Synthesis of 1,2,3-Triazolo Fused Allocolchicine Analogs via Intramolecular Oxidative Biaryl Coupling

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Supporting information

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General Considerations

NMR spectra were recorded on a Bruker 400 avance (400 MHz) or a Bruker 300 and 600 Avance II+ (600 MHz), and chemical shifts (δ) are reported part per million (ppm) referenced to tetramethylsilane (^{1}H). Melting points were determined using a Reichert Thermovar apparatus. For column chromatography 70-230 mesh silica 60 (E. M. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. Reaction dry solvents were used as received from commercial sources. TLC were carried out on Kieselgel 60 F254 plates (Merck) and visualized with UV-lamp 254 nm.

Exact mass spectra were acquired with a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3uL/min and spectra were obtained in positive (or: negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

General procedure for the preparation of 1,2,3-triazole substrate

To a screw-capped reaction tube equipped with a magnetic stirring bar was added the ketone (1.0 equiv.), primary amine (1.3 equiv.), 4-nitrophenyl azide (1.0 equiv.) and 4 Å molecular sieves (50 mg). The mixture was dissolved in dry toluene and stirred at 100 °C for 24 hours. The crude reaction mixture was then directly purified by column chromatography (silica gel) at first was used dichloromethane as eluent to remove 4-nitroaniline formed during the reaction followed by using a mixture of Petroleum ether and ethyl acetate as eluent to afford the corresponding 1,2,3-triazole compound.[1]

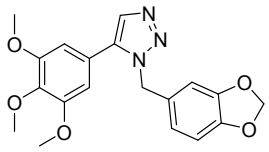
General Procedure Oxidative Coupling Reactions

To a stirred solution of 1,2,3-triazole substrate (1.0 equiv.) in dry dichloromethane (2.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (1.1 equiv.) in dry dichloromethane (2.0 mL) and $BF_3{\cdot}Et_2O$ (3.0 equiv.) at -40 °C under argon atmosphere and the mixture was stirred for 3 h. After confirmation that the starting material had been consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted with DCM. The crude was purified via column chromatography (silica gel) where as the eluent was used petroleum ether and ethyl acetate. In some cases, used preparative TLC was used for further purification.

4-Nitrophenyl Azide

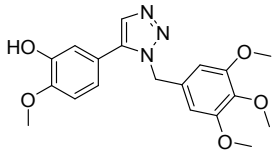
To a 3 L flask equipped **with mechanical stirrer**, 4-nitroaniline (28.0 g, 0.20 mol) was suspended in a concentrated solution of HCl (300 mL) then methanol (60 mL) was added and stirred for 2h at r.t. Next the mixture was cooled at 0-5 °C, if 4-nitroaniline still was not dissolved more concentrated HCl was added **until a clear solution was obtained**, then $NaNO_2$ solution (6 M, 50 mL) was added dropwise keeping the temperature below 5°C during the addition. The mixture was stirred at 0-5 °C for 30 minutes, after that a solution of NaN_3 (4.1 M, 80 mL) was added dropwise over 30 minutes and the whole reaction mixture was stirred for an hour at room temperature (**warning**: the volume of the reaction mixture increased drastically due to N_2 liberation therefore a large flask is needed to accommodate this foaming). The precipitate was filtered, washed with a saturated $NaHCO_3$ solution and water, dissolved in diethyl ether, dried over $MgSO_4$ and concentrated under reduced pressure at 30 °C to afford 4-nitrophenyl azide as a slightly yellow solid

with 98% yield (32.6 g). 4-nitrophenyl azide was used without further purification. Spectroscopic data for 4-nitrophenyl azide was consistent with previously reported data for this compound.[2]



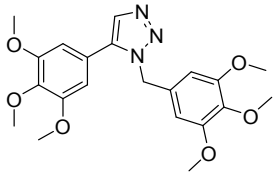
1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (**5**) : 3′,4′,5′-trimethoxyacetophenone (200 mg, 1.0 equiv., 0.951 mmol), piperonylamine (187 mg, 1.3 equiv., 1.237 mmol), 4-nitrophenyl azide (156 mg, 1.0 equiv., 0.951 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 3:7) affording **5** (334 mg, 95% yield) as off white solid. m.p. 126 ˚C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.66 (s, 1H), 6.58 (d, *J* = 8 Hz, 1H), 6.42 (s, 2H), 5.94 (s, 2H), 5.44 (s, 2H), 3.89 (s, 3H), 3.75 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.5, 148.1, 138.0, 133.1, 129.5, 122.1, 120.6, 108.3, 107.8, 106.3, 101.3, 60.9, 56.1, 51.6. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{19}N_3O_5H$, 370.1397; found, 370.1395.



2-Methoxy-5-(1-(3,4,5-trimethoxybenzyl)-1*H*-1,2,3-triazol-5-yl)-phenol (**6**): 3′-hydroxy-4′-methoxyaceto phenone (200 mg, 1.0 equiv., 1.1204 mmol), 3,4,5-trimethoxybenzylamine (309 mg, 1.3 equiv., 1.565 mmol), 4-nitrophenyl azide (198 mg, 1.0 equiv., 1.1204 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 2:8) affording **6** (326 mg, 73% yield) as off white solid m.p. 183 ˚C. Spectroscopic data for compound (**6**) was consistent with previously reported data for this compound. (m.p. literature 194–195 °C) [3]

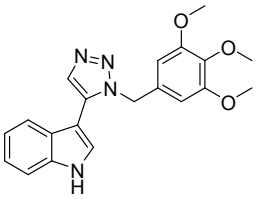
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 6.89 (d, *J* = 7.7 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.34 (s, 2H), 5.82 (s, 1H), 5.45 (s, 2H), 3.94 (s, 3H), 3.81 (s, 3H), 3.76 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.49, 147.6, 146.0, 137.9, 137.8, 133.1, 130.9, 121.1, 120.0, 115.3, 110.9, 104.7, 60.8, 56.1, 52.0. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}N_3O_5H$, 372.1553; found, 372.1544.



1-(3,4,5-Trimethoxybenzyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (**7**): 3′,4′,5′-trimethoxyaceto phenone (200 mg, 1.0 equiv., 0.951 mmol), 3,4,5-trimethoxybenzylamine (244 mg, 1.3 equiv., 1.237

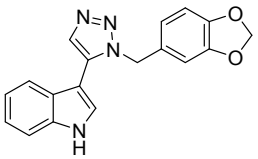
mmol), 4-nitrophenyl azide (156 mg, 1.0 equiv., 0.951 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 3:7) affording **7** (369 mg, 93% yield) as off white solid. m.p. 135 ˚C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 6.41 (s, 2H), 6.32 (s, 2H), 5.47 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.75 (d, *J* = 7.7 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.5, 139.1, 138.0, 137.9, 133.2, 131.4, 122.1, 106.5, 104.3, 60.8, 56.1, 52.0. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{25}N_3O_6H$, 416.1815; found, 416.1810.



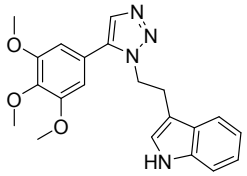
3-(1-(3,4,5-Trimethoxybenzyl)-1H-1,2,3-triazol-5-yl)-1*H*-indole (**8**): 3-acetylindole (200 mg, 1.0 equiv., 1.256 mmol), 3,4,5-trimethoxybenzylamine (322 mg, 1.3 equiv., 1.633 mmol), 4-nitrophenyl azide (206 mg, 1.0 equiv., 1.256 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 1:9) affording **8** (326 mg, 72% yield) as off white solid. m.p. 178 ˚C. Spectroscopic data for compound (**8**) was consistent with previously reported data for this compound. (m.p. literature 180–181 °C).[1]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.89 (s, 1H), 7.53 – 7.44 (m, 2H), 7.34 – 7.27 (m, 1H), 7.20 (m, 1H), 7.11 (s, 1H), 6.23 (s, 2H), 5.52 (s, 2H), 3.79 (s, 3H), 3.65 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.4, 137.7, 136.0, 133.7, 131.9, 131.4, 126.3, 124.3, 123.3, 121.1, 119.1, 111.7, 104.3, 102.3, 60.8, 56.0, 52.0. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{20}N_4O_3H$, 365.1608; found, 365.1607.



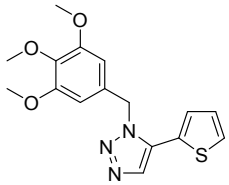
3-(1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1*H*-1,2,3-triazol-5-yl)-1*H*-indole (**9**): 3-acetylindole (200 mg, 1.0 equiv., 1.256 mmol), piperonylamine (247 mg, 1.3 equiv., 1.633 mmol), 4-nitrophenyl azide (206 mg, 1.0 equiv., 1.256 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 2:8) affording **9** (361 mg, 90% yield) as a brown solid. m.p. 196˚C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.89 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.31 (m, 1H), 7.25 – 7.18 (m, 1H), 7.10 (s, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.63 – 6.48 (m, 2H), 5.93 (s, 2H), 5.49 (s, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 133.6, 126.2, 124.0, 123.4, 121.2, 120.5, 119.2, 111.6, 108.4, 107.6, 101.2, 51.5. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{14}N_4O_2H$, 319.1189; found, 319.1190.



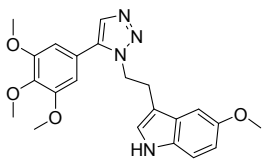
3-(2-(5-(3,4,5-Trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-indole (**10**): 3′,4′,5′-trimethoxyaceto phenone (300 mg, 1.0 equiv., 1.427 mmol), tryptamine (297 mg, 1.3 equiv., 1.855 mmol), 4-nitrophenyl azide (234 mg, 1.0 equiv., 1.427 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 4:6) affording **10** (451 mg, 84% yield) as a brown solid. m.p. 73 ˚C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.60 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.74 (s, 1H), 6.17 (s, 2H), 4.61 (t, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.63 (s, 6H), 3.39 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.4, 138.9, 138.5, 136.1, 132.8, 127.0, 122.5, 122.3, 122.2, 119.6, 118.1, 111.2, 111.2, 106.2, 60.9, 56.1, 48.7, 26.3. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{22}N_4O_3H$, 379.1764; found, 379.1764.



5-(Thiophen-2-yl)-1-(3,4,5-trimethoxybenzyl)-1*H*-1,2,3-triazole (**11**) 2-acetylthiophene (200 mg, 1.0 equiv., 1.585 mmol), 3,4,5-trimethoxybenzylamine (406 mg, 1.3 equiv., 2.061 mmol), 4-nitrophenyl azide (260 mg, 1.0 equiv., 1.585 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 6:4) affording **11** (511 mg, 97% yield) as slightly yellow semi solid.

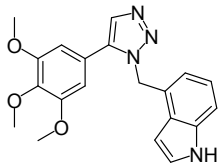
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.48 (d, *J* = 5.1 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.08 (d, *J* = 3.5 Hz, 1H), 6.32 (s, 2H), 5.57 (s, 2H), 3.81 (s, 3H), 3.76 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.5, 138.0, 134.0, 131.6, 130.6, 128.7, 128.2, 127.9, 126.7, 104.4, 60.8, 56.1, 52.2. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{17}N_3O_3S_1H$, 332.1063; found, 332.1057.



5-Methoxy-3-(2-(5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-indole (**12**): 3′,4′,5′-trimethoxyaceto phenone (200 mg, 1.0 equiv., 0.951 mmol), 5-methoxytryptamine (235 mg, 1.3 equiv., 1.237 mmol), 4-nitrophenyl azide (234 mg, 1.0 equiv., 0.951 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column

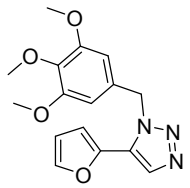
chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 3:7) affording **12** (291 mg, 75% yield) as off white solid. m.p. 152 ˚C.

^{1}H NMR (300 MHz, CDCl3) δ 7.87 (s, 1H), 7.58 (s, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.81 (dd, J = 8.7, 2.2 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 6.60 (d, J = 2.1 Hz, 1H), 6.12 (s, 2H), 4.59 (t, J = 6.8 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.64 (s, 6H), 3.38 (t, J = 6.6 Hz, 2H). **^{13}C NMR** (101 MHz, CDCl3) δ 154.2, 153.3, 138.7, 138.6, 132.8, 131.1, 127.5, 123.2, 122.2, 112.6, 111.8, 111.3, 106.0, 99.6, 60.8, 56.0, 55.7, 48.8, 26.3. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{24}N_4O_4H$, 409.1870; found, 409.1866.



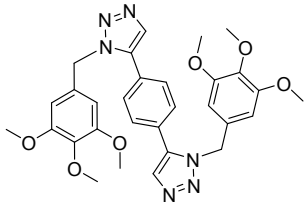
4-((5-(3,4,5-Trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-indole (**13**): 3′,4′,5′-trimethoxyaceto phenone (200 mg, 1.0 equiv., 0.951 mmol), 5-methoxytryptamine (181 mg, 1.3 equiv., 1.237 mmol), 4-nitrophenyl azide (156 mg, 1.0 equiv., 0.951 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 5:5) affording **13** (299 mg, 86% yield) as orange solid. m.p. 53 ˚C.

^{1}H NMR (300 MHz, CDCl3) δ 8.37 (s, 1H), 7.75 (s, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.10 (t, J = 7.7 Hz, 1H), 6.70 – 6.63 (m, 1H), 6.45 – 6.40 (m, 1H), 6.33 (s, 2H), 5.85 (s, 2H), 3.82 (s, 3H), 3.47 (s, 6H). **^{13}C NMR** (101 MHz, CDCl3) δ 153.3, 138.6, 138.3, 135.8, 133.0, 127.7, 125.3, 124.7, 122.2, 122.1, 118.2, 111.0, 105.9, 100.2, 60.8, 55.7, 50.4. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{20}N_4O_3H$, 365.1608; found, 365.1599.



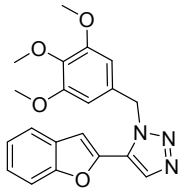
5-(Furan-2-yl)-1-(3,4,5-trimethoxybenzyl)-1*H*-1,2,3-triazole (**14**): 2-acetylfuran (200 mg, 1.0 equiv., 1.816 mmol), 3,4,5-trimethoxybenzylamine (466 mg, 1.3 equiv., 2.361 mmol), 4-nitrophenyl azide (298 mg, 1.0 equiv., 1.816 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 6:4) affording **14** (467 mg, 82% yield) as orange solid. m.p. 62 ˚C.

^{1}H NMR (300 MHz, CDCl3) δ 7.86 (s, 1H), 7.57 (dd, J = 1.8, 0.7 Hz, 1H), 6.56 (dd, J = 3.4, 0.7 Hz, 1H), 6.51 (dd, J = 3.4, 1.8 Hz, 1H), 6.39 (s, 2H), 5.69 (s, 2H), 3.80 (s, 3H), 3.76 (s, 6H). **^{13}C NMR** (101 MHz, CDCl3) δ 153.4, 143.6, 141.3, 137.8, 132.4, 130.6, 128.9, 111.9, 110.6, 104.3, 60.7, 56.0, 52.9. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{17}N_3O_4H$, 316.1291; found, 316.1283



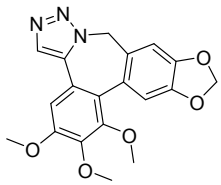
1,4-bis(1-(3,4,5-trimethoxybenzyl)-1*H*-1,2,3-triazol-5-yl)benzene (**15**): 1,4-diacetylbenzene (200 mg, 1.0 equiv., 1.233 mmol), 3,4,5-trimethoxybenzylamine (632 mg, 2.6 equiv., 3.21 mmol), 4-nitrophenyl azide (405 mg, 2.0 equiv., 2.466 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 0:10) affording **15** (555 mg, 79% yield) as slightly pink solid. m.p. 210 ˚C.

^{1}H NMR (300 MHz, CDCl3) δ 7.77 (s, 2H), 7.35 (s, 4H), 6.28 (s, 4H), 5.50 (s, 4H), 3.81 (s, 6H), 3.72 (s, 12H). **^{13}C NMR** (101 MHz, CDCl3) δ 153.6, 137.9, 136.9, 133.5, 130.6, 129.4, 128.2, 104.3, 60.8, 56.1, 52.2. **HRMS** (ESI-quadrupole) *m/z*: [M + H] $^+$ calcd for $C_{30}H_{32}N_6O_6H$, 573.2455; found, 573.2431.



5-(Benzofuran-2-yl)-1-(3,4,5-trimethoxybenzyl)-1*H*-1,2,3-triazole (**16**): 2-acetylbenzofuran (200 mg, 1.0 equiv., 1.249 mmol), 3,4,5-trimethoxybenzylamine (205 mg, 1.3 equiv., 1.249 mmol), 4-nitrophenyl azide (320 mg, 1.0 equiv., 1.623.749 mmol), 4 Å molecular sieves (50 mg) and toluene (0.8 mL), under argon atmosphere. Reaction time is 24 h. The product was purified by flash column chromatography (first with CH_2Cl_2 followed by petroleum ether/EtOAc = 6:4) affording **16** (343 mg, 75% yield) as slightly yellow solid. m.p. 71 ˚C.

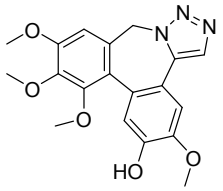
^{1}H NMR (300 MHz, CDCl3) δ 8.02 (s, 1H), 7.57 (dd, J = 13.1, 8.3 Hz, 2H), 7.37 (t, J = 7.7 Hz, 1H), 7.28 (dd, J = 9.1, 5.8 Hz, 1H), 6.91 (s, 1H), 6.43 (s, 2H), 5.80 (s, 2H), 3.77 (s, 3H), 3.66 (s, 6H). **^{13}C NMR** (101 MHz, CDCl3) δ 154.8, 153.4, 142.9, 137.8, 133.7, 130.3, 128.6, 127.7, 125.8, 123.8, 121.6, 111.2, 106.9, 104.5, 60.7, 55.9, 53.4. **HRMS** (ESI-quadrupole) *m/z*: [M + H] $^+$ calcd for $C_{20}H_{19}N_3O_4H$, 366.1448; found, 366.1436.



1,2,3-Trimethoxy-9*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*e*]benzo[*c*][1,2,3]triazolo[1,5-*a*]azepine (**5a**): To a stirred solution of compound **5** (100 mg, 1.0 equiv., 0,271 mmol) in dry dichloromethane (2.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (128 mg, 1.1 equiv., 0.298 mmol) in dry dichloromethane (2.0 mL) and $BF_3{\cdot}Et_2O$ (100 µL, 3.0 equiv., 0.812) at -40 °C under argon atmosphere and

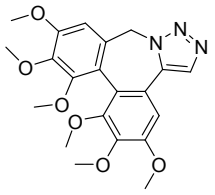
the mixture stirred for 3 h. After confirmation that the starting material is consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted 3x with DCM, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified via column chromatography (silica gel) were as eluent was used petroleum ether/EtOAc = 6:4. Affording **5a** (74 mg, 74% yield) as off white solid. m.p. 180 ˚C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.13 (s, 1H), 6.94 (s, 1H), 6.84 (s, 1H), 6.04 (s, 1H), 5.96 (s, 1H), 5.53 (d, *J* = 13.9 Hz, 1H), 4.89 (d, *J* = 13.9 Hz, 1H), 3.98 (d, *J* = 11.7 Hz, 6H), 3.68 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.1, 152.2, 147.5, 147.4, 143.5, 135.9, 131.3, 129.4, 127.5, 124.1, 122.0, 112.2, 108.2, 107.7, 101.6, 61.2, 61.1, 56.2, 51.5. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{17}N_3O_5H$, 368.1240; found, 368.1241.



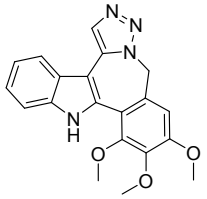
3,11,12,13-Tetramethoxy-9*H*-dibenzo[*c,e*][1,2,3]triazolo[1,5-*a*]azepin-2-ol (**6a**): To a stirred solution of compound **6** (100 mg, 1.0 equiv., 0,269 mmol) in dry dichloromethane (2.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (127 mg, 1.1 equiv., 0.296 mmol) in dry dichloromethane (2.0 mL) and $BF_3{\cdot}Et_2O$ (100 µL, 3.0 equiv., 0.808) at -40 °C under argon atmosphere and the mixture stirred for 3 h. After confirmation that the starting material is consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted 3x with DCM, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified via reparative TLC were as eluent was used DCM/Acetone = 9:1. Affording **6a** (23 mg, 23% yield) as off white solid. m.p. 226 ˚C.

^{1}H NMR (600 MHz, $C_2D_2Cl_4$) δ 7.78 (s, 1H), 7.37 (s, 1H), 7.12 (s, 1H), 6.78 (s, 1H), 5.52 (d, *J* = 13.9 Hz, 1H), 4.90 (d, *J* = 13.9 Hz, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.48 (s, 3H). **^{13}C NMR** (151 MHz, $C_2D_2Cl_4$) δ 146.4, 145.1, 142.7, 130.8, 125.2, 123.9, 114.5, 114.3, 107.4, 61.1, 60.9, 56.2, 56.0, 52.0. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{19}N_3O_5H$, 370.1397; found, 370.1397.



1,2,3,11,12,13-Hexamethoxy-9*H*-dibenzo [*c, e*][1,2,3]triazolo[1,5-*a*]azepine (**7a**): To a stirred solution of compound **7** (100 mg, 1.0 equiv., 0,241 mmol) in dry dichloromethane (2.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (114 mg, 1.1 equiv., 0.265 mmol) in dry dichloromethane (2.0 mL) and $BF_3{\cdot}Et_2O$ (90 µL, 3.0 equiv., 0.722) at -40 °C under argon atmosphere and the mixture stirred for 3 h. After confirmation that the starting material is consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted 3x with DCM, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified via column chromatography (silica gel) were as eluent was used petroleum ether/EtOAc = 2:8. Affording **7a** (55 mg, 55% yield) as off white solid. m.p. 82 ˚C.

