# Supporting Information

# Traversing Chemical Space via a Hybrid, Chiral Bioisostere of the Trifluoromethyl and Ethyl Groups: Gilenya® as a Case Study

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## Part 1. Experimental and Analytical Details

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## I. General Information

Chemicals were purchased as reagent grade and were used as received. Dry solvents were dried by a Grubbs purification system. Solvents for extractions and flash chromatography were technical grade and distilled prior to use. Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 $F_{254}$ aluminium plates from *Merck* and were visualized under UV-light and/or stained with $KMnO_4$ or CAM solutions. *Flukas* silica gel (230-400 mesh) was used for flash chromatography. NMR spectra were measured by the NMR service of the Organic Chemistry institute (WWU, Münster) on a *Bruker AV300*, *AV400* or an *Agilet DD2 600* at the given temperature. Chemical shifts (δ, ppm) are referenced to residual solvent signals. The coupling constants *J* are given in Hz. The multiplicities are abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Additional 1D and 2D NMR experiments (e.g., $^{1}H\{^{19}F\}$, $^{19}F\{^{1}H\}$, DEPT, COSY, HMBC and HSQC) were used for the assignment of the resonances of the new compounds. Melting points were determined on a *Büchi B-540* apparatus in oPentane capillaries. IR spectra were recorded on a *Perkin Elmer 100 FT-IR* (ATR) spectrometer. The selected adsorption bands are reported in wavenumbers ($cm^{-1}$) and intensities are given as: w (weak), m (medium) or s (strong). High resolution mass spectra (HR-ESI) were measured by the MS service of the Organic Chemistry department (WWU, Münster).

## II. Experimental

### II.1 General Procedures

#### General Procedure 1

To a flask containing DCM was added the alcohol (1.00 eq.), $Et_3N$ (1.30 eq.) and DMAP (0.02 eq.). The resulting mixture was cooled to 0 °C where after 4-toluenesulfonyl chloride (1.00 eq.) was added. The reaction mixture was then stirred at room temperature overnight. The mixture was diluted with DCM, washed (brine), dried ($MgSO_4$) and filtered through a plug of silica gel. The filtrate was then concentrated *in vacuo.*

#### General Procedure 2

A Teflon® reaction vessel (prepared by the mechanical workshop at the Westfälische Wilhelms-Universität Münster) was charged with the olefin (1.00 eq.), 4-iodotoluene (0.20 eq.), DCE (1.25 mL), a solution of amine : HF (1 : 5, 1.25 mL) and Selectfluor® (1.50 eq.). The reaction vessel was then sealed with a teflon screw cap and the mixture was stirred at room temperature for 24-72 h. The reaction mixture was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with DCM (x 3). The combined organic layers were then dried ($Na_2SO_4$) and concentrated under reduced pressure.

#### General Procedure 3

To a flame dried schlenk flask containing $Cs_2CO_3$ (1.50 eq.) was added **8** (1.00 eq.) in dry DMF (1 mL) and the designated alkyl tosylate or halide (1.00 eq.) in dry DMF (1 mL). Everything was added under a stream of argon and the mixture was stirred at room temperature overnight. The reaction mixture was then diluted with $H_2O$, extracted with EtOAc (x 4), washed (5% aq. LiCl), dried ($MgSO_4$) and concentrated *in vacuo*.

#### General Procedure 4

The acetate protected compound (1.00 eq.) was dissolved in a solution of MeOH and 2 M aq. LiOH (4 : 1, v/v) and the mixture was heated to and stirred under reflux until reaction was completed (2-3 h). The MeOH was then removed under reduced pressure and the residue was extracted with EtOAc (x 5), washed (brine), dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was dissolved in 4 M HCl/1,4-dioxane and the resulting solution was stirred at room temperature for 3 h. The solvent was removed *in vacuo* and the salt was collected after precipitation in MeOH/EtOAc.

## II.2 Synthesis of Reported Compounds

### 4-(Benzyloxy)benzaldehyde (2)

The product was synthesised from 4-hydroxybenzaldehyde according to M. Brindisi, S. Butini, S. Franceschini, S. Brogi, F. Trotta, S. Ros, A. Cagnotto, M. Salmona, A. Casagni, M. Andreassi, S. Saponara, B. Gorelli, P. Weiko, J. D. Mikkelsen, J. Scheel-Kruger, K. Sandager-Nielsen, E. Novellino, G. Campiani, S. Gemma *J. Med. Chem.* **2014**, *57*, 9578-9597. Spectral data were in good agreement with C-F. Lin, J-S. Yang, C-Y. Chang, S-C. Kuo, M-R. Lee, L-J. Huang *Bioorg. Med. Chem.* **2005**, *13*, 1537–1544.

### 1-(Benzyloxy)-4-vinylbenzene (3)

The compound was synthesised according to S. J. Cho, N. H. Jensen, T. Kurome, S. Kadari, M. L. Manzano, J. E. Malberg, B. Caldarone, B. L. Roth, A. P. Kozikowski *J. Med. Chem.* **2009**, *52*, 1885-1902. Analytical data were in good agreement with S. E. Denmark, C. R. Butler *J. Am. Chem. Soc.*, **2008**, *130*, 3690–3704.

### 2-(4-(Benzyloxy)phenyl)ethan-1-ol (4)

The product was synthesised according to R. A. Fernandes, M. S. Bodas, P. Kumar *Tetrahedron* **2002**, *58*, 1223-1227. Analytical data are in good agreement with R. A. Joshi, D. R. Garud, M. Muthukrishnan, R. R. Joshi, M. K. Gurjar *Tetrahedron: Asymmetry* **2005**, *16*, 3802-3806.

### Allyl 4-methylbenzenesulfonate (9a)

The product was synthesised according to M. Rössle, D. J. Del Valle, M. J. Krische *Org. Lett*. **2011**, *13*, 1482-1489.

### But-3-en-1-yl 4-methylbenzenesulfonate (9b)

The product was synthesised from 3-buten-1-ol (477 µL, 5.55 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The compound was isolated as a colourless oil (1.03 g, 82%). Spectral data are in good agreement with I. Gábor, R. Gilmour *J. Am. Chem. Soc.* **2016**, *138*, 5004-5007.

### Pentanet-4-en-1-yl 4-methylbenzenesulfonate (9c)

The compound was synthesised from 4-Pentaneten-1-ol (0.20 mL, 1.90 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The product was afforded as a colourless oil (441 mg, 97%). Spectral data are in agreement with T. Šmejkal, B. Breit *Angew. Chem. Int. Ed.* **2007**, *47*, 311-315.

**Hex-5-en-1-yl 4-methylbenzenesulfonate (9d)**

The compound was synthesised from 5-hexen-1-ol (0.18 mL, 1.50 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The product was obtained as a colourless oil (362 mg, 90%). Spectral data are in good agreement with [10] K. Asano, S. Matsubara *Org. Lett.* **2009**, *11*, 1757-1759.

**Hept-6-en-1-yl 4-methylbenzenesulfonate (9e)**

The compound was synthesised from 6-hepten-1-ol (101 mg, 0.89 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The product was obtained as a colourless oil (206 mg, 86%). Spectral data are in good agreement with H. Park, Y-L. Hong, Y. B. Kim, T-L. Choi *Org. Lett.*, **2010**, *12*, 3442–3445.

**3,4-Difluorobutyl 4-methylbenzenesulfonate (10b)**

The product was synthesised from **10b** (114 mg, 0.50 mmol, 1.00 eq.) following **General Procedure 2** (see page S4) (reaction time: 2.5 d). The product was purified *via* flash chromatography (CyH : EtOAc / 10 : 1) and was obtained as a colourless oil (60 mg, 45%). Spectral data are in good agreement with I. Gábor, R. Gilmour *J. Am. Chem. Soc.* **2016**, *138*, 5004-5007.

**Heptyl 4-methylbenzenesulfonate (S15.1e)**

The compound was synthesised from 1-heptanol (0.14 mL, 1.00 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The product was afforded as a colourless oil (233 mg, 86%). Spectral data are in good agreement with K. Asano, S. Matsubara *Org. Lett.* **2009**, *11*, 1757-1759.

**Hex-5-en-1-yl benzoate (S13.1d)**

The compound was synthesised according to K. D. Schleicher, T. F. Jamison *Org. Lett.* **2007**, *9*, 875-878.

**7,7,7-Trifluoroheptyl benzoate (S13.2d)**

The product was synthesised from **S13.1d** following H. Egami, Y. Usui, S. Kawamura, S. Nagashima, M. Sodeoka *Chem. Asian J.* **2015**, *10*, 2190-2199. Spectral data are in good agreement with Y. Imagawa, S. Yoshikawa, T. Fukuhara, S. Hara *Chem. Comm.* **2011**, *47*, 9191-9193.

**8,8,8-Trifluorooctan-1-ol (S13.3e)**

The compound was synthesised from **S13.2e** following a procedure described by H. Egami, Y. Usui, S. Kawamura, S. Nagashima, M. Sodeoka *Chem. Asian J.* **2015**, *10*, 2190-2199. Spectral data are in good agreement with M. Jagodzinska, F. Huguenot, G. Candiani, M. Zanda *Chem. Med. Chem.* **2009**, *4*, 49-51.

### *tert*-Butyl (5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (S18)

The product was synthesised according to R. S. Shaikh, S. S. Schilson, S. Wagner, S. Hermann, P. Keul, B. Levkau, M. Schäfers, G. Haufe *J. Med. Chem.* **2015**, *58*, 3471-3484.

### *tert*-Butyl (5-formyl-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (S19)

The compound was synthesised following a procedure described by R. S. Shaikh, S. S. Schilson, S. Wagner, S. Hermann, P. Keul, B. Levkau, M. Schäfers, G. Haufe *J. Med. Chem.* **2015**, *58*, 3471-3484.

### Bromo(4-bromobenzyl)triphenyl-l5-phosphane (S20.1)

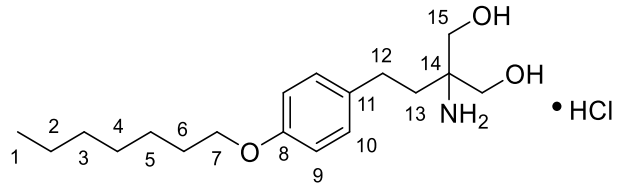
The product was prepared according to D. Rasina, M. Otikovs, J. Leitans, R. Recacha, O. V. Borysov, I. Kanepe-Lapsa, I. Domraceva, T. Pantelejevs, K. Tars, M. J. Blackman, K. Jaudzems, A. Jirgensons *J. Med. Chem.* **2016**, *59*, 374-387.

### Fingolimod hydrochloride (S23)

The compound was synthesised from **S22** (89 mg, 0.22 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (53 mg, 71%). Analytical data are in good agreement with J. Calzavara, J. McNulty *Tetrahedron Lett.* **2011**, *52*, 5672-5675 and S. Sugiyama, S. Arai, M. Kiriyama, K. Ishii *Chem. Pharm. Bull.* **2005**, *53*, 100-102.

## II.3 Synthesis of Reported Compounds with Novel Analytical Data

### 2-Amino-2-(4-(heptyloxy)phenethyl)propane-1,3-diol hydrochloride (16e)

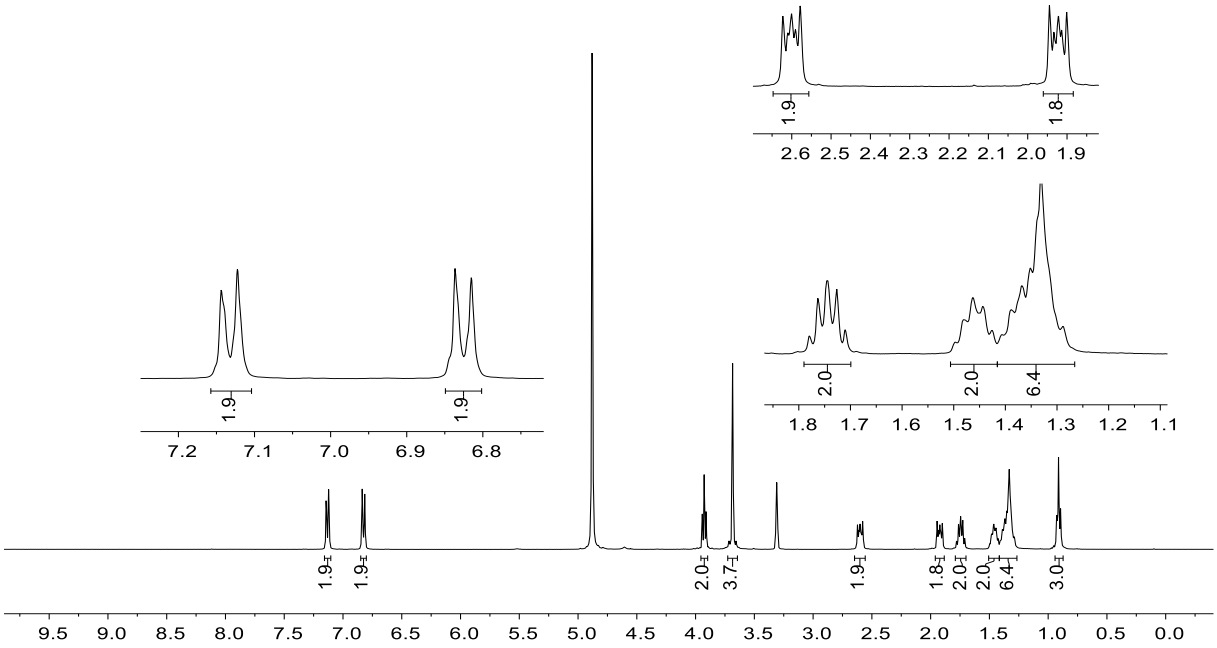



The compound was synthesised from **15e** (97 mg, 0.22 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in EtOH/EtOAc and was obtained as a white solid (76 mg, 99%).

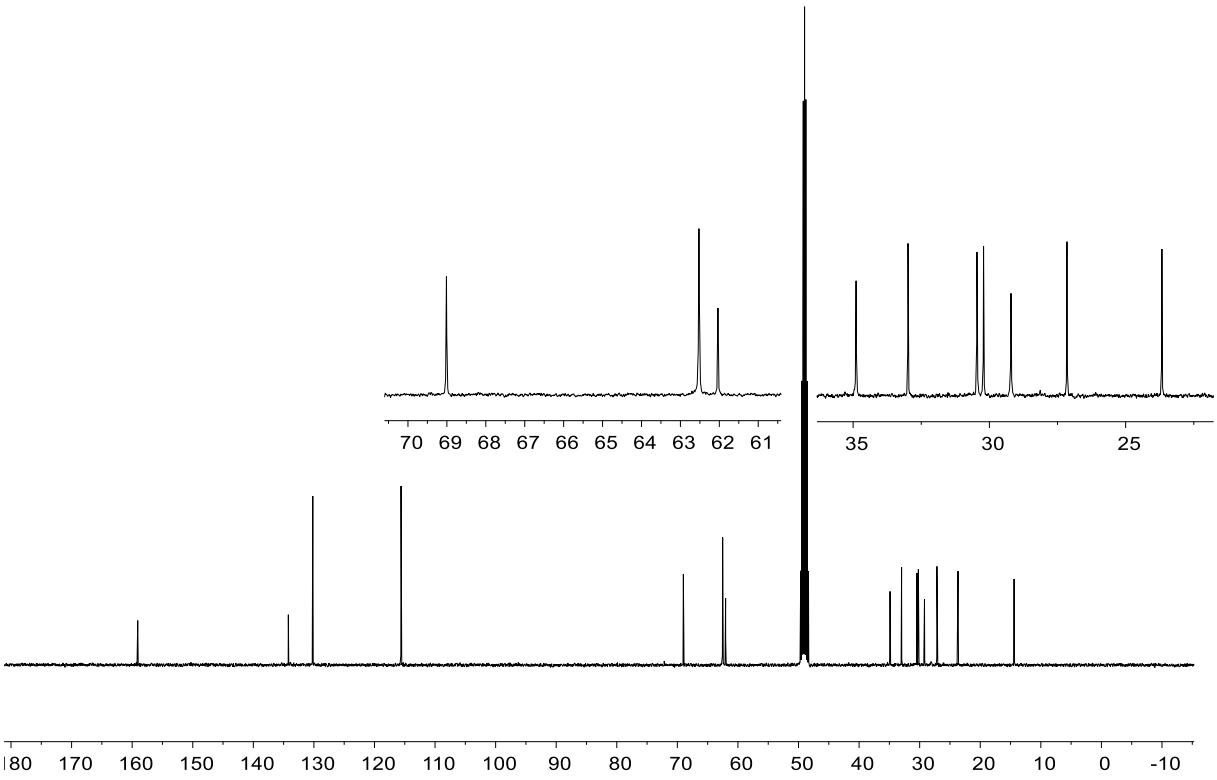
$^{1}$H NMR (400 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC10), 6.82 (m, 2H, HC9), 3.92 (t, $^{3}J_{HH}$ = 6.4 Hz, 2H, $H_2$C7), [3.70, 3.67 (each d, $^{2}J_{HH}$ = 11.6 Hz, each 2H)]($H_2$C15), 2.60 (m, 2H, $H_2$C12), 1.92 (m, 2H, $H_2$C13), 1.74 (m, 2H, $H_2$C6), 1.46 (m, 2H, $H_2$C5), 1.36 (m, 2H, $H_2$C4), 1.33 (m, 4H, $H_2$C2,3), 0.91 (m, 3H, $H_3$C1).

$^{13}$C{$^{1}$H} NMR (101 MHz, Methanol-$d_4$, 298 K) δ 159.1 (C8), 134.2 (C11), 130.2 (C10), 115.6 (C9), 69.0 (C7), 62.5 (C15), 62.0 (C14), 34.9 (C13), [33.0, 23.7](C3,2), 30.5 (C6), 30.2 (C4), 29.2 (C12), 27.2 (C5), 14.4 (C1).

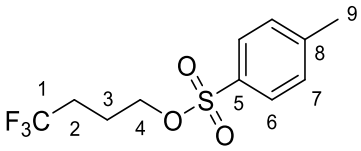
$^{1}$H NMR (400 MHz, Methanol-$d_4$, 298 K)



$^{13}C\{^{1}H\}$ NMR (101 MHz, Methanol-$d_4$, 298 K)




**4,4,4-Trifluorobutyl 4-methylbenzenesulfonate (S13.1a)**




The compound was synthesised from 4,4,4-trifluorobutan-1-ol (106 µL, 1.00 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The product was obtained as a colourless oil (223 mg, 79%). $^{1}H$ and $^{19}F$ NMR data are in good agreement with T. Tsushima, K. Kawada, S. Ishihara, N. Uchida, O. Shiratori, J. Higaki, M. Hirata *Tetrahedron* **1988**, *44*, 5375-5387 and K-R. Gassen, W. Kirmse *Chem. Ber.* **1986**, *119*, 2233-2248.

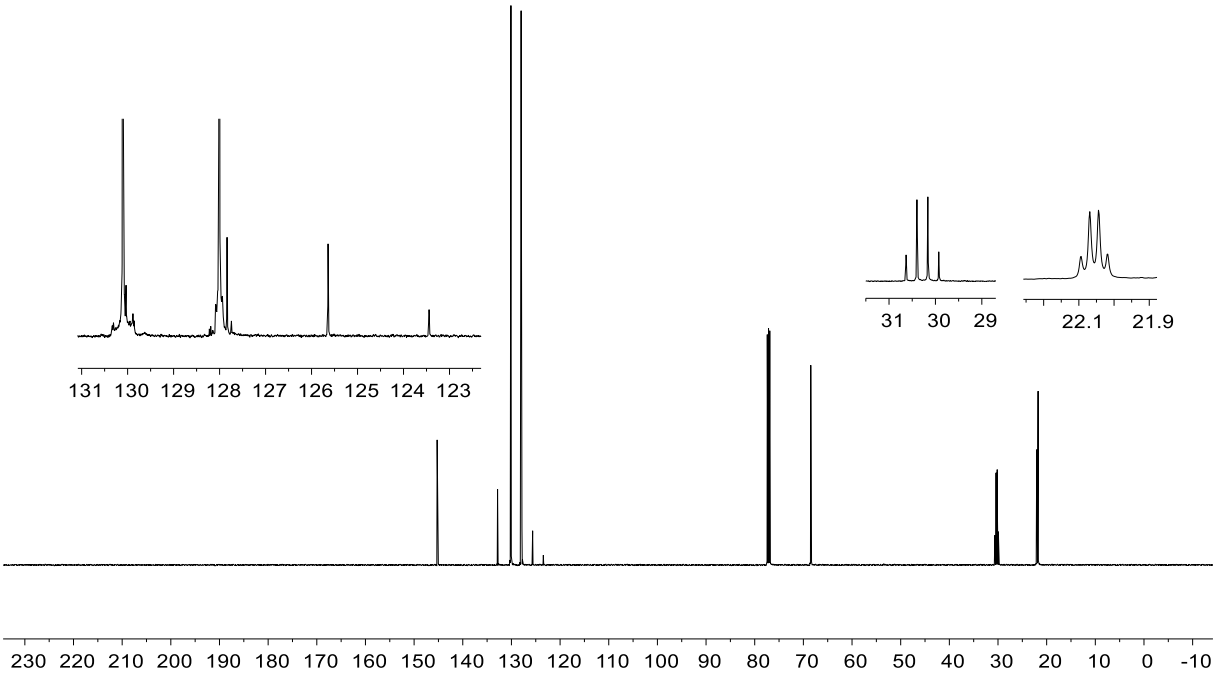
$R_f$ 0.50 (CyH : EtOAc / 2 : 1).

HRMS *m/z* (ESI); Calcd. for $C_{11}H_{13}O_3SF_3Na$ 305.0430, found 305.0438.

$^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*, 298 K) δ 145.3 (C8), 132.9 (C5), 130.1 (C7), 128.0 (C6), 126.7 (q, $^{1}J_{FC}$ = 276.1 Hz, C1), 68.5 (C4), 30.3 (q, $^{2}J_{FC}$ = 29.6 Hz, C2), 22.1 (q, $^{3}J_{FC}$ = 3.2 Hz, C3), 21.8 (C9).

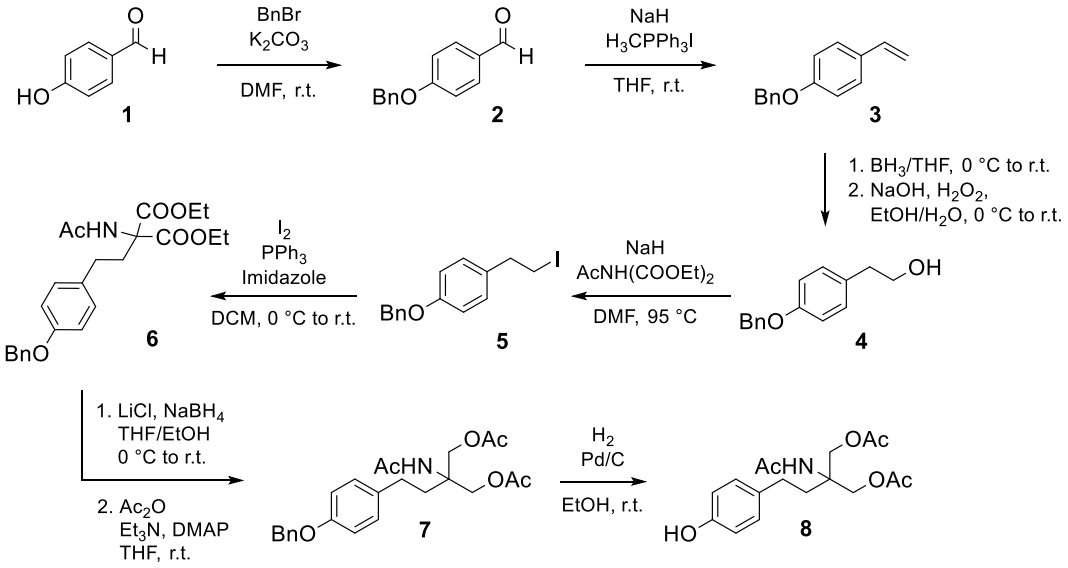
IR ($cm^{-1}$): 2963 (w), 1599 (w), 1496 (w), 1452 (w), 1400 (w), 1385 (w), 1359 (m), 1340 (m), 1308 (w), 1293 (w), 1255 (m), 1235 (m), 1212 (w), 1190 (m), 1175 (s), 1152 (m), 1133 (m), 1097 (m), 1083 (w), 1037 (m), 1020 (w), 992 (s), 923 (m), 843 (m), 813 (m), 741 (m), 706 (w), 690 (w), 660 (s).

$^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*, 298 K)

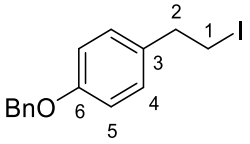


## II.4 Synthesis of Aromatic Moiety 8

**Scheme S1.**




### 1-(Benzyloxy)-4-(2-iodoethyl)benzene (5)



The product was synthesised from **4** (1.16 g, 5.07 mmol, 1.00 eq.) following a modified procedure described by S. Nakayama, Y. Uto, K. Tanimoto, Y. Okuno, Y. Sasaki, H. Nagasawa, E. Nakata, K. Arai, K. Momose, T. Fujita, T. Hashimoto, Y. Okamoto, Y. Asakawa, S. Goto, H. Hori *Bioorg. Med. Chem.* **2008**, *16*, 7705-7714.

M.p.: 77 °C.

$R_f$ 0.37 (CyH : EtOAc ca. 75 : 1).

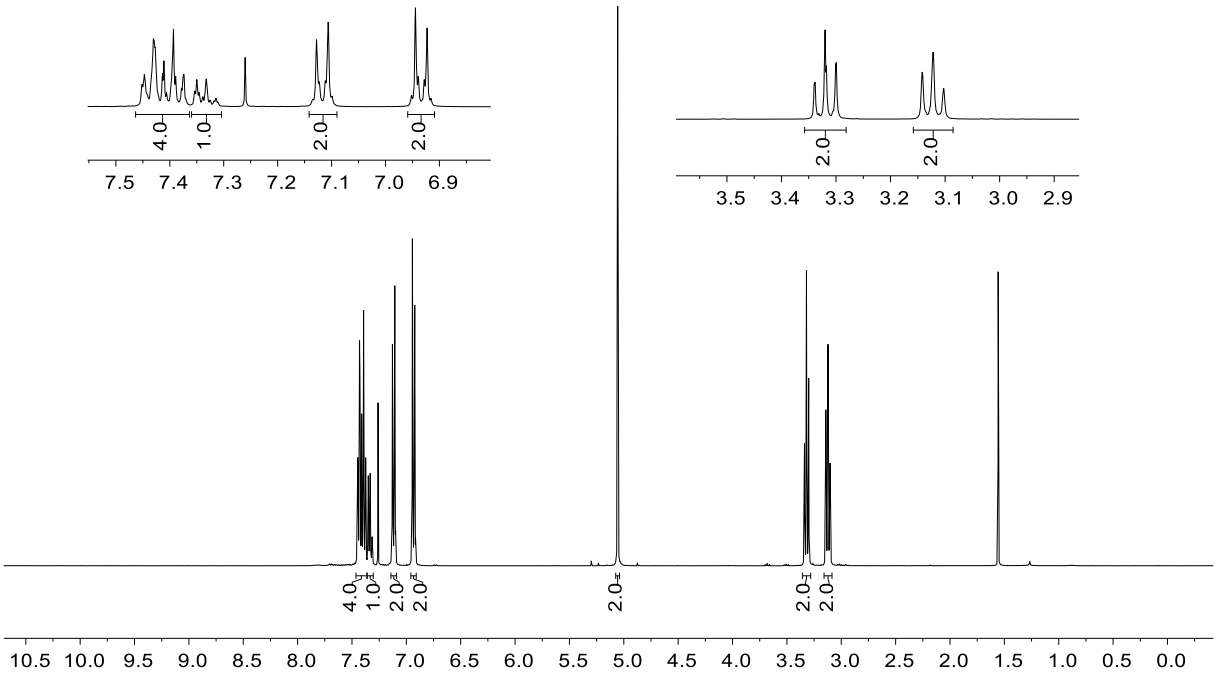
HRMS *m/z* (ESI) ); Calcd. for $C_{15}H_{15}OINa$ 361.0065, found 361.0040.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.44 (m, 2H, *o*-Ph), 7.39 (m, 2H, *m*-Ph), 7.33 (m, 1H, *p*-Ph), 7.12 (m, 2H, HC4), 6.93 (m, 2H, HC5), 5.06 (s, 2H, $H_2$C-Ph), 3.32 (m, 2H, $H_2$C1), 3.12 (t, $^3J_{HH}$ = 7.8 Hz, 2H, $H_2$C2).

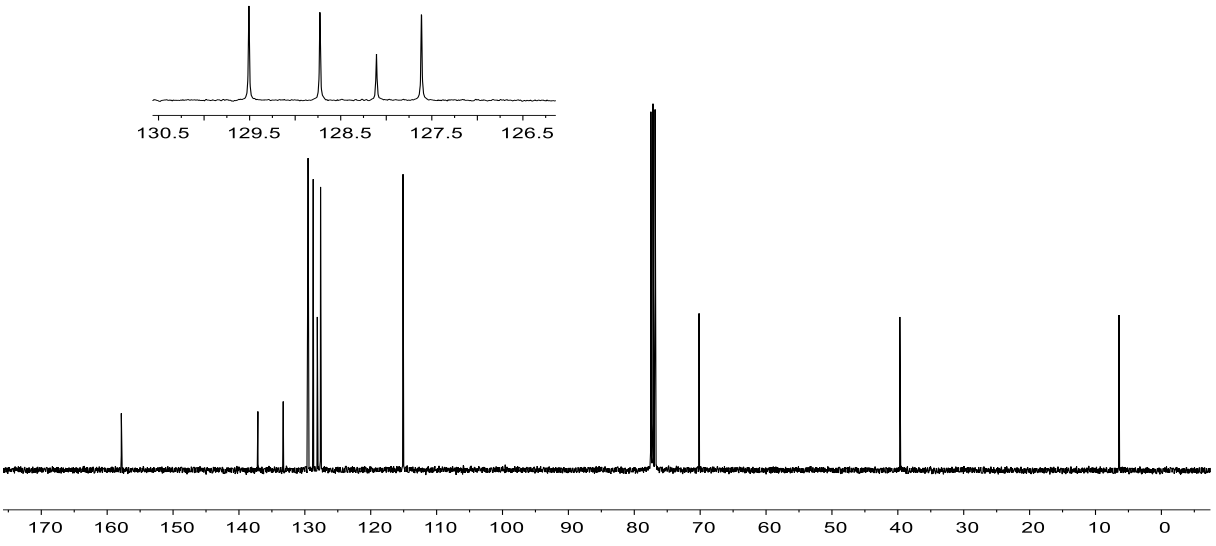
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 157.8 (C6), 137.1 (*i*-Ph), 133.3 (C3), 129.5 (C4), 128.7 (*m*-Ph), 128.1 (*p*-Ph), 127.6 (*o*-Ph), 115.1 (C5), 70.2 ($H_2$C-Ph), 39.7 (C2), 6.4 (C1).

IR (cm$^{-1}$): 3067 (w), 3026 (w), 2957 (w), 2931 (w), 2858 (w), 1960 (w), 1894 (w), 1824 (w), 1757 (w), 1653 (w), 1607 (m), 1580 (m), 1508 (m), 1450 (m), 1420 (w), 1385 (m), 1309 (m), 1297 (m), 1264 (m), 1252 (m), 1235 (m), 1168 (m), 1123 (m), 1080 (m), 1038 (m), 1027 (m), 973 (m), 929 (w), 906 (m), 858 (m), 832 (s), 818 (m), 777 (m), 734 (s), 696 (s).

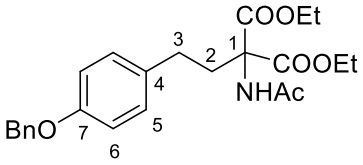
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**Diethyl 2-acetamido-2-(4-(benzyloxy)phenethyl)malonate (6)**




A flame dried schlenk flask was charged with NaH (60% in mineral oil, 290 mg, 7.20 mmol, 1.20 eq.), dry DMF (10 mL) and dimethyl acetamidomalonate (1.43 g, 6.60 mmol, 1.10 eq.) in DMF (10 mL). The mixture was stirred at room temperature for 45 min where after **5** (2.04 g, 6.00 mmol, 1.00 eq.) in DMF (20 mL) was added. The resulting mixture was then heated to and stirred at 95 °C for 40 h. After cooling down to room temperature the solvent was removed *in vacuo*. The residue was dissolved in 5% aq. LiCl and extracted with EtOAc (x 3). The combined organic layers were then washed (5% aq. LiCl), dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by flash chromatography (DCM : MeOH / 125 : 1) and was afforded as a white solid (1.61 g, 63%).

M.p.: 126 °C.

$R_f$ 0.24 (CyH : EtOAc / 2 : 1).

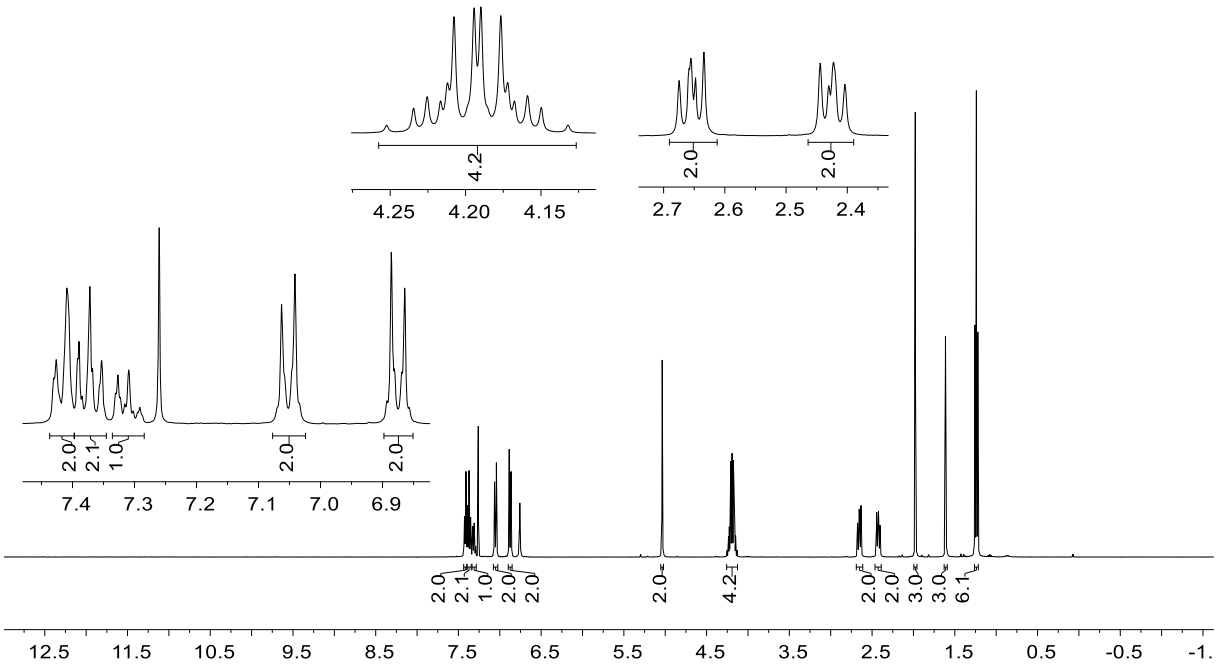
HRMS *m/z* (ESI); Calcd. for $C_{24}H_{29}NO_6Na$ 450.1887, found 450.1889.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.42 (m, 2H, *o*-Ph), 7.37 (m, 2H, *m*-Ph), 7.31 (m, 1H, *p*-Ph), 7.05 (m, 2H, HC5), 6.87 (m, 2H, HC6), 6.76 (s, 1H, HN), 5.04 (s, 2H, $H_2$C-Ph), [4.21, 4.17 (each dq, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 7.1 Hz, each 2H)](OEt), 2.65 (m, 2H, $H_2$C2), 2.42 (m, 2H, $H_2$C3), 1.98 (s, 3H, Ac), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 6H, OEt).

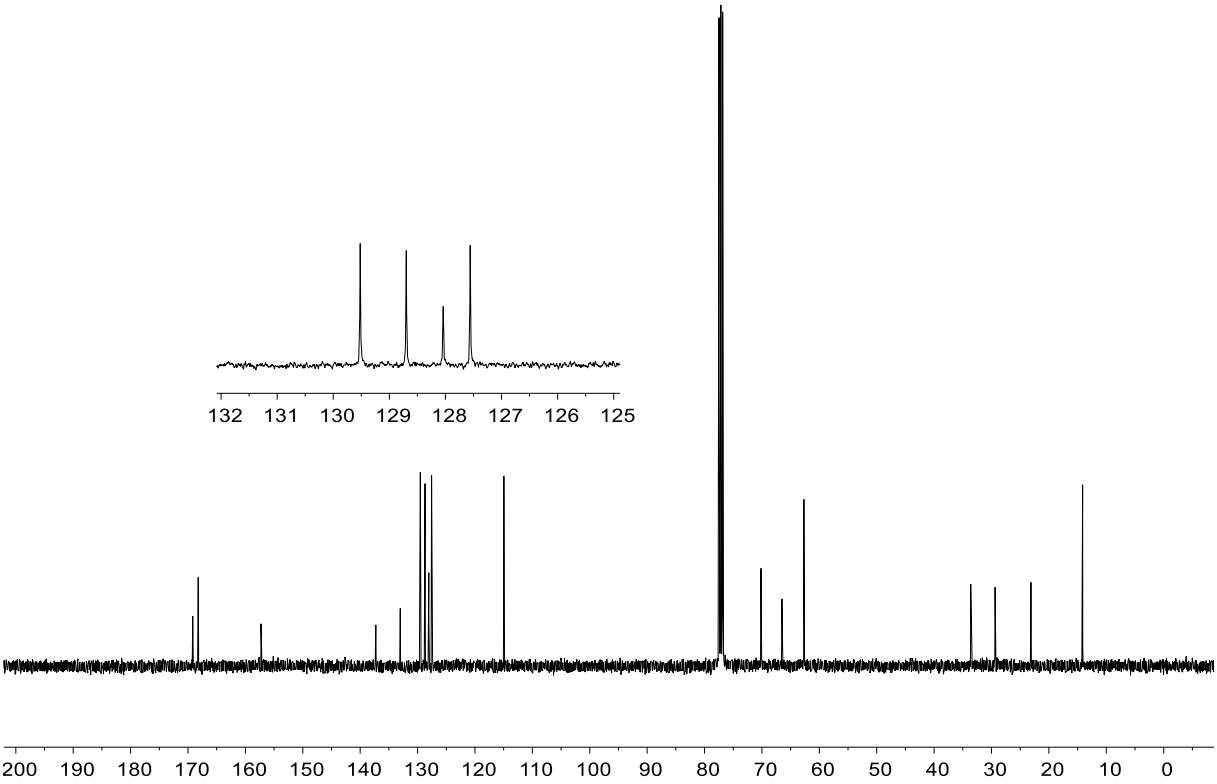
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 169.2 (Ac), 168.2 (C=O), 157.3 (C7), 137.3 (*i*-Ph), 133.0 (C4), 129.5 (C5), 128.7 (*m*-Ph), 128.0 (*p*-Ph), 127.6 (*o*-Ph), 115.0 (C6), 70.2 ($H_2$C-Ph), 66.5 (C1), 62.7 (OEt), 33.6 (C2), 29.4 (C3), 23.1 (Ac), 14.1 (OEt).

IR (cm$^{-1}$): 3675 (w), 3482 (w), 3251 (w), 2988 (m), 2971 (m), 2940 (w), 2902 (w), 1884 (w), 1759 (w), 1740 (s), 1639 (m), 1608 (w), 1584 (w), 1508 (m), 1474 (w), 1462 (w), 1443 (w), 1407 (w), 1393 (w), 1383 (m), 1288 (m), 1257 (m), 1231 (s), 1209 (m), 1183 (s), 1175 (s), 1159 (m), 1114 (w), 1080 (m), 1069 (m), 1033 (m), 1012 (m), 980 (w), 925 (w), 868 (m), 840 (w), 821 (m), 780 (w), 760 (w), 743 (m), 725 (w), 705 (m), 678 (m), 655 (w).

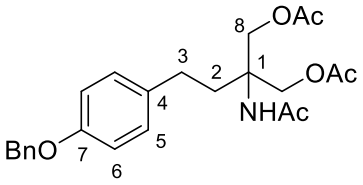
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-(benzyloxy)phenethyl)propane-1,3-diyl diacetate (7)**




To a flask containing THF (20 mL), **6** (1.60 g, 3.37 mmol, 1.00 eq.) was added and the resulting solution was cooled to 0 °C. LiCl (791 mg, 18.7 mmol, 5.00 eq.) and $NaBH_4$ (707 mg, 18.7 mmol, 5.00 eq.) were then added and the mixture was stirred at 0 °C for 15 min where after EtOH (40 mL) was added. The resulting mixture was stirred at 0 °C for 20 min and then at room temperature for 2.5 d. The pH of the reaction mixture was then adjusted to 3 by the addition of 10% aq. citric acid. The THF was then removed *in vacuo* and the residue was extracted with DCM (x 3), washed (brine), dried ($Na_2SO_4$) and concentrated under reduced pressure leaving a white solid. The solid was dissolved in THF (25 mL) and $Ac_2O$ (1.30 mL, 14.2 mmol, 4.00 eq.), $Et_3N$ (2.00 mL, 14.2 mmol, 4.00 eq.) and DMAP (22 mg, 0.18 mmol, 0.05 eq.) and the mixture was stirred at room temperature for 3 d. Water was then added and the mixture was extracted with EtOAc (x 3), washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was obtained as a white solid (1.13 g, 79%).

M.p.: 142 °C.

$R_f$ 0.72 (EtOAc).

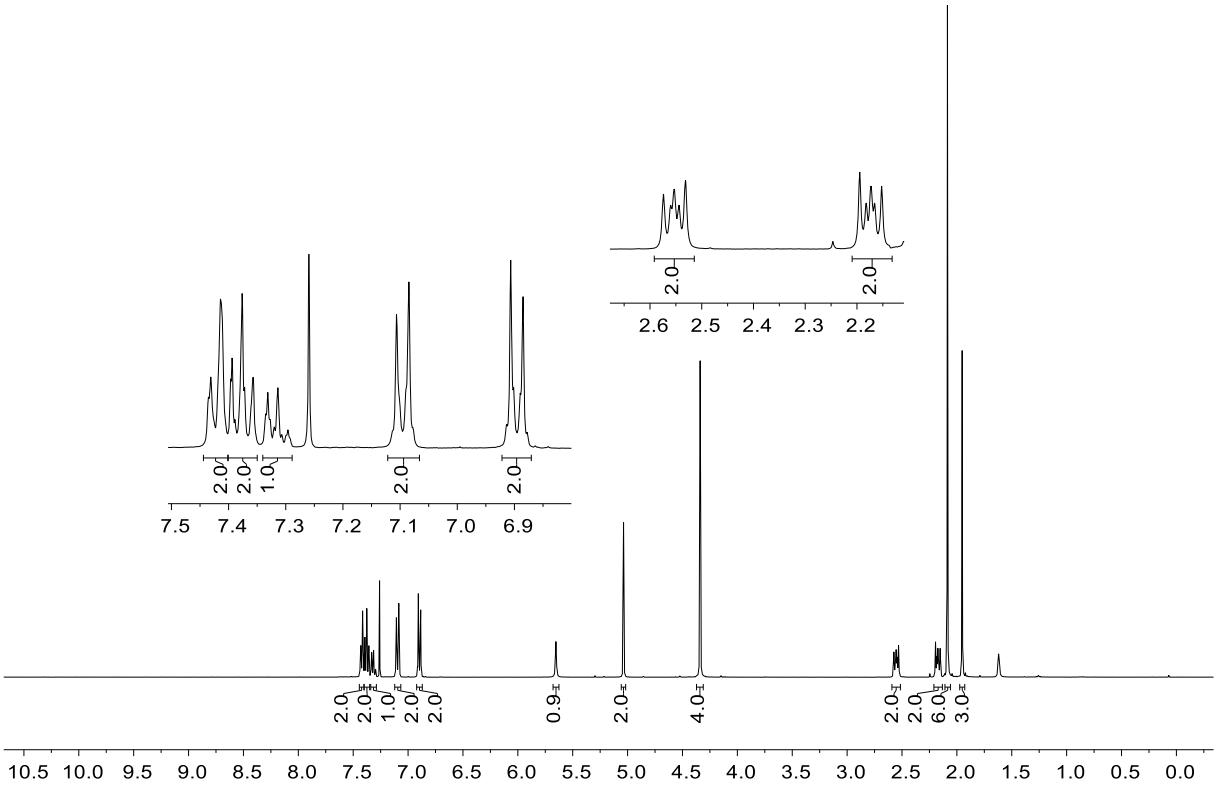
HRMS *m/z* (ESI); Calcd. for $C_{24}H_{29}NO_6Na$ 450.1887, found 450.1907.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.42 (m, 2H, *o*-Ph), 7.38 (m, 2H, *m*-Ph), 7.31 (m, 1H, *p*-Ph), 7.09 (m, 2H, HC5), 6.90 (m, 2H, HC6), 5.65 (s, 1H, HN), 5.04 (s, 2H, $H_2$C-Ph), 4.34 (s, 4H, $H_2$C8), 2.55 (m, 2H, $H_2$C3), 2.17 (m, 2H, $H_2$C2), 2.09 (s, 6H, OAc), 1.95 (s, 3H, NAc).

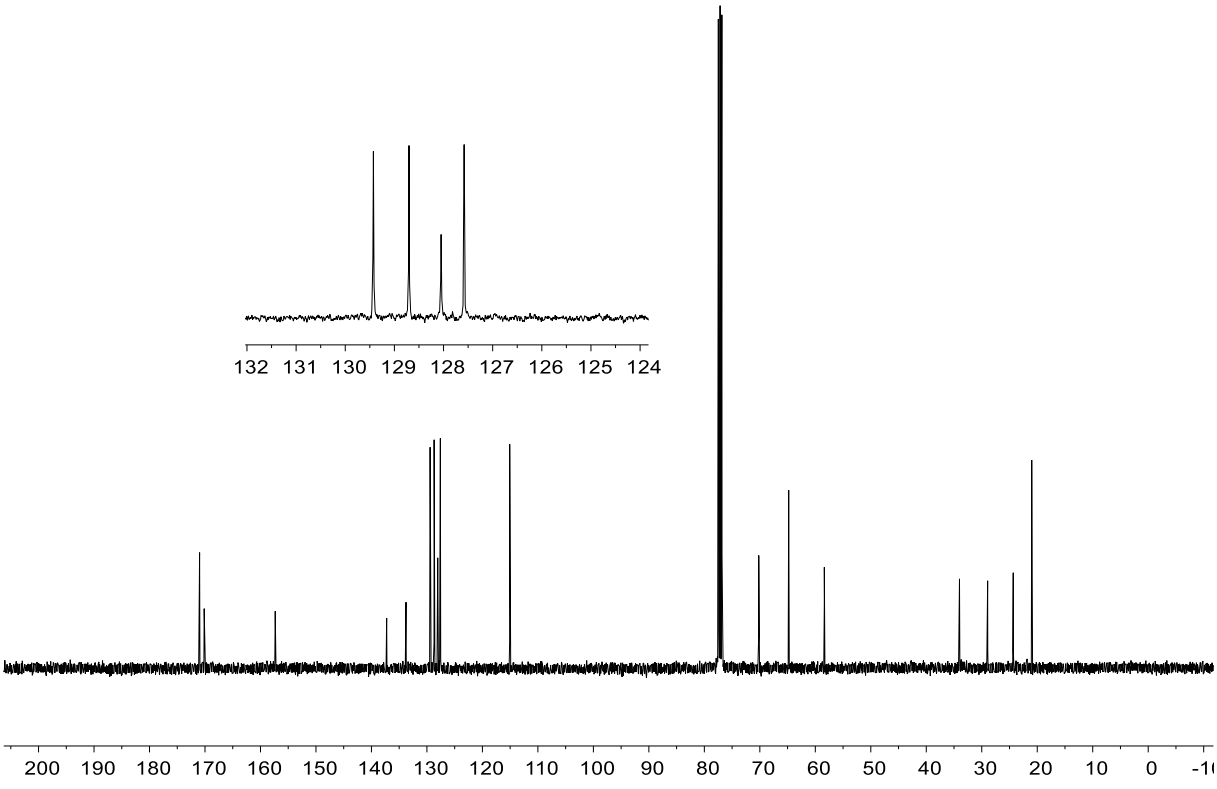
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.1 (NAc), 157.3 (C7), 137.3 (*i*-Ph), 133.8 (C4), 129.4 (C5), 128.7 (*m*-Ph), 128.0 (*p*-Ph), 127.6 (*o*-Ph), 115.1 (C6), 70.2 ($H_2$C-Ph), 64.8 (C8), 58.4 (C1), 34.0 (C2), 28.9 (C3), 24.3 (NAc), 21.0 (OAc).

IR (cm$^{-1}$): 3315 (w), 3077 (w), 3037 (w), 2963 (w), 2865 (w), 1891 (w), 1734 (m), 1696 (w), 1651 (m), 1615 (w), 1586 (w), 1552 (m), 1513 (m), 1467 (w), 1456 (m), 1428 (w), 1378 (m), 1316 (w), 1299 (w), 1246 (m), 1220 (s), 1187 (m), 1178 (m), 1162 (w), 1126 (w), 1102 (w), 1042 (m), 1029 (m), 984 (w), 966 (w), 919 (w), 847 (w), 823 (m), 815 (m), 782 (w), 733 (m), 697 (m), 653 (w), 628 (m), 621 (m), 600 (m), 578 (m), 569 (w), 548 (w), 527 (m), 523 (m).

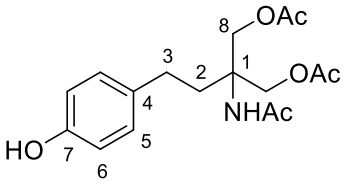
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)



$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-hydroxyphenethyl)propane-1,3-diyl diacetate (8)**




A flask was charged with **7** (428 mg, 1.00 mmol, 1.00 eq.), Pd/C (43 mg, 10 wt%) and EtOH (10 mL). The air in the flask was first evacuated with vacuum and then back filled with argon. This procedure was repeated 3 times where after the atmosphere was changed to $H_2$ (2 balloons). The mixture was then stirred at room temperature for 45 h. The reaction mixture was filtered over a plug of celite and the filtrate was concentrated *in vacuo.* The product was purified by flash chromatography (EtOAc) and was obtained as a white crystalline solid (309 mg, 92%).

M.p.: 94 °C.

$R_f$ 0.18 (CyH : EtOAc / 4 : 1).

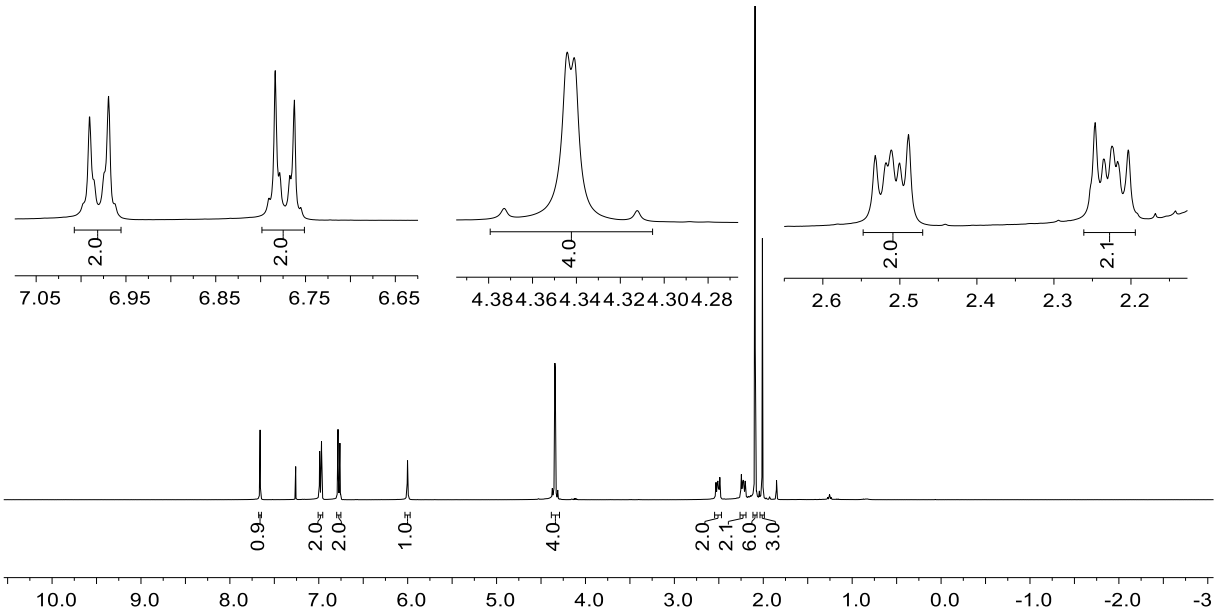
HRMS *m/z* (ESI); Calcd. for $C_{17}H_{23}NO_6Na$ 360.1423, found 360.1418.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.66 (s, 1H, OH), 6.98 (m, 2H, HC5), 6.77 (m, 2H, HC6), 6.00 (s, 1H, HN), [4.36, 4.33 (each d, $^2J_{HH}$ = 11.5 Hz, each 2H)]($H_2$C8), 2.51 (m, 2H, $H_2$C3), 2.22 (m, 2H, $H_2$C2), 2.09 (s, 6H, OAc), 2.01 (s, 3H, NAc).

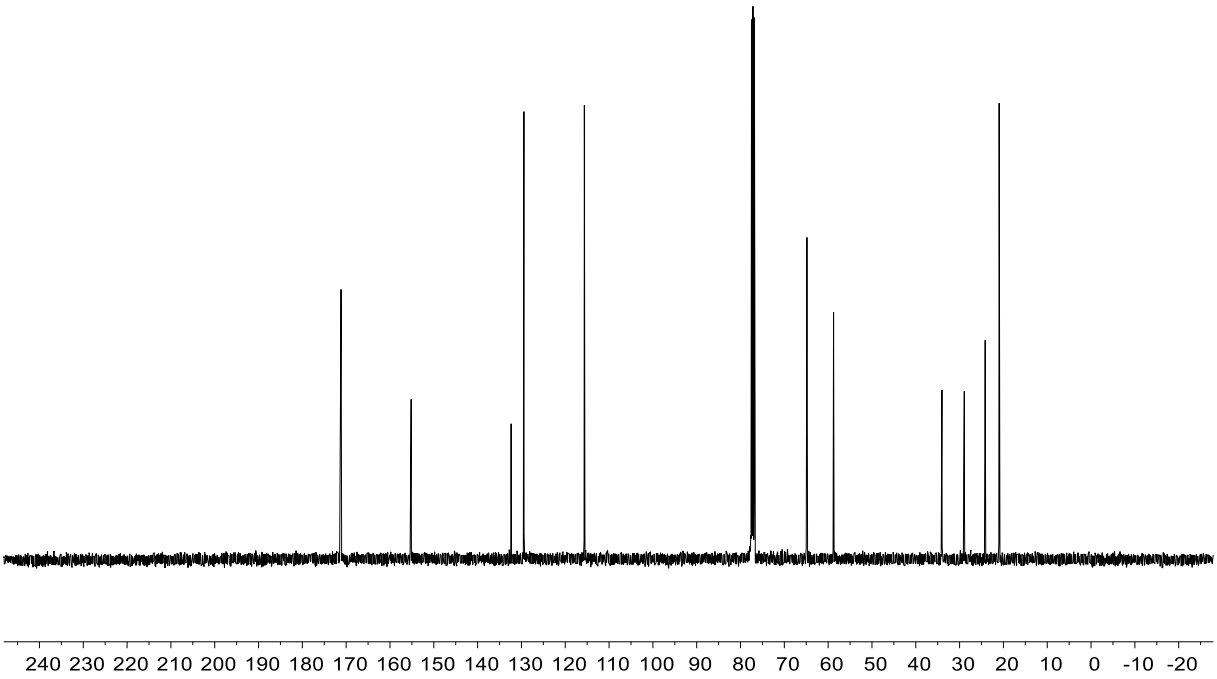
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 171.3 (NAc), 171.2 (OAc), 155.2 (C7), 132.4 (C4), 129.4 (C5), 115.6 (C6), 64.8 (C8), 58.8 (C1), 34.0 (C2), 28.9 (C3), 24.2 (NAc), 21.0 (OAc).

IR (cm$^{-1}$): 3349 (w), 3157 (w), 3010 (w), 2971 (w), 2942 (w), 2863 (w), 2820 (w), 2733 (w), 1745 (m), 1647 (m), 1613 (w), 1593 (w), 1547 (m), 1514 (m), 1471 (w), 1448 (m), 1375 (m), 1365 (m), 1316 (w), 1230 (s), 1170 (m), 1128 (w), 1095 (w), 1042 (m), 980 (w), 936 (w), 897 (w), 855 (w), 836 (w), 825 (w), 811 (m), 779 (m), 760 (m), 716 (w), 679 (w).

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K)



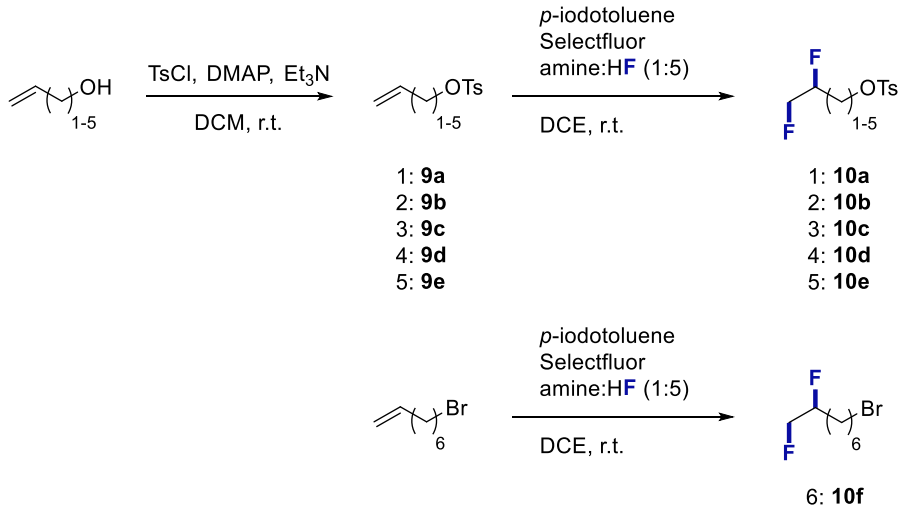
$^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*, 298 K)



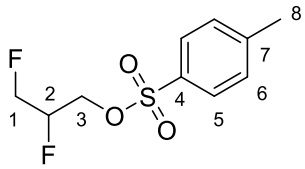
## II.5 Synthesis of 1,2-Difluorinated Fingolimod Analogues

### II.5.1 1,2-Difluorinated alkyl chains

**Scheme 2S.**




**2,3-Difluoropropyl 4-methylbenzenesulfonate (10a)**




The compound was synthesised from **9a** (106 mg, 0.50 mmol, 1.00 eq.) following **General Procedure 2** (see page S4) (reaction time: 3 d). The product was purified by flash chromatography (DCM : *n*-Pentane / 1 : 2 → 1 : 1.5) and was obtained as a colourless oil (60 mg, 48%).

$R_f$ 0.41 (DCM : *n*-Pentane / 1 : 1).

HRMS *m/z* (ESI); Calcd. for $C_{10}H_{12}O_3SF_2Na$ 273.0373, found 273.0377.

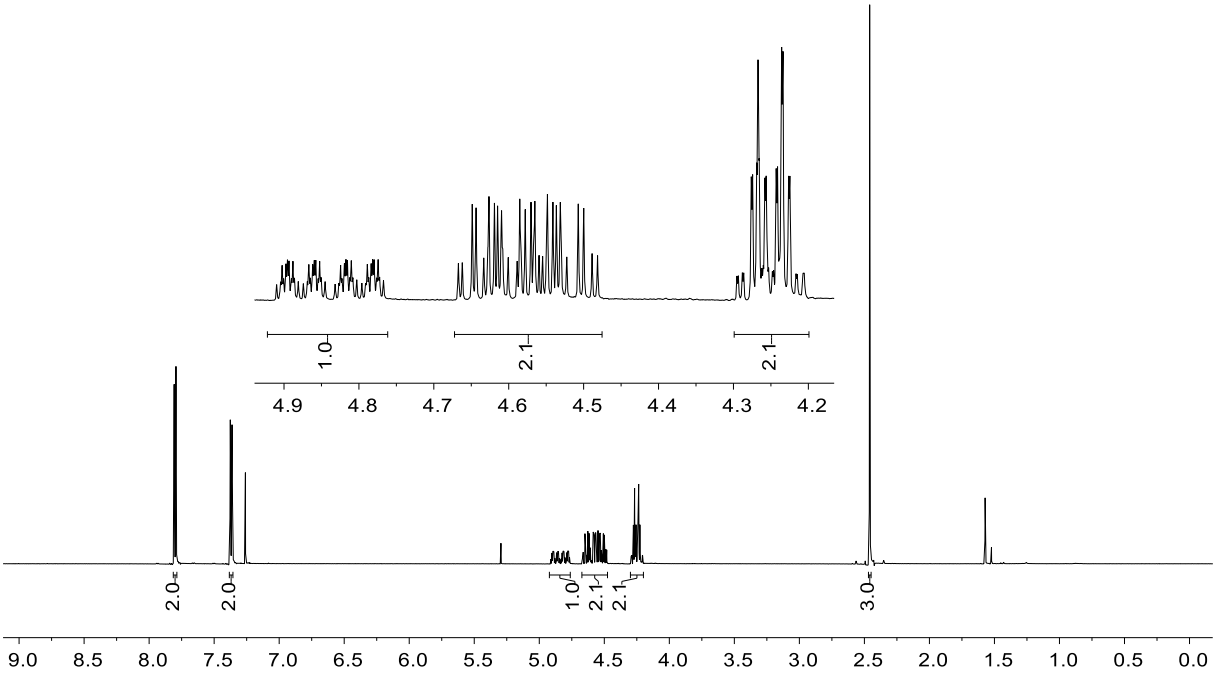
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.80 (m, 2H, HC5), 7.37 (m, 2H, HC6), 4.84 (ddddd, $^2J_{FH}$ = 46.8 Hz, $^3J_{FH}$ = 21.4 Hz, $^3J_{HH}$ = 5.6, 4.4, 4.3, 3.1 Hz, 1H, HC2), [4.60 (dddd, $^2J_{FH}$ = 46.9 Hz, $^3J_{FH}$ = 20.4 Hz, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 4.55 (dddd, $^2J_{FH}$ = 46.9 Hz, $^3J_{FH}$ = 24.7 Hz, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 4.4 Hz, 1H)]($H_2$C1), [4.26 (dddd, $^3J_{FH}$ = 19.8 Hz, $^2J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 4.3 Hz, $^4J_{FH}$ = 1.1 Hz, 1H), 4.24 (dddd, $^3J_{FH}$ = 18.9 Hz, $^2J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 5.6 Hz, $^4J_{FH}$ = 1.1 Hz, 1H)]$H_2$C3), 2.46 (s, 3H, $H_3$C8).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 145.6 (C7), 132.4 (C4), 130.2 (C6), 128.1 (C5), 88.2 (dd, $^1J_{FC}$ = 179.6 Hz, $^2J_{FC}$ = 20.7 Hz, C2), 81.0 (dd, $^1J_{FC}$ = 174.2 Hz, $^2J_{FC}$ = 23.7 Hz, C1), 66.8 (dd, $^2J_{FC}$ = 26.3 Hz, $^3J_{FC}$ = 8.1 Hz, C3), 21.8 (C8).

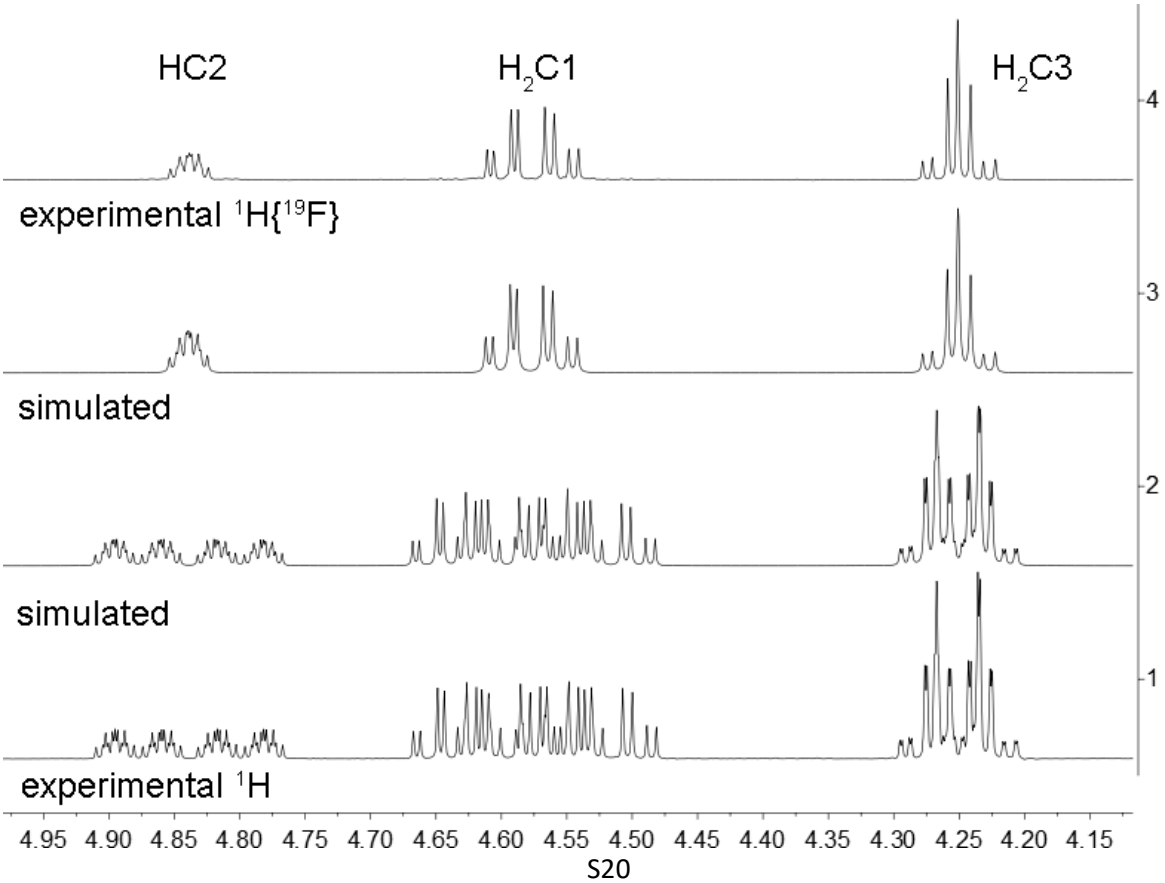
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -197.2 (dddddd, $^2J_{FH}$ = 46.8 Hz, $^3J_{FH}$ = 24.7, 20.4, 19.8, 18.9 Hz, $^3J_{FF}$ = 13.4 Hz, 1F, FC2), -235.3 (tddt, $^2J_{FH}$ = 46.9 Hz, $^3J_{FH}$ = 21.4 Hz, $^3J_{FF}$ = 13.4 Hz, $^4J_{FH}$ = 1.1 Hz, 1F, FC1).

IR ($cm^{-1}$): 2960 (w), 1598 (w), 1496 (w), 1454 (w), 1401 (w), 1360 (m), 1309 (w), 1293 (w), 1259 (w), 1212 (w), 1191 (m), 1175 (s), 1111 (m), 1096 (m), 1033 (m), 1019 (m), 1003 (m), 981 (m), 930 (m), 870 (m), 811 (s), 789 (m), 705 (w), 676 (m), 666 (s).

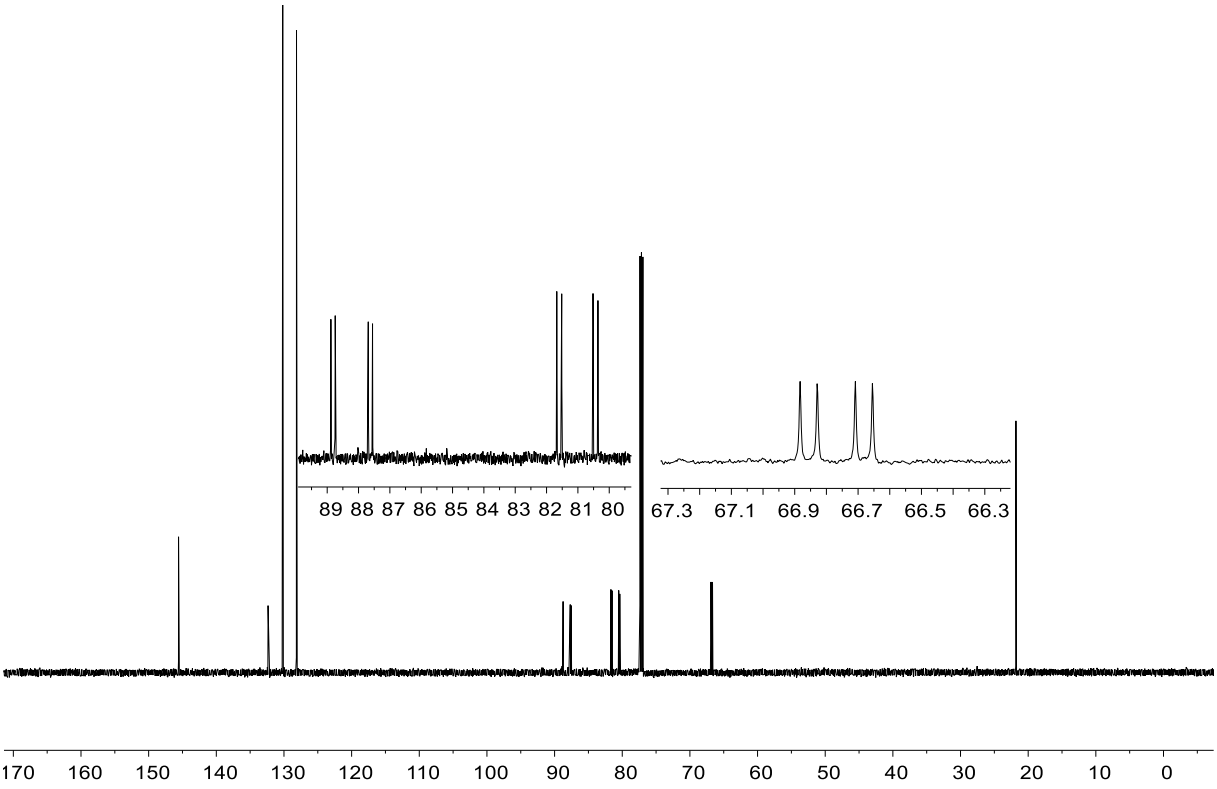
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K)



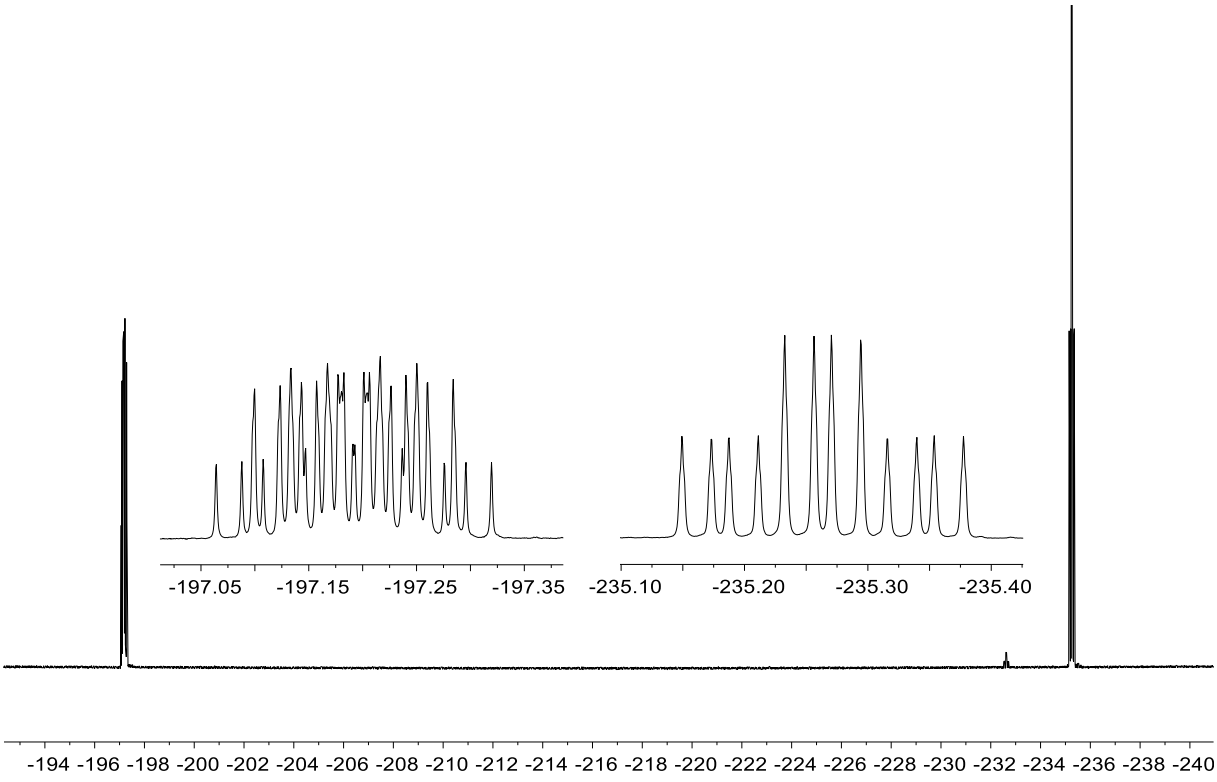

(1) Experimental $^1$H NMR (600 MHz, Chloroform-*d*, 298 K) and (4) $^1$H{$^{19}$F} NNMR spectra. (2,3) Simulated $^1$H NMR spectra (MestReNova 12.0.0-20080, 2017-09-26, 2017 Mestrelab Research S.L.) using the extracted experimental NMR data.



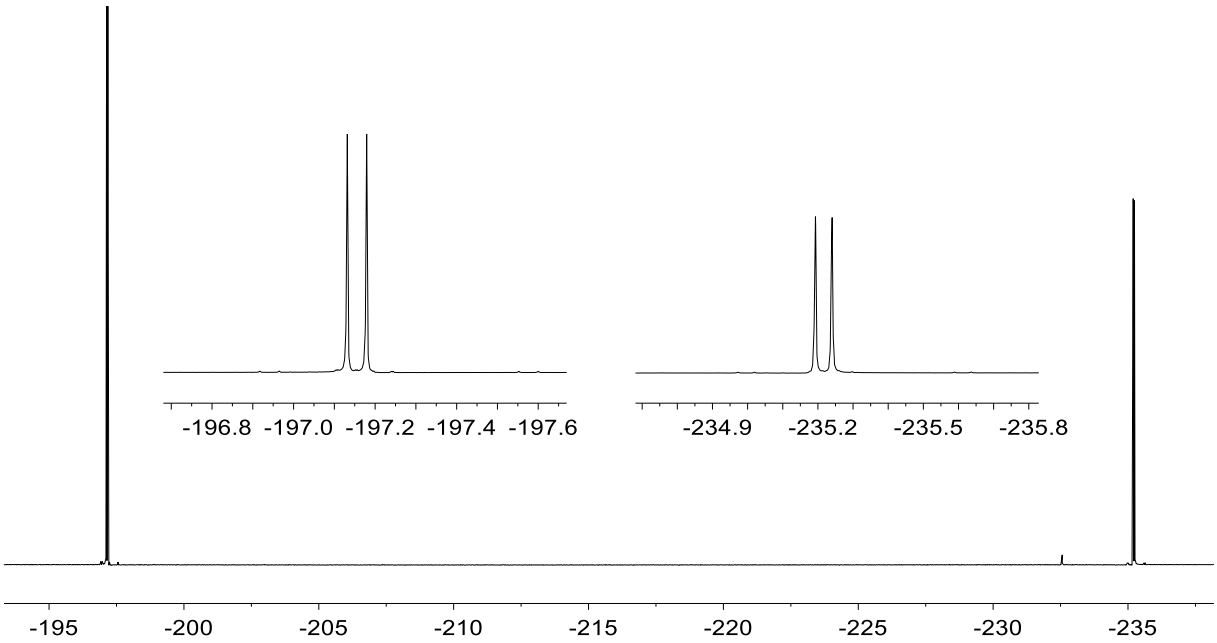
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)



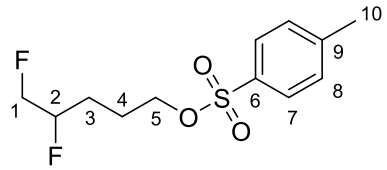

$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K)



$^{19}F\{^{1}H\}$ NMR (282 MHz, Chloroform-*d*, 298 K)




**4,5-Difluoropentyl 4-methylbenzenesulfonate (10c)**




The product was synthesised from **9c** (111 mg, 0.46 mmol, 1.00 eq.) following **General Procedure 2** (see page S4) (reaction time: 2.5 d). The product was purified *via* flash chromatography (CyH : EtOAc / 10 : 1) and was obtained as a colourless oil (92 mg, 72%).

