Design, synthesis, and biological evaluation of a novel series of 1,2,4-oxadiazole inhibitors of SLACK potassium channels: Identification of *in vitro* tool VU0935685

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Supplementary Material

Synthesis and Purification

Air-sensitive reactions were carried out under a nitrogen atmosphere. Starting materials, reagents, intermediates, and final compounds were weighed on a Mettler Toledo™ New Classic ME analytical balance or a Mettler Toledo™ New Classic ME toploader balance. Thin-layer chromatography (TLC) was conducted on glass plates coated with Silica Gel 60 F_{254} from Millipore Sigma. Normal-phase flash chromatography was carried out on either a CombiFlash® EZ Prep or CombiFlash® Rf+ automated flash chromatography system, both from Teledyne ISCO. Normal-phase flash chromatography was carried out using Redi*Sep*® Rf normal-phase, disposable

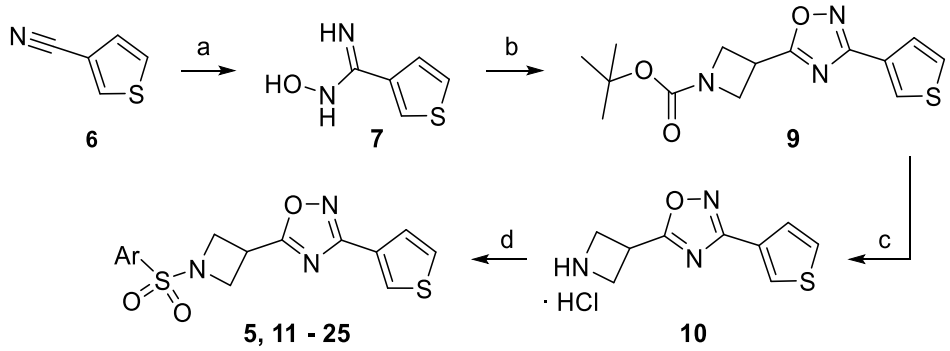
flash columns from Teledyne ISCO or SiliaSep normal-phase, disposable flash columns (40-63 micron) from SiliCycle, Inc. Reverse-phase preparative chromatography was carried out on the CombiFlash® EZ Prep using a reusable Redi*Sep*® Rf C18 reverse-phase column. Microwave reactions were carried out an Anton Paar Monowave 200 automated microwave synthesizer. The Monowave 200 has an output power of 850W with a maximum temperature of 260 ºC and a maximum pressure of 290 psi and is suitable for use with reaction volumes ranging from 0.5 to 20 mL.

Characterization

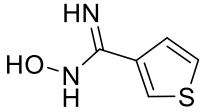
All NMR spectra were recorded on a 300 MHz Bruker Fourier 300HD NMR spectrometer equipped with a dual ^{1}H and ^{13}C probe with Z-Gradient and automatic tuning and matching, full computer control of all shims with TopShim™, 24-sample SampleCase™ automation system, and TopSpin™ software. All NMR samples were prepared with either chloroform-d with 0.03% TMS (99.8+ atom % D, Acros Organics Catalog No. 209561000) or d_6-dimethyl sulfoxide with 0.03% TMS (ACROS Organics Catalog No. 360000100). ^{1}H and ^{13}C chemical shifts are reported in δ values in ppm downfield. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). High resolution mass spectrometry was conducted on an Agilent 6230 Accurate-Mass Time-of-Flight (TOF) LC/MS with ESI source equipped with MassHunter Walkup software. MS parameters were as follows: fragmentor: 175 V, capillary voltage: 3500 V, nebulizer pressure: 35 psig, drying gas flow: 11 L/min, drying gas temperature: 325 ºC. Samples were introduced via an Agilent 1260 Infinity UHPLC comprised of a G4225A HiP Degasser, G1312B binary pump, G1367E ALS, G1316A TCC, and G1315C DAD VL+ with a 5 μL semi-micro flow cell with a 6

mm path length. UV absorption was observed at 220 nm and 254 nm with a 4 nm bandwidth. Column: Agilent Zorbax SB-C18, Rapid Resolution HT, 1.8 µm, 2.1 x 50 mm. Gradient conditions: Hold at 5% CH_3CN in H_2O (0.1% formic acid) for 1.0 min, 5% to 95% CH_3CN in H_2O (0.1% formic acid) over 5 min, hold at 95% CH_3CN in H_2O (0.1% formic acid) for 1.0 min, 0.5 mL/min. All samples submitted for biological testing were confirmed ≥ 95% pure by ^1H NMR.

Synthesis of Analogs 5, 11-25:

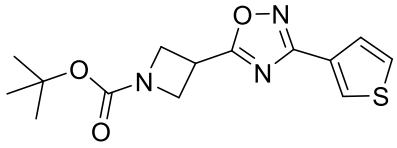


Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH, 60 ºC, 100%; (b) 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (**8**), HATU, DIEA, DCM, NMP, 140 ºC, *55%*; (c) 4M HCl in 1,4-dioxane, *99%*; (d) $ArSO_2Cl$, NEt_3, DCM, *17 - 79%*.

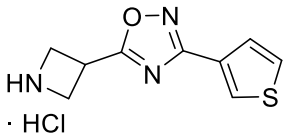


***N*-hydroxythiophene-3-carboximidamide (7).** Hydroxylamine hydrochloride (639 mg, 9.16 mmol, 2.0 eq) and sodium bicarbonate (773 mg, 9.16, 2.0 eq) were stirred in methanol (10 mL) for 30 minutes at room temperature. 3-Thiophenecarbonitrile (500 mg, 4.58 mmol, 1.0 eq) was

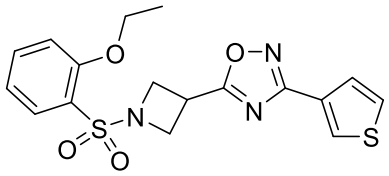
added to the previous suspension and heated at 50 ºC for 2 hours. The reaction was concentrated *in vacuo*, water was added, and extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated *in vacuo* to afford 651 mg (100%) of the title compound as a white solid that was used further without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (t, J = 2.1 Hz, 1H), 7.34 (m, 2H), 4.86 (bs, 2H).



***tert*-Butyl 3-(3-(thiophen-3-yl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (9).** Intermediate **7** (651 mg, 4.58, 1.0 eq), 1-boc-azetidine-3-carboxylic acid (**8**) (1.00 g, 5.04 mmol, 1.1 eq), hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) (2.09 g, 5.50 mmol, 1.2 eq), and *N*,*N*-diisopropylethylamine (DIEA) (2.40 mL, 13.7 mmol, 3.0 eq) were dissolved in Dichloromethane (DCM) (15 mL) and allowed to react for 3 hours at room temperature. Water was added, and the reaction was extracted with ethyl acetate (2x), washed with brine, dried over sodium sulfate (Na_2SO_4), filtered, and concentrated *in vacuo*. The reaction was dissolved in *N*-Methyl-2-pyrrolidone (NMP) (1.0 mL) and heated at 150 ºC for 1 hour. Water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 773 mg (55%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 3.0, 1.19 Hz, 1H), 7.64 (dd, J = 5.1, 1.2 Hz, 1H), 7.44 (dd, J = 5.1, 3.0 Hz, 1H), 4.35 (m, 4H), 4.04 (m, 1H), 1.47 (s, 9H).



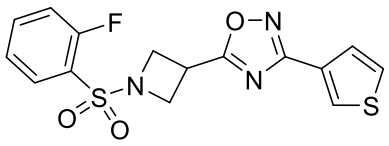
3-(3-(Thiophen-3-yl)-1,2,4-oxadiazol-5-yl)azetidine hydrochloride (10). Intermediate **9** (773 mg, 2.51 mmol, 1.0 eq) was dissolved in 4M hydrochloric acid (HCl) in 1,4-dioxane (5.0 mL) and stirred at room temperature for 30 minutes. The reaction was concentrated *in vacuo* to afford 604 mg (99%) of the title compound as a white solid that was used further without purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (dd, J = 2.8, 1.4 Hz, 1H), 7.63 (m, 2H), 4.64 – 4.42 (m, 5H).



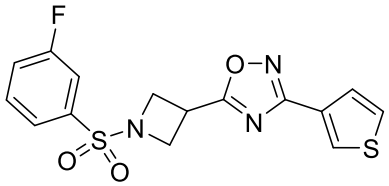
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (5). Intermediate **10** (25 mg, 0.10 mmol, 1.0 eq) and triethylamine (TEA) (28 µL, 0.20 mmol, 2.0 eq) were dissolved in DCM (2.0 mL). 2-Ethoxybeznene sulfonyl chloride (33 mg, 0.15 mmol, 1.5 eq) was added, and the reaction was stirred for 1 hour at room temperature. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 15 mg (38%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, J = 3.0, 1.2 Hz, 1H), 7.91 (dd, J = 7.9, 1.7 Hz, 1H), 7.60 (dd, J = 5.1, 1.2 Hz, 1H), 7.54 (m, 1H), 7.43 (dd, J = 3.0, 2.0 Hz, 1H), 7.06 (m, 2H), 4.46 (d, J = 2.7 Hz, 2H), 4.43 (d, J = 0.8 Hz, 2H), 4.20 (q, J = 7.0 Hz, 2H), 4.03 (m, 1H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 165.0, 156.7, 135.0, 131.2, 128.0, 127.8, 127.2, 126.0, 125.9, 120.4, 113.5, 65.1, 54.5, 25.3,

14.7 ppm. LCMS R_T = 5.09 min; HRMS, calc'd for $C_{17}H_{18}N_3O_4S_2^+$ [M+H], 392.0733; found 392.0740.

Analogs 11 - 30 were prepared using a method analogous to that used for analog 5.

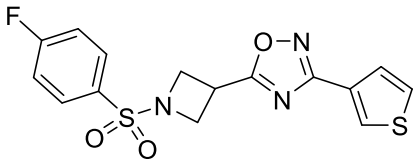


5-(1-((2-Fluorophenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (11). The title compound was prepared in 47% yield (17 mg) from intermediate **10** and 2-fluorobenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.91 (m, 1H), 7.64 (m, 1H), 7.58 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.43 (q, *J* = 3.0 Hz, 1H), 7.32 (m, 2H), 4.43 (t, *J* = 8.3 Hz, 2H), 4.35 (t, *J* = 6.9 Hz, 2H), 4.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 165.0, 159.3 (d, *J*(C,F) = 256.0 Hz), 135.7 (d, *J*(C,F) = 8.6 Hz), 131.2, 128.1, 127.7, 127.2, 126.0, 124.6 (d, *J*(C,F) = 3.78 Hz), 124.4 (d, *J*(C,F) = 14.7 Hz), 54.4 (d, *J*(C,F) = 2.1 Hz), 25.2 ppm. LCMS R_T = 5.00 min; HRMS, calc'd for $C_{15}H_{13}FN_3O_3S_2^+$ [M+H], 366.0377; found 366.0378.

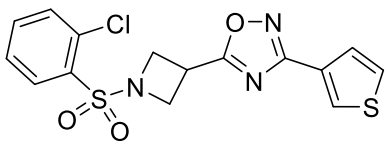


5-(1-((3-Fluorophenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (12). The title compound was prepared in 79% yield (29 mg) from intermediate **10** and 3-fluorobenzene

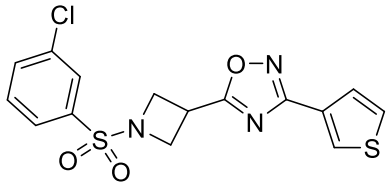
sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, J = 3.02, 1.20 Hz, 1H), 7.69 (dt, J = 7.65, 1.38 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.56 (dd, J = 5.08, 1.17 Hz, 1H), 7.43 (q, J = 3.16 Hz, 1H), 7.37 (m, 1H), 4.32 (t, J = 8.45 Hz, 2H), 4.17 (t, J = 6.32 Hz, 2H), 3.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 165.0, 162.6 (d, J(C,F) = 252.3 Hz), 136.4 (d, J(C,F) = 6.6 Hz), 131.2 (d, J(C,F) = 7.7 Hz), 128.1, 127.6, 127.3, 125.9, 124.2 (d, J(C,F) = 3.4 Hz), 120.9 (d, J(C,F) = 21.1 Hz), 115.7 (d, J(C,F) = 24.3 Hz), 54.5, 25.2 ppm. LCMS R_T = 5.04 min; HRMS, calc'd for $C_{15}H_{13}FN_3O_3S_2^+$ [M+H], 366.0377; found 366.0385.



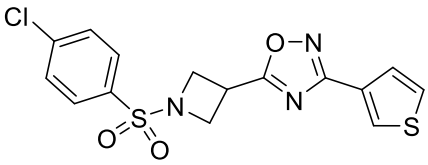
5-(1-((4-Fluorophenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (13). The title compound was prepared in 68% (25 mg) yield from intermediate **10** and 4-fluorobenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, J = 3.0, 1.2 Hz, 1H), 7.92 (m, 2H), 7.55 (dd, J = 5.0, 1.2 Hz, 1H), 7.43 (q, J = 3.0 Hz, 1H), 7.30 (m, 2H), 4.30 (t, J = 8.4 Hz, 2H), 4.13 (t, J = 6.3 Hz, 2H), 3.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 165.8 (d, J(C,F) = 256 Hz), 165.0, 131.2 (d, J(C,F) = 9.4 Hz), 130.4 (d, J(C,F) = 3.3 Hz), 128.0, 127.6, 127.3, 125.9, 116.7 (d, J(C,F) = 22.6 Hz), 54.4, 25.2 ppm. LCMS R_T = 5.00 min; HRMS, calc'd for $C_{15}H_{13}FN_3O_3S_2^+$ [M+H], 366.0377; found 366.0379.



5-(1-((2-Chlorophenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (14). The title compound was prepared in 45% (17 mg) yield from intermediate **10** and 2-chlorobenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 – 8.0 (m, 2H), 7.62 (dd, J = 5.0, 1.2 Hz, 1H), 7.56 (m, 2H), 7.46 – 7.39 (m, 2H), 4.48 (m, 4H), 4.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 165.1, 136.1, 134.1, 132.8, 132.1, 131.3, 128.1, 127.8, 127.2, 127.1, 126.0, 54.5, 25.1 ppm. LCMS R_T = 5.20 min; HRMS, calc'd for $C_{15}H_{13}ClN_3O_3S_2^+$ [M+H], 382.0081; found 382.0089.

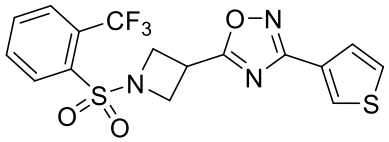


5-(1-((3-Chlorophenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (15). The title compound was prepared in 60% (23 mg) yield from intermediate **10** and 3-chlorobenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, J = 3.1, 1.2 Hz, 1H), 7.89 (t, J = 1.7 Hz, 1H), 7.77 (dt, J = 7.7, 1.3 Hz, 1H), 7.63 (m, 1H), 7.55 (m, 2H), 7.43 (q, J = 3.0 Hz, 1H), 4.32 (t, J = 8.5 Hz, 2H), 4.17 (t, J = 6.3 Hz, 2H), 3.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 165.0, 136.2, 135.7, 133.7, 130.6, 128.3, 128.1, 127.6, 127.3, 126.4, 125.9, 54.5, 25.2 ppm. LCMS R_T = 5.26 min; HRMS, calc'd for $C_{15}H_{13}ClN_3O_3S_2^+$ [M+H], 382.0081; found 382.0083.

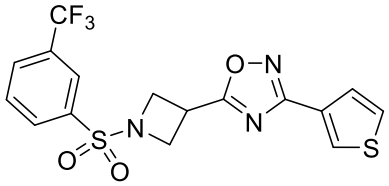


5-(1-((4-Chlorophenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (16). The title compound was prepared in 63% (24 mg) yield from intermediate **10** and 4-chlorobenzene

sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 3.0, 1.2 Hz, 1H), 7.84 (m, 2H), 7.63 – 7.52 (m, 3H), 7.43 (q, J = 3.0 Hz, 1H), 4.31 (t, J = 8.4 Hz, 2H), 4.13 (t, J = 6.3 Hz, 2H), 3.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 164.9, 140.3, 132.8, 129.9, 129.7, 128.1, 127.6, 127.3, 125.9, 54.6, 25.2 ppm. LCMS R_T = 5.27 min; HRMS, calc'd for $C_{15}H_{13}ClN_3O_3S_2^+$ [M+H], 382.0081; found 382.0088.

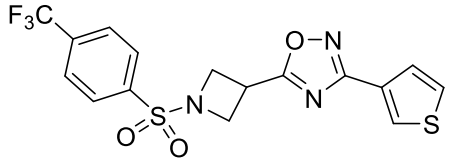


3-(Thiophen-3-yl)-5-(1-((2-(trifluoromethyl)phenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (17). The title compound was prepared in 63% (26 mg) yield from intermediate **10** and 2-trifluoromethylbenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (m, 1H), 8.05 (dd, J = 3.0, 1.2 Hz, 1H), 7.92 (m, 1H), 7.74 (m, 2H), 7.61 (dd, J = 5.1, 1.2 Hz, 1H), 7.43 (q, J = 3.0 Hz, 1H), 4.42 (m, 4H), 4.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 165.1, 137.0, 133.2, 132.5, 131.6, 128.5 (q, J(C,F) = 6.3 Hz), 128.4 (d, J(C,F) = 74.8 Hz), 128.1, 127.6, 127.2, 126.0, 122.5 (d, J(C,F) = 274 Hz), 54.5, 25.0 ppm. LCMS R_T = 5.34 min; HRMS, calc'd for $C_{16}H_{13}F_3N_3O_3S_2^+$ [M+H], 416.0345; found 416.0347.

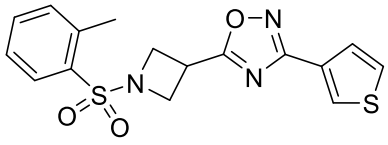


3-(Thiophen-3-yl)-5-(1-((3-(trifluoromethyl)phenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (18). The title compound was prepared in 51% (21 mg) yield from intermediate **10** and 3-trifluoromethylbenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (m, 1H), 8.08 (m,

1H), 8.00 – 7.89 (m, 2H), 7.76 (m, 1H), 7.55 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.43 (q, *J* = 3.0 Hz, 1H), 4.35 (t, *J* = 8.4 Hz, 2H), 4.19 (t, *J* = 6.3 Hz, 2H), 4.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 165.0, 136.2, 132.1, 131.9, 131.5, 130.2 (m, *J*(C,F)), 128.1, 127.8, 127.2, 125.9, 125.3 (q, *J*(C,F) = 3.8 Hz), 123.2 (d, *J*(C,F) = 273.1 Hz), 54.5, 25.2 ppm. LCMS R_T = 5.38 min; HRMS, calc'd for $C_{16}H_{13}F_3N_3O_3S_2^+$ [M+H], 416.0345; found 416.0345.

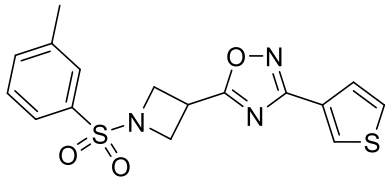


3-(Thiophen-3-yl)-5-(1-((4-(trifluoromethyl)phenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (19). The title compound was prepared in 55% (23 mg) yield from intermediate **10** and 4-trifluoromethylbenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.04 (m, 2H), 7.93 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.89 (m, 2H), 7.52 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.42 (q, *J* = 3.0 Hz, 1H), 4.35 (t, *J* = 8.4 Hz, 2H), 4.18 (t, *J* = 6.3 Hz, 2H), 4.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 165.0, 136.9 (d, *J*(C,F) = 230 Hz), 135.0, 128.9, 128.0, 127.6, 127.3, 126.5 (q, *J*(C,F) = 3.7 Hz), 125.5, 123.2 (d, *J*(C,F) = 273.2 Hz), 54.6, 25.2 ppm. LCMS R_T = 5.42 min; HRMS, calc'd for $C_{16}H_{13}F_3N_3O_3S_2^+$ [M+H], 416.0345; found 416.0349.

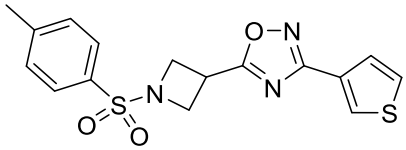


3-(Thiophen-3-yl)-5-(1-(*o*-tolylsulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (20). The title compound was prepared in 17% (6 mg) yield from intermediate **10** and 2-methylbenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.06 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.99 (m, 1H), 7.62 (dd, *J*

= 6, 1.2 Hz, 1H), 7.51 (td, *J* = 6.9, 1.4 Hz, 1H), 7.43 (q, *J* = 3.0 Hz, 1H), 7.39 – 7.31 (m, 2H), 4.35 (t, *J* = 7.7 Hz, 2H), 4.26 (t, *J* = 6.0 Hz, 2H), 4.05 (m, 1H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 165.1, 138.8, 134.8, 133.6, 132.8, 130.1, 128.1, 127.8, 127.2, 126.2, 126.0, 53.3, 25.3, 20.7 ppm. LCMS R_T = 5.23 min; HRMS, calc'd for $C_{16}H_{16}N_3O_3S_2^+$ [M+H], 362.0628; found 362.0627.

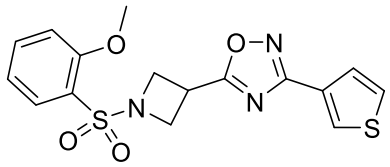


3-(Thiophen-3-yl)-5-(1-(*m*-tolylsulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (21). The title compound was prepared in 42% (15 mg) yield from intermediate **10** and 3-methylbenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.97 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.56 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.53 – 7.40 (m, 3H), 4.28 (t, *J* = 8.4 Hz, 2H), 4.16 (t, *J* = 6.3 Hz, 2H), 3.95 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 164.9, 139.7, 134.5, 134.0, 129.2, 128.7, 128.0, 127.7, 127.2, 125.9, 125.6, 54.3, 25.3, 21.5 ppm. LCMS R_T = 5.12 min; HRMS, calc'd for $C_{16}H_{16}N_3O_3S_2^+$ [M+H], 362.0628; found 362.0634.

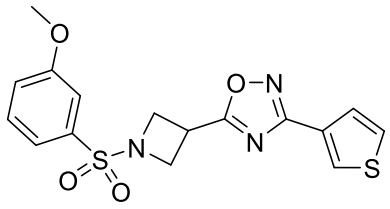


3-(Thiophen-3-yl)-5-(1-tosylazetidin-3-yl)-1,2,4-oxadiazole (22). The title compound was prepared in 28% yield (10 mg) from intermediate **10** and 4-methylbenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.96 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.78 (m, 2H), 7.55 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.45 – 7.36 (m, 3H), 4.28 (t, *J* = 8.5 Hz, 2H), 4.13 (t, *J* = 6.3 Hz, 2H), 3.93 (m, 1H), 2.43 (s,

3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 164.9, 144.6, 131.0, 130.0, 128.6, 128.0, 127.7, 127.2, 125.9, 54.3, 25.3, 21.6 ppm. LCMS R_T = 5.11 min; HRMS, calc'd for $C_{16}H_{16}N_3O_3S_2^+$ [M+H], 362.0628; found 362.0627.

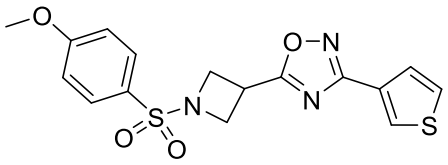


5-(1-((2-Methoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (23). The title compound was prepared in 61% (23 mg) yield from intermediate **10** and 2-methoxybenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.02 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.43 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.08 (m, 2H), 4.42 (m, 4H), 4.05 (m, 1H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 165.0, 157.1, 135.1, 131.3, 128.0, 127.8, 127.3, 126.0, 125.5, 120.6, 112.5, 56.2, 54.5, 25.2 ppm. LCMS R_T = 4.85 min; HRMS, calc'd for $C_{16}H_{16}N_3O_4S_2^+$ [M+H], 378.0577; found 378.0578.



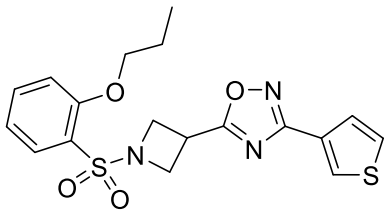
5-(1-((3-Methoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (24). The title compound was prepared in 61% (23 mg) yield from intermediate **10** and 3-methoxybenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.98 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.58 – 7.37 (m, 5H), 7.18 (m, 1H), 4.29 (t, *J* = 8.5 Hz, 2H), 4.17 (t, *J* = 6.3 Hz, 2H), 3.95 (m, 1H), 3.88 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 164.9, 160.2, 135.1, 130.4, 128.0, 127.7, 127.2, 125.9, 120.6, 119.9, 113.2, 55.8, 54.4, 25.2 ppm. LCMS R_T = 5.01 min; HRMS, calc'd for $C_{16}H_{16}N_3O_4S_2^+$ [M+H], 378.0577; found 378.0576.



5-(1-((4-Methoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (25). The title compound was prepared in 65% (25 mg) yield from intermediate **10** and 4-methoxybenzene sulfonyl chloride. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (dd, J = 3.0, 1.3 Hz, 1H), 7.84 – 7.76 (m, 3H), 7.49 (dd, J = 5.1, 1.2 Hz, 1H), 7.22 (m, 2H), 4.21-4.04 (m, 3H), 3.94 (m, 1H), 3.83 (s, 3H). LCMS R_T = 4.93 min; HRMS, calc'd for $C_{16}H_{16}N_3O_4S_2^+$ [M+H], 378.0577; found 378.0581.

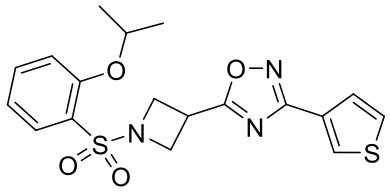
Synthesis of Analogs 26 – 29:



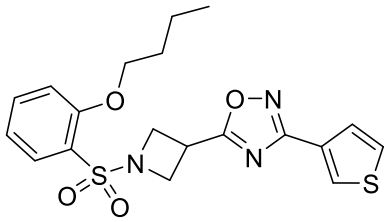
5-(1-((2-Propoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (26). Sodium hydride (NaH) (20 mg, 0.82 mmol, 10.0 eq) was added to *n*-propanol (2.0 mL) at 0 ºC and was allowed to stir for 15 minutes. Analog **11** (30 mg, 0.082 mmol, 1.0 eq) was added afterwards, and the reaction was warmed to room temperature, then heated at 60 ºC overnight. The reaction was cooled to room temperature and concentrated *in vacuo*. Water was added, and the reaction

was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 9 mg (28%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, J = 3.0, 1.0 Hz, 1H), 7.91 (dd, J = 7.8, 1.7 Hz, 1H), 7.60 (dd, J = 5.1, 1.0 Hz, 1H), 7.54 (m, 1H), 7.43 (m, 1H), 7.05 (m, 2H), 4.43 (m, 4H), 4.12 – 3.96 (m, 3H), 4.03 (m, 1H), 1.89 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 165.0, 156.9, 135.0, 131.3, 128.0, 127.8, 127.2, 126.0, 125.5, 120.3, 113.5, 70.9, 54.4, 25.3, 22.5, 10.4 ppm. LCMS R_T = 5.37 min; HRMS, calc'd for $C_{18}H_{20}N_3O_4S_2^+$ [M+H], 406.0890; found 406.0887.

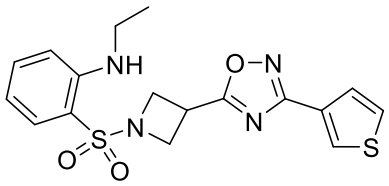
The following analogs were prepared using a method analogous to that used for compound **26**:



5-(1-((2-Isopropoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (27). The title compound was prepared in 26% (9 mg) yield from compound **11** and isopropanol using a method analogous to that described for the conversion of compound **11** into **26**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 3.0, 1.2 Hz, 1H), 7.91 (dd, J = 7.8, 1.6 Hz, 1H), 7.60 (dd, J = 5.1, 1.2 Hz, 1H), 7.52 (m, 1H), 7.43 (m, 1H), 7.09 – 6.99 (m, 2H), 4.75 (m, 1H), 4.50 – 4.40 (m, 4H), 4.02 (m, 1H), 1.43 (d, J = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 165.0, 155.9, 134.8, 131.3, 128.0, 127.9, 127.2, 126.8, 126.0, 120.1, 114.7, 72.0, 54.4, 25.3, 22.0 ppm. LCMS R_T = 5.33 min; HRMS, calc'd for $C_{18}H_{20}N_3O_4S_2^+$ [M+H], 406.0890; found 406.0889.



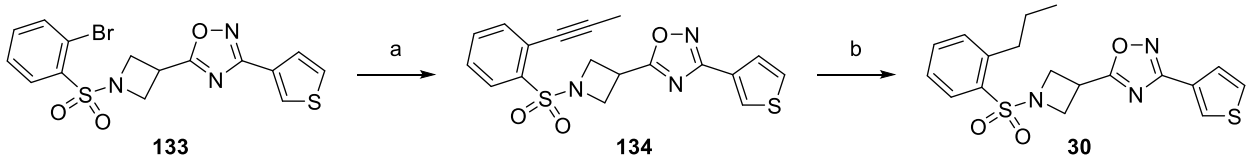
5-(1-((2-Butoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (28). The title compound was prepared in 17% (6 mg) yield from compound **11** and *n*-butanol using a method analogous to that described for the conversion of compound **11** into **26**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 3.0, 1.2 Hz, 1H), 7.91 (m, 1H), 7.60 (dd, J = 5.1, 1.2 Hz, 1H), 7.54 (m, 1H), 7.43 (m, 1H), 7.05 (m, 2H), 4.49 – 4.37 (m, 4H), 4.15 – 3.96 (m, 3H), 1.84 (m, 2H), 1.53 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 165.0, 156.9, 135.0, 131.3, 128.0, 127.8, 127.2, 126.0, 125.5, 120.3, 113.5, 69.2, 54.4, 31.2, 25.3, 19.1, 13.8 ppm. LCMS R_T = 5.59 min; HRMS, calc'd for $C_{19}H_{22}N_3O_4S_2^+$ [M+H], 420.1046; found 420.1053.



***N*-ethyl-2-((3-(3-(thiophen-3-yl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)sulfonyl)aniline (29).** Compound **11** (25 mg, 0.07 mmol, 1 eq) was dissolved in 2M ethylamine in tetrahydrofuran (THF) (2.0 mL). The reaction was heated at 90 ºC overnight. The reaction was cooled to room temperature and concentrated *in vacuo*. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 2 mg (7%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, J = 3.0, 1.2 Hz, 1H), 7.70 (d, J = 8.0, 1.6, 1H), 7.59 (dd, J = 5.1, 1.2 Hz, 1H), 7.49 – 7.39 (m, 2H), 6.75 (m, 2H), 6.14 (m, 1H), 4.25 (m, 4H),

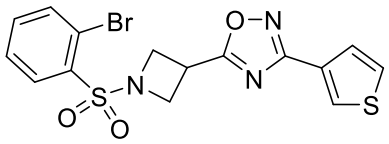
4.95 (m, 1H), 3.21 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 165.0, 147.8, 135.5, 131.3, 128.0, 127.8, 127.2, 126.0, 115.5, 114.8, 112.5, 53.8, 37.8, 25.4, 14.4 ppm. LCMS R_T = 5.50 min; HRMS, calc'd for $C_{17}H_{19}N_4O_3S_2^+$ [M+H], 391.0920; found 391.0896.

Synthesis of Analog 30:

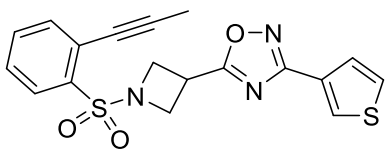


133 **134** **30**

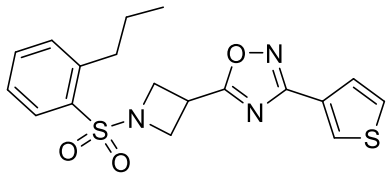
Reagents and conditions: (a) 1M propyne in DMF, NET_3, $PdCl_2(PPh_3)_2$, CuI, 80 ºC, *30%*; (b) 10% Pd/C, H-Cube, 60 ºC, *15%*.



5-(1-((2-Bromophenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (133). The title compound was prepared in 80% yield (150 mg) from intermediate **10** and 2-bromobenzene sulfonyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.10 (m, 1H), 8.06 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.78 (m, 1H), 7.62 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.51 – 7.38 (m, 3H), 4.48 (m, 4H), 4.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 165.1, 137.8, 135.7, 134.0, 131.6, 128.1, 127.8, 127.6, 127.2, 126.0, 121.0, 54.5, 25.1 ppm. LCMS R_T = 5.27 min; HRMS, calc'd for $C_{15}H_{13}BrN_3O_3S_2^+$ [M+H], 425.9576; found 425.9579.



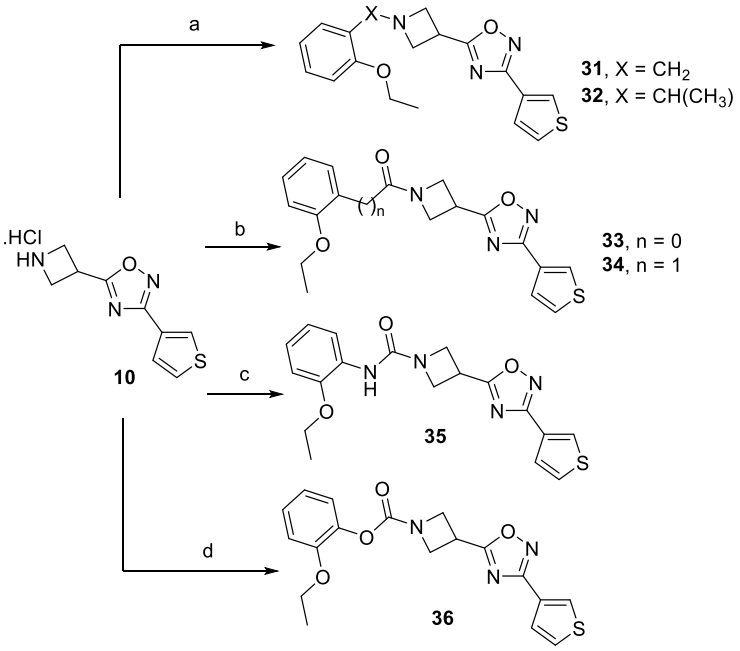
5-(1-((2-(Prop-1-yn-1-yl)phenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (134). Intermediate **133** (150 mg, 0.352 mmol, 1.0 eq), 1M propyne solution in dimethylformamide (DMF) (1.41 mL, 1.41 mmol, 4.0 eq), and triethylamine (195 µM, 1.41 mmol, 4.0 eq) were dissolved in DMF (2.0 mL), and the flask was back-filled with nitrogen (3x). Bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$) (12.3 mg, 0.0175 mmol, 0.05 eq), and cupper (I) iodide (CuI) (1.3 mg, 0.007 mmol, 0.02 eq) were added afterwards, and the reaction was heated at 80 ºC overnight. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 41 mg (30%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 3.0, 1.2 Hz, 1H), 7.97 (dd, J = 7.9, 1.2 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.52 (td, J = 7.5, 1.4 Hz, 1H), 7.47 – 7.38 (m, 2H), 4.51 – 4.36 (m, 4H), 4.03 (m, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 165.0, 137.8, 135.2, 132.6, 129.6, 128.0, 127.8, 127.6, 127.2, 126.0, 123.4, 94.8, 54.6, 25.3, 5.0 ppm. LCMS R_T = 5.24 min; HRMS, calc'd for $C_{18}H_{16}N_3O_3S_2^+$ [M+H], 386.0628; found 386.0628.



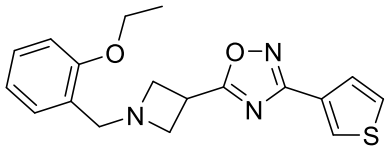
5-(1-((2-Propylphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (30). Intermediate **134** (35 mg, 0.098 mmol, 1.0 eq) was dissolved in methanol (5.0 mL) and was hydrogenated via H-cube utilizing 10% Pd/C CatCart at 60 ºC, and 1 mL/min flow rate. The reaction was concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 15% (6 mg) of the title compound.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 3.0,

1.2 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.61 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.49 – 7.30 (m, 3H), 4.39 – 4.19 (m, 4H), 4.03 (m, 1H), 2.99 (m, 2H), 1.73 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 165.1, 143.6, 134.4, 133.5, 131.8, 130.3, 128.1, 127.8, 127.2, 126.1, 126.0, 53.2, 35.3, 25.3, 24.9, 14.3 ppm. LCMS R_T = 5.72 min; HRMS, calc'd for $C_{18}H_{20}N_3O_3S_2^+$ [M+H], 390.0941; found 390.0938.

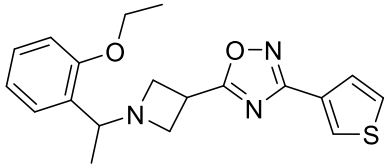
Synthesis of Analogs 31 – 36:



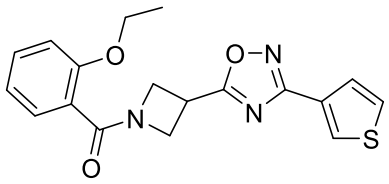
Reagents and conditions: (a) DIEA, CH_3COOH, $(CH_3COO)_3BHNa$, DCM, 2-ethoxybenzaldehyde (**31**, X = CH_2, *44%*) or 2-ethoxyacetophenone, (**32**, X = $CHCH_3$, *52%*); (b) DIEA, HATU, DCM, 2-ethoxybenzoic acid (**33**, n = 0, *16%*) or 2-ethoxyphenyl acetic acid (**34**, n = 1, *6%*); (c) $ClCOOC_6H_4$-4-(NO_2), 2-ethoxyphenol, KOH, PhMe, *20%*; (d) 2-ethoxyphenyl isocyanate, DIEA, DCM, *13%*.



5-(1-(2-Ethoxybenzyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (31). Intermediate **10** (30 mg, 0.12 mmol, 1.0 eq) and *N*,*N*-diisopropylethylamine (22 µL, 0.12 mmol, 1.0 eq) were dissolved in DCM (2.0 mL), followed by the addition of 2-ethoxybenzaldehyde (25 µL, 0.18 mmol, 1.5 eq) and 2 drops of acetic acid, the reaction was stirred for 30 minutes at room temperature. Sodium triacetoxyborohydride ($(CH_3COO)_3BHNa$) (51 mg, 0.24 mmol, 2.0 eq) was added to the reaction, and stirred at room temperature overnight. Water was added, and the reaction was extracted with ethyl acetate (2x), washed with saturated sodium bicarbonate, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 18 mg (44%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 3.0, 1.1 Hz, 1H), 7.65 (dd, J = 5.0, 1.1 Hz, 1H), 7.42 (dd, J = 5.1, 3.0 Hz, 1H), 7.32 – 7.18 (m, 2H), 6.93 (td, J = 7.4, 0.8 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 4.12 – 3.93 (m, 3H), 4.85 (t, J = 7.7 Hz, 2H), 3.75 (s, 2H), 3.61 (t, J = 7.5 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 164.9, 156.7, 129.6, 128.3, 127.7, 127.0, 126.1, 125.8, 120.4, 111.3, 63.6, 58.4, 56.9, 27.7, 14.9 ppm. LCMS R_T = 3.61 min; HRMS, calc'd for $C_{18}H_{20}N_3O_2S^+$ [M+H], 342.1271; found 342.1271.

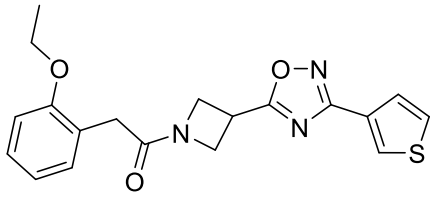


5-(1-(1-(2-Ethoxyphenyl)ethyl)azetidin-3-yl)-3-(thiophen-3-yl)-1,2,4-oxadiazole (32). The title compound was prepared in 52% (22 mg) yield from the intermediate **10** and 2-ethoxyacetophenone using a method analogous to that described for the conversion of **10** into compound **31**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, J = 3.0, 1.2 Hz, 1H), 7.64 (dd, J = 5.1, 1.2 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.19 (m, 1H), 6.95 (td, J = 7.5, 0.8 Hz, 1H), 6.85 (dd, J = 8.2, 0.8 Hz, 1H), 4.13 – 3.82 (m, 5H), 3.69 (t, J = 7.1 Hz, 1H), 3.59 (t, J = 6.8 Hz, 1H), 3.41 (t, J = 7.8 Hz, 1H), 1.45 (t, J = 7.0 Hz, 3H), 1.22 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 164.9, 156.2, 130.5, 128.3, 127.8, 127.7, 127.0, 126.1, 120.7, 111.3, 63.6, 60.1, 57.0, 57.0, 26.5, 18.9, 15.0 ppm. LCMS R_T = 3.62 min; HRMS, calc'd for $C_{19}H_{22}N_3O_2S^+$ [M+H], 356.1427; found 356.1395.

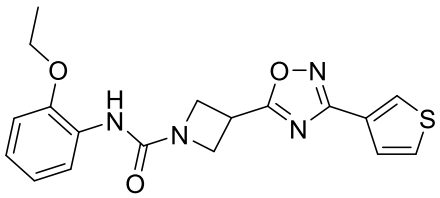


(2-Ethoxyphenyl)(3-(3-(thiophen-3-yl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methanone (33). 2-Ethoxybenzoic acid (30 mg, 0.18 mmol, 1.5 eq), *N*,*N*-diisopropylethylamine (63 µL, 0.36 mmol, 3.0 eq), and HATU (91 mg, 0.24 mmol, 2.0 eq) were dissolved in DCM (2.0 mL), and allowed to stir for 15 minutes at room temperature. Intermediate **10** (30 mg, 0.12 mmol, 1.0 eq) was added to the reaction and stirred overnight at room temperature. Water was added, and the reaction was extracted with DCM (2x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 7 mg (16%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 3.0, 1.2 Hz, 1H), 7.64 (dd, J = 5.1, 1.2 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.38 (m, 1H), 7.00 (td, J = 7.5, 0.9 Hz, 1H), 6.92 (d, J = 8.4 Hz,

1H), 4.72 – 4.37 (m, 4H), 4.20 – 4.05 (m, 3H), 1.47 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 169.3, 165.1, 155.4, 131.7, 129.6, 128.0, 127.9, 127.2, 126.0, 123.3, 120.9, 112.3, 64.2, 54.5, 52.5, 25.9, 14.8 ppm. LCMS R_T = 4.74 min; HRMS, calc'd for $C_{18}H_{18}N_3O_3S^+$ [M+H], 356.1063; found 356.1094.

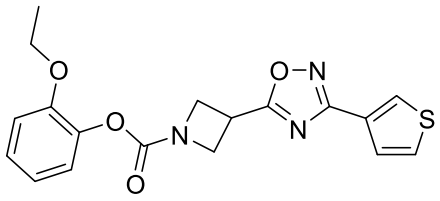


2-(2-Ethoxyphenyl)-1-(3-(3-(thiophen-3-yl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)ethan-1-one (34). The title compound was prepared in 6% (4 mg) yield from the intermediate **10** and 2-ethoxyphenyl acetic acid using a method analogous to that described for the conversion of intermediate **10** into compound **33**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.27 – 7.17 (m, 2H), 6.90 (m, 2H), 4.71 (t, *J* = 8.4 Hz, 1H), 4.61- 4.41 (m, 2H), 4.36 – 4.18 (m, 2H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.49 (m, 2H), 1.42 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 169.3, 165.1, 155.4, 131.7, 129.6, 128.0, 127.9, 127.2, 126.0, 123.3, 120.9, 112.3, 64.2, 54.5, 52.5, 25.9, 14.8 ppm. LCMS R_T = 4.92 min; HRMS, calc'd for $C_{19}H_{20}N_3O_3S^+$ [M+H], 370.1220; found 370.1223.



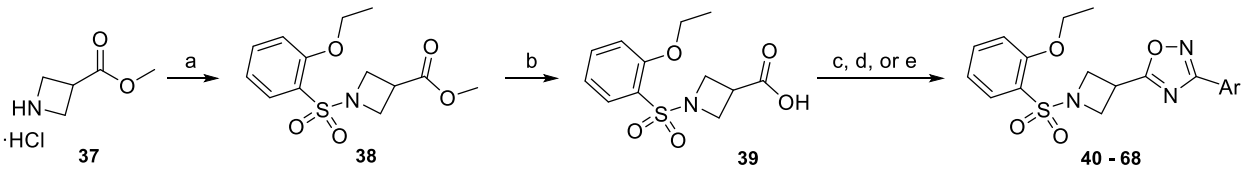
***N*-(2-ethoxyphenyl)-3-(3-(thiophen-3-yl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxamide (35).** Intermediate **10** (25 mg, 0.10 mmol, 1.0 eq) and *N*,*N*-diisopropylethylamine (87 µL, 0.50 mmol,

5.0 eq) were dissolved in DCM (2.0 mL), followed by the addition of 2-ethoxyphenyl isocyanate (22 µL, 0.15 mmol, 1.5 eq), and the reaction was stirred at room temperature for 1 hour. Water was added, and the reaction was extracted with DCM (2x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 5 mg (13%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (m, 1H), 8.09 (dd, J = 3.0, 1.2 Hz, 1H), 7.65 (dd, J = 5.1, 1.2 Hz, 1H), 7.44 (dd, J = 5.1, 3.0 Hz, 1H), 6.95 (m, 2H), 6.88 – 6.75 (m, 2H), 4.49 (m, 4H), 4.22- 4.03 (m, 3H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 165.1, 156.0, 146.8, 128.1, 128.0, 127.9, 127.2, 126.0, 122.4, 121.2, 118.6, 110.9, 64.2, 53.1, 25.5, 14.9 ppm. LCMS R_T = 5.05 min; HRMS, calc'd for $C_{18}H_{19}N_4O_3S^+$ [M+H], 371.1172; found 371.1177.

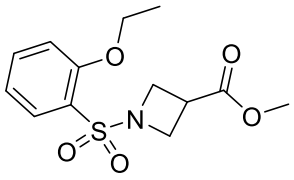


2-Ethoxyphenyl 3-(3-(thiophen-3-yl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (36). Intermediate **10** (30 mg, 0.12 mmol, 1.0 eq) and triethylamine (33 µL, 0.24 mmol, 2.0 eq) were dissolved in THF (1.0 mL), followed by the addition of *p*-nitrophenyl chloroformate ($ClCOOC_6H_4$-4-(NO_2)). The reaction was stirred overnight at room temperature. Water was added, and the reaction was extracted with ethyl acetate (2x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude intermediate, 2-ethoxyphenol (25 µL, 0.18 mmol, 1.5 eq) and potassium hydroxide (KOH) (10 mg, 0.18 mmol, 1.5 eq) were dissolved in toluene (3.0 mL), and the reaction was heated at reflux overnight. The reaction was cooled to room temperature, water was added, and the reaction was extracted with ethyl acetate (2x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash

chromatography on silica gel afforded 9 mg (20%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J = 3.01, 1.19 Hz, 1H), 7.66 (dd, J = 5.1, 1.2 Hz, 1H), 7.45 (dd, J = 3.0 Hz, 1H), 7.20 – 7.07 (m, 2H), 6.98 – 6.88 (m, 2H), 4.58 (bs, 4H), 4.19 (m, 1H), 4.08 (q, J = 7.0 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 165.1, 154.6, 150.8, 140.2, 128.0, 127.9, 127.2, 126.6, 126.0, 123.1, 120.7, 113.6, 64.4, 53.7, 26.2, 14.9 ppm. LCMS R_T = 5.26 min; HRMS, calc'd for $C_{18}H_{18}N_3O_4S^+$ [M+H], 372.1013; found 372.1016.

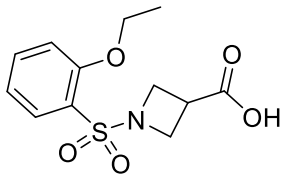


Reagents and conditions: Reagents and conditions: (a) 2-Ethoxybenzene sulfonyl chloride, NEt_3, DCM, *88%*; (b) LiOH, H_2O, THF, *95%*; (c) **40**, **59** ArC(NH)NHOH , HATU, DIEA, DMF, 140 ºC, *6 - 40%*; (d) **41** – **49**, **53** – **58**, **63 - 65** ArC(NH)NHOH, EDC, HOBt, DIEA, 1,4-dioxane, reflux, *5 –24%*, (e) **50** – **52** ArC(NH)NHOH, CDI (2X), DMF, 80 ºC, *39 - 43%* or (f) **60** – **62, 66 - 68** ArC(NH)NHOH, CDI, NaOH, DMSO, *27 - 65%*.

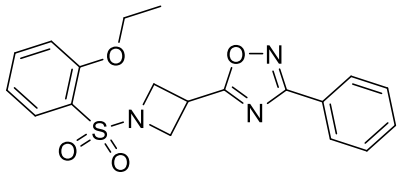


Methyl 1-((2-ethoxyphenyl)sulfonyl)azetidine-3-carboxylate (38). Methyl azetidine-3-carboxylate hydrochloride (**37**) (618 mg, 4.08 mmol, 1.2 eq) and *N*,*N*-diisopropylethylamine (1.78

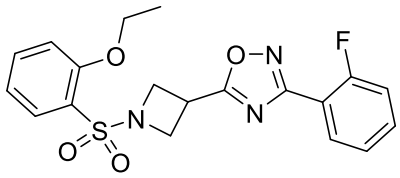
mL, 10.2 mmol, 3.0 eq) were dissolved in DCM (10 mL), followed by the addition of 2-ethoxybenzene sulfonyl chloride (750 mg, 3.40 mmol, 1.0 eq). The reaction was stirred for 2 hours at room temperature. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 830 mg (82%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.1, 1.8 Hz, 1H), 7.53 (m, 1H), 7.08 – 6.98 (m, 2H), 4.27 – 4.12 (m, 6H), 3.70 (s, 3H), 3.35 (m, 1H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 156.7, 134.8, 131.1, 126.1, 120.3, 113.5, 65.0, 53.1, 52.4, 31.5, 14.7 ppm. LCMS R_T = 3.94 min; HRMS, calc'd for $C_{13}H_{18}NO_5S^+$ [M+H], 300.0900; found 300.0899.



1-((2-Ethoxyphenyl)sulfonyl)azetidine-3-carboxylic acid (39). Intermediate **38** (830 mg, 2.77 mmol, 1.0 eq) was dissolved in THF (5.0 mL) and H_2O (5.0 mL), followed by the addition of lithium hydroxide (LiOH) monohydrate (233 mg, 5.54 mmol, 2.0 eq). The reaction was stirred at room temperature for 2 hours. The solvents were removed *in vacuo*, and the reaction was acidified with 1N HCl. The aqueous layer was extracted with ethyl acetate (2x), the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 720 mg (91%) as a white solid that was used further without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.2, 1.7 Hz, 1H), 7.53 (m, 1H), 7.08 – 6.99 (m, 2H), 4.30 – 4.12 (m, 6H), 3.38 (m, 1H), 1.51 (t, J = 7.0 Hz, 3H).

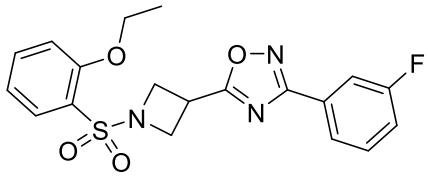


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-phenyl-1,2,4-oxadiazole (40). Intermediate **39** (50 mg, 0.18 mmol, 1.0 eq), *N*,*N*-diisopropylethylamine (94 µL, 0.54 mmol, 3.0 eq), and HATU (103 mg, 0.27 mmol, 1.5 eq) were dissolved in DMF (2.0 mL) and allowed to stir for 15 minutes, followed by the addition of benzamidoxime (49 mg, 0.36 mmol, 2.0 eq). The reaction was allowed to stir for 1 hour at room temperature, afterwards the reaction temperature was brought to 140 ºC and stirred for 2 hours. Water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 28 mg (40%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.91 (dd, J = 7.8, 1.8 Hz, 1H), 7.59 – 7.43 (m, 4H), 7.10 – 6.99 (m, 2H), 4.46 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.05 (m, 1H), 1.50 (t, J = 7. 0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 168.6, 156.7, 135.0, 131.5, 131.2, 128.9, 127.5, 126.4, 125.9, 120.4, 113.5, 65.1, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.27 min; HRMS, calc'd for $C_{19}H_{20}N_3O_4S^+$ [M+H], 386.1169; found 386.1177.



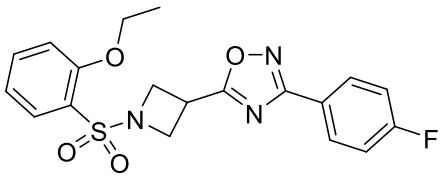
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(2-fluorophenyl)-1,2,4-oxadiazole (41). Intermediate **39** (50 mg, 0.18 mmol, 1.0 eq), DIEA (63 µL, 0.36 mmol, 2.0 eq), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (52 mg, 0.27 mmol, 1.5 eq), and Hydroxybenzotriazole

(HOBt) (41 mg, 0.27 mmol, 1.5 eq) were dissolved in 1,4-dioxane (2.0 mL). The reaction was allowed to stir for 30 minutes at room temperature, followed by the addition of 2-fluorobenzamidoxime (41 mg, 0.27 mmol, 1.5 eq). The reaction was stirred at room temperature for 2 hours, afterwards the reaction temperature was brought to 90 ºC and stirred overnight. Water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 4 mg (6%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (td, J = 7.3, 1.8 Hz, 1H), 7.91 (dd, J = 8.0, 1.6 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.34 – 7.19 (m, 2H), 7.10 – 6.99 (m, 2H), 4.46 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.08 (m, 1H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 163.9 (d, J(C,F) = 228 Hz), 159.0, 156.7, 135.0, 133.0 (d, J(C,F) = 8.6 Hz), 131.2, 130.7 (d, J(C,F) = 2.2 Hz), 125.9, 124.5 (d, J(C,F) = 3.8 Hz), 120.4, 116.8 (d, J(C,F) = 21.1 Hz), 114.7 (d, J(C,F) = 12.4 Hz), 113.5, 65.1, 54.6, 25.3, 14.7 ppm. LCMS R_T = 5.15 min; HRMS, calc'd for $C_{19}H_{19}FN_3O_4S^+$ [M+H], 404.1075; found 404.1080.

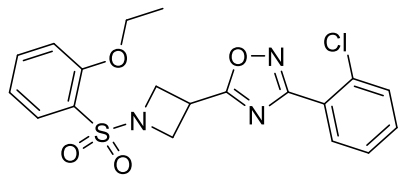


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(3-fluorophenyl)-1,2,4-oxadiazole (42). The title compound was prepared in 11% yield (8 mg) from intermediate **39** and 3-fluorobenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.8, 1.7 Hz, 1H), 7.84 (dt, J = 8.0, 1.2 Hz, 1H), 7.73 (m, 1H), 7.60 – 7.41 (m, 2H), 7.22 (m, 2H), 7.11 – 7.01 (m, 2H), 4.46 (m, 4H), 4.20 (q,

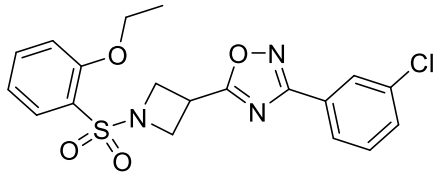
J = 7.0 Hz, 2H), 4.05 (m, 1H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 166.2 (d, *J*(C,F) = 244.4 Hz), 161.2, 156.7, 135.0, 131.2, 130.7 (d, *J*(C,F) = 8.0 Hz), 128.4 (d, *J*(C,F) = 8.6 Hz), 125.9, 123.2 (d, *J*(C,F) = 3.2 Hz), 120.4, 118.5 (d, *J*(C,F) = 21.3 Hz), 114.6 (d, *J*(C,F) = 23.8 Hz), 113.6, 65.1, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.38 min; HRMS, calc'd for $C_{19}H_{19}FN_3O_4S^+$ [M+H], 404.1075; found 404.1076.



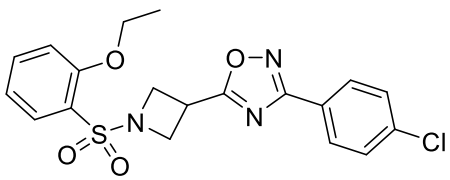
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (43). The title compound was prepared in 10% yield (7 mg) from intermediate **39** and 4-fluorobenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.04 (m, 2H), 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.54 (m, 1H), 7.17 (m, 2H), 7.10 – 6.99 (m, 2H), 4.46 (m, 4H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.04 (m, 1H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 167.8, 164.7 (d, *J*(C,F) = 252 Hz), 156.7, 135.0, 131.1, 129.6 (d, *J*(C,F) = 8.8 Hz), 126.0, 122.6 (d, *J*(C,F) = 3.4 Hz), 120.4, 116.2 (d, *J*(C,F) = 22.1 Hz), 113.5, 65.1, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.35 min; HRMS, calc'd for $C_{19}H_{19}FN_3O_4S^+$ [M+H], 404.1075; found 404.1084.



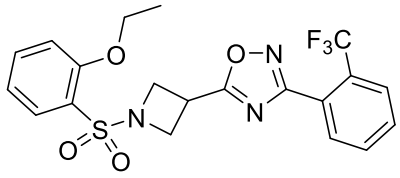
3-(2-Chlorophenyl)-5-(1-((2-ethoxyphenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (44). The title compound was prepared in 5% yield (4 mg) from intermediate **39** and 2-chlorobenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.59 – 7.33 (m, 4H), 7.10 – 6.99 (m, 2H), 4.47 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.09 (m, 1H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 167.4, 156.7, 135.0, 133.5, 131.9, 131.7, 131.2, 131.0, 126.9, 125.9, 125.6, 120.4, 113.6, 65.1, 54.5, 25.3, 14.8 ppm. LCMS R_T = 5.34 min; HRMS, calc'd for $C_{19}H_{19}ClN_3O_4S^+$ [M+H], 420.0779; found 420.0788.



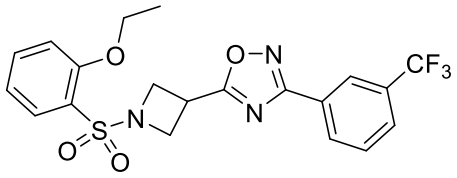
3-(3-Chlorophenyl)-5-(1-((2-ethoxyphenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (45). The title compound was prepared in 7% yield (5 mg) from intermediate **39** and 3-chlorobenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (t, J = 1.6 Hz, 1H), 7.93 (m, 2H), 7.61 – 7.38 (m, 3H), 7.12 – 7.01 (m, 2H), 4.46 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.05 (m, 1H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 167.6, 156.8, 155.0, 135.1, 131.5, 131.3, 130.3, 128.1, 127.6, 125.8, 125.5, 120.4, 113.6, 65.1, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.34 min; HRMS, calc'd for $C_{19}H_{19}ClN_3O_4S^+$ [M+H], 420.0779; found 420.0787.



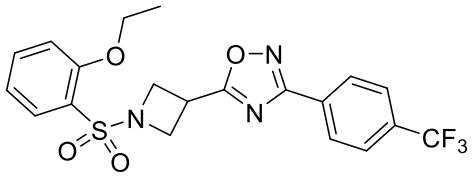
3-(4-Chlorophenyl)-5-(1-((2-ethoxyphenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (46). The title compound was prepared in 5% yield (4 mg) from intermediate **39** and 4-chlorobenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.91 (dd, J = 7.8, 1.8 Hz, 1H), 7.54 (m, 1H), 7.47 (m, 2H), 7.11 – 6.99 (m, 2H), 4.46 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.05 (m, 1H), 1.50 (t, J = 7. 0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 167.8, 156.7, 137.7, 135.0, 131.1, 129.3, 128.8, 126.0, 124.9, 120.4, 113.5, 65.1, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.34 min; HRMS, calc'd for $C_{19}H_{19}ClN_3O_4S^+$ [M+H], 420.0779; found 420.0788.



5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(2-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (47). The title compound was prepared in 11% yield (9 mg) from intermediate **39** and 2-trifluoromethylbenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 1H), 7.87 – 7.81 (m, 1H), 7.79 – 7.73 (m, 1H), 7.71 – 7.63 (m, 2H), 7.53 (m, 1H), 7.05 (m, 2H), 4.46 (m, 4H), 4.25 – 4.02 (m, 3H), 1.49 (t, J = 7. 0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 167.8, 156.7, 135.0, 131.9, 131.8, 131.1, 131.0, 129.6, 129.2, 127.0 (q, J(C,F) = 5.3 Hz), 125.8, 125.2 (q, J(C,F) = 3.4 Hz), 120.4, 113.5, 65.1, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.38 min; HRMS, calc'd for $C_{20}H_{19}F_3N_3O_4S^+$ [M+H], 454.1043; found 454.1044.

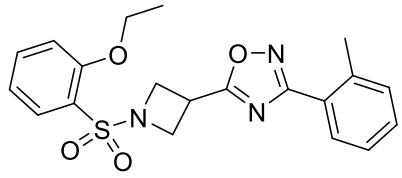


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (48). The title compound was prepared in 17% yield (14 mg) from intermediate **39** and 3-trifluoromethylbenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 – 8.19 (m, 2H), 7.92 (dd, J = 7.8, 1.6 Hz, 1H), 7.79 (m, 1H), 7.63 (m, 1H), 7.55 (m, 1H), 7.06 (m, 2H), 4.47 (m, 4H), 4.21 (q, J = 7.0 Hz, 2H), 4.07 (m, 1H), 1.51 (t, J = 7. 0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 167.6, 156.8, 135.1, 131.8, 131.3, 130.5, 129.6, 128.0 (q, J(C,F) = 3.7 Hz), 127.3, 125.8, 125.5, 124.5 (q, J(C,F) = 3.9 Hz), 120.4, 113.6, 65.1, 54.5, 25.2, 14.7 ppm. LCMS R_T = 5.69 min; HRMS, calc'd for $C_{20}H_{19}F_3N_3O_4S^+$ [M+H], 454.1043; found 454.1043.

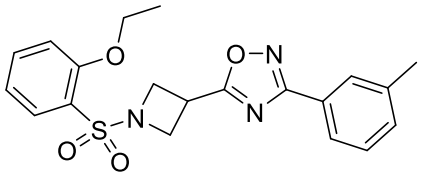


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (49). The title compound was prepared in 11% yield (9 mg) from intermediate **39** and 4-trifluoromethylbenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.1 Hz, 2H), 7.92 (dd, J = 7.8, 1.7 Hz, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.55 (m, 1H), 7.06 (m, 2H), 4.47 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.07 (m, 1H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 167.6, 156.6, 135.0, 133.1 (q, J(C,F) = 32.8 Hz), 131.1, 129.8, 125.8, 125.9 (q, J(C,F) = 3.5 Hz), 125.5, 121.9,

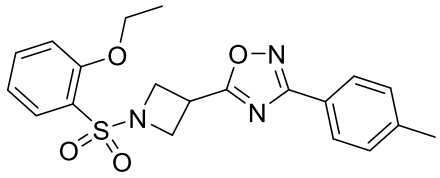
120.5, 113.6, 65.1, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.71 min; HRMS, calc'd for $C_{20}H_{19}F_3N_3O_4S^+$ [M+H], 454.1043; found 454.1042.



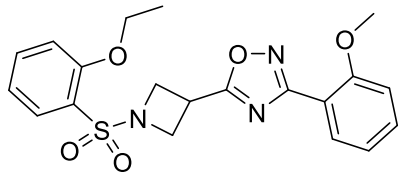
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(*o*-tolyl)-1,2,4-oxadiazole (50). Intermediate **39** (30 mg, 0.11 mmol, 1.0 eq) and 1,1'-carbonyldiimidazole (CDI) (27 mg, 0.17 mmol, 1.5 eq) were dissolved in anhydrous DMF (2.0 mL), and the reaction was allowed to stir for 30 minutes at room temperature followed by the addition of 2-methylbenzamidoxime (25 mg, 0.17 mmol, 1.5 eq), and another 1.5 eq of CDI. The reaction was stirred overnight at 80 ºC. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 19 mg (43%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.8, 1.7 Hz, 1H), 7.88 – 7.79 (m, 2H), 7.53 (m, 1H), 7.41 – 7.29 (m, 2H), 7.11 – 6.98 (m, 2H), 4.46 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.04 (m, 1H), 2.43 (s, 3H), 1.50 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 168.7, 156.7, 138.7, 135.0, 132.2, 131.2, 128.8, 128.0, 126.2, 126.0, 124.6, 120.4, 113.6, 65.1, 54.5, 25.4, 21.3, 14.7 ppm. LCMS R_T = 5.54 min; HRMS, calc'd for $C_{20}H_{22}N_3O_4S^+$ [M+H], 400.1326; found 400.1327.



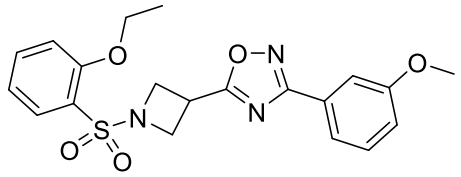
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(*m*-tolyl)-1,2,4-oxadiazole (51). The title compound was prepared in 43% yield (29 mg) from intermediate **39** and 3-methylbenzamidoxime using a method analogous to that described for the conversion of compound **39** into **50**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.87 (m, 2H), 7.53 (m, 1H), 7.44 – 7.35 (m, 1H), 7.34 – 7.27 (m, 2H), 7.09 – 6.99 (m, 2H), 4.46 (m, 4H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.06 (m, 1H), 2.60 (s, 3H), 1.49 (t, *J* = 7.0 Hz, 3H). LCMS R_T = 5.50 min; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 169.1, 156.7, 138.3, 135.0, 131.5, 131.2, 130.8, 130.1, 126.0, 125.9, 125.6, 120.4, 113.6, 65.1, 54.6, 25.3, 22.2, 14.7 ppm. LCMS R_T = 5.50 min; HRMS, calc'd for $C_{20}H_{22}N_3O_4S^+$ [M+H], 400.1326; found 400.1326.



5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(*p*-tolyl)-1,2,4-oxadiazole (52). The title compound was prepared in 39% yield (26 mg) from intermediate **39** and 4-methylbenzamidoxime using a method analogous to that described for the conversion of compound **39** into **50**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 3H), 7.53 (m, 1H), 7.28 (m, 2H), 7.09 – 6.99 (m, 2H), 4.45 (m, 4H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.03 (m, 1H), 2.42 (s, 3H), 1.49 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 168.6, 156.7, 141.8, 135.0, 131.2, 129.6, 127.4, 125.9, 123.5, 120.4, 113.6, 65.1, 54.5, 25.3, 21.6, 14.7 ppm. LCMS R_T = 5.53 min; HRMS, calc'd for $C_{20}H_{22}N_3O_4S^+$ [M+H], 400.1326; found 400.1327.

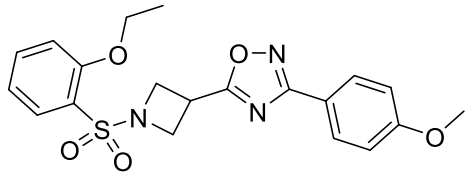


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(2-methoxyphenyl)-1,2,4-oxadiazole (53). The title compound was prepared in 11% yield (8 mg) from intermediate **39** and 2-methoxyamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.58 – 7.44 (m, 2H), 7.12 – 6.98 (m, 4H), 4.45 (m, 4H), 4.19 (q, J = 7.0 Hz, 2H), 4.07 (m, 1H), 3.97 (s, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 167.1, 158.1, 156.7, 135.0, 132.6, 131.4, 131.1, 125.8, 120.7, 120.4, 115.3, 113.5, 111.7, 65.1, 56.0, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.00 min; HRMS, calc'd for $C_{20}H_{22}N_3O_5S^+$ [M+H], 416.1275; found 416.1284.

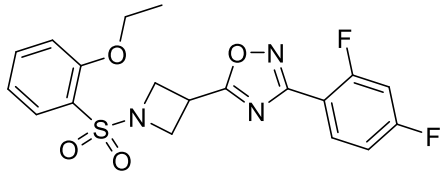


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(3-methoxyphenyl)-1,2,4-oxadiazole (54). The title compound was prepared in 17% yield (12 mg) from intermediate **39** and 3-methoxybenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.8, 1.7 Hz, 1H), 7.63 (dt, J = 1.2 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.11 – 6.99 (m, 3H), 4.46 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.05 (m, 1H), 3.88 (s, 3H), 1.50 (t, J = 7. 0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 168.5, 159.9, 156.7, 135.0, 131.2, 130.1, 127.5, 125.9, 120.4, 119.9, 117.9, 113.5,

112.1, 65.1, 56.0, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.30 min; HRMS, calc'd for $C_{20}H_{22}N_3O_5S^+$ [M+H], 416.1275; found 416.1278.

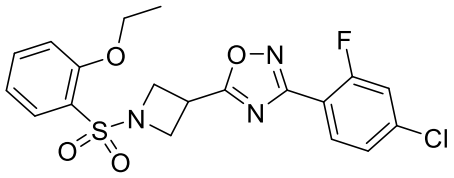


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (55). The title compound was prepared in 15% yield (11 mg) from intermediate **39** and 4-methoxybenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.87 (m, 3H), 7.54 (m, 1H), 7.11 – 6.92 (m, 4H), 4.45 (m, 4H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.03 (m, 1H), 3.88 (s, 3H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 168.3, 162.1, 156.7, 135.0, 131.2, 129.1, 125.9, 120.4, 118.8, 114.3, 113.5, 65.1, 55.4, 54.5, 25.3, 14.7 ppm. LCMS R_T = 5.25 min; HRMS, calc'd for $C_{20}H_{22}N_3O_5S^+$ [M+H], 416.1275; found 416.1284.

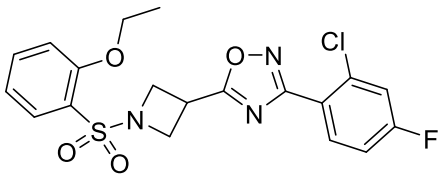


3-(2,4-Difluorophenyl)-5-(1-((2-ethoxyphenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (56). The title compound was prepared in 18% yield (13 mg) from intermediate **39** and 2,4-difluorobenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 1H), 7.91 (dd, *J* = 7.8, 1.6 Hz, 1H),

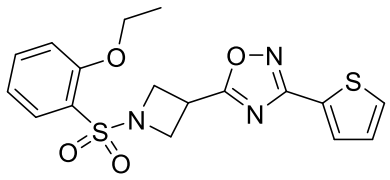
7.54 (m, 1H), 7.12 – 6.94 (m, 4H), 4.46 (m, 4H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.07 (m, 1H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 164.8 (d, *J*(C,F) = 260 Hz), 164.9, 164.8, 164.8 (d, *J*(C,F) = 253 Hz), 159.6, 169.5, 156.7, 135.0, 132.1 (d, *J*(C,F) = 10.5 Hz), 132.02 (d, *J*(C,F) = 10.1 Hz), 131.1, 126.0, 120.4, 113.6, 112.2 (d, *J*(C,F) = 21.6 Hz), 112.1 (d, *J*(C,F) = 21.5 Hz), 111.3 (d, *J*(C,F) = 4.4 Hz), 111.1 (d, *J*(C,F) = 3.8 Hz), 105.3 (d, *J*(C,F) = 25.2 Hz), 65.1, 54.4, 25.2, 14.7 ppm. LCMS R_T = 5.27 min; HRMS, calc'd for $C_{19}H_{18}F_2N_3O_4S^+$ [M+H], 422.0981; found 422.0985.



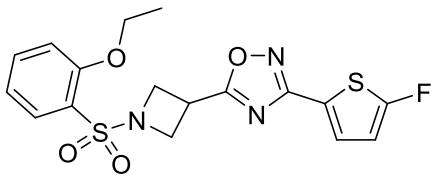
3-(4-Chloro-2-fluorophenyl)-5-(1-((2-ethoxyphenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (57). The title compound was prepared in 8% yield (6 mg) from intermediate **39** and 4-chloro-2-fluorobenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.02 – 7.86 (m, 2H), 7.54 (m, 1H), 7.34 – 7.23 (m, 2H), 7.11 – 6.99 (m, 2H), 4.46 (m, 4H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.07 (m, 1H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 164.9, 163.5 (d, *J*(C,F) = 192.4 Hz), 158.7, 156.7, 138.4 (d, *J*(C,F) = 9.9 Hz), 135.0, 131.4 (d, *J*(C,F) = 3.1), 131.1, 126.0, 125.1 (d, *J*(C,F) = 3.7 Hz), 120.4, 117.6 (d, *J*(C,F) = 24.4 Hz), 113.5, 65.1, 54.4, 25.2, 14.7 ppm. LCMS R_T = 5.56 min; HRMS, calc'd for $C_{19}H_{18}ClFN_3O_4S^+$ [M+H], 438.0685; found 438.0689.



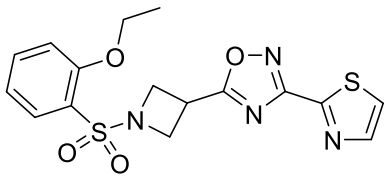
3-(2-Chloro-4-fluorophenyl)-5-(1-((2-ethoxyphenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (58). The title compound was prepared in 11% yield (8 mg) from intermediate **39** and 2-chloro-4-fluorobenzamidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.86 (m, 2H), 7.53 (m, 1H), 7.29 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.18 – 6.98 (m, 3H), 4.46 (m, 4H), 4.20 (q, *J* = 7. 0 Hz, 2H), 4.08 (m, 1H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 166.7, 163.7 (d, *J*(C,F) = 255.5 Hz), 156.7, 135.0, 134.8 (d, *J*(C,F) = 10.6 Hz), 133.3, 131.1, 126.0, 122.0 (d, *J*(C,F) = 5.5 Hz), 120.4, 118.6 (d, *J*(C,F) = 25.0 Hz), 114.6 (d, *J*(C,F) = 21.5 Hz), 113.6, 65.1, 54.5, 25.3, 14.8 ppm. LCMS R_T = 5.47 min; HRMS, calc'd for $C_{19}H_{18}ClFN_3O_4S^+$ [M+H], 438.0685; found 438.0688.



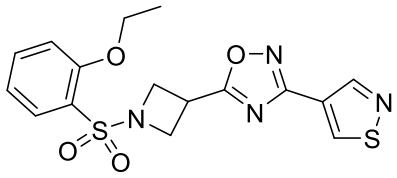
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiophen-2-yl)-1,2,4-oxadiazole (59). The title compound was prepared in 6% yield (4 mg) from intermediate **39** and thiophene-2-amidoxime using a method analogous to that described for the conversion of compound **39** into **40**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.76 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.16 (m, 1H), 7.06 (m, 2H), 4.44 (m, 4H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.04 (m, 1H), 1.51 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 164.6, 156.7, 135.1, 131.2, 129.8, 129.6, 128.1, 127.8, 125.8, 120.4, 113.5, 65.1, 54.4, 25.3, 14.8 ppm. LCMS R_T = 5.10 min; HRMS, calc'd for $C_{17}H_{18}N_3O_4S_2^+$ [M+H], 392.0733; found 392.0753.



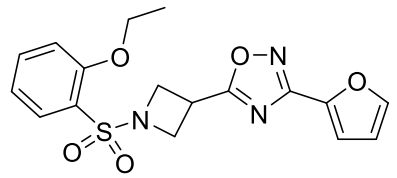
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(5-fluorothiophen-2-yl)-1,2,4-oxadiazole (60). CDI (24 mg, 0.15 mmol, 1.2 eq) was added to a solution of intermediate **39** (35 mg, 0.12 mmol, 1.1 eq) in dimethyl sulfoxide (DMSO) (0.5 mL). The reaction was stirred for 30 minutes at room temperature, followed by the addition of 5-fluorothiophene-2-amidoxime (18 mg, 0.11, 1.0 eq). The reaction was stirred at room temperature overnight, followed by the addition of sodium hydroxide (NaOH) (6 mg, 0.15 mmol, 1.2 eq), and was stirred for additional 2 hours at room temperature. The reaction was diluted with ice-cold water and extracted with DCM (2x). The combined organics were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 12 mg (27%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.3, 1.8 Hz, 1H), 7.55 (m, 1H), 7.42 (t, J = 4.0 Hz, 1H), 7.06 (m, 2H), 6.56 (dd, J = 4.2, 1.6 Hz, 1H), 4.43 (m, 4H), 4.21 (q, J = 7. 0 Hz, 2H), 4.01 (m, 1H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 168.1, 164.2, 156.7, 135.0, 131.2, 127.1 (d, J(C,F) = 4.3 Hz), 125.9, 120.4, 116.5 (d, J(C,F) = 4.7 Hz), 113.5, 108.8 (d, J(C,F) = 11.2 Hz), 65.1, 54.4, 25.2, 14.7 ppm. LCMS R_T = 5.40 min; HRMS, calc'd for $C_{17}H_{17}FN_3O_4S_2^+$ [M+H], 410.0639; found 410.0645.



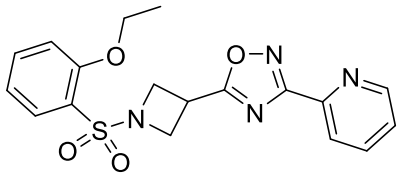
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(thiazol-2-yl)-1,2,4-oxadiazole (61). The title compound was prepared in 65% yield (43 mg) from intermediate **39** and thiazole-2-amidoxime using a method analogous to that described for the conversion of compound **39** into **60**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 3.2 Hz, 1H), 7.90 (dd, J = 8.3, 1.8 Hz, 1H), 7.6 (d, J = 3.1 Hz, 1H), 7.5 (m, 1H), 7.1 (m, 2H), 4.5 (m, 4H), 4.21 (q, J = 7.0 Hz, 2H), 4.10 (m, 1H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 164.2, 156.7, 153.8, 145.2, 135.0, 131.1, 126.0, 122.8, 120.4, 113.6, 65.1, 54.3, 25.4, 14.8 ppm. LCMS R_T = 4.57 min; HRMS, calc'd for $C_{16}H_{17}N_4O_4S_2^+$ [M+H], 393.0686; found 393.0689.



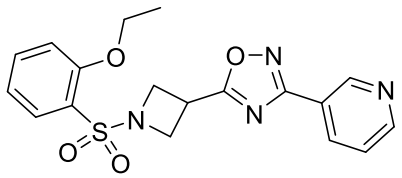
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(isothiazol-4-yl)-1,2,4-oxadiazole (62). The title compound was prepared in 39% yield (26 mg) from intermediate **39** and isothiazole-4-amidoxime using a method analogous to that described for the conversion of compound **39** into **60**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 9.00 (s, 1H), 7.91 (dd, J = 7.9, 1. 6 Hz, 1H), 7.55 (m, 1H), 7.06 (m, 2H), 4.46 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.06 (m, 1H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 163.2, 156.7, 156.1, 149.0, 135.0, 131.1, 126.0, 126.0, 120.4, 113.6, 65.1, 54.4, 25.2, 14.7 ppm. LCMS R_T = 4.76 min; HRMS, calc'd for $C_{16}H_{17}N_4O_4S_2^+$ [M+H], 393.0686; found 393.0691.



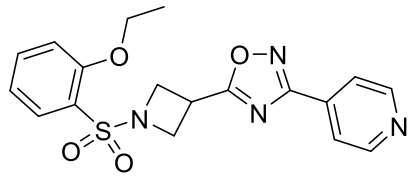
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(furan-2-yl)-1,2,4-oxadiazole (63). The title compound was prepared in 28% yield (18 mg) from intermediate **39** and furan-2-amidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.3, 1.8 Hz, 1H), 7.62 (dd, J = 1.8, 0.8 Hz, 1H), 7.54 (m, 1H), 7.11 (dd, J = 3.5, 0.8 Hz, 1H), 7.05 (m, 2H), 6.58 (dd, J = 3.5, 1.8 Hz, 1H), 4.44 (m, 4H), 4.20 (q, J = 7. 0 Hz, 2H), 4.04 (m, 1H), 1.50 (t, J = 7.0 Hz, 3H). LCMS R_T = 4.82 min; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 161.4, 156.7, 145.5, 141.9, 135.0, 131.1, 125.9, 120.4, 114.2, 113.5, 111.9, 65.1, 54.4, 25.3, 14.7 ppm. HRMS, calc'd for $C_{17}H_{18}N_3O_5S^+$ [M+H], 376.0962; found 376.0963.



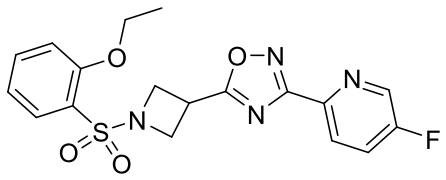
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(pyridin-2-yl)-1,2,4-oxadiazole (64). The title compound was prepared in 31% yield (20 mg) from intermediate **39** and pyridine-2-amidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (dq, J = 4.8, 0.9 Hz, 1H), 8.10 (dt, J = 7.9, 1.0 Hz, 1H), 7.96 – 7.82 (m, 2H), 7.58 – 7.39 (m, 2H), 7.05 (m, 2H), 4.48 (m, 4H), 4.26 – 4.04 (m, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 168.4, 156.7, 150.5, 145.9, 137.2, 135.0, 131.0, 126.0, 125.8, 123.3, 120.4,113.5, 65.1, 54.3, 25.5, 14.7 ppm. LCMS R_T = 4.45 min; HRMS, calc'd for $C_{18}H_{19}N_4O_4S^+$ [M+H], 387.1122; found 387.1124.



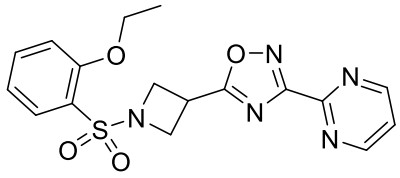
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole (65). The title compound was prepared in 24% yield (16 mg) from intermediate **39** and pyridine-3-amidoxime using a method analogous to that described for the conversion of compound **39** into **41**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.76 (d, J = 3.8 Hz, 1H), 8.32 (dt, J = 8.0, 1.9 Hz, 1H), 7.92 (m, 1H), 7.55 (m, 1H), 7.44 (m, 1H), 7.06 (m, 2H), 4.47 (m, 4H), 4.21 (q, J = 7.0 Hz, 2H), 4.08 (m, 1H), 1.51 (t, J = 7.0 Hz, 3H). LCMS R_T = 4.36 min; HRMS, calc'd for $C_{18}H_{19}N_4O_4S^+$ [M+H], 387.1122; found 387.1128.



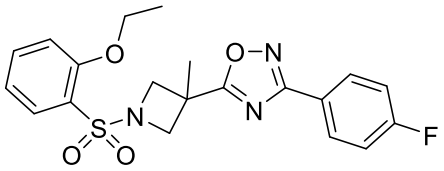
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(pyridin-4-yl)-1,2,4-oxadiazole (66). The title compound was prepared in 40% yield (26 mg) from intermediate **39** and pyridine-4-amidoxime using a method analogous to that described for the conversion of compound **39** into **60**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 5.9 Hz, 2H), 7.96 – 7.84 (m, 3H), 7.55 (m, 1H), 7.06 (m, 2H), 4.47 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 4.08 (m, 1H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 167.1, 156.7, 150.8, 135.0, 133.8, 131.1, 126.0, 121.2, 120.5, 113.6, 65.1, 54.4, 25.3, 14.7 ppm. LCMS R_T = 4.29 min; HRMS, calc'd for $C_{18}H_{19}N_4O_4S^+$ [M+H], 387.1122; found 387.1129.



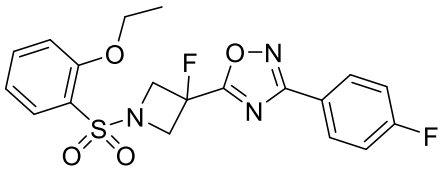
5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (67). The title compound was prepared in 29% yield (20 mg) from intermediate **39** and 4-fluoropyridine-2-amidoxime using a method analogous to that described for the conversion of compound **39** into **60**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 2.8 Hz, 1H), 8.14 (m, 1H), 7.90 (m, 1H), 7.63 – 7.47 (m, 2H), 7.05 (m, 2H), 4.48 (m, 4H), 4.28 – 4.03 (m, 3H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 167.6, 160.4 (d, J(C,F) = 261.9 Hz), 156.7, 142.1 (d, J(C,F) = 4.2 Hz), 139.2 (d, J(C,F) = 24.8 Hz), 135.0, 131.0, 126.1, 124.7 (d, J(C,F) = 5.2 Hz), 123.9 (d, J(C,F) = 18.8 Hz), 120.4, 113.5, 65.1, 54.3, 25.5, 14.7 ppm. LCMS R_T = 4.69 min; HRMS, calc'd for $C_{18}H_{18}FN_4O_4S^+$ [M+H], 405.1027; found 405.1031.



5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(pyrimidin-2-yl)-1,2,4-oxadiazole (68). The title compound was prepared in 29% yield (19 mg) from intermediate **39** and pyrimidine-2-amidoxime using a method analogous to that described for the conversion of compound **39** into **60**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, J = 4.9 Hz, 1H), 7.89 (dd, J = 8.1, 1.8 Hz, 1H), 7.58 – 7.43 (m, 2H), 7.09 – 6.97 (m, 2H), 4.50 (m, 4H), 4.28 – 4.08 (m, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 167.9, 158.1, 156.6, 155.8, 135.0, 131.0, 126.0, 122.4, 120.4, 113.5, 65.1, 54.2, 25.7, 14.7 ppm. LCMS R_T = 4.04 min; HRMS, calc'd for $C_{17}H_{18}N_5O_4S^+$ [M+H], 388.1074; found 388.1077.



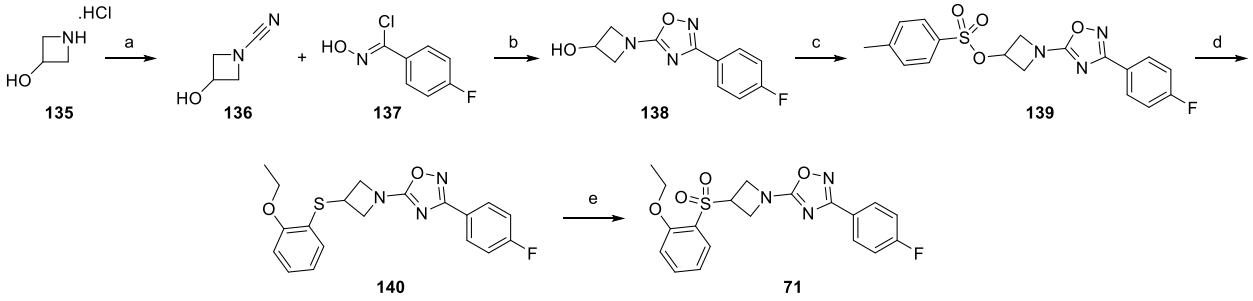
5-(1-((2-Ethoxyphenyl)sulfonyl)-3-methylazetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (69). The title compound was prepared in 47% overall yield (20 mg) from 1-boc-3-methylazetidine-3-carboxylic acid, 2-ethoxybenzene sulfonyl chloride, and 4-fluorobenzamidoxime using a method analogous to that described for the conversion of 1-boc-azetidine-3-carboxylic acid into compound **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.91 (dd, J = 7.8, 1.7 Hz, 1H), 7.52 (m, 1H), 7.16 (m, 2H), 7.09 – 6.98 (m, 2H), 4.54 (d, J = 8.1 Hz, 2H), 4.18 (q, J = 7.0 Hz, 2H), 4.09 (d, J = 8.2 Hz, 2H), 1.81 (s, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 167.7, 164.6 (d, J(C,F) = 251.9 Hz), 156.7, 134.9, 131.2, 129.7 (d, J(C,F) = 8.8 Hz), 126.0, 122.7 (d, J(C,F) = 3.3 Hz), 120.4, 116.1 (d, J(C,F) = 22.0 Hz), 113.5, 65.1, 60.7, 32.7, 23.1, 14.7 ppm. LCMS R_T = 5.59 min; HRMS, calc'd for $C_{20}H_{21}FN_3O_4S^+$ [M+H], 418.1231; found 418.1228.



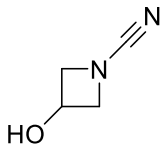
5-(1-((2-Ethoxyphenyl)sulfonyl)-3-fluoroazetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (70). The title compound was prepared in 33% overall yield (14 mg) from 1-boc-3-fluoroazetidine-3-carboxylic acid, 2-ethoxybenzene sulfonyl chloride, and 4-fluorobenzamidoxime using a method analogous to that described for the conversion of 1-boc-azetidine-3-carboxylic acid into compound **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (m, 2H), 7.92 (dd, J = 7.9, 1.7 Hz, 1H), 7.55 (m,

1H), 7.19 (m, 2H), 7.06 (m, 2H), 4.67 (m, 4H), 4.20 (q, *J* = 7.0 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.05 (d, *J*(C,F) = 29.0 Hz), 167.95, 164.92 (d, *J*(C,F) = 252.7 Hz), 156.6, 135.3, 131.0, 129.9 (d, *J*(C,F) = 8.9 Hz), 125.9, 122.0 (d, *J*(C,F) = 3.3 Hz), 120.5, 116.3 (d, *J*(C,F) = 22.2 Hz), 113.6, 84.2 (d, *J*(C,F) = 213.9 Hz), 65.2, 61.0, 60.7, 14.7 ppm. LCMS R_T = 5.58 min; HRMS, calc'd for $C_{19}H_{18}F_2N_3O_4S^+$ [M+H], 422.0981; found 422.0987.

Synthesis of Analog 71:

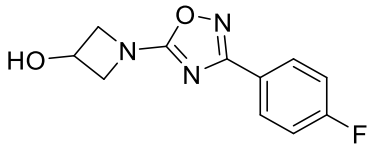


Reagents and conditions: (a) BrCN, Aq. $NaHCO_3$, DCM, *76%*; (b) NET_3, DME, 70 ºC, *12%*; (c) $TsSO_2Cl$, DMAP, NET_3, DCM, *67%*; (d) 2-ethoxythiophenol, Cs_2CO_3, DMF, *15%*; (e) *m*-CPBA, DCM, *83%*.

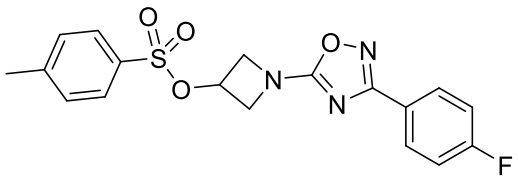


3-Hydroxyazetidine-1-carbonitrile (136). 3-Hydroxyazetidine hydrochloride **135** (1.00 g, 9.13 mmol, 1.0 eq) solution in DCM (5.0 mL) was added to a of sodium bicarbonate ($NaHCO_3$) (1.53 g, 18.26 mmol, 2.0 eq) in water (1.0 mL). The reaction was cooled to 0 ºC, followed by the addition of cyanogen bromide (BrCN) (6.1 mL, 18.26 mmol, 2.0 eq). The reaction was stirred at room temperature overnight. The reaction was poured into half-saturated sodium bicarbonate aqueous solution, that was extracted with a mixture of DCM and isopropanol in 3:1 ratio, respectively (3x).

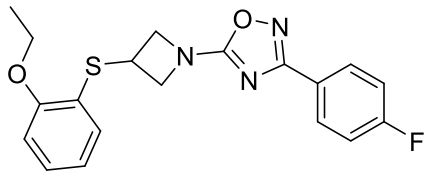
The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 680 mg (76%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (m, 1H), 4.35 (m, 2H), 4.11 (m, 2H), 3.30 (s, 1H).



1-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)azetidin-3-ol (138). Intermediate **136** (211 mg, 2.15 mmol, 1.0 eq) and 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride (**137**) (374 mg, 2.15 mmol, 1.0 eq) were dissolved in dimethoxyethane (DME) (5.0 mL), followed by the addition of triethylamine (TEA) (894 µL, 6.45 mmol, 3.0 eq). The reaction was stirred at 70 ºC overnight. The reaction was cooled to room temperature, and the solvents were removed *in vacuo*; water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 66 mg (12%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 2H), 7.12 (m, 2H), 4.86 (m, 1H), 4.51 (m, 2H), 4.19 (m, 2H). LCMS R_T = 3.93 min; HRMS, calc'd for $C_{11}H_{11}FN_3O_2^+$ [M+H], 236.0830; found 236.0830.

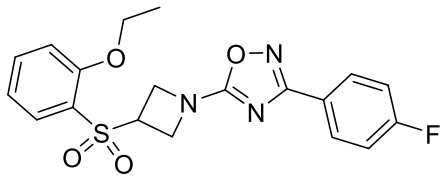


1-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)azetidin-3-yl 4-methylbenzenesulfonate (139). Intermediate **138** (66 mg, 0.28 mmol, 1.0 eq), 4-Dimethylaminopyridine (DMAP) (3.7 mg, 0.03 mmol, 0.1 eq), and triethylamine (194 µL, 1.40 mmol, 5.0 eq) were dissolved in DCM (2.0 mL), followed by the addition of *p*-toluene sulfonyl chloride (107 mg, 0.56 mmol, 2.0 eq) at 0 ºC. The reaction was stirred for 2 hours at room temperature. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 73 mg (67%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.81 (m, 2H), 7.39 (m, 2H), 7.11 (m, 2H), 5.25 (m, 1H), 4.48 (m, 2H), 4.29 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 167.9, 164.4 (d, *J*(C,F) = 251 Hz), 145.9, 132.6, 130.3, 129.4 (d, *J*(C,F) = 8.7 Hz), 128.0, 123.5 (d, *J*(C,F) = 3.3 Hz), 115.8 (d, *J*(C,F) = 22.1 Hz), 68.4, 58.9, 21.8 ppm.



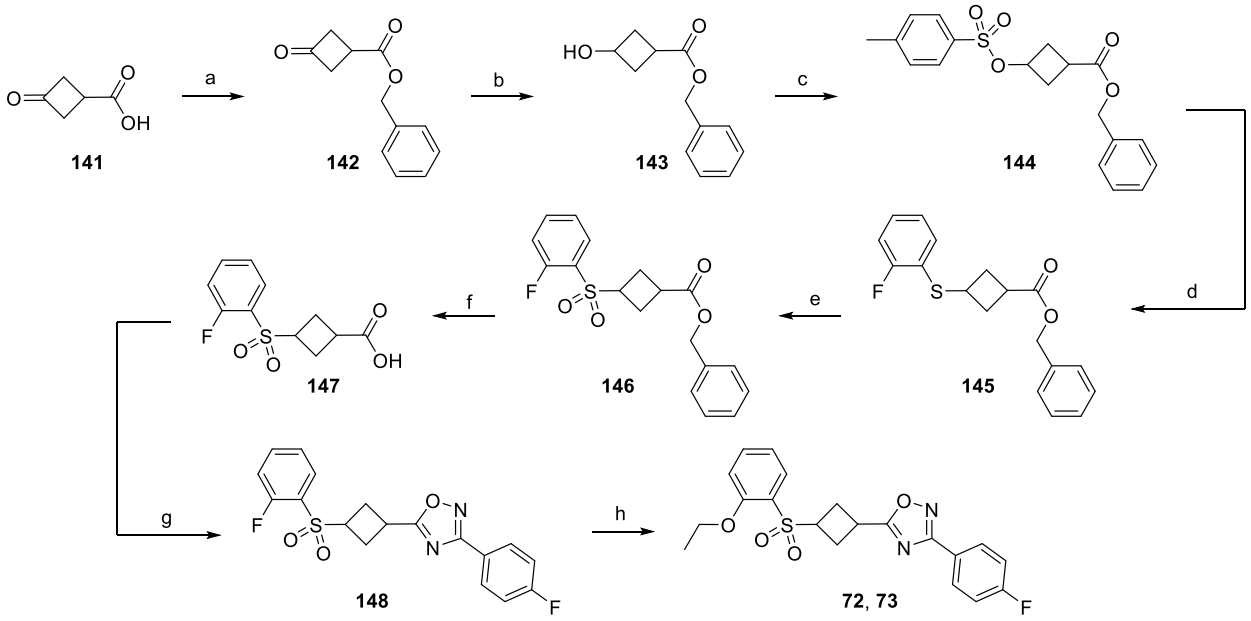
5-(3-((2-Ethoxyphenyl)thio)azetidin-1-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (140). Intermediate **139** (70 mg, 0.18 mmol, 1.0 eq), 2-(ethoxymercapto)phenol (38 µL, 0.36 mmol, 2.0 eq), and cesium carbonate (Cs_2CO_3) (176 mg, 0.54, 3.0 mmol) in DMF (2.0 mL). The reaction was heated at 65 ºC overnight. The reaction was cooled to room temperature and concentrated *in vacuo*. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 10 mg (15%) of the title compound. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.30 – 7.06 (m, 4H), 6.91 (m, 2H), 4.73 - 4.60 (m, 2H), 4.33 – 4.20 (m, 3H), 4.12 (q, J = 7.0 Hz, 2H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.9, 164.4 (d, J(C,F) = 250.6 Hz), 157.4, 131.4, 129.8 (d, J(C,F) = 8.7 Hz), 128.9, 123.8 (d, J(C,F) = 3.2 Hz), 122.0, 121.1, 115.8 (d, J(C,F) = 21.9 Hz), 111.9, 64.3, 59.1, 35.2, 14.8 ppm. LCMS R_T = 6.00 min; HRMS, calc'd for $C_{19}H_{19}FN_3O_2S^+$ [M+H], 372.1177; found 372.1177.

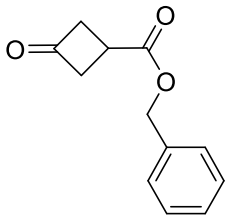


5-(3-((2-Ethoxyphenyl)sulfonyl)azetidin-1-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (71). meta-Chloroperoxybenzoic acid (*m*-CPBA) (12 mg, 0.072 mmol, 3.0 eq) was added to a solution of intermediate **140** (10 mg, 0.024 mmol, 1.0 eq) in DCM (2.0 mL). The reaction was stirred at room temperature for 1 hour. The reaction was diluted with DCM, quenched with aqueous solution of 10% sodium thiosulfate, followed by aqueous sodium bicarbonate (aq. $NaHCO_3$) wash. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 8 mg (83%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.92 (m, 3H), 7.62 (m, 1H), 7.18 – 7.00 (m, 4H), 4.74 - 4.59 (m, 3H), 4.54 – 4.29 (m, 2H), 4.25 (q, J = 7.0 Hz, 2H), 1.54 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 167.9, 164.4 (d, J(C,F) = 251 Hz), 156.9, 136.4, 131.0, 129.4 (d, J(C,F) = 8.6 Hz), 125.3, 123.5 (d, J(C,F) = 3.2 Hz), 121.0, 115.8 (d, J(C,F) = 21.9 Hz), 113.5, 65.4, 52.1, 51.7, 14.6 ppm. LCMS R_T = 5.20 min; HRMS, calc'd for $C_{19}H_{19}FN_3O_4S^+$ [M+H], 404.1075; found 404.1083.

Synthesis of Analogs 72 and 73:

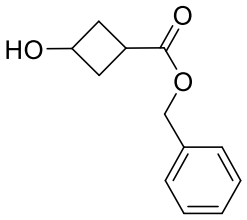


Reagents and conditions: (a) BnBr, K_2CO_3, CH_3CN, *73%*; (b) $NaBH_4$, MeOH, *35%*; (c) $TsSO_2Cl$, DMAP, NET_3, DCM, *65%*; (d) 2-fluorobenzothiol, K_2CO_3, CH_3CN, *56%*; (e) *m*-CPBA, DCM, *94%*; (f) $LiOH.H_2O$, H_2O, THF, *97%*; (g) 4-fluorobenzamidoxime, CDI, NaOH, DMSO, *66%*; (h) Cs_2CO_3, EtOH, 70 ºC, *37%*.

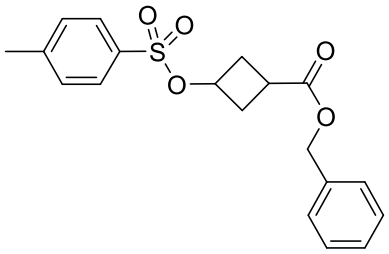


Benzyl 3-oxocyclobutane-1-carboxylate (142). To a solution of 3-oxycyclobutanecarboxylic acid **141** (1.00 g, 8.76 mmol, 1.0 eq) and potassium carbonate (K_2CO_3) (1.45 g, 10.5 mmol, 1.2 eq) in acetonitrile (8.0 mL), was added benzyl bromide (BnBr) (1.09 mL, 10.5, 1.2 eq). The reaction was stirred overnight at room temperature. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica

gel afforded 1.30 g (73%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 5H), 5.15 (s, 2H), 3.53 – 3.20 (m, 5H).

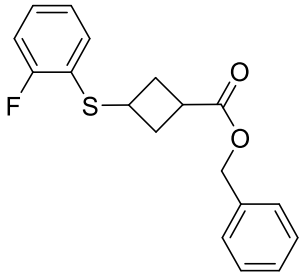


Benzyl 3-hydroxycyclobutane-1-carboxylate (143). To a solution of intermediate **142** (1.30 g, 6.36 mmol, 1.0 eq) in methanol (5.0 mL) was added sodium borohydride ($NaBH_4$) (120 mg, 3.18 mmol, 0.5 eq). The reaction was stirred for 1 hour at room temperature. The reaction was concentrated *in vacuo*, water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 465 mg (35%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 5H), 5.12 (s, 2H), 4.18 (m, 1H), 2.73 – 2.52 (m, 3H), 2.33 – 2.11 (m, 3H).

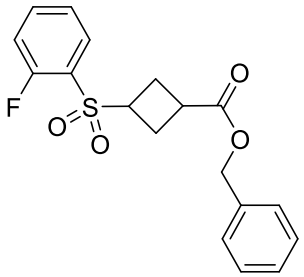


Benzyl 3-(tosyloxy)cyclobutane-1-carboxylate (144). The title compound was prepared in 65% yield from intermediate **143** and *p*-toluenesulfonyl chloride ($TsSO_2Cl$) using a method analogous to that described for the conversion of intermediate **138** into intermediate **139**. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.78 (m, 2H), 7.41 – 7.27 (m, 7H), 5.09 (s, 2H), 4.74 (m, 1H), 2.67 (m, 1H), 2.56 – 2.35 (m, 7H).

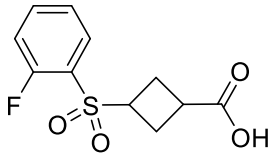


Benzyl 3-((2-fluorophenyl)thio)cyclobutane-1-carboxylate (145). The title compound was prepared in 56% yield from intermediate **144** and 2-fluorobenzothiol using a method analogous to that described for the conversion of intermediate **139** into intermediate **140**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 7.27 – 7.14 (m, 2H), 7.11 – 7.00 (m, 2H), 5.13 (s, 2H), 3.99 (m, 1H), 3.35 (m, 1H), 2.76 (m, 2H), 2.31 (m, 2H). LCMS R_T = 6.01 min; HRMS, calc'd for $C_{18}H_{18}FO_2S^+$ [M+H], 317.1006; found 317.1011.

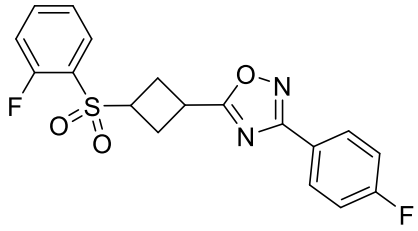


Benzyl 3-((2-fluorophenyl)sulfonyl)cyclobutane-1-carboxylate (146). The title compound was prepared in 94% yield from intermediate **145** using a method analogous to that described for the conversion of intermediate **140** into compound **71**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (m, 1H), 7.65 (m, 1H), 7.43 – 7.29 (m, 6H), 7.25 – 7.18 (m, 1H), 5.15 (s, 2H), 4.14 (m, 1H), 3.37 (m, 1H),

2.82 (m, 2H), 2.58 (m, 2H). LCMS R_T = 5.13 min; HRMS, calc'd for $C_{18}H_{18}FO_4S^+$ [M+H], 349.0904; found 349.0909.

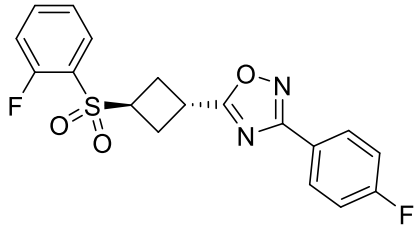


3-((2-Fluorophenyl)sulfonyl)cyclobutane-1-carboxylic acid (147). Intermediate **146** (230 mg, 0.660 mmol, 1.0 eq) was dissolved in THF (5.0 mL) and water (3.0 mL), followed by the addition of lithium hydroxide monohydrate (55.4 mg, 1.32 mmol, 2.0 eq). The reaction was stirred overnight at room temperature. The solvents were removed *in vacuo,* and the reaction was acidified with 1N HCl. The aqueous layer was extracted with ethyl acetate (2x), and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 165 mg (97%) of the title compound that was used further without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 1H), 7.66 (m, 1H), 7.40 – 7.31 (m, 1H), 7.24 (m, 1H), 4.15 (m, 1H), 3.37 (m, 1H), 2.85 (m, 2H), 2.60 (m, 2H).

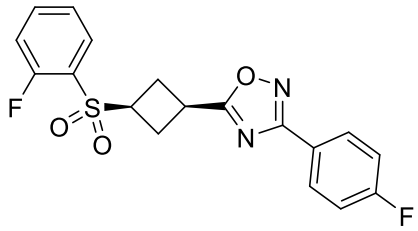


3-(4-Fluorophenyl)-5-(3-((2-fluorophenyl)sulfonyl)cyclobutyl)-1,2,4-oxadiazole (148). The title compound was prepared in 66% yield from intermediate **147** and 4-fluorobenzamidoxime using a method analogous to that described for the conversion of intermediate **39** into compound

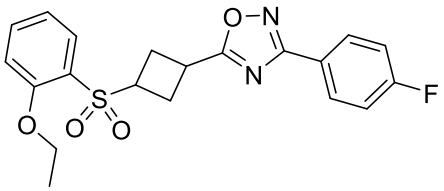
67. The title compound was obtained as a racemic mixture that was separated into cis (**148b**) and trans (**148a**) in 2:1 ratio, respectively.



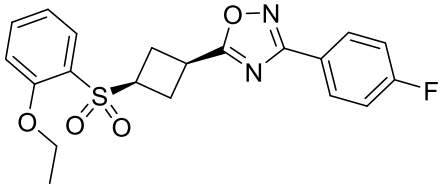
3-(4-Fluorophenyl)-5-((1r,3r)-3-((2-fluorophenyl)sulfonyl)cyclobutyl)-1,2,4-oxadiazole (148a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 – 7.95 (m, 3H), 7.69 (m, 1H), 7.44 – 7.10 (m, 4H), 4.32 (m, 1H), 4.06 (m, 1H), 3.12 (m, 2H), 2.83 (m, 2H). LCMS R_T = 5.45 min; HRMS, calc'd for $C_{18}H_{15}F_2N_2O_3S^+$ [M+H], 377.0766; found 377.0771.



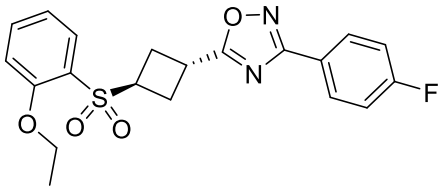
3-(4-Fluorophenyl)-5-((1s,3s)-3-((2-fluorophenyl)sulfonyl)cyclobutyl)-1,2,4-oxadiazole (148b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (m, 2H), 7.98 (m, 1H), 7.68 (m, 1H), 7.36 (td, J = Hz, 1H), 7.31 – 7.12 (m, 3H), 4.19 (m, 1H), 3.77 (m, 1H), 3.13 (m, 2H), 2.76 (m, 2H). LCMS R_T = 5.31 min; HRMS, calc'd for $C_{18}H_{15}F_2N_2O_3S^+$ [M+H], 377.0766; found 377.0772.



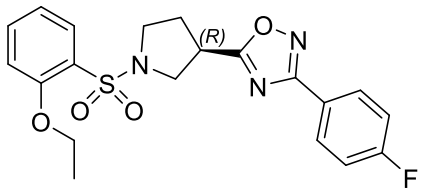
5-(3-((2-ethoxyphenyl)sulfonyl)cyclobutyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (72). The title compound was prepared in 54% yield (36 mg) from intermediate **148** and ethanol using a method analogous to that described for the conversion of analog **11** into compound **26**. The title compound was obtained as a racemic mixture that was separated into cis (**73a**) and trans (**73b**).



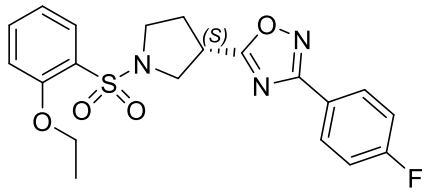
5-((1s,3s)-3-((2-ethoxyphenyl)sulfonyl)cyclobutyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (73a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (m, 2H), 7.98 (dd, *J* = 7.9, 1.74 Hz, 1H), 7.57 (m, 1H), 7.16 (m, 2H), 7.09 (td, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 4.36 (m, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.74 (m, 1H), 3.10 (m, 2H), 2.71 (m, 2H), 1.54 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 167.7, 164.5 (d, *J*(C,F) = 251 Hz), 157.0, 135.7, 131.0, 129.7 (d, *J*(C,F) = 8.8 Hz), 125.9, 122.9 (d, *J*(C,F) = 3.3 Hz), 120.7, 116.0 (d, *J*(C,F) = 22.0 Hz), 113.3, 65.2, 52.0, 27.9, 26.0, 14.7 ppm. LCMS R_T = 5.45 min; HRMS, calc'd for $C_{20}H_{20}FN_2O_4S^+$ [M+H], 403.1122; found 403.1130.



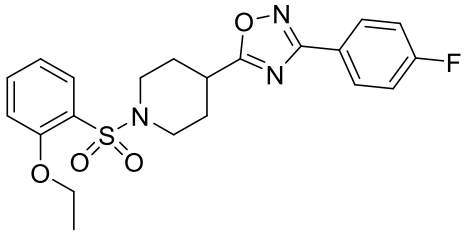
5-((1r,3r)-3-((2-ethoxyphenyl)sulfonyl)cyclobutyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (73b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 – 7.97 (m, 3H), 7.58 (m, 1H), 7.22 – 7.07 (m, 3H), 7.02 (d, J = 8.4 Hz, 1H), 4.53 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.06 (m, 1H), 3.07 (m, 2H), 2.78 (m, 2H), 1.52 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 167.6, 164.6 (d, J(C,F) = 252 Hz), 156.9, 135.8, 131.0, 129.6 (d, J(C,F) = 8.8 Hz), 125.4, 122.9 (d, J(C,F) = 3.3 Hz), 120.7, 116.1 (d, J(C,F) = 22.0 Hz), 113.3, 65.1, 53.1, 27.8, 27.4, 14.6 ppm. LCMS R_T = 5.46 min; HRMS, calc'd for $C_{20}H_{20}FN_2O_4S^+$ [M+H], 403.1122; found 403.1125.



(*R*)-5-(1-((2-Ethoxyphenyl)sulfonyl)pyrrolidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (74). The title compound was prepared in 8% overall yield (6 mg) from (*R*)-methyl pyrrolidine-3-carboxylate hydrochloride, 2-ethoxybenzene sulfonyl chloride, and 4-fluorobenzamidoxime using a method analogous to that described for the conversion of methyl azetidine-3-carboxylate hydrochloride into compound **40**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 3H), 7.43 (m, 1H), 7.16 (m, 2H), 7.01 (td, J = 8.1, 1.0 Hz, 1H), 6.91 (dd, J = 8.3, 0.7 Hz, 1H), 4.17 – 3.99 (m, 3H), 3.85 (m, 1H), 3.75 – 3.54 (m, 3H), 2.40 (m, 2H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 167.7, 164.7 (d, J(C,F) = 251.9 Hz), 156.3, 135.5, 135.0, 131.2, 129.6 (d, J(C,F) = 8.8 Hz), 128.7, 128.4, 127.6, 126.5, 122.6 (d, J(C,F) = 3.3 Hz), 120.8, 116.2 (d, J(C,F) = 22.1 Hz), 113.9, 71.2, 54.4, 25.2 ppm. LCMS R_T = 5.47 min; HRMS, calc'd for $C_{20}H_{21}FN_3O_4S^+$ [M+H], 418.1231; found 418.1232.

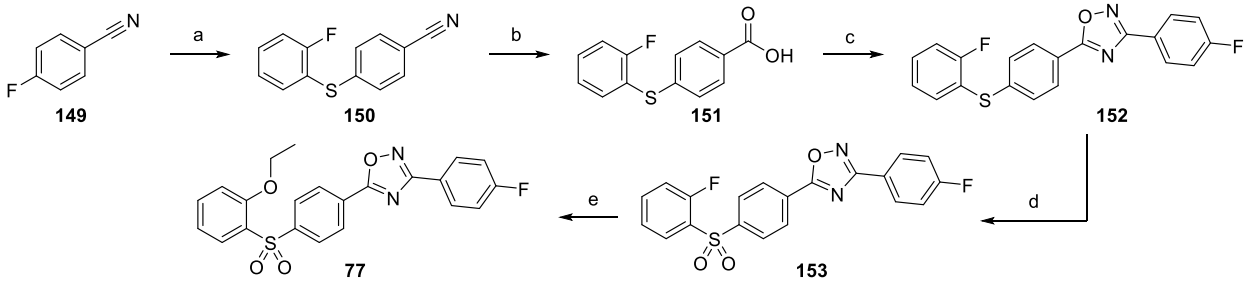


(*S*)-5-(1-((2-ethoxyphenyl)sulfonyl)pyrrolidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (75). The title compound was prepared in 17% overall yield (13 mg) from (*S*)-methyl pyrrolidine-3-carboxylate hydrochloride, 2-ethoxybenzene sulfonyl chloride, and 4-fluorobenzamidoxime using a method analogous to that described for the conversion of methyl azetidine-3-carboxylate hydrochloride into compound **40**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 3H), 7.43 (m, 1H), 7.16 (m, 2H), 7.01 (td, *J* = 8.1, 1.0 Hz, 1H), 6.91 (dd, *J* = 8.3, 0.7 Hz, 1H), 4.18 – 3.98 (m, 3H), 3.85 (m, 1H), 3.75 – 3.53 (m, 3H), 2.40 (m, 2H), 1.48 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 167.5, 164.6 (d, *J*(C,F) = 252 Hz), 156.4, 134.6, 132.2, 129.6 (d, *J*(C,F) = 8.8 Hz), 126.6, 122.7 (d, *J*(C,F) = 3.3 Hz), 120.3, 116.1 (d, *J*(C,F) = 22.1 Hz), 113.3, 65.1, 51.1, 46.9, 36.6, 30.2, 14.7 ppm. LCMS R_T = 5.45 min; HRMS, calc'd for $C_{20}H_{21}FN_3O_4S^+$ [M+H], 418.1231; found 418.1234.