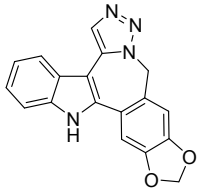
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 6.83 (s, 1H), 6.77 (s, 1H), 5.54 (d, *J* = 13.8 Hz, 1H), 4.93 (d, *J* = 13.8 Hz, 1H), 3.96 (s, 6H), 3.90 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 3.61 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.5, 153.5, 153.1, 152.9, 142.5, 142.2, 135.9, 132.3, 131.0, 122.3, 120.5, 120.4, 107.1, 106.6, 61.3, 61.1, 61.0, 60.9, 56.2, 56.0. **HRMS** (ESI-quadrupole) *m/z*: [M + H] $^+$ calcd for $C_{21}H_{23}N_3O_6H$, 414.1659; found, 414.1649.



11,12,13-Trimethoxy-9,14-dihydrobenzo[5,6][1,2,3]triazolo[1',5':1,2]azepino[4,3-*b*]indole (**8a**) : To a stirred solution of compound **8** (100 mg, 1.0 equiv., 0,274 mmol) in dry dichloromethane (2.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (130 mg, 1.1 equiv., 0.302 mmol) in dry dichloromethane (2.0 mL) and $BF_3{\cdot}Et_2O$ (102 µL, 3.0 equiv., 0.823) at -40 °C under argon atmosphere and the mixture stirred for 3 h. After confirmation that the starting material is consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted 3x with DCM, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified via column chromatography (silica gel) were as eluent was used petroleum ether/EtOAc = 1:9. Affording **8a** (93.7 mg, 94% yield) as off white solid. m.p. 187 ˚C.

1 mmol scale synthesis of (**8a**): To a stirred solution of compound **8** (400 mg, 1.0 equiv., 1,098 mmol) in dry dichloromethane (8.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (519 mg, 1.1 equiv., 1.207 mmol) in dry dichloromethane (8 mL) and $BF_3{\cdot}Et_2O$ (406 µL, 3.0 equiv., 3.29) at -40 °C under argon atmosphere and the mixture stirred for 3 h. After confirmation that the starting material is consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted 3x with DCM, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified via column chromatography (silica gel) were as eluent was used petroleum ether/EtOAc = 1:9. Affording **8a** (310 mg, 78% yield) as off white solid.

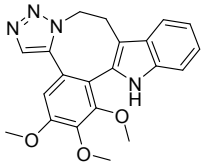
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.09 (s, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.71 (s, 1H), 5.78 (s, 2H), 3.94 (s, 3H), 3.76 (s, 3H), 3.11 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.0, 155.0, 154.4, 152.1, 143.7, 141.9, 130.6, 129.2, 128.9, 127.2, 125.3, 121.7, 114.7, 104.8, 60.6, 60.2, 57.3, 56.1, 47.7. **HRMS** (ESI-quadrupole) *m/z*: [M + H] $^+$ calcd for $C_{20}H_{18}N_4O_3H$, 363.1451; found, 363.1452.



9,15-Dihydro-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':5,6][1,2,3]triazolo[1',5':1,2]azepino[4,3-*b*]indole (**9a**) : To a stirred solution of compound **9** (100 mg, 1.0 equiv., 0,314 mmol) in dry dichloromethane (2.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (149 mg, 1.1 equiv., 0.346 mmol) in dry dichloromethane (2.0 mL) and $BF_3{\cdot}Et_2O$ (116 µL, 3.0 equiv., 0.942) at -40 °C under argon atmosphere

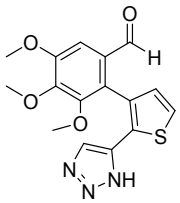
and the mixture stirred for 3 h. After confirmation that the starting material is consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted 3x with DCM, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified via column chromatography (silica gel) were as eluent was used petroleum ether/EtOAc = 1:9. Affording **9a** (61.7 mg, 62% yield) as off white solid. m.p. 208 ˚C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 9.3 Hz, 2H), 6.87 (s, 1H), 5.99 – 5.95 (m, 3H), 5.75 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.3, 155.4, 148.7, 148.5, 141.9, 130.5, 129.8, 129.6, 128.1, 123.3, 123.2, 122.1, 121.2, 106.6, 105.6, 101.9, 59.9, 48.2. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{12}N_4O_2H$, 317.1032; found, 317.1031.



1,2,3-Trimethoxy-10,15-dihydro-9*H*-benzo[6,7][1,2,3]triazolo[1',5':1,8]azocino[5,4-*b*]indole (**10a**) : To a stirred solution of compound **10** (100 mg, 1.0 equiv., 0,264 mmol) in dry dichloromethane (2.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (125 mg, 1.1 equiv., 0.291 mmol) in dry dichloromethane (2.0 mL) and $BF_3{\cdot}Et_2O$ (98 µL, 3.0 equiv., 0.793) at -40 °C under argon atmosphere and the mixture stirred for 3 h. After confirmation that the starting material is consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted 3x with DCM, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified via column chromatography (silica gel) were as eluent was used petroleum ether/EtOAc = 3:7. Affording **10a** (30 mg, 30% yield) as off white solid. m.p. 184 ˚C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.02 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.06 (s, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 4.76 (m, 2H), 3.94 (s, 3H), 3.77 (s, 3H), 3.00 (s, 3H), 2.42 – 2.32 (m, 1H), 1.79 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 177.1, 153.3, 153.1, 144.6, 143.0, 136.8, 134.2, 128.4, 126.4, 121.9, 121.8, 121.4, 108.7, 63.0, 60.6, 60.3, 56.1, 46.8, 34.7. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}N_4O_3H$, 377.1608; found, 377.1602.



2-(2-(1*H*-1,2,3-triazol-5-yl)thiophen-3-yl)-3,4,5-trimethoxybenzaldehyde (**11ab**) : To a stirred solution of compound **11** (100 mg, 1.0 equiv., 0.302 mmol) in dry dichloromethane (2.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) PIFA (143 mg, 1.1 equiv., 0.332 mmol) in dry dichloromethane (2.0 mL) and $BF_3{\cdot}Et_2O$ (112 µL, 3.0 equiv., 0.905) at -40 °C under argon atmosphere and the mixture stirred for 3 h. After confirmation that the starting material is consumed via TLC the reaction was quenched with $NaHCO_3$ solution and extracted 3x with DCM, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified via column chromatography (silica gel) were as eluent was used Petroleum ether/EtOAc = 4:6. Affording **11ab** (30 mg, 30% yield) as slightly yellow semi solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.88 (s, 1H), 7.43 (d, *J* = 3.6 Hz, 1H), 7.36 (m, 1H), 7.14 (s, 1H), 7.11 (m, 1H), 3.99 (s, 1H), 3.95 (d, *J* = 3.4 Hz, 8H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 191.2, 153.6, 143.6, 132.1, 131.7, 127.7, 125.8, 125.1, 106.8, 61.0, 56.3. **HRMS** (ESI-quadrupole) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}N_3O_4S_1H$, 346.0855; found, 346.0843.

Separation of atropoisomers of compound 7a by using Chiral HPLC

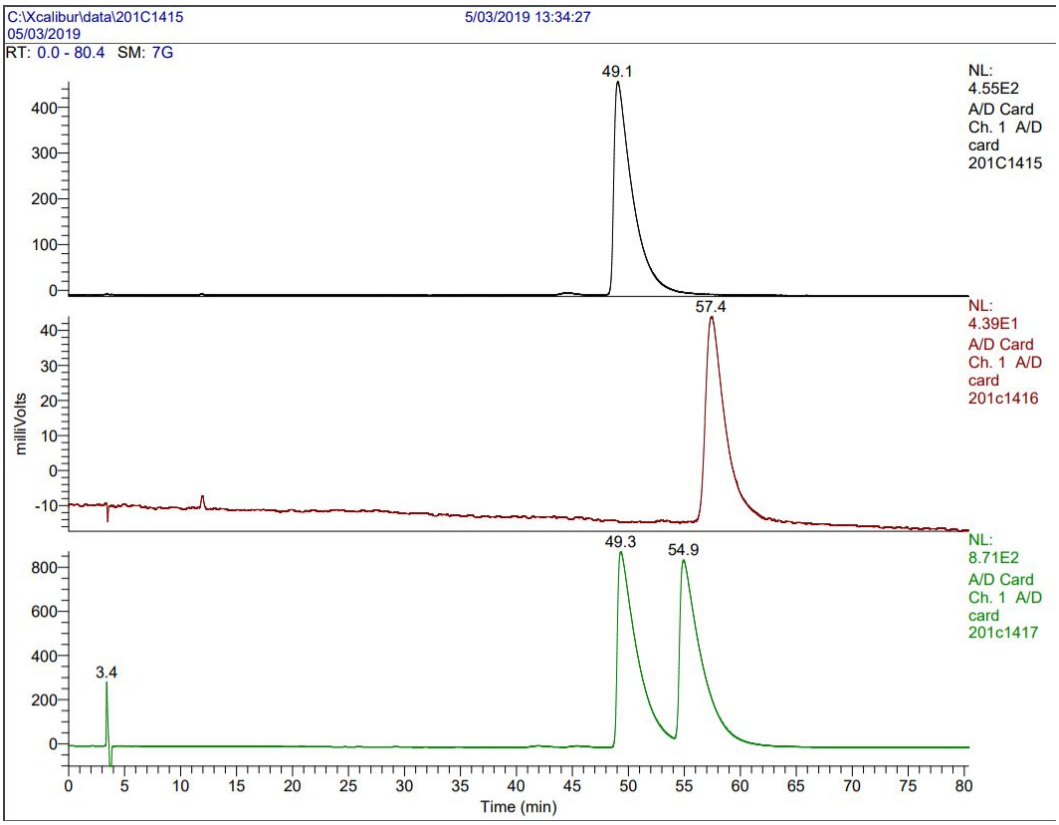


Figure S1. Device and method details for separation of atropoisomers. Device: ***HPLC system*** Waters Alliance 2695; ***detector*** Waters 2487 UV; **Column**: ***Analytic***: Daicel Chiralpak IB, 4.6 mm x 250 mm, 5 µL ***Semi-prep***: Daicel Chiralpak IB, 10 mm x 250 mm, 5 µL; **Method**: Solvent: heptane/ethylacetate (80/20), Flow: 1 ml/min (analytic), 5 ml/min (semi-prep).

References

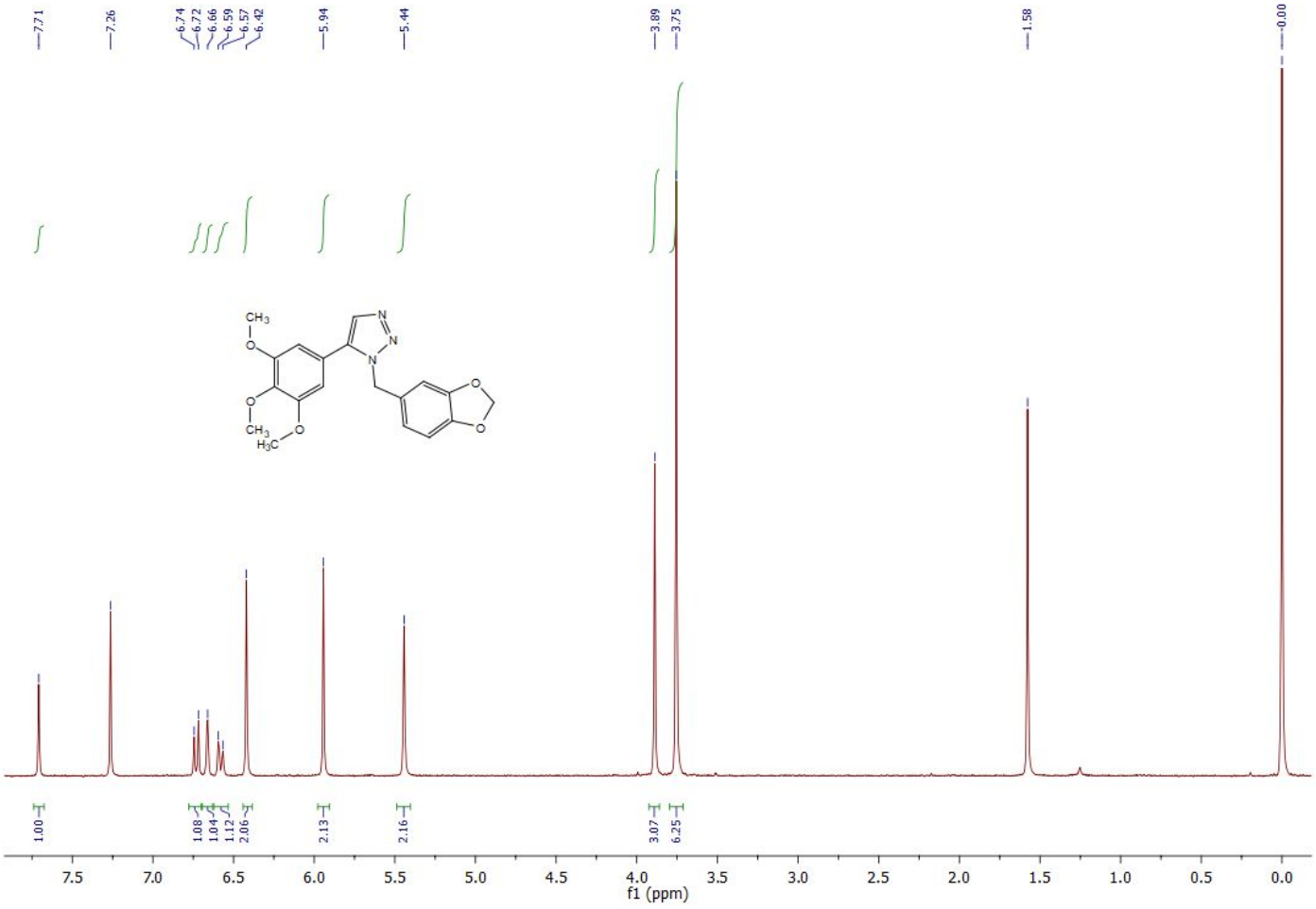
(1) Thomas, J.; Jana, S.; John, J.; Liekens, S.; Dehaen, W.; A general metal-free route towards the synthesis of 1,2,3-triazoles from readily available primary amines and ketones. *Chem. Commun.* **2016**, *52*, 2885-2888.

(2) Faucher, N.; Ambroise, Y.; Cintrat, J.-C.; Doris, E.; Pillon, F.; Rousseau, B.; Highly Chemoselective Hydrogenolysis of Iodoarenes. *J. Org. Chem.* **2002**, *67*, 932-934.

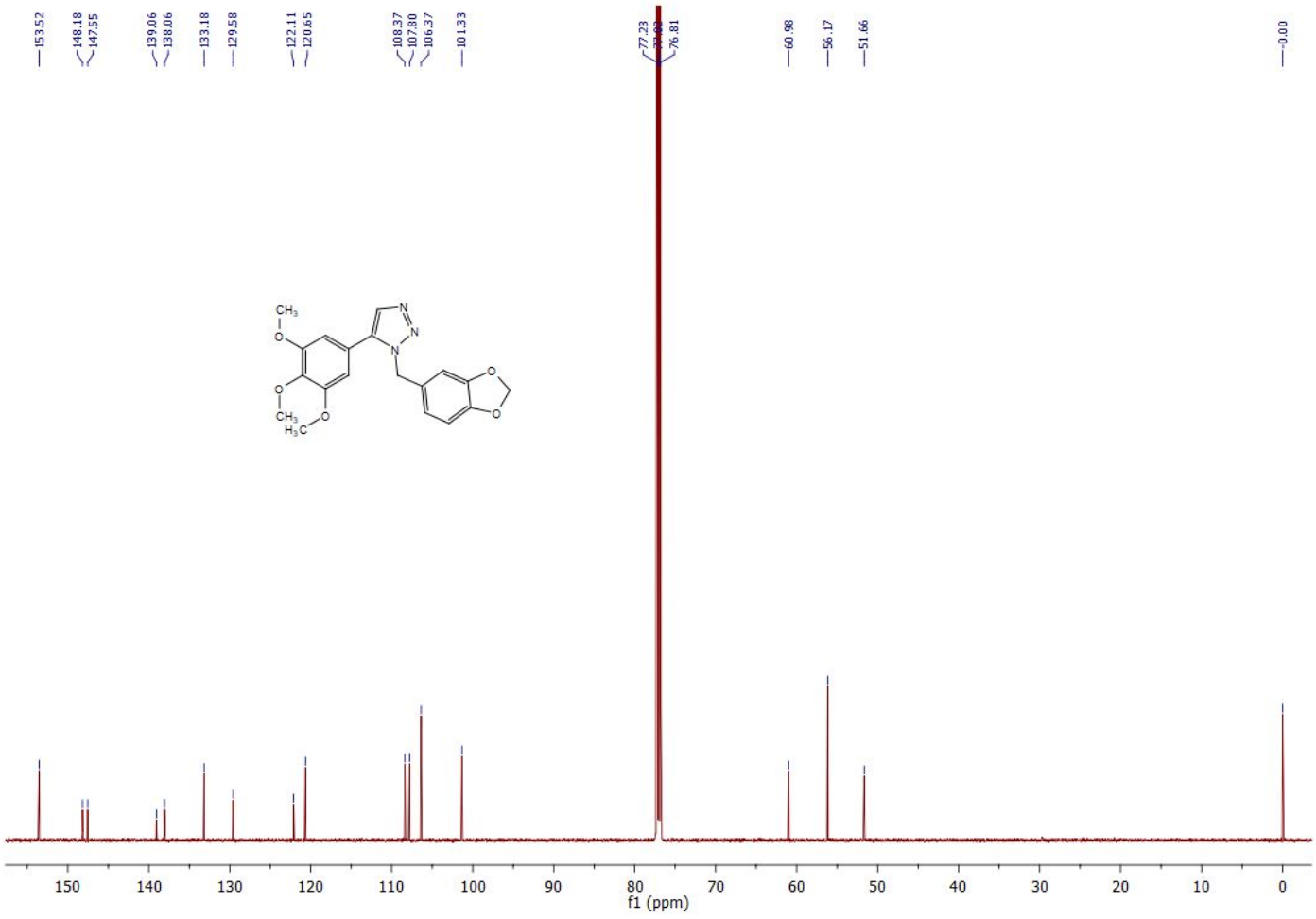
(3) Odlo, K.; Fournier-Dit-Chabert, J.; Ducki, S.; Gani, O. A. B. S. M.; Sylte, I.; Hansen, T. V.; 1,2,3-Triazole analogs of combretastatin A-4 as potential microtubule-binding agents. *Bioorg. Med. Chem.* **2010**, *18*, 6874-6885.

^{1}H and ^{13}C NMR spectra

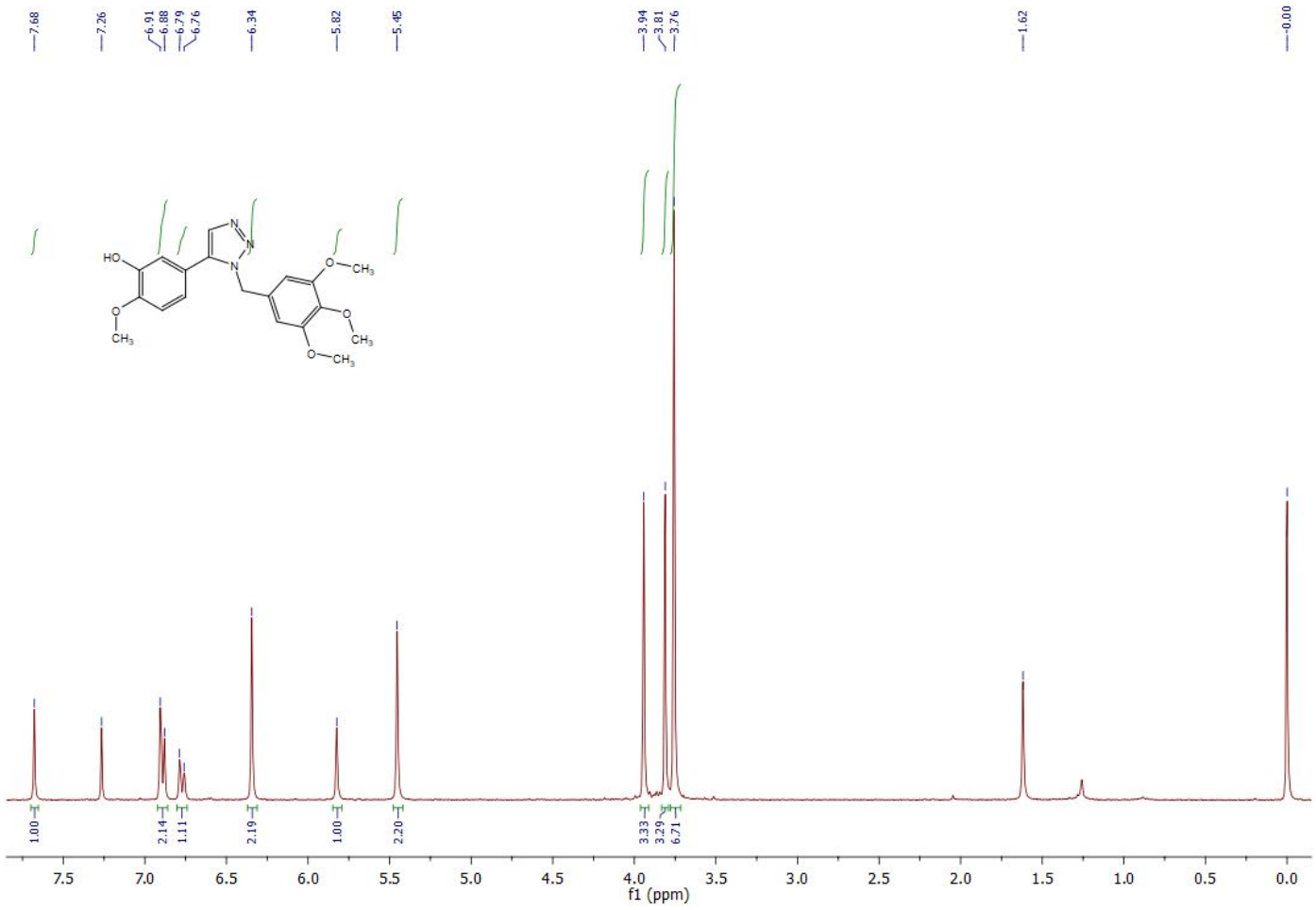
^{1}H NMR Spectra of (**5**) (300 MHz, $CDCl_3$):



