Supporting information

Experimental Section

Chemical Synthesis. Silica gel F_{254} plates were used for thin layer chromatography (TLC) in which the spots were examined under UV light at 254 nm and then developed by an iodine vapor. Flash chromatography was performed on silica gel H. Anhydrous solvents were purified according to standard procedures. All other commercial reagents were purchased from commercial sources and used without purification. NMR spectra were recorded on a Varian Mercury spectrometer (400 MHz and 600 MHz). Chemical shifts are reported as δ values in ppm and are calibrated according to TMS. LCMS/ HRMS were recorded on a Bruker Daltonics Data analysis 3.4 mass spectrometer and a Thermo LTQ Orbitrap-XL mass spectrometer. High performance liquid chromatography (HPLC) was performed with a YoungLin instrument SP930D, one equipped with Dikma C18 columns using methanol as an eluent. X-Ray data were collected on a Bruker APEX-II equipped with a CCD area detector using Mo/Kα radiation. The structures were solved by direct method using SHELXL-97. Unless specified otherwise, all tested compounds were confirmed to be >95% pure by HPLC.

General procedure for the preparation of 3-amino-l,2,4-triazole derivatives (3)[27]. A mixture of N-cyanoimidates (1mmol) and phenylhydrazine (1.2 mmol) were refluxed for 4h in methanol (3 mL). Then the solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel to afford **3**.

General procedure for the synthesis of 2-chloro-N-(1H-1,2,4-triazol-5-yl)acetamide derivatives (4). To a solution of **3** (14.4 mmol) in CH_2Cl_2 (80 mL) were added dropwise triethylamine (6 mL, 43.2 mmol) and 2-chloroacetyl chloride (4.3 mL, 57.6 mmol) in ice bath under N_2, the resultant mixture was stirred at room temperature for 5 h, diluted with CH_2Cl_2 (120 mL) and then the organic solution was washed with saturated Na_2CO_3 (2 x 100 mL), water (2 x 100 mL) and brine (100mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to afford **4**.

General procedure for the synthesis of N-(1,3-disubstituted-1H-1,2,4-triazol-5-yl)-2-phenoxy-acetamides (5). Phenol (744 mg, 6 mmol） was reacted with sodium hydride (244 mg, 12 mmol) in THF

(10mL) at room temperature for 1h，then concentrated and dried in vacuo to afford sodium phenoxide。To the flask containing in situ prepared sodium phenoxide were added 4 (2 mmol) and freshly distilled DMF (10 mL). The resultant mixture was stirred at 50 °C under N_2 for 5 h and quenched with water (100 mL). The reaction solution was extracted with ethyl acetate (3 x 60 mL). The combined organic layer was washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to afford **5**.

General procedure for the synthesis of 1,3-disubstituted-N-(2-phenoxyethyl)-1H-1,2,4-triazol-5-amines (6). To a solution of **5** (1.5 mmol) in redistilled THF (20 mL) was added $LiAlH_4$ (228 mg, 6 mmol) and $AlCl_3$ (339 mg, 3 mmol) at -20 °C under N_2. The reaction solution was warmed slowly to room temperature and continued to stir for 6 h, then diluted with ethyl acetate (60 mL). The organic layer was separated and washed with 10% H_2SO_4 solution (2 x 60 mL) and water (1 x 100 mL). After dried over Na_2SO_4, the solution was filtered and concentrated in vacuum. The residue was purified by flash chromatography to afford **6**.

General procedure for synthesis of 4-triazolyl-1-oxa-4-azaspiro[4,5]deca-6,9-dien-3,8-diones (1) and 4-triazolyl-1-oxa-4-azaspiro[4,5]deca-6,9-dien-8-ones (2). A flame dried round bottom flask was charged, under a nitrogen atmosphere, with 5 or 6 (0.1mmol), $PhI(CF_3CO_2)_2$ (0.25 mmol) and $Cu[(CH_3CN)_4]ClO_4$ (0.01 mmol, for 5 to 1) or $Cu(CF_3SO_3)_2$ (0.015 mmol, for 6 to 2). The fresh distilled dichloromethane (10 mL) was added. After stirred at room temperature for 5h, the mixture was washed with saturated NaCl solution and dried over $MgSO_4$. The solution was filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate as an eluent to give **1** or **2**.

^{1}H-NMR ($CDCl_3$),^{13}C-NMR ($CDCl_3$) and HR-MS data of compounds

4-(1,3-Diphenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-diene-3,8-dione (1a). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 8.07-8.05 (m, 2H), 7.56-7.50 (m, 5H), 7.45-7.42 (m, 3H), 6.56 (d, *J* = 10.0 Hz, 2H), 6.14 (d, *J* = 10.0 Hz, 2H), 4.56 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 183.5, 170.3, 161.8, 142.2, 141.7, 136.3, 131.1, 129.9, 129.9, 129.8, 129.6, 128.6, 126.4, 124.8, 88.1 and 66.0. HRMS (ESI) m/z (%) for $C_{22}H_{17}N_4O_3$ (M+H): Calcd. 385.1301; Found 385.1293.

4-(1,3-Diphenyl-1H-1,2,4-triazol-5-yl)-6-methoxy-1-oxa-4-azaspiro- [4.5]deca-6,9-diene-3,8-dione (1b). ^{1}H-NMR ($CDCl_3$,400MHz) δ (ppm): 8.05-8.02 (m, 2H), 7.55-7.51 (m, 5H), 7.44-7.41 (m, 3H), 6.30 (d, *J* = 10.0 Hz, 1H), 6.10 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.47 (d, *J* = 1.6 Hz, 1H), 4.70 (d, *J* = 14.4 Hz, 1H), 4.51 (d, *J* = 14.4 Hz, 1H), 3.69 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 185.1, 171.2, 168.9, 161.6, 138.2, 136.3, 132.1, 129.9, 129.8, 129.6, 129.4, 126.2, 124.6, 103.0, 88.0, 67.5 and 56.3. HRMS (ESI) for $C_{23}H_{19}N_4O_4$ (M+H): Calcd. 415.1406; Found 415.1402.

4-(1-Methyl-3-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]- deca-6,9-diene-3,8-dione (1c). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.91-7.90 (m, 2H), 7.39 (br, 3H), 6.90 (d, *J* = 10.0 Hz, 2H), 6.35 (d, *J* = 10.0 Hz, 2H), 4.64 (s, 2H), 3.88 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 183.6, 168.9, 160.6, 143.0, 141.7, 131.4, 130.1, 139.5, 128.5, 125.9, 88.0, 65.8 and 36.1. HRMS (ESI) m/z (%) for $C_{17}H_{14}N_4O_3Na$ (M+Na): Calcd. 345.0964; Found 345.0988.

4-(1-Methyl-5-phenyl-1H-1,2,4-triazol-3-yl)-1-oxa-4-azaspiro[4.5]- deca-6,9-diene-3,8-dione (1d). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.59-7.57 (m, 2H), 7.50-7.49 (m, 2H), 6.90 (d, *J* = 10.0 Hz, 2H), 6.31 (d, *J* = 10.0 Hz, 2H), 4.61 (s, 2H), 3.96 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 184.5, 168.9, 155.2, 151.1, 143.2, 130.9, 130.6, 128.9, 128.7, 119.1, 87.7, 66.4 and 29.3. HRMS (ESI) m/z (%) for $C_{17}H_{14}N_4O_3Na$ (M+Na): Calcd. 345.0964; Found 345.0965.

4-(3-(4-Nitrophenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-diene-3,8-dione (1e). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 8.30 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 7.59-7.57 (m, 3H), 7.52-7.51 (m, 2H), 6.57 (d, *J* = 10.0 Hz, 2H), 6.16 (d, *J* = 10.0 Hz, 2H), 4.58 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 183.4, 170.2, 159.8, 148.6, 143.1, 141.4, 136.0, 135.9, 131.2, 130.3, 129.8, 127.1, 124.7, 124.0, 88.2 and 65.9. HRMS (ESI) m/z (%) for $C_{22}H_{16}N_5O_5$ (M+H): Calcd. 430.1151; Found 430.1144.

4-(3-(5-Chloro-2-nitrophenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-diene-3,8-dione (1f). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.95 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.56-7.49 (m, 6H), 6.52 (d, *J* = 10.0 Hz, 2H), 6.22 (d, *J* = 10.0 Hz, 2H), 4.54 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 183.3, 170.0, 157.0, 142.6, 140.9, 138.1, 135.8, 131.5, 130.9, 130.4, 130.3, 130.2, 129.7, 125.4, 125.3, 124.6, 88.4 and 64.9. HRMS (ESI) m/z (%) for $C_{22}H_{15}ClN_5O_5$ (M+H): Calcd. 464.0762; Found 464.0749.

4-(3-(4-Chlorophenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-diene-3,8-dione (1g). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.90 (d, *J* = 4.4 Hz, 2H), 7.56-7.49 (m, 8H), 7.41(d, *J* = 8.4Hz, 3H), 6.55(d, *J* = 10.0 Hz, 2H), 6.14(d, *J* = 10.0 Hz, 2H), 4.57(s, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 183.4, 170.2, 160.8, 142.4, 141.5, 136.0, 135.8, 131.0, 130.0, 129.6, 128.8, 128.3, 127.6, 124.7, 88.0 and 65.9. HRMS (ESI) m/z (%) for $C_{22}H_{16}ClN_4O_3$ (M+H): Calcd. 419.0911; Found 419.0908.

4-(3-(2,4-Dichlorophenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-diene-3,8-dione (1h). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.81(d, *J* = 8.0 Hz, 1H), 7.55-7.51(m, 8H), 7.34-7.31(m, 1H), 6.58 (d, *J* = 10.0 Hz, 2H), 6.18 (d, *J* = 10.0 Hz, 2H), 4.57(s, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 183.4, 170.1, 159.5, 142.0, 141.4, 136.0, 133.7, 132.0, 131.2, 130.6, 130.1, 129.7, 129.5, 127.4, 127.1, 124.6, 88.3 and 66.0. HRMS (ESI) m/z (%) for $C_{22}H_{15}Cl_2N_4O_3$ (M+H): Calcd.453.0521; Found 453.0512.

4-(1-Phenyl-3-p-tolyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro- [4.5]deca-6,9-diene-3,8-dione (1i). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.94(d, *J* = 8.0 Hz, 2H), 7.56-7.50 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 4H), 6.55(d, *J* = 10.0 Hz, 2H), 6.13(d, *J* = 10.0 Hz, 2H), 4.56 (s, 2H), 2.39 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm):183.4, 170.2, 161.8, 142.1, 141.6, 140.0, 136.1, 130.9, 129.8, 129.5, 129.3, 127.0, 126.1, 124.7, 88.0, 65.9 and 21.4. HRMS (ESI) m/z (%) for $C_{23}H_{19}N_4O_3$ (M+H): Calcd.399.1457; Found 399.1458.

4-(3-(4-Methoxyphenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-diene-3,8-dione (1j). ^{1}H-NMR ($CDCl_3$, 400MHz) δ (ppm): 7.98 (d, *J* = 8.8 Hz, 2H), 7.54-7.50 (m, 5H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 10.0 Hz, 2H), 6.13 (d, *J* = 10.0 Hz, 2H), 4.56 (s, 2H), 3.86 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ (ppm): 183.4, 170.3, 161.7, 160.9, 141.7, 141.6, 136.2, 130.9, 129.8, 129.6, 127.8, 124.7, 122.5, 113.9, 88.1, 65.9 and 55.3. HRMS (ESI) for $C_{23}H_{19}N_4O_4$ (M+H): Calcd. 415.1406; Found 415.1415.

4-(1-(4-Methoxyphenyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione (1k). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.89 (s, 3H), 4.55 (s, 2H), 6.15 (d, *J* = 10.0 Hz, 2H), 6.85 (d, *J* = 10.0 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.44-7.41 (m, 5H), 8.06-8.03 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 183.5, 170.3, 161.6, 160.5, 141.8, 141.8, 130.9, 129.9, 129.8, 128.9, 128.6, 126.4, 126.3, 114.6, 88.0, 66.0 and 55.6. HRMS (ESI) for $C_{23}H_{19}N_4O_4$ (M+H): Calcd. 415.1406; Found 415.1396.

4-(1-Phenyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-diene-3,8-dione (1l). Gray solid, m.p. 136-138 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.68 (d, *J* = 3.6 Hz, 1H), 7.55-7.50 (m, 5H), 7.38 (d, *J* = 4.8 Hz, 1H), 7.10 (t, *J* = 4.0 Hz, 1H), 6.54 (d, *J* = 10.0 Hz, 2H), 6.13 (d, *J* = 10.0 Hz, 2H), 4.55 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 183.4, 170.3, 158.0, 142.2, 141.5, 135.9, 132.5, 131.0, 130.0, 129.6, 127.7, 127.3, 127.1, 124.8, 88.1 and 66.0. HRMS (ESI) for $C_{20}H_{15}N_4O_3S$ (M+H): Calcd. 391.0865; Found 391.0866.

4-(3-(Furan-2-yl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro- [4.5]deca-6,9-diene-3,8-dione (1m). White solid, m.p. 149-151 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.55-7.48 (m, 7H), 7.00 (d, *J* = 2.8 Hz, 1H), 6.54-6.51(m, 2H), 6.11(d, *J* = 10.0 Hz, 2H), 4.56 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 183.2, 170.3, 154.9, 145.0, 143.7, 142.2, 141.4, 135.7, 131.0, 130.0, 129.5, 124.7, 88.0 and 65.8. HRMS (ESI) for $C_{20}H_{15}N_4O_4$ (M+H): Calcd. 375.1093; Found 375.1094.

4-(1-(3-Chlorophenyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione (1n). Gray solid, m.p. 168-170 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.04-8.02 (m, 2H), 7.56-7.42 (m, 7H), 6.64 (d, *J* = 10.0 Hz, 2H), 6.20 (d, *J* = 10.0 Hz, 2H), 4.57 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 183.4, 170.2, 161.9, 142.5, 141.6, 137.3, 135.4, 131.2, 130.6, 130.1, 130.0, 129.6, 128.7, 126.4, 125.0, 122.5, 88.2 and 65.9. HRMS (ESI) for $C_{22}H_{16}ClN_4O_3$ (M+H): Calcd. 419.0911; Found 419.0907.

7-Bromo-4-(1,3-diphenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione (1o). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.06 (m, 2H), 7.58-7.57 (m, 3H), 7.52-7.49 (m, 2H), 7.46-7.43 (m, 3H), 6.81 (d, *J* = 10.0 Hz, 1H), 6.73 (dd, *J* = 10.0 and 2.8 Hz, 1H), 6.30 (d, *J* = 10.0 Hz, 1H), 4.56 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 176.4, 169.8, 161.9, 142.4, 142.3, 136.0, 130.1, 130.0, 129.8, 129.6, 128.6, 127.4, 126.3, 124.8, 89.6 and 65.9. HRMS (ESI) for $C_{22}H_{16}BrN_4O_3$ (M+H): Calcd. 463.0406; Found 463.0402.

4-(3-(3-Chlorophenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione (1p). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.09 (s, 1H), 7.96 (d, *J* = 6.9 Hz, 1H), 7.56-7.53 (m, 5H), 7.40-7.35 (m, 3H), 6.57 (d, *J* = 9.6 Hz, 2H), 6.16 (d, *J* = 9.6 Hz, 2H), 4.58 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 183.1, 170.3, 160.7, 142.5, 141.6, 136.1, 134.7, 131.7, 131.1, 130.1, 130.0, 129.9, 129.7, 126.5, 124.8, 124.4, 88.2 and 66.0. HRMS (ESI) for $C_{22}H_{16}ClN_4O_3$ (M+H): Calcd. 419.0911, 421.0881; Found 419.0906, 421.0881.

4-(1,3-Diphenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]- deca-6,9-dien-8-one (2a). Pale yellow solid, m.p. 119-121 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.05-8.03 (m, 2H), 7.41-7.37 (m, 8H), 6.49 (d, *J* = 10.4 Hz, 2H), 5.90 (d, *J* = 10.0 Hz, 2H), 4.27 (t, *J* = 6.0 Hz, 2H), 3.88(t, *J* = 6.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 184.8, 159.8, 153.5, 143.5, 137.5, 130.6, 129.5, 129.3, 128.9, 128.7, 128.5, 126.2, 125.4, 87.7, 66.0 and 50.0. HRMS (ESI) for $C_{22}H_{19}N_4O_2$ (M+H): Calcd. 371.1508; Found 371.1507.

4-(1-Phenyl-3-(p-tolyl)-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro- [4.5]deca-6,9-dien-8-one (2b). Pale yellow solid, m.p. 142-144 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.93 (d, *J* = 8.0 Hz, 2H), 7.46-7.37 (m, 5H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.47 (d, *J* = 10.0 Hz, 2H), 5.88 (d, *J* = 10.0 Hz, 2H), 4.25 (t, *J* = 6.4 Hz, 2H), 3.88 (t, *J* = 6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$,

100MHz) δ (ppm): 184.8, 159.8, 143.5, 139.2, 137.5, 131.9, 129.3, 128.7, 127.8, 126.0, 125.4, 120.2, 87.7, 66.0, 49.9, 29.6 and 21.3. HRMS (ESI) for $C_{23}H_{21}N_4O_2$ (M+H): Calcd. 385.1665; Found 385.1668.

4-(3-(4-Methoxyphenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-dien-8-one (2c). Pale yellow solid, m.p. 118-121 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.97 (d, *J* = 8.8 Hz, 2H), 7.46-7.37 (m, 5H), 6.94 (d, *J* = 9.2 Hz, 2H), 6.49 (d, *J* =10.0 Hz, 2H), 5.90 (d, *J* = 10.0 Hz, 2H), 4.26 (t, *J* = 6.0 Hz, 2H), 3.87 (t, *J* = 6.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 184.8, 160.5, 159.6, 153.3, 143.5, 137.5, 129.4, 128.9, 128.6, 127.6, 125.4, 123.3, 113.8, 87.7, 66.0, 55.2 and 49.9. HRMS (ESI) for $C_{23}H_{21}N_4O_3$ (M+H): Calcd. 401.1614; Found 401.1609.

4-(3-(4-Chlorophenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-dien-8-one (2d). Gray solid, m.p. 143-146 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.99 (d, *J* = 8.4 Hz, 2H), 7.47-7.29 (m, 7H), 6.50 (d, *J* = 10.0 Hz, 2H), 5.94 (d, *J* = 10.0 Hz, 2H), 4.28 (t, *J* = 6.0 Hz, 2H), 3.87 (t, *J* = 6.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 184.8, 158.8, 153.5, 143.4, 137.4, 135.1, 129.5, 129.2, 129.0, 128.9, 128.7, 127.5, 125.4, 87.7, 66.0 and 49.8. HRMS (ESI) for $C_{22}H_{18}ClN_4O_2$ (M+H): Calcd. 405.1118; Found 405.1103.

4-(3-(3-Chlorophenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-dien-8-one (2e). Gray solid, m.p. 185-187 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.06(s, 1H), 7.92-7.90 (m, 1H), 7.45-7.40 (m, 5H), 7.36-7.35 (m, 2H), 6.47 (d, *J* = 10.0 Hz, 2H), 5.90 (d, *J* = 10.0 Hz, 2H), 4.27 (t, *J* = 6.0 Hz, 2H), 3.88 (t, *J* = 6.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 184.7, 158.6, 153.7, 143.4, 132.4, 129.5, 129.3, 129.0, 128.9, 126.2, 125.4, 124.2, 87.7, 66.0 and 50.0. HRMS (ESI) m/z (%) for $C_{22}H_{17}ClN_4NaO_2$ (M+Na): Calcd. 427.0938; Found 427.0944.

4-(3-(2,4-Dichlorophenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-dien-8-one (2f). Pale yellow solid, m.p. 130-132 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.83 (d, *J* = 8.0 Hz, 1H), 7.49-7.40 (m, 6H), 7.30 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.50 (d, *J* = 10.0 Hz, 2H), 5.93 (d, *J* = 10.0 Hz, 2H), 4.26 (t, *J* = 6.0 Hz, 2H), 3.84 (t, *J* = 6.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 184.8, 157.6, 152.9, 143.4, 137.2, 135.2, 133.4, 131.8, 130.5, 129.5, 129.1, 128.9, 128.1, 127.0, 125.3, 87.8, 66.0 and 49.8. HRMS (ESI) for $C_{22}H_{17}Cl_2N_4O_2$ (M+H): Calcd. 439.0729; Found 439.0717.

4-(1-(3-Chlorophenyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-dien-8-one (2g). Pale yellow solid, m.p. 136-138 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.05-8.03 (m, 2H), 7.53 (s, 1H), 7.45-7.38 (m, 4H), 7.36-7.35 (m, 2H), 6.51(d, *J* = 10.0 Hz, 2H), 5.94 (d, *J* = 10.0 Hz, 2H), 4.30 (t, *J* = 6.0 Hz, 2H), 3.94 (t, *J* = 6.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 184.4, 160.1, 153.8, 143.3, 138.4, 135.0, 130.6, 129.5, 129.0, 128.6, 128.5, 126.2, 125.3, 123.2, 88.0, 66.0 and 50.2. HRMS (ESI) for $C_{22}H_{18}ClN_4O_2$ (M+H): Calcd. 405.1118; Found 405.1120.

4-(1-Phenyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5]deca-6,9-dien-8-one (2h). Pale yellow solid, m.p. 132-134 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.62(m, 1H), 7.43-7.38 (m, 5H), 7.34-7.32 (m, 1H), 7.09-7.07 (m, 1H), 6.47 (d, *J* = 10.0 Hz, 2H), 5.91(d, *J* = 10.0 Hz, 2H), 4.25 (t, *J* = 6.0 Hz, 2H), 3.86 (t, *J* = 6.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 184.7, 156.2, 153.3, 143.3, 137.3, 133.5, 129.0, 128.8, 127.6, 126.6, 126.4, 125.6, 87.7, 66.0 and 50.0. HRMS (ESI) for $C_{20}H_{17}N_4O_2S$ (M+H): Calcd. 377.1072; Found 377.1076.

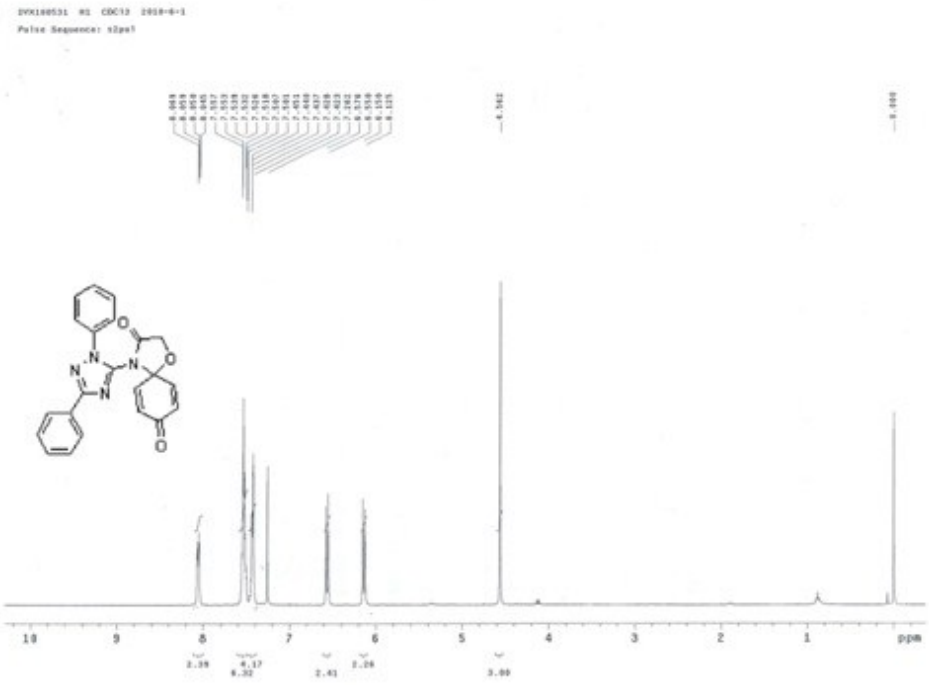
Cell Proliferation Assay.[18] Breast cancer cell lines, MDA-MB-231 and MCF-7, the cervical cancer cell line, HeLa, and the non-small cell lung carcinoma cell line, cell lines were purchased from ATCC. A549 were routinely cultured in DMEM medium supplemented with 10% FBS, 4 mM glutamine, 1 mM sodium pyruvate, 100 IU/mL penicillin, 100 µg/mL streptomycin and 0.25 µg/mL amphotericin. Cultures were maintained in 5% CO_2 at a temperature of 37°C. The cells were plated in 24-well plates at a density of 20,000 per well in 10% FBS DMED medium. The cells were then treated with Doxorubicin, or synthesized triazole-spirodienone conjugates separately at 5 different doses ranging from 0.01 mM to 1 nM for 5 days, while equal treatment volumes of DMSO were used as vehicle control. Cell numbers were counted with a cell viability analyzer (BeckmaneCoulter). The ratio of drug treated viable cell numbers to vehicle treated viable cell numbers were defined as percentage viability. IC_{50} values were obtained from dose response curves for each tested compound.

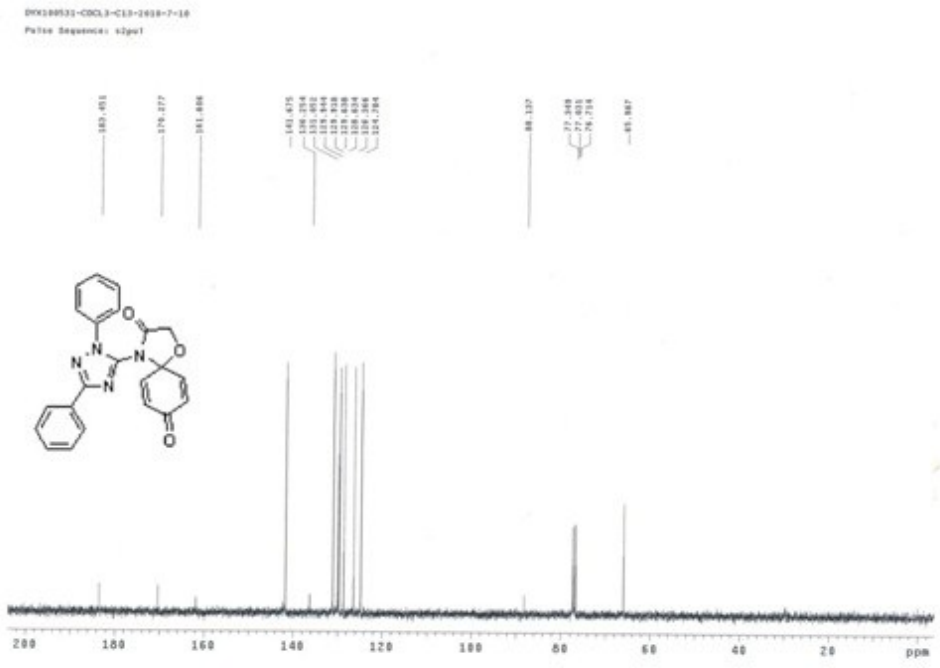
MCF-10A, the normal mammary epithelial cells, were cultured in 50 : 50 DMEM/Hams F12, with, 2.5 mM L-glutamine, 15 mM HEPES, 0.5 mM sodium pyruvate, 1.2 g/L sodium bicarbonate, 20 ng/ml human Epidermal Growth Factor (hEGF), 100 ng/ml cholera toxin, 10 µg/ml bovine insulin, 500 ng/ml hydrocortisone and 5% horse serum and grown at 5% CO_2, 37°C, and 100% humidity. The cells were plated in 24-well plates at a density of 20,000 per well in 10% FBS DMED medium. The cells were then treated with Doxorubicin, or compounds **1a**, **1d-f** and **1i-k** separately at two doses of 10 µM and 1 µM for 5 days, while equal treatment volumes of DMSO were used as vehicle control.