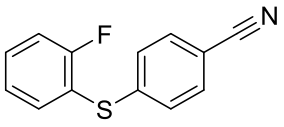


5-(1-((2-Ethoxyphenyl)sulfonyl)piperidin-4-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (76). The title compound was prepared in 16% overall yield (12 mg) from 1-boc-piperidine-4-carboxylic acid, 2-ethoxybenzene sulfonyl chloride, and 4-fluorobenzamidoxime using a method analogous

to that described for the conversion of 1-boc-azetidine-3-carboxylic acid into compound **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.92 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.51 (m, 1H), 7.16 (m, 2H), 7.02 (m, 2H), 4.24 – 4.05 (m, 2H), 3.89 (dt, *J* = 13.0, 3.8 Hz, 2H), 3.17 – 2.90 (m, 3H), 2.27 – 2.13 (m, 2H), 2.04 (m, 2H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 167.5, 164.6 (d, *J*(C,F) = 251.5 Hz), 156.4, 134.6, 131.7, 129.6 (d, *J*(C,F) = 8.7 Hz), 126.9, 123.0 (d, *J*(C,F) = 3.3 Hz), 120.3, 116.1 (d, *J*(C,F) = 22.1 Hz), 113.3, 64.9, 45.1, 33.9, 29.2, 14.7 ppm. LCMS R_T = 5.71 min; HRMS, calc'd for $C_{21}H_{23}FN_3O_4S^+$ [M+H], 432.1388; found 432.1404.

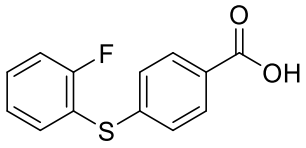


Reagents and conditions: (a) 2-fluorobenzothiol, K_2CO_3, CH_3CN, µwave, 150 ºC, 20 min, *71%*; (b) 2N NaOH, EtOH, *93%*; (c) 4-fluorobenzamidoxime, CDI, NaOH, DMSO, *39%*; (d) m-CPBA, DCM, *100%*; (e) Cs_2CO_3, ethanol, µwave, 100 ºC, 30 minutes, *31%*.

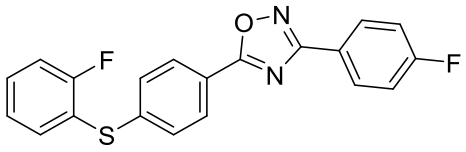


4-((2-Fluorophenyl)thio)benzonitrile (150). 4-fluorobenzonitrile (**149**) (400 mg, 3.30 mmol, 1.0 eq), 2-fluorobenzothiol (353 µL, 3.30 mmol, 1.0 eq), K_2CO_3 (1.14 g, 8.25 mmol, 2.5 eq), and acetonitrile (5.0 mL) were added to a microwave vial and heated in a microwave reactor at 150 ºC for 20 minutes. The reaction was cooled to room temperature and concentrated *in vacuo*, followed

by the addition of water, and extraction with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 540 mg (71%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.41 (m, 4H), 7.28 – 7.10 (m, 4H). LCMS R_T = 5.45 min; HRMS, calc'd for $C_{13}H_9FNS^+$ [M+H], 230.0434; found 230.0431.

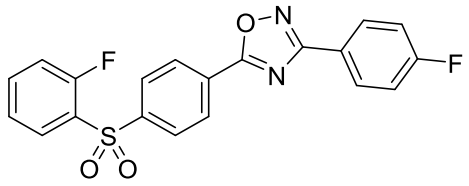


4-((2-Fluorophenyl)thio)benzoic acid (151). A solution of intermediate **150** (300 mg, 1.31 mmol, 1.0 eq) in 2N NaOH (5.0 mL) and ethanol (3.0 mL) was charged in a heat and pressure resistant vial and was heated at 100 ºC for 4 hours. The reaction was cooled to room temperature and neutralized with 1N HCl, followed by extraction of the aqueous layer with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afforded 300 mg (93%) of the title compound that was used further without purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.01 (s, 1H), 7.87 (m, 2H), 7.65 – 7.51 (m, 2H), 7.48 – 7.16 (m, 4H).

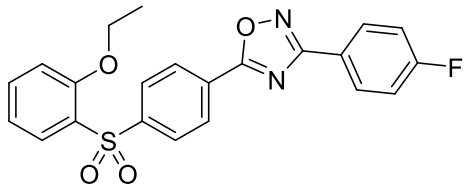


3-(4-Fluorophenyl)-5-(4-((2-fluorophenyl)thio)phenyl)-1,2,4-oxadiazole (152). The title compound was prepared in 39% yield from intermediate **151** and 4-fluorobenzamidoxime using a method analogous to that described for the conversion of intermediate **39** into compound **64**. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.06 (m, 4H), 7.72 – 7.57 (m, 2H), 7.52 – 7.32 (m, 6H). LCMS R_T = 6.69 min; HRMS, calc'd for $C_{20}H_{13}F_2N_2OS^+$ [M+H], 367.0711; found 367.0714.



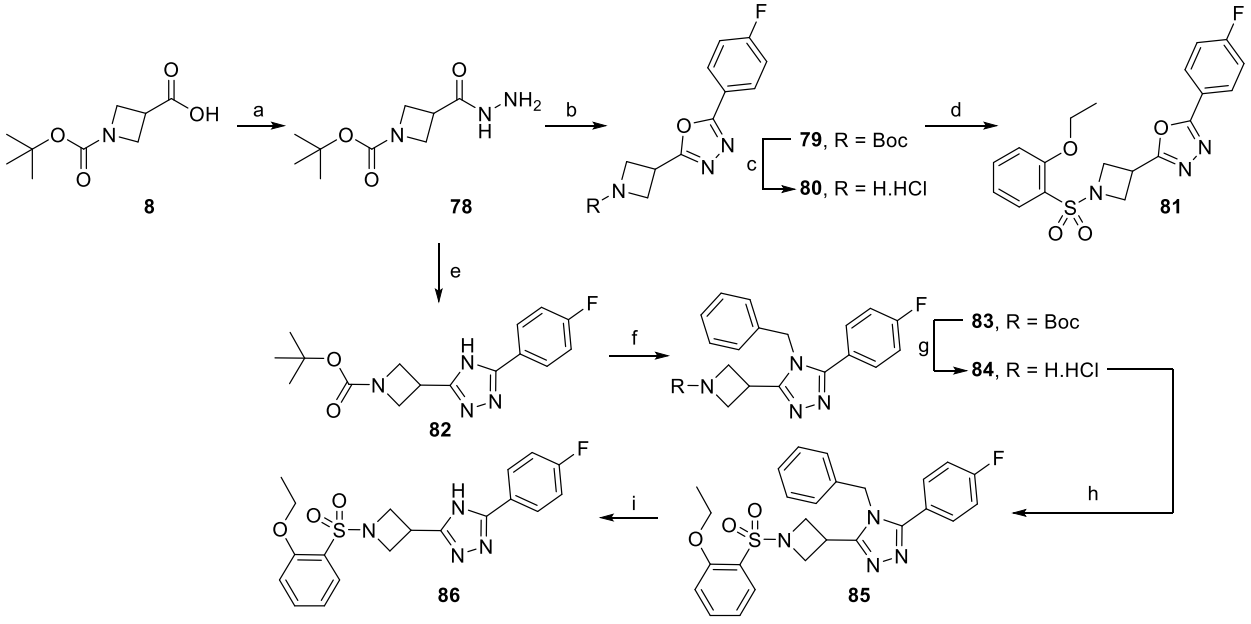
3-(4-Fluorophenyl)-5-(4-((2-fluorophenyl)sulfonyl)phenyl)-1,2,4-oxadiazole (153). The title compound was prepared in 100% yield from intermediate **152** using a method analogous to that described for the conversion of intermediate **140** into compound **71**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (m, 2H), 8.26 – 8.10 (m, 5H), 7.64 (m, 1H), 7.38 (m, 1H), 7.29 – 7.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 168.5, 164.8 (d, *J*(C,F) = 252.2 Hz), 144.6, 136.6 (d, *J*(C,F) = 8.5 Hz), 129.9, 129.8, 129.7, 129.0 (d, *J*(C,F) = 2.1 Hz), 128.8, 128.6, 124.9 (d, *J*(C,F) = 3.9 Hz), 117.5 (d, *J*(C,F) = 20.9 Hz), 116.2 (d, *J*(C,F) = 22.1 Hz) ppm. LCMS R_T = 5.93 min; HRMS, calc'd for $C_{20}H_{13}F_2N_2O_3S^+$ [M+H], 399.0609; found 399.0616.



5-(4-((2-Ethoxyphenyl)sulfonyl)phenyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (77). Intermediate **153** (40 mg, 0.1 mmol, 1.0 eq), cesium carbonate (Cs_2CO_3) (98 mg, 0.3 mmol, 3.0 eq), and ethanol (0.5 mL) were added to a microwave vial and heated in a microwave reactor at 100 ºC for 30 minutes. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in*

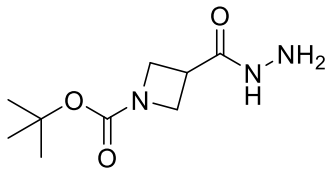
vacuo. Purification of the residue by flash chromatography on silica gel afforded 13 mg (31%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.25 – 8.11 (m, 5H), 7.57 (m, 1H), 7.26 – 7.09 (m, 3H), 6.90 (d, J = 8.1 Hz, 1H), 4.02 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 168.5, 164.8 (d, J(C,F) = 252.0 Hz), 156.6, 145.4, 136.0, 130.0, 129.8 (d, J(C,F) = 8.8 Hz), 129.4, 128.1, 127.9, 122.8 (d, J(C,F) = 3.3 Hz), 120.5, 116.2 (d, J(C,F) = 22.1 Hz), 113.1, 64.8, 14.2 ppm. LCMS R_T = 5.92 min; HRMS, calc'd for $C_{22}H_{18}FN_2O_4S^+$ [M+H], 425.0966; found 425.0969.

Synthesis of Analogs 81 and 86:

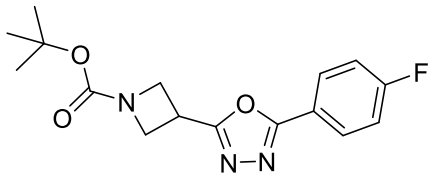


Reagents and conditions: (a) CDI, THF, $N_2H_4.H_2O$, *87%*; (b) 4-fluorobenzoic acid, HATU, DIEA, Burgess reagent, THF, *82%*; (c) 4M HCl in 1,4-dioxane, *93%*; (d) 2-ethoxybenzene sulfonyl chloride, NEt_3, DCM, *14%*, (e) 4-fluorobenzonitrile, K_2CO_3, BuOH, 160 ºC, *31%*; (f)

BnBr, K_2CO_3, DMF, *64%*; (g) 4M HCl in 1,4-dioxane, *100%*; (h) 2-ethoxybenzene sulfonyl chloride, DIEA, DCM, *54%*; (i) 20% $Pd(OH)_2/C$, MeOH, *25%*.

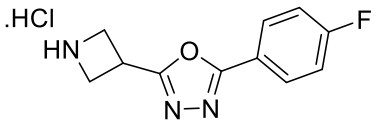


***tert*-Butyl 3-(hydrazinecarbonyl)azetidine-1-carboxylate (78).** 1-Boc-azetidine-3-carboxylic acid (**8**) (1.00 g, 4.97 mmol, 1.0 eq) and CDI (1.45 g, 8.95 mmol, 1.8 eq) were dissolved in THF (10.0 mL) and stirred for 1 hour at room temperature. Afterwards, it was added to a solution of hydrazine monohydrate (727 µL, 14.91 mmol, 3.0 eq) in THF (5.0 mL), and allowed to react overnight at room temperature. The reaction was concentrated *in vacuo*, saturated aqueous sodium carbonate solution was added, and the reaction was extracted (3x) with a mixture of DCM and isopropanol in 3:1 ratio, respectively. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 933 mg (87%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (s, 1H), 4.26 (s, 2H), 3.98 – 3.71 (m, 4H), 3.17 (m, 1H), 1.37 (s, 9H). LCMS R_T = 1.79 min; HRMS, calc'd for $C_9H_{18}N_3O_3^+$ [M+H], 216.1343; found 216.1338.

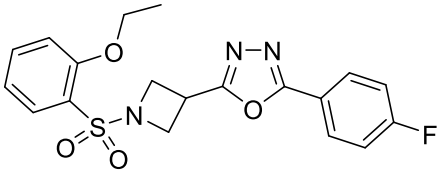


***tert*-Butyl 3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)azetidine-1-carboxylate (79).** Intermediate **78** (50 mg, 0.23 mmol, 1.0 eq), 4-fluorobenzoic acid (32 mg, 0.23 mmol, 1.0 eq),

HATU (88 mg, 0.23 mmol, 1.0 eq), and DIEA (80 µL, 0.46 mmol, 2.0 eq) were dissolved in THF (2.0 mL), and stirred at room temperature for 1 hour. Burgess reagent (192 mg, 0.81 mmol, 3.5 eq) was added, and the reaction was stirred for an overnight at room temperature. Water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed with saturated sodium bicarbonate, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 60 mg (82%) of the title compound.



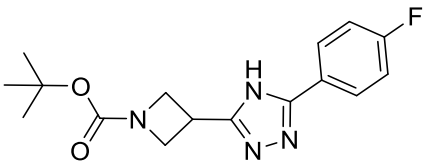
3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)azetidin-1-hydrochloride (80). Intermediate **79** (60 mg, 0.19 mmol, 1.0 eq) was dissolved in 4M HCl in 1,4-dioxane (1.0 mL), the reaction was stirred at room temperature for 1 hour. The reaction was concentrated *in vacuo* to afford 45 mg (93%) of the title compound that was used further without purification. LCMS R_T = 3.42 min; HRMS, calc'd for $C_{11}H_{11}FN_3O^+$ [M+H], 220.0881; found 220.0892.



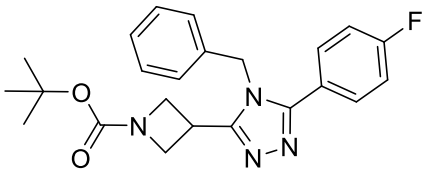
2-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (81). The title compound was prepared in 14% yield from intermediate **80** and 2-ethoxybenzene sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.92 (dd, J = 8.3, 1.8 Hz, 1H), 7.56 (m, 1H), 7.21 (m, 2H), 7.12 – 7.01 (m, 2H), 4.43 (d, J = 7.7 Hz, 4H), 4.21 (q, J = 7.0 Hz, 2H), 4.08 (m, 1H), 1.50 (t, J = 7.0 Hz, 3H). LCMS R_T = 4.85 min; HRMS, calc'd for $C_{19}H_{19}FN_3O_4S^+$ [M+H], 404.1075; found 404.1077.

Synthesis of Analog 86:

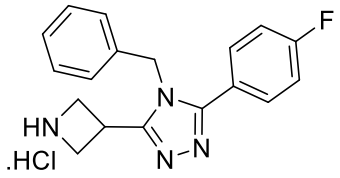


***tert*-Butyl 3-(5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)azetidine-1-carboxylate (82).** Intermediate **78** (250 mg, 1.16 mmol, 1.0 eq), 4-fluorobenzonitrile (211 mg, 1.74 mmol, 1.5 eq), and K_2CO_3 (80 mg, 0.58 mmol, 0.5 eq) in *n*-butanol (4.0 mL) were added to a heat and pressure resistant vial and heated at 160 ºC overnight. The reaction was cooled to room temperature and concentrated *in vacuo*, water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 114 mg (31%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.11 (m, 2H), 4.33 (m, 4H), 3.95 (m, 1H), 1.46 (s, 9H).

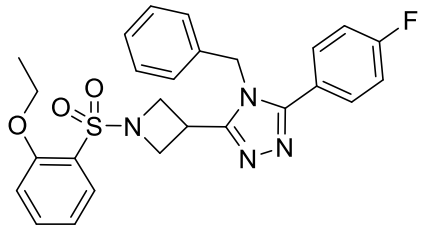


***tert*-Butyl 3-(4-benzyl-5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)azetidine-1-carboxylate (83).** To a solution of intermediate **82** (110 mg, 0.346 mmol, 1.0 eq) and K_2CO_3 (95.6 mg, 0.692 mmol,

2.0 eq) in DMF (2.0 mL), was added benzyl bromide (63.4 µL, 0.519 mmol, 1.5 eq). The reaction was stirred overnight at 40 ºC. The reaction was cooled to room temperature, water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 90 mg (64%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (m, 2H), 7.38 – 7.27 (m, 3H), 7.20 – 7.05 (m, 4H), 5.28 (s, 2H), 4.35 – 3.94 (m, 4H), 3.71 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.50 (d, *J*(C,F) = 248.1 Hz), 160.3, 156.1 (d, *J*(C,F) = 1.0 Hz), 135.2, 129.1, 128.5, 128.3 (d, *J*(C,F) = 8.4 Hz), 127.3 (d, *J*(C,F) = 3.1 Hz), 126.9, 115.7, 115.4, 97.8, 53.5, 52.4, 28.4, 25.0 ppm.

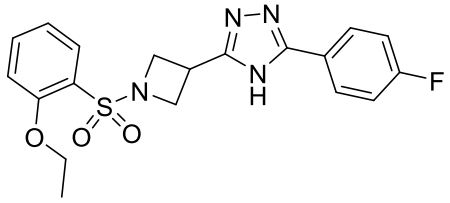


3-(4-Benzyl-5-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)azetidine-1-hydrochloride (84). The title compound was prepared in 100% yield from intermediate **83** using a method analogous to that described for the conversion of intermediate **9** into intermediate **10**.



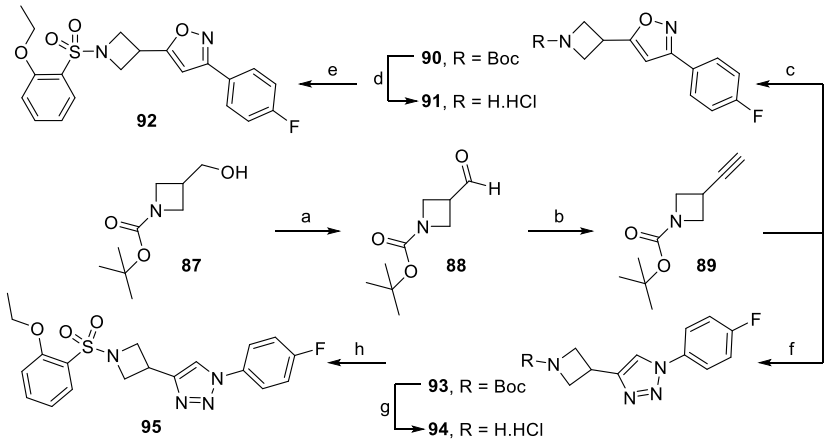
4-Benzyl-3-(1-((2-ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)-4H-1,2,4-triazole (85). The title compound was prepared in 54% yield from intermediate **84** and 2-ethoxybenzene

sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.87 (dd, J = 7.8, 1.7 Hz, 1H), 7.52 (m, 1H), 7.37 – 7.27 (m, 3H), 7.17 (m, 6H), 5.26 (s, 2H), 4.29 (m, 2H), 4.16 – 4.02 (m, 4H), 3.76 (m, 1H), 1.38 (t, J = 7.0 Hz, 3H). LCMS R_T = 4.63 min; HRMS, calc'd for $C_{26}H_{26}FN_4O_3S^+$ [M+H], 493.1704; found 493.1706.

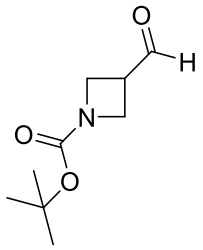


3-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)-4H-1,2,4-triazole (86). Hydrogenolysis for intermediate **85** (67 mg, 0.14 mmol, 1.0 eq) in methanol (5.0 mL) was achieved through H-cube utilizing 20% $Pd(OH)_2$/C CatCart at 70 ºC. The reaction was concentrated *in vacuo*, followed by purification of the residue by flash chromatography on silica gel to afford 14 mg (25%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.86 (m, 3H), 7.55 (m, 1H), 7.16 – 7.00 (m, 4H), 4.47 – 4.32 (m, 4H), 4.17 (q, J = 7.0 Hz, 2H), 3.98 (m, 1H), 2.19 (s, 1H), 1.43 (t, J = 7.00 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (d, J(C,F) = 398.3 Hz), 165.6, 156.8, 134.9, 131.2, 127.9 (d, J(C,F) = 8.7 Hz), 126.0, 123.6 (d, J(C,F) = 3.0 Hz), 120.5, 116.3 (d, J(C,F) = 22.1 Hz), 113.6, 100.0, 97.2, 65.2, 55.9, 25.2, 14.7 ppm. LCMS R_T = 4.63 min; HRMS, calc'd for $C_{19}H_{20}FN_4O_3S^+$ [M+H], 403.1235; found 403.1230.

Synthesis of Analogs 92 and 95:

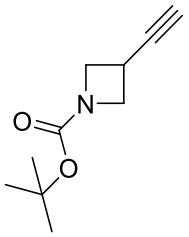


Scheme 5. Reagents and conditions: (a) Pyridine-sulfur trioxide complex, NET_3, DCM, DMSO, *60%*; (b) Bestmann-Ohira reagent, K_2CO_3, MeOH, *72%*; (c) 4-fluorobenzaldehyde oxime, PIFA, MeOH, H_2O, 52%; (d) 4M HCl in 1,4-dioxane, *100%*; (e) 2-ethoxybenzene sulfonyl chloride, DIEA, DCM 55%; (f) 1-azido-4-fluorobenzene, sodium ascorbate, $CuSO_4$, *tert*-BuOH, H_2O, *56%*; (g) 4M HCl in 1,4-dioxane, *100%*; (h) 2-ethoxybenzene sulfonyl chloride, NET_3, DCM, *31%*.

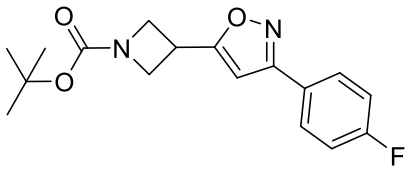


***tert*-Butyl 3-formylazetidine-1-carboxylate (88).** To a solution of 1-boc-azetidine-3-yl-methanol **87** (1.00 g, 5.34 mmol, 1.0 eq) and triethylamine (2.22 mL, 16.02 mmol, 3.0 eq) in DCM (10 mL) and dimethyl sulfoxide (DMSO) (1.0 mL), was added pyridine-sulfur trioxide complex (2.55 g, 16.02 mmol, 3.0 eq). The reaction was stirred at room temperature overnight. The reaction was poured in 1N HCl aqueous solution and was extracted with ethyl acetate (3x). The combined organics were washed with saturated sodium bicarbonate, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded

590 mg (60%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (d, J = 2.1 Hz, 1H), 4.11 (m, 4H), 3.36 (m, 1H), 1.44 (s, 9H).

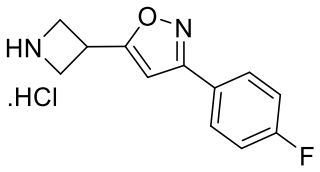


***tert*-Butyl 3-ethynylazetidine-1-carboxylate (89).** To a solution of intermediate **88** (550 mg, 2.97 mmol, 1.0 eq) and K_2CO_3 (615 mg, 4.45 mmol, 1.5 eq) in methanol (10 mL), was added Bestmann-Ohira reagent (1.0 mL, 4.45 mmol, 1.5 eq). The reaction was allowed to stir at room temperature overnight. The reaction was concentrated in vacuo, half-saturated sodium bicarbonate was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 389 mg (72%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (m, 2H), 3.94 (m, 2H), 3.30 (m, 1H), 2.30 (d, J = 2.5 Hz, 1H), 1.45 (s, 9H).

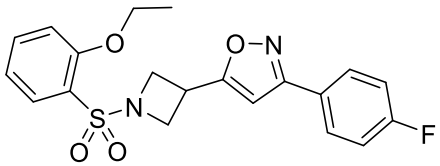


***tert*-Butyl 3-(3-(4-fluorophenyl)isoxazol-5-yl)azetidine-1-carboxylate (90).** To a solution of intermediate **89** (56 mg, 0.31 mmol, 1.0 eq) and 4-fluorobenzaldehyde oxime (86 mg, 0.62 mmol, 2.0 eq) in a mixture of water (1.0 mL) and methanol (5.0 mL), was added [bis(trifluoroacetoxy)iodo]benzene (533 mg, 1.24 mmol, 4.0 eq) in two equal portions over 2

hours, and was stirred for an additional 3 hours at room temperature. The reaction was concentrated *in vacuo*, water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 51 mg (52%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.15 (m, 2H), 6.46 (s, 1H), 4.35 (m, 2H), 4.13 (m, 2H), 3.94 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 163.8 (d, *J*(C,F) = 250 Hz), 161.7, 156.1, 128.71 (d, *J*(C,F) = 8.5 Hz), 125.1 (d, *J*(C,F) = 3.4 Hz), 116.1 (d, *J*(C,F) = 22.0 Hz), 99.2, 80.2, 54.0, 28.3, 26.0.

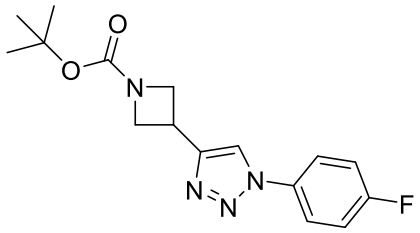


3-(3-(4-Fluorophenyl)isoxazol-5-yl)azetidine-1-hydrochloride (91). The title compound was prepared in 100% yield (76 mg) from intermediate **90** using a method analogous to that described for the conversion of intermediate **9** into intermediate **10**. **91** was taken to the next step without further purification.

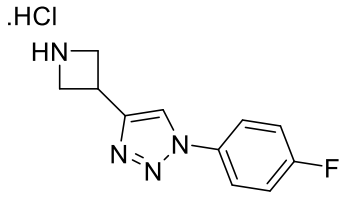


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)isoxazole (92). The title compound was prepared in 55% yield (22 mg) from intermediate **91** and 2-ethoxybenzene sulfonyl

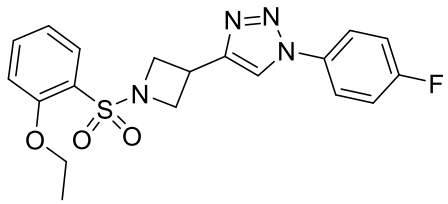
chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.1, 1.7 Hz, 1H), 7.75 (m, 2H), 7.55 (m, 1H), 7.20 – 7.02 (m, 4H), 6.38 (d, J = 0.5 Hz, 1H), 4.39 (t, J = 8.4 Hz, 2H), 4.29 – 4.15 (m, 4H), 3.93 (m, 1H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 163.9 (d, J(C,F) = 250.2 Hz), 161.7, 156.8, 135.0, 131.2, 128.7 (d, J(C,F) = 8.6 Hz), 125.8, 125.0 (d, J(C,F) = 3.4 Hz), 120.4, 116.1 (d, J(C,F) = 22.0 Hz), 113.6, 99.5, 65.1, 55.6, 25.6, 14.7 ppm. LCMS R_T = 5.34 min; HRMS, calc'd for $C_{20}H_{20}FN_2O_4S^+$ [M+H], 403.1122; found 403.1125.



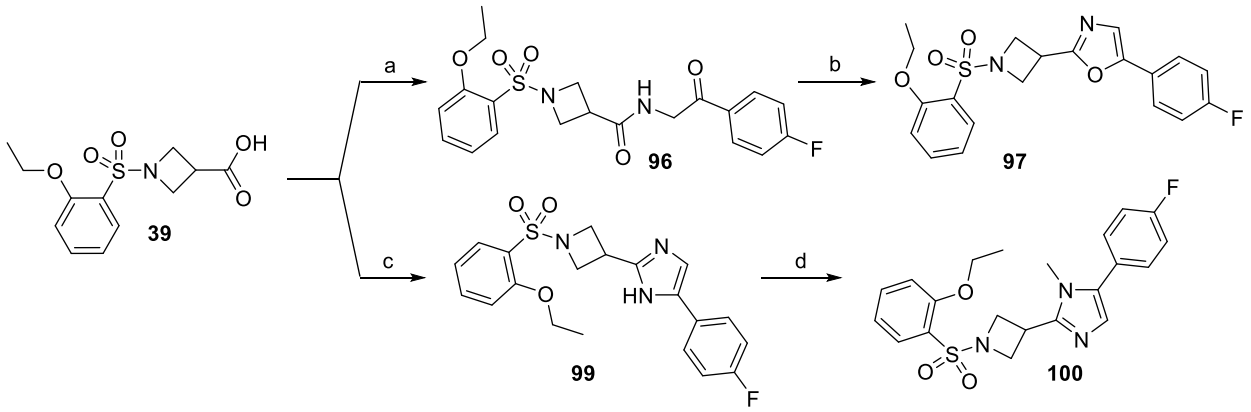
***tert*-Butyl 3-(1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)azetidine-1-carboxylate (93).** Intermediate **89** (70 mg, 0.39 mmol, 1.0 eq), 1-azido-4-fluorobenzene (107 mg, 0.78 mmol, 2.0 eq), sodium ascorbate (14 mg, 0.078 mmol, 0.020 eq), and copper sulfate (6.2 mg, 0.039 mmol, 0.010 eq), were dissolved in a mixture of *tert*-butanol (1.0 mL) and water (1.0 mL). The reaction was stirred overnight at 100 ºC. The reaction was cooled to room temperature, water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* at room temperature to afford 70 mg (56%) the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.69 (m, 2H), 7.72 (m, 2H), 7.22 (m, 2H), 4.36 (m, 2H), 4.13 (m, 2H), 3.98 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, J(C,F) = 249.2 Hz), 156.3, 149.5, 133.3 (d, J(C,F) = 3.1 Hz), 122.5 (d, J(C,F) = 8.6 Hz), 119.2, 116.7 (d, J(C,F) = 23.2 Hz), 79.7, 55.4, 28.4, 25.2 ppm.



3-(1-(4-Fluorophenyl)-1H-1,2,3-triazol-4-yl)azetidine-1-hydrochloride (94). The title compound was prepared in 100% yield (51 mg) from intermediate **93** using a method analogous to that described for the conversion of intermediate **9** into intermediate **10**.

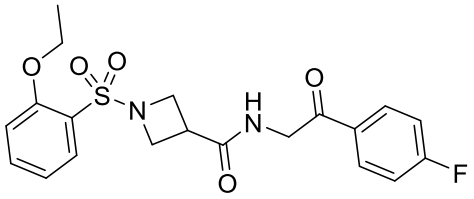


4-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-1-(4-fluorophenyl)-1H-1,2,3-triazole (95). The title compound was prepared in 31% yield (12 mg) from intermediate **94** and 2-ethoxybenzene sulfonyl chloride using a method analogous to that described for the conversion of intermediate **10** into intermediate **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.1, 1.7 Hz, 1H), 7.85 (s, 1H), 7.69 (m, 2H), 7.54 (m, 1H), 7.28 – 7.17 (m, 2H), 7.10 – 7.01 (m, 2H), 4.39 (t, J = 8.3 Hz, 2H), 4.27 – 4.15 (m, 4H), 3.97 (m, 1H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, J(C,F) = 249.3 Hz), 156.8, 149.0, 134.8, 133.3 (d, J(C,F) = 3.4 Hz), 131.2, 126.1, 122.5 (d, J(C,F) = 8.5 Hz), 120.3, 119.2, 116.8 (d, J(C,F) = 23.2 Hz), 113.6, 65.1, 57.1, 25.1, 14.7 ppm. LCMS R_T = 4.85 min; HRMS, calc'd for $C_{19}H_{20}FN_4O_3S^+$ [M+H], 403.1235; found 403.1239.



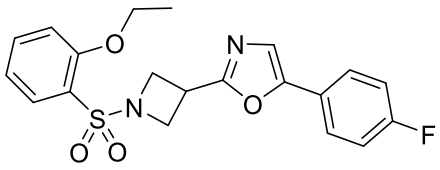
Reagents and conditions: (a) 2-amino-1-(4-fluorophenyl)ethenone hydrochloride, EDC, HOBt, DIEA, DCM, DMF, *6%*; (b) $POCl_3$, reflux, *25%*; (c) Cs_2CO_3, EtOH, 2-bromo-4'-fluoroacetophenone, DMF, NH_4OAc, PhMe, reflux, *63%*, (d) MeI, K_2CO_3, DMF, *78%*.

Synthesis of Analog 97:



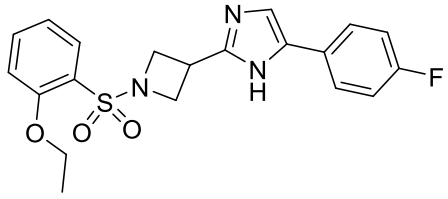
1-((2-Ethoxyphenyl)sulfonyl)-*N*-(2-(4-fluorophenyl)-2-oxoethyl)azetidine-3-carboxamide (96). Intermediate **39** (100 mg, 0.350 mmol, 1.0 eq), EDC (101 mg, 0.525 mmol, 1.5 eq), HOBt (80.4 mg, 0.525 mmol, 1.5 eq), and *N*,*N*-diisopropylethylamine (183 µL, 1.05 mmol, 3.0 eq) were dissolved in a mixture of DMF (1.0 mL) and DCM (3.0 mL), followed by the addition of 2-amino-1-(4-fluorophenyl)ethenone hydrochloride (99.5 mg, 0.525 mmol, 1.5 eq). The reaction was stirred overnight at room temperature. Water was added, and the reaction was extracted with ethyl acetate (2x), the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 10 mg (6%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.88 (m, 1H), 7.52 (m, 1H), 7.17 (m, 2H), 7.03 (m, 2H), 6.76 (m, 1H), 4.70 (d, J = 7.0 Hz, 2H), 4.29 – 4.07 (m, 4H), 3.37 (m,

1H), 1.50 (t, J = 7.0 Hz, 3H). LCMS R_T = 4.54 min; HRMS, calc'd for $C_{20}H_{22}FN_2O_5S^+$ [M+H], 421.1228; found 421.1231.



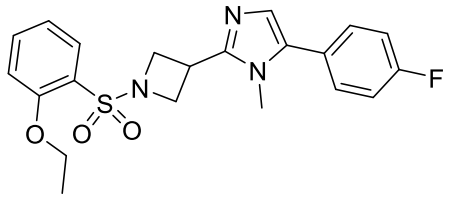
2-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)oxazole (97). Intermediate **96** (10 mg, 0.02 mmol, 1.0 eq) was heated at reflux in phosphorus oxychloride ($POCl_3$) (3.0 mL) overnight. The reaction was cooled to room temperature and quenched with cold sodium bicarbonate aqueous solution and was extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 2 mg (25%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.7, 1.76 Hz, 1H), 7.59 – 7.48 (m, 3H), 7.18 (s, 1H), 7.15 – 7.00 (m, 4H), 4.39 (m, 4H), 4.19 (q, J = 7.0 Hz, 2H), 3.95 (m, 1H), 1.48 (t, J = 7.0 Hz, 3H). LCMS R_T = 5.16 min; HRMS, calc'd for $C_{20}H_{20}FN_2O_4S^+$ [M+H], 403.1122; found 403.1131.

Synthesis of Analogs 99 and 100:



2-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)-1H-imidazole (99). Intermediate **39** (100 mg, 0.350 mmol, 1.0 eq) and Cs_2CO_3 (57.0 mg, 0.175 mmol, 0.5 eq) were stirred in ethanol (2.0 mL) at room temperature for 30 minutes. The reaction was concentrated *in*

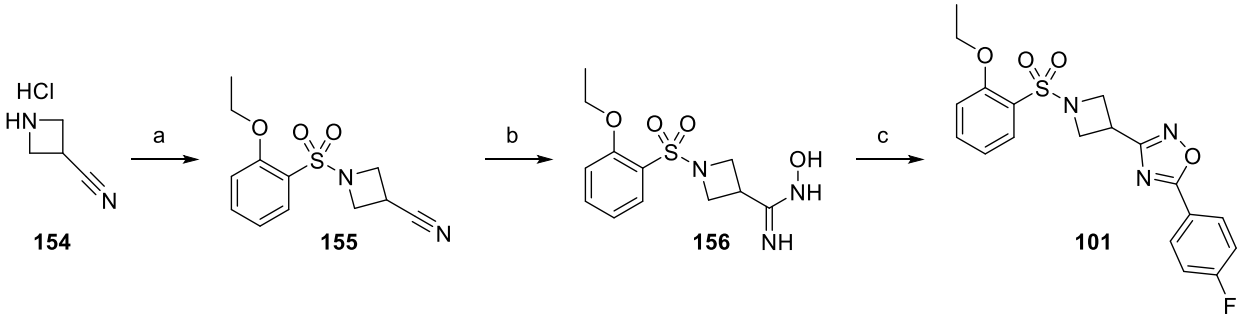
vacuo, the residue was dissolved in DMF (1.0 mL), followed by the addition of 2-bromo-4-fluoroacetophenone (**98**), and the reaction was allowed to stir at room temperature for 1 hour. The DMF was removed by azeotroping with toluene, followed by the addition of ethyl acetate, and the mixture was filtered through a syringe filter, the residue was washed with more ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The reaction residue was dissolved in toluene (PhMe) (3.0 mL), followed by the addition of ammonium acetate (NH_4OAc) (270 mg, 3.50 mmol, 10.0 eq). The reaction was heated at reflux for 2 hours. The reaction was cooled to room temperature, water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed with saturated aqueous sodium bicarbonate solution, and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 88 mg (63%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.8, 1.7 Hz, 1H), 7.63 – 7.48 (m, 3H), 7.15 (s, 1H), 7.07 – 6.93 (m, 4H), 4.28 (m, 4H), 4.12 (q, J = 7.0 Hz, 2H), 3.82 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 161.9 (d, J(C,F) = 245.6 Hz), 156.7, 147.6, 135.1, 131.1, 129.3, 126.3 (d, J(C,F) = 7.9 Hz), 125.4, 120.4, 115.5 (d, J(C,F) = 22 Hz), 113.7, 65.1, 56.1, 27.5, 14.6 ppm. LCMS R_T = 3.67 min; HRMS, calc'd for $C_{20}H_{21}FN_3O_3S^+$ [M+H], 402.1282; found 402.1283.



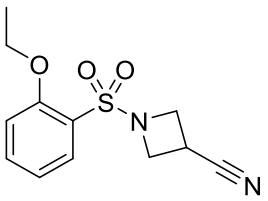
2-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)-1-methyl-1H-imidazole (100). To a solution of compound **99** (50 mg, 0.12 mmol, 1.0 eq) and K_2CO_3 (50 mg, 0.36 mmol, 3.0 eq) in DMF (1.0 mL), was added methyl iodide (CH_3I) (16 µL, 0.24 mmol, 2.0 eq). The reaction

was stirred at room temperature for 3 hours. Water was added, and the reaction was extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 39 mg (78%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.8, 1.7 Hz, 1H), 7.61 (m, 2H), 7.52 (m, 1H), 7.09 – 6.96 (m, 5H), 4.48 (t, J = 7.5 Hz, 2H), 4.34 (t, J = 8.2 Hz, 2H), 4.16 (q, J = 7.0 Hz, 2H), 3.85 (m, 1H), 3.53 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (d, J(C,F) = 245.0 Hz), 156.8, 146.8, 139.4, 134.7, 131.4, 130.3 (d, J(C,F) = 3.1 Hz), 126.2 (d, J(C,F) = 7.8 Hz), 125.8, 120.3, 116.7, 115.3 (d, J(C,F) = 21.5 Hz), 113.4, 64.9, 55.4, 32.6, 25.3, 14.7 ppm. LCMS R_T = 3.99 min; HRMS, calc'd for $C_{21}H_{23}FN_3O_3S^+$ [M+H], 416.1439; found 416.1439.

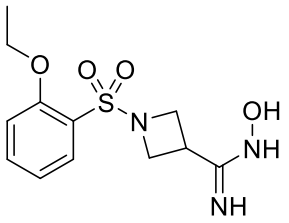
Synthesis of Analog 101:



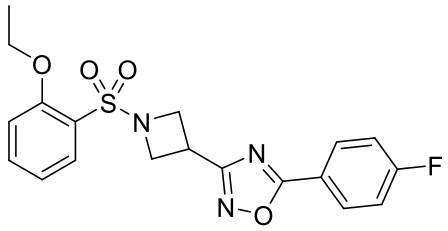
Reagents and conditions: (a) 2-ethoxybenzene sulfonyl chloride, NET_3, DCM, *78%*; (b) $NH_2OH.HCl$, $NaHCO_3$, MeOH, reflux, *90%*; (c) 4-fluorobenzoic acid, EDC, HOBt, DIEA, 1,4-dioxane, *29%*.



1-((2-Ethoxyphenyl)sulfonyl)azetidine-3-carbonitrile (155). The title compound was prepared in 78% yield (236 mg) from azetidine-3-carbonitrile hydrochloride (**154**) and 2-ethoxybenzene sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.04, 1.81 Hz, 1H), 7.57 (m, 1H), 7.06 (m, 2H), 4.35 – 4.17 (m, 6H), 3.41 (m, 1H), 1.52 (t, J = 7.01 Hz, 3H).



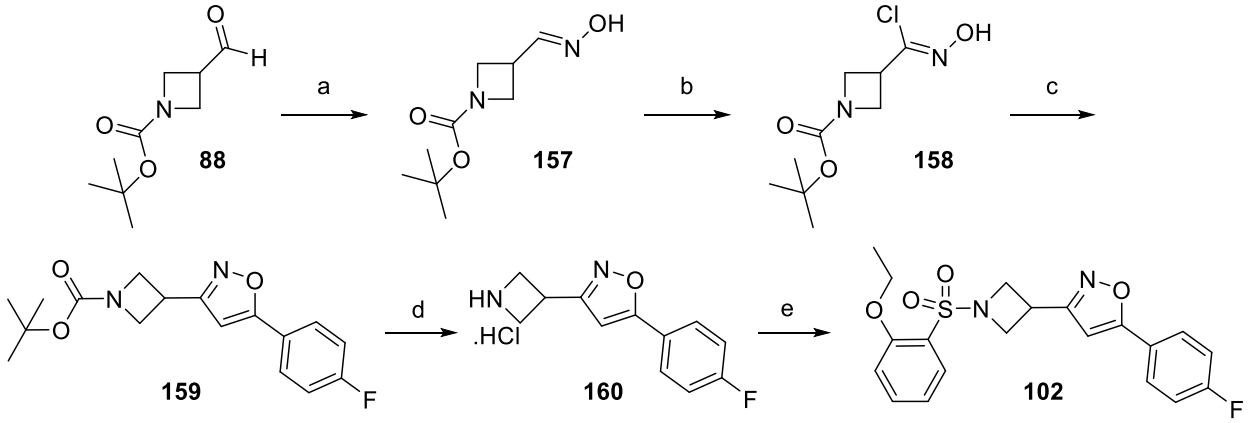
1-((2-Ethoxyphenyl)sulfonyl)-*N*-hydroxyazetidine-3-carboximidamide (156). The title compound was prepared in 90% yield (242 mg) from intermediate **155** using a method analogous to that described for the conversion of thiophene-3-carbonitrile **6** into intermediate **7**.



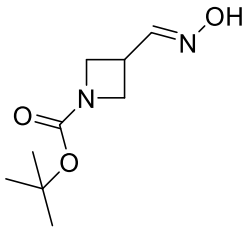
3-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)-1,2,4-oxadiazole (101). The title compound was prepared in 29% yield (21 mg) from intermediate **156** and 4-fluorobenzoic acid using a method analogous to that described for the conversion of intermediate **39** into compound **53**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.92 (dd, J = 8.0, 1.7 Hz, 1H), 7.54 (m, 1H), 7.22 (m, 2H), 7.10 – 7.01 (m, 2H), 4.40 (m, 4H), 4.20 (q, J = 7.0 Hz, 2H), 3.97 (m, 1H),

1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 170.5, 165.6 (d, *J*(C,F) = 255 Hz), 156.8, 134.7, 131.2, 130.6 (d, *J*(C,F) = 9.3 Hz), 126.3, 120.3 (d, *J*(C,F) = 4.8 Hz), 116.6 (d, *J*(C,F) = 22.4 Hz), 113.5, 65.0, 54.6, 24.9, 14.7 ppm. LCMS R_T = 5.35 min; HRMS, calc'd for $C_{19}H_{19}FN_3O_4S^+$ [M+H], 404.1075; found 404.1082.

Synthesis of Analog 102:

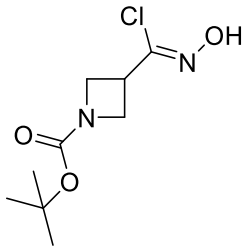


Reagents and conditions: (a) $NH_2OH.HCl$, $NaHCO_3$, H_2O, EtOH, *88%*; (b) NCS, DCM; (c) 4-ethynylfluorobenzene, $NaHCO_3$, EtOAc, *33%*; (d) 4M HCl in 1,4-dioxane, *100%*; (e) 2-ethoxybenzene sulfonyl chloride, DIEA, DCM, *67%*.

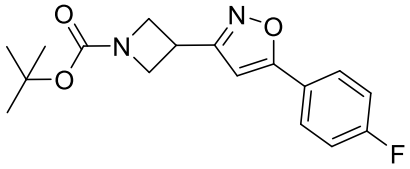


tert-Butyl (*E*)-3-((hydroxyimino)methyl)azetidine-1-carboxylate (157). Intermediate **88** (200 mg, 1.08 mmol, 1.0 eq), hydroxylamine hydrochloride (120 mg, 1.73 mmol, 1.6 eq), sodium bicarbonate (181 mg, 2.16 mmol, 2.0 eq) were dissolved in a mixture of water (1.0 mL) and ethanol (4.0 mL) and stirred overnight. The reaction was concentrated *in vacuo*, followed by the addition of water, and the reaction was extracted with ethyl acetate (2x). The combined organics were

washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 193 mg (88%) of the title compound, that was used further without purification.

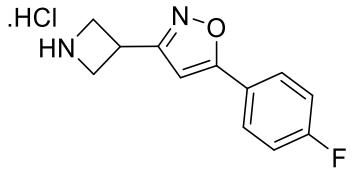


***tert*-Butyl (*Z*)-3-(chloro(hydroxyimino)methyl)azetidine-1-carboxylate (158).** Intermediate **157** (84 mg, 0.42 mmol, 1.0 eq) and *N*-chlorosuccinimide (67 mg, 0.48 mmol, 1.2 eq) were heated at reflux in DCM (3.0 mL) overnight. The reaction was cooled to room temperature, water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product weighed 130 mg and was used in the next step without further purification.

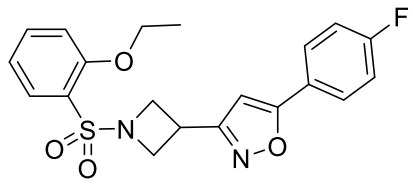


***tert*-Butyl 3-(5-(4-fluorophenyl)isoxazol-3-yl)azetidine-1-carboxylate (159).** Intermediate **158** (130 mg, 0.554 mmol, 1.0 eq), 1-ethynyl-4-fluorobenzene (86.5 mg, 0.720 mmol, 1.3 eq), and sodium bicarbonate (79.1 mg, 0.942 mmol, 1.7 eq) were dissolved in ethyl acetate (3.0 mL), and the reaction was allowed to stir overnight at room temperature. Water was added, and the reaction was extracted with ethyl acetate (2x), the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography

on silica gel afforded 42 mg (33%) (overall yield) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.17 (m, 2H), 6.53 (s, 1H), 4.36 (m, 2H), 4.09 (m, 2H), 3.89 (m, 1H), 1.47 (s, 9H).



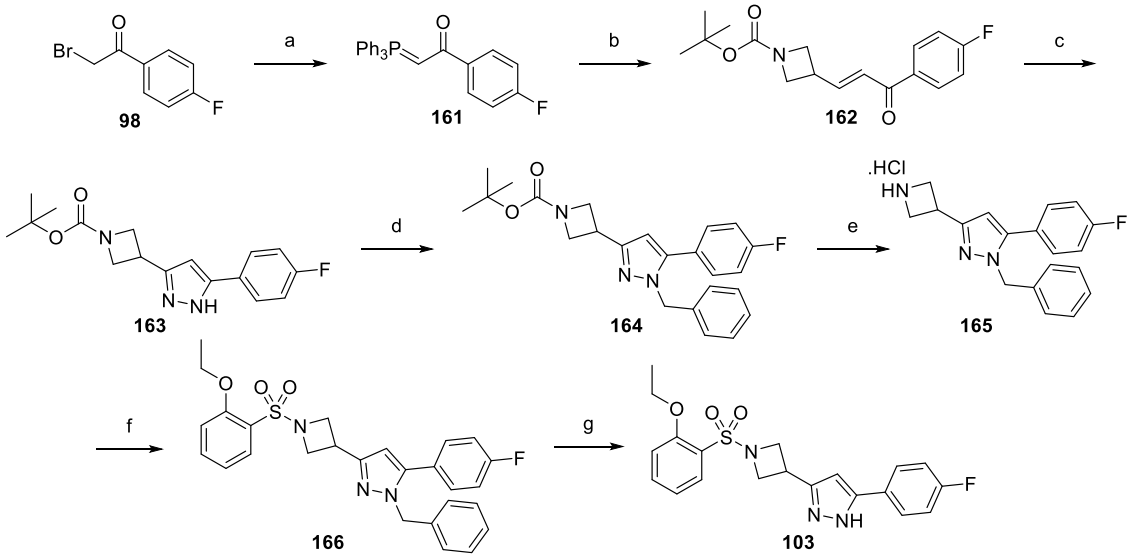
3-(5-(4-Fluorophenyl)isoxazol-3-yl)azetidine-1-hydrochloride (160). The title compound was prepared in 100% yield (33 mg) from intermediate **159** using a method analogous to that described for the conversion of intermediate **9** into intermediate **10**. The crude product was used further without purification.



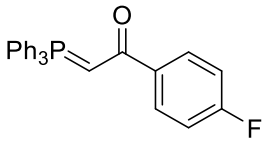
3-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)isoxazole (102). The title compound was prepared in 71% yield (29 mg) from intermediate **160** and 2-ethoxybenzene sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.2, 1.8 Hz, 1H), 7.75 (m, 2H), 7.56 (m, 1H), 7.17 (m, 2H), 7.11 – 7.03 (m, 2H), 6.49 (s, 1H), 4.39 (t, J = 8.4 Hz, 2H), 4.26 – 4.13 (m, 4H), 3.87 (m, 1H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (d, J(C,F) = 398.3 Hz), 165.6, 156.8, 134.9, 131.2, 127.9 (d, J(C,F) = 8.7 Hz), 126.0, 123.6 (d, J(C,F) = 3.0 Hz), 120.5,

116.3 (d, *J*(C,F) = 22.1 Hz), 113.6, 100.0, 97.2, 65.2, 55.9, 25.2, 14.7 ppm. LCMS R_T = 5.43 min; HRMS, calc'd for $C_{20}H_{20}FN_2O_4S^+$ [M+H], 403.1122; found 403.1129.

Synthesis of Analog 103:

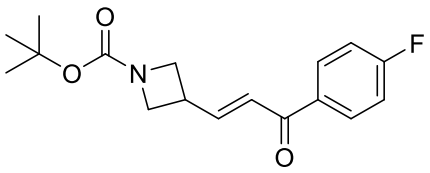


Reagents and conditions: (a) PPh_3, DCM, MeOH, 1N NaOH, *41%*; (b) **88**, PhMe, 60 ºC, *81%*; (c) $TsNHNH_2$, I_2, K_2CO_3, EtOH, 75 ºC, *41%*; (d) BnBr, K_2CO_3, DMF, *98%*; (e) 4M HCl in 1,4-dioxane, *100%*; (f) 2-ethoxybenzene sulfonyl chloride, NET_3, DCM, *65%*; (g) 10% Pd/C, AcOH, MeOH, 40 ºC, *9%*.

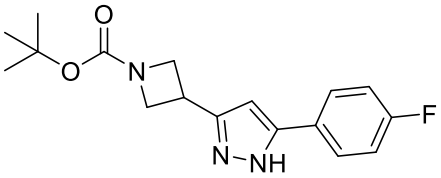


1-(4-Fluorophenyl)-2-(triphenyl-l5-phosphaneylidene)ethan-1-one (161). To a solution of 2-bromo-4-fluoroacetophenone **98** (500 mg, 2.30 mmol, 1.0 eq) in DCM (10 mL), was added a solution of triphenylphosphine (724 mg, 2.76 mmol, 1.2 eq). The reaction was allowed to stir at

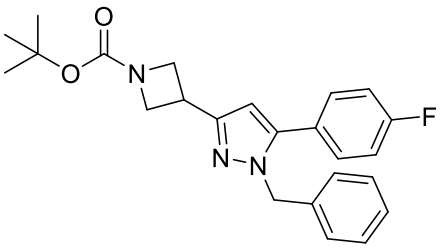
room temperature overnight. The reaction was concentrated *in vacuo*, followed by the addition of diethyl ether (10 mL). The reaction was stirred for 1 hour at room temperature, and the phosphonium salt was filtered, and the resulting precipitate was washed with more diethyl ether. The dried phosphonium salt was suspended in a mixture of water (5.0 mL) and methanol (5.0 mL) and stirred at room temperature for 1 hour. Aqueous sodium hydroxide solution (2N) was added to the reaction, until pH reached between 7 and 8. The reaction was stirred for additional 5 hours. Methanol was removed *in vacuo*, and the aqueous layer was extracted with DCM. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 376 mg (41%) of the title compound that was used further without purification. LCMS R_T = 4.13 min; HRMS, calc'd for $C_{26}H_{21}FOP^+$ [M+H], 399.1309; found 399.1315.



***tert*-Butyl (*E*)-3-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)azetidine-1-carboxylate (162).** To a solution of intermediate **88** (145 mg, 0.783 mmol, 1.0 eq) in toluene (PhMe) (5.0 mL), was added intermediate **161** (374 mg, 0.940 mmol, 1.2 eq). The reaction was stirred at 60 ºC for 4 hours. The reaction was cooled to room temperature, concentrated *in vacuo*, and purification of the residue by flash chromatography on silica gel afforded 193 mg (81%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.25 – 7.09 (m, 3H), 6.92 (dd, *J* = 15.3, 1.0 Hz, 1H), 4.20 (m, 2H), 3.88 (m, 2H), 3.46 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.37, 165.62 (d, *J*(C,F) = 254.9 Hz), 156.2, 147.8, 133.9 (d, *J*(C,F) = 3.1 Hz), 131.2 (d, *J*(C,F) = 9.3 Hz), 125.8, 115.8 (d, *J*(C,F) = 22.0 Hz), 79.7, 53.8, 31.2, 28.4 ppm.

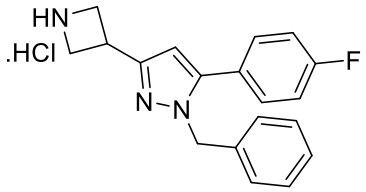


***tert*-Butyl 3-(5-(4-fluorophenyl)-1H-pyrazol-3-yl)azetidine-1-carboxylate (163).** Intermediate **162** (193 mg, 0.632 mmol, 1.0 eq) and *p*-toluenesulfonyl hydrazide ($TsNHNH_2$) (141 mg, 0.758 mmol, 1.2 eq) were dissolved in ethanol (2.0 mL), followed by the addition of iodine (I_2) (3.2 mg, 0.0126 mmol, 0.02 eq). The reaction was heated at 75 ºC for 15 minutes. The reaction was cooled to room temperature, and K_2CO_3 (131 mg, 0.948 mg, 1.5 eq) was added. The reaction was stirred open to air at 75 ºC for 3 hours. The reaction was cooled to room temperature, concentrated *in vacuo*, and purification of the residue by flash chromatography on silica gel afforded 83 mg (41%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.05 (m, 2H), 6.46 (s, 1H), 4.28 (m, 2H), 4.04 (m, 2H), 3.79 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (d, *J*(C,F) = 248 Hz), 156.5, 150.6, 147.3, 128.9 (d, *J*(C,F) = 96.3 Hz), 127.4 (d, *J*(C,F) = 8.2 Hz), 115.8 (d, *J*(C,F) = 21.8 Hz), 100.2, 79.9, 55.6, 28.4, 26.4 ppm. LCMS R_T = 4.93 min; HRMS, calc'd for $C_{17}H_{21}FN_3O_2^+$ [M+H], 318.1612; found 318.1616.

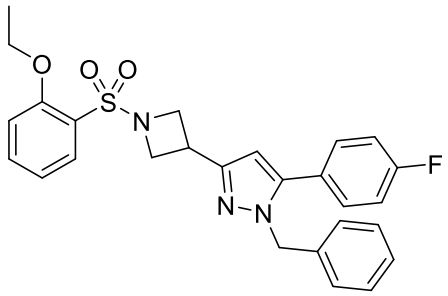


***tert*-Butyl 3-(1-benzyl-5-(4-fluorophenyl)-1H-pyrazol-3-yl)azetidine-1-carboxylate (164).** The title compound was prepared in 98% yield (103 mg) from intermediate **163** and benzyl bromide using a method analogous to that described for the conversion of intermediate **82** into intermediate

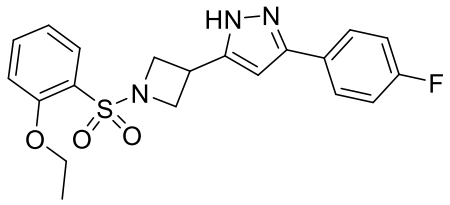
83. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.38 – 7.21 (m, 5H), 7.09 (m, 2H), 6.56 (s, 1H), 5.29 (s, 2H), 4.06 (m, 2H), 3.83 (m, 2H), 3.62 (m, 1H), 1.43 (s, 9H).



3-(1-Benzyl-5-(4-fluorophenyl)-1H-pyrazol-3-yl)azetidine-1-hydrochloride (165). The title compound was prepared in 100% yield (89 mg) from intermediate **164** using a method analogous to that described for the conversion of intermediate **9** into intermediate **10**.

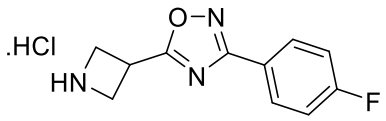


1-Benzyl-3-(1-((2-ethoxyphenyl)sulfonyl)azetidin-3-yl)-5-(4-fluorophenyl)-1H-pyrazole (166). The title compound was prepared in 68% (86 mg) yield from intermediate **165** and 2-ethoxybenzene sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.74, 1.71 Hz, 1H), 7.73 (m, 2H), 7.52 (m, 1H), 7.33 – 7.18 (m, 4H), 7.14 – 6.94 (m, 5H), 6.32 (s, 1H), 5.27 (s, 2H), 4.17 – 3.96 (m, 4H), 3.91 (m, 2H), 3.62 (m, 1H), 1.36 (t, J = 6.99 Hz, 3H).

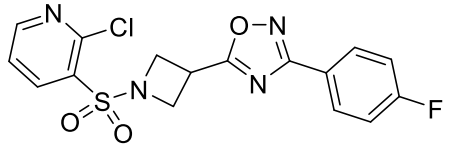


5-(1-((2-Ethoxyphenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1H-pyrazole (103). The title compound was prepared in 9% yield (6 mg) from intermediate **166** using a method analogous to that described for the conversion of intermediate **85** into compound **86**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.3, 1.8 Hz, 1H), 7.65 – 7.50 (m, 3H), 7.17 – 7.02 (m, 4H), 6.38 (s, 1H), 4.37 (t, J = 8.3 Hz, 2H), 4.26 – 4.09 (m, 4H), 3.81 (m, 1H), 1.48 (t, J = 7. 0 Hz, 3H). LCMS R_T = 4.85 min; HRMS, calc'd for $C_{20}H_{21}FN_3O_3S^+$ [M+H], 402.1282; found 402.1285.

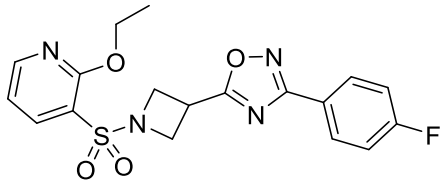
Synthesis of Analogs 111 – 118:



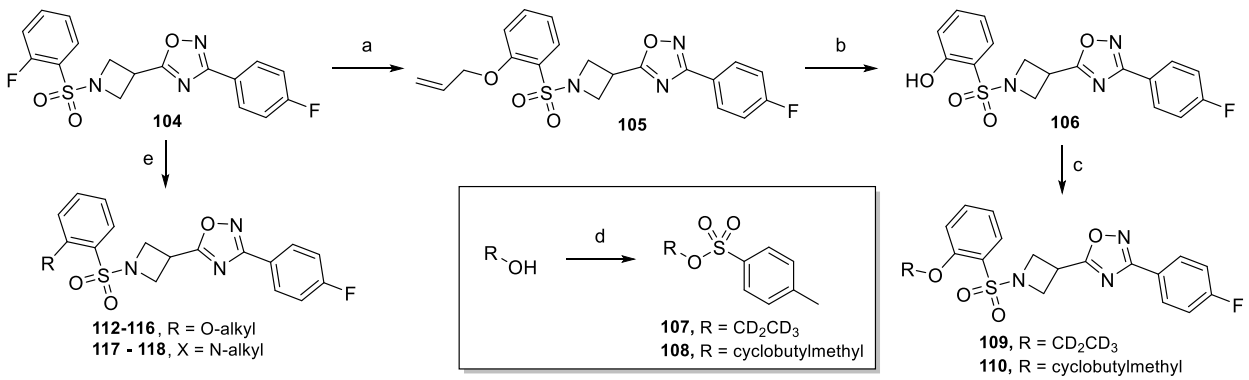
3-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-hydrochloride (167). The title compound was prepared in 53% yield from 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (**8**) and 4-fluorobenzamidoxime using a method analogous to that described for the conversion of compound **8** into **10**. The isolated salt was used without purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.24 (bs, 1H), 8.09 (m, 2H), 7.45 (m, 2H), 4.51 (m, 1H), 4.32 (m, 4H). LCMS R_T = 1.92 min; HRMS, calc'd for $C_{11}H_{10}FN_3O^+$ [M+H], 220.0881; found 220.0879.



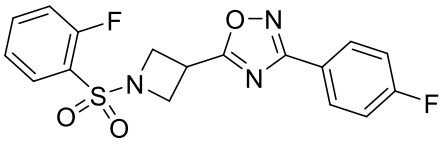
5-(1-((2-Chloropyridin-3-yl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (123). The title compound was prepared in 92% yield (500 mg) from intermediate **167** and 2-chloropyridine-3-sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, J = 4.80, 1.89 Hz, 1H), 8.37 (dd, J = 7.80, 1.90 Hz, 1H), 8.06 (m, 2H), 7.43 (q, J = 4.80 Hz, 1H), 7.17 (m, 2H), 4.56 (m, 4H), 4.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.93, 167.81, 164.67 (d, J(C,F) = 252.09 Hz), 152.70, 148.79, 139.81, 134.30, 129.67 (d, J(C,F) = 8.78 Hz), 122.52, 122.47, 116.14 (d, J(C,F) = 22.09 Hz), 55.02, 25.08 ppm. LCMS R_T = 5.10 min; HRMS, calc'd for $C_{16}H_{13}ClFN_4O_3S^+$ [M+H], 395.0375; found 395.0383.



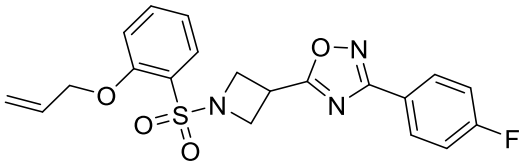
5-(1-((2-Ethoxypyridin-3-yl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (111). The title compound was prepared in 20% yield (6 mg) from intermediate **123** using a method analogous to that described for the conversion of intermediate **153** into compound **77**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, J = 4.94, 1.92 Hz, 1H), 8.18 (dd, J = 7.62, 1.95 Hz, 1H), 8.05 (m, 2H), 7.18 (m, 2H), 7.01 (dd, J = 7.62, 4.94 Hz, 1H), 4.61 – 4.42 (m, 6H), 4.08 (m, 1H), 1.46 (t, J = 7.09 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.24, 167.09 (d, J(C,F) = 106.46 Hz), 159.99, 151.71, 140.20, 129.66 (d, J(C,F) = 8.84 Hz), 122.52, 121.21, 116.36 (d, J(C,F) = 7.08 Hz), 116.02, 63.34, 54.72, 25.25, 14.54 ppm. LCMS R_T = 5.29 min; HRMS, calc'd for $C_{18}H_{18}FN_4O_4S^+$ [M+H], 405.1027; found 405.1035.



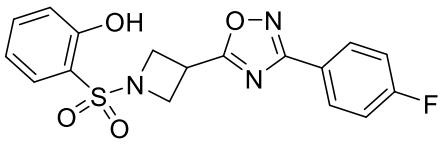
Reagents and conditions: (a) allyl alcohol, Cs_2CO_3, 70 ºC, *47%*; (b) $Pd(PPh_3)_4$, K_2CO_3, MeOH, *77%*; (c) Cs_2CO_3, DMF, 120 ºC, 20 min, µW, **107** (**109**, *70%*), **108** (**110**, *56%*); (d) TsCl, DMAP, NET_3, DCM, (**107**, *70%*), (**108**, *75%*); (e) RH or XH, Cs_2CO_3, DMF, *16 – 52%*.



3-(4-Fluorophenyl)-5-(1-((2-fluorophenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (104). The title compound was prepared in 81% yield (1.10 g) from intermediate **167** and 2-fluorobenzene-sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.90 (m, 1H), 7.64 (m, 1H), 7.31 (m, 2H), 7.16 (m, 2H), 4.40 (m, 4H), 4.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 164.7 (d, *J*(C,F) = 252 Hz), 159.4 (d, *J*(C,F) = 256 Hz), 135.7 (d, *J*(C,F) = 8.4 Hz), 131.1, 129.6 (d, *J*(C,F) = 8.8 Hz), 124.6 (d, *J*(C,F) = 3.8 Hz), 123.5 (d, *J*(C,F) = 153.8 Hz), 123.4 (d, *J*(C,F) = 135.9 Hz), 117.5 (d, *J*(C,F) = 21.8 Hz), 116.1 (d, *J*(C,F) = 22.1 Hz), 54.4 (d, *J*(C,F) = 2.1 Hz), 25.2 ppm.

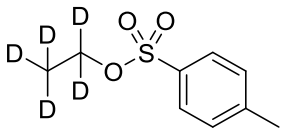


5-(1-((2-(Allyloxy)phenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (105). Intermediate **104** (1.10 g, 2.91 mmol, 1.0 eq), Cs_2CO_3 (2.84 g, 8.73 mmol, 3.0 eq), and allyl alcohol (10 mL) were heated at 70 ºC overnight. The reaction was cooled to room temperature, water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 630 mg (52%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.93 (dd, J = 7.8, 1.7 Hz, 1H), 7.54 (m, 1H), 7.17 (m, 2H), 7.12 – 7.00 (m, 2H), 6.08 (m, 1H), 5.54 (m, 1H), 5.32 (m, 1H), 4.69 (dt, J = 5.2, 1.5 Hz, 2H), 4.44 (m, 4H), 4.03 (m, 1H). LCMS R_T = 5.44 min; HRMS, calc'd for $C_{20}H_{19}FN_3O_4S^+$ [M+H], 416.1075; found 416.1081.

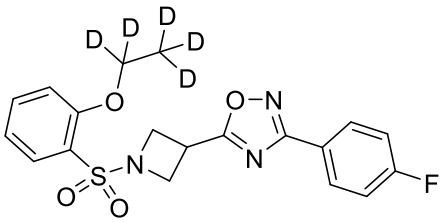


2-((3-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)sulfonyl)phenol (106). Tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (70 mg, 0.06 mmol, 0.01 eq) was added to a solution of intermediate **105** (630 mg, 1.52 mmol, 1.0 eq) and K_2CO_3 (840 mg, 6.08 mmol, 4.0 eq) in methanol (5.0 mL), and stirred overnight at room temperature. The reaction was concentrated *in vacuo*, followed by the addition of water, and extraction with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 435 mg (77%) of

the title compound as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.67 (dd, J = 9. 0, 1.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.23 – 6.96 (m, 4H), 4.26 (m, 4H), 3.98 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 167.7, 164.7 (d, J(C,F) = 252.2 Hz), 136.3, 129.7 (d, J(C,F) = 8.8 Hz), 129.6, 122.4 (d, J(C,F) = 3.2 Hz), 120.1, 119.5, 117.0, 116.1 (d, J(C,F) = 22.1 Hz), 54.3, 25.3 ppm. LCMS R_T = 4.98 min; HRMS, calc'd for $C_{17}H_{15}FN_3O_4S^+$ [M+H], 376.0762; found 376.0769.

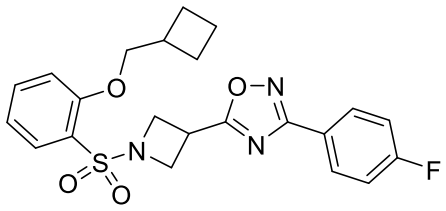


Ethyl-d_5 4-methylbenzenesulfonate (107). Ethanol-d_6 (534 mg, 10.5 mmol, 1.0 eq), and triethylamine (2.86 mL, 21.0 mmol, 2.0 eq) were dissolved in DCM (15 mL), followed by the addition of *p*-toluenesulfonyl chloride (1.80 g, 9.45 mmol, 0.9 eq), and DMAP (12 mg, 0.10 mmol, 0.01 eq). The reaction was stirred at room temperature overnight. Water was added and the reaction was extracted with DCM (2x). The combined organics were washed with 1N HCl, saturated $NaHCO_3$, and brine; dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 1.60 g (83%) of the title compound that was used further without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.35 (m, 2H), 2.45 (s, 3H).



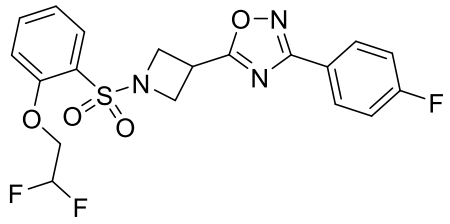
5-(1-((2-(Ethoxy-d_5)phenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (109). Intermediate **106** (30 mg, 0.08 mmol, 1.0 eq), intermediate **107** (33 mg, 0.16 mol, 2.0 eq), Cs_2CO_3

(78 mg, 0.24 mmol, 3.0 eq), and DMF (0.5 mL) were added to a microwave vial and heated in a microwave reactor at 120 ºC for 20 minutes. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 23 mg (70%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.91 (dd, J = 7.8, 1.8 Hz, 1H), 7.54 (m, 1H), 7.17 (m, 2H), 7.09 – 7.00 (m, 2H), 4.45 (m, 4H), 4.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 167.8, 164.7 (d, J(C,F) = 252.0 Hz), 156.7, 135.0, 131.1, 129.6 (d, J(C,F) = 8.7 Hz), 125.9, 122.6 (d, J(C,F) = 3.3 Hz), 122.4, 116.1 (d, J(C,F) = 22.1 Hz), 113.5, 54.5, 25.3 ppm. LCMS R_T = 5.35 min; HRMS, calc'd for $C_{19}H_{14}D_5FN_3O_4S^+$ [M+H], 409.1389; found 409.1400.

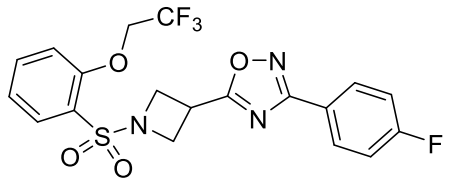


5-(1-((2-(Cyclobutylmethoxy)phenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (110). The title compound was prepared in 56% yield (12 mg) from intermediate **106** and cyclobutane methanol using a method analogous to that described for the conversion of compound **106** into **109**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.91 (m, 1H), 7.54 (m, 1H), 7.17 (m, 2H), 7.05 (m, 2H), 4.48 – 4.36 (m, 4H), 4.08 (d, J = 6.8 Hz, 2H), 4.02 (m, 1H), 2.86 (m, 1H), 2.23 – 2.09 (m, 2H), 2.04 – 1.83 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 165.4 (d, J(C,F) = 356.4 Hz), 157.1, 133.2 (d, J(C,F) = 279 Hz), 130 (d, J(C,F) = 8.8 Hz), 125.5, 122.6 (d, J(C,F) = 3.1 Hz), 120.3, 116.3, 116.0, 113.7, 73.6, 54.2, 34.4, 25.3, 25.0, 18.5 ppm. LCMS R_T = 5.87 min; HRMS, calc'd for $C_{22}H_{23}FN_3O_4S^+$ [M+H], 444.1388; found 444.1392.

Analogs **112** – **116** were prepared using a method analogous to that used for intermediate **105**:

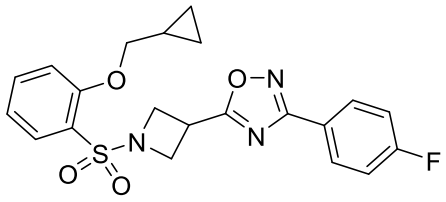


5-(1-((2-(2,2-Difluoroethoxy)phenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (112). The title compound was prepared in 52% yield (11 mg) from intermediate **104** and difluoroethanol using a method analogous to that described for the conversion of compound **104** into **105**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.95 (dd, J = 7.9, 1.7 Hz, 1H), 7.60 (m, 1H), 7.22 – 7.12 (m, 3H), 7.06 (dd, J = 8.3, 0.7 Hz, 1H), 6.21 (tt, J = 54.8, 4.1 Hz, 1H), 4.50 – 4.24 (m, 6H), 4.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 167.8, 164.7 (d, J(C,F) = 252.0 Hz), 155.5, 135.1, 131.4, 129.7 (d, J(C,F) = 8.7 Hz), 126.9, 122.6 (d, J(C,F) = 3.3 Hz), 122.3, 116.1 (d, J(C,F) = 22.1 Hz), 114.7, 113.2, 68.8 (t, J(C,F) = 29.7 Hz), 54.3, 25.2 ppm. LCMS R_T = 5.30 min; HRMS, calc'd for $C_{19}H_{17}F_3N_3O_4S^+$ [M+H], 440.0886; found 440.0892.

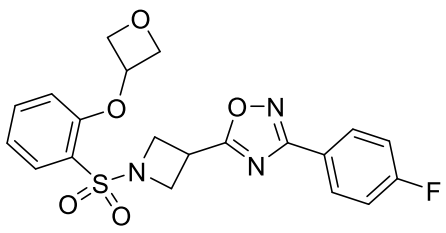


3-(4-Fluorophenyl)-5-(1-((2-(2,2,2-trifluoroethoxy)phenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (113). The title compound was prepared in 35% yield (8 mg) from intermediate **104** and trifluoroethanol using a method analogous to that described for the conversion of compound **104** into **105**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.96 (dd, J = 7.9 Hz, 1H), 7.61 (m, 1H),

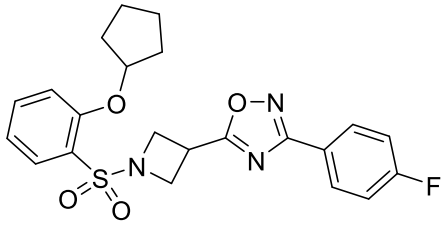
7.27 – 7.07 (m, 4H), 4.59 – 4.36 (m, 6H), 4.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 167.8, 164.7 (d, *J*(C,F) = 251.8 Hz), 155.0, 133.2 (d, *J*(C,F) = 285.3 Hz), 129.7 (d, *J*(C,F) = 8.8 Hz), 128.0, 124.8, 123.2, 122.6 (d, *J*(C,F) = 3.3 Hz), 121.1, 116.1 (d, *J*(C,F) = 22.1 Hz), 115.8, 67.8 (q, *J*(C,F) = 36.2 Hz), 54.3, 25.2 ppm. LCMS R_T = 5.43 min; HRMS, calc'd for $C_{19}H_{16}F_4N_3O_4S^+$ [M+H], 458.0792; found 458.0795.



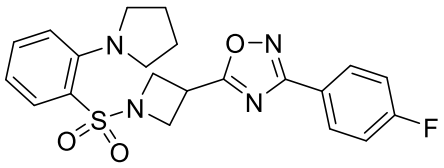
5-(1-((2-(Cyclopropylmethoxy)phenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (114). The title compound was prepared in 28% yield (6 mg) from intermediate **104** and cyclopropane methanol using a method analogous to that described for the conversion of compound **104** into **105**. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.04 (m, 2H), 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.52 (m, 1H), 7.17 (m, 2H), 7.10 – 6.95 (m, 2H), 4.52 (d, *J* = 7.7 Hz, 4H), 4.06 (m, 1H), 3.95 (d, *J* = 7.0 Hz, 2H), 1.35 (m, 1H), 0.66 (m, 2H), 0.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 167.8, 164.7 (d, *J*(C,F) = 251.9 Hz), 156.7, 133.0 (d, *J*(C,F) = 288.7 Hz), 129.6 (d, *J*(C,F) = 8.7 Hz), 126.3, 122.6 (d, *J*(C,F) = 3.3 Hz), 120.4, 116.3, 116.0, 113.7, 74.4, 54.5, 25.3, 10.1, 3.6 ppm. LCMS R_T = 5.59 min; HRMS, calc'd for $C_{21}H_{21}FN_3O_4S^+$ [M+H], 430.1231; found 430.1238.



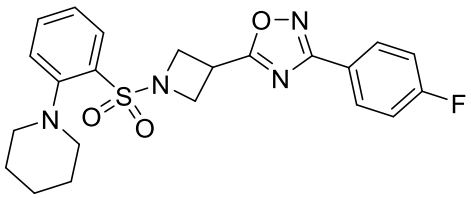
3-(4-Fluorophenyl)-5-(1-((2-(oxetan-3-yloxy)phenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (115). The title compound was prepared in 47% yield (10 mg) from intermediate **104** and oxetan-3-ol using a method analogous to that described for the conversion of compound **104** into **105**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.96 (dd, J = 7.9, 1.7 Hz, 1H), 7.53 (m, 1H), 7.22 – 7.09 (m, 3H), 6.60 (dd, J = 8.3, 0.7 Hz, 1H), 5.33 (m, 1H), 5.01 (m, 2H), 4.85 (m, 2H), 4.56 – 4.42 (m, 4H), 4.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 167.8, 164.7 (d, J(C,F) = 252.0 Hz), 154.4, 133.4 (d, J(C,F) = 253.4 Hz), 129.7 (d, J(C,F) = 8.7 Hz), 126.4, 122.5 (d, J(C,F) = 3.3 Hz), 121.6, 116.3, 116.0, 113.5, 71.7, 54.5, 25.3 ppm. LCMS R_T = 4.96 min; HRMS, calc'd for $C_{20}H_{19}FN_3O_5S^+$ [M+H], 432.1024; found 432.1027.



5-(1-((2-(cyclopentyloxy)phenyl)sulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (116). The title compound was prepared in 34% yield (7 mg) from intermediate **104** and cyclopentanol using a method analogous to that described for the conversion of compound **104** into **105**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.90 (dd, J = 7.8, 1.7 Hz, 1H), 7.52 (m, 1H), 7.17 (m, 2H), 7.08 – 6.97 (m, 2H), 4.93 (m, 1H), 4.48 – 4.35 (m, 4H), 4.02 (m, 1H), 2.00 – 1.76 (m, 6H), 1.71 – 1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 167.7, 164.7 (d, J(C,F) = 252 Hz), 156.1, 133.1 (d, J(C,F) = 251 Hz), 129.6 (d, J(C,F) = 8.8 Hz), 125.9, 122.6 (d, J(C,F) = 3.2 Hz), 119.9, 116.3, 116.0, 114.6, 81.1, 54.3, 32.8, 25.3, 24.0 ppm. LCMS R_T = 5.81 min; HRMS, calc'd for $C_{22}H_{23}FN_3O_4S^+$ [M+H], 444.1388; found 444.1400.



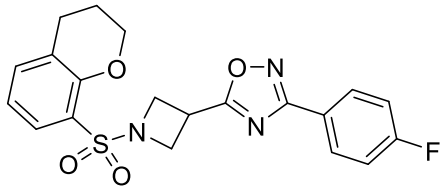
3-(4-Fluorophenyl)-5-(1-((2-(pyrrolidin-1-yl)phenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (117). NaH (26 mg, 1.1 mmol, 10.0 eq) was added to pyrrolidine (0.5 mL) at 0 ºC. Intermediate **104** (40 mg, 0.11 mmol, 1.0 eq) was added afterwards, and the reaction was warmed to room temperature, then heated at 80 ºC overnight. The reaction was cooled to room temperature and concentrated *in vacuo*. Water was added, and the reaction was extracted with DCM (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 7 mg (16%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.98 (d, J = 8.07, 1.7 Hz, 1H), 7.45 (m, 1H), 7.23 – 7.12 (m, 3H), 7.01 (m, 1H), 4.36 (m, 4H), 4.03 (m, 1H), 3.38 (m, 4H), 1.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 167.8, 164.7 (d, J(C,F) = 252.0 Hz), 150.0, 133.9, 131.5, 129.7 (d, J(C,F) = 8.8 Hz), 128.6, 122.7 (d, J(C,F) = 3.3 Hz), 120.6 (d, J(C,F) = 5.1 Hz), 116.3, 116.0, 53.9, 53.5, 25.4, 25.1 ppm. LCMS R_T = 5.84 min; HRMS, calc'd for $C_{21}H_{22}FN_4O_3S^+$ [M+H], 429.1391; found 429.1397.



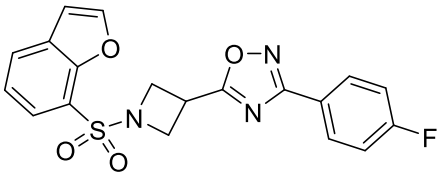
3-(4-Fluorophenyl)-5-(1-((2-(piperidin-1-yl)phenyl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (118). The title compound was prepared in 18% yield (9 mg) from intermediate **104** and piperidine

using a method analogous to that described for the conversion of compound **104** into **117**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 3H), 7.56 (m, 1H), 7.37 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.29 – 7.12 (m, 3H), 4.38 (m, 4H), 3.97 (m, 1H), 2.98 (m, 4H), 1.72 (m, 4H), 1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 167.0 (d, *J*(C,F) = 101 Hz), 154.6, 134.3, 132.2, 132.0, 129.6 (d, *J*(C,F) = 8.7 Hz), 124.4, 123.4, 122.6 (d, *J*(C,F) = 3.3 Hz), 116.3, 116.0, 55.8, 54.6, 26.1, 25.3, 24.0 ppm. LCMS R_T = 6.08 min; HRMS, calc'd for $C_{22}H_{24}FN_4O_3S^+$ [M+H], 443.1548; found 443.1554.

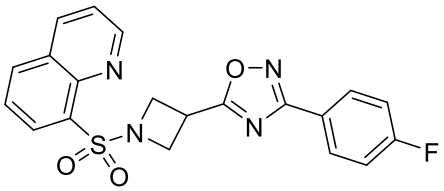
Analogs **119 – 122** were prepared using a method analogous to that used for compound **123**:



5-(1-(chroman-8-ylsulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (119). The title compound was prepared in 72% yield (32 mg) from intermediate **167** and chroman-8-sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.72 (m, 1H), 7.26 (m, 1H), 7.17 (m, 2H), 6.94 (t, *J* = 7.7 Hz, 1H), 4.49 – 4.39 (m, 4H), 4.33 (t, *J* = 5.2 Hz, 2H), 4.06 (m, 1H), 2.83 (t, *J* = 6.5 Hz, 2H), 2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 167.7, 164.7 (d, *J*(C,F) = 252.1 Hz), 152.8, 135.4, 129.6 (d, *J*(C,F) = 8.8 Hz), 129.2, 124.6, 124.3, 122.6 (d, *J*(C,F) = 3.3 Hz), 119.7, 116.2 (d, *J*(C,F) = 22.1 Hz), 67.3, 54.5, 25.3, 24.8, 21.4 ppm. LCMS R_T = 5.33 min; HRMS, calc'd for $C_{20}H_{19}FN_3O_4S^+$ [M+H], 416.1075; found 416.1076.

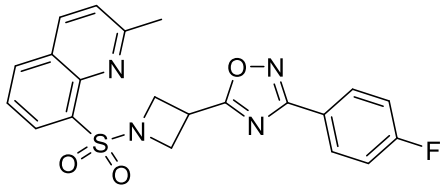


5-(1-(Benzofuran-7-ylsulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (120). The title compound was prepared in 63% yield (28 mg) from intermediate **167** and benzofuran-7-sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.76 (m, 4H), 7.79 (d, J = 2.2 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.15 (m, 2H), 6.89 (d, J = 2.2 Hz, 1H), 4.40 (m, 4H), 3.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 167.6, 164.7 (d, J(C,F) = 252 Hz), 150.5, 146.6, 129.9, 129.6 (d, J(C,F) = 8.8 Hz), 127.3, 126.3, 123.0, 122.4 (d, J(C,F) = 3.3 Hz), 119.4, 116.1 (d, J(C,F) = 22.1 Hz), 106.9, 54.4, 25.2 ppm. LCMS R_T = 5.23 min; HRMS, calc'd for $C_{19}H_{15}FN_3O_4S^+$ [M+H], 400.0762; found 400.0762.



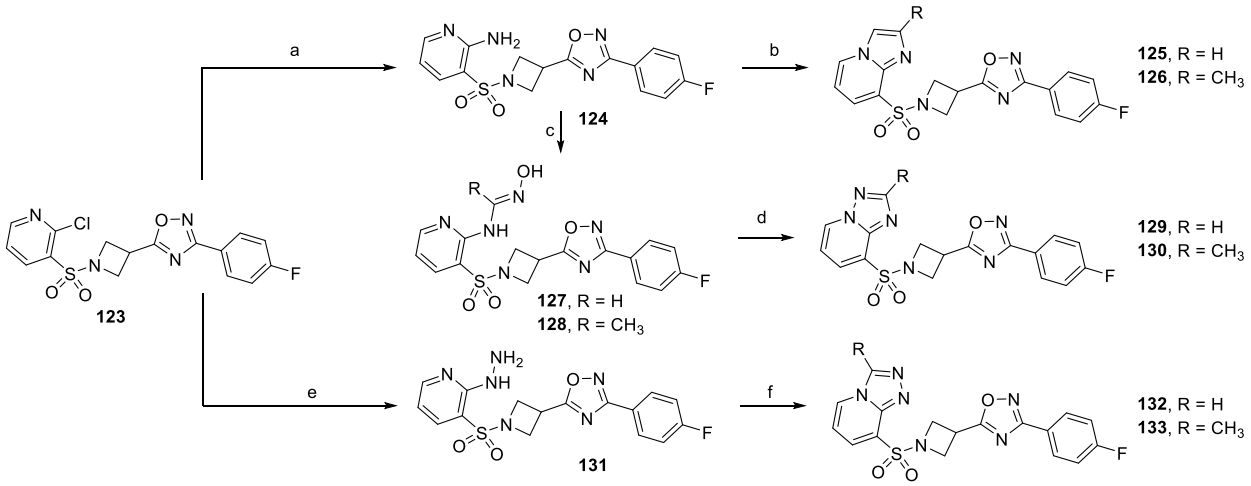
3-(4-Fluorophenyl)-5-(1-(quinolin-8-ylsulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (121). The title compound was prepared in 57% yield (26 mg) from intermediate **167** and 8-quinolinesulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (dd, J = 4.2, 1.8 Hz, 1H), 8.49 (dd, J = 7.4, 1.4 Hz, 1H), 8.23 (dd, J = 8.5, 1.8 Hz, 1H), 8.07 (dd, J = 8.2, 1.4 Hz, 1H), 7.95 (m, 2H), 7.66 (dd, J = 8.1, 7.5 Hz, 1H), 7.51 (q, J = 4.3 Hz, 1H), 7.15 (m, 2H), 4.71 (m, 4H), 4.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 167.6, 164.6 (d, J(C,F) = 252 Hz), 151.4, 144.2, 136.7, 136.4, 133.8, 132.4, 129.6 (d, J(C,F)

= 8.8 Hz), 129.1, 125.6, 122.6 (d, *J*(C,F) = 3.3 Hz), 122.2, 116.1 (d, *J*(C,F) = 22.1 Hz), 55.0, 25.4 ppm. LCMS R_T = 5.09 min; HRMS, calc'd for $C_{20}H_{16}FN_4O_3S^+$ [M+H], 411.0922; found 411.0927.

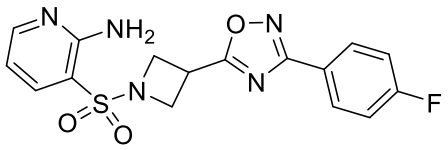


3-(4-Fluorophenyl)-5-(1-((2-methylquinolin-8-yl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (122). The title compound was prepared in 81% yield (38 mg) from intermediate **167** and 2-methylquinoline-8-sulfonyl chloride using a method analogous to that described for the conversion of compound **10** into **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 7.4, 1.43 Hz, 1H), 8.08 (d, *J* = 8.5, 1H), 8.04 – 7.90 (m, 3H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.15 (m, 2H), 4.74 (m, 4H), 4.05 (m, 1H), 2.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 167.6, 164.7 (d, *J*(C,F) = 252 Hz), 160.6, 143.8, 136.4, 136.3, 133.4, 132.1, 129.6 (d, *J*(C,F) = 8.8 Hz), 127.4, 124.6, 123.1, 122.6 (d, *J*(C,F) = 3.3 Hz), 116.1 (d, *J*(C,F) = 22.1 Hz), 54.9, 25.5, 25.4 ppm. LCMS R_T = 5.22 min; HRMS, calc'd for $C_{21}H_{18}FN_4O_3S^+$ [M+H], 425.1078; found 425.1074.

Synthesis of Analogs 125, 126, 129, 130, 132, and 133:

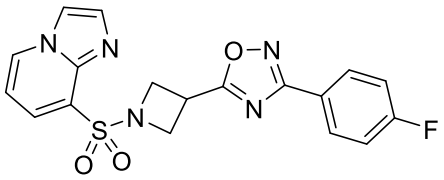


Scheme 8. Reagents and conditions: (a) NH_4OH, 1,4-dioxane, 100 ºC, *42%*; (b) R = H, $BrCH_2CH(OC_2H_5)_2$, *21%* or R = CH_3, $CH_3C(OCH_3)_2CH_2Br$, *12%*; (c) R = H, DMF.DMA, isopropanol, 80 ºC, $NH_2OH.HCl$, 50 ºC; R = CH_3, DMA.DMA, isopropanol, 80 ºC, $NH_2OH.HCl$; (d) TFAA, THF; R = H, *22%*; R = CH_3, *11%*; (e) $N_2H_4.H_2O$, ethanol, µW, 120 ºC, 15 min, *90%*; (f) R = H, $HC(OCH_3)_3$, µW, 180 ºC, 20 min, *47%*; or R = CH_3, $CH_3C(OCH_3)_3$, µW, 180 ºC, *59%*.

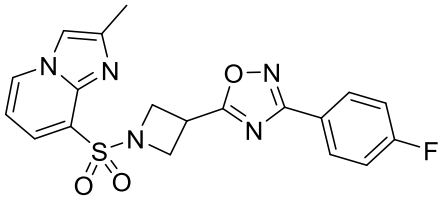


3-((3-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)sulfonyl)pyridin-2-amine (124). Ammonium hydroxide (NH_4OH) (10 mL) was added to a solution of intermediate **123** (500 mg, 1.28 mmol, 1.0 eq) in 1,4-dioxane (10 mL), and heated at 100 ºC overnight. The reaction was concentrated *in vacuo*, and purification of the residue by flash chromatography on silica gel afforded the title compound in 42% yield (201 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, J = 4.8, 1.6 Hz, 1H), 8.11 – 7.89 (m, 3H), 7.17 (m, 2H), 6.79 (dd, J = 7.8, 4.8 Hz, 1H), 5.92 (s, 2H), 4.32 (m, 4H), 4.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 167.8, 164.7 (d, J(C,F) = 252.1 Hz), 156.5, 145.2, 139.9, 129.9 (d, J(C,F) = 8.8 Hz), 122.4 (d, J(C,F) = 3.2 Hz), 116.2 (d, J(C,F)

= 22.1 Hz), 113.5, 112.1, 54.1, 25.3. LCMS R_T = 5.10 min; HRMS, calc'd for $C_{16}H_{15}FN_5O_3S^+$ [M+H], 376.0874; found 376.0874.

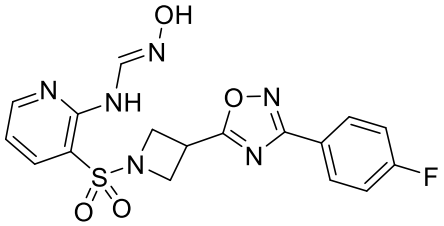


3-(4-Fluorophenyl)-5-(1-(imidazo[1,2-*a*]pyridin-8-ylsulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (125). Intermediate **124** (20 mg, 0.05 mmol, 1.0 eq), bromoacetal (250 µM), K_2CO_3 (17 mg, 0.13 mmol, 2.5 eq), and isopropanol (1.0 mL) were added to a microwave vial and heated in a microwave reactor at 170 ºC for 20 minutes. The reaction was concentrated *in vacuo*, and purification of the residue by flash chromatography on silica gel afforded the title compound in 21% yield (4 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (dd, J = 6.8, 1.20 Hz, 1H), 7.97 - 7.81 (m, 4H), 7.64 (d, J = 1.4 Hz, 1H), 7.25 (m, 2H), 7.09 (t, J = 7.0 Hz, 1H), 4.55 (m, 4H), 4.07 (m, 1H). LCMS R_T = 4.02 min; HRMS, calc'd for $C_{18}H_{15}FN_5O_3S^+$ [M+H], 400.0874; found 400.0879.

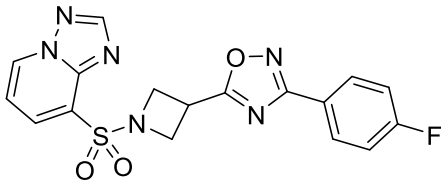


3-(4-Fluorophenyl)-5-(1-((2-methylimidazo[1,2-*a*]pyridin-8-yl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (126). The title compound was prepared in 12% yield (5 mg) from intermediate **124** and 1-bromo-2,2-dimethoxypropane using a method analogous to that described for the conversion of intermediate **124** into compound **125**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, J = 6.7, 1.2 Hz,

1H), 7.94 (m, 2H), 7.84 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.32 (d, *J* = 0.8 Hz, 1H), 7.17 (m, 2H), 6.86 (t, *J* = 6.8 Hz, 1H), 4.81 (m, 2H), 4.68 (t, *J* = 8.7 Hz, 2H), 4.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 167.4, 164.7 (d, *J*(C,F) = 252 Hz), 145.2, 140.3, 129.5 (d, *J*(C,F) = 8.9 Hz), 128.1, 125.7, 125.3, 122.6 (d, *J*(C,F) = 3.3 Hz), 116.1 (d, *J*(C,F) = 22.0 Hz), 110.7, 110.2, 55.0, 25.5, 14.6 ppm. LCMS R_T = 3.86 min; HRMS, calc'd for $C_{19}H_{17}FN_5O_3S^+$ [M+H], 414.1031; found 414.1033.

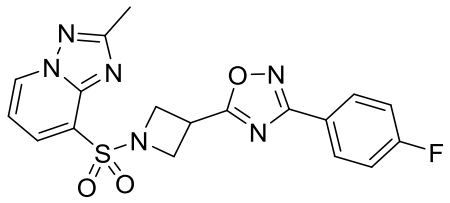


(*E*)-*N*-(3-((3-(3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)sulfonyl)pyridin-2-yl)-*N'*-hydroxyformimidamide (127). Intermediate **124** (50 mg, 0.13 mmol, 1.0 eq) was dissolved in isopropanol (1.0 mL), followed by the addition of dimethylformamide dimethyl acetal (35 µL, 0.26 mmol, 2.0 eq). The reaction was heated at 70 ºC for 3 hours, and subsequently cooled to 50 ºC. Hydroxylamine hydrochloride (18 mg, 0.26 mmol, 2.0 eq) was added, and the reaction was stirred at 50 ºC for additional 2 hours. The reaction was cooled and concentrated *in vacuo* to afford 18 mg (33%) of the title compound that was used further without purification.



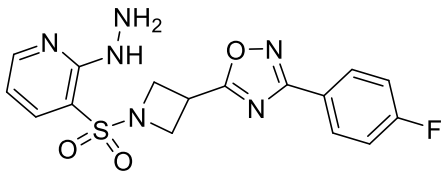
5-(1-([1,2,4]Triazolo[1,5-*a*]pyridin-8-ylsulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (128). The amidoxime intermediate **127** (18 mg, 0.04 mmol, 1.0 eq) was dissolved in

THF (2.0 mL), followed by the addition of trifluoroacetic anhydride (11 µL, 0.08, 2.0 eq) at 0 ºC. The reaction was stirred overnight at room temperature. The reaction was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel afforded 7 mg (22%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, J = 6.8, 1.2 Hz, 1H), 8.45 (s, 1H), 8.20 (dd, J = 6.4, 1.2 Hz, 1H), 7.92 (m, 2H), 7.25 – 7.11 (m, 3H), 4.68 (m, 4H), 4.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 167.6, 164.7 (d, J(C,F) = 252 Hz), 154.8, 147.3, 132.8, 132.6, 129.6 (d, J(C,F) = 8.8 Hz), 126.6, 122.4 (d, J(C,F) = 3.3 Hz), 116.2 (d, J(C,F) = 22.1 Hz), 112.7, 55.1, 25.3 ppm. LCMS R_T = 4.55 min; HRMS, calc'd for $C_{17}H_{14}FN_6O_3S^+$ [M+H], 401.0827; found 401.0829.

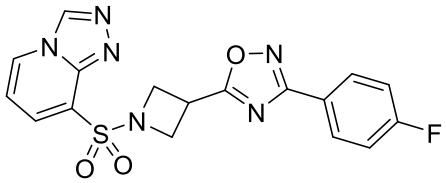


3-(4-Fluorophenyl)-5-(1-((2-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-8-yl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (129). The title compound was prepared in 11% yield (6 mg) from the intermediate **127** and dimethylacetamide dimethyl acetal using a method analogous to that described for the conversion of intermediate **127** into compound **128**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (dd, J = 6.8, 1.2 Hz, 1H), 8.14 (dd, J = 7.4, 1.2 Hz, 1H), 7.93 (m, 2H), 7.23 – 7.05 (m, 3H), 4.78 – 4.59 (m, 4H), 4.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 167.6, 165.5, 164.7 (d, J(C,F) = 252.2 Hz), 147.9, 132.6, 132.0, 129.5 (d, J(C,F) = 8.8 Hz), 125.4, 122.4 (d, J(C,F) = 3.4

Hz), 116.1 (d, *J*(C,F) = 22.1 Hz), 111.7, 55.1, 25.4, 14.6 ppm. LCMS R_T = 4.60 min; HRMS, calc'd for $C_{18}H_{16}FN_6O_3S^+$ [M+H], 415.0983; found 415.0990.

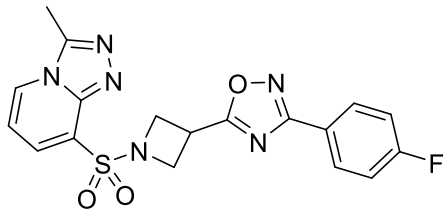


3-(4-Fluorophenyl)-5-(1-((2-hydrazineylpyridin-3-yl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (130). Compound **123** (100 mg, 0.253 mmol, 1.0 eq), hydrazine monohydrate (127 µM, 2.53 mmol, 10.0 eq), and ethanol (2.0 mL) were added to a microwave-compatible vial and heated in a microwave reactor at 120 ºC for 15 minutes. The reaction was concentrated *in vacuo*, water was added, and the reaction was extracted in ethyl acetate (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*, to afford 88 mg (90%) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (d, *J* = 6.8 Hz, 1H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.82 (m, 2H), 7.44 (m, 2H), 7.19 (t, *J* = 6.94 Hz, 1H), 4.46 (m, 4H), 4.15 (m, 1H), 3.30 (s, 1H), 2.54 (s, 2H). LCMS R_T = 4.19 min; HRMS, calc'd for $C_{18}H_{16}FN_6O_3S^+$ [M+H], 415.0983; found 415.0837.



5-(1-([1,2,4]Triazolo[4,3-*a*]pyridin-8-ylsulfonyl)azetidin-3-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (131). Intermediate **130** (35 mg, 0.09 mmol, 1.0 eq) and trimethyl orthoformate (1.5 mL) were added to a microwave vial and heated in a microwave reactor at 180 ºC for 20 minutes.

The reaction was concentrated *in vacuo*, followed by purification of the residue by flash chromatography on silica gel afforded 17 mg (47%) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.87 (dd, J = 6.9, 1.0 Hz, 1H), 7.97 (dd, J = 7.0, 1.0 Hz, 1H), 7.82 (m, 2H), 7.43 (m, 2H), 7.19 (t, J = 6.9 Hz, 1H), 4.53 (m, 4H), 4.16 (m, 1H). LCMS R_T = 4.14 min; HRMS, calc'd for $C_{17}H_{14}FN_6O_3S^+$ [M+H], 401.0827; found 401.0828.



3-(4-Fluorophenyl)-5-(1-((3-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-8-yl)sulfonyl)azetidin-3-yl)-1,2,4-oxadiazole (132). The title compound was prepared in 59% yield (22 mg) from the intermediate **130** and trimethyl orthoacetate using a method analogous to that described for the conversion of intermediate **130** into compound **131**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (d, J = 6.8, 1H), 7.95 (d, J = 7.0 Hz, 1H), 7.83 (m, 2H), 7.44 (m, 2H), 7.19 (t, J = 6.9 Hz, 1H), 4.56 (m, 4H), 4.15 (m, 1H). LCMS R_T = 4.19 min; HRMS, calc'd for $C_{18}H_{16}FN_6O_3S^+$ [M+H], 415.0983; found 415.0837.

Percent remaining and Intrinsic clearance in mouse liver microsomes

The metabolic stability assay was conducted as previously described (PMID: 26524606) with modifications optimized to obtain percent remaining at 10 minutes as described below. Test compounds and controls (5 µM) and mouse liver microsomes (0.5 mg/mL) were incubated in 100 mM potassium phosphate buffer (pH 7.4) for 5 minutes at 37 ºC. Afterward, NADPH (1 mM) and $MgCl_2$ (3 mM) were added to initiate the reaction. Next, 50 µL aliquots were taken at 0 and 10 minutes and were transferred into a 96-well plate containing 150 µL of cold acetonitrile containing 50 ng/mL carbamazepine as an internal standard. Plates were centrifuged for 10 minutes at 2500 rcf (4 ºC). Finally, 55 µL of the supernatant was diluted 1:1 with Milli-Q water for LC/MS/MS analysis. Verapamil and propranolol were used as controls for this assay.

For the determination of the half-life ($T_{1/2}$), intrinsic clearance (CL_{int}), and subsequent predicted hepatic clearance (CL_{hep}) for analog **121**, the same procedure above was followed, but aliquots were taken at 0, 3, 7, 15, 25, and 45 minutes. The following equations were employed:

$T_{1/2} = Ln(2)/k$

Where k is the slope from linear regression analysis of the natural percent remaining of test compound as function of incubation time.

$$CL_{int} = \frac{0.693}{in\ vitro\ T_{1/2}} \chi \frac{1\ mL\ incubation}{0.5\ mg\ microsomes} \chi \frac{45\ mg\ microsomes}{gram\ liver} \chi \frac{87.5^{a}\ gram\ liver}{kg\ body\ weight}$$

[a] scaling factor of 87.5 gm liver/kg body weight for mice.

$$CL_{hep} = \frac{Q_h . CL_{int}}{Q_h + CL_{int}}$$

Q_h is the hepatic blood flow for mice which is 90 mL/min/kg.

Plasma Protein Binding

The plasma protein binding assay was conducted as previously described (PMID: 26524606) as described below. Equilibrium dialysis was performed employing HTDialysis Teflon dialysis chamber and cellulose membranes (MWCO 12-14 K) (HTDialysis LLC, Gales Ferry, CT). Plasma was added to the 96-well plate containing test compound and mixed thoroughly for a final concentration of 5 μM. Subsequently, 150 μL of the plasma/compound mixture was transferred to the dialysis chamber, with an accompanying 150 μL of phosphate buffer (25 mM, pH 7.4) on the other side of the membrane. The device plate was sealed and incubated for 6 hours at 37 ºC with shaking at 200 rpm. Following the incubation, aliquots of 20 μL from each chamber were diluted 1:1 with either buffer (for the plasma sample) or plasma (for the buffer sample) and transferred to a new 96-well plate, at which ice-cold acetonitrile containing internal standard (50 ng/mL carbamazepine) (120 μL) was added to extract the matrices. The plate was centrifuged at 1500 rcf for 10 min, and 60 μL of supernatant solutions were transferred to a new 96-well plate and diluted 1:1 with Milli-Q water and were subjected to LC/MS/MS analysis. Each compound was run in triplicate within the same 96-well plate. Warfarin and verapamil were used as controls for this assay.

Stable Cell Line Generation

Stably transfected monoclonal HEK293 cell lines expressing human wild-type (WT) Slack, A934T Slack, Slick, and Maxi-K α1/β3 were generated as previously described (PMID: 33143429). Stably transfected monoclonal HEK293 cell lines expressing hERG (PMID: 23730969) were generated as previously described.

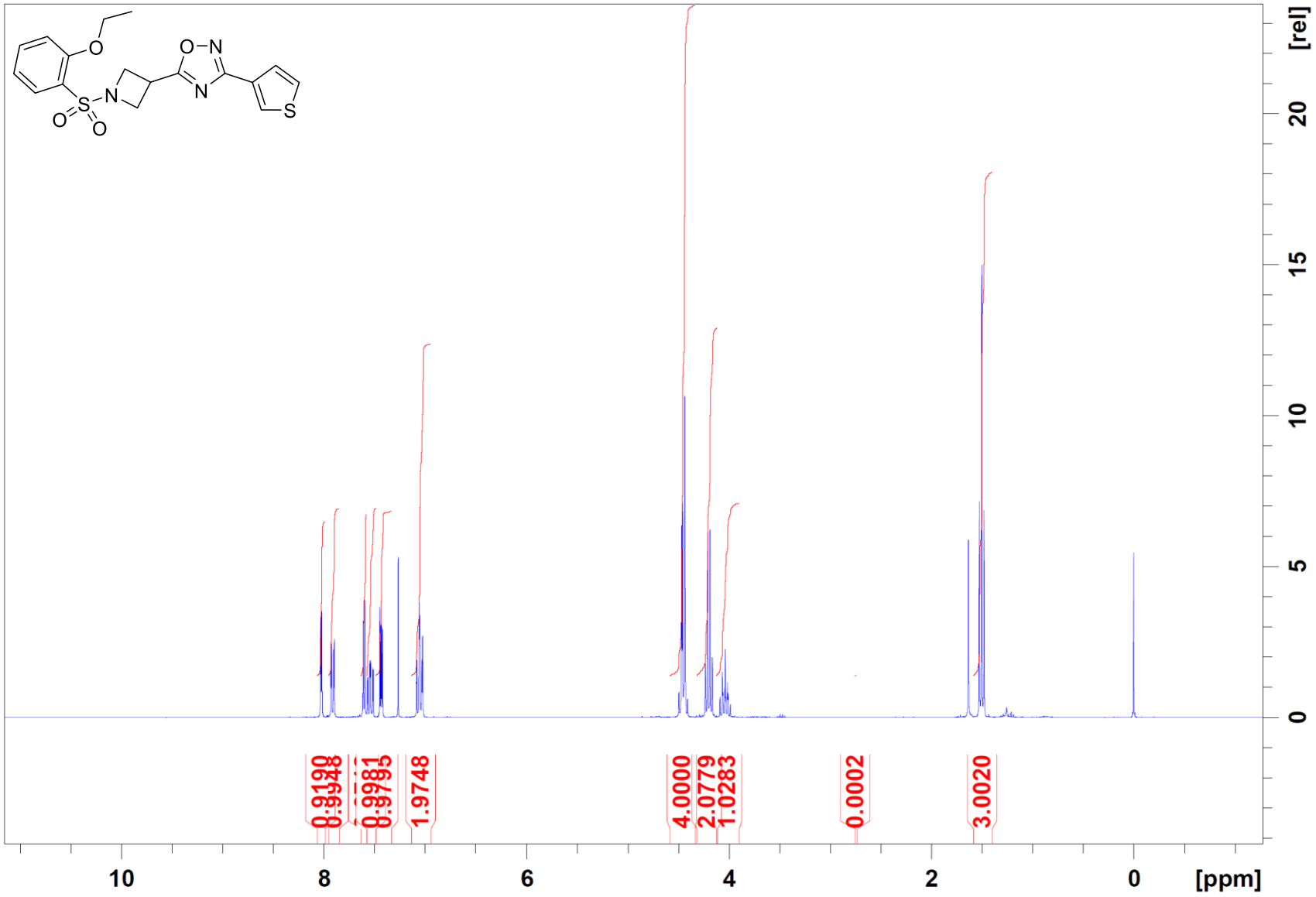
Tl^+ Flux Experiments

The SLACK Tl^+ flux assays were conducted as previously described (PMID: 30136838 and PMID: 33143429) with modifications optimized for WT SLACK and A934T SLACK cell lines as described below. Cells were plated at 20,000 cells/well in a 284-well format (Greiner Bio-One, Monroe, NC). Cells were first washed with 20 µL/well SLACK Assay Buffer (129 mM NaCl, 2.7 mM RbCl, 1.2 mM $CaCl_2$, 1 mM $MgSO_4$, 1 mM Na_2HPO_4, 4.17 mM $NaHCO_3$, 5.56 mM glucose, and 10 mM HEPES pH 7.3) to remove serum-containing cell-culture medium. Cells were then loaded with 20 µL/well of Tl^+-sensitive dye loading solution containing Thallos-AM (ION Biosciences, San Marcos, TX) in Slack Assay Buffer, 1.25 mM Probenecid, extracellular masking dye (TRS, ION Biosciences, San Marcos, TX) and 0.3% Pluronic F-127 (MilliporeSigma, Burlington, MA) in at room temperature for one-hour. Cell plates were then loaded onto a Panoptic kinetic imaging plate reader (WaveFront Biosciences, Franklin, TN). Data were acquired at 5 Hz (excitation 482 ± 35 nm, emission 536 ± 40 nm) for 10 s, at which time 20 µL/well of test compounds in SLACK Assay Buffer at 2-fold above the desired final concentration was added and allowed to incubate for 120 s. Next, 10 µL/well of Tl^+ stimulus buffer (129 mM Na gluconate, 1.2 mM $CaSO_4$, 1 $MgSO_4$ mM, 1 mM Na_2HPO_4, 4.17 mM $NaHCO_3$, 5.56 mM glucose, 2.5 mM Tl_2SO_4, and 10 mM HEPES pH 7.3) was added. Imaging was concluded after an additional 120 s. Compound potencies were determined using concentrations ranging from 1.5 nm to 30 µM in half-log steps and a minimum of three replicates wells per concentration series. Tl^+ flux experiments for hERG selectivity assays were conducted as previously described (PMID: 23730969). Use of SKF 96365 as the standard SLICK channel inhibitor in our Tl^+ flux assay for this target is based on an unpublished observation from the Weaver laboratory that the compound functions as such.

