Trifluoroacetaldehyde N-tosylhydrazone as a Precursor of Trifluorodiazoethane in Reactions of Insertion into Heteroatom–Hydrogen Bond

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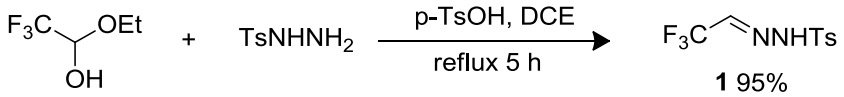
Experimental Procedures

General

All solvents were distilled prior to use. Acetonitrile and 1,2-dichloroethane were dried by distillation over P_2O_5. Chromatography was carried out using 230-400 mesh silica gel (Merck 40/60). ^{1}H NMR spectra were recorded on commercial instrument Agilent 400-MR (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). ^{13}C{1H} NMR spectra were collected on commercial instrument Agilent 400-MR (100 MHz) with complete proton decoupling. HRMS (ESI) were recorded on a commercial apparatus. Thin layer chromatographies (TLC) were performed using Merck aluminium-foil baked plates precoated with Kieselgel 60 F254. The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. All solvents and chemicals were purchased from Sigma-Aldrich or Acros, and used without further purification, unless otherwise stated. Dibenzyl phosphonate was prepared according to published procedure.[1]

Synthesis of trifluoroacetaldehyde N-tosylhydrazone (1)



To a round bottom flask surmounted with a reflux condenser was added tosyl hydrazide (4.172 g, 22.4 mmol), 1-ethoxy-2,2,2-trifluoroethanol (3.689 g, 25.6 mmol) and p-toluenesulfonic acid monohydrate (0.213 g, 1.1 mmol) in DCE (50 ml). The reaction mixture was then stirred at reflux for 5 h. The solution was cooled down to rt and the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and washed with sodium hydrogen carbonate. The solvent was removed under reduced pressure to obtain white solid which was sufficiently pure and used in the next step without further purification. In some cases the product was recrystallized from minimal amount of EtOAc.

Yield 5.660 g (95 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.2 Hz, 2H), 7.33 (d, J = 7.1 Hz, 2H), 7.10 (q, J = 3.9 Hz, 1H), 2.44 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -67.8 (d, J = 4.1 Hz).

NMR spectral data for this compound were consistent with those in literature.[2]

Typical Procedures

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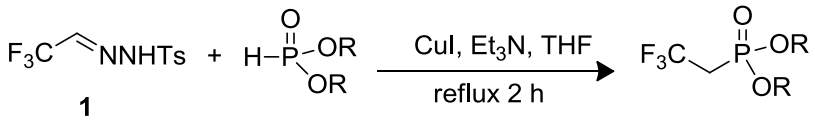
General Procedure A: P-H insertion

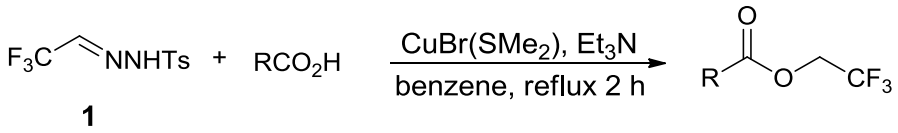


To a mixture of dialkyl phosphonate (0.6 mmol), **1** (133 mg, 0.5 mmol), CuI (19 mg, 0.1 mmol) in a Schlenk flask under argon atmosphere Et_3N (101 mg, 1.0 mmol) in THF(10 mL) was added. The reaction mixture was then stirred at reflux for 2 h. The solvent was removed under reduced pressure. The desired product was obtained after column chromatography (EtOAc/hexanes).

Gram-scale synthesis of diethyl 2,2,2-trifluoroethylphosphonate (2a)

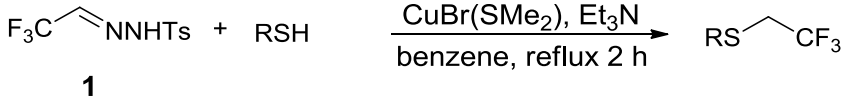
To a mixture of diethyl phosphonate (1.076 g, 7.8 mmol), **1** (1.729 g, 6.5 mmol), CuI (0.247 g, 1.3 mmol) in a Schlenk flask under argon atmosphere Et_3N (101 mg, 1.0 mmol) in THF(10 mL) was added. The reaction mixture was then stirred at reflux for 2 h. The solvent was removed under reduced pressure. The product was purified by column chromatography (petroleum ether/EtOAc 3:1) and obtained as a colorless oil in 70% yield (1.001 g).

General Procedure B: O-H insertion



A mixture of carboxylic acid (0.5 mmol), $CuBr(SMe_2)$ (10 mg, 0.05 mmol), Et_3N (61 mg, 0.6 mmol) and benzene (5 ml) were placed into a Schlenk flask under argon atmosphere and heated to reflux. Solution of **1** (166 mg, 0.6 mmol) in benzene (15 mL) was added via syringe in small portions. The reaction mixture was then stirred at reflux for 2 h. The solvent was removed under reduced pressure. The desired product was obtained after column chromatography (EtOAc/hexanes).

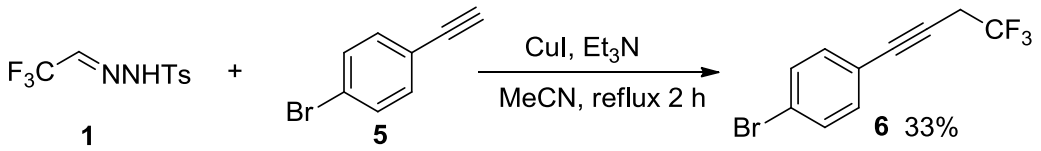
General Procedure C: S-H insertion



A mixture of **1** (166 mg, 0.6 mmol), $CuBr(SMe_2)$ (10 mg, 0.05 mmol), Et_3N (61 mg, 0.6 mmol) and benzene (10 ml) were placed into a Schlenk flask under argon atmosphere and heated to reflux. Solution of mercaptan (0.5 mmol) in benzene (5

mL) was added via syringe in small portions. The reaction mixture was then stirred at reflux for 2 h. The solvent was removed under reduced pressure. The desired product was obtained after column chromatography (EtOAc/hexanes).

C-H insertion



A mixture of **1** (166 mg, 0.6 mmol), CuI (9.5 mg, 0.05 mmol), Et_3N (61 mg, 0.6 mmol) and MeCN/water (10/0.5 ml) were placed into a Schlenk flask under argon atmosphere and heated to reflux. Solution of (4-bromophenyl)acetylene (**5**) (0.5 mmol) in MeCN (5 mL) was added via syringe in small portions. The reaction mixture was then stirred at reflux for 2 h. The solvent was removed under reduced pressure. The desired 1-(4-bromophenyl)-4,4,4-trifluorobut-1-yne (**6**) was purified by column chromatography (petroleum ether/EtOAc 10:1) and obtained as a colorless oil in 33% yield (43 mg).

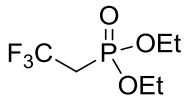
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 3.27 (q, J = 9.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 131.6, 124.0 (q, J_{CF} = 276.2 Hz), 123.0, 121.1, 83.3, 77.2, 26.8 (q, J_{CF} = 36.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.4 (t, J_{FH} = 9.5 Hz).

NMR spectral data for this compound were consistent with those in literature.[3]

Characterization of Products



Diethyl 2,2,2-trifluoroethylphosphonate 2a

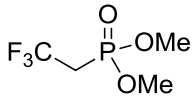
Prepared according to general procedure **A** from diethyl phosphonate, purified by silica gel chromatography (petroleum ether/EtOAc 3:1) and obtained as a colorless oil in 70% yield (77 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (dq, *J* = 7.2, 7.1 Hz, 4H), 2.72 (dq, *J* = 10.7, 19.5 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 6H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 16.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -58.7 (dt, *J* = 13.9, 10.8 Hz).

NMR spectral data for this compound were consistent with those in literature.[4]



Dimethyl 2,2,2-trifluoroethylphosphonate 2b

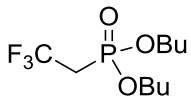
Prepared according to general procedure **A** from dimethyl phosphonate, purified by silica gel chromatography (petroleum ether/EtOAc 3:1) and obtained as a colorless oil in 76% yield (73 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.70 (s, 3H), 2.66 (dq, *J* = 10.8, 19.5 Hz, 2H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 18.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -58.8 (dt, *J* = 13.8, 10.4 Hz).

NMR spectral data for this compound were consistent with those in literature.[5]



Dibutyl 2,2,2-trifluoroethylphosphonate 2c

Prepared according to general procedure **A** from dibutyl phosphonate, purified by silica gel chromatography (petroleum ether/EtOAc 4:1) and obtained as a colorless oil in 67% yield (92 mg).

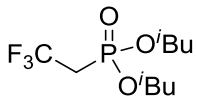
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (q, *J* = 6.7 Hz, 4H), 2.68 (dq, *J* = 10.7, 19.6 Hz, 2H), 1.62 (m, 4H), 1.30-1.41 (m, 4H), 0.89 (t, *J* = 6.7 Hz, 6H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 16.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -58.6 (dt, *J* = 13.6, 10.9 Hz).

HRMS (ESI) m/z calculated for $C_{10}H_{20}F_3PO_3Na$ ($[M+Na]^+$): 277.1181, observed: 277.1181.

NMR spectral data for this compound were consistent with those in literature.[4]



Di-isobutyl 2,2,2-trifluoroethylphosphonate 2d

Prepared according to general procedure **A** from di-isobutyl phosphonate, purified by silica gel chromatography (petroleum ether/EtOAc 4:1) and obtained as a colorless oil in 81% yield (112 mg).

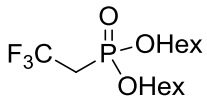
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (t, *J* = 6.6 Hz, 4H), 2.72 (dq, *J* = 10.7, 19.5 Hz, 2H), 1.89-2.00 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 123.5 (q, J = 272.1 Hz), 72.5 (d, J = 6.8 Hz), 33.0 (q, J = 31.4 Hz), 31.7 (q, J = 31.4 Hz), 29.1, 29.0, 18.5.

^{31}P NMR (162 MHz, $CDCl_3$) δ 16.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -58.5 (dt, J = 13.6, 10.9 Hz).

HRMS (ESI) m/z calculated for $C_{10}H_{20}F_3PO_3Na$ ($[M+Na]^+$): 277.1181, observed: 277.1171.



Dihexyl 2,2,2-trifluoroethylphosphonate 2e

Prepared according to general procedure **A** from dihexyl phosphonate, purified by silica gel chromatography (petroleum ether/EtOAc 3:1) and obtained as a colorless oil in 65% yield (108 mg).

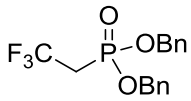
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (q, J = 6.6 Hz, 4H), 2.71 (dq, J = 10.7, 19.6 Hz, 2H), 1.66 (m, 4H), 1.22-1.41 (m, 12H), 0.88 (t, J = 7.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 123.5 (q, J = 272.7 Hz), 66.8 (d, J = 6.8 Hz), 33.3 (q, J = 31.3 Hz), 31.9 (q, J = 31.3 Hz), 31.2, 30.3 (d, J = 6.1 Hz), 25.0, 22.5, 13.9.

^{31}P NMR (162 MHz, $CDCl_3$) δ 16.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -58.6 (dt, J = 13.6, 10.9 Hz).

HRMS (ESI) m/z calculated for $C_{14}H_{28}F_3PO_3Na$ ($[M+Na]^+$): 355.1626, observed: 355.1628.



Dibenzyl 2,2,2-trifluoroethylphosphonate 2f

Prepared according to general procedure **A** from dibenzyl phosphonate, purified by silica gel chromatography (petroleum ether/EtOAc 2:1) and obtained as a colorless oil in 74% yield (127 mg).

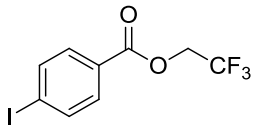
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.39 (m, 10H), 5.00-5.10 (m, 4H), 2.69 (dq, J = 10.8, 19.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 128.7, 128.6, 126.9, 123.5 (q, J = 275.9 Hz), 68.3 (d, J = 6.8 Hz), 33.8 (q, J = 31.4 Hz), 32.4 (q, J = 31.4 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 17.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -58.2 (dt, J = 13.9, 10.8 Hz).

HRMS (ESI) m/z calculated for $C_{16}H_{16}F_3PO_3Na$ ($[M+Na]^+$): 367.0687, observed: 367.0672.



2,2,2-trifluoroethyl 4-iodobenzoate 3a

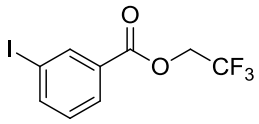
Prepared according to general procedure **B** from 4-iodobenzoic acid, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a white solid in 45% yield (74 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 4.67 (q, J = 8.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 131.3, 127.8, 123.5 (q, J = 277.4 Hz), 102, 61.0 (q, J = 36.6 Hz). Carbonyl carbon was not detected due to very low signal.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.7 (t, J = 8.2 Hz).

El. Analysis calculated for $C_9H_8F_3IO_2$: C 32.75, H 1.83; observed: C 32.80, H 1.89.



2,2,2-trifluoroethyl 3-iodobenzoate 3b

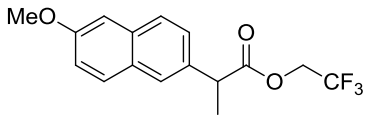
Prepared according to general procedure **B** from 3-iodobenzoic acid, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a colorless oil in 49% yield (81 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.03 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.93 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.16-7.27 (m, 1H), 4.69 (q, *J* = 8.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 142.8, 138.8, 130.3, 130.2, 129.2, 122.7 (q, *J* = 277.4 Hz), 93.9, 61.0 (q, *J* = 37.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.7 (t, *J* = 8.2 Hz).

HRMS (ESI) m/z calculated for $C_9H_6F_3IO_2$ ($[M+H]^+$): 330.9423, observed: 330.9383.



2,2,2-trifluoroethyl 2-(6-methoxy-2-naphthyl)propanoate 3c

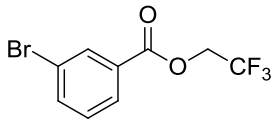
Prepared according to general procedure **B** from 2-(6-methoxy-2-naphthyl)propanoic acid (naproxen), purified by silica gel chromatography (petroleum ether/EtOAc 10:1) and obtained as a beige solid in 70% yield (109 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.76 (m, 2H), 7.70 (bs, 1H), 7.43 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 4.37-4.61 (m, 2H), 3.98 (q, *J* = 7.1 Hz, 1H), 3.92 (s, 3H), 1.65 (d, *J* = 7.1 Hz, 3H)..

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 157.7, 136.4, 134.4, 133.8, 128.8, 127.3, 126.0, 125.9, 122.5 (q, *J* = 277.4 Hz), 119.1, 105.5, 60.4 (q, *J* = 36.7 Hz), 55.2, 44.9, 18.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.8 (t, *J* = 8.2 Hz).

HRMS (ESI) m/z calculated for $C_{16}H_{16}F_3O_3$ ($[M+H]^+$): 313.1051, observed: 313.1044.



2,2,2-trifluoroethyl 3-bromobenzoate 3d

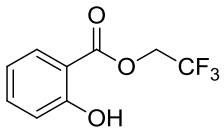
Prepared according to general procedure **B** from 3-bromobenzoic acid, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a colorless oil in 80% yield (113 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 4.71 (q, *J* = 8.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 136.8, 132.9, 130.1, 128.5, 128.0, 123.1 (q, *J* = 277.2 Hz), 122.8, 61.0 (q, *J* = 36.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.7 (t, *J* = 8.4 Hz).

El. Analysis calculated for $C_9H_8F_3BrO_2$: C 38.19, H 2.14; observed: C 38.33, H 2.23.



2,2,2-trifluoroethyl 2-hydroxybenzoate 3e

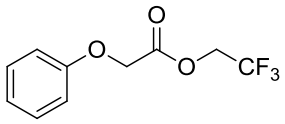
Prepared according to general procedure **B** from salicylic acid, purified by silica gel chromatography (petroleum ether/EtOAc 10:1) and obtained as a colorless oil in 40% yield (44 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.88 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.48-7.54 (m, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.1 Hz, 1H), 4.71 (q, *J* = 8.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 161.9, 136.8, 130.1, 122.8 (q, *J* = 277.2 Hz), 119.6, 117.8, 110.8, 60.7 (q, *J* = 37.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.6 (t, *J* = 8.2 Hz).

NMR spectral data for this compound were consistent with those in literature.[6]



2,2,2-trifluoroethyl phenoxyacetate 3f

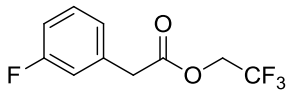
Prepared according to general procedure **B** from phenoxyacetic acid, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a colorless oil in 63% yield (74 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.35 (m, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.76 (s, 1H), 4.60 (q, *J* = 8.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 157.4, 129.7, 122.0 (q, *J* = 267.2 Hz), 122.1, 114.6, 64.7, 60.8 (q, *J* = 36.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.7 (t, *J* = 8.2 Hz).

El. Analysis calculated for $C_{10}H_9F_3O_3$: C 51.29, H 3.87; observed: C 51.19, H 3.88.



2,2,2-trifluoroethyl (3-fluorophenyl)acetate 3g

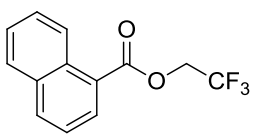
Prepared according to general procedure **B** from (3-fluorophenyl)acetic acid, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a colorless oil in 33% yield (39 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (q, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.69-7.07 (m, 2H), 4.50 (q, *J* = 8.4 Hz, 2H), 3.73 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 162.7 (d, *J* = 246.8 Hz), 134.9 (d, *J* = 7.8 Hz), 130.2 (d, *J* = 7.8 Hz), 124.9 (d, *J* = 3.1 Hz), 122.7 (q, *J* = 277.2 Hz), 116.3 (d, *J* = 21.8 Hz), 114.5 (d, *J* = 21.0 Hz), 60.6 (q, *J* = 36.6 Hz), 40.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.8 (t, *J* = 8.2 Hz, 3F), -112.8 (m, 1F).

HRMS (ESI) m/z calculated for $C_{10}H_8F_4O_2Na$ ($[M+Na]^+$): 259.0358, observed: 259.0324.



2,2,2-trifluoroethyl 1-naphthoate 3h

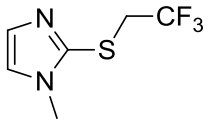
Prepared according to general procedure **B** from 1-naphthoic acid, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a colorless solid in 46% yield (59 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 8.7 Hz, 1H), 8.31 (dd, J = 7.3, 1.3 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.64-7.70 (m, 1H), 7.51-7.60 (m, 1H), 4.81 (q, J = 8.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 134.6, 133.8, 131.5, 131.2, 128.7, 128.3, 126.5, 125.4, 124.8, 124.5, 123.2 (q, J = 277.0 Hz), 60.7 (q, J = 36.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.5 (t, J = 8.2 Hz).

NMR spectral data for this compound were consistent with those in literature.[6]



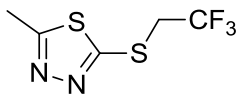
1-methyl-2-[(2,2,2-trifluoroethyl)thio]-1H-imidazole 4a

Prepared according to general procedure **C** from 1-methyl-2-thio-1H-imidazole, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a colorless oil in 27% yield (27 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.94 (s, 1H), 3.66 (s, 3H), 3.63 (q, J = 9.7 Hz, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -67.4 (t, J = 9.5 Hz).

NMR spectral data for this compound were consistent with those in literature.[7]



2-methyl-5-[(2,2,2-trifluoroethyl)thio]-1,3,4-thiadiazole 4b

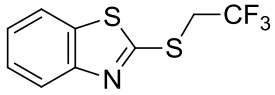
Prepared according to general procedure **C** from 2-methyl-5-thio-1,3,4-thiadiazole, purified by silica gel chromatography (petroleum ether/EtOAc 10:1) and obtained as a colorless oil in 33% yield (35 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (q, J = 9.5 Hz, 2H), 2.75 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 161.8, 130.2, 124.0 (q, J = 277.0 Hz), 34.7 (q, J = 34.3 Hz), 15.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.6.

HRMS (ESI) m/z calculated for $C_5H_6F_3N_2S_2$ ($[M+H]^+$): 214.9924, observed: 214.9914.



2-[(2,2,2-trifluoroethyl)thio]-1,3-benzothiazole 4c

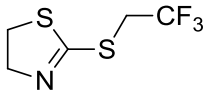
Prepared according to general procedure **C** from 2-thio-1,3-benzothiazole, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a colorless solid in 48% yield (60 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 4.15 (q, J = 9.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 152.5, 135.7, 126.5, 125.0, 124.8 (q, J = 277.0 Hz), 122.0, 121.3, 34.3 (q, J = 34.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.4 (t, J = 9.5 Hz).

NMR spectral data for this compound were consistent with those in literature.[8]



2-[(2,2,2-trifluoroethyl)thio]-4,5-dihydro-1,3-thiazole 4d

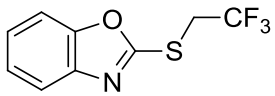
Prepared according to general procedure **C** from 2-thio-4,5-dihydro-1,3-thiazole, purified by silica gel chromatography (petroleum ether/EtOAc 15:1) and obtained as a colorless solid in 52% yield (53 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (t, J = 7.9 Hz, 2H), 3.86 (q, J = 9.7 Hz, 2H), 3.46 (t, J = 7.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 124.9 (q, J = 277.0 Hz), 63.7, 36.5, 33.7 (q, J = 34.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.6 (t, J = 9.6 Hz).

HRMS (ESI) m/z calculated for $C_5H_6F_3NS_2$ ($[M+H]^+$): 201.9972, observed: 201.9966.



2-[(2,2,2-trifluoroethyl)thio]-1,3-benzoxazole 4e

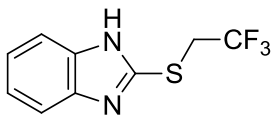
Prepared according to general procedure **C** from 2-thio-1,3-benzoxazole, purified by silica gel chromatography (petroleum ether/EtOAc 20:1) and obtained as a colorless solid in 80% yield (93 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.25-7.35 (m, 2H), 4.05 (q, J = 9.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 151.9, 141.0, 124.2, 124.15 (q, J = 276.2 Hz), 118.4, 109.7, 33.5 (q, J = 34.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.9 (t, J = 9.5 Hz).

HRMS (ESI) m/z calculated for $C_9H_7F_3NOS$ ($[M+H]^+$): 234.0200, observed: 234.0196.



2-[(2,2,2-trifluoroethyl)thio]-1*H*-benzimidazole 4f

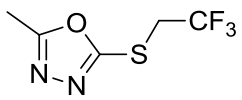
Prepared according to general procedure **C** from 2-thio-1*H*-benzimidazole, purified by silica gel chromatography (petroleum ether/EtOAc 5:1) and obtained as a colorless solid in 76% yield (88 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (bs, 2H), 7.23-7.29 (m, 2H), 4.02 (q, J = 9.6 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 147.1, 143.2, 135.7, 125.5 (q, J = 276.2 Hz), 122.2, 121.5, 117.7, 110.8, 32.4 (q, J = 33.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.9 (t, J = 9.5 Hz).

HRMS (ESI) m/z calculated for $C_9H_7F_3N_2S$ ($[M+H]^+$): 233.0360, observed: 233.0351.



2-methyl-5-[(2,2,2-trifluoroethyl)thio]-1,3,4-oxadiazole 4g

Prepared according to general procedure **C** from 2-methyl-5-thio-1,3,4-oxadiazole, purified by silica gel chromatography (petroleum ether/EtOAc 10:1) and obtained as a colorless oil in 5% yield (5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (q, J = 8.1 Hz, 2H), 2.43 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -69.8 (t, J = 8.1 Hz).

HRMS (ESI) m/z calculated for $C_5H_5F_3N_2OSNa$ ($[M+Na]^+$): 220.9972, observed: 220.9954.

^{13}C NMR was not detected due to small amount of compound.

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[7] T.S. Croft, J.J. McBrady, *J. Heterocycl. Chem.* **1975**, *12*, 845.

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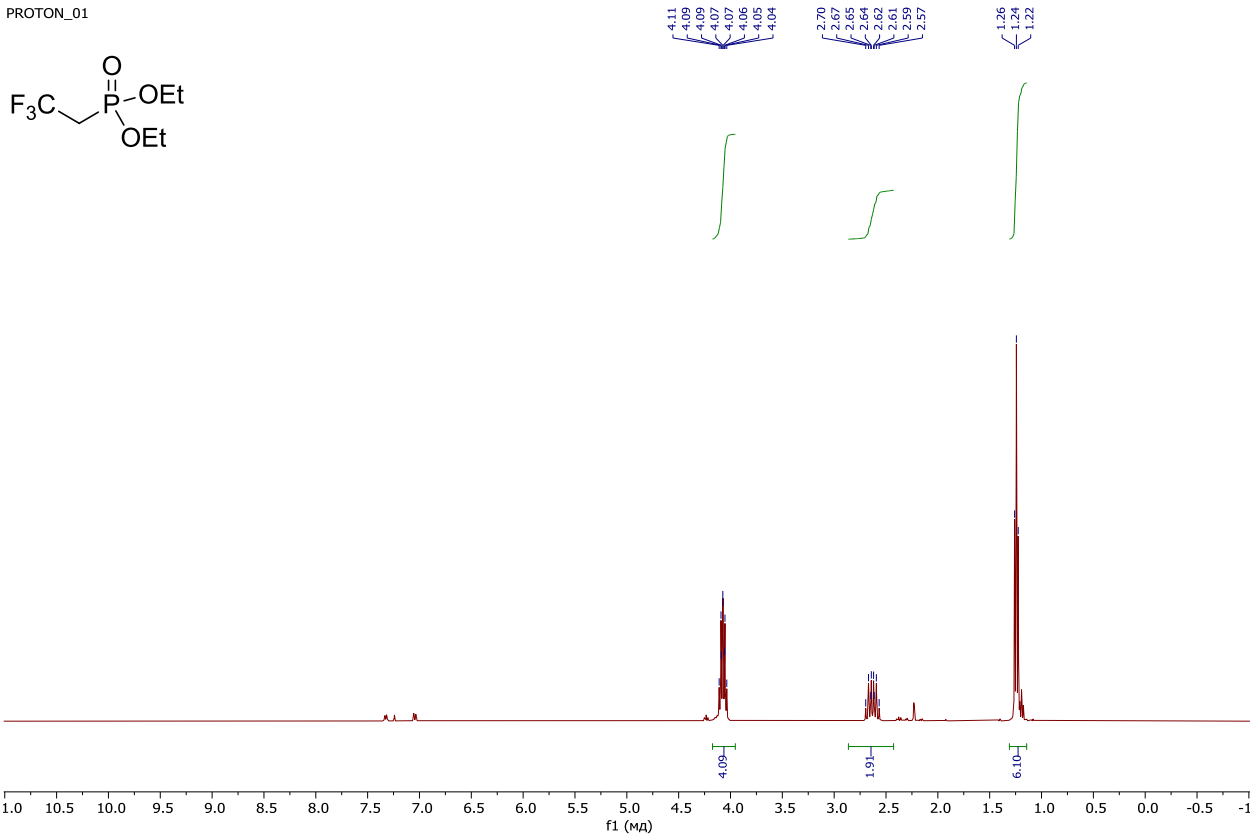
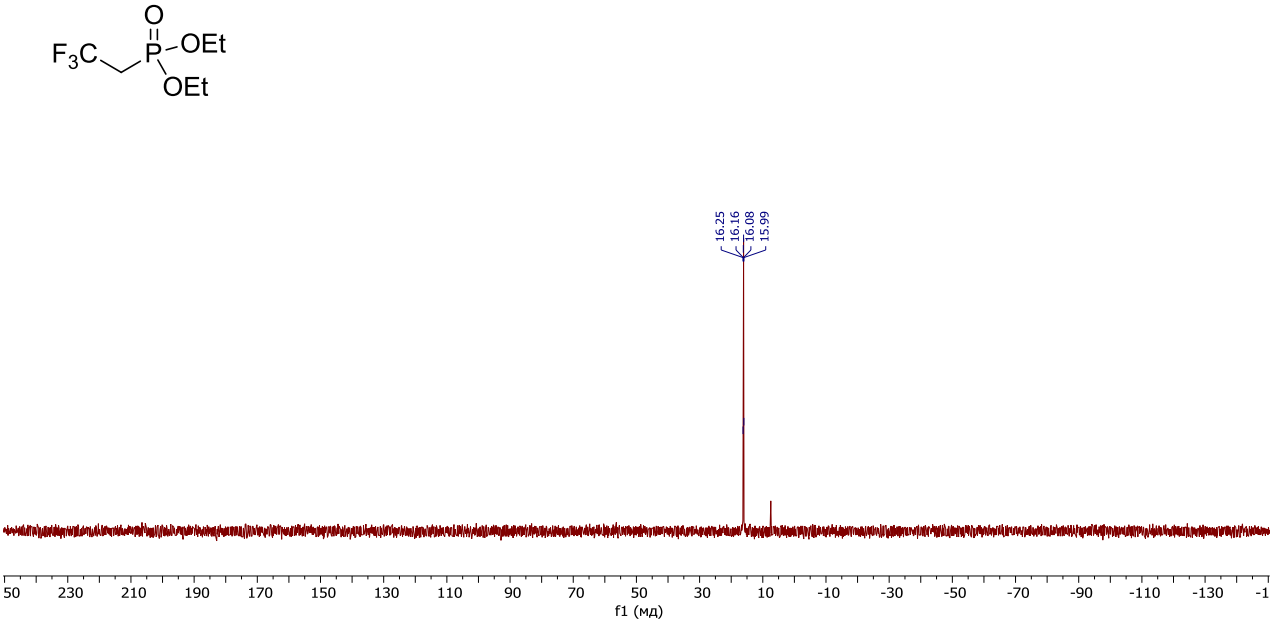
Spectra of synthesized compounds

