SUPPORTING INFORMATION

for

Synthesis of 5-amino- and 5-hydroxy-3,3-difluoropiperidines

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Synthetic procedures and spectroscopic data for all new compounds 5a, 6b-d, 8-11, 13-16.

2,2-Difluoropent-4-en-1-ol 4. To a solution of 19.8 g (145.5 mmol, 1 equiv) of 2,2-difluoro-4-pentenoic acid **3** in 500 mL of dry diethyl ether was added carefully 11.05 g (291 mmol, 2 equiv) of $LiAlH_4$ pellets in portions at 0°C. After stirring the reaction mixture for 2 hours at 0°C an additional portion of 5.5 g (145.5 mmol, 1 equiv) of $LiAlH_4$ was added and the mixture was further stirred for 3 hours at room temperature. After completion of the reaction, the mixture was cooled to 0°C and firstly 16.5 mL of water was added dropwise and secondly 16.5 mL of a 15% aq. NaOH solution was added dropwise. Finally 50 mL of water was added and the slurry was stirred for 1 hour and then filtered over a Celite plug. The filtrate was washed with 200 mL of water and the organic phase was dried over $MgSO_4$. After removal of the solvent in vacuo at room temperature, the crude 2,2-difluoropent-4-en-1-ol **4** was purified via distillation (32°C, 60 mbar) to yield 14.2 g of pure 2,2-difluoropent-4-en-1-ol **4** (116 mmol, 80% yield). Spectral data were in accordance with those found in the literature.[i]

2,2-Difluoropent-4-en-1-yl 4-methylbenzenesulfonate 5a. To a solution of 3.03 g (24.84 mmol, 1 equiv) of 2,2-difluoropent-4-en-1-ol **4** in 50 mL of pyridine was added 5.20 g (27.32 mmol, 1.1 equiv) of tosyl chloride at 0°C. After stirring for 15 hours at room temperature the reaction mixture was poured into 100 mL of water and was extracted with 3 × 50 mL of dichloromethane. The combined organic phases were washed with 100 mL of a saturated $NaHCO_3$ solution and then dried over $MgSO_4$. After evaporation of the solvents in vacuo 4.37 g of the crude 2,2-difluoropent-4-en-1-yl 4-methylbenzenesulfonate **5a** (15.83 mmol, 64% yield) was obtained as a red oil which was pure enough for further transformations. ^{1}H NMR ($CDCl_3$): δ 2.45 (3H, s, CH_3); 2.66 (2H, td, J = 16.3 Hz, 7.2 Hz, CH_2); 4.10 (2H, t, J = 11.6 Hz, OCH_2); 5.16-5.20 (1H, m, =C$\underline{H}_a$H$_b$); 5.22-5.24 (1H, m, =CH$_a$$\underline{H}_b$); 5.61-5.76 (1H, m,

=CH); 7.37 (2H, d, J = 8.2 Hz, 2 × CH_{ar}); 7.79 (2H, d, J = 8.2 Hz, 2 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ –104.7 (2F, tt, J = 16.3 Hz, 11.6 Hz, CF_2). ^{13}C NMR ($CDCl_3$): δ 21.5 (CH_3); 38.0 (t, J = 24.2 Hz, CH_2); 67.4 (t, J = 35.8 Hz, OCH_2); 119.6 (t, J = 244.6 Hz, CF_2); 121.6 (=CH_2); 127.4 (t, J = 5.8 Hz, =CH); 127.9 (2 × CH_{ar}); 129.9 (2 × CH_{ar}); 132.0 (SO_2C_{ar}); 145.5 ($\underline{C}_{ar}CH_3$). IR (NaCl, cm^{-1}): ν = 3084 (=CH); 1647 (C=C); 1599 (C_6H_4); 1373 (S=O). MS (ES+) *m/z* (%): 294 ($M+NH_4^+$, 100).

5-Azido-4,4-difluoro-1-pentene 6b. To a solution of 3.32 g (13.07 mmol, 1 equiv) of 2,2-difluoro-4-pentenyl trifluoromethanesulfonate **5b** in 100 mL of DMSO under a N_2 atmosphere was added 0.93 g (14.38 mmol, 1.1 equiv) of sodium azide at room temperature. The mixture was stirred for 24 hours at room temperature and then poured into 150 mL of diethyl ether. The organic phase was washed three times with 100 mL of brine and 100 mL of water. After drying the organic phase over $MgSO_4$, the solvent was evaporated in vacuo and the crude alkylazide was distilled under reduced pressure to yield 1.29 g of pure 5-azido-4,4-difluoro-1-pentene **6b** (8.78 mmol, 67% yield) as a colorless oil. B.p. = 30°C (10 mbar). ^{1}H NMR ($CDCl_3$): 2.71 (2H, tdt, J = 16.0 Hz, 7.3 Hz, 1.1 Hz, CH_2); 3.47 (2H, t, J = 12.8 Hz, CH_2N_3); 5.22-5.28 (1H, m, =C$\underline{H}_a$H$_b$); 5.28-5.33 (1H, m, =CH$_a\underline{H}_b$); 5.78 (1H, ddt, J = 17.5 Hz, 9.8 Hz, 7.3 Hz, =CH). ^{19}F NMR ($CDCl_3$): δ –101.8 (2F, tt, J = 16.0 Hz, 12.8 Hz, CF_2). ^{13}C NMR ($CDCl_3$): δ 38.8 (t, J = 24.2 Hz, CH_2); 53.2 (t, J = 30.6 Hz, CH_2N_3); 121.4 (=CH_2); 121.9 (t, J = 244.6 Hz, CF_2); 128.2 (t, J = 6.3 Hz, =CH). IR (NaCl, cm^{-1}): ν = 3087 (=CH); 2113 (N_3); 1647 (C=C). Compound **6b** decomposes upon LC-MS or GC-MS analysis.

***N*-Benzyl-*N*-(2,2-difluoropent-4-enyl)amine 6c.** To a solution of 5.44 g (21.42 mmol, 1 equiv) of 2,2-difluoro-4-pentenyl trifluoromethanesulfonate **5b** in 200 mL of THF under a nitrogen atmosphere was added 2.41 g (22.49 mmol, 1.05 equiv) of benzylamine and 6 g (42.84 mmol, 2 equiv) of potassium carbonate at room temperature. The reaction mixture was heated at reflux temperature during 15 hours. After completion of the reaction, the mixture was cooled to room temperature, filtered and poured into 200 mL of water and 100 mL of diethyl ether. The organic layer was separated and the aqueous layer was extracted twice with 100 mL of diethyl ether. The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated in vacuo to yield the crude amine **6c** which was further purified via an acid base extraction using dichloromethane and a 3 M aq. HCl solution. The acidic aqueous phase with the protonated amine was basified with a 3 M aq. NaOH solution and extracted with dichloromethane. After drying and evaporation of dichloromethane, 4.48 g of pure *N*-benzyl-*N*-(2,2-difluoropent-4-enyl)amine **6c** (21.21 mmol, 99% yield) was obtained as a red oil. ^{1}H NMR ($CDCl_3$): 1.39-1.67 (1H, s, broad, NH); 2.72 (2H, td, J = 16.2 Hz, 7.2 Hz, CH_2); 2.92 (2H, t, J = 13.9 Hz, NCH_2CF_2); 3.85 (2H, s, N$\underline{C}$H$_2$Ph); 5.19 (1H, d, J = 10.5 Hz, =C$\underline{H}_a$H$_b$); 5.21 (1H, d, J = 16.7 Hz, =CH$_a\underline{H}_b$); 5.78 (1H, ddt, J = 16.7 Hz, 10.5 Hz, 7.2 Hz, =CH); 7.30-7.36 (5H, m, 5 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ –101.9 (2F, tt, J = 16.2 Hz, 13.9 Hz, CF_2). ^{13}C NMR ($CDCl_3$): δ 39.1 (t, J = 24.8 Hz, CH_2); 51.8 (t, J = 27.7 Hz, $N\underline{C}H_2CF_2$); 53.5 (N$\underline{C}$H$_2$Ph); 120.1 (=CH_2); 123.5 (t, J = 241.7 Hz, CF_2); 127.0 (CH_{ar}); 127.9 (2 × CH_{ar}); 128.3 (2 × CH_{ar}); 129.4 (t, J = 5.8 Hz, =CH); 139.7 (C_{ar}). IR (NaCl, cm^{-1}): ν = 3349 (NH); 3085 (=C-H); 3028 (CH_{ar}); 2922; 2850; 1646 (C=C); 1603 (C_{ar}=C_{ar}); 1496 (C_{ar}=C_{ar}); 1454; 1431; 1340; 1282; 1121; 996; 927; 879; 741; 699. GC-MS (EI): *m/z* (%): 211 (M^+, 3); 196 (6); 120 (M^+-$C_6H_5CH_2$, 43); 106 (5); 91 ($C_6H_5CH_2^+$, 100); 77 (2); 65 (7). Anal. Calcd. for $C_{12}H_{15}F_2N$: C, 68.23; H, 7.16; N, 6.63. Found: C, 68.01; H, 7.22; N, 6.41.

***N*-Benzyl-*N*-chloro-2,2-difluoro-4-penten-1-amine 6d.** To a cooled solution (0°C) of 4.52 g (21.42 mmol, 1 equiv) of *N*-benzyl-*N*-(2,2-difluoropent-4-enyl)amine **6c** in 150 mL of dichloromethane was added portionwise 2.86 g (21.42 mmol, 1 equiv) of *N*-

chlorosuccinimide. After the mixture had been stirred for 2 hours at 0°C the solvent was removed and the residue was taken up in hexane. After removal of the solid succinimide by filtration, the filtrate was concentrated to yield 5.05 g of virtually pure *N*-benzyl-*N*-chloro-2,2-difluoro-4-penten-1-amine **6d** (20.56 mmol, 96% yield) as a yellow oil which was pure enough for further transformations. ^{1}H NMR ($CDCl_3$): 2.77 (2H, td, J = 16.2 Hz, 7.2 Hz, CH_2); 3.37 (2H, t, J = 11.8 Hz, NCH_2CF_2); 4.17 (2H, s, NCH_2Ph); 5.16-5.23 (1H, m, $=CH_aH_b$); 5.24-5.27 (1H, m, $=CH_aH_b$); 5.74 (1H, ddt, J = 17.2 Hz, 10.0 Hz, 7.2 Hz, =CH); 7.30-7.40 (5H, m, 5 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ –98.0 (2F, tt, J = 16.2 Hz, 11.8 Hz, CF_2). ^{13}C NMR ($CDCl_3$): δ 39.0 (t, J = 24.2 Hz, CH_2); 64.5 (t, J = 30.6 Hz, NCH_2CF_2); 68.9 (NCH_2Ph); 120.7 ($=CH_2$); 122.3 (t, J = 242.9 Hz, CF_2); 128.2 (CH_{ar}); 128.4 (2 × CH_{ar}); 128.8 (t, J = 5.8 Hz, =CH); 129.2 (2 × CH_{ar}); 136.1 (C_{ar}). IR (NaCl, cm^{-1}): ν = 3086 (=C-H); 3067 (=C-H); 3033 (CH_{ar}); 2919; 2855; 1740; 1721; 1647 (C=C); 1604 (C_{ar}=C_{ar}); 1497 (C_{ar}=C_{ar}); 1456; 1431; 1305; 1280; 1126; 1072; 1043; 994; 929; 879; 750; 699. GC-MS (EI): *m/z* (%): 244/246 (M^+-H, 3/1); 208 (M^+-H-HCl, 9); 196 (6); 154/156 (M^+-$C_6H_5CH_2$, 8/3); 120 (5); 104 (4); 91 ($C_6H_5CH_2$, 100); 77 (2).

1-Benzyl-5-chloro-3,3-difluoropiperidine 8a. To a suspension of 0.64 g (1.74 mmol, 0.1 equiv) of tetrabutylammonium iodide in 70 mL of chloroform at 50°C under N_2 atmosphere was added 4.27 g (17.4 mmol, 1 equiv) of *N*-benzyl-*N*-chloro-2,2-difluoro-4-penten-1-amine **6d**. The solution was kept at this temperature for 15 hours. After the mixture had cooled to room temperature, the solvent was evaporated in vacuo. The residue, which contained 18% of pyrrolidine **7a** and 82% of piperidine **8a**, was dissolved in 70 mL of dichloroethane and 0.73 g (17.4 mmol, 1 equiv) of LiCl was added. The mixture was heated at reflux temperature during 60 hours. When the conversion of pyrrolidine toward piperidine was complete, the mixture was cooled, filtered and the solvent was evaporated in vacuo. The crude piperidine was isolated from the residue by flash chromatography (hexane/EtOAc 99:1, R_f = 0.06) to yield 3.67 g of pure 1-benzyl-5-chloro-3,3-difluoropiperidine **8a** (15.0 mmol, 86% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): 1.89 (1H, dddd, J = 30.6 Hz, 13.1 Hz, 11.3 Hz, 6.1 Hz, CH_aH_b); 2.21 (1H, t, J = 11.3 Hz, NCH_aH_bCHCl); 2.31 (1H, ddd, J = 27.3 Hz, 11.1 Hz, 3.3 Hz, $NCH_aCH_bCF_2$); 2.57-2.74 (1H, m, CH_aH_b); 3.01 (1H, t, J = 11.1 Hz, $NCH_aH_bCF_2$); 3.14 (1H, d, J = 11.3 Hz, NCH_aH_bCHCl); 3.60 (1H, d, J = 13.5 Hz, NCH_aH_bPh); 3.64 (1H, d, J = 13.5 Hz, NCH_aH_bPh); 4.04 (1H, tt, J = 11.3 Hz, 4.9 Hz, CHCl); 7.22-7.35 (5H, m, 5 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ –97.5 (1F, d, J = 246.0 Hz, CF_aF_b); -99.7 (1F, dddt, J = 246.0 Hz, 30.6 Hz, 27.3 Hz, 11.1 Hz, CF_aF_b). ^{13}C NMR ($CDCl_3$): δ 42.5 (t, J = 24.2 Hz, CH_2); 50.3 (d, J = 11.5 Hz, CHCl); 57.0 (dd, J = 30.6 Hz, 24.8 Hz, NCH_2CF_2); 59.2 (NCH_2CHCl); 61.0 (NCH_2Ph); 119.3 (t, J = 243.4 Hz, CF_2); 127.5 (CH_{ar}); 128.4 (2 × CH_{ar}); 128.8 (2 × CH_{ar}); 136.5 (C_{ar}). IR (NaCl, cm^{-1}): ν = 3030 (CH_{ar}); 2924; 2821; 1604 (C_{ar}=C_{ar}); 1495 (C_{ar}=C_{ar}); 1455; 1351; 1310; 1289; 1189; 1097; 1010; 915; 774; 741; 699 (C-Cl). GC-MS (EI): *m/z* (%): 245/247 (M^+, 30/10); 244/246 (M^+-H, 28/13); 168/170 (M^+-C_6H_5, 30/10); 154/156 (M^+-$C_6H_5CH_2$, 25/8); 91 ($C_6H_5CH_2^+$, 100); 77 (2); 65 (10). Anal. Calcd. for $C_{12}H_{14}ClF_2N$: C, 58.66; H, 5.74; N, 5.70. Found: C, 58.42; H, 5.82; N, 5.63.

1-Benzyl-5-bromo-3,3-difluoropiperidine 8b. To a solution of 200 mg (0.95 mmol, 1 equiv) of *N*-benzyl-*N*-(2,2-difluoropent-4-enyl)amine **6c** in 5 mL of dichloromethane was added 170 mg (0.95 mmol, 1 equiv) of *N*-bromosuccinimide. After the mixture had been stirred for 2 hours at room temperature the mixture was poured into 20 mL of water and was extracted twice with 20 mL of dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was dissolved in acetone and stirred during 72 hours to convert the intermediate pyrrolidine **7b** into piperidine **8b**. The crude piperidine was then purified by flash chromatography (hexane/EtOAc 7:3, R_f = 0.58) to

yield 210 mg of pure 1-benzyl-5-bromo-3,3-difluoropiperidine **8b** (0.73 mmol, 77% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): 2.05 (1H, dtd, J = 30.0 Hz, 11.5 Hz, 4.9 Hz, C$\underline{H}_a$H$_b$); 2.35 (1H, t, J = 11.5 Hz, NC$\underline{H}_a$H$_b$CHBr); 2.35 (1H, ddd, J = 30.0 Hz, 11.5 Hz, 2.3 Hz, NC$\underline{H}_a$CH$_b$CF$_2$); 2.74 (1H, t, J = 11.5 Hz, CH$_a\underline{H}_b$); 3.06 (1H, t, J = 11.5 Hz, NCH$_a\underline{H}_b$CF$_2$); 3.22 (1H, d, J = 11.5 Hz, NCH$_a\underline{H}_b$CHBr); 3.62 (1H, d, J = 13.5 Hz, NC$\underline{H}_a$H$_b$Ph); 3.69 (1H, d, J = 13.5 Hz, NCH$_a\underline{H}_b$Ph); 4.09 (1H, tt, J = 11.5 Hz, 4.9 Hz, CHBr); 7.24-7.37 (5H, m, 5 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ –97.0 (1F, d, J = 245.3 Hz, CF_2); -100.6 (1F, dtt, J = 245.3 Hz, 30.0 Hz, 11.5 Hz, CF_2). ^{13}C NMR ($CDCl_3$): δ 40.1 (d, J = 11.5 Hz, CHBr); 43.3 (t, J = 24.2 Hz, CH_2); 56.9 (dd, J = 30.6 Hz, 24.8 Hz, N$\underline{C}$H$_2$CF$_2$); 59.7 (N$\underline{C}$H$_2$CHBr); 60.9 (N$\underline{C}$H$_2$Ph); 119.2 (t, J = 244.6 Hz, CF_2); 127.6 (CH_{ar}); 128.5 (2 × CH_{ar}); 128.8 (2 × CH_{ar}); 136.5 (C_{ar}). IR (ATR, cm^{-1}): ν = 3062; 3029; 2920; 2818; 1603; 1494; 1454; 1381; 1348; 1308; 1287; 1181; 1167; 1114; 1073; 1009; 981; 956; 913; 890; 829; 742; 722; 698. MS (ES+) *m/z* (%): 210 (M-Br$^-$, 100); 290/292 (M+H$^+$, 60). Anal. Calcd. for $C_{12}H_{14}BrF_2N$: C, 49.67; H, 4.86; N, 4.83. Found: C, 49.45; H, 4.93; N, 4.96.