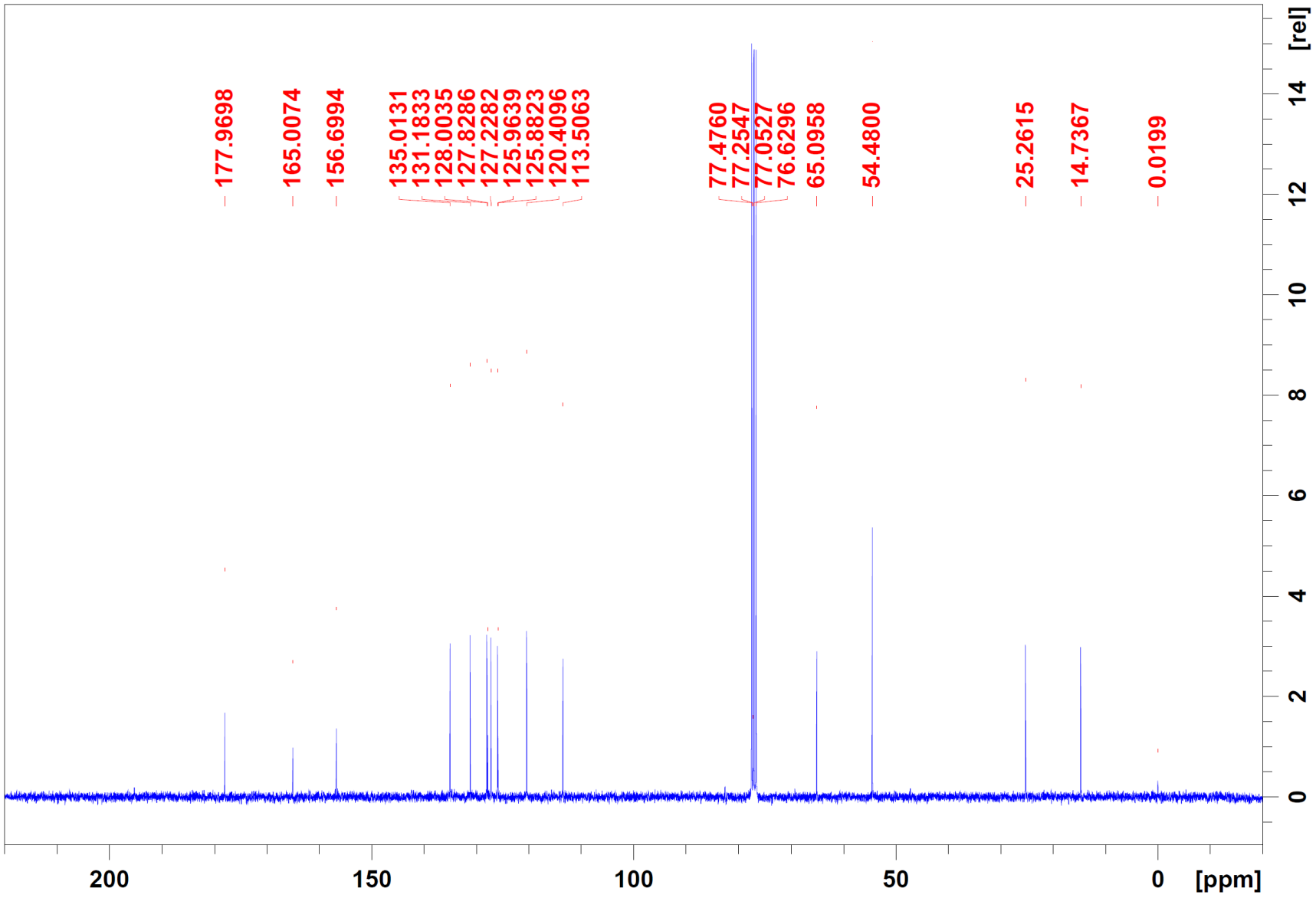
Automated Patch-Clamp Electrophysiology

Automated planar-array patch-clamp recording was performed with a SyncroPatch 768 PE system (Nanion, Munich, Germany) as previously described (PMID: 33143429 and PMID: 31560846). Whole-cell recordings were performed at room temperature. Cells were harvested by first washed with PBS without Mg^{2+} or Ca^{2+} (Gibco, Billings, MT) to remove cell culture media, followed by dissociation with TryPLE (Gibco, Billings, MT). Cells were then resuspended and diluted to 100,000 cells/mL in external solution. External solution contained 105 mM NaCl, 4 mM KCl, 1 mM $MgCl_2$, 5 mM $CaCl_2$, 10 mM HEPES, 40 mM N-Methyl-D-glucamine chloride, titrated to pH 7.4 and osmolarity of 300 mOsm/kg; internal solution contained 70 mM NaCl, 70 mM KF, 10 mM KCl, 5 mM EGTA, 5mM HEPES, titrated to a pH 7.2 and osmolarity of 295 mOsm/kg. Compound potencies generated using concentrations ranging from 0.125 to 30 μM in half-log steps and a minimum of three cells (replicates) per concentration series. The go whole cell pressure was set at -300mV and -275mV, once cells have been added and a pulse of -300 mBar forces cells into a whole-cell configuration the cycling protocol begins, cycling through 7 times for each buffer addition and 14 times for each of the compound concentrations. The SyncroPatch cycling protocol was set as following: The cell was holding at -80mV for 100ms, then a ramp was performed from -100mV to 80mV at 0.4mV/ms, hold the cell at -80mV for another 100ms, then steps were performed at-20mV, 0mV, +20mV, +40mV, and +60mV for 100ms of each step. Whole-cell currents were measured at 0 mV and normalized to current after external buffer addition. Compound response compared to "full block" E_{max} of 500 μM quinidine. To obtain the CRC graphs and IC50 values we take the median value of the last 7 current amplitude values obtained for each set of data points collected for a given concentration at a particular step.

