Synthesis of Water-Soluble Hypervalent Iodine Reagents for Fluoroalkylation of Biological Thiols

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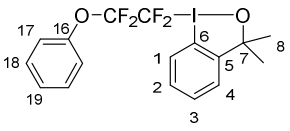
1. General

Reactions with air-sensitive materials were carried out under argon atmosphere using standard Schlenk techniques. Solvents were dried by activated molecular sieves (3 Å) and stored under argon. All commercially available chemicals were used as received unless stated otherwise. Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm). Automated flash column chromatography was performed on Teledyne ISCO CombiFlash Rf+ Lumen Automated Flash Chromatography System with UV/Vis detection. TLC analyses were done using TLC silica gel 60 F254 aluminum sheets, which were visualized under UV (254/366 nm) or using the $KMnO_4$ stain solution.

^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on Bruker Avance III™ HD 400 MHz at ambient temperature using 5 mm diameter NMR tubes. ^{13}C spectra were proton decoupled and for one sample also fluorine decoupled. The chemical shift values (δ) are reported in ppm relative to residual solvents (^{1}H and ^{13}C NMR) and to internal $CFCl_3$ or CF_3COOH[1] (^{19}F NMR). Structural elucidation was aided by additional acquisition of ^{13}C APT and/or various 2D spectra (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC). GC-MS spectra were recorded on Agilent 7890A GC (column HP-5MS, 30 m × 0.25 mm × 0.25 µm, 5% phenyl methylpolysiloxane) coupled with 5975C quadrupole mass selective electron impact (EI) detector (70 eV). UPLC-MS analyses were performed on Acquity UPLC Instrument (Waters Corporation). High resolution MS spectra (HRMS) were recorded on an LTQ Orbitrap XL using electrospray ionization (ESI), on a Waters Micromass AutoSpec Ultima or Agilent 7890A GC coupled with Waters GCT Premier orthogonal acceleration timeof-flight detector using electron impact (EI) or chemical ionization (CI), and on a Bruker solariX 94 ESI/MALDI-FT-ICR using dual ESI/MALDI ionization. UPLC-MS analyses were performed on Acquity UPLC Instrument. Fluroalkylations of short peptide **21** and gluathione were analyzed by LC-MS on I - Class – Waters SYNAPT G2 (ESI), which allows measurment of MSMS.

2. Characterization of compounds

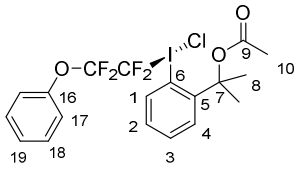
3,3-Dimethyl-1-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-1,3-dihydro-1λ³-benzo[d][1,2]iodaoxole (3a)



In a round bottom flask under argon, 1-fluoro-3,3-dimethyl-1,3-dihydro-1λ³-benzo[d][1,2]iodaoxole (4.19 g, 14.9 mmol, 1.3 equiv.) and TBAT (0.30 g, 0.55 mmol, 5 mol%) were dissolved in dry MeCN (30 ml). The solution was cooled to –35 °C. A solution of $PhOCF_2CF_2TMS$ (3.00 g, 11.26 mmol, 1 equiv.) in MeCN (9 ml) was added dropwise over 20 min, then the mixture was left to warmup to room temperature over 45 min while being stirred. The solvent was removed under reduced pressure; the product was redissolved in cyclohexane and filtered over activated alumina. The filtrate was evaporated to dryness, the product was redissolved in diethyl ether (10 ml) and the solution was cooled to 0 °C. 1.4 M solution of HCl in diethyl ether (15.7 ml, 2 equiv.) was added. The formed precipitate was filtered and washed with pentane (30 ml). Ice-cold saturated solution of $NaHCO_3$ (30 ml) was added and the product was extracted to diethyl ether (30 ml). Drying ($MgSO_4$), solvent removal and further drying in vacuum afforded pure product as a white solid.

Yield (3.35 g, 66%); ^{1}H NMR (400.10 MHz, CD_3OD): δ 1.50 (s, 6H, C(8)H_3), 7.24–7.27 (m, 2H, C(17)*H*), 7.31–7.35 (m, 1H, C(19)*H*), 7.41–7.46 (m, 2H, C(18)*H*), 7.49 (ddd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, C(2)*H*), 7.54 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, C(4)*H*), 7.60 (ddd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, C(3)*H*), 7.80 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, C(1)*H*); ^{19}F NMR (376.46 MHz, CD_3OD): δ –96.7 (t, $^3J_{FF}$ = 4.9 Hz, 2F, C*F*$_2$I), –85.4 (t, $^3J_{FF}$ = 4.9 Hz, 2F, C*F*$_2$O); ^{13}C {^{1}H, ^{19}F} NMR (100.62 MHz, CD_3OD): δ 31.0 (s, *C*(8)H_3), 77.5 (s, *C*(7)), 111.2 (s, *C*(6)), 112.5 (s, I*C*F$_2$), 118.5 (s, O*C*F$_2$), 122.7 (s, *C*(17)H), 128.2 (s, *C*(19)H), 129.1 (s, *C*(4)H), 130.2 (s, *C*(1)H), 131.0 (s, *C*(2)H, 131.1 (s, *C*(18)H), 132.1 (s, *C*(3)H), 150.1 (s, *C*(16)), 151.1 ((s, *C*(5)); HRMS (*m/z*, ESI$^+$): $[M+H]^+$ calc. for $C_{17}H_{16}O_2F_4I$ 455.0125, found 455.0123.

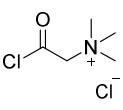
2-(2-(Chloro(1,1,2,2-tetrafluoro-2-phenoxyethyl)-λ³-iodanyl)phenyl)propan-2-yl acetate (3a·AcCl)



3a (227 mg, 0.5 mmol) was dissolved in dry $CHCl_3$ (1 ml) under argon atmosphere and acetyl chloride (1.5 mmol, 0.1 ml) was added in one portion. The mixture was stirred 15 minutes at laboratory temperature. After that volatiles were removed under reduced pressure and residue was washed with diethyl ether to give white particles as clean product.

Yield: 194 mg (73%); ^{1}H NMR (401.00 MHz, $CDCl_3$): δ 2.09 (s, 6H, C(8)H_3), 2.22 (s, 3H, C(10)H_3), 7.20 (d, $^3J_{HH}$ = 8.1 Hz, 2H, C(17)*H*), 7.27–7,37 (m, 2H, C(2)*H* and C (19)*H*), 7.42 (t, $^3J_{HH}$ = 7.8 Hz, 2H, C(18)*H*), 7.63–7.78 (m, 2H, C(3)*H* and C(4)*H*), 8.37 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C(1)*H*); ^{19}F NMR (377.28 MHz, $CDCl_3$): δ –87.8 (s, 2F, C*F*$_2$I), –84.3 (t, $^3J_{FF}$ = 6.8 Hz, 2F, C*F*$_2$O); ^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$): δ 22.9 (s, *C*(10)H_3), 28.7 (s, *C*(8)H_3), 82.2 (s, *C*(7)), 112.9 (tt, $^1J_{CF}$ = 345.1 Hz, $^2J_{CF}$ = 40.7 Hz, I*C*F$_2$), 114.4 (s, *C*(6)), 116.5 (tt, $^1J_{CF}$ = 277.2 Hz, $^2J_{CF}$ = 25.8 Hz, O*C*F$_2$), 121.5 (s, *C*(17)H), 127.3 (s, *C*(19)H), 129.6 (s, *C*(4)H), 130.0 (s, *C*(18)H), 131.0 (s, *C*(2)H), 133.2 (s, *C*(3)H), 141.8 (s, *C*(1)), 145.6 (s, *C*(5)), 148.2 (s, *C*(16)), 169.4 (s, *C*(9)); HRMS (*m/z*, ESI$^+$): $[M+Na]^+$ calc. for $C_{19}H_{18}O_3ClF_4INa$ 554.9818, found 554.9811.

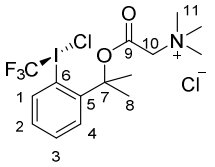
***N*-Chlorobetainyl chloride**



N-Chlorobetainyl chloride was prepared according to described procedure.[2] Betaine hydrochloride (1.54 g, 10 mmol) and thionyl chloride (25 mmol, 1.8 ml) was placed in 10 ml flask under argon atmosphere. The flask was sealed and suspension was heated 90 min to 70 °C. After the addition of dry toluene (4 ml), the mixture was let to cool to laboratory temperature.

The crystals of the product were formed and toluene was decanted. Another 4 ml of toluene were added and the suspension was heated to 80 °C to melt the crystals, which follow the cooling and decantation. Eventually the resting toluene was evaporated under reduced pressure to obtain pale yellow crystals. Flask with crystals was flushed with argon and stored in desiccator.
Yield: 1.53 g (89 %).

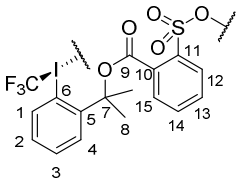
2-((2-(2-(Chloro(trifluoromethyl)-λ^3-iodanyl)phenyl)propan-2-yl)oxy)-*N,N,N*-trimethyl-2-oxoethan-1-aminium chloride (1·BetCl)



In 10 ml flask under argon atmosphere, *N*-chlorobetainyl chloride (56 mg, 0.33 mmol) was suspended in dry chloroform (3 ml). **1** (109 mg, 0.33 mmol) was added and the suspension was stirred 1 hour at laboratory temperature. The formed particles were filtered and washed with DCM (3 × 1 ml) and dried overnight under reduced pressure to obtain the mixture of product and betaine hydrochloride as white particles.

Yield: 118 mg (w = 0.75, with betaine hydrochloride and $CHCl_3$, 89 mg of **1·BetCl** 53 %);^{1}H NMR (401.00 MHz, DMSO-*d*$_6$): *δ* 2.00 (bs, 6H, C(8)*H*$_3$), 3.24 (s, 9H, C(11)*H*$_3$), 4.63 (s, 2H, C(10)*H*$_2$), 7.43 (t, $^3J_{HH}$ = 7.6 Hz, 1H, *C*(2)H) or *C*(3)H), 7.72 (t, $^3J_{HH}$ = 7.6 Hz, 1H, *C*(2)H) or *C*(3)H), 7.81 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C(4)*H*), 8.51 (d, $^3J_{HH}$ = 7.8 Hz, 1H, C(1)*H*); ^{19}F NMR (377.28 MHz, DMSO-*d*$_6$): *δ* –34.5 (s, 3F, C*F*$_3$); ^{13}C {^{1}H} NMR (100.84 MHz, DMSO-*d*$_6$): *δ* 27.3 (s, *C*(8)H$_3$), 53.4 (s, *C*(11)H3), 63.8 (s, *C*(10)H2), 84.9 (s, *C*(7)), 108.4 (q, $^1J_{CF}$ = 392.3 Hz, *C*F$_3$), 120.7 (s, *C*(6)), 128.6(s, *C*(4)H), 131.1 (s, *C*(2)H) or *C*(3)H), 132.3 (s, *C*(2)H or *C*(3)H), 141.4 (s, *C*(1)), 143.0 (s, *C*(5)), 163.5 (s, *C*(9)); Betaine hydrochloride: ^{1}H NMR (401.00 MHz, dmso-*d*$_6$): *δ* 3.23 (s, 9H, C*H*$_3$), 4.37 (s, 2H, C*H*$_2$); ^{13}C {^{1}H} NMR (100.84 MHz, DMSO-*d*$_6$): 52.9 (s, *C*H$_3$), 62.5 (s, *C*H$_2$) ,166.4 (s, *C*O); HRMS (*m/z*, ESI$^+$): [M-Cl]$^+$ calc. for $C_{15}H_{21}O_2NClF_3I$, 466.0252, found 466.0248.

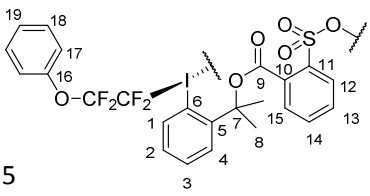
Polymeric reagent 6



1 (184 mg, 1 mmol) was dissolved in dry DCM (5 ml) under argon atmosphere and 3,3-dimethyl-1-(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[d][1,2]iodaoxole (330 mg, 1 mmol) was added in one portion. The mixture was stirred 20 minutes at laboratory temperature. After that volatiles were removed under reduced pressure and obtained particles were washed with diethyl ether (5 ml) to give white particles as clean product.

Yield: 383 mg (74 %); ^{1}H NMR (600.13 MHz, DMSO-*d*$_6$): *δ* 1.99 (bs, 6H, C(8)*H*$_3$), 7.38 (dd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, C(15)*H*), 7.53–7.58 (m, 3H, C(2)*H*, *C*(13)*H,* and C(14)*H*), 7.73 (dd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, C(12)*H*), 7.85 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, C(3)*H*), 7.95 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.7 Hz, 1H, C(4)*H*), 8.75 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, C(1)*H*); ^{19}F NMR (377.28 MHz, DMSO-*d*$_6$): *δ* –28.8 (s, 3F, C*F*$_3$); ^{13}C {^{1}H} NMR (150.92 MHz, DMSO-*d*$_6$): *δ* 31.0 (only in HSQC, *C*(8)H$_3$), 81.7 (s, *C*(7)), 100.1 (q, $^1J_{CF}$ = 367.8 Hz, *C*F$_3$), 115.2 (s, *C*(6)), 126.6 (s, *C*(15)H), 127.2 (s, *C*(12)H), 129.2 (s, *C*(4)H), 129.8 (s, *C*(13)H or *C*(14)H), 130.1 (s, *C*(13)H or *C*(14)H), 130.7 (s, *C*(11)), 131.2 (s, *C*(2)H), 133.5 (s, *C*(3)H), 140.7 (s, *C*(10)), 141.7 (s, *C*(1)), 144.5 (s, *C*(5)), 166.4 (s, *C*(9)); HRMS (*m/z*, ESI$^+$): [M+Na]$^+$ calc. for $C_{17}H_{14}O_5SF_3INa$ 536.9451, found 536.9445.

Polymeric reagent 7

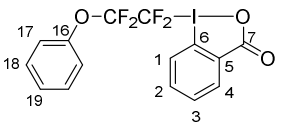


3a (227 mg, 0.5 mmol) was dissolved in dry DCM (2.5 ml) under argon atmosphere and 2,1-benzoxathiol-3-one-1,1-dioxide (92 mg, 0.5

mmol) was added in one portion. The mixture was stirred 15 minutes at laboratory temperature. After that volatiles were removed under reduced pressure and crude product was precipitated from DCM/diethyl ether mixture to obtain white particles as clean product.

Yield: 282 mg (88%); ^{1}H NMR (401.00 MHz, $CDCl_3$): δ 2.08 (s, 6H, C(8)H_3), 7.19–7.29 (m, 3H, C(15)*H* and C(17)*H*), 7.34 (t, $^{3}J_{HH}$ = 7.4 Hz, 1H, C (19)*H*), 7.38–7.52 (m, 5H, C(3)*H*, C(13)*H*, C(14)*H*, and C(18)*H*), 7.80 (t, $^{3}J_{HH}$ = 7.6 Hz, 1H, C (2)*H*), 7.94 (dd, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ = 1.7 Hz 1H, C (4)*H*), 7.99 (d, $^{3}J_{HH}$ = 7.7 Hz, 1H, C(12)*H*), 8.29 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H, C(1)*H*); ^{19}F NMR (377.28 MHz, $CDCl_3$): δ –84.3 (t, $^{3}J_{FF}$ = 8.2 Hz, 2F, CF_2O), –80.8 (s, 2F, CF_2I); ^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$): δ 28.5 (s, *C*(8)H_3), 81.2 (s, *C*(7)), 108.5 (tt, $^{1}J_{CF}$ = 279.1 Hz, $^{2}J_{CF}$ = 25.8 Hz, I*C*F_2), 109.7 (s, *C*(6)), 115.6 (tt, $^{1}J_{CF}$ = 337.6 Hz, $^{2}J_{CF}$ = 41.1 Hz, O*C*F_2), 121.3 (s, *C*(17)H), 126.4 (s, *C*(15)H), 127.7 (s, *C*(19)H), 127.8 (s, *C*(12)H), 130.0 (s, *C*(4)H), 130.0 (s, *C*(13)H or *C*(14)H), 130.2 (s, *C*(18)H), 130.3 (s, *C*(11)H), 131.1 (s, *C*(13)H or *C*(14)H), 131.6 (s, *C*(3)H), 134.3 (s, *C*(2)H), 140.0 (s, *C*(10)), 141.8 (s, *C*(1)), 146.0 (s, *C*(5)), 147.8 ((s, *C*(16)), 167.3 (s, *C*(9)); HRMS (*m/z*, ESI$^+$): $[M+Na]^+$ calc. for $C_{24}H_{19}O_6SF_4INa$ 660.9775, found 660.9768.

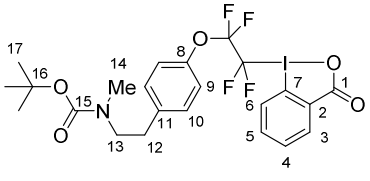
1-(1,1,2,2-Tetrafluoro-2-phenoxyethyl)-1λ^3-benzo[d][1,2]iodaoxol-3(1*H*)-one (4a)



A Schlenk flask under argon was charged with CsF (7.11 g, 23.6 mmol, 1 equiv.), 3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (10.877 g, 35 mmol, 1.5 equiv.) and dry DMF (42 ml). The mixture was stirred for 5 min and a solution of $PhOCF_2CF_2TMS$ (6.97 g, 26.25 mmol, 1 equiv.) in dry DMF (82 ml) was added. The reaction mixture was stirred for 2 h and then filtered. EtOAc (50 ml) was added to the filtrate and the mixture was washed with brine (3 × 40 ml), 1M aqueous $NaHCO_3$ (3 × 40 ml), 1M aqueous LiCl (3 × 40 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by trituration with a mixture of Et_2O/pentane (1:5), decantation and drying under vacuum to afford pure product as a pale yellow solid.

Yield: 6.70 g (58%); ^{1}H NMR (400.10 MHz, CD_3OD): δ 7.30–7.34 (m, 2H, C(17)*H*), 7.35–7.40 (m, 1H, C(19)*H*), 7.44–7.50 (m, 2H, C(18)*H*), 7.80 (ddd, $^{3}J_{HH}$ = 7.6 Hz, $^{3}J_{HH}$ = 7.2 Hz, $^{4}J_{HH}$ = 0.9 Hz, 1H, C(3)*H*), 7.90 (ddd, $^{3}J_{HH}$ = 8.4 Hz, $^{3}J_{HH}$ = 7.2 Hz, $^{4}J_{HH}$ = 1.8 Hz, 1H, C(2)*H*), 8.06 (dd, $^{3}J_{HH}$ = 8.4 Hz, $^{4}J_{HH}$ = 0.9 Hz, 1H, C(1)*H*), 8.32 (dd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.8 Hz, 1H, C(4)*H*); ^{19}F NMR (376.46 MHz, CD_3OD): δ –89.3 (t, $^{3}J_{FF}$ = 6.2 Hz, 2F, CF_2I), –85.2 (t, $^{3}J_{FF}$ = 6.2 Hz, 2F, CF_2O); ^{13}C {^{1}H} NMR (100.62 MHz, CD_3OD): δ 111.0 (tt, $^{1}J_{CF}$ = 334.8 Hz, $^{2}J_{CF}$ = 41.1 Hz, I*C*F_2), 116.1 (s, *C*(6)), 117.6 (tt, $^{1}J_{CF}$ = 276.4 Hz, $^{2}J_{CF}$ = 25.8 Hz, O*C*F_2), 122.7 (s, *C*(17)H), 128.6 (s, *C*(19)H), 130.4 (t, $^{1}J_{CF}$ = 6.1Hz *C*(1)H), 131.2 (s, *C*(18)H), 132.7 (s, *C*(3)H), 133.6 (s, *C*(5)), 134.2 (s, *C*(4)H), 136.8 (s, *C*(3)H), 149.7 (s, *C*(16)), 169.4 (s, *C*(7)); HRMS (*m/z*, ESI$^+$): $[M+H]^+$ calc. for $C_{15}H_{10}O_3F_4I$ 440.9605, found 440.9602.

***tert*-Butyl methyl(4-(1,1,2,2-tetrafluoro-2-(3-oxo-1λ^3-benzo[d][1,2]iodaoxol-1(3*H*)-yl)ethoxy)phenethyl)carbamate (4b·Boc)**

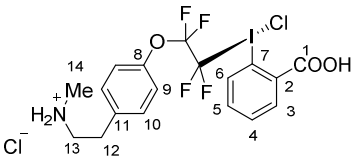


CsF (68 mg, 0.45 mmol) and 3-oxo-1λ^3-benzo[d][1,2]iodaoxol-1(3H)-yl acetate (918 mg, 3 mmol) were disolved in dry DMF (2.5 ml) under argon atmosphere. To the stirring suspension, solution of tert-butyl methyl(4-(1,1,2,2-tetrafluoro-2-(trimethylsilyl)ethoxy)phenethyl)carbamate (635 mg, 1.5 mmol) in dry DMF (5 ml) was added dropwise. After 2 hours the mixture was dilluted by EtOAc (50 ml), washed with H_2O (10 ml), 1 M $NaHCO_3$ (2 × 10 ml), 1 M LiCl (2 × 10 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by filtration through alumina (20 g). The impurities were

eluted with diethyl ether (150 ml) and the product was eluted with methanol (75 ml). The product was obtained after concentration under reduced pressure as colorless oil.

Yield: 604 mg (69%); ^{1}H NMR (401.00 MHz, $CDCl_3$): δ 1.34–1.39 (m, 9H, C(17)H_3), 2.76–2.83 (m, 5H, C(12)H_2 and C(14)H_3), 3.41 (t, $^{3}J_{HH}$ = 7.2 Hz, 2H, C(13)H_2), 7.12 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, C(9)*H* or C(10)*H*), 7.16–7.25 (m, 2H, C(9)*H* or C(10)*H*), 7.66–7.80 (m, 2H, C(4)*H* and C(5)*H*), 7.90 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H, C(6)*H*), 8.43 (dd, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 2.1 Hz, 1H, C(3)*H*); ^{19}F NMR (377.28 MHz, $CDCl_3$): δ –88.9 (bs, 2F, CF_2), –83.7 (bs, 2F, CF_2); ^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$): δ 28.2 (s, *C*(17)H_3), 33.3 and 33.7 (s, *C*(12)H_2), 34.1 and 34.6 (s, *C*(14)H_3), 49.9 and 50.4 (s, *C*(13)H_2), 79.3 (s, *C*(16)), 110.5 (tt, $^{1}J_{CF}$ = 335.4 Hz, $^{2}J_{CF}$ = 40.0 Hz, *C*F_2), 114.8 (s, *C*(7)), 117.2 (tt, $^{1}J_{CF}$ = 277.9 Hz, $^{2}J_{CF}$ = 25.6 Hz, *C*F_2), 121.4 (bs, *C*(9)H or *C*(10)H), 128.1 (t, $^{4}J_{CF}$ = 5.7 Hz, *C*(6)H), 130.3 (s, *C*(9)H or *C*(10)H), 131.5 (s, *C*(2)), 132.3 (s, *C*(4)), 133.7 (s, *C*(3)H), 135.2 (s, *C*(5)), 138.8 (m, *C*(11)), 146.4 (s, *C*(8)), 155.4 (s, *C*(15)), 165.9 (s, *C*(1)); HRMS (*m/z*, ESI$^+$): [M+Na]$^+$ calc. for $C_{23}H_{24}F_4INO_5Na$, 620.0528, found 620.0530.

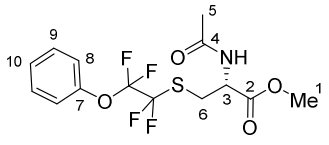
2-(4-(2-((2-Carboxyphenyl)chloro-λ^3-iodanyl)-1,1,2,2-tetrafluoroethoxy)phenyl)-*N*-methylethan-1-aminium chloride (4b·HCl)



4b·Boc (2.0 g, 3.4 mmol) was dissolved in 1,2-dichloroethane (68 ml) in a round bottom flask. HCl (4 M in dioxane, 34 mmol, 8.5 ml) was added. The mixture was stirred 1 hour at 60 °C. The solvent was evaporated and resulting particles were decantated in diethyl ether to obtain the pure product as white particles.

Yield: 1.46 g (75%); mp 120–123 °C; ^{1}H NMR (401.00 MHz, DMSO-d_6): δ 2.54 (t, $^{3}J_{HH}$ = 5.3 Hz, 3H, C(14)H_3), 2.98–3.01 (m, 2H, C(12)H_2, 3.06–3.21 (m, 2H, C(13)H_2), 7.25 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, C(9)*H*), 7.37 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H, C(10)*H*), 7.70 (t, $^{3}J_{HH}$ = 7.6 Hz, 1H, C(5)*H*), 7.82 (t, $^{3}J_{HH}$ = 7.6 Hz, 1H, C(4)*H*), 8.24 (d, $^{3}J_{HH}$ = 7.6 Hz, 1H, C(3)*H*), 8.49 (d, $^{3}J_{HH}$ = 7.6 Hz, 1H, C(6)*H*), 9.17 (s, 2H, NH_2); ^{19}F NMR (377.28 MHz, DMSO-d_6): δ –88.5 (bs, 2F, CF_2), –82.8 (t, $^{3}J_{FF}$ = 6.6 Hz, 2F, CF_2); ^{13}C {^{1}H} NMR (100.84 MHz, DMSO-d_6): δ 31.1 (s, *C*(12)H_2), 32.8 (s, *C*(14)H_3), 49.3 (s, *C*(13)H_2), 112.2 (tt, $^{1}J_{CF}$ = 341.8 Hz, $^{2}J_{CF}$ = 41.2 Hz, *C*F_2), 116.9 (tt, $^{1}J_{CF}$ = 275.5 Hz, $^{2}J_{CF}$ = 26.9 Hz, *C*F_2), 119.7 (s, *C*(7)), 121.5 (bs, *C*(9)H), 130.8 (s, *C*(10)H), 131.1 (s, *C*(2)), 132.2 (s, *C*(3)H), 133.1 (s, *C*(4)H), 135.5 (s, *C*(5)H), 137.0 (m, C(8)), 140.0 (s, *C*(6)H), 147.1 (s, *C*(11)), 165.5 (s, *C*(1)); HRMS (*m/z*, ESI$^+$): [M+H]$^+$ calc. for $C_{18}H_{17}F_4INO_3$, 498.0184, found 498.0183.

Methyl *N*-acetyl-*S*-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteinate (17a)

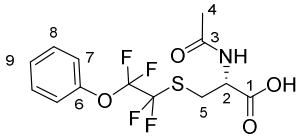


N-Acetyl-L-cysteine methyl ester (266 mg, 1.5 mmol) was dissolved in dry DCM (5 ml) under nitrogen atmosphere. The mixture was cooled to –78 °C and a solution of **3a** (681 mg, 1.5 mmol) in dry DCM (10 ml) was added dropwise. The mixture was stirred 1 hour at –78 °C and then absorbed to silica gel. The product was isolated by column chromatography (gradient eluent from cyclohexane to ethyl acetate) yielding colorless oil which solidified.

Yield: 422 mg (76%), R_f = 0.2 (Cyclohexane:ethyl acetate, 3:1); ^{1}H NMR (401.00 MHz, acetone-d_6): δ 1.98 (s, 3H, C(5)H_3), 3.40 (dd, $^{2}J_{HH}$ = 13.8 Hz, $^{3}J_{HH}$ = 7.4 Hz, 1H, C(6)H_2), 3.55 (dd, $^{2}J_{HH}$ = 13.8 Hz, $^{3}J_{HH}$ = 5.3 Hz, 1H, C(6)H_2), 3.73 (s, 3H, C(1)H_3), 4.80 (ddd, $^{3}J_{HH}$ = 7.9 Hz, $^{3}J_{HH}$ = 7.4 Hz, $^{3}J_{HH}$ = 5.3 Hz, 1H, (C(3)*H*), 7.27–7.31 (m, 2H, C(8)*H*), 7.33–7.41 (m 1H, C(10)*H*), 7.44–7.54 (m, 2H, C(9)*H*), 7.78 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, N*H*); ^{19}F NMR (377.28 MHz, $CDCl_3$): δ –90.4 (dt, $^{2}J_{FF}$ = 221.8 Hz, $^{3}J_{FF}$ = 6.6 Hz, 1F, SCF_2), –89.2 (dt, $^{2}J_{FF}$ = 221.8 Hz, $^{3}J_{FF}$ = 6.4

Hz, 1F, SCF_2), –85.0 (dd, $^3J_{FF}$ = 6.6 Hz, $^3J_{FF}$ = 6.4 Hz, 2F, CF_2O); ^{13}C {^{1}H} NMR (100.84 MHz, acetone-d_6): δ 22.6 (s, C(5)H$_3$), 30.4 (m, C(6)H$_2$), 52.8 (s, C(1)H$_3$), 53.1 (s, C(3)H), 118.2 (tt, $^1J_{CF}$ = 274.5 Hz, $^2J_{CF}$ = 33.3 Hz, CF$_2$), 122.5 (s, C(8)H), 124.1 (tt, $^1J_{CF}$ = 287.8 Hz, $^2J_{CF}$ = 38.9 Hz, CF$_2$), 127.9 (s, C(10)H), 130.9 (s, C(9)H), 149.6 (t, $^3J_{CF}$ = 1.8 Hz, C(7)), 170.4 (s, C(4)), 171.0 (s, C(2)); HRMS (*m/z*, EI$^+$): [M+H]$^+$ calc. for $C_{14}H_{15}F_4NO_4S$, 369.0658, found 369.0654.

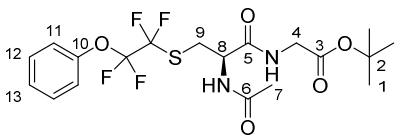
_N_-Acetyl-_S_-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteine (17b)



N-Acetyl-L-cysteine (245 mg, 1.5 mmol) was dispersed in dry DCM (5 ml) under nitrogen atmosphere. The mixture was cooled to –78 °C and a solution of **3a** (681 mg, 1.5 mmol) in dry DCM (10 ml) was added dropwise. The mixture was stirred 1 hour at –78 °C and then diluted with 1 M $NaHCO_3$ (10 ml). The layers were separated and water phase washed with DCM (2 × 5 ml) and carefully acidified with 35% HCl to pH < 2. The product was obtained as colorless white oil, which solidified, by extraction to DCM (3 × 5 ml), drying on $MgSO_4$ and concentration in vacuo.

Yield: 245 mg (46%); ^{1}H NMR (401.00 MHz, $CDCl_3$): δ 2.1 (s, 3H, C(4)H_3), 3.45 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, C(5)H_2), 3.60 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, C(5)H_2), 4.93 (ddd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, C(2)H), 6.62 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 7.12–7.22 (m, 2H, C(7)H), 7.23–7.29 (m 1H, C(9)H), 7.33–7.40 (m, 2H, C(8)H), 8.28 (bs, 1H, COOH); ^{19}F NMR (377.28 MHz, $CDCl_3$): δ –90.4 (dt, $^2J_{FF}$ = 222.1 Hz, $^3J_{FF}$ = 6.5 Hz, 1F, SCF_2), –88.8 (dt, $^2J_{FF}$ = 222.1 Hz, $^3J_{FF}$ = 6.4 Hz, 1F, SCF_2), –85.0 (m, 2F, CF_2O); ^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$): δ 22.5 (s, C(4)H$_3$), 29.8 (s, C(5)H$_2$), 52.1 (s, C(2)H), 117.1 (tt, $^1J_{CF}$ = 275.5 Hz, $^2J_{CF}$ = 32.8 Hz, CF$_2$), 121.6 (s, C(7)H), 122.6 (tt, $^1J_{CF}$ = 289.6 Hz, $^2J_{CF}$ = 39.4 Hz, CF$_2$), 126.6 (s, C(9)H), 129.6 (s, C(8)H), 148.8 (s, C(6)), 171.8 (s, C(3)), 172.2 (s, C(1)); HRMS (*m/z*, ESI$^-$): [M–H]$^-$ calc. for $C_{13}H_{12}F_4NO_4S$, 354.0429, found 354.0423.

Tert-butyl _N_-acetyl-_S_-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteinylglycinate

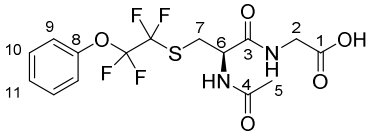


In a 10 ml dry flask flushed with nitrogen, **16b** (87 mg, 0.24 mmol) and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (67 mg, 0.27 mmol) were disolved in dry THF (1.2 ml) and stirred for 30 min at laboratory temperature. *Tert*-butyl gylcine hydrochloride (45 mg, 0.27 mmol) was added, followed by the addition of THF (1.2 ml) and *N*-methylmorpholine (30 µl, 0.27 mmol). The suspension was stirred 4 hours at laboratory temperature and then THF was evaporated. To the residue was added diethyl ether (50 ml) and the organic phase was washed with 1M HCl (7 ml), 0.1M phosphate buffer (pH = 7, 2 × 7 ml) and 1M HCl (7 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was obtained as a colorless oil by column chromatography on silikagel (cyclohexane:EtOAc, 75:25–0:100).

Yield: 47 mg (42%); ^{1}H NMR (401.00 MHz, acetone-d_6): δ 1.43 (s, 9H, C(1)H_3), 2.00 (s, 3H, C(7)H_3), 3.31 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 7.7 Hz, 1H, C(9)H_2), 3.52 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, C(9)H_2), 3.87 (d, $^3J_{HH}$ = 5.9 Hz, 2H, C(4)H_2), 4.85 (ddd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, C(8)H), 7.28–7.31 (m, 2H, C(11)H), 7.33–7.40 (m, 1H, C(13)H), 7.43–7.55 (m, 2H, C(12)H), 7.70 (d, $^3J_{HH}$ = 8.5 Hz, 1H, AcNH) 7.79 (t, $^3J_{HH}$ = 5.9 Hz, 1H, NH); ^{19}F NMR (377.28 MHz, acetone-d_6): δ –91.9 (td, $^3J_{FF}$ = 6.6 Hz, $^3J_{HF}$ = 1.5 Hz, 2F, SCF_2), –85.7 (t, $^3J_{FF}$ = 6.6 Hz, 2F, CF_2O); ^{13}C {^{1}H} NMR (100.84 MHz, acetone-d_6): δ 22.8 (s, C(6)H$_3$), 28.2 (s, C(1)H_3), 29.8 (t, $^3J_{CF}$ = 3.6 Hz, C(9)H$_2$), 42.5 (s, C(4)H$_2$), 53.2 (s, C(8)H), 81.7 (s, C(2)), 118.3 (tt, $^1J_{CF}$ = 274.5 Hz, $^2J_{CF}$ = 33.5 Hz, CF$_2$), 122.6 (s, C(11)H), 124.2 (tt, $^1J_{CF}$ = 286.9 Hz, $^2J_{CF}$ = 38.9 Hz, CF$_2$), 127.8 (s, C(13)H),

130.9 (s, *C*(12)H), 149.7 (t, $^3J_{CF}$ = 1.8 Hz, *C*(10)), 169.3 (s, *C*(3)), 170.6 (s, *C*(5)), 170.7 (s, C(6)); HRMS (*m/z*, ESI$^+$): [M+Na]$^+$ calc. for $C_{19}H_{24}F_4N_2O_5SNa$, 491.1234, found 491.1230.

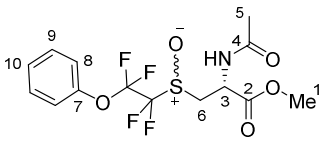
_N_-Acetyl-_S_-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteinylglycine (17c)



Tert-butyl N-acetyl-S-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteinylglycinate (17 mg, 0.04 mmol) was dissolved in DCM (1 ml) and trifluoroacetic acid (28 µl, 0.4 mmol) was added. The flask was sealed and heated to 45 °C. After 5 hours no deprotection took place, the mixture was concentrated under reduced pressure with some residual trifluoroacetic acid remaining (0.43 eq.). To the residue was added DCE (1 ml) and HCl (4M in dioxane, 0.1 ml, 0.4 mmol). The flask was sealed and heated 19 hours to 60 °C. To the cooled reaction mixture were added phosphate buffer (pH = 7, 5 ml) and the organic layer was separated. The water layer was washed with ether (2 × 5 ml), acidified with 1M HCl to pH = 2 and reextracted with diethyl ether (3 × 10 ml). The organic phase were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by filtration through a paster pippete with silicagel (100 mg). The impurities were eluted with DCM (2.5 ml) and the product was elutedwith methanol (2.5 ml). Solvent was removed under reduced pressure. The pure product was redisolved in diethyl ether and filtered through celite to remove silicagel. Evaporation of diethyl ether provided the clean product as colorless oil.

Yield: 11 mg (69%); ^{1}H NMR (401.00 MHz, acetone-d_6): δ 1.99 (s, 3H, C(4)H_3), 3.30 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 7.7 Hz, 1H, C(7)H_2), 3.51 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, C(7)H_2), 3.98 (d, $^3J_{HH}$ = 5.7 Hz, 2H, C(2)H_2), 4.85 (ddd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, (C(6)*H*), 7.29–7.31 (m, 2H, C(9)*H*), 7.33–7.41 (m, 1H, C(11)*H*), 7.45–7.53 (m, 2H, C(10)*H*), 7.72 (d, $^3J_{HH}$ = 8.5 Hz, 1H, AcN*H*) 7.82 (t, $^3J_{HH}$ = 5.7 Hz, 1H, N*H*); ^{19}F NMR (377.28 MHz, acetone-d_6): δ –91.9 (td, $^3J_{FF}$ = 6.5 Hz, $^3J_{HF}$ = 3.7 Hz, 2F, SCF_2), –85.7 (t, $^3J_{FF}$ = 6.6 Hz, 2F, CF_2O); ^{13}C {^{1}H} NMR (100.84 MHz, acetone-d_6): δ 22.7 (s, *C*(4)H$_3$), 30.5 (t, $^3J_{CF}$ = 3.6 Hz, *C*(7)H$_2$), 41.5 (s, *C*(2)H$_2$), 53.2 (s, *C*(6)H), 118.3 (tt, $^1J_{CF}$ = 274.5 Hz, $^2J_{CF}$ = 33.5 Hz, *C*F$_2$), 122.6 (s, *C*(9)H), 124.2 (tt, $^1J_{CF}$ = 286.8 Hz, $^2J_{CF}$ = 38.7 Hz, *C*F$_2$), 127.9 (s, *C*(11)H), 130.9 (s, *C*(10)H), 149.6 (s, *C*(8)), 170.7 (s, *C*(3)), 170.8 (s, *C*(4)), 171.1 (s, C(1)); HRMS (*m/z*, ESI$^+$): [M+Na]$^+$ calc. for $C_{15}H_{16}F_4N_2O_5SNa$, 435.0608, found 435.0609.

Methyl _N_-acetyl((1,1,2,2-tetrafluoro-2-phenoxyethyl)sulfinyl)-D-alaninate (18)



In analogy to the literature procedure,[3] **16a** (363 mg, 1 mmol), was disolved in a mixture of DCM (1 ml) and acetonitrile (2ml). Water (0.1 ml) was added and the mixture was cooled to 0 °C. Trichloroisocyanuric acid (232 mg, 1 mmol) was added in one portion and reaction was keeped at 0 °C for 5 min, after that the mixture was let to warm up to laboratory temperature and stirred overnight. The reaction was quenched with saturated $Na_2S_2O_3$ (5 ml) and the formed particles were filtered through celite and washed with diethyl ether (5 ml). The layers were separated and the aqueous layer extracted with additional diethyl ether (2× 5 ml). Organic layers were dried over $MgSO_4$ and concentrated under reduced pressure yielding as colorless oil, which solidified.

Yield: 324 mg (85%), mixture of two diastereoisomers (A:B = 30:70); ^{1}H NMR (400.13 MHz, acetone-d_6): δ 2.00 (m, *A* - 3H, *B* - 3H, C(5)H_3), 3.50–3.71 (m, *A* - 1H, *B* - 2H, C(6)H_2), 3.75 (m, *A* - 3H, *B* - 3H, C(1)H_3), 3.81 (ddd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 7.3 Hz, $^4J_{HF}$ = 2.4 Hz, *A* -1H, C(6)H_2), 4.91 (ddd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 3.9 Hz, *B* -1H, (C(3)*H*), 5.04 (td, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 5.3 Hz, *A* -1H, (C(3)*H*), 7.30–7.35 (m, *A* - 2H, *B* - 2H C(8)*H*), 7.37–7.46 (m, *A* - 1H, *B* - 1H, C(10)*H*), 7.47–7.55 (m, *A* - 2H, *B* - 2H, C(9)*H*), 7.93 (d, $^3J_{HH}$ = 7.3 Hz, *A* - 1H, N*H*), 8.02 (d, $^3J_{HH}$ = 8.2 Hz, *B* - 1H, N*H*); ^{19}F NMR (376.46 MHz, $CDCl_3$): *diastereomer B*: δ –123.2

(ddd, $^{2}J_{FF}$ = 233.0 Hz, $^{3}J_{FF}$ = 8.5 Hz, $^{3}J_{FF}$ = 4.4 Hz, 1F, S(O)C*F*$_2$), –118.1 (ddd, $^{2}J_{FF}$ = 233.0 Hz, $^{3}J_{FF}$ = 8.8 Hz, $^{3}J_{HF}$ = 2.3 Hz, 1F, S(O)C*F*$_2$), –81.7(ddd, $^{2}J_{FF}$ = 141.8 Hz, $^{3}J_{FF}$ = 8.8 Hz, $^{3}J_{FF}$ = 4.4 Hz, 1F, C*F*$_2$O), –80.5 (dd, $^{2}J_{FF}$ = 141.8 Hz, $^{3}J_{HH}$ = 8.5 Hz, 1F, C*F*$_2$O); *diastereomer A:* δ –122.6 (ddd, $^{2}J_{FF}$ = 233.1 Hz, $^{3}J_{FF}$ = 8.7 Hz, $^{3}J_{FF}$ = 4.1 Hz, 1F, S(O)C*F*$_2$), –118.0 (ddd, $^{2}J_{FF}$ = 233.1 Hz, $^{3}J_{FF}$ = 8.7 Hz, $^{3}J_{HF}$ = 1.9 Hz, 1F, S(O)C*F*$_2$), –81.8 (ddd, $^{2}J_{FF}$ = 141.9 Hz, $^{3}J_{FF}$ = 8.7 Hz, $^{3}J_{FF}$ = 4.1 Hz, 1F, C*F*$_2$O), –80.6 (dd, $^{2}J_{FF}$ = 141.9 Hz, $^{3}J_{HH}$ = 8.7 Hz, 1F, C*F*$_2$O); ^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$): δ 22.7 (s, *A* - *B* - *C*(5)H_3), 47.9 (s, *B* - *C*(3)H_2), 48.1 (s, *A* - *C*(3)H_2), 48.4 (t, $^{4}J_{CF}$ = 4.7 Hz, *B* - *C*(6)H), 48.8 (t, $^{4}J_{CF}$ = 4.5 Hz, *A* - *C*(6)H), 53.1 (s, *A* - *C*(1)H_3), 53.2 (s, *B* - *C*(1)H_3), 116.4 (tt, $^{1}J_{CF}$ = 277.9 Hz, $^{2}J_{CF}$ = 29.5 Hz, *A* - *B* - *C*F_2), 117.7 (tt, $^{1}J_{CF}$ = 309.0 Hz, $^{2}J_{CF}$ = 37.0 Hz, *B* - *C*F_2), 117.8 (tt, $^{1}J_{CF}$ = 308.6 Hz, $^{2}J_{CF}$ = 37.0 Hz, *A* - *C*F_2), 121.6 (s, *A* - *B* - *C*(8)H), 127.0 (s, *A* - *B* - *C*(10)H), 129.8 (s, *A* - *B* - *C*(9)H), 148.2 (s, *A* - *B* - *C*(7)), 169.8 (s, *A* - *C*(2)), 169.9 (s, *B* - *C*(2)), 170.7 (s, *B* - C(4)), 170.8 (s, *A* - C(4)); HRMS (*m/z*, APCI$^+$): $[M+H]^+$ calc. for $C_{14}H_{16}F_4NO_5S$, 386.0680, found 386.0681.

3. Stability of the reagents and conjugates

3.1. Reagents in water

Reagent **1**·BetCl (10 mg, 15 µmol) was placed in an NMR tube and D_2O (0.4 ml) was added. The salt dissolved and evolution of gas withing 5 minutes was observed. ^1H NMR spektra were recorded (Figures S1, S2).

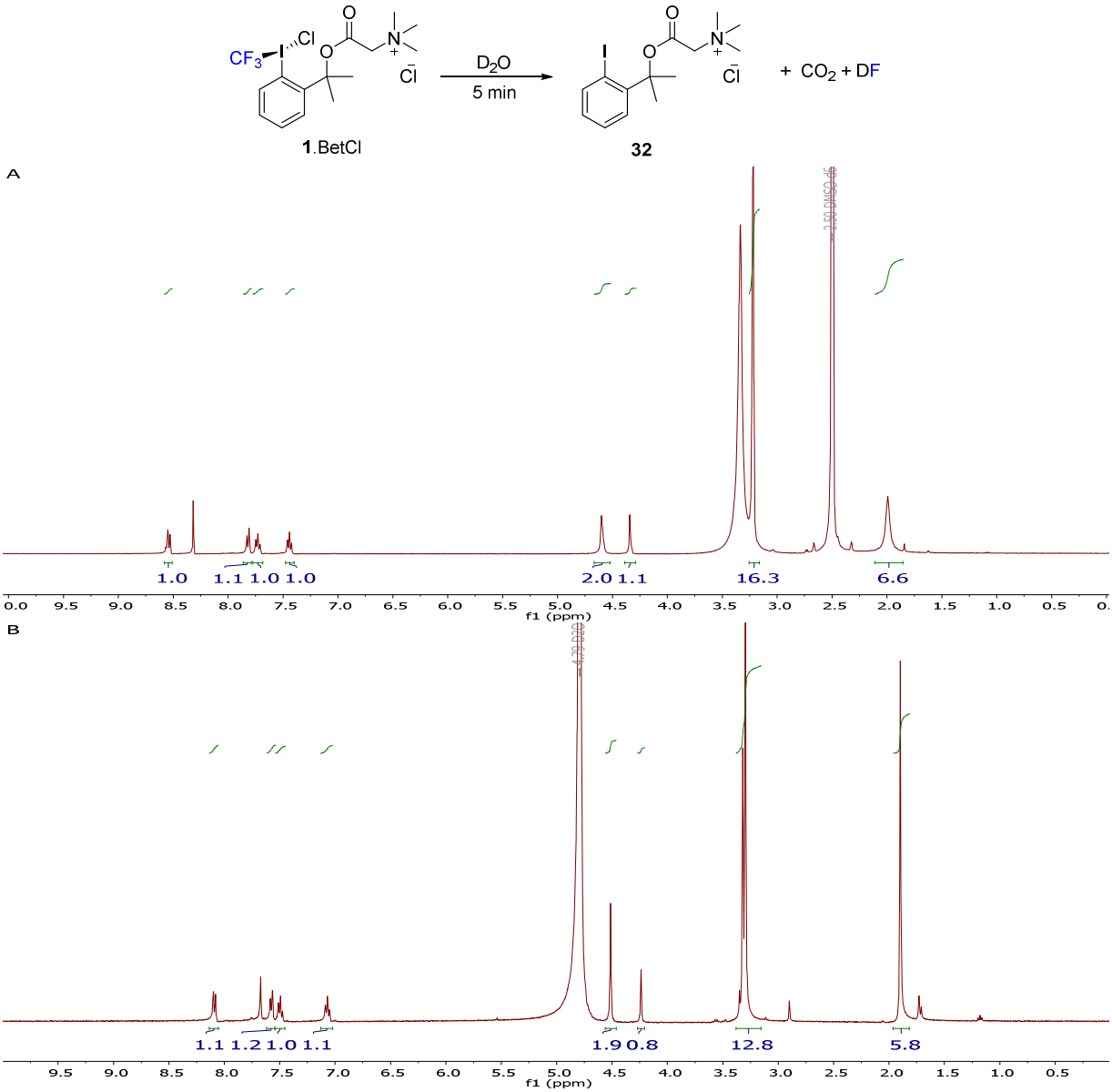


Figure S1: **A**: ^1H NMR (DMSO-d_6) of **1**·BetCl and betaine hydrochloride (2:1). **B**: ^1H NMR (D_2O) of **32** formed in 5 minutes from **1**·BetCl in D_2O (2:1 to betaine chloride).

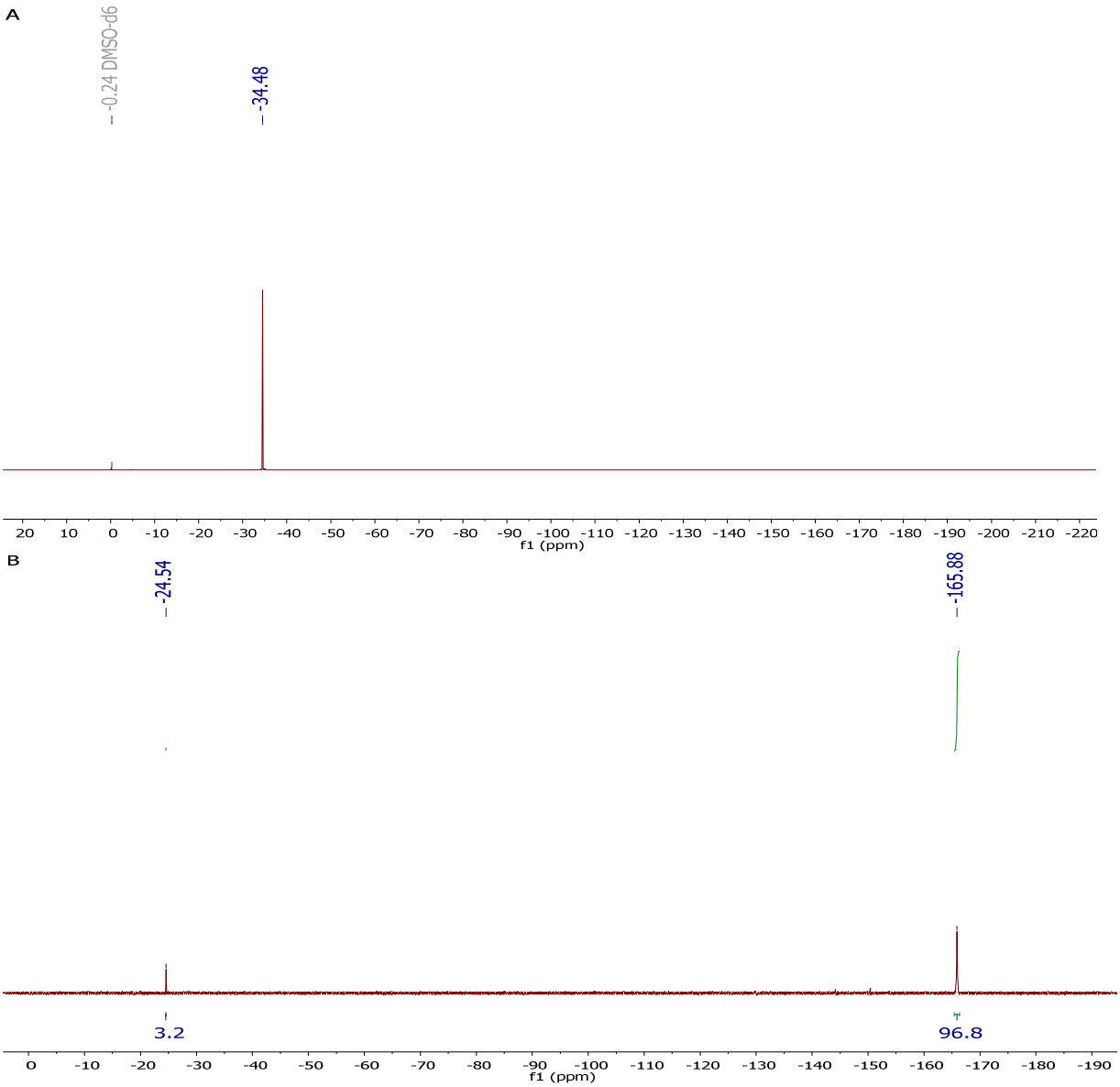
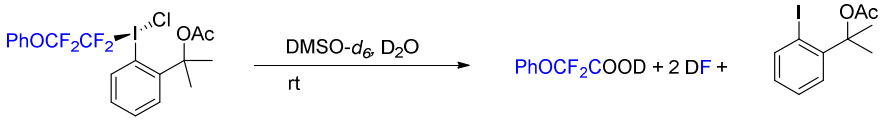


Figure S2: **A**: ^{19}F NMR (DMSO-d_6) of **1**·BetCl. **B**: ^{19}F NMR (D_2O) of DF formed in 5 minutes from **1**·BetCl in D_2O.