Cell Apoptosis Assay.[17] Cell apoptosis induced by triazole-spirodienone conjugates was detected by using the CellEvent™ Caspase-3/7 Green ReadyProbes® Reagent (ThermFisher Scientic Company). HeLa cells were grown on cover glasses in a 24-well plate at a concentration of 50,000 cells/well for 24 h incubation at 37 °C. HeLa cells were induced with **1b**, **1i**, **1f**, **1p** and doxorubicin at 1.0 µM for an additional 24 h, while equal treatment volumes of DMSO were used as vehicle control. CellEvent™ Caspase-3/7 Green ReadyProbes® Reagent (2 drops per mL of media) was added. After 40 min incubation at room temperature in the darkness, the stained cells were observed and taken pictures using fluorescence microscopy.

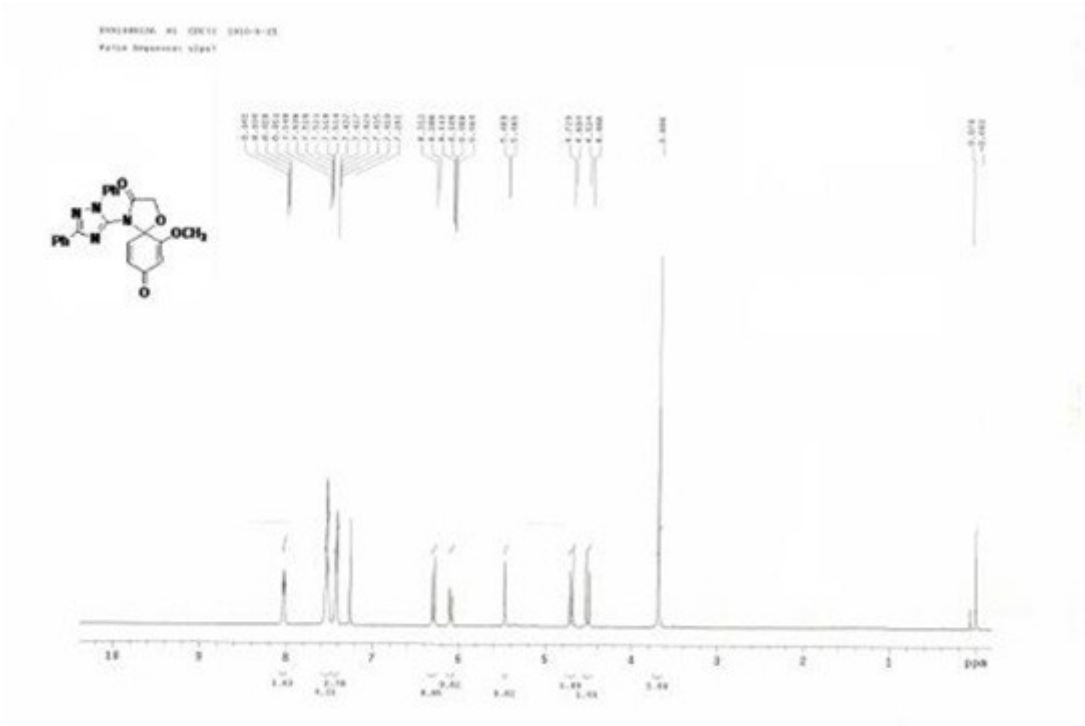
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compounds

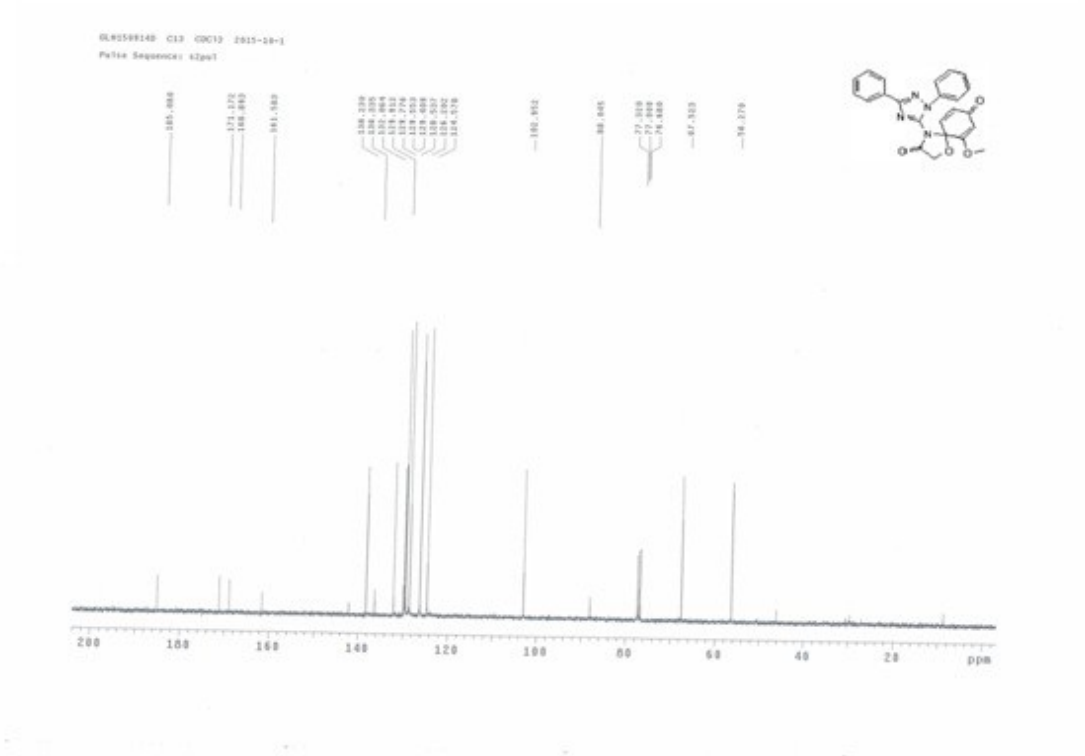
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1a.



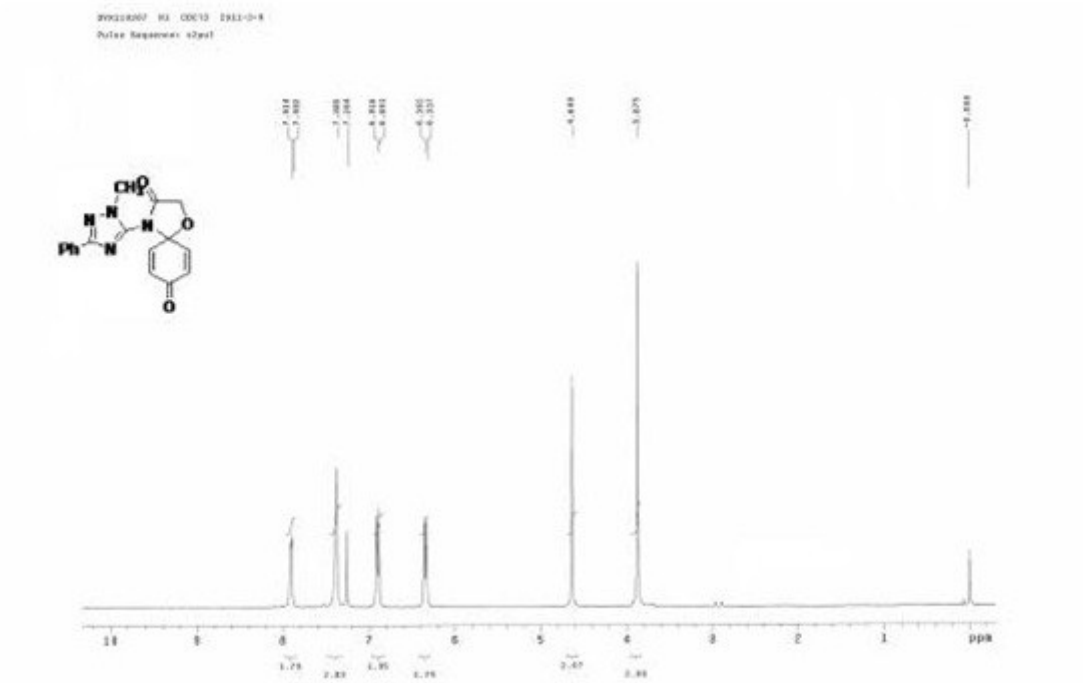


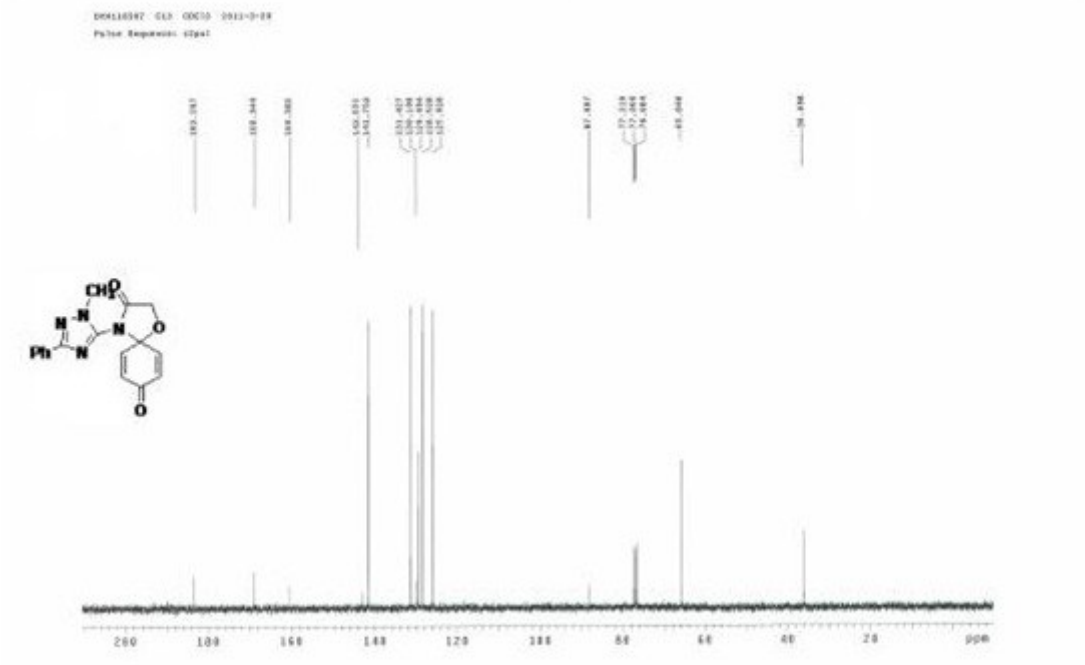
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1b.



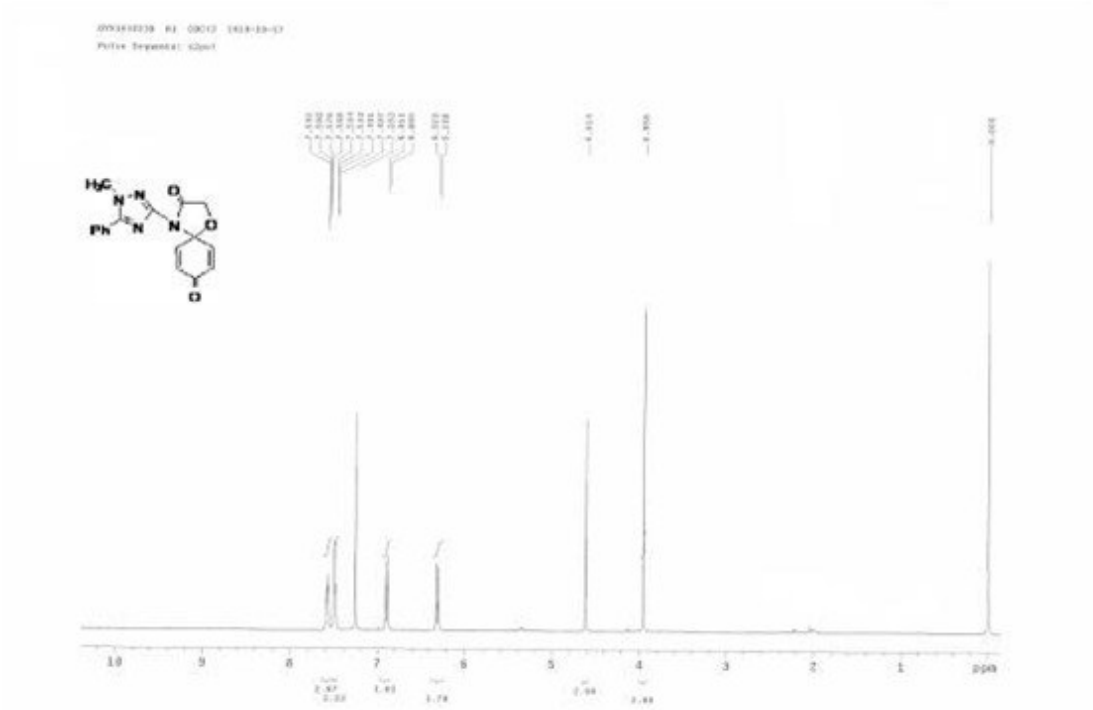


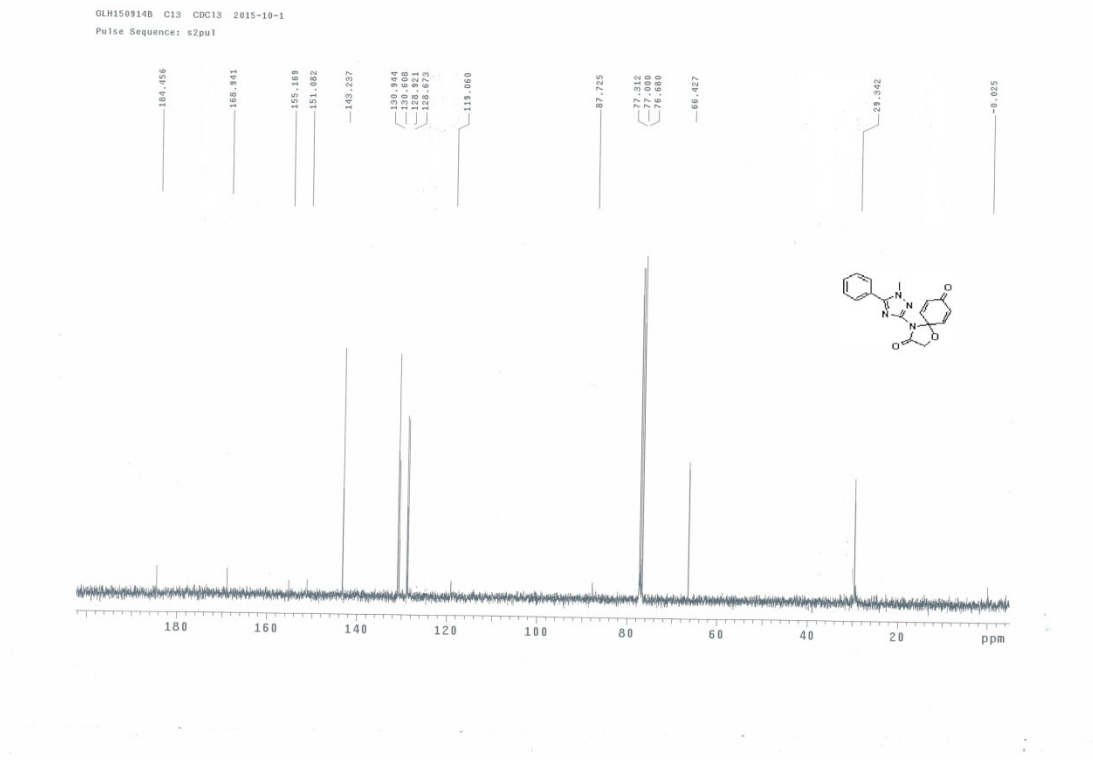
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1c.



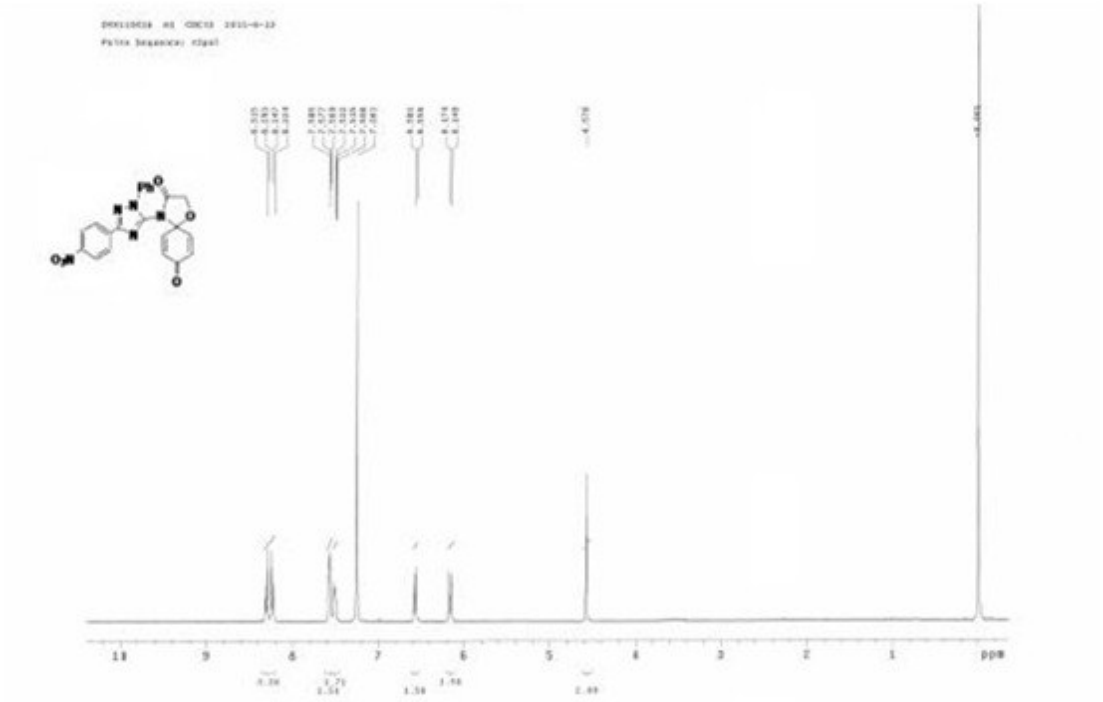


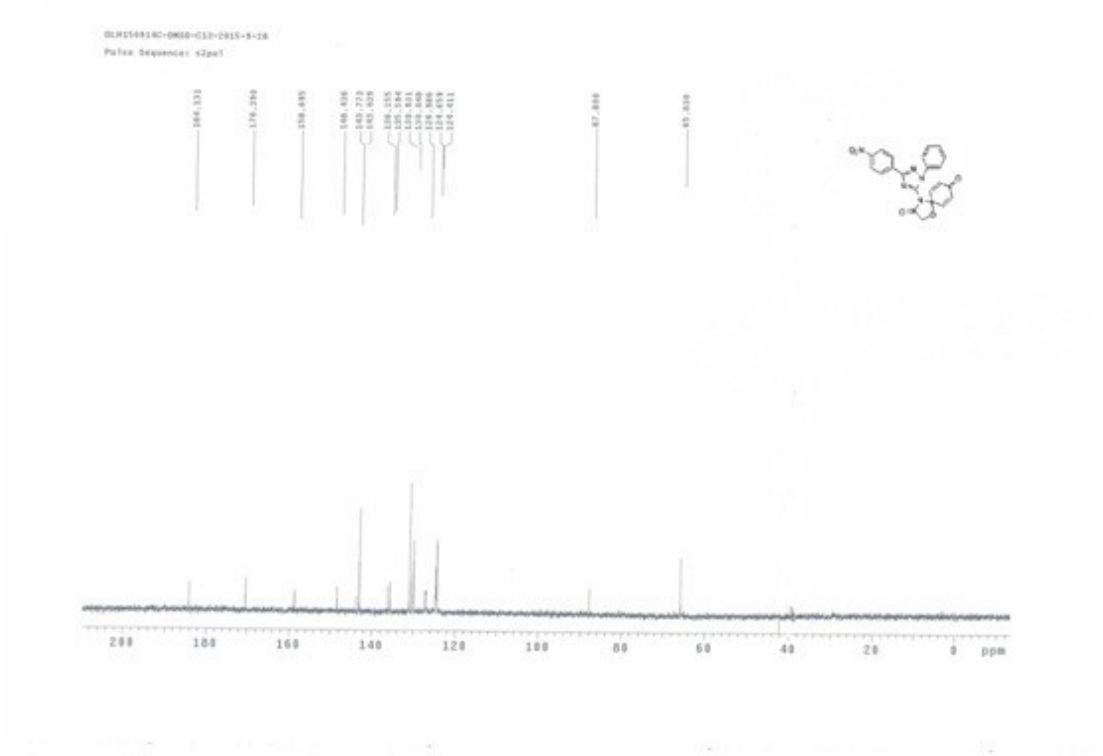
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1d.



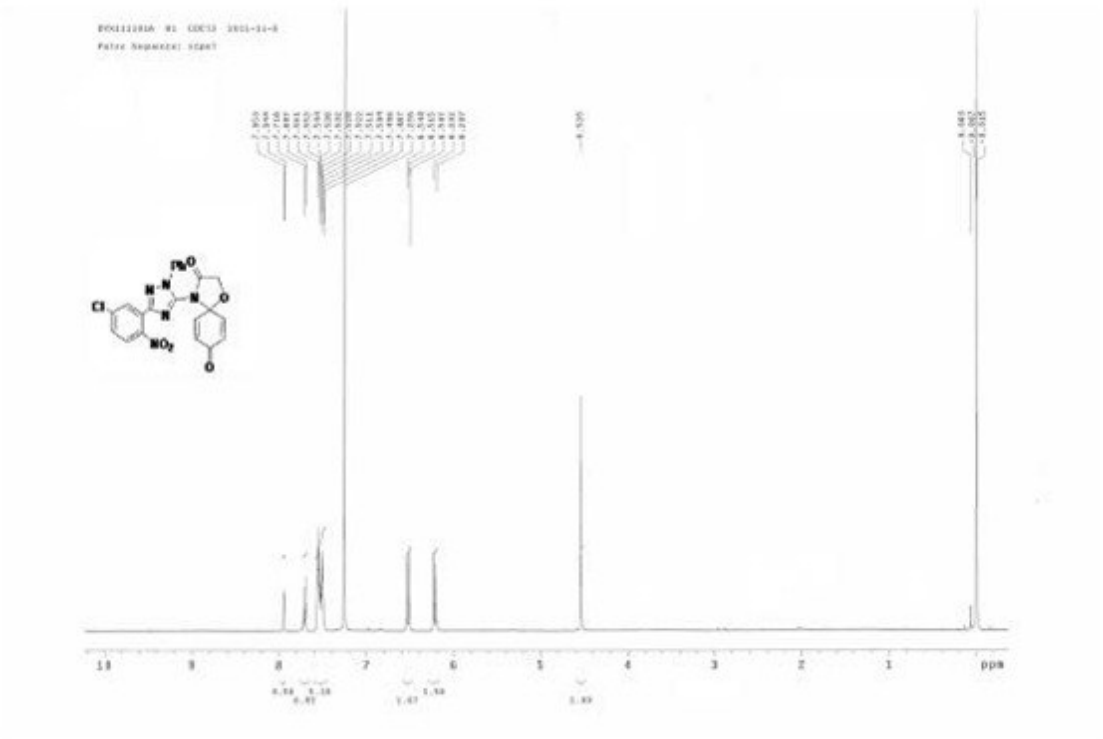


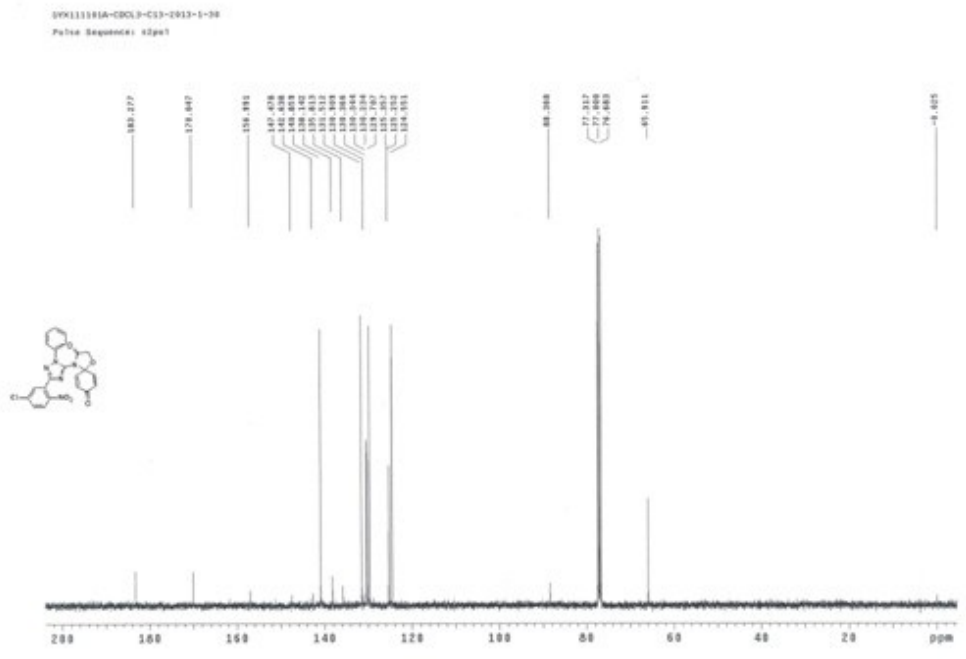
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1e.



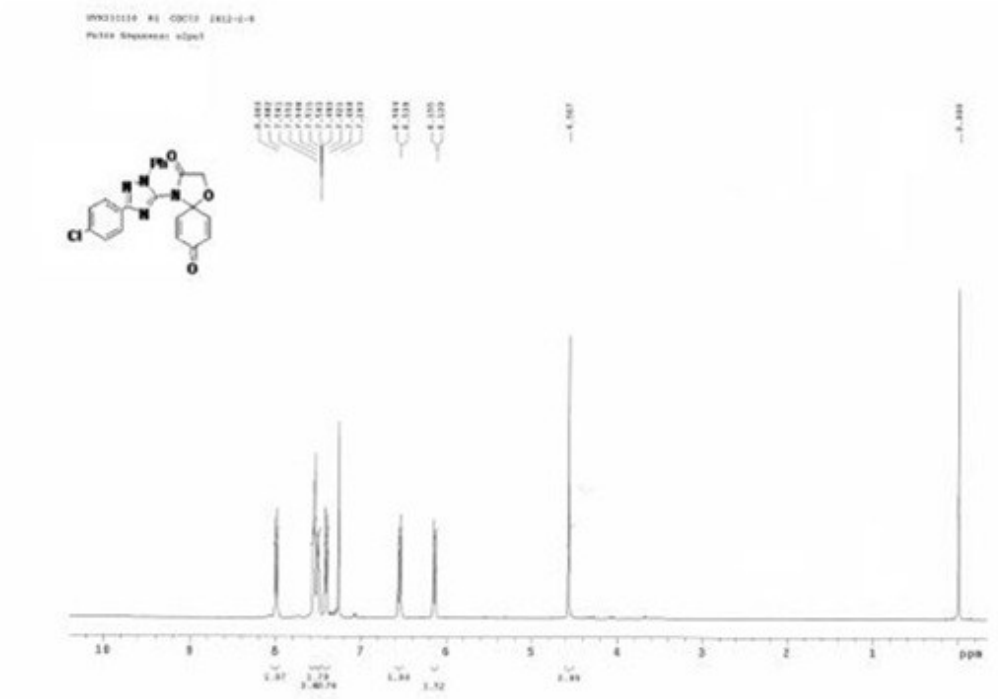


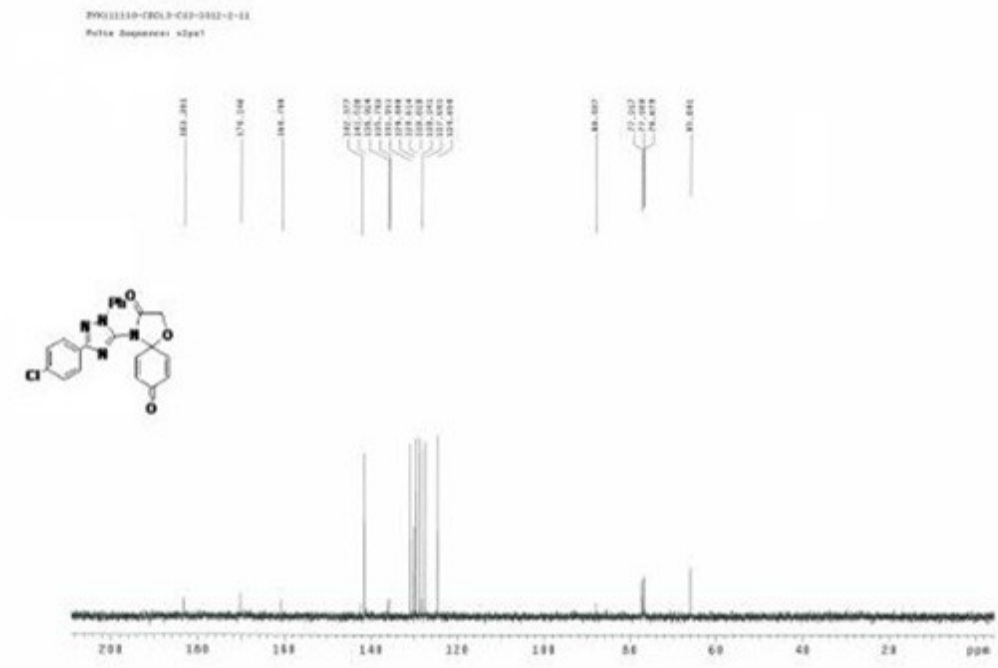
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1f.



