Electronic Supplementary Material (ESI) for RSC Advances.

Synthesis of Novel [3,1]-Benzothiazepines and [3,1]-Benzoxazepines Derivatives with Antitumoral Activity

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Contents

1. General Remarks

1.1. Material

All reagents and solvents used were previously purified and dried in agreement with the literature.[1] Isothiocyanates and isocyanates were purchased from Aldrich Chemical Co. All other commercially available reagents were used as received. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel 60 plates (F_{254}) using UV light as visualizing agents. Column chromatography purification was performed using Silica Gel 60 (230-400 mesh). All compounds purified by chromatography were sufficiently pure for use in further experiments.

1.2. Instrumentation

All spectra were performed at 300 and 75 MHz to ^{1}H and ^{13}C nuclei, respectively using a 5 mm PFG probe. The samples were solubilized in DMSO-d_6 or $CDCl_3$ and the residual signal of solvent was used as reference to chemical shift in ^{1}H and ^{13}C NMR spectrum. Pulse sequence *g*HMQC was optimized to $^{1}J_{C,H}$ equal to 140 Hz, acquisition time equal to 0.228 s, relaxation delay equal to 1.00 s and 4 transients x 512 increments were used. Pulse sequence *g*HMBC was optimized to $^{3}J_{C,H}$ equal to 8.0 Hz, acquisition time equal to 0.228 s, relaxation delay equal to 1.00 s and 8 transients x 400 increments were used. Low resolution mass spectra (70 eV) used helium 4.5 as a carrier gas and a DB-5 column (30 m x 0.25μm). The melting points (mp) are not corrected.

[1] Perrin, D. D.; Armarego, W. L. F. *In Purification of Laboratory Chemicals*; Pergamon: Oxford, **1980**.

2. Additional Experimental Procedures

2.1 General procedure for the preparation of *N*-allyl-arylamines (2a-d) A 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged with Na_2CO_3 (1.4g, 10 mmol) followed by DMF (250 mL) and the appropriate arylamine (1.5 equiv, 15 mmol). Allyl bromide (1.20 g, 1.0 equiv, 10 mmol) was then added using an addition funnel over an 8h period at 0°C. The reaction mixture was stirred for additional 16 h at room temperature and then filtered. The solution was diluted with CH_2Cl_2 (2 x 50 mL) and washed with water. The combined organic phases were dried over $MgSO_4$, filtered, and solvents were removed under reduced pressure followed by purification by a flash column chromatography [hexanes:EtOAc (60:1)].

***N*-allyl-aniline (2a):** Isolated as a yellow oil; obtained 1.0 g (77%); IR (thin film) ν_{max} 3413, 1643, 1603, 1506, 1316, 1262, 994, 920, 750, 693, 509 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (br s, 1H, -NH), 3.83 (dt, *J* =5.4, 1.5 Hz, 2H, N-CH_2), 5.24 (dq, *J* =10.5, 1.5 Hz, 1H, =CH_AH), 5.36 (dq, *J* =16.8, 1.5 Hz, 1H, =CHH_B), 6.09-5.96 (m, 1H, -CH=), 6.70 (dd, *J* =8.2, 1.0 Hz, 2H, H-2, H-6), 6.79 (t, *J* =7.5 Hz, 1H, H-4), 7.23-7.17 (m, 2H, H-3, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.4 (N-CH_2), 112.9 (2C, C-2, C-6), 116.1 (=CH_2), 117.4 (C-4), 129.1 (2C, C-3, C-5), 135.3 (-CH=), 147.9 (C-1); MS(EI-70 eV) *m/z* (%): 133 ($M^{\bullet+}$, 82) 106 (100), 104 (29), 92 (10), 77 (76), 65 (92).

***N*-allyl-4-choro-aniline (2b):** Isolated as a yellow oil; obtained 1.22 g (73%); IR (thin film) ν_{max} 3421, 1645, 1600, 1502, 1316, 994, 922, 815, 506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (dt, *J* =5.4, 1.5 Hz, 2H, N-CH_2), 5.20 (dq, *J* =10.2, 1.5 Hz, 1H, =CH_AH), 5.29 (dq, *J* =17.4, 1.5 Hz, 1H, =CHH_B), 6.01-5.88 (m, 1H, -CH=), 6.57 (d, *J* =9.0 Hz, 2H, H-2, H-6), 7.14 (d, *J* =9.0 Hz, 1H, H-3,H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.7 (N-CH_2), 114.2 (2C, C-2, C-6), 116.6 (=CH_2), 122.3 (C-4), 134.7 (-CH=), 129.0 (2C, C-3, C-5), 146.2 (C-1); MS(EI-70 eV) *m/z* (%): 167 ($M^{\bullet+}$, ^{35}Cl, 92) 140 (100), 138 (37), 126 (17), 111 (21), 99 (31).

***N*-allyl-4-fluoro-aniline (2c):** Isolated as a yellow oil; obtained 1.14 g (75%); IR (thin film) ν_{max} 3423, 1602, 1514, 1219, 922, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (br s, 1H, -NH), 3.74 (d, *J* =5.2 Hz, 2H, N-CH_2), 5.19 (dd, *J* =10.4, 1.6 Hz, 1H, =CH_AH), 5.30 (dd, *J* =17.2, 1.6 Hz, 1H, =CHH_B), 6.10-5.88 (m, 1H, -CH=), 6.72-6.50 (m, 2H, H-2, H-6), 7.09-6.83 (m, 2H, H-3, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.1 (N-CH_2), 113.7 (d, *J* =6.9 Hz, 2C, C-2, C-6), 115.5 (d, *J* =22.5 Hz, 2C, C-3, C-5), 116.2 (=CH_2), 135.3 (-CH=), 144.4 (C-1), 155.8 (d, *J* =233.9, C-4); MS(EI-70 eV) *m/z* (%): 151 ($M^{\bullet+}$, 85) 124 (100), 122 (24), 110 (20), 95 (29), 83 (38).

***N*-allyl-naphthylamine (2d):** Isolated as a red oil; obtained 1.63 g (89%); IR (thin film) ν_{max} 3440, 1643, 1582, 1525, 1480, 1407, 993, 920, 769, 570, 421 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 (dt, *J* =5.7, 1.5 Hz, 2H, N-CH_2-), 5.27 (dd, *J* =10.5, 1.8 Hz, 1H, =CH_AH), 5.40 (dd, *J* =16.8, 1.8 Hz, 1H, =CHH_B), 6.18-6.05 (m, 1H, -CH=), 6.66 (d, *J* =7.5 Hz, 1H, H-2), 7.29 (d, *J* =7.8 Hz, 1H, H-4), 7.38 (dd, *J* =7.8, 7.5 Hz, 1H, H-3),7.51-7.44 (m, 2H, H-6, H-7), 7.86-7.81 (m, 2H, H-5, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.8 (N-CH_2), 104.9 (C-2), 116.7 (=CH_2), 117.6 (C-4), 119.8 (C-8), 123.4 (C-8a), 124.7 (C-7), 125.7 (C-6), 126.5 (C-3), 128.7 (C-5),

134.2 (C-4a), 135.0 (-CH=), 142.9 (C-1); MS(EI-70 eV) *m/z* (%): 183 ($M^{\bullet+}$, 94), 156 (12), 154 (14),142 (33),127 (22), 115 (100).

2.2 General procedure for the preparation of 2-allyl-arylamines (3a-d) A 25 mL round-bottomed flask equipped with a reflux condenser was charged with the appropriate *N*-allyl-arylamine (**2a-d**) (1.0 equiv, 1.0 mmol) and BF_3•OEt_2 (212 mg, 1.5 equiv, 1.5 mmol)**.** The reaction mixture was heated at 140 ºC (**3a-c**) or 114 ºC (**3d**) for 12 hours, then treated with a saturated aqueous solution of Na_2CO_3 (10 mL) and extracted with CH_2Cl_2 (2x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered, and solvents were removed under reduced pressure followed by purification by a flash column chromatography [hexanes:EtOAc (40:1)].

2-Allyl-aniline (3a): Isolated as a yellow oil; obtained 0.83 g (62%); IR (thin film) ν_{max} 3448, 3369, 1622, 1494, 1458, 916, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (d, *J* =6.3 Hz, 2H, -CH_2-), 3.71 (br s, 2H, -NH_2), 5.18-5.10 (m, 2H, =CH_2), 6.05-5.91 (m, 1H, -CH=), 6.72 (d, *J* =7.5 Hz, 1H, H-6), 6.79 (t, *J* =7.0 Hz, 1H, H-4), 7.07-7.12 (m, 2H, H-3, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.4 (-CH_2-), 115.9 (C-6), 116.1 (=CH_2), 119.0 (C-4), 124.1 (C-2), 127.5 (C-5), 130.1 (C-3), 135.8 (-CH=), 144.4 (C-1); MS(EI-70 eV) *m/z* (%): 133 ($M^{\bullet+}$, 100), 118 (71), 106 (49), 132 (68), 91(22).

2-allyl-4-choro-aniline (3b): Isolated as a yellow oil; obtained 1.21 g (72%); IR (thin film) ν_{max} 3458, 3381, 1622, 1491, 1415, 1284, 997, 920, 814 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (d , *J* =6.0 Hz, 2H, -CH_2-), 3.67 (br s, 2H, -NH_2), 5.11 (d, *J* =17.2 Hz, 1H, =CHH_B), 5.16 (d, *J* =10.0 Hz, 1H, =CH_AH), 5.97-5.87 (m, 1H, -CH=), 6.61 (dd, *J* =6.4, 2.8 Hz, 1H, H-6), 7.03-7.01 (m, 2H, H-3, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.2 (-CH_2-), 116.7 (=CH_2), 116.8 (C-6), 123.3 (C-4), 125.7 (C-2), 127.1 (C-5), 129.7 (C-3), 134.9 (-CH=), 143.0 (C-1); MS(EI-70 eV) *m/z* (%): 167 ($M^{\bullet+}$, ^{35}Cl, 100), 152 (35), 140 (33), 132 (56), 125(6), 117 (76).

2-allyl-4-fluoro-aniline (3c): Isolated as a yellow oil; obtained 1.10 g (73%); IR (thin film) ν_{max} 3446, 3369, 1626, 1500, 1234, 918, 814 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (d, *J* =6.0 Hz, 2H, -CH_2-), 3.54 (br s, 2H, -NH_2), 5.20-5.07 (m, 2H, =CH_2), 6.00-5.90 (m, 1H, -CH=), 6.65-6.59 (m, 1H, H-6), 6.84-6.74 (m, 2H, H-3, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.1 (-CH_2-), 113.5 (d, *J* =21.8 Hz, C-5), 116.3 (d, *J* =20.1 Hz, C-3), 116.5 (d, *J* =5.8 Hz, C-6), 116.6 (=CH_2), 125.6 (d, *J* =6.8Hz, C-2), 134.9 (-CH=), 140.5 (C-1), 156.3 (d, *J* = 234.6 Hz, C-4) MS(EI-70 eV) *m/z* (%): 151 ($M^{\bullet+}$, ^{35}Cl, 100), 136 (74), 124 (45), 132 (4).

2-allyl-naphthylamine (3d): Isolated as a red oil; obtained 1.48 g (81%); IR (thin film) ν_{max} 3466, 3386, 3054, 1622, 1433, 1400, 996, 916, 802, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (d, *J* =6.3 Hz, 2H, -CH_2-), 4.17 (br s, 2H, -NH_2), 5.30-5.17 (m, 2H, =CH_2), 5.96-5.86 (m, 1H, -CH=), 7.31 (*d*, 8.1 Hz, 1H, H-4), 7.40 (*d*, *J* =8,4 Hz, 1H, H-3), 7.56-7.49 (m, 2H, H-6, H-7), 7.91-7.84 (*m*, 2H, H-5, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.7 (-CH_2-), 115.9 (=CH_2), 117.6 (C-2), 118.3 (C-4), 120.2 (C-8), 123.5 (C-8a), 124.7 (C-7), 125.0 (C-6), 128.3 (C-3), 128.7 (C-5), 133.2 (C-4a), 135.5 (-CH=), 139.4 (C-1); MS(EI-70 eV) *m/z* (%): 183 ($M^{\bullet+}$, 100) 168 (31), 156 (14), 182 (33), 141 (9).

2.3 General procedure for the syntheses of [3,1]-benzothiazepines (4b-k) and [3,1]-benzoxazepines (5a-c). A mixture of **3a-d** (1.0 equiv, 1.0 mmol) and the appropriate isothiocyanate or isocyanate (1.0 equiv, 1.0 mmol) in the appropriate solvent (dichloromethane for isothiocyanates and tetrahydrofuran for isocyanates) was heated to reflux and the progress of reaction was monitored by TLC. A 1M solution of iodine in dichloromethane (1 mL) was then added at room temperature and the mixture were stirred for 3h **(4b-k)** or 24h **(5a-c)**. After this period, the reaction mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and solvents were removed under reduced pressure followed by purification by a flash column chromatography [hexanes:EtOAc (21:1)].

2-(1´-amino-4´-chlorophenyl)-7-chloro-4-iodomethyl-4,5-dihydrobenzo[*d*][3,1]thiazepine (4b): Isolated as a yellow solid (mp 119-120 ^oC); obtained 0.34 g (74%); IR (KBr) ν_{max} 3386, 1618, 1506, 1306, 1114, 822, 565 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.69 (dd, *J* =13.2, 9.9 Hz, 1H, H_b-5), 3.14 (dd, *J* =13.2, 4.8 Hz, 1H, H_a-5), 3.58 (d, *J* = 6.6 Hz, 2H, -CH_2-I), 4.24-3.97 (m, 1H, H-4), 6.89 (d, *J* =8.4 Hz, 1H, H-9), 7.26 (dd, *J* =8.4, 2.1 Hz, 1H, H-8), 7.31 (d, *J* =2.1 Hz, 1H, H-6), 7.34 (d, *J* =9.0 Hz, 2H, H-2', H-6'), 7.91 (d, *J* =9.0 Hz, 2H, H-3', H-5'), 9.81 (s, 1H, -NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (-CH_2-I), 37.4 (C-5), 56.5 (C-4), 121.6 (C-9), 125.1 (2C, C-2', C-6'), 128.3 (C-8), 129.0 (2C, C-3', C-5'), 129.1 (C-6), 129.2 (C-5a) 129.8 (C-4'), 131.1 (C-7), 137.6 (C-1'), 141.0 (C-9a). HRMS (ESI, m/z) calcd for $C_{16}H_{14}Cl_2IN_2S$ $[M + H]^+$: 462.9299; found: 462.9300.

2-(1´-amino-3´,4´-dimethylphenyl)-7-choro-4-iodomethyl-4,5-dihydrobenzo[*d*][3,1]thiazepine (4c): Isolated as a white solid (mp 126-127 ^oC); obtained 0.17 g (37%); IR (KBr) ν_{max} 3400, 1604, 1506, 1309, 1157, 818, 546 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.16 (s, 3H, -CH_3), 2.18 (s, 3H, -CH_3), 2.66 (dd, *J* =13.2, 11.7 Hz, 1H, H_b-5), 3.14 (dd, *J* =13.2, 4.8 Hz, 1H, H_a-5), 3.66-3.51 (m, 2H, -CH_2-I), 4.05 (br s, 1H, H-4), 6.86 (d, *J* =8.7 Hz, 1H, H-9), 7.04 (d, *J* =8.1 Hz, 1H, H-5'), 7.25 (dd, *J* =8.7, 2.4 Hz, 1H, H-8), 7.29 (d, *J* =2.4 Hz, 1H, H-6), 7.59 (d, *J* =8.1 Hz, 1H, H-6'), 7.60 (s, 1H, H-2'), 9.48 (s, 1H, -NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (-CH_2-I), 19.1 (-CH_3,), 19.9 (-CH_3), 37.5 (C-5), 56.2 (C-4), 117.6 (C-5'), 121.3 (C-9), 125.0 (C-6), 128.0 (C-8), 128.3 (C-5a), 128.9 (C-2'), 129.7 (C-6'), 131.1 (C-7), 132.4 (C-4'), 137.1 (C-3'), 137.2 (C-1'), 146.0 (C-9a). HRMS (ESI, m/z) calcd for $C_{18}H_{19}ClIN_2S$ $[M + H]^+$: 457.0002; found: 457.0002.

2-(1´-amino-naphthyl)-7-chloro-4-iodomethyl-4,5-dihydrobenzo[*d*][3,1]thiazepine (4d): Isolated as a yellow solid (mp 113-114 ^oC); obtained 0.30 g (63%); IR (KBr) ν_{max} 3384, 1610, 1570, 1521, 1476, 1141, 771, 554 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.95 (t, *J* =12.8 Hz, 1H, H_b-5), 3.26 (d, *J* = 9.6 Hz, 1H, H_a-5), 3.45 (d, *J* =10.0 Hz, 2H, -CH_2-I), 3.96 (br s, 1H, H-4), 6.94 (d, *J* =6.0 Hz, 1H, H-9), 7.26 (br s, 2H, H-6, H-8), 7.66-7.43 (m, 3H, H-6', H-7', H-8'), 7.73 (d, *J* =7.2 Hz, 1H, H-4'), 8.02-7.87 (m, 2H, H-3', H-5'), 8.08 (br s, 1H, H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (-CH_2-I), 37.5 (C-5), 55.6 (C-4), 120.0 (C-4'), 121.0 (C-8'), 124.9 (C-9), 125.4 (C-8), 125.7 (C-6'), 126.2 (C-2'), 126.4 (C-3'), 126.8 (C-5a), 128.1 (C-7'), 128.8 (C-5'), 128.9 (C-1'), 129.1 (C-6), 130.4 (C-8a'), 131.5 (C-7), 134.2 (C-4a'), 149.5 (C-9a).HRMS (ESI, m/z) calcd for $C_{20}H_{17}ClIN_2S[M + H]^+$: 478.9846; found: 478.9846.

2-(1´-amino-4´-chlorophenyl)-7-fluoro-4-iodomethyl-4,5-dihydrobenzo[*d*][3,1]thiazepine (4e): Isolated as a yellow solid (mp 117-118 ^{o}C); obtained 0.31 g (69%); IR (KBr) ν_{max} 3413, 1620, 1479, 1304, 1140, 815 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (dd, *J* =13.2, 10.2 Hz, 1H, H_b-5), 3.14 (dd, *J* =13.2, 4.5 Hz, 1H, H_a-5), 3.58 (d, *J* = 6.6 Hz, 2H, -CH_2-I), 4.15-4.01 (m, 1H, H-4), 6.89 (dd, *J* =8.4, 5.4 Hz, 1H, H-9), 7.04 (dd, *J* =8.4, 2.7 Hz, 1H, H-8), 7.11 (dd, *J* =9.3, 2.7 Hz, 1H, H-6), 7.34 (d, *J* =9.0 Hz, 2H, H-2', H-6'), 7.92 (d, *J* =9.0 Hz, 2H, H-3', H-5'), 9.76 (s, 1H, -NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (-CH_2-I), 37.5 (C-5), 56.5 (C-4), 114.8 (d, *J* =22.5 Hz, C-8), 115.8 (d, *J* = 22.4 Hz, C-6), 121.1 (2C, C-2', C-6'), 125.0 (d, *J* =7.8 Hz, C-9), 128.6 (C-4'), 128.9 (2C, C-3', C-5'), 130.9 (d, *J* =7.8 Hz, C-5a), 138.0 (C-1'), 159.0 (d, *J* =241.6 Hz, C-7). HRMS (ESI, m/z) calcd for $C_{16}H_{14}ClFIN_2S$ $[M + H]^+$: 446.9595; found: 446.9595.

2-(1´-amino-naphthyl)-7-fluoro-4-iodomethyl-4,5-dihydrobenzo[*d*][3,1]thiazepine (4f): Isolated as a yellow solid (mp 116-117 ^{o}C); obtained 0.35 g (76%); IR (KBr) ν_{max} 3444, 1620, 1479, 1238, 1134, 775 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.90-2.70 (m, 1H, H_b-5), 3.23 (dd, *J* = 13.2, 4.2 Hz, 1H, H_a-5), 3.56 (br s, 2H, -CH_2-I), 3.98 (br s, 1H, H-4), 6.74 (br s, 1H, H-9), 7.06-6.96 (m, 1H, H-6), 7.11 (dd, 9.0, 2.7 Hz, 1H, H-8), 7.62-7.46 (m, 4H, H-3', H-6', H-7', H-8'), 7.81-7.71 (m, 1H, H-4'), 7.98-7.89 (m, 1H, H-5'), 8.12-8.00 (m, 1H, H-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (-CH_2-I), 37.5 (C-5), 55.4 (C-4), 114.8 (d, *J* =21.7 Hz, C-8), 115.9 (d, *J* =23.3 Hz , C-6), 119.8 (C-4'), 121.0 (C-8'), 125.0 (d, *J* =8.6 Hz , C-9), 125.3 (C-7'), 125.7 (C-6'), 126.1 (C-2'), 126.3 (C-3'), 126.9 (C-5a), 128.7 (C-5'), 134.4 (C-4'a), 147.1 (C-9a), 159.1 (d, *J* = 241.6 Hz, C-7). HRMS (ESI, m/z) calcd for $C_{20}H_{17}FIN_2S$ $[M + H]^+$: 463.0141; found: 463.0141.

2-(1´-amino-phenyl)-4-iodomethyl-4,5-dihydronaphtho[1,2-*d*][3,1]thiazepine (4g): Isolated as a white solid (mp 139-140 ^{o}C); obtained 0.23 g (52%); IR (KBr) ν_{max} 3484, 1610, 1585, 1514, 1381, 1309, 809, 754, 689, 576 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (dd, *J* =13.6, 9.6 Hz, 1H, H_b-5), 3.36 (dd, *J* =13.6, 4.4 Hz, 1H, H_a-5), 3.57-3.46 (m, 2H, -CH_2-I), 4.25-4.14 (m, 1H, H-4), 7.16 (t, *J* =7.2 Hz, 1H, H-4'), 7.38 (d, *J* =8.4 Hz, 1H, H-11), 7.43 (d, *J* =7.6 Hz, 2H, H-2', H-6'), 7.53-7.45 (m, 2H, H-7, H-9), 7.60 (d, *J* =8.4 Hz, 1H, H-10), 8.32-8.24 (m, 1H, H-8), 7.84-7.80 (m, 1H, H-6), 7.88 (d, *J* =7.6 Hz, 2H, H-3', H-5'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3 (-CH_2-I), 37.9 (C-5), 59.2 (C-4), 119.7 (C-2', C-6'), 123.6 (C-10), 123.7 (C-8), 124.2 (C-4'), 125.7 (C-9), 125.8 (C-7), 127.5 (C-6), 127.6 (C-11), 128.5 (C-11a), 129.1 (C-3', C-5'), 133.5 (C-7a), 139.8 (C-1'), 147.2 (C-11b). HRMS (ESI, m/z) calcd for $C_{20}H_{18}IN_2S$ $[M + H]^+$: 445.0230; found: 445.0131.

2-(1´-amino-4´-chlorophenyl)-4-iodomethyl-4,5-dihydronaphtho[1,2-*d*][3,1]thiazepine (4h): Isolated as a yellow solid (mp 131-132 ^{o}C); obtained 0.37 g (77%); IR (KBr) ν_{max} 3398, 1603, 1581, 1503, 1395, 1301, 1242, 807, 754, 681, 545, 433 cm^{-1}; ^{1}H NMR (300 MHz, Acetone-d_6) δ 3.03 (*dd*, *J* =13.5, 9.9 Hz, 1H, H_b-5), 3.40 (*dd*, *J* =13.5, 4.5 Hz, 1H, H_a-5), 3.63 (*dd*, *J* =10.2, 5.7 Hz, 1H, , -CHH_c-I), 3.69 (*dd*, *J* =18.3, 10.2 Hz, 1H, -CHH_d-I), 4.26-4.24 (*m*, 1H, H-4), 7.41 (*d*, *J* =8.7 Hz, 2H, H-3', H-5'), 7.44 (*d*, *J* =8.1 Hz, 1H, H-6), 7.50-7.47 (*m*, 2H, H-8, H-9), 7.61 (*d*, *J* =8.1 Hz, 1H, H-7), 7.87-7.84 (*m*, 1H, H-10), 8.16 (*d*, *J* =8.7 Hz, 2H, H-2', H-6'), 8.20 (*dd*, *J*= 9.9, 5.4 Hz, 1H, H-11), 8.98 (*br s*, 1H, -NH); ^{13}C NMR (75 MHz, Acetone-d_6) δ 12.8 (-CH_2-I), 38.9 (C-5), 60.2 (C-4), 122.2 (2C, C-2', C-6'), 124.0 (C-7), 125.0 (C-11), 126.4 (2C, C-8, C-9), 126.6 (C-11a), 128.1 (C-4'), 128.5 (C-10), 128.7 (C-6), 129.5 (3C, C-5a, C-5', C-3'), 134.6 (C-7a), 141.5 (C-1'), 144.5 (C-11b), 178.0 (C-2). HRMS (ESI, m/z) calcd for $C_{20}H_{17}ClIN_2S$ $[M + H]^+$: 478.9840; found: 478.9860.

2-(1´-amino-4´-fluorophenyl)-4-iodomethyl-4,5-dihydronaphtho[1,2-*d*][3,1]thiazepine (4i): Isolated as a white solid (mp 118-119 ^{o}C); obtained 0.32 g (70%); IR (KBr) ν_{max} 3392, 1602, 1587, 1502, 1401, 1307, 1211, 1152, 835, 750, 680, 557, 433 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.91 (dd, *J* =13.6, 10.0 Hz, 1H, H_b-5), 3.28 (dd, *J* =13.6, 4.8 Hz, 1H, H_a-5), 3.64-3.61 (m, 2H, -CH_2-I), 4.29-4.16 (m, 1H, H-4), 7.21 (t, *J* =8.8 Hz, 2H, H-3', H-5'), 7.40 (d, *J* =8.4 Hz, 1H, H-6), 7.50-7.43 (m, 2H, H-8, H-9), 7.58 (d, *J* =8.4, 1H, H-7), 7.87-7.85 (m, 1H, H-10), 8.10-8.06 (m, 3H, H-11, H-2', H-6'), 9.84 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.4 (-CH_2-I), 37.8 (C-5), 58.7 (C-4), 115.1 (d, *J* =21.5 Hz, 2C, C-3', C-5'), 121.4 (d, *J* =8.2 Hz, 2C, C-2', C-6'), 122.4 (C-10), 123.6 (C-8), 125.2 (C-5a), 125.4 (C-9), 125.6 (C-7), 127.5 (C-6), 127.8 (C-11), 128.0 (C-11a), 133.0 (C-7a), 137.4 (C-1'), 147.6 (C-11b), 156.6 (d, *J* =238.9 Hz, C-4'). HRMS (ESI, m/z) calcd for $C_{20}H_{17}FIN_2S$ $[M + H]^+$: 463.0141; found: 463.0141.

2-(1´-amino-4´-methoxyphenyl)-4-iodomethyl-4,5-dihydronaphtho[1,2-*d*][3,1]thiazepine (4j): Isolated as a yellow solid (mp 69-70 ^{o}C); obtained 0.30 g (64%); IR (KBr) ν_{max} 3386, 1604, 1585, 1507, 1241, 810, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (dd, *J* =13.6, 9.6 Hz, 1H, H_a-5), 3.36 (dd, *J* =13.6, 4.4 Hz, 1H, H_b-5), 3.51-3.47 (m, 2H, -CH_2-I), 3.84 (s, 3H, -OCH_3), 4.20-4.10 (m, 1H, H-4), 6.95 (d, *J* =8.4 Hz, 2H, H-2', H-6'), 7.37 (d, *J* =8.4 Hz, 1H, H-6), 7.49-7.43 (m, 2H, H-8, H-9), 7.57 (d, *J* =8.4 Hz, 1H, H-7), 7.77 (d, *J* =8.4 Hz, 2H, H-3', H-5'), 7.83-7.79 (m, 1H, H-10), 8.25-8.19 (m, 1H, H-11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3 (-CH_2-I), 38.0 (C-5), 55.5 (-OCH_3), 58.8 (C-4), 114.2 (2C, C-2, C-6'), 121.6 (2C, C-3', C-5'), 123.4 (C-8), 124.3 (C-10), 124.9 (C-5a), 125.6 (C-9), 125.8 (C-7), 127.4 (C-6), 127.5 (C-11), 128.6 (C-11a), 133.1 (C-1'), 133.5 (C-11b), 156.1 (C-4').HRMS (ESI, m/z) calcd for $C_{21}H_{20}IN_2OS$ $[M + H]^+$: 475.0336; found: 475.0342.

2-(1´-amino-3´,4´-dimethylphenyl)-4-iodomethyl-4,5-dihydronaphtho[1,2-*d*][3,1]thiazepine (4k): Isolated as a white solid (mp 135-136 ^{o}C); obtained 0.35 g (74%); IR (KBr) ν_{max} 3421, 1606, 1589, 1500, 1388, 1157, 818, 752, 537cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.20 (s, 3H, -CH_3), 2.23 (s, 3H, -CH_3), 2.91 (dd, *J* =13.6, 10.0 Hz, 1H, H_a-5), 3.28 (dd, *J* =13.6, 4.4 Hz, 1H, H_b-5) 3.61 (d, *J* =7.2 Hz, 2H, -CH_2-I), 4.26-4.16 (m, 1H, H-4), 7.11 (d, *J* =8.4 Hz, 1H, H-6'), 7.40 (d, *J* =8.4 Hz, 1H, H-6), 7.49-7.43 (m, 2H, H-8, H-9), 7.56 (d, *J* =8.4 Hz, 1H, H-7), 7.76 (d, *J* =8.4 Hz, 1H, H-5'), 7.87-7.82 (m, 2H, H-2', H-10), 8.12 (d, *J* =7.6 Hz, 1H, H-11), 9.60 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.3 (-CH_2-I), 18.8 (-CH_3), 19.7 (-CH_3), 37.8 (C-5), 58.3 (C-4), 117.4 (C-5'), 121.1 (1C, C-2'), 122.2 (C-10), 123.6 (C-8), 125.0 (C-5a), 125.3 (C-7), 125.5 (C-9), 127.4 (C-6), 127.8 (C-11), 128.1 (C-11a), 129.4 (C-6'), 130.4 (C-4'), 133.0 (C-7a), 135.9 (C-3'), 138.7 (C-1'), 147.4 (C-11b). HRMS (ESI, m/z) calcd for $C_{22}H_{22}IN_2S$ $[M + H]^+$: 473.0543; found: 473.0552.