$R_f$ 0.18 (CyH : EtOAc / 4 : 1).

HRMS *m/z* (ESI): Calcd. for $C_{12}H_{16}O_3SF_2Na$ 301.0680, found 301.0695.

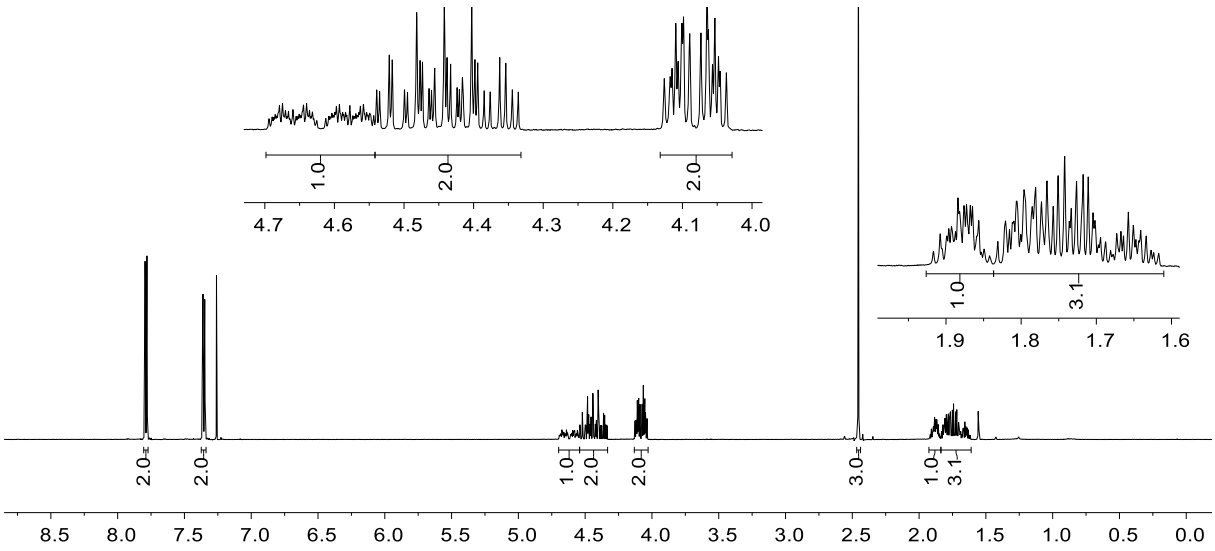
$^{1}H$ NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.79 (m, 2H, HC7), 7.35 (m, 2H, HC8), 4.62 (ddm, $^{2}J_{FH}$ = 49.2 Hz, $^{3}J_{FH}$ = 20.8 Hz, 1H, HC2), [4.47 (dddd, $^{2}J_{FH}$ = 47.5 Hz, $^{3}J_{FH}$ = 24.0 Hz, $^{2}J_{HH}$ = 10.8 Hz, $^{3}J_{HH}$ = 2.6 Hz, 1H), 4.41 (dddd, $^{2}J_{FH}$ = 47.5 Hz, $^{3}J_{FH}$ = 24.2 Hz, $^{2}J_{HH}$ = 10.8 Hz, $^{3}J_{HH}$ = 5.3 Hz, 1H)]($H_2$C1), [4.11 (ddd, $^{2}J_{HH}$ = 10.0 Hz, $^{3}J_{HH}$ = 6.8, 5.2 Hz, 1H), 4.05 (ddd, $^{2}J_{HH}$ = 10.0 Hz, $^{3}J_{HH}$ = 6.8, 5.4 Hz, 1H)]($H_2$C5), 2.45 (s, 3H, $H_3$C10), [1.87 (m, 1H), 1.80 (m, 1H)]($H_2$C4), [1.74 (m, 1H), 1.67 (dm, $^{3}J_{FH}$ = 32.4 Hz, 1H)]$H_2$C3).

$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K) δ 145.1 (C9), 133.1 (C6), 130.1 (C8), 128.0 (C7), 91.0 (dd, $^{1}J_{FC}$ = 173.6 Hz, $^{2}J_{FC}$ = 19.6 Hz, C2), 83.9 (dd, $^{1}J_{FC}$ = 174.3 Hz, $^{2}J_{FC}$ = 23.0 Hz, C1), 69.8 (C5), 26.4 (dd, $^{2}J_{FC}$ = 21.2 Hz, $^{3}J_{FC}$ = 6.6 Hz, C3), 24.6 (d, $^{3}J_{FC}$ = 4.1 Hz, C4), 21.8 (C10).

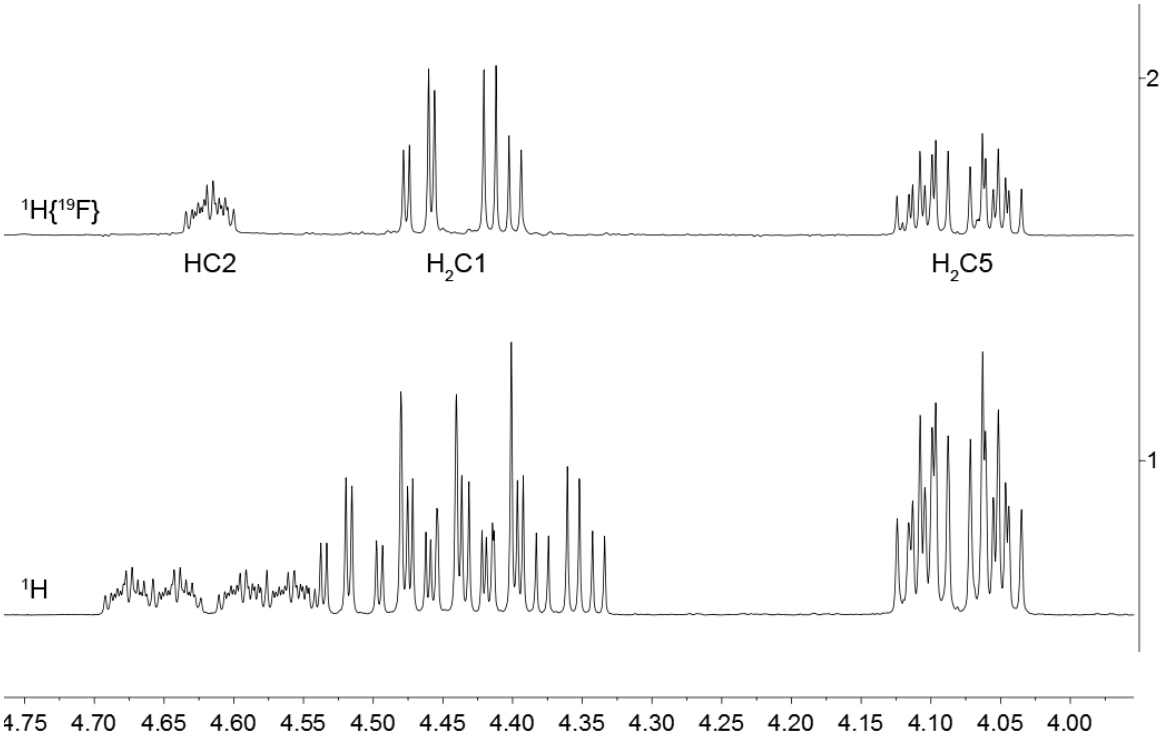
$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K) δ -190.9 (m, 1F, FC2), -230.5 (tdd, $^{2}J_{FH}$ = 47.5 Hz, $^{3}J_{FH}$ = 20.8 Hz, $^{3}J_{FF}$ = 13.4 Hz, 1F, FC1).

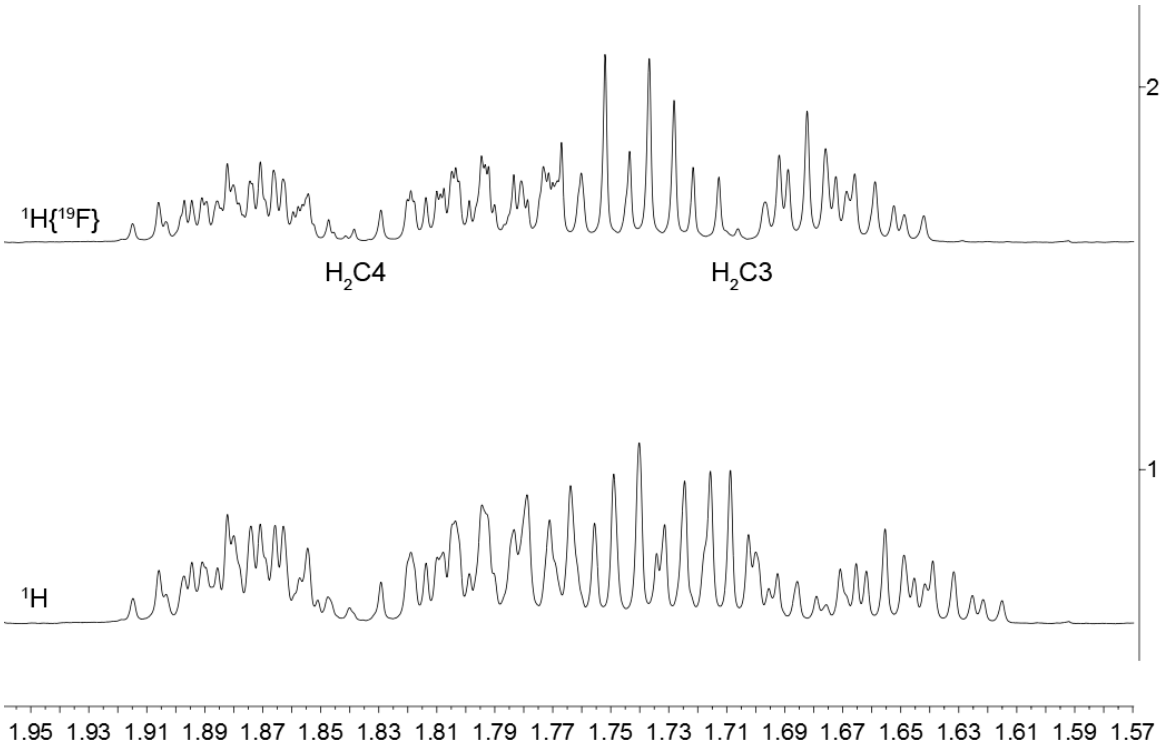
IR ($cm^{-1}$): 3664 (w), 2988 (m), 2971 (m), 2902 (m), 1928 (w), 1598 (w), 1496 (w), 1454 (w), 1404 (w), 1394 (w), 1354 (m), 1308 (w), 1292 (w), 1250 (w), 1242 (w), 1231 (w), 1189 (m), 1173 (s), 1097 (m), 1076 (m), 1066 (m), 1057 (m), 1028 (m), 962 (m), 915 (m), 861 (w), 814 (m), 792 (m), 737 (m), 706 (w), 689 (w), 661 (m).

$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)

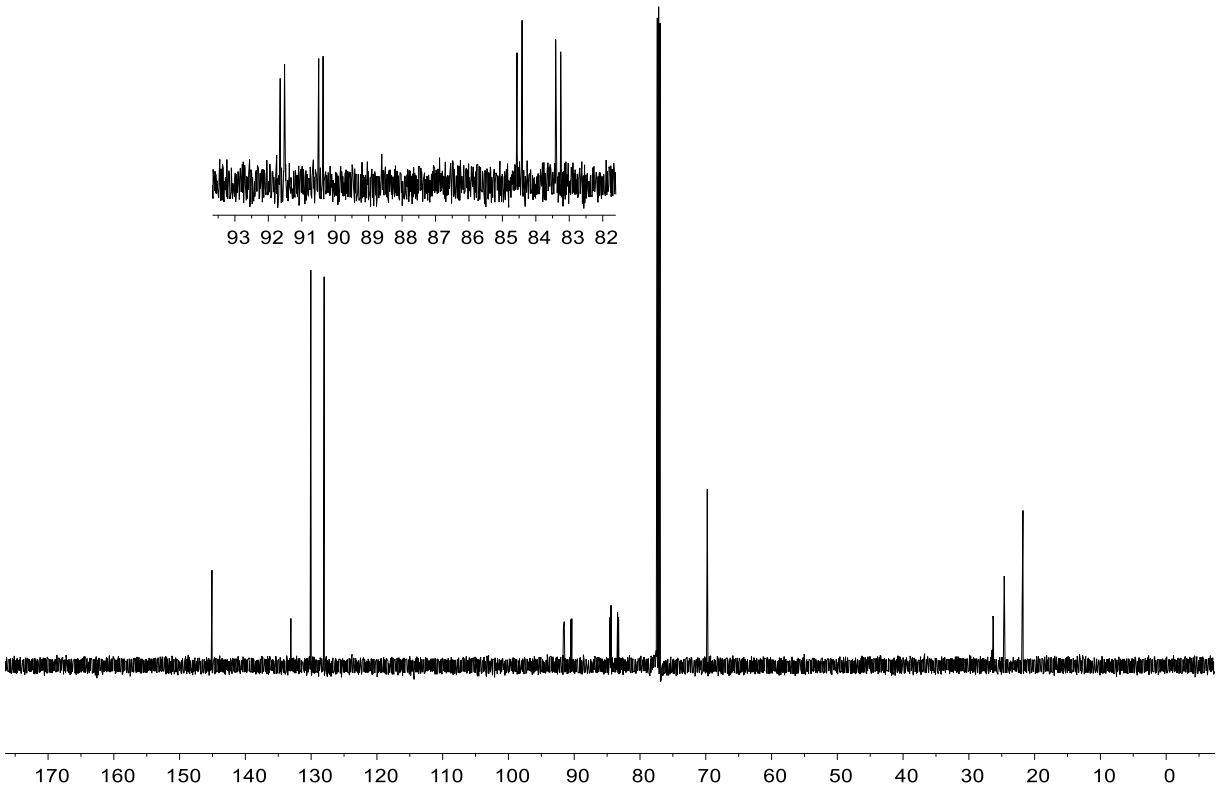


(1) $^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K) and (2) $^{1}$H{$^{19}$F} NMR spectra

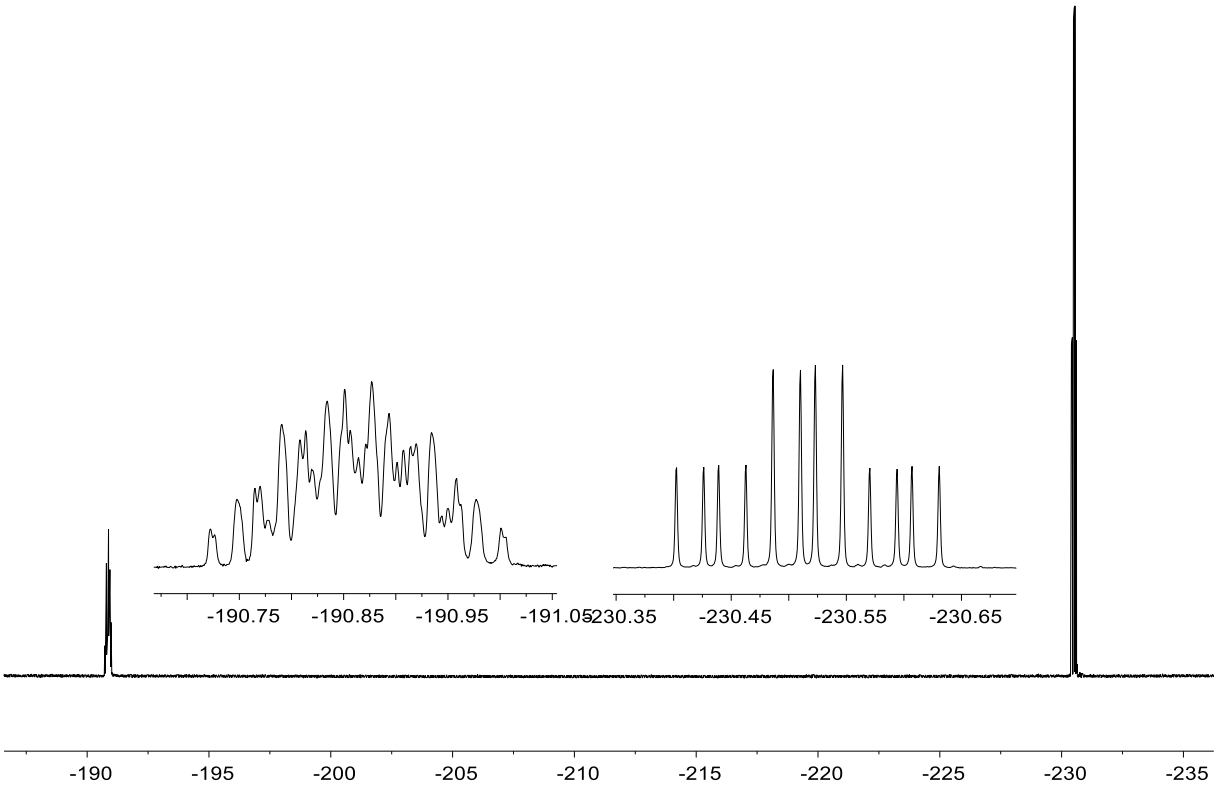




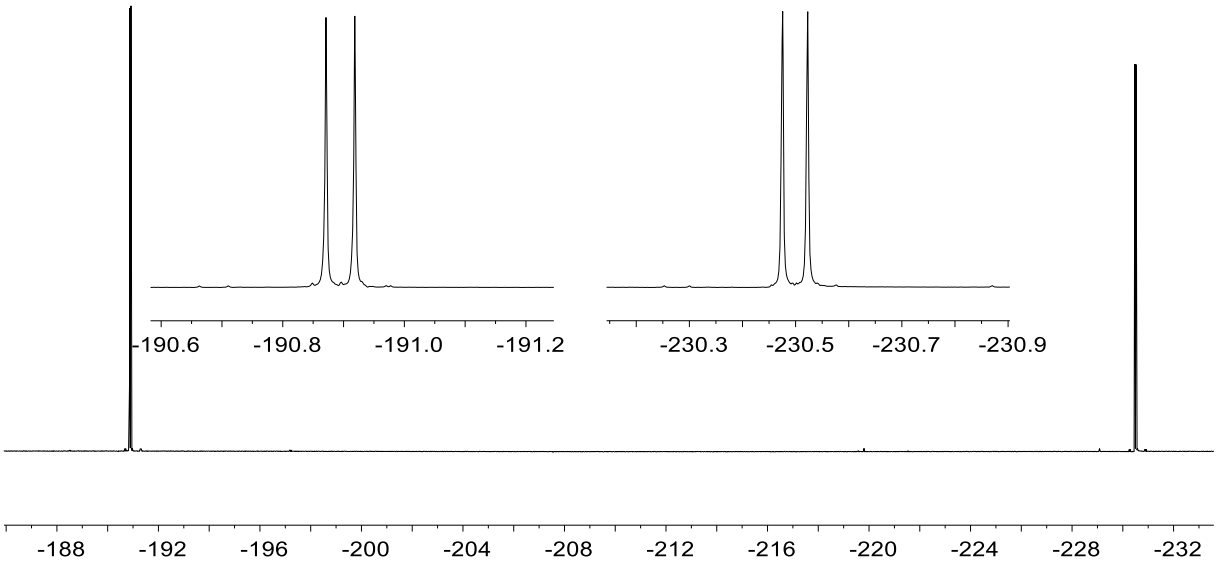

$^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)



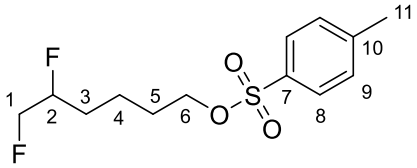
$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K)




$^{19}F\{^{1}H\}$ NMR (282 MHz, Chloroform-*d*, 298 K)



**5,6-Difluorohexyl 4-methylbenzenesulfonate (10d)**




The compound was synthesised from **9d** (134 mg, 0.50 mmol, 1.00 eq.) following **General Procedure 2** (see page S4) (reaction time: 2 d). The product was purified by flash chromatography (CyH : EtOAc / 7 : 1) and was obtained as a colourless oil (115 mg, 79%).

$R_f$ 0.26 (CyH : EtOAc / 3 : 1).

HRMS *m/z* (ESI); Calcd. for $C_{13}H_{18}O_3SF_2Na$ 315.0844, found 315.0842.

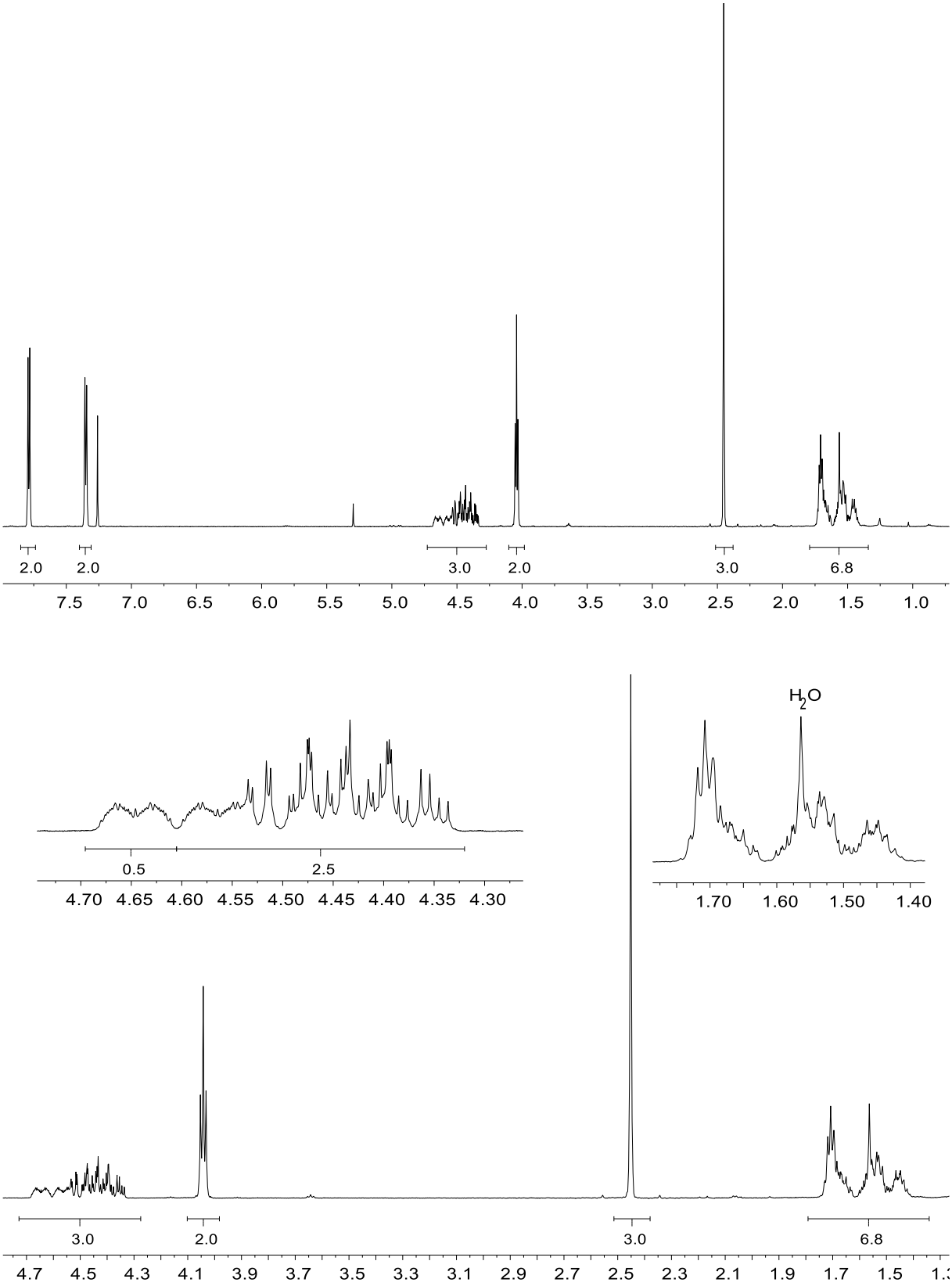
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.79 (m, 2H, HC8), 7.35 (m, 2H, HC9), 4.60 (ddm, $^2J_{FH}$ = 49.2 Hz, $^3J_{FH}$ = 20.6 Hz, 1H, HC2), [4.46 (dddd, $^2J_{FH}$ = 47.4 Hz, $^3J_{FH}$ = 24.4 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 2.5 Hz, 1H), 4.41 (dddd, $^2J_{FH}$ = 47.4 Hz, $^3J_{FH}$ = 24.1 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 5.4 Hz, 1H)]($H_2$C1), 4.04 (m, 2H, $H_2$C6), 2.45 (s, 3H, $H_3$C11), 1.71 (m, 2H, $H_2$C5), [1.67 (m, 1H), 1.55 (m, 1H)]($H_2$C3), [1.55 (m, 1H), 1.45 (m, 1H]($H_2$C4).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 145.0 (C10), 133.2 (C7), 130.0 (C9), 128.0 (C8), 91.5 (dd, $^1J_{FC}$ = 173.2 Hz, $^2J_{FC}$ = 19.4 Hz, C2), 84.0 (dd, $^1J_{FC}$ = 174.1 Hz, $^2J_{FC}$ = 23.1 Hz, C1), 70.1 (C6), 29.5 (dd, $^2J_{FC}$ = 21.1 Hz, $^3J_{FC}$ = 6.5 Hz, C3), 28.7 (C5), 21.8 (C11), 21.1 (d, $^3J_{FC}$ = 4.5 Hz, C4).

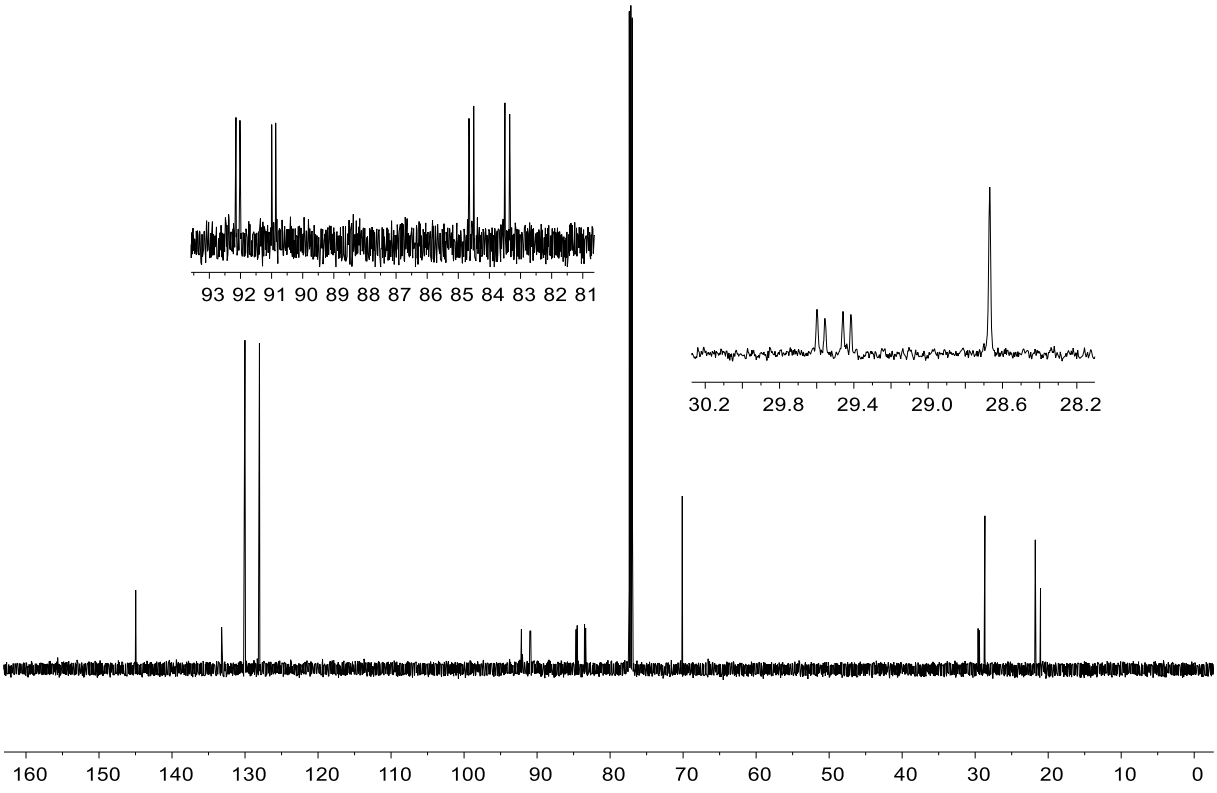
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -189.7 (m, 1F, FC2), -230.4 (tdd, $^2J_{FH}$ = 47.4 Hz, $^3J_{FH}$ = 20.6 Hz, $^3J_{FF}$ = 13.5 Hz, 1F, FC1).

IR (cm$^{-1}$): 2956 (w), 2874 (w), 1598 (w), 1496 (w), 1457 (w), 1354 (m), 1308 (w), 1292 (w), 1211 (w), 1189 (m), 1173 (s), 1097 (m), 1063 (w), 1020 (m), 997 (w), 962 (m), 926 (m), 833 (m), 815 (m), 774 (m), 730 (m), 706 (w), 689 (w), 662 (s).

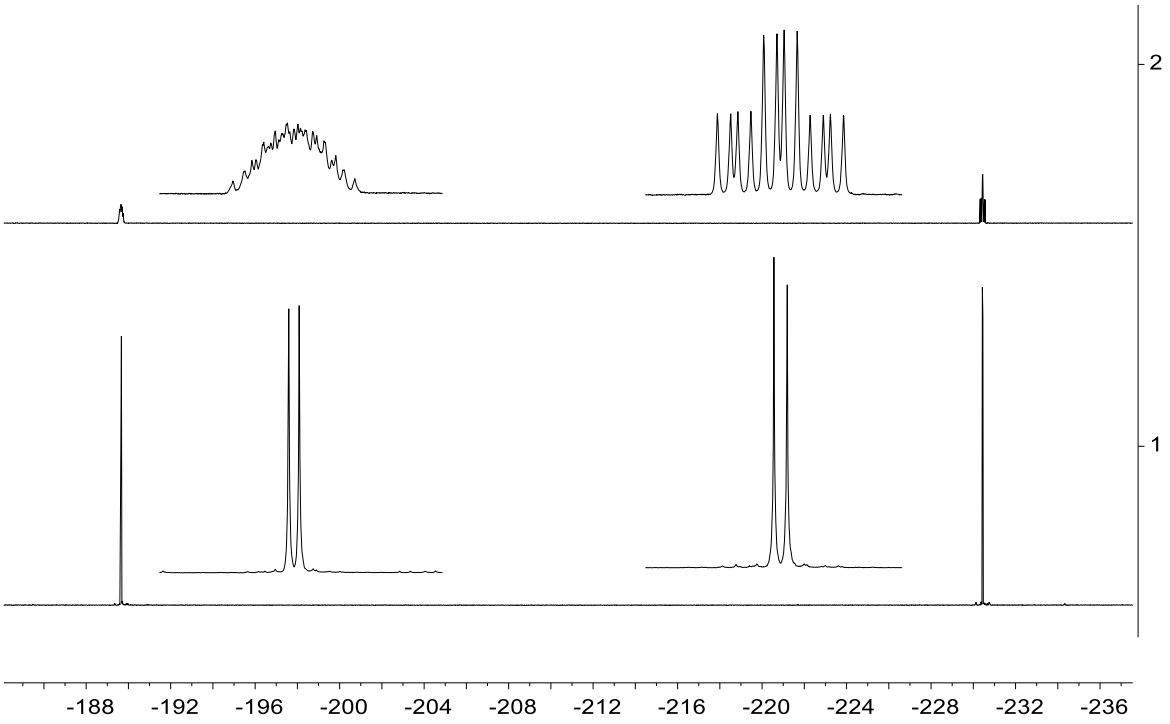
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



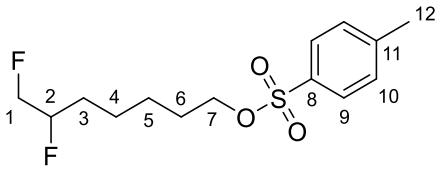
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




(1) $^{19}F\{^{1}H\}$ NMR (564 MHz, Chloroform-*d*, 298 K) and (2) $^{19}F$ NMR spectra



**6,7-Difluoroheptyl 4-methylbenzenesulfonate (10e)**




The compound was synthesised from **9e** (190 mg, 0.70 mmol, 1.00 eq.) following **General Procedure 2** (reaction time: 3 d). The crude was adsorbed to silica and the product was purified by flash chromatography (CyH : EtOAc / 7 : 1). The product was obtained as a colourless oil (117 mg, 55%).

$R_f$ 0.21 (CyH : EtOAc / 4 : 1).

HRMS *m/z* (ESI); Calcd. for $C_{14}H_{20}O_3SF_2Na$ 329.0999, found 329.1003.

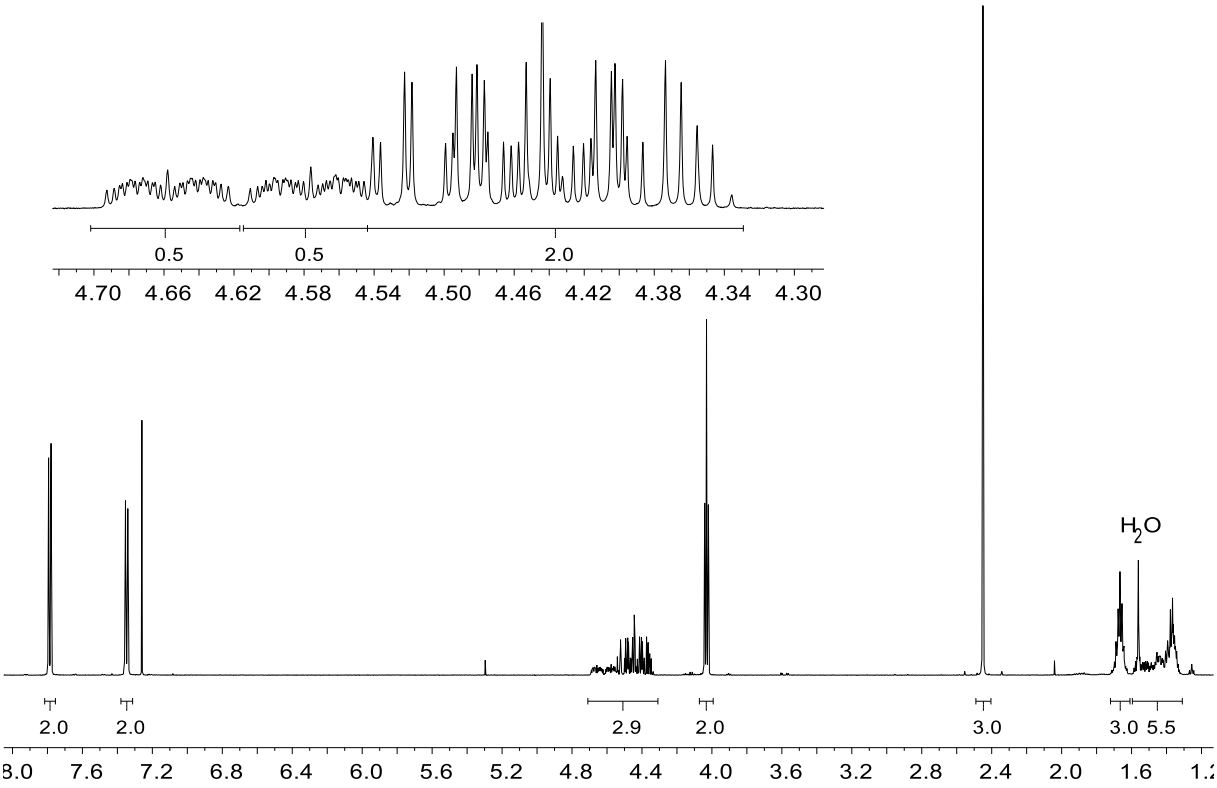
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.79 (m, 2H, HC9), 7.35 (m, 2H, HC10), 4.62 (ddm, $^2J_{FH}$ = 49.0 Hz, $^3J_{FH}$ = 20.7 Hz, 1H, HC2), [4.47 (dddd, $^2J_{FH}$ = 47.5 Hz, $^3J_{FH}$ = 24.9 Hz, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 2.5 Hz, 1H), 4.42 (dddd, $^2J_{FH}$ = 47.5 Hz, $^3J_{FH}$ = 23.9 Hz, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 5.5 Hz, 1H)]($H_2$C1), 4.03 (m, 2H, $H_2$C7), 2.45 (s, 3H, $H_3$C12), [1.67 (m, 1H), 1.53 (m, 1H)]($H_2$C3), 1.66 (m, 2H, $H_2$C6), [1.44 (m, 1H), 1.36 (m, 1H)]($H_2$C4), [1.39 (m, 1H), 1.36 (m, 1H)]($H_2$C5).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 144.9 (C11), 133.3 (C8), 130.0 (C10), 128.0 (C9), 91.6 (dd, $^1J_{FC}$ = 172.8 Hz, $^2J_{FC}$ = 19.4 Hz, C2), 84.1 (dd, $^1J_{FC}$ = 173.9 Hz, $^2J_{FC}$ = 23.1 Hz, C1), 70.4 (C7), 30.0 (dd, $^2J_{FC}$ = 21.0 Hz, $^3J_{FC}$ = 6.3 Hz, C3), 28.8 (C6), 25.3 (C5), 24.3 (d, $^3J_{FC}$ = 4.5 Hz, C4), 21.8 (C12).

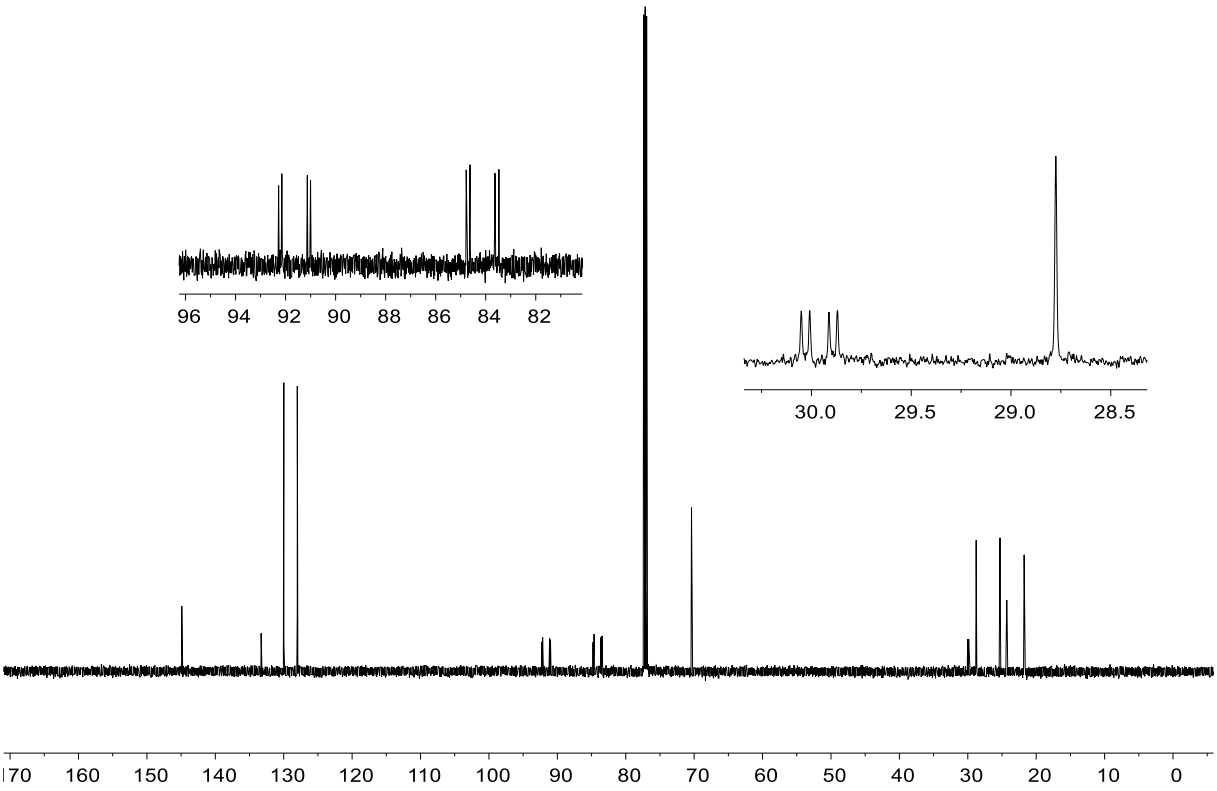
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -189.5 (m, 1F, FC2), -230.2 (tdd, $^2J_{FH}$ = 47.5 Hz, $^3J_{FH}$ = 20.7 Hz, $^3J_{FF}$ = 13.5 Hz, 1F, FC1).

IR (cm$^{-1}$): 2950 (w), 2866 (w), 1598 (w), 1496 (w), 1456 (w), 1354 (m), 1308 (w), 1292 (w), 1211 (w), 1189 (m), 1174 (s), 1120 (w), 1097 (m), 1042 (w), 1019 (w), 936 (m), 814 (m), 757 (m), 727 (w), 706 (w), 689 (w), 662 (s).

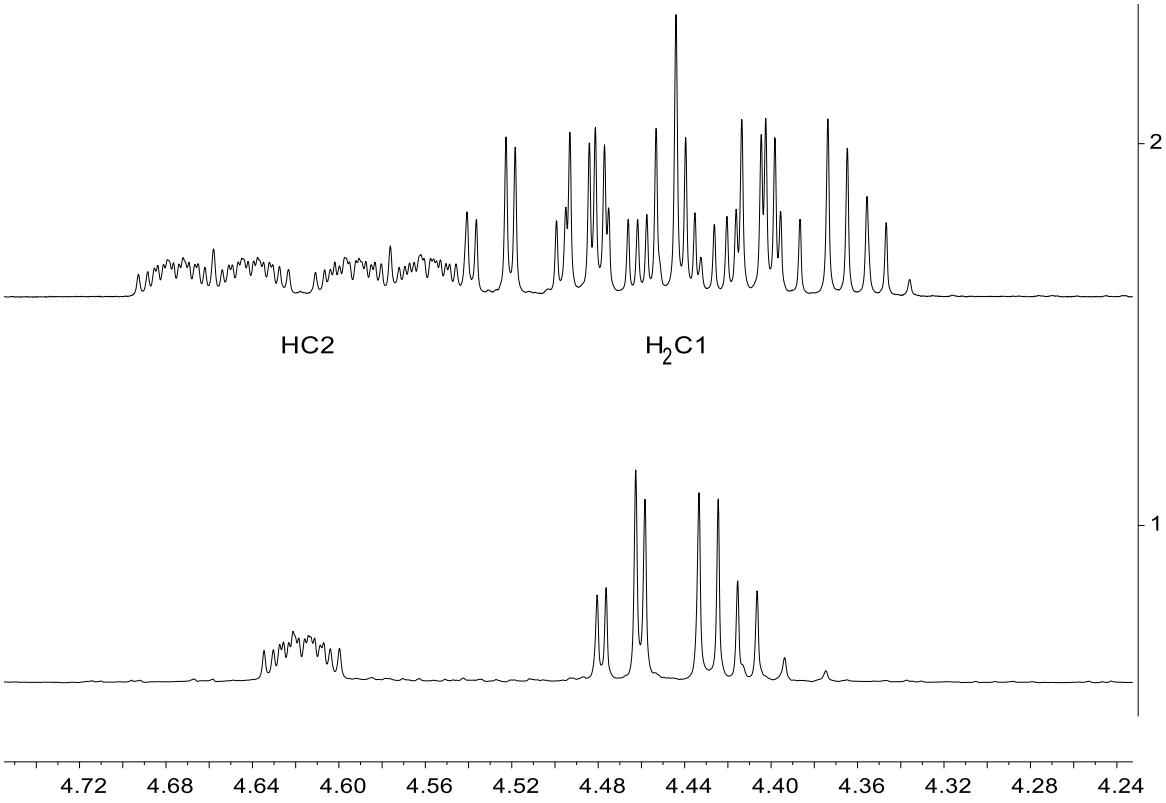
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



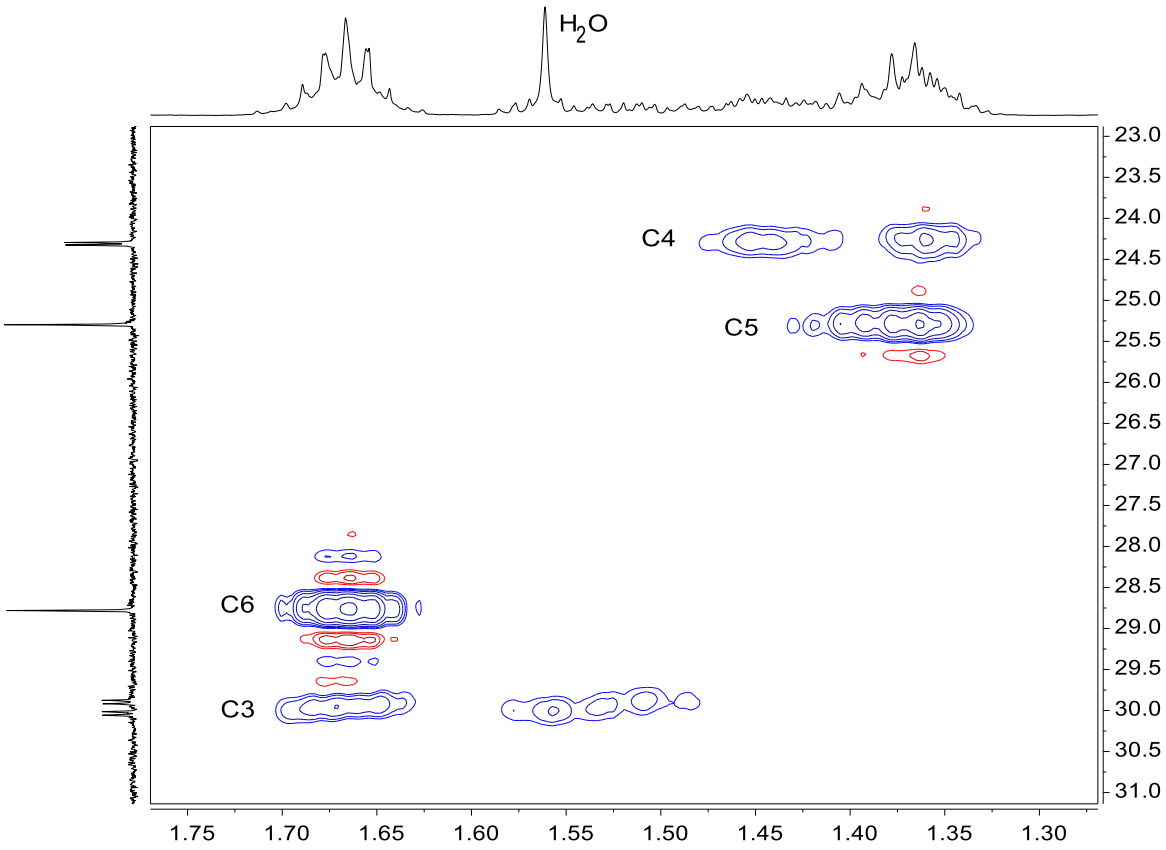

$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*, 298 K)



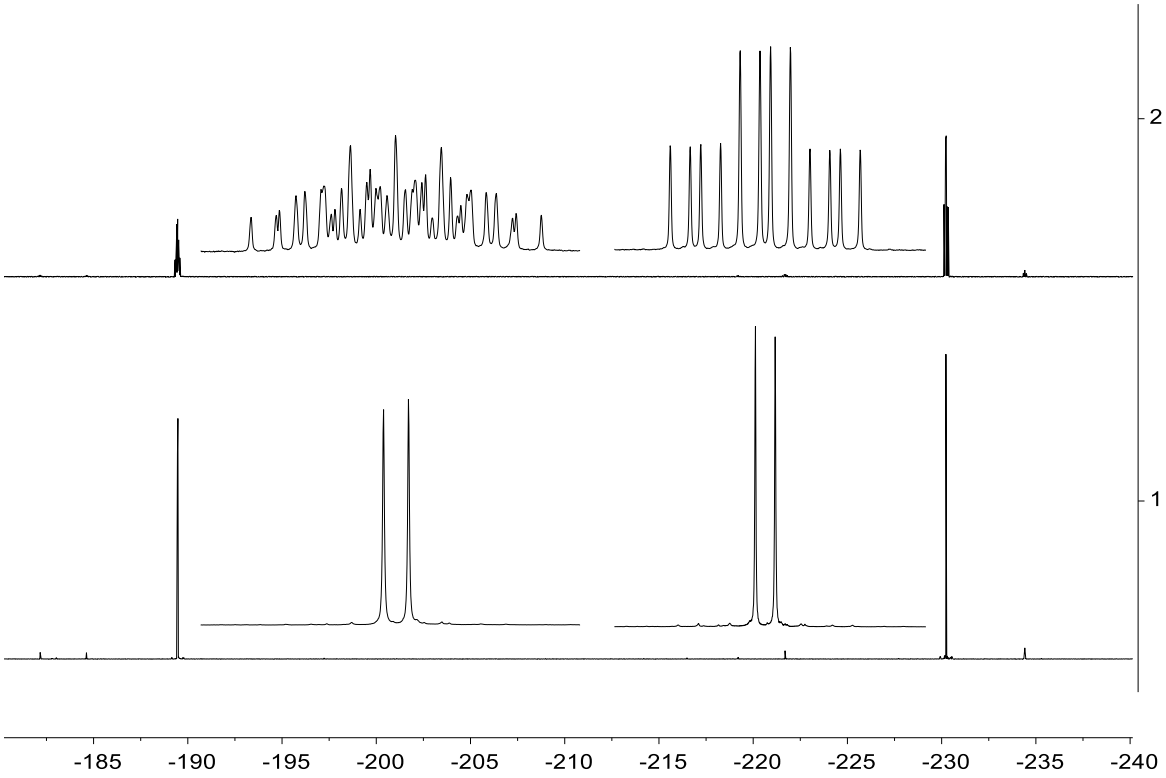
(1) $^{1}H\{^{19}F\}$ NMR (600 MHz, Chloroform-*d*, 298 K) and (2) $^{1}H$ NMR spectra



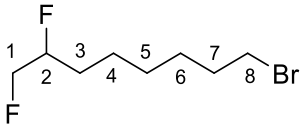

$^{1}H,^{13}C$ ghsqc (600/151 MHz, Chloroform-*d*, 298 K) spectrum



(1) $^{19}F\{^{1}H\}$ NMR (564 MHz, Chloroform-*d*, 298 K) and (2) $^{19}F$ NMR spectra




**8-Bromo-1,2-difluorooctane (10f)**




The compound was synthesised from 8-bromo-1-octene (0.18 mL, 1.50 mmol, 1.00 eq following **General Procedure 2** (see page S4) (reaction time: 18 h). The product was purified by flash chromatography (*n*-Pentane : $Et_2O$ / 20 : 1) and was obtained as a colourless oil (197 mg, 72%).

$R_f$ 0.41 (CyH : EtOAc / 14 : 1).

HRMS *m/z* (EI); Calcd. for $C_8H_{15}F_2Br$ 228.0, found 228.0.

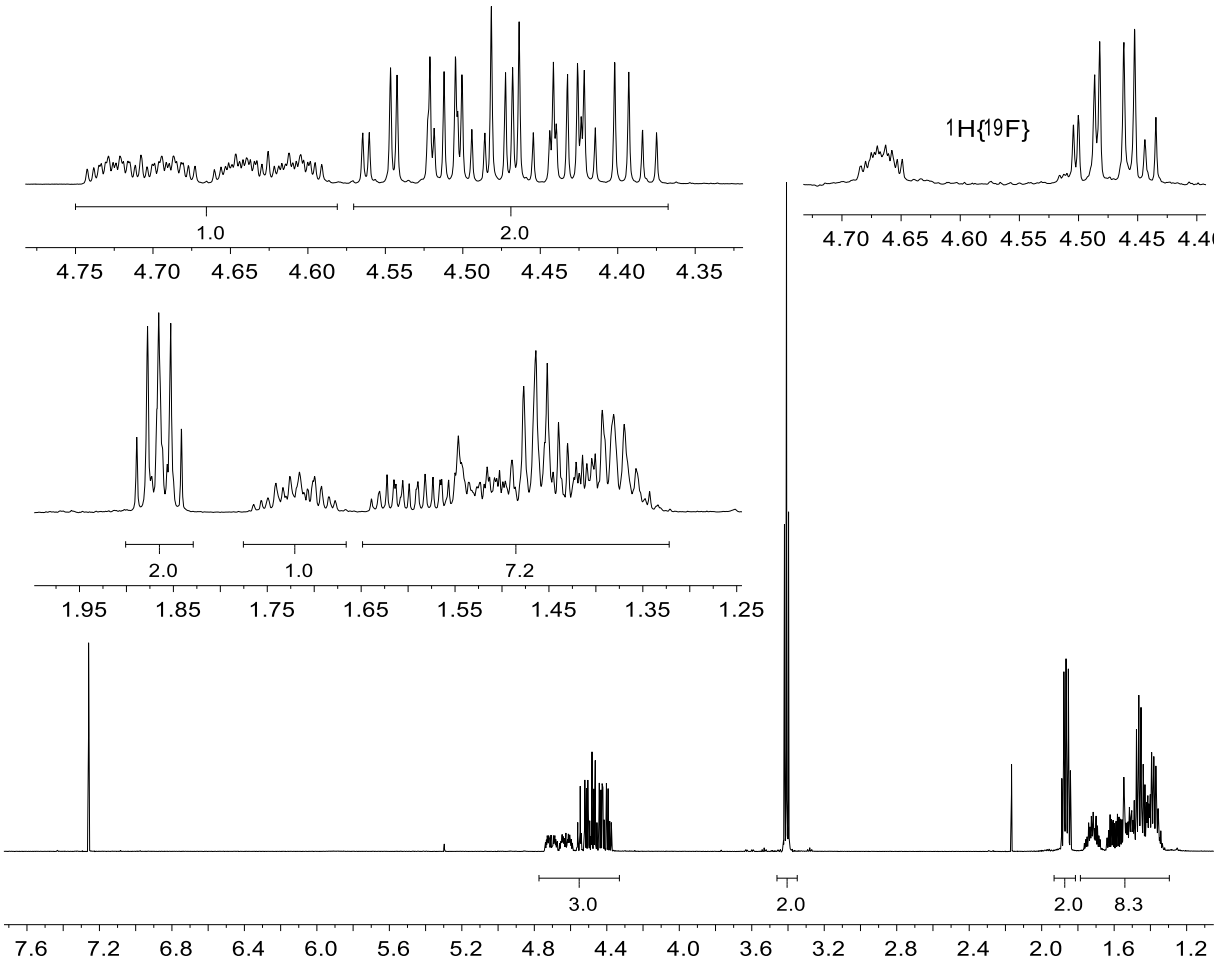
$^{1}H$ NMR (600 MHz, Chloroform-*d*, 298 K) δ 4.67 (ddm, $^{2}J_{FH}$ = 49.2 Hz, $^{3}J_{FH}$ = 20.7 Hz, 1H, HC2), [4.49 (dddd, $^{2}J_{FH}$ = 47.5 Hz, $^{3}J_{FH}$ = 25.2 Hz, $^{2}J_{HH}$ = 10.8 Hz, $^{3}J_{HH}$ = 2.6 Hz, 1H), 4.45 (dddd, $^{2}J_{FH}$ = 47.5 Hz, $^{3}J_{FH}$ = 23.7 Hz, $^{2}J_{HH}$ = 10.8 Hz, $^{3}J_{HH}$ = 5.5 Hz, 1H)]($H_2C1$), 3.41 (t, $^{3}J_{HH}$ = 6.8 Hz, 2H, $H_2C8$), 1.86 (m, 2H, $H_2C7$), [1.72 (m, 1H), 1.59 (m, 1H)]($H_2C3$), [1.51 (m, 1H), 1.41 (m, 1H)]($H_2C4$), 1.46 (m, 2H, $H_2C6$), 1.38 (m, 2H, $H_2C5$).

$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K) δ 91.9 (dd, $^{1}J_{FC}$ = 172.6 Hz, $^{2}J_{FC}$ = 19.2 Hz, C2), 84.2 (dd, $^{1}J_{FC}$ = 173.6 Hz, $^{2}J_{FC}$ = 23.1 Hz, C1), 33.9 (C8), 32.7 (C7), 30.1 (dd, $^{2}J_{FC}$ = 20.9 Hz, $^{3}J_{FC}$ = 6.4 Hz, C3), 28.6 (C5), 28.1 (C6), 24.8 (d, $^{3}J_{FC}$ = 4.6 Hz, C4).

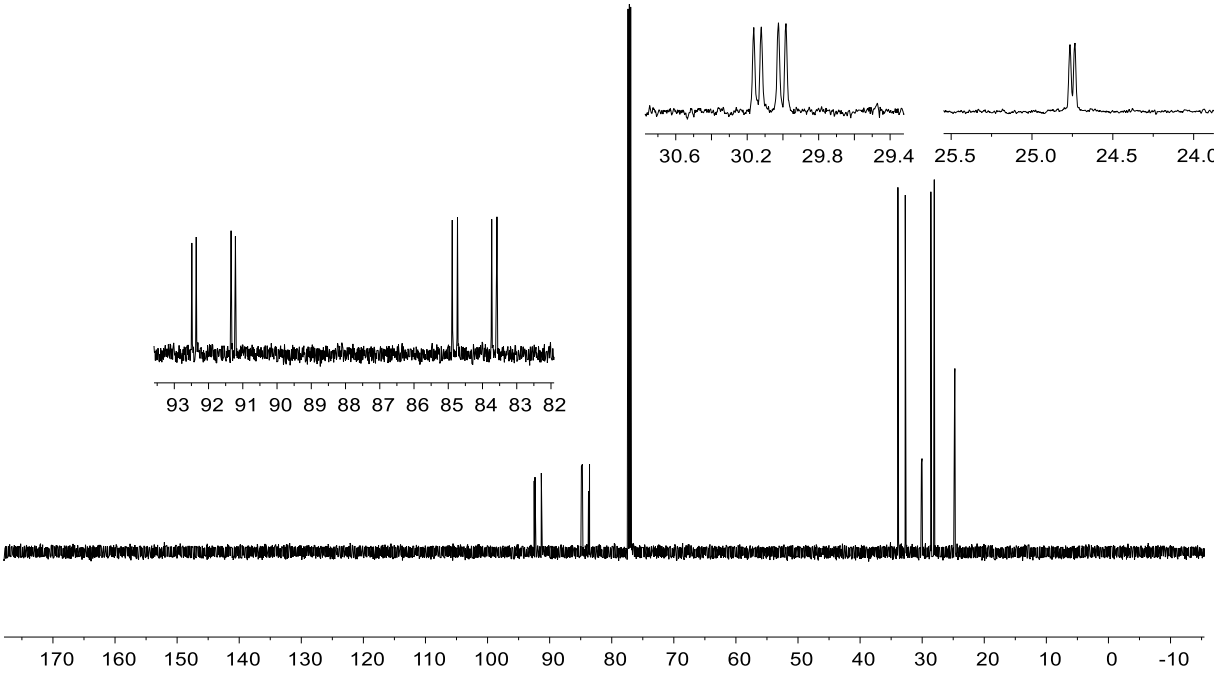
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -189.2 (m, 1F, FC2), -230.1 (tdd, $^{2}J_{FH}$ = 47.5 Hz, $^{3}J_{FH}$ = 20.6 Hz, $^{3}J_{FF}$ = 13.5 Hz, 1F, FC1).

IR (cm$^{-1}$): 2936 (w), 2861 (w), 1456 (w), 1433 (w), 1355 (w), 1259 (w), 1233 (w), 1148 (w), 1038 (w), 920 (w), 864 (w), 727 (w).

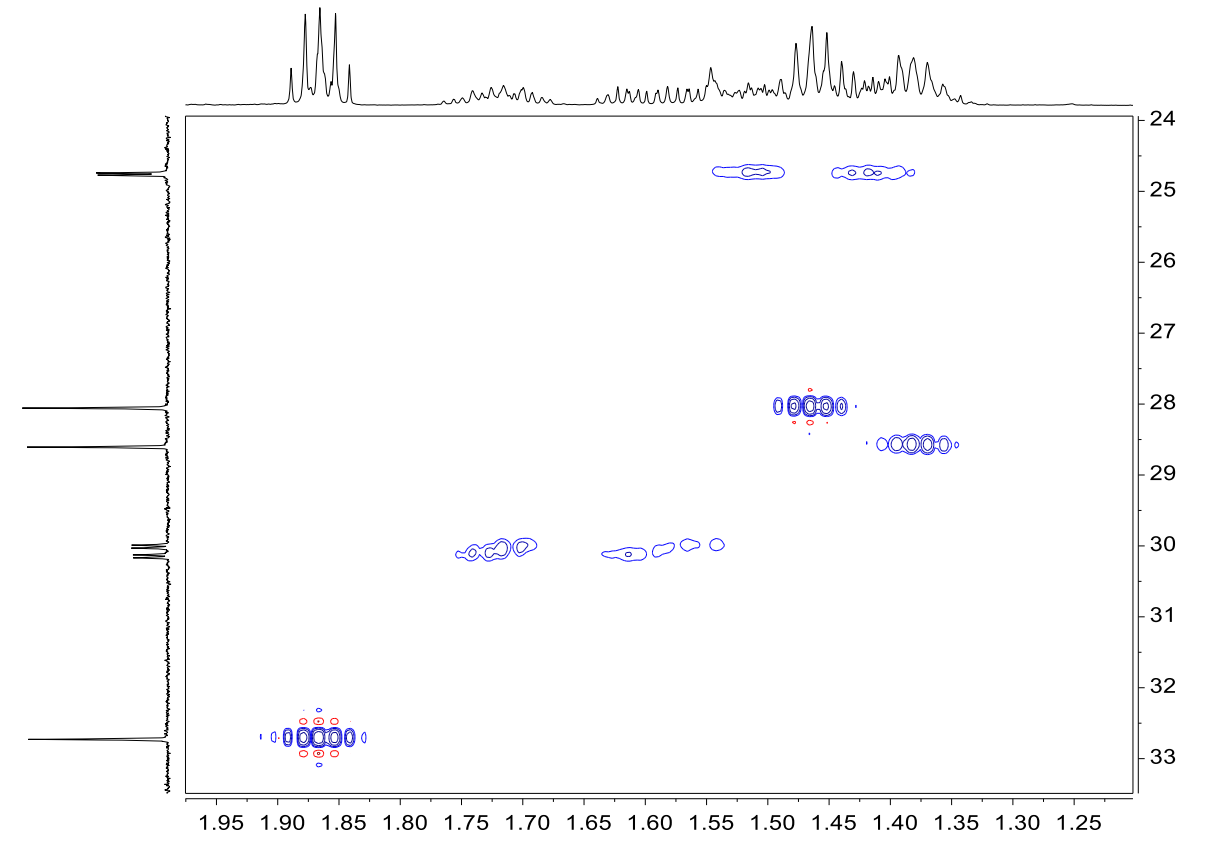
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



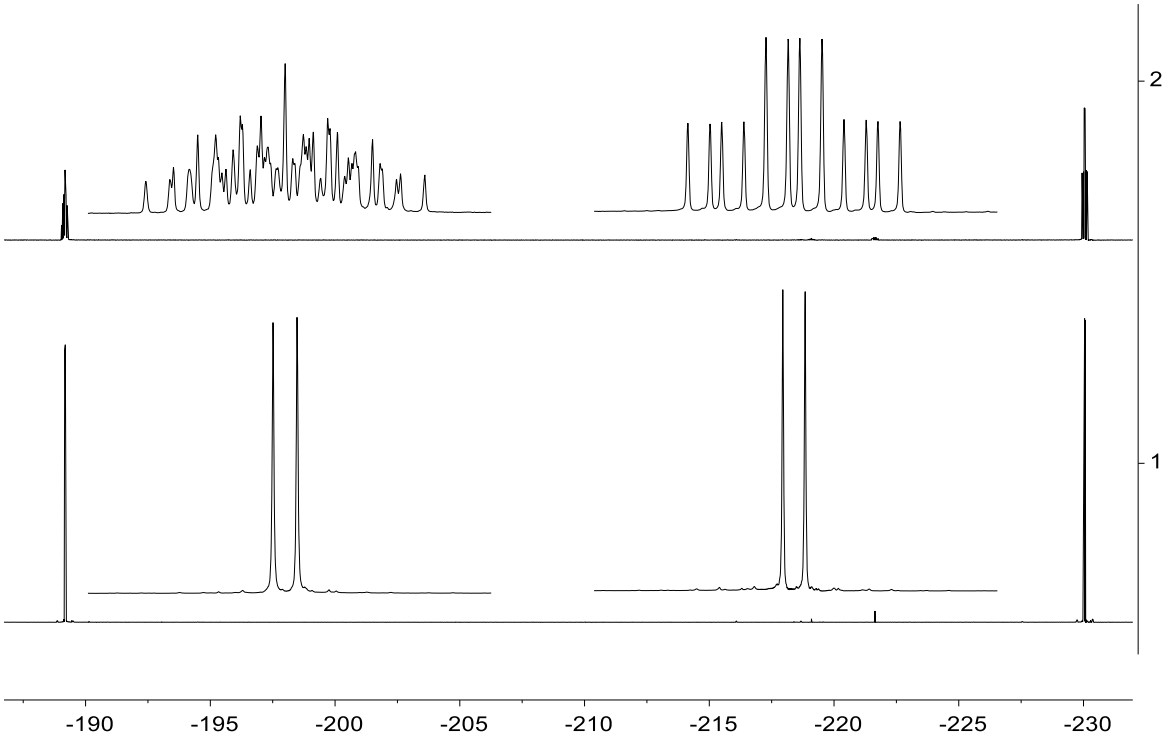
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




$^{1}H,^{13}C$ ghsqc (600/151 MHz, Chloroform-*d*, 298 K) spectrum

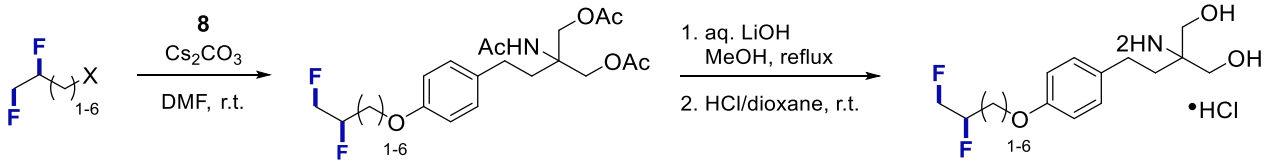


(1) $^{19}F\{^{1}H\}$ NMR (564 MHz, Chloroform-*d*, 298 K) and (2) $^{19}F$ NMR spectra



## II.5.2 Compounds 11a-f to 12a-f

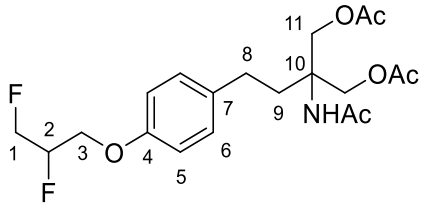
**Scheme S3.**




| | | |
|---|---|---|
| 1: **10a** | 1: **11a** | 1: **12a** |
| 2: **10b** | 2: **11b** | 2: **12b** |
| 3: **10c** | 3: **11c** | 3: **12c** |
| 4: **10d** | 4: **11d** | 4: **12d** |
| 5: **10e** | 5: **11e** | 5: **12e** |
| 6: **10f** | 6: **11f** | 6: **12f** |

For compounds 10a-e: X = OTs and 10f: X = Br.

### 2-Acetamido-2-(4-(2,3-difluoropropoxy)phenethyl)propane-1,3-diyl diacetate (11a)




The product was synthesised from **8** (60 mg, 0.18 mmol, 1.00 eq.) and **10a** (45 mg, 0.18 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1.7) and was isolated as a white solid (27 mg, 36%).

M.p.: 101 °C.

$R_f$ 0.43 (CyH : EtOAc / 1 : 3).

HRMS *m/z* (ESI); Calcd. for $C_{20}H_{27}NO_6F_2Na$ 438.1704, found 438.1692.

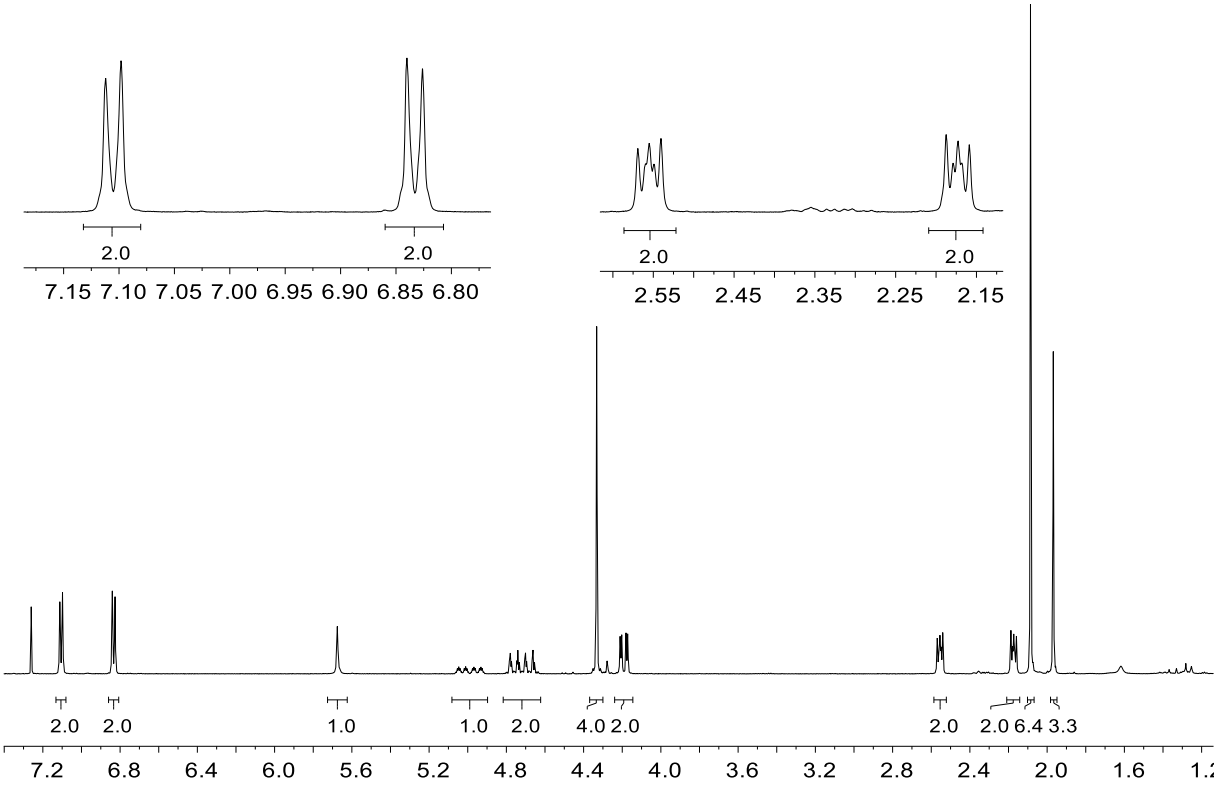
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.10 (m, 2H, HC6), 6.83 (m, 2H, HC5), 5.68 (s, 1H, HN), 4.99 (ddm, $^2J_{FH}$ = 47.3 Hz, $^3J_{FH}$ = 21.4 Hz, 1H, HC2), 4.72 (ddm, $^2J_{FH}$ = 47.1 Hz, $^3J_{FH}$ = 24.3 Hz, 2H, $H_2$C1), [4.333 (d, $^2J_{HH}$ = 11.3 Hz, 2H), 4.331 (d, $^2J_{HH}$ = 11.3 Hz, 2H)]($H_2$C11), [4.195 (ddd, $^3J_{FH}$ = 18.4 Hz, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 4.9 Hz, 1H), 4.187 (ddd, $^3J_{FH}$ = 18.4 Hz, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 4.9 Hz, 1H)]($H_2$C3), 2.55 (m, 2H, $H_2$C8), 2.17 (m, 2H, $H_2$C9), 2.09 (s, 6H, OAc), 1.97 (s, 3H, NAc).

$^{13}$C{$^1$H} NMR{$^1$H} (126 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.2 (NAc), 156.6 (C4), 134.6 (C7), 129.6 (C6), 114.8 (C5), 89.6 (dd, $^1J_{FC}$ = 176.5 Hz, $^2J_{FC}$ = 20.0 Hz, C2), 81.9 (dd, $^1J_{FC}$ = 172.9 Hz, $^2J_{FC}$ = 23.3 Hz, C1), 65.9 (dd, $^3J_{FC}$ = 26.0 Hz, $^4J_{FC}$ = 8.0 Hz, C3), 64.8 (C11), 58.4 (C10), 34.0 (C9), 29.0 (C8), 24.3 (NAc), 21.0 (OAc).

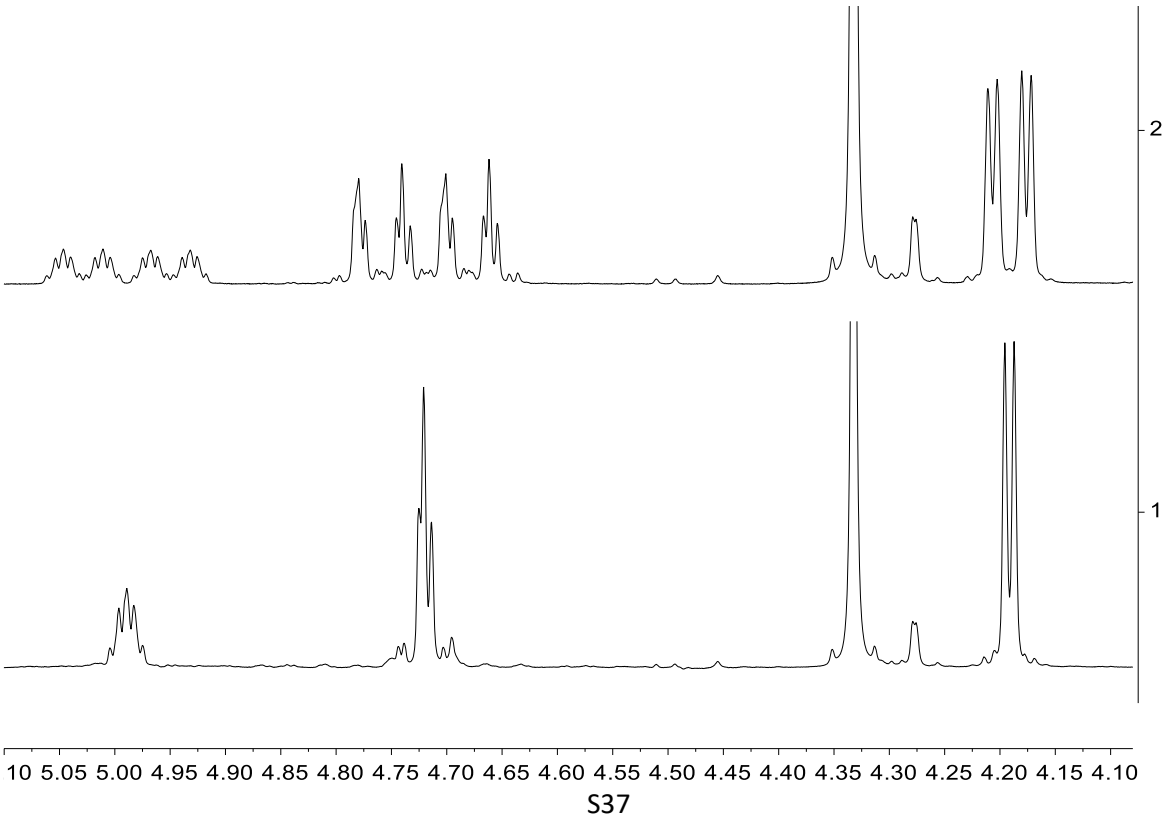
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -197.0 (m, 1F, FC2), -234.3 (tdd, $^2J_{FH}$ = 47.1 Hz, $^3J_{FH}$ = 21.4 Hz, $^3J_{FF}$ = 13.1 Hz, 1F, FC1).