1-Benzyl-3,3-difluoro-5-iodopiperidine 8c. To a solution of 200 mg (0.95 mmol,1 equiv) of *N*-benzyl-*N*-(2,2-difluoropent-4-enyl)amine **6c** in 5 mL of dichloromethane was added 213 mg (0.95 mmol, 1 equiv) of *N*-iodosuccinimide. After the mixture had been stirred for 2 hours at room temperature the mixture was poured into 20 mL of water and was extracted twice with 20 mL of dichloromethane. The combined organic layers were washed with aq. $NaHSO_3$ and dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 9:1, R_f = 0.51) to yield 262 mg of pure 1-benzyl-3,3-difluoro-5-iodopiperidine **8c** (0.78 mmol, 82% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): 2.20 (1H, dtd, J = 30.3 Hz, 11.8 Hz, 4.6 Hz, C$\underline{H}_a$H$_b$); 2.39 (1H, ddd, J = 30.3 Hz, 11.8 Hz, 1.7 Hz, NC$\underline{H}_a$CH$_b$CF$_2$); 2.50 (1H, t, J = 11.8 Hz, NC$\underline{H}_a$H$_b$CHI); 2.80 (1H, t, J = 11.8 Hz, CH$_a\underline{H}_b$); 3.12 (1H, t, J = 11.8 Hz, NCH$_a\underline{H}_b$CF$_2$); 3.25 (1H, d, J = 11.8 Hz, NCH$_a\underline{H}_b$CHI); 3.62 (1H, d, J = 13.5 Hz, NC$\underline{H}_a$H$_b$Ph); 3.71 (1H, d, J = 13.5 Hz, NCH$_a\underline{H}_b$Ph); 4.16 (1H, tt, J = 11.8 Hz, 4.6 Hz, CHI); 7.24-7.38 (5H, m, 5 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ –96.4 (1F, d, J = 243.5 Hz, CF_2); -101.8 (1F, dtt, J = 243.5 Hz, 30.3 Hz, 11.8 Hz, CF_2). ^{13}C NMR ($CDCl_3$): δ 15.4 (d, J = 10.4 Hz, CHI); 45.2 (t, J = 24.2 Hz, CH_2); 57.0 (dd, J = 30.0 Hz, 24.2 Hz, N$\underline{C}$H$_2$CF$_2$); 60.7 (N$\underline{C}$H$_2$Ph); 61.5 (N$\underline{C}$H$_2$CHI); 119.0 (t, J = 245.8 Hz, CF_2); 127.6 (CH_{ar}); 128.5 (2 × CH_{ar}); 128.8 (2 × CH_{ar}); 136.5 (C_{ar}). IR (ATR, cm^{-1}): ν = 3061; 3028; 2920; 2816; 1602; 1494; 1454; 1435; 1380; 1344; 1308; 1288; 1187; 1151; 1110; 1069; 1007; 980; 952; 912; 886; 824; 740; 697. MS (ES+) *m/z* (%): 210 (M-I$^-$, 100); 338 (M+H$^+$, 50). Anal. Calcd. for $C_{12}H_{14}F_2IN$: C, 42.75; H, 4.19; N, 4.15. Found: C, 42.53; H, 4.23; N, 4.13.

5-Azido-1-benzyl-3,3-difluoropiperidine 9. To a solution of 1.00 g (2.97 mmol) of 1-benzyl-3,3-difluoro-5-iodopiperidine **8c** in 20 mL of DMF was added 0.19 g (2.97 mmol, 1 equiv) of sodium azide and the mixture was stirred at room temperature for 24 hours. The mixture was poured into 30 mL of water and extracted with 3 x 30 mL of Et_2O. The combined organic phases were washed with brine (2 x 30 mL), dried ($MgSO_4$), concentrated and purified via flash chromatography (hexane/EtOAc 99:1, R_f = 0.08) to afford 0.53 g of 5-azido-1-benzyl-3,3-difluoropiperidine **9** (2.11 mmol, 71% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): 1.76 (1H, ddt, J = 24.0 Hz, 13.6 Hz, 11.5 Hz, C$\underline{H}_a$H$_b$); 2.17 (1H, t, J = 11.5 Hz, NC$\underline{H}_a$H$_b$CHN$_3$); 2.39 (1H, ddd, J = 24.0 Hz, 11.5 Hz, 6.9 Hz, NC$\underline{H}_a$CH$_b$CF$_2$); 2.39 (1H, t, J = 11.5 Hz, CH$_a\underline{H}_b$); 2.94 (1H, t, J = 11.5 Hz, NCH$_a\underline{H}_b$CF$_2$); 2.97 (1H, d, J = 11.5 Hz, NCH$_a\underline{H}_b$CHN$_3$); 3.62 (1H, d, J = 13.2 Hz, NC$\underline{H}_a$H$_b$Ph); 3.67 (1H, d, J = 13.2 Hz, NCH$_a\underline{H}_b$Ph); 3.71 (1H, tt, J = 11.5 Hz, 4.5 Hz, CHN$_3$); 7.24-7.38 (5H, m, 5 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ –97.7 (1F, d × quintet, J = 246.0 Hz, 6.9 Hz, C$\underline{F}_a$F$_b$); -99.0 (1F, dtt, J = 246.0 Hz, 24.0 Hz, 11.5 Hz, CF$_a\underline{F}_b$). ^{13}C NMR ($CDCl_3$): δ 37.8 (t, J = 23.7 Hz, CH_2); 54.3 (d, J = 10.4

Hz, CHN_3); 55.9 ($N\underline{C}H_2CHN_3$); 57.3 (dd, J = 29.46 Hz, 26.0 Hz, $N\underline{C}H_2CF_2$); 61.4 ($N\underline{C}H_2Ph$); 119.4 (t, J = 242.3 Hz, CF_2); 127.6 (CH_{ar}); 128.5 (2 × CH_{ar}); 128.9 (2 × CH_{ar}); 136.4 (C_{ar}). IR (NaCl, cm^{-1}): ν = 3331; 3029; 2922; 2819; 2102 (N_3); 1603; 1494; 1453; 1382; 1305; 1281; 1256; 1189; 1172; 1103; 1085; 1012; 976; 919; 825; 742; 699. GC-MS (EI): *m/z* (%): 252 (M^+, 1); 224 (M^+-N_2, 3); 204 (8); 196 (43); 175 (M^+-C_6H_5, 4); 132 (4); 120 (31); 119 (30); 113 (4); 106 (20); 91 ($C_7H_7^+$, 100); 77 ($C_6H_5^+$, 4); 65 (16); 55 (6); 42 (10). MS (ES+) *m/z* (%): 253 ($M+H^+$, 100).

5-Amino-1-benzyl-3,3-difluoropiperidine 10. To a solution of 0.75 g (2.98 mmol) of 5-azido-1-benzyl-3,3-difluoropiperidine **9** in 25 mL of MeOH was added 75 mg (10 wt%) of Pd/C and the mixture was presaturated with H_2 and stirred under H_2 at 1.2 bar for 48 h at room temperature. The mixture was filtered through Celite and the solvent was evaporated. The crude oil was purified via flash chromatography (hexane/EtOAc 3:7, R_f = 0.07) to afford 0.67 g of 5-amino-1-benzyl-3,3-difluoropiperidine **10** (2.95 mmol, 99% yield). Yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.56-1.82 (3H, m, $C\underline{H}_aH_b$ and NH_2); 2.08-2.20 (1H, m, $NC\underline{H}_aH_b$); 2.20-2.28 (1H, m, $CH_a\underline{H}_b$); 2.41-2.61 (1H, m, $NC\underline{H}_aH_bCF_2$); 2.63-2.71 (1H, m, $NCH_a\underline{H}_b$); 2.72-2.81 (1H, m, $NCH_a\underline{H}_bCF_2$); 3.12-3.22 (1H, m, NCH); 3.60 (2H, s, NCH_2Ph); 7.26-7.37 (5H, m, 5 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ -96.0 (1F, d, J = 245.3 Hz, $C\underline{F}_aF_b$); -97.2 (1F, d, J = 245.3 Hz, $CF_a\underline{F}_b$). ^{13}C NMR ($CDCl_3$): δ 41.1 (t, J = 21.9 Hz, CH_2); 45.5 (t, J = 5.2 Hz, NCH); 57.8 (t, J = 27.7 Hz, $N\underline{C}H_2CF_2$); 60.2 (NCH_2); 61.5 (NCH_2Ph); 120.3 (t, J = 241.7 Hz, CF_2); 127.2 (CH_{ar}); 128.2 (2 × CH_{ar}); 128.7 (2 × CH_{ar}); 136.9 (C_{ar}). IR (ATR, cm^{-1}): ν = 3294 (NH); 3062; 3029; 2954; 2814; 1654; 1560; 1495; 1454; 1438; 1386; 1294; 1174; 1117; 1093; 1062; 1028; 998; 919; 827; 745; 700. MS (ES+) *m/z* (%): 227 ($M+H^+$, 100). Anal. Calcd. for $C_{12}H_{16}F_2N_2$: C, 63.70; H, 7.13; N, 12.38. Found: C, 63.59; H, 7.36; N, 12.42.

***tert*-Butyl 5-chloro-3,3-difluoropiperidine-1-carboxylate 11.** To a solution of 3.50 g (14.26 mmol) of 1-benzyl-5-chloro-3,3-difluoropiperidine **8a** in 20 mL of EtOAc were added 3.42 g (15.69 mmol, 1.1 equiv) of di-*tert*-butyl dicarbonate and 1.40 g (40 wt%) of Pd/C. The mixture was stirred under H_2 at 4.8 bar at room temperature during 15 hours. The mixture was filtered, evaporated and purified via flash chromatography (hexane/EtOAc 95:5, R_f = 0.16) to afford 3.60 g of *tert*-butyl 5-chloro-3,3-difluoropiperidine-1-carboxylate **11** (14.12 mmol, 99% yield). M.p. = 52.9°C (Et_2O). White crystals. ^{1}H NMR ($CDCl_3$): 1.39 (9H, s, 3 × CH_3); 1.98 (1H, dtd, J = 30.8 Hz, 11.8 Hz, 4.7 Hz, $C\underline{H}_aH_b$); 2.57-2.68 (1H, m, $CH_a\underline{H}_b$); 2.68-2.89 (1H, m, $NC\underline{H}_aH_b$); 2.98 (1H, dd, J = 29.4 Hz, 14.0 Hz, $NC\underline{H}_aCH_bCF_2$); 3.89 (1H, tt, J = 11.8 Hz, 4.7 Hz, CHCl); 4.08-4.46 (2H, m, $NCH_a\underline{H}_bCF_2$ and $NCH_a\underline{H}_b$). ^{19}F NMR ($CDCl_3$): δ –100.2 and -100.6 (1F, d, J = 247.3 Hz, $C\underline{F}_aF_b$, 2 rotamers); -104.0 and -104.7 (1F, d, J = 247.3 Hz, $CF_a\underline{F}_b$, 2 rotamers). ^{13}C NMR ($CDCl_3$): δ 28.0 (3 × CH_3); 42.6 (t, J = 24.2 Hz, CH_2); 48.0 (t, J = 29.4 Hz, $N\underline{C}H_2CF_2$); 48.9 (d, J = 4.6 Hz, CHCl); 49.3 (NCH_2); 81.2 (OC_q); 118.2 (t, J = 246.9 Hz, CF_2); 153.8 (C=O). IR (ATR, cm^{-1}): ν = 2979; 2936; 1699 (C=O); 1456; 1415; 1368; 1300; 1259; 1249; 1218; 1156; 1117; 1090; 1004; 888; 832; 765. GC-MS (EI): *m/z* (%): 255 (M^+, 1); 240 (M^+-CH_3, 1); 200 (M^+-$CHC(CH_3)_2$, 10); 182 (M^+-O*t*Bu, 34); 155 (M^+-Boc+H, 17); 120 (M^+-Boc-Cl, 13); 57 ($^+C(CH_3)_3$, 100); 41 (19). MS (ES+) *m/z* (%): 241/243 (100); 200/202 (M-$^+C(CH_3)_3$+$2H^+$, 70). Anal. Calcd. for $C_{10}H_{16}ClF_2NO_2$: C, 46.97; H, 6.31; N, 5.48. Found: C, 46.79; H, 6.42; N, 5.55.

3,3-Difluoro-5-iodomethyldihydrofuran-2(3*H*)-one 13. To a solution of 0.41 g (3.02 mmol, 1 equiv) of 2,2-difluoro-4-pentenoic acid **3** in 10 mL of acetonitrile in a darkened flask was added 2.00 g (7.86 mmol, 2.6 equiv) of iodine at 0°C under N_2 atmosphere. The reaction mixture was then stirred for 15 hours at room temperature and quenched by the addition of a saturated $Na_2S_2O_3$ solution and a saturated $NaHCO_3$ solution (1:1). The aqueous layer was

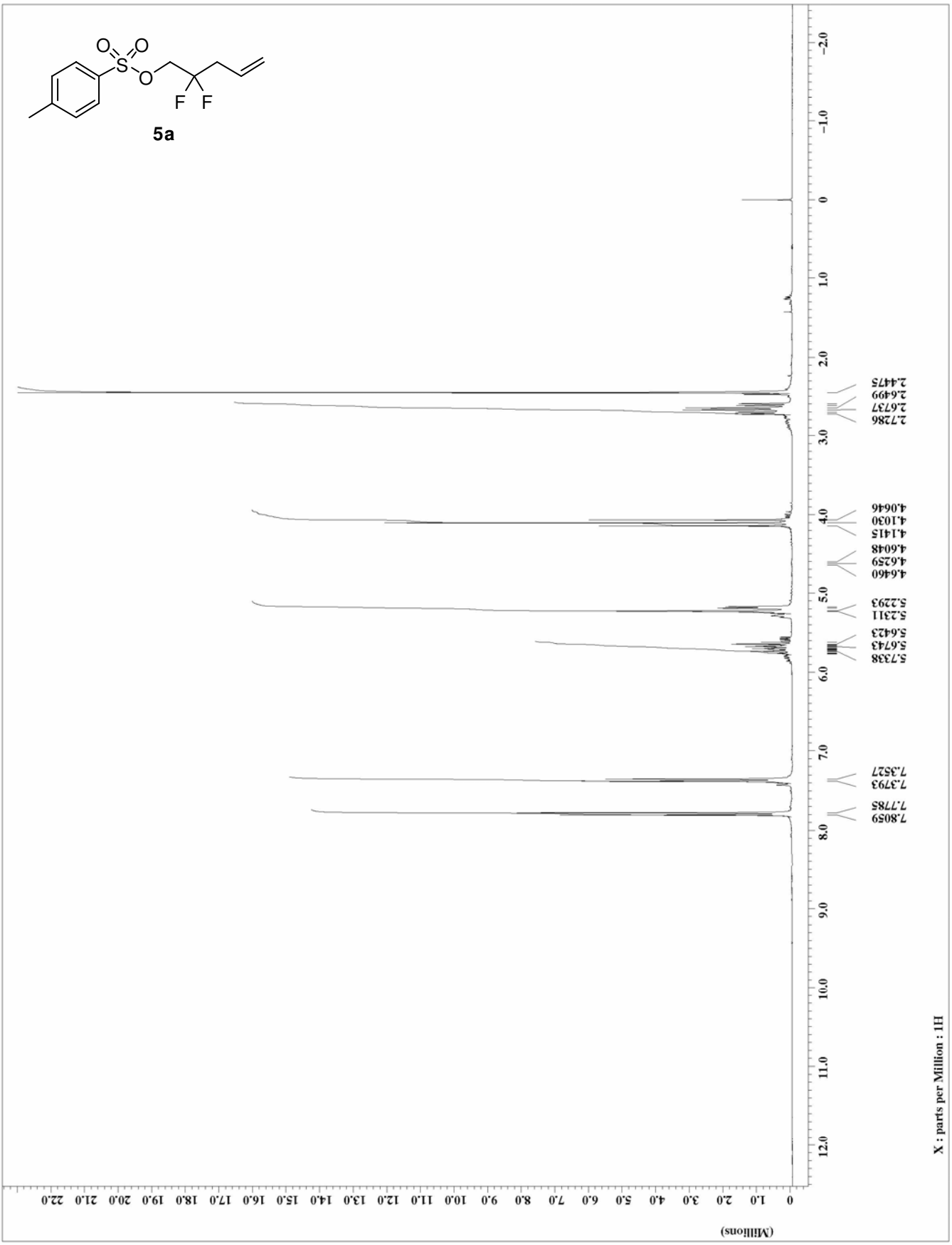
extracted with dichloromethane and the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The crude lactone was purified by flash chromatography (hexane/EtOAc 6:4, R_f = 0.31) to yield 0.71 g of 3,3-difluoro-5-iodomethyldihydrofuran-2(3*H*)-one **13** (2.72 mmol, 90% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.51 (1H, dtd, J = 20.4 Hz, 15.0 Hz, 7.2 Hz, C$\underline{H}_a$H$_b$); 2.96 (1H, tt, J = 15.0 Hz, 7.5 Hz, CH$_a\underline{H}_b$); 3.32 (1H, dd, J = 10.5 Hz, 7.7 Hz, C$\underline{H}_a$H$_b$I); 3.32 (1H, dd, J = 10.5 Hz, 4.4 Hz, CH$_a\underline{H}_b$I); 4.62-4.72 (1H, m, OCH). ^{19}F NMR ($CDCl_3$): δ –104.8 (1F, ddd, J = 281.0 Hz, 20.4 Hz, 15.0 Hz, C$\underline{F}_a$F$_b$); –106.8 (1F, ddd, J = 281.0 Hz, 15.0 Hz, 7.5 Hz, CF$_a\underline{F}_b$). ^{13}C NMR ($CDCl_3$): δ 5.2 (d, J = 2.3 Hz, CH_2I); 37.3 (t, J = 21.9 Hz, CH_2); 74.5 (dd, J = 5.6 Hz, 2.3 Hz, OCH); 115.5 (dd, J = 256.1 Hz, 251.5 Hz, CF_2); 164.5 (t, J = 33.5 Hz, C=O). IR (ATR, cm^{-1}): *v* = 3611; 3025; 2962; 1804 (C=O); 1429; 1361; 1314; 1262; 1220; 1171; 1096; 1045; 992; 976; 937; 864; 822; 742. GC-MS (EI): *m*/*z* (%): 262/263 (M^+, 69/3); 169 (3); 154 (4); 142 (6); 141 (9); 127 (13); 116 (4); 91 (M^+-CO_2-I, 100); 71 (24); 65 (11); 64 16); 51 (17); 43 (17). Anal. Calcd. for $C_5H_5F_2IO_2$: C, 22.92; H, 1.92. Found: C, 22.76; H, 1.98.