4-(iodomethyl)-N-phenyl-4,5-dihydrobenzo[d][1,3]oxazepin-2-amine (5a): Isolated as a white solid (mp 150-151 ^{o}C); obtained 0.18 g (47%); IR (KBr) ν_{max} 3315, 1643, 1522, 1375, 748 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.94 (dd, *J* =16.2, 2.1 Hz, 1H, H_a-5), 3.42 (dd, J= 16.2, 7.0 Hz, 1H, H_b-5), 3.48-3.32 (m, 1H, -CHH_d-I), 3.54 (dd, *J* =10.2, 3.0 Hz, 1H, -CHH_c-I), 4.92-4.81 (m, 1H, H-4), 6.93 (td, *J* =7.5, 1.0 Hz, 1H, H-7), 7.07-7.00 (m, 1H, H-4'), 7.14 (t, *J* =8.1 Hz, 1H, H-8), 7.23 (d, *J* =7.2 Hz, 1H, H-6), 7.34-7.26 (m, 2H, H-3', H-5'), 7.52 (dd, *J* =8.7, 0.9 Hz, 2H, H-2',H-6'), 7.74 (d, *J* =8.1 Hz, 1H, H-9), 8.85 (s, 1H, -NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.8 (-CH_2-I), 34.6 (C-5), 57.9 (C-4), 114.7 (C-9), 120.6 (2C, C-2', C-6'), 122.1 (C-7),

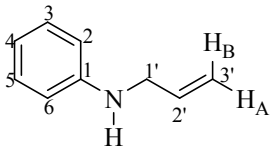
122.7 (C-4'), 124.8 (C-6), 127.1 (C-8), 128.4 (2C, C-3', C-5'), 129.0 (C-5a), 139.3 (C-1'), 143.0 (C-9a), 152.0 (C-2). HRMS (ESI, m/z) calcd for $C_{16}H_{16}IN_2O$ $[M + H]^+$: 379.0307; found: 379.0307.

7-chloro-4-(iodomethyl)-N-phenyl-4,5-dihydrobenzo[d][1,3]oxazepin-2-amine (5b): Isolated as a white solid (mp 148-149 ^oC); obtained 0.23 g (56%); IR (KBr) ν_{max} 3354, 1660, 1529, 1329, 1236, 814, 744, 580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.98 (d, *J* =16.8 Hz, 1H, H_a-5), 3.42-3.24 (m, 2H, -CHH_d-I, H_b-5), 3.59 (dd, *J* =9.6, 2.8 Hz, 1H, -CHH_c-I), 4.72-4.61 (m, 1H, H-4), 7.11 (t, J= 8.0 Hz, 1H, H-4'), 7.23-7.16 (m, 2H, H-3', H-5'), 7.44-7.27 (m, 5H, H-6, H-8, H-9, H-2', H-6'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3 (-CH_2-I), 34.5 (C-5), 61.1 (C-4), 114.8 (C-9), 120.2 (2C, C-2', C-6'), 124.0 (C-4'), 126.1 (C-6), 127.8 (C-8), 128.2 (C-5a), 129.1 (2C, C-3', C-5'), 132.0 (C-7), 137.6 (C-1'), 140.4 (C-9a), 151.7 (C-2). HRMS (ESI, m/z) calcd for $C_{16}H_{15}ClIN_2O$ $[M + H]^+$: 412.9918; found: 412.9918.

7-fluoro-4-(iodomethyl)-N-phenyl-4,5-dihydrobenzo[d][1,3]oxazepin-2-amine (5c): Isolated as a white solid (mp 139-140 ^oC); obtained 0.15 g (38%); IR (KBr) ν_{max} 3313, 1645, 1481, 1320, 744, 592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (d, *J* =16.8 Hz, 1H, H_a-5), 3.33-3.23 (m, 1H, -CHH_d-I), 3.37 (dd, *J* = 16.8, 9.6 Hz, 1H, H_b-5), 3.63-3.55 (m, 1H, -CHH_c-I), 4.69 (br s, 1H, H-4), 7.01-6.83 (m, 3H, H-3', H-4', H-5'), 7.15-7.06 (m, 1H, H-6), 7.44-7.29 (m, 4H, H-8, H-9, H-2', H-6'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4 (-CH_2-I), 34.7 (C-5), 61.2 (C-4), 113.3 (d, *J* =24.0 Hz, C-8), 114.1 (d, *J* =23.2 Hz, C-6), 114.6 (d, *J* =8.5 Hz, C-9), 120.1 (2C, C-2', C-6'), 123.9 (C-4'), 129.1 (2C, C-3', C-5'), 132.2 (d, *J* =8.5 Hz, C-5a), 137.7 (C-1'), 151.8 (C-2), 159.0 (d, *J* =240.8 Hz, C-7). HRMS (ESI, m/z) calcd for $C_{16}H_{15}FIN_2O$ $[M + H]^+$: 397.0213; found: 397.0213.

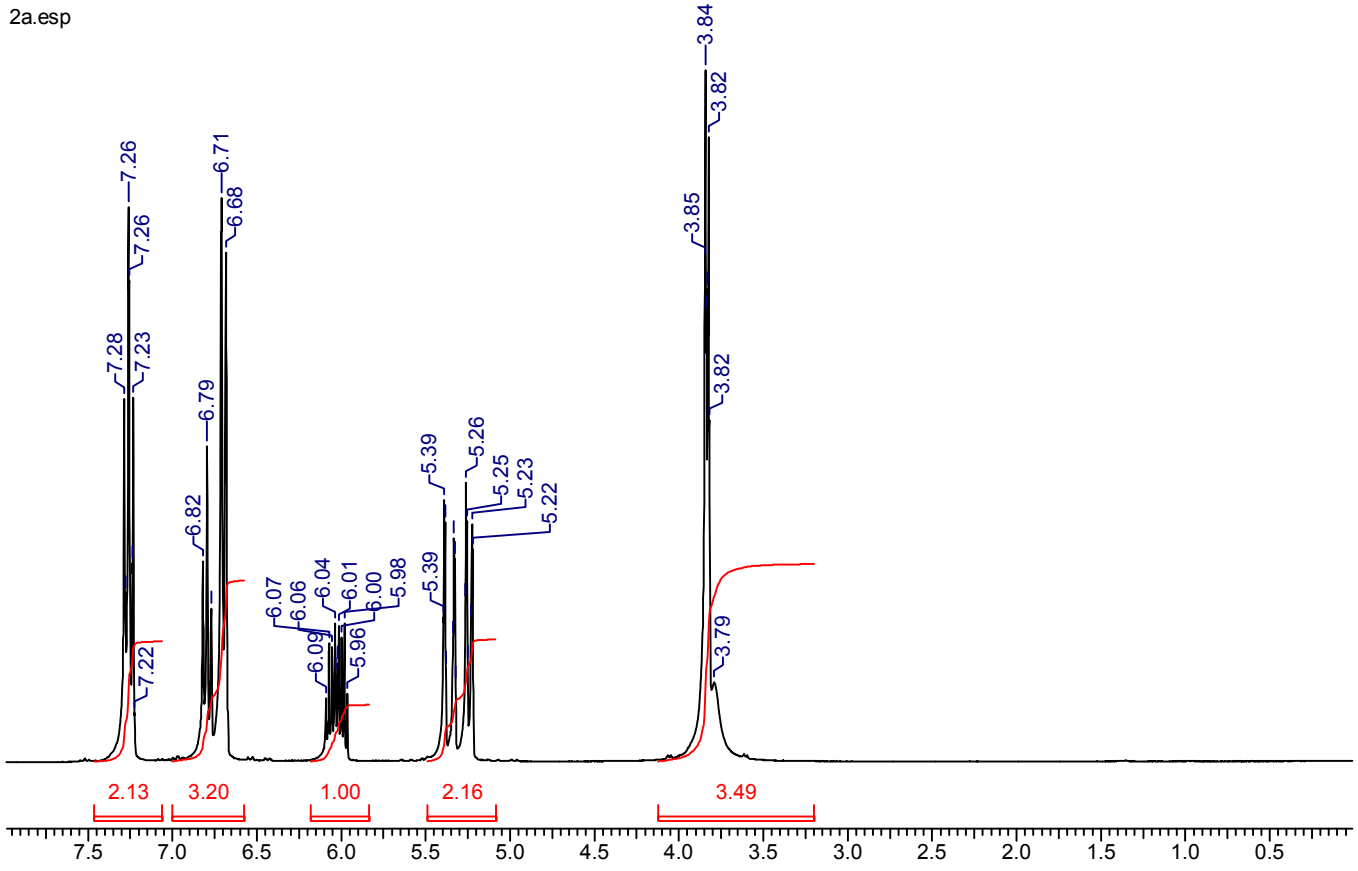
2.4 Antiproliferative Activity

HL-60 (human pro-myelocytic leukemia), NCI-H292 (human lung carcinoma), HEP-2 (human larynx carcinoma) and HT29 (human colon carcinoma) were obtained from Rio de Janeiro Cell Bank (RJ-Brazil). All cancer cells were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum, 2mM glutamine, 100 U/mL penicillin, 100μg/mL streptomycin at 37^{o}C with 5% CO_2. The cytotoxicity of all compounds was tested using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-*2H*-tetrazolium bromide (MTT) (Sigma Aldrich Co., St. Louis, MO/USA) reduction assay. For all experiments, tumor cells were plated in 96-well plates (10^5 cells/mL for adherent cells or 3×10^5 cells/mL for leukemias). Tested Compounds (0.1–25 μg/mL) dissolved in DMSO 1% were added to each well and incubated for 72 h. Control groups received the same amount of DMSO. After 69h of treatment 25 μL of MTT (5mg/mL) was added, three hours later, the MTT formazan product was dissolved in 100 μL of DMSO, and absorbance was measured at 595 nm in plate spectrophotometer. The IC_{50} values and their 95% confidence intervals for two different experiments were obtained by nonlinear regression using GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, California USA)

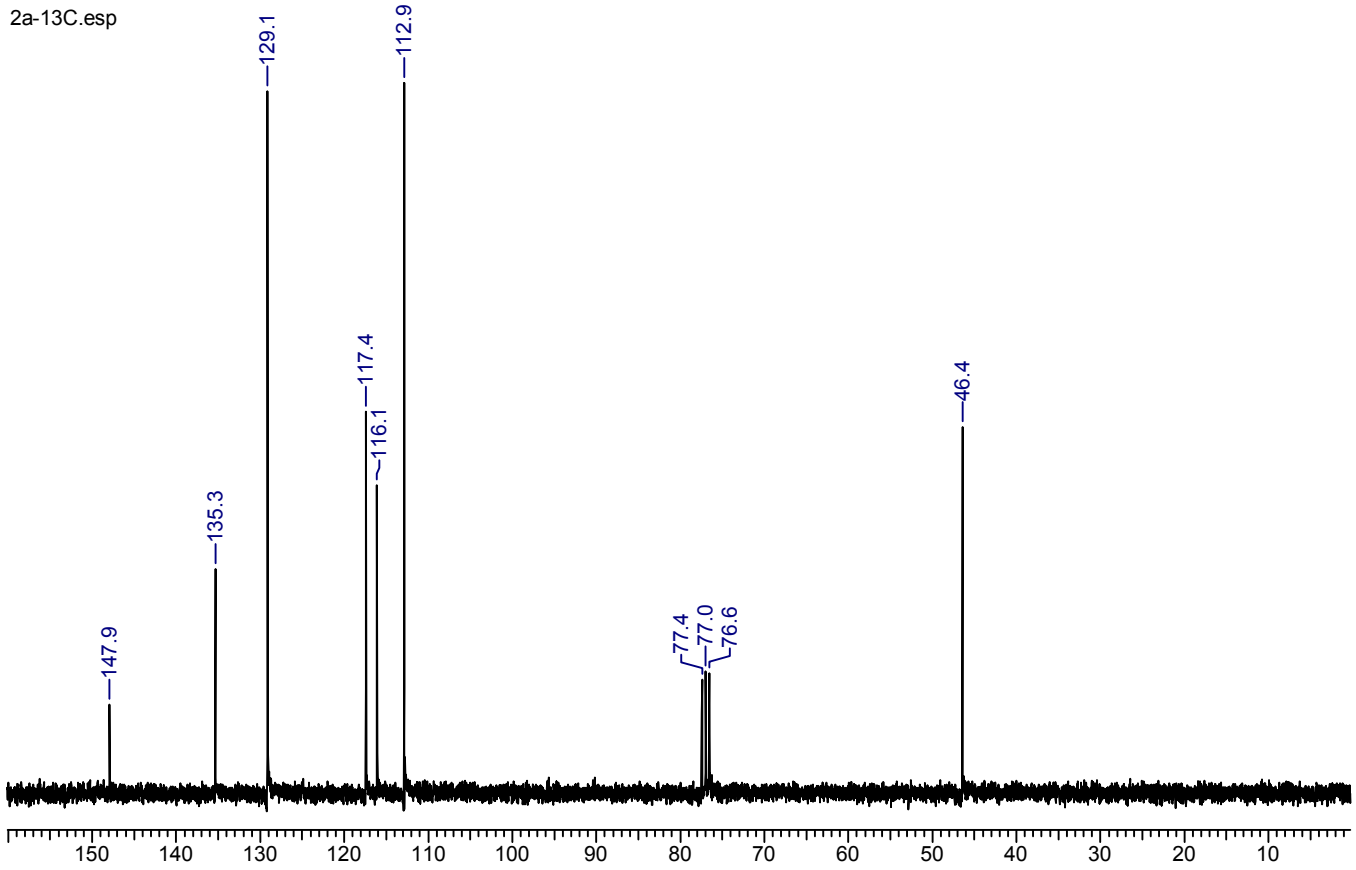


2a

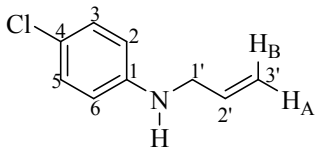
	^{13}C	**^{1}H**	
1	147.9	-	
2, 6	112.9	6.70 (dd; *J*= 8.2; 1.0 Hz)	
3,5	129.1	7.23-7.17 (m)	
4	117.4	6.79 (t; *J*= 7.5 Hz)	
1’	46.4	3.83(dt; *J*= 5.4; 1.5 Hz)	
2’	135.3	6.09-5.96 (m)	
3’	116.1	H_B	5.36 (dq; *J*= 16.8; 1.5 Hz)
		H_A	5.24 (dq; *J*= 10.5; 1.5 Hz)
-NH			3.79 (br s)



^{1}H NMR spectrum (300 MHz. $CDCl_3$) of compound **2a**.

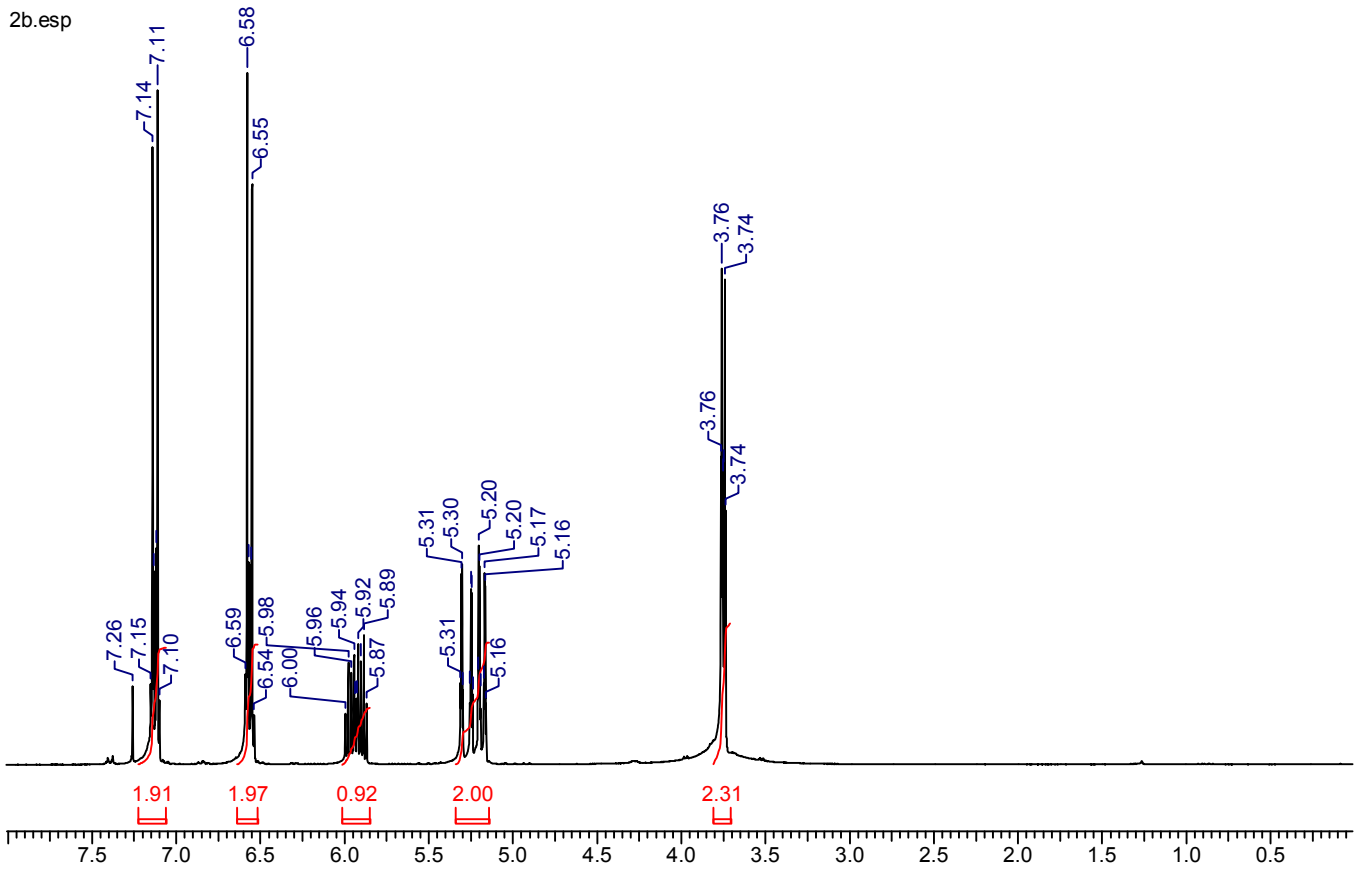


^{13}C NMR spectrum (75 MHz. $CDCl_3$) of compound **2a**.

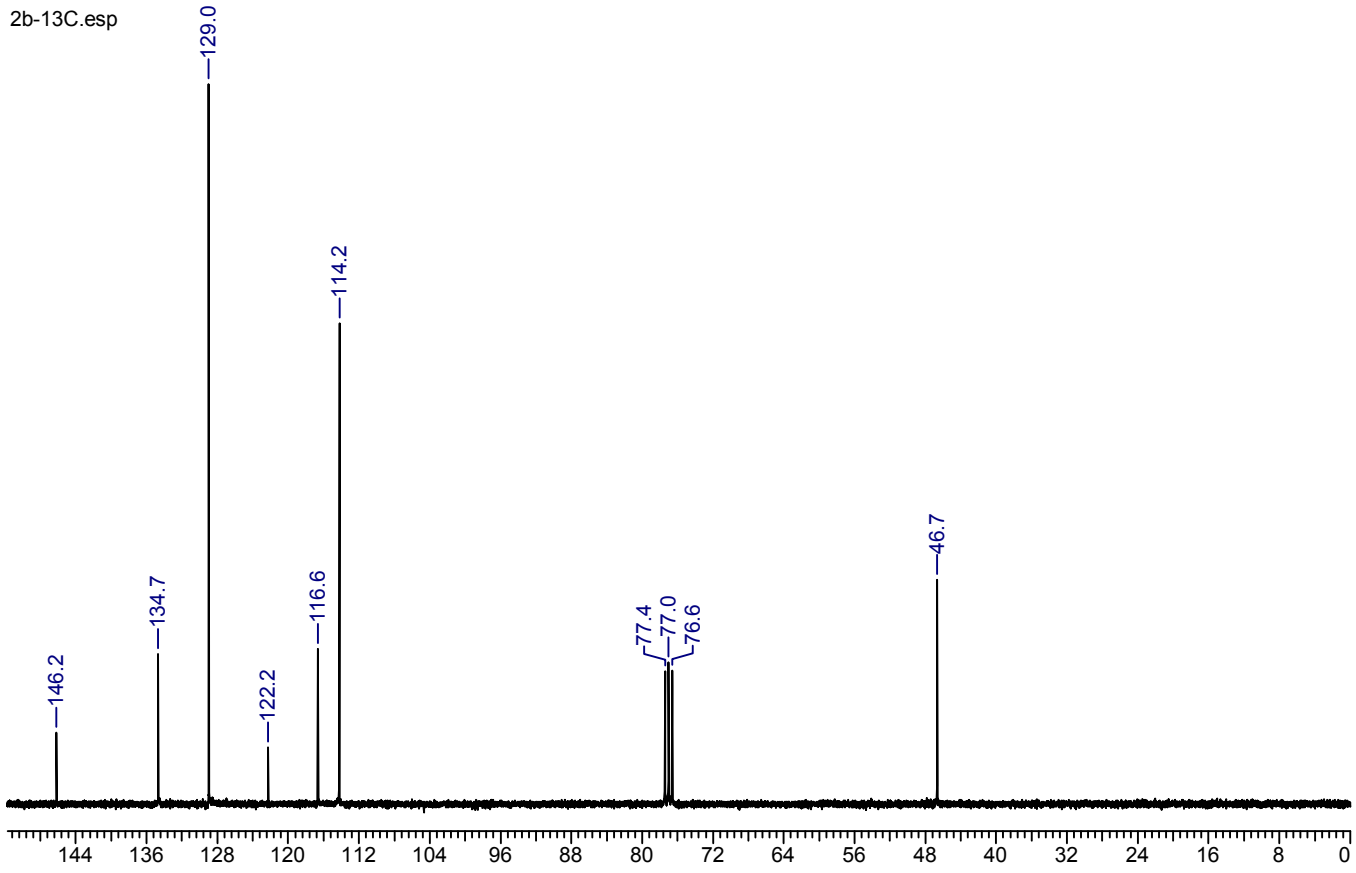


2b

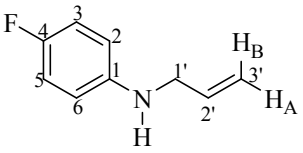
	^{13}C		^{1}H
1	146.2		-
2, 6	114.2		6.57(d; *J*= 9.0 Hz)
3,5	129.0		7.14 (d; *J*= 9.0 Hz)
4	122.3		-
1’	46.7		3.76 (dt; *J*= 5.4; 1.5 Hz)
2’	134.7		6.01-5.88 (m)
3’	116.6	H_B	5.29 (dq; *J*= 17.4; 1.5 Hz)
		H_A	5.20 (dq; *J*= 10.2; 1.5 Hz)



^{1}H NMR spectrum (300 MHz. $CDCl_3$) of compound **2b**.

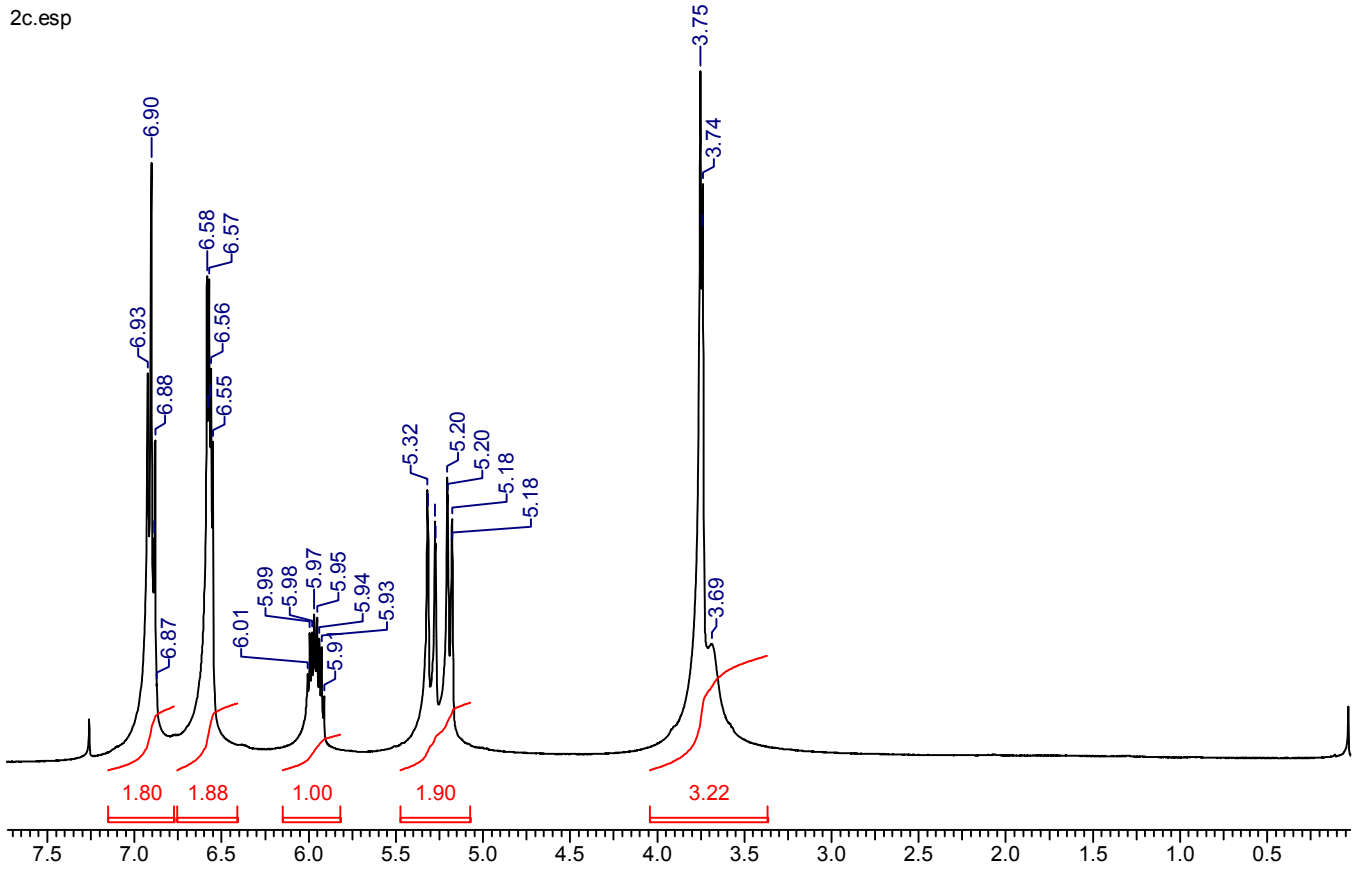


^{13}C NMR spectrum (75MHz. $CDCl_3$) of compound **2b**.

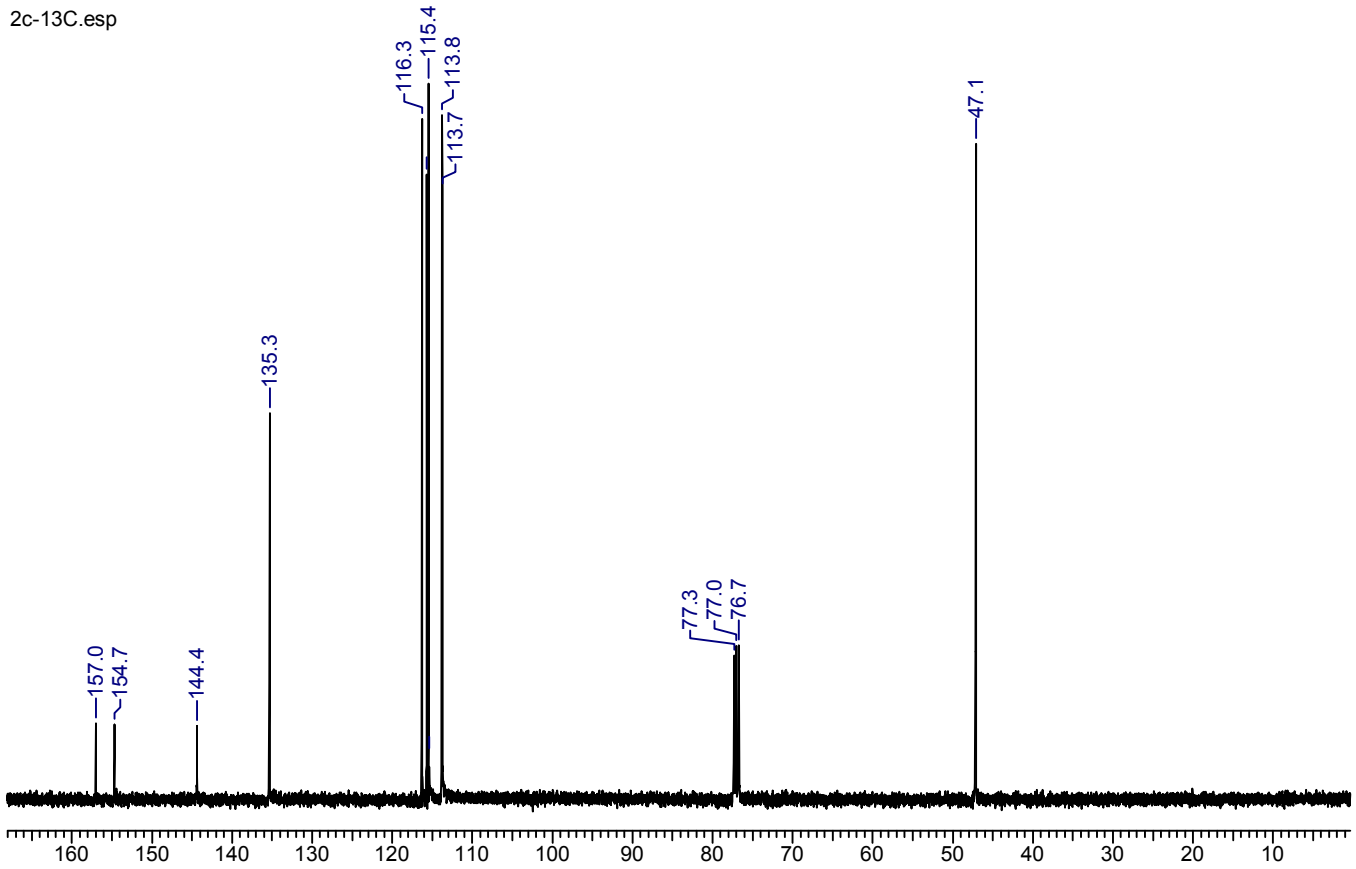


2t

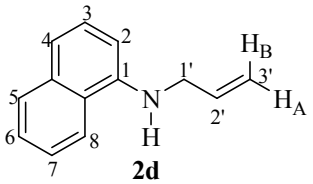
	^{13}C		^{1}H
1	144.4		-
2, 6	113.7 (d, *J* =6.9 Hz),		6.72-6.50 (m)
3,5	115.5 (d, *J* =22.5 Hz)		7.09-6.83 (m)
4	155.8 (d, *J* =233.9 Hz)		-
1’	47.1		3.74 (d; *J*= 5.2 Hz)
2’	135.3		6.10-5.88 (m)
3’	116.2	H_B	5.30 (dd; *J*= 17.2; 1.6 Hz)
		H_A	5.19 (dd; *J*= 10.4; 1.6 Hz)
-NH	-		3.69 (br s)



^{1}H NMR spectrum (400 MHz. $CDCl_3$) of compound **2c**.