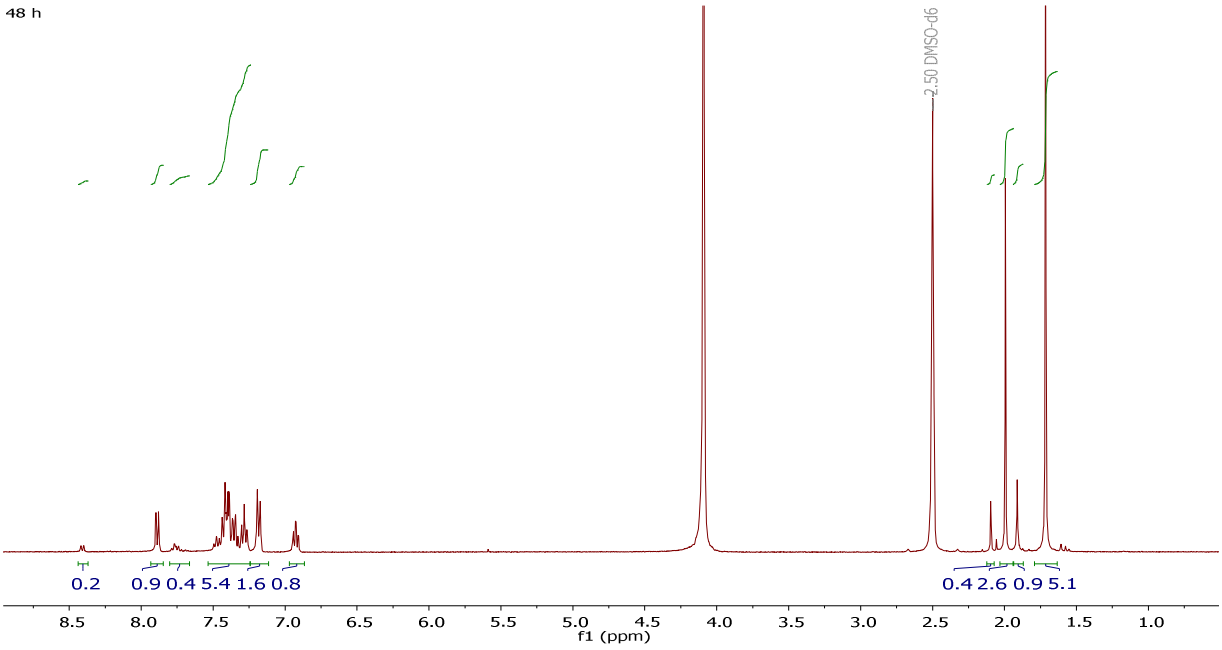
Reagent **3a**·AcCl (8 mg, 15 µmol) was placed in an NMR tube and disolved in DMSO-d_6 (0.3 ml), followed by the addition of D_2O (0.1 ml). The reaction was monitored by ^1H NMR and ^{19}F NMR (Table S1, Figure S3).



3a·AcCl **8**-D **33**

Time	^{19}F NMR yield (%)			^1H NMR yield (%)	
	3a·AcCl	**8**-D	2 DF	**3a**·AcCl	**33**
10 min	98	2	4	96	4
16 h	42	58	54	39	61
48 h	15	85	75	16	84

Table S1: Decomposition of **3a**·AcCl in the presence of D_2O.



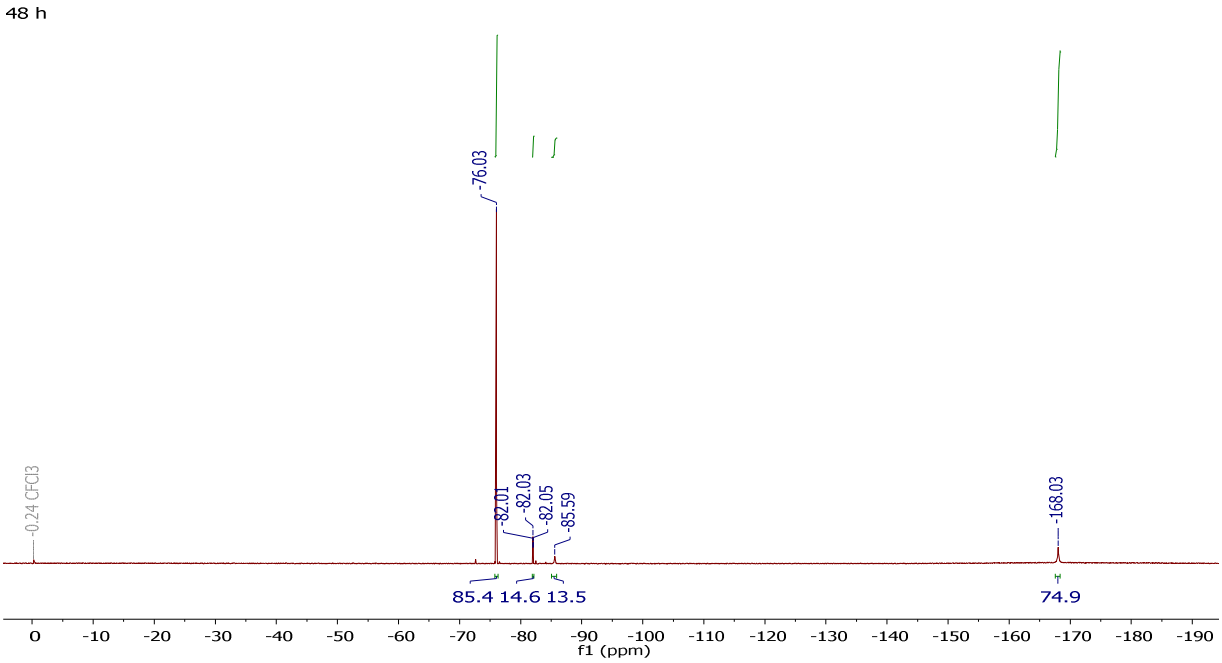


Figure S3: ^{1}H and ^{19}F NMR spectra of the decomposition of **3a**·AcCl in presence of water (after 48 h).

3.2. Stability of compounds 17

Compound **17b** (8 mg, 22.5 µmol) was placed in an NMR tube and disolved in 1M phosphate buffer (0.5 ml, pH 8). A 1M solution of CF_3COOK (22.5 µmol, 22.5 µl) was added and the reaction was monitrored by ^{19}F NMR.

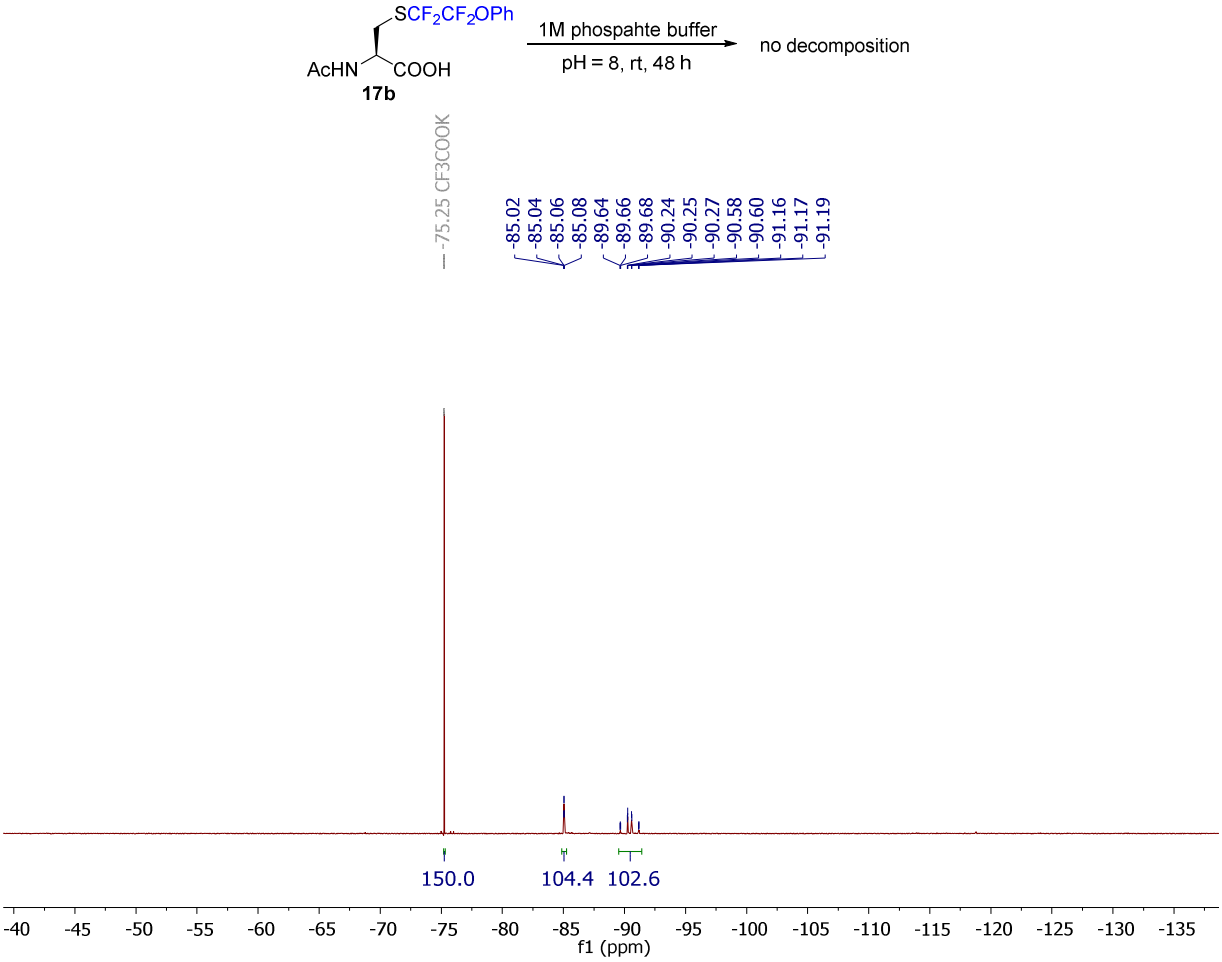


Figure S4: ^{19}F NMR spectrum of **17b** in 1M phosphate buffer.

Compoud **17c** (4.4 mg, 10.5 µmol) was placed in an NMR tube and disolved in a freshly prepared solution of NH_4HCO_3 (1M, 0.23 ml). A 1M solution of CF_3COOK (10.5 µmol, 10.5 µl) was added and the mixture was monitrored by ^{19}F NMR.

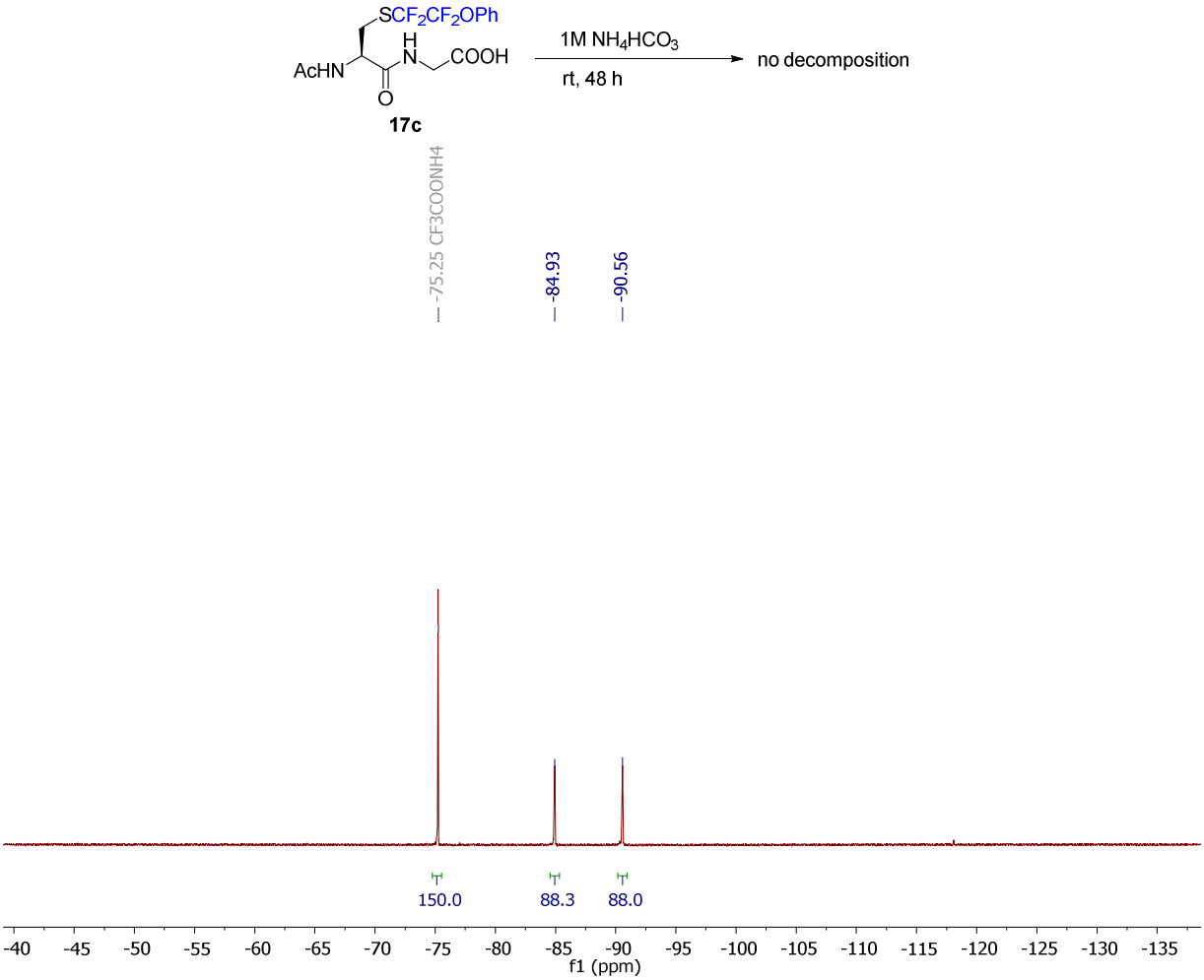


Figure S5: ^{19}F NMR spectrum of **17c** in 1M NH_4HCO_3.

Compound **17a** (5.5 mg, 15 µmol) was placed in an NMR tube and disolved in $CDCl_3$ (0.4 ml). CF_3COOH (30 µmol, 2.3 µl) was added and the mixture was monitrored by ^{19}F NMR.

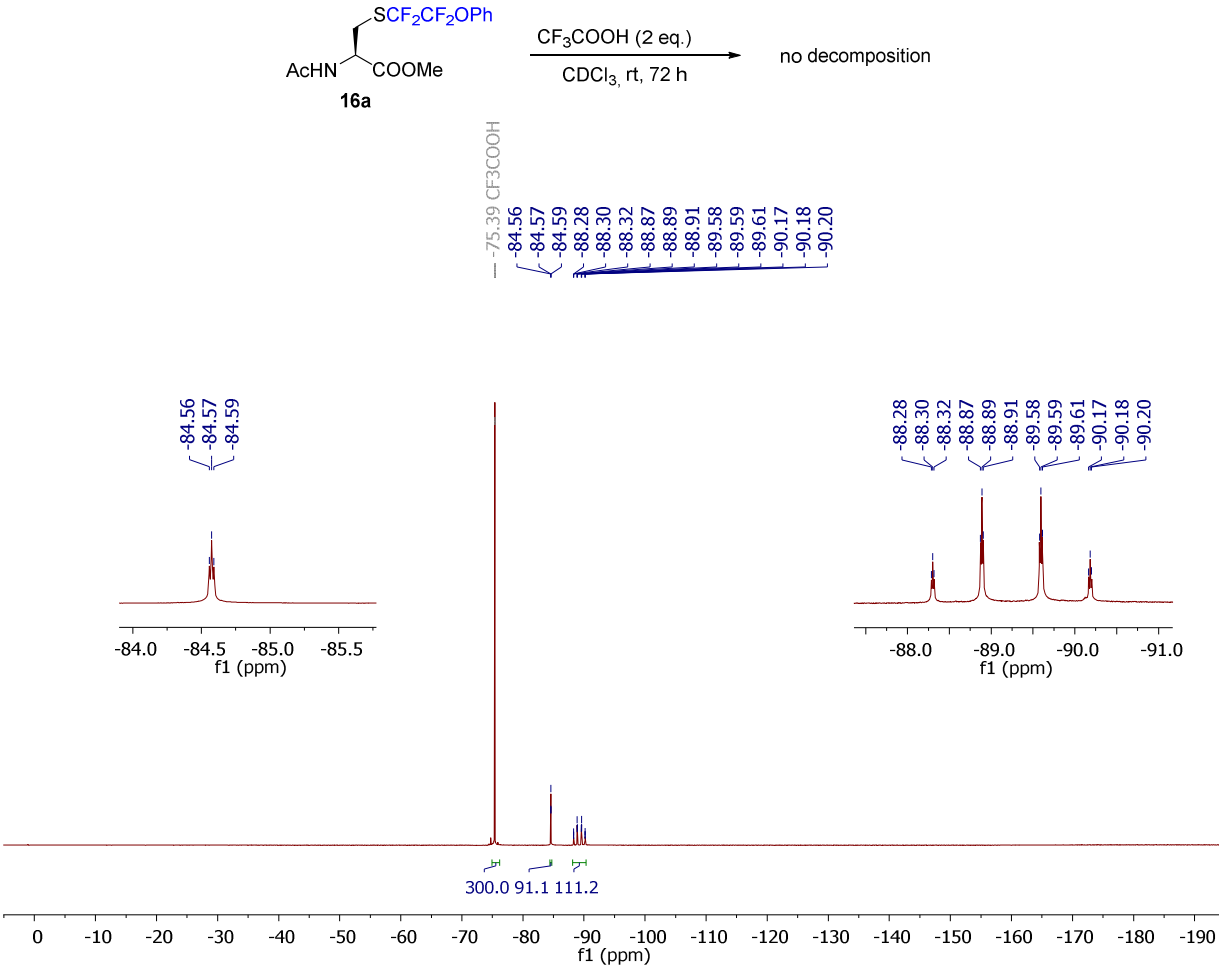
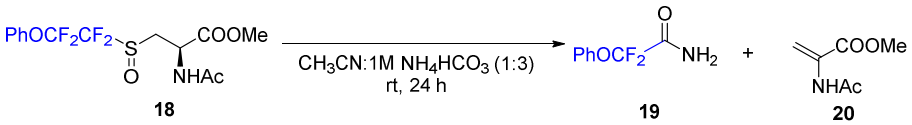


Figure S6: ^{19}F NMR spectrum of **17a** in the presence of CF_3COOH.



82 % (**19**:**20** = 1:1)

Compound **18** (46 mg, 0.12 mmol) was placed in a flask and suspended in 1M NH_4HCO_3 (2.4 ml) and CH_3CN (0.8 ml). After stirring overnight, the suspension was extracted with DCM (3 × 7 ml), dried over $MgSO_4$ and concentrated under vacuum to give 33 mg of solid, which was analyzed by ^1H NMR and ^{19}F NMR. ^1H NMR shifts of **20** are consistent with the reported one by Wang.[5] 2,2-Difluoro-2-phenoxyacetamide (**19**): ^1H NMR (401.00 MHz, $CDCl_3$): δ 6.07 (bs, 1H, N*H*), 6.43 (bs, 1H, N*H*), 7.22–7.30 (m, 3H, C(3)*H* and C(5)*H*), 7.39 (t, $^3J_{HH}$ = 7.8 Hz, 2H, C(4)*H*); ^{19}F NMR (377.28 MHz, $CDCl_3$): δ –77.4 (s, 2F, CF_2); ^{13}C {^1H} NMR (100.84 MHz, $CDCl_3$): δ 114.4 (t, $^1J_{CF}$ = 273.4 Hz, CF_2), 121.7 (s, *C*(3)H), 126.5 (s, *C*(5)H), 129.6 (s, *C*(4)H), 149.2 (t, $^3J_{CF}$ = 1.7 Hz, *C*(2)), 161.4 (t, $^2J_{CF}$ = 37.3 Hz *C*(1)); HRMS (*m/z*, CI^+): $[M+H]^-$ calc. for $C_8H_8F_2NO_2$, 188.0523, found 188.0522.

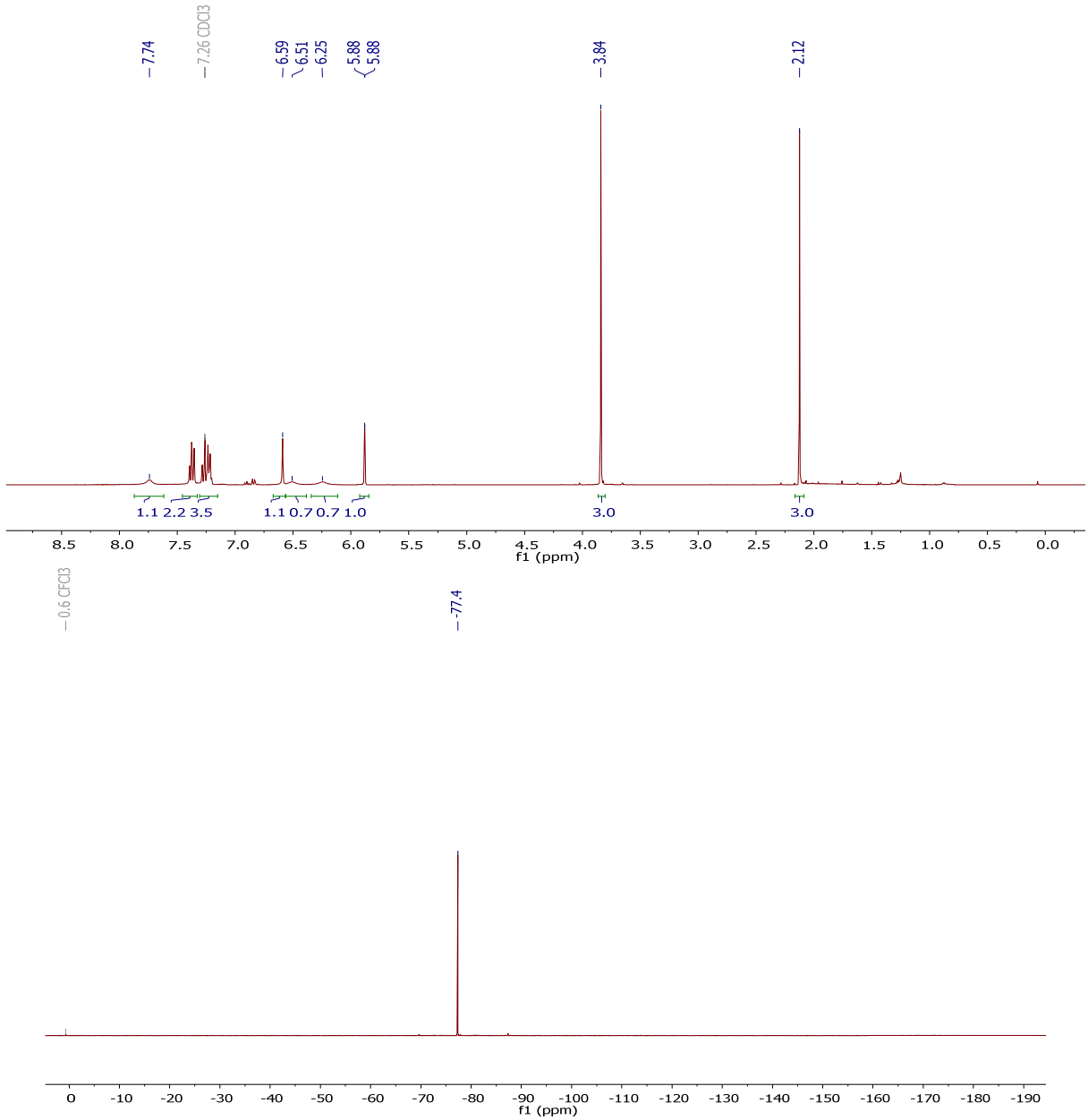
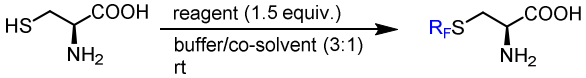


Figure S7: ^{1}H and ^{19}F NMR spectra of a mixture of **19** and **20**.

4. Cysteine fluoroalkylation



9a, **9b** or **11**

For the cysteine fluoroalkylation, two reaction procedure were used, in both cases the concentration of cysteine was 30mM:

Procedure A: In a 1.5 ml eppendorf vial cysteine (150 µl of a 0.1 M solution in buffer with 1 eq. CF_3CH_2OH) and CH_3CN (125 µl) were mixed, followed by the addition of reagent **3b**·TFA or **4b**·HCl (225 µl, 0.1M solution in water). The mixture was vortexed for 30 min and the soluble part was transferred to an NMR tube containing a capilary with acetone-d_6.

Procedure B: In a 1.5 ml eppendorf vial cysteine 150 µl (0.1 M solution in water with 1 eq. CF_3COOK) and buffer (225 µl) were mixed, followed by the addition of reagent **1**·BetCl, **3a**, **3a**·AcCl or **4a** (125 µl, 0.18 M solution in DMSO-d_6). The mixture was vortexed for 30 min (or 5 min in the case of **1**·BetCl) and the soluble part was transferred to an NMR tube.

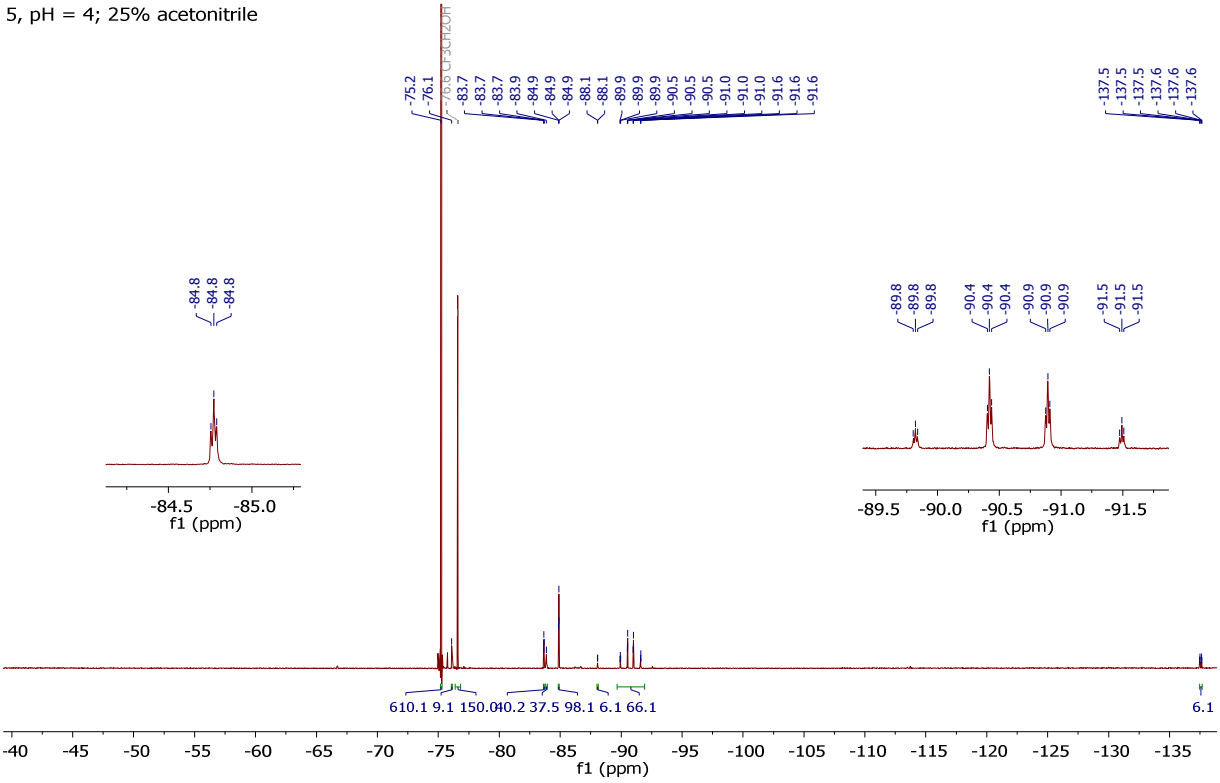


Figure S8: Example of a ^{19}F NMR spectrum of the reaction of cysteine with **3b**·TFA at pH 4 (rt, 30 min).

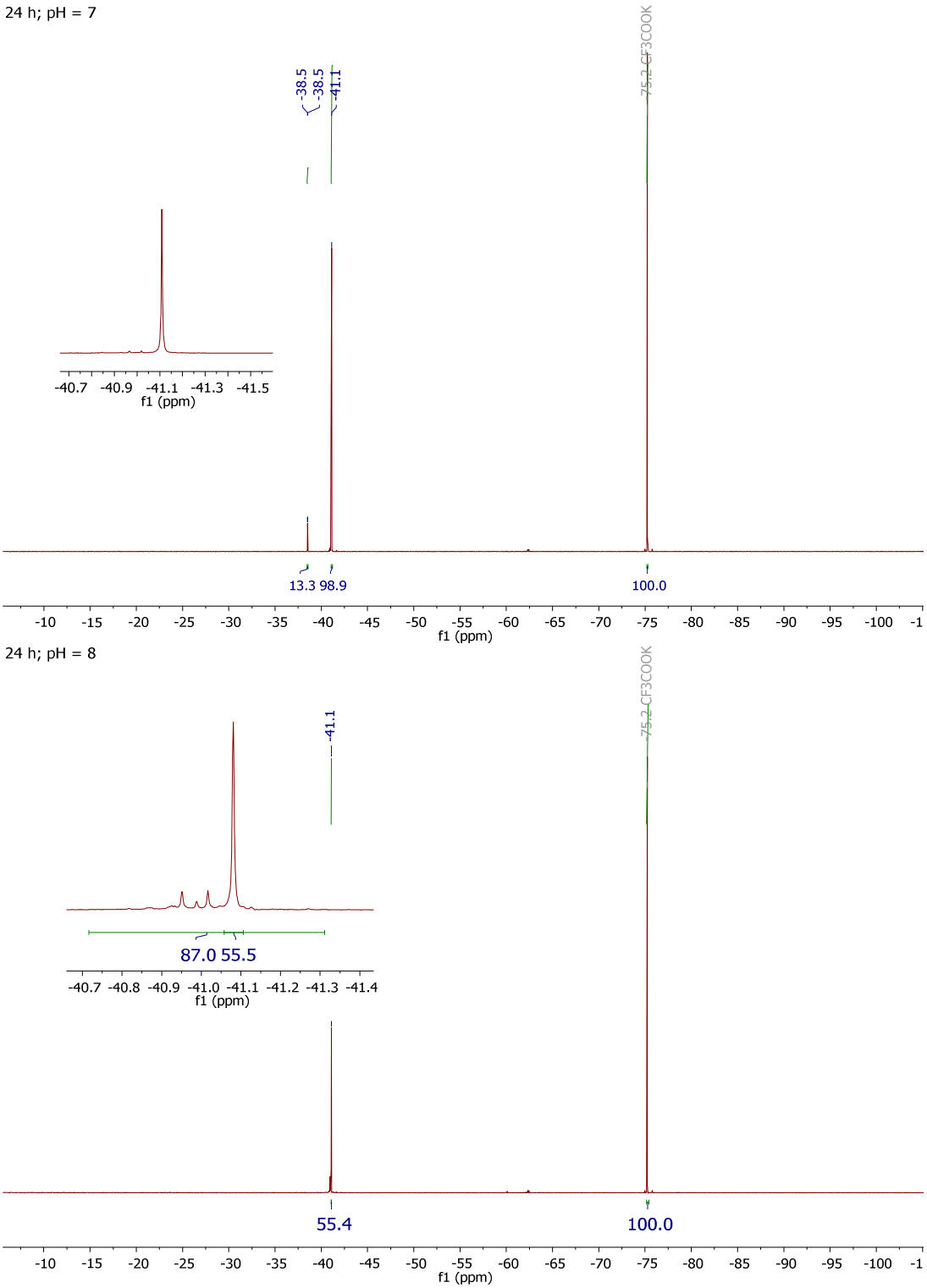


Figure S9: Examples of a ^{19}F NMR spectrum of the reaction of cysteine with **1**·BetCl at pH 7 and 8 (rt, 24 h).

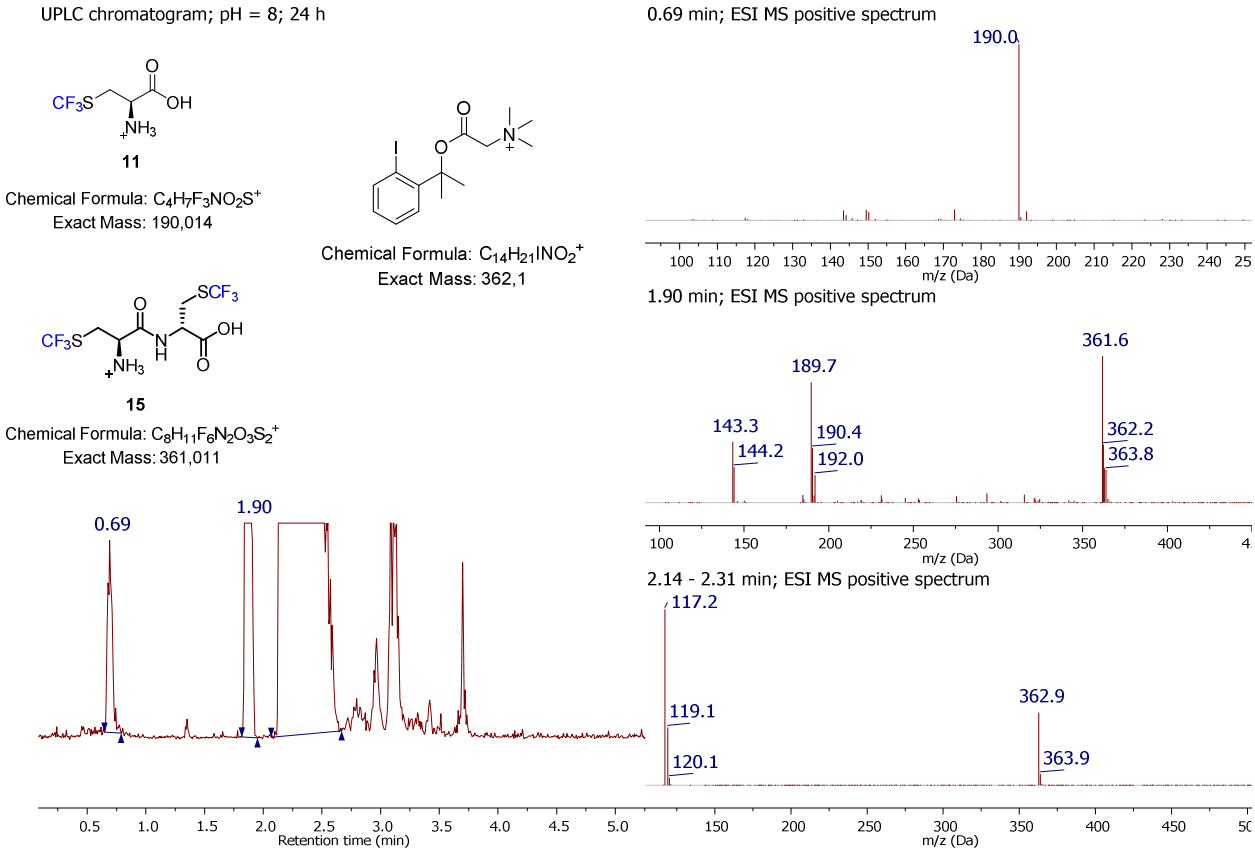
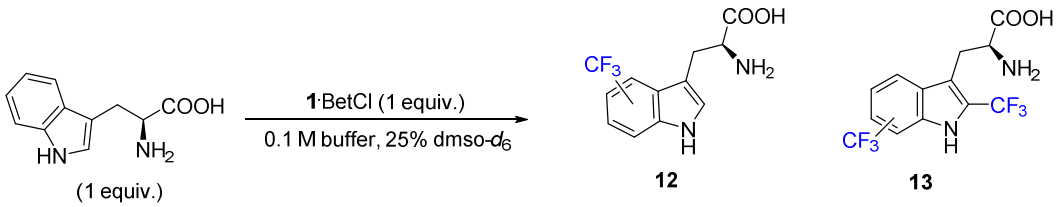


Figure S10: UPLC-MS spectrum of the crude reaction mixture of cysteine with **1**·BetCl at pH 8 (rt, 24 h).

5. Tyrosine and Tryptophane fluoroalkylation



acetate buffer pH = 4	0%	0%
phospate buffer pH = 7; 10 min	<1%	0%
phospate buffer pH = 7; 3 h	9%	3%

Procedure: In a 1.5 ml eppendorf vial tryptophane (187.5 µl, 0.08 M solution in solution 25 % DMSO-d_6 in buffer), CF_3COOK (15 µl, 1M in water) and buffer (225 µl) were mixed, followed by the addition of reagent **1**·BetCl (87.5 µl, 0.17 M solution in DMSO-d_6) at 0°C. The mixture was vortexed for 5 min at rt and transferred to an NMR tube and ^{19}F NMR was measured after 10 min and 3 hours.

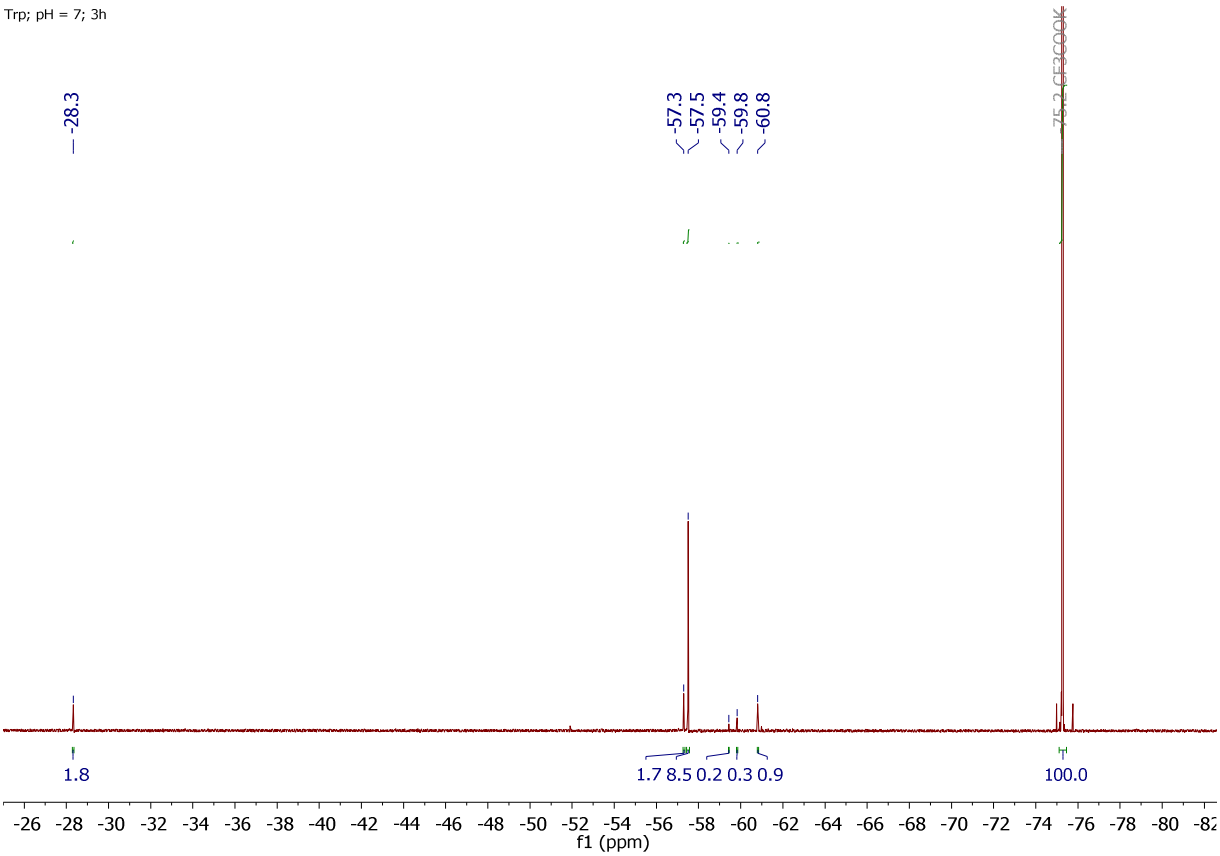
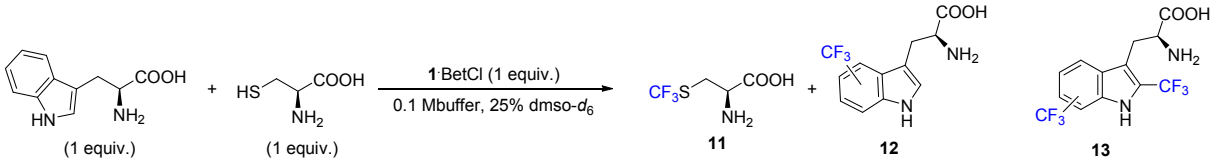


Figure S11: Example of a ^{19}F NMR spectrum of the reaction of tryptophane with **1**·BetCl at pH 7 (rt, 3 h).



acetate buffer pH = 4	30%	24%	8%
phospate buffer pH = 7	46%	17%	5%

Procedure: In a 1.5 ml eppendorf vial cysteine (150 µl, 0.1 M solution in buffer), tryptophane (187.5 µl, 0.08 M solution in solution 25 % DMSO-d_6 in buffer), CF_3COOK (15 µl, 1M in water) and buffer (75 µl) were mixed, followed by the addition of reagent **1**·BetCl (87.5 µl, 0.17 M solution in DMSO-d_6) at 0°C. The mixture was vortexed for 5 min at rt and transferred to an NMR tube.

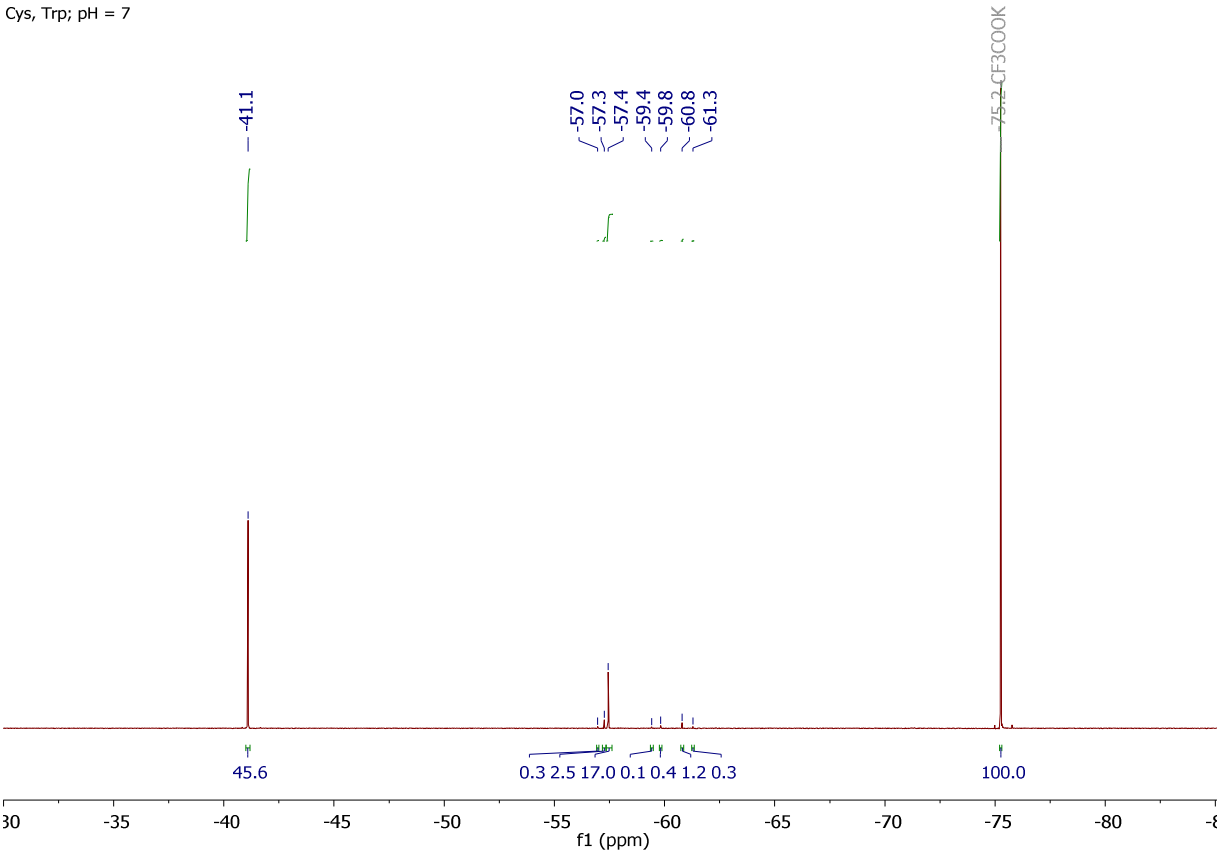
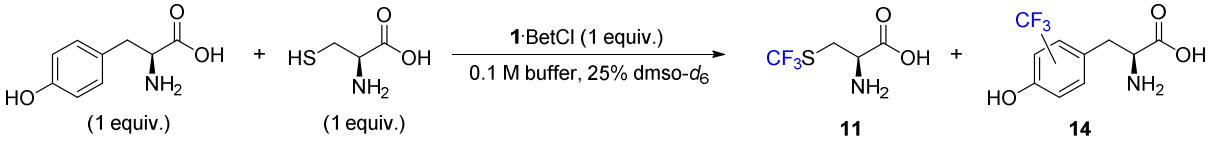


Figure S12: Example of a ^{19}F NMR spectrum of the reaction of tryptophane, cysteine mixture (1:1) with **1**·BetCl at pH 7 (rt, 5 min).



acetate buffer pH = 4	79%	2%
phospate buffer pH = 7	73%	<1%

Procedure: In a 1.5 ml eppendorf vial cysteine (150 µl, 0.1 M solution in buffer), tyrosine (187.5 µl, 0.08 M solution in solution 25 % DMSO-d_6 in buffer), CF_3COOK (15 µl, 1M in water) and buffer (75 µl) were

mixed, followed by the addition of reagent **1**·BetCl (87.5 µl, 0.17 M solution in DMSO-d_6) at 0°C. The mixture was vortexed for 5 min at rt and transferred to an NMR tube.

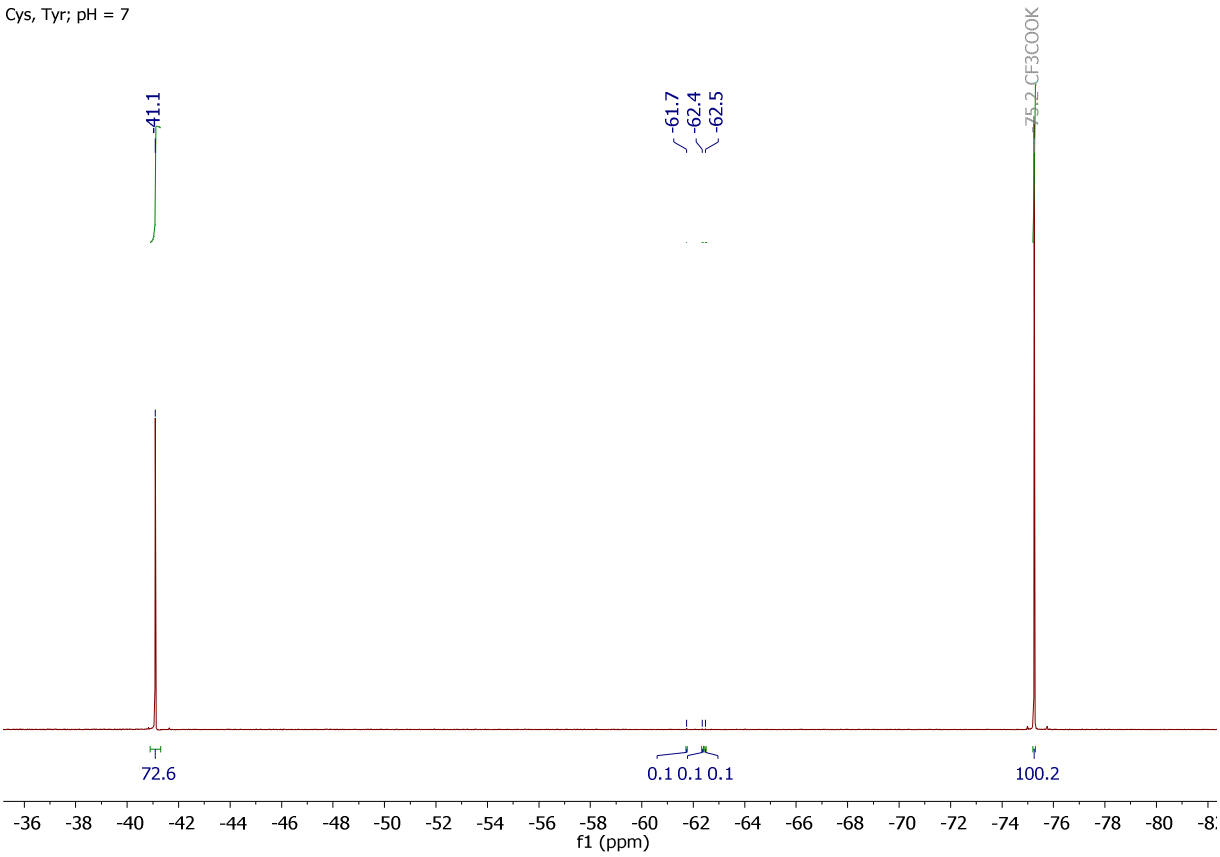


Figure S13: Example of a ^{19}F NMR spectrum of the reaction of tyrosine, cysteine mixture (1:1) with **1**·BetCl at pH 7 (rt, 5 min).