5-Azidomethyl-3,3-difluorodihydrofuran-2(3*H*)-one 14. To a solution of 1.22 g (4.66 mmol, 1 equiv) of 3,3-difluoro-5-iodomethyldihydrofuran-2(3*H*)-one **13** in 10 mL of DMSO was added 0.36 g (5.59 mmol, 1.2 equiv) of NaN_3 and the mixture was stirred for 24 hours at room temperature. After completion of the reaction, the mixture was poured into 30 mL of water and extracted with 3 × 30 mL of diethyl ether. The combined organic phases were washed with brine and dried over $MgSO_4$. After evaporation of the solvent in vacuo the residue was purified via flash chromatography (hexane/EtOAc 7:3, R_f = 0.15) to yield 0.57 g of 5-azidomethyl-3,3-difluorodihydrofuran-2(3*H*)-one **13** (3.22 mmol, 69% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.62 (1H, dtd, J = 22.0 Hz, 15.3 Hz, 7.5 Hz, C$\underline{H}_a$H$_b$); 2.84 (1H, tt, J = 15.3 Hz, 7.5 Hz, CH$_a\underline{H}_b$); 3.55 (1H, dd, J = 13.8 Hz, 5.0 Hz, C$\underline{H}_a$H$_b$N$_3$); 3.77 (1H, dd, J = 13.8 Hz, 3.3 Hz, CH$_a\underline{H}_b$N$_3$); 4.78-4.87(1H, m, OCH). ^{19}F NMR ($CDCl_3$): δ –104.4 (1F, ddd, J = 280.5 Hz, 22.0 Hz, 15.3 Hz, C$\underline{F}_a$F$_b$); –106.8 (1F, ddd, J = 280.5 Hz, 15.3 Hz, 7.5 Hz, CF$_a\underline{F}_b$). ^{13}C NMR ($CDCl_3$): δ 33.5 (t, J = 23.1 Hz, CH_2); 52.3 (CH_2N_3); 74.3 (dd, J = 6.9 Hz, 2.3 Hz, OCH); 115.2 (dd, J = 256.7 Hz, 249.8 Hz, CF_2); 164.6 (t, J = 32.9 Hz, C=O). IR (ATR, cm^{-1}): *v* = 3613; 2922; 2851; 2107 (N_3); 1806 (C=O); 1669; 1434; 1318; 1288; 1256; 1232; 1210; 1131; 1090; 1029; 960; 924; 903; 863; 742. GC-MS (EI): *m*/*z* (%): 177 (M^+, 3); 122 (M^+-CH_2N_3+H^+, 80); 93 (M^+-CO_2-N_3+2H^+, 44); 77 (M^+-CH_2N_3-CO_2, 42); 73 (13); 65 (CF_2CH_2, 100); 64 (26); 51 (14); 45 (21); 41 (17).

3,3-Difluoro-5-hydroxy-2-piperidinone 15. To a solution of 0.57 g (3.22 mmol, 1 equiv) of 5-azidomethyl-3,3-difluorodihydrofuran-2(3*H*)-one **14** in 30 mL of ethanol in a pressure vessel was added 114 mg (20 wt%) of 10% Pd/C. The mixture was stirred under H_2 pressure (4.8 bar) for 24 hours. The solution was filtered through a Celite plug to remove the catalyst, and the catalyst was washed twice with 10 mL of hot ethanol. The filtrates were combined and concentrated in vacuo. The residue was purified via flash chromatography ($CHCl_3$/MeOH 4:1, R_f = 0.23) to yield 0.29 g of 3,3-difluoro-5-hydroxy-2-piperidinone **15** (1.93 mmol, 60% yield) as white crystals. M.p. = 136.2°C (Et_2O). ^{1}H NMR (CD_3OD): δ 2.33 (1H, dtd, J = 19.3 Hz, 14.1 Hz, 8.3 Hz, C$\underline{H}_a$H$_b$); 2.51 (1H, qd, J = 14.1 Hz, 3.3 Hz, CH$_a\underline{H}_b$); 3.18 (1H, dd, J = 12.6 Hz, 6.3 Hz, NC$\underline{H}_a$H$_b$); 3.43 (1H, dd, J = 12.6 Hz, 3.9 Hz, NCH$_a\underline{H}_b$); 4.07-4.18 (1H, m, OCH). ^{19}F NMR (dmso-d6): δ –94.0 (1F, dt, J = 283.2 Hz, 19.3 Hz, C$\underline{F}_a$F$_b$); –96.6 (1F, dtd, J = 283.2 Hz, 13.2 Hz, 3.9 Hz, CF$_a\underline{F}_b$). ^{13}C NMR (CD_3OD): δ 39.5 (t, J = 21.3 Hz, CH_2); 47.5 (NCH_2); 61.7 (t, J = 5.8 Hz, OCH); 112.1 (dd, J = 246.9 Hz, 241.1 Hz, CF_2); 163.4 (t, J = 30.0 Hz, C=O). IR (ATR, cm^{-1}): *v* = 3450; 3357 (NH); 3232 (OH); 2906; 2491; 2361; 1693; 1682 (C=O); 1424; 1360; 1327; 1228; 1193; 1148; 1114; 1020; 980;

938; 874; 820; 696. MS (ES+) *m/z* (%): 169 ($M+NH_4^+$, 100). Anal. Calcd. for $C_5H_7F_2NO_2$: C, 39.74; H, 4.67; N, 9.27. Found: C, 39.51; H, 4.34; N, 8.90.

Benzyl 3,3-difluoro-5-hydroxypiperidine-1-carboxylate 16. A solution of 0.22 g (1.46 mmol, 1 equiv) of 3,3-difluoro-5-hydroxy-2-piperidinone **15** in 6 mL of dry THF at 0°C under N_2 atmosphere was reacted with 6.2 mL (6.2 mmol, 4.2 equiv) 1M BH_3.THF complex. After all the borane was added, the solution was heated to 60°C for 1.5 hours. The reaction was cooled and then quenched by the cautious addition of methanol. The solvent was removed under reduced pressure to give a yellow residue of crude 5-hydroxypiperidine that was immediately dissolved in 2.8 mL of water containing 0.32 g (3.8 mmol, 2.6 equiv) of $NaHCO_3$. A solution of 0.68 g (4 mmol, 2.7 equiv) of carbobenzyloxy chloride in 2 mL of toluene was added dropwise, and after adjusting the pH to 8 with 50% NaOH, the reaction was stirred overnight at room temperature. The solution was diluted with 12 mL of diethyl ether and the organic layer was washed with water and brine and dried over $MgSO_4$. After filtration and evaporation of the solvents in vacuo, the crude material was purified via flash chromatography (hexane/EtOAc 4:1, R_f = 0.12) to yield 0.26 g of benzyl 3,3-difluoro-5-hydroxypiperidine-1-carboxylate **16** (0.95 mmol, 65% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.87-2.12 (1H, m, C$\underline{H}_a$H$_b$); 2.27-2.48 (1H, m, CH$_a\underline{H}_b$); 2.89 (1H, s(broad), OH); 3.10-3.24 (1H, m, NC$\underline{H}_a$H$_b$); 3.48-3.68 (1H, m, NCH$_a\underline{H}_b$); 3.70-3.95 (2H, m, NCH_2); 3.96-4.05 (1H, m, OCH); 5.15 (2H, s, OCH_2); 7.31-7.39 (5H, m, 5 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ -98.7 to -101.5 (2F, m, CF_2). ^{13}C NMR ($CDCl_3$): δ 40.2 (t, J = 22.5 Hz, CH_2); 48.4-49.7 (m, NCH_2); 49.5 (NCH_2); 63.4-64.3 (m, OCH); 67.9 (OCH_2); 118.9 (t, J = 244.6 Hz, CF_2); 127.8 (2 × CH_{ar}); 128.2 (CH_{ar}); 128.5 (2 × CH_{ar}); 135.9 (C_{ar}); 155.6 (C=O). IR (ATR, cm^{-1}): ν = 3424 (OH); 2923; 2360; 1682 (C=O); 1466; 1432; 1364; 1314; 1257; 1215; 1177; 1114; 1095; 1052; 1002; 975; 943; 900; 815; 766; 738; 698. MS (ES+) *m/z* (%): 270 ($M-H^+$, 100). Anal. Calcd. for $C_{13}H_{15}F_2NO_3$: C, 57.56; H, 5.57; N, 5.16. Found: C, 57.33; H, 5.68; N, 5.10.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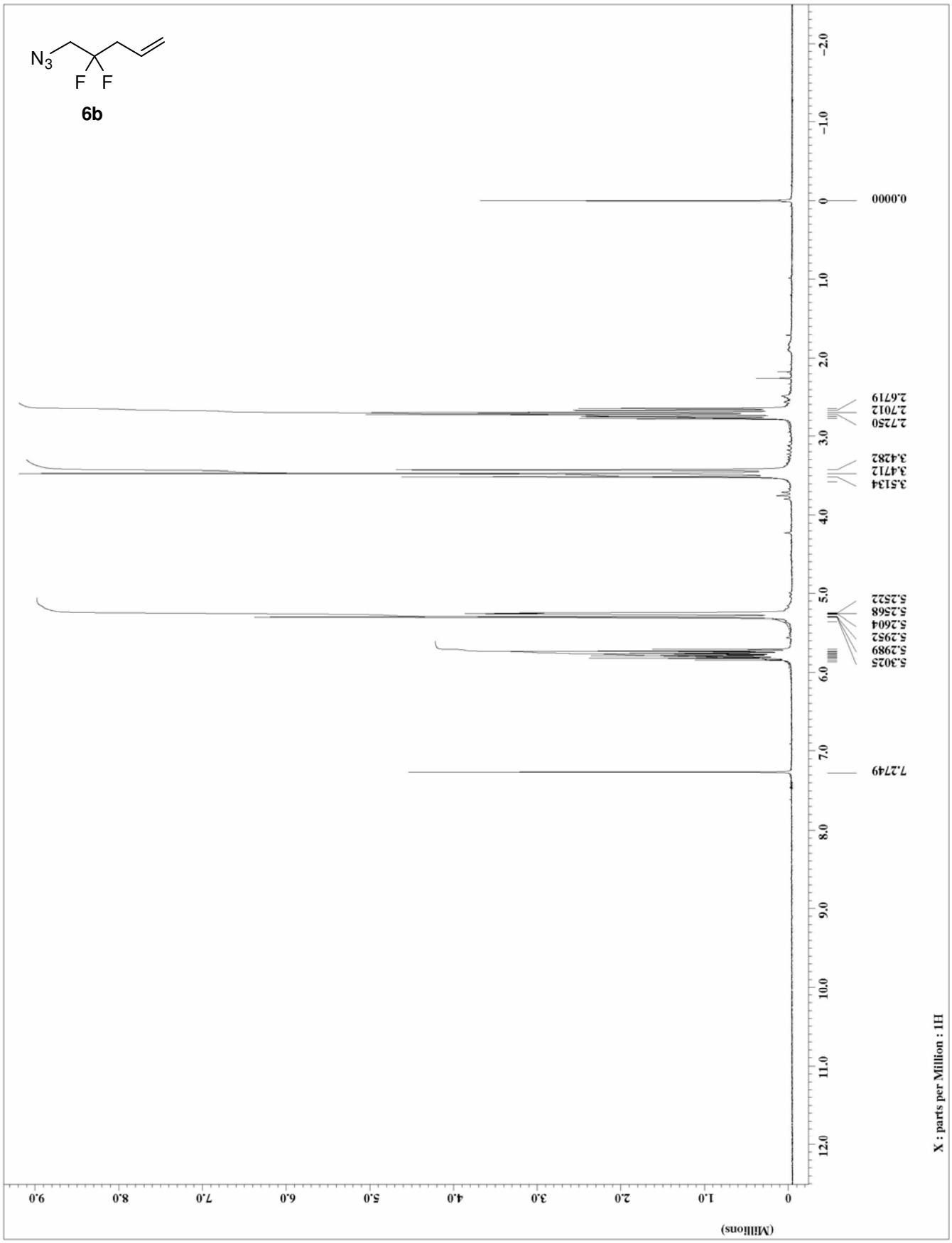
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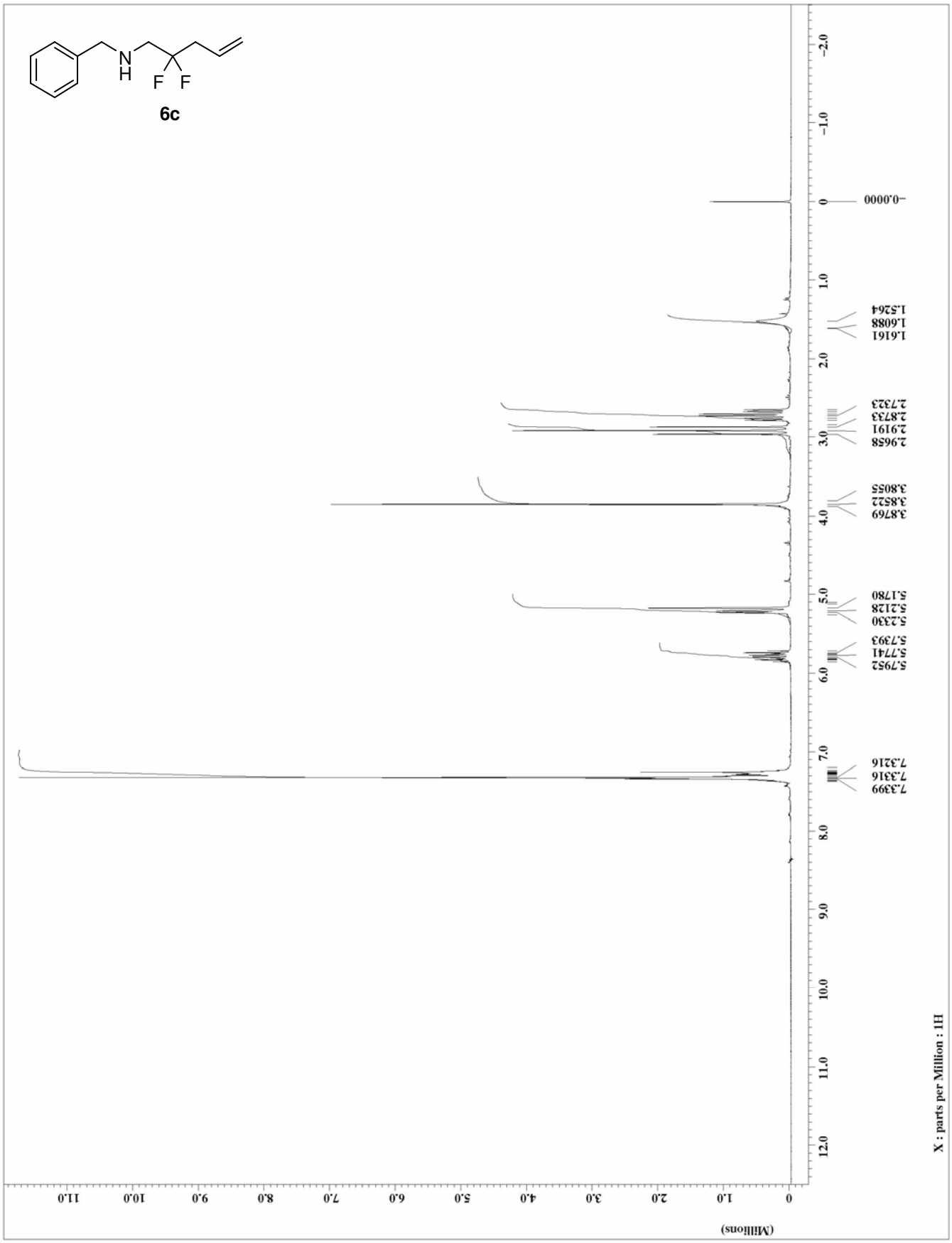
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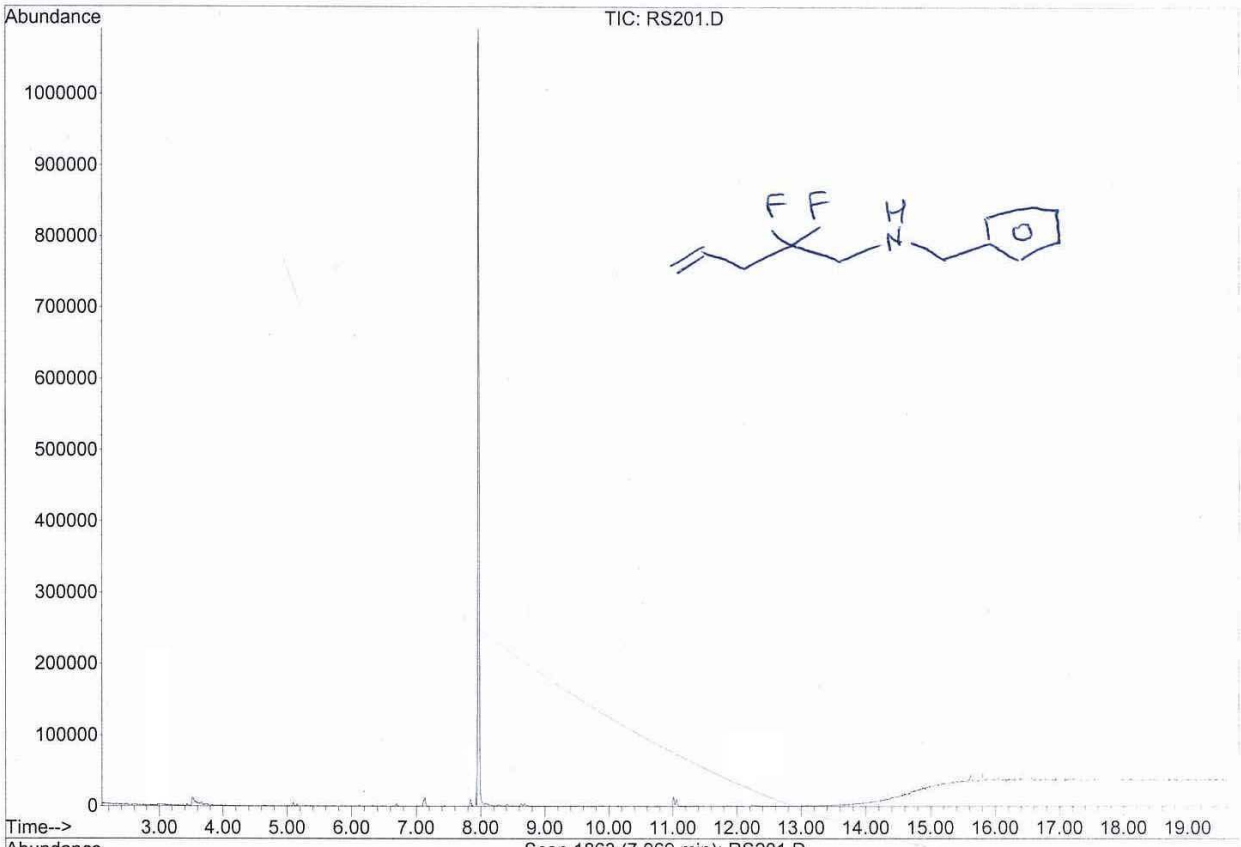