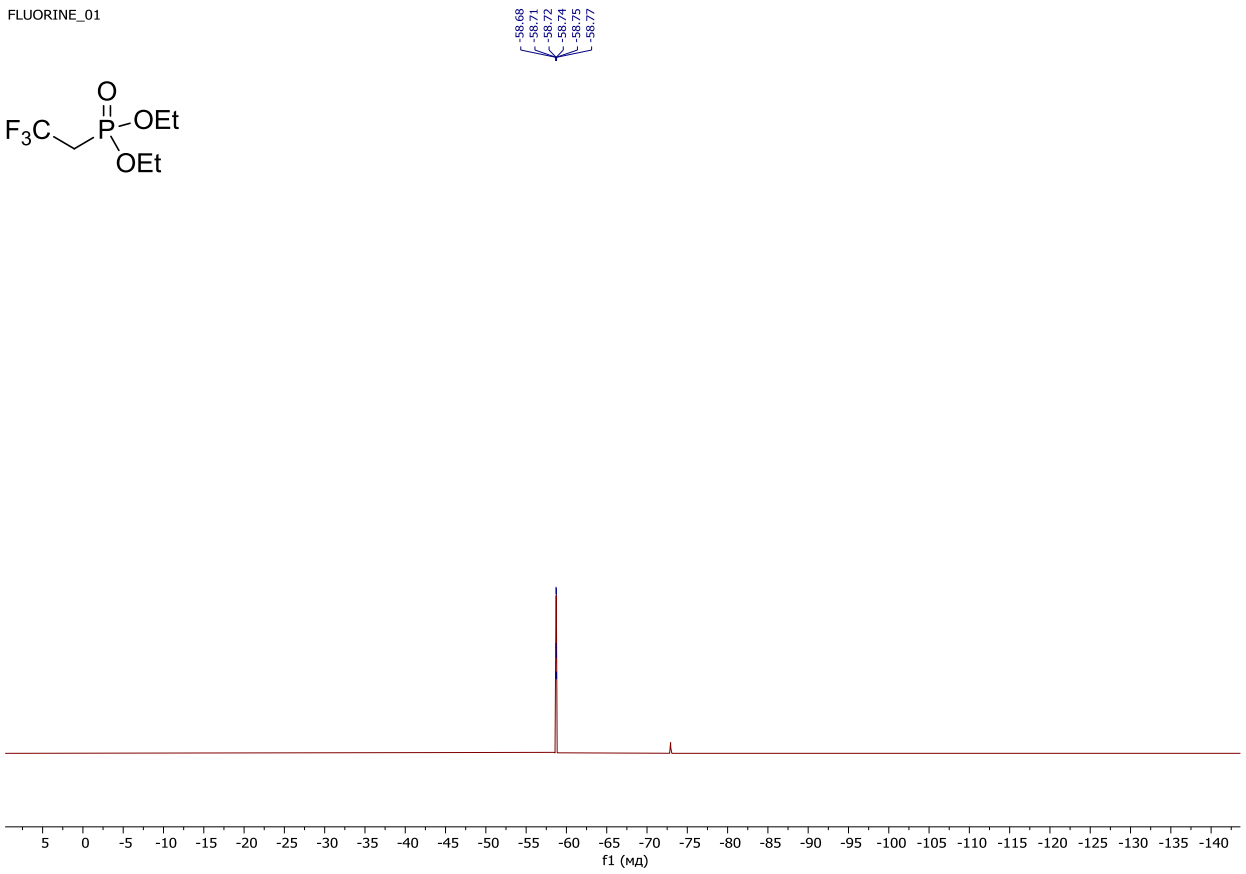
Diethyl 2,2,2-trifluoroethylphosphonate 2a **^{1}H NMR (400 MHz, $CDCl_3$)**



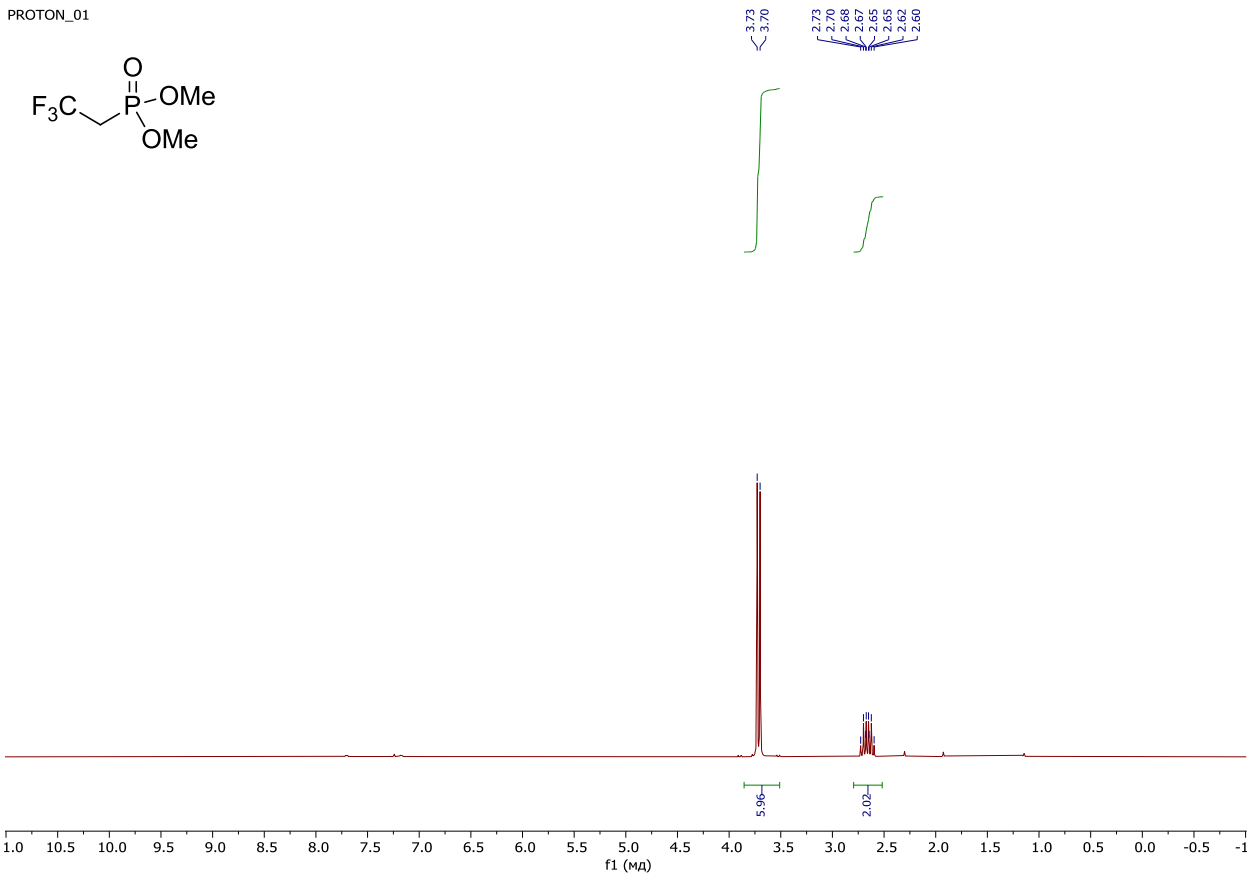
Diethyl 2,2,2-trifluoroethylphosphonate 2a **^{31}P NMR (162 MHz, $CDCl_3$)**



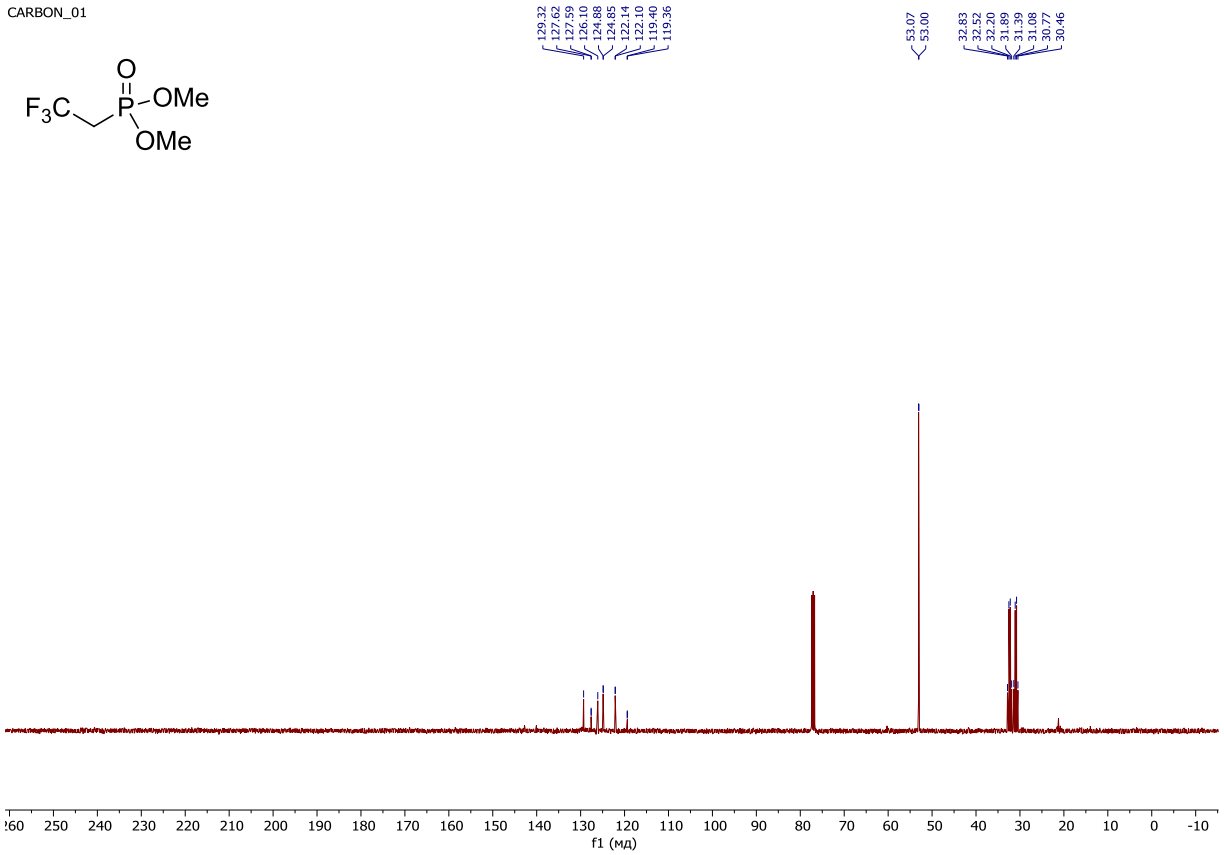
Diethyl 2,2,2-trifluoroethylphosphonate 2a **^{19}F NMR (376 MHz, $CDCl_3$)**



Dimethyl 2,2,2-trifluoroethylphosphonate 2b **^{1}H NMR (400 MHz, $CDCl_3$)**

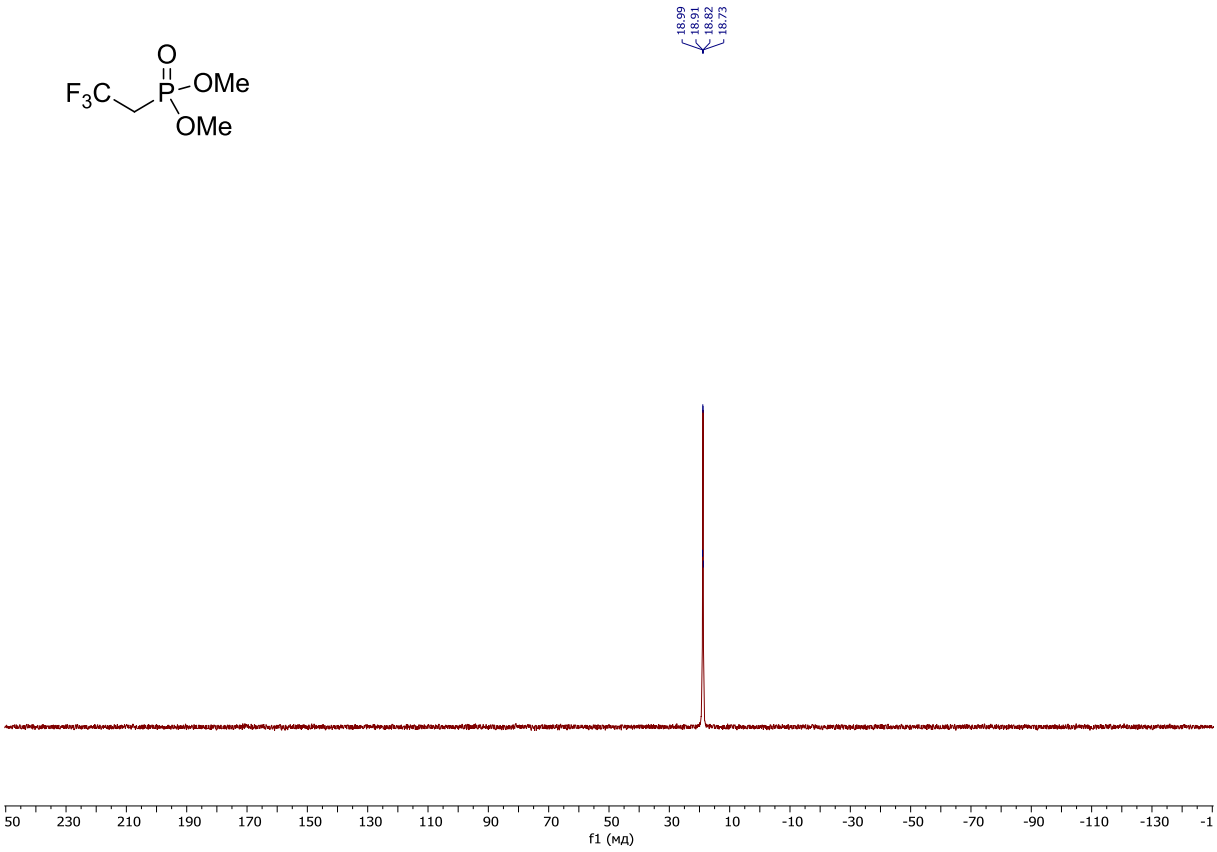


Dimethyl 2,2,2-trifluoroethylphosphonate 2b **^{13}C NMR (100 MHz, $CDCl_3$)**



Dimethyl 2,2,2-trifluoroethylphosphonate 2b

^{31}P NMR (162 MHz, $CDCl_3$)



Dimethyl 2,2,2-trifluoroethylphosphonate 2b

^{19}F NMR (376 MHz, $CDCl_3$)

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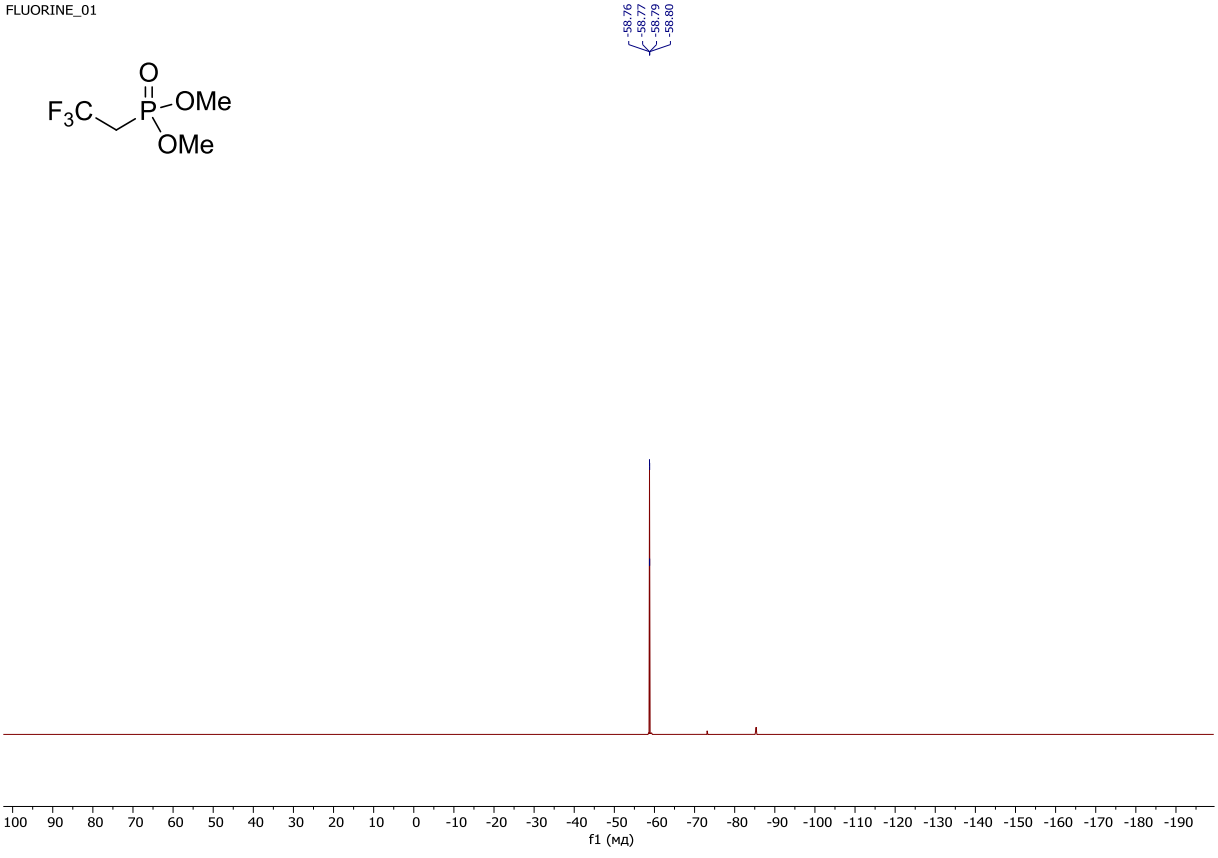
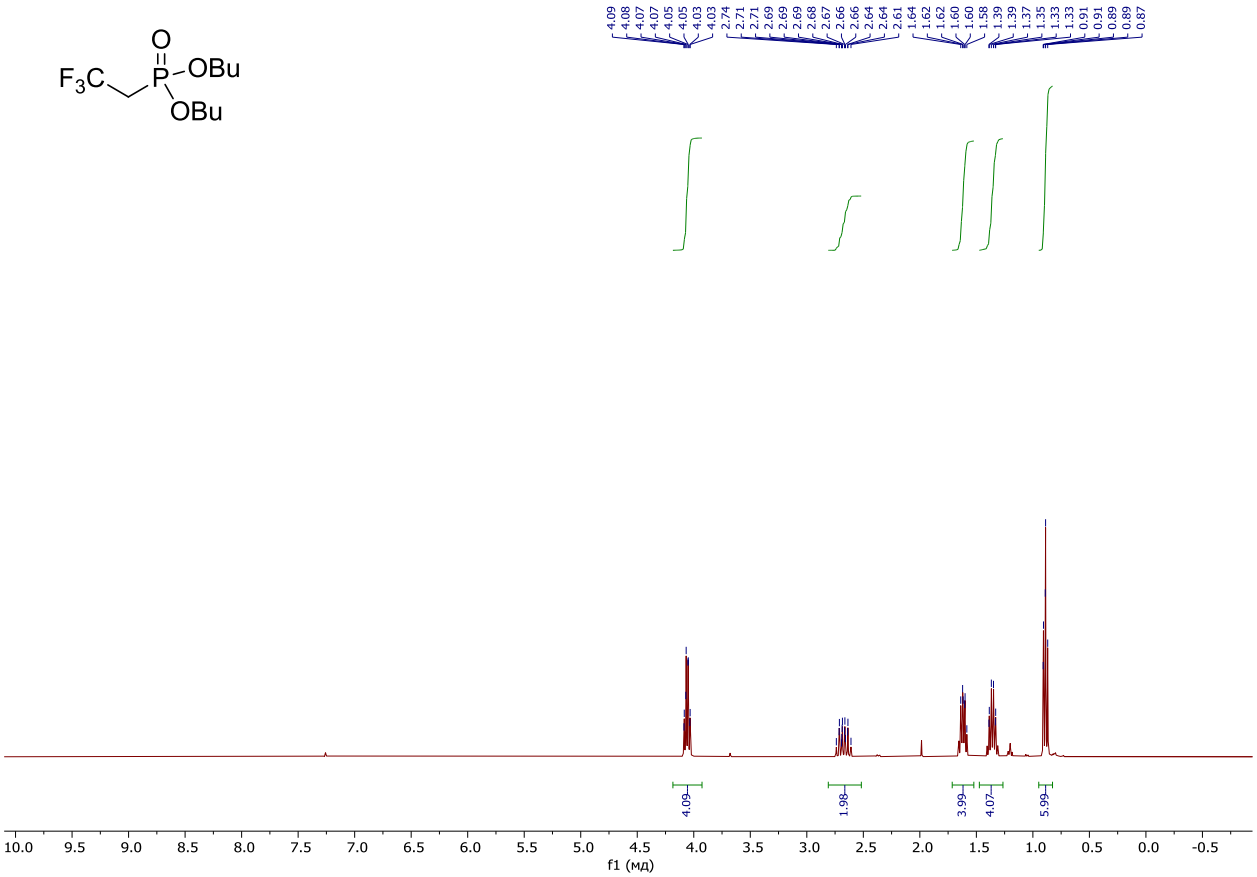
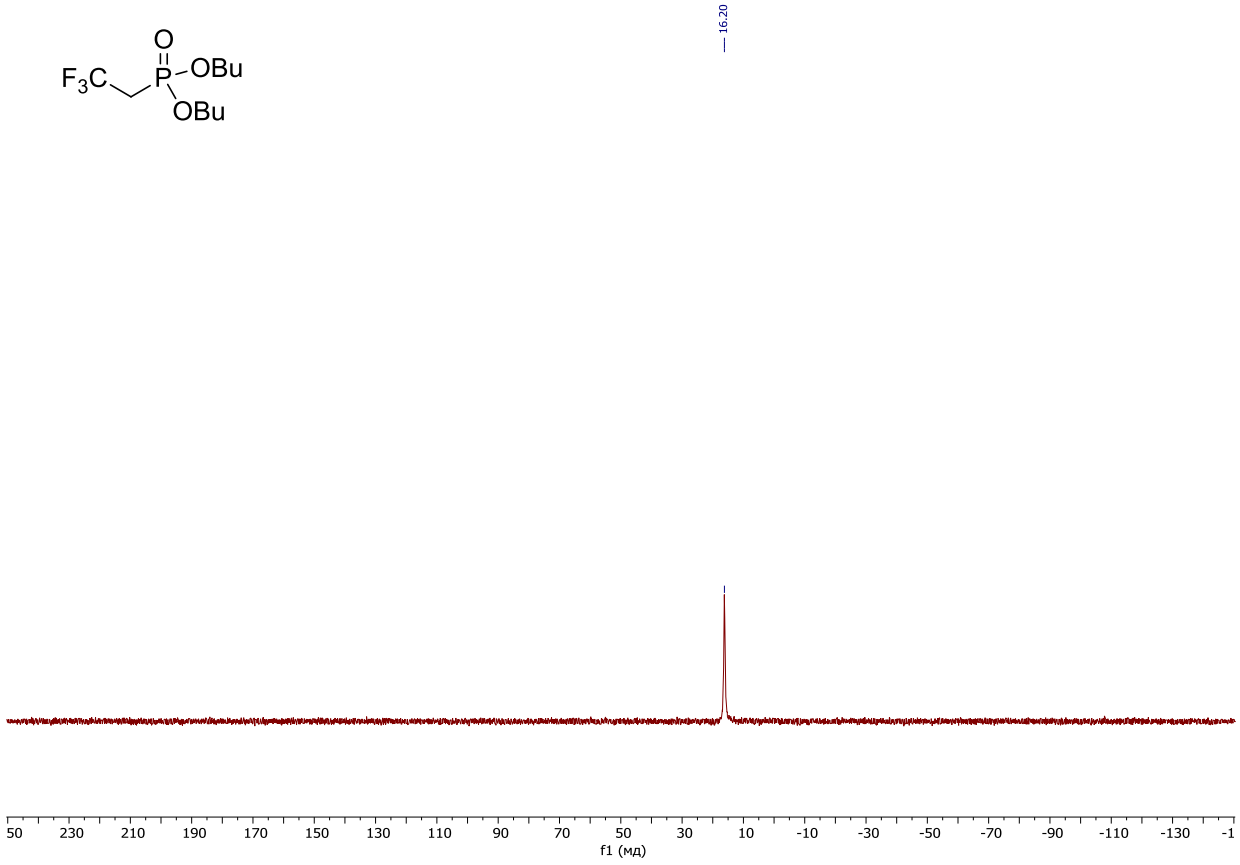


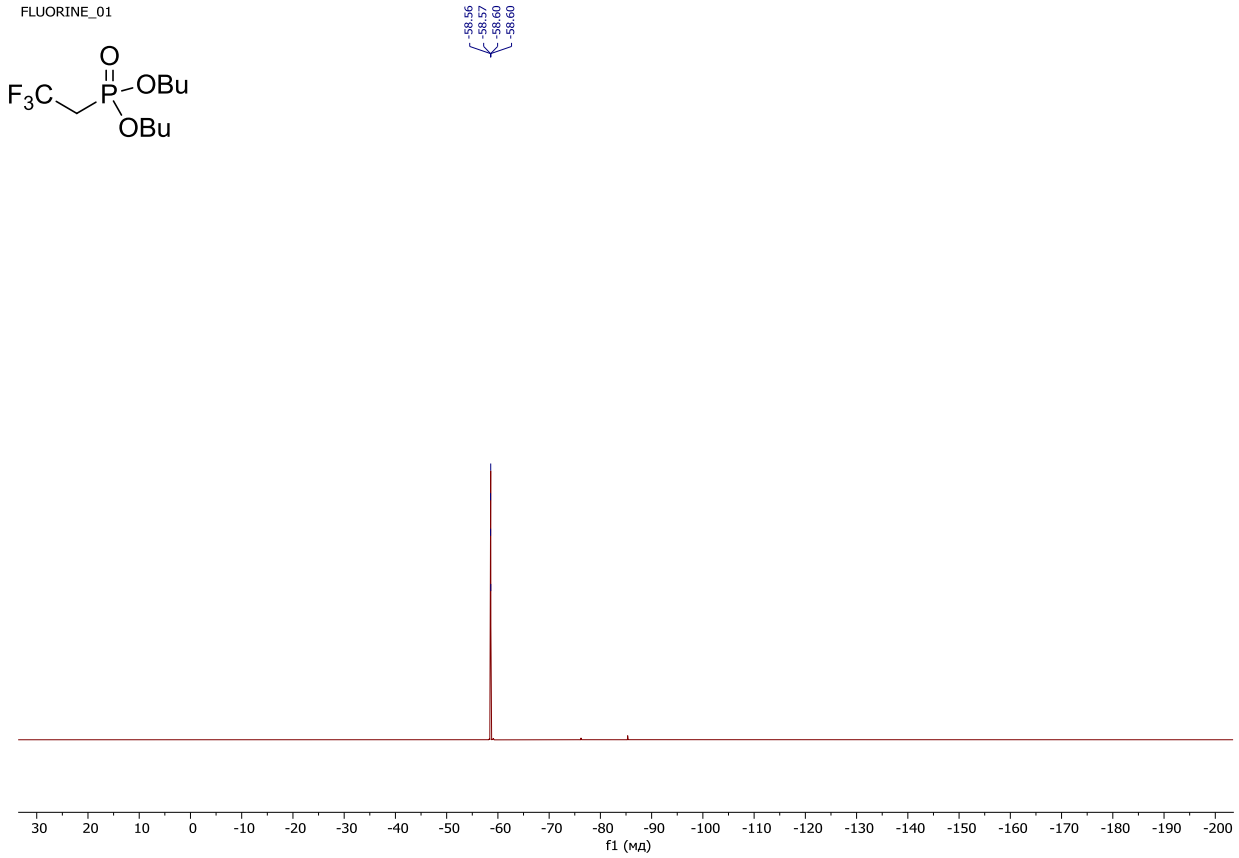
Dibutyl 2,2,2-trifluoroethylphosphonate 2c **^{1}H NMR (400 MHz, $CDCl_3$)**



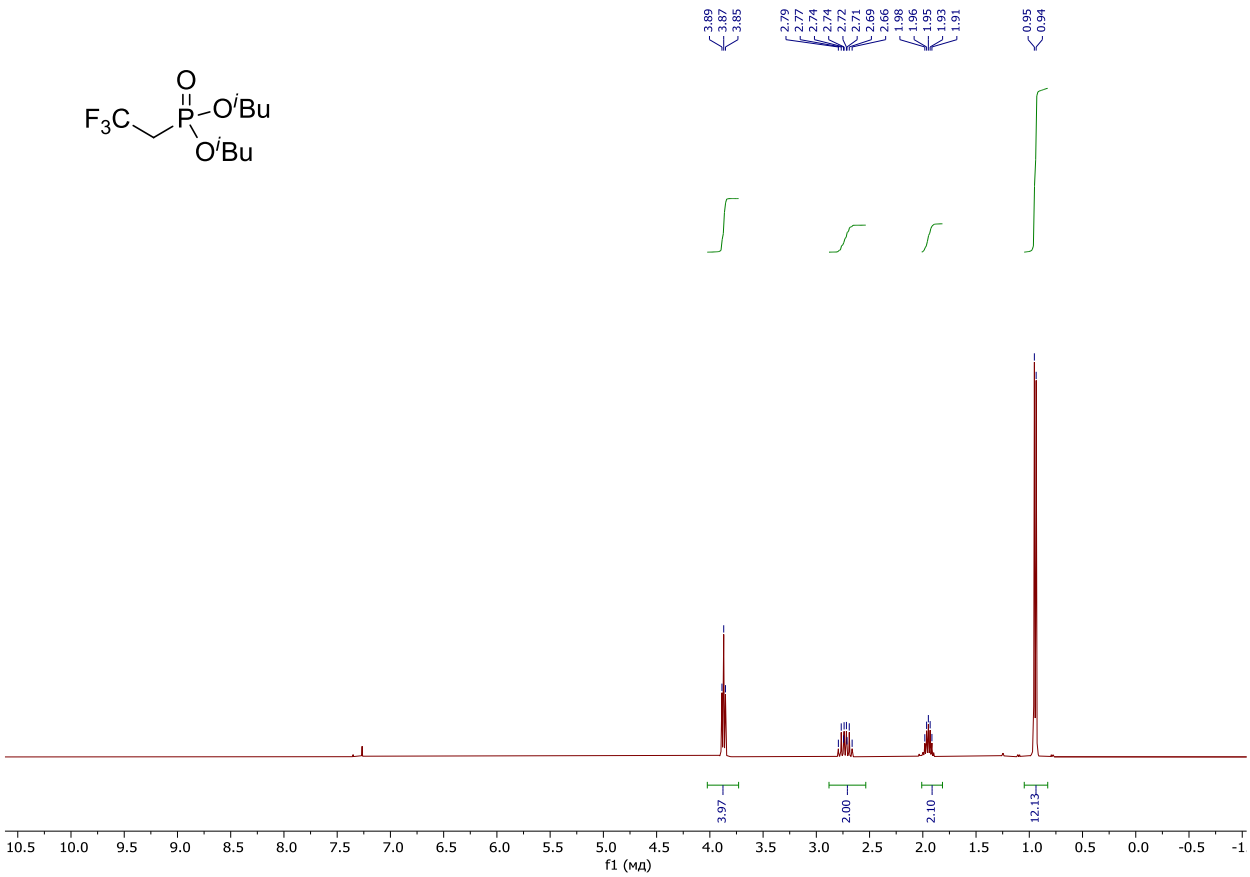
Dibutyl 2,2,2-trifluoroethylphosphonate 2c **^{31}P NMR (162 MHz, $CDCl_3$)**



