Oriented synthesis and in vitro anticancer activity of biquinazoline-2,2'-diones

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General Experimental Methods

THF was distilled from sodium-benzophenone just prior to use. All the reactions were conducted under N_2 atmosphere. Melting Points are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX-400 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. The exact mass measurements were obtained by high resolution mass instrument (GCT-TOF instrument).

General procedure for the synthesis of 1 is represented as follows

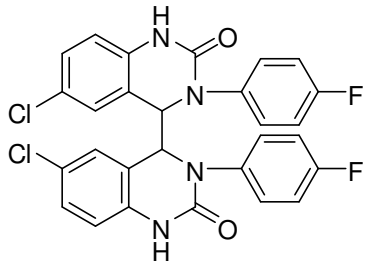
$TiCl_4$ (0.5 mL, 4 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (0.6 g, 4 mmol) in freshly distilled anhydrous THF (10 mL) at r.t. under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t. and a solution of *N*-(2-nitrobenzylidene)anilines (1 mmol) and triphosgene (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 2 h under N_2 atmosphere. After this period, the TLC analysis of the mixture showed the completion of this reaction. The mixture was then quenched with 5% HCl (30 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 50 mL). The extracts were washed with water (3 × 50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by recrystallization from 95% ethanol and DMF.

Cytotoxicity assay of products 1 analogues

The compounds were dissolved in DMF as 100 mg/mL stock solutions before use and stored at -20°C. Human liver cancer Bel7402 cells (the American Type Culture Collection, Rockville, MD) were cultured in MEM medium supplemented with 10% Fetal Bovine Serum. Bel7402 cells were maintained in a 37°C, 5% CO_2 humidified incubator. For cytotoxicity assays, 5000 of HepG2 cells were plated in 100 μl per well into 96-well micro titer plates. Cells were allowed to adhere for 24 h. Each compound

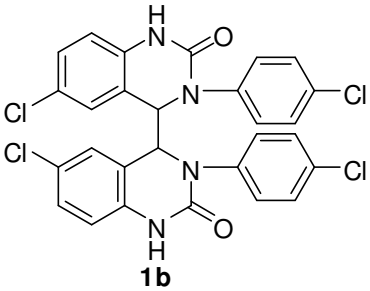
ranging from 0.1 μg/mL to 100 μg/mL in 100 μL was added to cells in duplicate wells. After 24 h incubation, cell viability was determined by sulforhodamine B (SRB) assay. IC_{50} is defined as the concentration of compounds required for inhibiting cell growth by 50%.

Characterizations for compounds



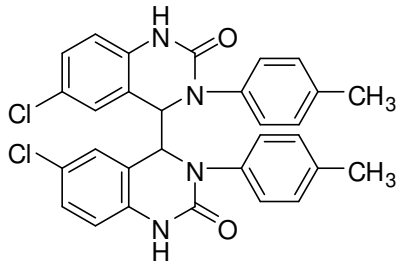
1a

6,6'-dichloro-3,3'-bis(4-fluorophenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1a) IR (KBr) *v*: 3197, 3054, 2931, 1684, 1597, 1507, 1447, 1392, 1306, 1218, 1156, 1091, 941, 857, 831, 817, 743, 716, 663 cm^{-1}, ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.53 (br, s, 2H, 2 × NH), 7.40-7.36 (m, 4H, ArH), 7.23 (d, J = 2.4 Hz, 2H, ArH), 7.16 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 2H, ArH), 7.06 (t, J = 8.8 Hz, 4H, ArH), 6.59 (d, J = 8.8 Hz, 2H, ArH), 5.25 (s, 2H, 2 × CH), ^{13}C NMR (100 Hz, DMSO-d_6) (δ, ppm): 161.9, 158.7, 152.1, 137.9, 137.8, 137.6, 129.4, 129.4, 129.2, 127.2, 125.3, 119.4, 115.9, 115.4, 65.3 (4 C), HRMS (ESI): m/z calcd for $C_{28}H_{18}Cl_2F_2N_4O_2Na$: 573.0673 $[M+Na]^+$, found: 573.0674.



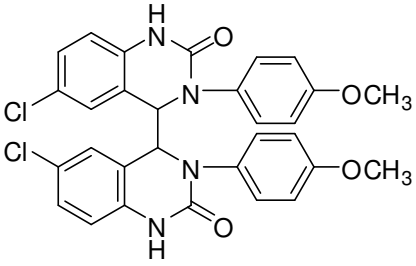
1b

6,6'-dichloro-3,3'-bis(4-chlorophenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1b) IR (KBr) *v*: 3188, 3087, 2965, 1685, 1605, 1573, 1494, 1448, 1388, 1312, 1301, 1257, 1231, 1184, 1156, 1095, 1009, 939, 897, 820, 748, 710, 664 cm^{-1}.^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.62 (br. s, 2H, 2 × NH), 7.38 (d, J = 8.8 Hz, 4H, ArH), 7.28 (d, J = 8.8 Hz, 4H, ArH), 7.19-7.15 (m, 4H, ArH), 6.61 (d, J = 9.2 Hz, 2H, ArH), 5.33 (s, 2H, 2 × CH). ^{13}C NMR (100 Hz, DMSO-d_6) (δ, ppm): 150.7, 139.4, 136.2, 129.2, 128.0, 127.6, 127.4, 126.1, 124.1, 118.2, 114.3, 63.8 (4 C). HRMS (ESI): m/z calcd for $C_{28}H_{18}Cl_4N_4O_2Na$: 605.0082 $[M+Na]^+$, found: 605.0069.



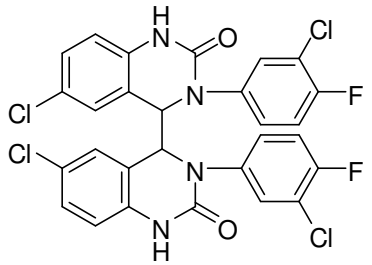
1c

6,6'-dichloro-3,3'-bis(4-methylphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1c) IR (KBr) *v*: 3197, 3052, 2925, 1679, 1598, 1501, 1447, 1389, 1312, 1212, 1165, 1132, 1111, 1091, 1018, 995, 935, 821, 741, 717, 669 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.35 (br, s, 2H, 2 × NH), 7.25 (d, J = 8.4 Hz, 4H, ArH), 7.22 (d, J = 2.4 Hz, 2H, ArH), 7.19 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 2H, ArH), 7.07 (d, J = 8.4 Hz, 4H, ArH), 6.58 (d, J = 8.4 Hz, 2H, ArH), 5.15 (s, 2H, 2 × CH), 2.28 (s, 6H, 2 × CH_3). ^{13}C NMR (100 Hz, DMSO-d_6) (δ, ppm): 152.2, 139.1, 137.7, 135.8, 129.8, 129.3, 127.3, 127.2, 125.1, 119.1, 115.2, 64.6 (4 C), 21.2. HRMS (ESI): m/z calcd for $C_{30}H_{24}Cl_2N_4O_2Na$: 565.1174 $[M+Na]^+$, found: 565.1235.



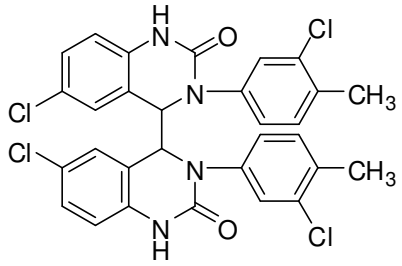
1d

6,6'-Dichloro-3.3'-bis(4-methoxyphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1d) IR (KBr) *v*: 3206, 3090, 2934, 1671, 1598, 1512, 1455, 1396, 1298, 1253, 1213, 1169, 1130, 1107, 1089, 1031, 993, 828, 745, 725, 669 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.33 (br. s, 2H, 2 × NH), 7.28 (d, J = 8.8 Hz, 4H, ArH), 7.24 (d, J = 2.0 Hz, 2H, ArH), 7.18 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 2H, ArH), 6.82 (d, J = 8.8 Hz, 4H, ArH), 6.57 (d, J = 8.8 Hz, 2H, ArH), 5.11 (s, 2H, 2 × CH), 3.74 (s, 6H, 2 × CH_3O). ^{13}C NMR (100 Hz, DMSO-d_6) (δ, ppm): 157.9, 152.3, 137.7, 134.3, 129.2, 128.9, 127.2, 125.1, 119.1, 115.2, 114.5, 64.8 (4 C), 55.9. HRMS (ESI): m/z calcd for $C_{30}H_{24}Cl_2N_4O_4Na$: 597.1073 $[M+Na]^+$, found: 597.1088.



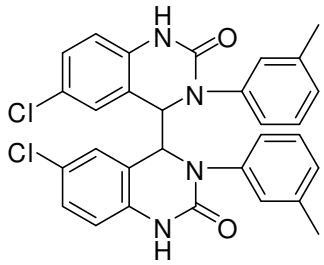
1e

6,6'-Dichloro-3.3'-bis(3-chloro-4-fluorophenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1e)[a] IR (KBr) *v*: 3194, 3054, 2945, 1684, 1602, 1499, 1441, 1388, 1311, 1257, 1211, 1150, 1130, 1084, 1060, 1002, 954, 932, 870, 819, 776, 744, 721, 706, 672, 643 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.80 (br. s, 2H, 2 × NH), 7.43 (dd, J_1 = 2.8 Hz, J_2 = 6.8 Hz, 2H, ArH), 7.18-7.24 (m, 4H, ArH), 7.30-7.35 (m, 2H, ArH), 7.11 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 2H, ArH), 6.68 (d, J = 8.4 Hz, 2H, ArH), 5.52 (s, 2H, 2 × CH). HRMS (ESI): m/z calcd for $C_{28}H_{16}Cl_4F_2N_4O_2Na$: 640.9893 $[M+Na]^+$, found: 640.9880.



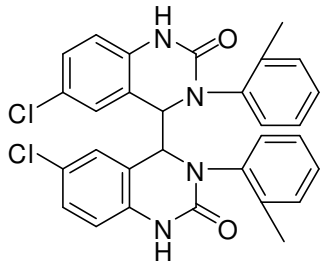
1f

6,6'-Dichloro-3.3'-bis(3-chloro-4-methylphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1f) IR (KBr) *v*: 3193, 3052, 2930, 1684, 1598, 1485, 1457, 1397, 1314, 1264, 1211, 1089, 1048, 1014, 939, 898, 873, 822, 743, 706, 667 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.61 (br, s, 2H, 2 × NH), 7.30 (d, J = 2.0 Hz, 2H, ArH), 6.64 (d, J = 8.4 Hz, 2H, ArH), 7.24-7.12 (m, 8H, ArH), 5.37 (s, 2H, 2 × CH), 2.27 (s, 6H, 2 × CH_3). HRMS (ESI): m/z calcd for $C_{30}H_{22}Cl_4N_4O_2Na$: 633.0395 $[M+Na]^+$, found: 633.0396.



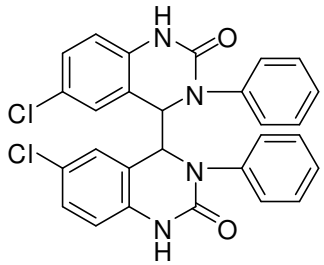
1g

6,6'-Dichloro-3.3'-bis(3-methylphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2, 2'-dione (1g) [a] IR (KBr) *v*: 3199, 3065, 2919, 1679, 1603, 1496, 1458, 1428, 1317, 1223, 1161, 1051, 1009, 865, 811, 754, 743, 657 cm^{-1}. ^{1}H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.40 (br, s, 2H, 2 × NH), 7.22 (d, J = 1.2 Hz, 2H, ArH), 7.16-7.10 (m, 8H, ArH), 6.94 (d, J = 8.4 Hz, 2H, ArH), 6.58 (d, J = 11.6 Hz, 2H, ArH), 5.23 (s, 2H, 2 × CH), 2.19 (s, 6H, 2 × CH_3). ^{13}C NMR (100 Hz, DMSO-d_6) (δ, ppm): 152.2, 141.7, 138.6, 137.6, 129.2, 128.9, 127.4, 127.3, 127.1, 125.2, 124.4, 119.3, 115.3, 64.9 (4 C), 21.5. HRMS (ESI): m/z calcd for $C_{30}H_{24}Cl_2N_4O_2Na$: 565.1174 $[M+Na]^+$, found: 565.1229.



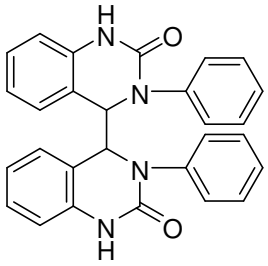
1h

6,6'-Dichloro-3.3'-bis(2-methylphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2, 2'-dione (1h) IR (KBr) *v*: 3203, 3085, 2944, 1673, 1596, 1558, 1540, 1496, 1458, 1394, 1309, 1209, 1193, 1089, 819, 765, 741, 722, 667 cm^{-1}. ^{1}H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.35 (br. s, 2H, 2 × NH), 7.57-7.53 (m, 2H, ArH), 7.41 (d, J = 2.0 Hz, 2H, ArH), 7.25-7.13 (m, 8H, ArH), 6.59 (d, J = 8.4 Hz, 2H, ArH), 4.76 (s, 2H, 2 × CH), 1.93 (s, 6H, 2 × CH_3). HRMS (ESI): m/z calcd for $C_{30}H_{24}Cl_2N_4O_2Na$: 565.1174 $[M+Na]^+$, found: 565.1195.



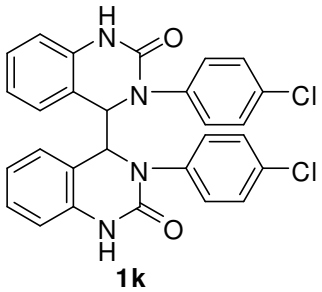
1i

6,6'-Dichloro-3.3'-diphenyl-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1i) IR (KBr) *v*: 3199, 3055, 2931, 1674, 1598, 1496, 1456, 1391, 1306, 1212, 1090, 819, 762, 740, 693, 668 cm^{-1}. ^{1}H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.45 (br. s, 2H, 2 × NH), 7.37 (d, J = 7.6 Hz, 4H, ArH), 7.29-7.14 (m, 10H, ArH), 6.59 (d, J = 8.4 Hz, 2H, ArH), 5.24 (s, 2H, 2 × CH). ^{13}C NMR (100 Hz, DMSO-d_6) (δ, ppm): 152.2, 141.7, 137.6, 129.3, 129.2, 127.4, 127.2, 126.5, 125.2, 119.1, 115.3, 64.6 (4 C). HRMS (ESI): m/z calcd for $C_{28}H_{20}Cl_2N_4O_2Na$: 537.0861 $[M+Na]^+$, found: 537.0884.



1j

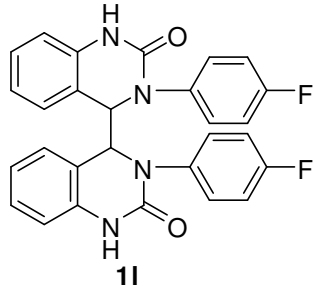
3,3'-diphenyl-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1j) IR (KBr) *v*: 3208, 3063, 2918, 1673, 1602, 1498, 1458, 1310, 1264, 1221, 1156, 1118, 1075, 1034, 857, 742, 696, 657 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.10 (br, s, 2H, 2 × NH), 7.36 (d, J = 8.0 Hz, 4H, ArH), 7.29-7.22 (m, 6H, ArH), 7.17 (t, J = 7.2 Hz, 2H, ArH), 7.12 (t, J = 7.6 Hz, 2H, ArH), 6.88 (t, J = 7.6 Hz, 2H, ArH), 6.54 (d, J = 8.0 Hz, 2H, ArH), 5.16 (s, 2H, 2 × CH). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 152.3, 141.8, 138.4, 129.4, 129.3, 127.4, 127.3, 126.4, 121.5, 117.2, 113.7, 64.7 (4 C). HRMS (ESI): m/z calcd for $C_{28}H_{22}N_4O_2Na$: 469.1681 $[M+Na]^+$, found: 469.1641.



