Supporting Information

^{18}F-Labelling of Nitrogen-containing Aryl Boronates – Anti-cancer Drug Melflufen as a Case Study

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Table of Contents

1. General Information

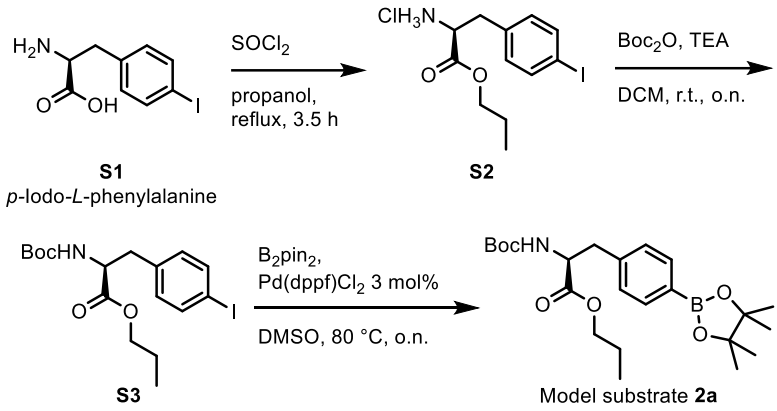
Reagents were purchased from commercial suppliers and used without further purification, unless otherwise stated. Solvents were purchased from commercial suppliers and dried through a Vacuum Atmospheres Solvent Purifier system. Radiofluorinations were carried out in dry conical glass vials. For all radiofluorinations solvents, such as dry DMF and dry MeCN were purchased from commercial suppliers and stored in an N_2-filled glovebox. For column chromatography silica gel (40-63 µm) from VWR Chemicals was used. TLC was performed with a suitable solvent system on aluminium sheets 60 F254 pre-coated with silica gel from Merck KGaA. UV active components were visualized by UV fluorescence using a UV-lamp (254 nm).

^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded by a spectrometer of the type DPX-400 (400 MHz) by Bruker. The spectra were recorded in $CDCl_3$ (internal standard: 7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C), DMSO-d_6 (internal standard: 2.50 ppm, ^{1}H; 39.52 ppm, ^{13}C) or CD_3OD (internal standard: 3.31 ppm, ^{1}H; 49.00 ppm, ^{13}C). ^{1}H-NMR spectra are represented as follows: chemical shift δ in ppm (s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, sext = sextet, m = multiplet), coupling constant J in Hz and integrals. ^{13}C-NMR spectra are represented as follows: chemical shift δ in ppm. High resolution mass data (HRMS) were obtained by using a MicrOTOF® by Bruker with Electron Spray Ionisation (ESI) technique. Specific optical rotation α was measured with an Autopol IV® polarimeter by Rudolph Reasearch Analytical (l = 1 dm). The unit of α is °·ml·(g·dm)$^{-1}$ and the unit of the concentration (c) is g/100 ml. The general information of the radiochemical studies can be found in section 5.1.

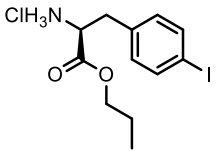
2. Synthesis and Characterisation of Pinacol Boronates

2.1. Synthesis of Model Substrate 2a

The model substrate for the benchmark reaction was synthesised from **S1** according to the scheme below.



Propyl-(*S*)-2-amino-3-(4-iodophenyl)propanoate hydrochloride **S2**



S2

Thionyl chloride (300 µl, 4.1 mmol, 1.5 equiv.) was added dropwise to a stirred, ice-cold suspension of (*S*)-Iodo-phenylalanine (**S1**) (800.0 mg, 2.8 mmol, 1.0 equiv.) in absolute ^{n}propanol (12 ml). Afterwards the reaction mixture was heated at reflux for 3.5 h. After evaporation of the solvent the propylester **S2** could be obtained as a white solid (1.02 g, 2.8 mmol, quant.) without further purification.

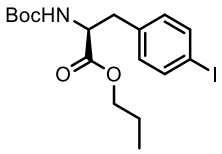
^{1}H-NMR (400 MHz, CD_3OD): δ = 7.73 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 4.30 (t, *J* = 7.0 Hz, 1H), 4.20-4.10 (m, 2H), 3.22-3.11 (m, 2H), 1.68-1.59 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR (101 MHz, CD_3OD): δ = 170.0, 139.4, 135.2, 132.5, 94.1, 69.2, 54.9, 37.1, 22.8, 10.5.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{12}H_{16}INO_2Na^+$: 356.0118, found: 356.0114.

$[\alpha]_{589}^{26}$:+57.20 (*c* = 0.25, $CHCl_3$).

Propyl-(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate **S3**



S3

Boc-anhydride (367 µl, 1.6 mmol, 1.2 equiv.) and triethylamine (560 µl, 4.1 mmol, 3.0 equiv.) were added to a solution of hydrochloride salt **S2** (500.0 mg, 1.5 mmol, 1.0 equiv.) in DCM (2.7 ml, 0.5 M) at r.t. The reaction mixture was stirred for 16 h at r.t. and concentrated under reduced pressure. The product was purified by silica-gel chromatography (^{n}pentane:EtOAc = 9:1) yielding Boc-protected amine **S3** as a viscous oil (570.0 mg, 1.3 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 4.98 (d, *J* = 8.0 Hz, 1H), 4.57-4.52 (m, 1H), 4.10-4.00 (m, 2H), 3.09-2.96 (m, 2H), 1.62 (sext, *J* = 7.2 Hz, 2H), 1.41 (s, 9H), 0.90 (t, *J* = 7.5 Hz, 3H).

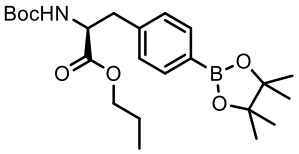
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.8, 155.1, 137.7, 136.0, 131.5, 92.6, 80.1, 67.2, 54.4, 38.1, 28.4, 22.0, 10.5.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{17}H_{24}INO_4Na^+$: 456.0642, found: 456.0642.

$[\alpha]_{589}^{28}$:+33.2 (*c* = 0.25, $CHCl_3$).

Melting point: 99.0-99.6 °C.

Propyl-(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) propanoate - Model Substrate **2a**



Model substrate **2a**

Synthesis of **2a** from **S3** is based on the procedure by Weil and co-workers.[1] A round bottom flask was charged with iodoarene **S3** (300.0 mg, 0.7 mmol, 1.0 equiv.), $Pd(dppf)Cl_2$ (15.2 mg, 0.02 mmol, 0.03 equiv.), B_2pin_2 (229.0 mg, 0.9 mmol, 1.3 equiv.) and KOAc (204.0 mg, 2.1 mmol, 3.0 equiv.) and degassed (N_2, 3x). After addition of dry degassed DMSO (7 ml) the solution was stirred at 80 °C for 18 h under N_2. Then, DCM and water were added to the black reaction mixture. After phase separation the water phase was extracted with DCM (x3). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (^{n}pentane:EtOAc = 9:1) yielded the desired pinacol boronate **2a** as a colourless viscous oil (218.0 mg, 0.5 mmol, 73 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 4.94 (d, *J* = 8.1 Hz, 1H), 4.59-4.55 (m, 1H), 4.05 (t, *J* = 6.7 Hz, 2H), 3.16-3.06 (m, 2H), 1.62 (sext, *J* = 7.1 Hz, 2H), 1.42 (s, 9H), 1.34 (s, 12H), 0.90 (t, *J* = 7.3 Hz, 3H).

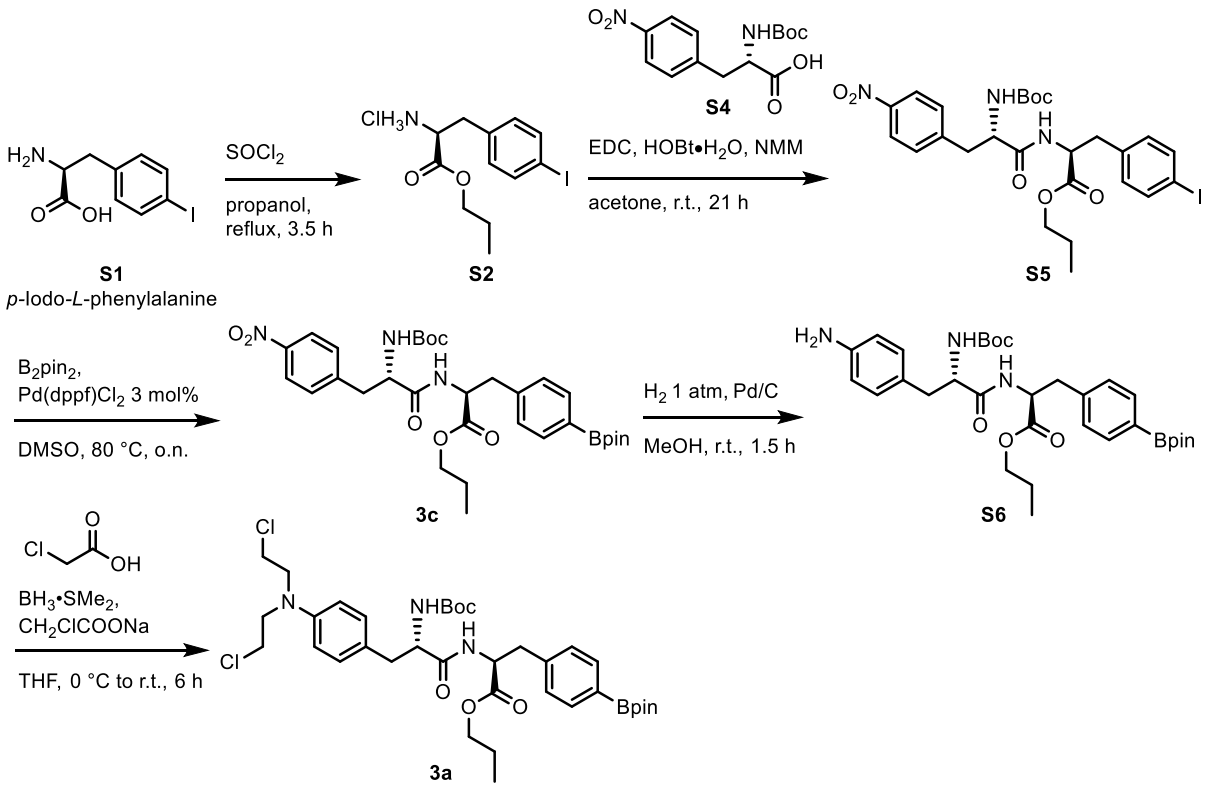
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.0, 155.2, 139.5, 135.1, 128.9, 83.9, 80.0, 67.1, 54.5, 38.6, 28.5, 25.0, 22.0, 10.5.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{23}H_{36}BNO_6Na^+$: 456.2532, found: 456.2550.

$[\alpha]_{589}^{28}$:+25.2 (*c* = 0.25, $CHCl_3$).

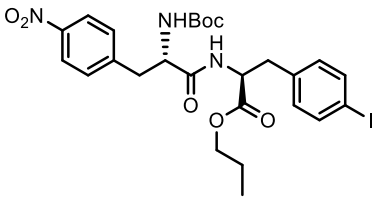
2.2. Synthesis of Propyl Melflufen Boronate Analogues 3

The melflufen pinacol boronate analogues **3** were synthesised according to the scheme shown down below. The synthesis of **S2** from **S1** is described in section 2.1.



2.2.1. Synthesis of Propyl Melflufen Boronate Analogue 3a and 3c

Propyl-(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-nitrophenyl)propanamido)-3-(4-iodophenyl) propanoate **S5**



S5

Synthesis of **S5** from **S2** is based on the procedure published by Wennerberg and co-workers.[2] To a round bottom flask charged with acetone (7 ml) was added *L*-Boc-4-nitrophenylalanine **S4** (600.0 mg, 1.9 mmol, 1.0 equiv.), N-methylmorpholine (920 µl, 6.8 mmol, 3.5 equiv.), hydrochloride salt **S2** (730.4 mg, 2.0 mmol, 1.02 equiv.), HOBt·H_2O (29.0 mg, 0.7 mmol, 0.1 equiv.), and EDC·HCl (370 µl, 2.1 mmol, 1.1 equiv.). The resulting suspension

was stirred at r.t. for 21 h. The solvent was removed under reduced pressure and replaced by EtOAc and water. Phases were allowed to separate after stirring for 5 min. The aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with $NaHCO_3$ solution (sat.), NH_4Cl solution (sat.), and brine. Purification by silica gel chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the dipeptide **S5** as a white solid (1050.0 mg, 1.7 mmol, 87%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 1H), 4.51-4.46 (m, 1H), 4.28-4.22 (m, 1H), 3.99-3.90 (m, 2H), 3.03-2.79 (m, 4H), 1.50 (sext, *J* = 7.1 Hz, 2H), 1.27 (s, 9H), 0.81 (t, *J* = 7.5 Hz, 3H).

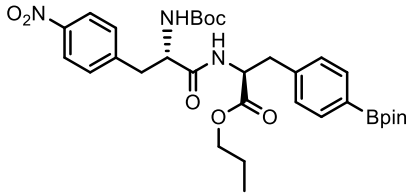
^{13}C-NMR (101 MHz, DMSO-d_6): δ = 171.3, 171.1, 155.1, 146.5, 146.2, 137.0, 136.8, 131.6, 130.5, 123.1, 92.5, 78.1, 66.1, 55.0, 53.3, 37.3, 36.1, 28.0, 21.4, 10.1.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{26}H_{32}IN_3O_7Na^+$: 648.1177, found: 648.1162.

$[\alpha]_{589}^{28}$:+14.8 (*c* = 0.25, $CHCl_3$).

Melting point: 169.0-171.0 °C.

Propyl-(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-nitrophenyl)propanamido)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate **3c**



3c

Synthesis of **3c** from **S5** is based on the procedure published by Weil and co-workers.[1] A round bottom flask was stocked with Iodoarene **S5** (1050.0 mg, 1.0 mmol, 1.0 equiv.), $Pd(dppf)Cl_2$ (36.9 mg, 0.05 mmol, 0.03 equiv.), B_2pin_2 (554.2 mg, 2.2 mmol, 1.3 equiv.) and KOAc (494.3 mg, 5.0 mmol, 3.0 equiv.) and degassed (N_2, 3x). After addition of dry degassed DMSO (17 ml) the solution was stirred at 80 °C for 18 h under one atmosphere of N_2. Then, DCM and water were added to the black reaction mixture. After phase separation the water phase was extracted with DCM (3x). The combined organic phases were dried through Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography (^{n}pentane:EtOAc = 4:1) yielded the desired pinacol boronate **3c** as a white solid (862.0 mg, 1.4 mmol, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 7.5 Hz, 2H), 6.28 (d, *J* = 7.6 Hz, 1H), 4.92 (s, 1H), 4.81-4.76 (m, 1H), 4.36 (m_c, 1H), 4.09-3.98 (m, 2H), 3.23-3.05 (m, 4H), 1.62 (sext, *J* = 7.2 Hz, 2H), 1.39 (s, 9H), 1.33 (s, 12H), 0.90 (t, *J* = 7.3 Hz, 3H).

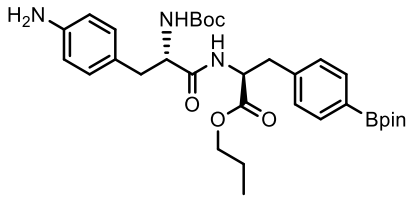
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.0, 170.1, 155.3, 147.2, 144.5, 138.8, 135.2, 131.0, 130.4, 128.8, 123.9, 84.0, 80.8, 67.5, 55.3, 53.3, 38.3, 38.2, 28.4, 25.0, 22.0, 10.4.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{32}H_{44}BN_3O_9Na^+$: 648.3068, found: 648.3095.

$[\alpha]_{589}^{28}$:+13.2 (*c* = 0.25, $CHCl_3$).

Melting point: 154.5-157.8 °C.

Propyl-(*S*)-2-((*S*)-3-(4-aminophenyl)-2-((*tert*-butoxycarbonyl)amino)propanamido)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate **S6**



S6

Synthesis of **S6** from **3c** is based on the procedure by Wennerberg and co-workers.[2] A round bottom flask containing a solution of nitro compound **3c** (850.0 mg, 1.4 mmol, 1.0 equiv.), and Pd/C (10% Pd loaded on C, 55% moist; 165.5 mg, 0.07 mmol, 5 mol%) in MeOH (27 ml) was equipped with a H_2 balloon. The reaction mixture was stirred for 1.5 h at r.t. while H_2 passed through it. Then, the suspension was filtered through a plug of Celite®. Removal of the solvent yielded the amine **S6** without further purification as a white solid (805.0 mg, 1.4 mmol, quant.).

^{1}H-NMR (400 MHz, DMSO-d_6): δ =8.20 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.5 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 6.67(d, J = 8.8 Hz, 1H), 6.43 (d, J = 8.20 Hz, 2H), 4.83 (s, 2H), 4.51-4.46 (m, 1H), 4.06-4.02 (m, 1H), 3.99-3.91 (m, 2H), 3.04 (dd, J = 13.8, 6.0 Hz, 1H), 2.97(dd, J = 13.8, 8.2 Hz, 1H), 2.70 (dd, J = 14.0, 4.1 Hz, 1H), 2.52-2.50 (m, 1H), 1.50 (sext, J = 7.0 Hz, 2H), 1.30 (s, 9H), 1.27 (s, 12H), 0.81 (t, J = 7.5 Hz, 3H).

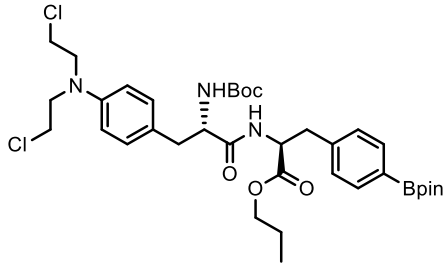
^{13}C-NMR (101 MHz, DMSO-d_6): δ = 172.0, 171.2, 155.0, 146.8, 140.5, 134.4, 129.5, 128.7, 124.8, 113.6, 83.5, 77.9, 66.0, 55.9, 53.3, 36.9, 36.6, 28.1, 24.6, 21.4, 10.2.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{32}H_{46}BN_3O_7Na^+$: 618.3327, found: 618.3341.

