

**Functionalization of 1,2-diphenylpyrazolidine-3,5-dione  
with polyfluoroalkyl-containing 2- and 3-oxo esters**

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## 1. Experimental section

### 1.1. Chemistry: General procedures

NMR spectra were recorded in DMSO-d<sub>6</sub> solution on Bruker DRX-400 (<sup>1</sup>H: 400 MHz, relative to SiMe<sub>4</sub>; <sup>19</sup>F: 376 MHz, relative to C<sub>6</sub>F<sub>6</sub>) and Bruker Avance 500 spectrometers (<sup>1</sup>H: 500 MHz, relative to SiMe<sub>4</sub>; <sup>19</sup>F: 470 MHz, relative to C<sub>6</sub>F<sub>6</sub>; <sup>13</sup>C: 126 MHz, relative to the solvent signal). IR spectra were recorded on a Perkin Elmer Spectrum One IR Fourier spectrometer in the range of 4000-400 cm<sup>-1</sup> using a diffuse reflection unit. Melting points were measured in open capillaries on a Stuart SMP30 melting point device. Column chromatography was performed on silica gel 60 (0.063-0.2 mm). Mass spectra were recorded on a MaXis Impact HD quadrupole time-of-flight mass spectrometer (Bruker Daltonik GmbH) in electrospray ionization mode for solutions in methanol at a sample feed rate of 180 μl/h with default parameters using the method of infusion analysis of small molecules. Mass calibration was performed by external HPC (high precision calibration) using the G1969-85000 calibration solution (Agilent Technologies). 1,2-Diphenylpyrazolidin-3,5-dione was obtained by a reported technique.<sup>1</sup>

*1.2. General procedure for the synthesis of ethyl (2E)-3-(3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)-3-polyfluoroalkylprop-2-enoates 3a,b.* 1,2-Diphenylpyrazole-3,5-dione **1** (252 mg, 1 mmol) and *L*-proline catalyst (23 mg, 0.2 mmol) were added to a solution of 3-oxo ester **2a,b** (1 mmol) in benzene (8 ml). The reaction mixture was then heated for 12-18 h at 50-60 °C and concentrated to dryness. The residue was triturated with an ethyl acetate:hexane mixture, 1:4. The resulting white precipitate was filtered off and washed with chloroform.

*Ethyl (2E)-3-(3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)-4,4,4-trifluorobut-2-enoate 3a.* White powder, yield 217 mg (52 %), m.p. 198–200°C (decomp.). <sup>1</sup>H NMR (500 MHz) δ: 1.19 (t, 3H-*E*, OCH<sub>2</sub>CH<sub>3</sub>, *J* 7.1 Hz), 1.22 (t, 3H-*Z*, OCH<sub>2</sub>CH<sub>3</sub>, *J* 7.1 Hz), 4.11 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>, *J* 7.1 Hz), 6.28 (br.s, 1H-*E*, CH=), 6.90 (br.s, 1H-*Z*, CH=), 7.10 (t, 2H-*E*, H<sub>p</sub>, *J* 7 Hz), 7.04 (t, 2H-*Z*, H<sub>p</sub>, *J* 7 Hz), 7.23-7.26 (m, 8H-*Z*, H<sub>m</sub>, H<sub>o</sub>), 7.28-7.34 (m, 8H-*E*, H<sub>m</sub>, H<sub>o</sub>), 7.91 (br.s, 1H, H-4.). <sup>13</sup>C NMR (126 MHz), *E*-isomer, δ: 13.97 (OCH<sub>2</sub>CH<sub>3</sub>), 60.16 (OCH<sub>2</sub>CH<sub>3</sub>), 80.37 (C-4), 122.22 (CH=), 122.53 (C<sub>o</sub>), 123.08 (q, CF<sub>3</sub>, *J* 278.5 Hz), 125.19 (C<sub>p</sub>), 128.61 (C<sub>m</sub>), 132.36 (q, =C-CF<sub>3</sub>, *J* 31 Hz), 139.00 (C<sub>i</sub>), 164.35 (CO<sub>2</sub>Et), 165.18 (N-C=O). <sup>19</sup>F NMR (470 MHz) δ: 99.04 (s, 3F-*E*, CF<sub>3</sub>), 104.27 (s, 3F-*Z*, CF<sub>3</sub>). IR (ν/cm<sup>-1</sup>): 3272, 2444 (OH), 3073, 2985 (C-H), 1734 (CO<sub>2</sub>Et, C=O amide), 1593, 1522, 1492 (C=C), 1130–1285 (C-F). Mass spectrum, *m/z*: 419.1212 [*M* + H]<sup>+</sup> (calculated for C<sub>21</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup>: 419.1213).

*Ethyl (2E)-3-(3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)-4,4,5,5,5-pentafluoropent-2-enoate 3b.* White powder, yield 187 mg (40 %), m.p. 206–207°C (decomp.). <sup>1</sup>H NMR (400 MHz), *E*-isomer, δ: 1.19 (t,

3H, OCH<sub>2</sub>CH<sub>3</sub>, *J* 7.1 Hz), 4.11 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>, *J* 7.1 Hz), 4.35 (br.s, 1H, H-4), 6.22 (br.s, 1H, CH=), 7.09 (t, 2H, H<sub>p</sub>, *J* 7 Hz), 7.26-7.33 (m, 8H, H<sub>m</sub>, H<sub>o</sub>). <sup>13</sup>C NMR (126 MHz), *E*-isomer, δ: 13.92 (OCH<sub>2</sub>CH<sub>3</sub>), 60.02 (OCH<sub>2</sub>CH<sub>3</sub>), 80.42 (C-4), 112.76 (t.q, CF<sub>2</sub>CF<sub>3</sub>, <sup>1</sup>*J*<sub>C-F</sub> 258.8 Hz, <sup>2</sup>*J*<sub>C-F</sub> 39 Hz), 118.68 (q.t, CF<sub>2</sub>CF<sub>3</sub>, <sup>1</sup>*J*<sub>C-F</sub> 287 Hz, <sup>2</sup>*J*<sub>C-F</sub> 39 Hz), 122.24 (C<sub>o</sub>), 124.47 (br.s, CH=), 124.80 (C<sub>p</sub>), 128.44 (C<sub>m</sub>), 132.00 (t, =C-CF<sub>2</sub>, <sup>2</sup>*J*<sub>C-F</sub> 23.7 Hz), 139.43 (C<sub>i</sub>), 164.08 (CO<sub>2</sub>Et), 165.38 (N-C=O). <sup>19</sup>F NMR (376 MHz), *E*-isomer, δ: 49.87 (br.s, 2F, CF<sub>2</sub>), 80.30 (br.s, 3F, CF<sub>3</sub>). IR (ν/cm<sup>-1</sup>): 2445 (OH), 3069, 2986 (C-H), 1719 (CO<sub>2</sub>Et, C=O amide), 1589, 1531, 1495 (C=C), 1142–1299 (C-F). Mass spectrum, *m/z*: 469.1182 [*M* + H]<sup>+</sup> (calculated for C<sub>22</sub>H<sub>18</sub>F<sub>5</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup>: 469.1181).

*1.3. General procedure for the synthesis of ethyl 2-(3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate 5.* 1,2-Diphenylpyrazole-3,5-dione **1** (252 mg, 1 mmol) and *L*-proline catalyst (6 mg, 0.05 mmol) were added to a solution of trifluoropiruvate **4** (170 mg, 1 mmol) in benzene (8 ml). The reaction mixture was stirred for 3 h at room temperature and concentrated to dryness. The residue was washed with a chloroform:hexane mixture, 3:2. Pale yellow powder, yield 245 mg (58 %), m.p. 186-188°C. <sup>1</sup>H NMR (400 MHz) δ: 1.15 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>, <sup>3</sup>*J* 7.1 Hz), 4.10 (q.d, 2H, CH<sub>2</sub>CH<sub>3</sub>, <sup>3</sup>*J* 7.1 Hz, *J* 2.4 Hz), 6.98 (t.t, 2H, H<sub>p</sub>, <sup>3</sup>*J* 7.0 Hz, <sup>4</sup>*J* 1.2 Hz), 7.07 (br.s, 1H, H-4), 7.21 (m, 4H, H<sub>m</sub>), 7.27 (d.d, 4 H, H<sub>o</sub>, <sup>3</sup>*J* 8.6, <sup>4</sup>*J* 1.2 Hz), 8.6 (s, 1H, OH). <sup>19</sup>F NMR (376 MHz) δ: 84.69 (s, CF<sub>3</sub>). IR (ν/cm<sup>-1</sup>): 3445 (O-H), 3070, 2987, 2942 (C-H), 1766 (CO<sub>2</sub>Et), 1728 (C=O amide), 1596, 1496 (C=C), 1154–1311 (C-F). Mass spectrum, *m/z*: 423.1169 [*M* + H]<sup>+</sup> (calculated for C<sub>20</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub><sup>+</sup>: 423.1162).