1k

3,3'-bis(4-chlorophenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1k)[a]

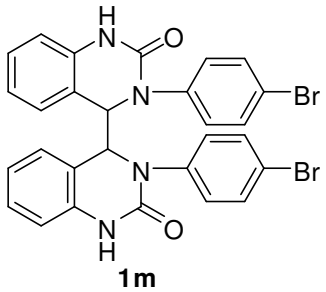
IR (KBr) *v*: 3212, 3068, 2918, 1674, 1600, 1491, 1448, 1419, 1389, 1311, 1286, 1247, 1218, 1155, 1092, 1035, 1014, 872, 847, 828, 744, 659 cm^{-1}. ^{1}H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.31 (br. s, 2H, 2 × NH), 7.40 (d, J = 8.8 Hz, 4H, ArH), 7.29 (d, J = 8.8 Hz, 4H, ArH), 7.15 (d, J = 7.2 Hz, 2H, ArH), 7.11 (t, J = 7.6 Hz, 2H, ArH), 6.85 (t, J = 7.6 Hz, 2H, ArH), 6.56 (d, J = 7.6 Hz, 2H, ArH), 5.19 (s, 2H, 2 × CH). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 152.1, 140.6, 138.3, 130.5, 129.4, 129.3, 128.9, 127.4, 121.6, 117.4, 113.8, 65.1 (4 C). HRMS (ESI): m/z calcd for $C_{28}H_{20}Cl_2N_4O_2Na$: 537.0861 $[M+Na]^+$, found: 537.0877.



1l

3,3'-bis(4-fluorophenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1l)[a]

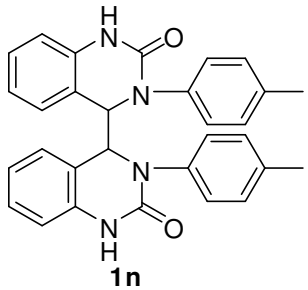
IR (KBr) *v*: 3208, 3066, 2909, 1682, 1598, 1558, 1506, 1455, 1425, 1312, 1282, 1261, 1219, 1154, 1118, 1093, 1014, 876, 838, 749, 655 cm^{-1}. ^{1}H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.19 (br. s, 2H, 2 × NH), 7.42-7.38 (m, 4H, ArH), 7.22 (d, J = 7.6 Hz, 2H, ArH), 7.13-7.04 (m, 6H, ArH), 6.88-6.83 (m, 2H, ArH), 6.53 (d, J = 7.6 Hz, 2H, ArH), 5.15 (s, 2H, 2 × CH). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 151.0, 137.1, 136.7, 136.7, 128.5, 128.4, 128.1, 126.1, 120.3, 116.0, 114.7, 114.5, 112.5, 108.8, 63.9 (4 C). HRMS (ESI): m/z calcd for $C_{28}H_{20}F_2N_4O_2Na$: 505.1452 $[M+Na]^+$, found: 505.1467.



1m

3,3'-bis(4-bromophenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1m)[a]

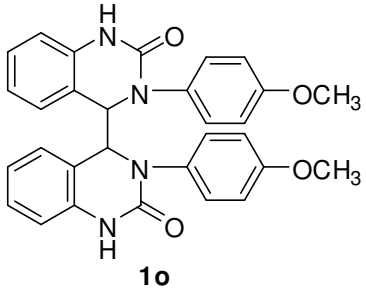
IR (KBr) *v*: 3210, 3064, 2919, 1682, 1601, 1489, 1448, 1424, 1397, 1313, 1295, 1248, 1156, 1101, 1071, 1011, 826, 745, 723, 659 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.32 (br. s, 2H, 2 × NH), 7.42 (t, J = 8.8 Hz, 4H, ArH), 7.34 (d, J = 8.8 Hz, 4H, ArH), 7.15-7.08 (m, 4H, ArH), 6.84 (t, J = 7.6 Hz, 2H, ArH), 6.56 (d, J = 7.6 Hz, 2H, ArH), 5.19 (s, 2H, 2 × CH). HRMS (ESI): m/z calcd for $C_{28}H_{20}Br_2N_4O_2Na$: 624.9851 $[M+Na]^+$, found: 624.9872.



1n

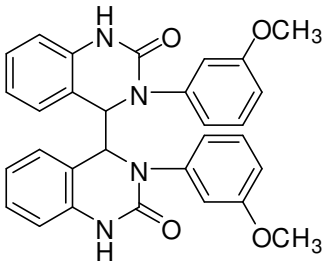
3,3'-bis(4-methylphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1n)

IR (KBr) *v*: 3208, 3064, 2919, 1675, 1601, 1558, 1541, 1509, 1449, 1424, 1295, 1156, 817, 752, 663 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.24 (br. s, 1H, NH), 9.03 (br. s, 1H, NH), 7.25-7.18 (m, 4H, ArH), 7.13-7.04 (m, 5H, ArH), 6.89-6.84 (m, 3H, ArH), 6.79-6.72 (m, 2H, ArH), 6.52 (d, J = 8.0 Hz, 1H, ArH), 6.39 (d, J = 7.2 Hz, 1H, ArH), 5.10 (s, 1H, CH), 5.09 (s, 1H, CH), 2.29 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). HRMS (ESI): m/z calcd for $C_{30}H_{26}N_4O_2Na$: 497.1954 $[M+Na]^+$, found: 497.1980.



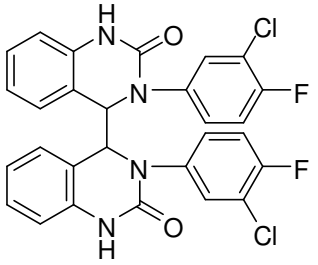
1o

3,3'-bis(4-methoxyphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1o)[a] IR (KBr) *v*: 3184, 3061, 2994, 2937, 1679, 1602, 1496, 1443, 1421, 1302, 1265, 1226, 1204, 1169, 1045, 815, 773, 760, 743, 697 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.14 (br. s, 2H, 2 × NH), 7.23-7.16 (m, 4H, ArH), 7.11 (t, J = 7.2 Hz, 2H, ArH), 7.00 (d, J = 7.6 Hz, 2H, ArH), 6.91-6.85 (m, 4H, ArH), 6.75 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 2H, ArH), 6.53 (d, J = 8.0 Hz, 2H, ArH), 5.20 (s, 2H, 2 × CH), 3.65 (s, 6H, 2 × CH_3O). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 157.7, 152.3, 139.5, 135.2, 129.43, 129.2, 129.1, 121.3, 117.7, 114.1, 104.9, 67.9 (4 C), 55.9. HRMS (ESI): m/z calcd for $C_{30}H_{27}N_4O_4$: 507.2032 $[M+H]^+$, found: 507.2040.



1p

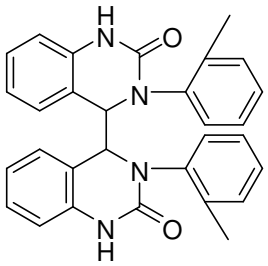
3,3'-bis(3-methoxyphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1p) IR (KBr) *v*: 3184, 3061, 2994, 1937, 1679, 1602, 1496, 1443, 1421, 1302, 1265, 1226, 1204, 1169, 1045, 815, 773, 760, 743, 697 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.14 (br. s, 2H, 2 × NH), 7.20-7.07 (m, 6H, ArH), 6.99 (d, J = 10.0 Hz, 2H, ArH), 6.89-6.83 (m, 4H, ArH), 6.73 (d, J = 10.4 Hz, 2H, ArH), 6.54 (d, J = 10.4 Hz, 2H, ArH), 5.19 (s, 2H, 2 × CH), 3.64 (s, 6H, 2 × CH_3O). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 160.2, 152.2, 142.9, 138.3, 129.7, 129.3, 127.5, 121.5, 119.9, 117.3, 113.7, 112.6, 112.4, 64.7 (4 C), 55.8. HRMS (ESI): m/z calcd for $C_{30}H_{26}N_4O_4Na$: 529.1852 $[M+Na]^+$, found: 529.1883.



1q

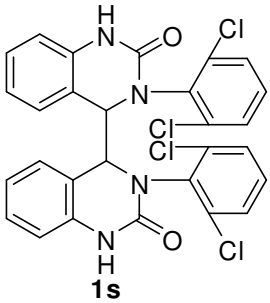
3,3'-bis(3-chloro-4-fluorophenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dio

ne (1q)[a] IR (KBr) *v*: 3219, 3064, 2927, 1673, 1602, 1501, 1450, 1418, 1299, 1264, 1216, 1159, 1097, 1060, 880, 830, 753, 718, 652 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.51 (br. s, 1H, NH), 9.49 (br. s, 1H, NH), 7.51-7.47 (m, 1H, ArH), 7.42-7.30 (m, 3H, ArH), 7.27-7.15 (m, 3H, ArH), 7.09-7.03 (m, 2H, ArH), 6.82-6.73 (m, 3H, ArH), 6.60 (d, J = 8.0 Hz, 1H, ArH), 6.48 (d, J = 7.2 Hz, 1H, ArH), 5.36 (s, 1H, CH), 5.28 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 152.1, 151.9, 139.1, 138.9, 138.2, 130.3, 129.6, 129.6, 129.3, 129.3, 127.8, 127.7, 127.5, 127.3, 121.7, 121.5, 119.6, 119.3, 119.3, 117.9, 117.4, 116.8, 116.8, 116.5, 114.1, 113.9, 67.4 (4 C), 66.2 (4' C). HRMS (ESI): m/z calcd for $C_{28}H_{18}Cl_2F_2N_4O_2Na$: 573.0673 $[M+Na]^+$, found: 573.0724.



1r

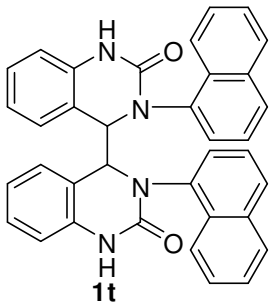
3,3'-bis(2-methylphenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1r)[a] IR (KBr) *v*: 3208, 3063, 2912, 1672, 1598, 1558, 1540, 1488, 1456, 1422, 1308, 1262, 1214, 1170, 1114, 1034, 746, 720, 657 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.06 (br. s, 2H, 2 × NH), 7.53 (d, J = 7.2 Hz, 2H, ArH), 7.38 (d, J = 7.2 Hz, 2H, ArH), 7.20-7.12 (m, 8H, ArH), 6.90 (t, J = 7.2 Hz, 2H, ArH), 6.54 (d, J = 8.0 Hz, 2H, ArH), 4.72 (s, 2H, 2 × CH), 1.90 (s, 6H, 2 × CH_3), HRMS (ESI): m/z calcd for $C_{30}H_{26}N_4O_2Na$: 497.1954 $[M+Na]^+$, found: 497.1988.



1s

3,3'-bis(2,6-dichlorophenyl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1s)

IR (KBr) *v*: 3206, 3066, 2920, 1680, 1599, 1462, 1316, 1204, 873, 784, 770 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.57 (br. s, 2H, 2 × NH), 7.51(d, J = 9.6 Hz, 2H, ArH), 7.44-7.41 (m, 2H, ArH), 7.29-7.18 (m, 4H, ArH), 6.96 (t, J = 10.0 Hz, 2H, ArH), 6.77 (t, J = 9.6 Hz, 2H, ArH), 6.52 (d, J = 10.0 Hz, 2H, ArH), 5.30 (s, 2H, 2 × CH). HRMS (ESI): m/z calcd for $C_{28}H_{18}Cl_4N_4O_2Na$: 605.0082 $[M+Na]^+$, found: 605.0099.



1t

3,3'-di(naphthalene-1-yl)-3,3',4,4'-tetrahydro-4,4'-biquinazoline-2,2'-dione (1t) IR (KBr) *v*: 3210, 3065, 2914, 1667, 1600, 1504, 1458, 1424, 1396, 1313, 1263, 1215, 1174, 1125, 1098, 1018, 909, 875, 851, 804, 779, 753, 676 cm^{-1}. ^1H NMR (400 Hz, DMSO-d_6) (δ, ppm): 9.23 (br. s, 2H, 2 × NH), 7.91 (d, J = 7.6 Hz, 2H, ArH), 7.69 (d, J = 8.0 Hz, 2H, ArH), 7.44-7.56 (m, 8H, ArH), 7.39 (t, J = 8.4 Hz, 2H, ArH), 7.25 (t, J = 7.2 Hz, 2H, ArH), 7.17 (t, J = 7.6 Hz, 2H, ArH), 6.99 (t, J = 7.6 Hz, 2H, ArH), 6.65 (d, J = 8.0 Hz, 2H, ArH), 4.99 (s, 2H, 2 × CH). HRMS (ESI): m/z calcd for $C_{36}H_{26}N_4O_2Na$: 569.1954 $[M+Na]^+$, found: 569.1953.

2-(4-Methylphenyl)-2*H*-indazole (7): m.p. 97-98 °C. IR (KBr): *v*: 3118, 3039, 2946, 1624, 1522, 1453, 1418, 1392, 1378, 1346, 1311, 1258, 1230, 1196, 1146, 1126, 1108, 1047, 1017, 953, 822, 791, 756, 738 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.06 (1H, s, CH=), 7.98 (2H, d, J = 8.4 Hz, ArH), 7.77 (1H, d, J = 8.8 Hz, ArH), 7.71 (1H, d, J = 8.8 Hz, ArH), 7.40 (2H, d, J = 8.4 Hz, ArH), 7.33-7.29 (1H, m, ArH), 7.12-7.09 (1H, m, ArH), 2.39 (3H, s, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) (δ, ppm): 148.9, 137.9, 137.5, 130.2, 126.7, 122.6, 122.1, 121.4, 121.0, 120.3, 117.5, 20.7.

Crystal structures of compounds

Crystal data for 1e

$C_{31}H_{23}Cl_4F_2N_5O_3$; M = 693.34, colorless block crystals, 0.26 × 0.20 × 0.10 mm, triclinic, space group P-1, a = 10.829(2) Å, b = 12.178(3) Å, c = 13.012(3) Å, α = 91.451(4)º, β = 107.953(4)º, γ = 98.299(4)º, V = 1610.9(6) Å^3, Z = 2, D_c = 1.429 g·cm^{-1}, F(000) = 784, μ (Mo$K\alpha$) = 0.420 mm^{-1}. Intensity data were collected on a diffractometer with graphite monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) using ω scan mode with 1.65º< θ < 25.01º. 5663 unique reflections were measured and 3044 reflections with $I>2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R = 0.0311 and wR = 0.0754.