$[\alpha]_{589}^{28}$:+28.4 (c = 0.25, $CHCl_3$).

Melting point: 66.5-70.5 °C.

Propyl-(*S*)-2-((*S*)-3-(4-(bis(2-chloroethyl)amino)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanamido)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate **3a**



3a

Synthesis of **3a** from **S6** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask containing THF (4.2 ml) was added amine **S6** (500.0 mg, 0.84 mmol, 1.0 equiv.). After decreasing the temperature to 0 °C monochloroacetic acid (2.06 g, 21.8 mmol, 26.0 equiv.) and sodium monochloroacetate (978 mg, 8.4 mmol, 10.0 equiv.) were added portion wise after each other. Borane dimethylsulfide (1.1 ml, 10.9 mmol, 13.0 equiv.) was added dropwise over 30 min at 0 °C. After stirring for further 1 h at 0 C the cooling bath was removed and the reaction mixture was stirred for 2 h at r.t. Subsequently, the reaction mixture was cooled to

0 °C again, quenched by slow addition of $NaHCO_3$ solution (sat.) and EtOAc. After stirring for 2 h at 0 °C the phases were separated and the water phase was extracted with DCM (3x). The combined organic phases were washed with NH_4Cl solution (sat.) and brine. After removal of the solvent column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the alkylator **3a** as a white solid (471.2 mg, 0.6 mmol, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.61 (d, *J* = 8.6 Hz, 2H), 6.37 (d, *J* = 7.5 Hz, 1H), 4.91 (s, 1H), 4.81-4.76 (m, 1H), 4.30 (s, 1H), 4.06-3.94 (m, 2H), 3.71-3.67 (m, 4H), 3.61-3.58 (m, 4H), 3.12-3.03 (m, 2H), 2.98-2.90 (m, 2H), 1.60 (sext, *J* = 7.2 Hz, 2H), 1.40 (s, 9H), 1.33 (s, 12H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.0, 171.0, 155.4, 145.2, 139.1, 135.1, 130.9, 128.8, 125.4, 112.4, 83.9, 80.4, 67.2, 55.8, 53.6, 53.3, 40.5, 38.2, 37.2, 28.4, 25.0, 21.9, 10.5.

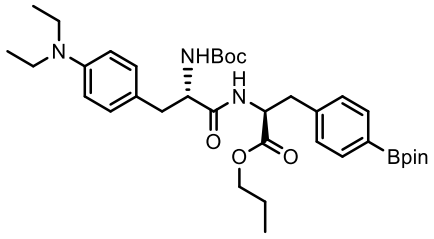
HRMS (ESI): $[M+Na]^+$, calcd for $C_{36}H_{52}BCl_2N_3O_7Na^+$: 742.3174, found: 742.3168.

[α] $^{28}_{589}$:+30.8 (*c* = 0.25, $CHCl_3$).

Melting point: 92.5-93.5 °C.

2.2.2. Synthesis of Propyl Melflufen Boronate Analogue 3b

Propyl-(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(diethylamino)phenyl)propanamido)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate **3b**



3b

Synthesis of **3b** from **S6** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask containing THF (840 µl) was added amine **S6** (100.0 mg, 0.17 mmol, 1.0 equiv.). After decreasing the temperature to 0 °C acetic acid (262.2 g, 4.4 mmol, 26.0 equiv.) and sodium acetate (137.8 mg, 1.7 mmol, 10.0 equiv.) were added portion wise after each other. Borane dimethylsulfide (220 µl, 2.2 mmol, 13.0 equiv.) was added dropwise over 30 min at 0 °C. After stirring for further 1 h at 0 °C the cooling bath was removed and the reaction mixture was stirred for 48 h at r.t. Then, the reaction mixture was cooled to 0 °C again, quenched by slow addition of $NaHCO_3$ solution (sat.) and EtOAc. After stirring for 2 h at 0 °C the phases were separated and the aqueous phase was extracted with DCM (3x). The combined organic phases were washed with NH_4Cl solution (sat.) and brine. After removal of the solvent purification by silica gel column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the tertiary amine **3b** as a white solid (80.0 mg, 0.12 mmol, 73%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 7.3 Hz, 1H), 4.91 (s, 1H), 4.79-4.75 (m, 1H), 4.27 (s, 1H), 4.05-3.93 (m, 2H), 3.32 (q, *J* = 7.2 Hz, 4H), 3.10-2.87 (m, 4H), 1.58 (sext, *J* = 7.2 Hz, 2H), 1.40 (s, 9H), 1.33 (s, 12H), 1.13 (t, *J* = 7.2 Hz, 6H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.2, 171.0, 155.4, 147.0, 139.2, 135.1, 130.4, 128.8, 122.7, 112.2, 83.8, 80.2, 67.1, 55.9, 53.4, 44.4, 38.3, 37.3, 28.4, 25.0, 21.9, 12.7, 10.4.

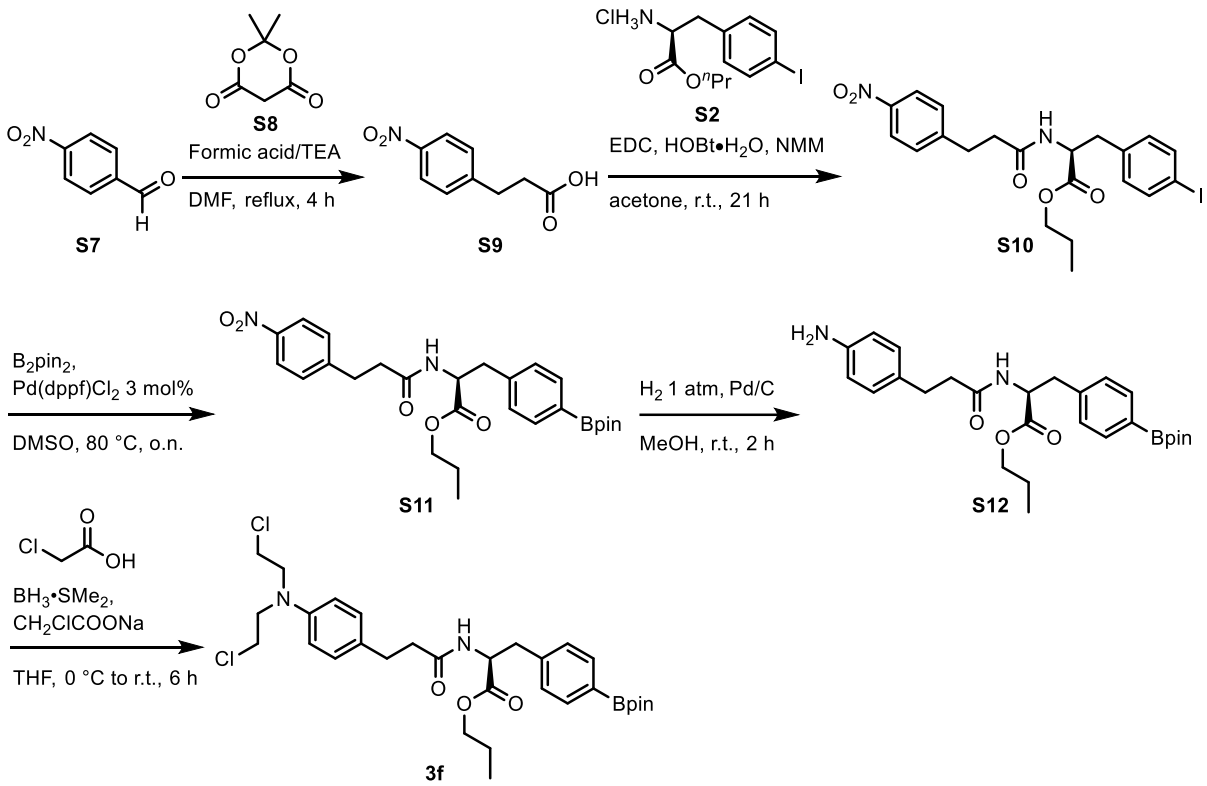
HRMS (ESI): $[M+H]^+$, calcd for $C_{36}H_{54}BN_3O_7H^+$: 652.4134, found: 652.4125.

$[\alpha]_{589}^{27}$:+26.80 (c = 0.25, $CHCl_3$).

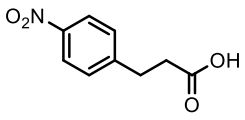
Melting point: 63.5-65.5 °C.

2.2.3. Synthesis of Propyl Melflufen Boronate Analogue 3f

The melflufen pinacol boronate analogue **3f** was synthesised from **S7** according to the scheme shown down below.



3-(4-nitrophenyl)propanoic acid **S9**



S9

Synthesis of **S9** from **S7** is based on the procedure by Mykhailiuk and co-workers.[3] TEA (515 µl, 3.7 mmol, 1.4 equiv.) was added dropwise to stirred formic acid (396 µl, 9.3 mmol, 3.5 equiv.) at 0 °C. To the resulting reaction mixture DMF (1 ml), Meldrum´s acid **S8** (381.5 mg, 2.6 mmol, 1.0 equiv.) and *p*-nitro benzaldehyde **S7** (400.0 mg, 2.6 mmol, 1.0 equiv.) were added. This reaction mixture was heated at reflux for 4 h. The residue resulted after removal of the solvent was dissolved in water. The solution was acidified with HCl (conc.) to pH = 2.

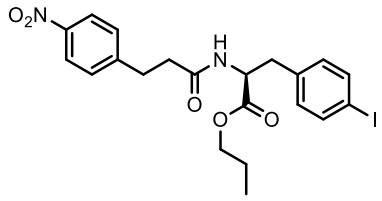
The resulted precipitate was filtered off, washed with ice-cold EtOAc and dried under vacuum. The carboxylic acid **S9** was obtained as a brownish solid (283.0g, 1.5 mmol, 55%) and used without further purification.

^{1}H-NMR (400 MHz, CD_3OD): δ = 8.16 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H).

^{13}C-NMR (101 MHz, CD_3OD): δ = 176.0, 150.4, 148.0, 130.6, 124.5, 35.8, 31.7.

The analytical data is in accordance to the literature.[3]

Propyl-(*S*)-3-(4-iodophenyl)-2-(3-(4-nitrophenyl)propanamido)propanoate **S10**



S10

Synthesis of **S10** from **S9** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask charged with acetone (4 ml) was added carboxylic acid **S9** (200.0 mg, 1.3 mmol, 1.0 equiv.), N-methylmorpholine (390 µl, 3.6 mmol, 3.5 equiv.), hydrochloride salt **S2** (387.1 mg, 1.05 mmol, 1.02 equiv.), HOBt·H_2O (15.3 mg, 0.1 mmol, 0.1 equiv.), and EDC·HCl (200 µl, 1.1 mmol, 1.1 equiv.). The resulting suspension was stirred at r.t. for 21 h. The solvent was removed under reduced pressure and replaced by EtOAc and water. The phases were allowed to separate after stirring for 5 min. The aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with $NaHCO_3$ solution (sat.), NH_4Cl solution (sat.), and brine. Purification by silical gel column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the dipeptide **S10** as a white solid (180.0 mg, 0.4 mmol, 46%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.36 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 4.46-4.41 (m, 1H), 3.94 (t, *J* = 6.6 Hz, 2H), 2.97-2.79 (m, 4H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.49 (sext, *J* = 7.2 Hz, 2H), 0.80 (t, *J* = 7.4 Hz, 3H).

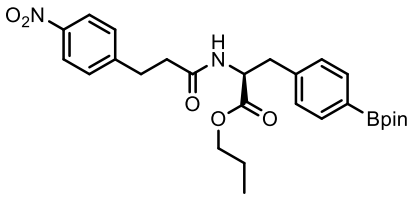
^{13}C-NMR (101 MHz, DMSO-d_6): δ = 171.4, 171.0, 149.6, 145.9, 137.0, 136.9, 131.5, 129.5, 123.3, 92.4, 66.0, 53.3, 36.2, 35.5, 30.5, 21.4, 10.1.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{21}H_{23}IN_2O_7Na^+$: 533.0544, found: 533.0555.

$[\alpha]_{589}^{28}$:+52.8 (*c* = 0.25, $CHCl_3$).

Melting point: 150.2-150.9 °C.

Propyl-(*S*)-2-(3-(4-nitrophenyl)propanamido)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate **S11**



S11

Synthesis of **S11** from **S10** is based on the procedure by Weil and co-workers.[1] A round bottom flask was charged with iodoarene **S10** (250.0 mg, 1.0 mmol, 1.0 equiv.), $Pd(dppf)Cl_2$ (10.8 mg, 0.02 mmol, 0.03 equiv.), B_2pin_2 (161.7 mg, 0.6 mmol, 1.3 equiv.) and KOAc (144.2 mg, 1.5 mmol, 3.0 equiv.) and degassed (N_2, 3x). After addition of dry degassed DMSO (4.9 ml) the solution was stirred at 80 °C for 18 h under one atmosphere of N_2. After completion DCM and water were added to the black reaction mixture. After phase separation the water phase was extracted with DCM (3x). The combined organic phases were dried through Na_2SO_4 and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (^{n}pentane:EtOAc = 4:1) yielded the desired pinacol boronate **S11** as a colourless oil (210.0 mg, 0.4 mmol, 84%).

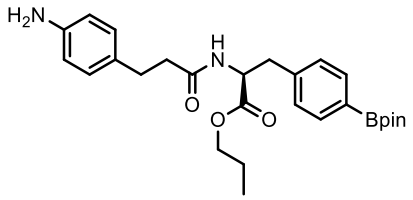
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 5.82 (d, *J* = 7.7 Hz, 1H), 4.87 (dt, *J* = 7.8, 5.7 Hz, 1H), 4.11-4.01 (m, 2H), 3.16-3.07 (m, 2H), 3.04 (t, *J* = 7.5 Hz, 2H), 2.56-2.44 (m, 2H), 1.64 (sext, *J* = 7.2 Hz, 2H), 1.34 (s, 12H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.6, 170.7, 148.6, 146.8, 139.0, 135.2, 129.4, 128.8, 123.9, 84.8, 67.4, 53.1, 38.1, 37.2, 31.1, 25.0, 22.0, 10.5.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{27}H_{35}BN_2O_7Na^+$: 533.2434, found: 533.2437.

$[\alpha]_{589}^{28}$:+26.0 (*c* = 0.25, $CHCl_3$).

Propyl-(*S*)-2-(3-(4-aminophenyl)propanamido)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate **S12**



S12

Synthesis of **S12** from **S11** is based on the procedure by Wennerberg and co-workers.[2] A round bottom flask containing a solution of nitro compound **S11** (180.0 mg, 0.4 mmol, 1.0 equiv.), and Pd/C (10% Pd loaded on C, 55% moist; 47.3 mg, 0.02 mmol, 5 mol%) in MeOH (7 ml) was equipped with a H_2 balloon. The reaction was stirred for 1.5 h at r.t. while H_2 passed through the reaction mixture. Then, the suspension was filtered through a plug of Celite®. Removal of the solvent yielded the amine **S12** without further purification as a white solid (169 mg, 0.4 mmol, quant.).

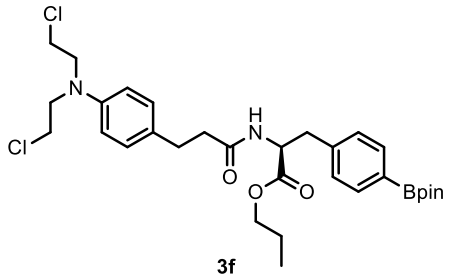
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.26 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 7.84 (d, J = 8.6 Hz, 2H), 6.44 (d, J = 8.6 Hz, 2H), 4.80 (s, 2H), 4.48-4.42 (m, 1H), 3.96-3.93 (m, 2H), 3.00 (dd, J = 13.5, 5.9 Hz, 1H), 2.89 (dd, J = 8.8, 13.8 Hz, 1H), 2.46-2.44 (m, 2H), 2.27-2.23 (m, 2H), 1.50 (sext, J = 7.1 Hz, 2H), 1.28 (s, 12H), 0.80 (t, J = 7.2 Hz, 3H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ = 171.8, 171.6, 146.5, 140.8, 134.4, 134.1, 128.6, 128.5, 128.1, 113.9, 83.6, 65.9, 53.5, 37.3, 37.0, 30.3, 24.7, 21.4, 10.2.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{27}H_{37}BN_2O_5Na^+$: 503.2692, found: 503.2697.

$[\alpha]_{589}^{27}$:+8.80 (c = 0.25, $CHCl_3$).

Propyl-(*S*)-2-(3-(4-(bis(2-chloroethyl)amino)phenyl)propanamido)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate **3f**



3f

Synthesis of **3f** from **S12** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask containing THF (1.2 ml) was added amine **S12** (120.0 mg, 0.25 mmol, 1.0 equiv.). After decreasing the temperature to 0 °C monochloroacetic acid (613.7 mg, 6.5 mmol, 26.0 equiv.) and sodium monochloroacetate (291.0 mg, 2.5 mmol, 10.0 equiv.) were added portion wise after each other. Borane dimethylsulfide (325 µl, 10.9 mmol, 13.0 equiv.) was added dropwise over 30 min at 0 °C. After stirring for further 1 h at 0 °C the cooling bath was removed and the reaction mixture was stirred for 2 h at r.t. Then, the reaction mixture was cooled to 0 °C again, quenched by slow addition of $NaHCO_3$ solution (sat.) and EtOAc. After stirring for 2 h at 0 °C the phases were separated and the water phase was extracted with DCM (3x). The combined organic phases were washed with NH_4Cl solution (sat.) and brine. After removal of the solvent purification by siliga gel column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the alkylator **3f** as a white solid (115.0 mg, 0.19 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 7.9 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 7.9 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 5.85 (s, 1H), 4.88 (dt, J = 7.6, 5.4 Hz, 1H), 4.09-3.98 (m, 2H), 3.72-3.68 (m, 4H), 3.62-3.58 (m, 4H), 3.09 (d, J = 5.5 Hz, 2H), 2.92-2.79 (m, 2H), 2.52-2.35 (m, 2H), 1.63 (sext, J = 7.1 Hz, 2H), 1.34 (s, 12H), 0.91 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.7, 171.6, 144.7, 139.2, 135.1, 129.8, 128.9, 112.3, 83.9, 67.3, 53.7, 53.1, 40.6, 38.7, 38.1, 30.5, 25.0, 22.0, 10.5.