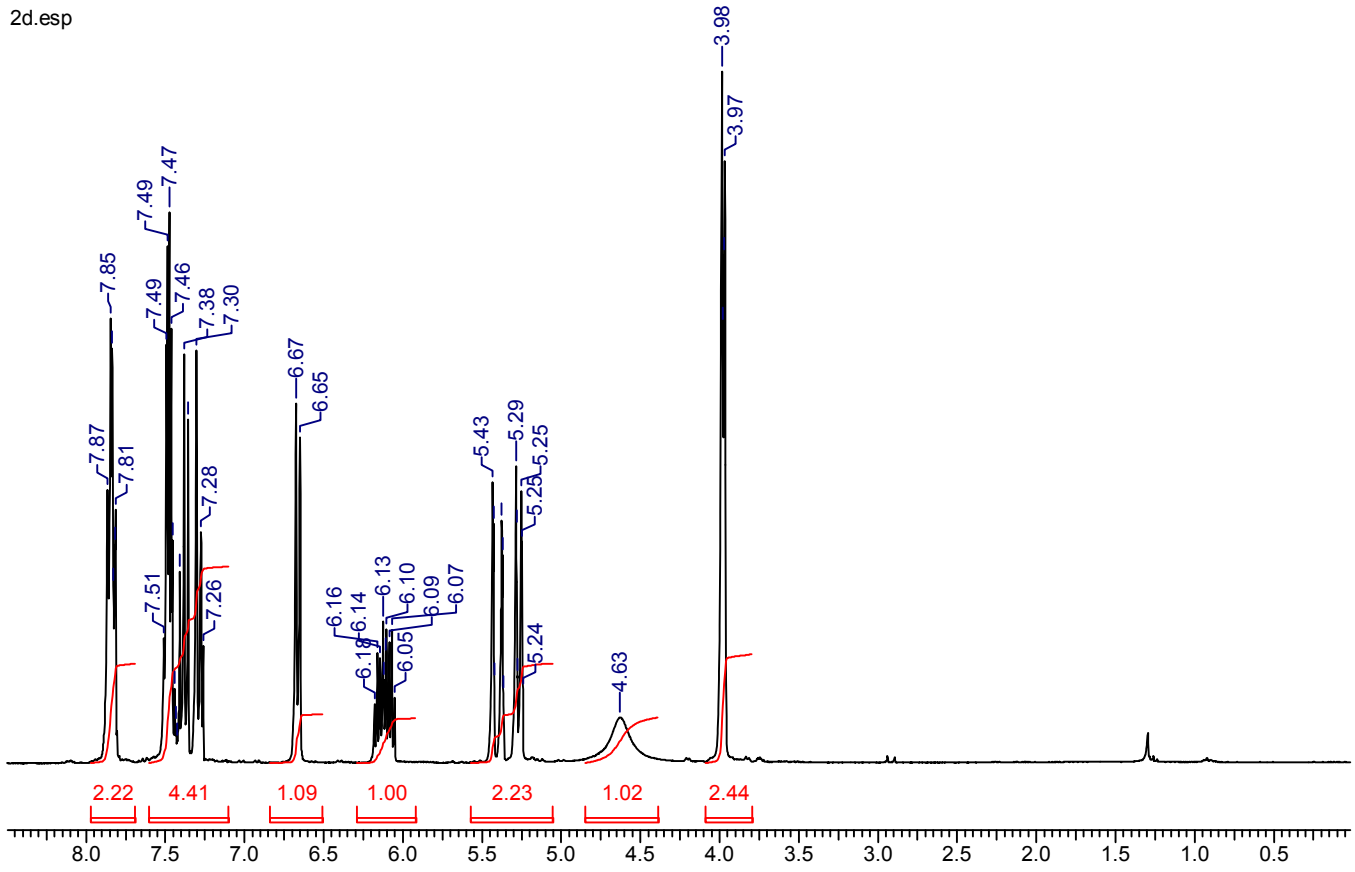


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **2c**.

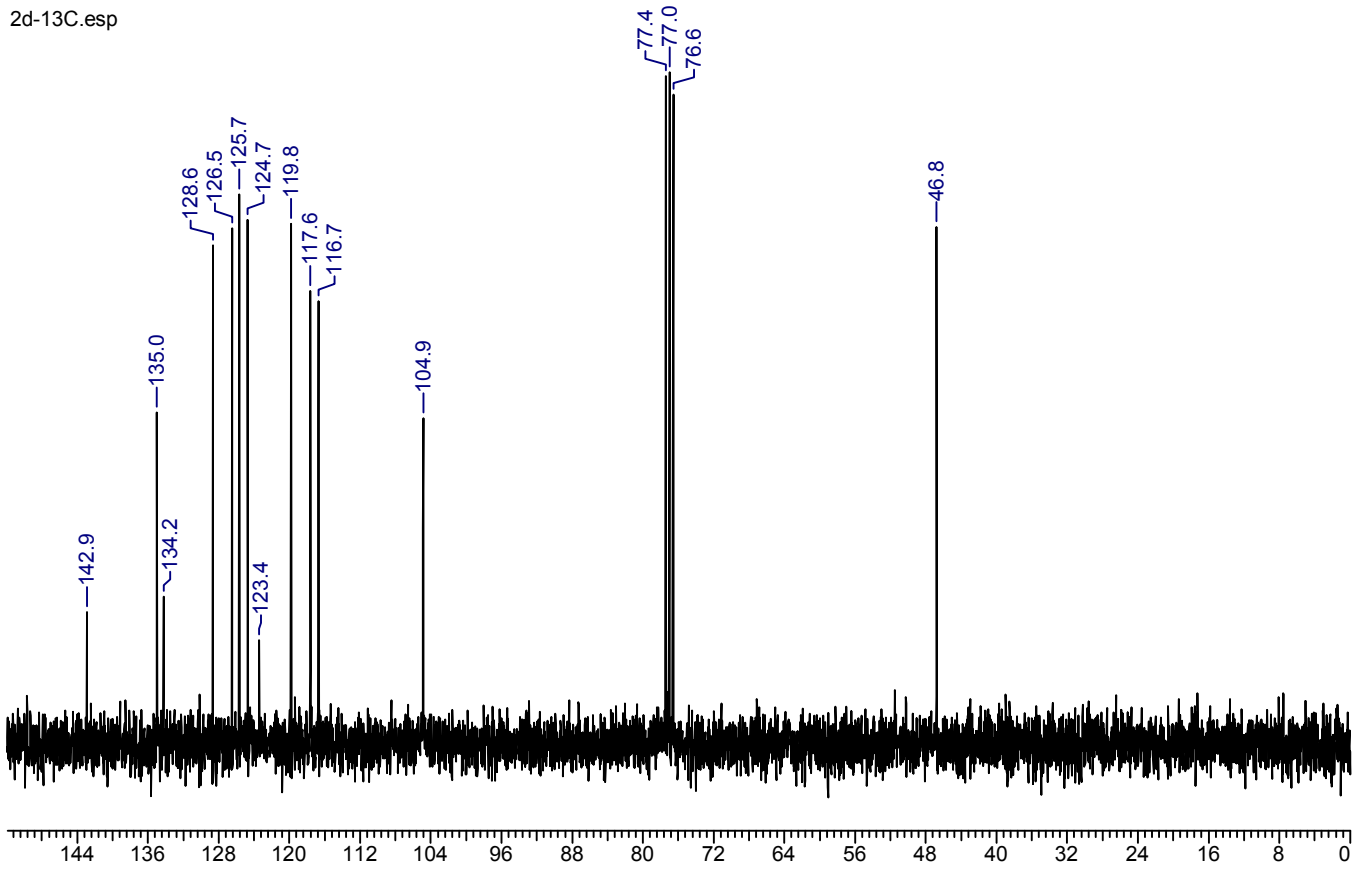


2d

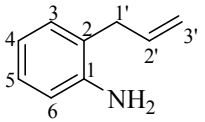
	^{13}C	^{1}H	
1	142.9	-	
2	104.9	6.66 (d; *J*= 7.5 Hz)	
3	126.5	7.38 (dd; *J*= 7.8; 7.5 Hz)	
4	117.6	7.29 (d; *J*= 7.8 Hz)	
4a	134.2	-	
5	128.7	7.86-7.81 (m)	
8	119.8		
8a	123.4	-	
6	125.7	7.51-7.44 (m)	
7	124.7		
1’	46.8	3.98 (dt; *J*=5.7; 1.5 Hz)	
2’	135.0	6.18-6.05 (m)	
3’	116.7	H_B	5.40 (dd; *J*= 16.8; 1.8 Hz)
		H_A	5.27 (dd; *J*=10.5; 1.8 Hz)



^{1}H NMR spectrum (300 MHz. $CDCl_3$) of compound **2d**.

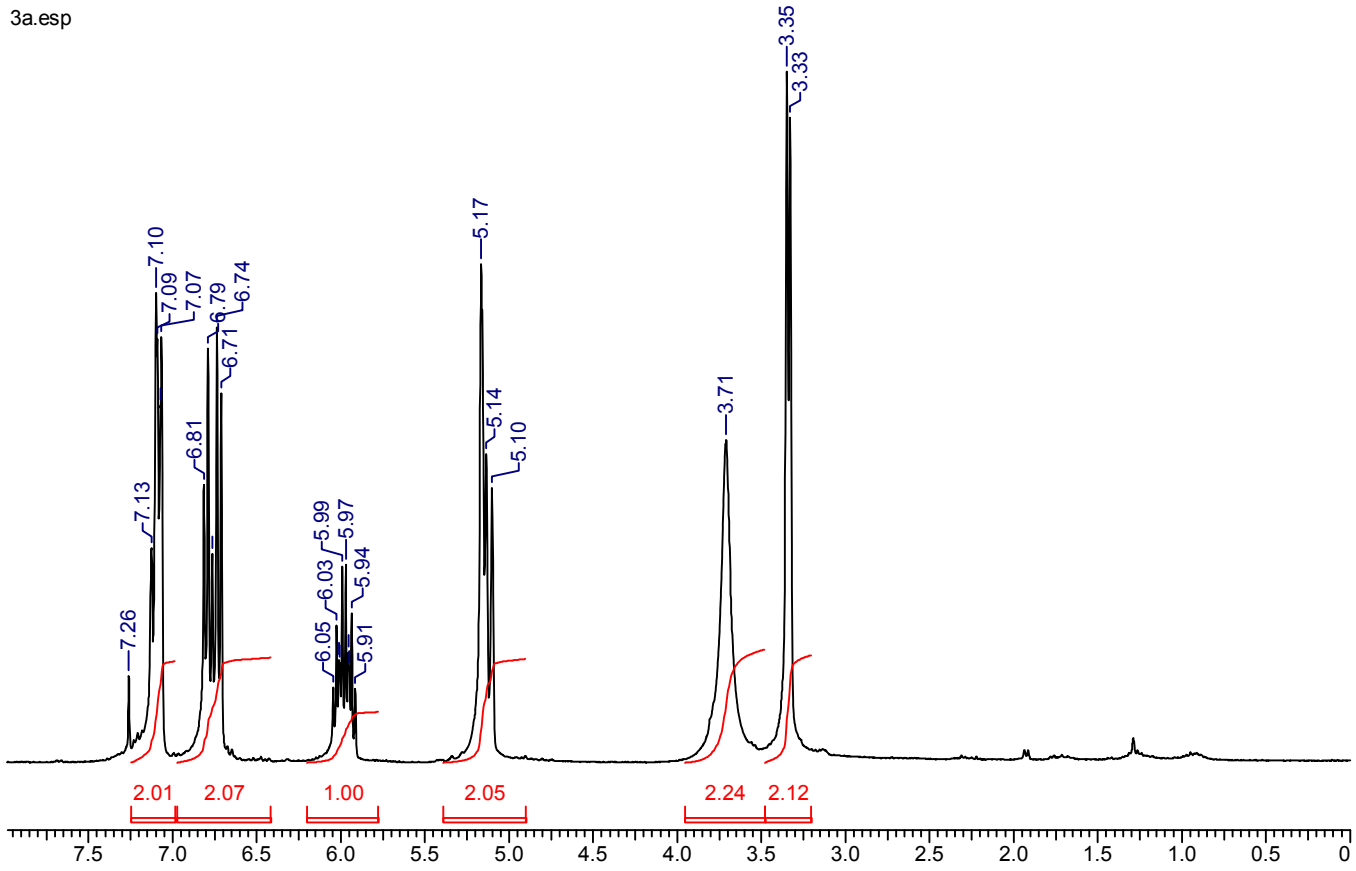


^{13}C NMR spectrum (75 MHz. $CDCl_3$) of compound **2d**.

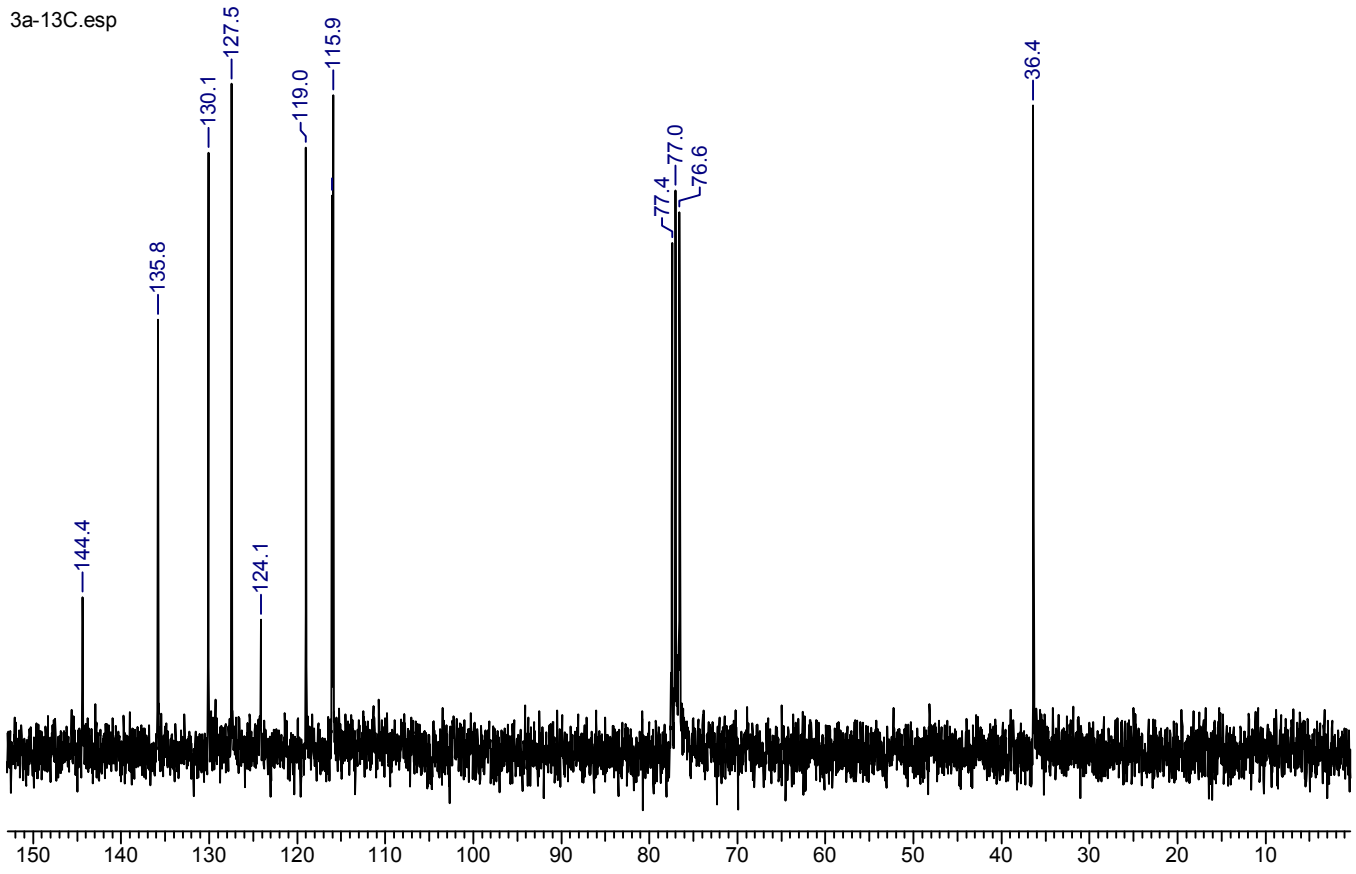


3a

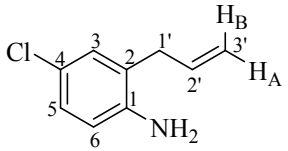
	^{13}C	^{1}H
1	144.4	-
2	124.1	-
3	130.1	7.12-7.07 (m)
5	127.5	
4	119.0	6.79 (t; *J*= 7.0 Hz)
6	115.9	6.72 (d; *J*= 7.5 Hz)
1’	36.4	3.34 (d; *J*= 6.3 Hz)
2’	135.8	6.05- 5.91 (m)
3’	116.1	5.18-5.10 (m)
-NH_2	-	3.71 (br s)



^{1}H NMR spectrum (300 MHz. $CDCl_3$) of compound **3a**.

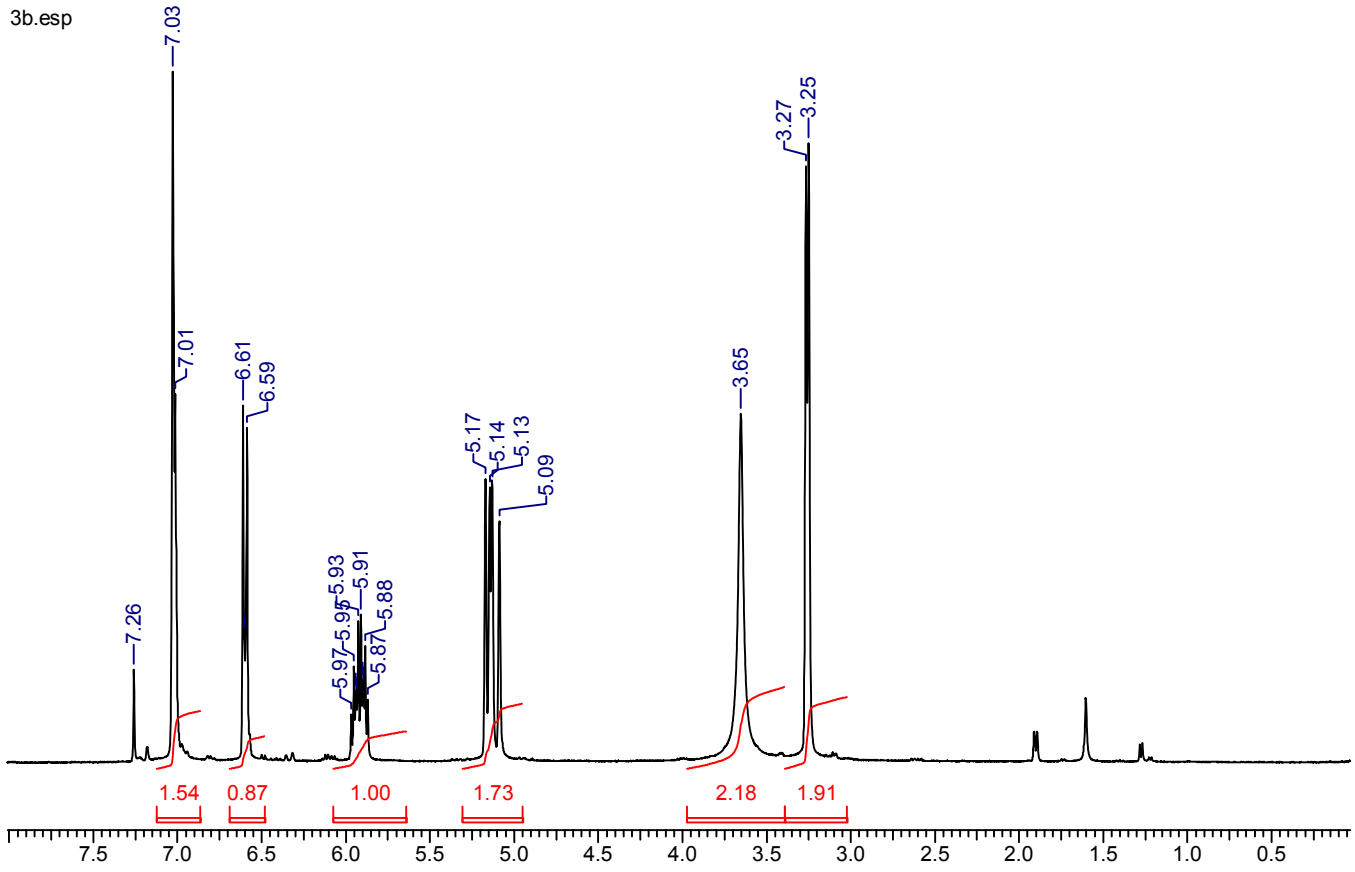


^{13}C NMR spectrum (75 MHz. $CDCl_3$) of compound **3a**.

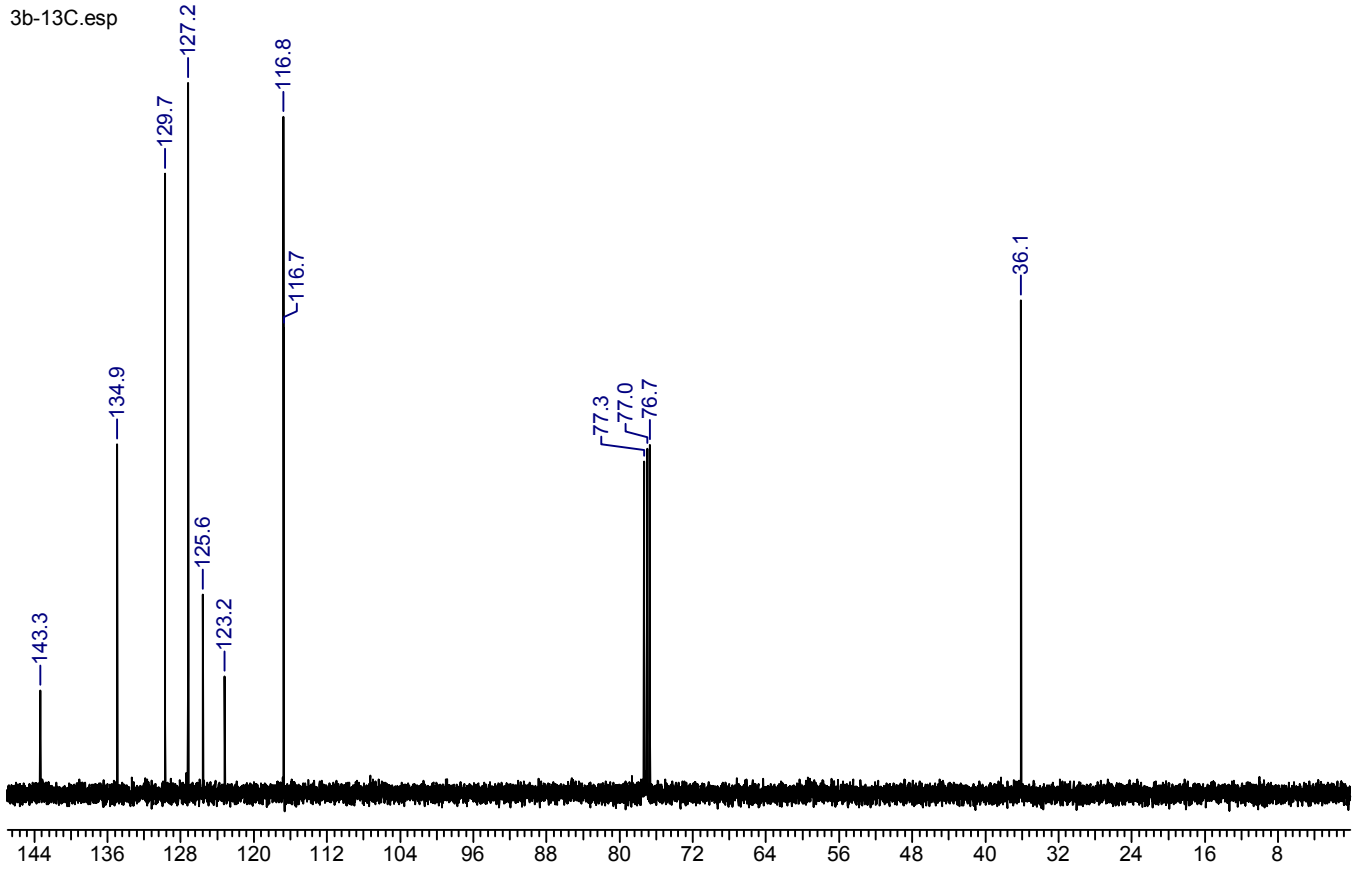


3b

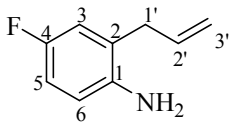
	^{13}C		^{1}H
1	143.0		-
2	125.7		-
3	129.7		7.03-7.01 (m)
5	127.1		
4	123.3		-
6	116.8		6.61 (dd; *J*= 6.4; 2.8 Hz)
1’	36.2		3.26 (d; *J*= 6.0 Hz)
2’	134.9		5.97-5.87 (m)
3’	116.7	H_B H_A	5.11 (d; *J*= 17.2 Hz) 5.16 (d; *J*= 10.0 Hz)
$-NH_2$	-		3.67 (br s)



^{1}H NMR spectrum (400 MHz. $CDCl_3$) of compound **3b**.

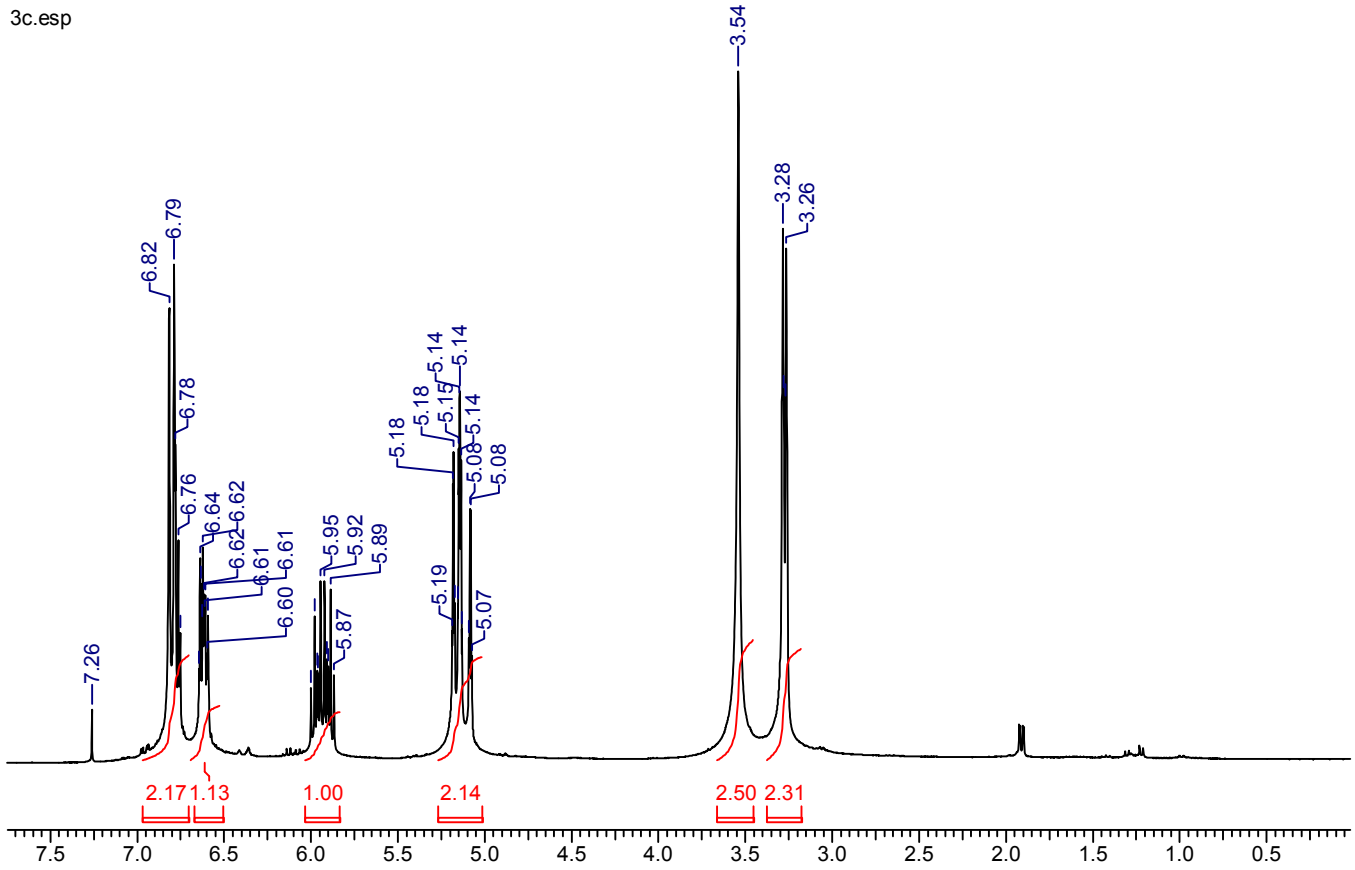


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **3b**.

