obtained as pale yellow solid. Yield: 85%; m.p. = 223 ^{o}C. IR (KBr): 1332, 1588, 1710, 3172, 3242 cm^{-1} ;(300 MHz, DMSO-d_6) δ_H 3.51 (d, 1H, *J*=5.7 Hz, 1′-NH), 4.50 (d, 1H, *J*=10.2 Hz), 5.80 (dd, 1H, *J*=9.6, 5.7 Hz), 6.39 (t, 1H, *J*=10.2 Hz), 6.69 (d, 1H, *J*=7.5 Hz), 7.03 (d, 2H, *J*=8.7 Hz), 7.11-7.37 (m, 7H), 7.60 (d, 2H, *J*=7.8 Hz), 7.73 (d, 1H, *J*=7.2 Hz), 9.90 (br s, 1H, 1-NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 54.0, 59.8, 70.8, 89.8, 109.2, 121.6, 122.9, 127.0, 127.1, 127.3, 127.5, 128.4, 128.7, 130.3, 132.7, 137.6, 141.3, 178.9. Anal. Calcd for $C_{23}H_{18}ClN_3O_3$: C, 65.79; H, 4.32; N, 10.01%. Found C, 65.72; H, 4.41; N, 9.93%

3'-(3-Nitrophenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3c)

Obtained as yellow solid. Yield: 81%; m.p. = 241 ^{o}C. IR (KBr): 1351, 1546, 1704, 3176, 3322 cm^{-1}; (300 MHz, DMSO-d_6) δ_H 3.28 (d, 1H, *J*=5.1 Hz, 1′-NH), 4.65 (d, 1H, *J*=9.9 Hz), 5.81-5.83 (m, 1H), 6.45-6.52 (m, 1H), 6.66 (d, 1H, *J*=6.9 Hz), 7.17-7.23 (m, 1H), 7.33-7.45 (m, 5H), 7.63 (d, 2H, *J*=6.8 Hz), 7.80 (d, 1H, *J*=6.8 Hz), 7.93-8.08 (m, 3H), 10.1 (br s, 1H, 1-NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 53.8, 59.7, 70.6, 89.5, 109.1, 121.4, 121.5, 122.0, 122.8, 126.6, 126.9, 127.3, 128.5, 128.7, 133.5, 133.9, 137.3, 141.0, 146.8, 178.5. Anal. Calcd for $C_{23}H_{18}N_4O_5$: C, 64.18; H, 4.22; N, 13.02%. Found C, 64.27; H, 4.14; N, 13.10%.

3'-(3-Chlorophenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3d)

Obtained as pale yellow solid. Yield: 85%; m.p. = 240 ^{o}C. IR (KBr): 1369, 1546, 1714, 3160, 3331 cm^{-1}; (300 MHz, DMSO-d_6) δ_H 2.69 (br s, 1H, 1 -NH), 4.57 (d, 1H, *J*=9.9 Hz), 5.88 (d, 1H, *J*=9.6 Hz), 6.32 (t, 1H, *J*=9.9 Hz), 6.69-6.71 (m, 1H), 6.90-6.95 (m, 1H), 7.05-7.30 (m, 6H), 7.36-7.42 (m, 3H, 1-NH and ArH), 7.55-7.64 (m, 2H), 7.79 (d, 1H, *J*=6.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 55.2, 60.8, 71.5, 90.7, 110.0, 122.4, 123.5, 126.3, 127.5, 127.7, 127.8, 127.9, 128.2, 129.3, 129.6, 133.8, 134.5, 137.7, 142.0, 179.4 Anal. Calcd for $C_{23}H_{18}ClN_3O_3$: C, 65.79; H, 4.32; N, 10.01%. Found C, 65.87; H, 4.25; N, 10.09%.

3'-(4-Fluorophenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3e)

Obtained as pale yellow solid. Yield: 88%; m.p. = 224 ^{o}C. IR (KBr): 1363, 1554, 1706, 3199, 3347 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 2.58 (br s, 1H, 1′-NH), 4.51 (d, 1H, *J*=10.3 Hz), 5.81 (dd, 1H, *J*=9.6, 5.7 Hz), 6.38 (t, 1H, *J*=10.3 Hz), 6.67 (d, 1H, *J*=7.8 Hz), 6.84 (m, 2H), 7.04-7.09 (m, 2H), 7.12-7.24 (m, 2H), 7.28-7.39 (m, 3H), 7.60 (d, 2H, *J*=6.3 Hz), 7.73 (d, 1H, *J*=6.9 Hz), 9.82 (br s, 1H,1- NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 55.8, 61.4, 71.9, 91.3, 115.4, 115.7, 123.5, 124.4, 127.8, 128.0, 128.2, 128.3, 128.8, 129.6, 129.7, 137.7, 140.7, 161.1, 179.5. Anal. Calcd for $C_{23}H_{18}FN_3O_3$: C, 68.48; H, 4.50; N, 10.42%. Found C, 68.37; H, 4.59; N, 10.35%.

3'-Phenyl-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3f)

Obtained as pale yellow solid. Yield: 80%; m.p. = 239 ^{o}C. IR (KBr): 1363, 1550, 1704, 3264, 3342 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 2.58 (br s, 1H, 1′-NH), 4.53 (d, 1H, *J*=10.1 Hz), 5.82 (dd, 1H, *J*=9.9, 5.7 Hz), 6.43 (t, 1H, *J*=10.1 Hz), 6.67 (d, 1H, *J*=7.2 Hz), 7.05-7.38 (m, 11H), 7.61 (d, 2H, *J*=7.2 Hz), 7.74 (d, 1H, *J*=7.2 Hz), 9.80 (br s, 1H, 1-NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 54.9, 60.1, 71.0, 90.2, 109.3, 121.7, 123.1, 127.1, 127.2, 127.6, 127.7, 128.8, 131.7, 137.8, 141.5, 179.3. Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90%. Found C, 71.58; H, 4.91; N, 10.99%.

3'-(4-Methylphenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3g)

Obtained as pale yellow solid. Yield: 83%; m.p. = 240 ^{o}C. IR (KBr): 1363, 1552, 1706, 3147, 3326 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 2.21 (s, 3H), 2.57 (br s, 1H, 1′-NH), 4.48 (d, 1H, *J*=10.2 Hz), 5.79 (dd, 1H, *J*=9.5, 5.7 Hz), 6.40 (t, 1H, *J*=10.2 Hz), 6.67 (d, 1H, *J*=7.5 Hz), 6.94-7.37 (m, 9H), 7.60 (d, 2H, *J*=6.6 Hz), 7.73 (d, 1H, *J*=6.9 Hz), 9.83 (br s, 1H, 1-NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 20.0, 54.4, 59.9, 70.8, 90.2, 109.2, 121.5, 123.0, 126.9, 127.0, 127.1, 127.5, 127.7, 128.1, 128.5, 128.6, 136.7, 137.8, 141.4, 179.2. Anal. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52%. Found C, 72.09; H, 5.37; N, 10.61%.

3'-(4-Bromophenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3h)

Obtained as pale yellow solid. Yield: 84%; m.p. = 219 ^{o}C. IR (KBr): 1363, 1548, 1705, 3104, 3334 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 3.45 (d, 1H, *J*=5.7 Hz, 1′-NH), 4.49 (d, 1H, *J*=10.0 Hz), 5.80 (dd, 1H, *J*=9.6, 5.7 Hz), 6.39 (t, 1H, *J*=10.0 Hz), 6.71 (d, 1H, *J*=7.2 Hz), 6.96-6.98 (m, 2H), 7.13-7.38 (m, 7H), 7.60 (d, 2H, *J*=6.9 Hz), 7.73 (d, 1H, *J*=6.9 Hz), 9.89 (br s, 1H, 1-NH). ^{13}C

NMR (75 MHz, DMSO-d_6) δ_C 54.2, 59.9, 70.8, 89.9, 109.4, 121.1, 121.7, 123.0, 127.0, 127.1, 127.3, 127.5, 128.9, 130.5, 130.9, 137.6, 141.3, 179.0. Anal. Calcd for $C_{23}H_{18}BrN_3O_3$: C, 59.50; H, 3.91; N, 9.05%. Found C, 59.58; H, 3.84; N, 9.12%.

3'-(2,5-Dimethoxyphenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (3i)

Obtained as orange solid. Yield: 81%; m.p. = 231 ^oC. IR (KBr): 1349, 1549, 1701, 3181, 3347 cm^{-1}; (300 MHz, DMSO-d_6) δ_H 2.58 (br s, 1H, 1′-NH), 3.33 (s, 3H), 3.70 (s, 3H), 5.24 (d, 1H, *J*=9.9 Hz), 5.81 (dd, 1H, *J*=9.3, 5.4 Hz), 6.28 (t, 1H, *J*=9.9 Hz), 6.57-6.67 (m, 3H), 7.02-7.18 (m, 3H), 7.29-7.35 (m, 3H), 7.60 (d, 2H, *J*=7.2 Hz), 7.72 (d, 1H, *J*=7.2 Hz), 9.93 (br s, 1H, 1-NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 46.6, 54.5, 54.9, 60.4, 70.7, 91.4, 108.7, 111.0, 112.2, 113.2, 120.8, 121.6, 124.1, 126.9, 127.1, 127.3, 128.1, 141.1, 151.1, 152.1, 179.4. Anal. Calcd for $C_{25}H_{23}N_3O_5$: C, 67.41; H, 5.20; N, 9.43%. Found C, 67.48; H, 5.11; N, 9.34%.

General procedure for the synthesis of 2'-(aryl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4) and 6'-(aryl)-7'-nitro-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-*c*]thiazol]-2-one (5).

A mixture of β-nitrostyrene **1** (1 mmol), isatin **2** (1 mmol) and proline/thiaproline (1 mmol) in methanol (10 mL) was heated to reflux for 1 h. After completion of the reaction (TLC), the mixture was poured into crushed ice, the precipitated solid was filtered and washed with water (100 mL) to obtain pure **4/5** as solid.

2'-(4-Methoxyphenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4a)

Obtained as yellow solid. Yield: 87%; m.p. = 179 ^oC (200-202 ^oC).[15a] IR (KBr): 1342, 1546, 1706, 3181 cm^{-1}; (300 MHz, DMSO-d_6) δ_H 1.46-1.54 (m, 1H), 1.78-1.87 (m, 1H), 1.96-2.00 (m, 1H), 2.09-2.16 (m, 1H), 2.84-2.89 (m, 1H), 3.21-3.30 (m, 1H), 3.67 (s, 3H), 4.46 (d, 1H, *J*=10.2 Hz), 4.80-4.88 (m, 1H), 6.24 (t, 1H, *J*=10.2 Hz), 6.62 (d, 2H, *J*=7.8 Hz), 6.69(d, 1H, *J*=7.8Hz), 7.00 (d, 2H, *J*=7.8 Hz), 7.10 (d, 1H, *J*=7.5 Hz), 7.23 (d, 1H, *J*=7.5 Hz), 7.55 (d, 1H, *J*=7.5 Hz), 7.73 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 25.6, 27.8, 51.0, 52.6, 55.0, 64.1, 75.1, 91.9, 110.2, 113.9, 122.4, 124.3, 125.3, 126.1, 129.3, 130.0, 141.8, 159.1, 178.0. Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08%. Found C, 66.38; H, 5.50; N, 11.02%.

2'-(4-Chlorophenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrro-lizin]-2-one (4b)

Obtained as pale yellow solid. Yield: 83%; m.p. = 173 ^{o}C (202-204 ^{o}C).[15a] IR (KBr): 1338, 1546, 1710, 3160 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1.51-1.56 (m, 1H), 1.77-1.87 (m, 1H), 1.98-2.00 (m, 1H), 2.11-2.20 (m, 1H), 2.86-2.90 (m, 1H), 3.20-3.29 (m, 1H), 4.47 (d, 1H, *J*=10.5 Hz), 4.81-4.90 (m, 1H), 6.21-6.27 (m, 1H), 6.71 (d, 1H, *J*=7.5 Hz), 7.02-7.14 (m, 5H), 7.23-7.28 (m, 1H), 7.55 (d, 1H, *J*=7.5Hz), 7.67 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 25.6, 27.8, 51.1, 52.6, 64.2, 75.1, 91.6, 110.4, 122.6, 124.9, 126.1, 128.8, 129.6, 130.2, 131.1, 133.9, 141.7, 177.5. Anal. Calcd for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; N, 10.95%. Found C, 62.66; H, 4.65; N, 10.88%.

2'-(3-Nitrophenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4c)

Obtained as yellow solid. Yield: 81%; m.p. = 208 ^{o}C (210-211 ^{o}C).[15a]. IR (KBr): 1354, 1546, 1707, 3108 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1.34-1.49 (m, 1H), 1.62-1.80 (m, 1H), 1.92-2.10 (m, 2H), 2.67-2.72 (m, 1H), 3.20-3.40 (m, 1H), 4.69-4.76 (m, 2H), 6.45 (t, 1H, *J*=9.6 Hz), 6.65 (d, 1H, *J*=7.8 Hz), 7.04 (t, 1H, *J*=7.5 Hz), 7.20 (t, 1H, *J*=7.5 Hz), 7.46-7.49 (m, 1H), 7.62 (d, 1H, *J*=7.2 Hz), 7.87 (d, 1H, *J*=7.2 Hz), 8.00-8.05 (m, 2H), 10.37 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 23.4, 26.1, 36.9, 49.0, 61.6, 72.9, 88.8, 108.2, 119.9, 120.9, 121.1, 122.3, 125.0, 128.0, 128.2, 133.3, 134.0, 141.1, 145.9, 175.2. Anal. Calcd for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21%. Found C, 70.02; H, 4.66; N, 14.14%.