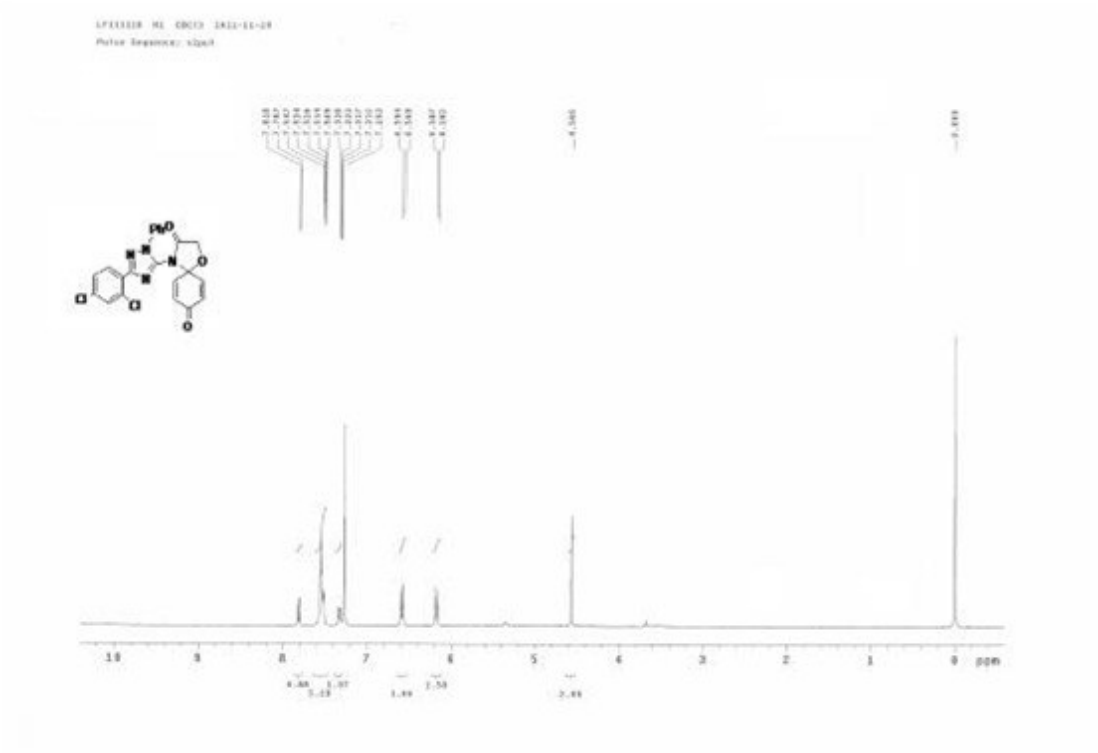


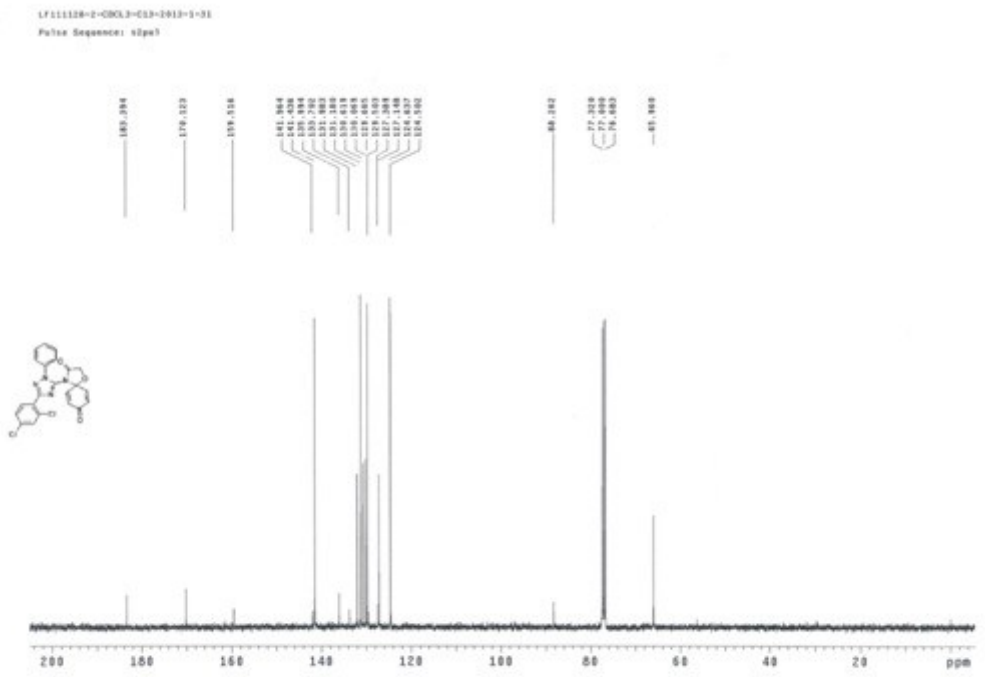
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1g.



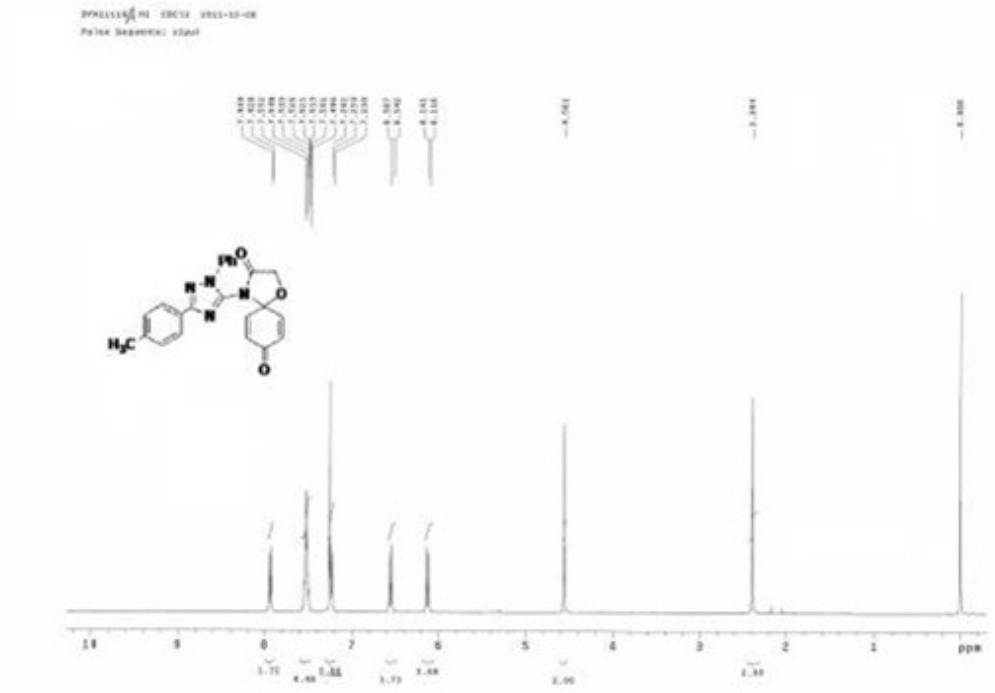


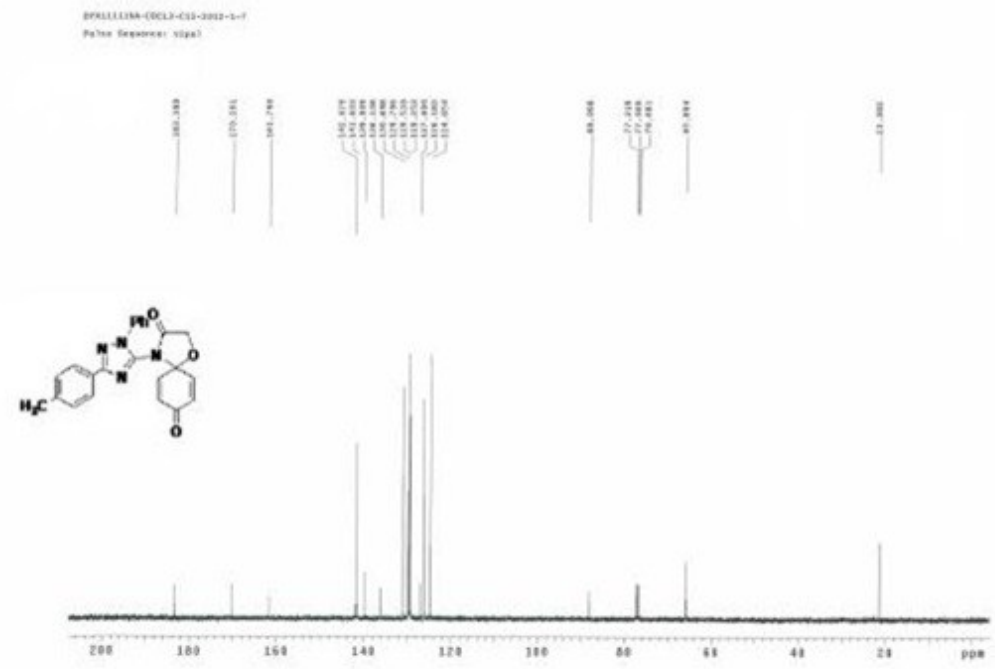
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1h.



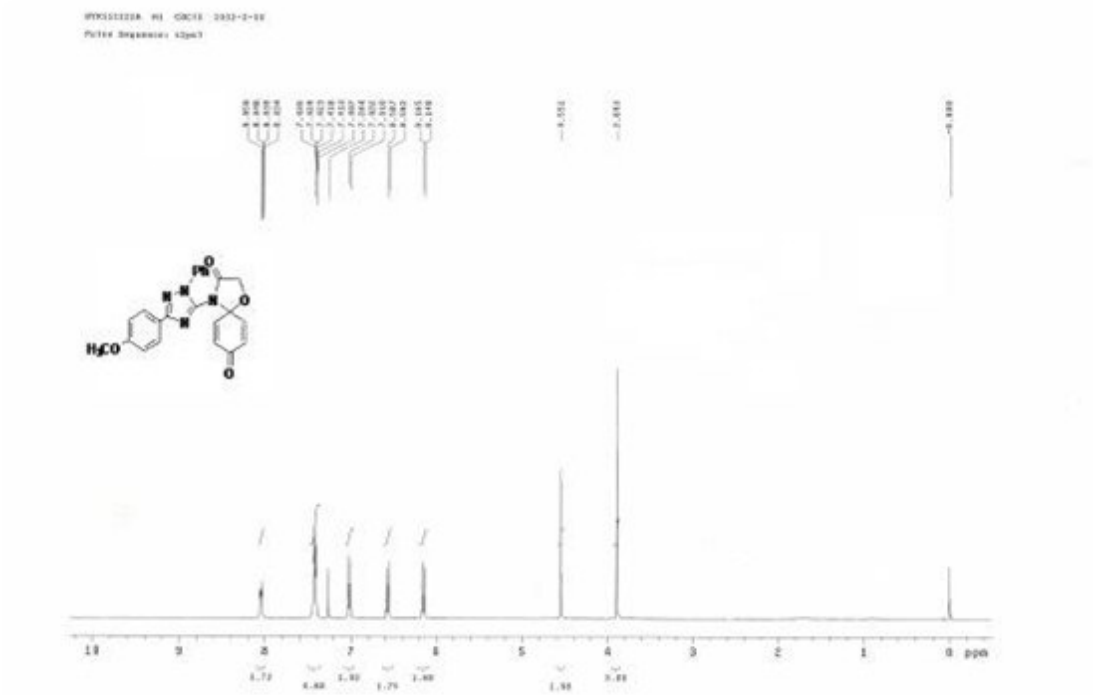


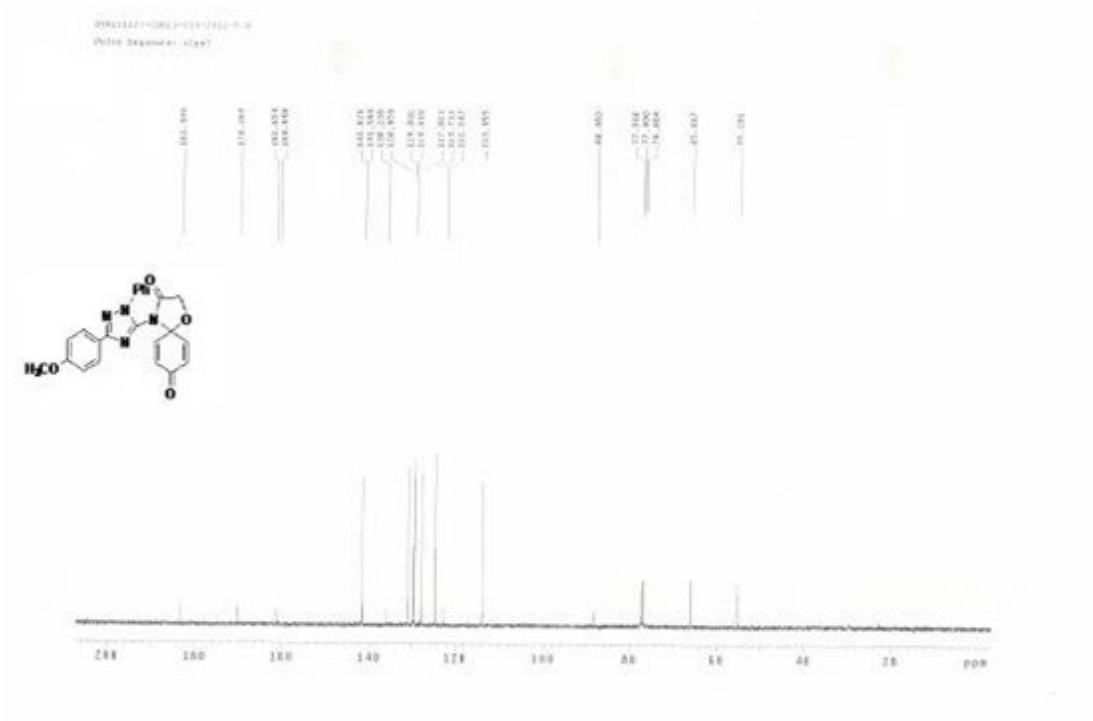
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1i.



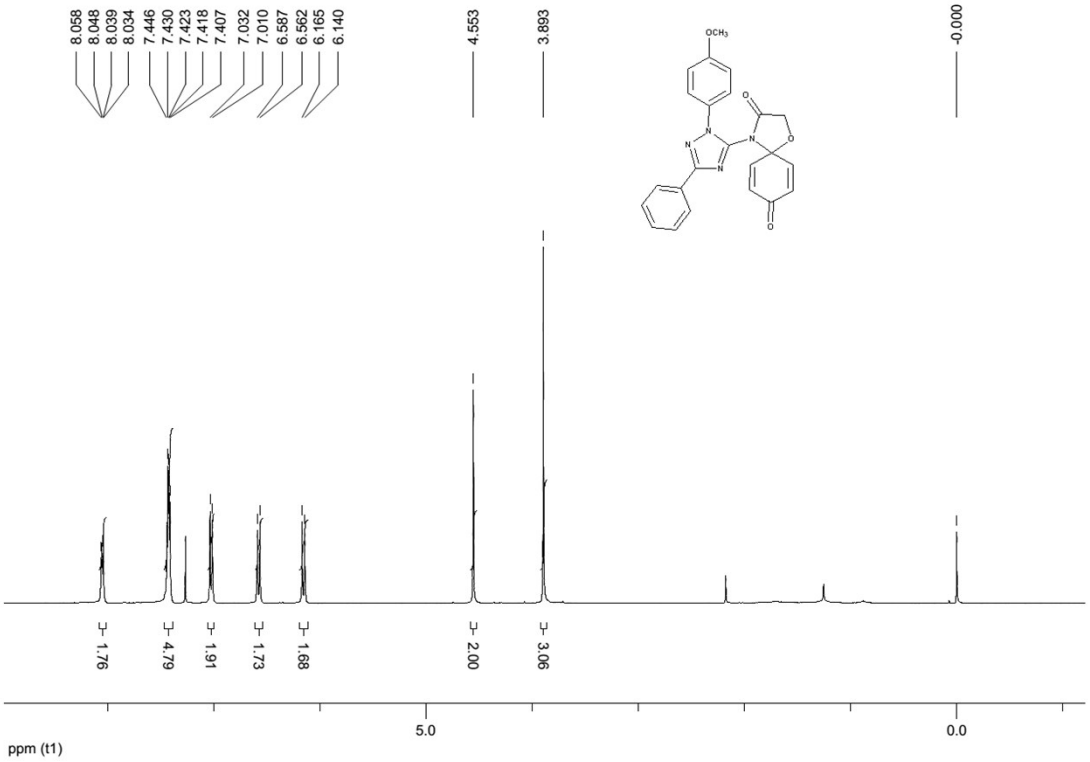


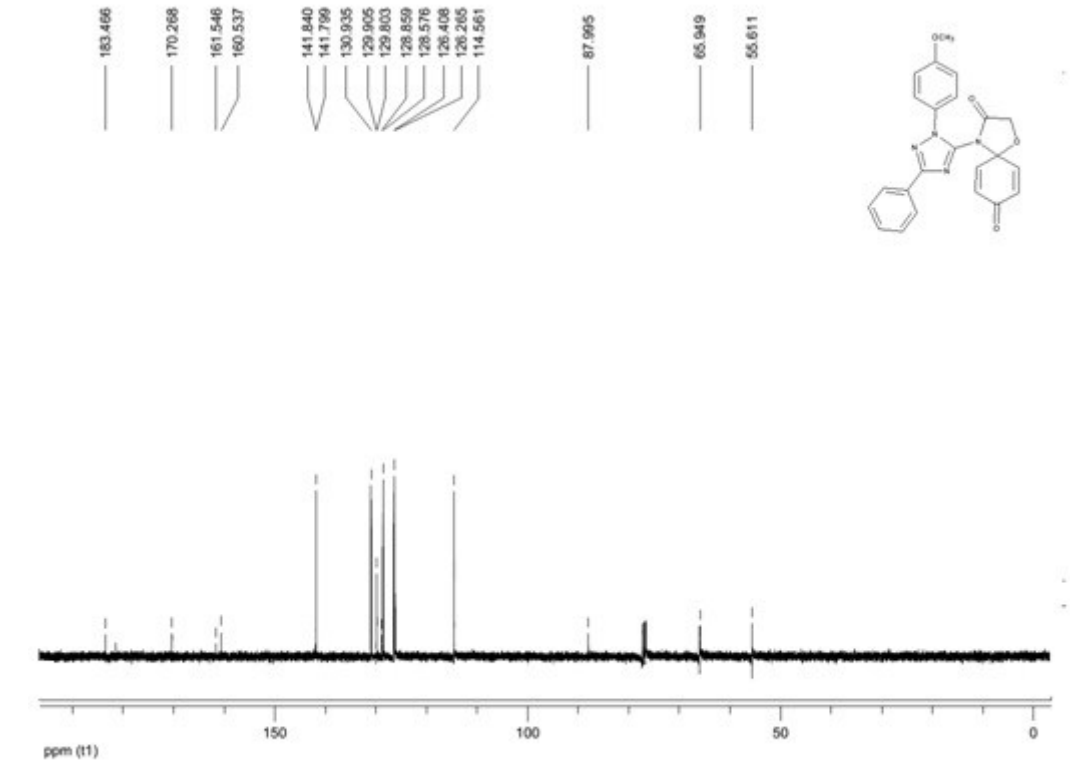
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1j.



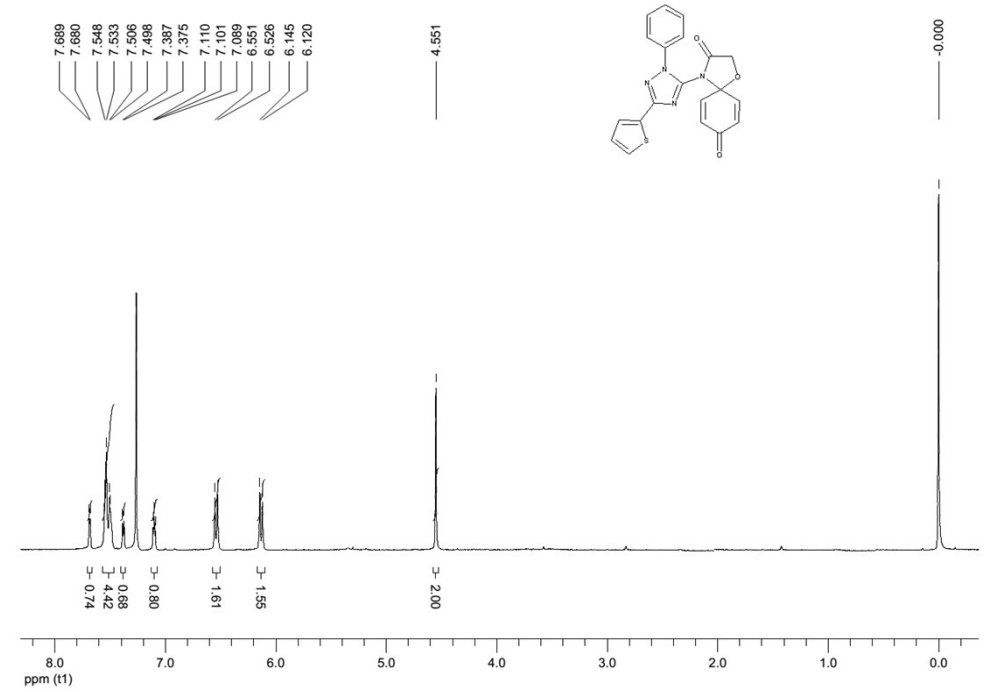


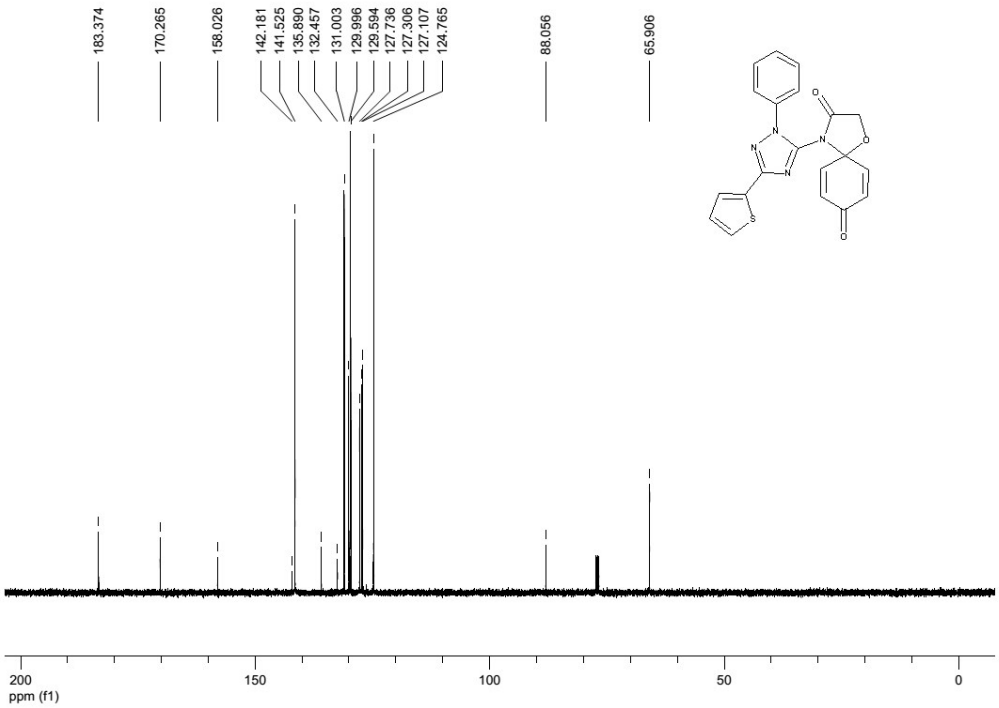
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1k.