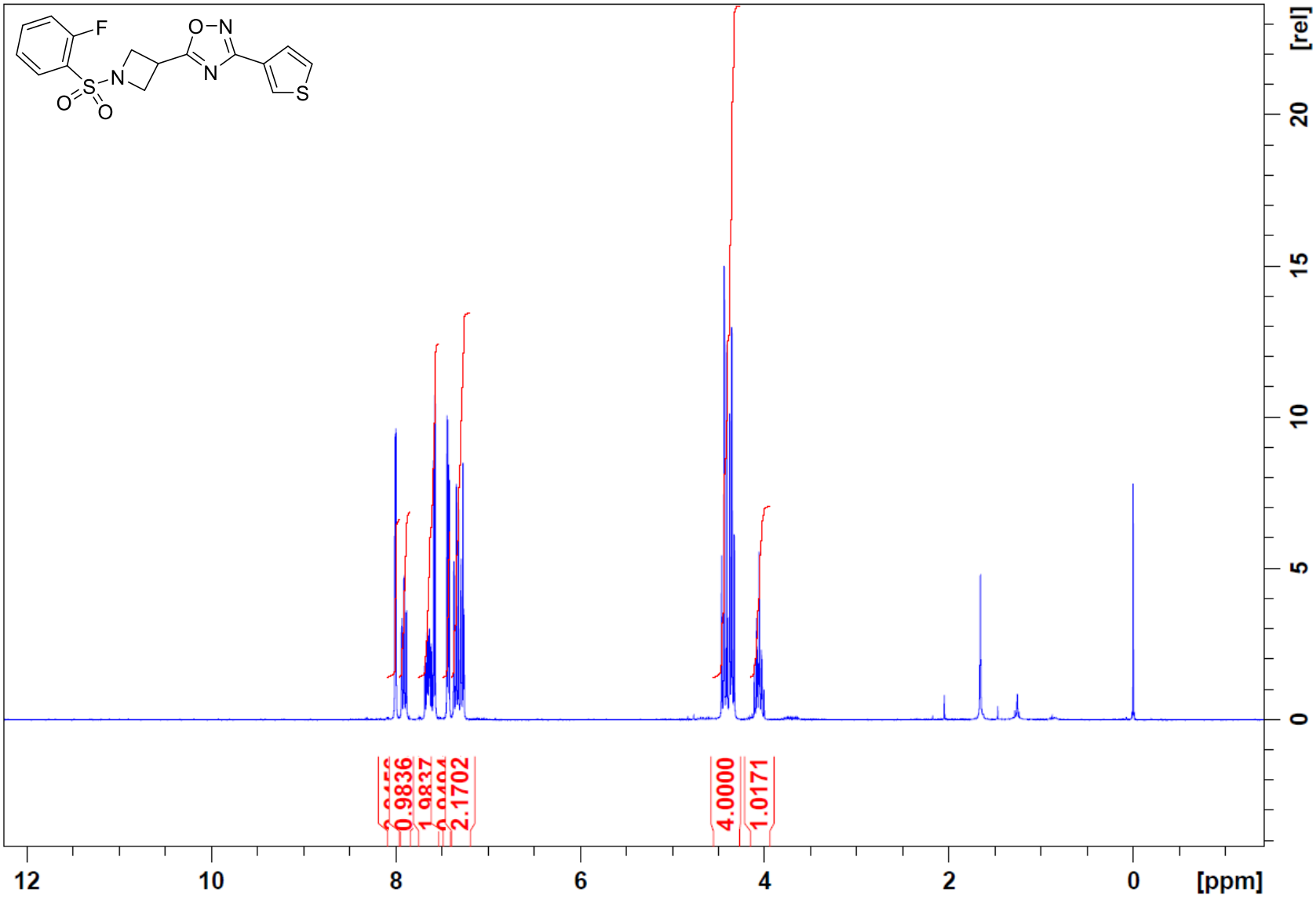
Analog **5** – ^{1}H NMR



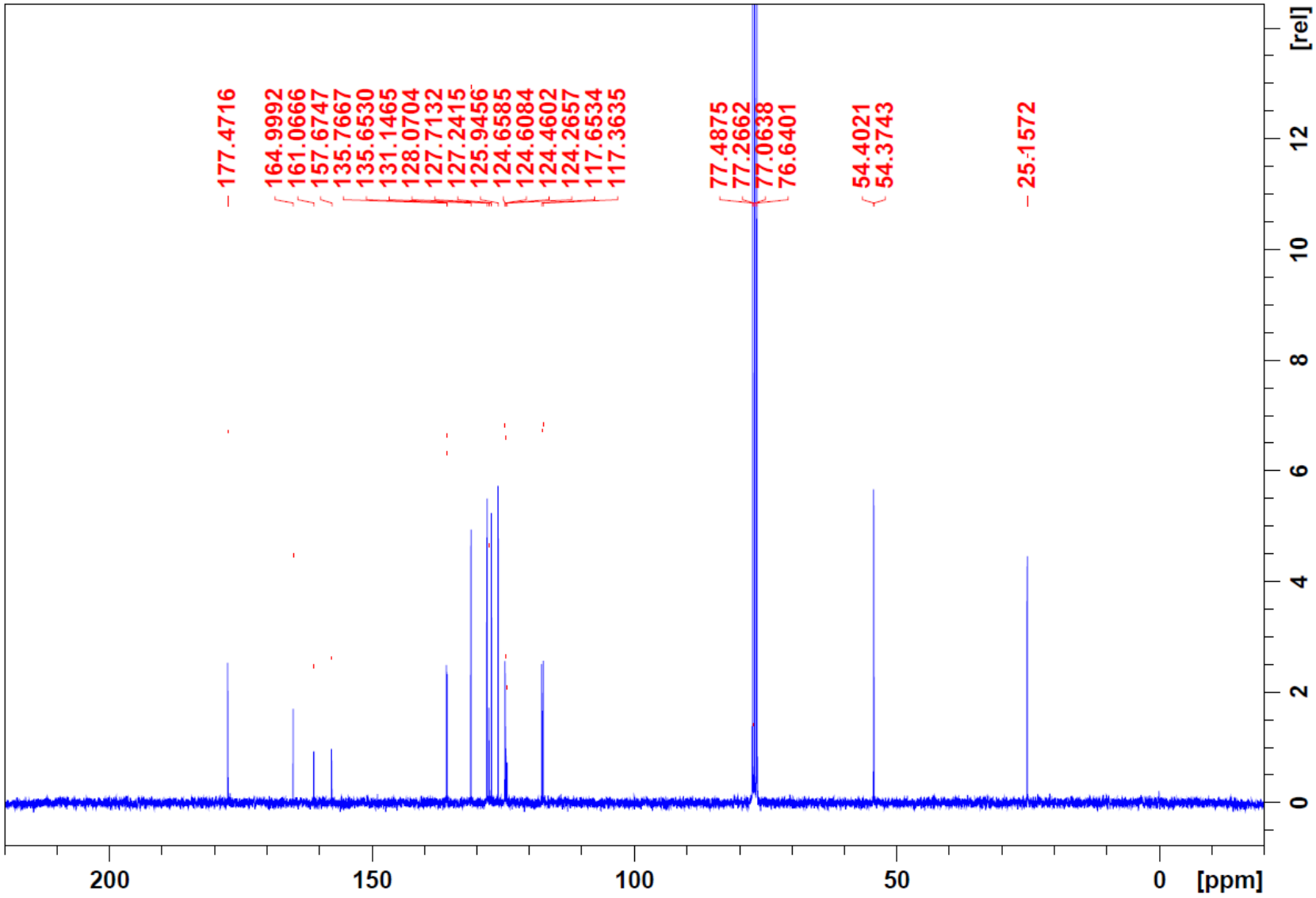
Analog **5** – ^{13}CNMR



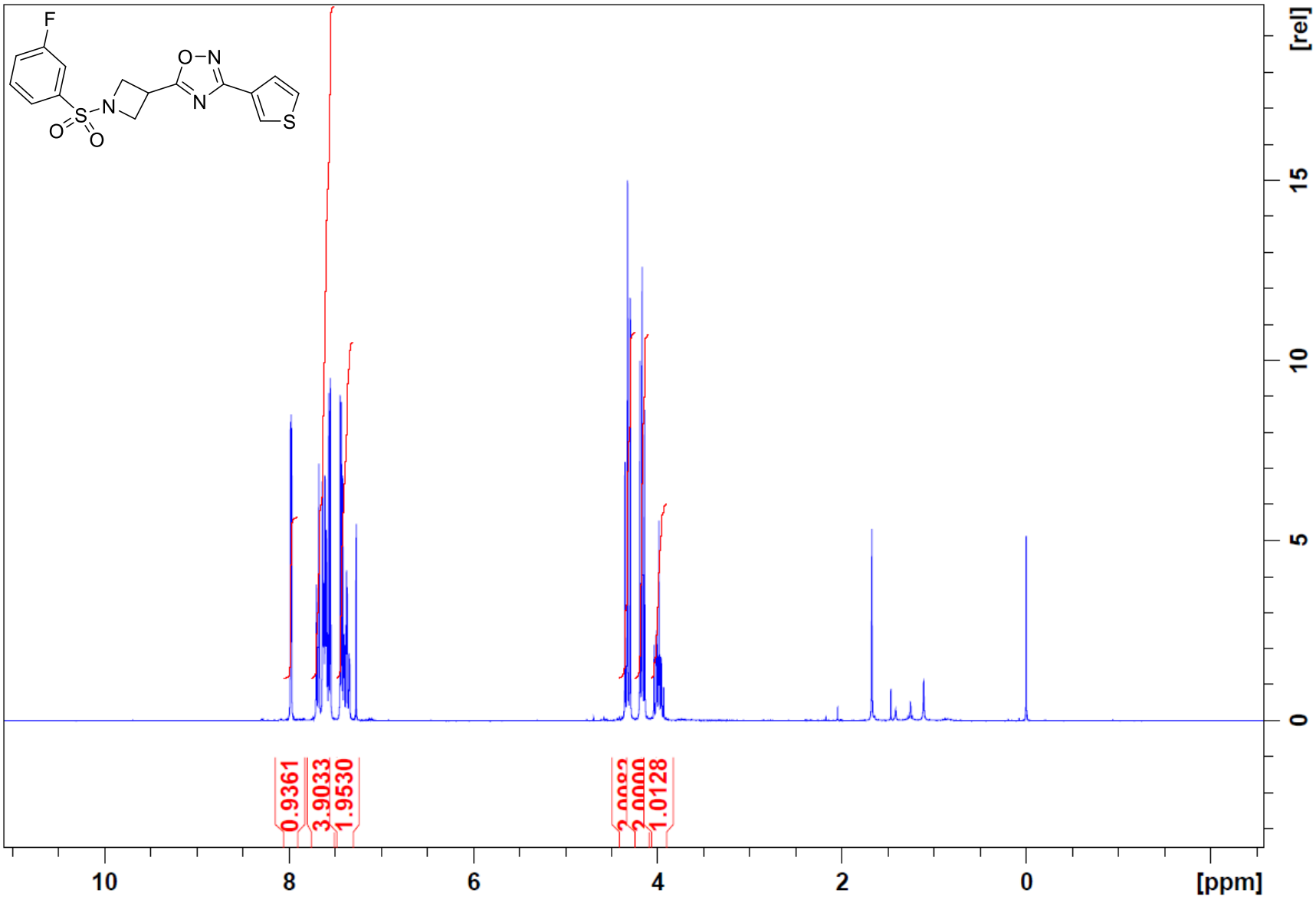
Analog **11** – ^{1}H NMR



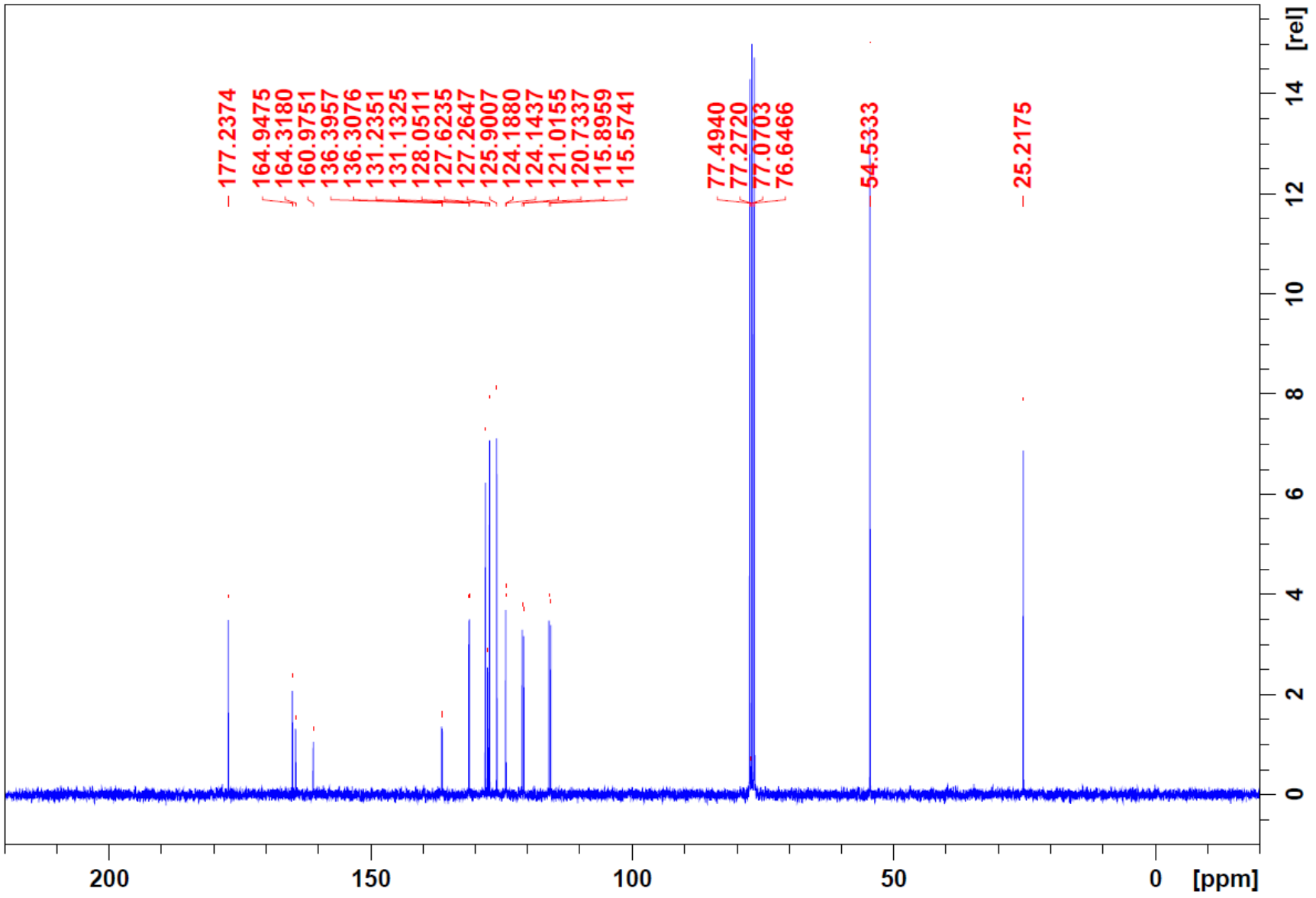
Analog **11** – ^{13}C NMR



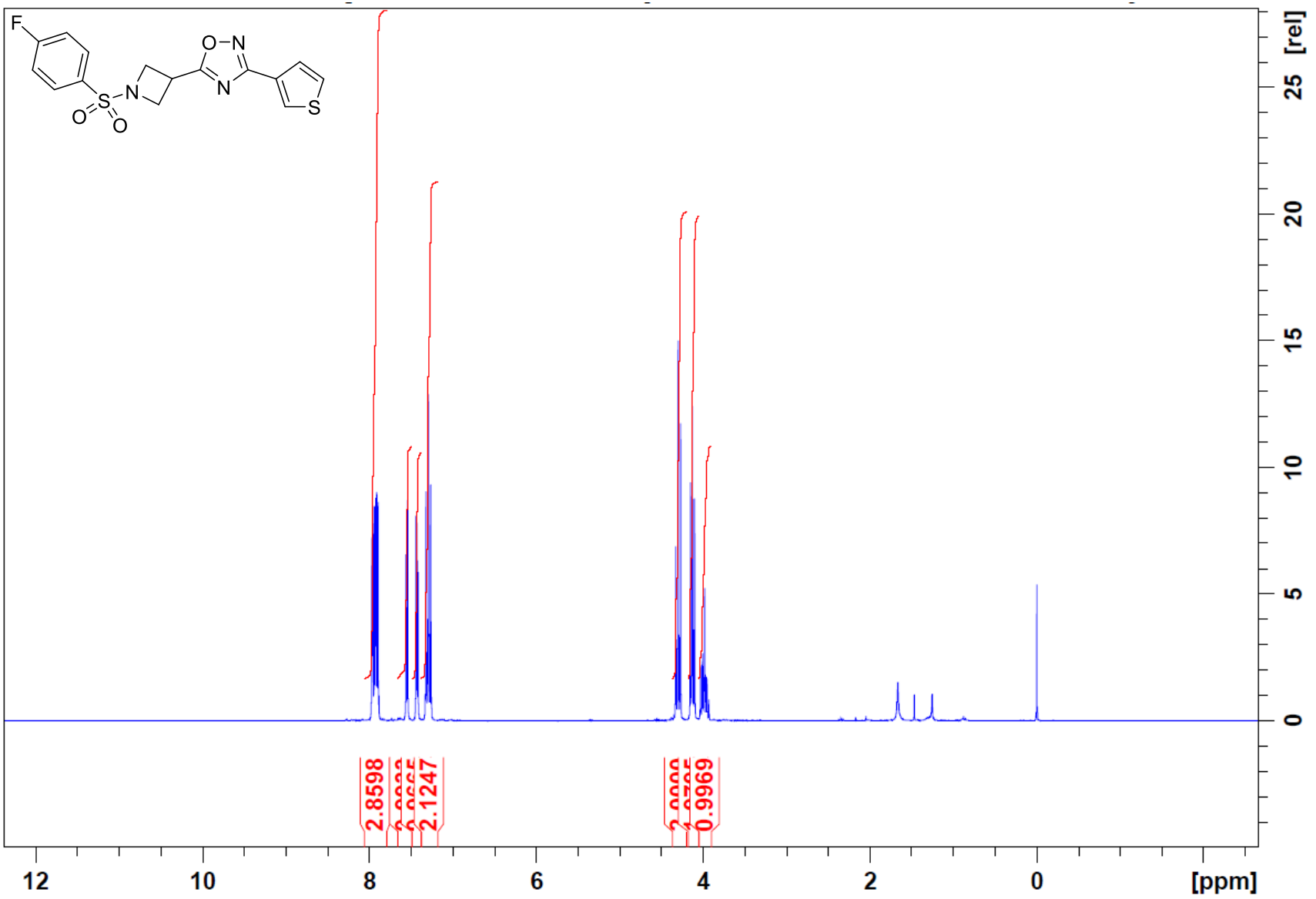
Analog **12** – ^{1}H NMR



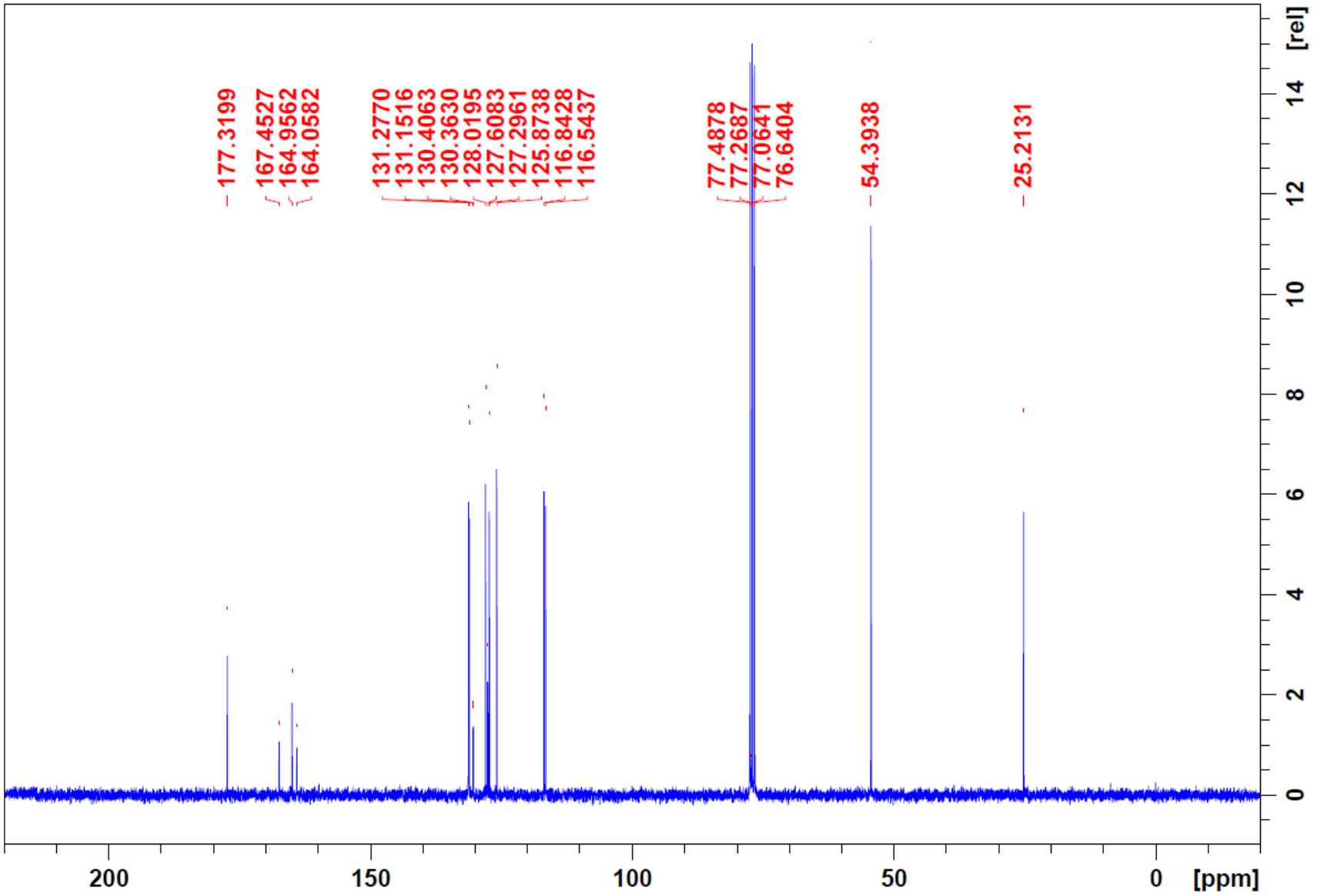
Analog **12** – ^{13}C NMR



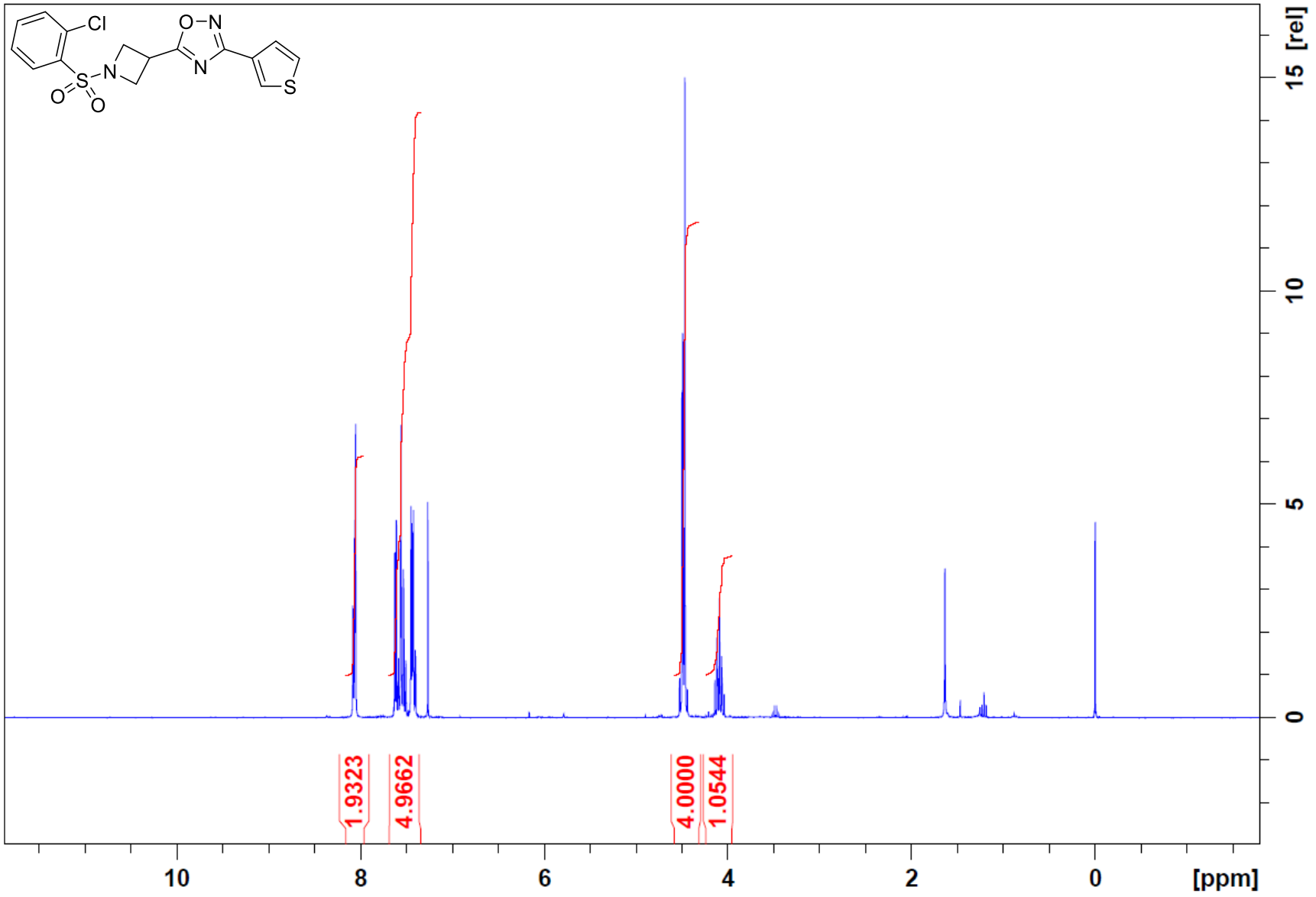
Analog **13** – ^{1}H NMR



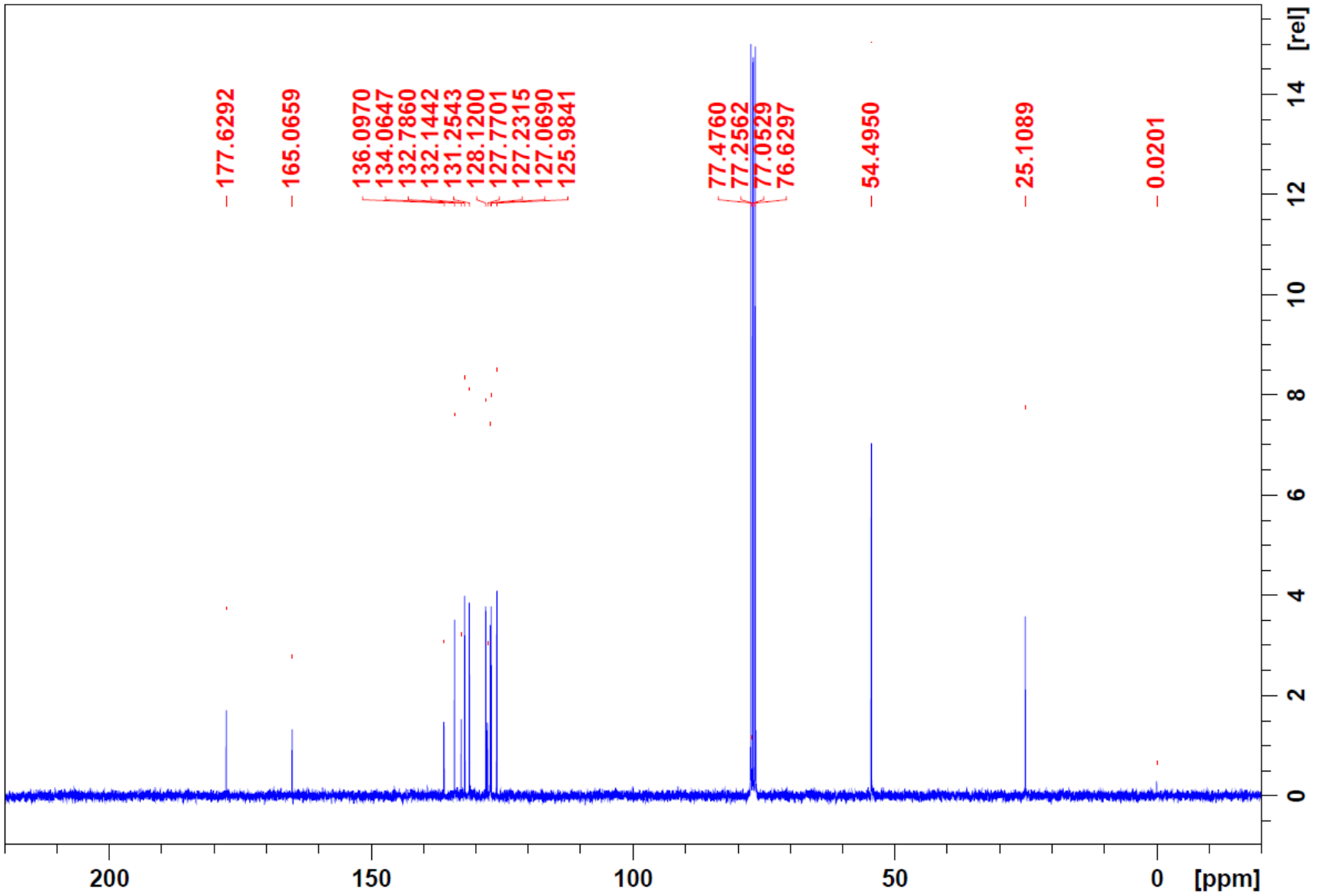
Analog **13** – ^{13}C NMR



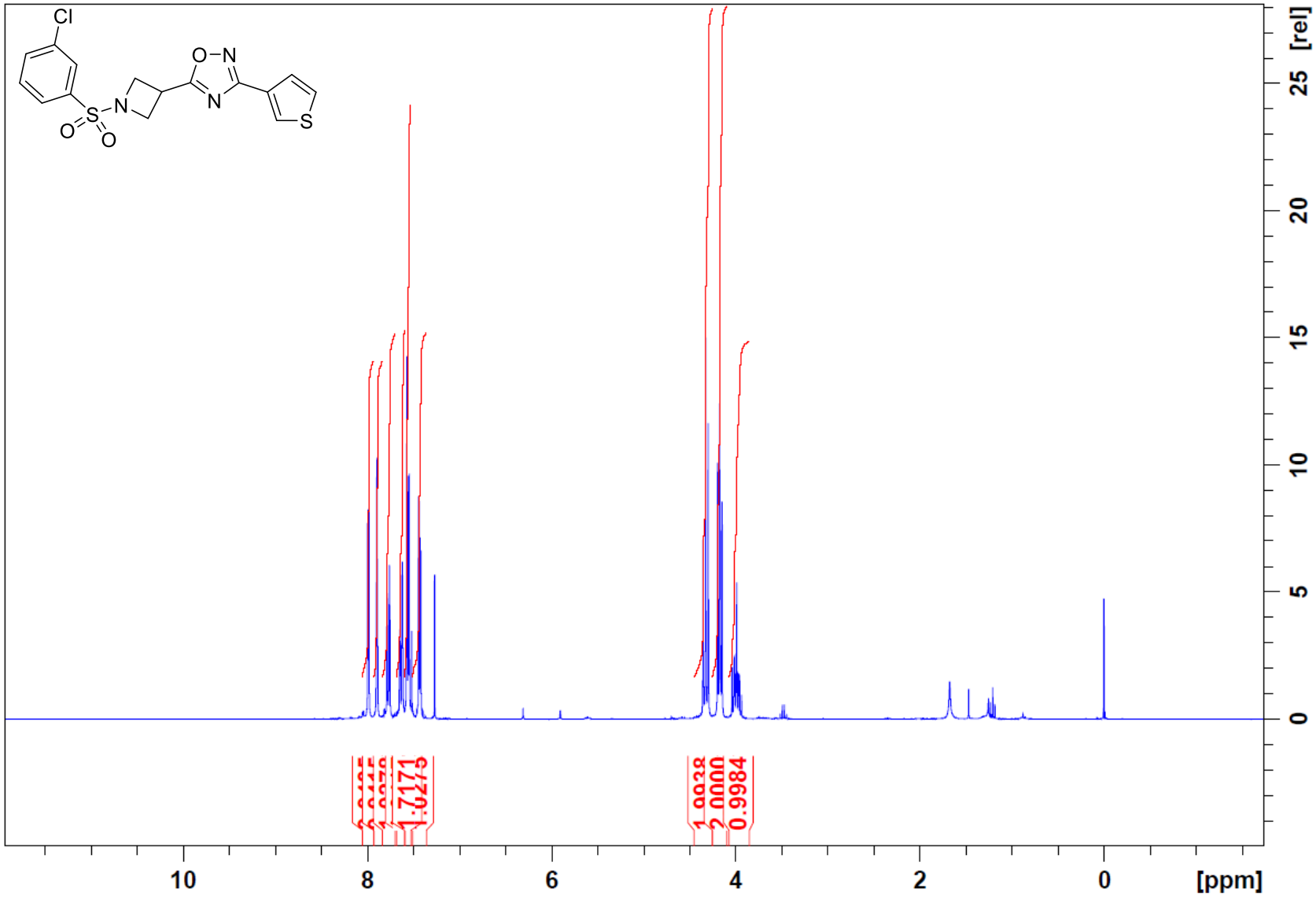
Analog **14** – ^{1}H NMR



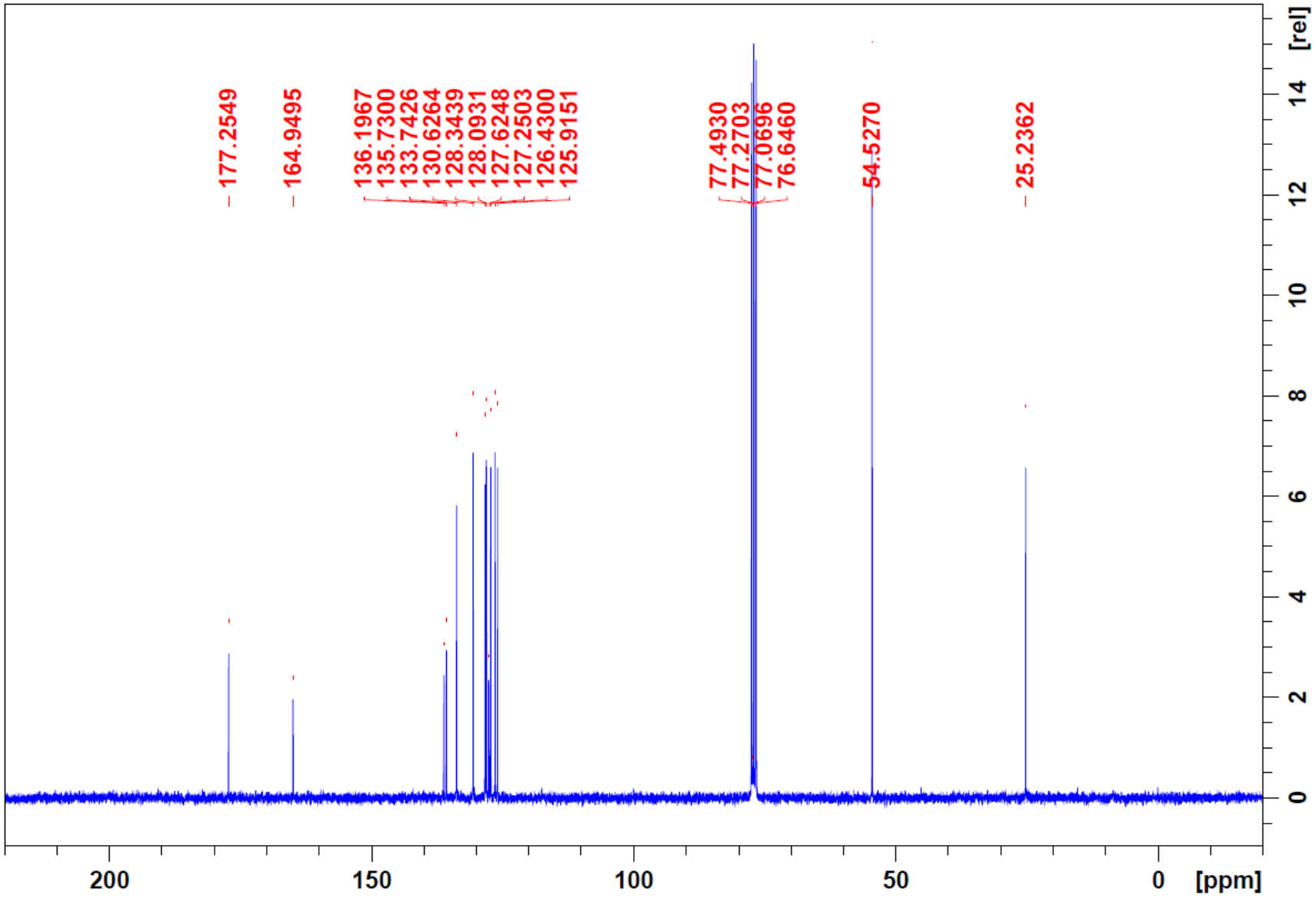
Analog **14** – ^{13}C NMR



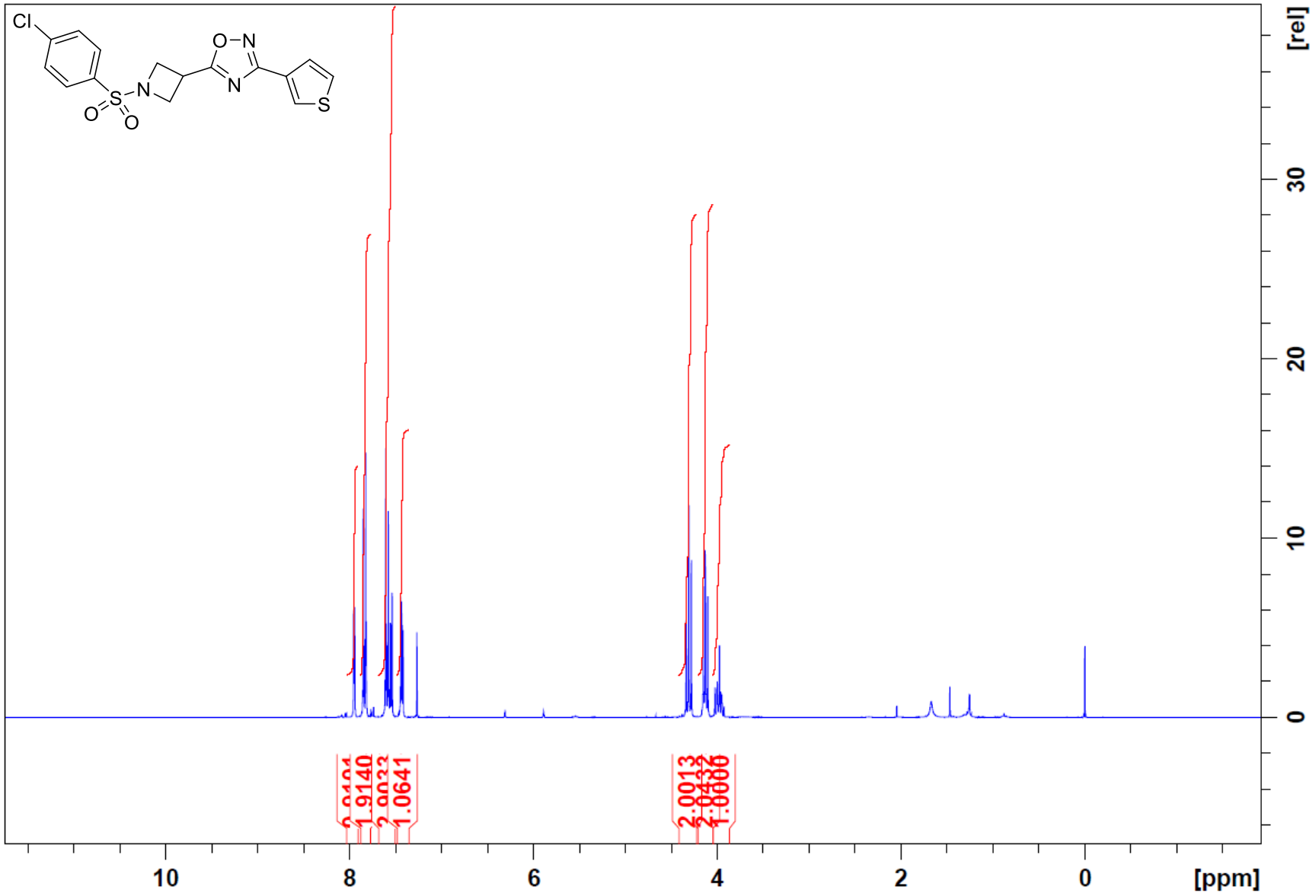
Analog **15** – ^{13}H NMR



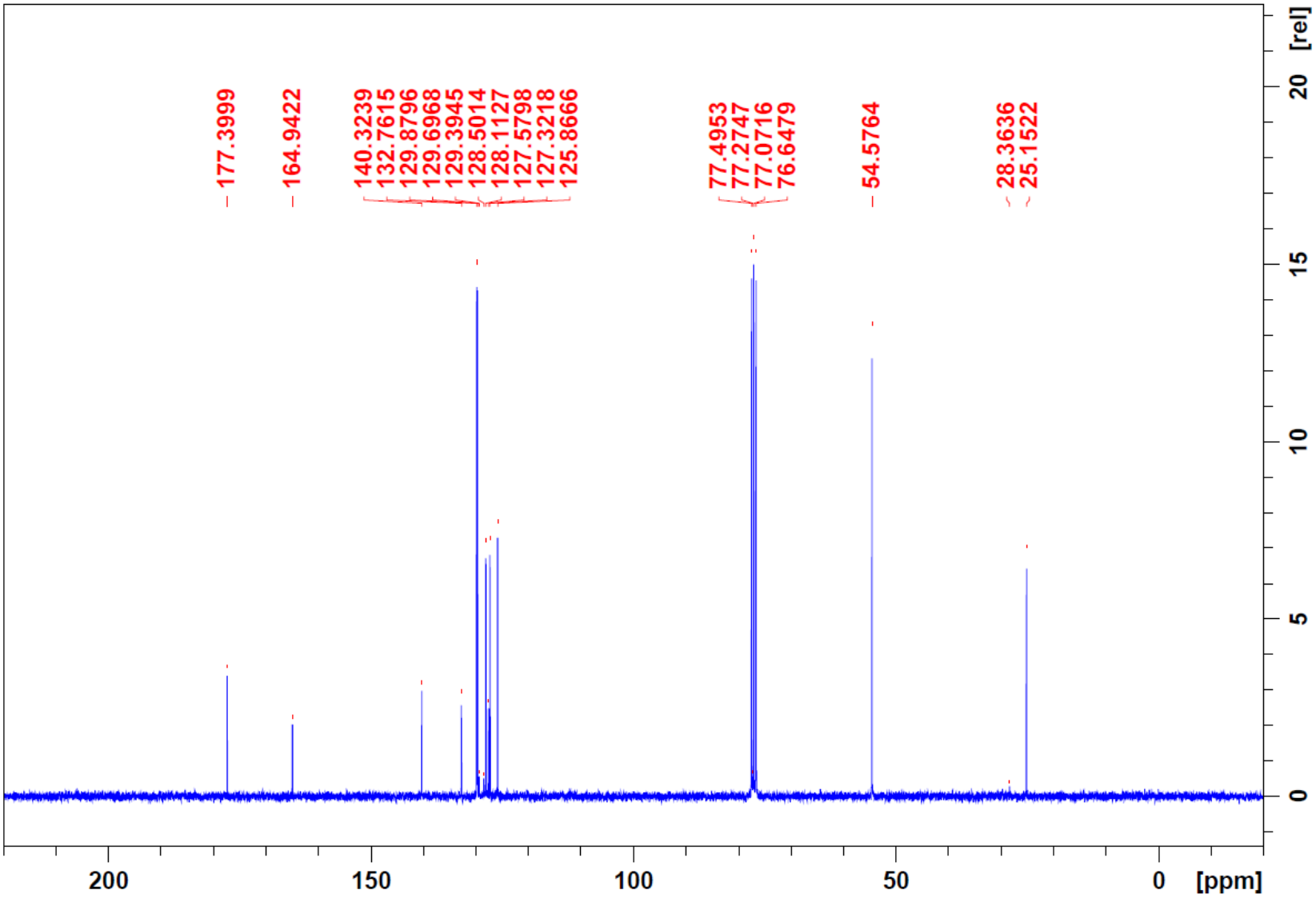
Analog **15** – ^{13}C NMR



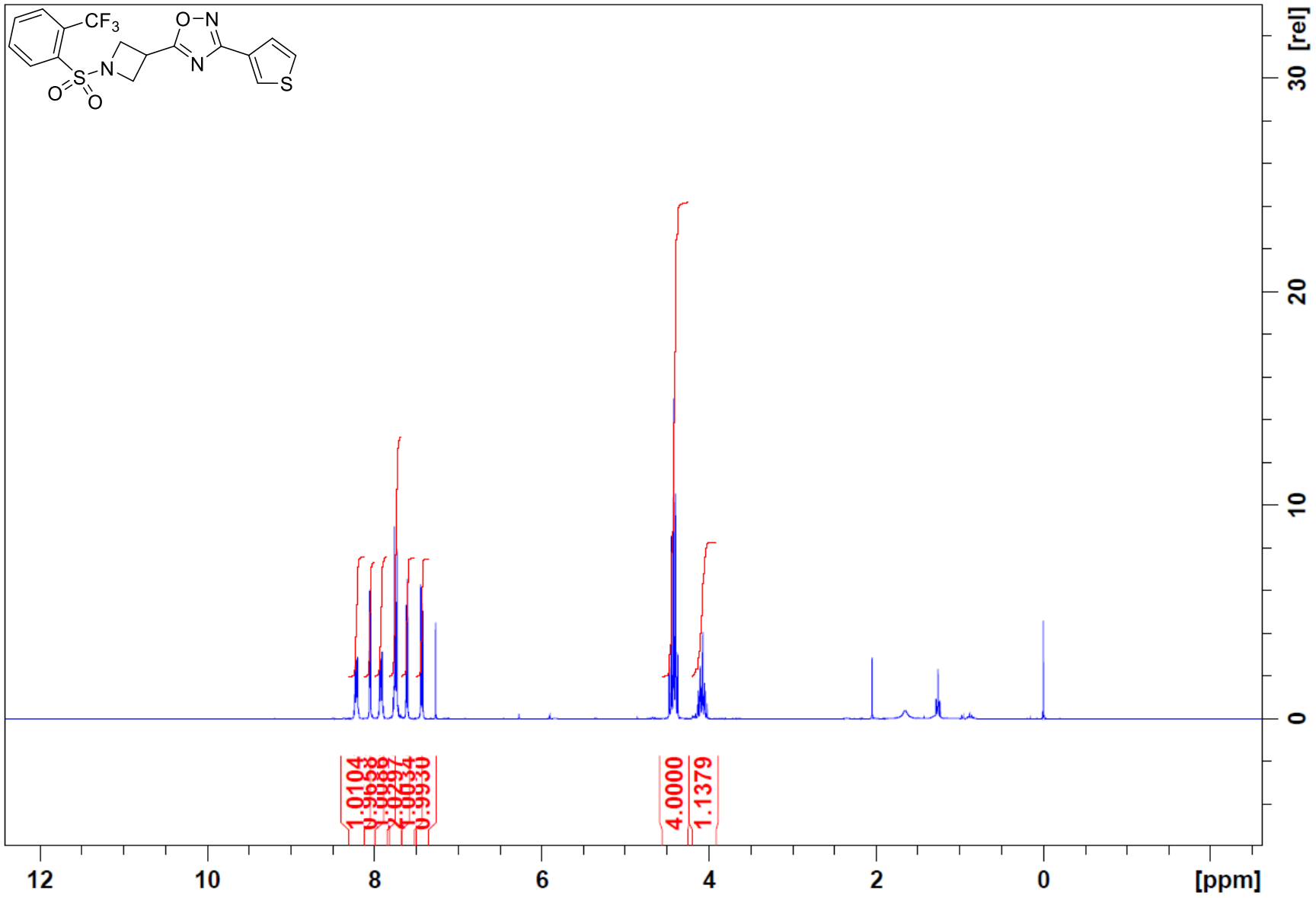
Analog **16** – ^{1}H NMR



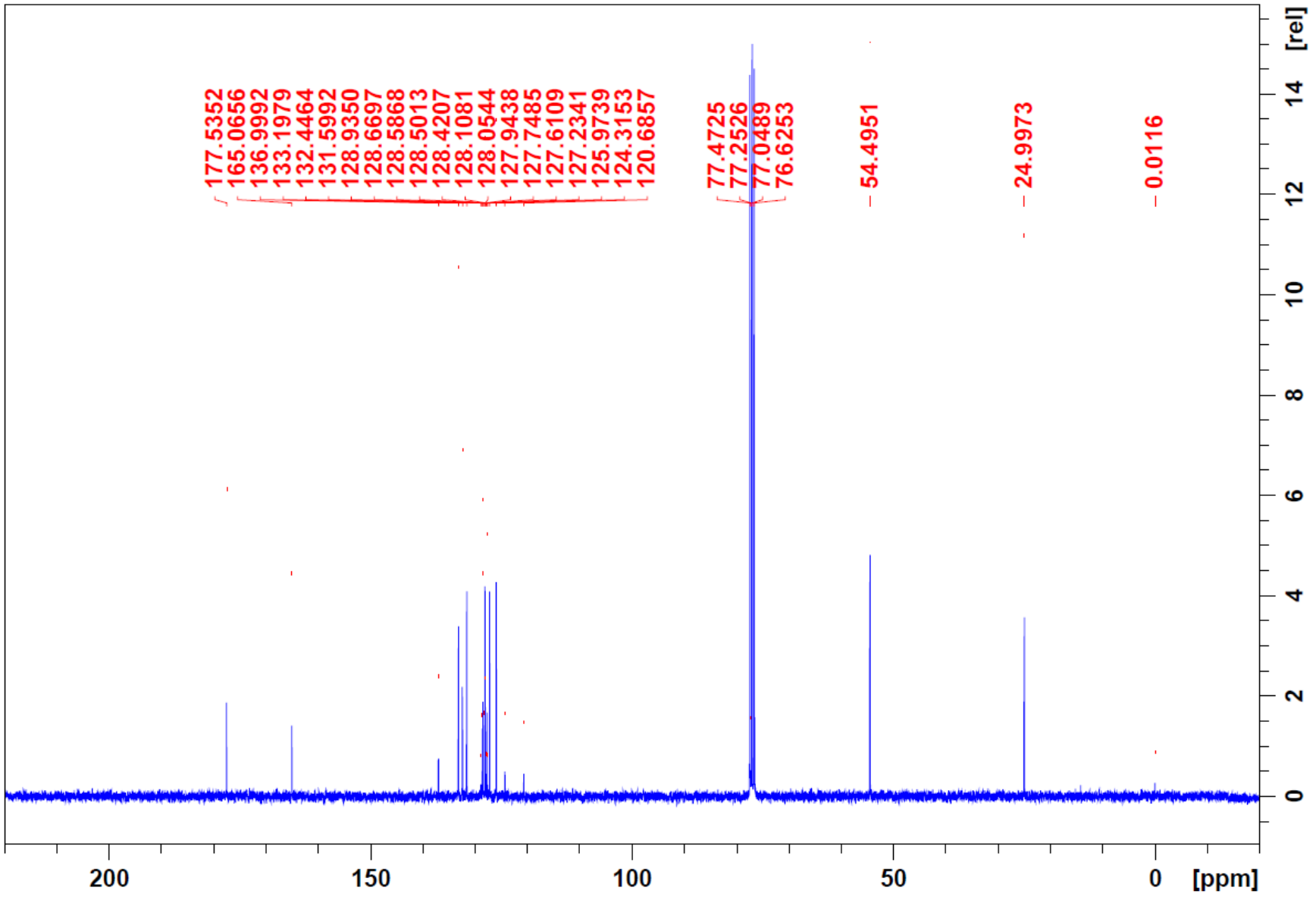
Analog **16** – ^{13}C NMR



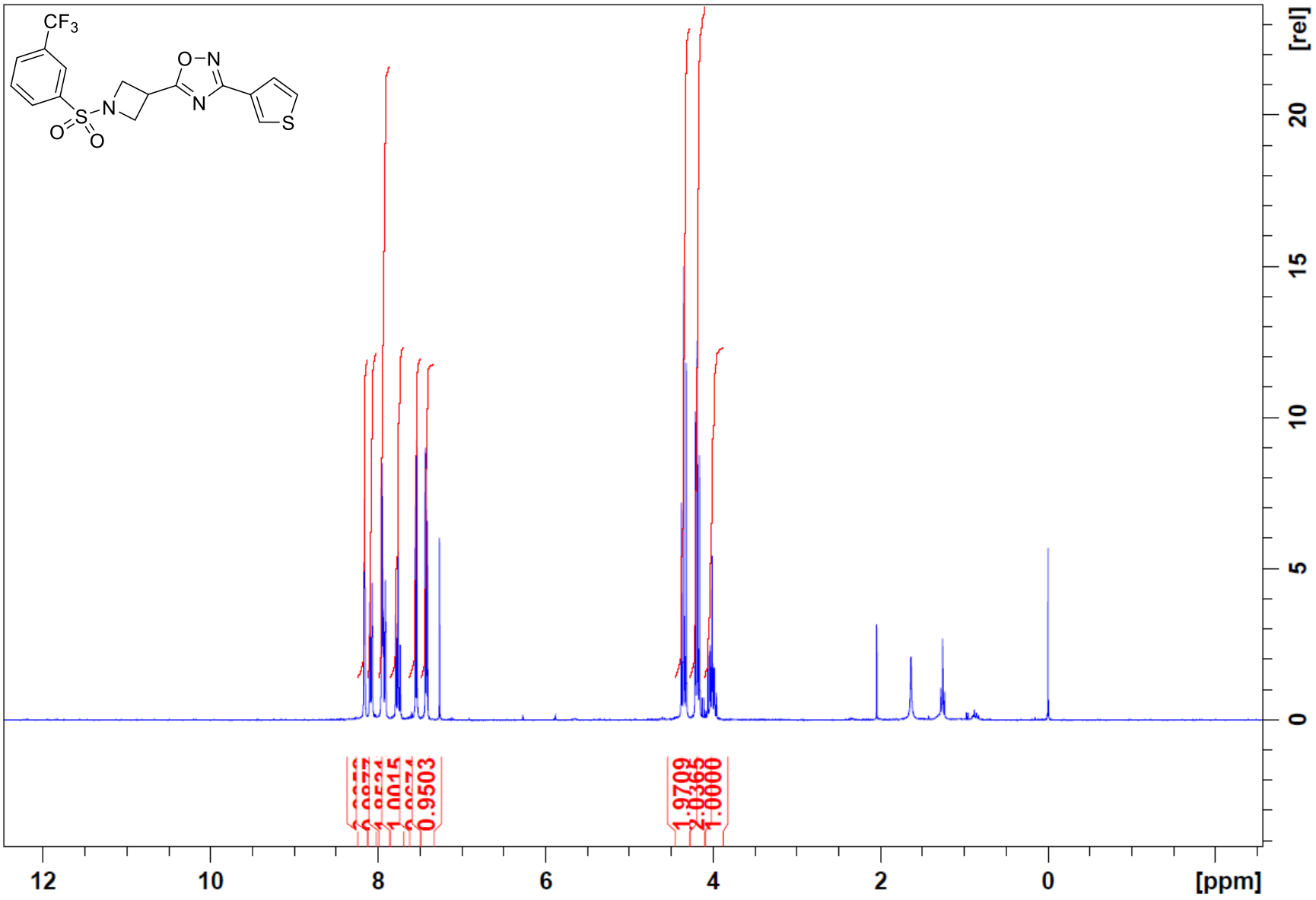
Analog **17** – ^{1}H NMR



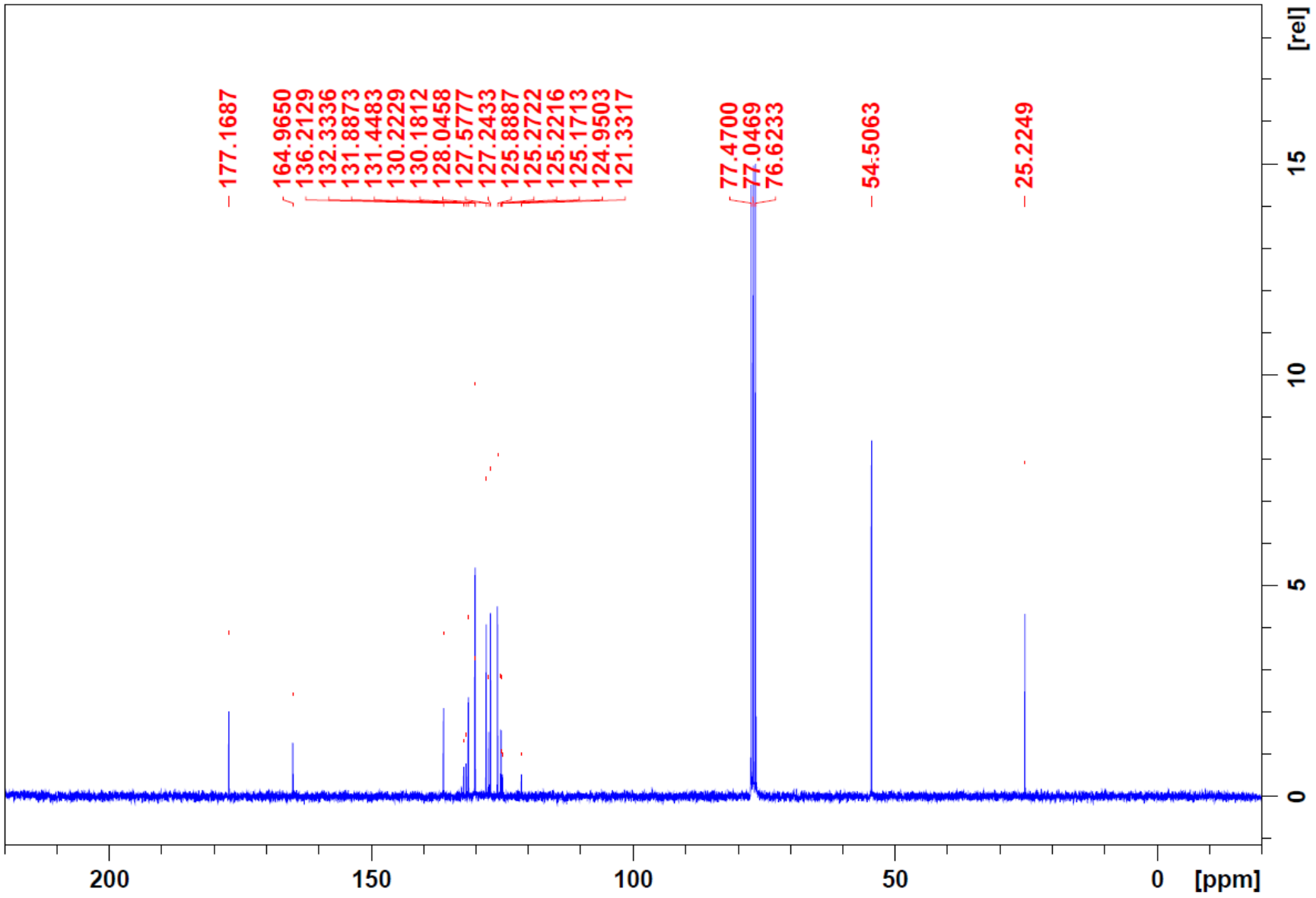
Analog **17** – ^{13}C NMR



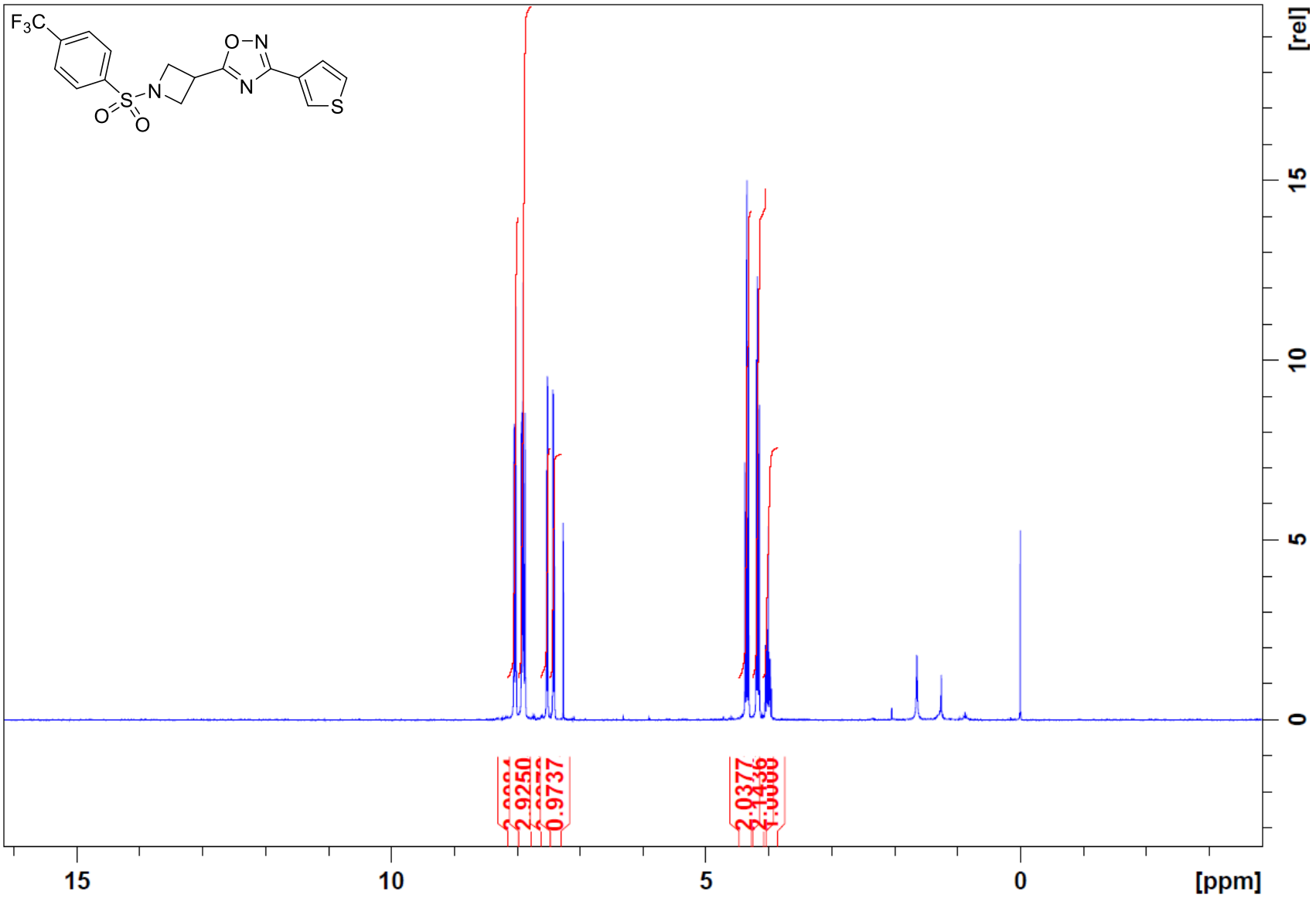
Analog **18** – ^{1}H NMR



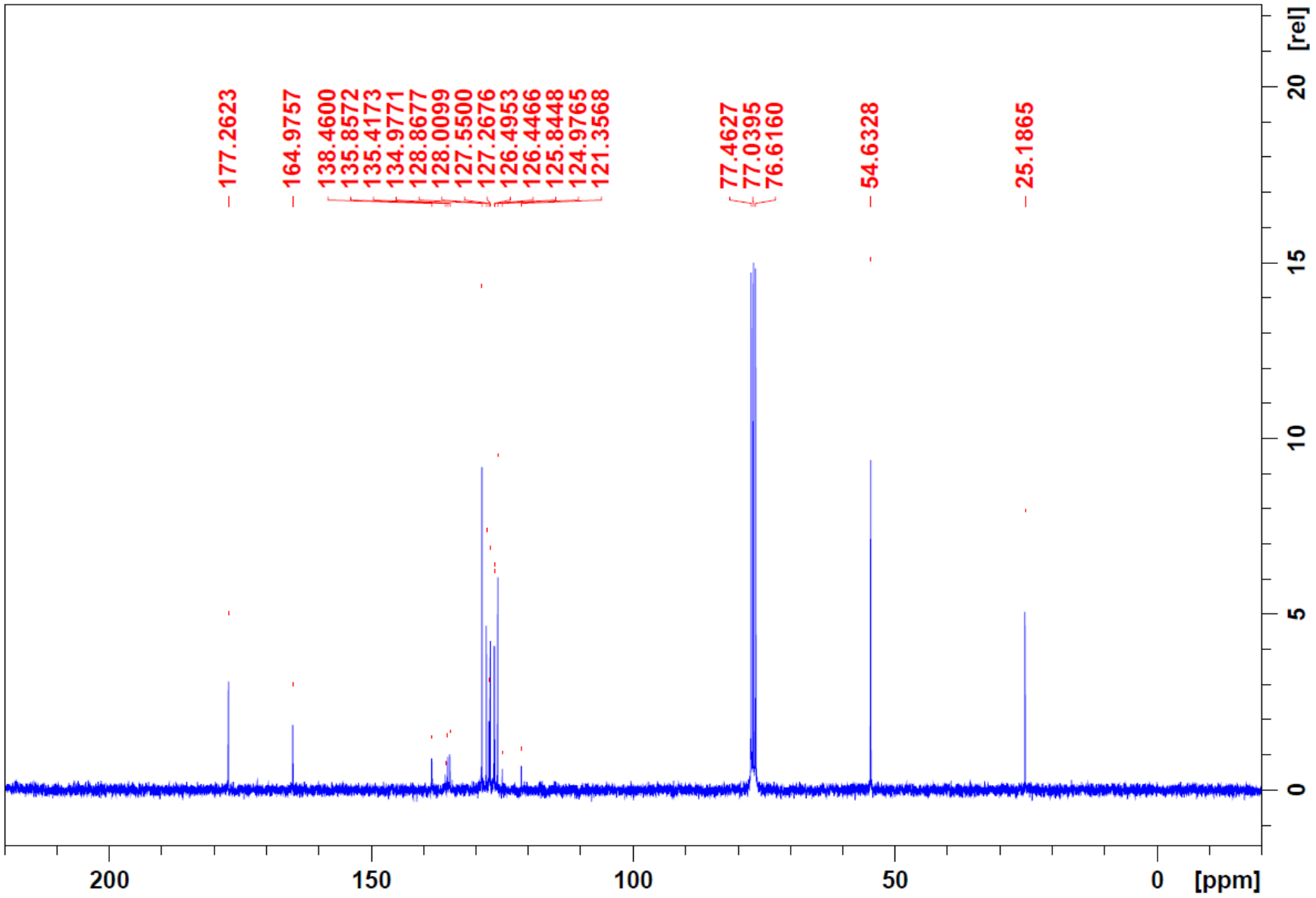
Analog **18** – ^{13}C NMR



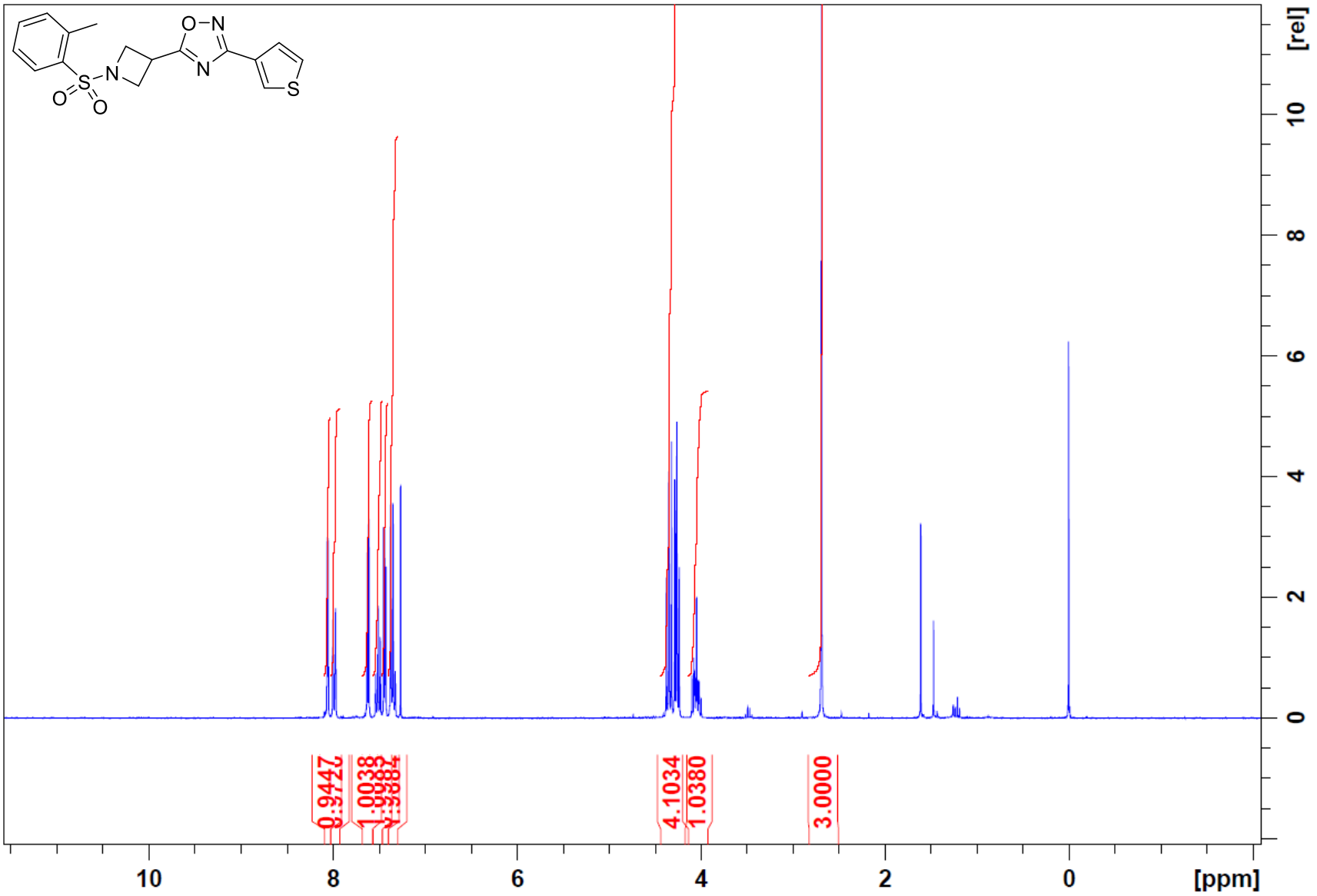
Analog **19** – ^{1}H NMR



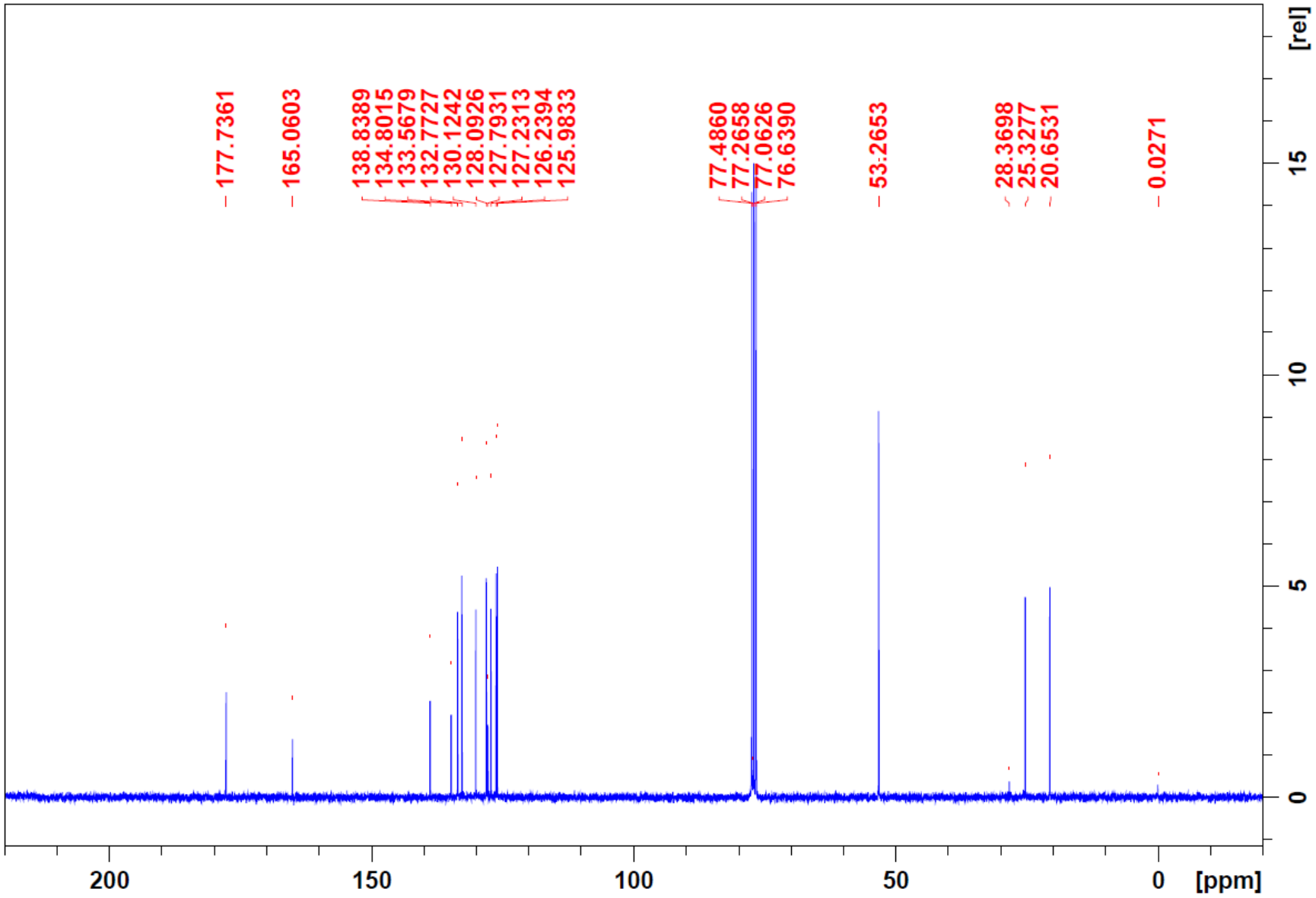
Analog **19** – ^{13}C NMR



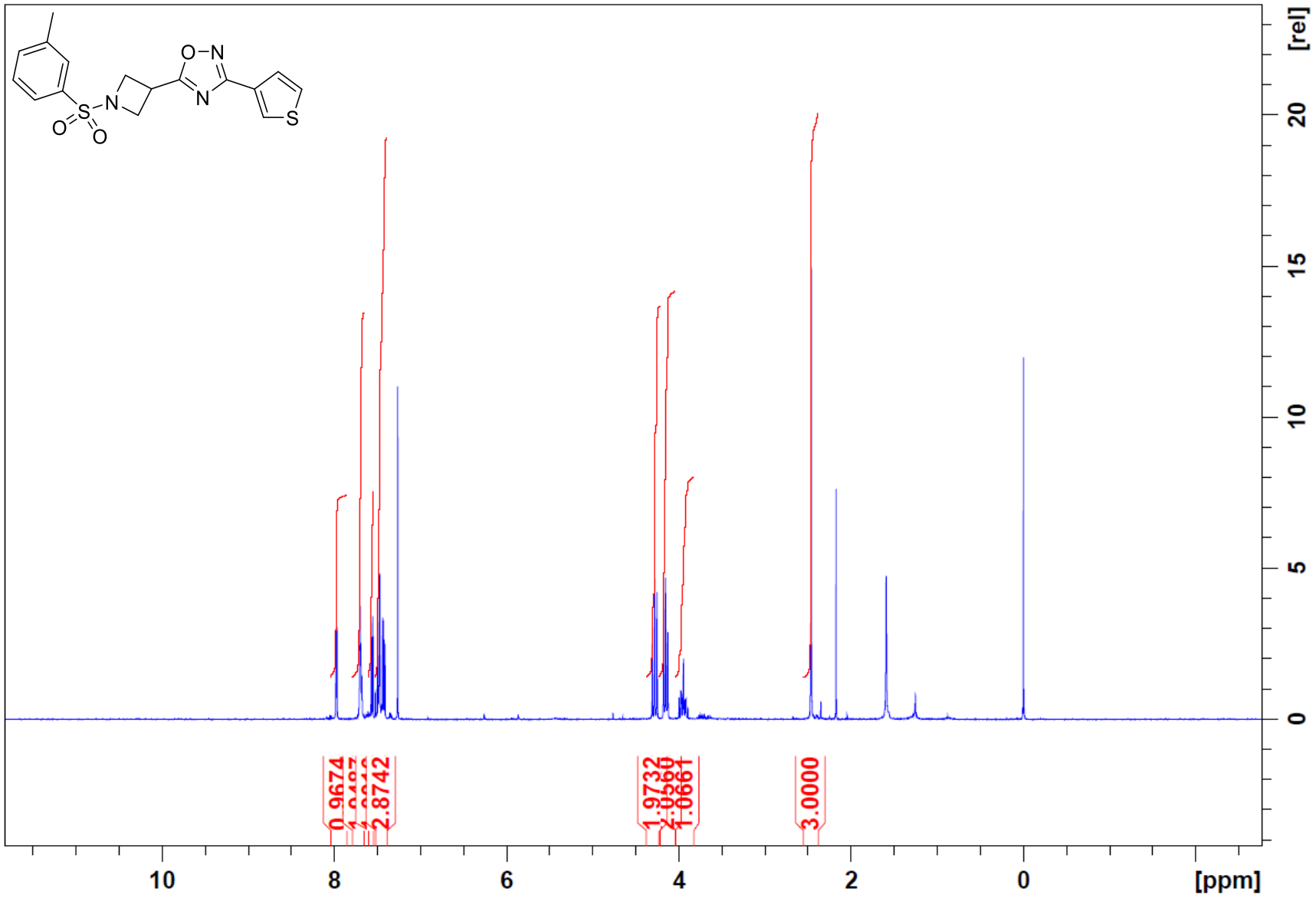
Analog **20** – ^{1}H NMR



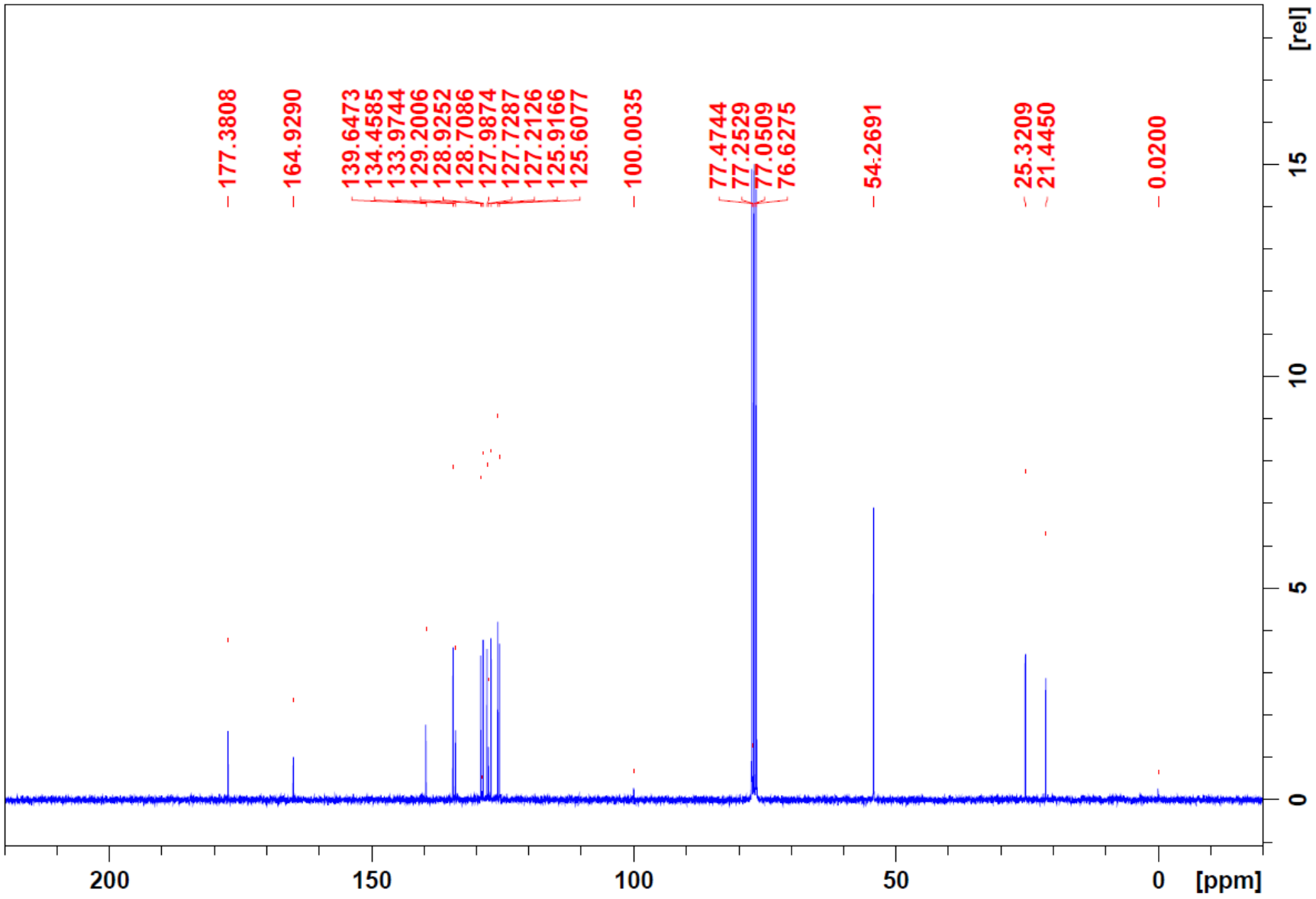
Analog **20** – ^{13}C NMR



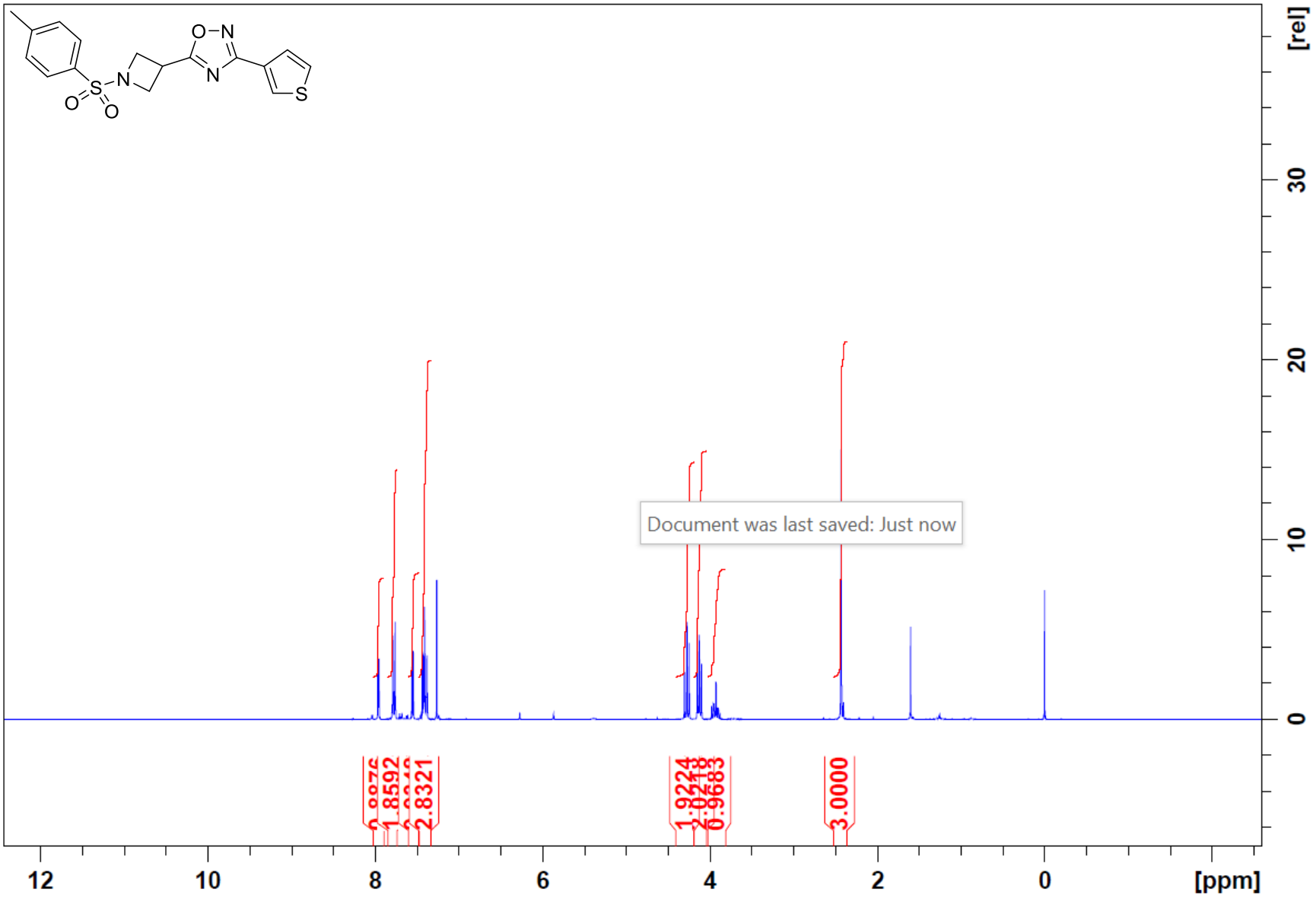
Analog **21** – ^{1}H NMR



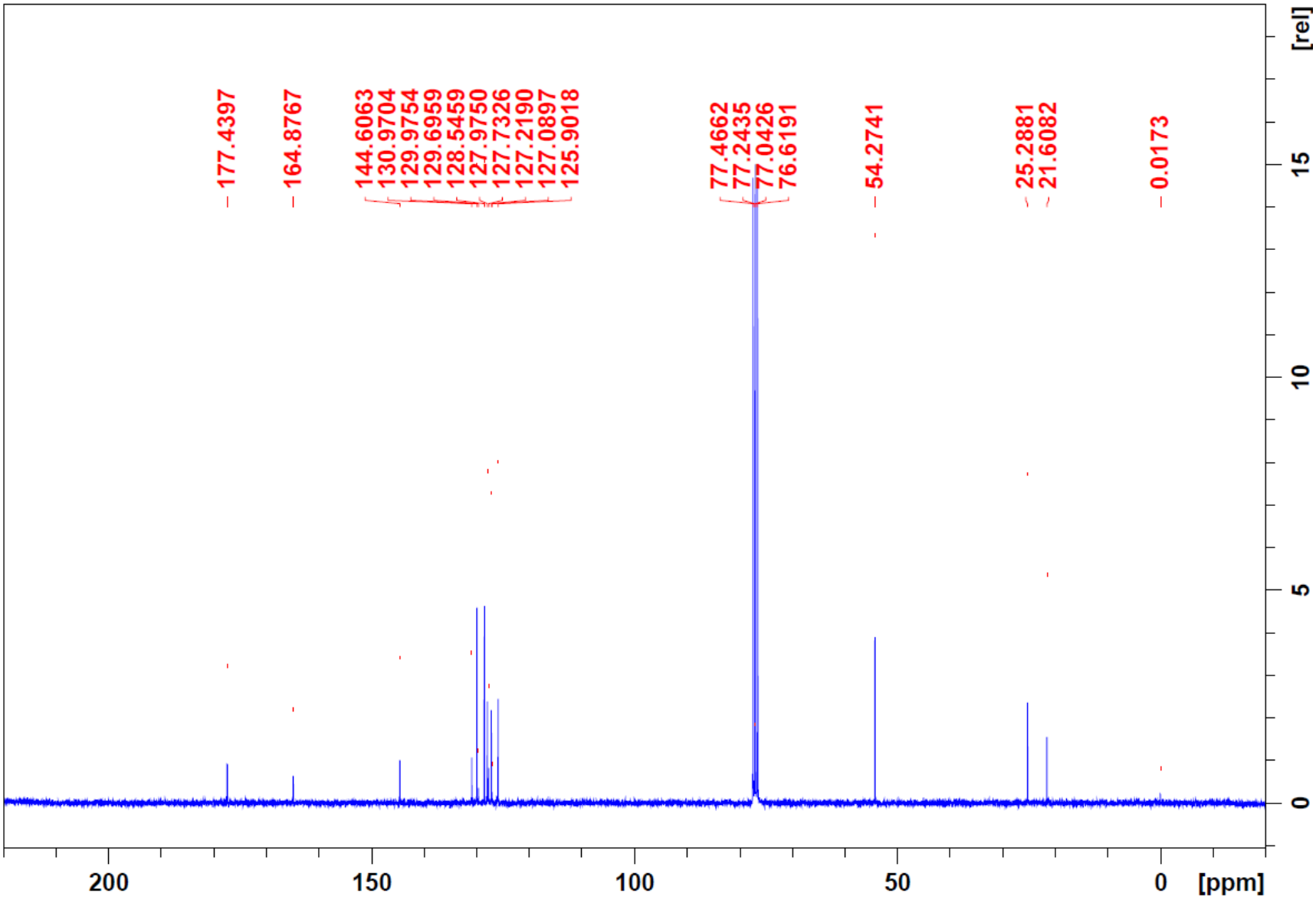
Analog **21** – ^{13}C NMR



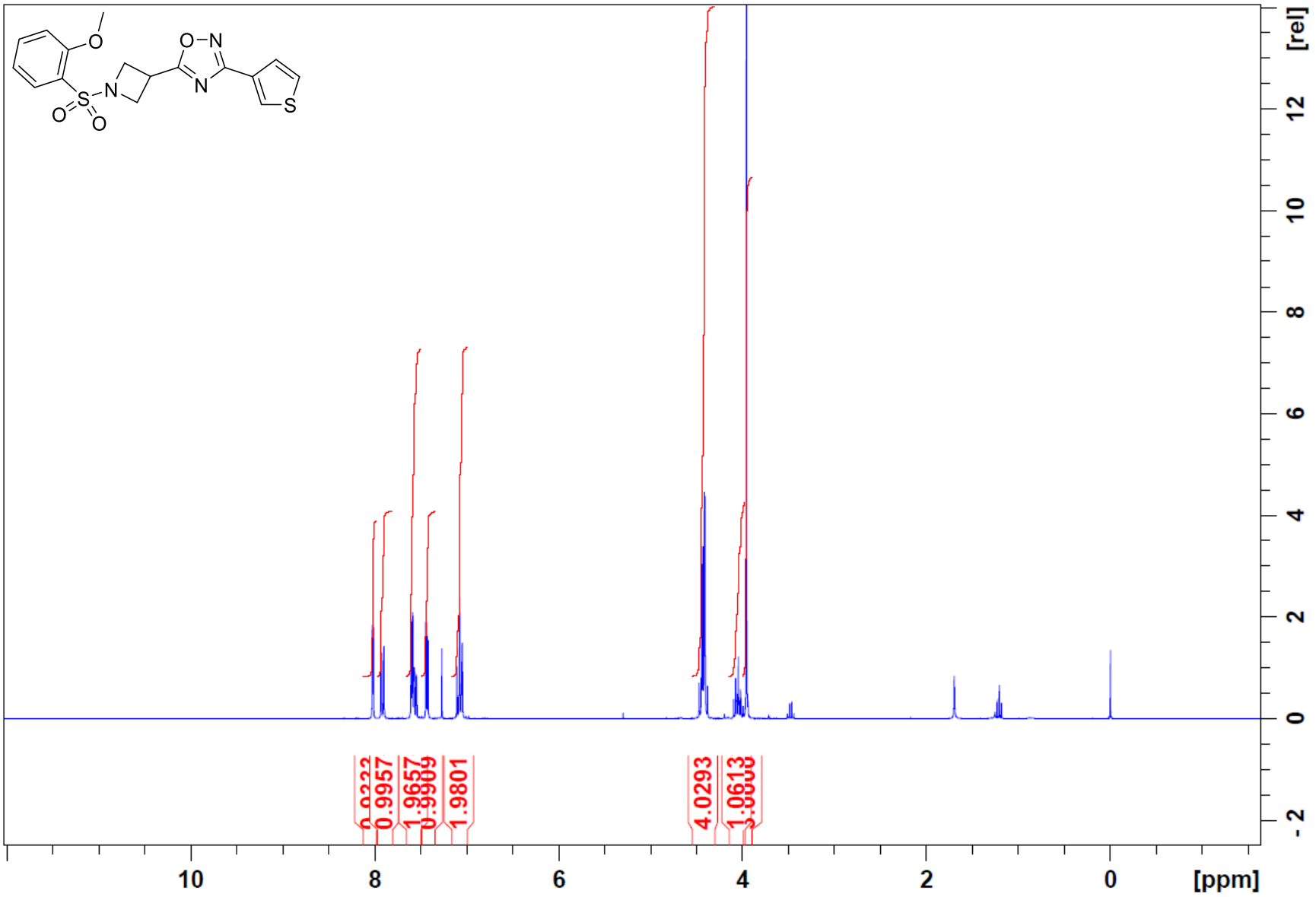
Analog **22** – ^{1}H NMR



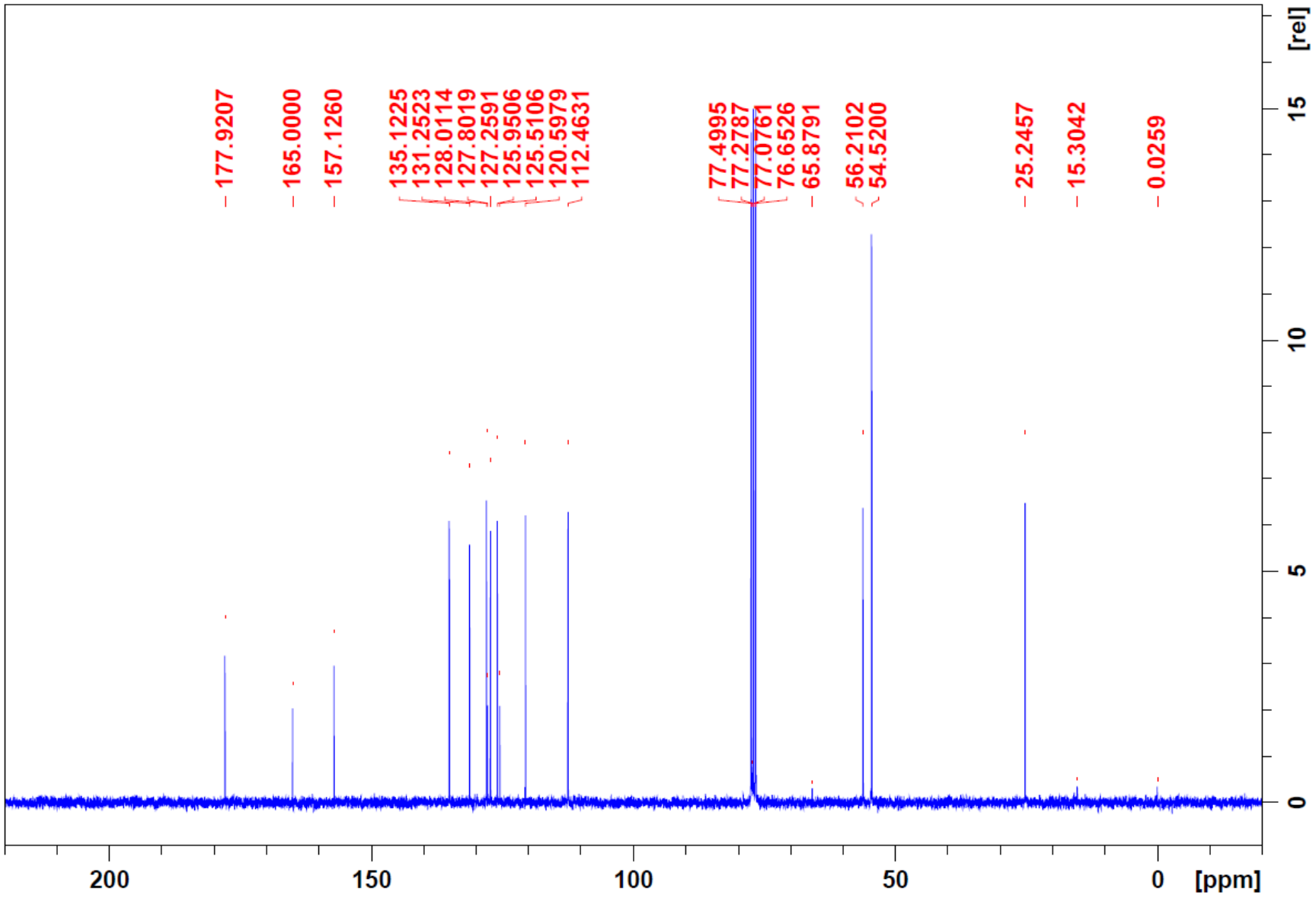
Analog **22** – ^{13}C NMR



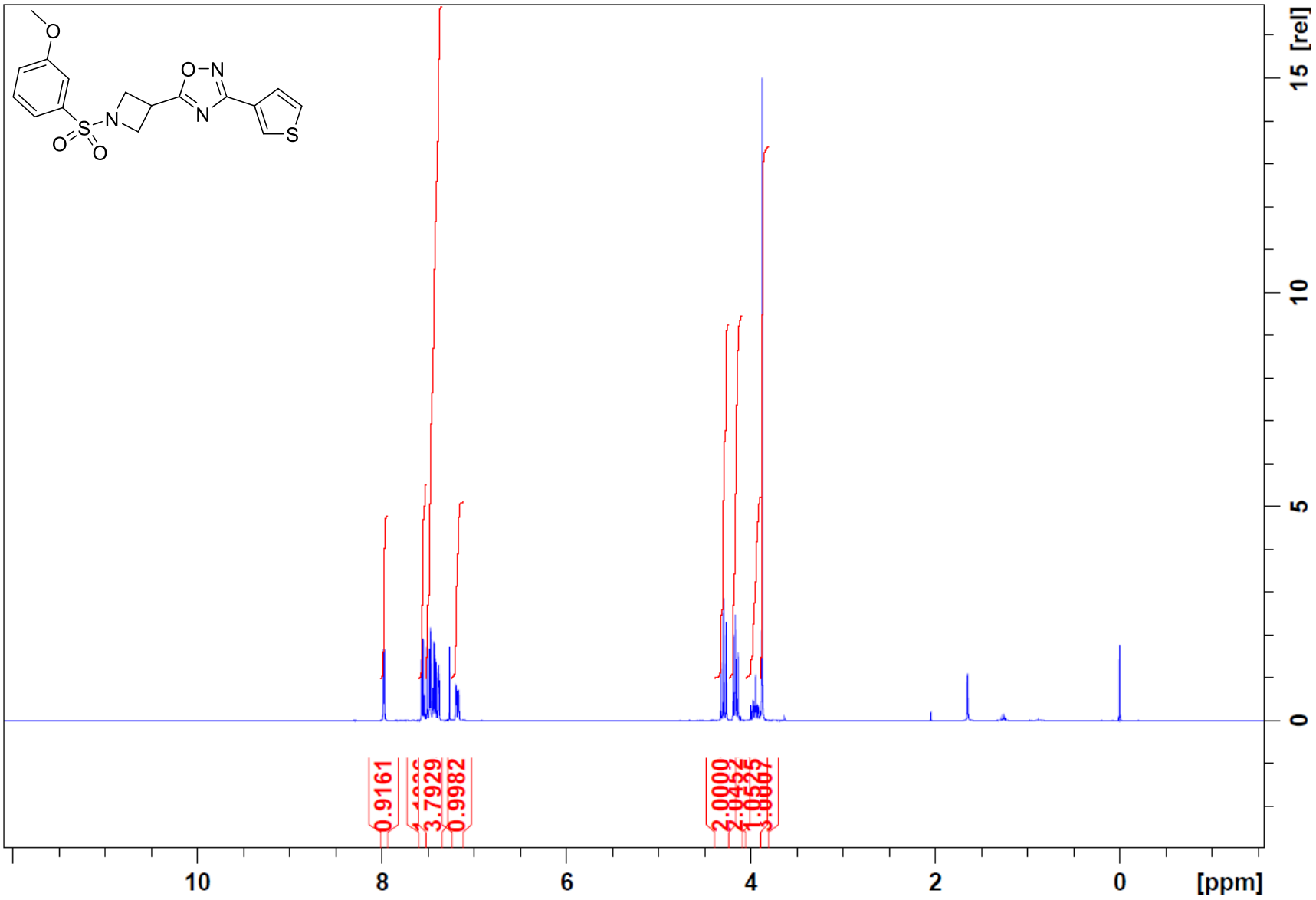
Analog **23** – ^{1}H NMR



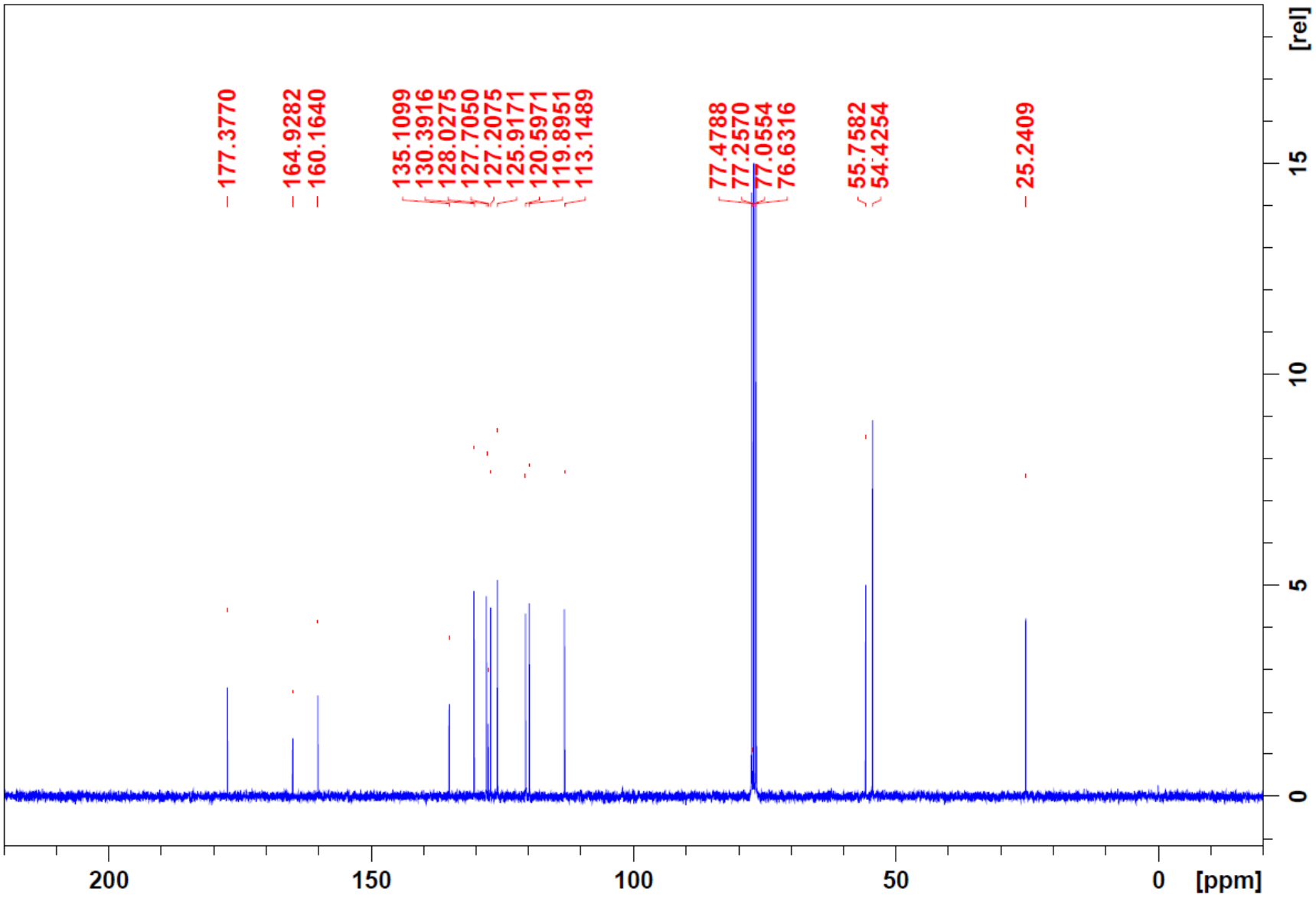
Analog **23** – ^{13}C NMR



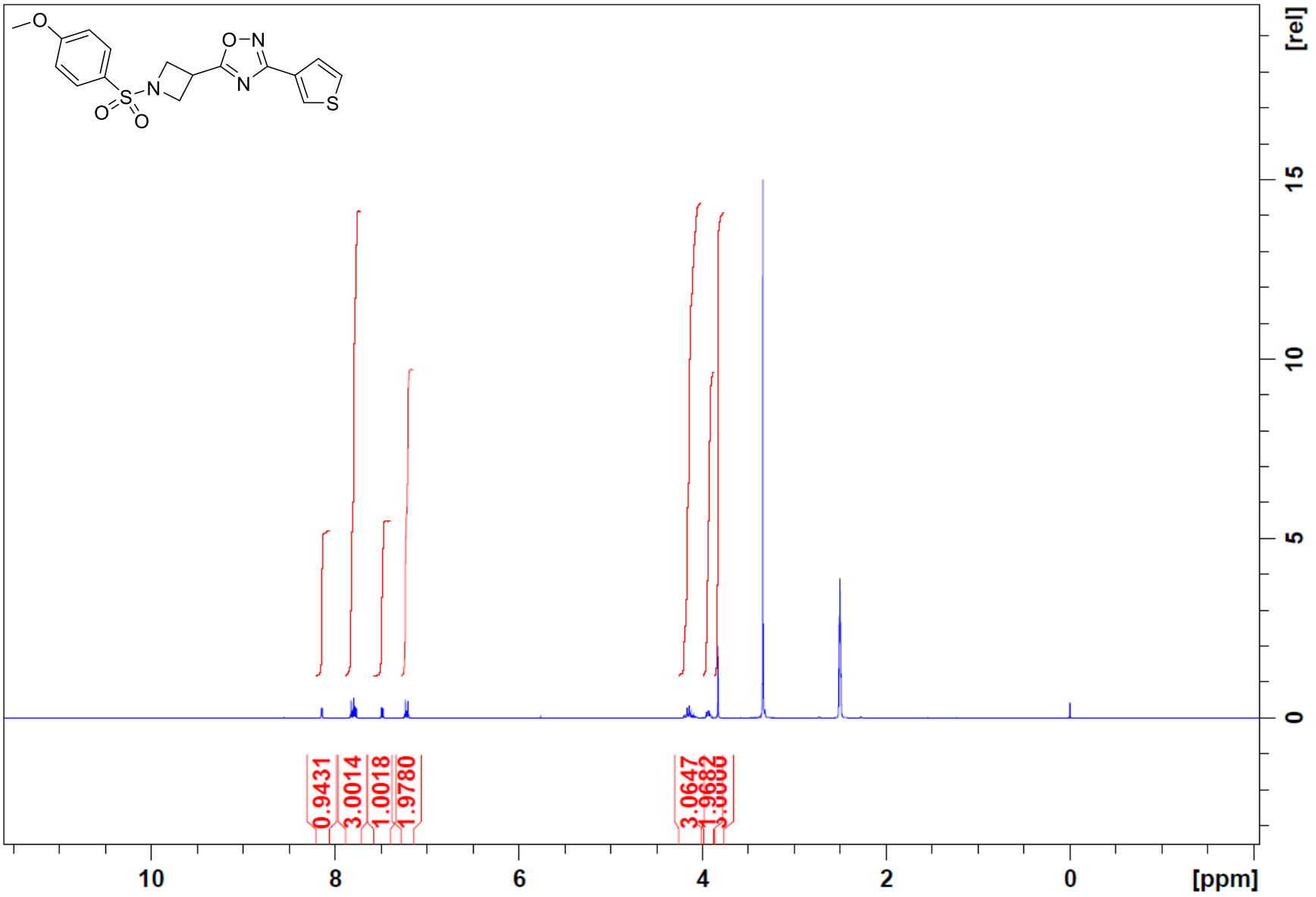
Analog **24** – ^{1}H NMR



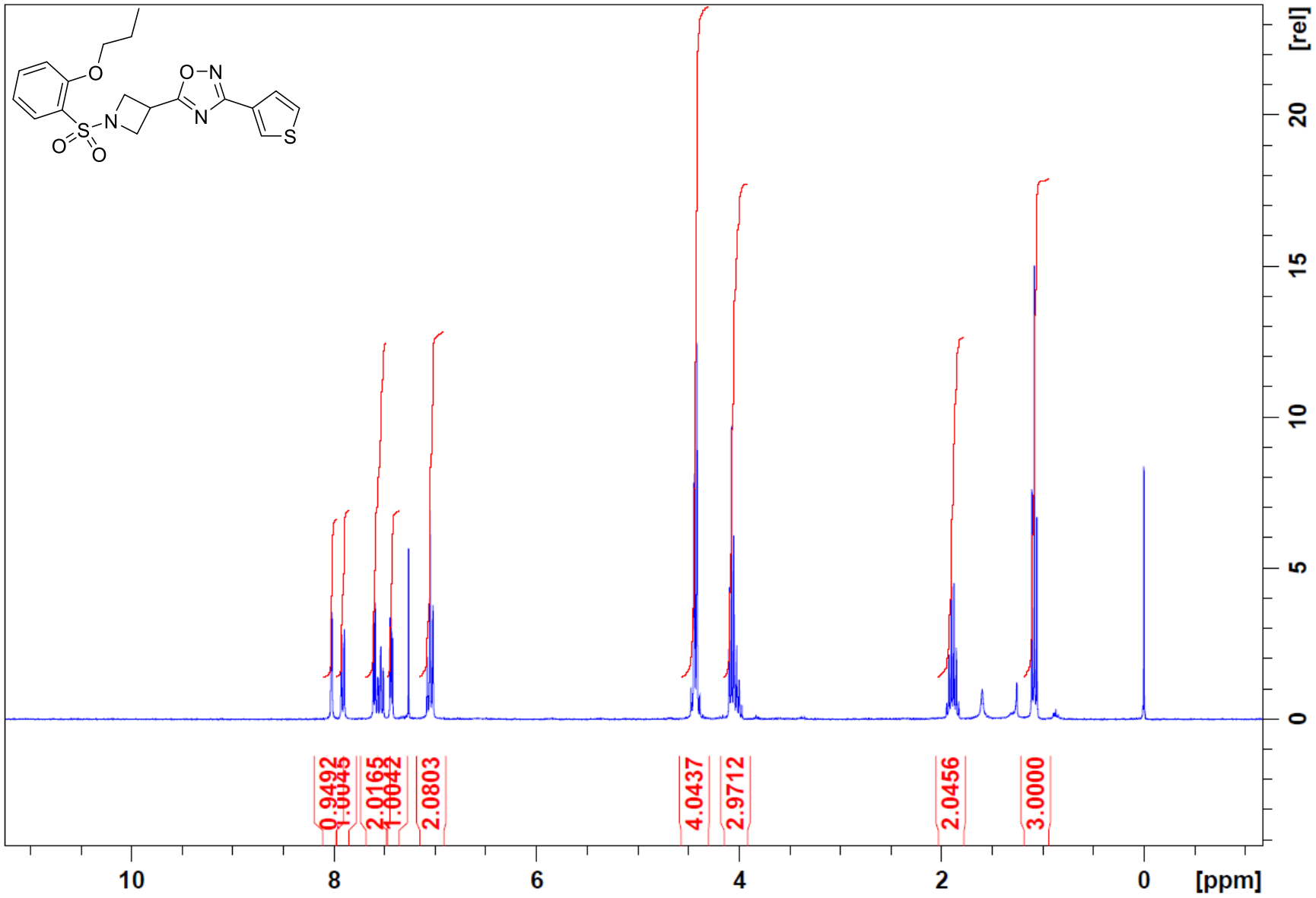
Analog **24** – ^{13}C NMR



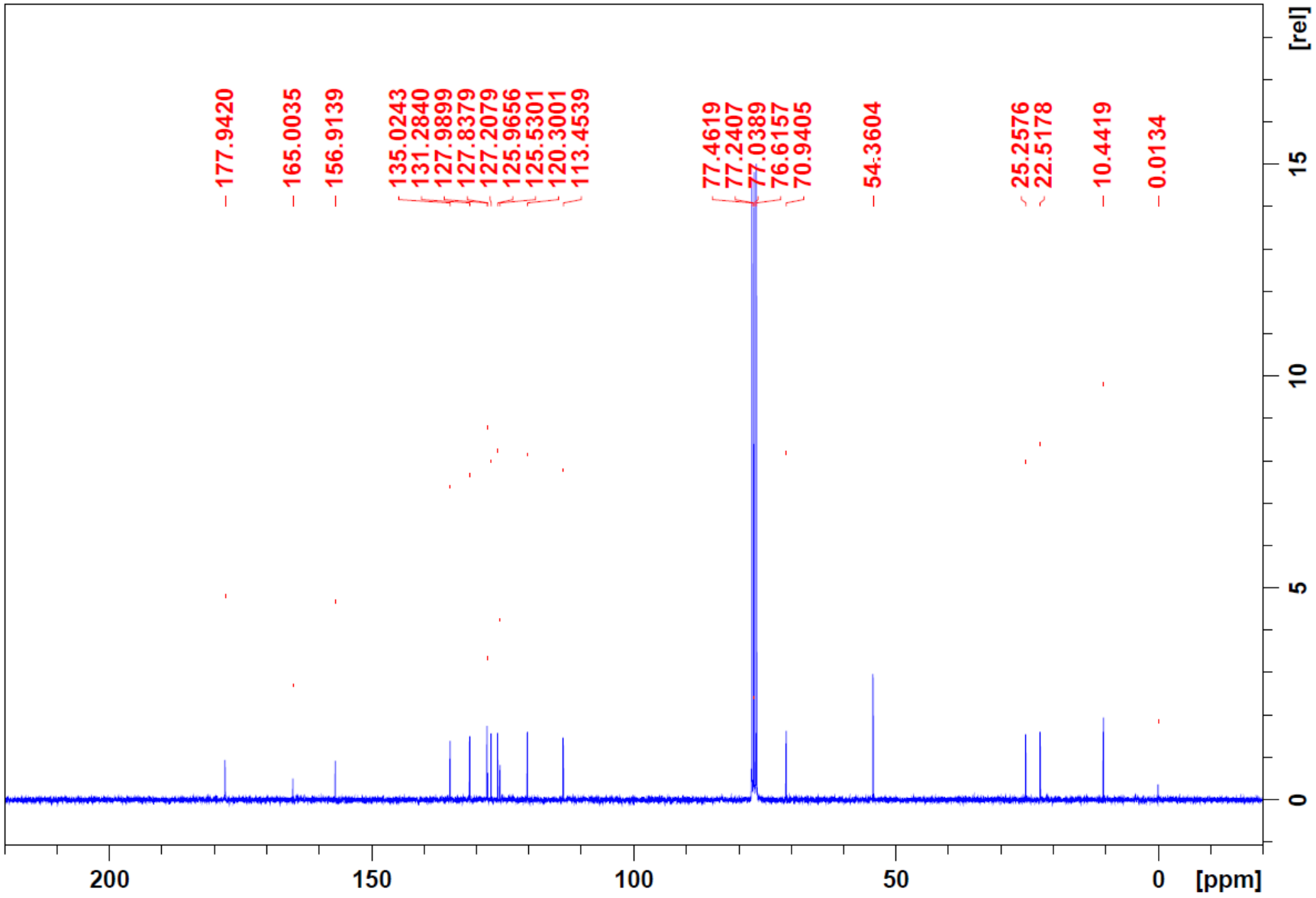
Analog **25** – ^{1}H NMR



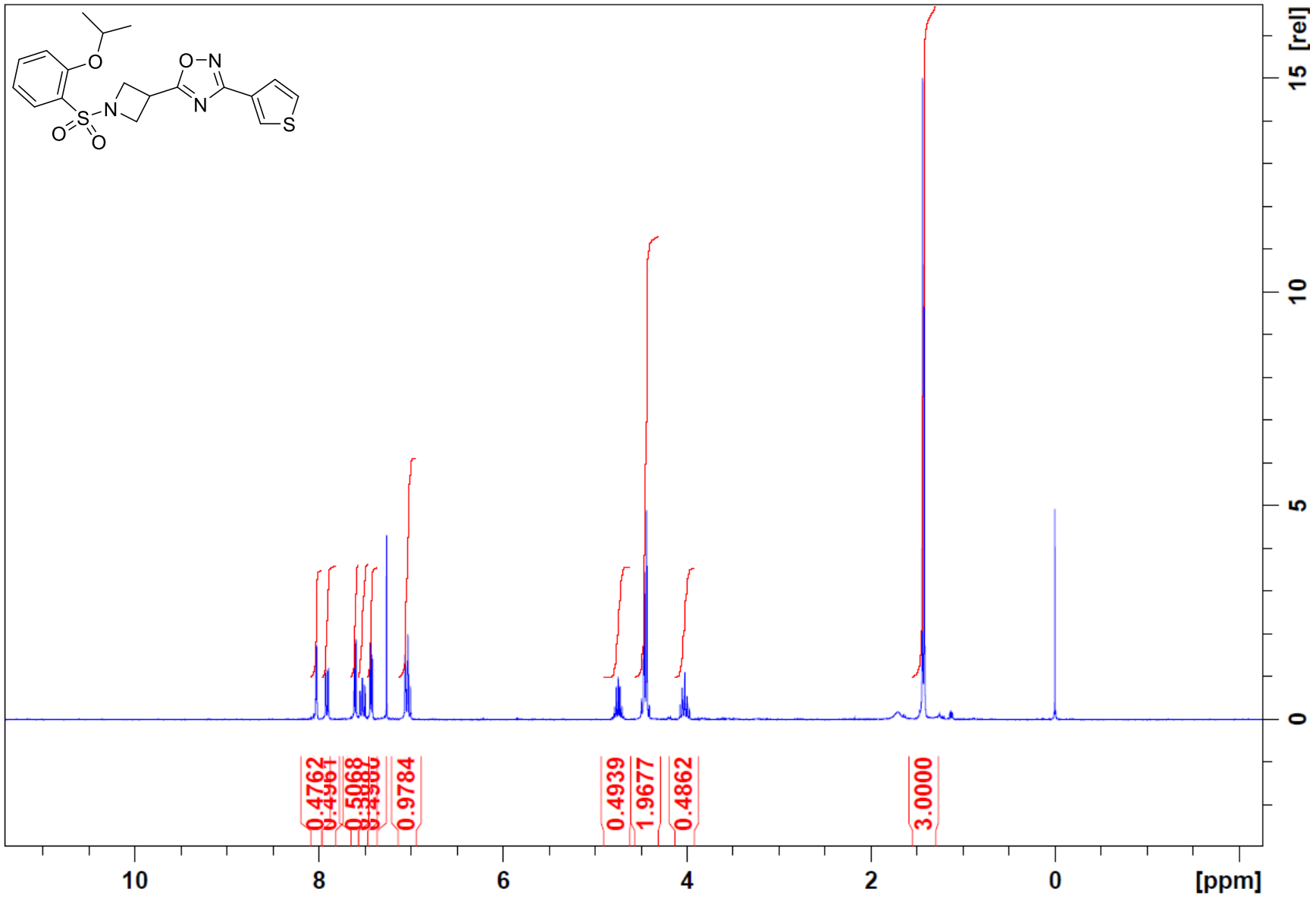
Analog **26** – ^{1}H NMR



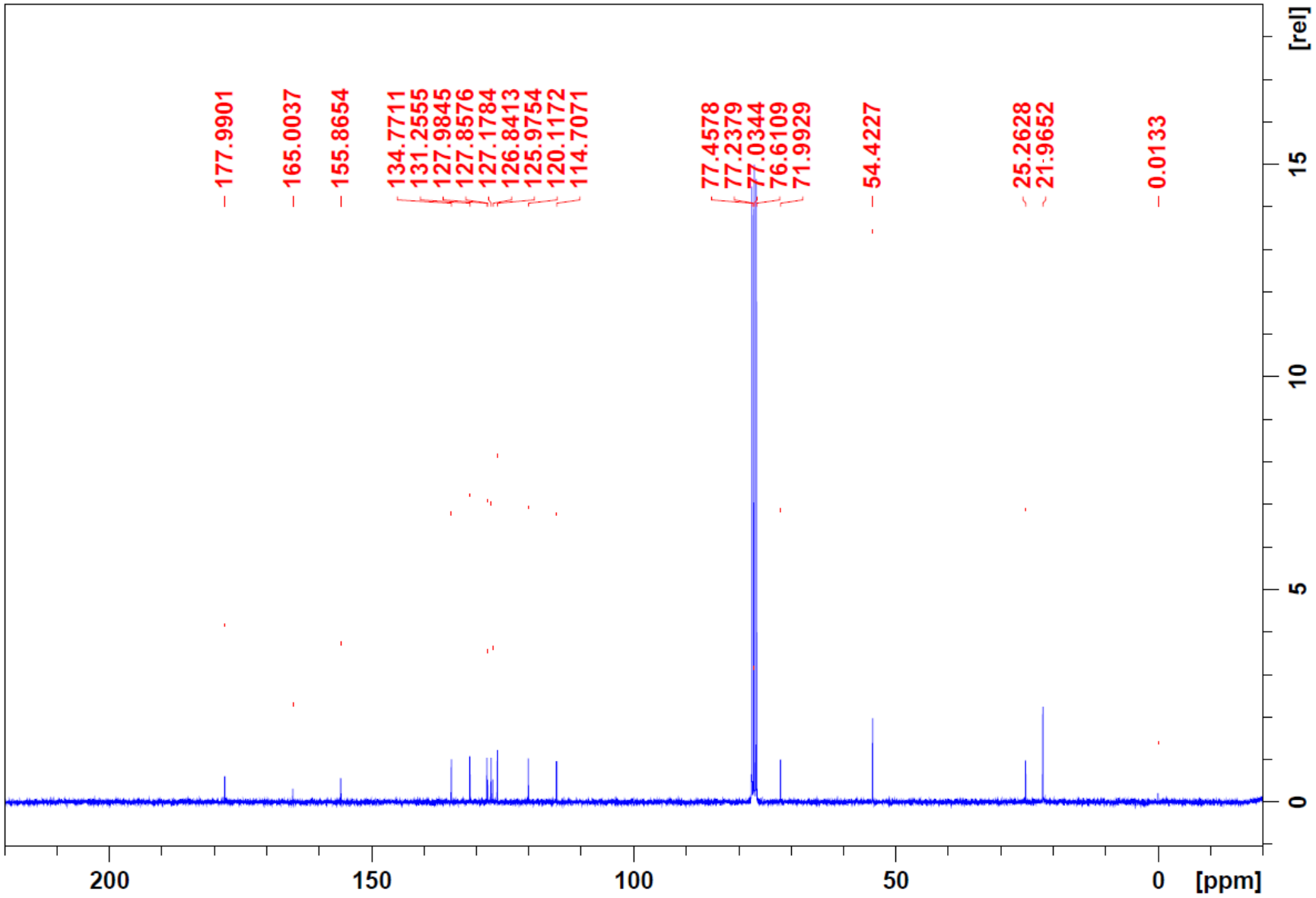
Analog **26** – ^{13}C NMR



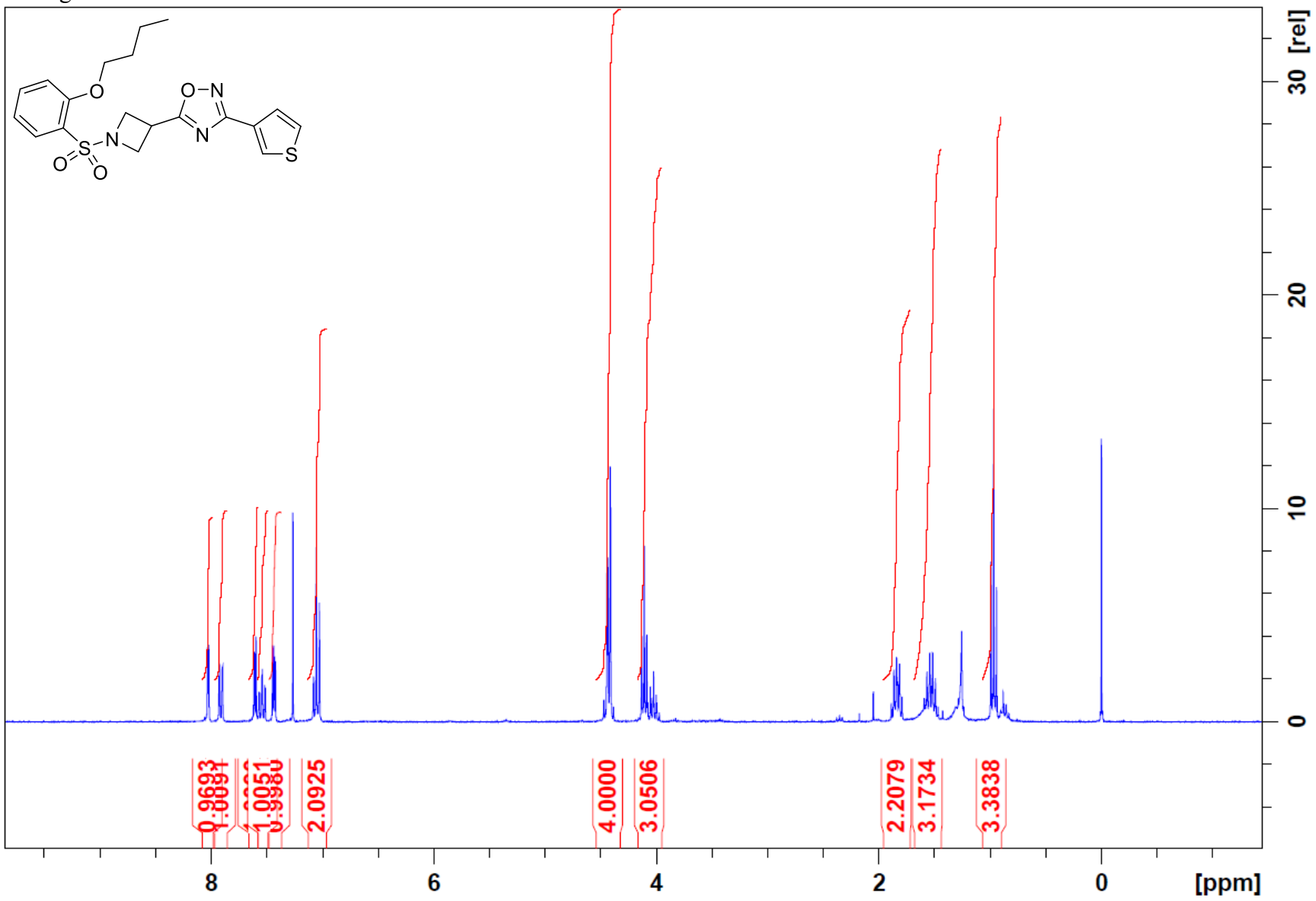
Analog **27** – ^{1}H NMR



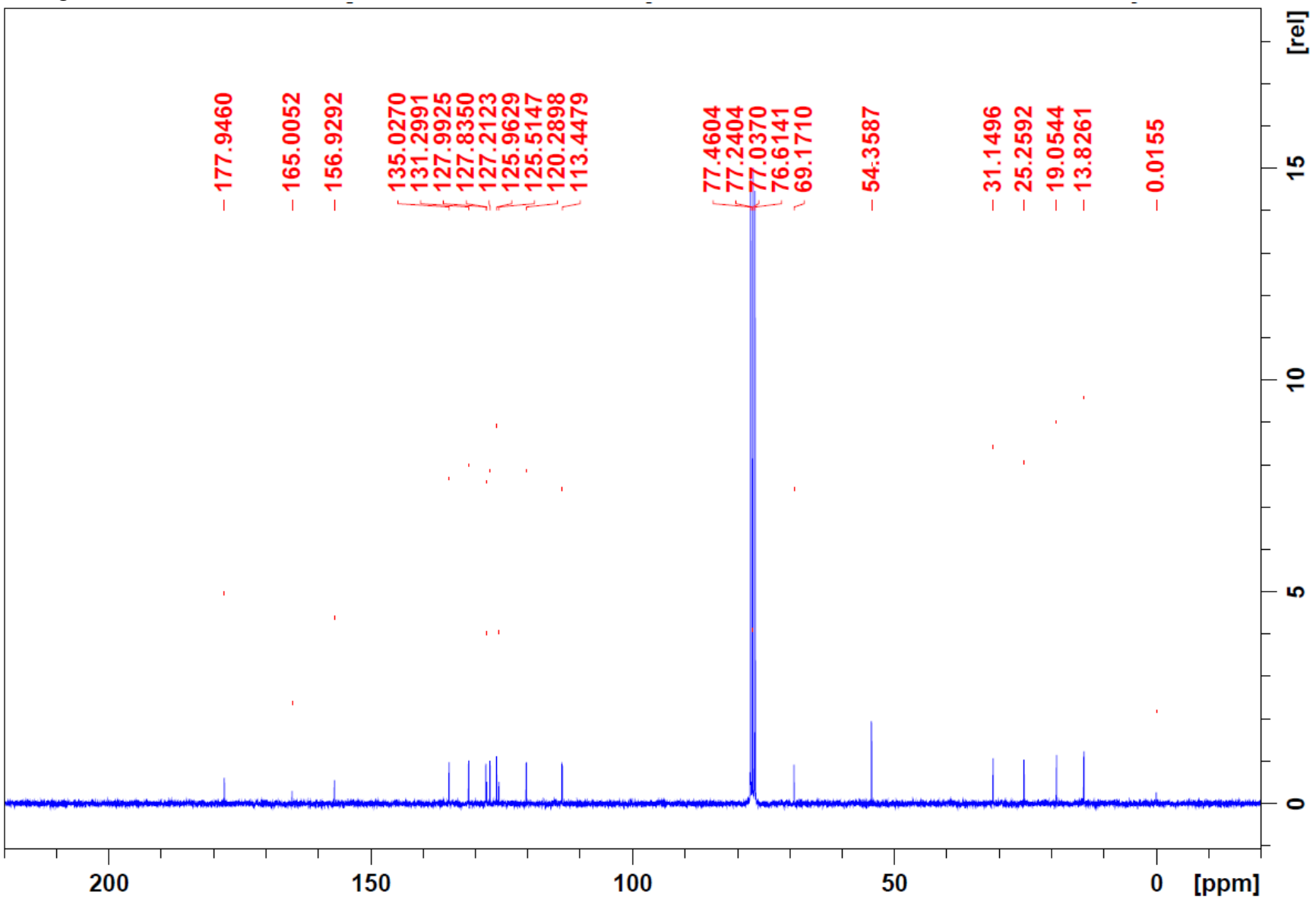
Analog **27** – ^{13}C NMR



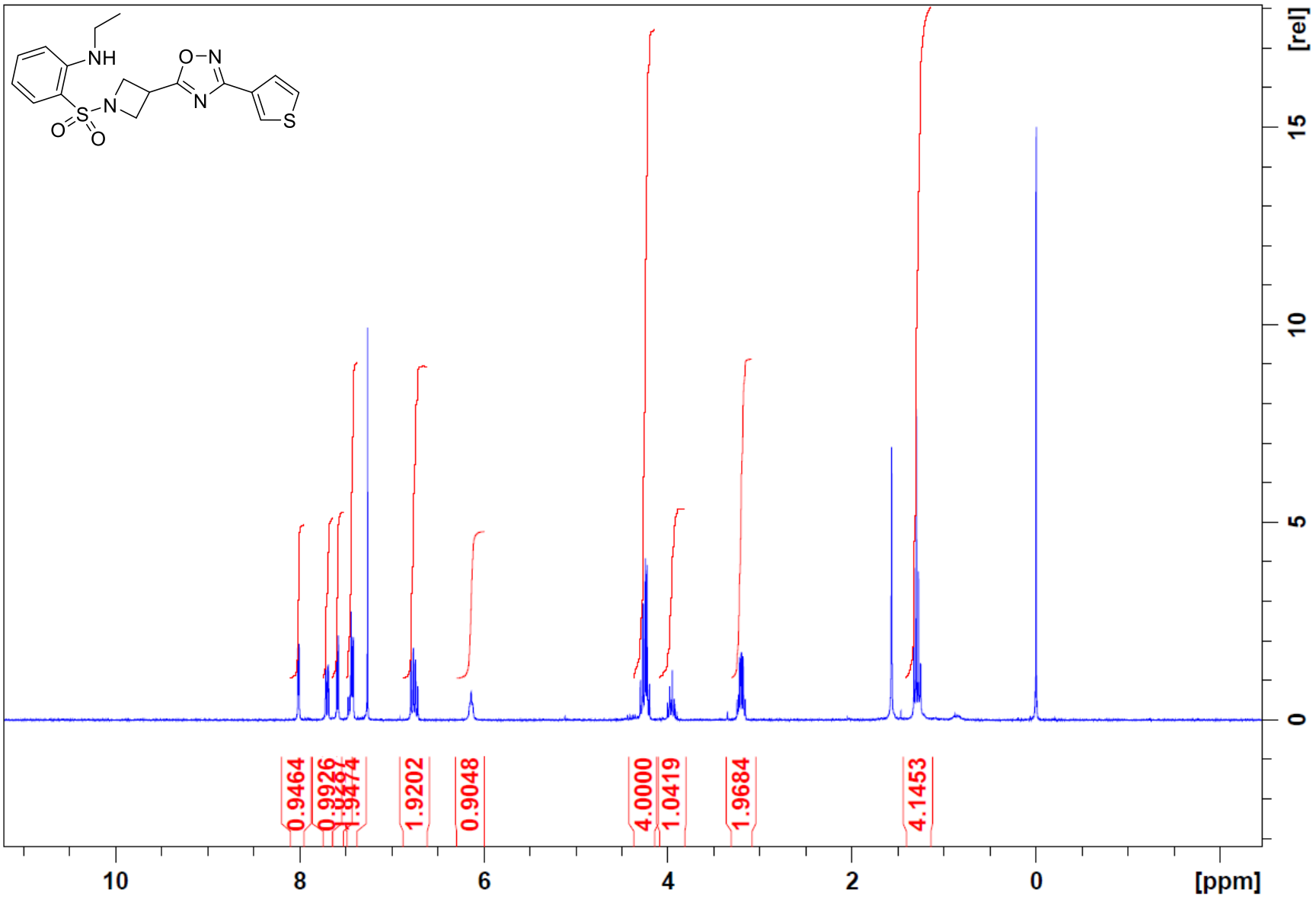
Analog **28** – ^{1}H NMR



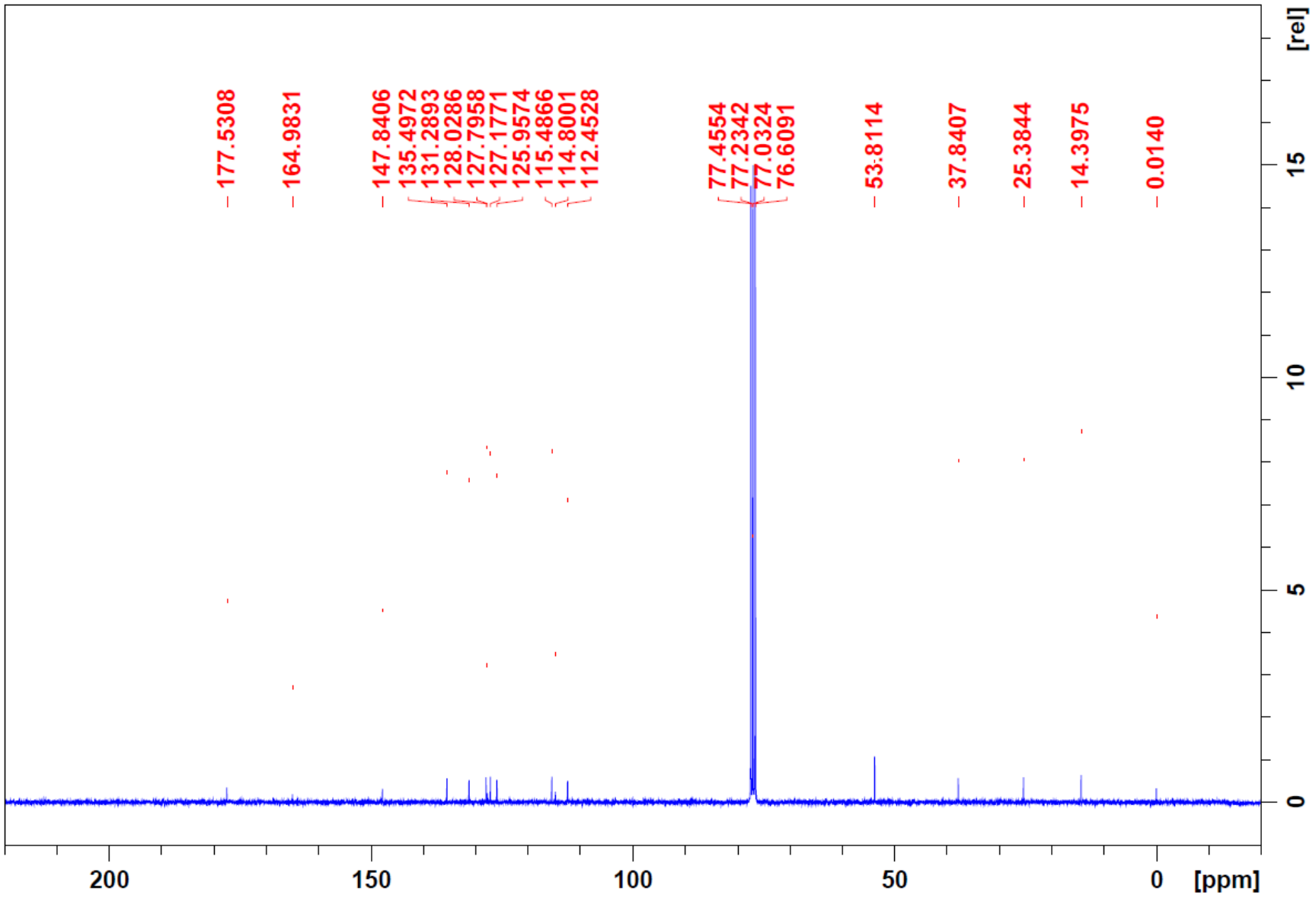
Analog **28** – ^{13}C NMR