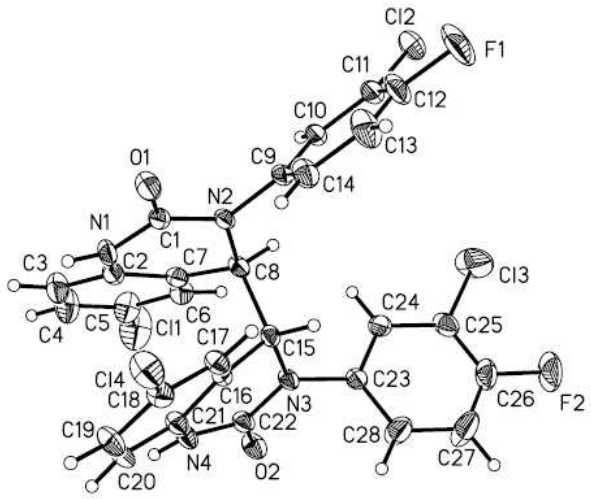


FIGURE 1**.** ORTEP plot of the molecular structure of compound **1e** in crystal

TABLE 1 Bond lengths (Å) for **1e**

Bond	Bond Lengths	Bond	Bond Lengths	Bond	Bond Lengths
Cl(1)-C(5)	1.733(5)	N(2)-C(8)	1.470(4)	C(8)-C(15)	1.569(5)
Cl(2)-C(11)	1.719(5)	N(3)-C(22)	1.372(4)	C(9)-C(14)	1.375(5)
Cl(3)-C(25)	1.708(5)	N(3)-C(23)	1.438(4)	C(9)-C(10)	1.391(5)
Cl(4)-C(18)	1.744(4)	N(3)-C(15)	1.470(4)	C(10)-C(11)	1.375(5)
F(1)-C(12)	1.368(5)	N(4)-C(22)	1.357(5)	C(11)-C(12)	1.369(7)
F(2)-C(26)	1.365(5)	N(4)-C(21)	1.388(4)	C(12)-C(13)	1.355(7)
O(1)-C(1)	1.241(4)	C(2)-C(3)	1.382(5)	C(13)-C(14)	1.382(6)
O(2)-C(22)	1.236(4)	C(2)-C(7)	1.391(5)	C(15)-C(16)	1.500(5)
N(1)-C(1)	1.350(5)	C(3)-C(4)	1.367(6)	C(16)-C(17)	1.379(5)
N(1)-C(2)	1.390(4)	C(4)-C(5)	1.370(6)	C(16)-C(21)	1.389(5)

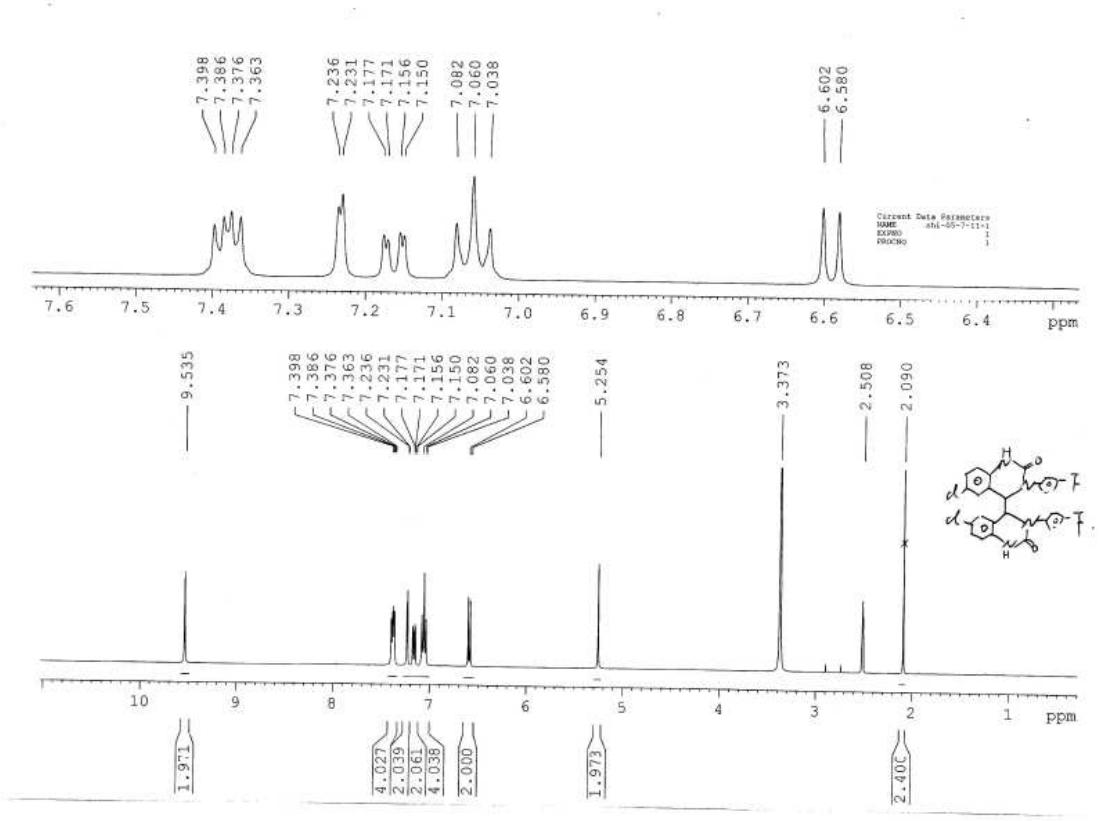
N(1)-H(1)	0.8600	C(5)-C(6)	1.383(6)	C(17)-C(18)	1.373(5)
N(2)-C(1)	1.376(4)	C(6)-C(7)	1.385(5)	C(18)-C(19)	1.377(5)
N(2)-C(9)	1.439(4)	C(7)-C(8)	1.497(5)	C(19)-C(20)	1.377(5)
C(20)-C(21)	1.397(5)	C(25)-C(26)	1.337(6)	N(5)-C(29)	1.302(6)
C(23)-C(28)	1.356(5)	C(26)-C(27)	1.358(7)	N(5)-C(30)	1.423(8)
C(23)-C(24)	1.369(5)	C(27)-C(28)	1.379(6)	N(5)-C(31)	1.433(6)
C(24)-C(25)	1.398(5)	O(3)-C(29)	1.218(6)		

TABLE 2 Bond angles (°) for **1e**

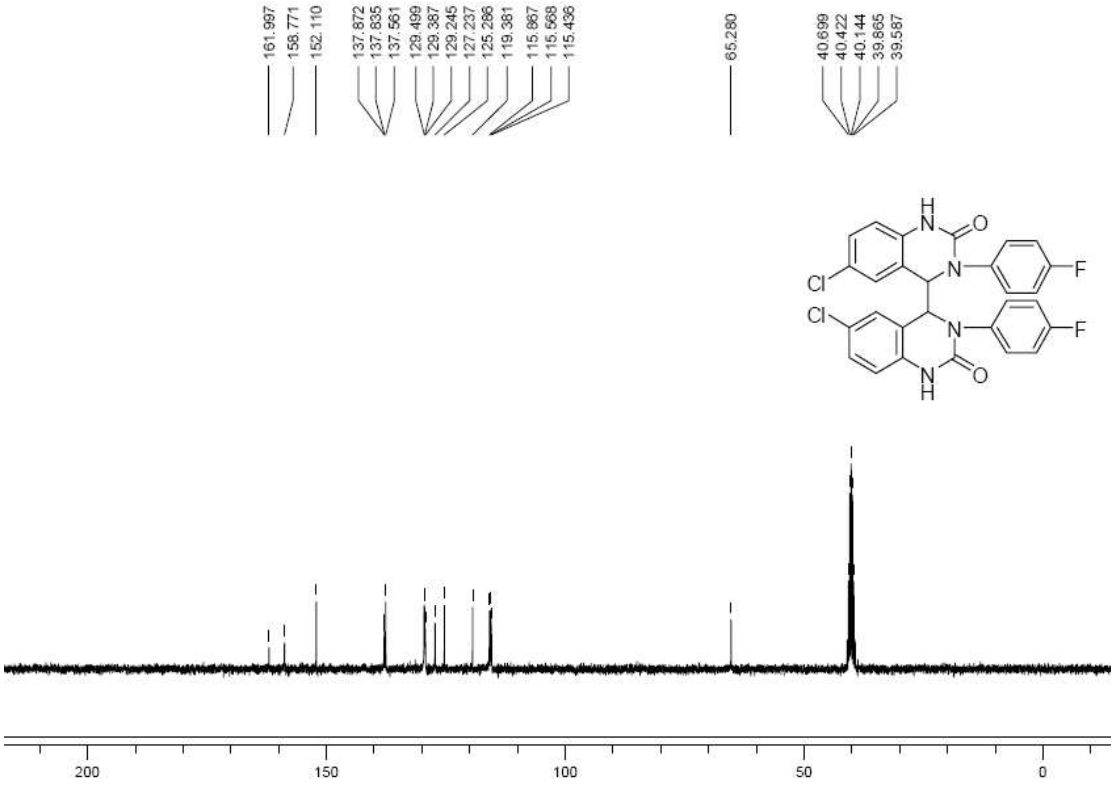
Angles	(°)	Angles	(°)
C(1)-N(1)-C(2)	124.4(3)	C(12)-C(13)-C(14)	119.2(5)
C(1)-N(2)-C(9)	120.2(3)	C(9)-C(14)-C(13)	119.4(4)
C(1)-N(2)-C(8)	121.5(3)	N(3)-C(15)-C(16)	109.9(3)
C(9)-N(2)-C(8)	118.0(3)	N(3)-C(15)-C(8)	111.4(3)
C(22)-N(3)-C(23)	120.0(3)	C(16)-C(15)-C(8)	112.6(3)
C(22)-N(3)-C(15)	121.7(3)	C(17)-C(16)-C(21)	119.5(3)
C(23)-N(3)-C(15)	118.1(3)	C(17)-C(16)-C(15)	122.8(3)
C(22)-N(4)-C(21)	123.6(3)	C(21)-C(16)-C(15)	117.5(3)
O(1)-C(1)-N(1)	121.7(3)	C(18)-C(17)-C(16)	120.2(4)
O(1)-C(1)-N(2)	121.9(3)	C(17)-C(18)-C(19)	121.2(4)
N(1)-C(1)-N(2)	116.4(3)	C(17)-C(18)-Cl4)	119.1(3)
C(3)-C(2)-N(1)	121.7(3)	C(19)-C(18)-Cl4)	119.7(3)
C(3)-C(2)-C(7)	120.1(4)	C(18)-C(19)-C(20)	119.0(4)
N(1)-C(2)-C(7)	118.1(3)	C(19)-C(20)-C(21)	120.6(4)
C(4)-C(3)-C(2)	119.7(4)	N(4)-C(21)-C(16)	118.9(3)
C(3)-C(4)-C(5)	120.8(4)	N(4)-C(21)-C(20)	121.8(3)
C(4)-C(5)-C(6)	120.2(4)	C(16)-C(21)-C(20)	119.3(3)
C(4)-C(5)-C(l1)	120.8(4)	O(2)-C(22)-N(4)	122.0(3)
C(6)-C(5)-C(l1)	119.0(4)	O(2)-C(22)-N(3)	121.9(3)
C(5)-C(6)-C(7)	119.6(4)	N(4)-C(22)-N(3)	116.1(3)
C(6)-C(7)-C(2)	119.4(3)	C(28)-C(23)-C(24)	120.3(4)
C(6)-C(7)-C(8)	122.2(3)	C(28)-C(23)-N(3)	118.8(3)
C(2)-C(7)-C(8)	118.4(3)	C(24)-C(23)-N(3)	120.7(3)
N(2)-C(8)-C(7)	110.7(3)	C(23)-C(24)-C(25)	118.9(4)
N(2)-C(8)-C(15)	109.5(3)	C(26)-C(25)-C(24)	119.5(4)
C(7)-C(8)-C(15)	112.7(3)	C(26)-C(25)-C(l3)	119.9(4)
C(14)-C(9)-C(10)	120.4(4)	C(24)-C(25)-C(l3)	120.6(4)
C(14)-C(9)-N(2)	121.9(4)	C(25)-C(26)-C(27)	122.1(4)
C(10)-C(9)-N(2)	117.6(3)	C(25)-C(26)-F(2)	118.6(5)
C(11)-C(10)-C(9)	119.8(4)	C(27)-C(26)-F(2)	119.3(5)
C(12)-C(11)-C(10)	118.4(4)	C(26)-C(27)-C(28)	118.5(5)
C(12)-C(11)-C(l2)	120.8(4)	C(23)-C(28)-C(27)	120.6(5)
C(10)-C(11)-C(l2)	120.8(4)	C(29)-N(5)-C(30)	119.0(5)
C(13)-C(12)-F(1)	119.0(5)	C(29)-N(5)-C(31)	125.0(5)

C(13)-C(12)-C(11)	122.7(4)	C(30)-N(5)-C(31)	115.8(5)
F(1)-C(12)-C(11)	118.3(5)	O(3)-C(29)-N(5)	127.4(5)

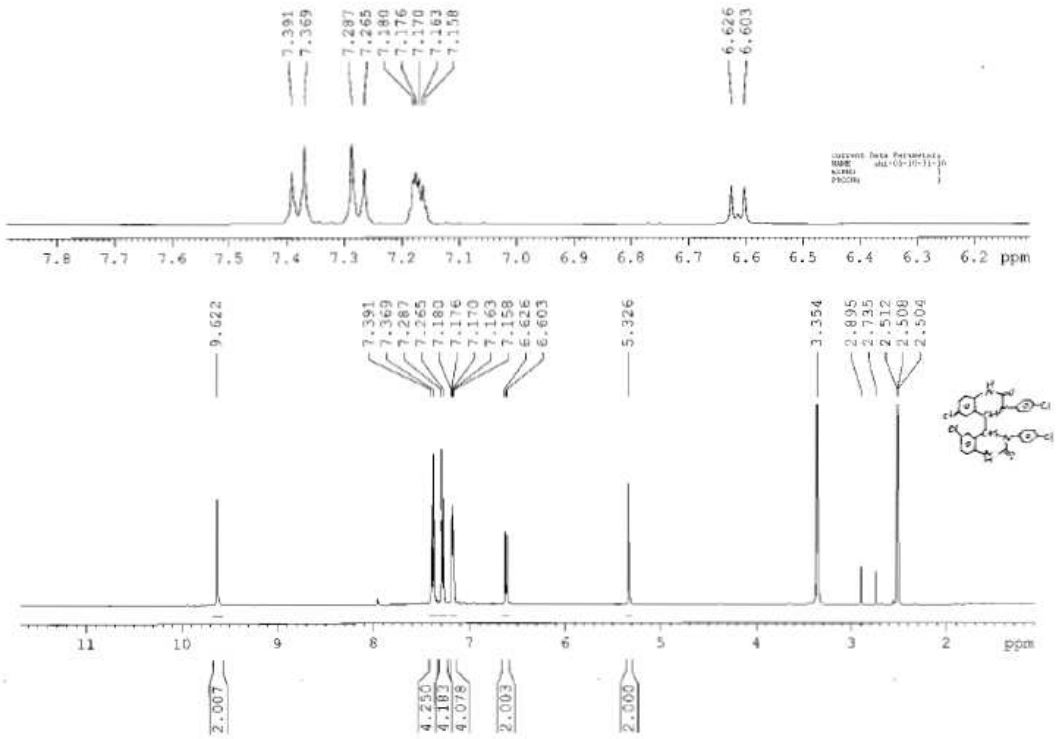
Copies of ^{1}H NMR, ^{13}C NMR and HRMS of compounds