*1.4. General procedure for the synthesis of piperidinium 4-(3-ethoxy-1,1,1-trifluoro-2-hydroxy-3-oxopropan-2-yl)-3,5-dioxo-1,2-diphenylpyrazolidin-4-ide 6.* 1,2-Diphenylpyrazole-3,5-dione **1** (252 mg, 1 mmol) and piperidine catalyst (85 mg, 1 mmol) were added to a solution of trifluoropiruvate **4** (170 mg, 1 mmol) in benzene (8 ml). The reaction mixture was refluxed for 1 h. The resulting white precipitate was filtered off and recrystallized from chloroform. White powder, yield 340 mg (67 %), m.p. 185–186°C (decomp.). <sup>1</sup>H NMR (500 MHz) δ: 1.15 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>, <sup>3</sup>*J* 7.1 Hz), 1.52-1.57 (m, 2H, CH<sub>2</sub>), 1.64 (quint, 4H, 2 CH<sub>2</sub>, *J* 5.6 Hz), 3.00 (t, 4H, 2 CH<sub>2</sub>N, *J* 5.6 Hz), 4.1 (q.d, 2H, OCH<sub>2</sub>CH<sub>3</sub>, <sup>3</sup>*J* 7.1 Hz, *J* 3.5 Hz), 6.98 (t, 2H, H<sub>p</sub>, *J* 7.3 Hz), 7.21 (t, 4H, H<sub>m</sub>, *J* 7.3 Hz), 7.26-7.28 (m, 4H, H<sub>o</sub>), 8.21 (br.s, 2H, <sup>+</sup>NH<sub>2</sub>), 8.59 (s, 1H, OH). <sup>13</sup>C NMR (126 MHz) δ: 13.92 (OCH<sub>2</sub>CH<sub>3</sub>), 21.59 (CH<sub>2</sub>), 22.17 (2 CH<sub>2</sub>), 43.78 (2 CH<sub>2</sub>N), 60.56 (OCH<sub>2</sub>CH<sub>3</sub>), 72.74 (C-4), 76.13 (q, CF<sub>3</sub>COH, <sup>2</sup>*J* 30 Hz), 120.82 (C<sub>o</sub>), 123.17 (C<sub>p</sub>), 125.07 (q, CF<sub>3</sub>, <sup>1</sup>*J* 287.5 Hz), 128.09 (C<sub>m</sub>), 140.77 (C<sub>i</sub>), 167.36 (CO<sub>2</sub>Et), 169.25 (N-C=O). <sup>19</sup>F NMR (470 MHz) δ: 84.70 (s, CF<sub>3</sub>). IR (ν/cm<sup>-1</sup>): 3490 (O-H), 2957 (C-H), 2797 (CH<sub>2</sub>-N), 2548,

2451 (<sup>+</sup>N-H<sub>2</sub>), 1740 (CO<sub>2</sub>Et, C=O amide), 1640 (NH), 1598, 1587 (C=C), 1159–1291 (C-F). Mass spectrum, *m/z*: 508.2048 [*M* + H]<sup>+</sup> (calculated for C<sub>25</sub>H<sub>29</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub><sup>+</sup>: 508.2054).

*1.5. General procedure for the synthesis of 1,2-diphenyl-4-(propan-2-ylidene)pyrazolidin-3,5-dione*

**8**. 1,2-Diphenylpyrazole-3,5-dione **1** (252 mg, 1 mmol) and *L*-proline catalyst (12 mg, 0.1 mmol) were added to a solution of trifluoroacetylacetone **7** (154 mg, 1 mmol) in benzene. The reaction mixture was heated for 12 h at 40 °C and concentrated to dryness. Product **8** was purified by column chromatography (eluent: ethyl acetate:hexane, 1:4). Bright yellow powder (34%), m.p. 112-113 °C (*cf.*<sup>2</sup>).

## 2. References

1. A. Singh, H. Hakk and S. J. Lupton, *J. Labelled Compd. Radiopharm.*, 2018, **61**, 386.
2. J. L. Vennerstrom and T. J. J. Holmes, *J. Med. Chem.*, 1987, **30**, 563.

### 3. NMR, IR and Mass spectra of compounds 3a,b, 5, 6

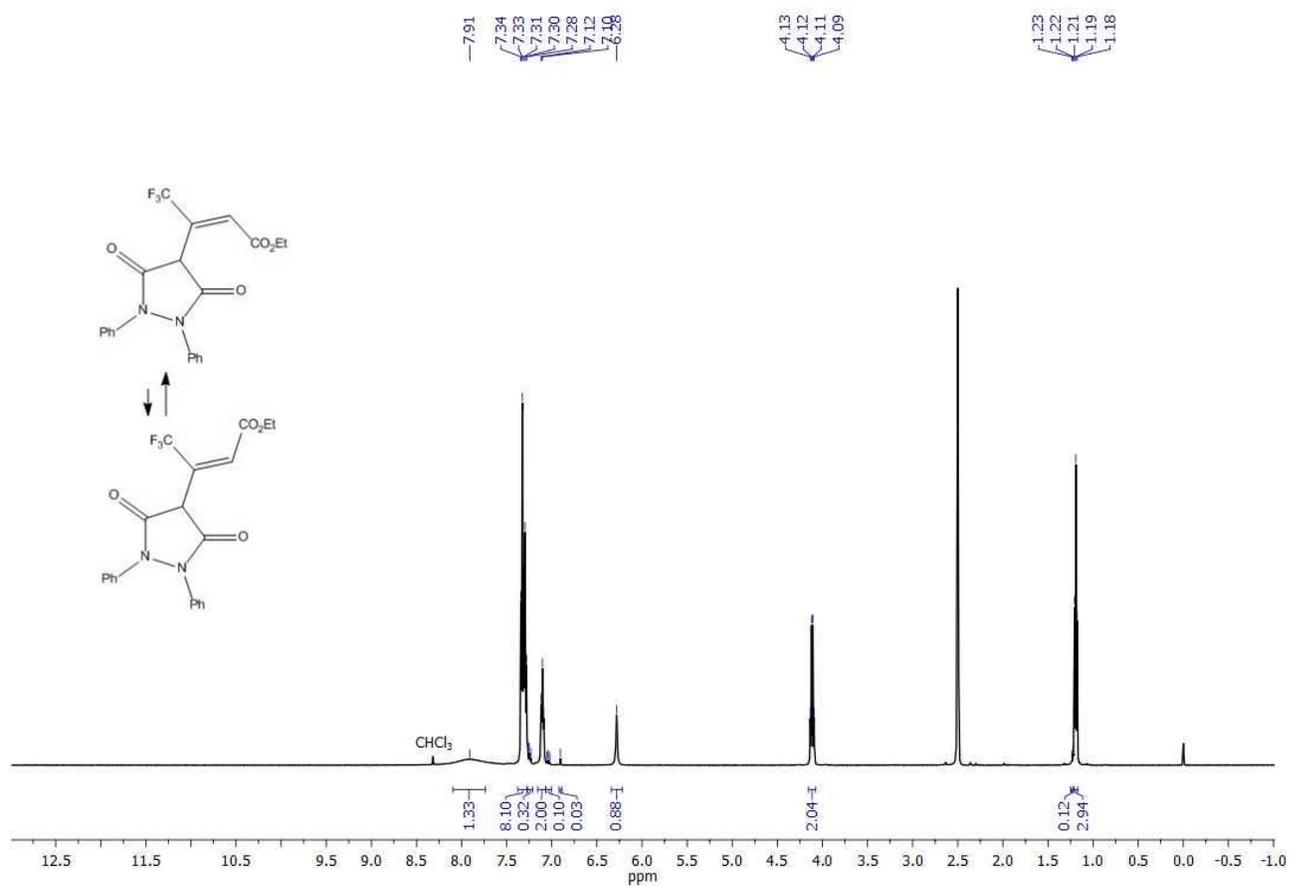
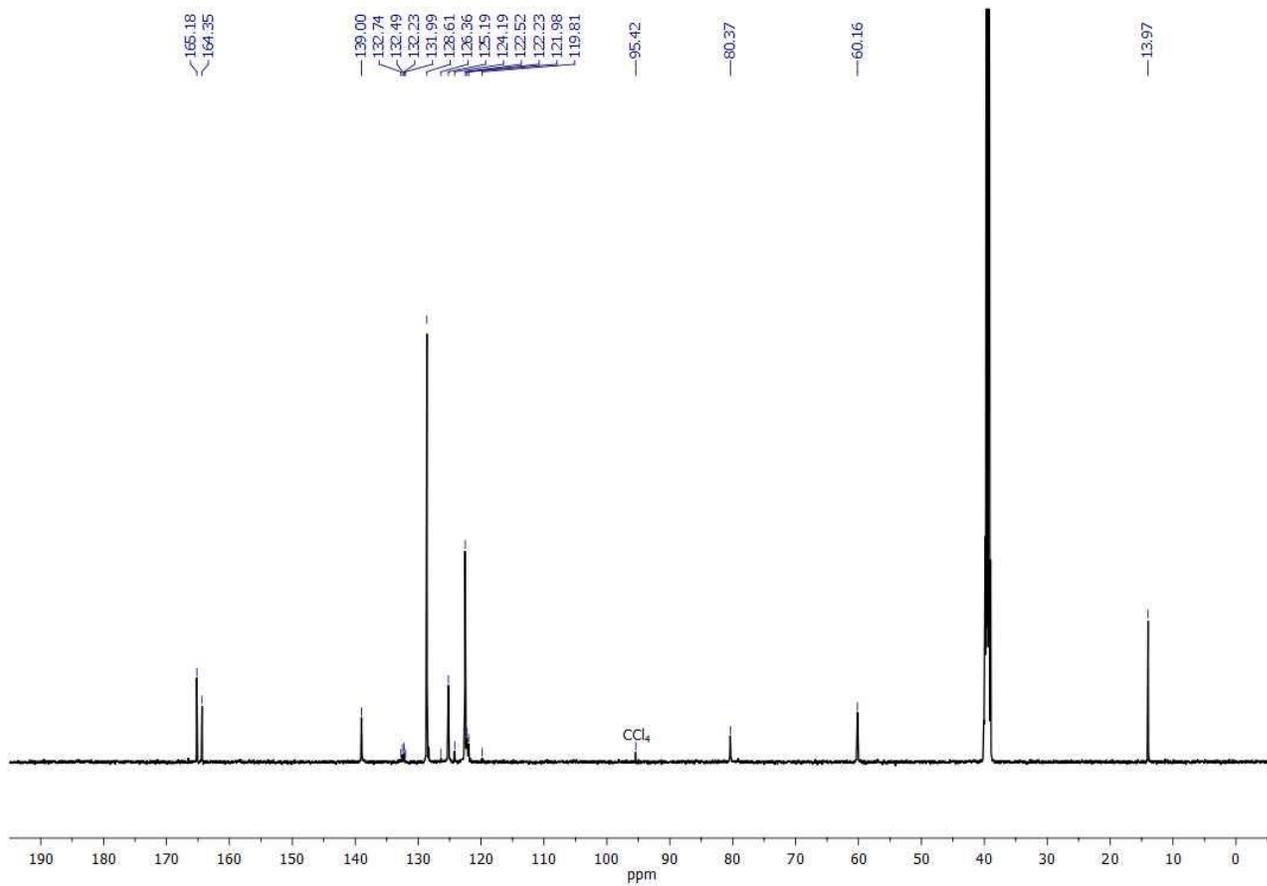
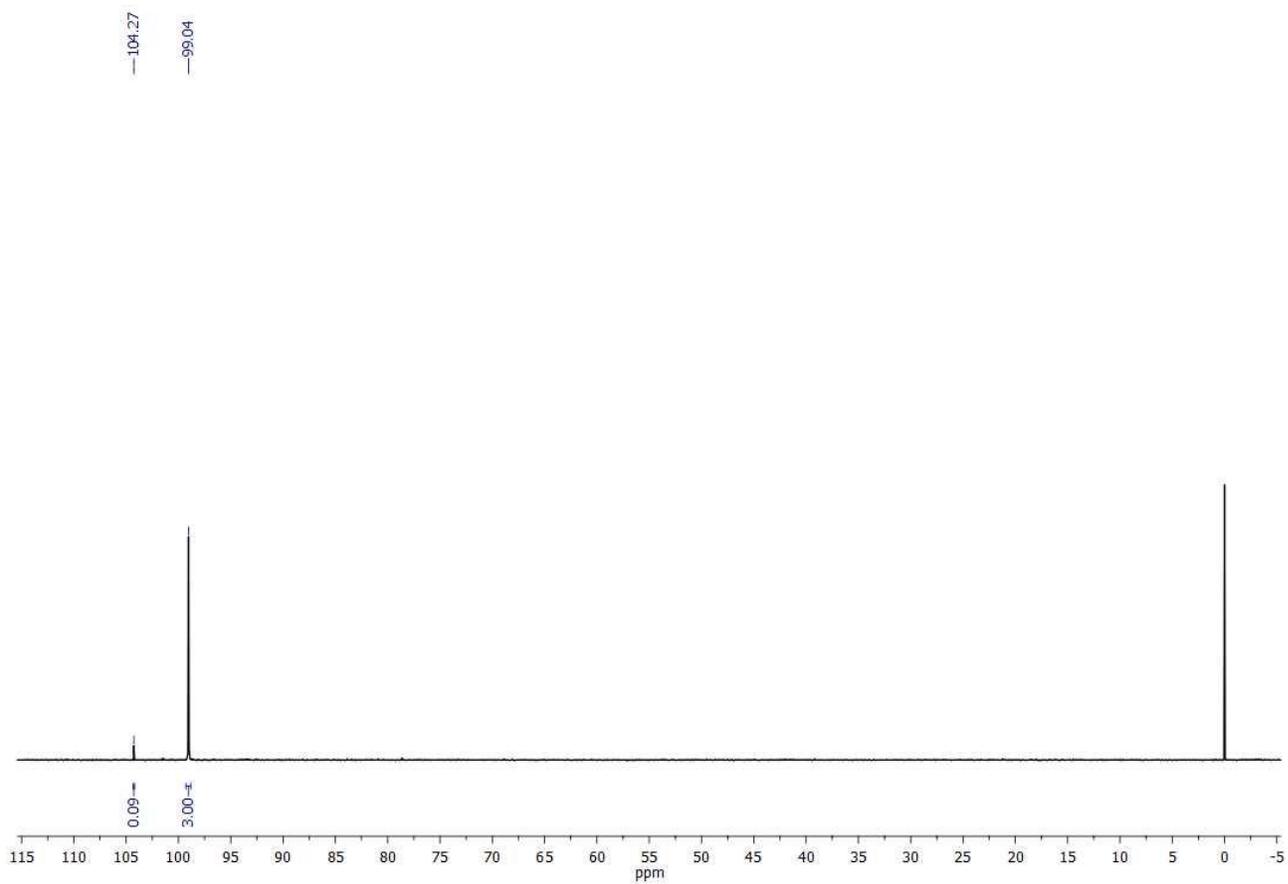