IR ($cm^{-1}$): 3676 (w), 3311 (w), 2970 (w), 2901 (w), 1735 (m), 1651 (w), 1612 (w), 1588 (w), 1552 (w), 1512 (w), 1467 (w), 1380 (m), 1304 (w), 1226 (m), 1102 (w), 1054 (m), 1007 (m), 968 (w), 924 (w), 866 (w), 814 (w), 778 (w), 732 (w), 689 (w).

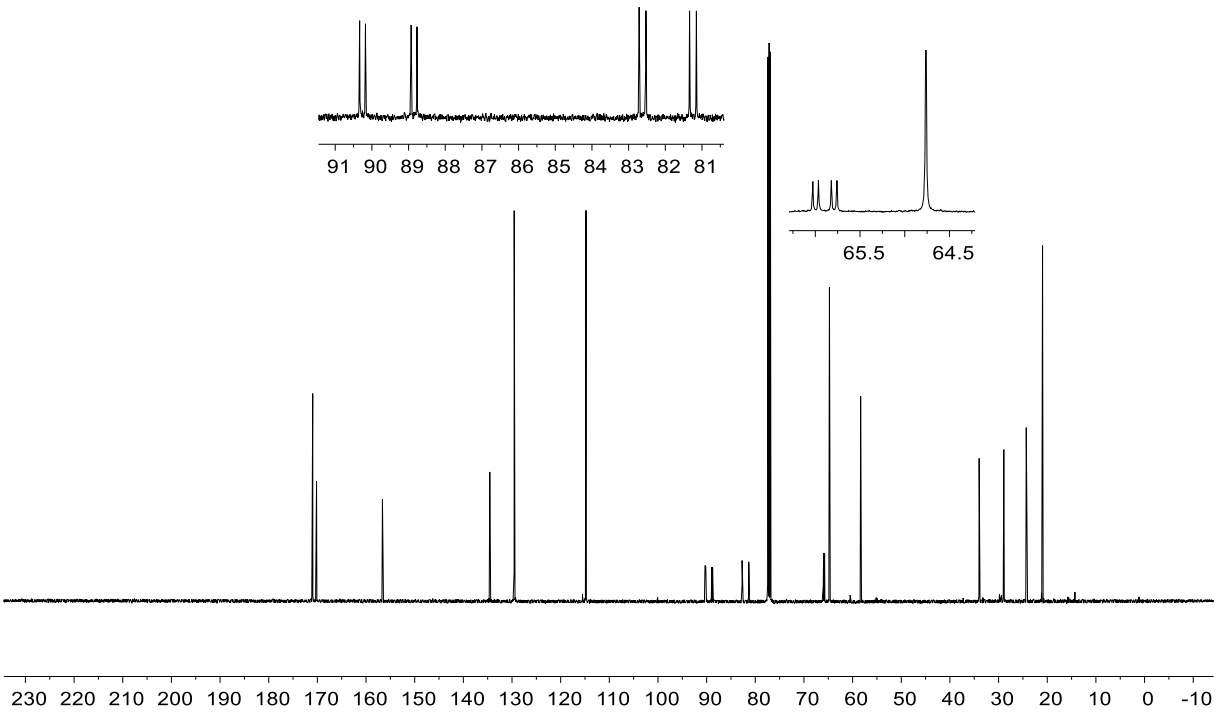
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



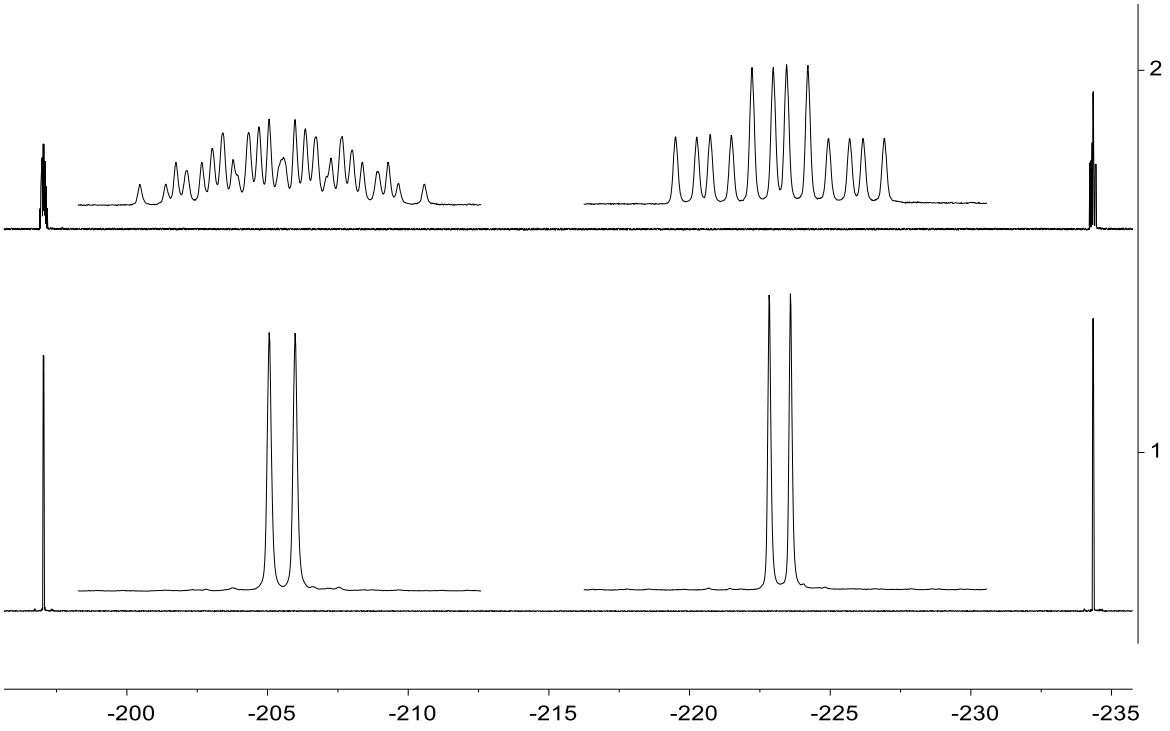

(1) $^{1}$H{$^{19}$F} NMR (600 MHz, Chloroform-*d*, 298 K) and (2) $^{1}$H NMR spectra



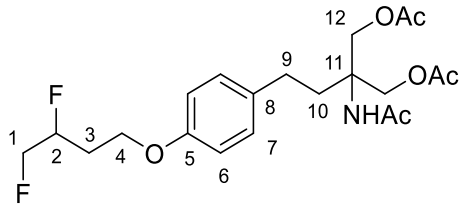
$^{13}C\{^{1}H\}$ NMR$\{^{1}H\}$ (151 MHz, Chloroform-*d*, 298 K)




(1) $^{19}F\{^{1}H\}$ NMR (564 MHz, Chloroform-*d*, 298 K) and (2) $^{19}F$ NMR spectra



**2-Acetamido-2-(4-(3,4-difluorobutoxy)phenethyl)propane-1,3-diyl diacetate (11b)**




The product was synthesised from **8** (150 mg, 0.44 mmol, 1.00 eq.) and **10b** (118 mg, 0.44 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1.2) and was isolated as a white solid (120 mg, 65%).

M.p.: 88 °C.

$R_f$ 0.33 (CyH : EtOAc / 1 : 2.5).

HRMS *m/z* (ESI); Calcd. for $C_{21}H_{29}NO_6F_2Na$ 452.1855, found 452.1843.

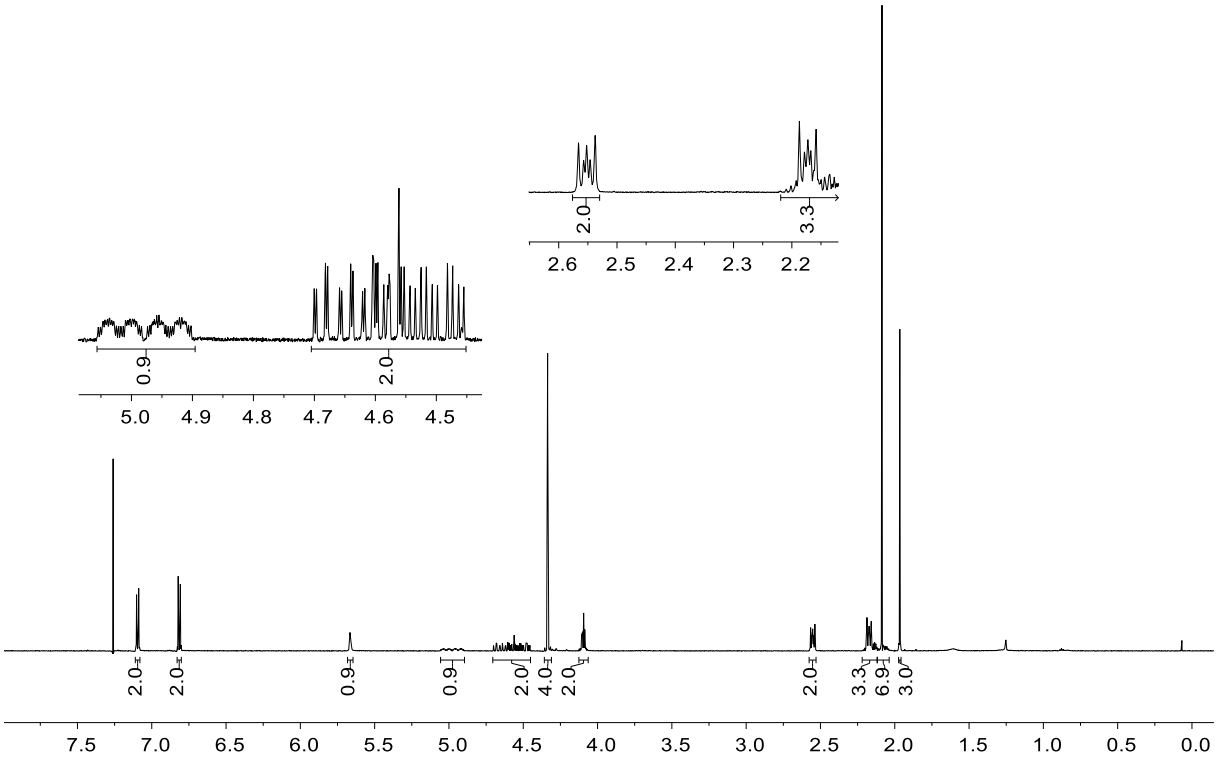
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.09 (m, 2H, HC7), 6.81 (m, 2H, HC6), 5.66 (s, 1H, HN), 4.98 (ddm, $^2J_{FH}$ = 48.8 Hz, $^3J_{FH}$ = 22.4 Hz, 1H, HC2), [4.63 (dddd, $^2J_{FH}$ = 47.5 Hz, $^3J_{FH}$ = 24.7 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.2 Hz, 1H), 4.53 (dddd, $^2J_{FH}$ = 47.5 Hz, $^3J_{FH}$ = 25.9 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.2 Hz, 1H)]($H_2$C1), [4.336 (d, $^2J_{HH}$ = 11.3 Hz, 2H), 4.335 (d, $^2J_{HH}$ = 11.3 Hz, 2H)]($H_2$C12), 4.14 – 4.05 (m, 2H, $H_2$C4), 2.55 (m, 2H, $H_2$C9), 2.17 (m, 2H, $H_2$C10), [2.15 (m, 1H), 2.09 (m, 1H)]($H_2$C3), 2.09 (s, 6H, OAc), 1.97 (s, 3H, NAc).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.1 (NAc), 157.0 (C5), 134.0 (C8), 129.5 (C7), 114.7 (C6), 89.2 (dd, $^1J_{FC}$ = 173.0 Hz, $^2J_{FC}$ = 19.5 Hz, C2), 84.3 (dd, $^1J_{FC}$ = 174.0 Hz, $^2J_{FC}$ = 22.2 Hz, C1), 64.8 (C12), 63.1 (d, $^3J_{FC}$ = 5.2 Hz, C4), 58.4 (C11), 34.1 (C10), 30.4 (dd, $^2J_{FC}$ = 21.2 Hz, $^3J_{FC}$ = 6.8 Hz, C3), 29.0 (C9), 24.3 (NAc), 21.0 (OAc).

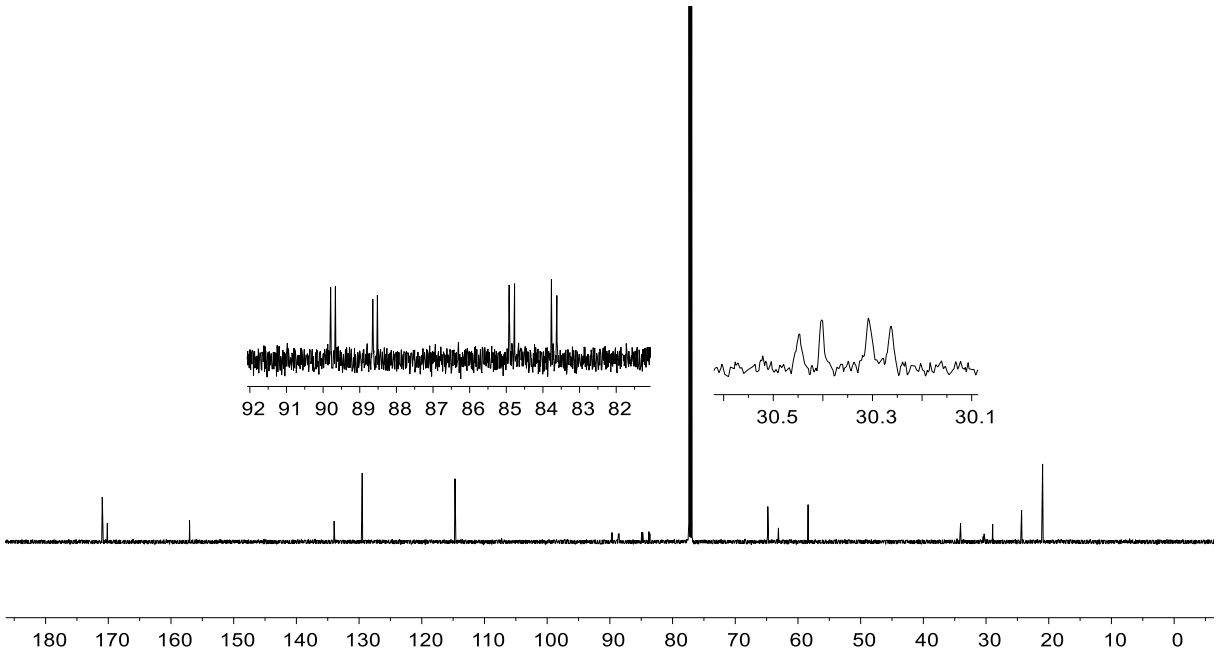
$^{19}$F NMR (282 MHz, Chloroform-*d*, 298 K) δ -191.8 (m, 1F, FC2), -230.2 (tdd, $^2J_{FH}$ = 47.5 Hz, $^3J_{FH}$ = 22.6 Hz, $^3J_{FF}$ = 12.8 Hz, 1F, FC1).

IR (cm$^{-1}$): 3308 (w), 3080 (w), 2961 (w), 1735 (m), 1651 (m), 1613 (w), 1586 (w), 1553 (m), 1513 (m), 1467 (w), 1429 (w), 1378 (m), 1316 (w), 1303 (w), 1291 (w), 1240 (m), 1219 (s), 1180 (m), 1127 (w), 1100 (w), 1052 (m), 1031 (m), 985 (w), 967 (m), 936 (w), 905 (w), 882 (w), 849 (w), 816 (m), 772 (w), 758 (w), 691 (w).

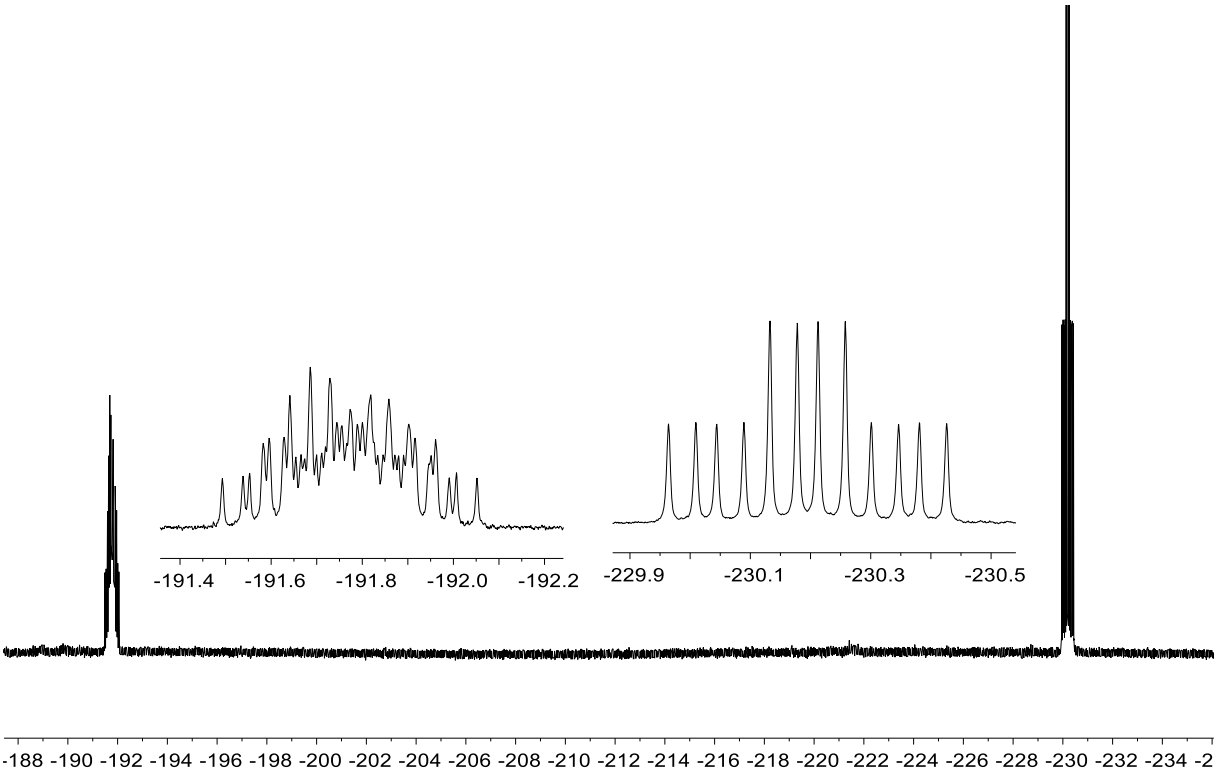
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



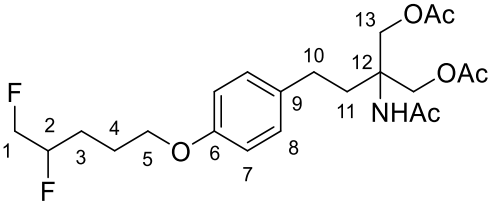

$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*, 298 K)



$^{19}$F NMR (282 MHz, Chloroform-*d*, 298 K)




**2-Acetamido-2-(4-((4,5-difluoroPentanetyl)oxy)phenethyl)propane-1,3-diyl diacetate (11c)**




The compound was synthesised from **8** (145 mg, 0.43 mmol, 1.00 eq.) and **10c** (120 mg, 0.43 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1.2) and was isolated as a white solid (140 mg, 74%).

M.p.: 74 °C.

$R_f$ 0.16 (CyH : EtOAc / 1 : 1.2).

HRMS *m/z* (ESI); Calcd. for $C_{22}H_{31}NO_6F_2Na$ 466.2012, found 466.1995.

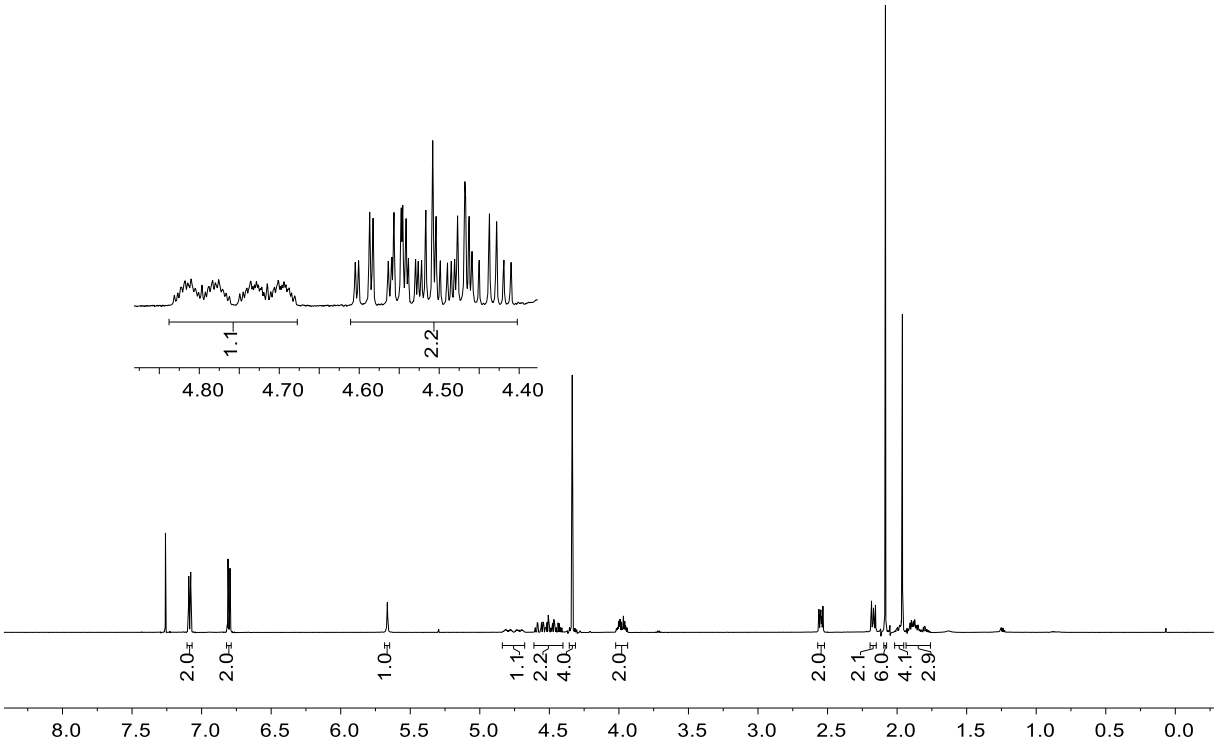
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.09 (m, 2H, HC8), 6.80 (m, 2H, HC7), 5.66 (s, 1H, HN), 4.76 (ddm, $^2J_{FH}$ = 49.0 Hz, $^3J_{FH}$ = 20.6 Hz, 1H, HC2), [4.53 (dddd, $^2J_{FH}$ = 47.4 Hz, $^3J_{FH}$ = 24.8 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 2.5 Hz, 1H), 4.48 (dddd, $^2J_{FH}$ = 47.4 Hz, $^3J_{FH}$ = 23.9 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 5.4 Hz, 1H)]($H_2$C1), [4.336 (d, $^2J_{HH}$ = 11.3 Hz, 2H), 4.335 (d, $^2J_{HH}$ = 11.3 Hz, 2H)]($H_2$C13), 4.03 – 3.93 (m, 2H, $H_2$C5), 2.55 (m, 2H, $H_2$C10), 2.17 (m, 2H, $H_2$C11), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), [1.98 (m, 1H), 1.90 (m, 1H)]($H_2$C4), [1.88 (m, 1H), 1.83 (m, 1H)]($H_2$C3).

$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K) δ 170.9 (OAc), 170.1 (NAc), 157.3 (C6), 133.7 (C9), 129.4 (C8), 114.7 (C7), 91.6 (dd, $^{1}J_{FC}$ = 173.0 Hz, $^{2}J_{FC}$ = 19.3 Hz, C2), 84.2 (dd, $^{1}J_{FC}$ = 173.9 Hz, $^{2}J_{FC}$ = 22.9 Hz, C1), 67.3 (C5), 64.8 (C13), 58.4 (C12), 34.1 (C11), 28.9 (C10), 27.1 (dd, $^{2}J_{FC}$ = 21.1 Hz, $^{3}J_{FC}$ = 6.7 Hz, C3), 24.9 (d, $^{3}J_{FC}$ = 4.5 Hz, C4), 24.3 (NAc), 21.0 (OAc).

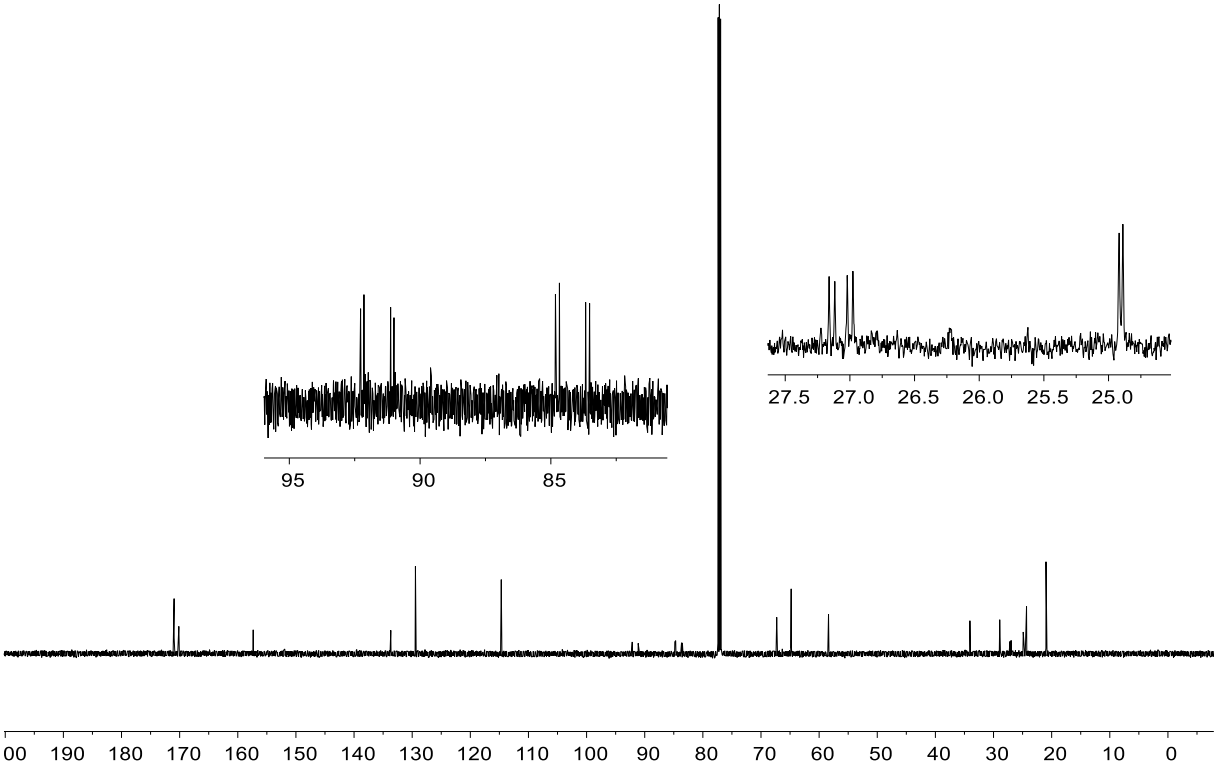
$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K) δ -189.9 (m, 1F, FC2), -230.2 (tdd, $^{2}J_{FH}$ = 47.4 Hz, $^{3}J_{FH}$ = 20.6 Hz, $^{3}J_{FF}$ = 13.4 Hz, 1F, FC1).

IR ($cm^{-1}$): 3312 (w), 3079 (w), 2962 (w), 2871 (w), 1735 (m), 1651 (m), 1614 (w), 1585 (w), 1552 (m), 1514 (m), 1468 (m), 1379 (m), 1316 (w), 1304 (w), 1241 (m), 1218 (s), 1180 (m), 1129 (w), 1101 (w), 1051 (s), 1031 (m), 986 (m), 967 (m), 918 (w), 901 (w), 847 (m), 812 (m), 783 (w), 770 (w), 738 (w), 691 (w), 662 (w).

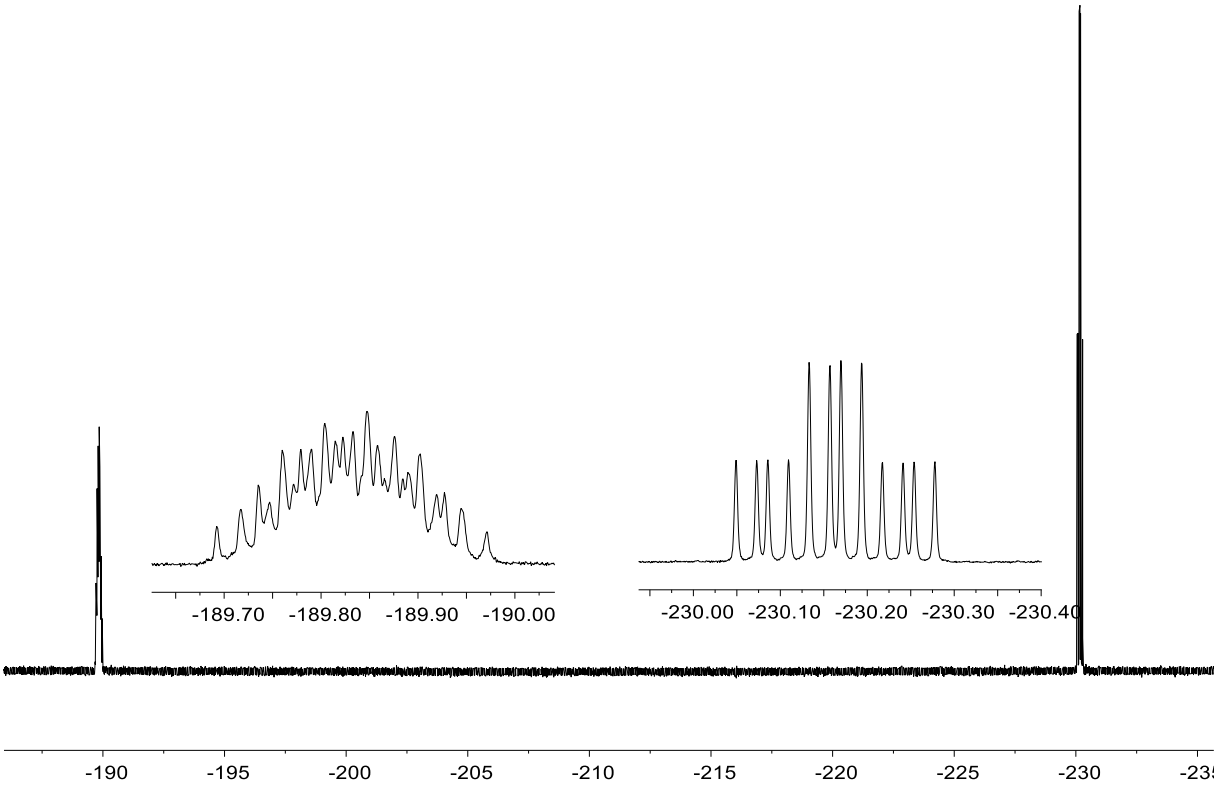
$^{1}H$ NMR (600 MHz, Chloroform-*d*, 298 K)



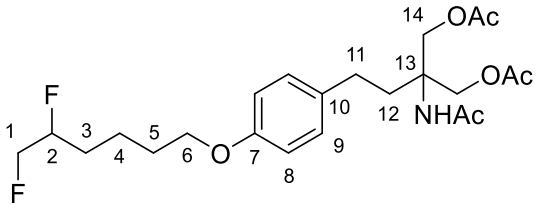
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-((5,6-difluorohexyl)oxy)phenethyl)propane-1,3-diyl diacetate (11d)**




The compound was synthesised from **8** (140 mg, 0.41 mmol, 1.00 eq.) and **10d** (120 mg, 0.41 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1.1) and was isolated as a white solid (124 mg, 66%).

M.p.: 97 °C.

$R_f$ 0.22 (CyH : EtOAc / 1 : 1.1).

HRMS *m/z* (ESI); Calcd. for $C_{23}H_{33}NO_6F_2Na$ 480.2168, found 480.2188.

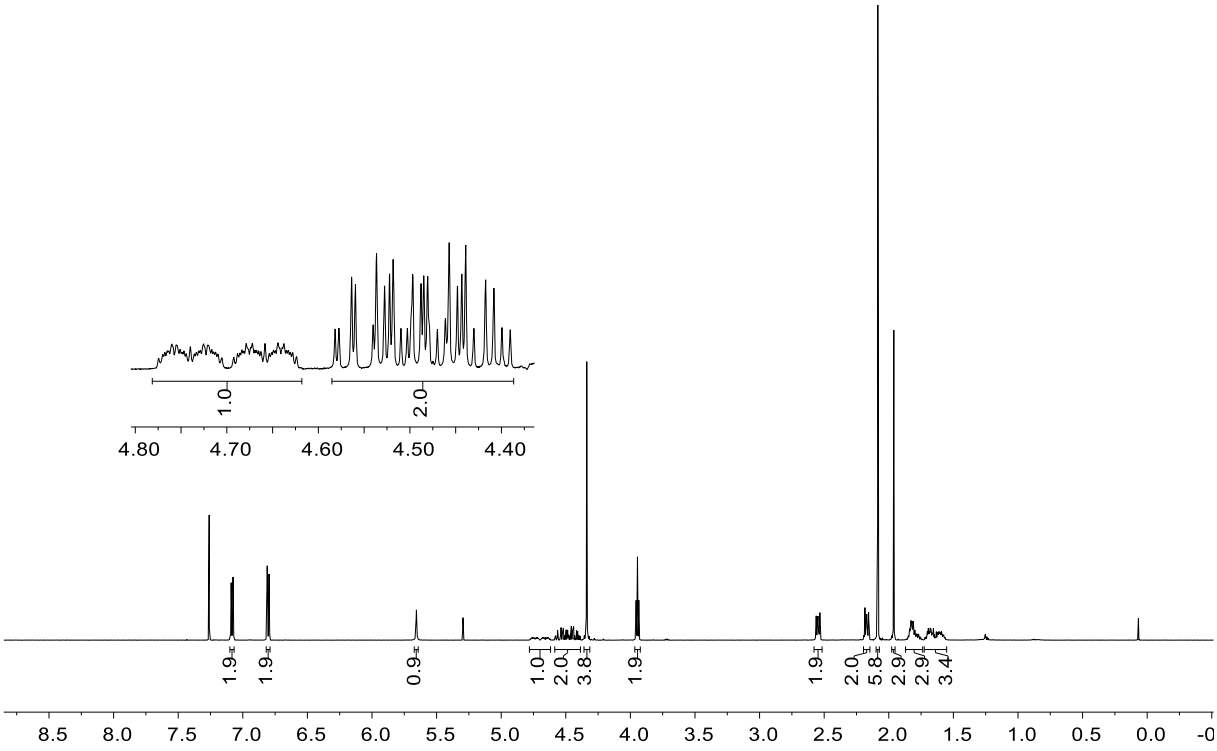
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC9), 6.80 (m, 2H, HC8), 5.66 (s, 1H, HN), 4.70 (ddm, $^2J_{FH}$ = 49.0 Hz, $^3J_{FH}$ = 20.7 Hz, 1H, HC2), [4.51 (dddd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 24.9 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 2.5 Hz, 1H), 4.46 (dddd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 23.9 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 5.3 Hz, 1H)]($H_2$C1), [4.338 (d, $^2J_{HH}$ = 11.3 Hz, 2H), 4.337 (d, $^2J_{HH}$ = 11.3 Hz, 2H)]($H_2$C14), 3.95 (t, $^3J_{HH}$ = 6.3 Hz, 2H, $H_2$C6), 2.55 (m, 2H, $H_2$C11), 2.17 (m, 2H, $H_2$C12), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.82 (m, 2H, $H_2$C5), [1.79 (m, 1H), 1.66 (m, 1H)]($H_2$C3), [1.68 (m, 1H), 1.59 (m, 1H)]($H_2$C5).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.1 (NAc), 157.5 (C7), 133.5 (C10), 129.4 (C9), 114.7 (C8), 91.8 (dd, $^1J_{FC}$ = 172.8 Hz, $^2J_{FC}$ = 19.3 Hz, C2), 84.2 (dd, $^1J_{FC}$ = 173.7 Hz, $^2J_{FC}$ = 23.0 Hz, C1), 67.6 (C6), 64.8 (C14), 58.4 (C13), 34.1 (C12), 30.0 (dd, $^2J_{FC}$ = 20.9 Hz, $^3J_{FC}$ = 6.4 Hz, C3), 29.1 (C5), 28.9 (C11), 24.3 (NAc), 21.7 (d, $^3J_{FC}$ = 4.7 Hz, C4), 21.0 (OAc).

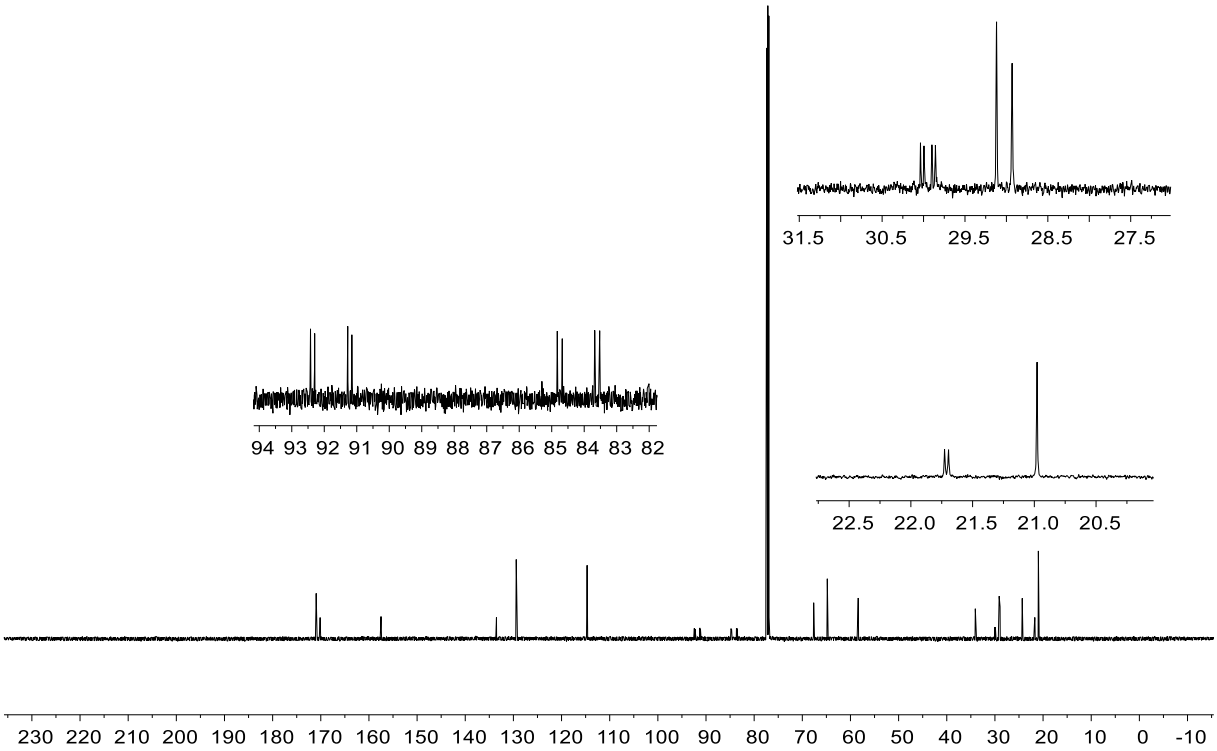
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -189.3 (m, 1F, FC2), -230.2 (tdd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 20.7 Hz, $^3J_{FF}$ = 13.5 Hz, 1F, FC1).

IR (cm$^{-1}$): 3314 (w), 3079 (w), 2947 (w), 2869 (w), 1982 (w), 1897 (w), 1735 (m), 1652 (m), 1613 (w), 1585 (w), 1552 (m), 1514 (m), 1468 (m), 1429 (w), 1379 (m), 1317 (w), 1303 (w), 1290 (w), 1221 (s), 1180 (m), 1142 (w), 1110 (m), 1089 (w), 1053 (m), 1034 (m), 1012 (m), 988 (m), 967 (m), 944 (w), 920 (m), 905 (w), 845 (m), 819 (m), 768 (w), 735 (w), 690 (w), 673 (w), 654 (w).

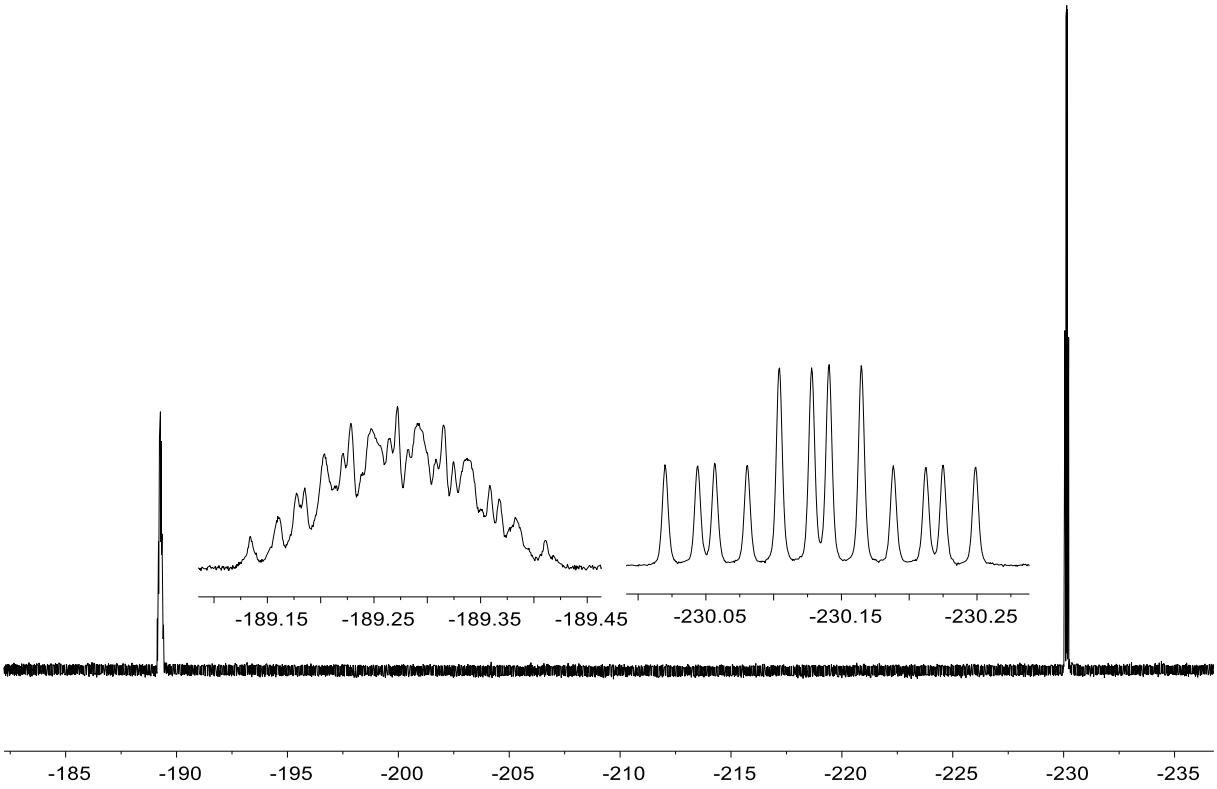
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



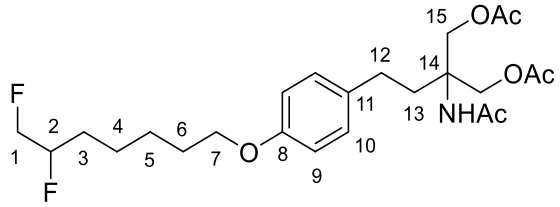

$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*, 298 K)



$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K)




**2-Acetamido-2-(4-((6,7-difluoroheptyl)oxy)phenethyl)propane-1,3-diyl diacetate (11e)**




The compound was synthesised from **8** (128 mg, 0.38 mmol, 1.00 eq.) and **10e** (186 mg, 0.38 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 2) and was isolated as a white solid (141 mg, 79%).

M.p.: 75 °C.

$R_f$ 0.29 (CyH : EtOAc / 1 : 2).

HRMS *m/z* (ESI); Calcd. for $C_{24}H_{35}NO_6F_2Na$ 494.2330, found 494.2322.

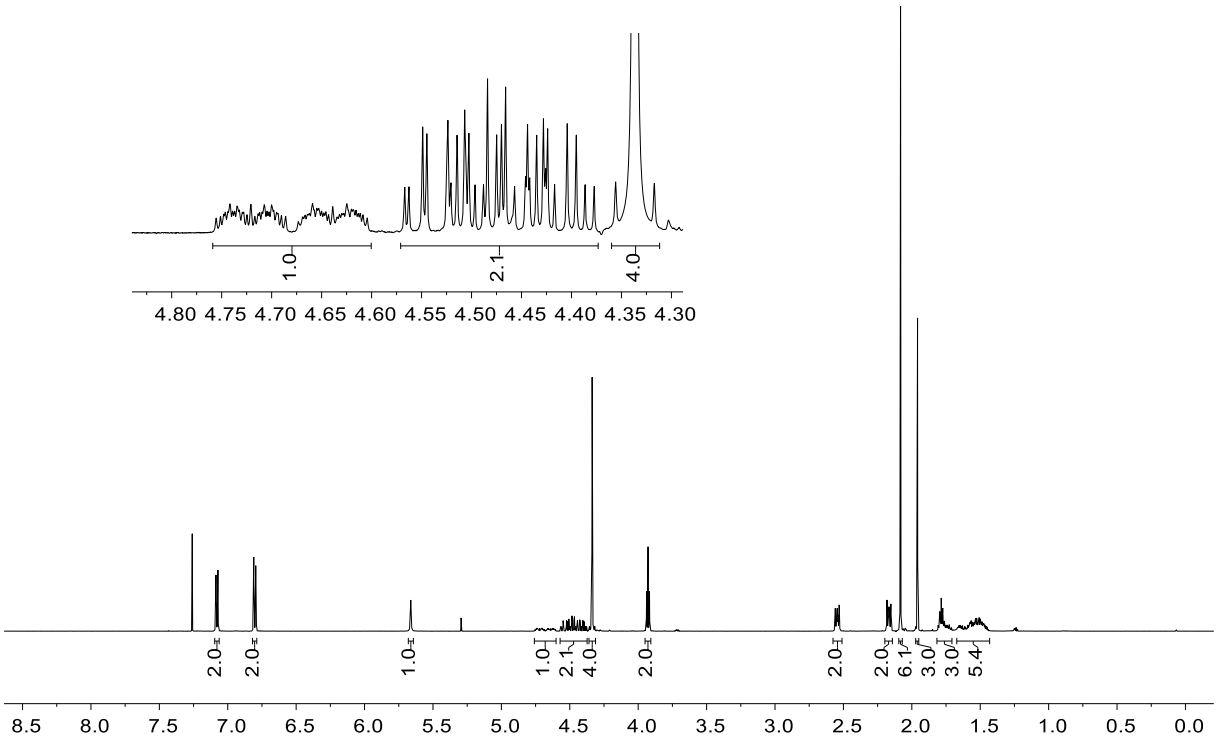
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC10), 6.80 (m, 2H, HC9), 5.66 (s, 1H, HN), 4.68 (ddm, $^2J_{FH}$ = 49.2 Hz, $^3J_{FH}$ = 20.7 Hz, 1H, HC2), [4.50 (dddd, $^2J_{FH}$ = 47.4 Hz, $^3J_{FH}$ = 25.2 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 2.5 Hz, 1H), 4.45 (dddd, $^2J_{FH}$ = 47.4 Hz, $^3J_{FH}$ = 23.7 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 5.4 Hz, 1H)]($H_2$C1), [4.337 (d, $^2J_{HH}$ = 11.4 Hz, 2H), 4.336 (d, $^2J_{HH}$ = 11.4 Hz, 2H)]($H_2$C15), 3.93 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C7), 2.55 (m, 2H, $H_2$C12), 2.17 (m, 2H, $H_2$C13), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.78 (m, 2H, $H_2$C6), [1.75 (m, 1H), 1.60 (m, 1H)]($H_2$C3), [1.56 (m, 1H), 1.47 (m, 1H)]($H_2$C4), [1.52 (m, 1H), 1.50 (m, 1H)]($H_2$C5).

$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K) δ 170.9 (OAc), 170.1 (NAc), 157.6 (C8), 133.4 (C11), 129.4 (C10), 114.7 (C9), 91.8 (dd, $^{1}J_{FC}$ = 172.6 Hz, $^{2}J_{FC}$ = 19.2 Hz, C2), 84.2 (dd, $^{1}J_{FC}$ = 173.7 Hz, $^{2}J_{FC}$ = 23.1 Hz, C1), 67.8 (C7), 64.8 (C15), 58.4 (C14), 34.1 (C13), 30.1 (dd, $^{2}J_{FC}$ = 20.8 Hz, $^{3}J_{FC}$ = 6.3 Hz, C3), 29.2 (C6), 28.9 (C12), 26.0 (C5), 24.7 (d, $^{3}J_{FC}$ = 4.4 Hz, C4), 24.3 (NAc), 21.0 (OAc).

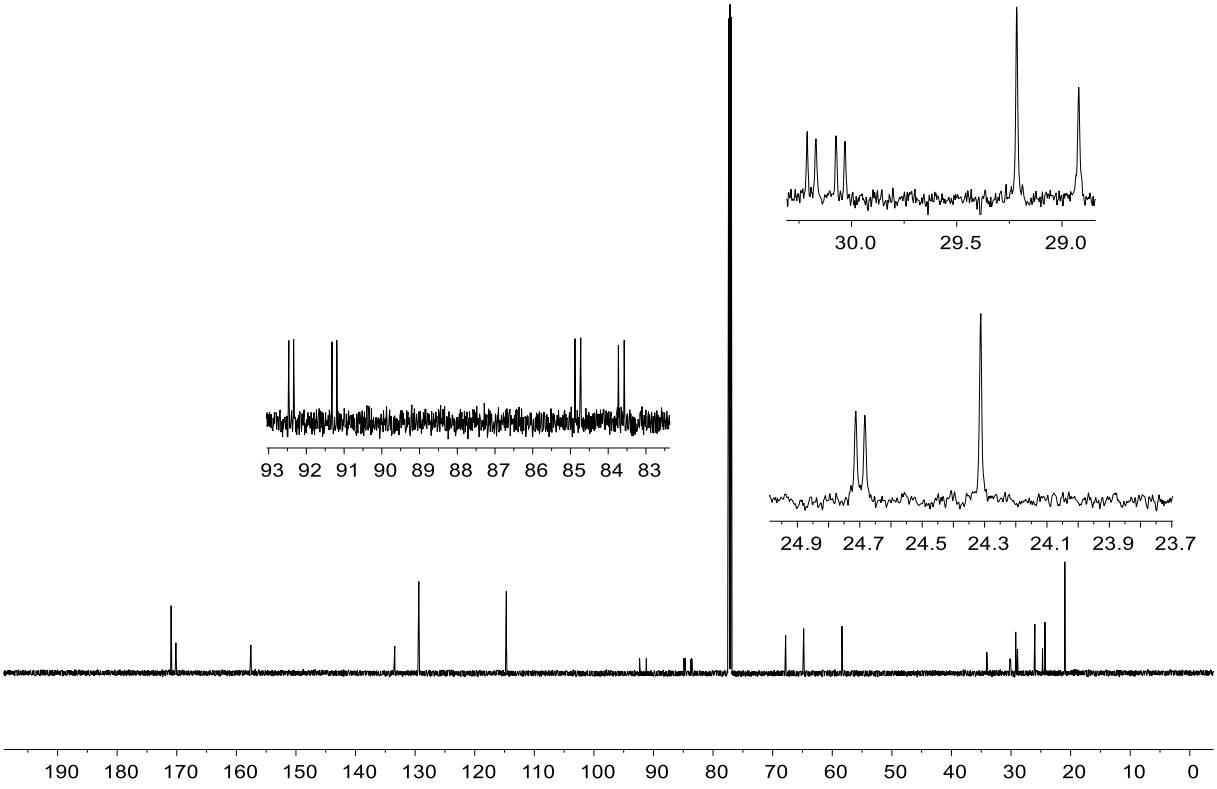
$^{19}F$ NMR (282 MHz, Chloroform-*d*, 298 K) δ -189.1 (m, 1F, FC2), -229.9 (tdd, $^{2}J_{FH}$ = 47.4 Hz, $^{3}J_{FH}$ = 20.7 Hz, $^{3}J_{FF}$ = 13.5 Hz, 1F, FC1).

IR ($cm^{-1}$): 3313 (w), 3079 (w), 2938 (w), 2857 (w), 1736 (m), 1651 (m), 1614 (w), 1584 (w), 1552 (m), 1513 (m), 1467 (w), 1427 (w), 1380 (m), 1316 (w), 1304 (w), 1290 (w), 1226 (m), 1179 (m), 1127 (w), 1102 (w), 1055 (m), 1031 (m), 990 (m), 967 (w), 954 (w), 926 (w), 903 (w), 887 (w), 851 (w), 813 (m), 788 (w), 770 (w), 749 (w), 725 (w), 670 (w), 691 (w).

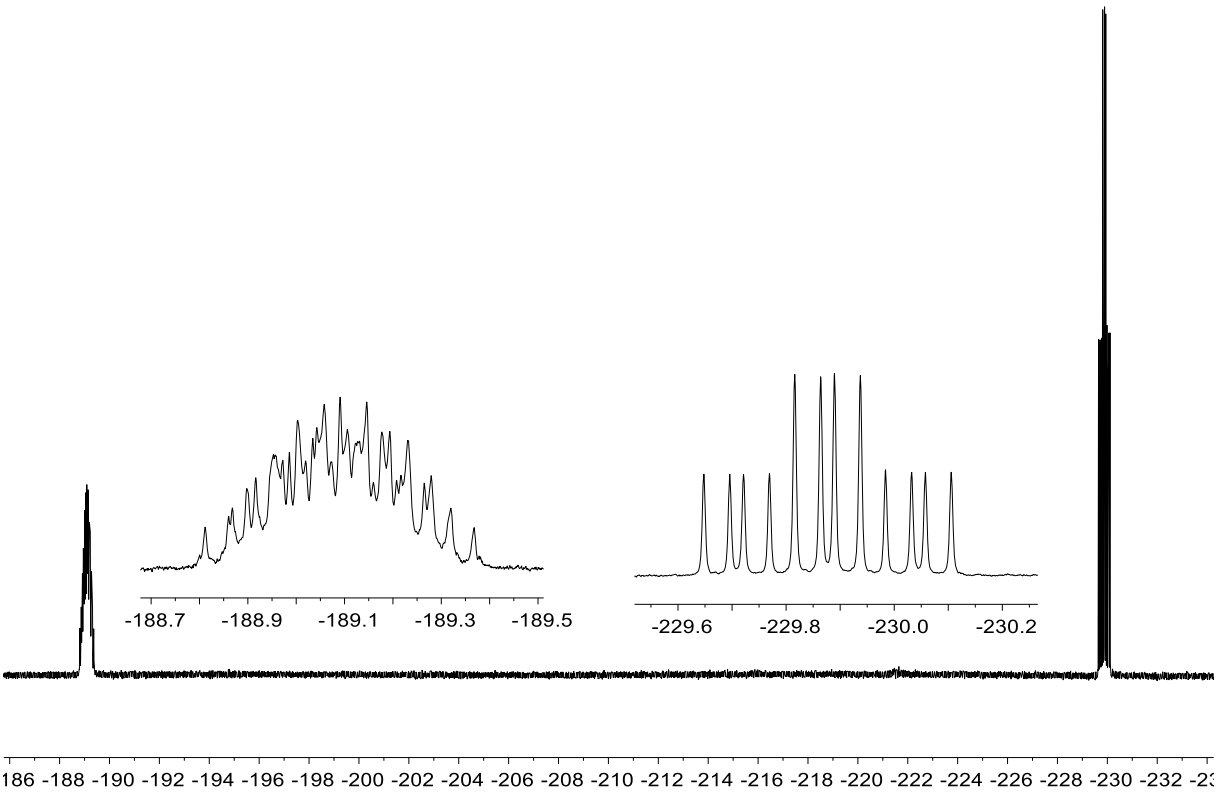
$^{1}H$ NMR (600 MHz, Chloroform-*d*, 298 K)



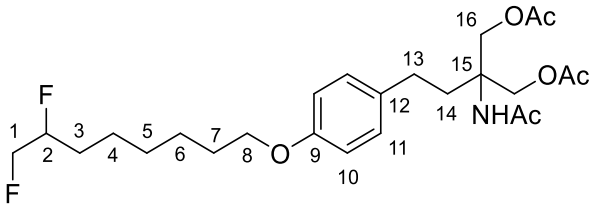
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




$^{19}F$ NMR (282 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-((7,8-difluorooctyl)oxy)phenethyl)propane-1,3-diyl diacetate (11f)**




The compound was synthesised from **8** (60 mg, 0.18 mmol, 1.00 eq.) and **10f** (45 mg, 0.20 mmol, 1.10 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (81 mg, 94%).

M.p.: 96 °C.

$R_f$ 0.54 (CyH : EtOAc / 1 : 4).

HRMS *m/z* (ESI); Calcd. for $C_{25}H_{37}NO_6F_2Na$ 508.2481, found 508.2484.

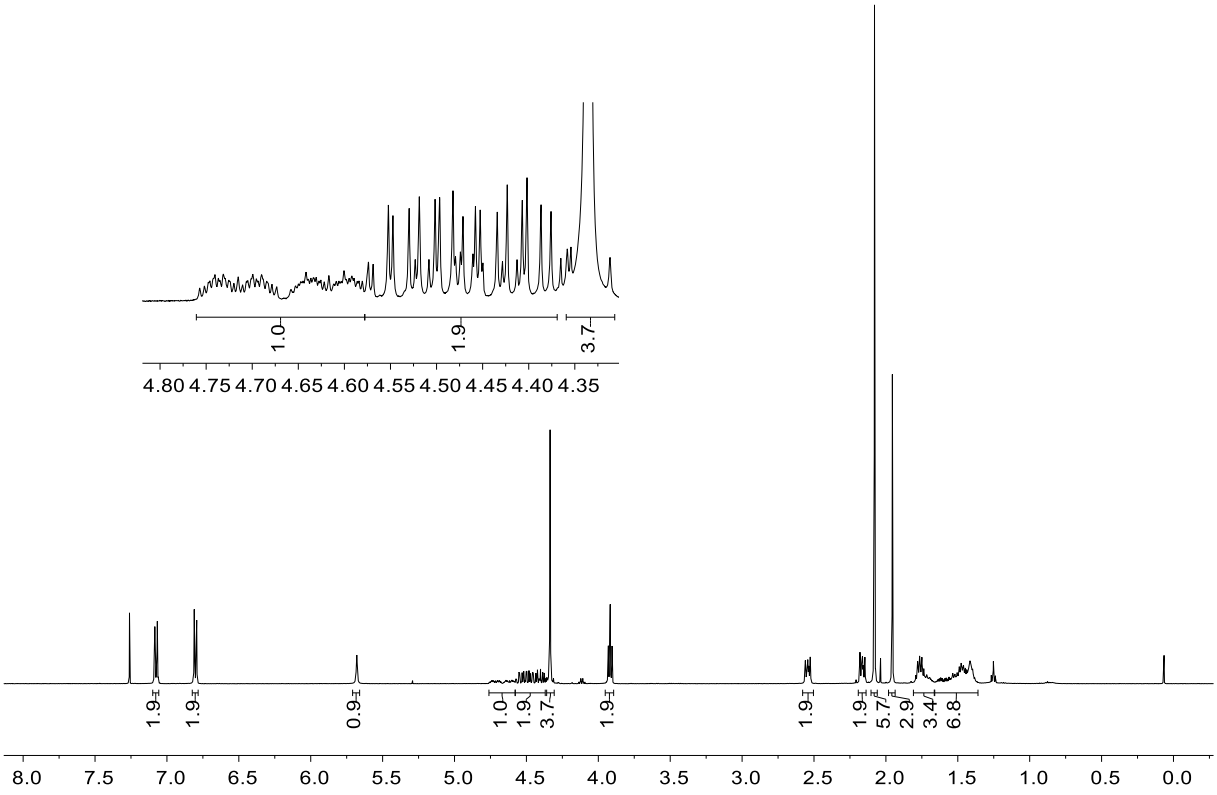
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC11), 6.80 (m, 2H, HC10), 5.68 (s, 1H, HN), 4.67 (ddm, $^2J_{FH}$ = 49.3 Hz, $^3J_{FH}$ = 20.6 Hz, 1H, HC2), [4.49 (dddd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 25.4 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 2.4 Hz, 1H), 4.44 (dddd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 23.8 Hz, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 5.5 Hz, 1H)]($H_2$C1), [4.336 (d, $^3J_{HH}$ = 11.3 Hz, 2H), 4.334 (d, $^3J_{HH}$ = 11.3 Hz, 2H)]($H_2$C16), 3.92 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C8), 2.54 (m, 2H, $H_2$C13), 2.16 (m, 2H, $H_2$C14), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.77 (m, 2H, $H_2$C7), [1.72 (m, 1H), 1.59 (m, 1H)]($H_2$C3), [1.52 (m, 1H), 1.42 (m, 1H)]($H_2$C4), [1.48 (m, 1H), 1.46 (m, 1H)]($H_2$C6), 1.42 (m, 2H, $H_2$C5).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 170.9 (OAc), 170.2 (NAc), 157.6 (C9), 133.3 (C12), 129.4 (C11), 114.7 (C10), 91.9 (dd, $^1J_{FC}$ = 172.5 Hz, $^2J_{FC}$ = 19.2 Hz, C2), 84.2 (dd, $^1J_{FC}$ = 173.6 Hz, $^2J_{FC}$ = 23.0 Hz, C1), 68.0 (C8), 64.8 (C16), 58.4 (C15), 34.1 (C14), 30.1 (dd, $^2J_{FC}$ = 20.7 Hz, $^3J_{FC}$ = 6.4 Hz, C3), 29.3 (C7), 29.2 (C5), 28.9 (C13), 26.0 (C6), 24.8 (d, $^3J_{FC}$ = 4.6 Hz, C4), 24.3 (NAc), 21.0 (OAc).

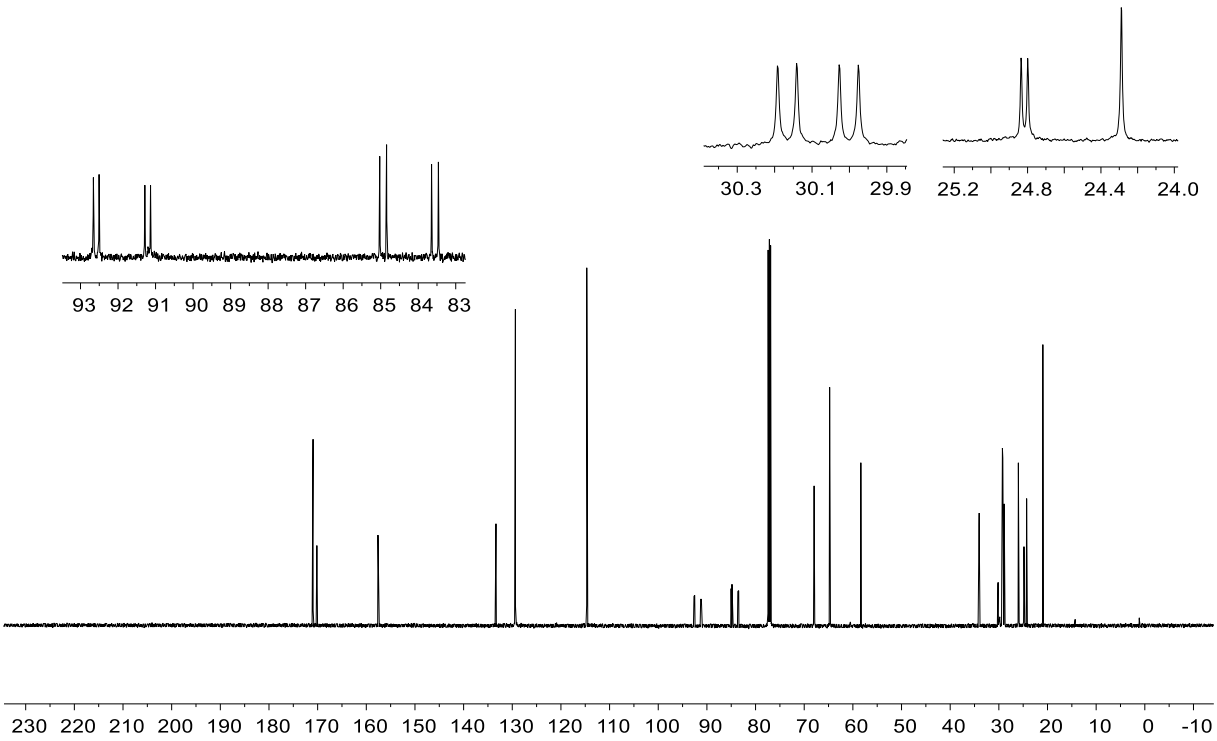
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -189.0 (m, 1F, FC2), -229.9 (tdd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 20.6 Hz, $^3J_{FF}$ = 13.5 Hz, 1F, FC1).

IR (cm$^{-1}$): 3316 (w), 3077 (w), 2931 (w), 2855 (w), 1735 (m), 1651 (m), 1613 (w), 1584 (w), 1552 (m), 1514 (m), 1468 (w), 1430 (w), 1380 (m), 1317 (w), 1303 (w), 1291 (w), 1227 (m), 1180 (w), 1144 (w), 1115 (w), 1101 (w), 1055 (m), 1033 (m), 986 (w), 964 (w), 921 (w), 852 (w), 819 (m), 769 (w), 741 (w), 723 (w), 691 (w), 671 (w).

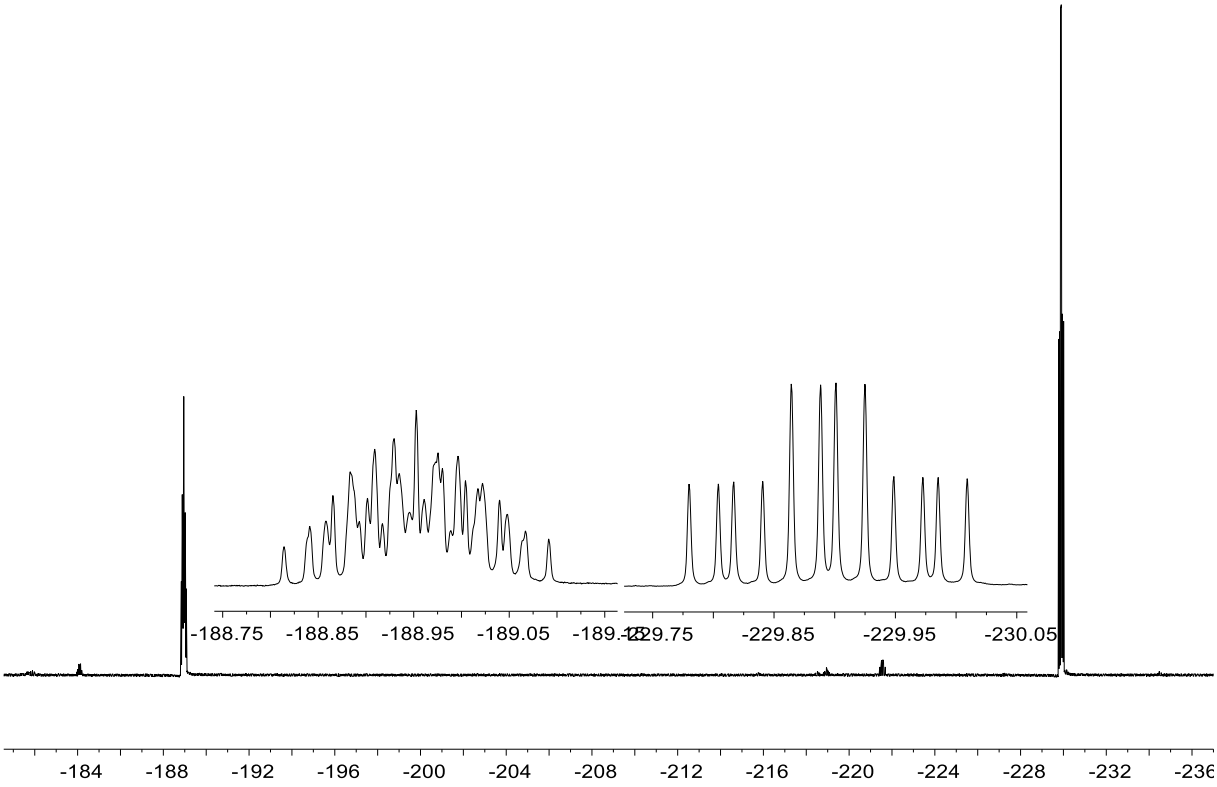
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



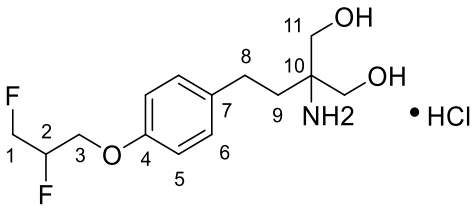

$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*, 298 K)



$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K)




**2-Amino-2-(4-(2,3-difluoropropoxy)phenethyl)propane-1,3-diol hydrochloride (12a)**




The compound was synthesised from **11a** (25 mg, 0.06 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (8 mg, 42%).

M.p.: 131 °C.

$R_f$ 0.58 (DCM : MeOH / 10 : 3).

HRMS *m/z* (ESI); Calcd. for $C_{14}H_{22}NO_3F_2$ 290.1562, found 290.1561.

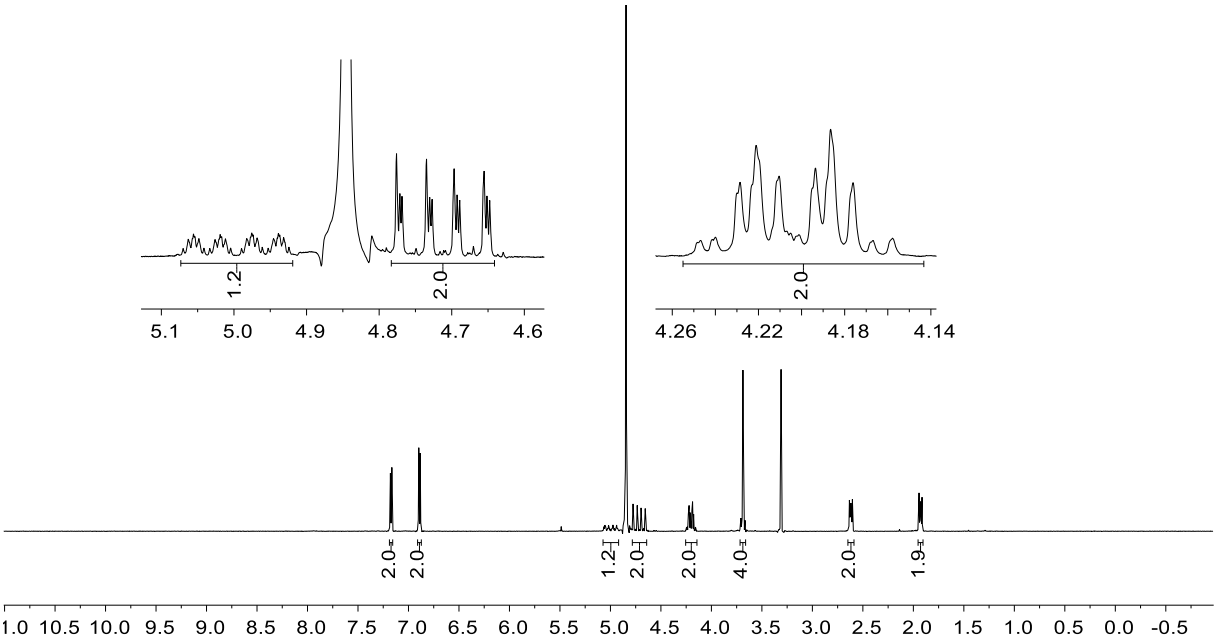
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.17 (m, 2H, HC6), 6.89 (m, 2H, HC5), 5.00 (ddm, $^2J_{FH}$ = 48.1 Hz, $^3J_{FH}$ = 22.1 Hz, 1H, HC2), 4.71 (ddm, $^2J_{FH}$ = 47.7 Hz, $^3J_{FH}$ = 24.8 Hz, 2H, $H_2$C1), [4.21 (ddd, $^3J_{FH}$ = 20.5 Hz, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 4.1 Hz, 1H), 4.19 (ddd, $^3J_{FH}$ = 20.5 Hz, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 5.5 Hz, 1H),($H_2$C3), [3.689 (d, $^2J_{HH}$ = 11.7 Hz, 2H), 3.686 (d, $^2J_{HH}$ = 11.7 Hz, 2H)]($H_2$C11), 2.62 (m, 2H, $H_2$C8), 1.93 (m, 2H, $H_2$C9).

$^{13}C\{^{1}H\}$ NMR (151 MHz, Methanol-$d_4$, 298 K) δ 158.4 (C4), 135.2 (C7), 130.4 (C6), 115.8 (C5), 91.3 (dd, $^{1}J_{FC}$ = 175.7 Hz, $^{2}J_{FC}$ = 19.7 Hz, C2), 83.3 (dd, $^{1}J_{FC}$ = 170.5 Hz, $^{2}J_{FC}$ = 22.5 Hz, C1), 67.4 (dd, $^{2}J_{FC}$ = 24.3 Hz, $^{3}J_{FC}$ = 8.7 Hz, C3), 62.5 (C11), 62.0 (C10), 34.8 (C9), 29.2 (C8).