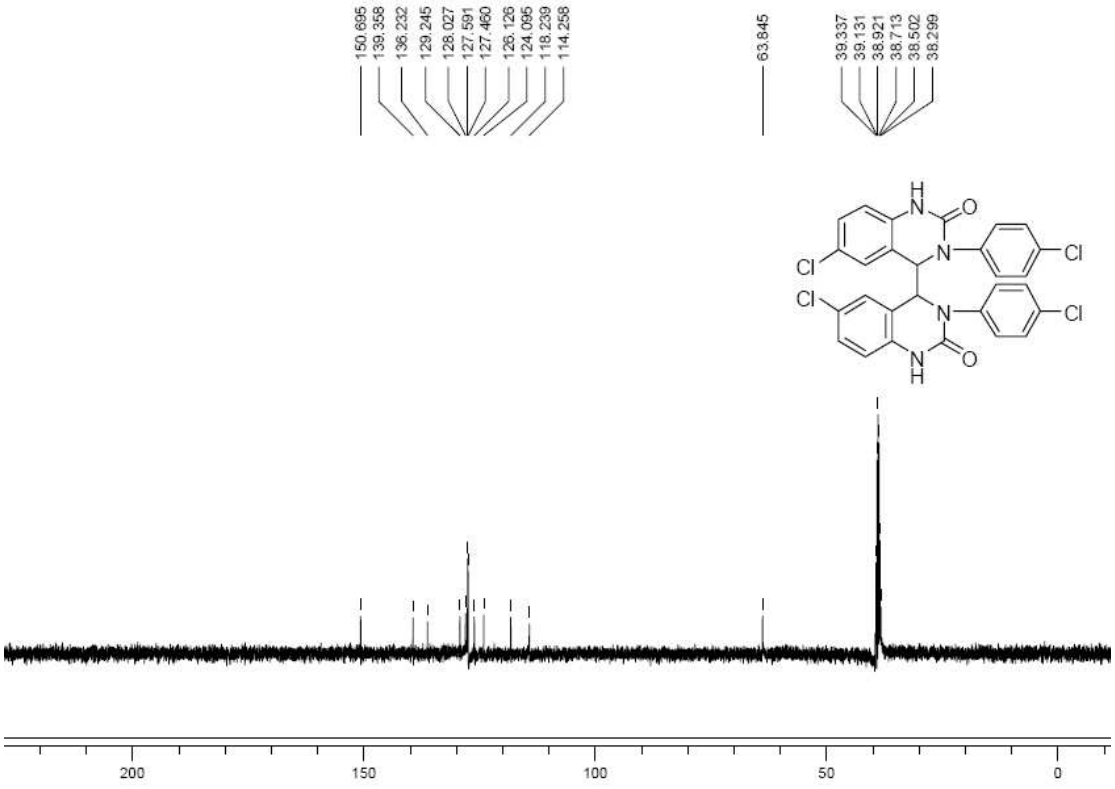
^{1}H NMR Spectrum of Compound 1a



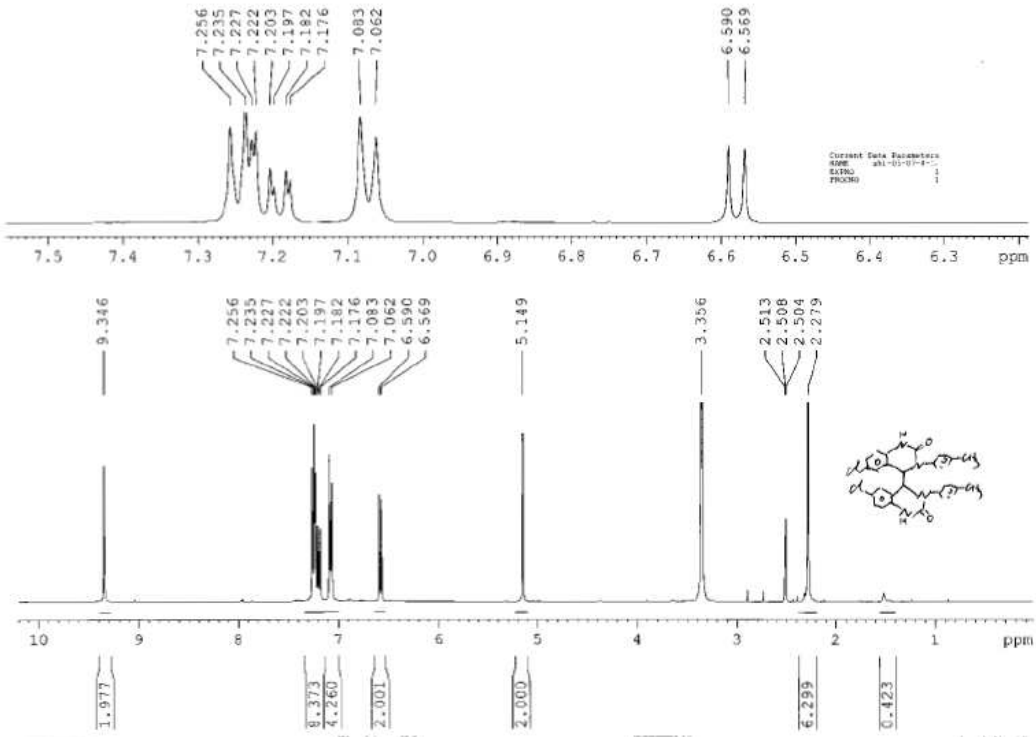
^{13}C NMR Spectrum of Compound 1a



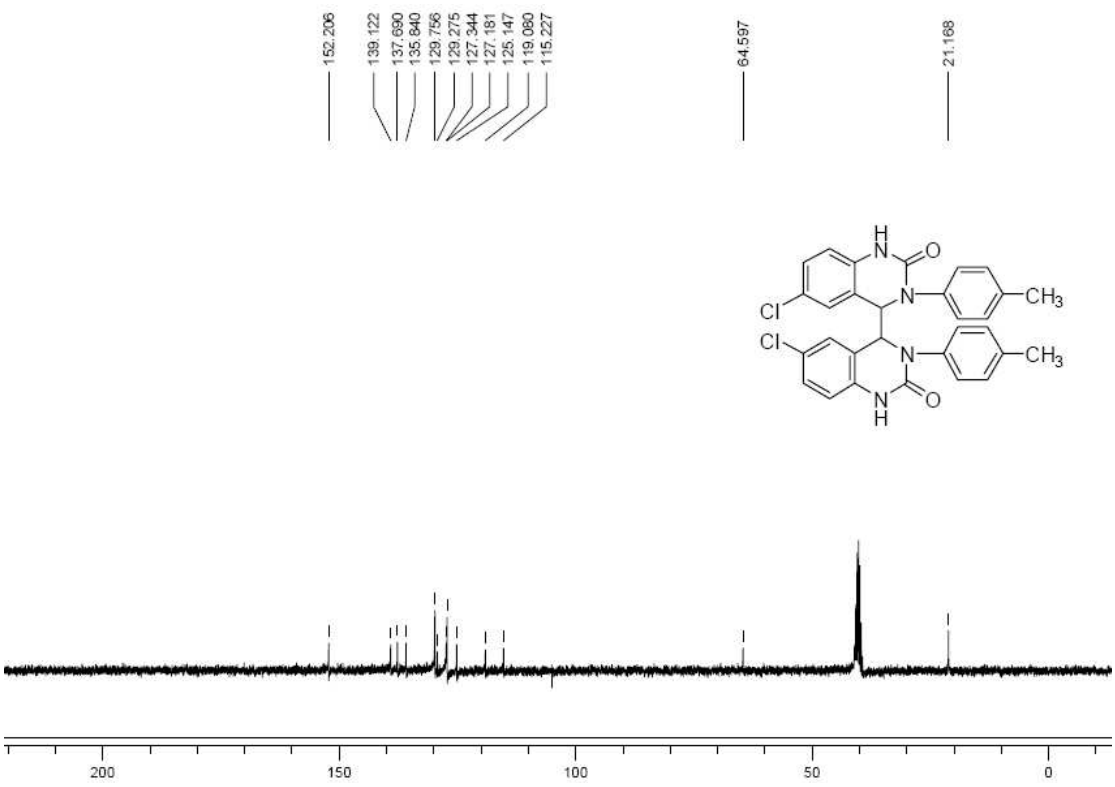
^{1}H NMR Spectrum of Compound 1b



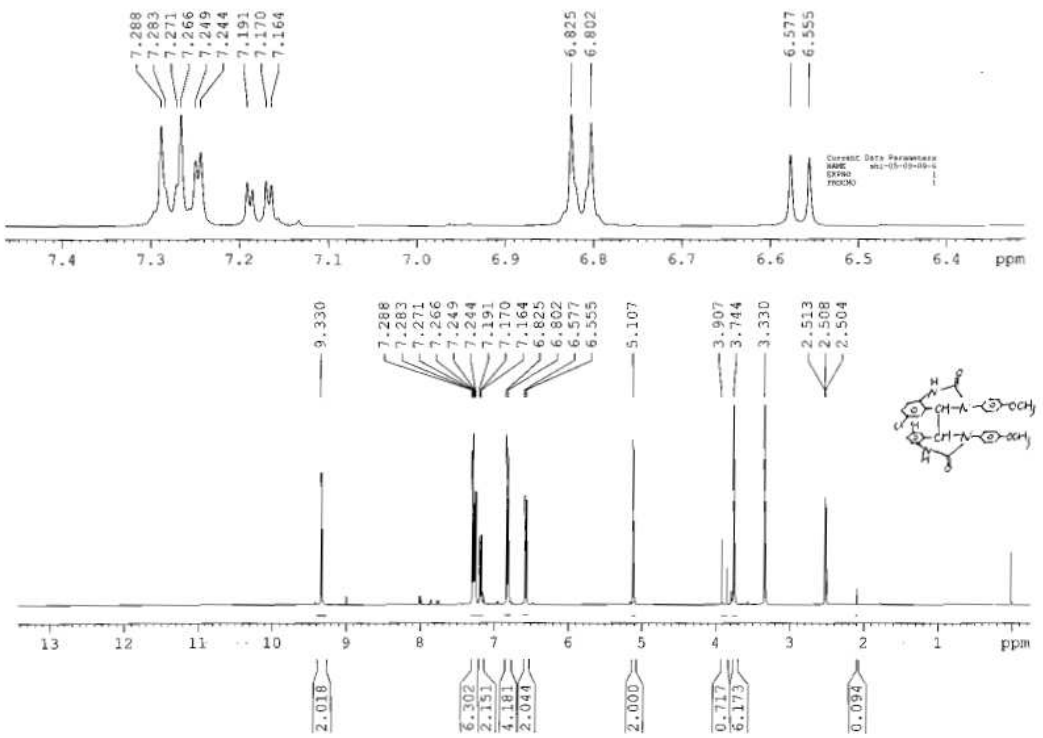
^{13}C NMR Spectrum of Compound 1b



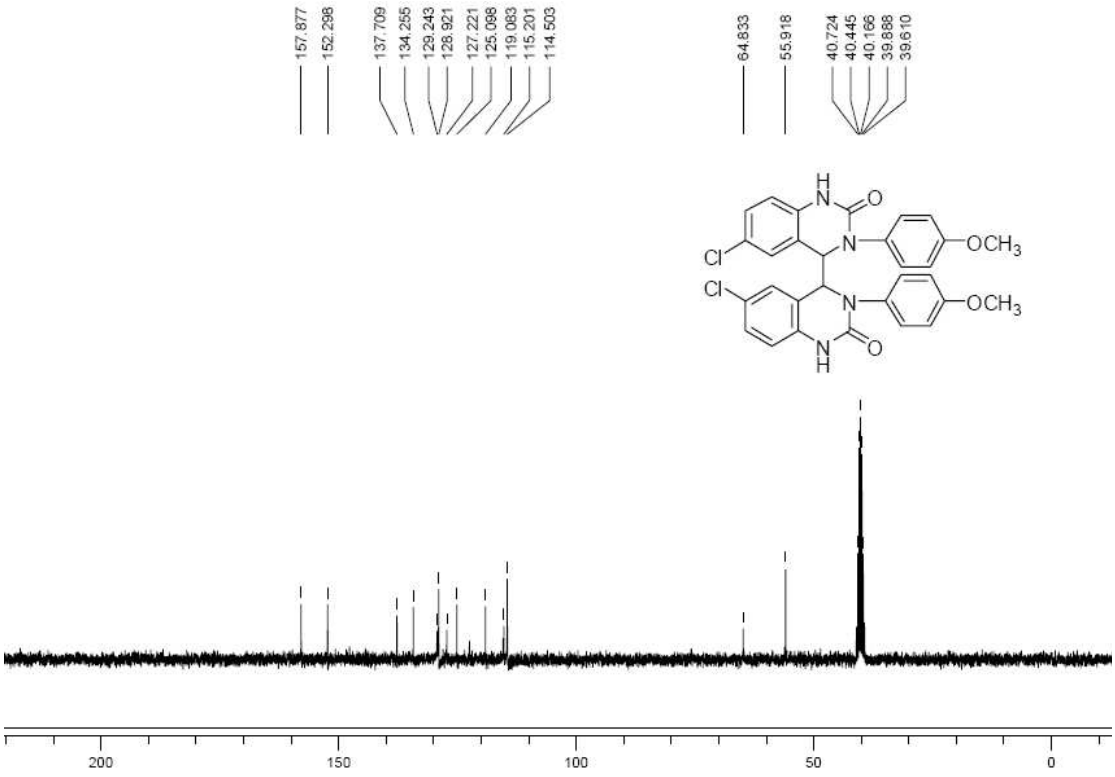
^{1}H NMR Spectrum of Compound 1c



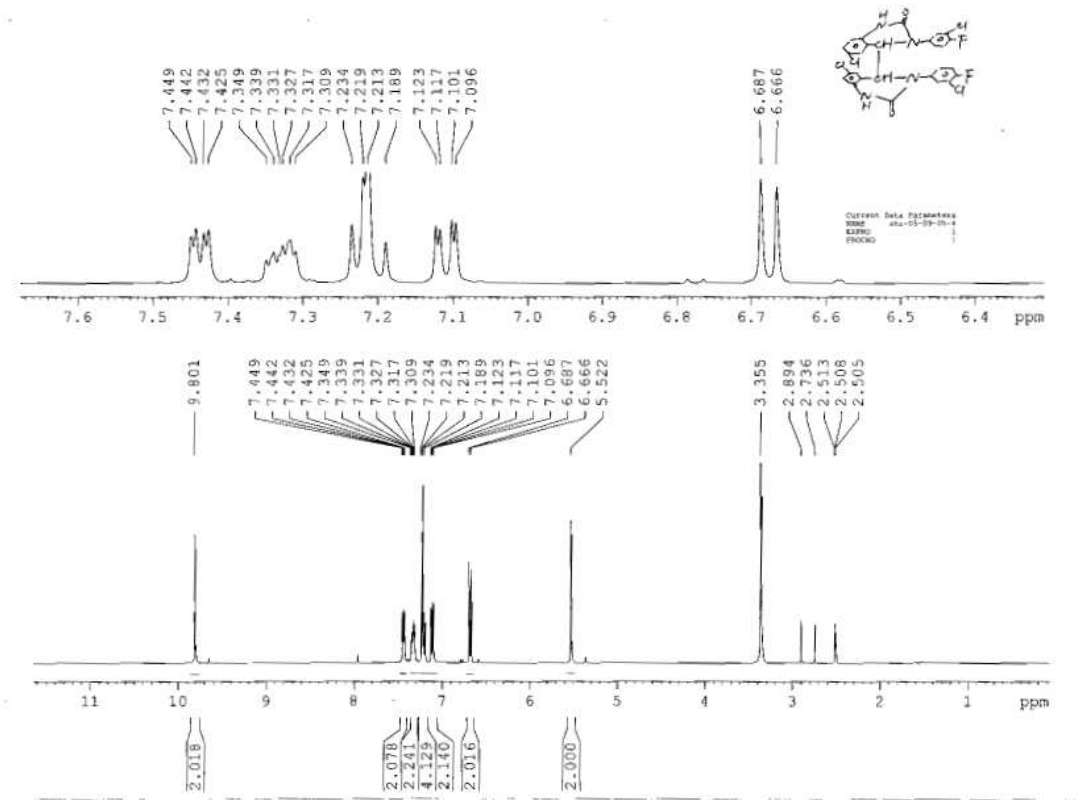
^{13}C NMR Spectrum of Compound 1c



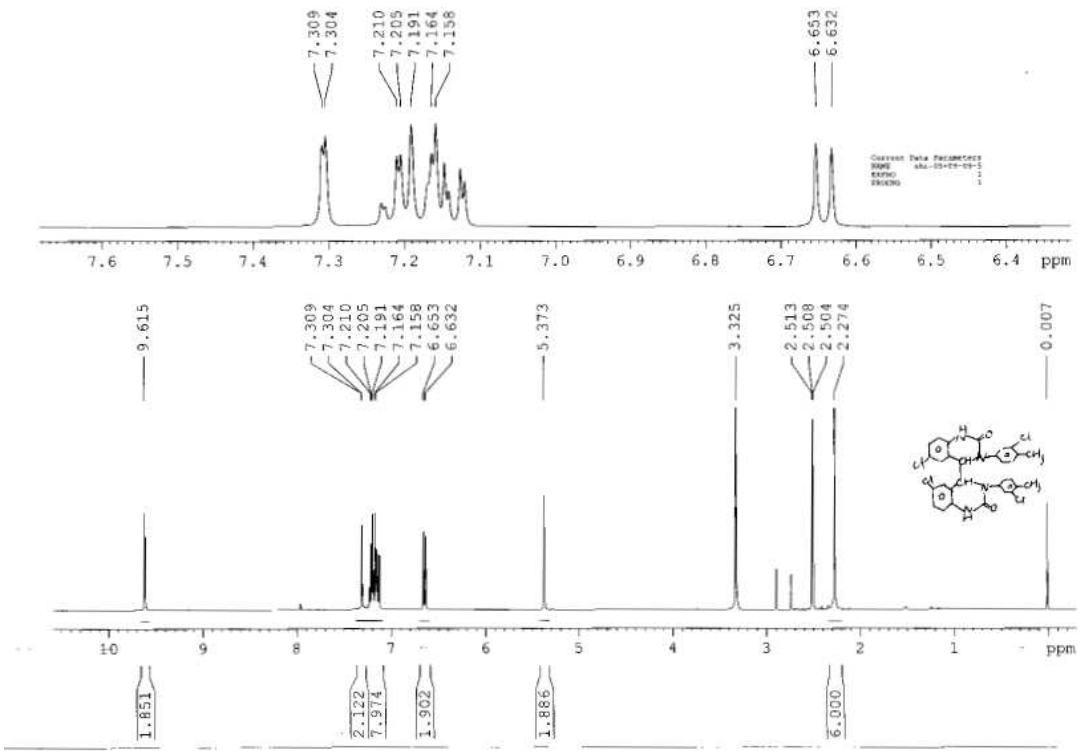
^{1}H NMR Spectrum of Compound 1d



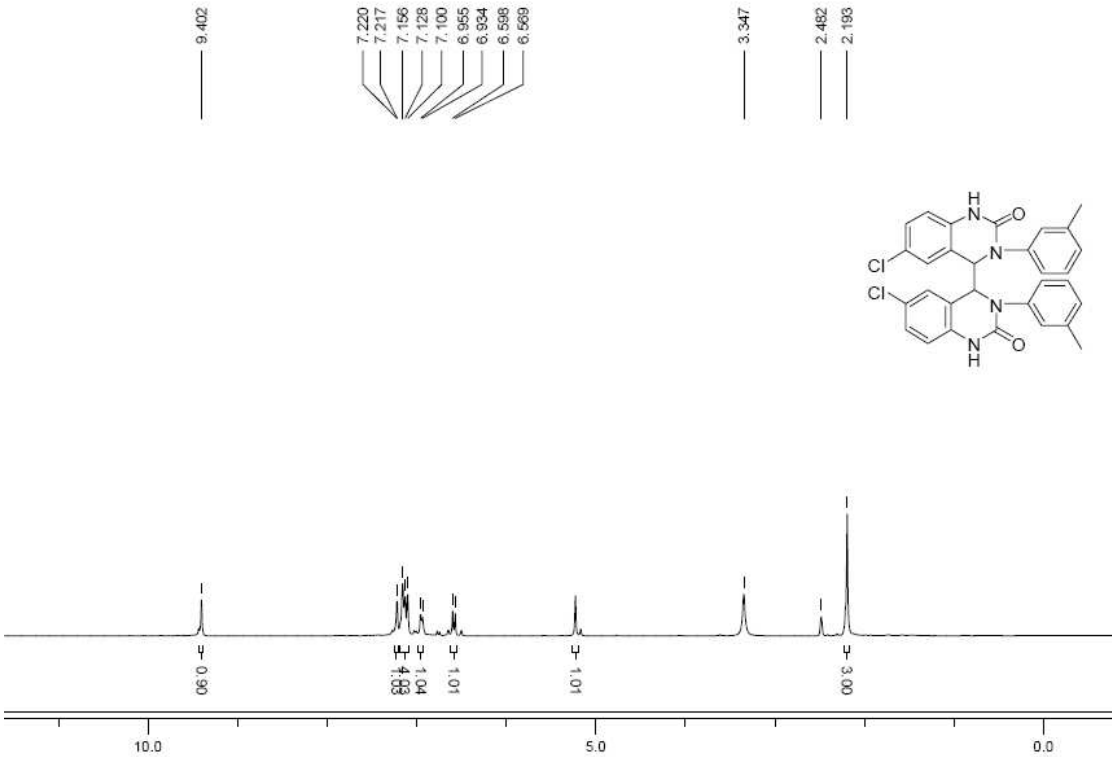