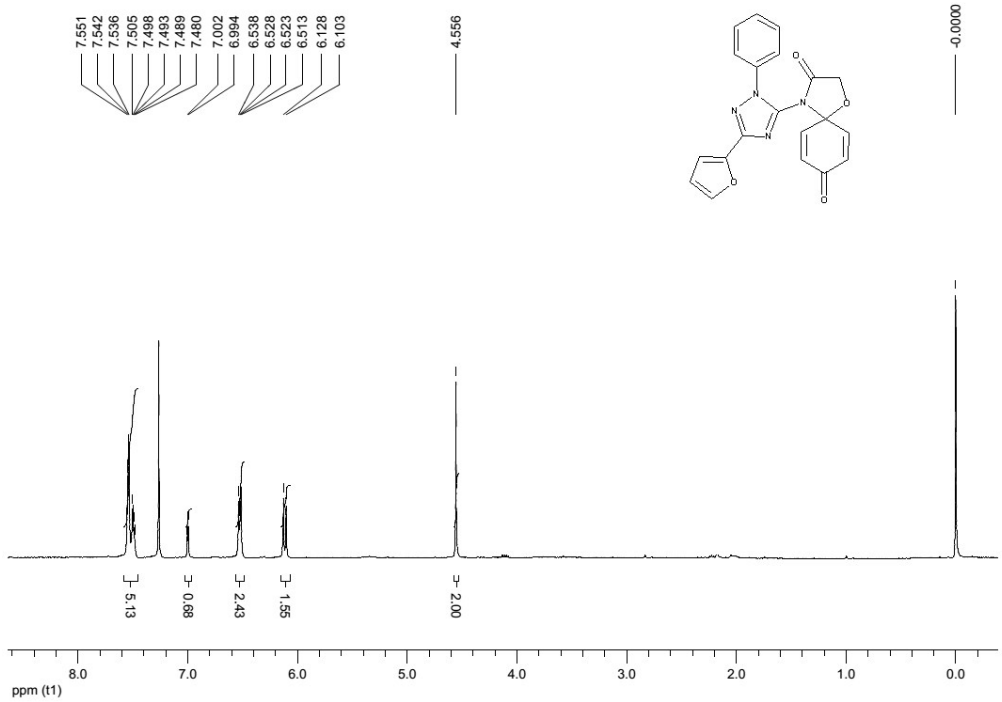


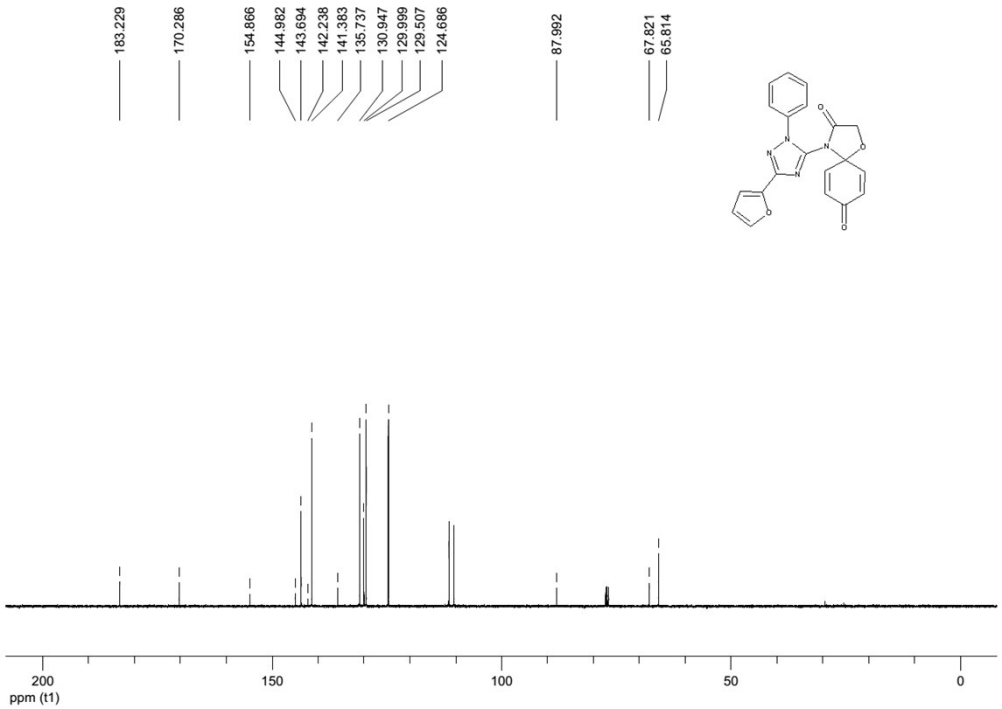
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1l.



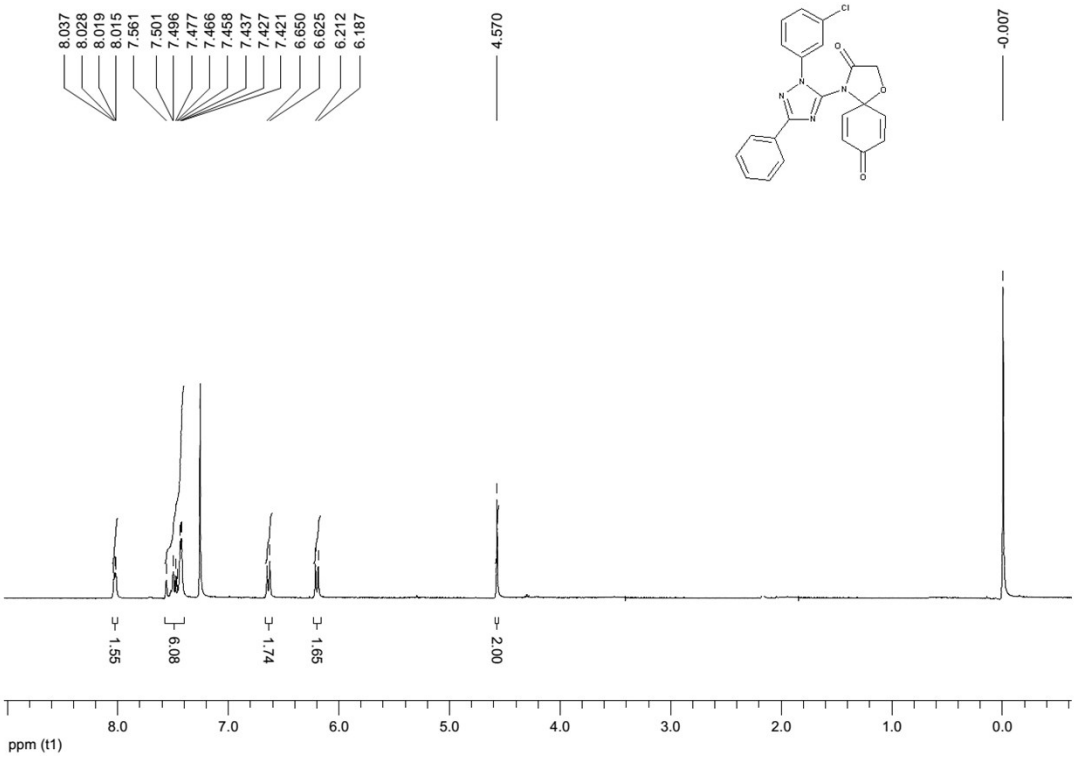


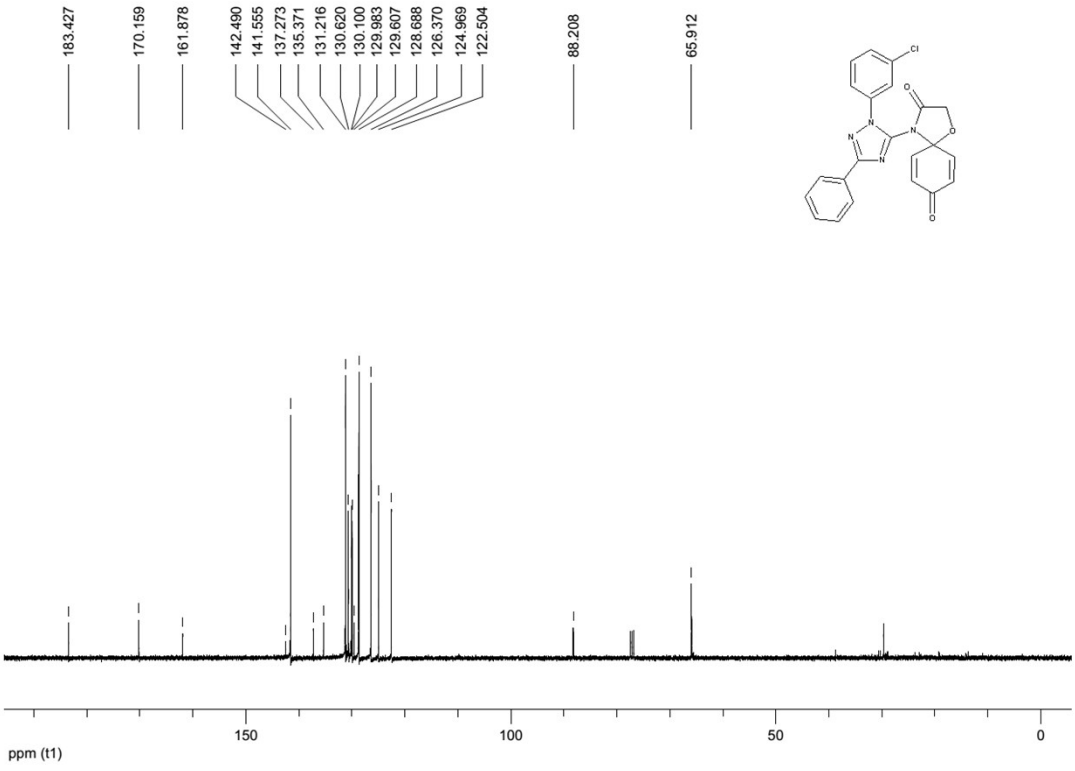
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1m.



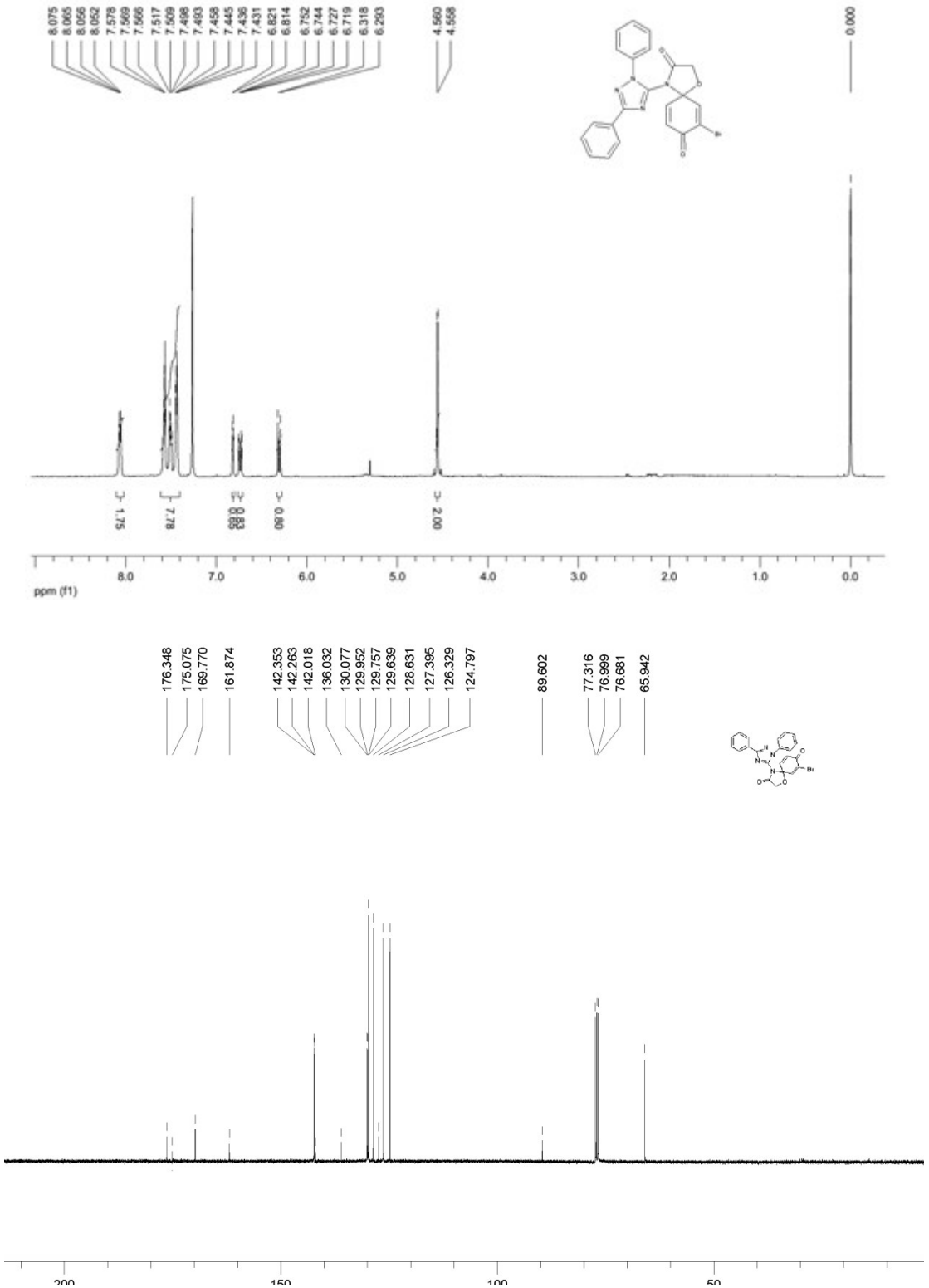


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1n.

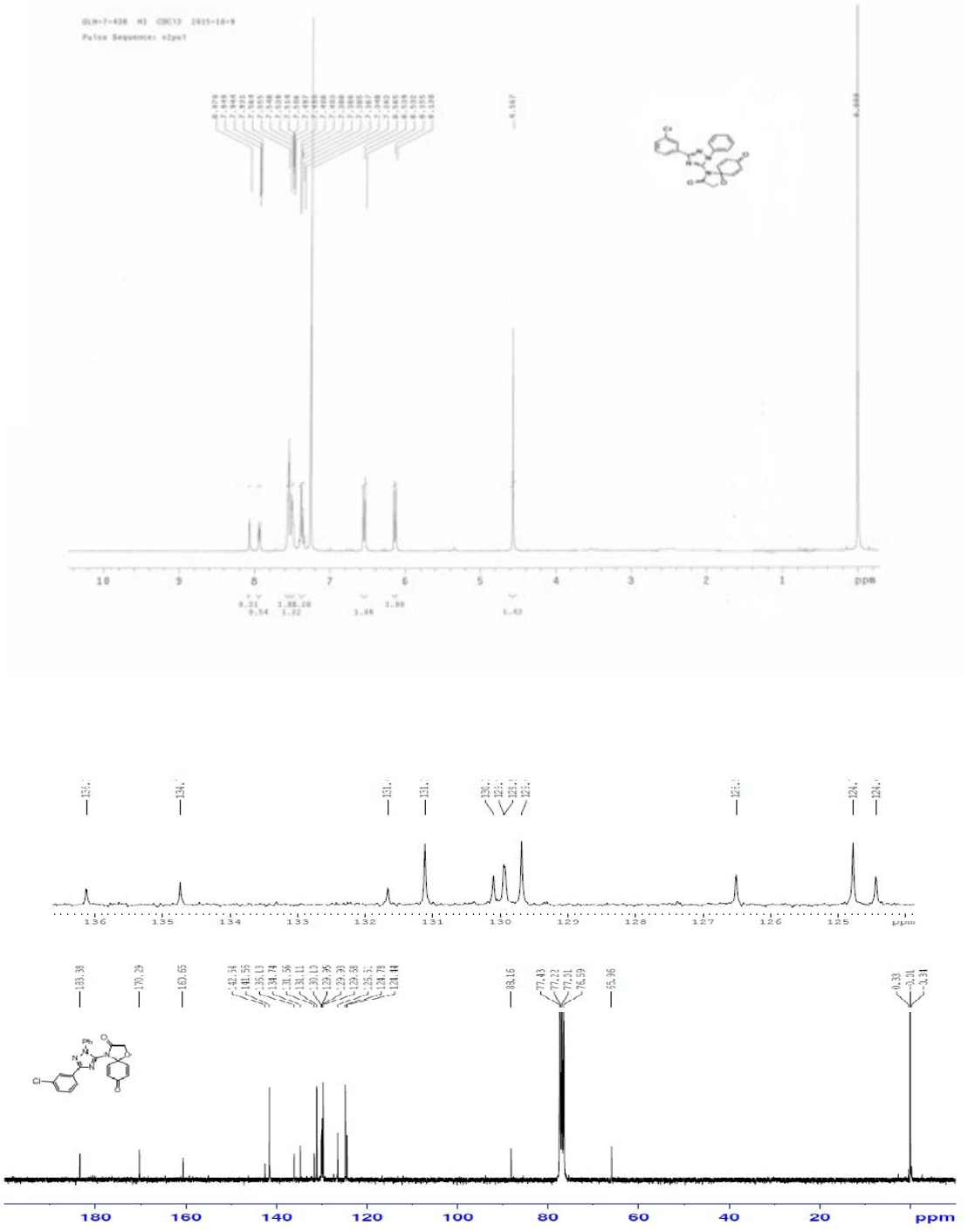




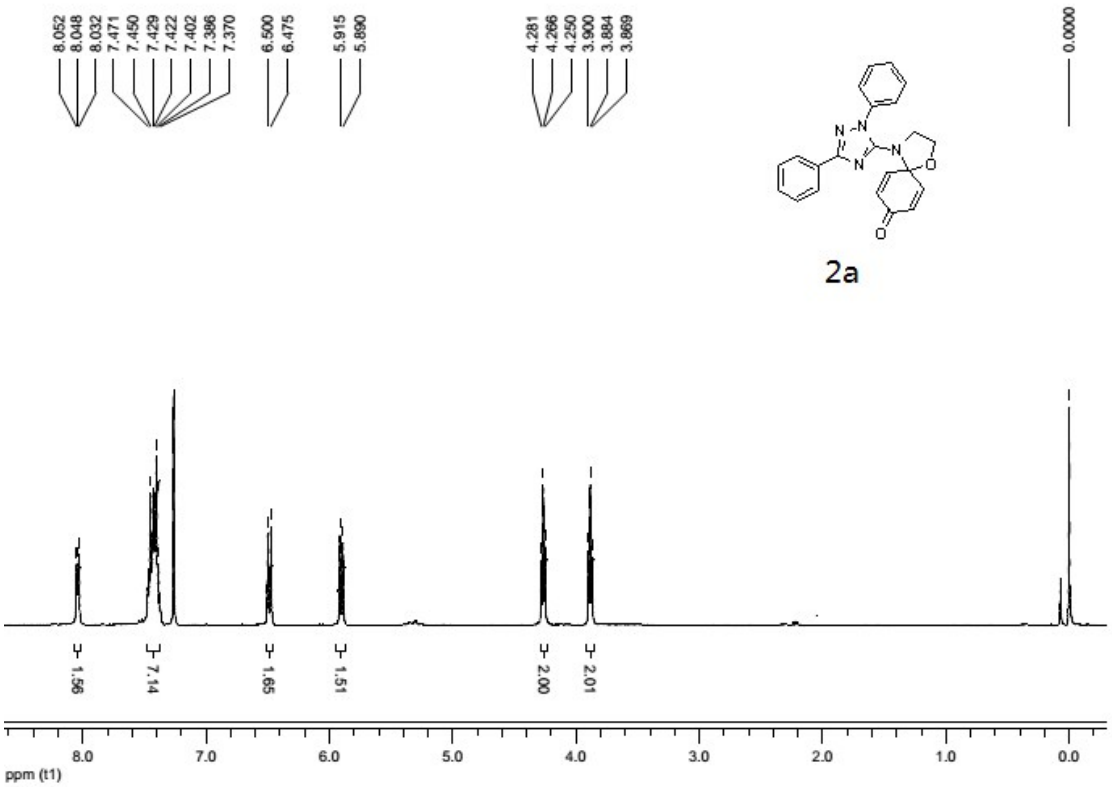
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1o.

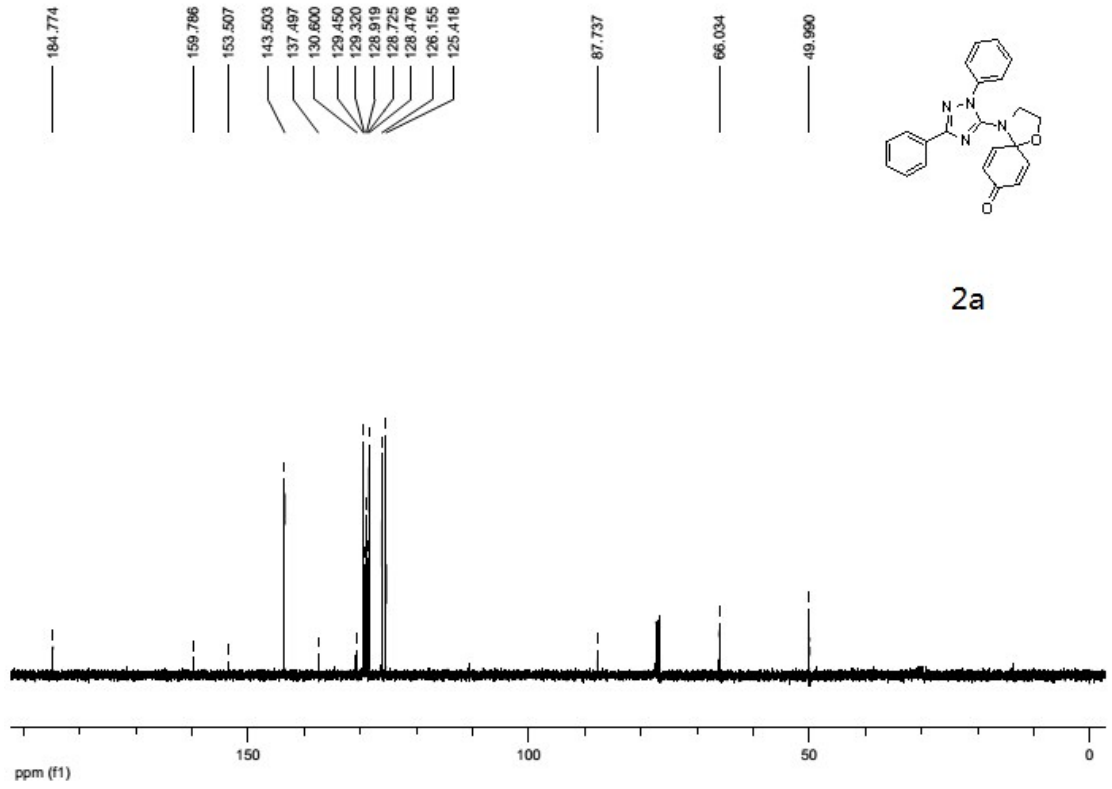


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 1P.

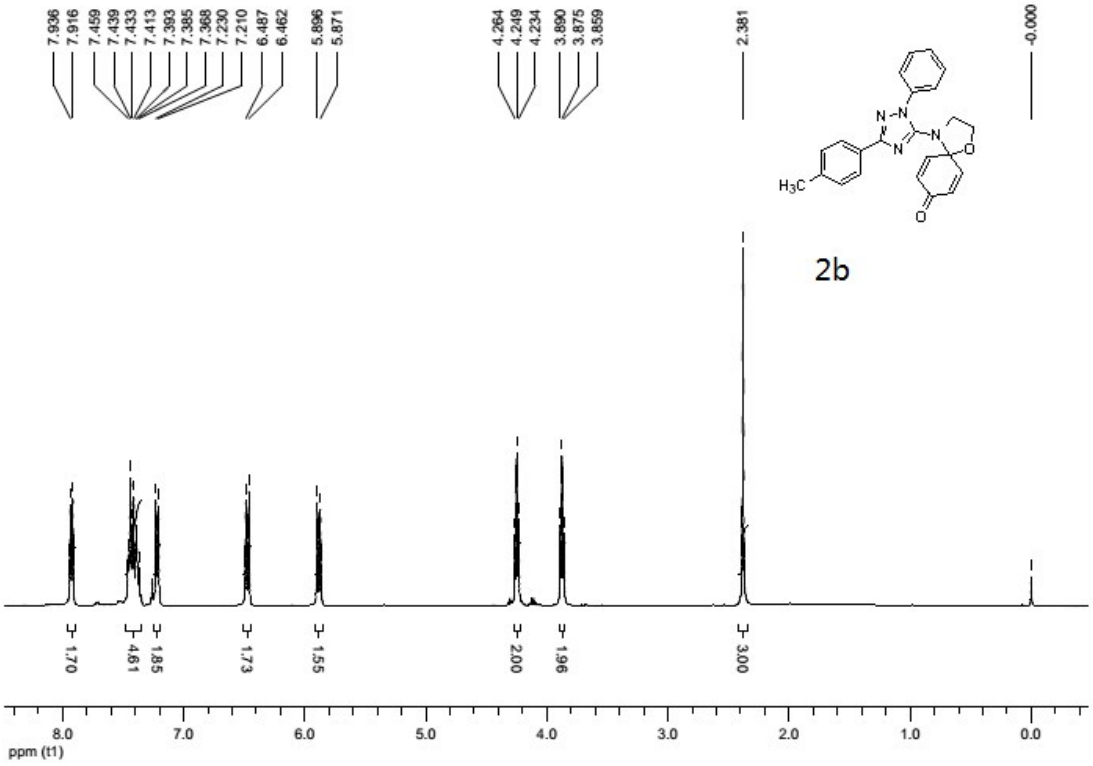


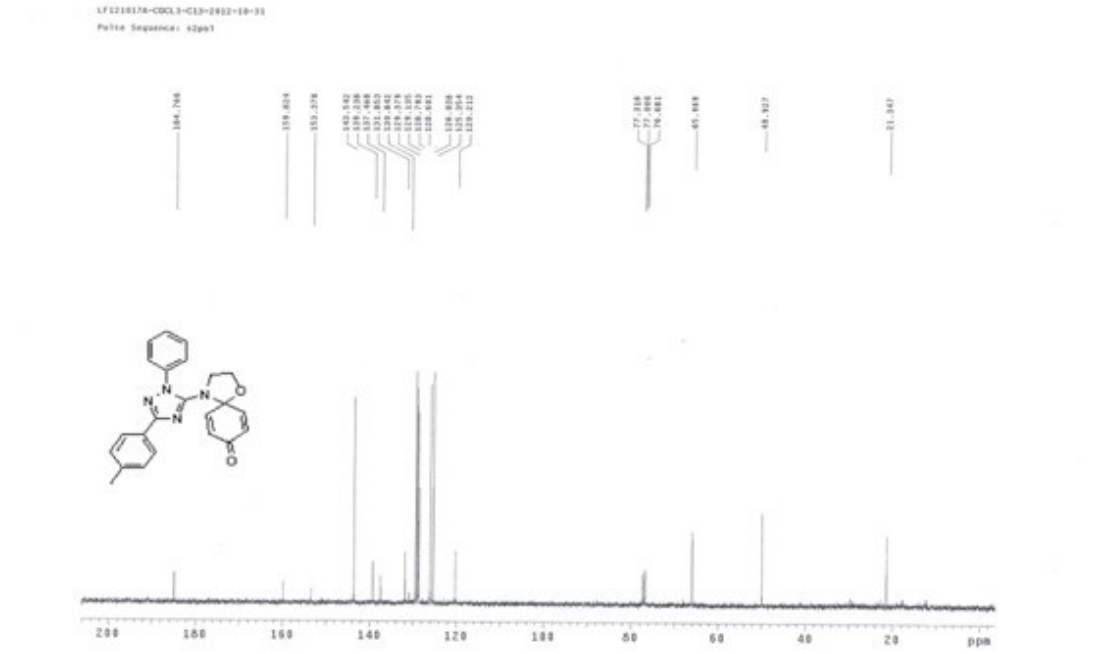
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 2a.