2'-(3-Chlorophenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4d)

Obtained as pale yellow solid. Yield: 85%; m.p. = 205 ^{o}C. IR (KBr): 1342, 1542, 1707, 3191 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1.39-1.50 (m, 1H), 1.71-1.79 (m, 1H), 1.96-1.98 (m, 1H), 2.04-2.13 (m, 1H), 2.75-2.80 (m, 1H), 3.23-3.36 (m, 1H), 4.48 (d, 1H, *J*=10.8 Hz), 4.72-4.80 (m, 1H), 6.27-6.34 (m, 1H), 6.68 (d, 1H, *J*=7.8 Hz), 7.02-7.22 (m, 6H), 7.65 (d, 1H, *J*=7.2 Hz), 10.11 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 23.9, 26.4, 49.5, 50.2, 62.1, 73.3, 89.8, 108.7, 120.3, 123.1, 124.8, 125.6, 126.4, 126.6, 128.4, 128.5, 132.2, 134.1, 141.7, 175.9. Anal. Calcd for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; N, 10.95%. Found C, 62.69; H, 4.80; N, 11.02%.

2'-(4-Fluorophenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4e)

Obtained as pale yellow solid. Yield: 83%; m.p. = 209 ^{o}C. IR (KBr): 1346, 1531, 1705, 3183 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1. 42-1.51 (m, 1H), 1.72-1.86 (m, 1H), 1.95-2.03 (m, 1H), 2.05-2.14 (m, 1H), 2.78-2.83 (m, 2H), 4.46 (d, 1H, *J*=10.8 Hz), 4.73-4.82 (m, 1H), 6.25-6.31 (m, 1H), 6.68 (d, 1H, *J*=7.5 Hz), 6.81-6.87 (m, 2H), 7.02-7.07 (m, 1H), 7.11-7.22 (m, 3H), 7.60 (d, 1H, *J*=7.5 Hz), 10.11 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 25.6, 27.8, 51.0, 52.7, 52.9, 64.2, 75.1, 91.8, 110.3, 115.4, 115.7, 122.5, 125.1, 126.1, 128.3, 129.8, 129.9, 130.2, 141.8, 164.0, 177.7. Anal. Calcd for $C_{20}H_{18}FN_3O_3$: C, 65.39; H, 4.94; N, 11.44%. Found C, 65.46; H, 4.86; N, 11.54%.

2'-(Phenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4f)

Obtained as pale yellow solid. Yield: 90%; m.p. = 210 ^{o}C (208-210 ^{o}C).[15a] IR (KBr): 1369, 1547, 1702, 3127 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1.46-1.53 (m, 1H), 1.72-1.83 (m, 1H), 1.99-2.03 (m, 1H), 2.07-2.14 (m, 1H), 2.82-2.87 (m, 1H), 3.15- 3.21 (m, 1H), 4.47 (d, 1H, *J*=10.5 Hz), 4.81-4.87 (m, 1H), 6.30-6.36 (m, 1H), 6.69 (d, 1H, *J*=7.8 Hz), 7.03-7.22 (m, 7H), 7.57-7.61 (m, 1H), 9.95 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 24.9, 27.1, 50.4, 52.0, 63.2, 74.3, 90.9, 109.7, 121.1, 124.3, 125.2, 127.1, 127.6, 127.7, 129.2, 132.2, 142.4, 177.1. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03%. Found C, 68.68; H, 5.56; N, 11.94%.

2'-(4-Methylphenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4g)

Obtained as pale yellow solid. Yield: 87%; m.p. = 212 ^{o}C (217-218 ^{o}C).[15a] IR (KBr): 1342, 1547, 1705, 3172 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1.46-1.57 (m, 1H), 1.78-1.91 (m, 1H), 1.98-2.04 (m, 1H), 2.10-2.17 (m, 1H), 2.19 (s, 3H), 2.85-2.90 (m, 1H), 3.22-3.30 (m, 1H), 4.48 (d, 1H, *J*=10.2 Hz), 4.81-4.89 (m, 1H), 6.28 (t, 1H, *J*=10.2 Hz), 6.69 (d, 1H, *J*=7.8 Hz), 6.88-7.35 (m, 6H), 7.57 (d, 1H, *J*=7.2 Hz), 7.74 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 20.9, 25.6, 27.8, 51.1, 52.8, 64.1, 75.1, 91.7, 110.2, 122.4, 125.3, 126.1, 128.0, 129.2, 130.0, 137.6, 141.8, 177.9. Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56%. Found C, 69.49; H, 5.91; N, 11.45%.

2'-(4-Bromophenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4h)

Obtained as pale yellow solid. Yield: 88%; m.p. = 206 ^{o}C. IR (KBr): 1342, 1545, 1705, 3147 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1.40-1.53 (m, 1H), 1.77-1.86 (m, 1H), 1.98-2.00 (m, 1H), 2.08-2.18 (m, 1H), 2.84-2.91 (m, 1H), 3.21-3.29 (m, 1H), 4.43 (d, 1H, *J*=10.0 Hz), 4.80-4.88 (m, 1H), 6.28 (t, 1H, *J*=10.0 Hz), 6.72 (d, 1H, *J*=7.5 Hz), 7.00-7.08 (m, 3H), 7.19-7.26 (m, 2H), 7.45-7.46 (m, 1H), 7.54 (d, 1H, *J*=7.5 Hz), 9.77 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 25.1, 27.4, 50.7, 51.8, 63.5, 74.6, 91.0, 110.2, 121.3, 121.5, 124.3, 125.4, 129.6, 129.7, 131.0, 131.6, 177.2. Anal. Calcd for $C_{20}H_{18}BrN_3O_3$: C, 56.09; H, 4.24; N, 9.81%. Found C, 56.17; H, 4.33; N, 9.90%.

2'-(2,5-Dimethoxyphenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4i)

Obtained as green solid. Yield: 94%; m.p. = 217 ^{o}C. IR (KBr): 1342, 1543, 1705, 3191 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1.40-1.48 (m, 1H), 1.72-1.75 (m, 1H), 1.96-2.02 (m, 1H), 2.05-2.12 (m, 1H), 2.72-2.77 (m, 1H), 3.26-3.27 (m, 1H), 3.51 (s, 3H), 3.66 (s, 3H), 4.69-4.77 (m, 1H), 5.22 (d, 1H, *J*=10.5 Hz), 6.18 (t, 1H, *J*=10.5 Hz), 6.62-6.67 (m, 3H), 6.95-7.00 (m, 2H), 7.15 (t, 1H, *J*=7.5 Hz), 7.57 (d, 1H, *J*=7.5 Hz), 10.26 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 23.7, 26.1, 41.5, 49.3, 53.6, 54.2, 61.9, 73.1, 90.9, 108.1, 110.4, 111.2, 112.5, 119.3, 121.0, 123.0, 125.6, 127.9, 141.4, 150.1, 151.4, 176.1. Anal. Calcd for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26%. Found C, 64.43; H, 5.75; N, 10.19%.

2'-(3,4,5-Trimethoxyphenyl)-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (4j)

Obtained as brown solid. Yield: 86%; m.p. = 123 ^{o}C. IR (KBr): 1367, 1542, 1708, 3166 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 1.43-1.58 (m, 1H), 1.79-1.85 (m, 1H), 1.95-2.08 (m, 1H), 2.11-2.21 (m, 1H), 2.88-2.92 (m, 1H), 3.24-3.30 (m, 1H), 3.62 (s, 6H), 3.73 (s, 3H), 4.45 (d, 1H, *J*=10.5 Hz), 4.83-4.91 (m, 1H), 6.26-6.31 (m, 3H), 6.66-6.73 (m, 1H), 7.09-7.14 (m, 1H), 7.23-7.27 (m, 1H), 7.59 (d, 1H, *J*=7.5 Hz), 7.78 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 25.6, 27.8, 51.1, 53.4, 55.8, 60.7, 64.1, 75.1, 91.3, 104.9, 110.4, 122.3, 125.4, 126.1, 127.9, 130.1, 137.3, 152.8, 177.7. Anal. Calcd for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56%. Found C, 62.94; H, 5.82; N, 9.45%.

6'-(4-Methoxyphenyl)-7'-nitro-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo-[1,2-*c*]thiazol]-2-one (5a)

Obtained as yellow solid. Yield: 91%; m.p. = 243 ^{o}C. IR (KBr): 1369, 1547, 1707, 3239 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 2.90-2.97 (m, 1H), 3.08-3.15 (m, 1H), 3.70 (s, 3H), 3.99 (d, 1H, *J*=10.2 Hz), 4.17 (d, 1H, *J*=10.2 Hz), 4.25 (d, 1H, *J*=11.7 Hz), 4.55-4.62 (m, 1H), 6.48 (dd, 1H, *J*=11.7, 7.2 Hz), 6.64-6.71 (m, 3H), 6.81-6.84 (m, 2H), 7.07 (br s, 1H, NH), 7.18-7.26 (m, 1H), 7.29-7.34 (m, 1H), 7.82 (d, 1H, *J*=7.2 Hz). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 32.3, 52.2, 53.7, 54.1, 66.3, 73.6, 83.5, 109.0, 112.3, 120.9, 122.5, 123.1, 124.4, 127.6, 129.2, 141.7, 157.8, 176.1. Anal. Calcd for $C_{20}H_{19}N_3O_4S$: C, 60.44; H, 4.82; N, 10.57%. Found C, 60.37; H, 4.89; N, 10.49%.

6'-(4-Chlorophenyl)-7'-nitro-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo-[1,2-*c*]thiazol]-2-one (5b)

Obtained as pale yellow solid. Yield: 90%; m.p. = 185 ^{o}C. IR (KBr): 1332, 1547, 1703, 3184 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 2.89-2.92 (m, 1H), 3.02-3.09 (m, 1H), 4.00 (d, 1H, *J*=10.2 Hz), 4.15 (d, 1H, *J*=10.2 Hz), 4.24 (d, 1H, *J*=11.7 Hz), 4.56-4.63 (m, 1H), 6.55 (dd, 1H, *J*=11.7, 7.2 Hz), 6.74 (d, 1H, *J*=7.8 Hz), 6.89 (d, 2H, *J*=7.5 Hz), 7.11-7.17 (m, 3H), 7.21-7.32 (m, 1H), 7.77 (d, 1H, *J*=7.5 Hz), 9.90 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 33.0, 52.8, 54.8, 66.9, 74.2, 83.6, 109.8, 121.7, 123.2, 124.9, 127.6, 128.4, 129.9, 132.9, 142.1, 176.5. Anal. Calcd for $C_{19}H_{16}ClN_3O_3S$: C, 56.79; H, 4.01; N, 10.46 %. Found C, 57.68; H, 4.10; N, 10.53%.

6'-(3-Nitrophenyl)-7'-nitro-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo-[1,2-*c*]thiazol]-2-one (5c)

Obtained as pale yellow solid. Yield: 93%; m.p. = 255 ^{o}C. IR (KBr): 1344, 1547, 1707, 3187 cm^{-1}; (300 MHz, DMSO-d$_6$) δ_H 2.86-2.92 (m, 1H), 3.14-3.20 (m, 1H), 4.02 (d, 1H, *J*=10.2 Hz), 4.15 (d, 1H, *J*=10.2 Hz), 4.38 (d, 1H, *J*=11.7 Hz), 4.62-4.69 (m, 1H), 6.65-6.74 (m, 2H), 7.16-7.21 (m, 1H), 7.28-7.33 (m, 2H), 7.38-7.43 (m, 1H), 7.70-7.85 (m, 2H), 8.07 (d, 1H, *J*=8.1 Hz), 10.05 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ_C 33.0, 52.5, 54.8, 66.6, 74.1, 83.4, 109.8, 121.6, 122.1, 122.5, 124.9, 128.6, 130.0, 133.4, 133.6, 141.8, 146.8, 176.1. Anal. Calcd for $C_{19}H_{16}N_4O_5S$: C, 55.33; H, 3.91; N, 13.58%. Found C, 55.41; H, 3.85; N, 13.51%.

6'-(3-Chlorophenyl)-7'-nitro-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo-[1,2-*c*]thiazol]-2-one (5d)

Obtained as pale yellow solid. Yield: 81%; m.p. = 257 ^{o}C. (300 MHz, DMSO-d_6) δ_H 2.85 -3.14 (m, 2H), 4.02 (d, 1H, *J*=10.5 Hz), 4.15 (d, 1H, *J*=10.5 Hz), 4.24 (d, 1H, *J*=11.6 Hz), 4.57-4.62 (m, 1H), 6.55 (dd, 1H, *J*=11.6, 7.2 Hz), 6.74 (d, 1H, *J*=7.5 Hz), 6.79 (d, 1H, *J*=7.8 Hz), 6.97-7.32 (m, 5H), 7.79 (d, 1H, *J*=7.5 Hz), 9.93 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 33.0, 53.1, 55.0, 67.0, 74.3, 83.8, 110.0, 121.9, 123.3, 125.1, 125.7, 127.0, 127.6, 129.0, 130.1, 133.2, 133.6, 142.2, 176.7. Anal. Calcd for $C_{19}H_{16}ClN_3O_3S$: C, 56.79; H, 4.01; N, 10.46%. Found C, 56.88; H, 4.12; N, 10.38%.

6'-(4-Fluorophenyl)-7'-nitro-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo-[1,2-*c*]thiazol]-2-one (5e)

Obtained as pale yellow solid. Yield: 82%; m.p. = 215 ^{o}C. IR (KBr): 1336, 1547, 1705, 3100 cm^{-1}; (300 MHz, DMSO-d_6) 2.88-3.10 (m, 2H), 3.99 (d, 1H, *J*=10.5 Hz), 4.11 (d, 1H, *J*=10.5 Hz), 4.18 (d, 1H, *J*=11.7 Hz), 4.27-4.56 (m, 1H), 6.51-6.58 (m, 1H), 6.74 (d, 1H, *J*=7.2 Hz), 6.94-7.03 (m, 1H), 7.10-7.16 (m, 2H), 7.28-7.34 (m, 1H), 7.51-7.6 (m, 2H), 7.78 (d, 1H, *J*= 6.9 Hz), 10.00 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 33.2, 53.1, 55.1, 67.2, 74.5, 84.1, 110.0, 114.6, 120.0, 121.9, 125.1, 126.4, 128.9, 131.0, 142.5, 164.3, 177.1. Anal. Calcd for $C_{19}H_{16}FN_3O_3S$: C, 59.21; H, 4.18; N, 10.90%. Found C, 59.11; H, 4.09; N, 11.01%.