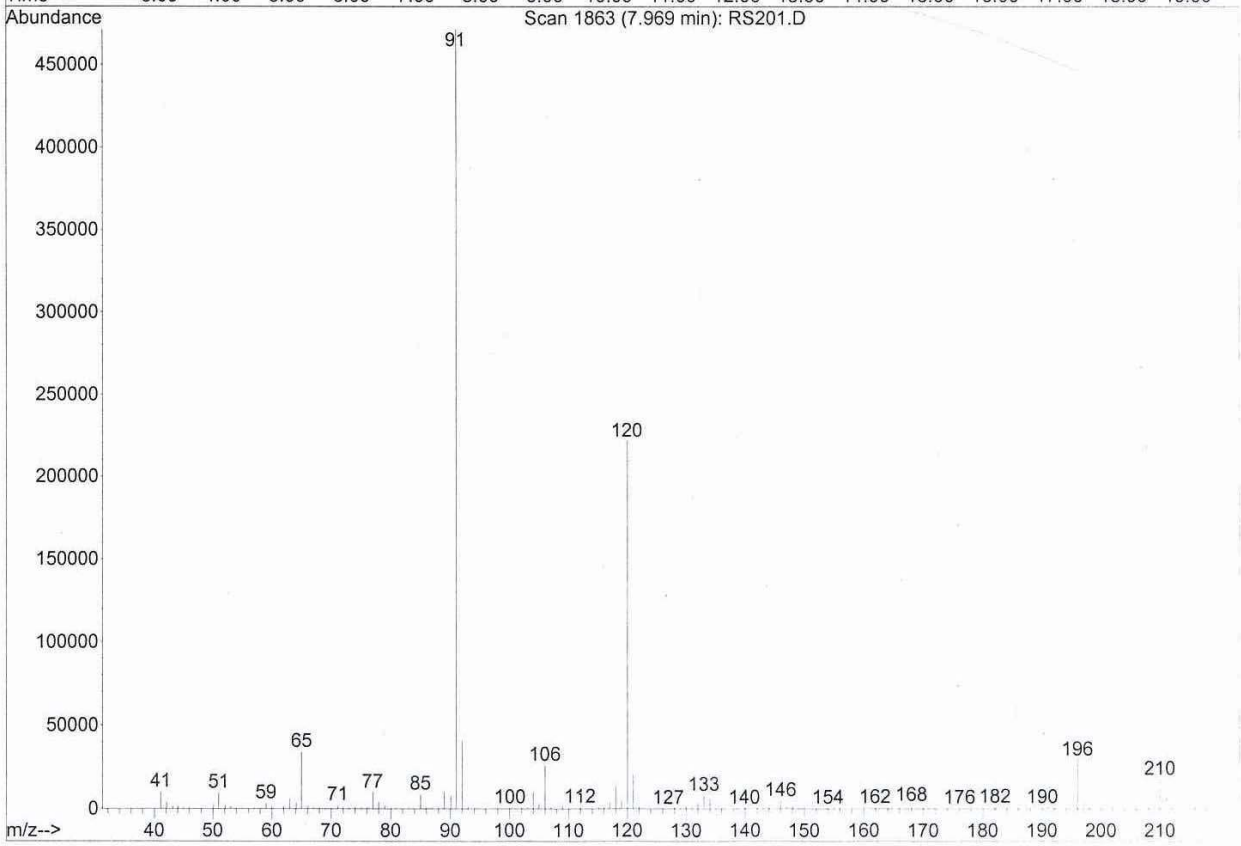

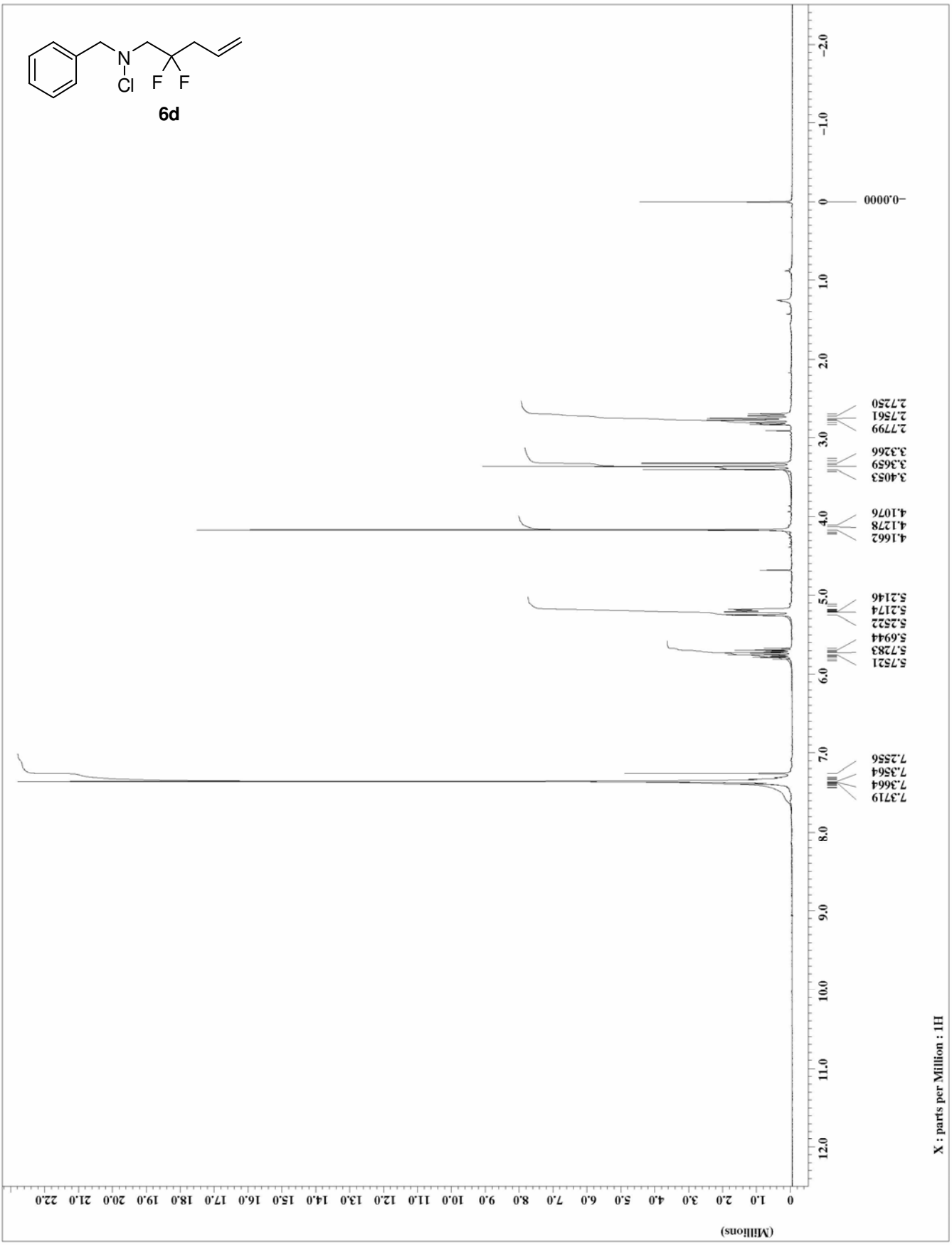
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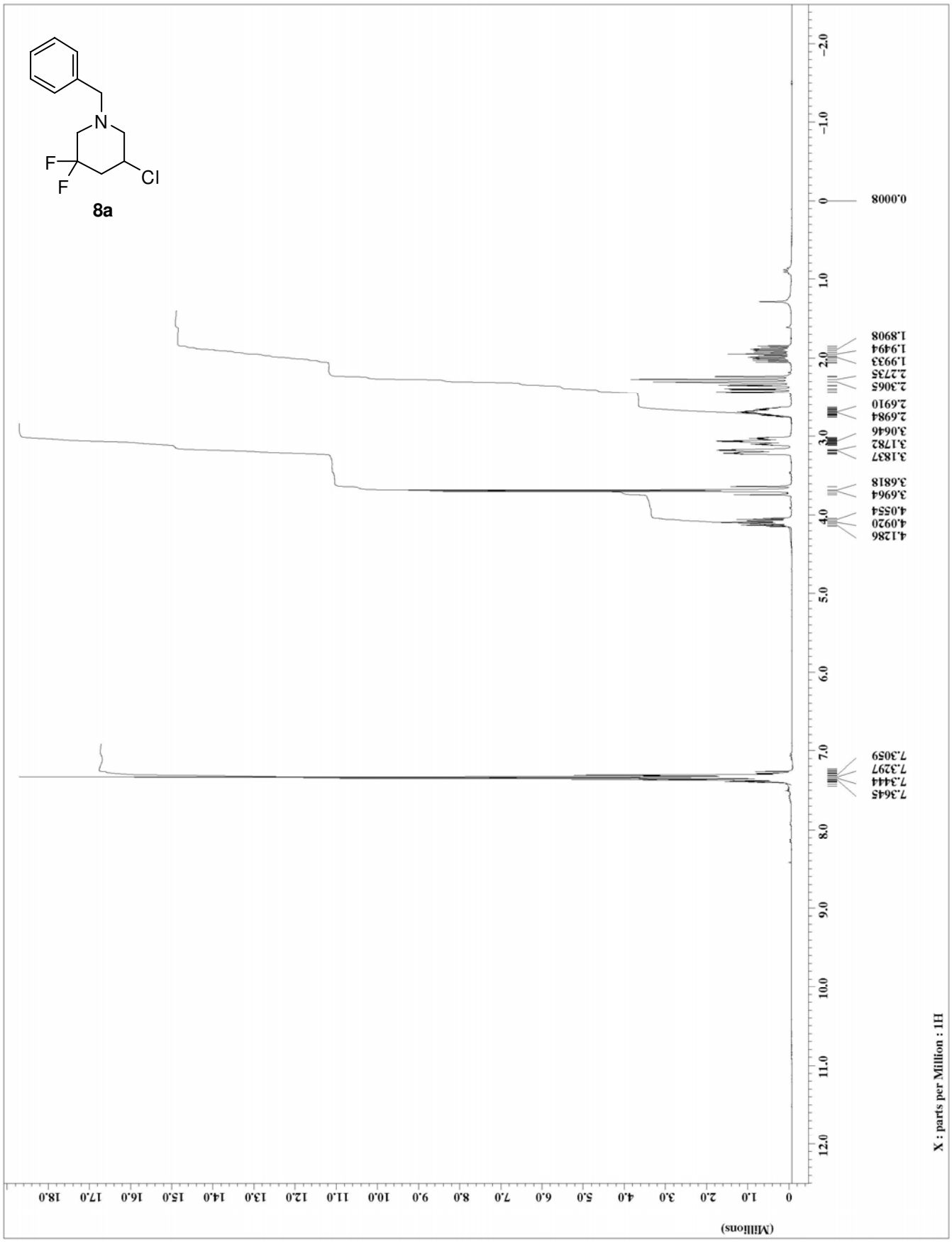
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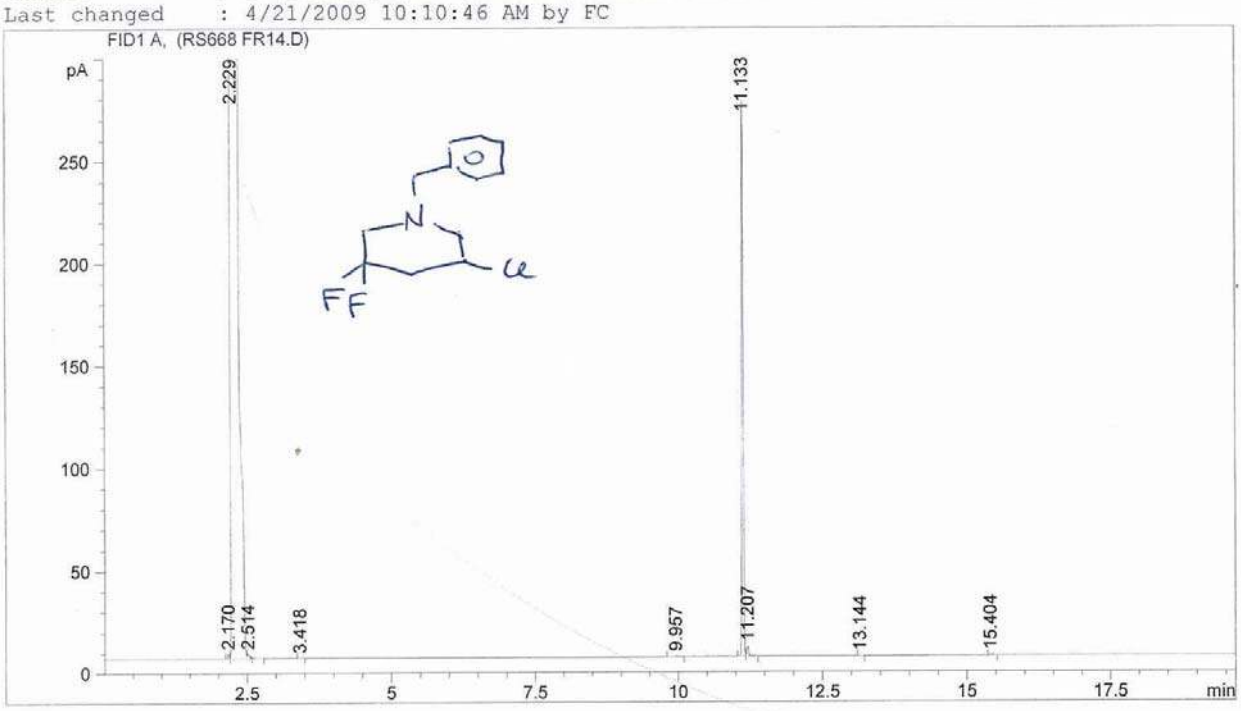