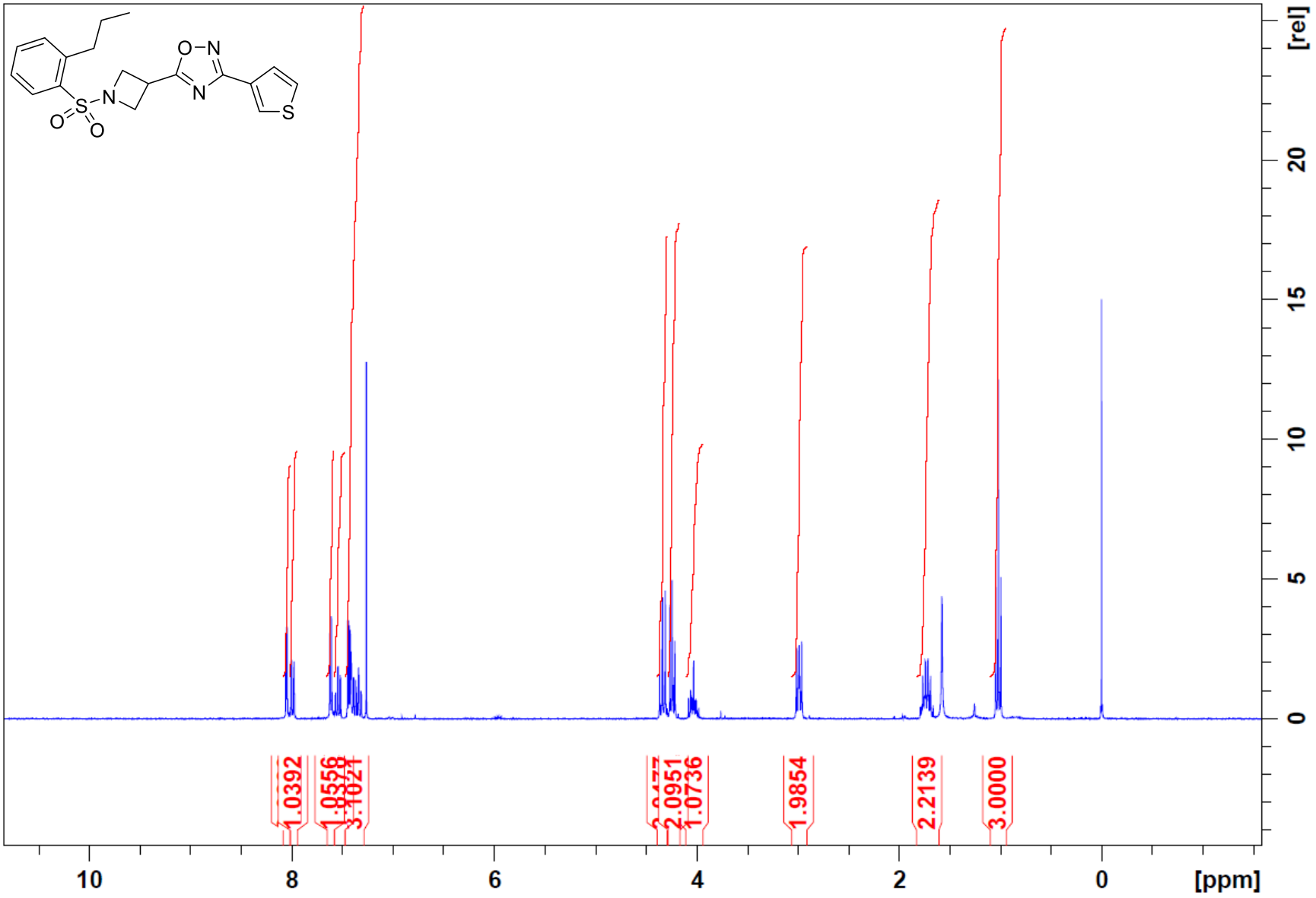
Analog **29** – ^{1}H NMR



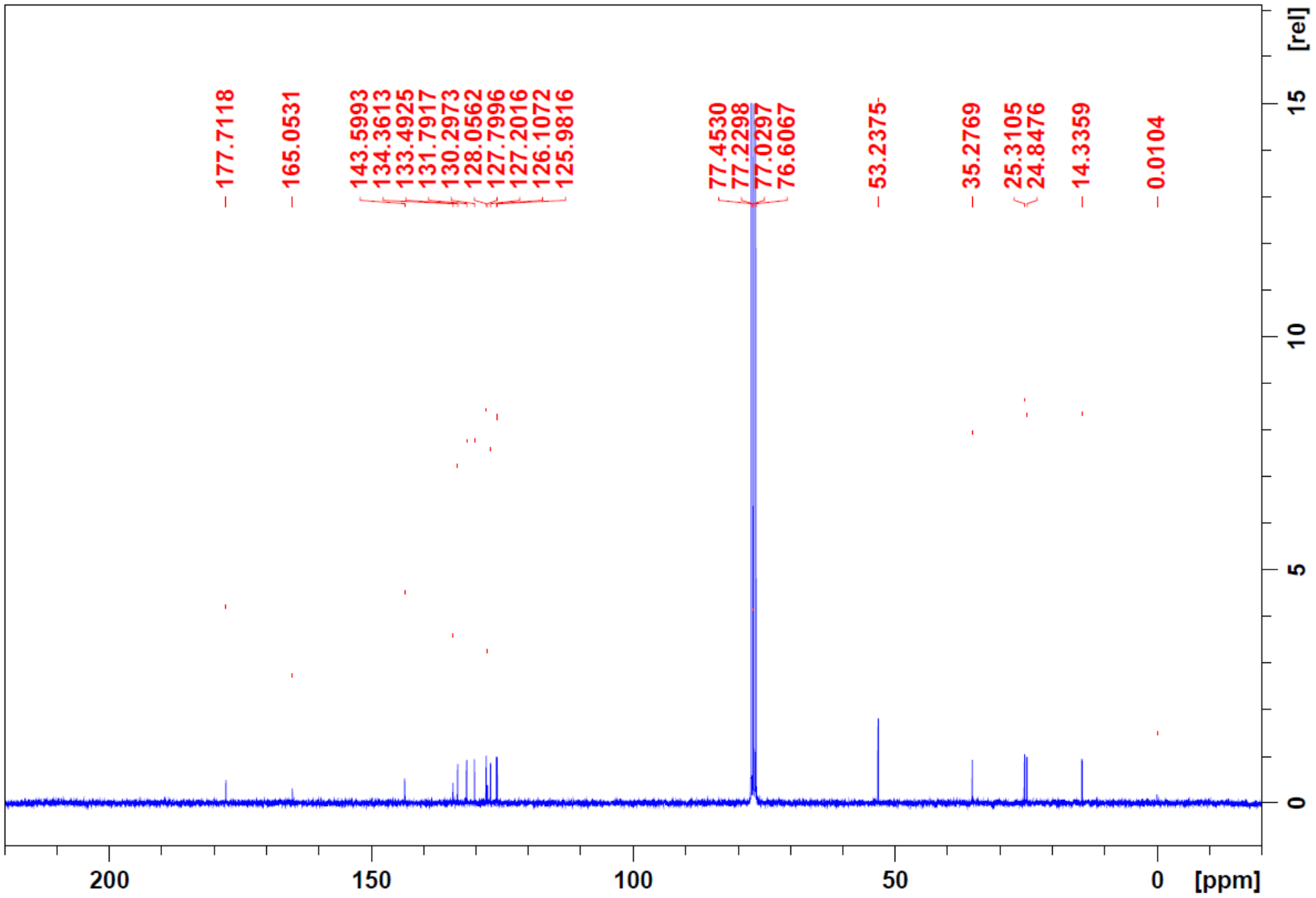
Analog **29** – ^{13}C NMR



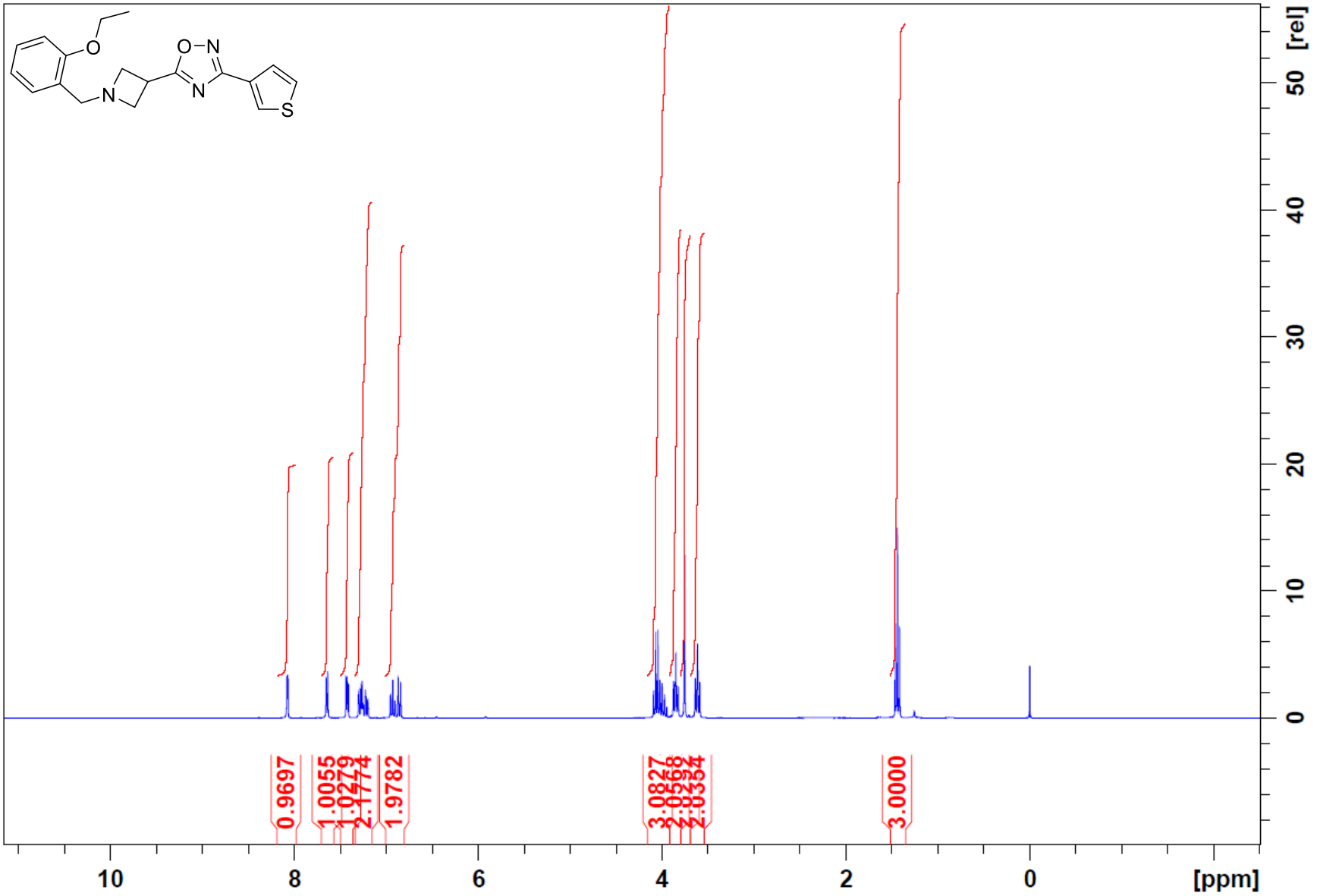
Analog **30** – ^{1}H NMR



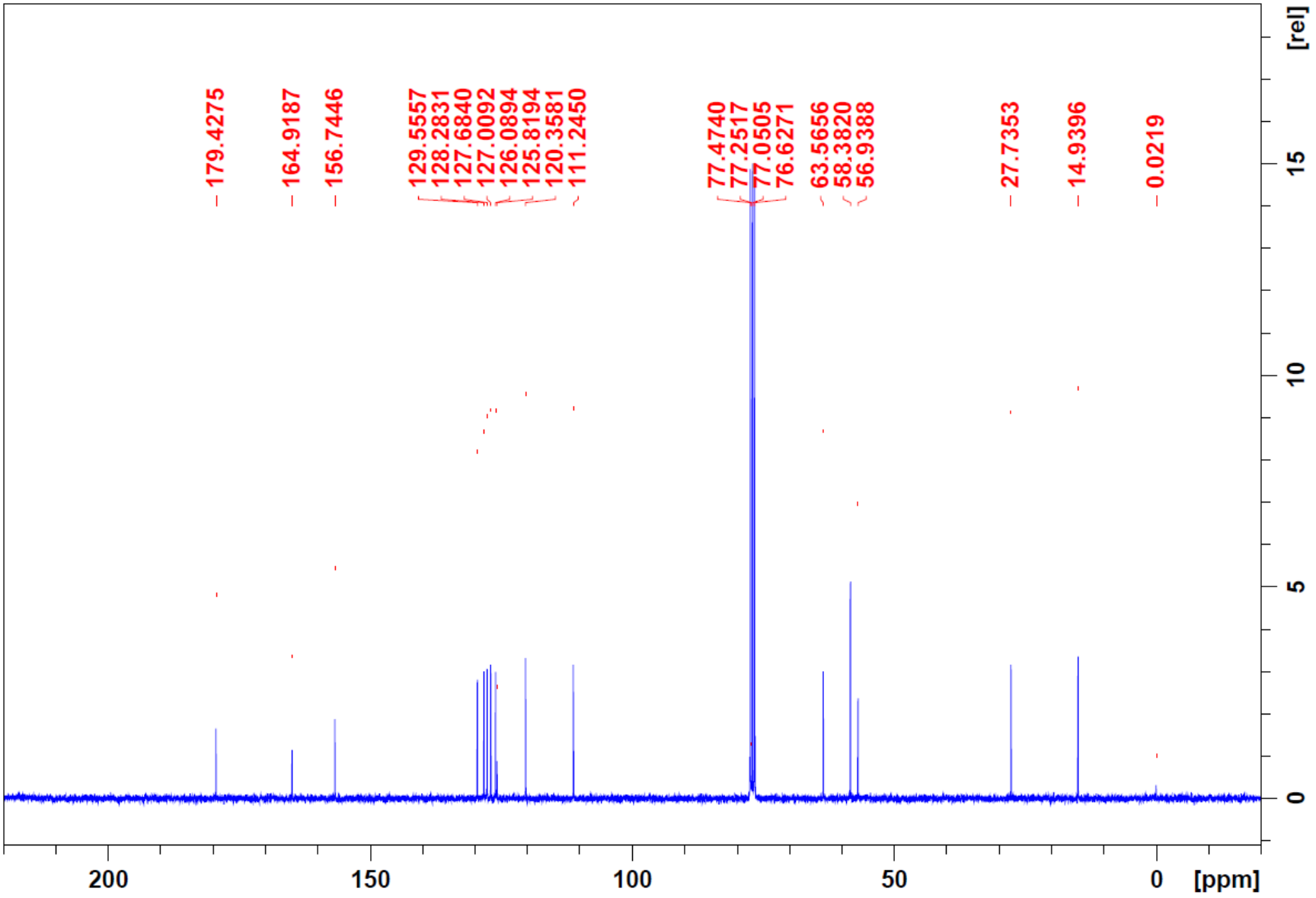
Analog **30** – ^{13}C NMR



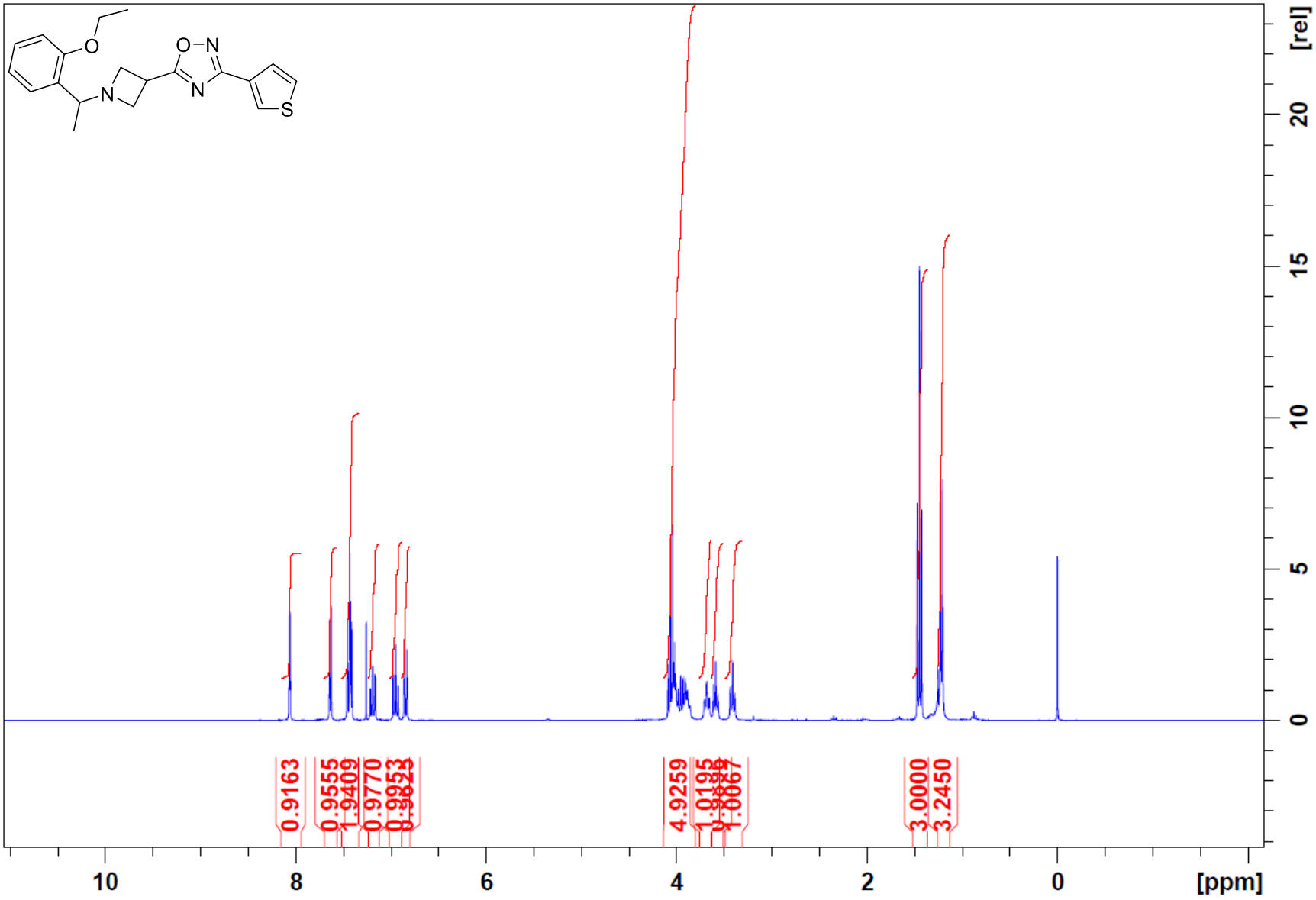
Analog **31** – ^{1}H NMR



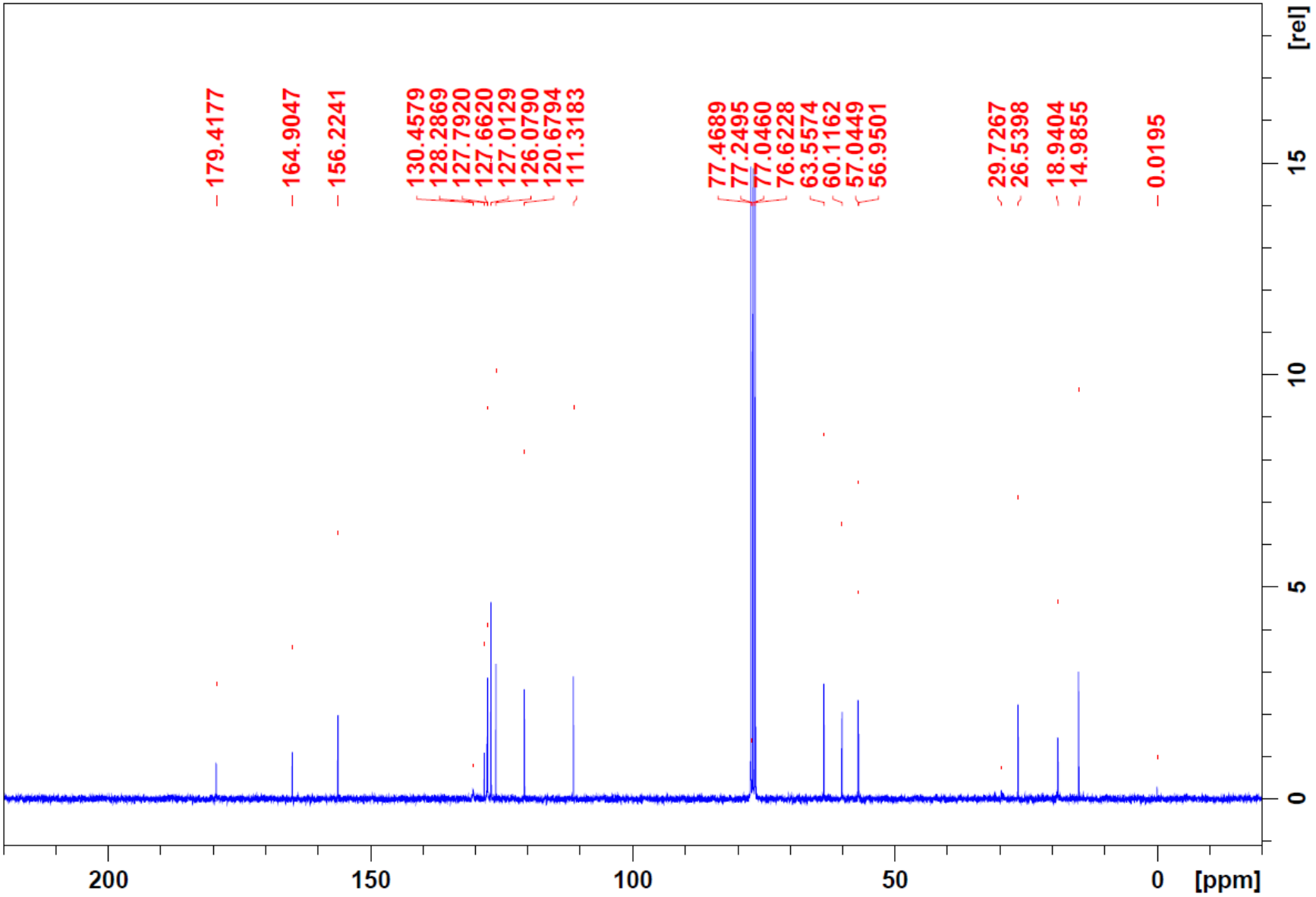
Analog **31** – ^{13}C NMR



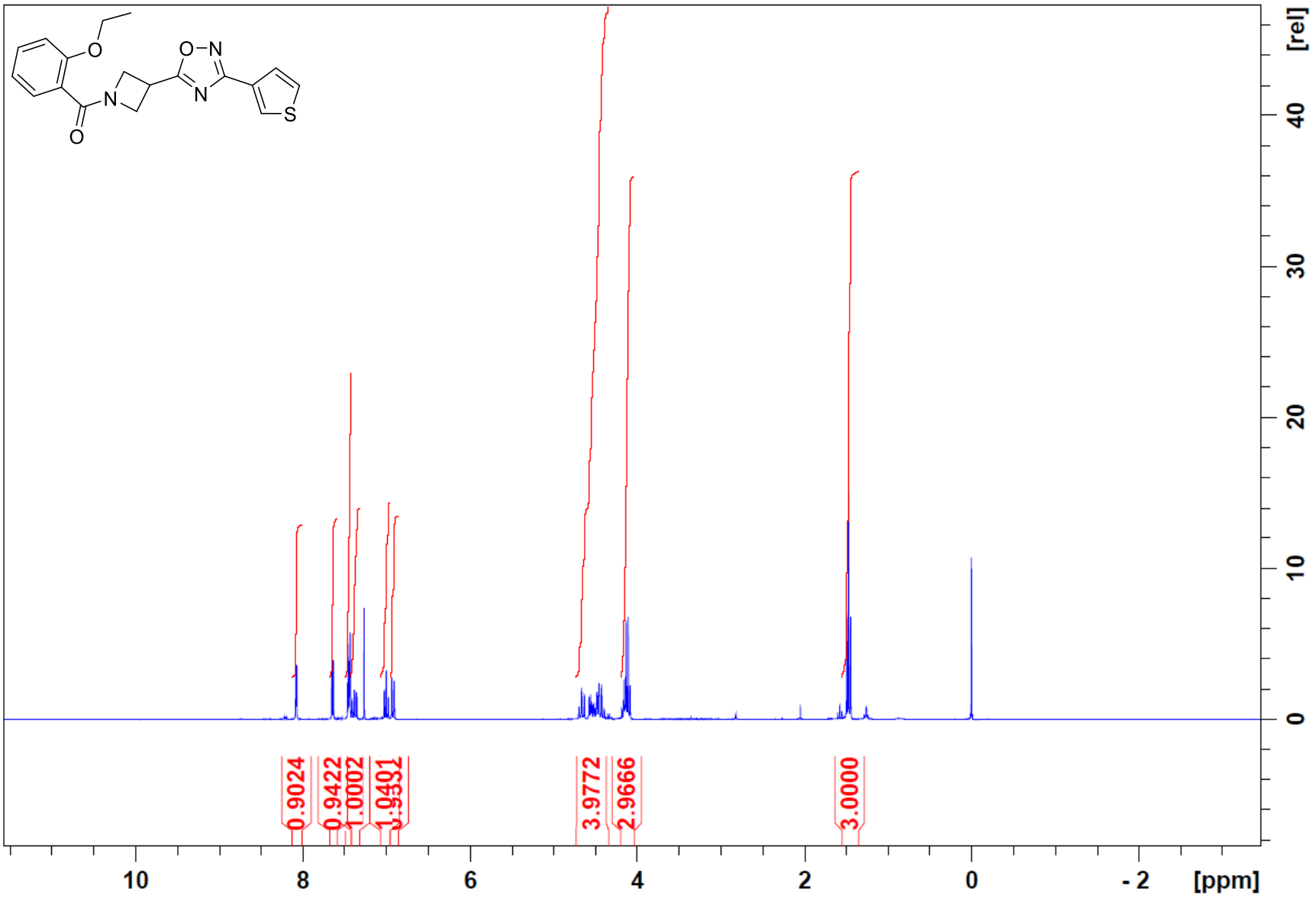
Analog **32** – ^{1}H NMR



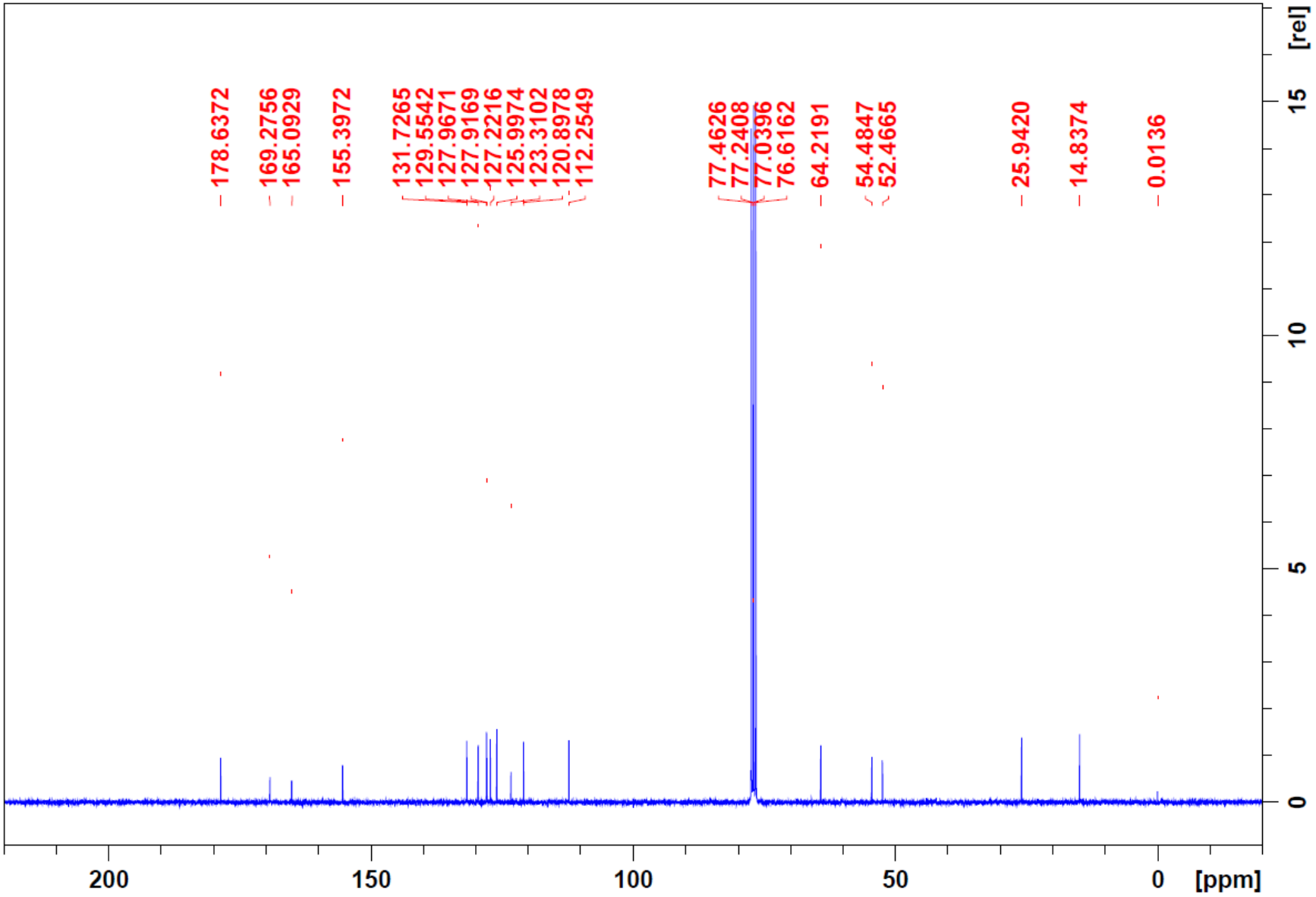
Analog **32** – ^{13}C NMR



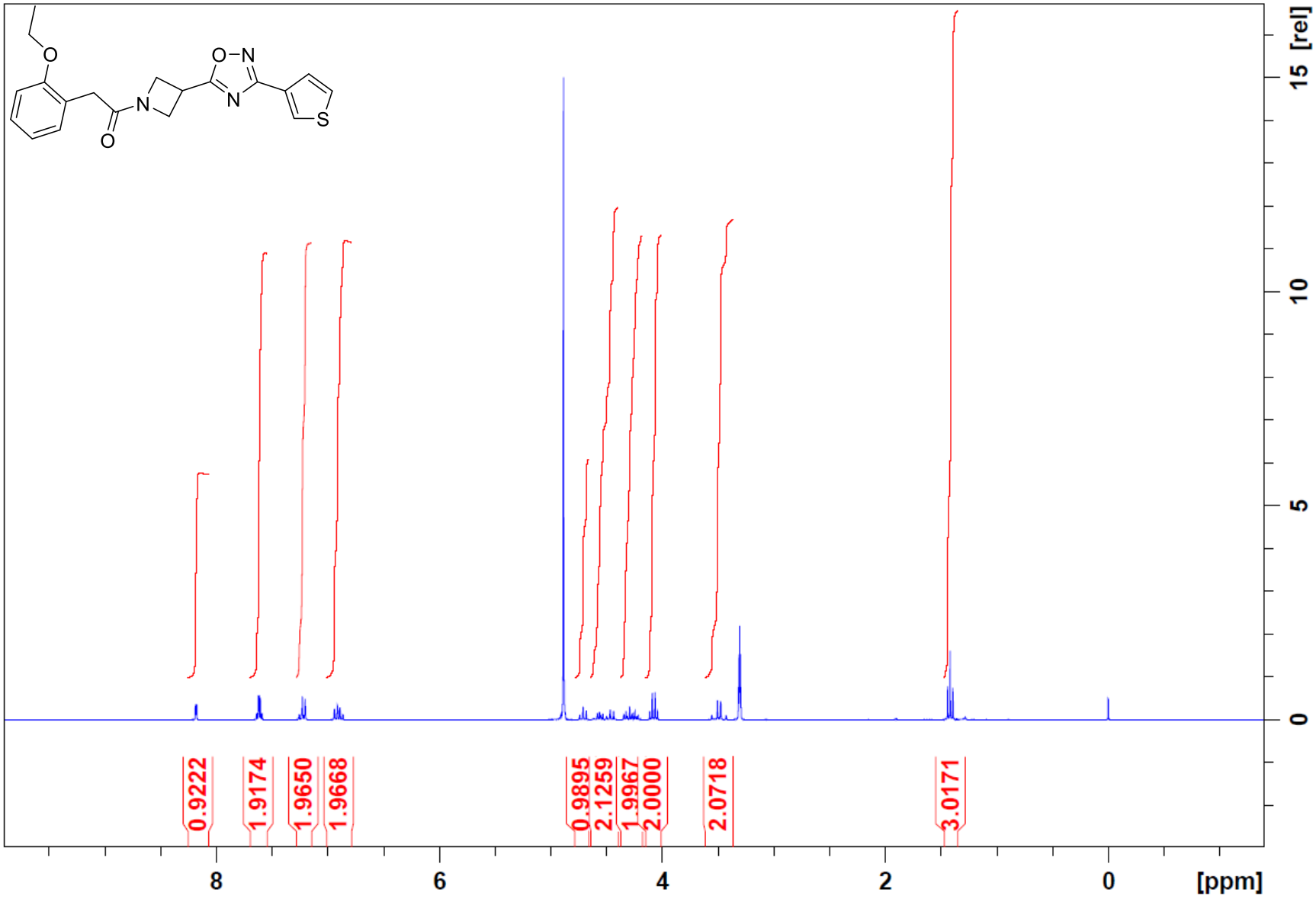
Analog **33** – ^{1}H NMR



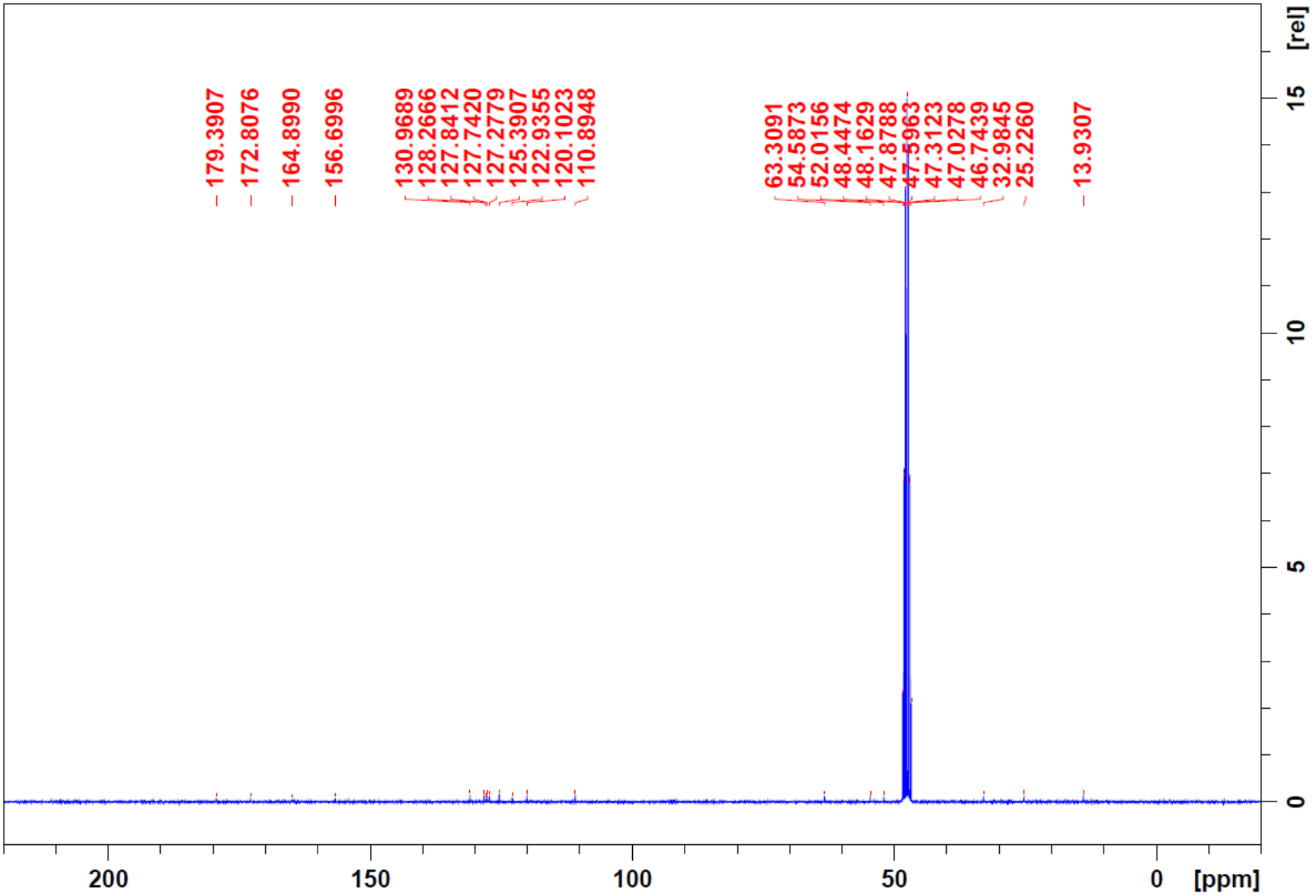
Analog **33** – ^{13}C NMR



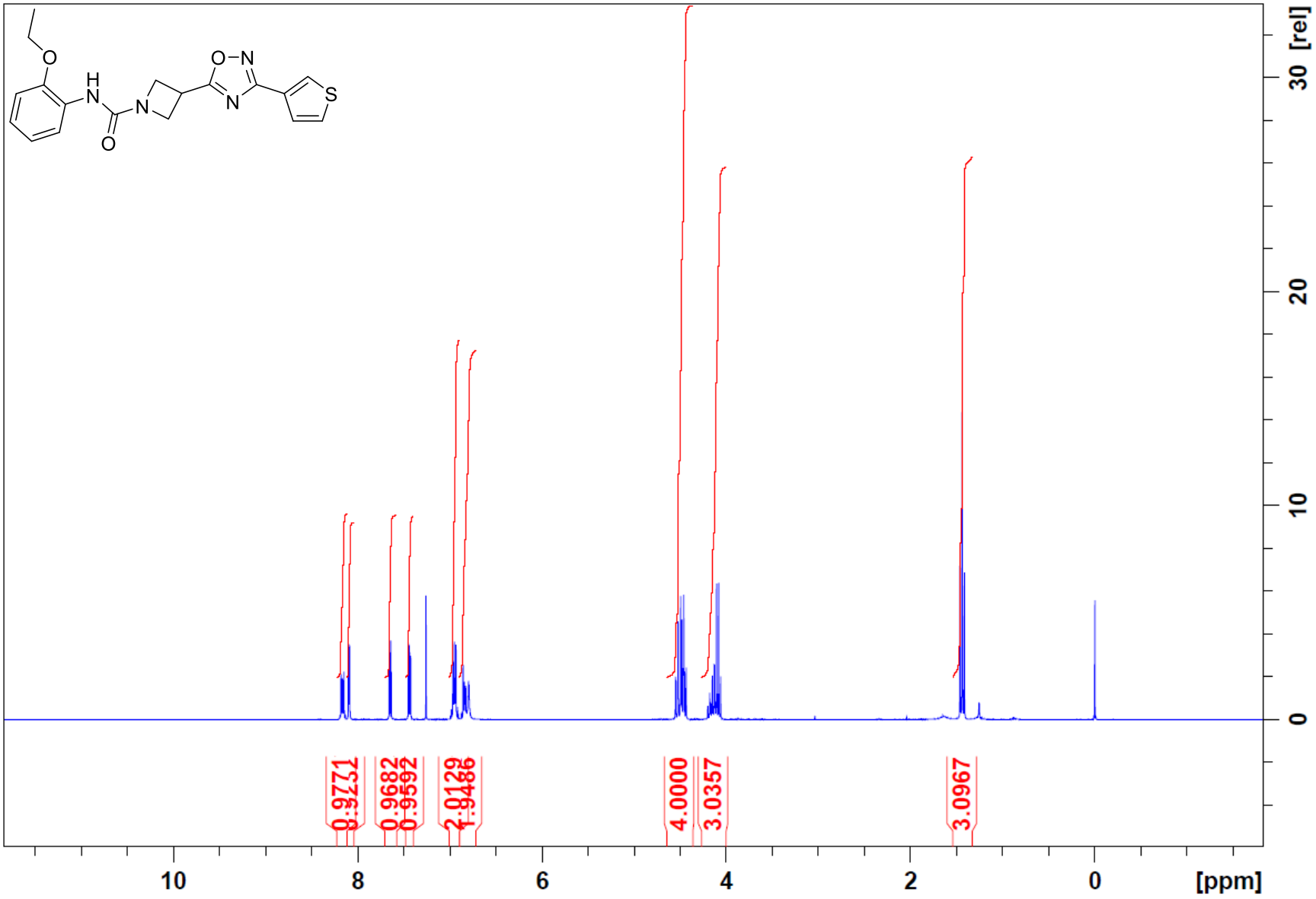
Analog **34** – ^{1}H NMR



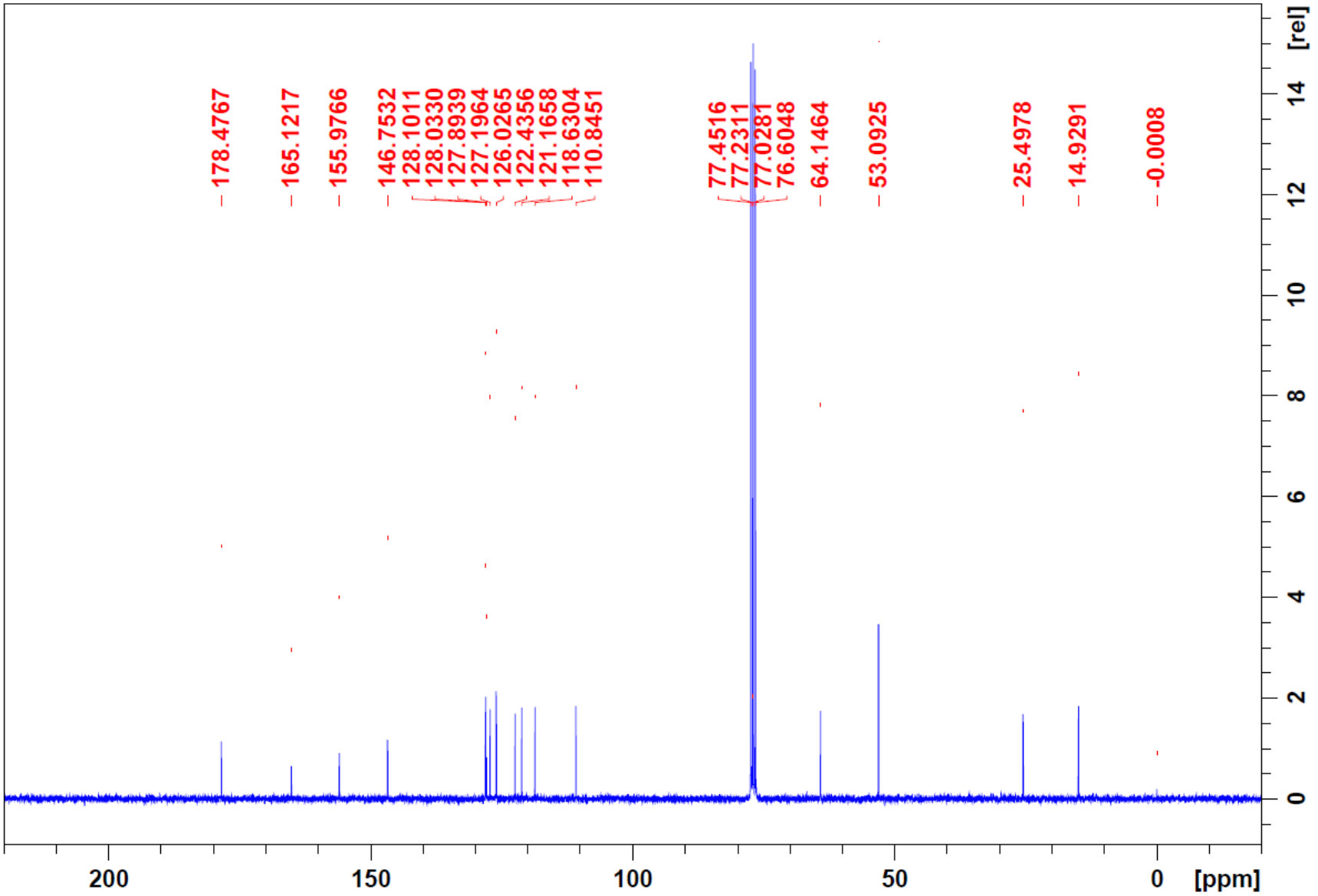
Analog **34** – ^{13}C NMR



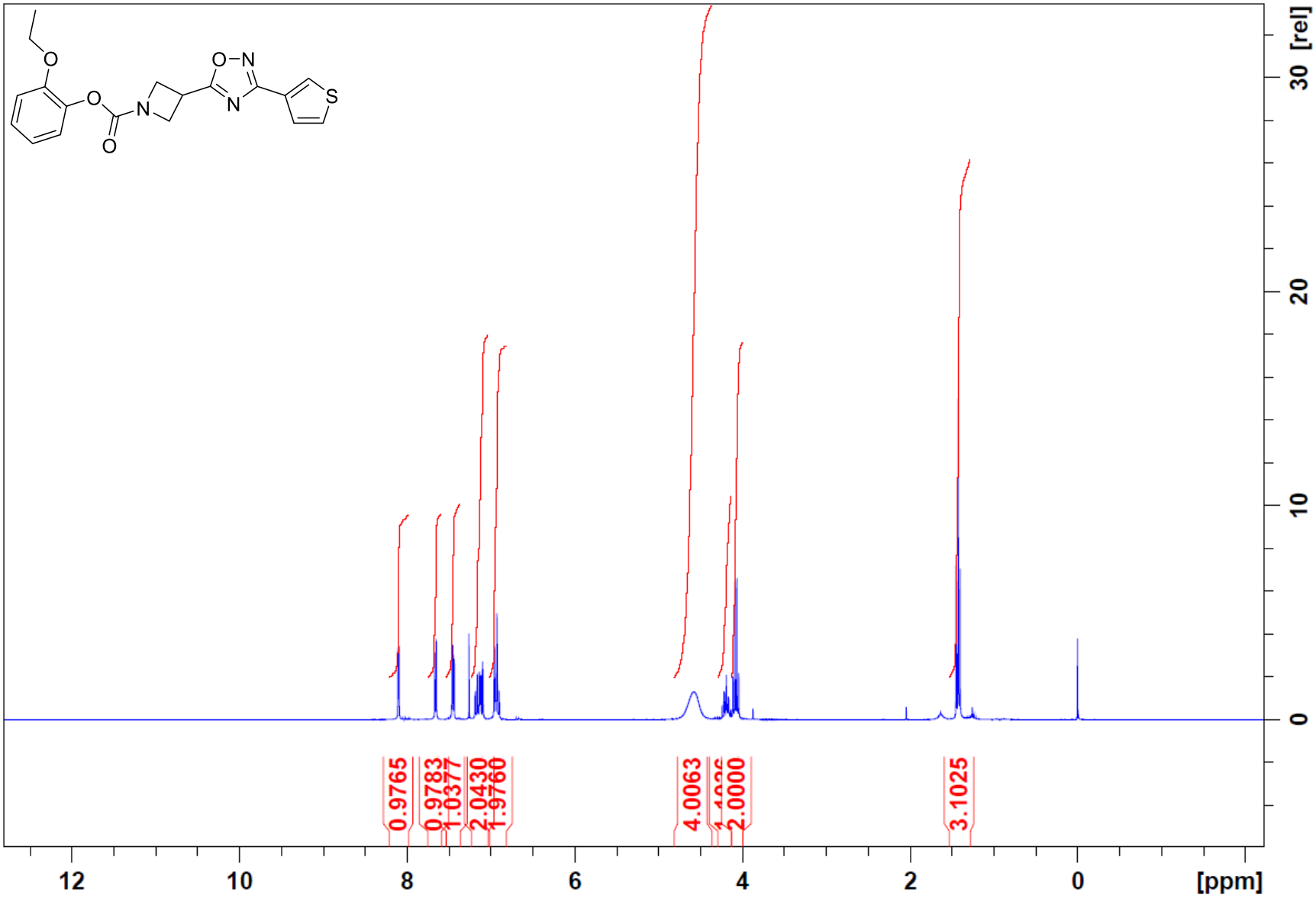
Analog **35** – ^{1}H NMR



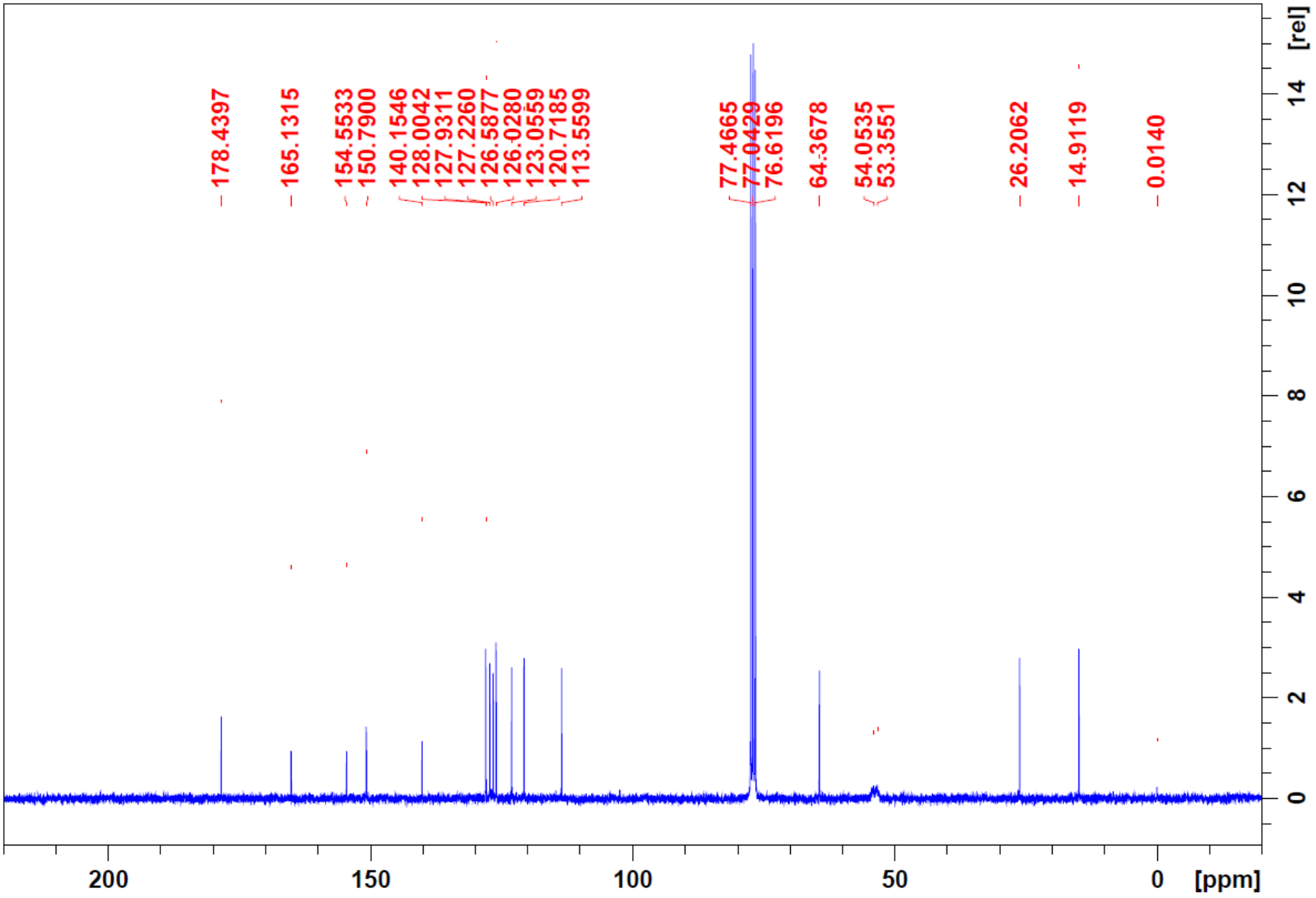
Analog **35** – ^{13}C NMR



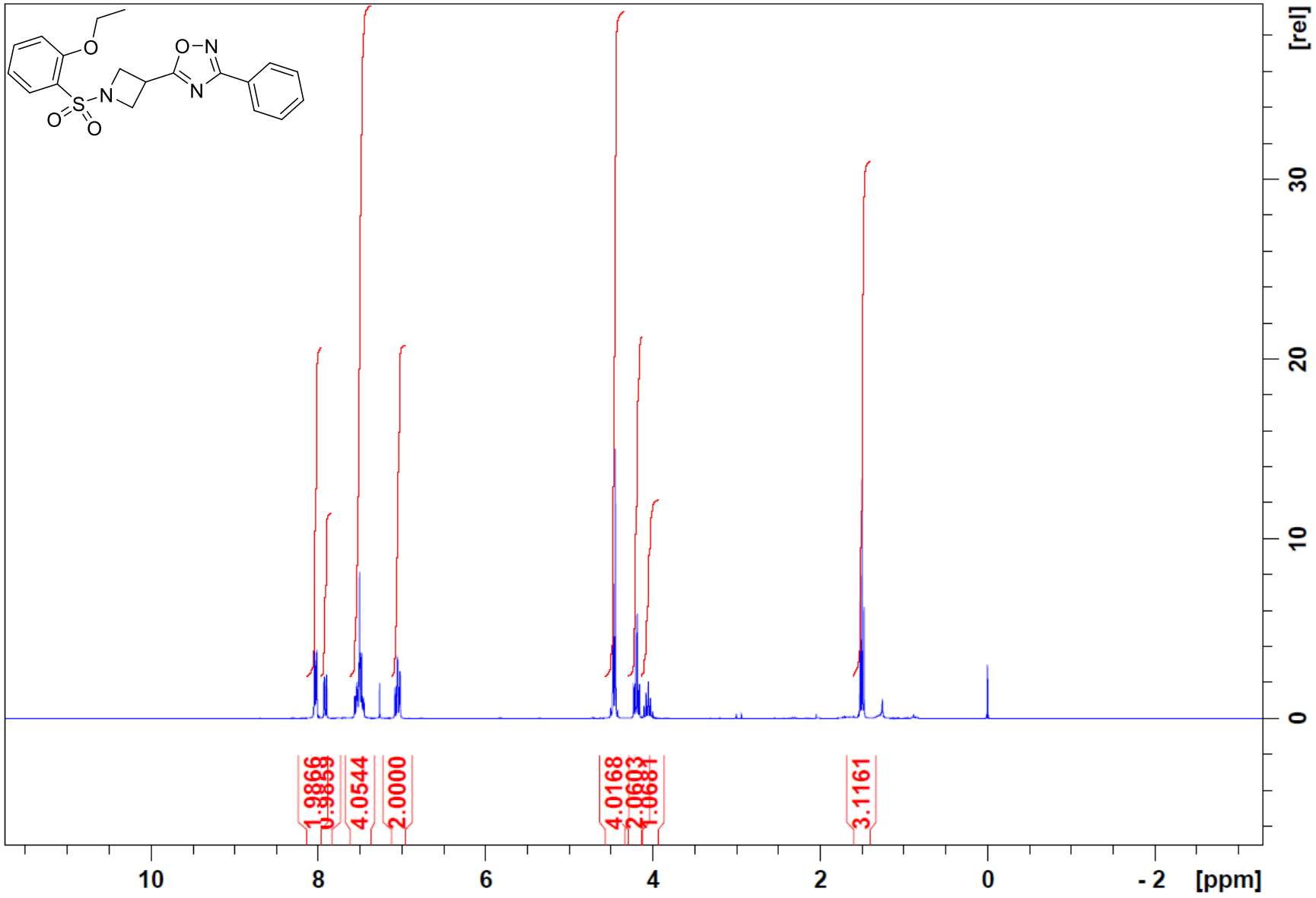
Analog **36** – ^{1}H NMR



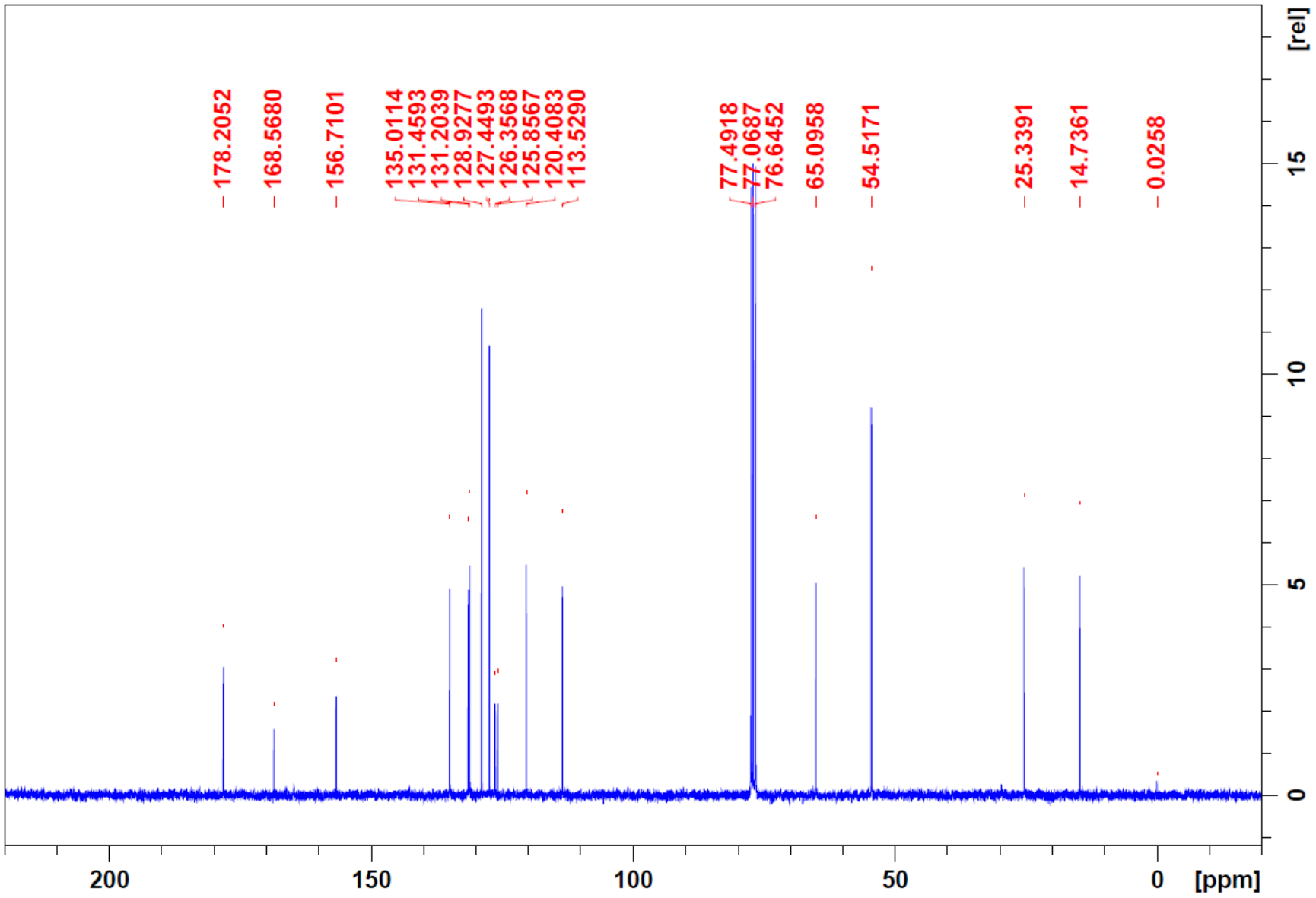
Analog **36** – ^{13}C NMR



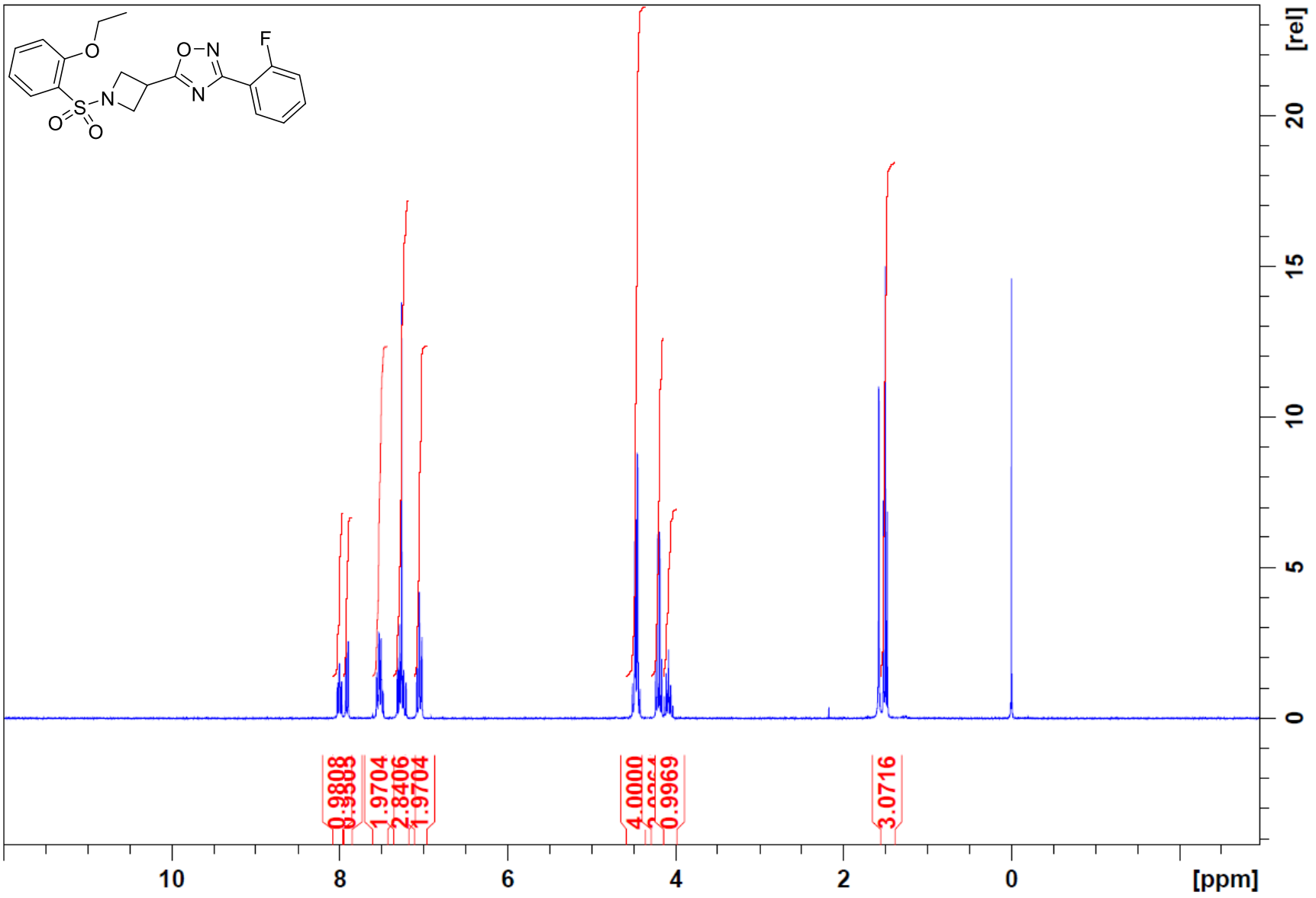
Analog **40** – ^{1}H NMR



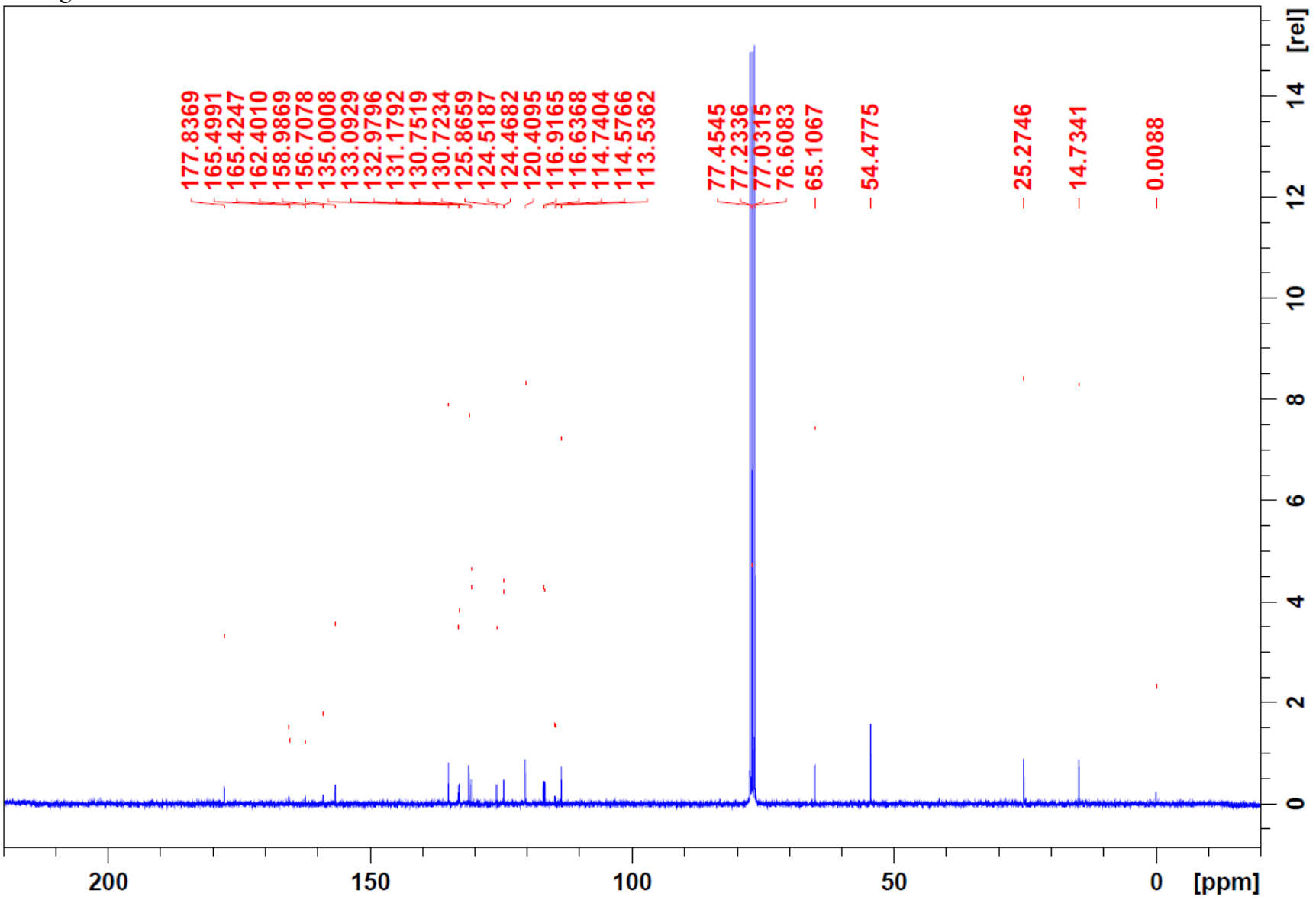
Analog **40** – ^{13}C NMR



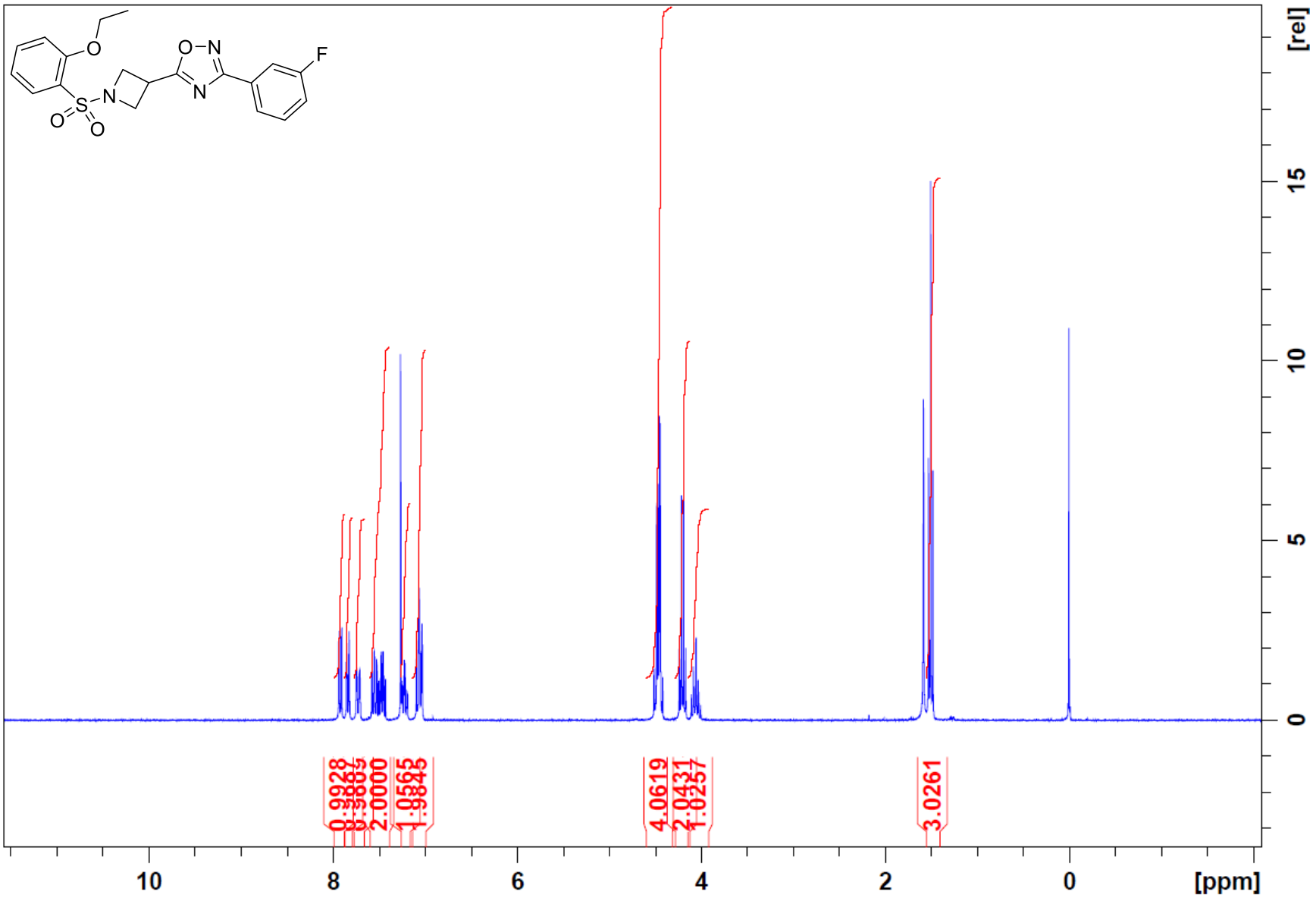
Analog **41** – ^{1}H NMR



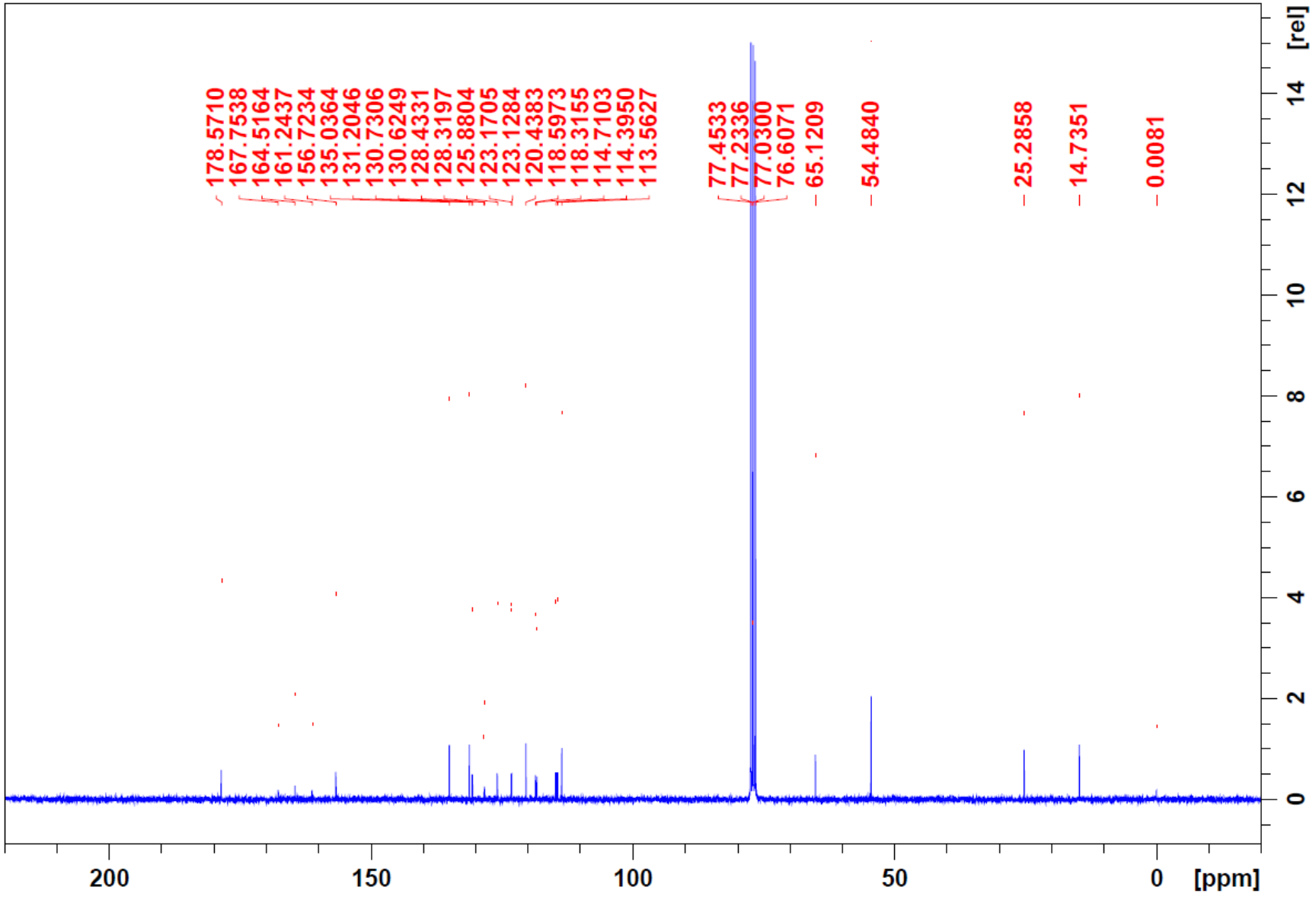
Analog **41** – ^{13}C NMR



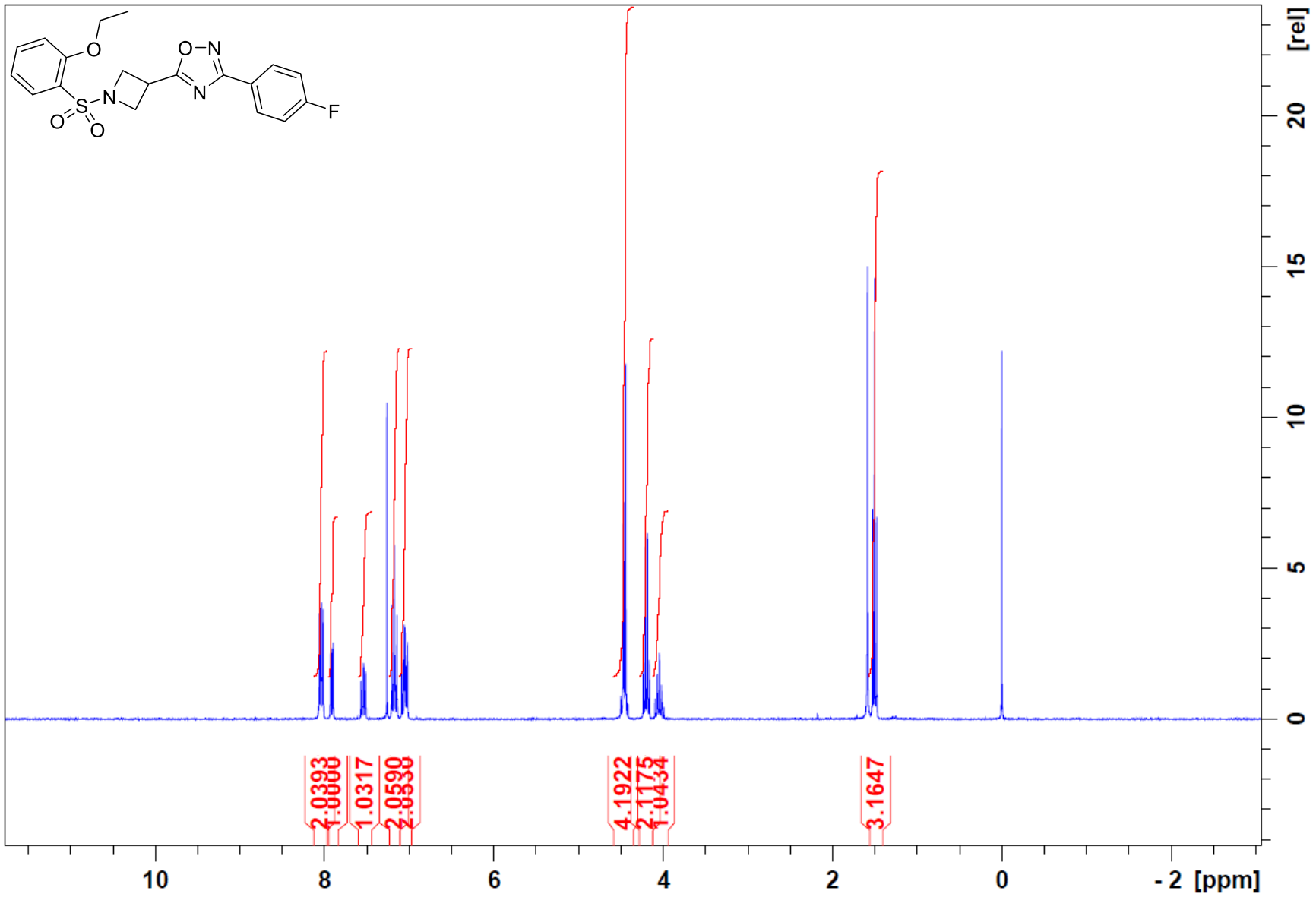
Analog **42** – ^{1}H NMR



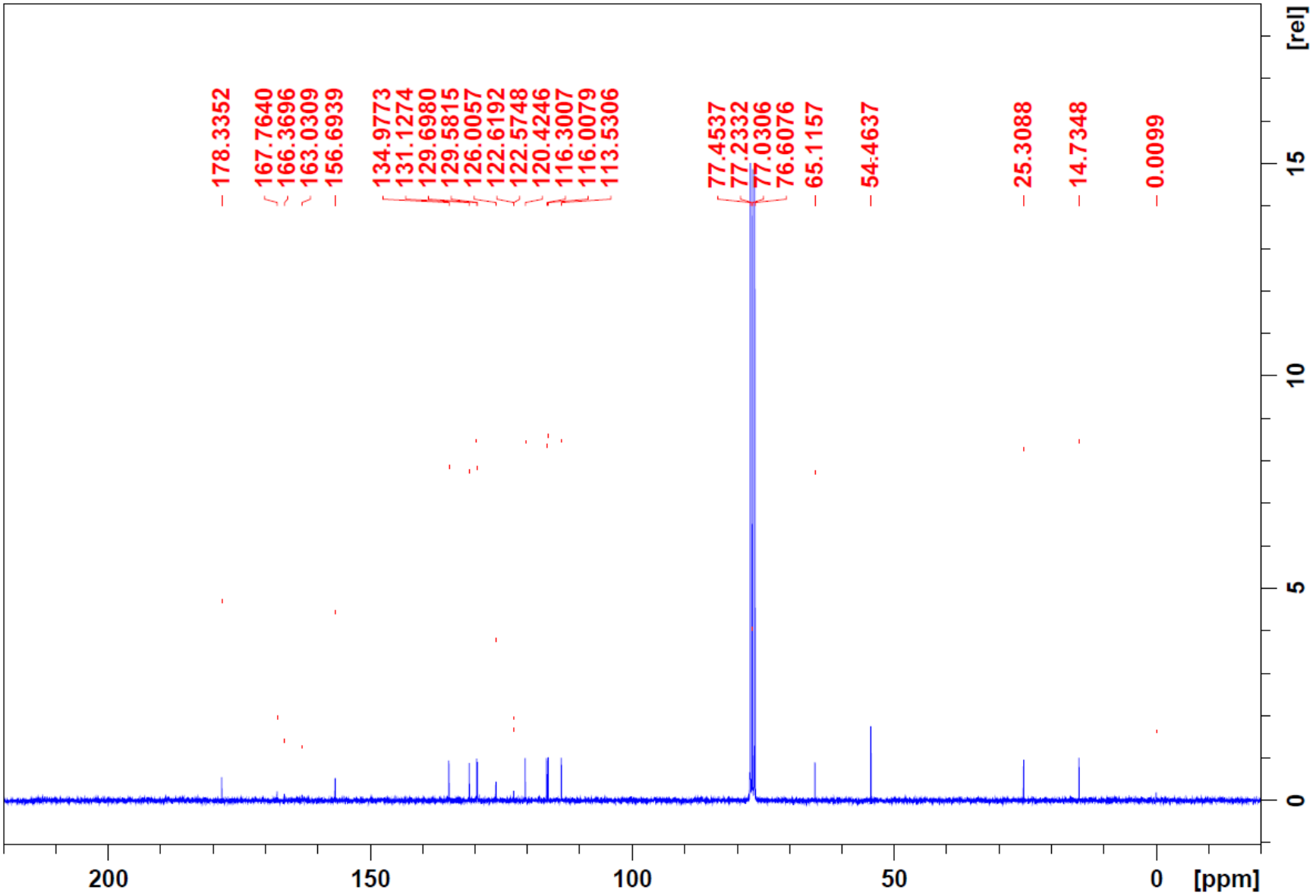
Analog **42** – ^{13}C NMR



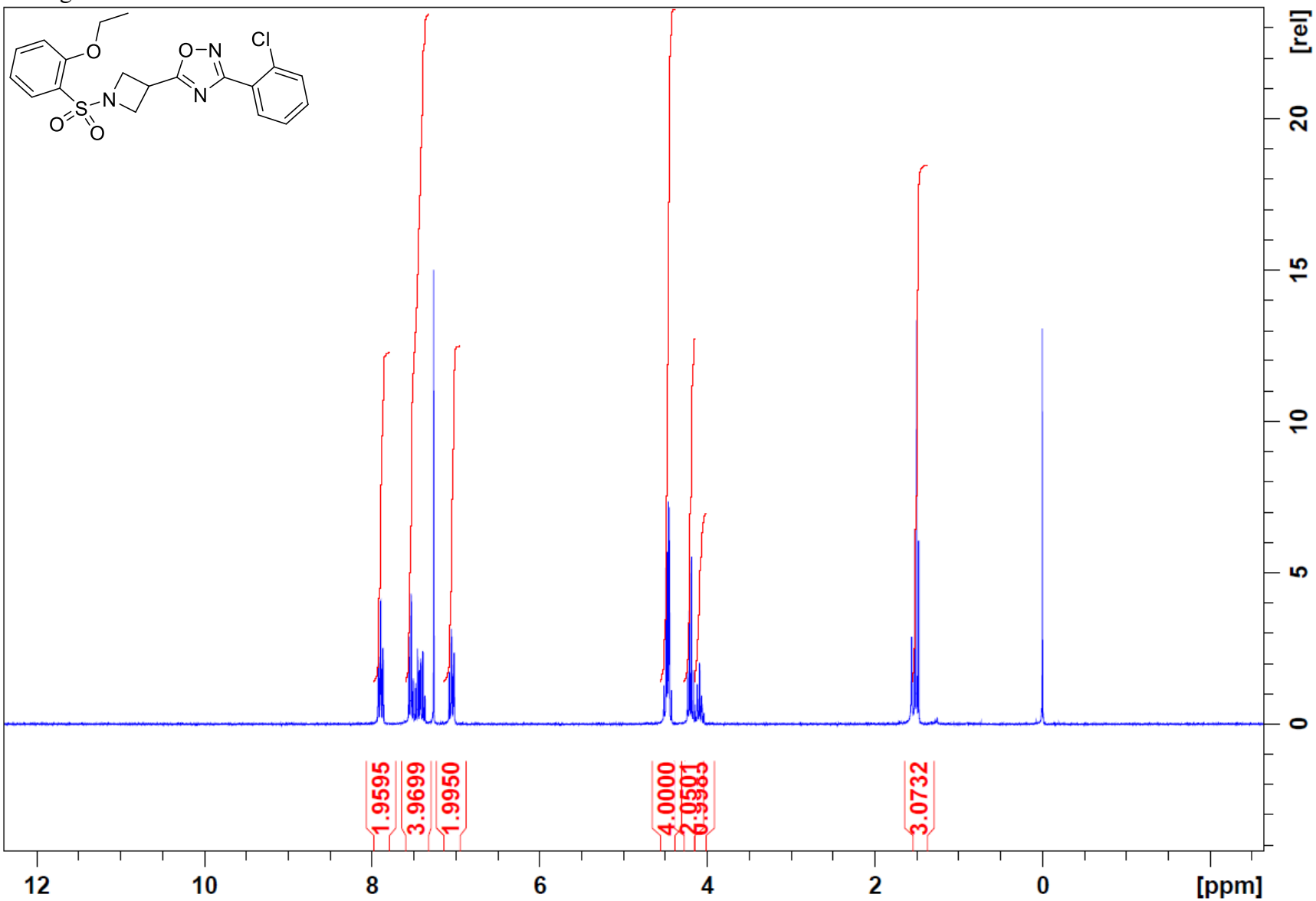
Analog **43** – ^{1}H NMR



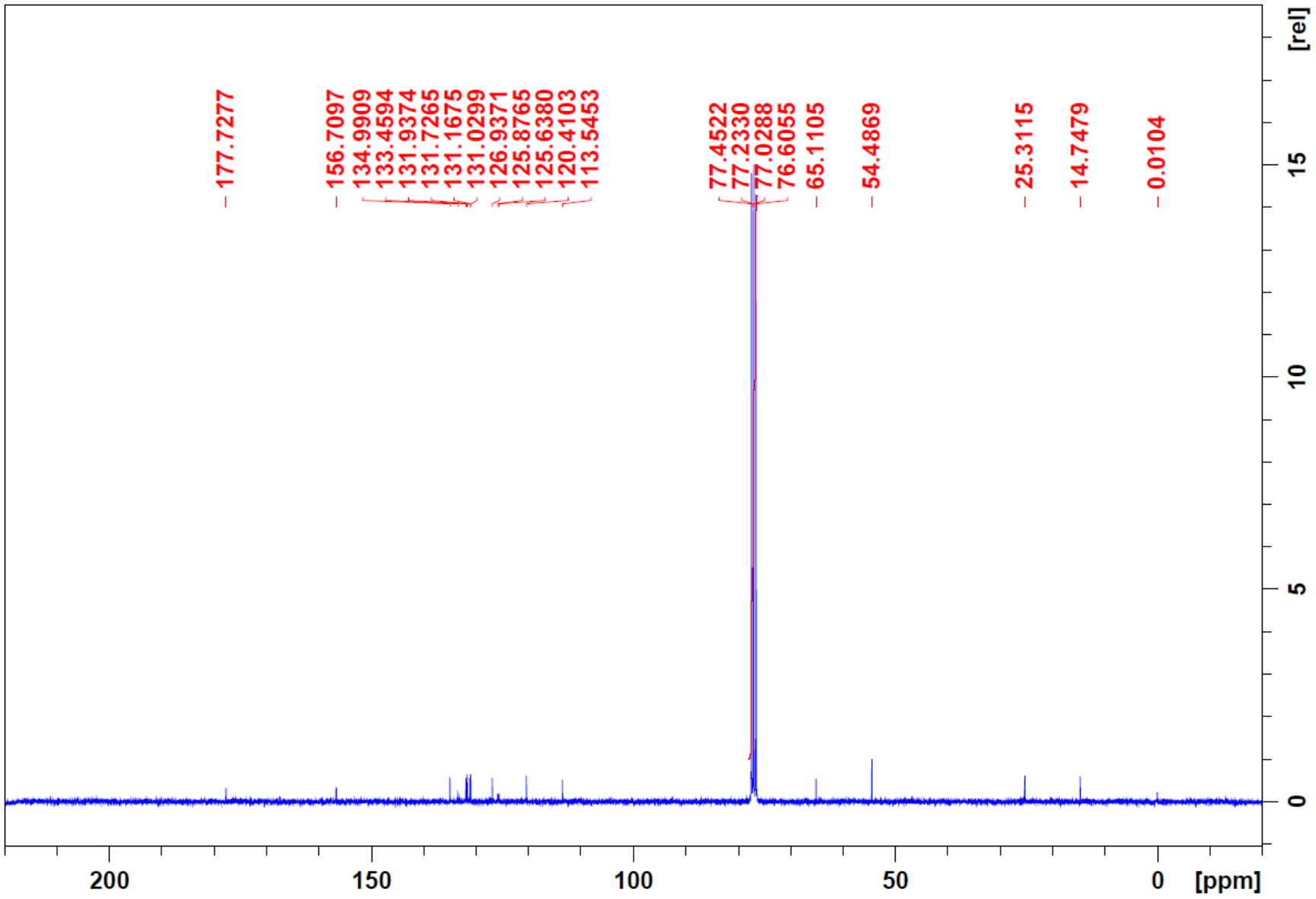
Analog **43** – ^{13}C NMR



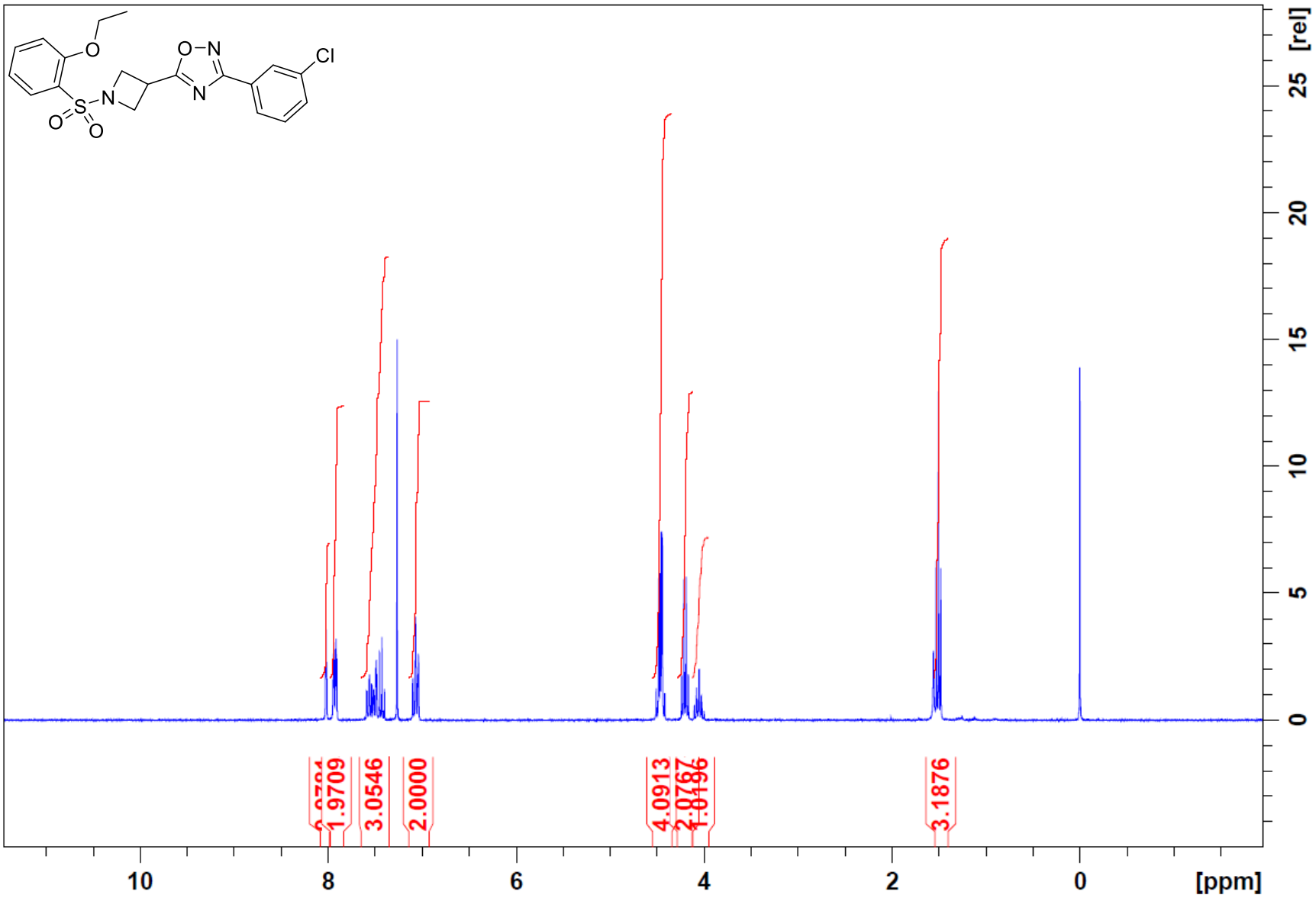
Analog **44** – ^{1}H NMR



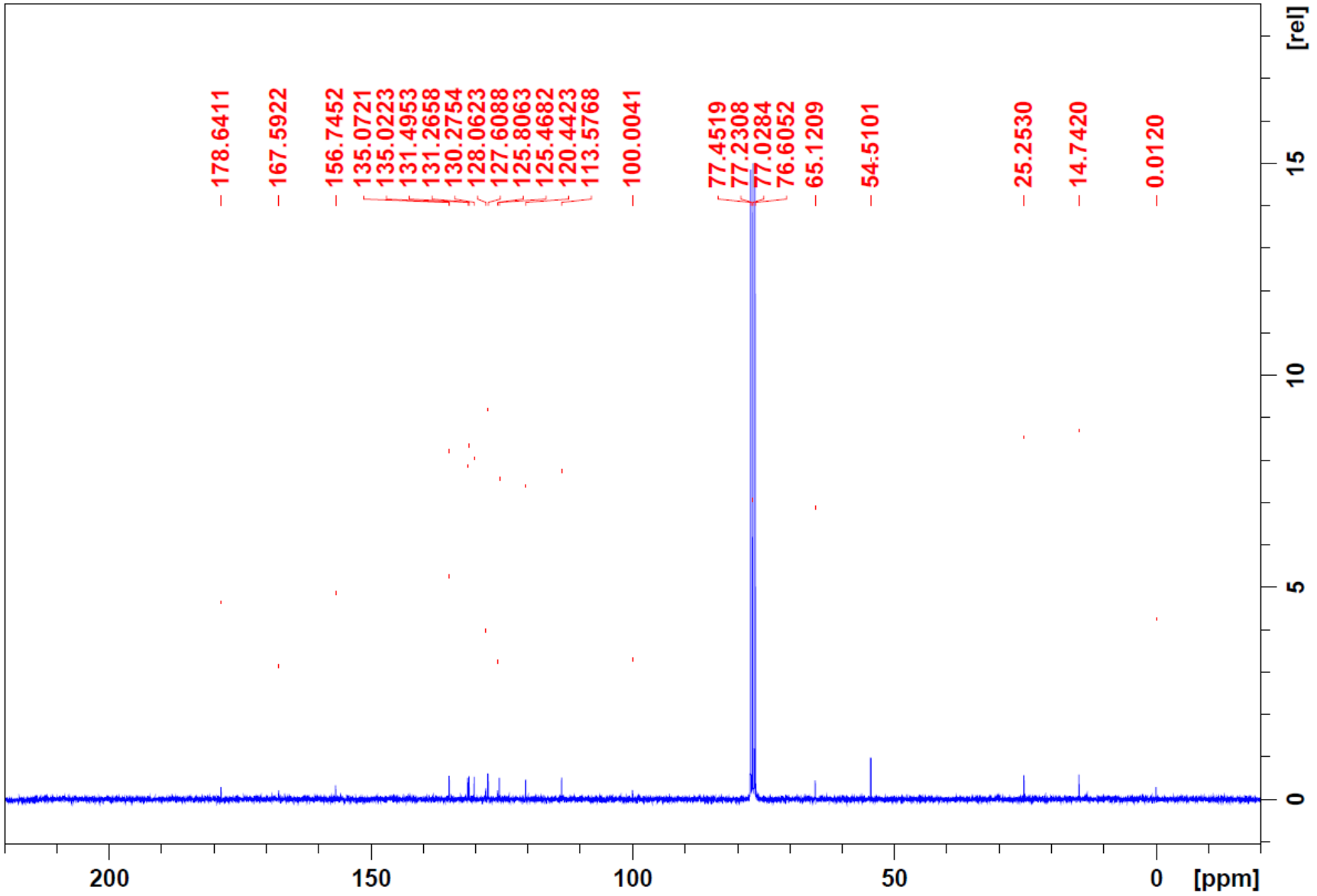
Analog **44** – ^{13}C NMR



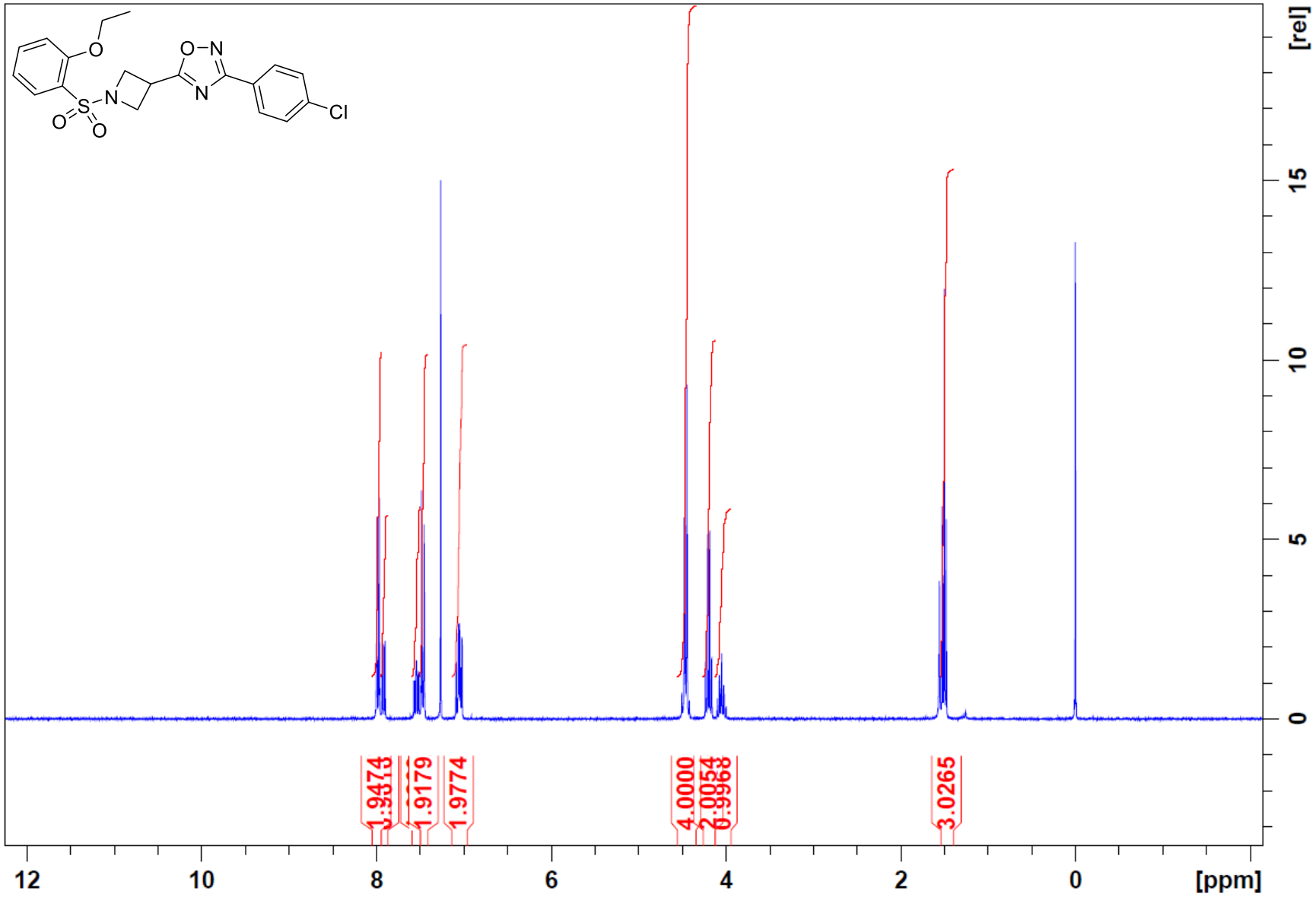
Analog **45** – ^{1}H NMR



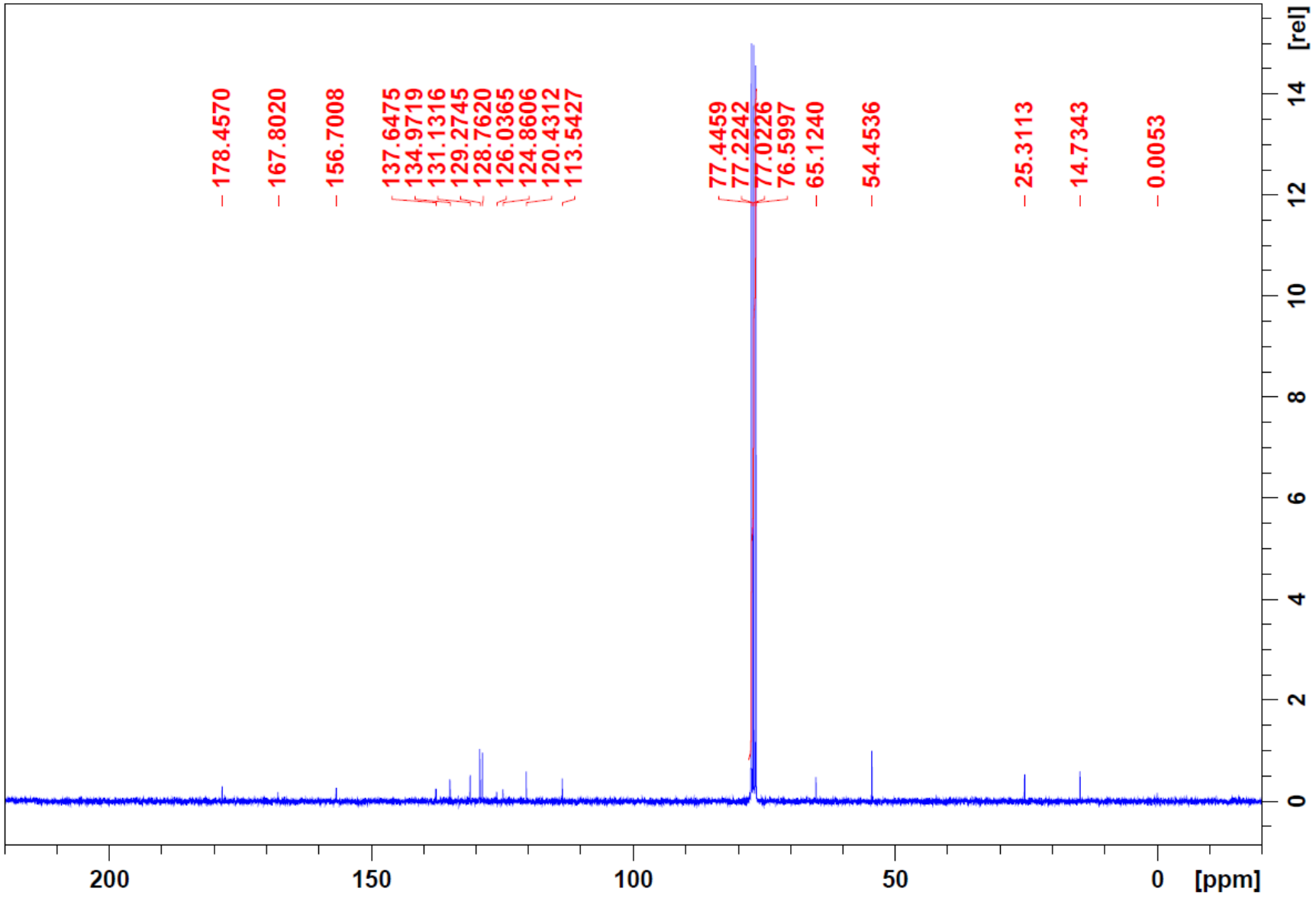
Analog **45** – ^{13}C NMR



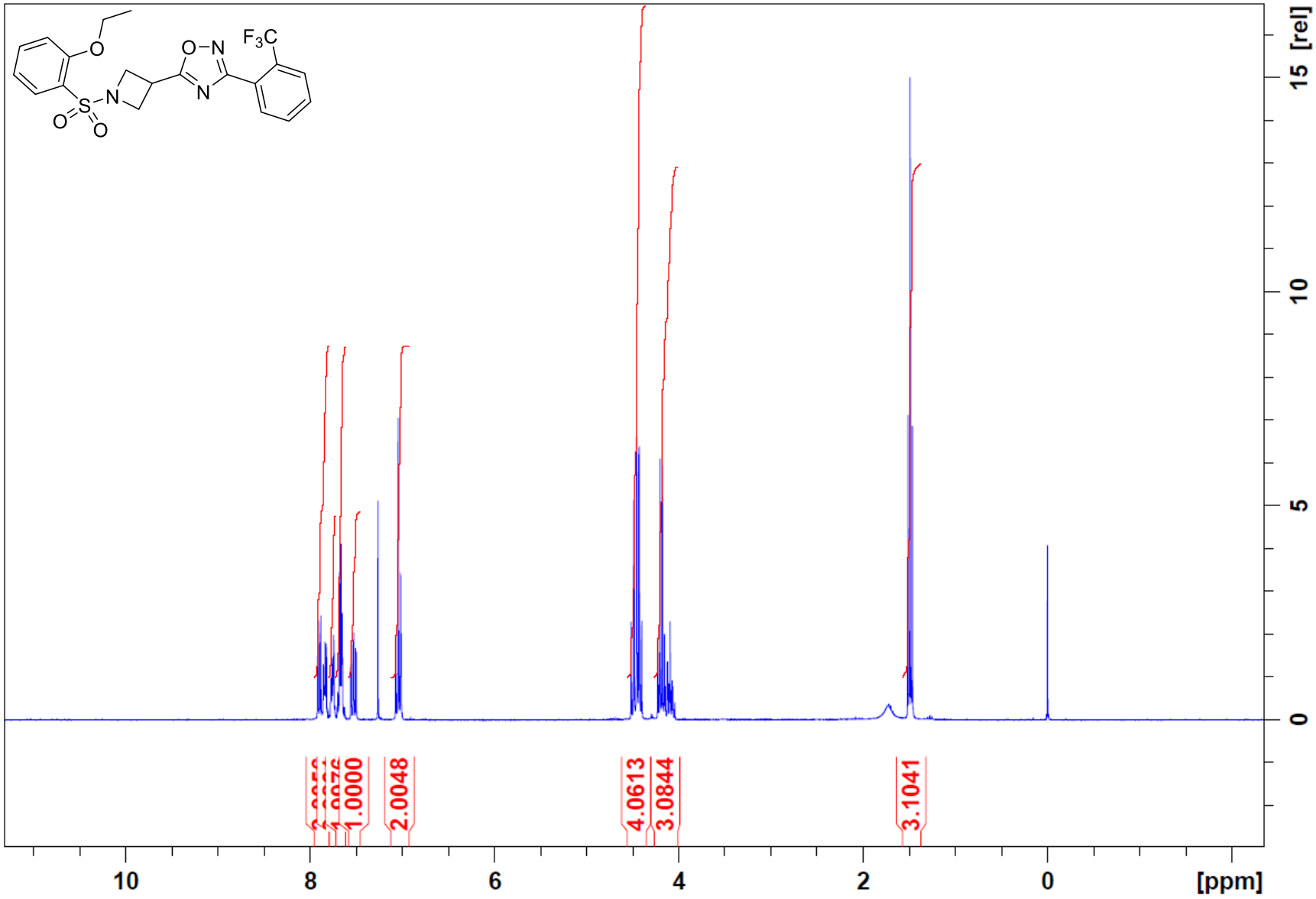
Analog **46** – ^{1}H NMR



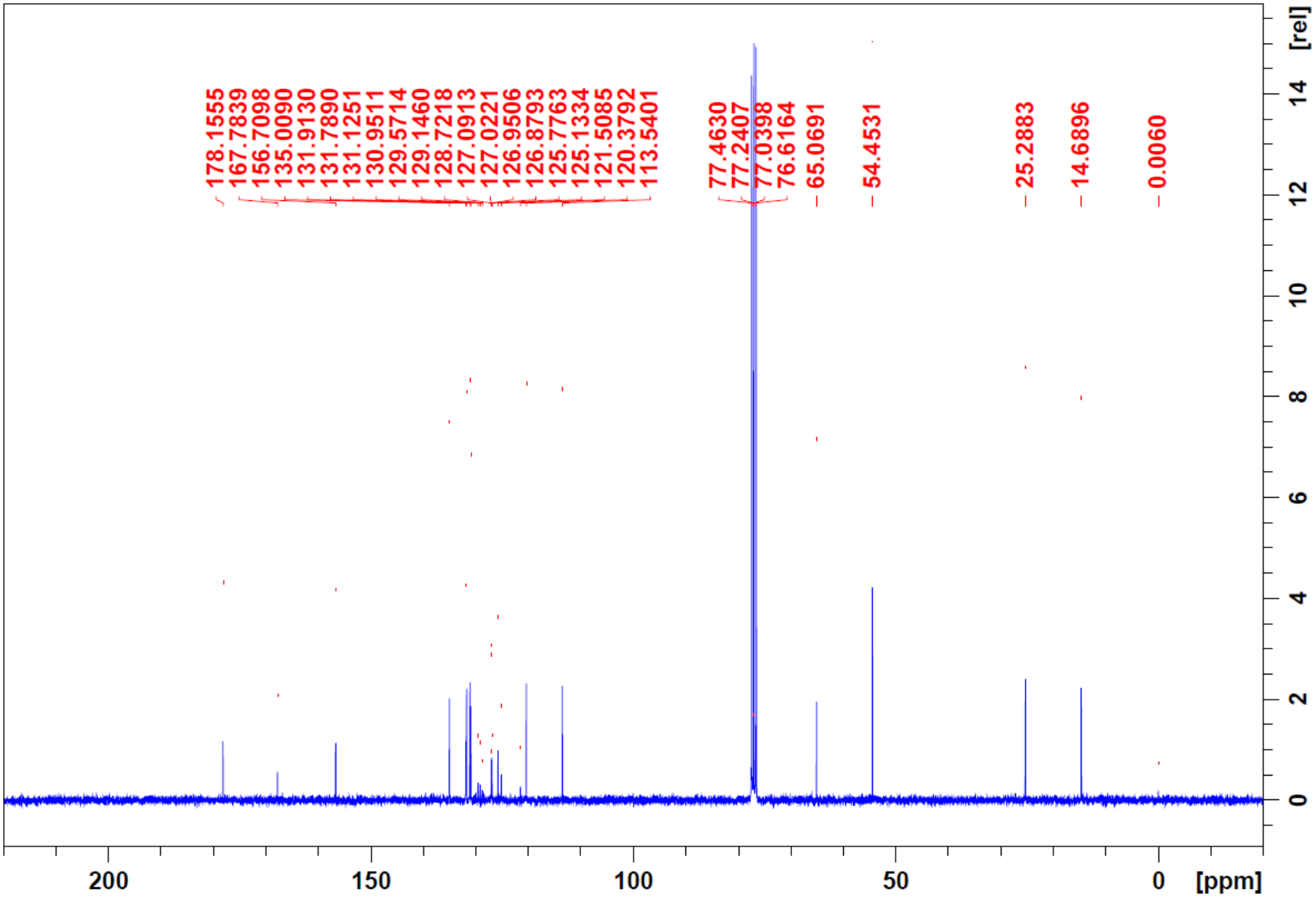
Analog **46** – ^{13}C NMR



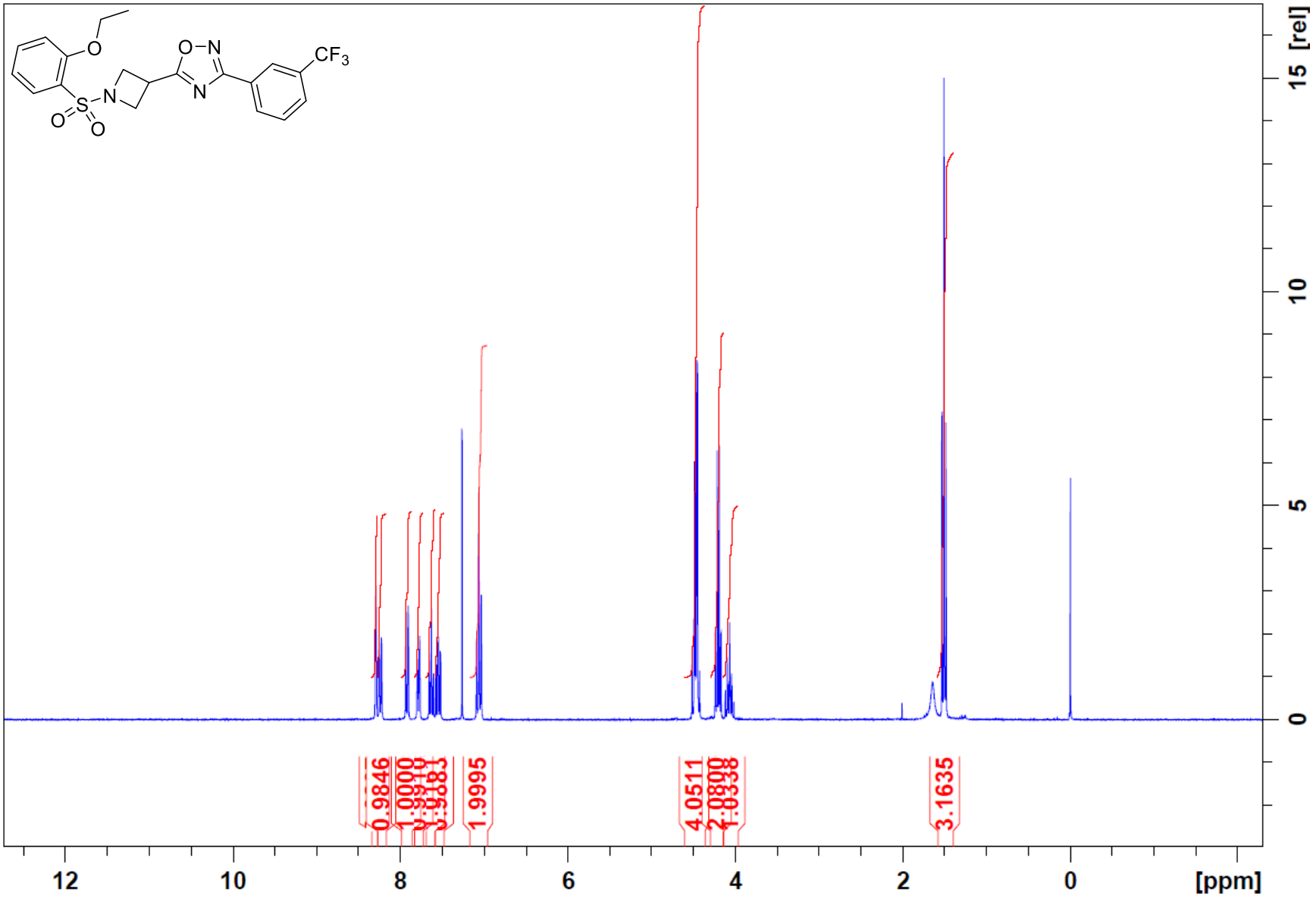
Analog **47** – ^{1}H NMR



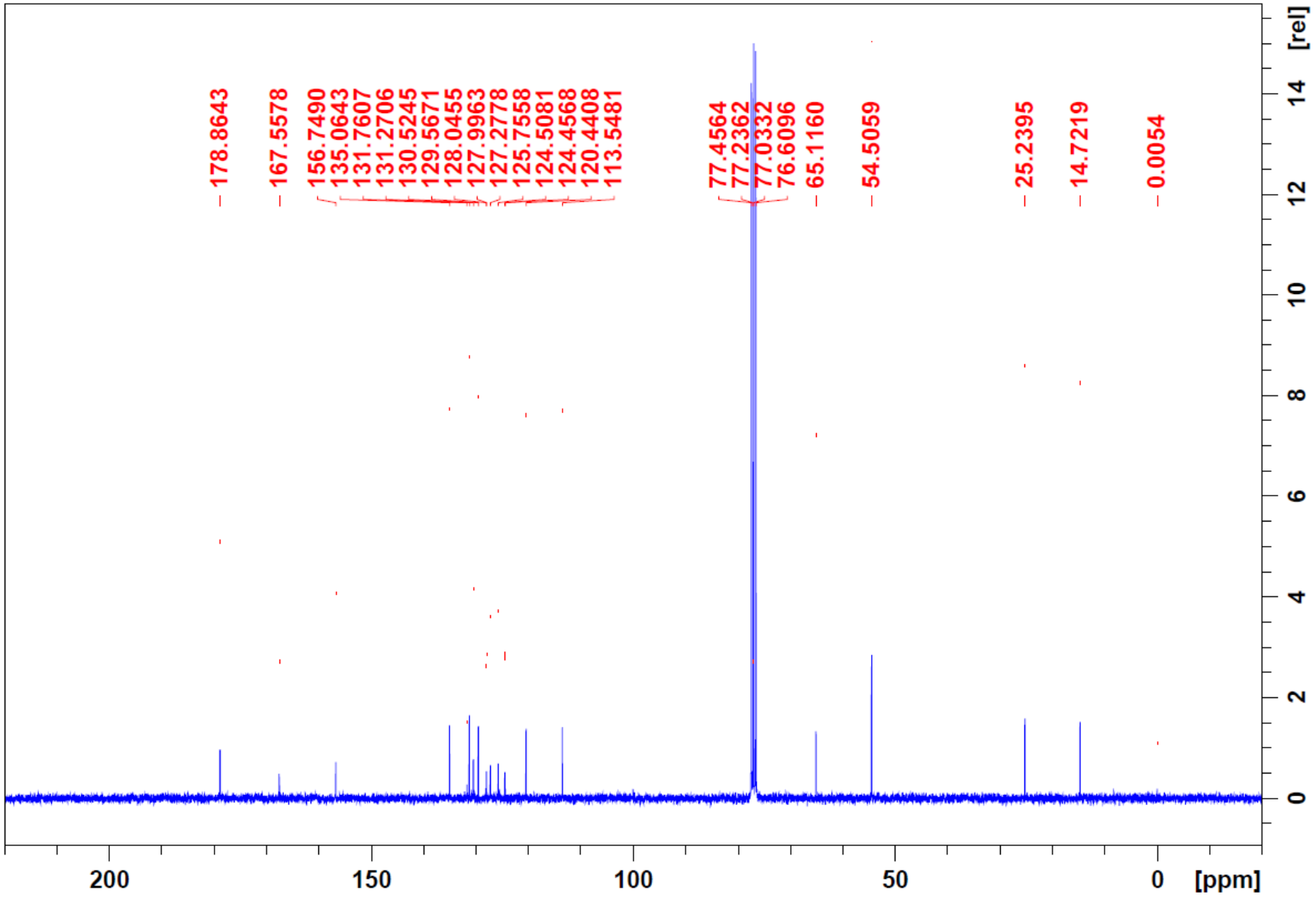
Analog **47** – ^{13}C NMR



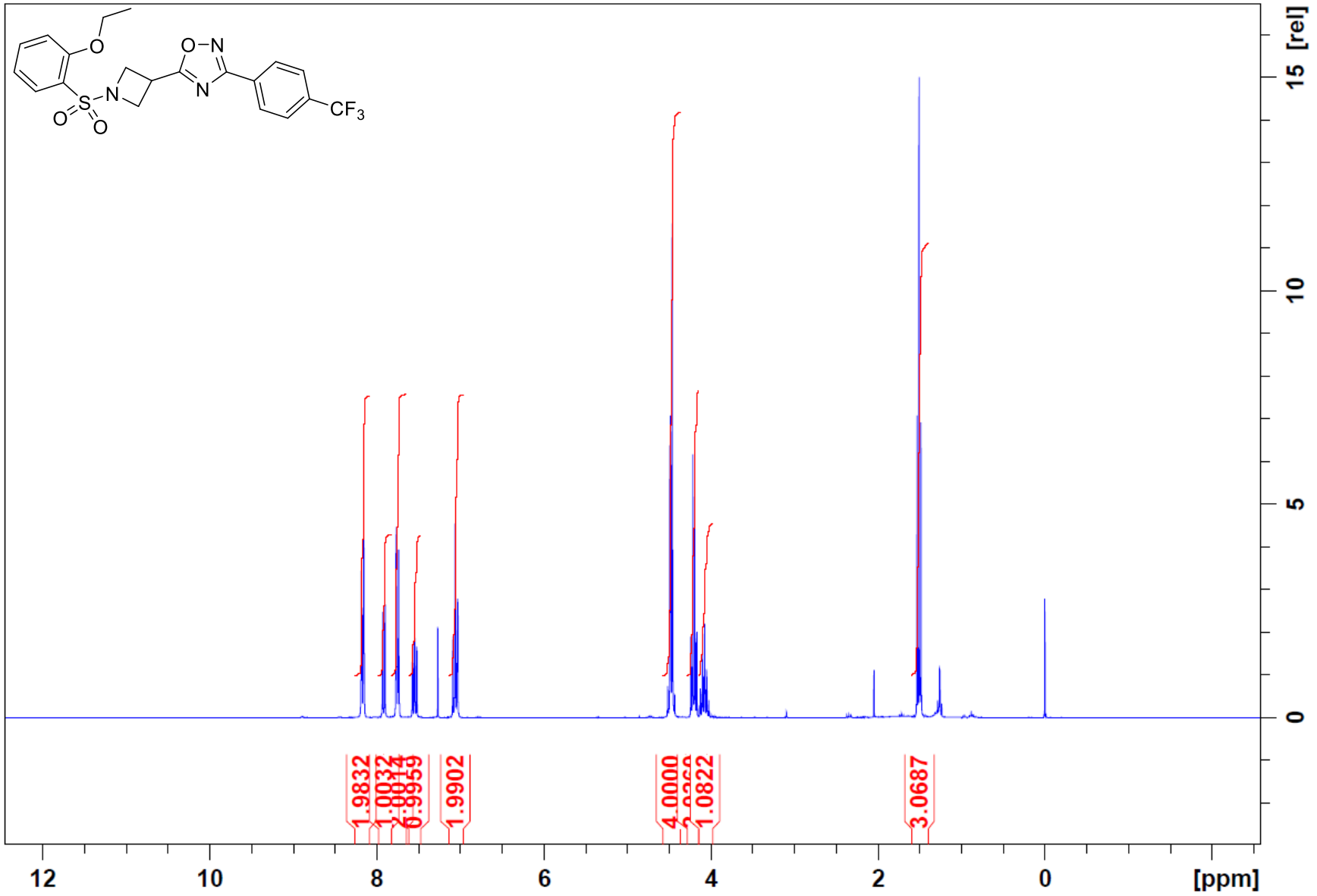
Analog **48** – ^{1}H NMR



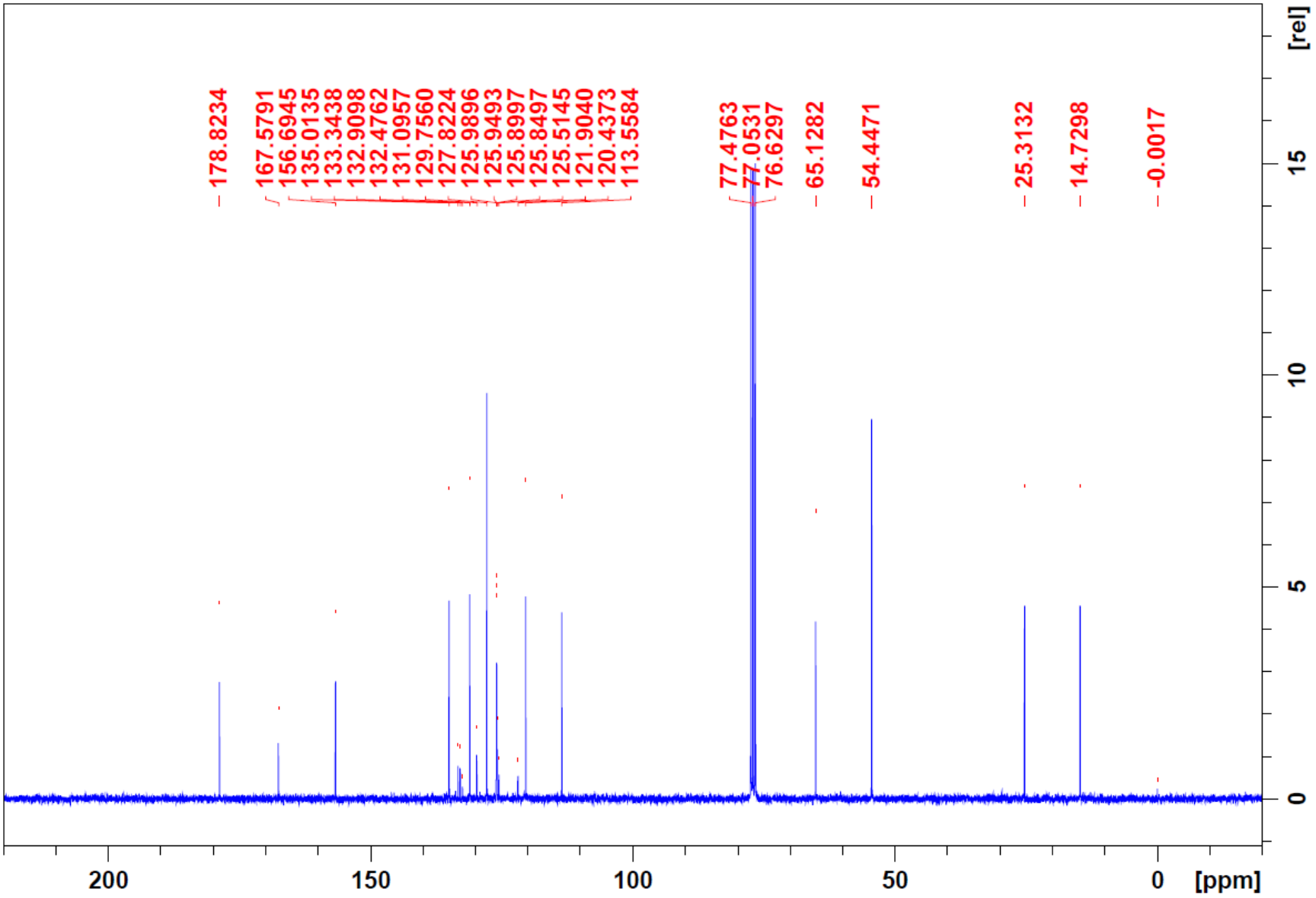
Analog **48** – ^{13}C NMR



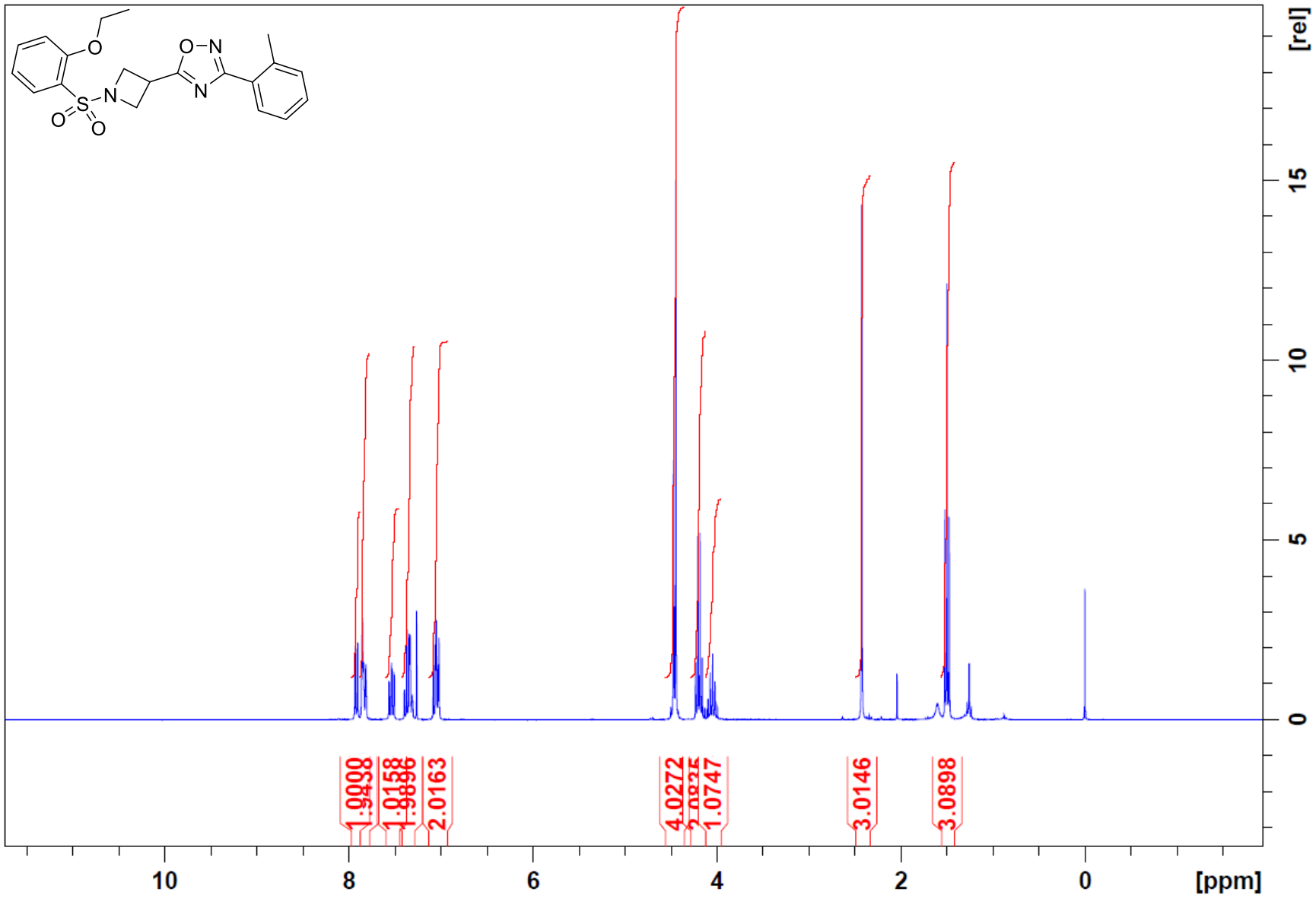
Analog **49** – ^{1}H NMR



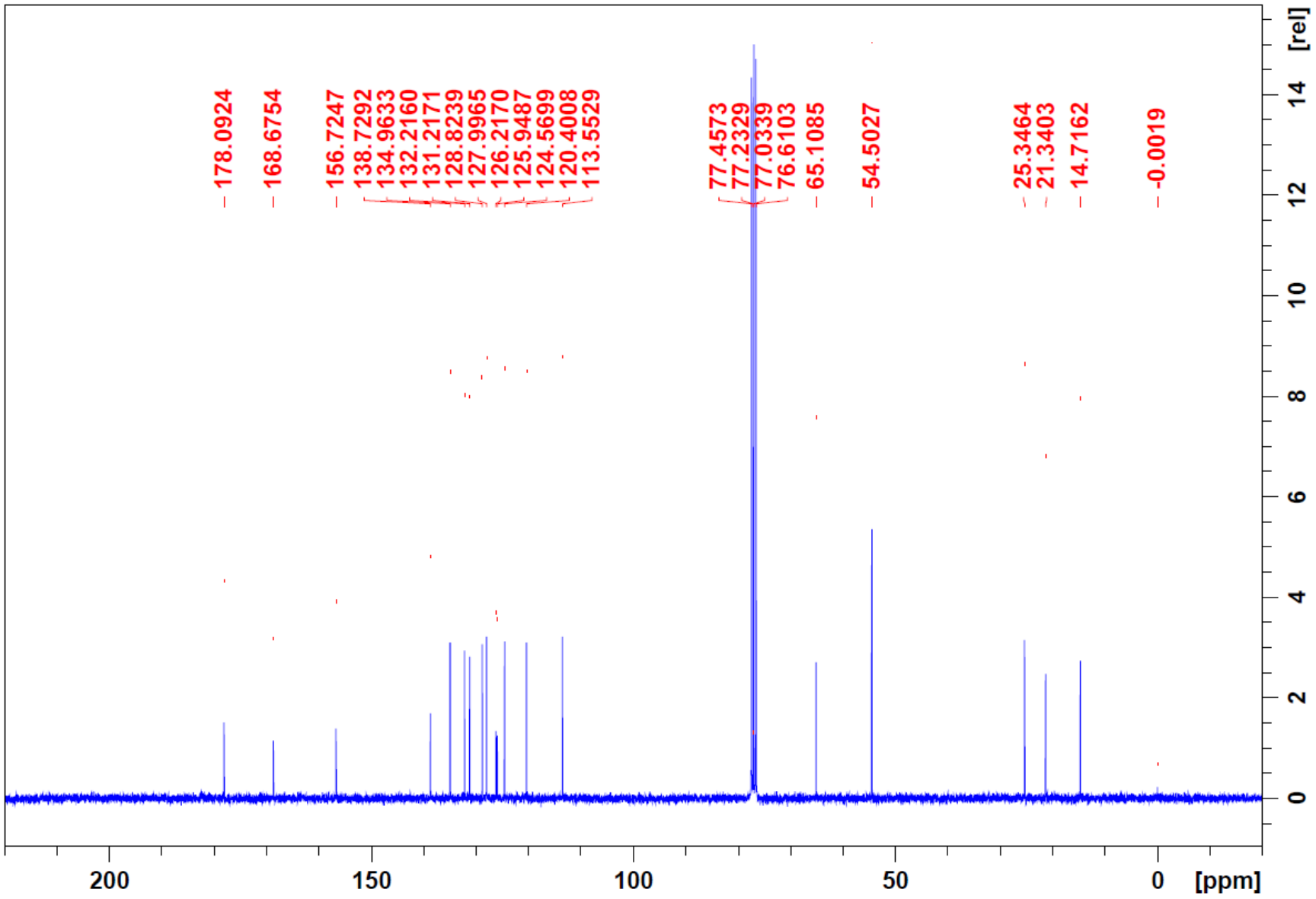
Analog **49** – ^{13}C NMR



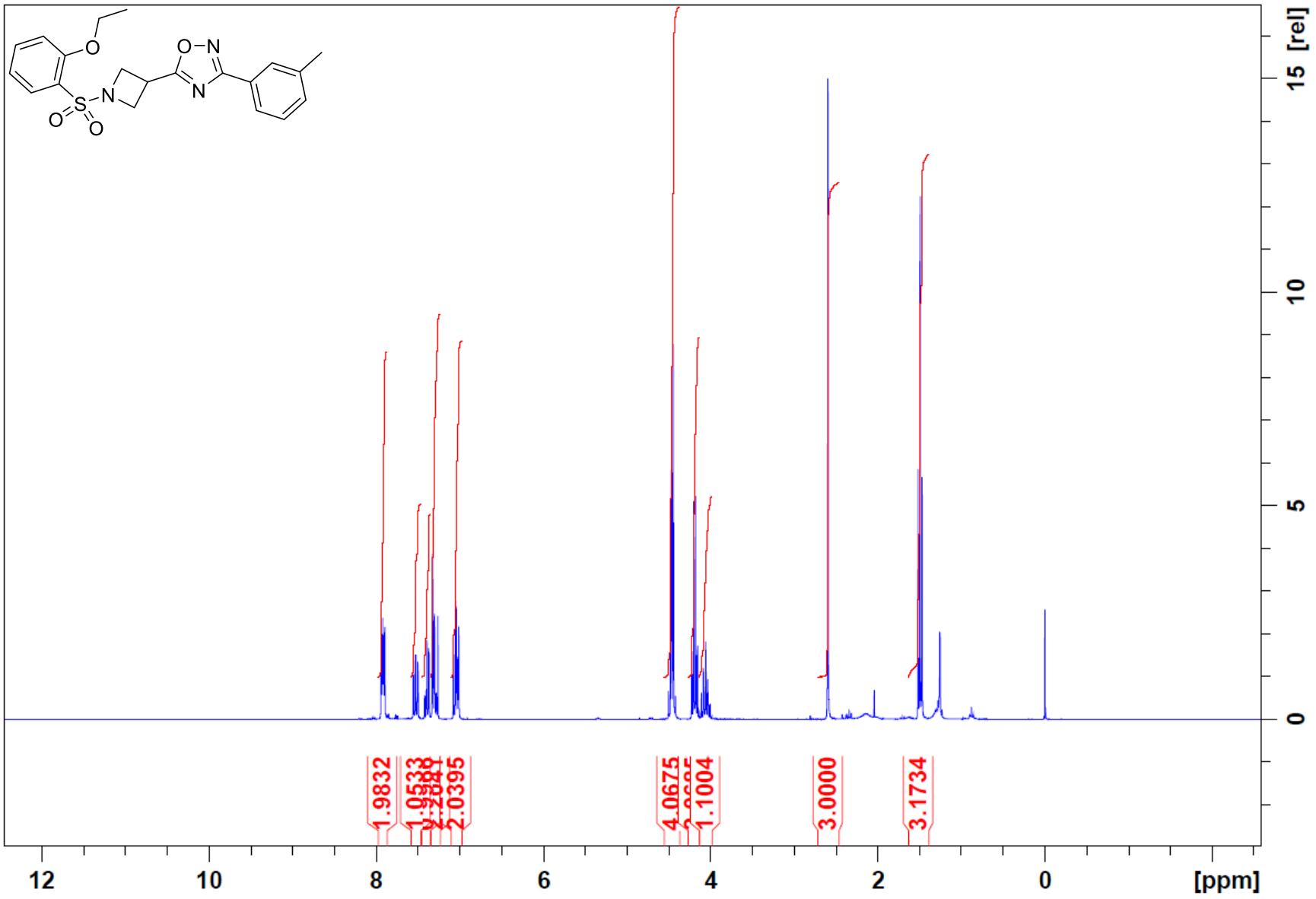