Spectral Details

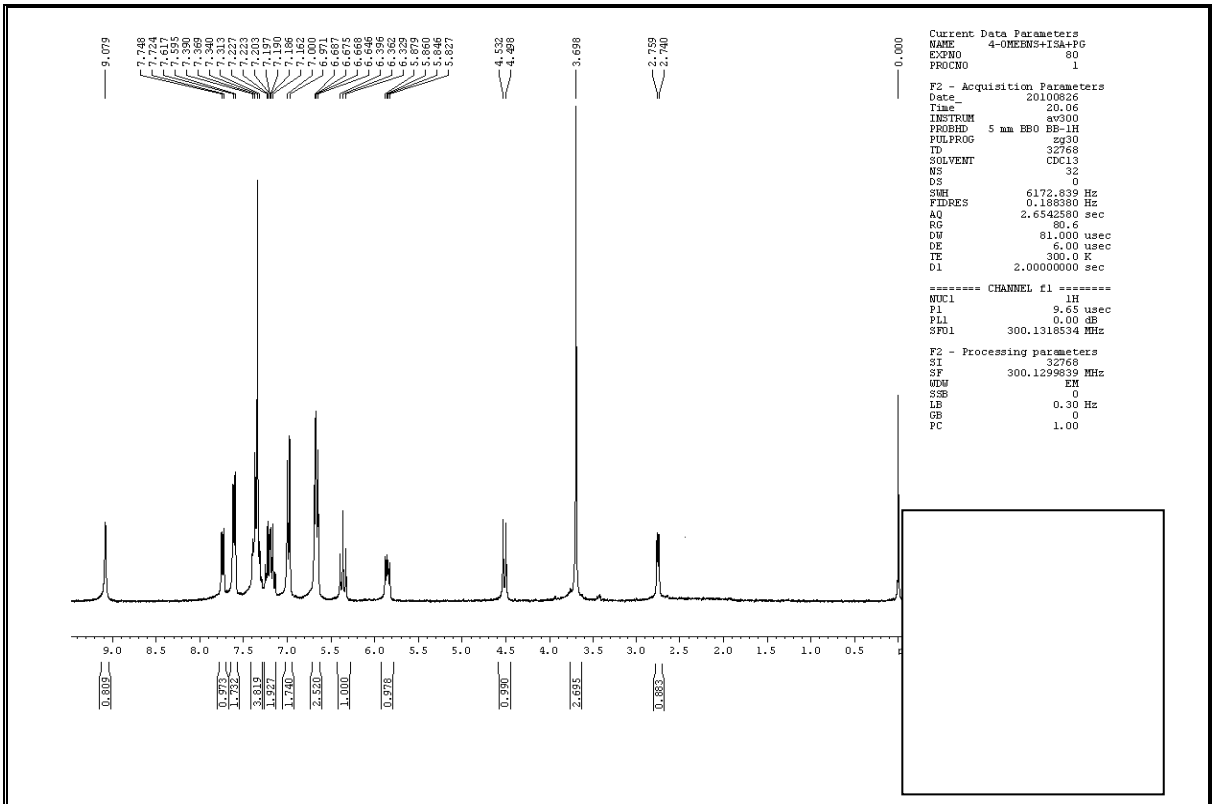


Figure 6.1 ^{1}H NMR Spectrum of **3a**

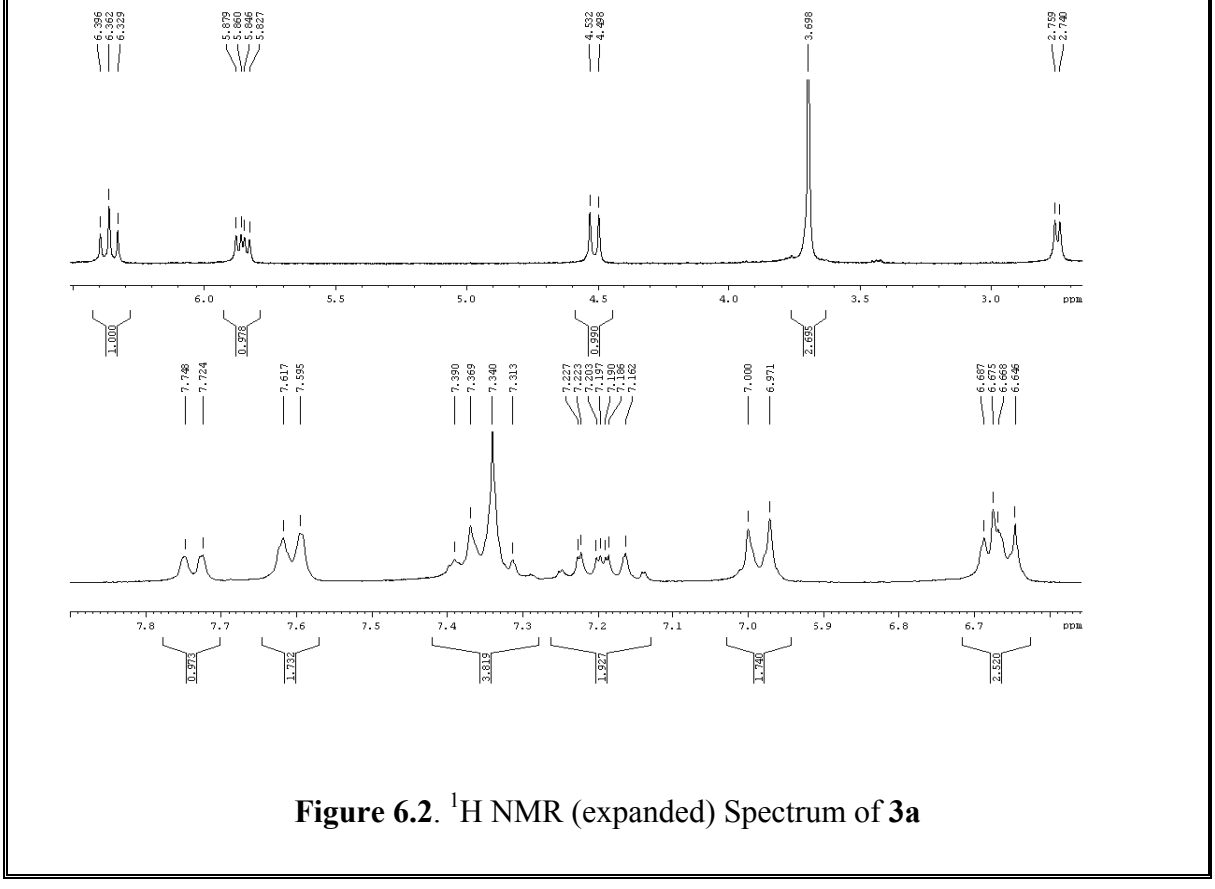


Figure 6.2. ^{1}H NMR (expanded) Spectrum of **3a**

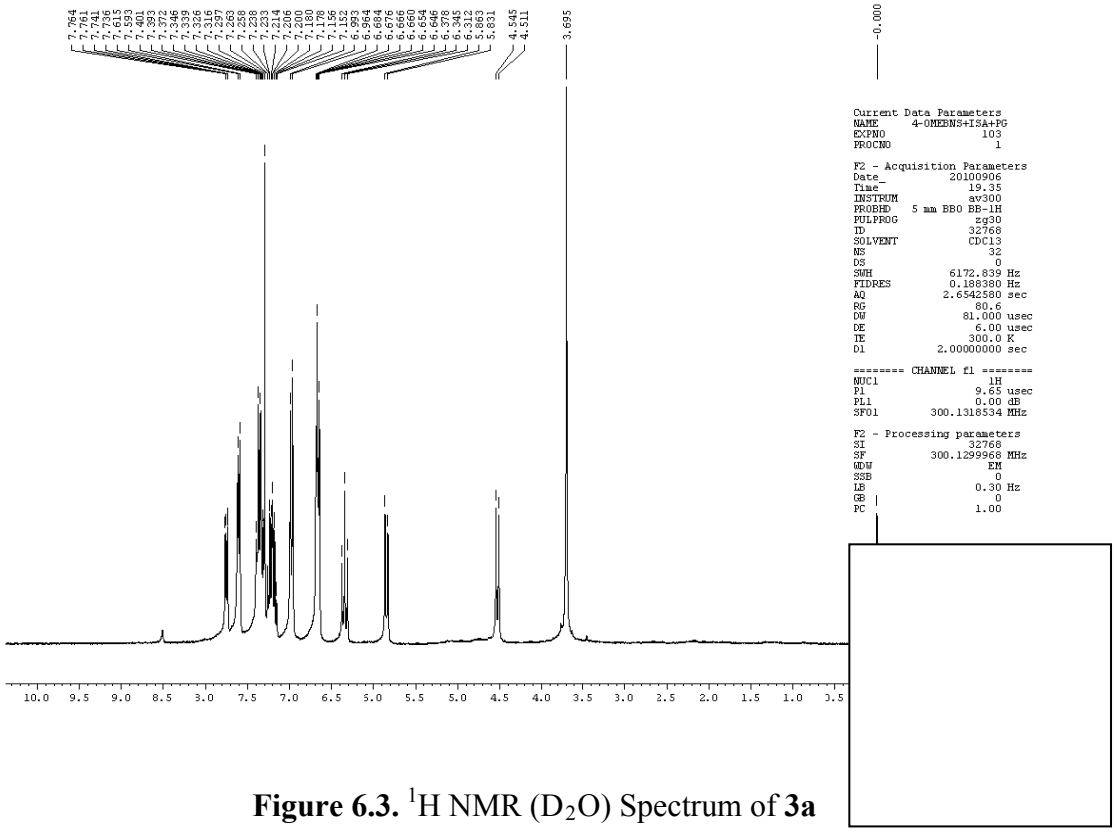


Figure 6.3. ^{1}H NMR (D_2O) Spectrum of **3a**

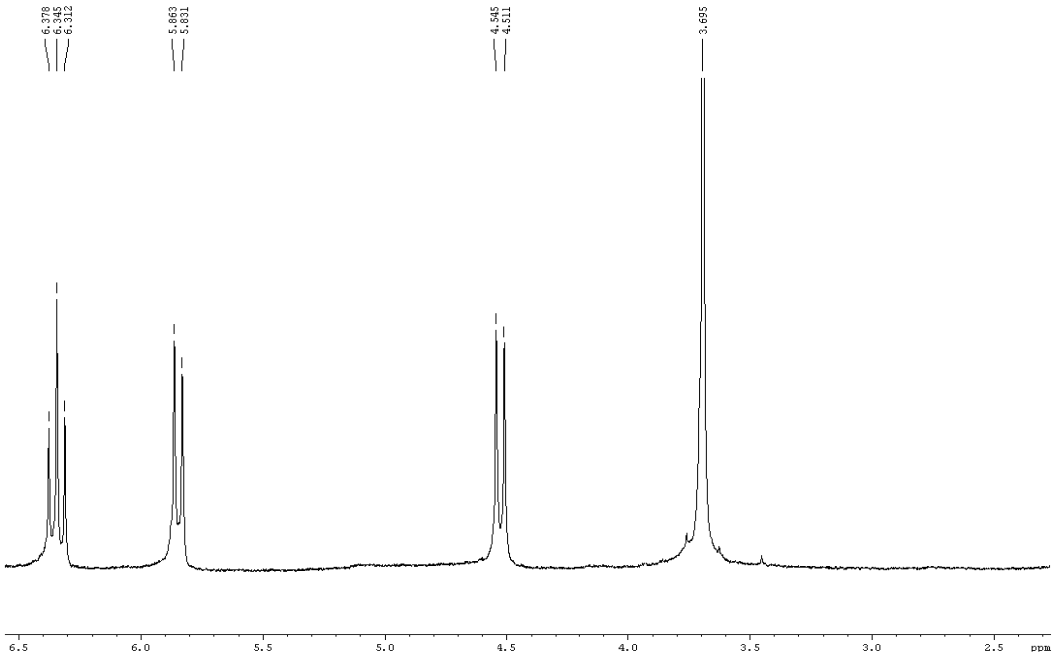


Figure 6.4. ^{1}H NMR (D_2O) Spectrum of **3a** (expanded)