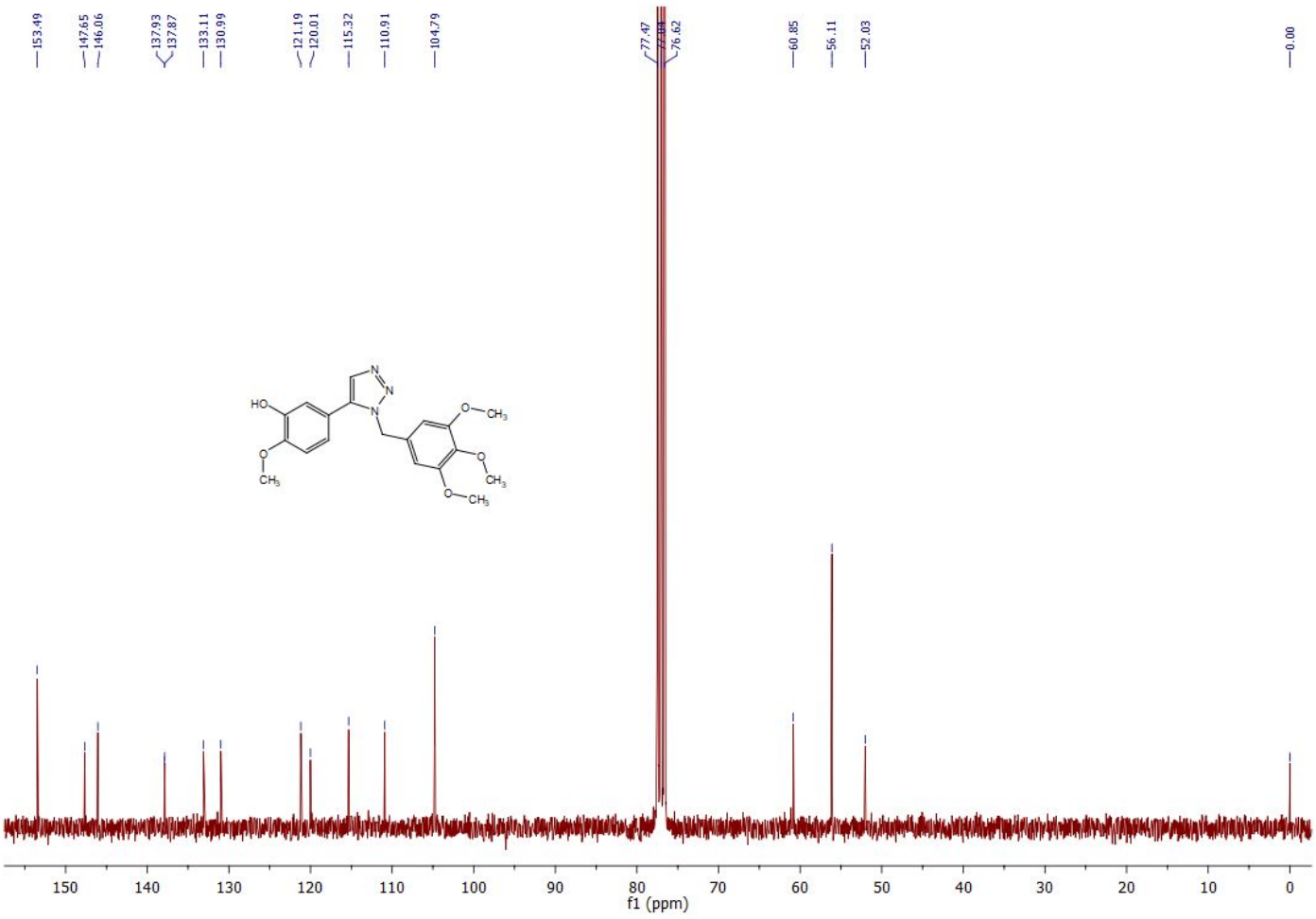
^{13}C NMR Spectra of (**5**) (600 MHz, $CDCl_3$):



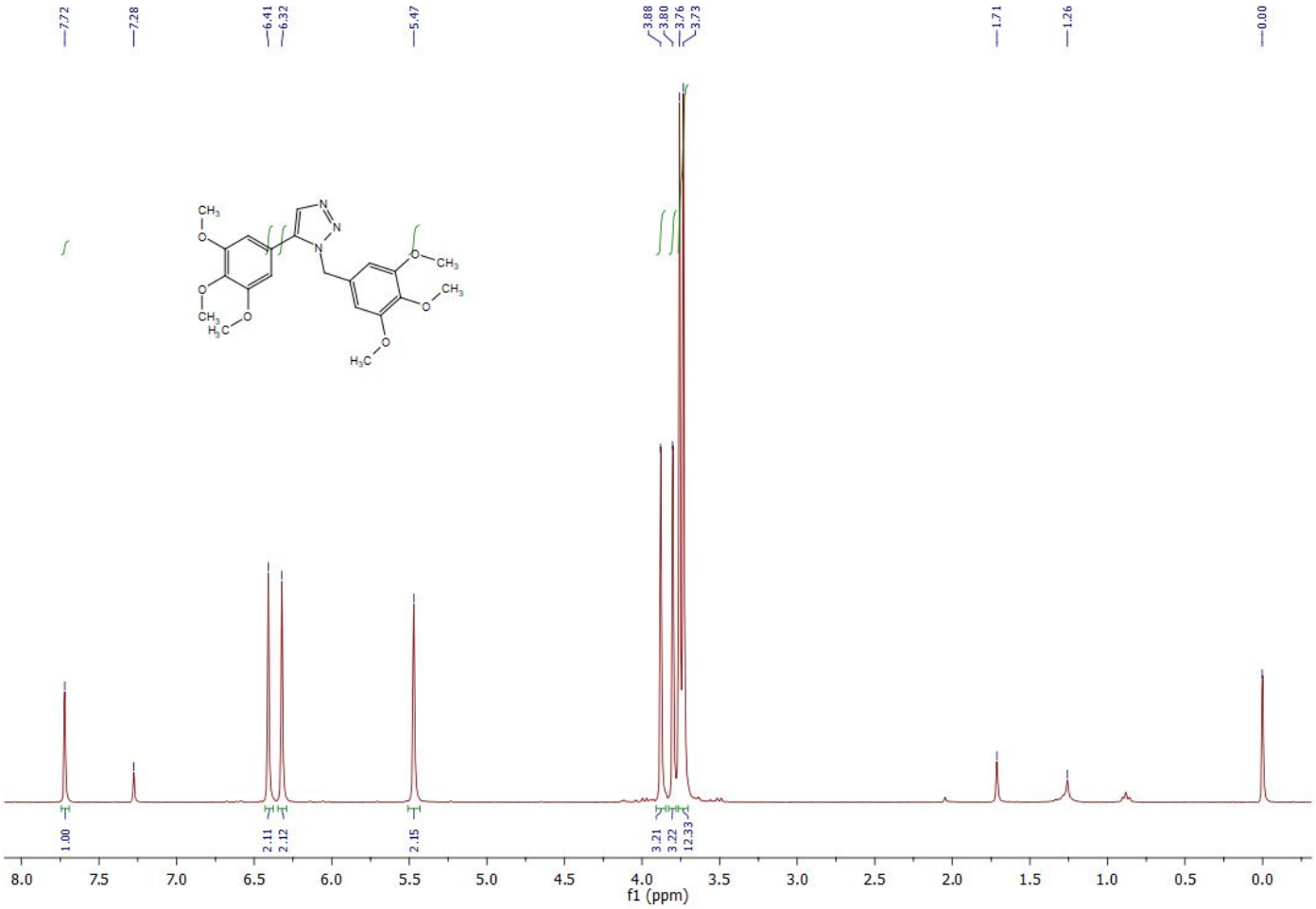
^{1}H NMR Spectra of (**6**) (300 MHz, $CDCl_3$):



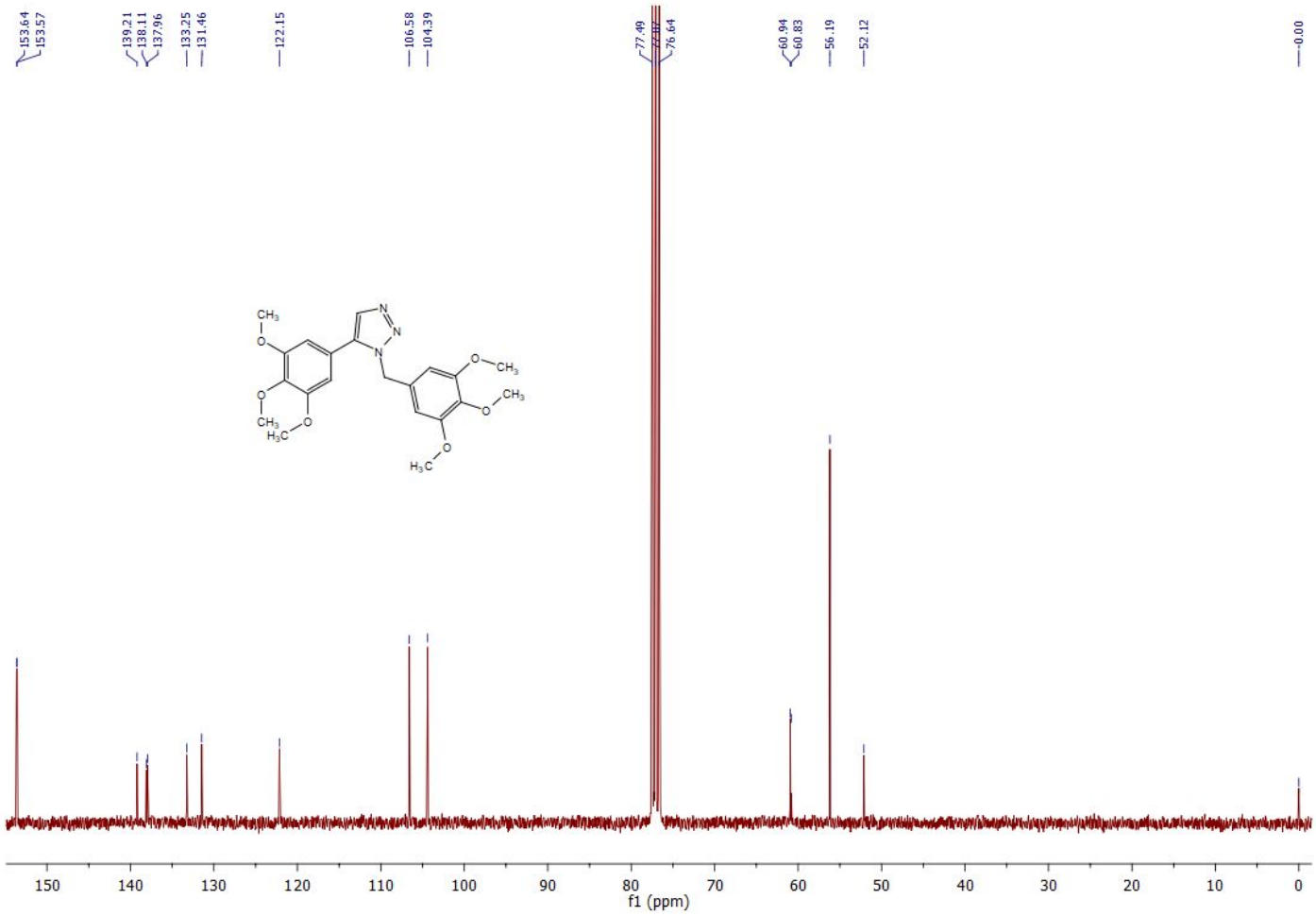
^{13}C NMR Spectra of (**6**) (300 MHz, $CDCl_3$):



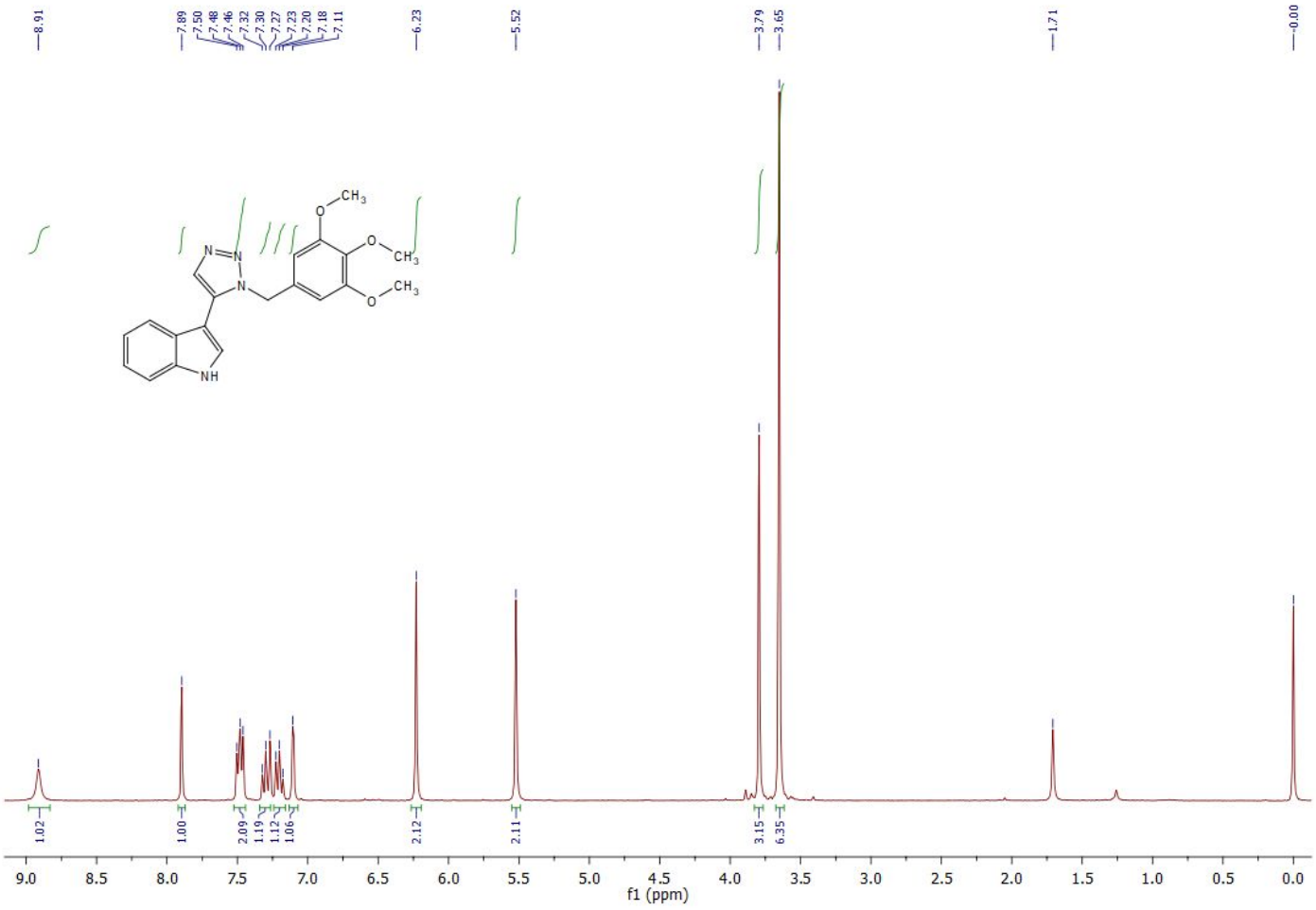
^{1}H NMR Spectra of (**7**) (300 MHz, $CDCl_3$):



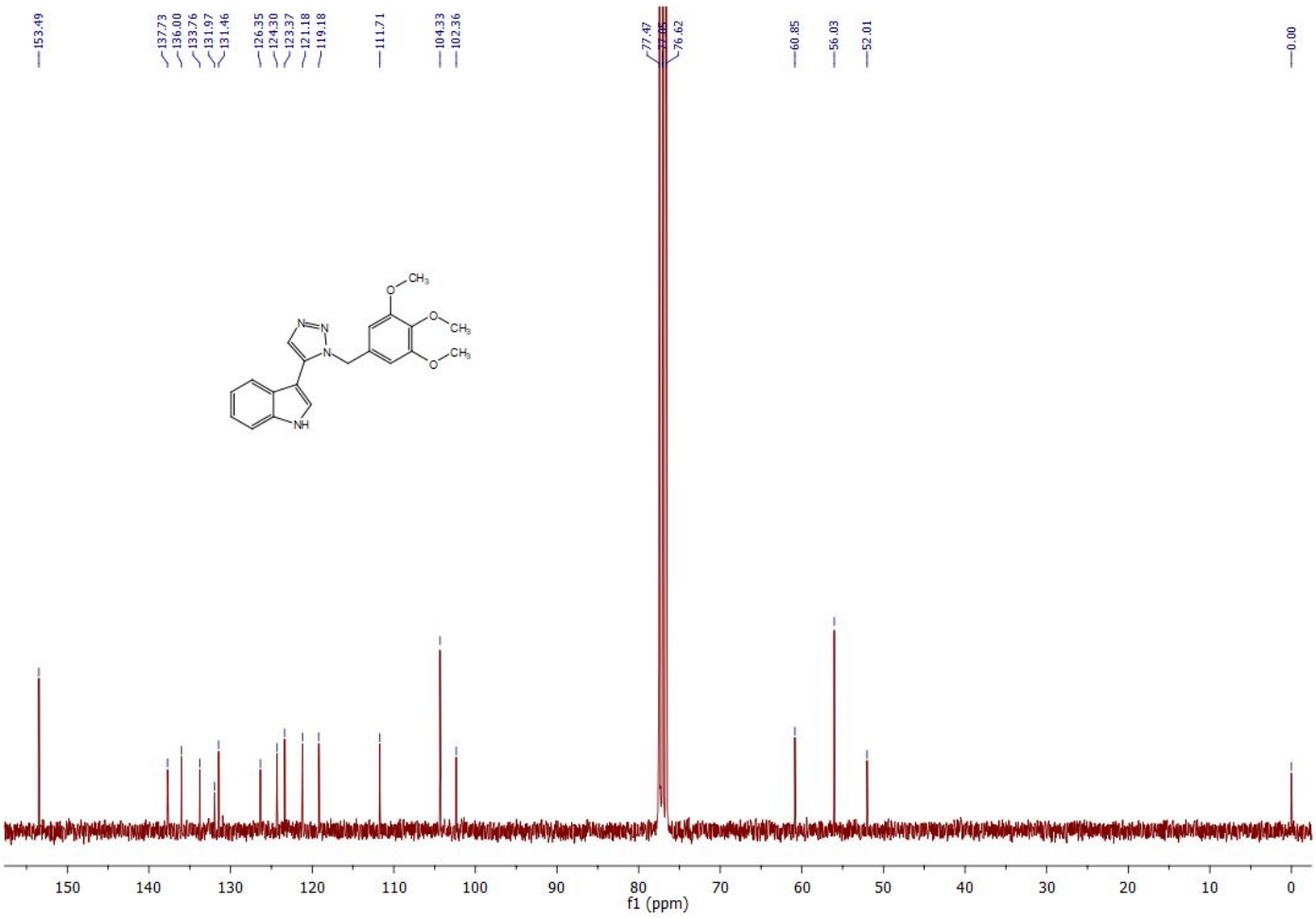
^{13}C NMR Spectra of (**7**) (300 MHz, $CDCl_3$):



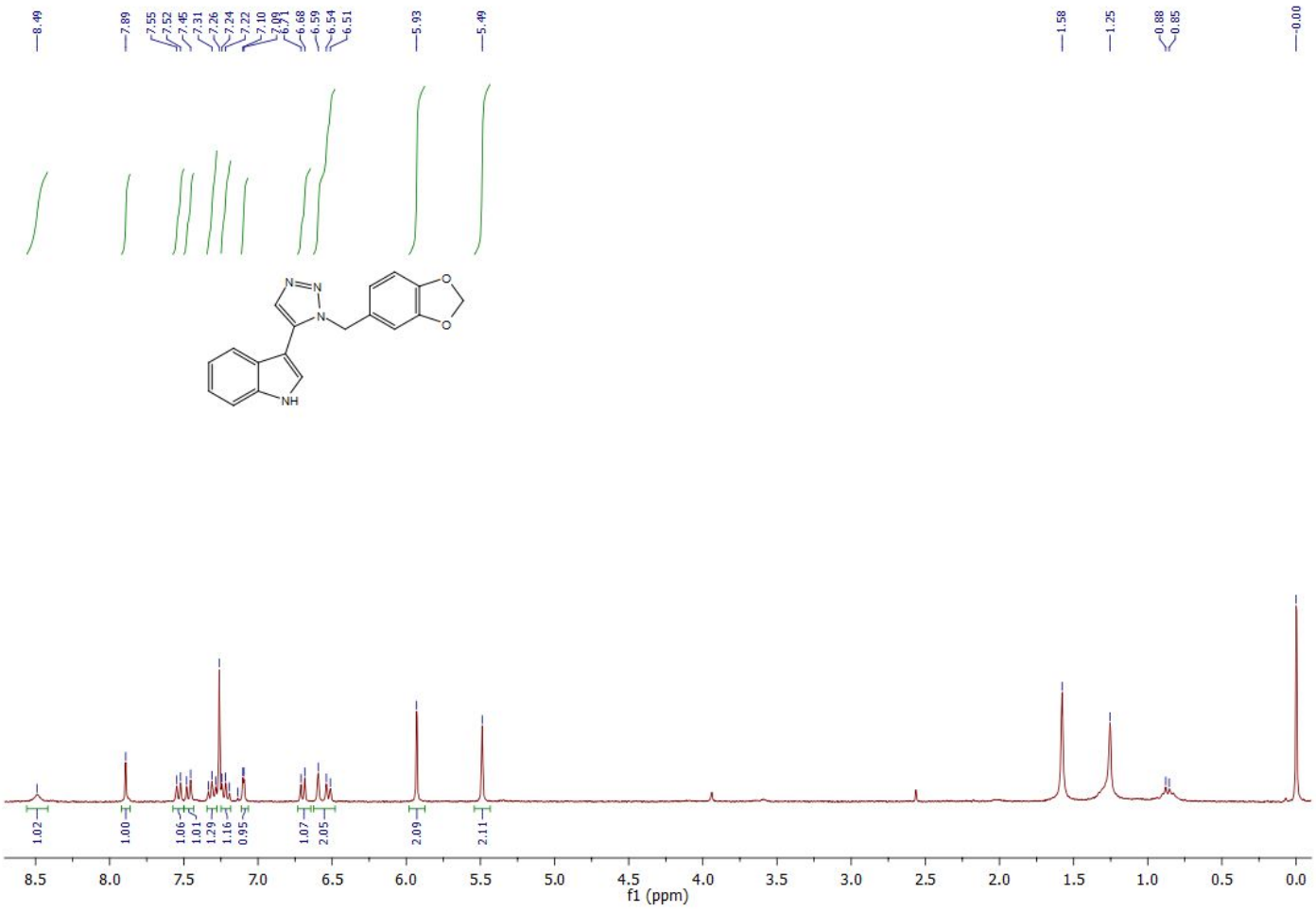
^{1}H NMR Spectra of (**8**) (300 MHz, $CDCl_3$):