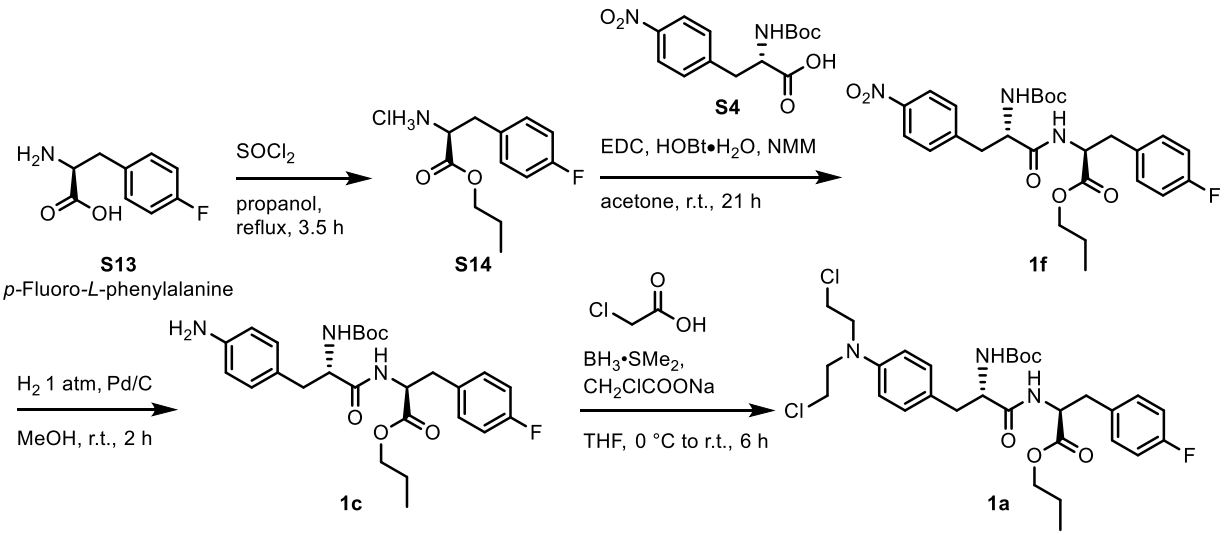
HRMS (ESI): $[M+Na]^+$, calcd for $C_{31}H_{43}BCl_2N_2O_5Na^+$: 627.2540, found: 627.2557.

$[\alpha]_{589}^{28}$:+56.00 (c = 0.25, $CHCl_3$).

Melting point: 98.0-99.0 °C.

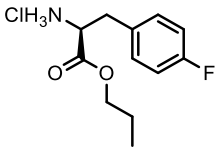
3. Synthesis and Characterisation of Propyl Melflufen Analogues 1

The melflufen pinacol boronate analogues were synthesised according to the scheme shown down below.



3.1. Synthesis of Propyl Melflufen Analogues 1a, 1c and 1f

Propyl-(*S*)-2-amino-3-(4-fluorophenyl)propanoate hydrochloride **S14**



S14

Thionyl chloride (600 µl, 8.2 mmol, 1.5 equiv.) was added dropwise to a stirred, ice-cold suspension of (*S*)-Fluoro-phenylalanine **S13** (1.0 g, 5.5 mmol, 1.0 equiv.) in absolute ^{n}propanol (24 ml). Afterwards the reaction mixture was heated at reflux for 3.5 h. After evaporation of the solvent under reduced pressure and no further purification the propyl ester **S14** could be obtained as a white solid (1.4 g, 5.5 mmol, quant.).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.52 (s, 3H), 7.32-7.27 (m, 2H), 7.20-7.14 (m, 2H), 4.28 (t, *J* = 6.9 Hz, 1H), 4.02 (t, *J* = 6.6 Hz, 2H), 3.16 (dd, *J* = 14.1, 8.2 Hz, 1H), 3.06 (dd, *J* = 14.1, 7.9 Hz, 1H), 1.55-1.46 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H).

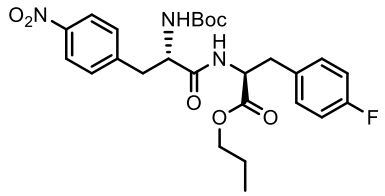
^{13}C-NMR (101 MHz, DMSO-d_6): δ = 169.0, 161.5 (d, *J* = 242.8 Hz), 131.4 (d, *J* = 8.4 Hz), 130.8 (d, *J* = 3.1 Hz), 115.35 (d, *J* = 21.4 Hz), 67.1, 53.1, 35.2, 21.2, 10.1.

^{19}F-NMR (377 MHz, DMSO-d_6): δ = −115.60.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{12}H_{16}FNO_2Na^+$: 248.1057, found: 248.1062.

$[\alpha]_{589}^{28}$:+55.60 (*c* = 0.25, $CHCl_3$).

Propyl-(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-nitrophenyl)propanamido)-3-(4-fluorophenyl)propanoate **1f**



1f

Synthesis of **1f** from **S4** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask charged with acetone (7 ml) was added carboxylic acid **S4** (600.0 mg, 1.9 mmol, 1.0 equiv.), N-methylmorpholine (745 µl, 6.8 mmol, 3.5 equiv.), hydrochloride salt **S14** (517.2 mg, 2.0 mmol, 1.02 equiv.), HOBt·H_2O (28.9 mg, 0.2 mmol, 0.1 equiv.), and EDC·HCl (200 µl, 1.1 mmol, 1.1 equiv.). The resulting suspension was stirred at r.t. for 21 h. The solvent was removed under reduced pressure and replaced by EtOAc and water. Phases were allowed to separate after stirring for 5 min. The water phase was extracted with EtOAc (3x). The combined organic phases were washed with $NaHCO_3$ solution (sat.), NH_4Cl solution (sat.), and brine. Purification by siliga gel column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the dipeptide **1f** as a white solid (807.5 mg, 1.6 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.05-7.00 (m, 2H), 6.97-6.91 (m, 2H), 6.29 (d, *J* = 7.7 Hz, 1H), 4.96 (d, *J* = 8.7 Hz, 1H), 4.74 (dd, *J* = 7.7, 6.1 Hz, 1H), 4.38-4.33 (m, 1H), 4.09-3.97 (m, 2H), 3.19 (dd, *J* = 13.9, 6.7 Hz, 1H), 3.11-2.99 (m, 3H), 1.60 (sext, *J* = 7.1 Hz, 2H), 1.41 (s, 9H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.0, 170.1, 162.2 (d, *J* = 245.7 Hz),155.3, 147.2, 144.4, 131.4 (d, *J* = 3.3 Hz), 130.9 (d, *J* = 8.0 Hz), 130.4, 123.9, 115.6 (d, *J* = 21.3 Hz), 80.8, 67.5, 55.5, 53.4, 38.3, 37.4, 28.4, 22.0, 10.4.

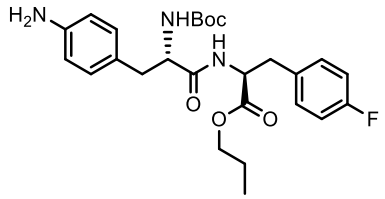
^{19}F-NMR (377 MHz, $CDCl_3$): δ = −116.57.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{26}H_{32}FN_3O_7Na^+$: 540.2116, found: 540.2112.

[α] $^{28}_{589}$:+17.60 (*c* = 0.25, $CHCl_3$).

Melting point: 157.5-158.5 °C.

Propyl-(*S*)-2-((*S*)-3-(4-aminophenyl)-2-((*tert*-butoxycarbonyl)amino)propanamido)-3-(4-fluorophenyl) propanoate **1c**



1c

Synthesis of **1c** from **1f** is based on the procedure by Wennerberg and co-workers.[2] A round bottom flask containing a solution of nitro compound **1f** (300.0 mg, 0.6 mmol, 1.0 equiv.), and Pd/C (10% Pd loaded on C, 55% moist; 68.6 mg, 0.03 mmol, 5 mol%) in MeOH (12 ml) was charged with a H_2 balloon. The reaction was stirred for

1.5 h at r.t. while H_2 passed through the reaction mixture. Then, the suspension was filtered through a plug of Celite®. Removal of the solvent yielded the amine **1c** without further purification as a white solid (281.0 mg, 0.6 mmol, quant.).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.25 (d, J = 7.6 Hz, 1H), 7.27-7.24 (m, 2H), 7.08 (t, J = 8.9 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 6.67 (d, J = 8.7 Hz, 1H), 6.44 (d, J = 8.2 Hz, 2H), 4.84 (s, 2H), 4.46 (dd, J = 14.6, 7.6 Hz, 1H), 4.07-4.01 (m, 1H), 3.99-3.90 (m, 2H), 3.05-2.91 (m, 2H), 2.69 (dd, J = 13.9, 4.1 Hz, 1H), 2.52-2.46 (m, 1H, under solvent signal), 1.51 (sext, J = 7.0 Hz, 2H), 1.30 (s, 9H), 0.81 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ = 172.1, 171.3, 161.1 (d, J = 242.0 Hz), 155.1, 146.9, 133.2 (d, J = 2.5 Hz), 131.0 (d, J = 7.9 Hz), 129.5, 124.8, 114.9 (d, J = 21.0 Hz), 113.6, 77.9, 66.0, 55.9, 53.5, 36.7, 35.9, 28.1, 21.4, 10.2.

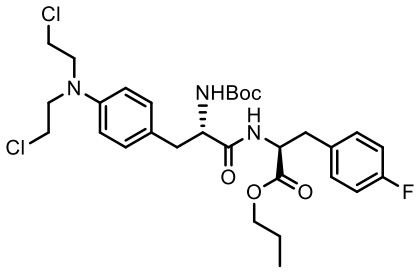
^{19}F-NMR (377 MHz, DMSO-d_6): δ = −116.65.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{26}H_{34}FN_3O_5Na^+$: 510.2375, found: 510.2392.

$[\alpha]_{589}^{28}$:+40.40 (c = 0.25, $CHCl_3$).

Melting point: 96.7-98.0 °C.

Propyl-(*S*)-2-((*S*)-3-(4-(bis(2-chloroethyl)amino)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanamido)-3-(4-fluorophenyl)propanoate **1a**



1a

Synthesis of **1a** from **1c** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask containing THF (5.1 ml) was added amine **1c** (500.0 mg, 1.03 mmol, 1.0 equiv.). After decreasing the temperature to 0 °C monochloroacetic acid (2.52 g, 26.7 mmol, 26.0 equiv.) and sodium monochloroacetate (1.2 g, 10.3 mmol, 10.0 equiv.) were added portion wise after each other. Borane dimethylsulfide (1.3 ml, 13.3 mmol, 13.0 equiv.) was added dropwise over 30 min at 0 °C. After stirring for further 1 h at 0 °C the cooling bath was removed and the reaction mixture was stirred for 2 h at r.t. Then, the reaction mixture was cooled to 0 °C again, quenched by slow addition of $NaHCO_3$ solution (sat.) and EtOAc. After stirring for 2 h at 0 °C the phases were separated and the water phase was extracted with DCM (3x). The combined organic phases were washed with NH_4Cl solution (sat.) and brine. After removal of the solvent silica gel column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the alkylator **1a** as a white solid (475.3 mg, 0.78 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.06 (d, J = 8.5 Hz, 2H), 7.00-6.90 (m, 4H), 6.60 (d, J = 8.6 Hz, 2H), 6.32 (d, J = 7.7 Hz, 1H), 4.97-4.88 (m, 1H), 4.78-4.74 (m, 1H), 4.31-4.22 (m, 1H), 4.08-3.95 (m, 2H), 3.72-3.68 (m, 4H), 3.62-3.58 (m, 4H), 3.09-2.99 (m, 2H), 2.96-2.91 (m, 2H), 1.60 (sext, J = 7.3 Hz, 2H), 1.41 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.1, 171.1, 162.1 (d, *J* = 245.3 Hz), 155.4, 145.2, 131.7 (d, *J* = 3.3 Hz), 131.0 (d, *J* = 7.9 Hz), 130.8, 125.4, 115.5 (d, *J* = 21.2 Hz), 112.4, 80.4, 67.3, 56.0, 53.6, 53.4, 40.6, 37.4, 37.3, 28.4, 22.0, 10.4.

^{19}F-NMR (377 MHz, $CDCl_3$): δ = −115.69.

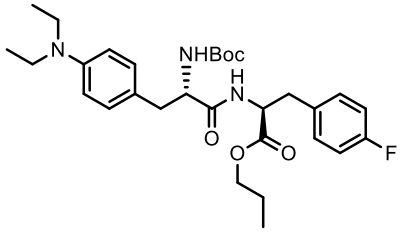
HRMS (ESI): $[M+Na]^+$, calcd for $C_{30}H_{40}Cl_2FN_3O_5Na^+$: 634.2221, found: 634.2243.

[α] $\mathbf{^{28}_{589}}$:+27.60 (*c* = 0.25, $CHCl_3$).

Melting point: 138.0-138.5 °C.

3.2. Synthesis of Propyl Melflufen Analogue 1d

Propyl-(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(diethylamino)phenyl)propanamido)-3-(4-fluorophenyl)propanoate **1d**



1d

Synthesis of **1d** from **1c** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask containing THF (3 ml) was added amine **1c** (100.0 mg, 0.2 mmol, 1.0 equiv.). After decreasing the temperature to 0 °C acetic acid (320.2 g, 5.3 mmol, 26.0 equiv.) and sodium acetate (168.3 mg, 2.1 mmol, 10.0 equiv.) were added portion wise after each other. Borane dimethylsulfide (267 µl, 2.7 mmol, 13.0 equiv.) was added dropwise over 30 min at 0 °C. After stirring for further 1 h at 0 °C the cooling bath was removed and the reaction mixture was stirred for 48 h at r.t. Then, the reaction mixture was cooled to 0 °C again, quenched by slow addition of $NaHCO_3$ solution (sat.) and EtOAc. After stirring for 2 h at 0 °C the phases were separated and the water phase was extracted with DCM (3x). The combined organic phases were washed with NH_4Cl solution (sat.) and brine. After removal of the solvent silica gel column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the tertiary amine **1d** as a white solid (93.1 mg, 0.17 mmol, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, *J* = 8.2 Hz, 2H), 6.96-6.87 (m, 4H), 6.60 (d, *J* = 8.5 Hz, 2H), 6.37 (d, *J* = 7.7 Hz, 1H), 4.94 (bs, 1H), 4.78-4.74 (m, 1H), 4.27 (s, 1H), 4.06-3.93 (m, 2H), 3.31 (q, *J* = 7.0 Hz, 4H), 3.07-2.97 (m, 3H), 2.87 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.58 (sext, *J* = 7.1 Hz, 2H), 1.41 (s, 9H), 1.13 (t, *J* = 7.0 Hz, 6H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.3, 171.0, 162.0 (d, *J* = 245.1 Hz), 155.5, 147.0, 131.7 (d, *J* = 3.3 Hz), 130.9 (d, *J* = 8.0 Hz), 130.4, 122.6, 115.4 (d, *J* = 21.2 Hz), 112.1, 80.2, 67.1, 56.0, 53.5, 44.4, 37.4, 37.2, 28.4, 21.9, 12.7, 10.4.

^{19}F-NMR (377 MHz, $CDCl_3$): δ = −115.89.

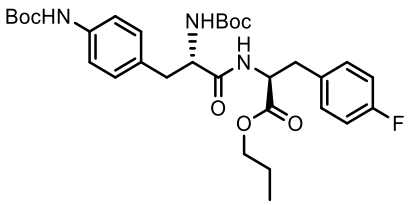
HRMS (ESI): $[M+Na]^+$, calcd for $C_{30}H_{42}FN_3O_5Na^+$: 566.3001, found: 566.2996.

$[\alpha]_{589}^{27}$:+46.20 (*c* = 0.25, $CHCl_3$).

Melting point: 117.0-117.3 °C.

3.3. Synthesis of Additive Propyl Melflufen Analogue 1e

Propyl-(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-((*tert*-butoxycarbonyl)amino)phenyl) propanamido)-3-(4-fluorophenyl)propanoate **1e**



1e

To a solution of amine **1c** (70.0 mg, 0.1 mmol, 1.0 equiv.) in DCM (287 µl) were added Boc-anhydride (37 µl, 0.12 mmol, 1.2 equiv.) and TEA (60 µl, 0.3 mmol, 3.0 equiv.) at r.t. The reaction mixture was stirred for 16 h at r.t. After completion the solvent was removed under reduced pressure. Purification by silica gel column chromatography (^{n}pentane:EtOAc = 9:1, dry loaded) yielded the Boc-protected amine **1e** as a white solid (83.5 mg, 0.14 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.97-6.88 (m, 4H), 6.53 (s, 1H), 6.35 (d, *J* = 7.5 Hz, 1H), 4.94 (bs, 1H), 4.73 (dd, *J* = 13.3, 6.2 Hz, 1H), 4.30 (bs, 1H), 4.06-3.93 (m, 2H), 3.06-9.92 (m, 4H), 1.58 (sext, *J* = 7.2 Hz, 2H), 1.50 (s, 9H), 1.40 (s, 9H), 0.87 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.0, 170.9, 162.1 (d, *J* = 245.3 Hz), 155.4, 152.8, 137.5, 131.6 (d, *J* = 3.2 Hz), 131.0, 130.9 (d, *J* = 7.8 Hz), 130.0, 118.8, 115.5 (d, *J* = 21.3 Hz), 80.7, 80.4, 67.3, 55.9, 53.5, 37.6, 37.4, 28.4, 28.4, 21.9, 10.4.

^{19}F-NMR (377 MHz, $CDCl_3$): δ = −115.73.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{31}H_{42}FN_3O_7Na^+$: 610.2899, found: 610.2897.

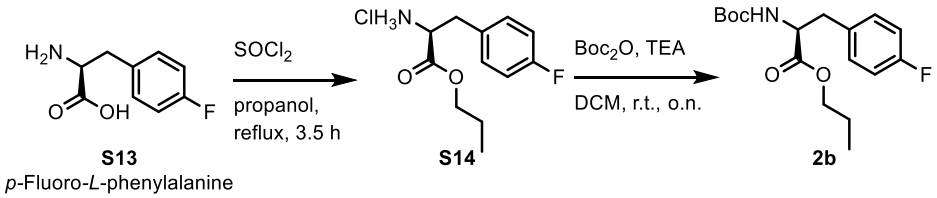
$[\alpha]_{589}^{26}$:+25.20 (*c* = 0.25, $CHCl_3$).