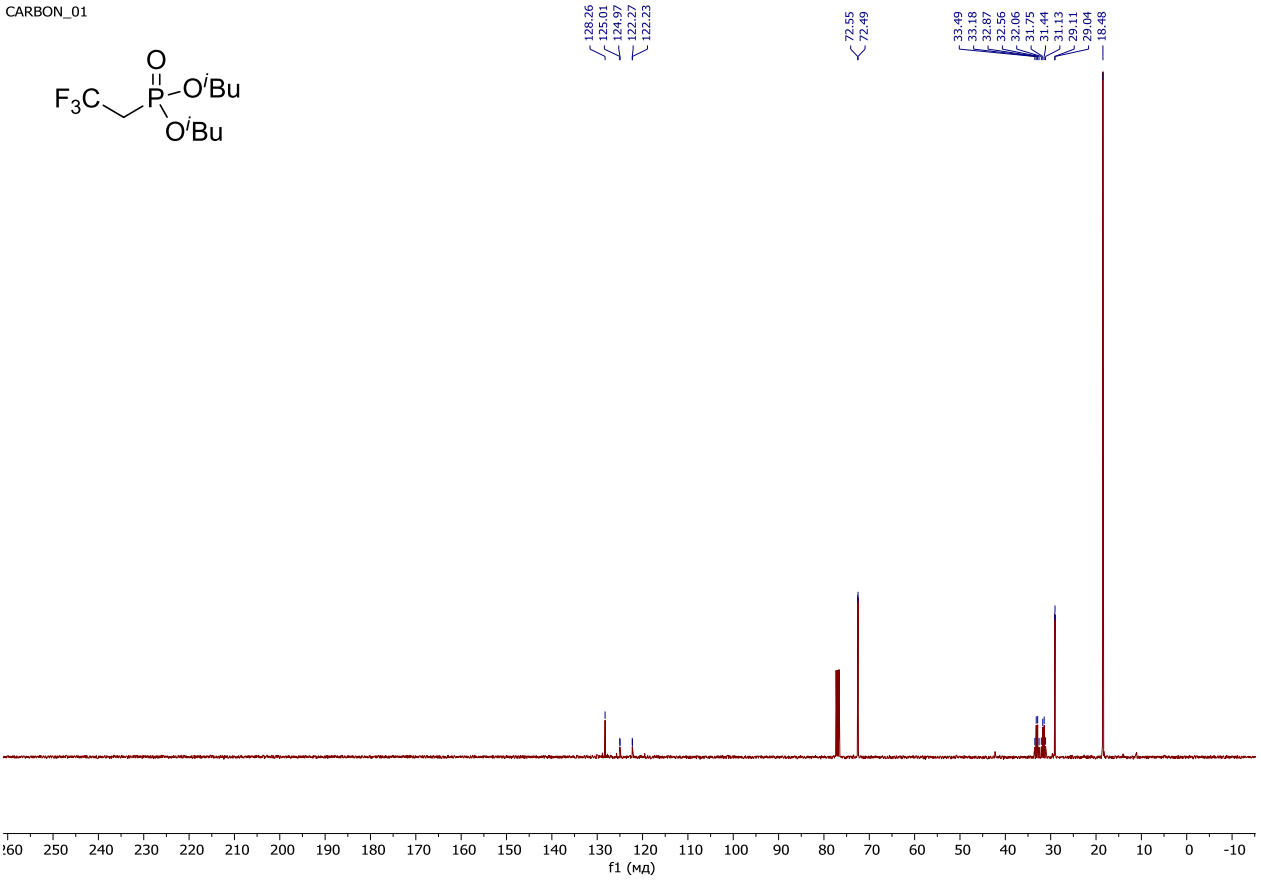
Dibutyl 2,2,2-trifluoroethylphosphonate 2c **^{19}F NMR (376 MHz, $CDCl_3$)**



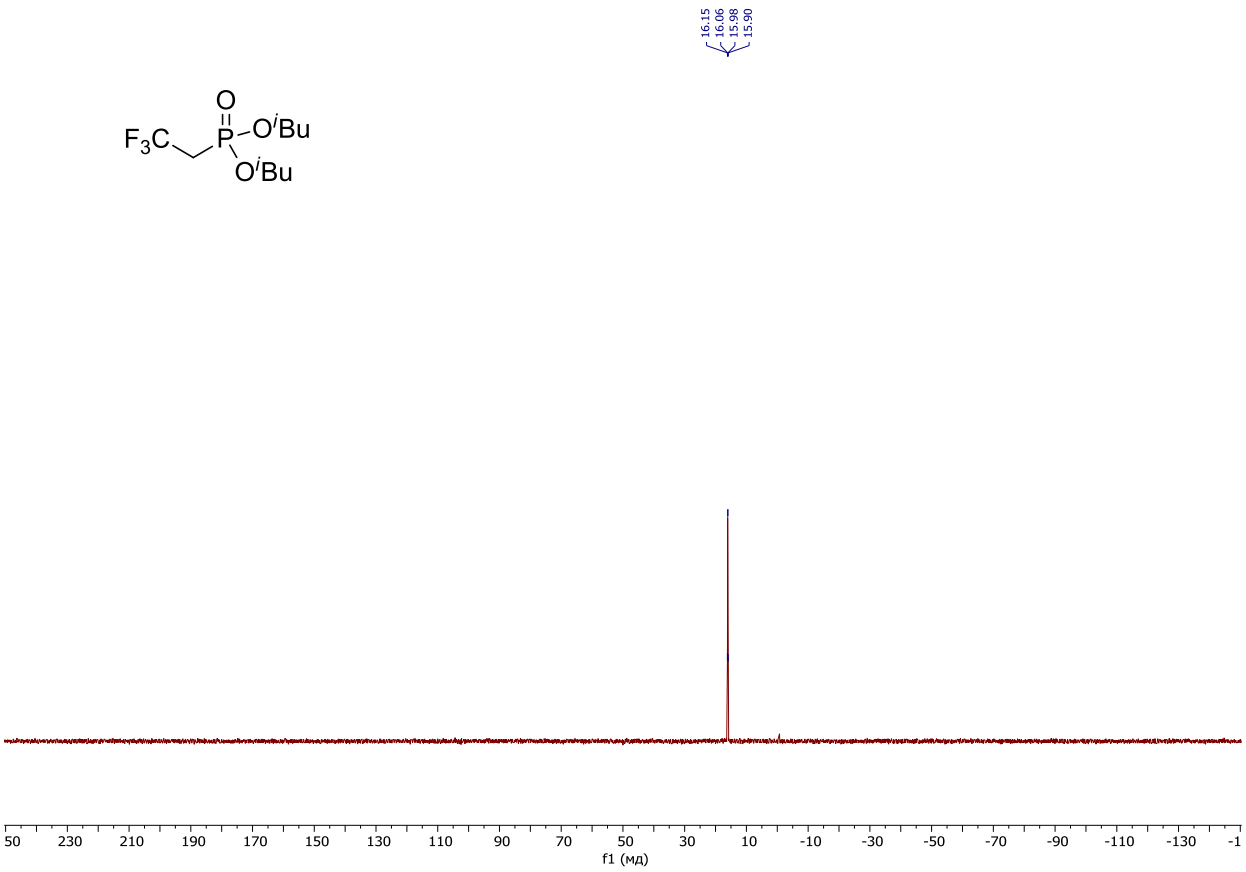
Di-isobutyl 2,2,2-trifluoroethylphosphonate 2d **^{1}H NMR (400 MHz, $CDCl_3$)**



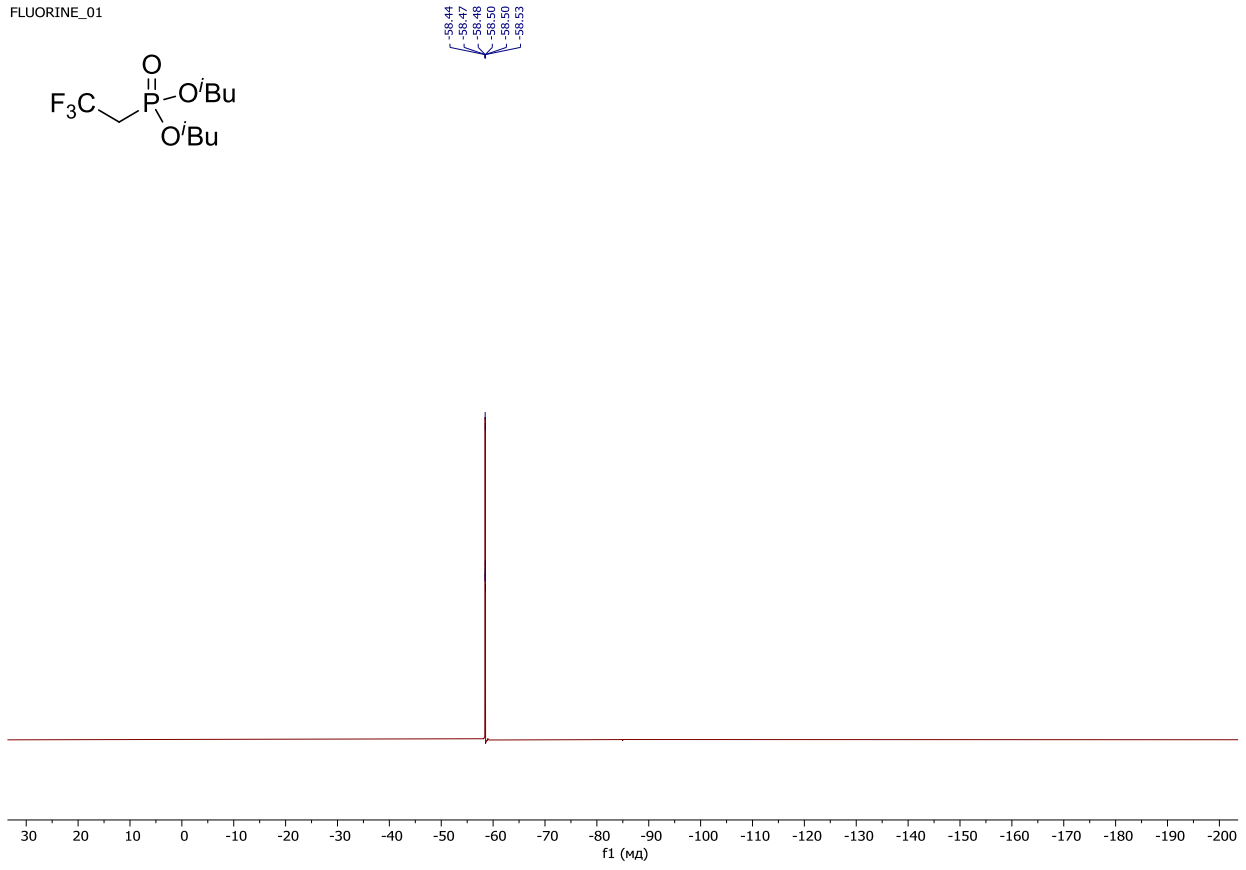
Di-isobutyl 2,2,2-trifluoroethylphosphonate 2d **^{13}C NMR (100 MHz, $CDCl_3$)**



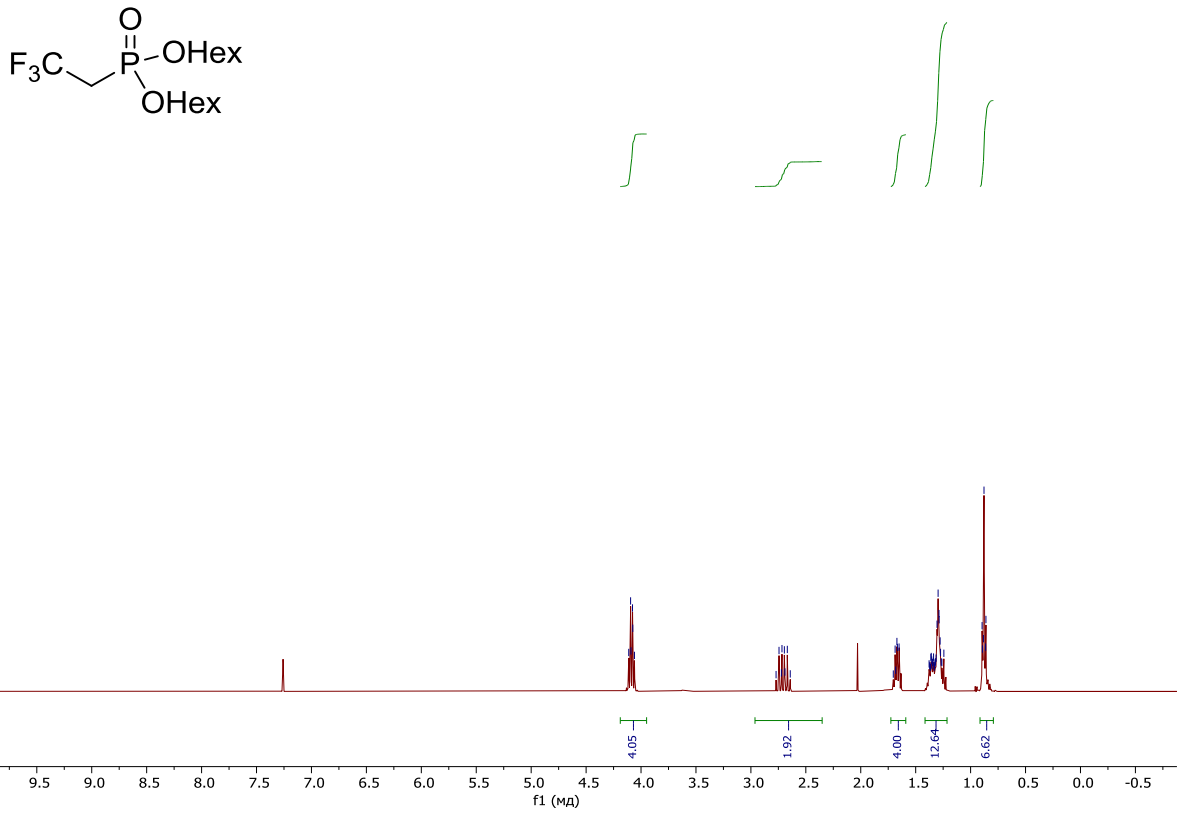
Di-isobutyl 2,2,2-trifluoroethylphosphonate 2d **^{31}P NMR (162 MHz, $CDCl_3$)**



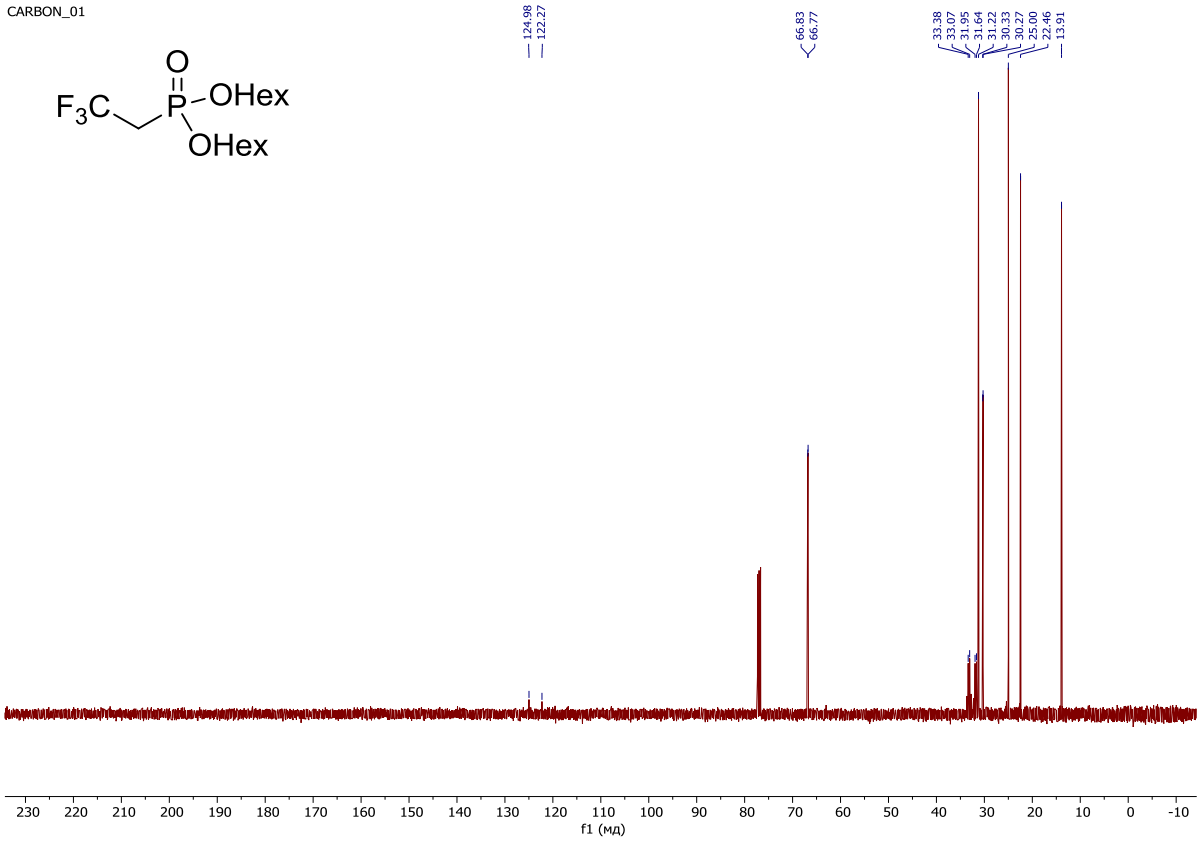
Di-isobutyl 2,2,2-trifluoroethylphosphonate 2d **^{19}F NMR (376 MHz, $CDCl_3$)**



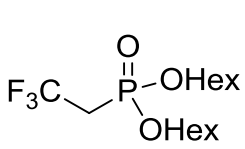
Dihexyl 2,2,2-trifluoroethylphosphonate 2e **^{1}H NMR (400 MHz, $CDCl_3$)**

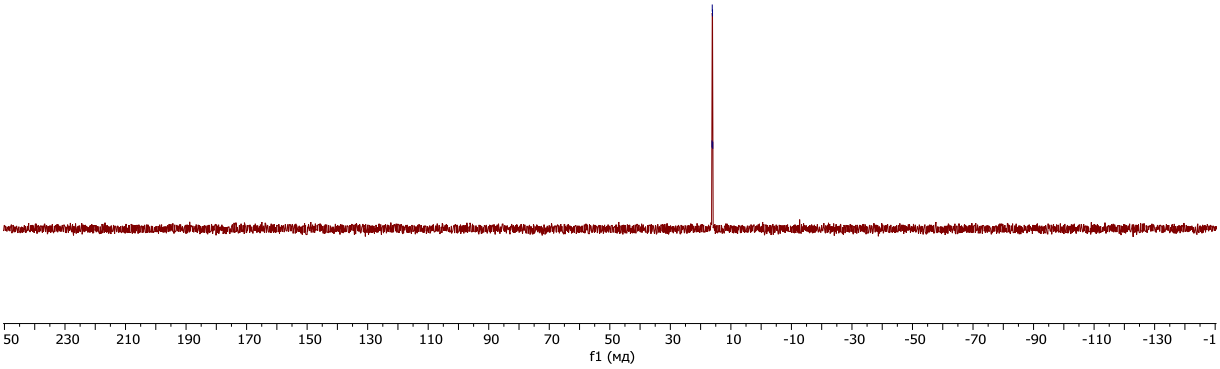


Dihexyl 2,2,2-trifluoroethylphosphonate 2e **^{13}C NMR (100 MHz, $CDCl_3$)**



Dihexyl 2,2,2-trifluoroethylphosphonate 2e **^{31}P NMR (162 MHz, $CDCl_3$)**





Dihexyl 2,2,2-trifluoroethylphosphonate 2e **^{19}F NMR (376 MHz, $CDCl_3$)**

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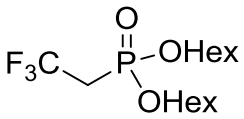
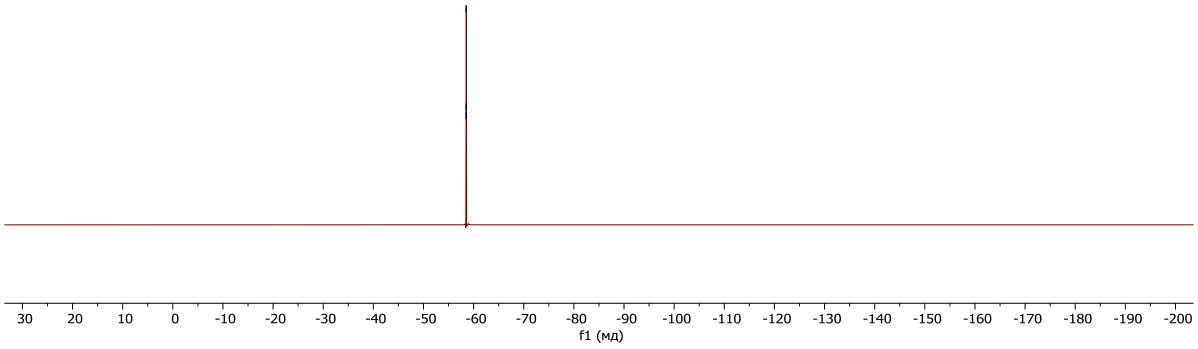
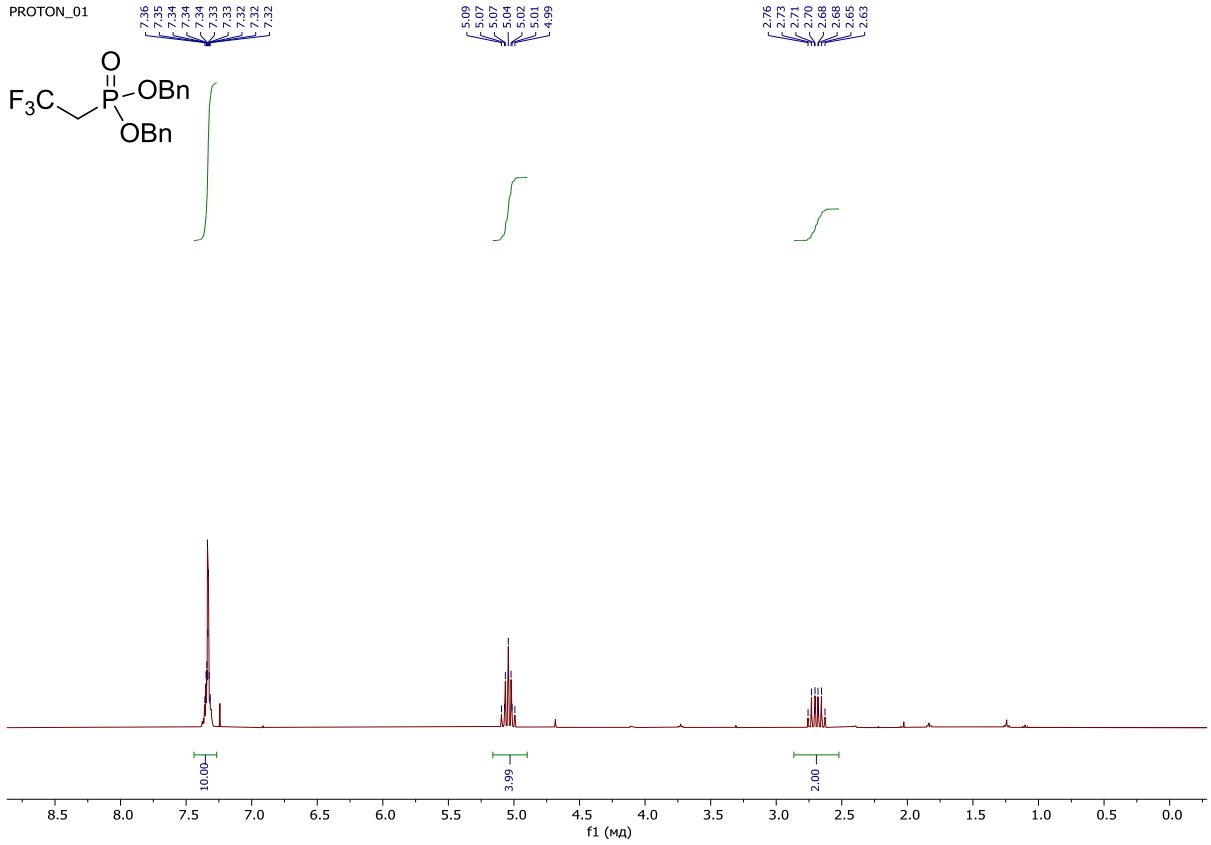
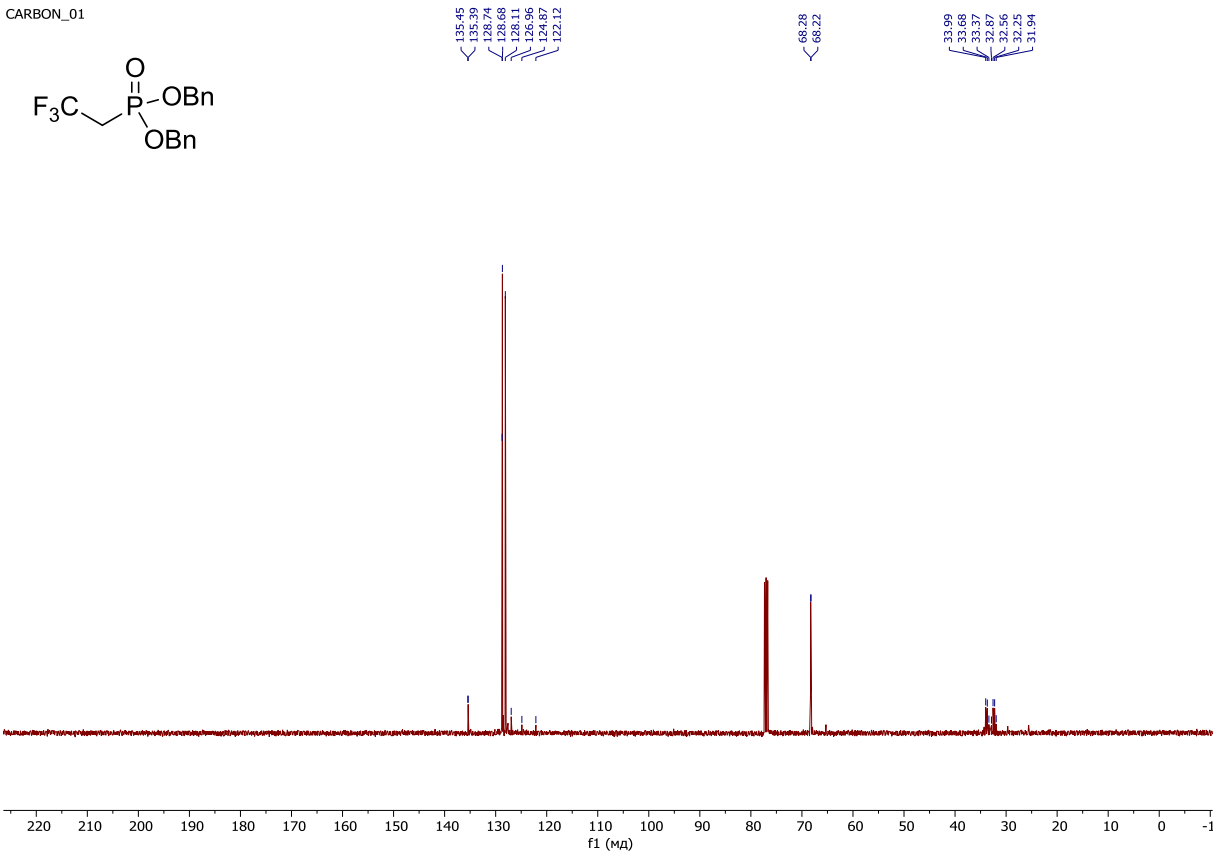




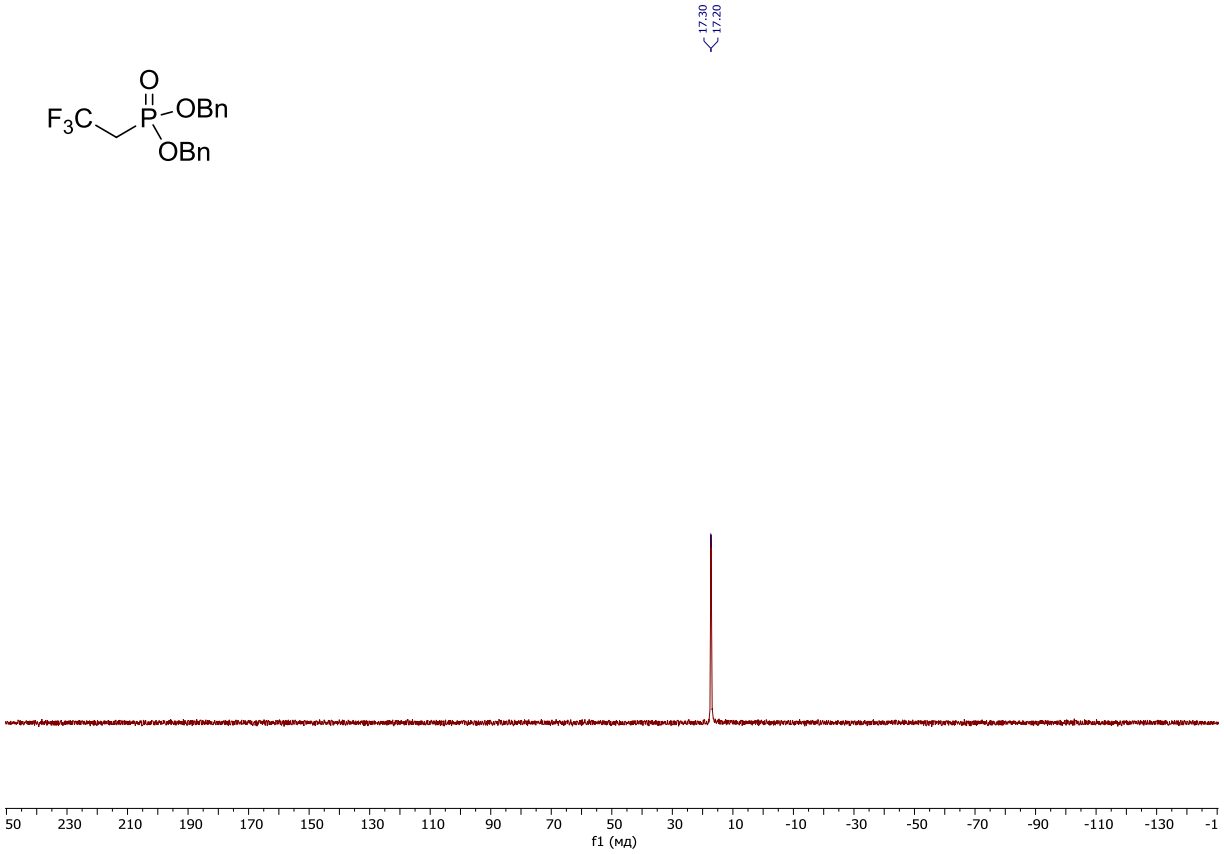
Dibenzyl 2,2,2-trifluoroethylphosphonate 2f **^{1}H NMR (400 MHz, $CDCl_3$)**