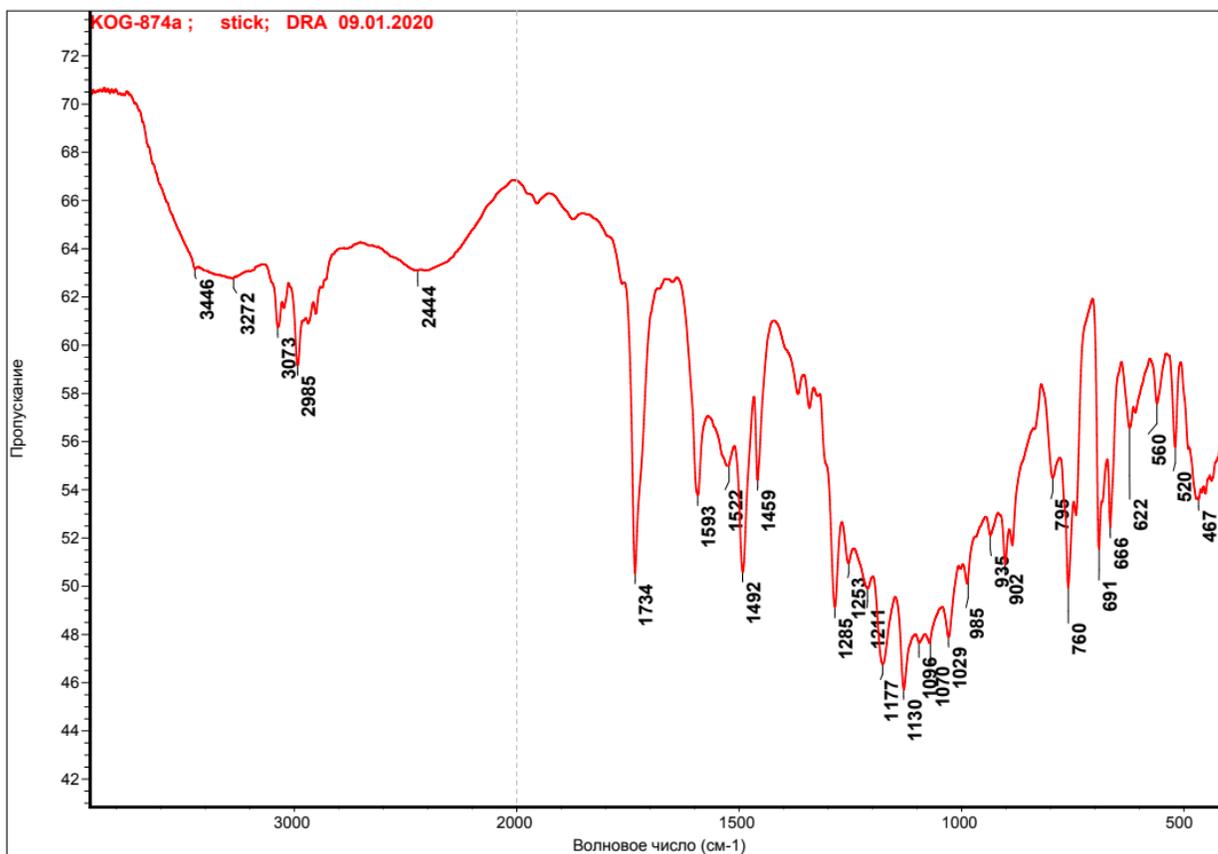
Figure S1 <sup>1</sup>H NMR spectrum of compound 3a.



**Figure S2**  $^{13}\text{C}$  NMR spectrum of compound **3a**.



**Figure S3**  $^{19}\text{F}$  NMR spectrum of **3a**.



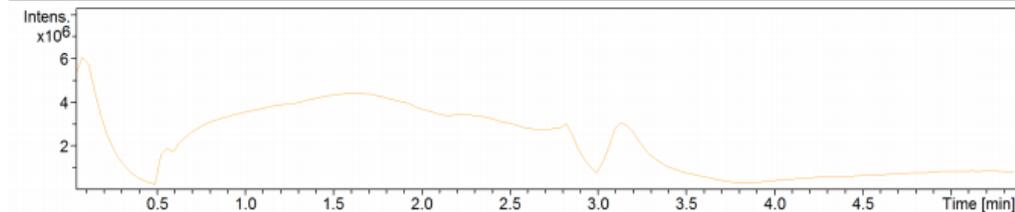
**Figure S4** IR spectrum of compound **3a**.