Melting point: 148.5-151.5 °C.

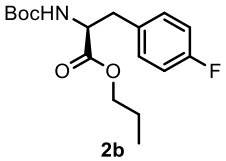
4. Synthesis and Characterisation of Fluorine-19 References

4.1. Synthesis of Fluorine-19 Reference 2b for [^{18}F]2b

The reference **2b** for **^{18}F-2b** reaction was synthesised from **S13** according to the scheme shown down below. The synthesis of **S14** is described in section 3.1.



Propyl-(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-fluorophenyl)propanoate **2b**



Boc-anhydride (207 µl, 0.9 mmol, 1.2 equiv.) and triethylamine (320 µl, 2.3 mmol, 3.0 equiv.) were added to a solution of hydrochloride salt **S14** (200.0 mg, 0.8 mmol, 1.0 equiv.) in DCM (1.5 ml, 0.5 M) at r.t. The reaction mixture was stirred for 16 h at r.t. and concentrated under reduced pressure. Column chromatography (^{n}pentane:EtOAc = 9:1) yielded the Boc-protected amine **2b** as a viscous oil (210.0 mg, 0.6 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.12-7.08 (m, 2H), 6.97 (t, *J* = 8.2 Hz, 2H), 4.98 (d, *J* = 8.3 Hz, 1H), 4.55 (dd, *J* = 13.6, 6.5 Hz, 1H), 4.10-4.00 (m, 2H), 3.12-2.99 (m, 2H), 1.62 (sext, *J* = 7.1 Hz, 2H), 1.42 (s, 9H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.0, 162.1 (d, *J* = 245.1 Hz), 155.2, 132.0 (d, *J* = 2.9 Hz), 131.0 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 21.4 Hz), 80.1, 67.2, 54.6, 37.9, 28.4, 22.0, 10.5.

^{19}F-NMR (377 MHz, $CDCl_3$): δ = −116.00.

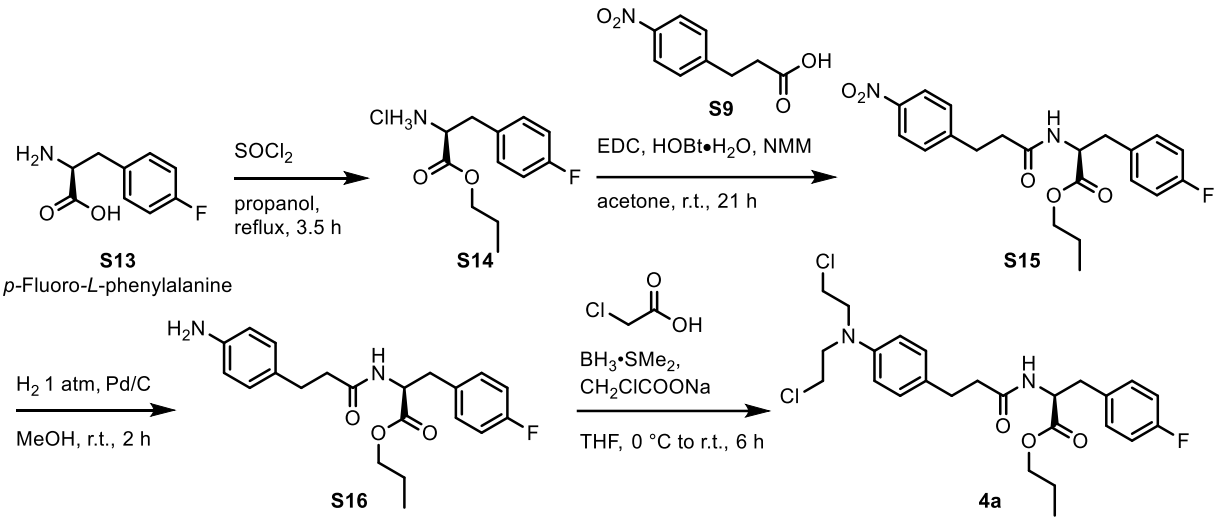
HRMS (ESI): $[M+Na]^+$, calcd for $C_{17}H_{24}FNO_4Na^+$: 348.1582, found: 348.1570.

$[\alpha]_{589}^{28}$:+34.00 (*c* = 0.25, $CHCl_3$).

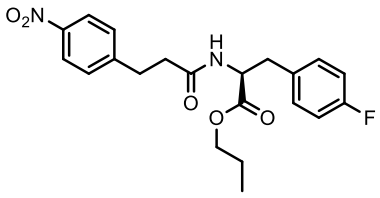
Melting point: 51.4-52.0 °C.

4.2. Synthesis of Fluorine-19 Reference 4a for [^{18}F]4a

The fluorine-19 reference **4a** for radiotracer **[^{18}F]4a** was synthesised from **S13** according to the scheme shown down below. The synthesis of **S14** and **S9** are described in section 3.1 and section 2.2.3, respectively.



Propyl-(*S*)-3-(4-fluorophenyl)-2-(3-(4-nitrophenyl)propanamido)propanoate **S15**



S15

Synthesis of **S9** from **S15** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask charged with acetone (5.7 ml) was added carboxylic acid **S9** (300.0 mg, 1.5 mmol, 1.0 equiv.), N-methylmorpholine (590 µl, 5.4 mmol, 3.5 equiv.), hydrochloride salt **S14** (411.1 mg, 1.6 mmol, 1.02 equiv.), HOBt·H_2O (23.0 mg, 0.2 mmol, 0.1 equiv.), and EDC·HCl (300 µl, 1.7 mmol, 1.1 equiv.). The resulting suspension was stirred at r.t. for 21 h. The solvent was removed under reduced pressure and replaced by EtOAc and water. The phases were allowed to separate after stirring for 5 min. The water phase was extracted with EtOAc (3x). The combined organic phases were washed with $NaHCO_3$ solution (sat.), NH_4Cl solution (sat.), and brine. Purification by silica gel column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the dipeptide **S15** as a white solid (455.7 mg, 1.1 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.97-6.90 (m, 4H), 5.86 (d, *J* = 7.6 Hz, 1H), 4.83 (dt, *J* = 7.7, 5.9 Hz, 1H), 4.11-4.00 (m, 2H), 3.10-3.00 (m, 4H), 2.59-2.45 (m, 2H), 1.63 (sext, *J* = 7.2 Hz, 2H), 0.91 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.6, 170.6, 162.15 (d, *J* = 245.8 Hz), 148.6, 146.8, 131.6 (d, *J* = 3.3 Hz), 130.8 (d, *J* = 8.0 Hz), 123.9 115.5 (d, *J* = 21.3 Hz), 67.5, 53.3, 37.4, 37.2, 31.1, 22.0, 10.4.

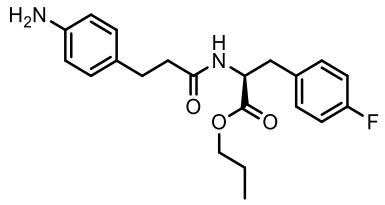
^{19}F-NMR (377 MHz, $CDCl_3$): δ = −116.58.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{21}H_{23}FN_2O_5Na^+$: 425.1483, found: 425.1482.

$[\alpha]_{589}^{28}$:+60.80 (*c* = 0.25, $CHCl_3$).

Melting point: 87.0-87.7 °C.

Propyl-(*S*)-2-(3-(4-aminophenyl)propanamido)-3-(4-fluorophenyl)propanoate **S16**



S16

Synthesis of **S16** from **S15** is based on the procedure by Wennerberg and co-workers.[2] A round bottom flask containing a solution of nitro compound **S15** (450.0 mg, 1.1 mmol, 1.0 equiv.), and Pd/C (10% Pd loaded on C, 55% moist; 108.5 mg, 0.06 mmol, 5 mol%) in MeOH (22 ml) was equipped with a H_2 balloon. The reaction was stirred for 2.0 h at r.t. while H_2 passed through the reaction mixture. Then, the suspension was filtered through a plug of Celite®. Removal of the solvent yielded the amine **S16** without further purification as a white solid (405.0 mg, 1.1 mmol, 97%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.26 (d, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.08 (t, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.45 (d, *J* = 8.4 Hz, 2H), 4.82 (s, 2H), 4.44-4.39 (m, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.00-2.84 (m, 2H), 2.57-2.53 (m, 2H), 2.27 (t, *J* = 7.6 Hz, 2H), 1.51 (sext, *J* = 7.6 Hz, 2H), 0.82 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ = 171.7, 171.6, 161.1 (d, *J* = 242.0 Hz), 146.6, 133.4 (d, *J* = 3.1 Hz), 130.9 (d, *J* = 8.0 Hz), 128.5, 128.0, 114.9 (d, *J* = 21.1 Hz), 113.9, 65.9, 53.6, 37.2, 35.9, 30.2, 21.4, 10.1.

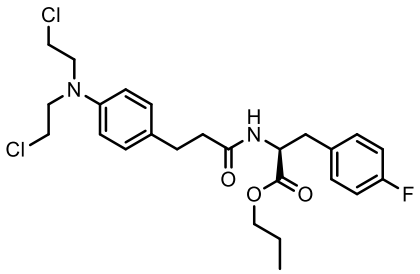
^{19}F-NMR (377 MHz, $CDCl_3$): δ = −116.62.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{21}H_{25}FN_2O_3Na^+$: 395.1741, found: 395.1726.

$[\alpha]_{589}^{28}$:+62.00 (*c* = 0.25, $CHCl_3$).

Melting point: 101.0-101.6 °C.

Propyl-(*S*)-2-(3-(4-(bis(2-chloroethyl)amino)phenyl)propanamido)-3-(4-fluorophenyl)propanoate **4a**



4a

Synthesis of **4a** from **S16** is based on the procedure by Wennerberg and co-workers.[2] To a round bottom flask containing THF (3.5 ml) was added amine **S16** (405.0 mg, 1.09 mmol, 1.0 equiv.). After decreasing the temperature to 0 °C monochloroacetic acid (2.67 g, 28.3 mmol, 26.0 equiv.) and sodium monochloroacetate (1.27 g, 10.9 mmol, 10.0 equiv.) were added in portions. Borane dimethylsulfide (1.4 ml, 14.1 mmol, 13.0 equiv.)

was added dropwise over 30 min at 0 °C. After stirring for further 1 h at 0 °C the cooling bath was removed and the reaction mixture was stirred for 2 h at r.t. Then, the reaction mixture was cooled to 0 °C again, quenched by slow addition of $NaHCO_3$ solution (sat.) and EtOAc. After stirring for 2 h at 0 °C the phases were separated and the water phase was extracted with DCM (3x). The combined organic phases were washed with NH_4Cl solution (sat.) and brine. After removal of the solvent purification by silica gel column chromatography (^{n}pentane:EtOAc = 2:1, dry loaded) yielded the alkylator **4a** as a white solid (383.2 mg, 0.77 mmol, 71%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8.6 Hz, 2H), 6.95-6.88 (m, 4H), 6.62 (d, *J* = 8.7 Hz, 2H), 5.85 (d, *J* = 7.7 Hz, 1H), 4.85 (dt, *J* = 7.7, 5.7 Hz, 1H), 4.11-3.99 (m, 2H), 3.72-3.68 (m, 4H), 3.62-3.58 (m, 4H), 3.09-3.01 (m, 2H), 2.92-2.79 (m, 2H), 2.52-2.37 (m, 2H), 1.63 (sext, *J* = 7.2 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.8, 171.7, 162.1 (d, *J* = 245.2 Hz), 144.7, 131.7 (d, *J* = 3.2 Hz), 130.9 (d, *J* = 7.9 Hz), 129.9, 129.8, 115.5 (d, *J* = 21.3 Hz),112.4, 67.3, 53.7, 53.2, 40.6, 38.6, 37.4, 30.5, 22.0, 10.5.

^{19}F-NMR (377 MHz, $CDCl_3$): δ = −115.69.

HRMS (ESI): $[M+Na]^+$, calcd for $C_{25}H_{31}Cl_2FN_2O_3Na^+$: 519.1588, found: 519.1596.

[α] $^{28}_{589}$:+54.80 (*c* = 0.25, $CHCl_3$).

Melting point: 72.0-72.9 °C.

5. Radiochemical Studies

5.1. General Information

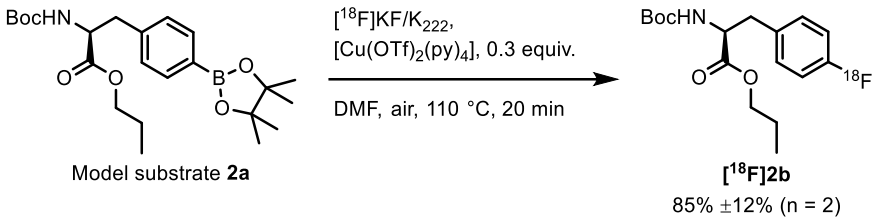
[^{18}F]Fluoride was produced through bombardment of [^{18}O]Oxygen-enriched water with protons by the $^{18}O(p,n)^{18}F$ nuclear reaction in a cyclotron (Scanditronix MC-17). [^{18}F]Fluoride was trapped on an anion exchange cartridge (quaternary methyl ammonium, Sep-Pak® Accell Plus QMA Light by Waters) after preconditioning with a K_2CO_3 solution (10 ml, 0.5 M, aq.) and deionized water (10 ml). The radiofluorinated compounds were characterised by comparing the radio-HPLC signal with the UV-HPLC signal of an authentic ^{19}F-reference, which was synthesised as described in sections 3 and 4. Radiochemical conversions (RCC) were determined from a small aliquot of the reaction mixture by analytical radio HPLC (rHPLC). The analytical radio HPLC was performed with an Agilent 1260 Infinity II with a UV-detector (λ = 254 nm) in series with a Flow-Count PMT radioactivity detector system by Eckert & Ziegler using a small aliquot (~10 µl) diluted in a solution of MeCN:H_2O = 1:1 (~500 µl). The analysis was performed using a C-18 reversed phase column (Phenomenex, Kinetex 2.6µ, 100 Å, 100x4.6 mm) and an eluent gradient system of ammonium formate (50 mM aq.)/MeCN (1.5 ml/min flow; linear increase 30% to 90% MeCN 0-10 min; isocratic 10-12 min; linear decrease 90% to 30% MeCN 12-13 min).

5.2. Preparation of [^{18}F]KF/K_{222}

[^{18}F]Fluoride was separated from [^{18}O]oxygen-enriched water by trapping on a cartridge (quaternary methyl ammonium, Sep-Pak® Accell Plus QMA Light by Waters) and subsequently released as [^{18}F]KF/K_{222} using a 4:1 solution of MeCN:H_2O (3 mg K_2CO_3 and 15 mg K_{222} per 1 mL of solution). 550 µL of the prepared solution was

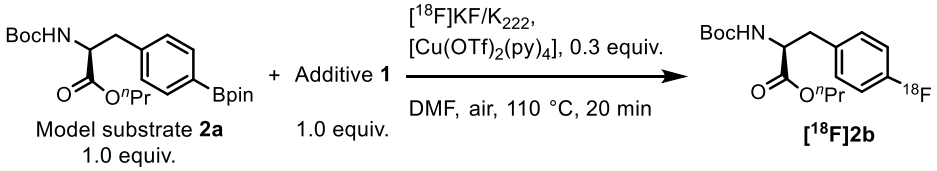
directly eluded through the cartridge into a 5 ml V-shaped vial. Azeotropic drying was performed in five cycles using 200 µL of MeCN in two-minute intervals at 120 °C under a flow of N_2. After the last drying interval, the cylinder was allowed to warm up to r.t. for 5 min under a flow of N_2. The obtained [^{18}F]KF/K_{222} was redissolved in dry MeCN (300 – 1000 µl).

5.3. Fluorine-18 Labelling of Phenylalanine derivative 2a (Table 1)



Unless otherwise stated, a dry 1 ml V-shaped vial containing a magnetic stirring bar was charged with substrate **2a** (30 µmol, 1.0 equiv.), the Cu mediator [Cu(OTf)$_2$(py)$_4$] (9 µmol, 0.3 equiv.). The vial was sealed and purged with N_2 (~10 s) before addition of dry DMF (150 µl). It was stirred vigorously until all components were dissolved (~30 s). A solution of [^{18}F]KF/K_{222} in dry MeCN (~300 MBq in ~30 µl) was added through the septum to the reaction mixture before it was heated and stirred at 110 °C for 20 min. An aliquot (~10 µl) was removed and added to a solution of MeCN:H_2O = 1:1 (~500 µl) for radio HPLC analysis.

5.4. Functional Group Tolerance Test (Figure 3)



A dry 1 ml V-shaped vial containing a magnetic stirring bar was charged with **2a** (30 µmol, 1.0 equiv.), Cu mediator [Cu(OTf)$_2$(py)$_4$] (9 µmol, 0.3 equiv.), additive **1** (30 µmol, 1.0 equiv.) and with dry DMF (150 µl). The vial was sealed under air and stirred vigorously until all components were dissolved (~30 s). A solution of [^{18}F]KF/K_{222} in dry MeCN (~300 MBq in ~30 µl) was added through the septum to the reaction mixture before it was heated and stirred at 110 °C for 20 min. An aliquot (~10 µl) was removed and added to a solution of MeCN:H_2O = 1:1 (~500 µl) for radio HPLC analysis.