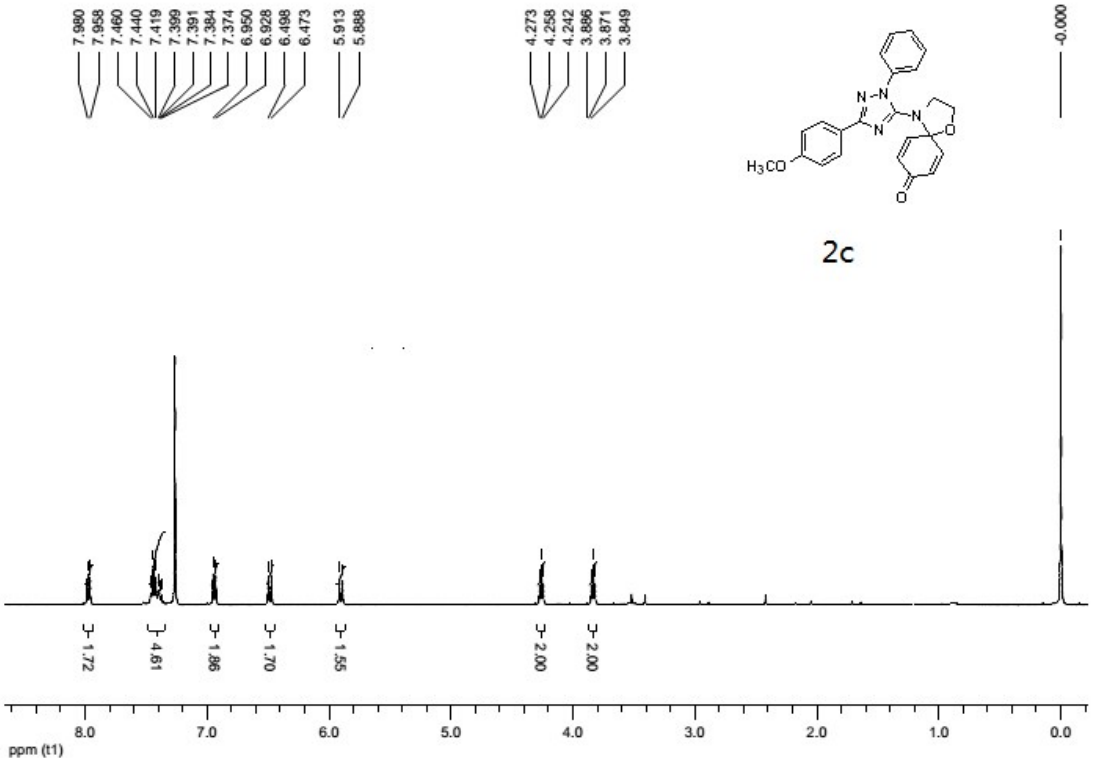


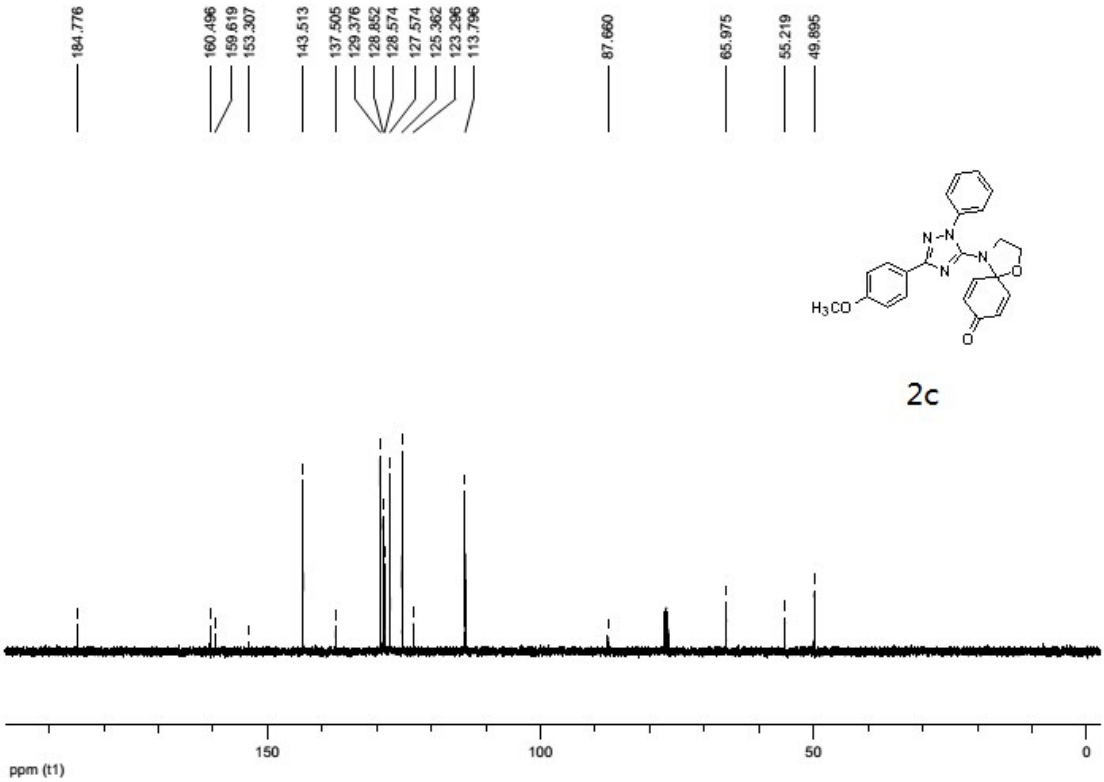
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 2b.



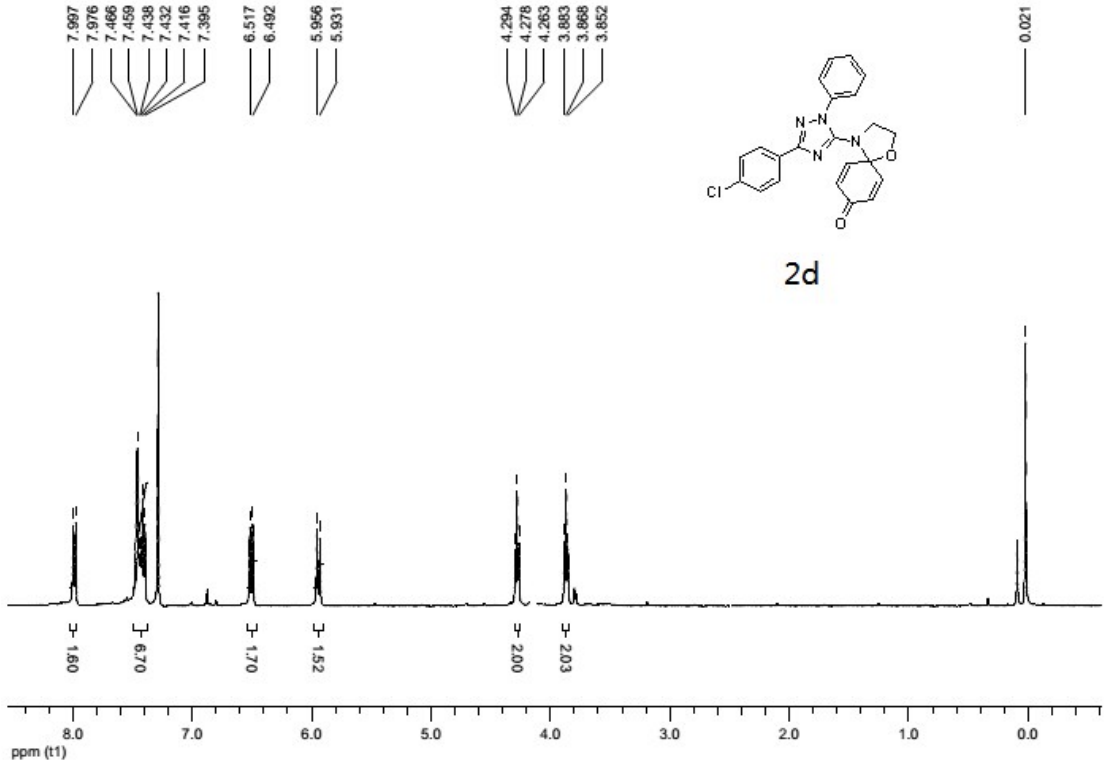


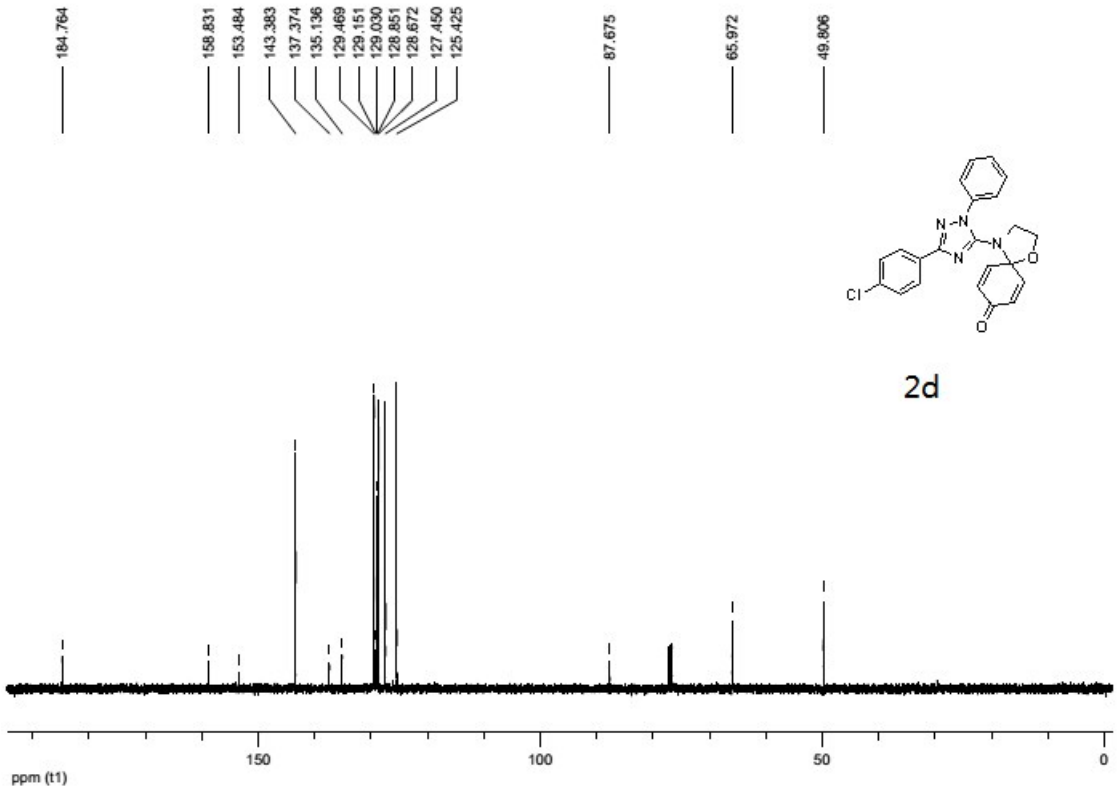
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 2c.



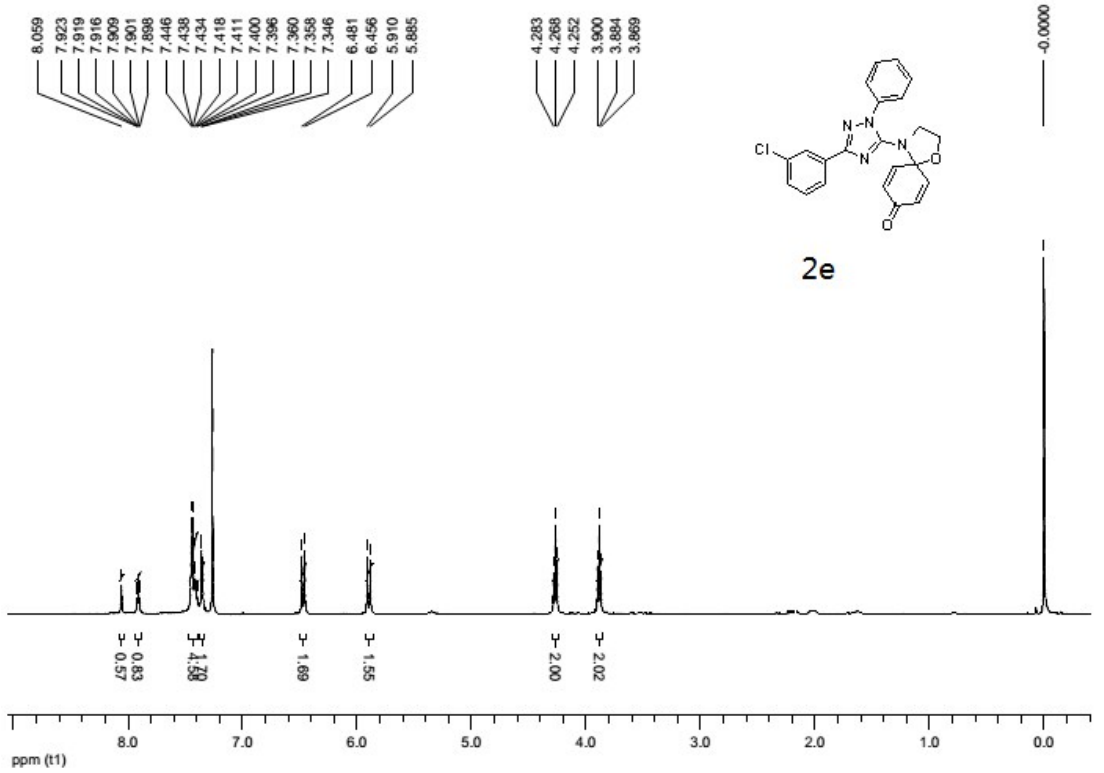


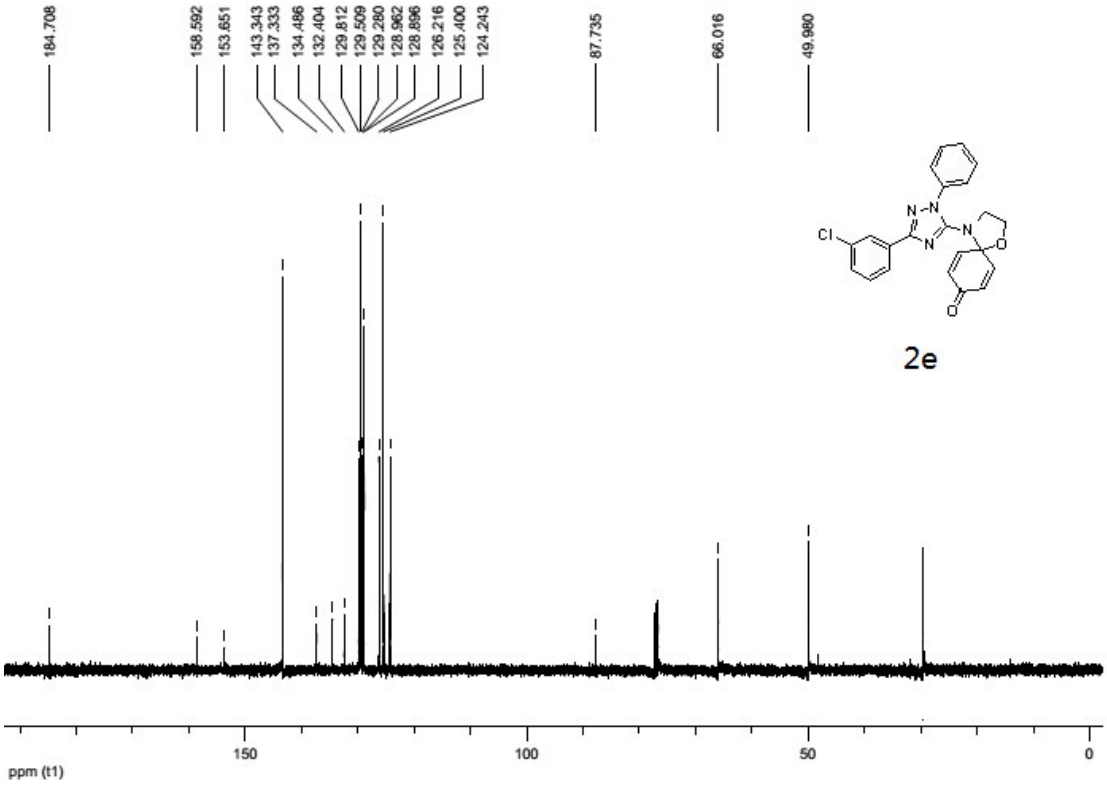
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 2d.



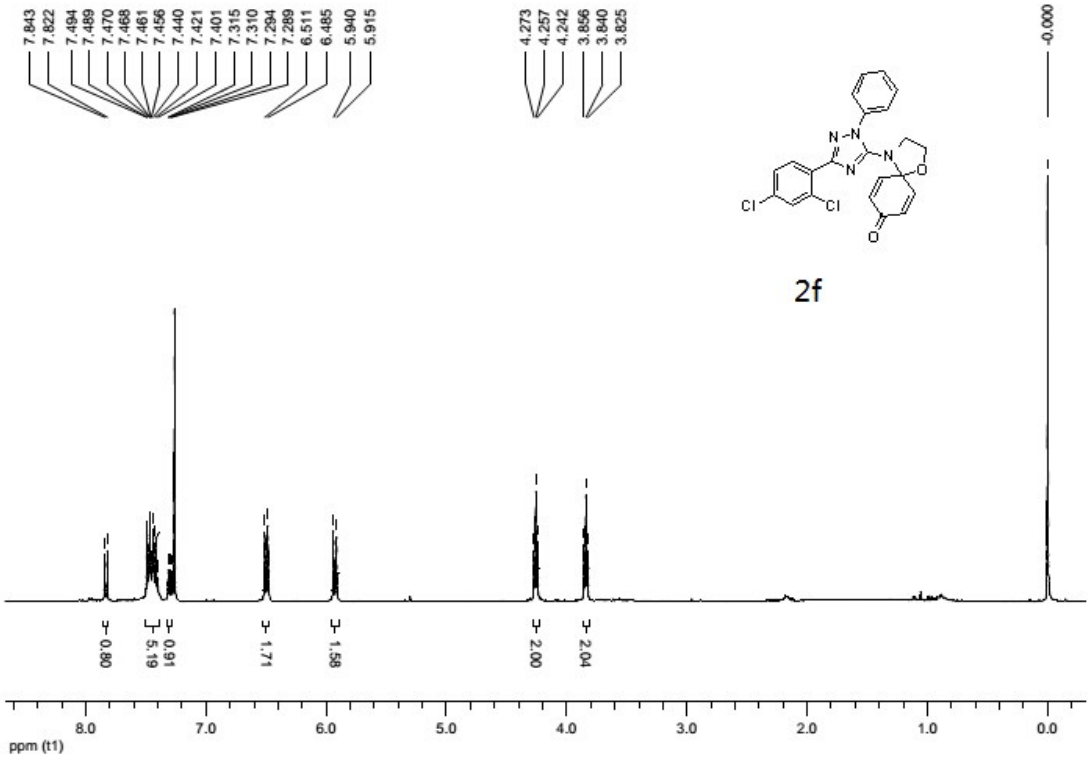


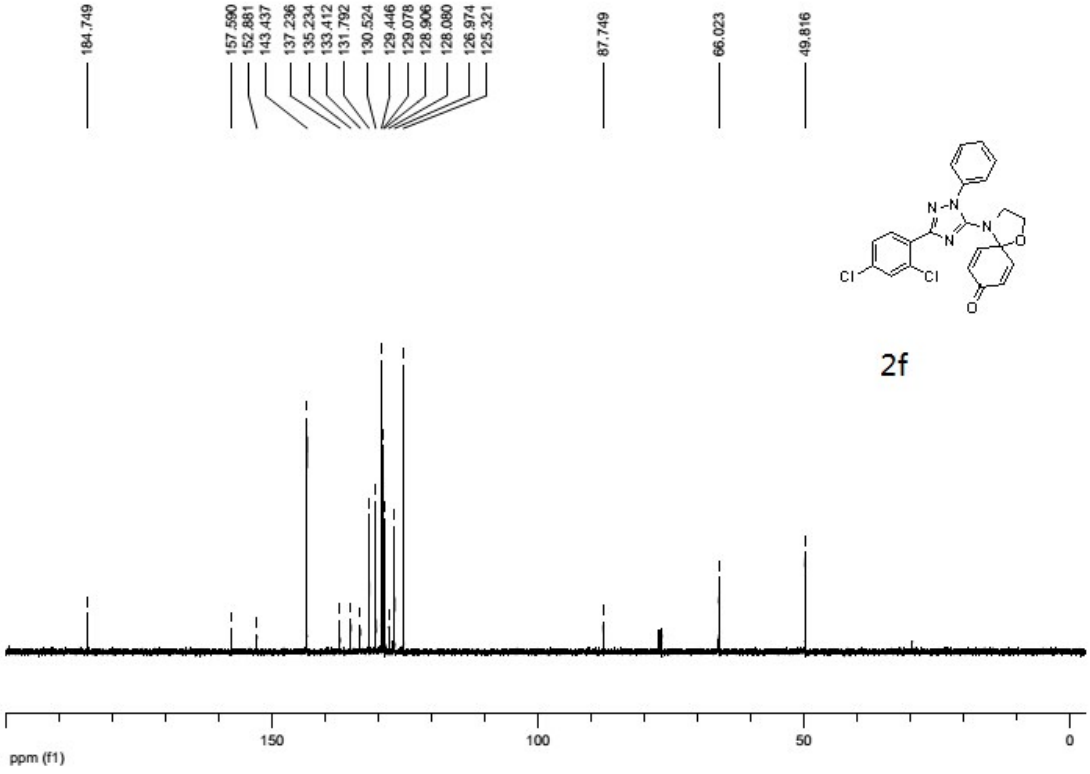
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 2e.



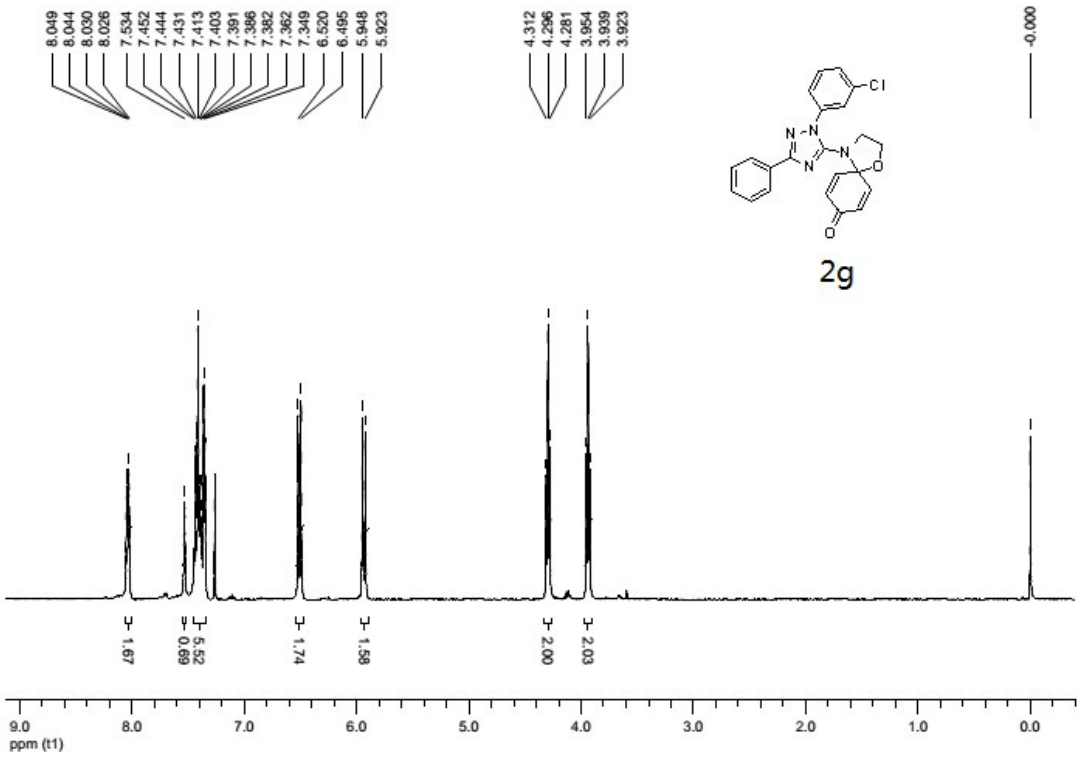


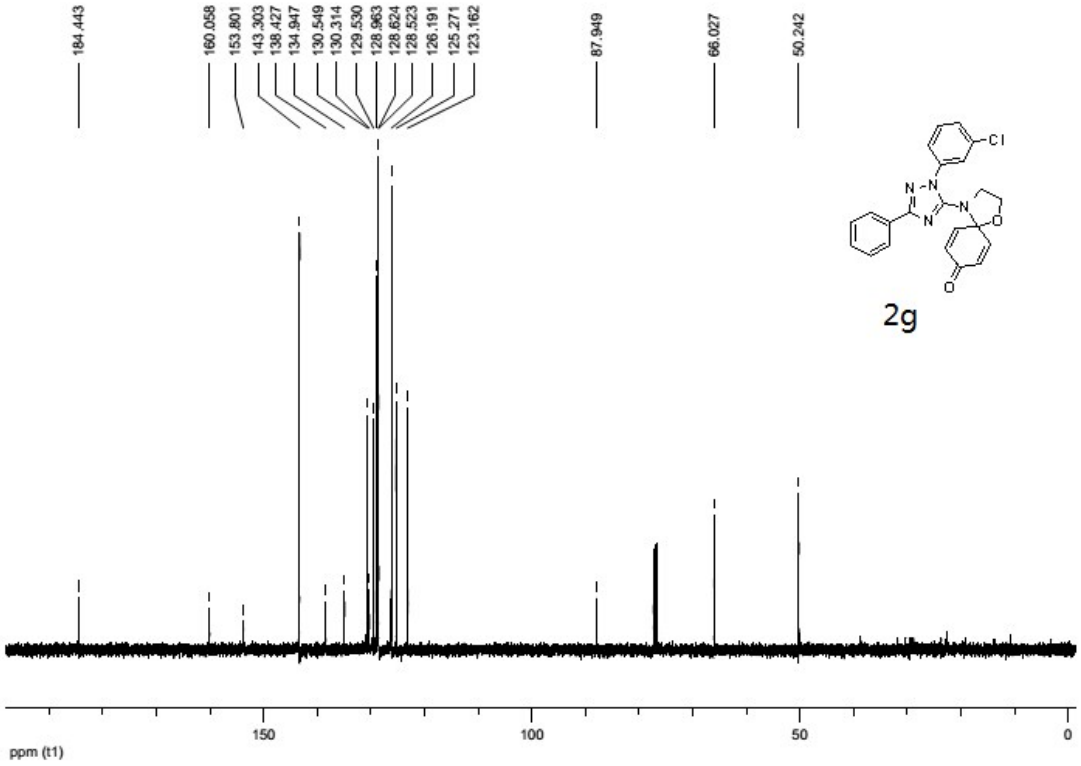
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 2f.



