Supporting Information

A dual-modal ^{19}F MRI / ^{18}F PET approach using water-soluble chemical tags

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A. Chemistry.

A.1. General information.

All chemical reagents and solvents (HPLC grade) were purchased from commercial sources (Acros Organics, Sigma-Aldrich, Merck, ThermoFisher) and used without further purification. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F254 aluminum sheets. Visualization of compounds was achieved by UV-Vis or $KMnO_4$ stain. Flash chromatography and plug filtrations were performed manually using silica gel or automated using a Teledyne Isco CombiFlash MPLC system with prepacked silica columns. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance III 500 or a Bruker NEO 600 instrument, and data were processed using MestReNova. All spectra were recorded at 25 °C, unless otherwise stated. Chemical shifts (δ) for ^{1}H, ^{13}C and ^{19}F NMR spectra were reported in parts per million (ppm). When mentioned, HFIP was used as internal standard for ^{19}F NMR. Coupling constants (*J*) are given in Hertz (Hz). Coupling patterns are abbreviated as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet). HRMS Analyses were performed on a LC apparatus Waters Acquity UPLC equipped with a Waters reverse phase Acquity UPLC BEH C18 column (2.1 x 75 mm, 1.7 µm) eluted with a gradient of MeOH/H_2O-0.1% formic acid [linear gradient from 10:90 to 90:10 (20 min), then isocratic mode at 10:90 (10 min)] at a flow rate of 0.3 mL/min, linked to electrospray MS Waters Q-TOF micro spectrometer. The source temperature of MS was 300 °C and the analyses were performed in the appropriate electron ionization mode (ESI^+ or ESI^-).

A.2. Synthesis of starting alcohols 5 and 6, and propargylic butane sultone.

The alcohols **5** and **6**, as well as propargylic butane sultone, used as starting materials in the synthesis of sultones **1** and **2** and of sulfo products **3** and **4** were prepared according to previously described procedures.

For preparation of alcohol **5**, see: Z-H. Jiang and Y. B. Yu. *Tetrahedron* **2007**, *63*, 3982–3988.

For preparation of alcohol **6**, see: a) Z-H. Jiang and Y. B. Yu. *Tetrahedron* **2007**, *63*, 3982–3988; b) M. Rosati, A. Acocella, A. Pizzi, G. Turtù, G. Neri, N. Demitri, Nonappa, G. Raffaini, B. Donnio, F. Zerbetto, F. Baldelli Bombelli, G. Cavallo and P. Metrangolo. *Macromolecules* **2022**, 55, 2486–2496.

For preparation of propargylic butanesultone, see: C. Maingueneau, A.-E. Lafargue, S. Guillouet, F. Fillesoye, T.T.C. Pham, B. Jordan and C. Perrio. *JACS Au*, **2024**, *4*, 3248.

A.3. Synthesis of azido compounds 7 and 8.

2-(3-Azido-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)-1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propane (7). To alcohol **5** (3,40 g, 4.30 mmol, 1 equiv.) in anhydrous dichloromethane (50 mL) were added at 0 °C under nitrogen mesyl chloride (1,0 mL, 12.91 mmoles, 3 equiv.) and triethylamine (2,86 mL, 21.48 mmoles, 5 equiv). The yellow reaction mixture was stirred for 48 h under nitrogen at room temperature. The reaction was quenched by adding water (5 mL). After extraction with dichloromethane (3 x 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The yellow solid obtained was recrystallized in methanol to afford the mesylate of alcohol **5** (3.18 g, 85% yield) as a white solid. Mp 64-65 °C. Rf 0.41 (pentane/Et_2O 8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.20 (s, 2H), 4.10 (s, 6H), 3.01 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 120.1 (q, J = 294.3 Hz, 9*C*F_3), 81.2–78.3 (m, 3*C*(CF_3)), 64.9, 64.4, 45.8, 37.1. ^{19}F NMR (471 MHz, $CDCl_3$) δ -70.3. HRMS (ESI^+) calcd for $C_{18}H_{12}F_{27}O_6S$: 868.923 $[M+H]^+$; found 868.9961. Mesylate of alcohol **5** (4.10 g, 4.72 mmole, 1.0 equiv.) was dissolved in dry DMF (80 mL) under argon atmosphere. After addition of NaN_3 (1.73 g, 26.61 mmoles, 5.6 equiv.), the colorless reaction mixture was stirred for 76 h under nitrogen at room temperature. The reaction was quenched by adding iced water. After extraction with pentane (3 x 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the azido compound **7** (3.15 g, 82% yield) as a white oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.01 (s, 6H), 3.49 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 125.15–116.33 (m, 9*C*F_3), 79.64 (m, 3*C*(CF_3)), 65.62, 48.68, 45.78. ^{19}F NMR (565 MHz, $CDCl_3$) δ -70.6. IR (cm^{-1}) 2117 ($\nu_{N=N=N}$). HRMS (ESI^+) calcd for $C_{17}H_9F_{27}N_3O_3$: 816.0213 $[M+H]^+$; found 816.0224.

2-(3-(3-Azidopropoxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)-1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propane (8). To alcohol **6** (6.03 g, 7.11 mmol, 1 equiv.) in anhydrous dichloromethane (50 mL) were added at 0 °C under nitrogen mesyl chloride (1,60 mL, 20.67 mmoles, 3 equiv.) and triethylamine (4.70 mL, 35.30 mmoles, 5 equiv). The yellow reaction mixture was stirred for 48 h under nitrogen at room temperature. The reaction was quenched by adding water (10 mL). After extraction with dichloromethane (3 x 25 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford an orange oil. After addition of MeOH (3 mL) then decantation, a lower white fluorous layer appeared, which was collected to afford the mesylate of alcohol **6** (6.44 g, 98% yield), *CAS Registry Number 1403503-15-0*). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.3 (t, *J* = 6.3 Hz, 2H), 4.0 (s, 6H), 3.5 (t, *J* = 6.1 Hz, 2H), 3.4 (s, 2H), 3.0 (s, 3H), 2.0 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 125.0–113.4 (m, 9 *C*F3), 82.8–78.3 (3 *C*(CF_3)), 67.2, 66.7, 66.2, 65.4, 46.3, 37.5, 29.6. ^{19}F NMR (565 MHz, $CDCl_3$ in the presence of HFIP as internal standard δ -77.3) δ -72.0. Mesylate of alcohol **6** (1.35 g, 1.46 mmoles, 1 equiv.) was dissolved in dry DMF (15 mL) under argon atmosphere. After addition of NaN_3 (530 mg, 8.15 mmoles, 5.6 equiv.) to the solution, the yellow reaction mixture was stirred for 48 h under nitrogen at room temperature. The reaction was quenched by adding iced water. After extraction with pentane (3x30 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford an orange oil. After addition of MeOH (3 mL) then decantation, a lower white fluorous layer appeared that was collected to afford the azido compound **8** (1.26 g, quantitative yield; *CAS Registry Number 2774618-72-1*). ^{1}H NMR (600 MHz, $CDCl_3$) δ. 4.05 (s, 6H), 3.47 (td, *J* = 6.0 Hz, 1.5 Hz, 2H), 3.39 (s, 2H), 3.33 (t, *J* = 6.7 Hz, 2H), 1.82 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 120.3 (q, *J* = 293.6 Hz, 9*C*F_3), 79.7 (dq, *J* = 59.9, 30.2 Hz, 3*C*(CF_3)), 68.5, 66.1, 65.5, 48.4, 46.4, 29.0. ^{19}F NMR (565 MHz, $CDCl_3$ in the presence of HFIP as internal standard δ -77.3) δ -72.1. IR (cm^{-1}) 2117 ($\nu_{N=N=N}$).

A.4. Synthesis of butanesultones 1 and 2

3-((1-(3-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propyl)-1H-1,2,3-triazol-4-yl)methyl)-1,2-oxathiane 2,2-dioxide (1). Azido compound **7** (800 mg, 0.98 mmol, 1.1 equiv.), propargylic butane sultone (156 mg, 0.89 mmol, 1 equiv.) and CuI (17 mg, 0.09 mmol, 0.1 equiv.) were dissolved in DMF (8 mL). The mixture was stirred at 55 °C for 24 h then concentrated under reduced pressure (by co-evaporating with toluene). The resulted residue was stirred in MeOH at reflux in the presence of charcoal. The hot mixture was filtered, and the filtrate was left at room temperature until crystallization to afford the title butanesultone **1** (720 mg, 81% yield) as a white solid. Mp 122-123 °C. Rf 0.8 (pentane/EtOAc, 6:4, $KMnO_4$ stains). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (s, 1H), 4.61–4.52 (m, 1H), 4.52–4.45 (m, 3H), 4.16–4.11 (m, 7H), 3.51 (dddd, *J* = 14.2, 6.8, 5.9, 3.3 Hz, 1H), 3.39 (dd, *J* = 15.2, 6.3 Hz, 1H), 3.06 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.30 – 2.22 (m, 1H), 2.03 (dtd, *J* = 14.4, 11.2, 3.7 Hz, 1H), 1.98–1.82 (m, 2H, H_2). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.01, 124.83, 119.13 (q, 9 *C*F_3), 79.65 (dd, *J* = 60.4, 30.1 Hz, 3*C*(CF_3)), 73.95, 67.00, 59.18, 48.51, 46.06, 28.73, 25.16, 24.07. ^{19}F NMR (565 MHz, $CDCl_3$ in the presence of HFIP as internal standard δ -77.3) δ -71.8. IR (cm^{-1}) 2949 ($\nu_{C\text{-}H}$), 1047 ($\nu_{C\text{-}F}$). HRMS (ESI^+) calcd for $C_{24}H_{19}F_{27}N_3O_6S$: 990.0563 $[M+H]^+$; found 990.0569.

3-((1-(3-(3-((1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)propyl)-1H-1,2,3-triazol-4-yl)methyl)-1,2-oxathiane 2,2-dioxide (2). Azido compound **8** (1.00 g, 1.14 mmol, 1.05 equiv.), propargylic butane sultone (190 mg, 1.09 mmol, 1 equiv.) and CuI (21 mg, 0.10 mmol, 0.1 equiv.) were dissolved in DMF (8 mL). The mixture was stirred at 55 °C for 24 h then concentrated under reduced pressure (by co-evaporation with toluene). The resulting orange oil was dissolved in MeOH and heated at reflux in the presence of charcoal. The hot reaction mixture was filtered. Purification of the filtrate by flash chromatography using pentane/Et_2O 8:2 as eluent afforded a crude residue that precipitated with pentane when cold. Filtration gave the title butane sultone **2** (837 mg, 70% yield) as a white solid. Mp: 91-92 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (s, 1H), 4.56 (td, *J* = 11.2, 2.9 Hz, 1H), 4.51–4.43 (m, 1H), 4.36 (td, *J* = 7.1, 2.2 Hz, 2H), 4.04 (s, 6H), 3.49 (dddd, *J* = 11.3, 7.9, 5.7, 3.8 Hz, 1H), 3.45–3.36 (m, 5H), 3.03 (dd, *J* = 15.1, 7.9 Hz, 1H), 2.30 (dtd, *J* = 14.2, 5.7, 3.9 Hz, 1H), 2.15 (m, 2H), 2.03 (dtd, *J* = 14.6, 11.2, 3.9 Hz, 1H), 1.97–1.81 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.8, 122.7, 120.2 (q, *J* = 296.1 Hz, 9*C*F_3), 80.0 – 79.1 (m, 3*C*(CF_3)), 74.0, 68.1, 66.2, 65.3, 59.3, 47.3, 46.3, 30.4, 28.7, 25.1,

24.0. ^{19}F NMR (565 MHz, $CDCl_3$ in the presence of HFIP as internal standard δ -77.3) δ -71.8. HRMS (ESI^+) calcd for $C_{27}H_{25}F_{27}N_3O_7S$: 1048.0982 $[M+H]^+$; found 1048.0992.

A.5. Synthesis of sulfo compounds 3 and 4

Tetrabutylammonium 5-fluoro-1-(1-(3-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propyl)-1H-1,2,3-triazol-4-yl)pentane-2-sulfonate (3). Sultone **1** (100 mg, 0.101 mmol, 1.0 equiv.) and TBAF (1M in THF, 106 µL, 0.106 mmol, 1.05 equiv.) were dissolved in DMF (1 mL) under nitrogen. The mixture was stirred at reflux for 24 h then concentrated under reduced pressure (co-evaporated with toluene). The residue was dissolved in chloroform (3 mL) and washed three times with water (3 x 0.5 mL). The organic layer was concentrated to give the title compound **3** (119 mg, 94% yield) as a green oil. ^1H NMR (600 MHz, CD_3CN) δ 7.59 (s, 1H), 4.51 (s, 2H), 4.38 (td, *J* = 5.8, 1.2 Hz, 1H), 4.30 (td, *J* = 5.7, 1.2 Hz, 1H), 4.20 (s, 6H), 3.31–3.25 (m, 1H), 3.11–3.05 (m, 8H), 2.82–2.72 (m, 2H), 1.93–1.72 (m, 2H), 1.64–1.51 (m, 10H), 1.35 (h, *J* = 7.4 Hz, 8H), 0.97 (t, *J* = 7.4 Hz, 12H). ^{13}C NMR (151 MHz, CD_3CN) δ 147.0, 125.8, 124.5–118.8 (m, 9*C*F_3), 85.3 (d, J = 161.6 Hz), 81.2–79.8 (m, 3*C*(CF_3)), 68.1, 59.6, 59.4–59.2 (m), 48.7, 46.7, 29.1 (d, *J* = 19.2 Hz), 28.0, 26.5 (d, *J* = 5.8 Hz), 24.3, 21.1–19.8 (m), 13.8. ^{19}F NMR (565 MHz, CD_3CN in the presence of HFIP as internal standard δ -77.3) δ -71.9 (s, 27F), -220.2 (s, 1F). HRMS (ESI^+) calcd for $C_{16}H_{36}N$: 242.2848 $[M+H]^+$; found 242.2849. HRMS (ESI^-) calcd for $C_{24}H_{18}F_{28}N_3O_6S$: 1008.0469 $[M-H]^-$; found 1008.0447.

