Electronic supplementary materials *Mendeleev Commun.*, 2023, **33**, 21–23

Diazo chemistry in the access to novel fatty acids linked to spiro-fused oxetane-pyrazolone scaffold

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Experimental procedures and characterization data

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To the pre-stirred (over 30 minutes) mixture of 3-(chlorosulfonyl)benzoic acid (1.34 mmol), sodium azide (1.5 mmol) and potassium carbonate (2 mmol) in water (8 mL), compound **3** (1 mmol) was added. The resulting emulsion was stirred at room temperature for 2 h whereupon the diazo transfer was complete. The mixture was extracted with chloroform (2×10 mL). The extract was separated, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was dissolved in acetonitrile (20 mL) and was treated with a solution of KOH (140 mg, 5 mmol) in water (4 mL). The resulting mixture was stirred at room temperature for 3 h and extracted with chloroform (2×10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product **4** was used on the next step without further purification.

To a vigorously stirred solution of the corresponding diazo compound **4** (1 mmol) in dry dichloromethane (5 mL), 2-bromoethanol (1.1 mmol) was added followed by $Rh_2(esp)_2$ (0.003 mmol, 0.3 mol.%). After completion of the reaction (TLC control, up to 30 min), the reaction mixture was concentrated to dryness. The product **5** was used on the next step without further purification.

To a solution of crude compound **5** (1 mmol) in DMF (5 mL), NaH (1.1 mmol) was added in one portion at 0 °C. The resulting mixture was stirred at this temperature under inert atmosphere for 1 h. Upon completion of the reaction, the resulting mixture was carefully diluted with water (40 mL), extracted with ether (3×20 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting oil was purified by column chromatography using ethyl acetate-*n*-hexane (1:2) as the eluent.

Yield 251 mg, 25%. Yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm. 7.48–7.40 (m, 1H), 7.32–7.28 (m, 2H), 7.28–7.23 (m, 2H), 7.20–7.12 (m, 1H), 7.04–6.94 (m, 2H), 5.17 (s, 2H), 4.31–4.19 (m, 2H), 4.16–4.09 (m, 2H), 3.92 (q, *J* = 7.1 Hz, 2H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm. 163.3, 162.7 (d, *J* = 243.6 Hz), 159.0, 146.7, 140.4 (d, *J* = 7.7 Hz), 130.9 (d, *J* = 8.2 Hz), 130.9, 127.5, 126.1, 123.9 (d, *J* = 2.8 Hz), 115.0 (d, *J* = 20.9 Hz), 114.6 (d, *J* = 21.8 Hz), 114.3, 68.8 (d, *J* = 2.0 Hz), 65.9, 63.6, 60.2, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{20}FO_5^+$ 359.1295, found 359.1311.

8-[4-(4-Fluorobenzyloxy)phenyl]-1-oxa-6,7-diazaspiro[3.4]oct-7-en-5-one (7)

A mixture of compound **6** (1 mmol), hydrazine hydrate (5 mmol) and butan-1-ol (3 mL) was heated under Ar atmosphere in a sealed tube at 140 °C for 18 h. Upon completion, the solution was cooled, and ethyl acetate (20 mL) was added. The resulting solution was washed with water (2×10 mL), dried over anhydrous Na_2SO_4 and evaporated to give the pure title compound.

Yield 239 mg, 73%. White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm. 8.98 (s, 1H), 7.51–7.41 (m, 1H), 7.33–7.23 (m, 4H), 7.20–7.13 (m, 1H), 7.01–6.90 (m, 2H), 5.15 (s, 2H), 4.25–4.18 (m, 4H), 4.12–4.06 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm. 162.7 (d, *J* = 243.7 Hz), 162.5, 158.5, 140.5 (d, *J* = 7.3 Hz), 140.3, 131.0 (d, *J* = 8.4 Hz), 130.4, 128.4, 127.3, 124.0 (d, *J* = 2.8 Hz), 115.1 (d, *J* = 21.0 Hz), 114.7 (d, *J* = 21.6 Hz), 114.1, 68.8 (d, *J* = 2.1 Hz), 65.4, 63.9. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calculated for $C_{18}H_{16}FN_2O_3^+$ 327.1145, found 327.1131.