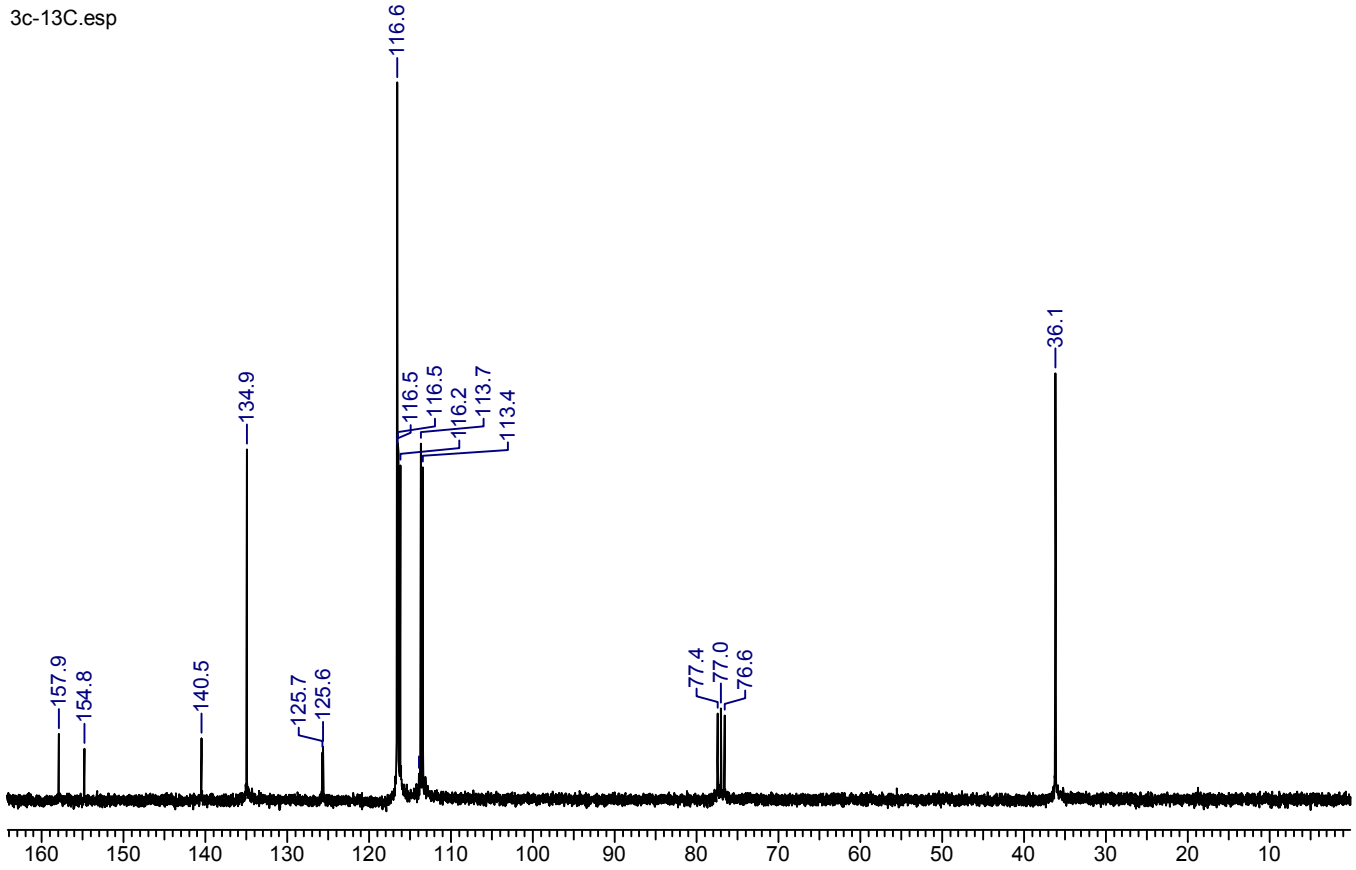


3c

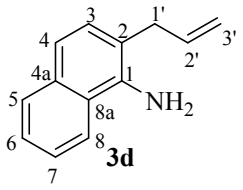
	^{13}C	**^{1}H**
1	140.5	-
2	125.6 (d, *J* =6.8 Hz)	-
3	116.3 (d, *J* =20.1 Hz)	6.84-6.74 (*m)*
5	113.5 (d, *J* =21.8 Hz)	
4	156.3 (d, *J* = 234.6 Hz)	-
6	116.5 (d, *J*= 5.8 Hz)	6.65-6.59 (*m)*
1’	36.1	3.27 (*d; J*= 6.0 Hz)
2’	134.9	6.00-5.90 (*m)*
3’	116.6	5.20-5.07 (*m)*
-NH_2	-------	3.54 (*br s)*



^{1}H NMR spectrum (300 MHz. $CDCl_3$) of compound **3c**.

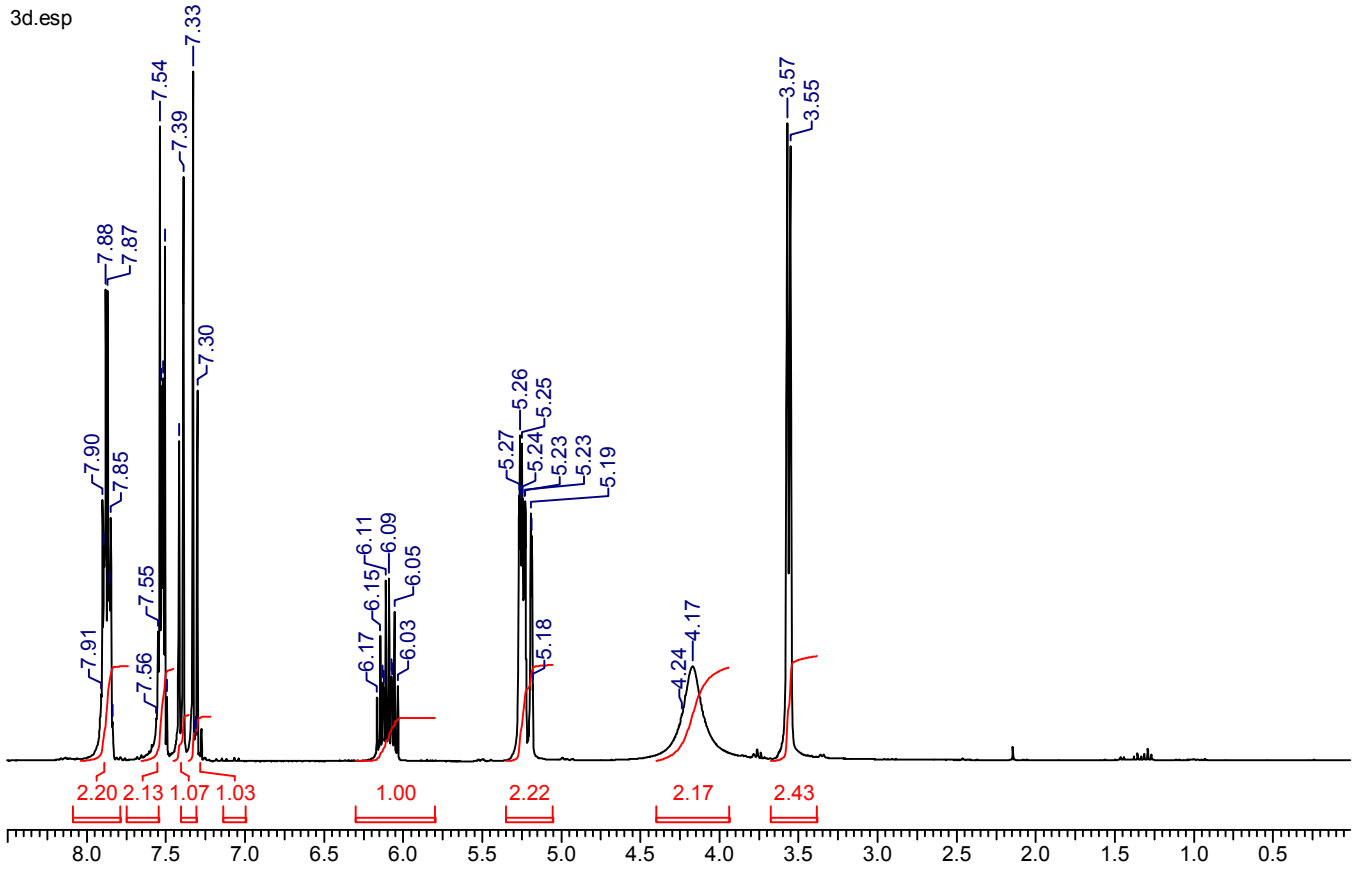


^{13}C NMR spectrum (75 MHz. $CDCl_3$) of compound **3c**.

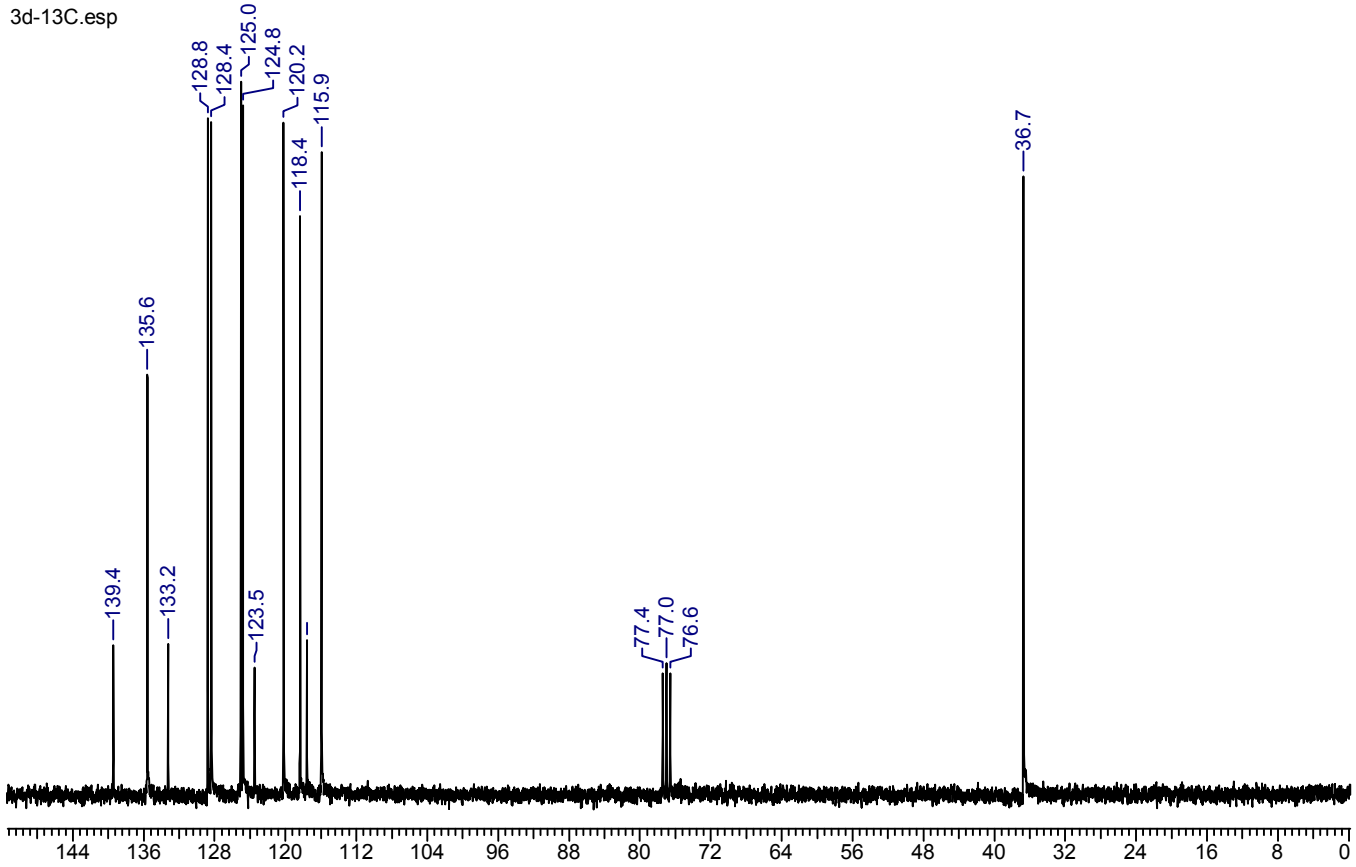


3d

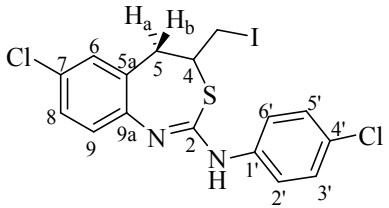
	^{13}C	^{1}H
1	139.4	-
2	117.6	
3	128.3	7.40 (*d;*J= 8.4 Hz)
4	118.3	7.31 (*d;*J=8.1 Hz)
4a	133.2	-
5	128.7	7.91-7.84 (*m)*
8	120.2	
8a	123.5	-
6	125.0	7.56-7.49 (m)
7	124.7	
1’	36.7	3.56 (*d;*J= 6.3 Hz)
2’	135.5	5.96- 5.86 (*m)*
3’	115.9	5.30-5.17 (*m)*
-NH_2	-	4.17 (*br s)*



^{1}H NMR spectrum (300 MHz. $CDCl_3$) of compound **3d**.

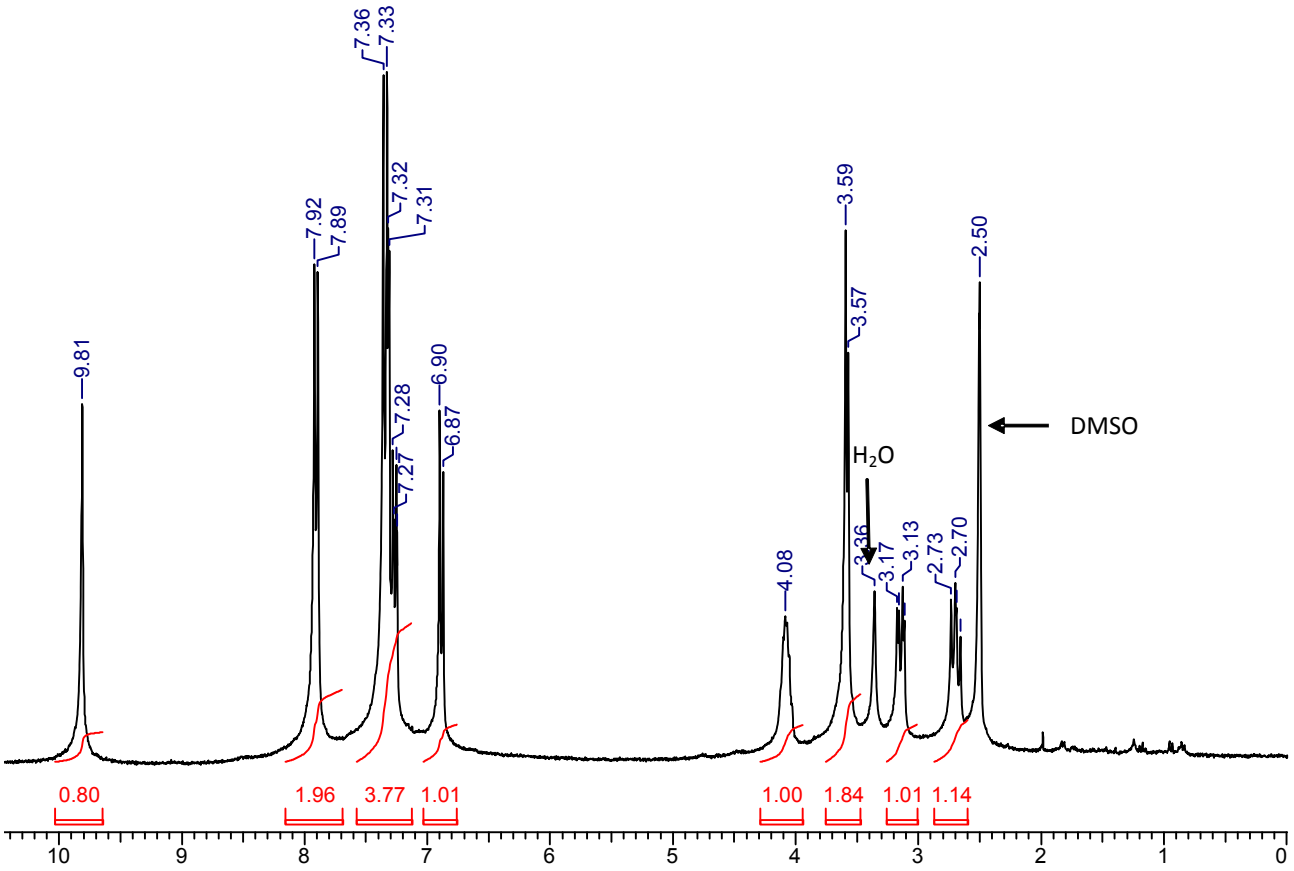


^{1}H NMR spectrum (75 MHz. $CDCl_3$) of compound **3d**.

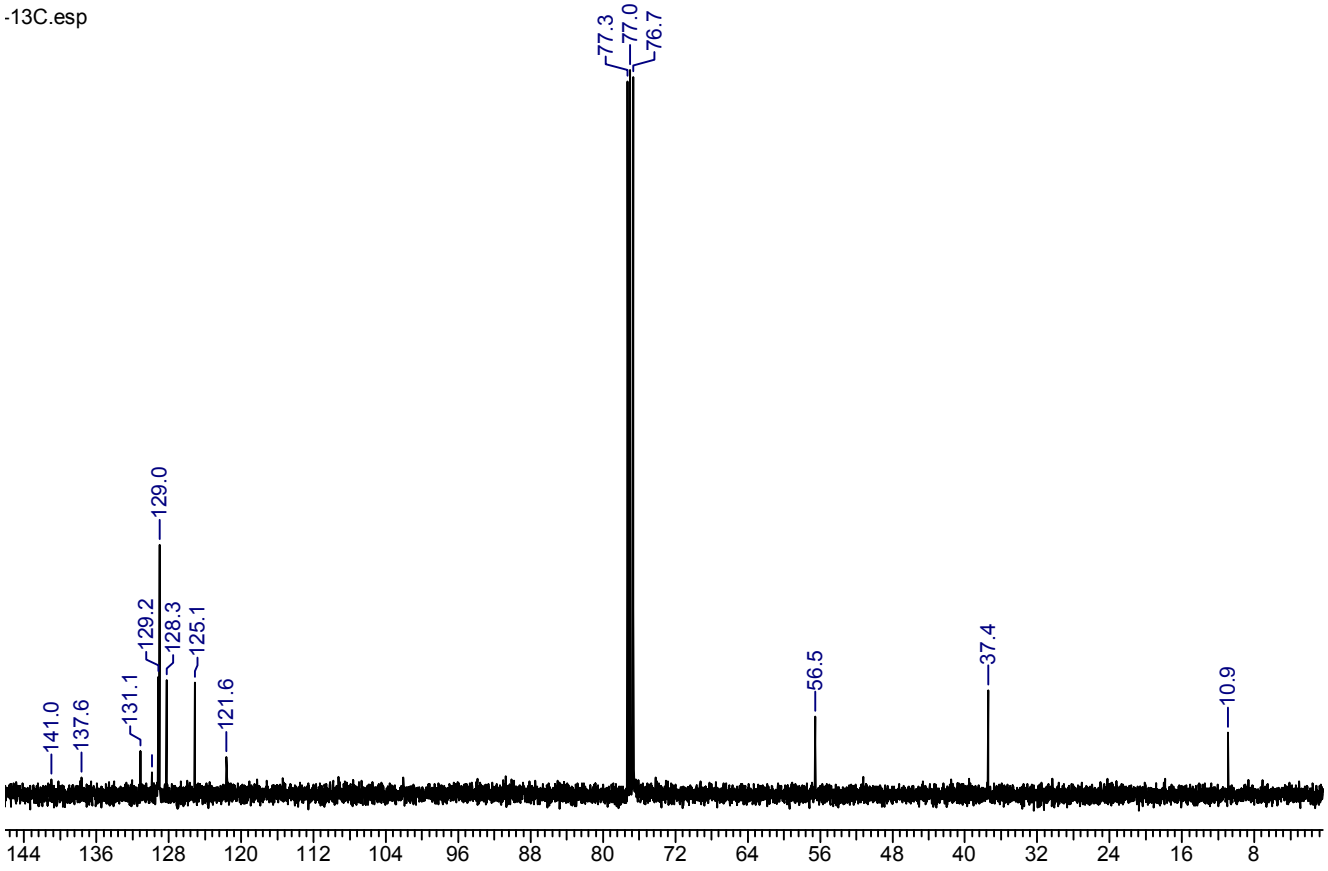


4b

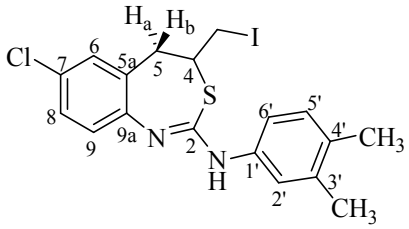
	^{13}C		**^{1}H**
2	-		-
4	56.5		4.24-3.97 (m)
5	37.4	H_b	2.69 (dd; *J*= 13.2; 9.9 Hz)
		H_a	3.14 (dd; J= 13.2; 4.8 Hz)
5a	129, 2		-
6	129.1		7.31 (d; *J*= 2.1 Hz)
7	131.1		
8	128.3		7.26 (dd; *J*= 8.4; 2.1 Hz)
9	121.6		6.89 (d; *J*= 8.4 Hz)
9a	141.0		-
1’	137.6		-
2’, 6’	125.1		7.34 (d; *J*= 9.0 Hz)
3’, 5’	129.0		7.91 (d; *J*= 9.0 Hz)
4’	129.8		-
-CH_2-I	10.8		3.58 (d; *J*= 6.6 Hz)
-NH	-		9.81 (s)



^{1}H NMR spectrum (300 MHz. DMSO-d_6) of compound **4b**.

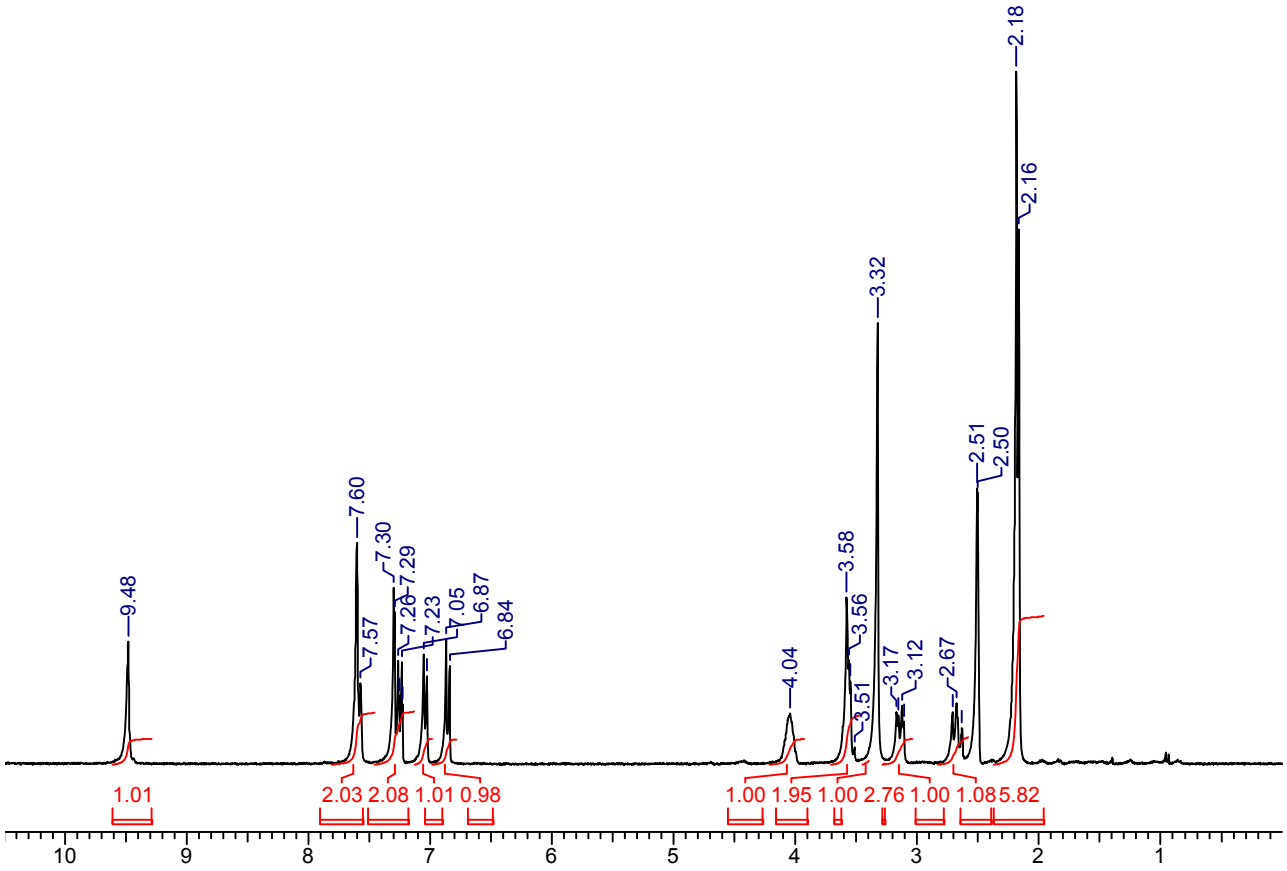


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **4b**.

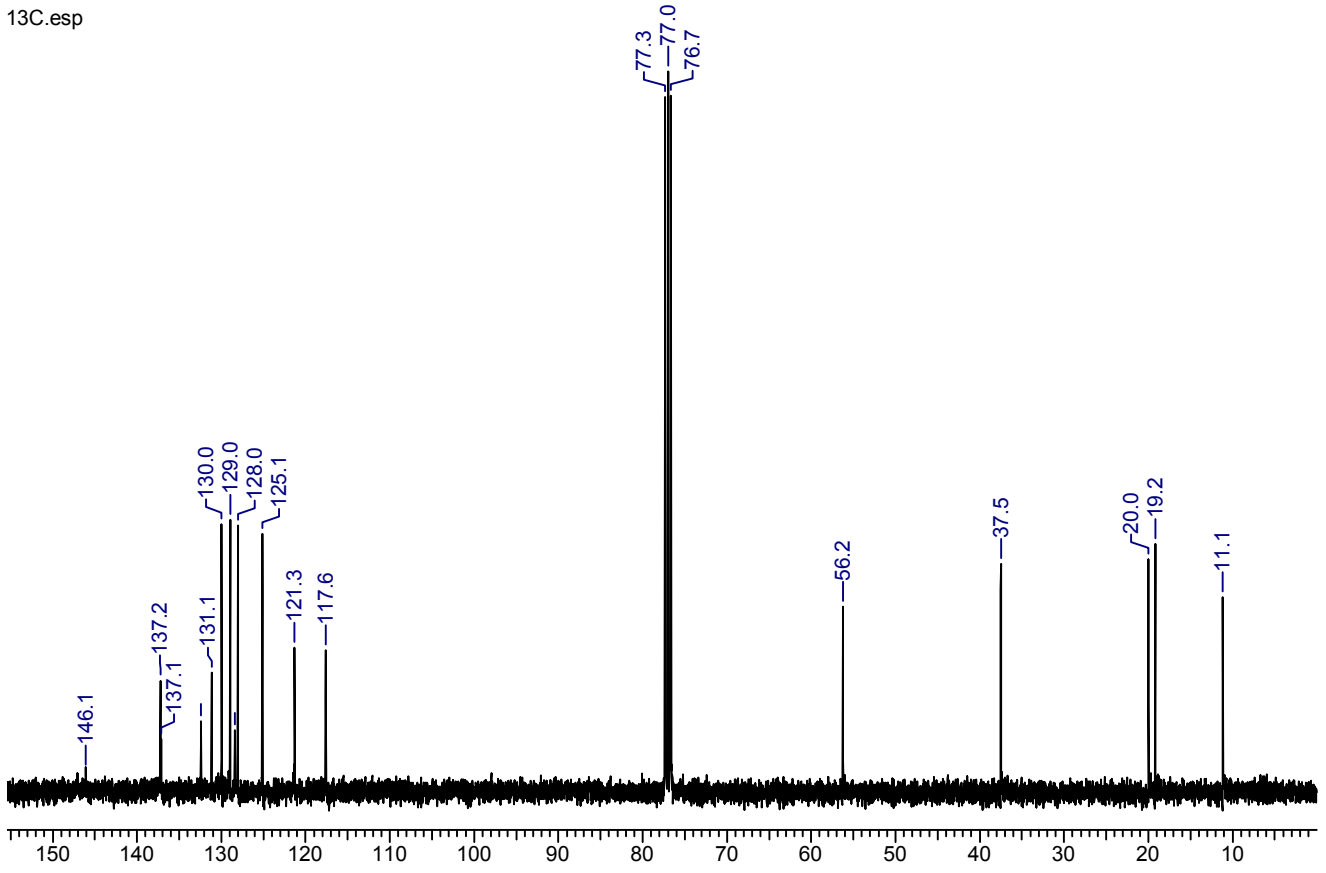


4c

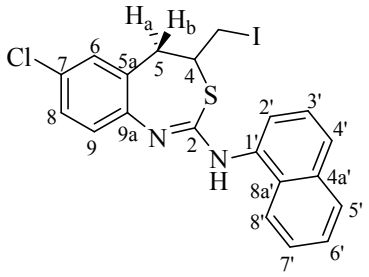
	^{13}C		**^{1}H**
2	-		-
4	56.2		4.05 (br s)
5	37.5	H_b	2.66 (dd; *J*= 13.2; 11.7 Hz)
		H_a	3.14 (dd; *J*= 13.2; 4.8 Hz)
5a	128.3		-
6	125.0		7.29 (d; *J*= 2.4 Hz)
7	131.1		-
8	128.0		7.25 (dd; *J*= 8.7; 2.4 Hz)
9	121.3		6.86 (d; *J*= 8.7 Hz)
9a	146.0		-
1’	137.2		-
2’	128.9		7.60 (s)
3’	137.1		-
4’	132.4		-
5’	117.6		7.04 (d; *J*= 8.1 Hz)
6’	129.7		7.59 (d; *J*= 8.1 Hz)
-CH_2-I	11.1		3.66-3.51 (m)
-CH_3	19.1		2.16 (s)
-CH_3	19.9		2.18 (s)
-NH	-		9.48 (s)



^{1}H NMR spectrum (300 MHz. DMSO-d_6) of compound **4c**.