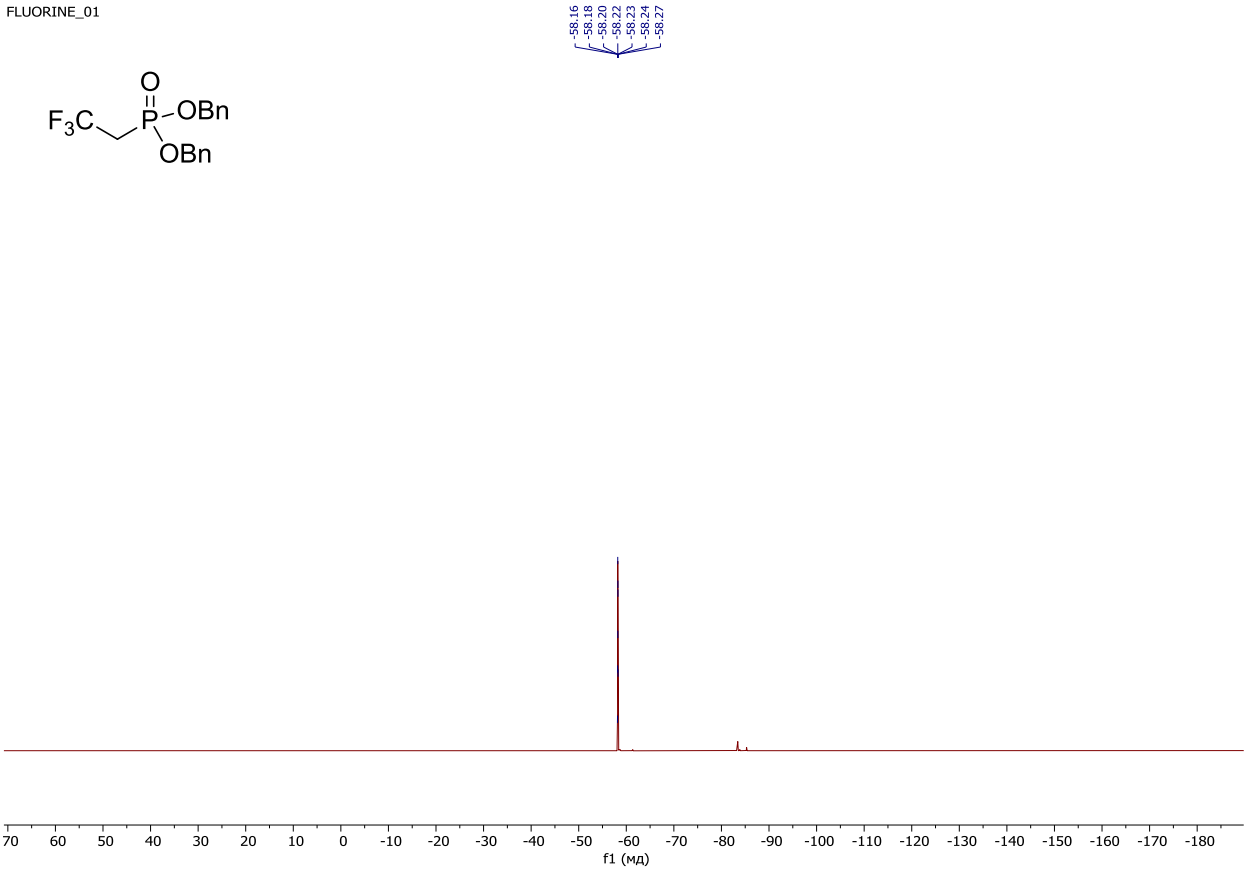
Dibenzyl 2,2,2-trifluoroethylphosphonate 2f **^{13}C NMR (100 MHz, $CDCl_3$)**



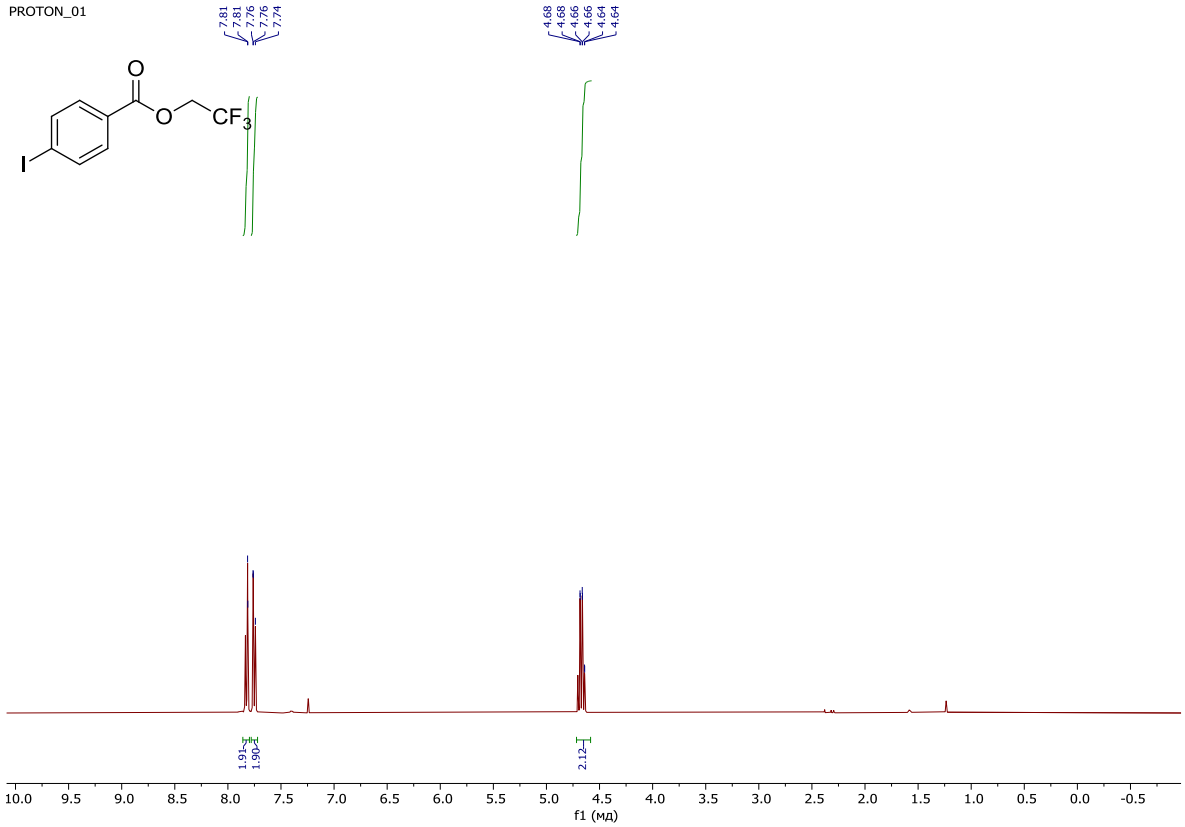
Dibenzyl 2,2,2-trifluoroethylphosphonate 2f **^{31}P NMR (162 MHz, $CDCl_3$)**



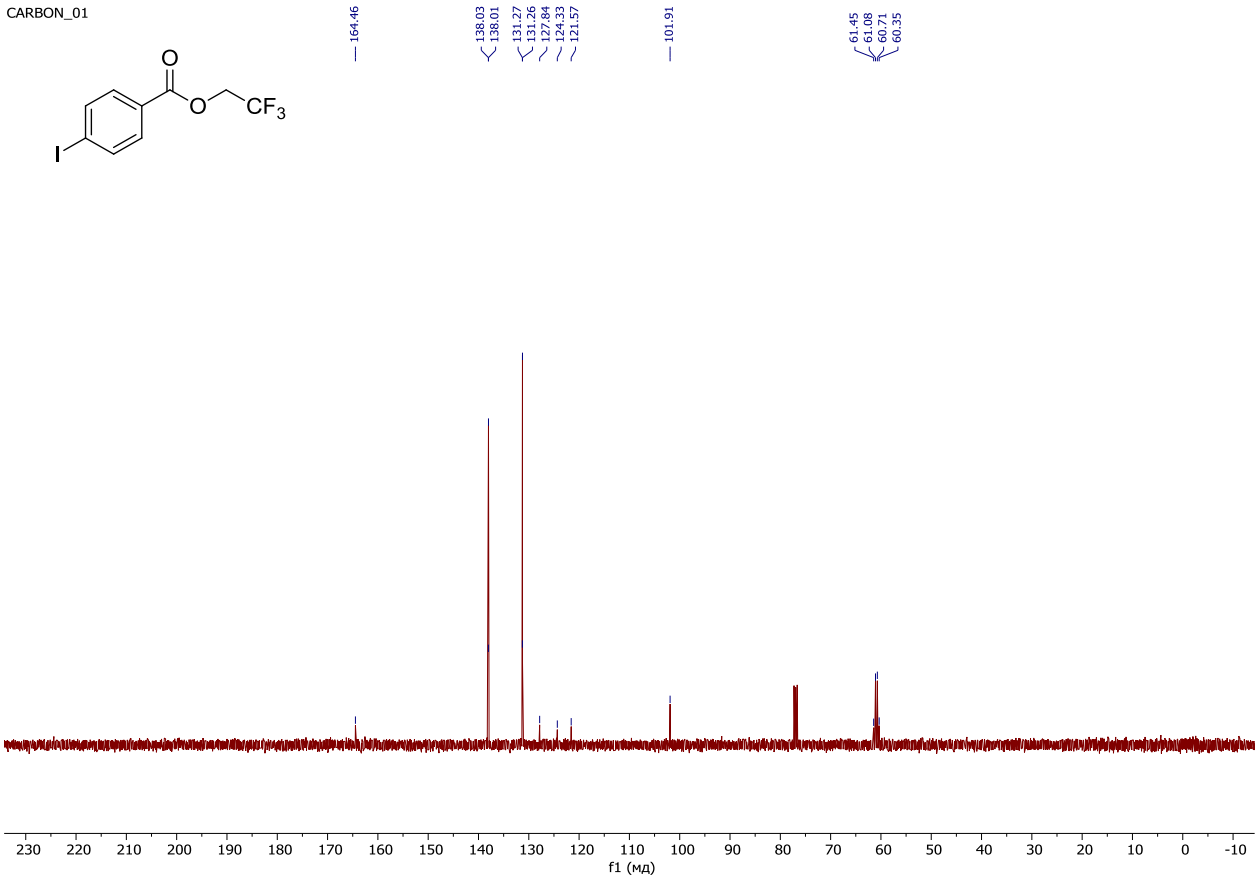
Dibenzyl 2,2,2-trifluoroethylphosphonate 2f **^{19}F NMR (376 MHz, $CDCl_3$)**



2,2,2-trifluoroethyl 4-iodobenzoate 3a **^{1}H NMR (400 MHz, $CDCl_3$)**

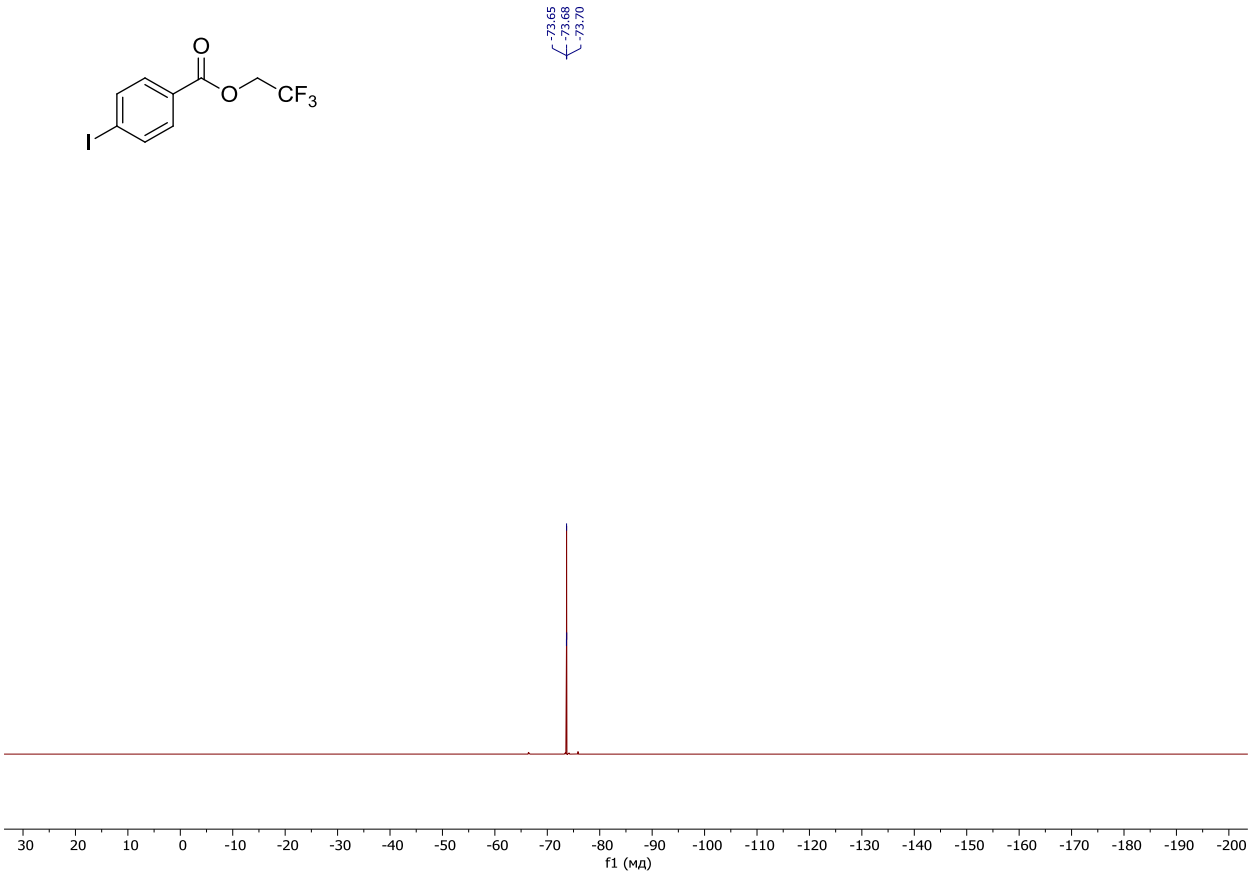


2,2,2-trifluoroethyl 4-iodobenzoate 3a **^{13}C NMR (100 MHz, $CDCl_3$)**

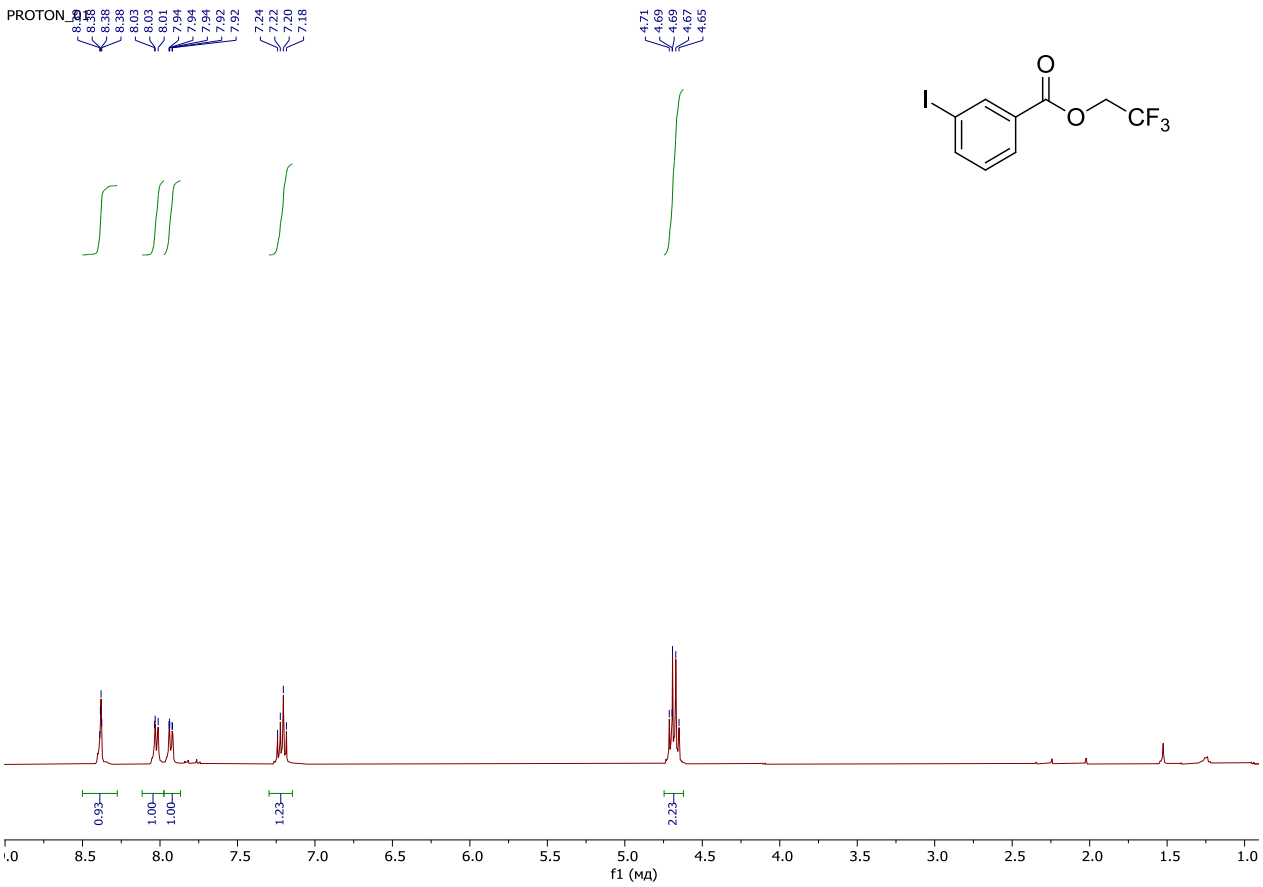


2,2,2-trifluoroethyl 4-iodobenzoate 3a

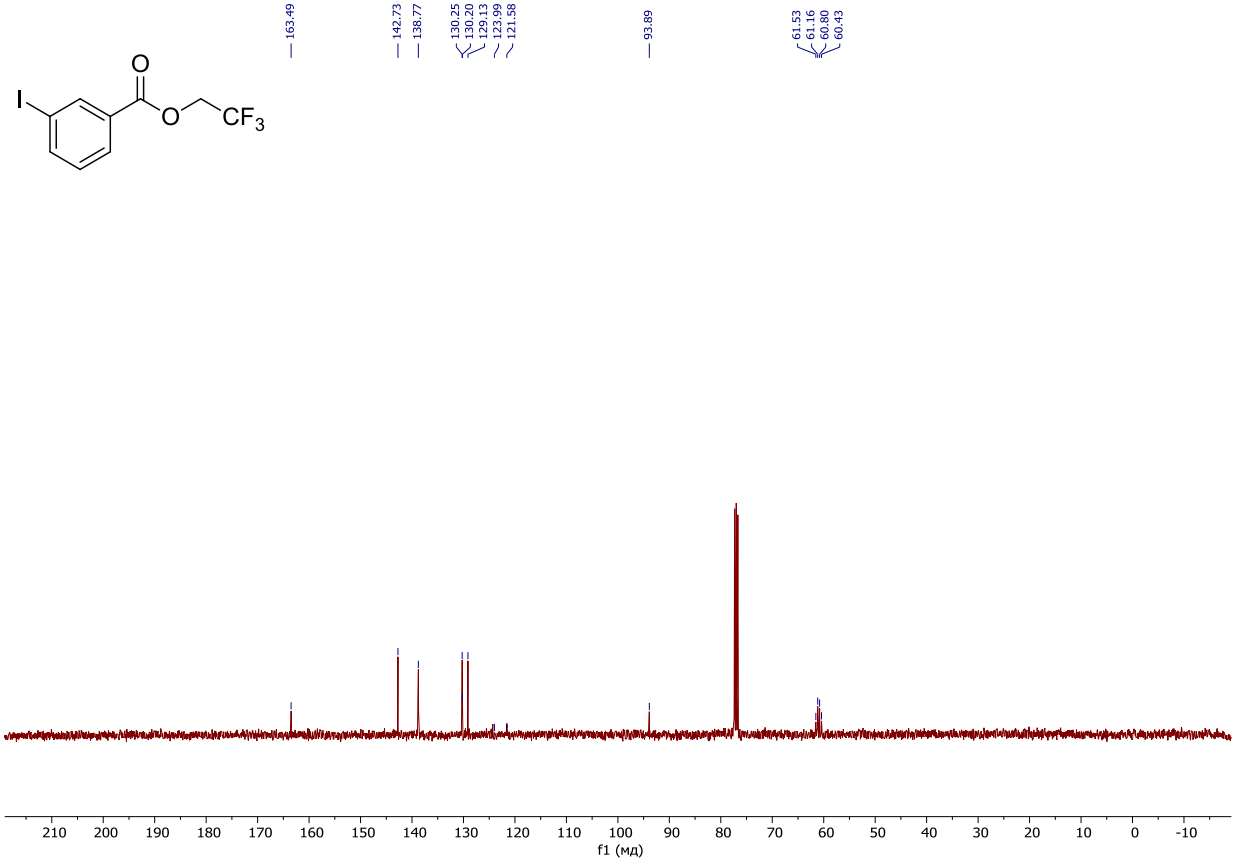
^{19}F NMR (376 MHz, $CDCl_3$)



2,2,2-trifluoroethyl 3-iodobenzoate 3b **^{1}H NMR (400 MHz, $CDCl_3$)**

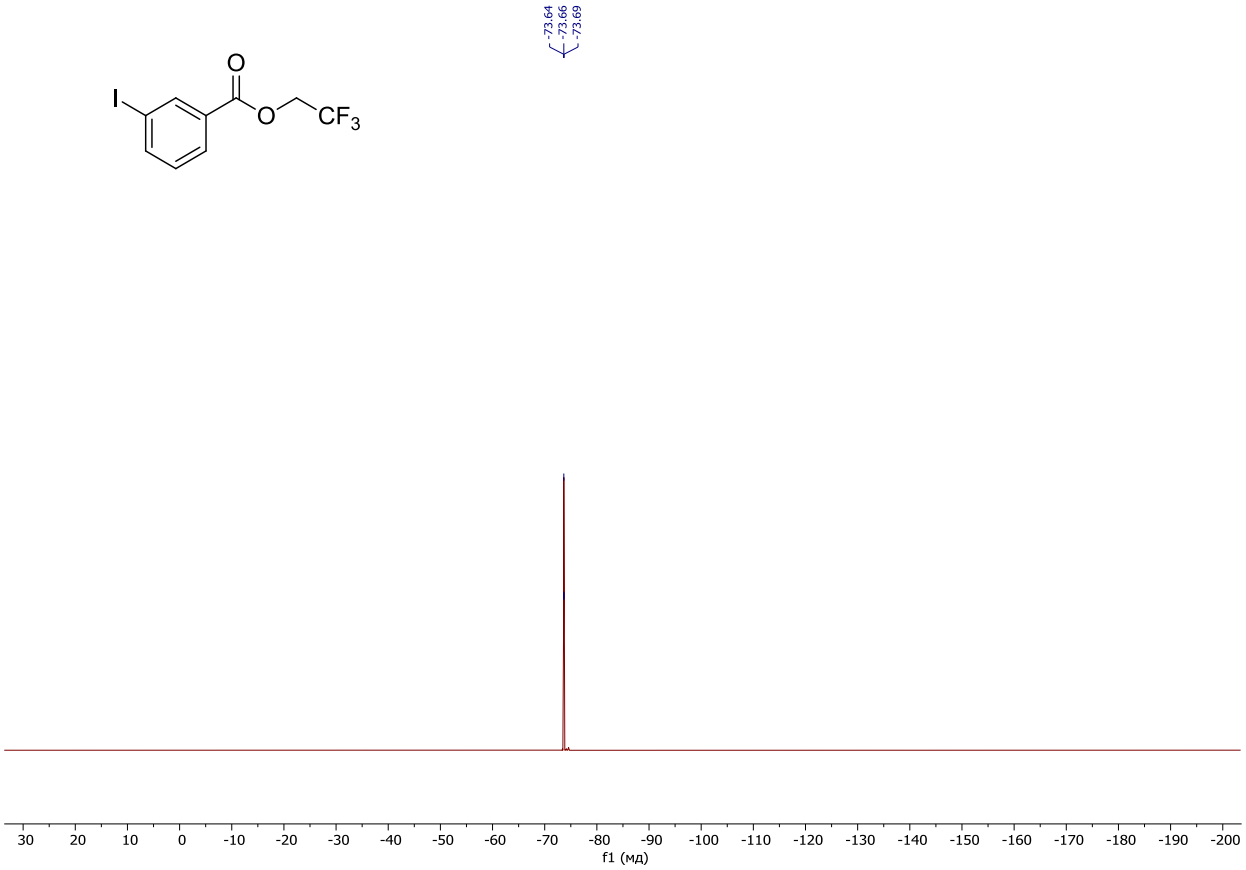


2,2,2-trifluoroethyl 3-iodobenzoate 3b **^{13}C NMR (100 MHz, $CDCl_3$)**

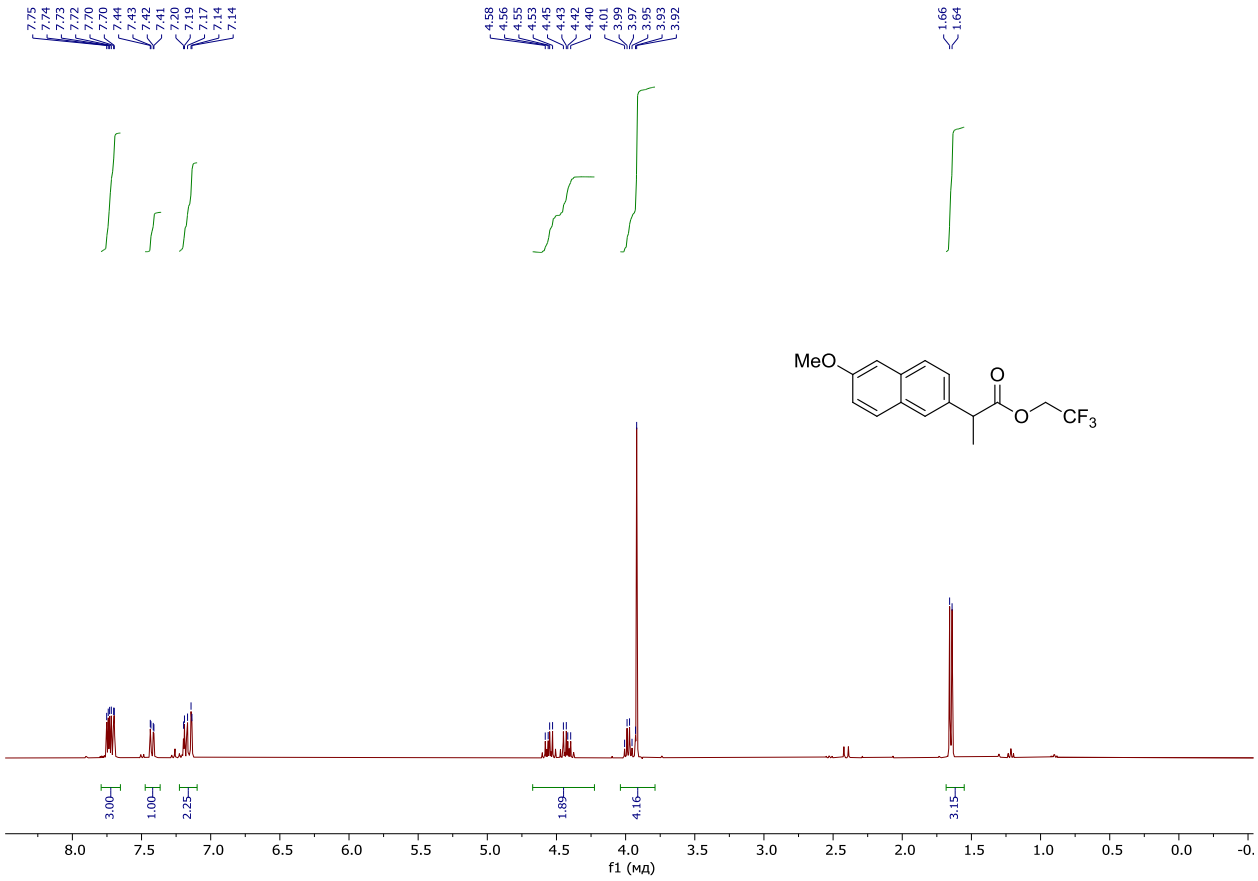


2,2,2-trifluoroethyl 3-iodobenzoate 3b

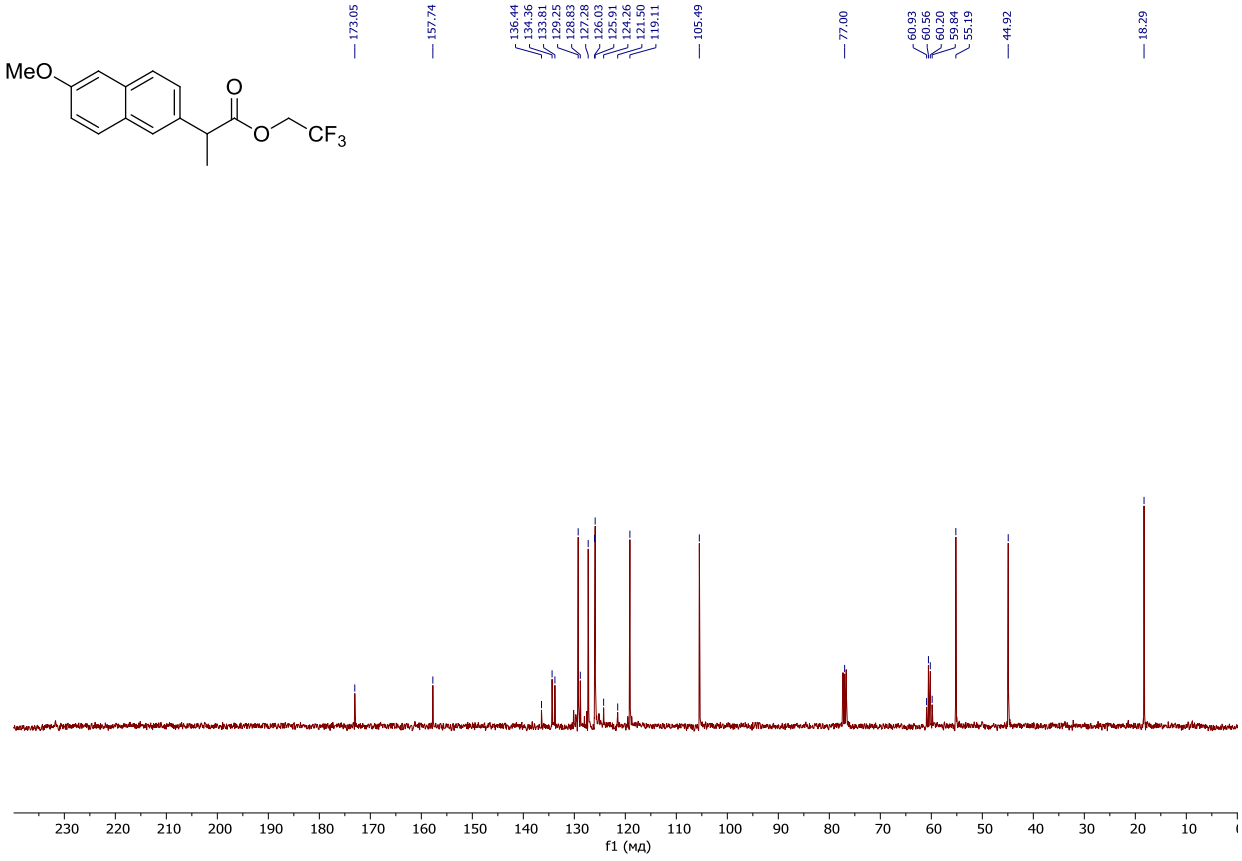
^{19}F NMR (376 MHz, $CDCl_3$)