^{13}C NMR Spectrum of Compound 1d



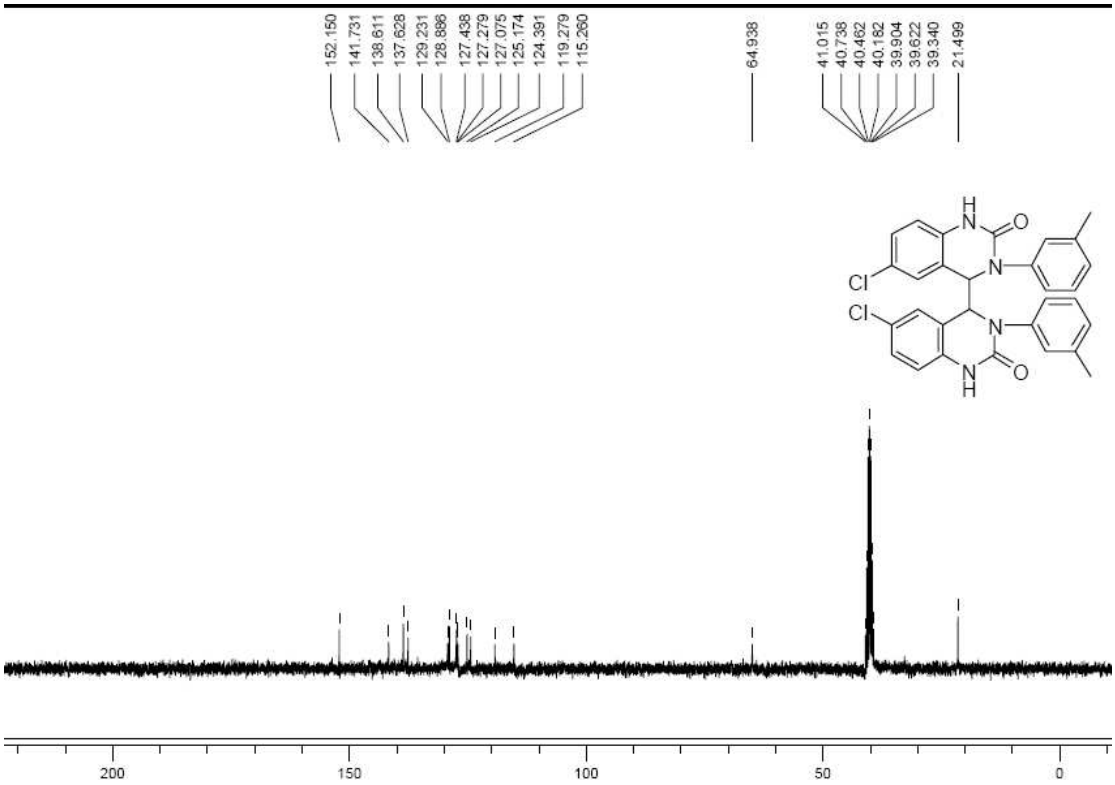
^{1}H NMR Spectrum of Compound 1e



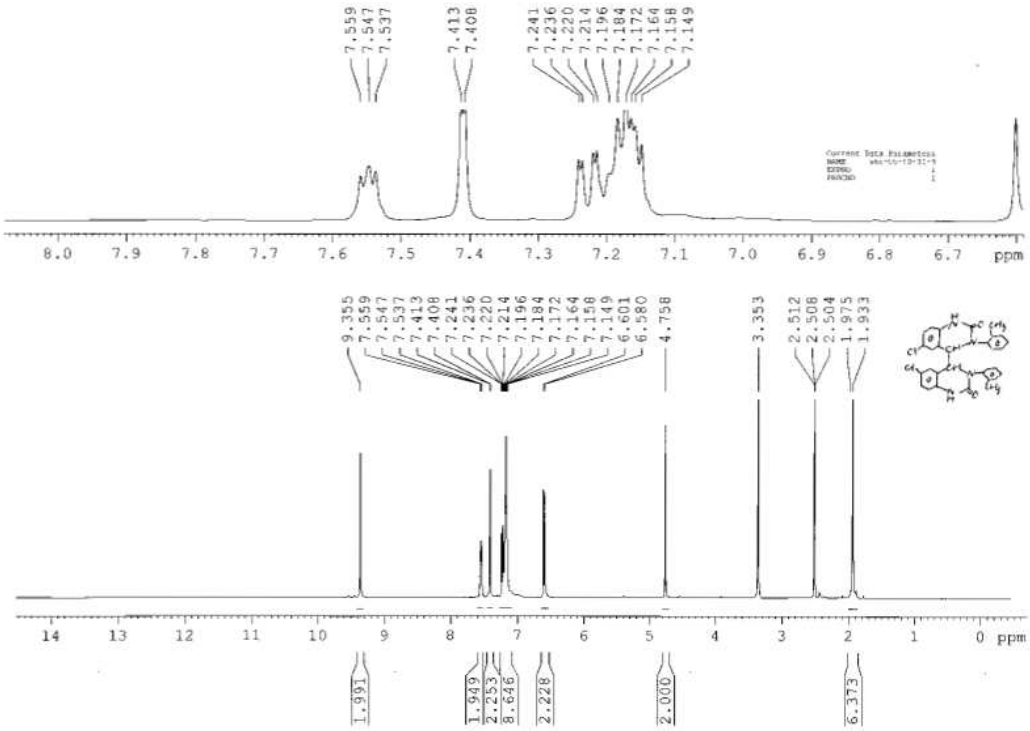
^{1}H NMR Spectrum of Compound 1f



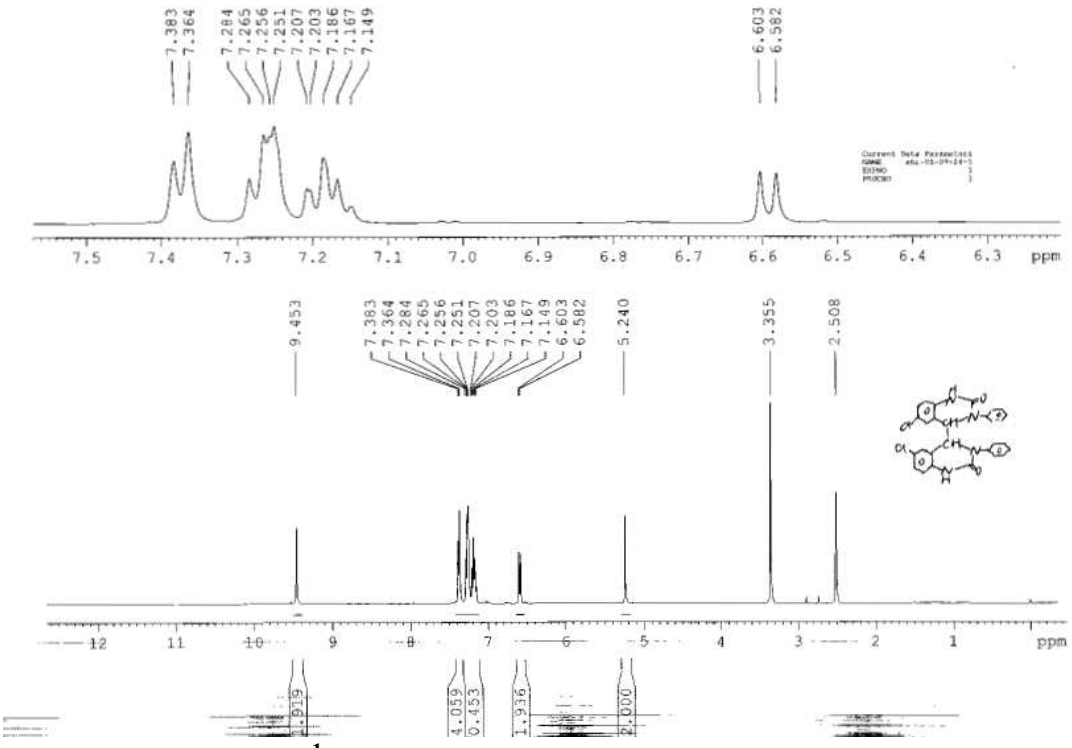
^{1}H NMR Spectrum of Compound 1g



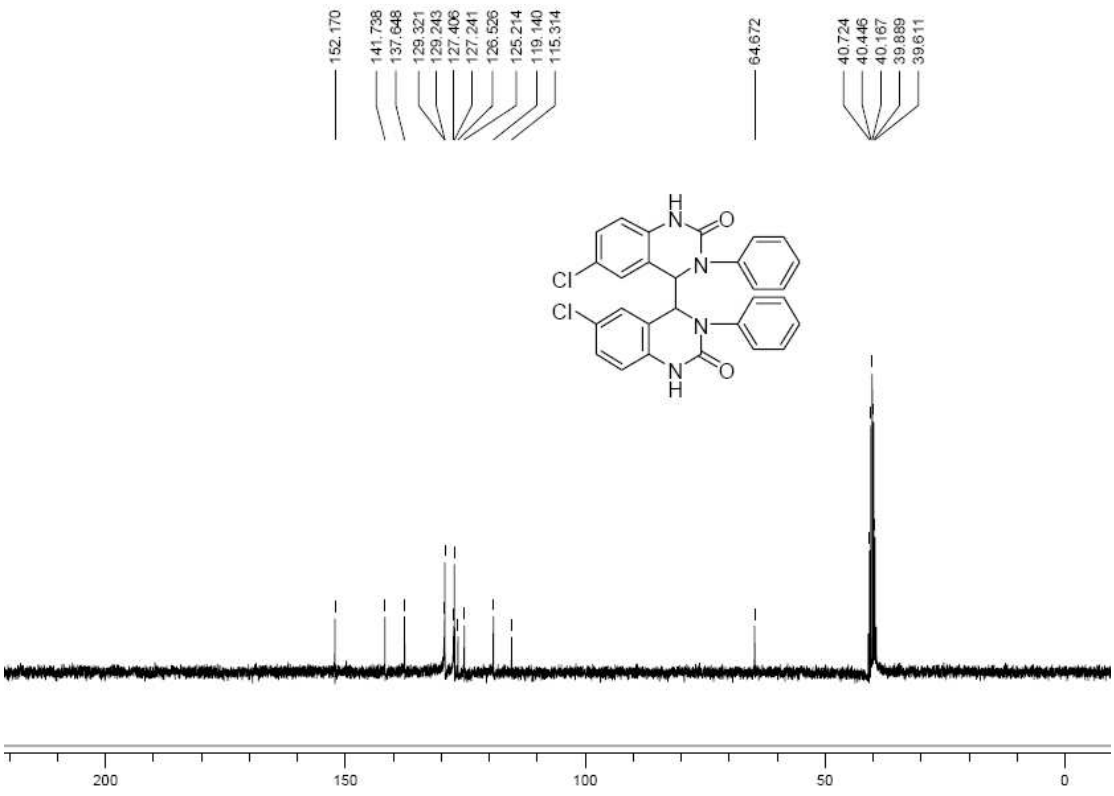
^{13}C NMR Spectrum of Compound 1g



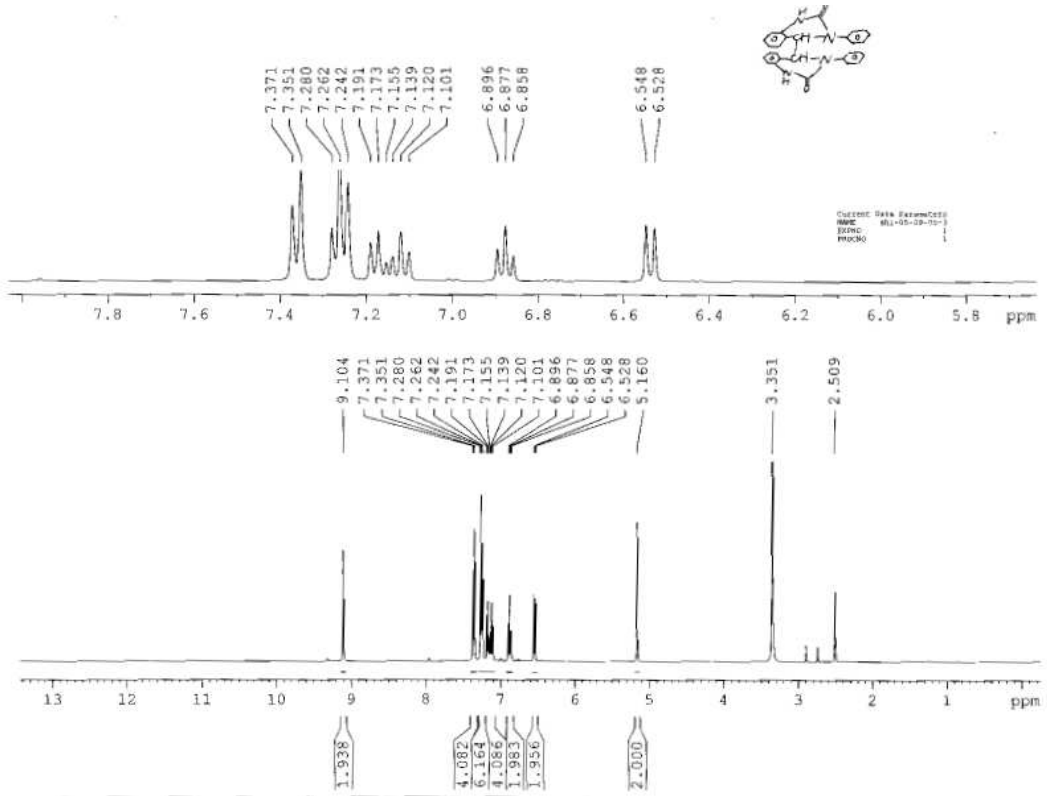
^{1}H NMR Spectrum of Compound 1h



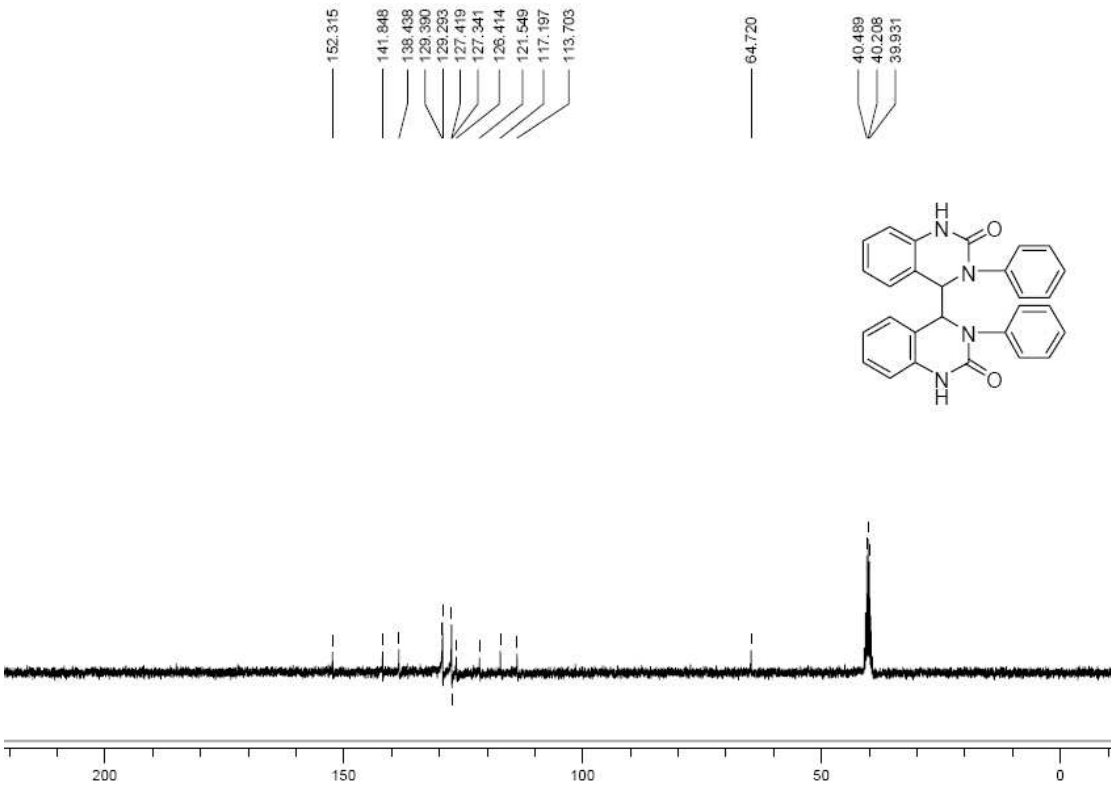
^{1}H NMR Spectrum of Compound 1i



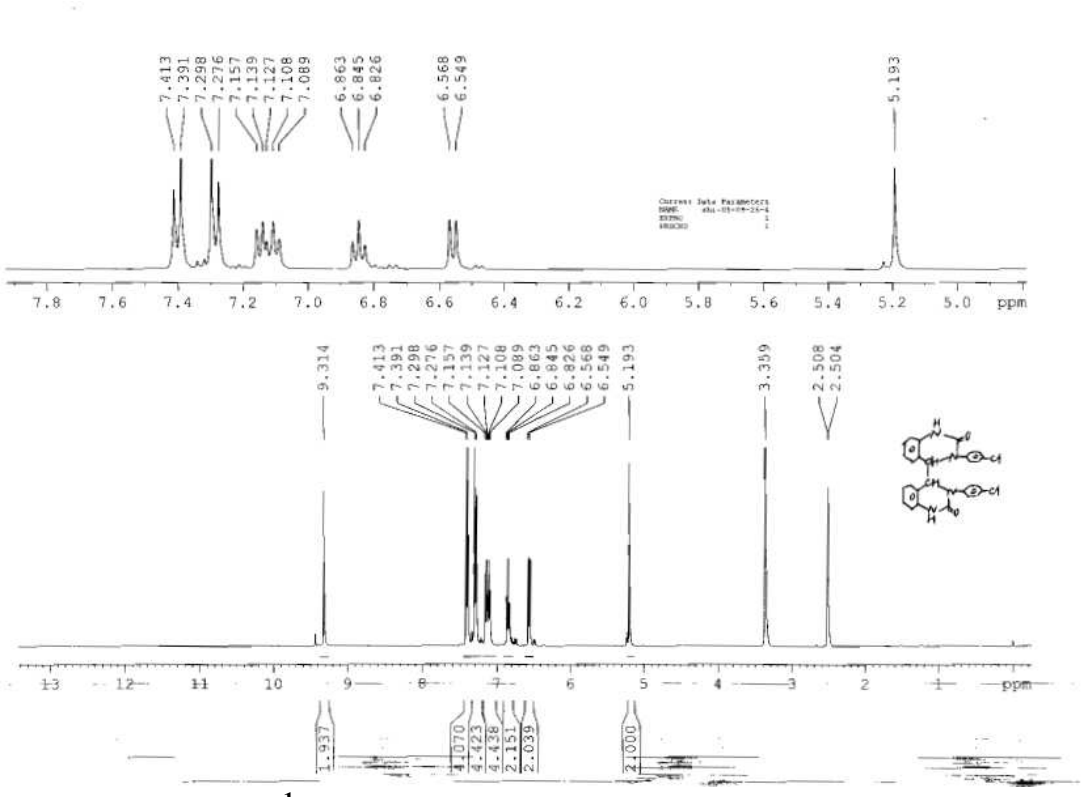
^{13}C NMR Spectrum of Compound 1i



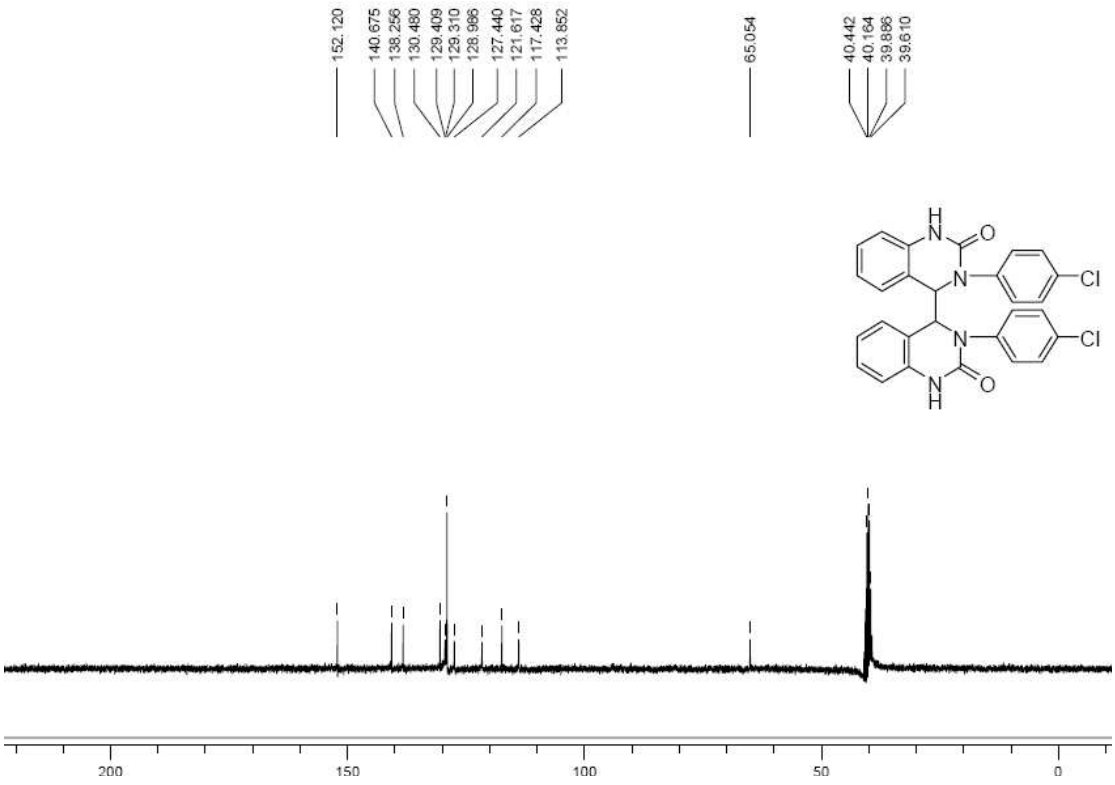