5.5. Fluorine-18 Labelling of Melflufen Analogues 3 (Scheme 1)

General Procedure for Fluorine-18 Labelling of Melflufen Analogues 3 (Scheme 1)

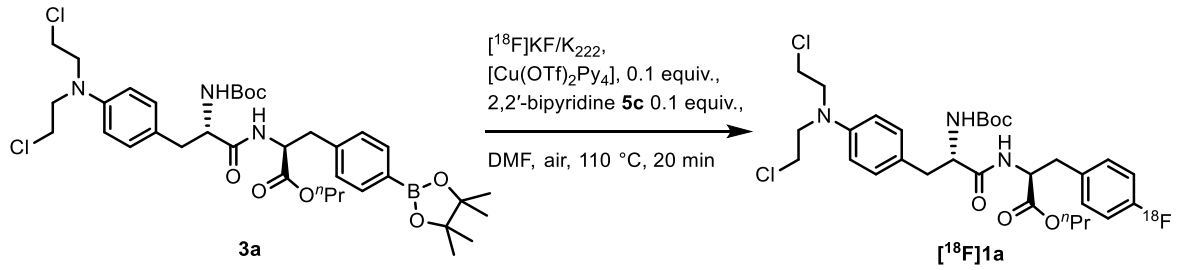
Unless otherwise stated, a dry 1 ml V-shaped vial containing a magnetic stirring bar was charged with the pinacol boronate precursor (30 µmol, 1.0 equiv.), the Cu mediator $[Cu(OTf)_2(py)_4]$ (3 µmol, 0.1 equiv.) and subsequently with dry DMF (150 µl). The vial was sealed under an atmosphere of ambient air and stirred vigorously until all components were dissolved (~30 s). A solution of $[^{18}F]KF/K_{222}$ in dry MeCN (~300 MBq in ~30 µl) was added through the septum to the reaction mixture before it was heated and stirred at 110 °C for 20 min. An aliquot (~10 µl) was removed and added to a solution of MeCN:H_2O = 1:1 (~500 µl) for radio HPLC analysis.

5.6. Examination of the Role of Additive in the Synthesis of Melflufen Propyl Ester Radiotracer $[^{18}F]$1a and $[^{18}F]$4a (Figure 4)

General Procedure for Synthesis of Melflufen Propyl Ester Radiotracer $[^{18}F]$1a and $[^{18}F]$4a in the presence of Additives (Figure 4)

A dry 1 ml V-shaped vial containing a magnetic stirring bar was charged with melflufen pinacol boronate analogue **3a/3f** (30 µmol, 1.0 equiv.), Cu mediator $[Cu(OTf)_2(py)_4]$ (3 µmol, 0.1 equiv.), additive **5** (0.05-1.0 equiv.) and with dry DMF (150 µl). The vial was sealed under air and stirred vigorously until all components were dissolved (~30 s). A solution of $[^{18}F]KF/K_{222}$ in dry MeCN (~300 MBq in ~30 µl) was added through the septum to the reaction mixture before it was heated and stirred at 110 °C for 20 min. An aliquot (~10 µl) was removed and added to a solution of MeCN:H_2O = 1:1 (~500 µl) for radio HPLC analysis.

5.7. Radiosynthesis and Isolation of Melflufen Propyl Ester Analogue Radiotracer $[^{18}F]$1a



A dry 1 ml V-shaped vial containing a magnetic stirring bar was charged with the melflufen pinacol boronate analogue **3a** (30 µmol, 1.0 equiv.), the Cu mediator $[Cu(OTf)_2(py)_4]$ (3 µmol, 0.1 equiv.), the 2,2′-bipyridine (**5c**) (3 µmol, 0.1 equiv.) and subsequently with dry DMF (150 µl). The vial was sealed under air and stirred vigorously until all components were dissolved (~30 s). A solution of $[^{18}F]KF/K_{222}$ (3.4 GBq) in dry MeCN (~30 µl) was added through the septum to the reaction mixture, then it was heated and stirred at 110 °C for 20 min. An aliquot

(~10 µl) was removed and added to a solution of MeCN:H_2O = 1:1 (~500 µl) for analytical radio HPLC analysis (38% RCC).

The crude reaction mixture was purified by semi-preparative HPLC using a C-18 reversed phase column (ACE, ACE 5 SuperC18, 150x10 mm) and an eluent gradient system of ammonium formate (50 mM aq.)/MeCN (5.0 ml/min flow; linear increase 10% to 50% MeCN 0-15 min; isocratic 15-20 min; linear increase 50% to 90% MeCN 20-35 min; isocratic 35-40 min). Radiotracer **[^{18}F]1a** was collected in a fraction over 23 s with a retention time of t_R = 34.5 min.

Radiotracer **[^{18}F]1a** was obtained with an activity of 50 MBq, an activity yield AY = 1.5 %, a molar activity A_m = 2940 GBq/µmol and a radiochemical purity RCP = 100%.

Radiotracer **[^{18}F]1a** was characterised by comparing the radio-HPLC signal with the UV-HPLC signal of an authentic ^{19}F-reference (Figure S1).

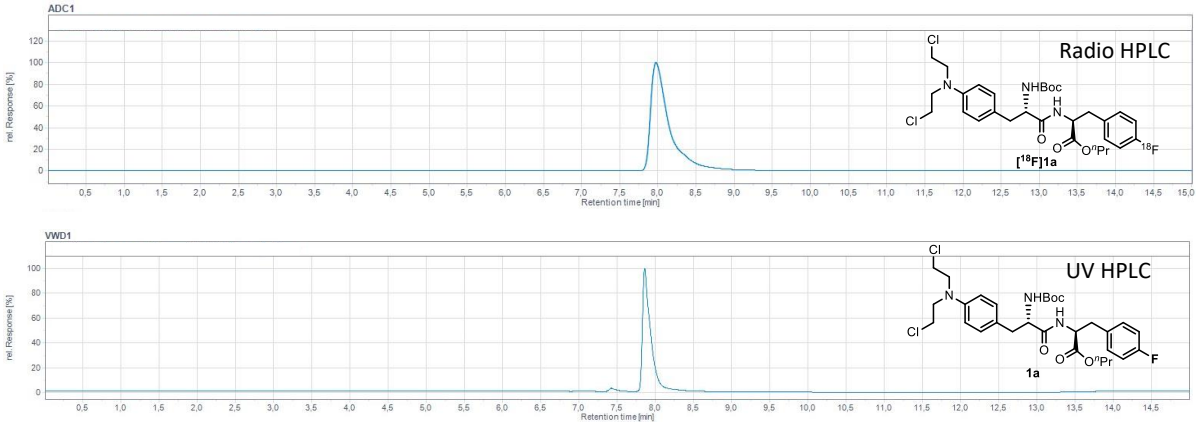


Figure S1. Radio-HPLC of **[^{18}F]1a** and UV-HPLC of authentic 19-fluorine reference **1a**.

Calibration Curve Melflufen Propyl Ester Analogue 1a

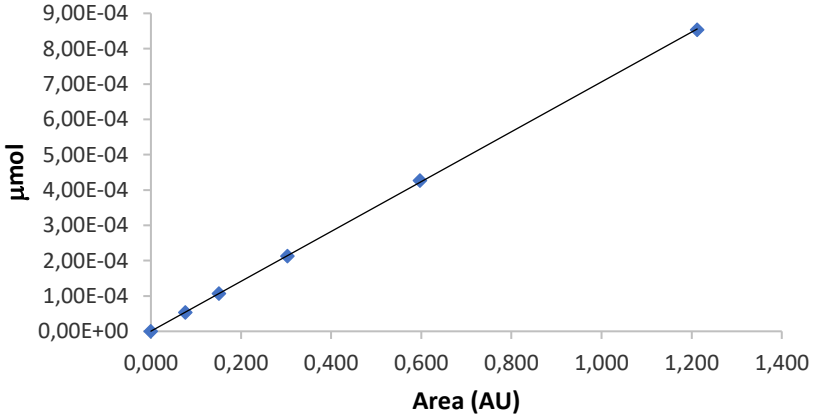


Figure S2. Calibration curve of **1a** for the determination of molar activity.

Table S 1. Data of calibration curve of **1a** (Figure S2).

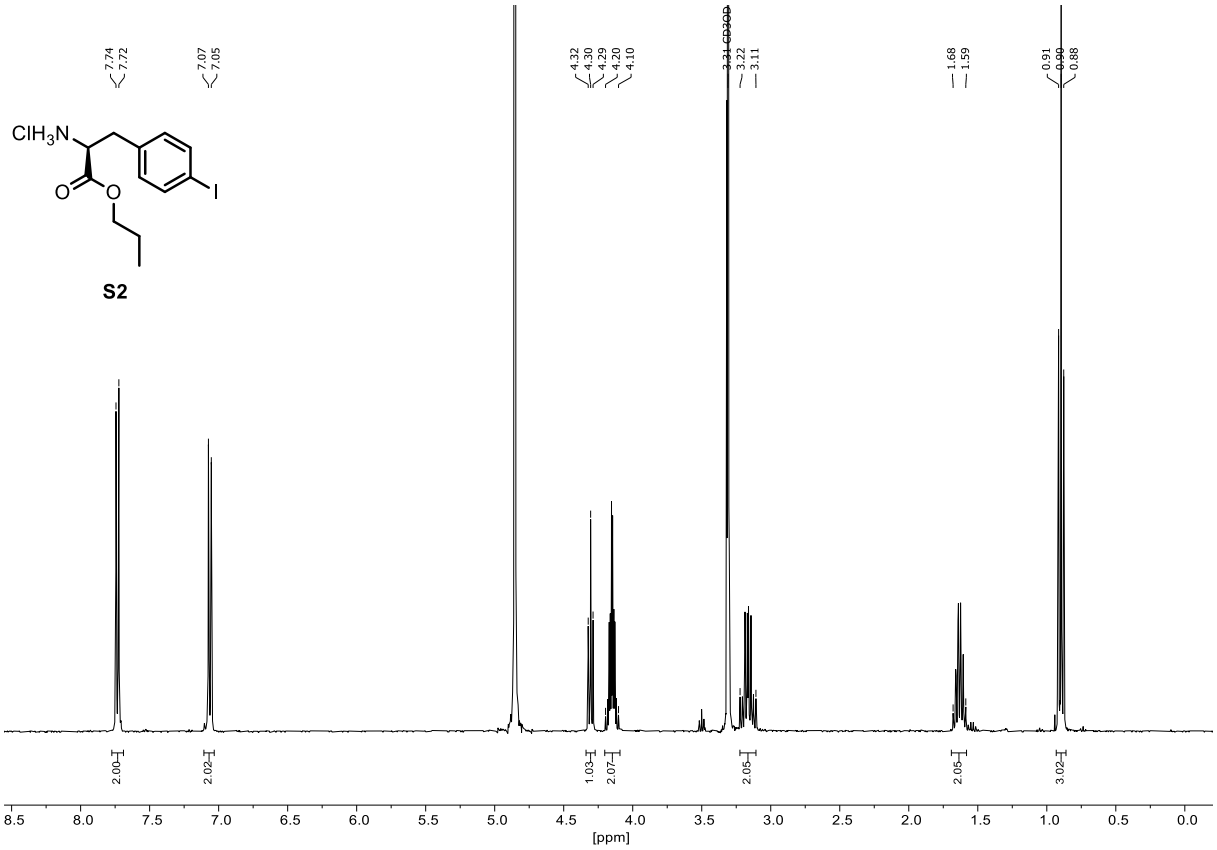
Injection	Concentration [µmol/µl]	Area [AU]	Injected amount [mmol]
1	$9{,}48 \cdot 10^{-6}$	1,212324	$8{,}54 \cdot 10^{-4}$
2	$4{,}74 \cdot 10^{-6}$	0,597181	$4{,}27 \cdot 10^{-4}$
3	$2{,}37 \cdot 10^{-6}$	0,303031	$2{,}13 \cdot 10^{-4}$
4	$1{,}19 \cdot 10^{-6}$	0,151382	$1{,}07 \cdot 10^{-4}$
5	$5{,}93 \cdot 10^{-7}$	0,076885	$5{,}33 \cdot 10^{-4}$

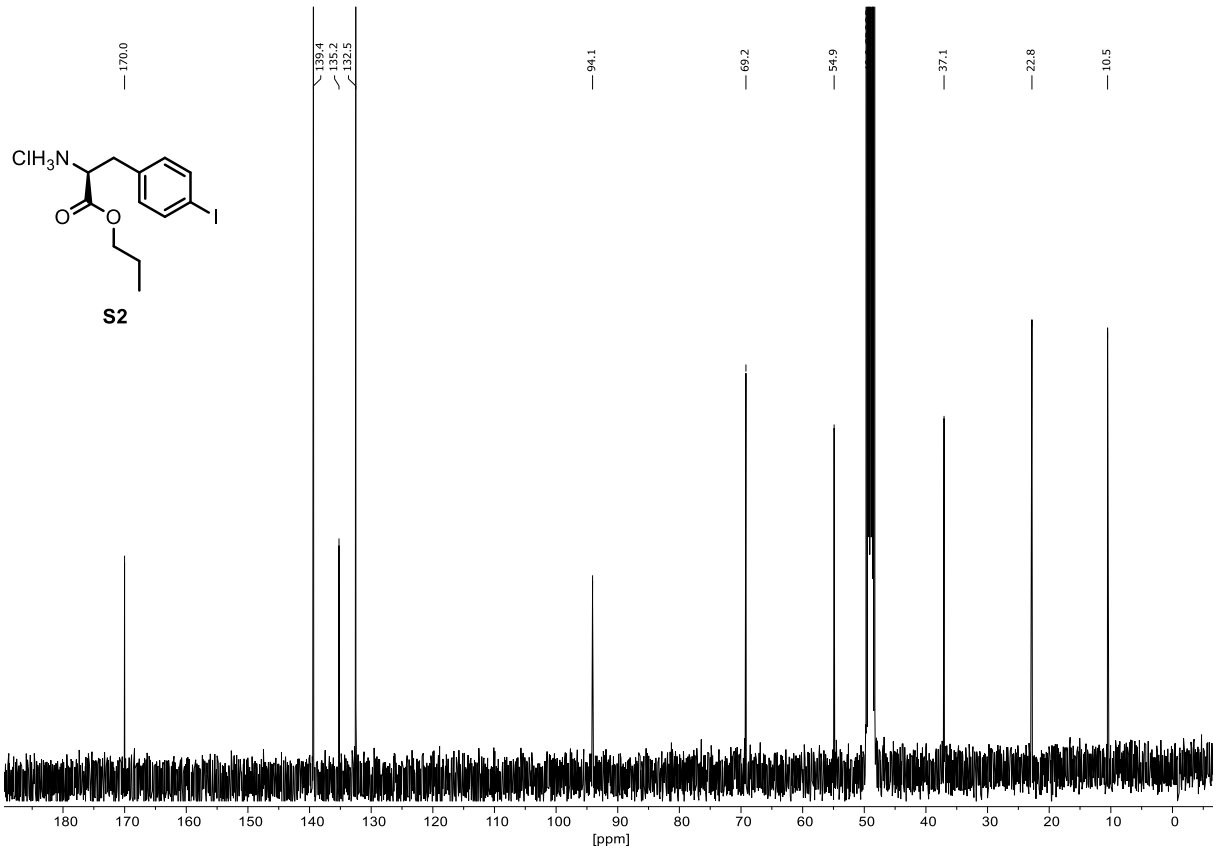
6. References

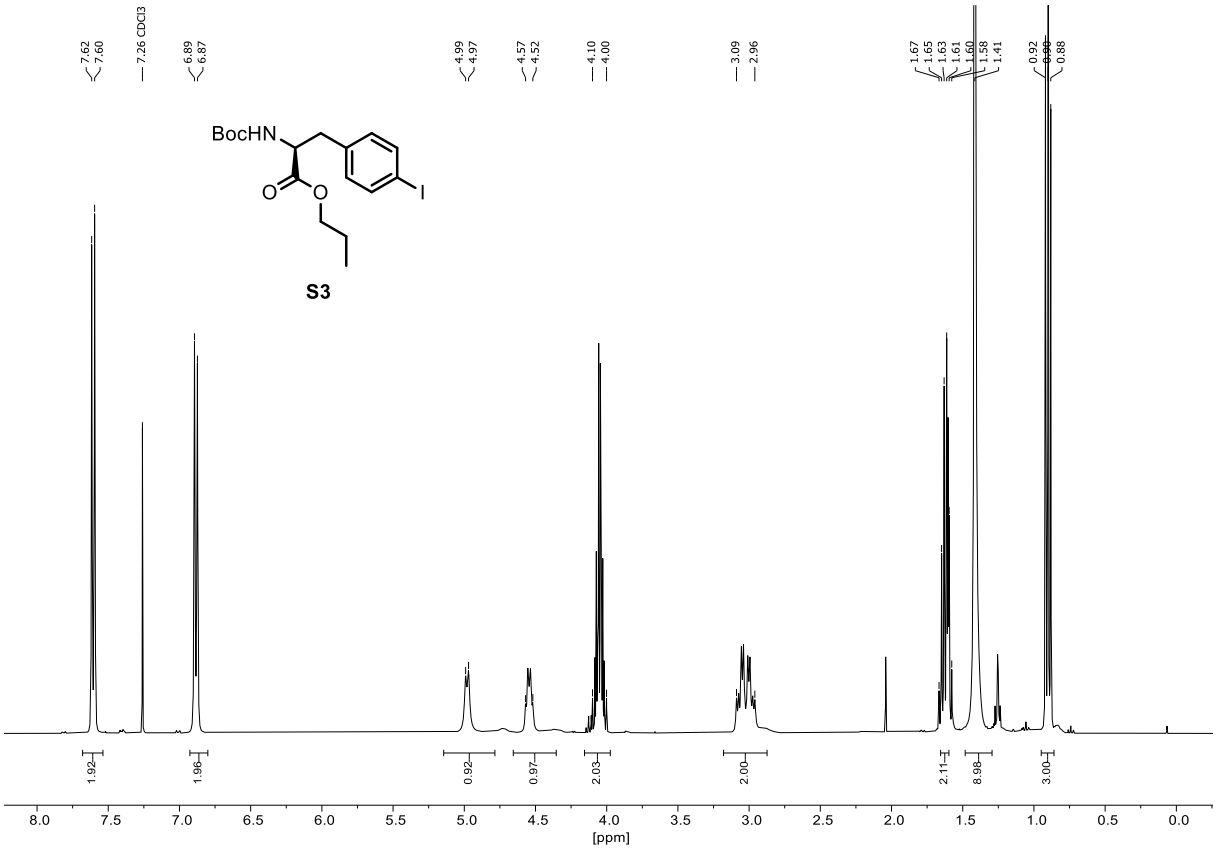
1. M. Hebel, A. Riegger, M. M. Zegota, G. Kizilsavas, J. Gačanin, M. Pieszka, T. Lückerath, J. A. S. Coelho, M. Wagner, P. M. P. Gois, D. Y. W. Ng and Tanja Weil, *J. Am. Chem. Soc.*, 2019, **141** (36), 14026.
2. H. Cotton, B. Bäckström, I. Fritzson, F. Lehmann, T. Monemi, V. Oltner, E. Sölver, N. Wahlström and J. Wennerberg, *Org. Process Res. Dev.*, 2019, **23** (6), 1191.
3. S. Trofymchuk, A. Bezdudny, Y. Pustovit and P. K. Mykhailiuk, *Journal of Fluorine Chemistry*, 2015, **171**, 174.