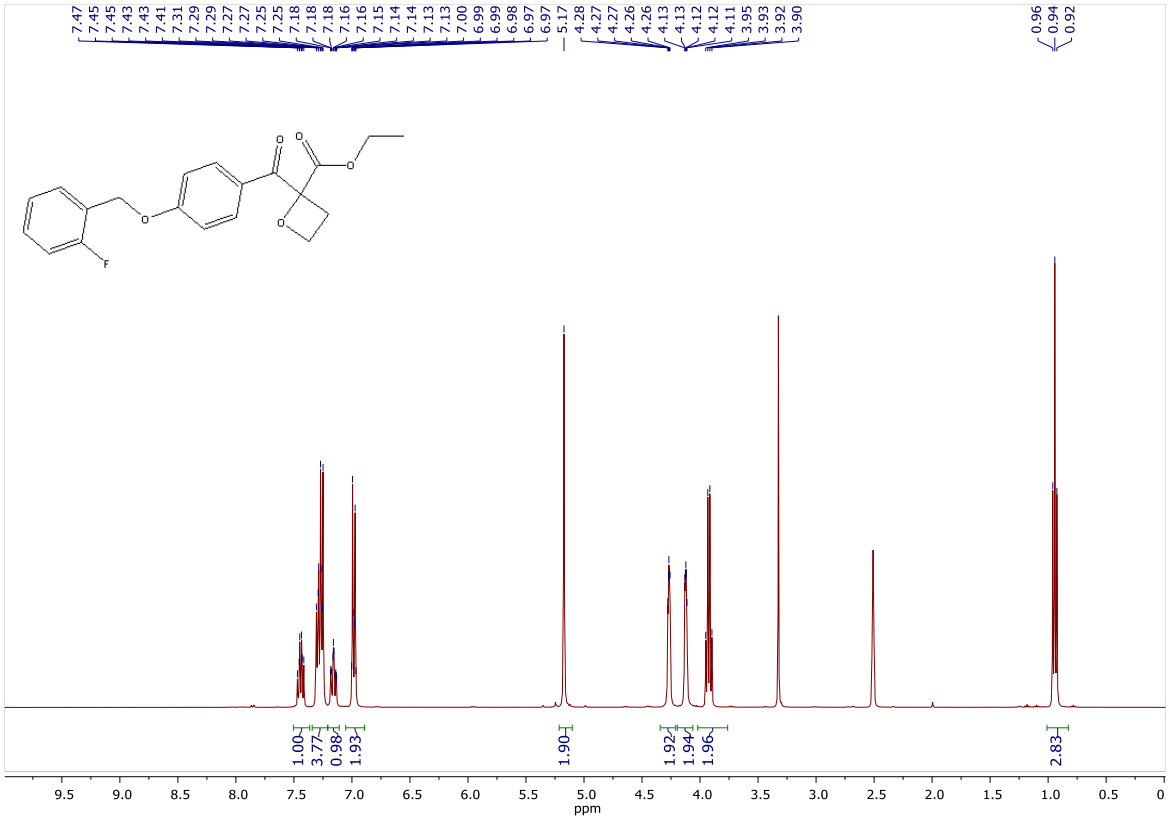
3-{8-[4-(3-Fluorobenzyloxy)phenyl]-5-oxo-1-oxa-6,7-diazaspiro[3.4]oct-7-en-6-yl}propanic acid (2)