6. Fluoroalkylation of peptide DAVACAK

6.1. LC-MS and MS/MS product characterization

Peptide DAVACAK (**21**)

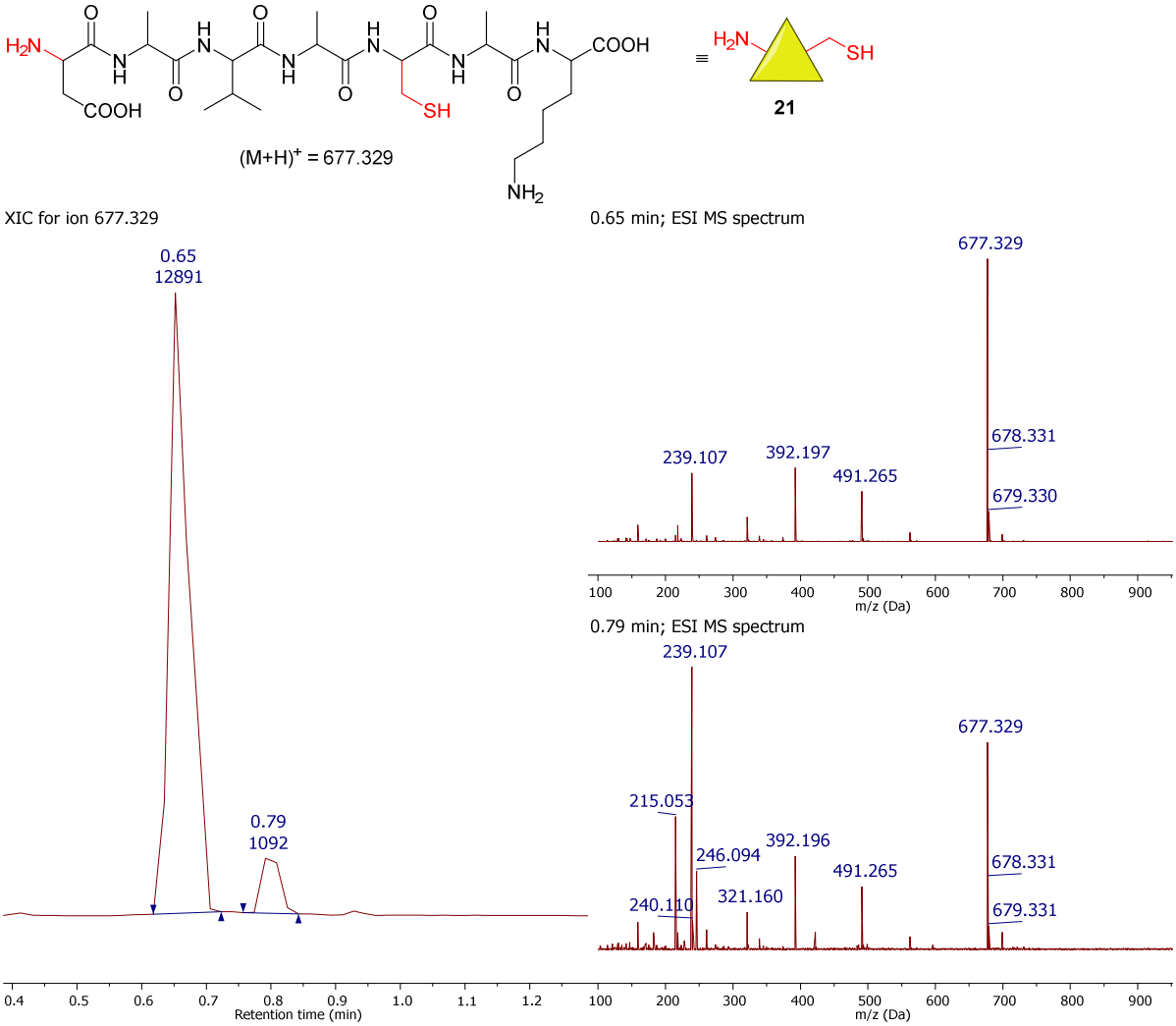


Figure S14: Extracted ion chromatogram for the ion *m/z* = 677.329 and corresponding electrospray spectra (ESI-MS). Two peaks were detected in extracted ion chromatogram, which were considered to be diastereoisomers of **21**. Therefore the AUC reported in the following tables is the sum of AUC of both peaks.

Conjugate **22b**

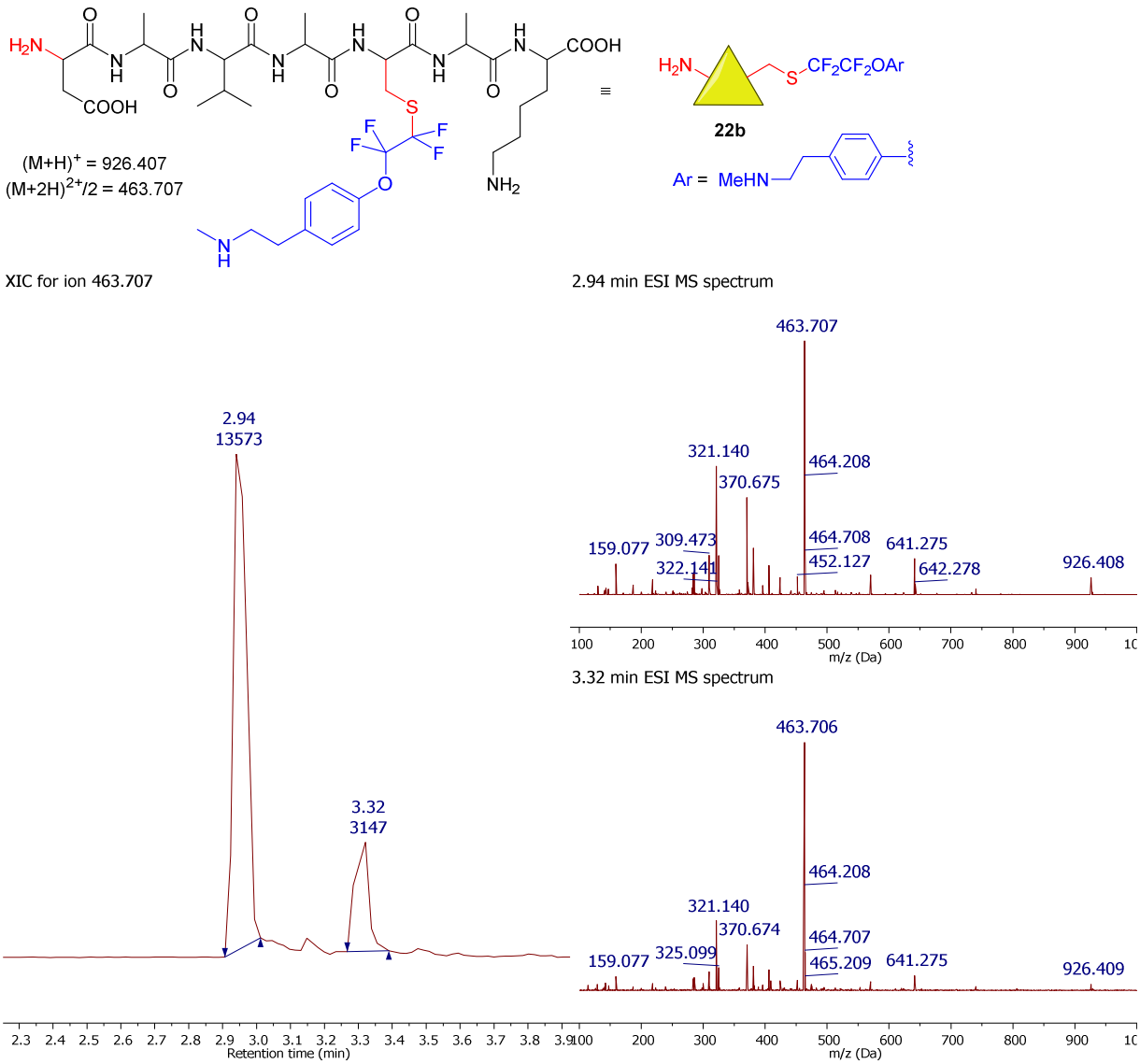
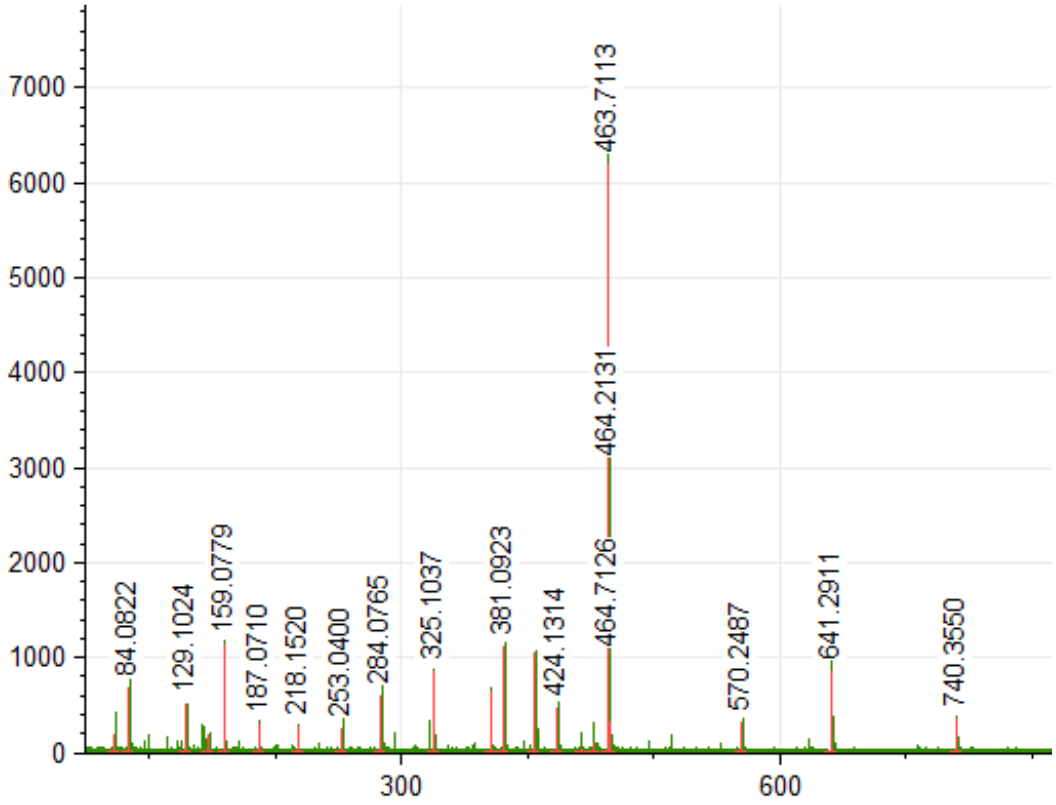


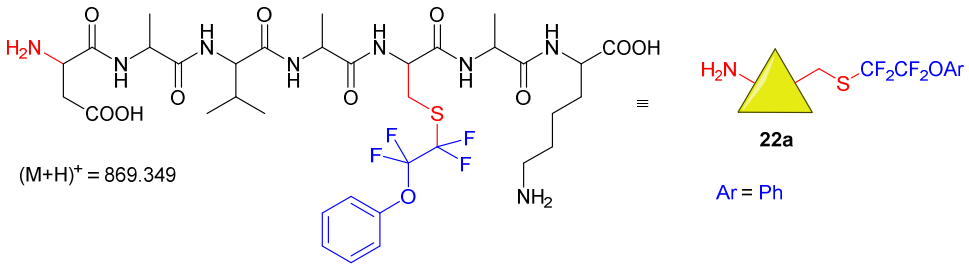
Figure S15: Extracted ion chromatogram for the ion *m/z* = 463.707 and corresponding MS electrospray spectra (ESI-MS). Two peaks were detected in extracted ion chromatogram, which were considered to be diastereoisomers of **22b**. Therefore the AUC reported in the following tables is the sum of AUC of both peaks.



Seq	#	B	Y	#
D	1	116.03426	926.40673	7
A	2	187.07138	811.37979	6
V	3	286.13979	740.34267	5
A	4	357.17691	641.27426	4
C	5	709.26409	570.23715	3
A	6	780.30120	218.14996	2
K	7	908.39617	147.11285	1

Figure S16: MS/MS fragmetantion spectrum of the ion *m/z* = 463.71. Table of theoretical b and y fragment masses[7] with ions detected in the spectrum highlighted in red.

Conjugate **22a**



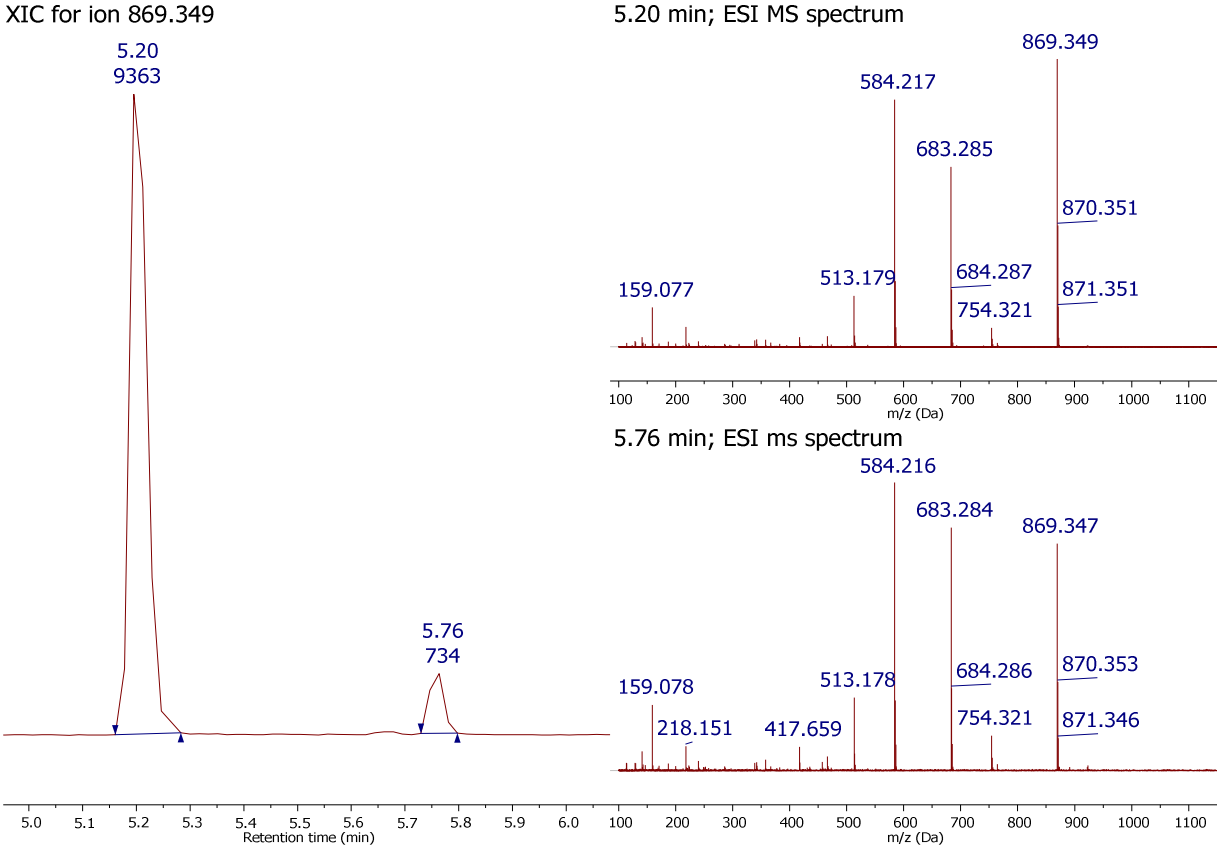
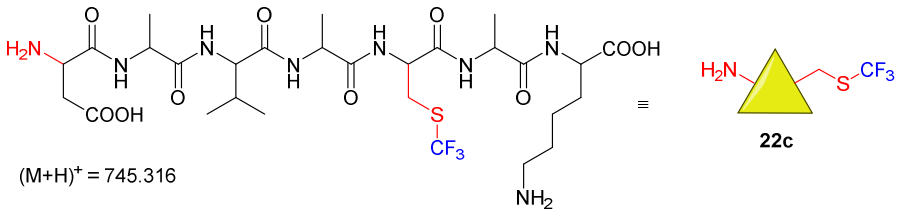


Figure S17: Extracted ion chromatogram for the ion *m/z* = 869.349 and corresponding electrospray MS spectra (ESI-MS). Two peaks were detected in extracted ion chromatogram, which were considered to be diastereoisomers of **22a**. Therefore the AUC reported in the following tables is the sum of AUC of both peaks.

Conjugate **22c**



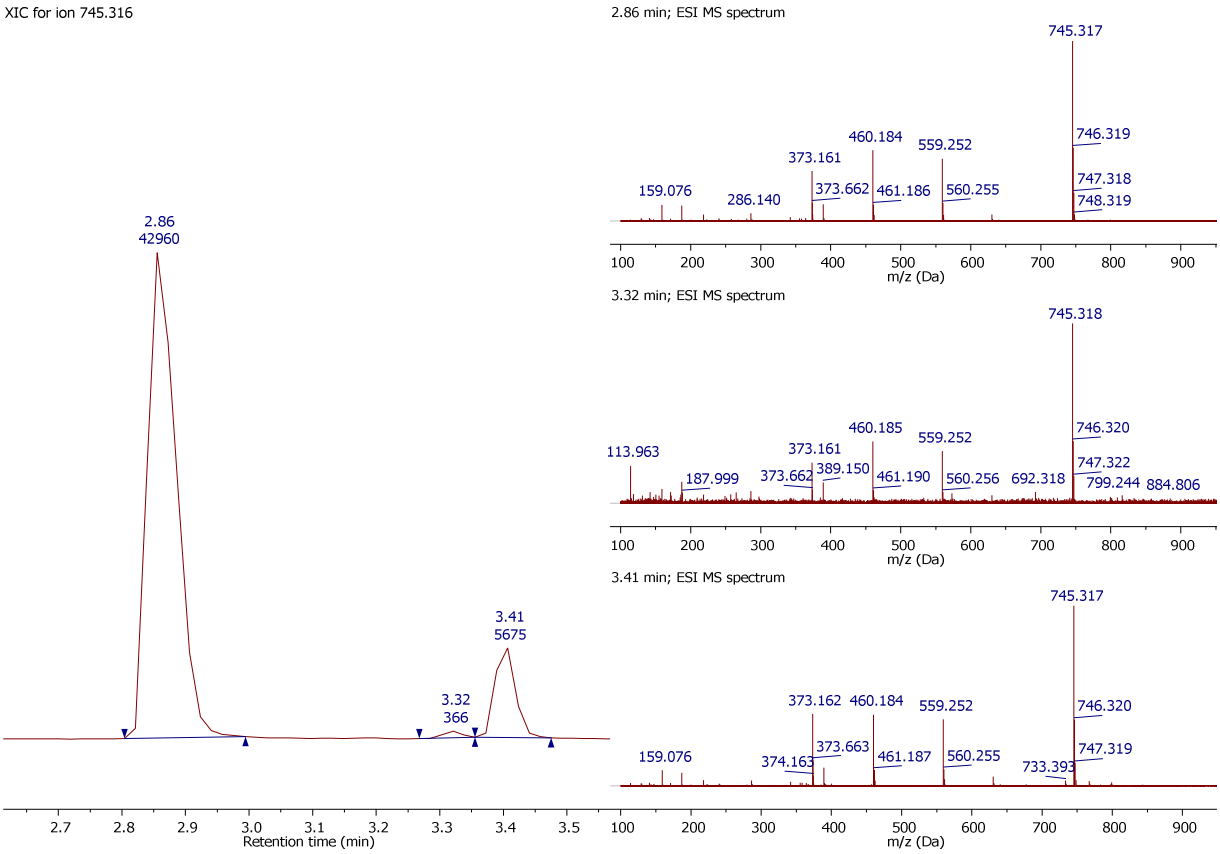


Figure S18: Extracted ion chromatogram for the ion *m/z* = 745.316 and corresponding electrospray MS spectra (ESI-MS). Three peaks were detected in extracted ion chromatogram, which were considered to be diastereoisomers of **22c**. Therefore the AUC reported in the following tables is the sum of AUC of all peaks.

Conjugate **23b**

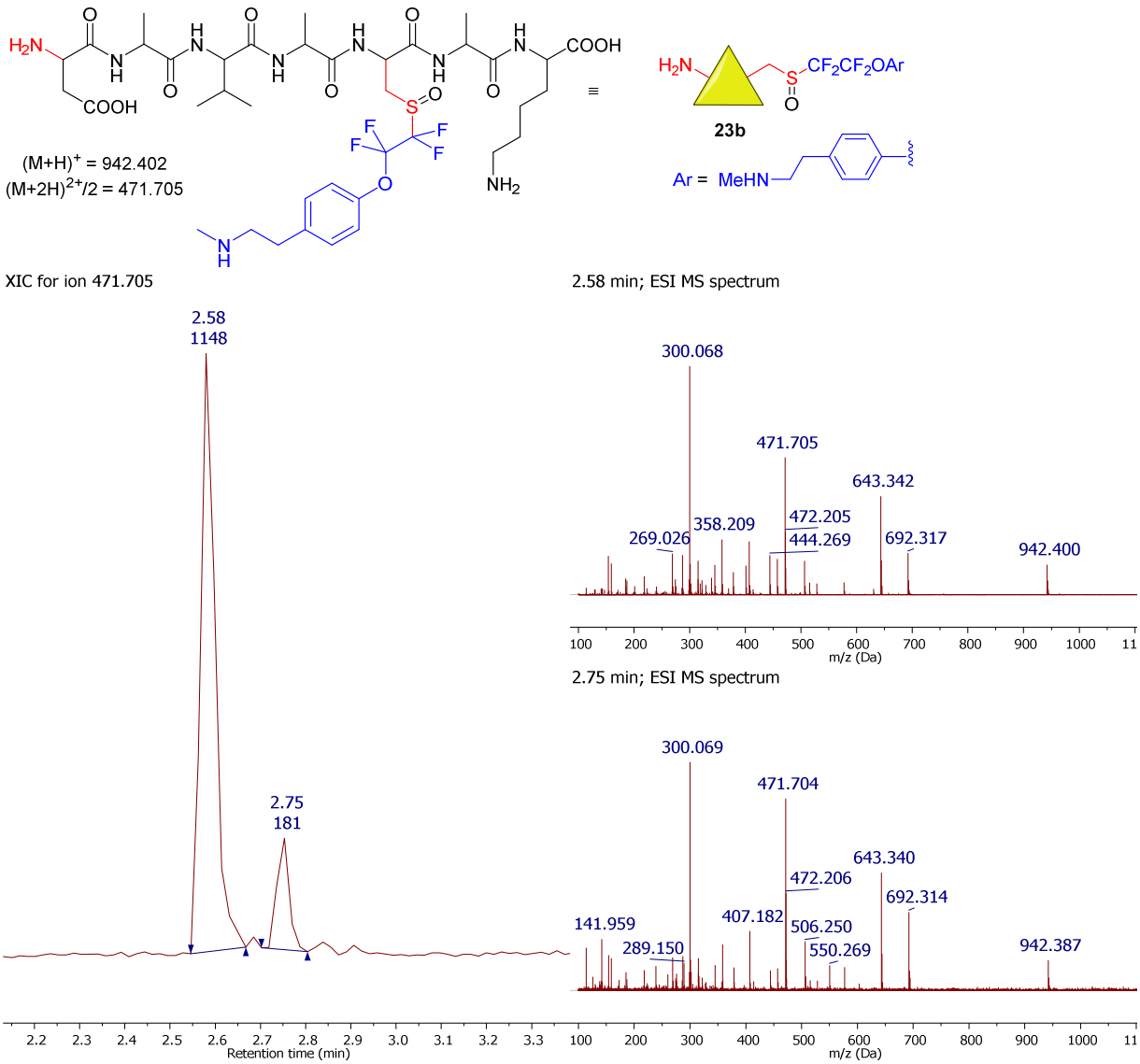
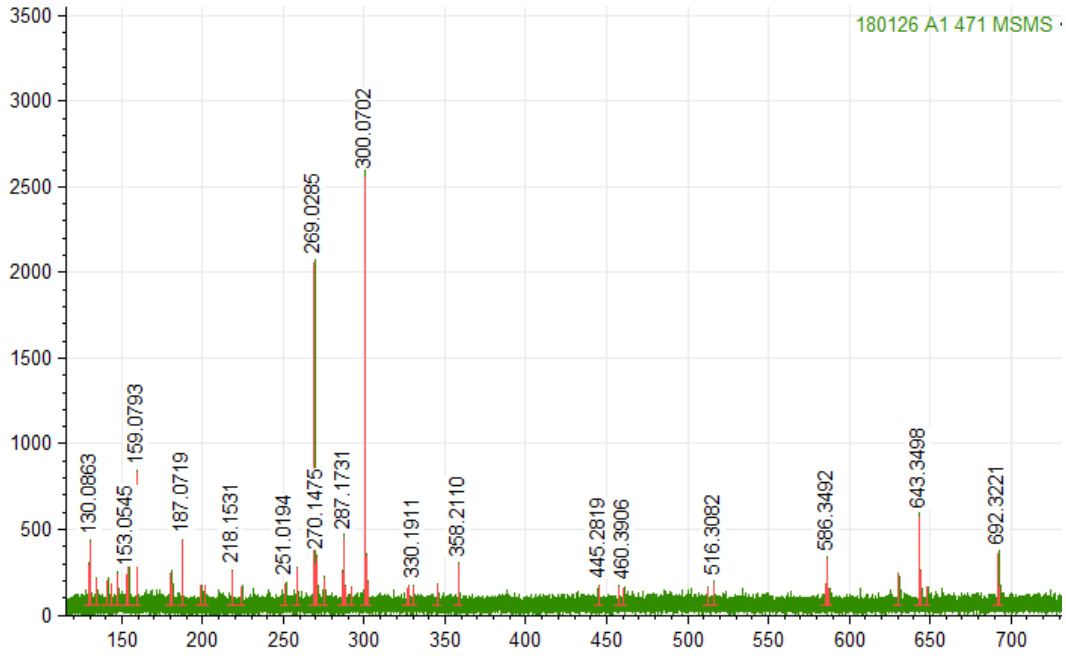
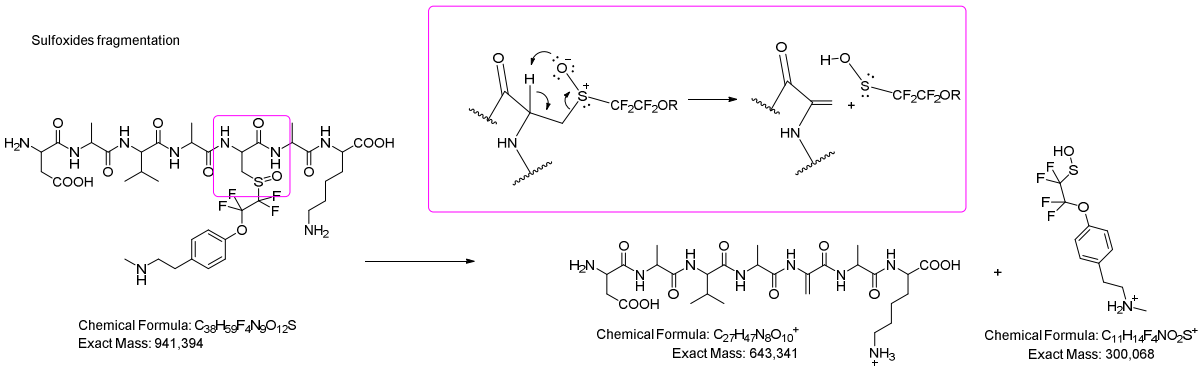


Figure S19: Extracted ion chromatogram for the ion *m/z* = 471.705 and corresponding electrospray MS spectra (ESI-MS). Two peaks were detected in extracted ion chromatogram, which were considered to be diastereoisomers of **23b**. Therefore the AUC reported in the following tables is the sum of AUC of both peaks.



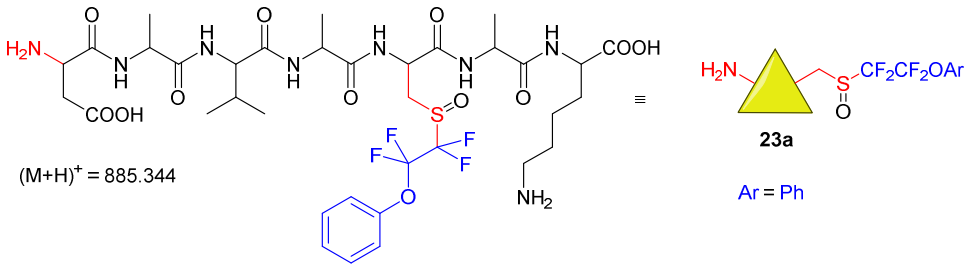
Seq	#	B	Y	#
D	1	116.03426	942.40173	7
A	2	187.07138	827.37479	6
V	3	286.13979	756.33767	5
A	4	357.17691	657.26926	4
C	5	725.25909	586.23215	3
A	6	796.29620	218.14996	2
K	7	924.39117	147.11285	1

Figure S20: MS/MS fragmentation spectrum of the ion *m/z* = 471.705. Table of theoretical b and y fragment masses[7] with ions detected in the spectrum highlighted in red. The main peaks 300.07 and 643.35 are due to the fragmentation of the sulfoxide group, see the scheme S1.



Scheme S1: Fragmentation scheme of CID fragmentation of ion 471.705 to the peaks 300.07 and 643.35 that appear in the MS/MS spectra.[6]

Conjugate **23a**



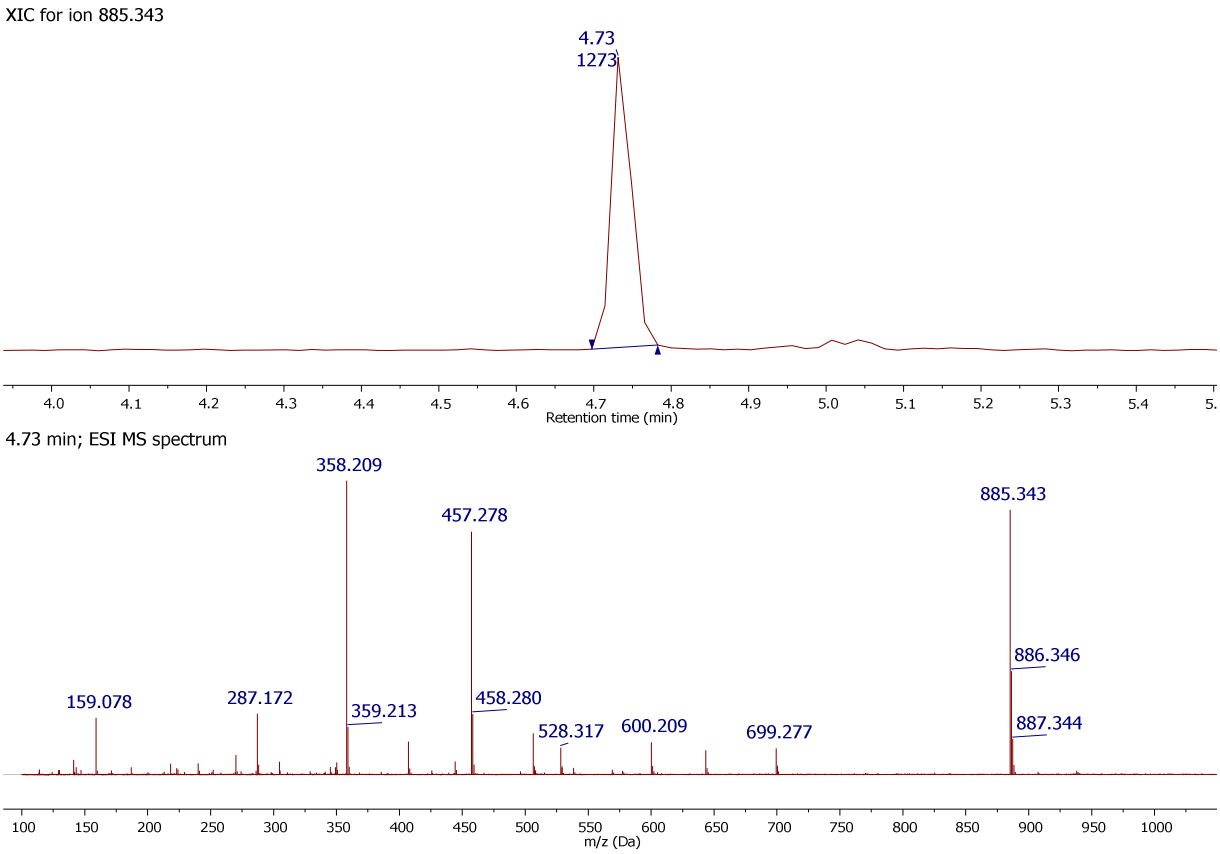
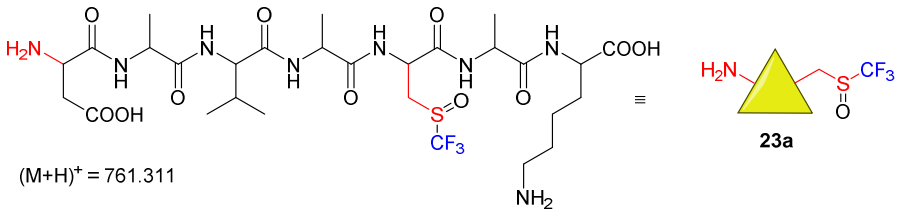


Figure S21: Extracted ion chromatogram for the ion *m/z* = 885.343 and corresponding electrospray MS spectrum (ESI-MS).

Conjugate **23c**



$(M+H)^+ = 761.311$

XIC for ion 761.311

1.87 min; ESI MS spectrum

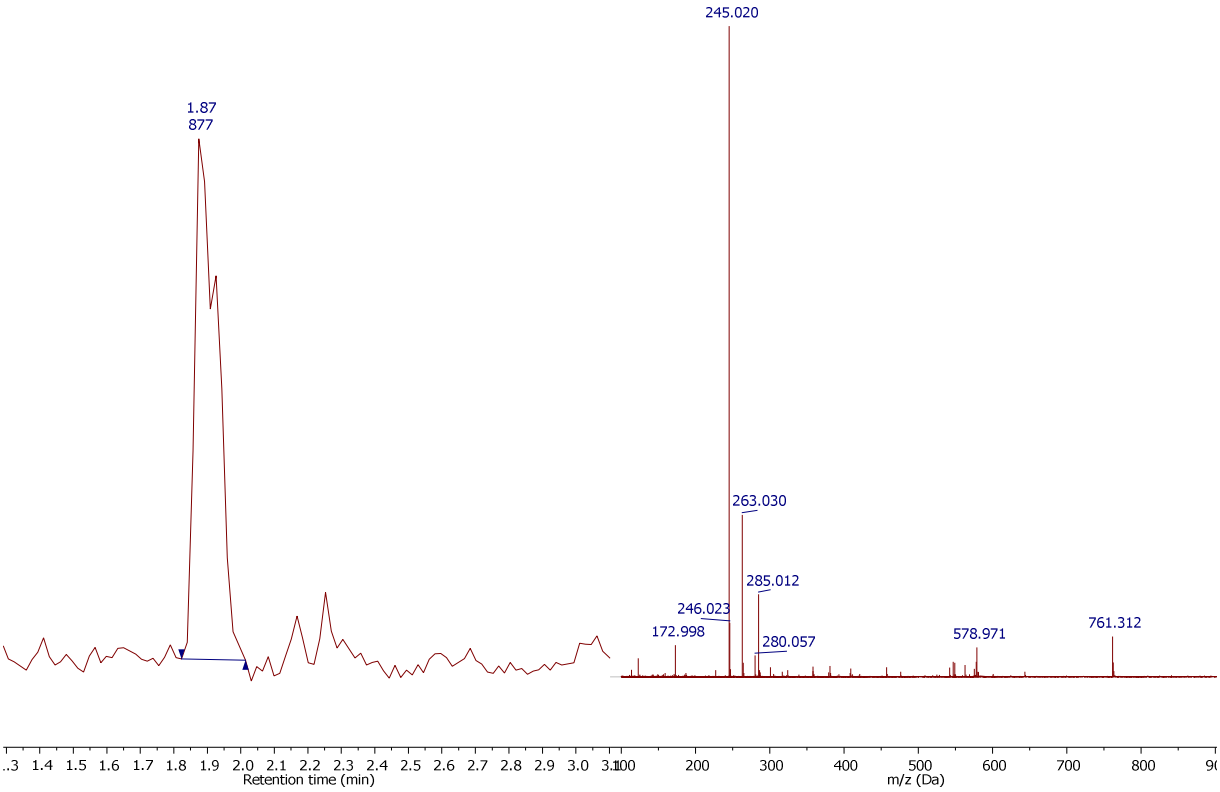
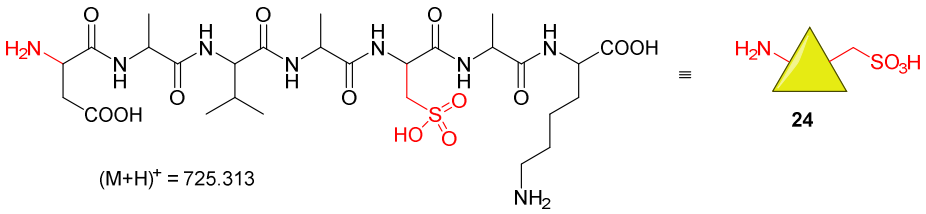
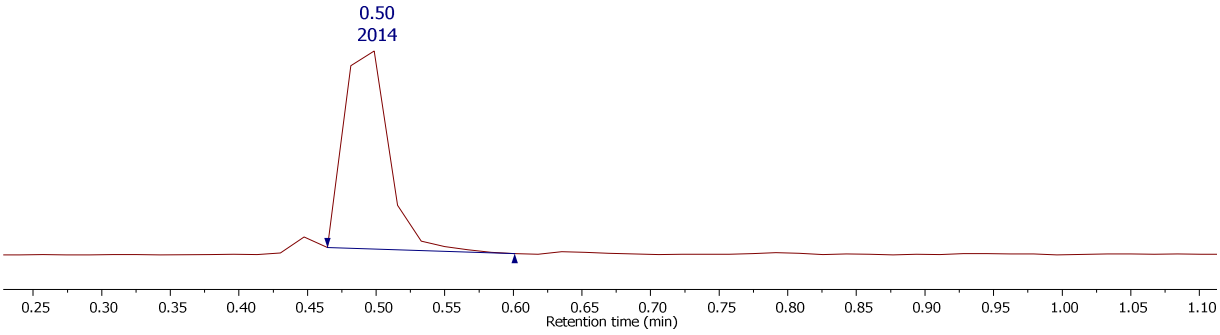


Figure S22: Extracted ion chromatogram for the ion *m/z* = 885.343 and corresponding electrospray MS spectrum (ESI-MS).

Sulfonic acid **24**



XIC for ion 725.313



0.50 min; ESI MS spectrum

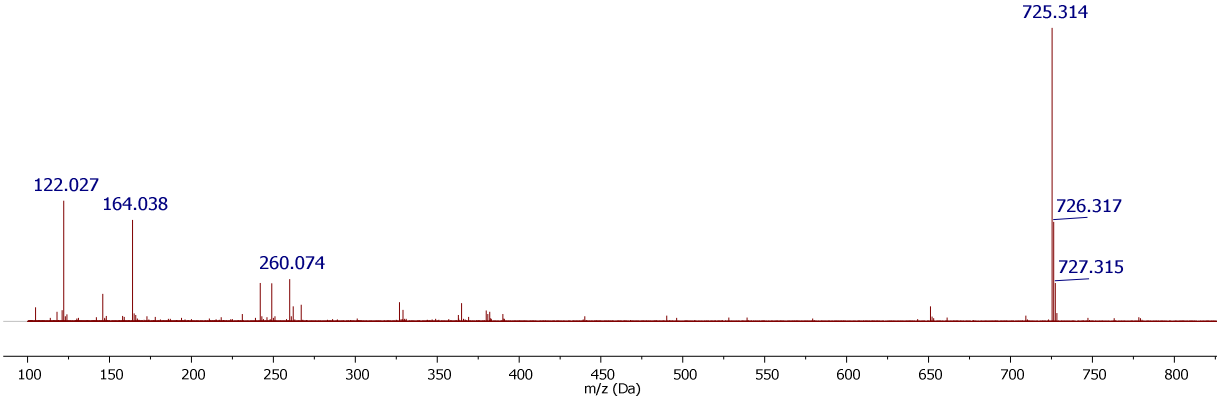
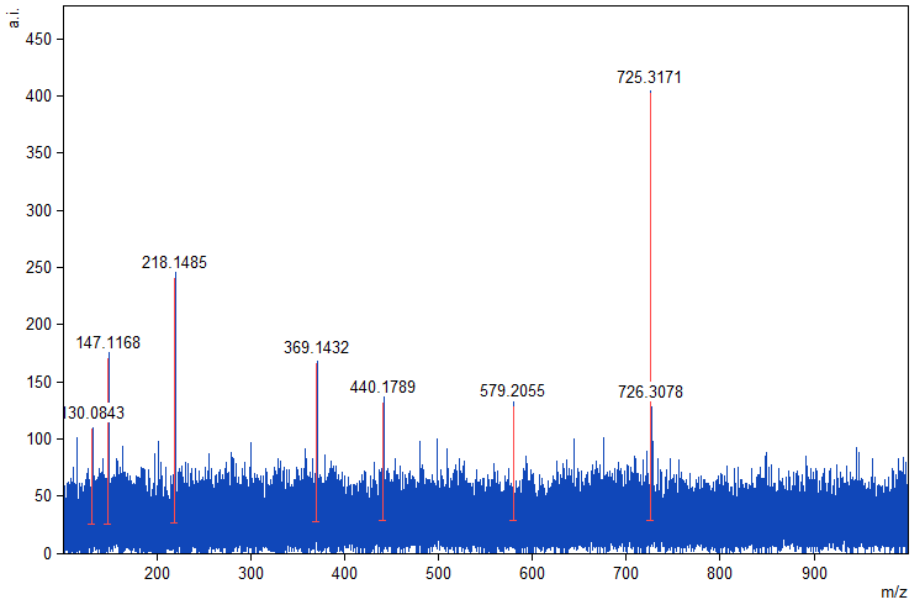


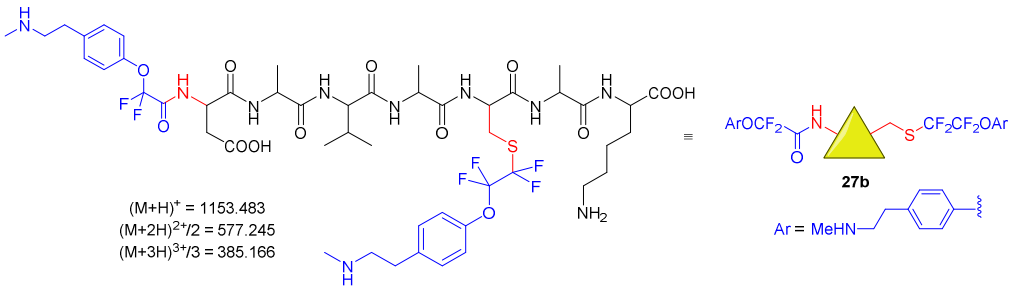
Figure S23: Extracted ion chromatogram for the ion *m/z* = 725.313 and corresponding electrospray MS spectrum (ESI-MS).



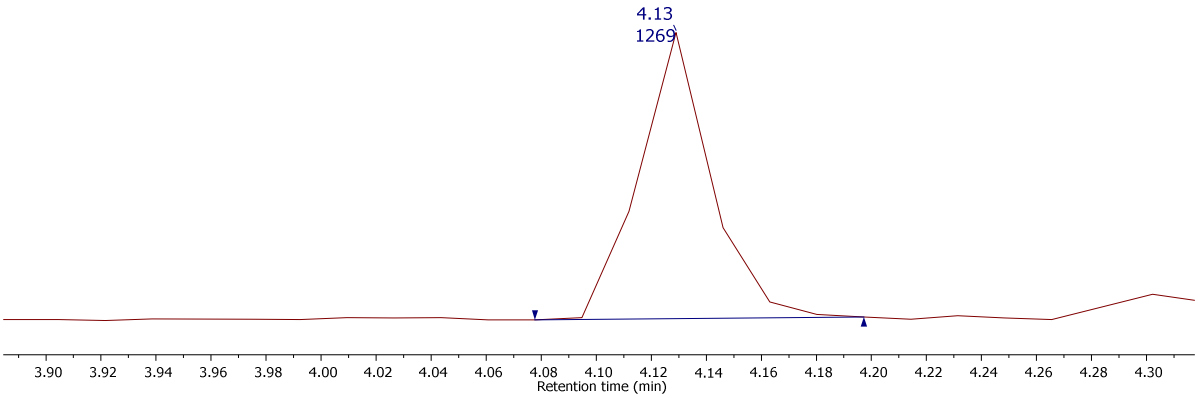
Seq	#	B	Y	#
D	1	116.03426	725.31373	7
A	2	187.07138	610.28679	6
V	3	286.13979	539.24967	5
A	4	357.17691	440.18126	4
C	5	508.17109	369.14415	3
A	6	579.20820	218.14996	2
K	7	707.30317	147.11285	1

Figure S24: MS/MS fragmentation spectrum of the ion *m/z* = 725.313. Table of theoretical b and y fragment masses[7] with ions detected in the spectrum highlighted in red.

Side product **27b**



XIC for ion 577.245



4.13 min; ESI MS spectrum

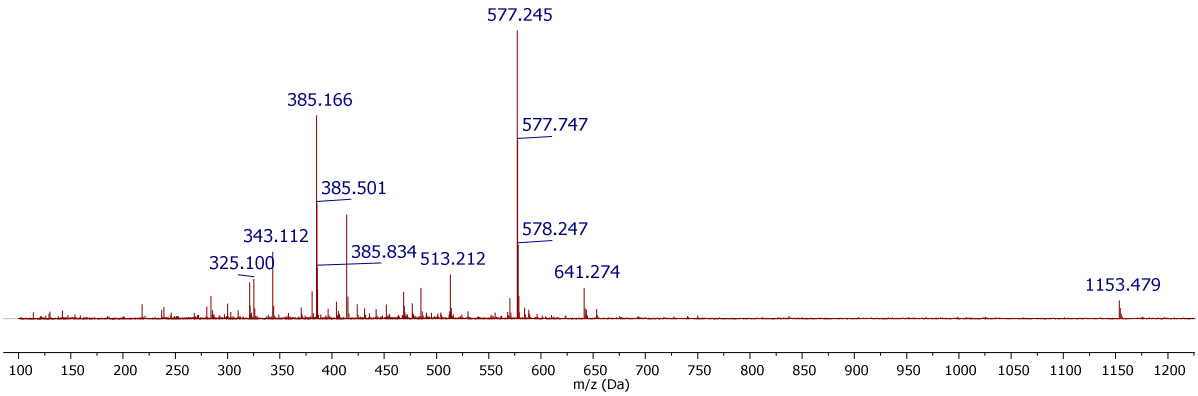
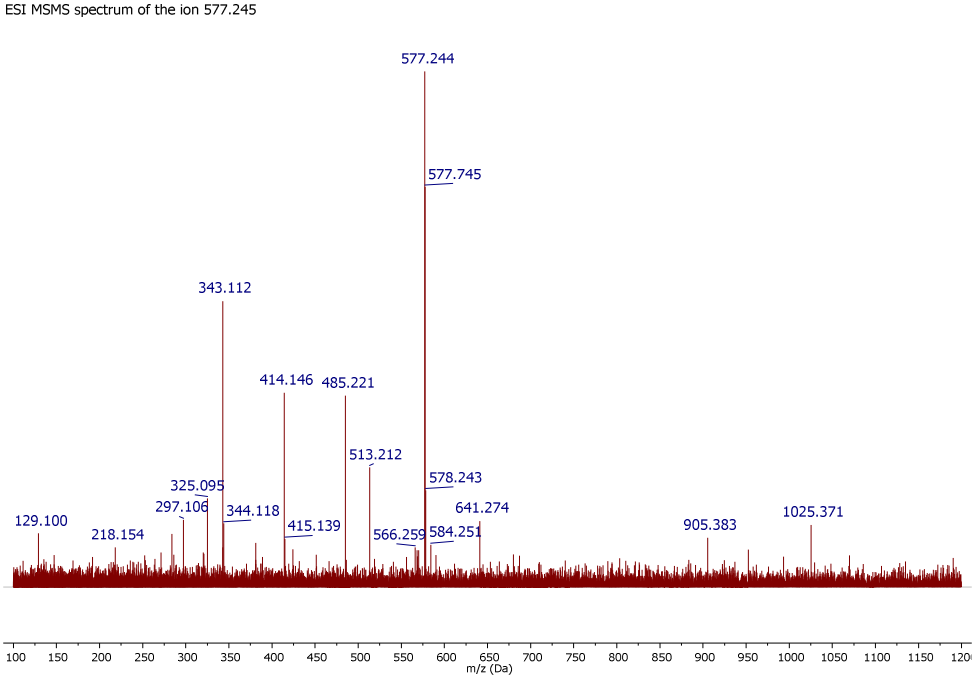


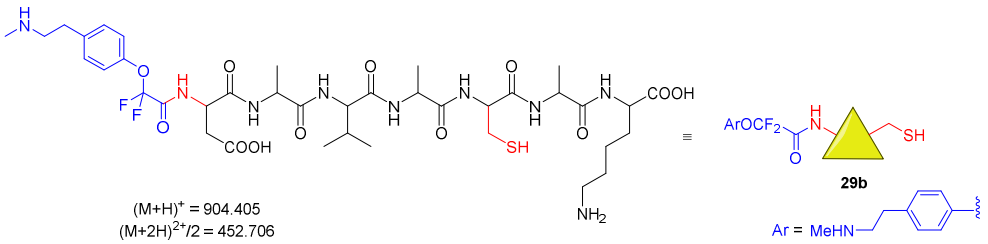
Figure S25: Extracted ion chromatogram for the ion *m/z* = 577.245 and corresponding electrospray MS spectrum (ESI-MS).



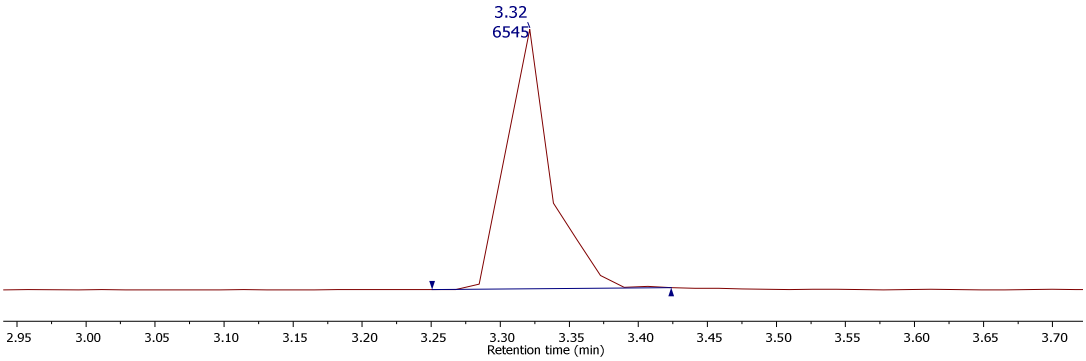
Seq	#	B	Y	#
D	1	343.11026	1153.48273	7
A	2	414.14738	811.37979	6
V	3	513.21579	740.34267	5
A	4	584.25291	641.27426	4
C	5	936.34009	570.23715	3
A	6	1007.37720	218.14996	2
K	7	1135.47217	147.11285	1

Figure S26: MS/MS fragmetantion spectrum of the ion m/z = 577.245. Table of theoretical b and y fragment masses[7] with ions detected in the spectrum highlighted in red.