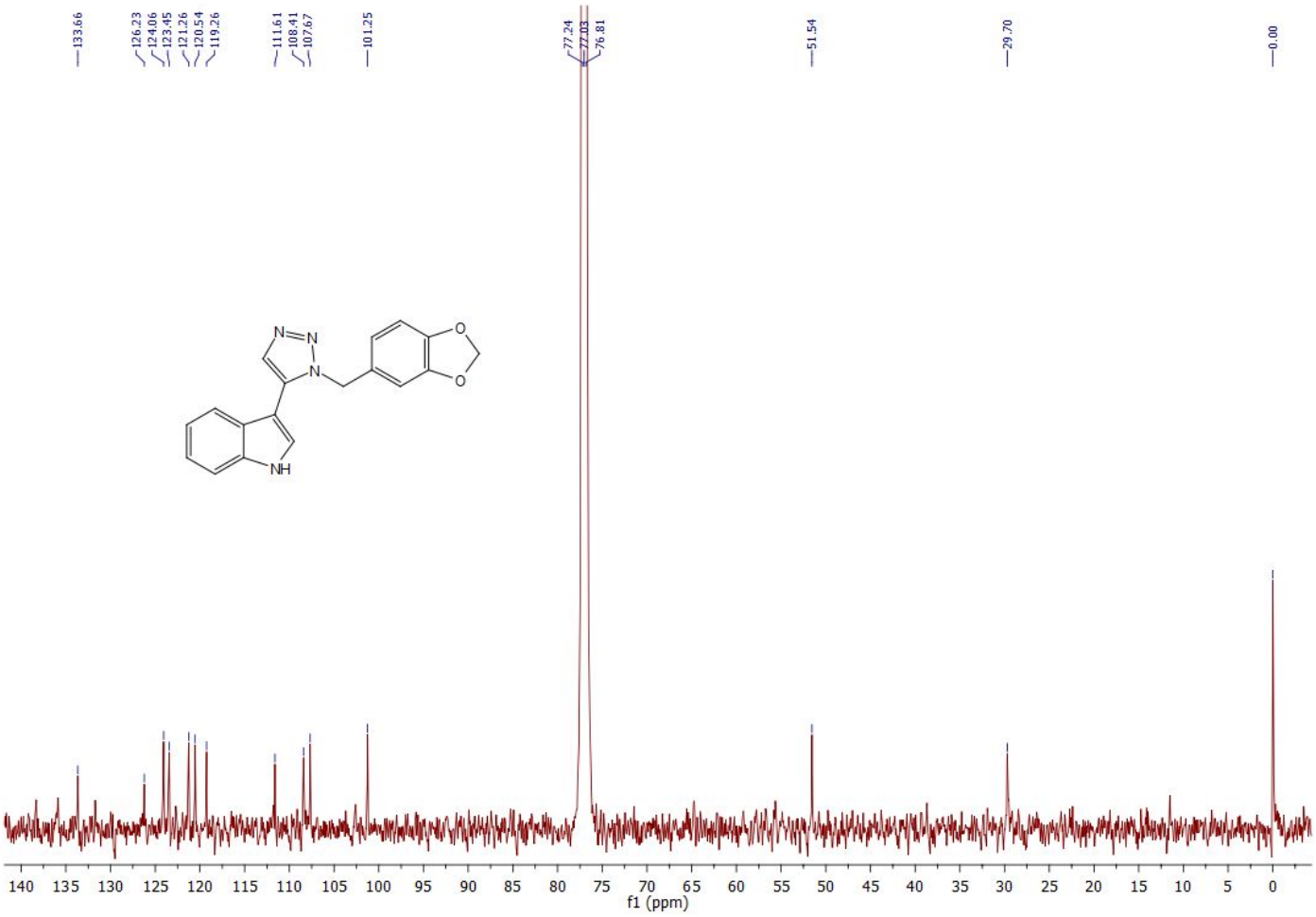
^{13}C NMR Spectra of (**8**) (300 MHz, $CDCl_3$):



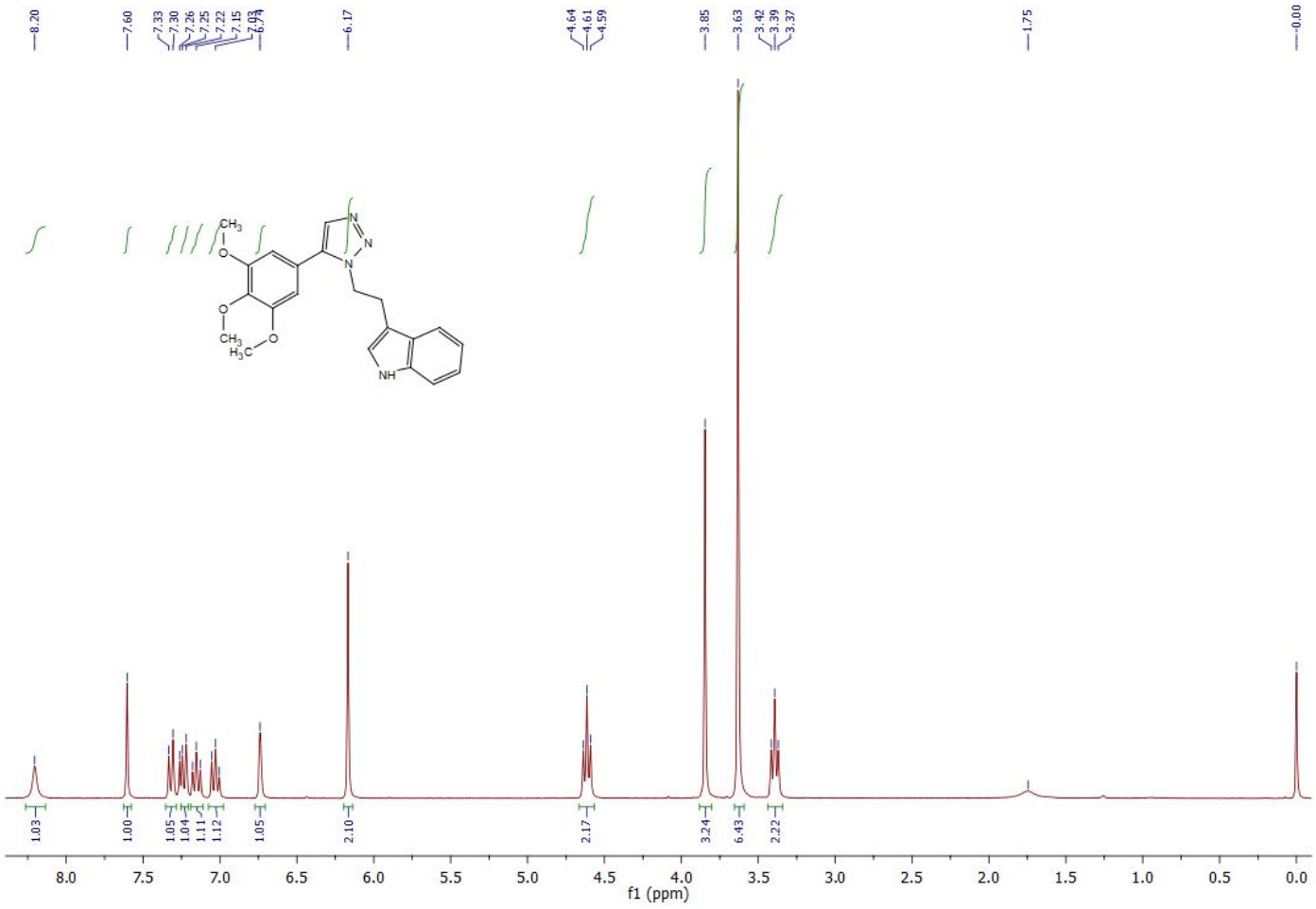
^{1}H NMR Spectra of (**9**) (300 MHz, $CDCl_3$):



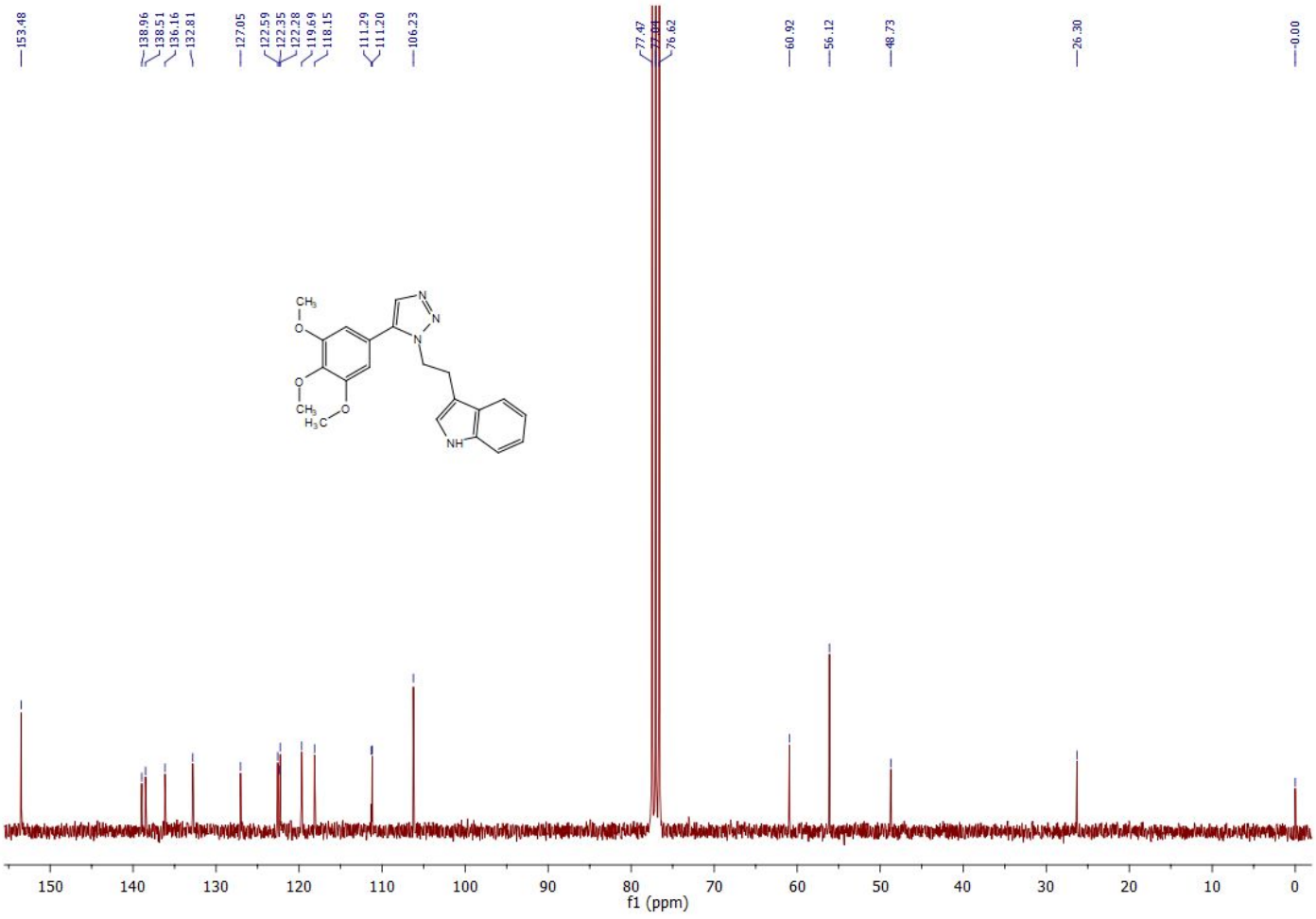
^{13}C NMR Spectra of (**9**) (600 MHz, $CDCl_3$):



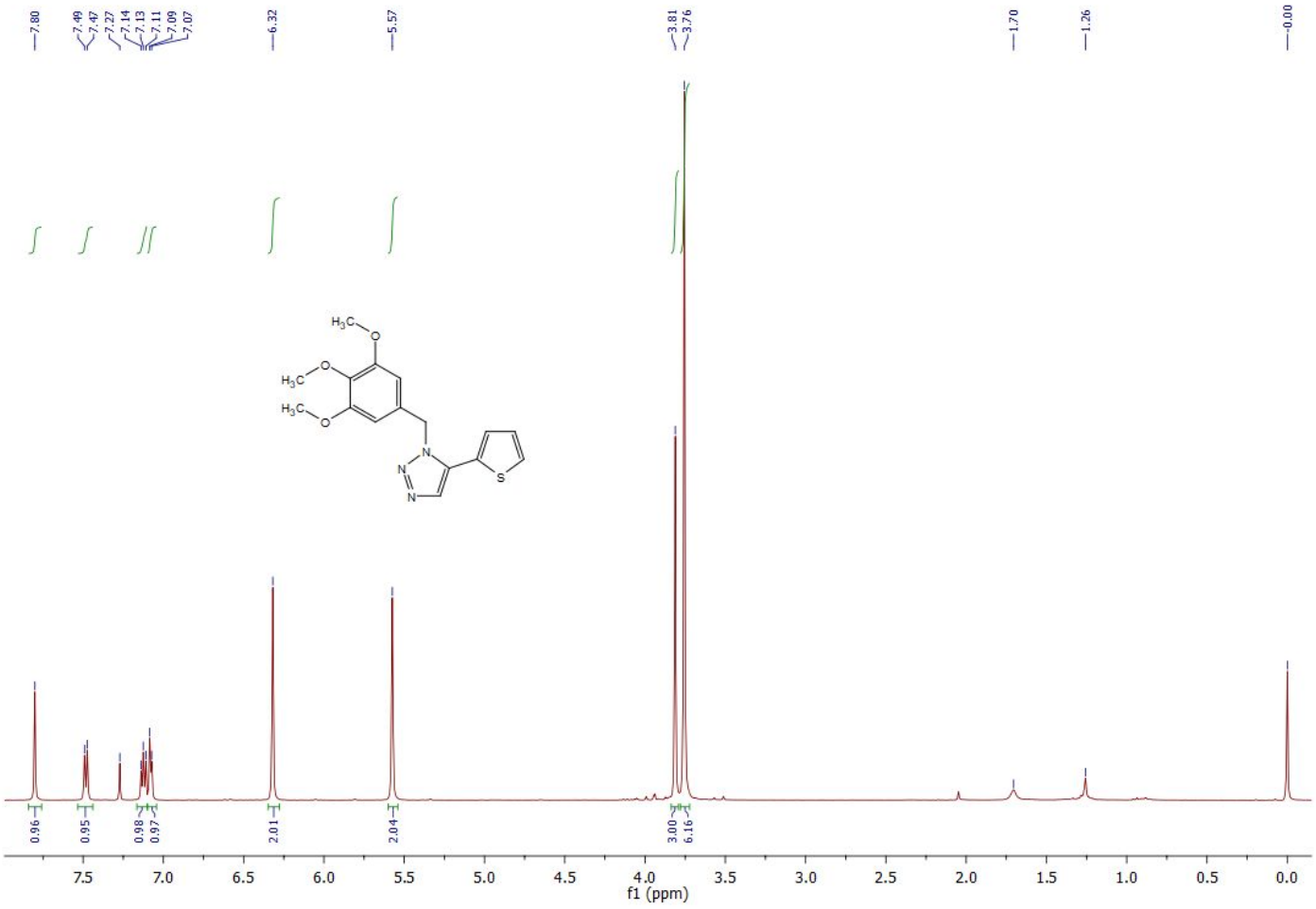
^{1}H NMR Spectra of (**10**) (300 MHz, $CDCl_3$):



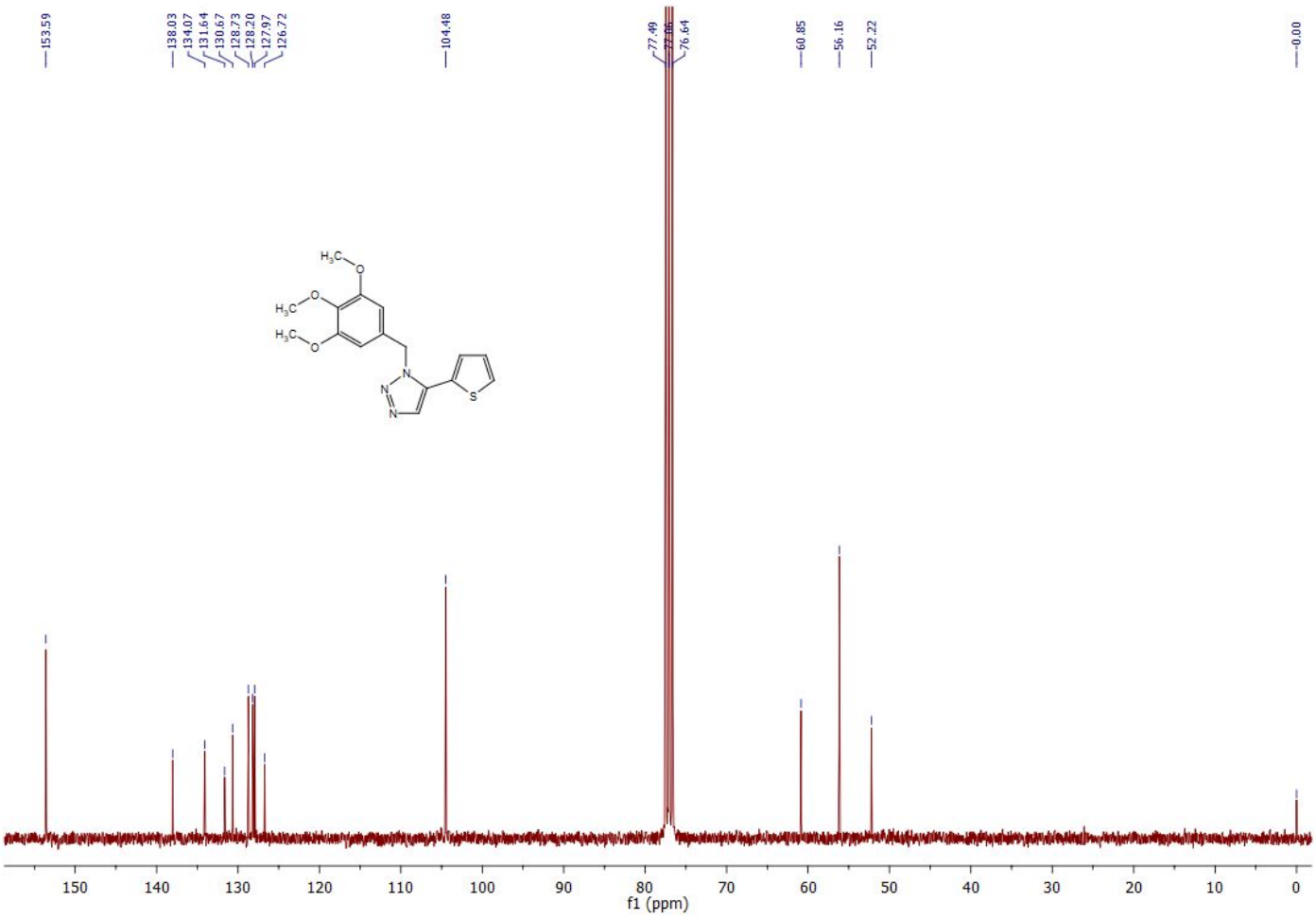
^{13}C NMR Spectra of (**10**) (300 MHz, $CDCl_3$):