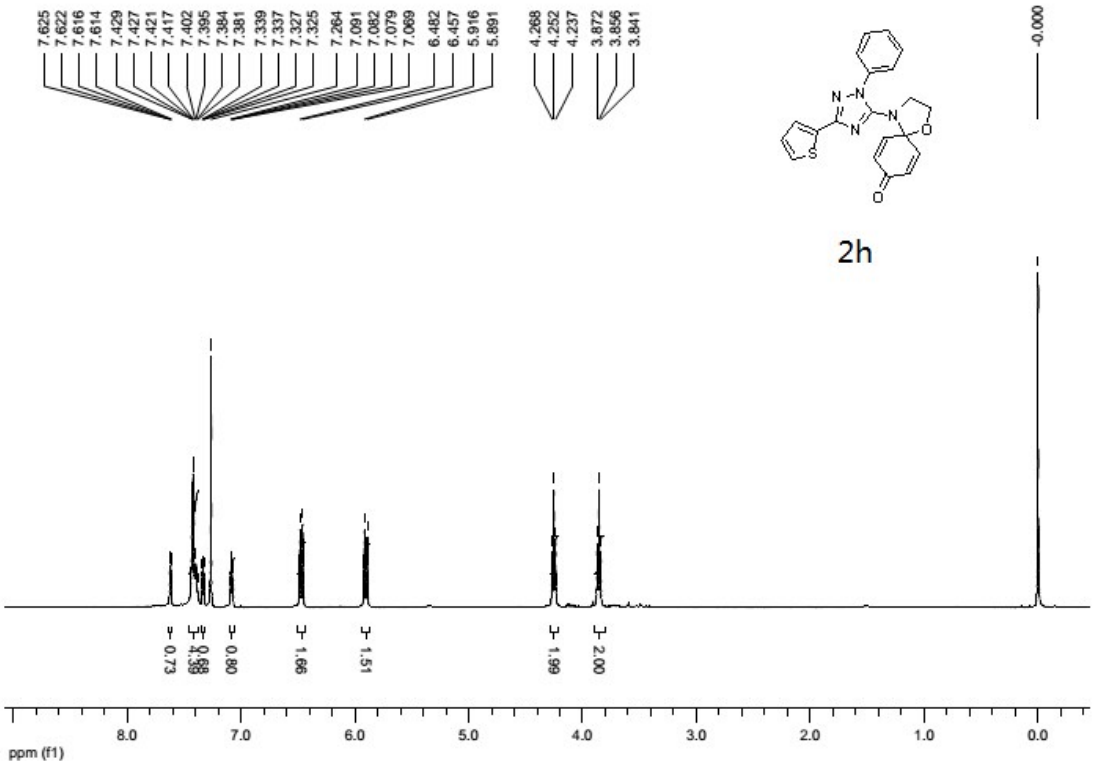


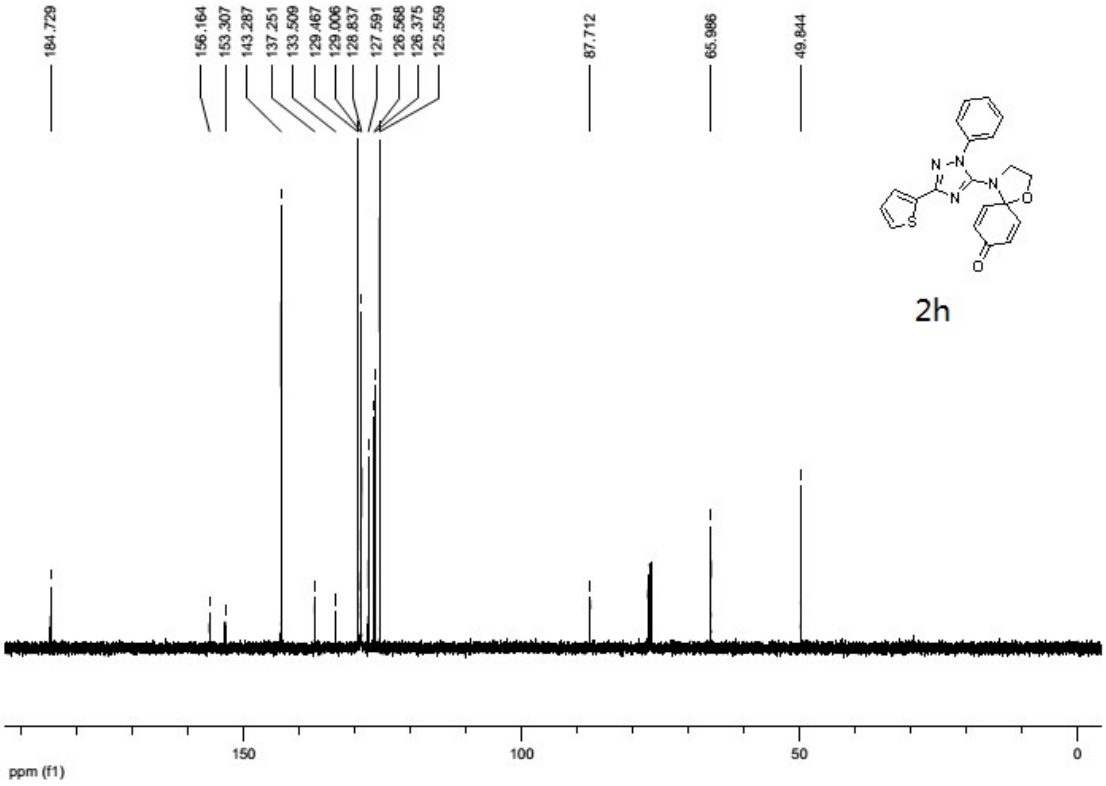
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 2g.

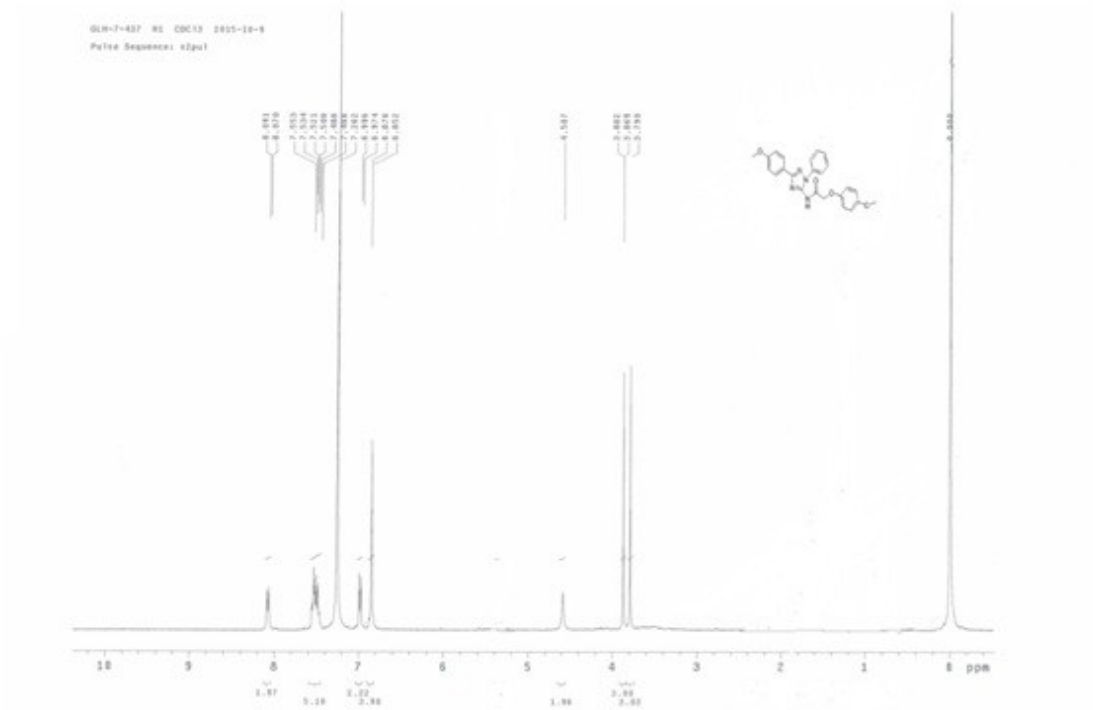




^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) of compound 2h.



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9
8
7
6
5
4
3
2
1
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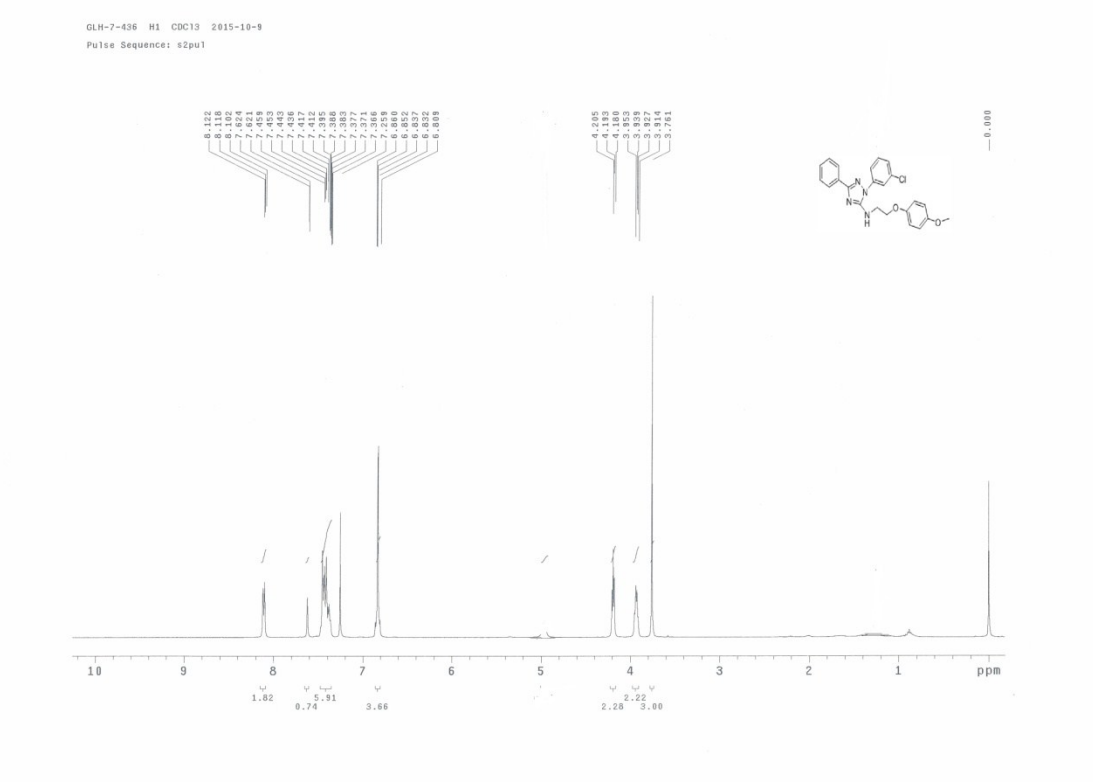
GLH-7-436 H1 CDCl3 2015-10-9
Pulse Sequence: s2pul
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9
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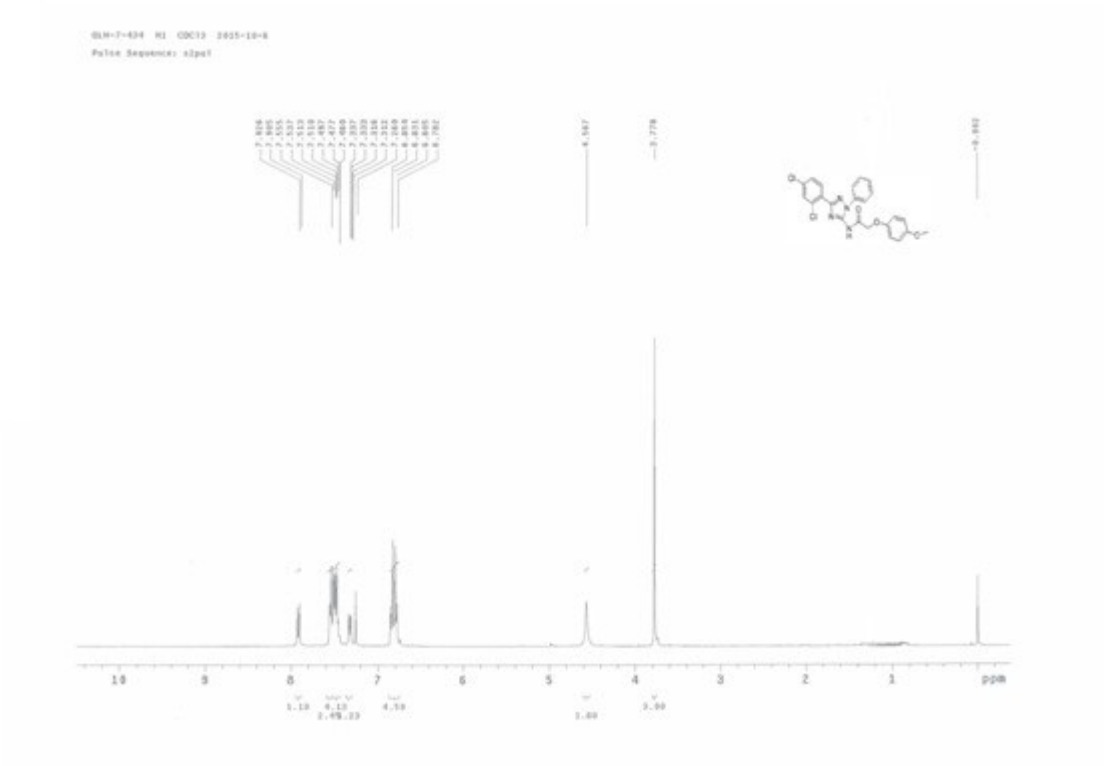
3
2
1
ppm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7
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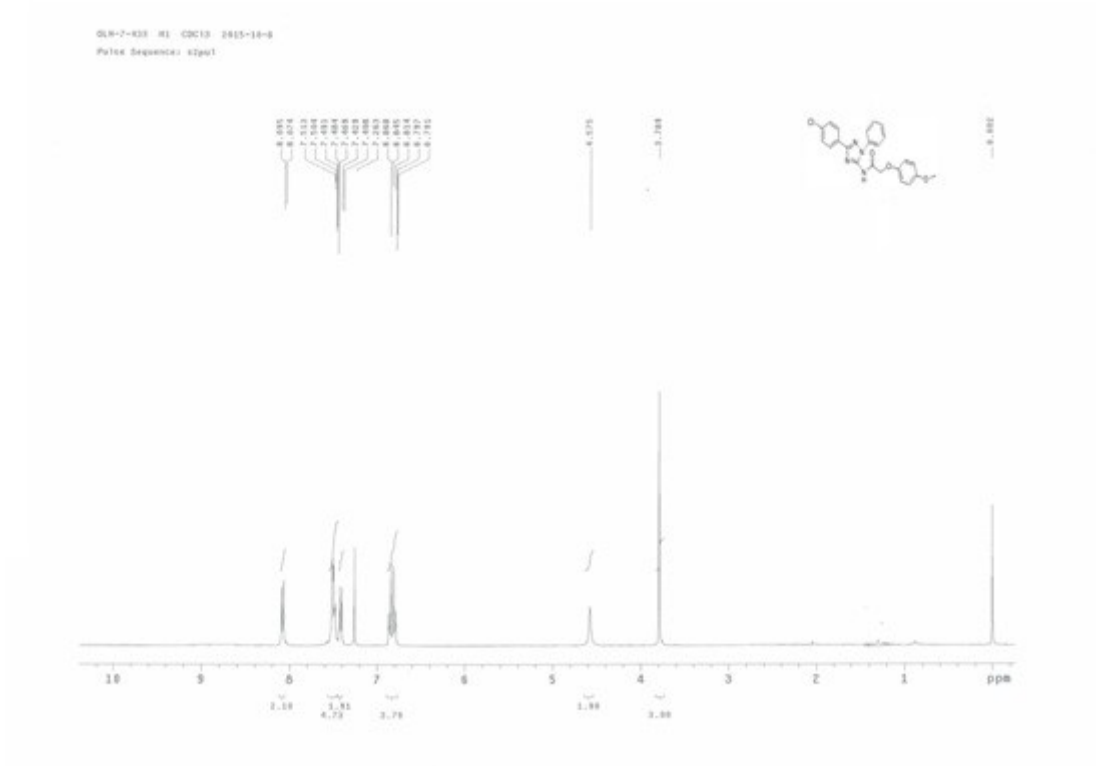
3
2
1
ppm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4
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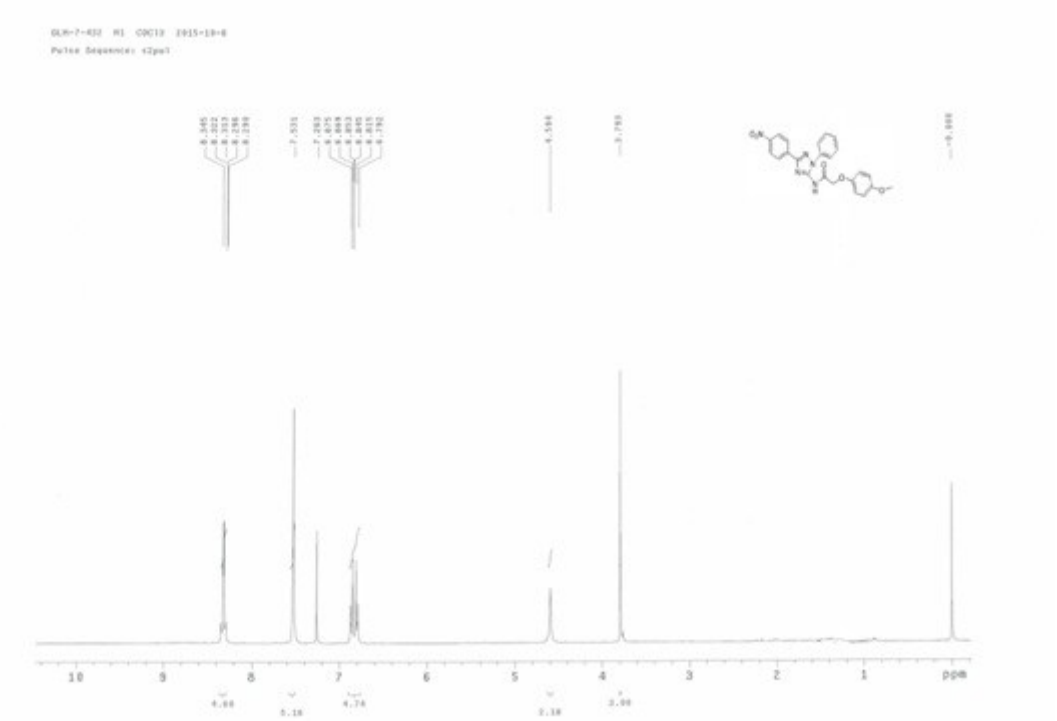
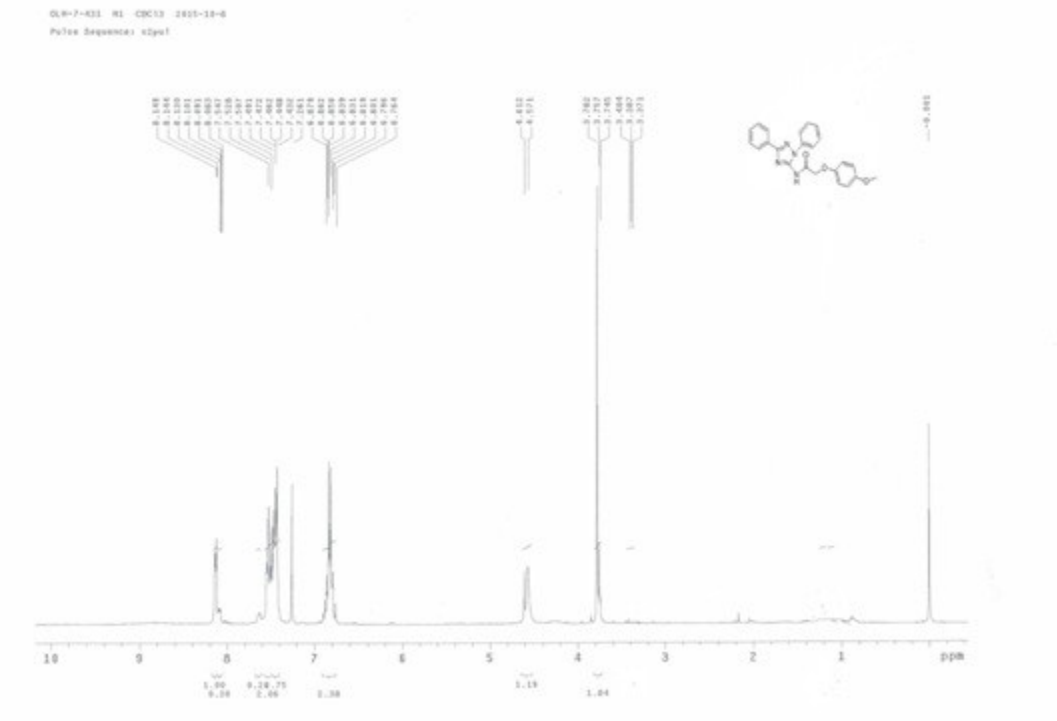
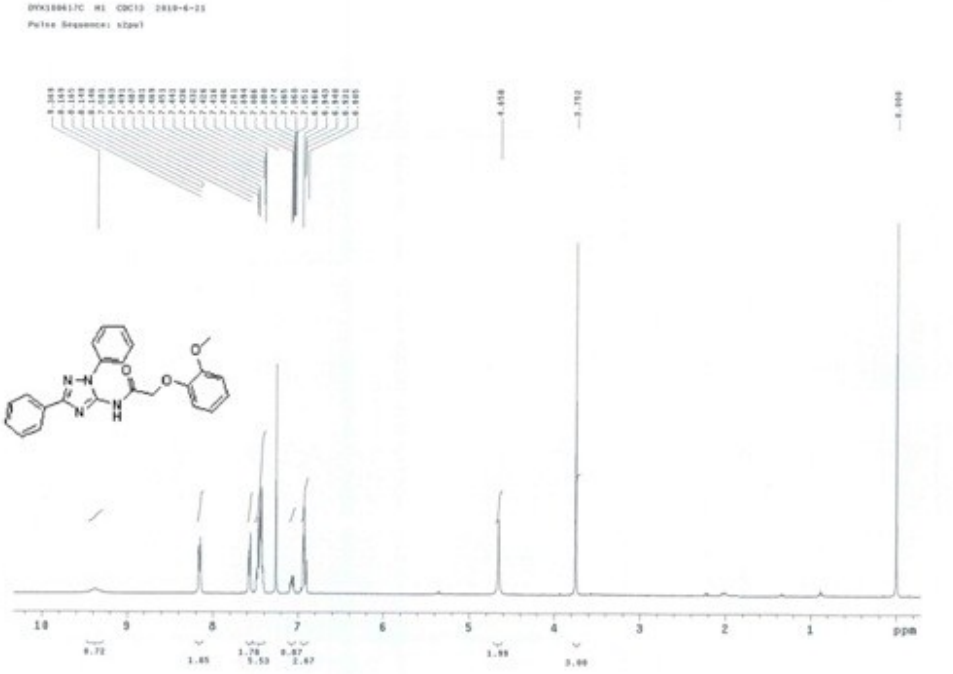
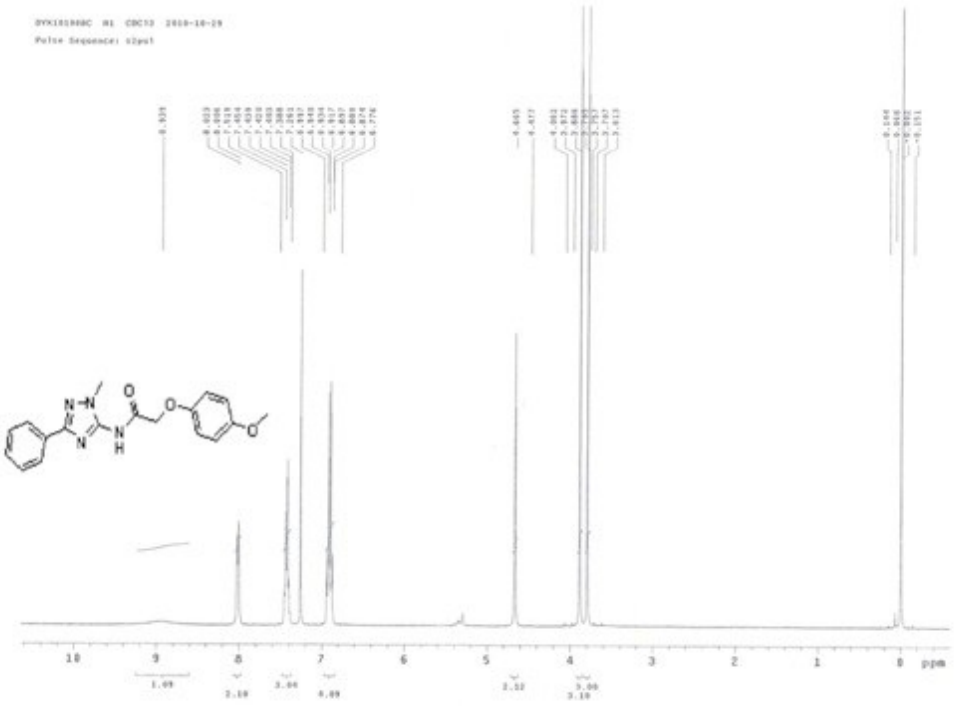
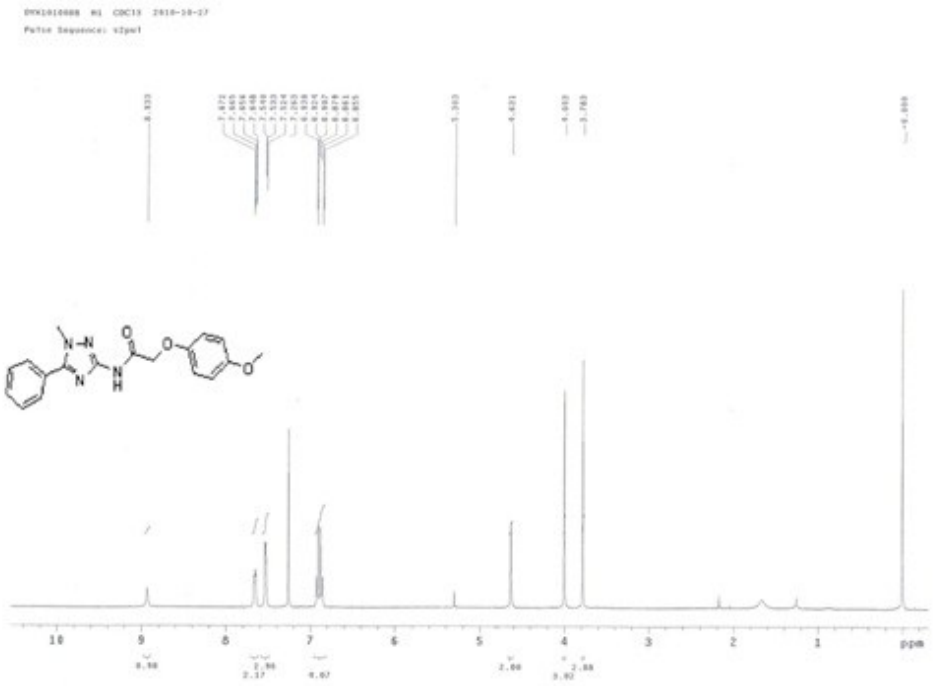
2
1
ppm