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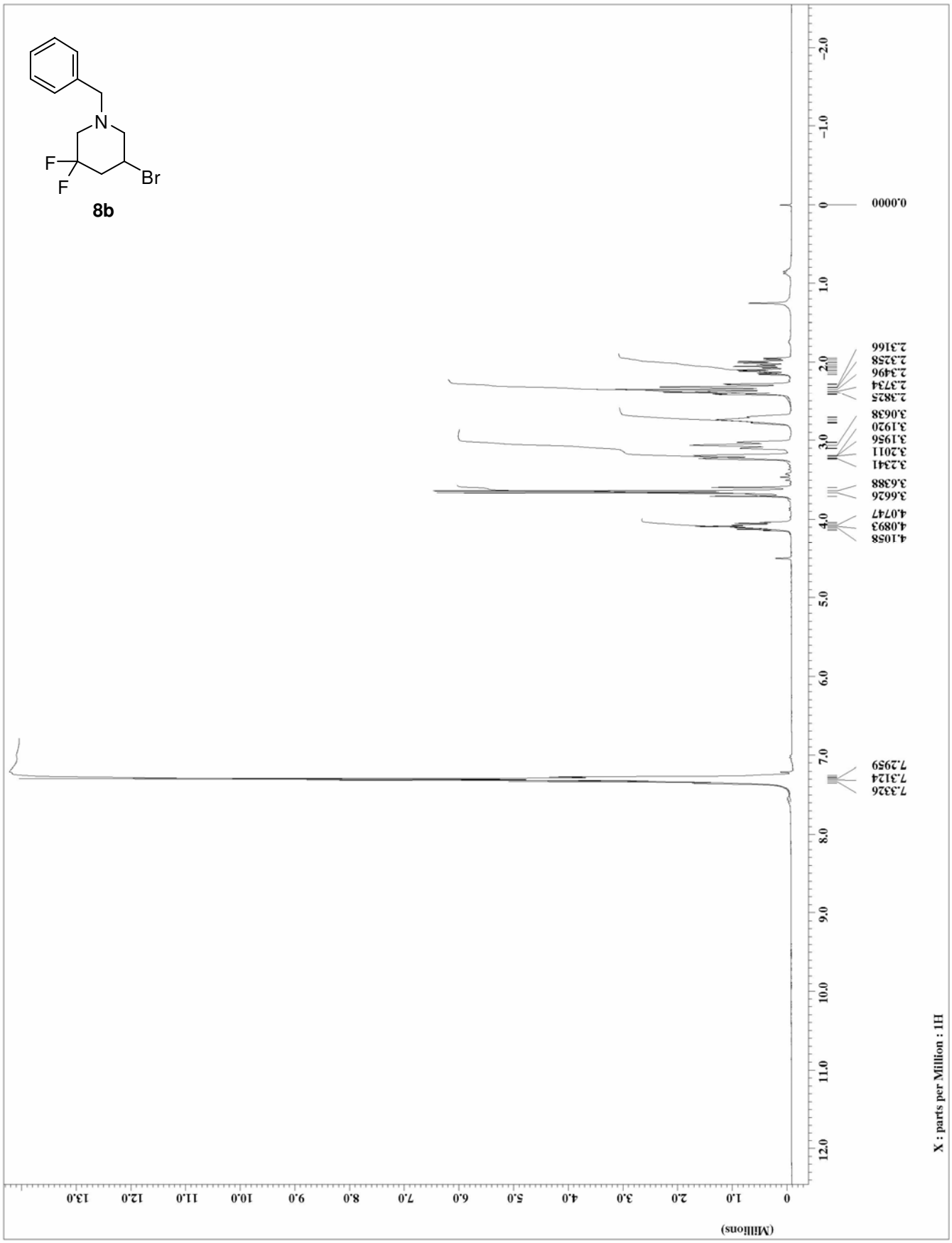
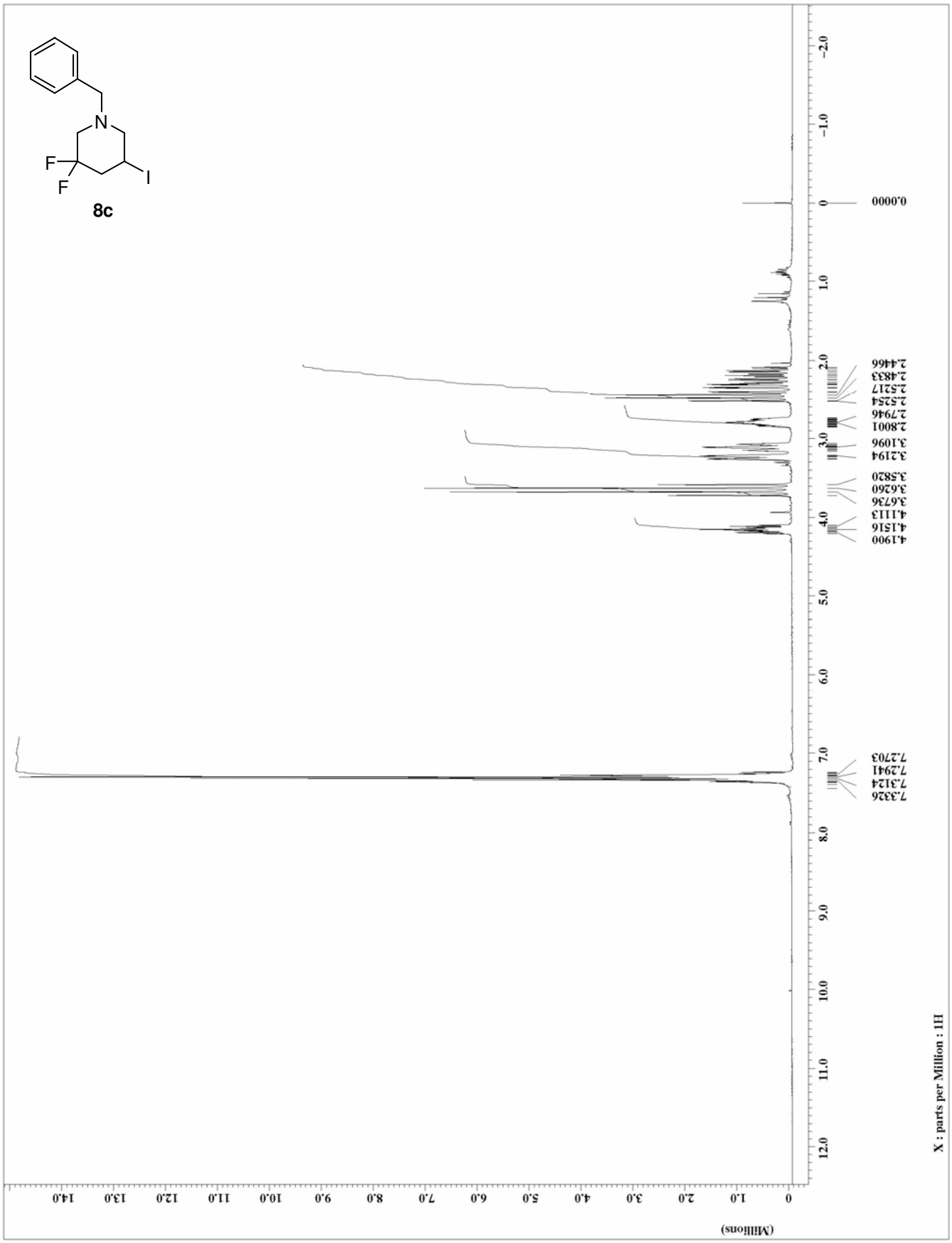
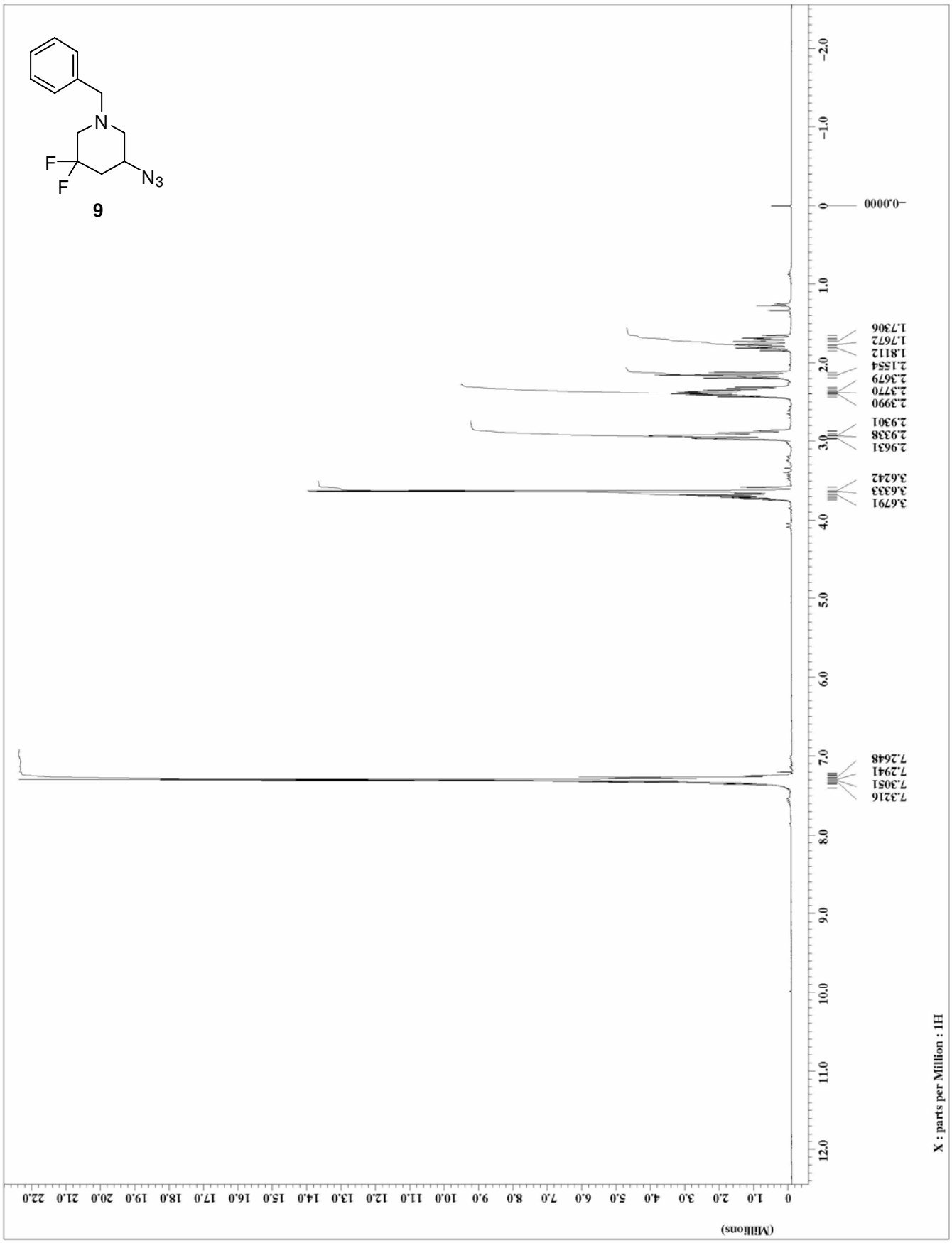
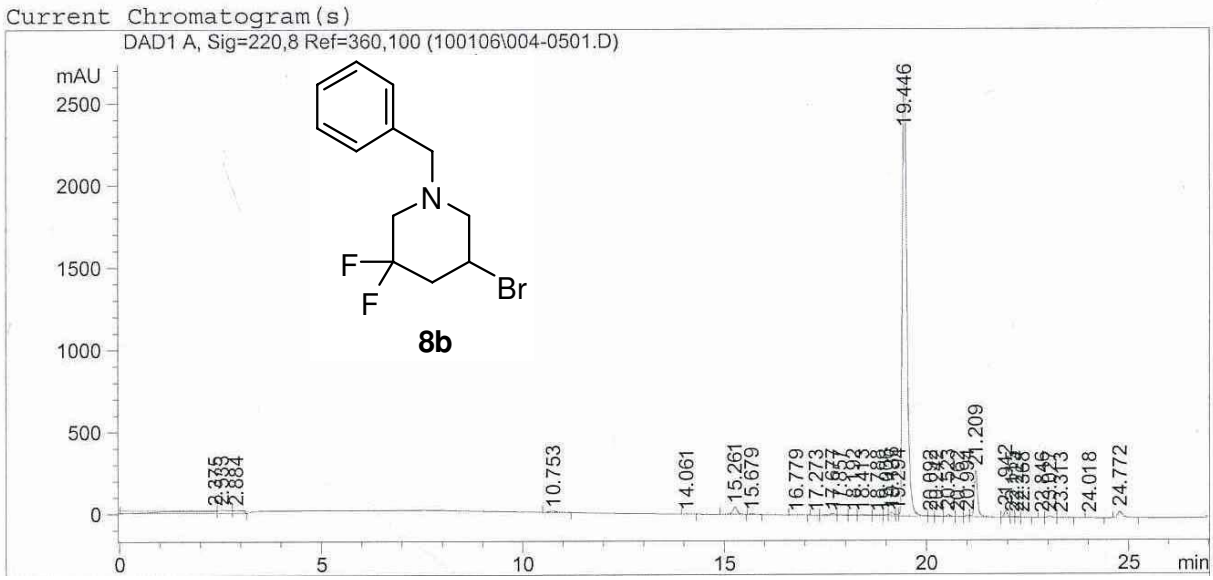
Signal 1: FID1 A,

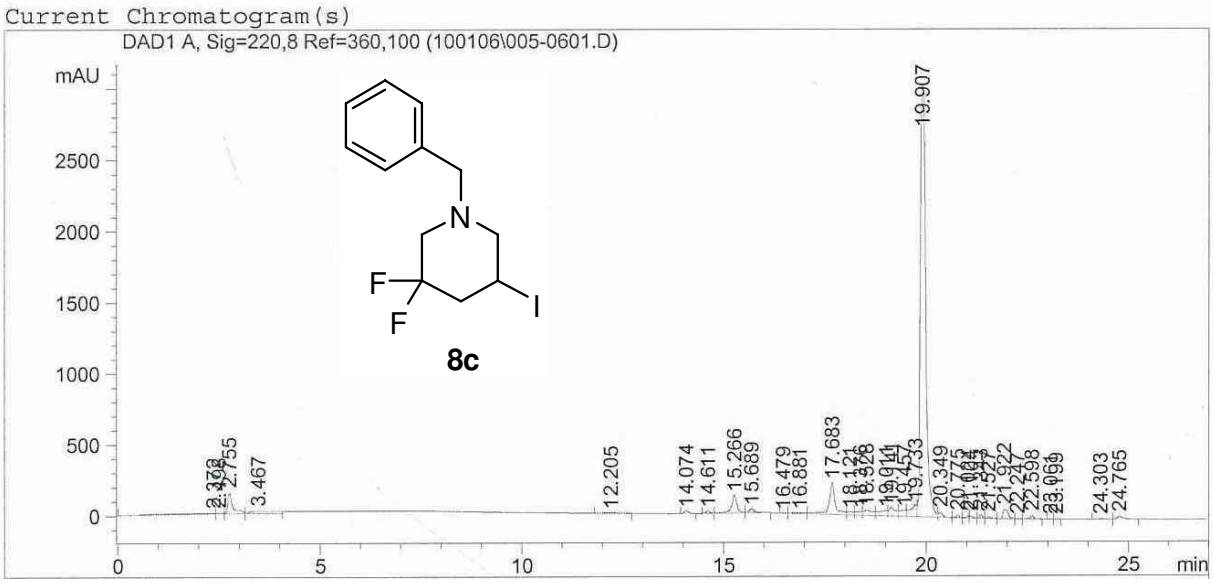
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	2.170	BV	0.0246	3.20740	2.01182	0.00252
2	2.229	VB S	0.0584	1.26566e5	3.18205e4	99.59959
3	2.514	BB X	0.0403	2.84648	9.69320e-1	0.00224
4	3.418	BB	0.0412	2.64014e-1	8.16496e-2	0.00021
5	9.957	BB	0.0585	8.53561e-1	1.98972e-1	0.00067
6	11.133	BV	0.0286	489.37607	270.10559	0.38511
7	11.207	VB	0.0320	10.76870	5.03246	0.00847
8	13.144	BB	0.0367	2.93374e-1	1.15331e-1	0.00023
9	15.404	BV	0.0674	1.20266	2.32111e-1	0.00095
Totals :				1.27074e5	3.20992e4	

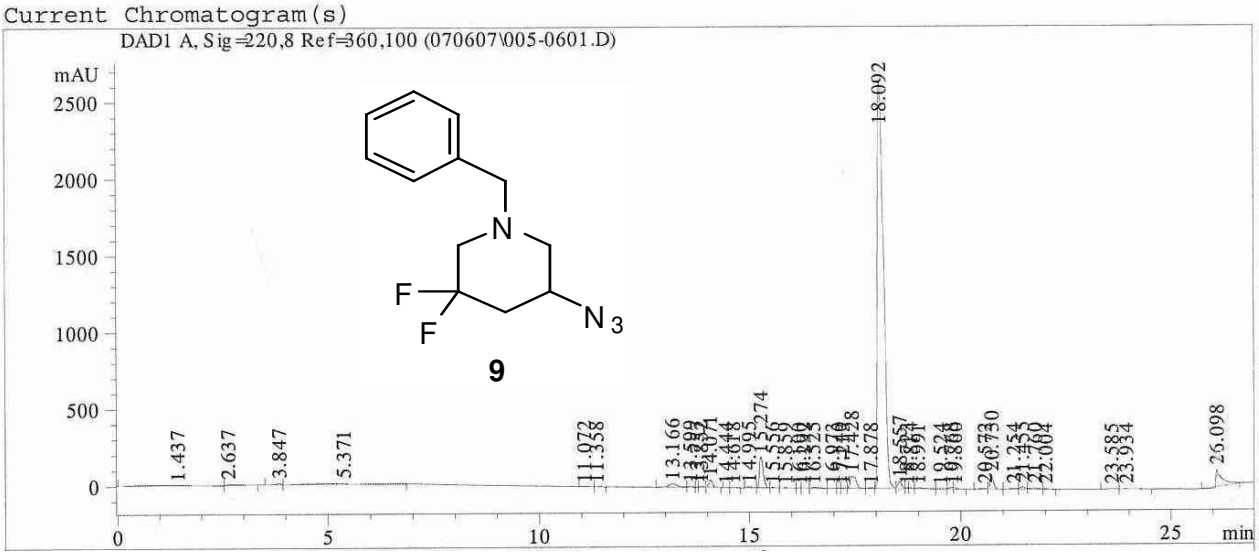

N
F
F
Br
8b
0.0000
2.3166
2.3258
2.3496
2.3734
2.3825
3.0638
3.1920
3.1956
3.2011
3.2341
3.6388
3.6626
4.0747
4.0893
4.1058
7.2959
7.3124
7.3326
(Millions)
X : parts per Million : 1H