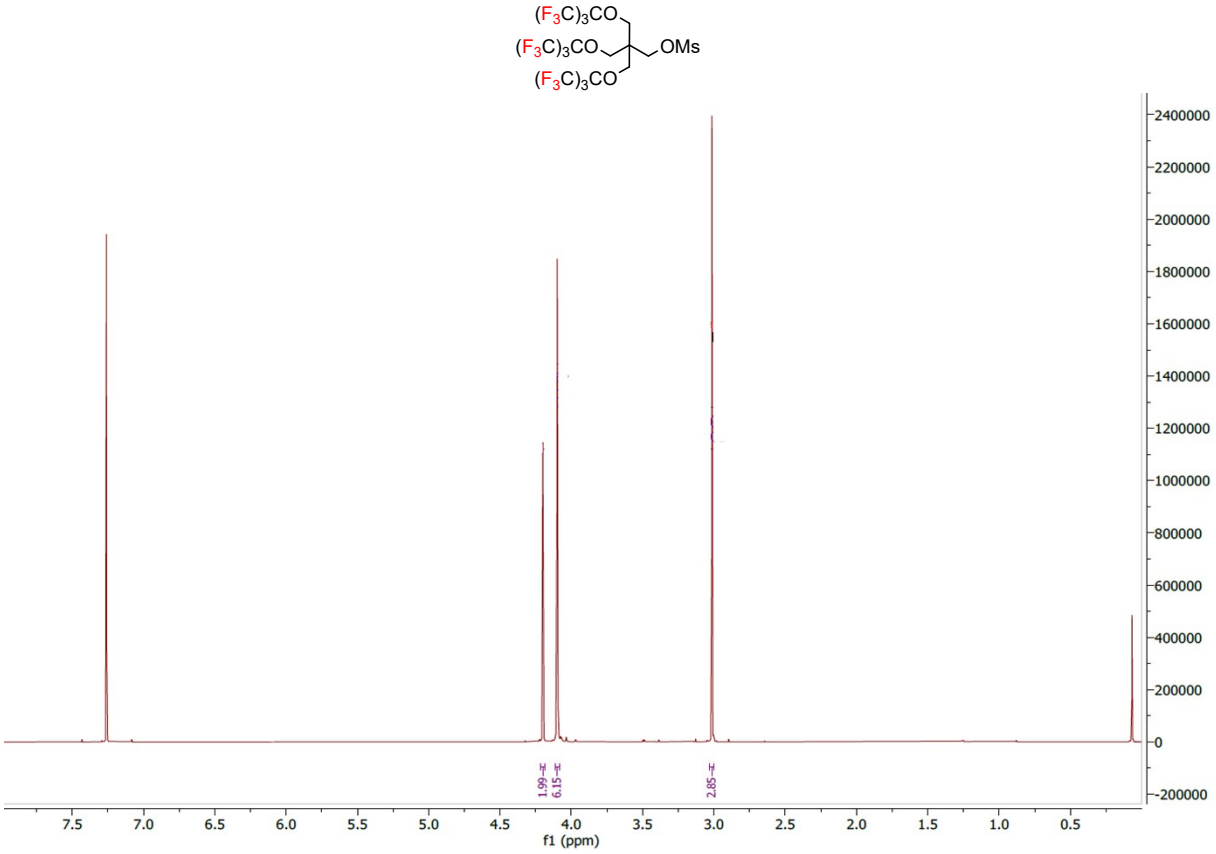
Tetrabutylammonium 5-fluoro-1-(1-(3-(3-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2,2-bis(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)propoxy)propyl)-1H-1,2,3-triazol-4-yl)pentane-2-sulfonate (4). Sultone **2** (100 mg, 0.095 mmol, 1.0 equiv.) and TBAF (1M in THF, 99 µL, 0.99 mmol, 1.05 equiv.) were dissolved in DMF (1 mL) under nitrogen. The mixture was stirred at reflux for 24 h then concentrated under reduced pressure (co-evaporated with toluene). The residue was dissolved in chloroform (3 mL) and washed three times with water (3 x 0.5 mL). The organic layer was concentrated to give the title compound **4** (122 mg, 98% yield) as a colorless oil. ^1H NMR (600 MHz, CD_3CN) δ 7.59 (s, 1H), 4.40–4.26 (m, 4H), 4.10 (s, 6H), 3.40 (t, *J* = 6.1 Hz, 2H), 3.37 (s, 2H), 3.31–3.25 (m, 1H), 3.11–3.05 (m, 9H), 2.81–2.70 (m, 2H), 2.10–2.03 (m, 2H), 1.92–1.80 (m, 1H), 1.80–1.70 (m, 1H), 1.64–1.50 (m, 9H), 1.36 (dt, *J* = 14.8, 7.4 Hz, 8H), 0.96 (t, *J* = 7.4 Hz, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.0, 123.4, 124.4–119.1 (m, 9*C*F_3), 85.3 (d, *J* = 161.5 Hz), 80.5 (q, *J* = 29.2 Hz, 3*C*(CF_3)), 68.9, 66.4 (d, *J* = 20.7 Hz), 59.8, 59.4–59.1 (m), 47.7, 47.3, 31.1, 29.1 (d, *J* = 19.2 Hz), 28.2, 26.5 (d, *J* = 5.9 Hz), 24.3, 21.6–19.2 (m), 13.8. ^{19}F NMR (565 MHz, CD_3CN in the presence of HFIP as internal standard δ -77.3) δ -72.0 (s, 27F), -220.1 (s, 1F). HRMS (ESI^+) calcd for $C_{16}H_{36}N$: 242.2848 $[M+H]^+$; found 242.2850. HRMS (ESI^-) calcd for $C_{27}H_{24}F_{28}N_3O_7S$: 1066.0888 $[M-H]^-$; found 1066.0859.

A.6. Preparation of solution of sulfo compounds 3 and 4 for injection

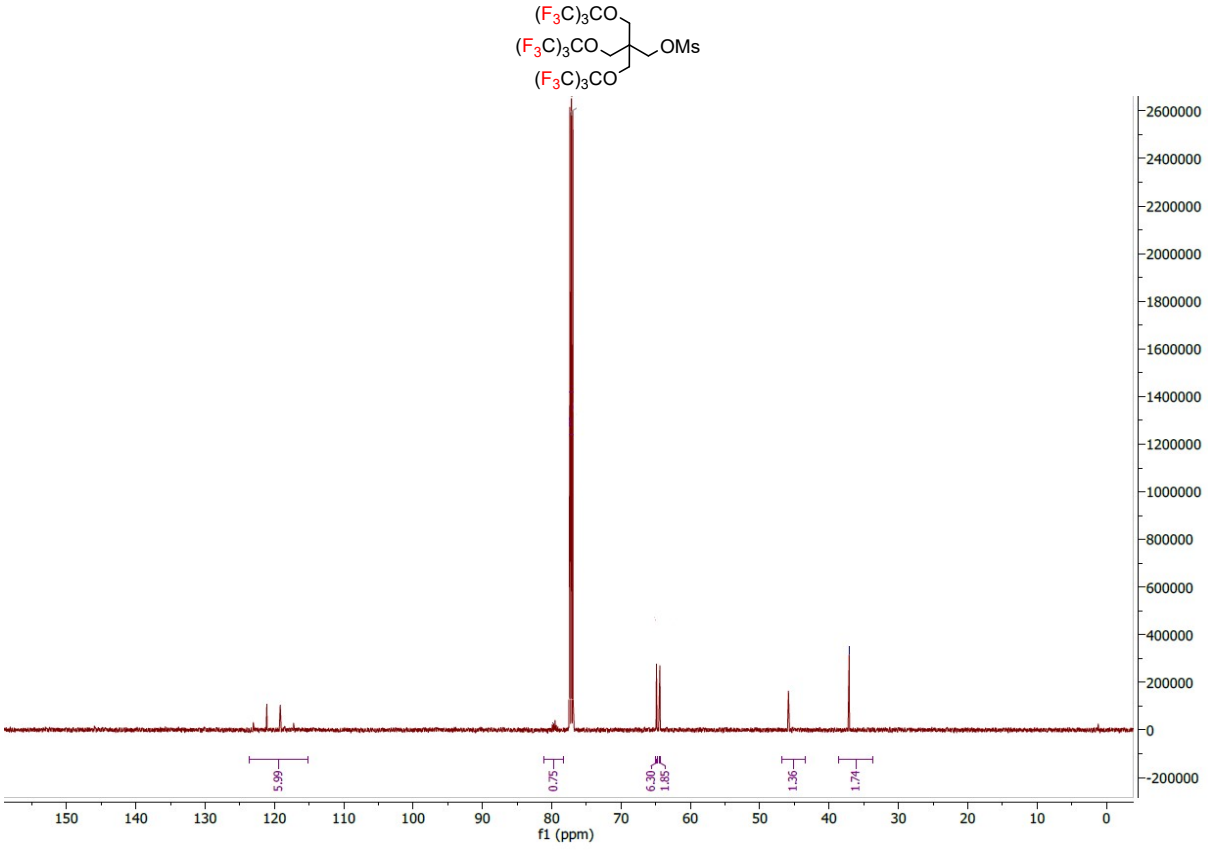
Sulfo-compound **3** or **4** (30 mg) was diluted in 100 µl of ethanol. After mixing using a vortex for 2 min, 900 µl of physiological serum were added to obtain 1 mL of injectable solution.

A.7. ^{1}H, ^{13}C and ^{19}F NMR spectra.

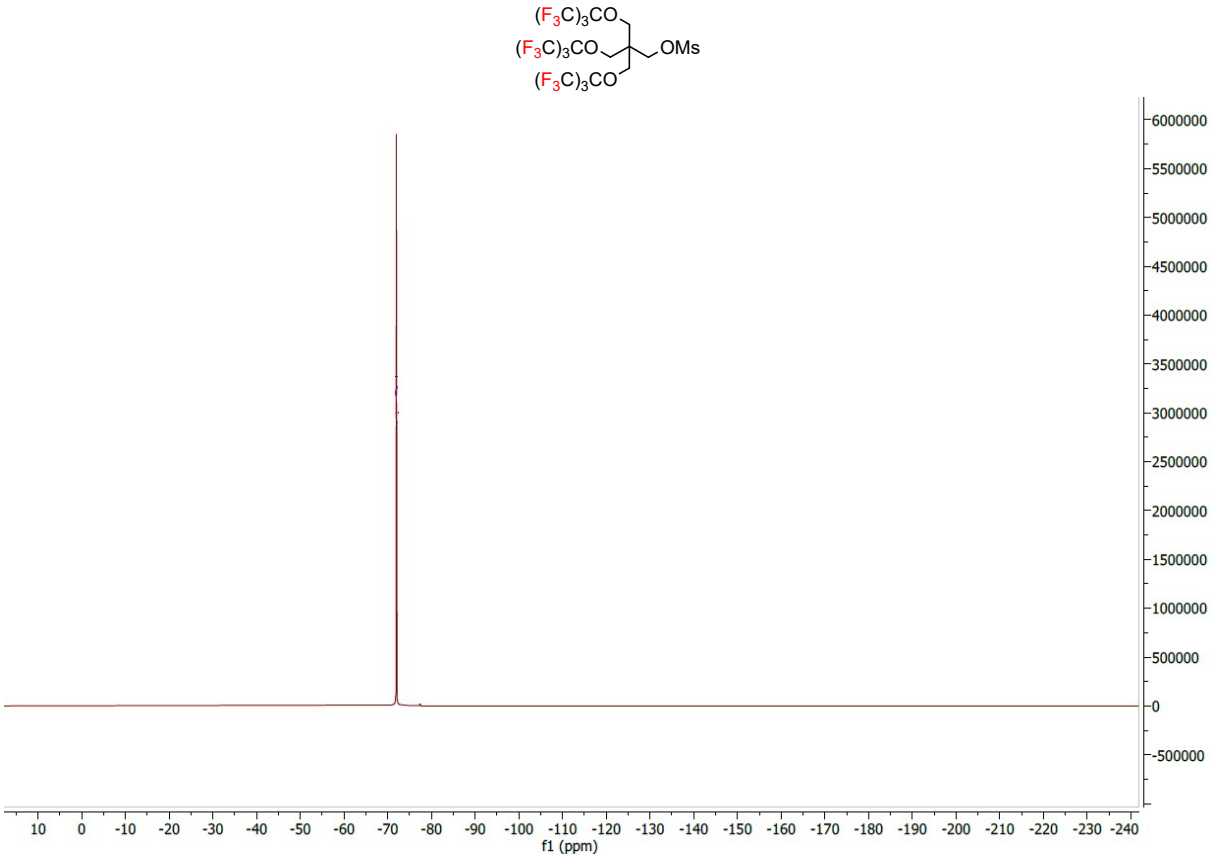
^{1}H NMR spectrum of mesylate of alcohol 5.