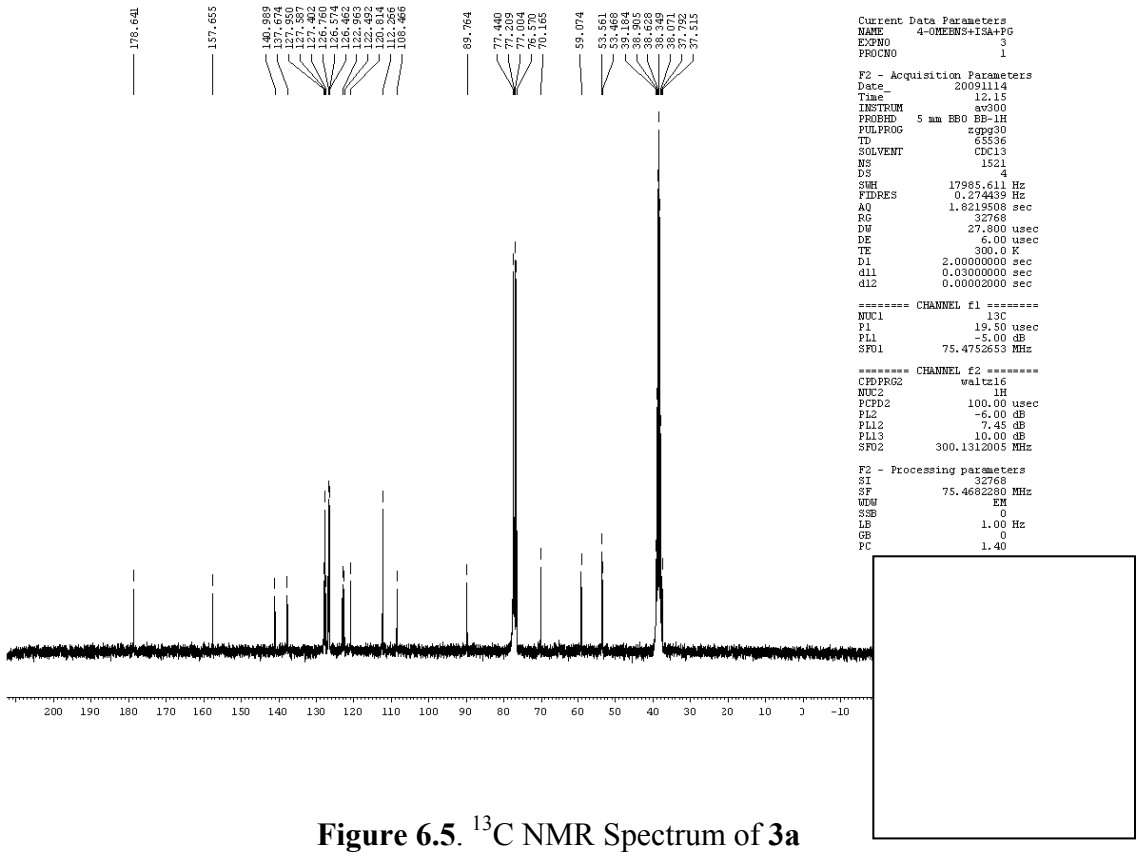


Figure 6.5. ^{13}C NMR Spectrum of **3a**

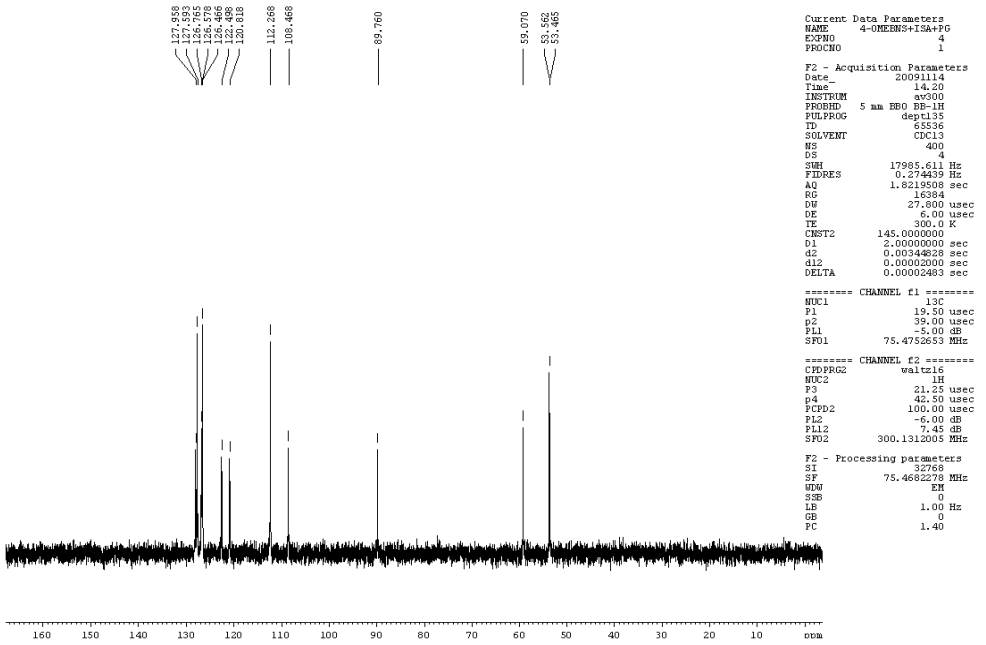


Figure 6.6. DEPT-135 Spectrum of **3a**

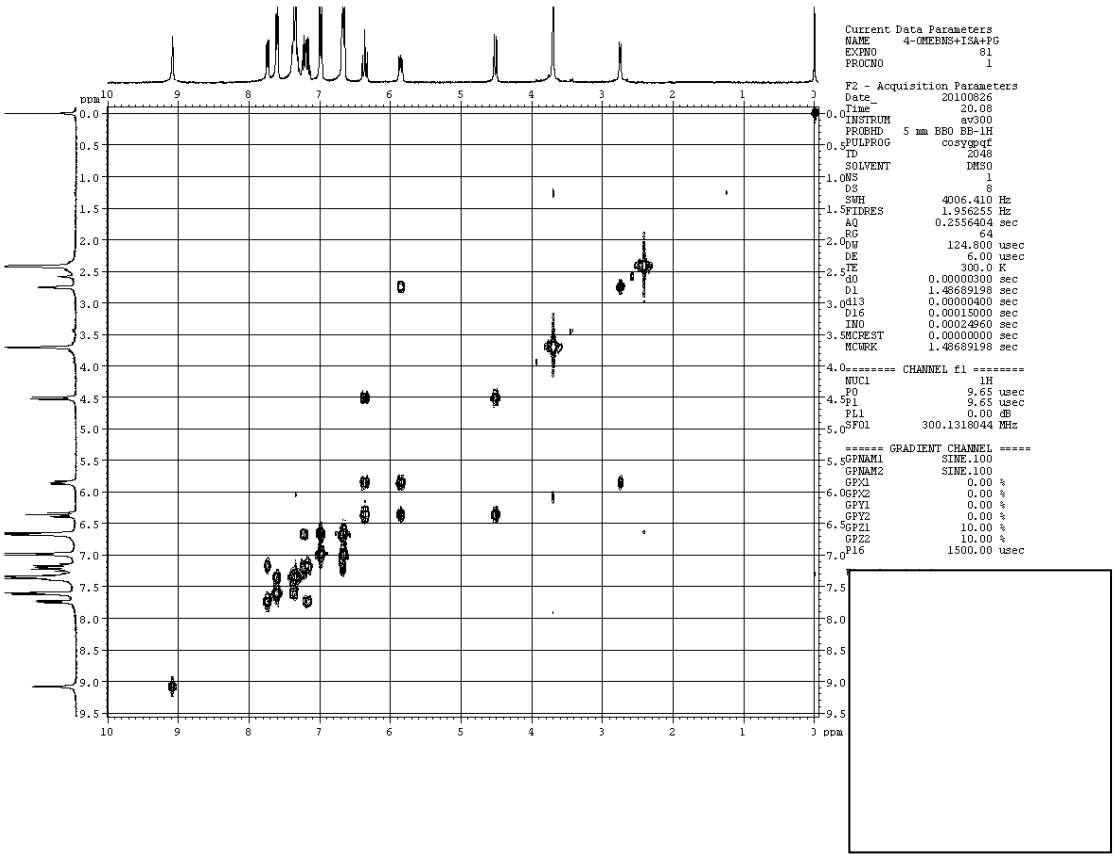


Figure 6.7. H,H-COSY Spectrum of **3a**

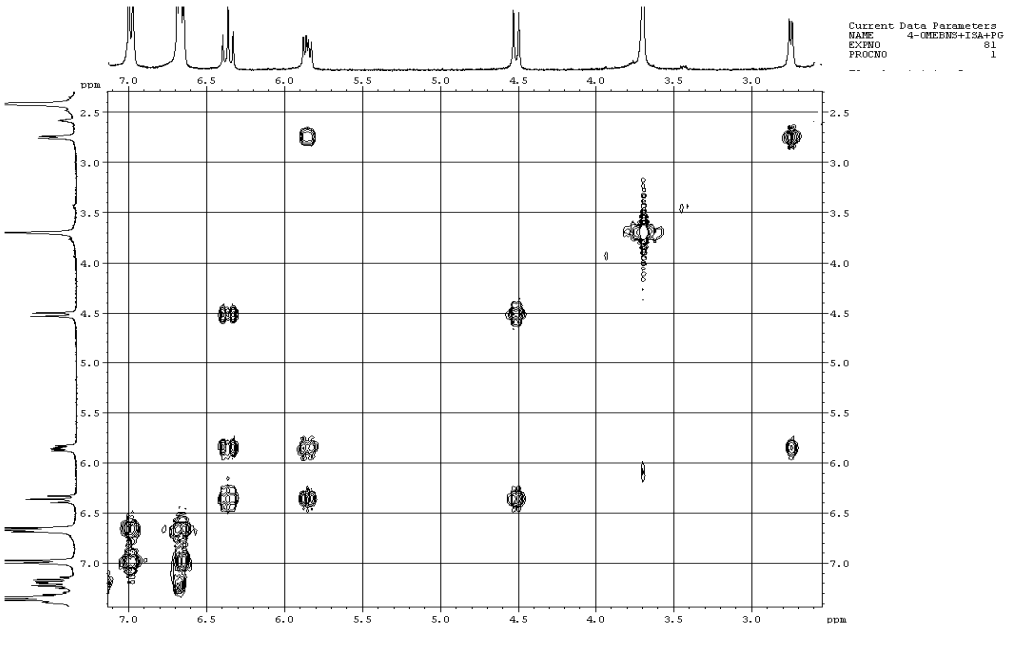


Figure 6.8. H,H-COSY Spectrum of **3a** (expanded)