Side product **29b**



XIC for ion 452.706



3.21 min; ESI MS pectrum

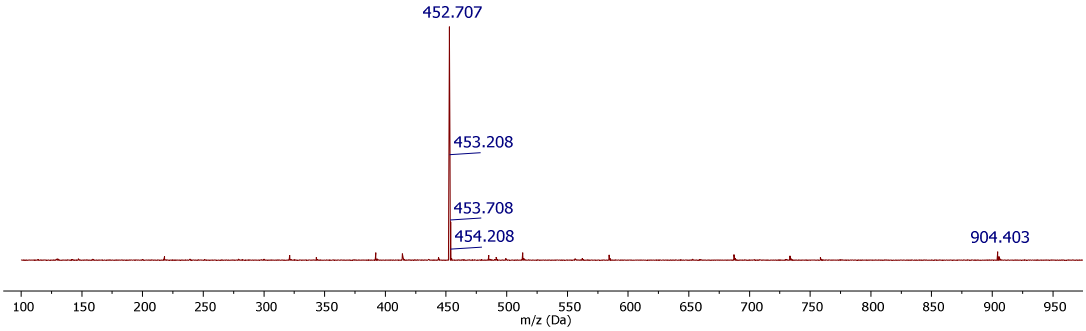
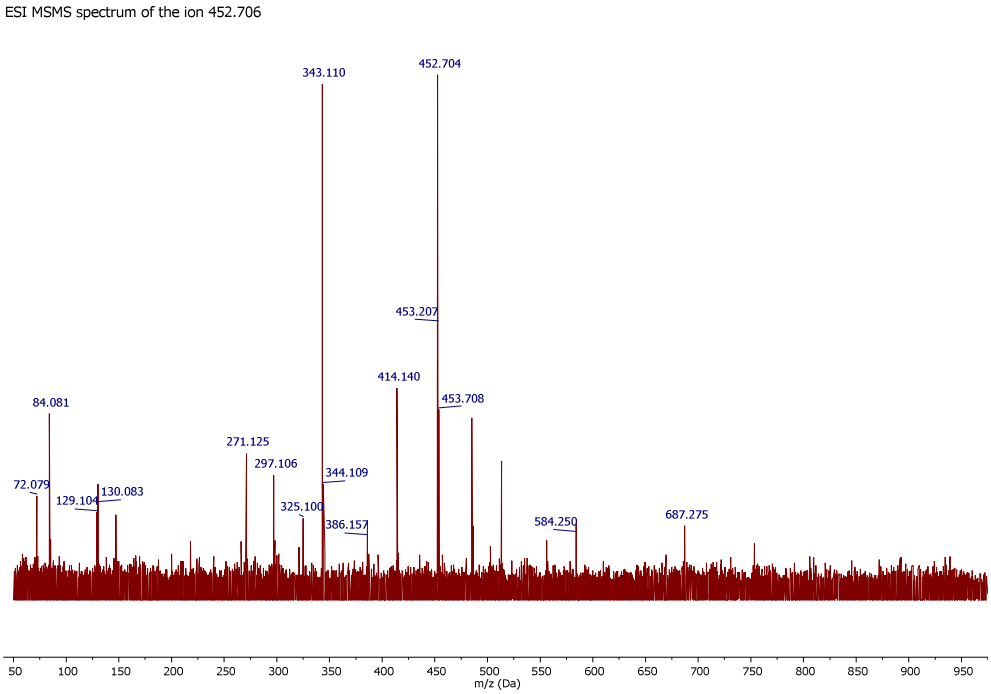


Figure S27: Extracted ion chromatogram for the ion *m/z* = 452.706 and corresponding electrospray MS spectrum (ESI-MS).



Seq.	#	B	Y	#
D	1	343.11026	904.40473	7
A	2	414.14738	562.30179	6
V	3	513. 21579	491.26467	5
A	4	584.25291	392.19626	4
C	5	687.26209	321.15915	3
A	6	758.29920	218.14996	2
K	7	886.39417	147.11285	1

Figure S28: MS/MS fragmetantion spectrum of the ion *m/z* = 452.706. Table of theoretical b and y fragment masses7 with ions detected in the spectrum highlighted in red.

6.2. Experiment 1 (reagents 3b·TFA and 4b·HCl , quench with *N*-Acetylcysteine)

Peptide: DAVACAK
Reduction: TCEP (3 eq.), 30 min, 37 °C
Fluoroalkylation: c(peptide) = 0.6 mM, reagent (10 eq.), 1 h or 24 h, rt
Quench: *N*-Acetylcysteine (100 eq.) in one portion, overnight, rt
Preparation of the sample for ESI: samples were acidified with 1 % formic acid (0.03 µg of peptide/1 µl).
Buffers: 1) 0.1M acetate buffer (CH_3COOH/CH_3COONH_4), pH = 4
2) 0.1M NH_4HCO_3, pH = 8.5

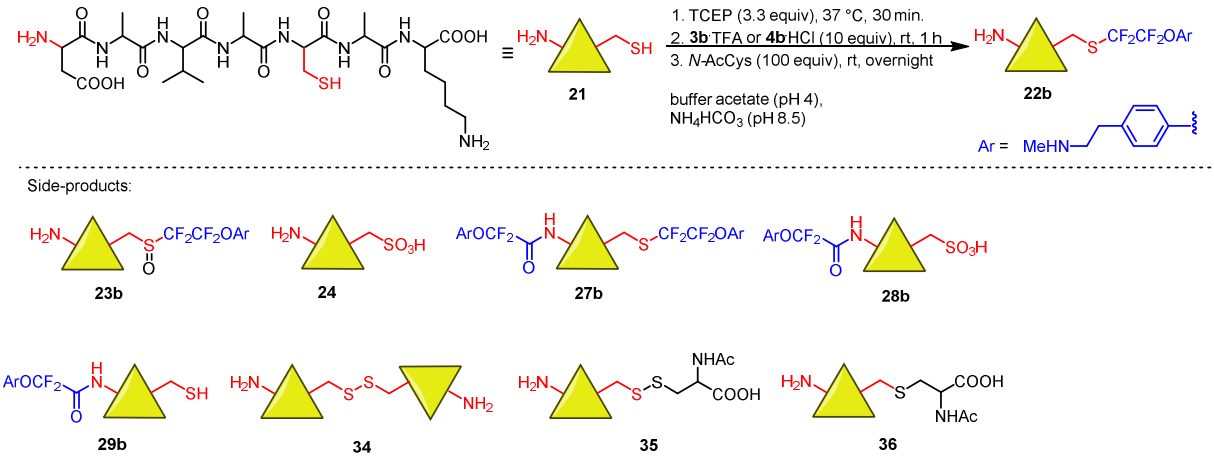
Procedure A (pH = 4):

The buffer solution (0.1 ml) was added to a solution of DAVACAK peptide (0.1 ml, 1 mg/ml) in water. Tris(2-carboxyethyl)phosphine hydrochloride (TCEP) (4.5 µl, 0.1M in water) was added and the mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted to three eppendorf tubes SA, A1, A2 (30 µl each). Water was added to SA (6 µl). Water (3.6 µl) and **3b**·TFA (2.4 µl, 0.1M in water) were added to A1. Water (3.6 µl) and **4b**·HCl (2.4 µl, 0.1M in water) were added to A2. The samples were vortexed for 5 minutes. After 1 hour and 24 hours an aliquote (5 µl) was taken and dilluted with buffer solution (15 µl, 0.1M), followed by the addition of *N*-acetyl cysteine (3.1 µl, 0.1M in water). The samples were vortexed for 5 min and left to stay overnight at room temperature. Before the measurment 1 % formic acid (57 µl) was added to each sample.

Procedure B (pH = 8.5):

To a solution of DAVACAK peptide (0.1 ml, 1 mg/ml) in water was added buffer solution (0.1 ml). Tris(2-carboxyethyl)phosphine hydrochloride (TCEP) (4.5 µl, 0.1M in water) was added and mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted to three eppendorf tubes SB, B1, B2 (30 µl each). Water (6 µl) was added to SB . Water (3.6 µl) and **3b**·TFA (2.4 µl, 0.1M in water) were added to B1. Water (3.6 µl) and **4b**·HCl (2.4 µl, 0.1M in water) were added to B2 . The samples were vortexed for 5 minutes. After 1 hour and 24 hours an aliquote (5 µl) was taken and dilluted with buffer solution (15 µl, 0.1M NH_4HCO_3), followed by addition of *N*-acetyl cysteine (3.1 µl, 0.1M in water). The samples were vortexed for 5 min and left to stay overnight at room temperature. Before the measurment 1 % formic acid (57 µl) was added to each sample.

Table S2: Area under curve (AUC) determined by the integration of extracted ion chromatogram (XIC) for the selected precursor ion (with an error of +- 0.1 Da) of LC-MS measurement.



			pH 4					pH 8.5				
	m/z	min	Blank [AUC] 10^2	**3b**·TFA 1h [AUC] 10^2	**3b**·TFA 24h [AUC] 10^2	**4b**·HCl 1h [AUC] 10^2	**4b**·HCl 24h [AUC] 10^2	Blank [AUC] 10^2	**3b**·TFA 1h [AUC] 10^2	**3b**·TFA 24h [AUC] 10^2	**4b**·HCl 1h [AUC] 10^2	**4b**·HCl 24h [AUC] 10^2
21	677.329	0.55+0.67	144	25	21	25	22	135	39	21	14	8
22b	463.707	2.96+3.32	-	38	40	20	20	-	58	53	167	141
23b	471.705	2.58+2.75	-	13	14	11	13	-	1	1	-	0.5
24	725.313	0.50	1	20	22	35	38	1	6	8	6	7
27b	385.166	3.92	-	-	-	-	-	-	4	5	5	31
28b	952.389	3.01	-	-	-	-	-	-	0.5	1	0.5	0.5
29b	452.706	3.10	-	-	-	-	-	-	15	16	7	10
34	676.321	0.76	-	18	12	5	5	-	-	-	-	-
35	838.343	0.79+0.93	-	29	24	29	22	2	8	6	5	2
36	806.371	0.53	-	-	-	-	-	-	4	4	4	3

6.3. Experiment 2 (concentration 1.5 mM and 0.15 mM)

Peptide: DAVACAK

Reduction: TCEP (3.3 eq.), 30 min, 37 °C

Fluoroalkylation: c(peptide) = 1.5 mM or 0.15 mM, **4b**·HCl reagent (10 eq.), 1 h, rt

Quench: *N*-acetylcysteine (100 eq.), 48 h, rt

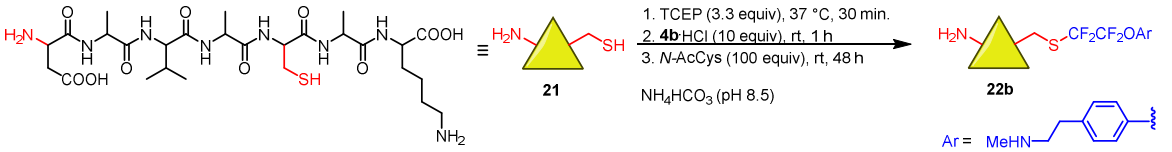
Preparation of the sample for ESI: samples were acidified with 0.1 % formic acid (0.02 µg of peptide/1 µl)

Buffer: degassed 0.1M NH_4HCO_3 (pH = 8.5)

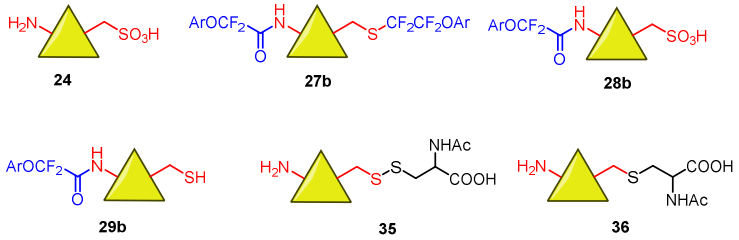
Procedure A (0.15mM): DAVACAK (1 mg/ml) was disolved in degassed buffer. The DAVACAK solution (20 µl) was dilluted with buffer (180 µl) in an eppendorf tube. Tris(2-carboxyethyl)phosphine hydrochloride (1 µl, 0.1M in water) was added and mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, reagent **4b**·HCl (1.5 µl, 0.1M in water) was added and the solution was vortexed for 5 minutes. After 1 hour an aliquote (20 µl) was taken and reaction quenched with *N*-acetyl cysteine (3 µl, 0.1M in water), vortexed for 5 min and left to stay for 48 h at room temperature. Before the measurment 0.1 % formic acid (78 µl) was added.

Procedure B (1.5mM): DAVACAK (1 mg/ml) was disolved in degassed buffer. To the DAVACAK solution (200 µl) in an eppendorf tube was added tris(2-carboxyethyl)phosphine hydrochloride (10 µl, 0.1M in water) and mixture was vortexed 30 min at at 37 °C. After cooling to the laboratory temperature, reagent **4b**·HCl (15 µl, 0.1M in water) was added and the solution was vortexed for 5 minutes. After 1 hour an aliquote (20 µl) was taken, dilluted with water (180 µl) and quenched with *N*-acetyl cysteine (30 µl, 0.1M in water). The sample was vortexed for 5 min and left to stay for 48 h at room temperature. Before the measurement an aliquote (20 µl) was taken and 0.1 % formic acid (52 µl) was added.

Table S3: Area under curve (AUC) determined by integration of extracted ion chromatogram (XIC) for selected precursor ion (with an error of +- 0.1 Da) of LC-MS measurement.



Side-products:



Product	*m/z*	min	c = 0.15mM [AUC]	c = 1.5mM [AUC]
21	677.329	0.55+0.67	300	170
22b	463.707	2.99+3.34	1100	5500
24	725.313	0.48	630	90
27b	385.166	3.92	20	420
28b	952.389	3.01	10	10
29b	452.706	3.10	40	90
35	838.343	0.79	230	100
36	806.371	0.53	200	80

6.4. Experiment 3 (Reagent 3a, 3a□AcCl, 4a, 3b□TFA , 4a□HCl; quench TCEP)

Peptide: DAVACAK

Reduction: TCEP (3.3 eq.), 30 min, 37 °C

Fluoroalkylation: c(peptide) = 1.2 mM, reagent (10 eq.), 1 h, rt

Quench: TCEP (50 eq.) in one portion, 30 min, rt

Preparation of the sample for ESI: 1) Solvent evaporation
2) Sample stored in freezer
3) Directly before measurement, samples were disolved in 0.1 % formic acid (0.2 µg of peptide/1 µl)

Buffers: 1) degassed 0.1M acetate buffer (CH_3COOH/CH_3COONa), pH = 4
2) degassed 0.1M phosphate buffer (KH_2PO_4/K_2HPO_4), pH = 7

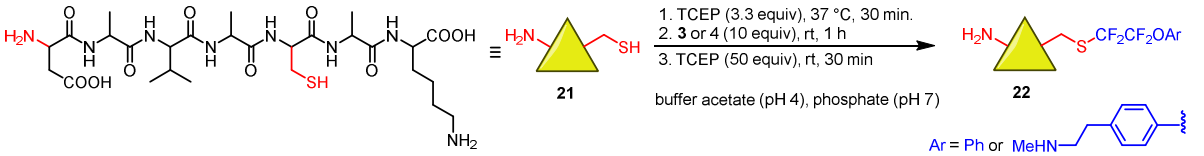
Procedure A (acetate buffer pH = 4):

A solution of DAVACAK peptide (0.2 ml, 1 mg/ml) in acetate buffer was placed in a 0.5 ml eppendorf tube. Tris(2-carboxyethyl)phosphine hydrochloride (8.8 µl, 0.1M in water) was added and mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted to four eppendorf tubes SA, A1, A2, A3 (30 µl each). Water (4.3 µl) was added to SA, **3b**·TFA (4.3 µl, 0.1M in water) was addedto A1, **3a** (4.3 µl, 0.1M in DMSO) was added to A2 and **3a**□AcCl (4.3 µl, 0.1M in DMSO) was added to A3. The samples were vortexed for 1 hour at laboratory temperature, followed by the addition of tris(2-carboxyethyl)phosphine hydrochloride (43 µl, 0.1M in water). Then, the samples were vortexed for another 30 min and solvent was removed under high vacuum. Samples were disolved in 0.1% formic acid (144 µl) and measured by LC-MS.

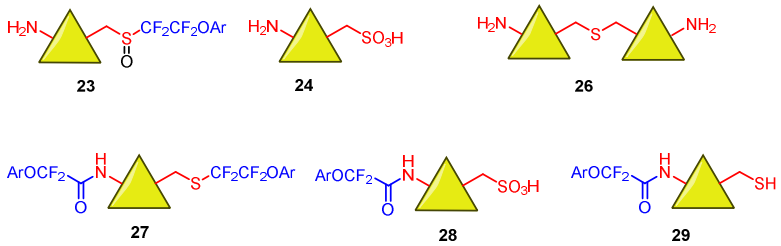
Procedure B (phosphate buffer pH = 7):

A solution of DAVACAK peptide (0.2 ml, 1 mg/ml) in phosphate buffer was placed in a 0.5 ml eppendorf tube. Tris(2-carboxyethyl)phosphine hydrochloride (8.8 µl, 0.1M in water) was added and mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted into six eppendorf tubes SB, B1, B2, B3, B4, B5 (30 µl each). Water (4.3 µl) was added to SB, **3b**·TFA (4.3 µl, 0.1M in water) was added to B1, **3a** (4.3 µl, 0.1M in DMSO) was added to B2, **3a**□AcCl (4.3 µl, 0.1M in DMSO) was added to B3, **4b**·HCl (4.3 µl, 0.1M in water) was added to B4 and **4a** (4.3 µl, 0.1M in DMSO) was added to B5. The samples were vortexed for 1 hour at laboratory temperature, followed by the addition of tris(2-carboxyethyl)phosphine hydrochloride (43 µl, 0.1M in water). Then, the samples were vortexed for another 30 min and solvent was removed under high vacuum. Samples were disolved in 0.1% formic acid (144 µl) and measured by LC-MS.

Table S4: Area under curve (AUC) determined by integration of extracted ion chromatogram (XIC) for selected precursor ion (with error +- 0.1 Da) of LC-MS measurement.



Side-products:



				pH 4				pH 7					
	5 or **9** *m/z*	**3** or **4** *m/z*	min	Blank [AUC] 10^2	**3b**·TFA [AUC] 10^2	**3a** [AUC] 10^2	**3a**·AcCl [AUC] 10^2	Blank [AUC] 10^2	**3b**·TFA [AUC] 10^2	**4b**·HCl [AUC] 10^2	**3a** [AUC] 10^2	**4a** [AUC] 10^2	**3a**·AcCl [AUC] 10^2
21	677.329	677.329	0.64+0.77	405	91	137	11	313	59	59	210	47	13
22	463.707	869.349	3.17+3.51/ 5.19+5.75	-	46	101	243	0	55	86	56	79	94
23	942.401	885.343	2.80+2.96/ 4.73	-	65	4	13	0	4	2	-	7	2
24	725.313	725.313	0.53	2	56	8	20	2	28	25	9	8	17
26	660.335	660.335	0.71	-	-	-	1	-	-	0.5	-	3	6
27	577.245	1039.366	4.04/6.88	-	-	-	-	-	2	1	3	0.5	0.5
28	952.389	895.331	3.20/5.23	-	-	-	-	-	25	0.5	1	0.5	-
29	452.706	847.347	3.27/5.42	-	-	-	-	-	10	5	0.5	4	-

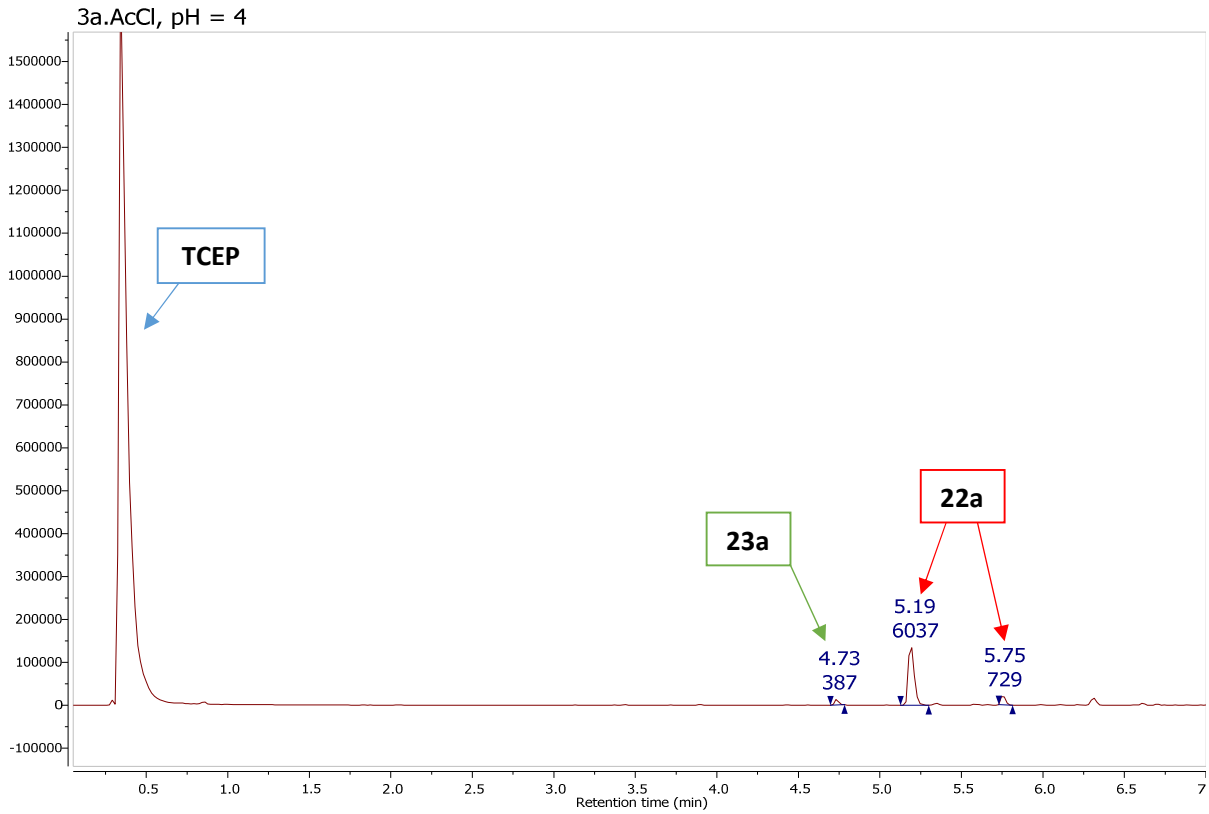


Figure S29: Base peak chromatogram, for the fluoroalkylation at pH = 4, by **3a**·AcCl. Peaks for the compounds **21** and **24** are covered by peak of TCEP.

6.5. Experiment 4 (Reagent 1·BetCl, pH = 4)

Peptide: DAVACAK

Reduction: TCEP (3 eq.), 30 min, 37 °C

Fluoroalkylation: c(peptide) = 1.2 mM, **1**·BetCl reagent (10 eq.), 30 min, rt

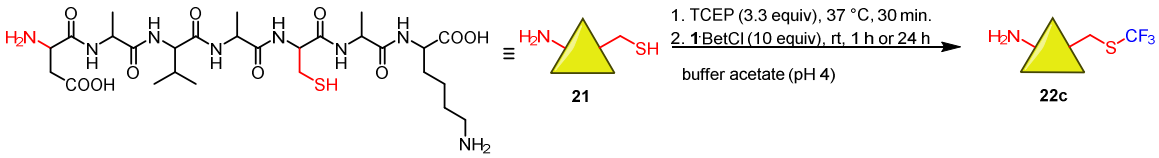
Quench: no quench

Preparation of the sample for ESI: 1) Solvent evaporation
2) Sample stored in freezer
3) Directly before measurement, sample were dislolved in 0.1 % formic acid (0.2 µg of peptide/1 µl)

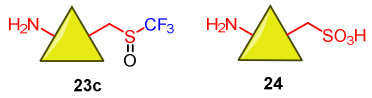
Buffer: 0.1M acetate buffer (pH 4)

Procedure: A solution of DAVACAK peptide (0.1 ml, 1 mg/ml) in 0.1M acetate buffer was placed in a 0.5 ml eppendorf tube, tris(2-carboxyethyl)phosphine hydrochloride (4.4 µl, 0.1M in H_2O) was added and mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted to two eppendorf tubes S1 (15 µl), and A (30 µl). **1**·BetCl reagent (4.3 µl, 0.1M in DMSO) was added to sample A and the sample was vortexed at laboratory temperature. After 30 min an aliquote (15 µl) was taken from sample A, which was followed by solvent evaporation from S1 and A (15 µl). The samples were disolved in 0.1% formic acid (71.8 µl for S1 and 62.8 µl for A) before the measurement.

Table S5: Area under curve (AUC) determined by integration of extracted ion chromatogram (XIC) for selected precursor ion (with error +- 0.1 Da) of LC-MS measurement.



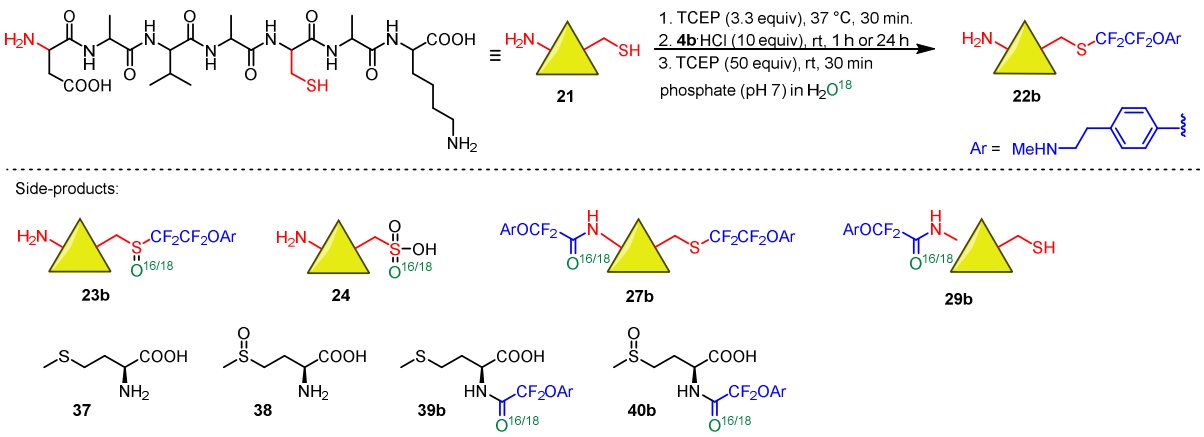
Side-products:



	DAVACAK	
	blank	**1**·BetCl
21	470	73
22c	0	490
23c	0	9
24	7	14

6.6. Experiment 5 (pH 7; H_2O^{18})

H_2O^{18} experiments: H_2O^{18} (97% O^{18}) was purchased from Sigma Aldrich.
Peptide: DAVACAK
Reduction: TCEP (3 eq.), 30 min, 37 °C
Fluoroalkylation: c(peptide) = 1 or 1.3 mM, reagent (10 eq.), 1 h or 24 h, rt
Quench: TCEP (50 eq.) in one portion, 30 min, rt
Preparation of the sample for ESI: 1) Solvent evaporation
2) Sample stored in freezer
3) Directly before measurement, sample were dislolved in 0.1 % formic acid (0.2 µg of peptide/1 µl)
Buffer: 0.1M phosphate buffer (pH 7), prepared directly before the reaction by disolving KH_2PO_4 (1.1 mg) and K_2HPO_4 (2.1 mg) in H_2O^{18} (200 µl)
Procedure: A solution of DAVACAK peptide (0.15 ml, 1 mg/ml) in 0.1M phosphate buffer (H_2O^{18}) was placed in a 0.5 ml eppendorf tube, tris(2-carboxyethyl)phosphine hydrochloride (2.2 µl, 0.3M in H_2O^{18}) was added and the mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted to three eppendorf tubes A0 (75 µl), SB (15 µl) and B (40 µl). Methionine (21 µl, 0.1M in H_2O^{18}) was added to A0 solution and the mixture was splited to two eppendorf tubes SA (19.2 µl) and A (51.2 µl). Tris(2-carboxyethyl)phosphine hydrochloride (3.5 µl, 0.3M in H_2O^{18}) was added to samples SA and SB. **4b**·HCl (5.66 µl, 0.1M in H_2O^{18}) was added to samples A and B and the samples were vortexed for 1 hour at laboratory temperature and left to stay for 24 h at rt. After 1 hour and 24 hours an aliquote (21.3 µl) from the solution A and an aliquote (17.1 µl) from the solution B were taken, followed by the addition of tris(2-carboxyethyl)phosphine hydrochloride (3.5 µl, 0.3M in H_2O^{18}) to each sample. After the quench with tris(2-carboxyethyl)phosphine hydrochloride, all samples were vortexed for 30 min, which was followed by solvent evaporation. Before the measurment the samples were disolved in 0.1% formic acid (71.8 µl in H_2O^{16}).



Scheme S2: Compounds, which were analyzed in the crude reaction mixture by LC-MS. O^{18} was clearly incorporated in structures **23b**, **24**, **27b**, **29b**, **39b** and **40b**.

			With methionine[a]			Without methionine[a]		
	m/z	min	blank [AUC] 10^2	1 h [AUC] 10^2	24 h [AUC] 10^2	blank [AUC] 10^2	1 h [AUC] 10^2	24 h [AUC] 10^2
21 (O^{16}/ O^{18})	677.329/679.333	0.62+0.76	690/22 3%[b]	220/4 2%[b]	276/7 2%[b]	595/17 3%[b]	163/3 2%[b]	144/3 2%[b]
22b (O^{16}/ O^{18})	463.707/464.709	3.11+3.49	-	155/2 1%[b]	175/3 2%[b]	-	177/3 2%[b]	171/2 1%[b]
23b (O^{16}/ O^{18})	300.069/302.073	2.79+2.92	-	7/2 22%[b]	7/3 30%[b]	-	36/4 10%[b]	38/6 14%[b]
24 (O^{16}/ O^{18})	725.313/727.317	0.52	10/-	18/6 25%[b]	22/11 33%[b]	16/-	34/32 48%[b]	37/59 61%[b]
27b (O^{16}/ O^{18})	577.245/578.247	4.08	-	4/6 60%[b]	4/7 64%[b]	-	2/5 71%[b]	2/5 71%[b]
29b (O^{16}/ O^{18})	452.706/453.708	3.28	-	32/72 69%[b]	37/80 68%[b]	-	13/43 77%[b]	11/34 76%[b]
37 (O^{16}/ O^{18})	150.058/152.062	0.38	5/-	3/-	3/-	-	-	-
38 (O^{16}/ O^{18})	166.053/168.057	0.33	-	2/-	2/-	-	-	-
39b (O^{16}/ O^{18})	377.134/379.138	3.85	-	51/31 38%[b]	59/37 39%[b]	-	-	-
40b (O^{16}/ O^{18})	393.129/395.133	1.68	-	18/11 38%[b]	20/13 39%[b]	-	-	-

Table S6: Area under curve (AUC) determined by the integration of extracted ion chromatogram (XIC) for the selected precursor ion (with an error of +- 0.1 Da) of LC-MS measurement. a) The amount of O^{18} labeled compound is corrected to pure O^{18} isotope by the use of mass intensity[8] of O^{16} containing isotopes; b) O^{18} isotope content of the corresponding compound.

Due to easy fragmentation of compound **23b** in the ESI-MS spectra, the O^{18} content was determined from the fragment *m/z* = 300.069/302.073.

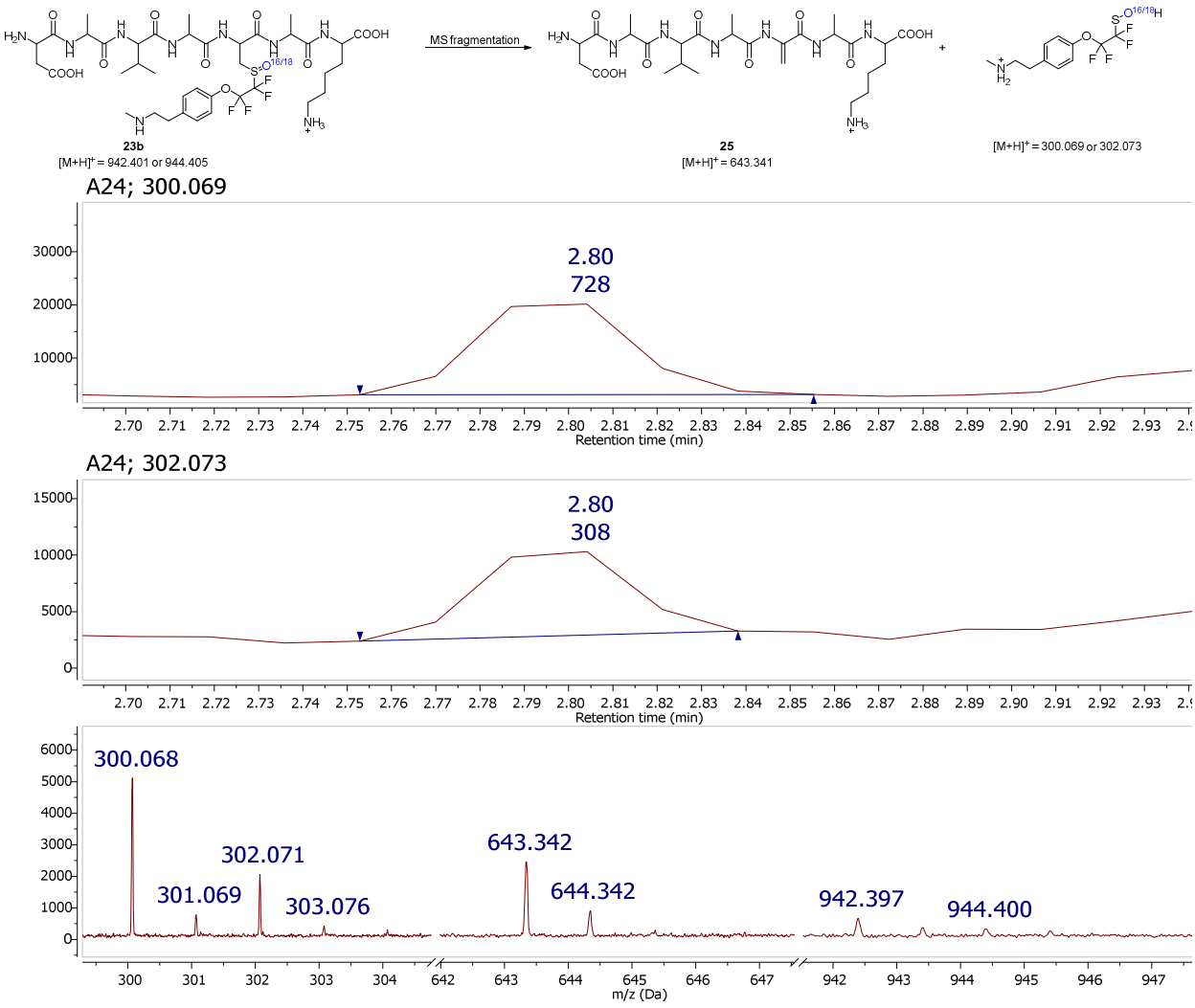


Figure S30: Extracted ion chromatograms for ions *m/z* = 300.069 and 302.073 (upper two panels). Zoomed ESI MS spectrum is shown in the bottom panel.

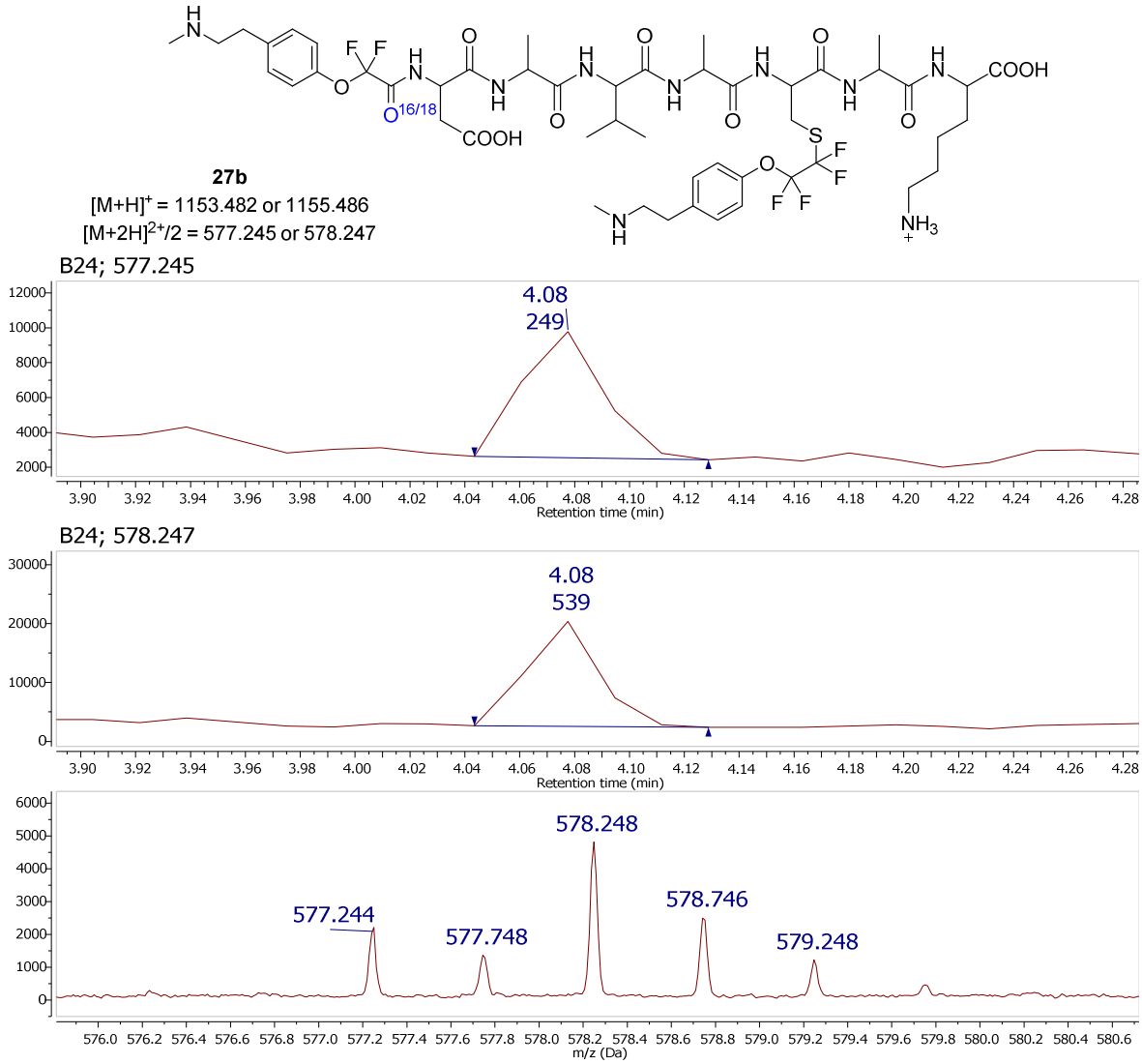


Figure S31: Extracted ion chromatograms for ions *m/z* = 577.245 and 578.247 (upper two panels). Zoomed ESI MS spectrum is shown in the bottom panel.

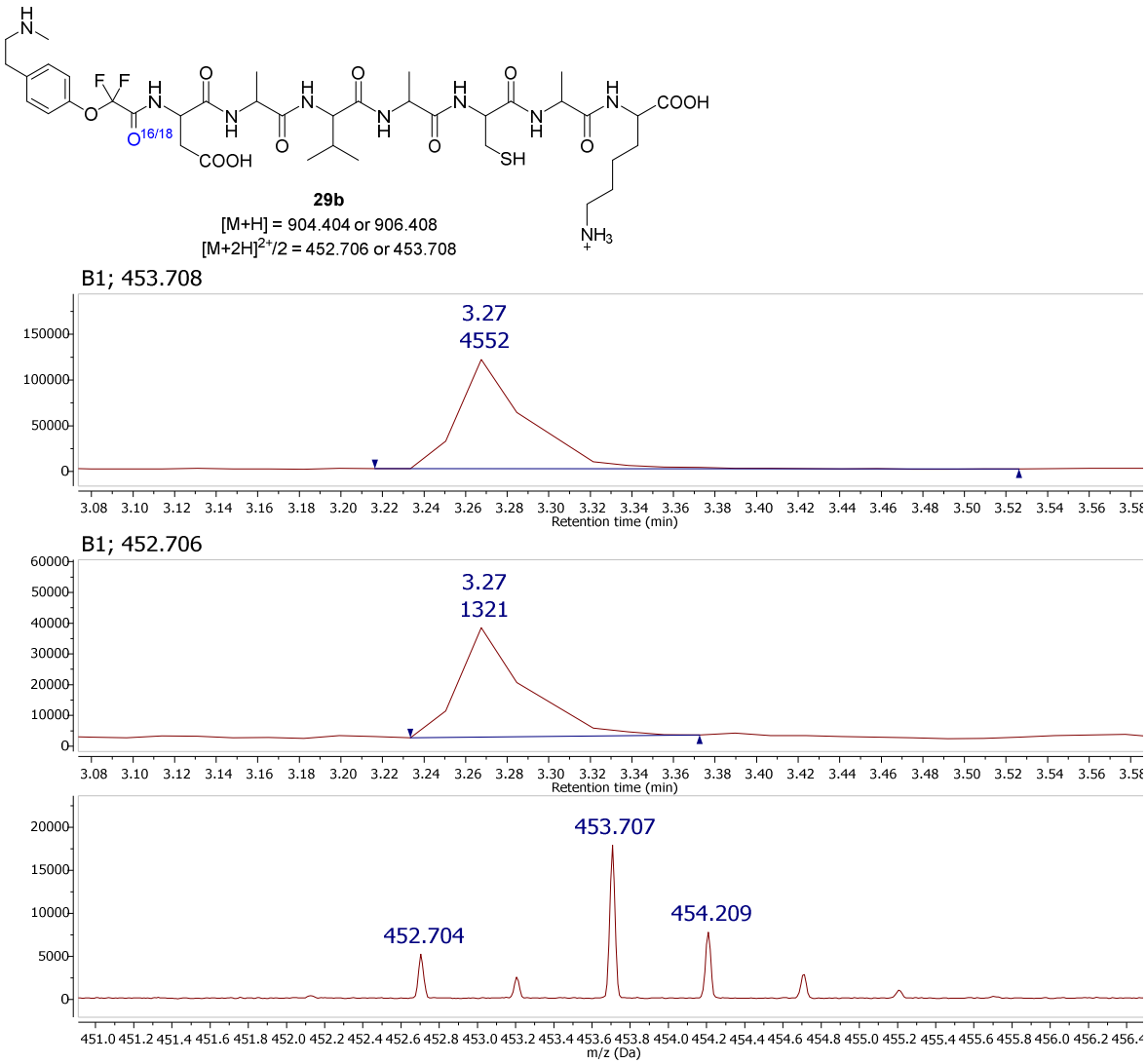
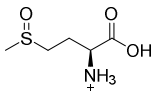


Figure S32: Extracted ion chromatograms for ions *m/z* = 452.706 and 453.708 (upper two panels). Zoomed ESI MS spectrum is shown in the bottom panel.



37

$[M+H]^+$ = 166.053

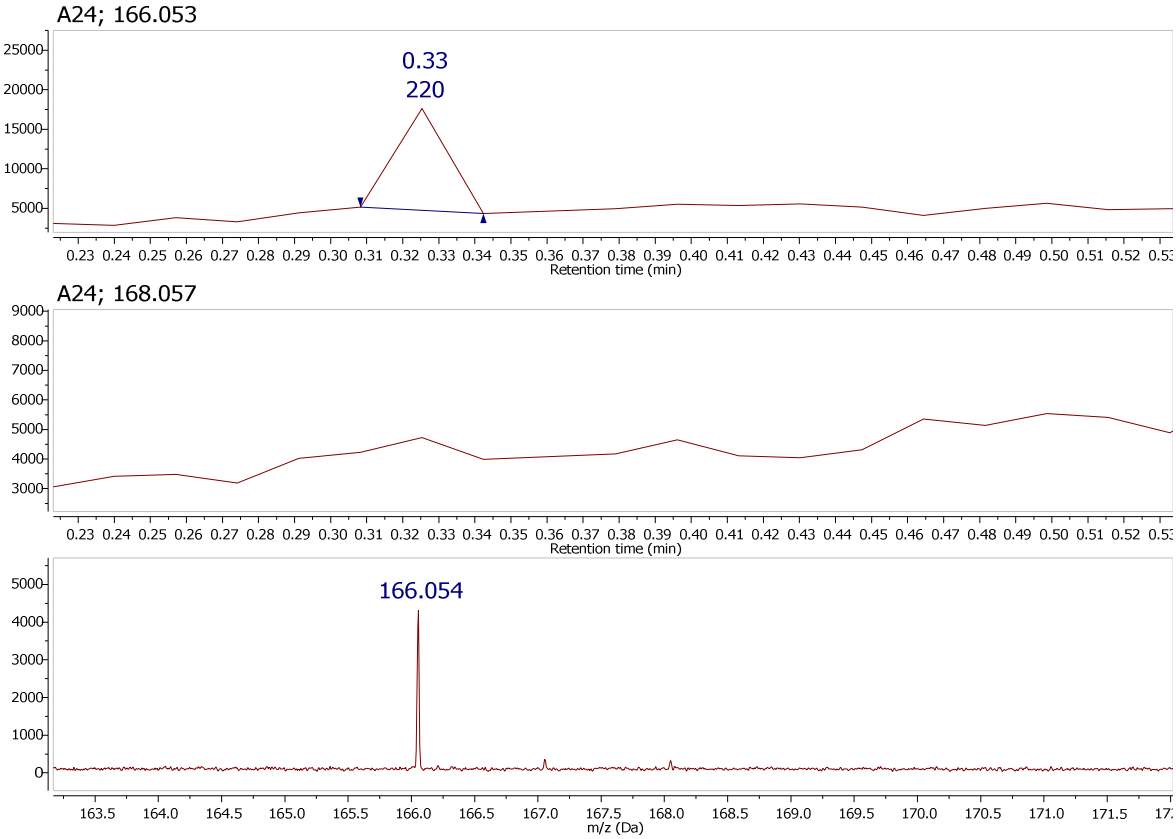


Figure S33: Extracted ion chromatogram for the ion *m/z* = 166.054 and ion *m/z* = 168.057 (upper two panels). Ion *m/z* = 168.057 was not recorded. Zoomed ESI MS spectrum is shown in the bottom panel.

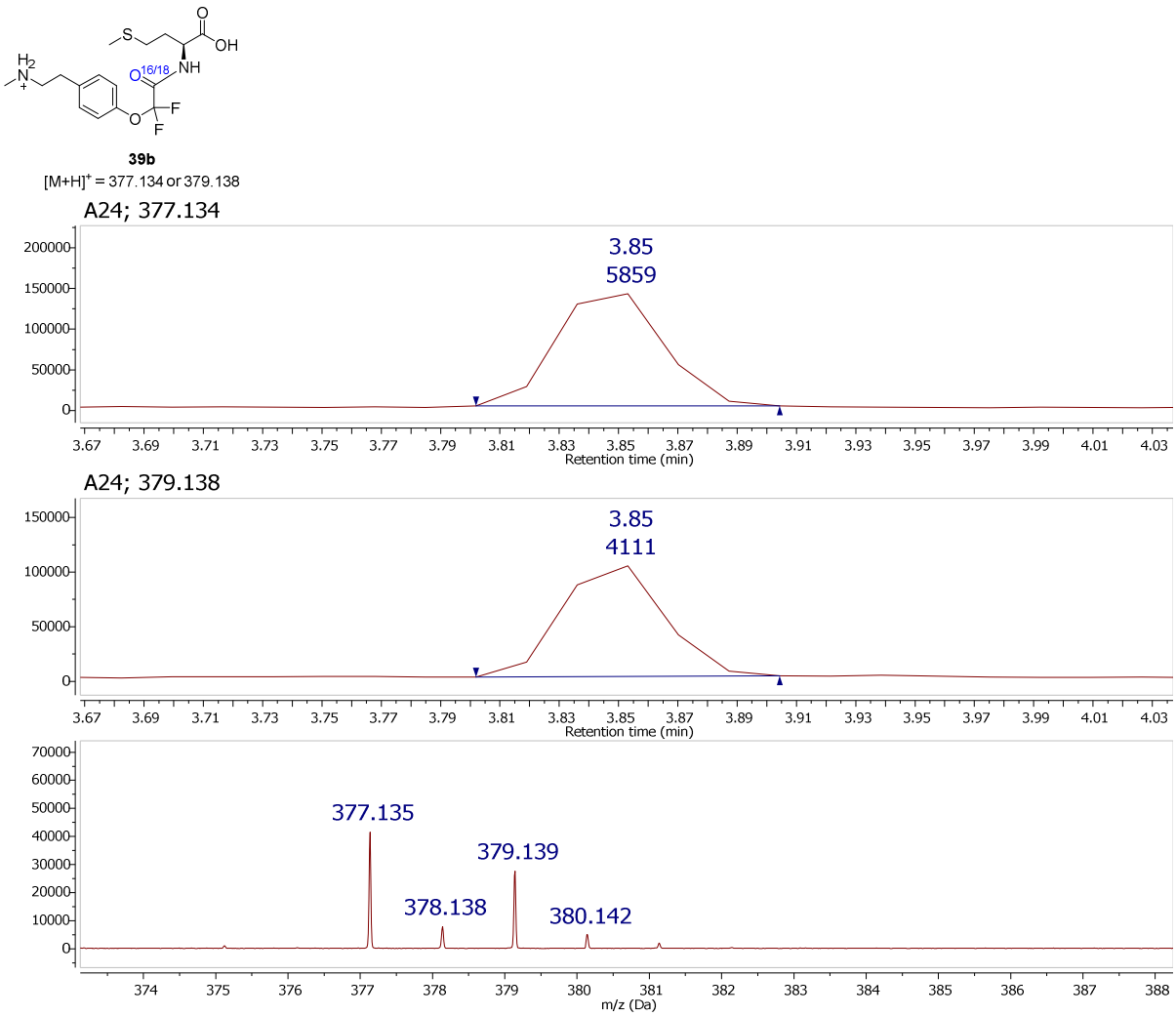


Figure S34: Extracted ion chromatograms for ions *m/z* = 377.134 and 379.138 (upper two panels). Zoomed ESI MS spectrum is shown in the bottom panel.