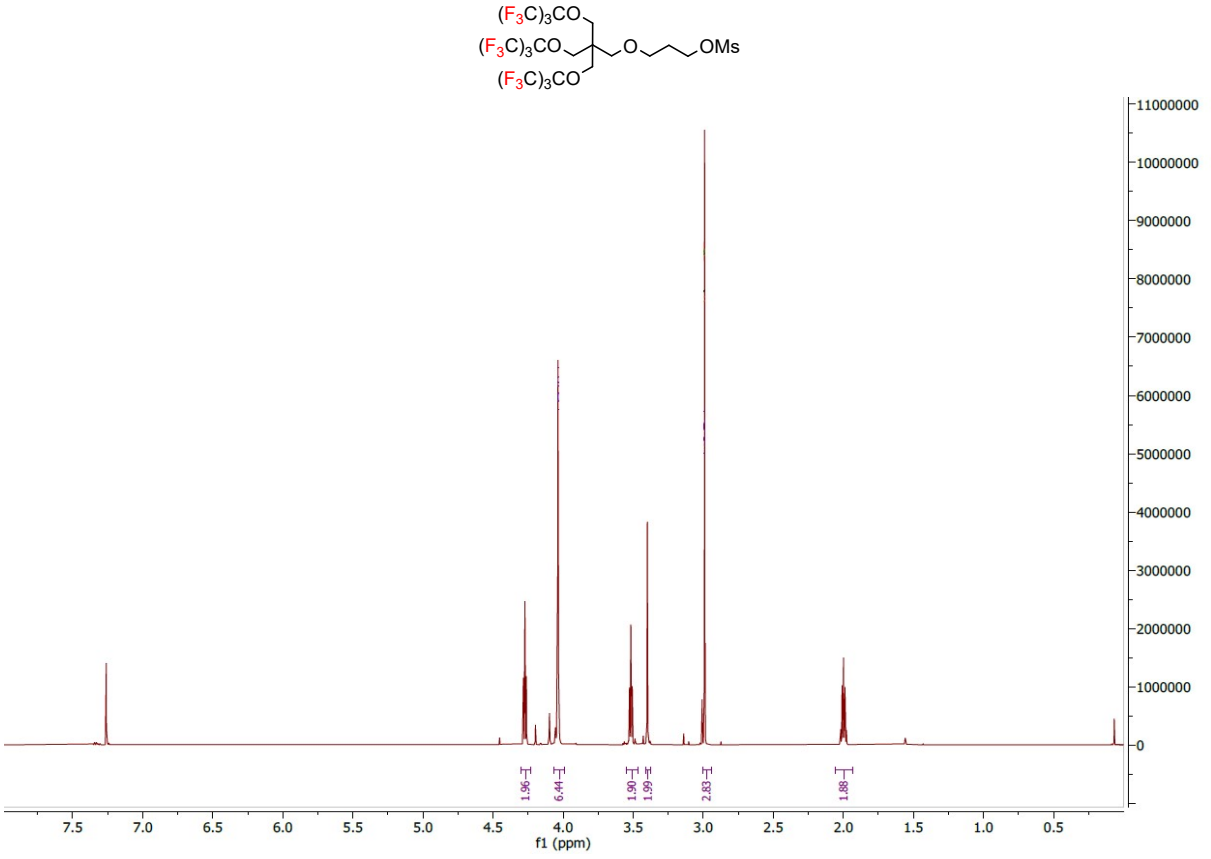
^{13}C NMR spectrum of mesylate of alcohol 5.



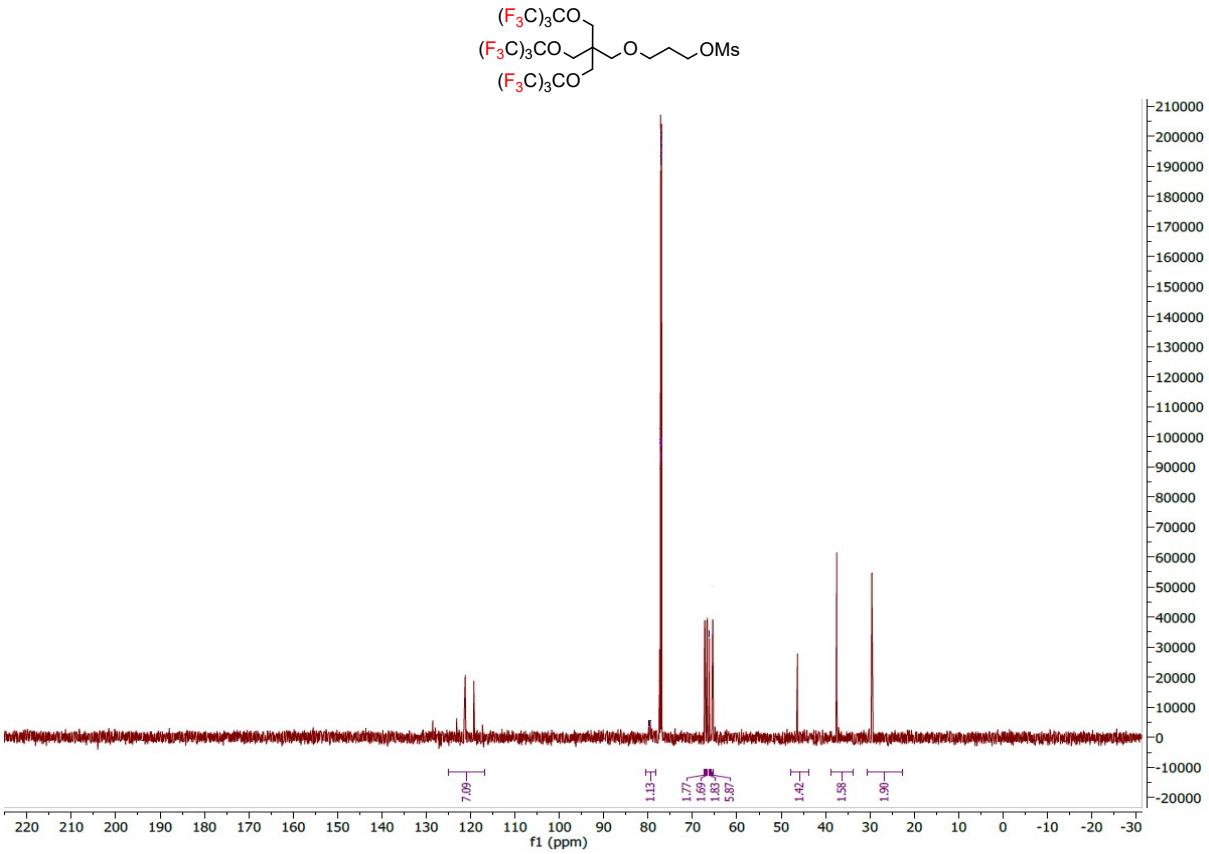
^{19}F NMR spectrum of mesylate of alcohol 5.



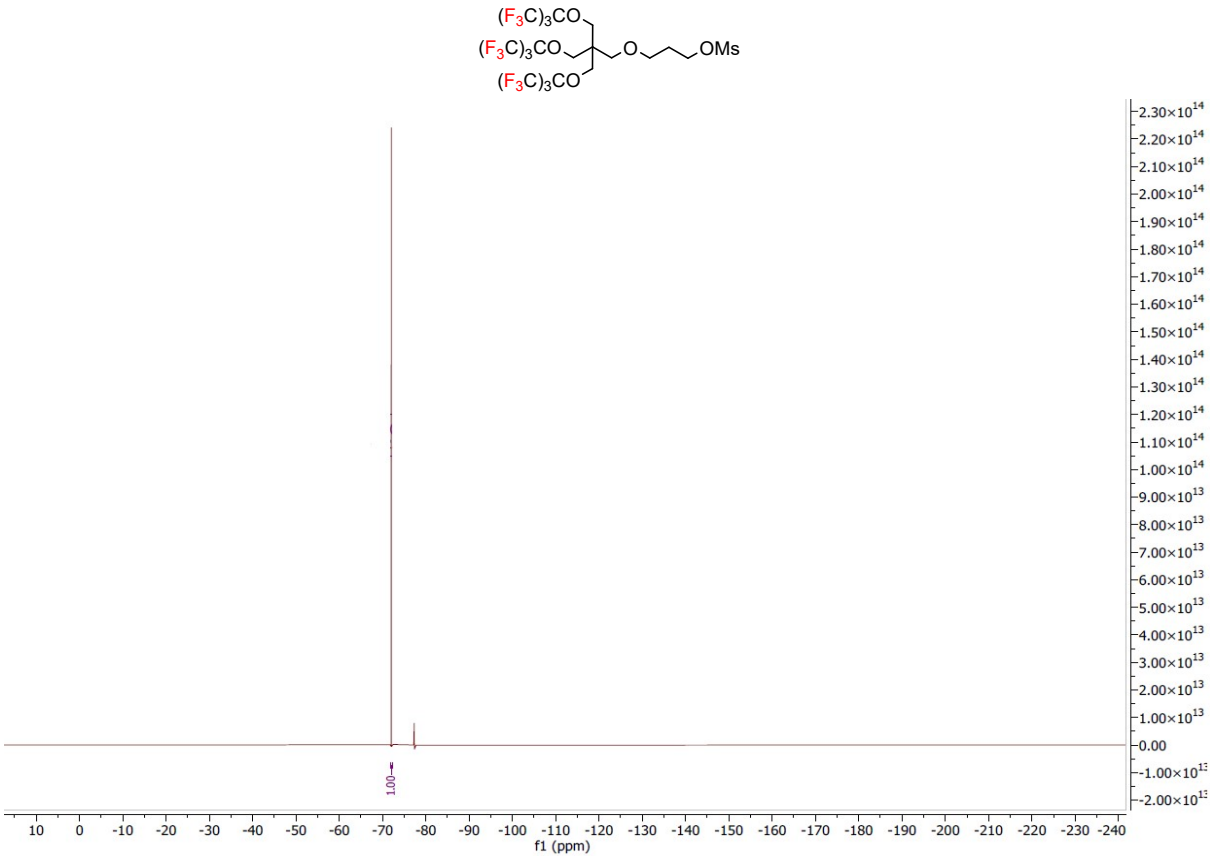
^{1}H NMR spectrum of mesylate of alcohol 6.



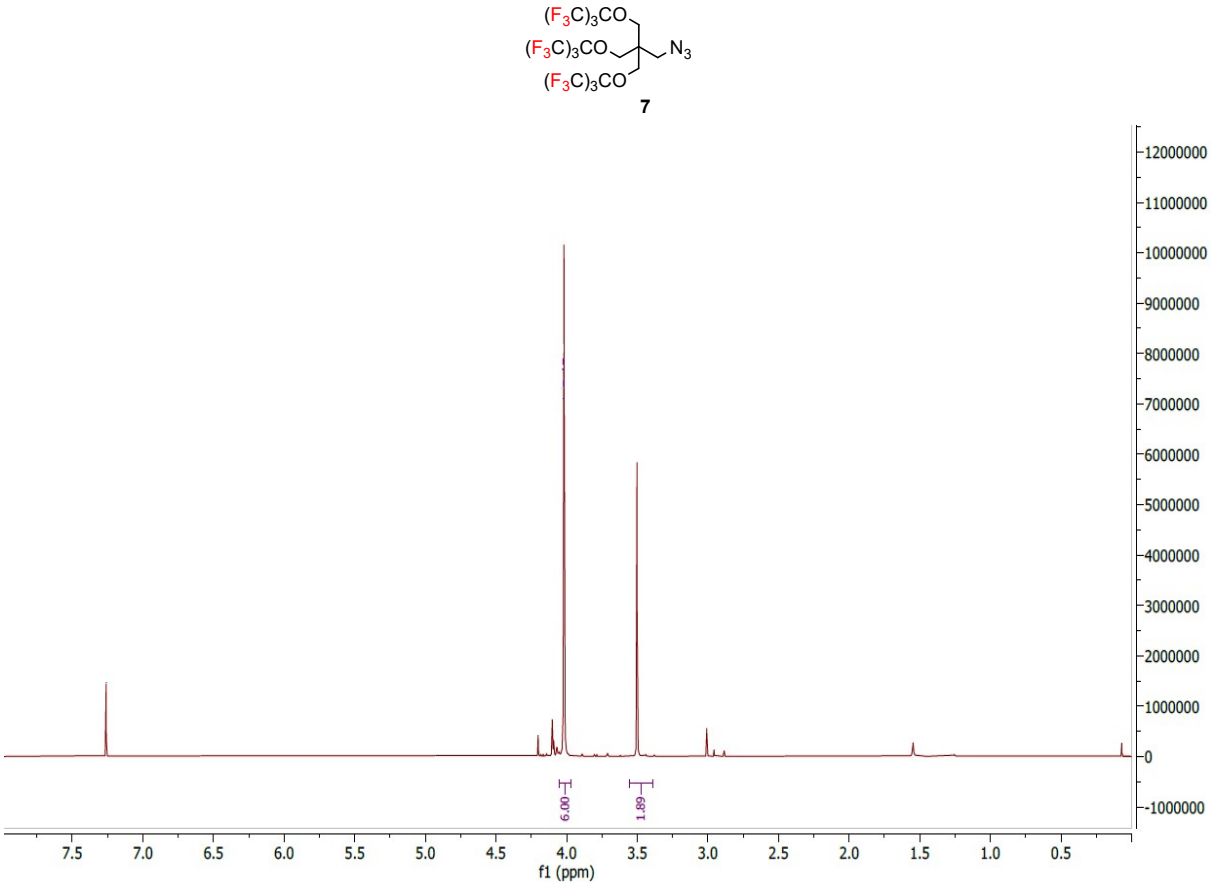
^{13}C NMR spectrum of mesylate of alcohol 6.