7. Appendix

7.1. NMR Spectra



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2.96
1.67
1.65
1.63
1.61
1.60
1.58
1.41
0.92
0.88
BocHN
O
O
I
S3
1.92
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0.92
0.97
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7.5
7.0
6.5
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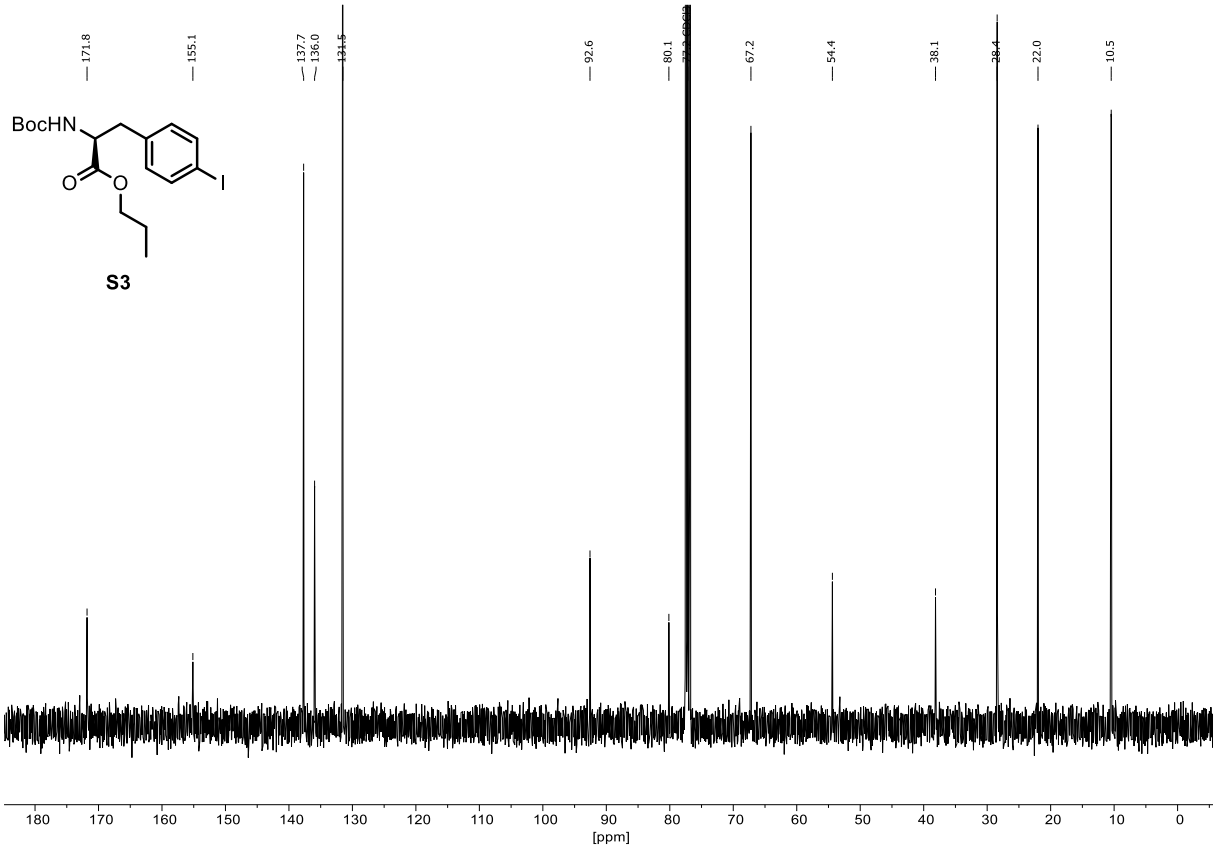
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10.5
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O
O
I
S3
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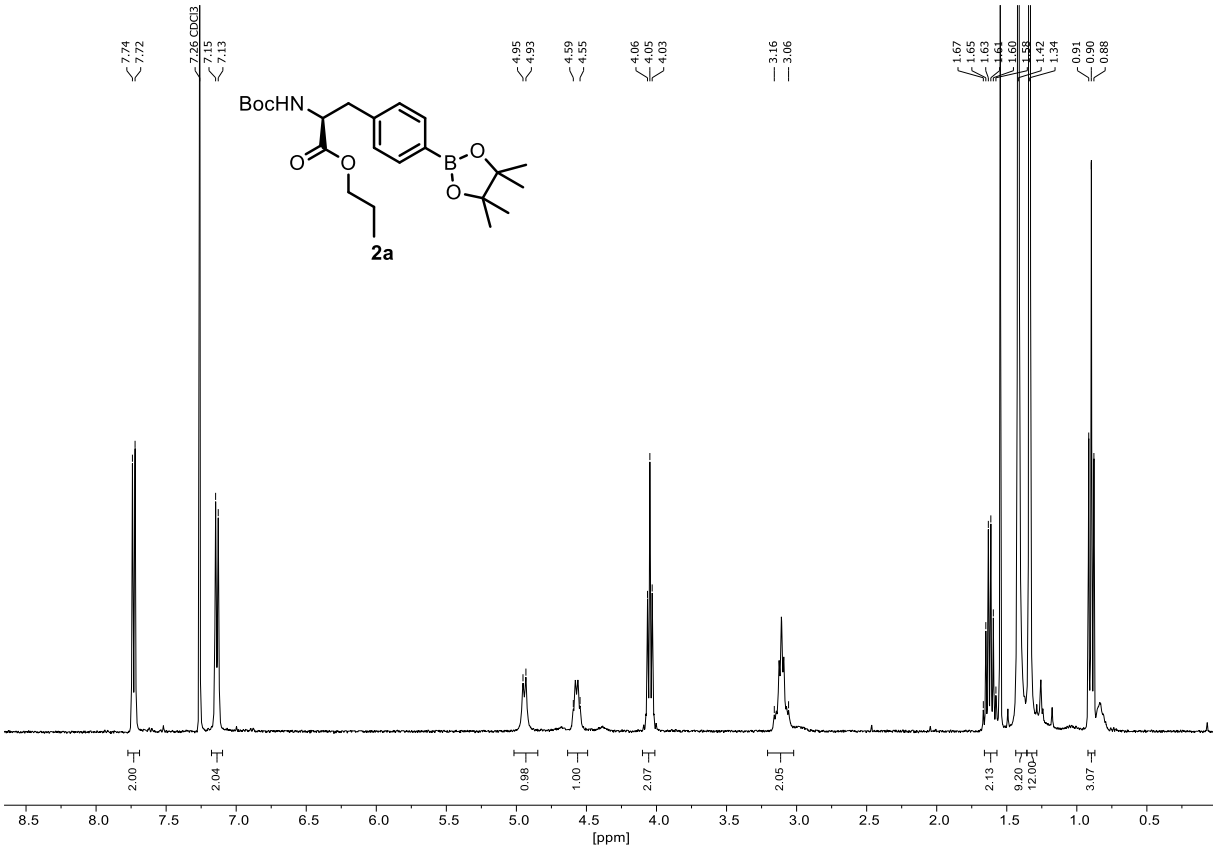
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3.06
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1.60
1.58
1.42
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0.90
0.88
BocHN
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O
O
B
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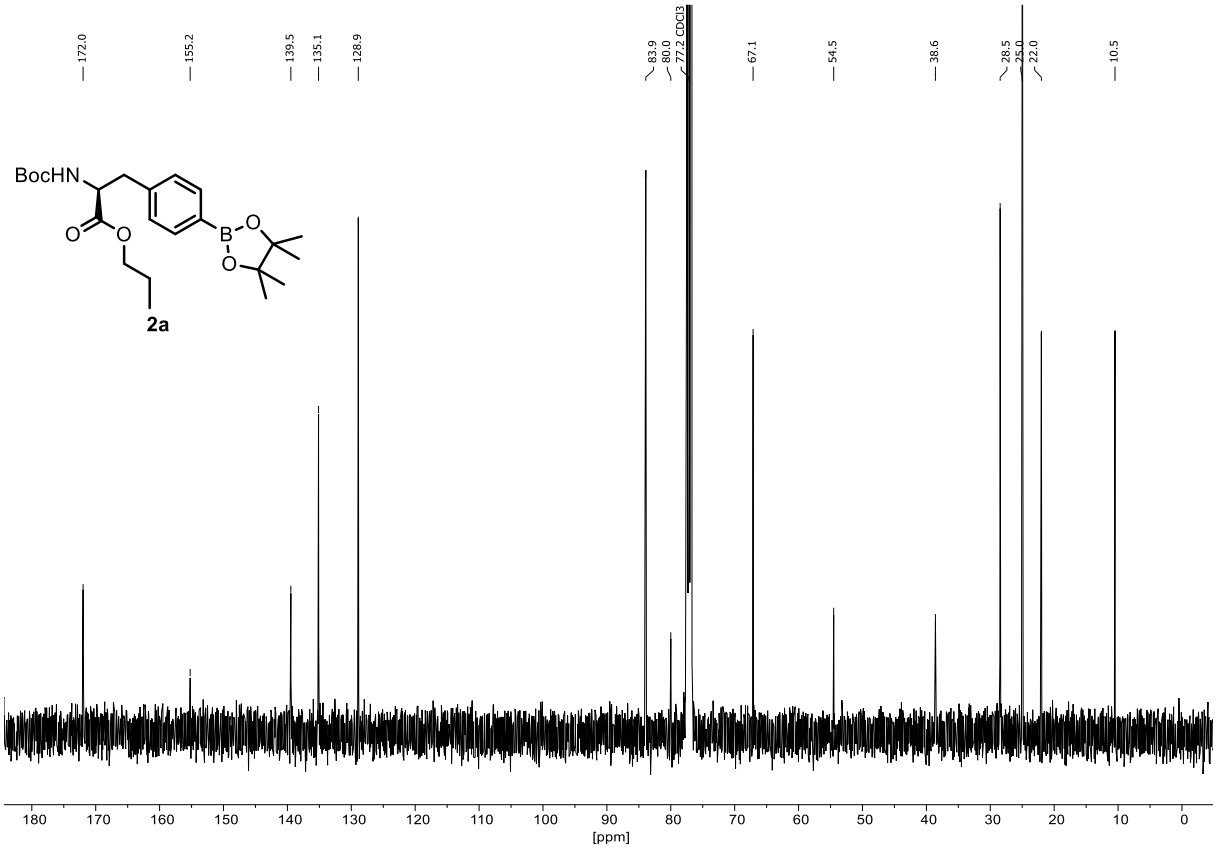
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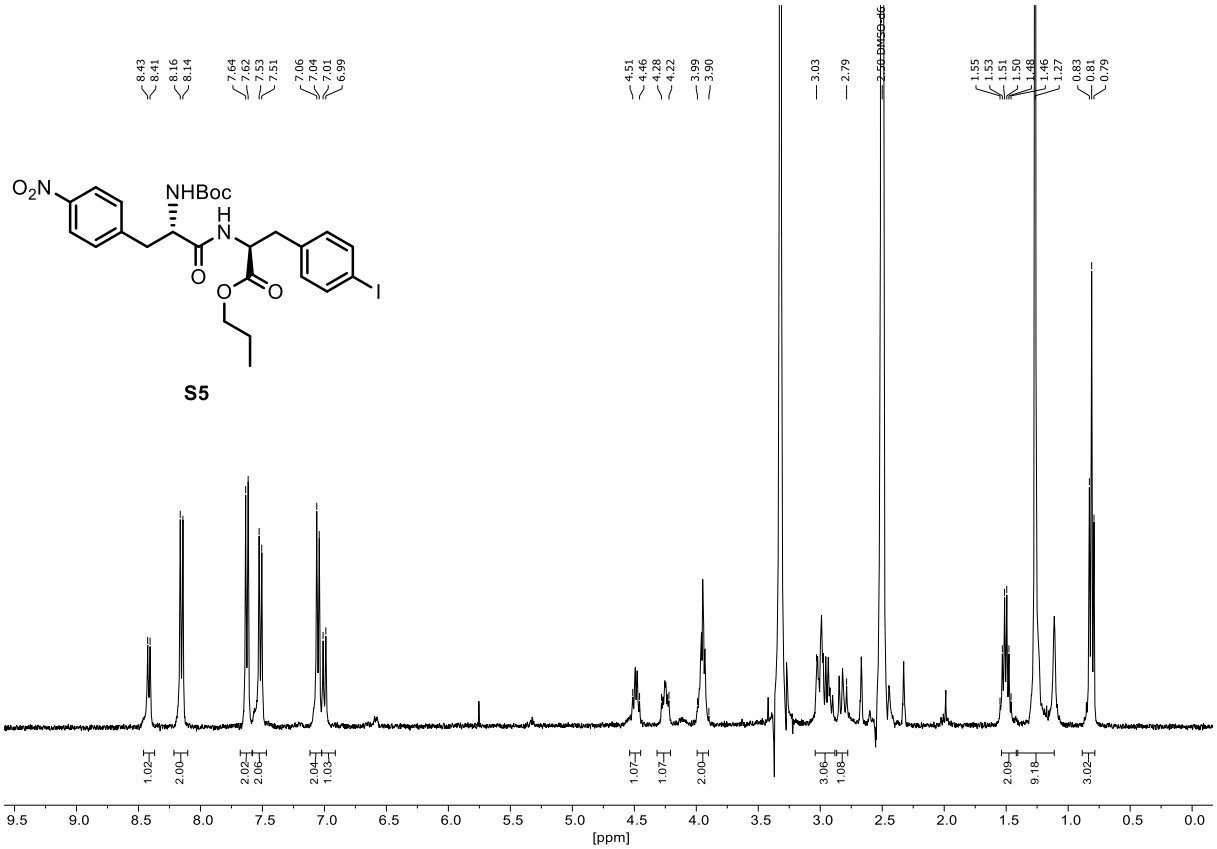
B
O
2a
[ppm]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1.53