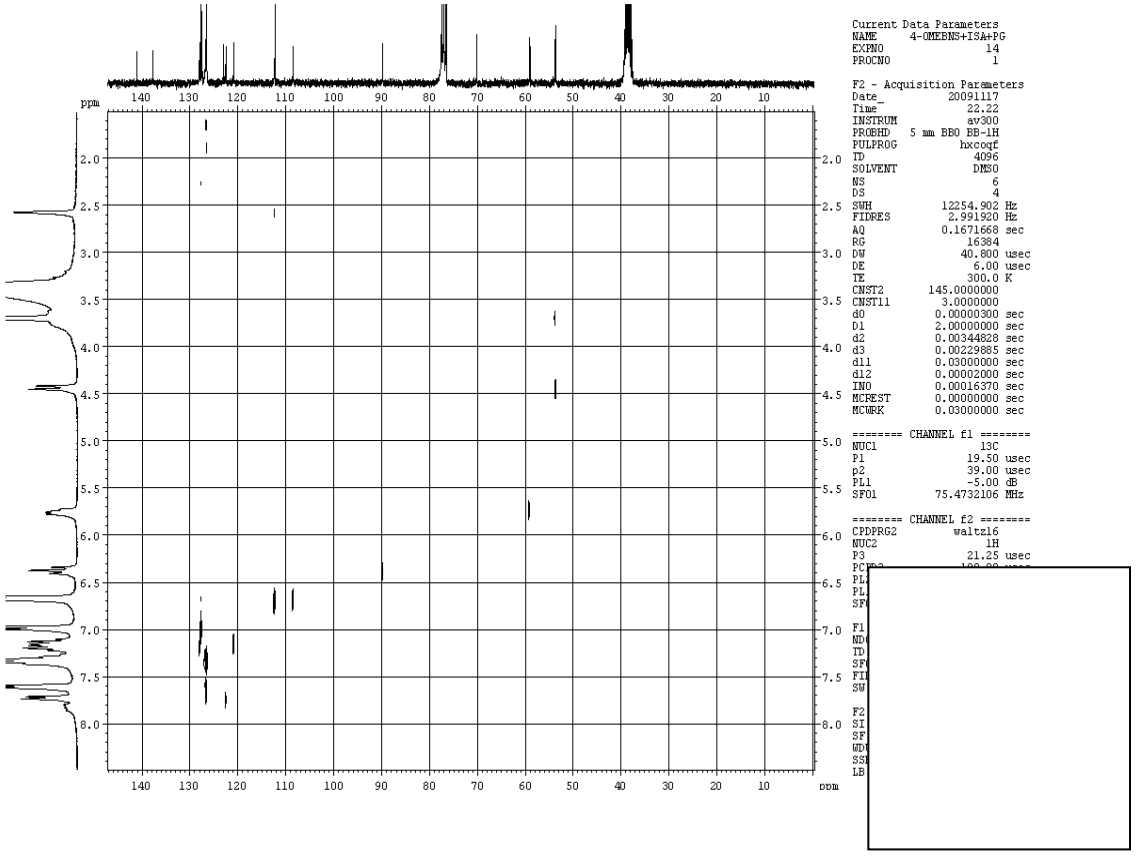


Figure 6.9. C,H-COSY Spectrum of **3a**

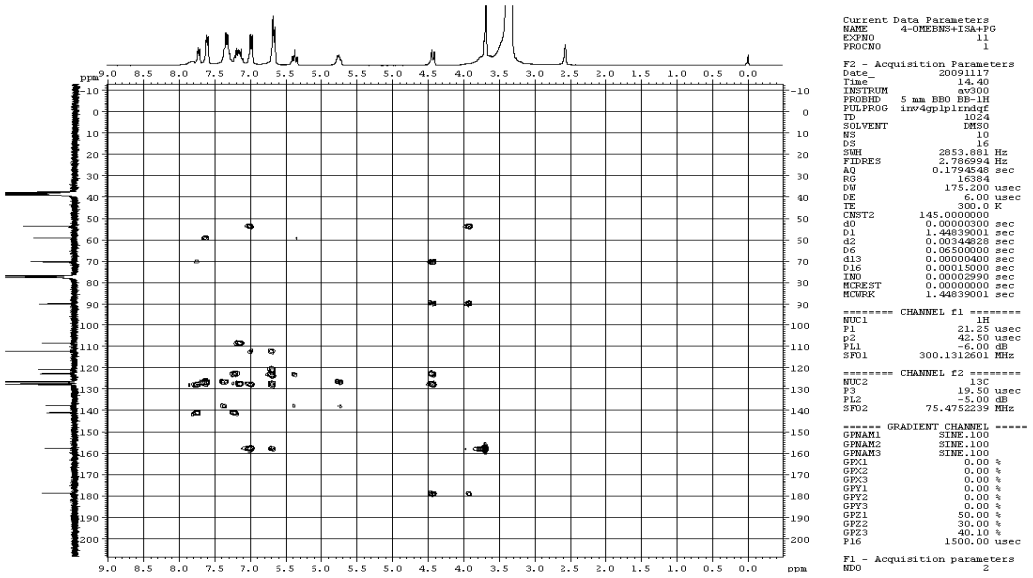


Figure 6.10. HMBC Spectrum of **3a**

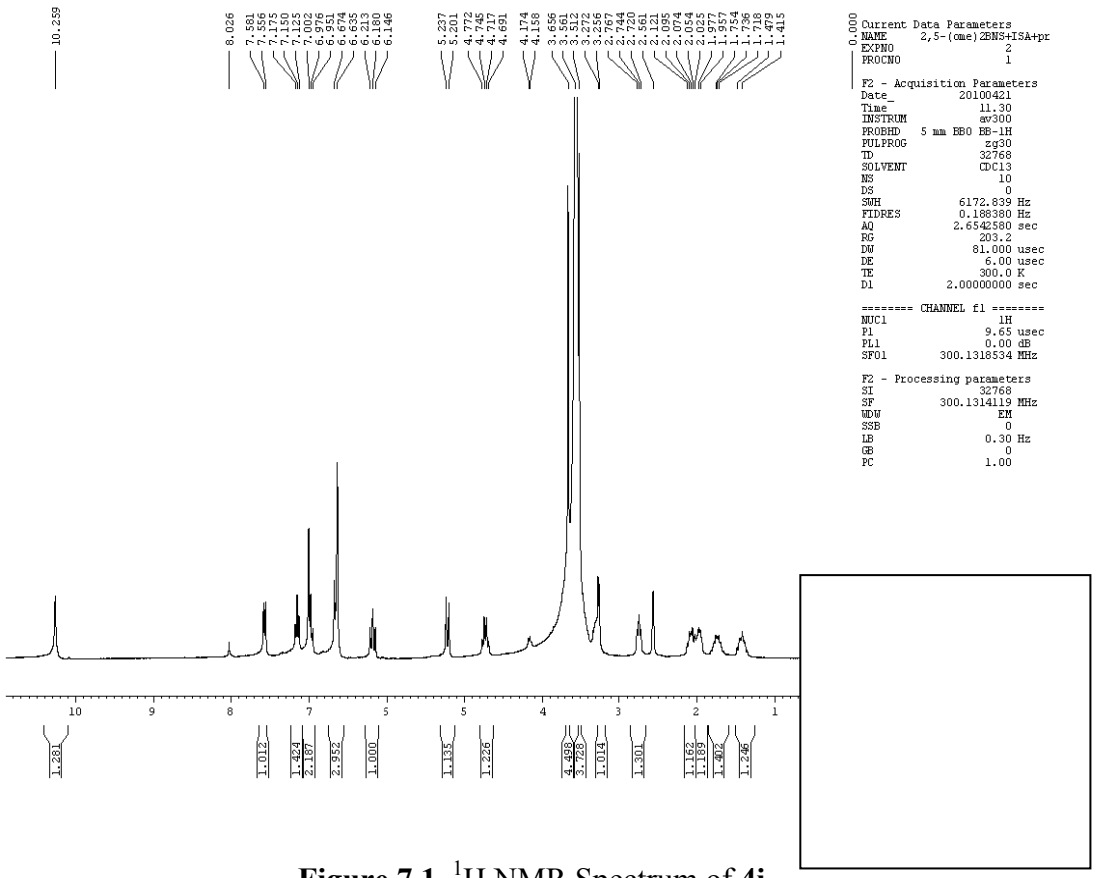


Figure 7.1. ^{1}H NMR Spectrum of **4i**

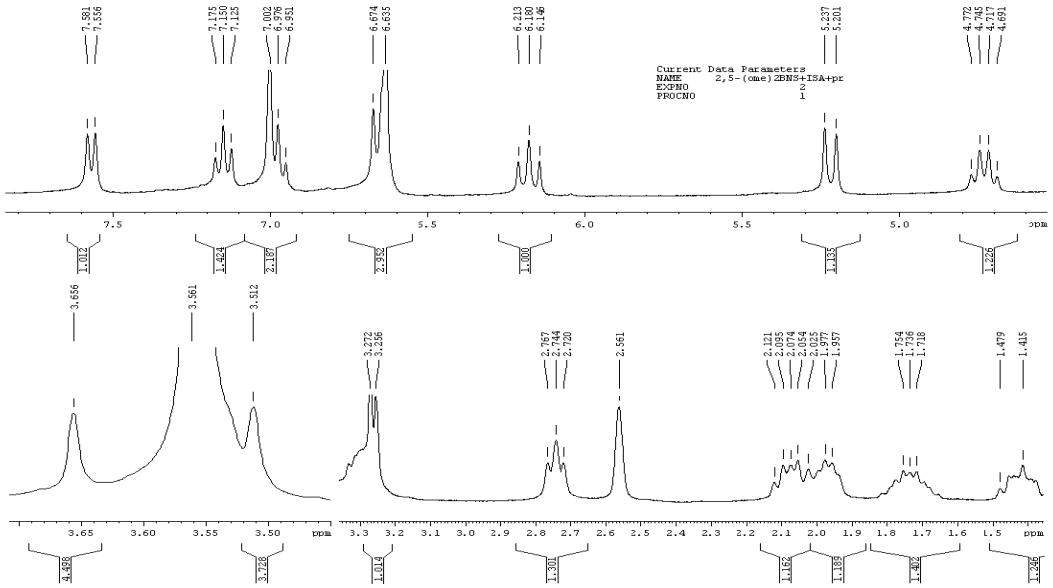


Figure 7.2. ^{1}H NMR Spectrum of **4i** (expanded)

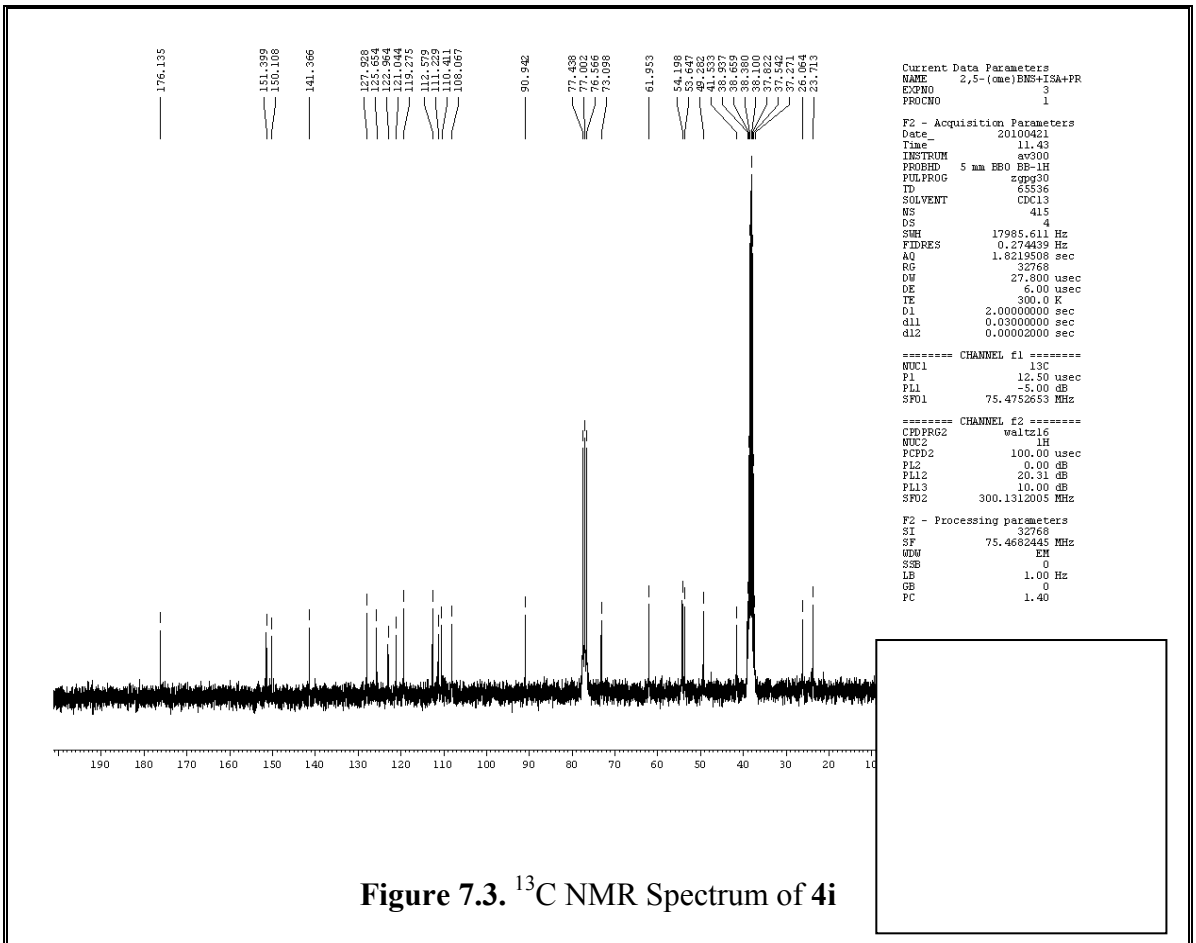


Figure 7.3. ^{13}C NMR Spectrum of **4i**

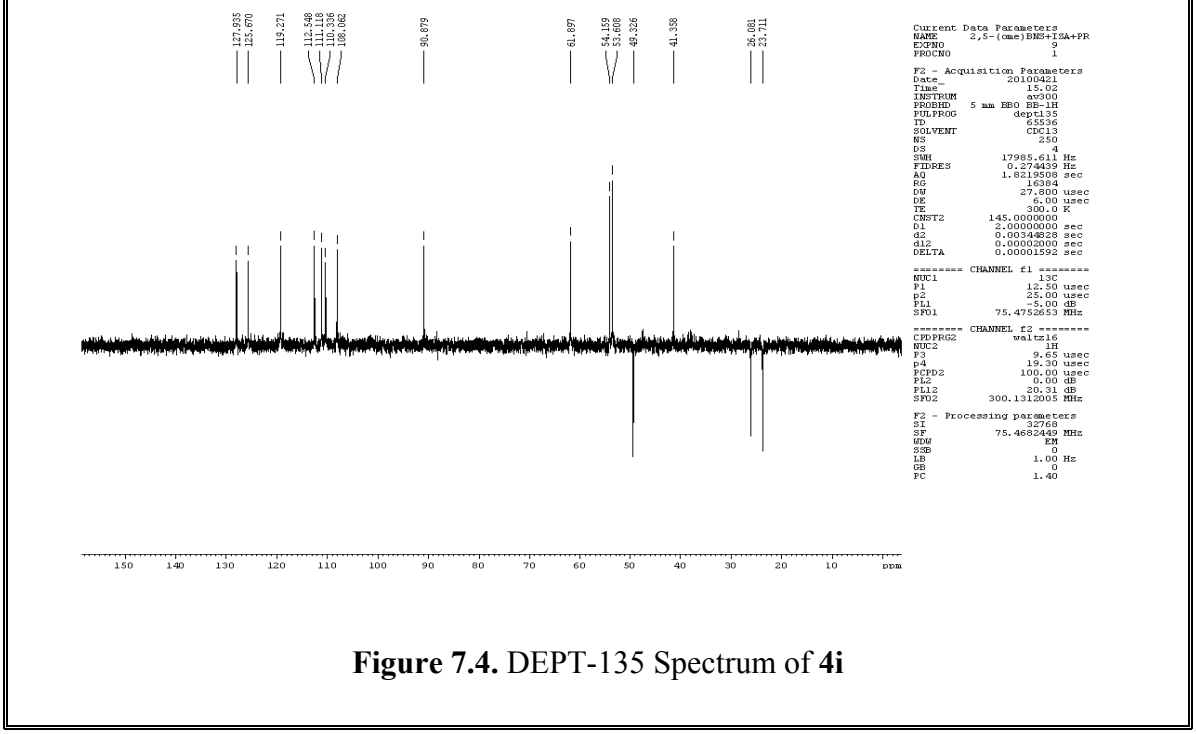
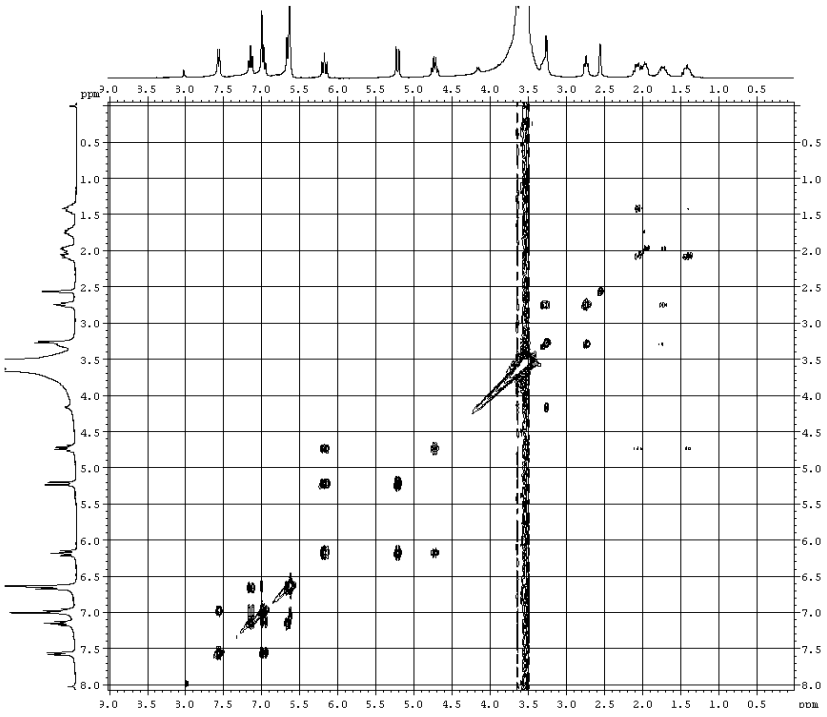