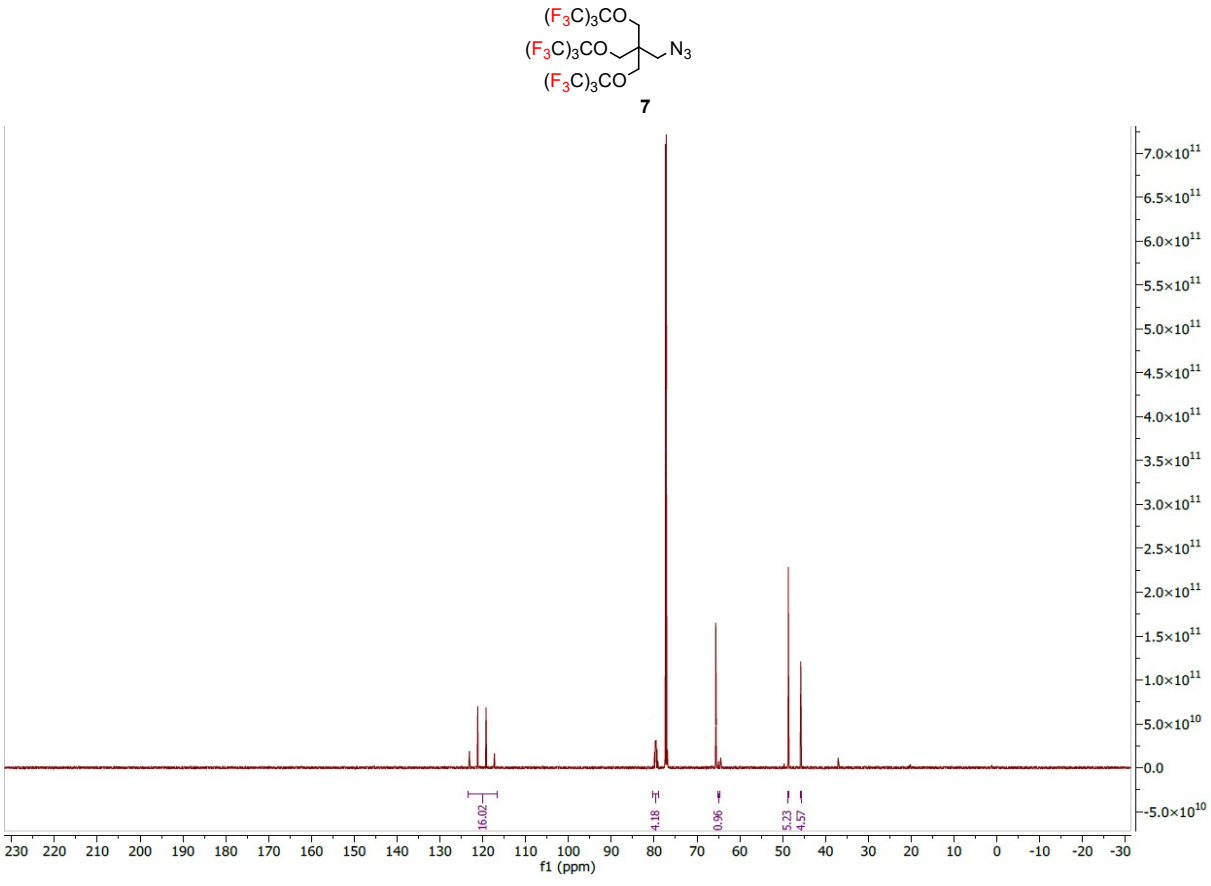
^{19}F NMR spectrum of mesylate of alcohol 6 (in the presence of HFIP as internal standard).



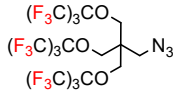
^{1}H NMR spectrum of azido compound 7.



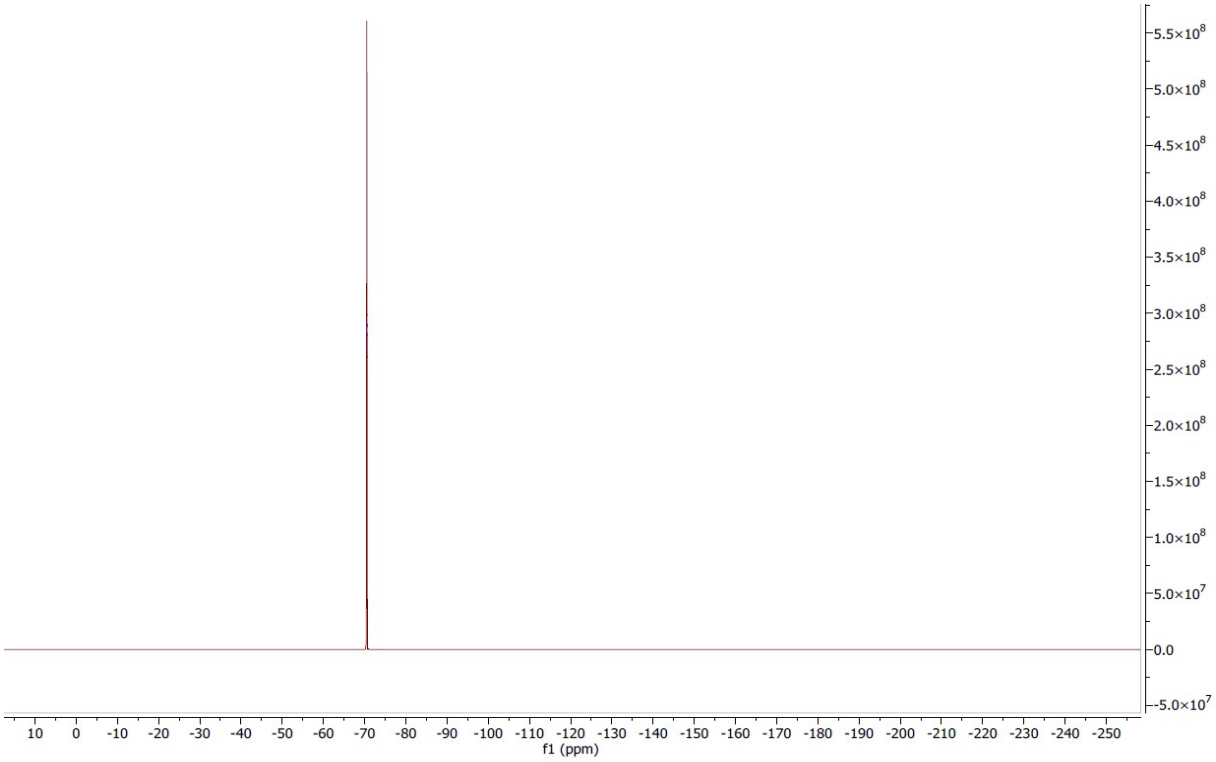
^{13}C NMR spectrum of azido compound 7.



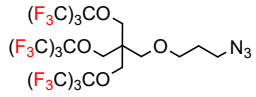
^{19}F NMR spectrum of azido compound 7.



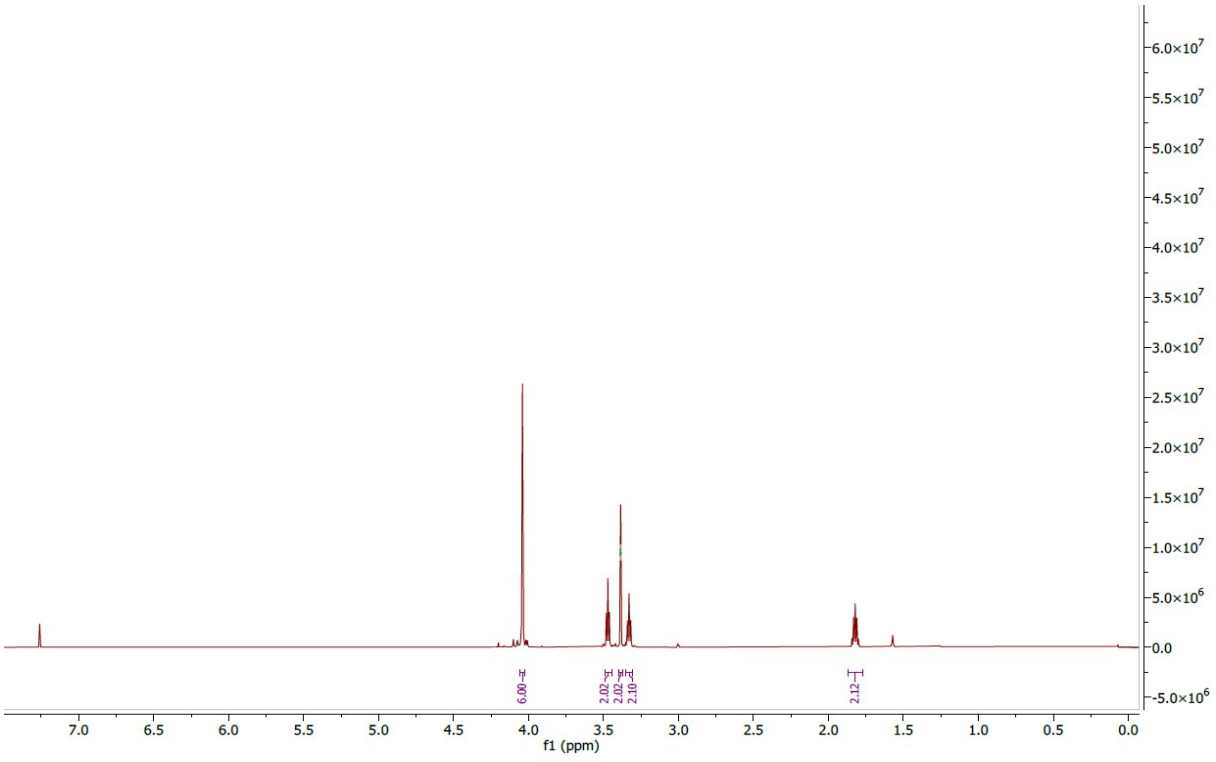
7



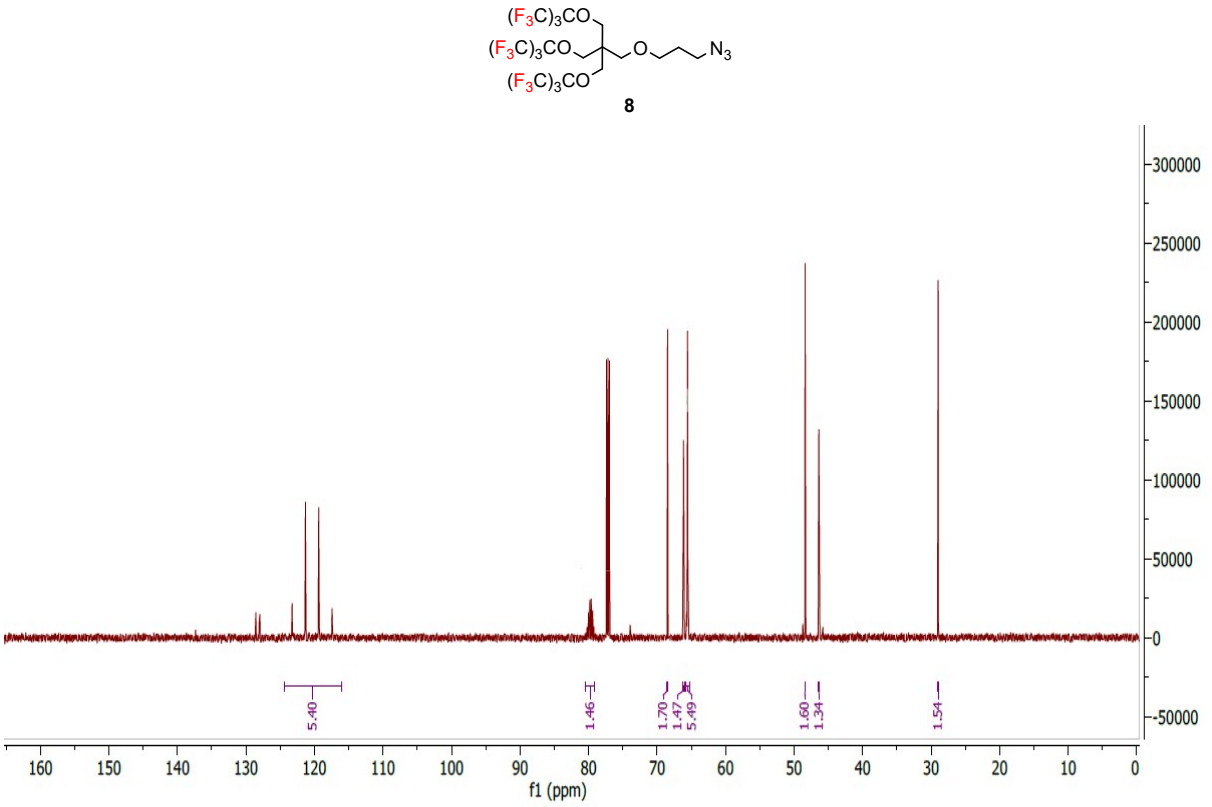
^{1}H NMR spectrum of azido compound 8.