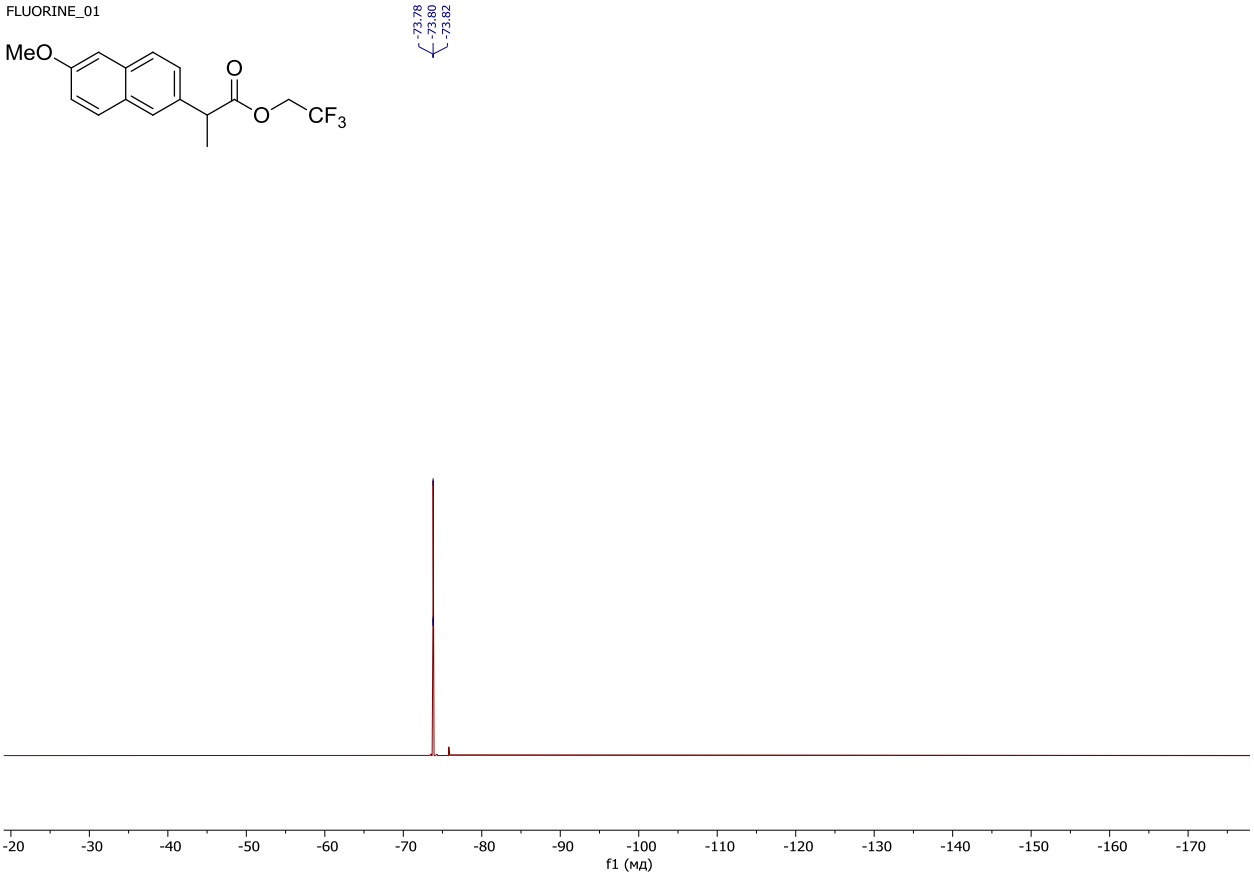
2,2,2-trifluoroethyl 2-(6-methoxy-2-naphthyl)propanoate 3c **^{1}H NMR (400 MHz, $CDCl_3$)**



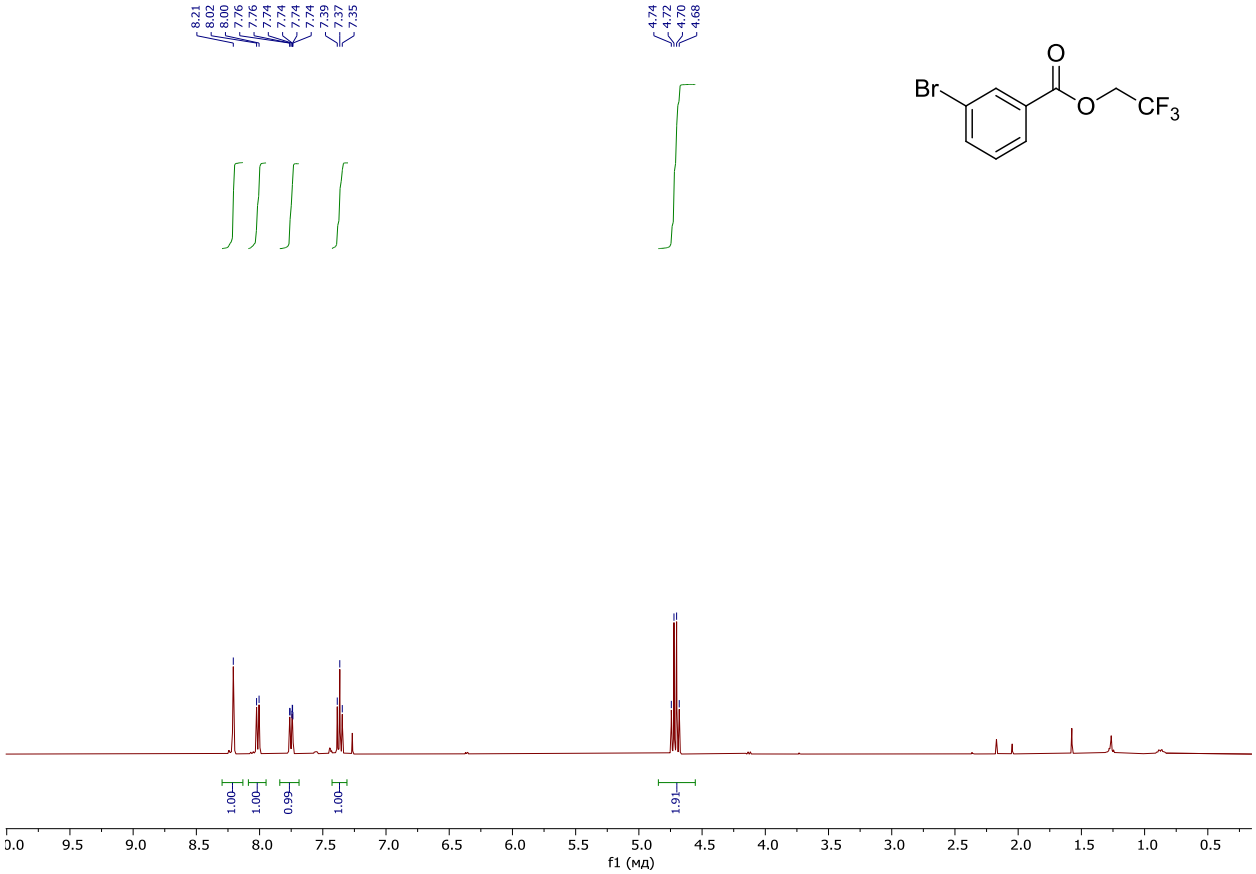
2,2,2-trifluoroethyl 2-(6-methoxy-2-naphthyl)propanoate 3c **^{13}C NMR (100 MHz, $CDCl_3$)**



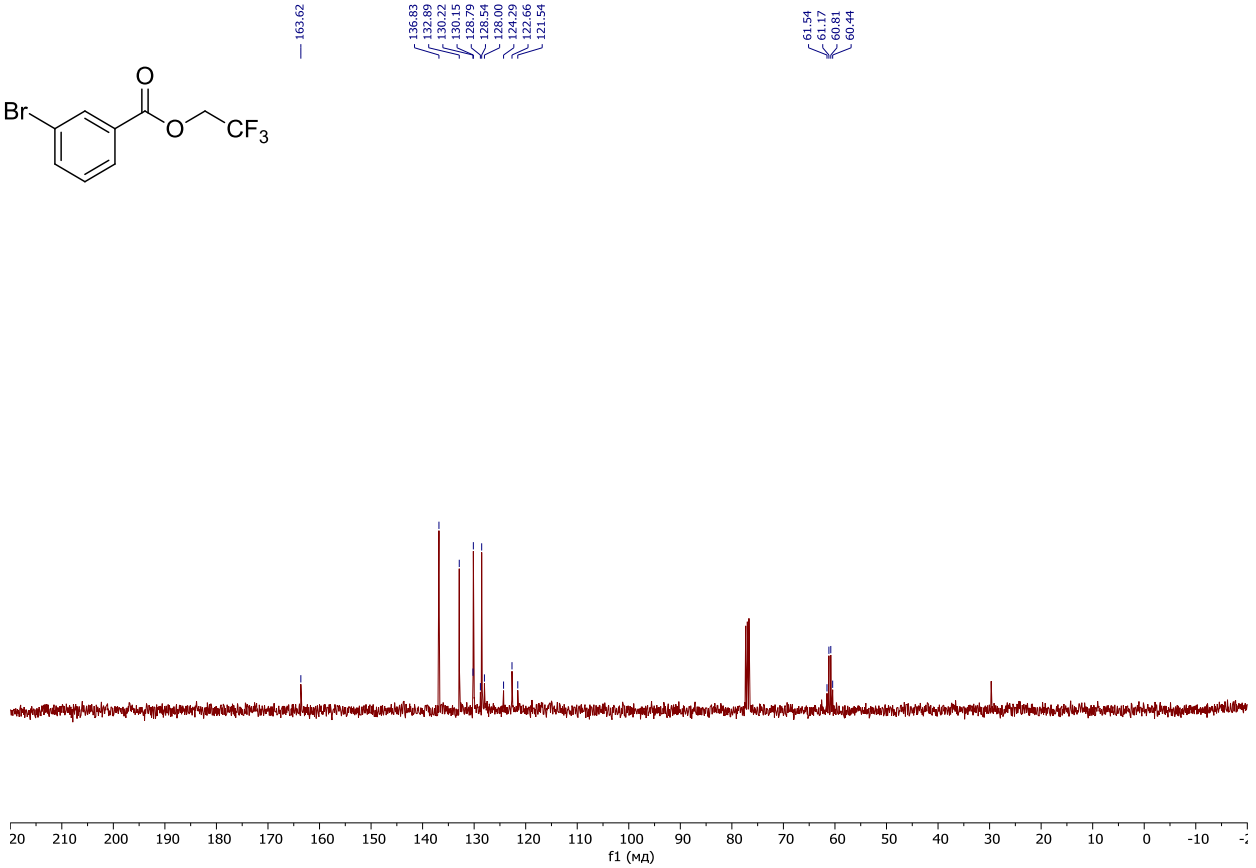
2,2,2-trifluoroethyl 2-(6-methoxy-2-naphthyl)propanoate 3c **^{19}F NMR (376 MHz, $CDCl_3$)**



2,2,2-trifluoroethyl 3-bromobenzoate 3d **^{1}H NMR (400 MHz, $CDCl_3$)**

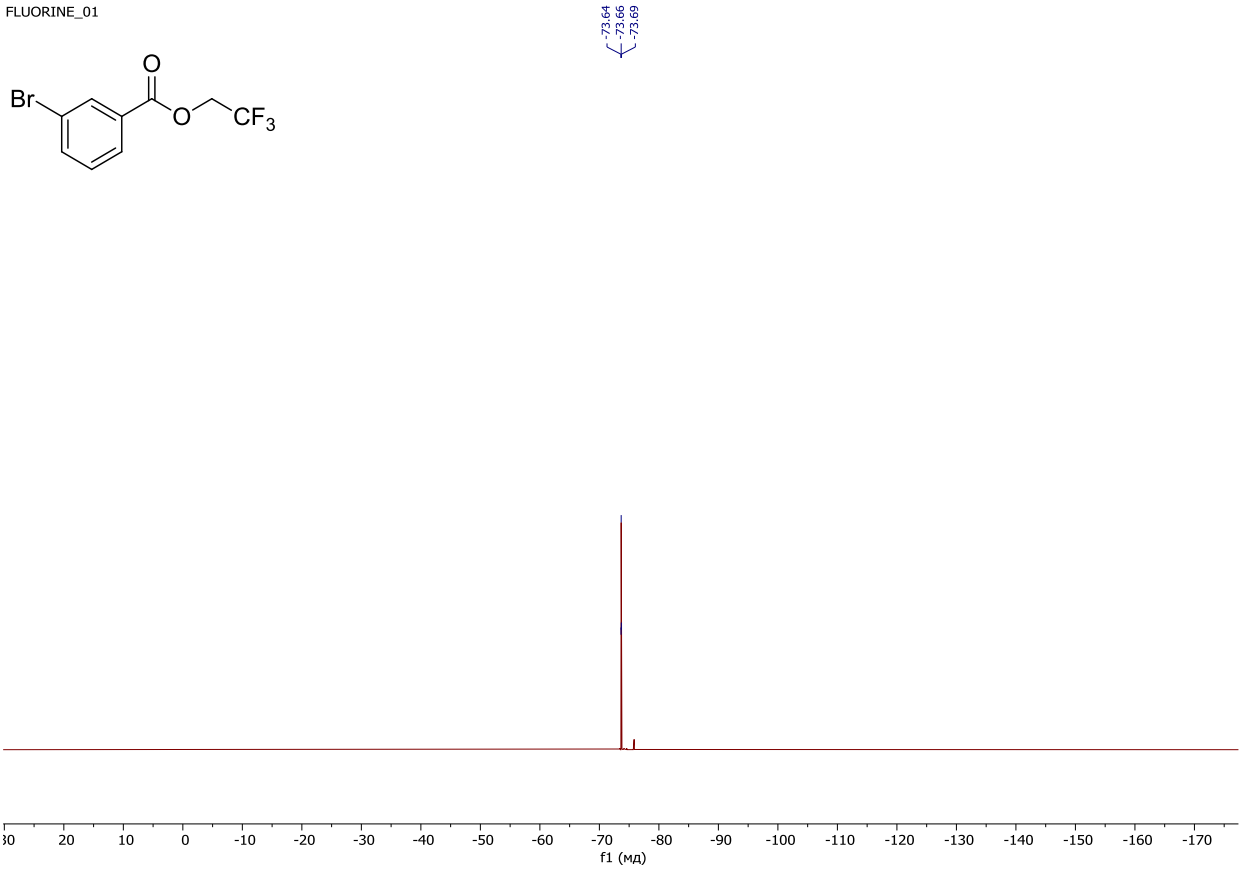


2,2,2-trifluoroethyl 3-bromobenzoate 3d **^{13}C NMR (100 MHz, $CDCl_3$)**

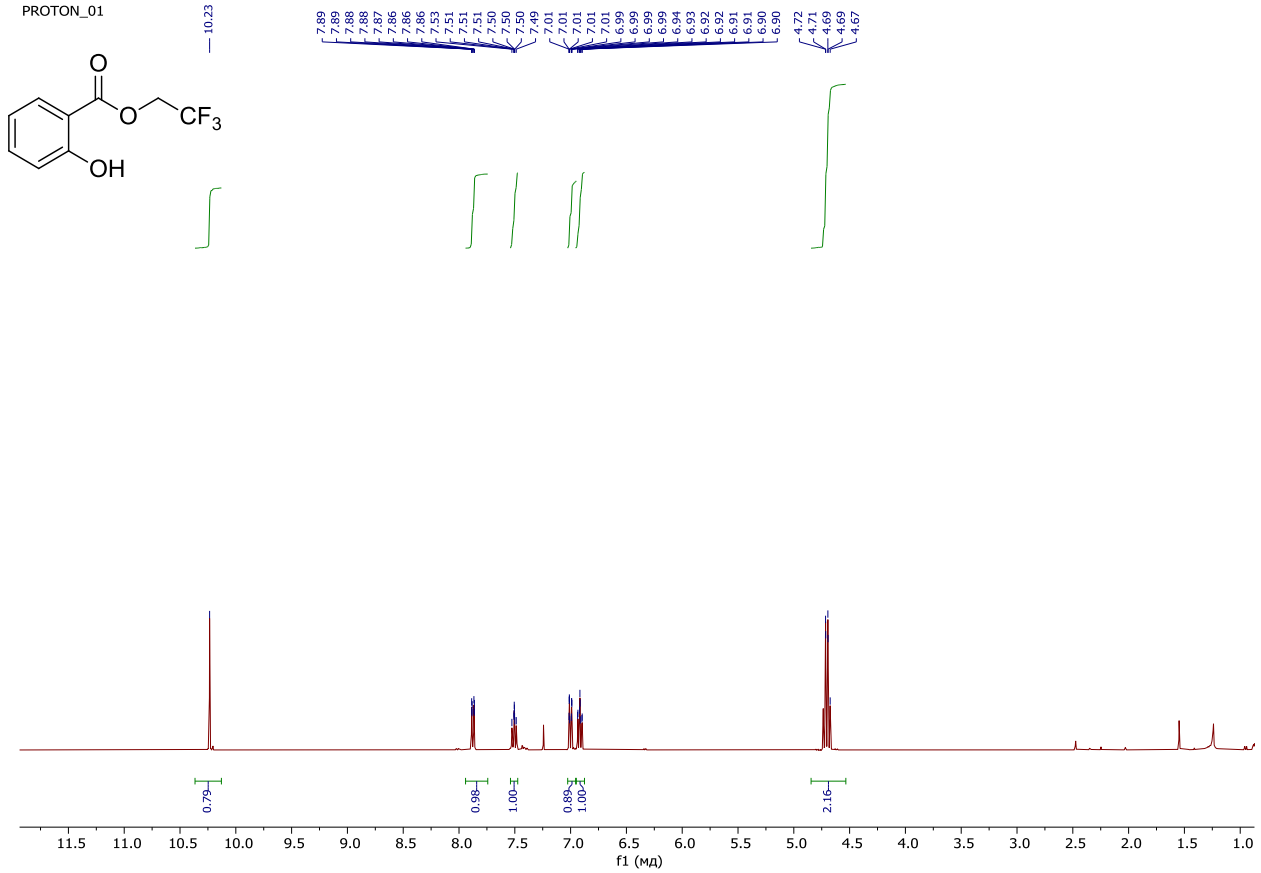


2,2,2-trifluoroethyl 3-bromobenzoate 3d

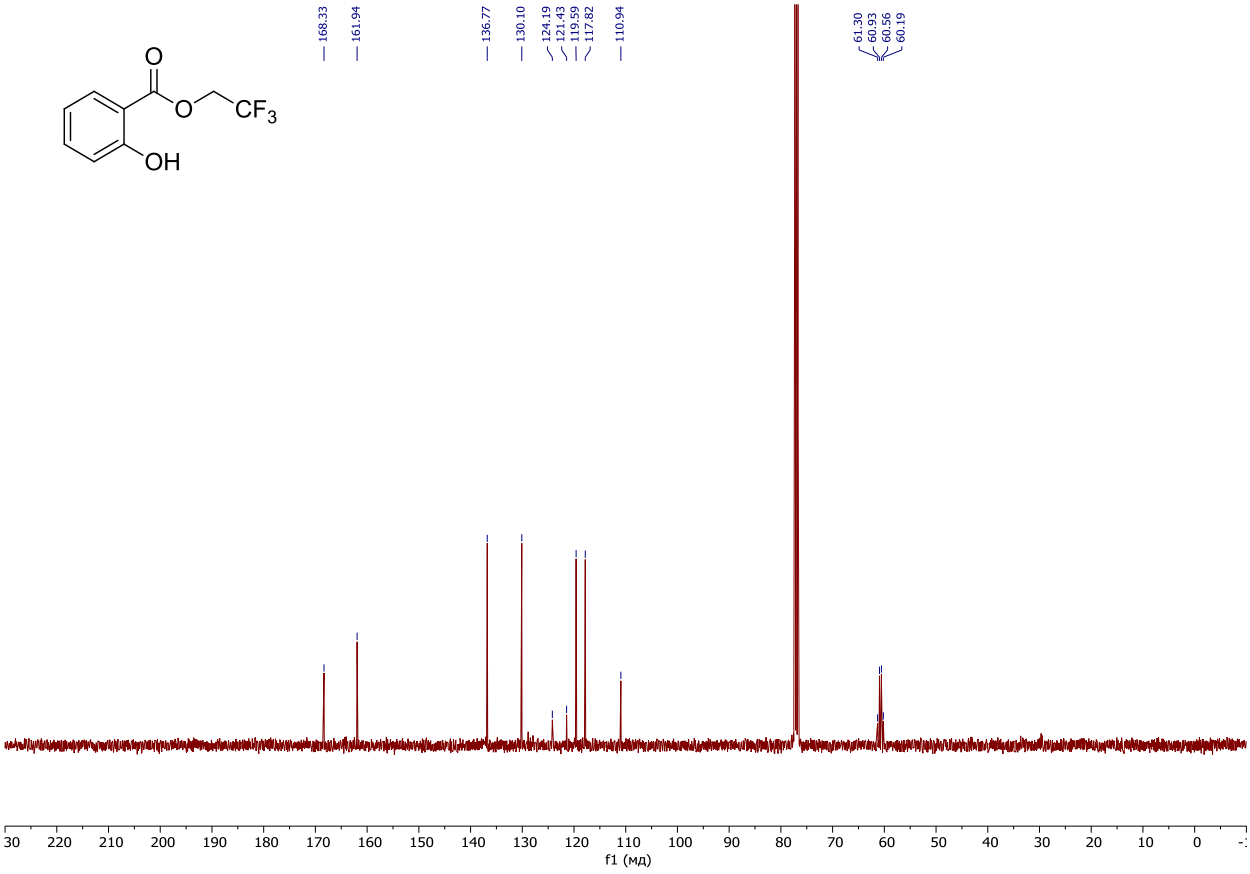
^{19}F NMR (376 MHz, $CDCl_3$)



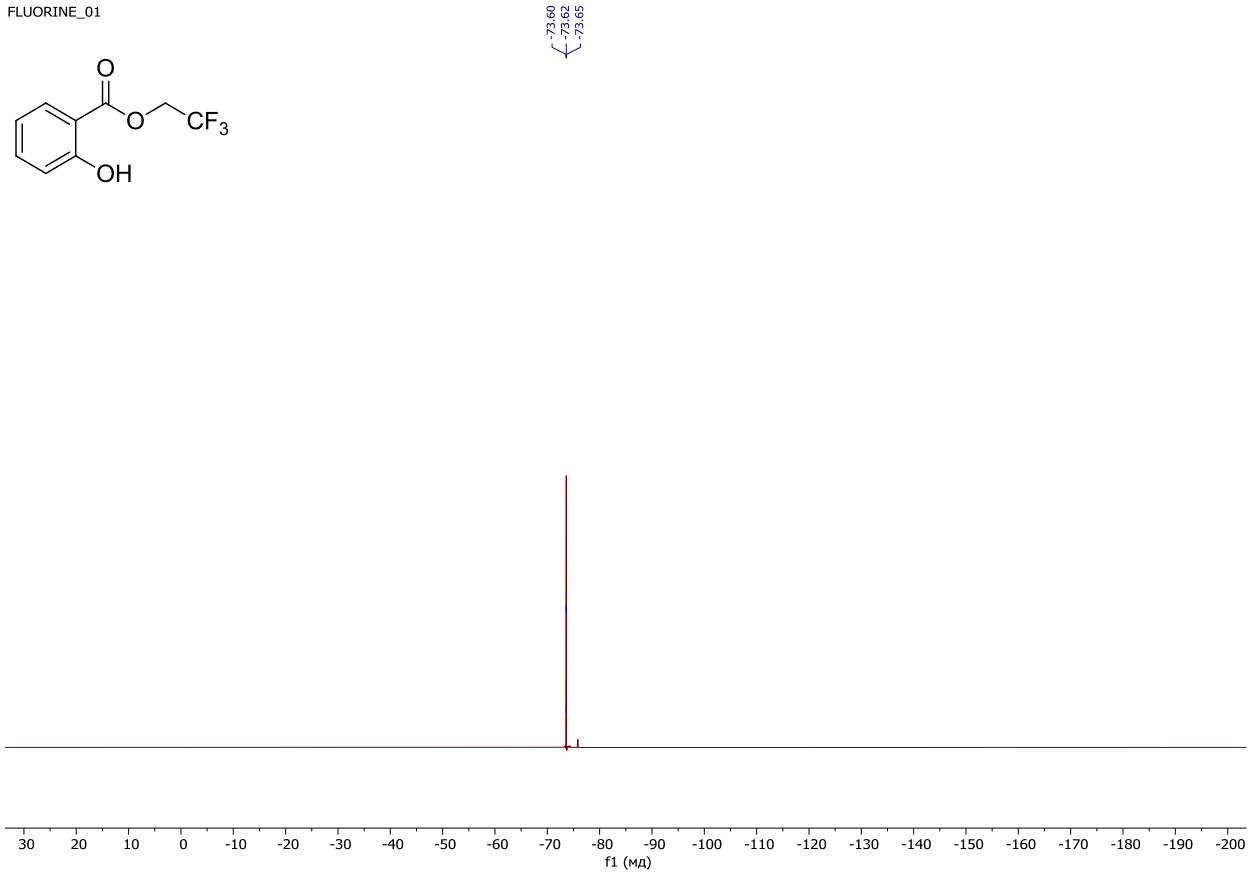
2,2,2-trifluoroethyl 2-hydroxybenzoate 3e **^{1}H NMR (400 MHz, $CDCl_3$)**



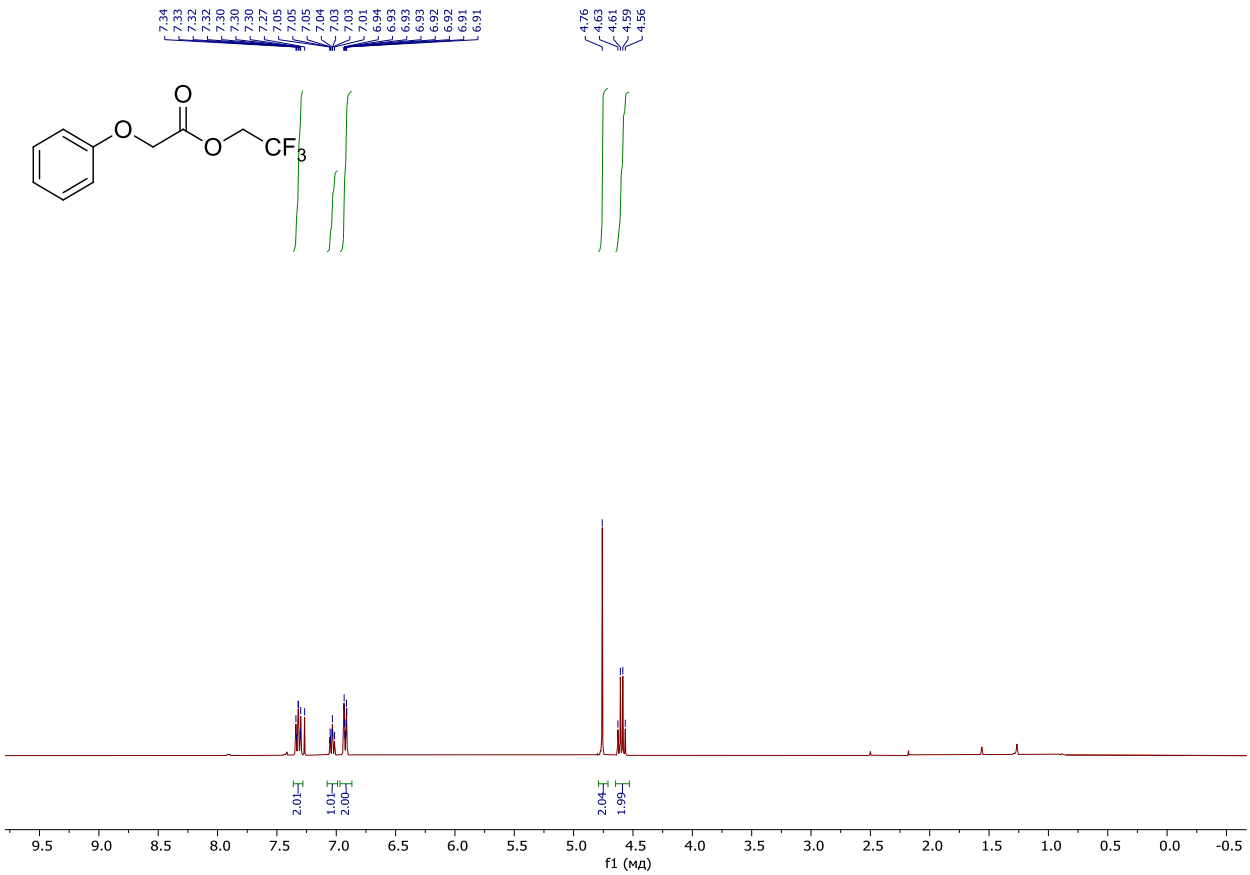
2,2,2-trifluoroethyl 2-hydroxybenzoate 3e **^{13}C NMR (100 MHz, $CDCl_3$)**



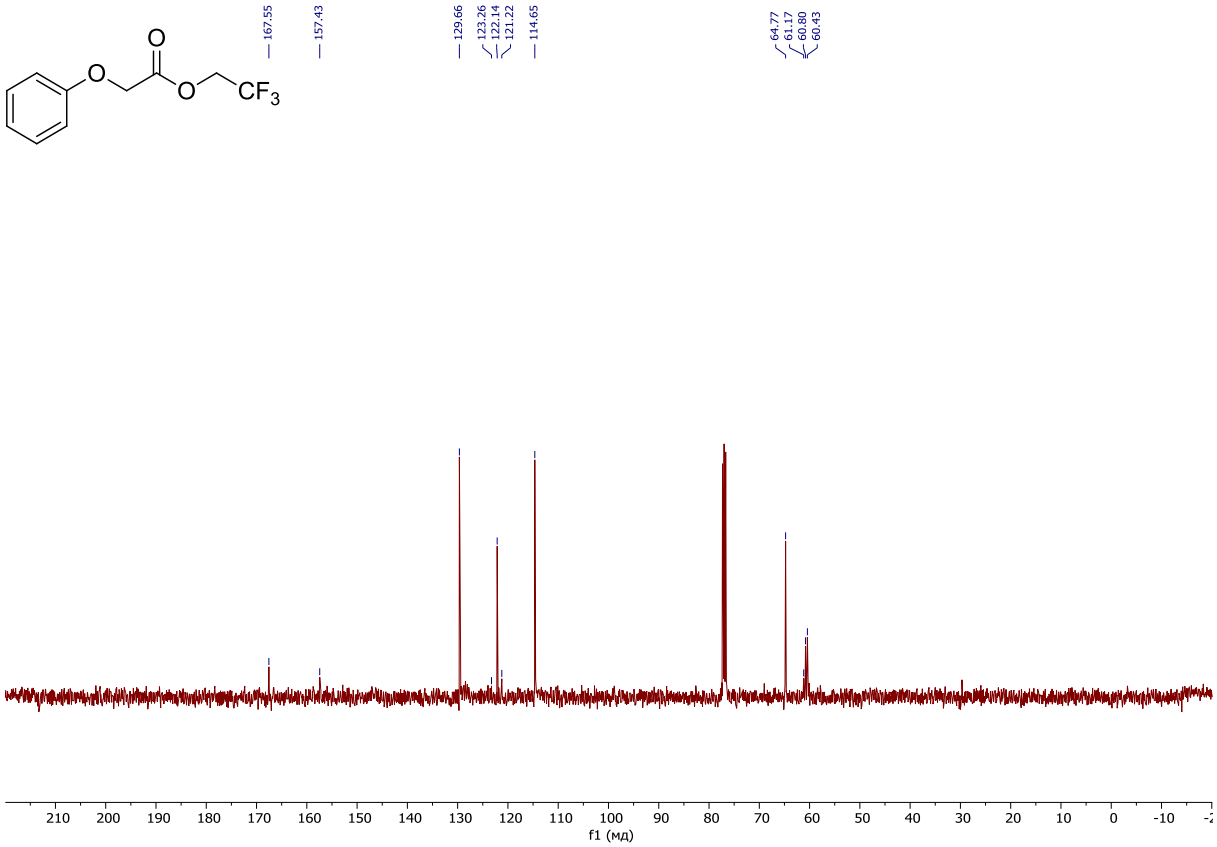
2,2,2-trifluoroethyl 2-hydroxybenzoate 3e **^{19}F NMR (376 MHz, $CDCl_3$)**