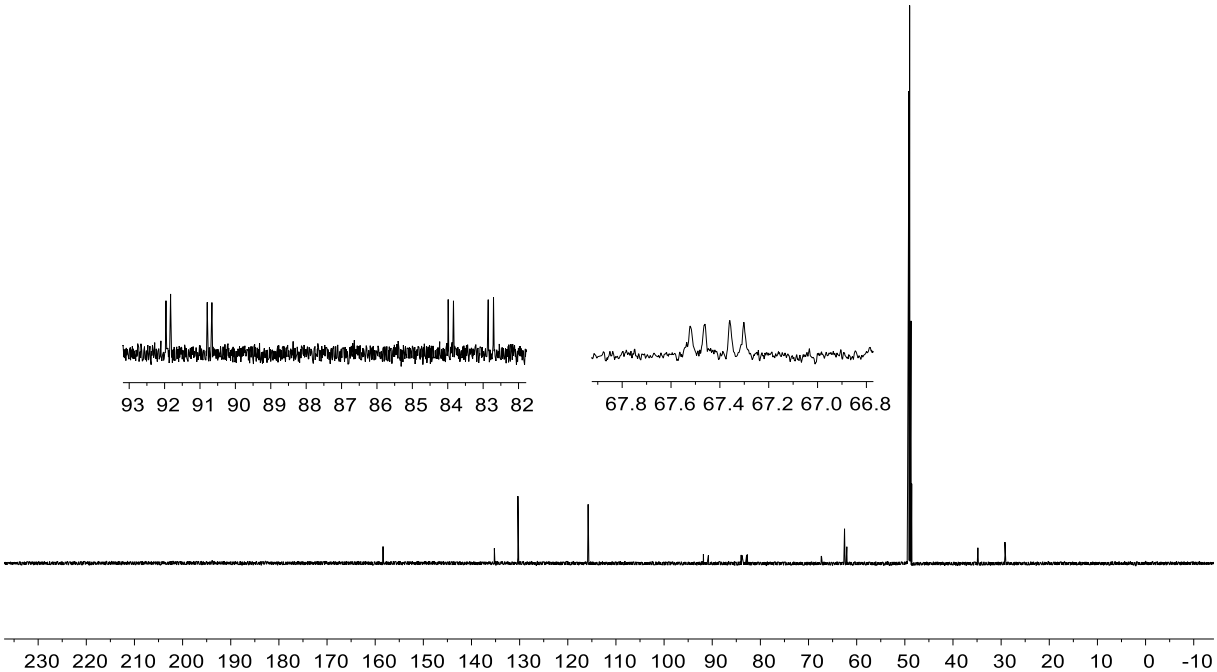
$^{19}F$ NMR (282 MHz, Chloroform-*d*, 298 K) δ -197.1 (m, 1F, FC2), -234.5 (tdd, $^{2}J_{FH}$ = 47.4 Hz, $^{3}J_{FH}$ = 21.3 Hz, $^{3}J_{FF}$ = 13.2 Hz, 1F, FC1).

IR ($cm^{-1}$): 3334 (w), 2955 (m), 2893 (m), 2800 (w), 2702 (w), 2591 (w), 2499 (w), 2060 (w), 1612 (w), 1585 (w), 1510 (m), 1457 (m), 1402 (w), 1375 (w), 1353 (w), 1299 (w), 1242 (m), 1224 (m), 1180 (m), 1107 (m), 1059 (m), 1035 (m), 948 (w), 924 (m), 869 (m), 848 (m), 830 (m), 797 (m), 765 (m), 753 (m), 665 (m).

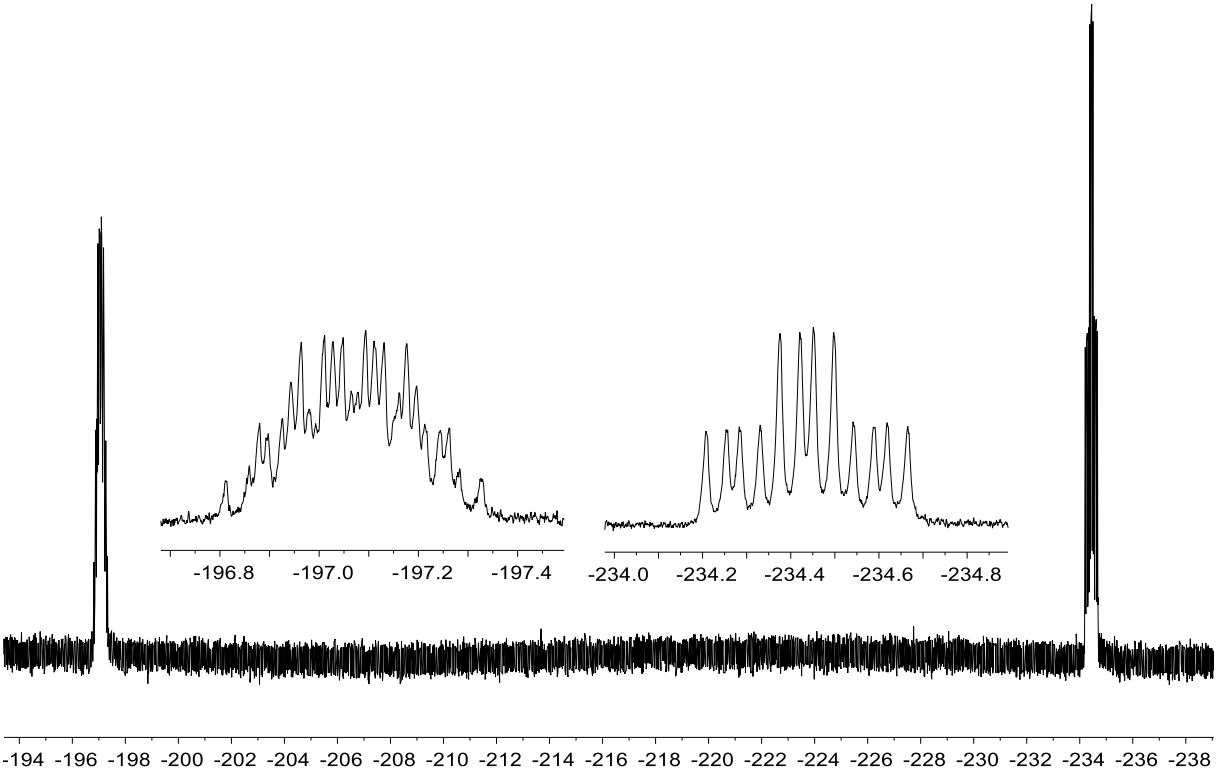
$^{1}H$ NMR (600 MHz, Methanol-$d_4$, 298 K)



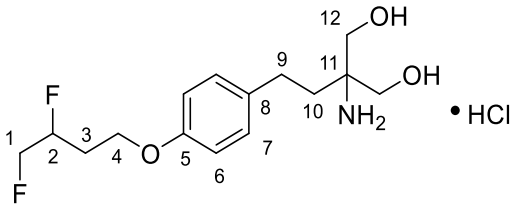

$^{13}C\{^{1}H\}$ NMR (151 MHz, Methanol-$d_4$, 298 K)



$^{19}$F NMR (282 MHz, Chloroform-*d*, 298 K)




**2-Amino-2-(4-(3,4-difluorobutoxy)phenethyl)propane-1,3-diol hydrochloride (12b)**




The compound was synthesised from **11b** (90 mg, 0.21 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (37 mg, 52%).

M.p.: 133 °C.

$R_f$ 0.13 (DCM : MeOH / 2 : 1 ).

HRMS *m/z* (ESI); Calcd. for $C_{15}H_{24}NO_3F_2$ 304.1719, found 304.1728.

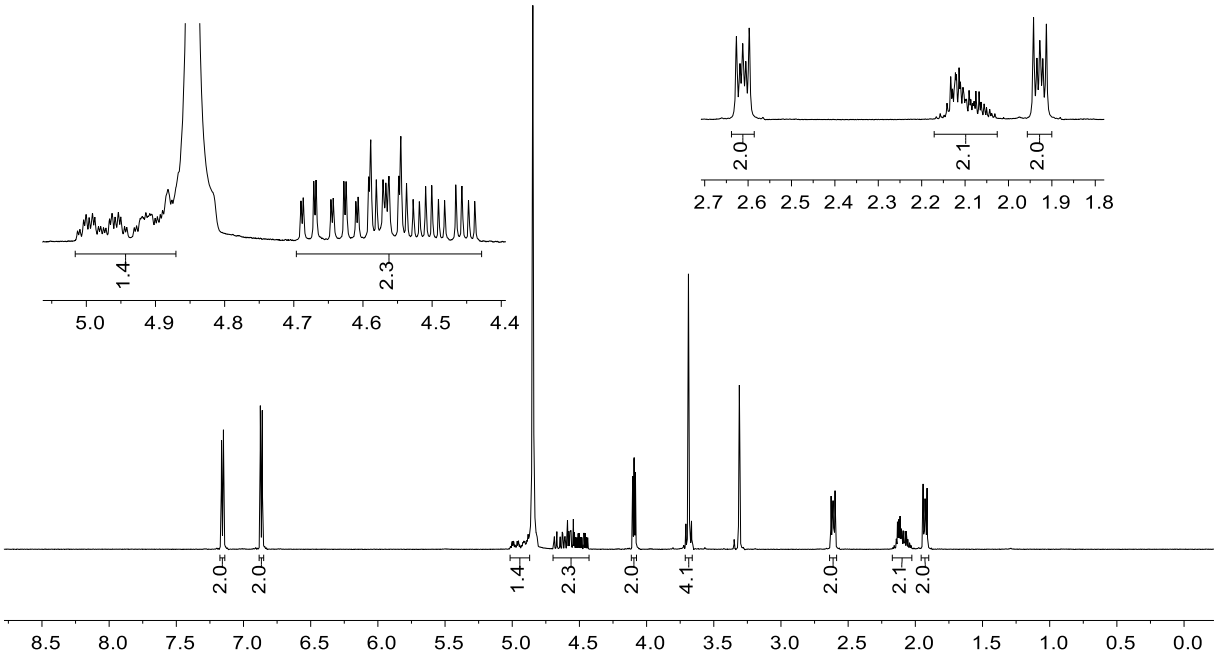
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.16 (m, 2H, HC7), 6.87 (m, 2H, HC6), 4.94 (ddm, $^2J_{FH}$ = 49.0 Hz, $^3J_{FH}$ = 22.6 Hz, 1H, HC2), [4.62 (dddd, $^2J_{FH}$ = 47.9 Hz, $^3J_{FH}$ = 26.1 Hz, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 2.0 Hz, 1H), 4.51 (dddd, $^2J_{FH}$ = 47.9 Hz, $^3J_{FH}$ = 26.2 Hz, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 5.3 Hz, 1H)]($H_2$C1), 4.12 (dd, $^3J_{HH}$ = 6.9, 5.3 Hz, 2H, $H_2$C4), [3.69 (d, $^2J_{HH}$ = 11.6 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.6 Hz, 2H)]($H_2$C12), 2.61 (m, 2H, $H_2$C9), [2.10 (m, 1H), 2.08 (m, 1H)]($H_2$C3), 1.93 (m, 2H, $H_2$C10).

$^{13}C\{^{1}H\}$ NMR (151 MHz, Methanol-$d_4$, 298 K) δ 158.6 (C5), 134.7 (C8), 130.3 (C7), 115.7 (C6), 90.6 (dd, $^{1}J_{FC}$ = 171.8 Hz, $^{2}J_{FC}$ = 19.2 Hz, C2), 85.4 (dd, $^{1}J_{FC}$ = 171.9 Hz, $^{2}J_{FC}$ = 21.5 Hz, C1), 64.4 (d, $^{3}J_{FC}$ = 5.1 Hz, C4), 62.6 (C12), 62.0 (C11), 34.9 (C10), 31.1 (dd, $^{2}J_{FC}$ = 21.4 Hz, $^{3}J_{FC}$ = 7.4 Hz, C3), 29.2 (C9).

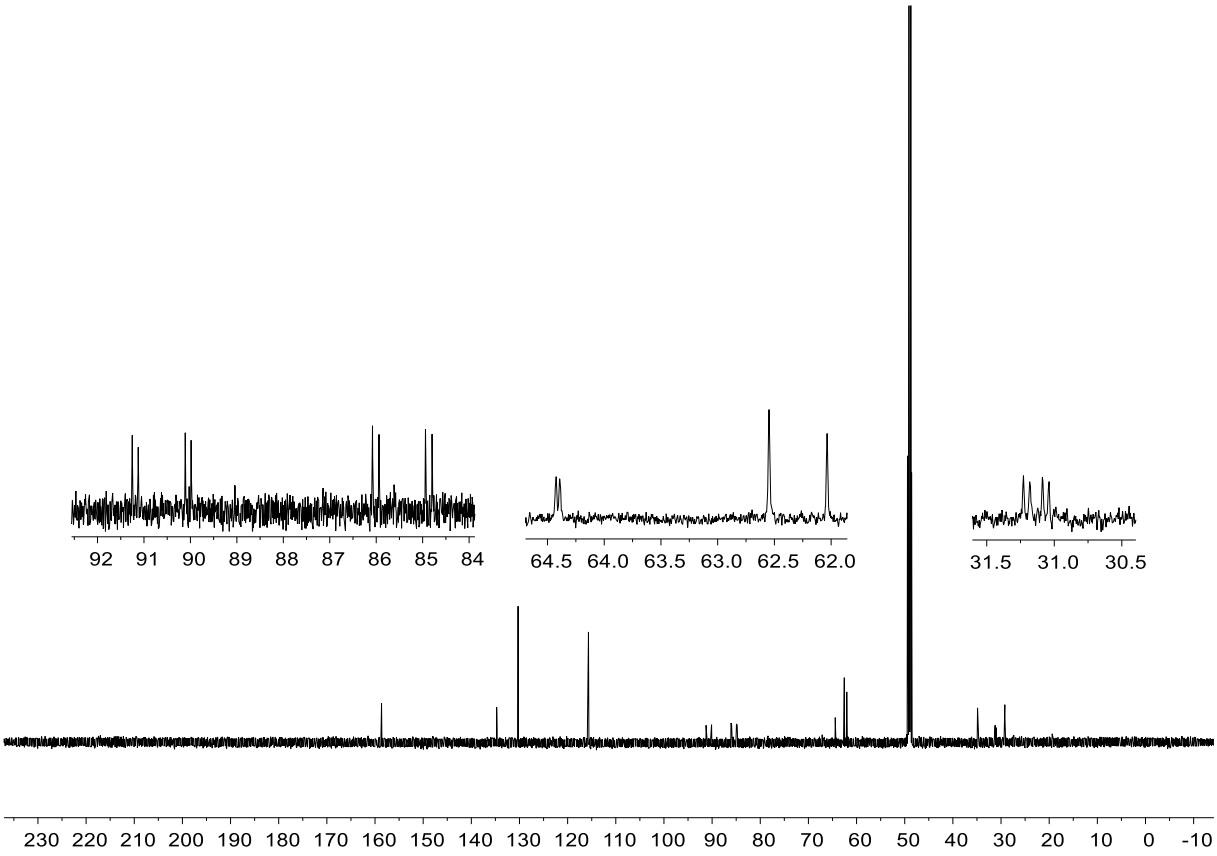
$^{19}F$ NMR (282 MHz, Methanol-$d_4$, 298 K) δ -193.0 (m, 1F, FC2), -232.0 (tdd, $^{2}J_{FH}$ = 47.9 Hz, $^{3}J_{FH}$ = 22.6 Hz, $^{3}J_{FF}$ = 12.5 Hz, 1F, FC1).

IR ($cm^{-1}$): 3365 (w), 2958 (w), 2538 (w), 1971 (w), 1614 (w), 1580 (w), 1515 (m), 1475 (w), 1455 (w), 1409 (w), 1397 (w), 1358 (w), 1345 (w), 1303 (w), 1253 (m), 1180 (w), 1114 (w), 1103 (w), 1062 (m), 1052 (m), 1035 (m), 996 (m), 965 (w), 933 (w), 896 (w), 867 (w), 839 (m), 817 (w), 781 (w), 750 (w), 679 (w), 666 (w).

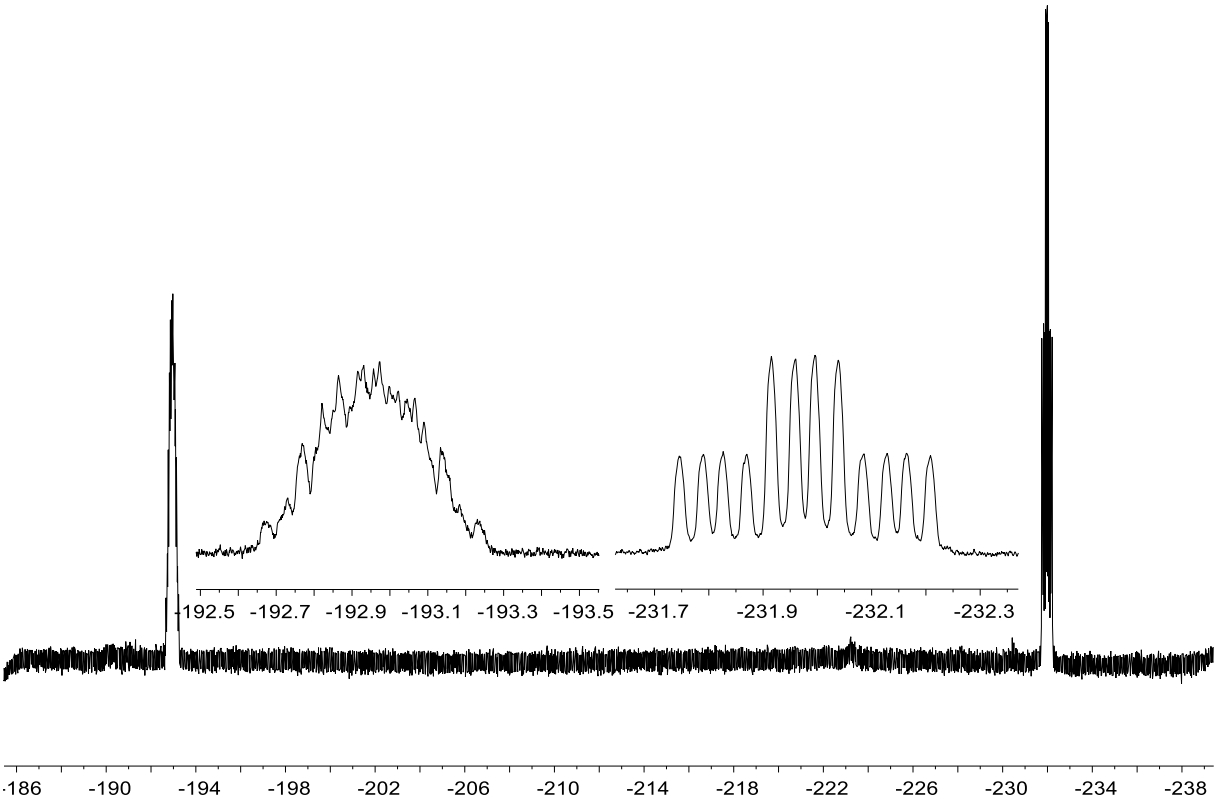
$^{1}H$ NMR (600 MHz, Methanol-$d_4$, 298 K)



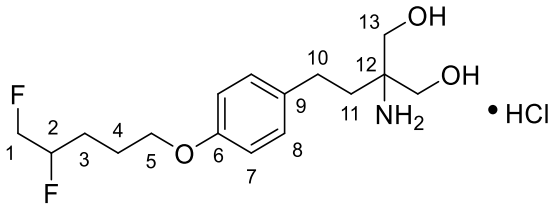
$^{13}C\{^{1}H\}$ NMR (151 MHz, Methanol-$d_4$, 298 K)




$^{19}F$ NMR (282 MHz, Methanol-$d_4$, 298 K)



**2-Amino-2-(4-((4,5-difluoropentyl)oxy)phenethyl)propane-1,3-diol hydrochloride (12c)**




The compound was synthesised from **11c** (123 mg, 0.28 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (39 mg, 39%).

M.p.: 116 °C.

$R_f$ 0.27 (DCM : MeOH / 1 : 1 ).

HRMS *m/z* (ESI); Calcd. for $C_{16}H_{26}NO_3F_2$ 318.1875, found 318.1876.

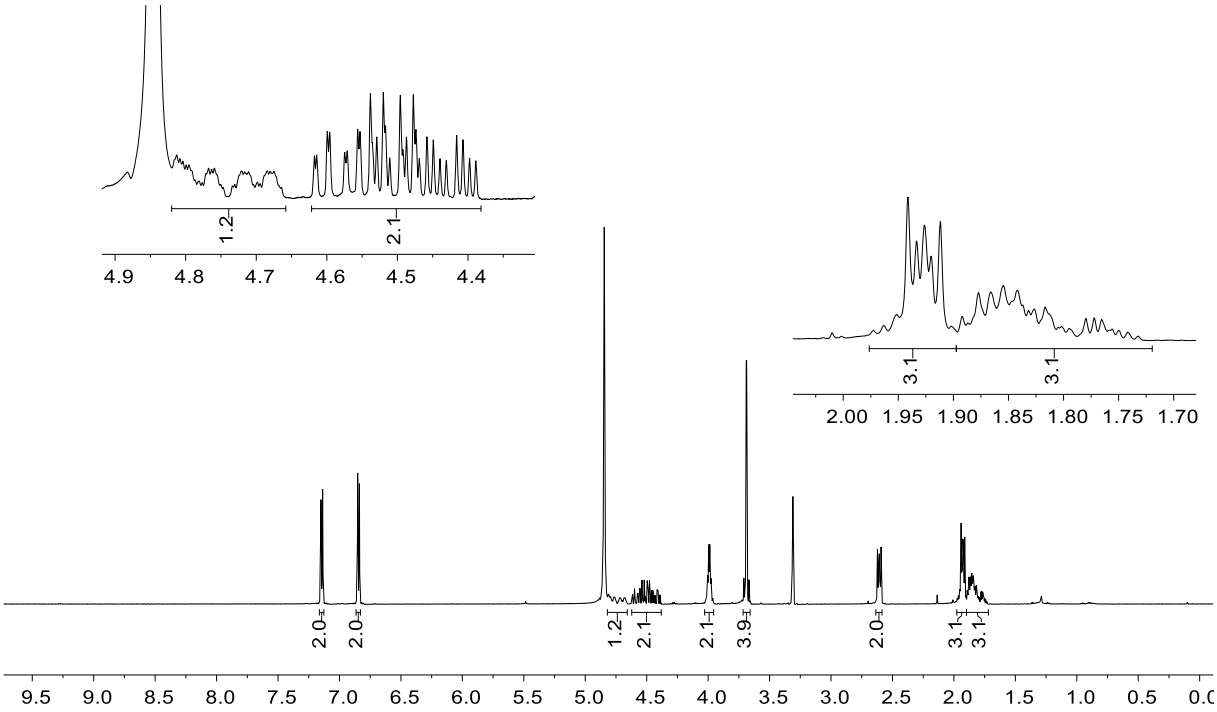
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.14 (m, 2H, HC8), 6.84 (m, 2H, HC7), 4.74 (ddm, $^2J_{FH}$ = 50.1 Hz, $^3J_{FH}$ = 21.8 Hz, 1H, HC2), [4.54 (dddd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 25.9 Hz, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 2.1 Hz, 1H), 4.46 (dddd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 25.1 Hz, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 5.4 Hz, 1H)]($H_2$C1), 3.99 (m, 2H, $H_2$C5), [3.69 (d, $^2J_{HH}$ = 11.7 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.7 Hz, 2H)]($H_2$C13), 2.61 (m, 2H, $H_2$C10), [1.94 (m, 1H), 1.87 (m, 1H)]($H_2$C4), 1.93 (m, 2H, $H_2$C11), [1.85 (m, 1H), 1.79 (m, 1H)]($H_2$C3).

$^{13}$C{$^1$H} NMR (151 MHz, Methanol-$d_4$, 298 K) δ 158.9 (C6), 134.5 (C9), 130.2 (C8), 115.6 (C7), 93.1 (dd, $^1J_{FC}$ = 171.7 Hz, $^2J_{FC}$ = 19.1 Hz, C2), 85.3 (dd, $^1J_{FC}$ = 171.9 Hz, $^2J_{FC}$ = 22.2 Hz, C1), 68.5 (C5), 62.5 (C13), 62.1 (C12), 34.9 (C11), 29.2 (C10), 27.8 (dd, $^2J_{FC}$ = 21.1 Hz, $^3J_{FC}$ = 7.1 Hz, C3), 25.9 (d, $^3J_{FC}$ = 4.4 Hz, C4).

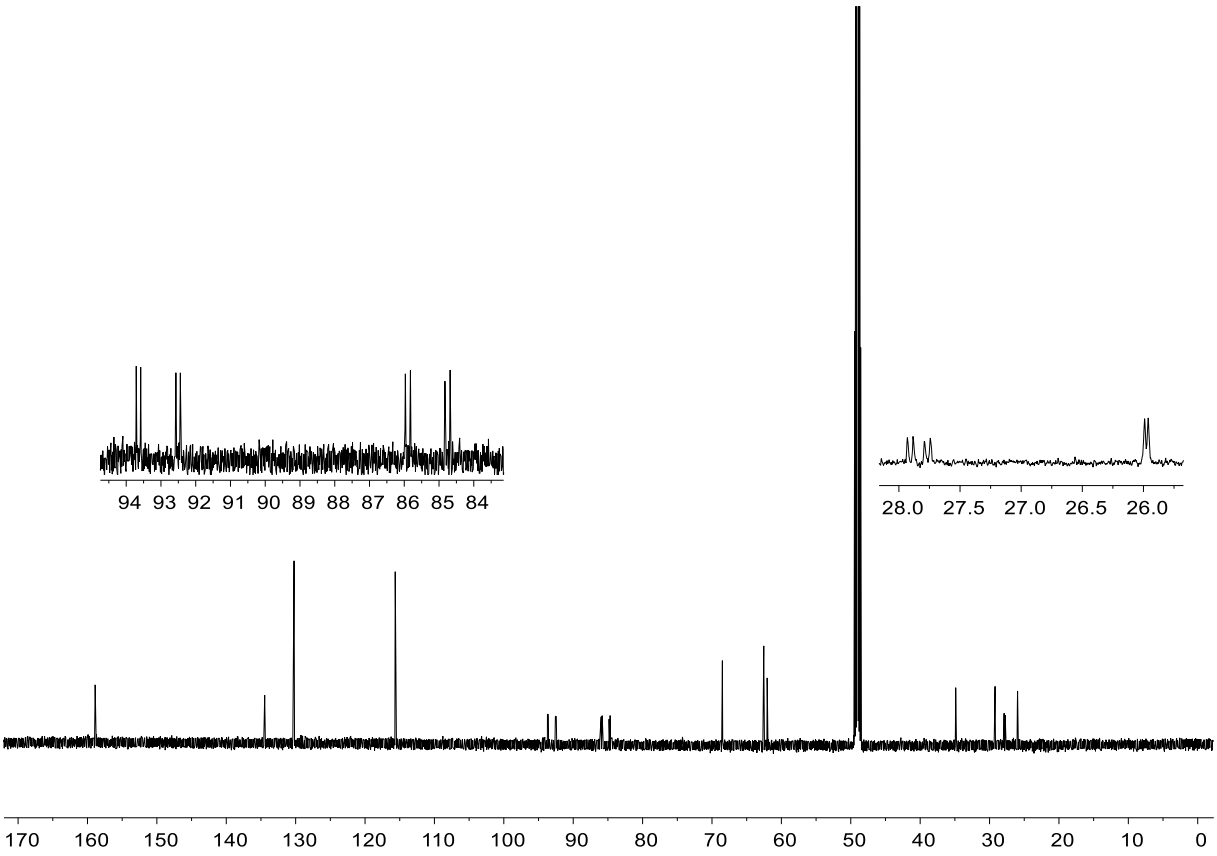
$^{19}$F NMR (282 MHz, Methanol-$d_4$, 298 K) δ -190.9 (m, 1F, FC2), -232.5 (tdd, $^2J_{FH}$ = 47.6 Hz, $^3J_{FH}$ = 21.8 Hz, $^3J_{FF}$ = 12.6 Hz, 1F, FC1).

IR (cm$^{-1}$): 3264 (w), 3027 (w), 2929 (m), 1993 (w), 1748 (w), 1610 (w), 1583 (w), 1512 (m), 1473 (w), 1456 (w), 1393 (w), 1300 (w), 1243 (m), 1178 (m), 1107 (w), 1065 (m), 1043 (m), 1030 (m), 1000 (m), 921 (w), 879 (w), 830 (m), 792 (m), 762 (w).

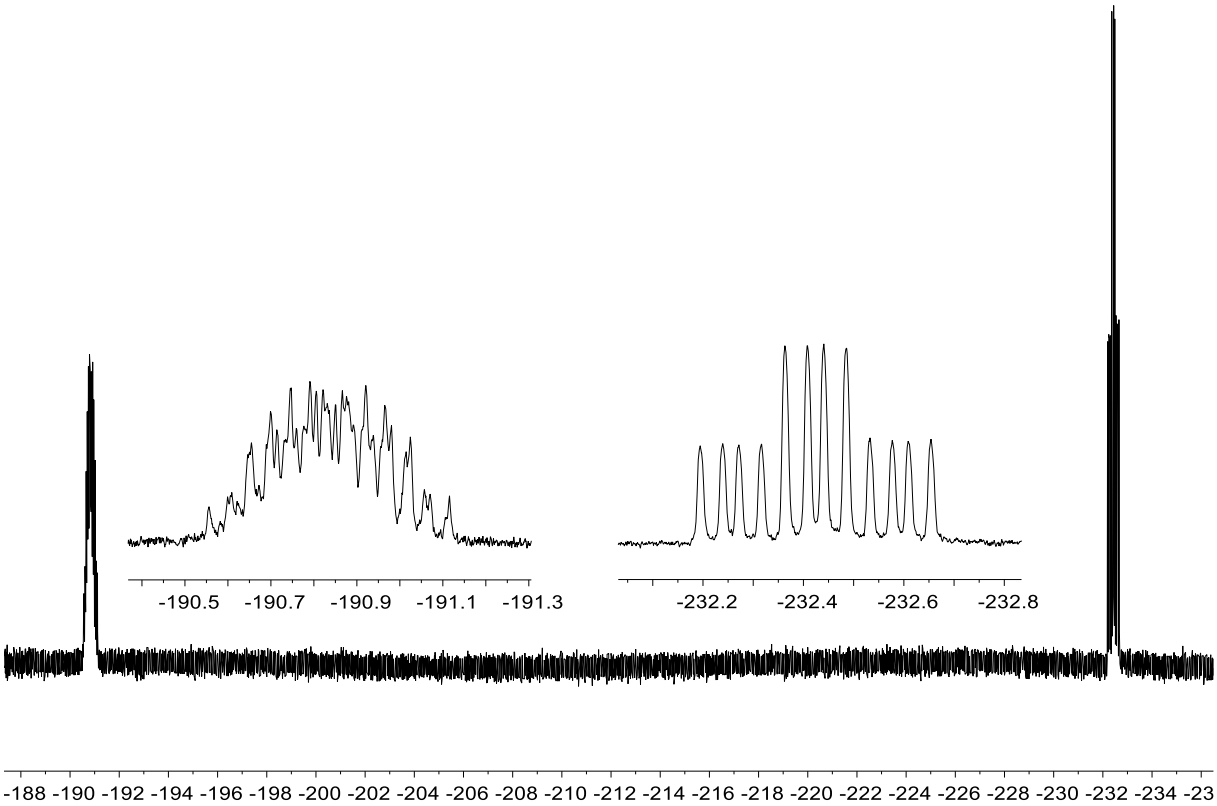
$^{1}$H NMR (600 MHz, Methanol-$d_4$, 298 K)



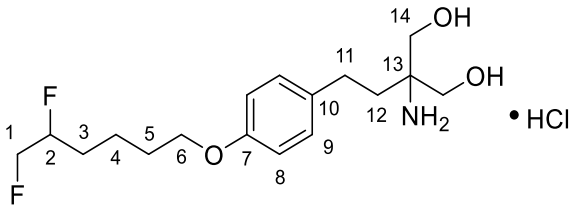

$^{13}$C{$^{1}$H} NMR (151 MHz, Methanol-$d_4$, 298 K)



$^{19}$F NMR (282 MHz, Methanol-$d_4$, 298 K)




**2-Amino-2-(4-((5,6-difluorohexyl)oxy)phenethyl)propane-1,3-diol hydrochloride (12d)**




The compound was synthesised from **11d** (84 mg, 0.18 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (45 mg, 68%).

M.p.: 120 °C.

$R_f$ 0.16 (DCM : MeOH / 1 : 1 ).

HRMS *m/z* (ESI); Calcd. for $C_{17}H_{28}NO_3F_2$ 332.2032, found 332.2034.

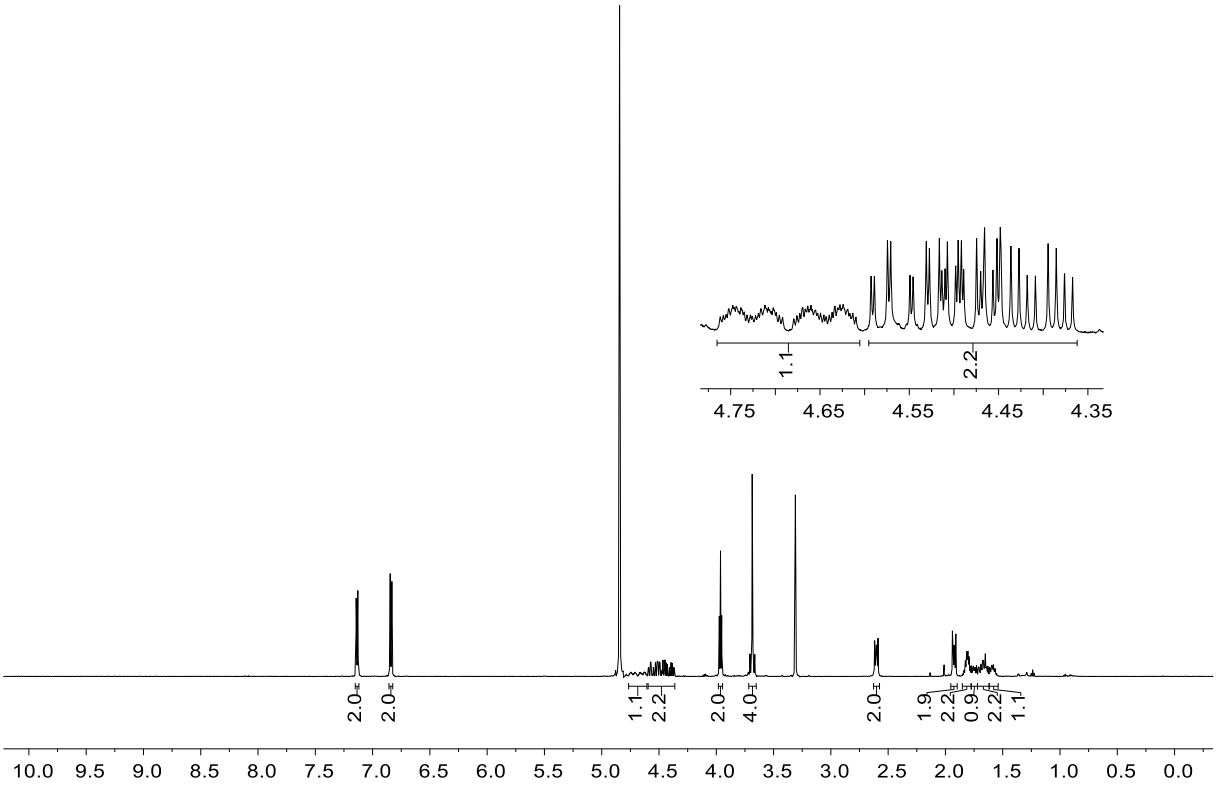
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.14 (m, 2H, HC9), 6.84 (m, 2H, HC8), 4.68 (ddm, $^2J_{FH}$ = 49.3 Hz, $^3J_{FH}$ = 21.6 Hz, 1H, HC2), [4.52 (dddd, $^2J_{FH}$ = 48.0 Hz, $^3J_{FH}$ = 26.1 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.1 Hz, 1H), 4.44 (dddd, $^2J_{FH}$ = 48.0 Hz, $^3J_{FH}$ = 25.0 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz, 1H)]($H_2$C1), 3.96 (t, $^3J_{HH}$ = 6.3 Hz, 2H, $H_2$C6), [3.69 (d, $^2J_{HH}$ = 11.6 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.6 Hz, 2H)]($H_2$C14), 2.60 (m, 2H, $H_2$C11), 1.92 (m, 2H, $H_2$C12), 1.81 (m, 2H, $H_2$C5), [1.74 (m, 1H), 1.66 (m, 1H)]($H_2$C3), [1.66 (m, 1H), 1.58 (m, 1H)]($H_2$C4).

$^{13}C\{^{1}H\}$ NMR (151 MHz, Methanol-$d_4$, 298 K) δ 159.0 (C7), 134.3 (C10), 130.2 (C9), 115.6 (C8), 93.2 (dd, $^{1}J_{FC}$ = 171.8 Hz, $^{2}J_{FC}$ = 18.8 Hz, C2), 85.3 (dd, $^{1}J_{FC}$ = 171.9 Hz, $^{2}J_{FC}$ = 22.1 Hz, C1), 68.7 (C6), 62.5 (C14), 62.0 (C13), 34.9 (C12), 30.7 (dd, $^{2}J_{FC}$ = 20.8 Hz, $^{3}J_{FC}$ = 6.7 Hz, C3), 30.2 (C5), 29.2 (C11), 22.7 (d, $^{3}J_{FC}$ = 4.6 Hz, C4).

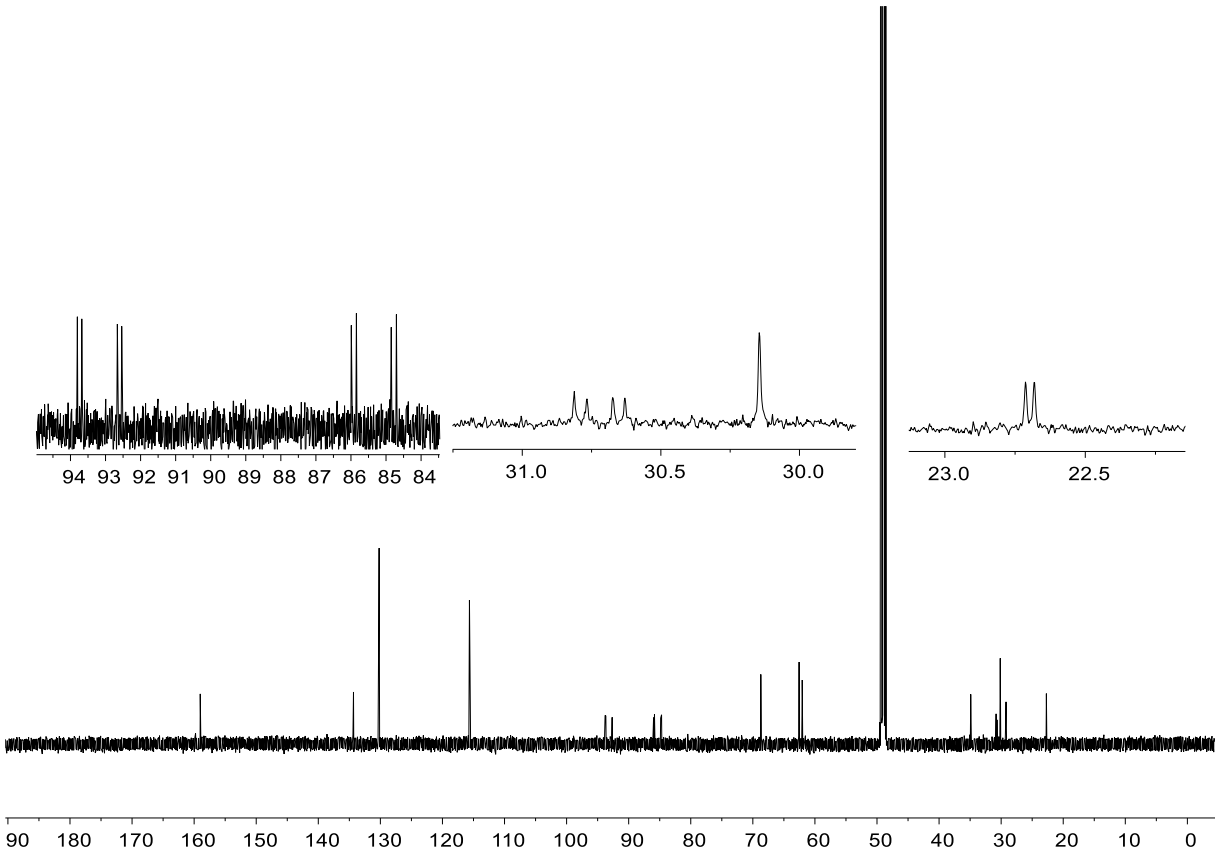
$^{19}F$ NMR (564 MHz, Methanol-$d_4$, 298 K) δ -190.6 (m, 1F, FC2), -232.4 (tdd, $^{2}J_{FH}$ = 48.0 Hz, $^{3}J_{FH}$ = 21.6 Hz, $^{3}J_{FF}$ = 12.6 Hz, 1F, FC1).

IR ($cm^{-1}$): 3365 (w), 2923 (w), 1992 (w), 1612 (w), 1581 (w), 1513 (m), 1489 (w), 1468 (w), 1455 (w), 1395 (w), 1357 (w), 1300 (w), 1244 (m), 1177 (w), 1104 (w), 1065 (m), 1029 (m), 1008 (m), 935 (w), 916 (w), 839 (w), 812 (w), 788 (w), 761 (w), 672 (w).

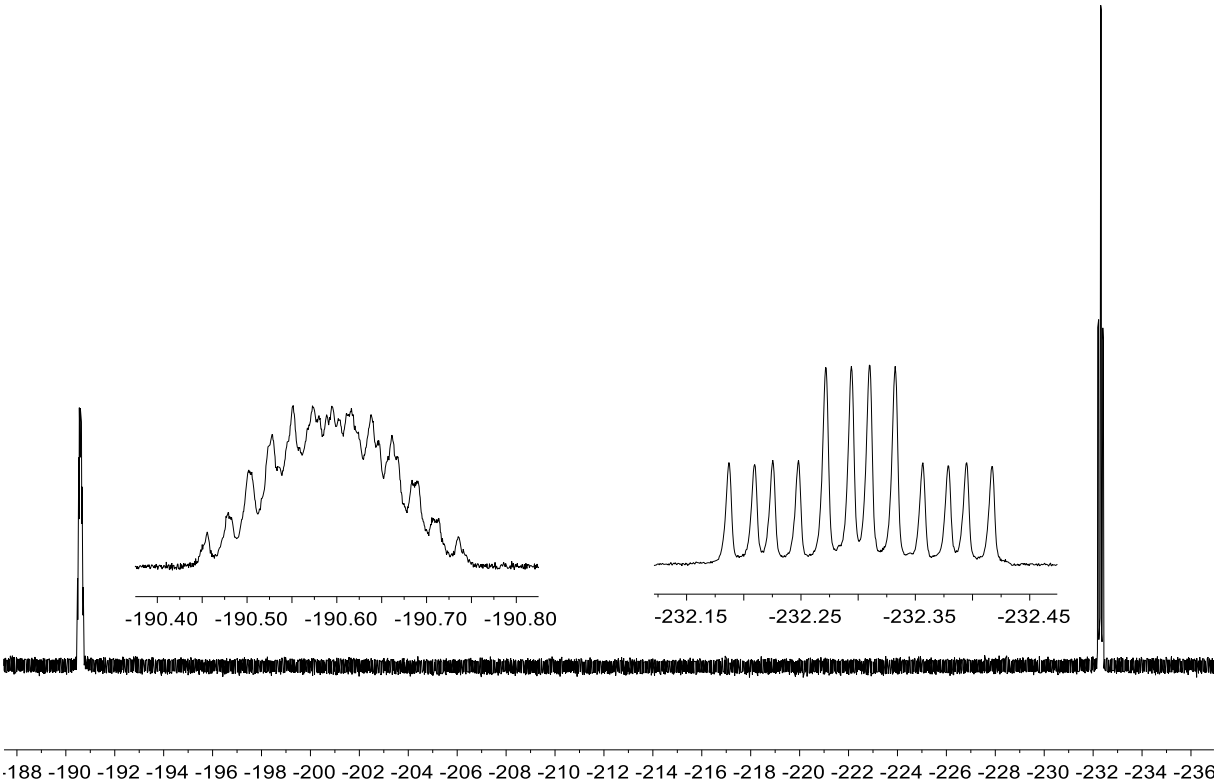
$^{1}H$ NMR (600 MHz, Methanol-$d_4$, 298 K)



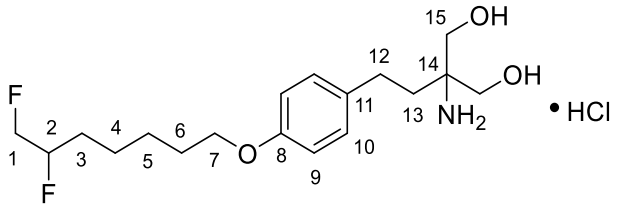
$^{13}C\{^{1}H\}$ NMR (151 MHz, Methanol-$d_4$, 298 K)




$^{19}F$ NMR (564 MHz, Methanol-$d_4$, 298 K)



**2-Amino-2-(4-((6,7-difluoroheptyl)oxy)phenethyl)propane-1,3-diol hydrochloride (12e)**




The compound was synthesised from **11e** (108 mg, 0.23 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (79 mg, 90%).

M.p.: 94 °C.

$R_f$ 0.11 (DCM : MeOH / 4 : 1 ).

HRMS *m/z* (ESI); Calcd. for $C_{18}H_{30}NO_3F_2$ 346.2188, found 346.2194.

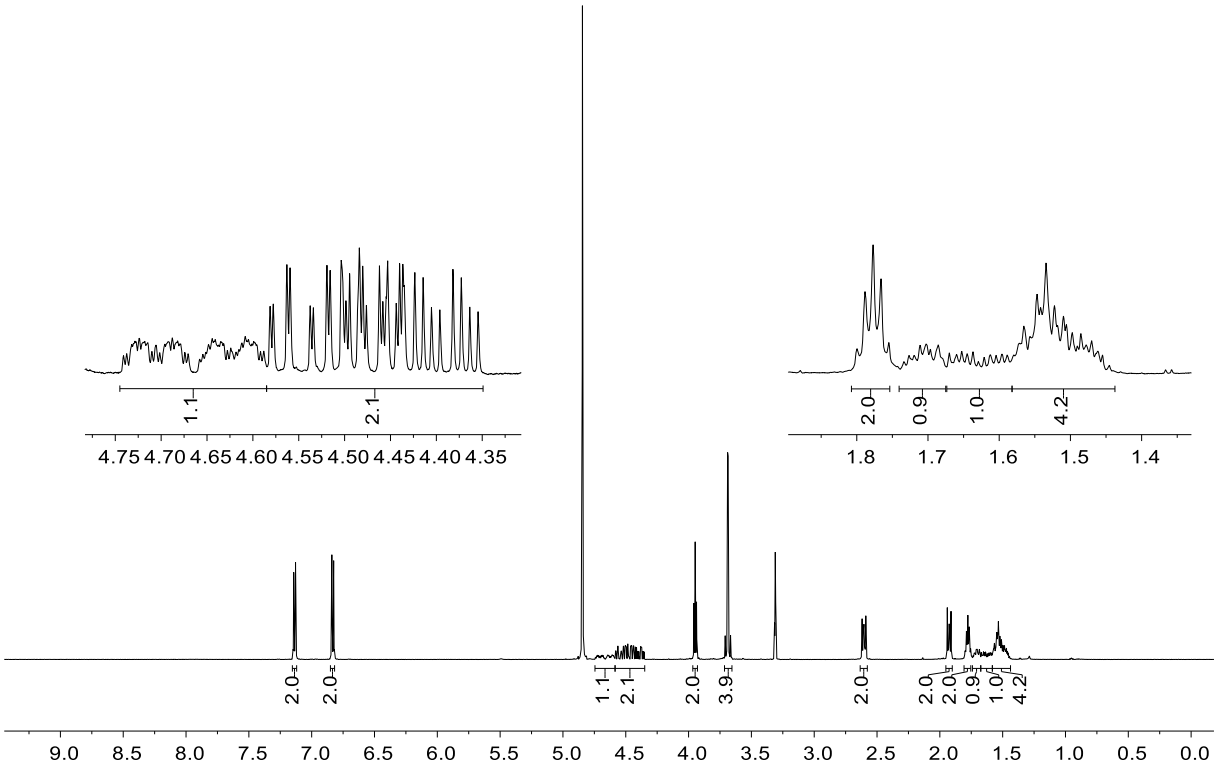
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC10), 6.83 (m, 2H, HC9), 4.66 (ddm, $^2J_{FH}$ = 49.6 Hz, $^3J_{FH}$ = 21.7 Hz, 1H, HC2), [4.51 (dddd, $^2J_{FH}$ = 47.8 Hz, $^3J_{FH}$ = 26.2 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.1 Hz, 1H), 4.43 (dddd, $^2J_{FH}$ = 47.8 Hz, $^3J_{FH}$ = 25.0 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz, 1H)]($H_2$C1), 3.95 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C7), [3.69 (d, $^2J_{HH}$ = 11.5 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.5 Hz, 2H)]($H_2$C15), 2.60 (m, 2H, $H_2$C12), 1.92 (m, 2H, $H_2$C13), 1.78 (m, 2H, $H_2$C6), [1.69 (m, 1H), 1.62 (m, 1H)]($H_2$C3), [1.55 (m, 1H), 1.48 (m, 1H)]($H_2$C4), [1.53 (m, 1H), 1.51 (m, 1H)]($H_2$C5).

$^{13}$C{$^1$H} NMR (151 MHz, Methanol-$d_4$, 298 K) δ 159.0 (C8), 134.3 (C11), 130.2 (C10), 115.6 (C9), 93.2 (dd, $^1J_{FC}$ = 171.6 Hz, $^2J_{FC}$ = 18.8 Hz, C2), 85.4 (dd, $^1J_{FC}$ = 171.8 Hz, $^2J_{FC}$ = 22.2 Hz, C1), 68.8 (C7), 62.5 (C15), 62.1 (C14), 34.9 (C13), 30.9 (dd, $^2J_{FC}$ = 20.7 Hz, $^3J_{FC}$ = 6.8 Hz, C3), 30.2 (C6), 29.2 (C12), 27.0 (C5), 25.7 (d, $^3J_{FC}$ = 4.6 Hz, C4).

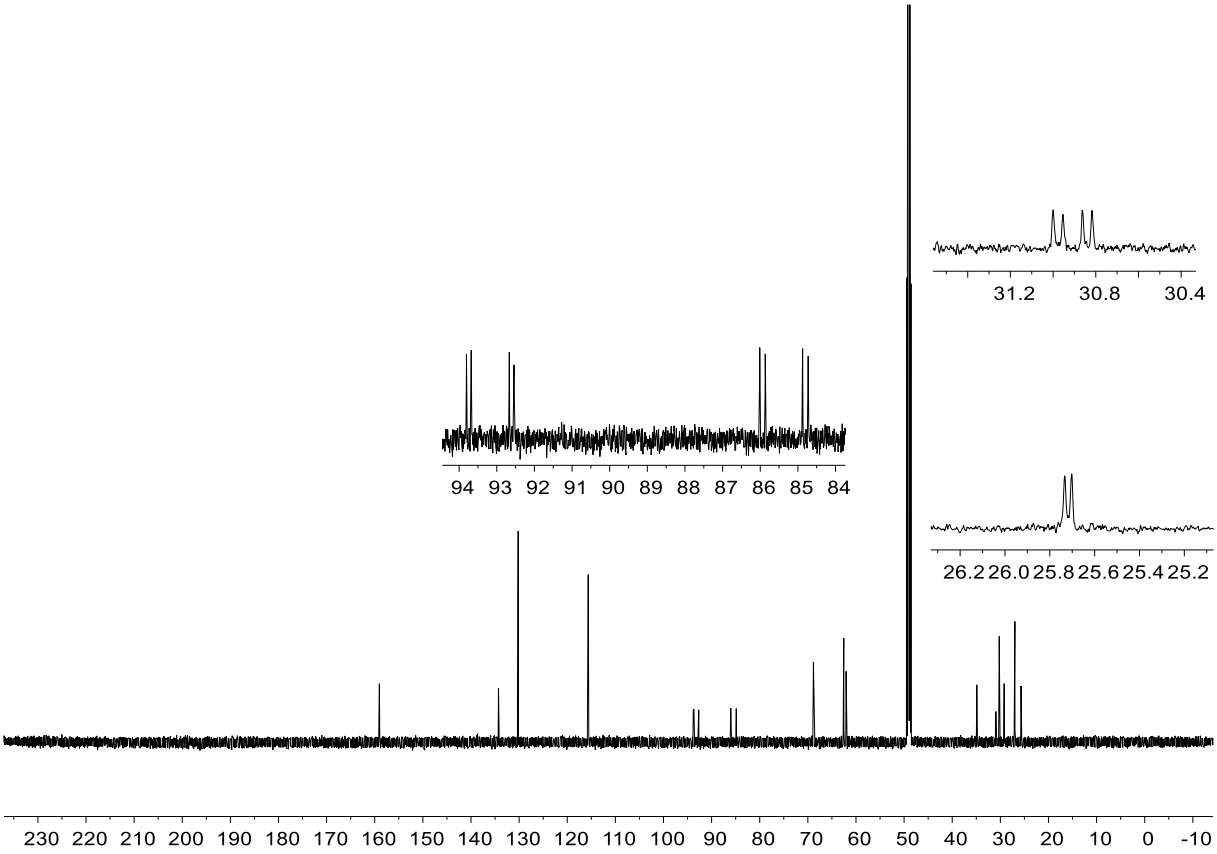
$^{19}$F NMR (282 MHz, Methanol-$d_4$, 298 K) δ 190.4 (m, 1F, FC2), -232.2 (tdd, $^2J_{FH}$ = 47.8 Hz, $^3J_{FH}$ = 21.7 Hz, $^3J_{FF}$ = 12.6 Hz, 1F, FC1).

IR (cm$^{-1}$): 3261 (w), 3027 (w), 2941 (m), 2866 (w), 2326 (w), 1972 (w), 1610 (w), 1583 (w), 1512 (m), 1473 (w), 1456 (w), 1440 (w), 1395 (w), 1346 (w), 1300 (w), 1243 (m), 1178 (m), 1151 (w), 1106 (w), 1066 (m), 1045 (m), 1028 (m), 920 (w), 865 (w), 849 (w), 829 (m), 791 (w), 763 (w), 751 (w), 732 (w), 671 (w).

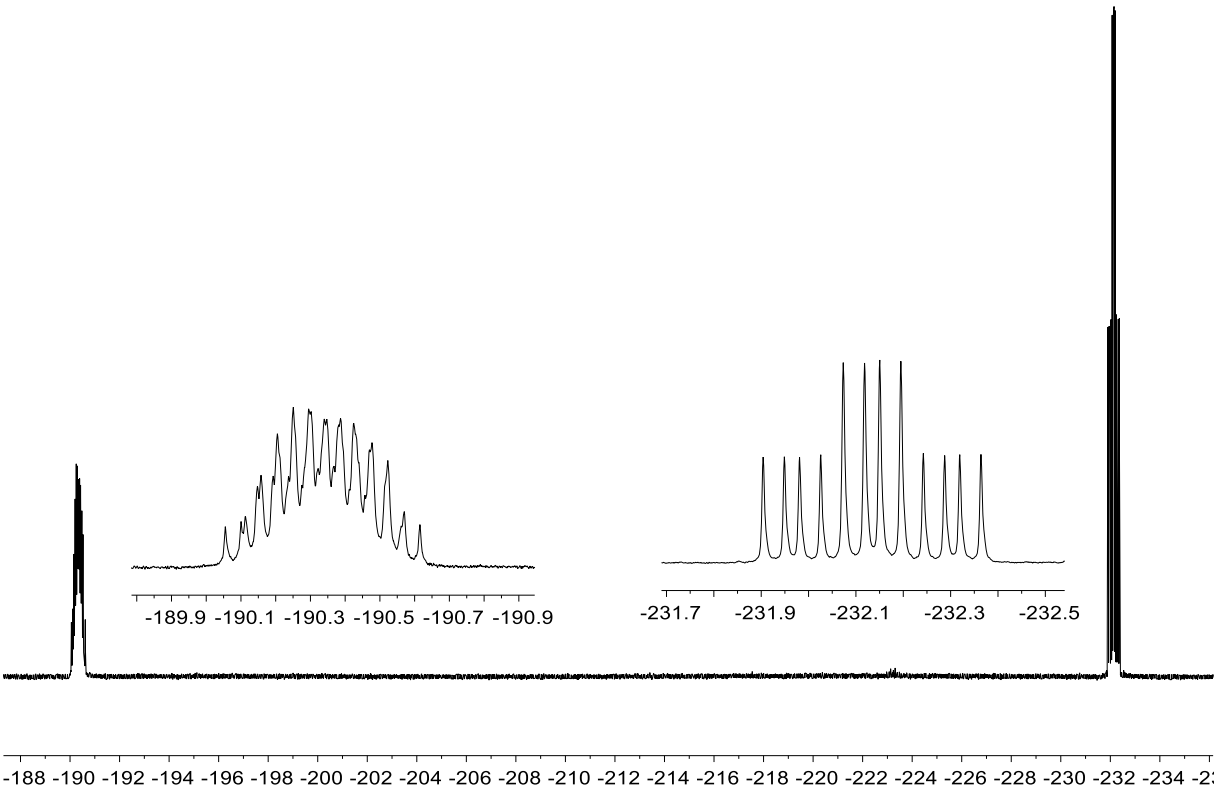
$^{1}$H NMR (600 MHz, Methanol-$d_4$, 298 K)



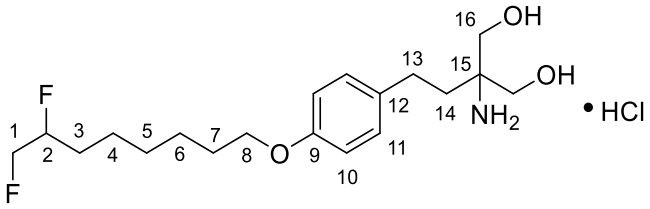

$^{13}$C{$^{1}$H} NMR (151 MHz, Methanol-$d_4$, 298 K)



$^{19}$F NMR (282 MHz, Methanol-$d_4$, 298 K)




**2-Amino-2-(4-((7,8-difluorooctyl)oxy)phenethyl)propane-1,3-diol hydrochloride (12f)**




The compound was synthesised from **11f** (79 mg, 0.16 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (35 mg, 55%).

M.p.: 92 °C.

$R_f$ 0.62 (DCM : MeOH / 10 : 3).

HRMS *m/z* (ESI); Calcd. for $C_{19}H_{32}NO_3F_2$ 360.2345, found 360.2346.

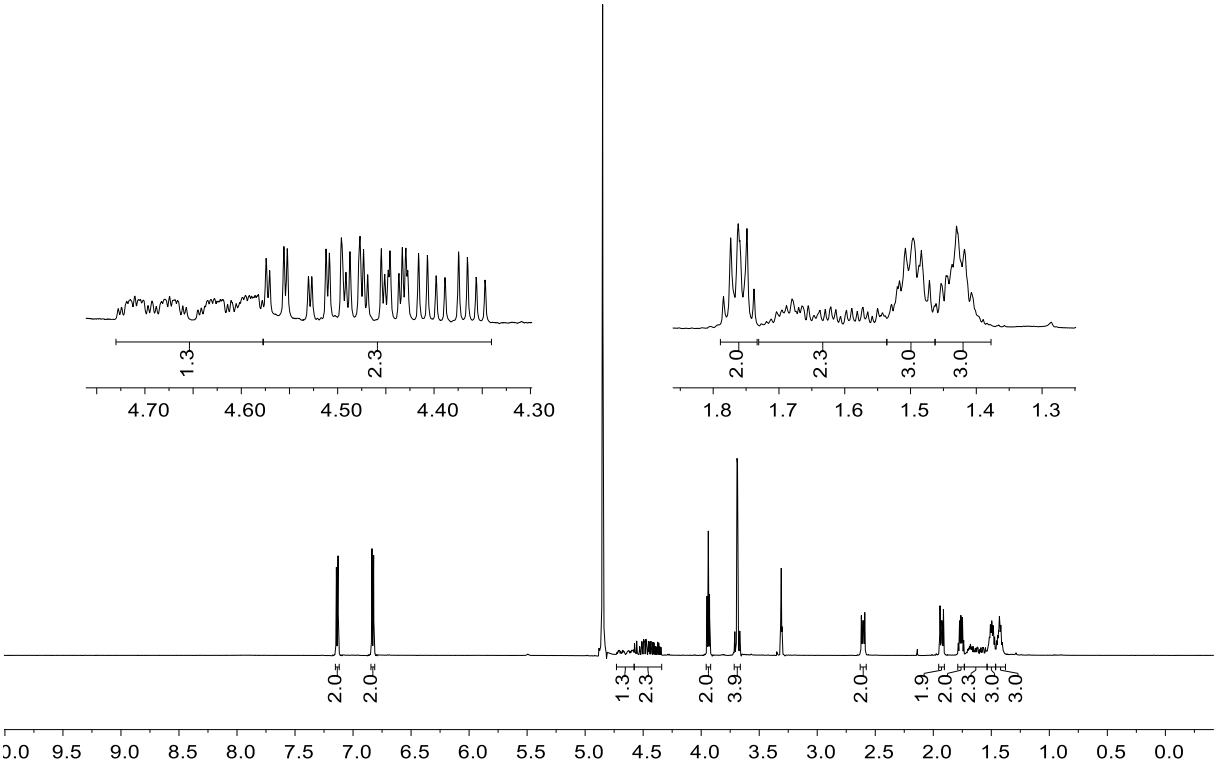
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.14 (m, 2H, HC11), 6.83 (m, 2H, HC10), 4.65 (ddm, $^2J_{FH}$ = 49.5 Hz, $^3J_{FH}$ = 21.6 Hz, 1H, HC2), [4.50 (dddd, $^2J_{FH}$ = 47.8 Hz, $^3J_{FH}$ = 26.3 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.1 Hz, 1H), 4.42 (dddd, $^2J_{FH}$ = 47.8 Hz, $^3J_{FH}$ = 24.9 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz, 1H)]($H_2$C1), 3.94 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C8), [3.69 (d, $^2J_{HH}$ = 11.6 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.6 Hz, 2H)]($H_2$C16), 2.61 (m, 2H, $H_2$C13), 1.93 (m, 2H, $H_2$C14), 1.76 (m, 2H, $H_2$C7), [1.68 (m, 1H), 1.59 (m, 1H)]($H_2$C3), [1.51 (m, 1H), 1.43 (m, 1H)]($H_2$C4), [1.50 (m, 1H), 1.48 (m, 1H)]($H_2$C6), [1.43 (m, 1H), 1.41 (m, 1H)]($H_2$C5).

$^{13}C\{^{1}H\}$ NMR (151 MHz, Methanol-$d_4$, 298 K) δ 159.0 (C9), 134.3 (C12), 130.2 (C11), 115.6 (C10), 93.2 (dd, $^{1}J_{FC}$ = 171.7 Hz, $^{2}J_{FC}$ = 18.7 Hz, C2), 85.4 (dd, $^{1}J_{FC}$ = 171.9, $^{2}J_{FC}$ = 22.1 Hz, C1), 68.9 (C8), 62.5 (C16), 62.1 (C15), 34.9 (C14), 30.9 (dd, $^{2}J_{FC}$ = 20.8 Hz, $^{3}J_{FC}$ = 6.8 Hz, C3), 30.3 (C7), 30.2 (C5), 29.2 (C13), 27.0 (C6), 25.8 (d, $^{3}J_{FC}$ = 4.8 Hz, C4).

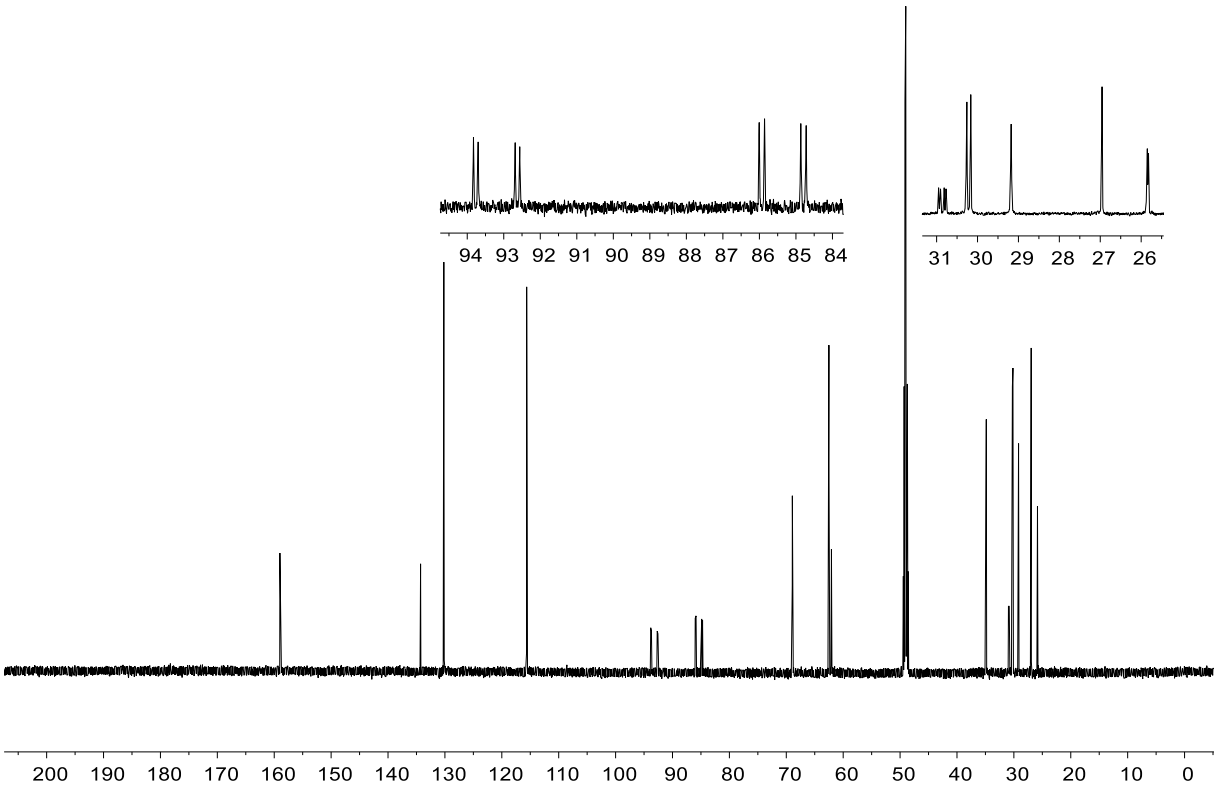
$^{19}F$ NMR (564 MHz, Methanol-$d_4$, 298 K) δ -190.3 (m, 1F, FC2), -232.2 (tdd, $^{2}J_{FH}$ = 47.8 Hz, $^{3}J_{FH}$ = 21.6 Hz, $^{3}J_{FF}$ = 12.6 Hz, 1F, FC1).

IR ($cm^{-1}$): 3267 (w), 3036 (w), 2939 (m), 2862 (w), 1611 (w), 1582 (w), 1512 (m), 1473 (w), 1456 (w), 1440 (w), 1393 (w), 1300 (w), 1243 (m), 1178 (w), 1106 (w), 1066 (m), 1037 (m), 981 (w), 920 (w), 881 (w), 850 (m), 828 (m), 791 (m), 763 (w), 750 (w), 728 (w), 671 (w).

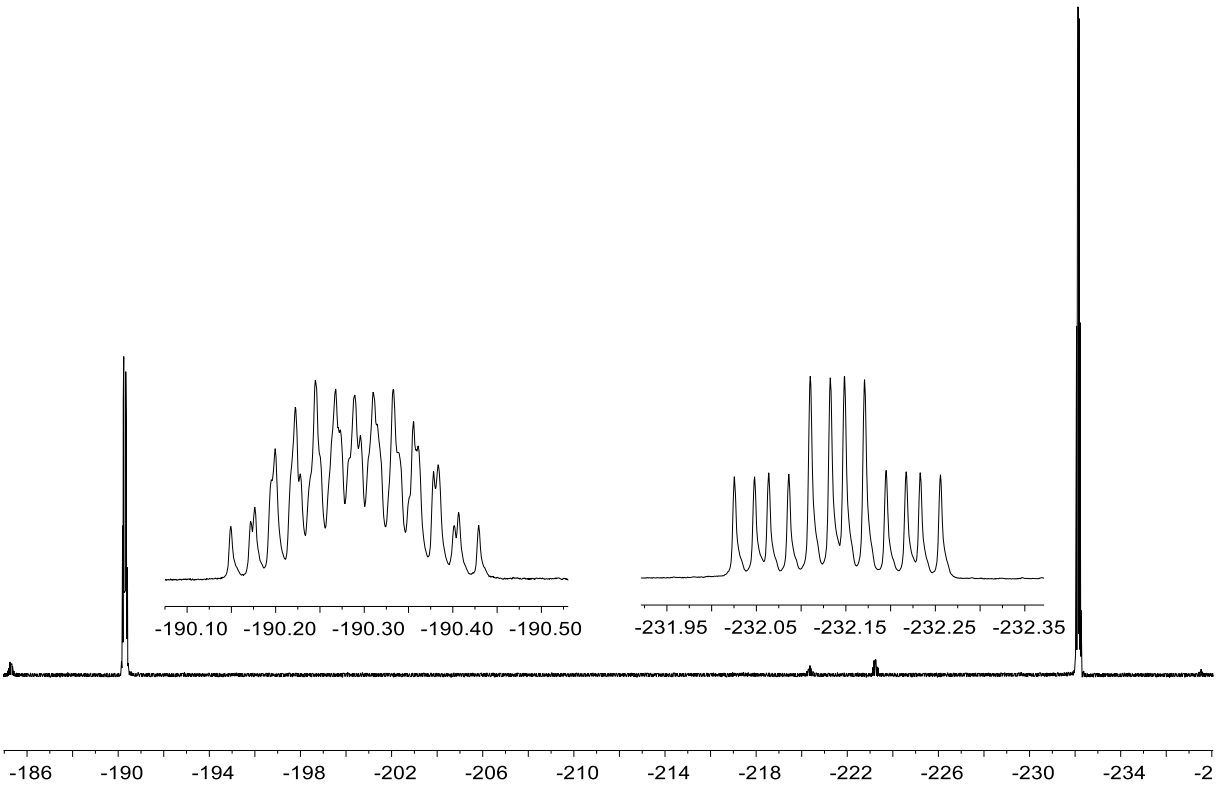
$^{1}H$ NMR (599 MHz, Methanol-$d_4$, 298 K)



$^{13}C\{^{1}H\}$ NMR (151 MHz, Methanol-$d_4$, 298 K)



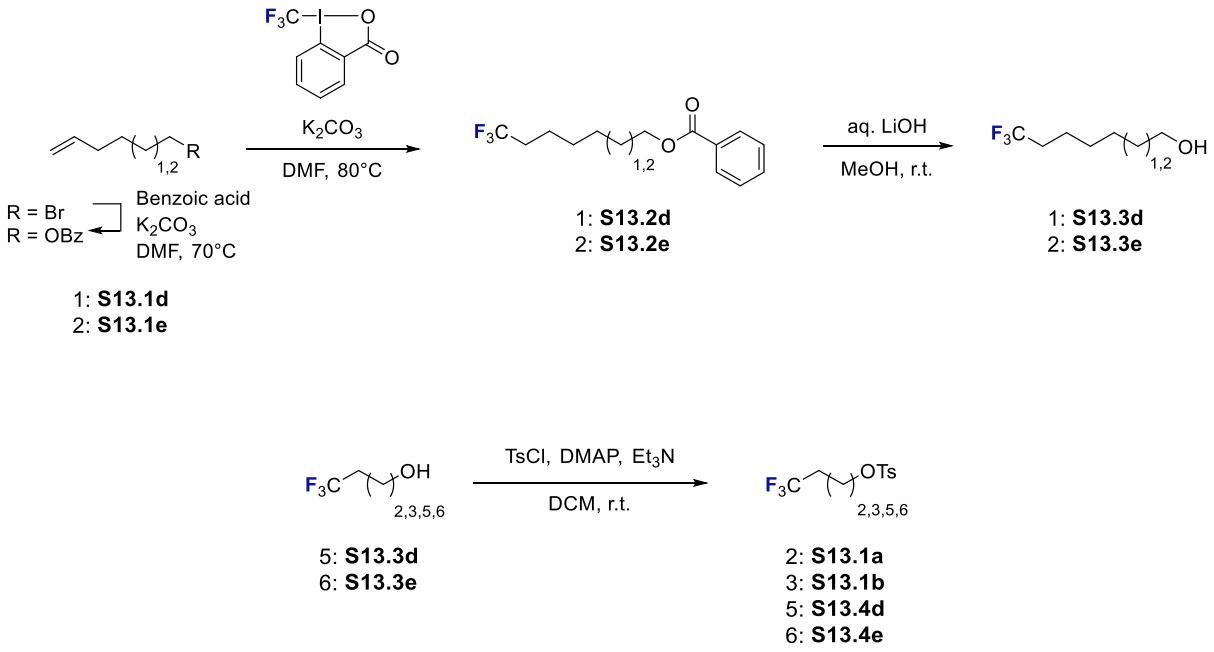

$^{19}F$ NMR (564 MHz, Methanol-$d_4$, 298 K)



## II.6 Synthesis of Trifluoromethylated Fingolimod Analogues

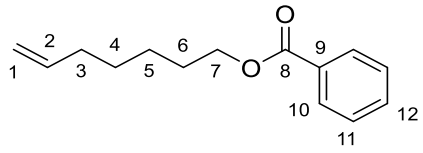
### II.6.1 Trifluoromethylated alkyl chains

**Scheme S4.**




Starting materials 4,4,4-trifluorobutan-1-ol and 5,5,5-trifluoropentan-1-ol were used for the synthesis of compound S13.1a and S13.1b, respectively and were obtained commercially.

**Hept-6-en-1-yl benzoate (S13.1e)**




$K_2CO_3$ (415 mg, 3.00 mmol, 2.00 eq.) was flame dried in a schlenk flask where after benzoic acid (183 mg, 1.50 mmol, 1.00 eq.), dry DMF (3 mL) and 7-bromo-1-heptene (229 µl, 1.50 mmol, 1.00 eq.) was added under an atmosphere of argon. The resulting mixture was then stirred at 70 °C for 8 h. The solvent was removed under reduced pressure and the residue was diluted with water followed by extraction with DCM (x 3). The collected organic layers were then washed with 5% aq. LiCl, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash chromatography (CyH : EtOAc / 20 : 1) and was afforded as a colourless oil (305 mg, 93%).

$R_f$ 0.46 (CyH : EtOAc / 10 : 1).