^{1}H NMR Spectrum of Compound 1j



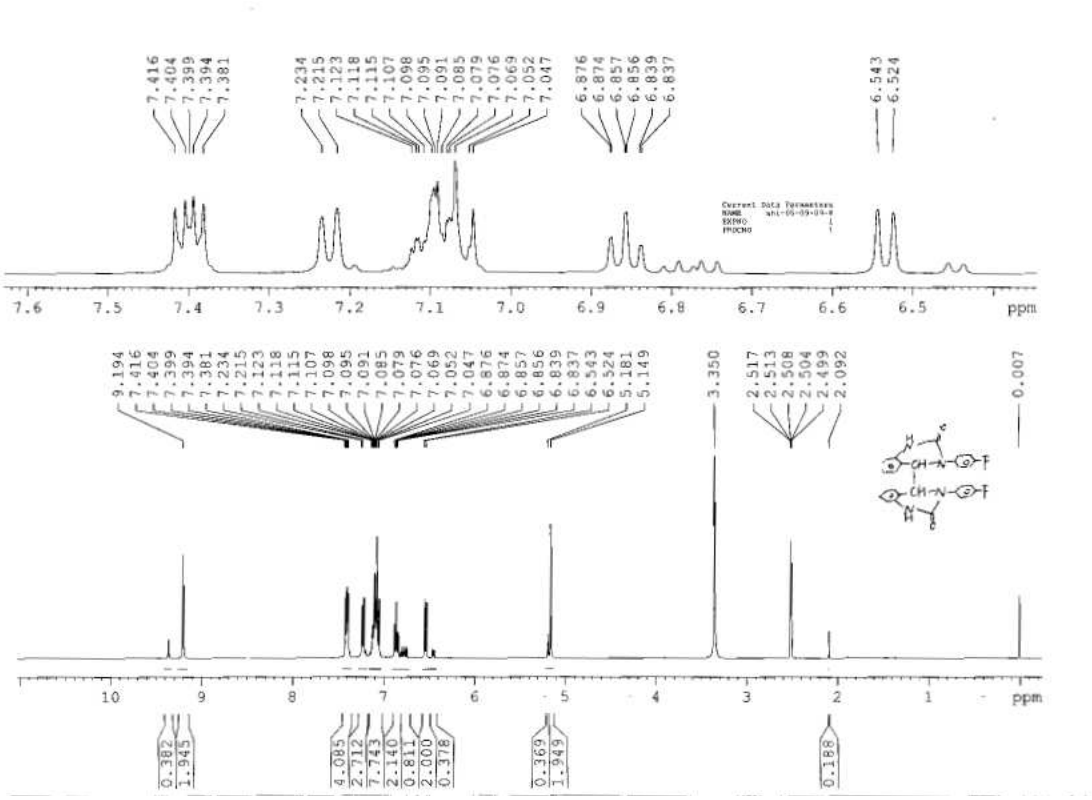
^{13}C NMR Spectrum of Compound 1j



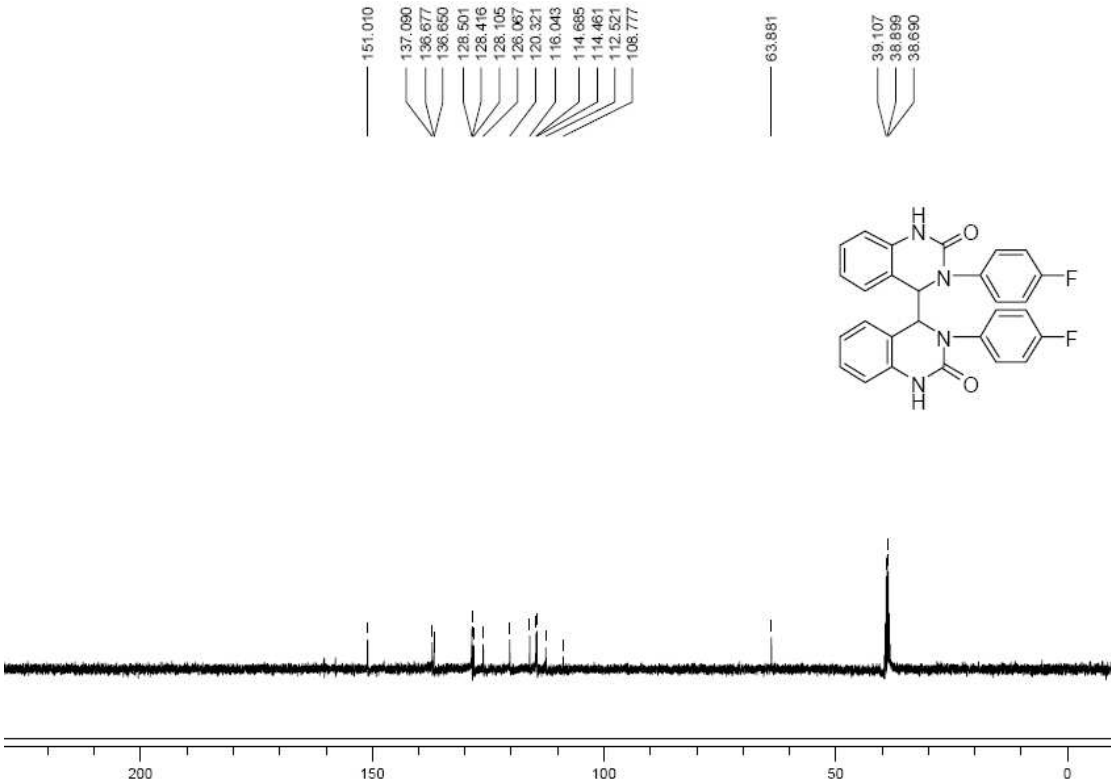
^{1}H NMR Spectrum of Compound 1k



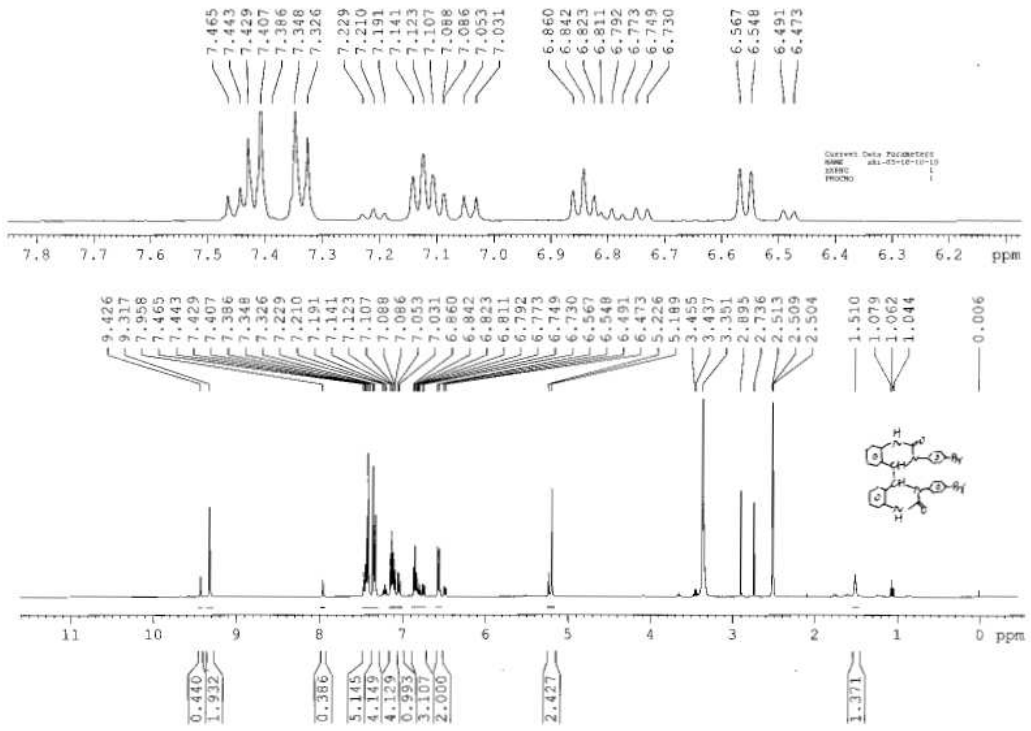
^{13}C NMR Spectrum of Compound 1k



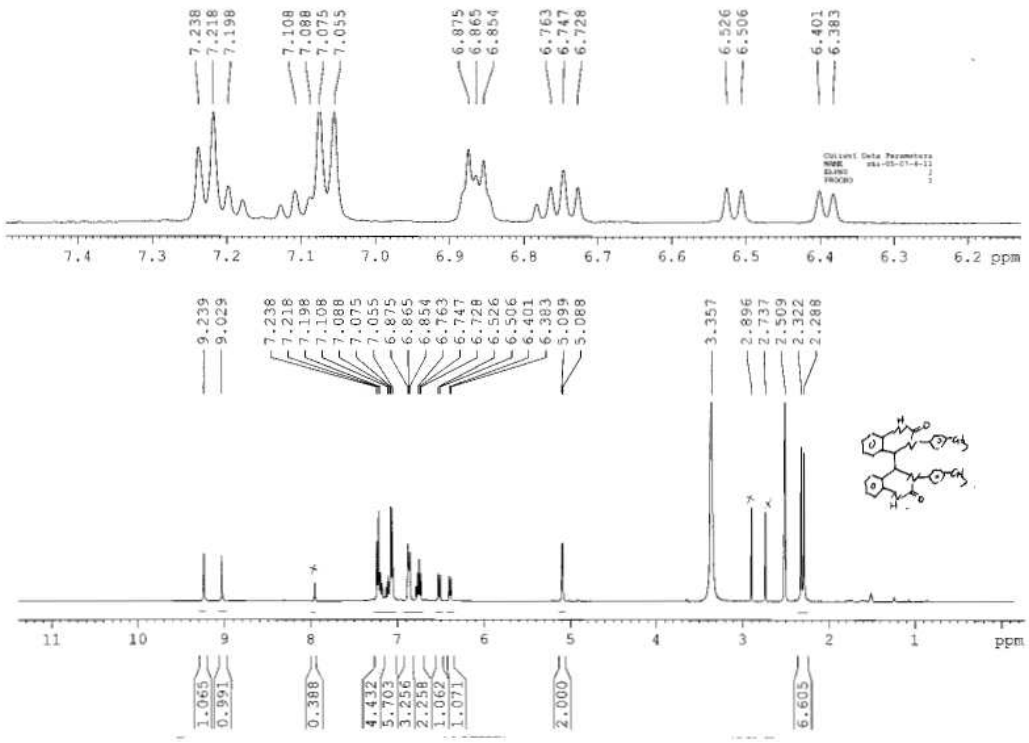
^{1}H NMR Spectrum of Compound 1l



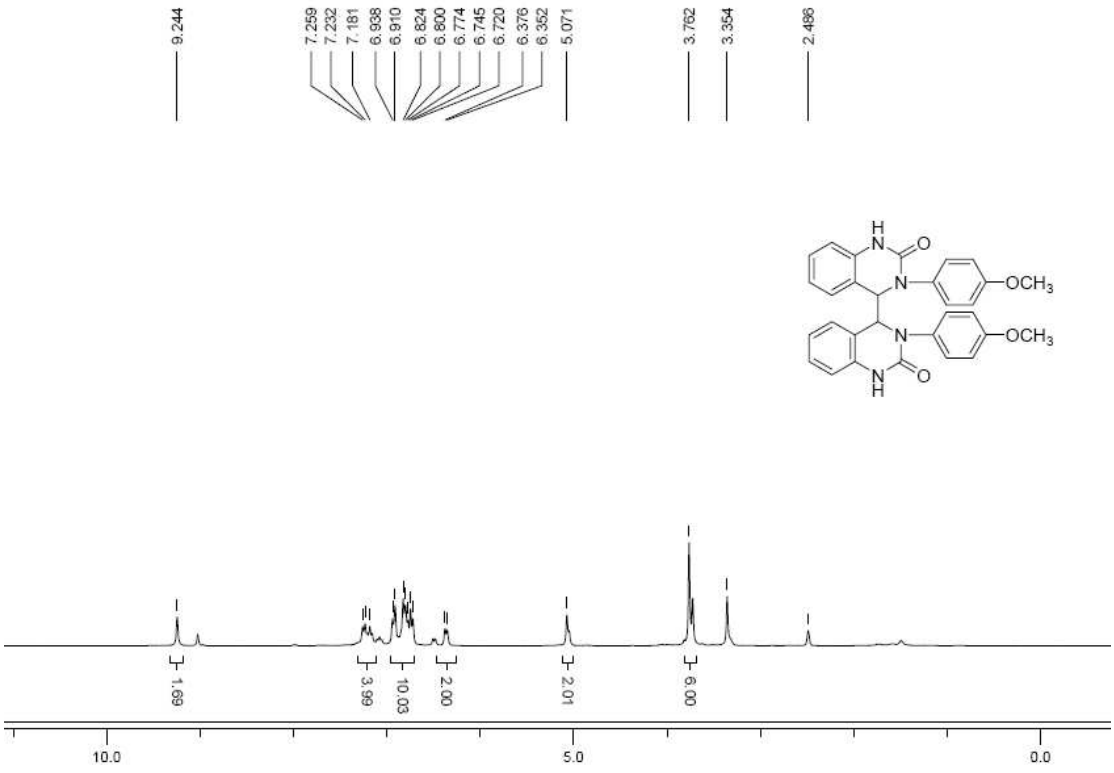
^{13}C NMR Spectrum of Compound 1l



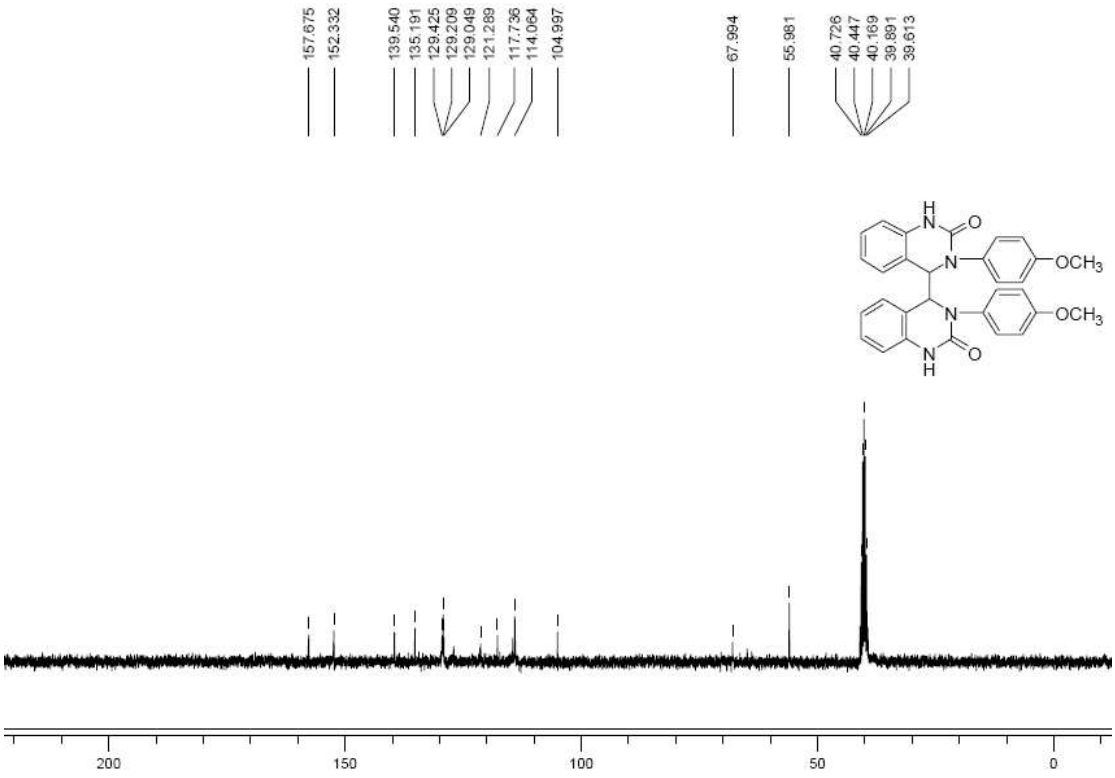
^{1}H NMR Spectrum of Compound 1m



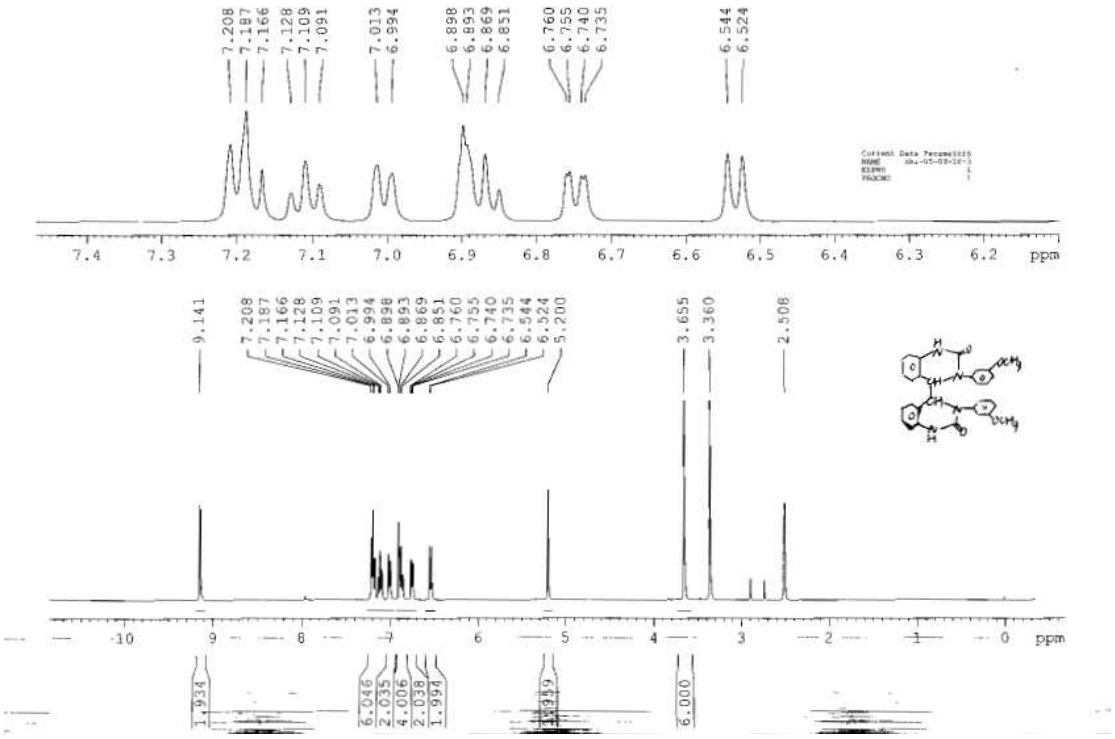
^{1}H NMR Spectrum of Compound 1n



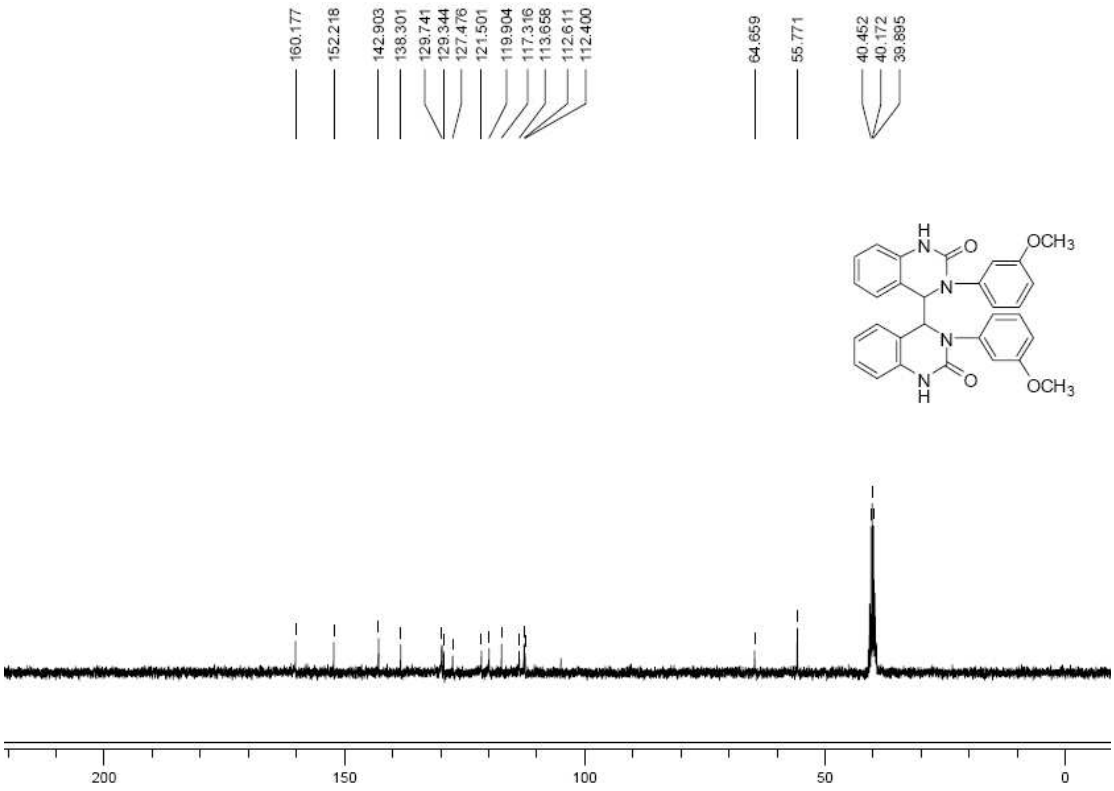