## Compound Spectrum SmartFormula Report

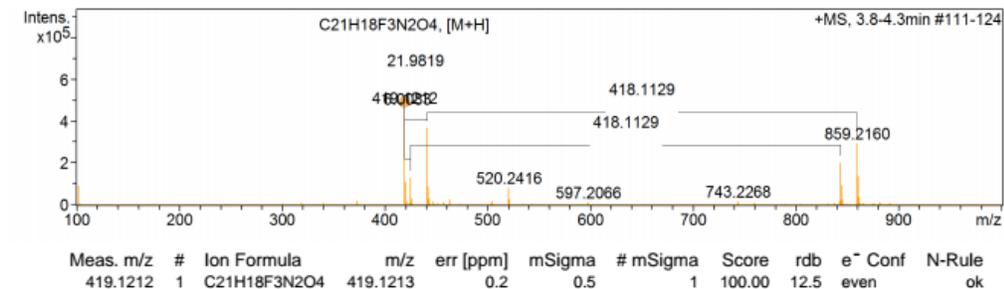
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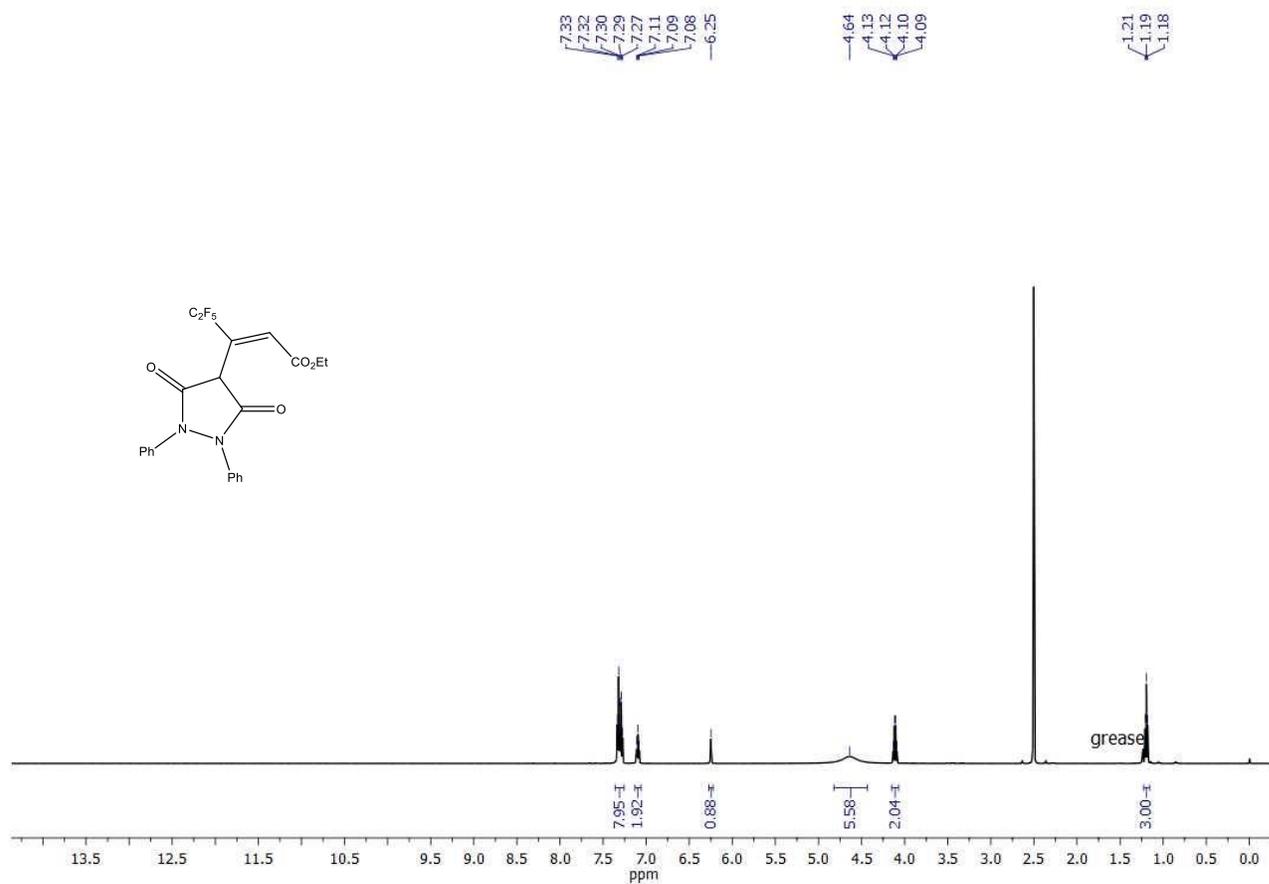
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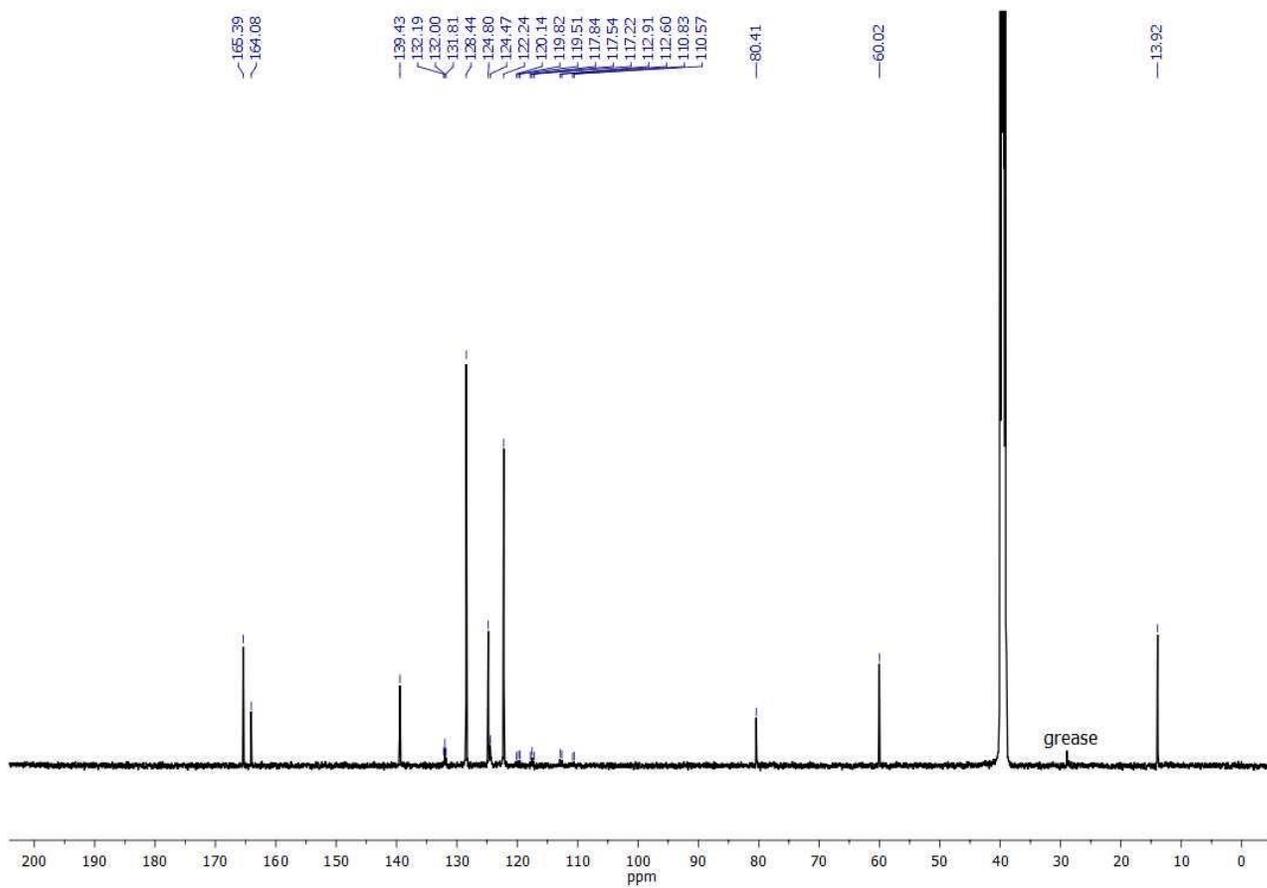
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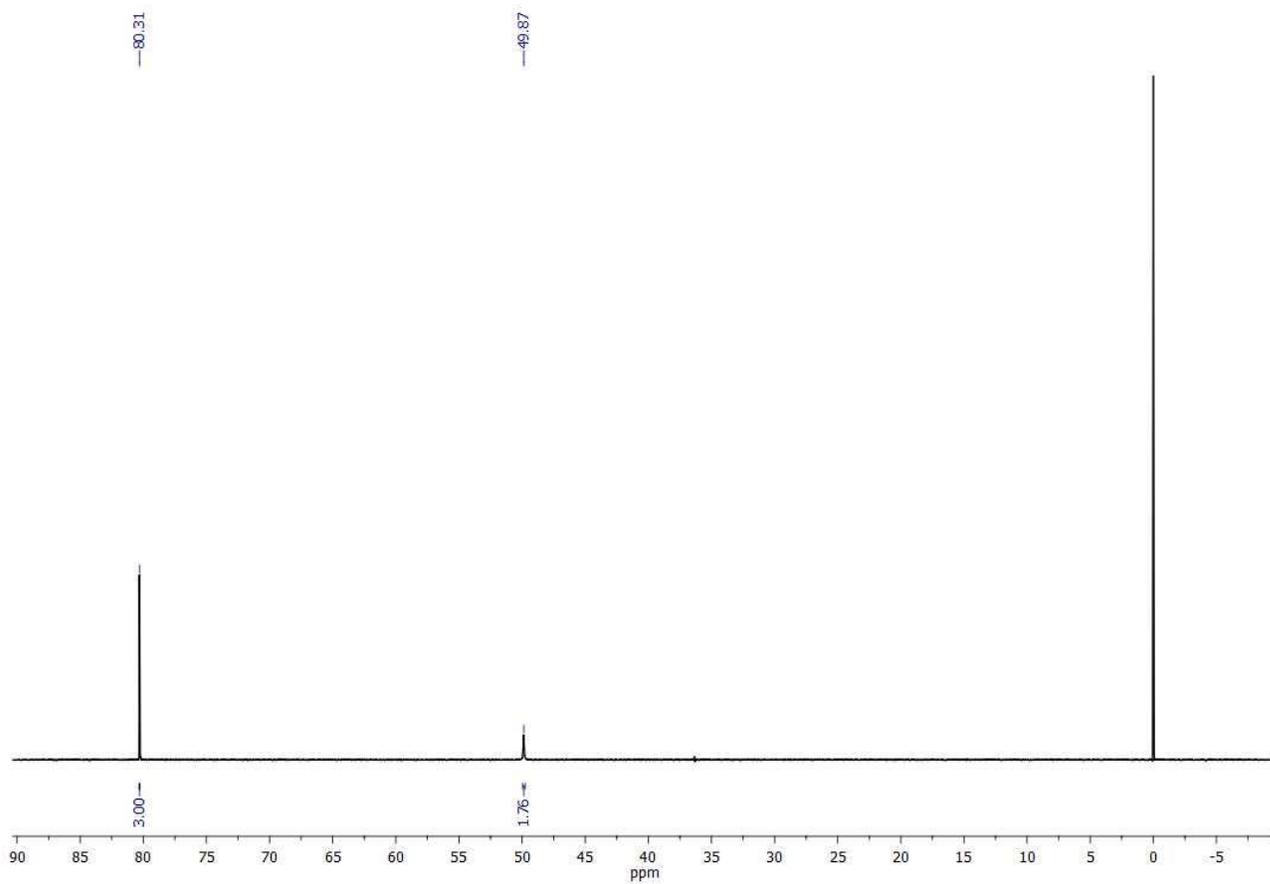
**Figure S5** Mass spectrum of compound **3a**.