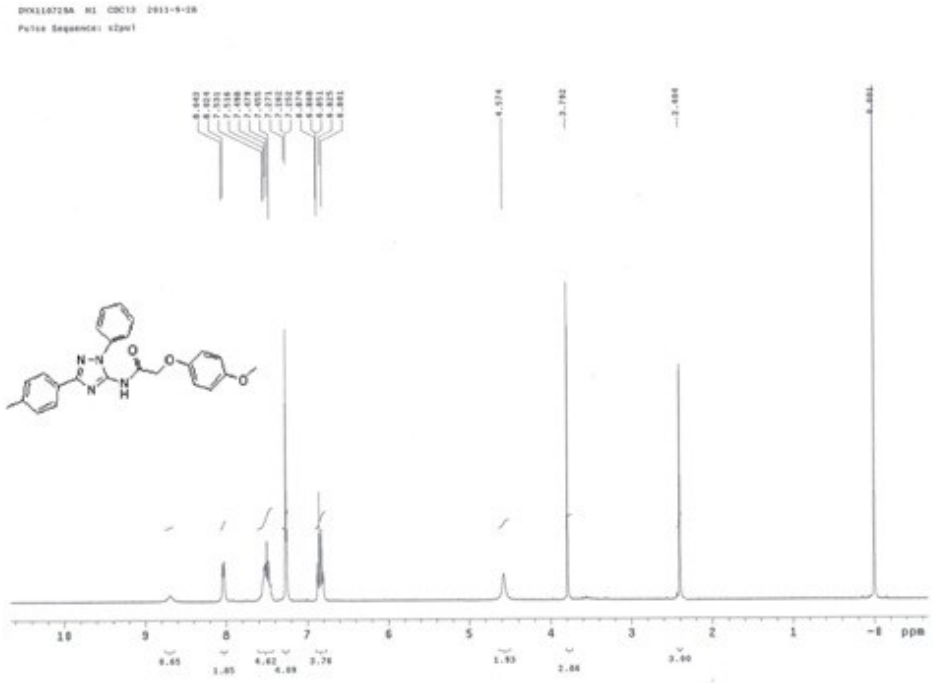


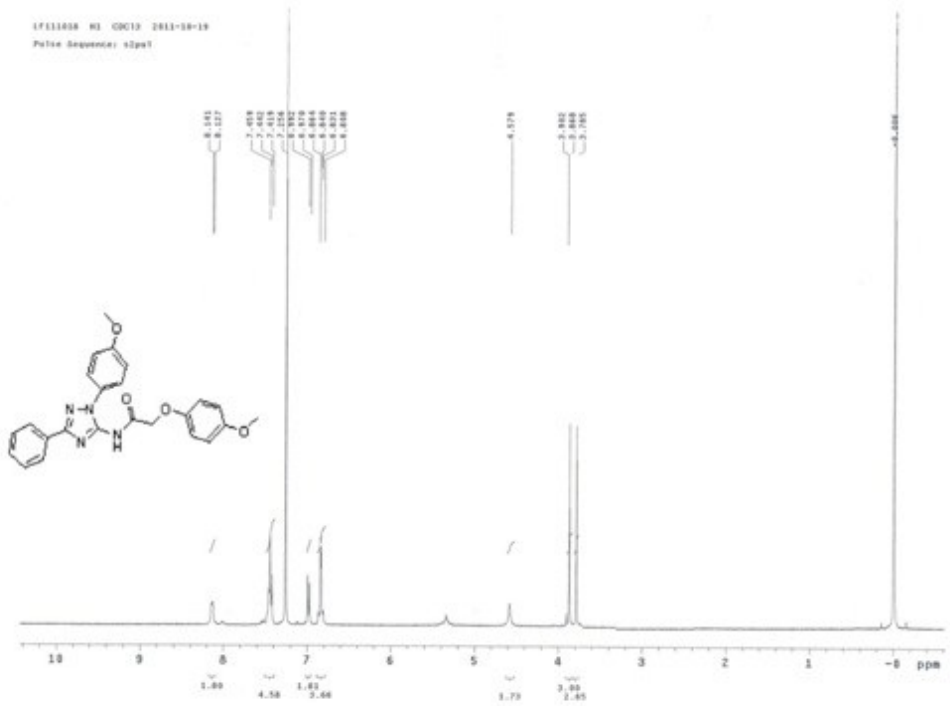


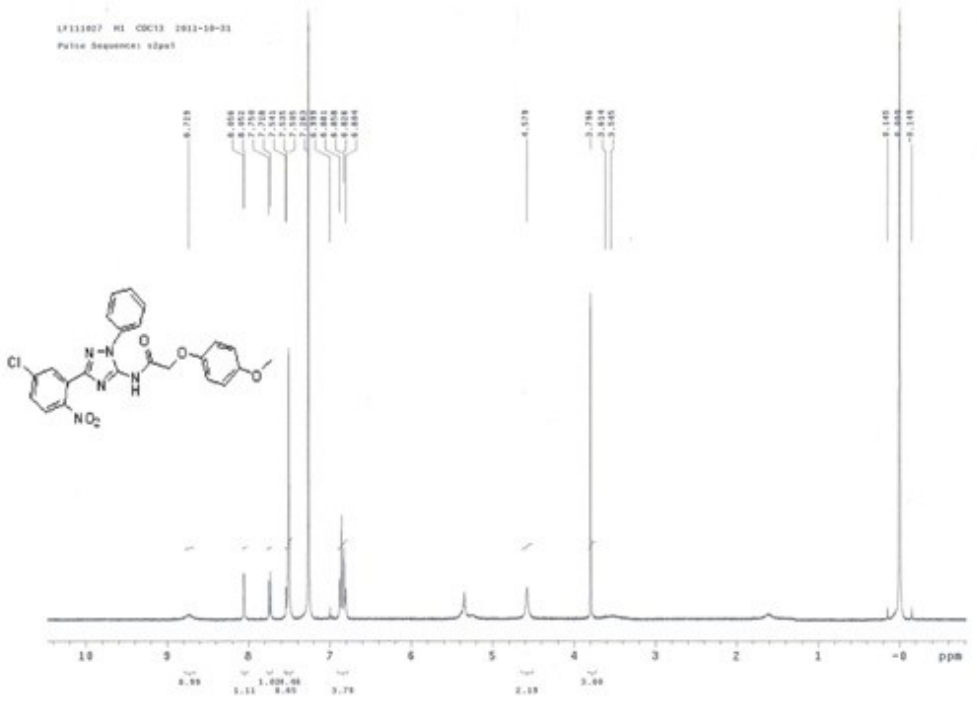


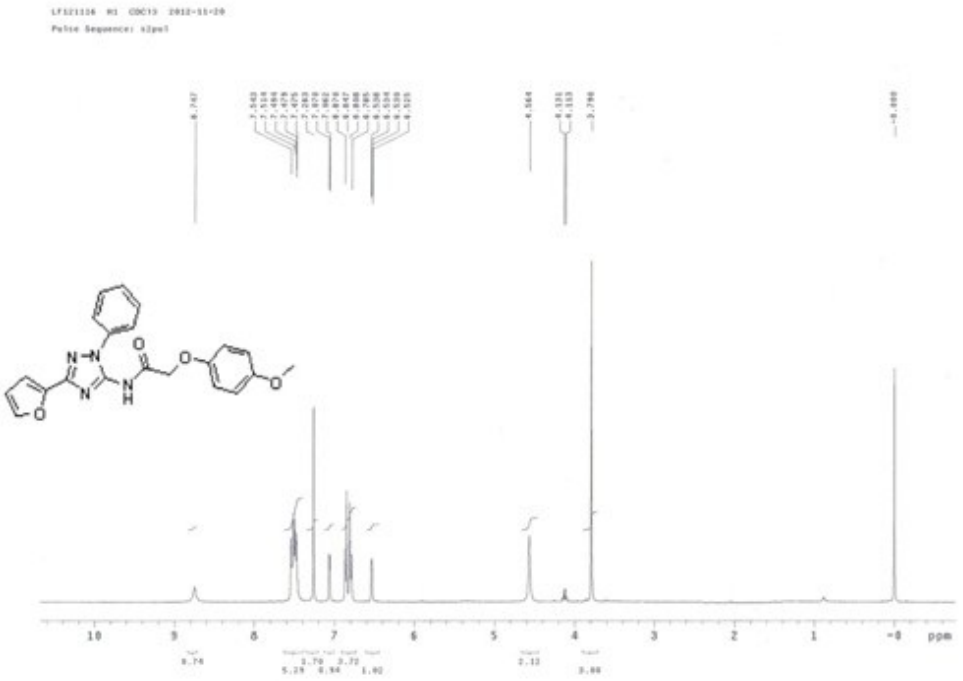


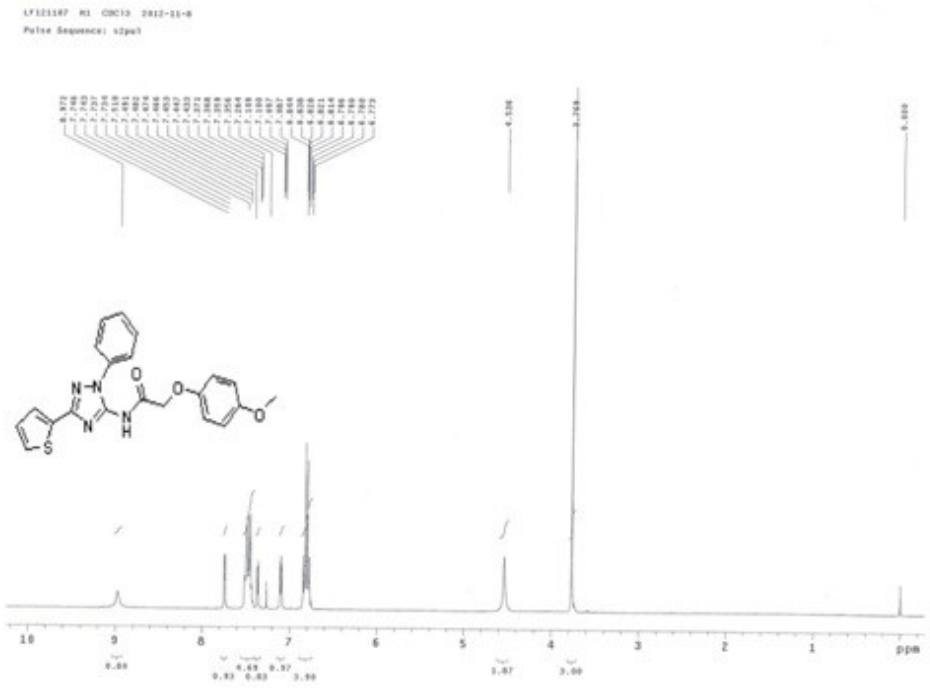


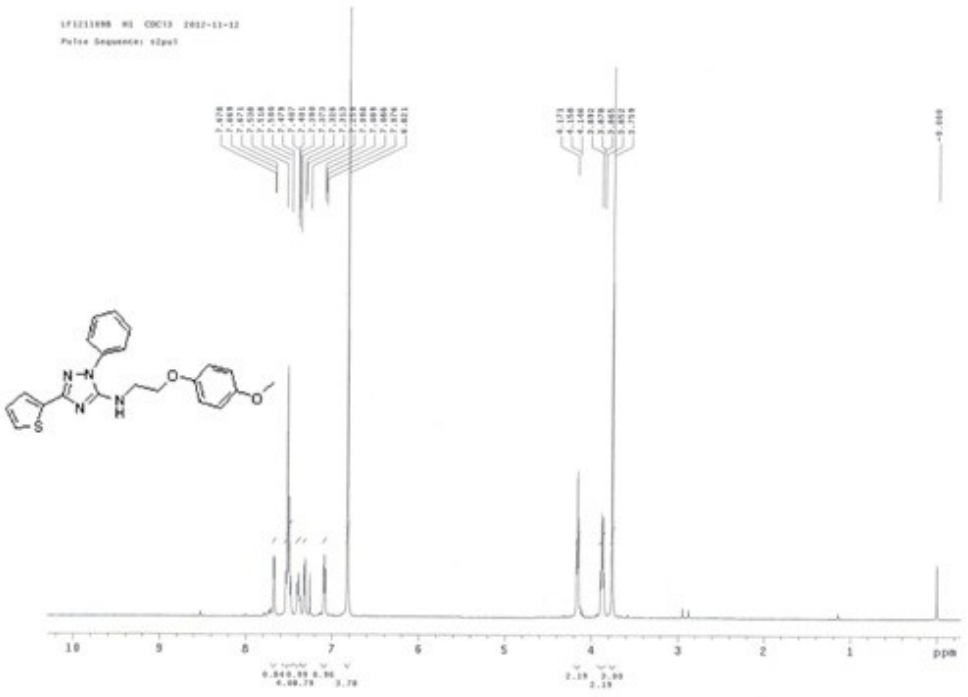


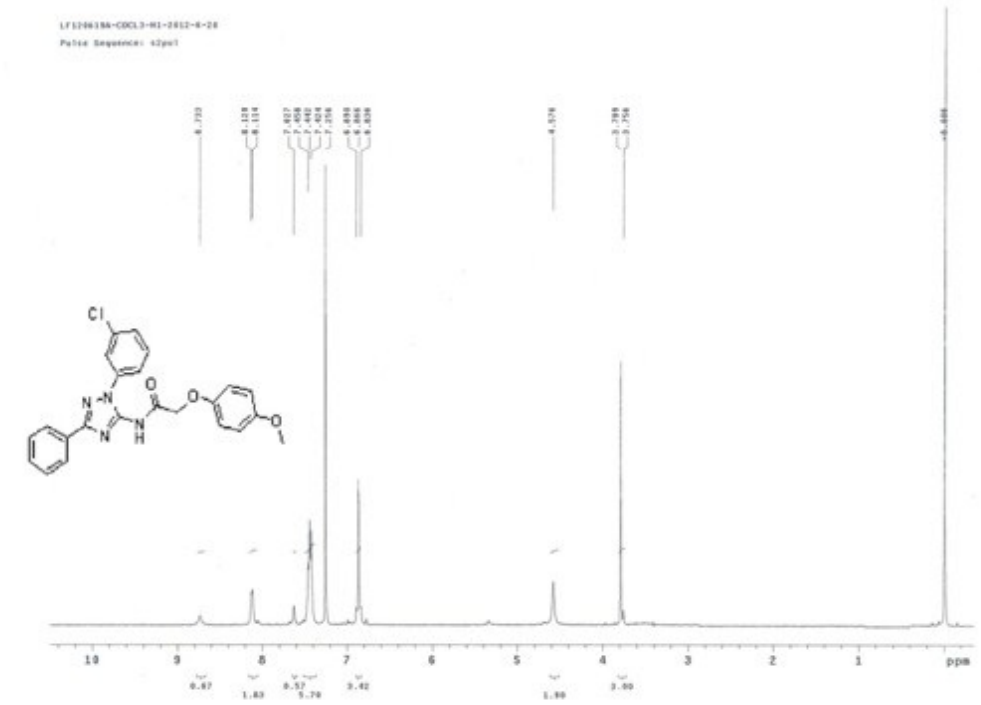











Cl
O
N
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N
H
O
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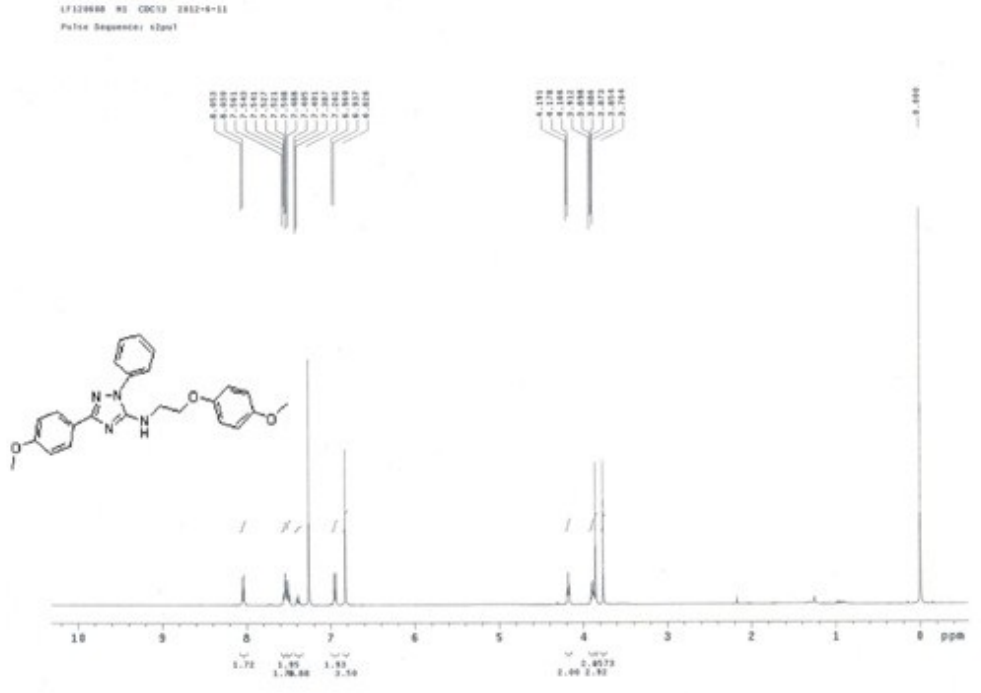
ppm


N
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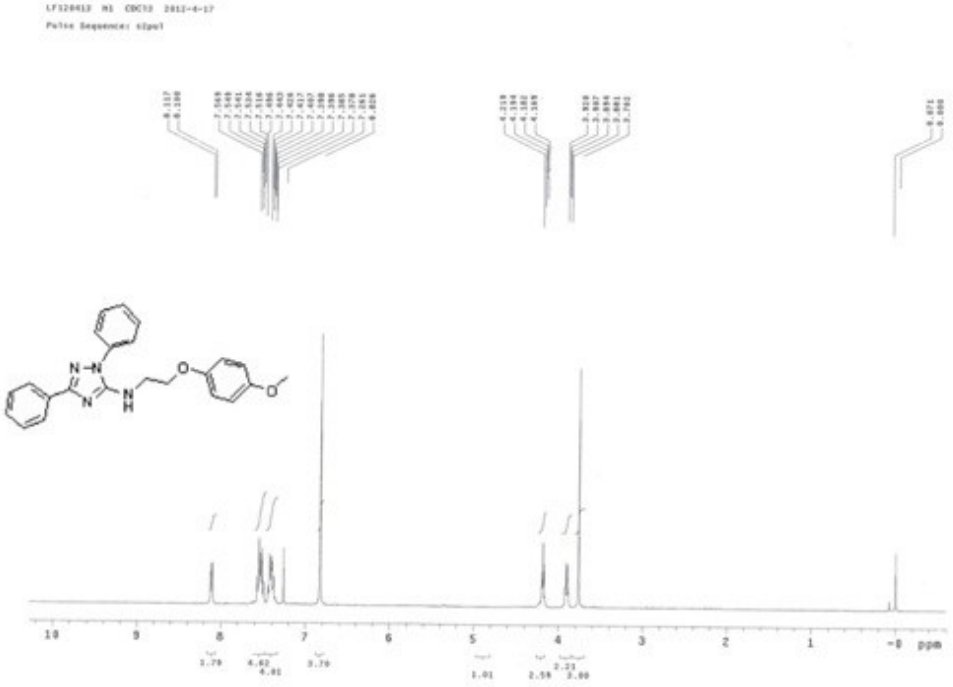
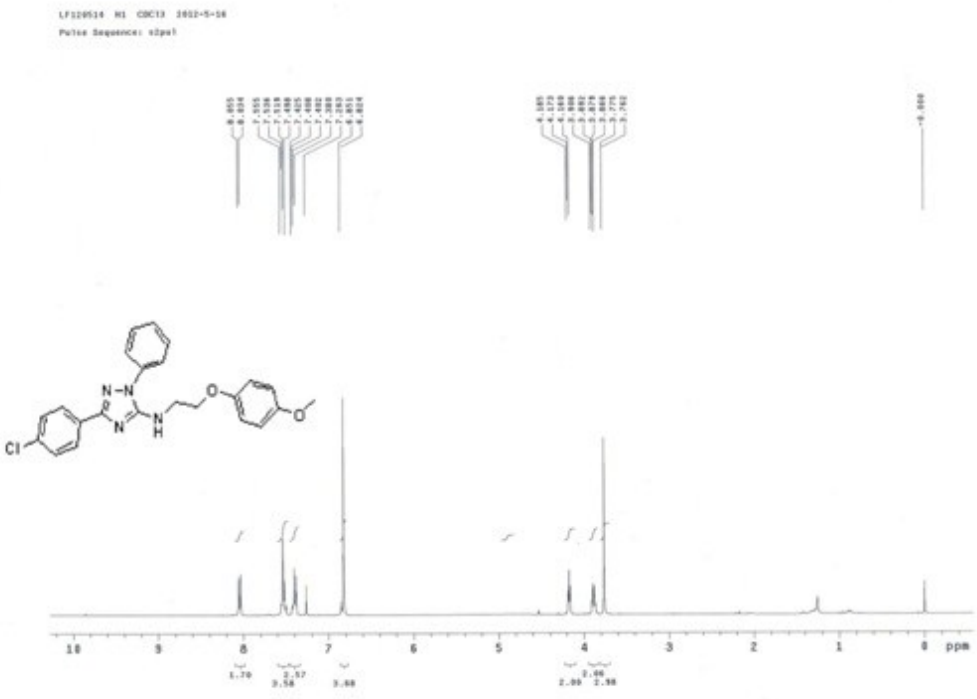
O
ppm





HPLC Purity Data for Compounds

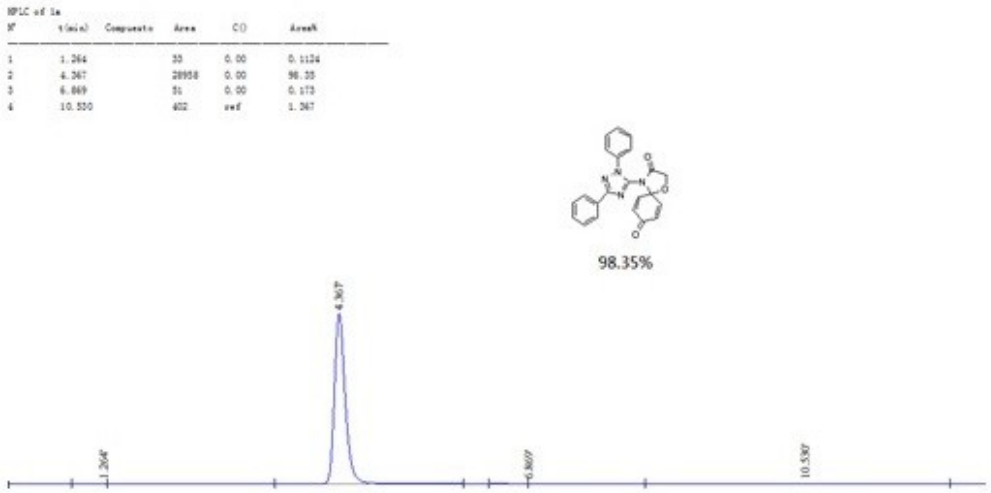
Table 1. HPLC Purity Data for Compounds**1a-2i.**

Compound	**Retention time (min)**	**Purity from integration** (%)
1a	4.37[a]	98.4
1b	4.38[a]	96.7
1c	4.37[a]	99.8
1d	3.87[a]	95.3
1e	4.35[a]	92.9
1f	4.25[a]	99.3
1g	4.75[a]	93.8
1h	4.74[a]	98.3
1i	4.51[a]	99.3
1j	4.35[a]	99.6
1k	4.39[a]	99.1
1l	4.19[a]	98.0
1m	3.98[a]	97.5
1n	4.66[a]	95.6
1o	4.10[a]	98.3
1p	5.74[a]	97.2
2a	4.13[a]	94.6
2b	4.73[a]	98.8

2c	4.52[a]	99.8
2d	4.96[a]	98.0
2e	4.54[a]	98.7
2f	5.04[a]	97.0
2g	4.42[a]	98.1
2h	4.33[a]	97.3
2i	4.08[a]	98.9

a. The mobile phase was CH_3OH,eluted isocratically at a flow rate of 0.5mL/min at room over 10 min, at room temperature and UV detection at 254 nm.

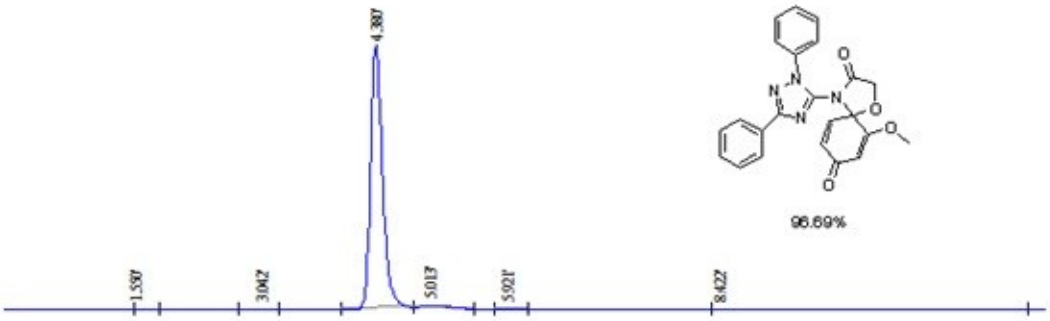
HPLC traces of compound **1a.**



HPLC traces of compound **1b.**

HPLC of 1b

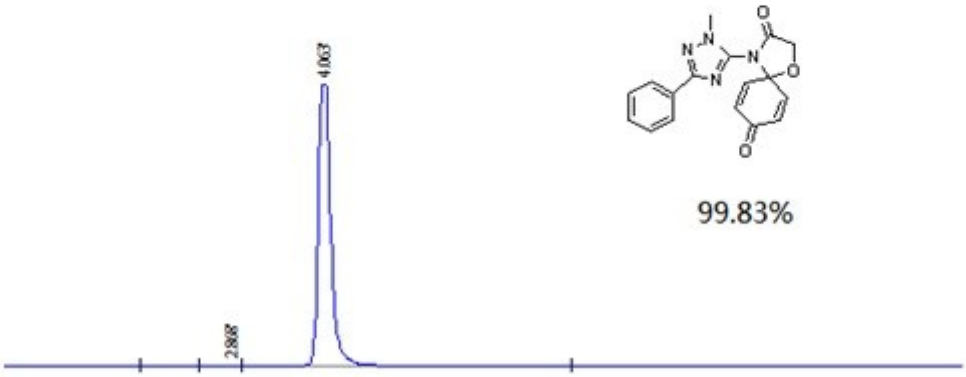
N°	t(min)	Compuesto	Area	CO	Area%
1	1.550		21	0.00	0.07284
2	3.042		22	0.00	0.07664
3	4.380		27944	0.00	96.69
4	5.013		531	0.00	1.837
5	5.921		101	0.00	0.3479
6	8.422		281	ref	0.9735



HPLC traces of compound **1c.**

HPLC of 1c

N°	t(min)	Compuesto	Area	C()	Area%
1	2.868		85	0.00	0.163
2	4.367		51921	ref	99.83

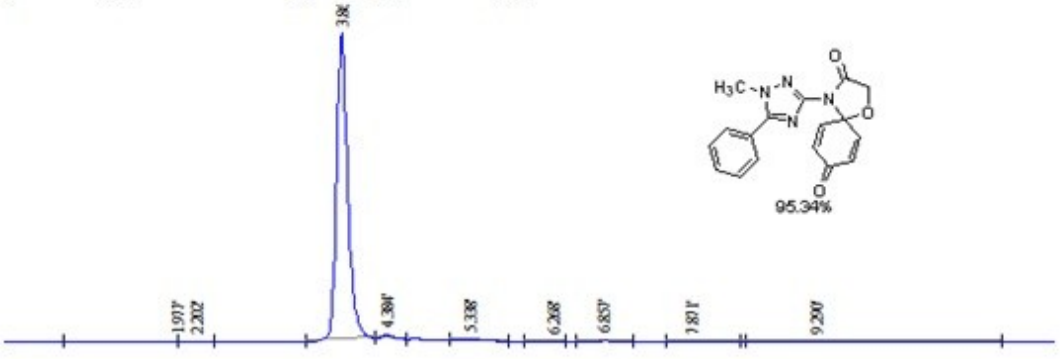


99.83%

HPLC traces of compound **1d.**

HPLC of 1d

N°	t(min)	Compuesto	Area	C()	Area%
1	1.977		43	0.00	0.1212
2	2.202		13	0.00	0.03777
3	3.865		33510	0.00	95.34
4	4.384		332	0.00	0.9435
5	5.338		165	0.00	0.4703
6	6.268		52	0.00	0.1492
7	6.857		177	0.00	0.5041
8	7.871		163	0.00	0.463
9	9.290		694	ref	1.973

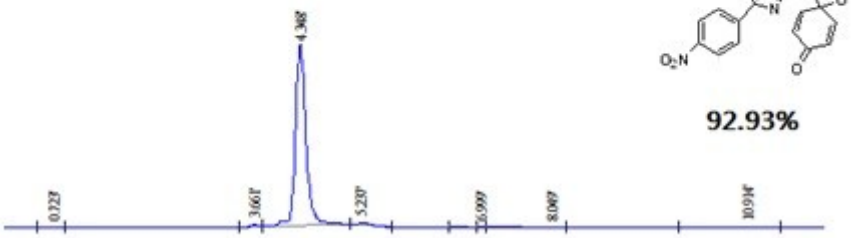


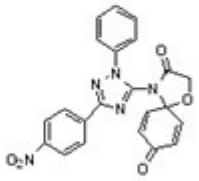
95.34%

HPLC traces of compound **1e.**

HPLC of 1e

N°	t(min)	Compuesto	Area	C()	Area%
1	0.723		22	0.00	0.301
2	3.661		74	0.00	1.008
3	4.368		6816	0.00	92.93
4	5.237		132	0.00	1.794
5	6.999		82	0.00	1.121
6	8.049		80	0.00	1.092
7	10.914		128	ref	1.749