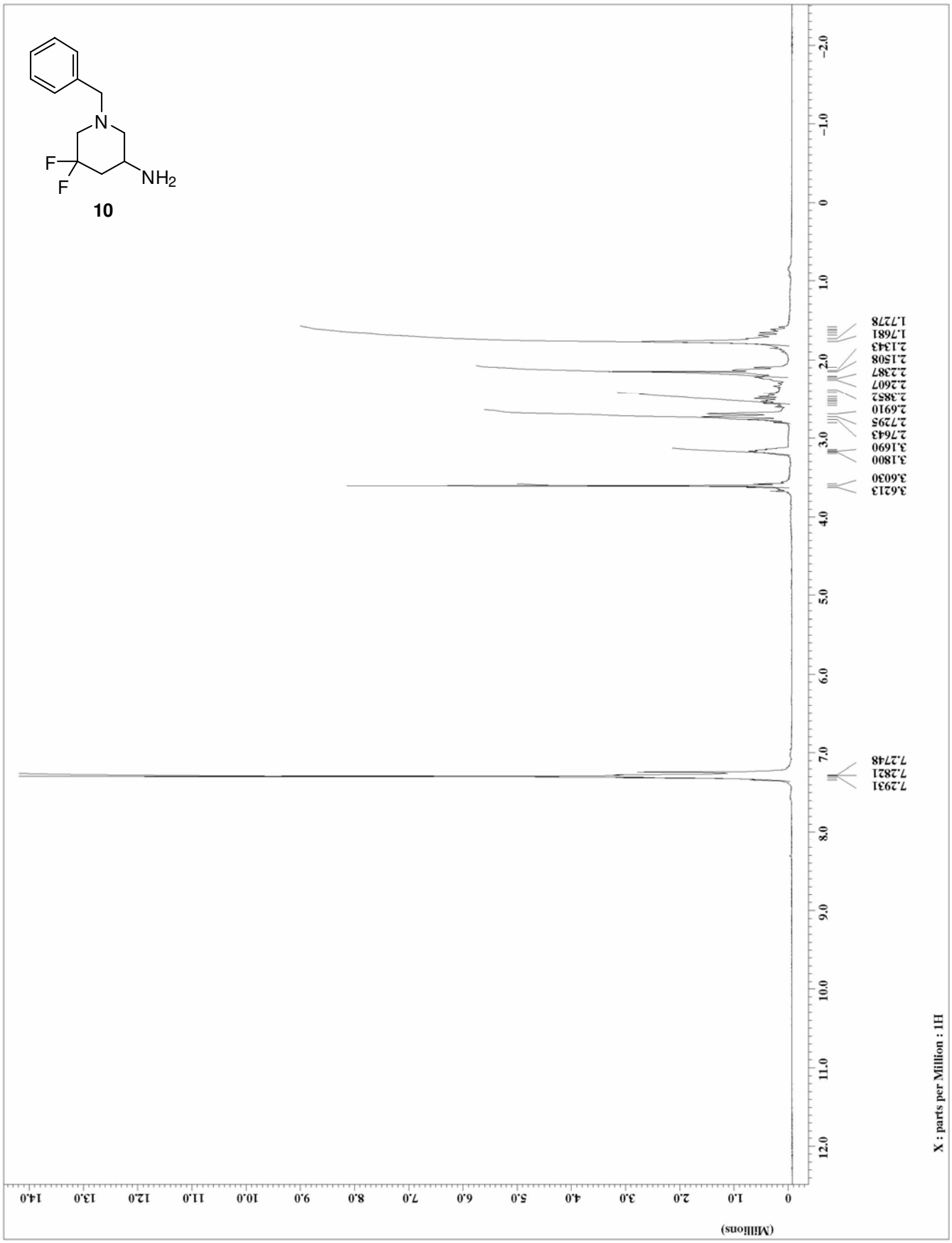

N
F
F
I
8c
0.0000
2.4466
2.4833
2.5217
2.5254
2.7946
2.8001
3.1096
3.2194
3.5820
3.6260
3.6736
4.1113
4.1516
4.1900
7.2703
7.2941
7.3124
7.3326
(Millions)
X : parts per Million : 1H

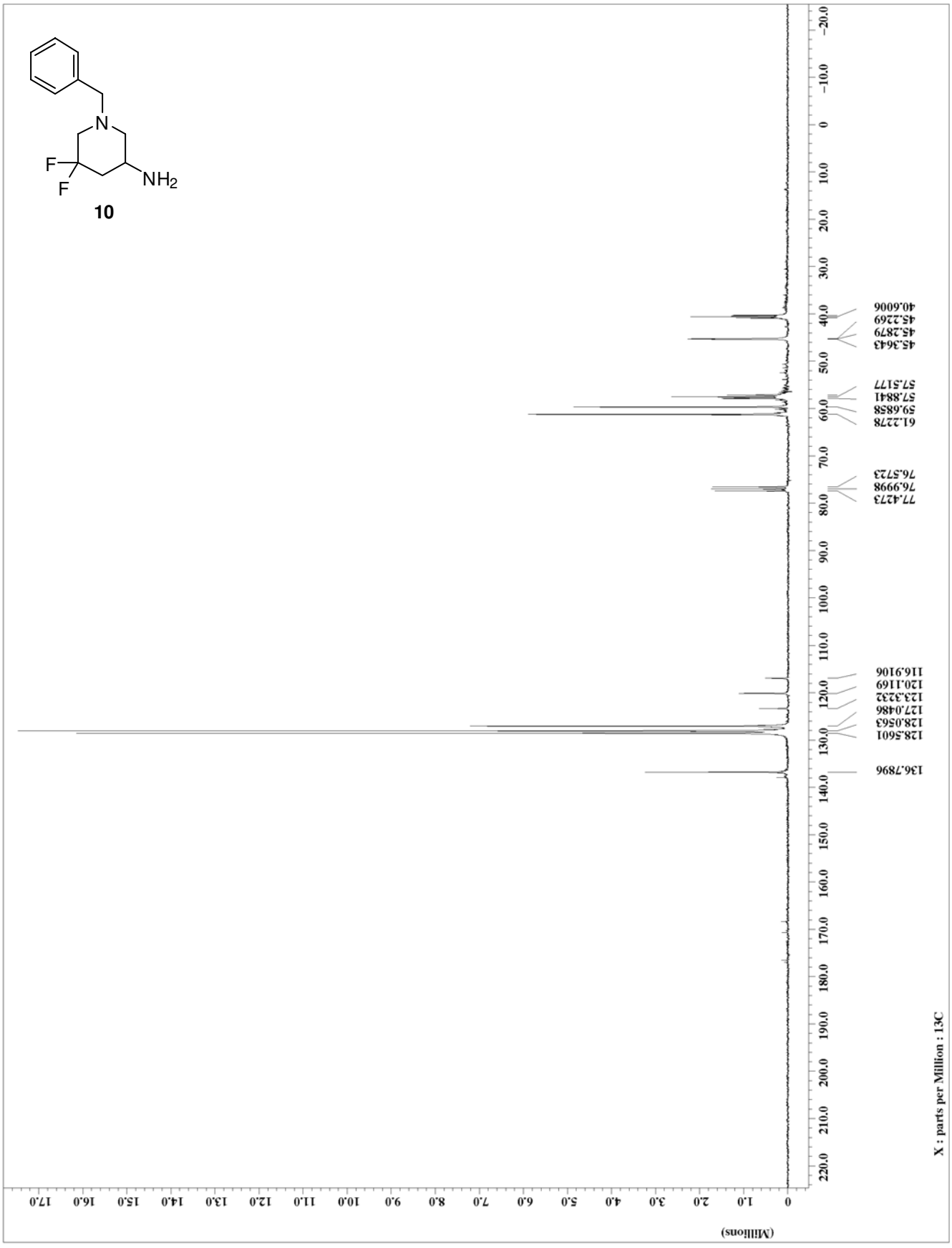

N
F
F
N3
9
0.0000
1.7306
1.7672
1.8112
2.1554
2.3679
2.3770
2.3990
2.9301
2.9338
2.9631
3.6242
3.6333
3.6791
7.2648
7.2941
7.3051
7.3216
X : parts per Million : 1H
(Millions)


Current Chromatogram(s)
DAD1 A, Sig=220,8 Ref=360,100 (100106\004-0501.D)
mAU
2500
2000
1500
1000
500
0
N
F
F
Br
8b
19.446
21.209
10.753
14.061
15.261
15.679
16.779
17.273
24.018
24.772
0
5
10
15
20
25
min

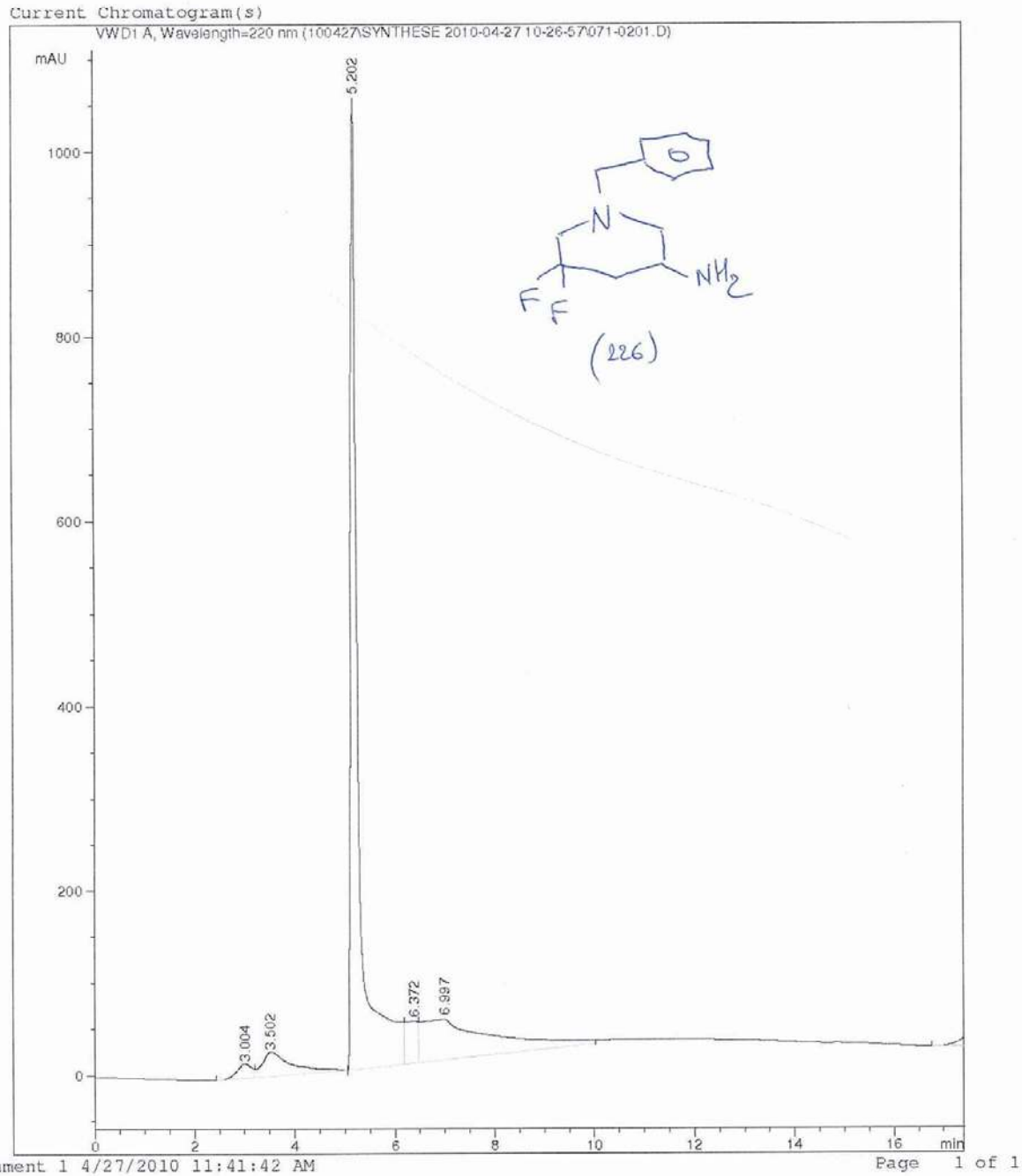

Current Chromatogram(s)
DAD1 A, Sig=220,8 Ref=360,100 (100106\005-0601.D)
mAU
2500
2000
1500
1000
500
0
N
F
F
I
8c
19.907
12.205
14.074
14.611
15.266
15.689
16.479
16.881
17.683
24.303
24.765
0
5
10
15
20
25
min

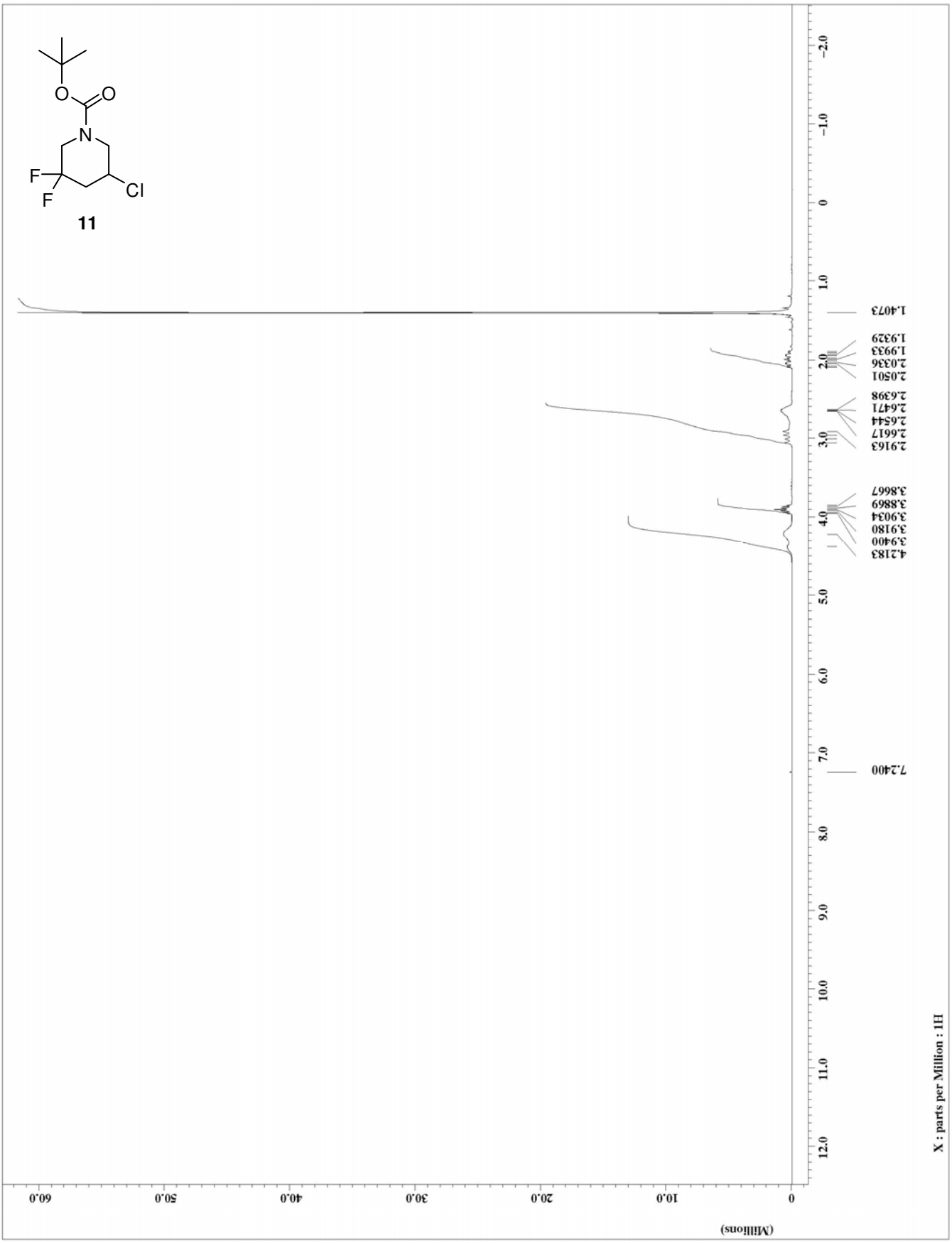

Current Chromatogram(s)
DAD1 A, Sig=220,8 Ref=360,100 (070607\005-0601.D)
mAU
2500
2000
1500
1000
500
0
N
F
F
N3
9
18.092
1.437
2.637
3.847
5.371
11.358
17.878
23.585
23.934
26.098
0
5
10
15
20
25
min


N
F
F
NH2
10
7.2931
7.2821
7.2748
3.6213
3.6030
3.1800
3.1690
2.7643
2.7295
2.6910
2.3852
2.2607
2.2387
2.1508
2.1343
1.7681
1.7278
(Millions)
X : parts per Million : 1H


F
F
N
NH2
10
136.7896
128.5601
128.0563
127.0486
123.3232
120.1169
116.9106
77.4273
76.9998
76.5723
61.2278
59.6858
57.8841
57.5177
45.3643
45.2879
45.2269
40.6006
X : parts per Million : 13C
(Millions)