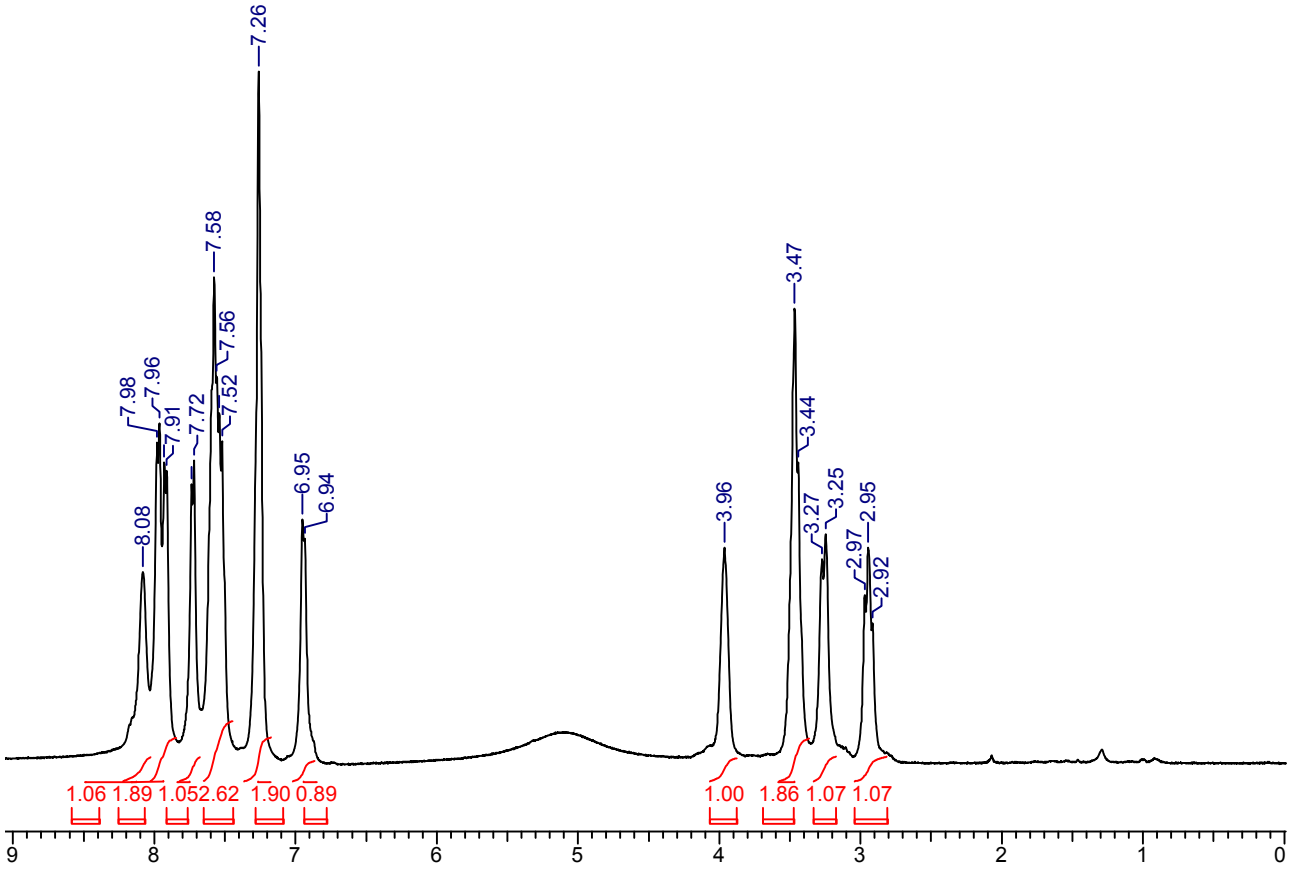


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **4c**.

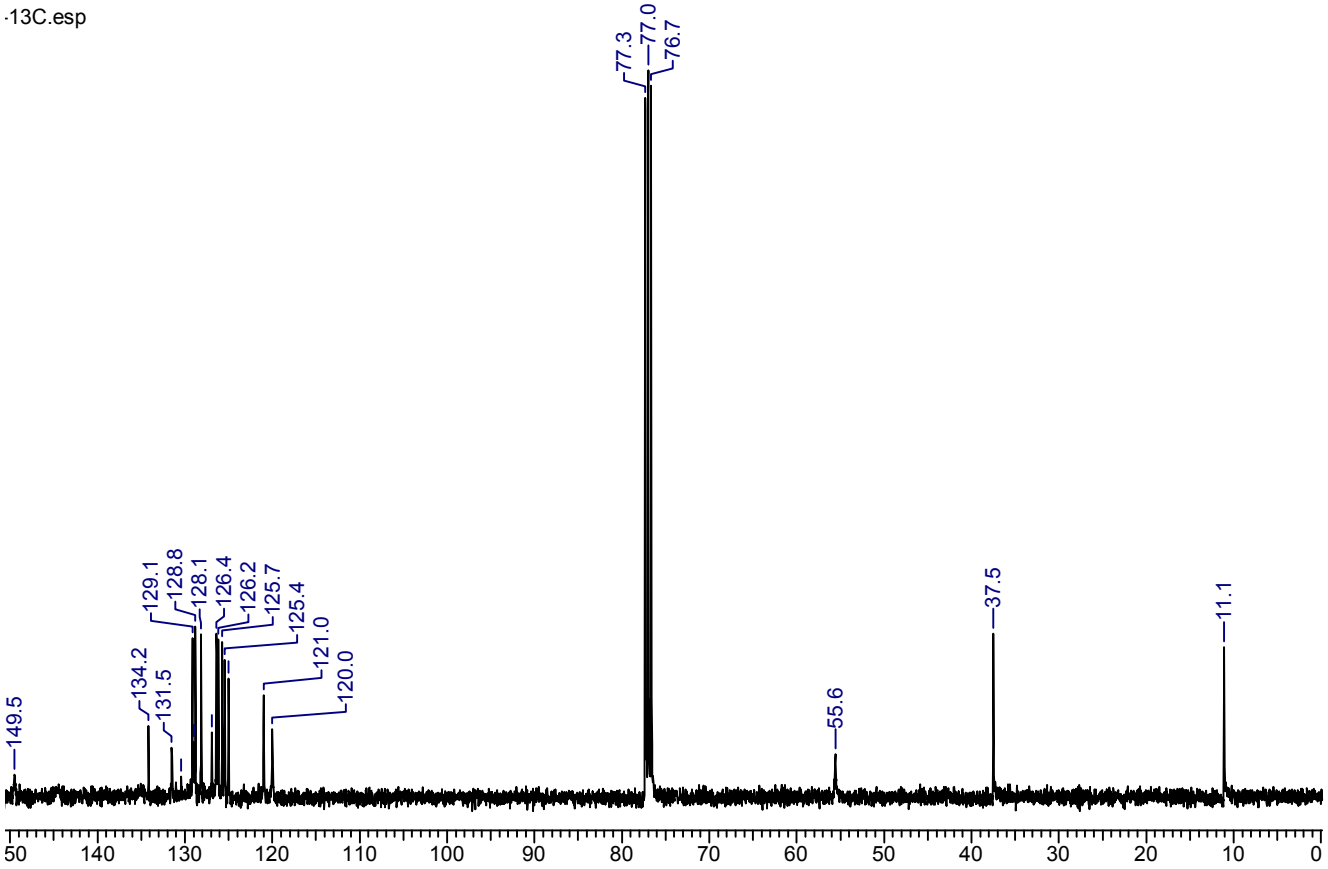


4d

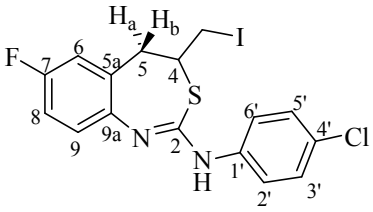
	^{13}C		**^{1}H**
2	-		-
4	55.6		3.96 (br s)
5	37.5	H_b	2.95 (t; *J*= 12.8 Hz)
		H_a	3.26 (d; *J*= 9.6 Hz)
5a	126.8		-
6	129.1		7.26 (br s)
8	125.4		
7	131.5		-
9	124.9		6.94 (d; *J*= 6.0 Hz)
9a	149.5		-
1’	128.9		-
2’	126.2		8.08 (br s)
3’	126.4		8.02-7.87 (m)
5’	128.8		
4’	120.0		7.73 (d; *J*= 7.2 Hz)
4a’	134.2		-
6’	125.7		7.66-7.43 (m)
7’	128.1		
8’	121.0		
8a’	130.4		-
-CH_2-I	11.1		3.45 (d; *J*= 10 Hz)



^{1}H NMR spectrum (400 MHz. $CDCl_3$) of compound **4d**.

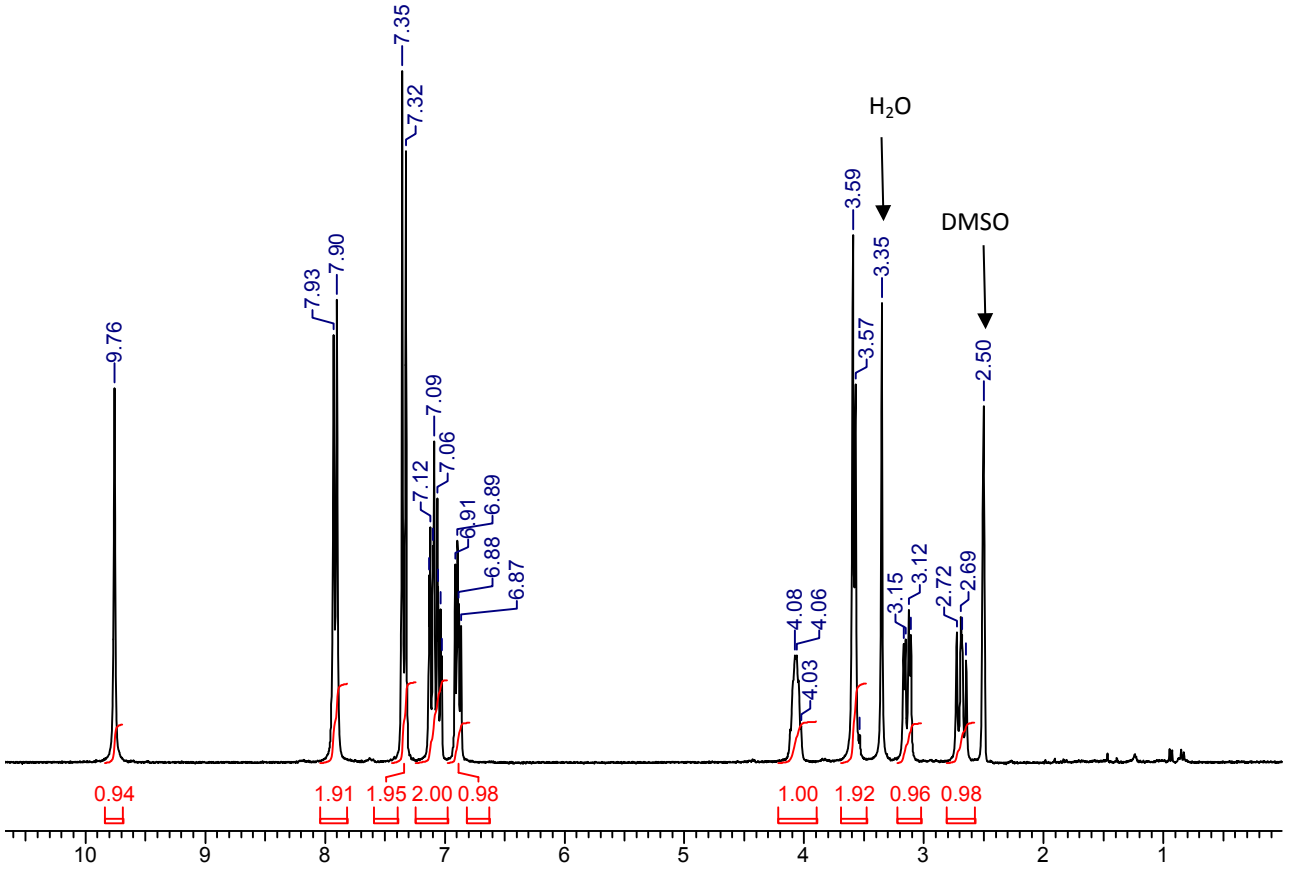


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **4d**.

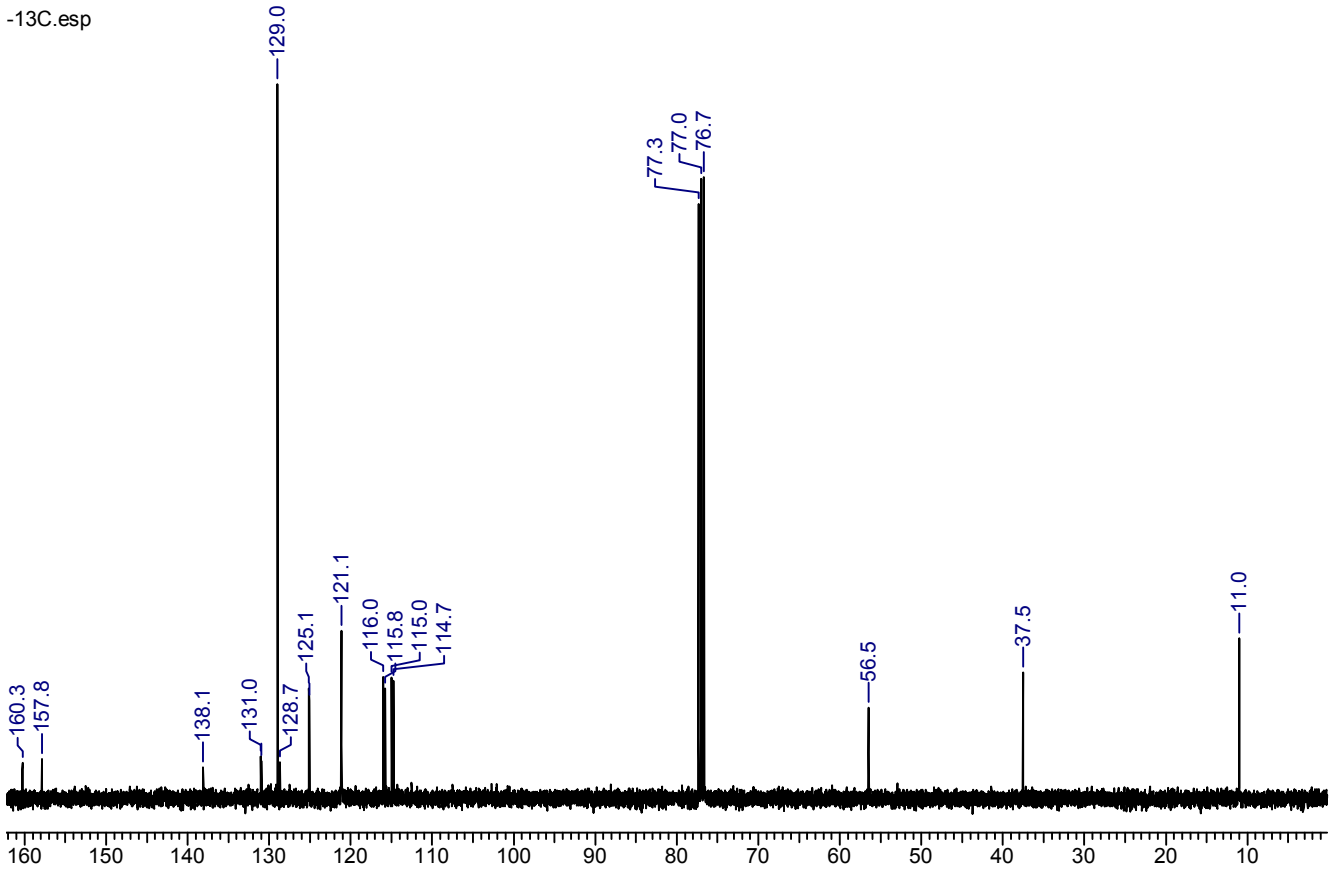


4e

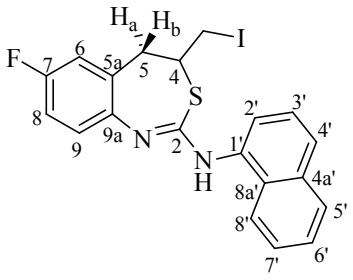
	^{13}C		**^{1}H**
2	-		-
4	56.5		4.15-4.01 (m)
5	37.5	H_b	2.68 (dd; *J*= 13.2; 10.2 Hz)
		H_a	3.14 (dd; *J*= 13.2; 4.5 Hz)
5a	130.9 (d, *J* =7.8 Hz)		
6	115.8 (d, *J* = 22.4 Hz)		7.11 (dd; *J*= 9.3; 2.7 Hz)
7	159.0 (d, *J* =241.6 Hz)		
8	114.8 (d, *J* =22.5 Hz)		7.04 (dd; *J*= 8.4; 2.7 Hz)
9	125.0 (d, *J* =7.8 Hz)		6.89 (dd; *J*= 8.4; 5.4 Hz)
9a	-		-
1’	138.0		-
2’, 6’	121.1		7.34 (d; *J*= 9.0 Hz)
3’,5’	128.9		7.92 (d; *J*= 9.0 Hz)
4’	128.6		-
-CH_2-I	11.0		3.58 (d; *J*= 6.6 Hz)
-NH	-		9.76 (s)



^{1}H NMR spectrum (300 MHz. DMSO-d_6) of compound **4e**.

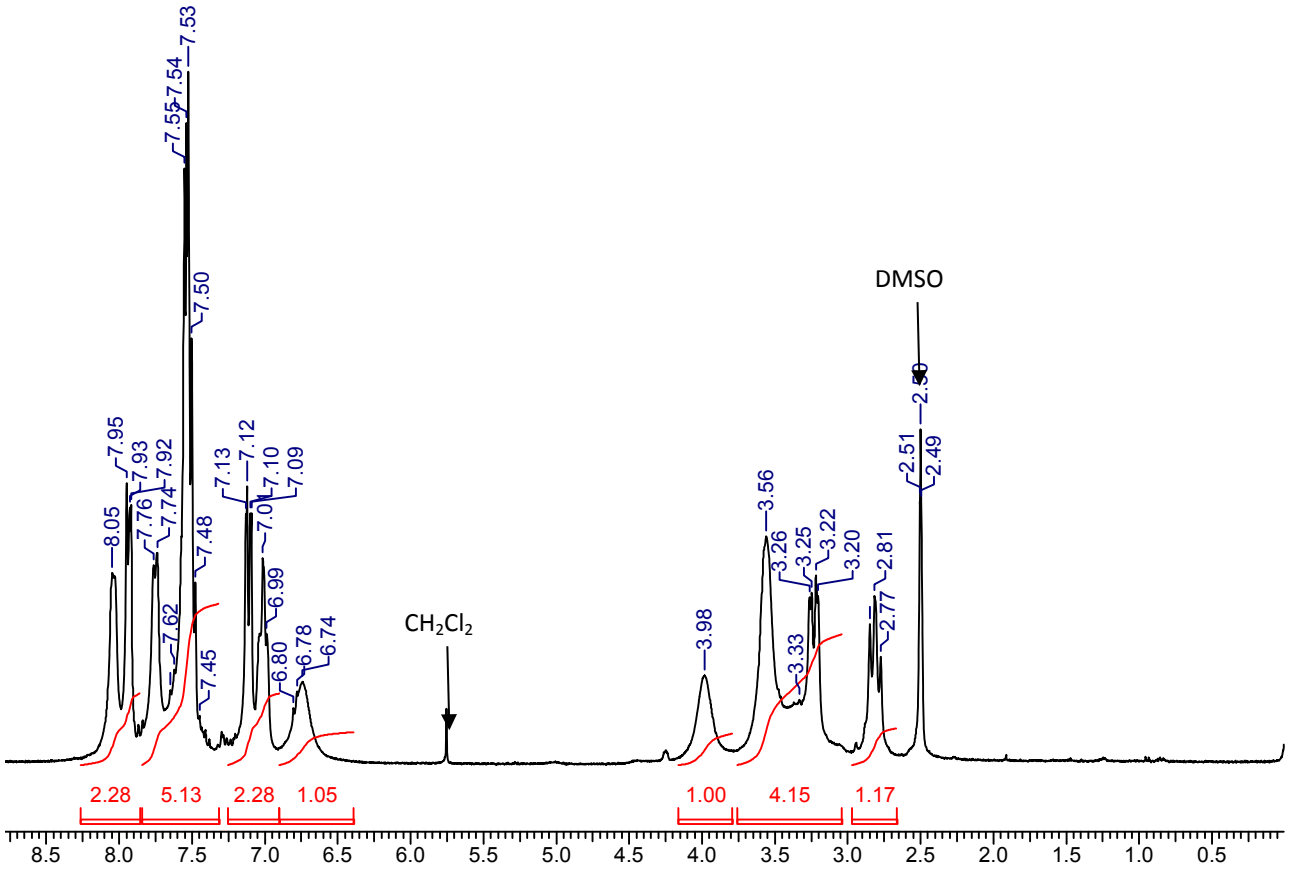


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **4e**.

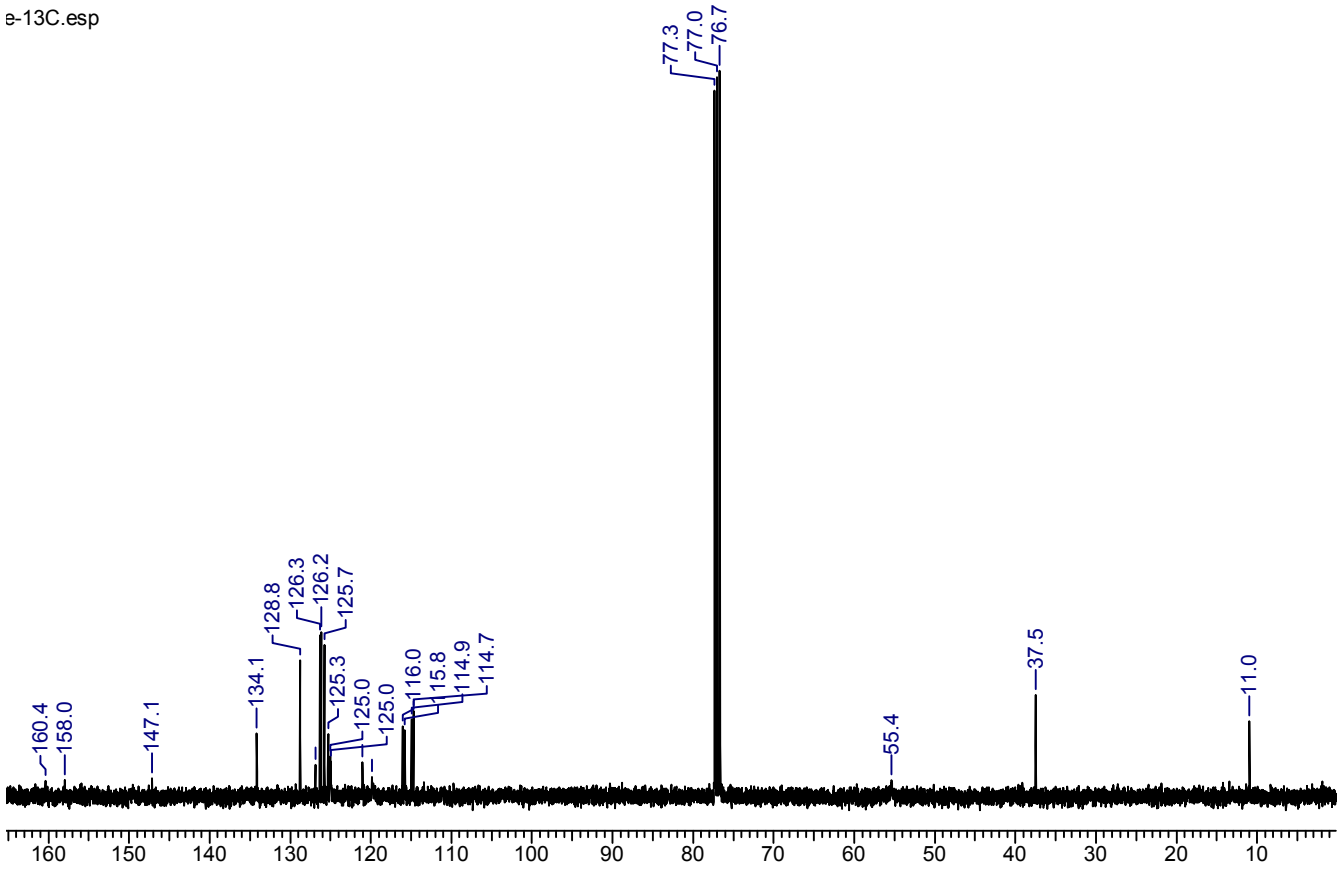


4f

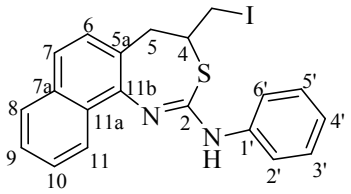
	^{13}C		**^{1}H**
2	-		-
4	55.4		3.98 (br s)
5	37.5	H_b	2.90-2.70 (m)
		H_a	3.23 (dd; *J*= 13.2; 4.2 Hz)
5a	126.9		-
6	115.9 (d, *J* =23.3 Hz)		7.06-6.96 (m)
8	114.8 (d; *J* =21.7 Hz)		7.11 (dd; *J*= 9.0; 2.7 Hz)
7	159.1 (d; *J* = 241.6 Hz)		-
9	125.0 (d, *J* =8.6 Hz)		6.74 (br s)
9a	147.1		-
1’	-		-
2’	126.1		8.12-8.00 (m)
5’	128.7		7.98-7.89 (m)
4’	119.8		7.81-7.71 (m)
4a’	134.4		-
3’	126.3		7.62-7.46 (m)
6’	125.7		
7’	125.3		
8’	121.0		
8a’	-		-
-CH_2-I	11.0		3.56 (br s)



^{1}H NMR spectrum (300 MHz. DMSO-d_6) of compound **4f**.

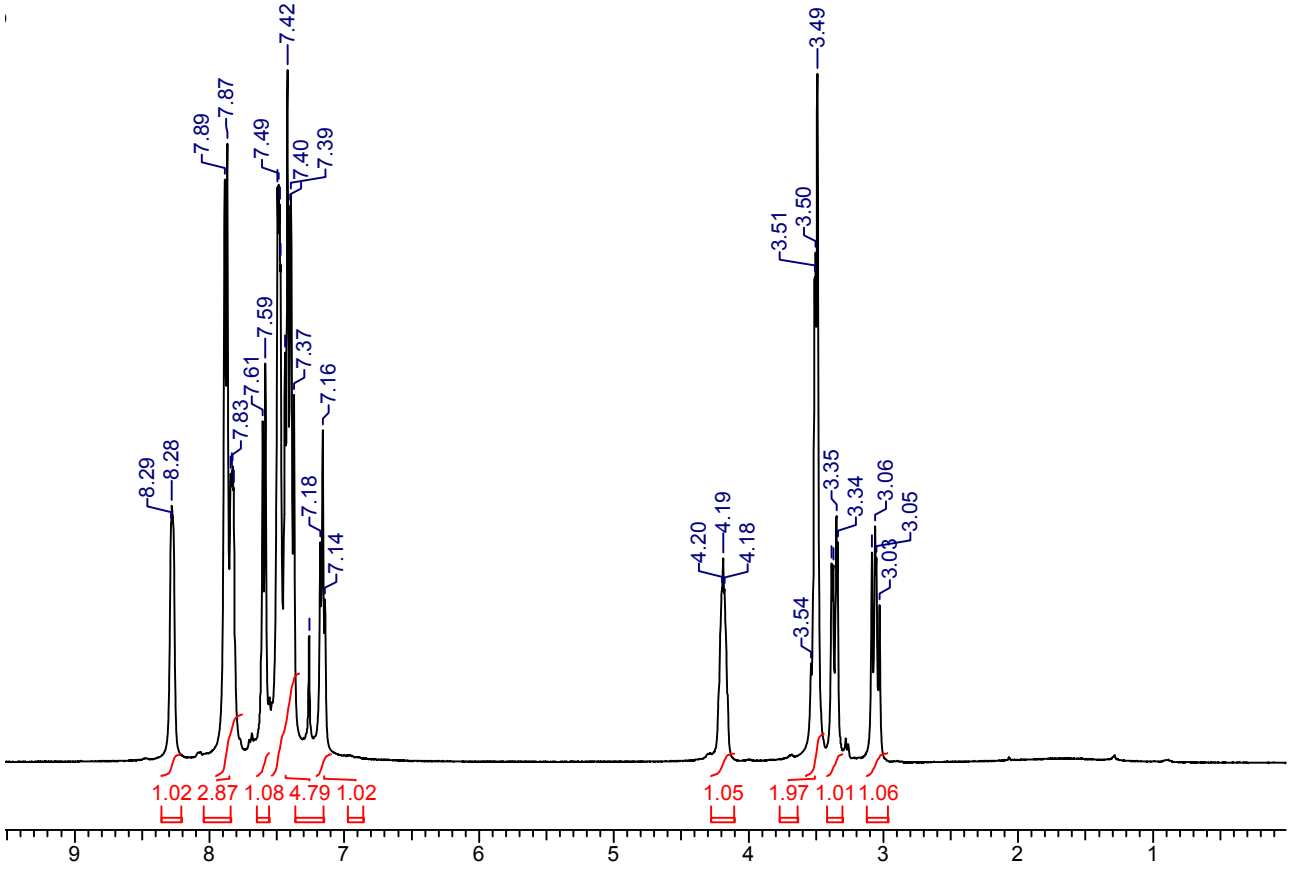


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **4f**.