^{1}H NMR Spectrum of Compound 1o



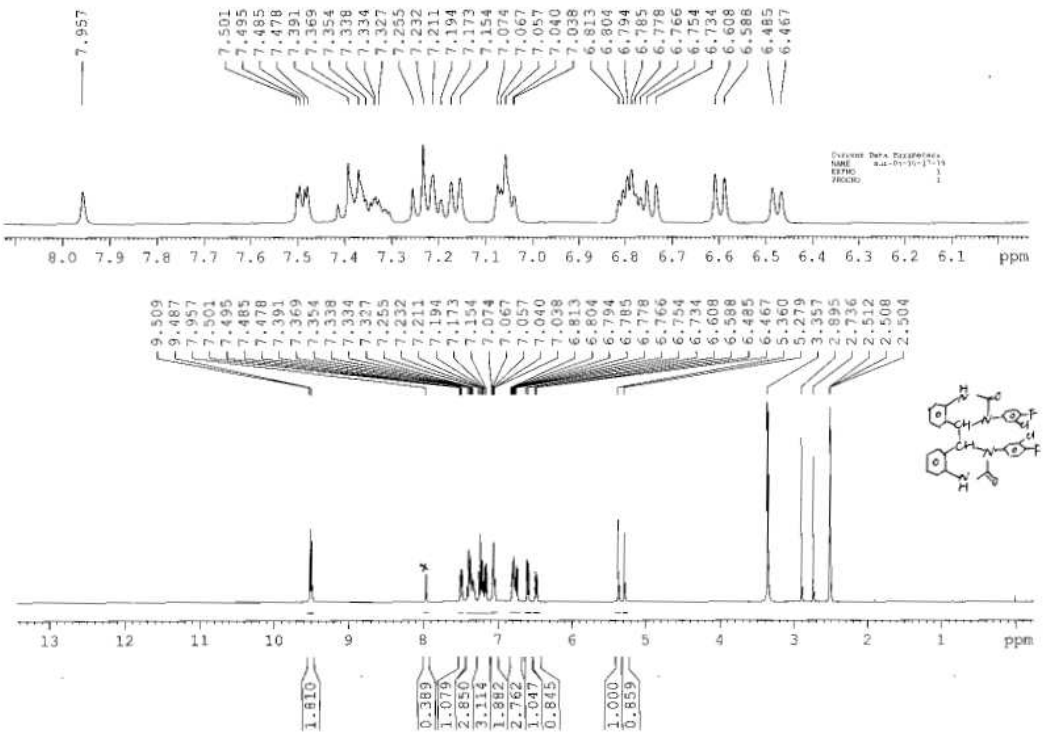
^{13}C NMR Spectrum of Compound 1o



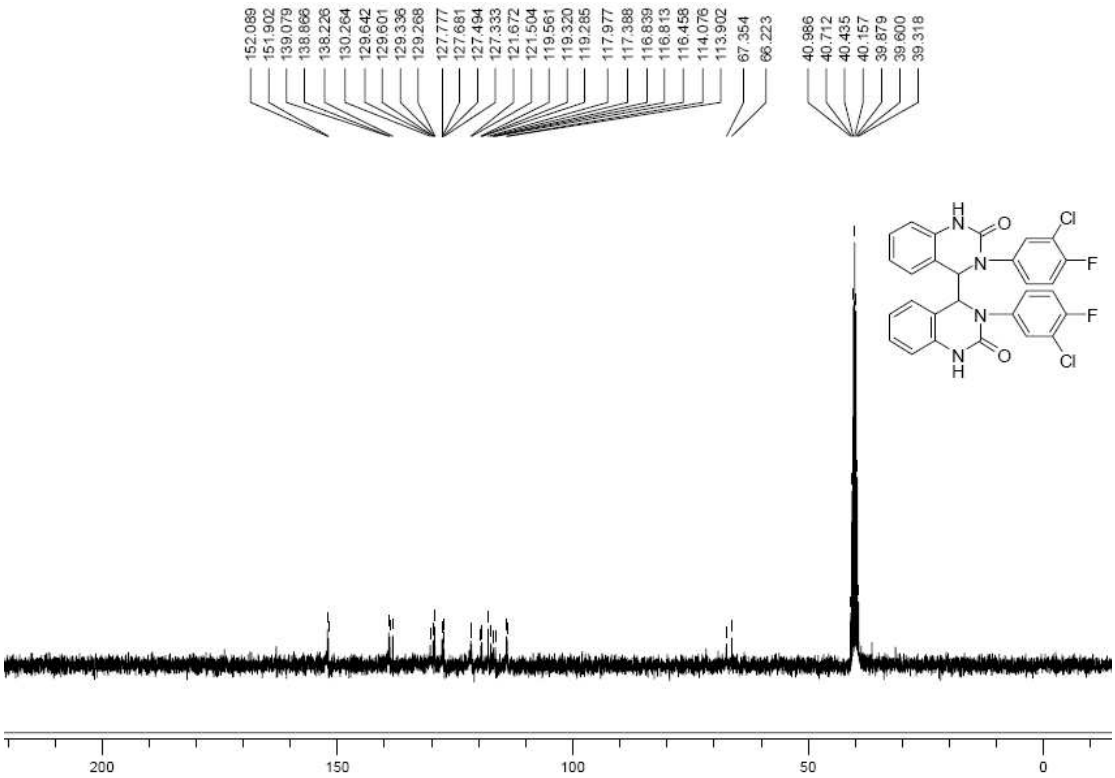
^{1}H NMR Spectrum of Compound 1p



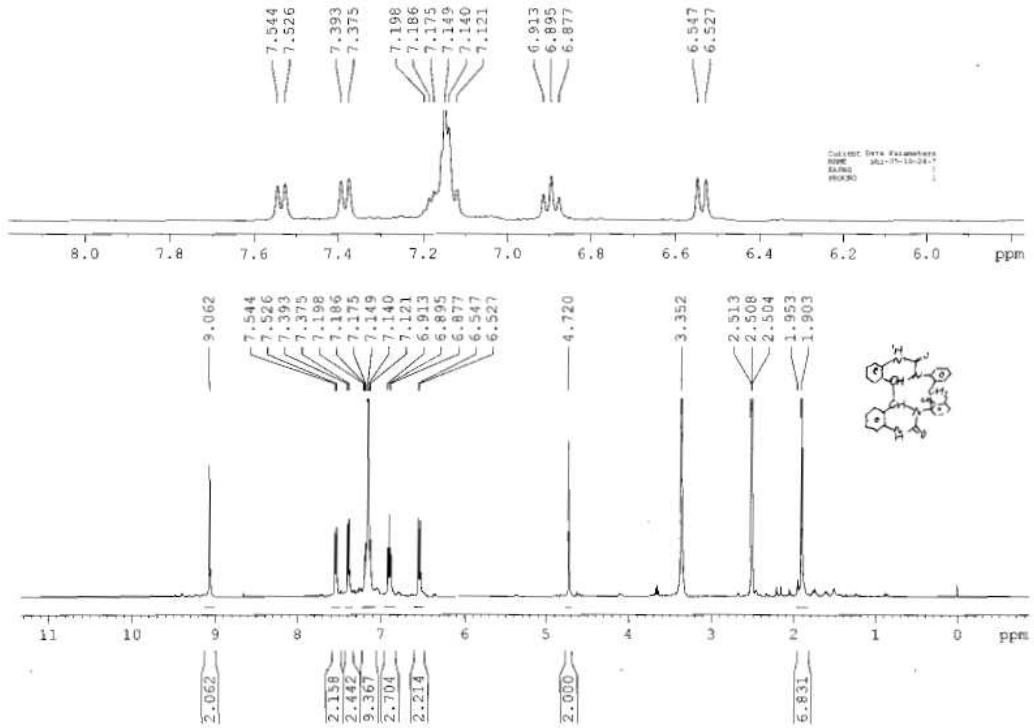
^{13}C NMR Spectrum of Compound 1p



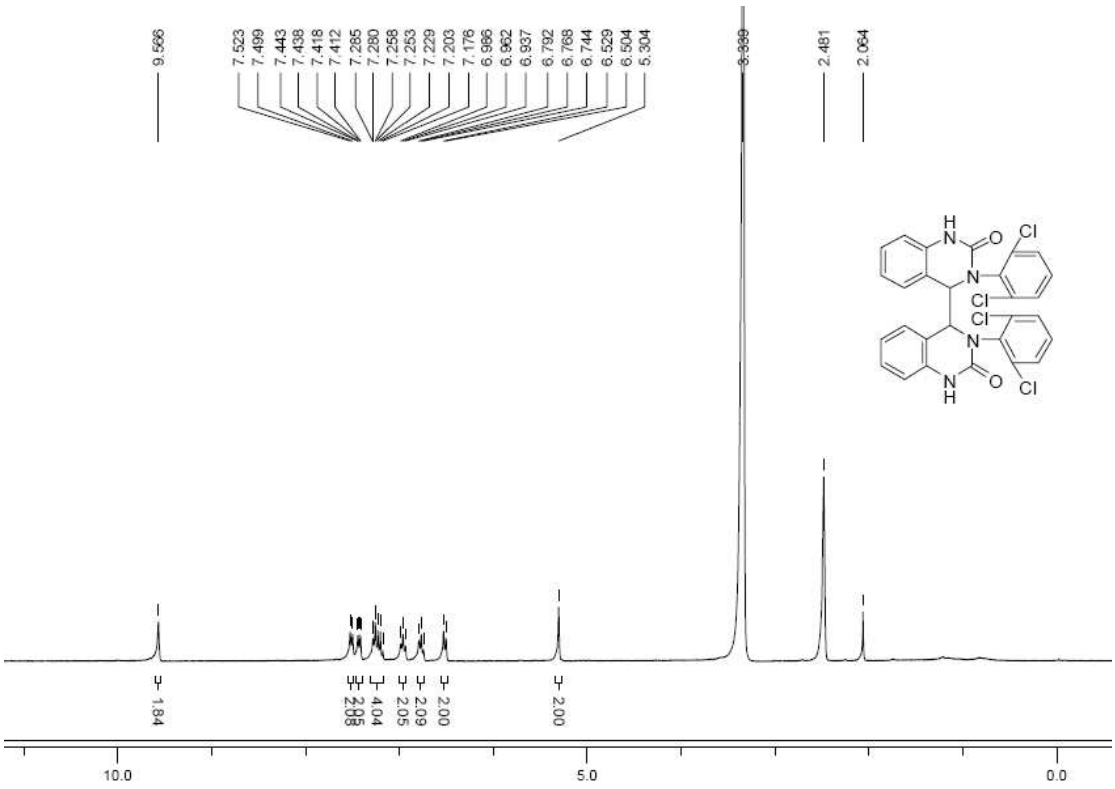
^{1}H NMR Spectrum of Compound 1q



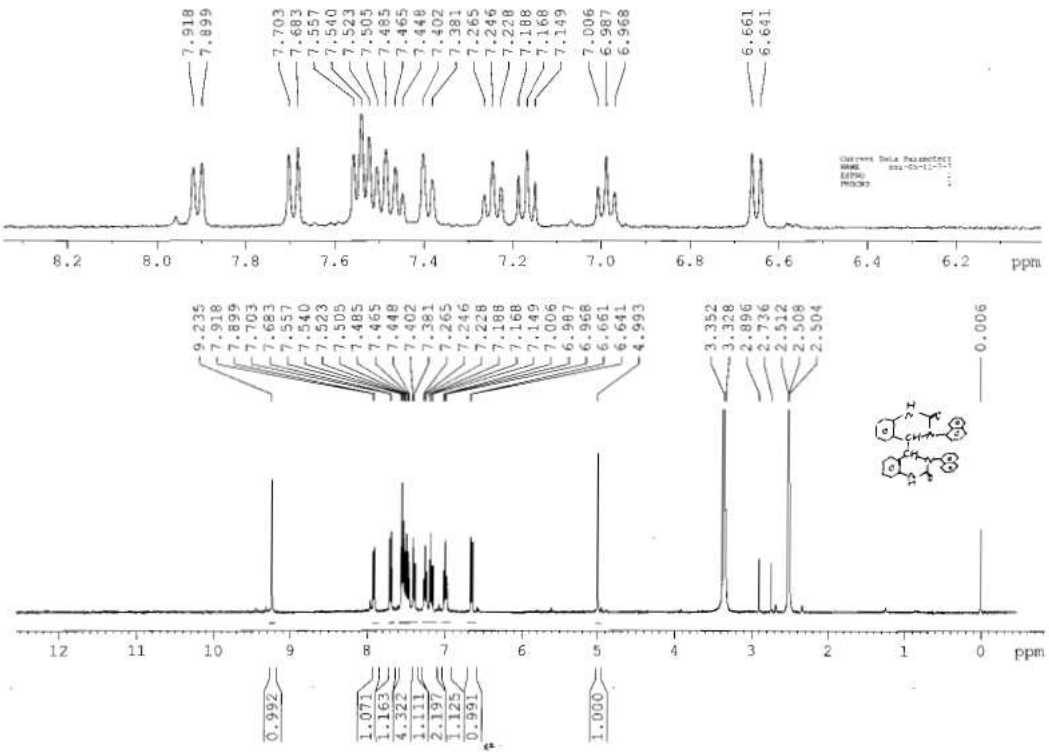
^{13}C NMR Spectrum of Compound 1q



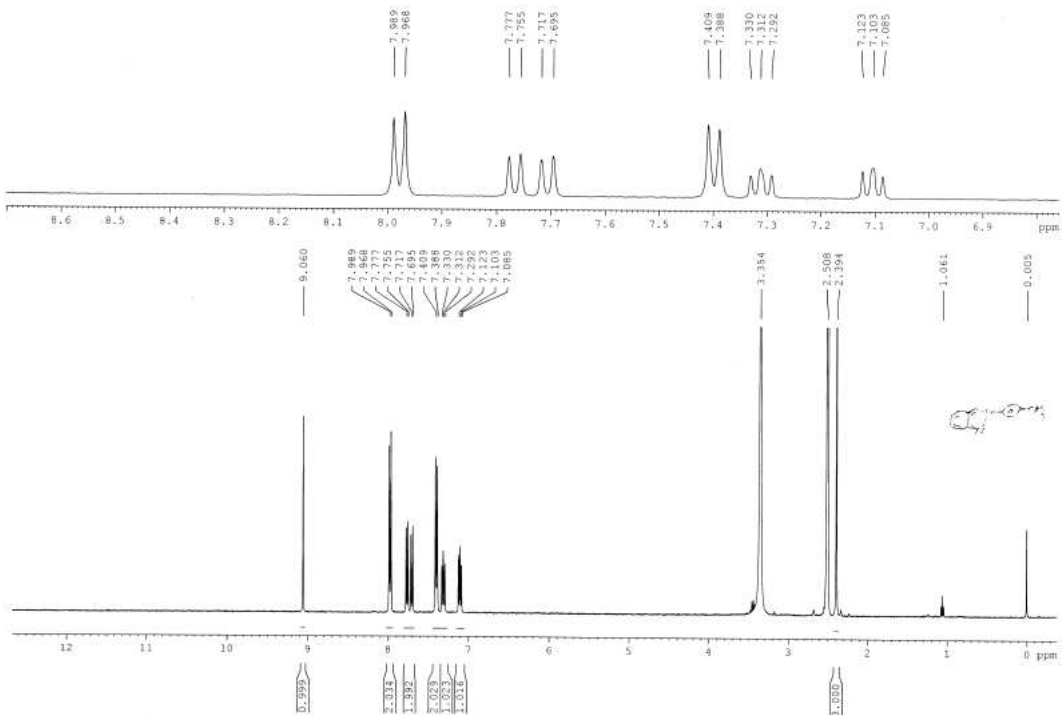
^{1}H NMR Spectrum of Compound 1r



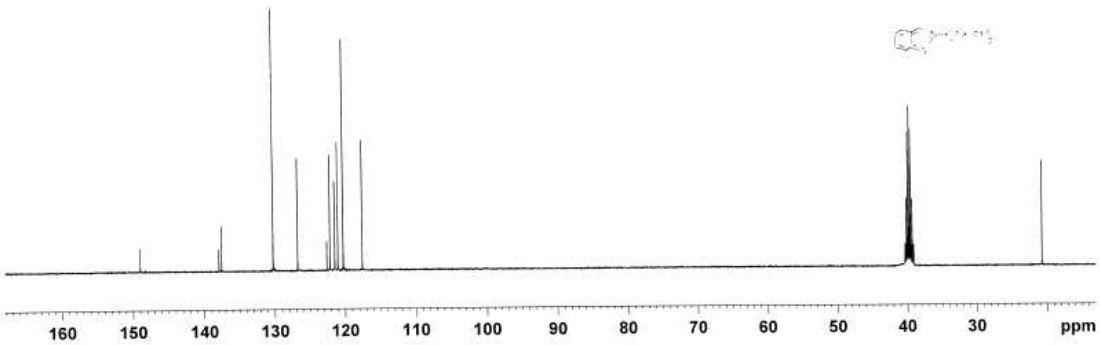
^{1}H NMR Spectrum of Compound 1s



^{1}H NMR Spectrum of Compound 1t



^{1}H NMR Spectrum of Compound 7



^{13}C NMR Spectrum of Compound 7

[a] Some of the products synthesized are mixtures of *cis* and *trans* isomers. According to ^{1}H NMR, among them, **1e**, **1g**, **1k**, **1l**, **1m**, **1o** and **1r** are mixtures of *cis* and *trans* isomers, and because of the low contents of *trans* isomers, the separation is difficult and the ^{13}C NMR show only a set of signals. Products **1n** and **1q** are also mixtures of *cis* and *trans* isomers which the ratios are close to 1:1. All of the other products are not mixture of isomers.