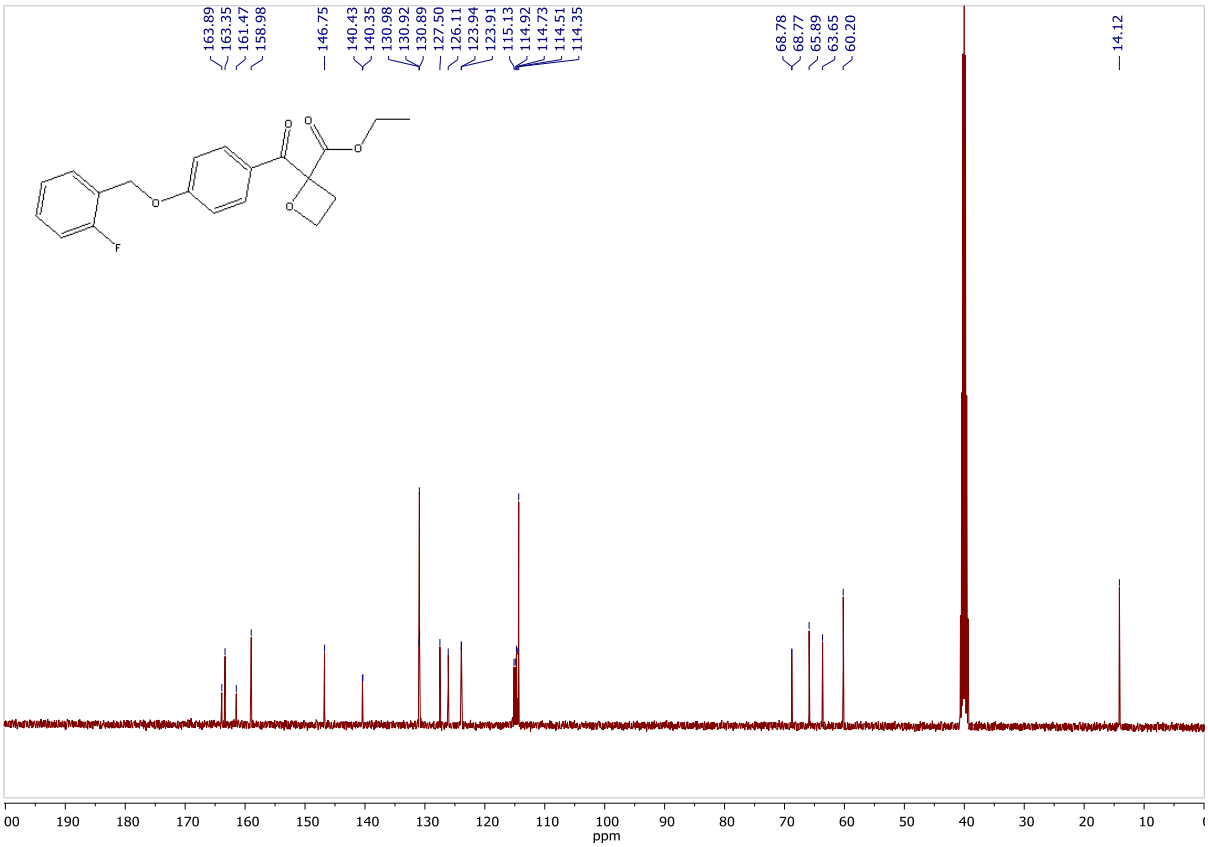
To a solution of compound **7** (1 mmol) and methyl acrylate (1.2 mmol) in DMF (5 mL), Bu^{t}OK (0.2 mmol) was added at 0 °C. The resulting mixture was stirred at this temperature for 30 min. Upon completion of the reaction, ethyl acetate (30 mL) was added, and the mixture was washed with water (4×20 mL), dried over Na_2SO_4 and evaporated. The desired ester was purified using HPLC chromatography using acetone-hexane 0→45% gradient as the eluent. The proper fractions were evaporated, dissolved in MeOH (5 mL), and LiOH (2 mmol) was added. The mixture was stirred for 18 h. Upon completion of the reaction, acetic acid (2 mmol) was added followed by ethyl acetate (30 mL), and the resulting mixture was washed with water (2×10 mL), dried over anhydrous Na_2SO_4 and evaporated to give the pure title compound.