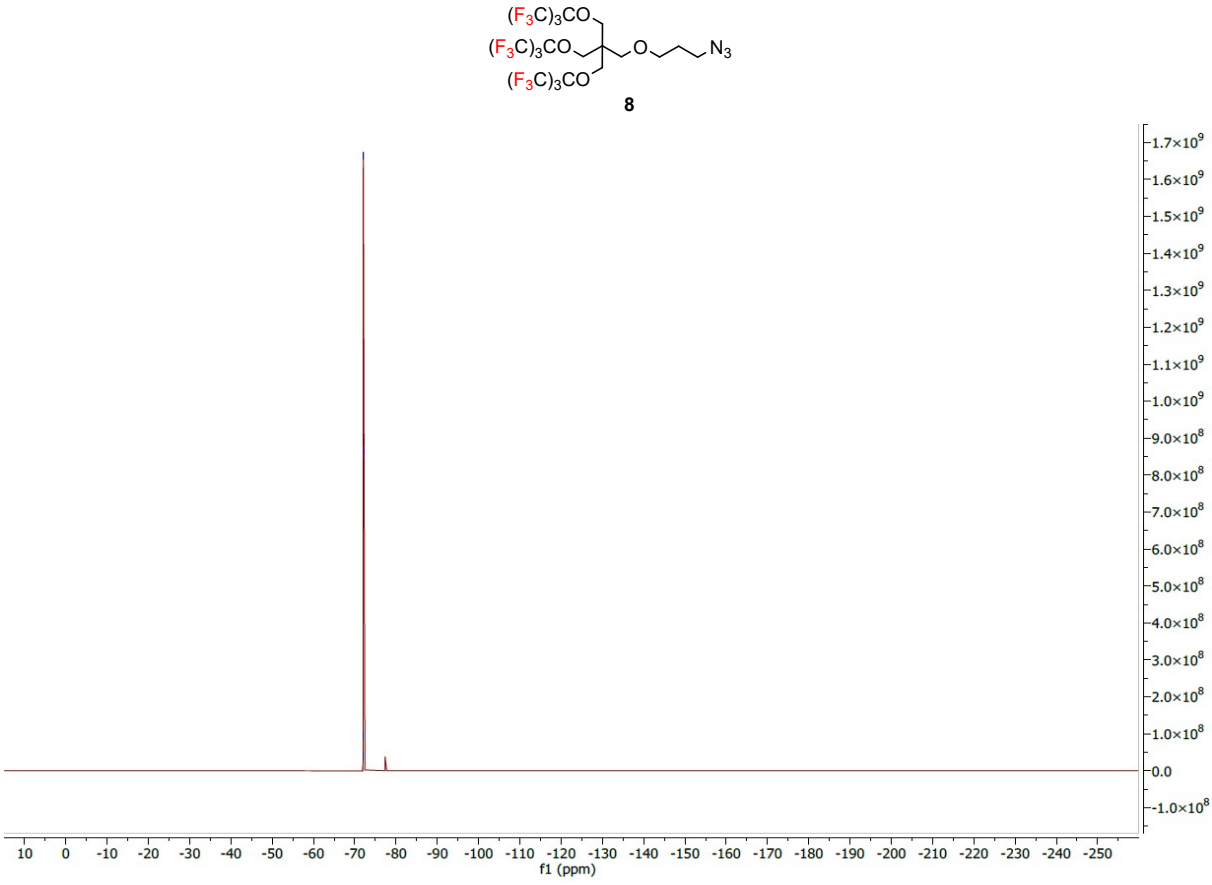
8



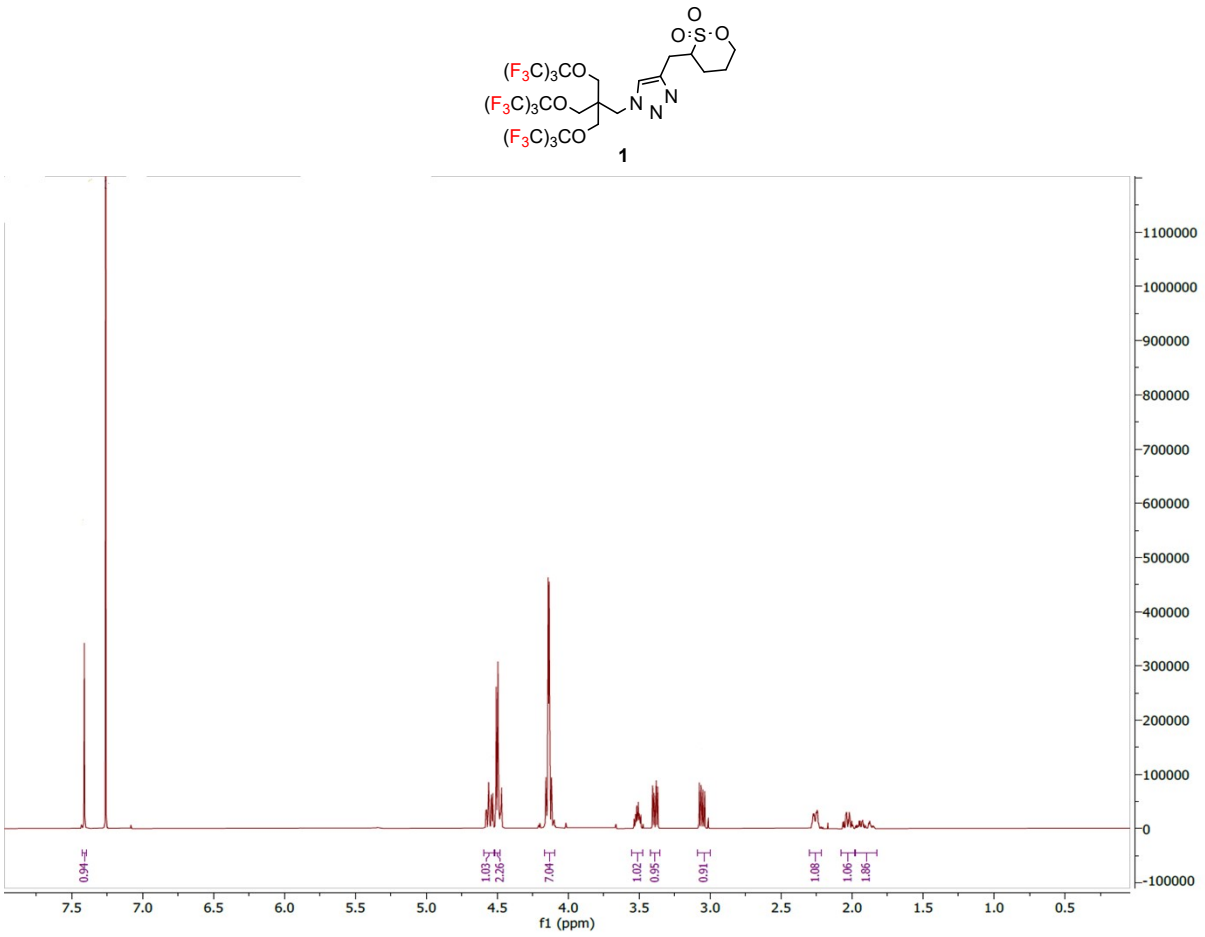
^{13}C NMR spectrum of azido compound 8.



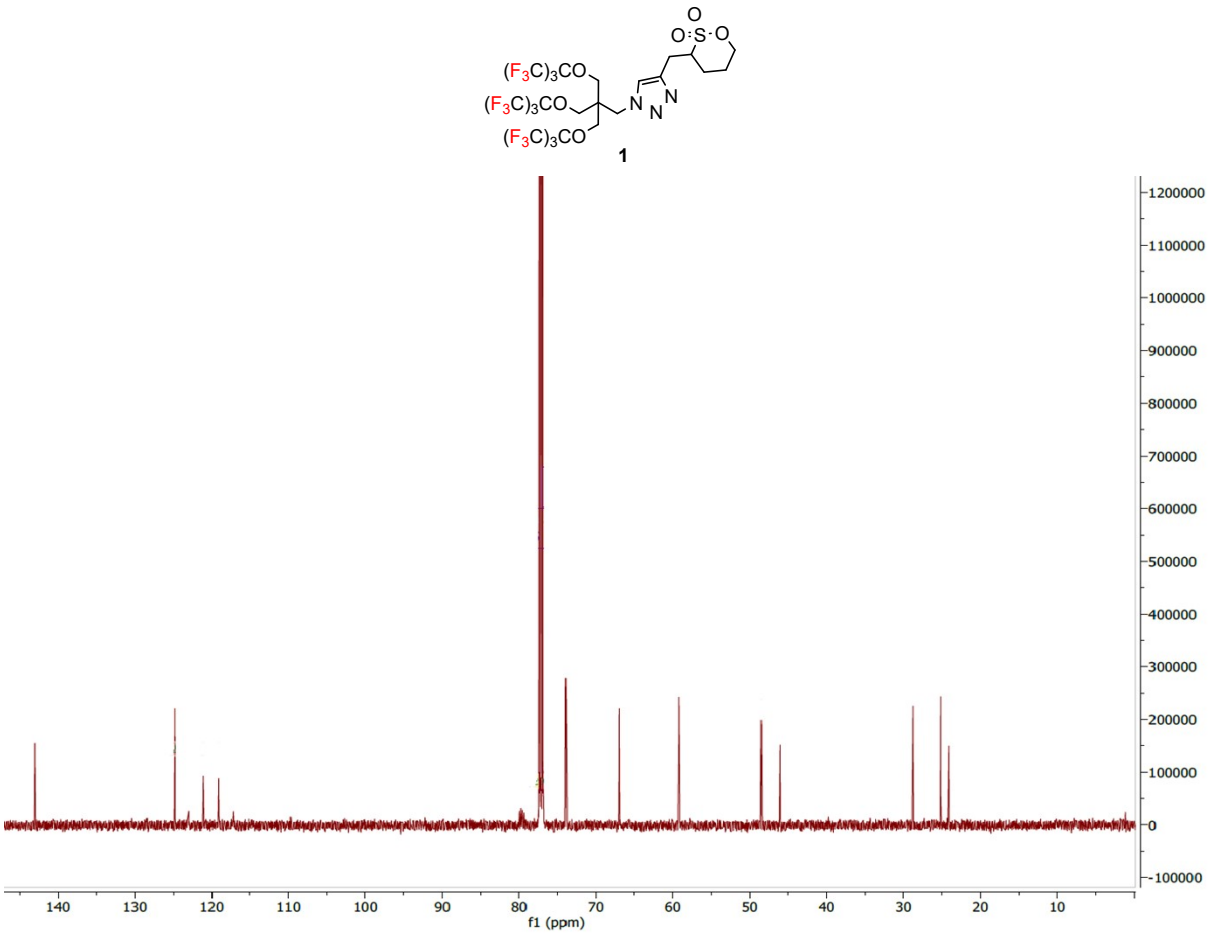
^{19}F NMR spectrum of azido compound 8 (in the presence of HFIP as internal standard).



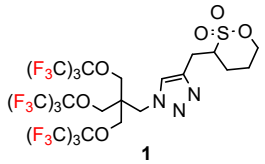
^{1}H NMR spectrum of sultone 1.



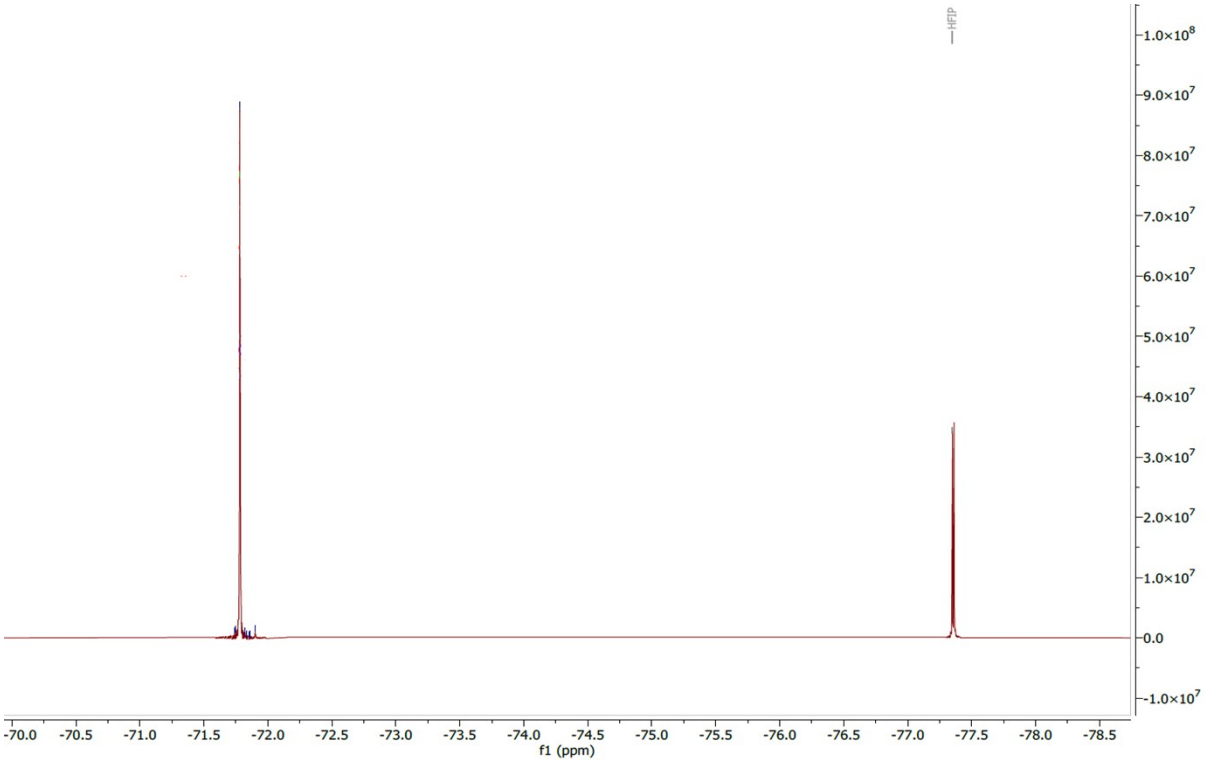
^{13}C NMR spectrum of sultone 1.