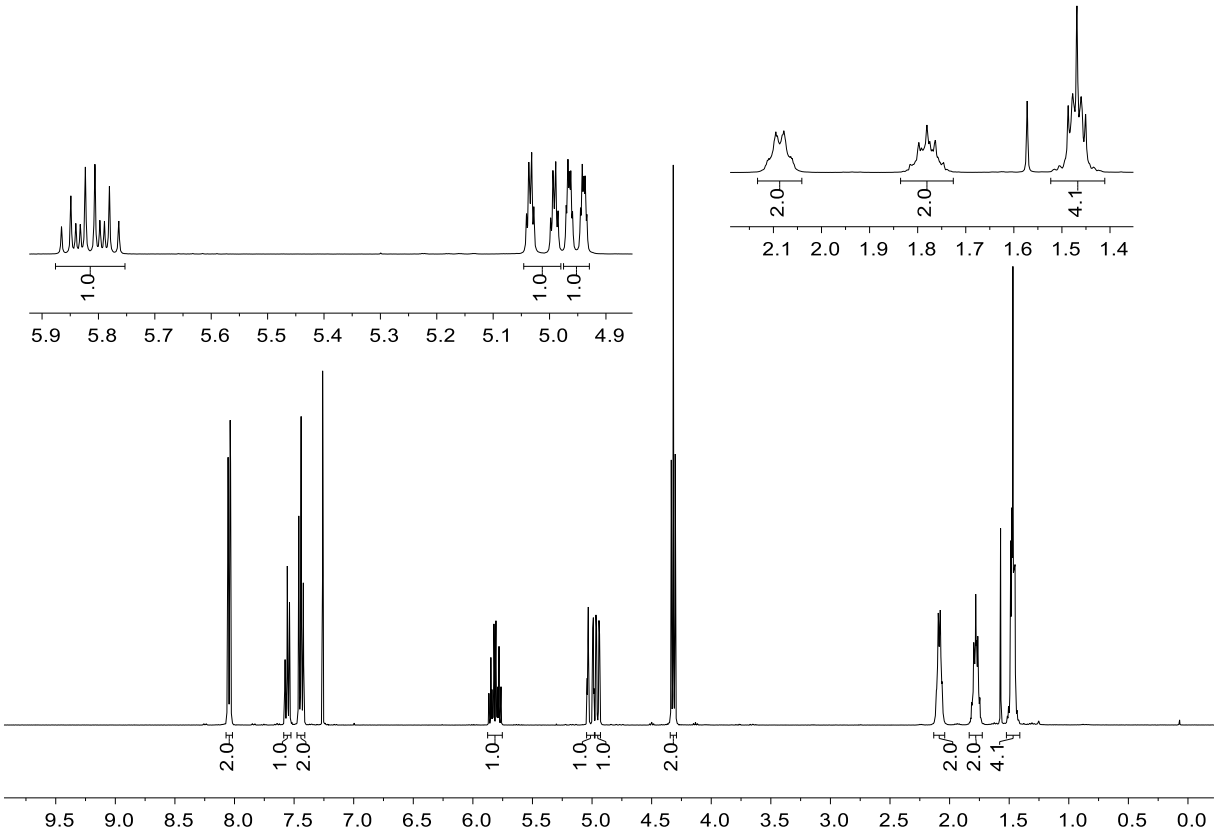
HRMS *m/z* (ESI); Calcd. for $C_{14}H_{18}O_2Na$ 241.1199, found 241.1213.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 8.05 (m, 2H, HC10), 7.56 (m, 1H, HC12), 7.44 (m, 2H, HC11), 5.81 (ddt, $^3J_{HH}$ = 17.2, 10.2, 6.7 Hz, 1H, HC2), [5.01 (dm, $^3J_{HH}$ = 17.2 Hz, 1H), 4.95 (dm, $^3J_{HH}$ = 10.2 Hz, 1H)]($H_2$C1), 4.32 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2$C7), 2.09 (m, 2H, $H_2$C3), 1.78 (m, 2H, $H_2$C6), 1.47 (m, 4H, $H_2$C4,5).

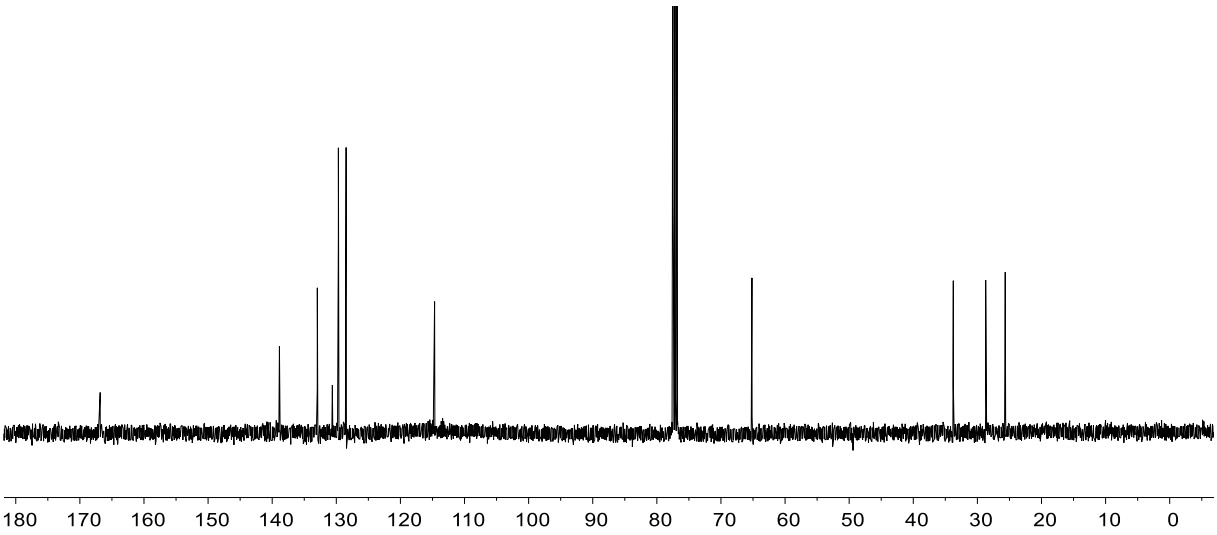
$^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*, 298 K) δ 166.8 (C8), 138.9 (C2), 133.0 (C12), 130.6 (C9), 129.7 (C10), 128.5 (C11), 114.7 (C1), 65.2 (C7), 33.8 (C3), [28.71, 28.65](C4,6), 25.7 (C5).

IR ($cm^{-1}$): 3074 (w), 2932 (w), 2858 (w), 1717 (s), 1641 (w), 1602 (w), 1585 (w), 1492 (w), 1452 (w), 1387 (w), 1314 (w), 1269 (s), 1176 (w), 1111 (m), 1070 (m), 1027 (m), 994 (w), 953 (w), 910 (m), 850 (w), 806 (w), 708 (s), 687 (m), 675 (s).

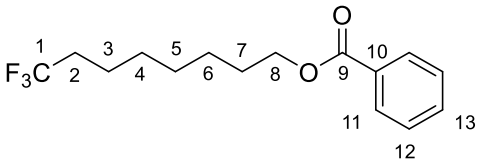
$^{1}H$ NMR (400 MHz, Chloroform-*d*, 298 K)



$^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*, 298 K



**8,8,8-Trifluorooctyl benzoate (S13.2e)**




The product was synthesised from **S13.1e** (170 mg, 0.78 mmol, 1.00 eq.) following H. Egami, Y. Usui, S. Kawamura, S. Nagashima, M. Sodeoka *Chem. Asian J.* **2015**, *10*, 2190-2199. The product was purified by preparative TLC ($SiO_2$, CyH : EtOAc / 30 : 1 → 20 : 1) and was afforded as a colourless oil (109 mg, 48%).

$R_f$ 0.38 (CyH : EtOAc / 20 : 1)

HRMS *m/z* (ESI); Calcd. for $C_{15}H_{19}O_2F_3Na$ 311.1229, found 311.1233.

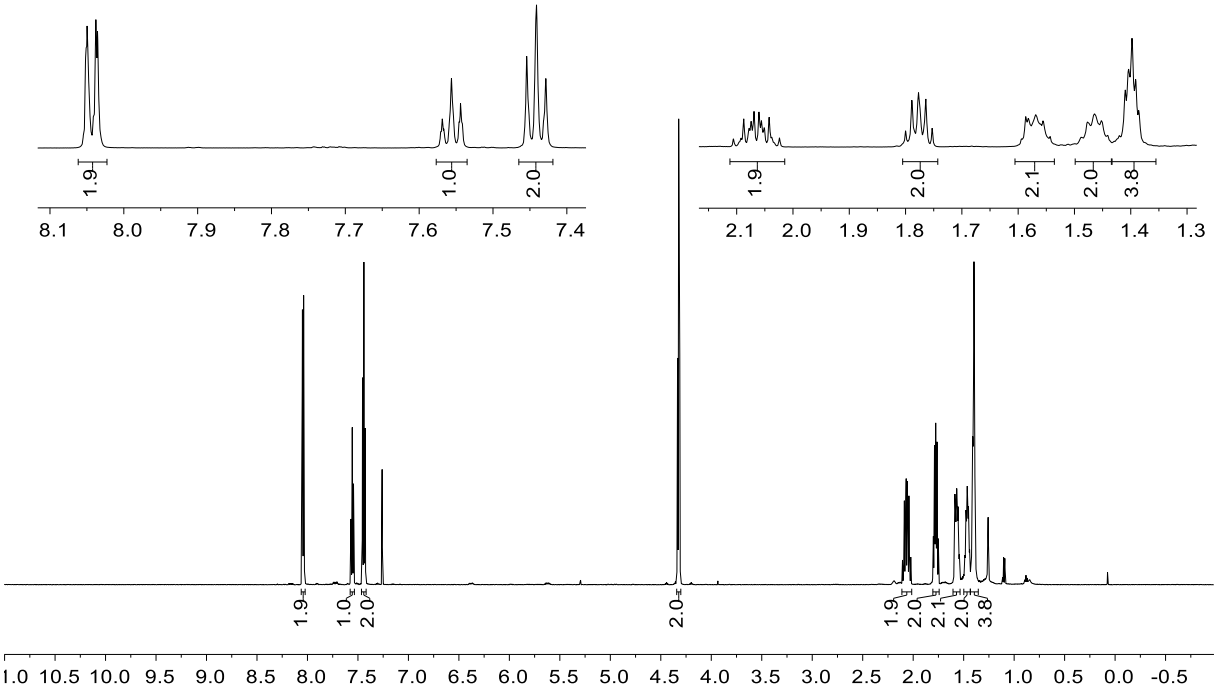
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 8.04 (m, 2H, HC11), 7.56 (m, 1H, HC13), 7.43 (m, 2H, HC12), 4.32 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2$C8), 2.06 (qm, $^3J_{FH}$ = 10.8 Hz, 2H, $H_2$C2), 1.78 (m, 2H, $H_2$C7), 1.57 (m, 2H, $H_2$C3), 1.46 (m, 2H, $H_2$C6), 1.40 (m, 4H, $H_2$C4,5).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 166.8 (C9), 133.0 (C13), 130.6 (C10), 129.7 (C11), 128.5 (C12), 127.4 (q, $^1J_{FC}$ = 276.3 Hz, C1), 65.1 (C8), 33.8 (q, $^2J_{FC}$ = 28.3 Hz, C2), [29.0, 28.7](C4,5), 28.8 (C7), 26.0 (C6), 21.9 (q, $^3J_{FC}$ = 2.9 Hz, C3).

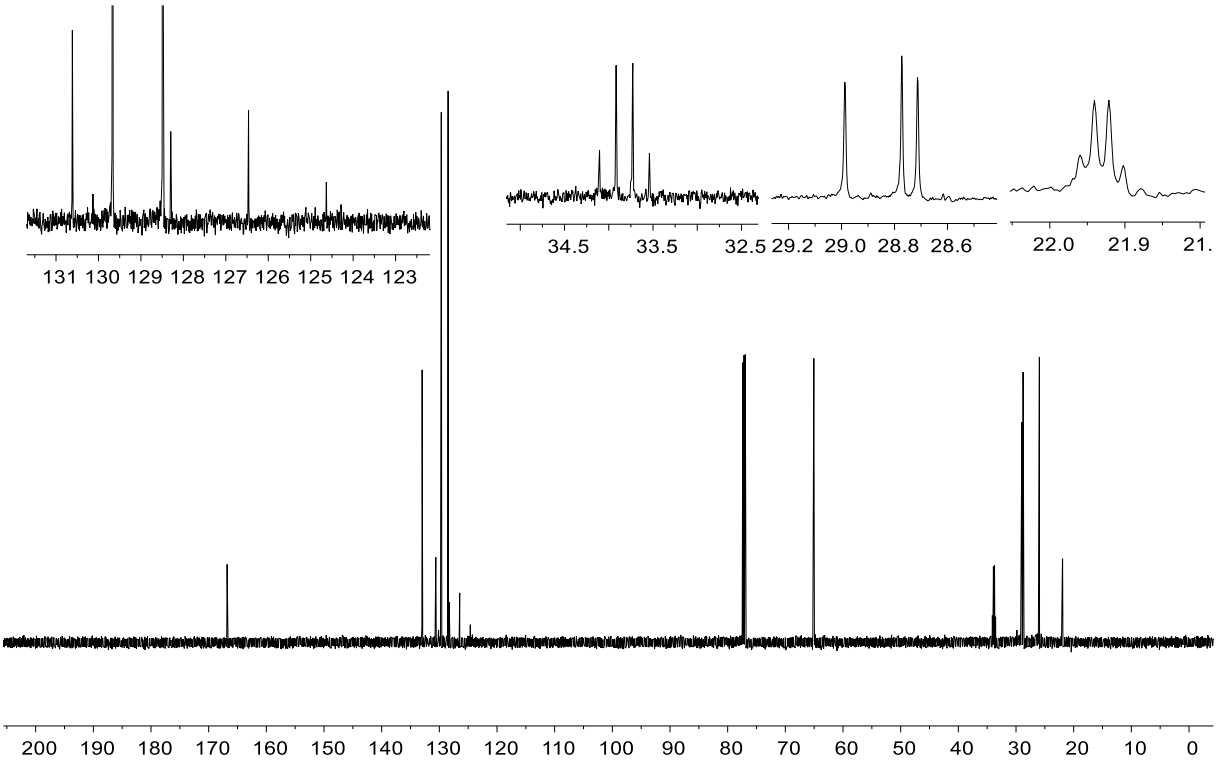
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.5 (t, $^3J_{FH}$ = 10.8 Hz, $F_3$C1).

IR ($cm^{-1}$): 2940 (w), 2861 (w), 1717 (m), 1603 (w), 1585 (w), 1492 (w), 1468 (w), 1452 (w), 1388 (w), 1336 (w), 1315 (w), 1271 (s), 1252 (m), 1221 (w), 1177 (m), 1136 (m), 1111 (m), 1098 (m), 1070 (m), 1050 (m), 1027 (m), 936 (w), 915 (w), 836 (w), 807 (w), 709 (s), 688 (w), 675 (w), 654 (w).

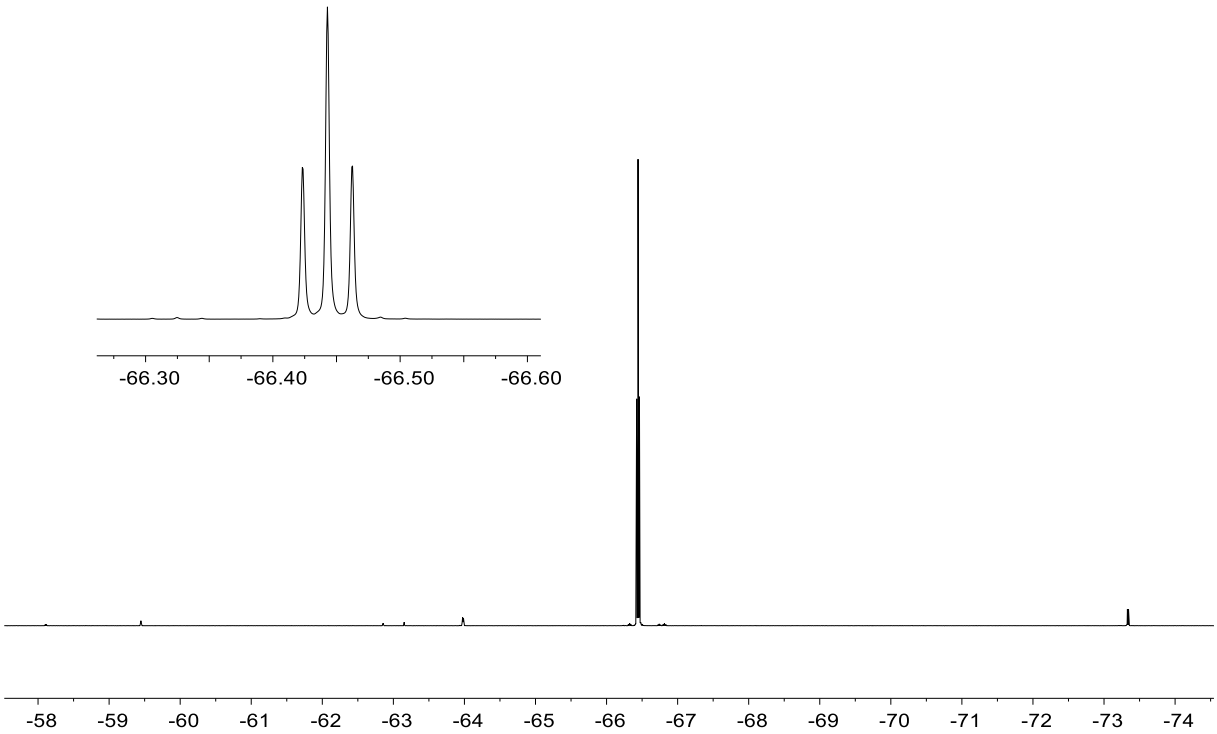
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K)



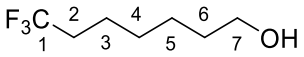
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K)



**7,7,7-Trifluoroheptan-1-ol (S13.3d)**



To a solution of **S13.2d** (63 mg, 0.23 mmol, 1.00 eq.) in MeOH (2 mL) $Na_2CO_3$ (73 mg, 0.69 mmol, 3.00 eq.) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was filtered over a plug of celite and the solvent was removed under reduced pressure. The product was purified *via* flash chromatography (*n*-Pentane : $Et_2O$ / 4 : 1) and was obtained as a colourless oil (34 mg, 87%).

$R_f$ 0.21 (CyH : EtOAc / 2 : 1).

HRMS *m/z* (ESI); Calcd. for $C_7H_{14}OF_3$ 171.0991, found 171.0991.

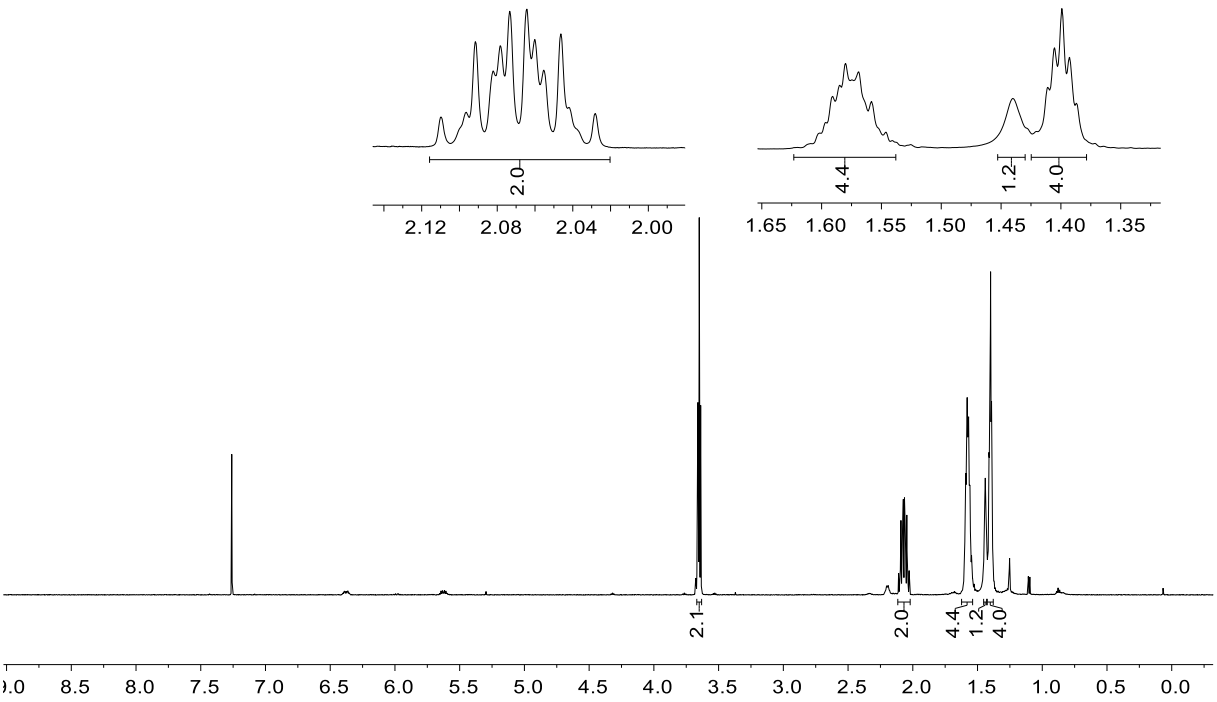
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 3.65 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2C7$), 2.07 (qm, $^3J_{FH}$ = 11.0 Hz, 2H, $H_2C2$), 1.57 (m, 4H, $H_2C3$,6), 1.43 (s, 1H, OH), 1.40 (m, 4H, $H_2C4$,5).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 127.4 (q, $^1J_{FC}$ = 276.3 Hz, C1), 62.9 (C7), 33.8 (q, $^2J_{FC}$ = 28.3 Hz, C2), 32.6 (C6), [28.6, 25.5](C4,5), 22.0 (q, $^3J_{FC}$ = 2.9 Hz, C3).

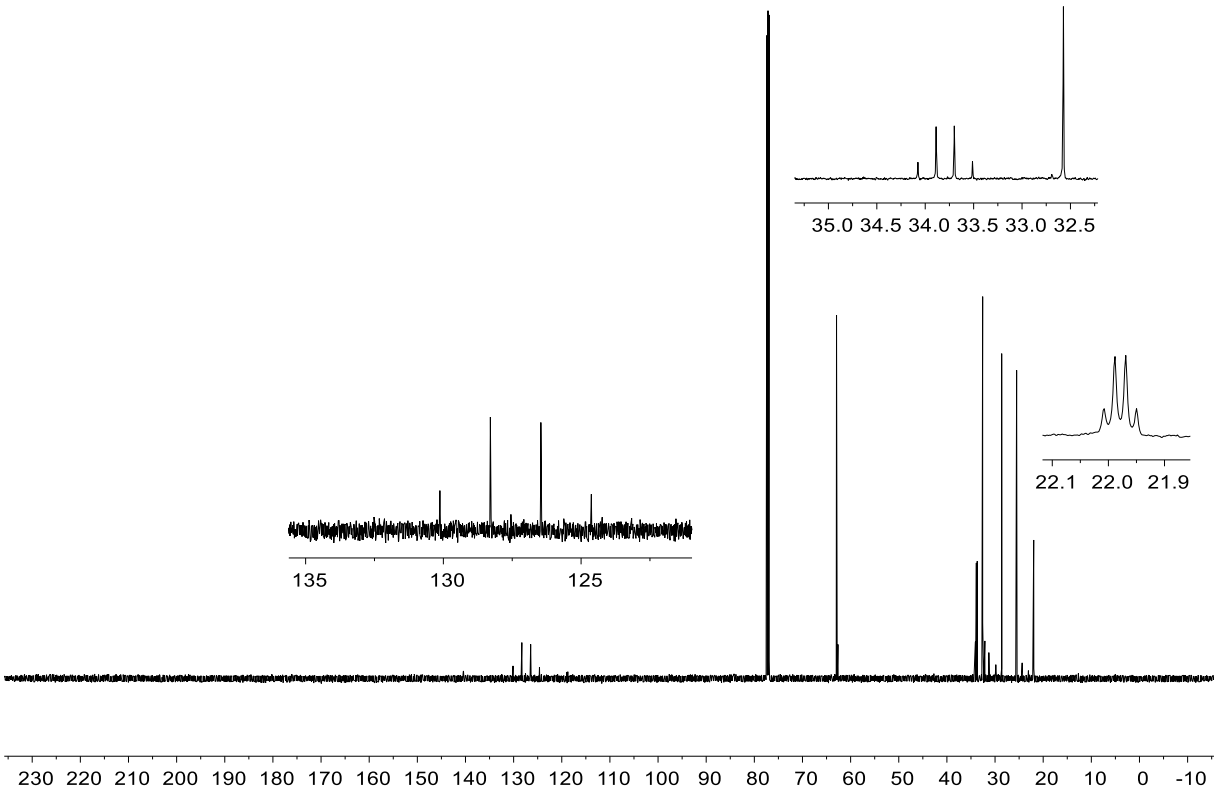
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.5 (t, $^3J_{FH}$ = 11.0 Hz, $F_3C1$).

IR ($cm^{-1}$): 3332 (w), 2941 (w), 2864 (w), 1681 (w), 1463 (w), 1441 (w), 1388 (w), 1336 (w), 1315 (w), 1252 (m), 1222 (w), 1179 (w), 1132 (m), 1075 (m), 1046 (m), 974 (m), 906 (w), 836 (w), 814 (w), 730 (w), 654 (m).

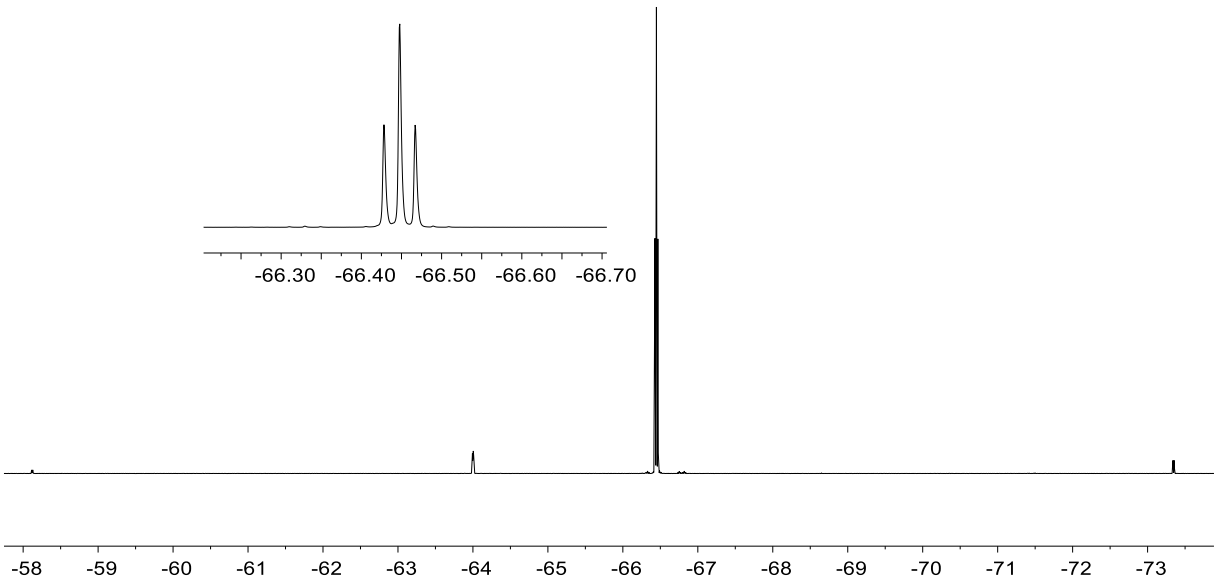
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K)



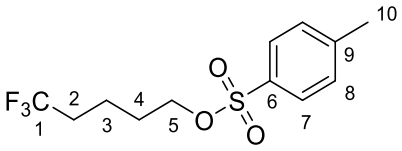
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K)



**5,5,5-TrifluoroPentanetyl 4-methylbenzenesulfonate (S13.1b)**




The compound was synthesised from 5,5,5-trifluoropentan-1-ol (50 mg, 0.35 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The product was obtained as a colourless oil (85 mg, 82%).

$R_f$ 0.25 (CyH : EtOAc / 8 : 1).

HRMS *m/z* (ESI); Calcd. for $C_{12}H_{15}O_3SF_3Na$ 319.0592, found 319.0586.

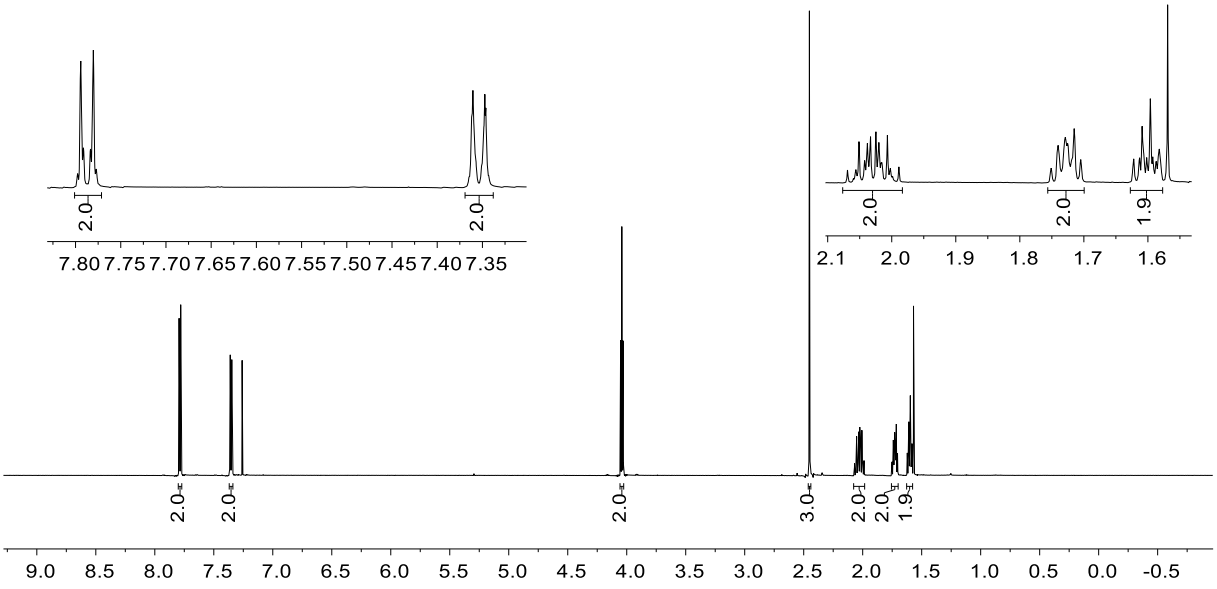
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.79 (m, 2H, HC7), 7.35 (m, 2H, HC8), 4.04 (t, $^3J_{HH}$ = 6.1 Hz, 2H, $H_2$C5), 2.45 (s, 3H, $H_3$C10), 2.03 (qm, $^3J_{FH}$ = 10.8 Hz, 2H, $H_2$C2), 1.73 (m, 2H, $H_2$C4), 1.60 (m, 2H, $H_2$C3).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 145.1 (C9), 133.1 (C6), 130.1 (C8), 128.0 (C7), 127.0 (q, $^1J_{FC}$ = 276.3 Hz, C1), 69.6 (C5), 33.2 (q, $^2J_{FC}$ = 28.8 Hz, C2), 28.0 (C4), 21.8 (C10), 18.4 (q, $^3J_{FC}$ = 3.1 Hz, C3).

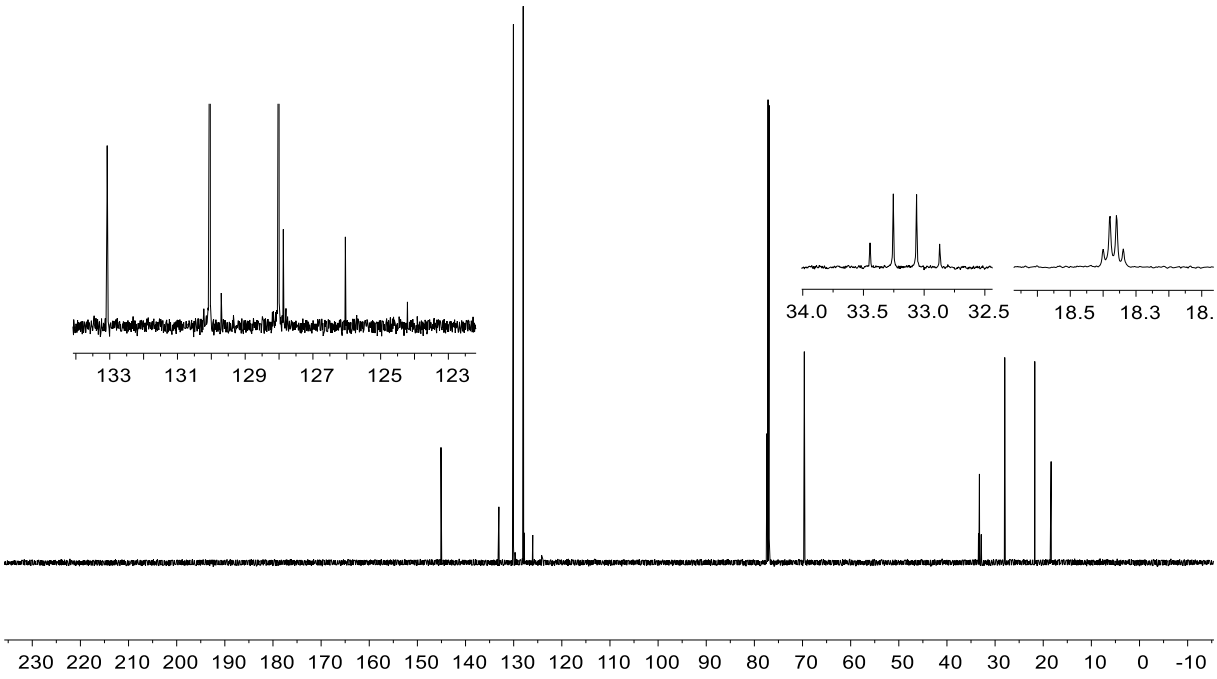
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.4 (t, $^3J_{FH}$ = 10.8 Hz, $F_3$C1).

IR (cm$^{-1}$): 2959 (w), 1599 (w), 1496 (w), 1462 (w), 1441 (w), 1395 (w), 1356 (m), 1308 (w), 1290 (w), 1257 (m), 1219 (w), 1189 (m), 1175 (s), 1139 (m), 1097 (m), 1072 (m), 1039 (m), 1020 (w), 931 (s), 835 (m), 814 (m), 779 (m), 732 (m), 706 (w), 689 (w), 662 (s).

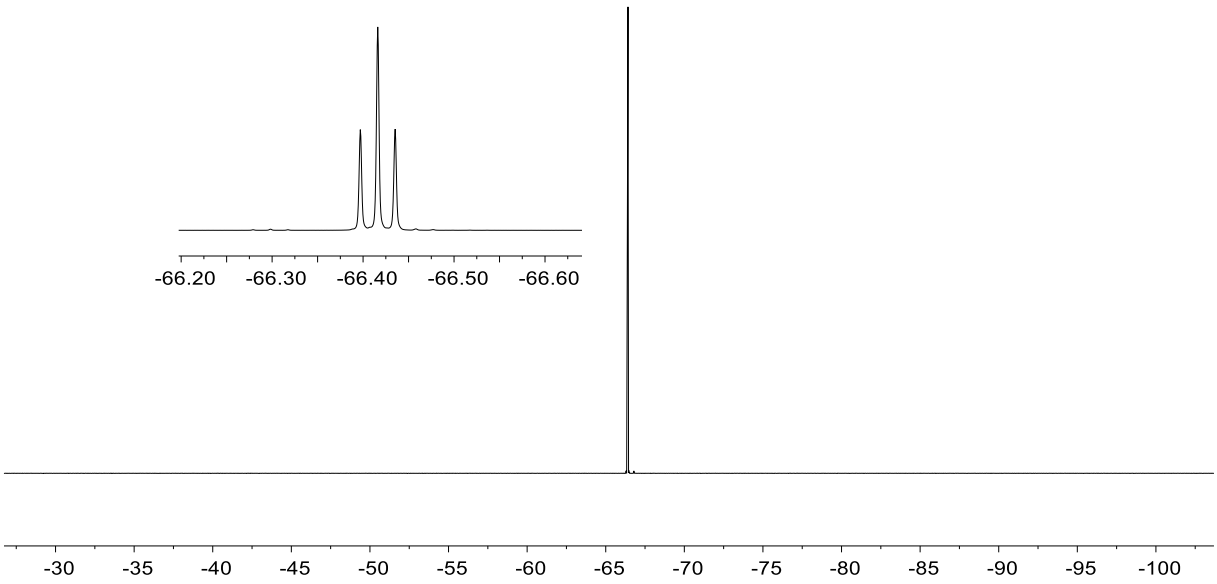
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K)



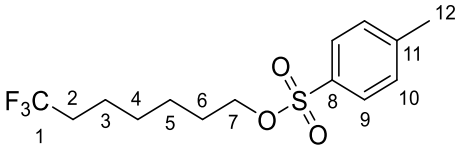
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K)



**7,7,7-Trifluoroheptyl 4-methylbenzenesulfonate (S13.4d)**




The compound was synthesised from **S13.3d** (34 mg, 0.20 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The product was obtained as a colourless oil (39 mg, 60%).

$R_f$ 0.28 (CyH : EtOAc / 9 : 1).

HRMS *m/z* (ESI); Calcd. for $C_{14}H_{19}O_3SF_3Na$ 347.0905, found 347.0896.

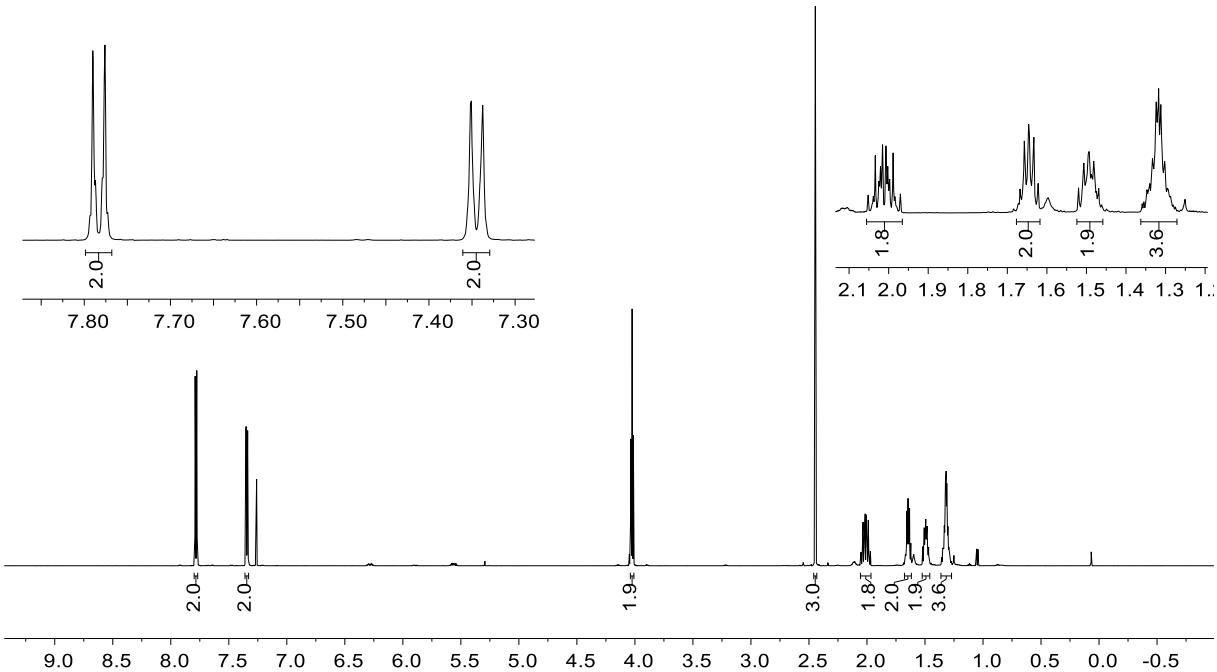
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.78 (m, 2H, HC9), 7.35 (m, 2H, HC10), 4.02 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C7), 2.45 (s, 3H, $H_3$C12), 2.01 (qm, $^3J_{FH}$ = 10.9 Hz, 2H, $H_2$C2), 1.65 (m, 2H, $H_2$C6), 1.49 (m, 2H, $H_2$C3), 1.32 (m, 4H, $H_2$C4,5).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 144.9 (C11), 133.3 (C8), 130.0 (C10), 128.0 (C9), 127.3 (q, $^1J_{FC}$ = 276.3 Hz, C1), 70.4 (C7), 33.7 (q, $^2J_{FC}$ = 28.4 Hz, C2), 28.7 (C6), 28.1, 25.2 (C4,5), 21.8 (q, $^3J_{FC}$ = 2.9 Hz, C3), 21.7 (C12).

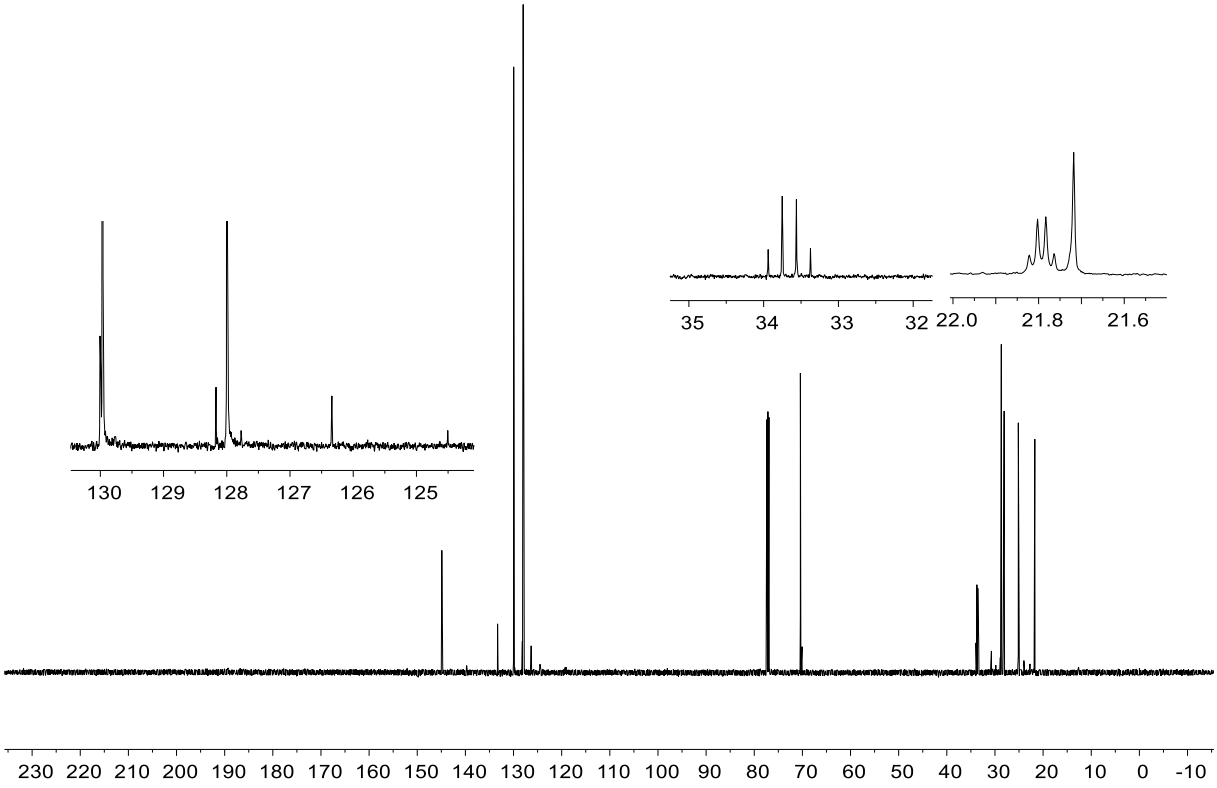
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.4 (t, $^3J_{FH}$ = 10.9 Hz, $F_3$C1).

IR (cm$^{-1}$): 2944 (w), 2871 (w), 1599 (w), 1496 (w), 1468 (w), 1441 (w), 1388 (w), 1358 (m), 1308 (w), 1291 (w), 1253 (m), 1229 (w), 1189 (m), 1175 (s), 1136 (m), 1096 (m), 1051 (m), 1020 (w), 955 (m), 915 (m), 831 (m), 815 (m), 782 (m), 752 (w), 727 (w), 706 (w), 689 (w), 662 (s).

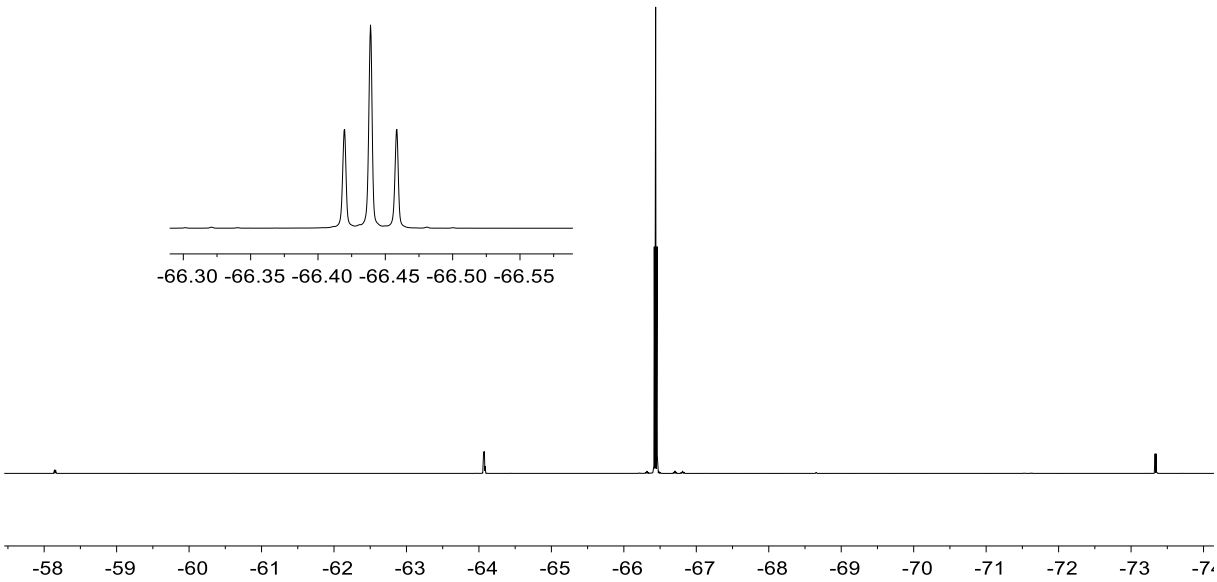
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K)



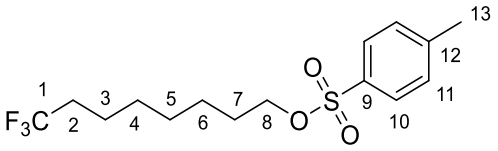
$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K)



**8,8,8-Trifluorooctyl 4-methylbenzenesulfonate (S13.4e)**




The compound was synthesised from **S13.3e** (26 mg, 0.14 mmol, 1.00 eq.) following **General Procedure 1** (see page S4). The product was obtained as a colourless oil (45 mg, 96%).

$R_f$ 0.26 (CyH : EtOAc / 6 : 1).

HRMS *m/z* (ESI); Calcd. for $C_{15}H_{21}O_3SF_3Na$ 361.1056, found 361.1074.

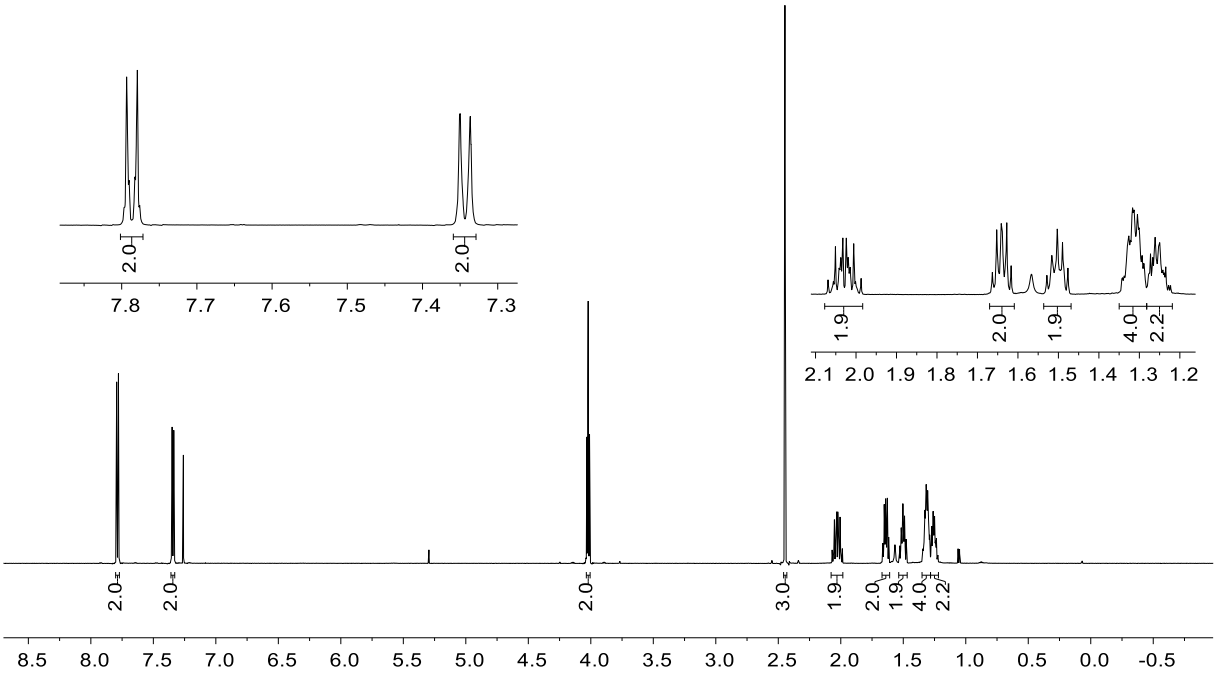
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.79 (m, 2H, HC10), 7.34 (m, 2H, HC11), 4.02 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C8), 2.45 (s, 3H, $H_3$C13), 2.03 (qm, $^3J_{FH}$ = 11.0 Hz, 2H, $H_2$C2), 1.64 (m, 2H, $H_2$C7), 1.50 (m, 2H, $H_2$C3), [1.31 (m, 4H), 1.25 (m, 2H)]($H_2$C4,5,6).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 144.8 (C12), 133.4 (C9), 129.9 (C11), 128.0 (C10), 127.3 (q, $^1J_{FC}$ = 276.3 Hz, C1), 70.6 (C8), 33.8 (q, $^2J_{FC}$ = 28.4 Hz, C2), 28.9 (C7), [28.63, 28.57](C4,5), 25.3 (C6), 21.9 (q, $^3J_{FC}$ = 2.8 Hz, C3), 21.8 (C13).

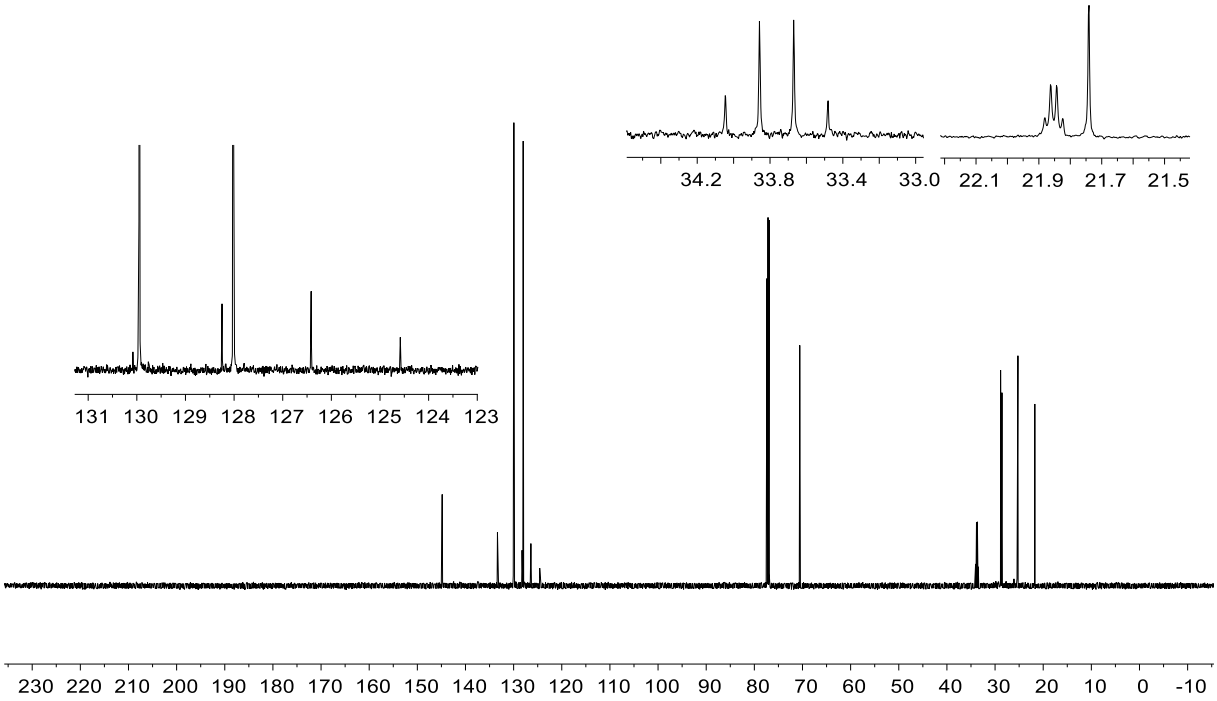
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.4 (t, $^3J_{FH}$ = 11.0 Hz, $F_3$C1).

IR (cm$^{-1}$): 2931 (w), 2860 (w), 1722 (w), 1599 (w), 1495 (w), 1463 (w), 1387 (w), 1360 (m), 1308 (w), 1253 (m), 1212 (w), 1189 (m), 1175 (s), 1136 (m), 1097 (m), 1048 (m), 1020 (w), 960 (m), 925 (m), 814 (m), 770 (m), 740 (w), 725 (w), 688 (w), 662 (m).

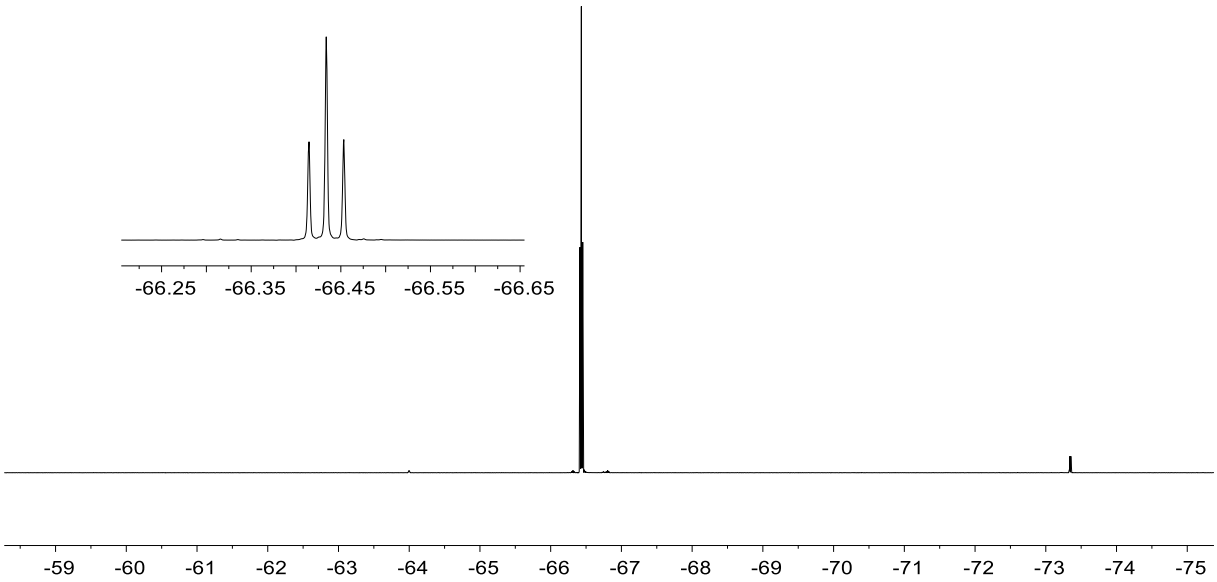
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K)



$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)

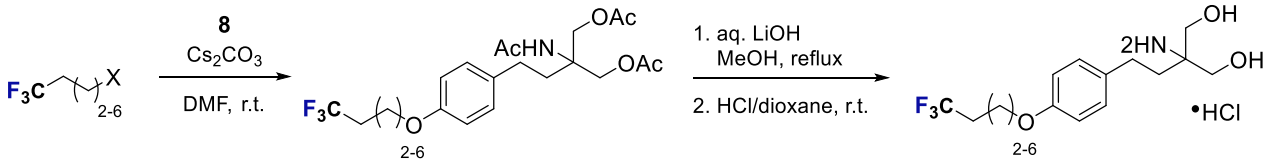



$^{19}F$ NMR (564 MHz, Chloroform-*d*, 298 K)



## II.6.2 Compounds 13a-e to 14a-e

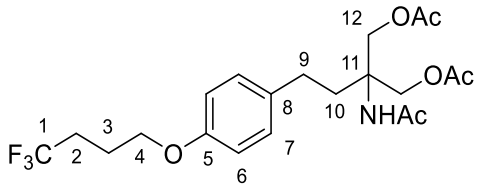
**Scheme S5.**




| | | |
|---|---|---|
| 2: **S13.1a** | 2: **13a** | 2: **14a** |
| 3: **S13.1b** | 3: **13b** | 3: **14b** |
| 5: **S13.4d** | 4: **13c** | 4: **14c** |
| 6: **S13.4e** | 5: **13d** | 5: **14d** |
| | 6: **13e** | 6: **14e** |

Commercially purchased 6-bromo-1,1,1-trifluoro hexane was used as starting material for compound 13c. For compounds S13.1a-b and S13.4d-e: X = OTs.

### 2-Acetamido-2-(4-(4,4,4-trifluorobutoxy)phenethyl)propane-1,3-diyl diacetate (13a)




The compound was synthesised from **8** (50 mg, 0.15 mmol, 1.00 eq.) and **S13.1a** (42 mg, 0.15 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (59 mg, 88%).

M.p.: 84 °C.

$R_f$ 0.44 (EtOAc).

HRMS *m/z* (ESI); Calcd. for $C_{21}H_{28}NO_6F_3Na$ 470.1766, found 470.1781.

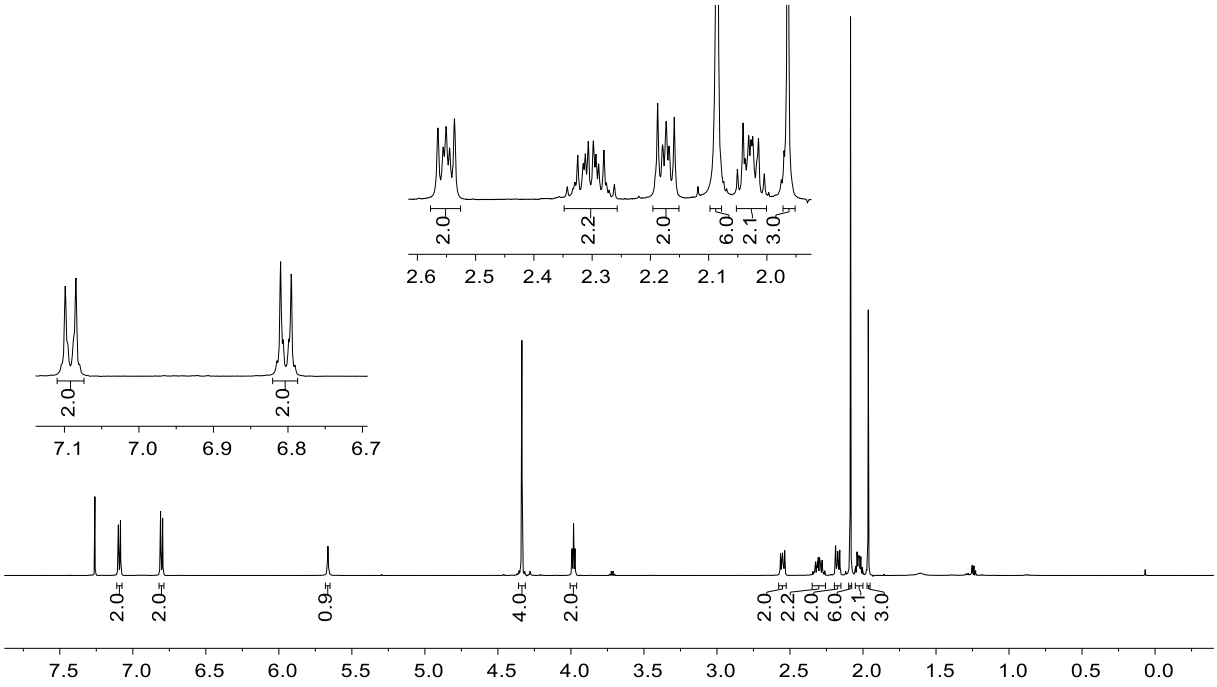
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.09 (m, 2H, HC7), 6.80 (m, 2H, HC6), 5.66 (s, 1H, HN), [4.336 (d, $^2J_{HH}$ = 11.2 Hz, 2H), 4.335 (d, $^2J_{HH}$ = 11.2 Hz, 2H)]($H_2$C12), 3.98 (t, $^3J_{HH}$ = 6.0 Hz, 2H, $H_2$C4), 2.55 (m, 2H, $H_2$C9), 2.30 (qm, $^3J_{FH}$ = 10.9 Hz, 2H, $H_2$C2), 2.17 (m, 2H, $H_2$C10), 2.09 (s, 6H, OAc), 2.03 (m, 2H, $H_2$C3), 1.96 (s, 3H, NAc).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.1 (NAc), 157.2 (C5), 133.9 (C8), 129.5 (C7), 127.3 (q, $^1J_{FC}$ = 276.1 Hz, C1), 114.7 (C6), 66.2 (C4), 64.8 (C12), 58.4 (C11), 34.1 (C10), 30.9 (q, $^2J_{FC}$ = 28.9 Hz, C2), 29.0 (C9), 24.3 (NAc), 22.4 (q, $^3J_{FC}$ = 3.2 Hz, C3), 21.0 (OAc).

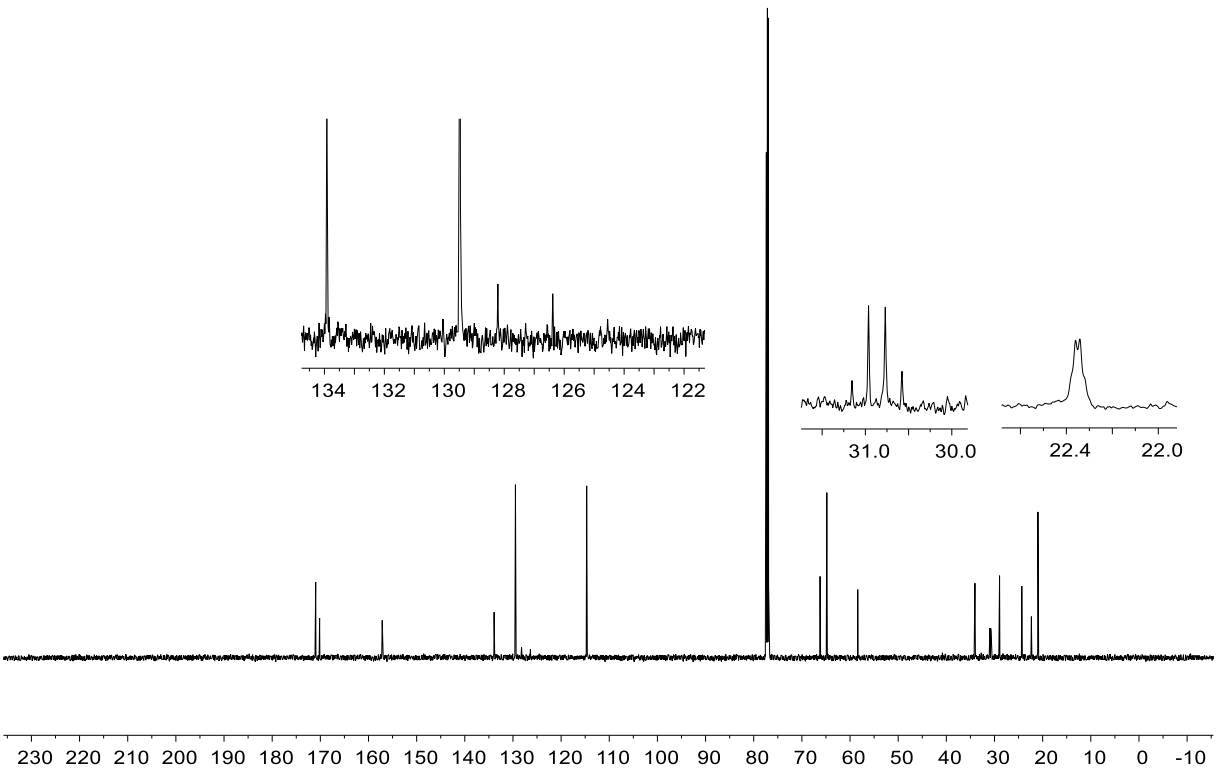
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.4 (t, $^3J_{FH}$ = 10.9 Hz, $F_3$C1).

IR (cm$^{-1}$): 3310 (w), 3082 (w), 2960 (w), 1735 (m), 1650 (m), 1614 (w), 1584 (w), 1554 (m), 1513 (m), 1467 (m), 1453 (w), 1379 (m), 1338 (w), 1316 (w), 1302 (w), 1242 (m), 1223 (s), 1176 (m), 1149 (m), 1134 (m), 1099 (w), 1047 (m), 1026 (s), 985 (w), 967 (m), 933 (w), 846 (m), 816 (m), 790 (w), 773 (w), 748 (w), 691 (w), 662 (w).

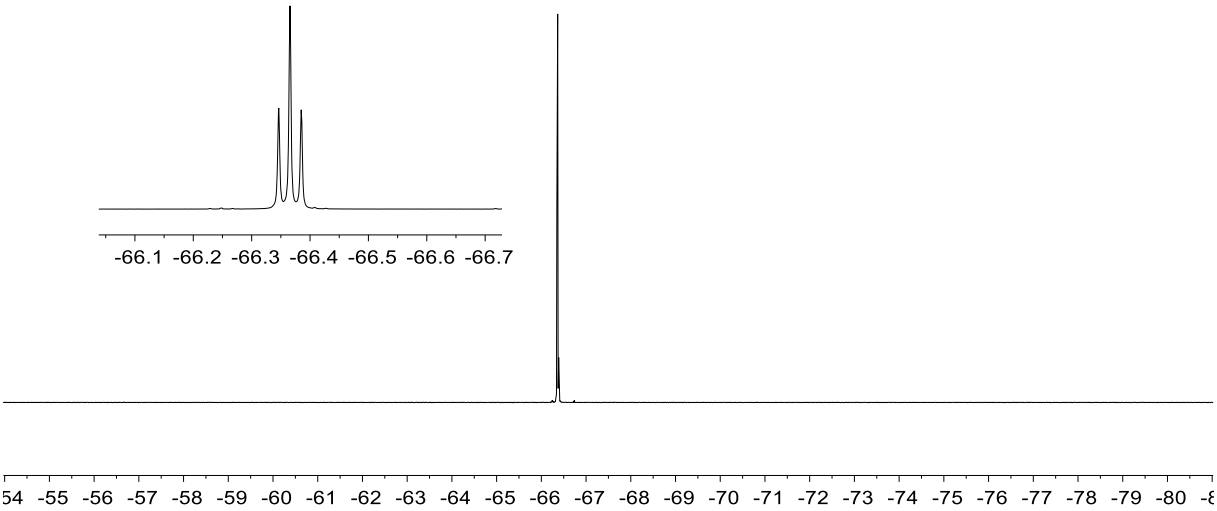
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



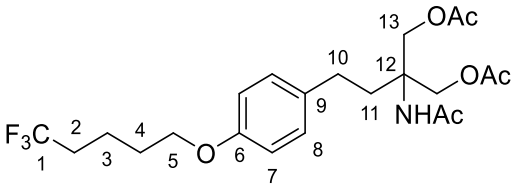
$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*, 298 K)



$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K)




**2-Acetamido-2-(4-((5,5,5-trifluoroPentanetyl)oxy)phenethyl)propane-1,3-diyl diacetate (13b)**




The compound was synthesised from **8** (37 mg, 0.11 mmol, 1.00 eq.) and **S13.1b** (32 mg, 0.11 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (41 mg, 83%).

M.p.: 82 °C.

$R_f$ 0.42 (CyH : EtOAc / 1 : 3).

HRMS *m/z* (ESI); Calcd. for $C_{22}H_{30}NO_6F_3Na$ 484.1917, found 484.1924.

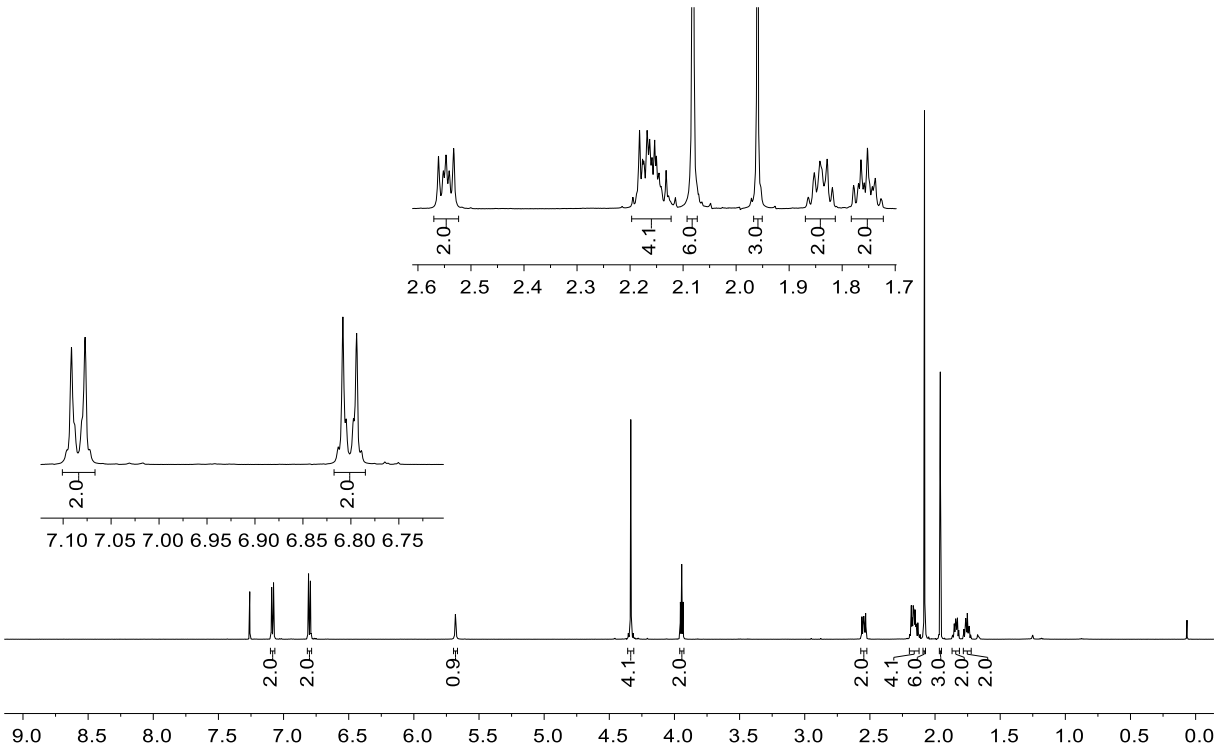
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC8), 6.80 (m, 2H, HC7), 5.68 (s, 1H, HN), [4.337 (d, $^2J_{HH}$ = 11.2 Hz, 2H), 4.335 (d, $^2J_{HH}$ = 11.2 Hz, 2H)]($H_2$C13), 3.95 (t, $^3J_{HH}$ = 6.0 Hz, 2H, $H_2$C5), 2.55 (m, 2H, $H_2$C10), 2.18 (m, 2H, $H_2$C11), 2.16 (m, 2H, $H_2$C2), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.84 (m, 2H, $H_2$C4), 1.76 (m, 2H, $H_2$C3).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 170.9 (OAc), 170.2 (NAc), 157.3 (C6), 133.6 (C9), 129.4 (C8), 127.2 (q, $^1J_{FC}$ = 276.3 Hz, C1), 114.7 (C7), 67.3 (C5), 64.8 (C13), 58.3 (C12), 34.0 (C11), 33.6 (q, $^2J_{FC}$ = 28.6 Hz, C2), 28.9 (C10), 28.5 (C4), 24.3 (NAc), 20.9 (OAc), 19.0 (q, $^3J_{FC}$ = 3.1 Hz, C3).

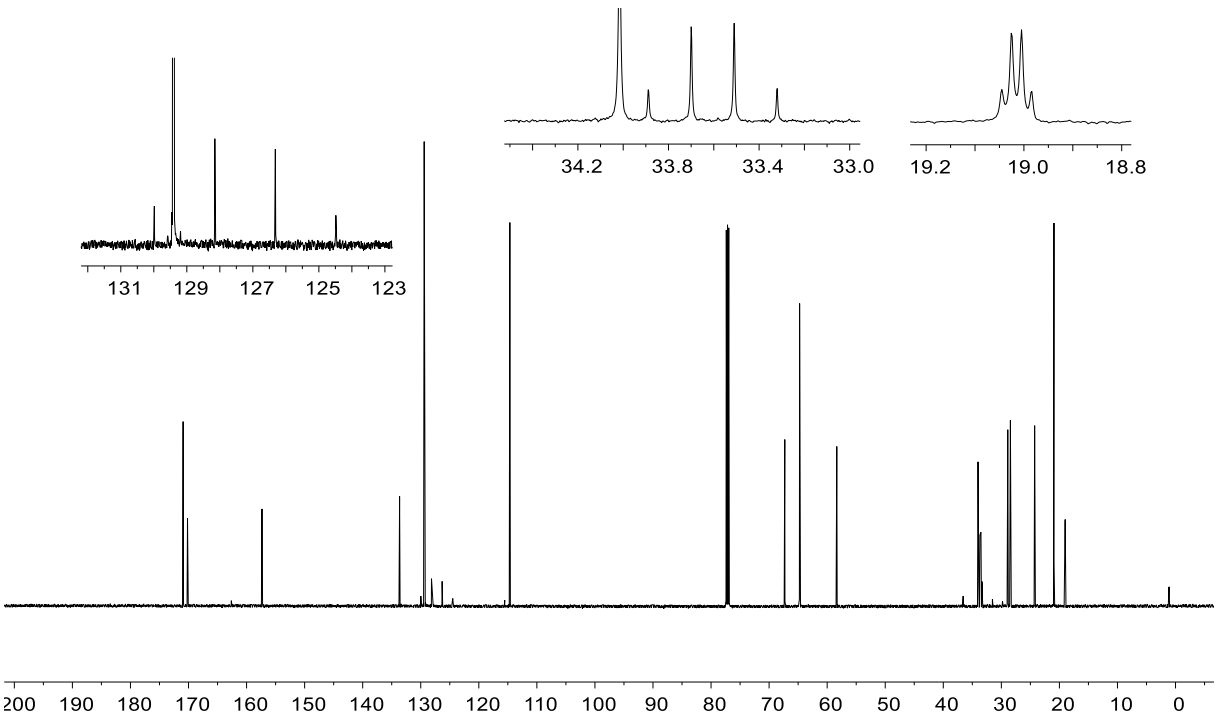
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.4 (t, $^3J_{FH}$ = 10.9 Hz, $F_3$C1).

IR ($cm^{-1}$): 3313 (w), 3076 (w), 2949 (w), 1737 (m), 1651 (m), 1614 (w), 1582 (w), 1553 (m), 1514 (m), 1467 (w), 1439 (w), 1379 (m), 1317 (w), 1303 (w), 1292 (w), 1246 (m), 1213 (m), 1177 (m), 1137 (m), 1071 (m), 1053 (m), 1033 (m), 984 (w), 959 (m), 912 (w), 866 (w), 845 (w), 816 (m), 777 (w), 740 (w), 691 (w).