Analog **50** – ^{1}H NMR



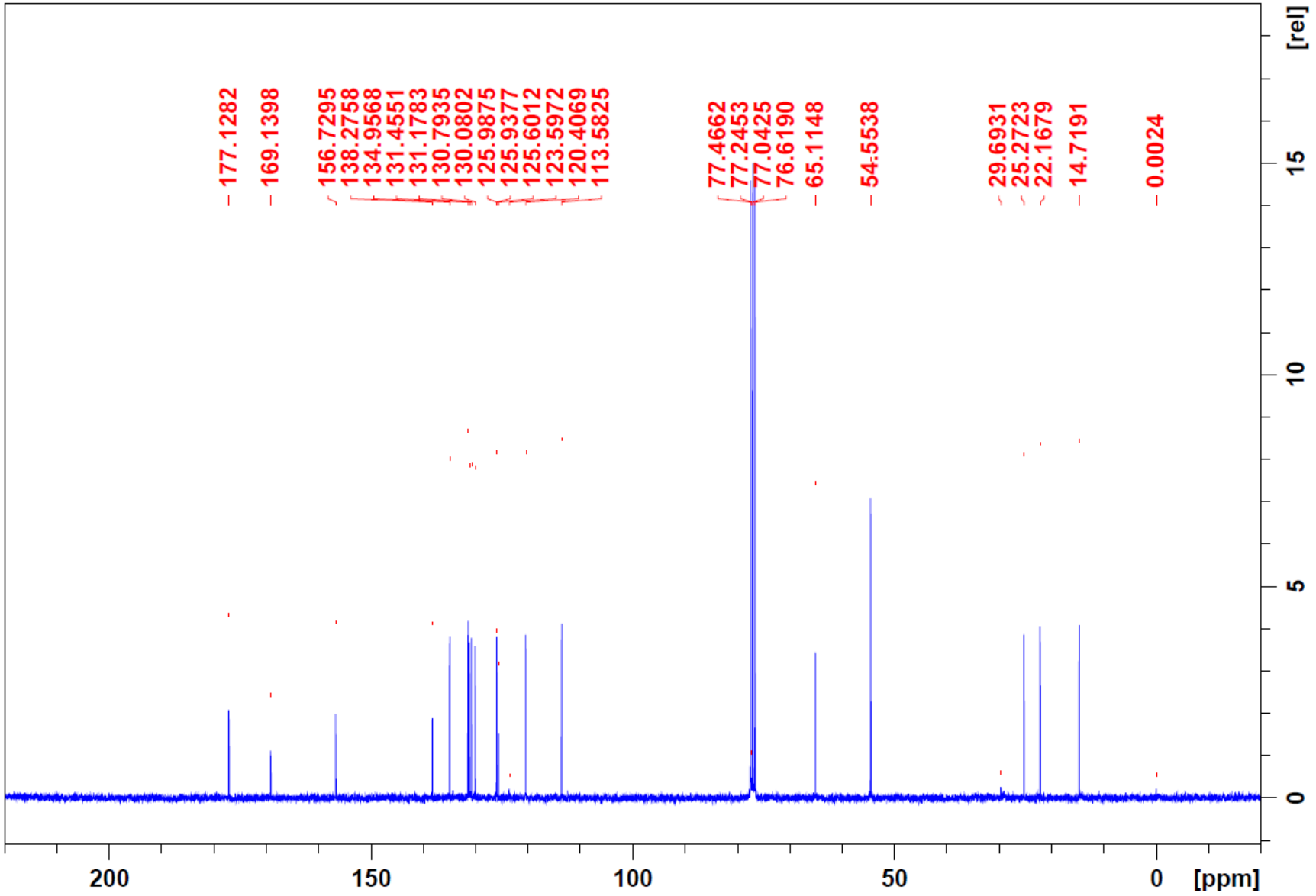
Analog **50** – ^{13}C NMR



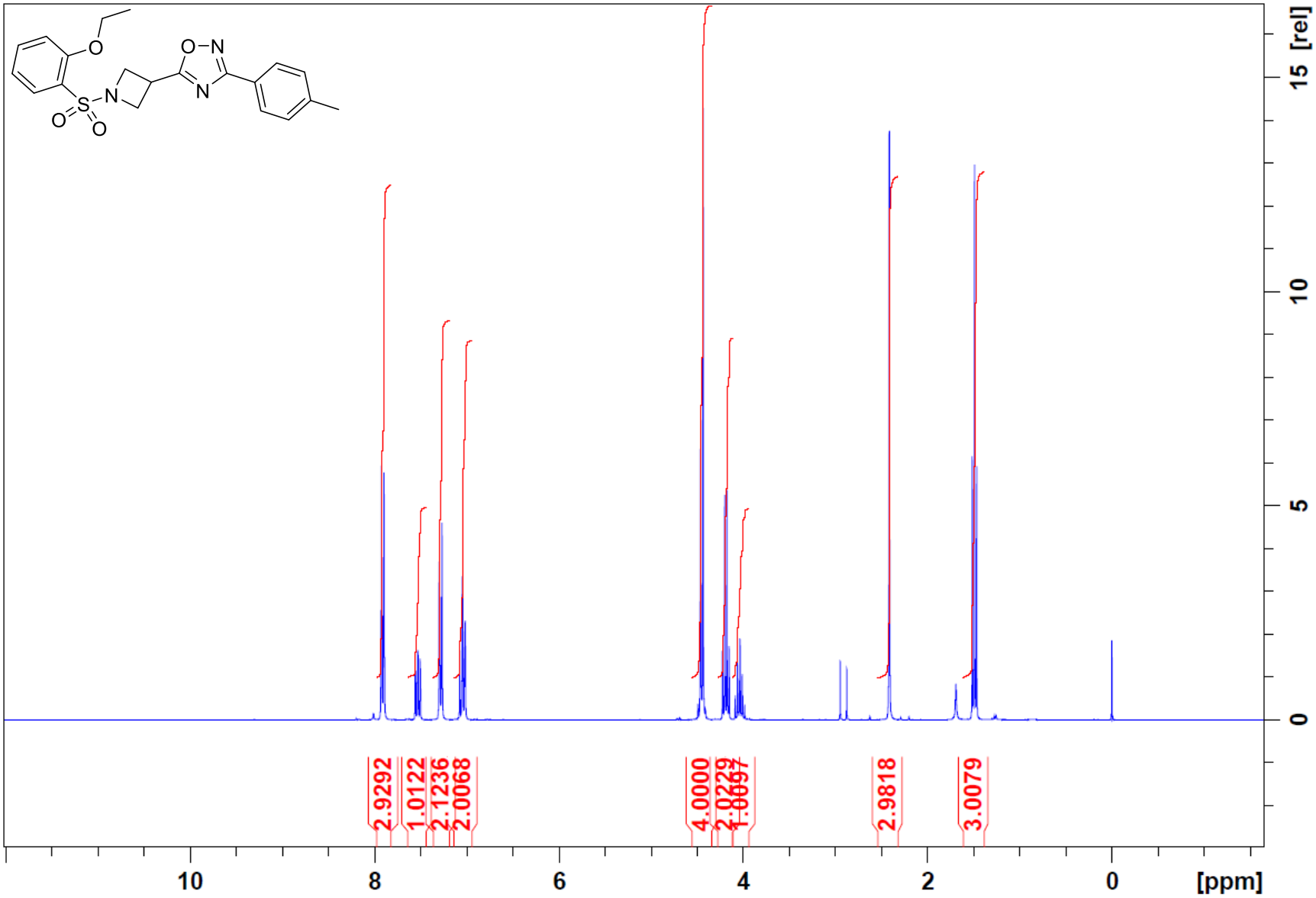
Analog **51** – ^{1}H NMR



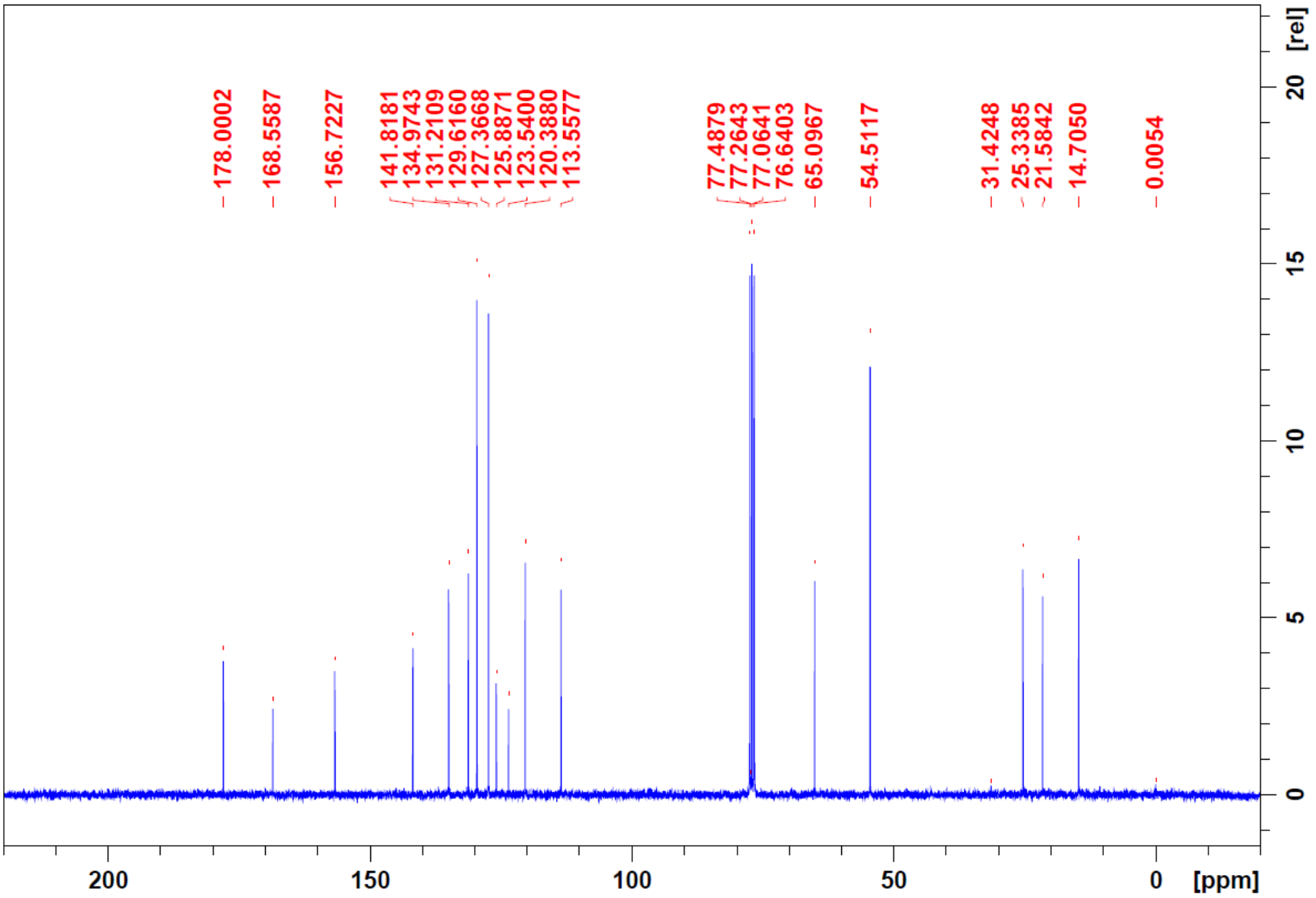
Analog **51** – ^{13}C NMR



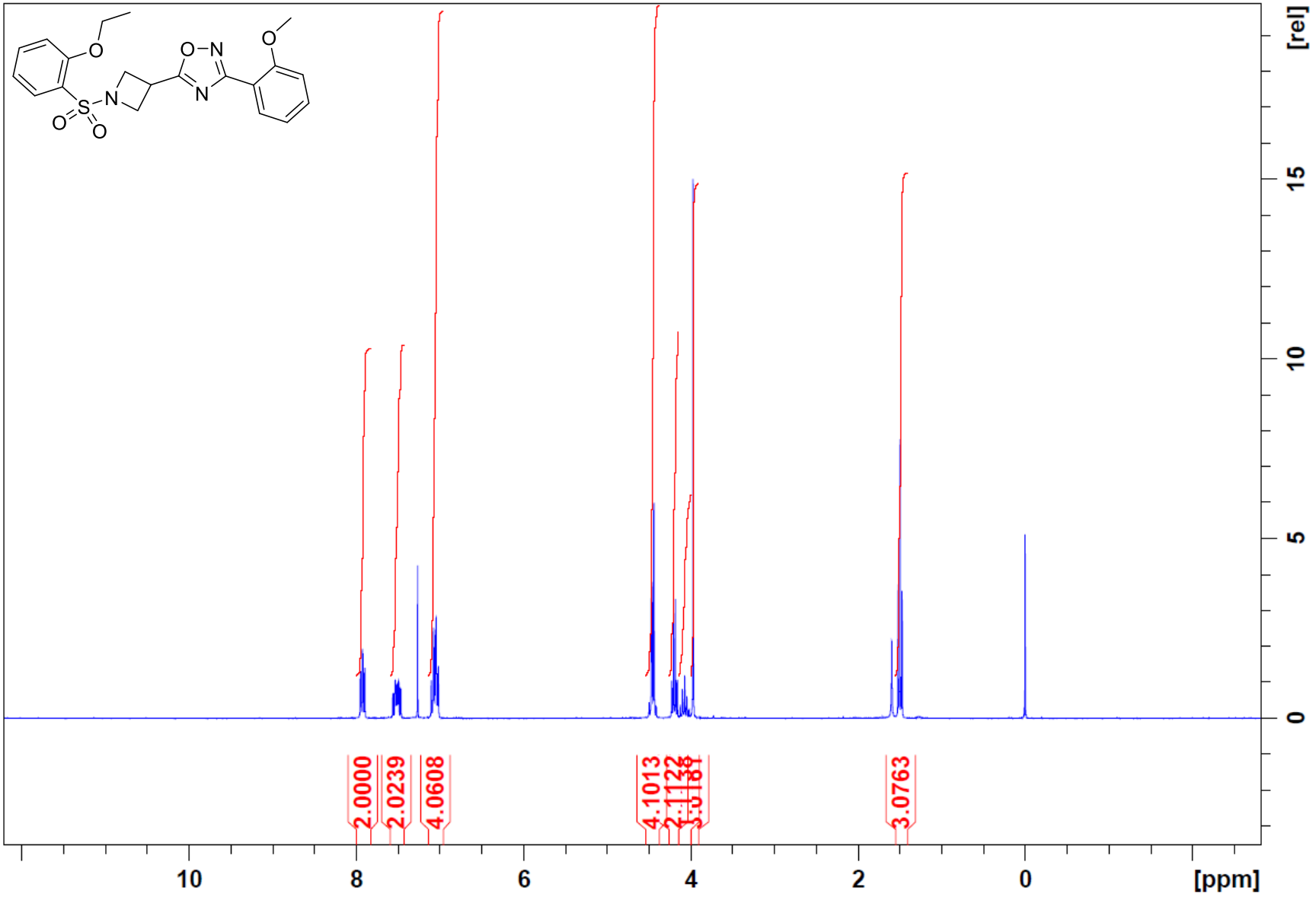
Analog **52** – ^{1}H NMR



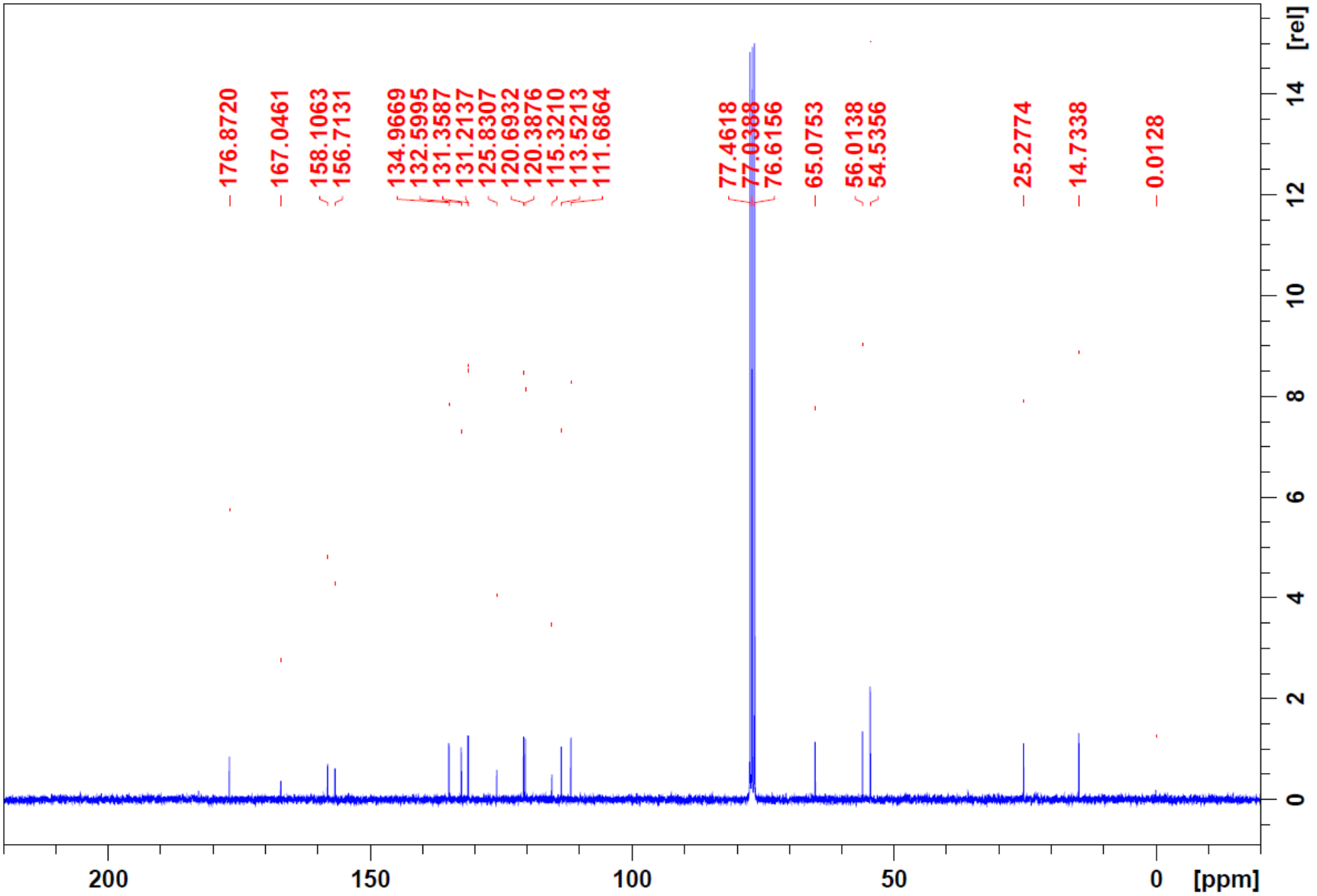
Analog **52** – ^{13}C NMR



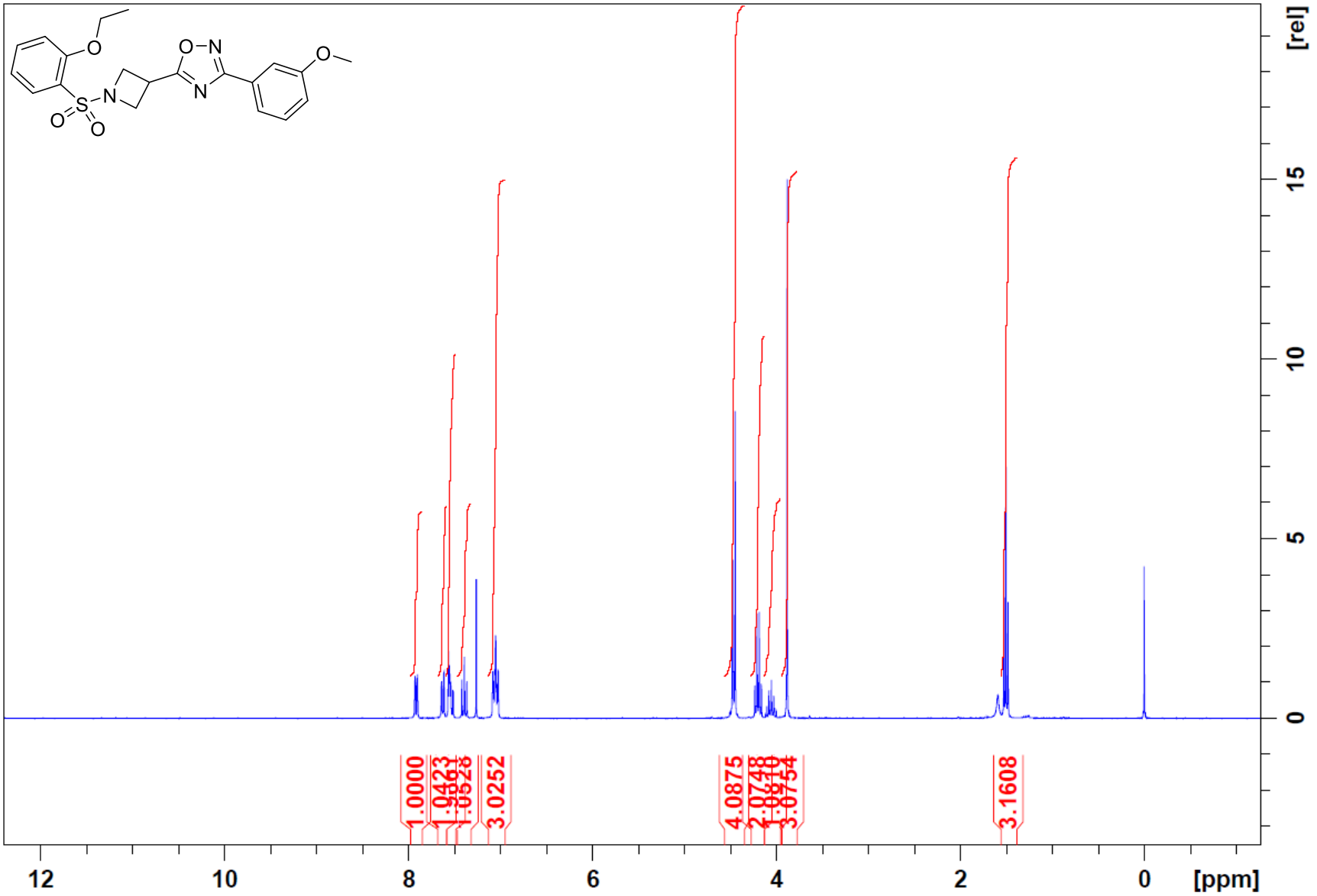
Analog **53** – ^{1}H NMR



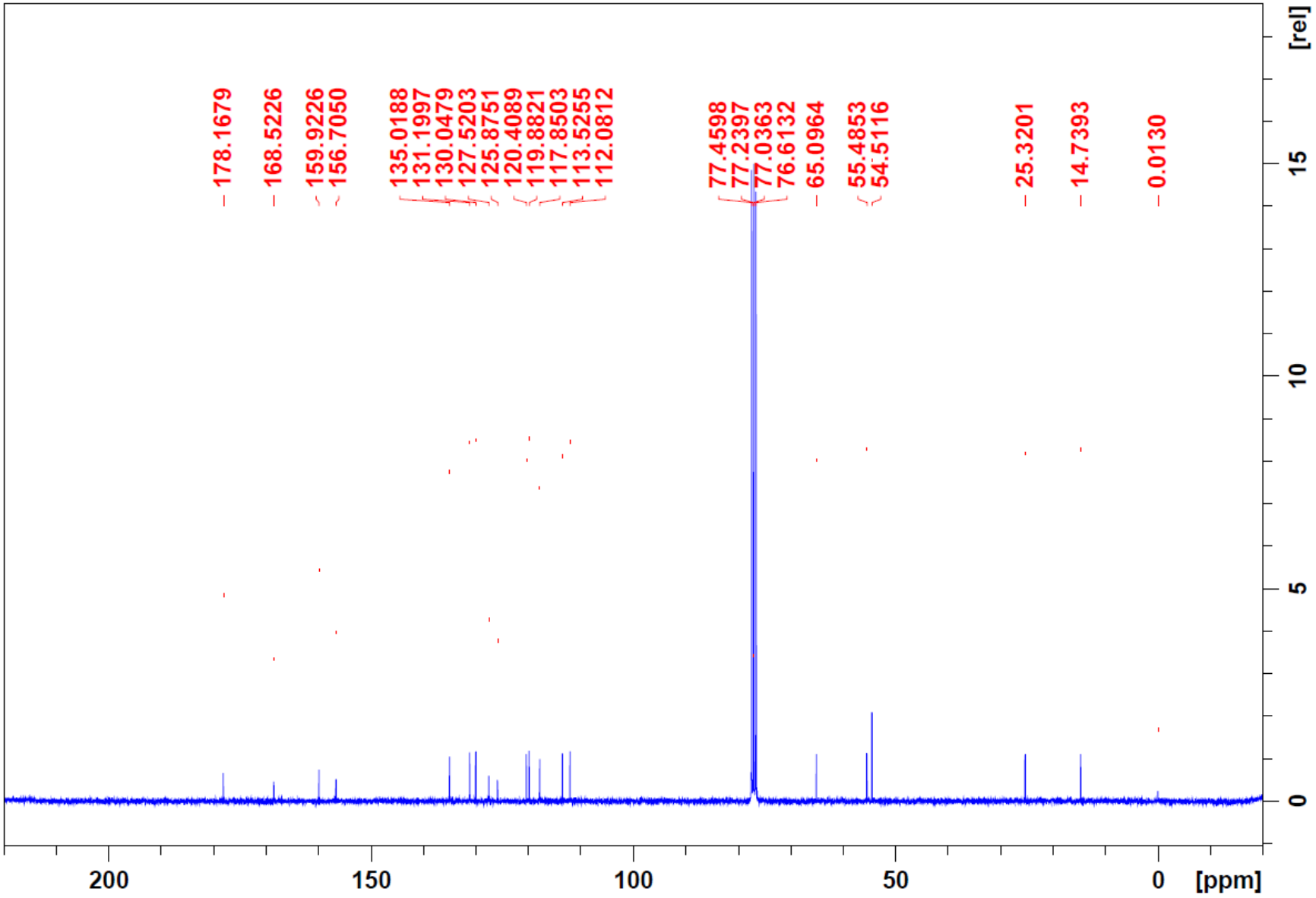
Analog **53** – ^{13}C NMR



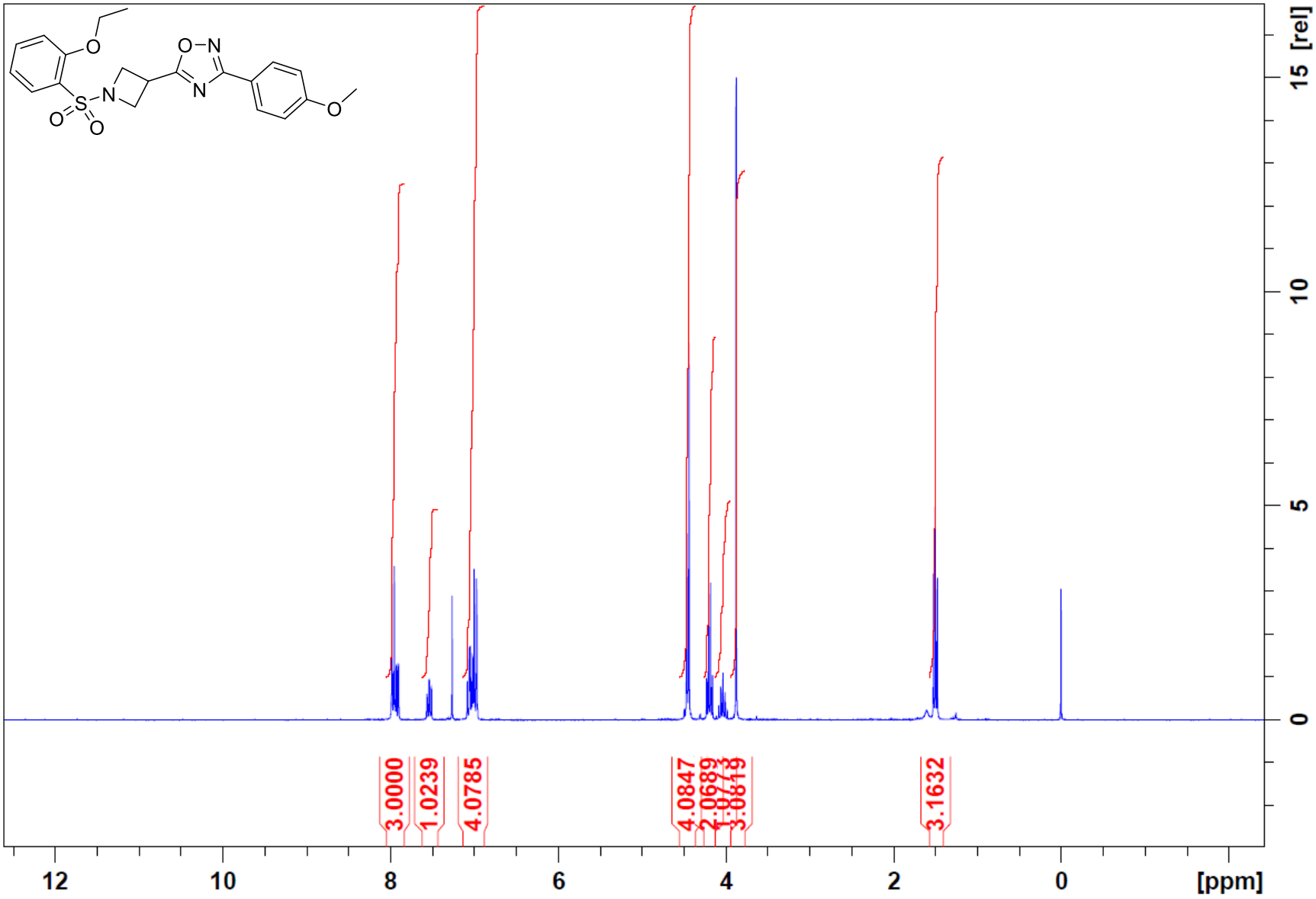
Analog **54** – ^{1}H NMR



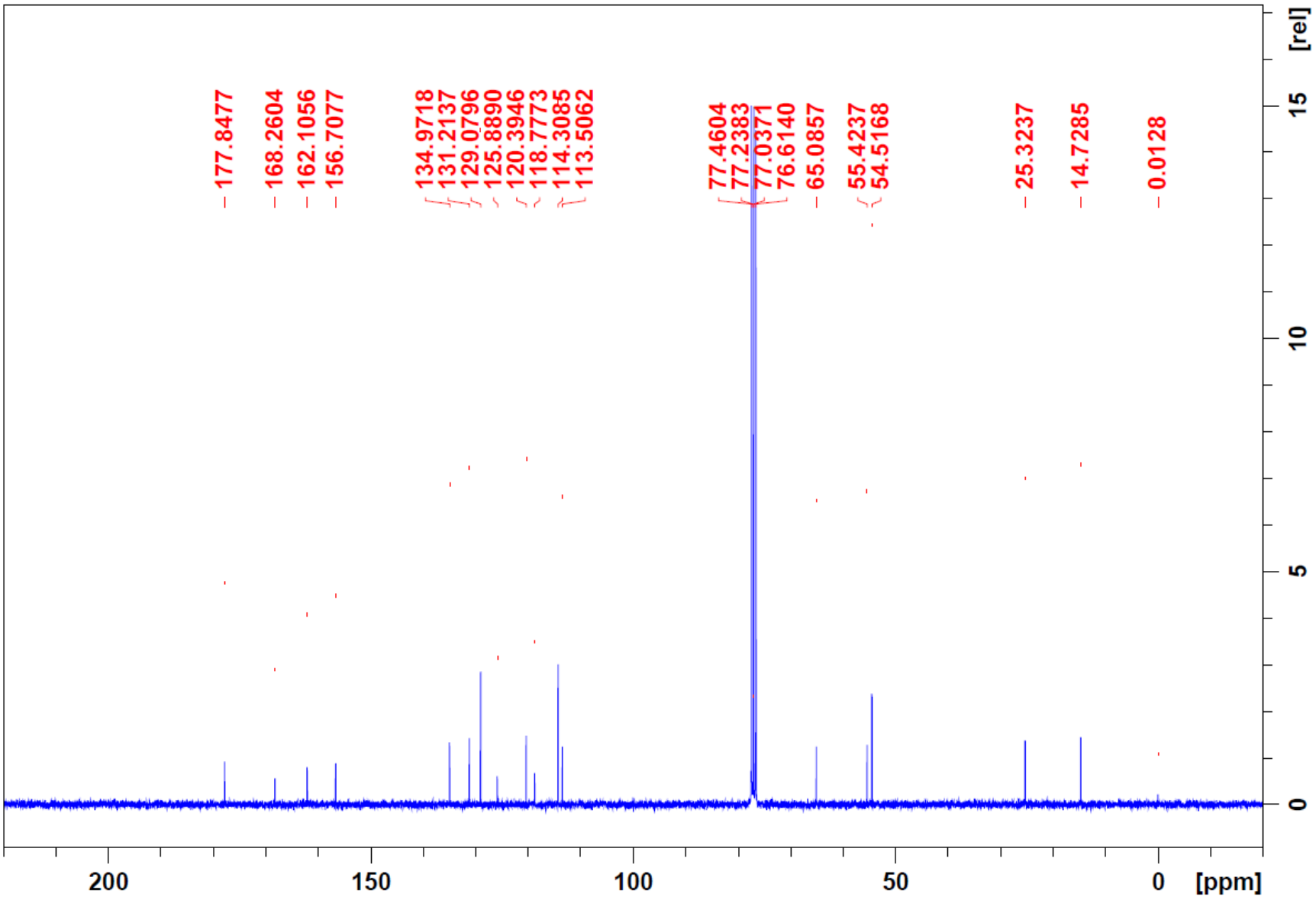
Analog **54** – ^{13}C NMR



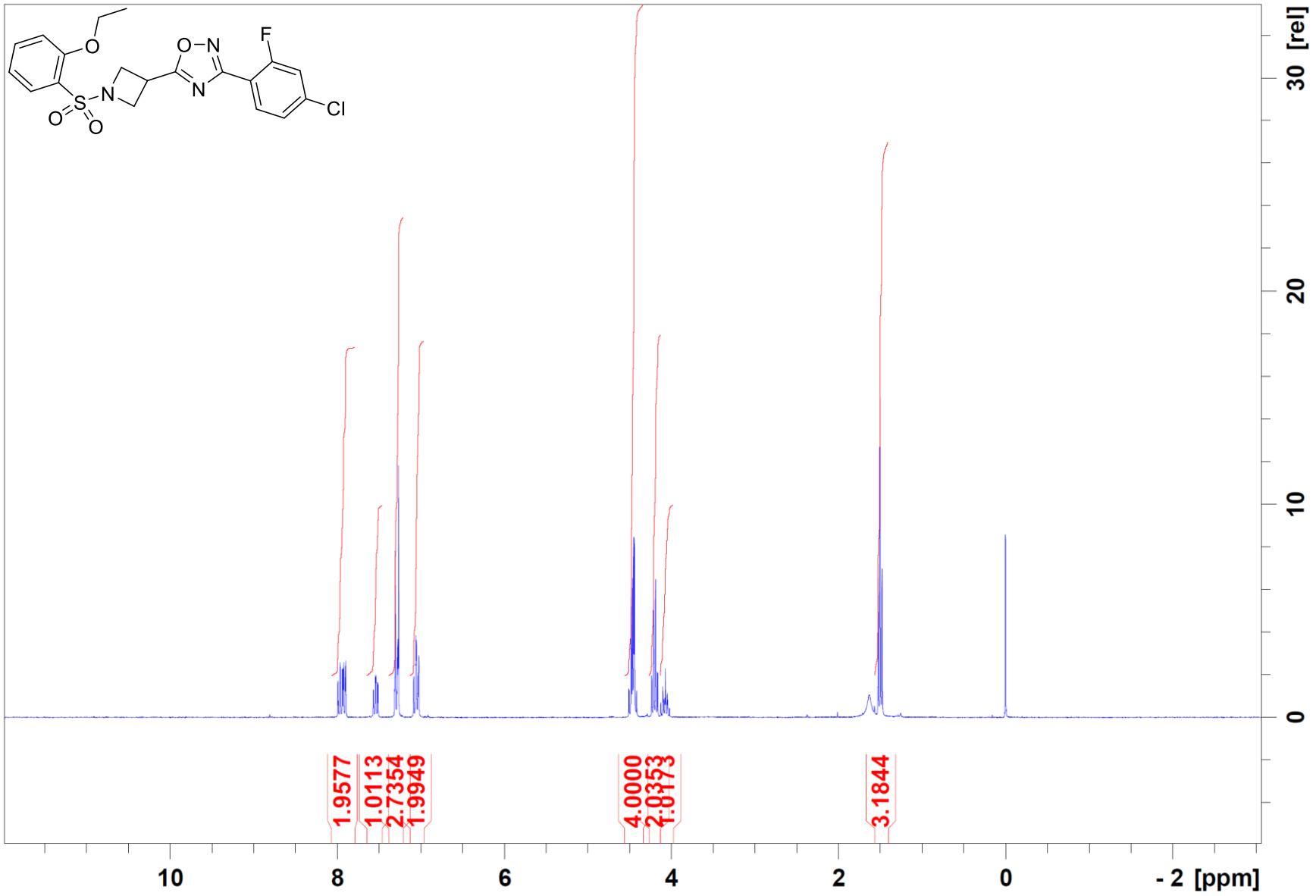
Analog **55** – ^{1}H NMR



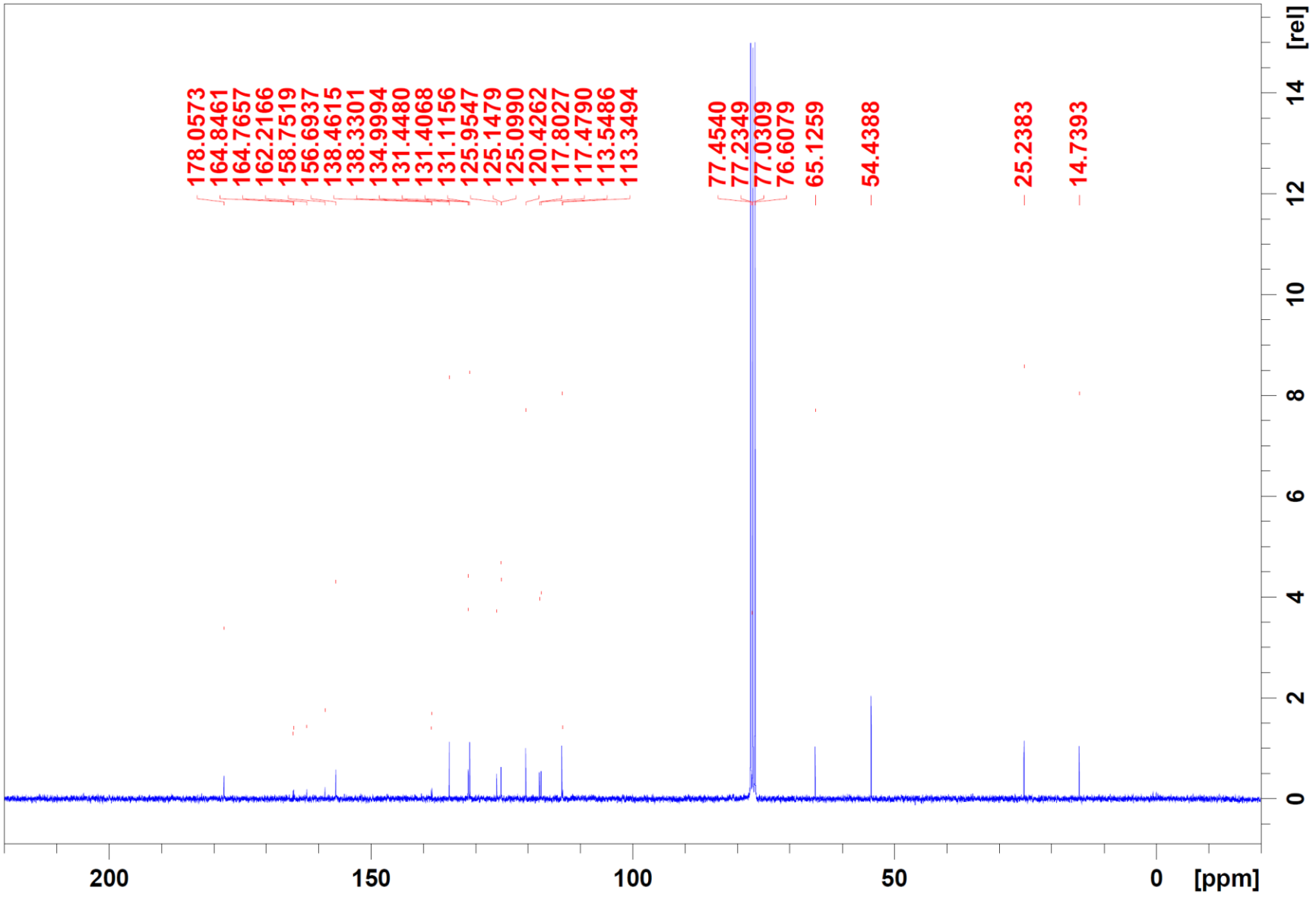
Analog **55** – ^{13}C NMR



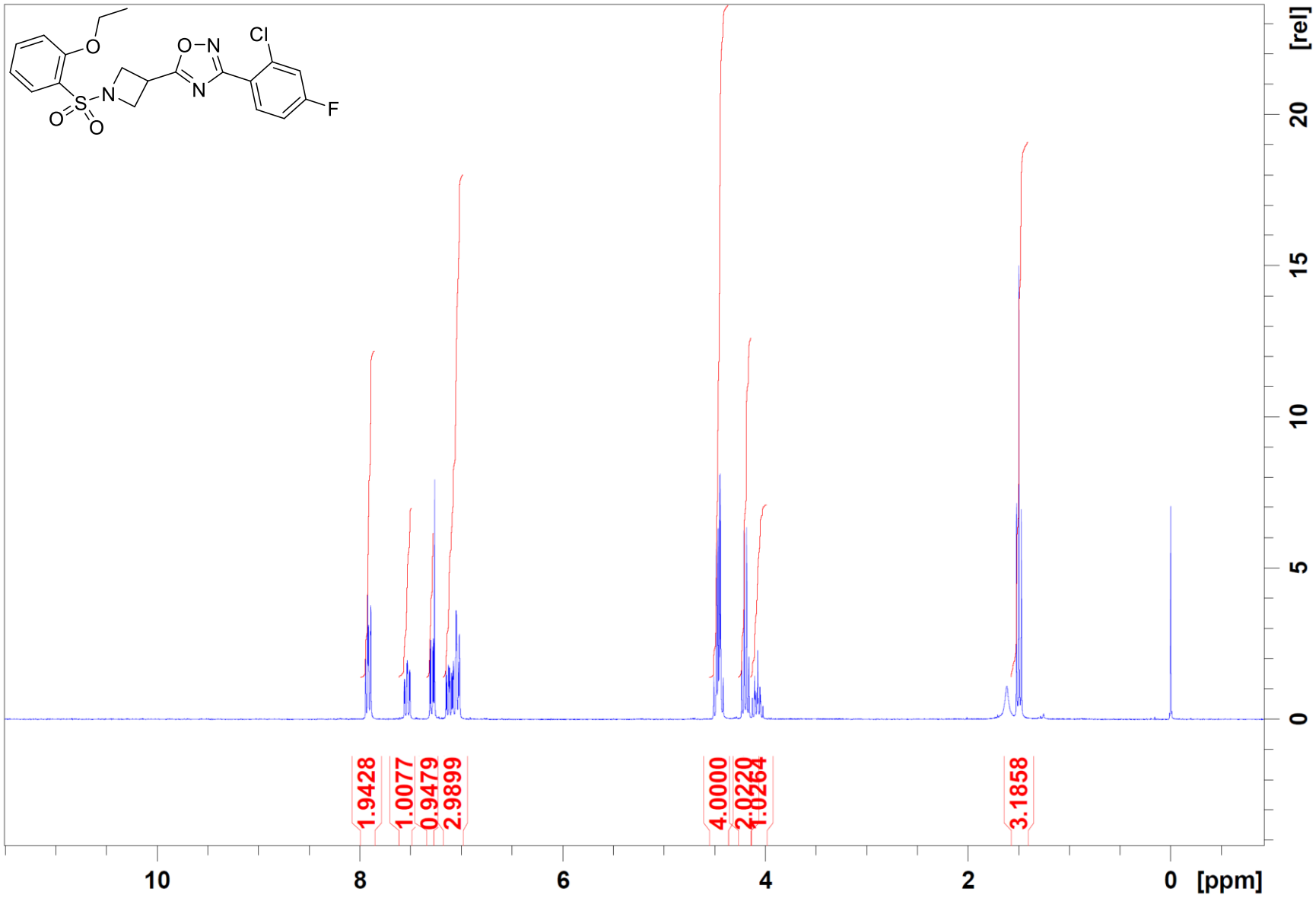
Analog **57** – ^{1}H NMR



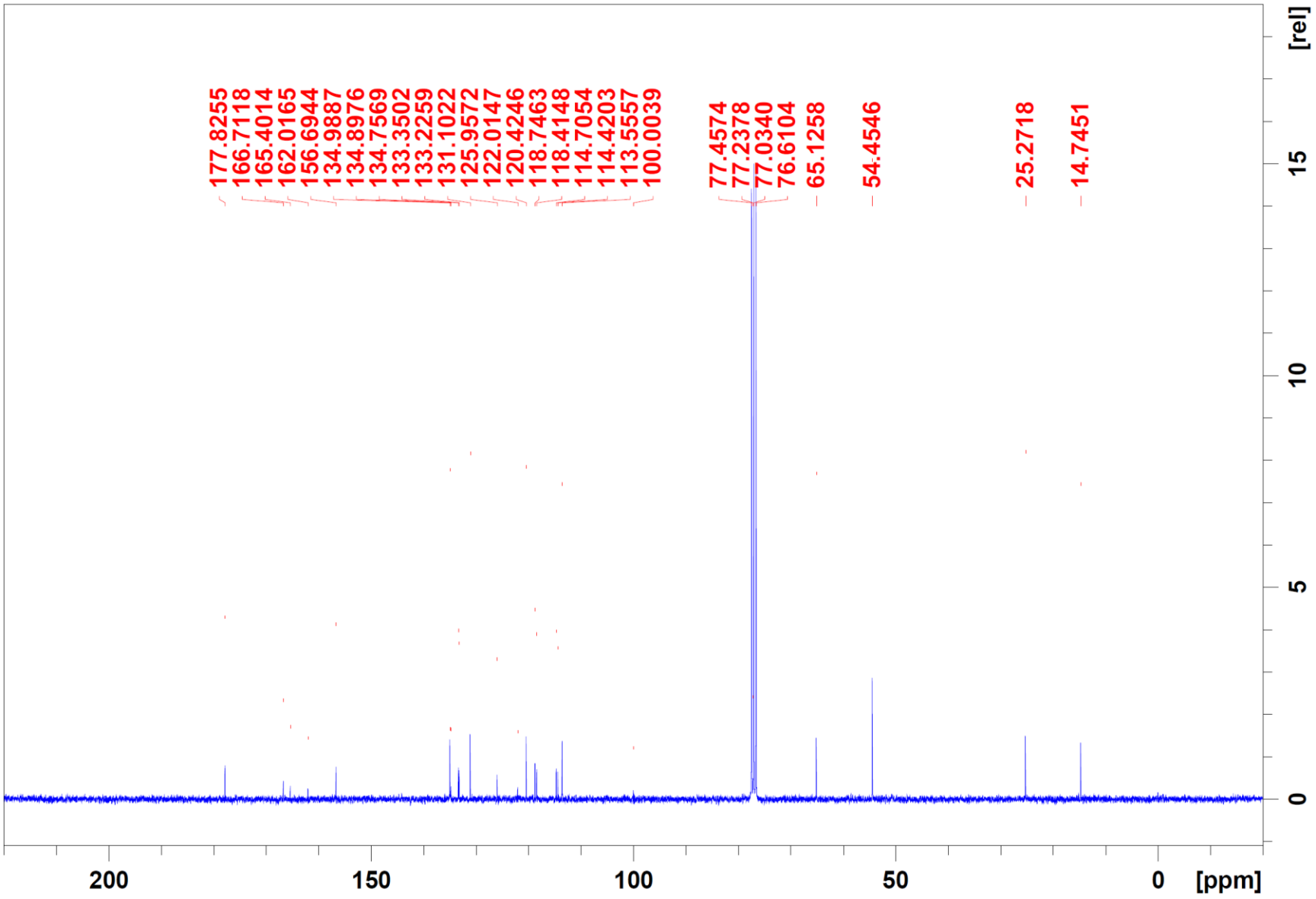
Analog **57** – ^{13}C NMR



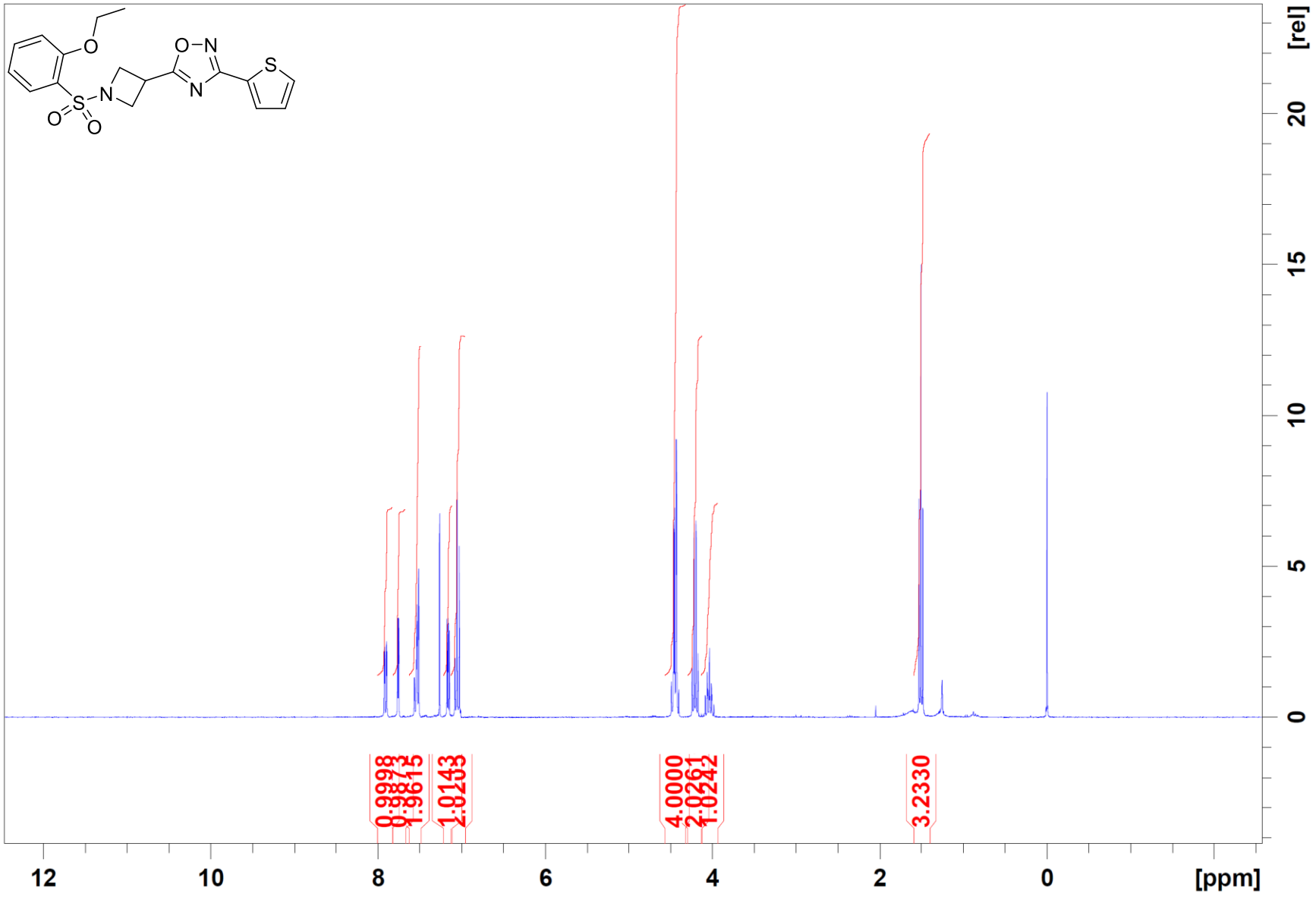
Analog **58** – ^{1}H NMR



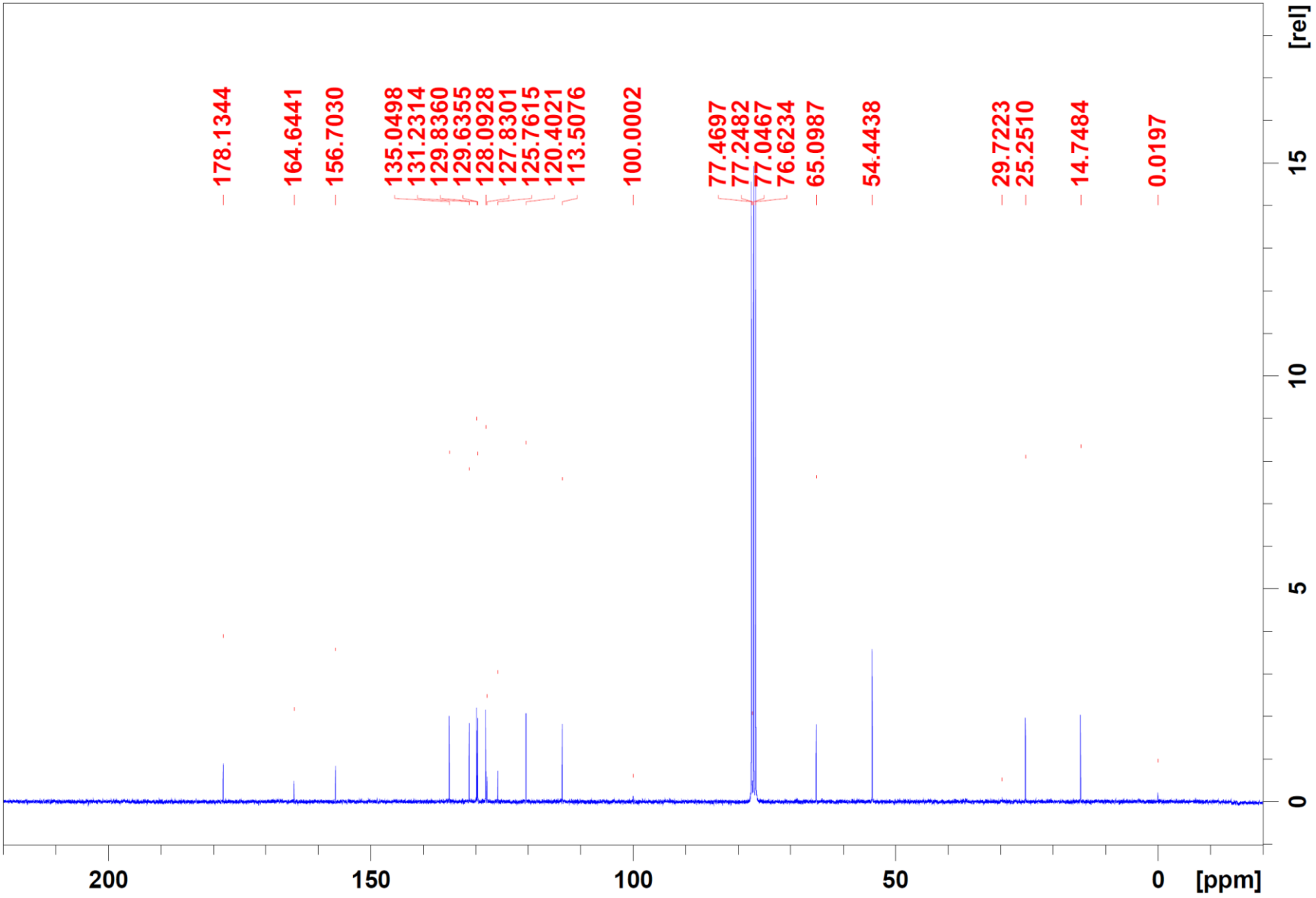
Analog **58** – ^{13}C NMR



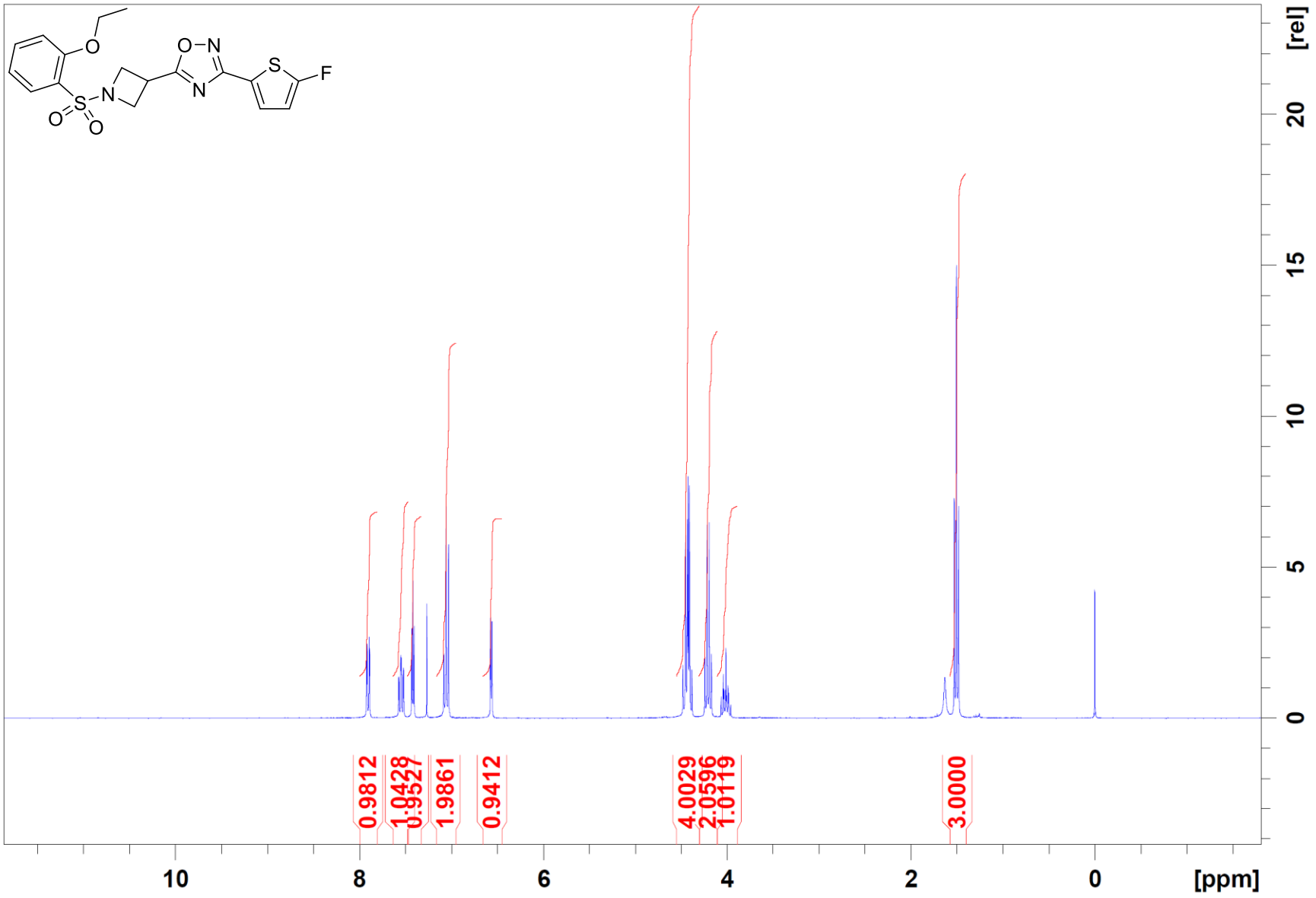
Analog **59** – ^{1}H NMR



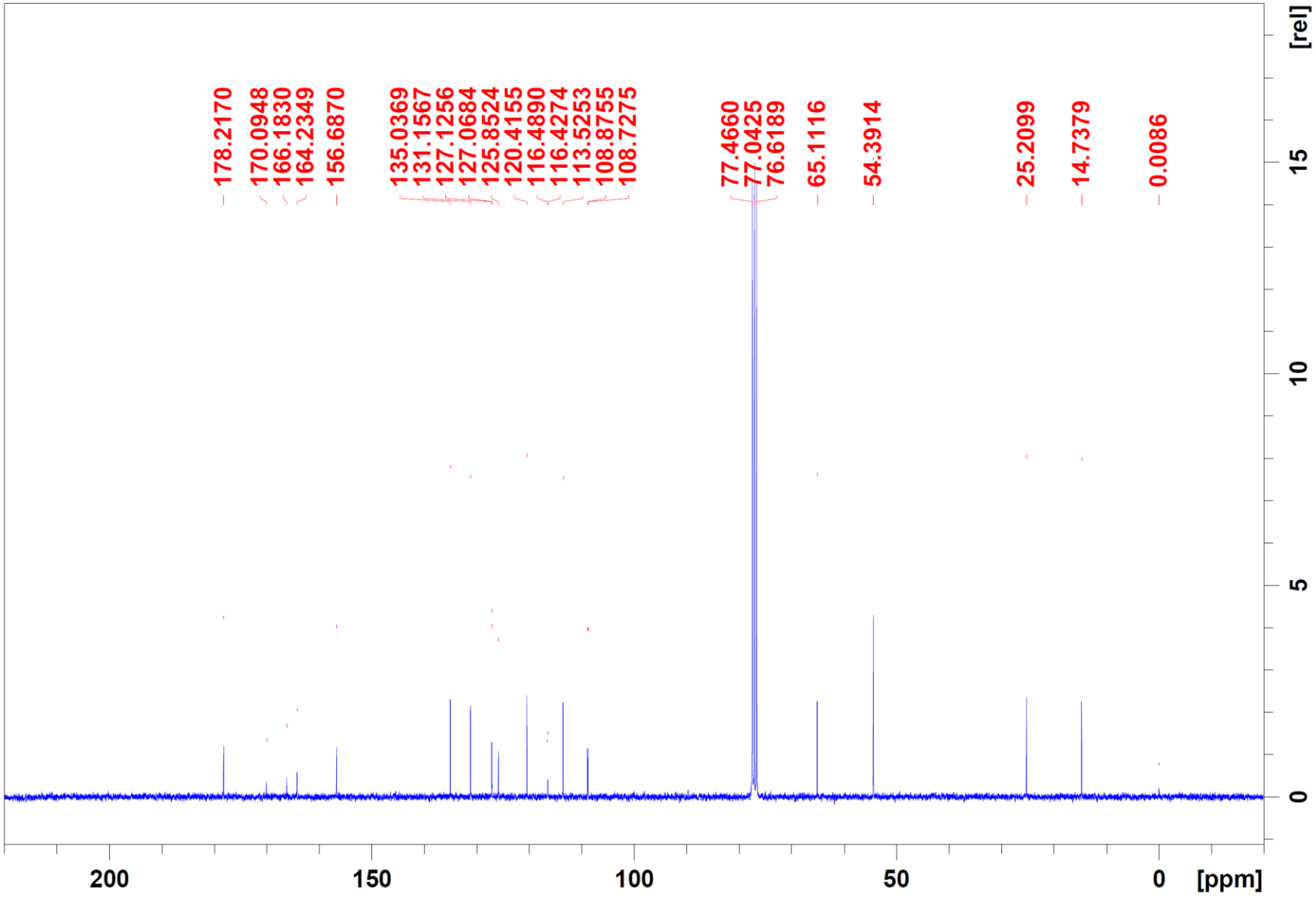
Analog **59** – ^{13}C NMR



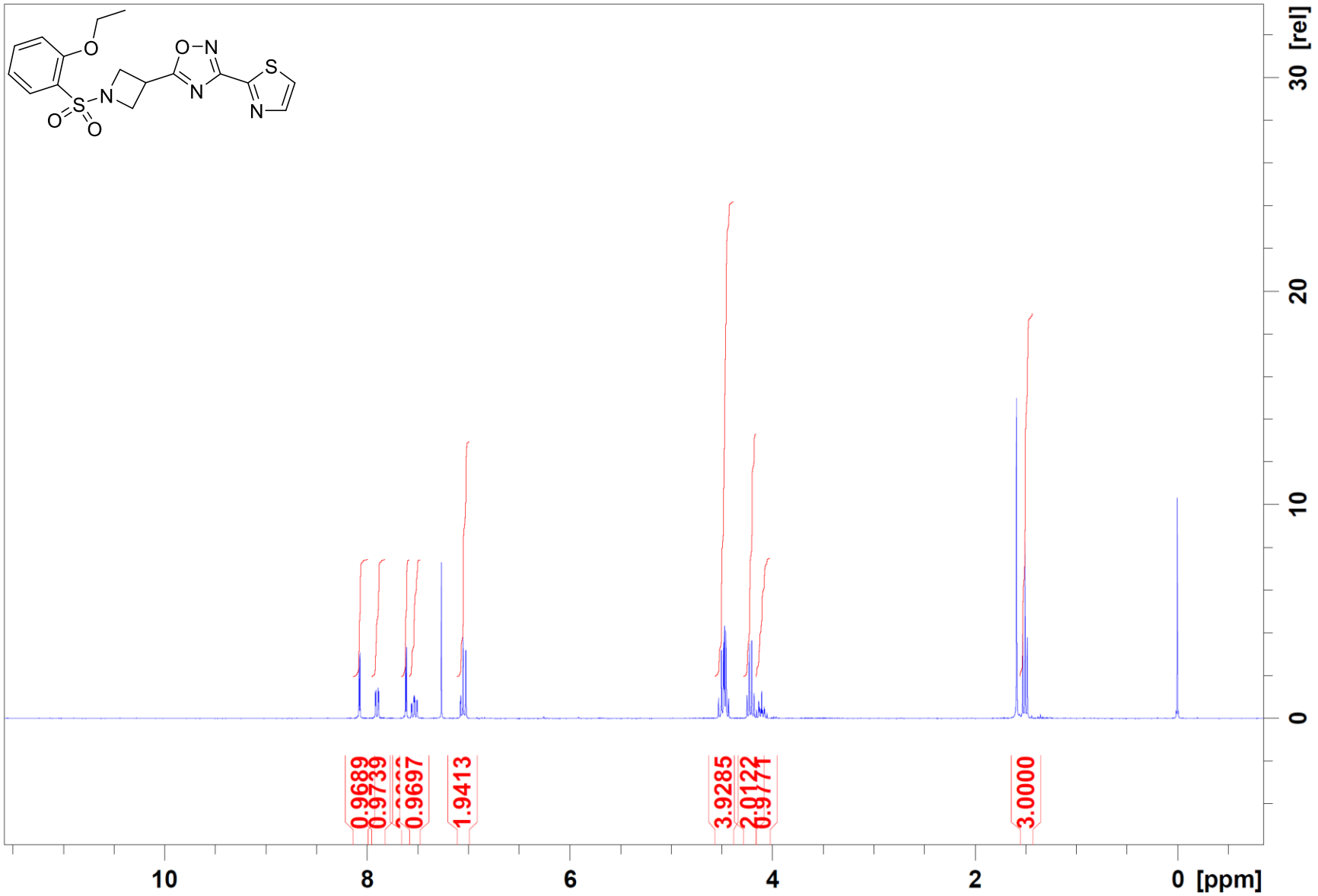
Analog **60** – ^{1}H NMR



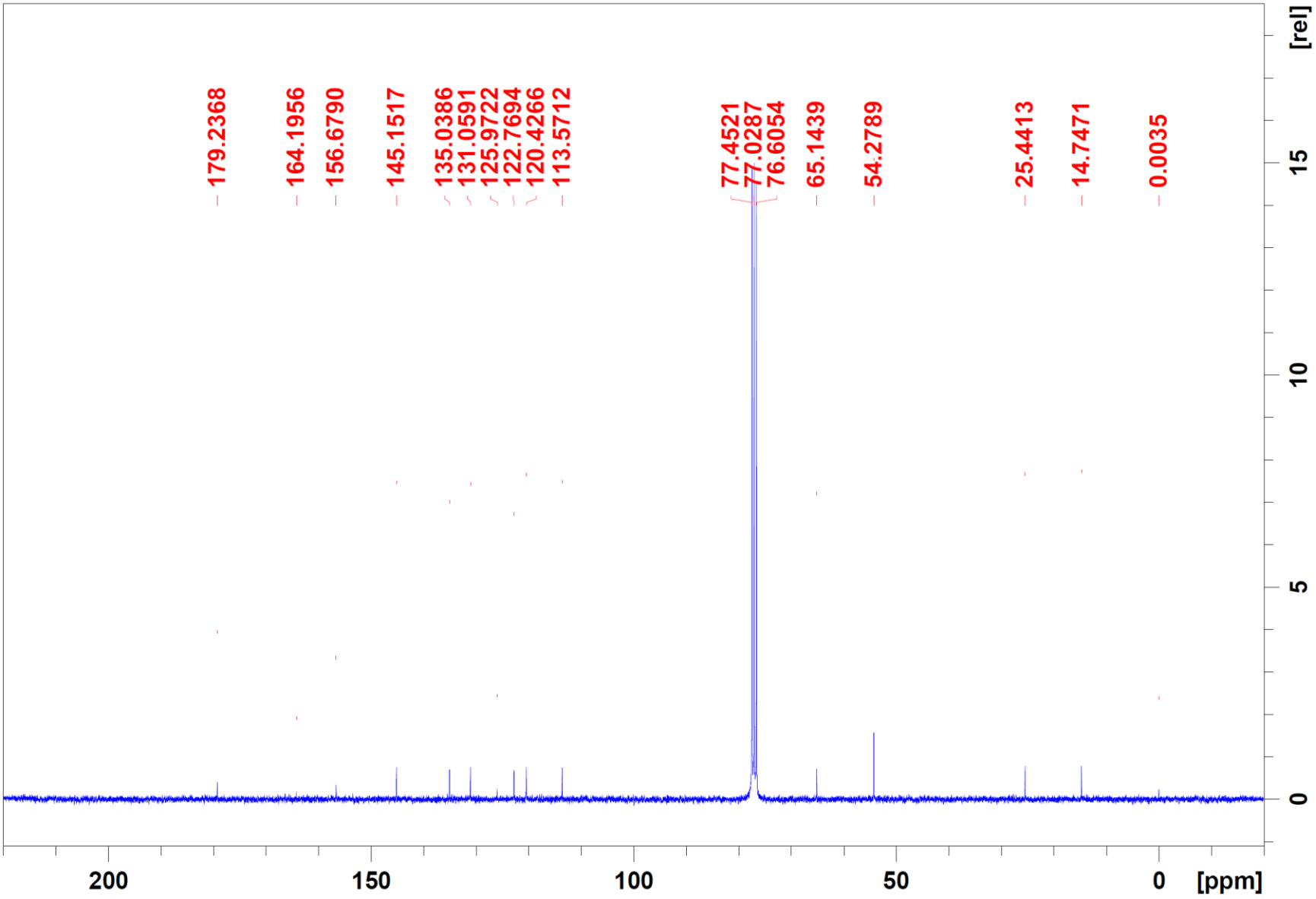
Analog **60** – ^{13}C NMR



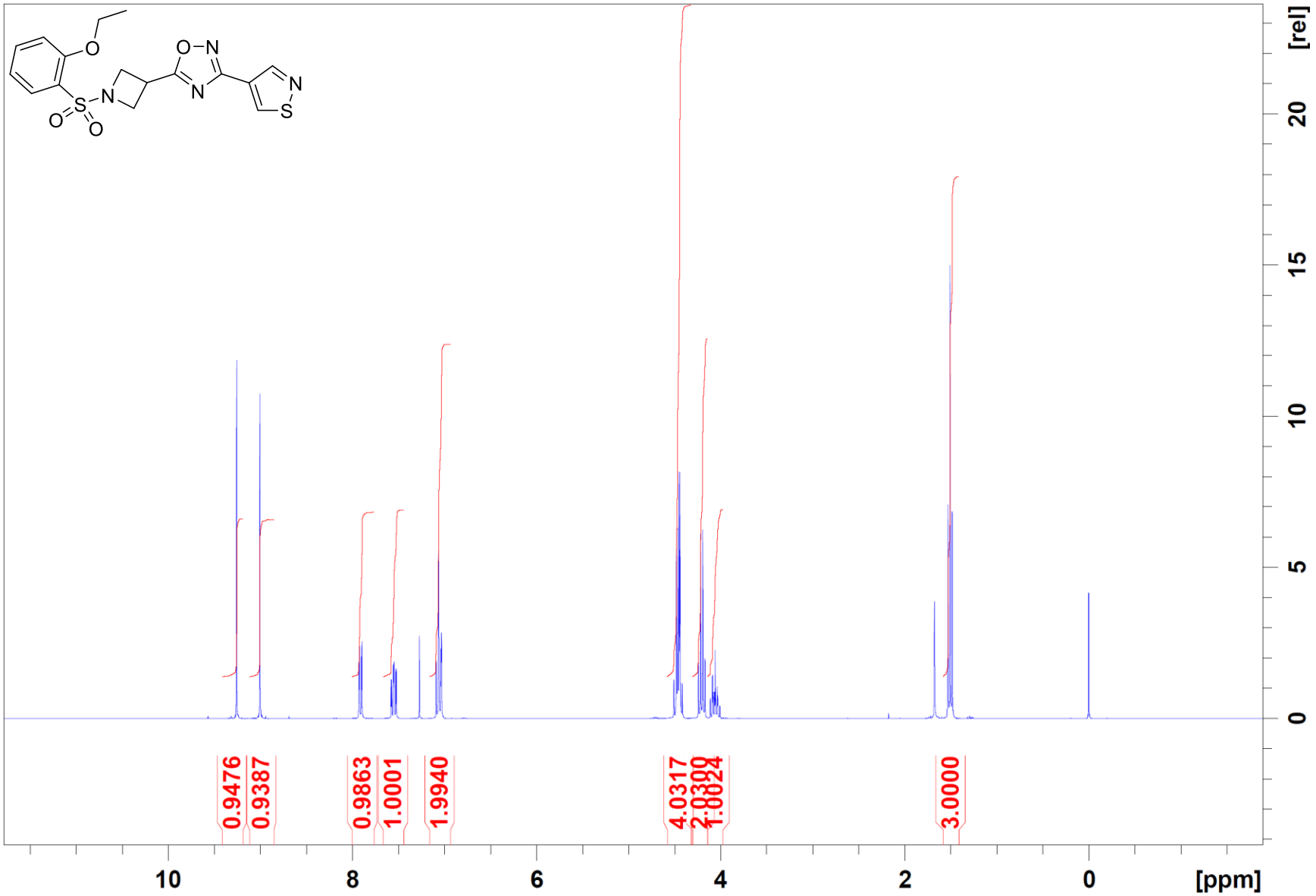
Analog **61** – ^{1}H NMR



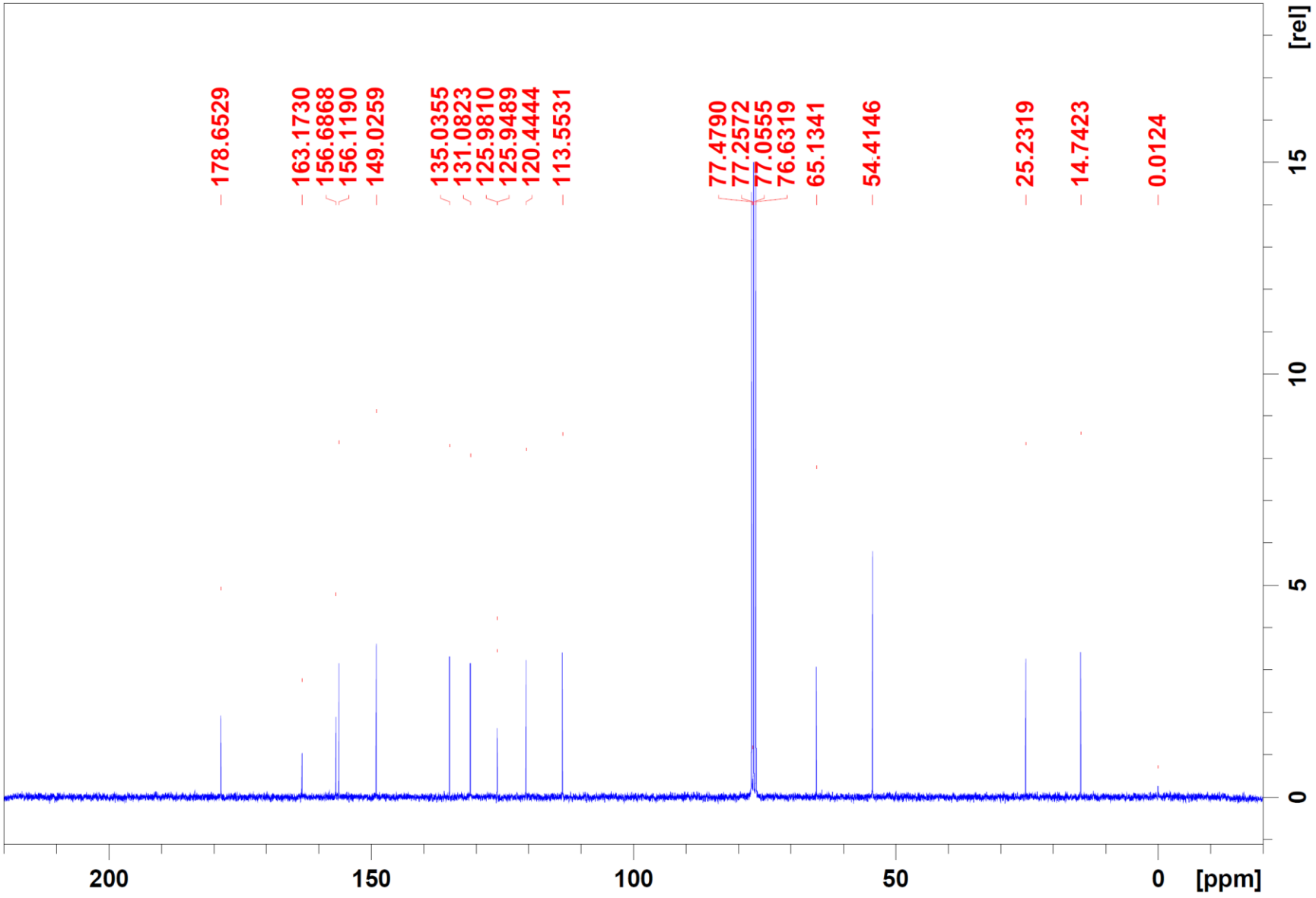
Analog **61** – ^{13}C NMR



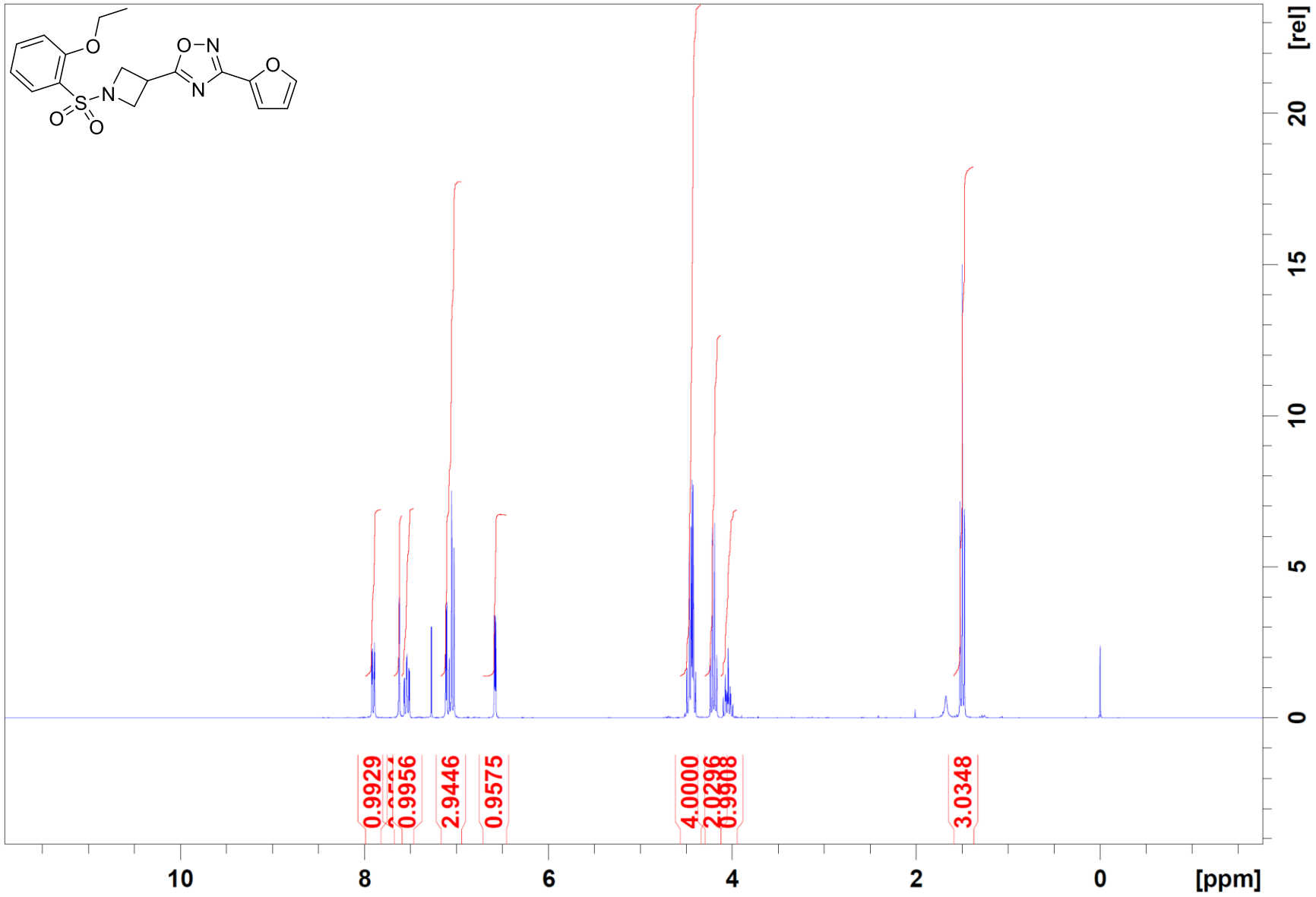
Analog **62** – ^{1}H NMR



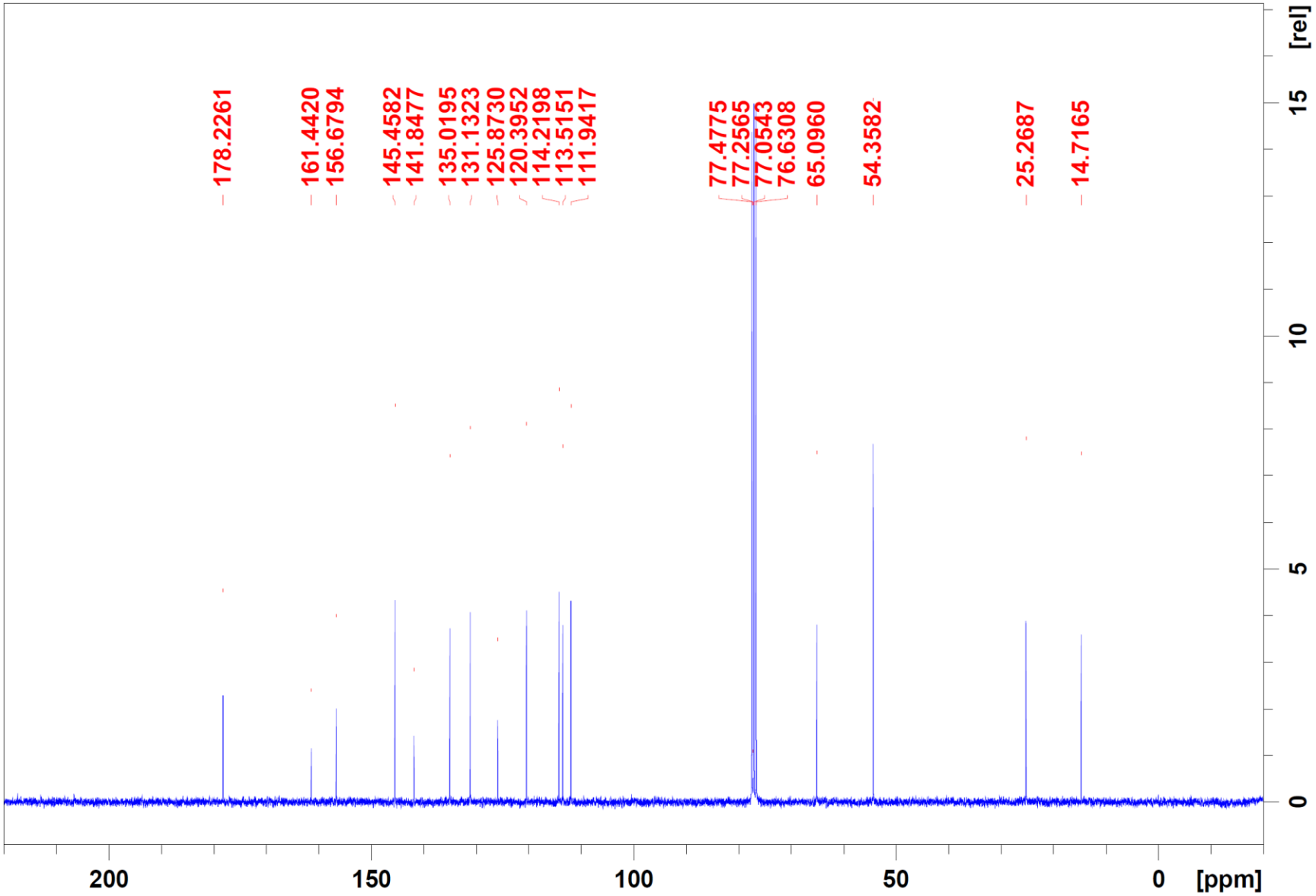
Analog **62** – ^{13}C NMR



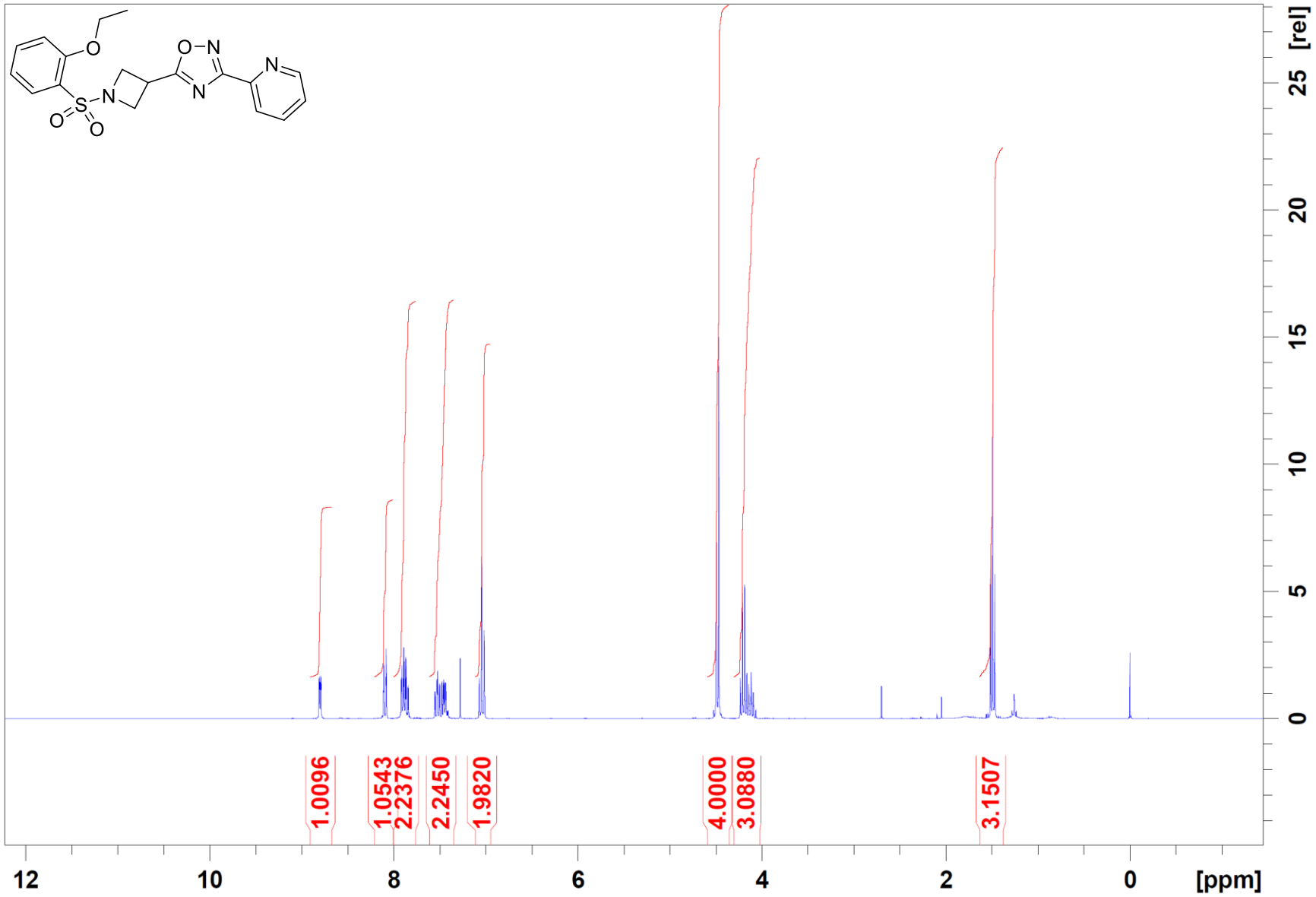
Analog **63** – ^{1}H NMR



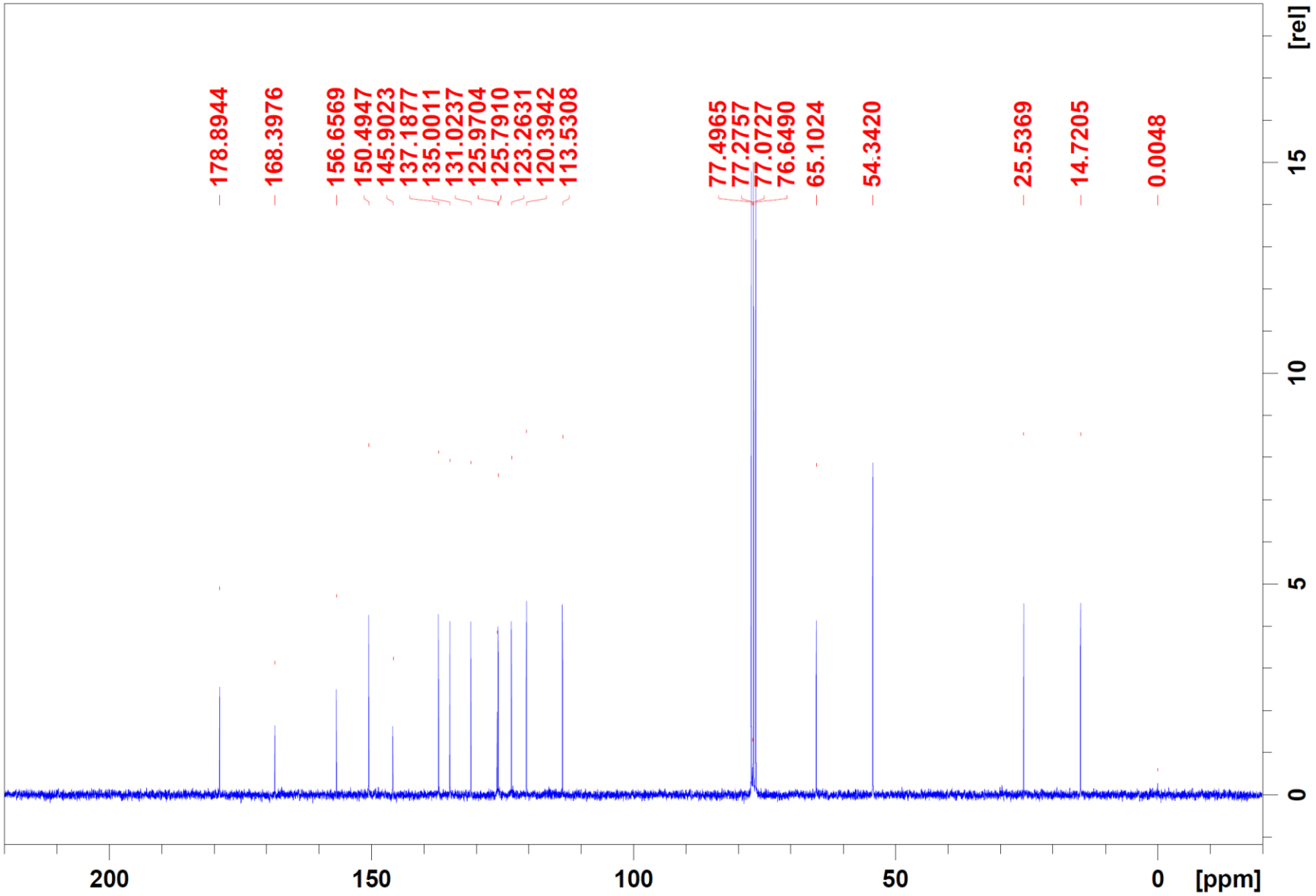
Analog **63** – ^{13}C NMR



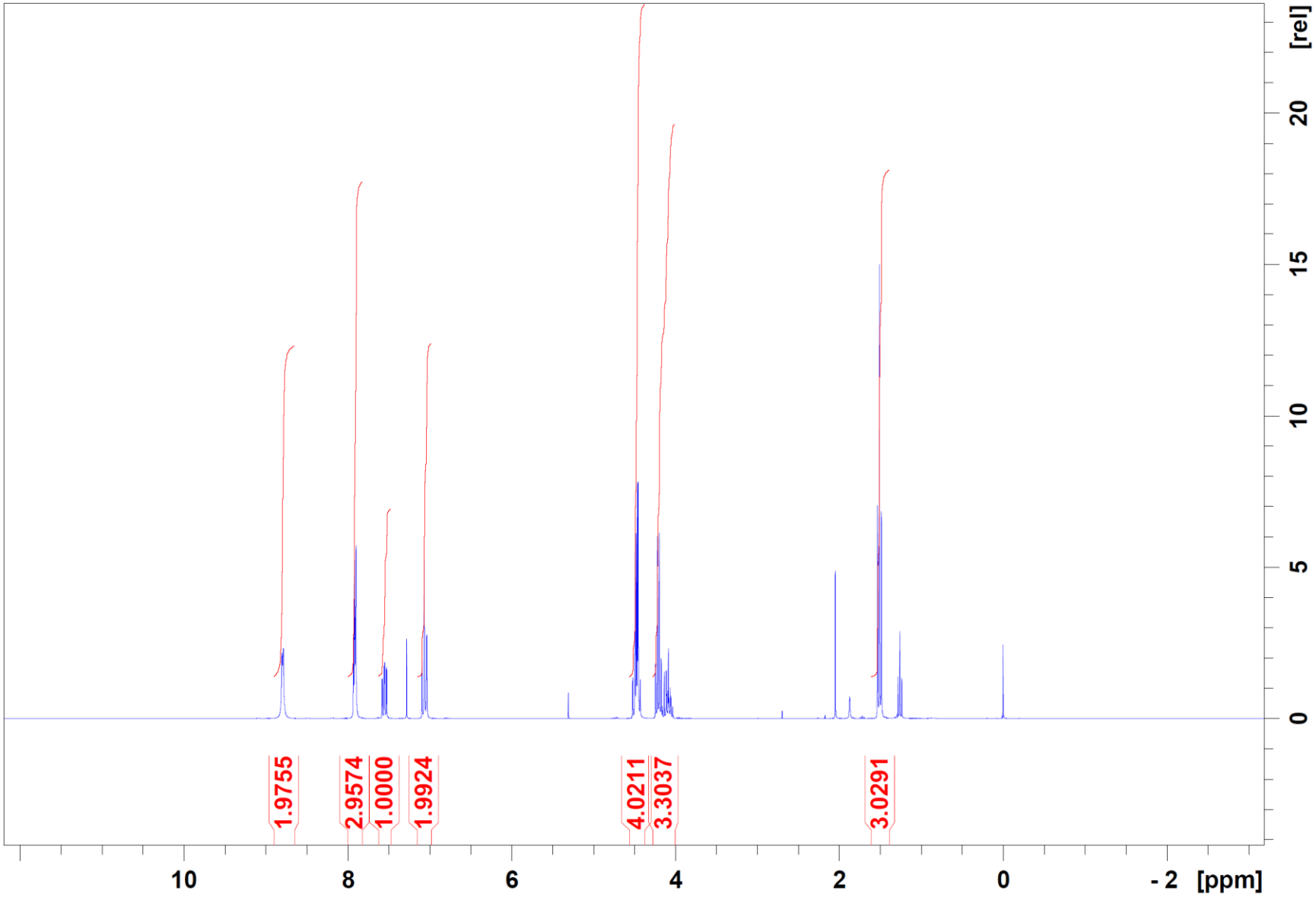
Analog **64** – ^{1}H NMR



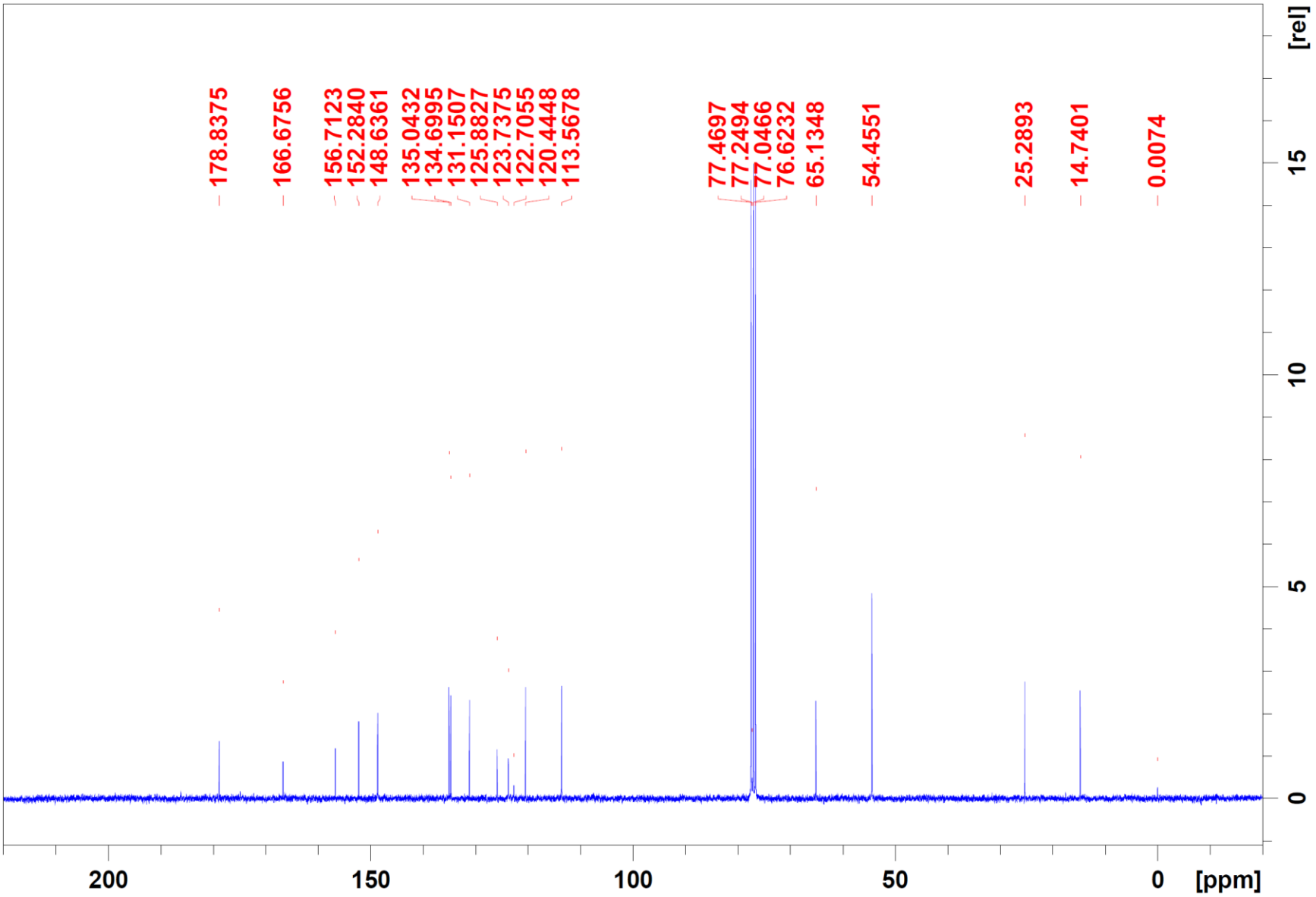
Analog **64** – ^{13}C NMR



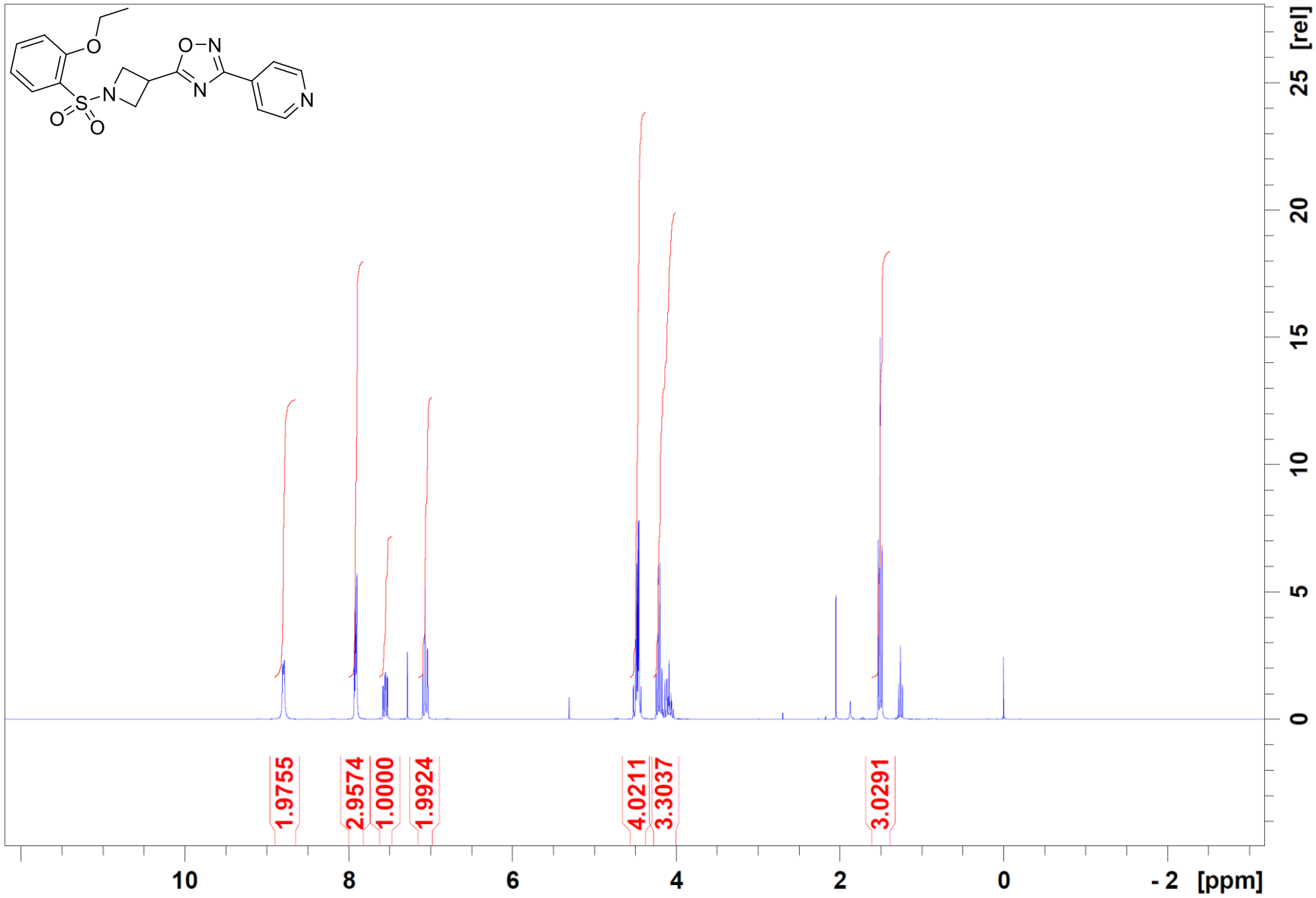
Analog **65** – ^{1}H NMR



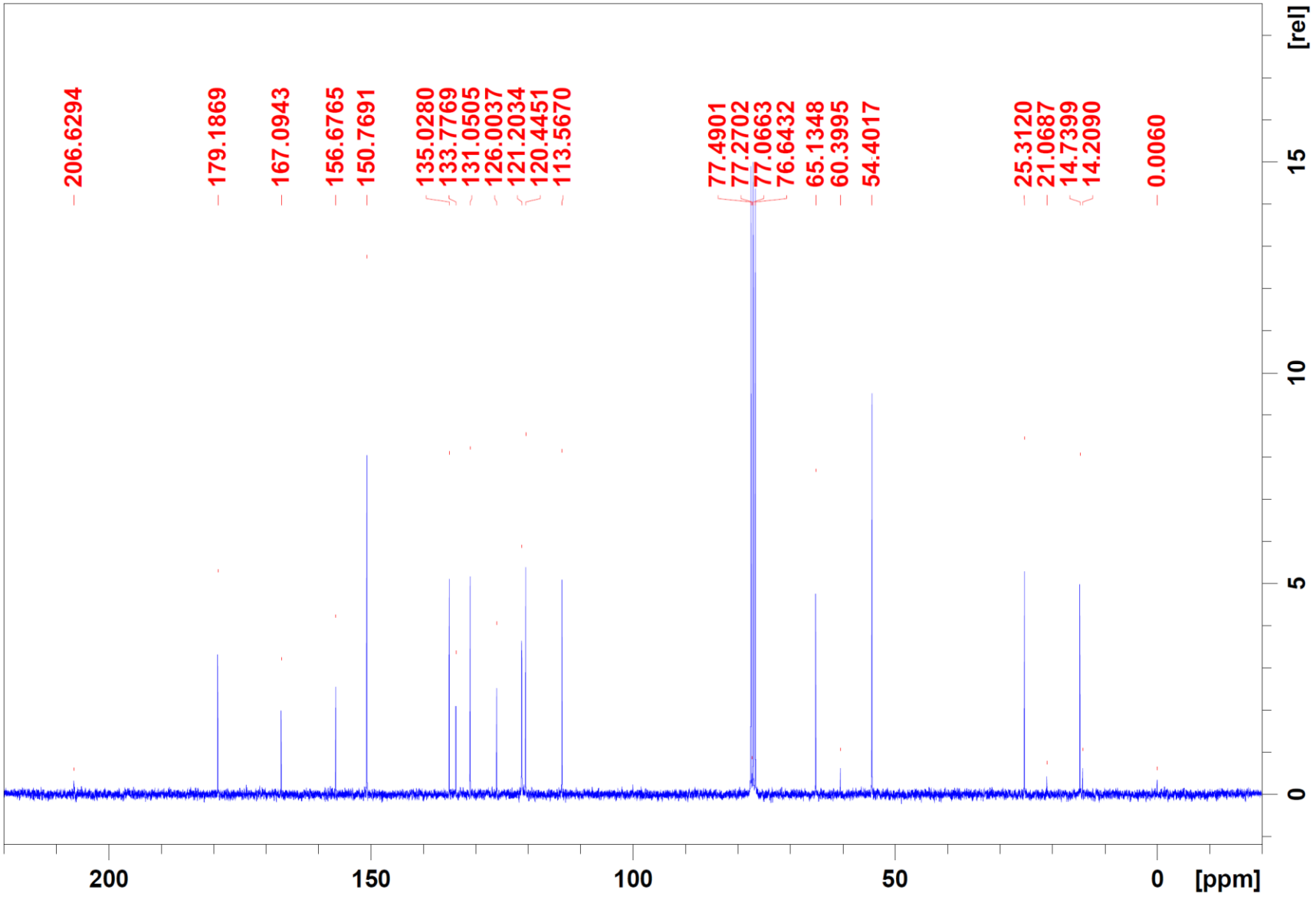
Analog **65** – ^{13}C NMR



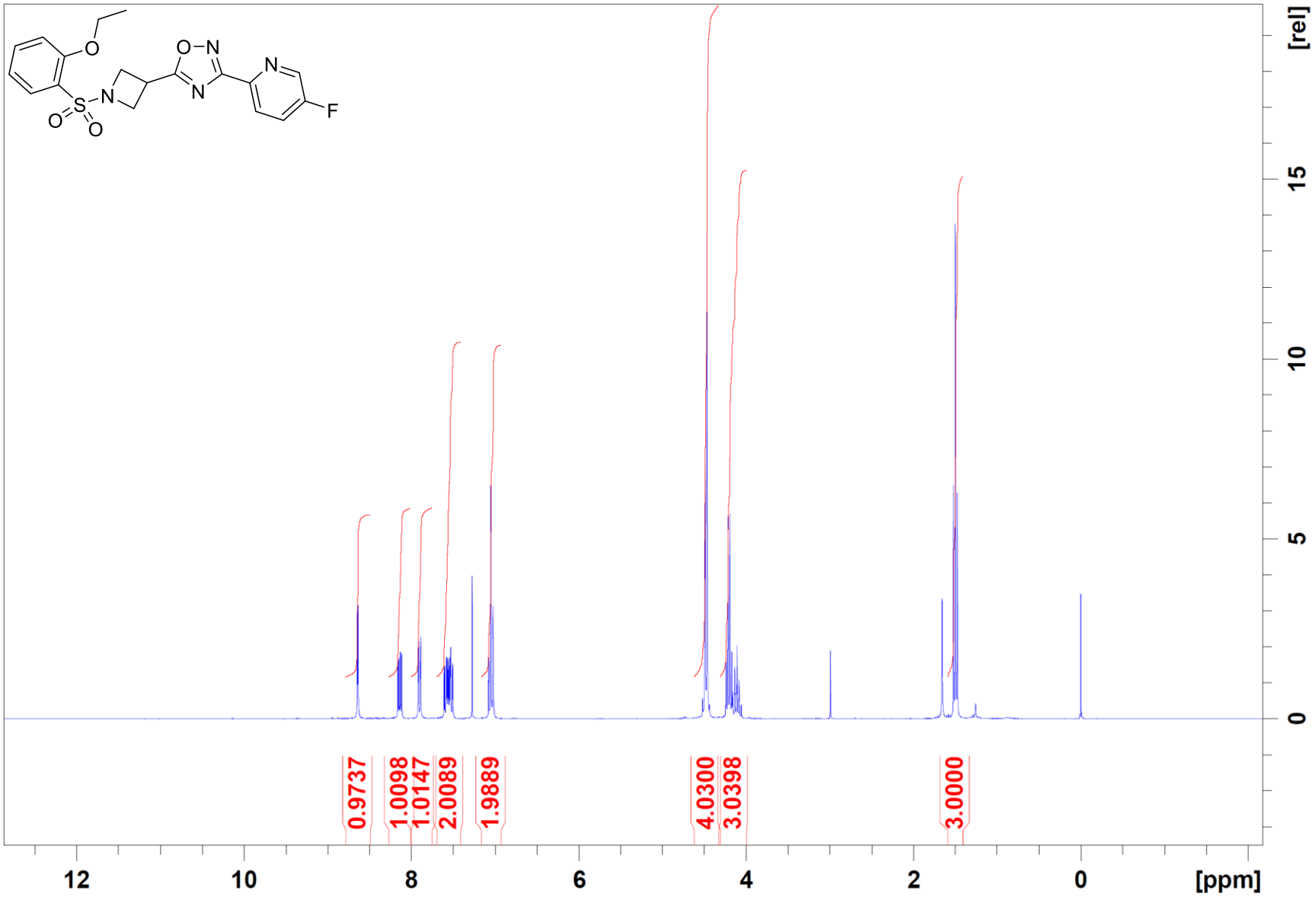
Analog **66** – ^{1}H NMR



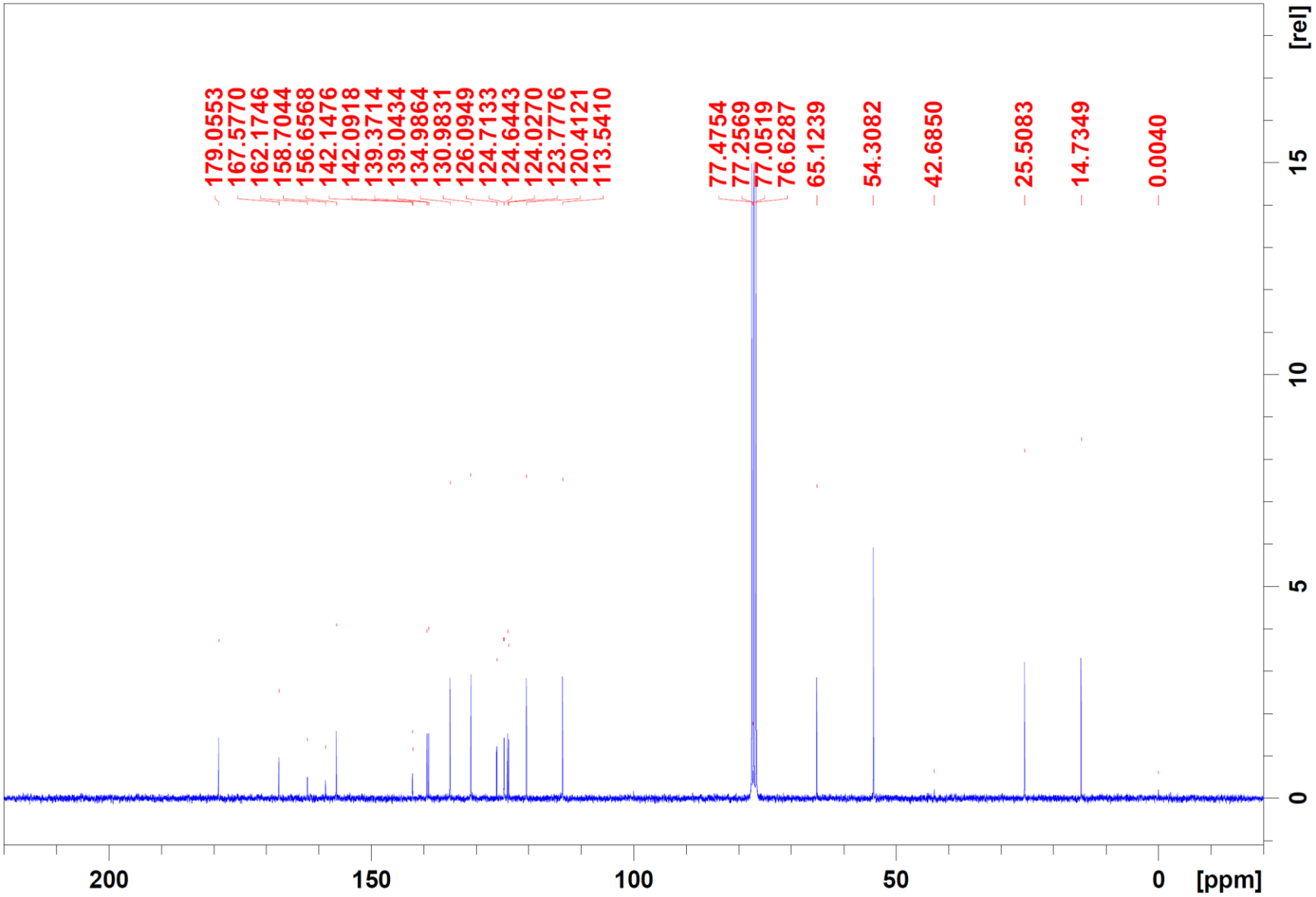
Analog **66** – ^{13}C NMR



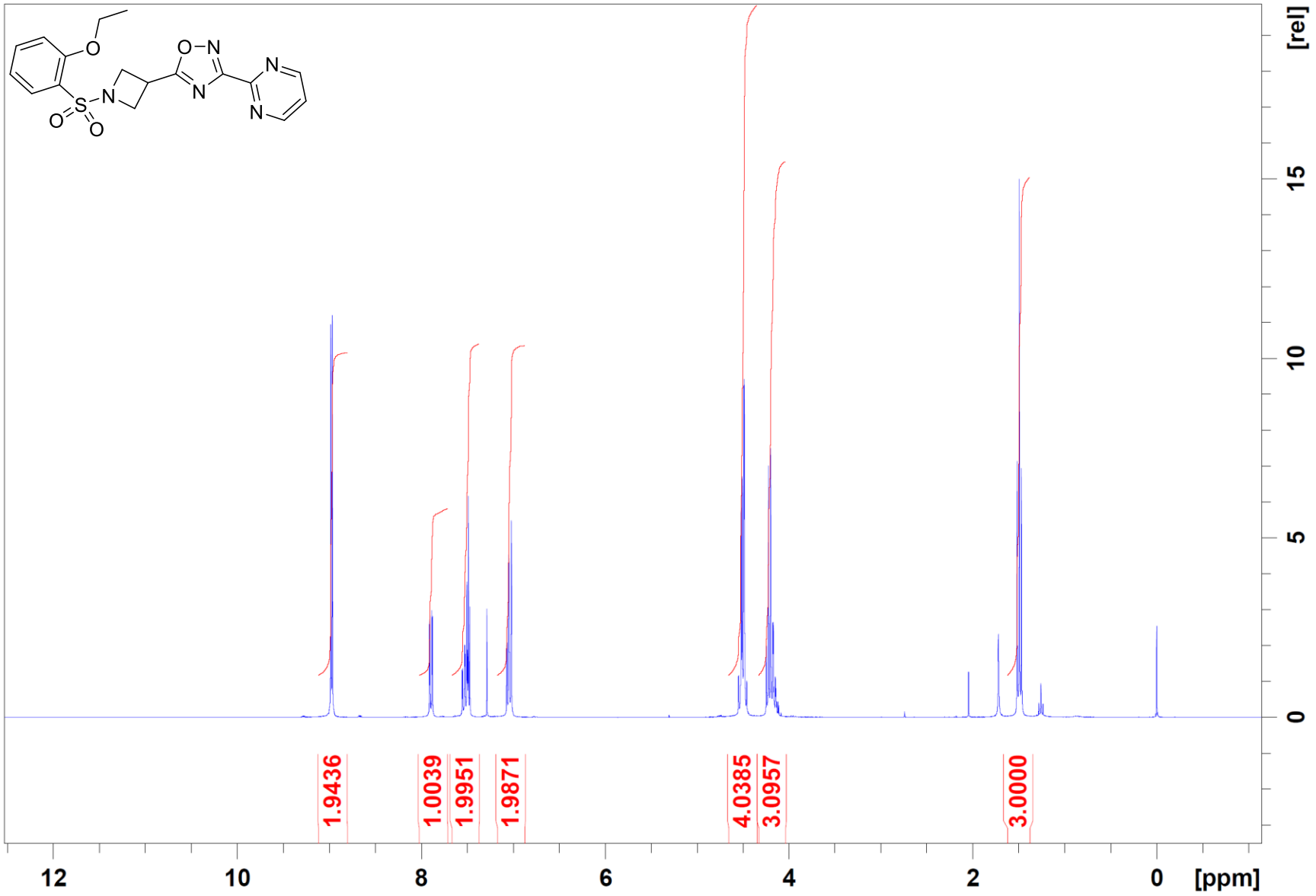
Analog **67** – ^{1}H NMR



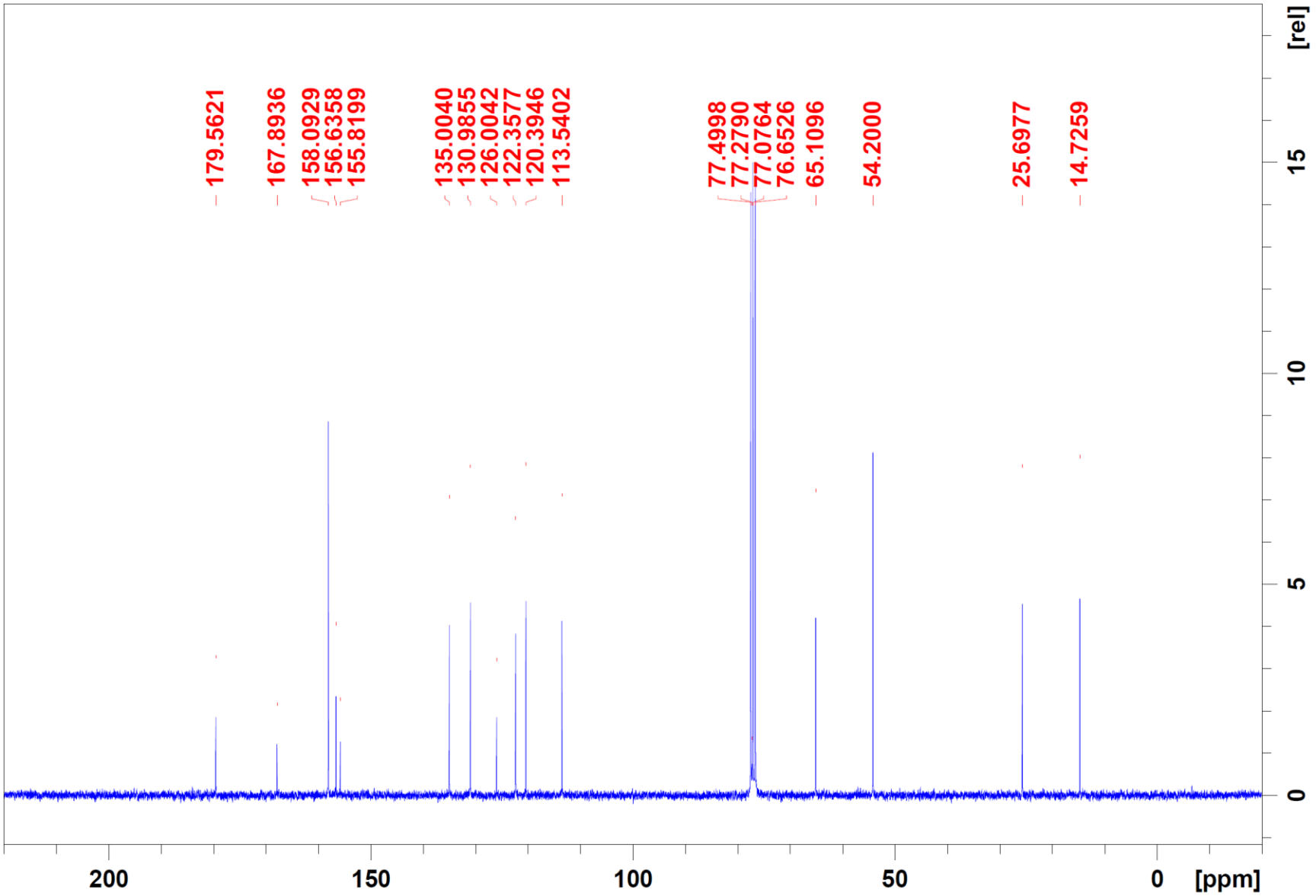
Analog **67** – ^{13}C NMR



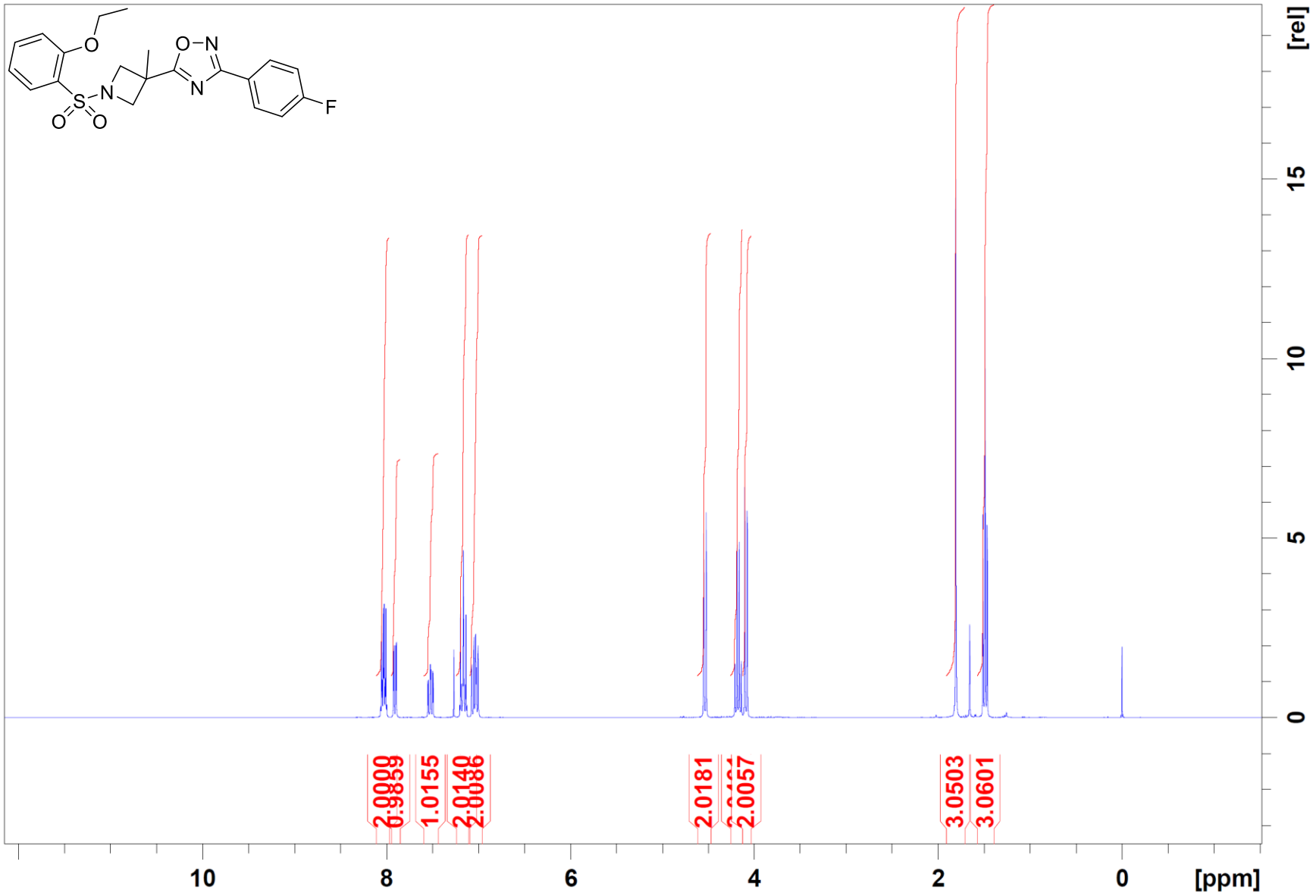
Analog **68** – ^{1}H NMR



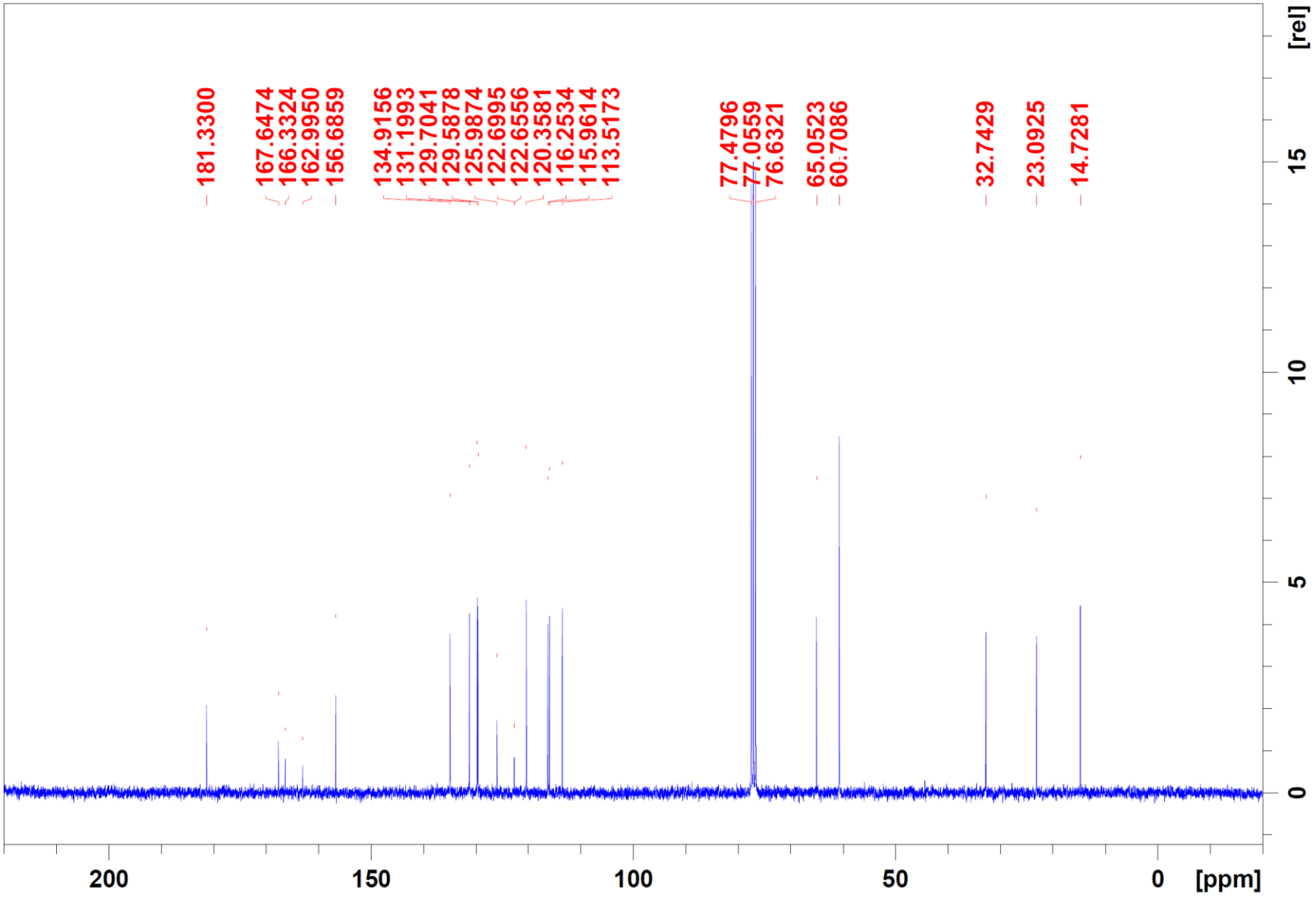
Analog **68** – ^{13}C NMR



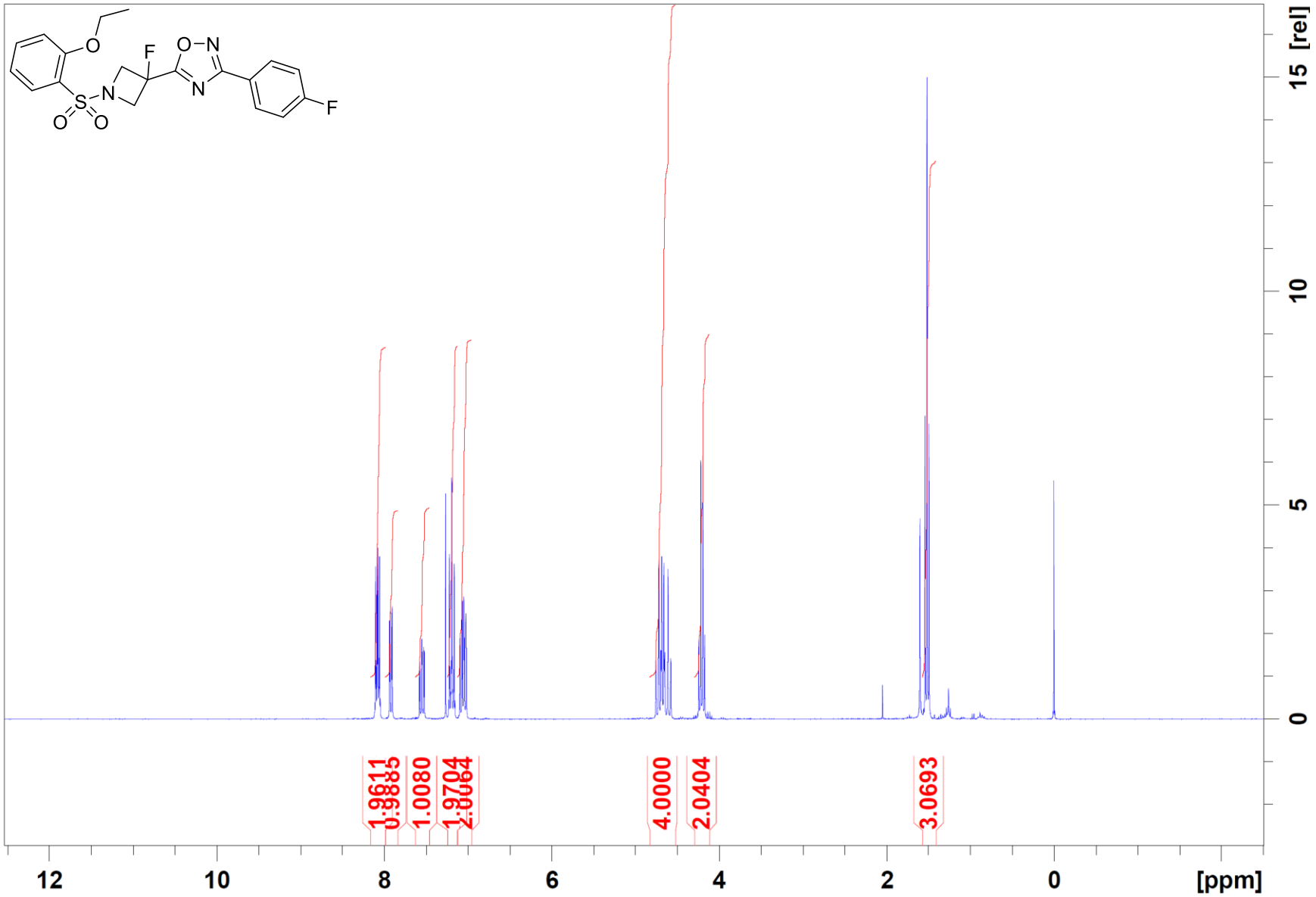
Analog **69** – ^{1}H NMR



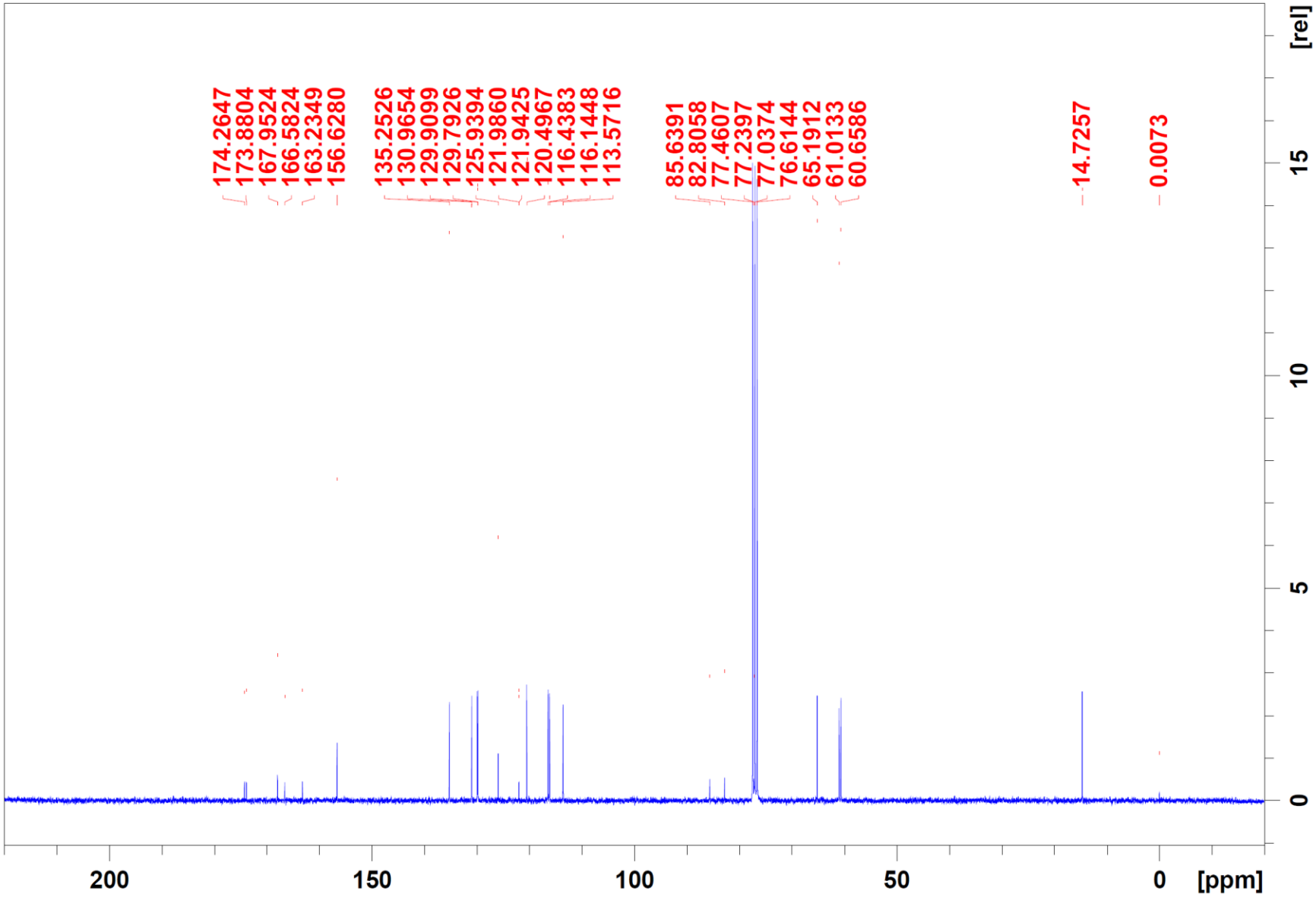