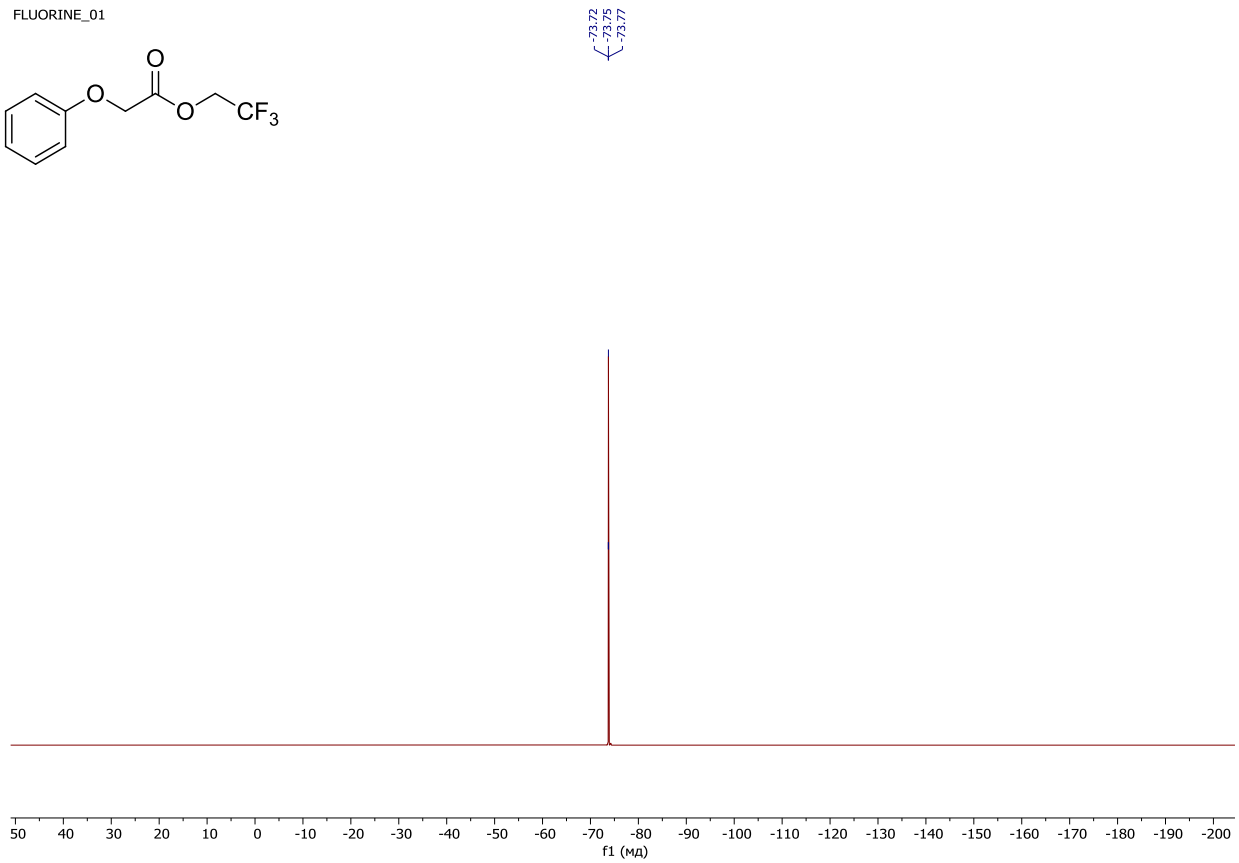
2,2,2-trifluoroethyl phenoxyacetate 3f **^{1}H NMR (400 MHz, $CDCl_3$)**



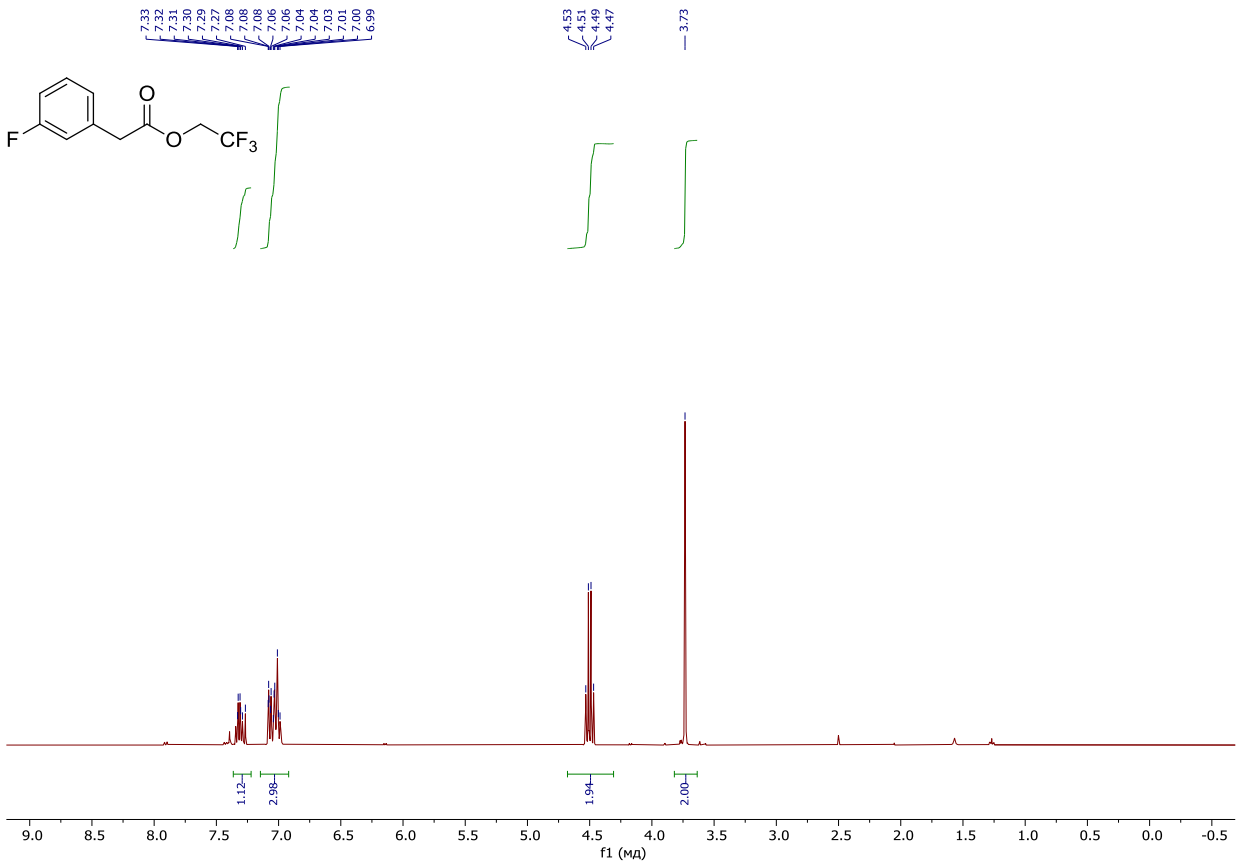
2,2,2-trifluoroethyl phenoxyacetate 3f **^{13}C NMR (100 MHz, $CDCl_3$)**



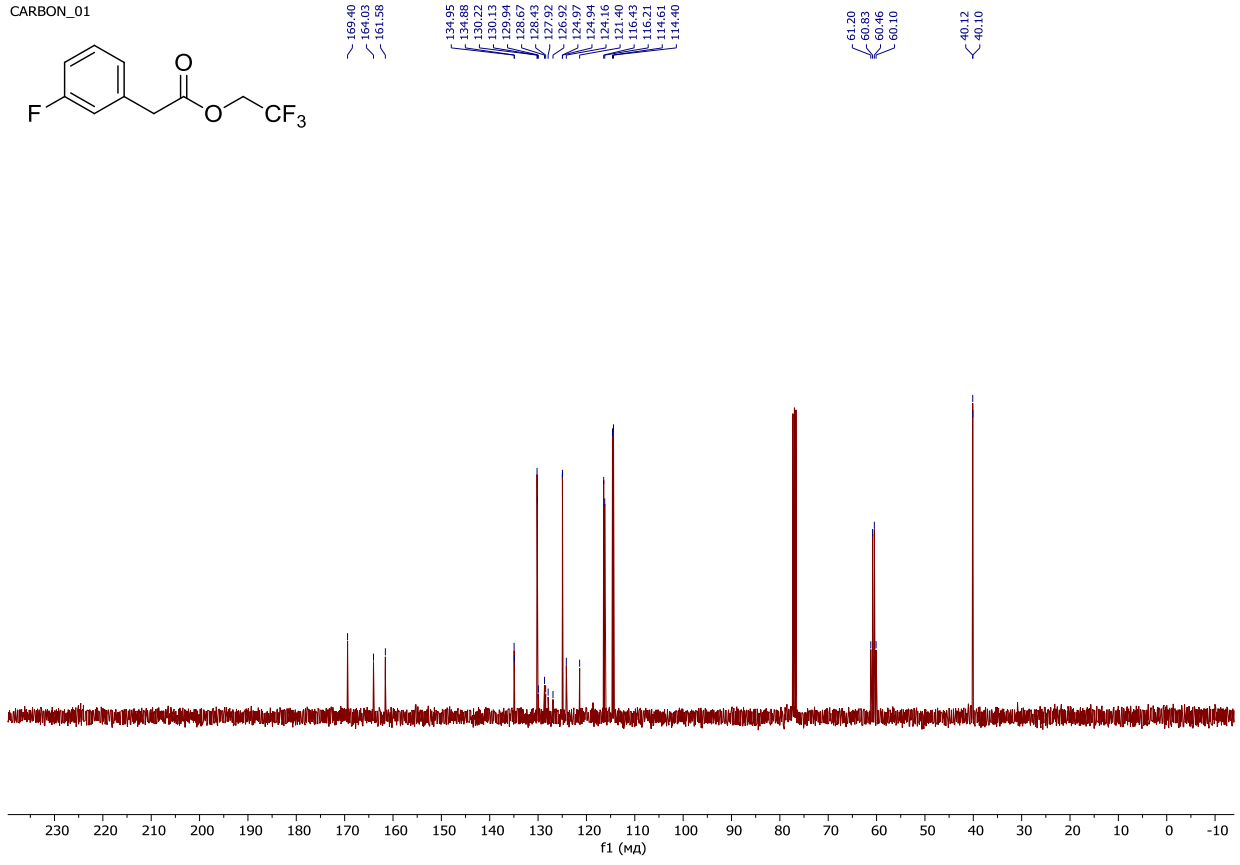
2,2,2-trifluoroethyl phenoxyacetate 3f **^{19}F NMR (376 MHz, $CDCl_3$)**



2,2,2-trifluoroethyl (3-fluorophenyl)acetate 3g **^{1}H NMR (400 MHz, $CDCl_3$)**



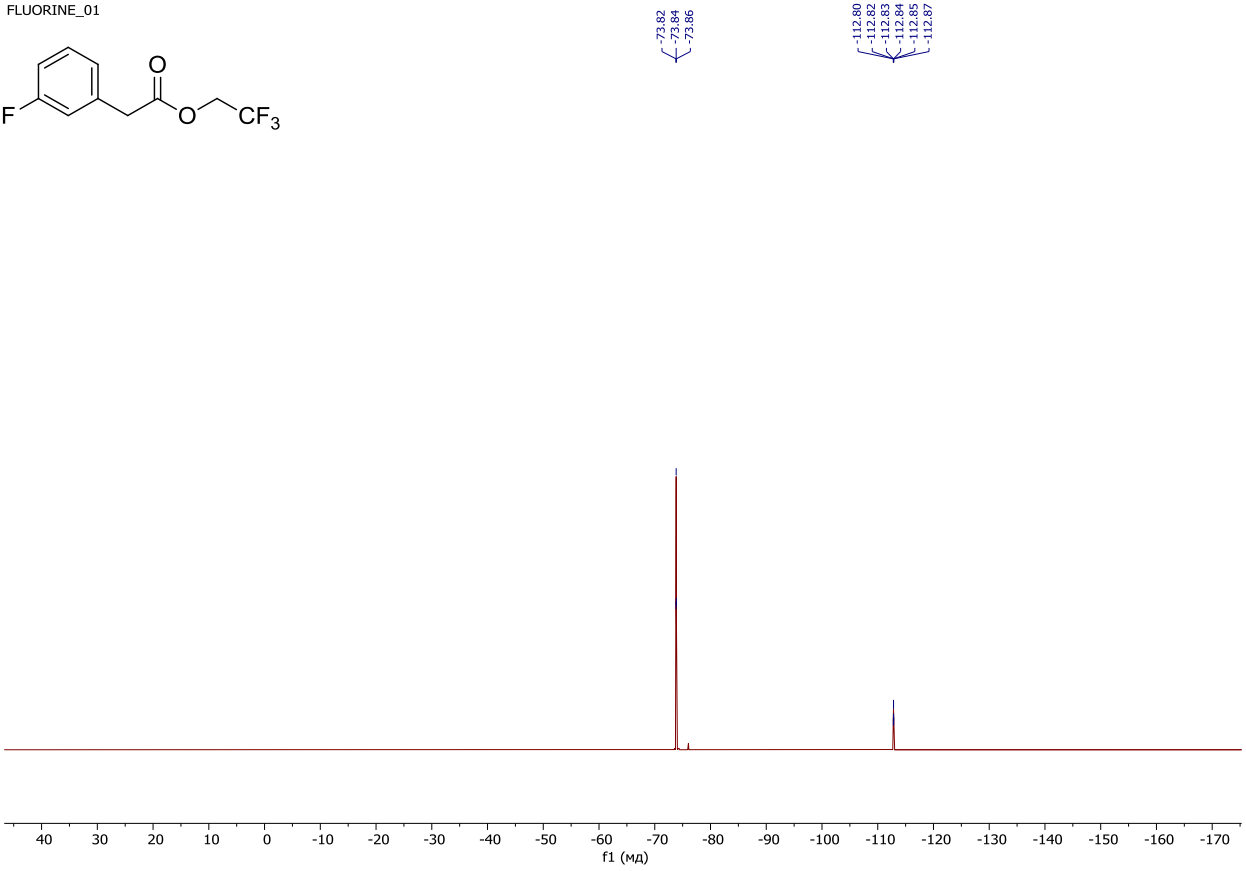
2,2,2-trifluoroethyl (3-fluorophenyl)acetate 3g **^{13}C NMR (100 MHz, $CDCl_3$)**



2,2,2-trifluoroethyl (3-fluorophenyl)acetate 3g

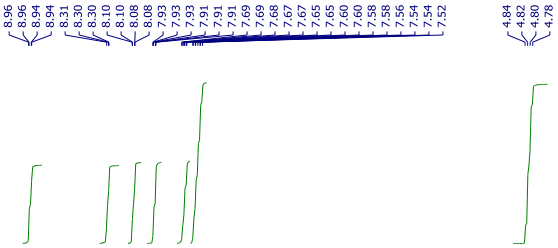
^{19}F NMR (376 MHz, $CDCl_3$)

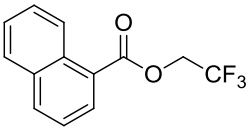
FLUORINE_01

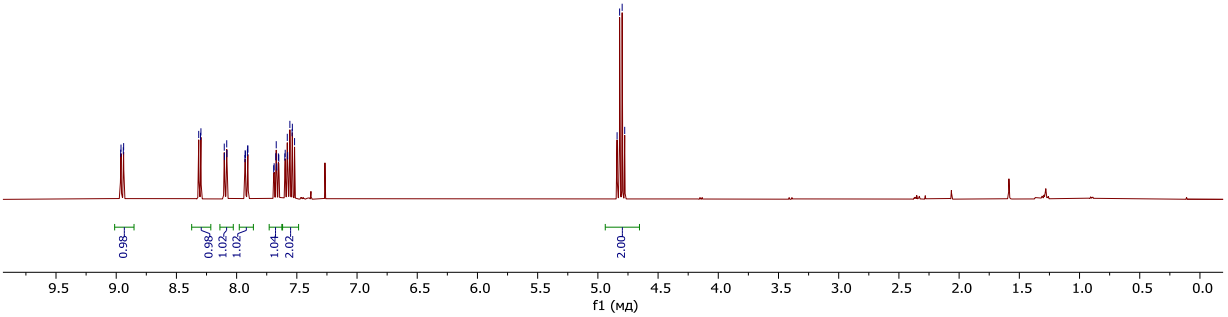


2,2,2-trifluoroethyl 1-naphthoate 3h

^{1}H NMR (400 MHz, $CDCl_3$)



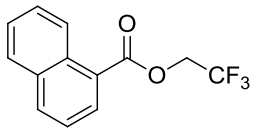


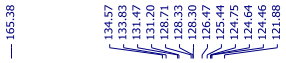


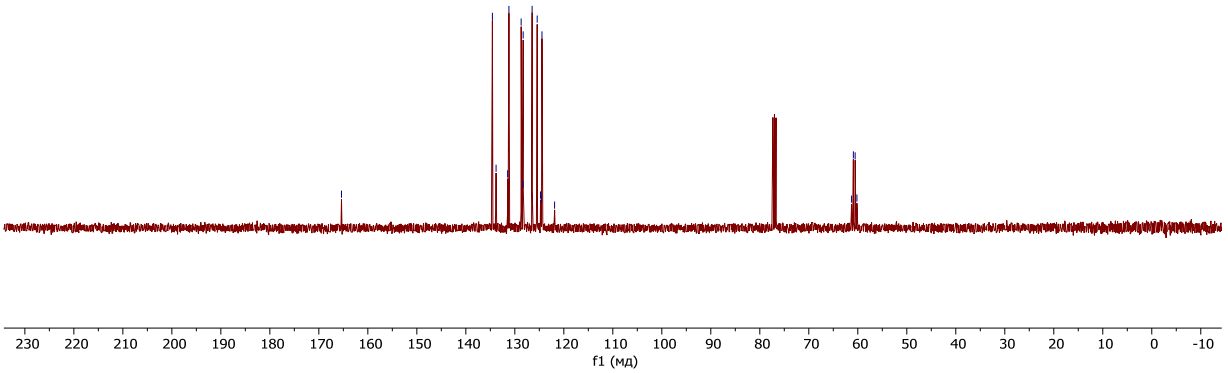
2,2,2-trifluoroethyl 1-naphthoate 3h

^{13}C NMR (100 MHz, $CDCl_3$)

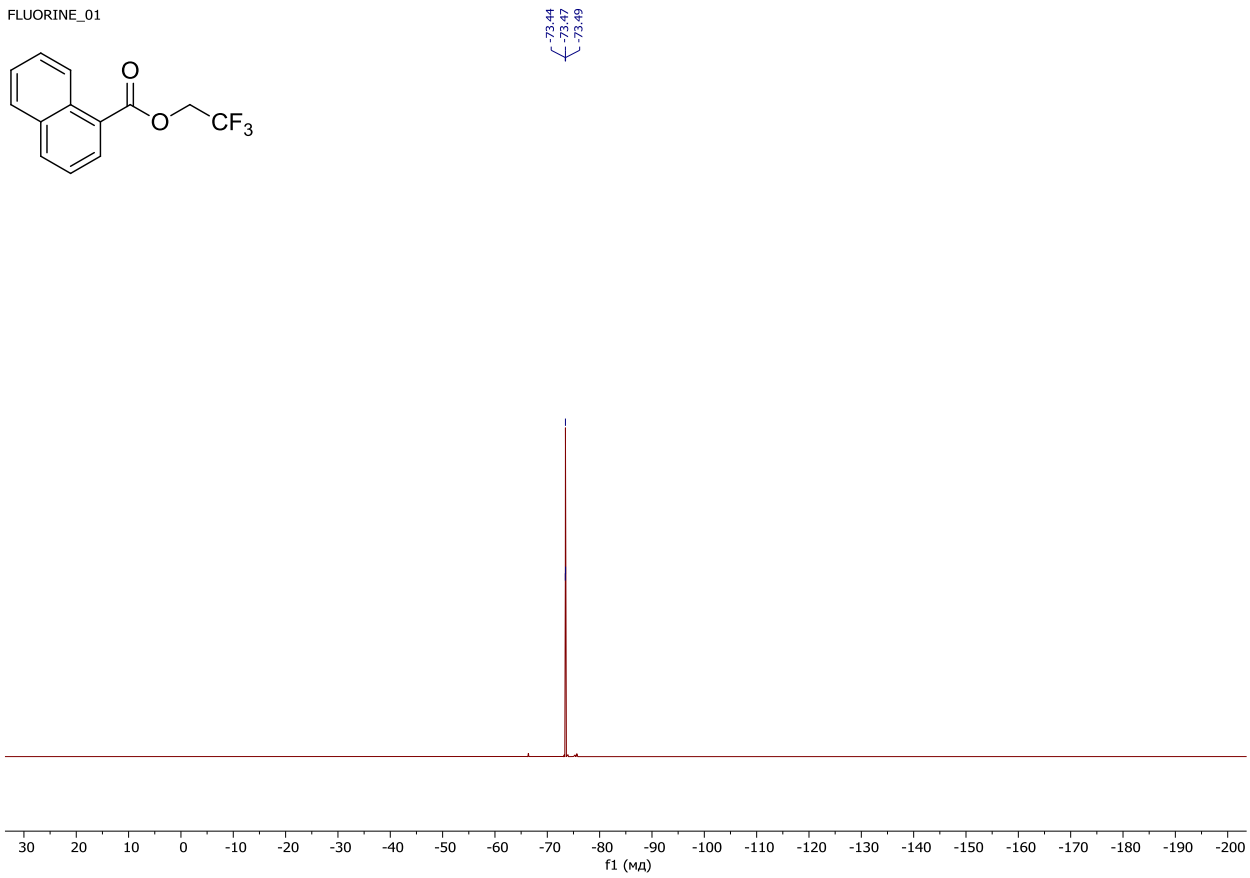
CARBON_01



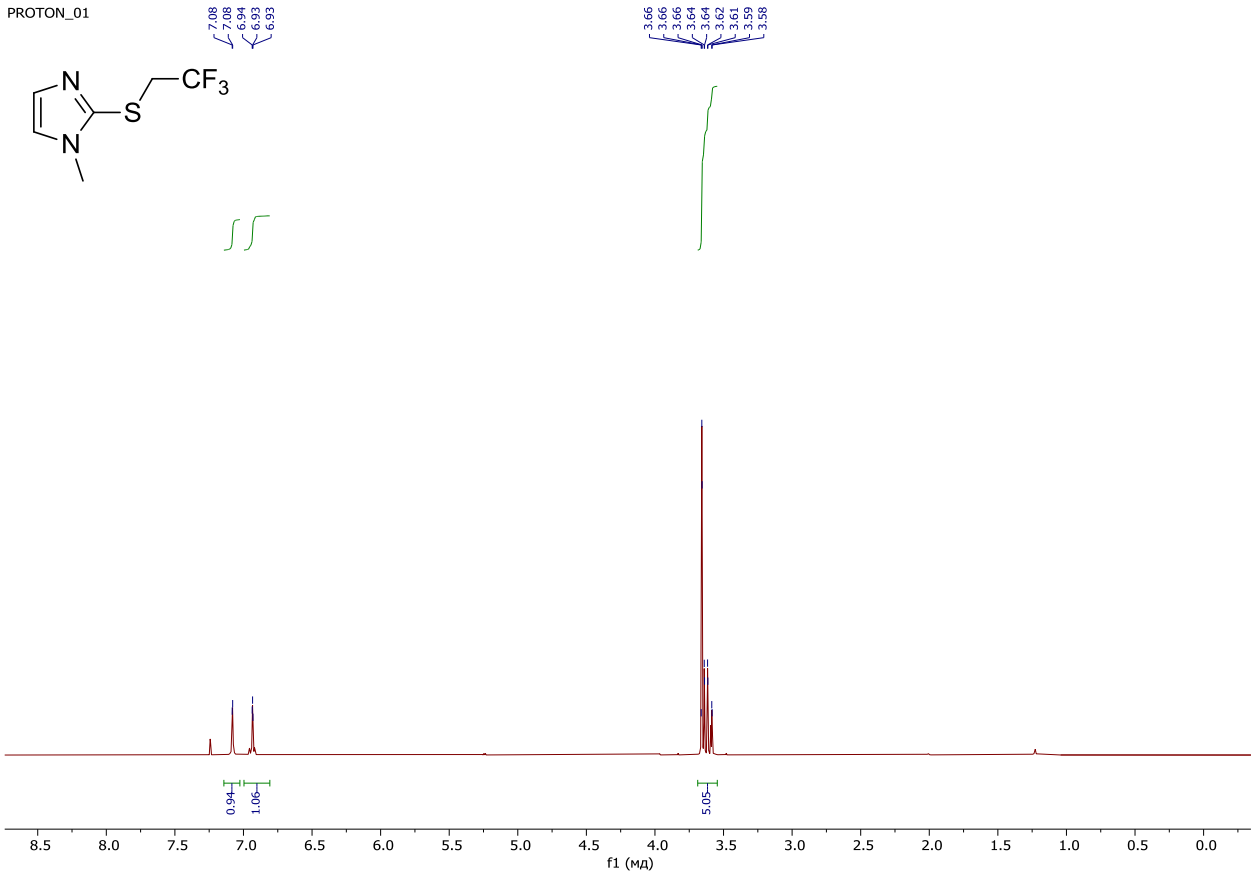




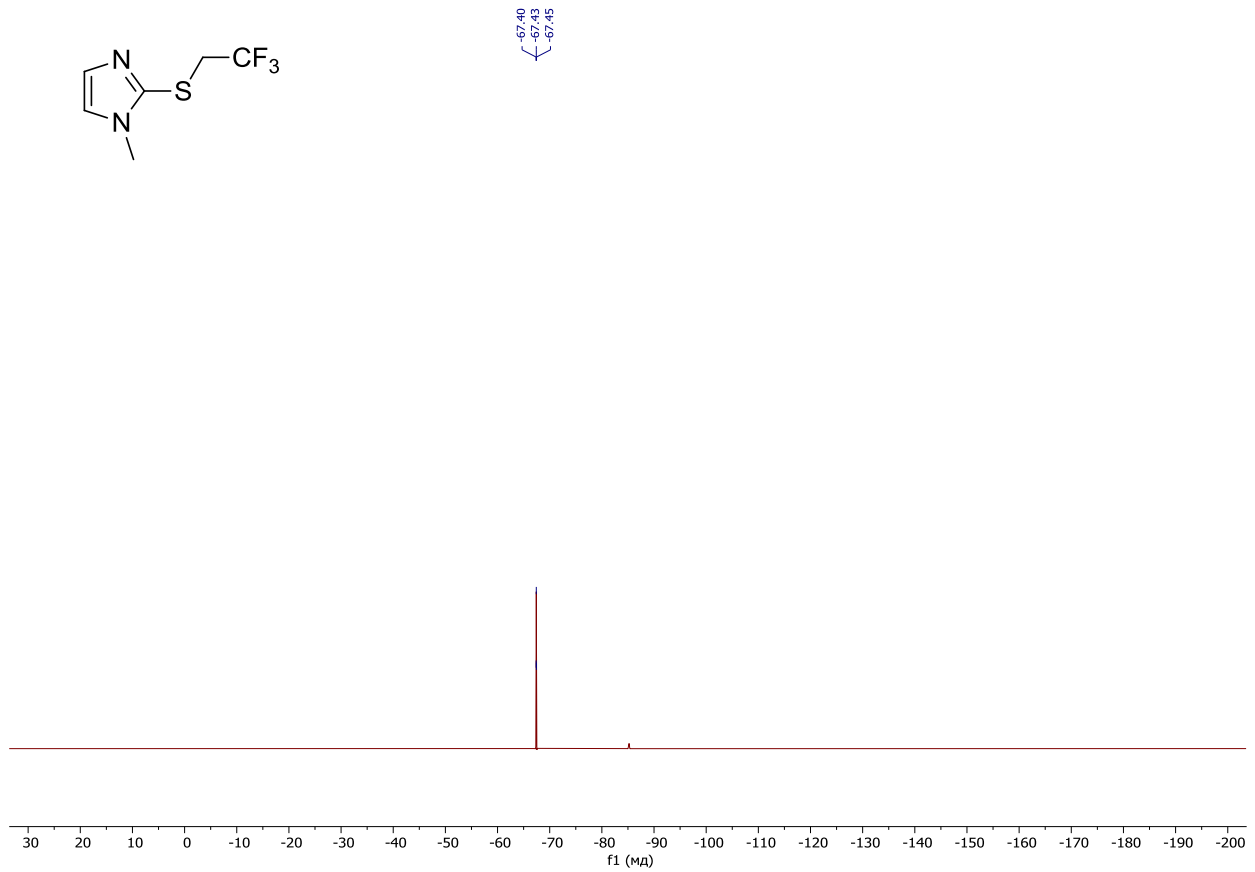
2,2,2-trifluoroethyl 1-naphthoate 3h **^{19}F NMR (376 MHz, $CDCl_3$)**



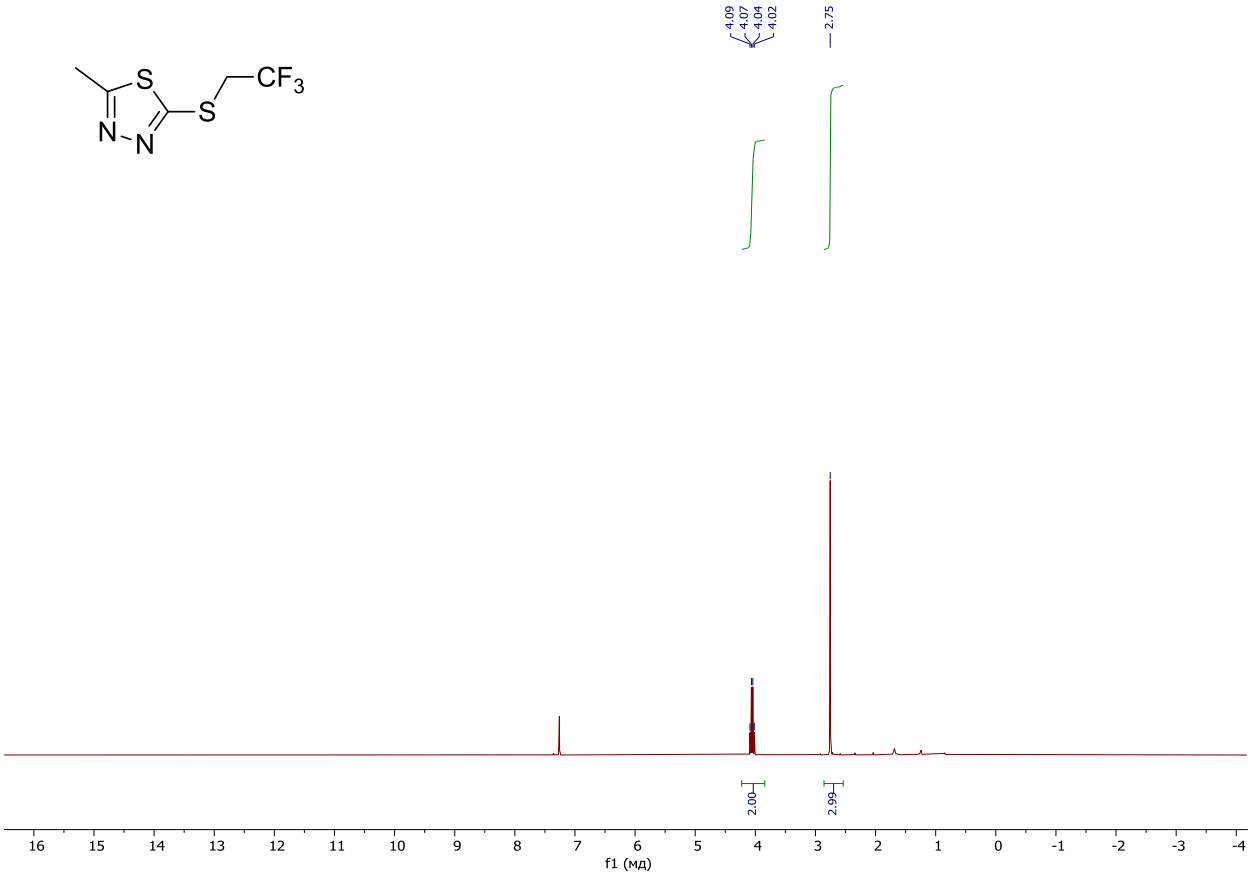
1-methyl-2-[(2,2,2-trifluoroethyl)thio]-1H-imidazole 4a **^{1}H NMR (400 MHz, $CDCl_3$)**