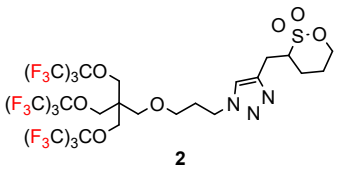
^{19}F NMR spectrum of sultone 1 (in the presence of HFIP as internal standard).



1



^{1}H NMR spectrum of sultone 2.



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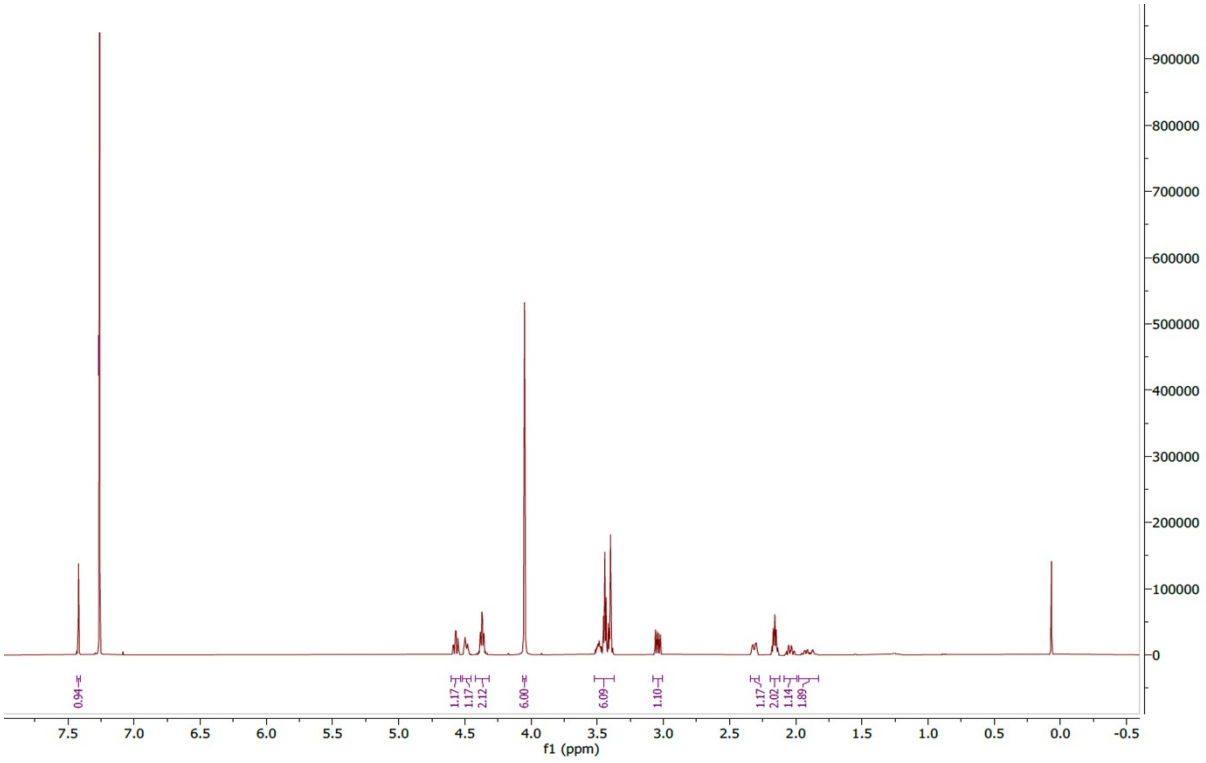
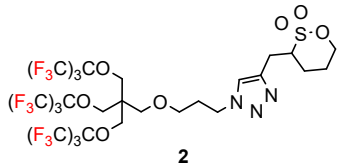


^{13}C NMR spectrum of sultone 2.



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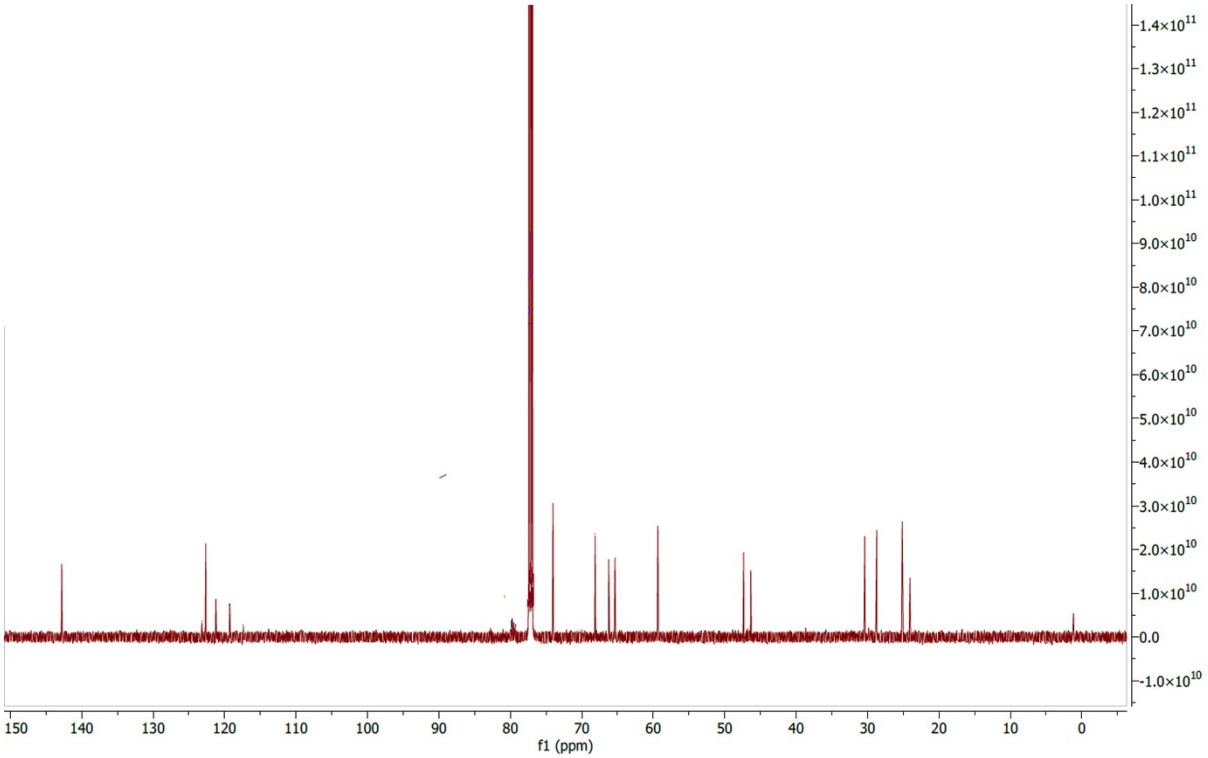
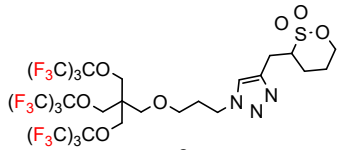


^{19}F NMR spectrum of sultone 2 (in the presence of HFIP as internal standard).



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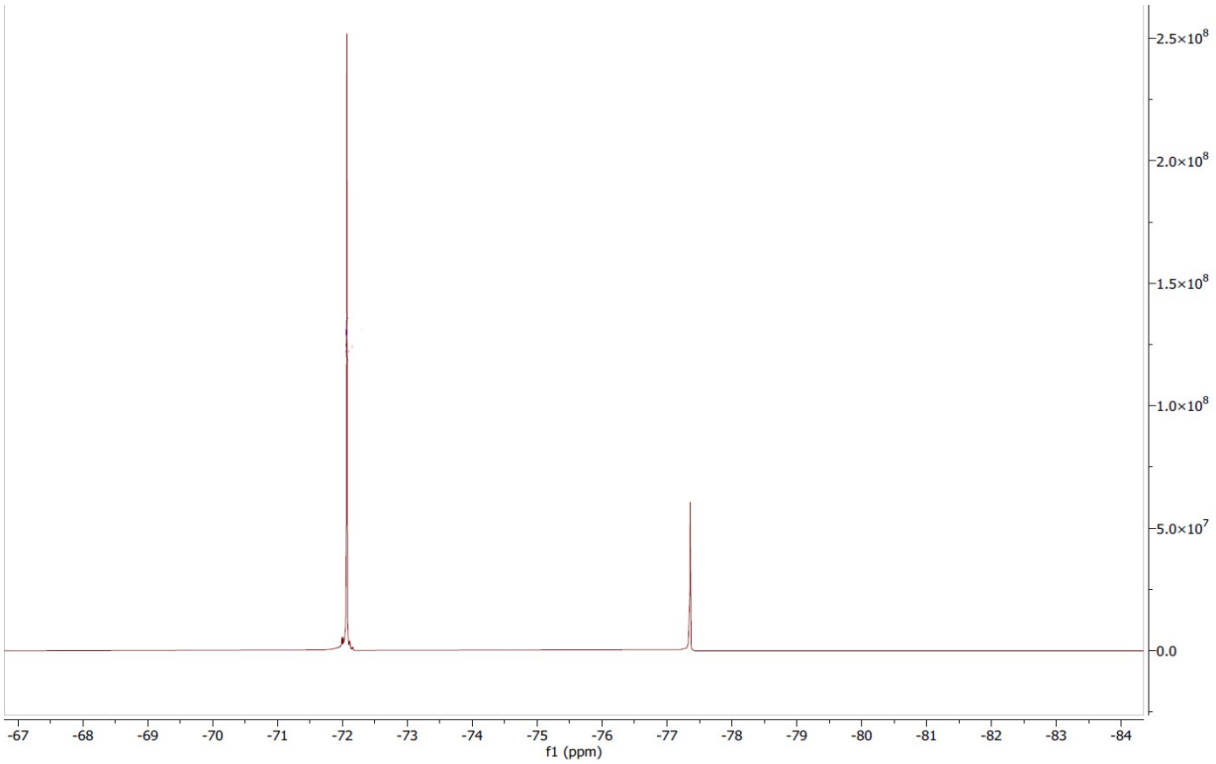
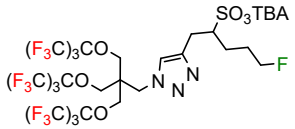


^{1}H NMR spectrum of sulfo compound 3.



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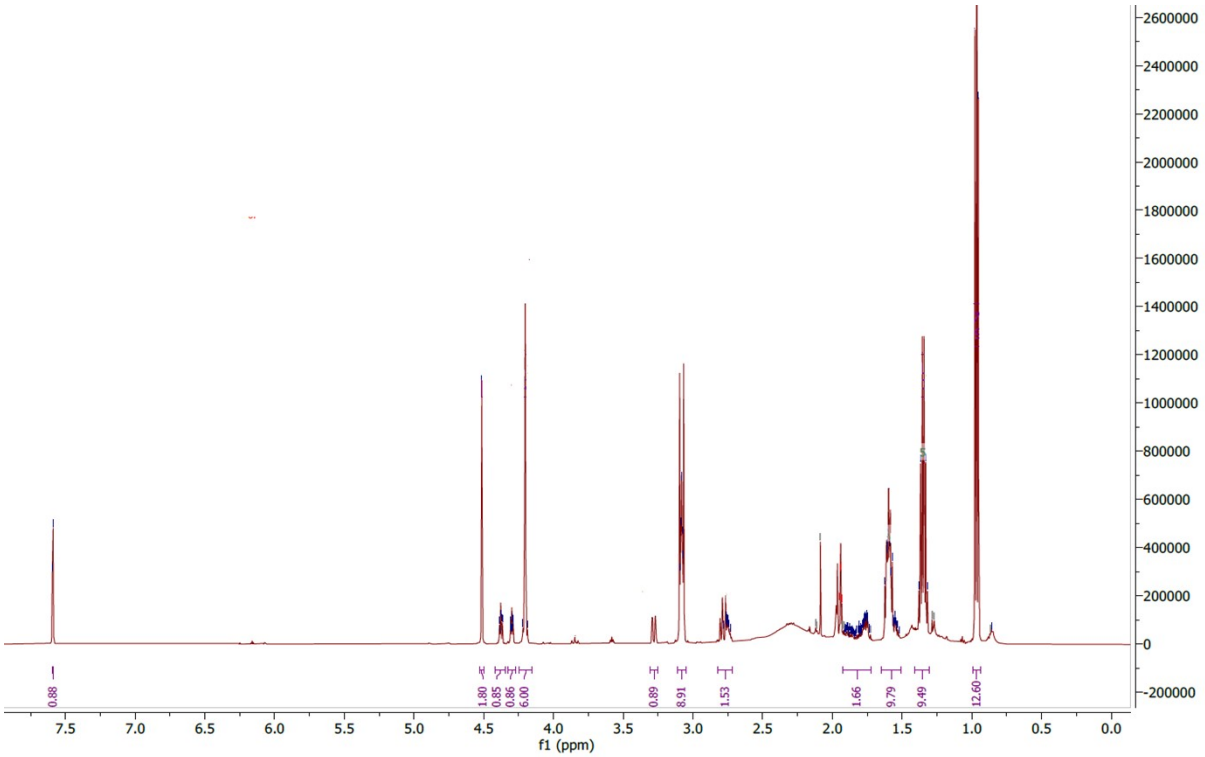
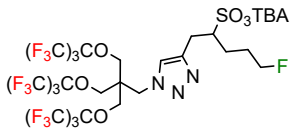


^{13}C NMR spectrum of sulfo compound 3.