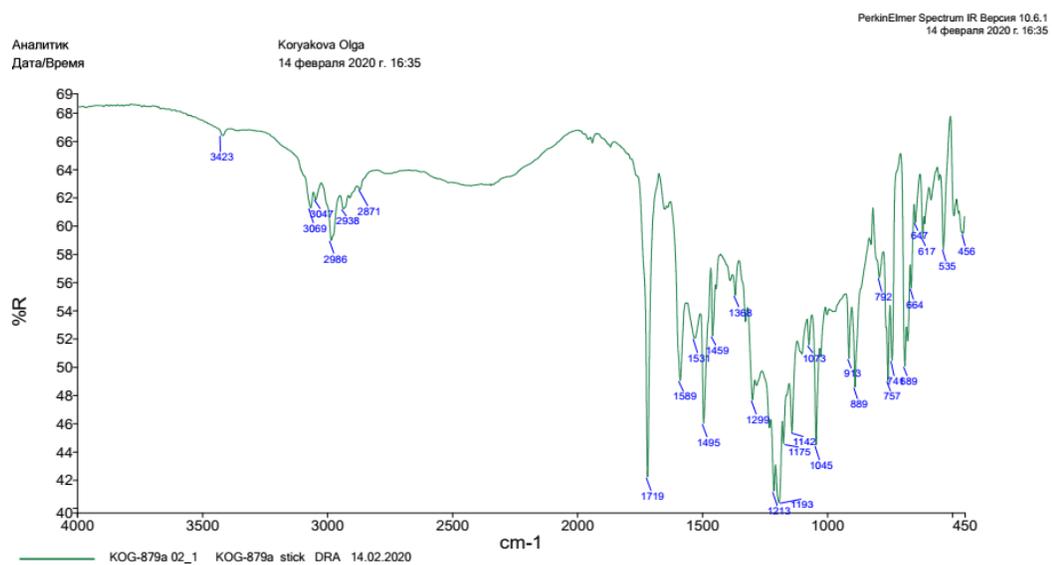
**Figure S6** <sup>1</sup>H NMR spectrum of compound **3b**.



**Figure S7**  $^{13}\text{C}$  NMR spectrum of compound **3b**.



**Figure S8**  $^{19}\text{F}$  NMR spectrum of compound **3b**.



Стр. 1

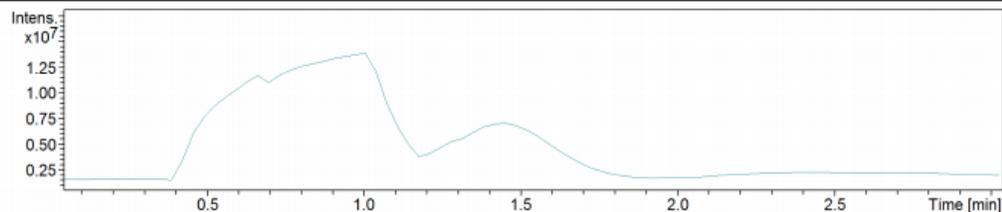
**Figure S9** IR spectrum of compound **3b**.

## Compound Spectrum SmartFormula Report

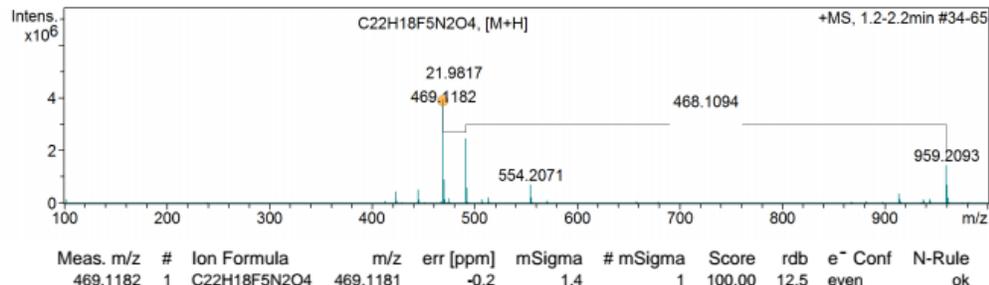
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**Figure S10** Mass spectrum of compound **3b**.