Analog **69** – ^{13}C NMR



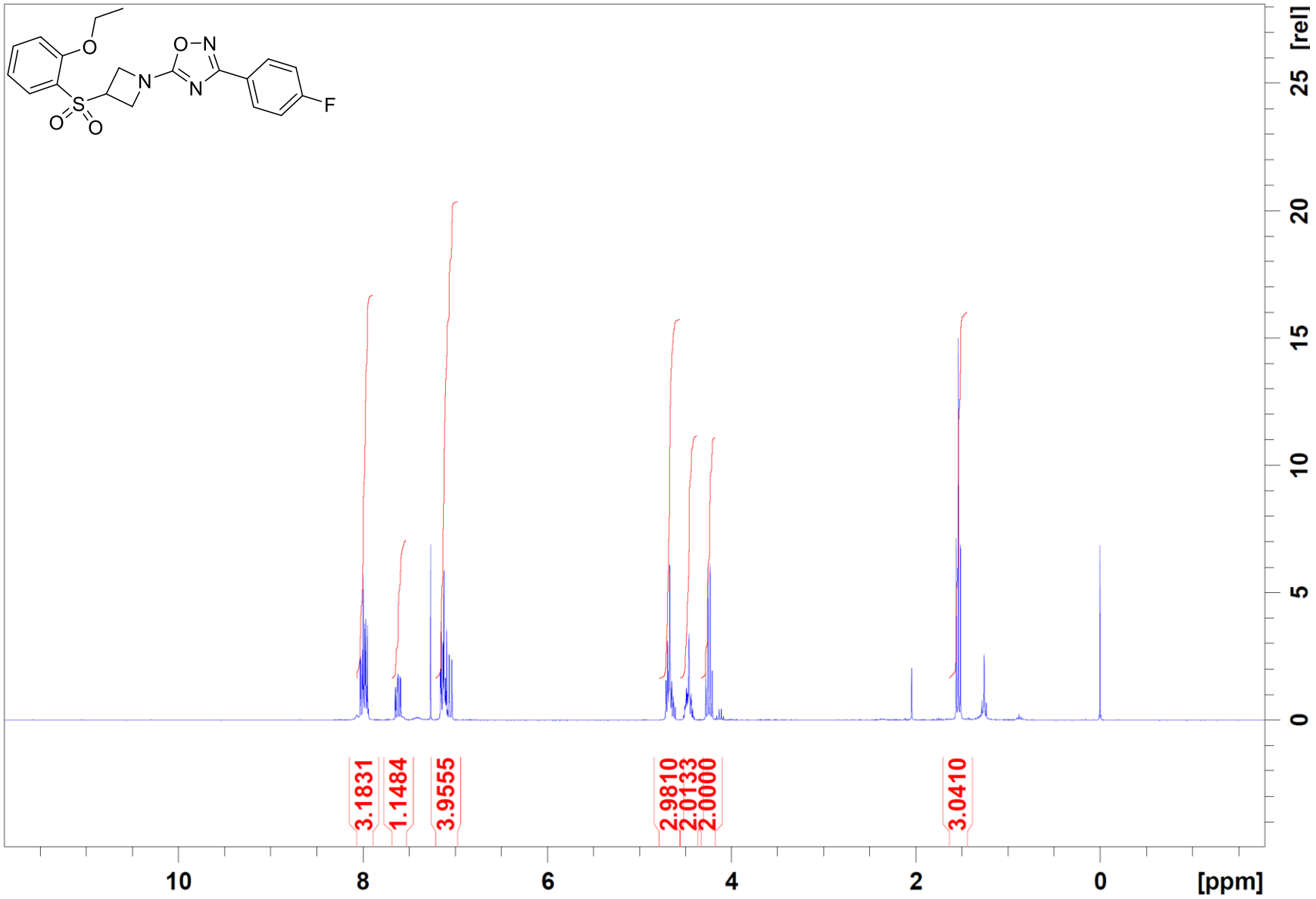
Analog **70** – ^{1}H NMR



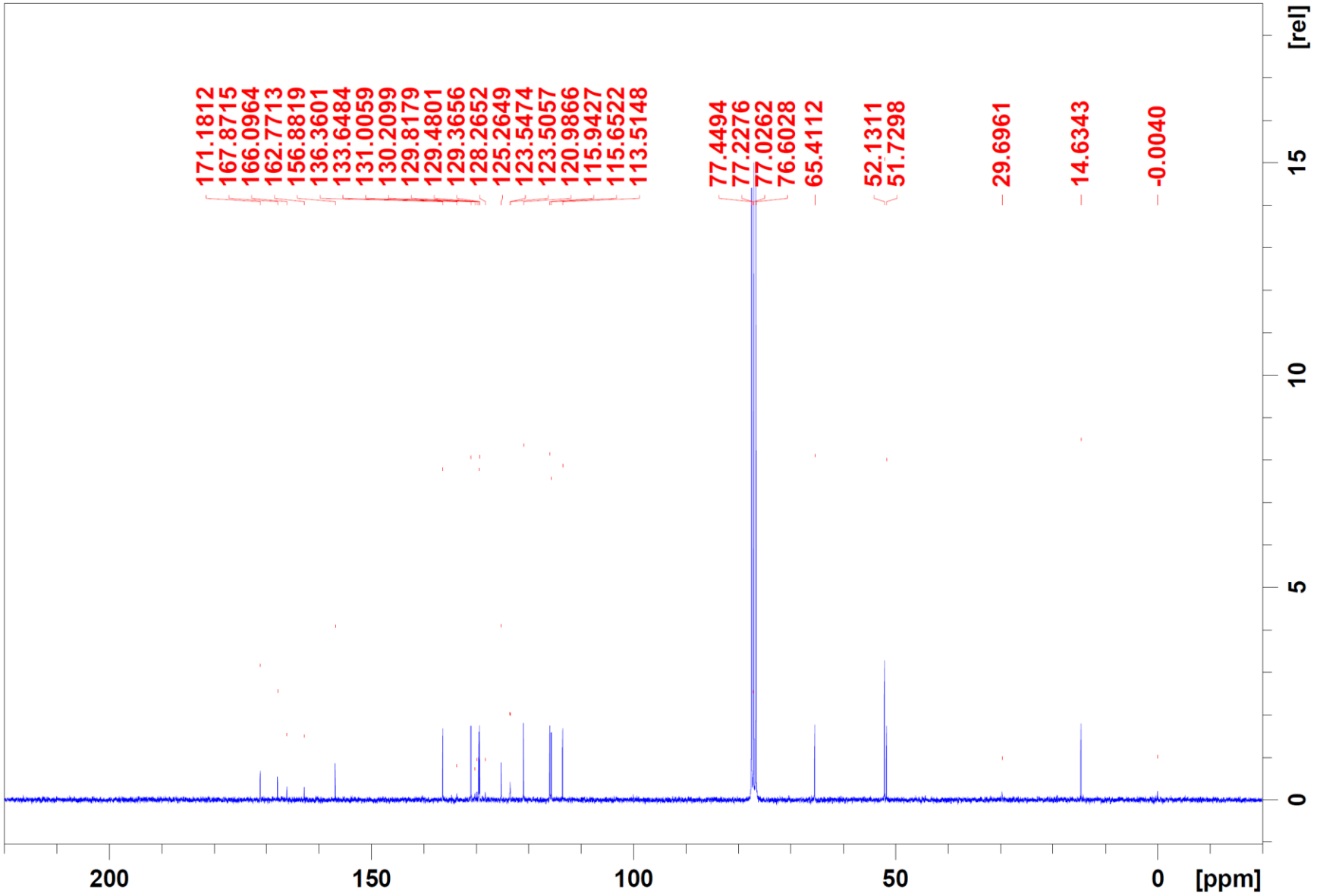
Analog **70** – ^{13}C NMR



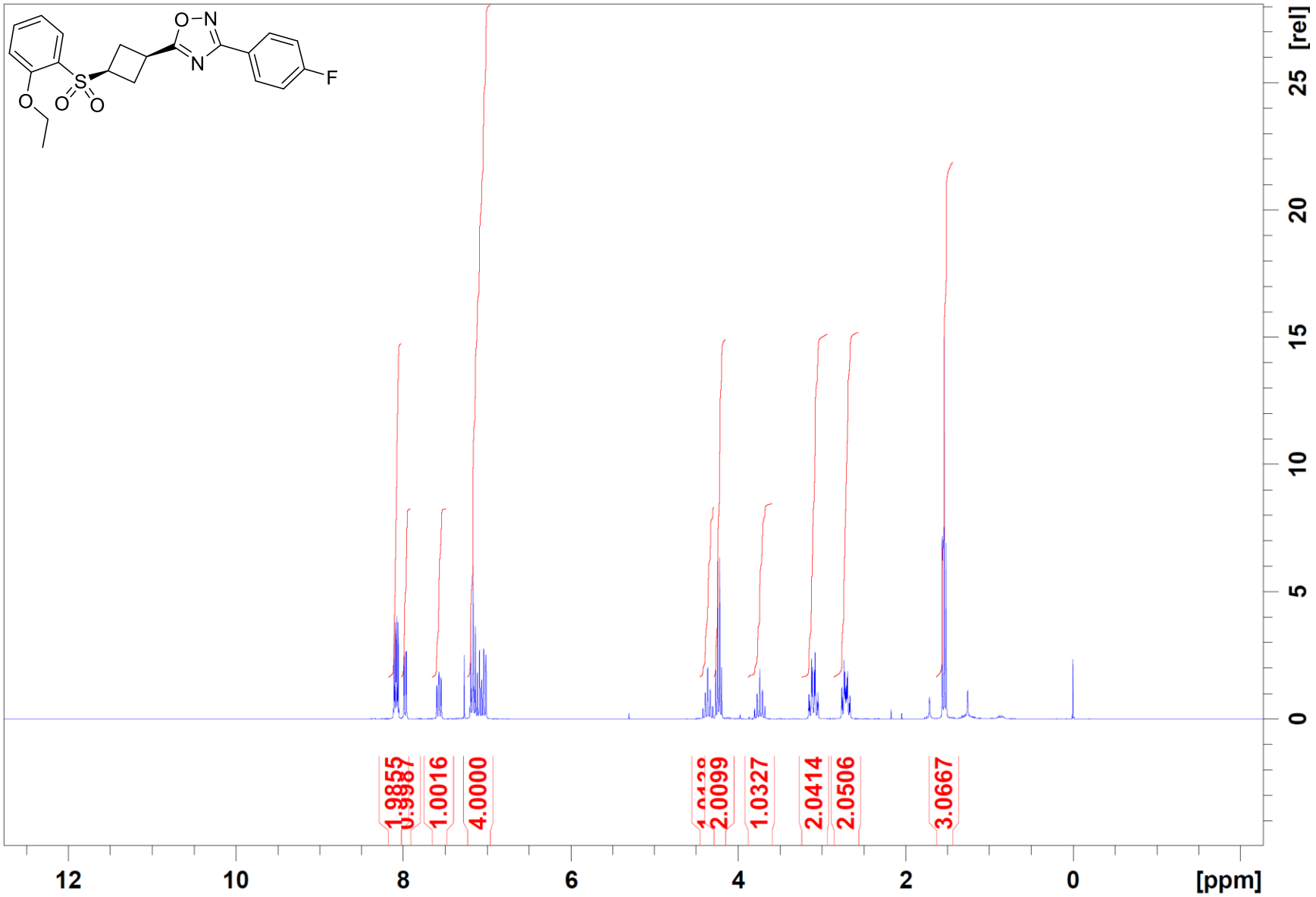
Analog **71** – ^{1}H NMR



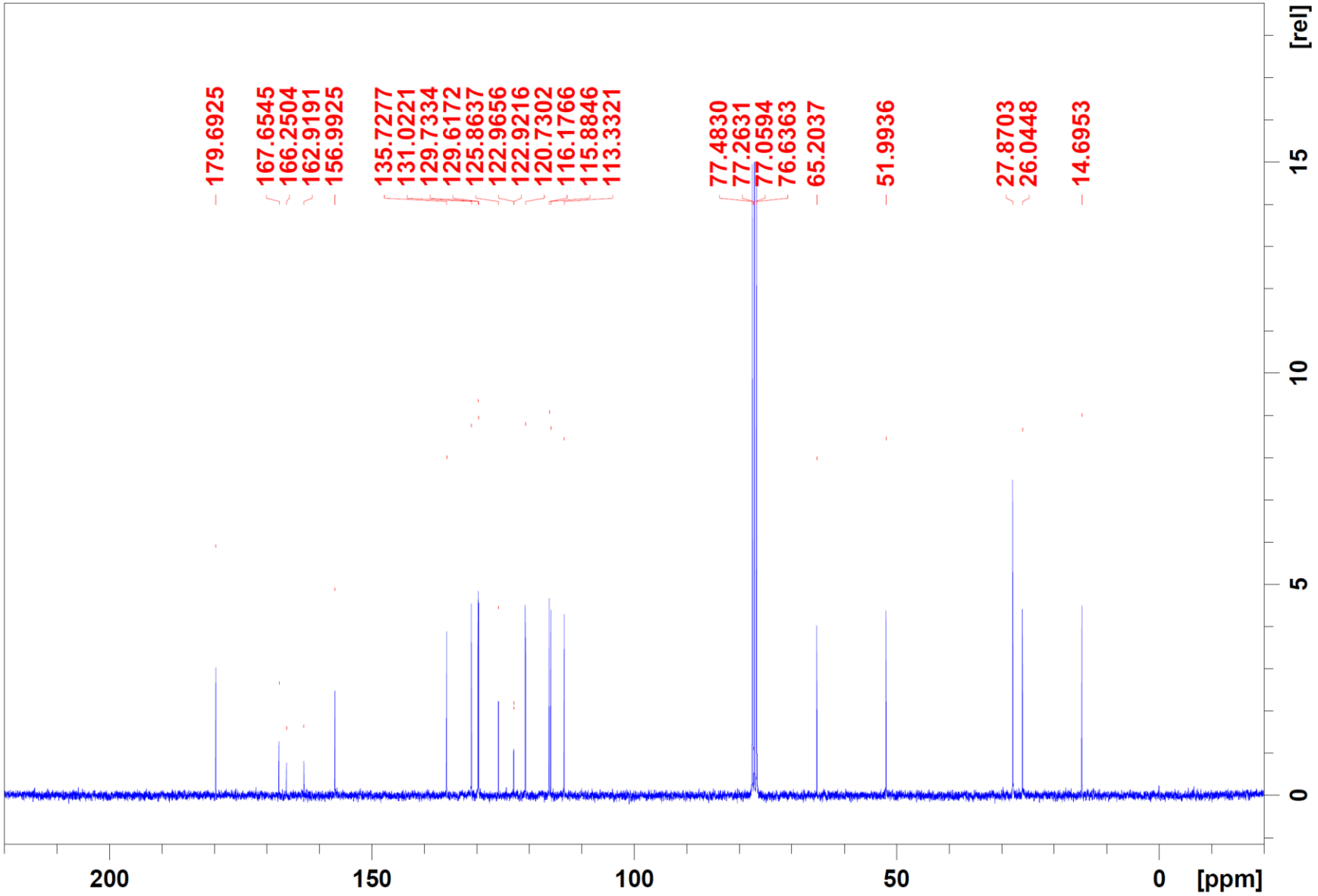
Analog **71** – ^{13}C NMR



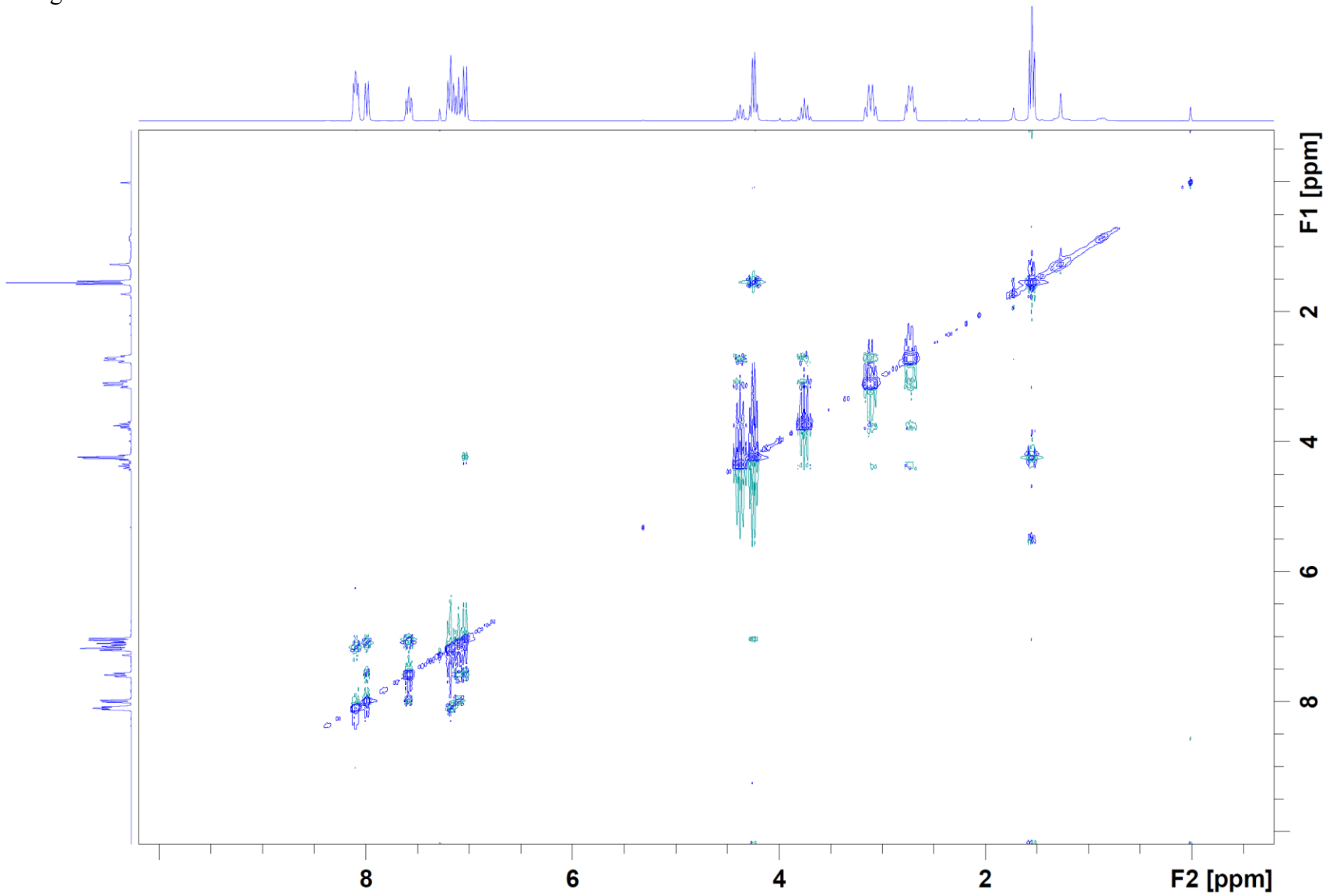
Analog **73a** – ^{1}H NMR



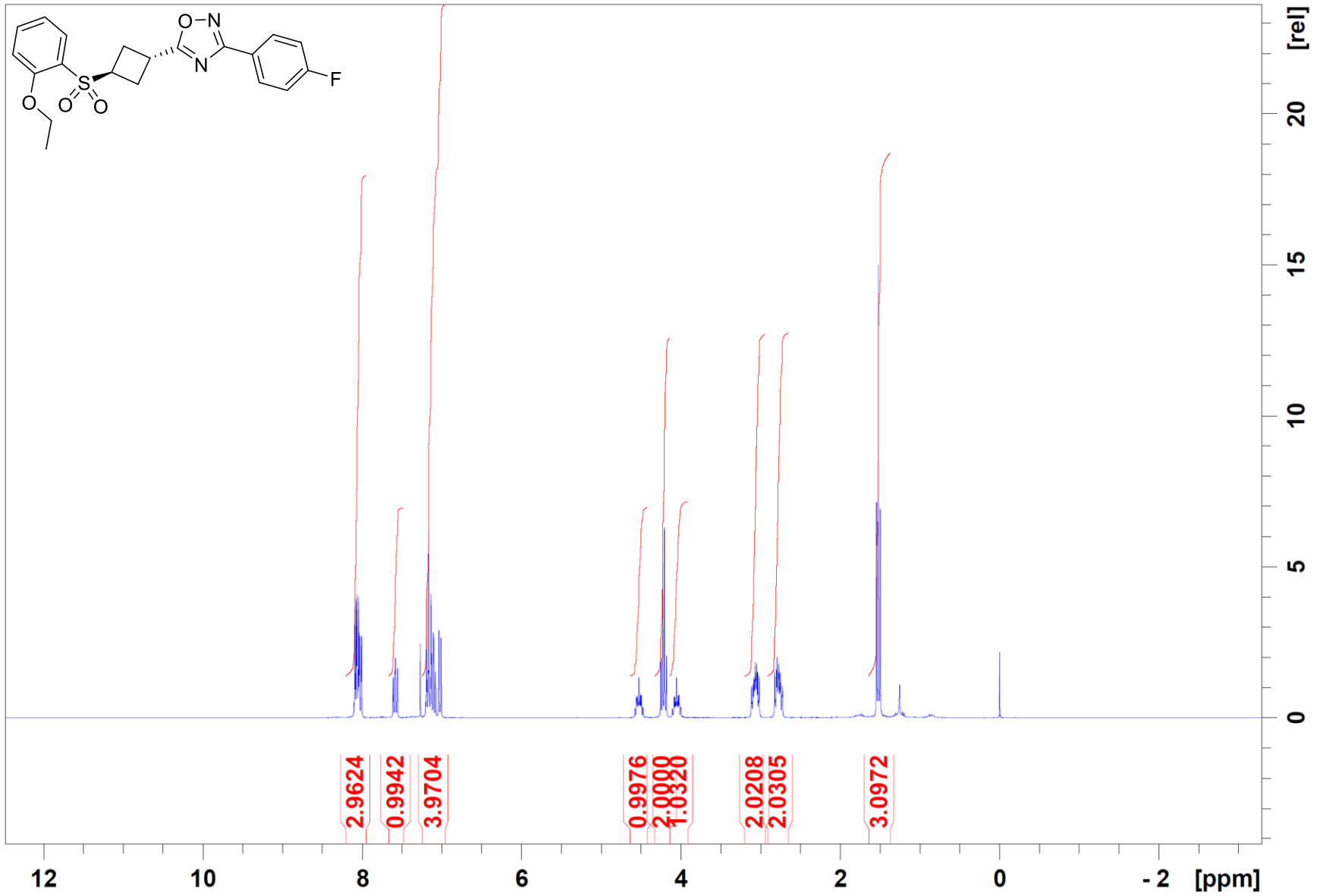
Analog **73a** – ^{13}C NMR



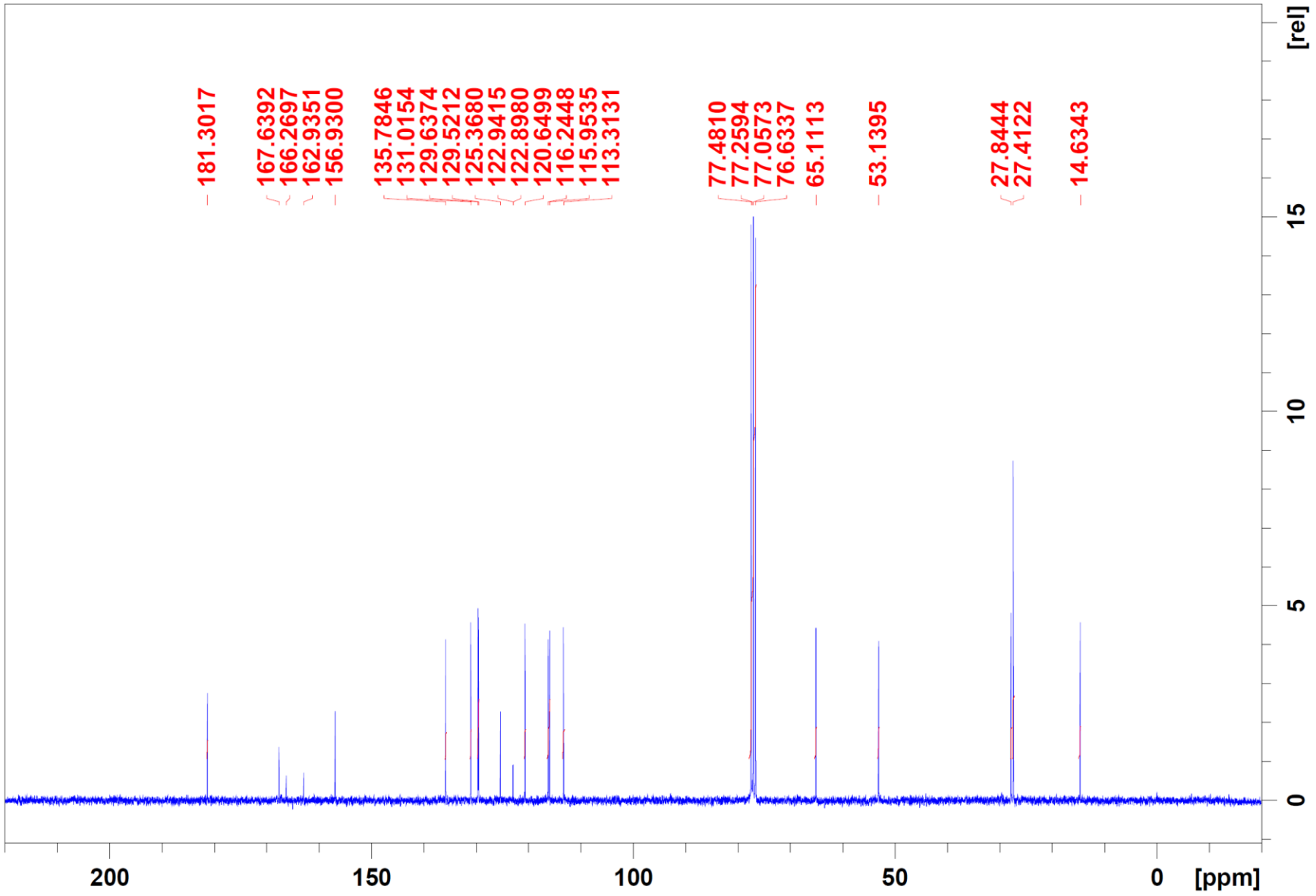
Analog **73a** – NOESY NMR



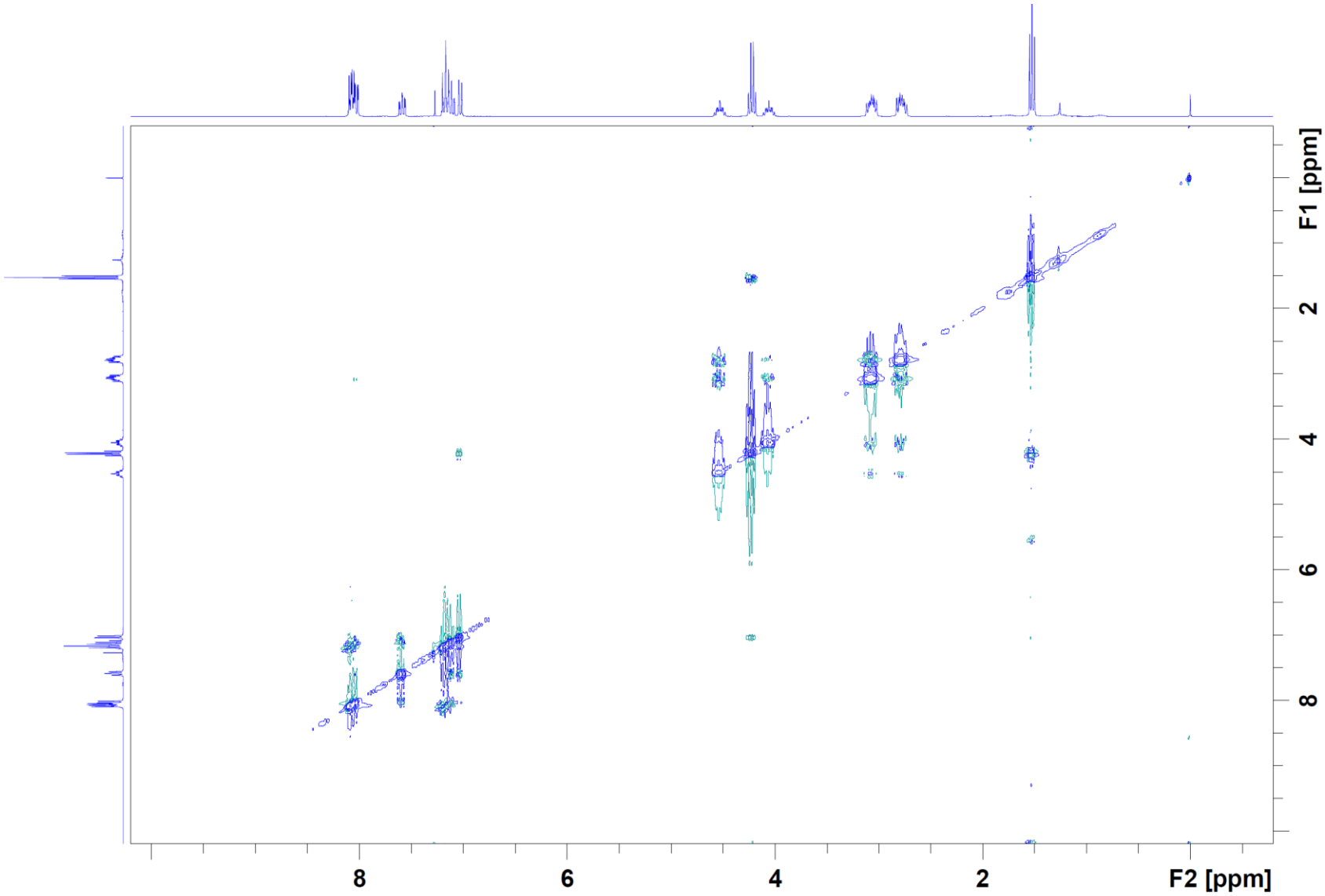
Analog **73b** – ^{1}H NMR



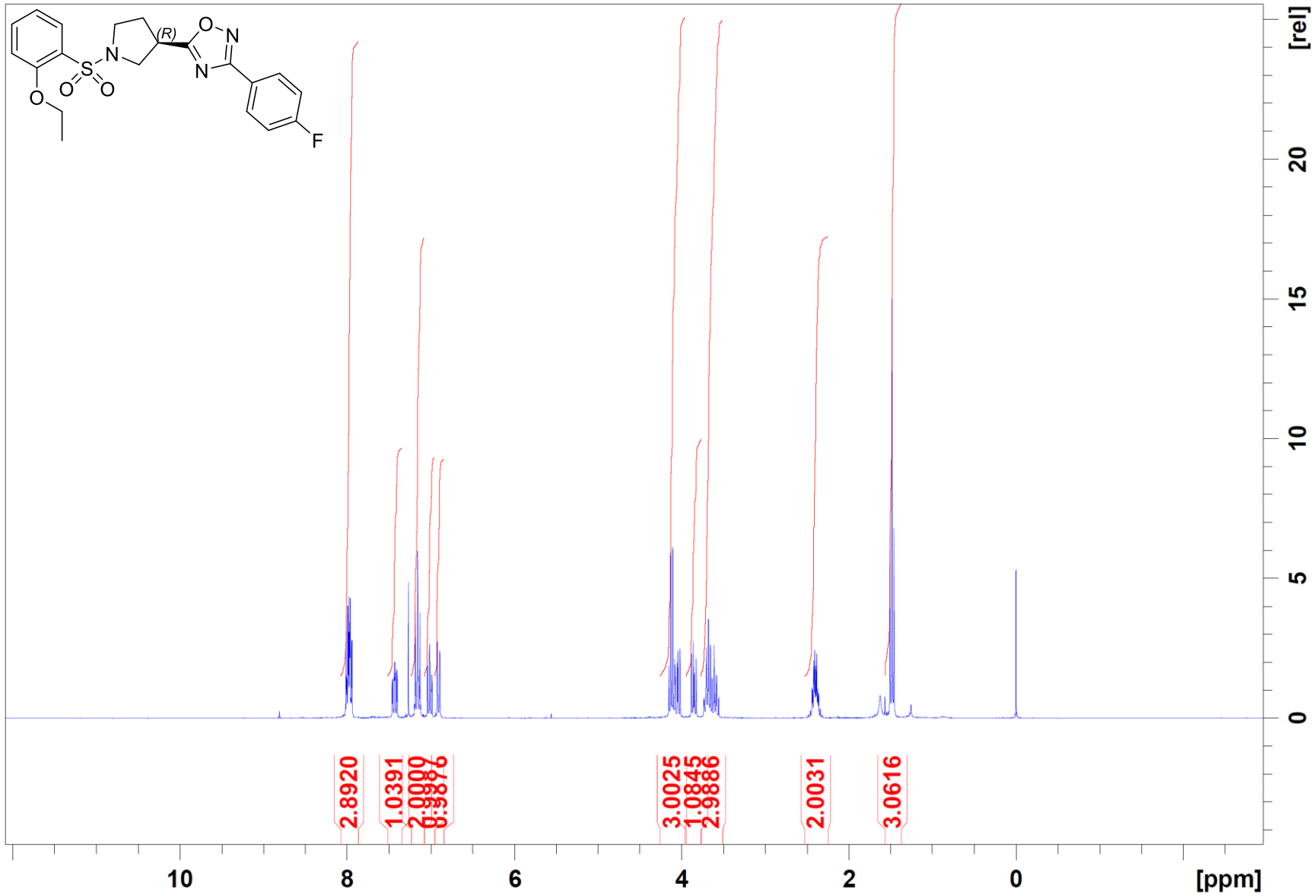
Analog 73b – ^{13}CNMR



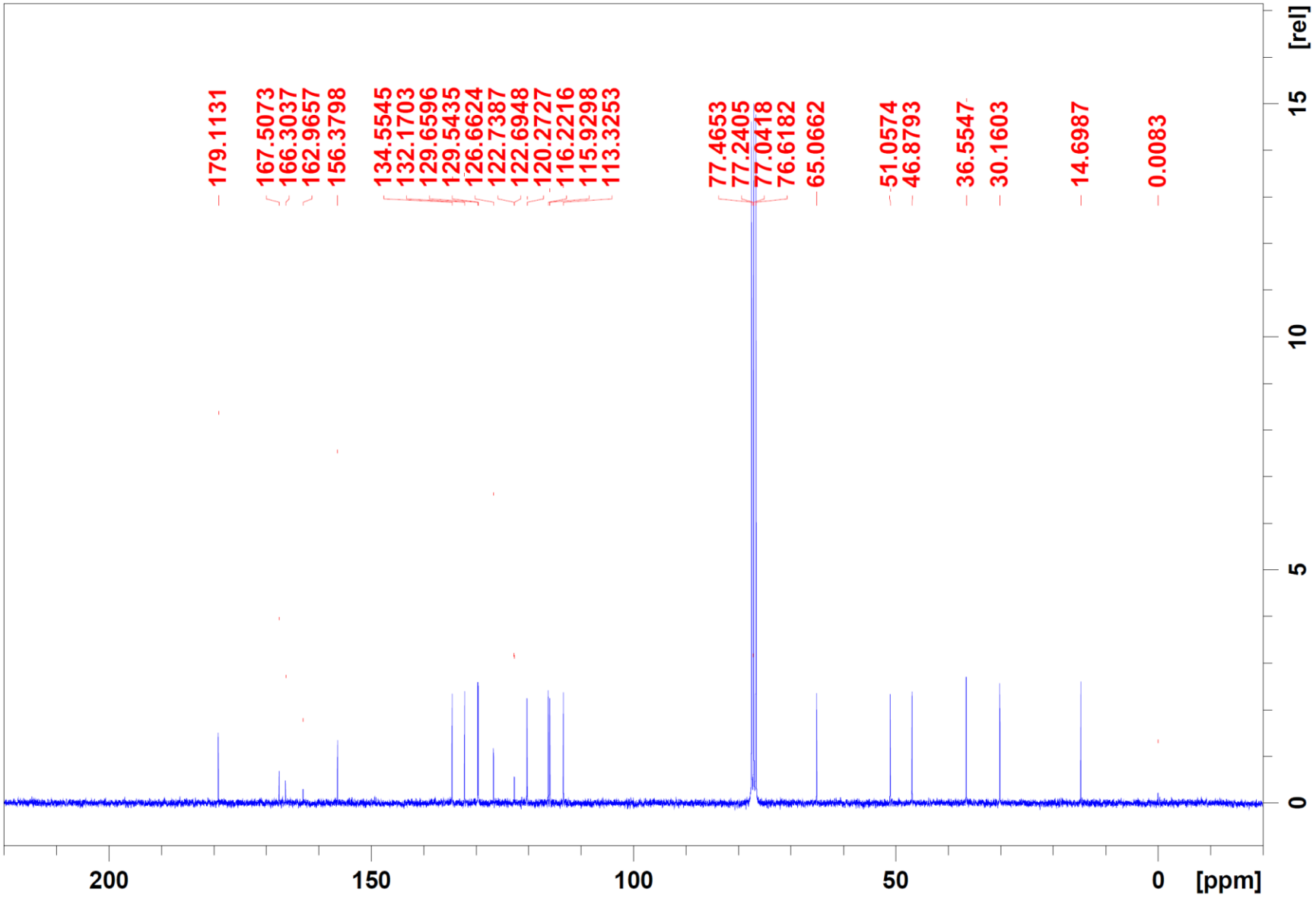
Analog **73b** – NOESY NMR



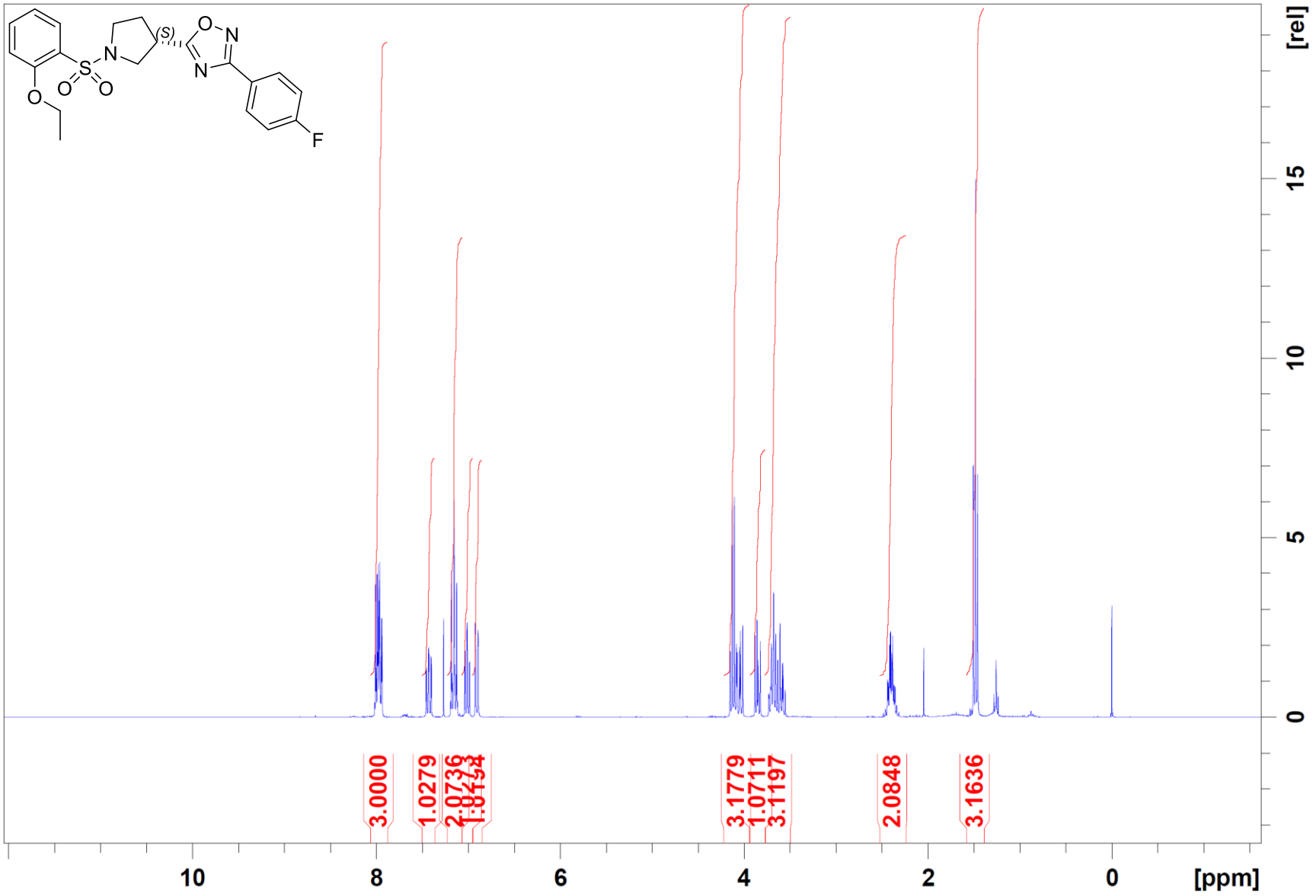
Analog **74** – ^{1}H NMR



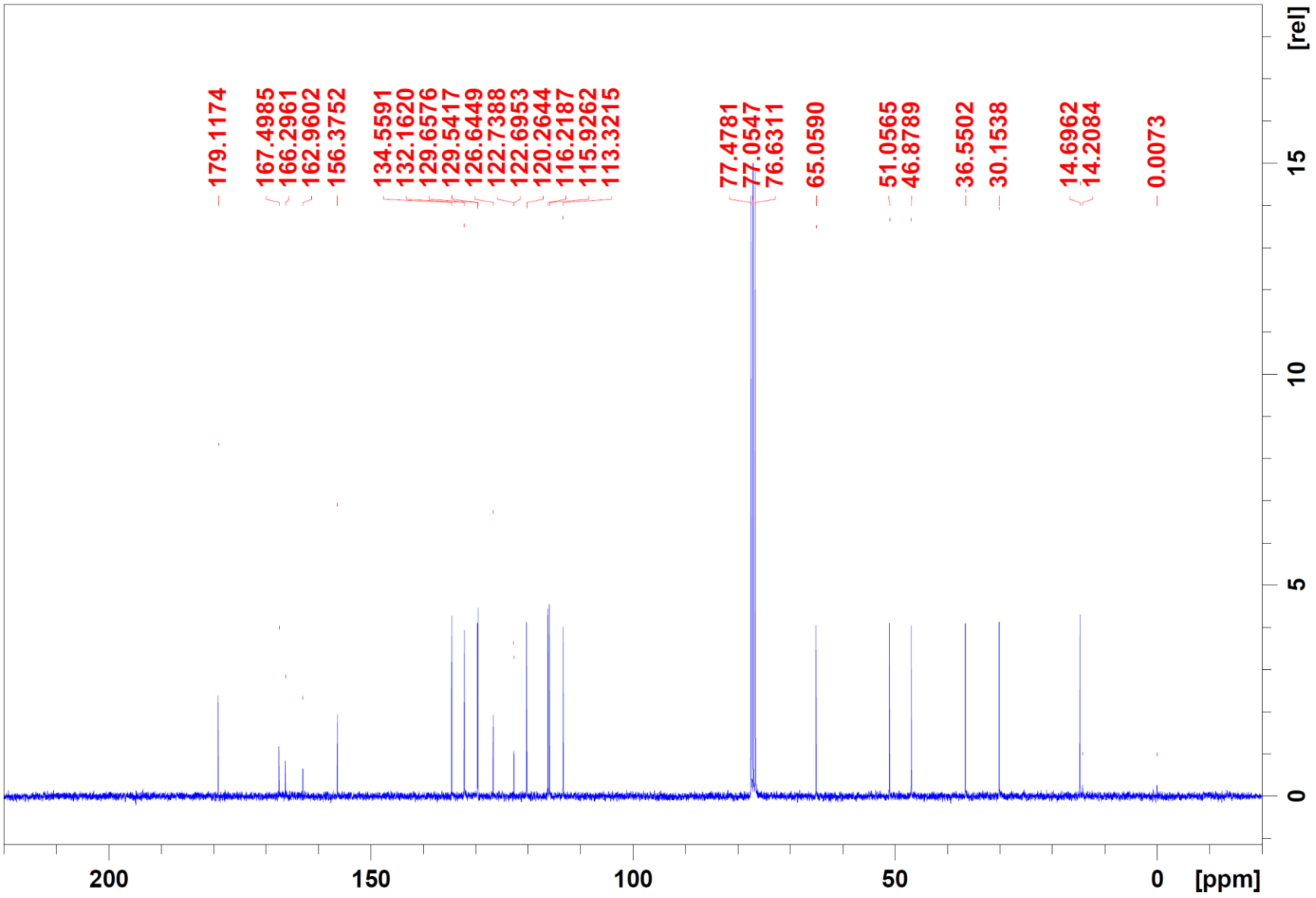
Analog **74** – ^{13}C NMR



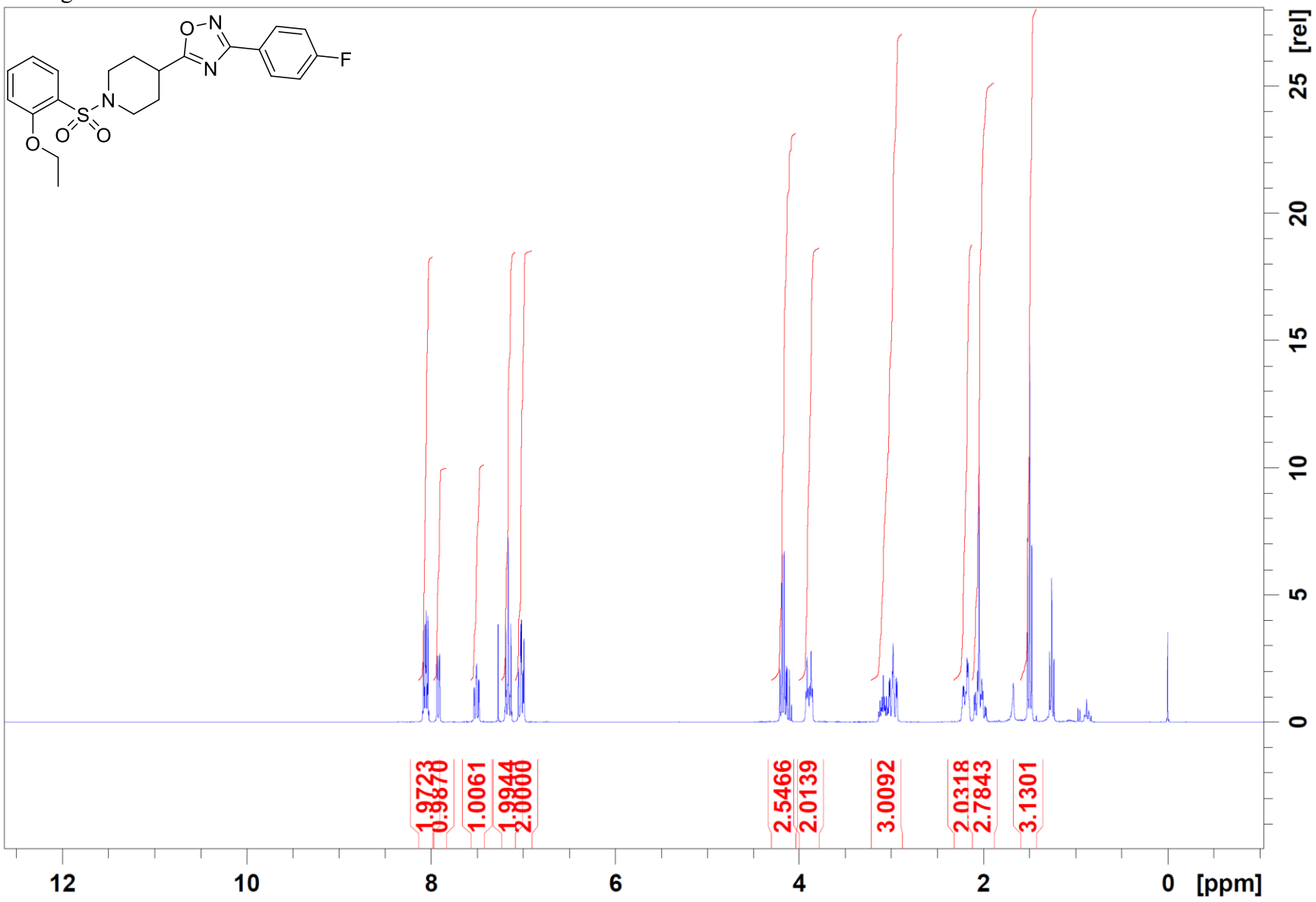
Analog **75** – ^{1}H NMR



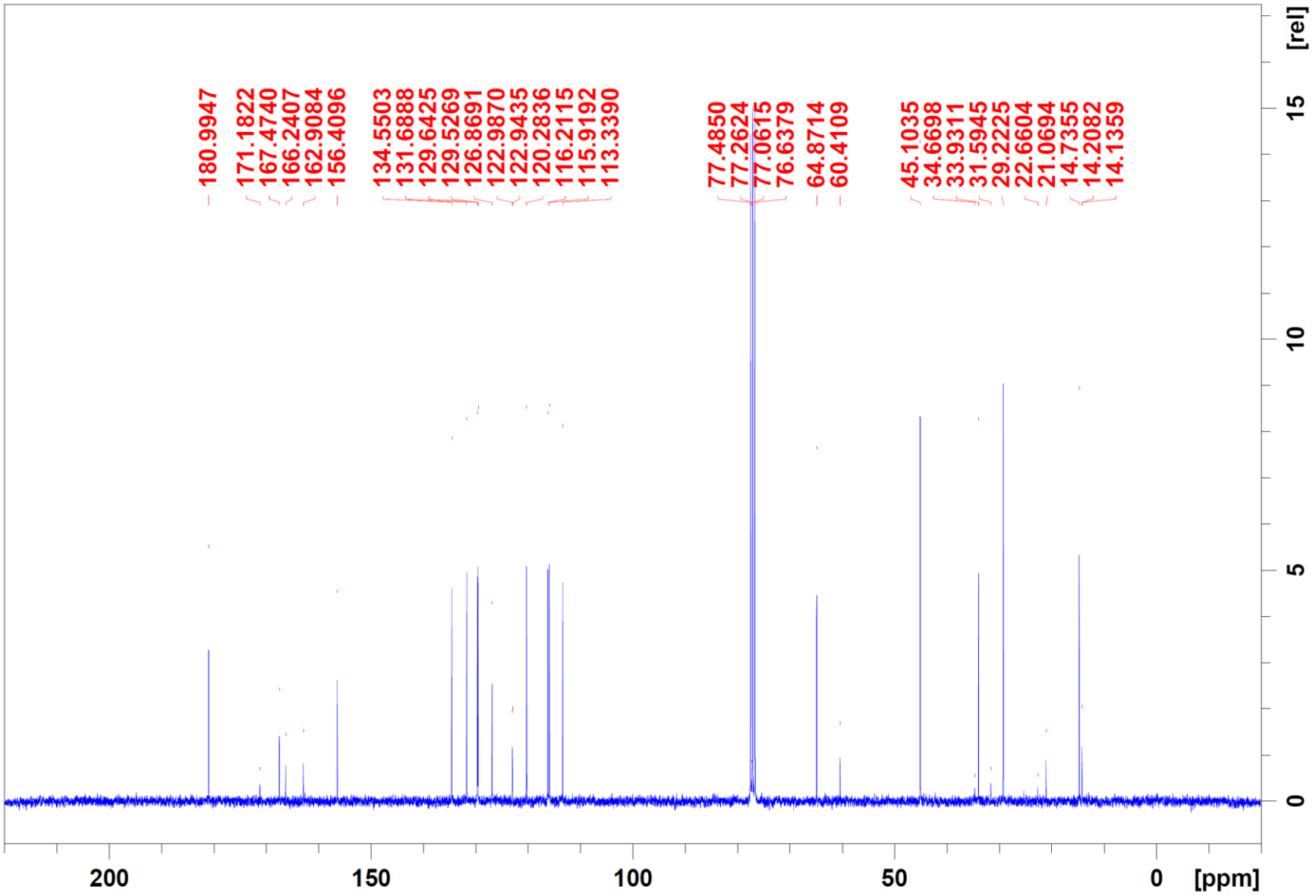
Analog **75** – ^{13}C NMR



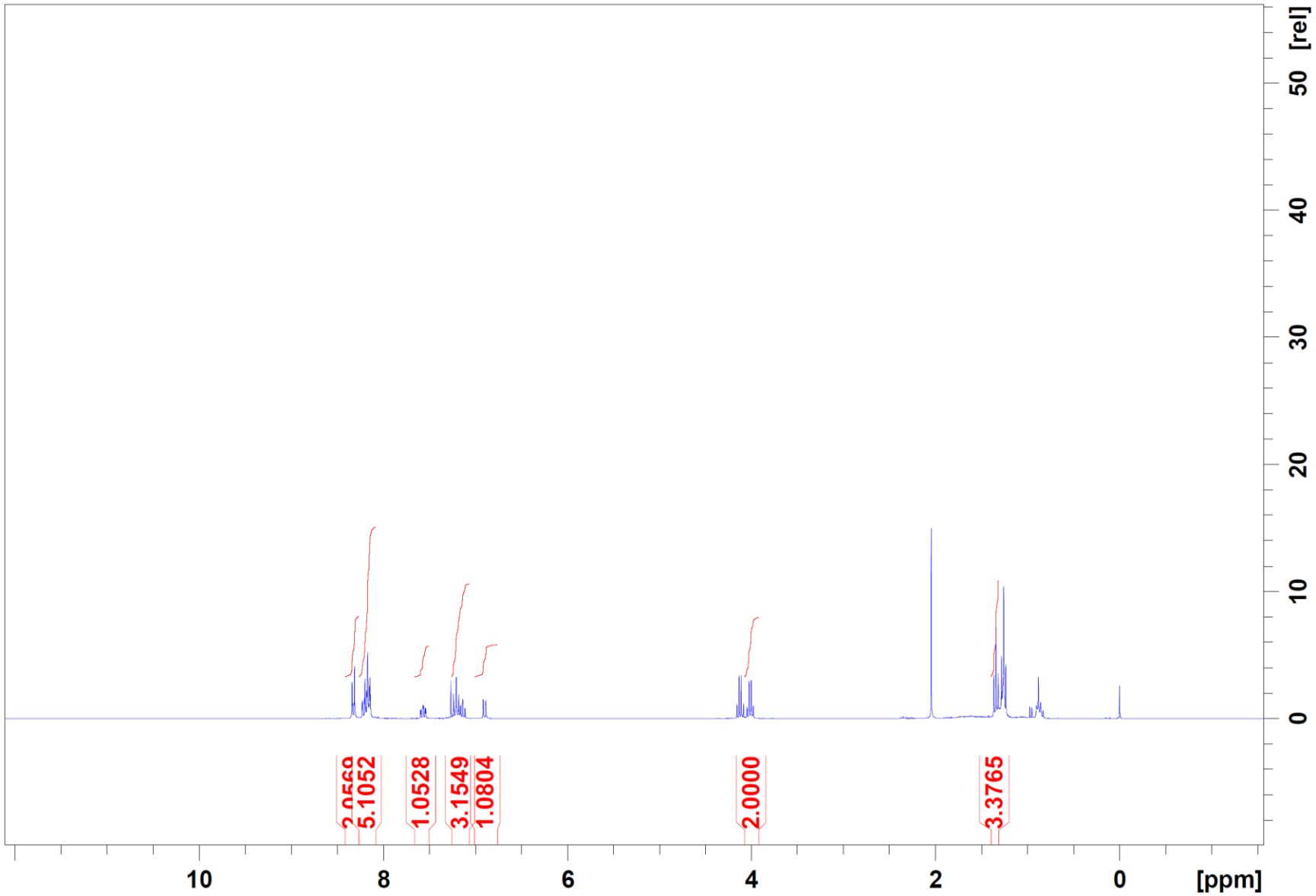
Analog **76** – ^{1}H NMR



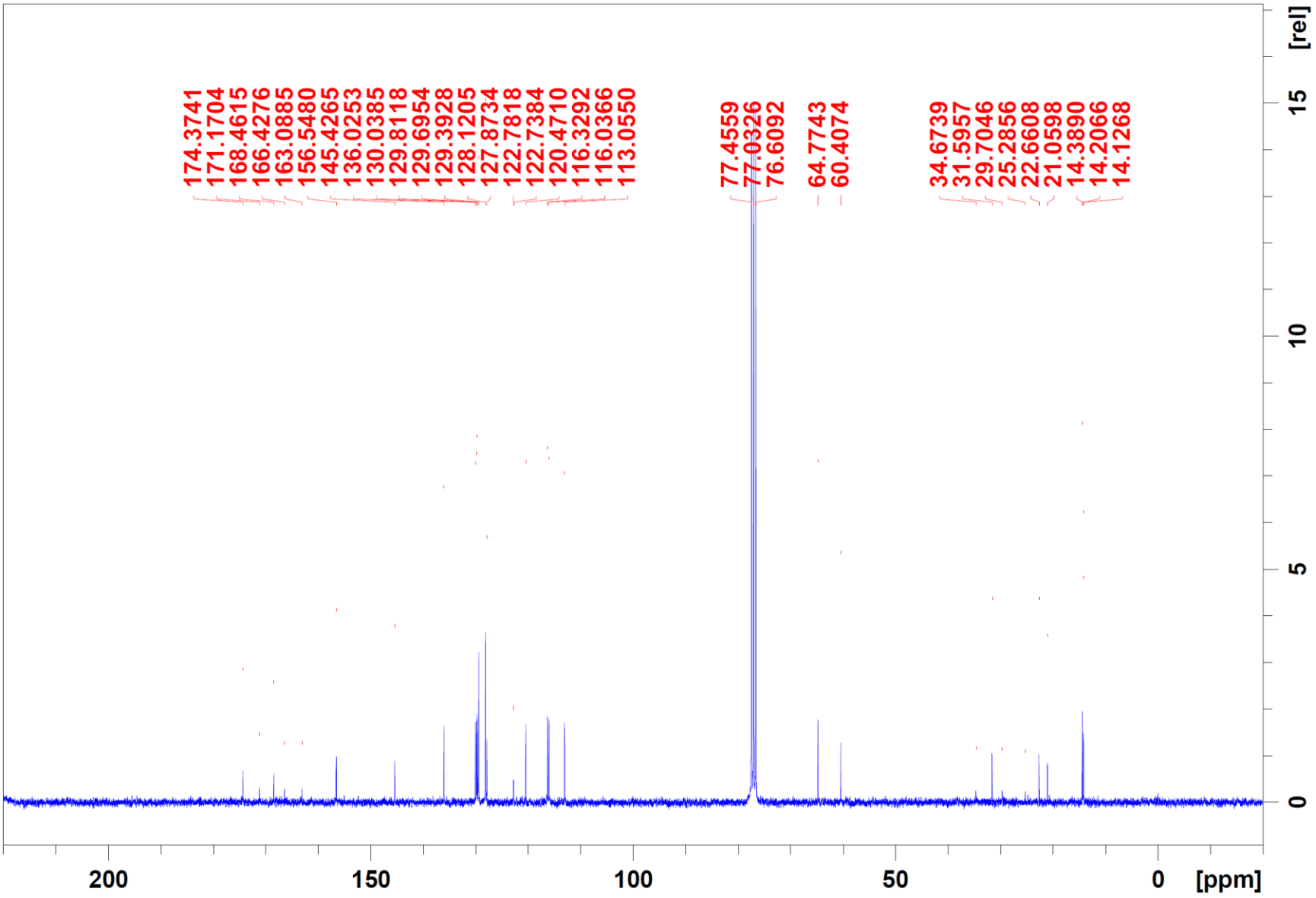
Analog **76** – ^{13}C NMR



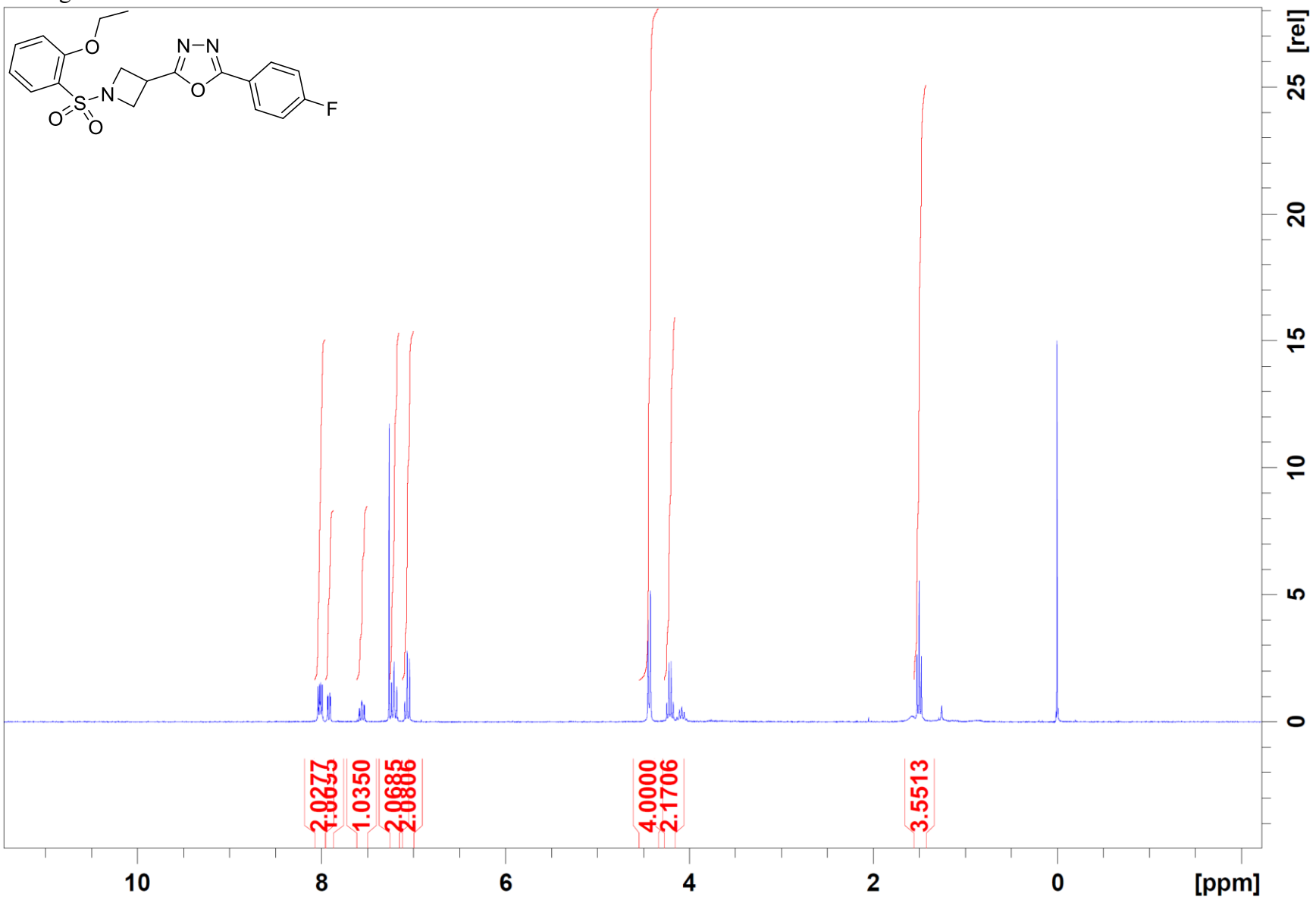
Analog **77** - ^{1}H NMR



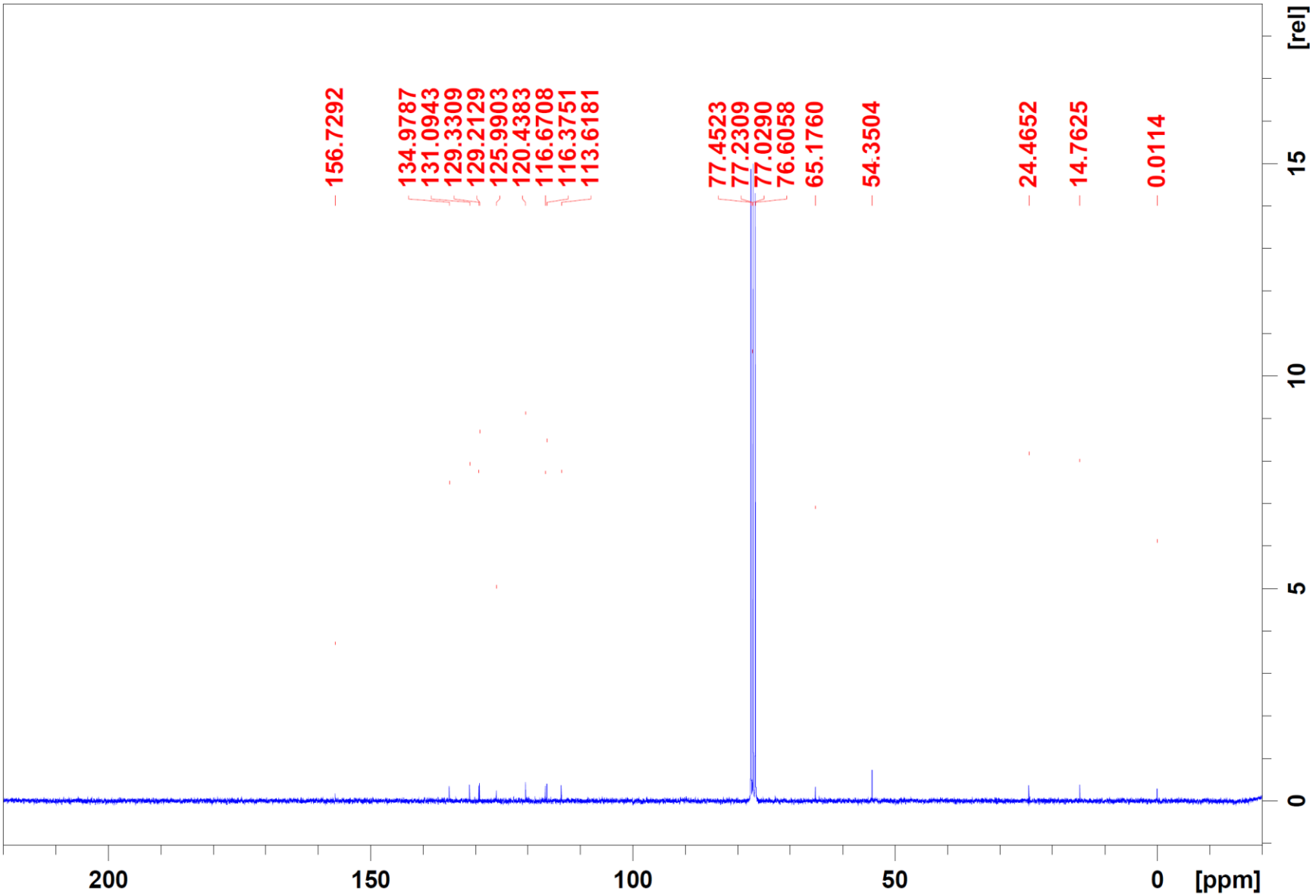
Analog **77** - ^{13}C NMR



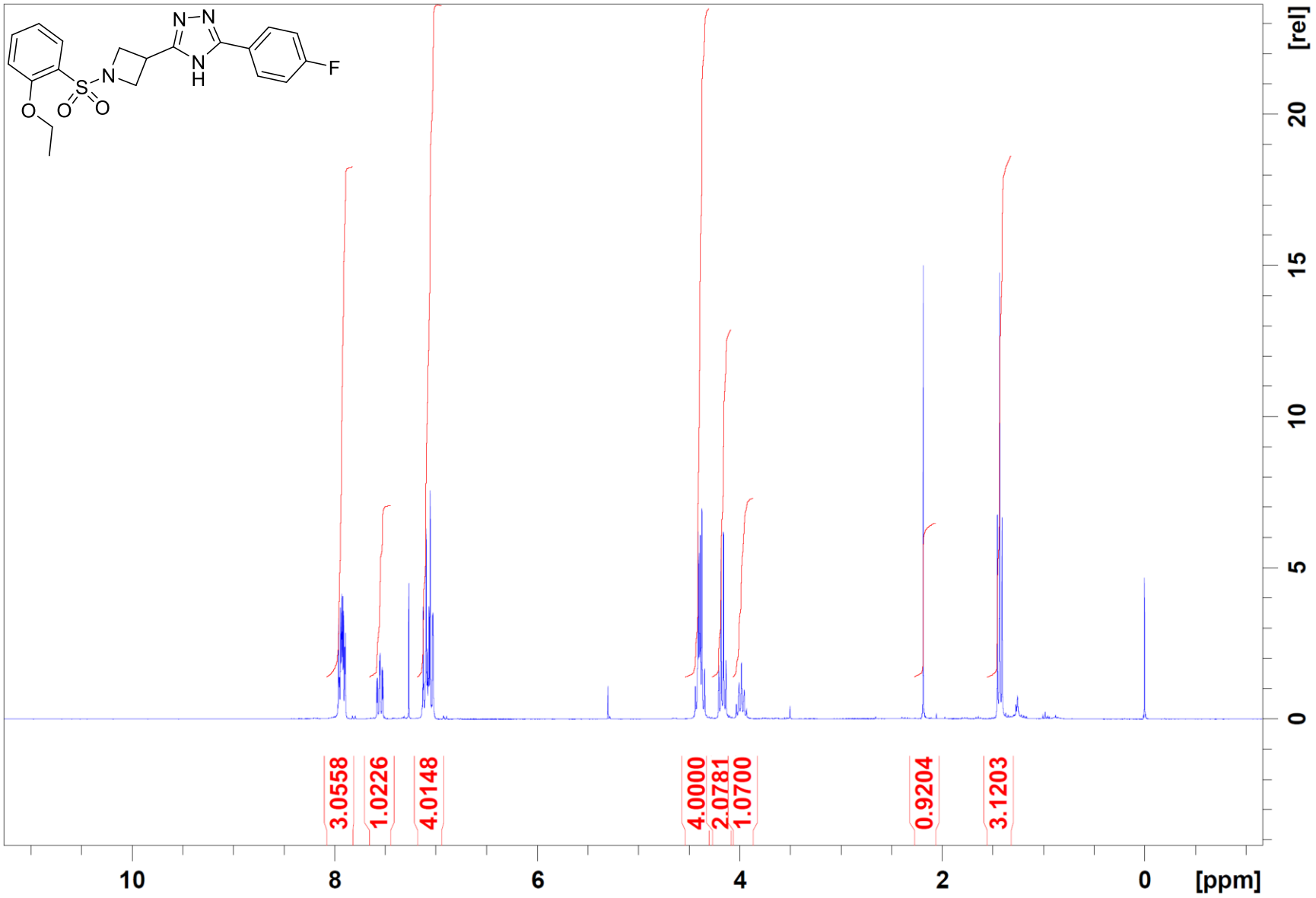
Analog **81** – ^{1}H NMR



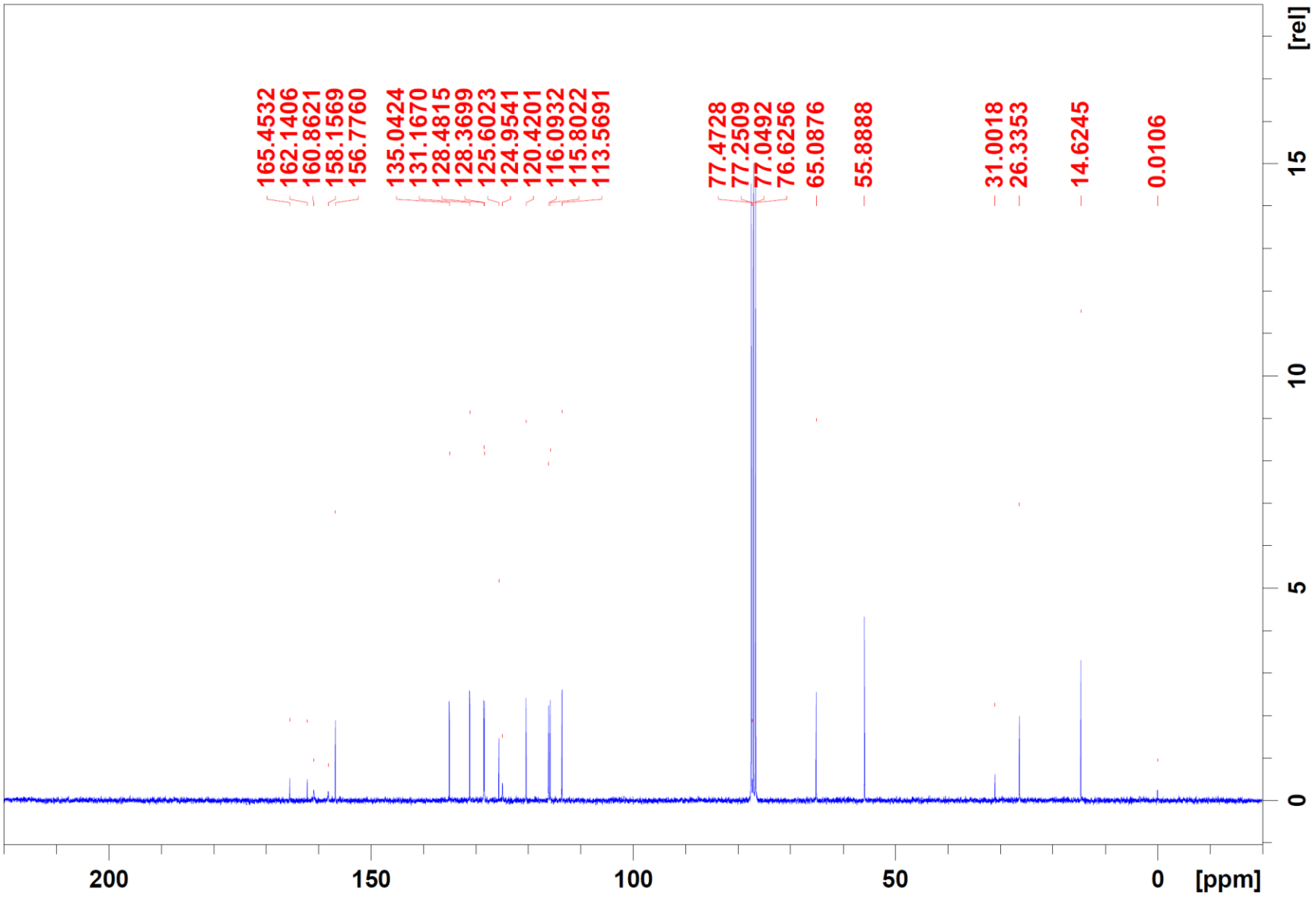
Analog **81** – ^{13}C NMR



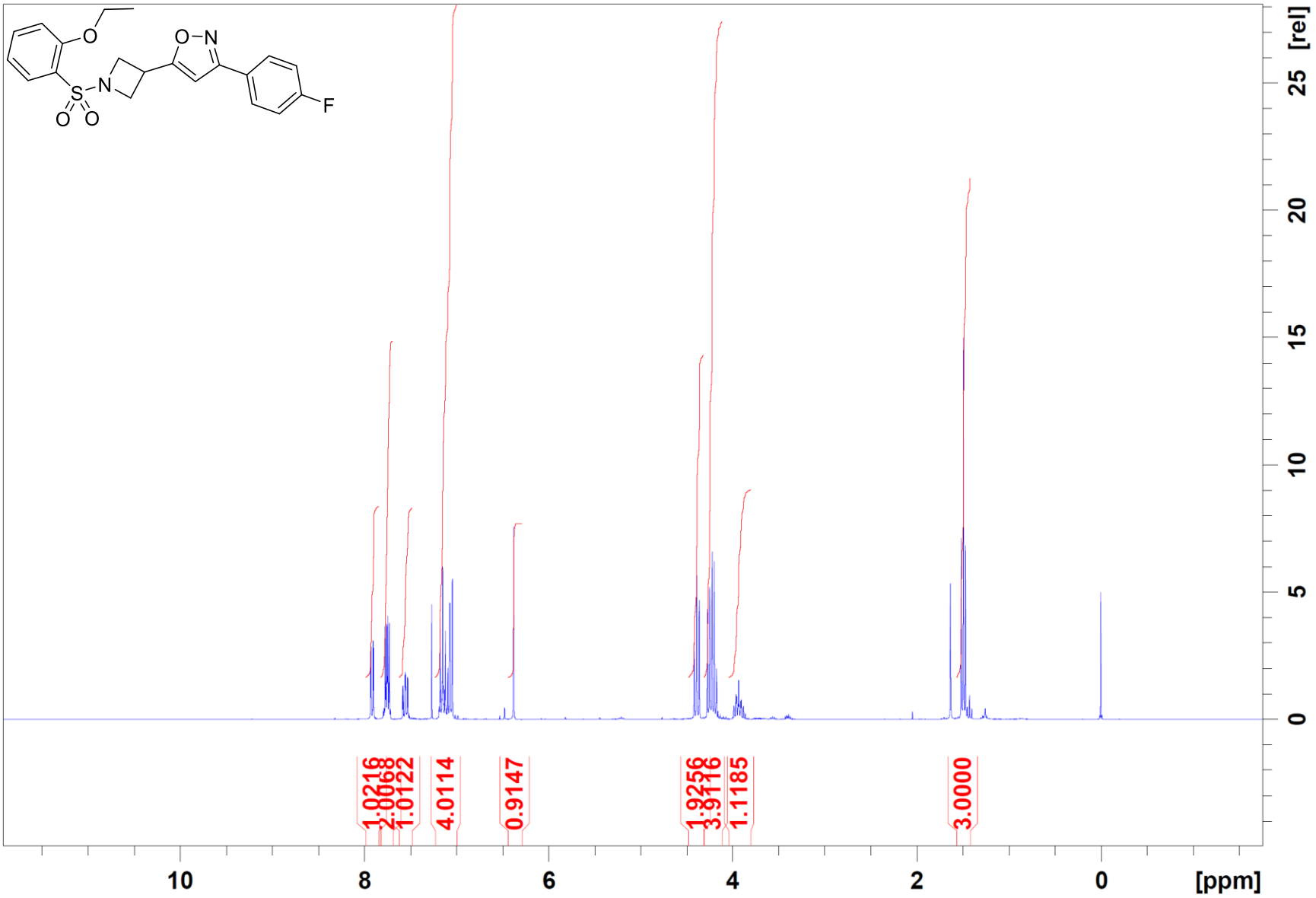
Analog **86** – ^{1}H NMR



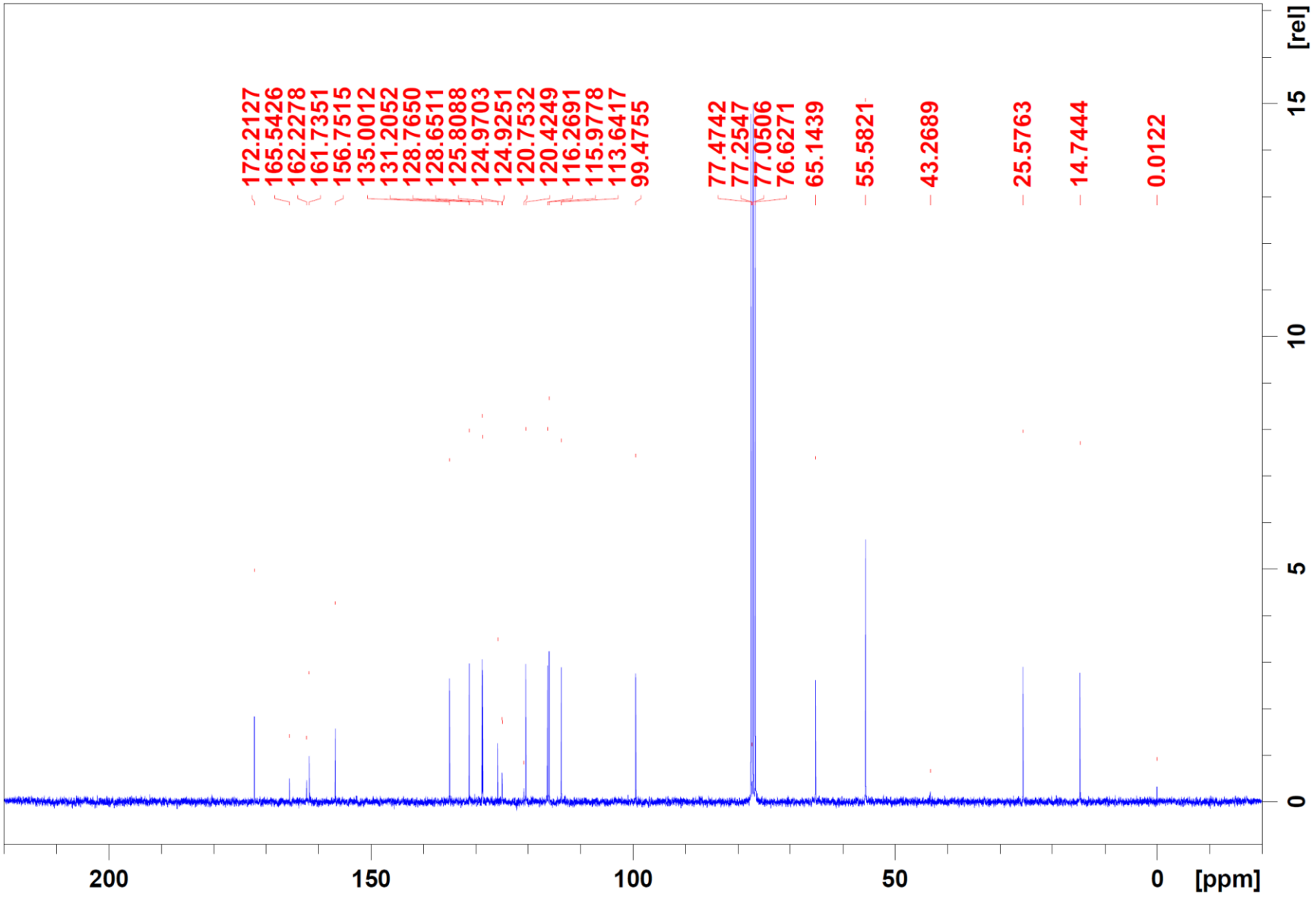
Analog **86** – ^{13}C NMR



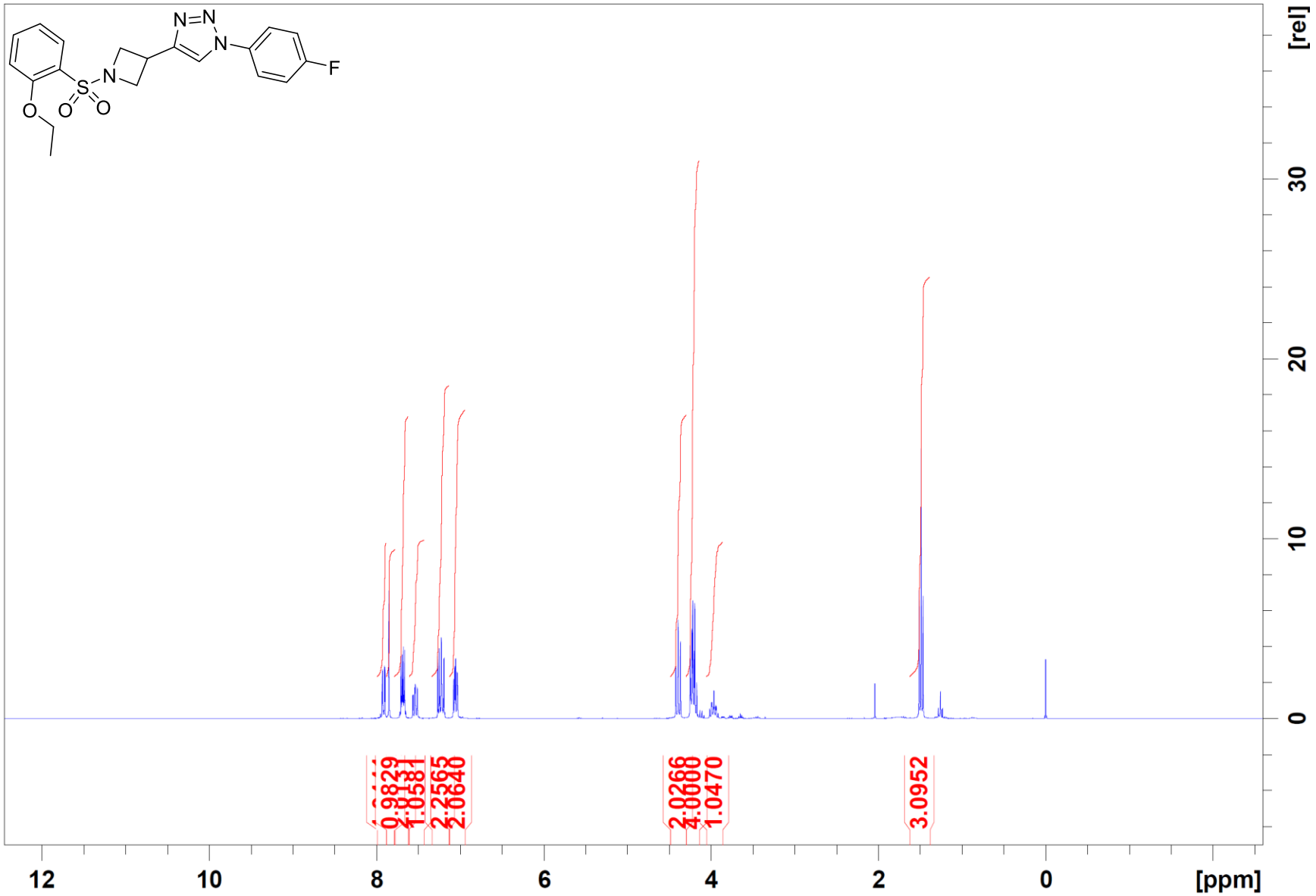
Analog **92** – ^{1}H NMR



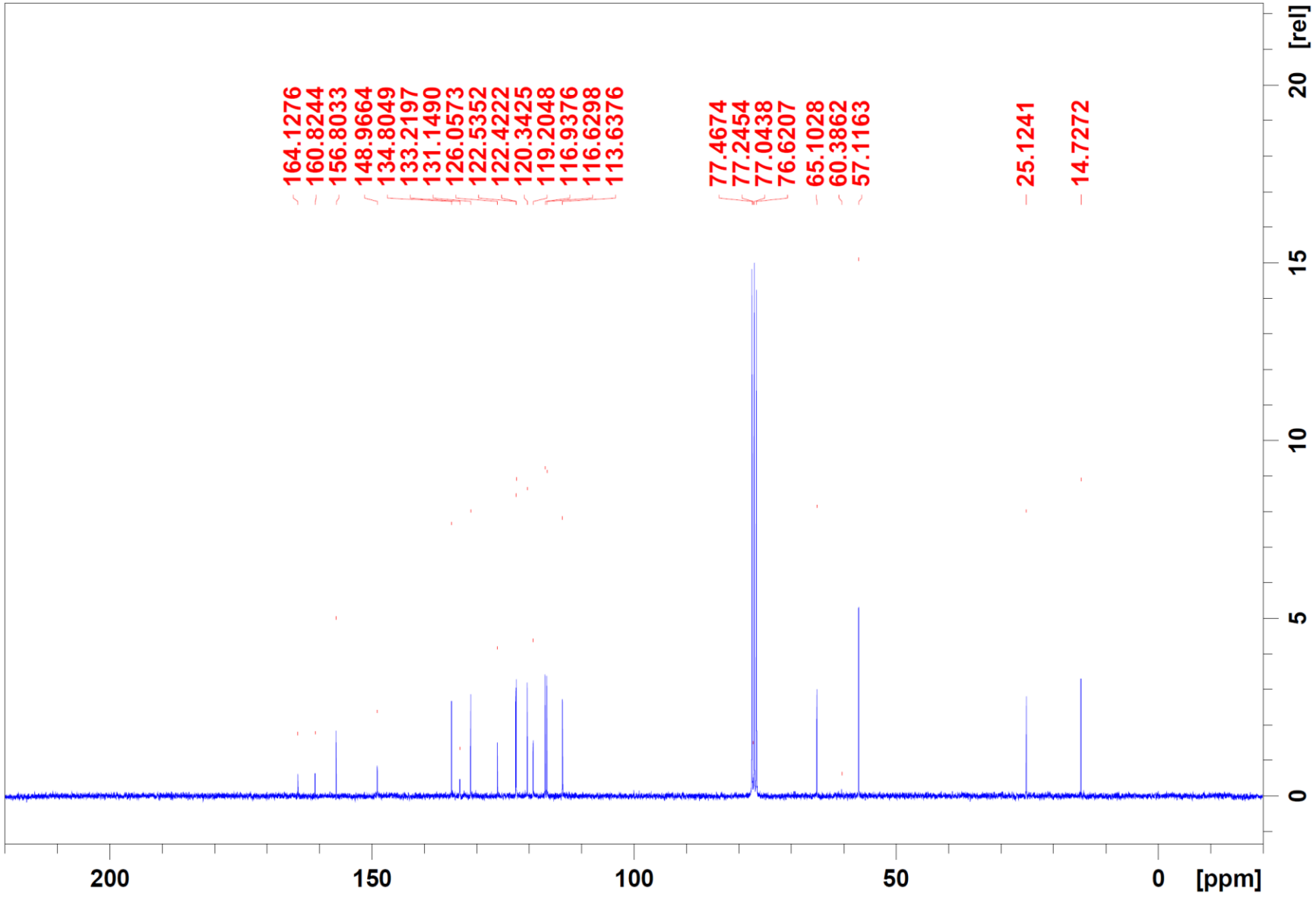
Analog **92** – ^{13}C NMR



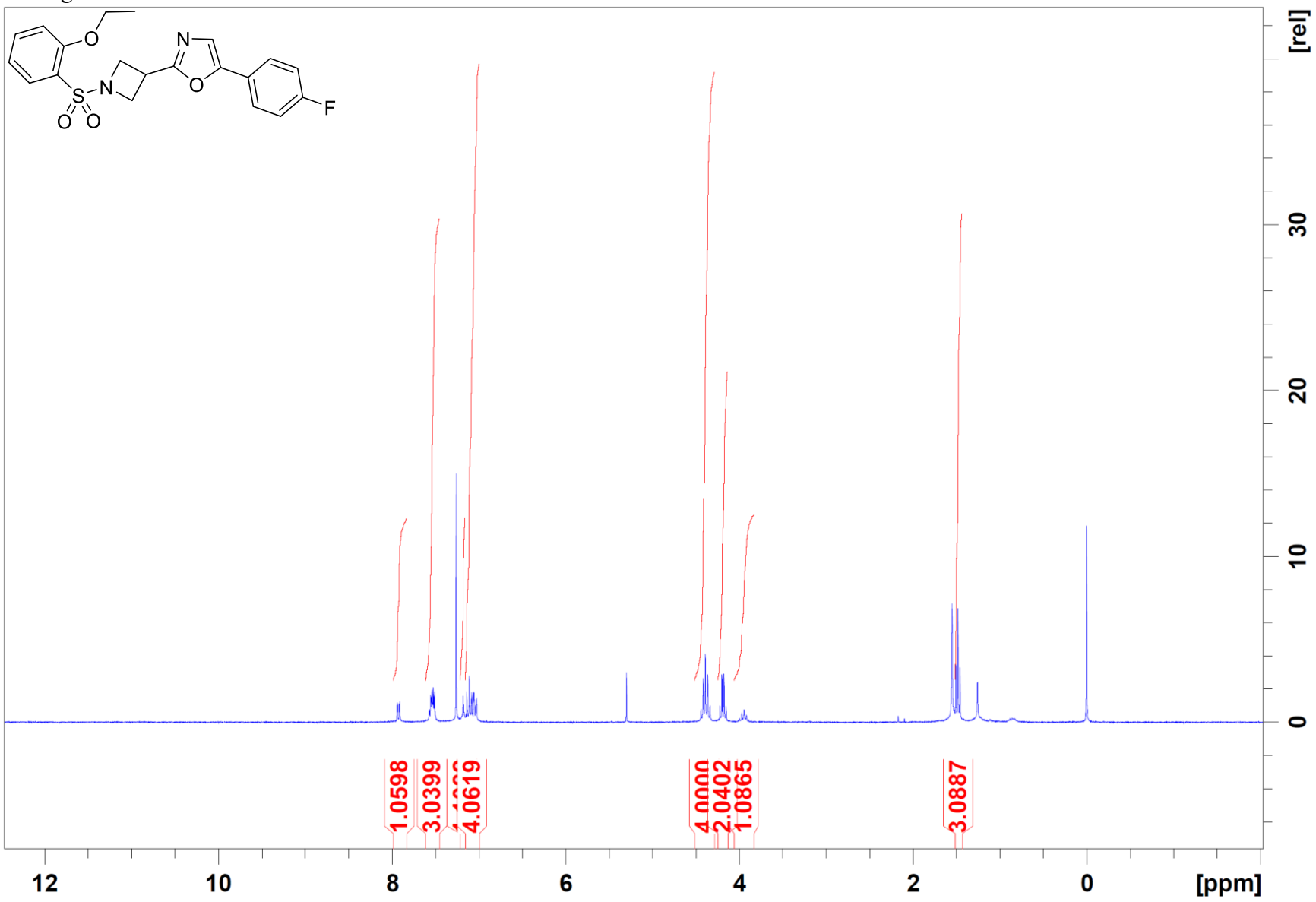
Analog **95** – ^{1}H NMR



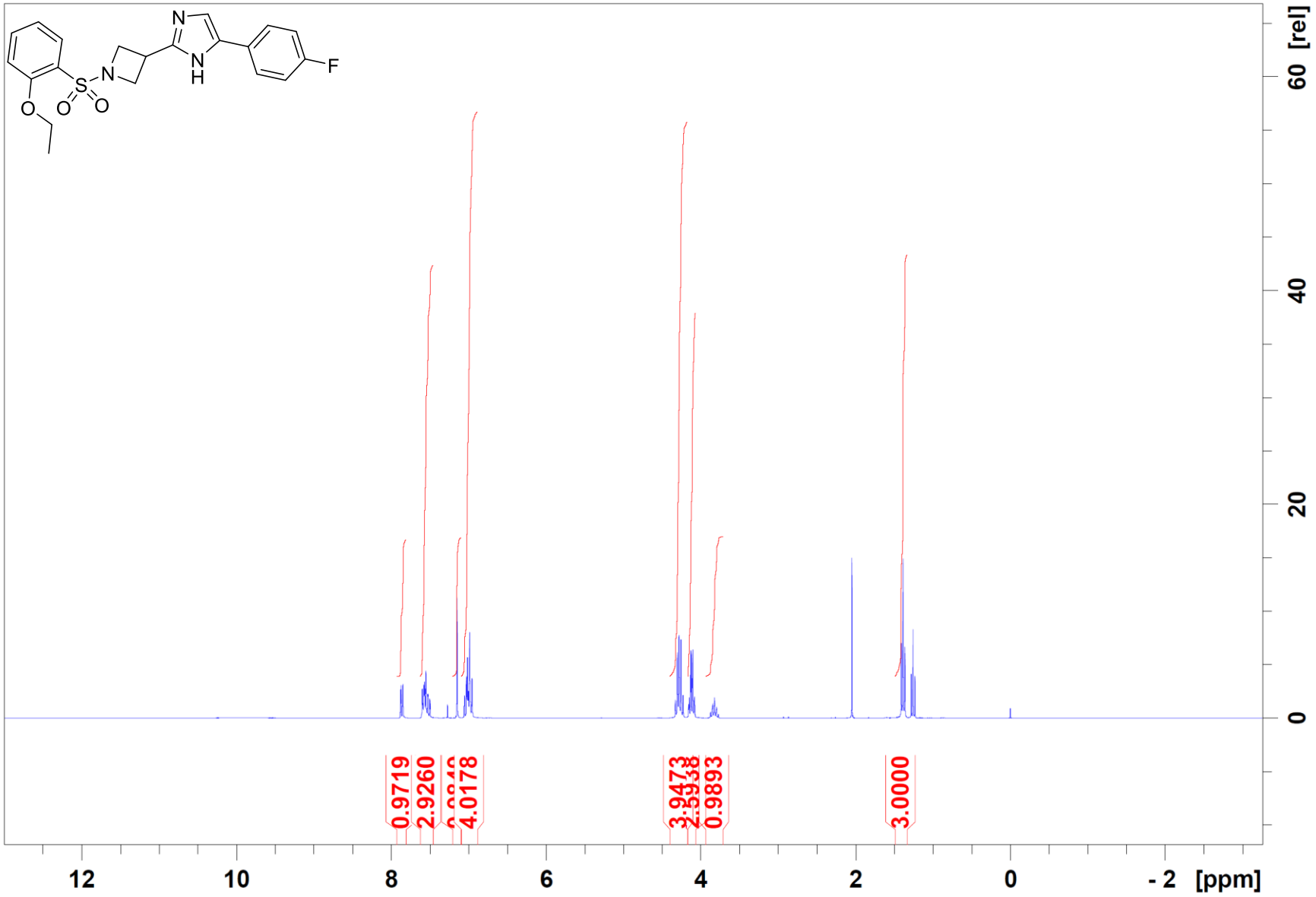
Analog **95** – ^{13}C NMR



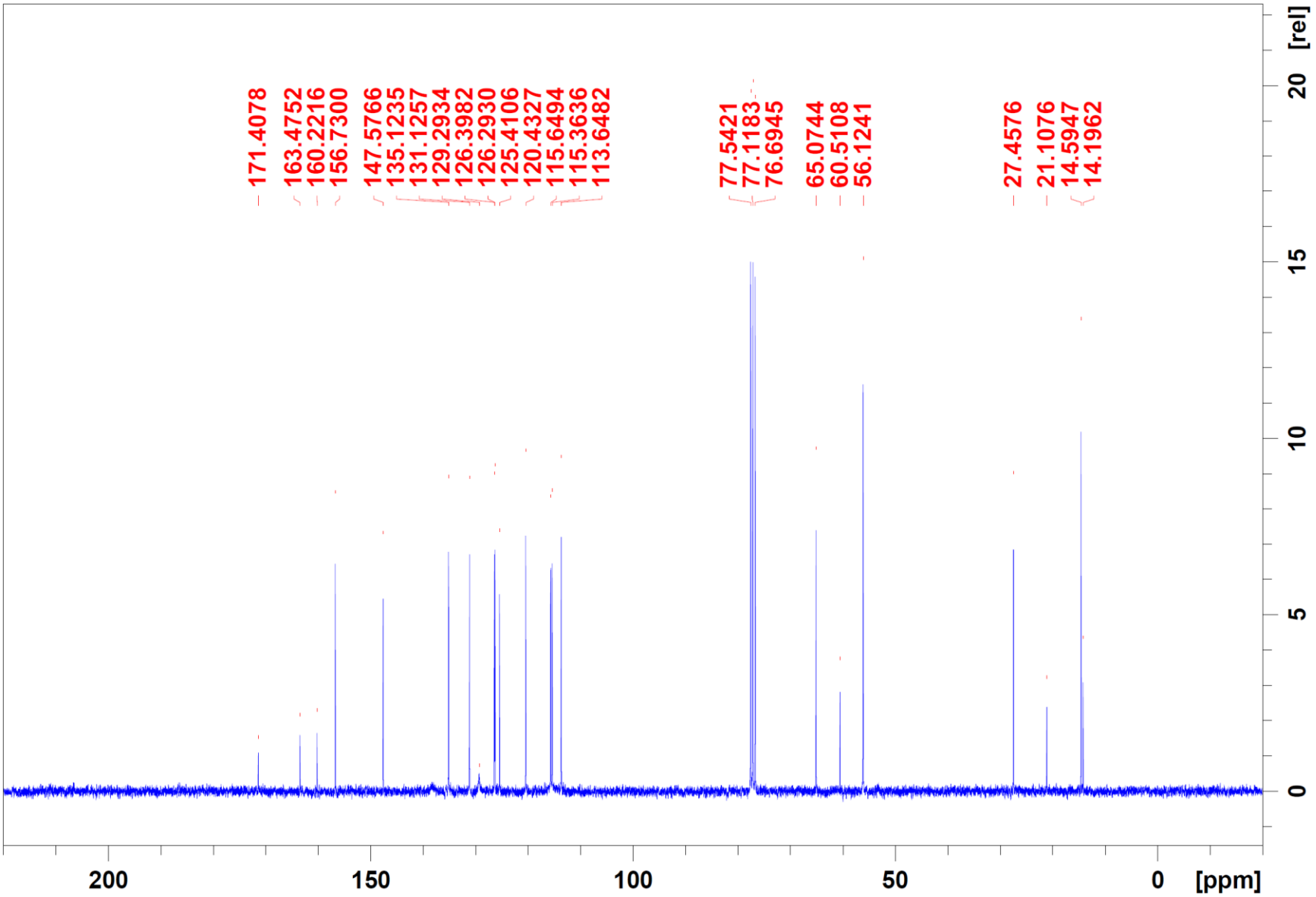
Analog **97** – ^{1}H NMR



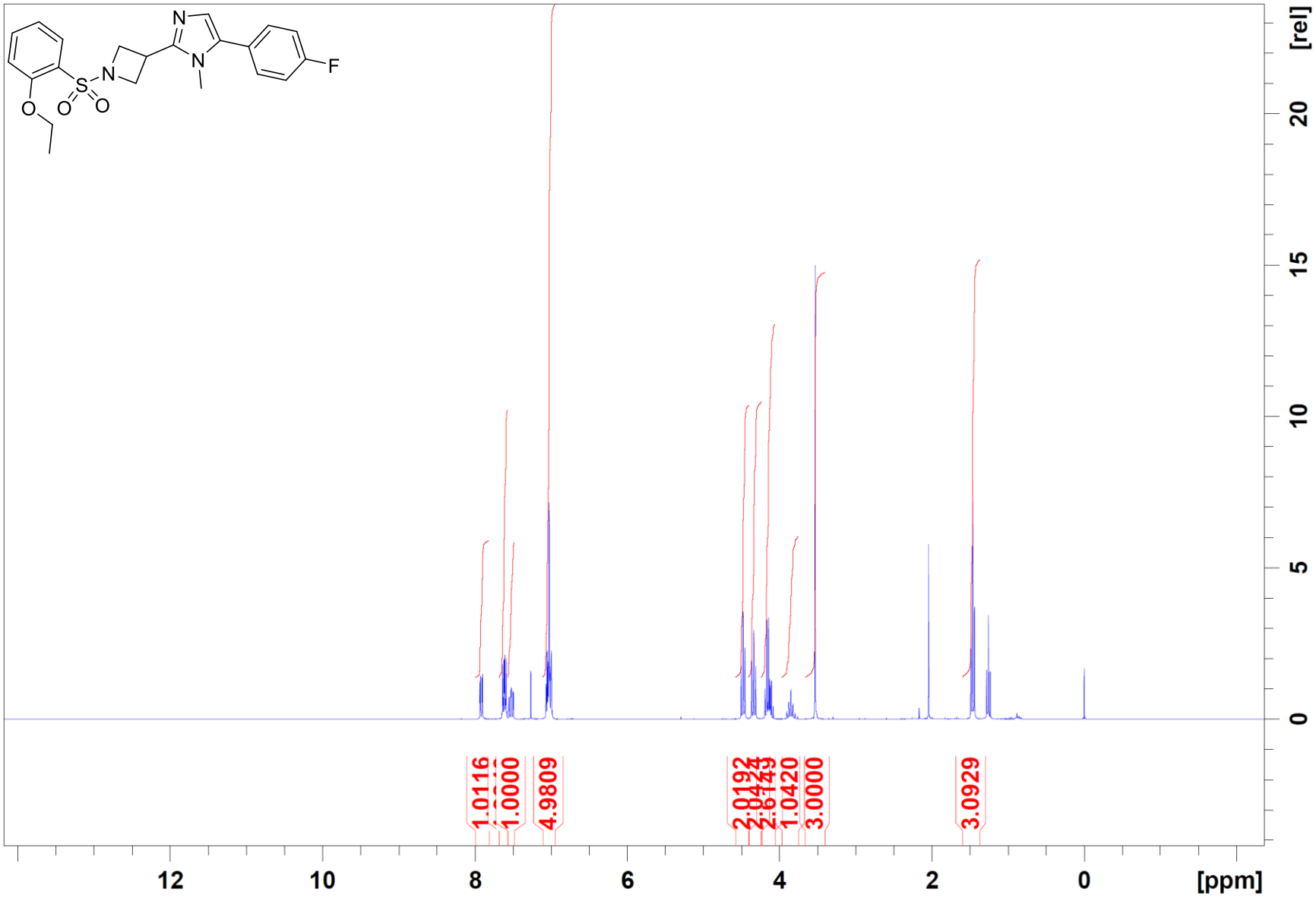
Analog **99** – ^{1}H NMR



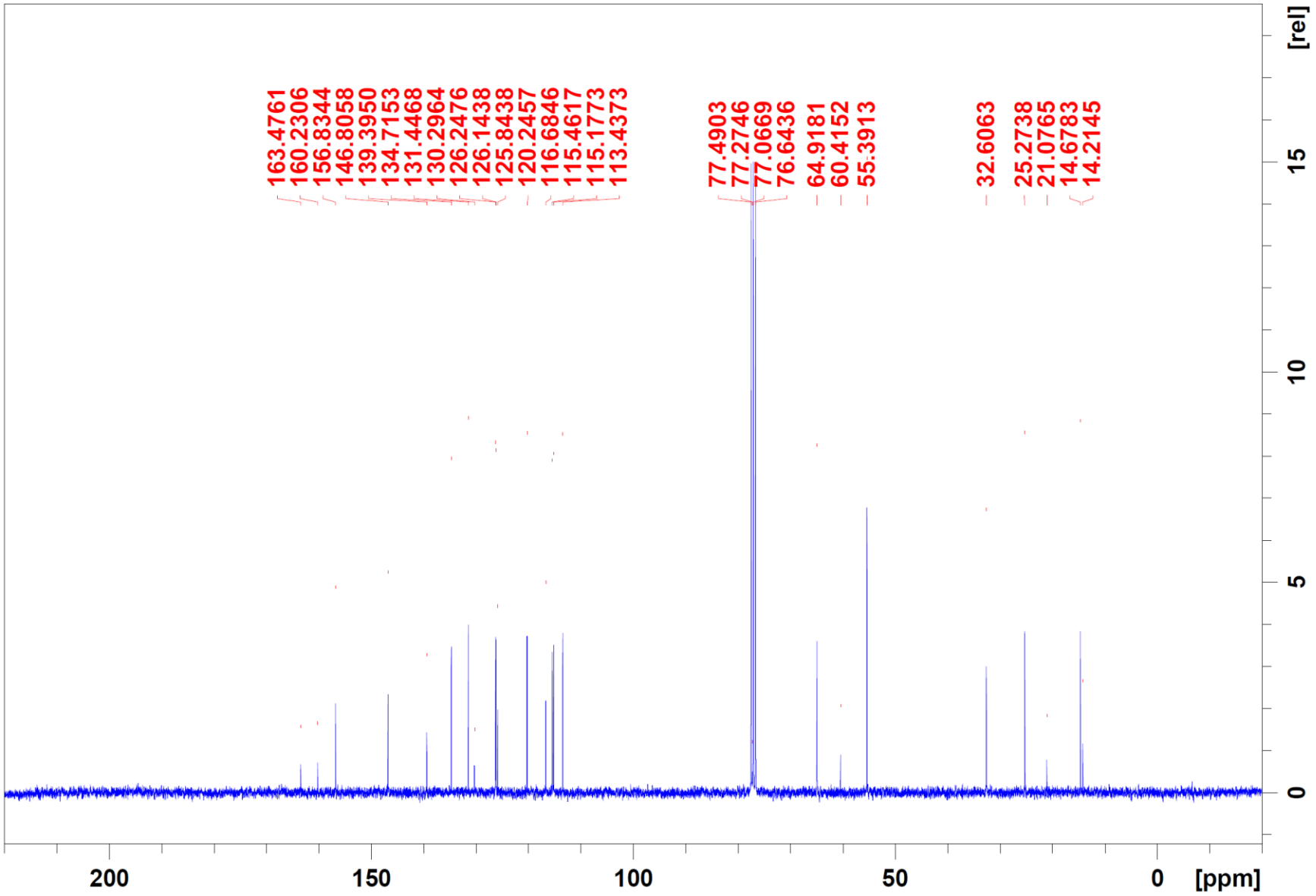
Analog **99** – ^{13}C NMR



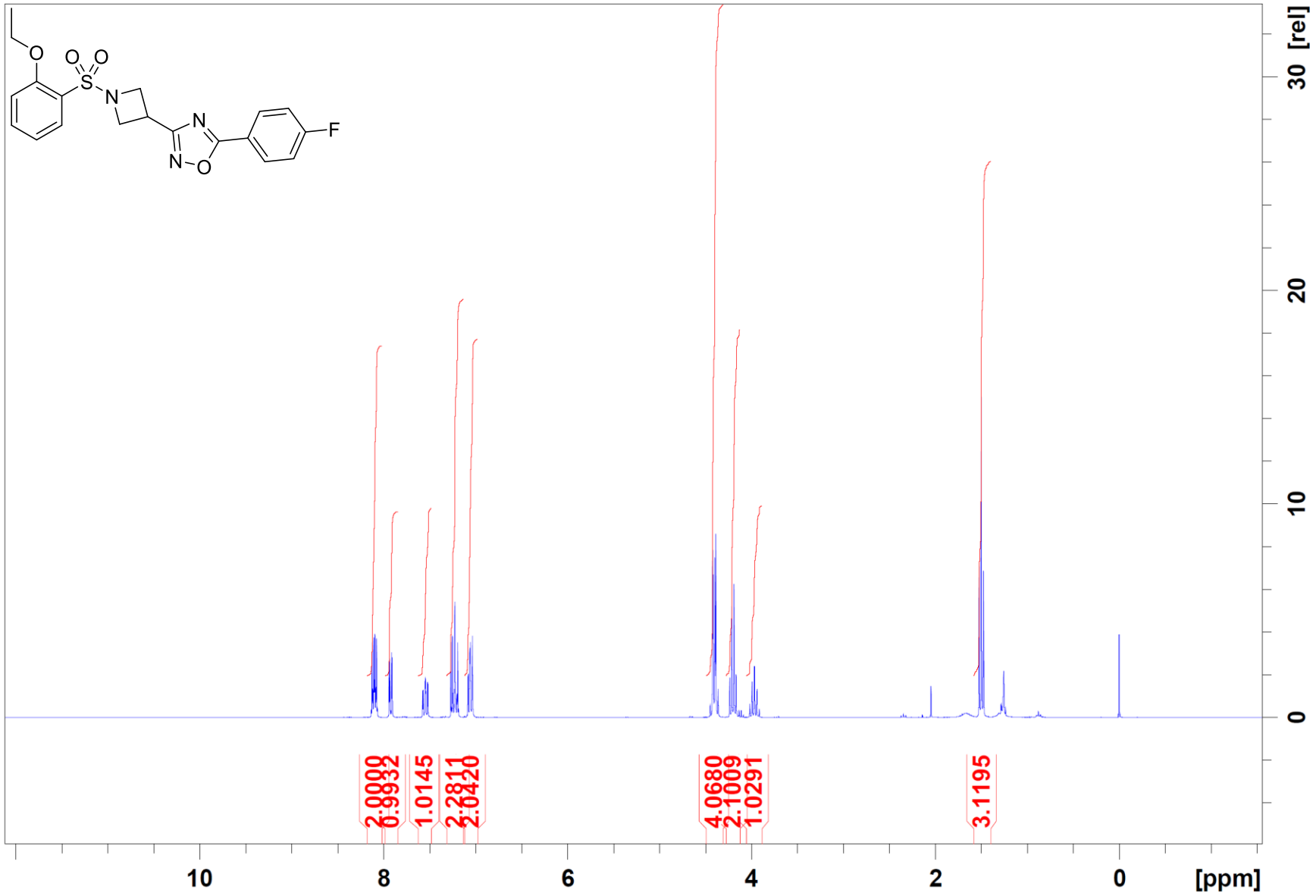
Analog **100** – ^{1}H NMR



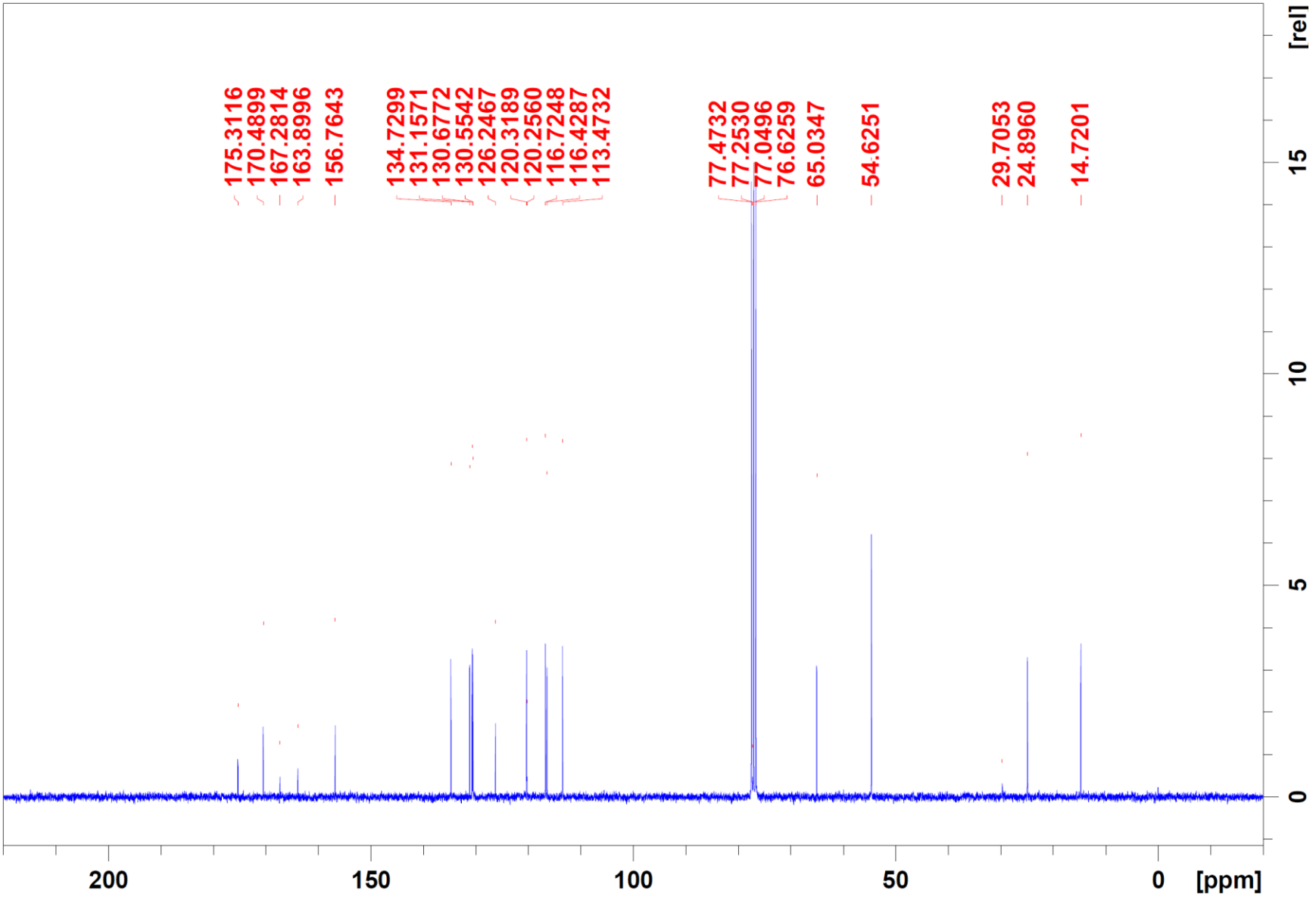
Analog **100** – ^{13}C NMR



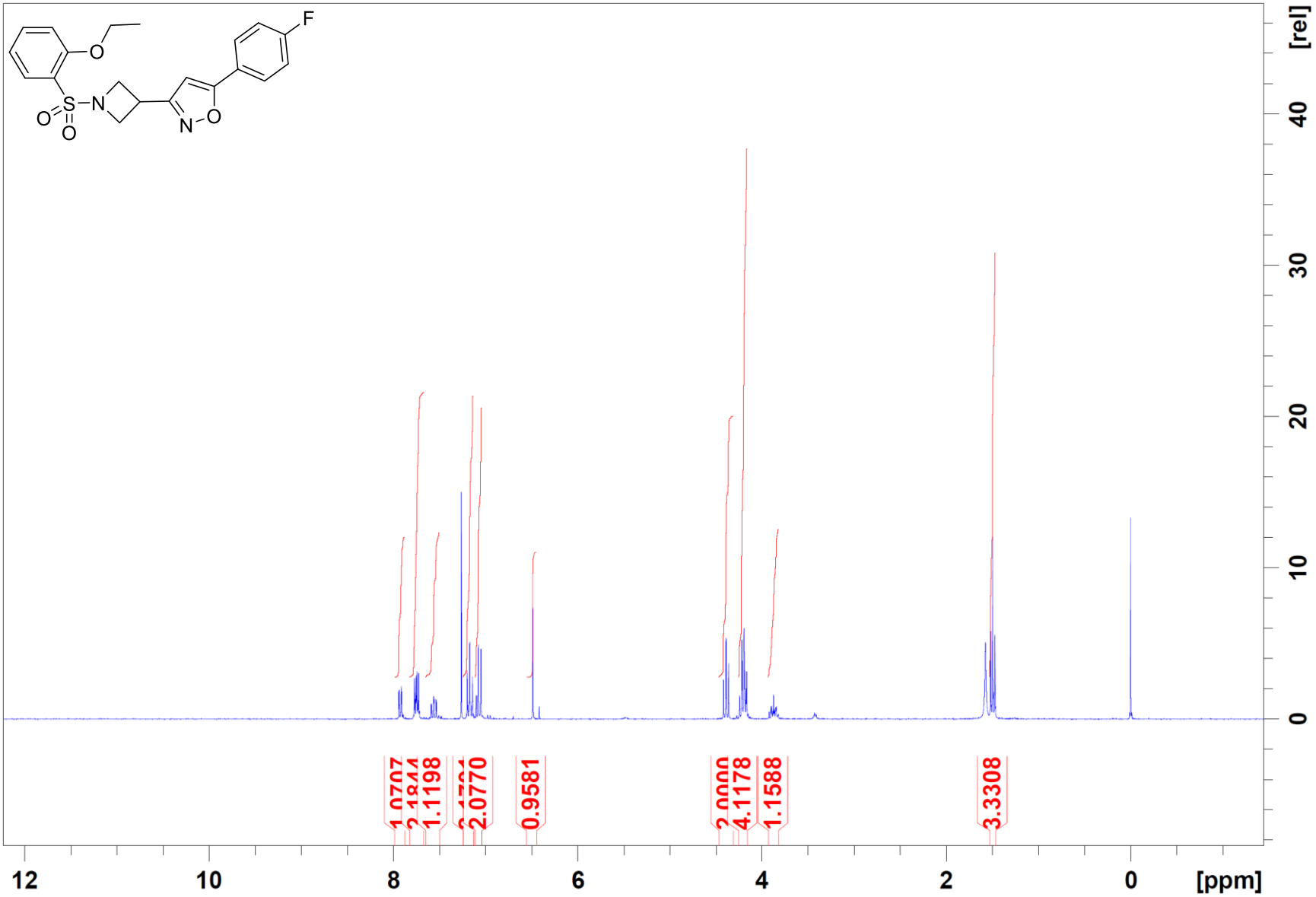
Analog **101** – ^{1}H NMR



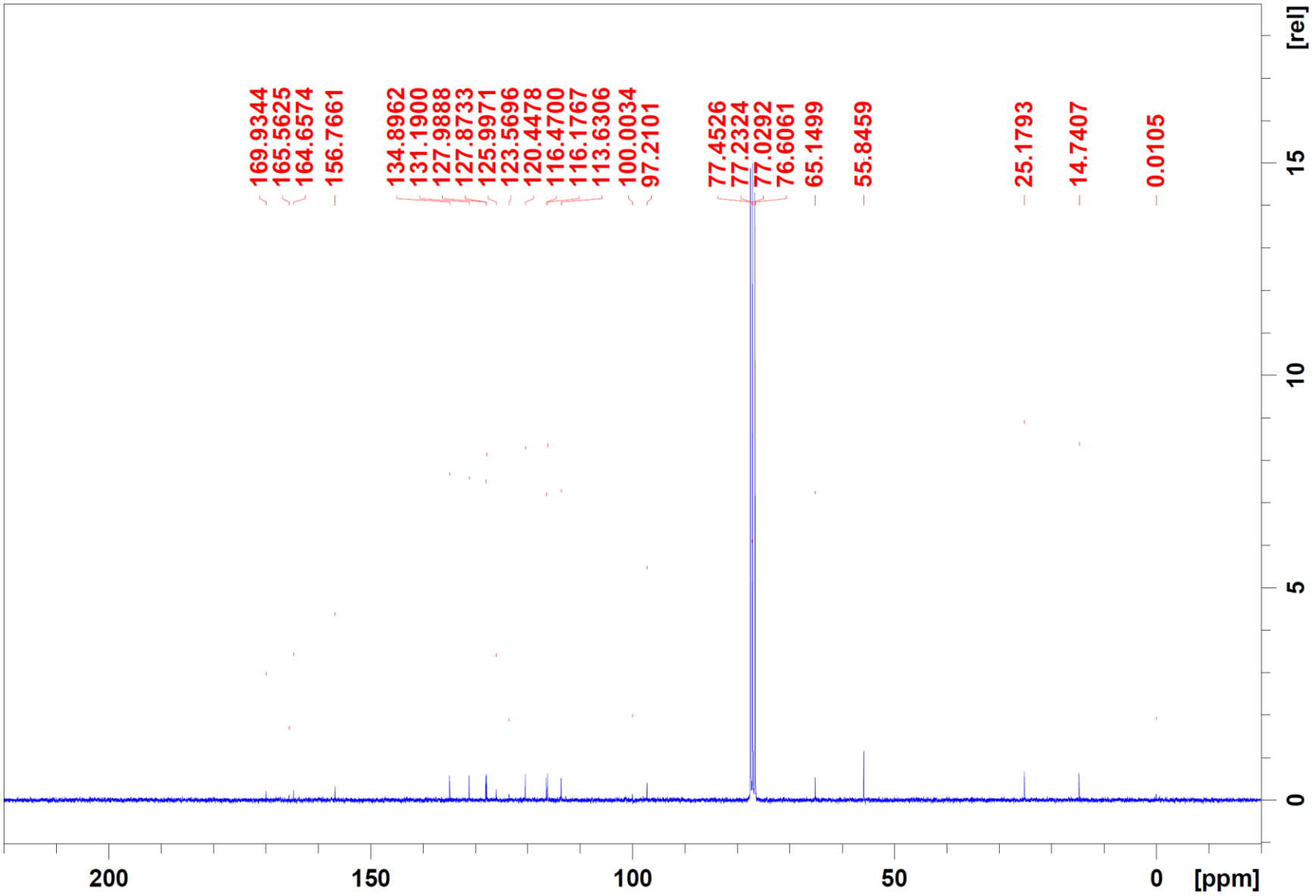
Analog **101** – ^{13}C NMR



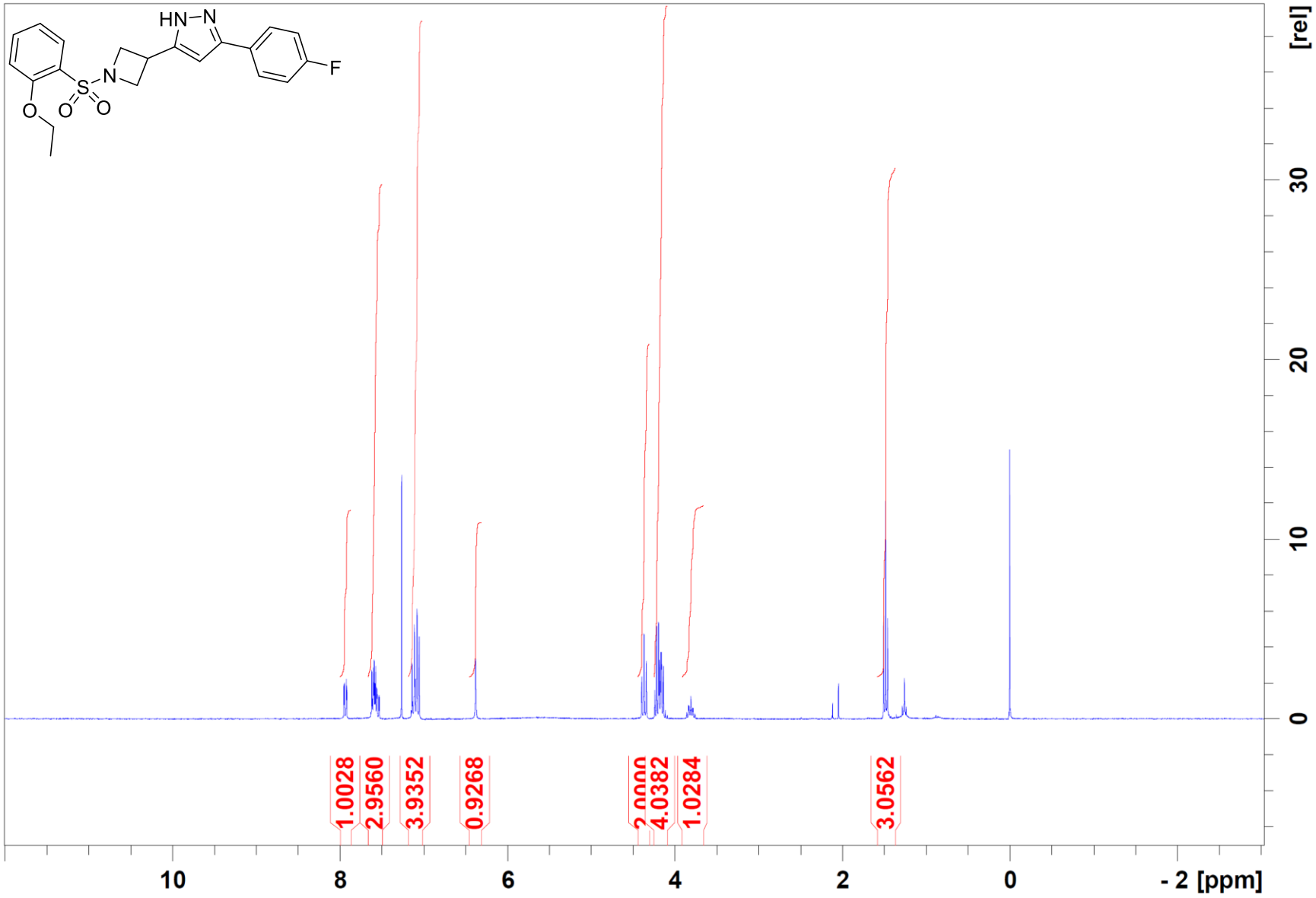
Analog **102** – ^{1}H NMR



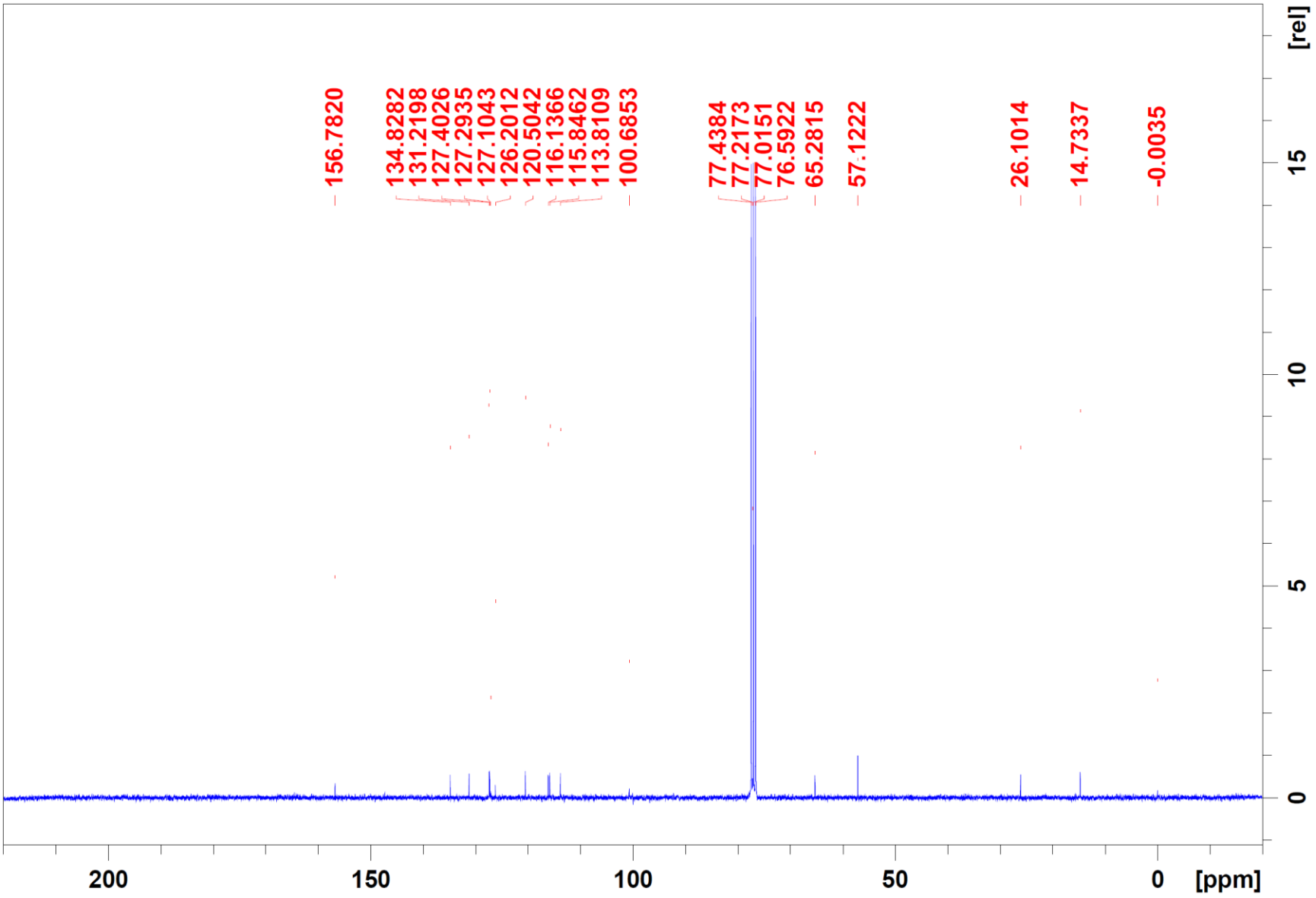
Analog **102** – ^{13}C NMR



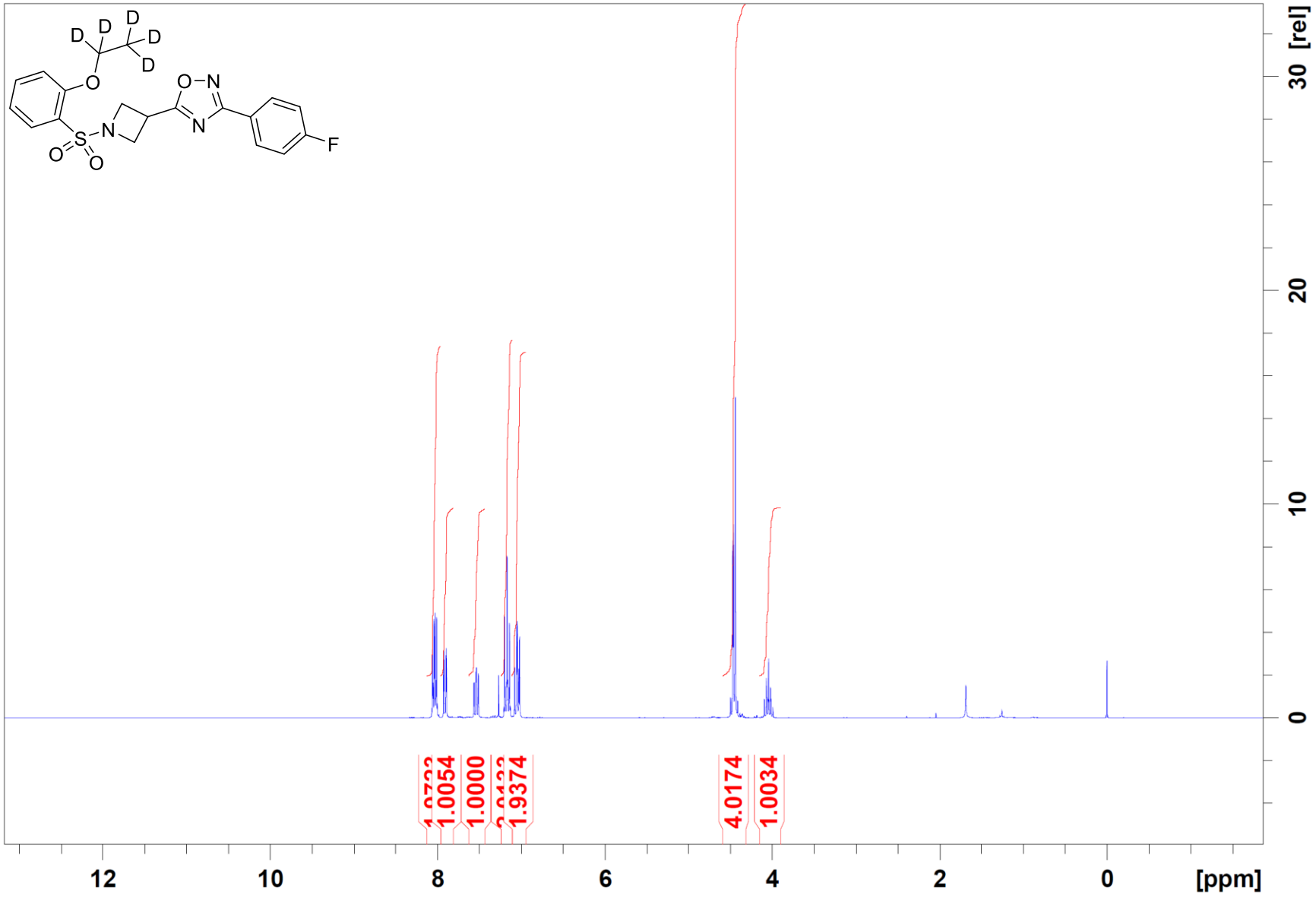
Analog **103** – ^{1}H NMR