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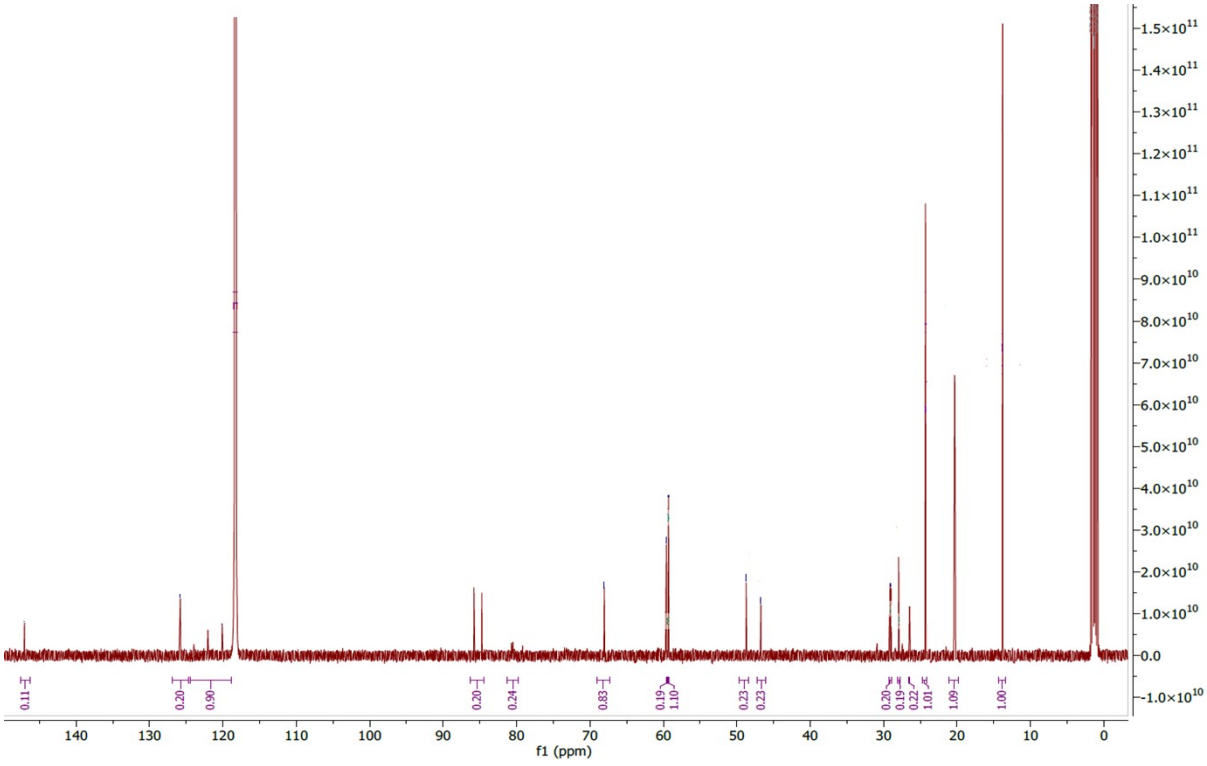
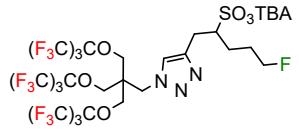


^{19}F NMR spectrum of sulfo compound 3 (in the presence of HFIP as internal standard).



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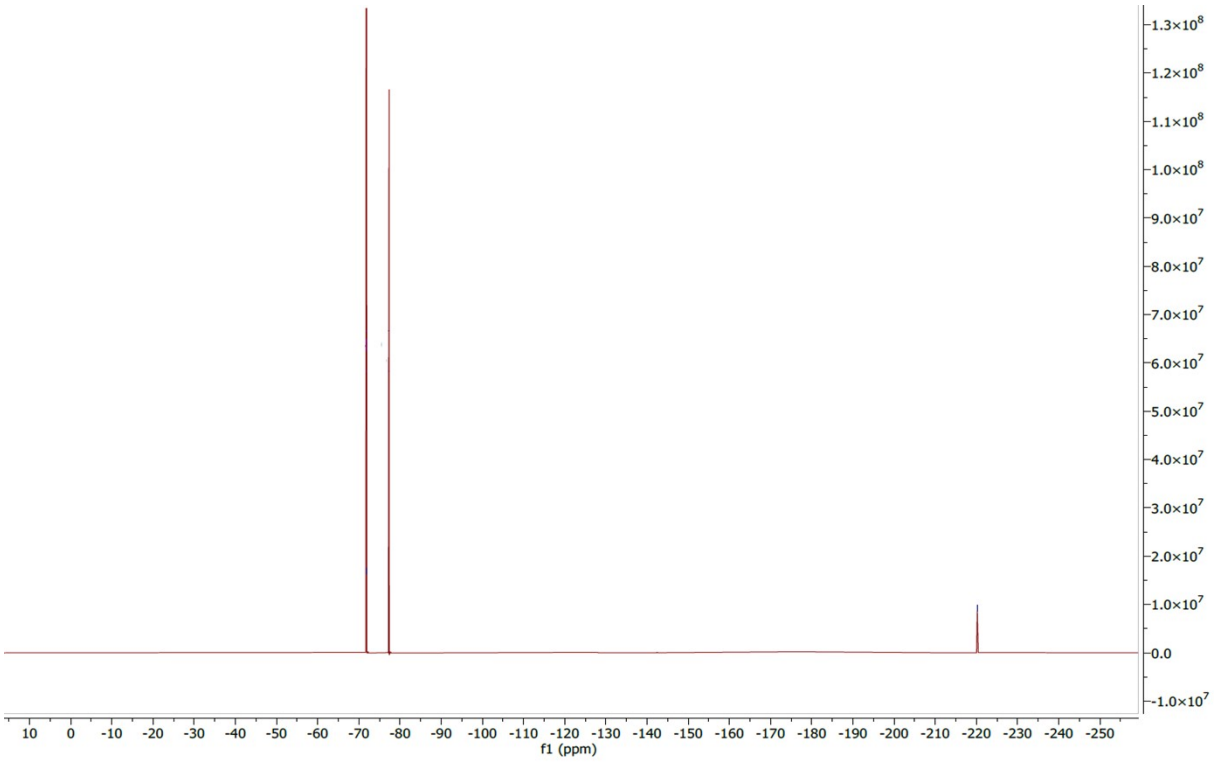
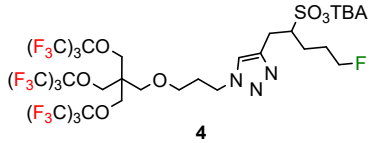


^{1}H NMR spectrum of sulfo compound 4.



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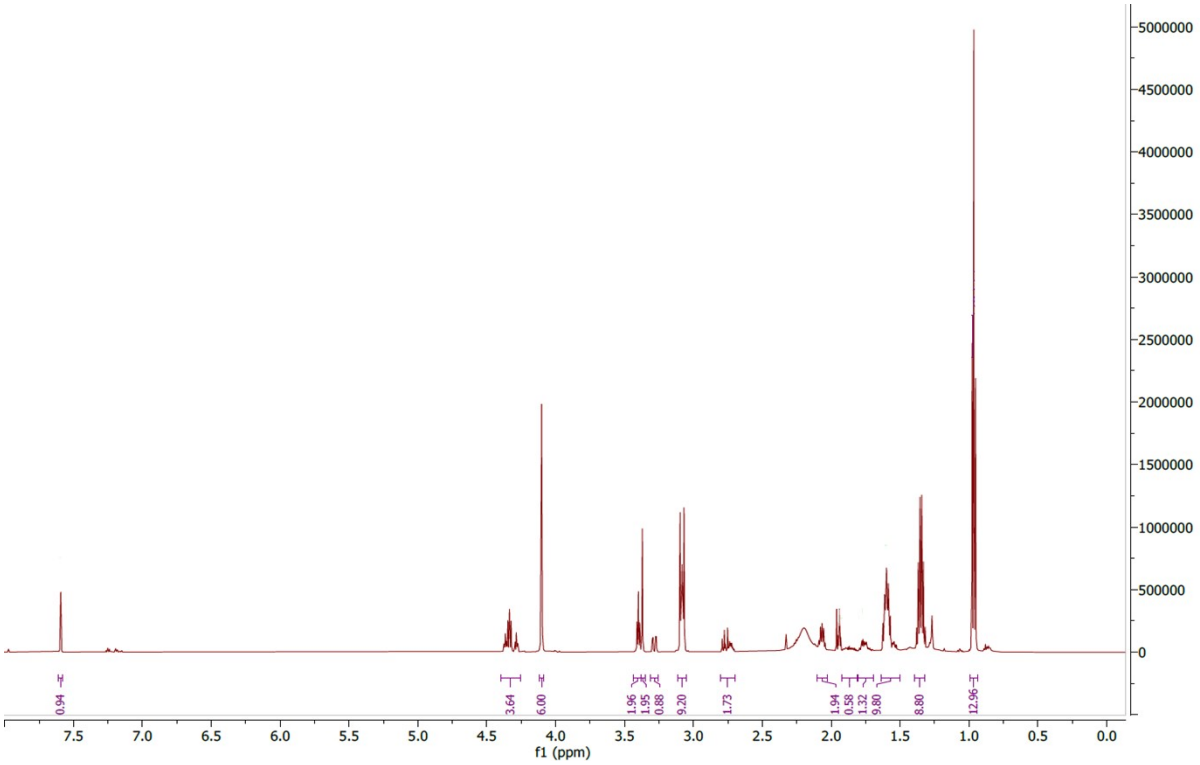
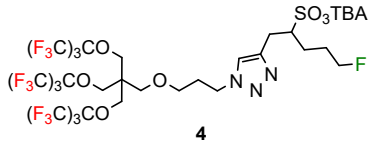


^{13}C NMR spectrum of sulfo compound 4.



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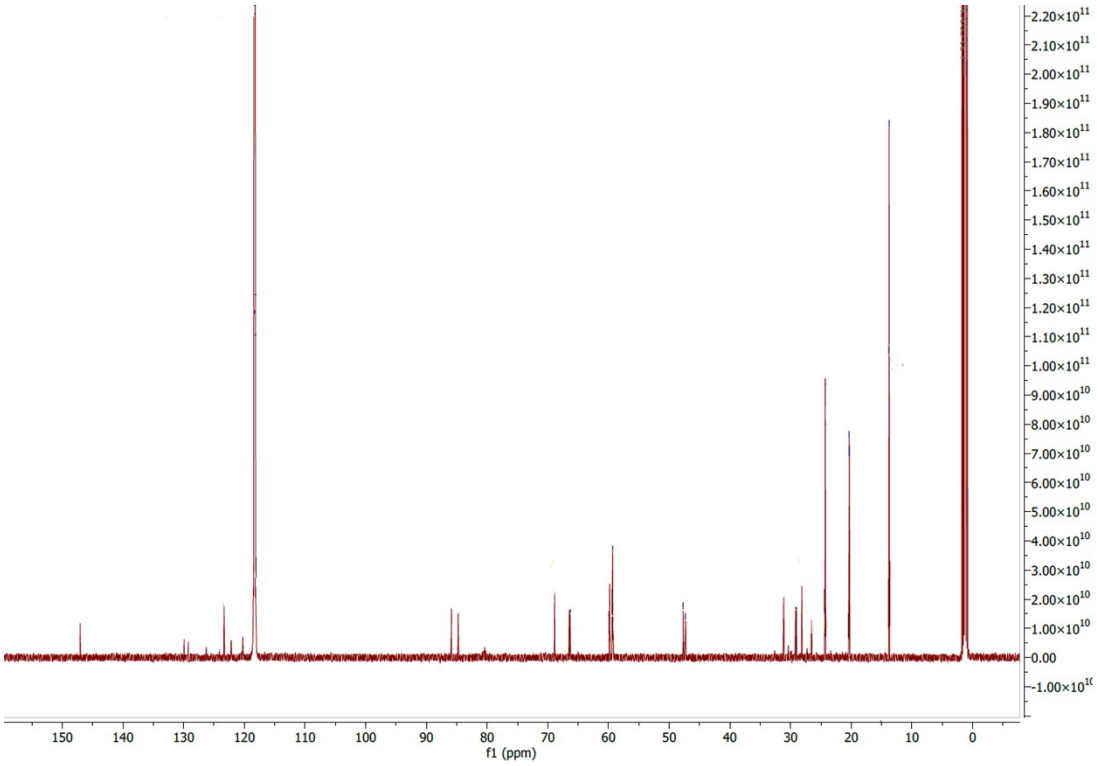
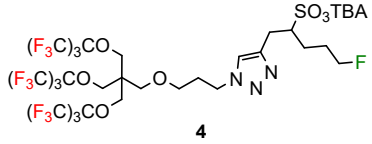


^{19}F NMR spectrum of sulfo compound 4 (in the presence of HFIP as internal standard).