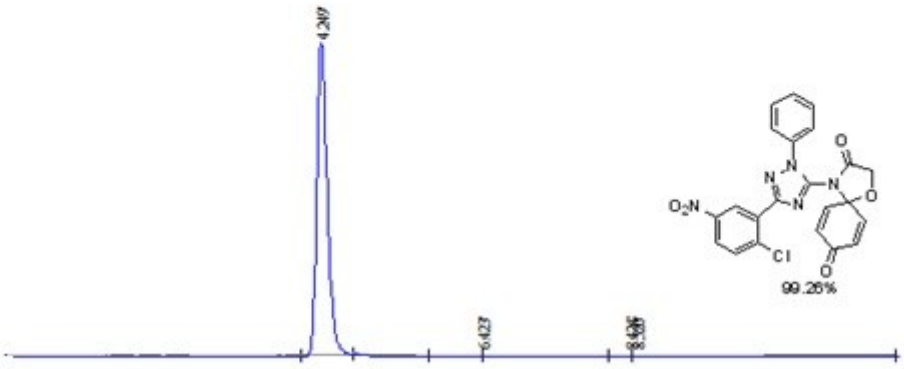


92.93%

HPLC traces of compound **1f.**

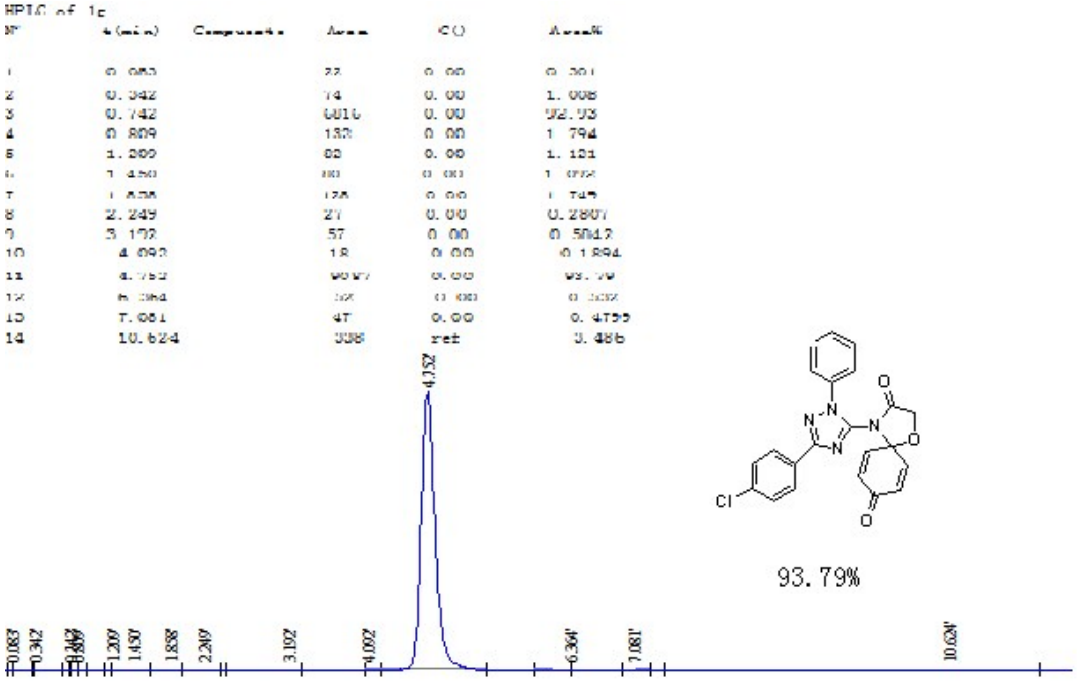
HPLC of 1f

N°	t(min)	Compuesto	Area	C()	Area%
1	4.249		19632	0.00	99.26
2	6.423		66	0.00	0.3339
3	8.424		30	0.00	0.1522
4	8.520		51	ref	0.2603



99.26%

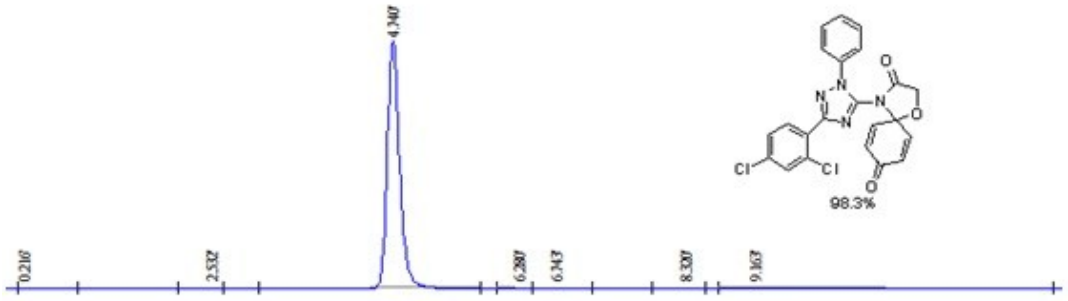
HPLC traces of compound **1g.**



HPLC traces of compound **1h.**

HPLC of 1h

N°	t(min)	Compuesto	Area	CO	Area%
1	0.216		26	0.00	0.1201
2	2.532		36	0.00	0.1654
3	4.740		21372	0.00	98.3
4	6.280		67	0.00	0.3067
5	6.743		77	0.00	0.3495
6	8.320		92	0.00	0.4208
7	9.163		74	ref	0.339



HPLC traces of compound **1i.**

HPLC of 1i

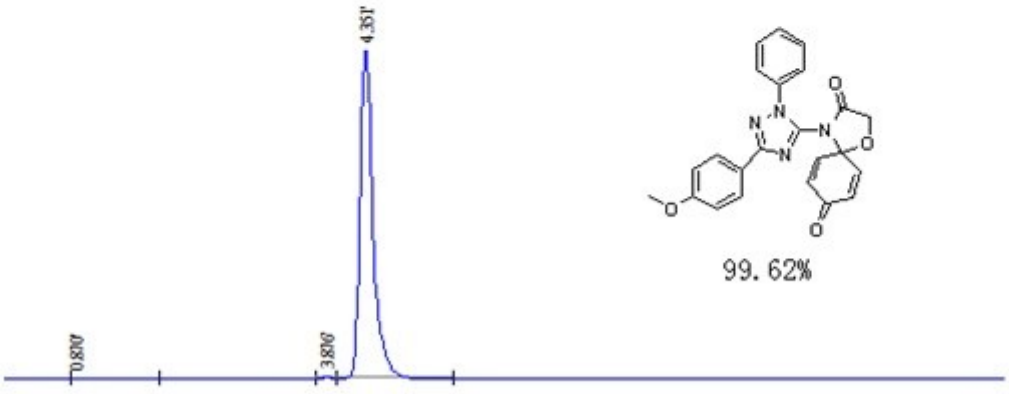
N°	t(min)	Compuesto	Area	C()	Area%
1	4.508		32998	0.00	99.32
2	5.109		21	0.00	0.06253
3	5.158		26	0.00	0.07697
4	5.968		180	ref	0.5428

99.32%

HPLC traces of compound **1j.**

HPLC of 1j

N°	t(min)	Compuesto	Area	C()	Area%
1	0.870		38	0.00	0.07662
2	3.876		152	0.00	0.3058
3	4.351		49663	ref	99.62

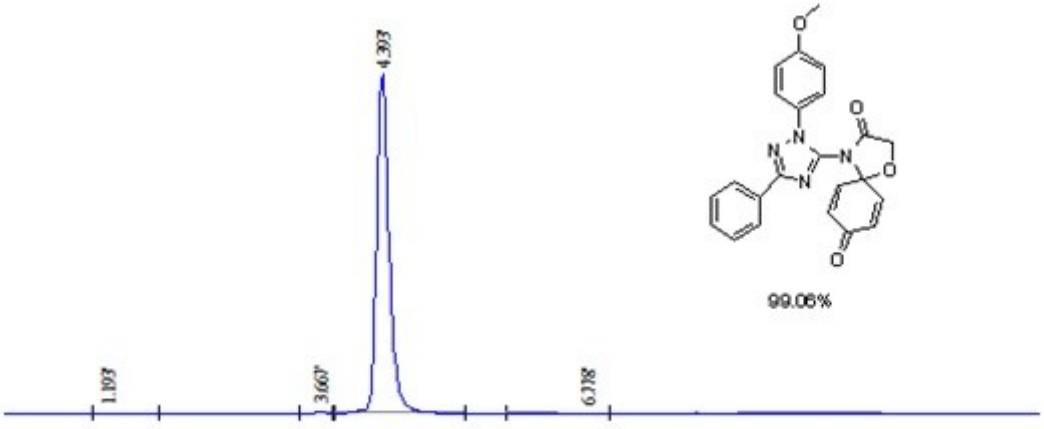


99.62%

HPLC traces of compound **1k.**

HPLC of 1k

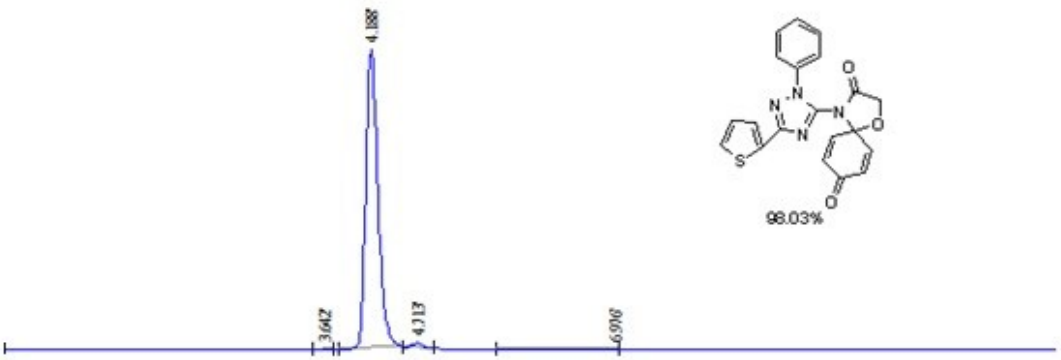
N°	t(min)	Compuesto	Area	CO	Area%
1	1.193		46	0.00	0.1627
2	3.667		141	0.00	0.4992
3	4.393		28004	0.00	99.06
4	6.778		78	ref	0.2758



HPLC traces of compound **1l.**

HPLC of 1l

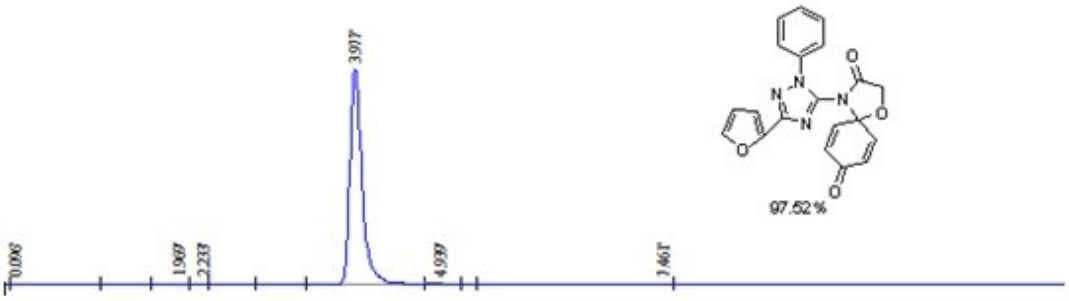
N°	t(min)	Compuesto	Area	CO	Area%
1	3.642		50	0.00	0.1872
2	4.188		26032	0.00	98.03
3	4.713		311	0.00	1.172
4	6.976		162	ref	0.6091



HPLC traces of compound **1m.**

HPLC of 1m

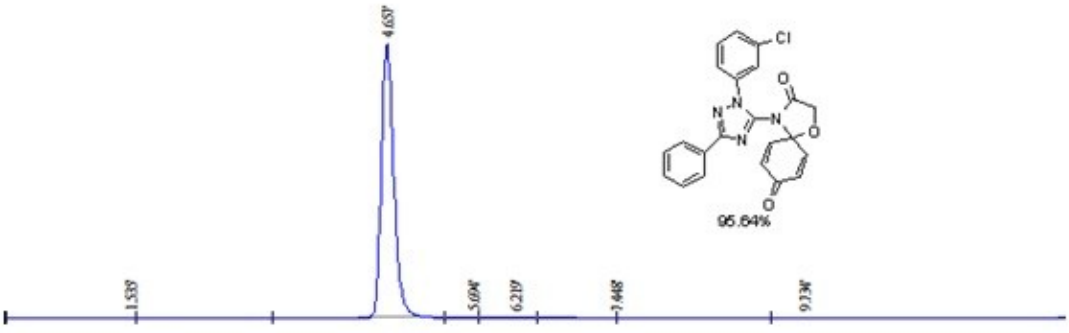
N°	t(min)	Compuesto	Area	C()	Area%
1	0.096		53	0.00	0.4092
2	1.969		35	0.00	0.2683
3	2.233		35	0.00	0.2725
4	3.977		12559	0.00	97.52
5	4.939		69	0.00	0.5394
6	7.461		128	ref	0.993



HPLC traces of compound **1n.**

HPLC of 1n

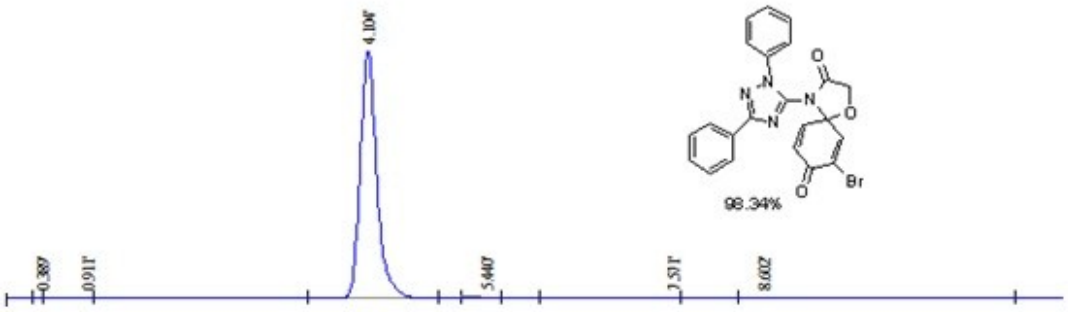
N°	t(min)	Compuesto	Area	C()	Area%
1	1.535		121	0.00	0.4943
2	4.657		23490	0.00	95.64
3	5.694		78	0.00	0.3166
4	6.219		166	0.00	0.6777
5	7.448		99	0.00	0.4018
6	9.734		607	ref	2.469



HPLC traces of compound **1o.**

HPLC of 1o

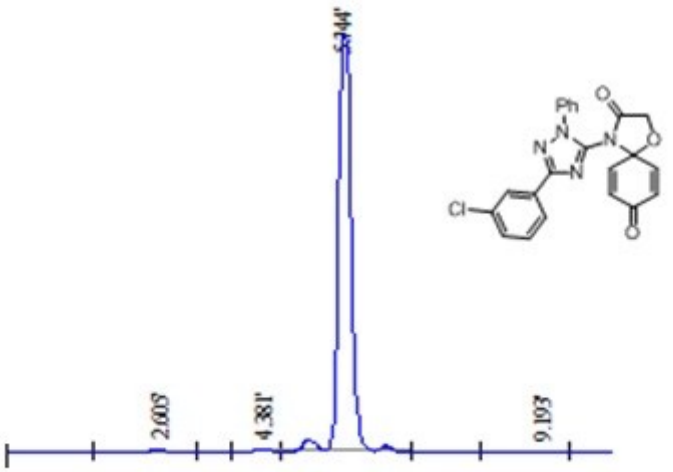
N°	t(min)	Compuesto	Area	C()	Area%
1	0.389		14	0.00	0.09174
2	0.911		39	0.00	0.2619
3	4.104		14578	0.00	98.34
4	5.440		44	0.00	0.2953
5	7.571		44	0.00	0.2995
6	8.602		106	ref	0.714



HPLC traces of compound **1P.**

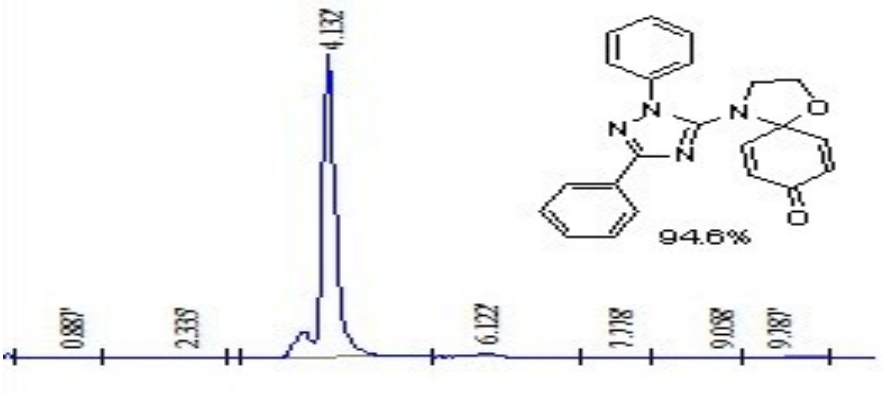
HPLC of 1P

N°	t (min)	Compuesto	Area	C()	Area%
1	2.605		30	0.00	1.409
2	4.381		24	0.00	0.9809
3	5.744		4546	0.00	97.25
4	9.193		8	ref	0.3579



HPLC traces of compound **2a.**

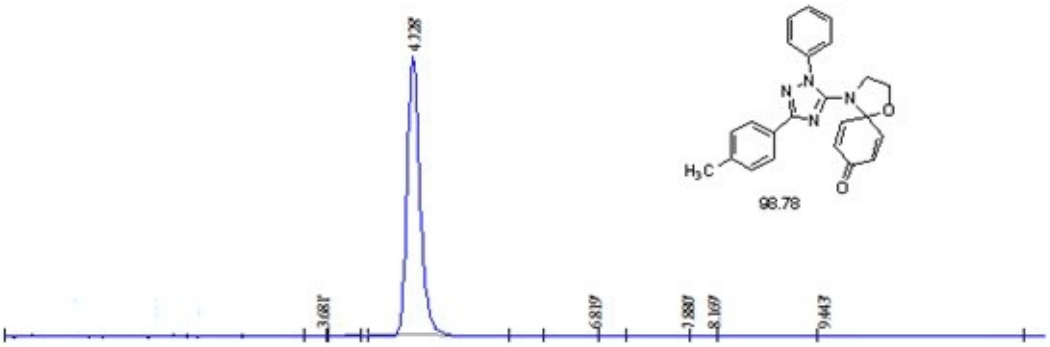
N°	t (min)	Compuesto	Area	c []	%Area
1	0.887		214	0.00	0.7124
2	2.335		228	0.00	0.7582
3	4.132		28445	0.00	94.65
4	6.122		776	0.00	2.582
5	7.778		137	0.00	0.4545
6	9.058		193	0.00	0.6407
7	9.787		62	ref	0.2073



HPLC traces of compound **2b.**

HPLC of 2b

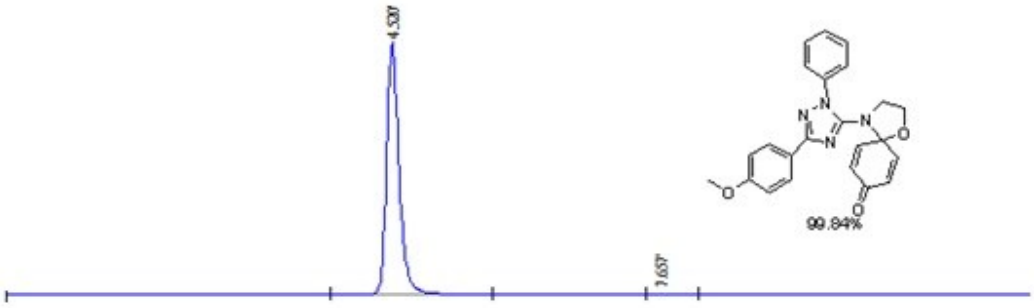
N°	t (min)	Compuesto	Area	C()	Area%
1	3.972		73	0.00	0.332
2	4.728		31137	0.00	98.78
3	6.819		39	0.00	0.1229
4	7.880		40	0.00	0.1261
5	8.169		22	0.00	0.07122
6	9.443		81	ref	0.257



HPLC traces of compound **2c.**

HPLC of 2c

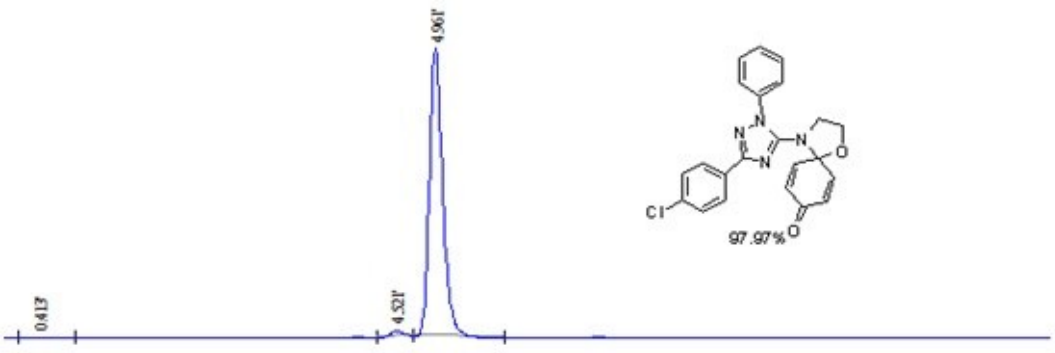
N°	t(min)	Compuesto	Area	C()	Area%
1	4.520		16365	0.00	99.84
2	4.367		25	ref	0.1525



HPLC traces of compound **2d.**

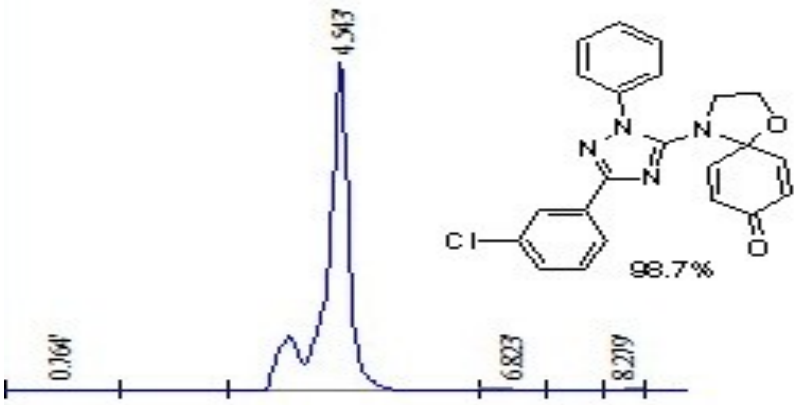
HPLC of 2d

N°	t(min)	Compuesto	Area	C()	Area%
1	0.413		63	0.00	0.1885
2	4.521		613	0.00	1.84
3	4.961		32638	ref	97.97



HPLC traces of compound **2e.**

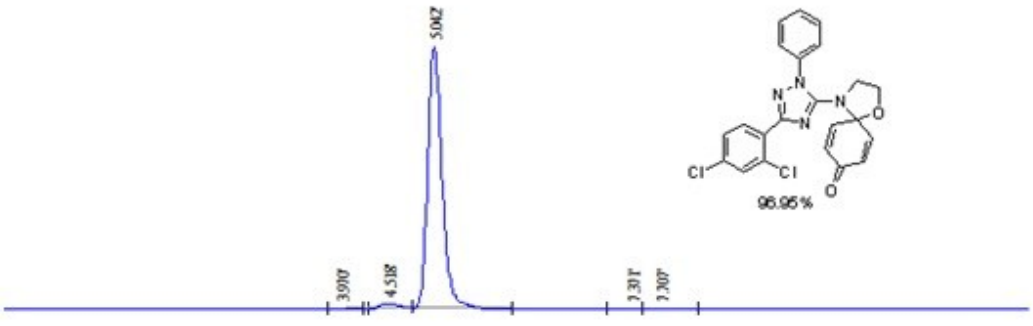
N°	t (min)	Compuesto	Area	C ()	%Area
1	0.764		398	0.00	0.8204
2	4.543		47903	0.00	98.77
3	6.823		135	0.00	0.2776
4	8.279		67	ref	0.1386



HPLC traces of compound **2f.**

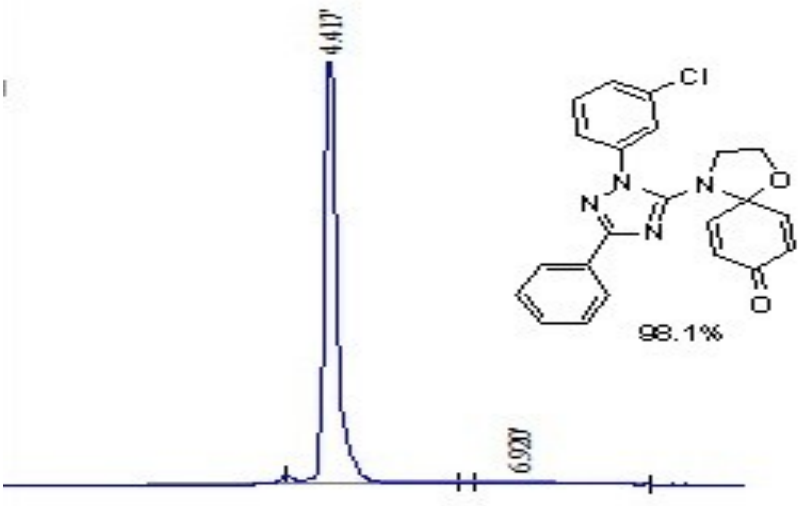
HPLC of 2f

N°	t (min)	Compuesto	Area	C()	Area%
1	3.970		92	0.00	0.3767
2	4.518		587	0.00	2.396
3	5.042		23756	0.00	96.95
4	7.371		33	0.00	0.1343
5	7.707		35	ref	0.1416



HPLC traces of compound **2g.**

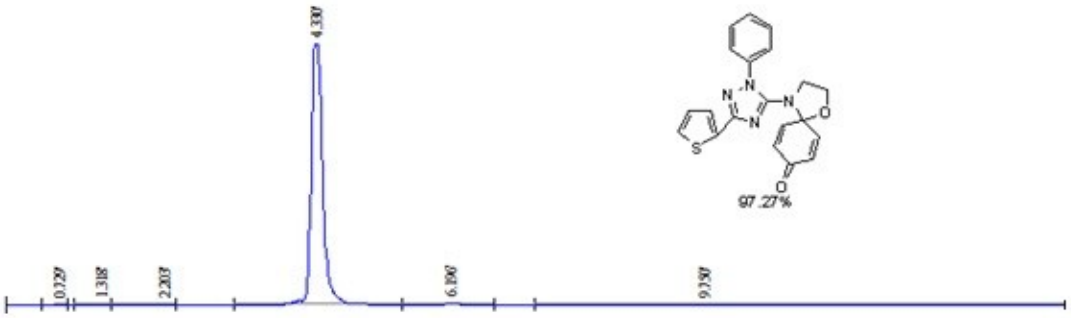
N°	t (min)	Compuesto	Area	C ()	%Area
1	4.417		60630	0.00	98.17
2	6.920		1135	ref	1.837



HPLC traces of compound **2h.**

HPLC of 2h

N°	t(min)	Compuesto	Area	C()	Area%
1	0.729		122	0.00	0.2255
2	1.318		145	0.00	0.2683
3	2.203		110	0.00	0.2042
4	4.330		52460	0.00	97.27
5	6.196		675	0.00	1.252
6	9.750		424	ref	0.7856



HPLC traces of compound **2i.**

HPLC of 2i

N°	t(min)	Compuesto	Area	C()	Area%
1	0.357		18	0.00	0.172
2	1.829		20	0.00	0.1891
3	4.079		10384	0.00	98.94
4	4.693		21	0.00	0.2029
5	5.434		39	0.00	0.3742