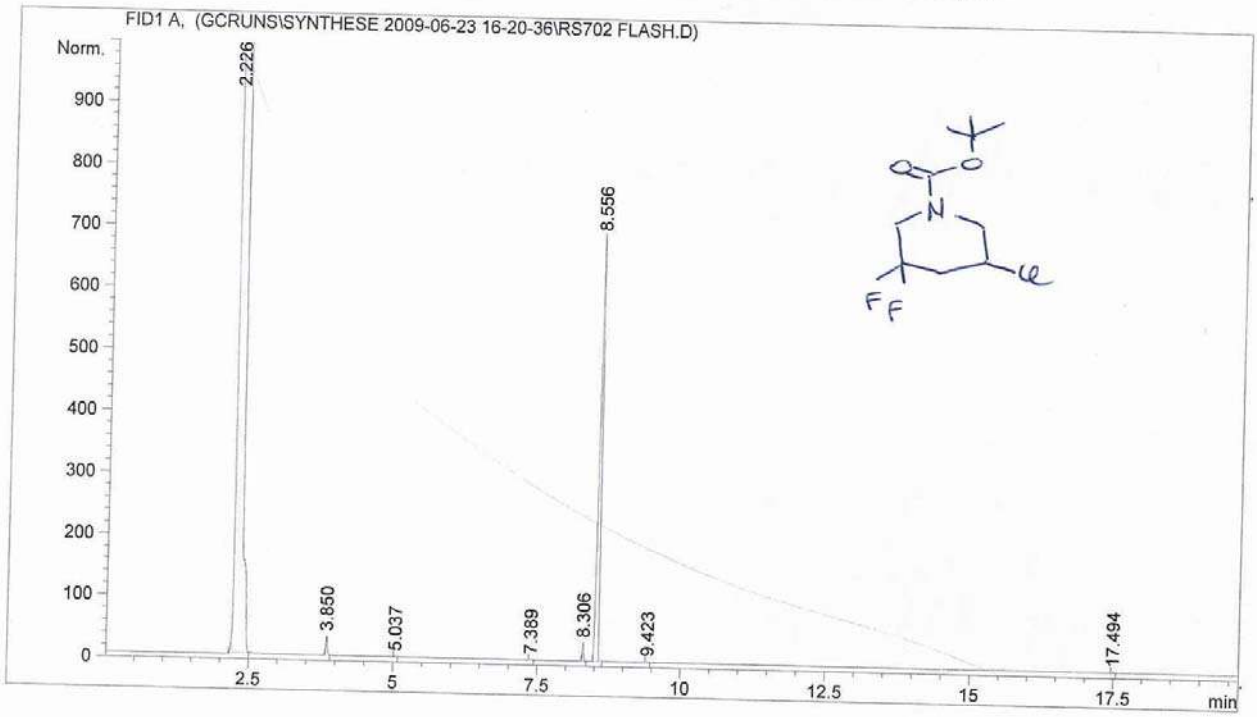
```
Print of window 38: Current Chromatogram(s)
Data File  : C:\CHEM32\1\DATA\100427\SYNTHESE 2010-04-27 10-26-57\071-0201.D
Sample Name : RSNH2
==================================================================
Acq. Operator   :                              Seq. Line :   2
Acq. Instrument : Instrument 1                  Location : Vial 71
Injection Date  : 4/27/2010 10:58:22 AM             Inj :   1
                                               Inj Volume : 20 µl
Acq. Method     : C:\Chem32\1\DATA\100427\SYNTHESE 2010-04-27 10-26-57\SYNTHESE-ALGEMEEN.M
Last changed    : 4/22/2010 4:57:52 PM
Analysis Method : C:\CHEM32\1\DATA\100427\SYNTHESE 2010-04-27 10-26-57\071-0201.D\DA.M (
                  SYNTHESE-ALGEMEEN.M)
Last changed    : 4/27/2010 11:28:35 AM
Method Info     : Methode algemeen synthese
```




O
O
N
F
F
Cl
11
1.4073
1.9329
1.9933
2.0336
2.0501
2.6398
2.6471
2.6544
2.6617
2.9163
3.8667
3.8869
3.9034
3.9180
3.9400
4.2183
7.2400
X : parts per Million : 1H
(Millions)

Data File C:\CHEM32\1\DATA\GCRUNS\SYNTHESE 2009-06-23 16-20-36\RS702 FLASH.D
Sample Name: RS702 flash

Acq. Operator	: FC
Acq. Instrument	: GC 6890A
Injection Date	: 23-Jun-09, 17:40:42
Seq. Line	: 3
Location	: Vial 1
Inj	: 1
Inj Volume	: 1 µl
Acq. Method	: C:\Chem32\1\DATA\GCRUNS\SYNTHESE 2009-06-23 16-20-36\SYNTS2.M
Last changed	: 4/21/2009 10:10:46 AM by FC
Analysis Method	: C:\CHEM32\1\METHODS\CYD190M.M
Last changed	: 6/23/2009 9:08:19 AM by FC (modified after loading)
Method Info	: METHODE VOOR scheiding stalen op chirale kolom CYDEX B



Area Percent Report

Sorted By	:	Signal
Calib. Data Modified	:	5/10/00 6:28:37 PM
Multiplier	:	1.0000
Dilution	:	1.0000

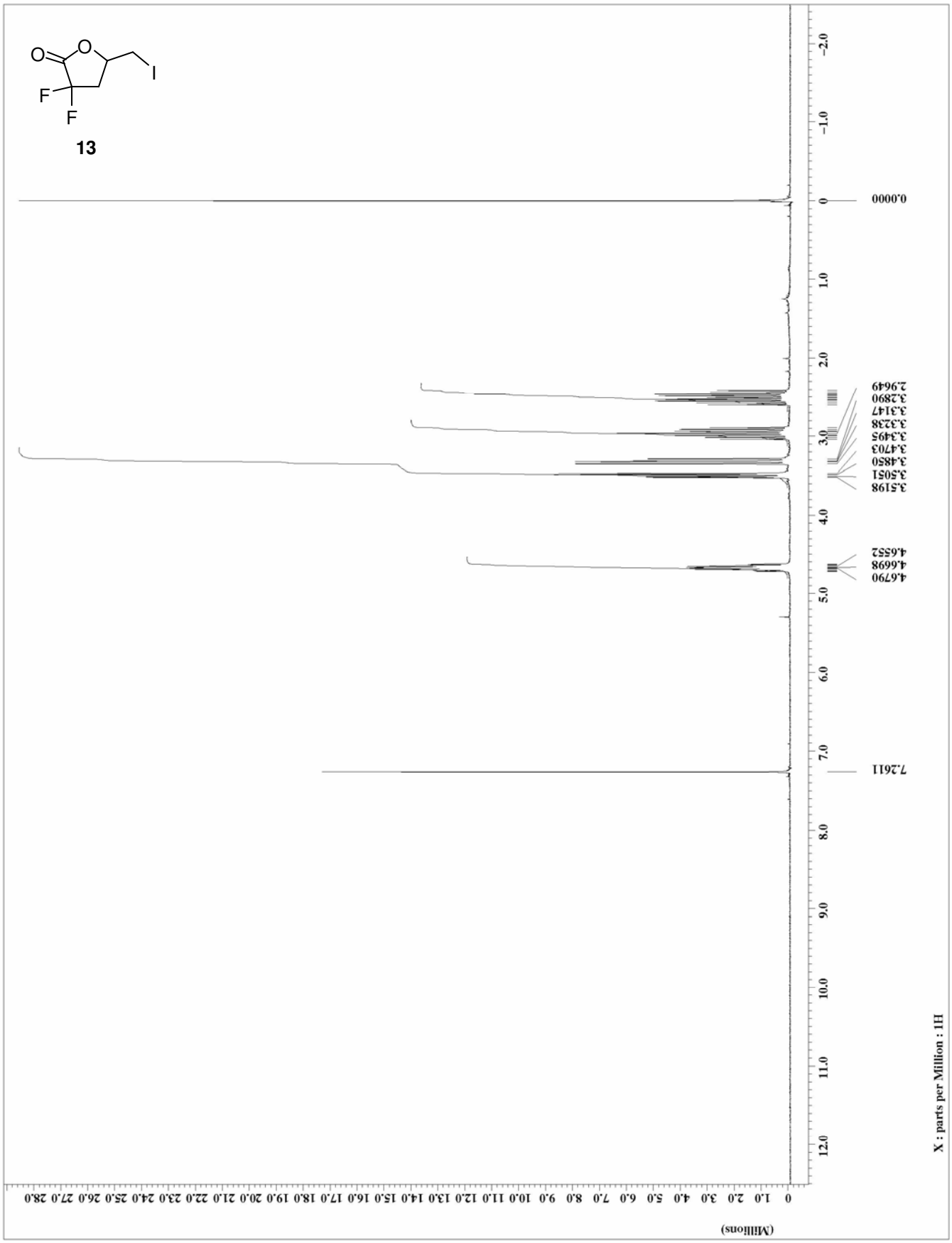
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

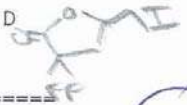
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Area %	Name
1	2.226	BB S	0.0650	1.33652e5	98.55521	?
2	3.850	BB	0.0273	56.12193	0.04138	?
3	5.037	BB	0.0251	2.25967	0.00167	?
4	7.389	BB	0.0262	2.07265	0.00153	?
5	8.306	BB	0.0273	51.54955	0.03801	?
6	8.556	BB	0.0362	1841.76550	1.35812	?
7	9.423	BB	0.0273	2.55805	0.00189	?
8	17.494	BB	0.0280	2.96302	0.00218	?

GC 6890A 6/24/2009 10:44:52 AM FC

Page 1 of 2

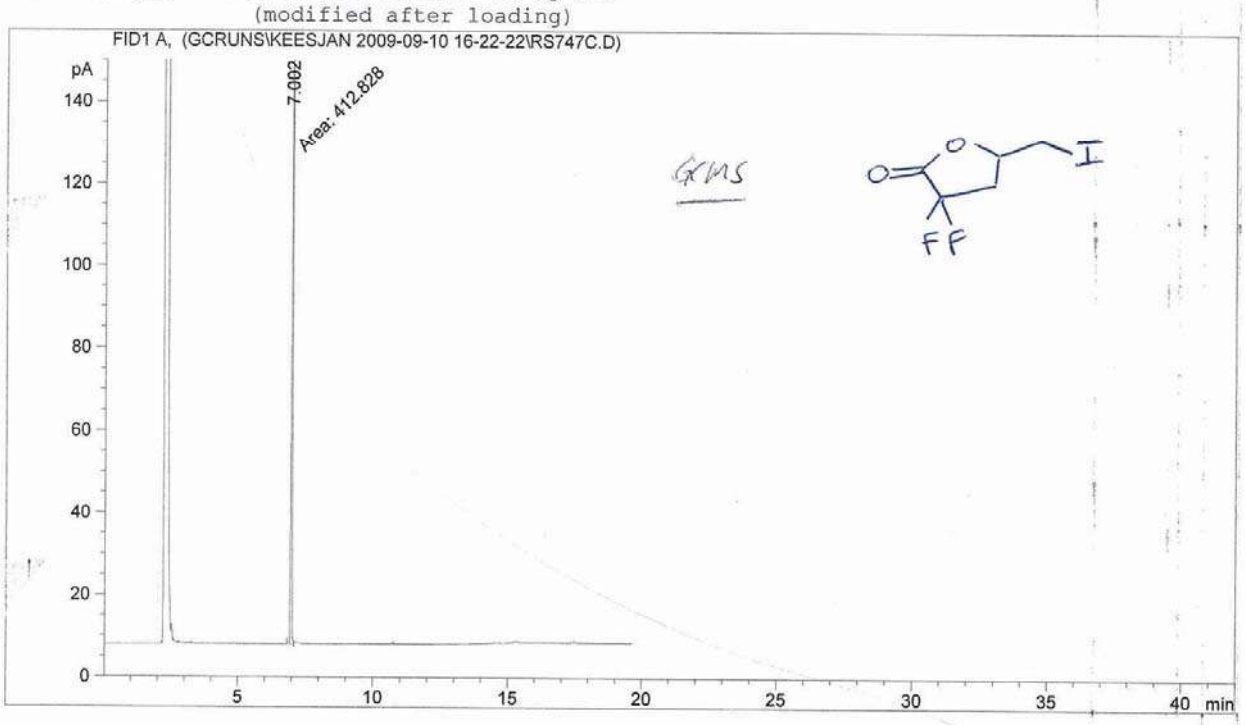

O
O
I
F
F
13
0.0000
2.9649
3.2890
3.3147
3.3238
3.3495
3.4703
3.4850
3.5051
3.5198
4.6552
4.6698
4.6790
7.2611
(Millions)
X : parts per Million : 1H

Data File C:\CHEM32\1\DATA\GCRUNS\KEESJAN 2009-09-10 16-22-22\RS747C.D
Sample Name: RS747c



(13)

Acq. Operator : vvh
Seq. Line : 2
Acq. Instrument : GC 6890A
Location : Vial 5
Injection Date : 10-Sep-09, 17:01:55
Inj : 1
Inj Volume : 1 µl
Acq. Method : C:\Chem32\1\DATA\GCRUNS\KEESJAN 2009-09-10 16-22-22\SYNTS2.M
Last changed : 4/21/2009 10:10:46 AM by FC
Analysis Method : C:\CHEM32\1\METHODS\STERVVII.M
Last changed : 9/10/2009 5:26:04 PM by vvh
(modified after loading)



GCMS

Area Percent Report

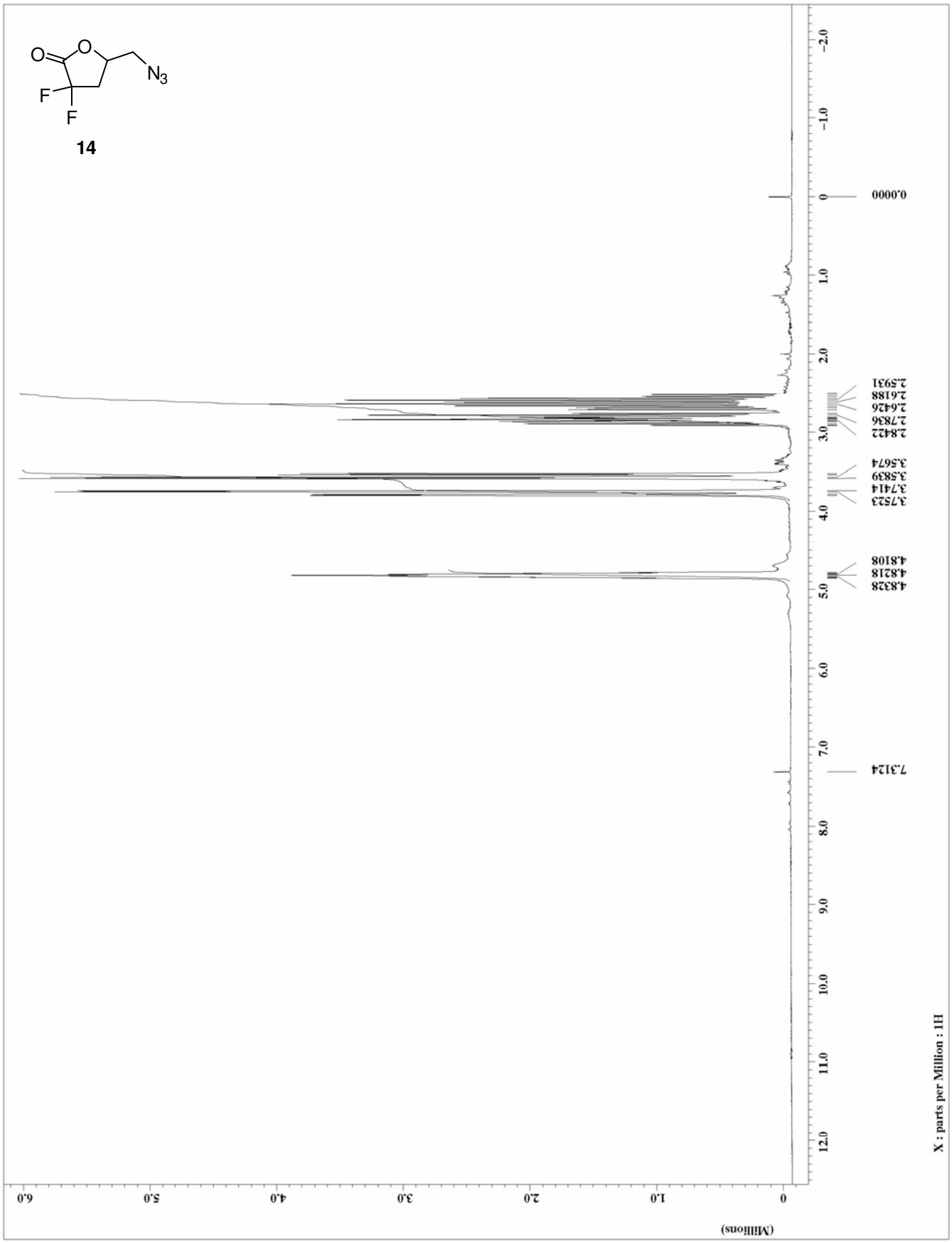
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

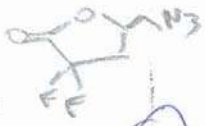
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.002	MM	0.0456	412.82843	150.84726	1.000e2
Totals :				412.82843	150.84726	

Summed Peaks Report

Signal 1: FID1 A,

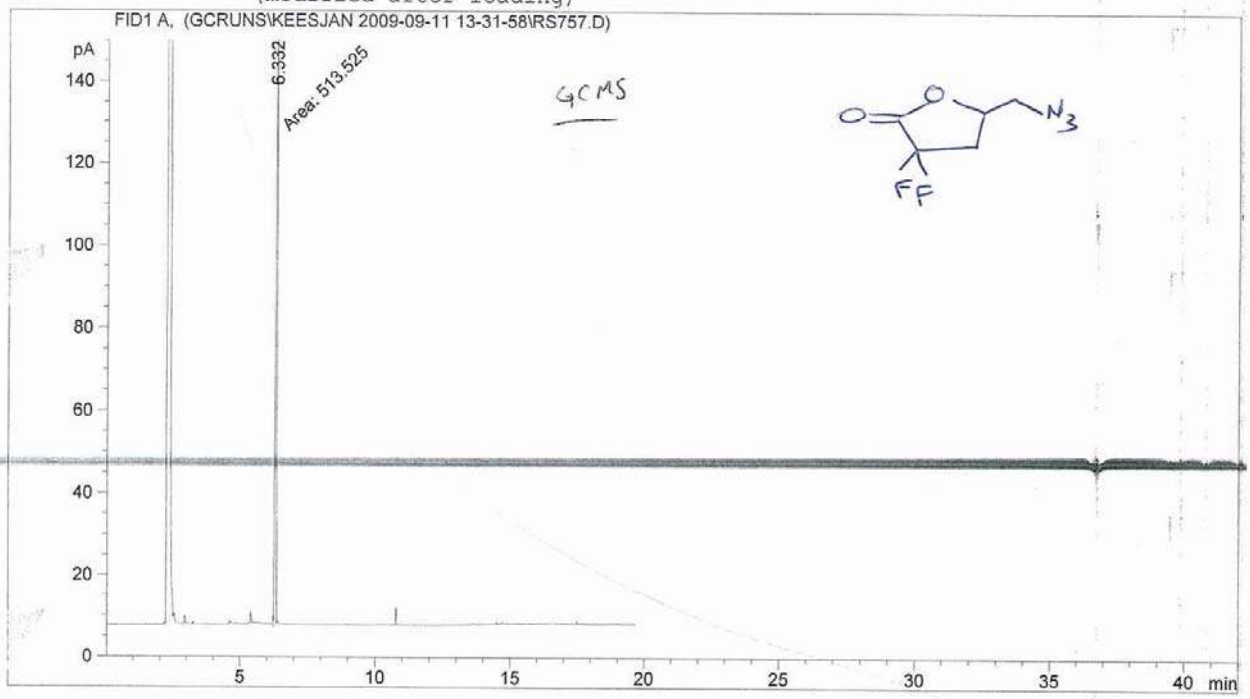

O
O
N3
F
F
14
0.0000
2.5931
2.6188
2.6426
2.7836
2.8422
3.5674
3.5839
3.7414
3.7523
4.8108
4.8218
4.8328
7.3124
X : parts per Million : 1H
(Millions)