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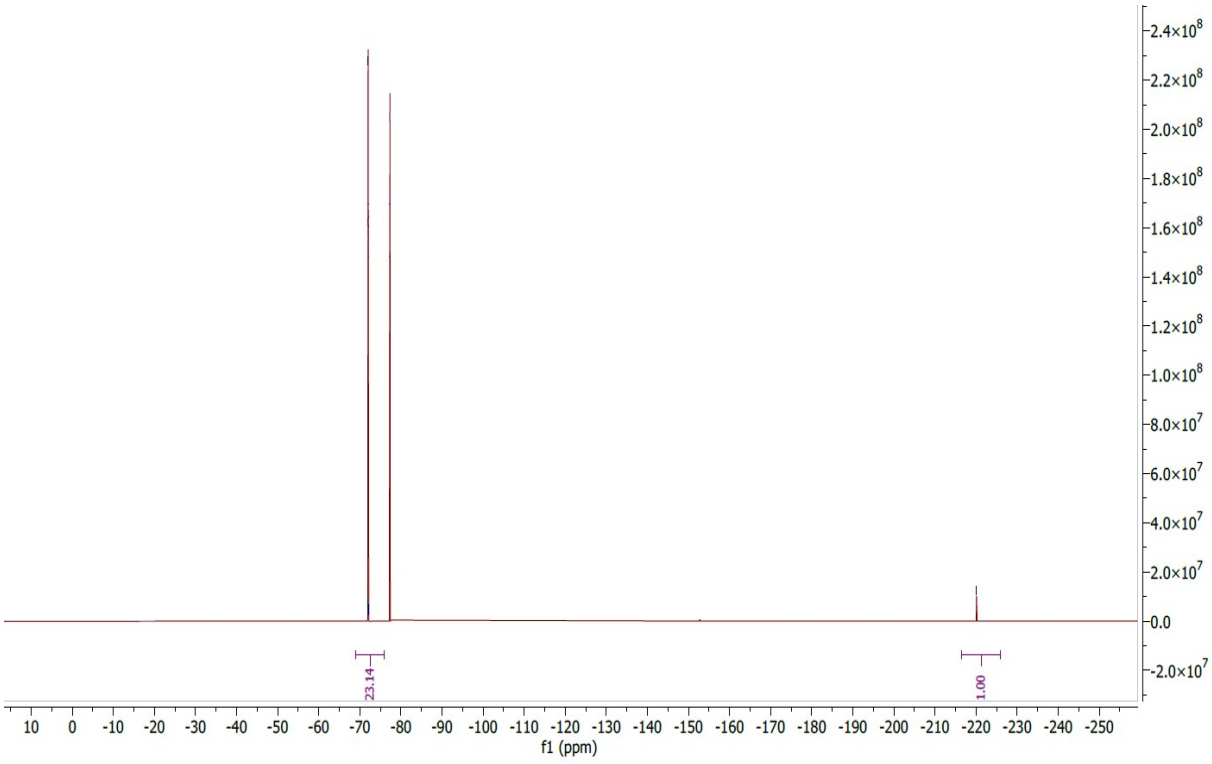
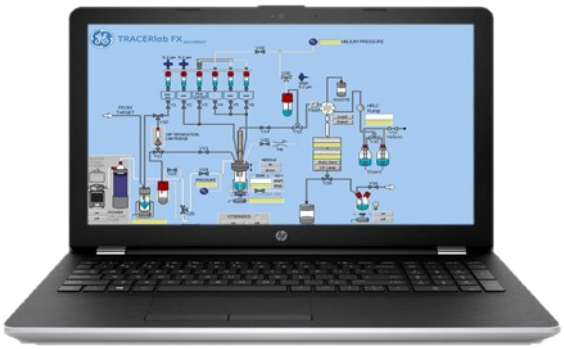


B. Radiochemistry.

B.1. General information.

No-carrier added [^{18}F]fluoride was produced using the ^{18}O(p, n)^{18}F nuclear reaction. Irradiation occurred on target filled with ^{18}O-enriched water (97%, Euriso-top) using Cyclone 18/9 (IBA) Cyclotron. At the end of the irradiation, [^{18}F]fluoride was transferred to the target vial, and its initial activity was measured. For low activities, radiosyntheses were performed under a fume hood equipped with 5 cm lead shielding and lead-shielded glass screens, with initial [^{18}F]fluoride radioactivity below 2 mCi (~740 MBq). For high activities, radiosyntheses were conducted in a hot cell using an automated TRACERlab FXFN (GE) apparatus, with initial radioactivity up to 200 mCi (~7 GBq). Radioactivity mesurement was carried out with a Capintec R15C.



B.2. Radiofluorination of sultones 1 and 2 with low radioactivity.

The cyclotron produced [^{18}F]fluoride in aqueous solution was trapped on a Sep-Pak® Light QMA cartridge then eluted with an aqueous solution of tetra-n-butylammonium bicarbonate ($TBAHCO_3$) (200 µL in water) and acetonitrile (600 µL). The water was removed azeotropically with acetonitrile (2 x 1 mL) by heating at 110 °C under a steam of nitrogen to afford dried [^{18}F]TBAF. A solution of sultone **1** or **2** (8 mg) in acetonitrile (1 mL) was added to around 1 mCi (37 MBq) of [^{18}F]TBAF. The mixture in the sealed reaction vial, was heated at 100 °C for 30 min. After cooling to room temperature, analysis of the crude mixture was carried out by analytical HPLC and radioTLC.

B.3. Radiofluorination of sultones 1 and 2 with high radioactivity.

At the end of bombardment, the aqueous solution of [^{18}F]fluoride was delivered to a TRACERlab FXFN module (GE). The [^{18}F]fluoride was trapped on a Sep-Pak® Light QMA cartridge and eluted with an aqueous solution of $TBAHCO_3$ (200 µL in water) and acetonitrile (600 µL, vial 1). The resulting aqueous [^{18}F]TBAF solution was transferred into the reactor, where it was dried by azeotropic distillation under vacuum and helium flow by heating at 90 °C for 10 min. After cooling the reactor to 40 °C, a solution of the sultone **1** or **2** (8 mg) in acetonitrile (1 mL, vial 3) was introduced into the reactor, and the fluorination reaction was carried out in the sealed reactor at 100 °C for 30 minutes. After cooling to 40 °C, water (3 mL, vial 6) was added and the final mixture was injected into a semi-preparative reverse-phase HPLC system (Phenomenex Gemini column, 10×250 mm, 8:2 CH_3CN/TFA (0.1% in H_2O) as eluent, 5 mL/min flow rate, λ = 254 nm,) for isolation and purification of the radiotracer [^{18}F]**3** or [^{18}F]**4**. The fraction containing the radiolabeled compound [^{18}F]**3** (t_R = 17-20 min) or [^{18}F]**4** (t_R = 18-21 min) was collected in a flask loaded with ultrapure water (95 mL). After stirring, the mixture was passed through a solid-phase extraction cartridge (chromabond C18 ec shorty 20 mg, Macherey-Nagel), and the cartridge was washed with water (5 mL). Afterwards, radiotracer [^{18}F]**3** or [^{18}F]**4** was eluted with ethanol (200 µL) and diluted in saline solution (2.5 mL). Formulated [^{18}F]**3** (1.3-1.8 GBq, 35-50 mCi, 18-25% activity yield, n=5) and [^{18}F]**4** 0.9-1.3 GBq, 24-35 mCi, 12-18% activity yield, n=5) were obtained after 75 min total radiosynthesis time from end of bombardment.

B.4. Analyses of radioactive products [^{18}F]3 and [^{18}F]4.

Analysis of aliquots of crude or isolated radiotracer [^{18}F]**3** or [^{18}F]**4** was performed by analytical reverse phase HPLC using a Waters equipment including an Alliance e2695 separation module, a 2998 photodiode arrays detector (190-380 nm), a Berthold Herm LB 500 activity detector, and a Phenomenex Gemini column (5 µm, 4.6×250 mm) with 8:2 CH_3CN/TFA (0.1% in H_2O) as mobile phase and detection at λ= 226 nm. For identity confirmation, chromatograms were compared to those of corresponding non-radioactive references **3** (t_R = 26.3 min for flow rate of 1.0 mL/min) or **4** (t_R = 14.7 min for flow rate of 1.4 mL/min).

RadioTLC analysis was also carried out on a Raytest scanner using silica plates and 75:25 CH_3CN/TFA (0.1% in H_2O) as eluent.

HPLC and radioTLC chromatograms are shown in the paper.

C. LogP and Log$D_{7.4}$ determination.

The Log P and Log D7.4 values were measured using a standard shake flask method. Approximately 0.148 MBq of formulated [^{18}F]**3** or [^{18}F]**4** (10 µL, concentration of 14.8 MBq/mL) were added into hemolysis tube containing a 1/1 mixture (2 mL) of water or phosphate buffer pH 7.4 (0.01 M) and 1-octanol. Hemolysis tubes were shaken at 25 °C for 40 min then centrifugated at 4000 g for 5 min. Three aliquots (100 µL each) withdrawn from organic and buffer layers were gamma-counted. The experiment was carried out in triplicate.

D. In vitro stability studies.

Aliquots of formulated [^{18}F]**3** or [^{18}F]**4** were added to human serum samples. After incubation at 37 °C up to 160 min, serum samples were centrifuged (4024 g, 10 min, 4 °C) then analyzed by analytical radioHPLC.

E. Animal experiments.

The animal investigations were performed under the current European directive (2010/63/EU) as incorporated in national legislations and protocols were approved by the French (#47590) and Belgian (2024/UCL/MD/63) committees on animal ethics. In vivo experiments were performed using healthy Swiss mice (35 ± 5 g, n=10, in-house breeding stock). All animals were housed in groups of 2 or more in a 12 h light/12 h dark cycle with food and water ad libitum. The general condition of the animals was monitored daily. Animals were maintained under isoflurane anesthesia throughout all experimental procedures (induction 5%, maintenance around 2.5%, with 70% N_2O/30% O_2). Body temperature was maintained close to 37.5 °C using a feedback controlled system and a catheter was inserted into the tail vein for radiotracer administration (~22 ± 5 MBq). Animals were euthanized at the end of the procedure by decapitation under deep anesthesia (isoflurane 5%).

F. PET/ ^{1}H MRI Experiments.

Imaging experiments were developed using a preclinical PET/MRI (7T) system (Bruker, Germany). Scans were performed with emphasis on the abdomen. Respiratory rate was monitored during imaging sessions to insure a stable and reproducible anesthesia from one animal to another and between successive acquisitions. For anatomical MRI reference, T1_Fisp_3D scans were performed including 3 stitched volumes, allowing to obtain a whole body image of a mice, with the following parameters: 3D, repetition time (TR) 5.5 ms, echo time (TE) 2.6 ms, number of averages (NA) 3, voxel spacing 0.5/0.5/0.5 mm, and a field of view (FOV) 40/40/108 mm. High-resolution T2*-weighted images were acquired with a surface coil (Bruker, Germany), using a 3D FLASH gradient echo imaging (spatial resolution of 78 µm by 156 µm by 300 µm) with TE/TR 8.6 ms/50 ms, and a flip angle of 20°. Simultaneous injection of radiotracer (50-120 µL) and initiation of PET acquisition were performed, data were acquired in list-mode and PET images were reconstructed using iterative OSEM3D/MAP algorithm. Images analysis was performed with P-Mod 3.7 software (P-MOD Tech-nologies). Briefly, PET and MR images were co-registered and volumes of interest (VOIs) were semi-automatically delimitated on following organs: liver, heart, kidney, lung, muscle. Time activity curves (TAC) were extracted from PET images and normalized as Standardized Uptake Value (SUV).

G. $^{1}H/^{19}F$ MRI Experiments.

Imaging experiments were conducted on a 11.7T MRI (Bruker Biospec 117/16) using a $^{1}H/^{19}F$ surface coil. Female Swiss mice were first anesthetized in an induction chamber at 3% of isoflurane in air. After we confirmed that the mice were anesthetized, the solution (100 µL) containing the contrast agent **3** or **4** was inoculated in the peritoneal cavity. The mice were placed in a cradle for MRI acquisition with a warm blanket, a rectal temperature probe and a pressure pad to monitor the breathing rate during the acquisition. The isoflurane was maintained at around 1.5% during the experiment (in accordance to the breathing rate). A series of proton images were made to ensure proper placement of the animal in the cradle followed by ^{1}H and ^{19}F image with corresponding field of view. A ^{1}H RARE (spin echo) sequence of coronal view was acquired with the following parameters: FOV 60*60 mm², matrix: 256*256, in plane resolution : 0.23 mm, number of slices: 9 slices, thickness : 1 mm, slice gap : 0.3 mm. TR : 600 ms, TE : 20.5 ms. A ^{19}F FLASH (gradient echo) sequence was obtained with the following parameters: TR 150 ms, TE 1.7 ms, FA: 30°, NEX : 128, total acquisition time : 10 min 14 sec, in plane resolution : 1.87*1.87 mm², slice thickness : 10 mm. Image co-registration was then performed using an homemade script in Matlab.