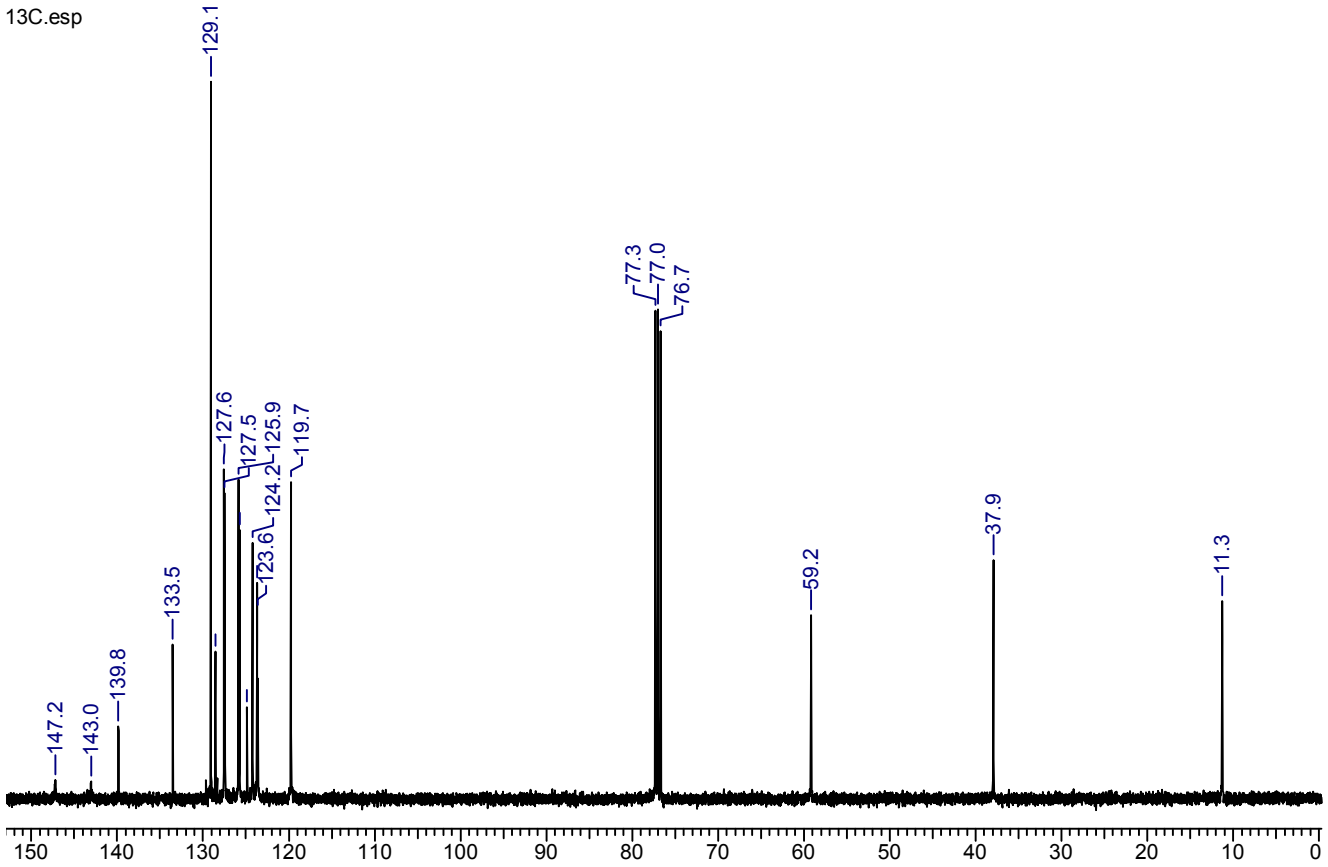


4g

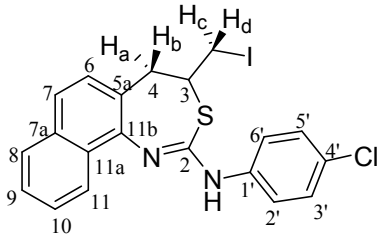
	^{13}C		^{1}H
2	-		-
4	59.2		4.25-4.14 (m)
5	37.9	H_b	3.06 (dd; *J*= 13.6; 9.6 Hz)
		H_a	3.36 (dd; *J*= 13.6; 4.4 Hz)
5a	-		-
6	127.5		7.84-7.80 (m)
7a	133.5		-
8	123.7		8.32-8.24 (m)
9	125.7		7.53-7.45 (m)
7	125.8		
10	123.6		7.60 (d; *J*= 8.4 Hz)
11	127.6		7.38 (d; *J*= 8.4 Hz)
11a	128.5		-
11b	147.2		-
1’	139.8		-
2’, 6’	119.7		7.43 (d; *J*= 7.6 Hz)
3’, 5’	129.1		7.88 (d; *J*= 7.6 Hz)
4’	124.2		7.16 (t; *J*= 7.2 Hz)
-CH_2-I	11.3		3.57-3.46 (m)



^{1}H NMR spectrum (400 MHz. $CDCl_3$) of compound **4g**.

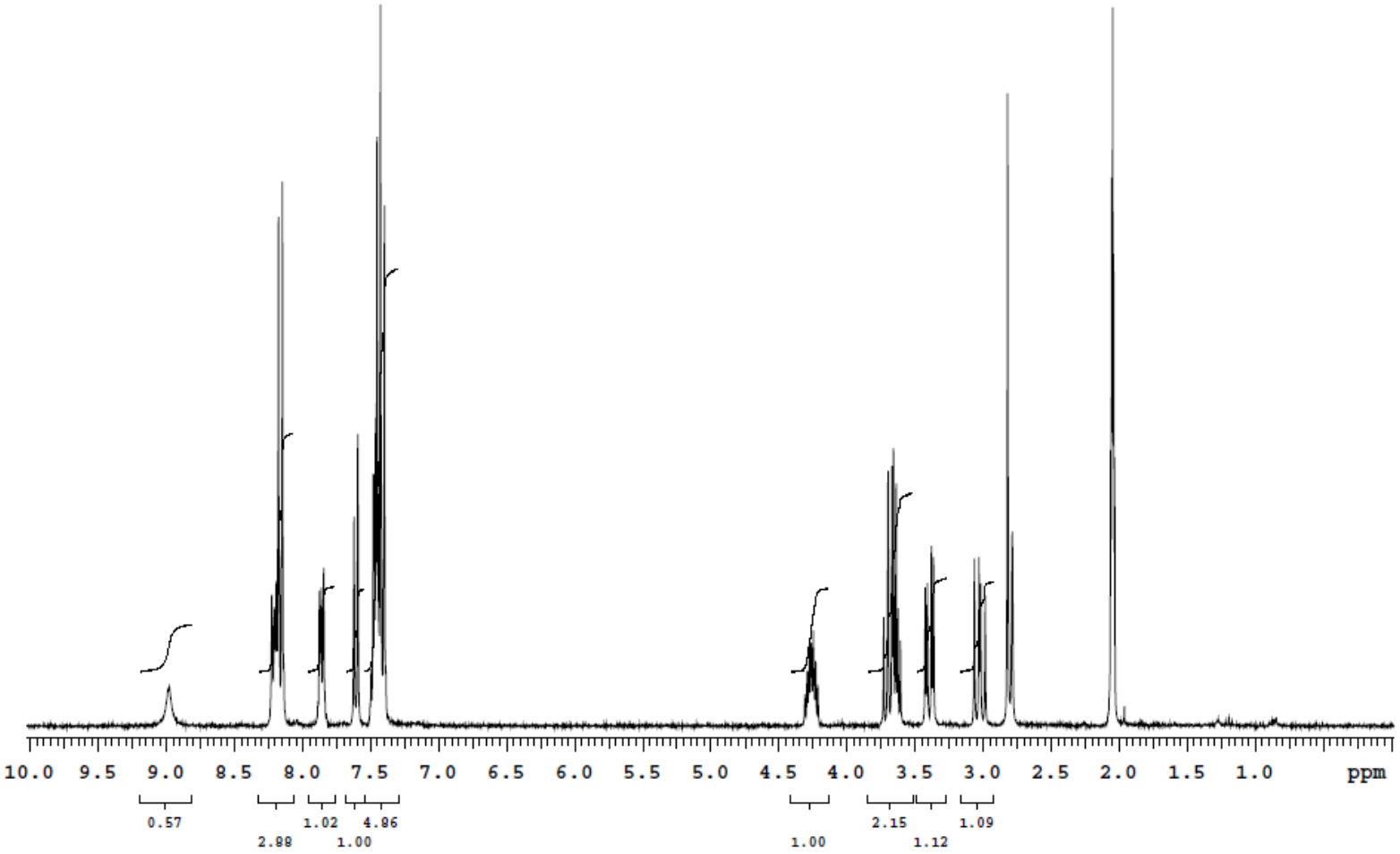


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **4g**.

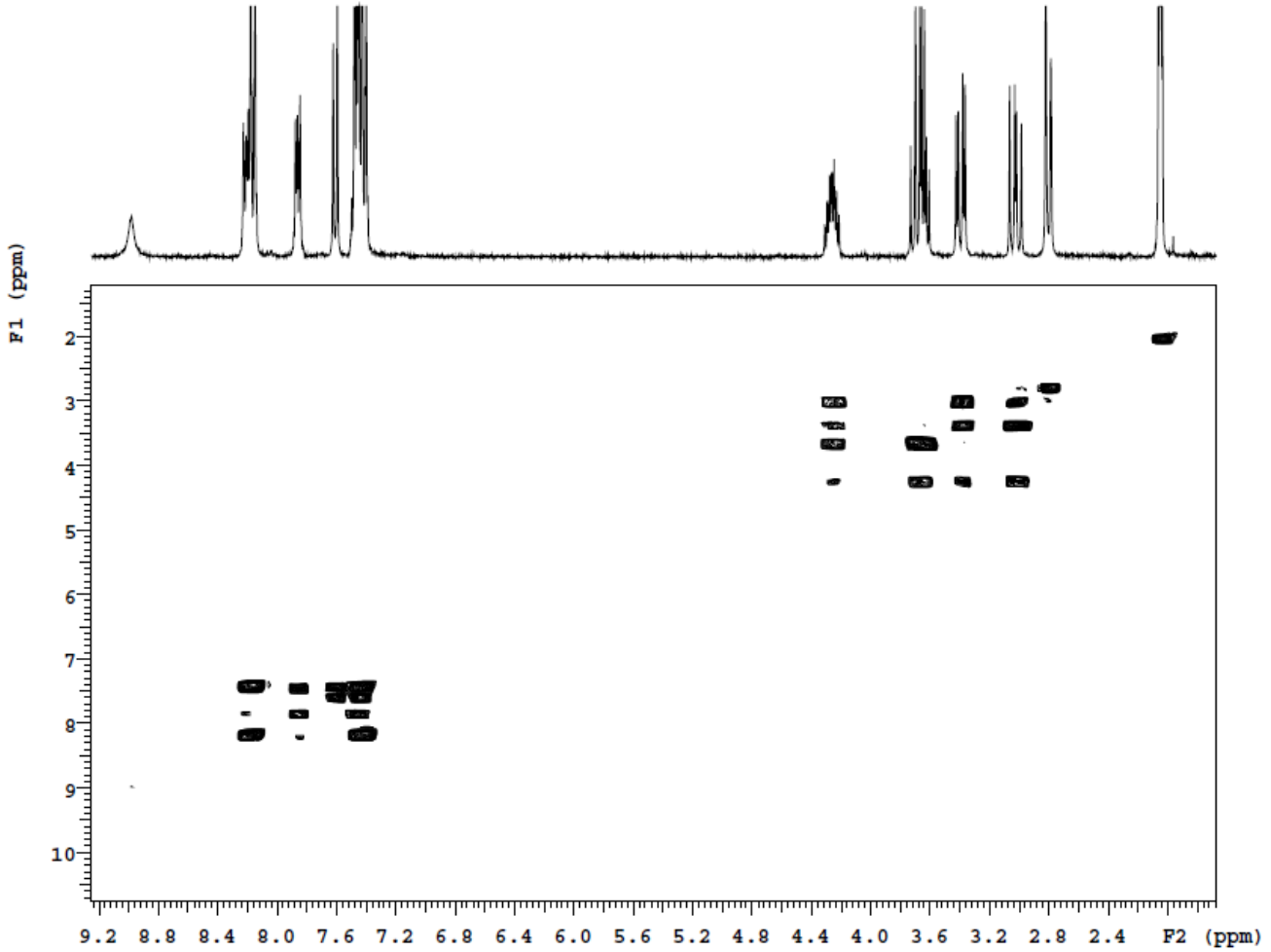


4h

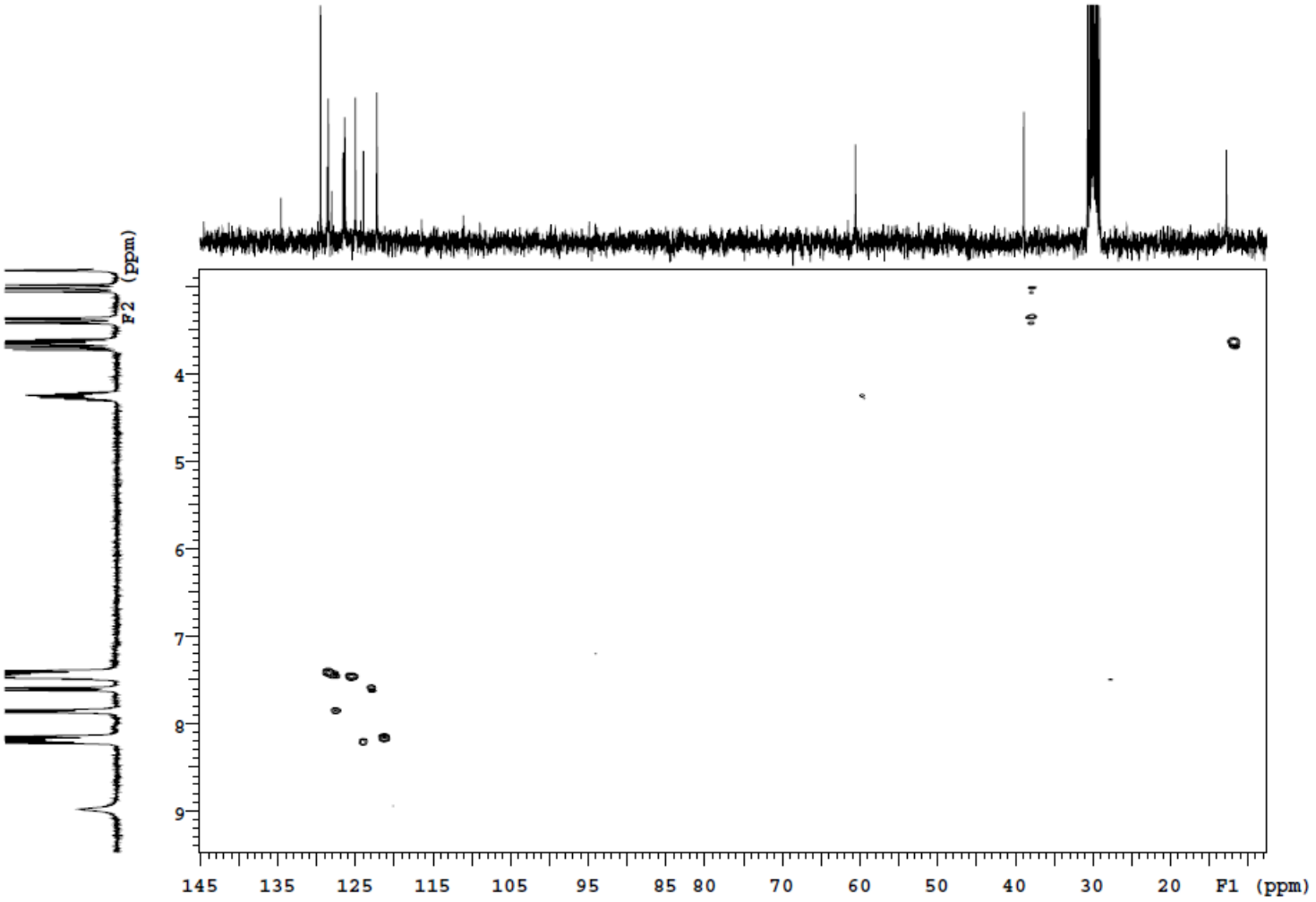
	^{13}C		**^{1}H**
2	178.0		-
4	60.2		4.26-4.24 (m)
5	38.9	H_b	3.03 (dd; J=13.5, 9.9 Hz)
		H_a	3.40 (dd; J=13.5, 4.5 Hz)
5a	129.5		-
6	128.7		7.44 (d; J= 8.1 Hz)
7	124.0		7.61 (d; J= 8.1 Hz)
7a	134.6		-
8, 9	126.4		7.50-7.47 (m)
10	128.5		7.87-7.84 (m)
11	125.0		8.20 (dd, J= 9.9, 5.4 Hz)
11a	126.6		-
11b	144.5		-
1’	141.5		-
2’, 6’	122.2		8.16 (d; J= 8.7 Hz)
3’, 5’	129.5		7.41 (d; J= 8.7 Hz)
4’	128.1		-
$-CH_2-I$	12.8	H_c	3.63 (dd; J= 10.2, 5.7 Hz)
		H_d	3.69 (dd; J= 18.3, 10.2 Hz)
-NH	-		8.98 (br)



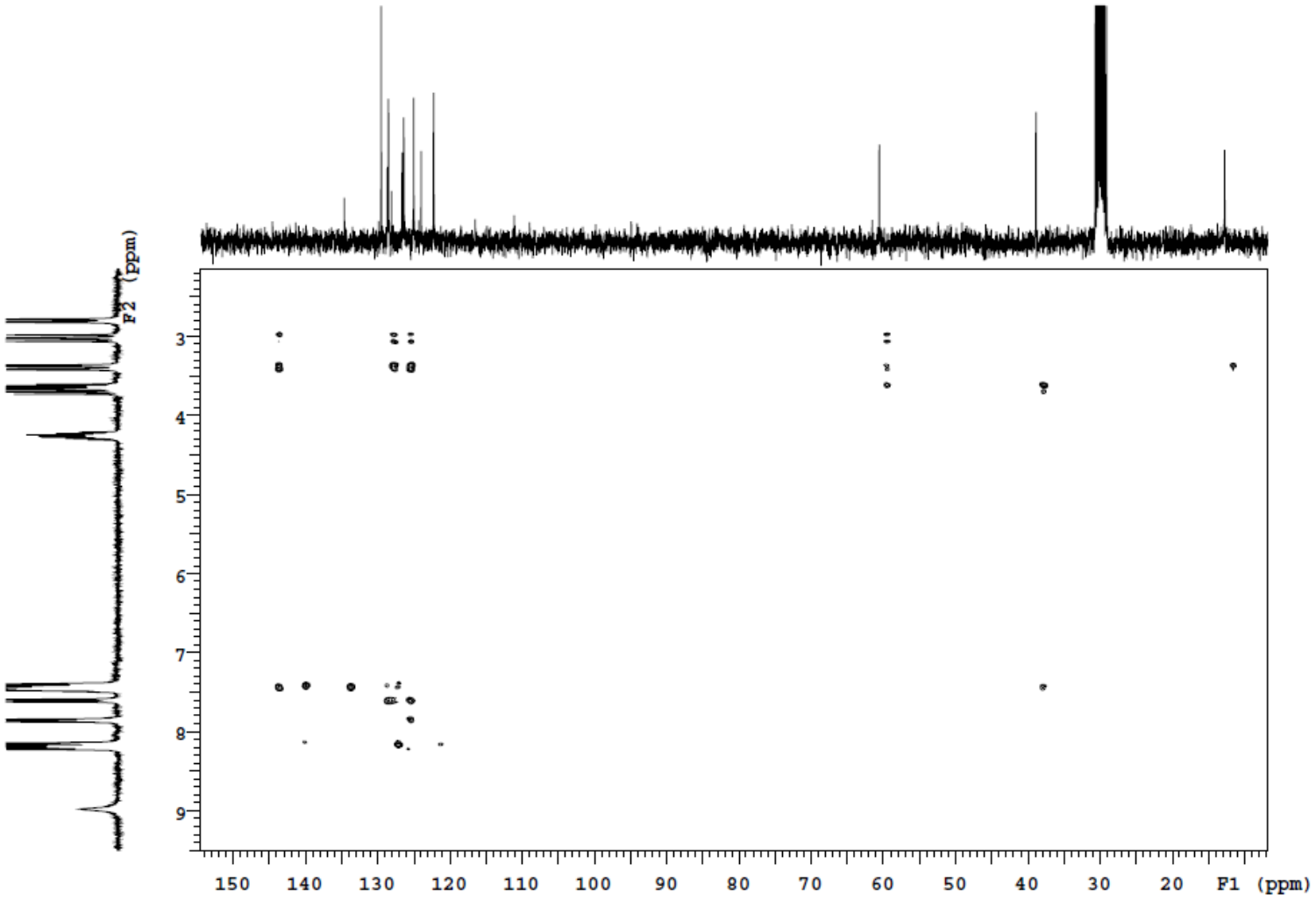
^{1}H NMR spectrum (300 MHz. Acetone-d_6) of compound **4h**.



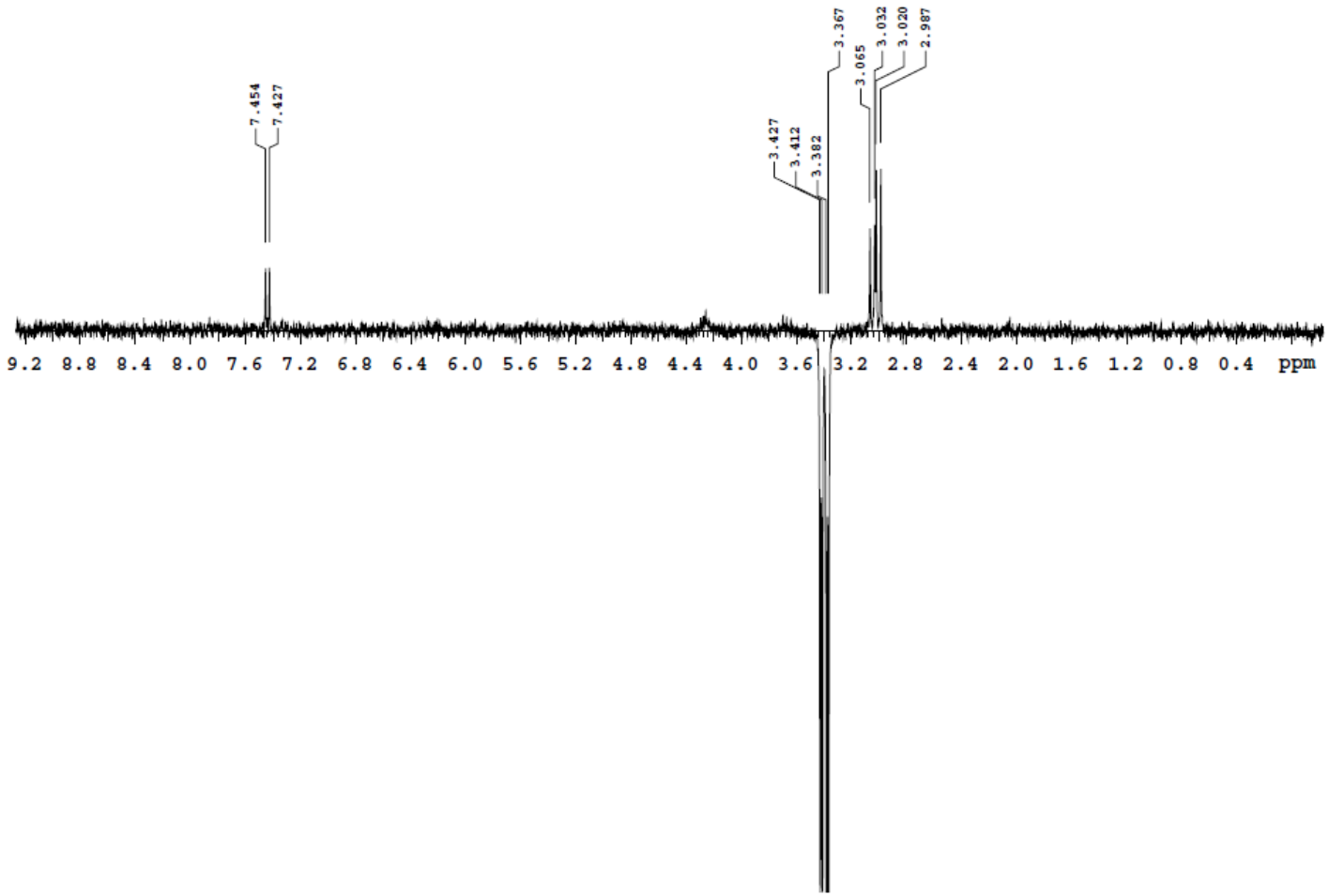
COSY spectrum of **4h** (Acetone-d_6)



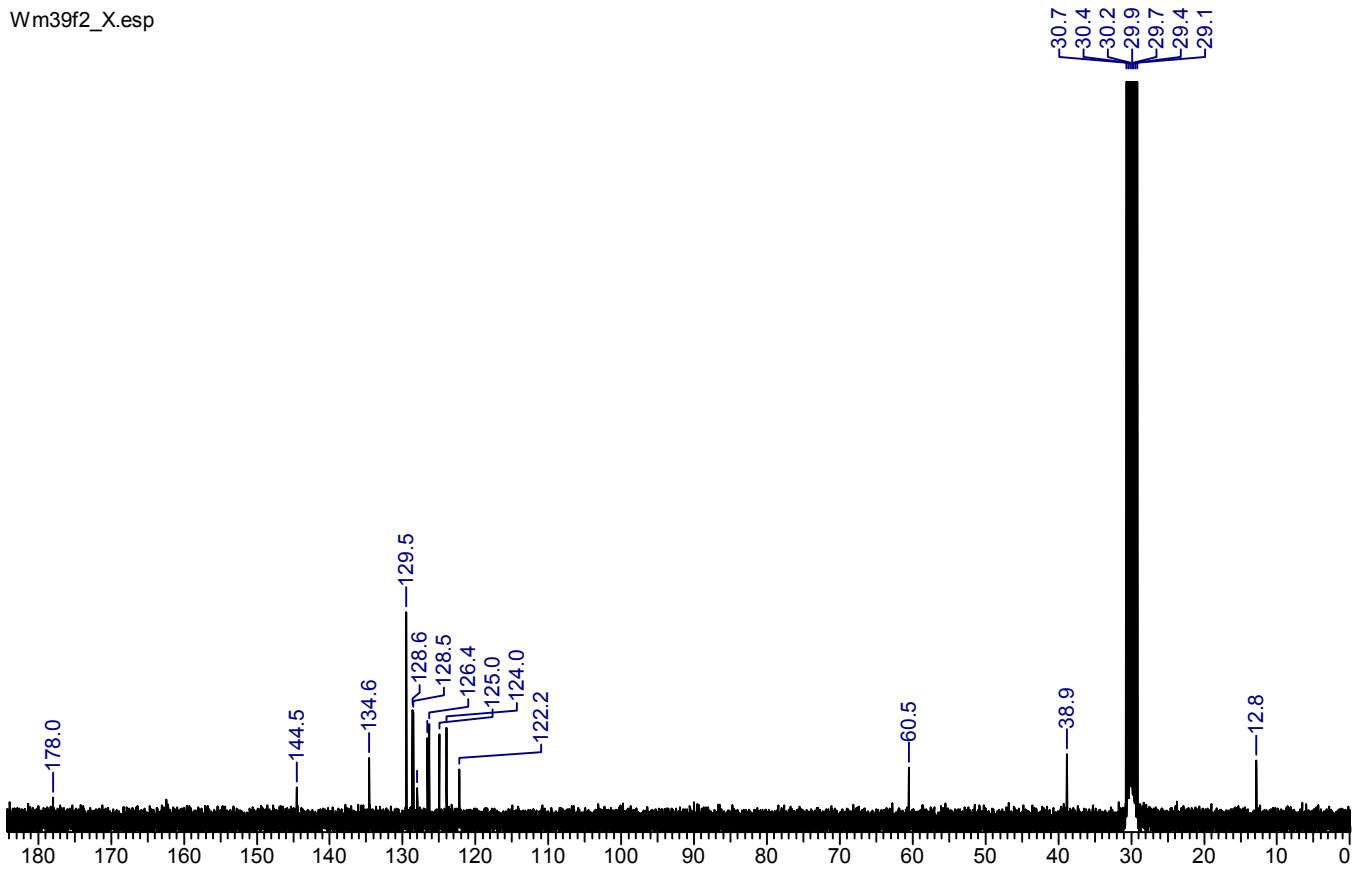
HMQC spectrum of **4h** (Acetone-d_6)



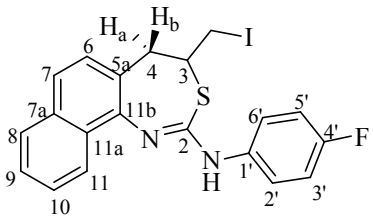
HMBC spectrum of **4h** (Acetone-d_6)



NOESY 1D spectrum of **4h** (Acetone-d_6, 300 MHz) irradiating the signal at δ 3.40.

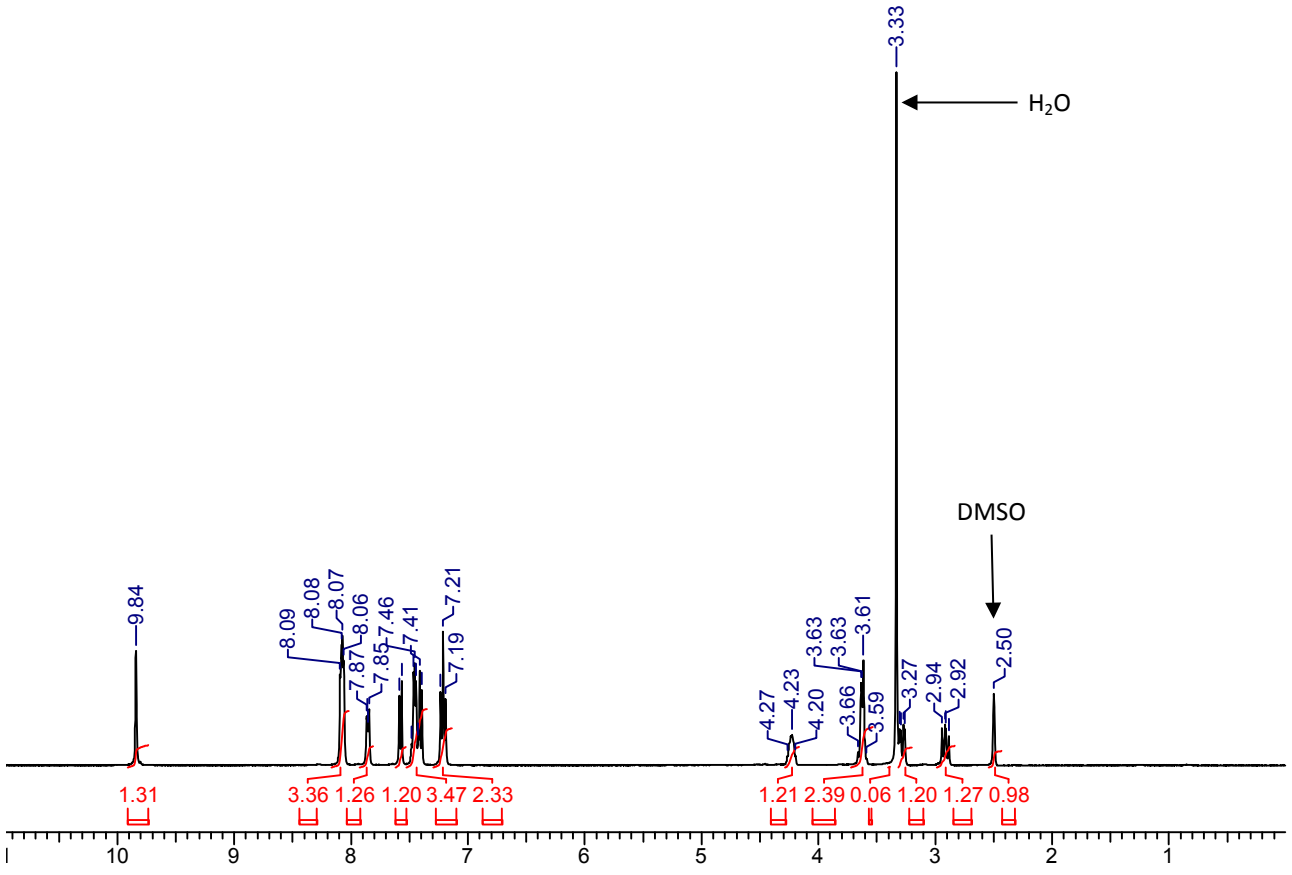


^{13}C NMR spectrum (75 MHz. Acetone-d_6) of compound **4h**.