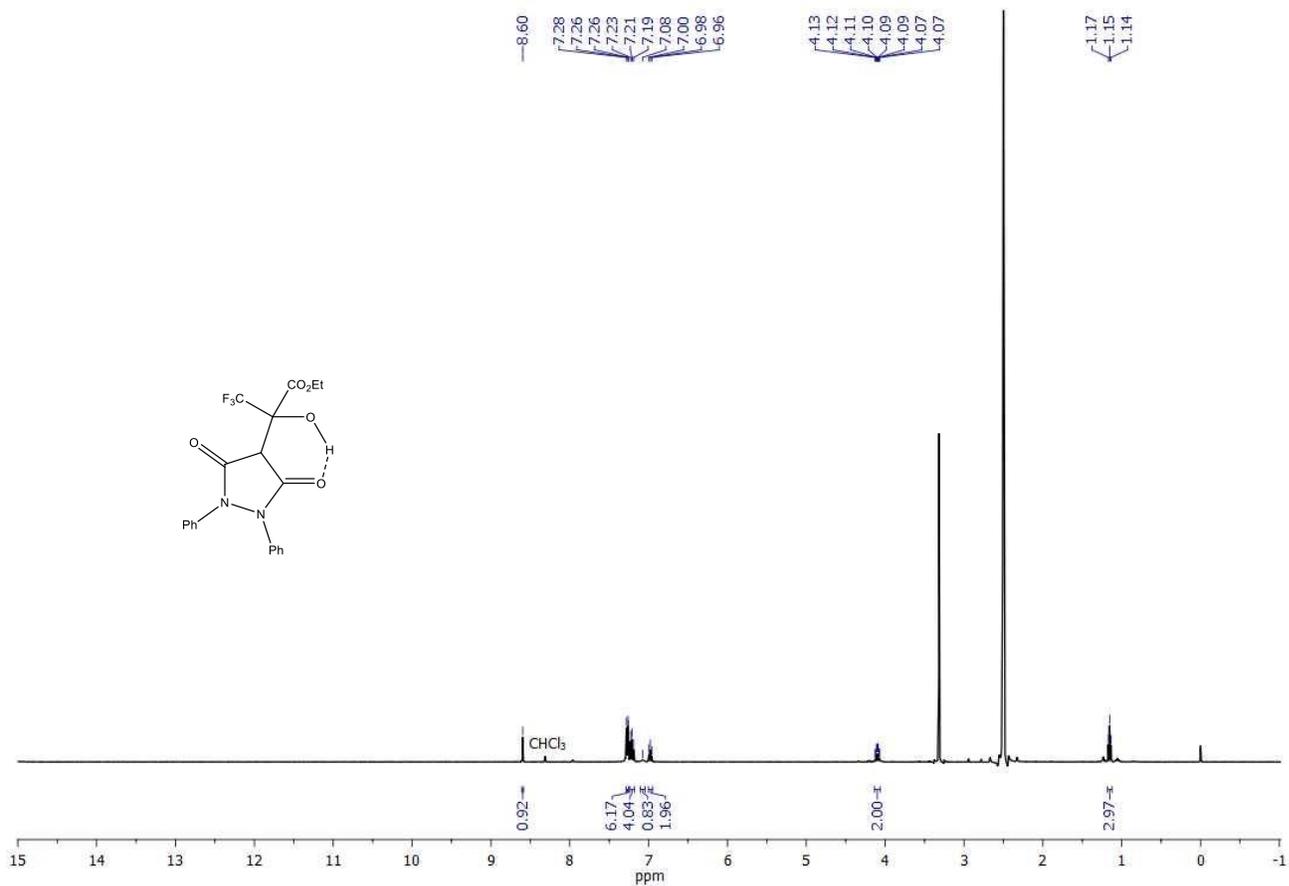
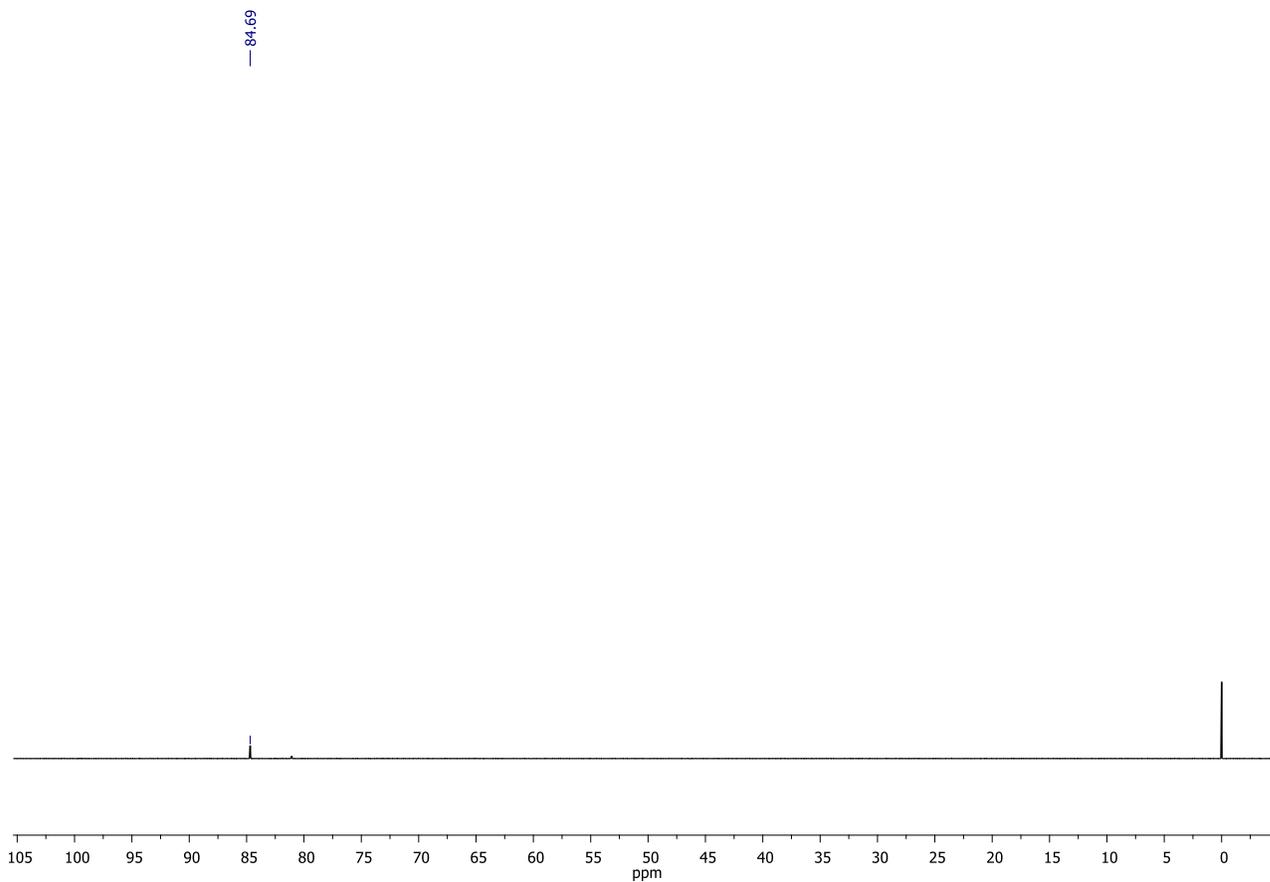
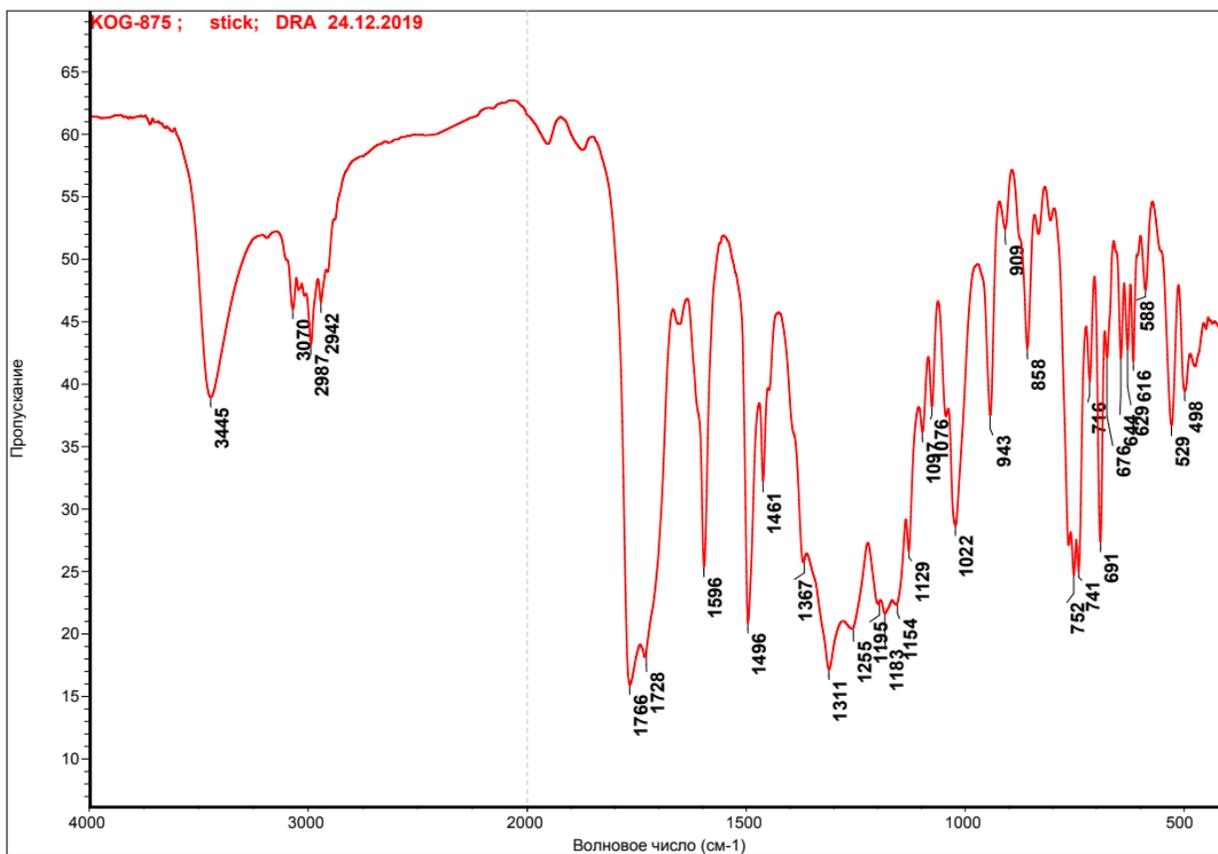


Figure S11 <sup>1</sup>H NMR spectrum of compound 5.



**Figure S12**  $^{19}\text{F}$  NMR spectrum of compound **5**.



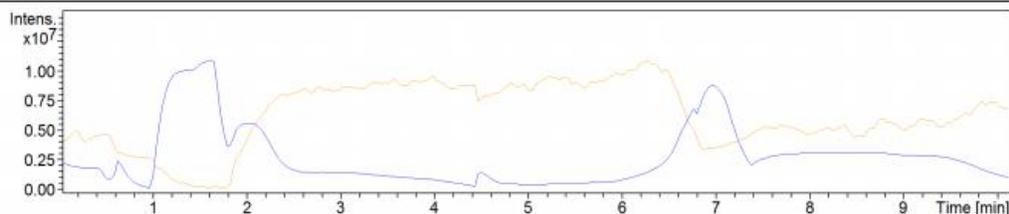
**Figure S13** IR spectrum of compound **5**.