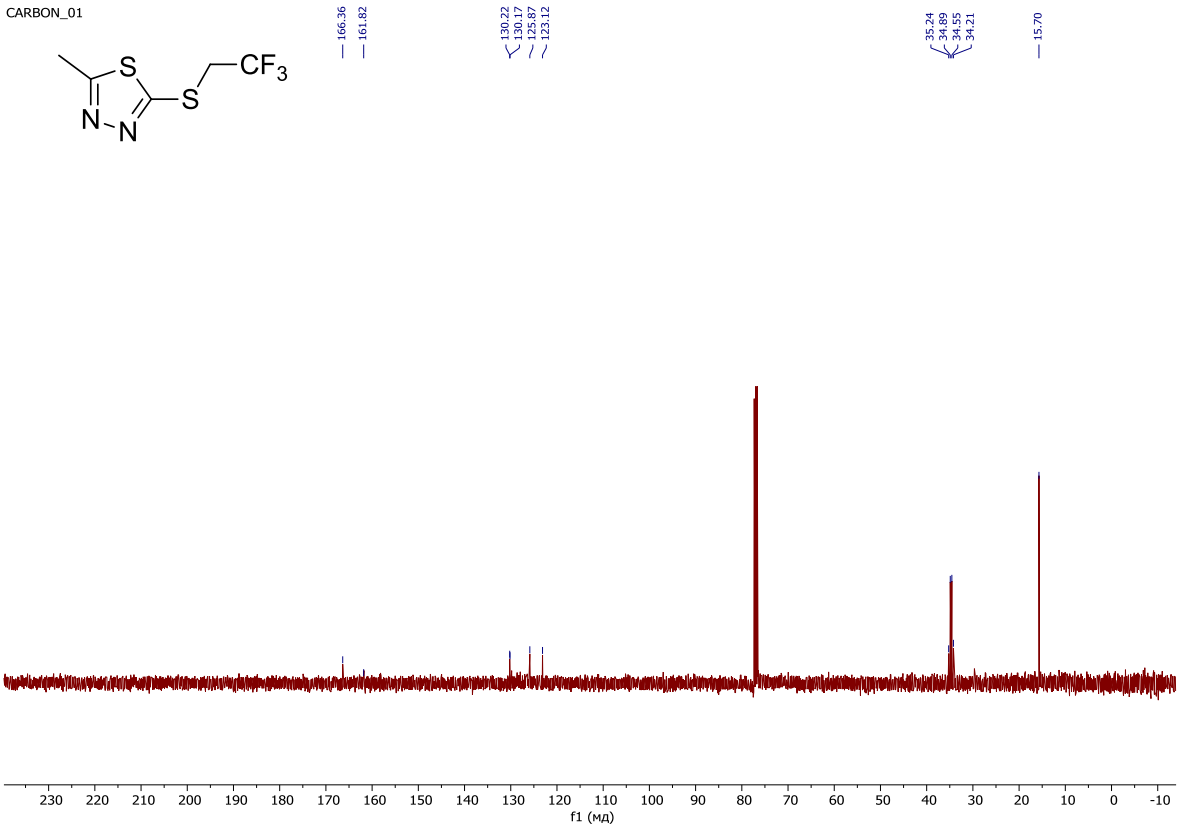
1-methyl-2-[(2,2,2-trifluoroethyl)thio]-1H-imidazole 4a **^{19}F NMR (376 MHz, $CDCl_3$)**



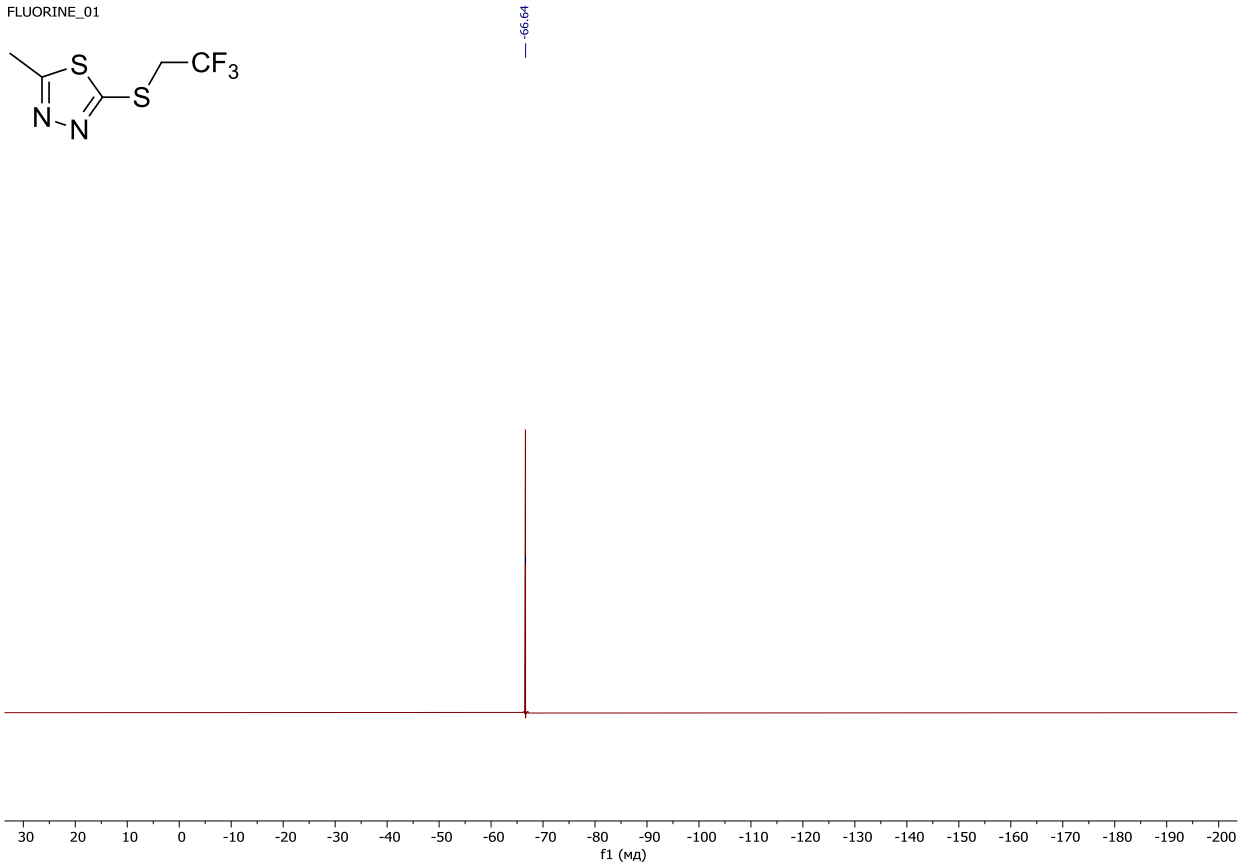
2-methyl-5-[(2,2,2-trifluoroethyl)thio]-1,3,4-thiadiazole 4b **^{1}H NMR (400 MHz, $CDCl_3$)**



2-methyl-5-[(2,2,2-trifluoroethyl)thio]-1,3,4-thiadiazole 4b **^{13}C NMR (100 MHz, $CDCl_3$)**

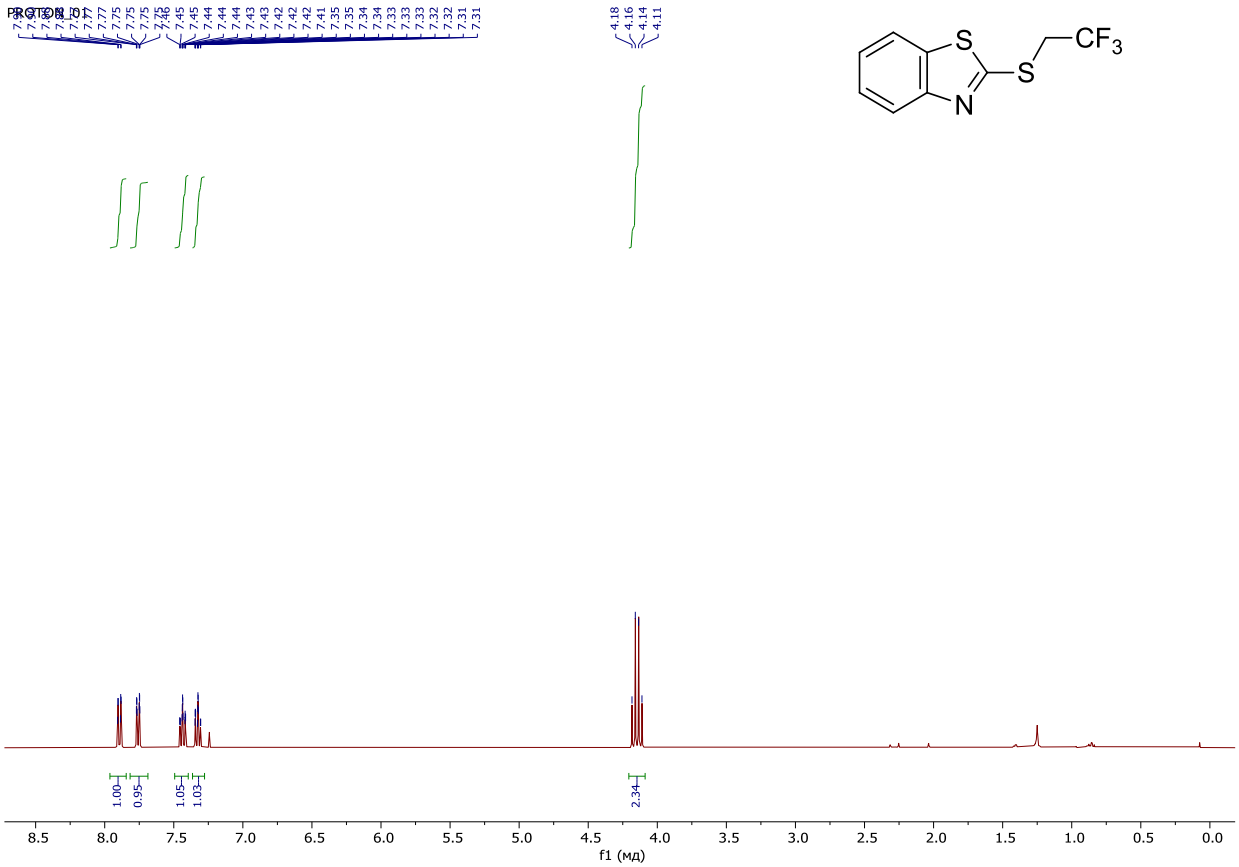


2-methyl-5-[(2,2,2-trifluoroethyl)thio]-1,3,4-thiadiazole 4b **^{19}F NMR (376 MHz, $CDCl_3$)**



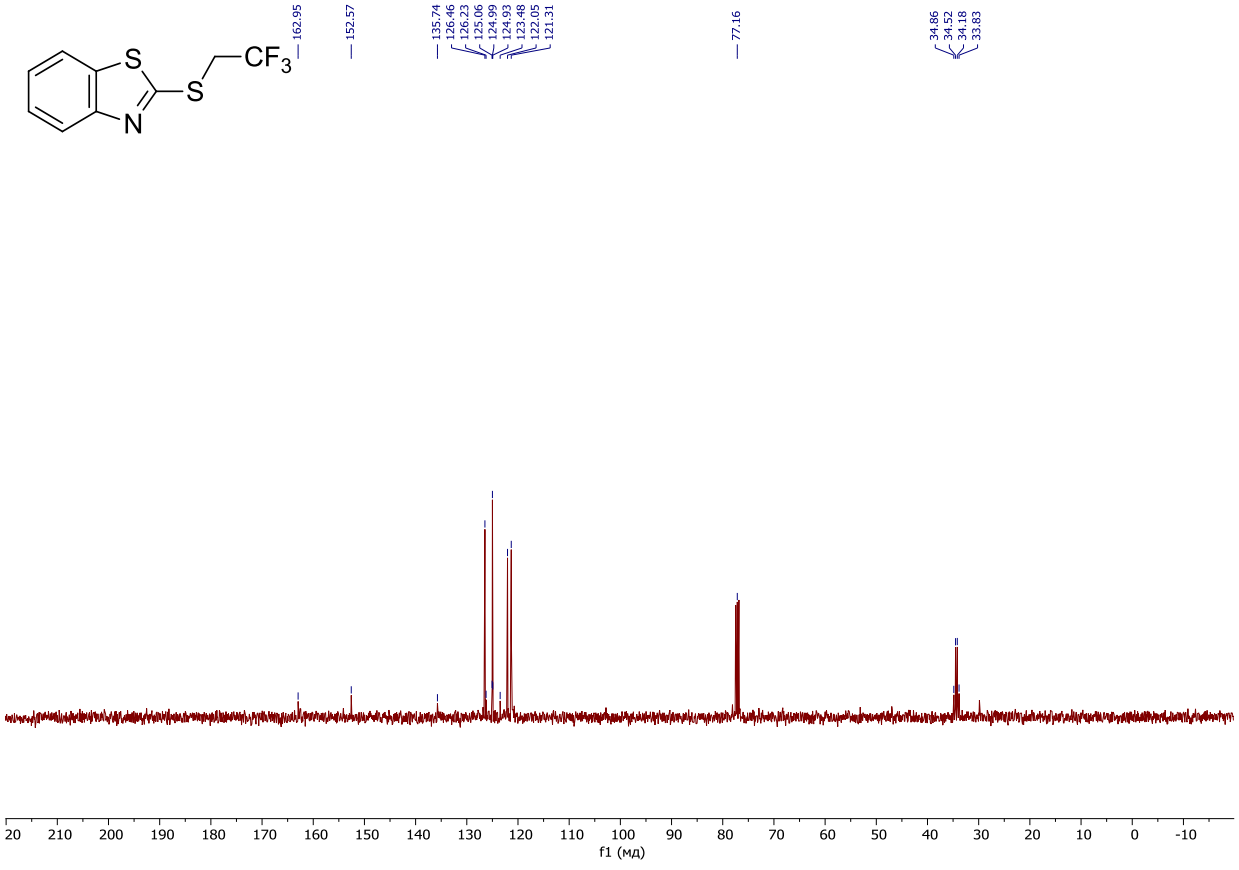
2-[(2,2,2-trifluoroethyl)thio]-1,3-benzothiazole 4c

^{1}H NMR (400 MHz, $CDCl_3$)



2-[(2,2,2-trifluoroethyl)thio]-1,3-benzothiazole 4c

^{13}C NMR (100 MHz, $CDCl_3$)



2-[(2,2,2-trifluoroethyl)thio]-1,3-benzothiazole 4c

^{19}F NMR (376 MHz, $CDCl_3$)

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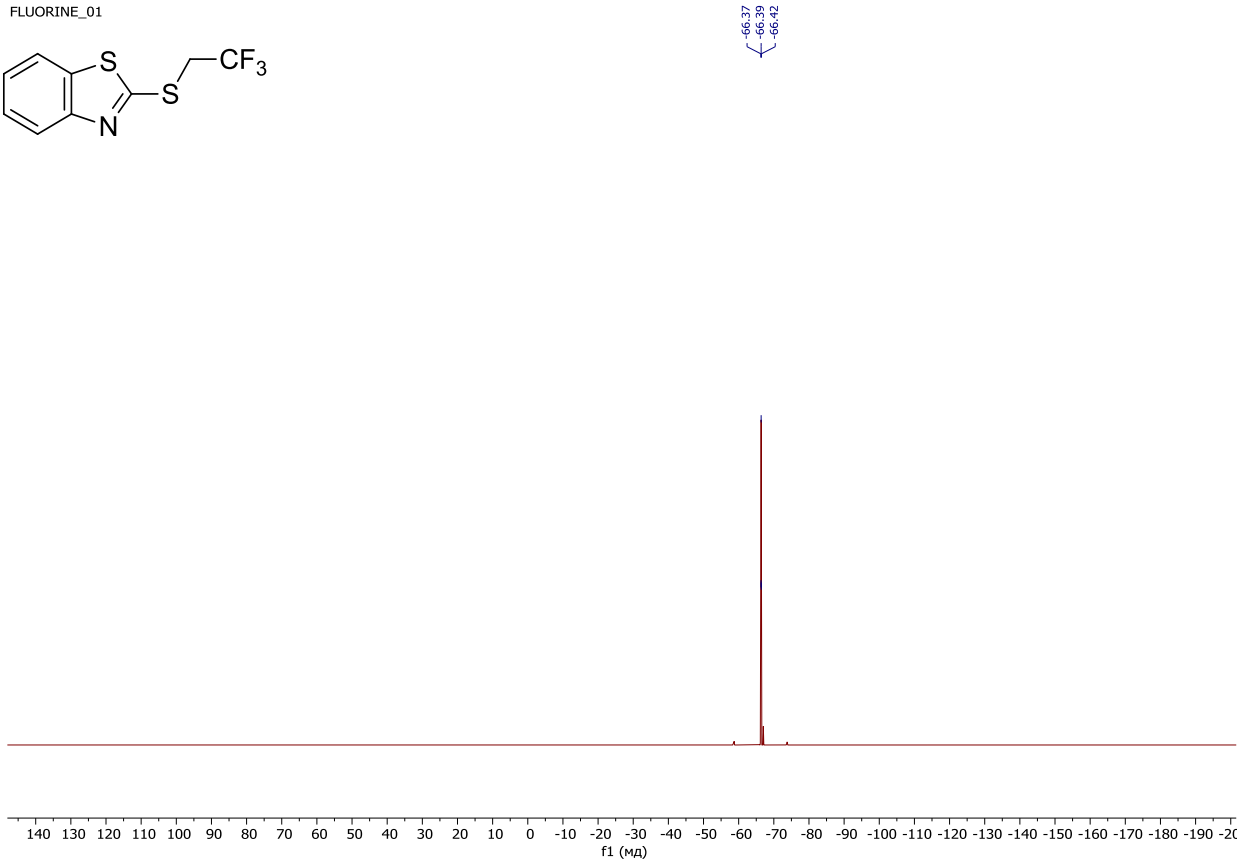
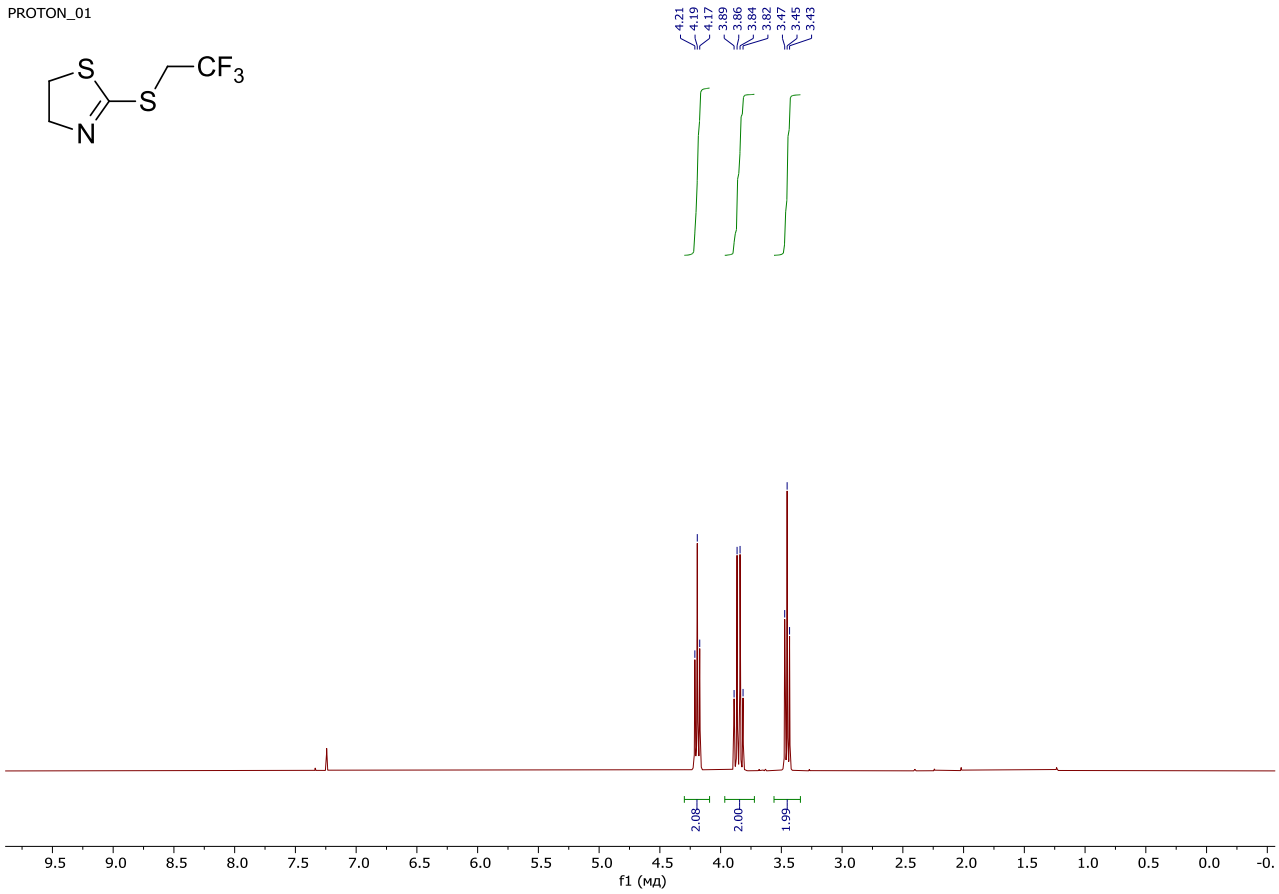
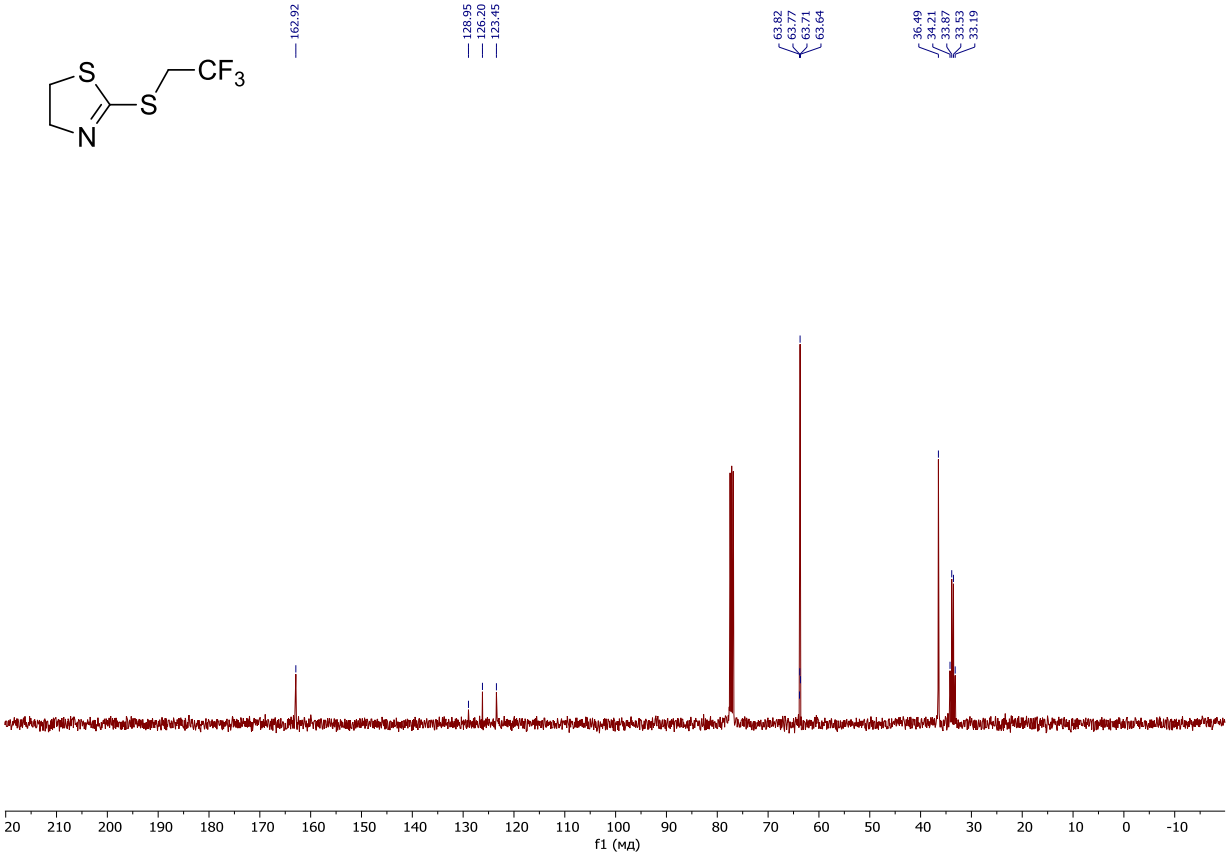


2-[(2,2,2-trifluoroethyl)thio]-4,5-dihydro-1,3-thiazole 4d **^{1}H NMR (400 MHz, $CDCl_3$)**

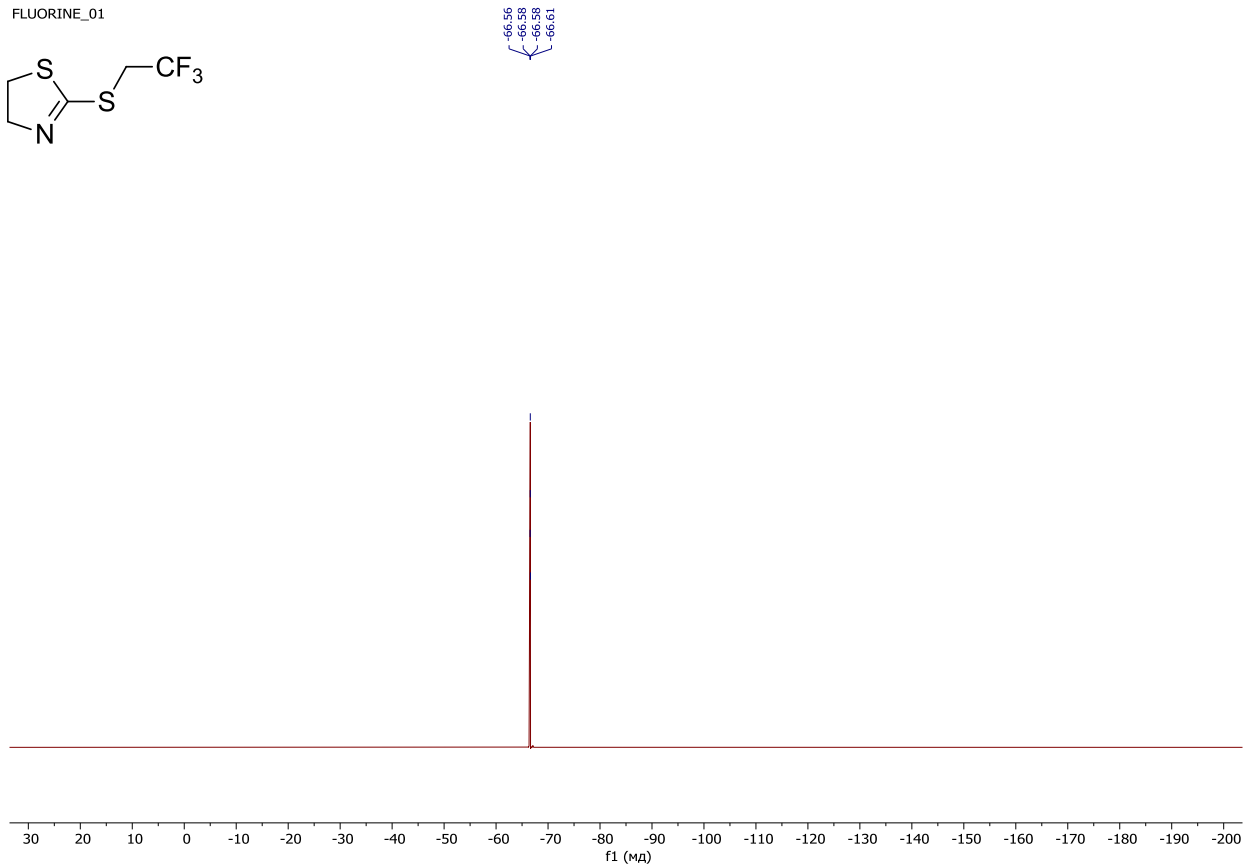


2-[(2,2,2-trifluoroethyl)thio]-4,5-dihydro-1,3-thiazole 4d **^{13}C NMR (100 MHz, $CDCl_3$)**



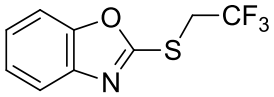
2-[(2,2,2-trifluoroethyl)thio]-4,5-dihydro-1,3-thiazole 4d

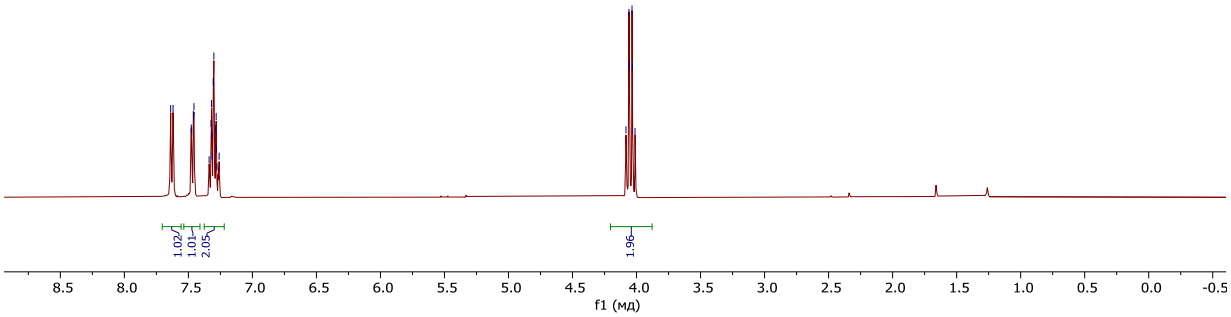
^{19}F NMR (376 MHz, $CDCl_3$)