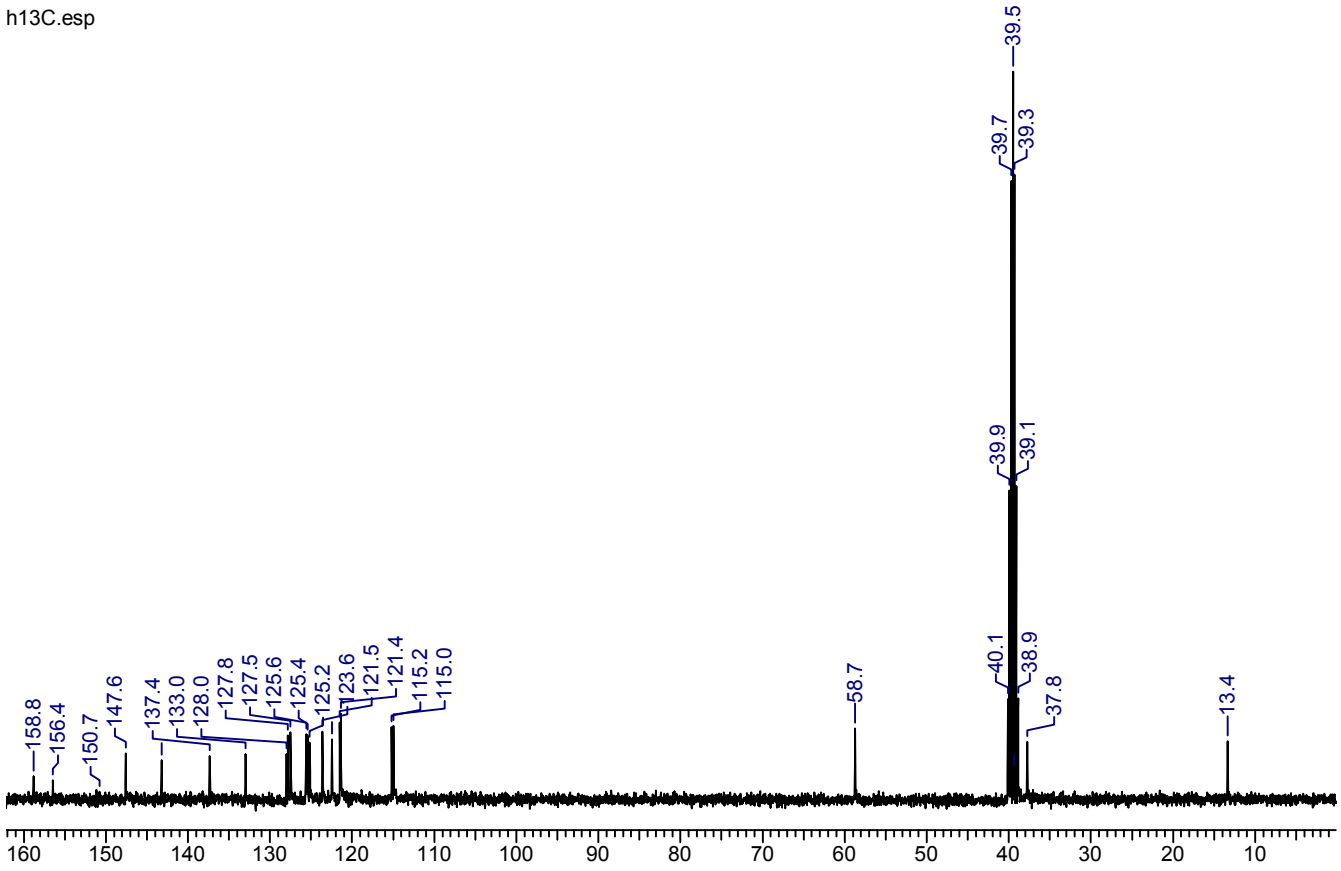


4i

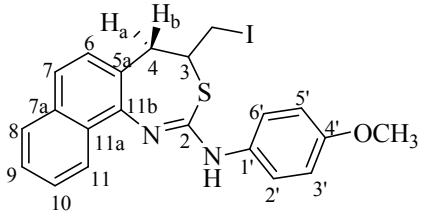
	^{13}C	**^{1}H**
2	-	-
4	58.7	4.29-4.16 (m)
5	37.8	H_b 2.91 (dd; *J*=13.6; 10.0 Hz) H_a 3.28 (dd; *J*= 13.6; 4.8Hz)
5a	125.2	-
6	127.5	7.40 (d; *J*= 8.4 Hz)
7	125.6	7.58 (d; *J*= 8.4 Hz)
7a	133.0	-
8	123.6	7.50-7.43 (m)
9	125.4	
10	122.4	7.87-7.85 (m)
11a	128.0	-
11b	147.6	
11	127.8	8.10-8.06 (m)
2', 6'	121.4 (d, *J* =8.2 Hz)	
1'	137.4	
3', 5'	115.1 (d, *J* =21.5 Hz)	7.21 (t; *J*= 8.8 Hz)
4'	156.6 (d, *J* =238.9 Hz)	
-CH_2-I	13.4	3.64-3.61 (m)
-NH	-	9.84 (s)



^{1}H NMR spectrum (400 MHz. DMSO-d_6) of compound **4i**.

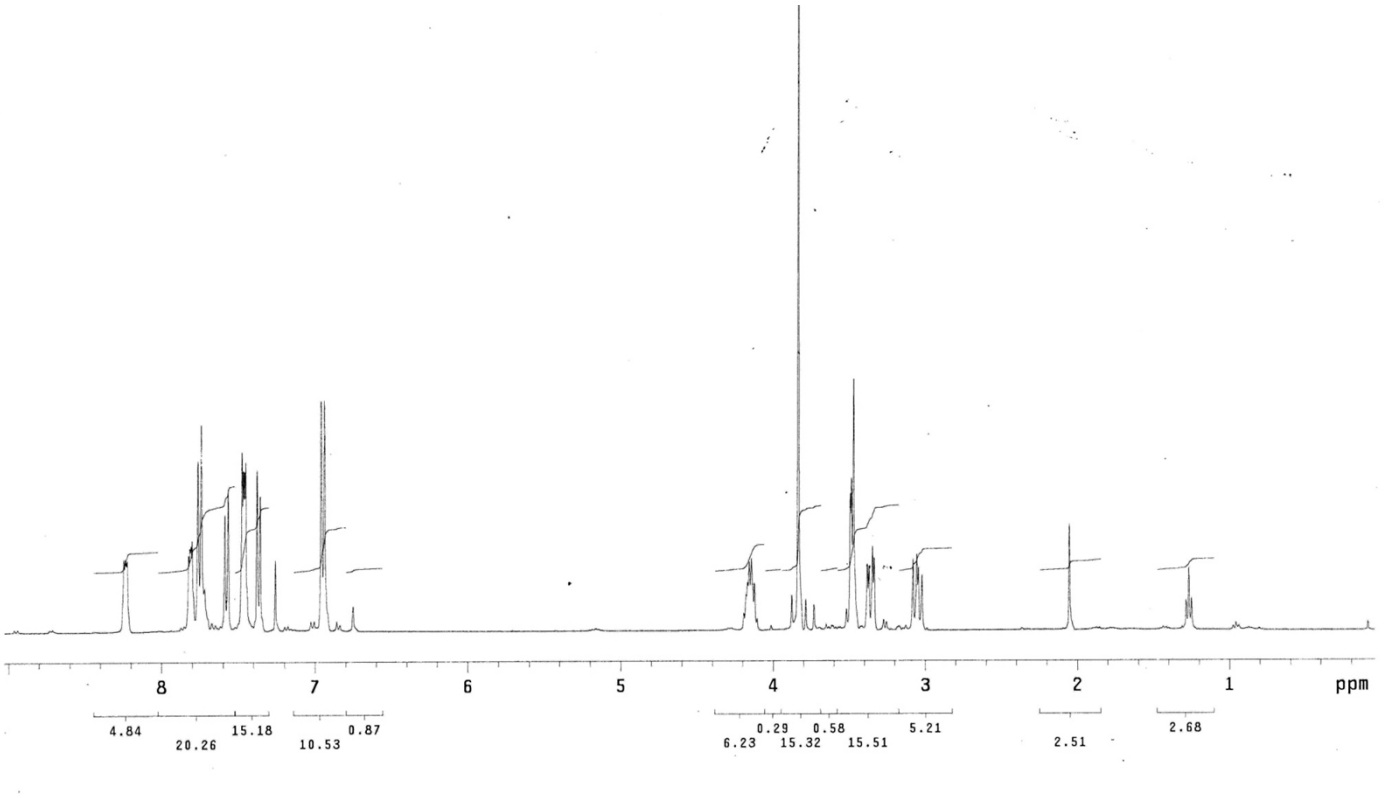


^{13}C NMR spectrum (100 MHz. DMSO-d_6) of compound **4i**.

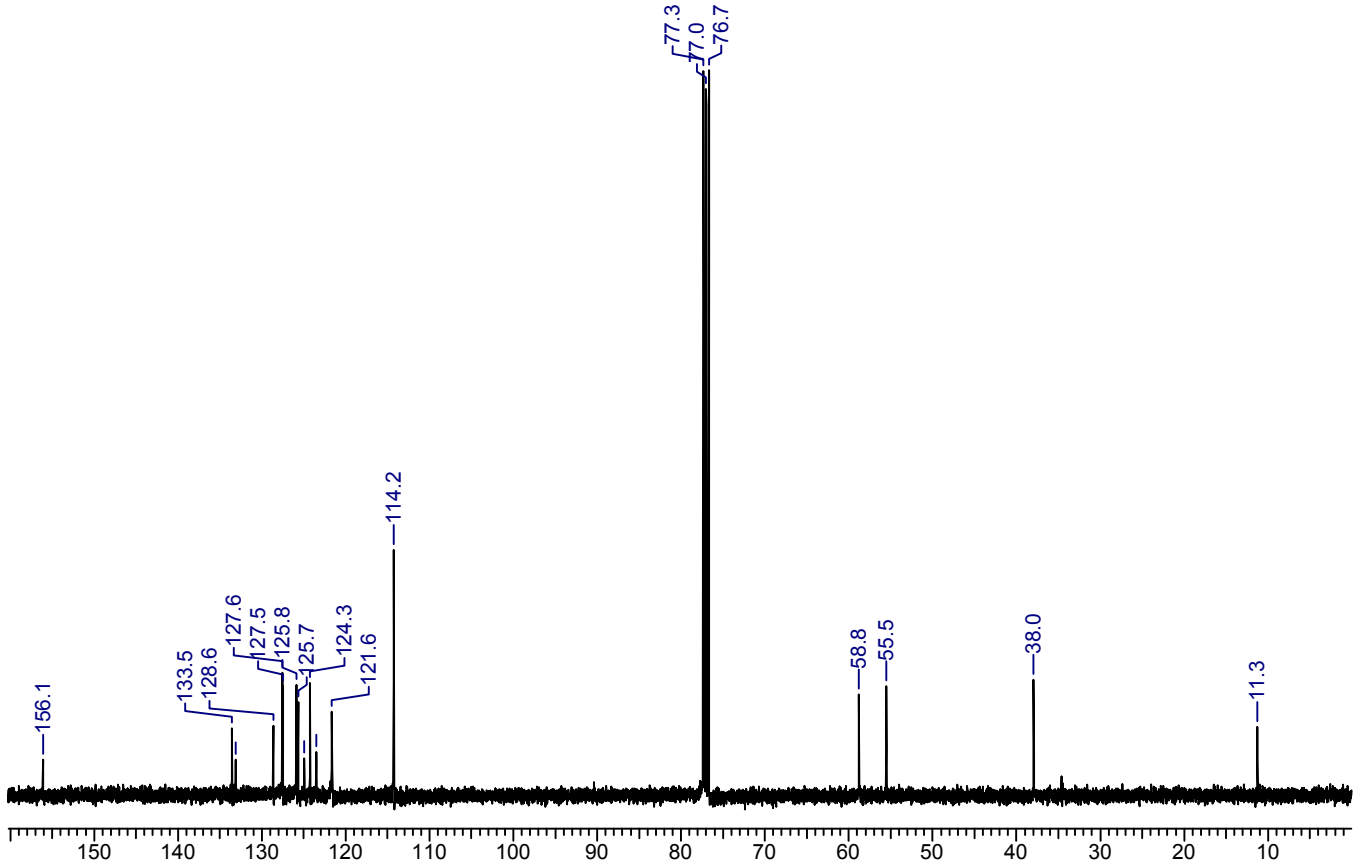


4j

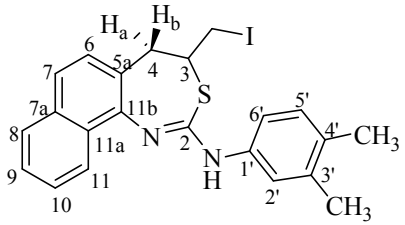
	^{13}C		^{1}H
2	-		-
4	58.8		4.20-4.10 (m)
5	38.0	H_b	3.36 (dd; *J*= 13.6; 4.4 Hz)
		H_a	3.05 (dd; *J*= 13.6; 9.6 Hz)
5a	124.9		
6	127.4		7.37 (d; *J*= 8.4 Hz)
7	125.8		7.57 (d; *J*= 8.4 Hz)
7a	-		-
8	123.4		7.49-7.43 (m)
9	125.6		
10	124.3		7.83-7.79 (m)
11a	128.6		-
11b	133.5		-
11	127.5		8.25-8.19 (m)
2', 6'	114.2		6.95 (d; *J*= 8.4 Hz)
1'	133.1		
3', 5'	121.6		7.77 (d; *J*= 8.4 Hz)
4'	156.1		-
$-CH_2-I$	11.3		3.51-3.47 (m)
$-OCH_3$	55.5		3.84 (s)



^{1}H NMR spectrum (400 MHz. $CDCl_3$) of compound **4j**.

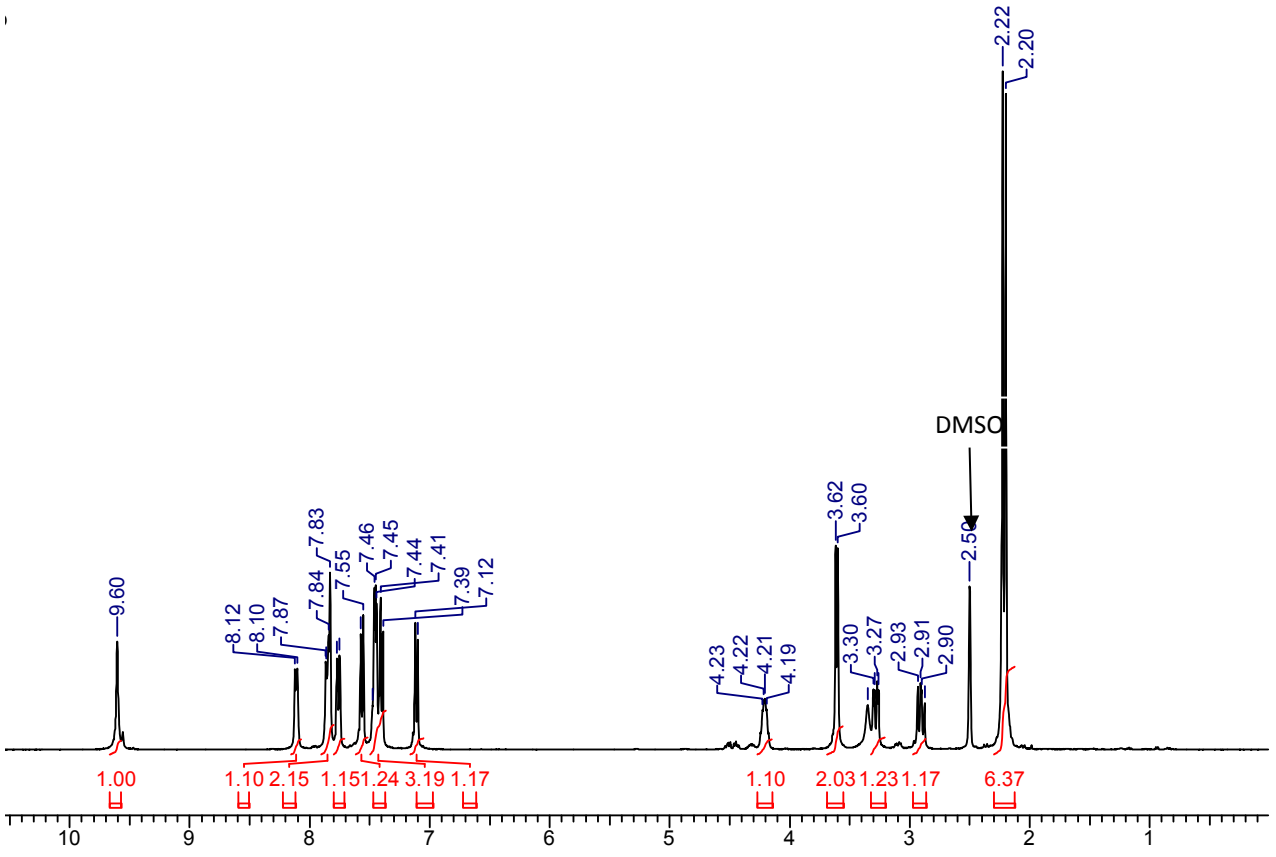


^{13}C NMR spectrum (100 MHz. $CDCl_3$) of compound **4j**.

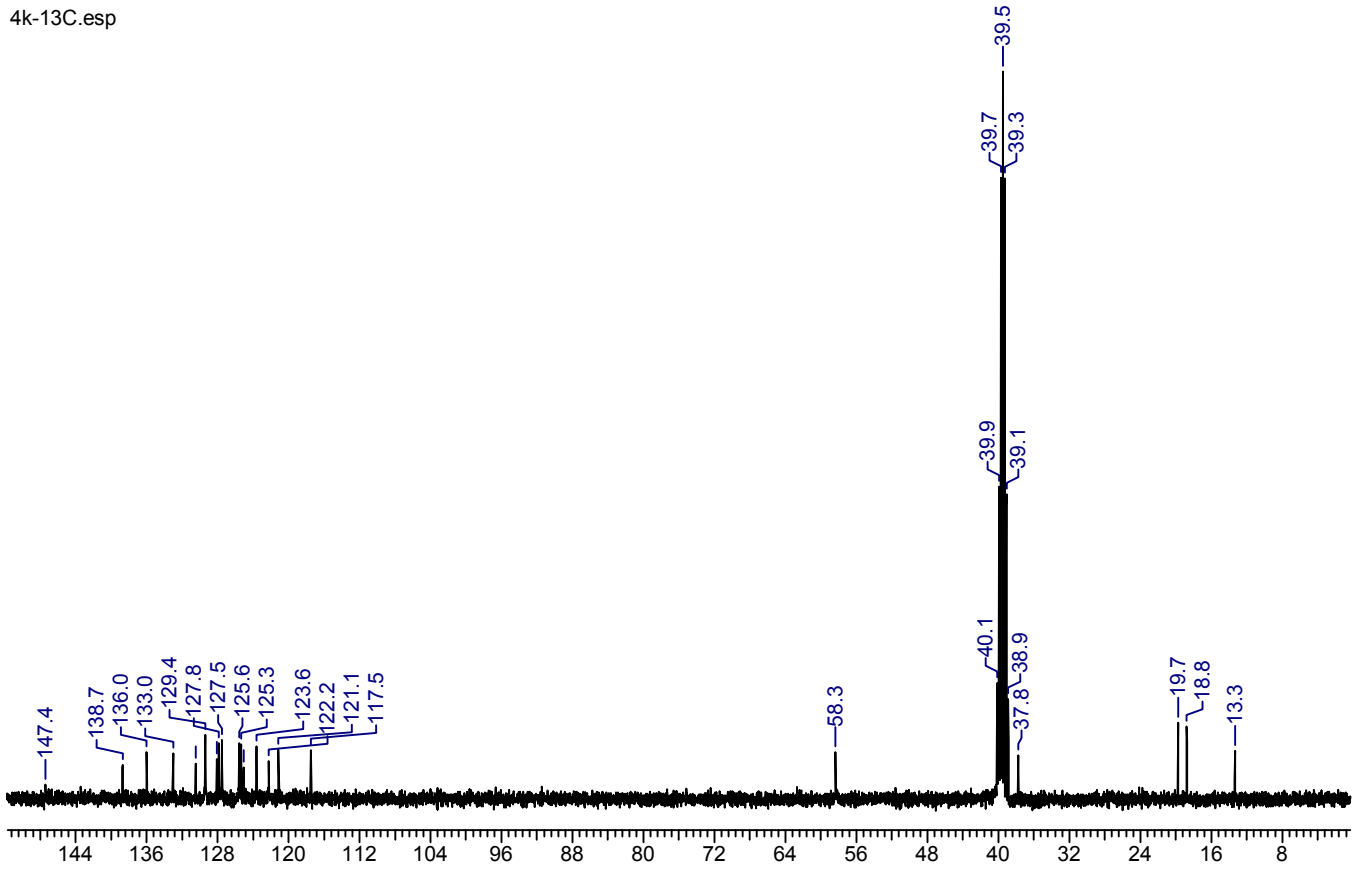


4k

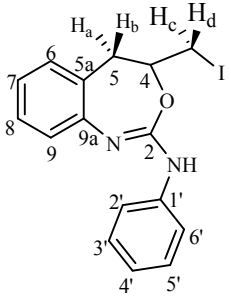
	^{13}C		^{1}H
2	-		-
4	58.3		4.26-4.16 (m)
5	37.8	H_b	3.28 (dd; *J*=13.6; 4.4 Hz)
		H_a	2.91 (dd; *J*= 13.6; 10.0 Hz)
5a	125.0		-
6	127.4		7.40 (d; *J*= 8.4 Hz)
7	125.3		7.56 (d; *J*= 8.4 Hz)
7a	133.0		-
8	123.6		7.49-7.43 (m)
9	125.5		
10	122.2		7.87-7.82 (m)
2’	121.1		
11a	128.1		-
11b	147.4		-
11	127.8		8.12 (d; *J*= 7.6 Hz)
1’	138.7		-
3’	135.9		-
4’	130.4		-
5’	117.4		7.76 (d; *J*= 8.4 Hz)
6’	129.4		7.11 (d; *J*= 8.4 Hz)
-CH_2-I	13.3		3.61 (d; *J*= 7.2 Hz)
-CH_3	18.8		2.20 (s)
-CH_3	19.7		2.23 (s)
-NH	-		9.60 (s)



^{1}H NMR spectrum (400 MHz, DMSO-d_6) of compound **4k.**

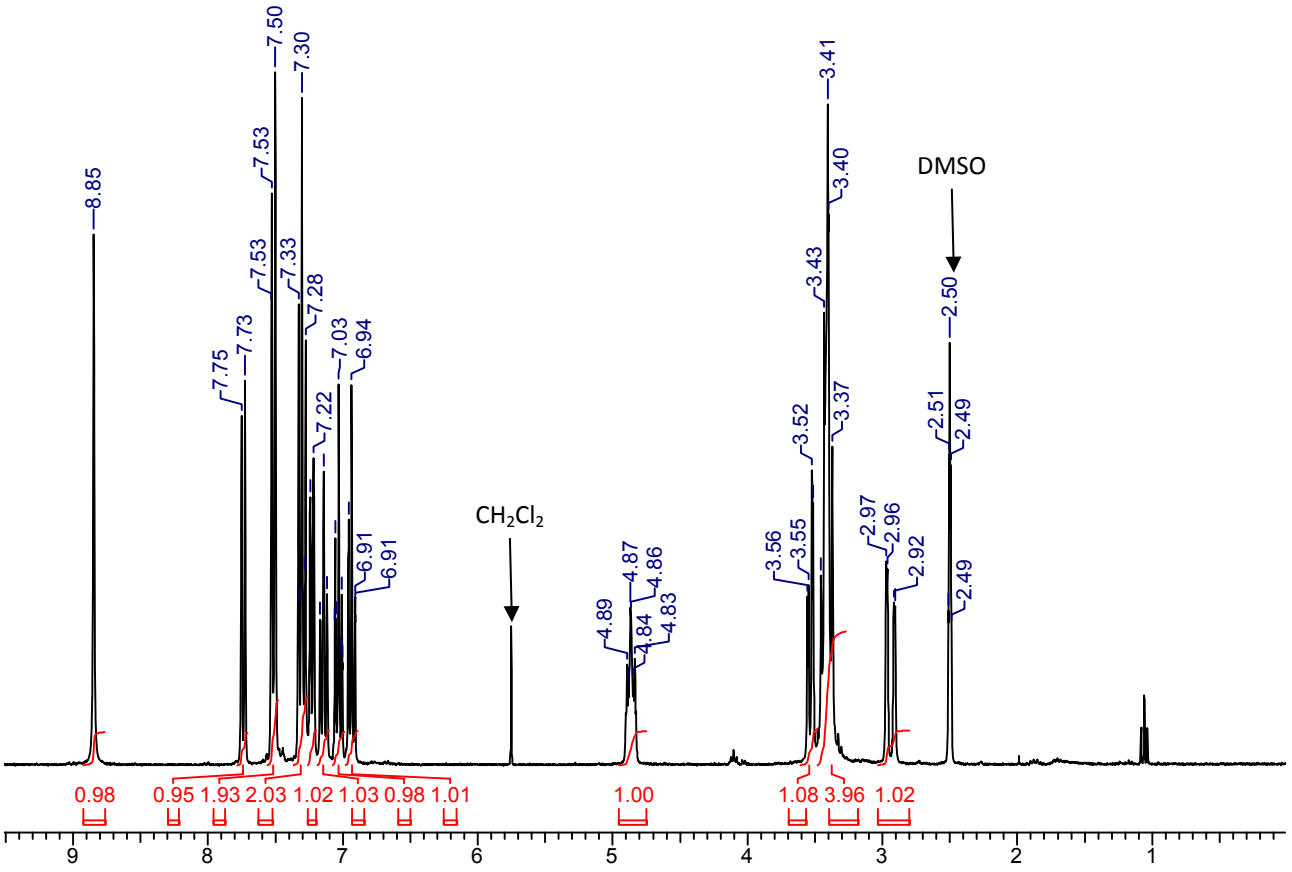


^{13}C NMR spectrum (100 MHz, DMSO-d_6) of compound **4k**.