## Compound Spectrum SmartFormula Report

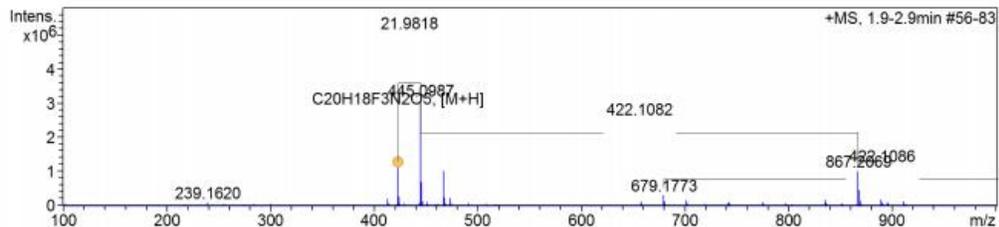
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**Figure S14** Mass spectrum of compound **5**.

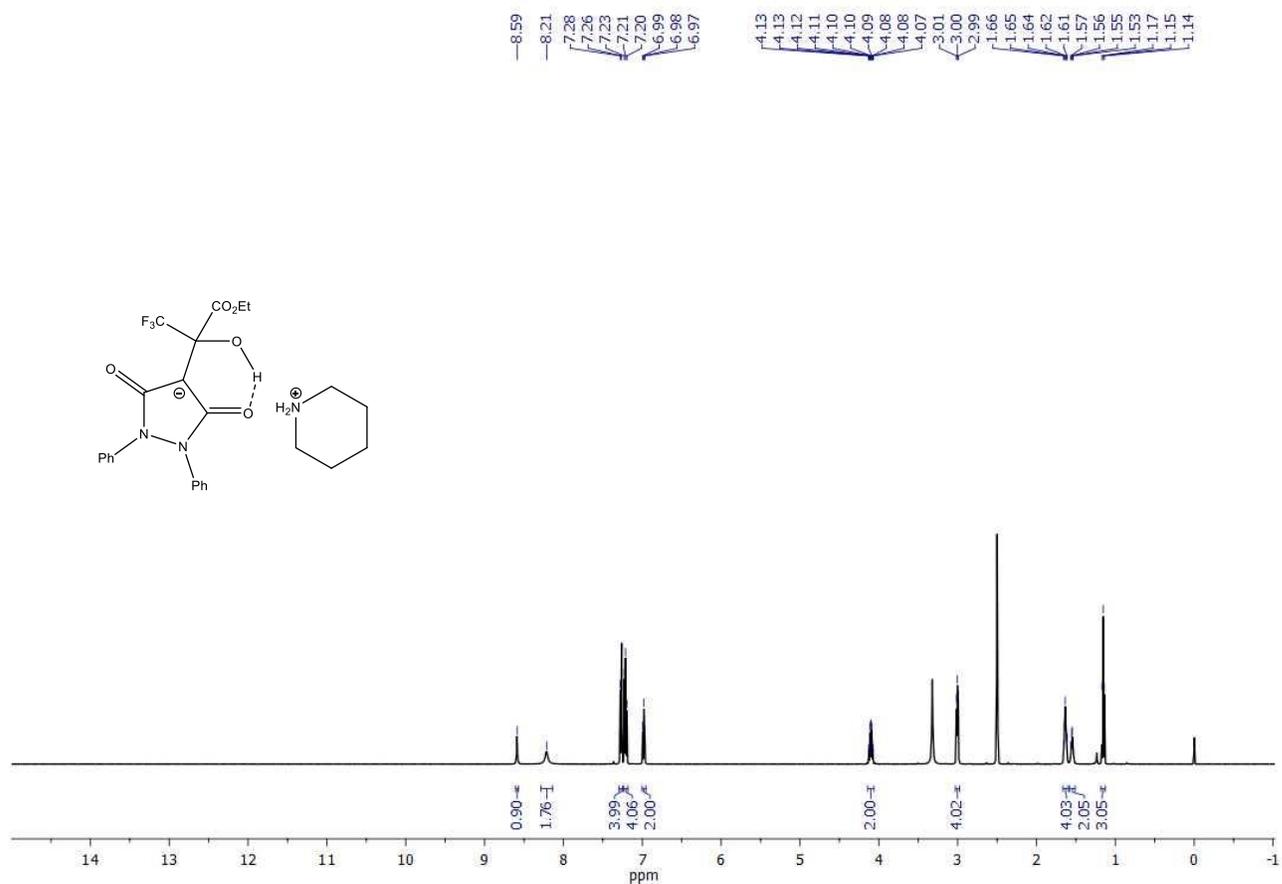
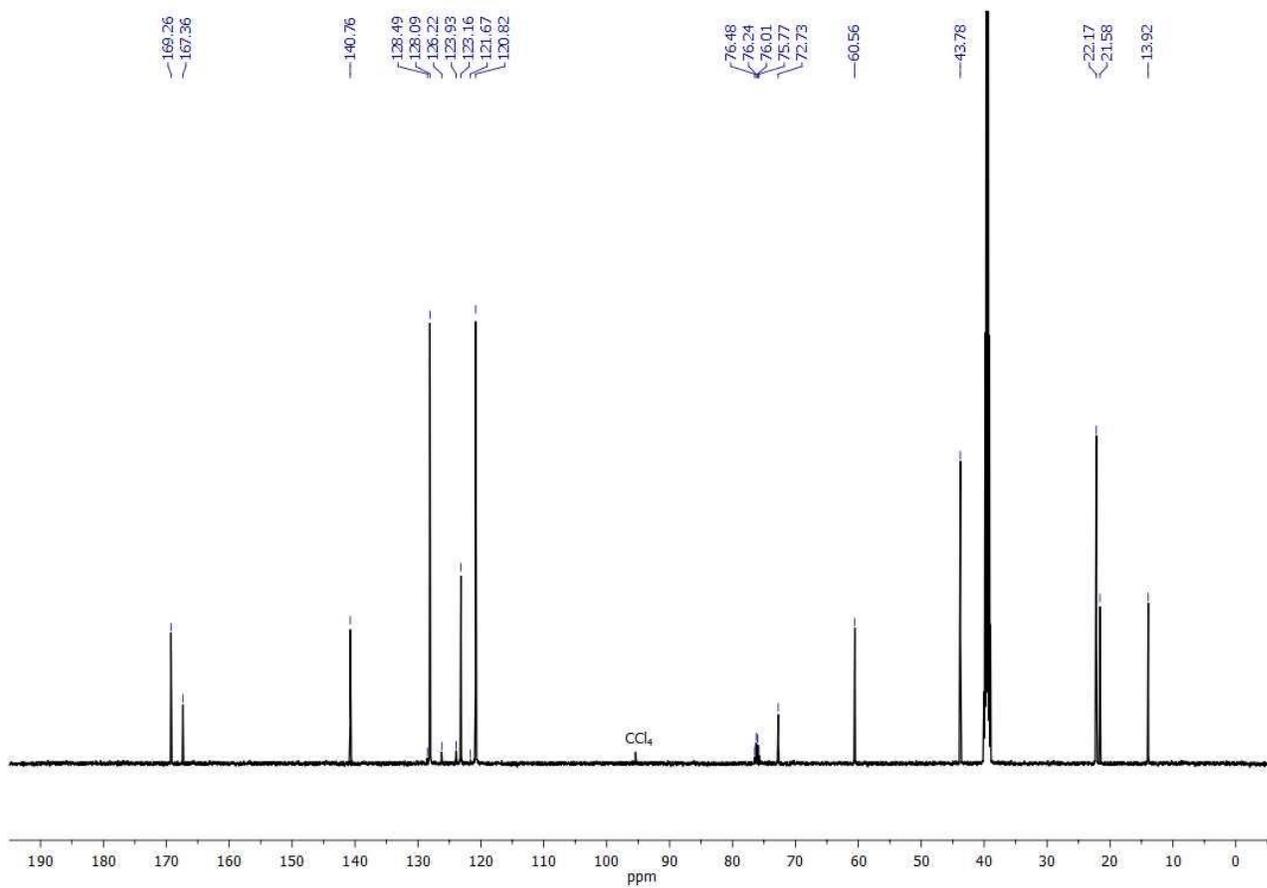
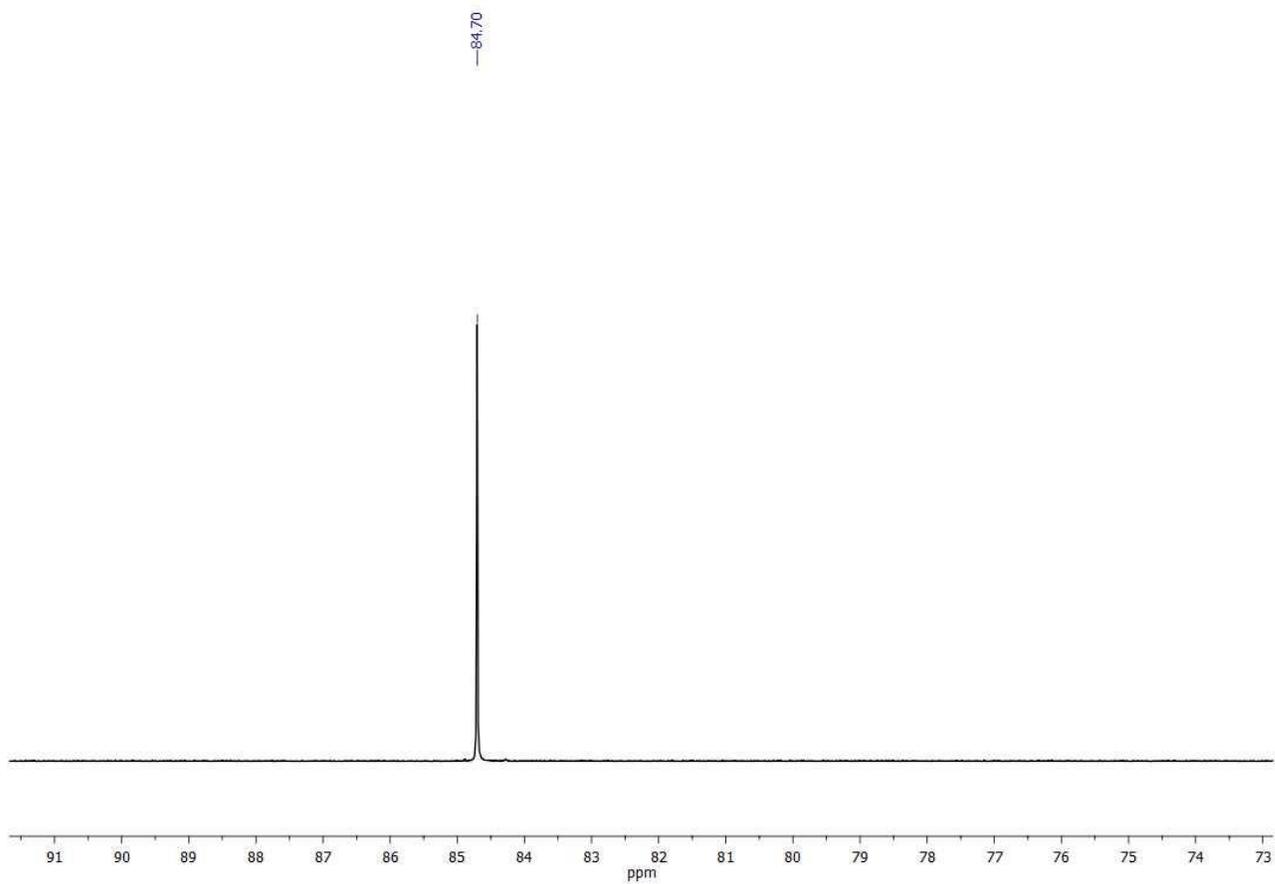