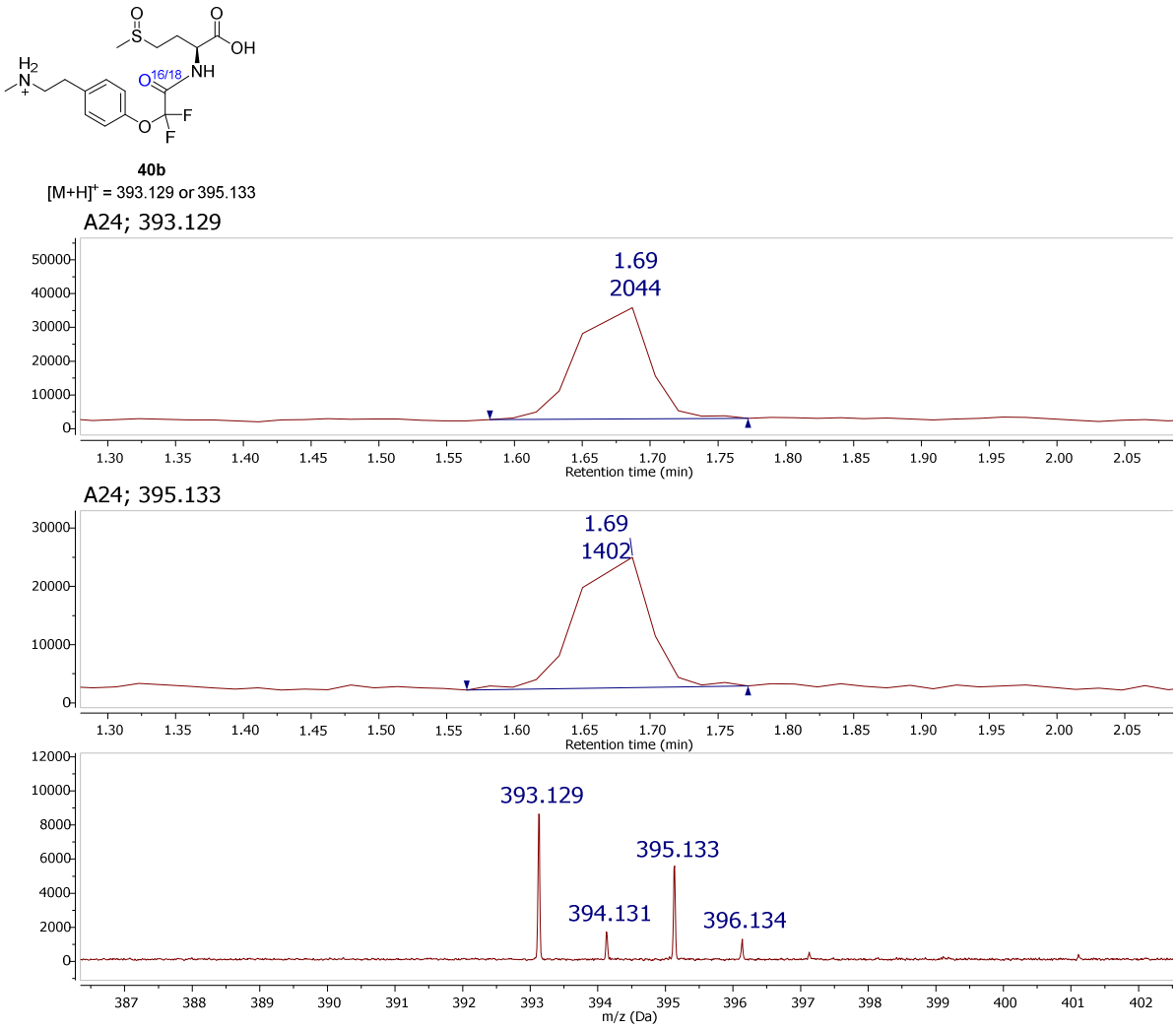


Figure S35: Extracted ion chromatograms for ions *m/z* = 393.129 and 395.133 (upper two panels). Zoomed ESI MS spectrum is shown in the bottom panel.

6.7. Experiment 6 (pH 4; H_2O^{18})

Peptide: DAVACAK

Reduction: TCEP (3 eq.), 30 min, 37 °C

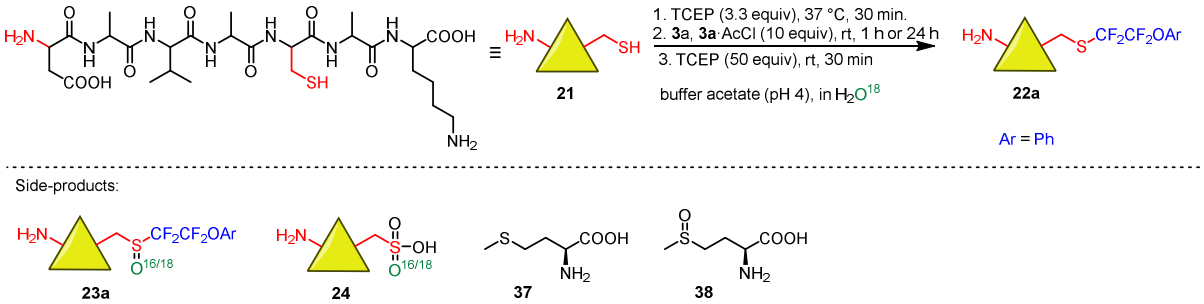
Fluoroalkylation: c(peptide) = 1 or 1.3 mM, reagent (10 eq.), 1 h or 24 h, rt

Quench: TCEP (50 eq.) in one portion, 30 min, rt

Preparation of the sample for ESI: 1) Solvent evaporation
2) Sample stored in freezer
3) Directly before measurement, sample were dislolved in 0.1 % formic acid (0.2 µg of peptide/1 µl)

Buffer: 0.1M acetate buffer (pH 4), prepared directly before reaction by disolving of NaOAc (0.4 mg) and AcOH (1.26 µl) in H_2O^{18} (270 µl)

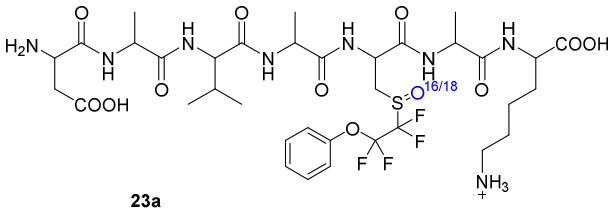
Procedure: A solution of DAVACAK peptide (0.24 ml, 1 mg/ml) in 0.1M acetate buffer (H_2O^{18}) was placed in a 0.5 ml eppendorf tube, tris(2-carboxyethyl)phosphine hydrochloride (3.6 µl, 0.3M in H_2O^{18}) was added and mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted to four eppendorf tubes M (120 µl), S2 (15 µl) C (40 µl) and D (40 µl). Methionine (35 µl, 0.1M in H_2O^{18}) was added to M solution and the mixture was splited to three eppendorf tubes S2 (19.2 µl) and A (51.2 µl) and B (51.2 µl). Tris(2-carboxyethyl)phosphine hydrochloride (3.5 µl, 0.3M in H_2O^{18}) was added to samples S1 and S2. **3a** reagent (5.66 µl, 0.1M in DMSO) was added to samples A, C and **3a**□AcCl reagent (5.66 µl, 0.1M in DMSO) was added to samples B, D , the samples were vortexed for 1 hour at laboratory temperature and left to stay for 24 h at rt. After 1 hour and 24 hours, aliquotes (21.3 µl) were taken from solutions A and C and aliquotes (17.1 µl) were taken from solutions B and D, followed by the addition of tris(2-carboxyethyl)phosphine hydrochloride (3.5 µl, 0.3M in H_2O^{18}) to each sample. After the quench with tris(2-carboxyethyl)phosphine hydrochloride, all samples were vortexed for 30 min, which was followed by solvent evaporation. The samples were disolved in 0.1% formic acid (71.8 µl in H_2O^{16}) before the measurement.



Scheme S3: Compounds analyzed from the crude reaction mixture by LC-MS. O^{18} was clearly incorporated in structures **20a** and **21**.

			With methionine[a]					Without methionine[a]				
	m/z	min	blank [AUC] 10^2	**3a** 1 h [AUC] 10^2	**3a** 24 h [AUC] 10^2	**3a**·AcCl 1 h [AUC] 10^2	**3a**·AcCl 24 h [AUC] 10^2	blank [AUC] 10^2	**3a** 1 h [AUC] 10^2	**3a** 24 h [AUC] 10^2	**3a**·AcCl 1 h [AUC] 10^2	**3a**·AcCl 24 h [AUC] 10^2
21 (O^{16}/ O^{18})	677.329/679.333	0.62+0.76	586/25 4%[b]	263/9 3%[b]	125/3 2%[b]	210/5 2%[b]	38/-	514/22 4%[b]	319/8 2%[b]	141/4 3%[b]	58/1 2%[b]	2/-
22a (O^{16}/ O^{18})	869.349/871.353	5.18+5.73	-	100/3 3%[b]	129/4 3%[b]	164/5 3%[b]	100/4 4%[b]	-	93/2 2%[b]	154/5 3%[b]	210/8 4%[b]	128/6 4%[b]
23a (O^{16}/ O^{18})	885.343/887.347	4.71	-	-	1/0.5 33%[b]	2/3 60%[b]	2/4 66%[b]	-	4/5 55%[b]	4/10 71%[b]	3/2 40%[b]	3/2 40%[b]
24 (O^{16}/ O^{18})	725.313/727.317	0.53	7/-	7/-	13/2 13%[b]	11/3 21%[b]	12/4 25%[b]	7/-	7/-	18/12 40%[b]	13/6 32%[b]	15/9 38%[b]
37 (O^{16}/ O^{18})	150.058/152.062	0.40	32/-	23/-	37/1 3%[b]	22/-	19/-	-	-	-	-	-
38 (O^{16}/ O^{18})	166.053/168.057	0.33	-	0.6/-	3/-	-	2/-	-	-	-	-	-

Table S7: Area under curve (AUC) determined by the integration of extracted ion chromatogram (XIC) for selected precursor ion (with an error of +- 0.1 Da) of LC-MS measurement; a) The amount of O^{18} labeled compound is corrected to pure O^{18} isotope by the use of mass intensity[8] of O^{16} containing isotopes; b) O^{18} isotope content of the corresponding compound.



23a

$[M+H]^+$ = 885.343 or 887.347

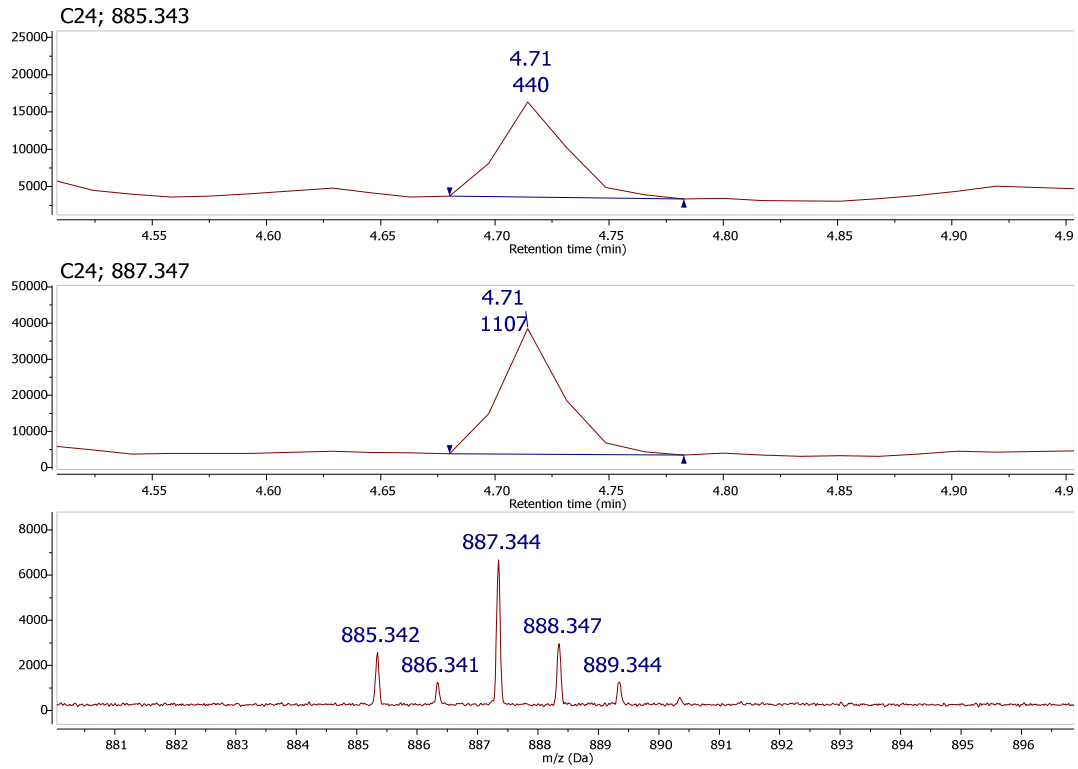
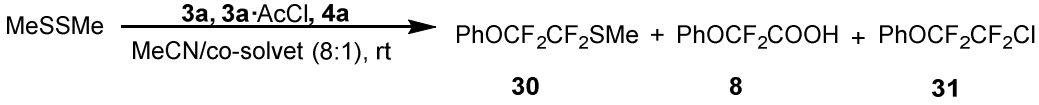


Figure S36: Extracted ion chromatogram for ions *m/z* = 885.343 and 887.347 (upper two panels). Zoomed ESI MS spectrum is shown in the bottom panel.

7. Reaction with disulfides

7.1. Reaction with dimethyldisulfide



8a ^{19}F NMR (377.28 MHz, CD_3CN/D_2O): δ –77.5 (s, 2F, PhOC*F*$_2$COOH);
30 ^{19}F NMR (377.28 MHz, CD_3CN/D_2O): δ –94.5 (t, $^3J_{FF}$ = 6.4 Hz, 2F, SC*F*$_2$), –85.3 (t, $^3J_{FF}$ = 6.4 Hz, 2F, OC*F*$_2$);
31 ^{19}F NMR (377.28 MHz, CD_3CN/D_2O): δ –86.8 (t, $^3J_{FF}$ = 3.6 Hz, 2F, OC*F*$_2$), –73.7 (t, $^3J_{FF}$ = 3.6 Hz, 2F, ClC*F*$_2$);

Procedure for 1.5 eq. MeSSMe, no water:

3a□AcCl (15 µmol, 8 mg) was disolved in CD_3CN (0.4 ml) in an NMR tube. Dimethyldisulfide (22.5 µmol, 2 µl) was added, the tube was closed and vortexed for 5 minutes. After 30 min ^{1}H and ^{19}F NMR spectra were collected.

Procedure for 1.5 eq. MeSSMe and co-solvent:

Reagents **3a** (15 µmol, 6.8 mg), **4a** (15 µmol, 6.6 mg) or **3a**□AcCl (15 µmol, 8 mg) were disolved in CD_3CN (0.4 ml) in an NMR tube. Dimethyldisulfide (22.5 µmol, 2 µl) was added, followed by additon of 1M buffer solution or D_2O (50 µl) and CF_3COOK (15 µl 1M solution in water, only to buffer solutions). The mixture was vortexed for 5 minutes and ^{1}H NMR and ^{19}F NMR spectra were collected.

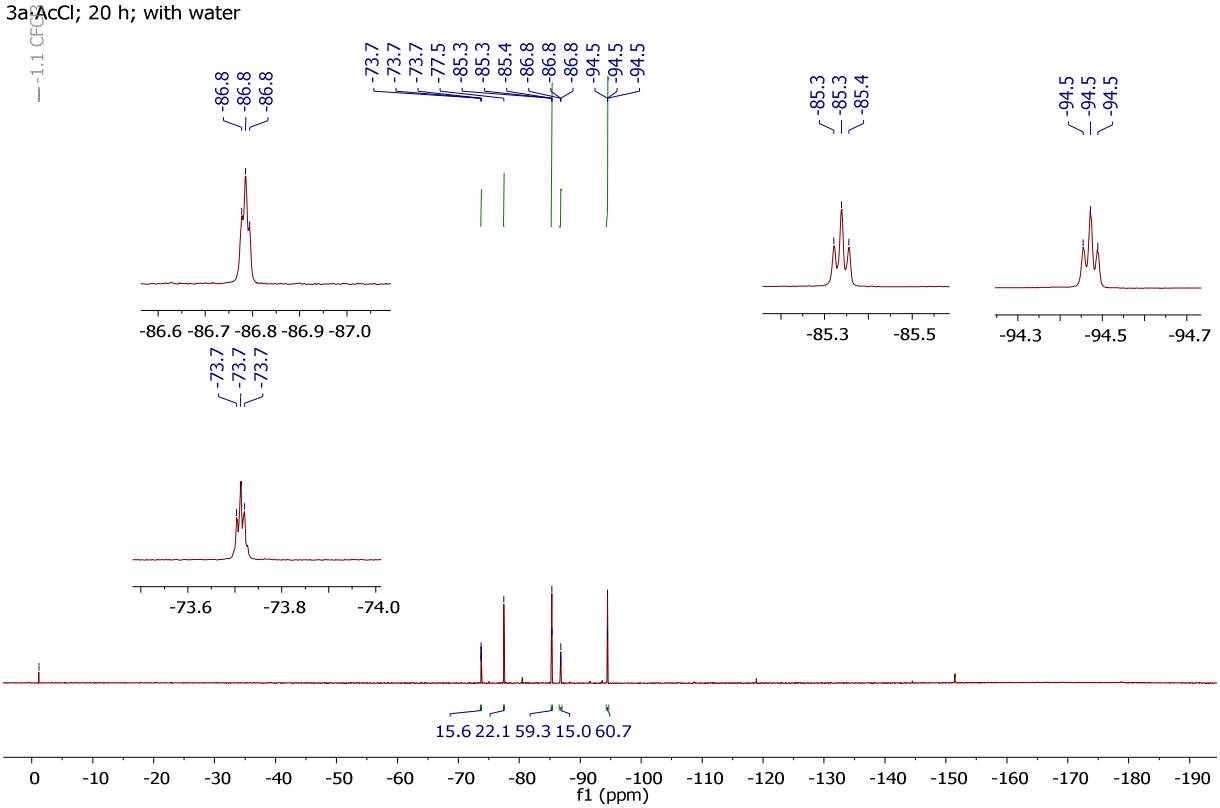


Figure S37: Example of a ^{19}F NMR spectrum of the reaction of dimethyl disulfide with **3a**□AcCl in the presence of D_2O (rt, 20 h).

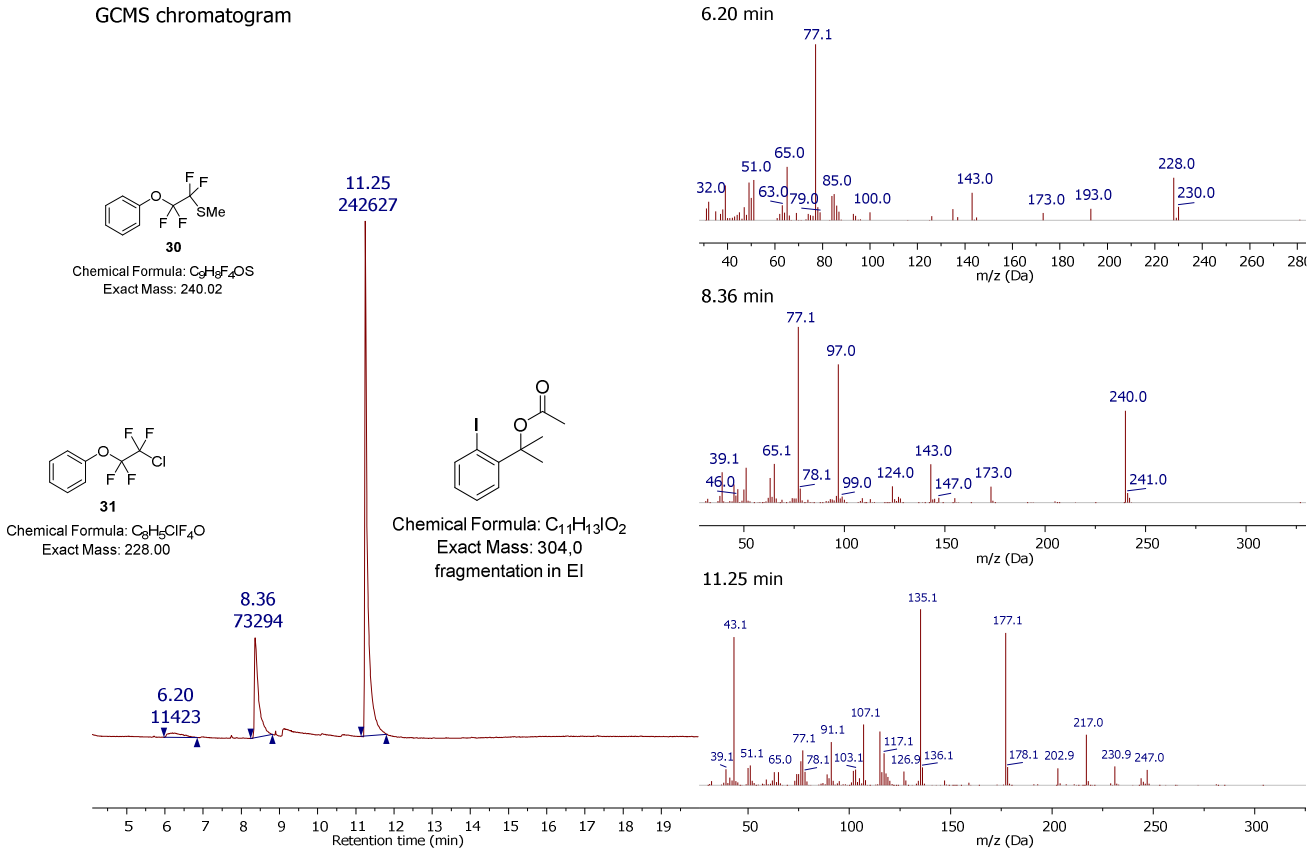


Figure S38: GC-MS chromatogram of a sample from the reaction mixture of dimethyl disulfide with **3a**□AcCl in the presence of D_2O (rt, 20 h). The GC-MS sample preparation: The crude mixture was transferred to a vial, DCM (1.5 ml) and water (0.5 ml) were added and layers were separated. The organic layer was washed with 0.1M phosphate buffer (2 × 0.5 ml) and dried over $MgSO_4$. After filtration the solution was directly analyzed by GC-MS.

7.2. Reaction with GSSG (glutathione disulfide)

Peptide: glutathione disulfide (GSSG)
Reduction: TCEP (3.3 eq.), 30 min, 37 °C or no reduction
Fluoroalkylation: c(peptide) = 1.2mM or 1.3mM, reagent (10 eq. to disulfide), 1 h, rt
Quench: TCEP (100 eq.to disulfide) in one portion, 1 h, rt
Preparation of the sample for ESI: 1) Solvent evaporation
2) Sample stored in freezer
3) Directly before measurement, sample were disolved in 0.1 % formic acid (0.2 µg of peptide/1 µl)
Buffers: 1) degassed 0.1M acetate buffer (CH_3COOH/CH_3COONa), pH 4
2) degassed 0.1M phosphate buffer (KH_2PO_4/K_2HPO_4), pH 7

Procedure 1 (acetate buffer pH 4, no reduction):
GSSG was disolved in acetate buffer (1 mg/ml). The solution was splitted to three eppendorf tubes S1, A1, B1 (15 µl each). DMSO (2.45 µl) was added to S1, **3a**·AcCl (2.45 µl, 0.1M in DMSO) was added to A1, **3a** (2.45 µl, 0.1M in DMSO) was added to B1. The samples were vortexed for 1 hour at laboratory temperature, followed by the addition of tris(2-carboxyethyl)phosphine hydrochloride (24.5 µl, 0.1M in water). Then, the samples were vortexed for another 1 hour at rt and solvent was removed under high vacuum. Samples were disolved in 0.1% formic acid (75 µl) and measured by LC-MS.

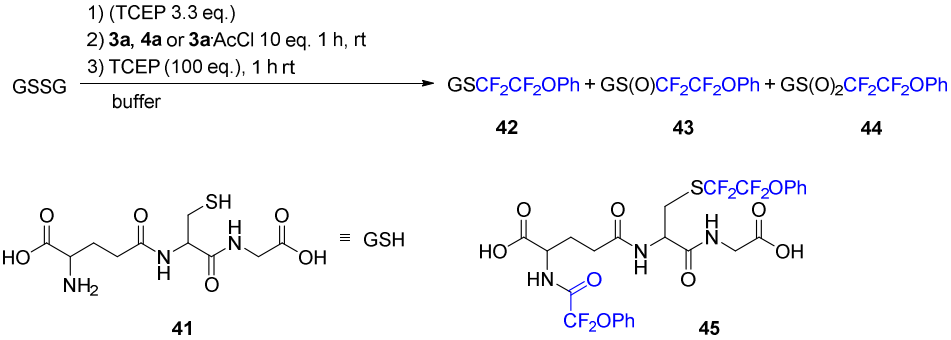
Procedure 2 (phosphate buffer pH 7, no reduction):
GSSG peptide was disolved in phosphate buffer (1 mg/ml). The solution was splitted to four eppendorf tubes S2, A2, B2, C2 (15 µl each). DMSO (2.45 µl) was added to S2, **3a**·AcCl (2.45 µl, 0.1M in DMSO) was added to A2, **3a** (2.45 µl, 0.1M in DMSO) was added to B2 and **4a** (2.45 µl, 0.1M in DMSO) was added to C2. The samples were vortexed for 1 hour at laboratory temperature, followed by the addition of tris(2-carboxyethyl)phosphine hydrochloride (24.5 µl, 0.1M in water). Then, the samples were vortexed for another 1 hour at rt and solvent was removed under high vacuum. Samples were disolved in 0.1% formic acid (75 µl) and measured by LC-MS.

Procedure 3 (acetate buffer pH 4, TCEP reduction):
A solution of GSSG (0.1 ml, 1 mg/ml) in acetate buffer was placed in a 0.5 ml eppendorf tube. Tris(2-carboxyethyl)phosphine hydrochloride (2.44 µl, 0.1M in water) was added and the mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted to three eppendorf tubes S3, A3, B3 (15.37 µl each). DMSO (2.45 µl) was added to S3, **3a**·AcCl (2.45 µl, 0.1M in DMSO) was added to A3 and **3a** (2.45 µl, 0.1M in DMSO) was added to B3. The samples were vortexed for 1 hour at laboratory temperature, followed by the addition of tris(2-carboxyethyl)phosphine hydrochloride (24.5 µl, 0.1M in water). Then, the samples were vortexed for another 1 hour at rt and solvent was removed under high vacuum. Samples were disolved in 0.1% formic acid (75 µl) and measured by LC-MS.

Procedure 4 (phosphate buffer pH = 4, TCEP reduction):
A solution of GSSG (0.1 ml, 1 mg/ml) in phosphate buffer was placed in a 0.5 ml epprndorf tube. Tris(2-carboxyethyl)phosphine hydrochloride (2.44 µl, 0.1M in water) was added and mixture was vortexed for 30 min at 37 °C. After cooling to the laboratory temperature, the mixture was splitted to four eppendorf tubes S4, A4, B4, C4 (15.37 µl each). DMSO (2.45 µl) was added to S4, **3a**·AcCl (2.45 µl, 0.1M in DMSO) was added to A4, **3a** (2.45 µl, 0.1M in DMSO) was added to B4 and **4a** (2.45 µl, 0.1M in DMSO) was added to C4. The samples were vortexed for 1 hour at laboratory temperature, followed by the addition of tris(2-carboxyethyl)phosphine hydrochloride (24.5 µl, 0.1M in water). Then, the samples were

vortexed for another 1 hour at rt and solvent was removed under high vacuum. Samples were disolved in 0.1% formic acid (75 µl) and measured by LC-MS.

Table S8: Area under curve (AUC) determined by integration of extracted ion chromatogram (XIC) for the selected precursor ion (with an error of +- 0.1 Da) of LC-MS measurement.



			pH 4						pH 7							
			no reduction			TCEP reduction			no reduction				TCEP reduction			
	m/z	min	Blank [AUC] 10^2	**3a**·AcCl [AUC] 10^2	**3a** [AUC] 10^2	Blank [AUC] 10^2	**3a**·AcCl [AUC] 10^2	**3a** [AUC] 10^2	blank[a] [AUC] 10^2	**3a**·AcCl [AUC] 10^2	**3a** [AUC] 10^2	**4a** [AUC] 10^2	Blank [AUC] 10^2	**3a**·AcCl [AUC] 10^2	**3a** [AUC] 10^2	**4a** [AUC] 10^2
41	308.091	0.38	70	23	40	68	20	34	44	41	30	48	60	5	21	21
42	500.111	5.90	-	887	364	-	1502	667	-	450	227	83	-	1730	454	838
43	516.106	5.09 +5.16	-	4	-	-	82	81	-	3	-	-	-	37	62	119
44	532.101	5.76	-	-	-	-	15	-	-	-	-	-	-	9	-	-
45	670.129	7.12	-	-	-	-	-	-	-	-	-	-	-	40	3	-

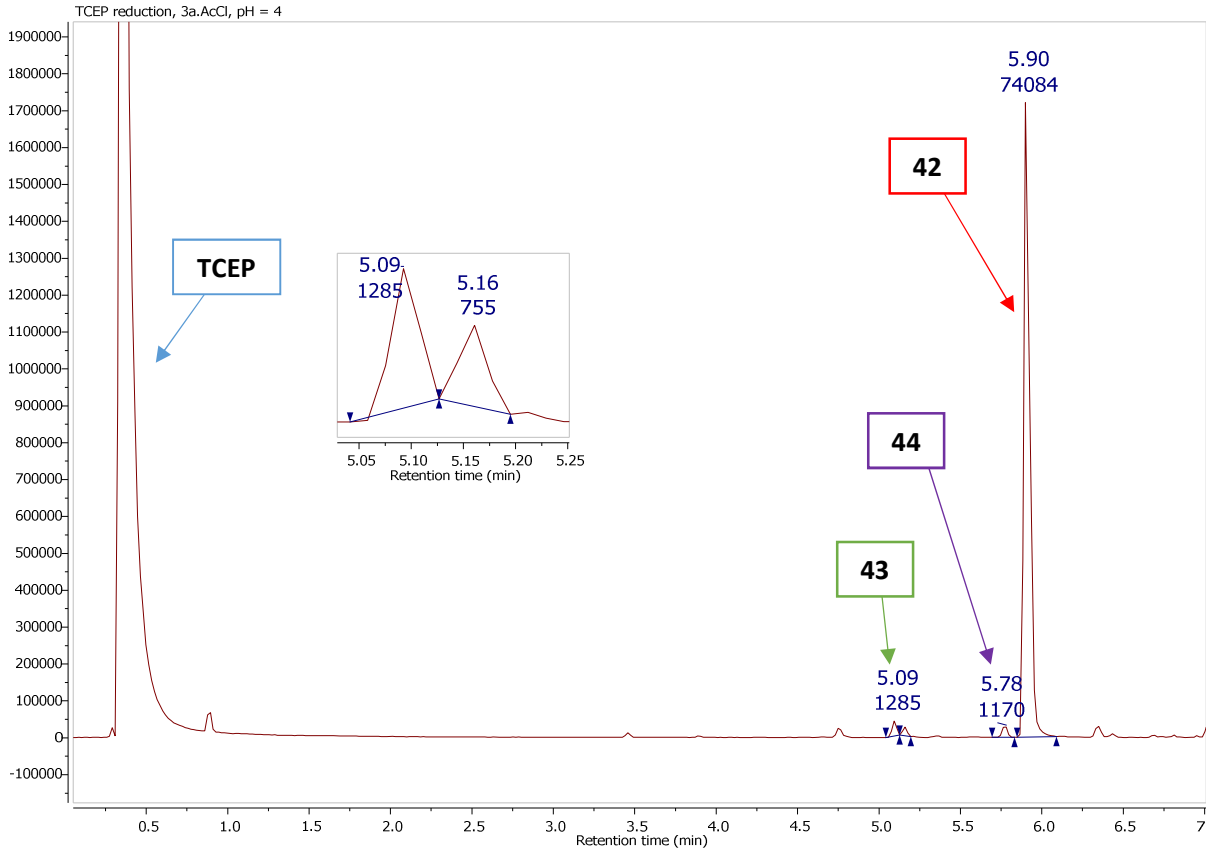
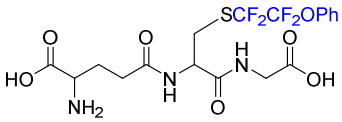


Figure S39: Base peak chromatogram, for the reduced sample, which was fluoroalkylated at pH = 4, by **3a**·AcCl. Peak for the compound **38** is covered by peak of TCEP.

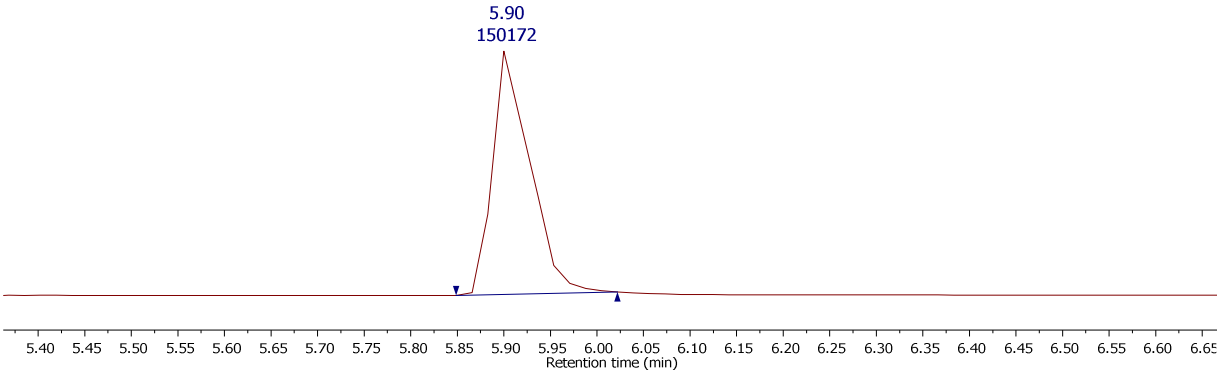
Conjugate **42**



42

$(M+H)^+$ = 500.111

XIC for ion 500.111



5.90 min; ESI MS spectrum

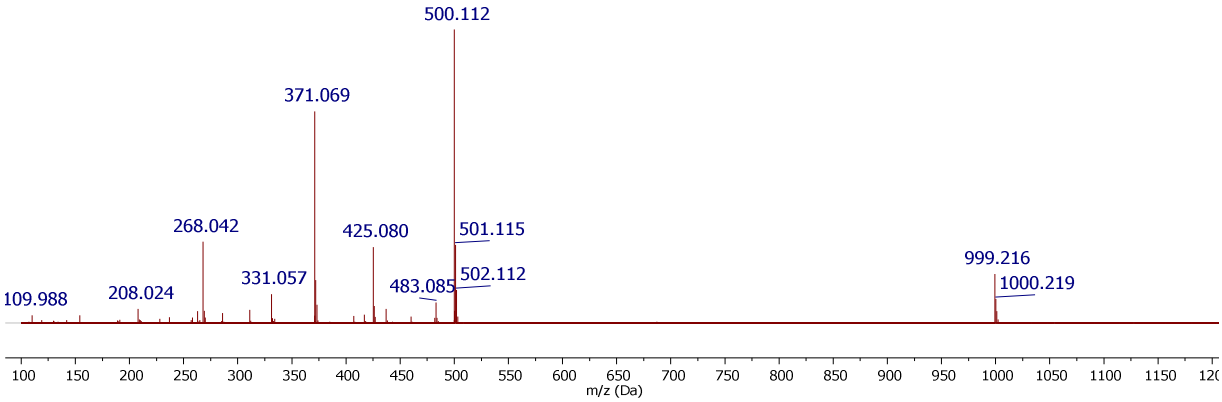


Figure S40: Extracted ion chromatogram for the ion *m/z* = 500.111 (upper panel) and corresponding electrospray MS spectrum (ESI-MS).

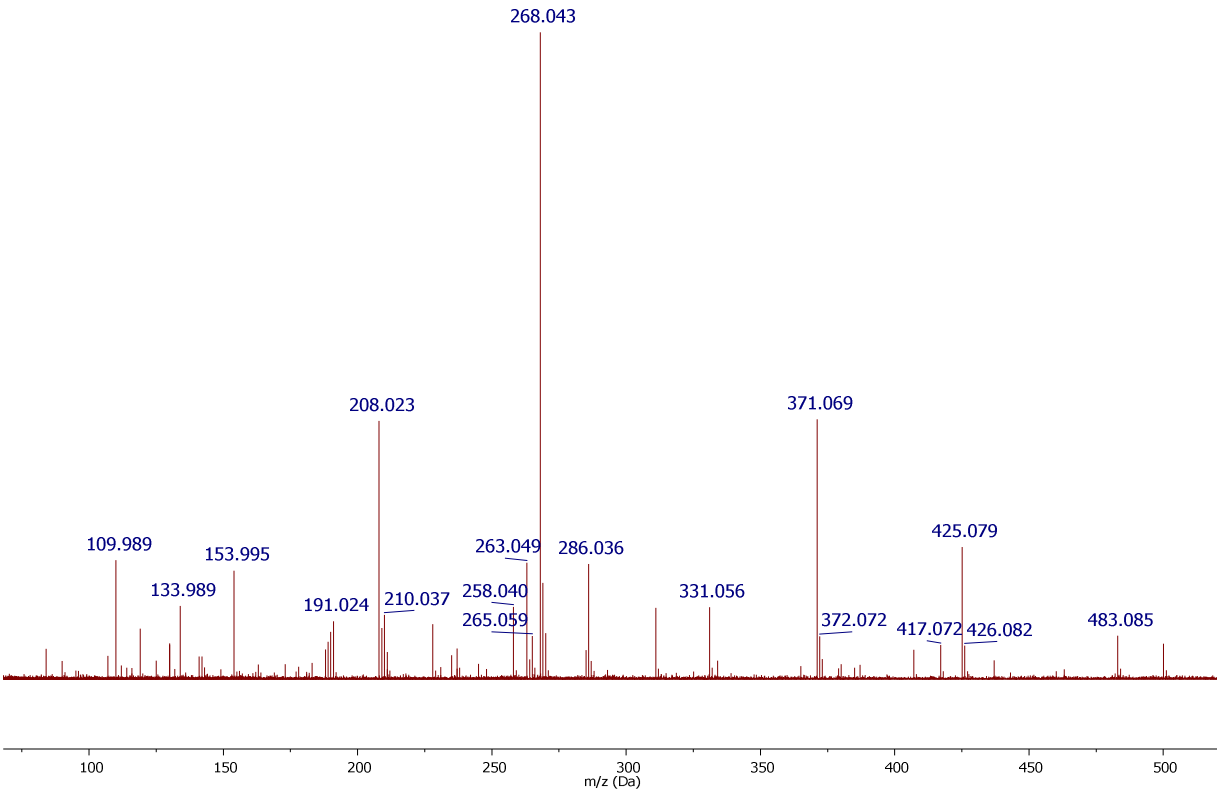
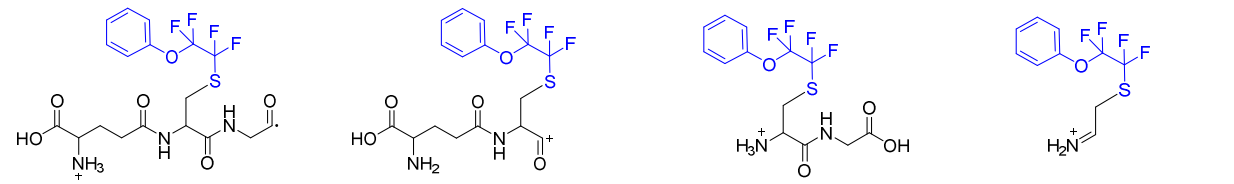


Figure S41: MS/MS fragmetantion spectrum of the ion *m/z* = 500.111.



Chemical Formula: $C_{18}H_{21}F_4N_3O_6S^{+\bullet}$
Exact Mass: 483,108

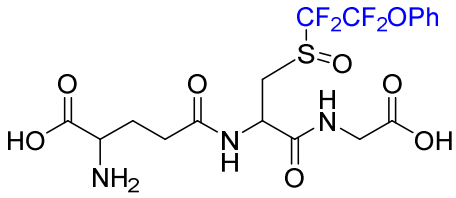
Chemical Formula: $C_{16}H_{17}F_4N_2O_5S^{+}$
Exact Mass: 425,079

Chemical Formula: $C_{13}H_{15}F_4N_2O_4S^{+}$
Exact Mass: 371,068

Chemical Formula: $C_{10}H_{10}F_4NOS^{+}$
Exact Mass: 268,041

Scheme S4: Fragments of the ion m/z = 500.111 in the MS/MS spectrtum.

Conjugate **43**



43

$(M+H)^+ = 516.106$

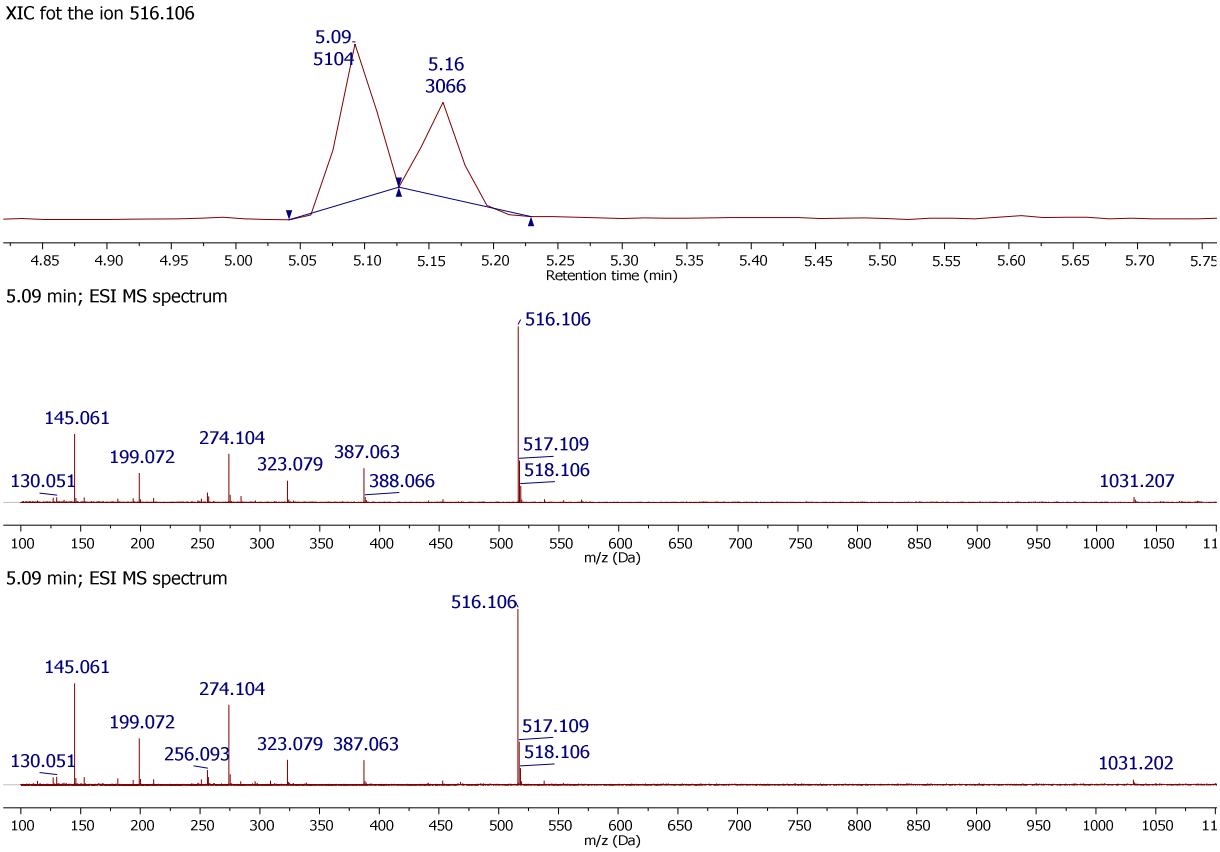
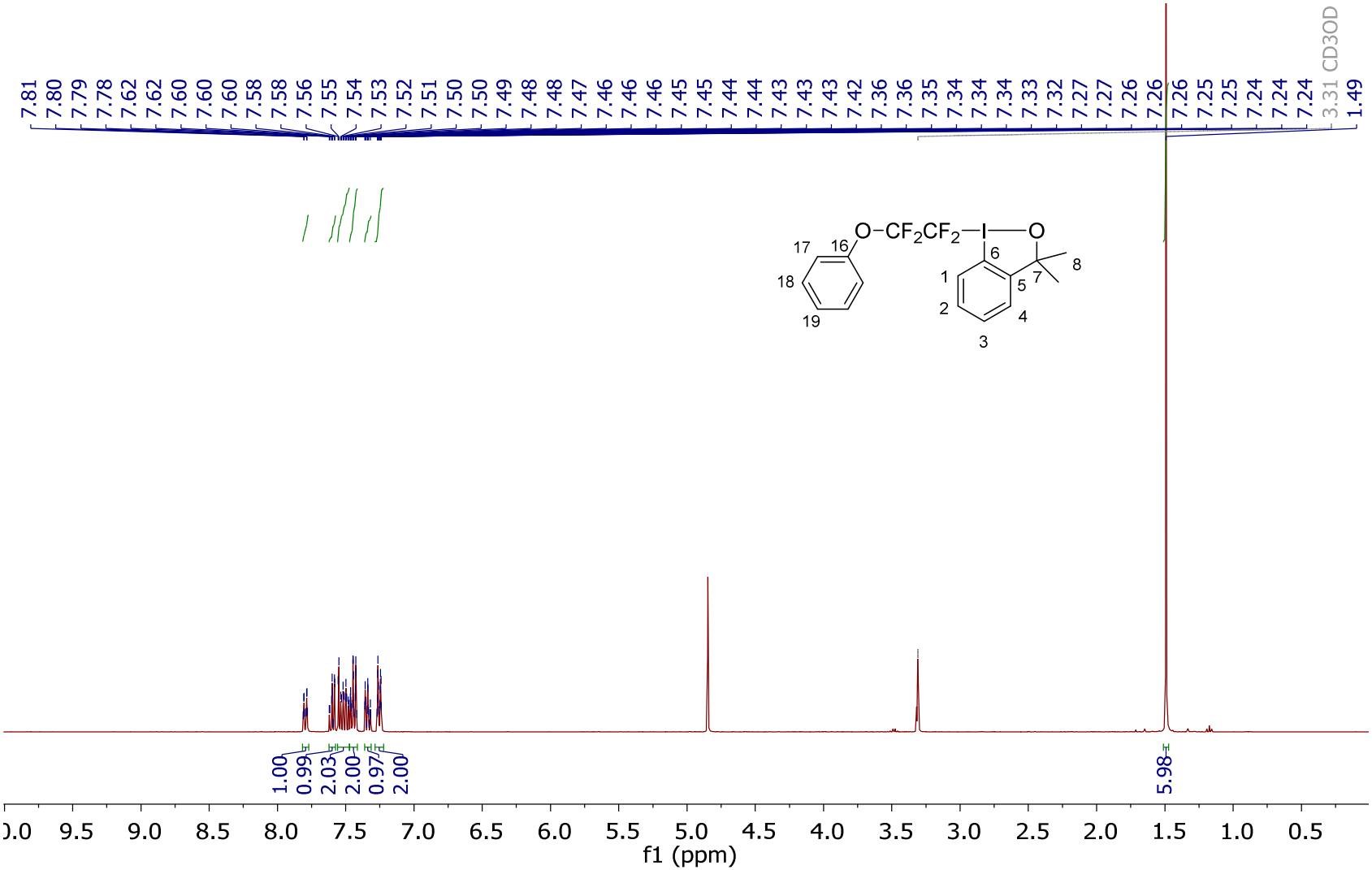


Figure S42: Extracted ion chromatogram for the ion *m/z* = 516.106 (upper panel). Two peaks were detected in extracted ion chromatogram, which were considered to be diastereoisomers of **43**. Therefore the AUC reported in previous table is the sum of AUC of both peaks.