5a

	^{13}C		**^{1}H**
2	152.0		-
4	57.9		4.92-4.81 (m)
5	34.6	*Ha*	2.94 (dd; *J* = 16.2; 2.1 Hz)
		H_b	3.42 (dd; *J* =16.2, 7.0 Hz)
5a	129.0		
6	124.8		7.23 (d; *J* =7.2 Hz)
7	122.1		6.93 (td; *J* =7.5; 1.0 Hz)
8	127.1		7.14 (t; *J* =8.1 Hz)
9	114.7		7.74 (d, *J* =8.1 Hz)
9a	143.0		-
1’	139.3		-
2’, 6’	120.6		7.52 (dd; *J* =8.7, 0.9 Hz)
3’, 5’	128.4		7.34-7.26 (m)
4’	122.7		7.07-7.00 (m)
$-CH_2-I$	11.8	H_c	3.54 (dd; *J* =10.2, 3.0 Hz)
		H_d	3.48-3.32 (m)
-NH	-		8.85 (s)



^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **5a**.

```
Walter
Amostra WM62F1
Solicitacao N. K1018_11
26.12.12  UFPE

Pulse Sequence: gCOSY

 Solvent: DMSO
 Temp. 25.0 C / 298.1 K
File: K1018_1.gCOSY
UNITYplus-300  "UFPEu300"


 Relax. delay 1.000 sec
 Acq. time 0.228 sec
 Width    4499.4 Hz
 2D Width 4499.4 Hz
 2 repetitions
 128 increments
OBSERVE   H1, 299.9484859 MHz
DATA PROCESSING
 Sq. sine bell 0.114 sec
F1 DATA PROCESSING
 Sq. sine bell 0.028 sec
FT size 2048 x 2048
Total time 5 min, 41 sec
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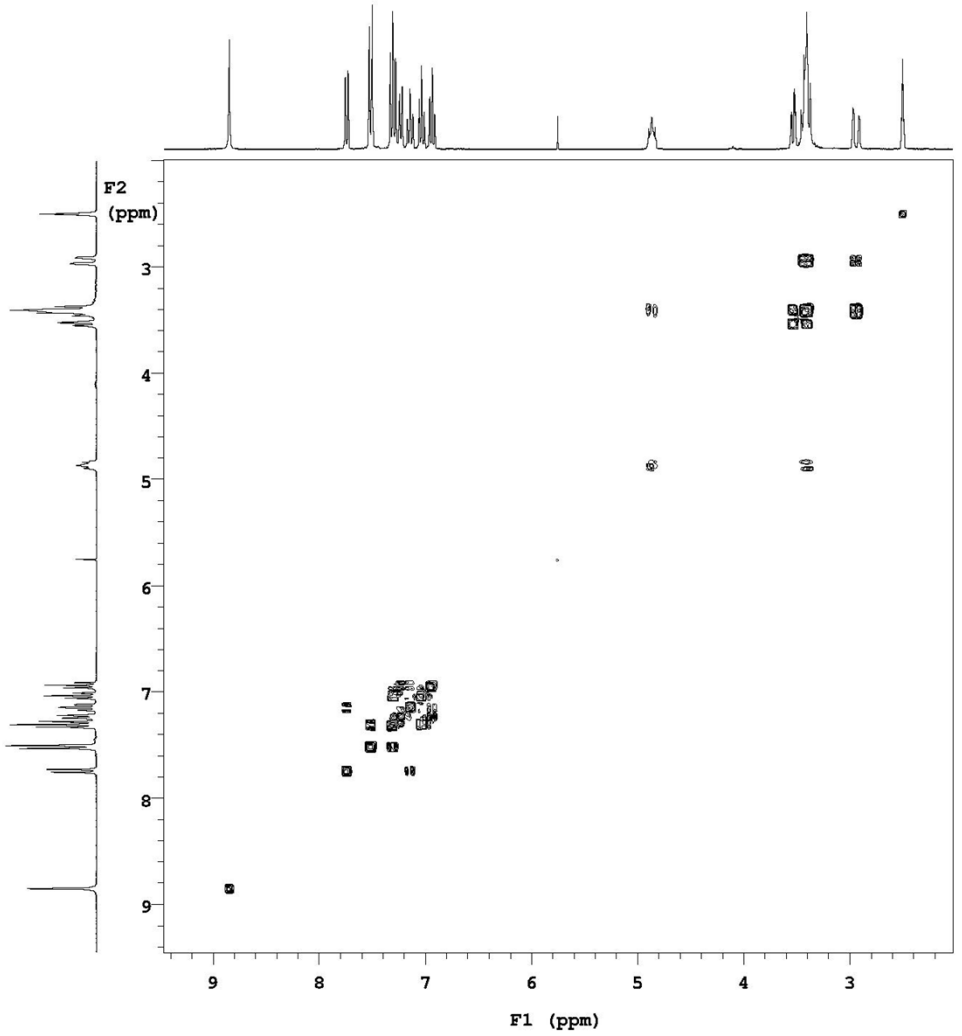
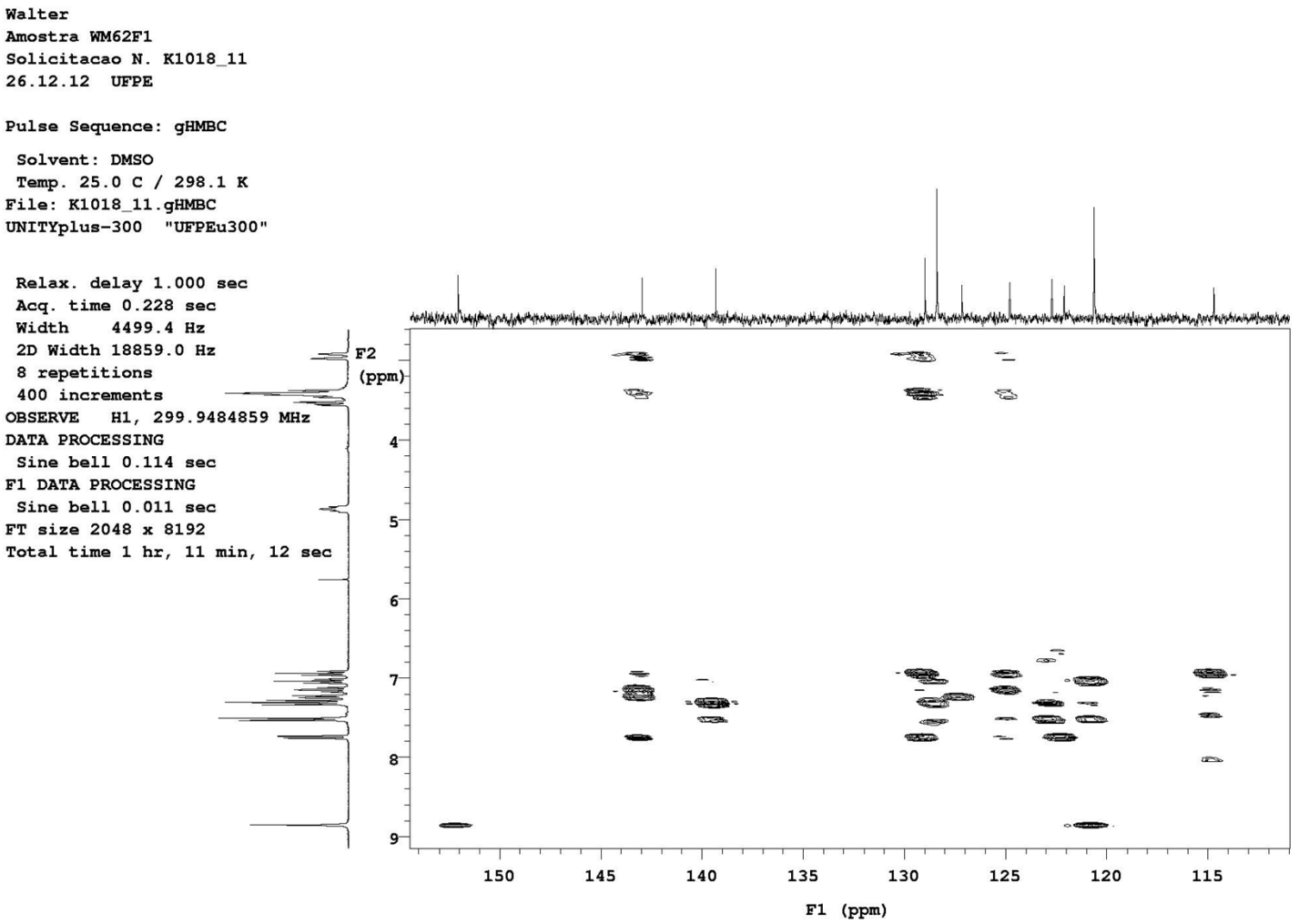
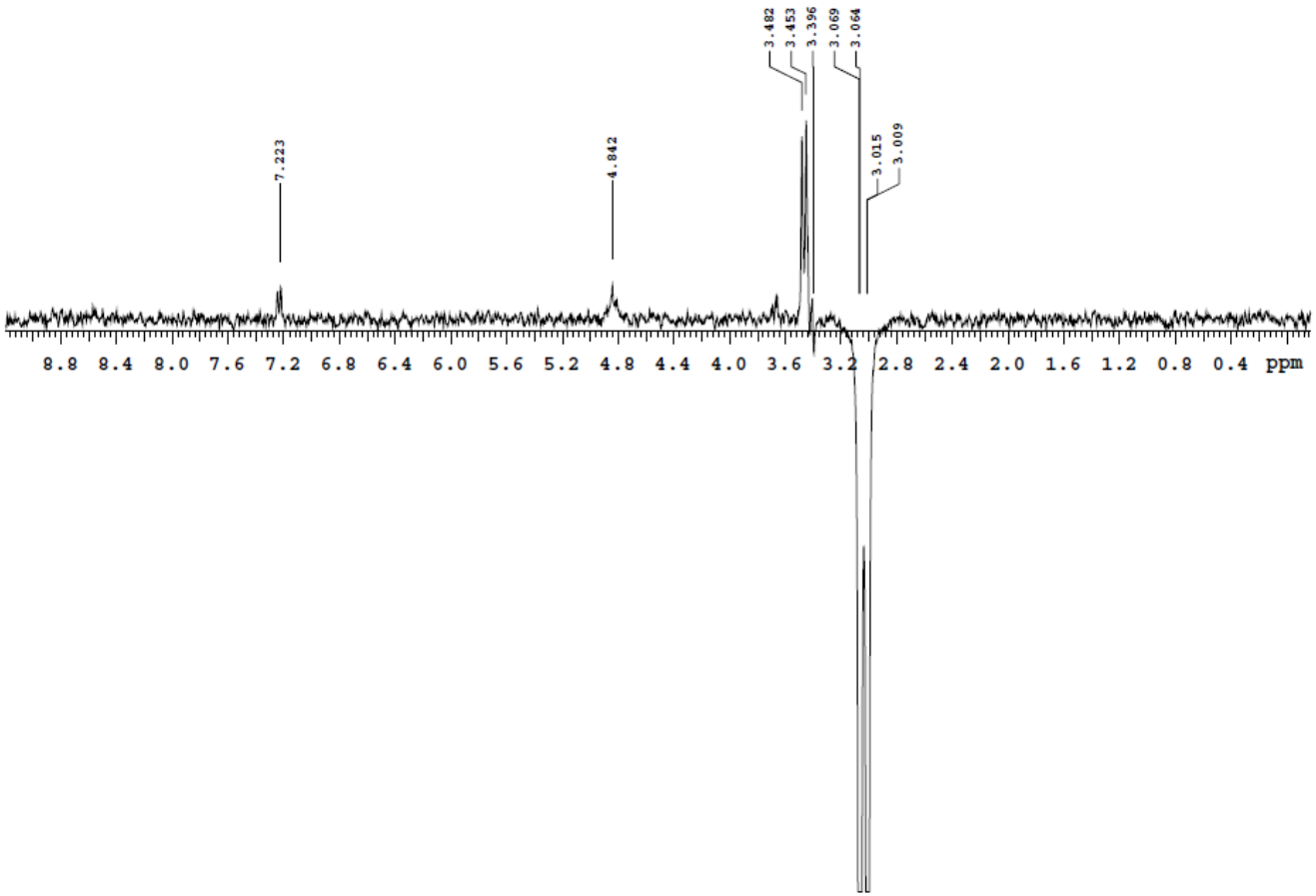


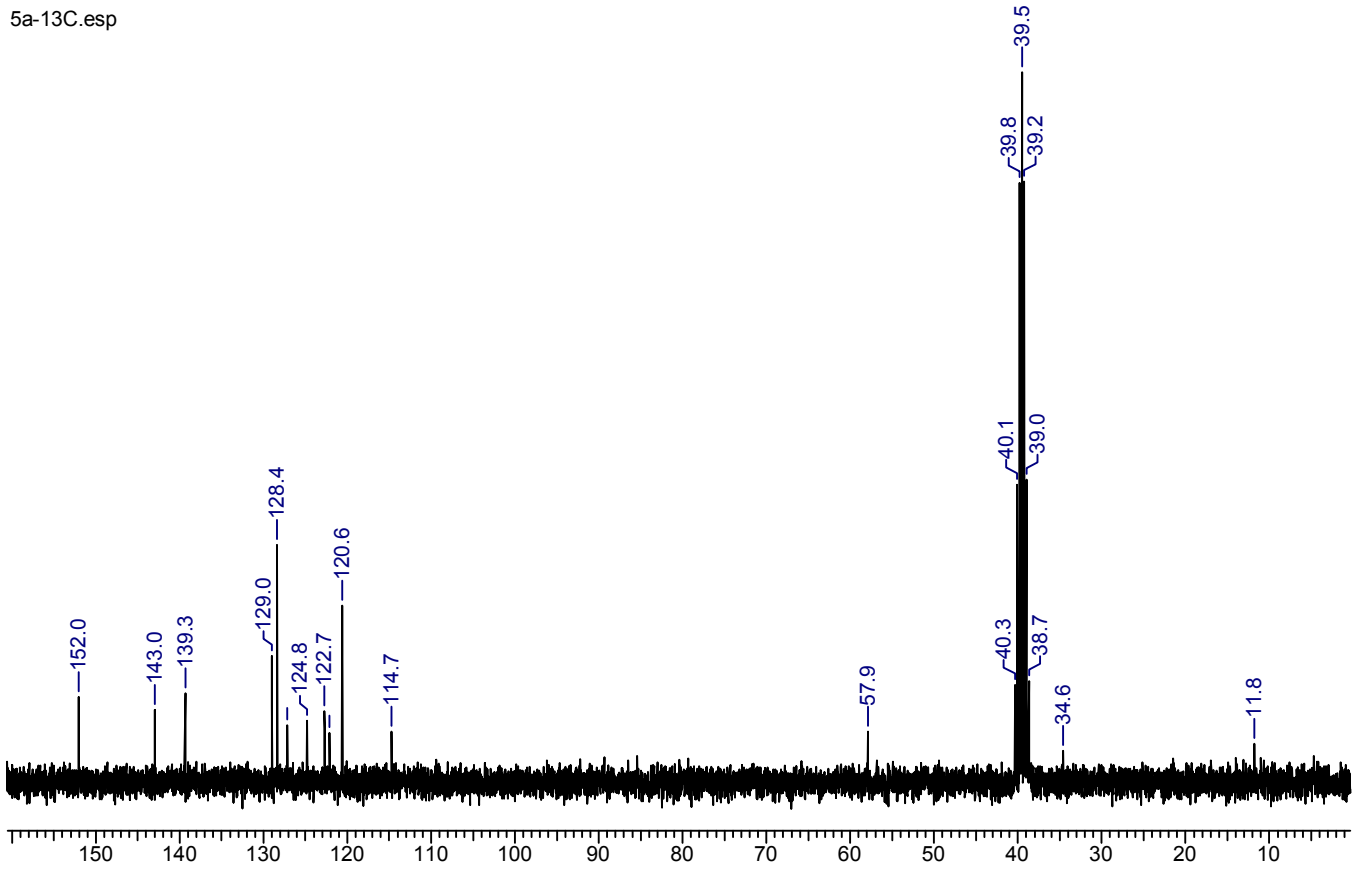
COSY spectrum of compound **5a** (DMSO-d_6)



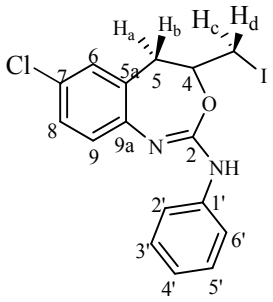
HMBC of compound **5a** (DMSO-d_6)



NOESY 1D spectrum of **5a** (Acetone-d_6, 300 MHz) irradiating the signal at δ 2.94.

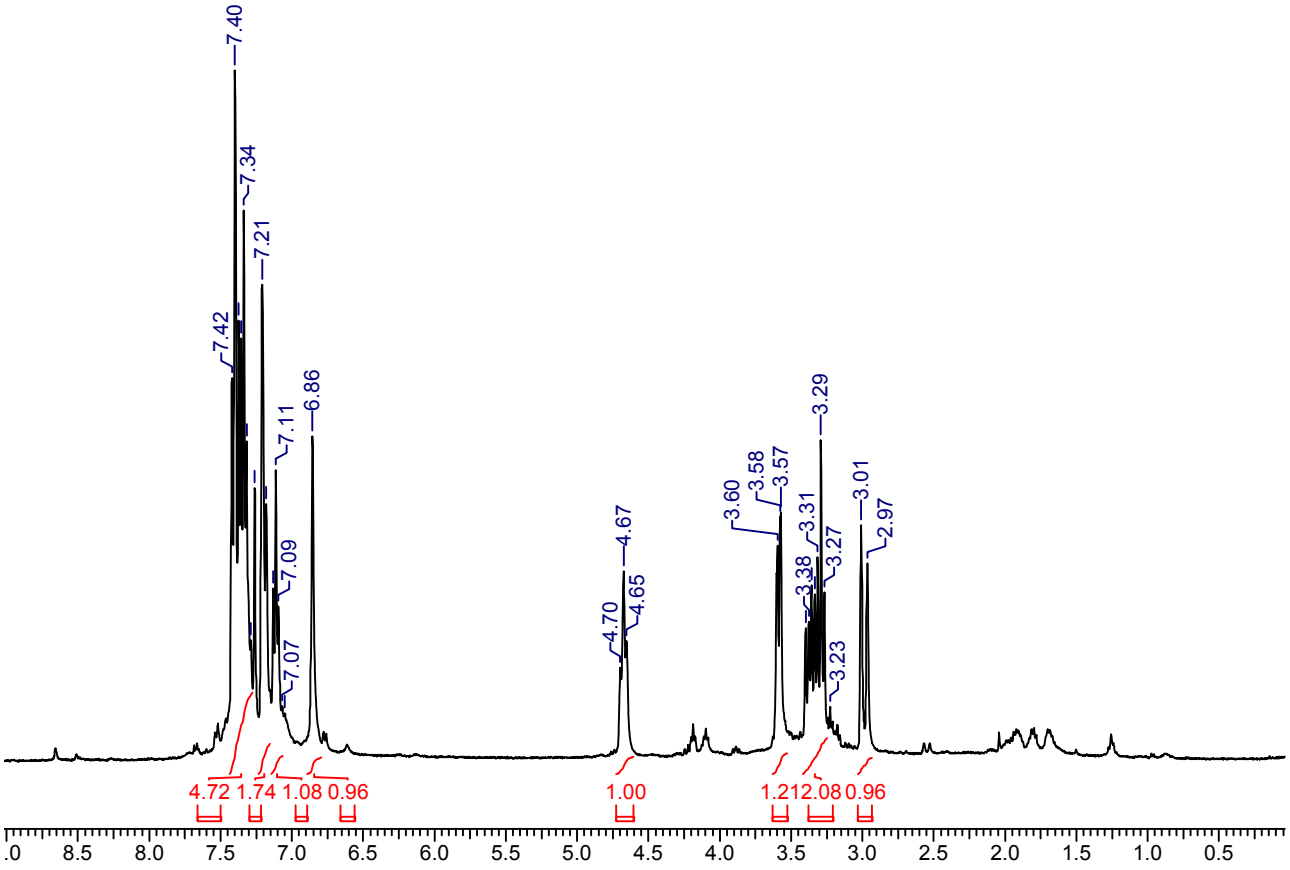


^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **5a**.

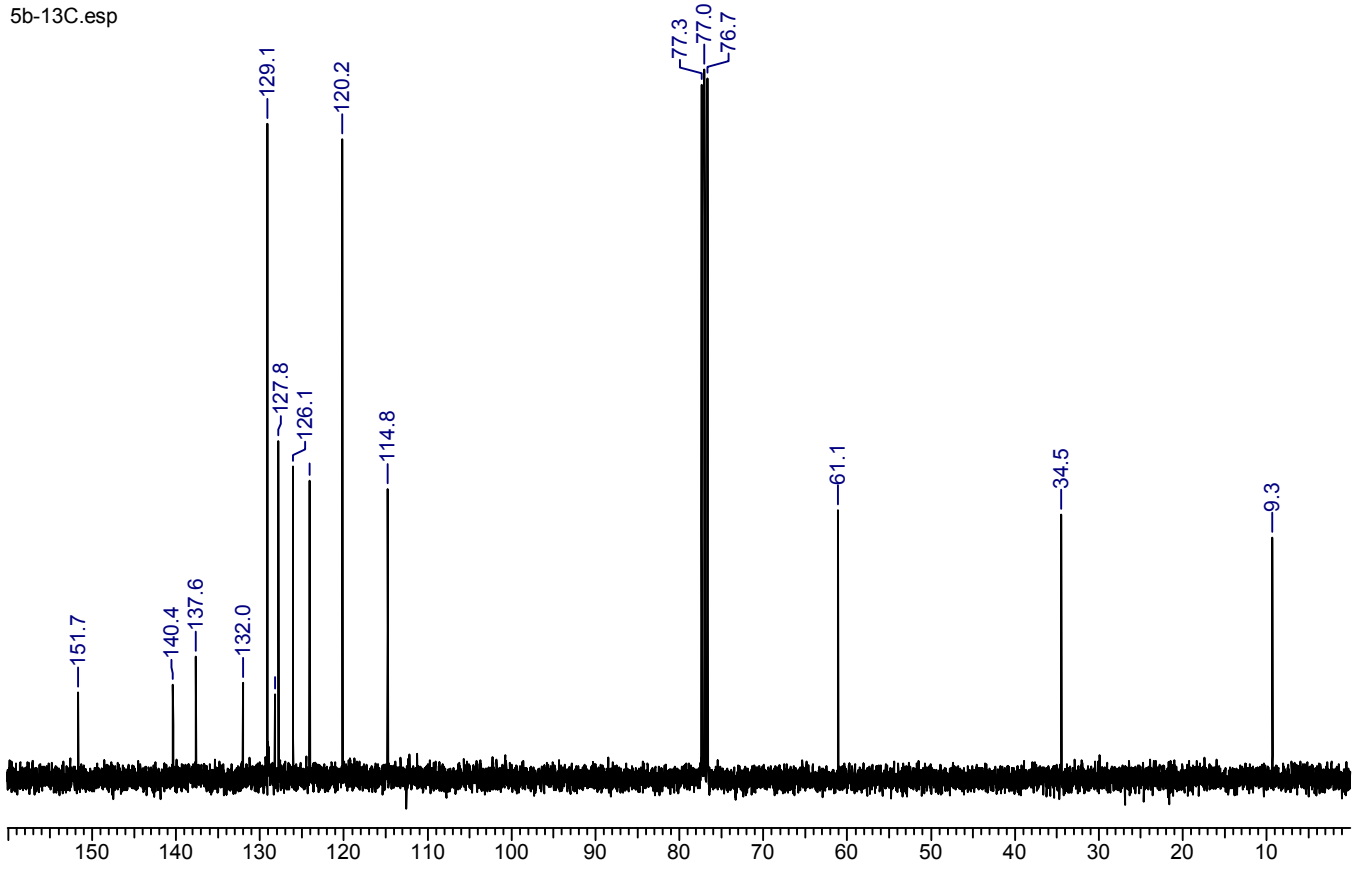


5b

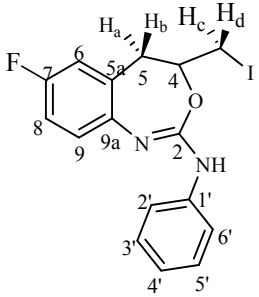
	^{13}C		**^{1}H**
2	151.7		-
4	61.1		4.72-4.61 (m)
5	34.5	H_a	2.98 (d; *J* =16.8 Hz)
		H_b	3.42-3.24 (m)
5ª	128.2		
6	126.1		
8	127.8		7.44-7.27 (m)
9	114.8		
2', 6'	120.2		
9a	140.4		-
1'	137.6		-
7	132.0		
3', 5'	129.1		7.23-7.16 (m)
4'	124.0		7.11 (t; *J* = 8.0 Hz)
$-CH_2-I$	9.3	H_c	3.59 (dd; *J* =9.6; 2.8 Hz)
		H_d	3.42-3.24 (m)
-NH	-		-



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **5b**.

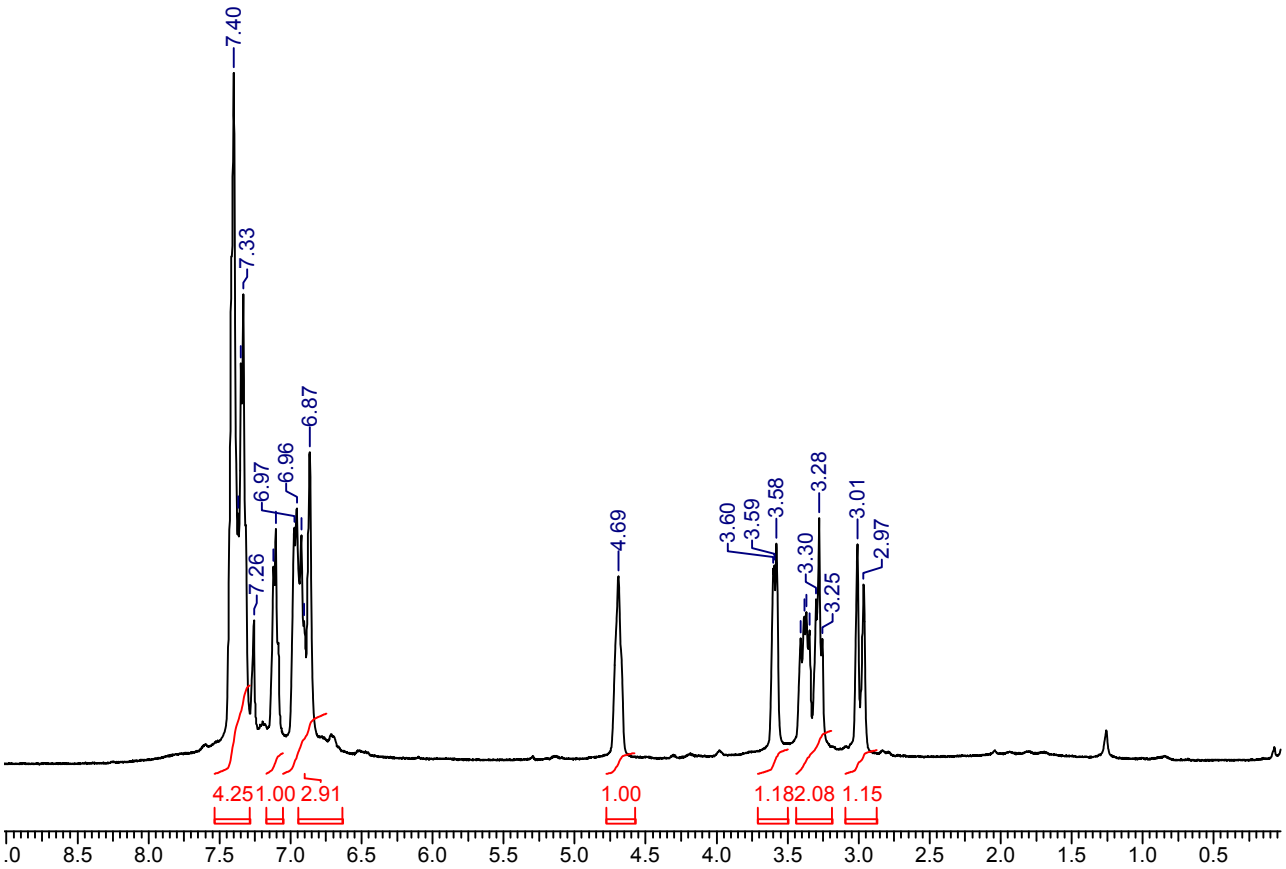


^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **5b**.

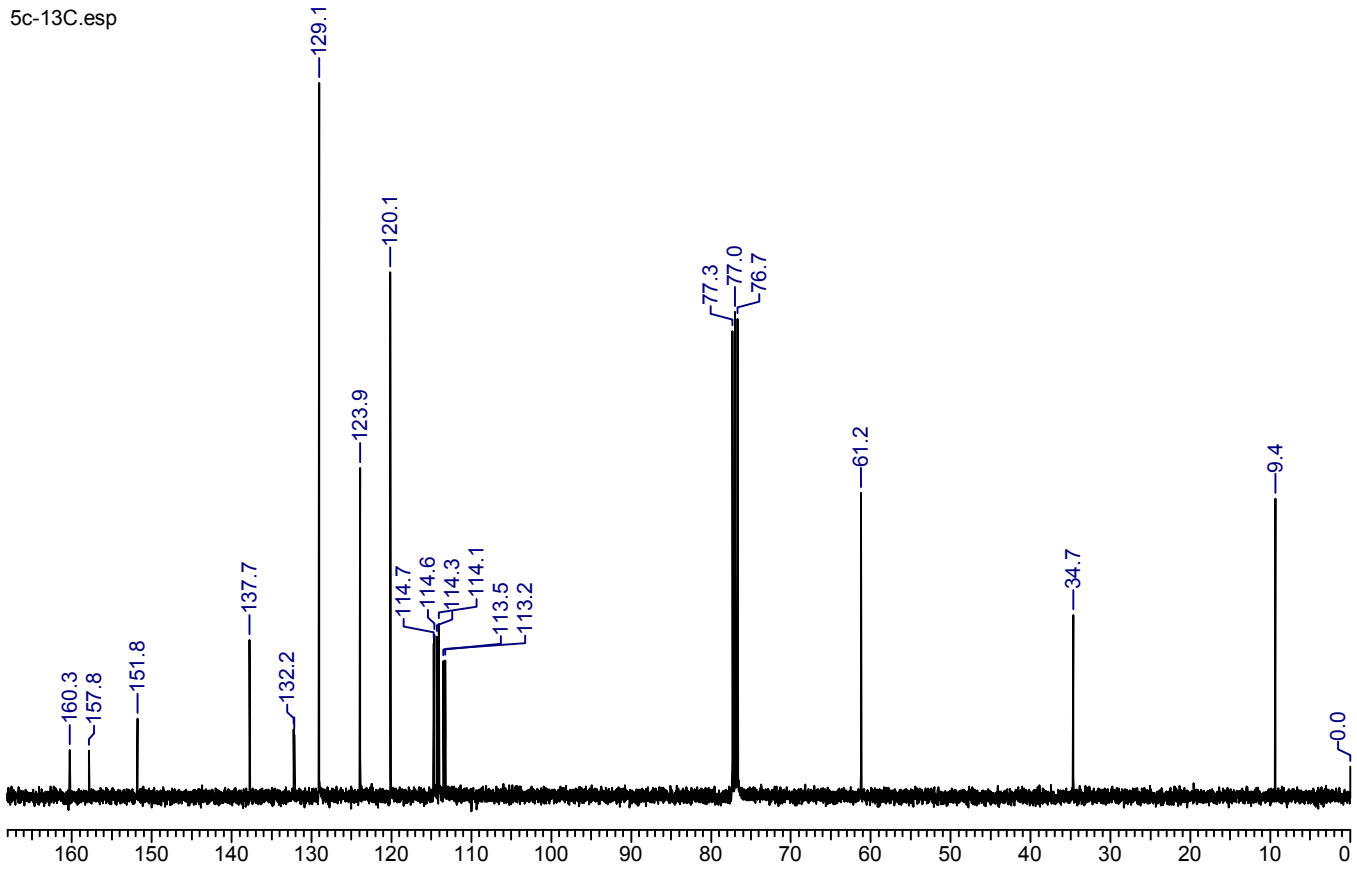


5c

	^{13}C		**^{1}H**
2	151.8		-
4	61.2		4.69 (br s)
5	34.7	H_a	2.99 (d; *J* =16.8 Hz)
		H_b	3.37 (dd; *J* = 16.8; 9.6 Hz)
5a	132.2 (d, *J* =8.5 Hz)		-
6	114.1 (d, *J* =23.2 Hz)		7.15-7.06 (m)
8	113.3 (d, *J* =24.0 Hz)		
9	114.6 (d, *J* =8.5 Hz)		7.44-7.29 (m)
2', 6'	120.1		
9a	-		-
1'	137.7		-
7	159.0 (d, *J* =240.8)		-
3', 5'	129.1		7.01-6.83 (m)
4'	123.9		
-CH_2-I	9.4	H_c	3.63-3.55 (m)
		H_d	3.33-3.23 (m)



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **5c**.



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **5c**