Figure S15 <sup>1</sup>H NMR spectrum of compound 6.



**Figure S16**  $^{13}\text{C}$  NMR spectrum of compound 6.



**Figure S17**  $^{19}\text{F}$  NMR spectrum of compound **6**.

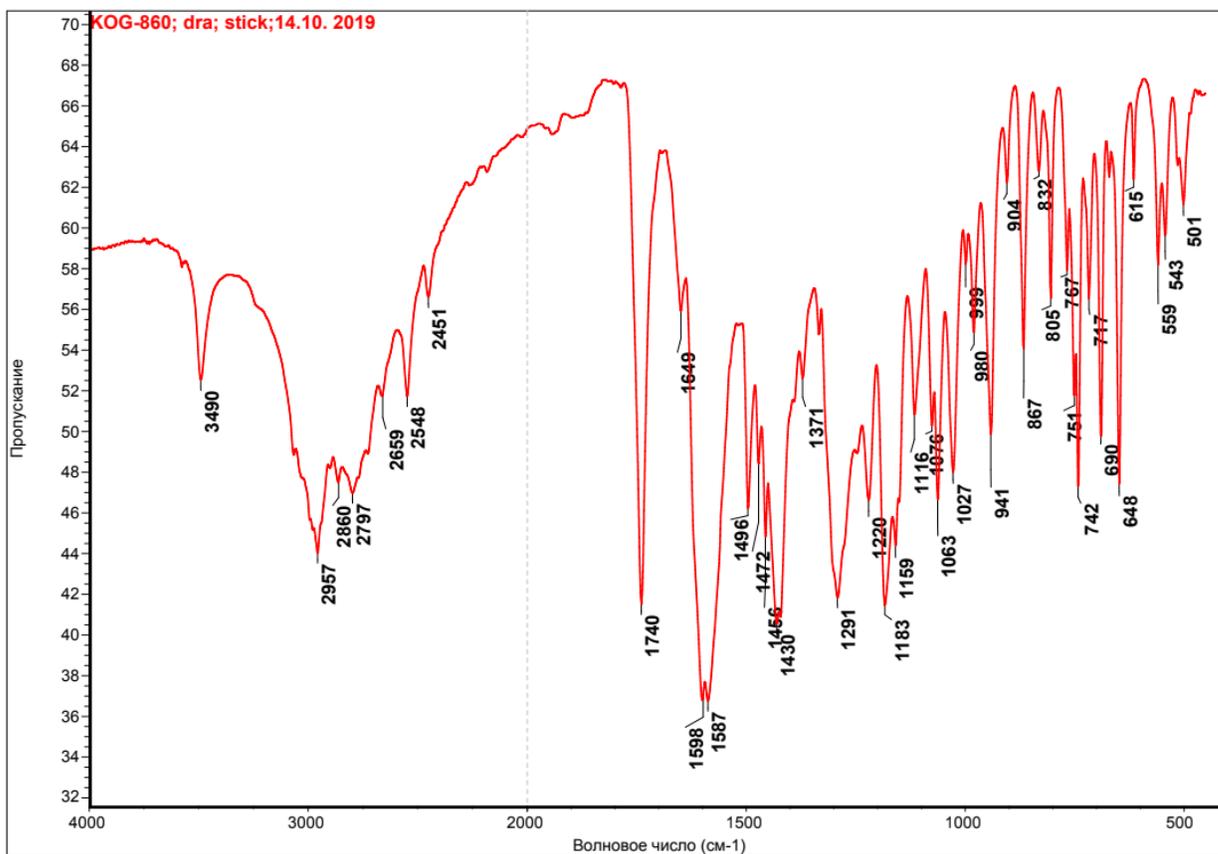


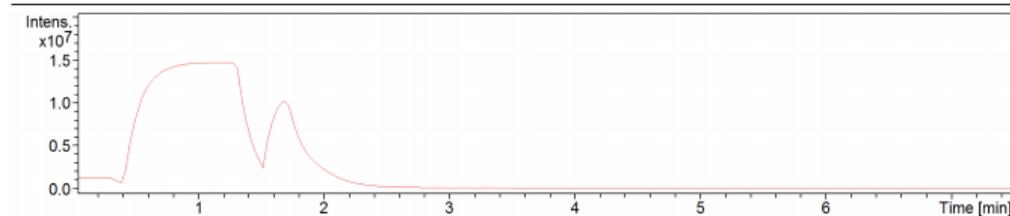
Figure S18 IR spectrum of compound 6.

## Compound Spectrum SmartFormula Report

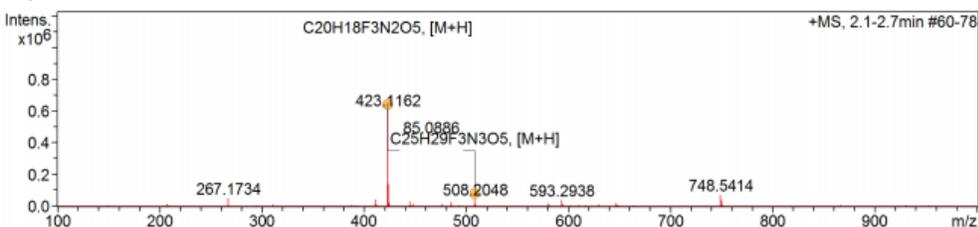
**Analysis Info** Acquisition Date 3/12/2020 9:30:12 AM  
 Analysis Name D:\Data\ING20\KOG-860.C-1.6.12ct.ESI-POS-180.4976-12c0930.d  
 Method EP180-TA24\_50-2800\_epo500c4500n0.3dg3.0dt200\_1f3002 Operator ing@ios.uran.ru  
 f150hrf50ie5lm120ce10crf550t120pps8x3x0.5\_nf\_hpc\_st.m  
 Sample Name Instrument maXis impact 1819696.00172  
 Comment +Bckgnd: 118.09, 322.05, 622.03, 922.01, 1221.99, 1521.97, 1821.95, 2121.93, 2421.91, 2721.89  
 (G1969-85000; HPC)

**Acquisition Parameter**

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	2800 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



**+MS, 2.1-2.7min #60-78**



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e <sup>-</sup>	Conf	N-Rule
423.1162	1	C20H18F3N2O5	423.1162	0.1	4.0	1	100.00	11.5	even		ok
423.1151	2	C23H17F2N2O4	423.1151	-2.6	14.8	2	47.73	15.5	even		ok
508.2048	1	C25H29F3N3O5	508.2054	1.2	2.1	1	100.00	11.5	even		ok

KOG-860.C-1.6.12ct.ESI-POS-180.4976-12c0930.d

Bruker Compass DataAnalysis 4.2

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**Figure S19** Mass spectrum of compound 6.