Figure 7.4. DEPT-135 Spectrum of **4i**



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DE                6.00 usec
TE               300.0 K
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D16           0.00015000 sec
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======== CHANNEL f1 ========
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PL1               0.00 dB
SFO1       300.1313506 MHz

====== GRADIENT CHANNEL =====
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GPNAM2          SINE.100
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GPX2              0.00 %
GPY1              0.00 %
GPY2              0.00 %
GPZ1             10.00 %
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F1 - Acquisition parameters
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Figure 7.5. H,H-COSY Spectrum of **4i**

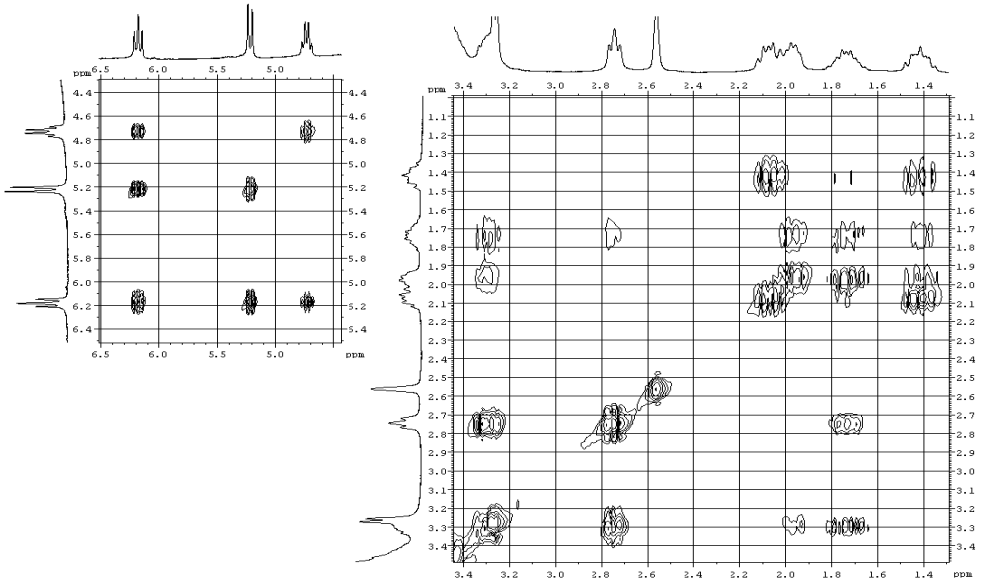
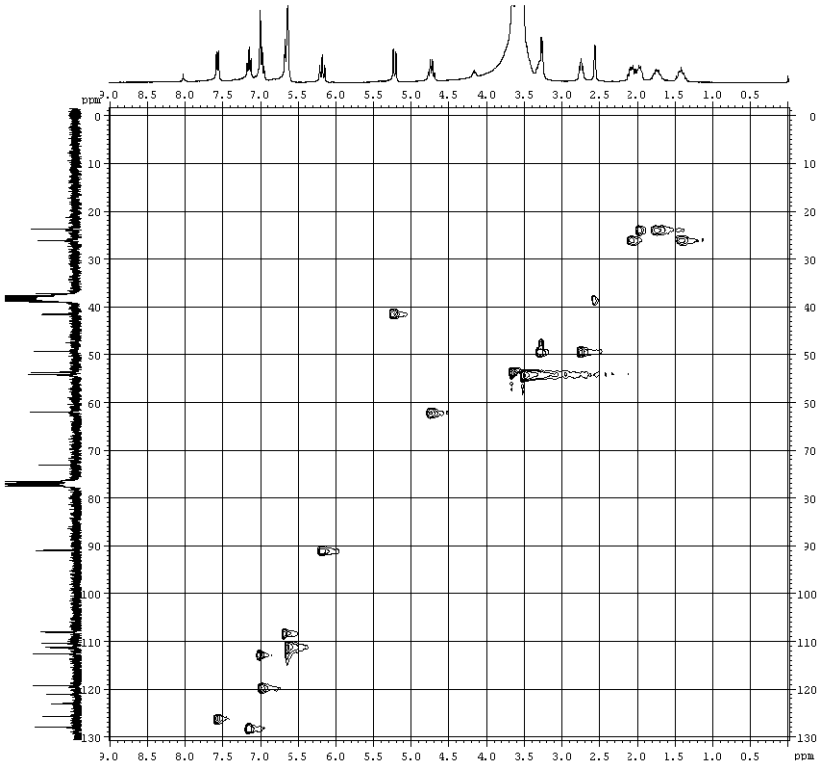


Figure 7.6. H,H-COSY Spectrum of **4i** (expanded)



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DS                      16
SWH                4006.410 Hz
FIDRES             3.912510 Hz
AQ                 0.1278452 sec
RG                   18390.4
DW                  124.800 usec
DE                    6.00 usec
TE                   300.0 K
CNST2             145.0000000
d0                 0.00000300 sec
D1                 2.00000000 sec
d4                 0.00172414 sec
d11                0.03000000 sec
d13                0.00000400 sec
D16                0.00015000 sec
DELTA              0.00167530 sec
DELTA1             0.00021614 sec
IN0                0.00004000 sec
MCREST             0.00000000 sec
MCWRK              0.40000001 sec
ST1CNT                  128

======== CHANNEL f1 ========
NUC1                      1H
P1                     9.65 usec
p2                    19.30 usec
P28                    0.50 usec
PL1                    0.00 dB
SFO1          300.1318044 MHz