Yield 128 mg, 32%. White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm. 11.94 (s, 1H), 7.49–7.38 (m, 1H), 7.32–7.22 (m, 4H), 7.16–7.09 (m, 1H), 6.99–6.94 (m, 2H), 5.15 (s, 2H), 4.24 (s, 2H), 4.12 (s, 2H), 3.72 (s, 2H), 2.37 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm. 175.3, 172.6, 162.8 (d, *J* = 244.0 Hz), 158.8, 140.5 (d, *J* = 7.4 Hz), 136.8, 130.8 (d, *J* = 8.2 Hz), 129.4, 129.1, 126.9, 123.8, 115.1, 114.9 (d, *J* = 21.6 Hz), 114.5 (d, *J* = 21.9 Hz), 69.2, 65.1, 64.2, 24.8, 20.2. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ calculated for $C_{21}H_{18}FN_2O_5^-$ 397.1200, found 397.1212.

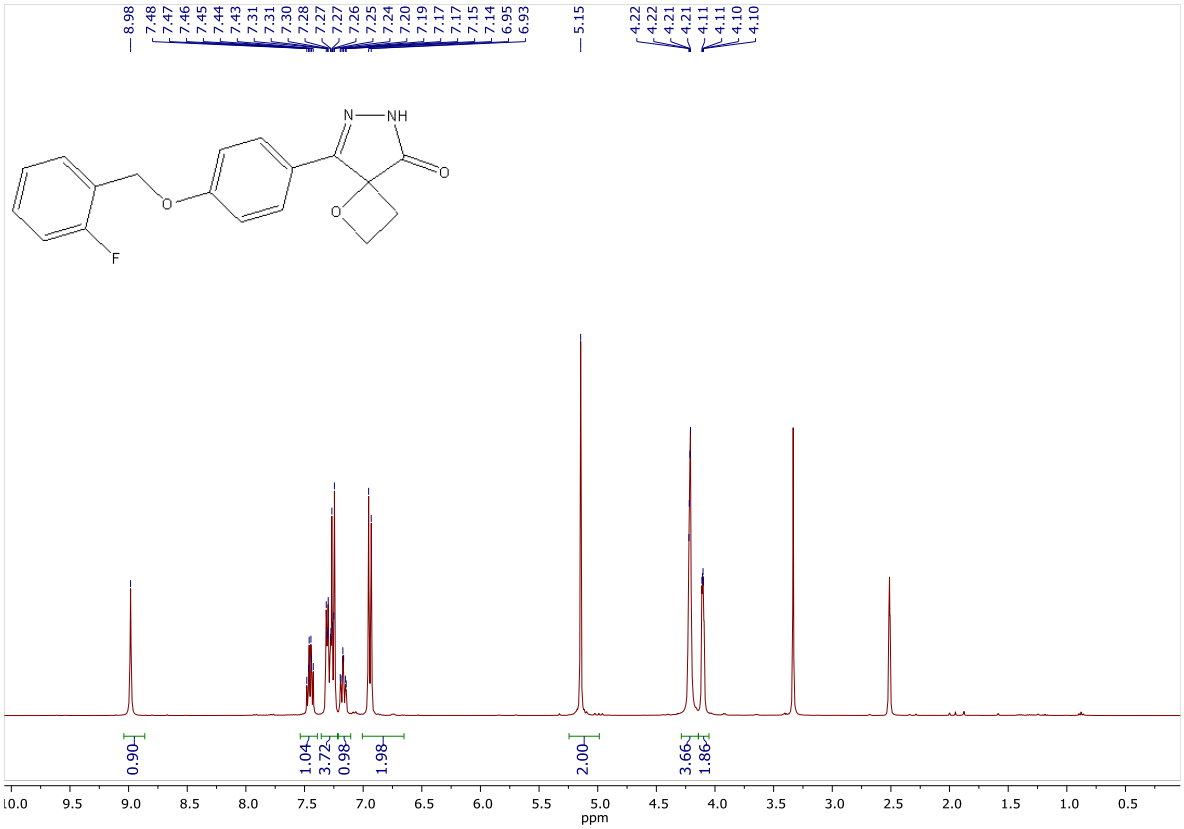
Copies of ^{1}H and ^{13}C NMR spectra

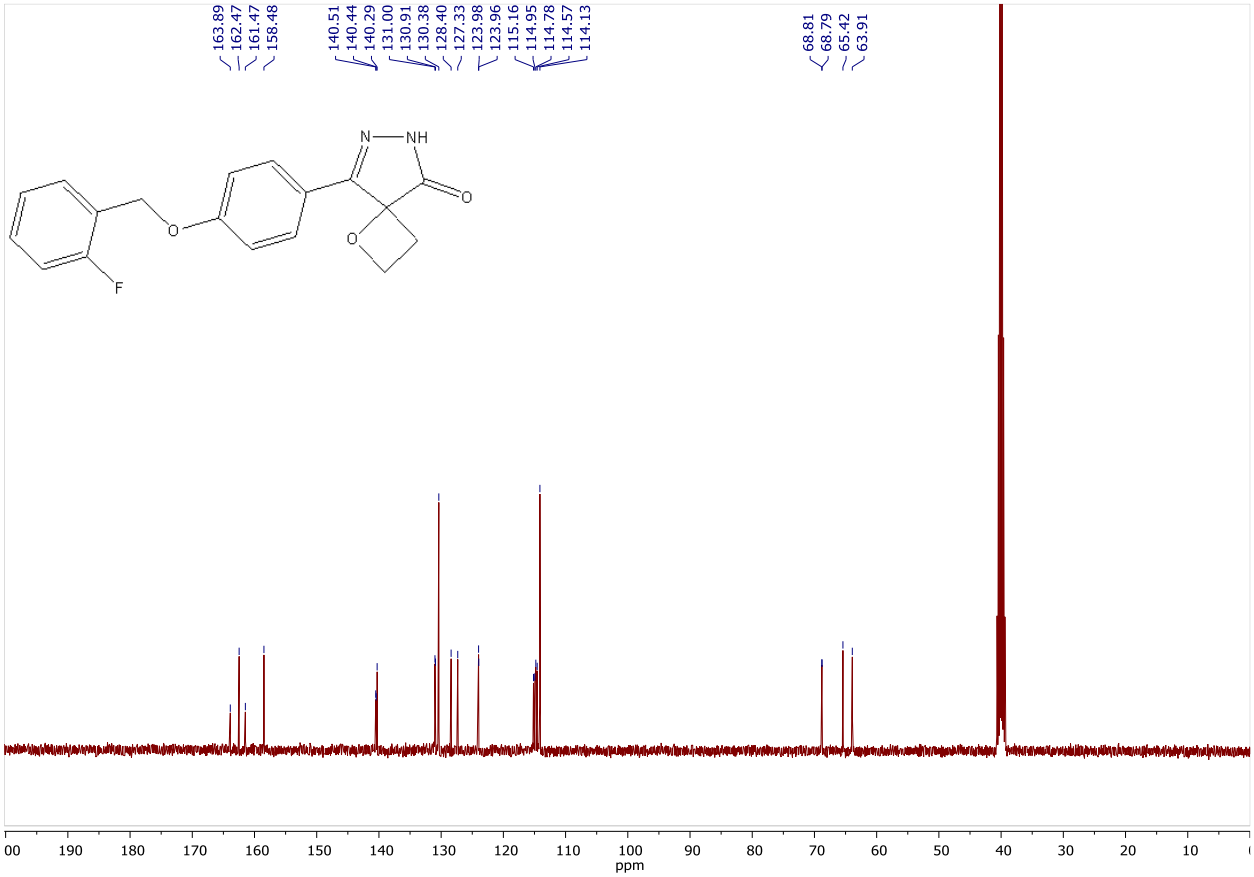
^{1}H and ^{13}C spectra of compound **6**