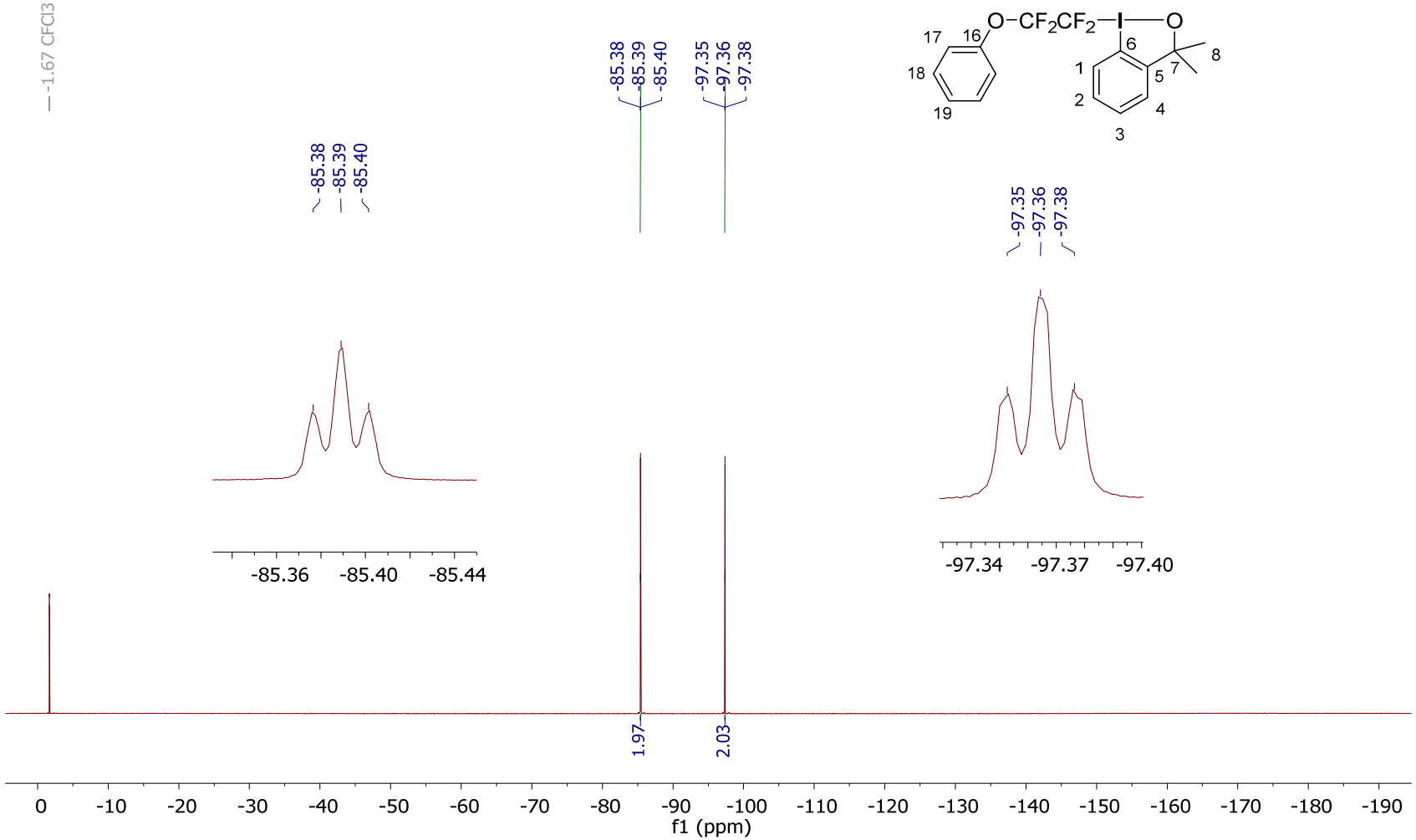
8. Spectra of compounds

3,3-Dimethyl-1-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-1,3-dihydro-1λ³-benzo[d][1,2]iodaoxole (3a)

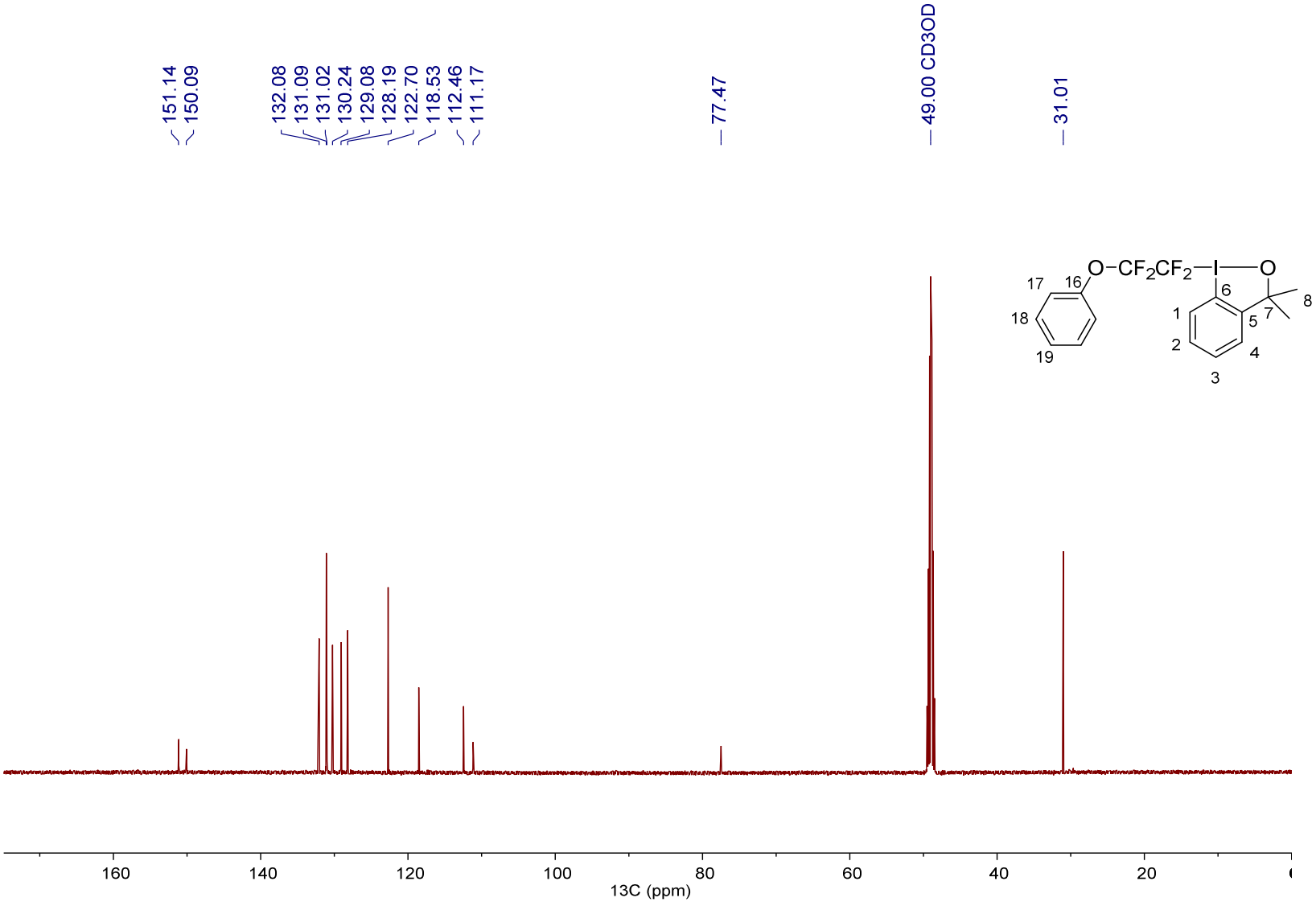
^{1}H NMR (400.10 MHz, CD_3OD):



^{19}F NMR (376.46 MHz, CD_3OD):

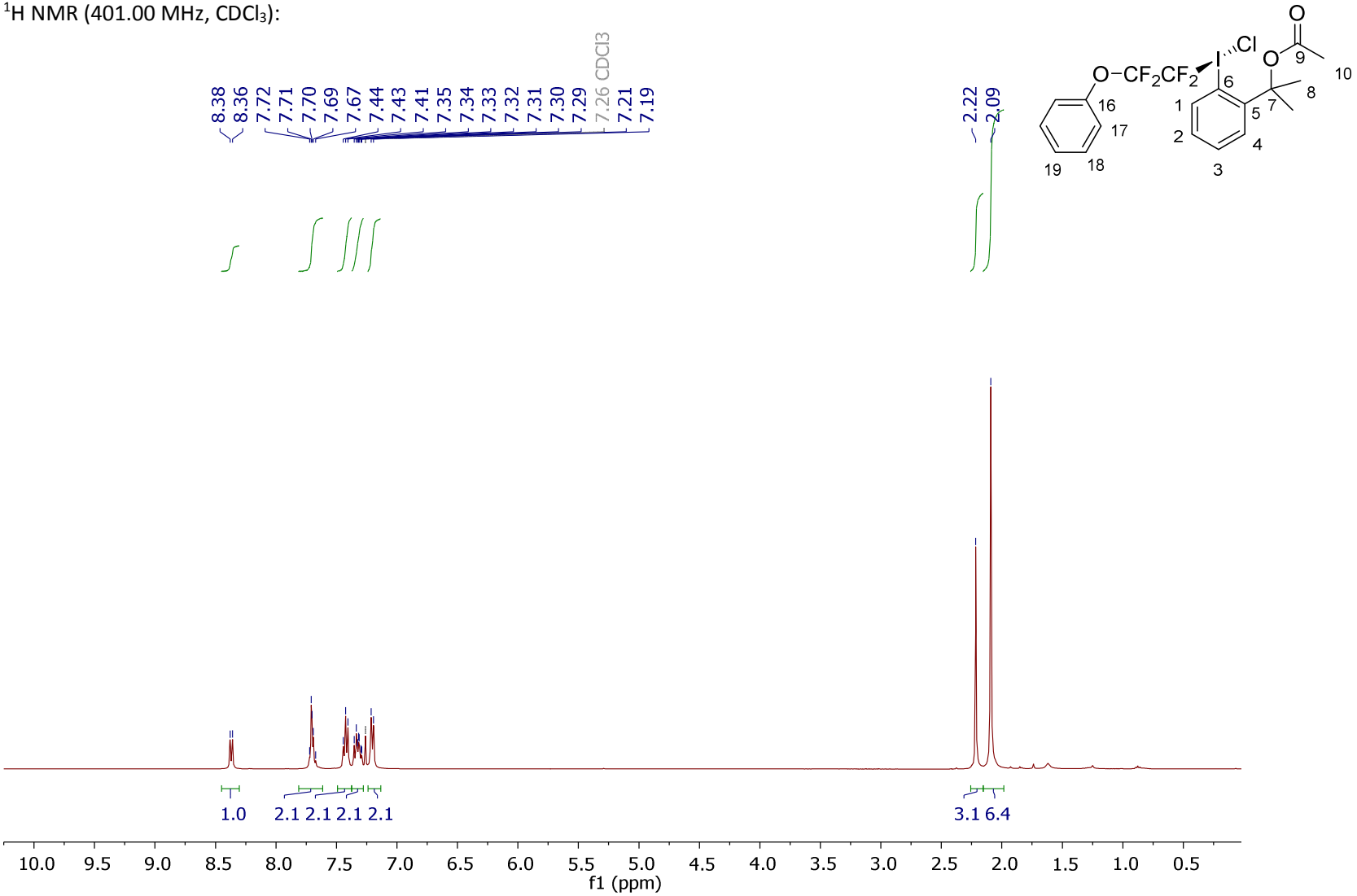


^{13}C {^{1}H, ^{19}F} NMR (100.62 MHz, CD_3OD):

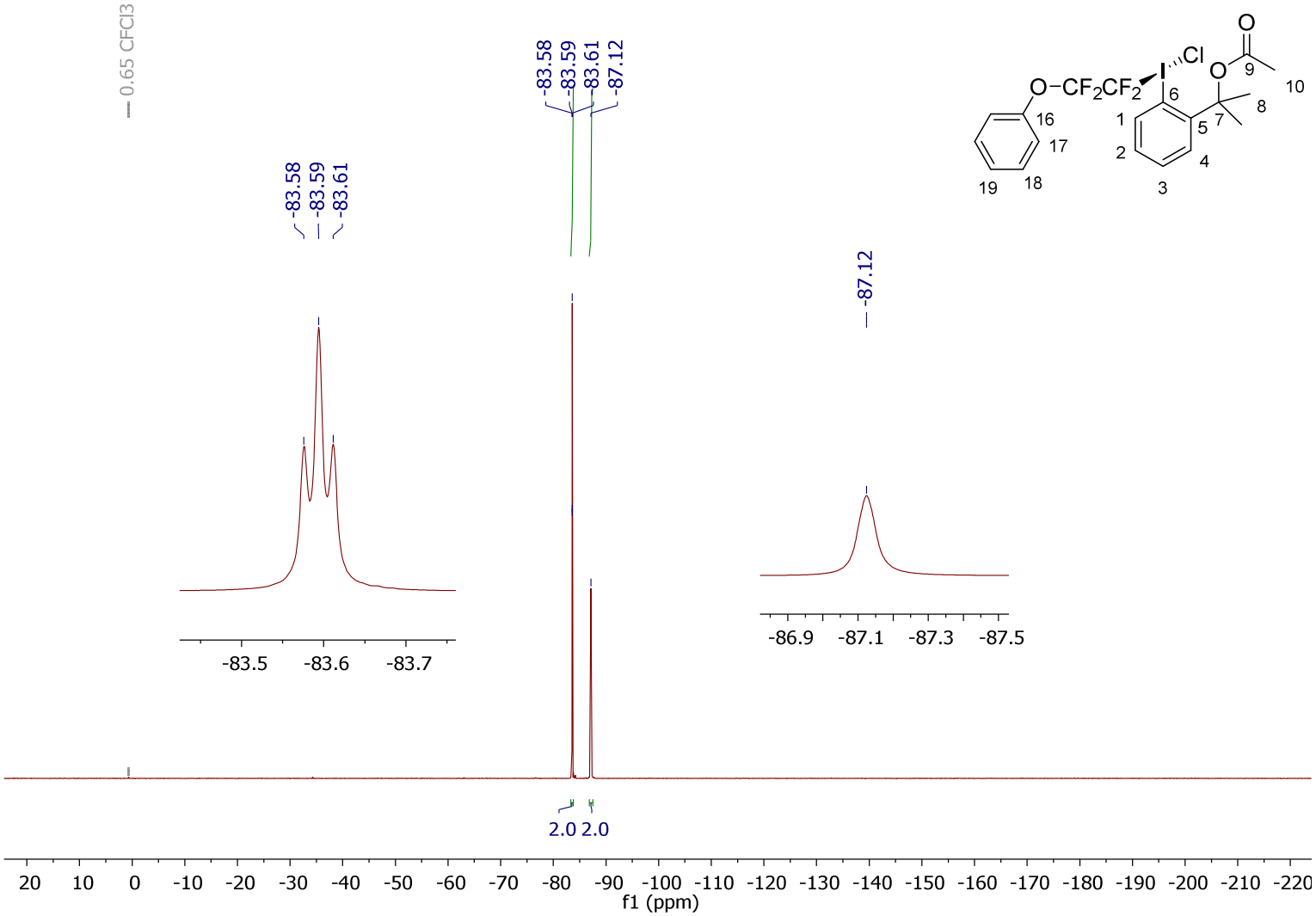


2-(2-(Chloro(1,1,2,2-tetrafluoro-2-phenoxyethyl)-λ³-iodanyl)phenyl)propan-2-yl acetate (3a·AcCl)

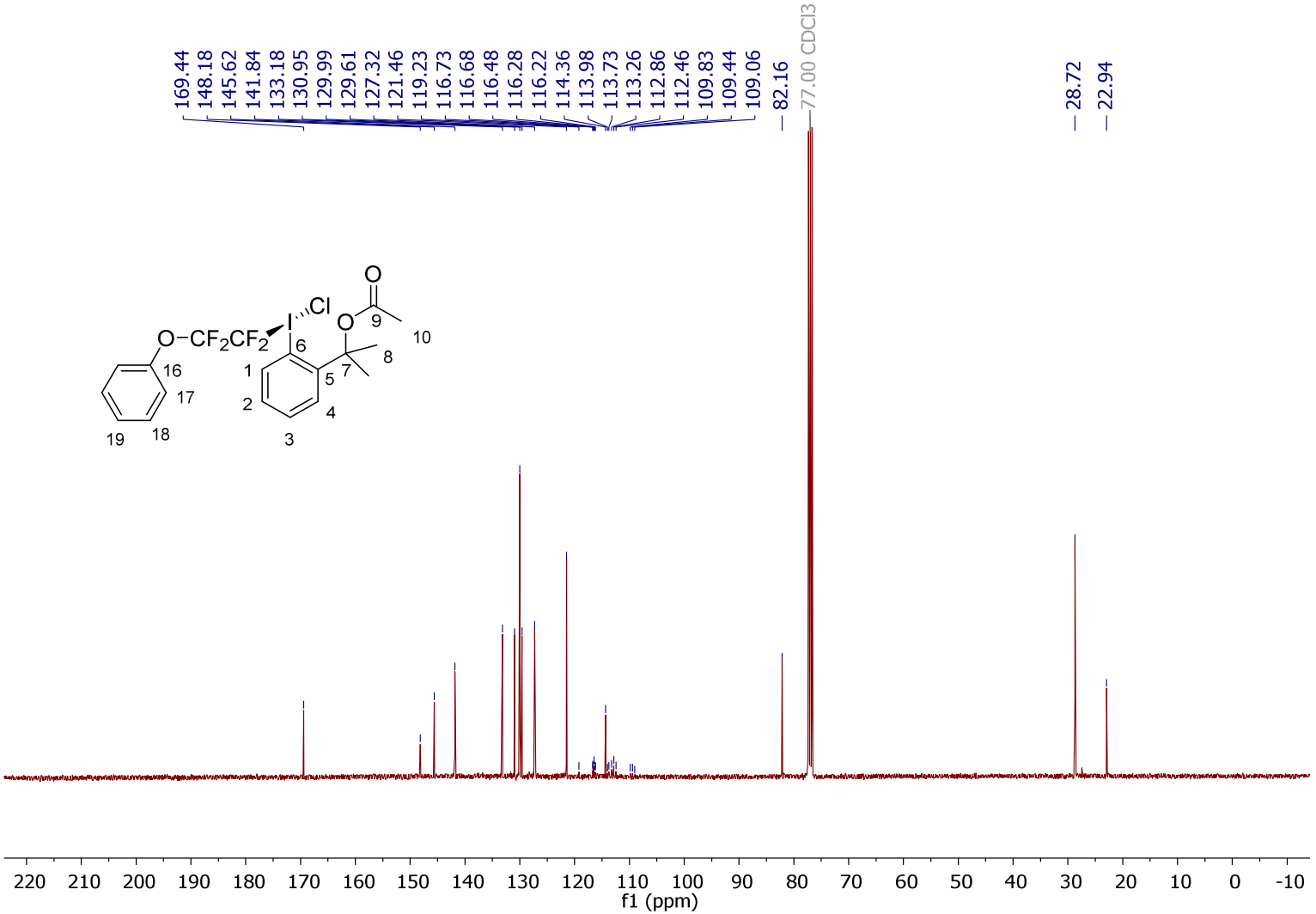
^{1}H NMR (401.00 MHz, $CDCl_3$):



^{19}F NMR (377.28 MHz, $CDCl_3$):

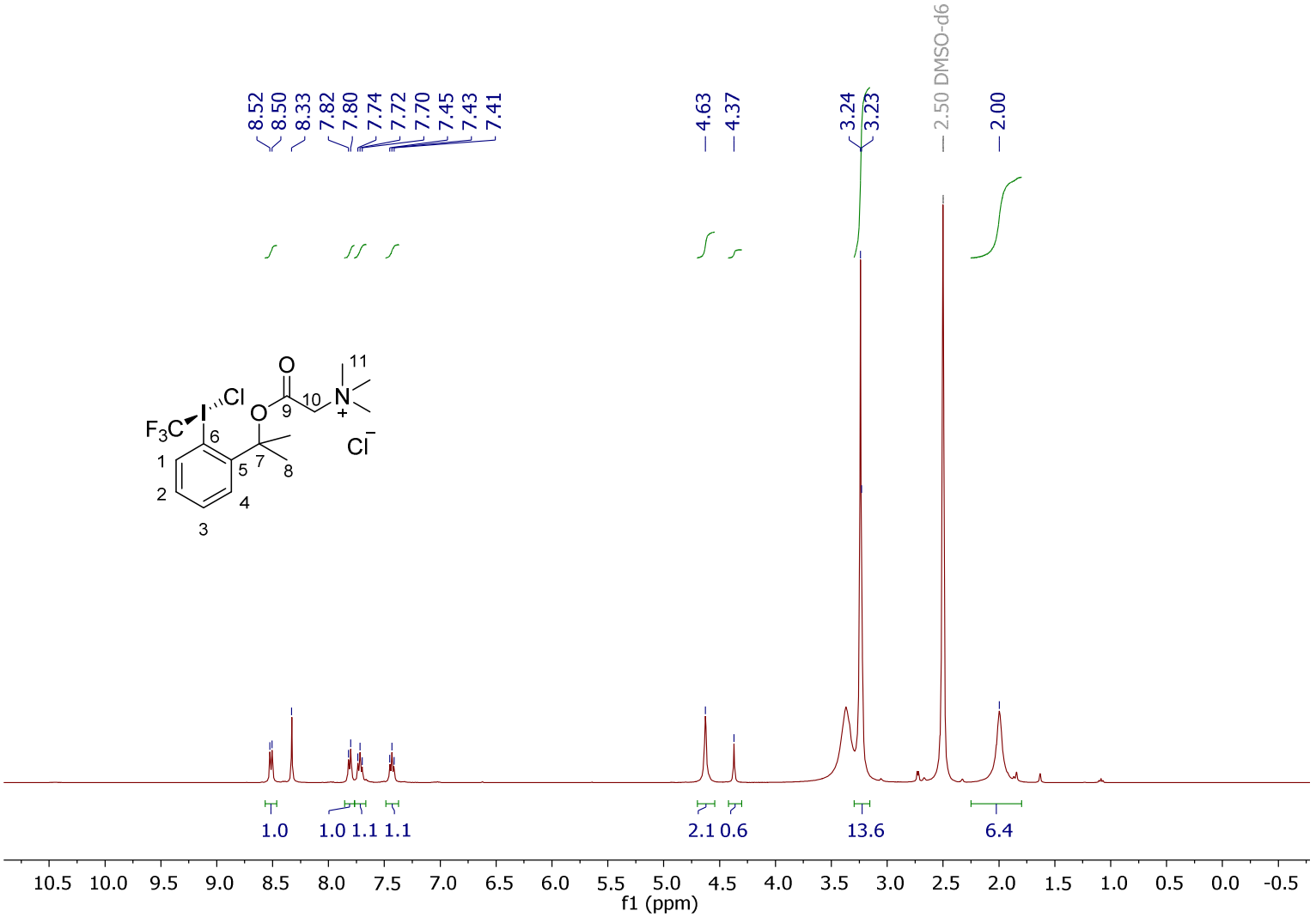


^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$):

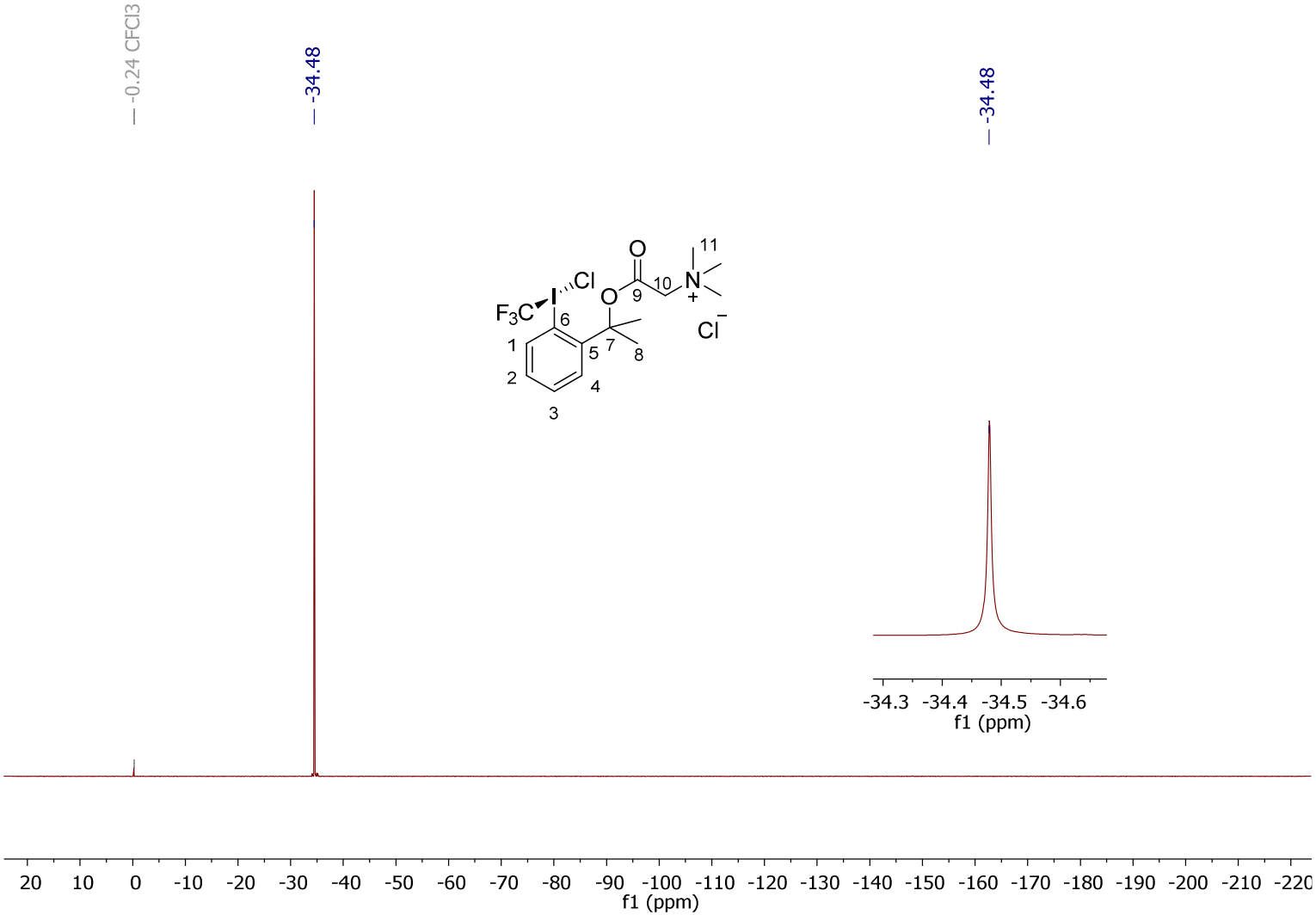


2-((2-(2-(Chloro(trifluoromethyl)-λ³-iodanyl)phenyl)propan-2-yl)oxy)-N,N,N-trimethyl-2-oxoethan-1-aminium chloride (1·BetCl)

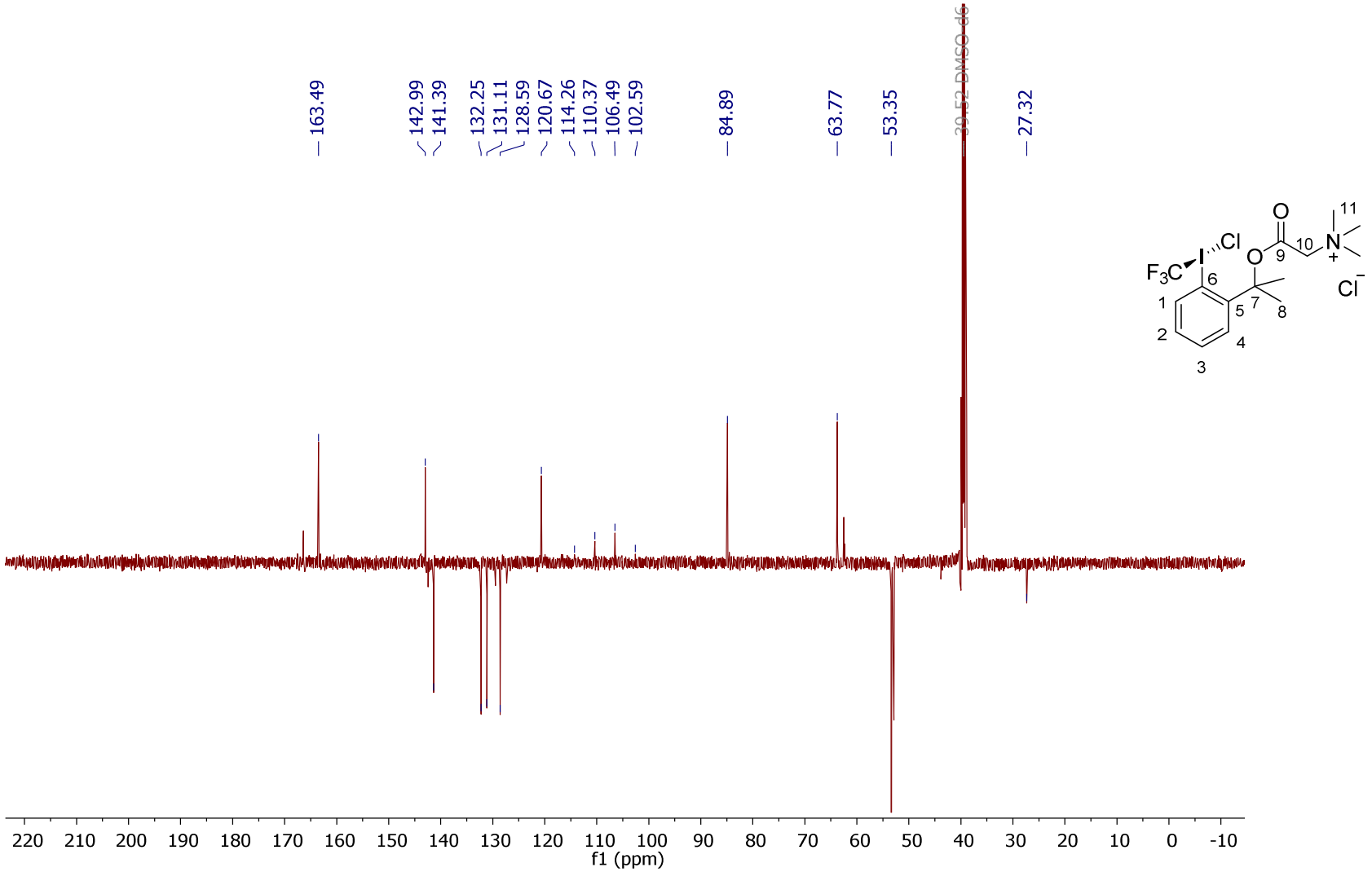
^{1}H NMR (401.00 MHz, DMSO-d_6):



^{19}F NMR (377.28 MHz, DMSO-d_6):

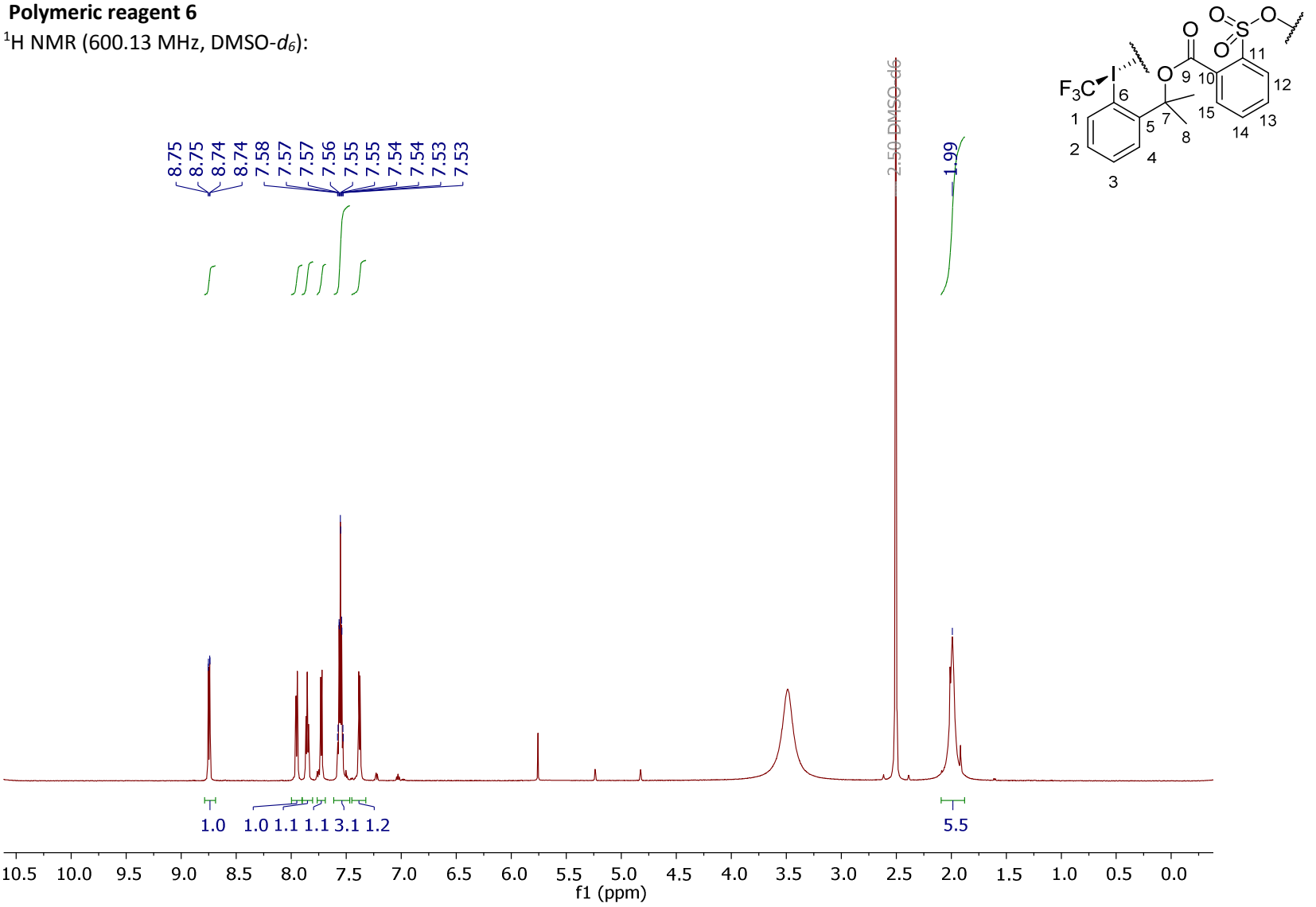


^{13}C {^{1}H} NMR (100.84 MHz, DMSO-d_6):

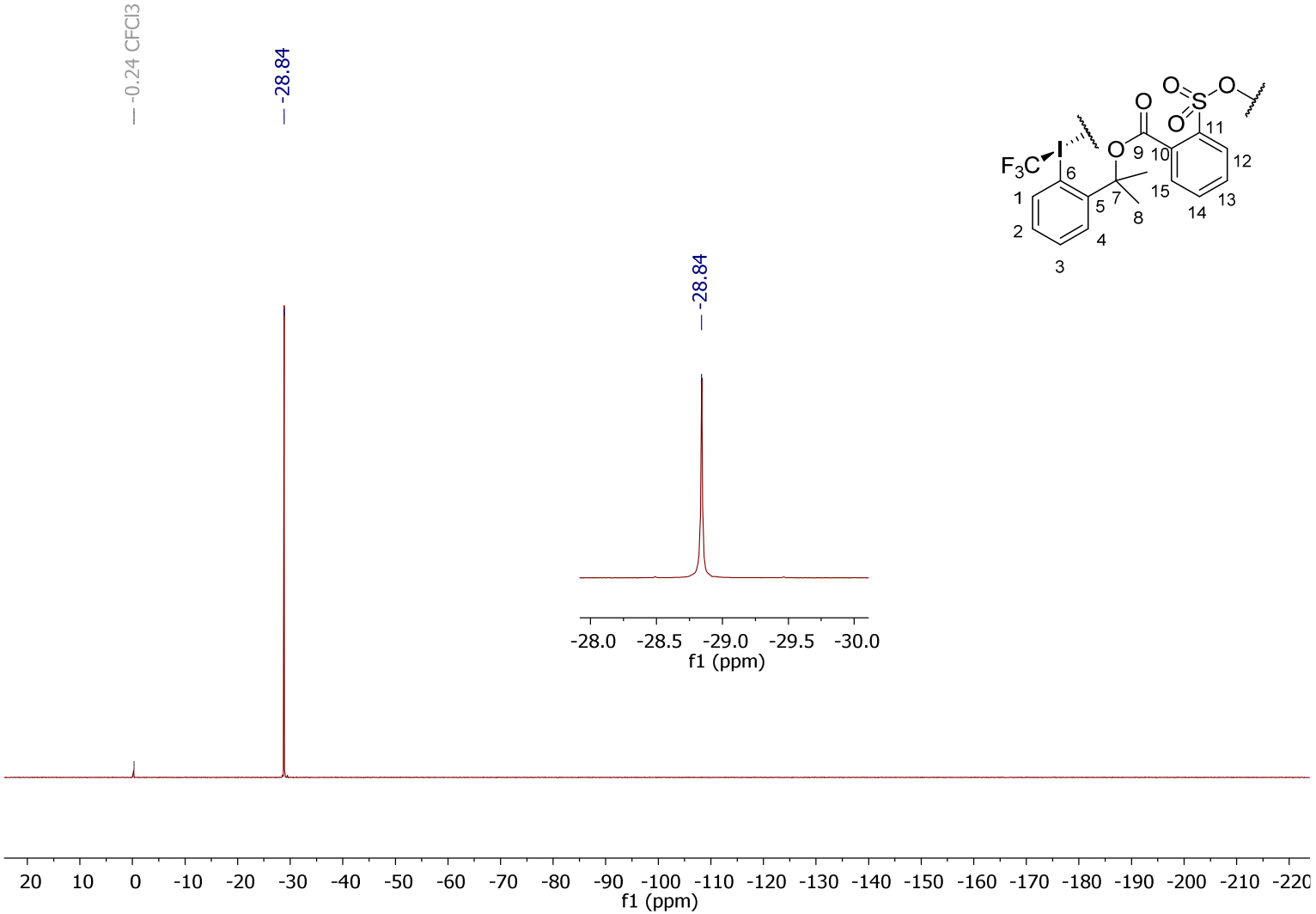


Polymeric reagent 6

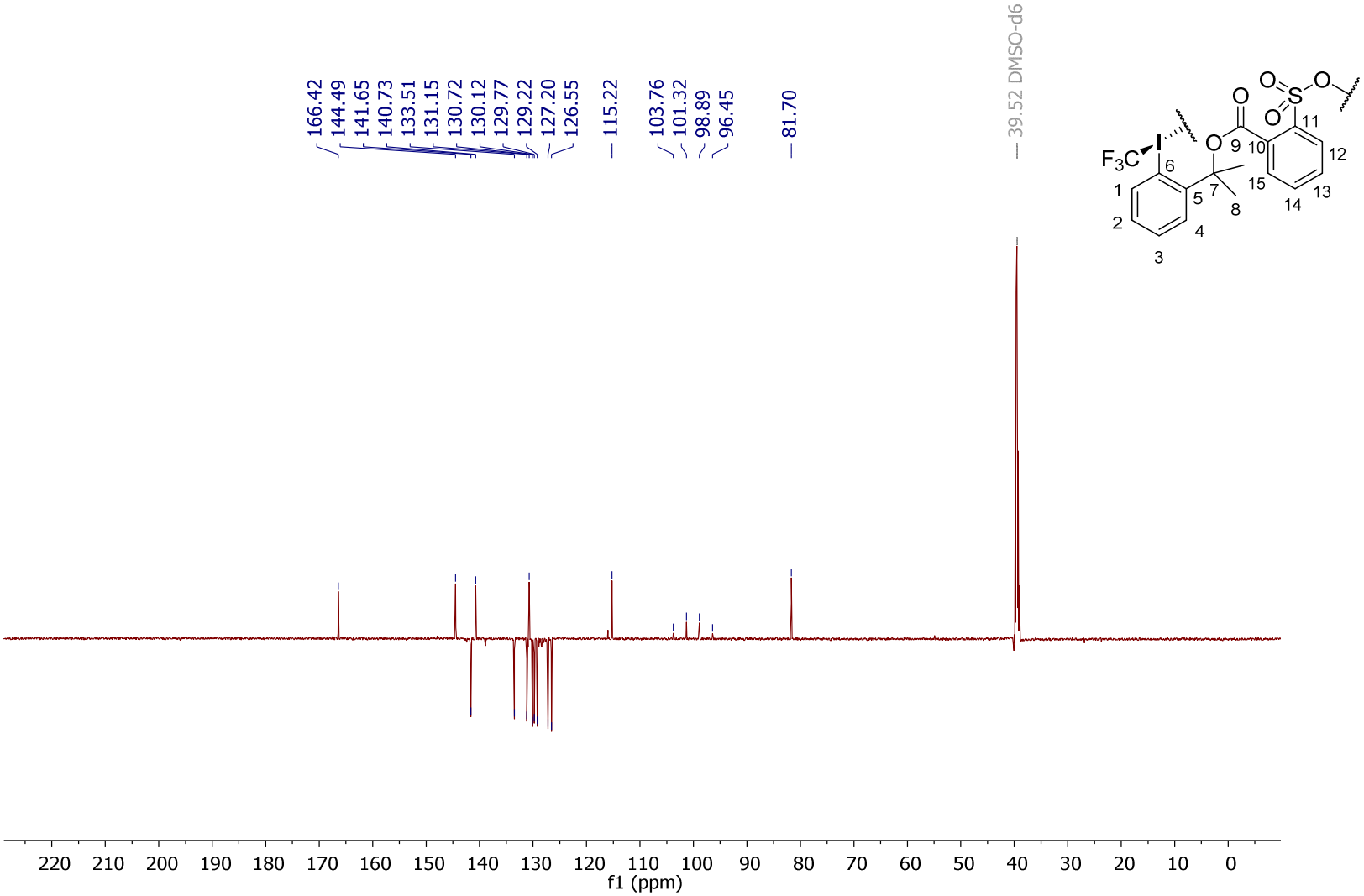
^{1}H NMR (600.13 MHz, DMSO-d_6):



^{19}F NMR (377.28 MHz, DMSO-d_6):

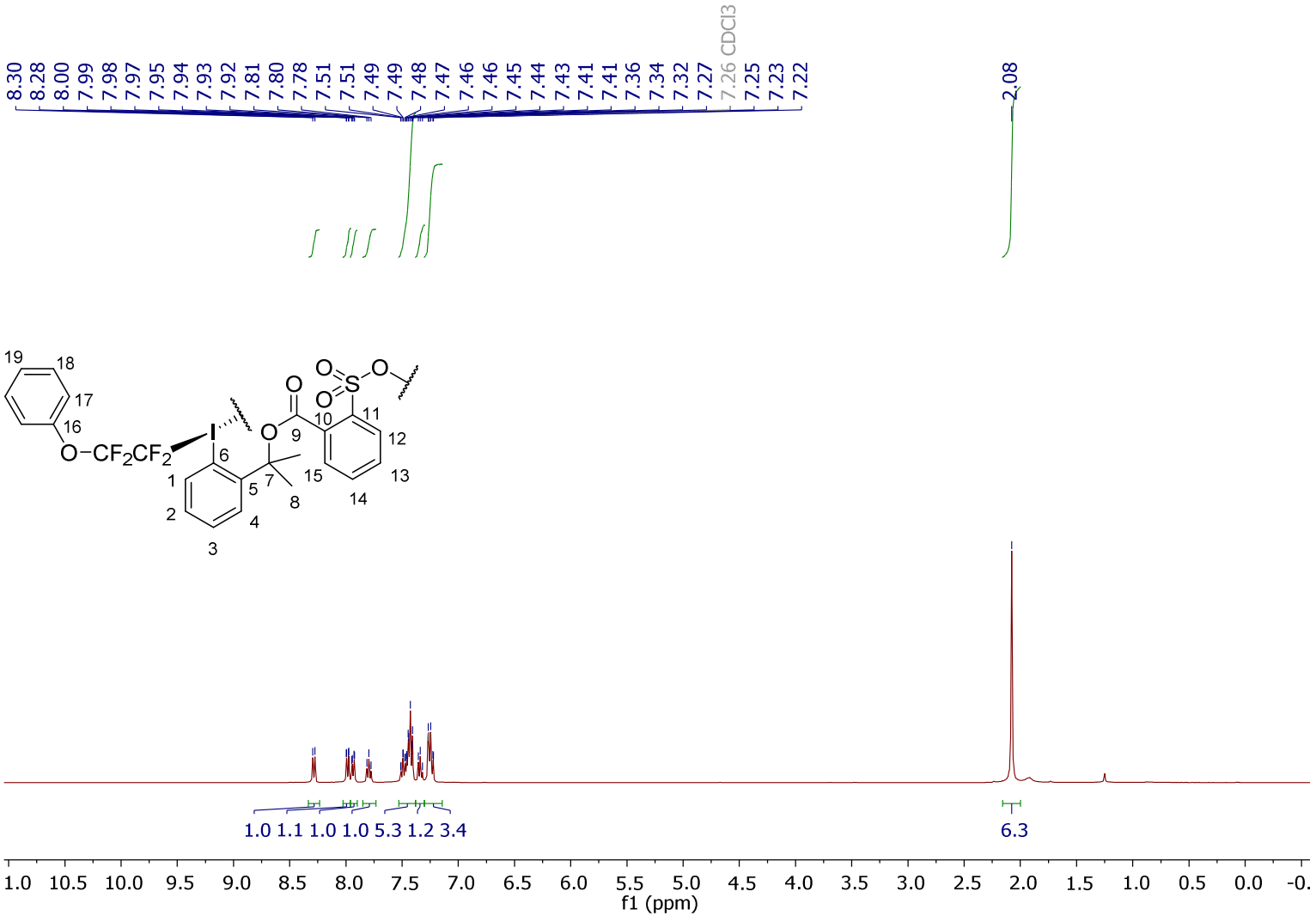


^{13}C {^{1}H} NMR (150.92 MHz, DMSO-d_6):

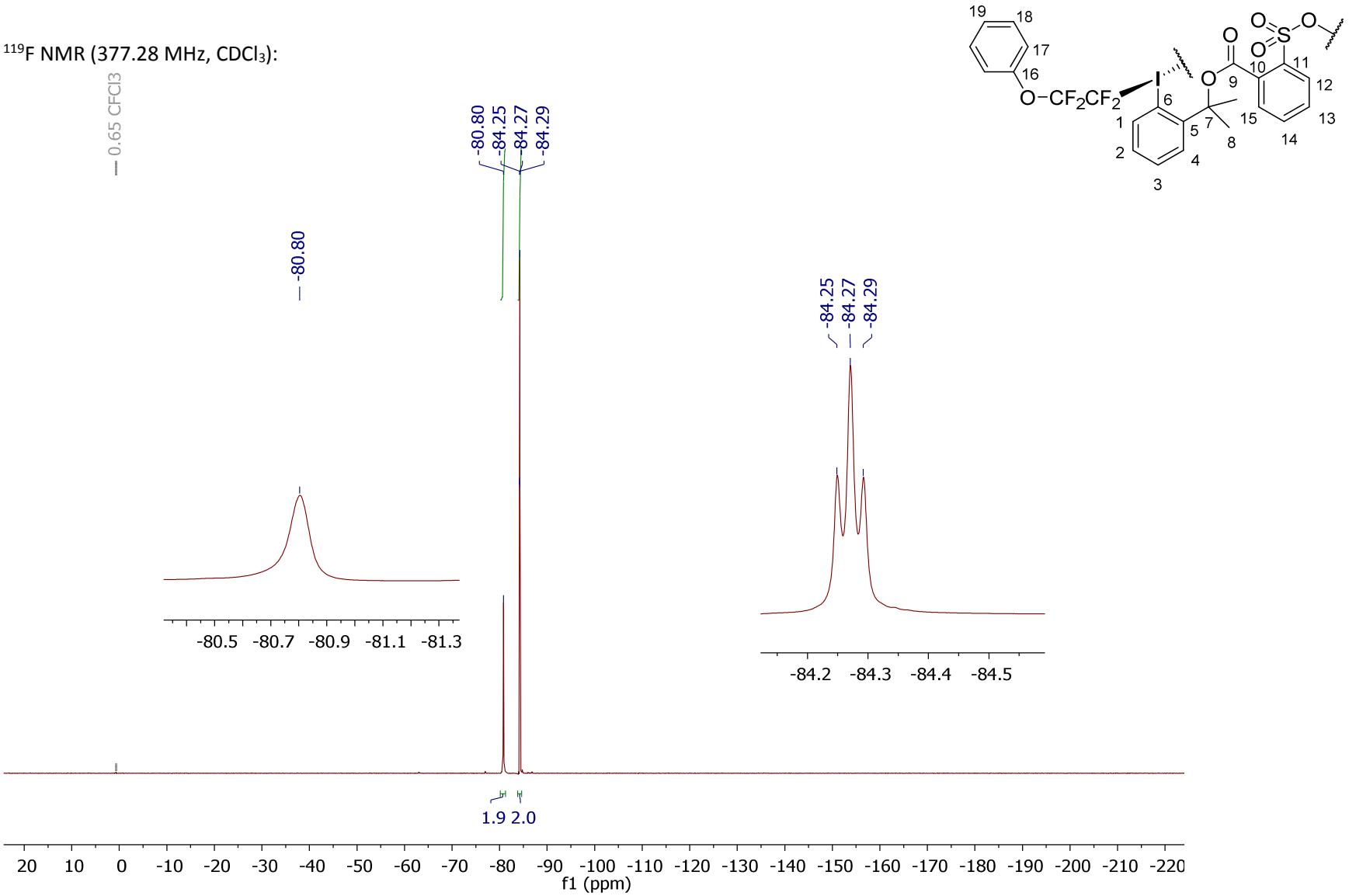


Polymeric reagent 7

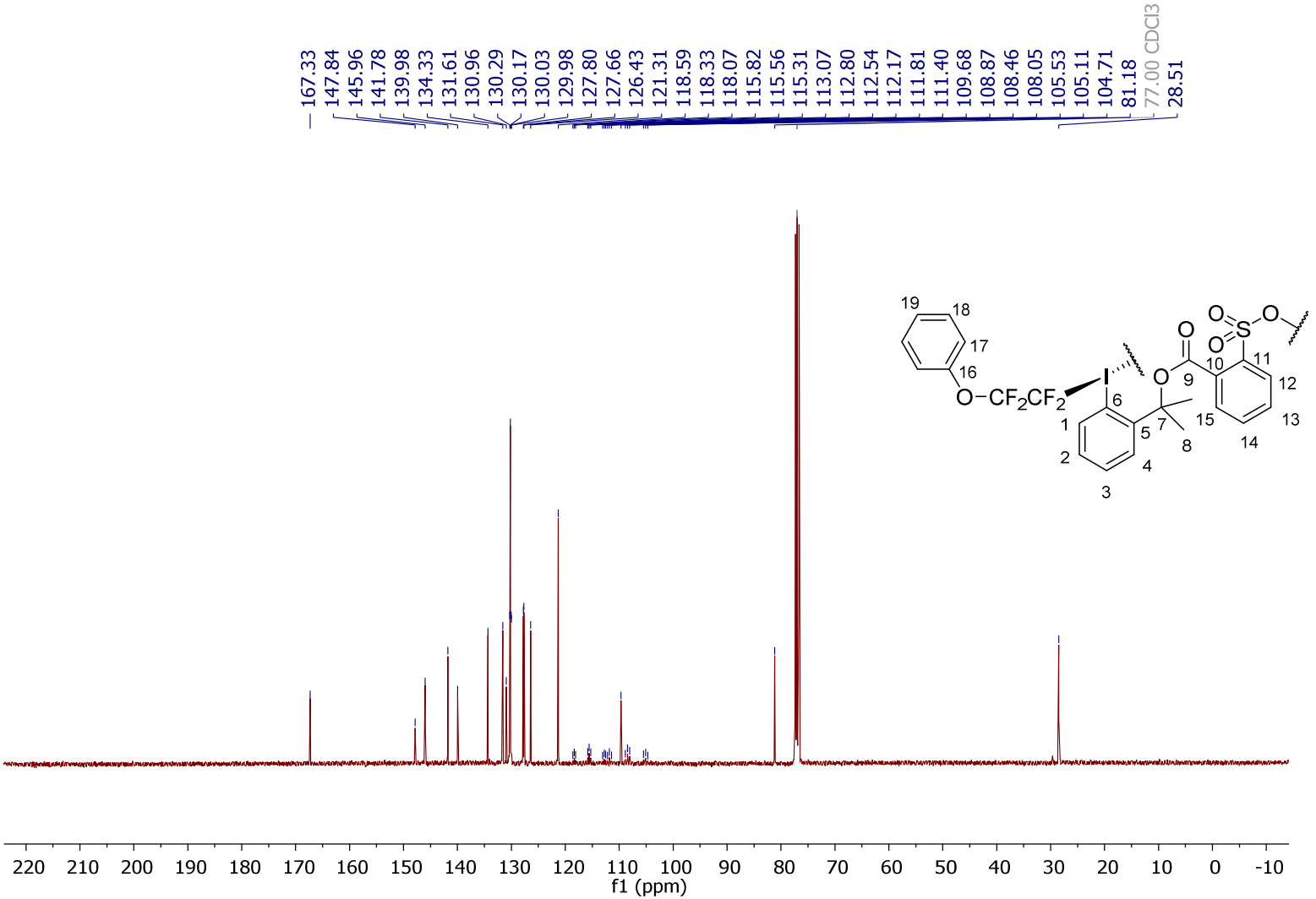
^{1}H NMR (401.00 MHz, $CDCl_3$):



^{119}F NMR (377.28 MHz, $CDCl_3$):

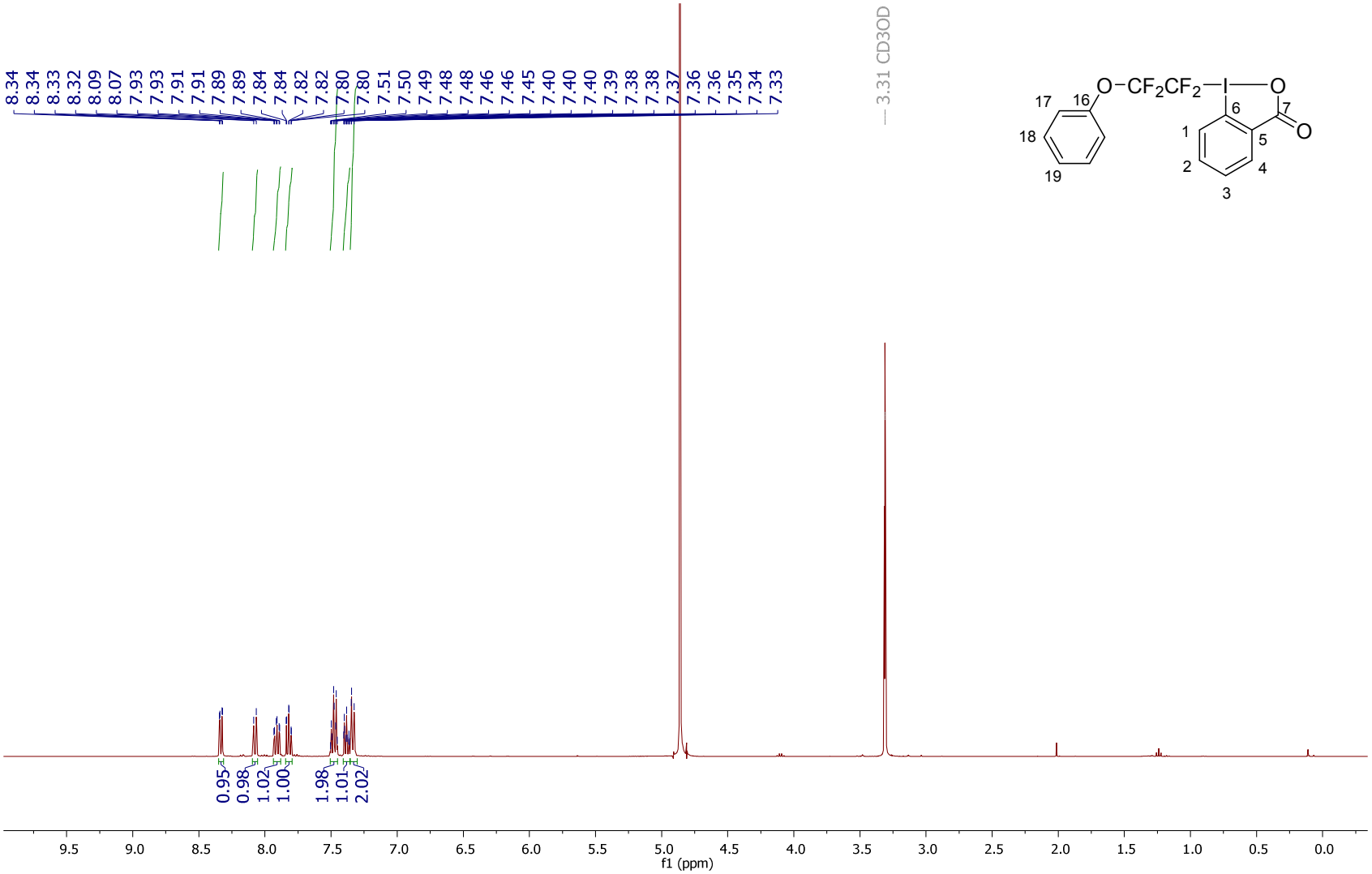


^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$):