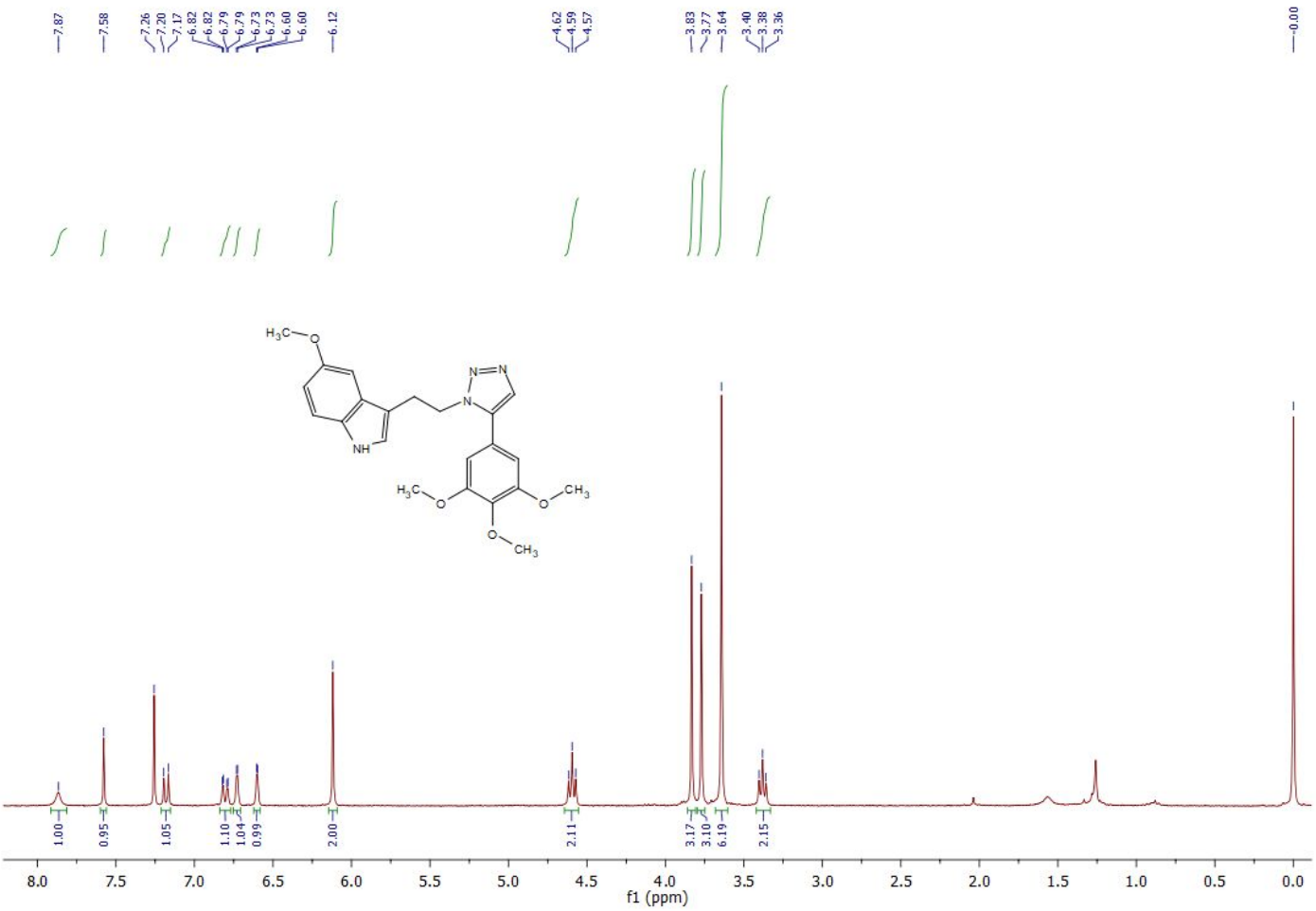
^{1}H NMR Spectra of (**11**) (300 MHz, $CDCl_3$):



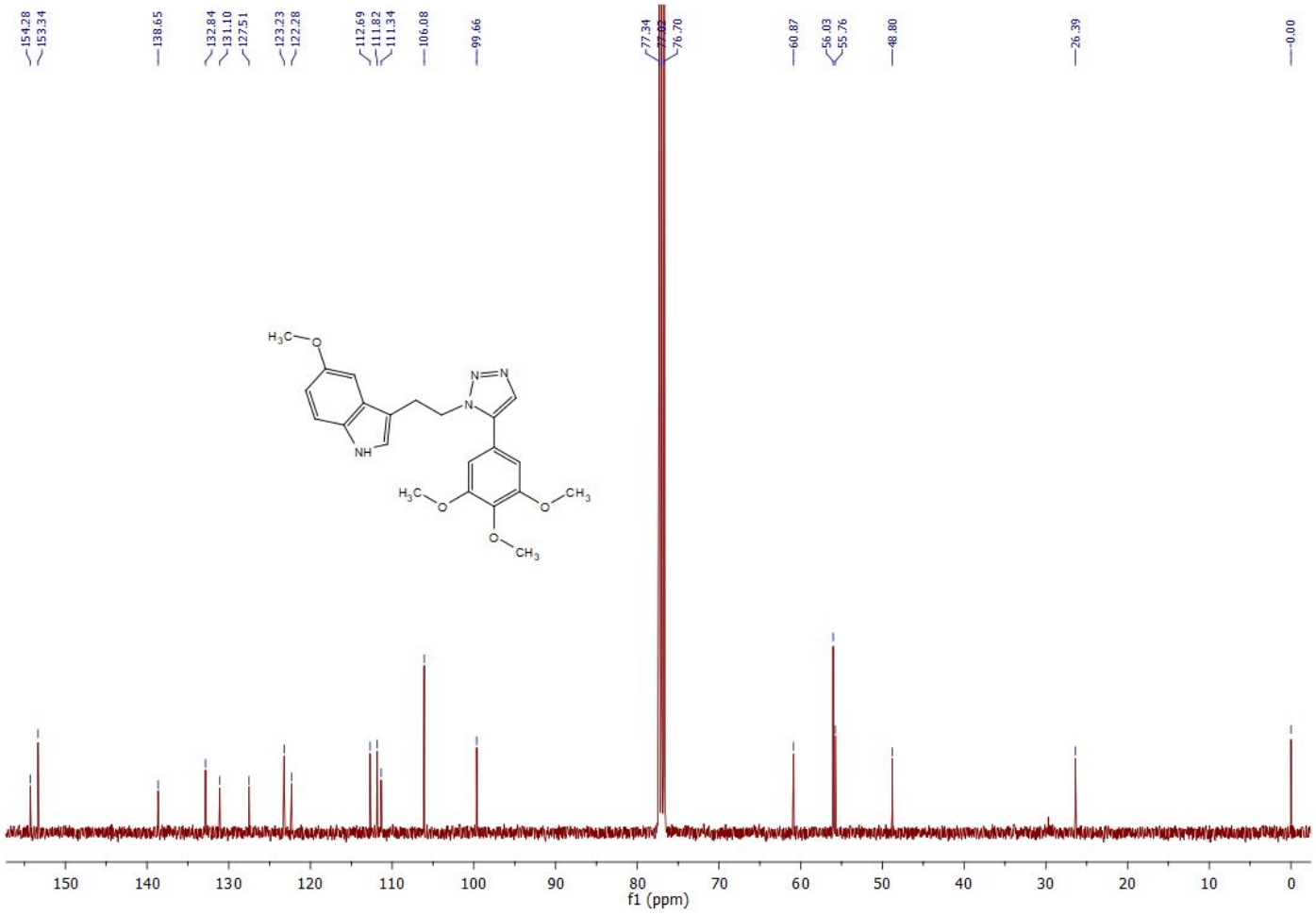
^{13}C NMR Spectra of (**11**) (300 MHz, $CDCl_3$):



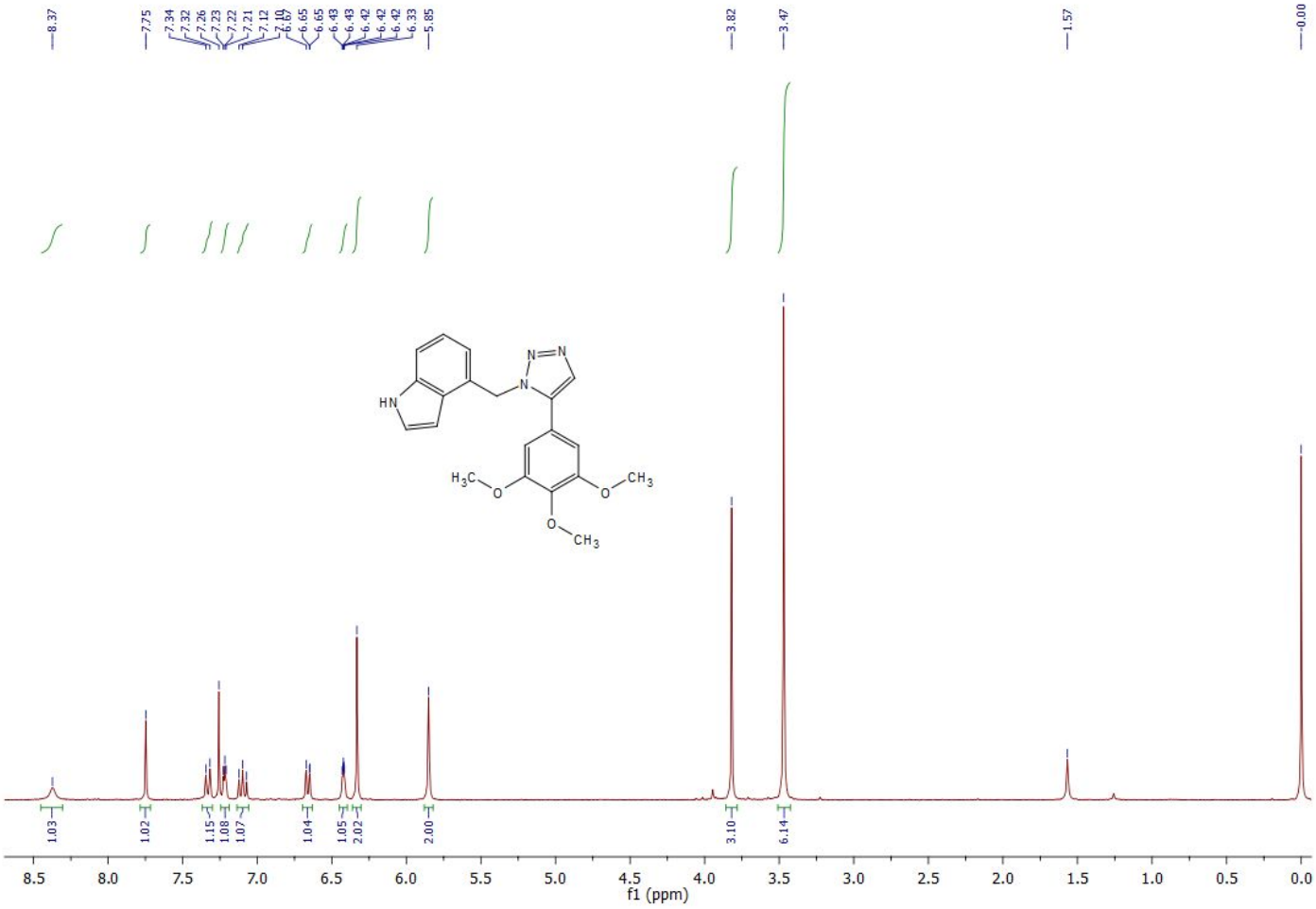
^{1}H NMR Spectra of (**12**) (300 MHz, $CDCl_3$):



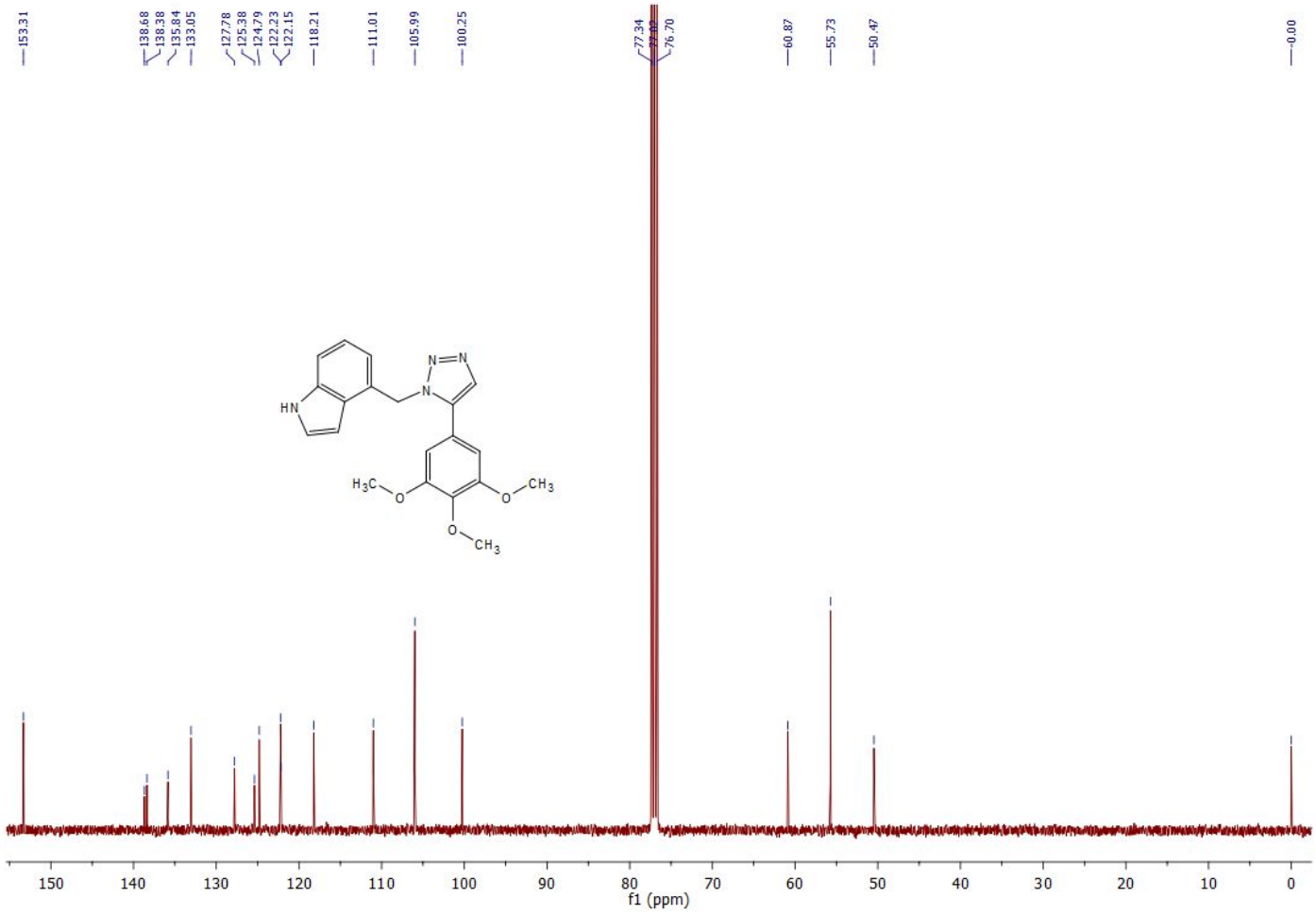
^{13}C NMR Spectra of (**12**) (400 MHz, $CDCl_3$):



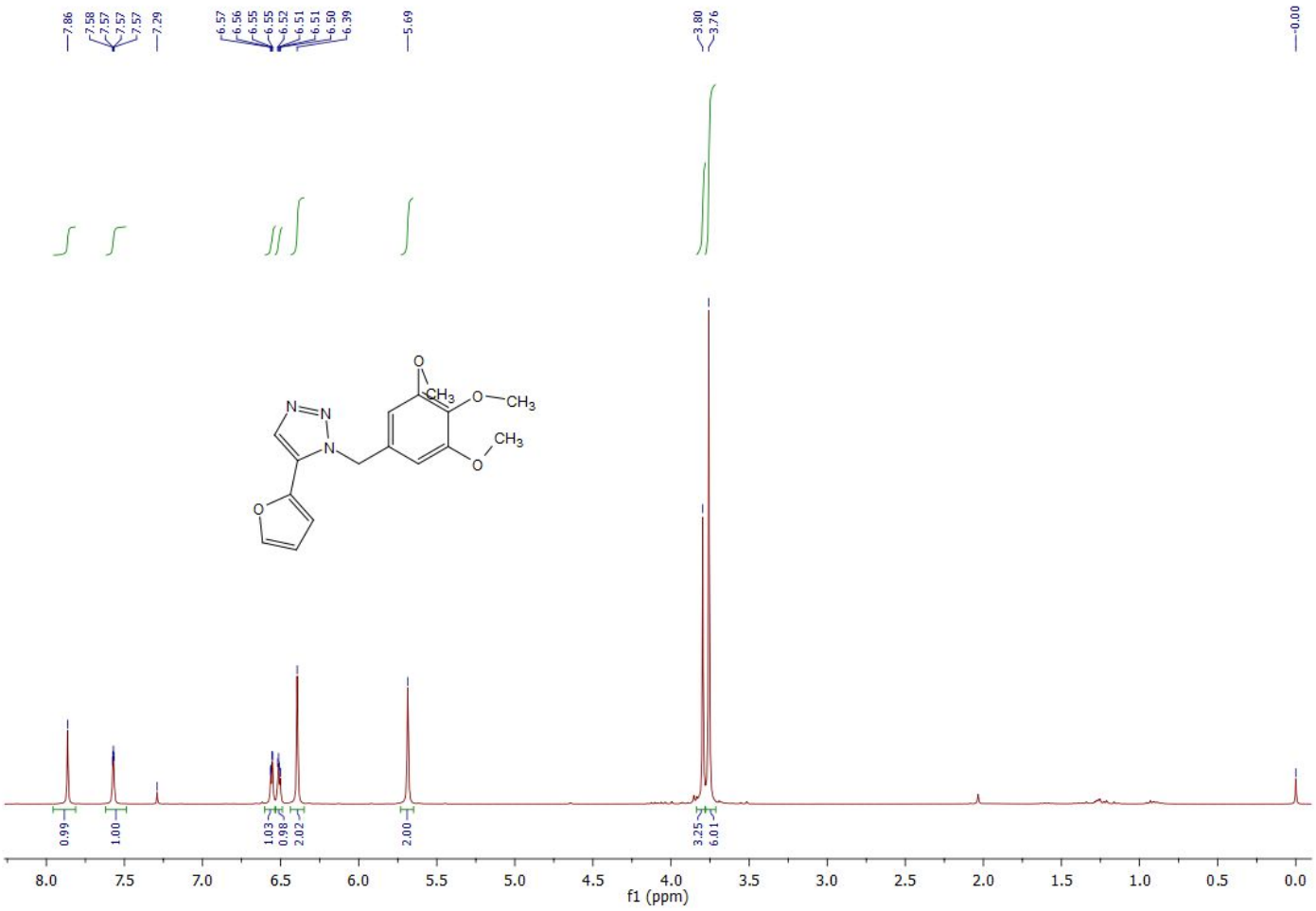
[1]H NMR Spectra of (**13**) (300 MHz, $CDCl_3$):



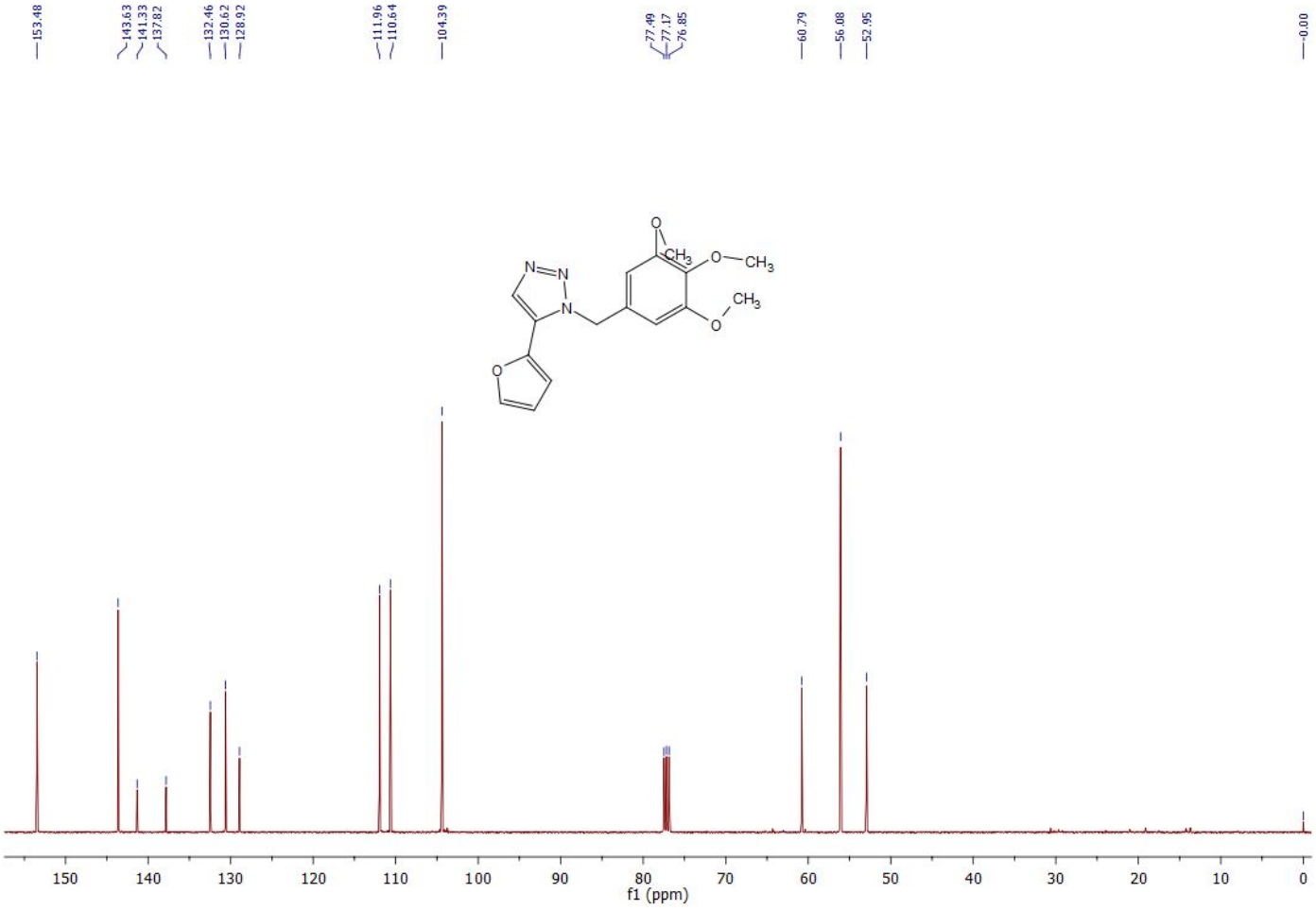
^{13}C NMR Spectra of (**13**) (400 MHz, $CDCl_3$):