======== CHANNEL f2 ========
CPDPRG2                garp
NUC2                    13C
P3                    12.50 usec
p4                    25.00 usec
```

Figure 7.7. C,H-COSY Spectrum of **4i**

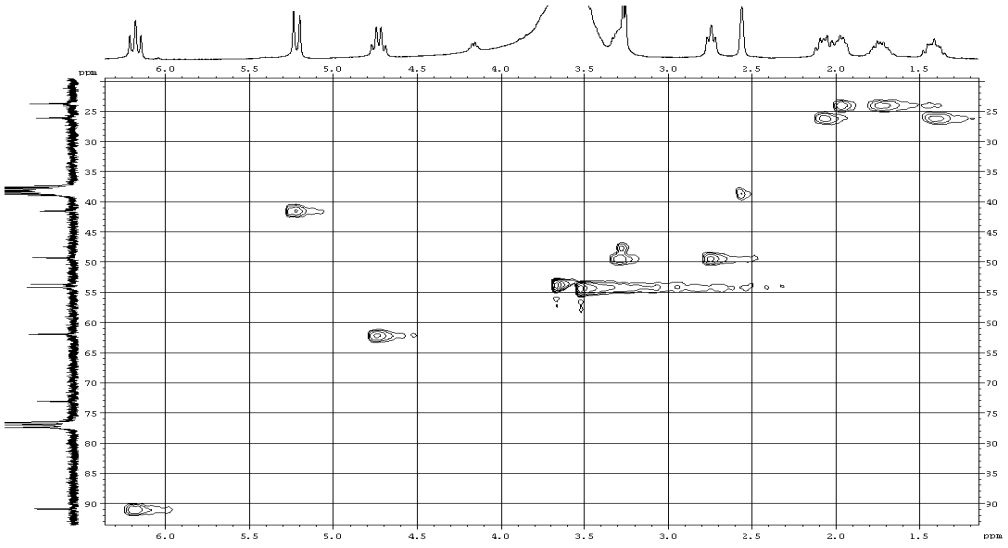

Figure 7.8. C,H-COSY Spectrum of **4i** (expanded)

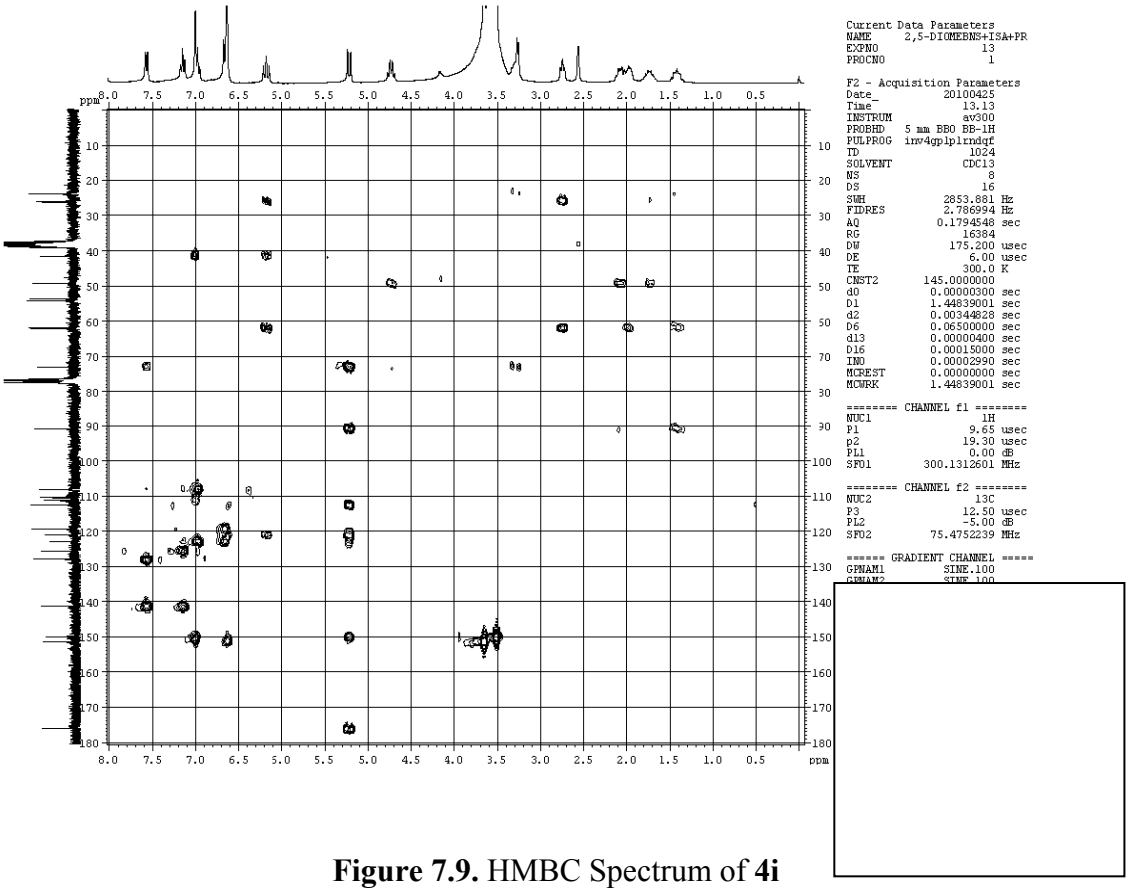

Figure 7.9. HMBC Spectrum of **4i**

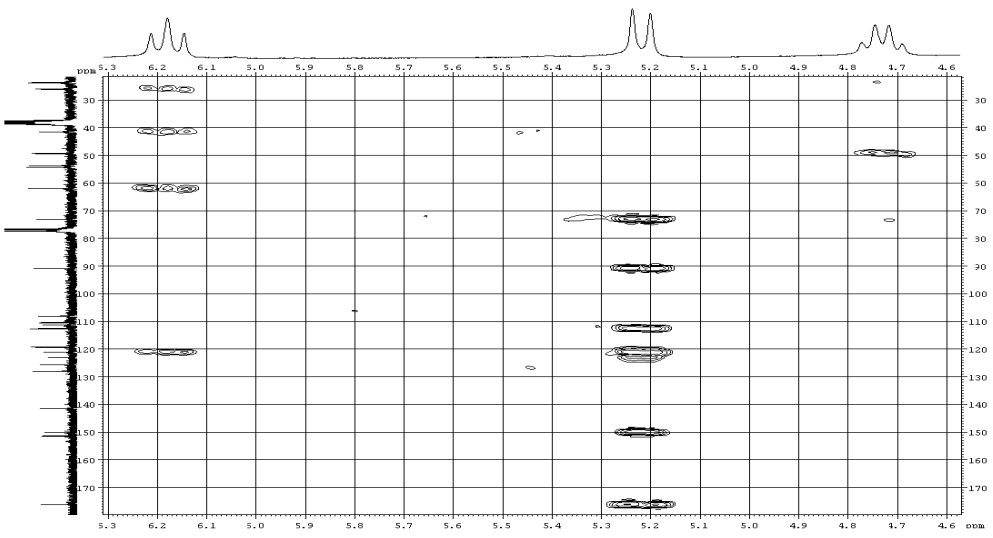

Figure 7.10. HMBC Spectrum of **4i** (expanded)

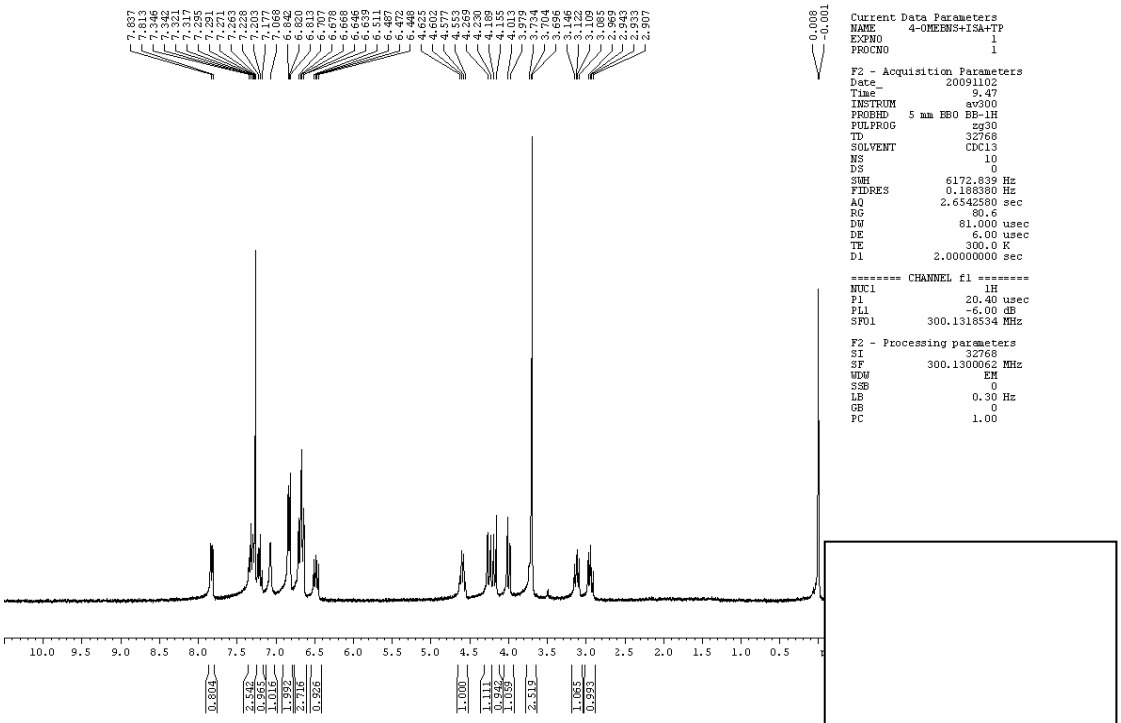

Figure 8.1. ^{1}H NMR Spectrum of **5a**

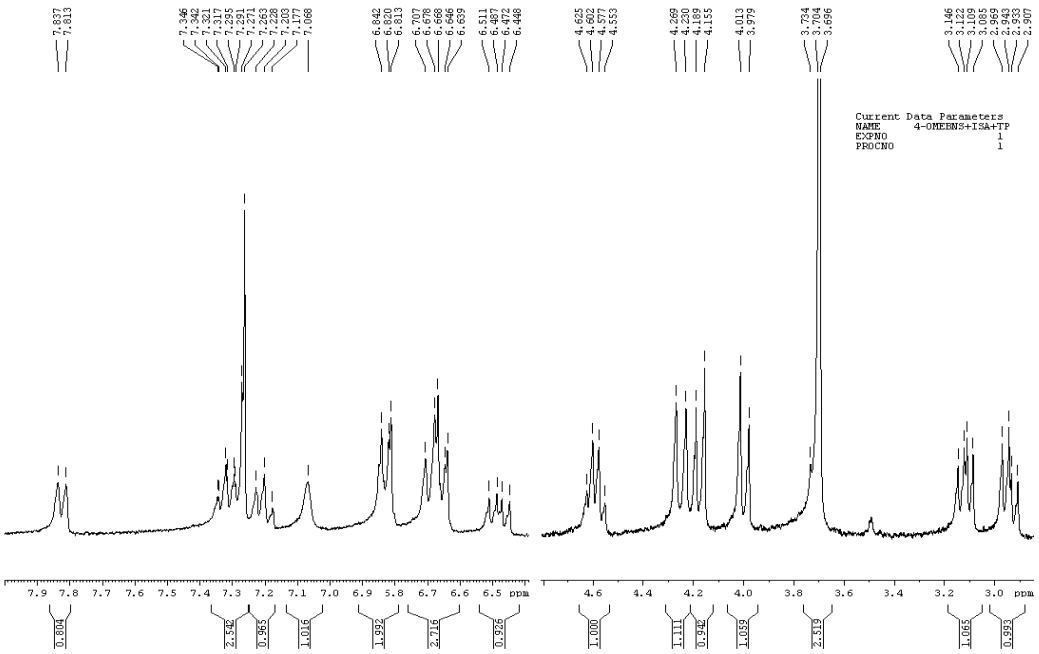

Figure 8.2. ^{1}H NMR Spectrum of **5a** (expanded)

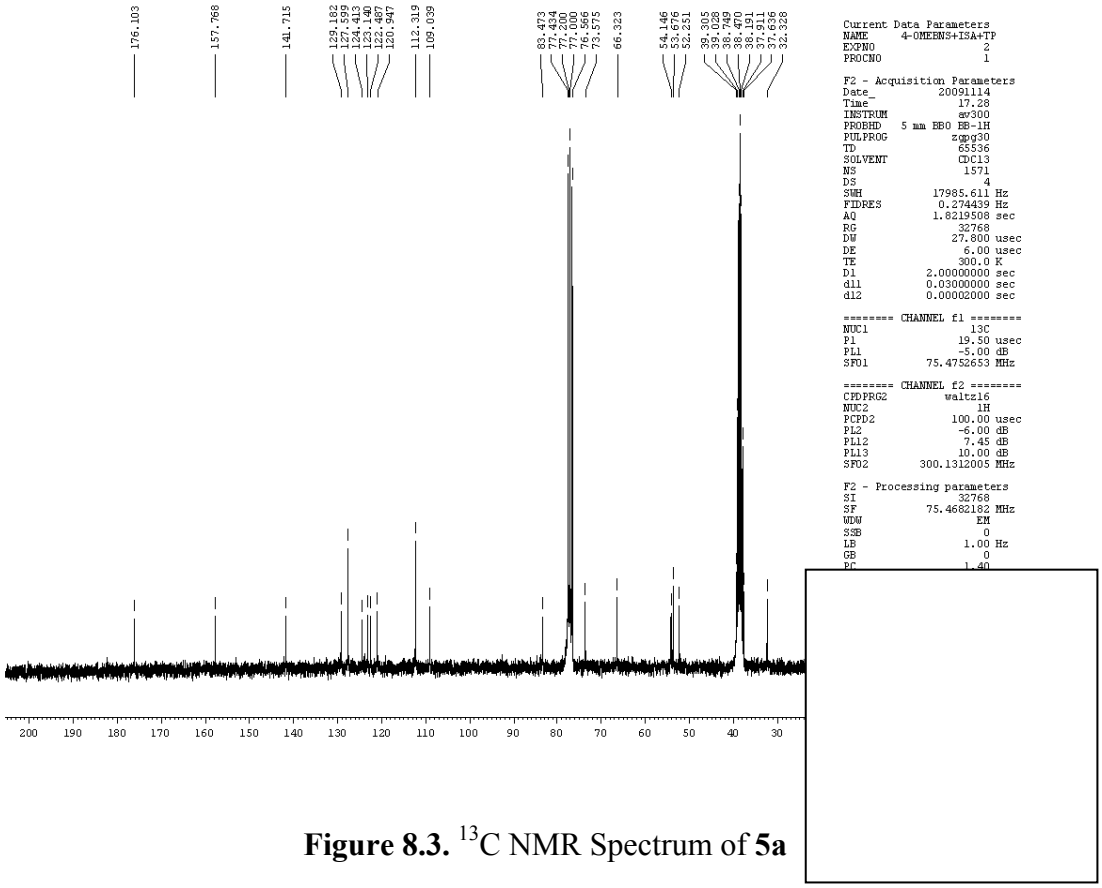

Figure 8.3. ^{13}C NMR Spectrum of **5a**