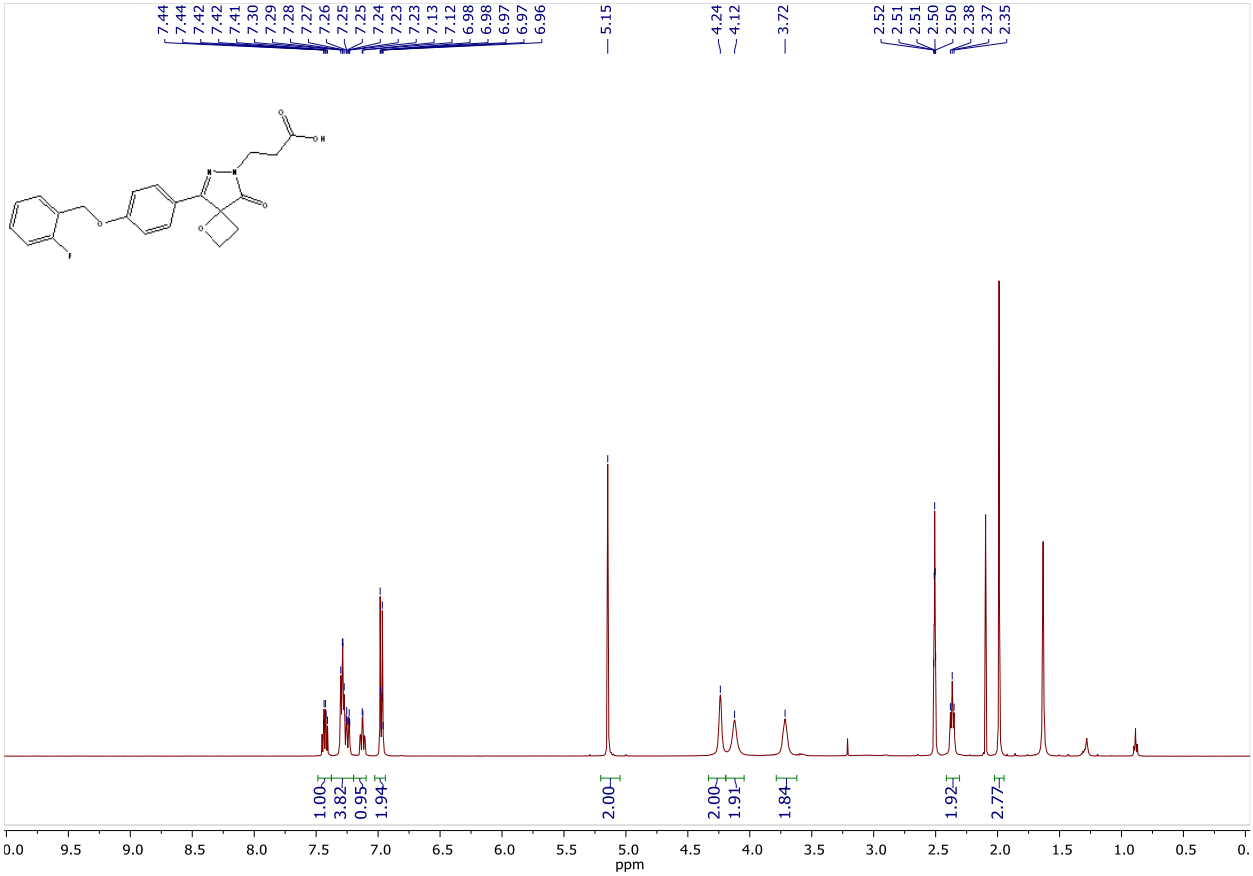


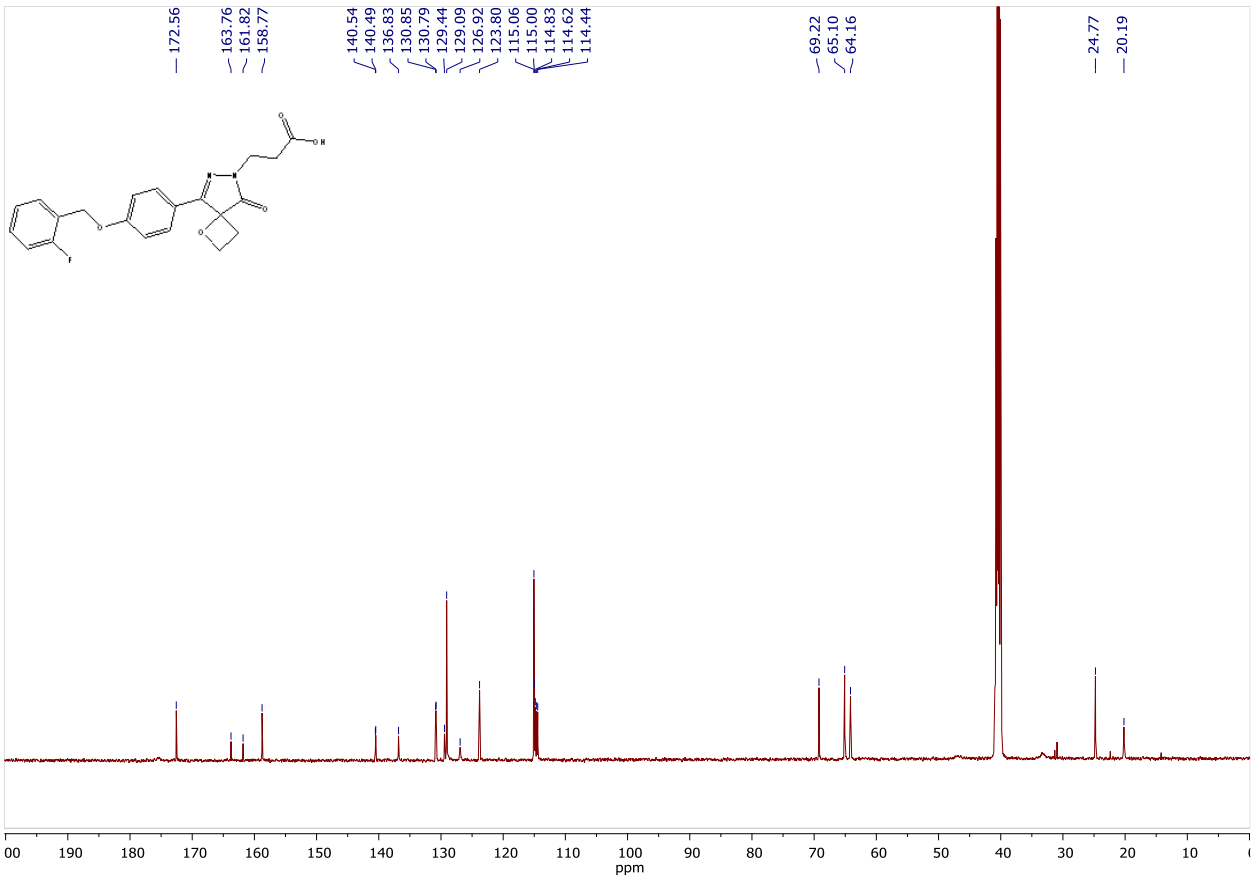
^{1}H and ^{13}C spectra of compound **7**





^{1}H and ^{13}C spectra of compound **2**

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114.44
69.22
65.10
64.16
24.77
20.19
ppm