1.51
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1.46
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0.79
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NHBoc
H
N
O
O
O
I
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2.00
2.02
2.06
2.04
1.03
1.07
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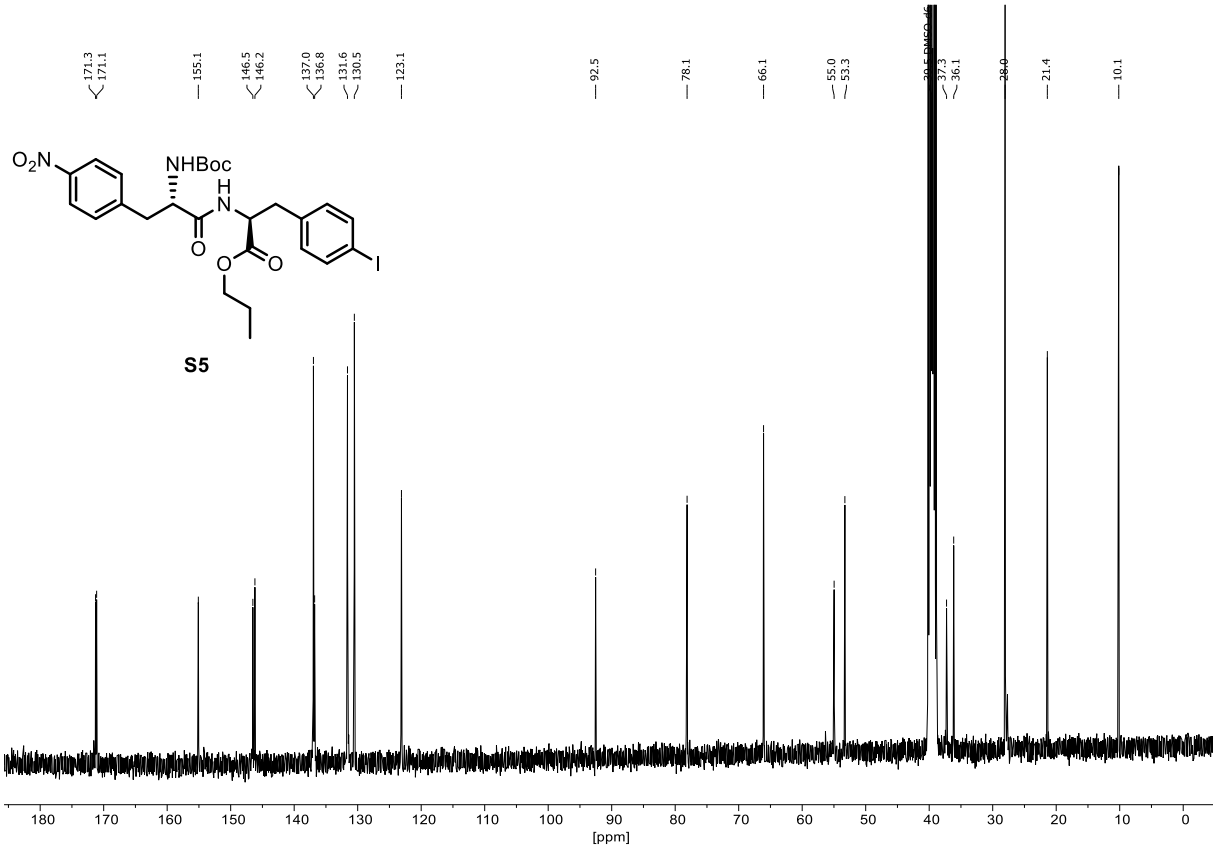
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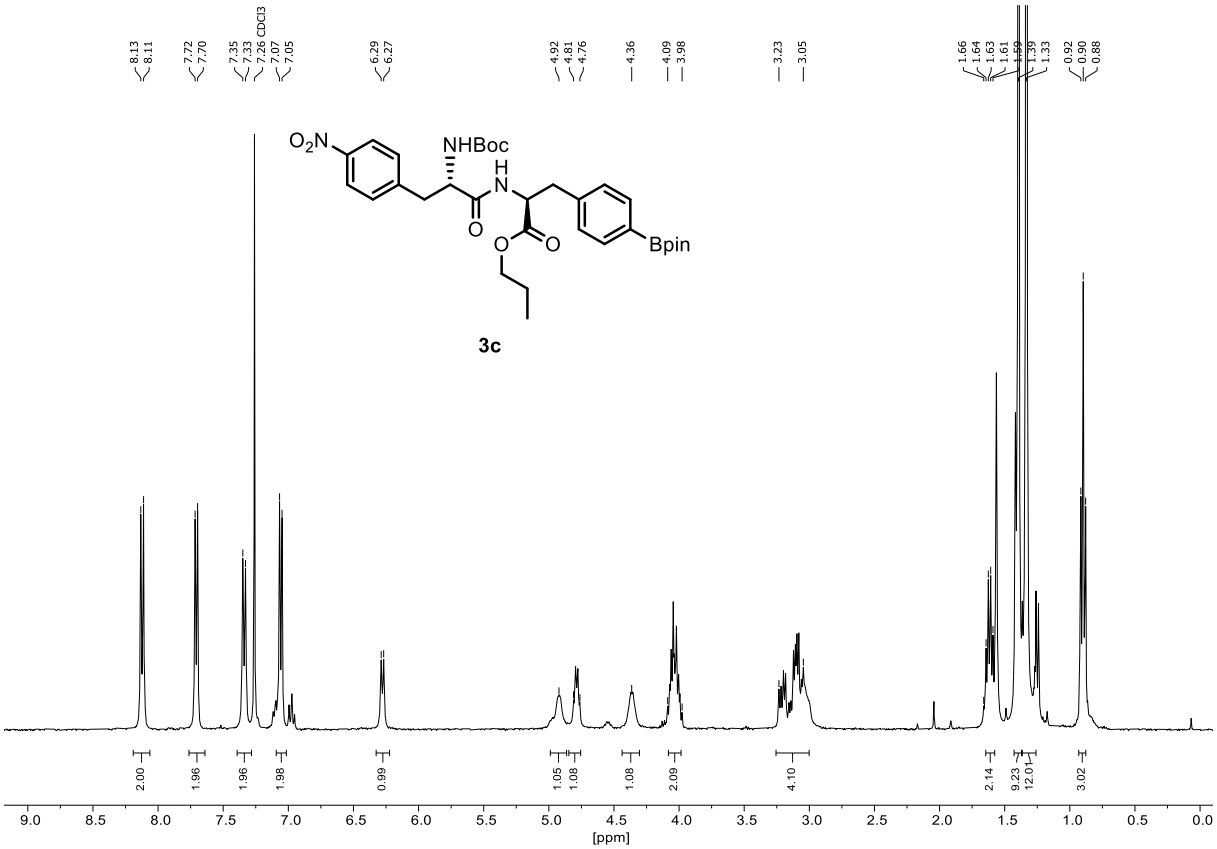
S5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1.61
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0.88
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NHBoc
H
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O
O
O
Bpin
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1.96
1.98
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1.05
1.08
1.08
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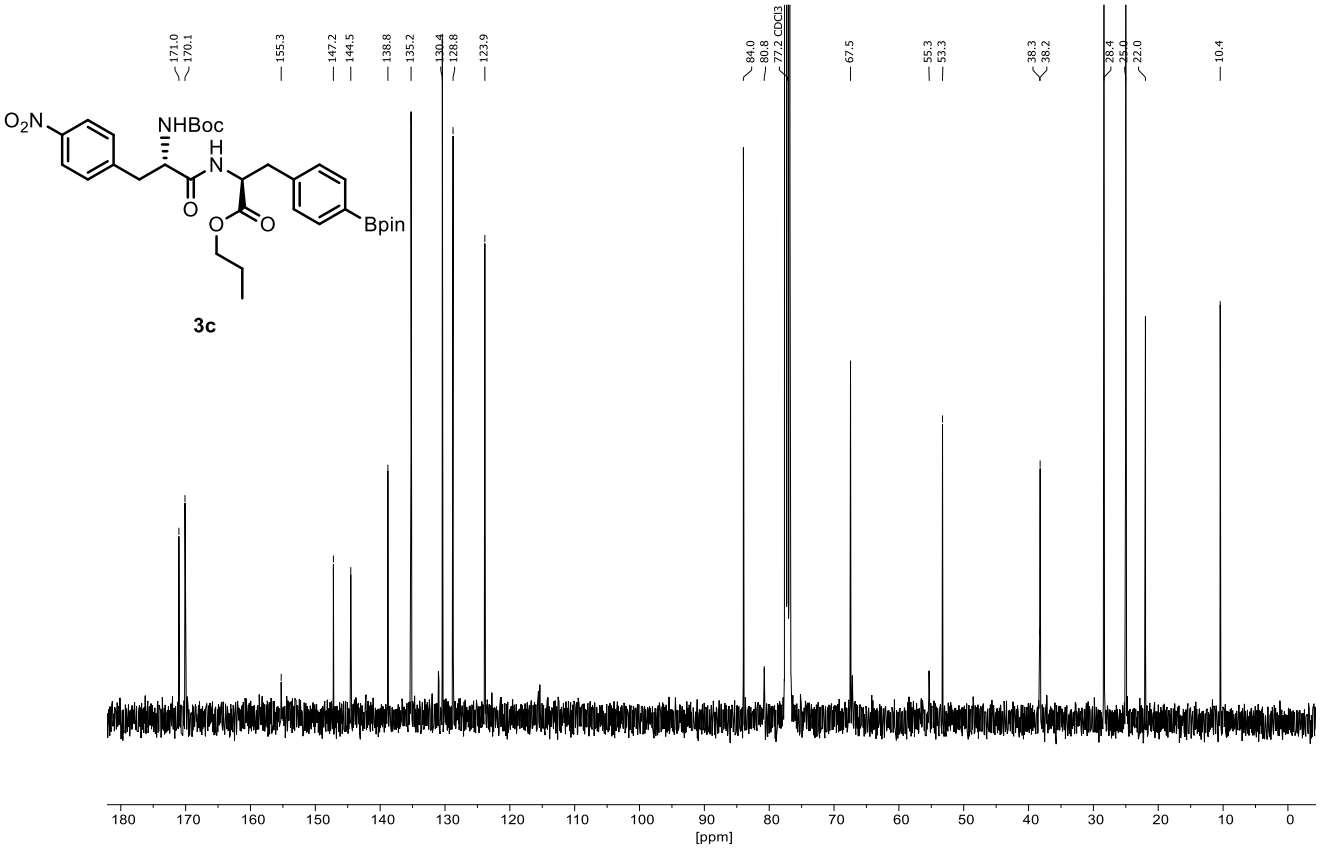
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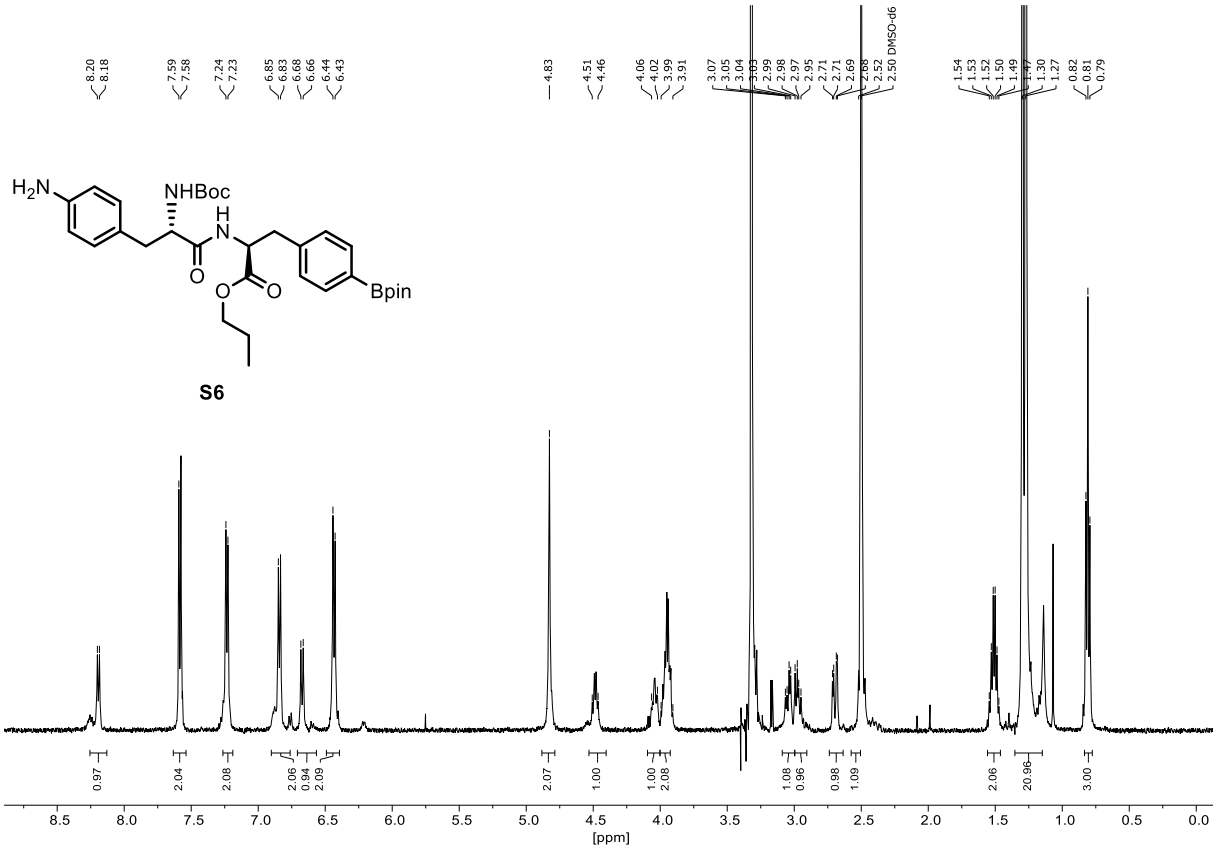