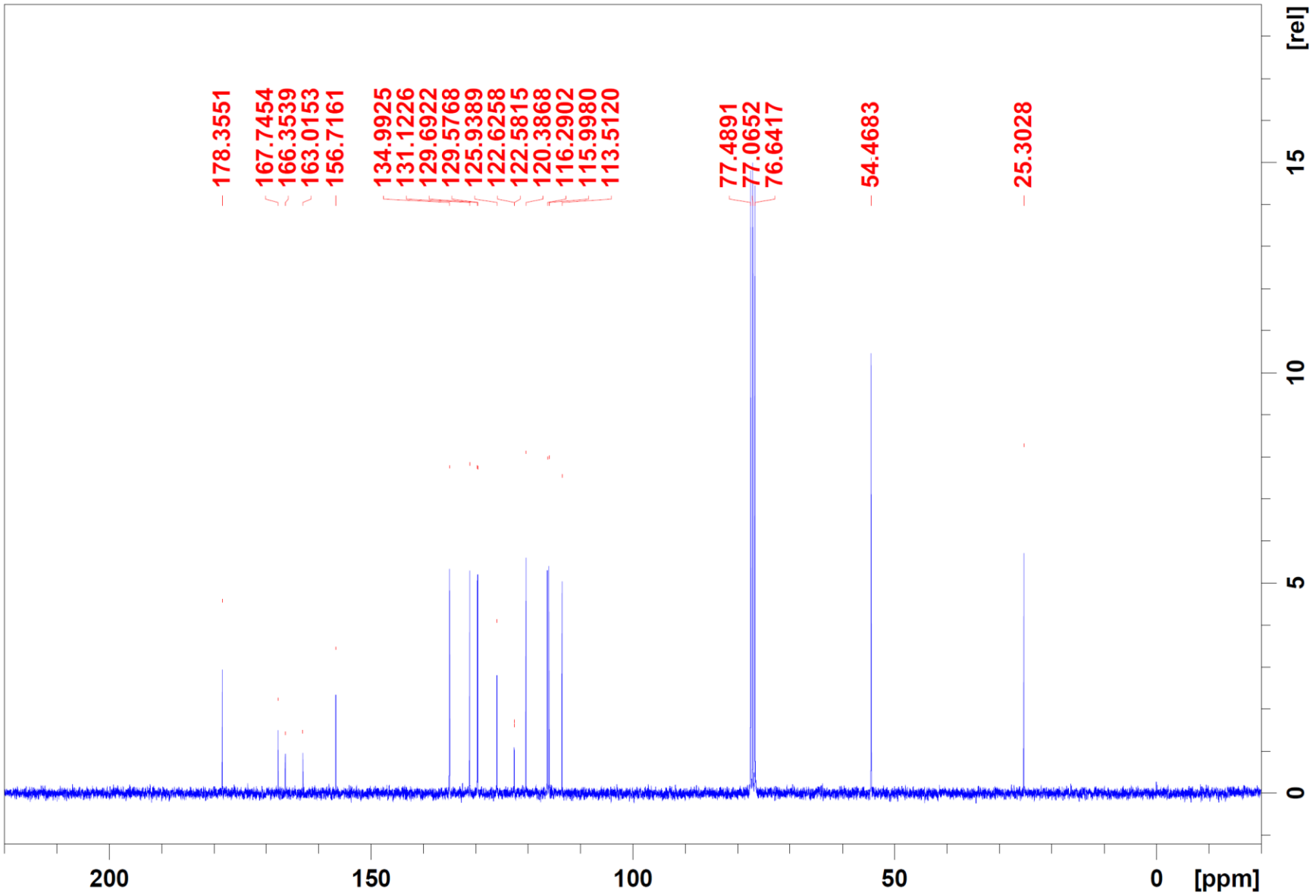
Analog **103** – ^{13}C NMR



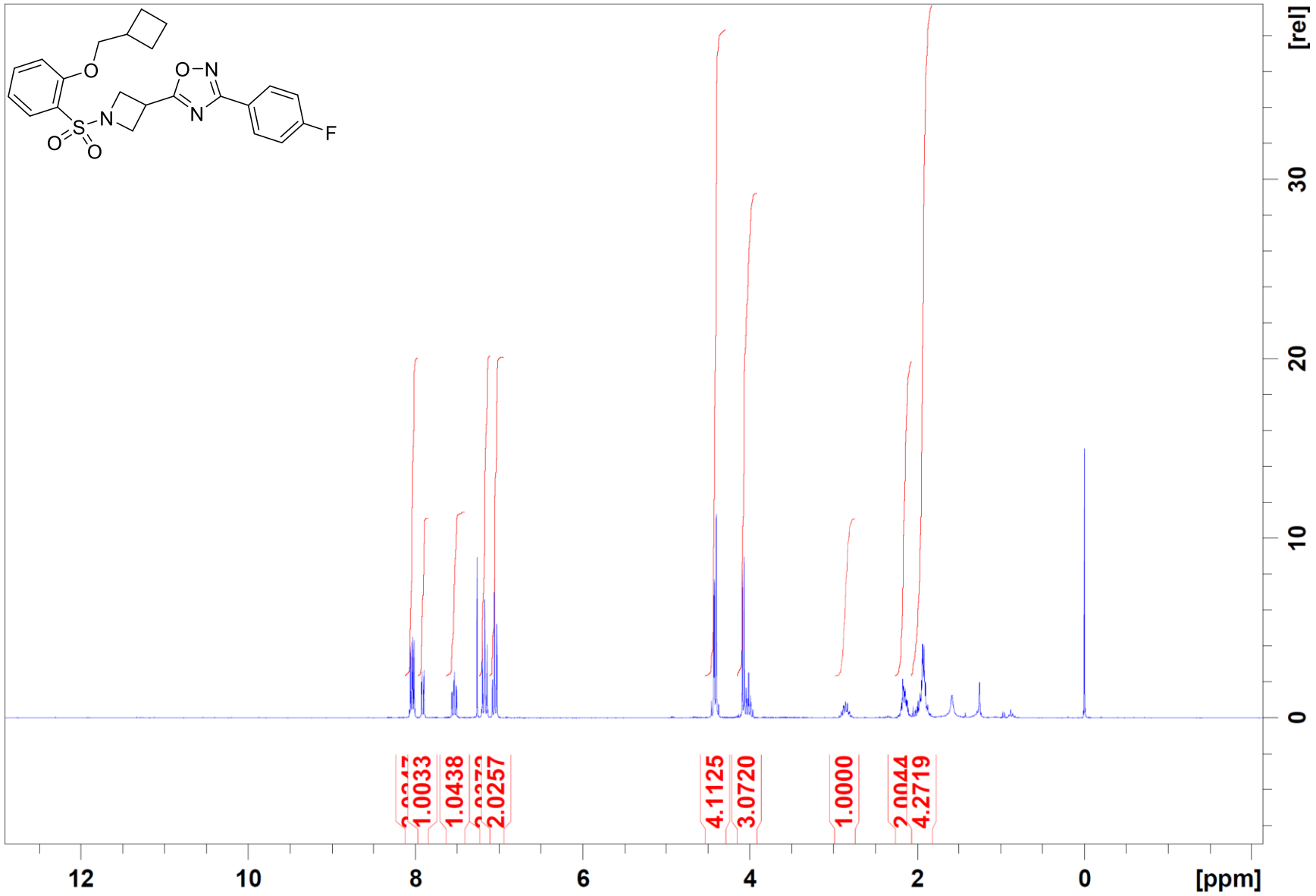
Analog **109** – ^{1}H NMR



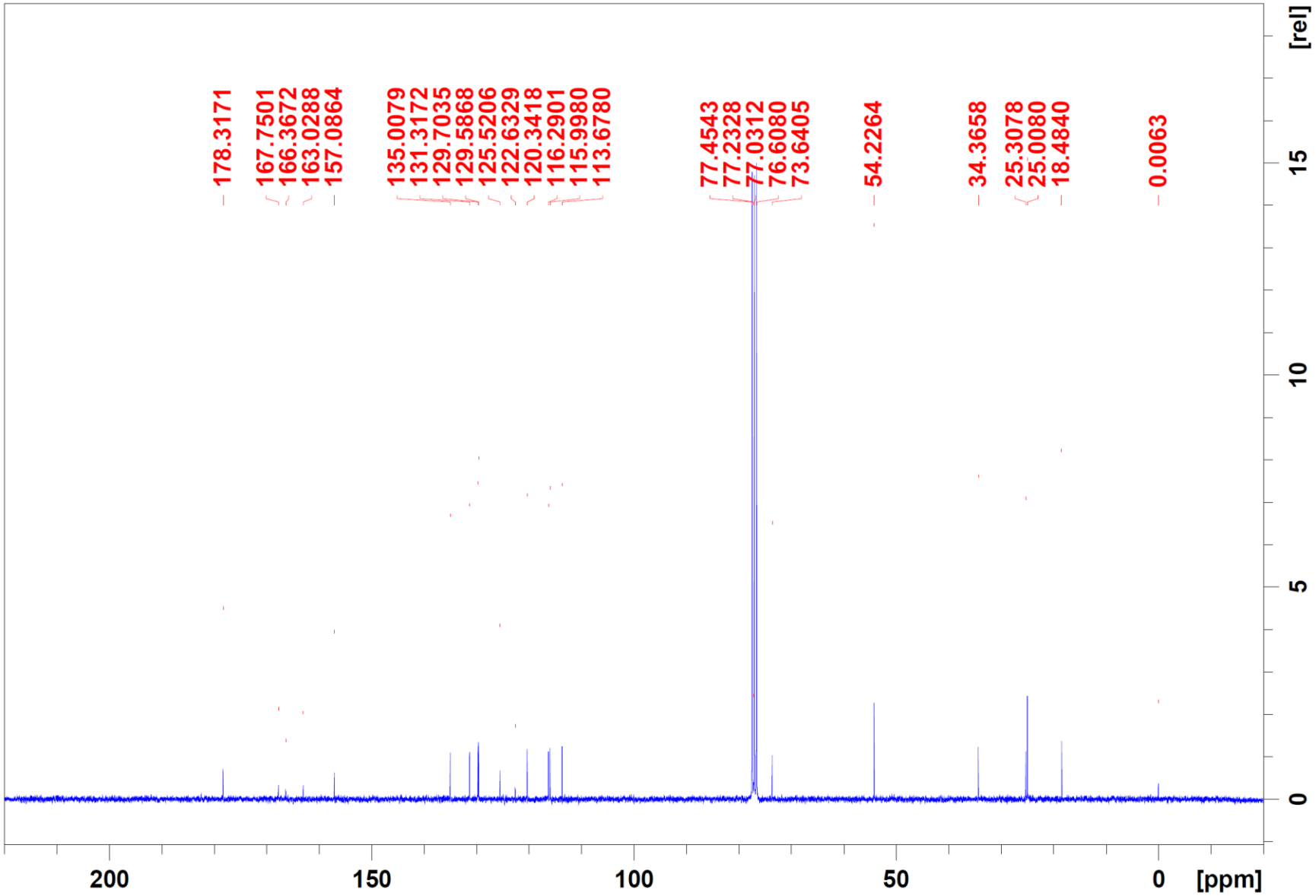
Analog **109** – ^{13}C NMR



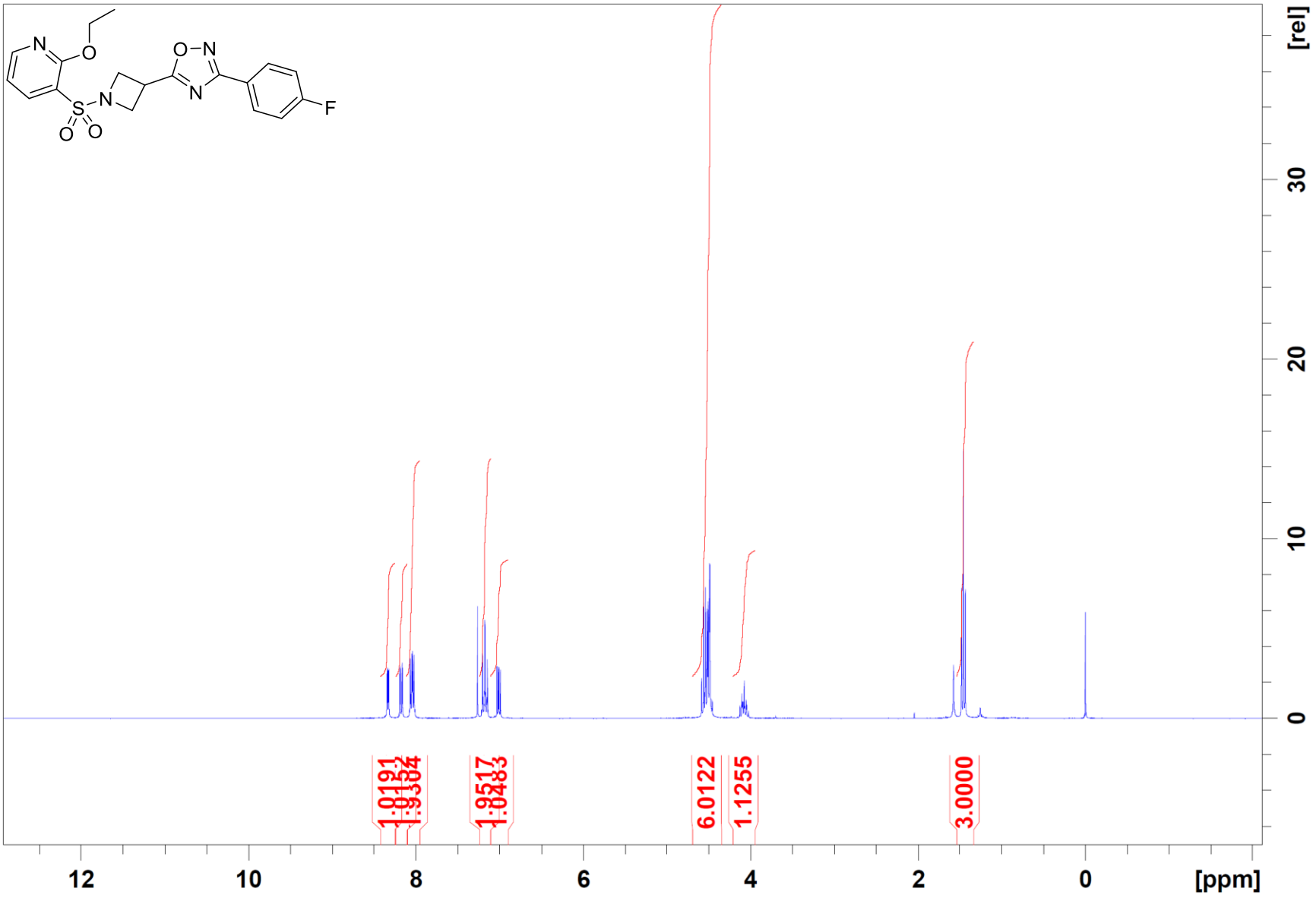
Analog **110** – ^{1}H NMR



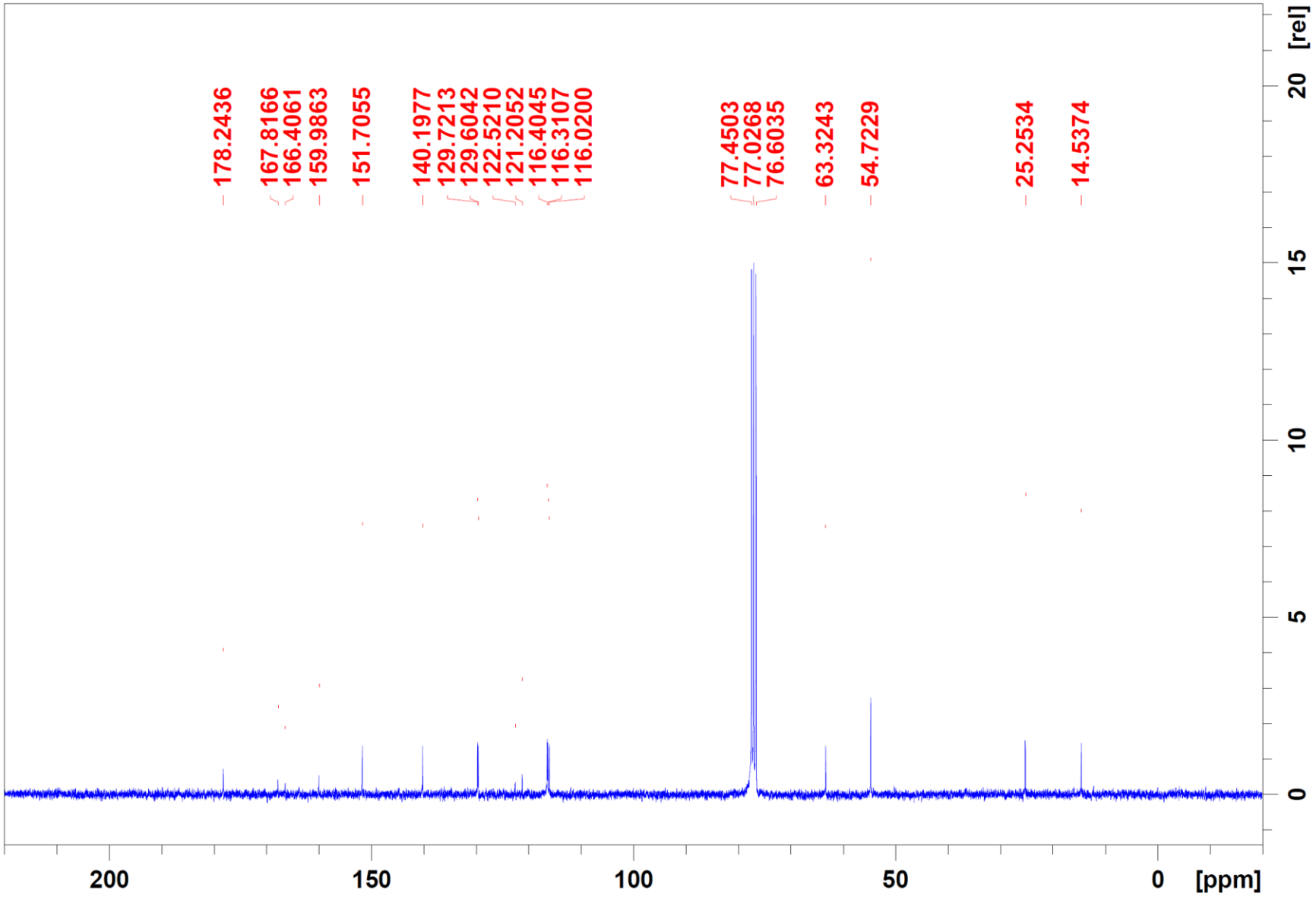
Analog **110** – ^{13}C NMR



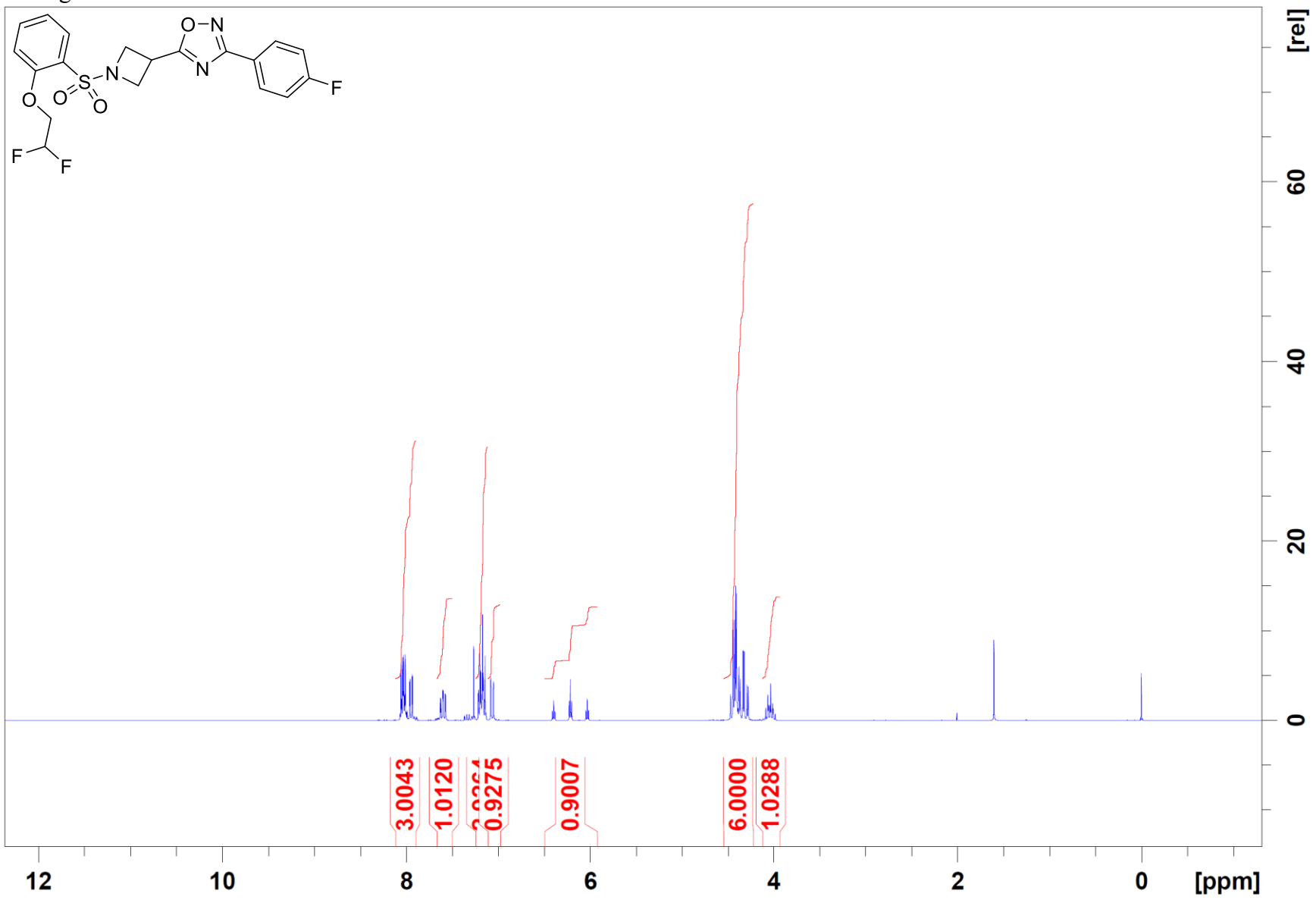
Analog **111** – ^{1}H NMR



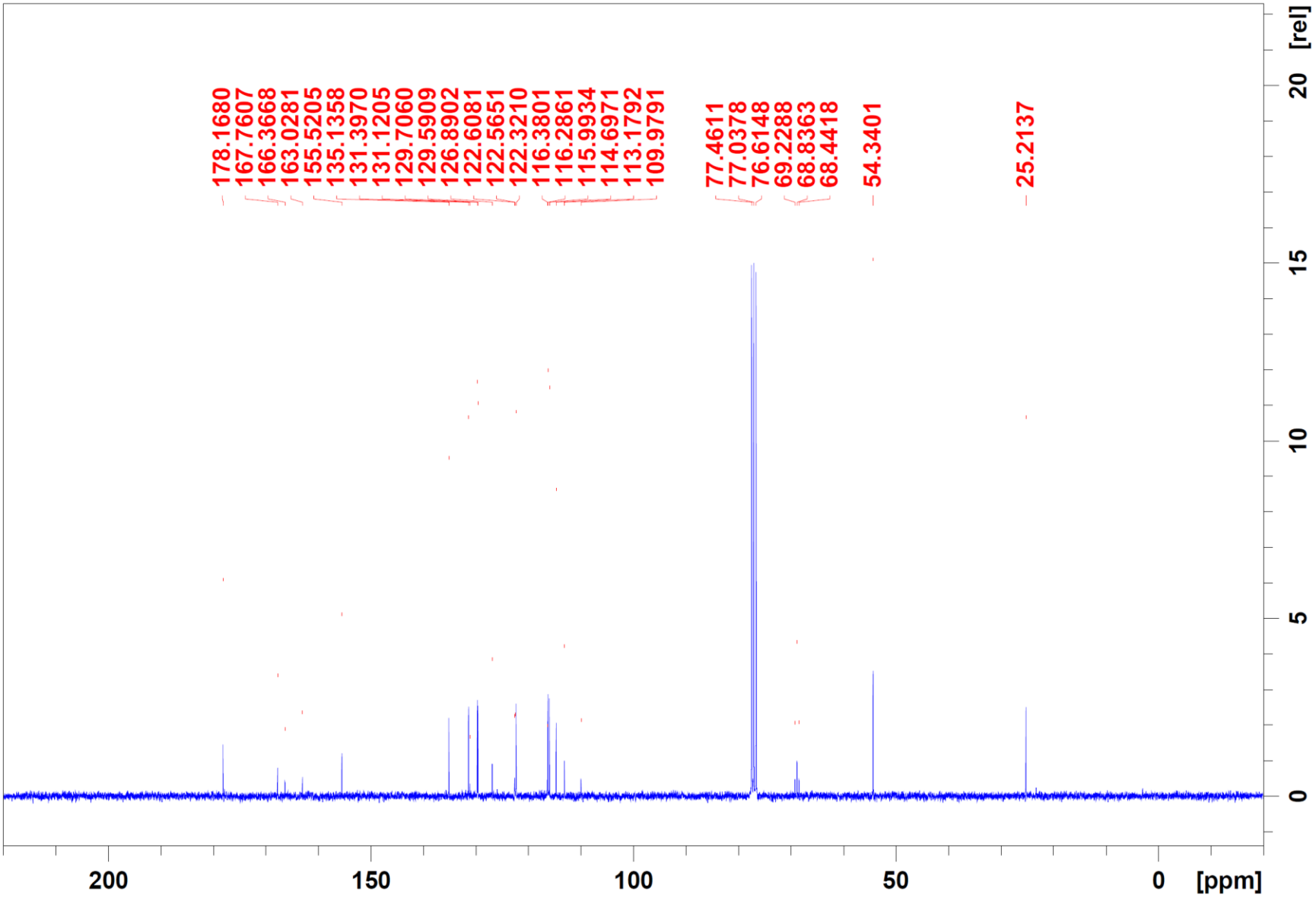
Analog **111** – ^{13}C NMR



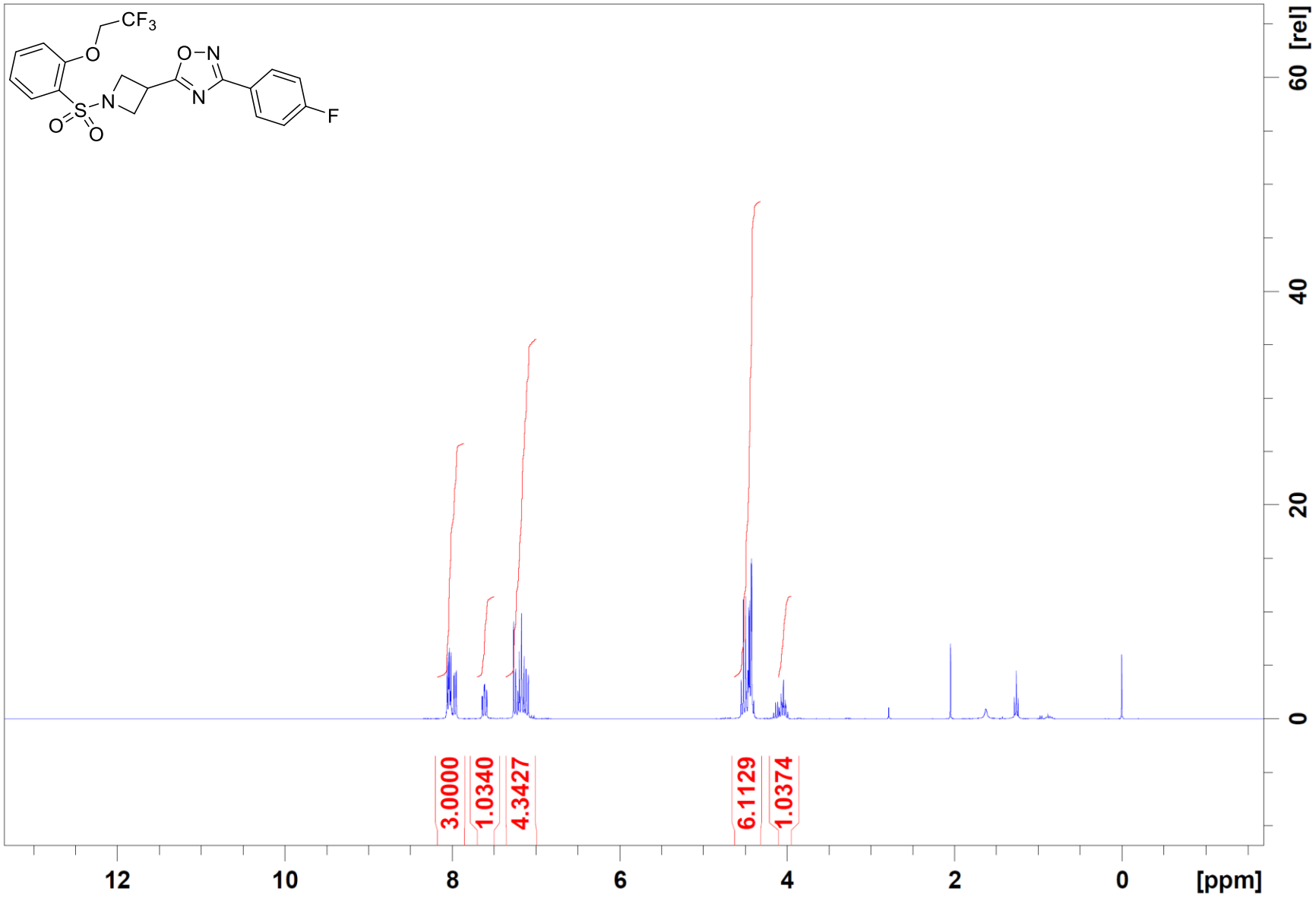
Analog **112** – ^{1}H NMR



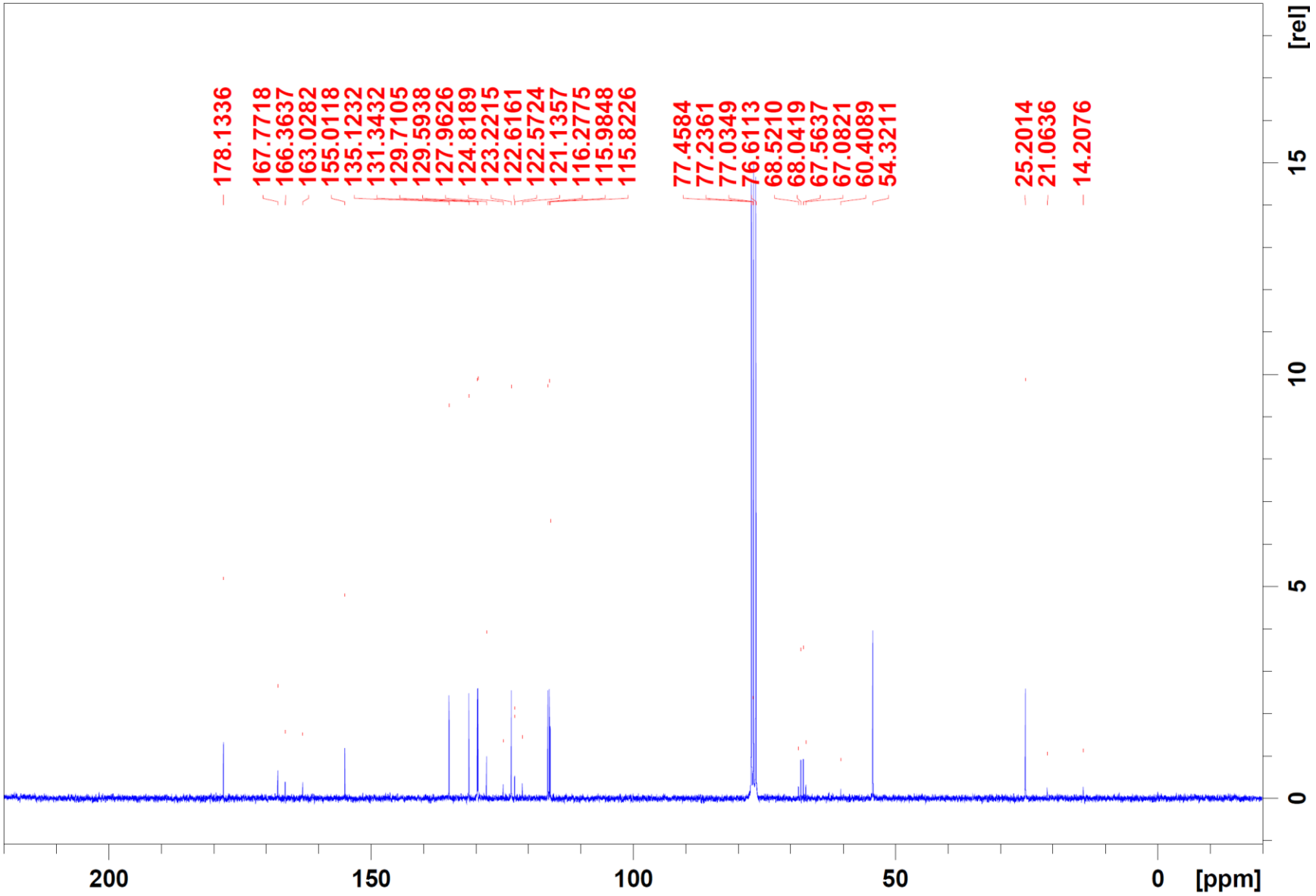
Analog **112** – ^{13}C NMR



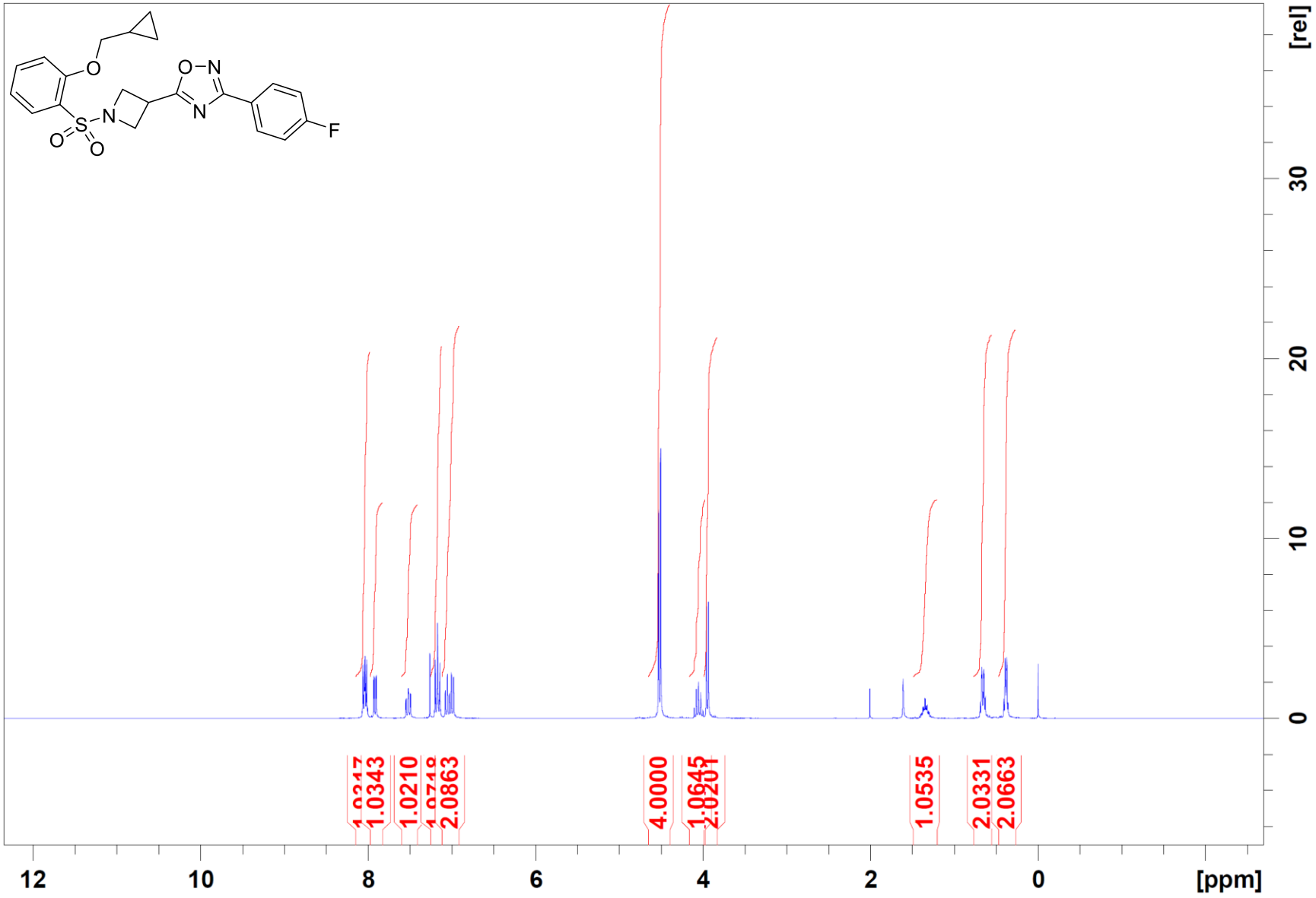
Analog **113** – ^{1}H NMR



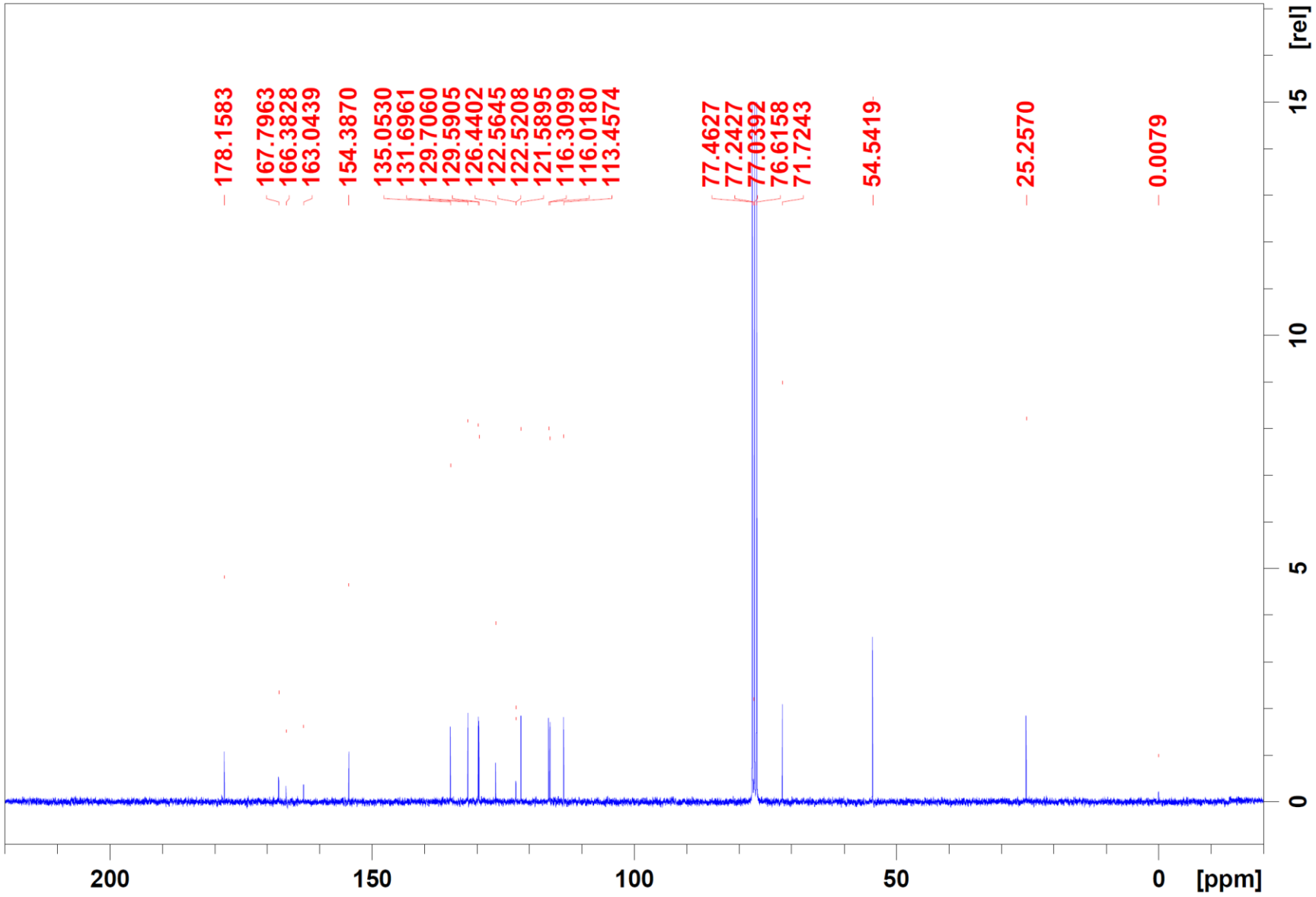
Analog **113** – ^{13}C NMR



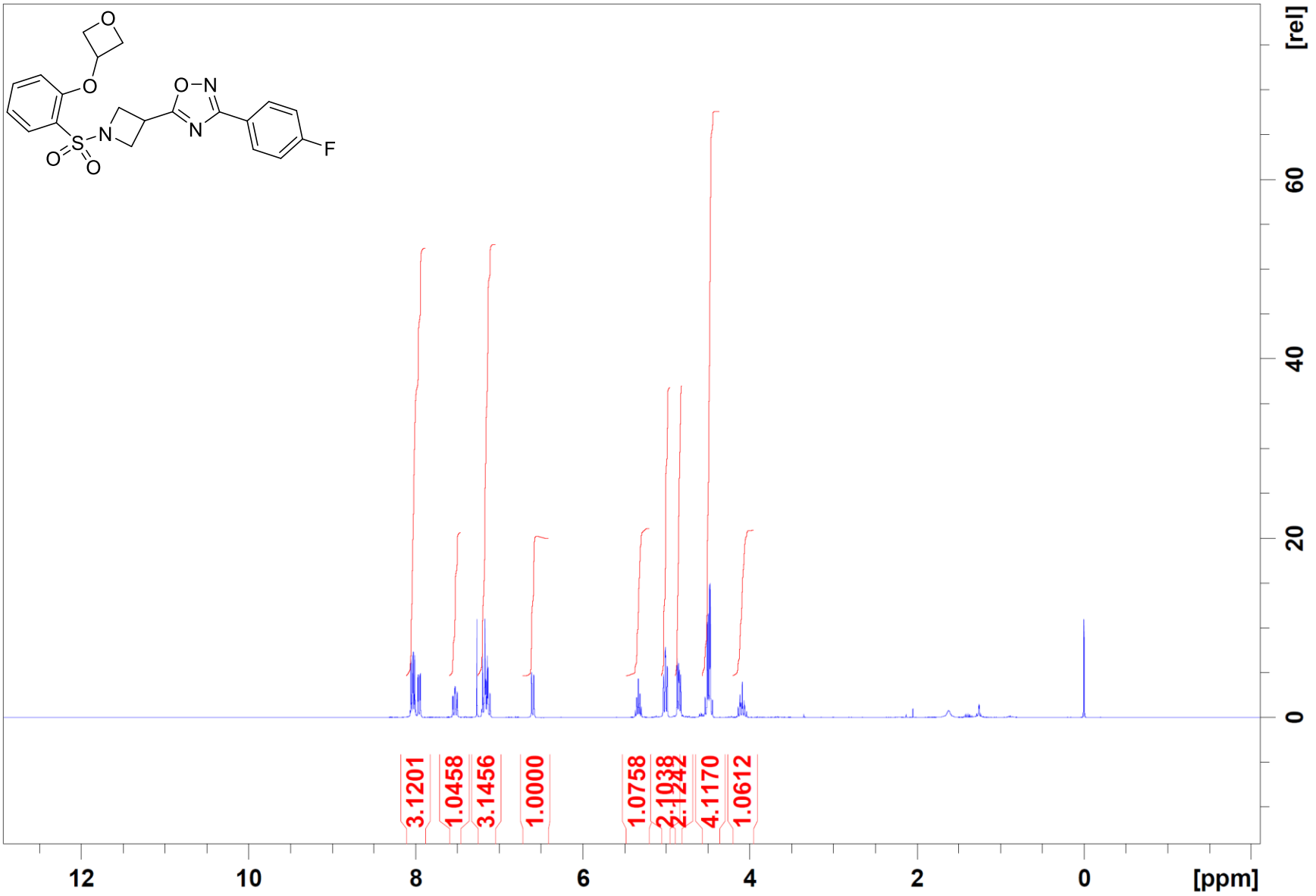
Analog **114** – ^{1}H NMR



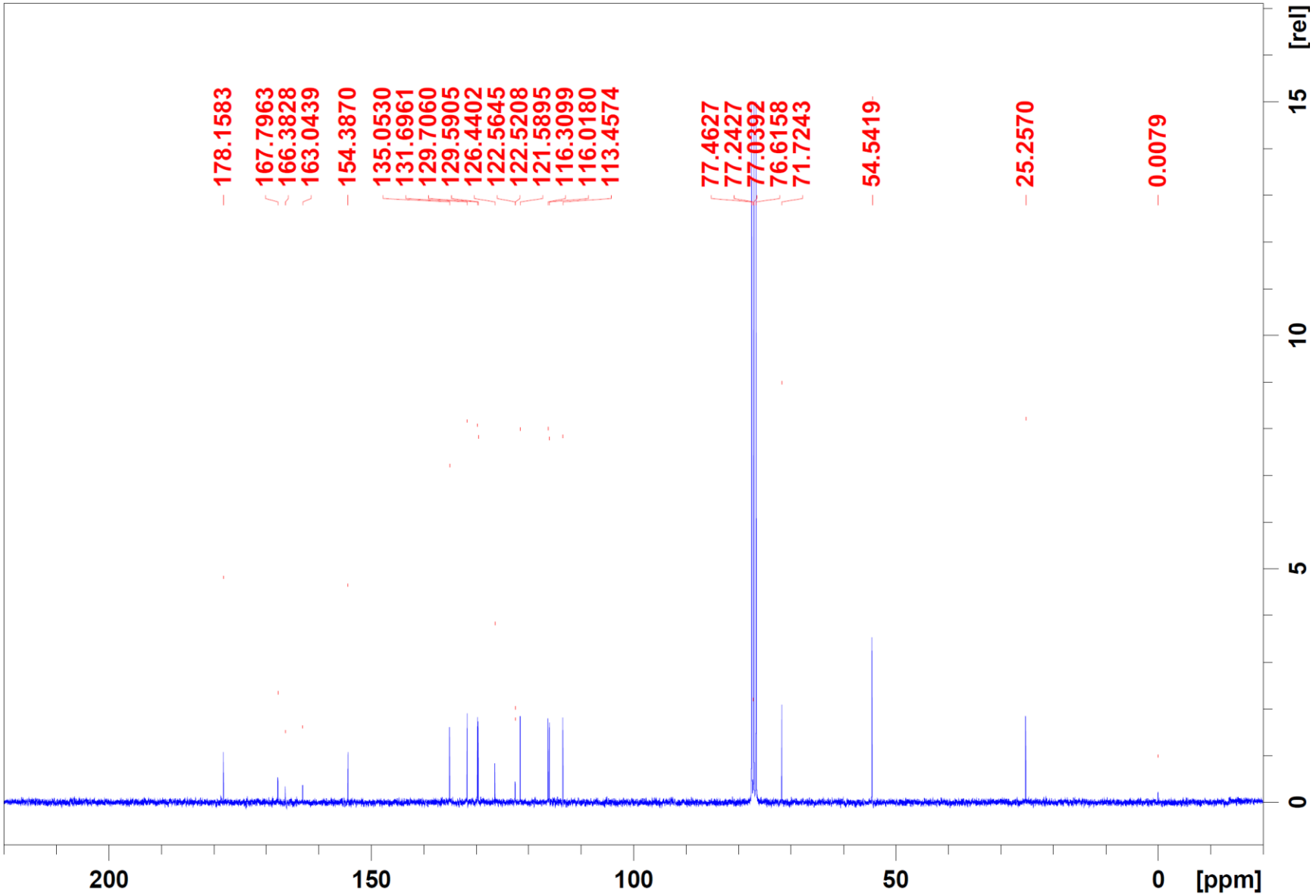
Analog **114** – ^{13}C NMR



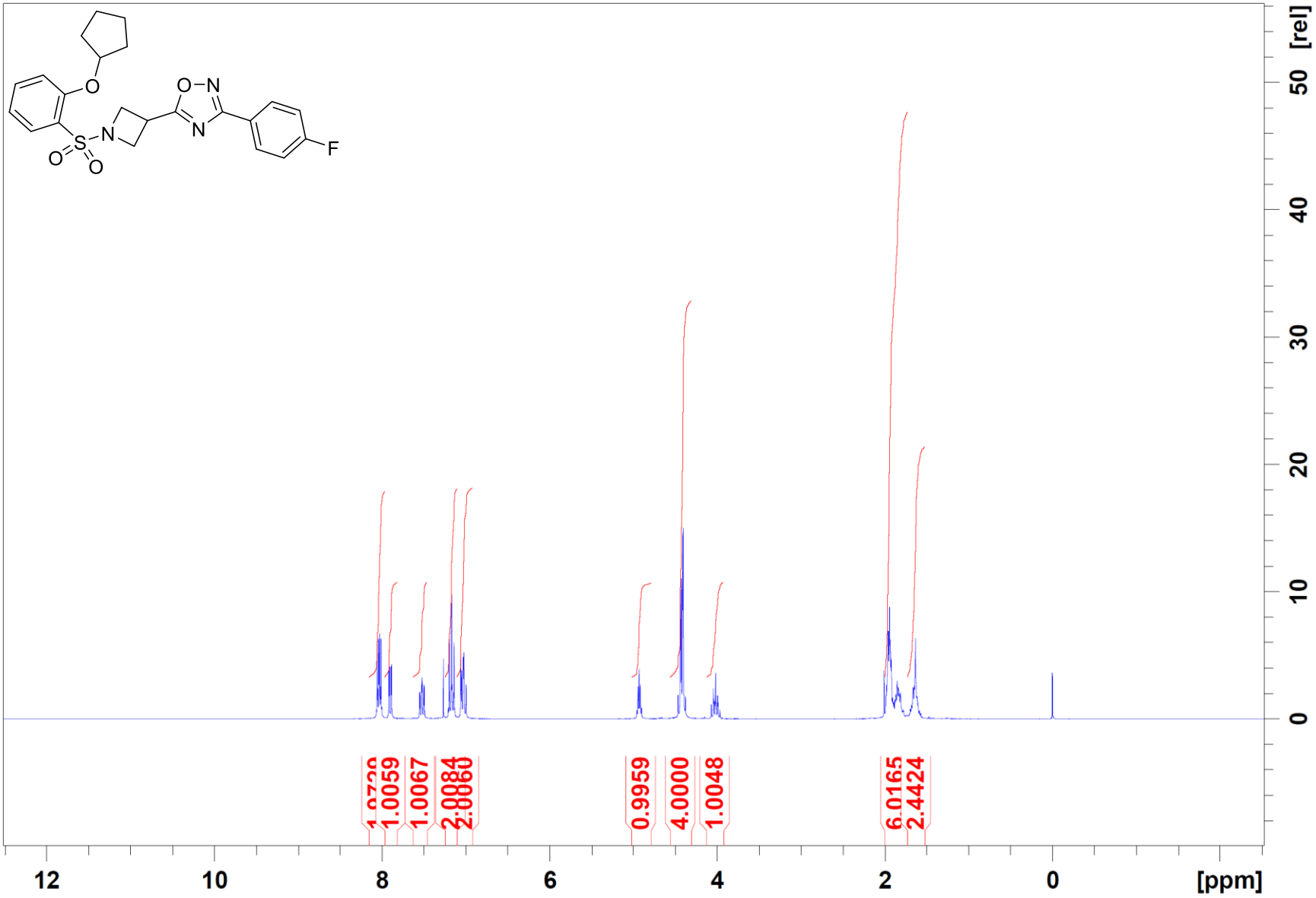
Analog **115** – ^{1}H NMR



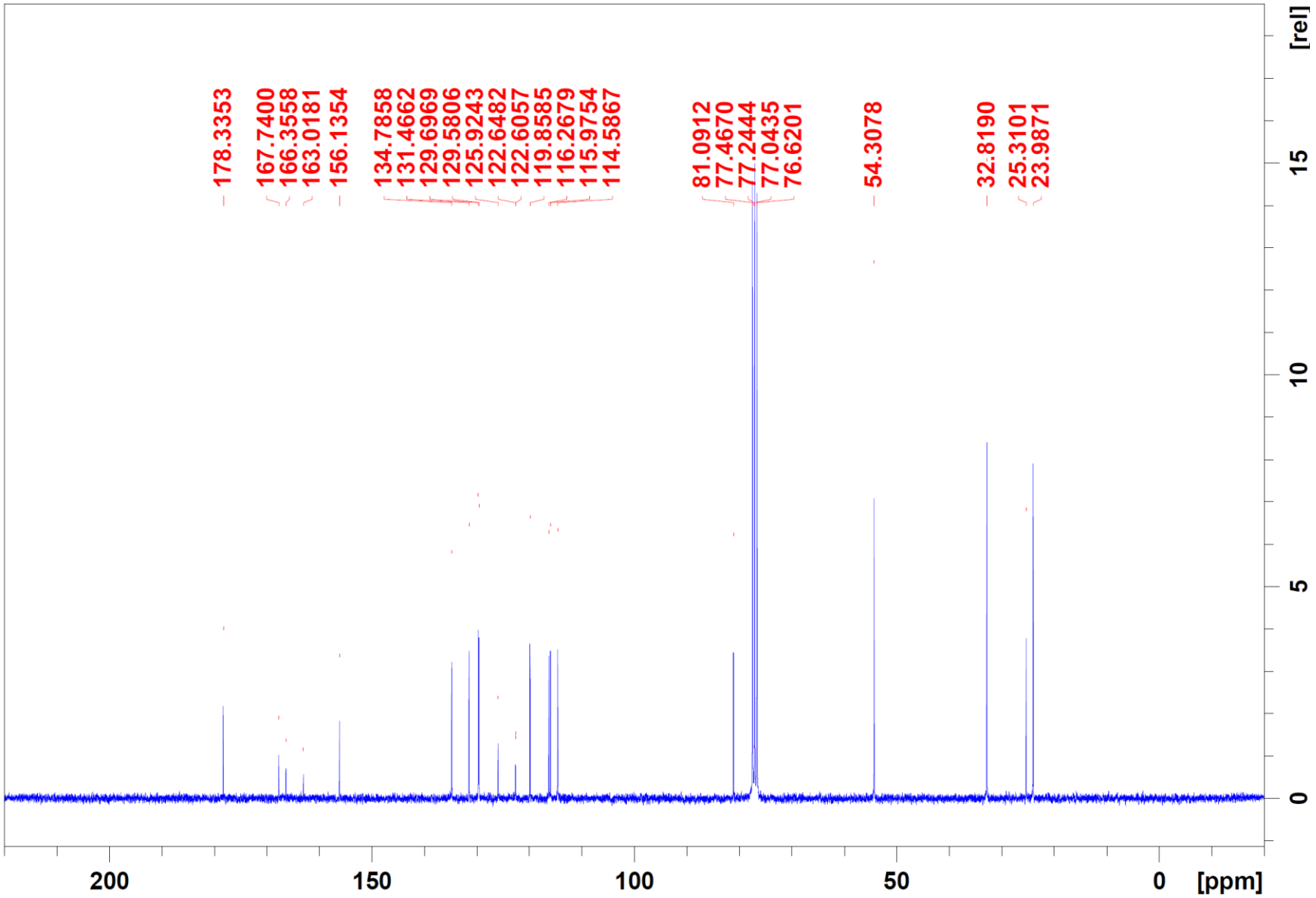
Analog **115** – ^{13}C NMR



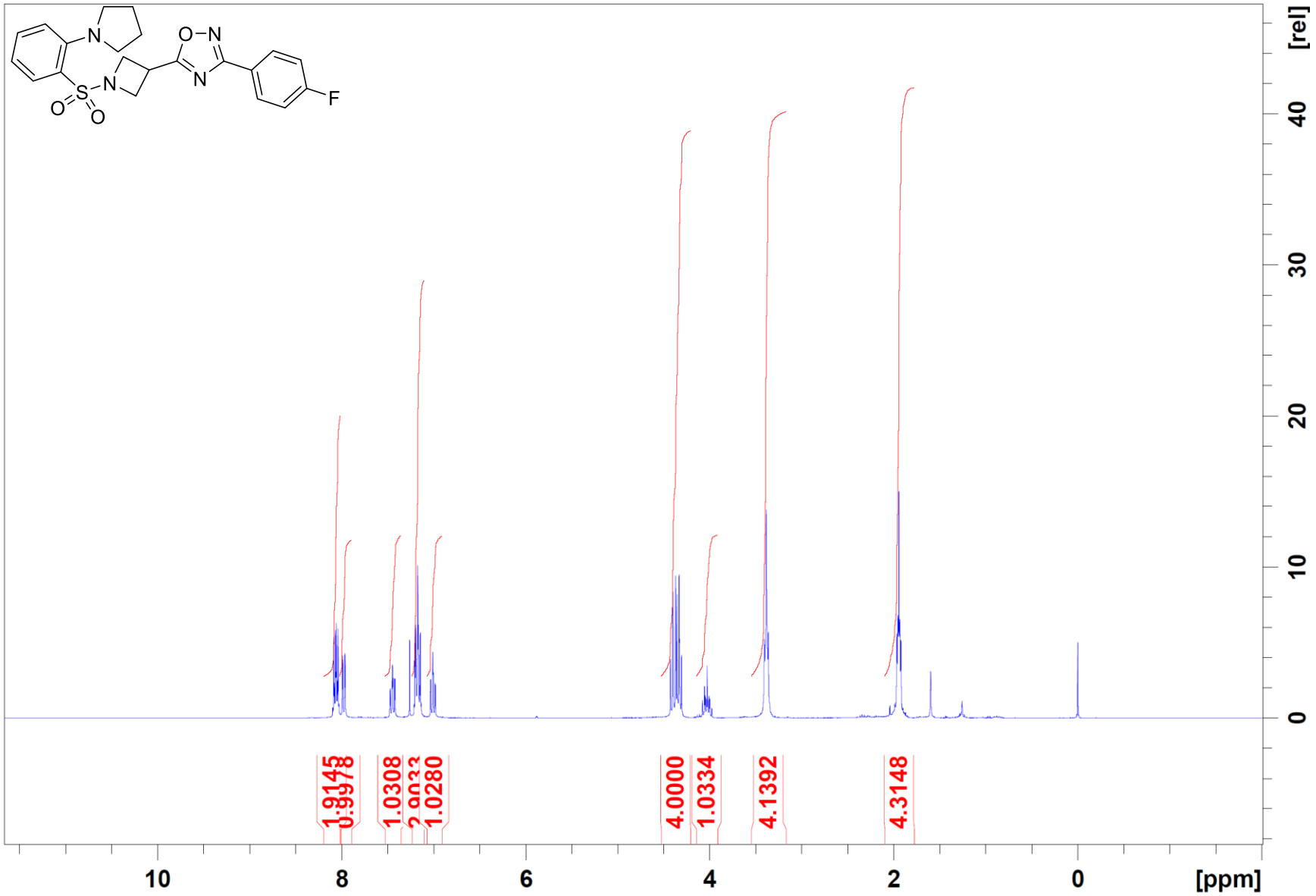
Analog **116** – ^{1}H NMR



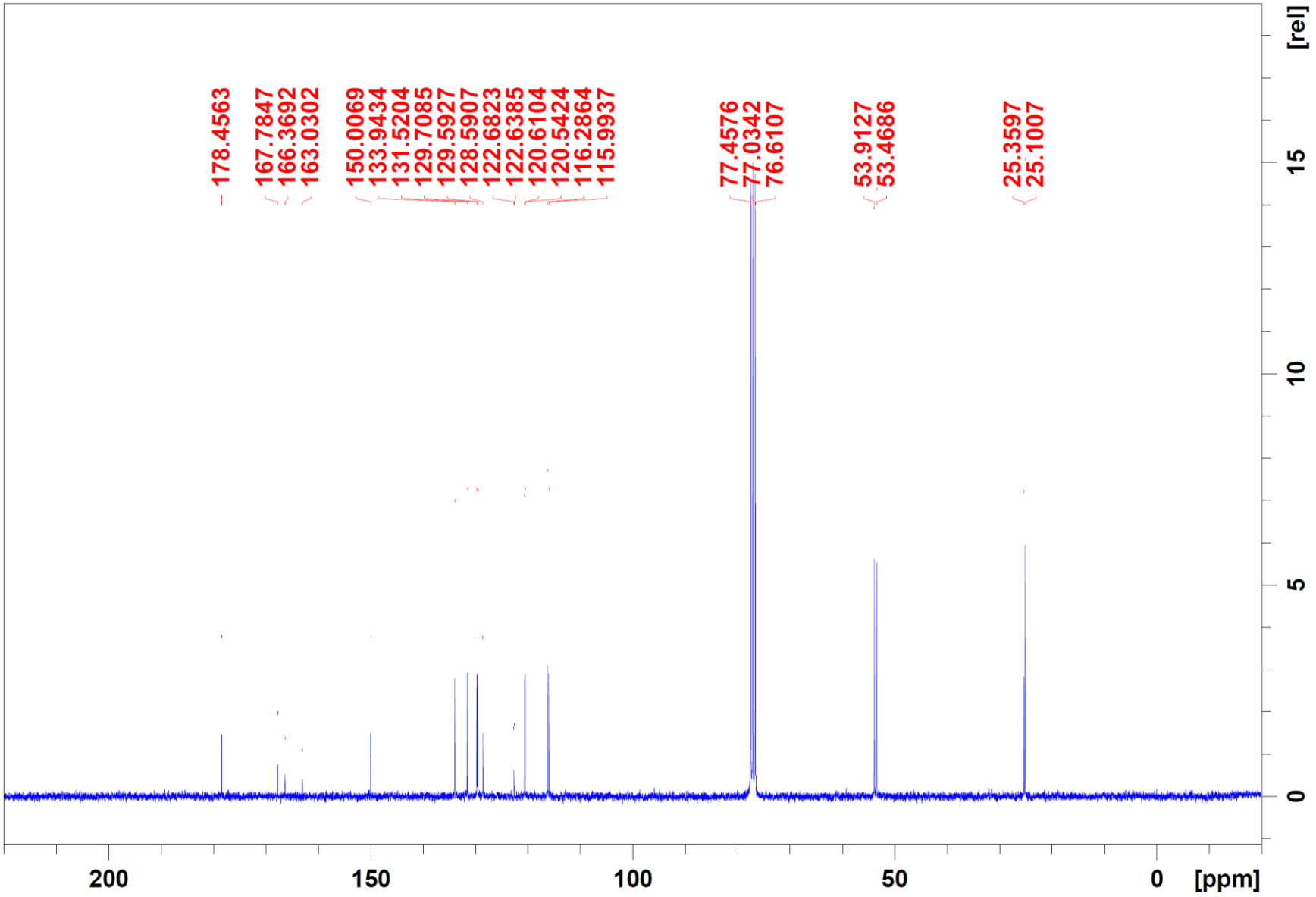
Analog **116** – ^{13}C NMR



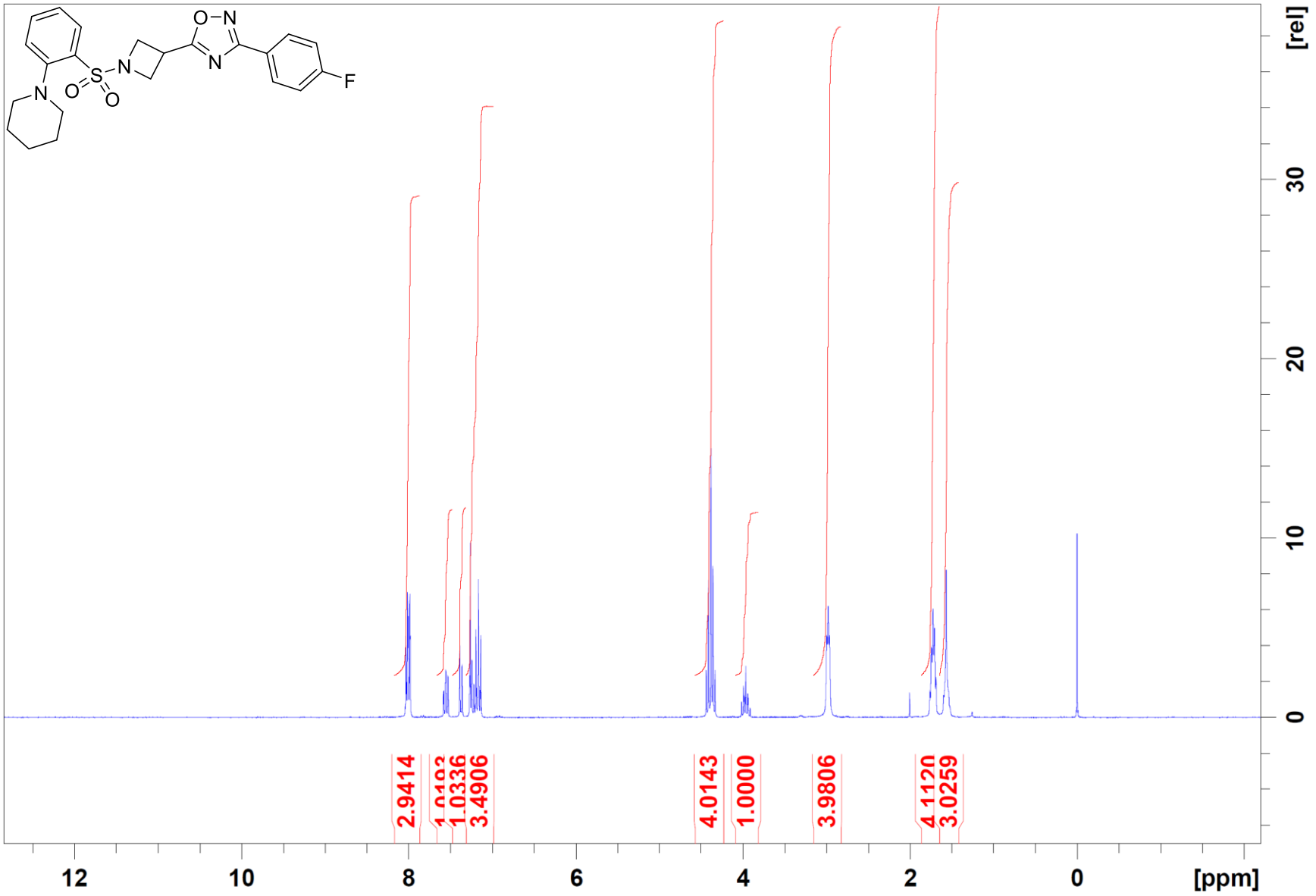
Analog **117** – ^{1}H NMR



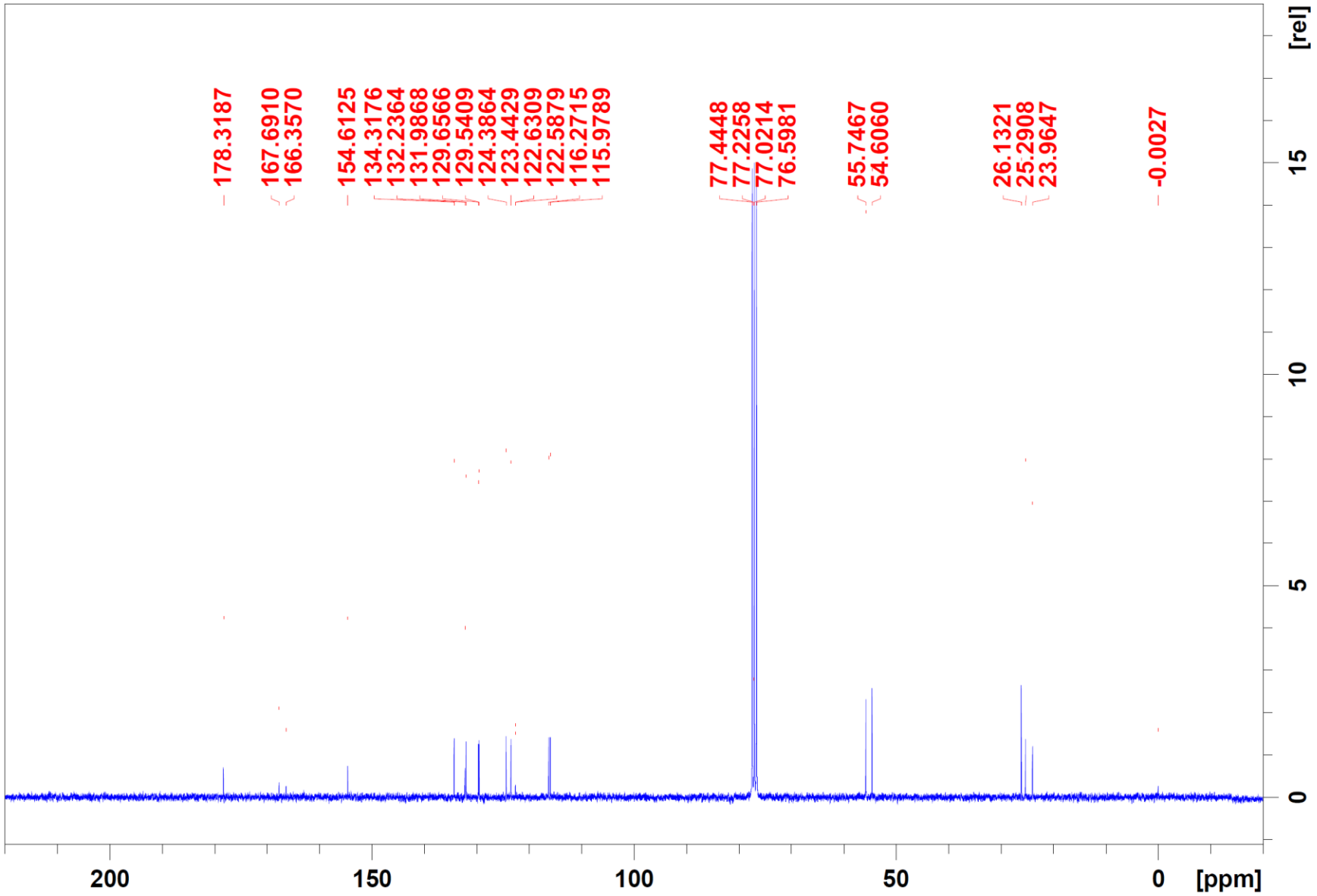
Analog **117** – ^{13}C NMR



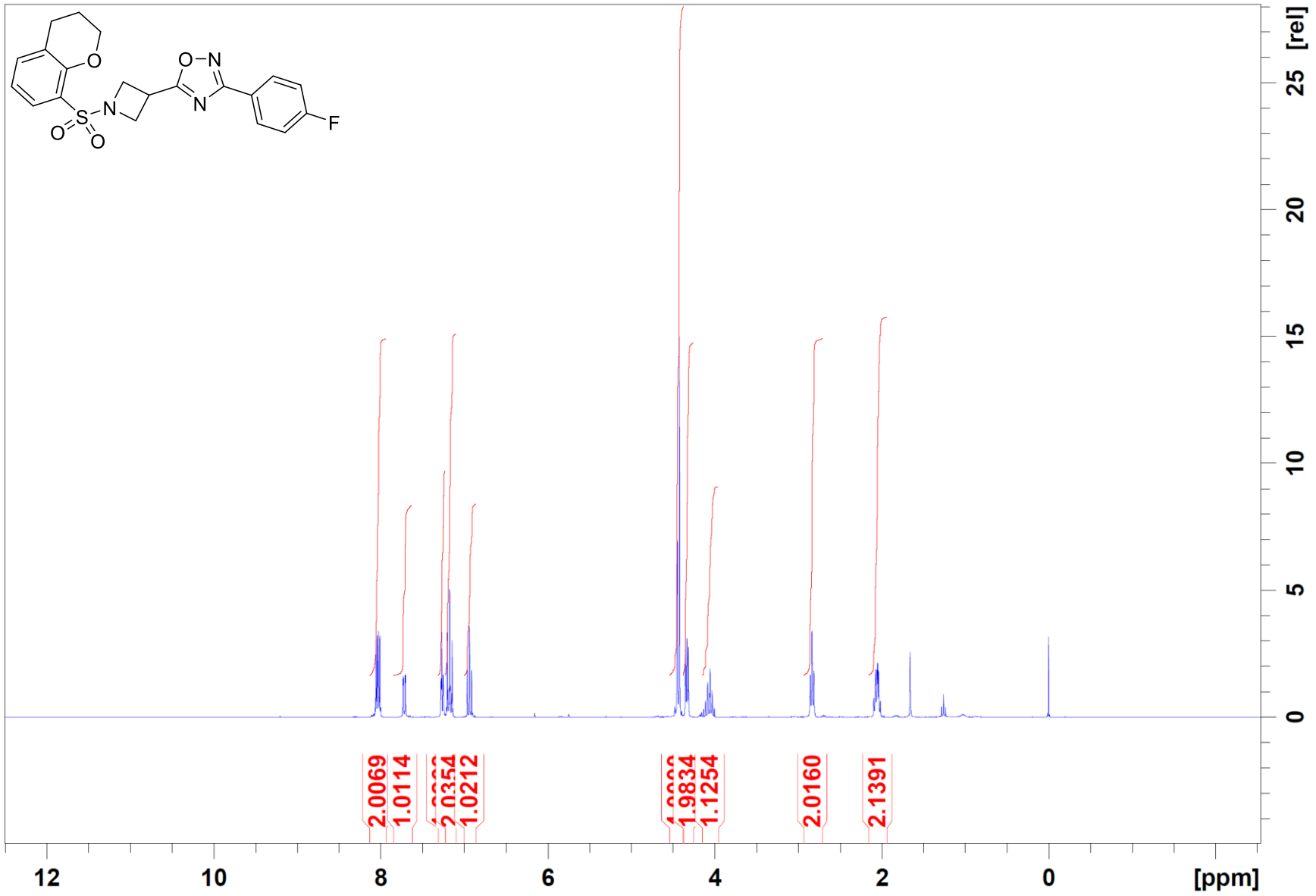
Analog **118** – ^{1}H NMR



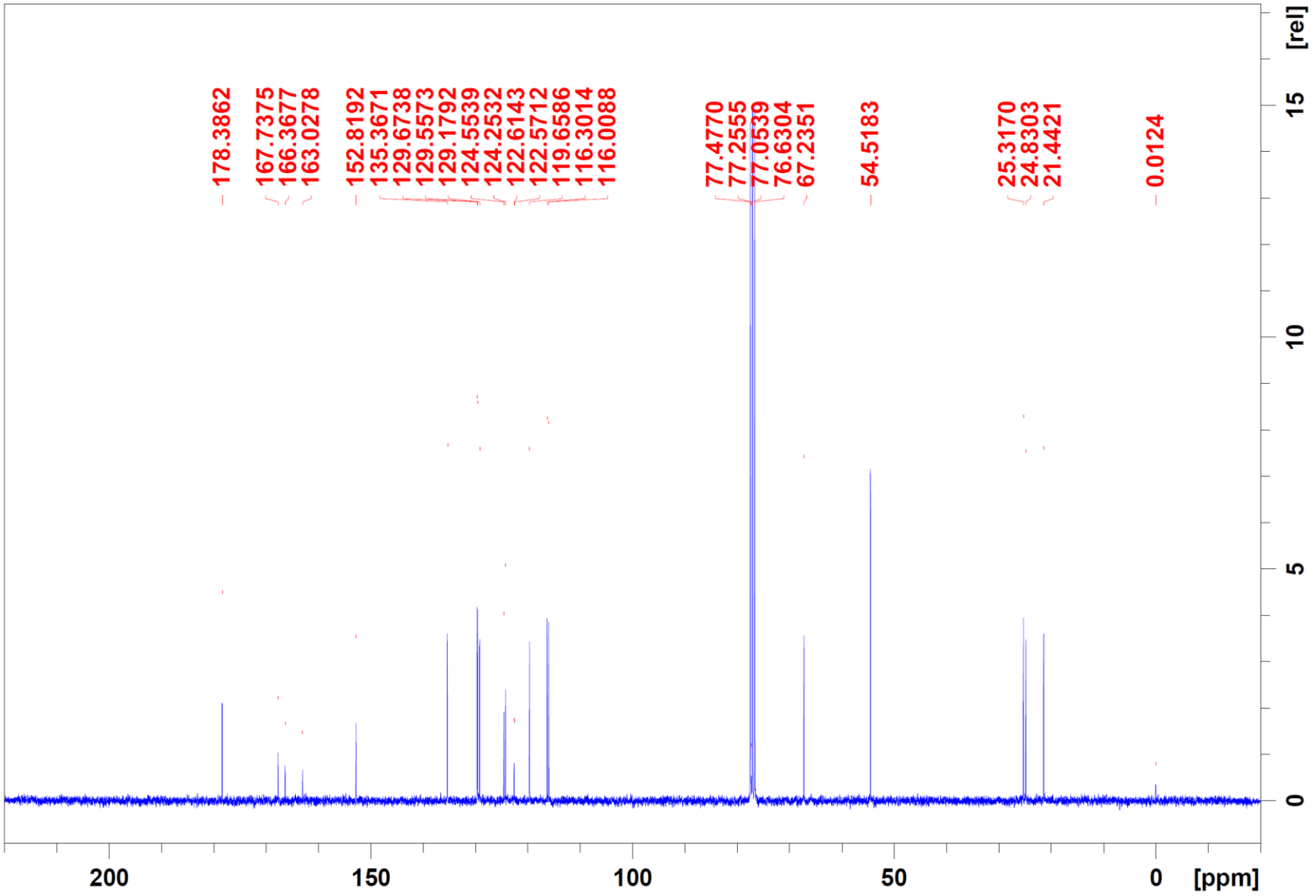
Analog **118** – ^{13}C NMR



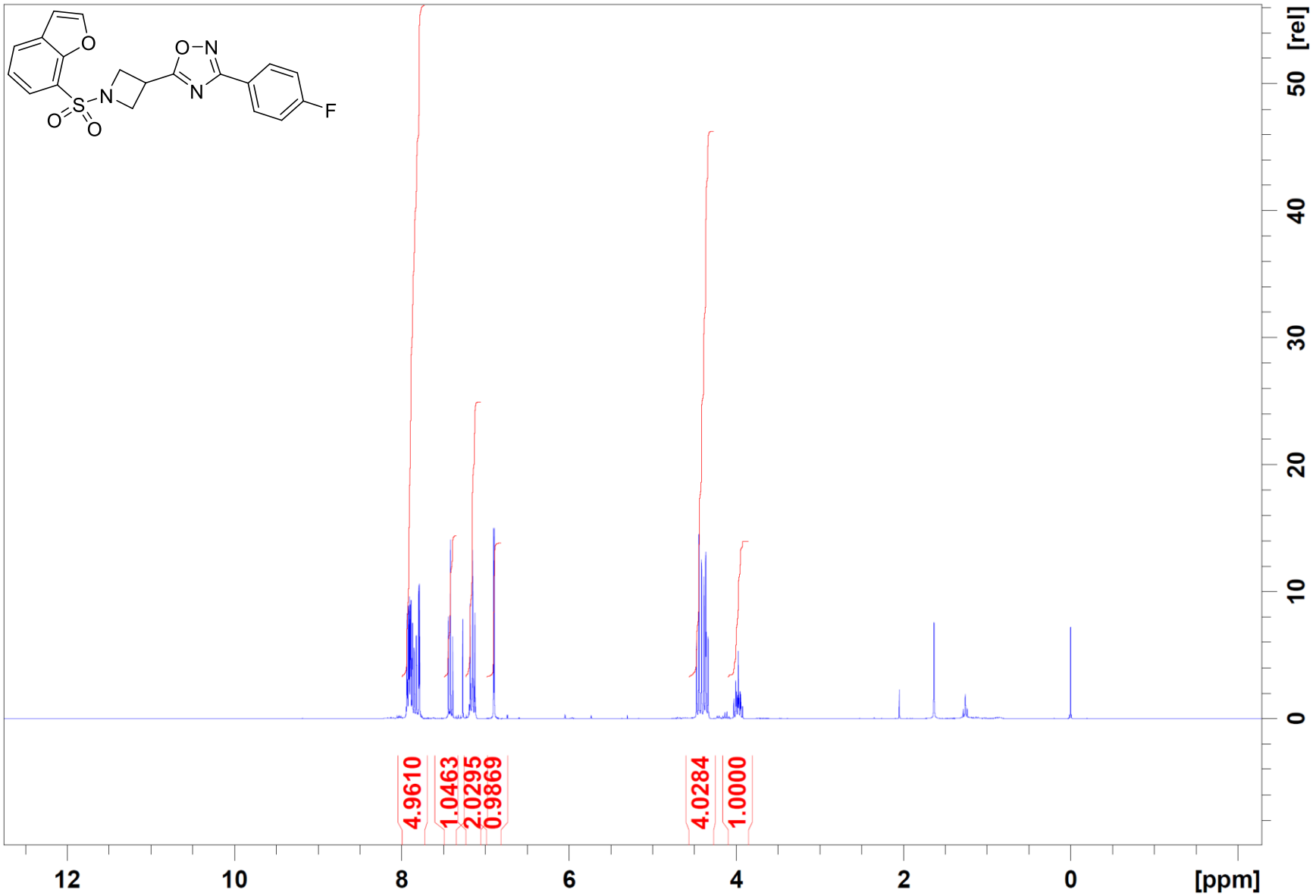
Analog **119** – ^{1}H NMR



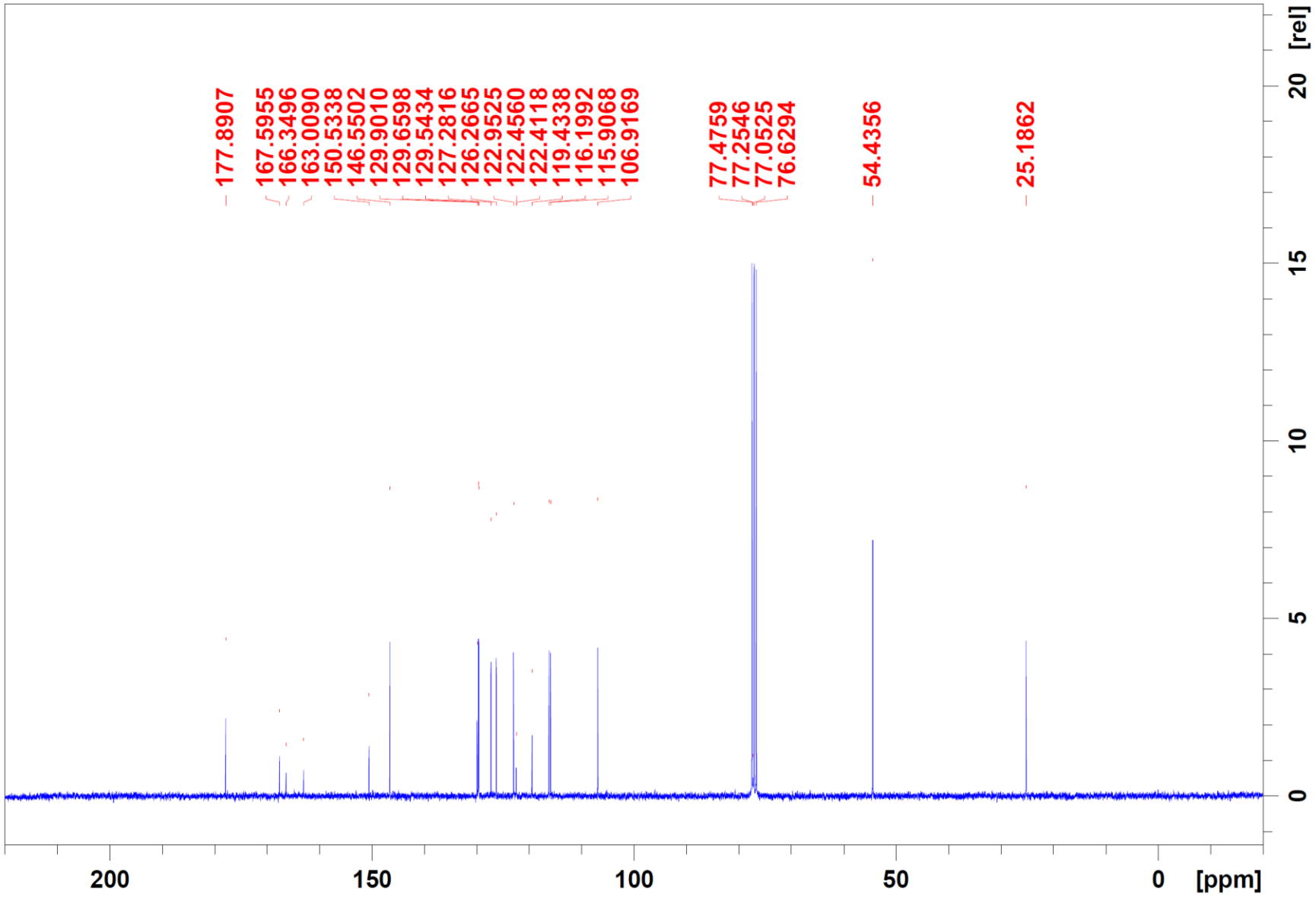
Analog **119** – ^{13}C NMR



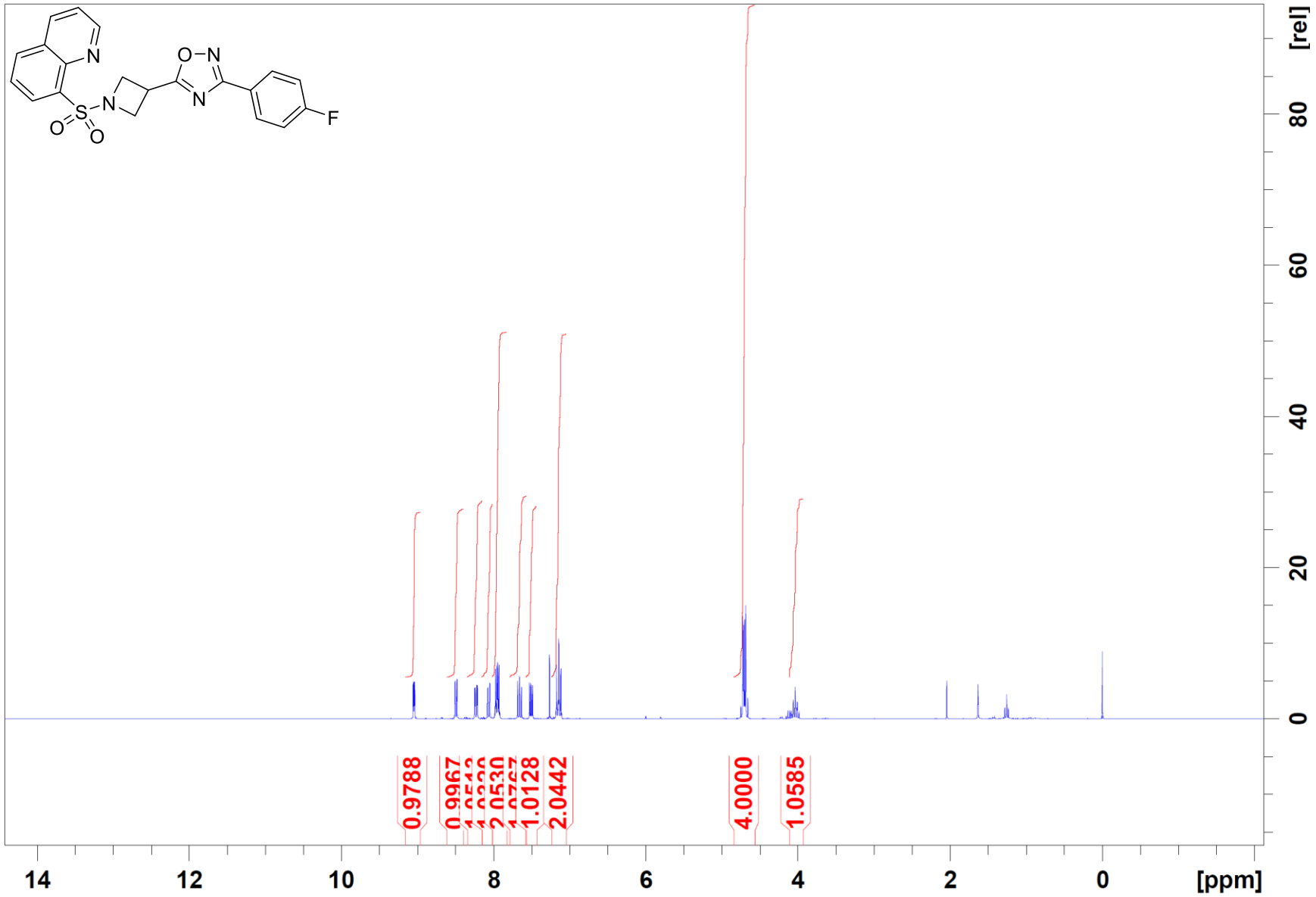
Analog **120** – ^{1}H NMR



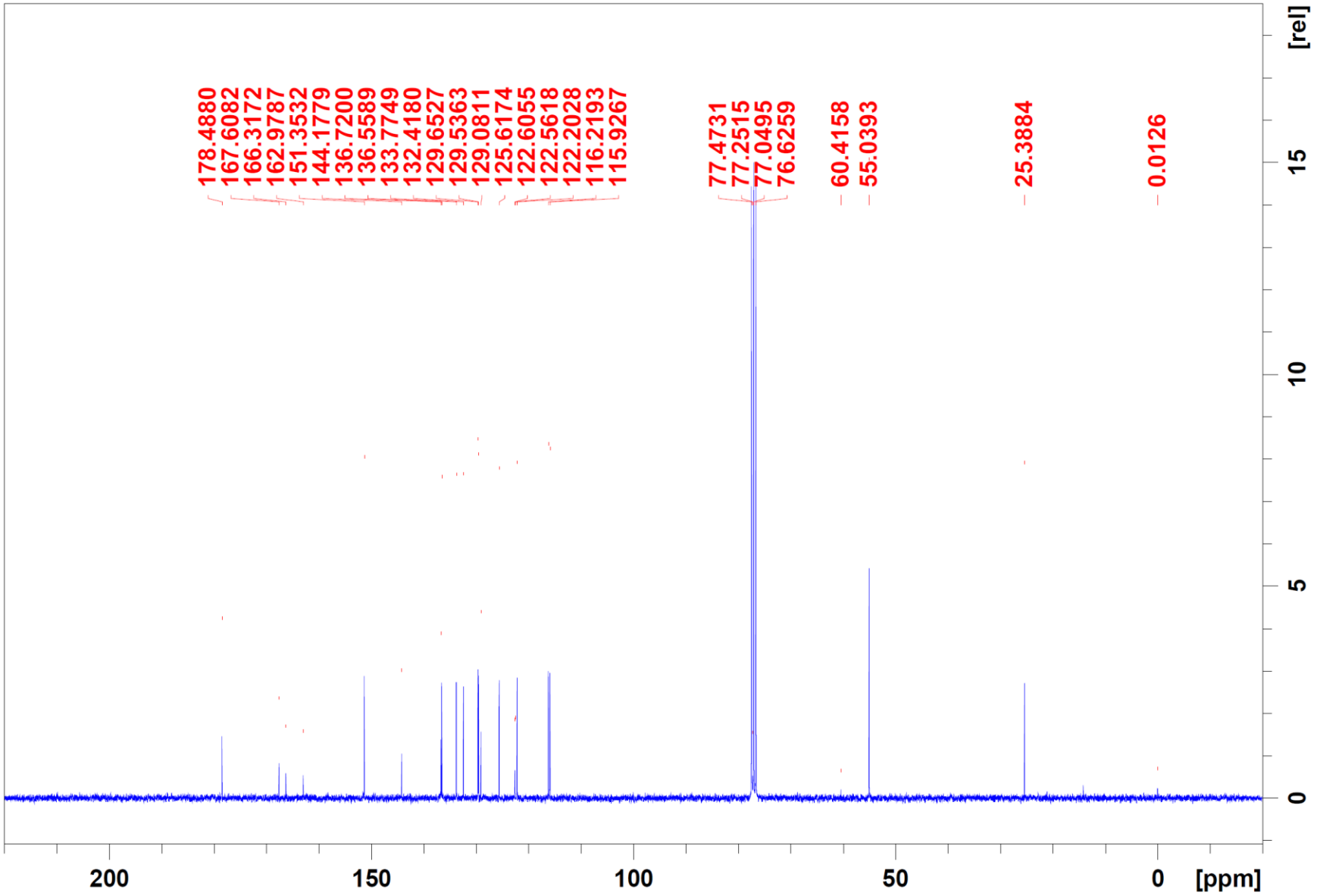
Analog **120** – ^{13}C NMR



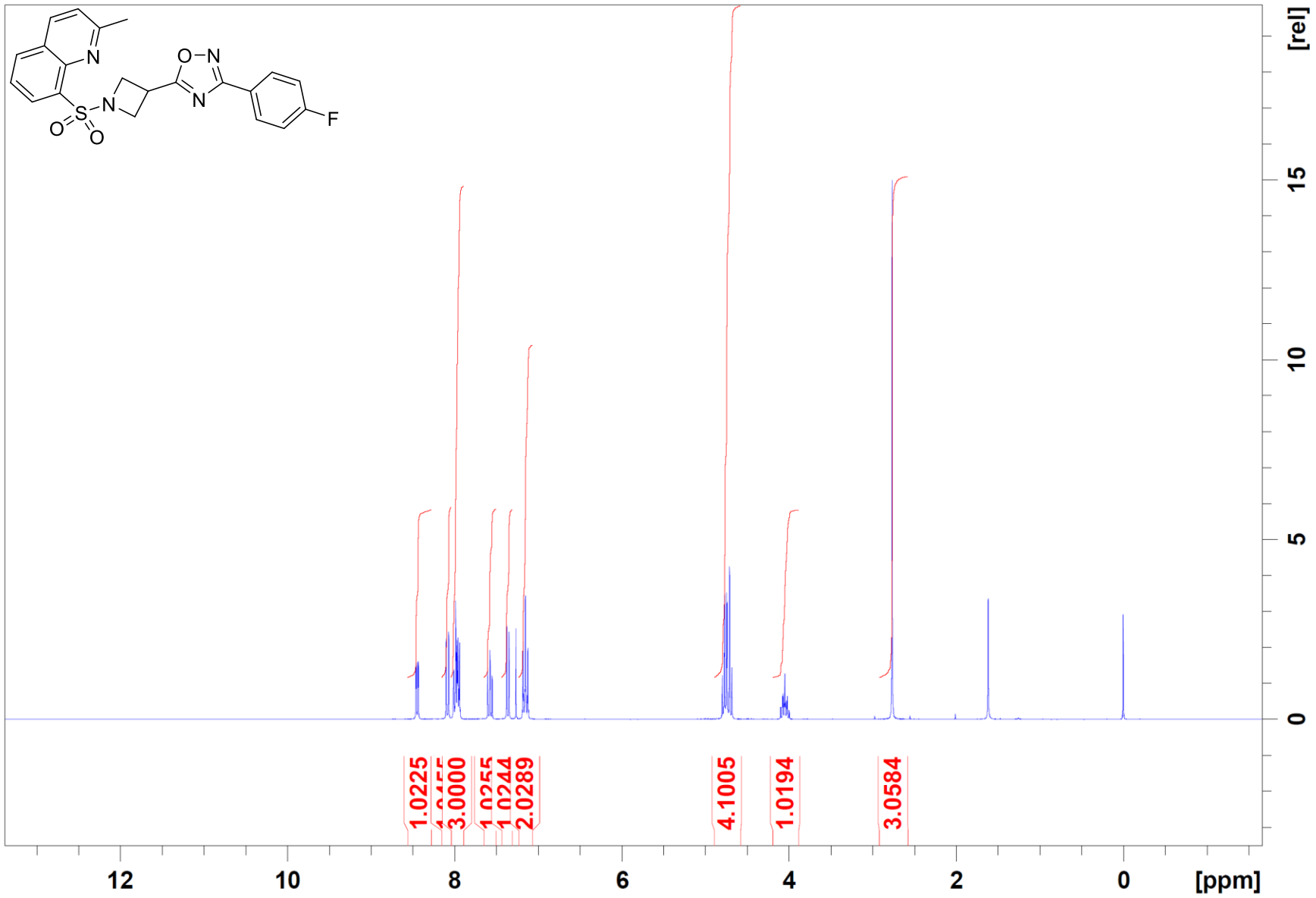
Analog **121** – ^{1}H NMR



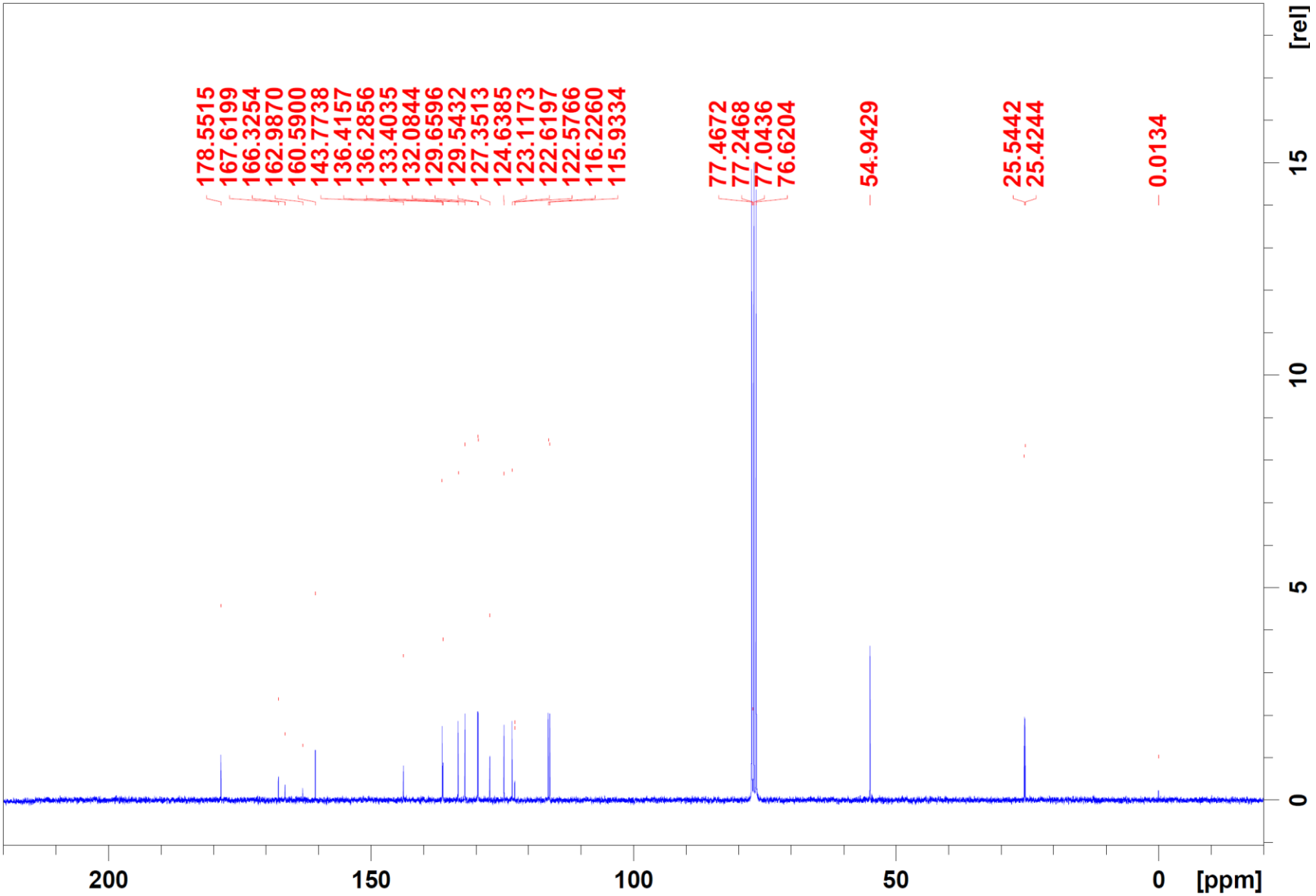
Analog **121** – ^{13}C NMR



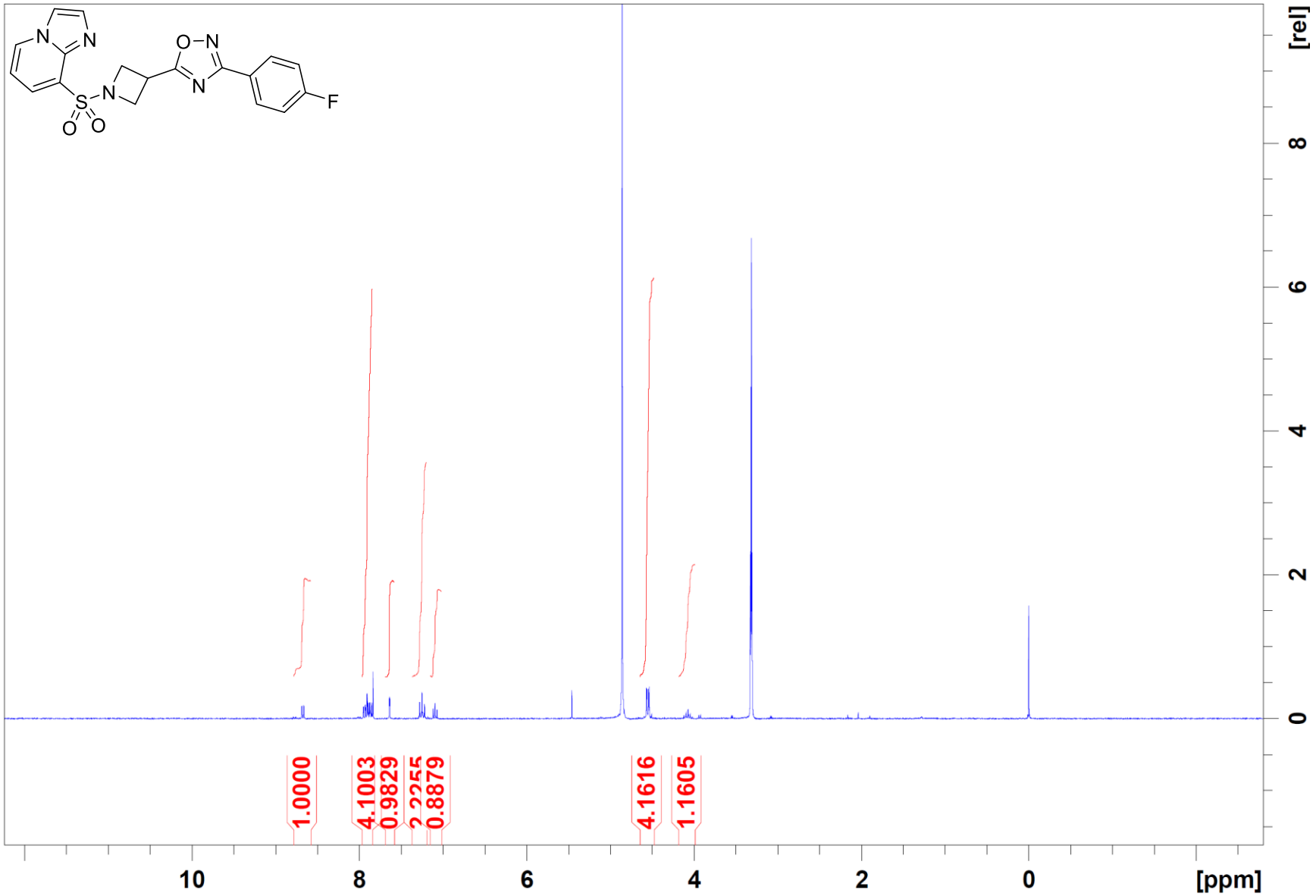
Analog **122** – ^{1}H NMR



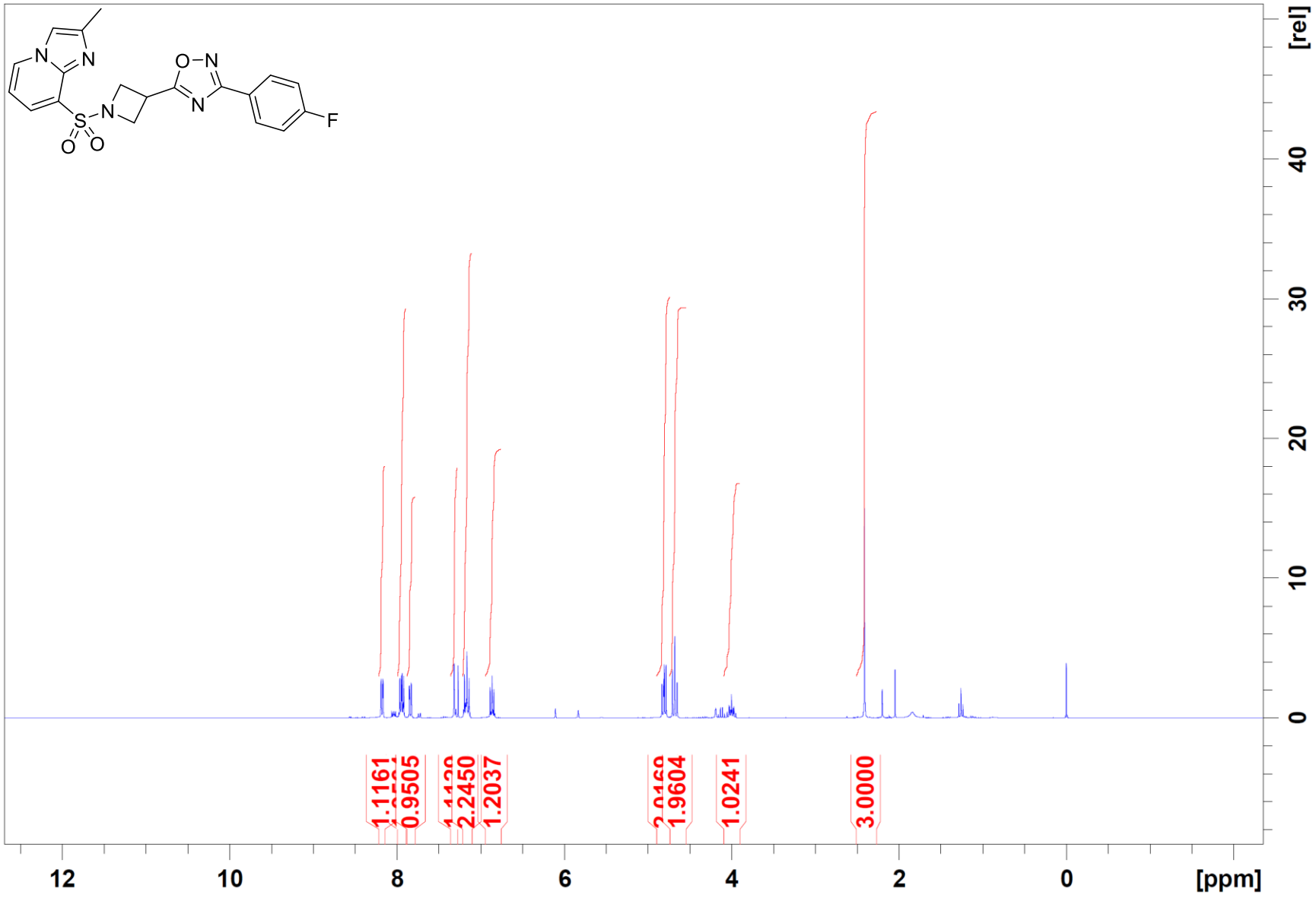
Analog **122** – ^{13}C NMR



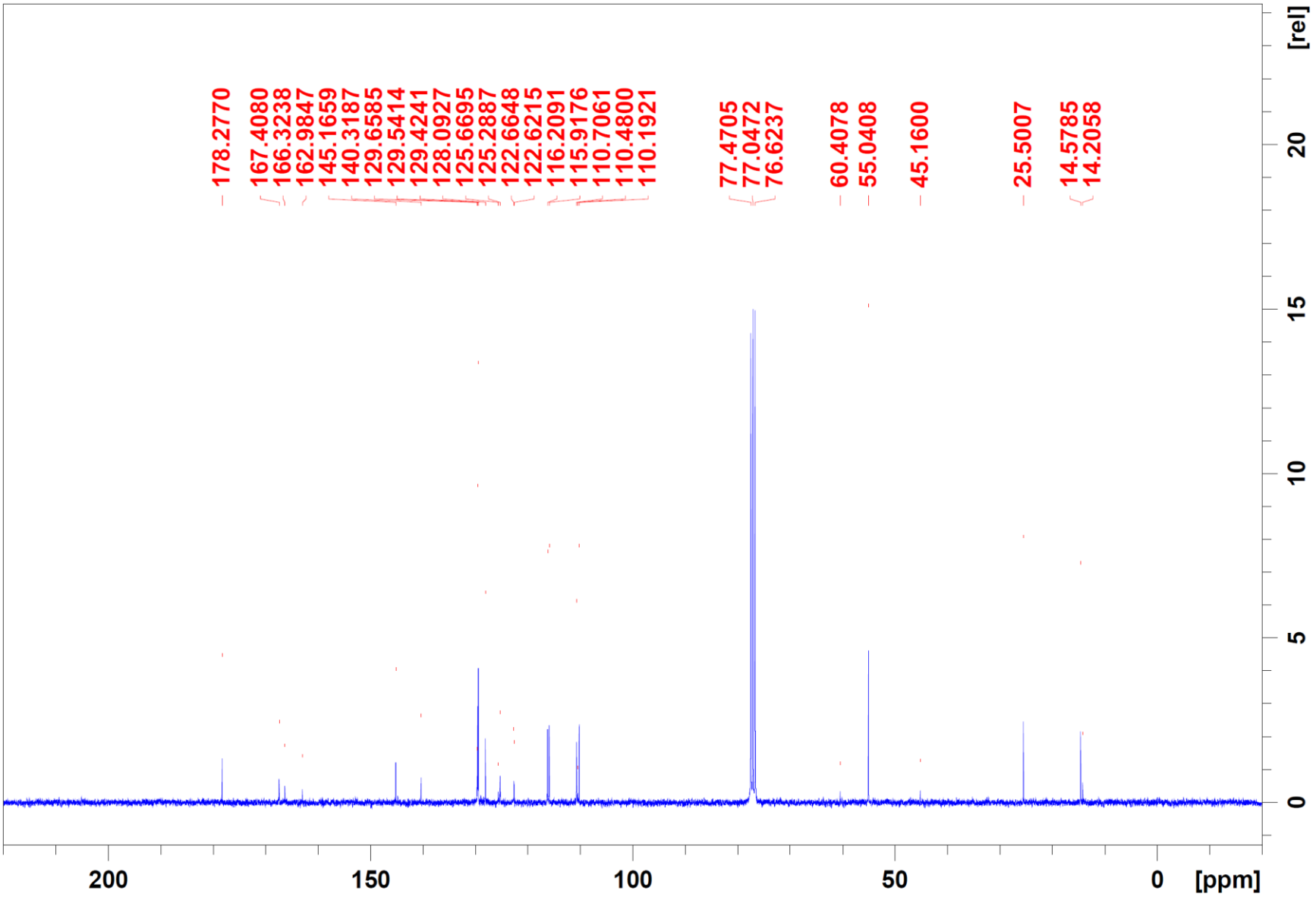
Analog **125** – ^{1}H NMR



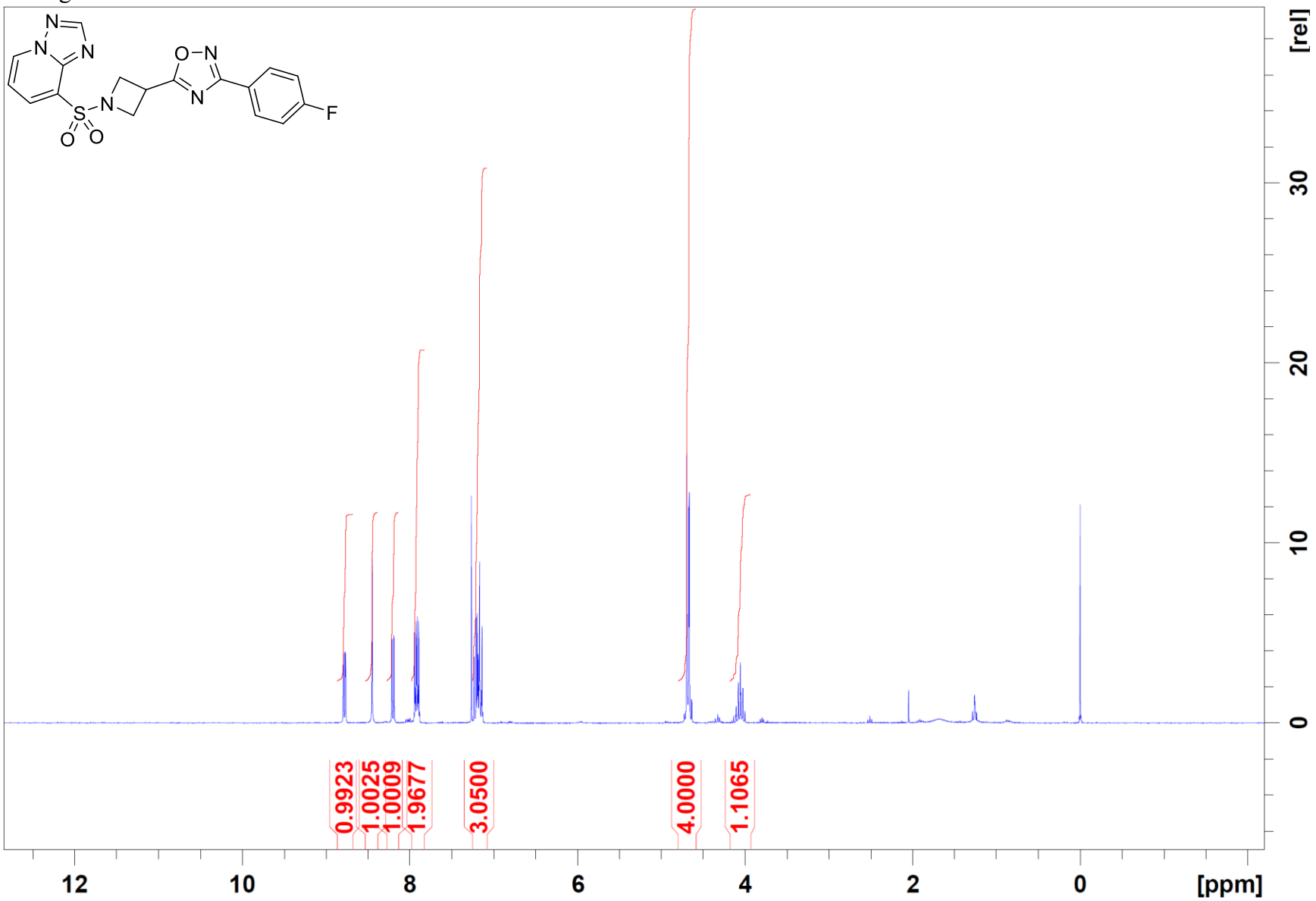
Analog **126** – ^{1}H NMR



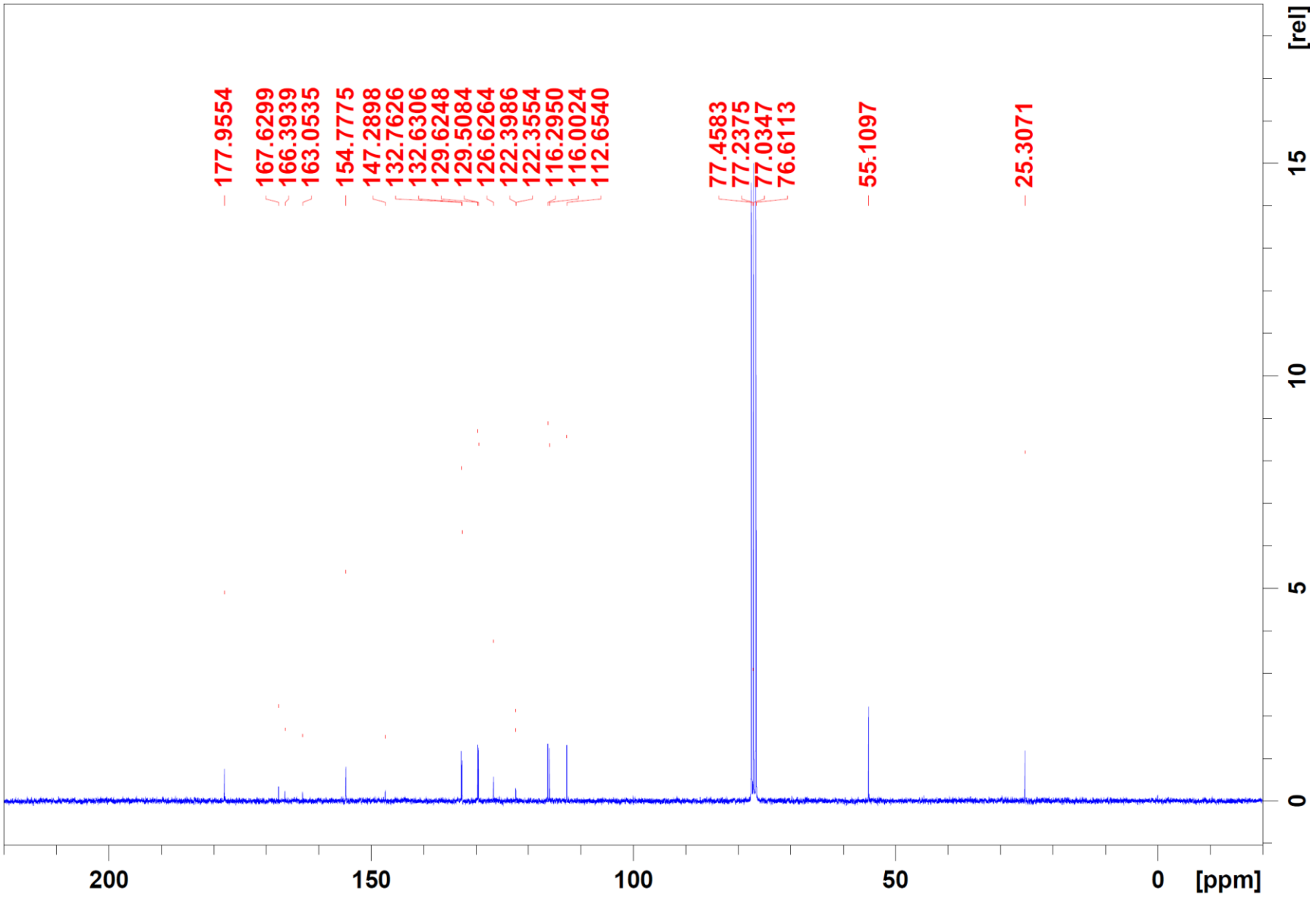
Analog **126** – ^{13}C NMR



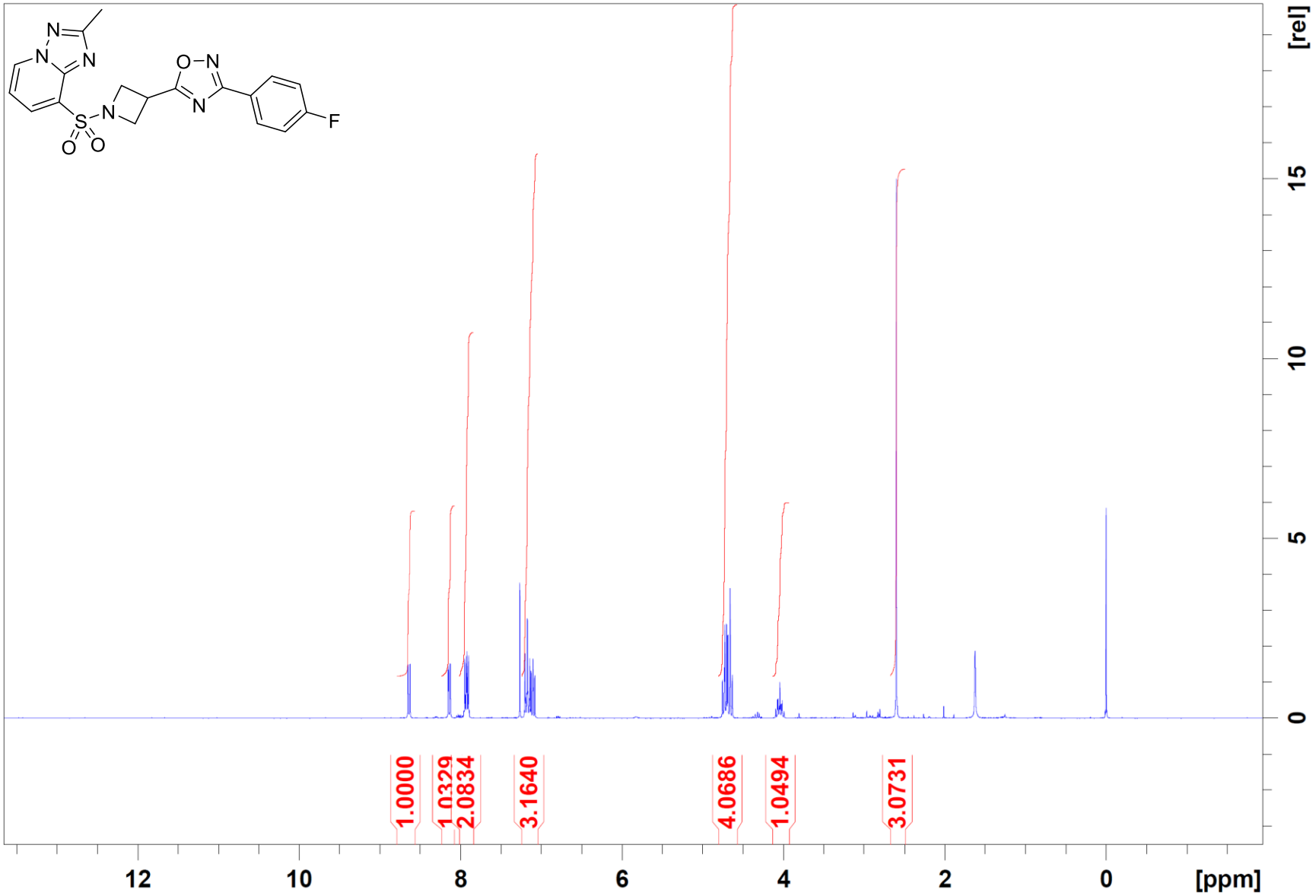
Analog **128** – ^{1}H NMR



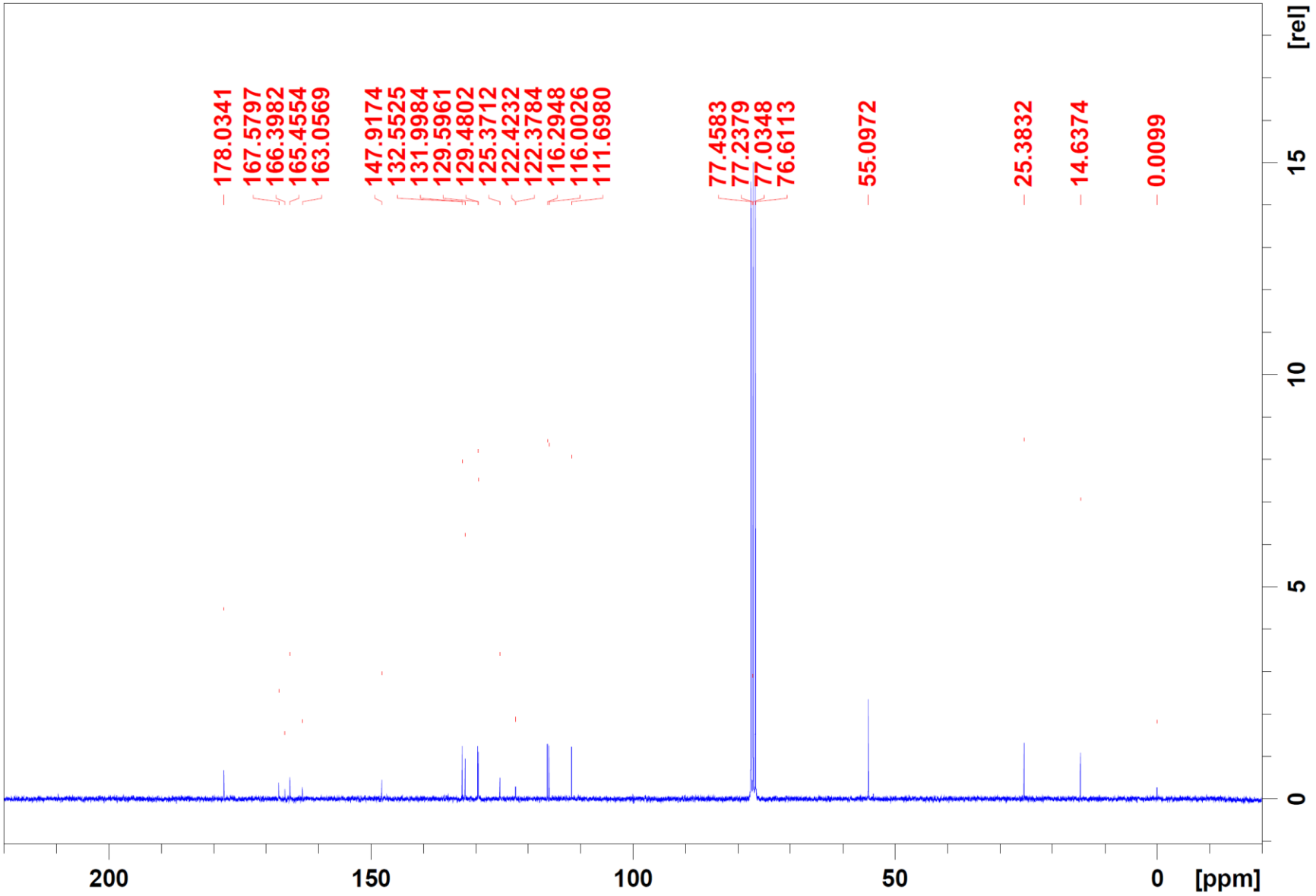
Analog **128** – ^{13}C NMR



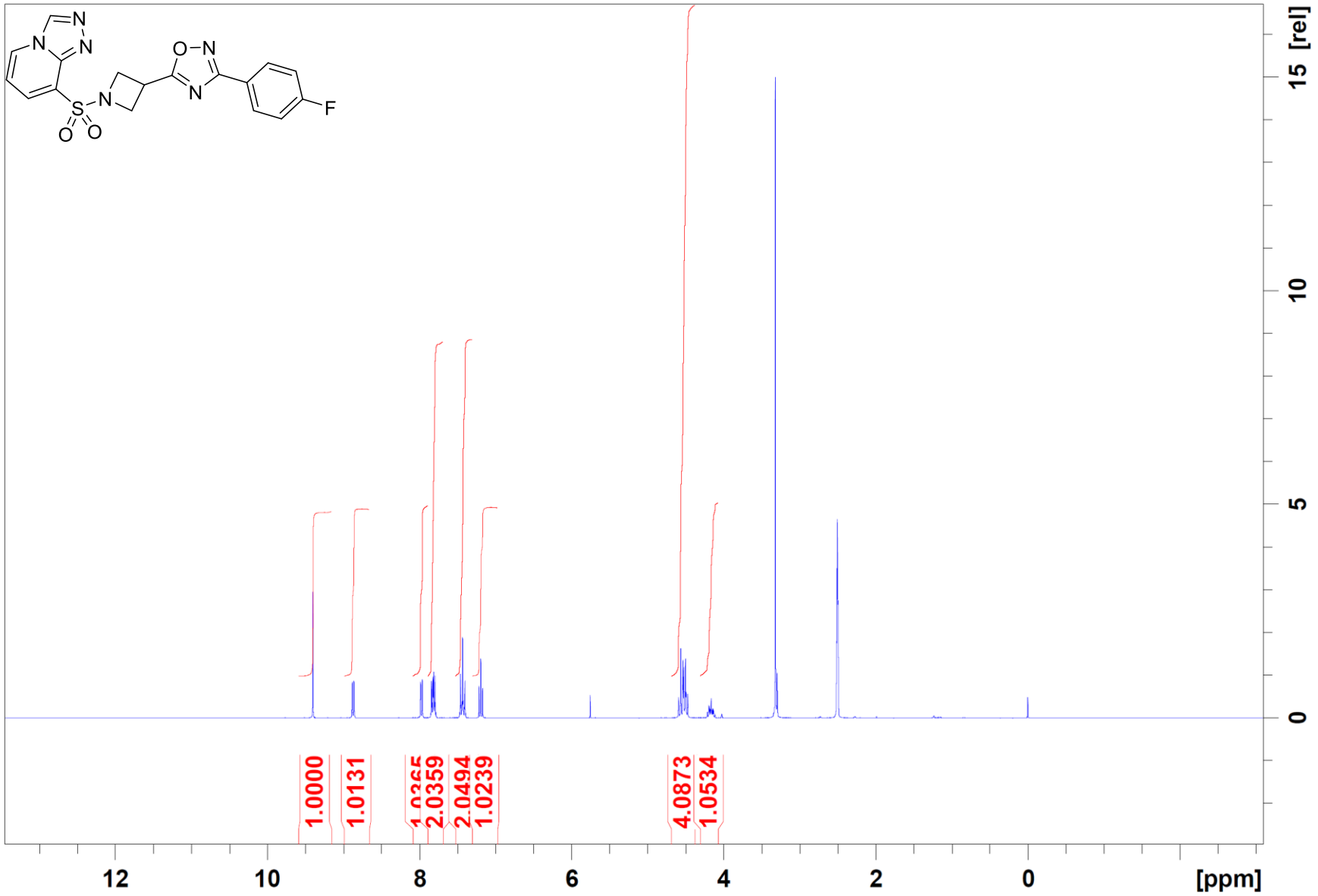
Analog **129** – ^{1}H NMR



Analog **129** – ^{13}C NMR



Analog **131** – ^{1}H NMR



Analog **132** – ^{1}H NMR