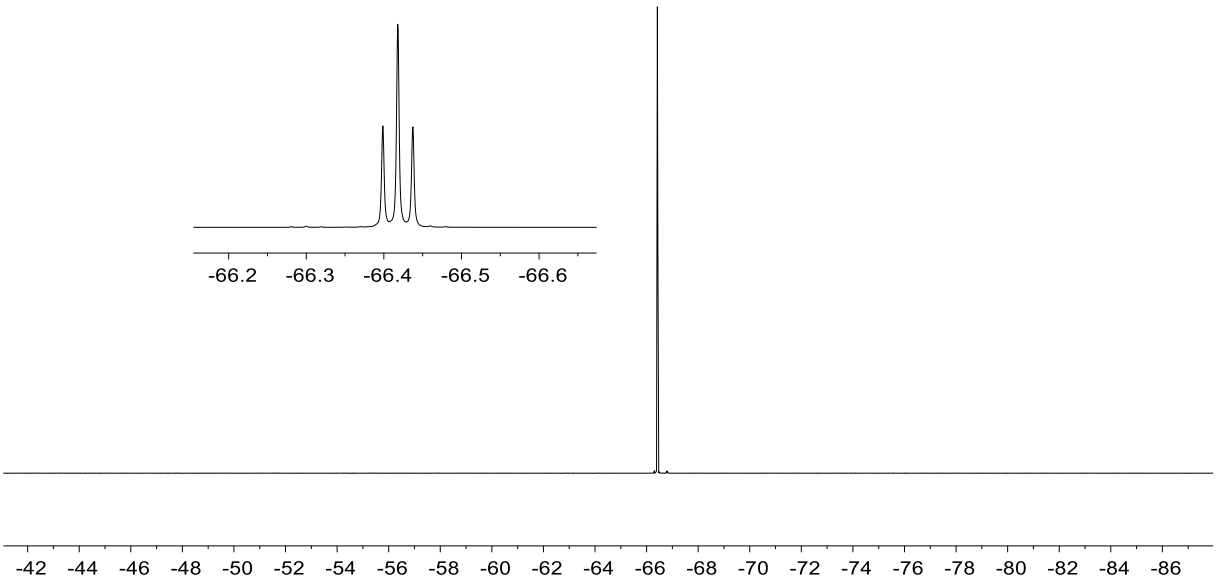
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



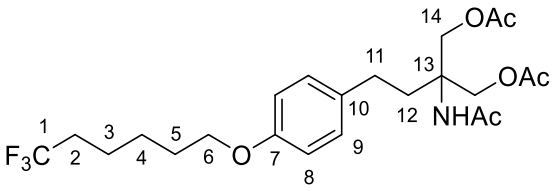

$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*,



$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K)




**2-Acetamido-2-(4-((6,6,6-trifluorohexyl)oxy)phenethyl)propane-1,3-diyl diacetate (13c)**




The compound was synthesised from **8** (50 mg, 0.15 mmol, 1.00 eq.) and 6-bromo-1,1,1-trifluoro hexane (235 µL, 0.15 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (58 mg, 82%).

M.p.: 59 °C.

$R_f$ 0.30 (CyH : EtOAc / 1 : 2).

HRMS *m/z* (ESI); Calcd. for $C_{23}H_{32}NO_6F_3Na$ 498.2074, found 498.2084.

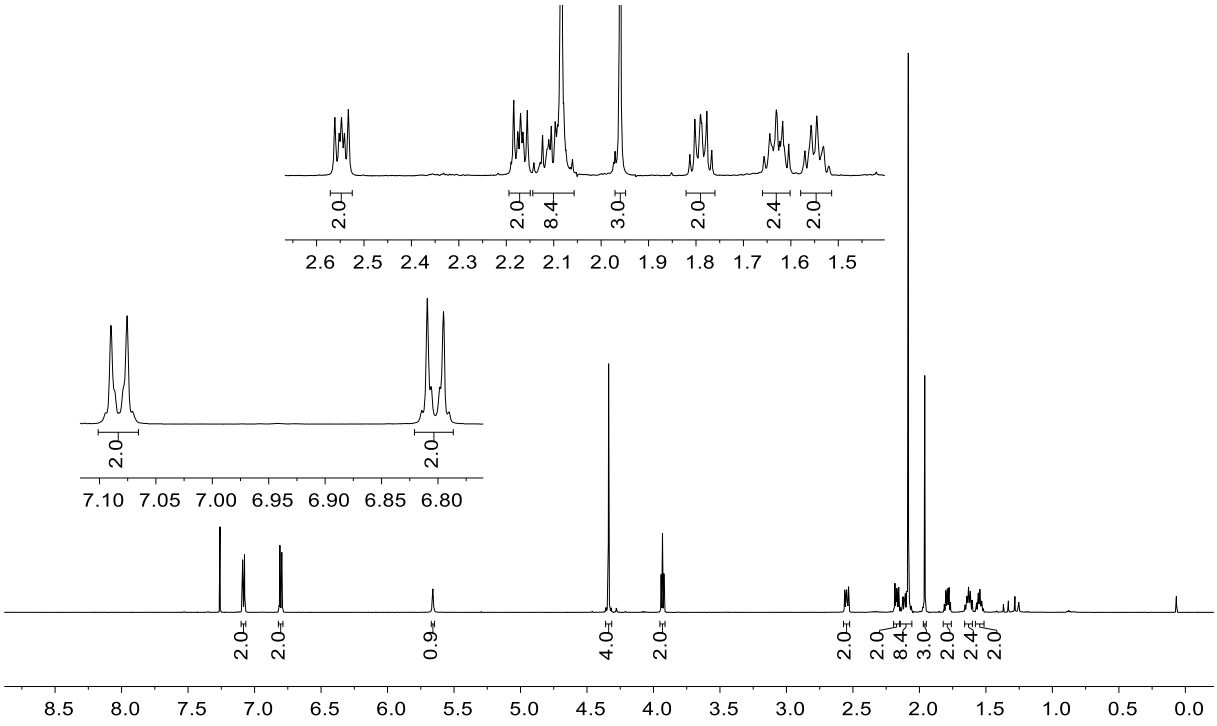
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC9), 6.80 (m, 2H, HC8), 5.66 (s, 1H, HN), [4.338 (d, $^2J_{HH}$ = 11.2 Hz, 2H), 4.337 (d, $^2J_{HH}$ = 11.2 Hz, 2H)]($H_2$C14), 3.93 (t, $^3J_{HH}$ = 6.3 Hz, 2H, $H_2$C6), 2.55 (m, 2H, $H_2$C11), 2.17 (m, 2H, $H_2$C12), 2.10 (qm, $^3J_{FH}$ = 10.9 Hz, 2H, $H_2$C2), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.79 (m, 2H, $H_2$C5), 1.63 (m, 2H, $H_2$C3), 1.55 (m, 2H, $H_2$C4).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.1 (NAc), 157.5 (C7), 133.5 (C10), 129.4 (C9), 127.3 (q, $^1J_{FC}$ = 276.4 Hz, C1), 114.7 (C8), 67.6 (C6), 64.8 (C14), 58.4 (C13), 34.1 (C12), 33.8 (q, $^2J_{FC}$ = 28.4 Hz, C2), 29.1 (C5), 28.9 (C11), 25.5 (C4), 24.3 (NAc), 21.9 (q, $^3J_{FC}$ = 2.9 Hz, C3), 21.0 (OAc).

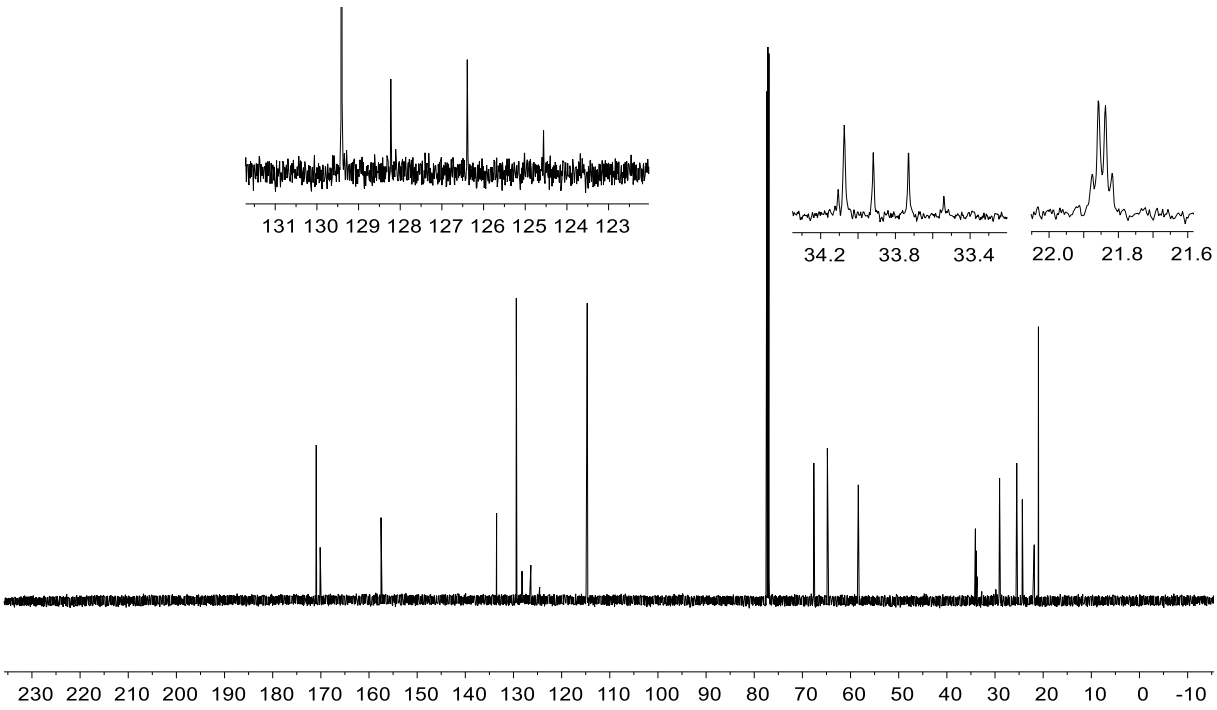
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.4 (t, $^3J_{FH}$ = 10.9 Hz, $F_3$C1).

IR ($cm^{-1}$): 3308 (w), 3081 (w), 2948 (w), 2859 (w), 1737 (m), 1650 (m), 1614 (w), 1555 (m), 1513 (m), 1467 (m), 1436 (w), 1378 (m), 1338 (w), 1317 (w), 1298 (w), 1245 (m), 1210 (m), 1176 (m), 1143 (m), 1089 (w), 1041 (s), 984 (w), 967 (m), 923 (w), 903 (w), 886 (w), 846 (m), 834 (w), 823 (m), 805 (w), 791 (w), 773 (w), 756 (w), 733 (w), 693 (w), 654 (m).

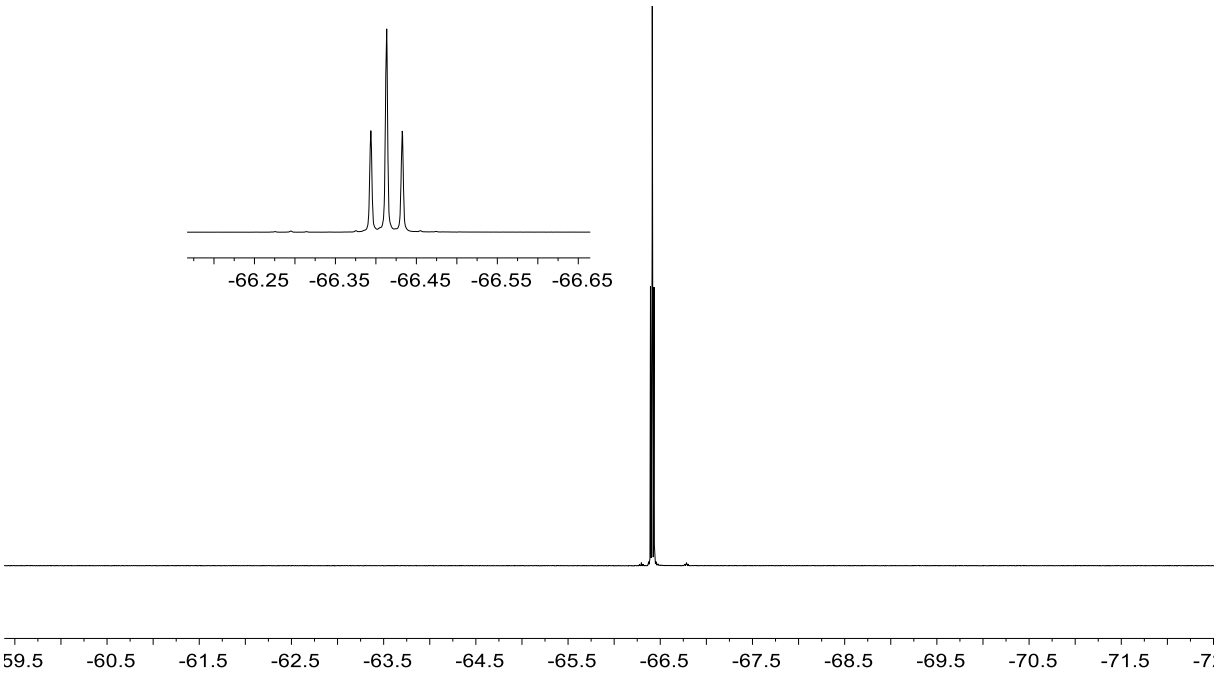
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



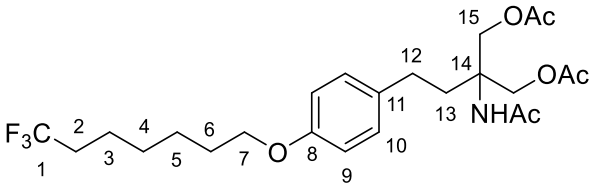
$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*, 298 K)



$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K)




**2-Acetamido-2-(4-((7,7,7-trifluoroheptyl)oxy)phenethyl)propane-1,3-diyl diacetate (13d)**




The compound was synthesised from **8** (45 mg, 0.13 mmol, 1.10 eq.) and **S13.4d** (40 mg, 0.12 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (45 mg, 76%).

M.p.: 55 °C.

$R_f$ 0.48 (CyH : EtOAc / 1 : 2).

HRMS *m/z* (ESI); Calcd. for $C_{24}H_{34}NO_6F_3Na$ 512.2236, found 512.2239.

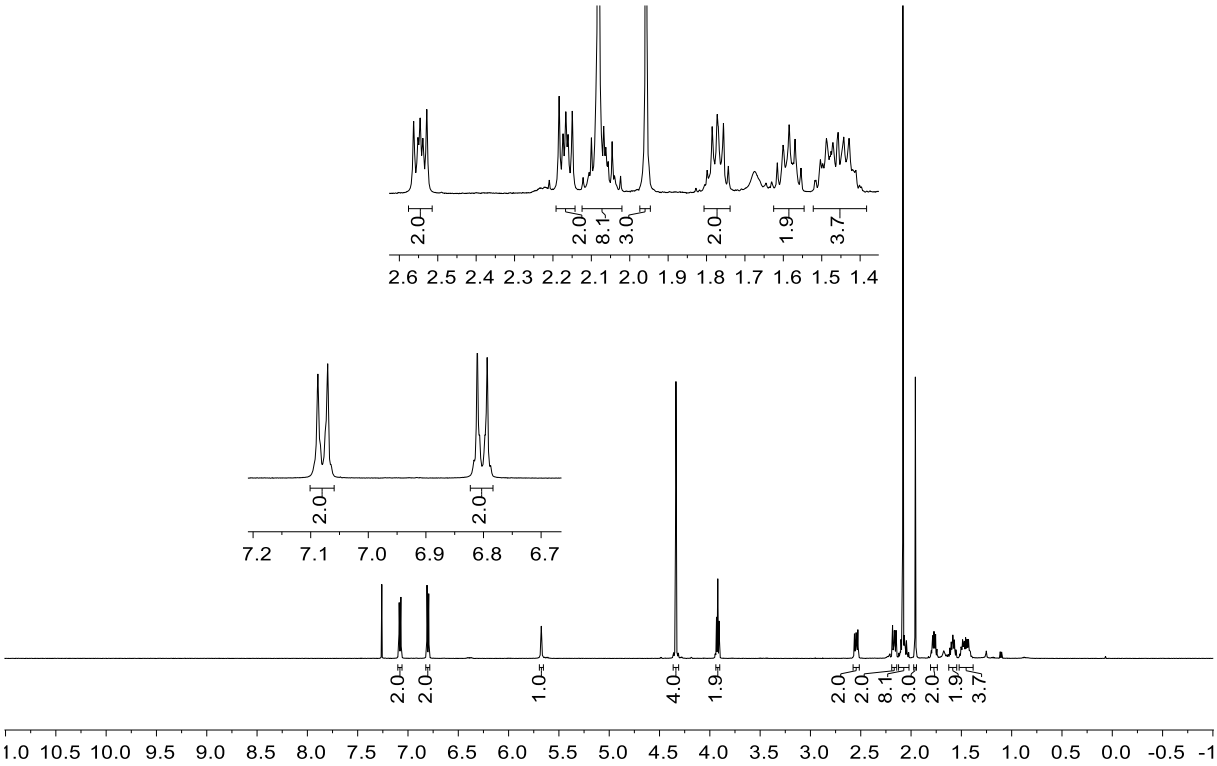
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC10), 6.80 (m, 2H, HC9), 5.68 (s, 1H, HN), [4.338 (d, $^2J_{HH}$ = 11.1 Hz, 2H), 4.336 (d, $^2J_{HH}$ = 11.1 Hz, 2H)]($H_2$C15), 3.92 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C7), 2.55 (m, 2H, $H_2$C12), 2.17 (m, 2H, $H_2$C13), 2.07 (qm, $^3J_{FH}$ = 11.0 Hz, 2H, $H_2$C2), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.77 (m, 2H, $H_2$-C6), 1.59 (m, 2H, $H_2$C3), 1.49 (m, 2H, $H_2$C5), 1.44 (m, 2H, $H_2$C4).

$^{13}$C{$^1$H} NMR (126 MHz, Chloroform-*d*, 298 K) δ 170.9 (OAc), 170.1 (NAc), 157.6 (C8), 133.4 (C11), 129.4 (C10), 127.4 (q, $^1J_{FC}$ = 276.4 Hz, C1), 114.7 (C9), 67.9 (C7), 64.8 (C15), 58.4 (C14), 34.1 (C13), 33.8 (q, $^2J_{FC}$ = 28.3 Hz, C2), 29.2 (C6), 28.9 (C12), 28.6 (C4), 25.9 (C5), 24.3 (NAc), 22.0 (q, $^3J_{FC}$ = 2.9 Hz, C3), 21.0 (OAc).

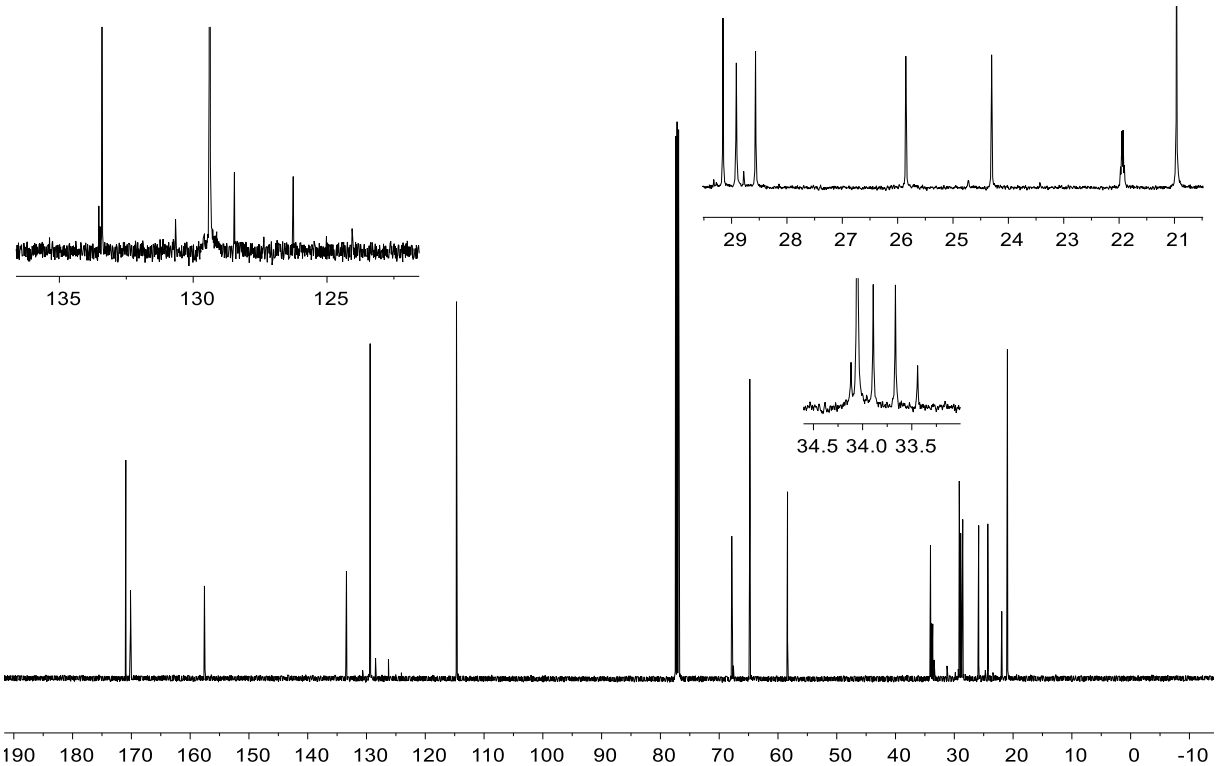
$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K) δ -66.4 (t, $^3J_{FH}$ = 11.0 Hz, $F_3$C1).

IR ($cm^{-1}$): 3315 (w), 3079 (w), 2930 (w), 2859 (w), 1736 (m), 1651 (m), 1615 (w), 1586 (w), 1552 (m), 1513 (m), 1468 (m), 1436 (w), 1377 (m), 1315 (m), 1291 (w), 1242 (s), 1217 (s), 1193 (m), 1179 (m), 1146 (m), 1103 (w), 1094 (w), 1043 (s), 1020 (m), 982 (m), 967 (m), 917 (w), 851 (m), 836 (w), 819 (m), 811 (m), 777 (w), 743 (w), 723 (w), 687 (w), 655 (m).

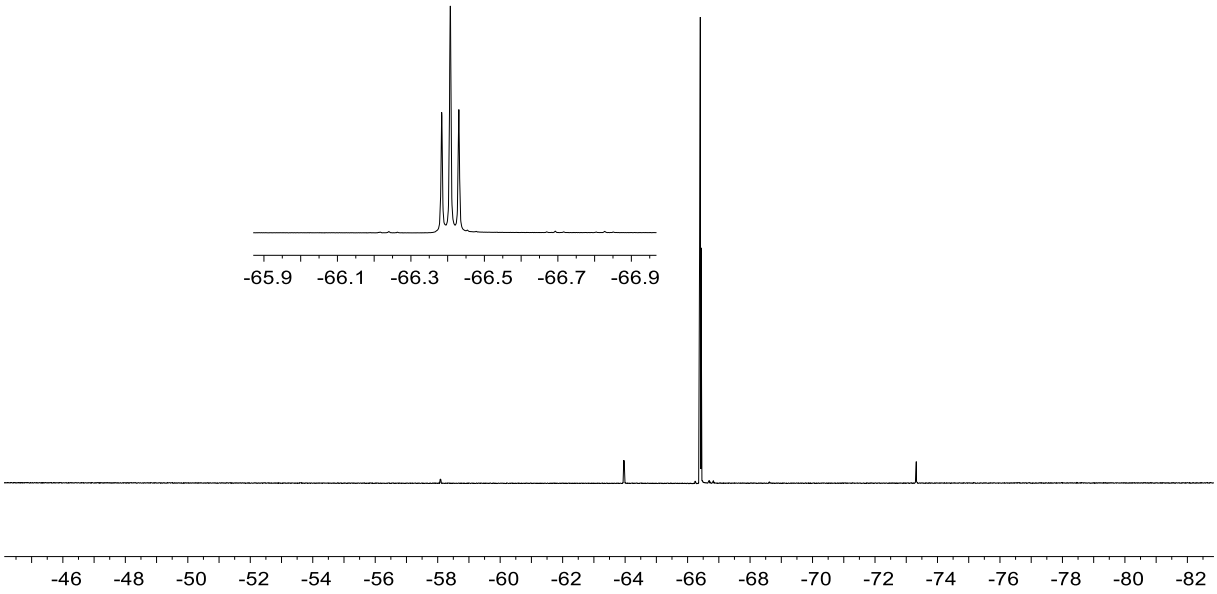
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



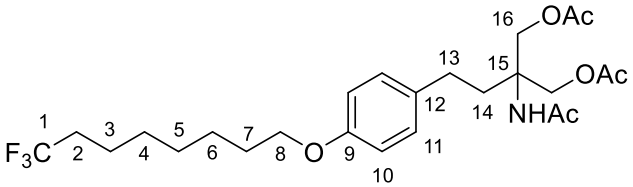
$^{13}$C{$^{1}$H} NMR (126 MHz, Chloroform-*d*, 298 K)



$^{19}$F NMR (564 MHz, Chloroform-*d*, 298 K)




**2-Acetamido-2-(4-((8,8,8-trifluorooctyl)oxy)phenethyl)propane-1,3-diyl diacetate (13e)**




The compound was synthesised from **8** (36 mg, 0.11 mmol, 1.00 eq.) and **S13.4e** (43 mg, 0.13 mmol, 1.20 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (35 mg, 66%).

M.p.: 60 °C.

$R_f$ 0.45 (CyH : EtOAc / 1 : 2).

HRMS *m/z* (ESI); Calcd. for $C_{25}H_{36}NO_6F_3Na$ 526.2387, found 526.2385.

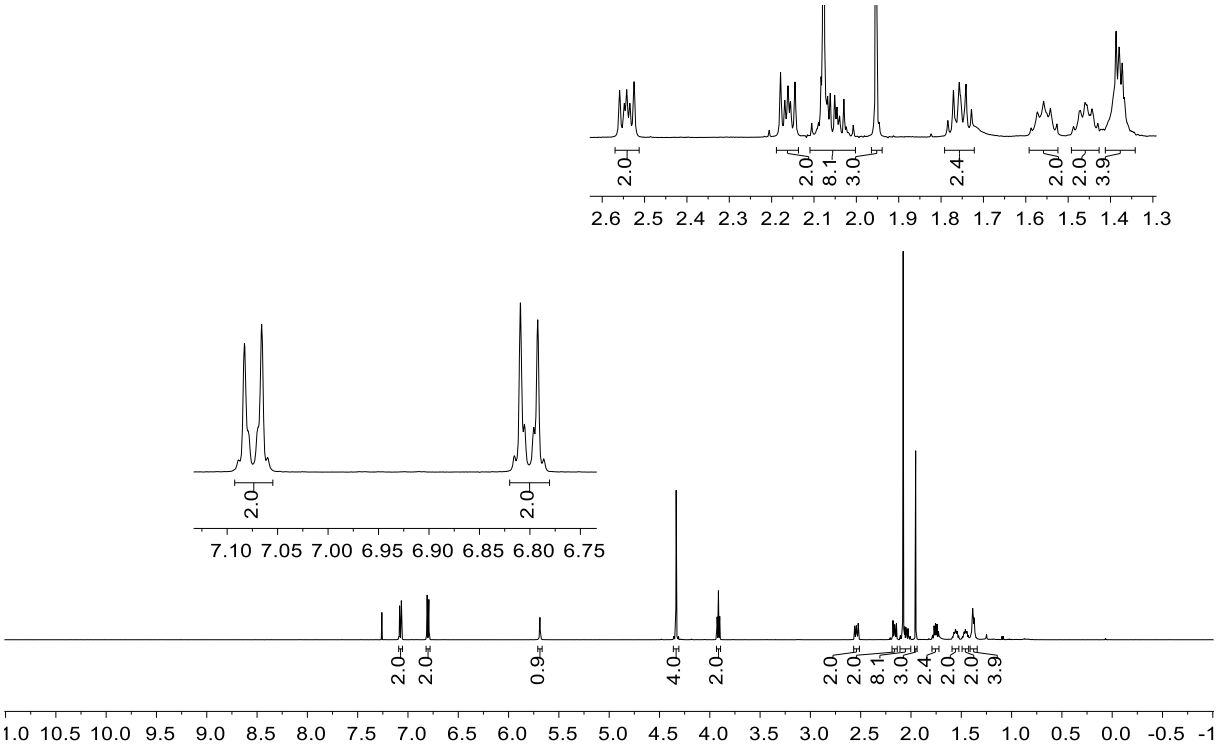
$^1$H NMR (600 MHz, Chloroform-*d*, 298 K) δ 7.07 (m, 2H, HC11), 6.80 (m, 2H, HC10), 5.69 (s, 1H, HN), [4.335 (d, $^2J_{HH}$ = 11.0 Hz, 2H), 4.333 (d, $^2J_{HH}$ = 11.0 Hz, 2H)]($H_2$C16), 3.91 (t, $^3J_{HH}$ = 6.5 Hz, 2H, $H_2$C8), 2.54 (m, 2H, $H_2$C13), 2.16 (m, 2H, $H_2$C14), 2.06 (qm, $^3J_{FH}$ = 11.0 Hz, 2H, $H_2$C2), 2.08 (s, 6H, OAc), 1.95 (s, 3H, NAc), 1.76 (m, 2H, $H_2$C7), 1.56 (m, 2H, $H_2$C3), 1.46 (m, 2H, $H_2$C6), 1.38 (m, 4H, $H_2$C4,5).

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ 170.9 (OAc), 170.2 (NAc), 157.6 (C9), 133.3 (C12), 129.4 (C11), 127.4 (q, $^1J_{FC}$ = 276.3 Hz, C1), 114.7 (C10), 68.0 (C8), 64.8 (C16), 58.4 (C15), 34.0 (C14), 33.8 (q, $^2J_{FC}$ = 28.3 Hz, C2), 29.3 (C7), [29.1, 28.7](C4,5), 28.9 (C13), 25.9 (C6), 24.3 (NAc), 21.9 (q, $^3J_{FC}$ = 2.9 Hz, C3), 21.0 (OAc).

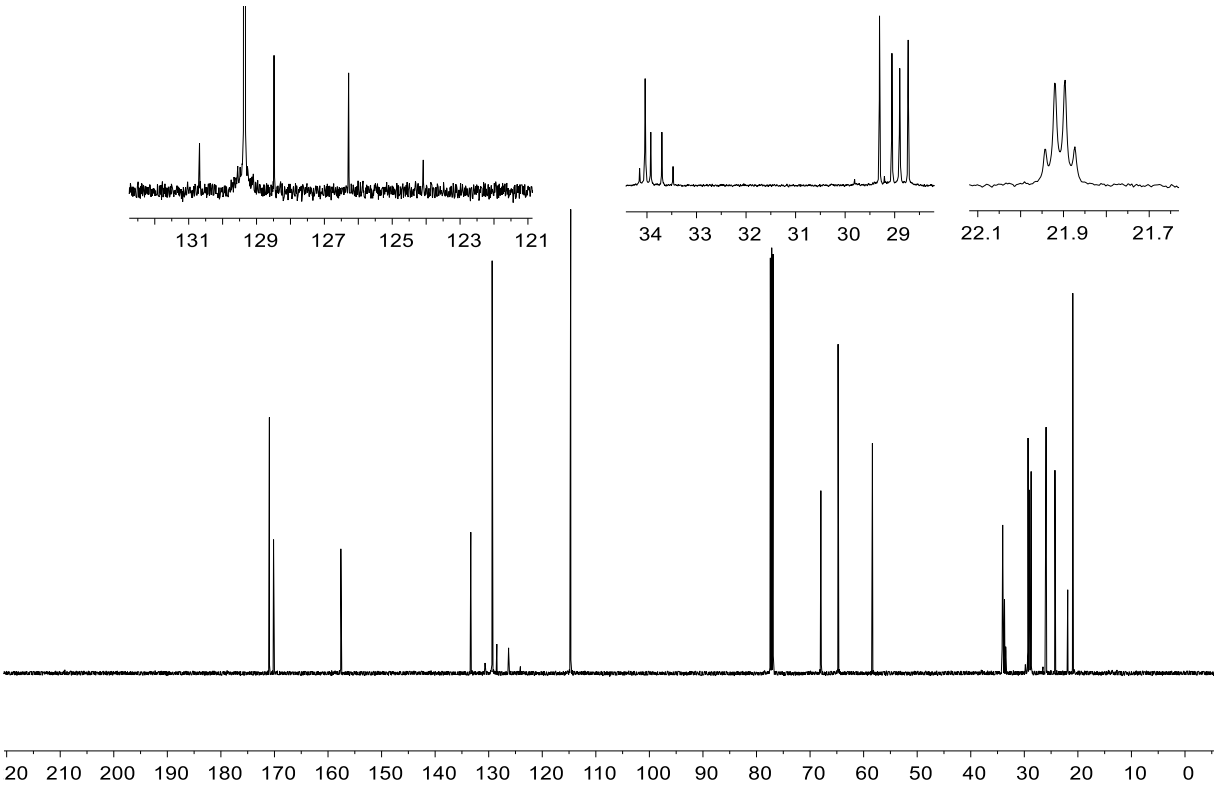
$^{19}$F NMR (470 MHz, Chloroform-*d*, 298 K) δ -66.4 (t, $^3J_{FH}$ = 11.0 Hz, $F_3$C1).

IR ($cm^{-1}$): 3306 (w), 3204 (w), 3082 (w), 2942 (w), 2859 (w), 1737 (m), 1650 (m), 1612 (w), 1556 (m), 1511 (m), 1467 (m), 1441 (w), 1379 (m), 1337 (w), 1317 (w), 1294 (w), 1243 (s), 1213 (s), 1189 (m), 1175 (m), 1099 (m), 1049 (m), 1032 (m), 966 (m), 924 (w), 866 (w), 846 (m), 822 (m), 777 (m), 727 (w), 694 (w), 654 (m).

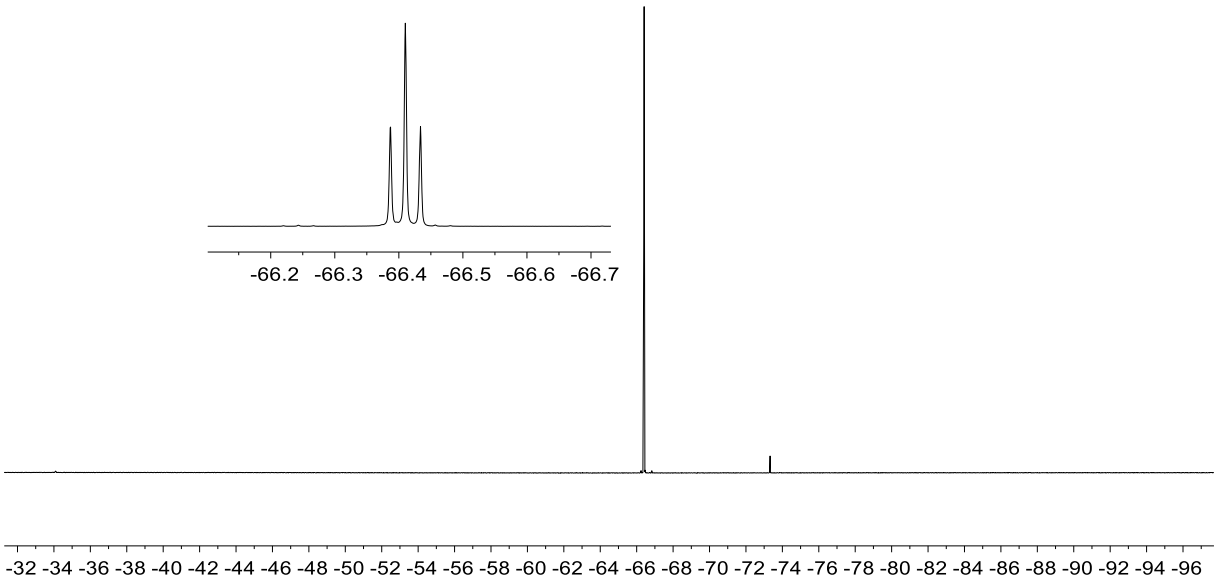
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



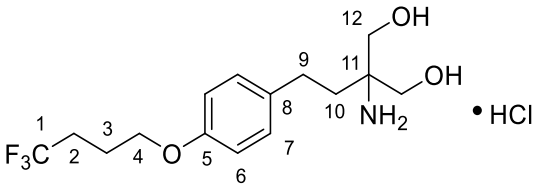
$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*, 298 K)



$^{19}$F NMR (470 MHz, Chloroform-*d*, 298 K)




**2-Amino-2-(4-(4,4,4-trifluorobutoxy)phenethyl)propane-1,3-diol hydrochloride (14a)**




The compound was synthesised from **13a** (51 mg, 0.11 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (28 mg, 73%).

M.p.: 151 °C.

$R_f$ 0.17 (DCM : MeOH / 10 : 2).

HRMS *m/z* (ESI); Calcd. for $C_{15}H_{23}NO_3F_3$ 322.1625, found 322.1630.

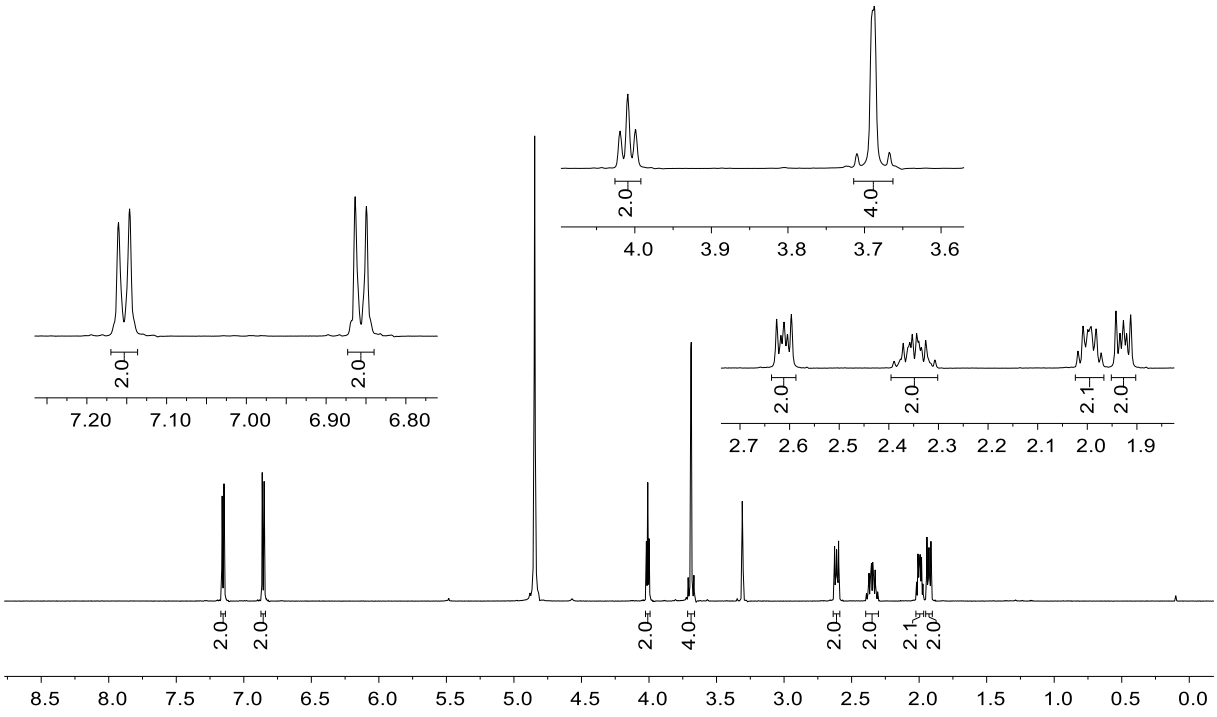
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.15 (m, 2H, HC7), 6.86 (m, 2H, HC6), 4.01 (t, $^3J_{HH}$ = 6.1 Hz, 2H, $H_2$C4), [3.70 (d, $^2J_{HH}$ = 12.0 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 12.0 Hz, 2H)]($H_2$C12), 2.61 (m, 2H, $H_2$C9), 2.35 (qm, $^3J_{FH}$ = 11.1 Hz, 2H, $H_2$C2), 2.00 (m, 2H, $H_2$C3), 1.93 (m, 2H, $H_2$C10).

$^{13}$C{$^1$H} NMR (151 MHz, Methanol-$d_4$, 298 K) δ 158.7 (C5), 134.7 (C8), 130.3 (C7), 128.9 (q, $^1J_{FC}$ = 275.1 Hz, C1), 115.7 (C6), 67.3 (C4), 62.5 (C12), 62.1 (C11), 34.9 (C10), 31.4 (q, $^2J_{FC}$ = 29.0 Hz, C2), 29.2 (C9), 23.3 (q, $^3J_{FC}$ = 2.9 Hz, C3).

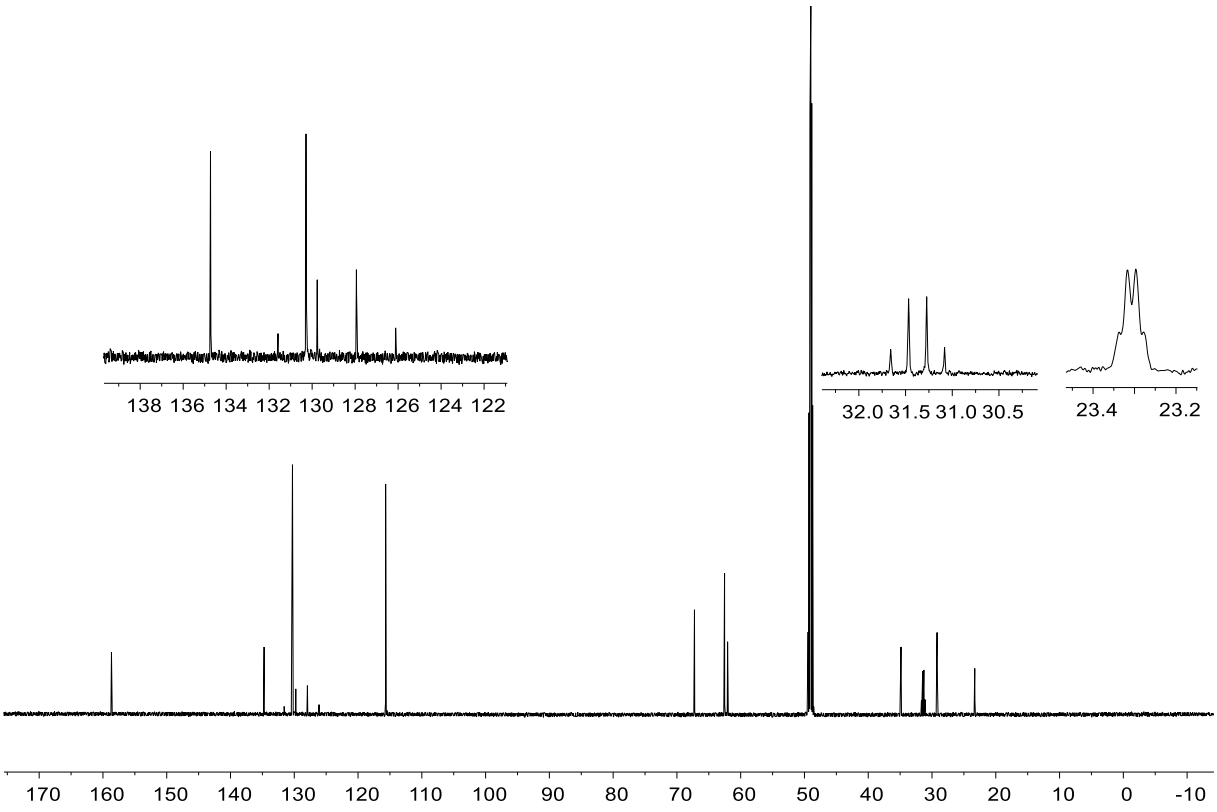
$^{19}$F NMR (282 MHz, Methanol-$d_4$, 298 K) δ -68.1 (t, $^3J_{FH}$ = 11.1 Hz, $F_3$C1).

IR (cm$^{-1}$): 3269 (w), 3035 (w), 2937 (w), 2435 (w), 2216 (w), 1611 (w), 1583 (w), 1513 (m), 1473 (w), 1453 (w), 1385 (w), 1338 (w), 1317 (w), 1300 (w), 1244 (m), 1234 (m), 1176 (w), 1152 (m), 1130 (m), 1108 (w), 1084 (w), 1059 (m), 1026 (m), 933 (w), 831 (m), 811 (w), 795 (w), 763 (w), 737 (w), 660 (w).

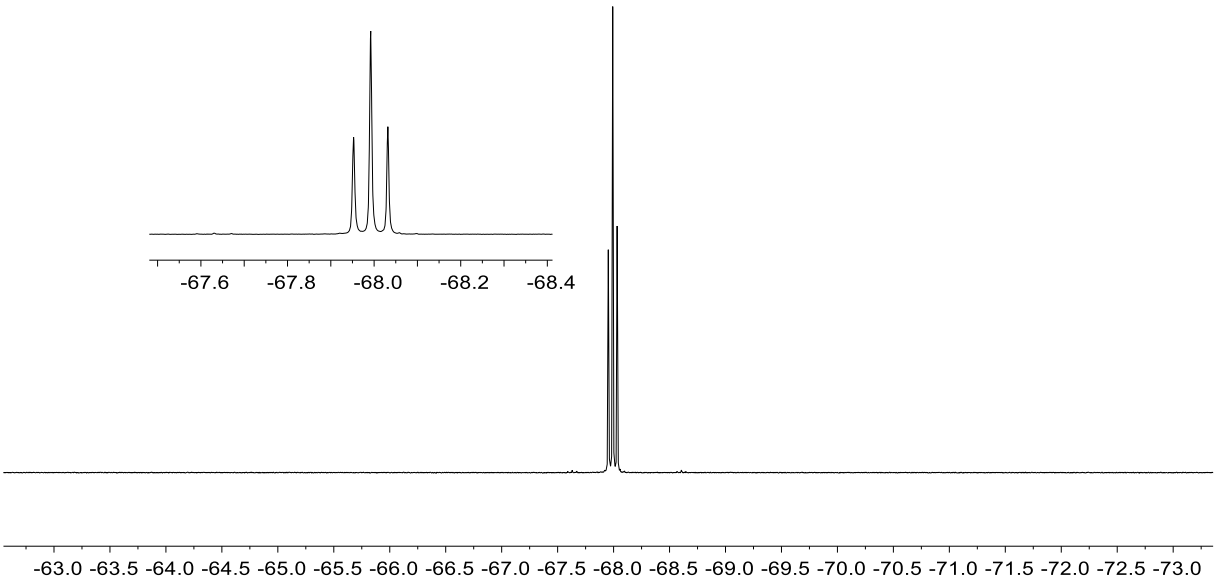
$^{1}$H NMR (600 MHz, Methanol-$d_4$, 298 K)



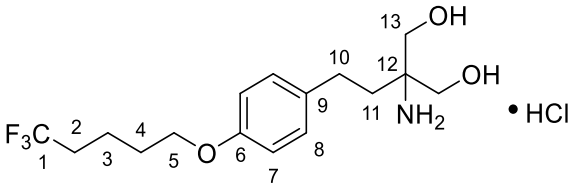

$^{13}$C{$^{1}$H} NMR (151 MHz, Methanol-$d_4$, 298 K)



$^{19}$F NMR (282 MHz, Methanol-$d_4$, 298 K)




**2-Amino-2-(4-((5,5,5-trifluoroPentanetyl)oxy)phenethyl)propane-1,3-diol hydrochloride (14b)**




The compound was synthesised from **13b** (38 mg, 0.08 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (22 mg, 71%).

M.p.: 124 °C.

$R_f$ 0.17 (DCM : MeOH / 10 : 3).

HRMS *m/z* (ESI); Calcd. for $C_{16}H_{25}NO_3F_3$ 336.1781, found 336.1789.

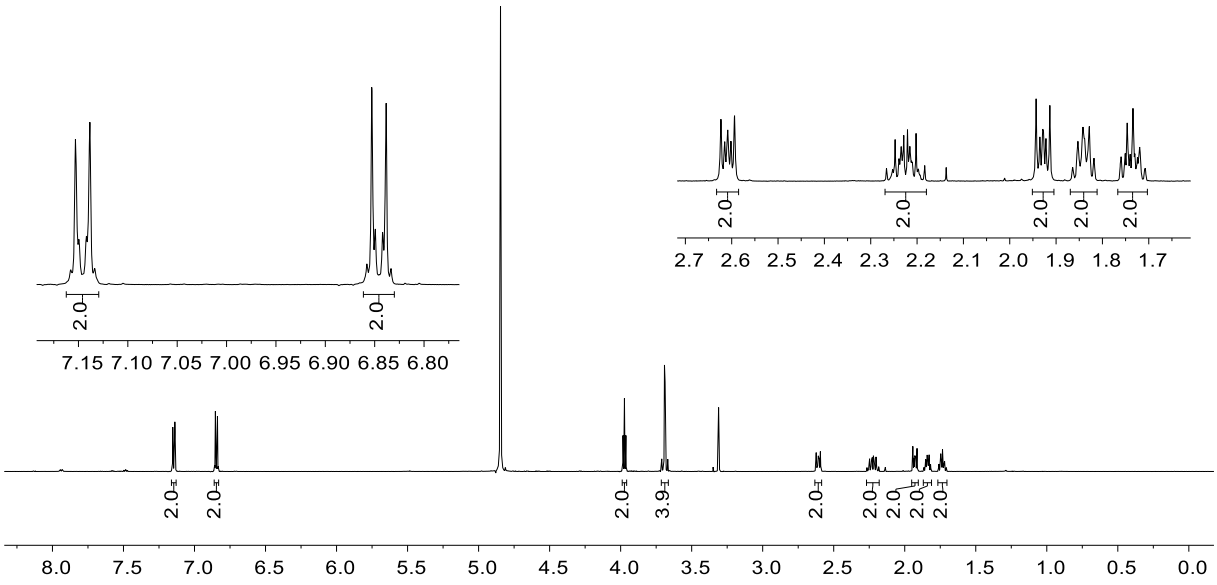
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.14 (m, 2H, HC8), 6.84 (m, 2H, HC7), 3.97 (t, $^3J_{HH}$ = 6.1 Hz, 2H, $H_2$C5), [3.70 (d, $^2J_{HH}$ = 11.6 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.6 Hz, 2H)]($H_2$C13), 2.61 (m, 2H, $H_2$C10), 2.22 (qm, $^3J_{FH}$ = 11.1 Hz, 2H, $H_2$C2), 1.93 (m, 2H, $H_2$C11), 1.84 (m, 2H, $H_2$C4), 1.74 (m, 2H, $H_2$C3).

$^{13}$C{$^1$H} NMR (151 MHz, Methanol-$d_4$, 298 K) δ 158.9 (C6), 134.5 (C9), 130.2 (C8), 128.8 (q, $^1J_{FC}$ = 275.4 Hz, C1), 115.6 (C7), 68.4 (C5), 62.5 (C13), 62.1 (C12), 34.9 (C11), 34.2 (q, $^2J_{FC}$ = 28.4 Hz, C2), 29.4 (C4), 29.2 (C10), 20.0 (q, $^3J_{FC}$ = 3.2 Hz, C3).

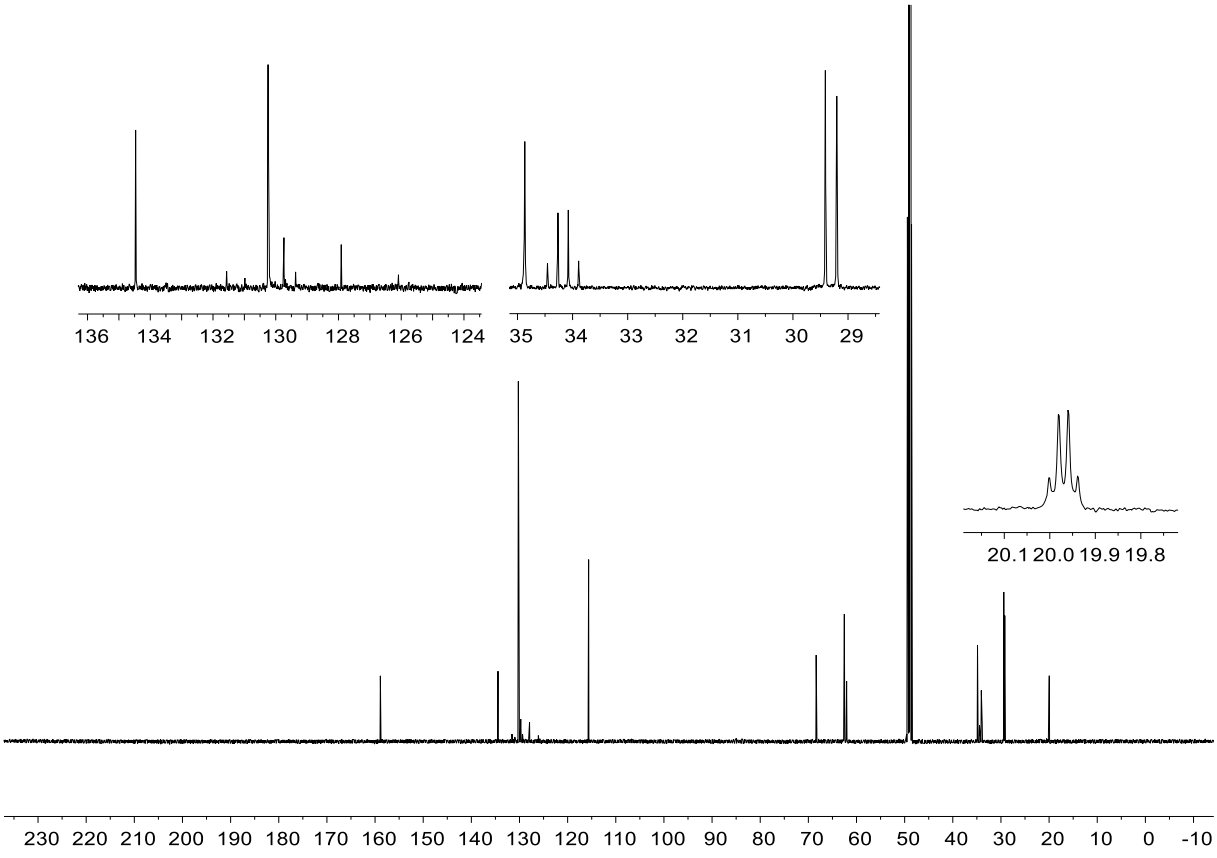
$^{19}$F NMR (564 MHz, Methanol-$d_4$, 298 K) δ -68.1 (t, $^3J_{FH}$ = 11.1 Hz, $F_3$C1).

IR ($cm^{-1}$): 3273 (w), 3034 (w), 2940 (w), 2878 (w), 2504 (w), 2437 (w), 2295 (w), 2226 (w), 1734 (w), 1612 (w), 1582 (w), 1513 (m), 1470 (w), 1456 (w), 1440 (w), 1390 (w), 1373 (w), 1347 (w), 1300 (m), 1244 (s), 1219 (m), 1178 (m), 1138 (m), 1054 (m), 1040 (s), 953 (m), 921 (w), 831 (m), 808 (w), 790 (w), 764 (w), 742 (w), 731 (w), 654 (m).

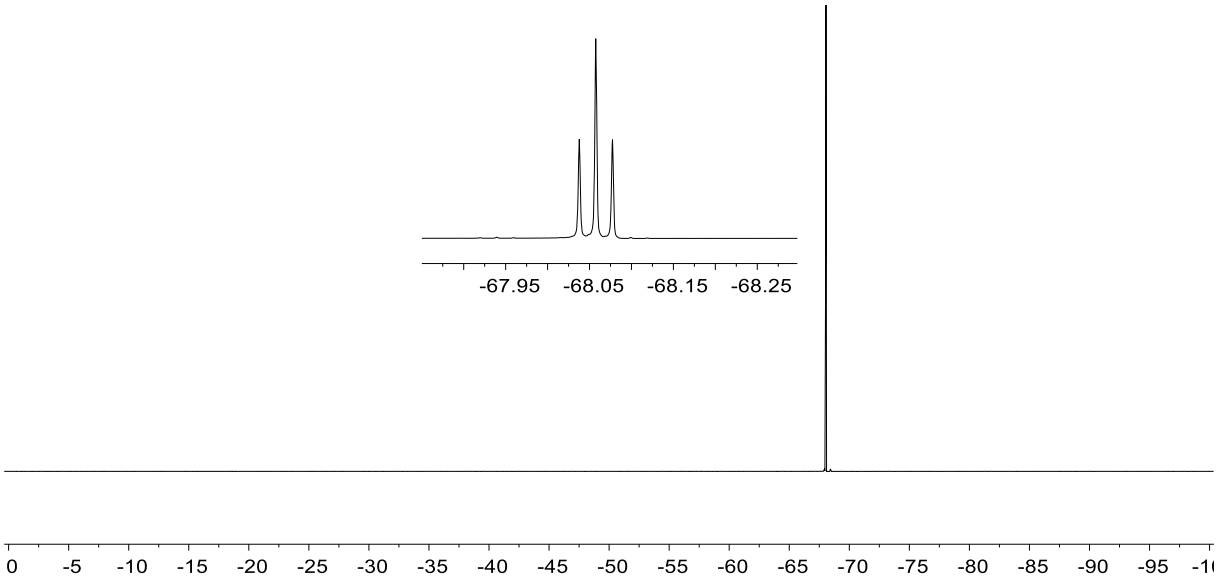
$^{1}$H NMR (600 MHz, Methanol-$d_4$, 298 K)



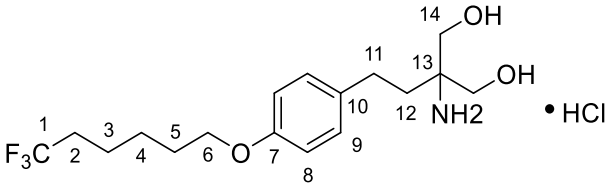
$^{13}$C{$^{1}$H} NMR (151 MHz, Methanol-$d_4$, 298 K)



$^{19}$F NMR (564 MHz, Methanol-$d_4$, 298 K)




**2-Amino-2-(4-((6,6,6-trifluorohexyl)oxy)phenethyl)propane-1,3-diol hydrochloride (14c)**




The compound was synthesised from **13c** (39 mg, 0.08 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (15 mg, 48%).

M.p.: 121 °C.

$R_f$ 0.56 (DCM : MeOH / 10 : 3).

HRMS *m/z* (ESI); Calcd. for $C_{17}H_{27}NO_3F_3$ 350.1938, found 350.1942.

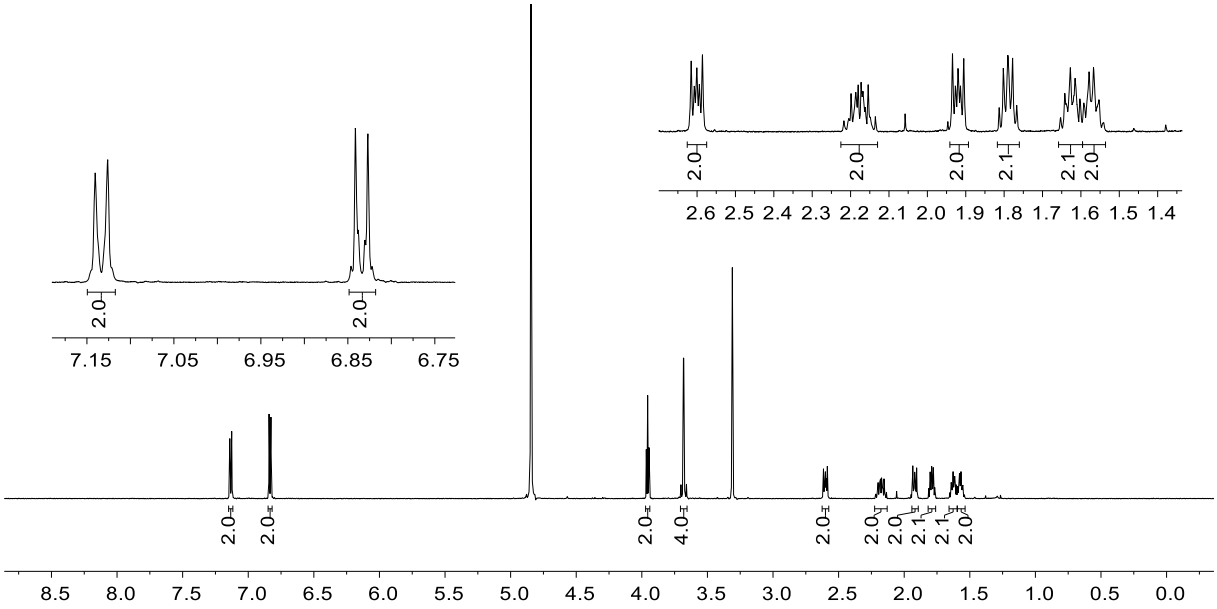
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC9), 6.83 (m, 2H, HC8), 3.95 (t, $^3J_{HH}$ = 6.2 Hz, 2H, $H_2$C6), [3.69 (dm, $^2J_{HH}$ = 11.6 Hz, 2H), 3.67 (dm, $^2J_{HH}$ = 11.6 Hz, 2H)]($H_2$C14), 2.60 (m, 2H, $H_2$C11), 2.18 (qm, $^3J_{FH}$ = 11.1 Hz, 2H, $H_2$C2), 1.92 (m, 2H, $H_2$C12), 1.79 (m, 2H, $H_2$C5), 1.63 (m, 2H, $H_2$C3), 1.57 (m, 2H, $H_2$C4).

$^{13}$C{$^1$H} NMR (126 MHz, Methanol-$d_4$, 298 K) δ 159.0 (C7), 134.3 (C10), 130.2 (C9), 128.9 (q, $^1J_{FC}$ = 275.4 Hz, C1), 115.6 (C8), 68.7 (C6), 62.6 (C14), 62.0 (C13), 34.9 (C12), 34.4 (q, $^2J_{FC}$ = 28.2 Hz, C2), 30.0 (C5), 29.2 (C11), 26.4 (C4), 22.8 (q, $^3J_{FC}$ = 3.1 Hz, C3).

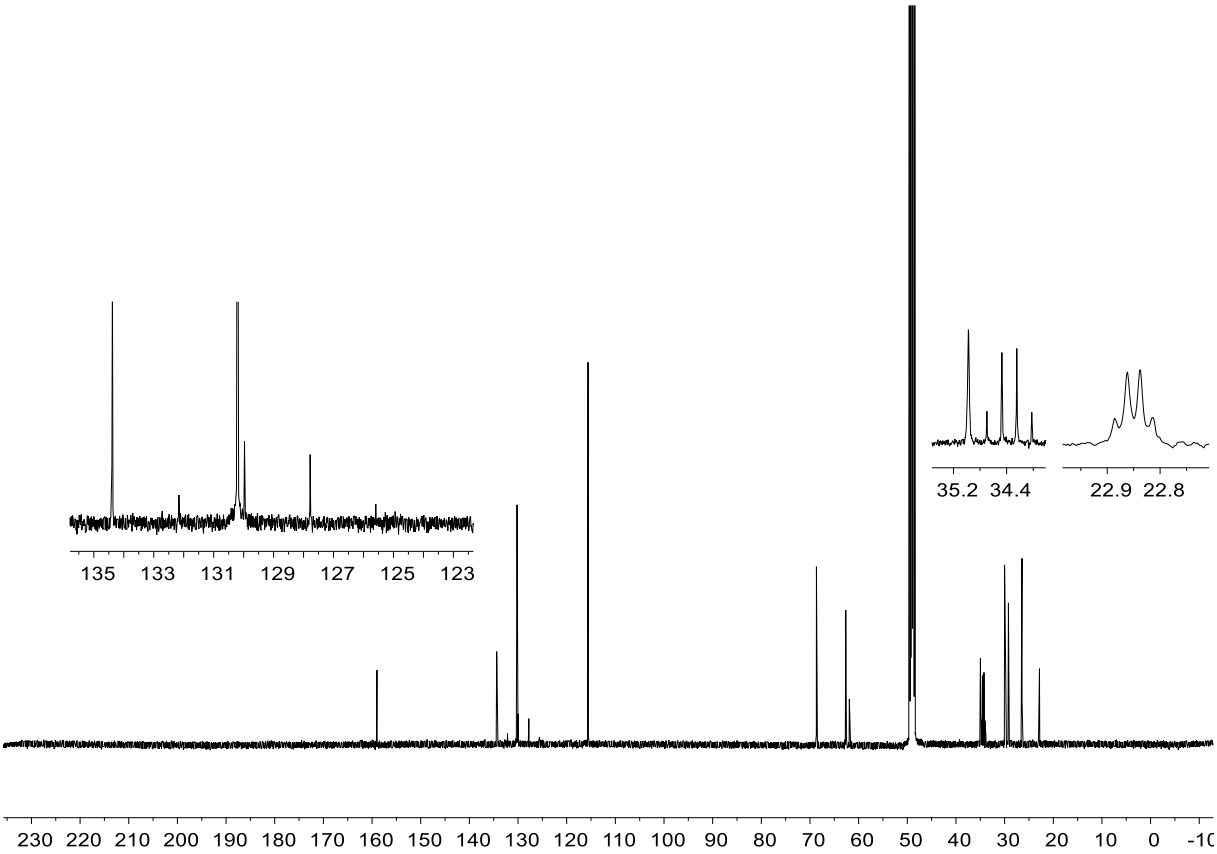
$^{19}$F NMR (564 MHz, Methanol-$d_4$, 298 K) δ -68.0 (t, $^3J_{FH}$ = 11.1 Hz, $F_3$C1).

IR (cm$^{-1}$): 3276 (w), 3024 (w), 2948 (m), 2875 (w), 2442 (w), 2260 (w), 1612 (w), 1582 (w), 1512 (m), 1473 (w), 1457 (w), 1440 (w), 1390 (m), 1338 (w), 1317 (m), 1300 (m), 1244 (s), 1204 (m), 1177 (m), 1136 (m), 1091 (m), 1041 (s), 969 (w), 953 (w), 921 (w), 887 (w), 866 (w), 831 (m), 790 (w), 764 (w), 749 (w), 733 (w), 655 (m).

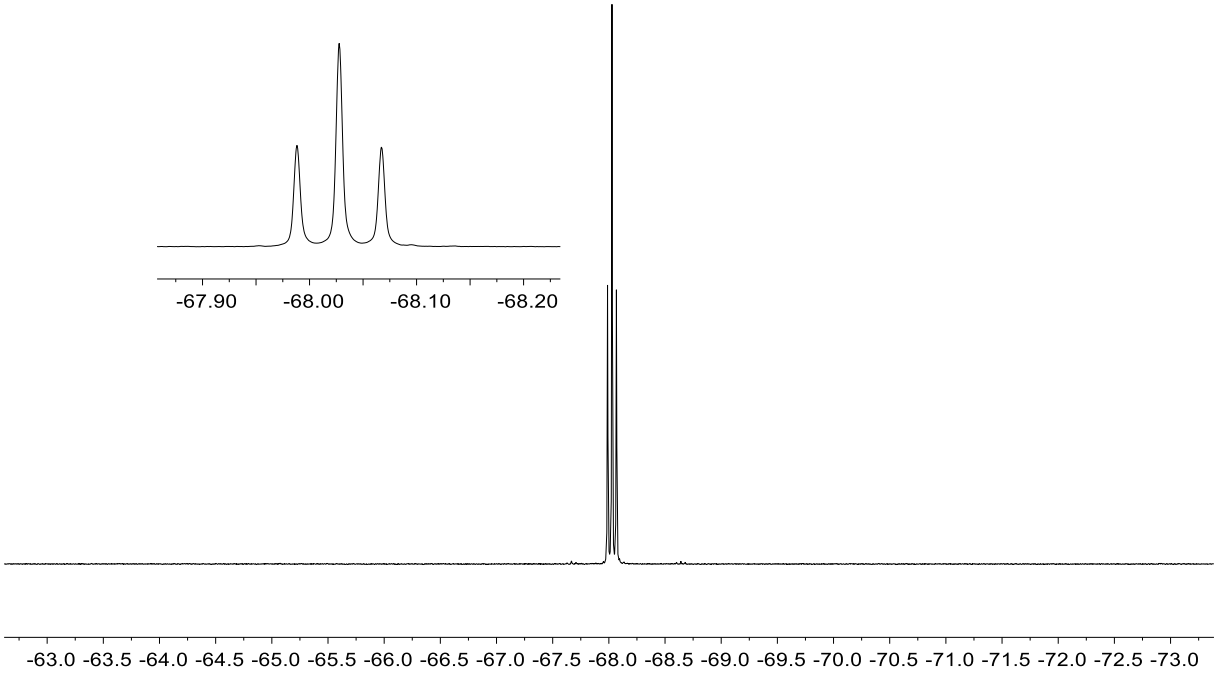
$^{1}$H NMR (600 MHz, Methanol-$d_4$, 298 K)



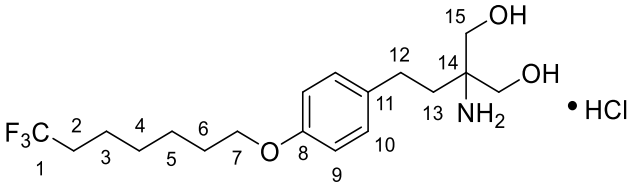
$^{13}$C{$^{1}$H} NMR (126 MHz, Methanol-$d_4$, 298 K)



$^{19}$F NMR (564 MHz, Methanol-$d_4$, 298 K)




**2-Amino-2-(4-((7,7,7-trifluoroheptyl)oxy)phenethyl)propane-1,3-diol hydrochloride (14d)**




The compound was synthesised from **13d** (44 mg, 0.09 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (21 mg, 58%).

M.p.: 115 °C.

$R_f$ 0.66 (DCM : MeOH / 10 : 3).

HRMS *m/z* (ESI); Calcd. for $C_{18}H_{29}NO_3F_3$ 364.2094, found 364.2089.

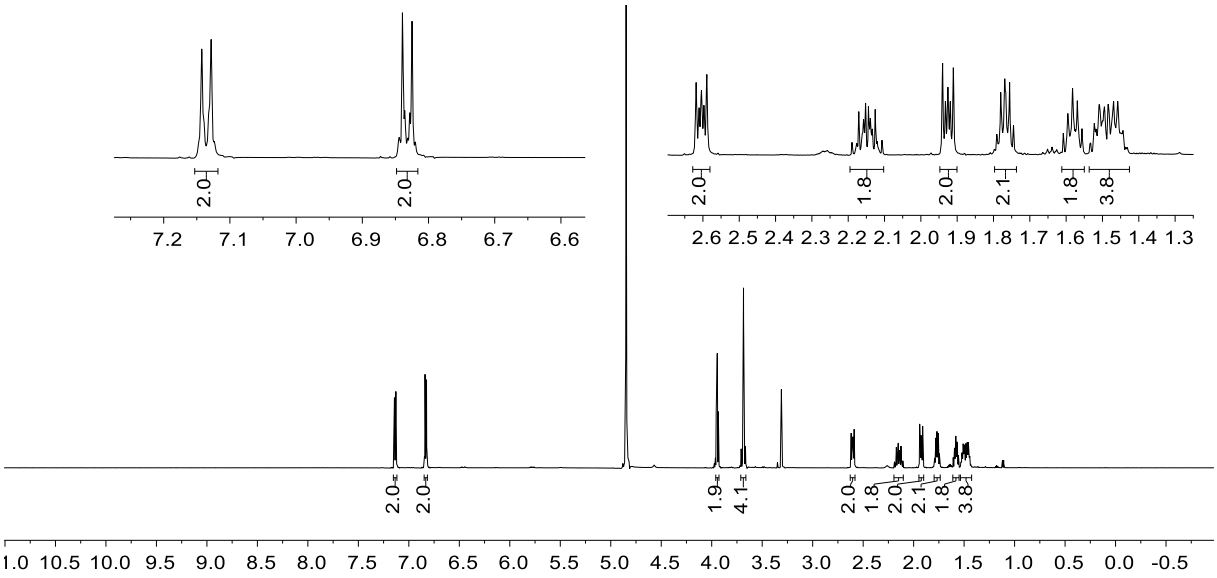
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.14 (m, 2H, HC10), 6.83 (m, 2H, HC9), 3.94 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C7), [3.69 (dm, $^2J_{HH}$ = 11.6 Hz, 2H), 3.68 (dm, $^2J_{HH}$ = 11.6 Hz, 2H)]($H_2$C15), 2.60 (m, 2H, $H_2$C12), 2.15 (qm, $^3J_{FH}$ = 11.1 Hz, 2H, $H_2$C2), 1.92 (m, 2H, $H_2$C13), 1.77 (m, 2H, $H_2$C6), 1.58 (m, 2H, $H_2$C3), 1.51 (m, 2H, $H_2$C5), 1.47 (m, 2H, $H_2$C4).

$^{13}$C{$^1$H} NMR (151 MHz, Methanol-$d_4$, 298 K) δ 159.0 (C8), 134.3 (C11), 130.2 (C10), 128.9 (q, $^1J_{FC}$ = 275.1 Hz, C1), 115.6 (C9), 68.9 (C7), 62.5 (C15), 62.1 (C14), 34.9 (C13), 34.3 (q, $^2J_{FC}$ = 28.3 Hz, C2), 30.2 (C6), 29.5 (C4), 29.2 (C12), 26.8 (C5), 23.0 (q, $^3J_{FC}$ = 3.2 Hz, C3).

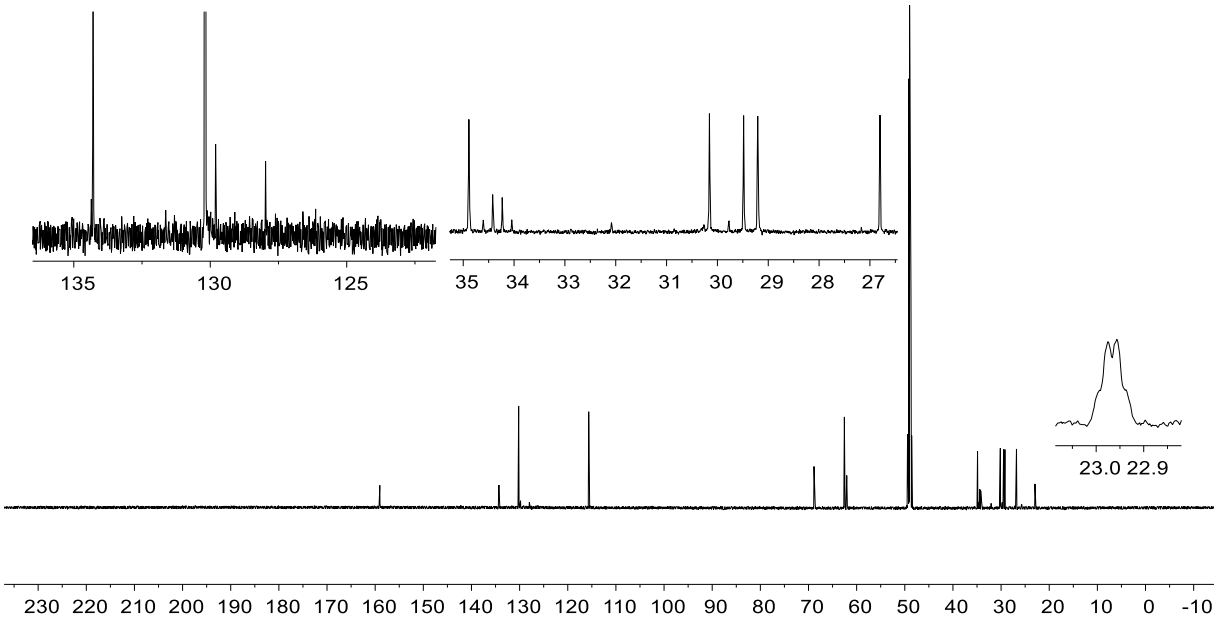
$^{19}$F NMR (282 MHz, Methanol-$d_4$, 298 K) δ -68.0 (t, $^3J_{FH}$ = 11.1 Hz, $F_3$C1).

IR ($cm^{-1}$): 3273 (w), 3059 (w), 2946 (w), 2873 (w), 2438 (w), 2294 (w), 1612 (w), 1581 (w), 1512 (m), 1473 (w), 1457 (w), 1440 (w), 1389 (w), 1299 (w), 1244 (m), 1197 (w), 1178 (w), 1139 (m), 1098 (w), 1048 (m), 983 (w), 829 (m), 788 (w), 763 (w), 736 (w), 655 (w).