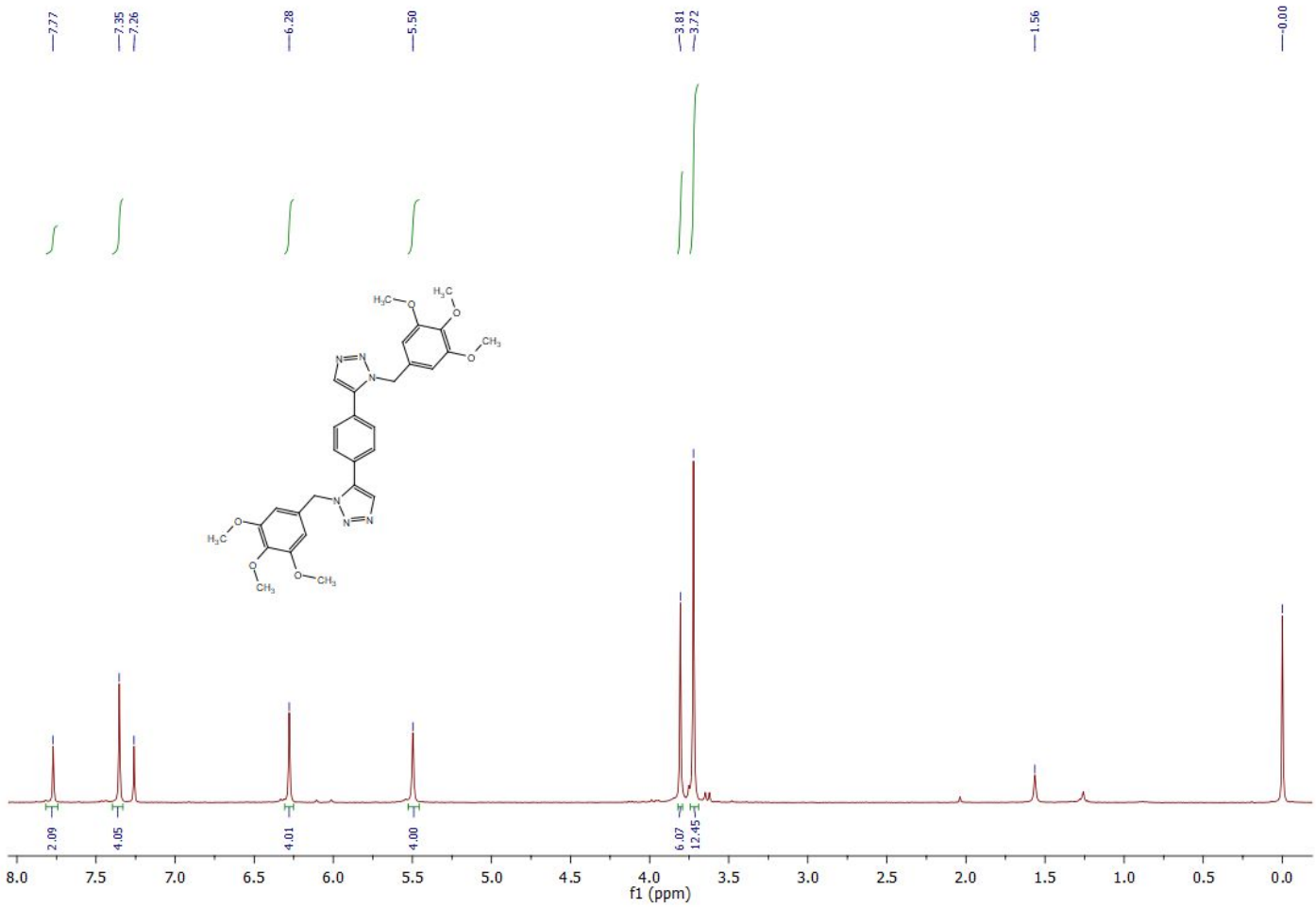
^{1}H NMR Spectra of (**14**) (300 MHz, $CDCl_3$):



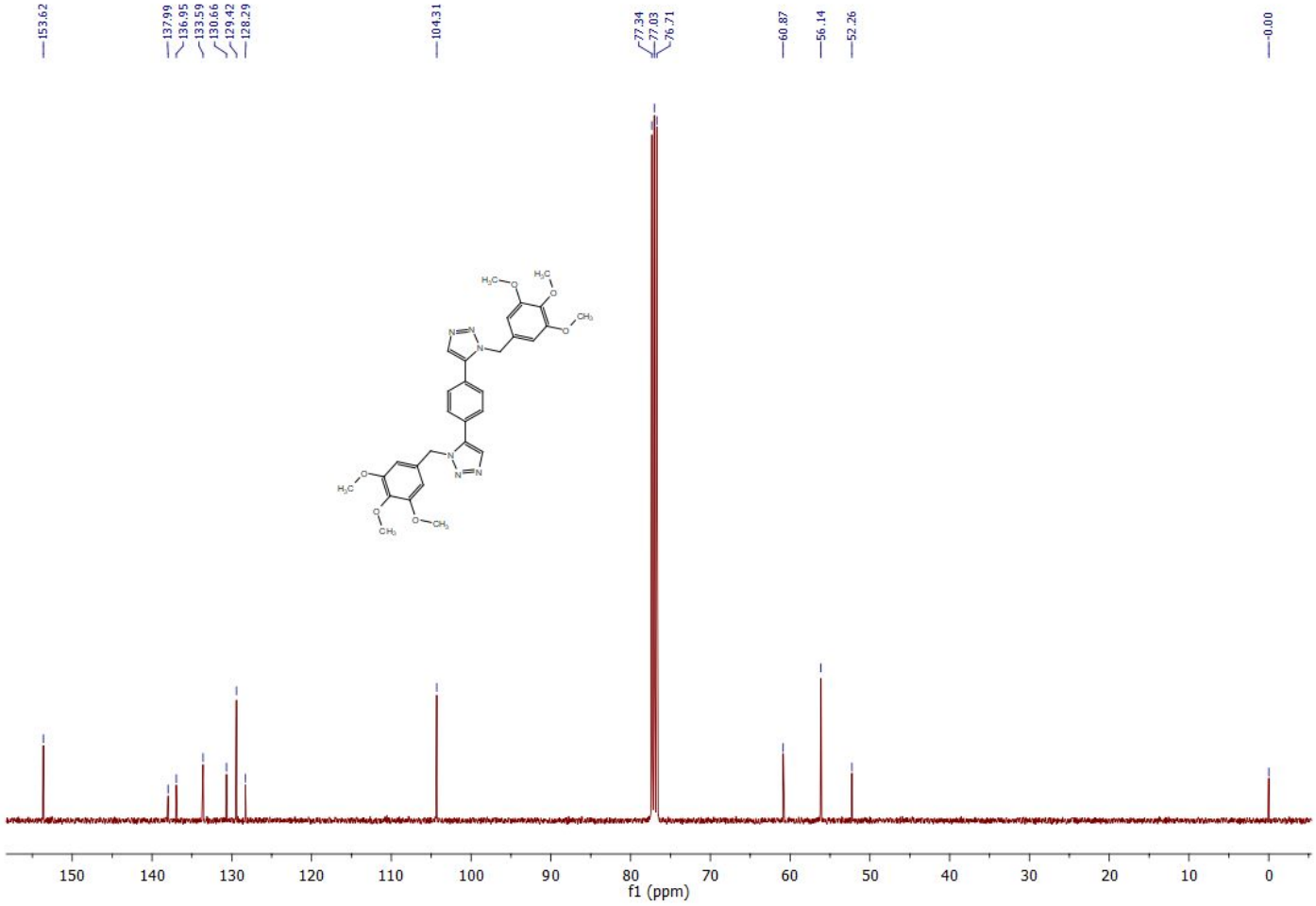
^{13}C NMR Spectra of (**14**) (400 MHz, $CDCl_3$):



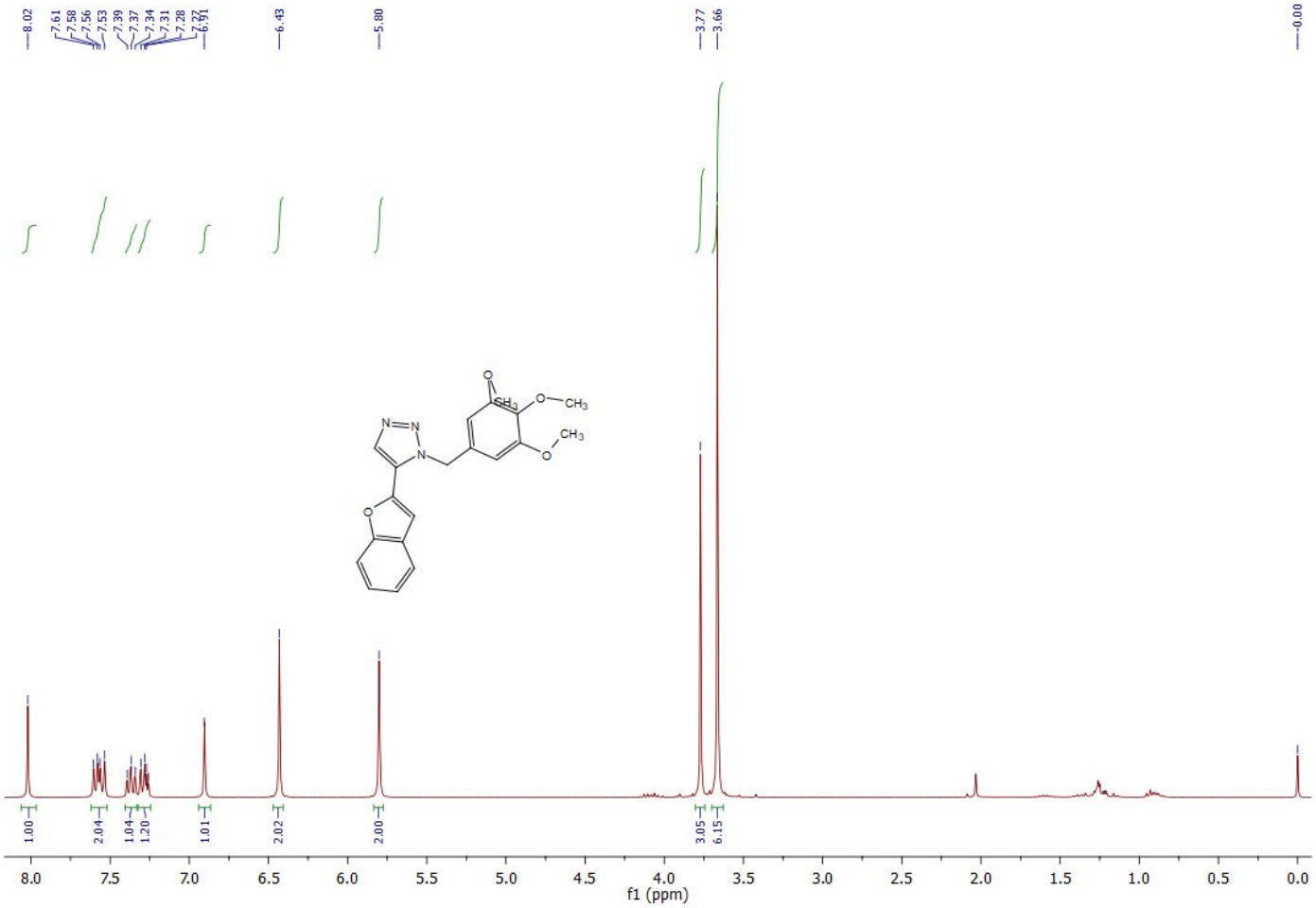
^{1}H NMR Spectra of (**15**) (300 MHz, $CDCl_3$):



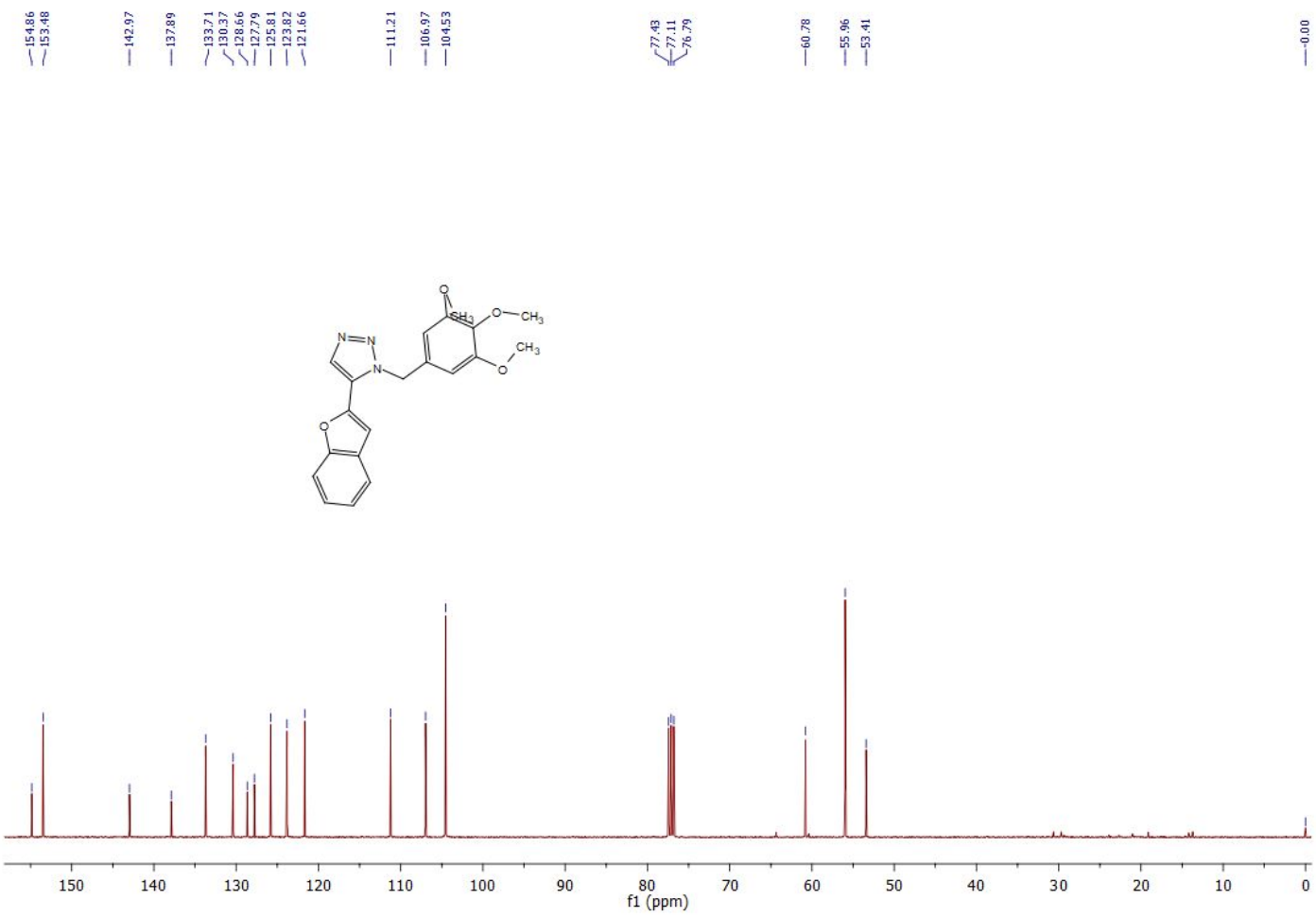
^{13}C NMR Spectra of (**15**) (400 MHz, $CDCl_3$):



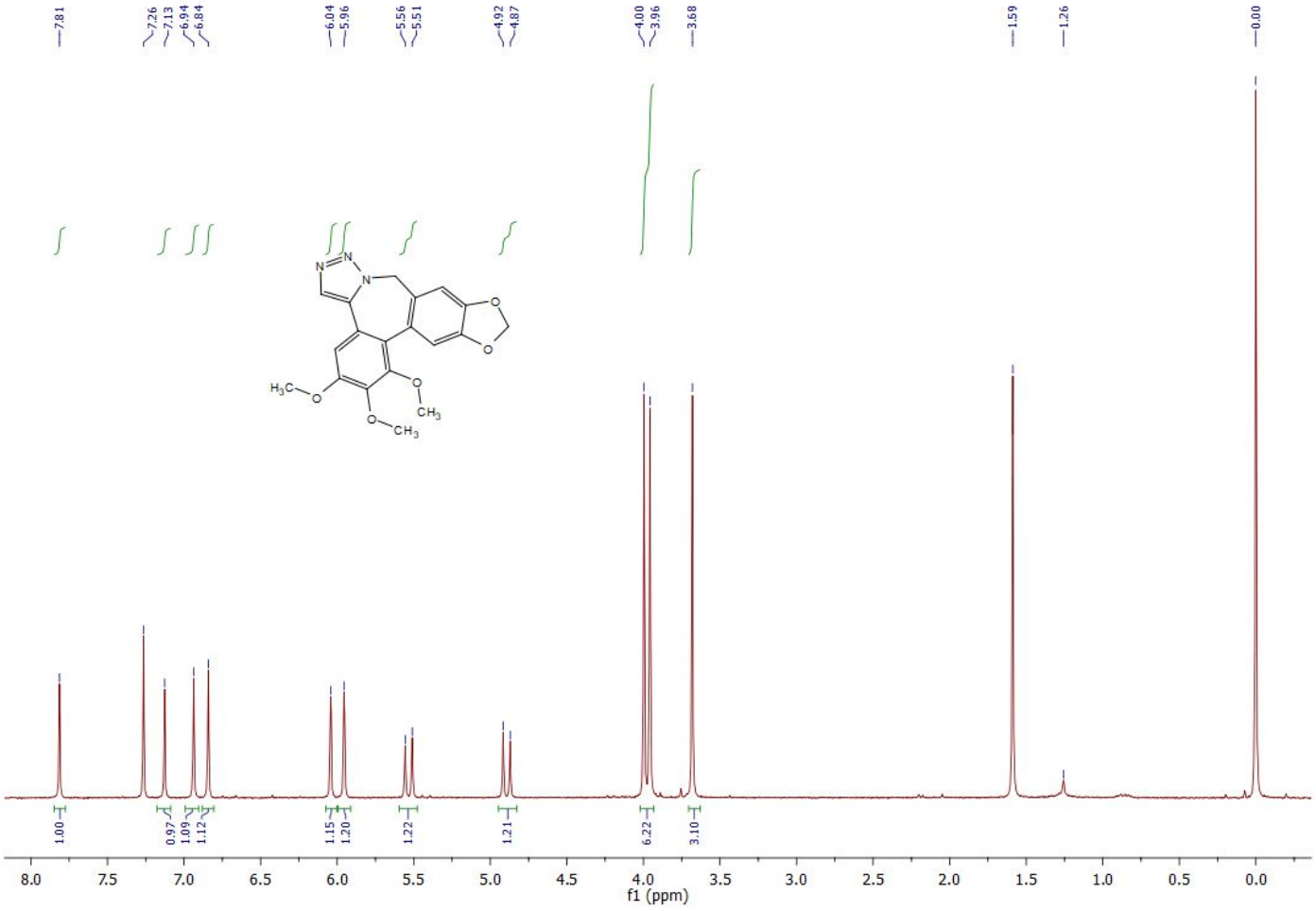
^{1}H NMR Spectra of (**16**) (300 MHz, $CDCl_3$):



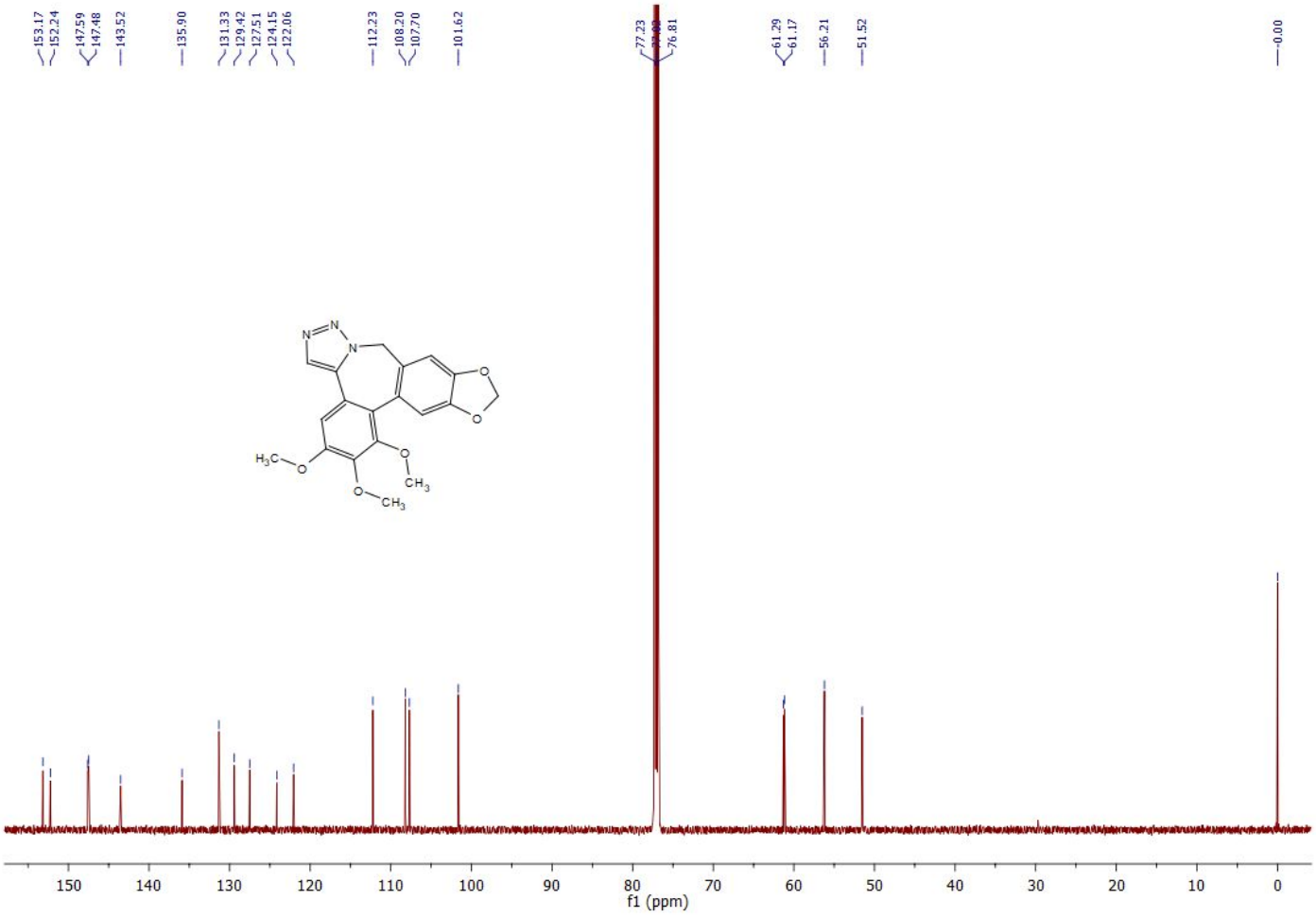
^{13}C NMR Spectra of (**16**) (400 MHz, $CDCl_3$):