Data File C:\CHEM32\1\DATA\GCRUNS\KEESJAN 2009-09-11 13-31-58\RS757.D
Sample Name: RS757



14

Acq. Operator : vvh
Seq. Line : 1
Acq. Instrument : GC 6890A
Location : Vial 4
Injection Date : 11-Sep-09, 13:43:11
Inj : 1
Inj Volume : 1 µl
Acq. Method : C:\Chem32\1\DATA\GCRUNS\KEESJAN 2009-09-11 13-31-58\SYNTS2.M
Last changed : 4/21/2009 10:10:46 AM by FC
Analysis Method : C:\CHEM32\1\METHODS\STERVVII.M
Last changed : 9/10/2009 5:26:04 PM by vvh
(modified after loading)



GCMS

Area Percent Report

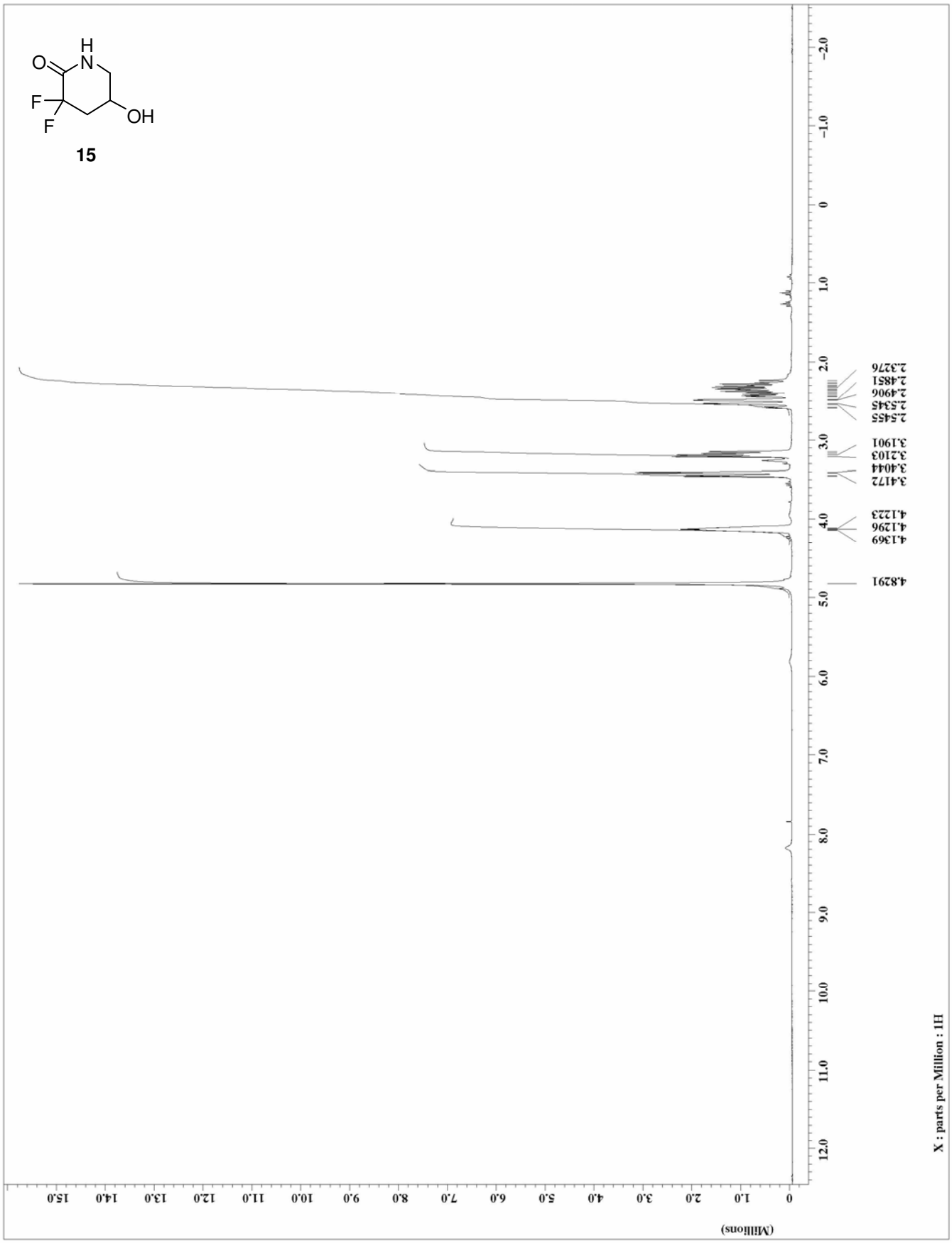
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

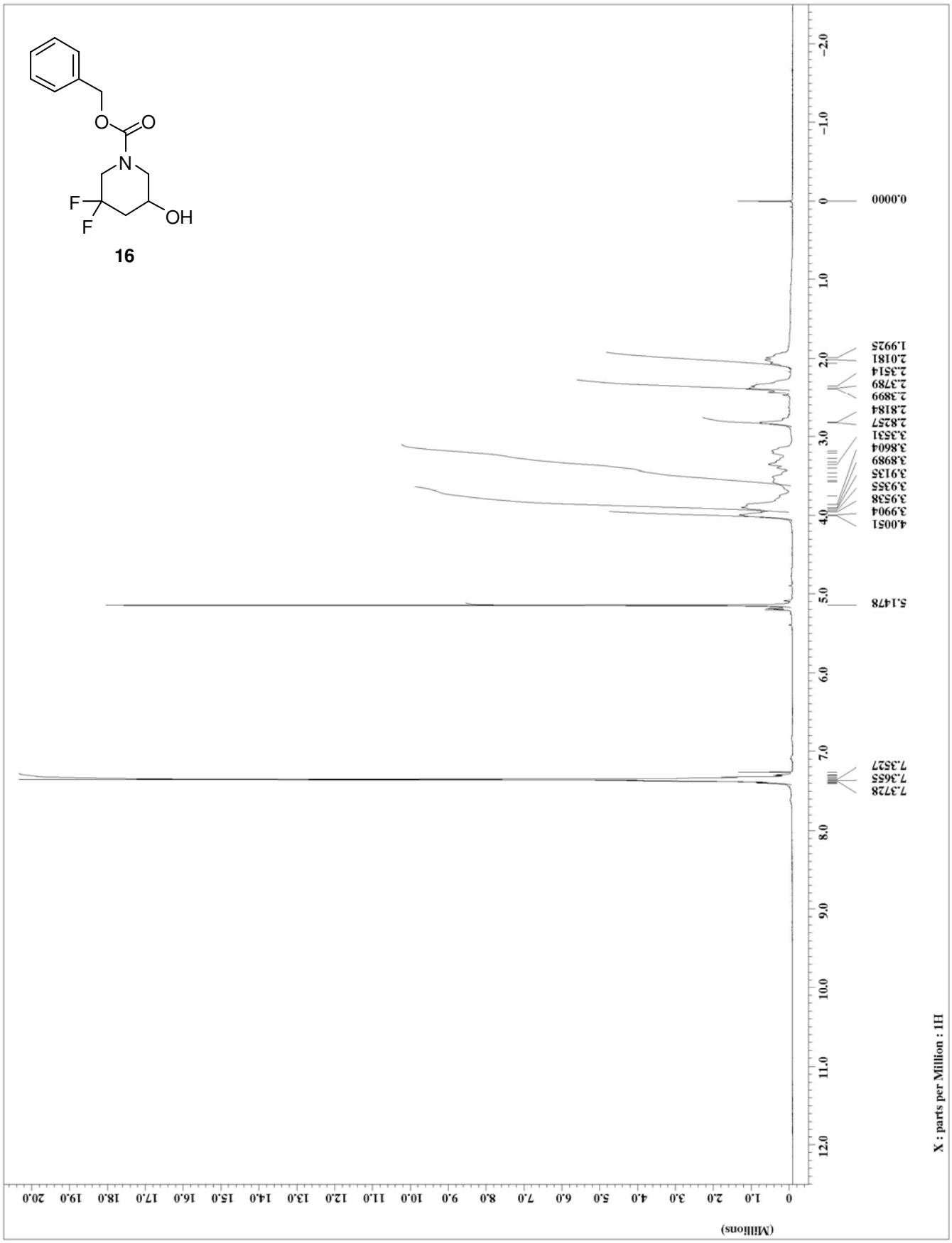
Signal 1: FID1 A,

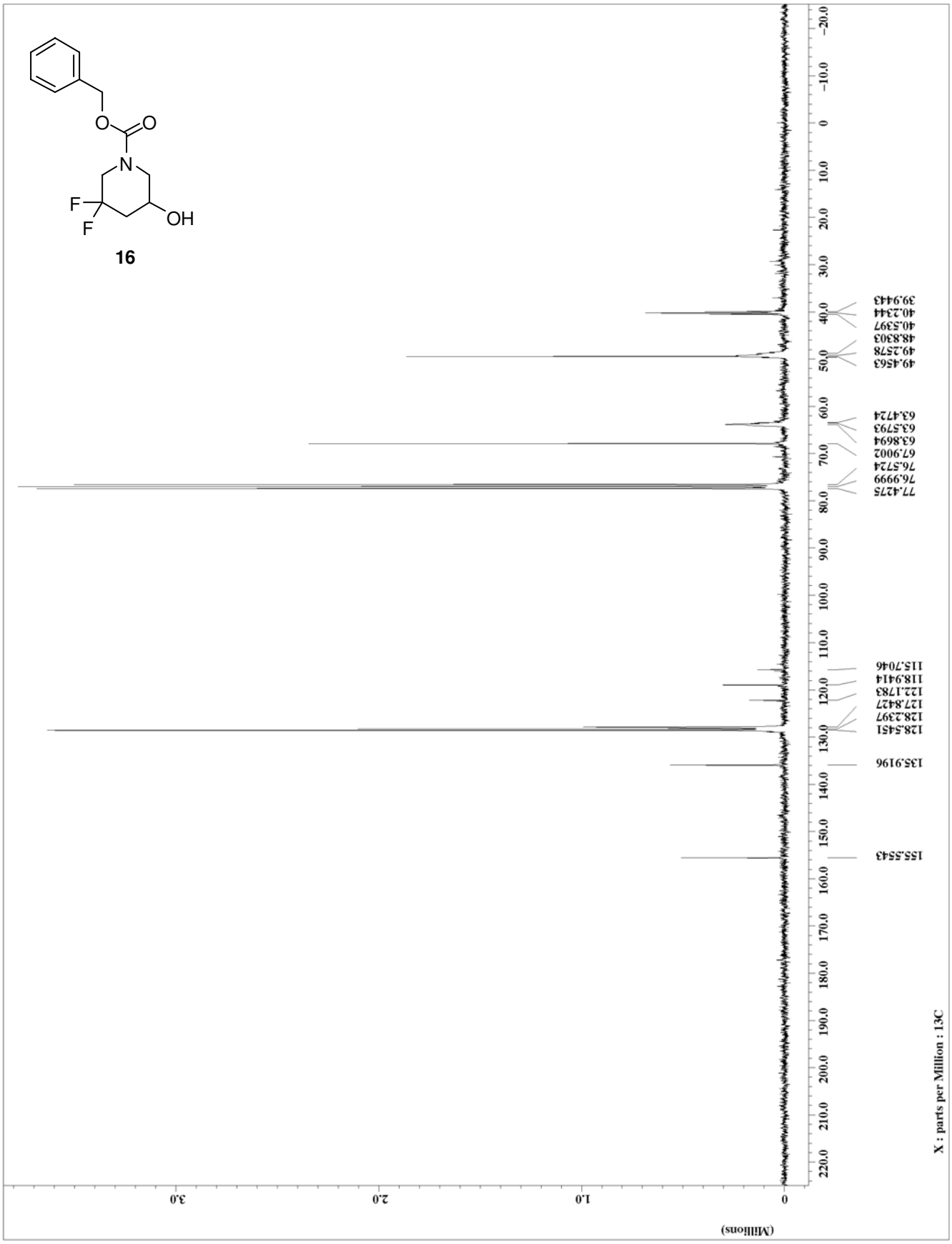
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.332	MM	0.0547	513.52527	156.34250	1.000e2
Totals :				513.52527	156.34250	

Summed Peaks Report

Signal 1: FID1 A,


H
O
N
F
F
OH
15
2.3276
2.4851
2.4906
2.5345
2.5455
3.1901
3.2103
3.4044
3.4172
4.1223
4.1296
4.1369
4.8291
X : parts per Million : 1H
(Millions)

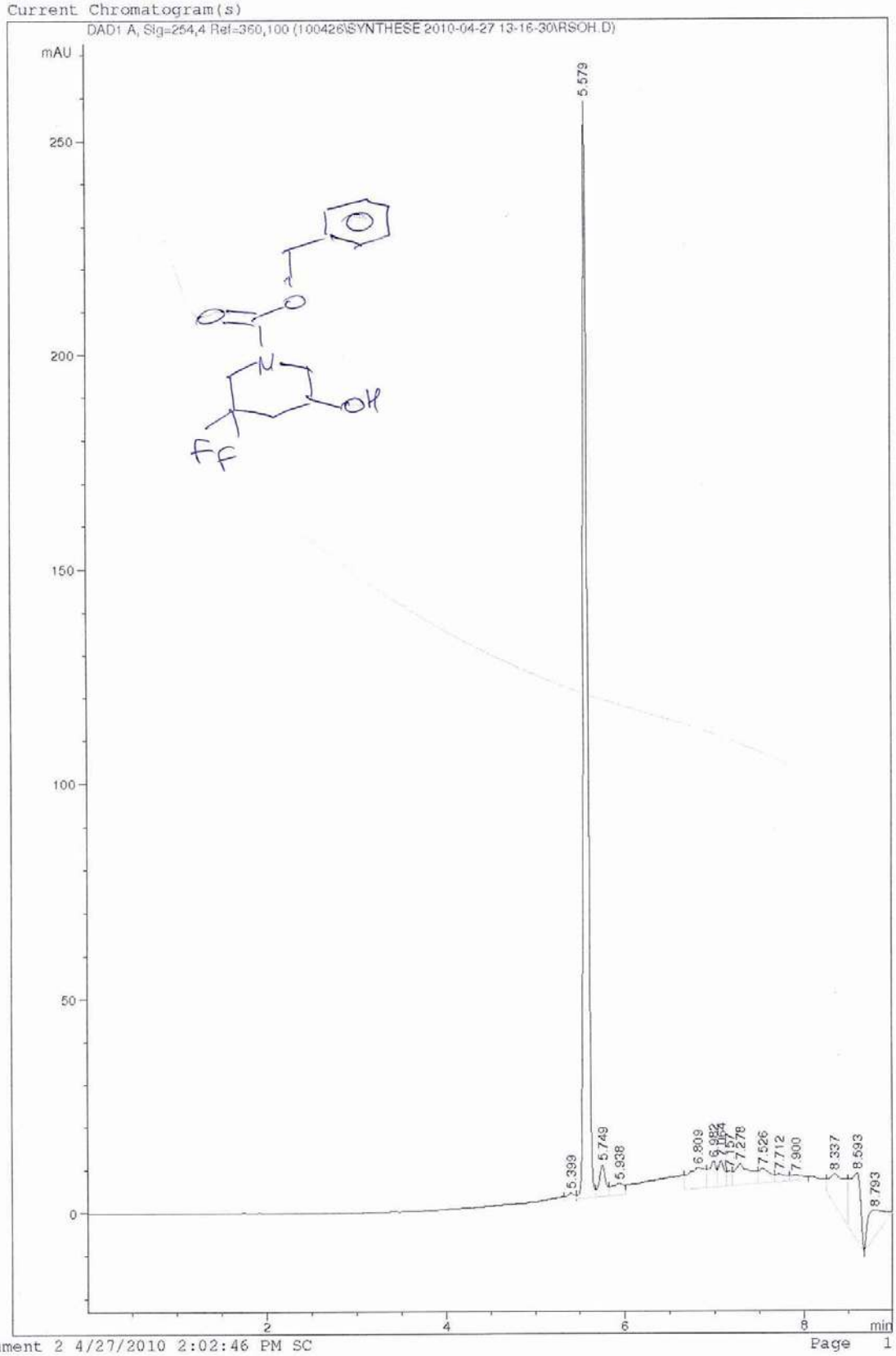

O
O
N
F
F
OH
16
0.0000
1.9925
2.0181
2.3514
2.3789
2.3899
2.8184
2.8257
3.3531
3.8604
3.8989
3.9135
3.9355
3.9538
3.9904
4.0051
5.1478
7.3528
7.3655
7.3527
(Millions)
X : parts per Million : 1H


O
O
N
F
F
OH
16
39.9443
40.2344
40.5397
48.8303
49.2578
49.4563
63.4724
63.5793
63.8694
67.9002
76.5724
76.9999
77.4275
115.7046
118.9414
122.1783
127.8427
128.2397
128.5451
135.9196
155.5543
X : parts per Million : 13C
(Millions)

Print of window 38: Current Chromatogram(s)

16

Current Chromatogram(s)



Instrument 2 4/27/2010 2:02:46 PM SC

Page 1 of 1

[i] Kendrick, D. A.; Danzin, C.; Kolb, M. *J. Med. Chem.* **1989**, *32*, 170.