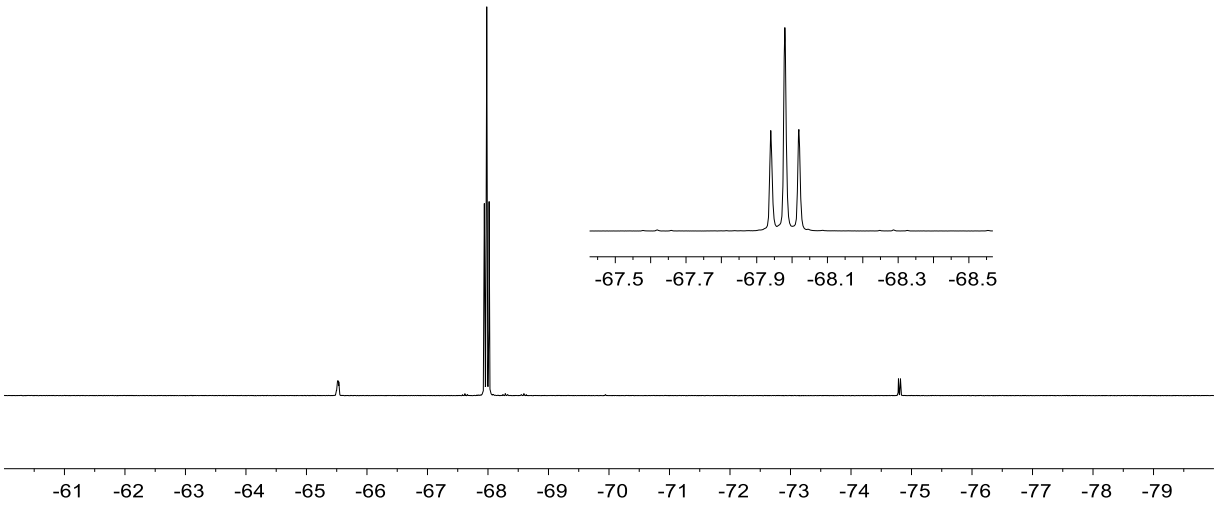
$^{1}$H NMR (600 MHz, Methanol-$d_4$, 298 K)



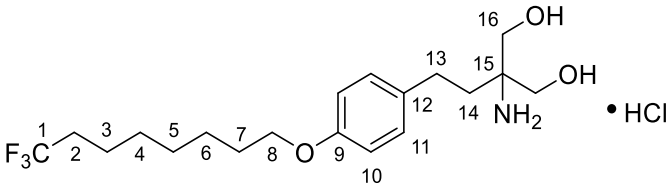
$^{13}$C{$^{1}$H} NMR (151 MHz, Methanol-$d_4$, 298 K)



$^{19}$F NMR (282 MHz, Methanol-$d_4$, 298 K)




**2-Amino-2-(4-((8,8,8-trifluorooctyl)oxy)phenethyl)propane-1,3-diol hydrochloride (14e)**




The compound was synthesised from **13e** (32 mg, 0.06 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (18 mg, 69%).

M.p.: 114 °C.

$R_f$ 0.85 (DCM : MeOH / 10 : 3).

HRMS *m/z* (ESI); Calcd. for $C_{19}H_{31}NO_3F_3$ 378.2251, found 378.2247.

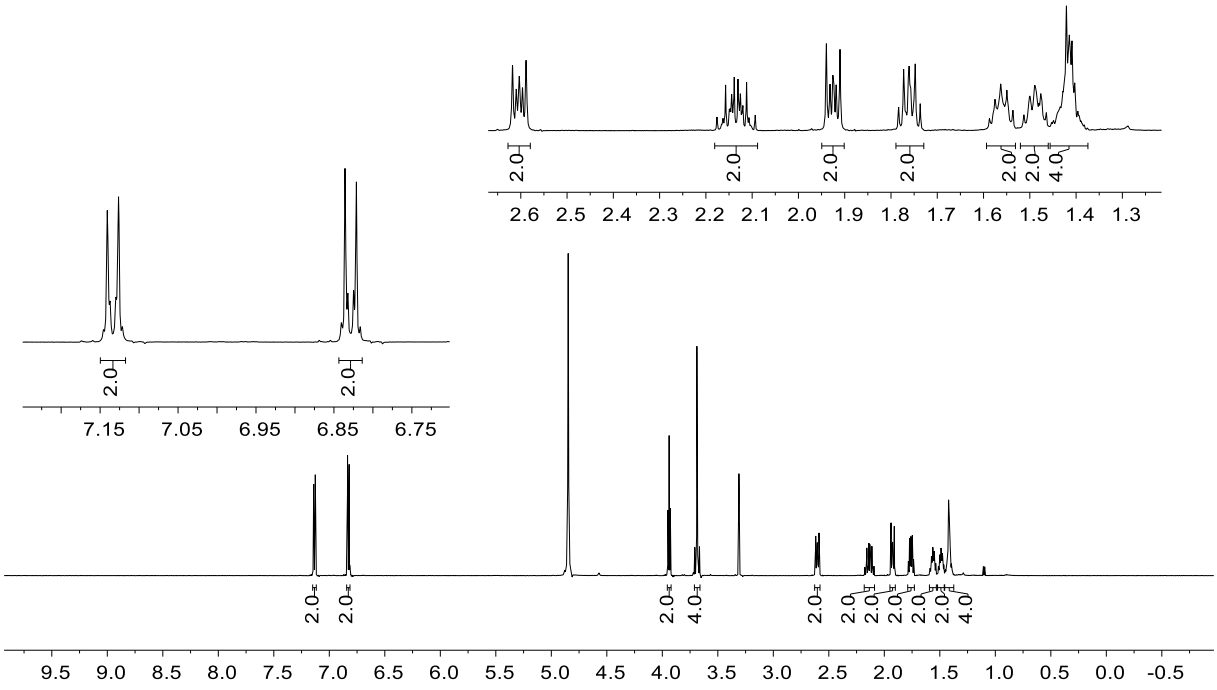
$^1$H NMR (600 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC11), 6.83 (m, 2H, HC10), 3.94 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C8), [3.69 (dm, $^2J_{HH}$ = 11.5 Hz, 2H), 3.68 (dm, $^2J_{HH}$ = 11.5 Hz, 2H)]($H_2$C16), 2.60 (m, 2H, $H_2$C13), 2.13 (qm, $^3J_{FH}$ = 11.2 Hz, 2H, $H_2$C2), 1.92 (m, 2H, $H_2$C14), 1.76 (m, 2H, $H_2$C7), 1.56 (m, 2H, $H_2$C3), 1.49 (m, 2H, $H_2$C6), 1.41 (m, 4H, $H_2$C4,5).

$^{13}$C{$^1$H} NMR (151 MHz, Methanol-$d_4$, 298 K) δ 159.1 (C9), 134.3 (C12), 130.2 (C11), 128.9 (q, $^1J_{FC}$ = 275.4 Hz, C1), 115.6 (C10), 68.9 (C8), 62.6 (C16), 62.0 (C15), 34.9 (C14), 34.4 (q, $^2J_{FC}$ = 28.2 Hz, C2), 30.3 (C7), [30.0, 29.7](C4,5), 29.2 (C13), 26.9 (C6), 23.0 (q, $^3J_{FC}$ = 2.9 Hz, C3).

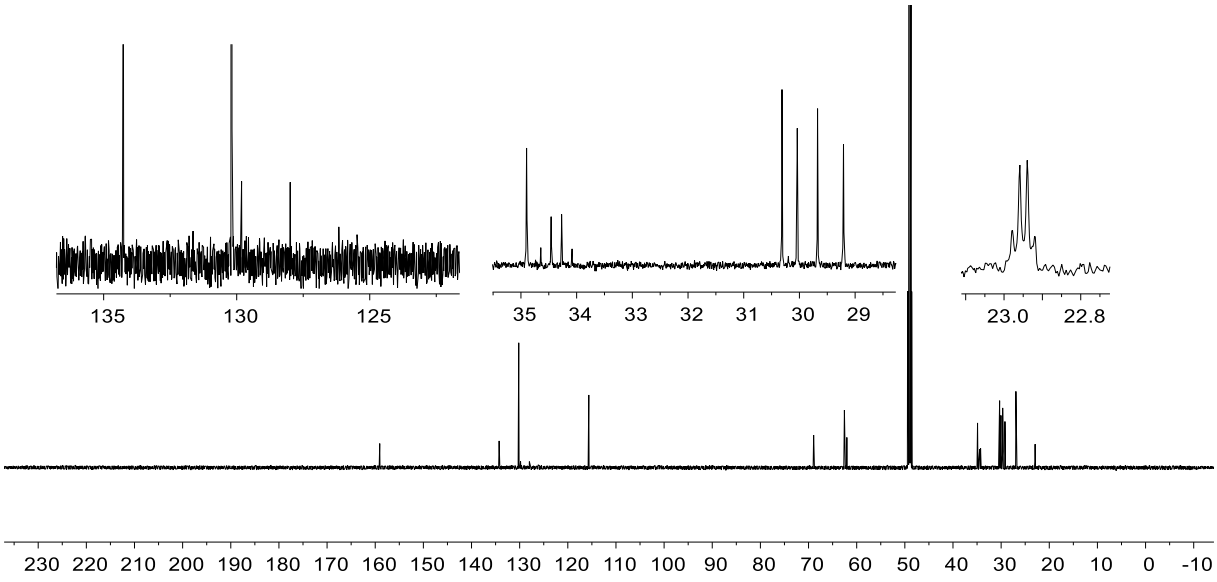
$^{19}$F NMR (564 MHz, Methanol-$d_4$, 298 K) δ -68.0 (t, $^3J_{FH}$ = 11.2 Hz, $F_3$C1).

IR (cm$^{-1}$): 3271 (w), 3024 (w), 2940 (w), 2860 (w), 2438 (w), 2302 (w), 1612 (w), 1582 (w), 1512 (m), 1473 (w), 1457 (w), 1440 (w), 1391 (w), 1337 (w), 1321 (w), 1299 (w), 1243 (s), 1191 (m), 1179 (m), 1134 (m), 1101 (m), 1052 (s), 937 (w), 911 (w), 823 (m), 807 (w), 788 (w), 763 (w), 727 (w), 655 (m).

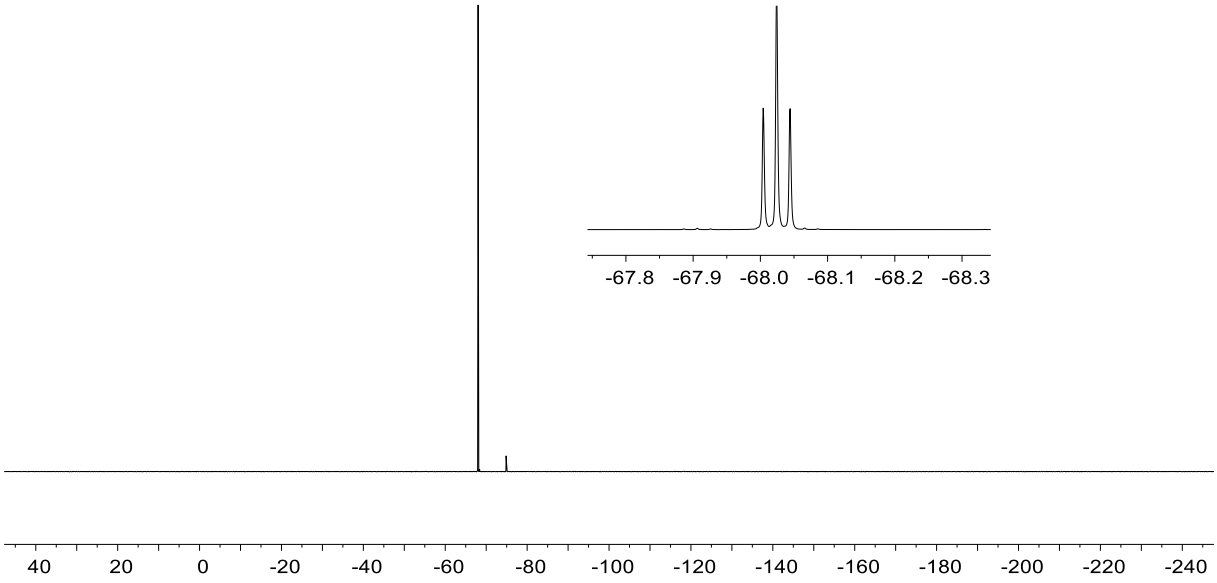
$^{1}$H NMR (600 MHz, Methanol-$d_4$, 298 K)



$^{13}$C{$^{1}$H} NMR (151 MHz, Methanol-$d_4$, 298 K)



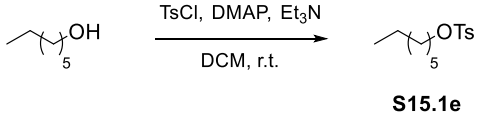
$^{19}$F NMR (564 MHz, Methanol-$d_4$, 298 K)

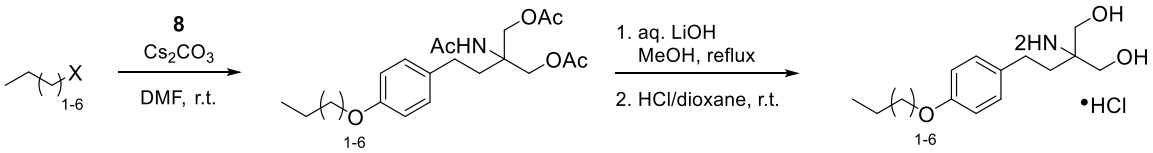


## II.7 Synthesis of Non-fluorinated Fingolimod Analogues

### II.7.1 Compounds 15a-f to 16a-f

**Scheme S6.**

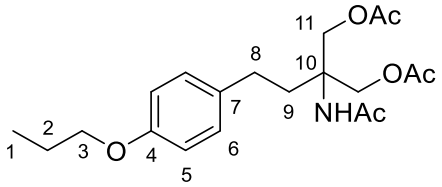



| | | |
|---|---|---|
| 1: X = **I** | 1: **15a** | 1: **16a** |
| 2: X = Br | 2: **15b** | 2: **16b** |
| 3: X = **I** | 3: **15c** | 3: **16c** |
| 4: X = Br | 4: **15d** | 4: **16d** |
| 5: X = OTs (**S15.1e**) | 5: **15e** | 5: **16e** |
| 6: X = Br | 6: **15f** | 6: **16f** |

Halogenated starting materials for compounds 15a-d and 15f were obtained commercially.

#### 2-Acetamido-2-(4-propoxyphenethyl)propane-1,3-diyl diacetate (15a)




The compound was synthesised from **8** (60 mg, 0.18 mmol, 1.00 eq.) and 1-iodopropane (18 µl, 0.18 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (55 mg, 81%).

M.p.: 110 °C.

$R_f$ 0.22 (CyH : EtOAc / 1 : 1).

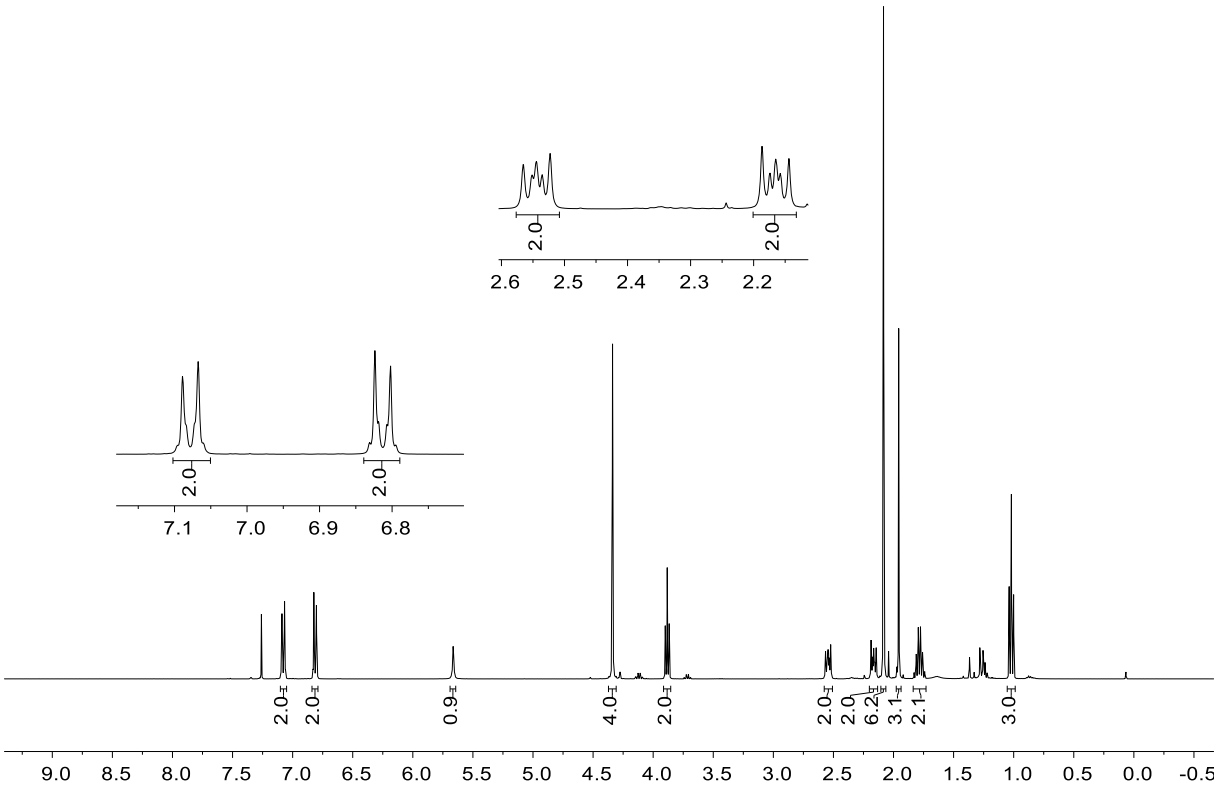
HRMS *m/z* (ESI); Calcd. for $C_{20}H_{29}NO_6Na$ 402.1893, found 402.1875.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC6), 6.81 (m, 2H, HC5), 5.66 (s, 1H, HN), [4.339 (d, $^2J_{HH}$ = 11.3 Hz, 2H), 4.337 (d, $^2J_{HH}$ = 11.3 Hz, 2H)]($H_2$C11), 3.88 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2$C3), 2.54 (m, 2H, $H_2$C8), 2.16 (m, 2H, $H_2$C9), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.78 (qt, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2$C2), 1.02 (t, $^3J_{HH}$ = 7.4 Hz, 3H, $H_3$C1).

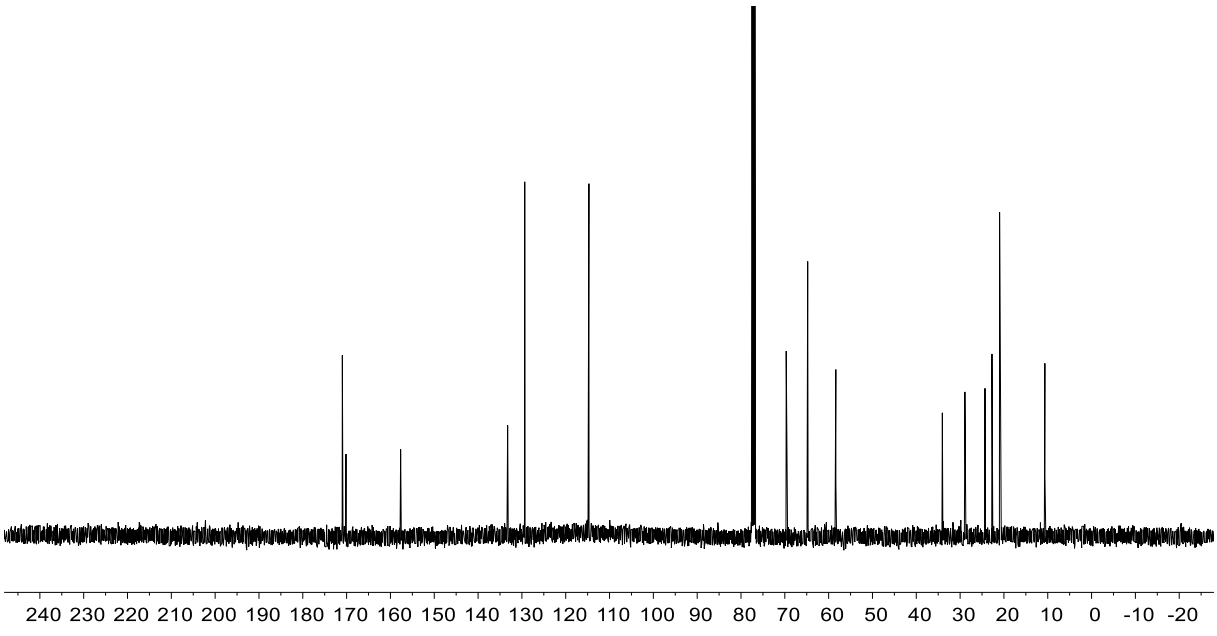
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.1 (NAc), 157.7 (C4), 133.2 (C7), 129.3 (C6), 114.7 (C5), 69.7 (C3), 64.8 (C11), 58.4 (C10), 34.1 (C9), 28.9 (C8), 24.3 (NAc), 22.7 (C2), 21.0 (OAc), 10.7 (C1).

IR ($cm^{-1}$): 3315 (w), 3075 (w), 2964 (w), 2944 (w), 2881 (w), 1735 (m), 1651 (m), 1616 (w), 1584 (w), 1551 (m), 1513 (m), 1485 (w), 1466 (m), 1429 (w), 1378 (m), 1302 (w), 1290 (w), 1246 (m), 1218 (s), 1175 (m), 1126 (w), 1100 (w), 1048 (m), 1032 (m), 1019 (m), 984 (w), 967 (m), 906 (m), 851 (m), 814 (m), 779 (w), 762 (w), 690 (w).

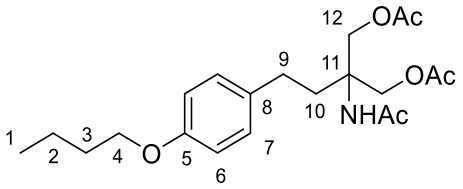
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-butoxyphenethyl)propane-1,3-diyl diacetate (15b)**




The compound was synthesised from **8** (50 mg, 0.15 mmol, 1.00 eq.) and 1-bromobutane (16 µl, 0.15 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (49 mg, 83%).

M.p.: 106 °C.

$R_f$ 0.23 (CyH : EtOAc / 1 : 1).

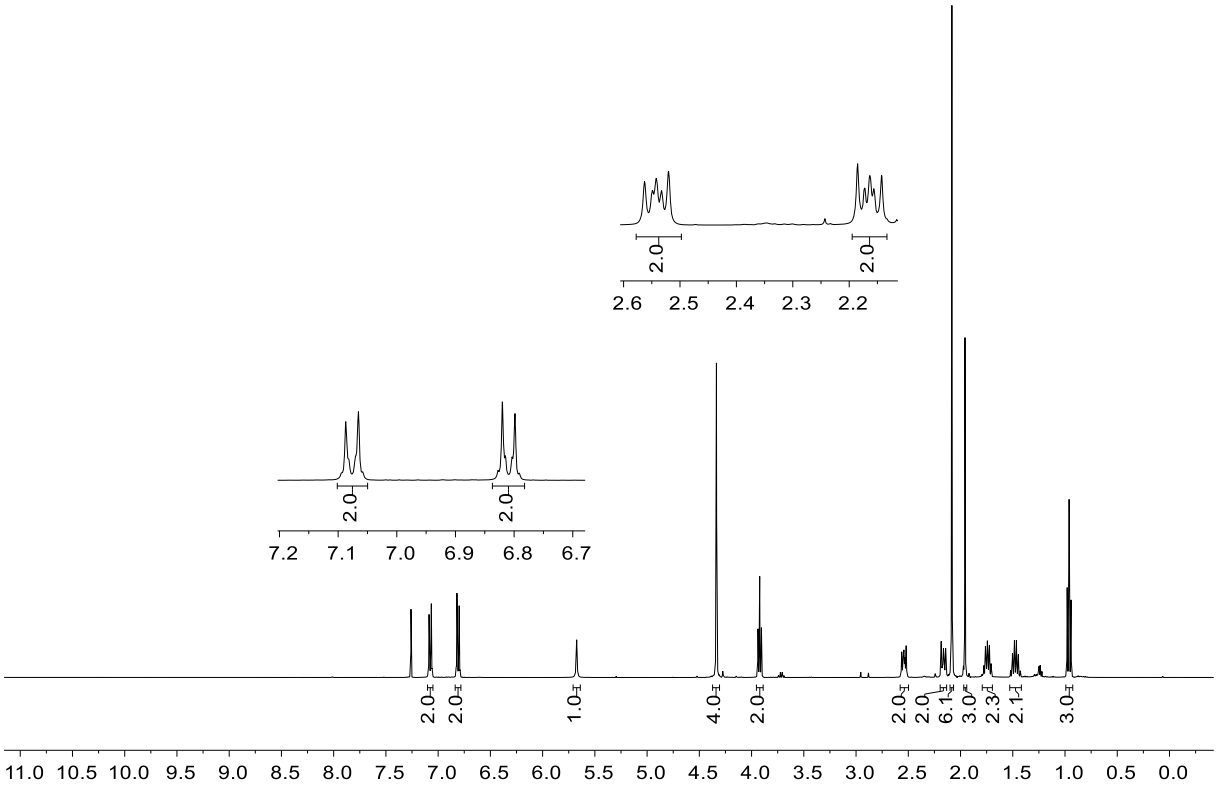
HRMS *m/z* (ESI); Calcd. for $C_{21}H_{31}NO_6Na$ 416.2044, found 416.2053.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC7), 6.81 (m, 2H, HC6), 5.67 (s, 1H, HN), [4.337 (d, $^2J_{HH}$ = 11.1 Hz, 2H), 4.336 (d, $^2J_{HH}$ = 11.1 Hz, 2H)]($H_2$C12), 3.92 (t, $^3J_{HH}$ = 6.5 Hz, 2H, $H_2$C4), 2.54 (m, 2H, $H_2$C9), 2.16 (m, 2H, $H_2$C10), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.74 (m, 2H, $H_2$C3), 1.47 (m, 2H, $H_2$C2), 0.96 (t, $^3J_{HH}$ = 7.4 Hz, 3H, $H_3$C1).

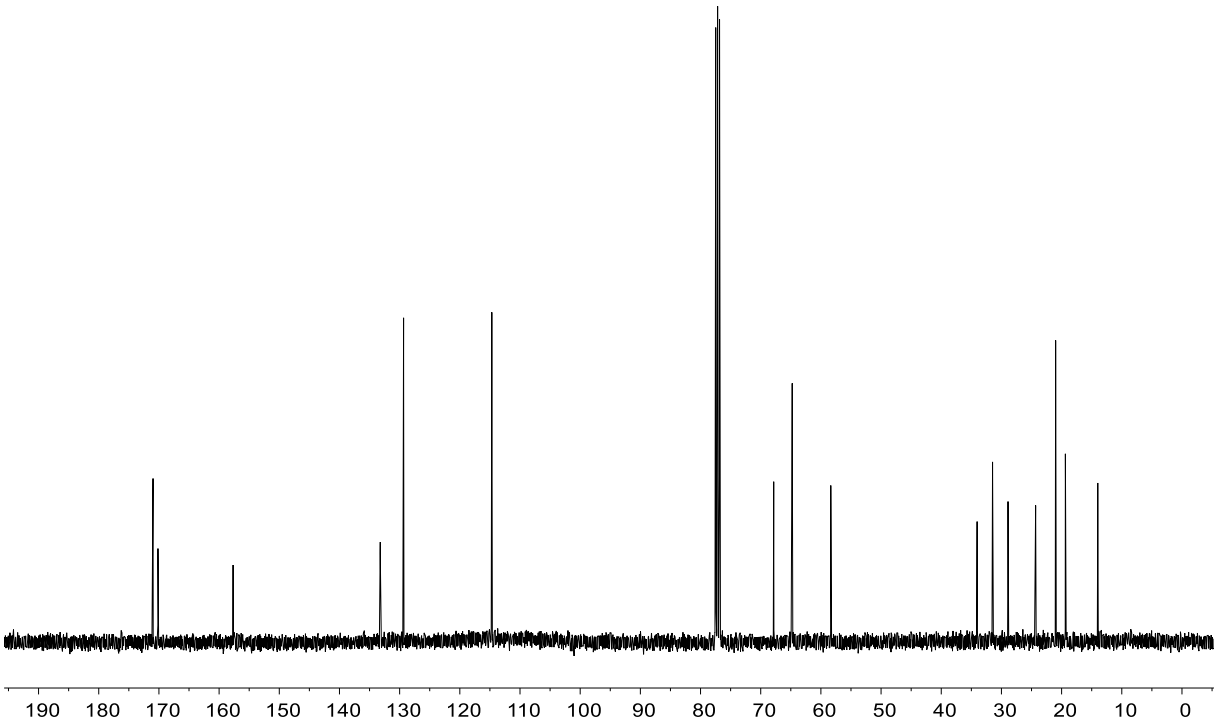
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.2 (NAc), 157.7 (C5), 133.2 (C8), 129.3 (C7), 114.7 (C6), 67.8 (C4), 64.8 (C12), 58.4 (C11), 34.1 (C10), 31.5 (C3), 28.9 (C9), 24.3 (NAc), 21.0 (OAc), 19.4 (C2), 14.0 (C1).

IR (cm$^{-1}$): 3310 (w), 3204 (w), 3081 (w), 2956 (w), 2874 (w), 1885 (w), 1735 (m), 1650 (m), 1615 (w), 1584 (w), 1553 (w), 1512 (m), 1467 (m), 1429 (w), 1377 (m), 1315 (w), 1303 (w), 1291 (w), 1242 (s), 1217 (s), 1176 (m), 1126 (w), 1100 (w), 1051 (m), 1032 (m), 1010 (m), 985 (w), 967 (m), 921 (w), 877 (w), 848 (m), 820 (m), 810 (m), 777 (w), 768 (w), 741 (w), 691 (w).

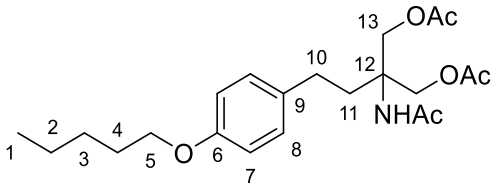
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-(Pentanetyloxy)phenethyl)propane-1,3-diyl diacetate (15c)**




The compound was synthesised from **8** (50 mg, 0.15 mmol, 1.00 eq.) and 1-iodopentane (20 µl, 0.15 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (44 mg, 72%).

M.p.: 94 °C.

$R_f$ 0.56 (EtOAc).

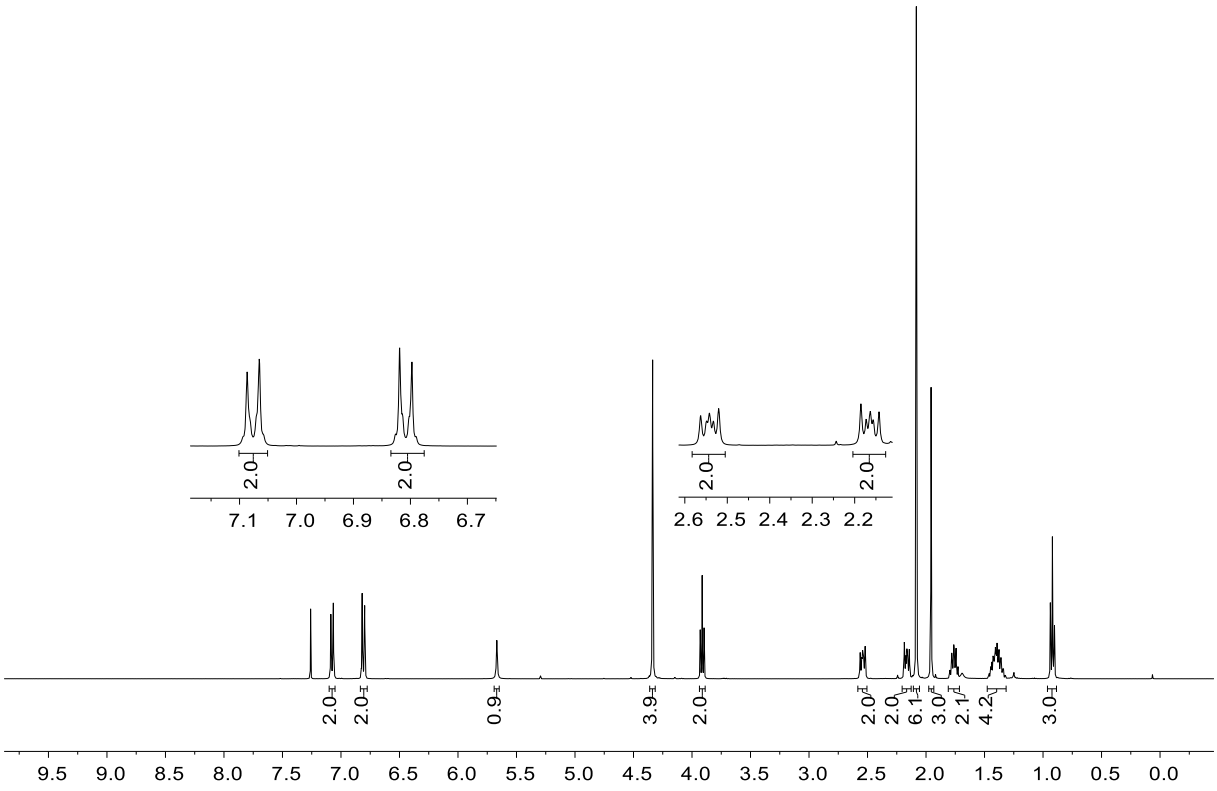
HRMS *m/z* (ESI); Calcd. for $C_{22}H_{33}NO_6Na$ 430.2206, found 430.2210.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC8), 6.81 (m, 2H, HC7), 5.67 (s, 1H, HN), [4.337 (d, $^2J_{HH}$ = 11.1 Hz, 2H), 4.336 (d, $^2J_{HH}$ = 11.1 Hz, 2H)]($H_2$C13), 3.91 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2$C5), 2.54 (m, 2H, $H_2$C10), 2.16 (m, 2H, $H_2$C11), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.76 (m, 2H, $H_2$C4), 1.41 (m, 2H, $H_2$C3), 1.37 (m, 2H, $H_2$C2), 0.92 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $H_3$C1).

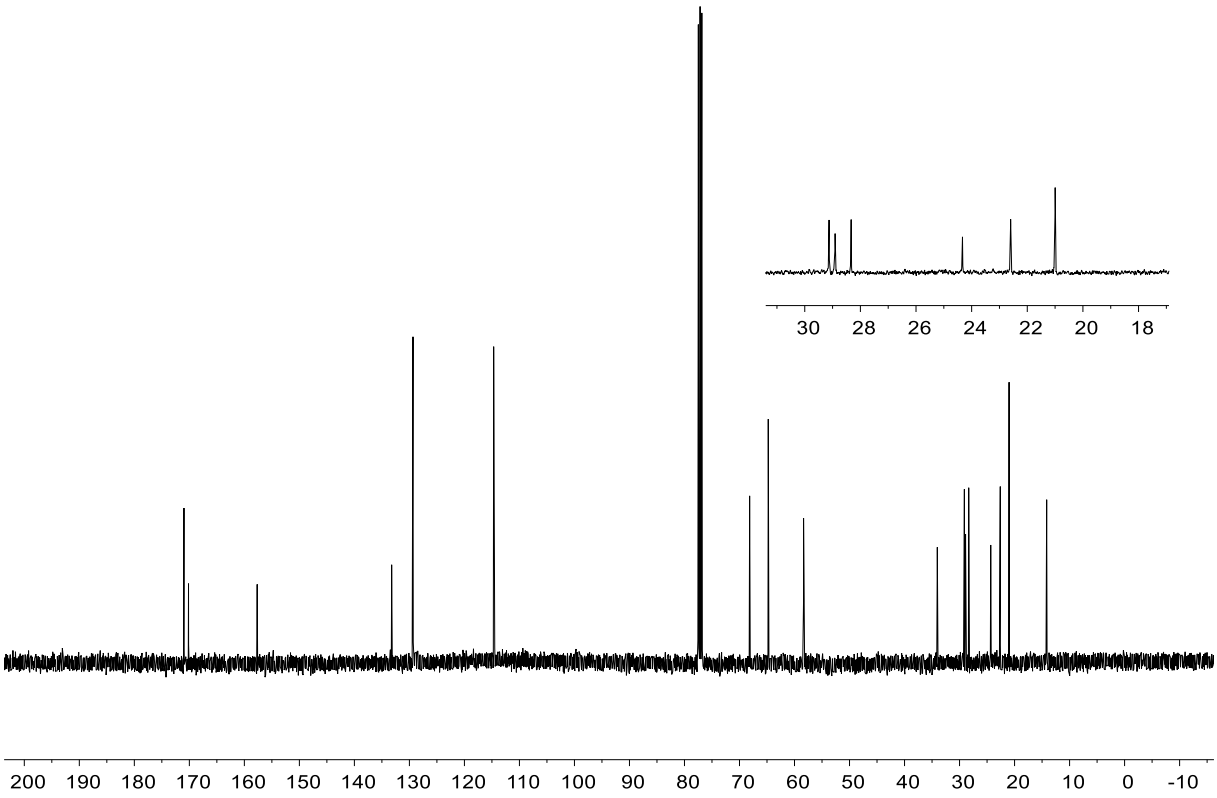
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.1 (NAc), 157.6 (C6), 133.2 (C9), 129.3 (C8), 114.7 (C7), 68.2 (C5), 64.8 (C13), 58.4 (C12), 34.1 (C11), 29.1 (C4), 28.9 (C10), 28.3 (C3), 24.3 (NAc), 22.6 (C2), 21.0 (OAc), 14.2 (C1).

IR (cm$^{-1}$): 3305 (w), 3083 (w), 2964 (w), 2932 (w), 2863 (w), 1736 (m), 1650 (m), 1614 (w), 1584 (w), 1555 (m), 1512 (m), 1466 (m), 1428 (w), 1378 (m), 1315 (w), 1302 (w), 1291 (w), 1246 (m), 1216 (m), 1192 (m), 1176 (m), 1126 (w), 1100 (w), 1051 (m), 1032 (m), 986 (m), 967 (w), 911 (w), 848 (w), 812 (w), 794 (w), 770 (w), 755 (w), 724 (w), 695 (w).

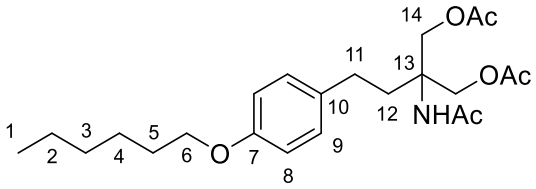
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-(hexyloxy)phenethyl)propane-1,3-diyl diacetate (15d)**




The compound was synthesised from **8** (50 mg, 0.15 mmol, 1.00 eq.) and 1-bromohexane (21 µl, 0.15 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (52 mg, 83%).

M.p.: 100 °C.

$R_f$ 0.53 (EtOAc).

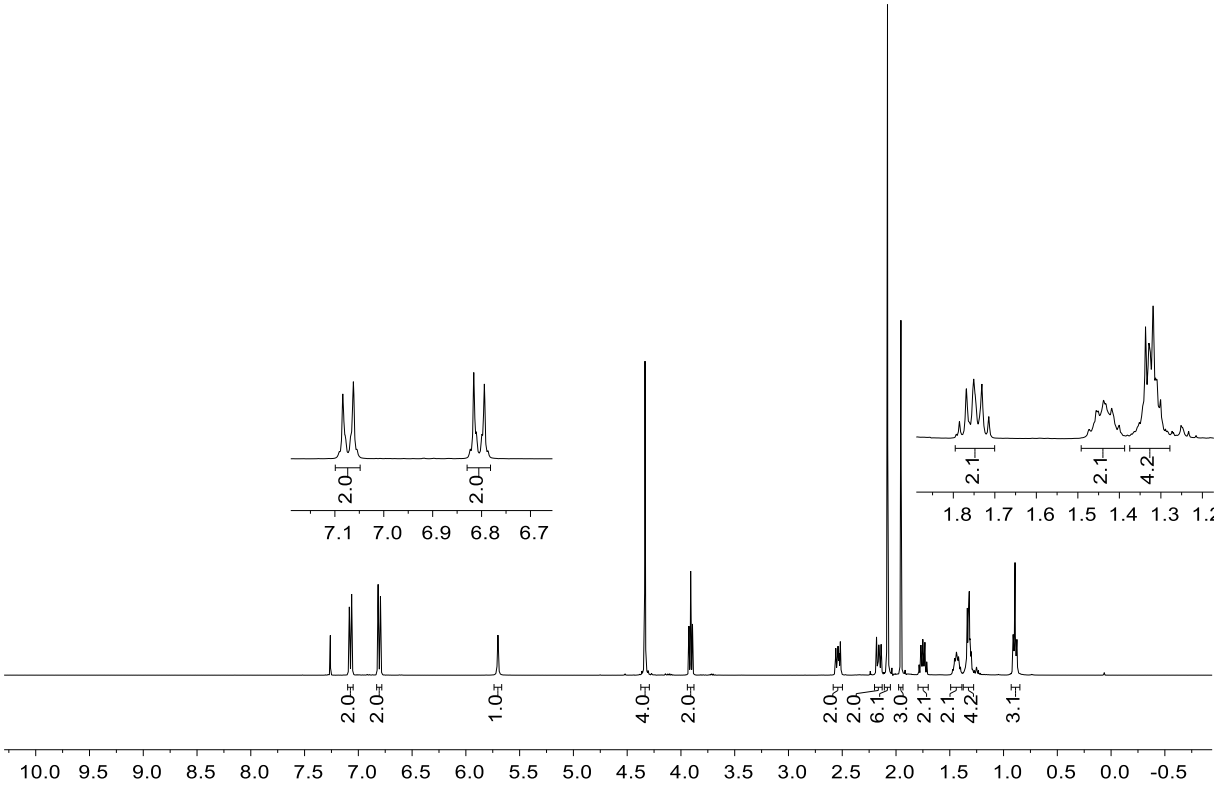
HRMS *m/z* (ESI); Calcd. for $C_{23}H_{35}NO_6Na$ 444.2357, found 444.2349.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.07 (m, 2H, HC9), 6.80 (m, 2H, HC8), 5.70 (s, 1H, HN), [4.335 (d, $^2J_{HH}$ = 11.2 Hz, 2H), 4.334 (d, $^2J_{HH}$ = 11.2 Hz, 2H)]($H_2$C14), 3.91 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2$C6), 2.54 (m, 2H, $H_2$C11), 2.16 (m, 2H, $H_2$C12), 2.08 (s, 6H, OAc), 1.95 (s, 3H, NAc), 1.75 (m, 2H, $H_2$C5), 1.43 (m, 2H, $H_2$C4), 1.32 (m, 4H, $H_2$C2,3), 0.89 (m, 3H, $H_3$C1).

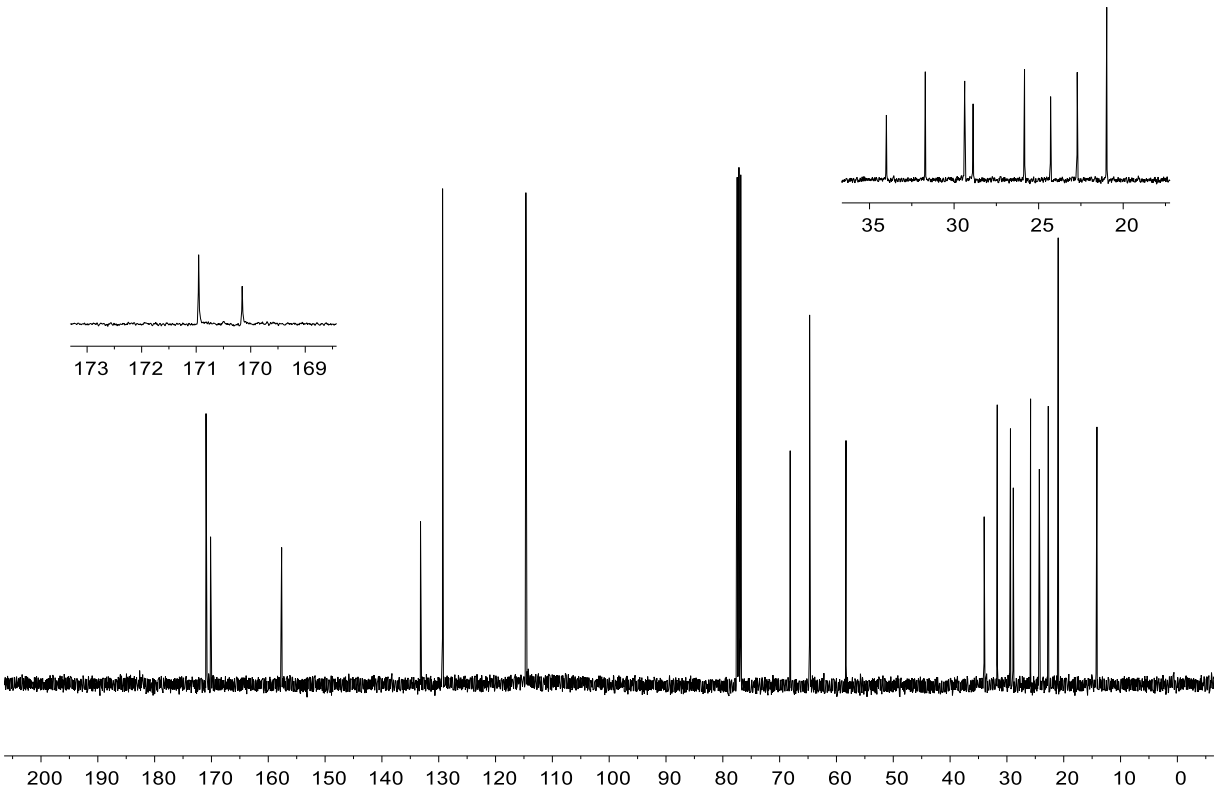
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 170.9 (OAc), 170.2 (NAc), 157.6 (C7), 133.2 (C10), 129.3 (C9), 114.7 (C8), 68.1 (C6), 64.7 (C14), 58.3 (C13), 34.0 (C12), 31.7 (C3), 29.4 (C5), 28.9 (C11), 25.8 (C4), 24.3 (NAc), 22.7 (C2), 21.0 (OAc), 14.2 (C1).

IR (cm$^{-1}$): 3305 (w), 3082 (w), 2929 (w), 2851 (w), 1736 (w), 1650 (m), 1614 (w), 1585 (w), 1555 (w), 1513 (w), 1467 (w), 1379 (w), 1316 (w), 1303 (w), 1245 (m), 1225 (m), 1176 (w), 1126 (w), 1100 (w), 1049 (w), 1033 (w), 996 (w), 967 (w), 935 (w), 845 (w), 820 (w), 811 (w), 779 (w), 769 (w), 724 (w), 692 (w).

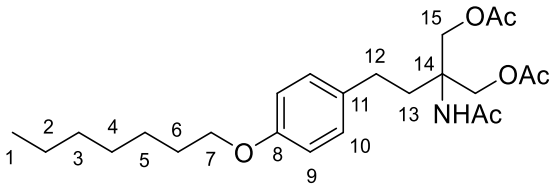
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-(heptyloxy)phenethyl)propane-1,3-diyl diacetate (15e)**




The compound was synthesised from **8** (68 mg, 0.20 mmol, 1.00 eq.) and **S15.1e** (54 mg, 0.20 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by flash chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (74 mg, 84%).

M.p.: 91 °C.

$R_f$ 0.17 (CyH : EtOAc / 2 : 1).

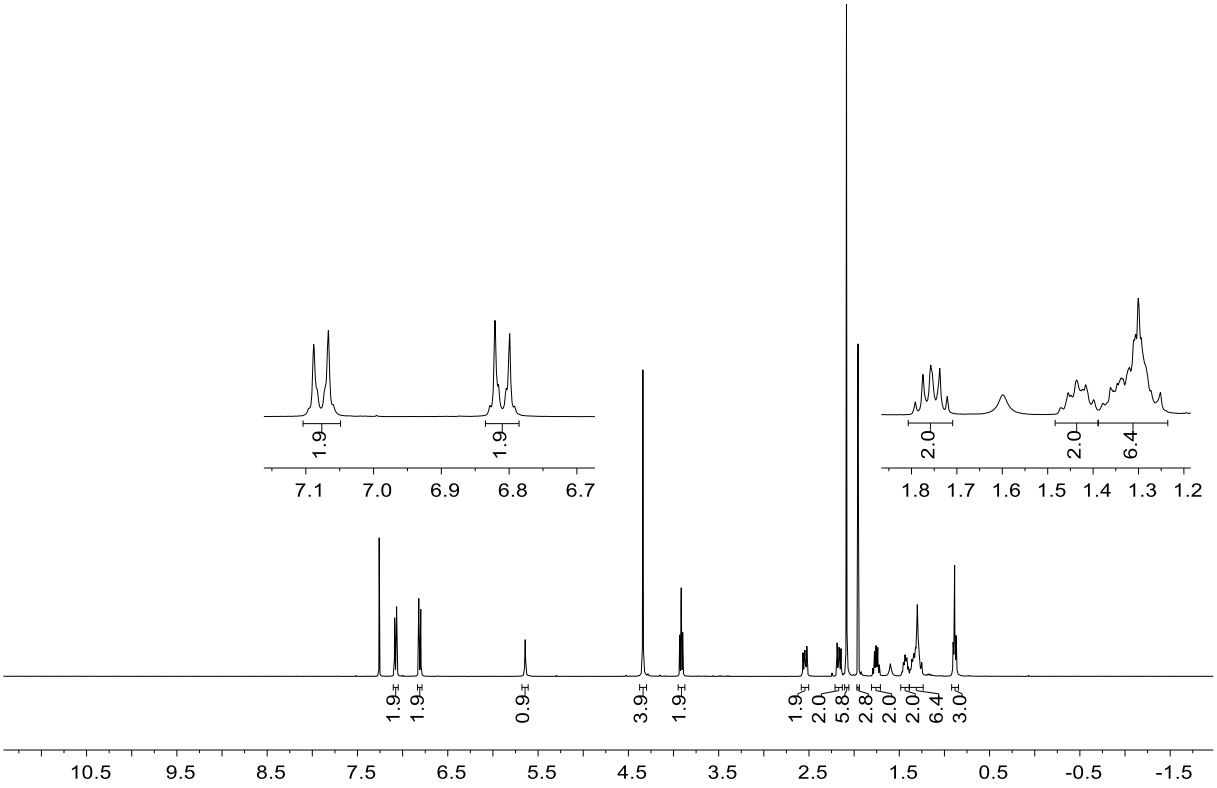
HRMS *m/z* (ESI); Calcd. for $C_{24}H_{37}NO_6Na$ 458.2513, found 458.2515.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC10), 6.81 (m, 2H, HC9), 5.64 (s, 1H, HN), 4.34 (s, 4H, $H_2$C15), 3.92 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2$C7), 2.55 (m, 2H, $H_2$C12), 2.17 (m, 2H, $H_2$C13), 2.09 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.76 (m, 2H, $H_2$C6), 1.44 (m, 2H, $H_2$C5), 1.39 – 1.23 (m, 6H, $H_2$C2,3,4), 0.89 (m, 3H, $H_3$C1).

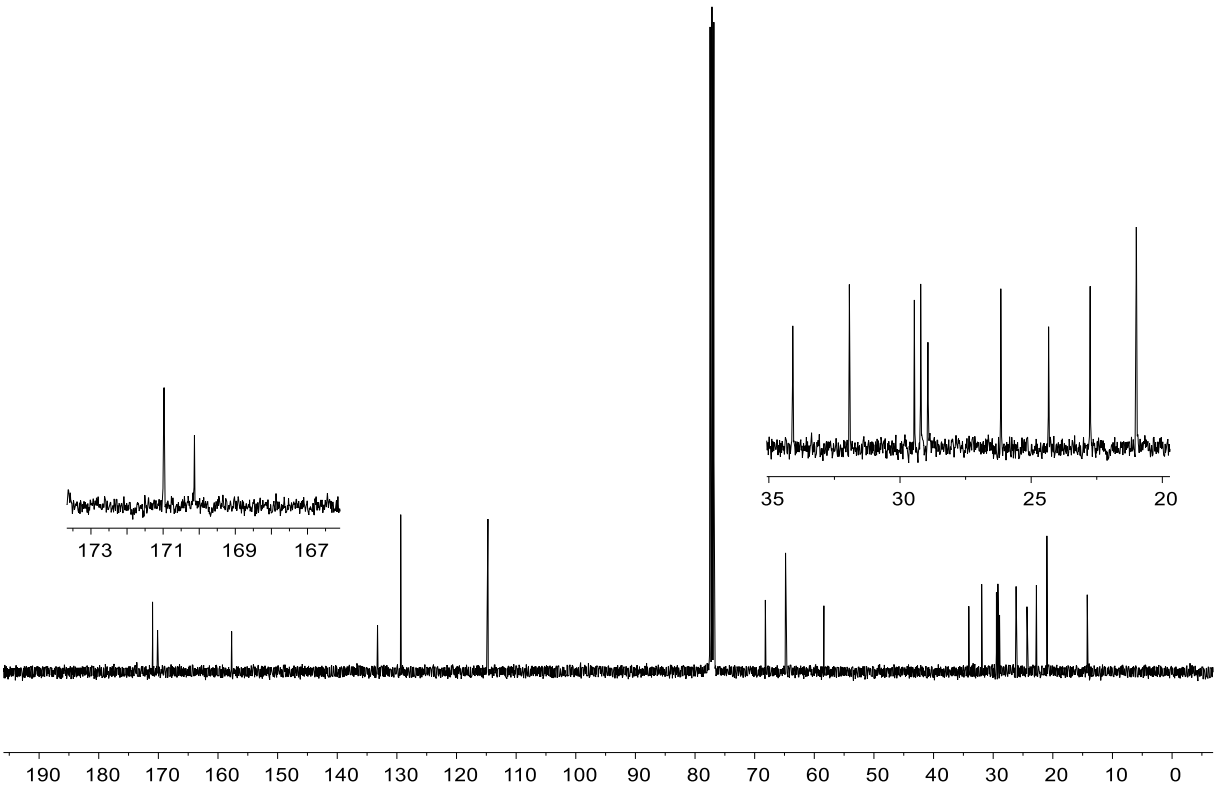
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.1 (NAc), 157.7 (C8), 133.2 (C11), 129.4 (C10), 114.7 (C9), 68.2 (C7), 64.8 (C15), 58.4 (C14), 34.1 (C13), 31.9 (C3), 29.5 (C6), 29.2 (C4), 28.9 (C12), 26.2 (C5), 24.3 (NAc), 22.8 (C2), 21.0 (OAc), 14.2 (C1).

IR (cm$^{-1}$): 3296 (w), 3204 (w), 3085 (w), 2963 (w), 2932 (w), 2849 (w), 1736 (m), 1650 (m), 1615 (w), 1583 (w), 1557 (m), 1513 (m), 1466 (m), 1429 (w), 1378 (m), 1316 (w), 1303 (w), 1290 (w), 1242 (s), 1216 (s), 1193 (m), 1176 (m), 1126 (w), 1101 (w), 1050 (m), 1034 (m), 1007 (m), 967 (m), 949 (w), 923 (w), 883 (w), 847 (w), 813 (m), 796 (w), 771 (w), 761 (w), 721 (w), 697 (w).

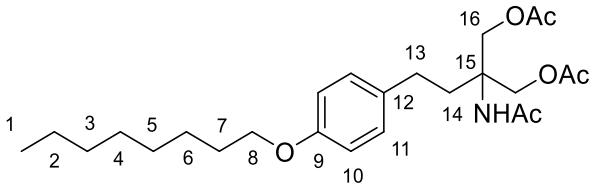
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**2-Acetamido-2-(4-(octyloxy)phenethyl)propane-1,3-diyl diacetate (15f)**




The compound was synthesised from **8** (50 mg, 0.15 mmol, 1.00 eq.) and 1-bromooctane (26 µl, 0.15 mmol, 1.00 eq.) following **General Procedure 3** (see page S4). The product was purified by column chromatography (CyH : EtOAc / 1 : 1) and was isolated as a white solid (64 mg, 97%).

M.p.: 95 °C.

$R_f$ 0.34 (CyH : EtOAc / 1 : 2).

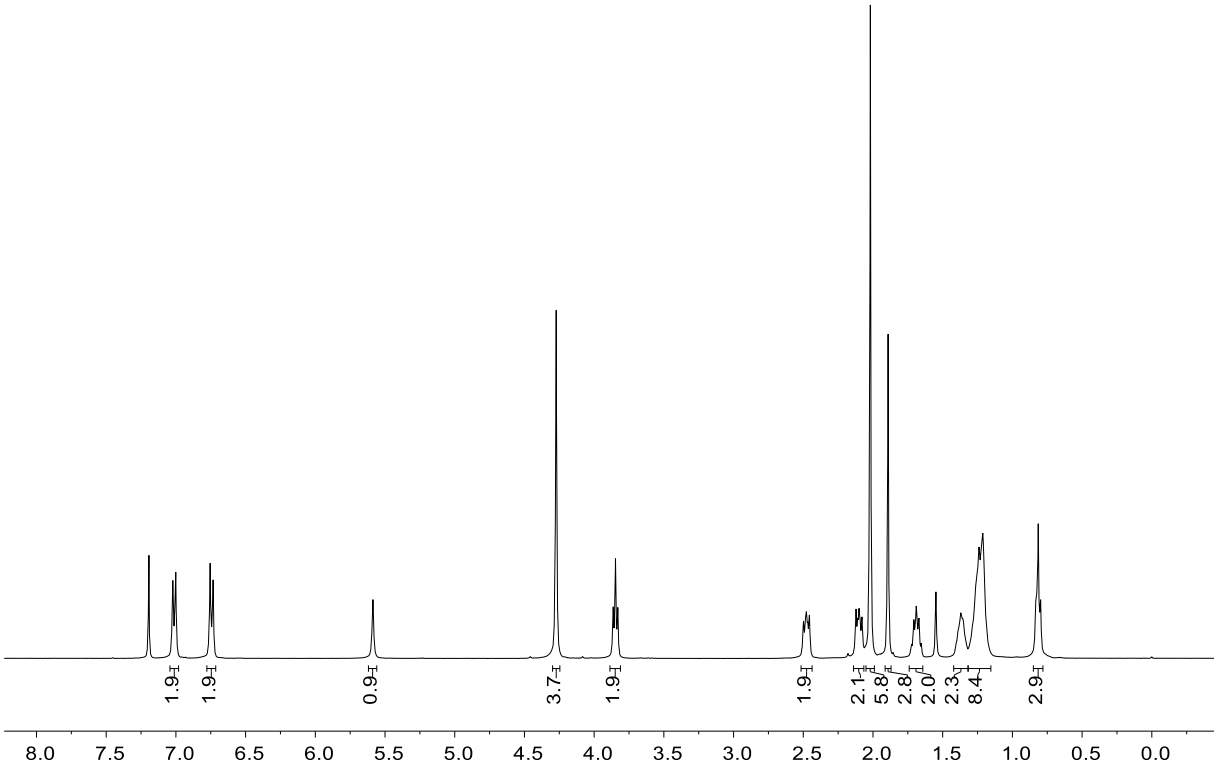
HRMS *m/z* (ESI); Calcd. for $C_{25}H_{39}NO_6Na$ 472.2670, found 472.2700.

$^1$H NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.08 (m, 2H, HC11), 6.81 (m, 2H, HC10), 5.65 (s, 1H, HN), 4.34 (s, 4H, $H_2$C16), 3.91 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $H_2$C8), 2.54 (m, 2H, $H_2$C13), 2.17 (m, 2H, $H_2$C14), 2.08 (s, 6H, OAc), 1.96 (s, 3H, NAc), 1.75 (m, 2H, $H_2$C7), 1.44 (m, 2H, $H_2$C6), 1.38 – 1.21 (m, 8H, $H_2$C2,3,4,5), 0.88 (m, 3H, $H_3$C1).

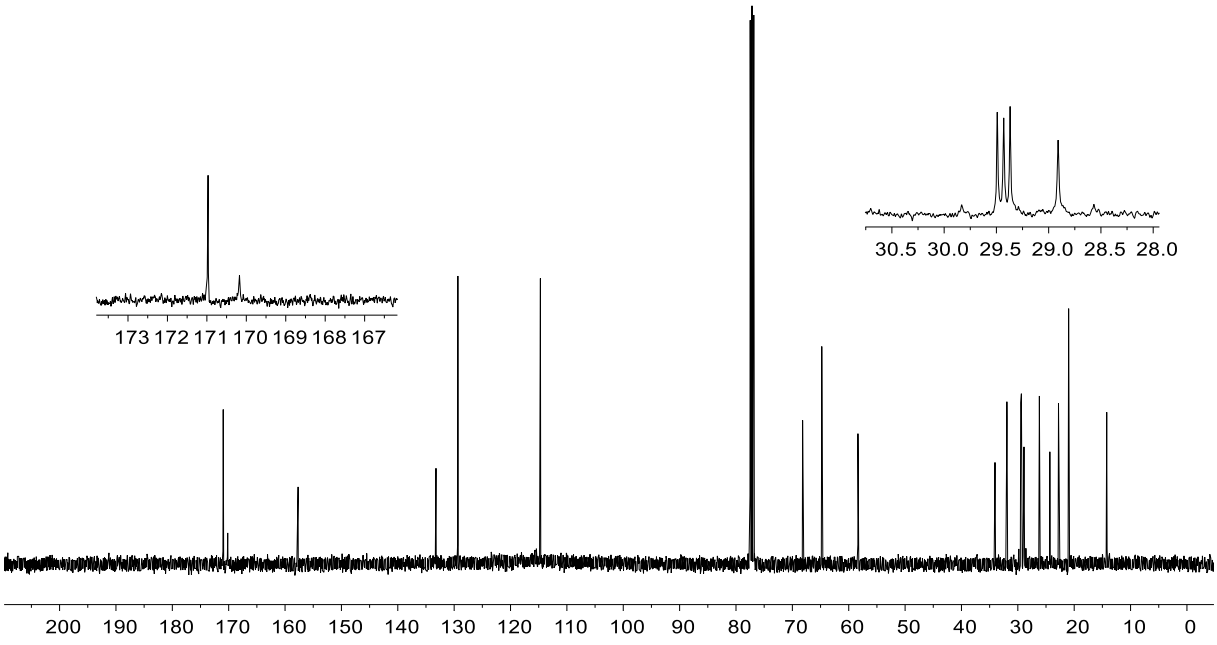
$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ 171.0 (OAc), 170.2 (NAc), 157.7 (C9), 133.2 (C12), 129.3 (C11), 114.7 (C10), 68.2 (C8), 64.8 (C16), 58.4 (C15), 34.1 (C14), 32.0 (C3), 29.5 (C5), 29.44 (C7), 29.37 (C4), 28.9 (C13), 26.2 (C6), 24.3 (NAc), 22.8 (C2), 21.0 (OAc), 14.2 (C1).

IR (cm$^{-1}$): 3308 (w), 3083 (w), 2951 (w), 2917 (m), 2871 (w), 2851 (w), 1736 (m), 1651 (m), 1615 (w), 1584 (w), 1555 (m), 1513 (m), 1467 (m), 1430 (w), 1378 (m), 1316 (w), 1303 (w), 1292 (w), 1244 (s), 1216 (s), 1192 (m), 1176 (m), 1127 (w), 1100 (w), 1051 (m), 1034 (m), 999 (w), 985 (w), 964 (m), 901 (w), 850 (w), 843 (w), 820 (m), 811 (m), 780 (w), 769 (w), 747 (w), 723 (w), 693 (w).

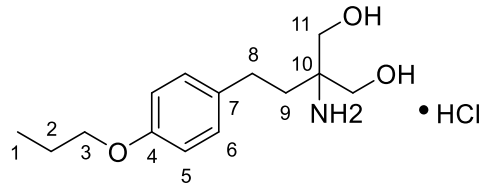
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K)



**2-Amino-2-(4-propoxyphenethyl)propane-1,3-diol hydrochloride (16a)**




The compound was synthesised from **15a** (36 mg, 0.09 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (16 mg, 60%).

M.p.: 114 °C.

$R_f$ 0.55 (DCM : MeOH / 10 : 3).

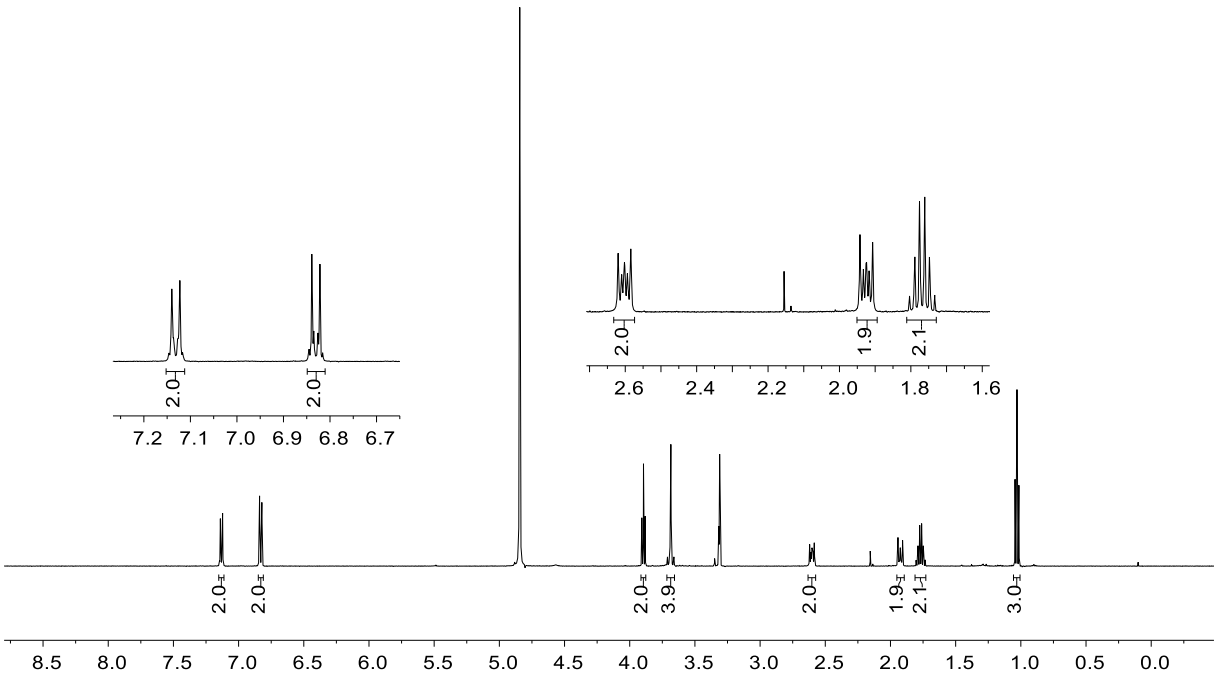
HRMS *m/z* (ESI); Calcd. for $C_{14}H_{24}NO_3$ 254.1751, found 254.1750.

$^1$H NMR (500 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC6), 6.83 (m, 2H, HC5), 3.89 (t, $^3J_{HH}$ = 6.5 Hz, 2H, $H_2$C3), [3.69 (d, $^2J_{HH}$ = 11.7 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.7 Hz, 2H](H$_2$C11), 2.60 (m, 2H, $H_2$C8), 1.93 (m, 2H, $H_2$C9), 1.77 (qt, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 6.5 Hz, 2H, $H_2$C2), 1.03 (t, $^3J_{HH}$ = 7.4 Hz, 3H, $H_3$C1).

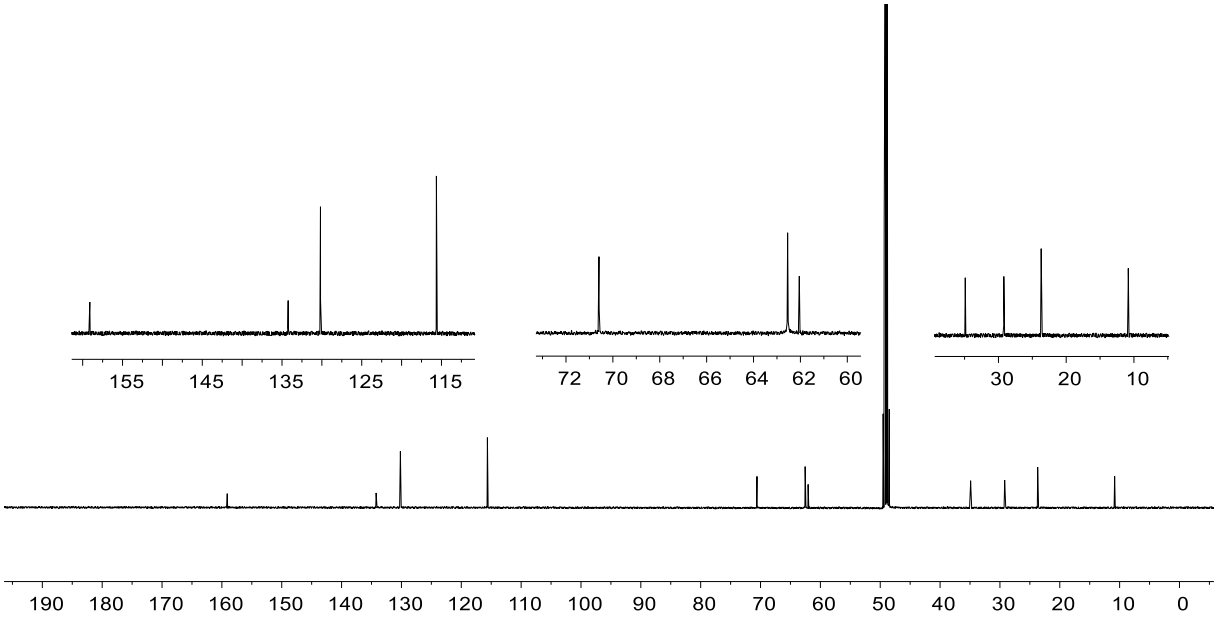
$^{13}$C{$^1$H} NMR (126 MHz, Methanol-$d_4$, 298 K) δ 159.1 (C4), 134.2 (C7), 130.2 (C6), 115.6 (C5), 70.6 (C3), 62.5 (C11), 62.1 (C10), 34.9 (C9), 29.2 (C8), 23.7 (C2), 10.8 (C1).

IR (cm$^{-1}$): 3368 (w), 3275 (w), 3056 (w), 3026 (w), 2963 (m), 2937 (w), 2895 (w), 2877 (w), 2509 (w), 2437 (w), 2343 (w), 2308 (w), 1986 (w), 1883 (w), 1614 (w), 1581 (w), 1511 (m), 1473 (m), 1456 (m), 1423 (w), 1390 (w), 1379 (w), 1333 (w), 1297 (m), 1244 (s), 1178 (m), 1130 (w), 1106 (w), 1052 (s), 1022 (m), 980 (w), 954 (w), 911 (w), 902 (w), 848 (w), 828 (m), 821 (m), 789 (m), 763 (m), 738 (w), 715 (w), 669 (w).

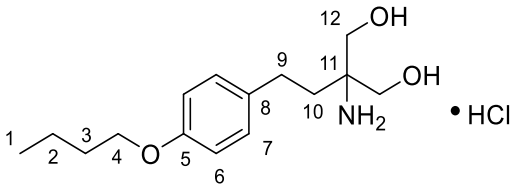
$^1$H NMR (500 MHz, Methanol-$d_4$, 298 K)



$^{13}C\{^{1}H\}$ NMR (126 MHz, Methanol-$d_4$, 298 K)




**2-Amino-2-(4-butoxyphenethyl)propane-1,3-diol hydrochloride (16b)**




The compound was synthesised from **15b** (32 mg, 0.08 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (19 mg, 79%).

M.p.: 106 °C.

$R_f$ 0.46 (DCM : MeOH / 10 : 3).

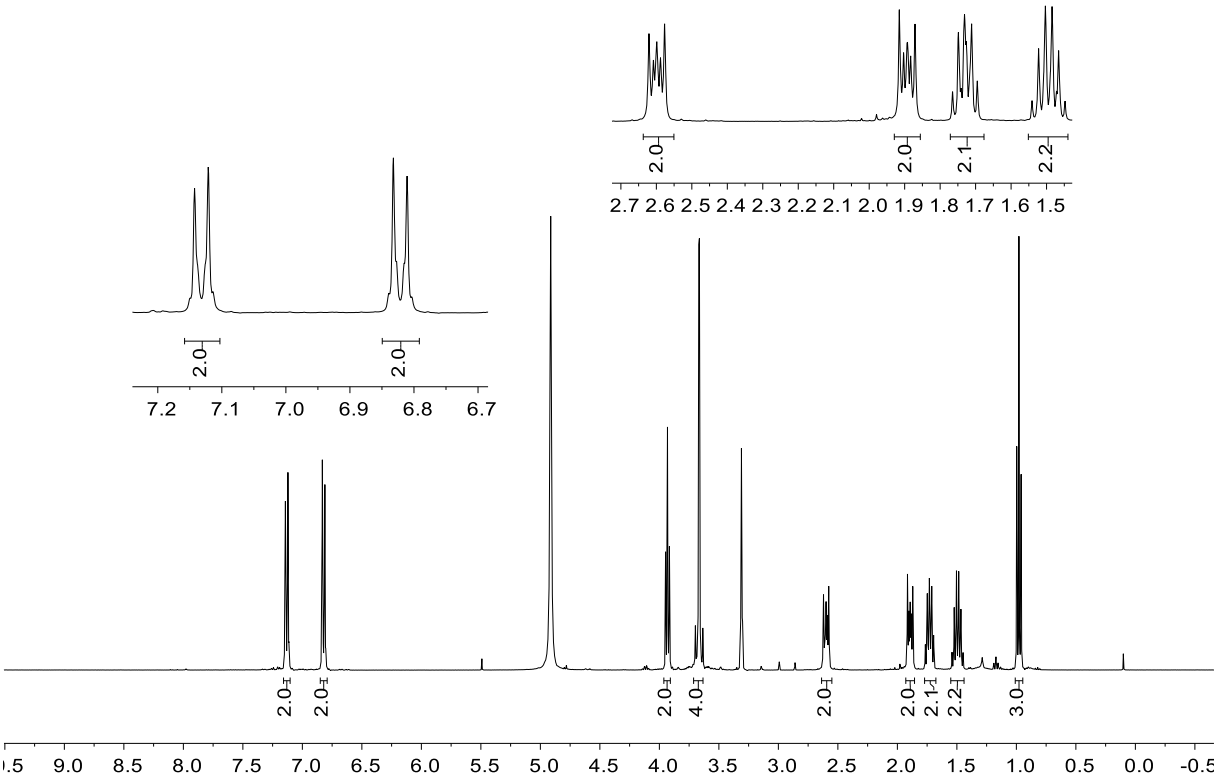
HRMS *m/z* (ESI); Calcd. for $C_{15}H_{26}NO_3$ 268.1907, found 268.1913.

$^{1}H$ NMR (400 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC7), 6.82 (m, 2H, HC6), 3.93 (t, $^{3}J_{HH}$ = 6.4 Hz, 2H, $H_2C4$), [3.67 (d, $^{2}J_{HH}$ = 11.6 Hz, 2H), 3.66 (d, $^{2}J_{HH}$ = 11.6 Hz, 2H](H$_2$C12), 2.60 (m, 2H, $H_2C9$), 1.89 (m, 2H, $H_2C10$), 1.73 (m, 2H, $H_2C3$), 1.49 (m, 2H, $H_2C2$), 0.98 (t, $^{3}J_{HH}$ = 7.4 Hz, 3H, $H_3C1$).