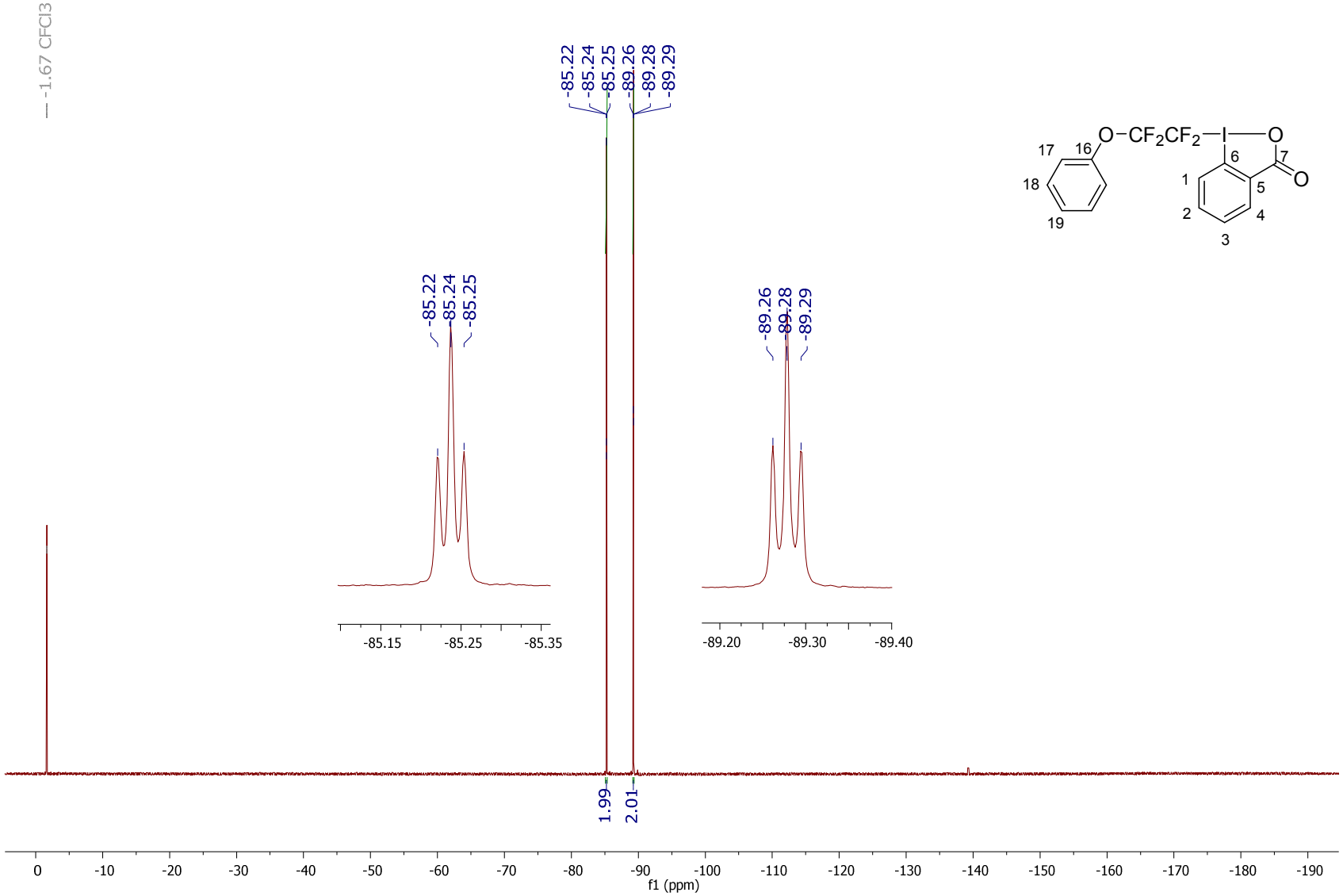


1-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-1λ³-benzo[d][1,2]iodaoxol-3(1H)-one (4a)

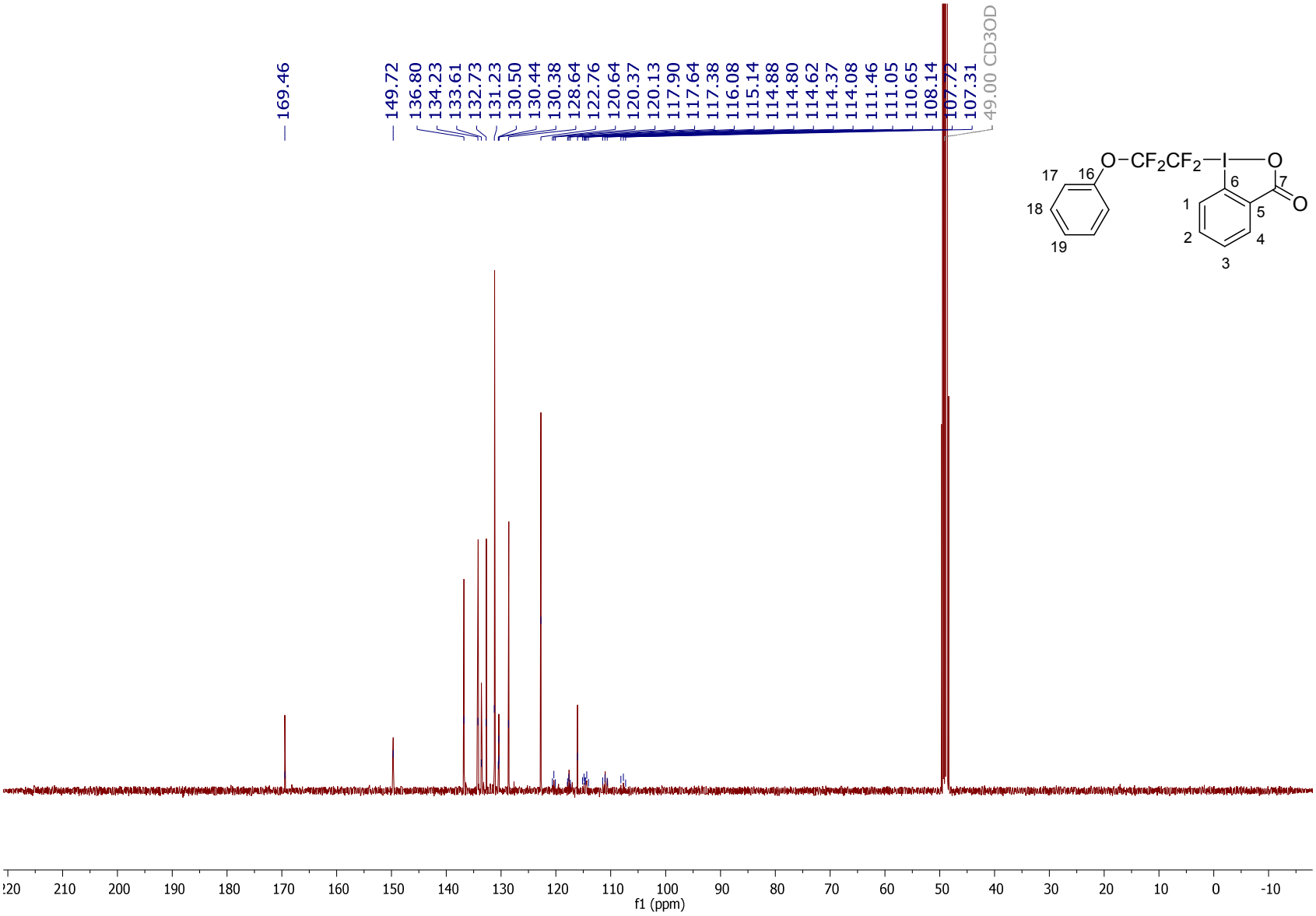
^{1}H NMR (400.10 MHz, CD_3OD):



^{19}F NMR (376.46 MHz, CD_3OD):

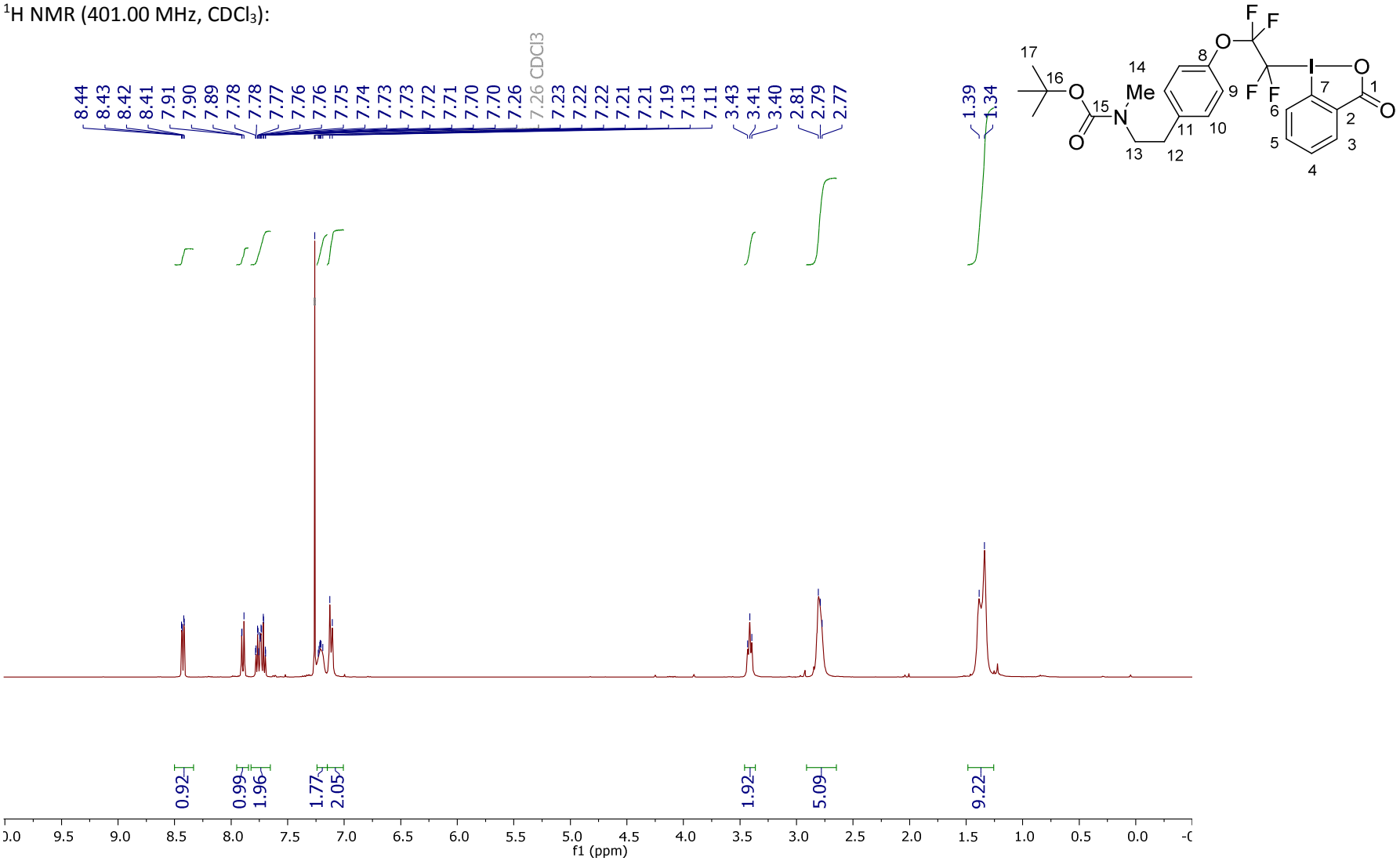


^{13}C {^{1}H} NMR (100.62 MHz, CD_3OD):

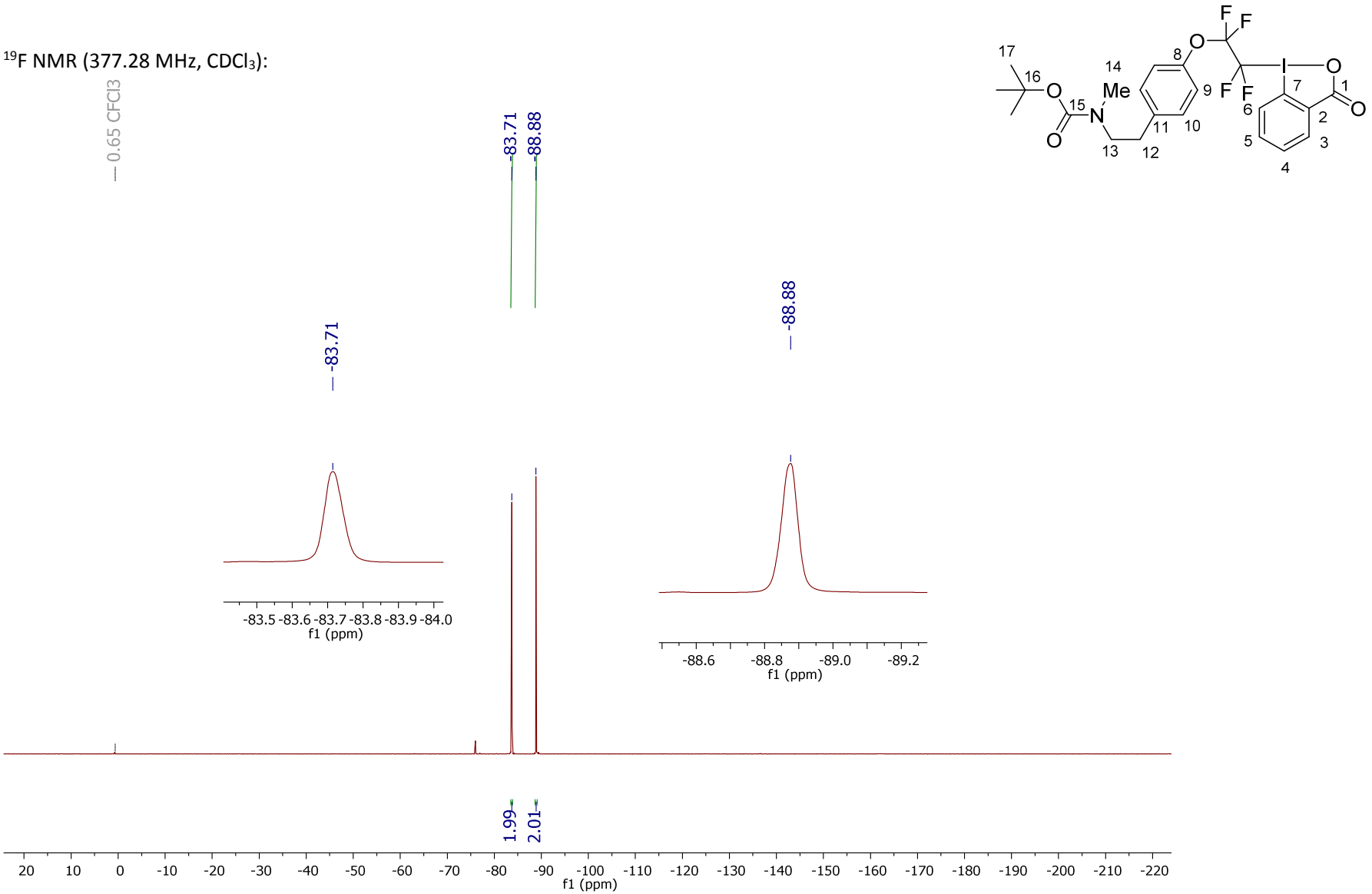


***tert*-Butyl methyl(4-(1,1,2,2-tetrafluoro-2-(3-oxo-1λ³-benzo[d][1,2]iodaoxol-1(3*H*)-yl)ethoxy)phenethyl)carbamate (4b·Boc)**

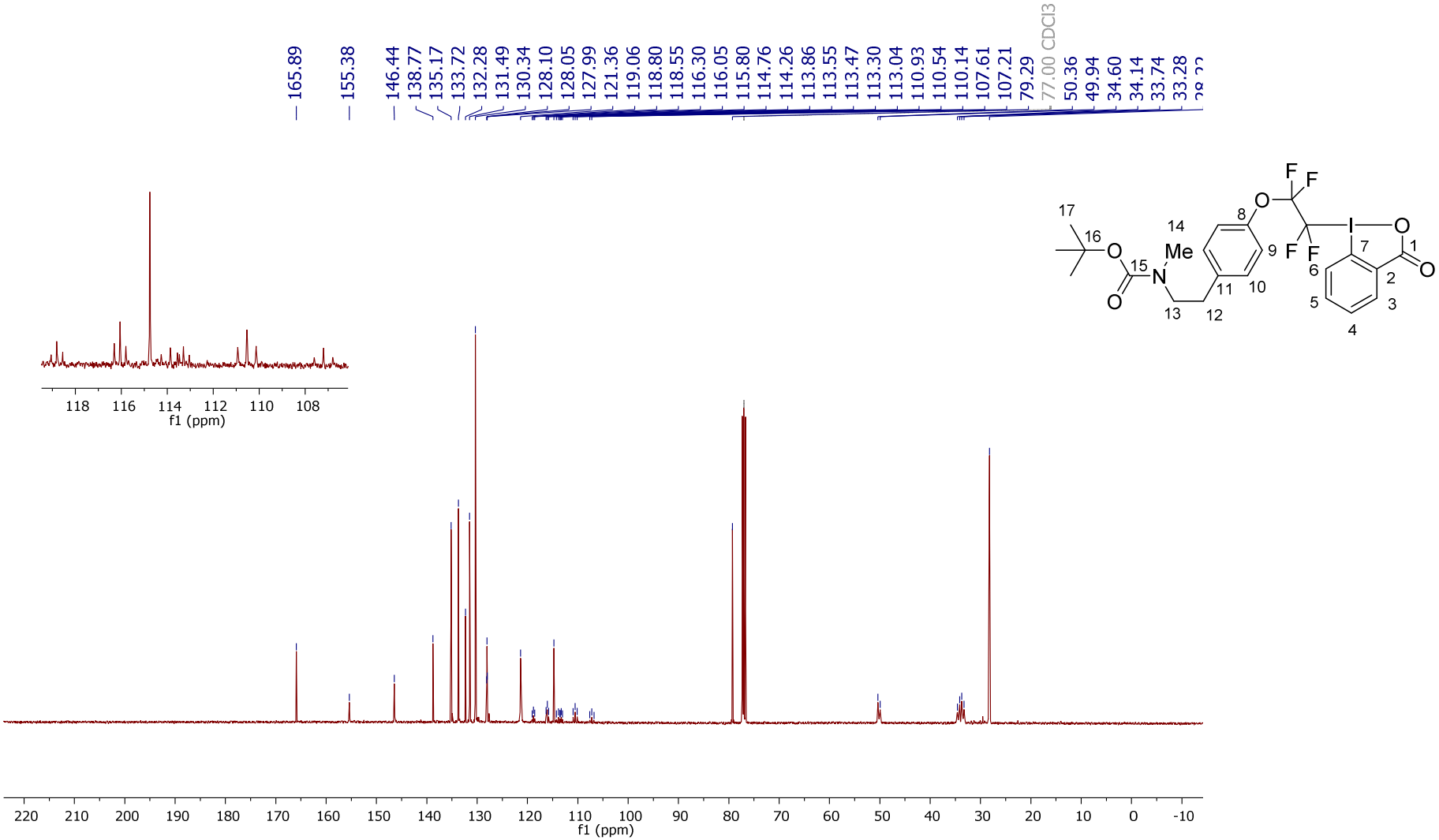
^{1}H NMR (401.00 MHz, $CDCl_3$):



^{19}F NMR (377.28 MHz, $CDCl_3$):

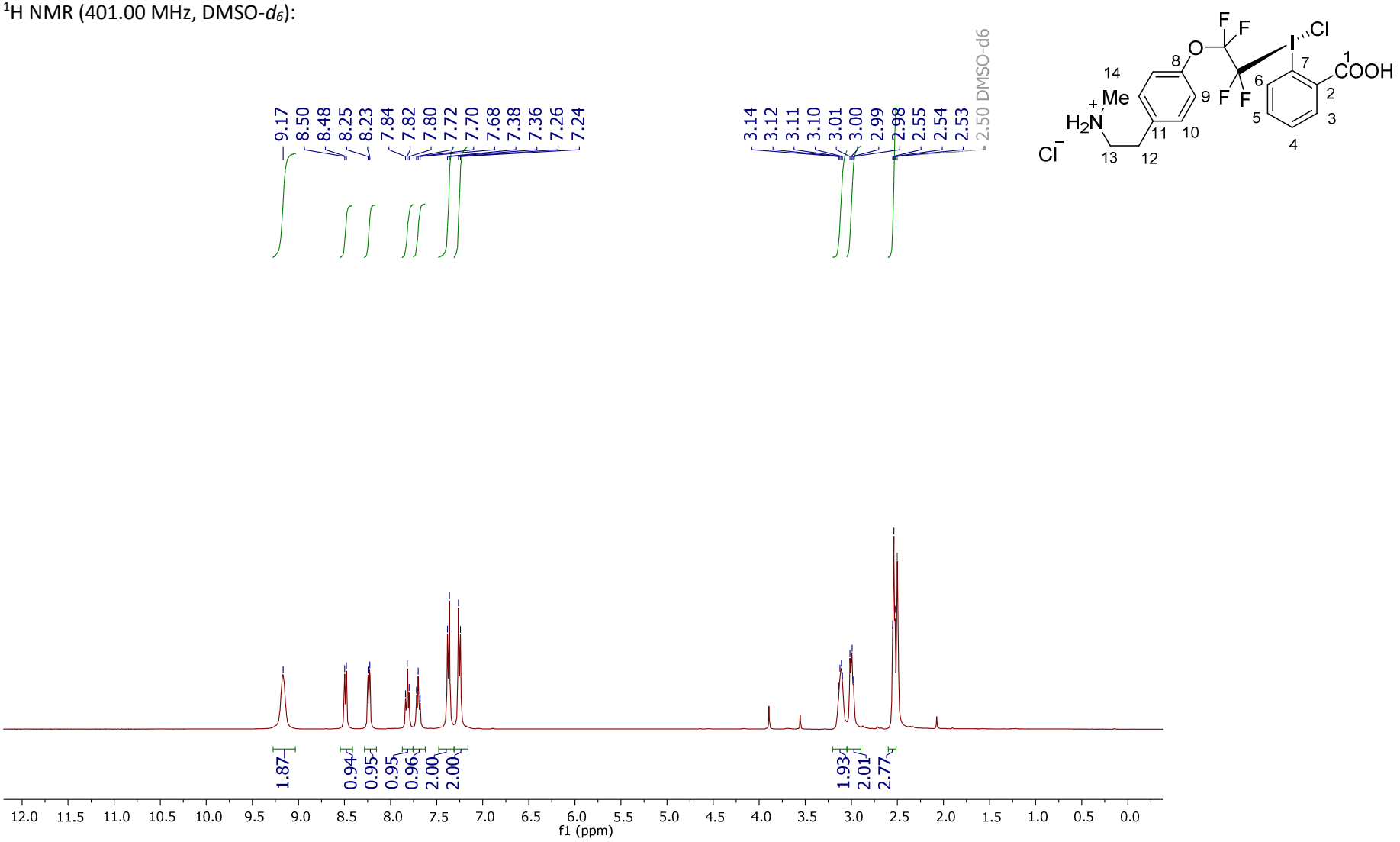


^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$):

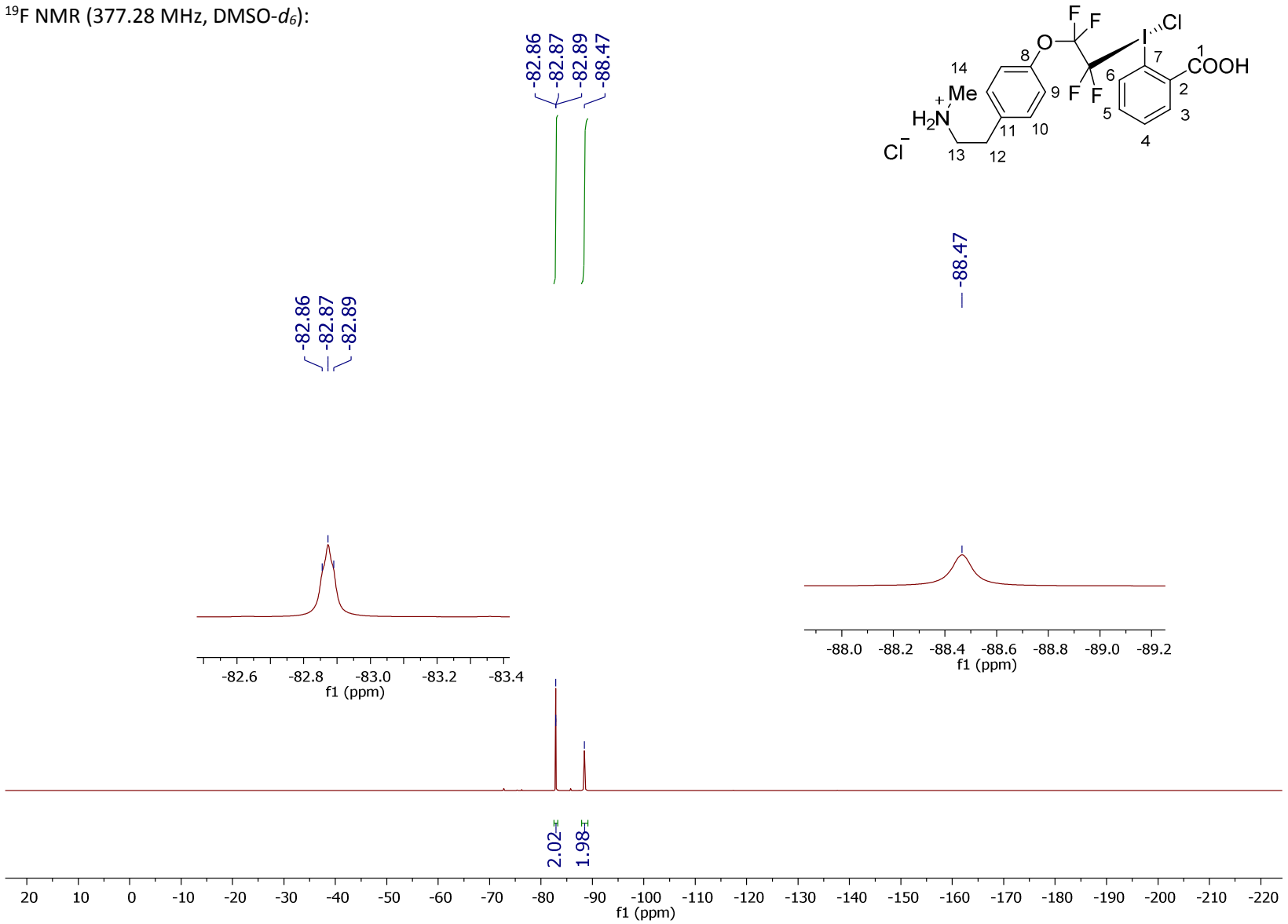


2-(4-(2-((2-Carboxyphenyl)chloro-λ^3-iodanyl)-1,1,2,2-tetrafluoroethoxy)phenyl)-*N*-methylethan-1-aminium chloride (4b·HCl)

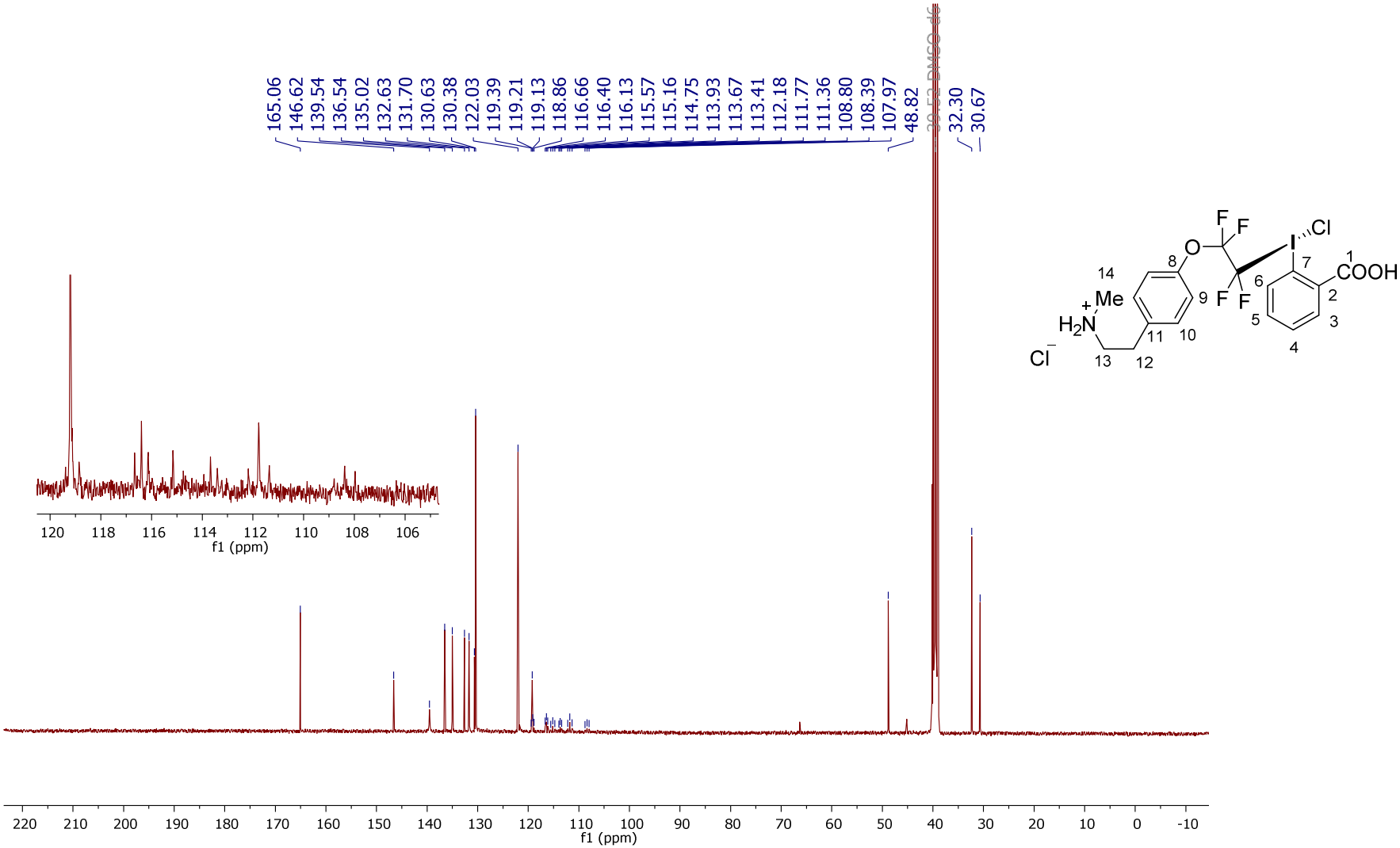
^{1}H NMR (401.00 MHz, DMSO-d_6):



^{19}F NMR (377.28 MHz, DMSO-d_6):



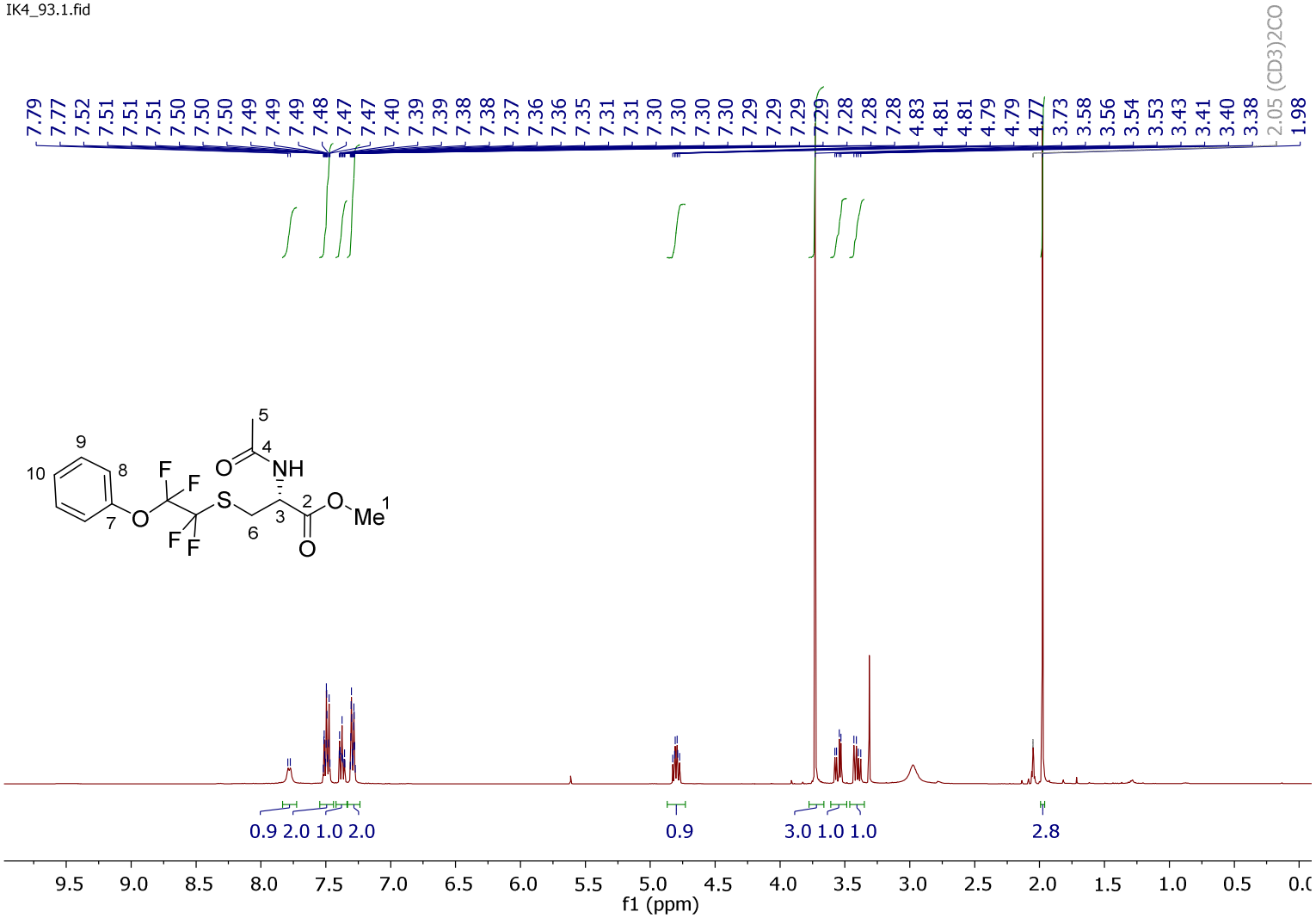
^{13}C {^{1}H} NMR (100.84 MHz, DMSO-d_6):



Methyl *N*-acetyl-*S*-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteinate (17a)

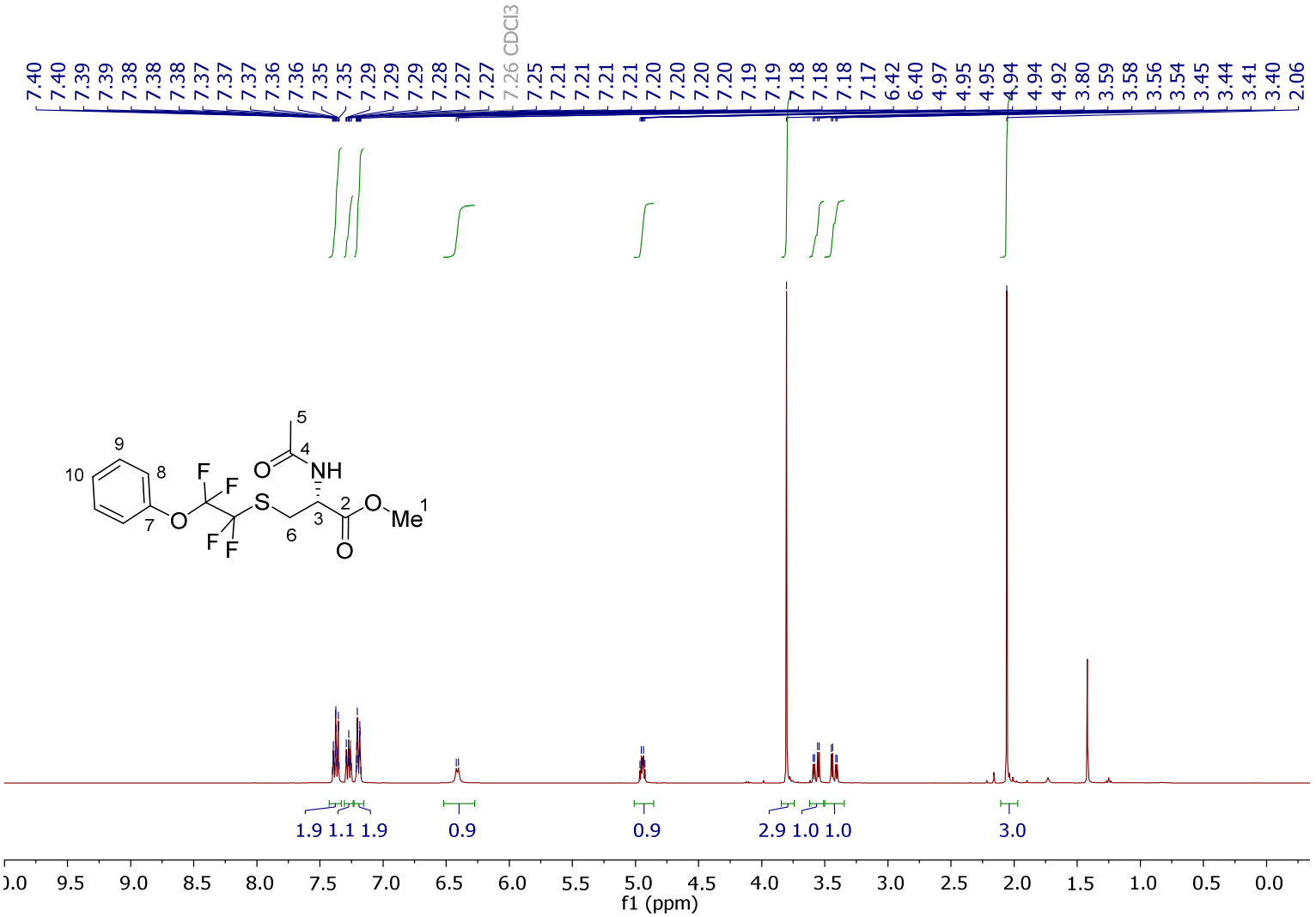
^{1}H NMR (401.00 MHz, acetone-d_6):

IK4_93.1.fid

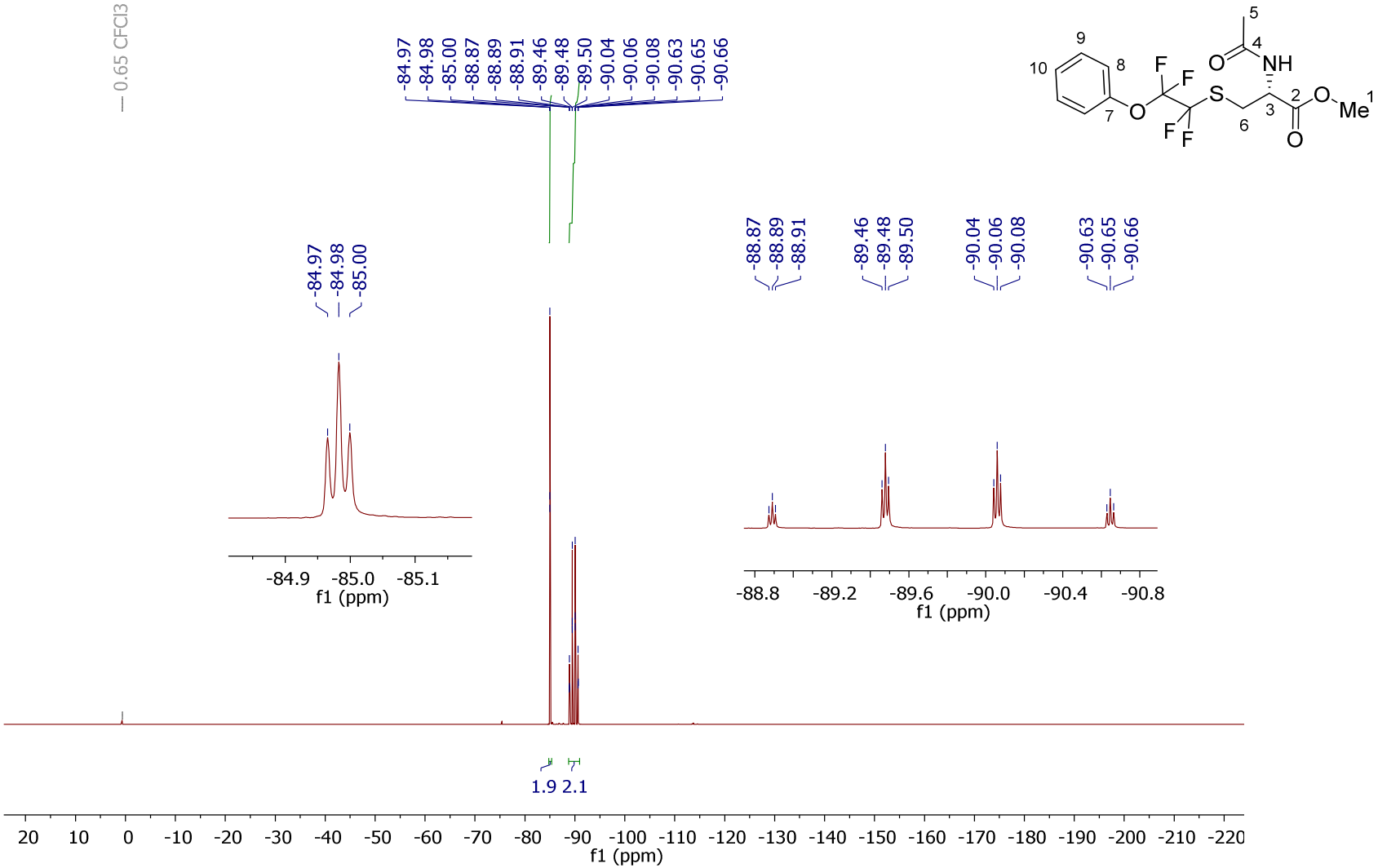


Methyl *N*-acetyl-*S*-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteinate

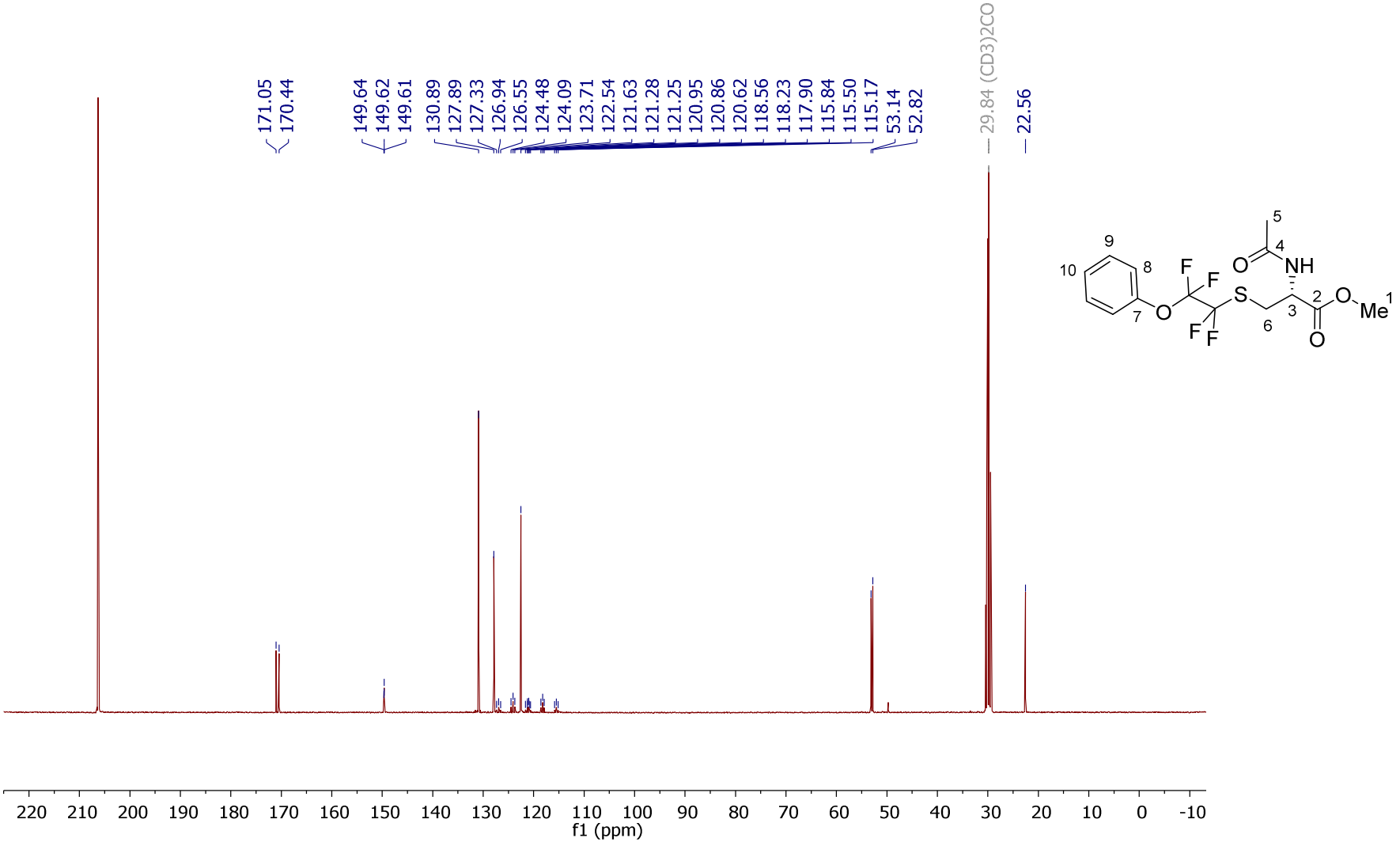
^{1}H NMR (401.00 MHz, $CDCl_3$):



^{19}F NMR (377.28 MHz, $CDCl_3$):

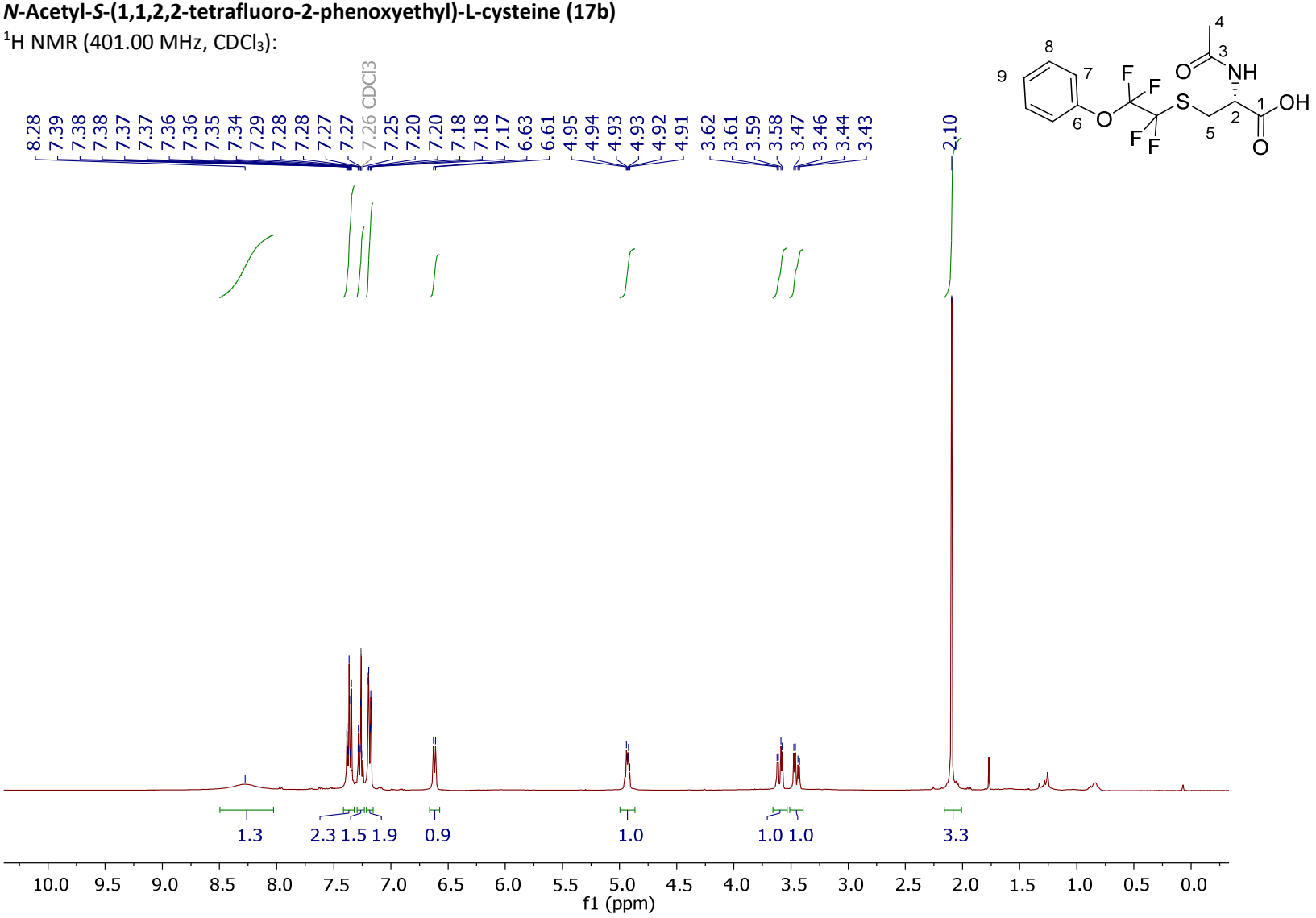


^{13}C {^{1}H} NMR (100.84 MHz, acetone-d_6):