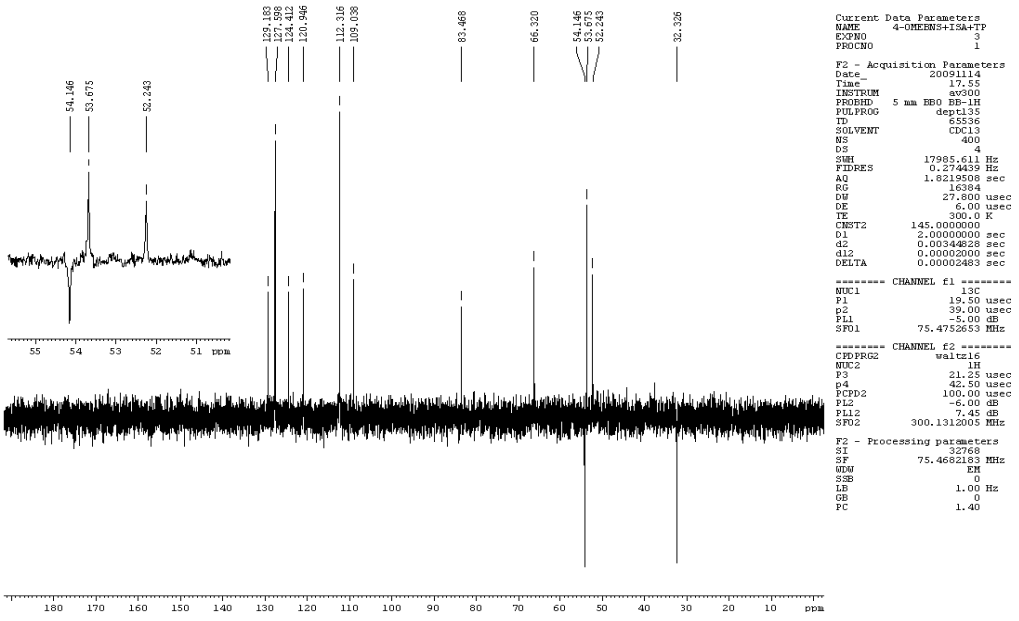

Figure 8.4. DEPT-135 Spectrum of **5a**

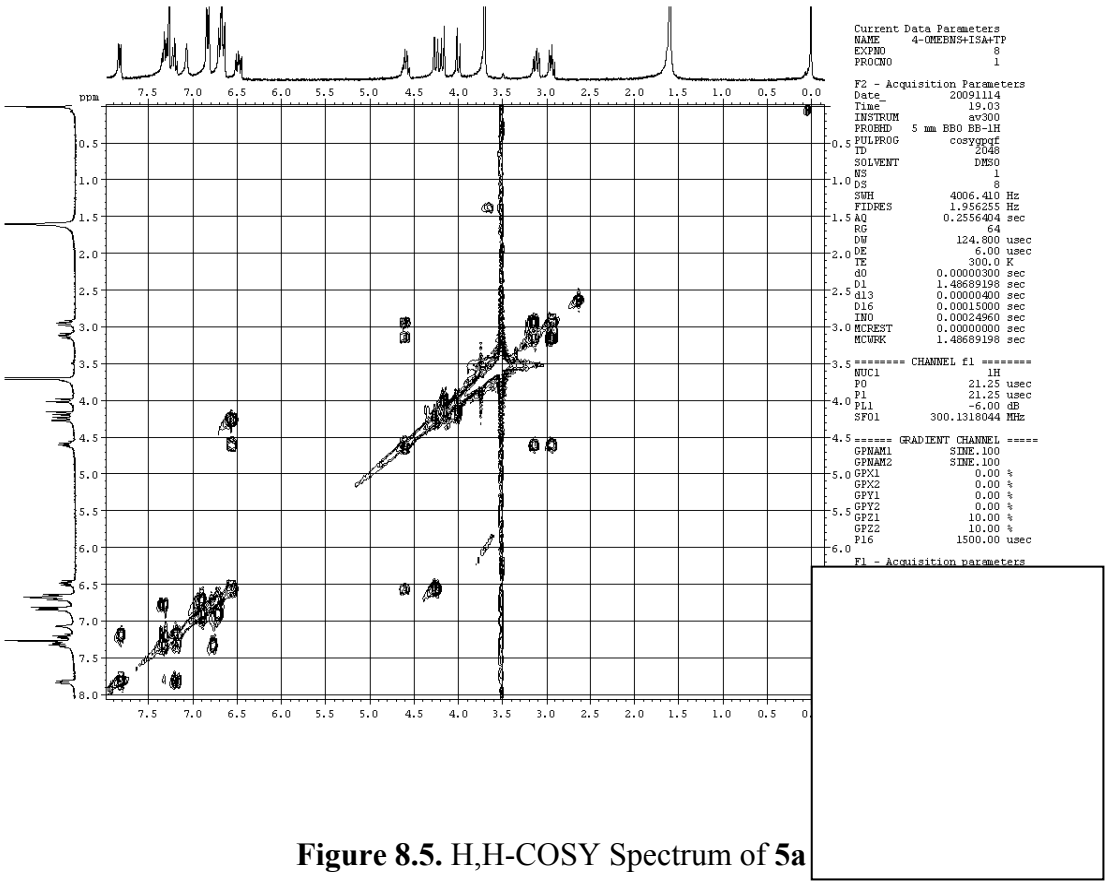

Figure 8.5. H,H-COSY Spectrum of **5a**

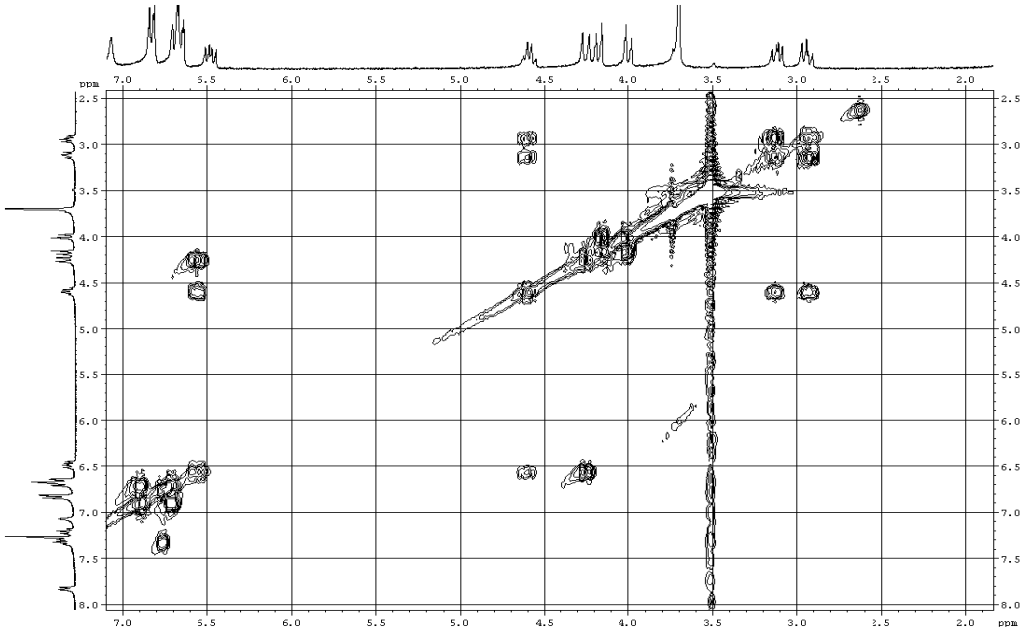

Figure 8.6. H,H-COSY Spectrum of **5a** (expanded)

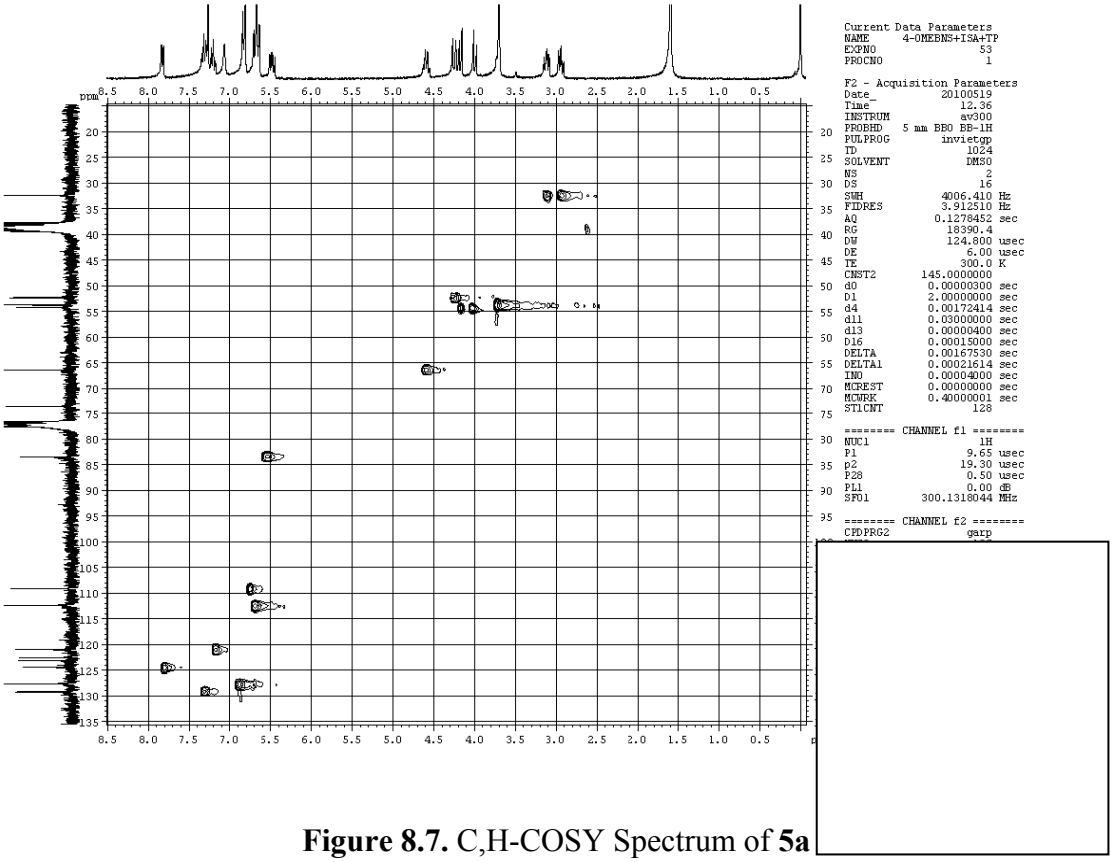

Figure 8.7. C,H-COSY Spectrum of **5a**

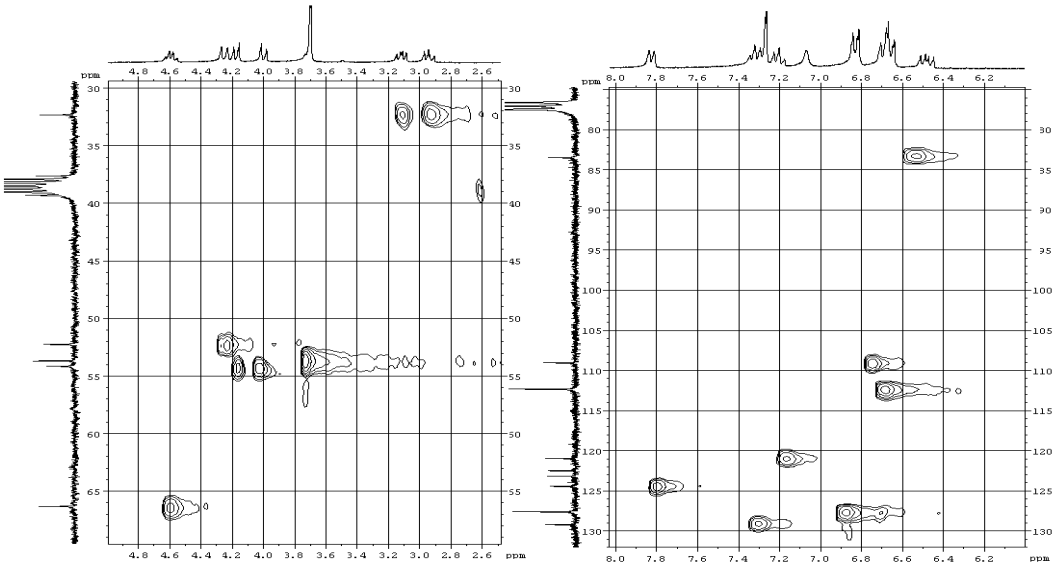

Figure 8.8. C,H-COSY Spectrum of **5a** (expanded)

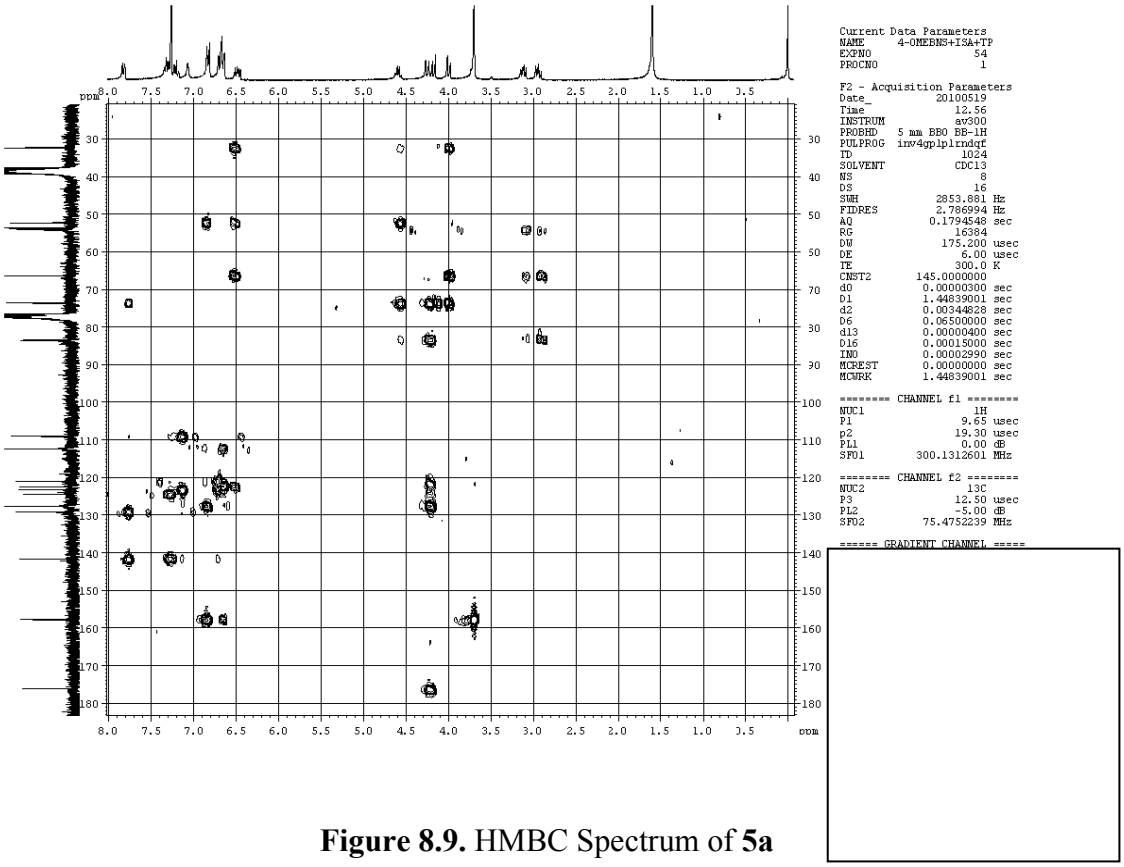

Figure 8.9. HMBC Spectrum of **5a**

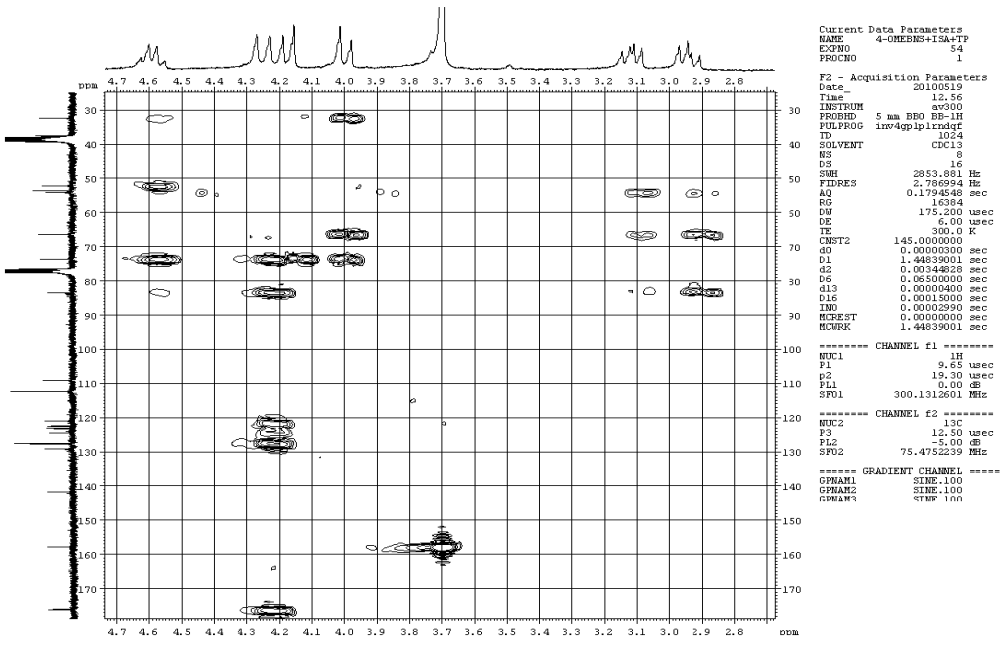

Figure 8.10. HMBC Spectrum of **5a** (expanded)

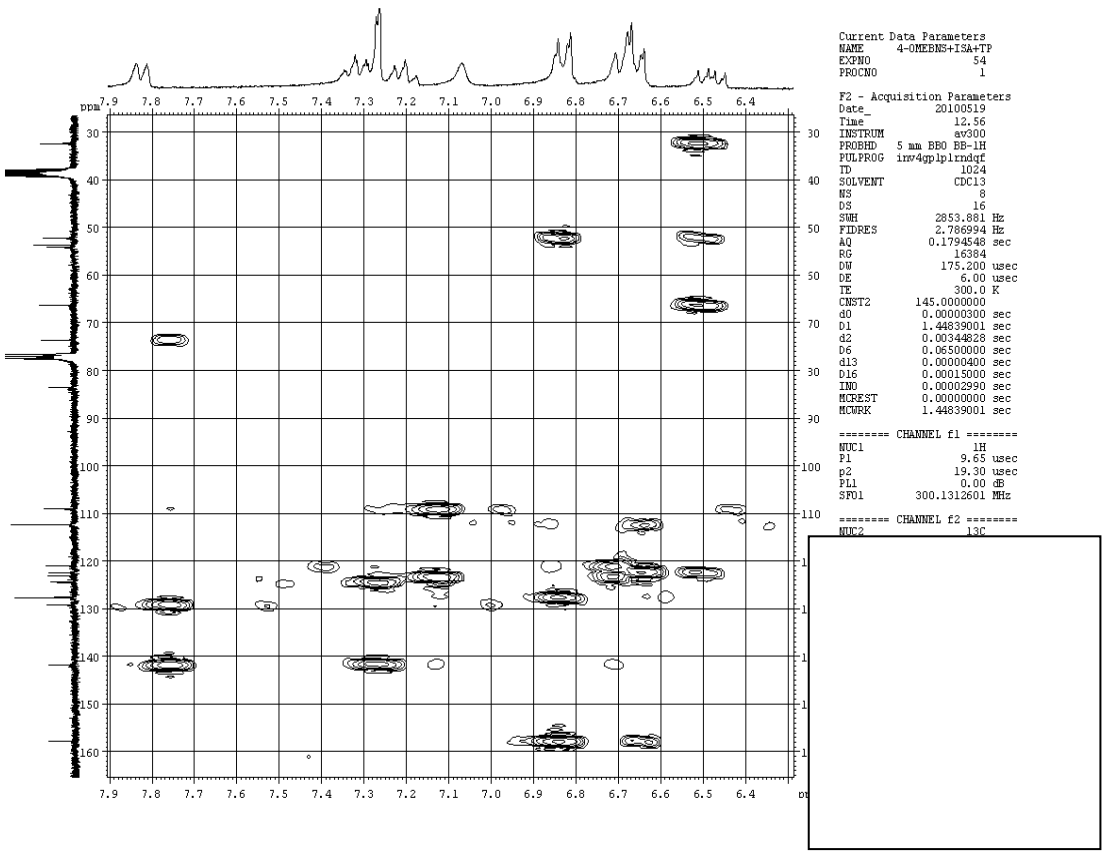

Figure 8.11. HMBC Spectrum of **5a** (expanded)