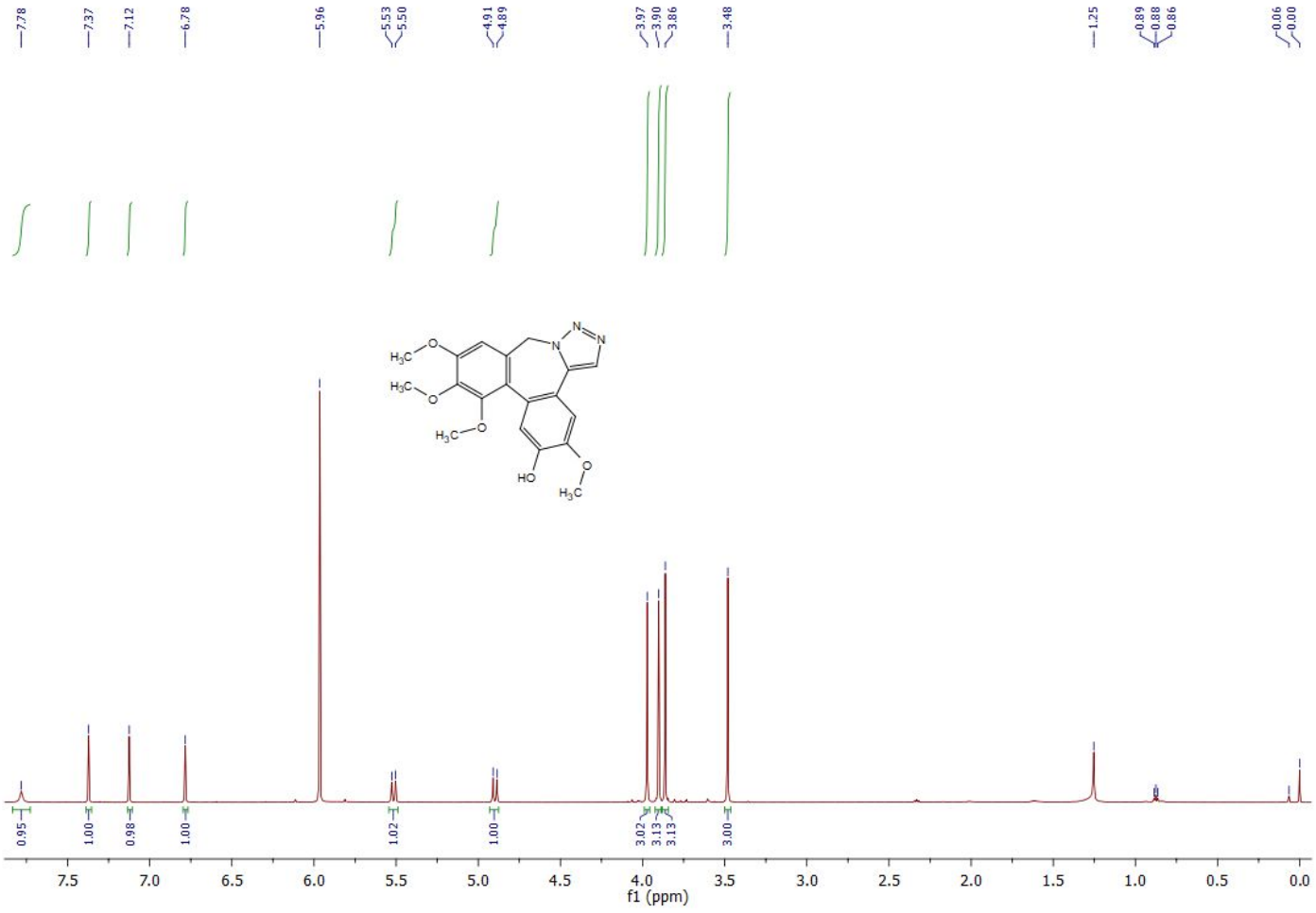
^{1}H NMR Spectra of (**5a**) (300 MHz, $CDCl_3$):



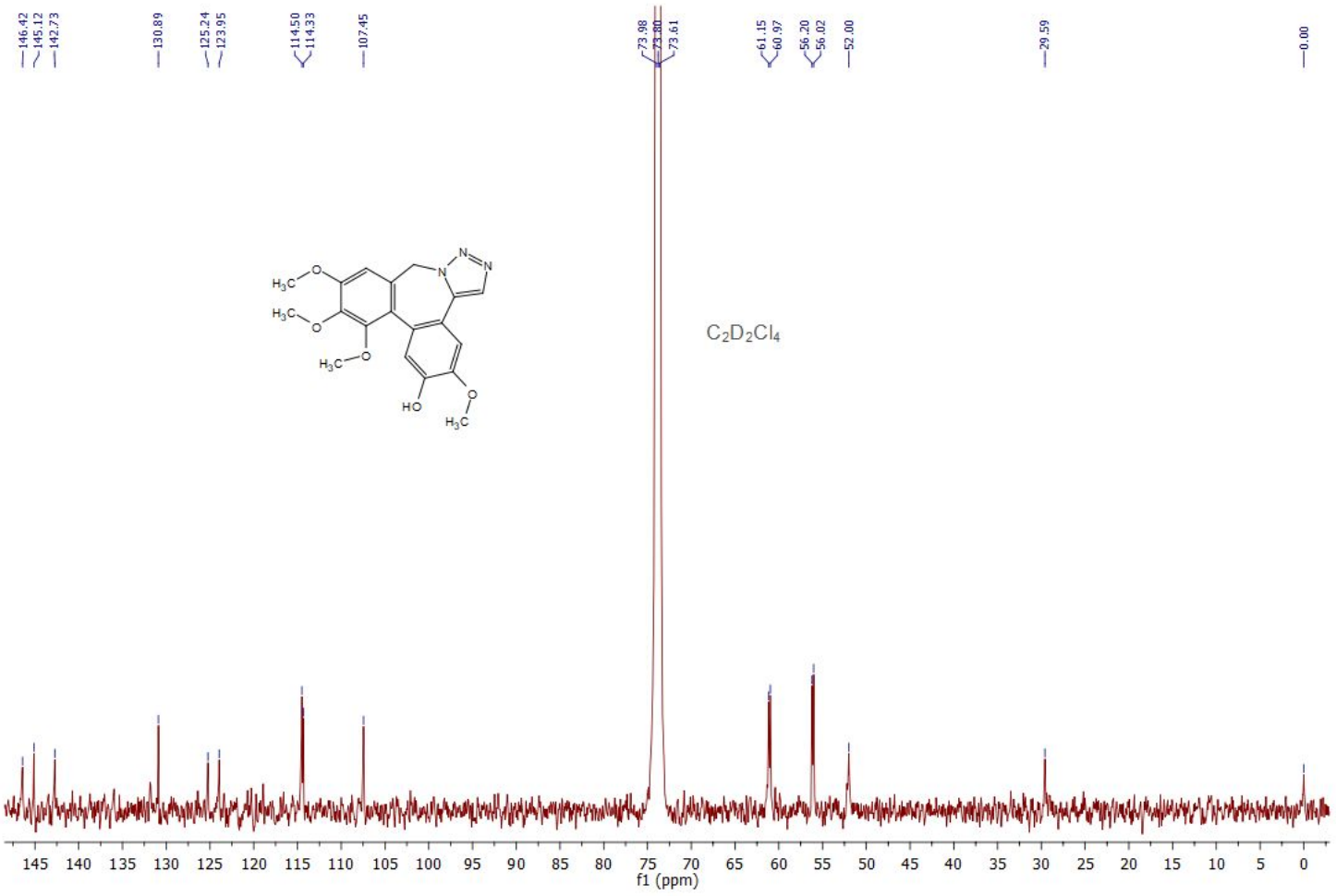
^{13}C NMR Spectra of (**5a**) (600 MHz, $CDCl_3$):



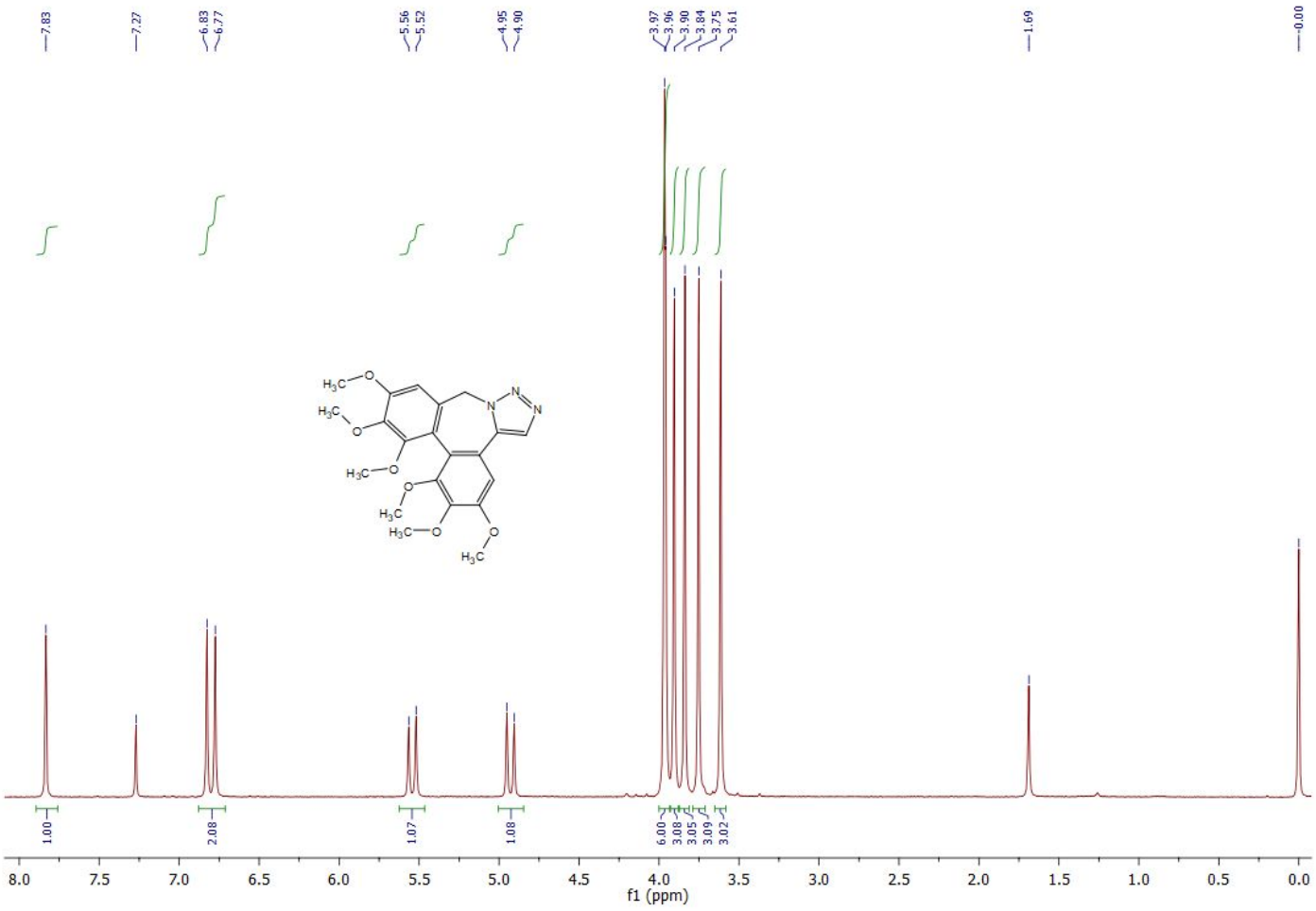
^{1}H NMR Spectra of (**6a**) (600 MHz, $C_2D_2Cl_4$):



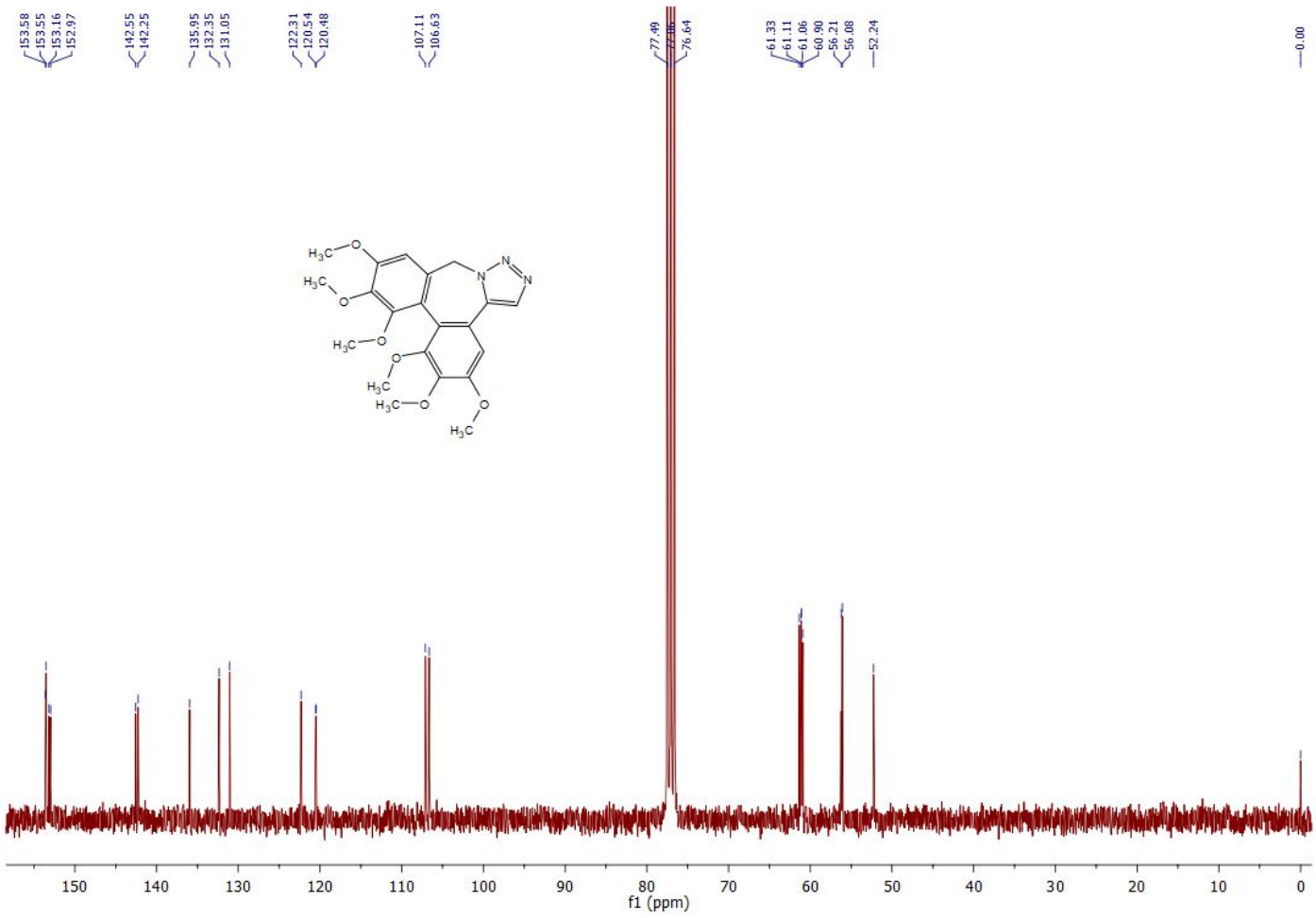
^{13}C NMR Spectra of (**6a**) (600 MHz, $C_2D_2Cl_4$):



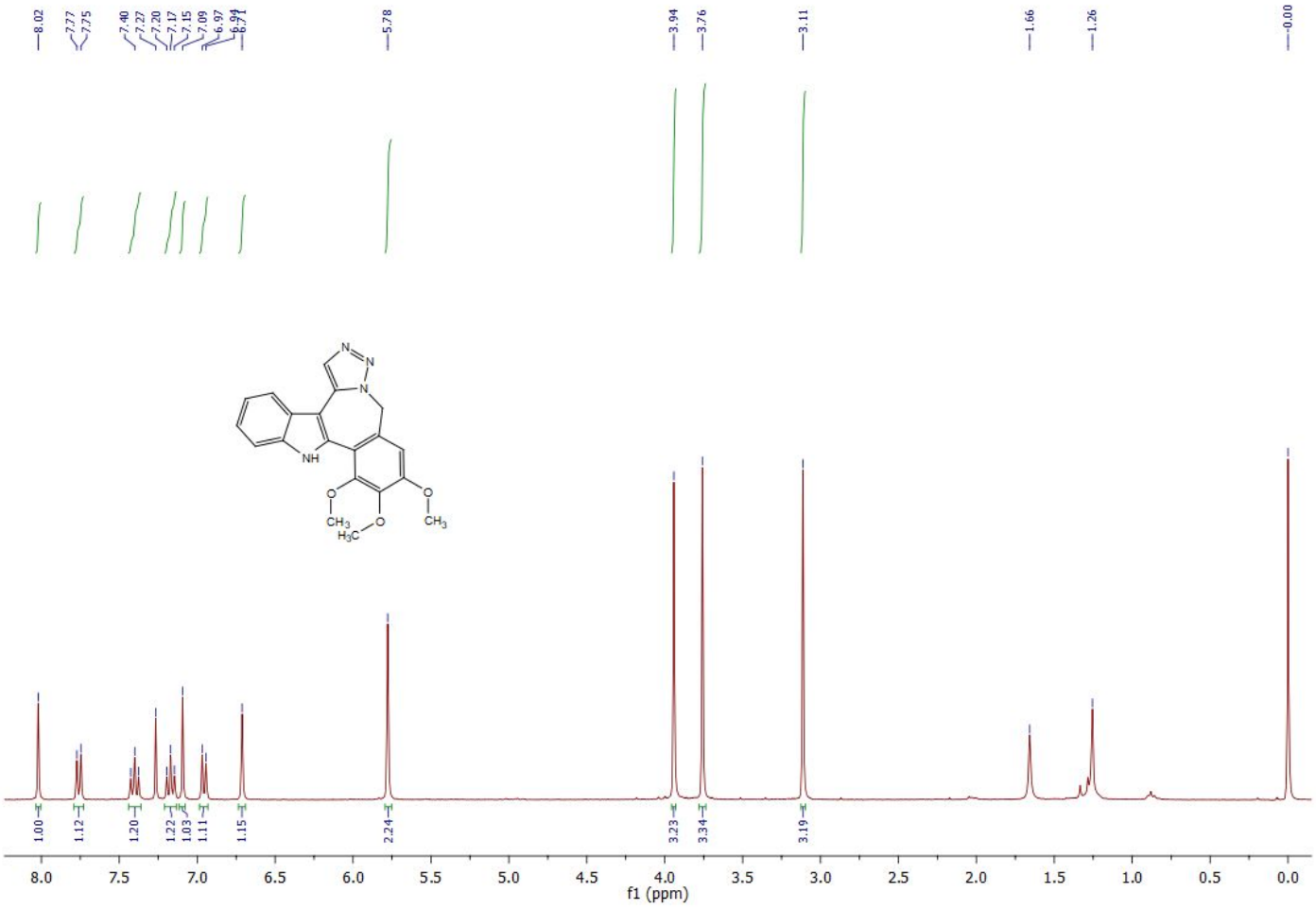
^{1}H NMR Spectra of (**7a**) (300 MHz, $CDCl_3$):