2-[(2,2,2-trifluoroethyl)thio]-1,3-benzoxazole 4e

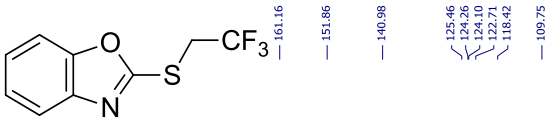
^{1}H NMR (400 MHz, $CDCl_3$)

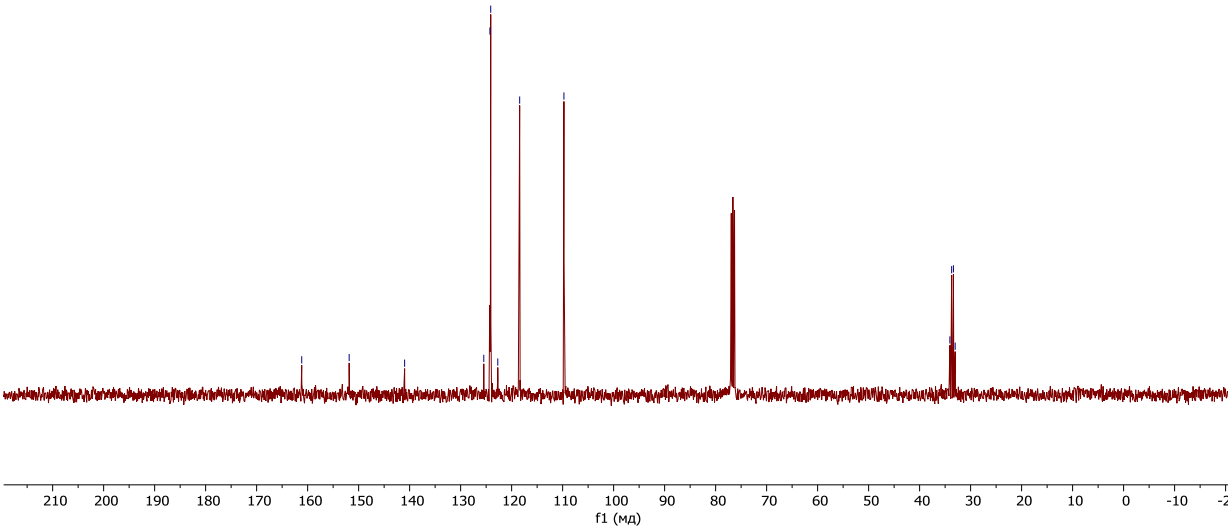




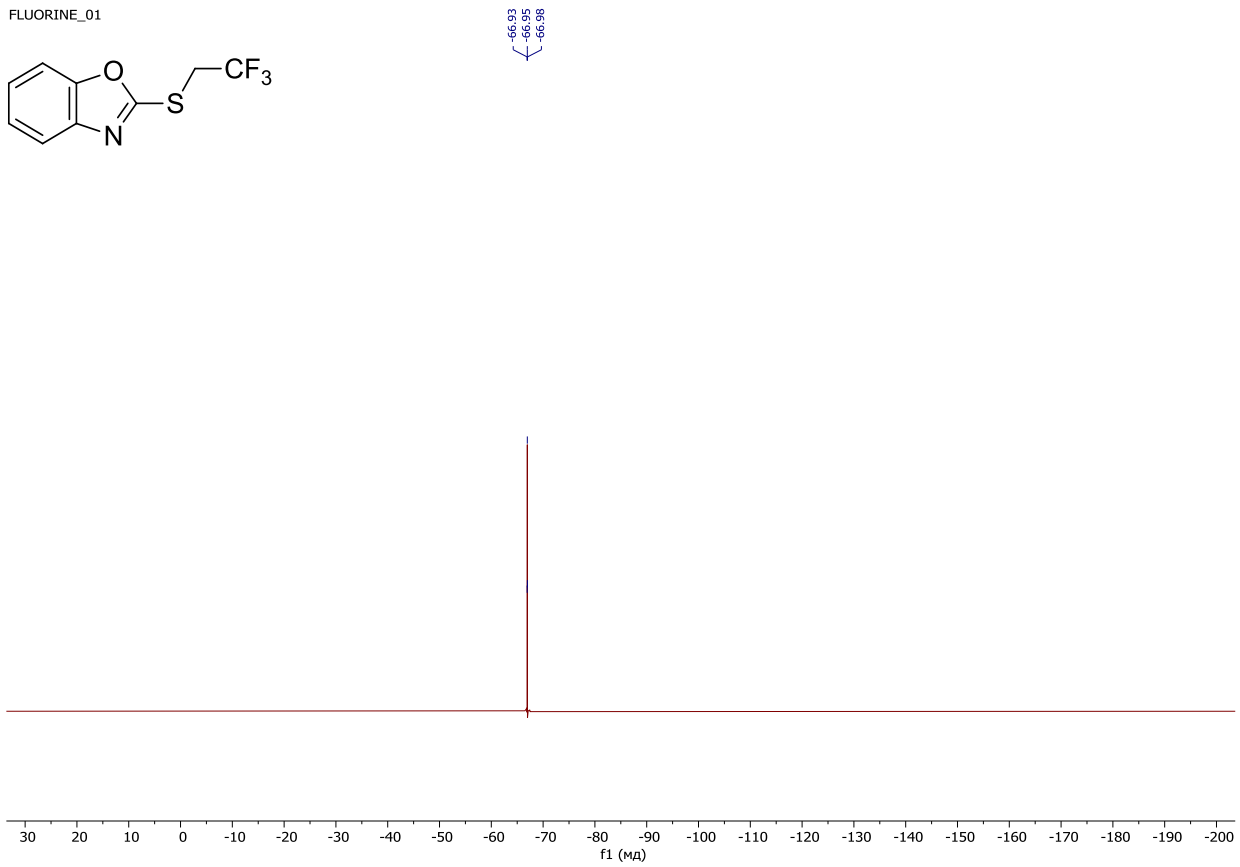
2-[(2,2,2-trifluoroethyl)thio]-1,3-benzoxazole 4e

^{13}C NMR (100 MHz, $CDCl_3$)

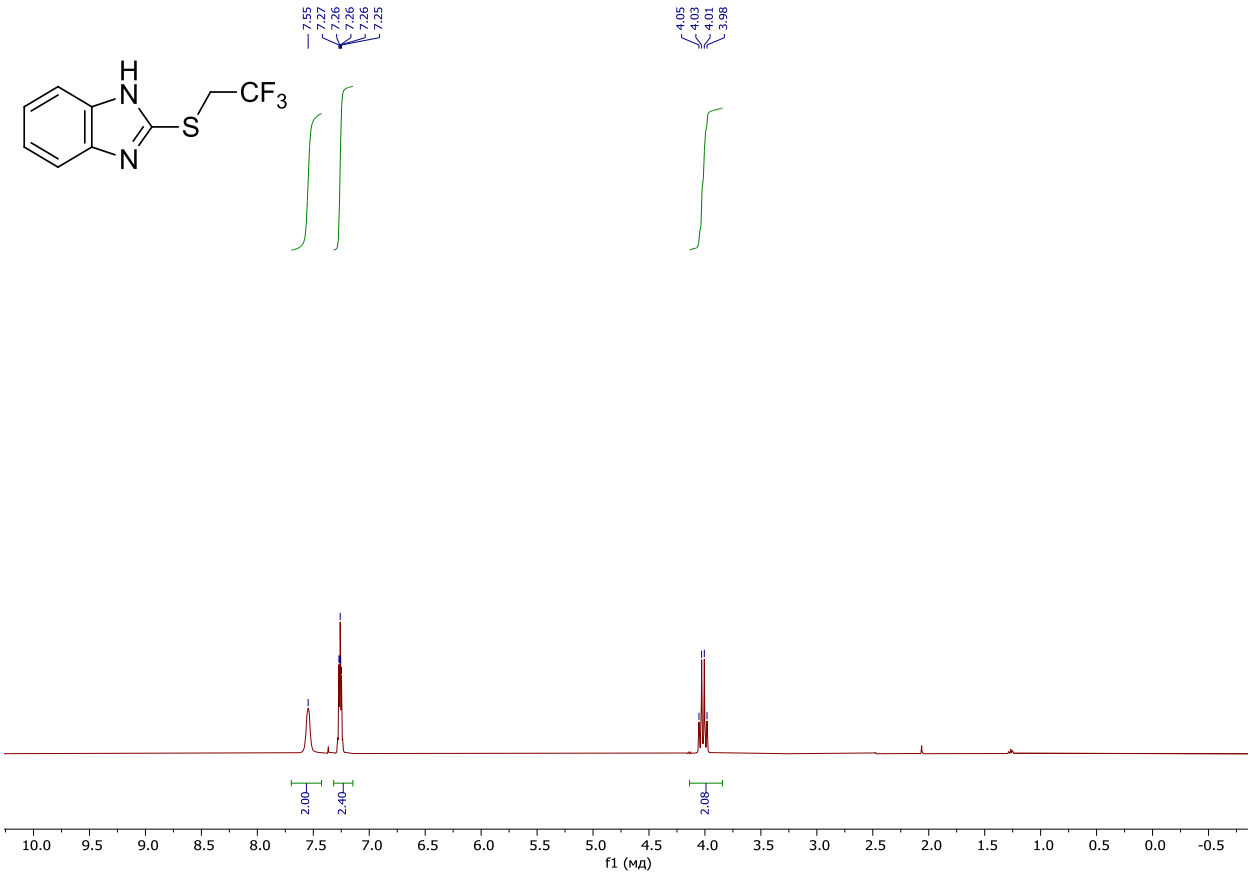




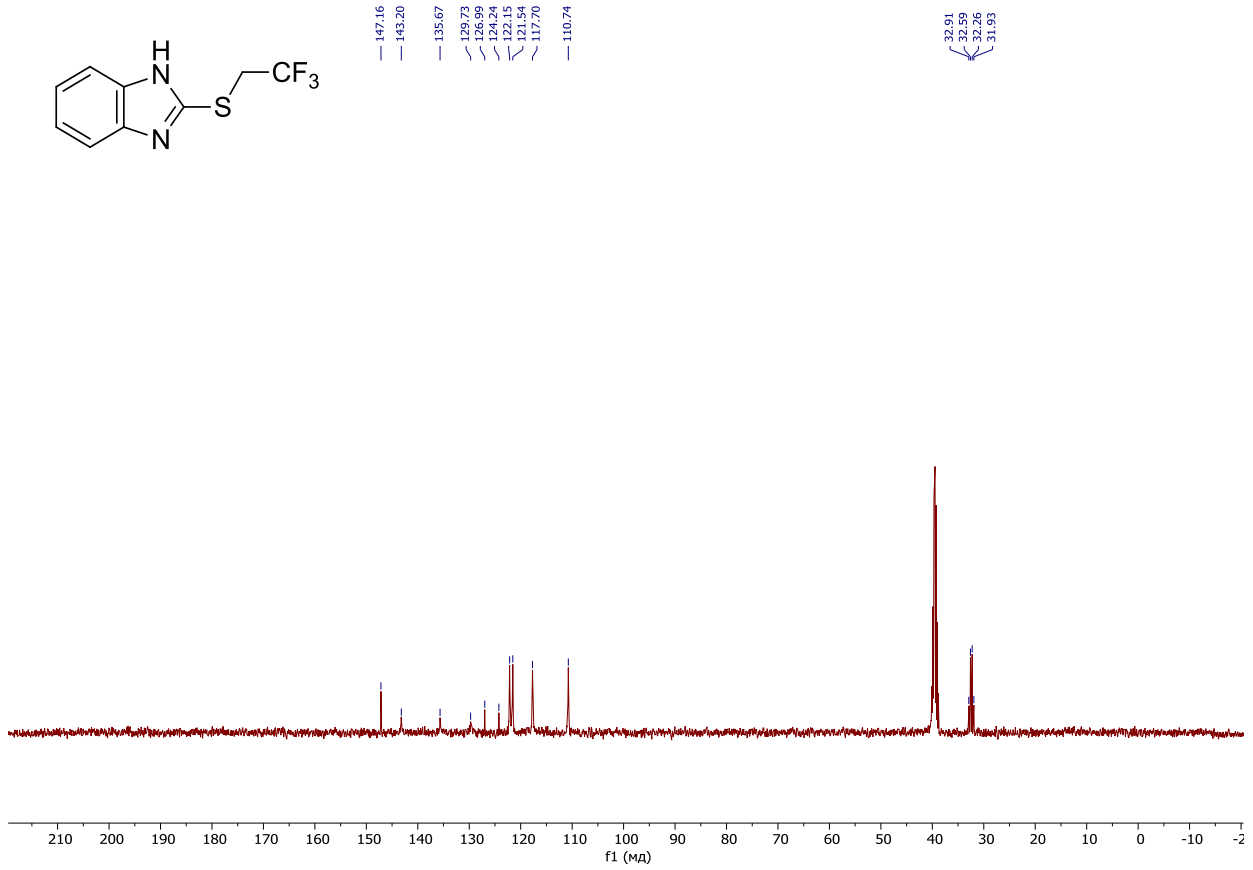
2-[(2,2,2-trifluoroethyl)thio]-1,3-benzoxazole 4e **^{19}F NMR (376 MHz, $CDCl_3$)**



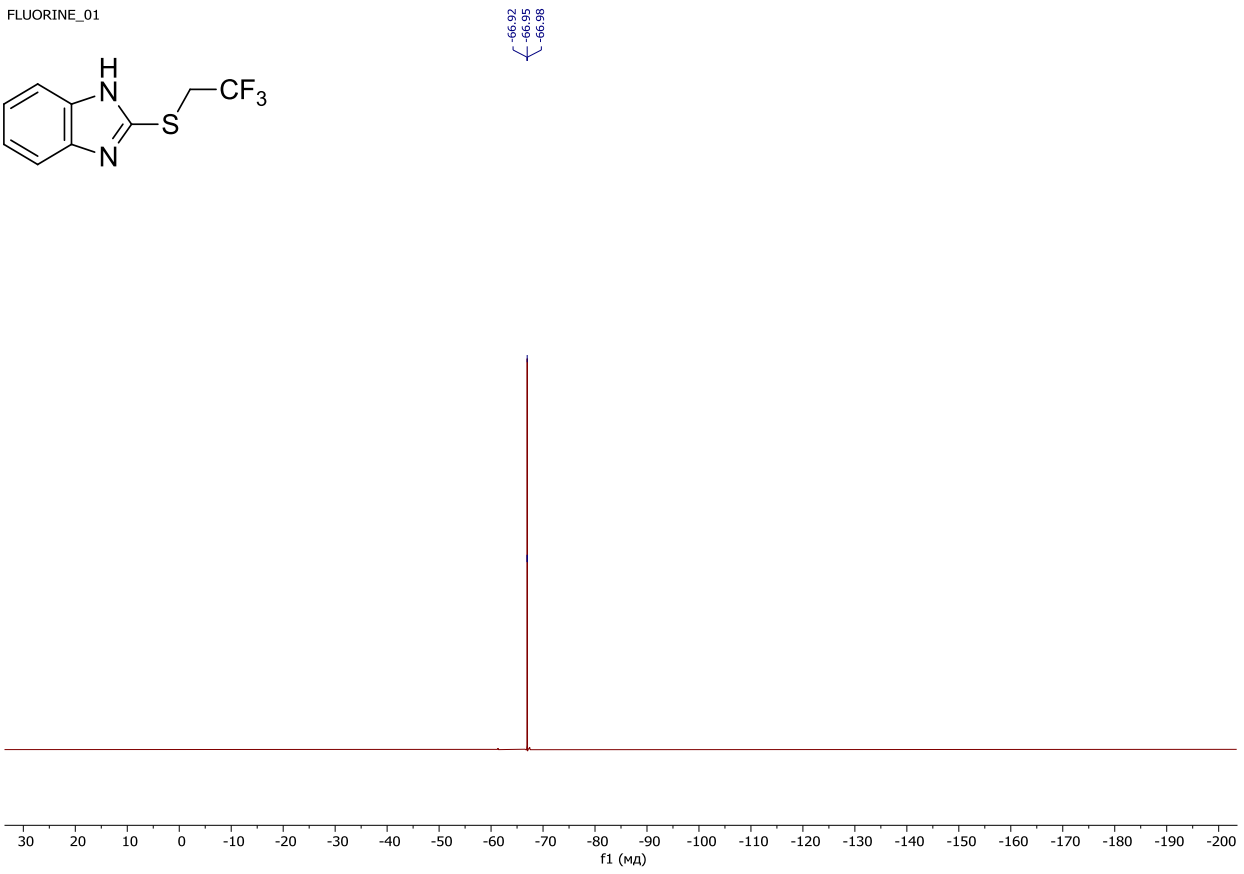
2-[(2,2,2-trifluoroethyl)thio]-1*H*-benzimidazole 4f **^{1}H NMR (400 MHz, $CDCl_3$)**



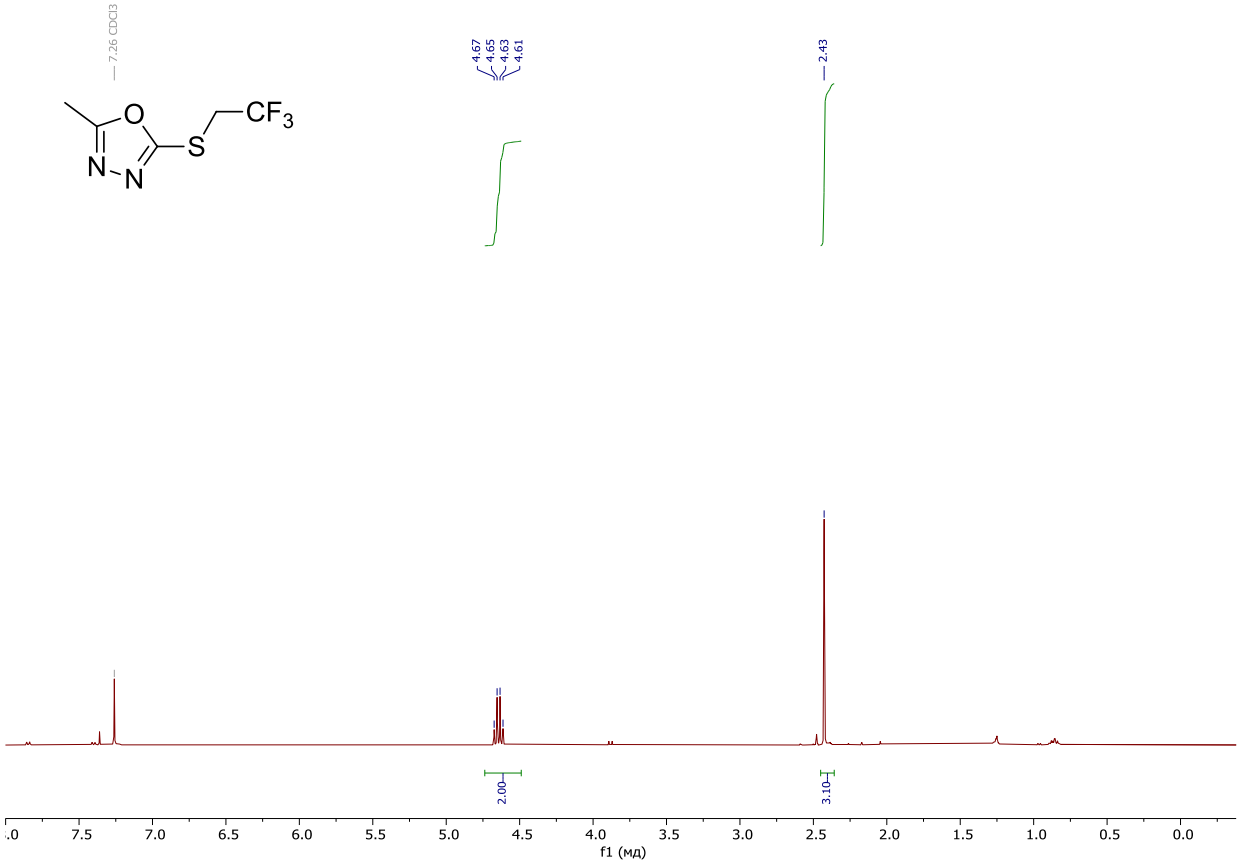
2-[(2,2,2-trifluoroethyl)thio]-1*H*-benzimidazole 4f **^{13}C NMR (100 MHz, DMSO-d_6)**



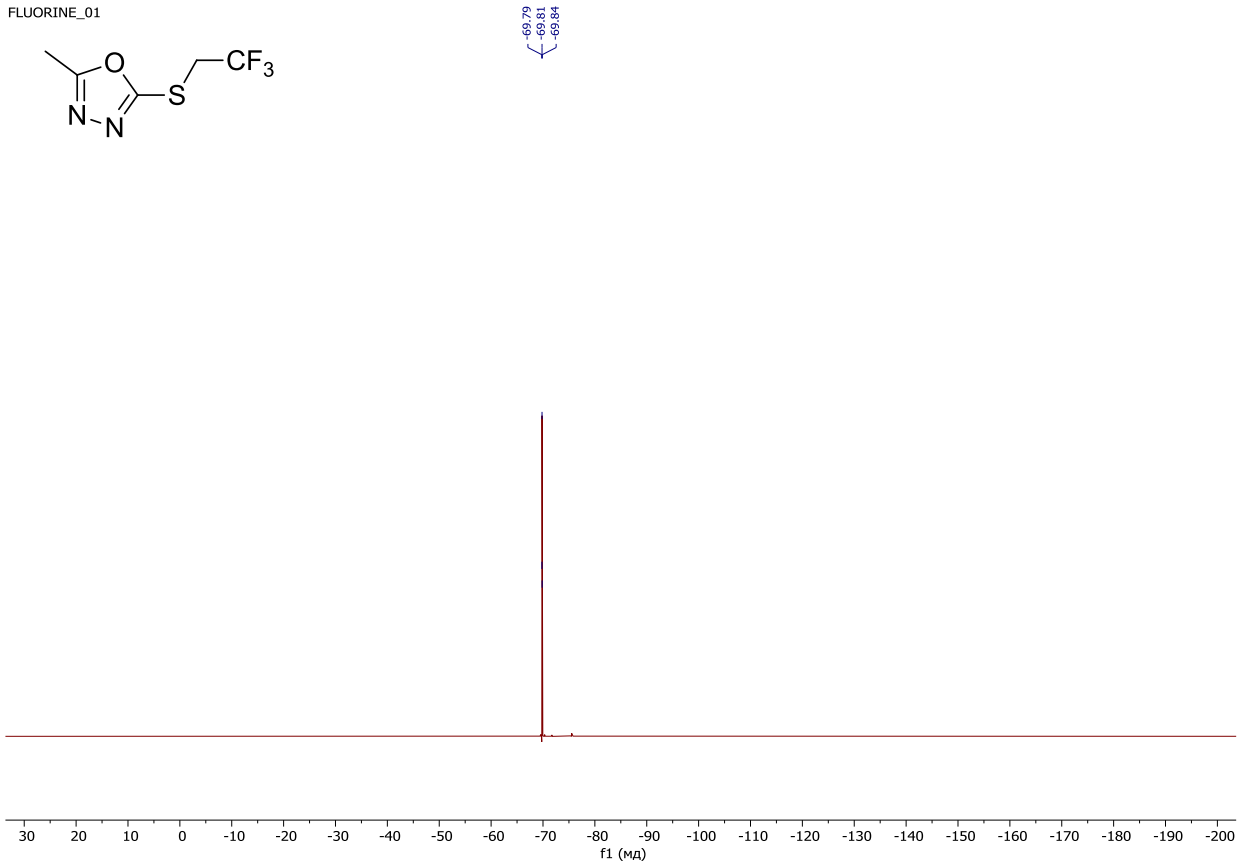
2-[(2,2,2-trifluoroethyl)thio]-1*H*-benzimidazole 4f **^{19}F NMR (376 MHz, $CDCl_3$)**



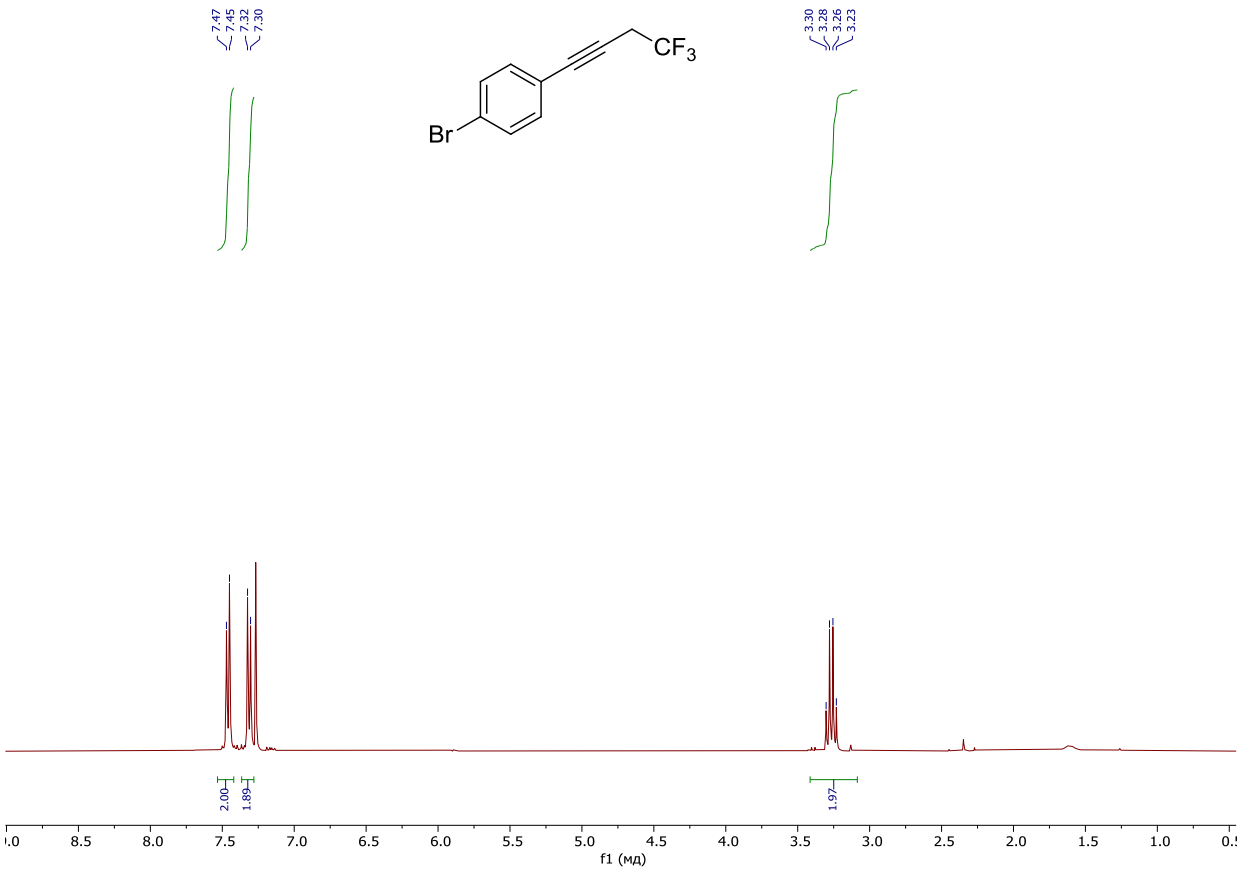
2-methyl-5-[(2,2,2-trifluoroethyl)thio]-1,3,4-oxadiazole 4g **^{1}H NMR (400 MHz, $CDCl_3$)**



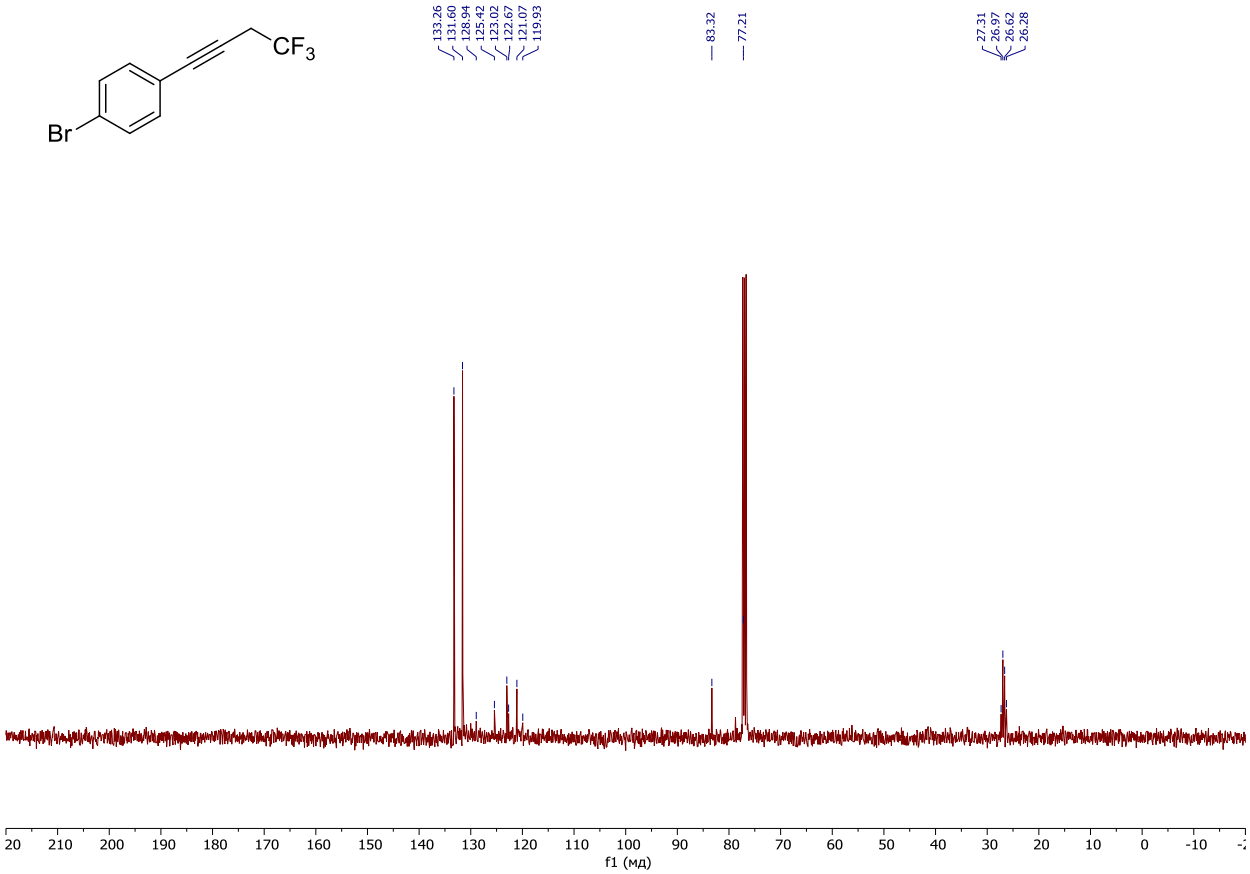
2-methyl-5-[(2,2,2-trifluoroethyl)thio]-1,3,4-oxadiazole 4g **^{19}F NMR (376 MHz, $CDCl_3$)**



1-(4-bromophenyl)-4,4,4-trifluorobut-1-yne 6 **^{1}H NMR (400 MHz, $CDCl_3$)**



1-(4-bromophenyl)-4,4,4-trifluorobut-1-yne 6 **^{13}C NMR (100 MHz, $CDCl_3$)**



1-(4-bromophenyl)-4,4,4-trifluorobut-1-yne 6 **^{19}F NMR (376 MHz, $CDCl_3$)**