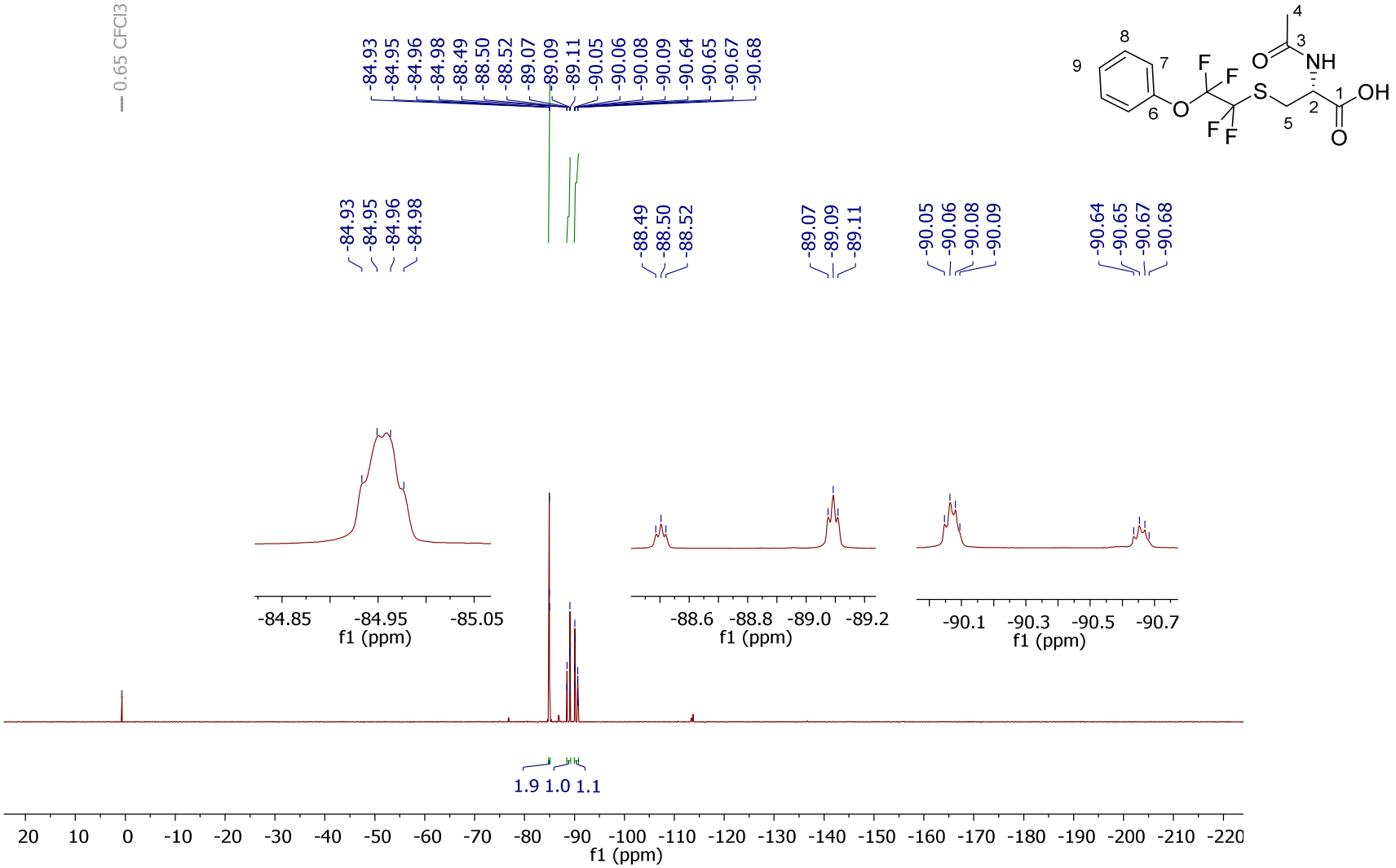


_N_-Acetyl-_S_-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteine (17b)

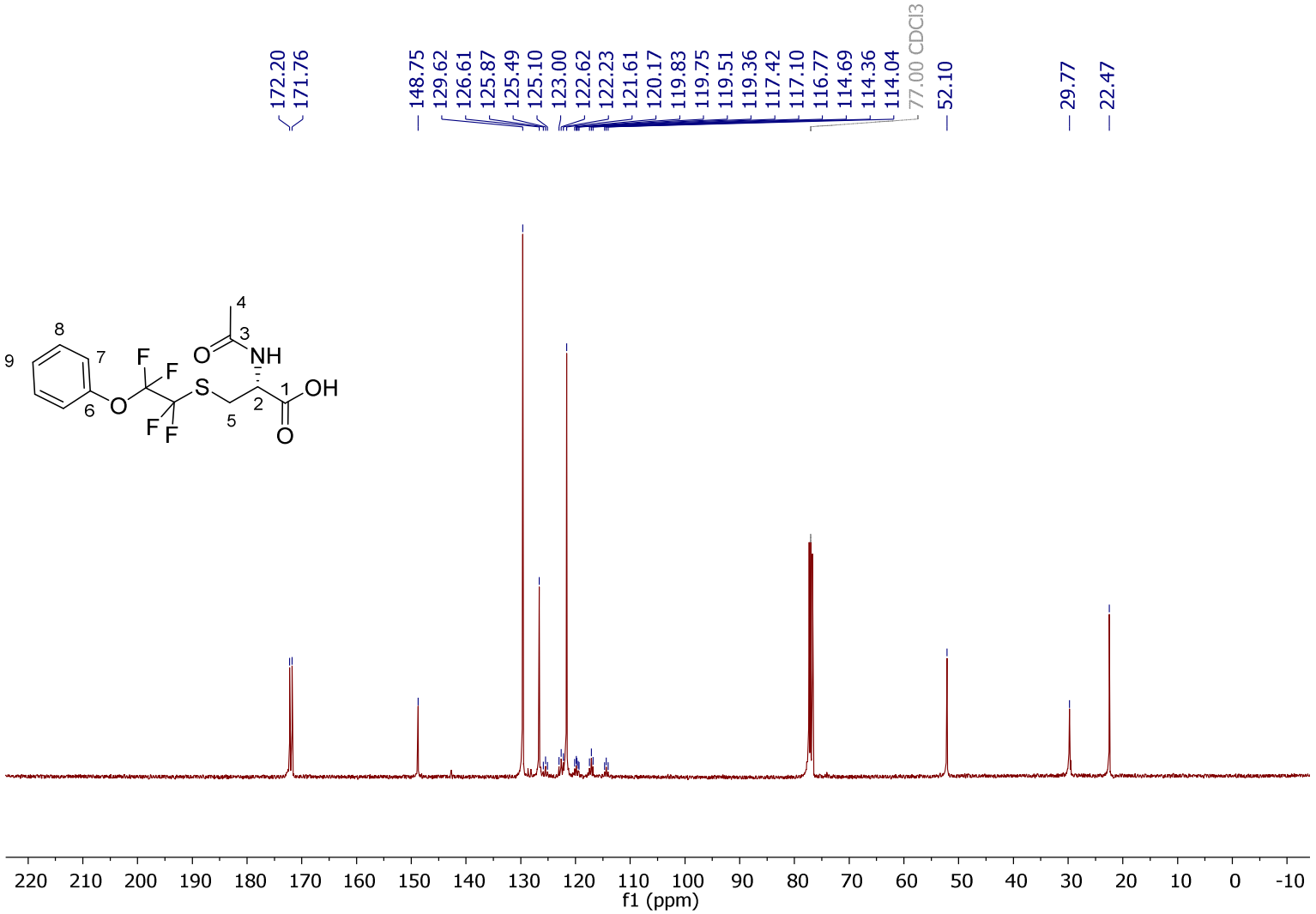
^{1}H NMR (401.00 MHz, $CDCl_3$):



^{19}F NMR (377.28 MHz, $CDCl_3$):

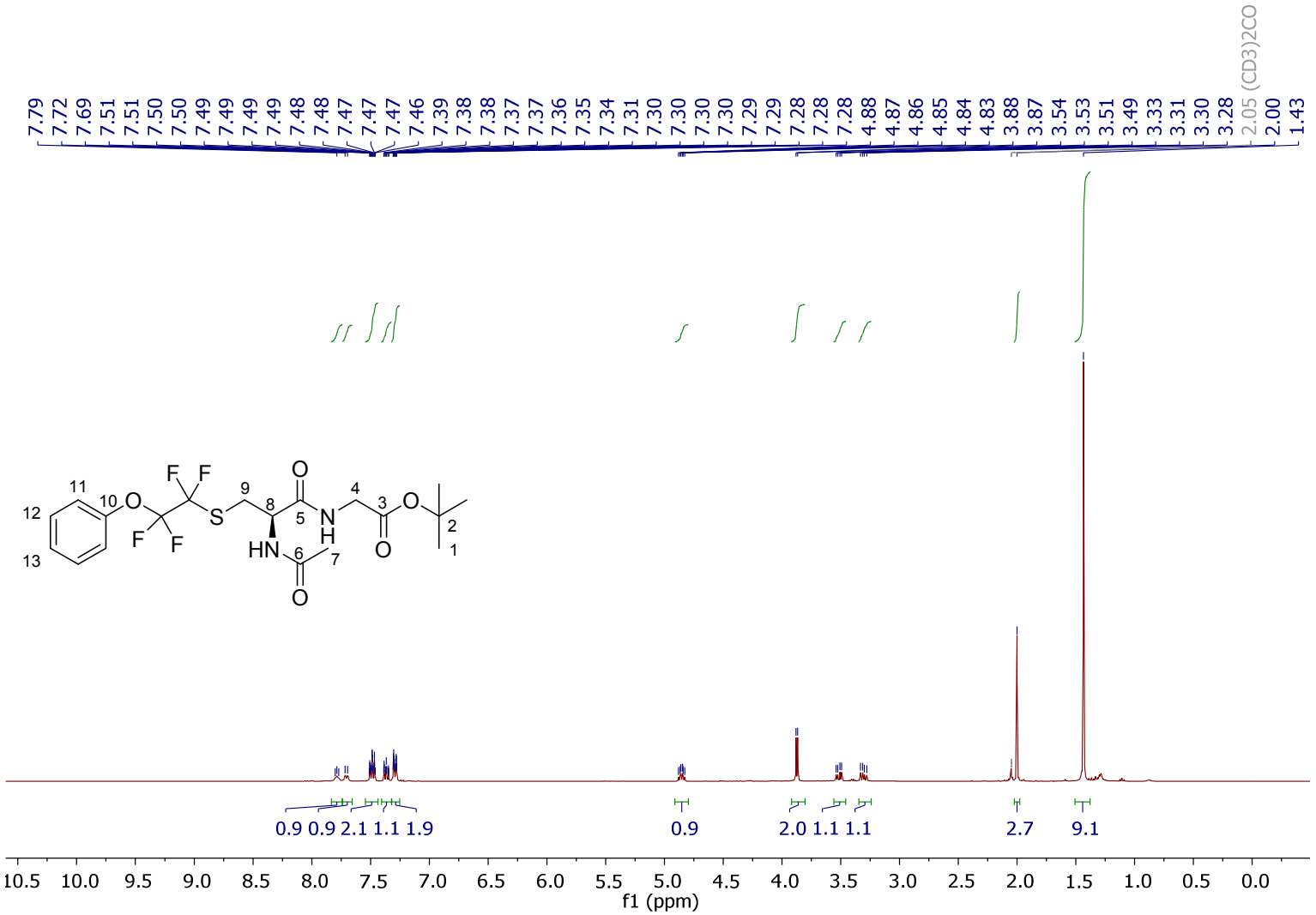


^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$):

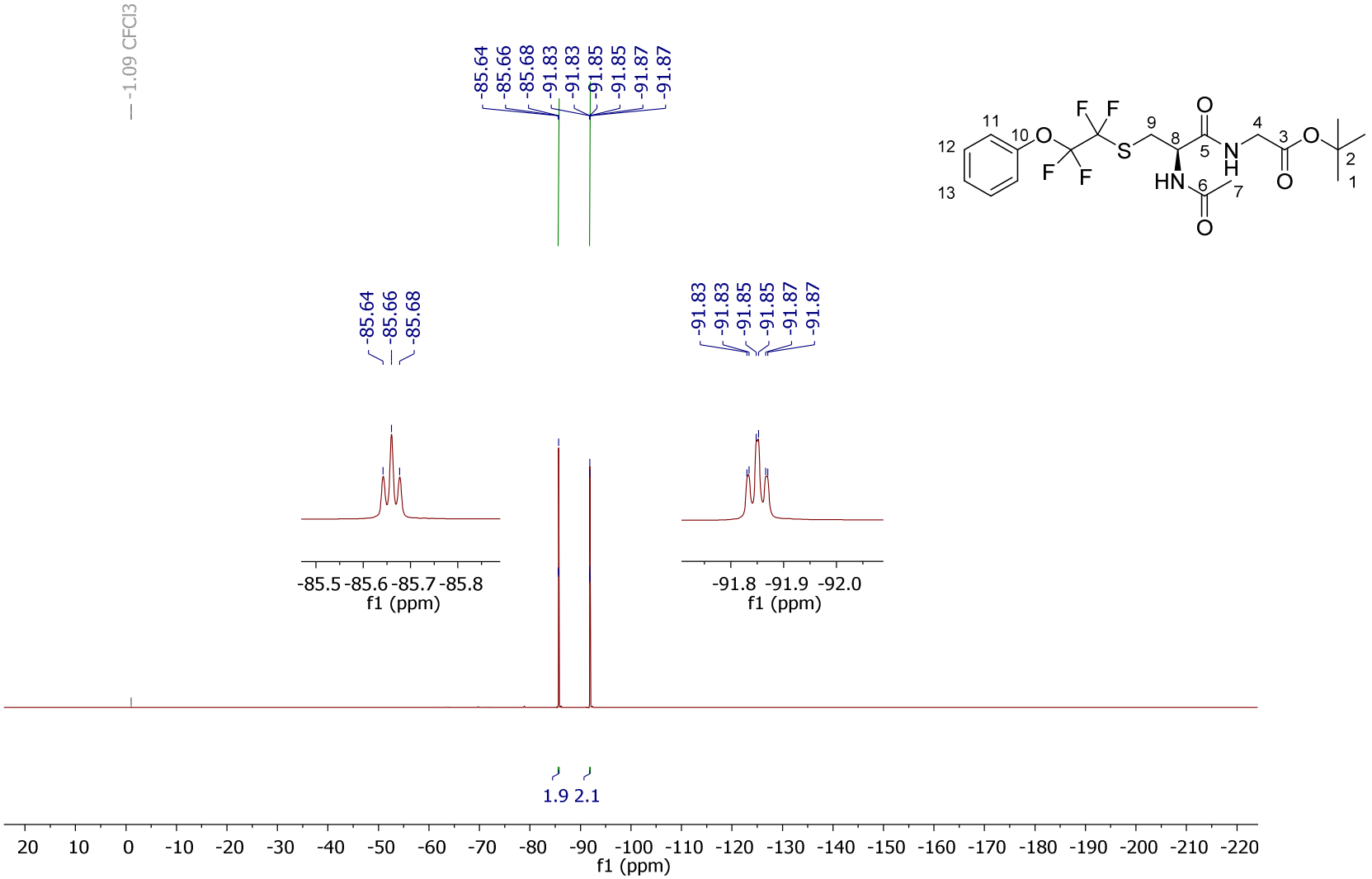


***Tert*-butyl *N*-acetyl-*S*-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteinylglycinate**

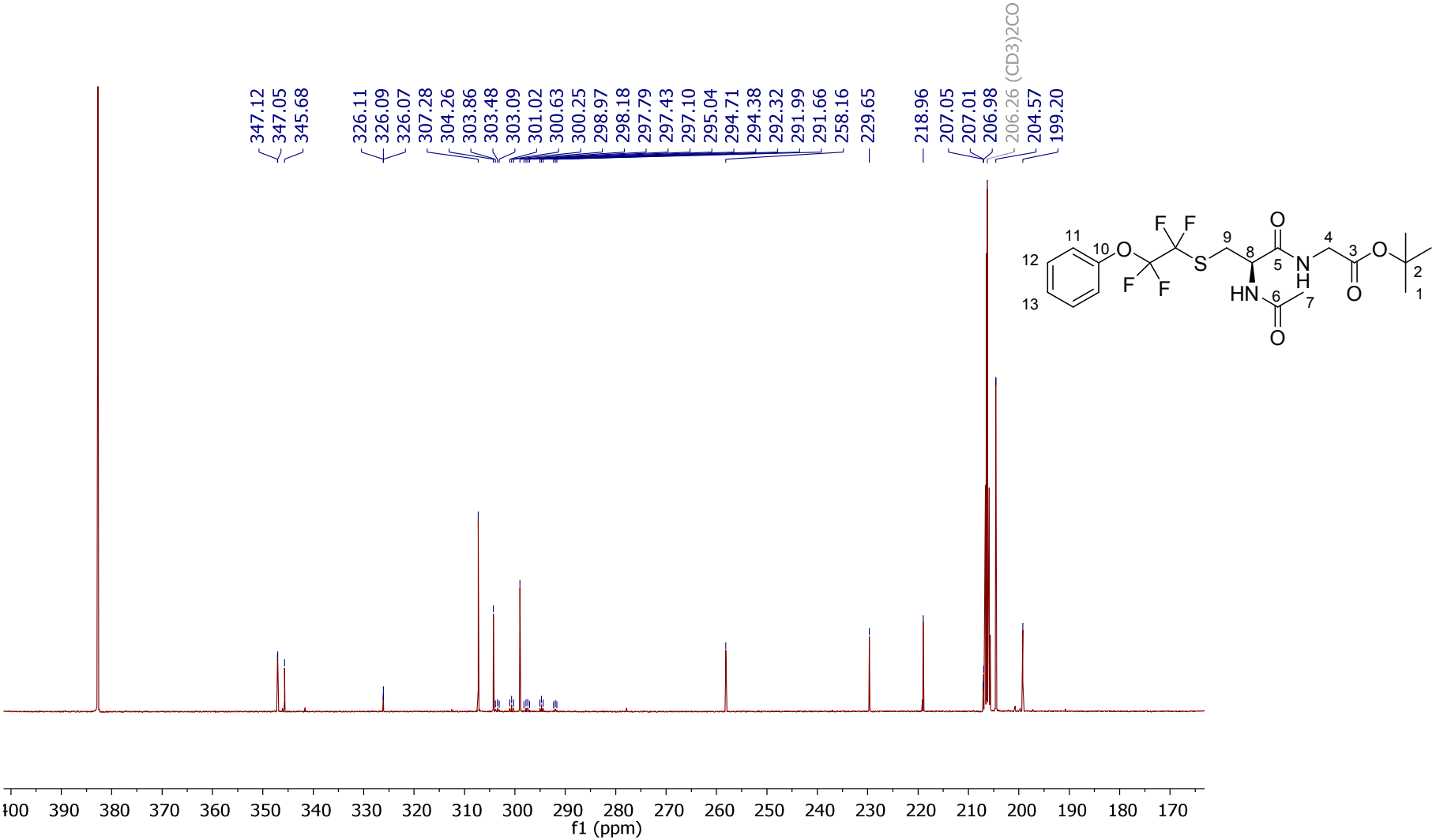
^{1}H NMR (401.00 MHz, acetone-d_6):



^{19}F NMR (377.28 MHz, acetone-d_6):

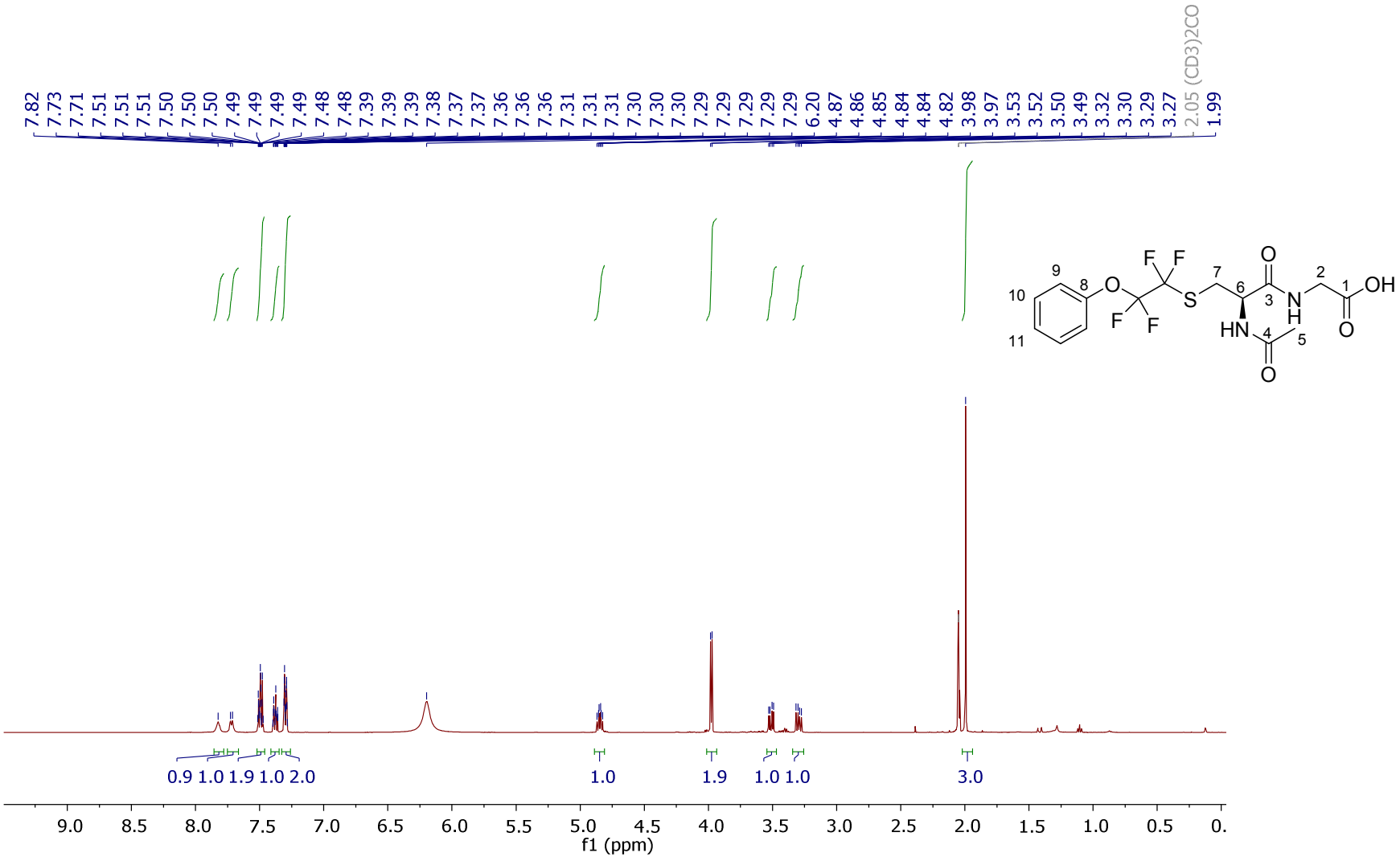


^{13}C {^{1}H} NMR (100.84 MHz, acetone-d_6):

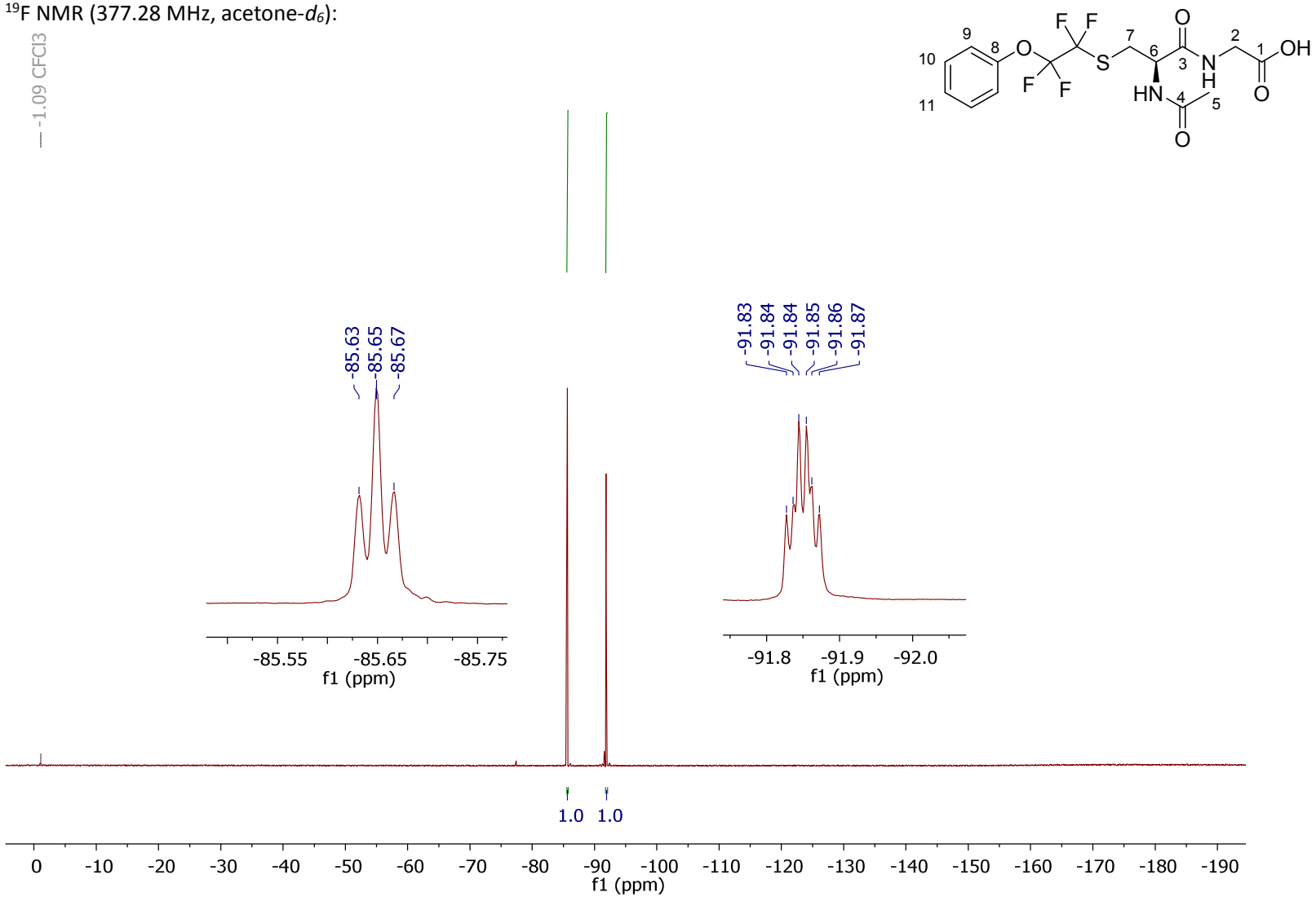


_N_-Acetyl-_S_-(1,1,2,2-tetrafluoro-2-phenoxyethyl)-L-cysteinylglycine (17c)

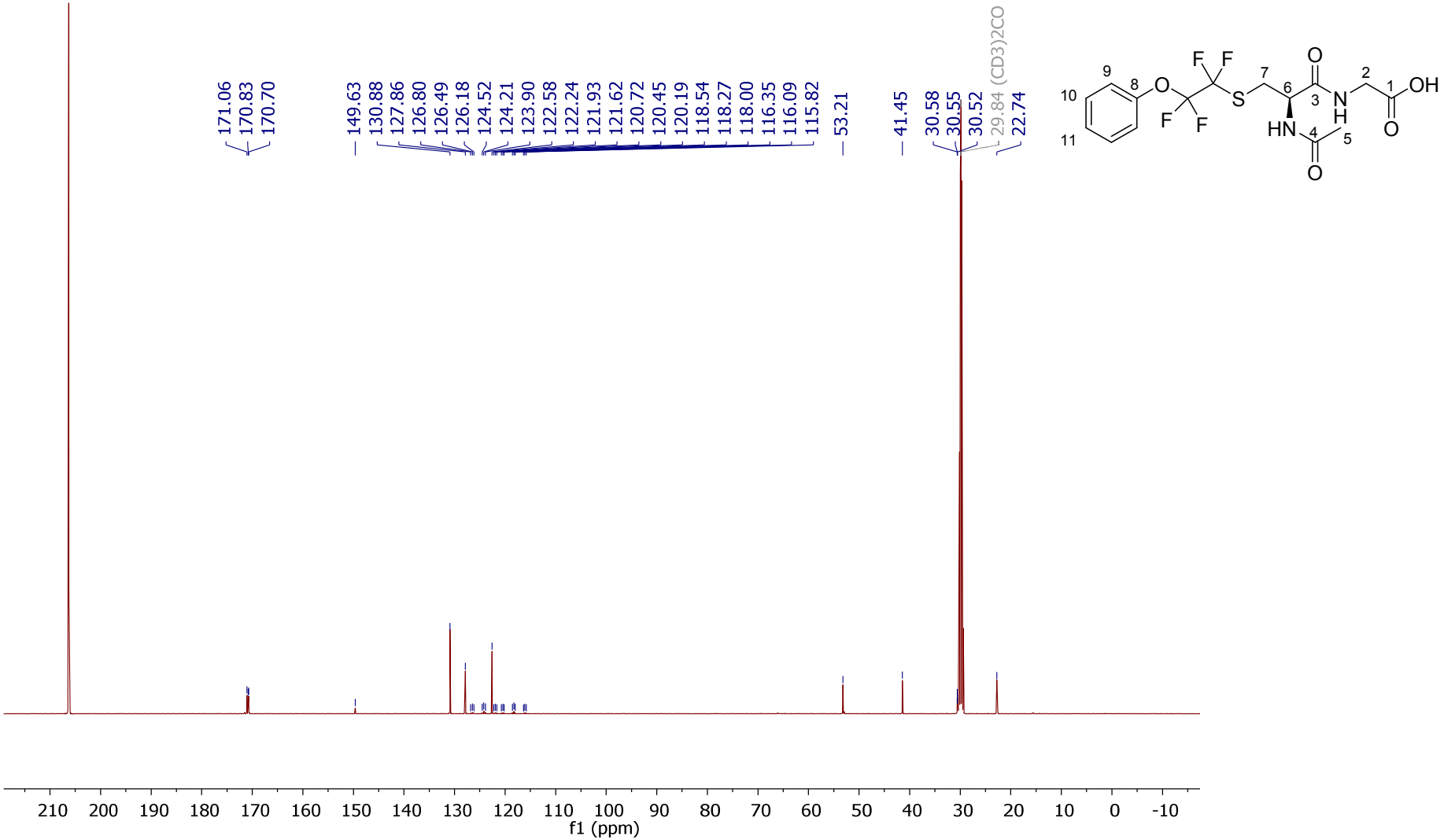
^{1}H NMR (401.00 MHz, acetone-d_6):



^{19}F NMR (377.28 MHz, acetone-d_6):

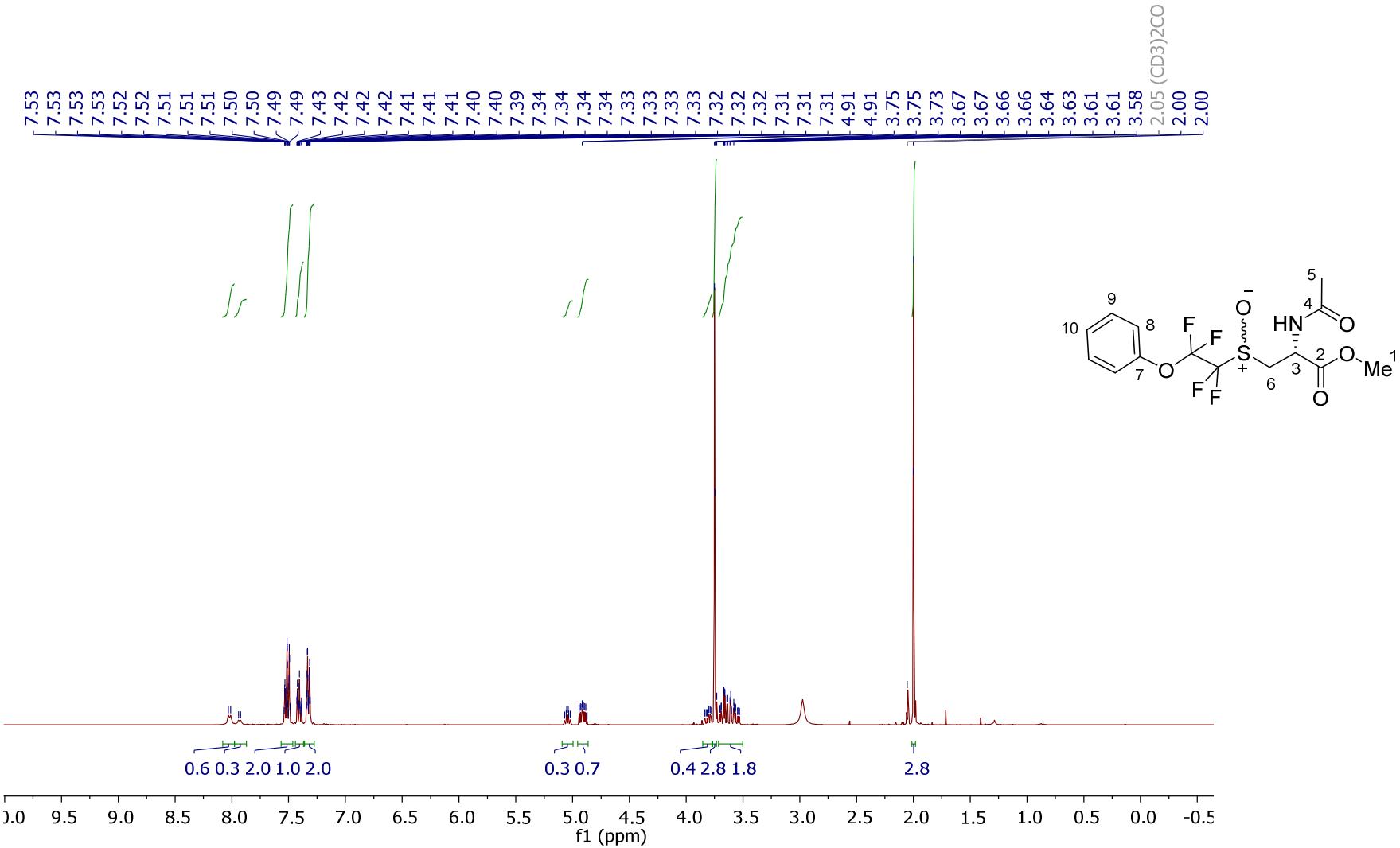


^{13}C {^{1}H} NMR (100.84 MHz, acetone-d_6):

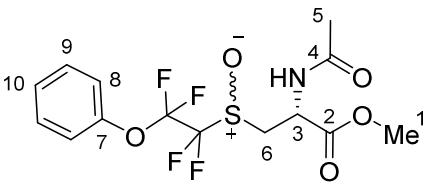


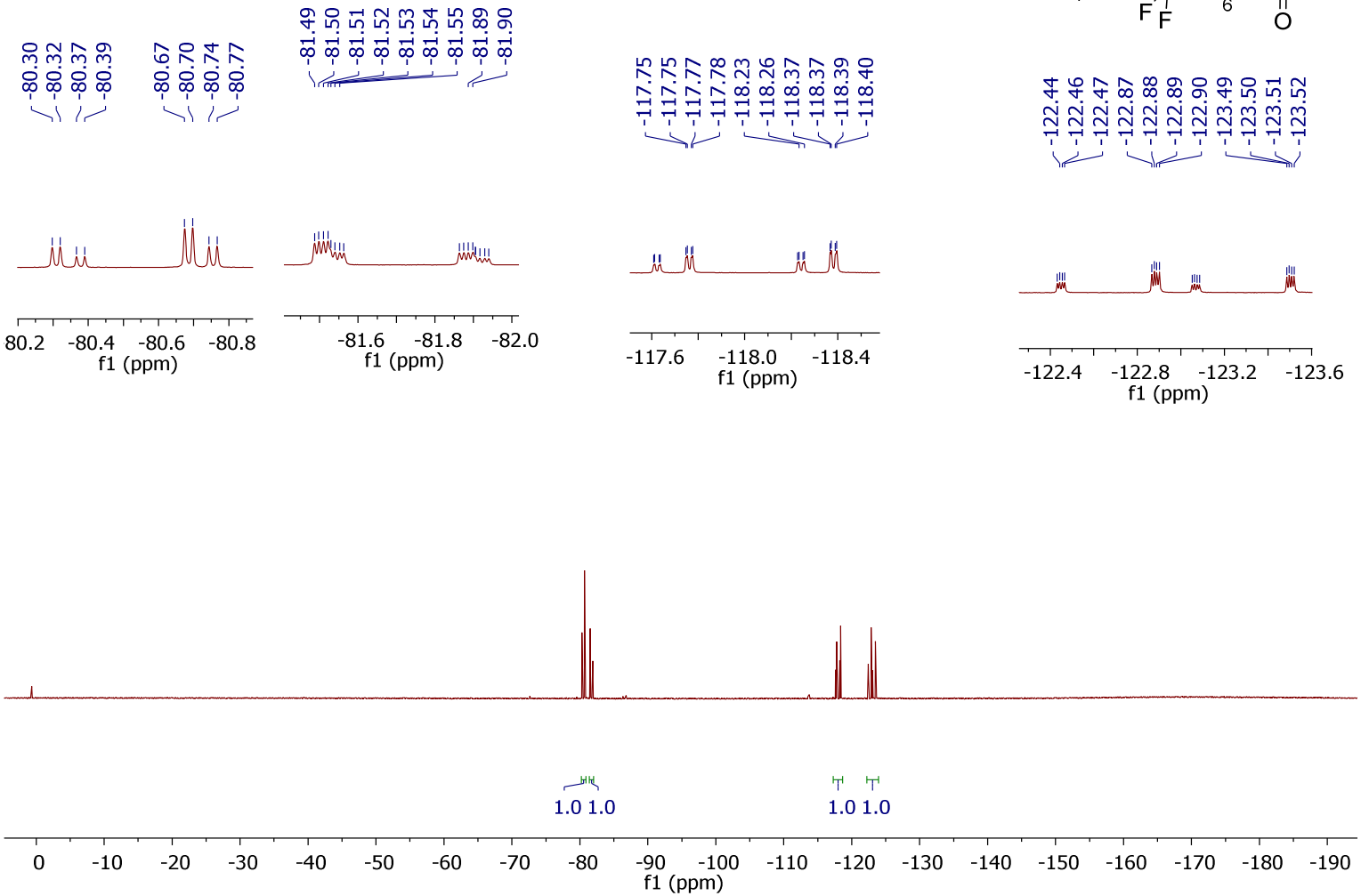
Methyl *N*-acetyl((1,1,2,2-tetrafluoro-2-phenoxyethyl)sulfinyl)-D-alaninate (18)

^{1}H NMR (400.13 MHz, acetone-d_6):

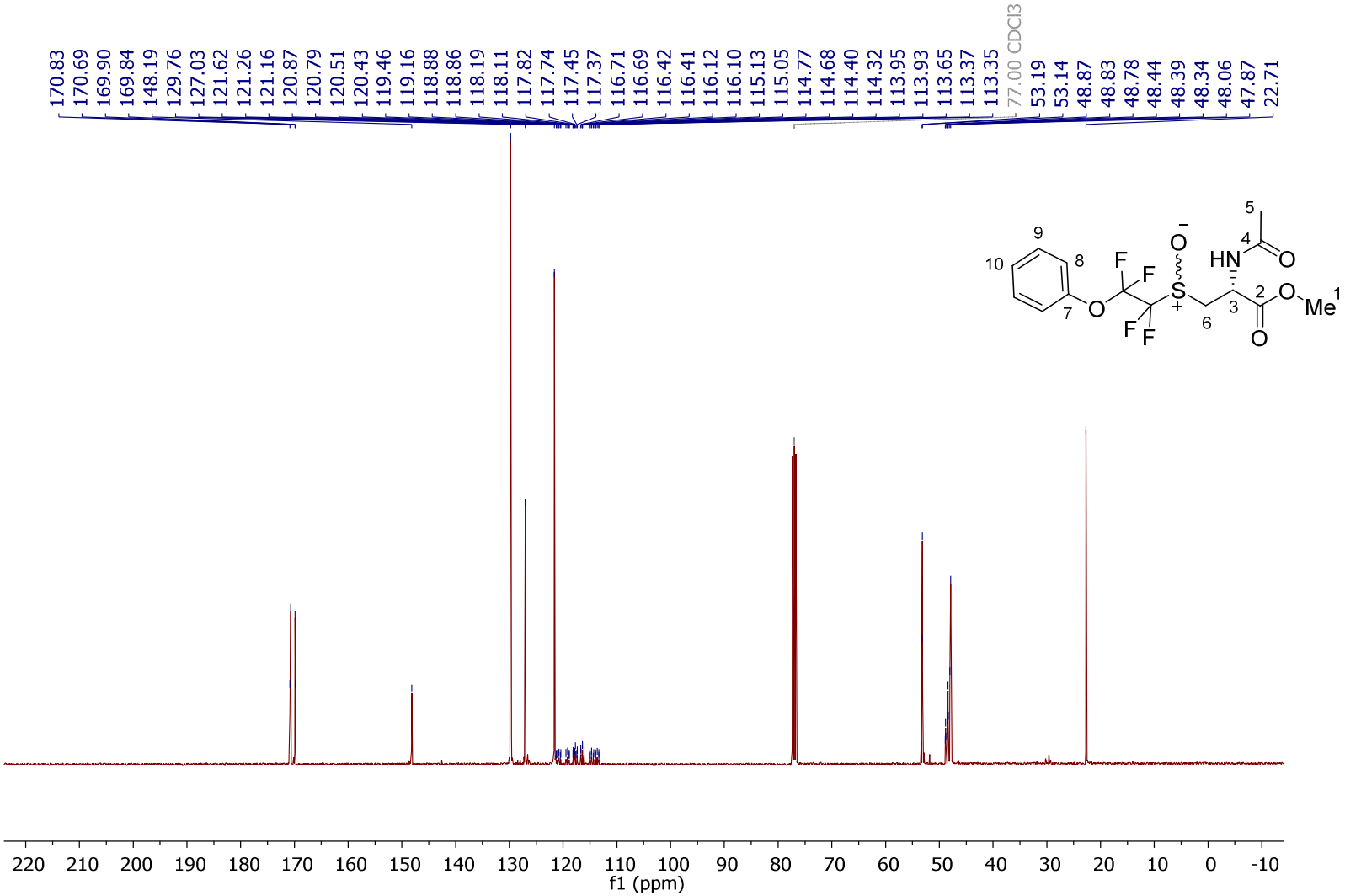


^{19}F NMR (376.46 MHz, $CDCl_3$):



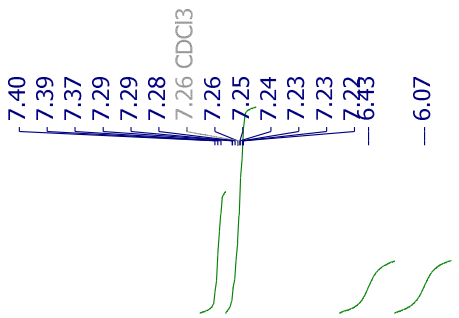


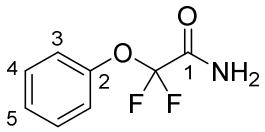
^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$):

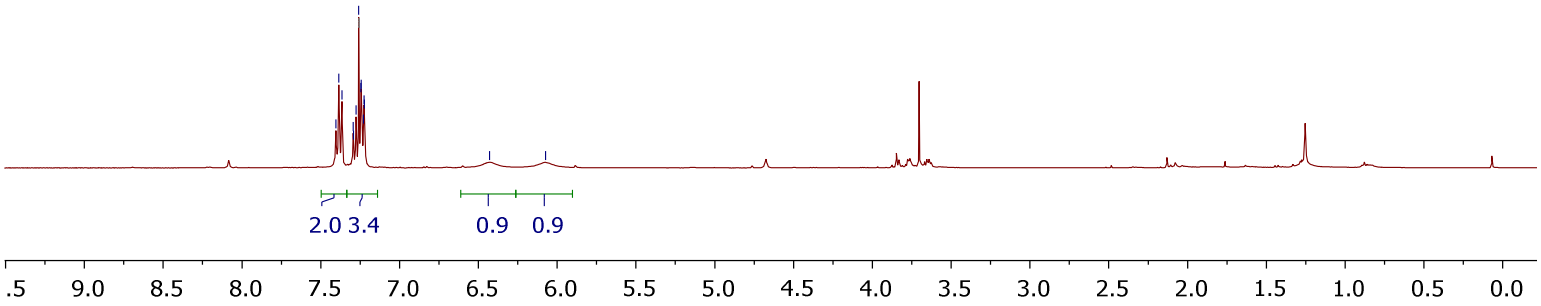


2,2-Difluoro-2-phenoxyacetamide (19)

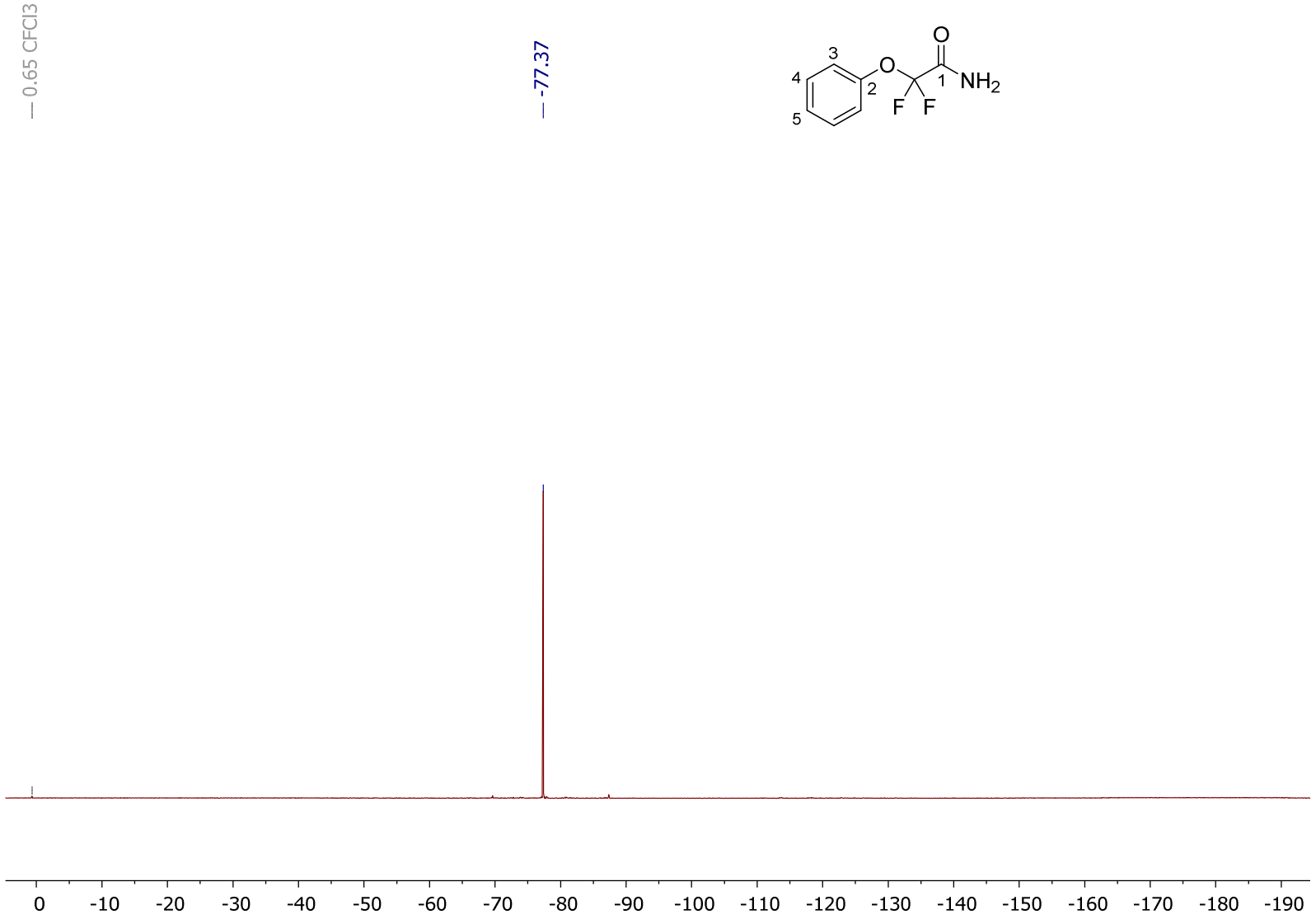
^{1}H NMR (401.00 MHz, $CDCl_3$):



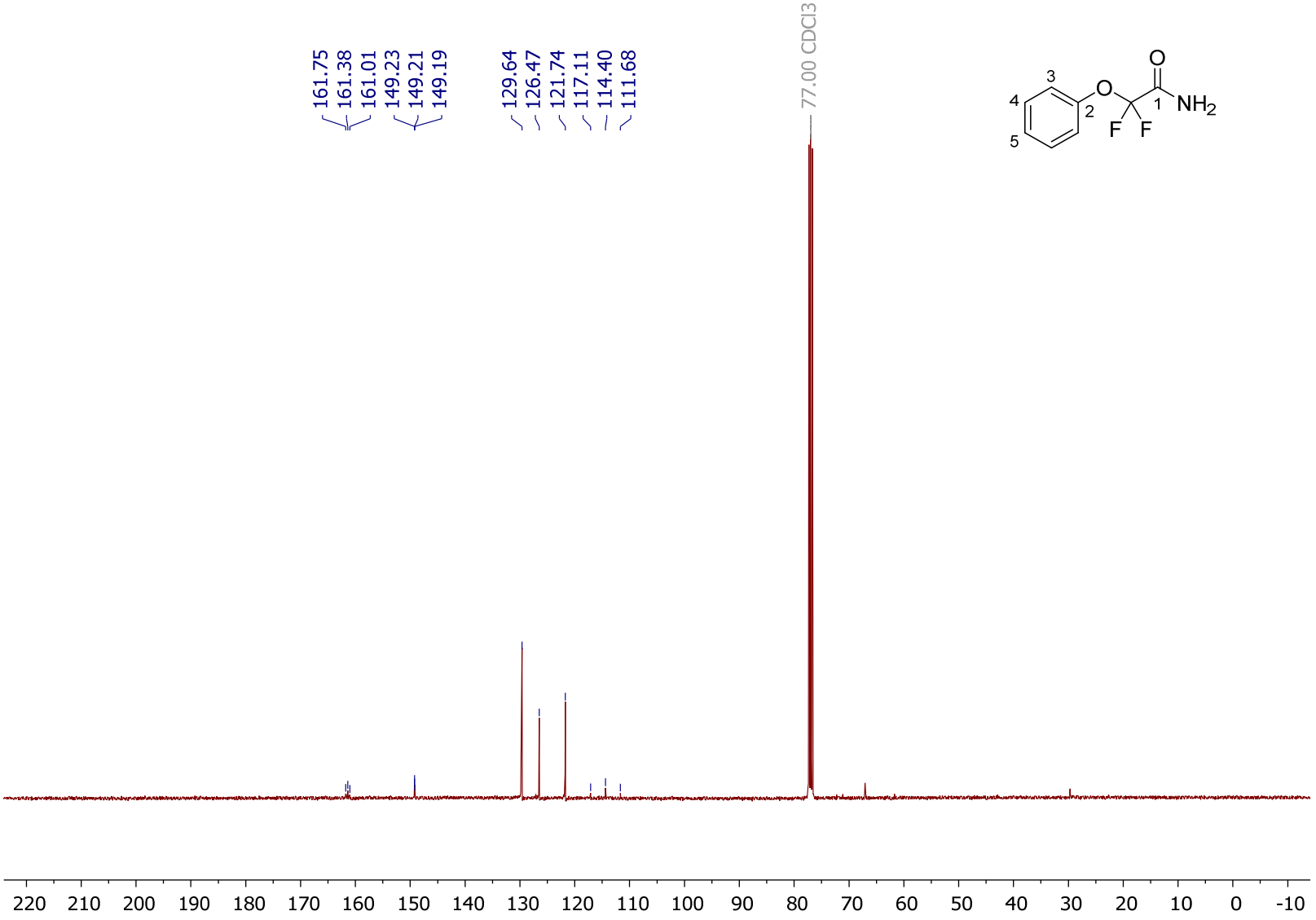




^{19}F NMR (377.28 MHz, $CDCl_3$):



^{13}C {^{1}H} NMR (100.84 MHz, $CDCl_3$):



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5 H. Wang, J. Zhang and M. Xian, *J. Am. Chem. Soc.*, 2009, **131**, 13238–13239.

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