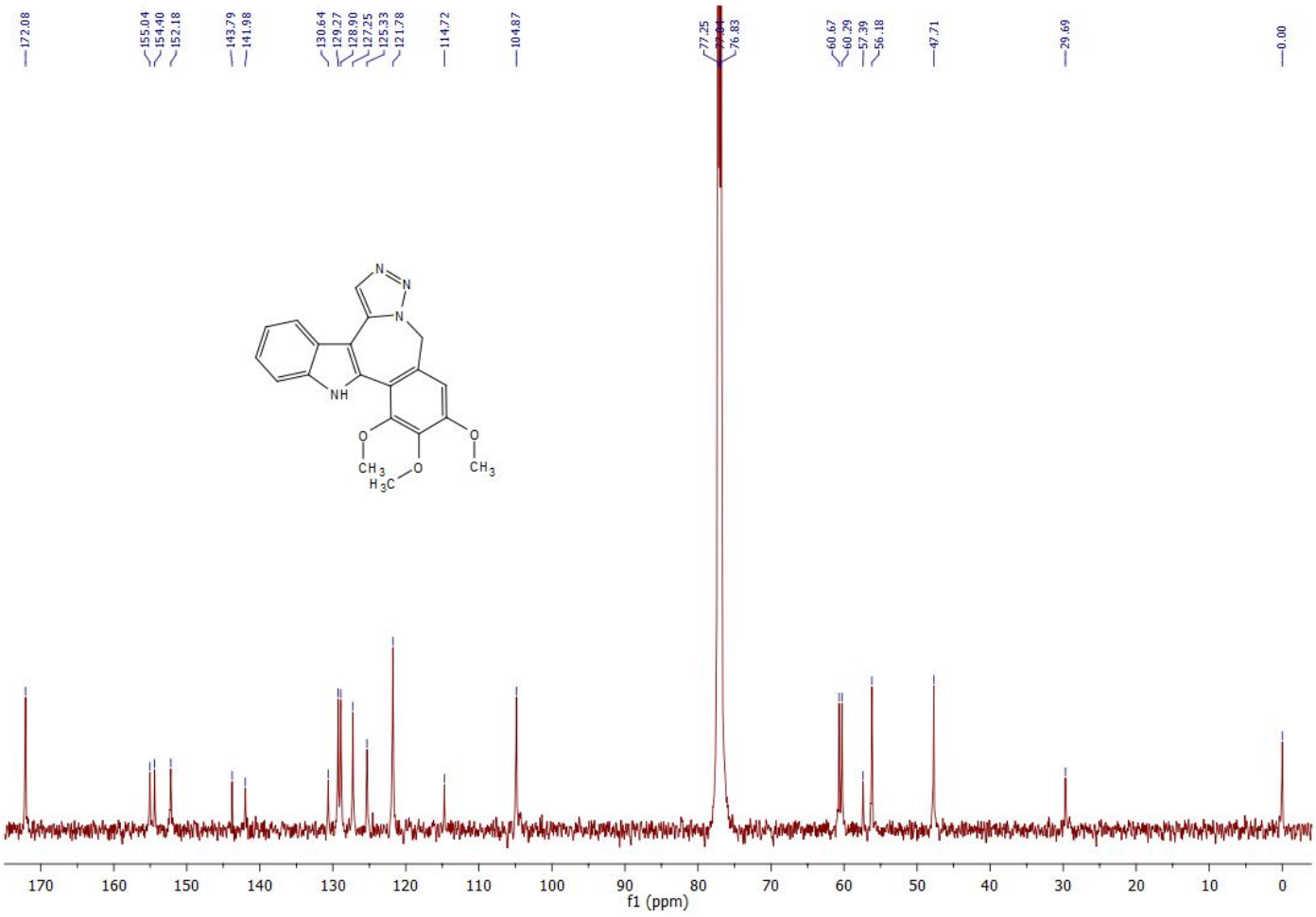
^{13}C NMR Spectra of (**7a**) (300 MHz, $CDCl_3$):



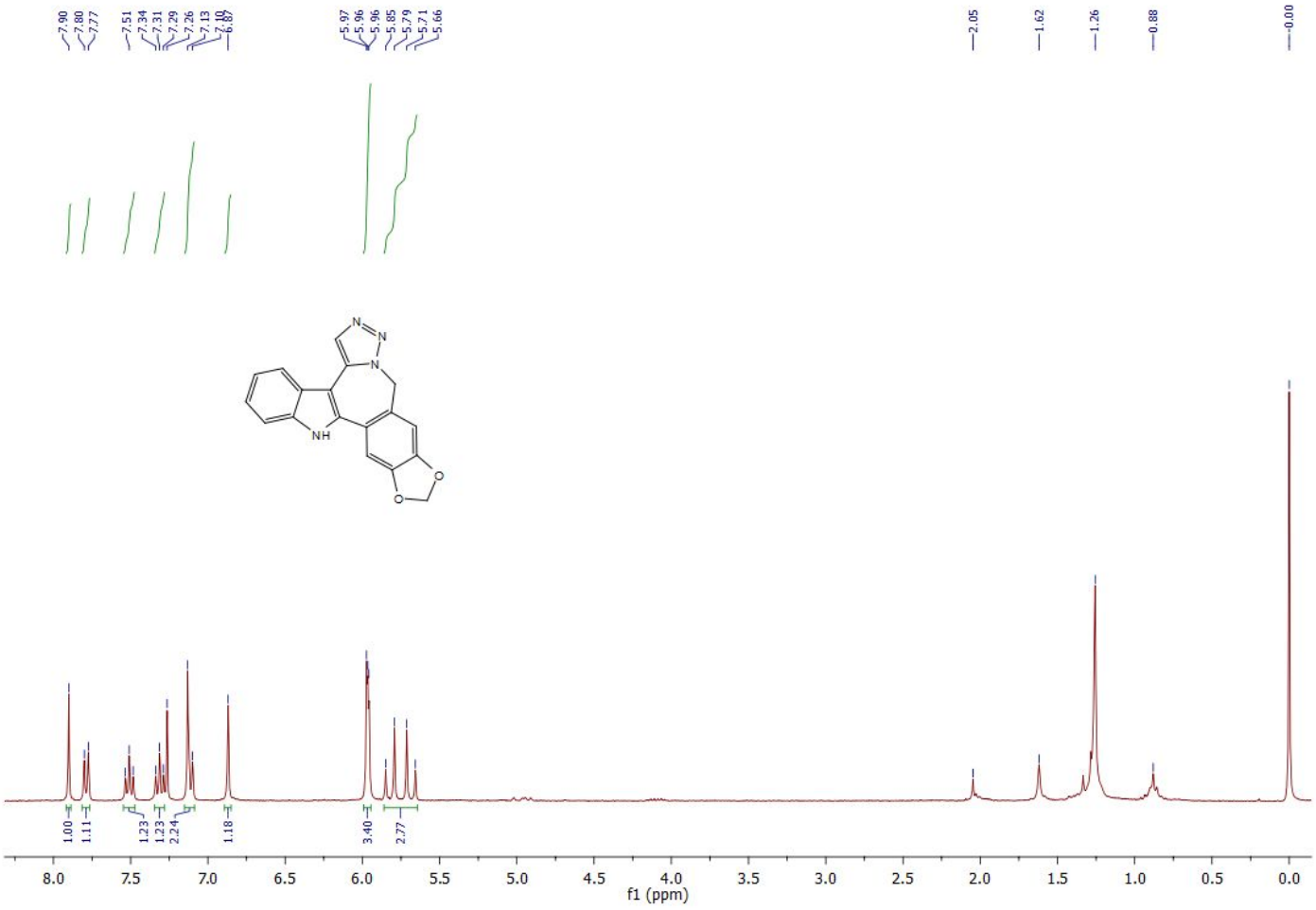
^{1}H NMR Spectra of (**8a**) (300 MHz, $CDCl_3$):



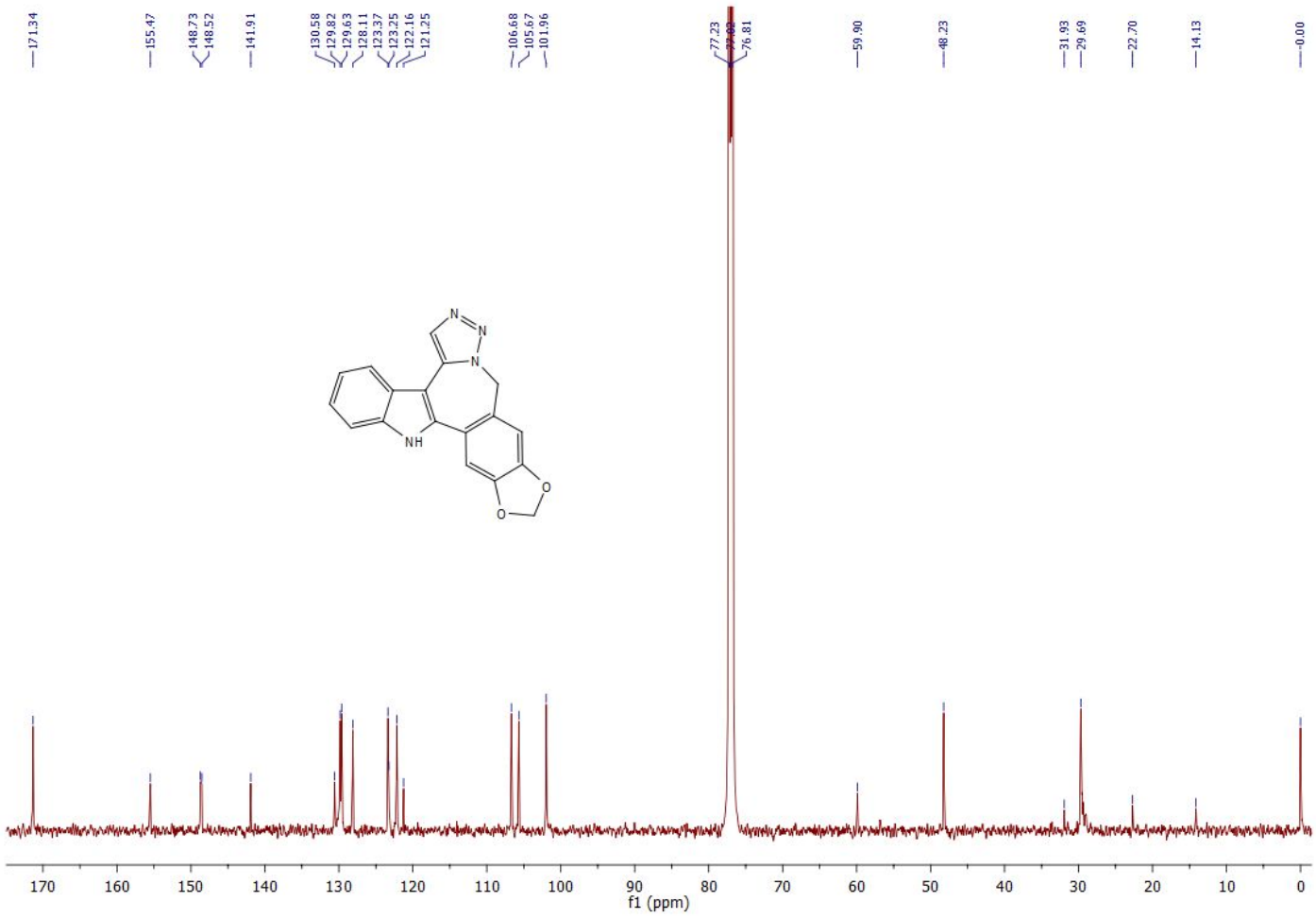
^{13}C NMR Spectra of (**8a**) (600 MHz, $CDCl_3$):



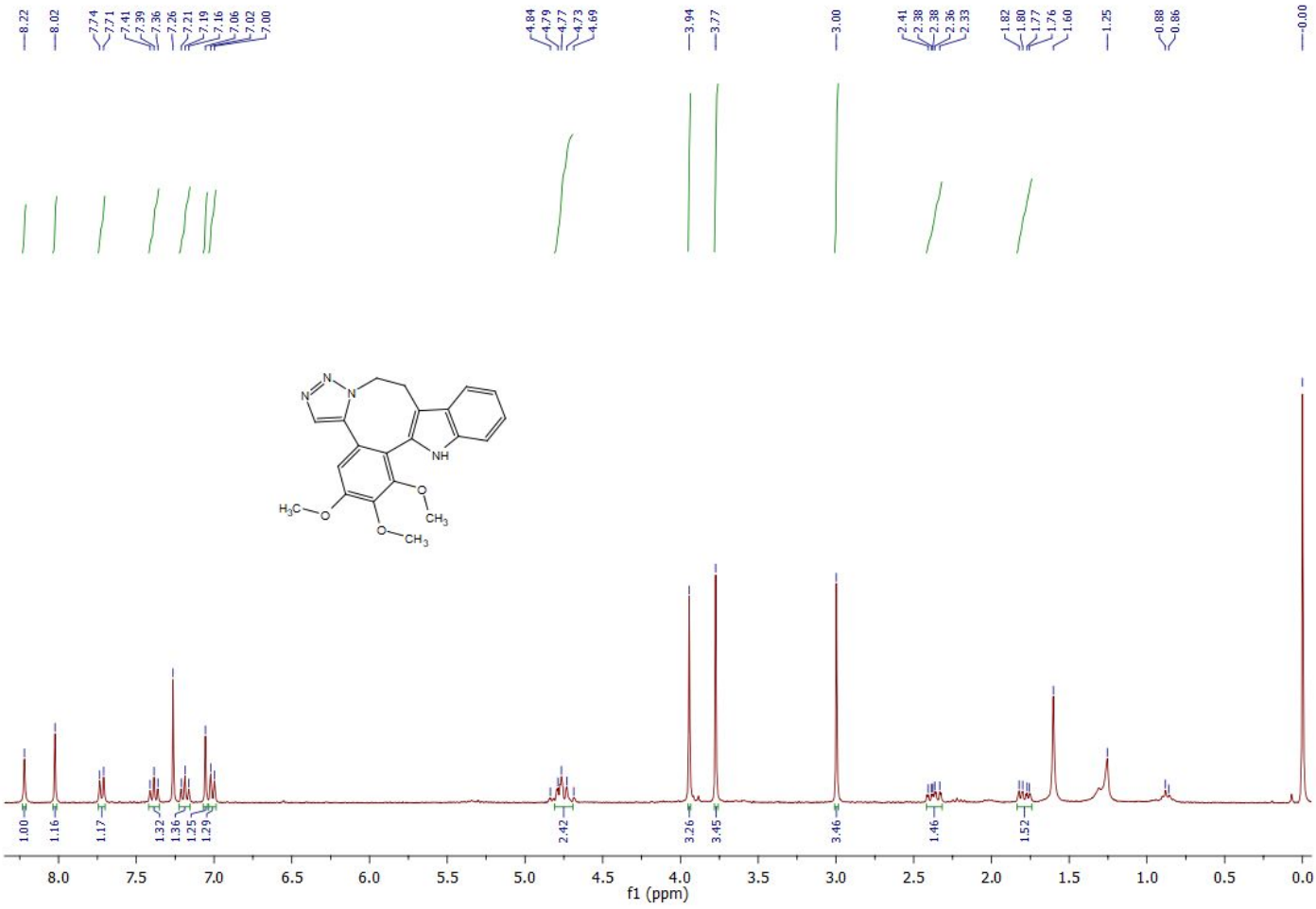
^{1}H NMR Spectra of (**9a**) (300 MHz, $CDCl_3$):



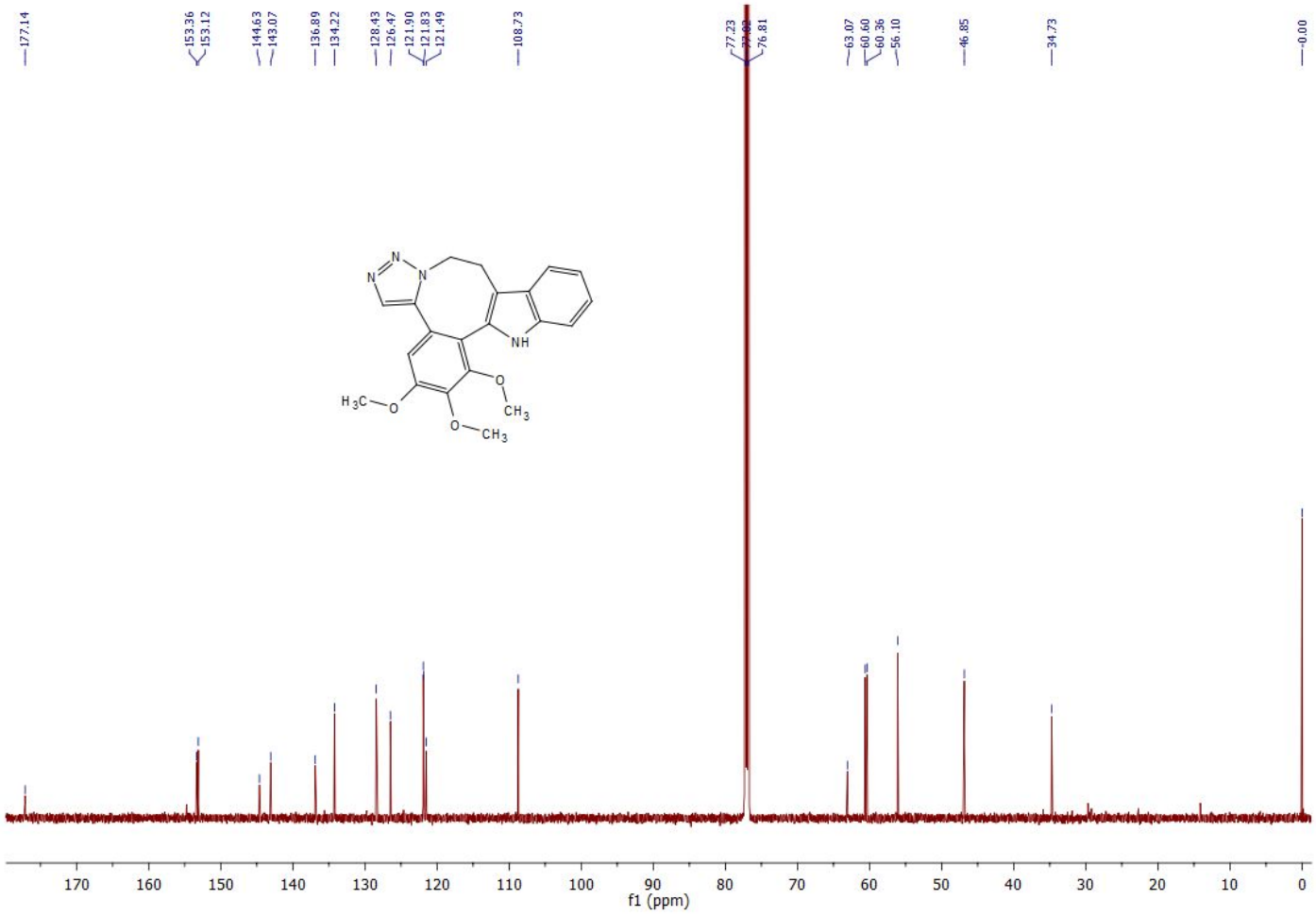
^{13}C NMR Spectra of (**9a**) (600 MHz, $CDCl_3$):



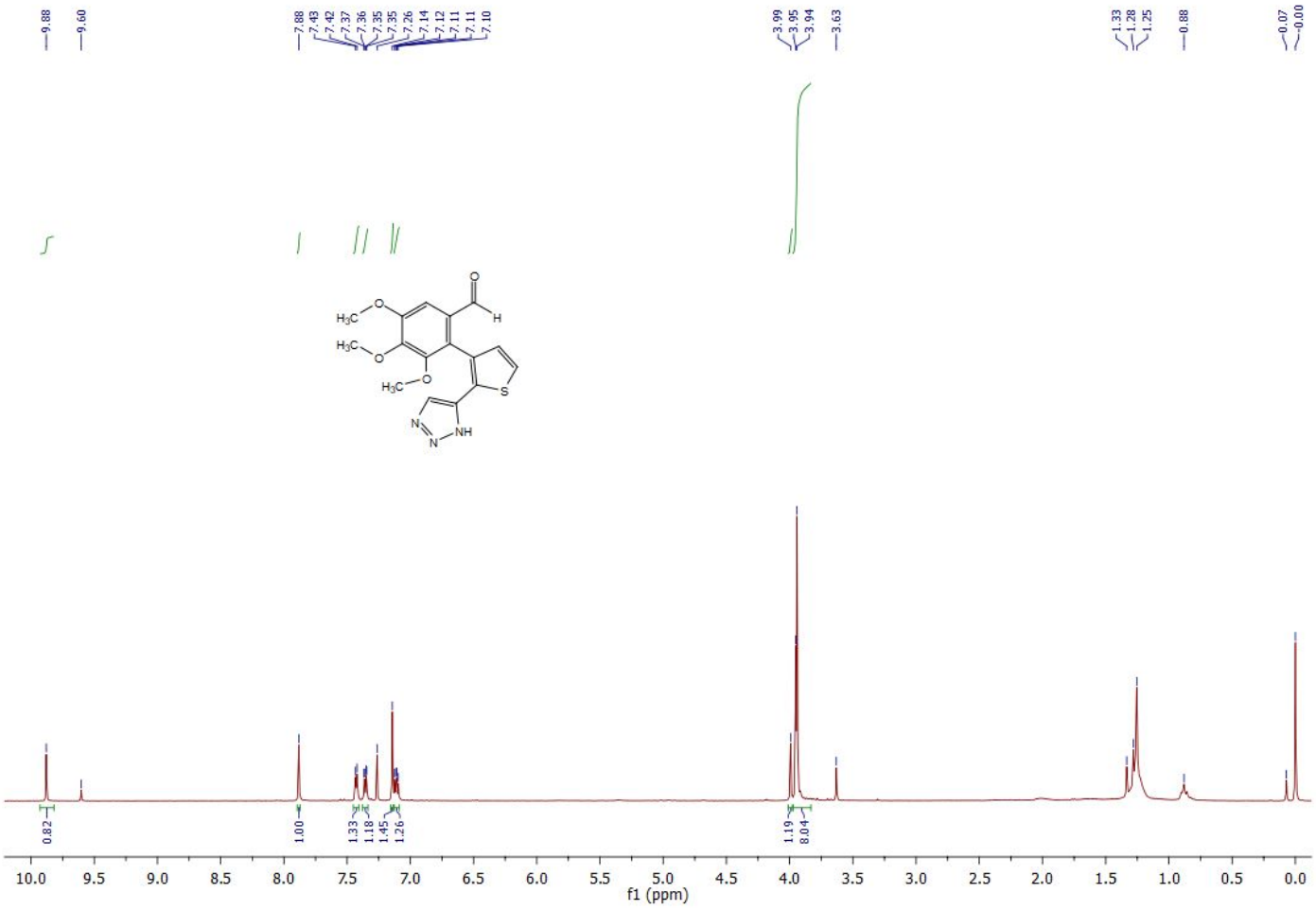
^{1}H NMR Spectra of (**10a**) (300 MHz, $CDCl_3$):



^{13}C NMR Spectra of (**10a**) (600 MHz, $CDCl_3$):



^{1}H NMR Spectra of (**11ab**) (300 MHz, $CDCl_3$):



^{13}C NMR Spectra of (**11ab**) (600 MHz, $CDCl_3$):