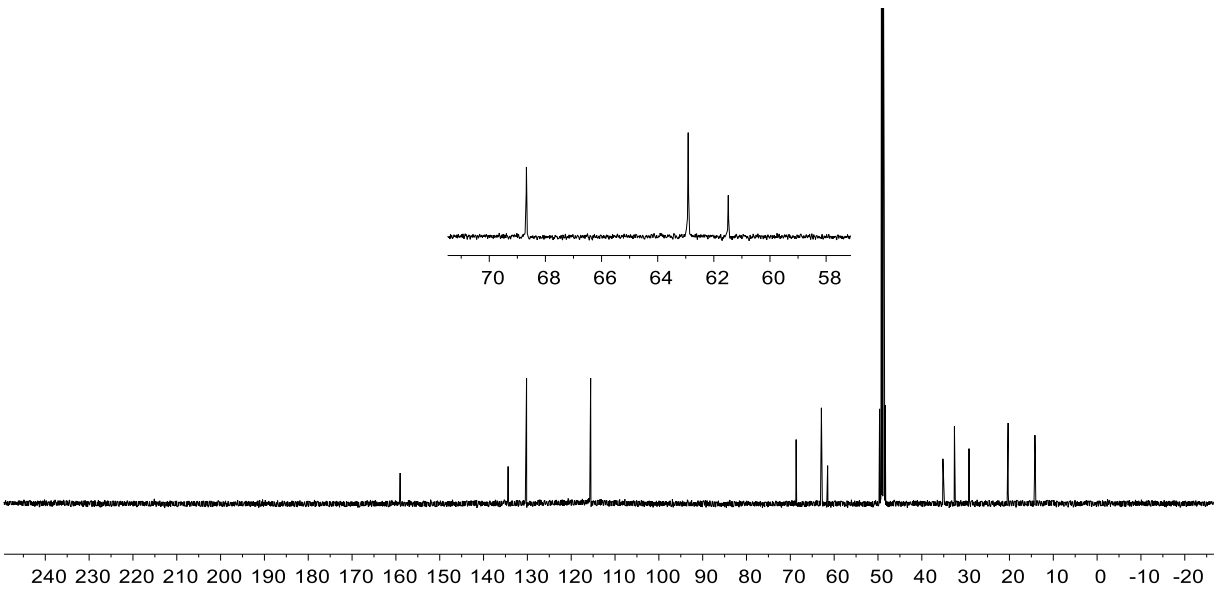
$^{13}C\{^{1}H\}$ NMR (101 MHz, Methanol-$d_4$, 298 K) δ 159.0 (C5), 134.4 (C8), 130.2 (C7), 115.6 (C6), 68.7 (C4), 62.9 (C12), 61.5 (C11), 35.2 (C10), 32.6 (C3), 29.2 (C9), 20.3 (C2), 14.2 (C1).

IR ($cm^{-1}$): 3265 (w), 3029 (w), 2956 (m), 2934 (m), 2871 (w), 2431 (w), 2300 (w), 1731 (w), 1612 (w), 1582 (w), 1511 (m), 1474 (m), 1456 (m), 1422 (w), 1393 (w), 1300 (m), 1243 (s), 1177 (m), 1125 (w), 1105 (w), 1062 (m), 1013 (m), 974 (m), 907 (w), 873 (w), 822 (m), 761 (m), 739 (m).

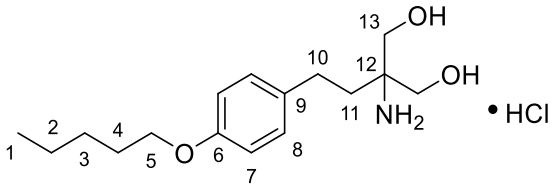
$^{1}$H NMR (400 MHz, Methanol-$d_4$, 298 K)



$^{13}$C{$^{1}$H} NMR (101 MHz, Methanol-$d_4$, 298 K)



**2-Amino-2-(4-(Pentanetyloxy)phenethyl)propane-1,3-diol hydrochloride (16c)**




The compound was synthesised from **15c** (38 mg, 0.09 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (17 mg, 59%).

M.p.: 111 °C.

$R_f$ 0.17 (DCM : MeOH / 10 : 2).

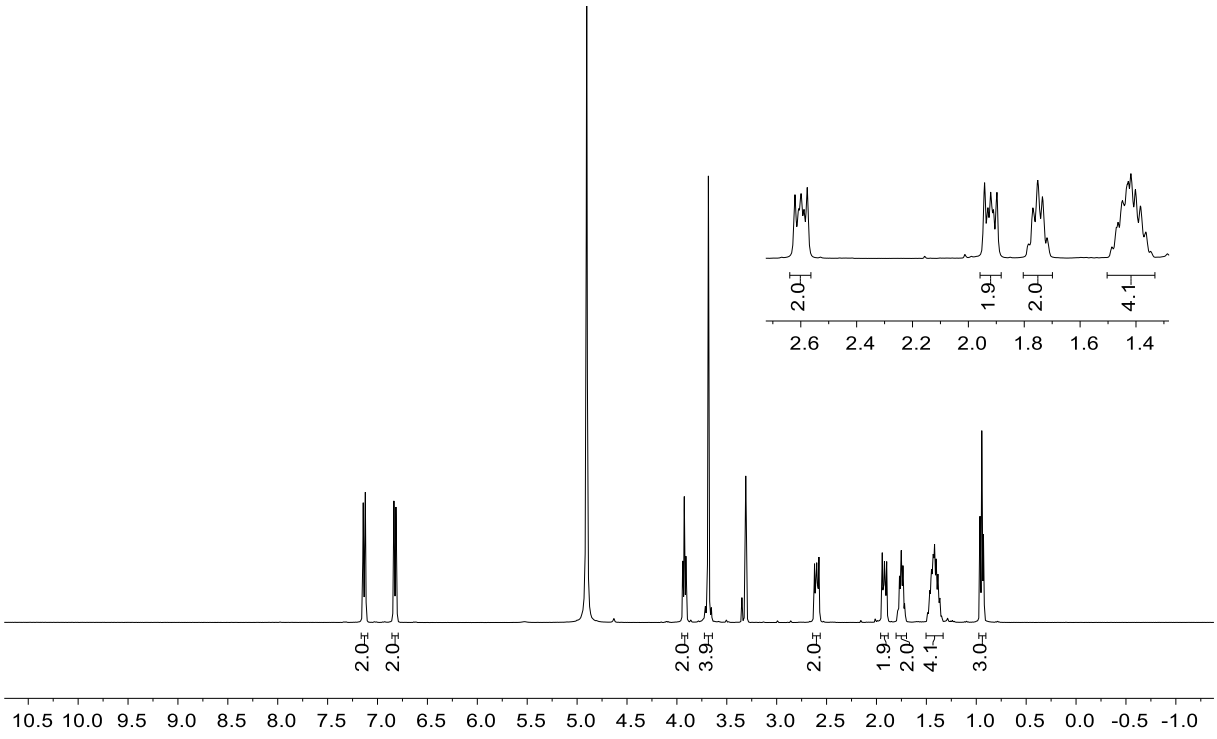
HRMS *m/z* (ESI); Calcd. for $C_{16}H_{28}NO_3$ 282.2064, found 282.2062.

$^1$H NMR (400 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC8), 6.82 (m, 2H, HC7), 3.92 (t, $^3J_{HH}$ = 6.5 Hz, 2H, $H_2$C5), [3.69 (d, $^2J_{HH}$ = 11.3 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.3 Hz, 2H]($H_2$C13), 2.60 (m, 2H, $H_2$C10), 1.92 (m, 2H, $H_2$C11), 1.75 (m, 2H, $H_2$C4), 1.44 (m, 2H, $H_2$C3), 1.40 (m, 2H, $H_2$C2), 0.94 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $H_3$C1).

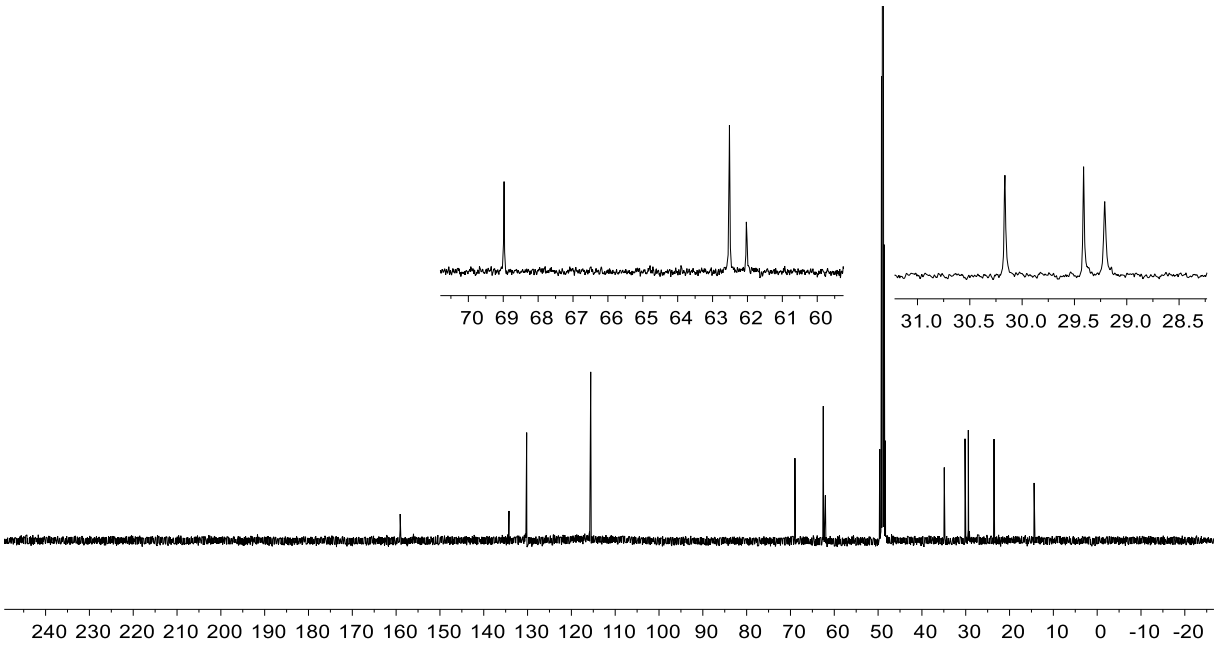
$^{13}$C{$^1$H} NMR (101 MHz, Methanol-$d_4$, 298 K) δ 159.1 (C6), 134.2 (C9), 130.2 (C8), 115.6 (C7), 69.0 (C5), 62.5 (C13), 62.0 (C12), 34.9 (C11), 30.2 (C4), 29.4 (C3), 29.2 (C10), 23.6 (C2), 14.4 (C1).

IR (cm$^{-1}$): 3266 (w), 3032 (w), 2935 (m), 2870 (w), 2498 (w), 2435 (w), 2276 (w), 1612 (w), 1582 (w), 1512 (m), 1473 (m), 1456 (m), 1440 (w), 1393 (w), 1299 (w), 1243 (m), 1177 (m), 1105 (w), 1063 (m), 1026 (m), 921 (w), 893 (w), 848 (w), 825 (m), 792 (w), 762 (w), 742 (w).

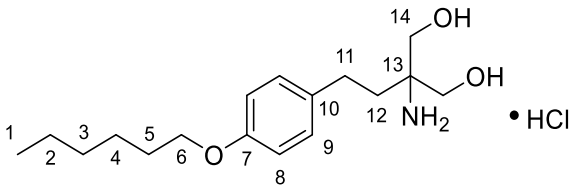
$^1$H NMR (400 MHz, Methanol-$d_4$, 298 K)



$^{13}C\{^{1}H\}$ NMR (101 MHz, Methanol-$d_4$, 298 K)




**2-Amino-2-(4-(hexyloxy)phenethyl)propane-1,3-diol hydrochloride (16d)**




The compound was synthesised from **15d** (43 mg, 0.10 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (16 mg, 47%).

M.p.: 106 °C.

$R_f$ 0.20 (DCM : MeOH / 10 : 2).

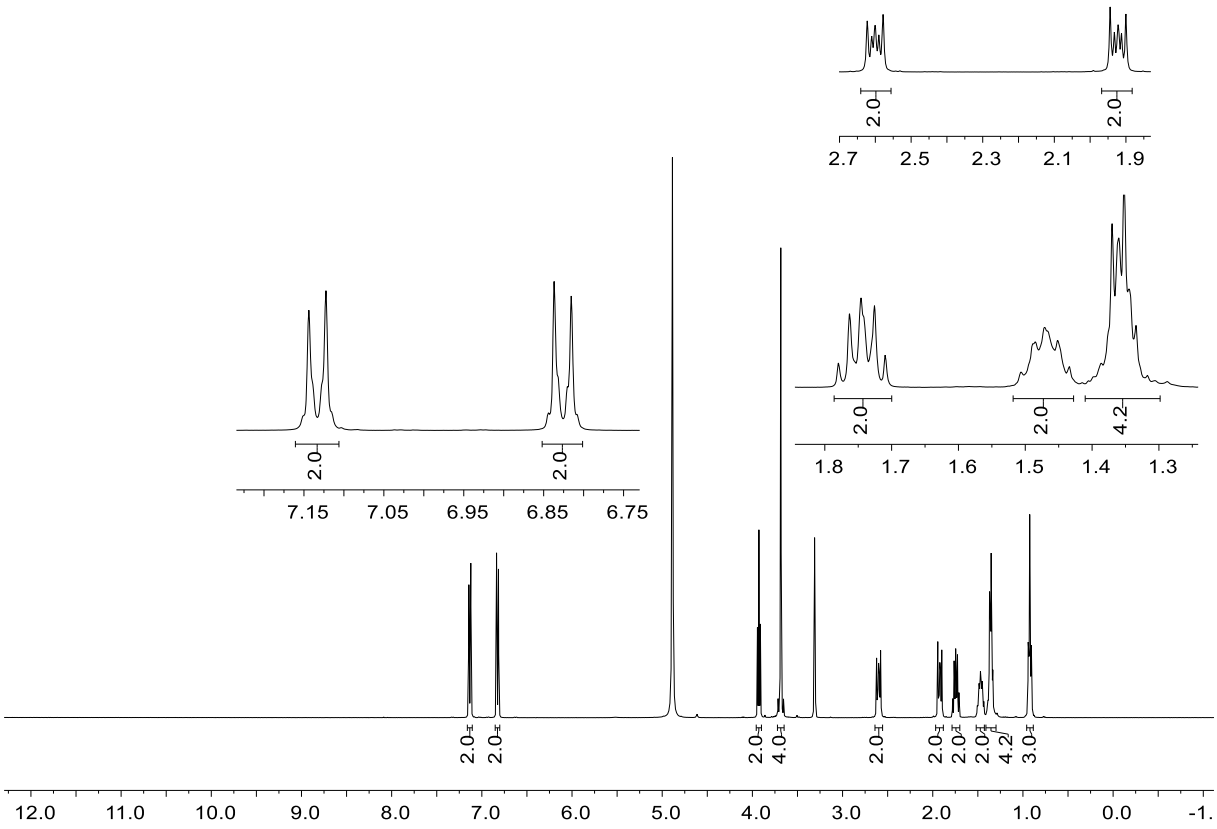
HRMS *m/z* (ESI); Calcd. for $C_{17}H_{30}NO_3$ 296.2220, found 296.2235.

$^{1}H$ NMR (400 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC9), 6.83 (m, 2H, HC8), 3.93 (t, $^{3}J_{HH}$ = 6.4 Hz, 2H, $H_2C6$), [3.69 (d, $^{2}J_{HH}$ = 11.5 Hz, 2H), 3.68 (d, $^{2}J_{HH}$ = 11.5 Hz, 2H)]($H_2C14$), 2.60 (m, 2H, $H_2C11$), 1.92 (m, 2H, $H_2C12$), 1.74 (m, 2H, $H_2C5$), 1.46 (m, 2H, $H_2C4$), 1.36 (m, 4H, $H_2C2,3$), 0.92 (m, 3H, $H_3C1$).

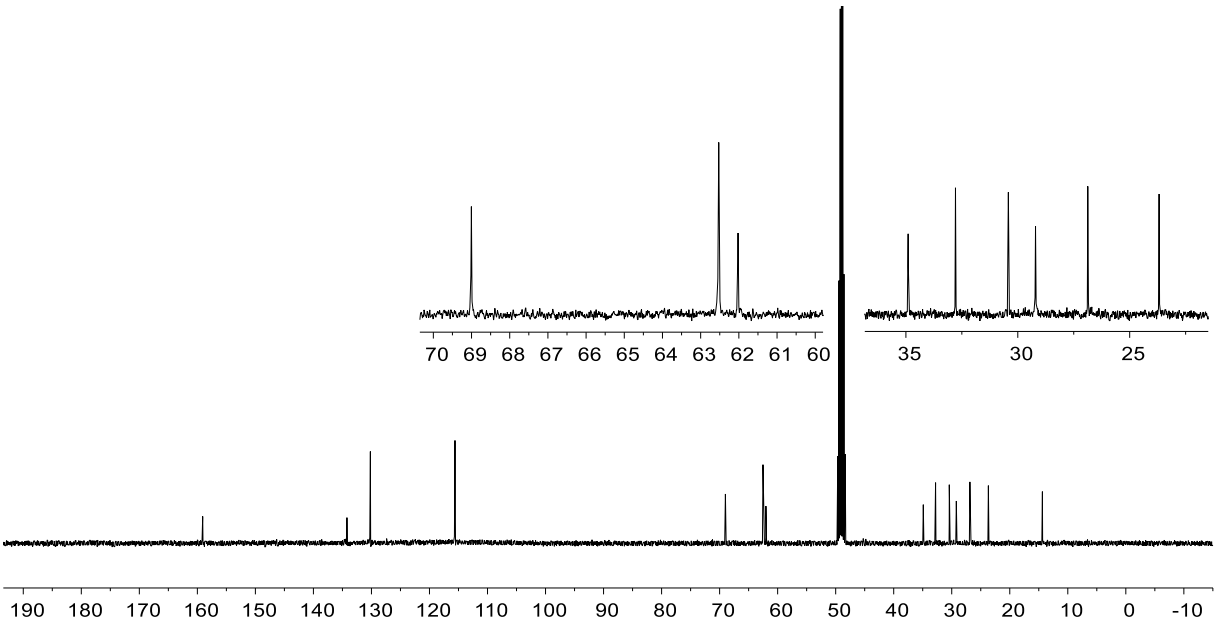
$^{13}C\{^{1}H\}$ NMR (101 MHz, Methanol-$d_4$, 298 K) δ 159.1 (C7), 134.2 (C10), 130.2 (C9), 115.6 (C8), 69.0 (C6), 62.5 (C14), 62.0 (C13), 34.9 (C12), 32.8 (C3), 30.4 (C5), 29.2 (C11), 26.9 (C4), 23.7 (C2), 14.4 (C1).

IR ($cm^{-1}$): 3265 (w), 3029 (w), 2930 (m), 2867 (w), 2496 (w), 2433 (w), 2284 (w), 1613 (w), 1582 (w), 1512 (s), 1473 (m), 1456 (w), 1440 (w), 1422 (w), 1393 (w), 1301 (w), 1244 (s), 1177 (m), 1128 (w), 1105 (w), 1062 (m), 1034 (m), 998 (w), 966 (w), 899 (w), 828 (m), 803 (w), 790 (w), 762 (w), 725 (w).

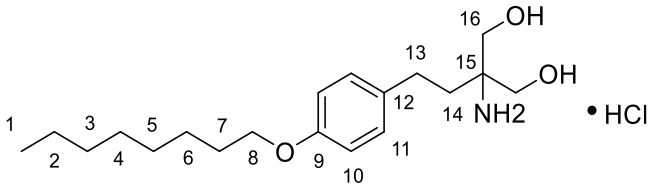
$^{1}$H NMR (400 MHz, Methanol-$d_4$, 298 K)



$^{13}$C{$^{1}$H} NMR (101 MHz, Methanol-$d_4$, 298 K)



**2-Amino-2-(4-(octyloxy)phenethyl)propane-1,3-diol hydrochloride (16f)**




The compound was synthesised from **15f** (42 mg, 0.09 mmol, 1.00 eq.) following **General Procedure 4** (see page S4). The product was purified by precipitation in MeOH/EtOAc and was obtained as a white solid (17 mg, 54%).

M.p.: 103 °C.

$R_f$ 0.22 (DCM : MeOH / 10 : 2).

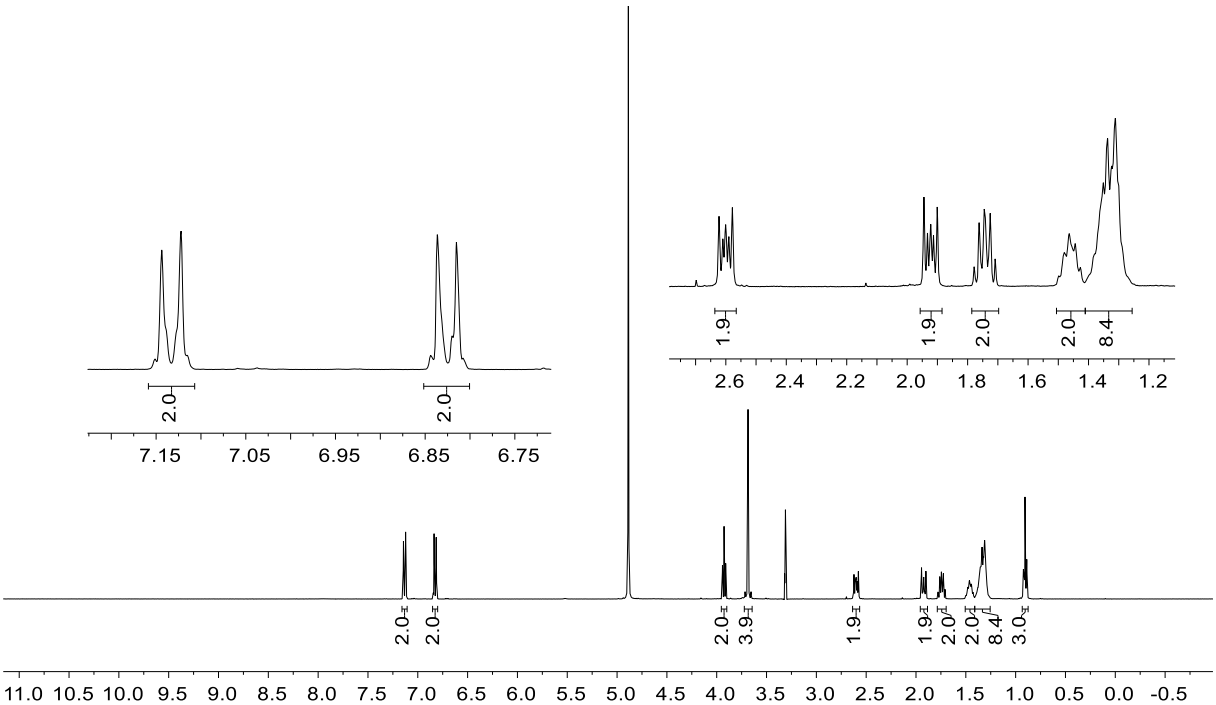
HRMS *m/z* (ESI); Calcd. for $C_{19}H_{34}NO_3$ 324.2533, found 324.2541.

$^1$H NMR (400 MHz, Methanol-$d_4$, 298 K) δ 7.13 (m, 2H, HC11), 6.82 (m, 2H, HC10), 3.93 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $H_2$C8), [3.69 (d, $^2J_{HH}$ = 11.5 Hz, 2H), 3.68 (d, $^2J_{HH}$ = 11.5 Hz, 2H)]($H_2$C16), 2.60 (m, 2H, $H_2$C13), 1.92 (m, 2H, $H_2$C14), 1.74 (m, 2H, $H_2$C7), 1.46 (m, 2H, $H_2$C6), 1.41 – 1.25 (m, 8H, $H_2$C2,3,4,5), 0.90 (m, 3H, $H_3$C1).

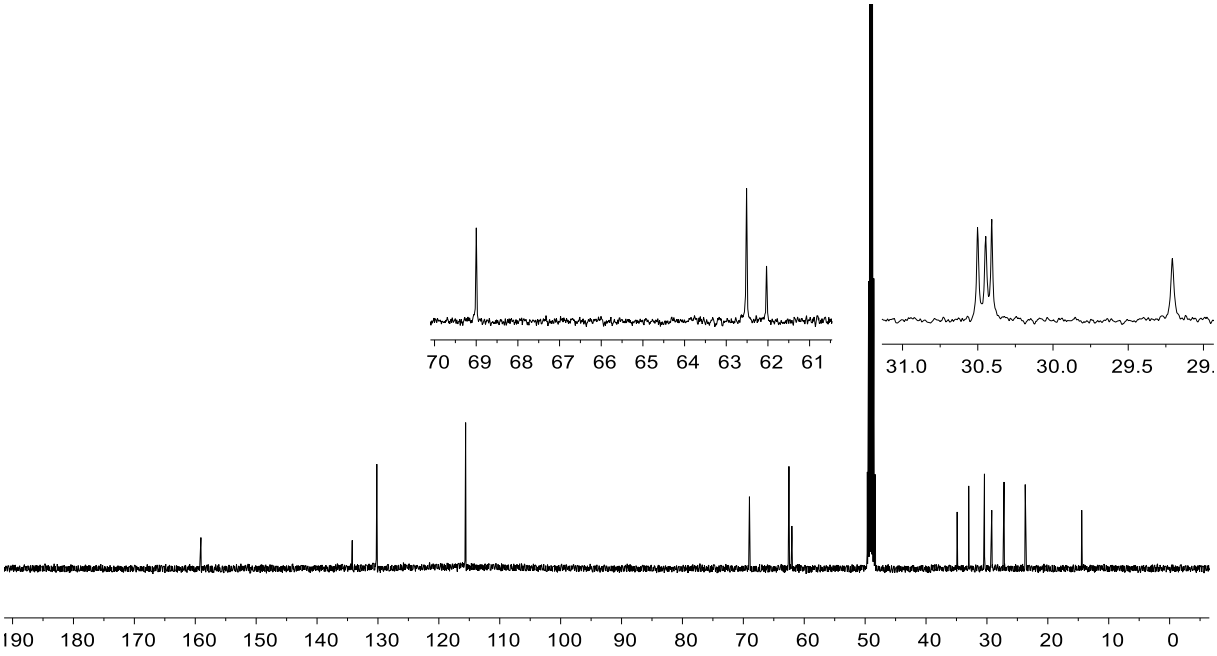
$^{13}$C{$^1$H} NMR (101 MHz, Methanol-$d_4$, 298 K) δ 159.1 (C9), 134.2 (C12), 130.2 (C11), 115.6 (C10), 69.0 (C8), 62.5 (C16), 62.0 (C15), 34.9 (C14), 33.0 (C3), [30.50, 30.45, 30.41](C4,5,7), 29.2 (C13), 27.2 (C6), 23.7 (C2), 14.4 (C1).

IR (cm$^{-1}$): 3269 (w), 3028 (w), 2922 (m), 2853 (m), 2500 (w), 2434 (w), 2309 (w), 1613 (w), 1582 (w), 1512 (m), 1472 (m), 1456 (m), 1393 (m), 1300 (w), 1245 (s), 1177 (m), 1130 (w), 1103 (w), 1063 (m), 1002 (m), 973 (w), 848 (w), 823 (m), 790 (m), 761 (w), 737 (w), 722 (w).

$^1$H NMR (400 MHz, Methanol-$d_4$, 298 K)

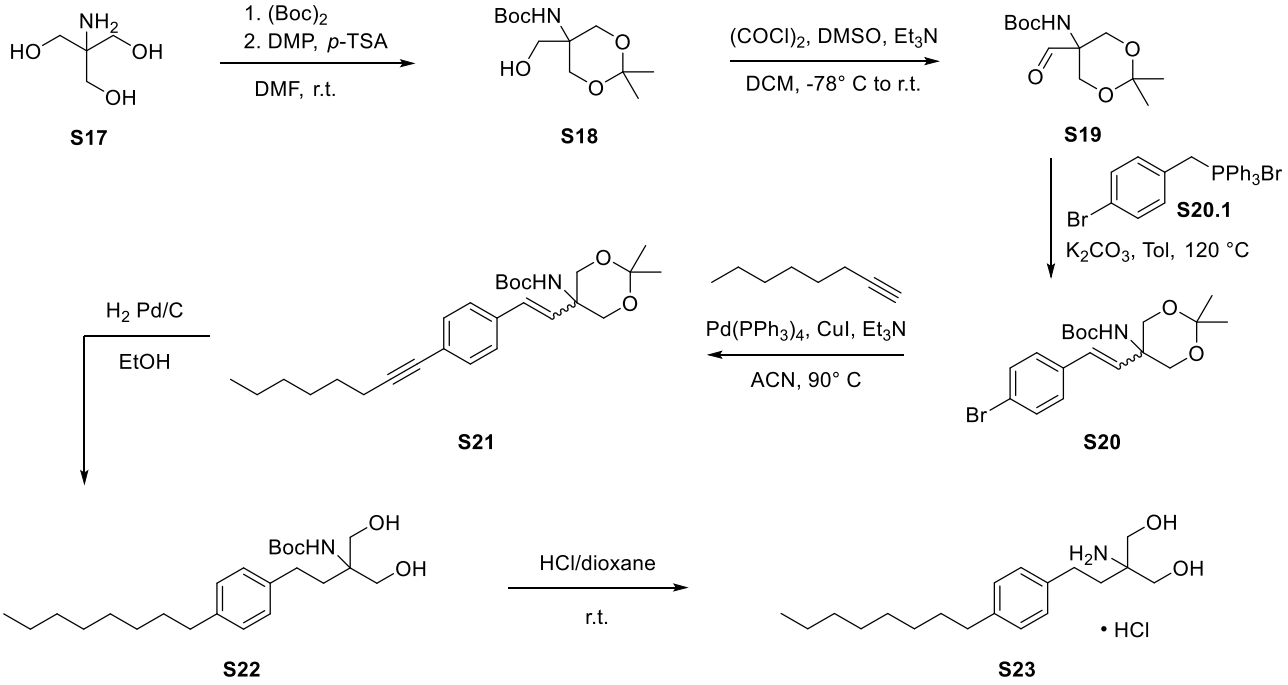


$^{13}C\{^{1}H\}$ NMR (101 MHz, Methanol-$d_4$, 298 K)

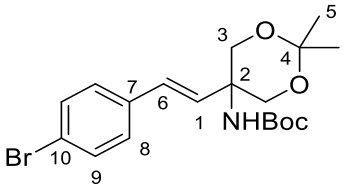


## II.8 Synthesis of Fingolimod

**Scheme S7.**




### *tert*-Butyl (5-(4-bromostyryl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (S20)




$K_2CO_3$ (249 mg, 1.80 mmol, 3.00 eq.) was flame dried in a schlenk flask where after **S20.1** (369 mg, 0.72 mmol, 1.20 eq.) and toluene was added (3 mL). The suspension was stirred at room temperature for 45 min and **S19** (156 mg, 0.60 mmol, 1.00 eq.) was added. The reaction mixture was heated to and stirred at 105 °C overnight. Everything was done under an atmosphere of argon. The mixture was let to cool down to room temperature and then filtered over a plug of celite. The solvent was removed *in vacuo* and the product was purified by column chromatography (CyH : EtOAc / 6 : 1) to give the *Z/E*-isomeric products (ca. dr 4:1, $^1$H) as a white solid (227 mg, 92%).

M.p.: 85 °C.

$R_f$ (minor) 0.31 (CyH : EtOAc / 3 : 1).

$R_f$ (major) 0.26 (CyH : EtOAc / 3 : 1).

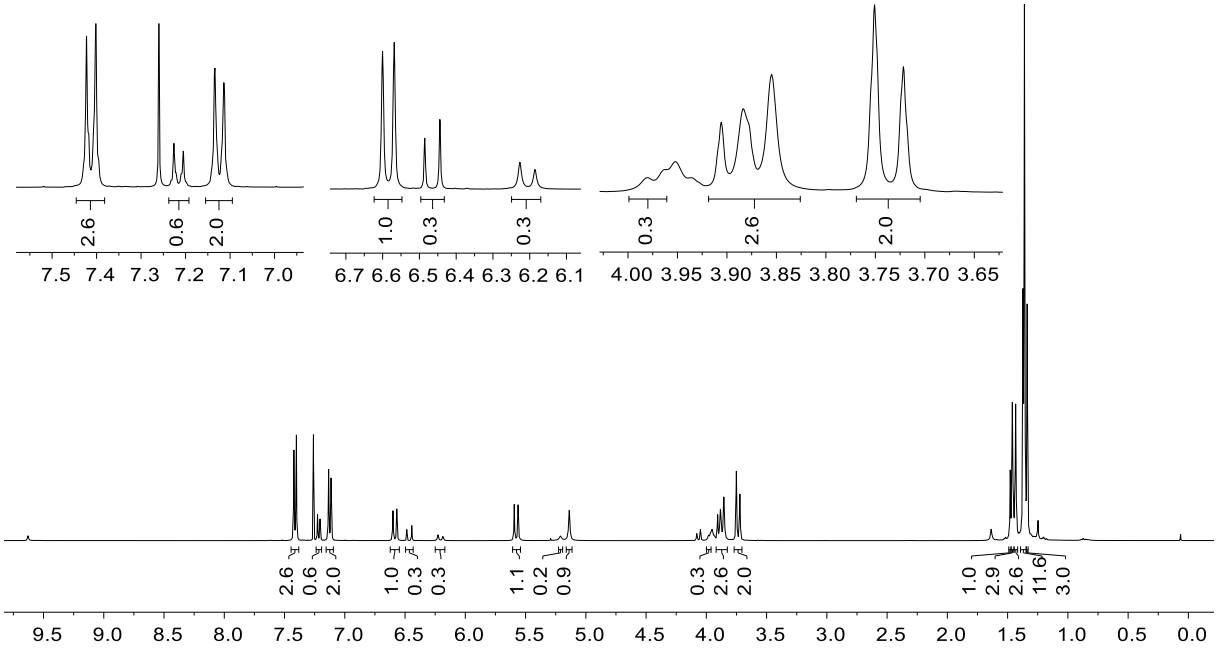
HRMS *m/z* (ESI); Calcd. for $C_{19}H_{26}BrNO_4Na$ 434.0943, found 434.0936.

$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K) δ (major) = 7.41 (m, 2H, HC9), 7.12 (m, 2H, HC8), 6.58 (d, $^{3}J_{HH}$ = 12.6 Hz, 1H, HC6), 5.58 (d, $^{3}J_{HH}$ = 12.7 Hz, 1H, HC1), 5.14 (s, 1H, NH), [3.87 (d, $^{2}J_{HH}$ = 11.7 Hz, 2H), 3.74 (d, $^{2}J_{HH}$ = 11.7 Hz, 2H)]($H_2$C3), [1.37, 1.34](each s, each 3H, $H_3$C5), 1.36 (s, 9H, Boc); δ (minor) = 7.41 (m, 2H, HC9), 7.22 (m, 2H, HC8), 6.46 (d, $^{3}J_{HH}$ = 16.4 Hz, 1H, HC6), 6.21 (br d, $^{3}J_{HH}$ = 16.4 Hz, 1H, HC1), 5.21 (s, 1H, NH), [3.97 (br d, $^{2}J_{HH}$ = 11.2 Hz, 2H), 3.89 (d, $^{2}J_{HH}$ = 11.2 Hz, 2H)]($H_2$C3), [1.48, 1.46](each s, each 3H, $H_3$C5), 1.43 (s, 3H, Boc).

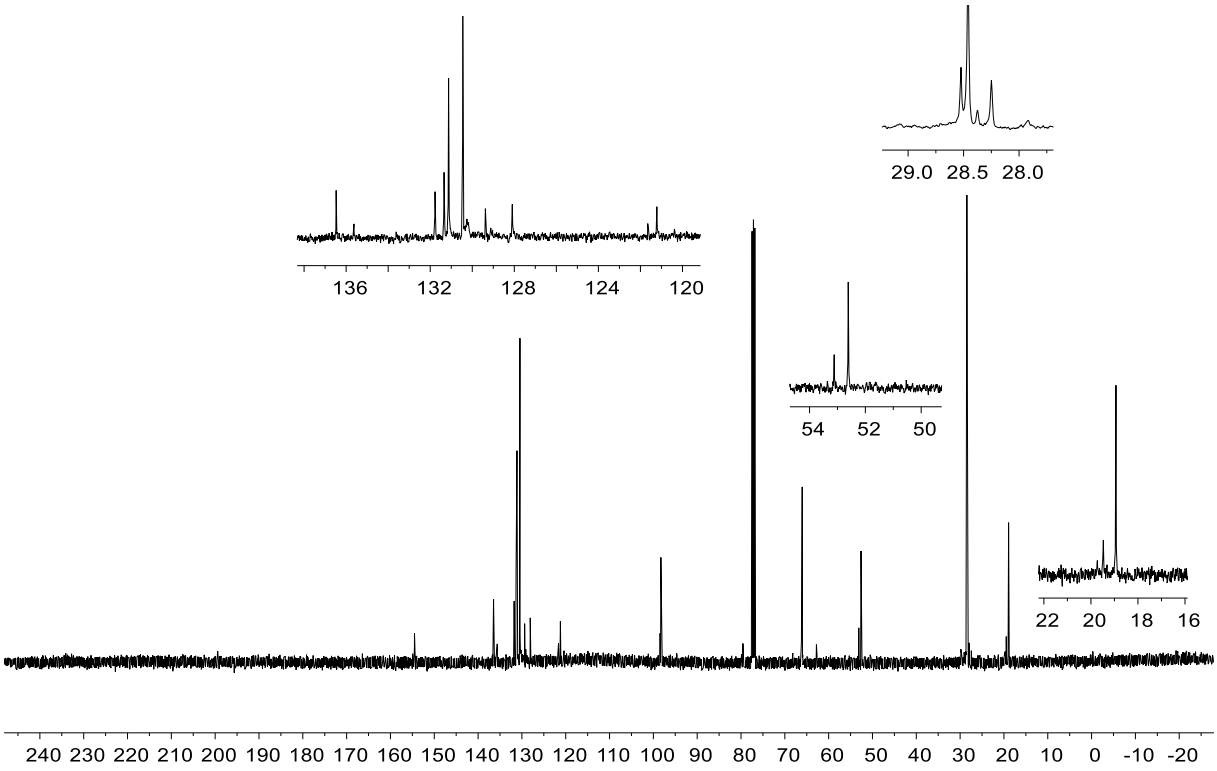
$^{13}$C{$^{1}$H} NMR (101 MHz, Chloroform-*d*, 298 K) δ (major) = 154.5 (C=O), 136.5 (C7), 131.3 (C6), 131.1 (C9), 130.5 (C8), 130.3 (br, C1), 121.2 (C10), 98.3 (C4), 79.6 (Boc), 66.0 (C3), 52.6 (C2), 28.5 (Boc), [28.3, 18.9](C5); δ (minor) = 154.9 (C=O), 135.6 (C7), 131.8 (C9), 129.4 (C6), 129.1 (br, C1), 128.1 (C8), 121.7 (C10), 98.5 (C4), 79.8 (Boc), 66.2 (C3), 53.1 (C2), 28.5 (Boc), [27.9, 19.5](C5).

IR (cm$^{-1}$): 3424 (w), 2993 (w), 2979 (w), 2940 (w), 1707 (m), 1587 (w), 1504 (m), 1486 (m), 1450 (w), 1385 (m), 1366 (m), 1278 (m), 1248 (m), 1203 (m), 1162 (m), 1116 (m), 1072 (m), 1060 (m), 1036 (m), 1010 (m), 960 (w), 947 (w), 936 (w), 912 (w), 860 (m), 830 (m), 798 (m), 779 (m), 731 (m), 707 (w), 696 (w), 642 (w), 626 (w), 608 (w).

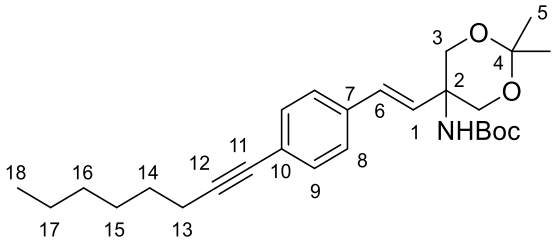
$^{1}$H NMR (400 MHz, Chloroform-*d*, 298 K)



$^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*, 298 K)




**_tert_-Butyl (2,2-dimethyl-5-(4-(oct-1-yn-1-yl)styryl)-1,3-dioxan-5-yl)carbamate (S21)**




A flame dried pressure tube was charged with **S20** (222 mg, 0.63 mmol, 1.00 eq.) in dry ACN (9 mL), $Pd(PPh_3)_4$ (38 mg, 0.03 mmol, 0.05 eq.), CuI (15 mg, 0.08 mmol, 0.13 eq.), $Et_3N$ (262 µL, 1.88 mmol, 3.00 eq.) and 1-octyne (277 µL, 1.88 mmol, 3.00 eq.). Everything was added under an argon atmosphere. The reaction mixture was heated to and stirred at 90 °C for 20 h After being cooled down to room temperature the mixture was diluted with EtOAc, filtered over celite and concentrated under reduced pressure. Purification of the crude mixture *via* column chromatography (CyH : EtOAc / 16 : 1) afforded the *Z/E*-isomeric products (ca. dr 3.5:1, $^{1}H$) as a yellow oil (196 mg, 71%).

$R_f$ (minor) 0.45 (CyH : EtOAc / 3 : 1).

$R_f$ (major) 0.43 (CyH : EtOAc / 3 : 1).

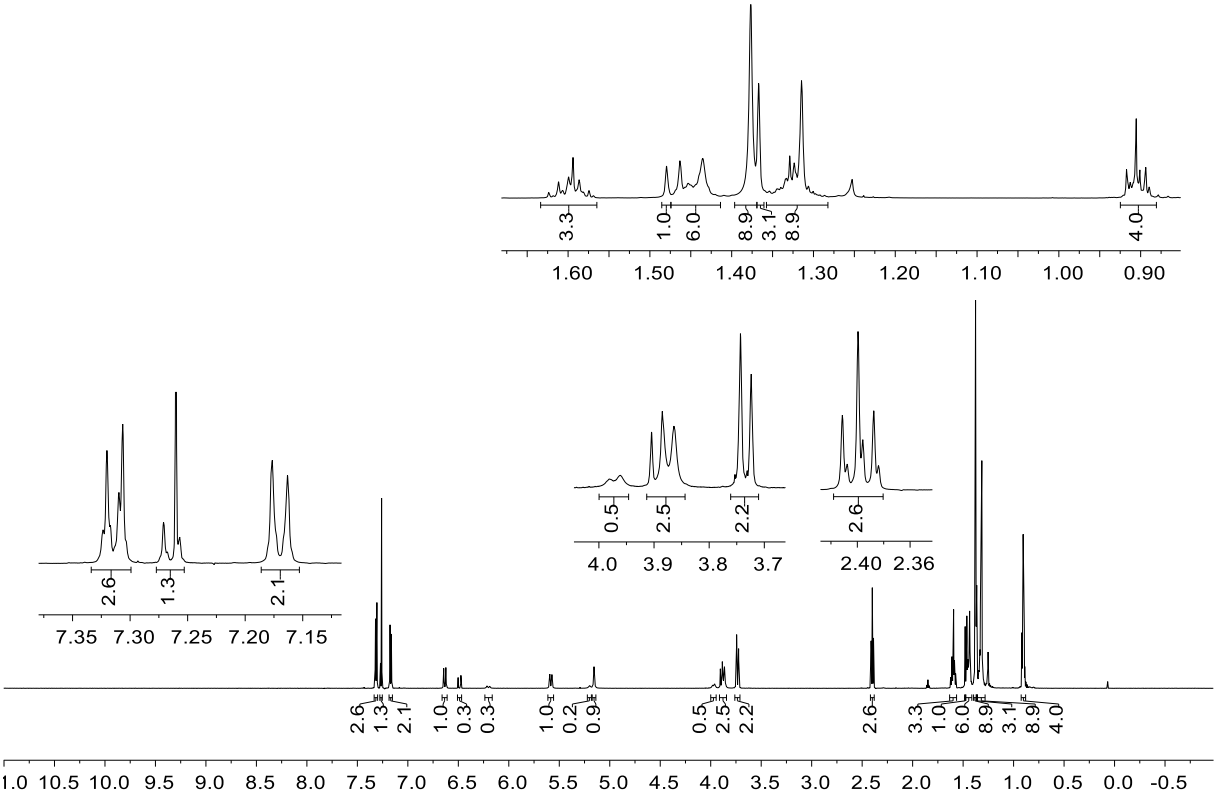
HRMS *m/z* (ESI); Calcd. for $C_{27}H_{39}NO_4Na$ 464.2771, found 464.2765.

$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K) δ (major) = 7.31 (m, 2H, HC9), 7.17 (m, 2H, HC8), 6.63 (d, $^{3}J_{HH}$ = 12.7 Hz, 1H, HC6), 5.58 (d, $^{3}J_{HH}$ = 12.7 Hz, 1H, HC1), 5.16 (s, 1H, NH), [3.87 (d, $^{2}J_{HH}$ = 11.7 Hz, 2H), 3.73 (d, $^{2}J_{HH}$ = 11.7 Hz, 2H)]($H_2$C3), 2.40 (t, $^{3}J_{HH}$ = 7.1 Hz, 2H, $H_2$C13), 1.60 (m, 2H, $H_2$C14), 1.45 (m, 2H, $H_2$C15), 1.38 (s, 9H, Boc), [1.37, 1.31](each s, each 3H, $H_3$C5), 1.33 (m, 2H, $H_2$C17), 1.31 (m, 2H, $H_2$C16), 0.91 (m, 3H, $H_3$C18); δ (minor) = 7.31 (m, 2H, HC9), 7.26 (m, 2H, HC8), 6.49 (d, $^{3}J_{HH}$ = 16.5 Hz, 1H, HC6), 6.20 (br d, $^{3}J_{HH}$ = 16.4 Hz, 1H, HC1), 5.20 (s, 1H, NH), [3.97 (br d, $^{2}J_{HH}$ = 11.9 Hz, 2H), 3.89 (d, $^{2}J_{HH}$ = 11.9 Hz, 2H)]($H_2$C3), 2.40 (t, $^{3}J_{HH}$ = 7.1 Hz, 2H, $H_2$C13), [1.48, 1.46](each s, each 3H, $H_3$C5), 1.44 (s, 9H, Boc), 0.90 (m, 3H, $H_3$C18), n.o. ($H_2$C14,15,16,17),

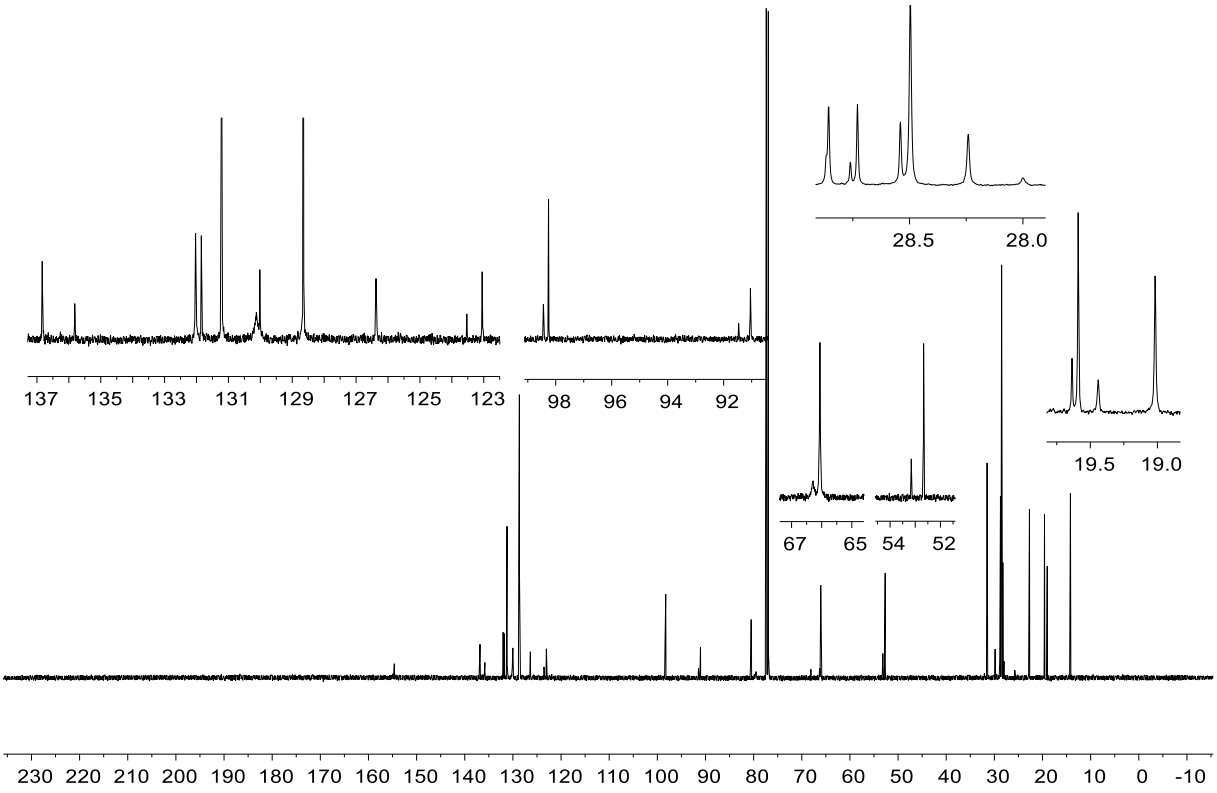
$^{13}$C{$^{1}$H} NMR (151 MHz, Chloroform-*d*, 298 K) δ (major) = 154.6 (C=O), 136.8 (C7), 132.0 (C6), 131.2 (C9), 130.1 (br, C1), 128.7 (C8), 123.1 (C10), 98.3 (C4), 91.0 (C12), 80.5 (C11), 79.5 (br, Boc), 66.1 (C3), 52.7 (C2), 31.5 (C16), 28.9 (C14), 28.7 (C15), 28.5 (Boc), [28.2, 19.0](C5), 22.7 (C17), 19.6 (C13), 14.2 (C18); δ (minor) = 155.0 (C=O), 135.8 (C7), 131.9 (C9), 130.0 (C6), 128.7 (br, C1), 126.4 (C8), 123.5 (C10), 98.4 (C4), 91.5 (C12), 80.7 (C11), 79.8 (br, Boc), 66.3 (br, C3), 53.2 (C2), 31.5 (C16), 28.9 (C14), 28.8 (C15), 28.5 (Boc), [28.0, 19.4](C5), 22.7 (C17), 19.6 (C13), 14.2 (C18).

IR (cm$^{-1}$): 2930 (w), 2858 (w), 1717 (m), 1493 (w), 1471 (w), 1455 (w), 1382 (w), 1367 (m), 1244 (m), 1198 (m), 1163 (m), 1119 (w), 1070 (m), 1039 (w), 962 (w), 935 (w), 909 (w), 889 (w), 863 (w), 831 (m), 807 (w), 781 (w), 731 (m), 644 (w), 635 (w), 617 (w), 611 (w).

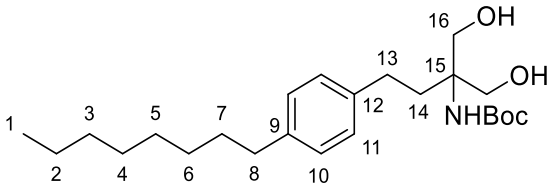
$^{1}$H NMR (600 MHz, Chloroform-*d*, 298 K)



$^{13}C\{^{1}H\}$ NMR (151 MHz, Chloroform-*d*, 298 K)




**_tert_-Butyl (1-hydroxy-2-(hydroxymethyl)-4-(4-octylphenyl)butan-2-yl)carbamate (S22)**




A round-bottom was charged with **S21** (193 mg, 0.44 mmol, 1.00 eq.), EtOH (10 mL) and Pd/C (19 mg, 10 wt%). The atmosphere was changed to $H_2$ (using 2 balloons) and the suspension was stirred at room temperature for 80 h. The reaction mixture was then filtered over celite and the solvent was removed *in vacuo* leaving the product as a white solid (145 mg, 82%).

M.p.: 65 °C.

$R_f$ 0.75 (CyH : EtOAc / 3 : 1).

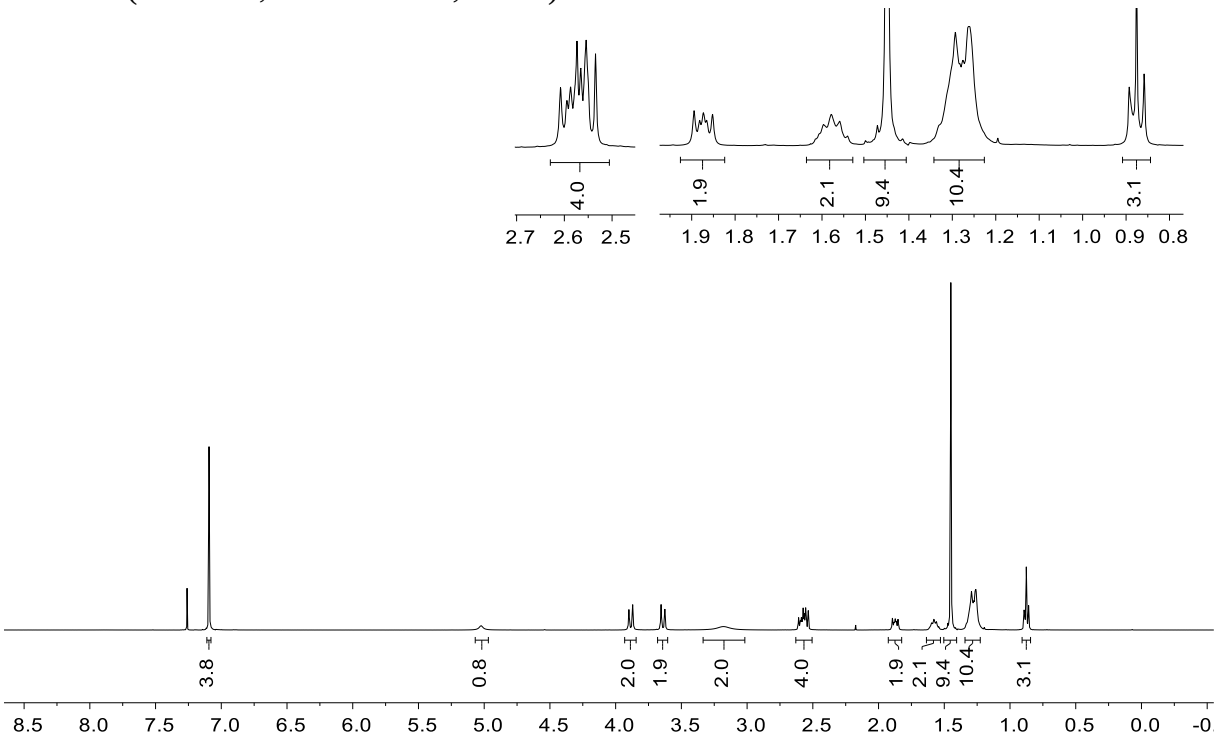
HRMS *m/z* (ESI); Calcd. for $C_{27}H_{45}NO_4Na$ 470.3241, found 470.3255.

$^{1}H$ NMR (400 MHz, Chloroform-*d*, 298 K) δ 7.09 (m, 4H, HC10,11), 5.02 (br, 1H, NH), [3.88 (d, $^{2}J_{HH}$ = 11.5 Hz, 2H), 3.64 (d, $^{2}J_{HH}$ = 11.5 Hz, 2H)]($H_2$C16), 3.18 (br, 2H, OH), 2.59 (m, 2H, $H_2$C13), 2.55 (m, 2H, $H_2$C8), 1.87 (m, 2H, $H_2$C14), 1.57 (m, 2H, $H_2$C7), 1.45 (s, 9H, Boc), 1.36 – 1.19 (m, 10H, $H_2$C2,3,4,5,6), 0.88 (m, 3H, $H_3$C1).

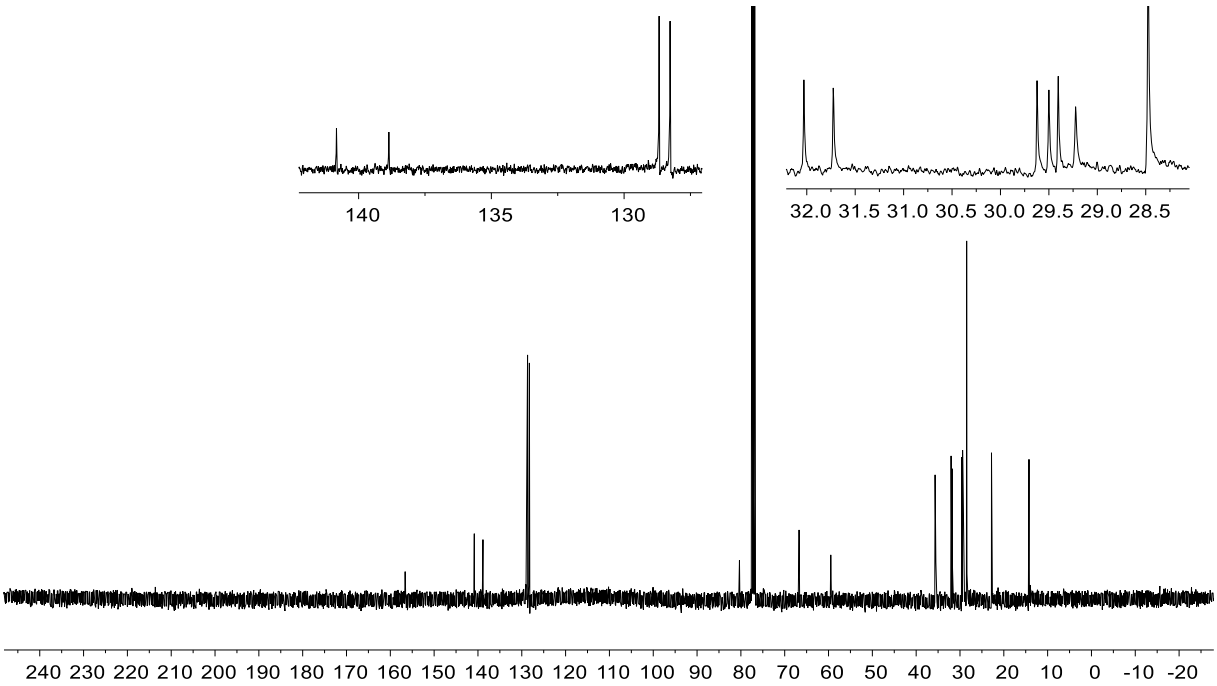
$^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*, 298 K) δ 156.6 (C=O), 140.8 (C9), 138.9 (C12), 128.7 (C10), 128.3 (C11), 80.3 (Boc), 66.7 (C16), 59.5 (C15), 35.7 (C8), 35.5 (C14), 32.0 (C3), 31.7 (C7), [29.6, 29.5, 29.4](C4,5,6), 29.2 (C13), 28.5 (Boc), 22.8 (C2), 14.3 (C1).

IR ($cm^{-1}$): 3289 (w), 3130 (w), 2922 (m), 2853 (w), 1668 (m), 1553 (w), 1515 (w), 1466 (w), 1454 (w), 1402 (m), 1383 (m), 1364 (m), 1319 (w), 1253 (w), 1172 (m), 1121 (w), 1106 (w), 1079 (m), 1056 (m), 1043 (m), 1027 (m), 1009 (m), 982 (w), 942 (w), 919 (w), 868 (w), 848 (w), 817 (w), 780 (m), 742 (w), 722 (w), 670 (w).

$^{1}H$ NMR (400 MHz, Chloroform-*d*, 298 K)




$^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*, 298 K)



## Part 2. Description of *in vitro* Assays

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### II.9 LogD7.4

LogD measurements were performed on a Hamilton Microlab STAR Workstation (Hamilton Robotics AB, Kista, Sweden). The incubation was carried out in a 96 deep well plate. The following volumes were dispensed into each well of the incubation plate, 500 µl octanol (saturated with phosphate buffer pH 7.4), 10 µl cocktail of test compounds in DMSO and 500 µl phosphate buffer pH 7.4 (saturated with octanol). The final concentration of DMSO is 1% v/v. The LogD plate was shaken at 25°C, 2000 rpm for 2 hours. The samples were centrifuged at 4000 rpm at 25°C for 30 minutes to separate the phases. 100 µL were transferred from the octanol and buffer phases to a new 96-well plate. 5 µL of octanol sample is transferred to a new 96-well plate, followed by addition of 495 µL of a mixture of $H_2O$ and acetonitrile containing internal standard as 100 fold octanol samples. Vortex for 5 minutes at 1000 rpm. 50 µL of 100 fold samples were transferred to new 96-well plate, followed by addition of 450 µL of a mixture of $H_2O$ and acetonitrile containing internal standard (1:1) as 1000 fold octanol samples. Vortex for 5 minutes at 1,000 rpm. The 1,000 folds octanol samples were serially diluted into 10,000, 100,000 and 1,000,000 folds with a mixture of $H_2O$ and acetonitrile containing internal standard (1:1). 50 µL of buffer samples were transferred to new 96-well plate, followed by addition of 450 µL of a mixture of $H_2O$ and acetonitrile containing internal standard (1:1) as 10 folds buffer samples. Vortex for 5 minutes at 1,000 rpm. The 10 folds buffer samples were serially diluted into 100, 1,000 and 10,000 folds with a mixture of $H_2O$ and acetonitrile containing internal standard (1:1).

The analyses were performed on an Acquity ultra-performance liquid chromatography (UPLC) system interfaced with an Micromass TQS (Waters, Milford, MA, USA).The analytical column used for chromatographic separation was an Acquity UPLC HSS T3 column (1.8 µm, 2.1 × 30 mm). The mobile phases consisted of 0.1% (v/v) formic acid in water and acetonitrile, respectively. The LC gradient was as follow: 0–0.3 min 0.2% B, 0.3-1.3 95% B, 1.3-1.6 95% B, 1.6-1.61 0.2% B, 1.61-1.8 0.2% B at a flow rate of 1.0 mL/min and the temperature set to 40°. Generic tune files were used. MassLynx 4.1 (Waters) was used for the data acquisition and the chromatographic peaks are integrated by Target Lynx software (Waters).

## II.10 Solubility

DMSO/HBSS solubility measured at pH=7.4 Compounds, dissolved in DMSO and stored in 96-well plates, are transferred and diluted with buffer into new plates. The plates are shaken for 24 hours, then filtered, and the filtered solutions are analysed to give an estimate of the solubility. As standards for the concentration estimations, samples with the same degree of dilution are prepared, but using organic solvent (ethanol, acetonitrile, etc). The diluted samples, and the standards are analysed with LC-UV/MS.

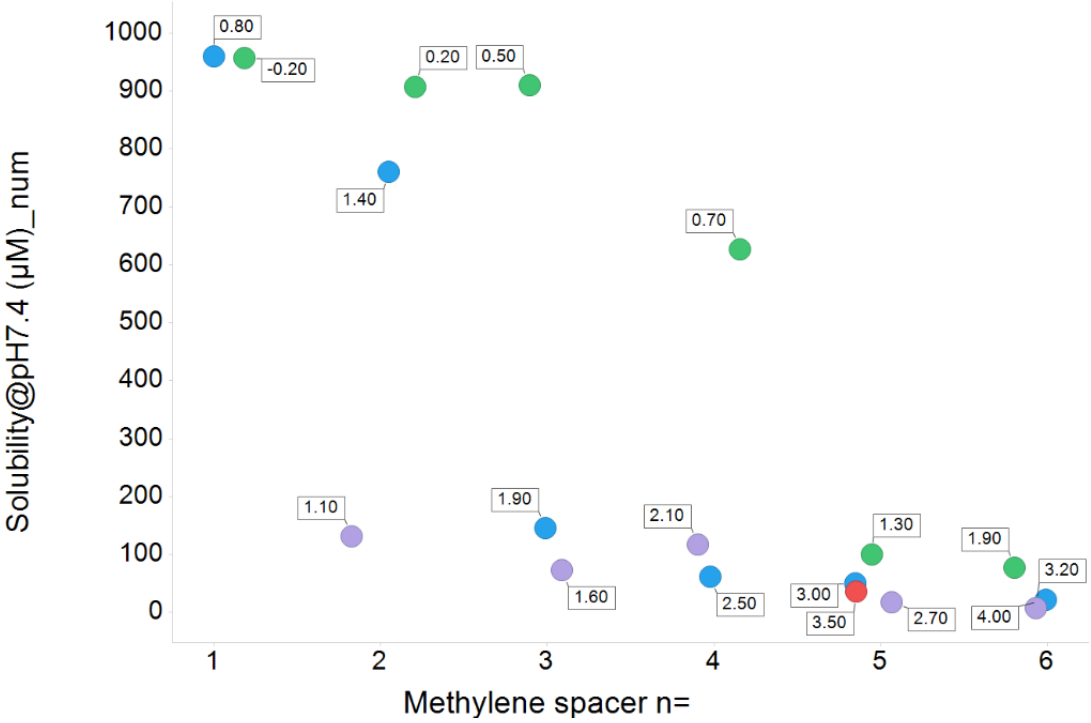


**Figure S1** Aqueous solubility as function of alkyl group length. Color coded according to series: difluoroethyl (green), alkyl (blue) and trifluoromethyl (purple). Fingolimod has been added as reference (red). The labels indicate the individual measured $logD_{7,4}$ values.

## II.11 Caco AB Permeability

Permeability measured in Caco-2 cells in the A to B direction, pH=6.5. Please see for more details: Over B, McCarren P, Artursson P, Foley M, Giordanetto F, Grönberg G, Hilgendorf C, Lee MD,4th, Matsson P, Muncipinto G, Pellisson M, Perry MW, Svensson R, Duvall JR, Kihlberg J. Impact of stereospecific intramolecular hydrogen bonding on cell permeability and physicochemical properties. *J. Med. Chem. 57*(6):2746-2754 (2014).

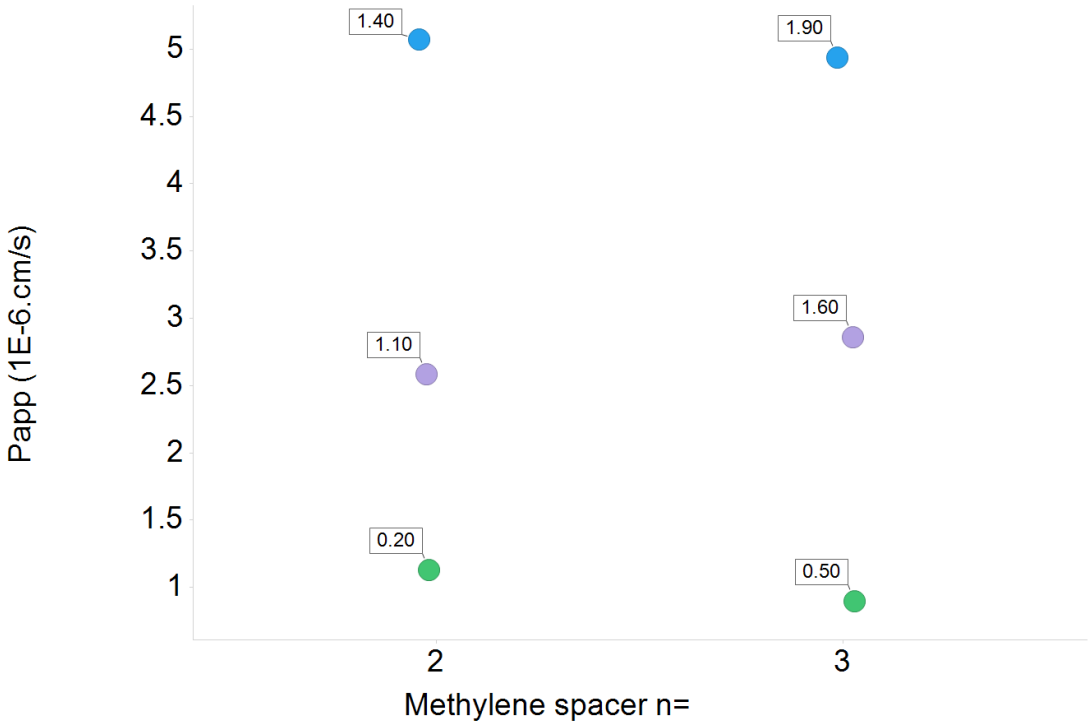


**Figure S2** Caco-2 permeability as function of alkyl group length. Color coded according to series: difluoroethyl (green), alkyl (blue) and trifluoromethyl (purple). The labels indicate the individual measured $logD_{7,4}$ values.

## II.12 Clint in Human Liver Microsomes

Incubations in human liver microsomes (BioreclamationIVT InVitroCYP$^{TM}$, Brussels, Belgium) were performed on a Hamilton Microlab STAR Workstation (Hamilton Robotics AB, Kista, Sweden). Test compounds were incubated at 37°C in 96-well microtiter plates at 1 µM with human liver microsomes (1 mg/mL) and potassium phosphate buffer containing NADPH at a concentration of 1mM. Aliquots of 40 µL were taken at 0.7, 6.0, 12, 17, 22 and 30 min and quenched 1:5 with ice-cold acetonitrile containing 0.8% (v/v) formic acid and 1 µM of internal standard/volume marker. The samples were then centrifuged at 3100 g for 20 min at 4 °C. Thereafter, 35 µL of the supernatant was diluted with 35 µL of water prior to analysis.

The analyses were performed on an Acquity ultra-performance liquid chromatography (UPLC) system interfaced with an ACQUITY® Xevo TQS (Waters, Milford, MA, USA).The analytical column used for chromatographic separation was an Acquity UPLC HSS T3 column (1.8 µm, 2.1 × 30 mm). The mobile phases consisted of 0.1% (v/v) formic acid in water and acetonitrile, respectively. The LC gradient was as follow: 0–0.1 min 0.2% B, 0.1-0.7 95% B, 0.7-1.0 95%B, 1.0-1.01 0.2% B at a flow rate of 1.0 mL/min and the temperature set to 40°. Generic tune files were used. MassLynx 4.1 (Waters) was used for the data acquisition and the chromatographic peaks are integrated by Target Lynx software (Waters).

## II.13 Clint in Rat Hepatocytes

The hepatocyte incubations were performed on a Hamilton Microlab STAR Workstation (Hamilton Robotics AB, Kista, Sweden). The incubation was made on a CAT orbital shaking plate heater (Hamilton Robotics AB, Kista, Sweden). Shaking speed of 900rpm and a temperature of 37°C in the wells. The assay was run in a 96-deepwell plate with an incubation volume of 250 µl with 1 µM substrate concentration and rat hepatocytes ($1 \times 10^6$ cells/mL, BioreclamationIVT, Brussels, Belgium). The incubation media used was L-15 Leibovitz. From each incubation 12.5 µl was taken out and quenched in 75 µl stop solution (acetonitrile including an internal standard). The time points used were 0.5, 5, 15, 30, 45, 60, 80, 100 and 120 min. The quenched samples were centrifuged at 3000 g for 15 min at 4 °C and the supernatant was diluted 1:1 with water prior to analysis.

The analyses were performed on an Acquity ultra-performance liquid chromatography (UPLC) system interfaced with an Ultima Platinum, Premier, Xevo TQS (Waters, Milford, MA, USA).The analytical column used for chromatographic separation was a Kinetex C18 column (2.6 µm, 2.1 × 50 mm). The mobile phases consisted of 0.1% (v/v) formic acid in water and methanol, respectively. The LC gradient was as follow: 0–0.1 min 5% B, 0.1-0.5 95% B, 0.5-0.95 95%B, 0.95-0.96 5% B at a flow rate of 800 µL/min and the temperature set to 60°. Generic tune files were used. MassLynx 4.1 (Waters) was used for the data acquisition and the chromatographic peaks are integrated by Target Lynx software (Waters).

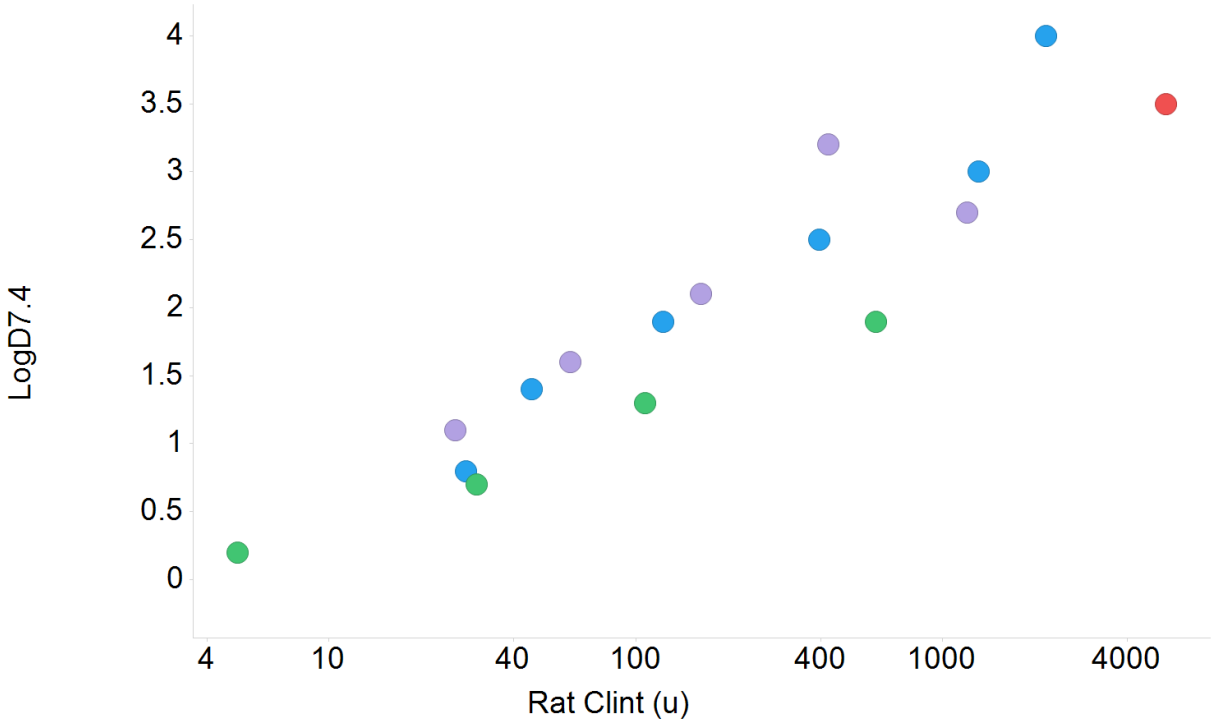


**Figure S3** Correlation between rat Clint unbound (corrected for protein binding) and LogD7.4. Colour coded according to series: difluoroethyl (green), alkyl (blue) and trifluoromethyl (purple). Fingolimod has been added as reference (red).

### II.14 Clint in Human Hepatocytes

The hepatocyte incubations were performed on a Hamilton Microlab STAR Workstation (Hamilton Robotics AB, Kista, Sweden). The incubation was made on a CAT orbital shaking plate heater (Hamilton Robotics AB, Kista, Sweden). Shaking speed of 900rpm and a temperature of 37°C in the wells. The assay was run in a 96-deepwell plate with an incubation volume of 250 µl with 1 µM substrate concentration and human hepatocytes ($1 \times 10^6$ cells/mL, BioreclamationIVT, Brussels, Belgium). The incubation media used was L-15 Leibovitz. From each incubation 20 µl was taken out and quenched in 80 µl stop solution (acetonitrile including an internal standard). The time points used were 0.5, 5, 15, 30, 45, 60, 80, 100 and 120 min. The quenched samples were centrifuged at 4000 g for 20 min at 4 °C and the supernatant was diluted 1:1 with water prior to analysis.

The analyses were performed on an Acquity ultra-performance liquid chromatography (UPLC) system interfaced with an Ultima Platinum, Premier, Xevo TQS (Waters, Milford, MA, USA).The analytical column used for chromatographic separation was a Acquity UPLC HSS T3 column (1.8 µm, 2.1 × 30 mm). The mobile phases consisted of 0.1% (v/v) formic acid in water and acetonitrile, respectively. The LC gradient was as follow: 0–0.1 min 5% B, 0.1-0.5 95% B, 0.5-0.95 95% B, 0.95-0.96 5% B at a flow rate of 800 µL/min and the temperature set to 60°. Generic tune files were used. MassLynx 4.1 (Waters) was used for the data acquisition and the chromatographic peaks are integrated by Target Lynx software (Waters).