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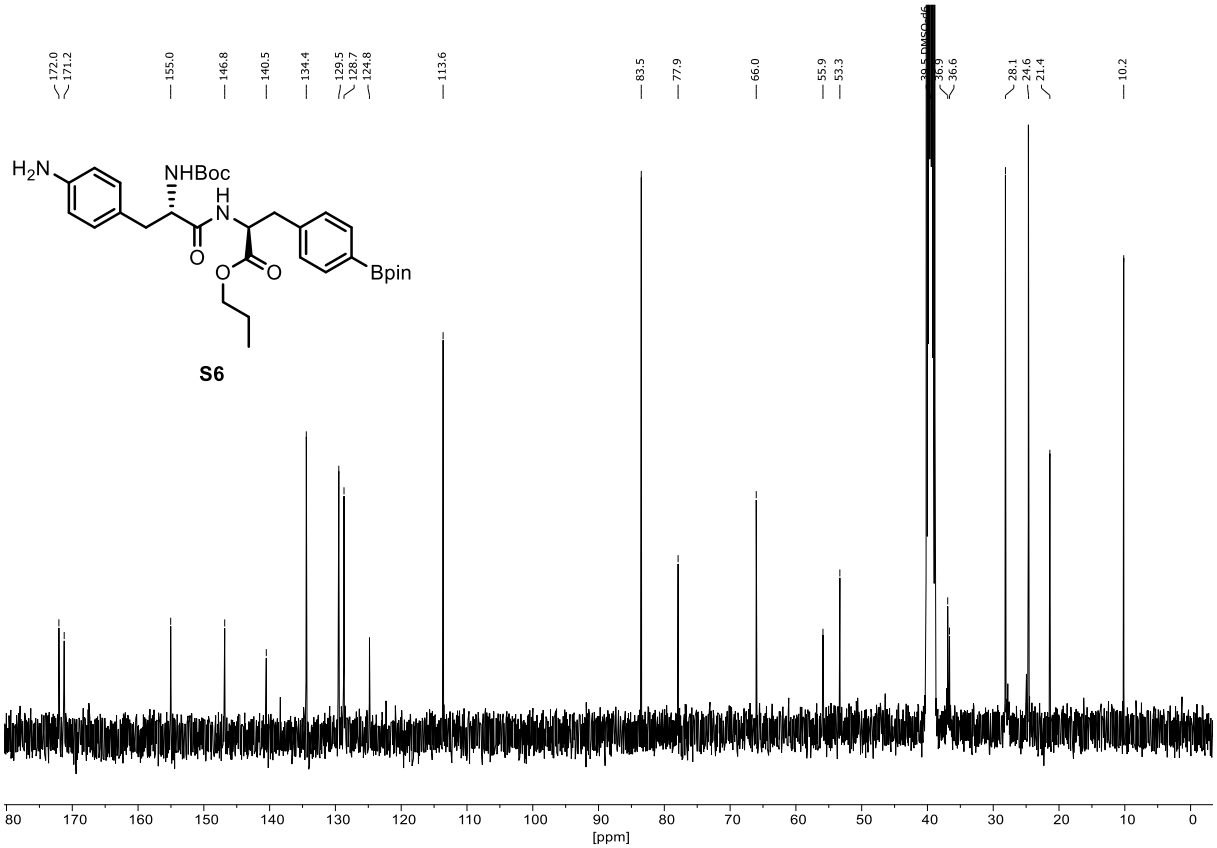
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10.2
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NHBoc
H
N
O
O
O
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Bpin
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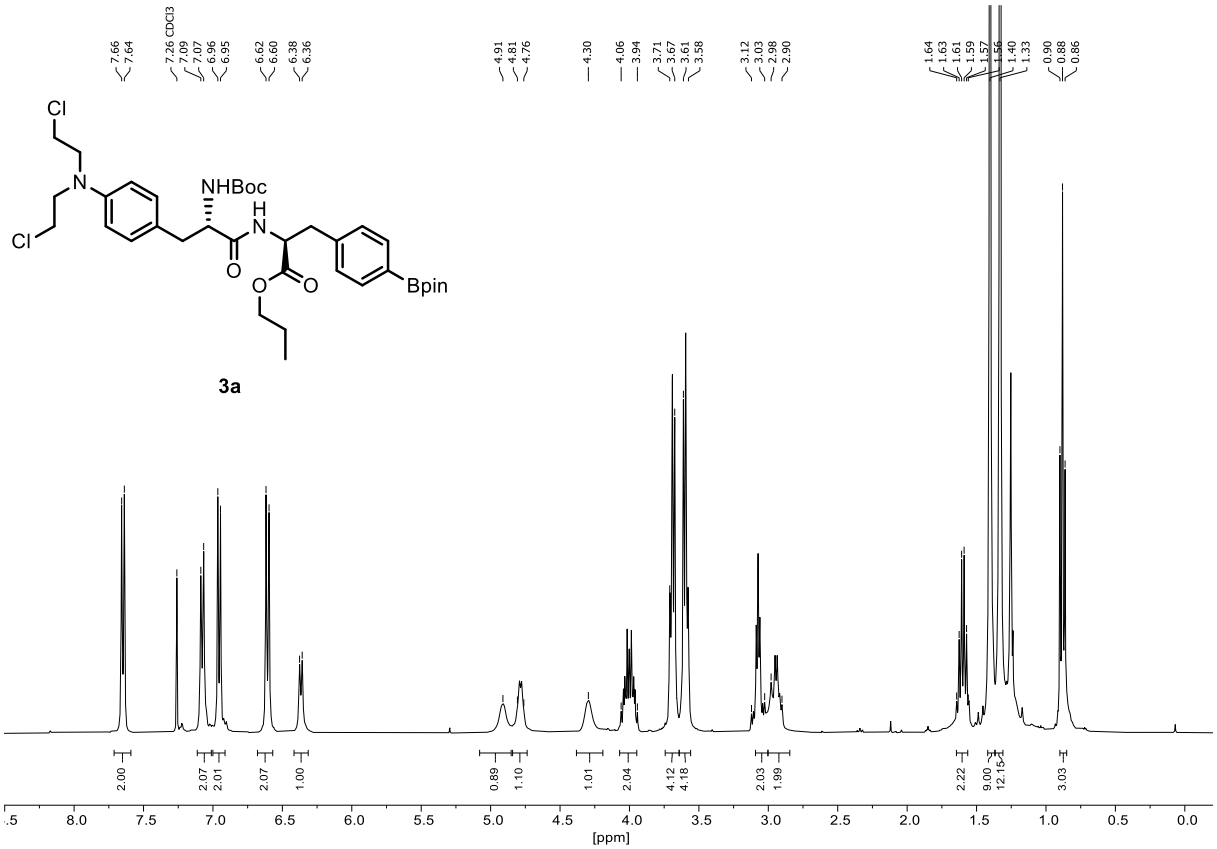
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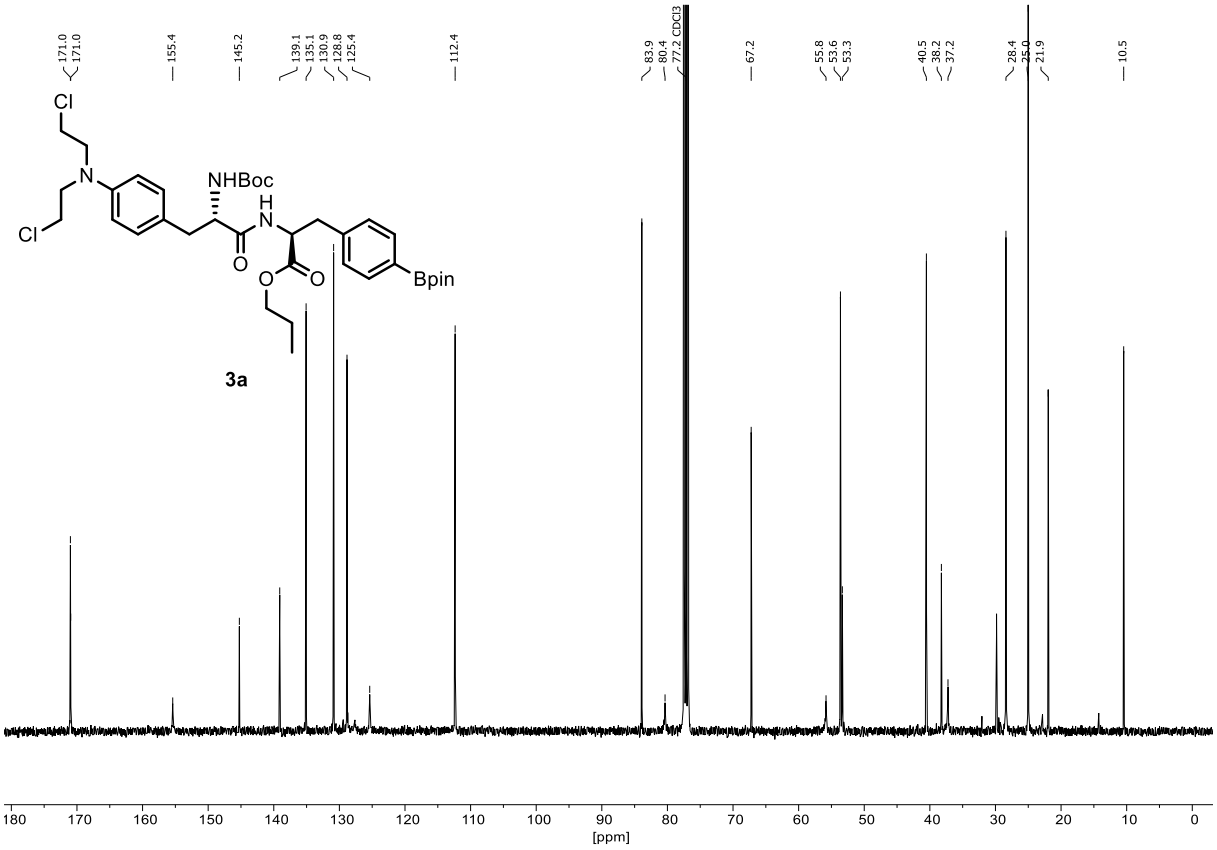
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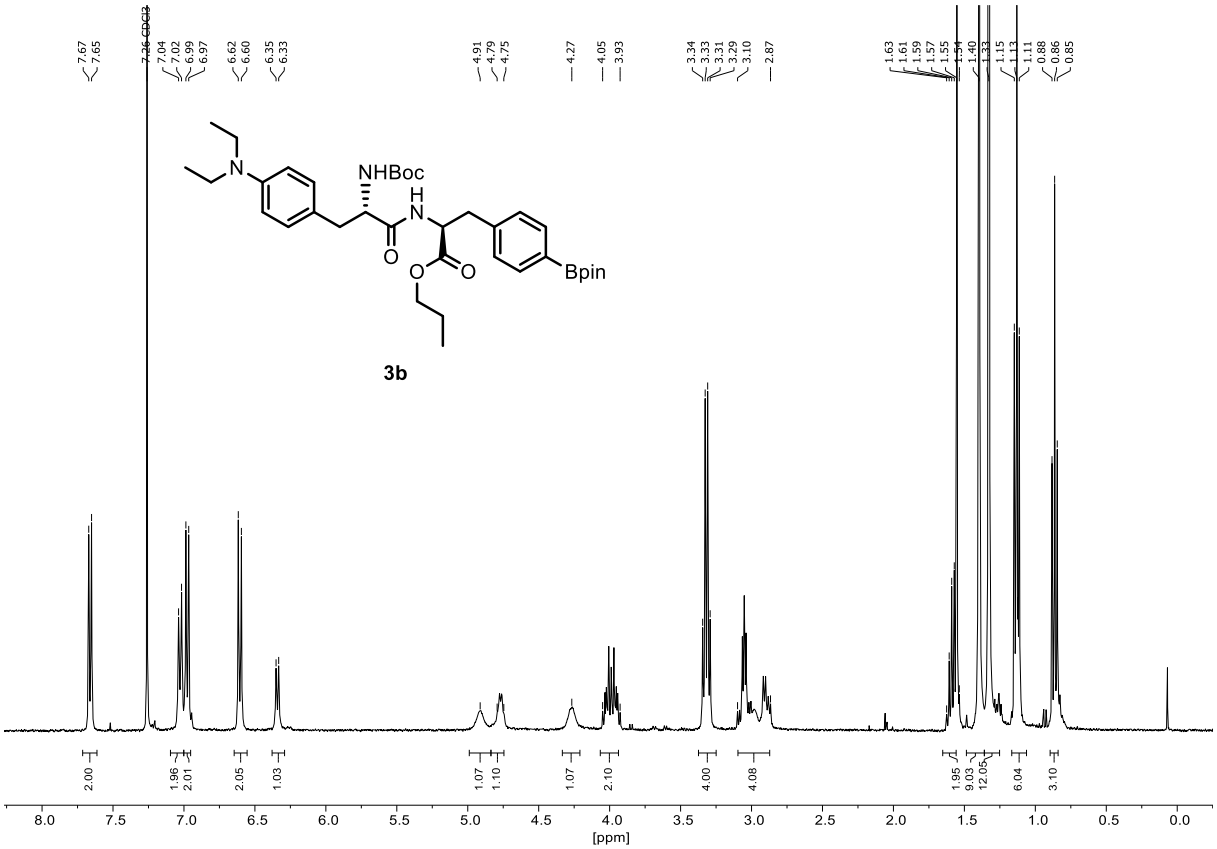
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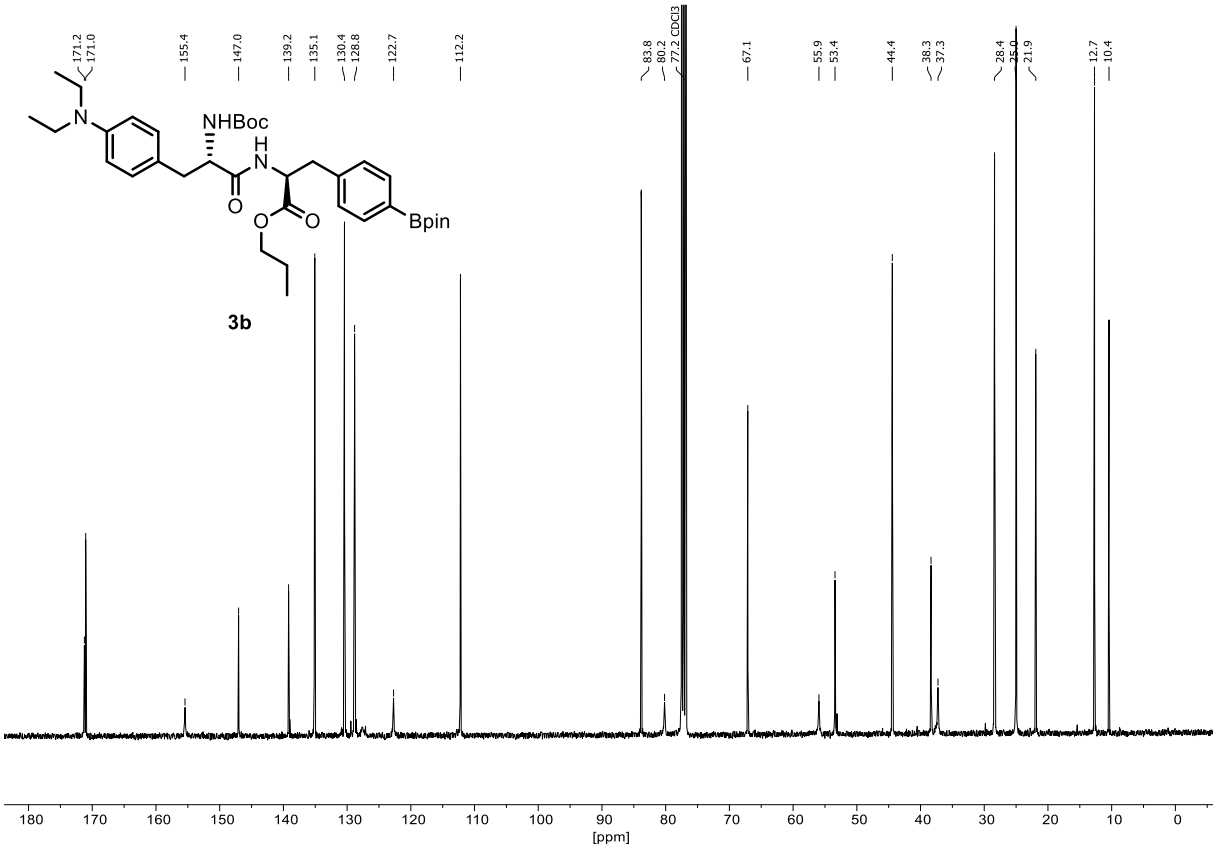
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12.7
10.4
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O
O
Bpin
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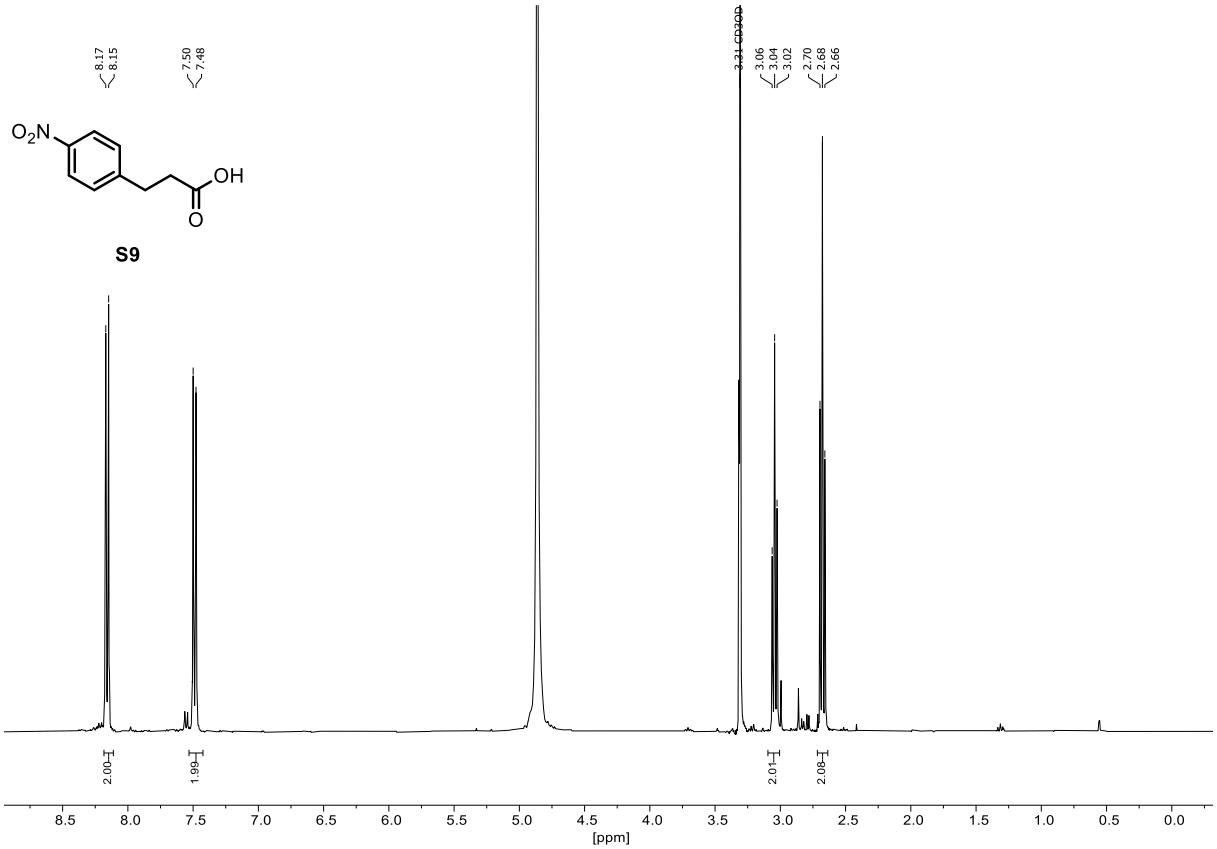
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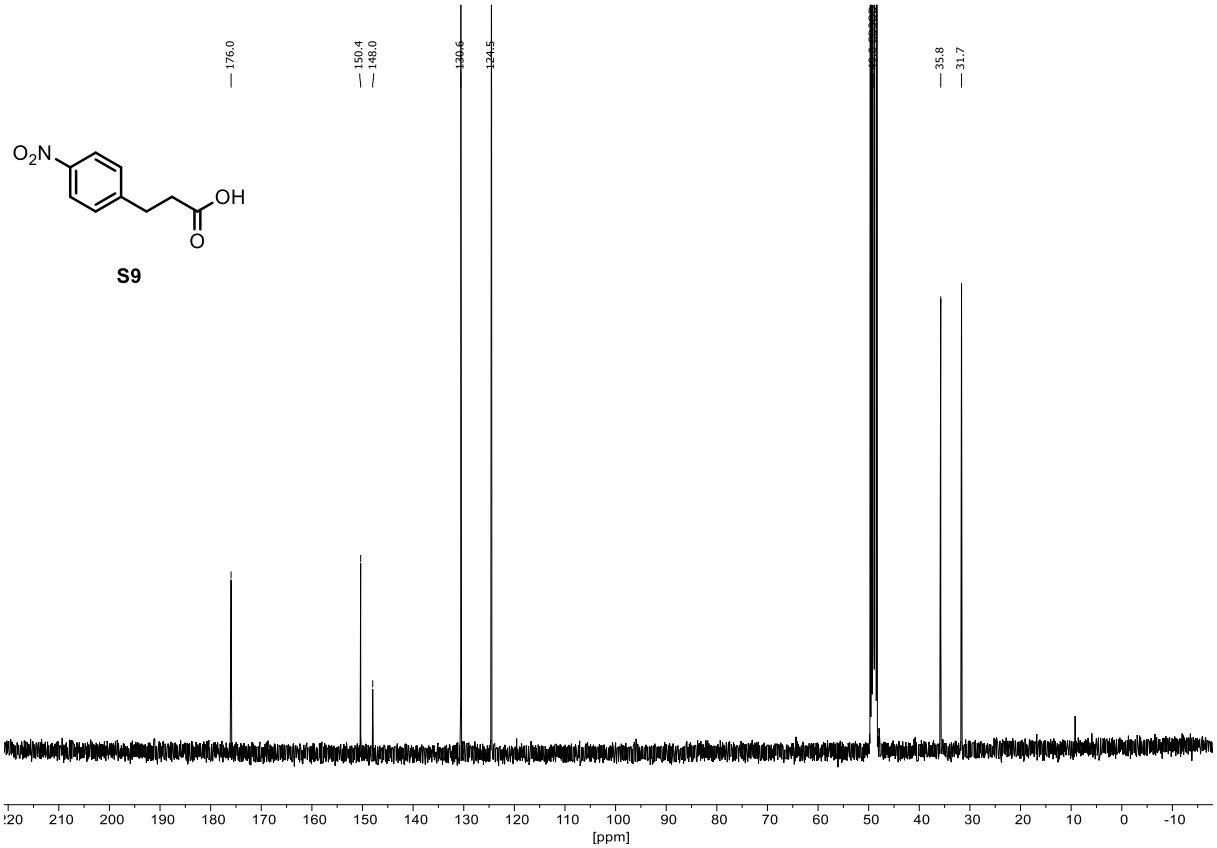
S9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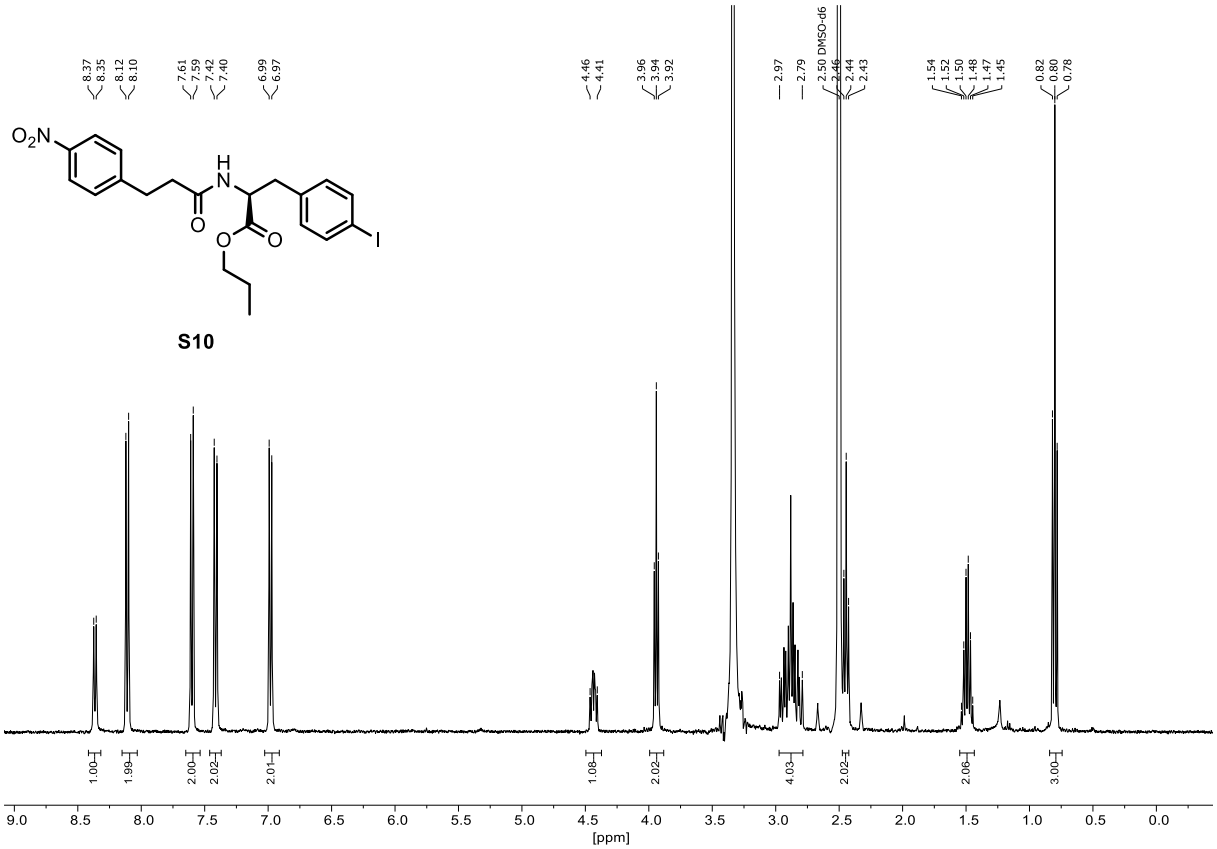
S9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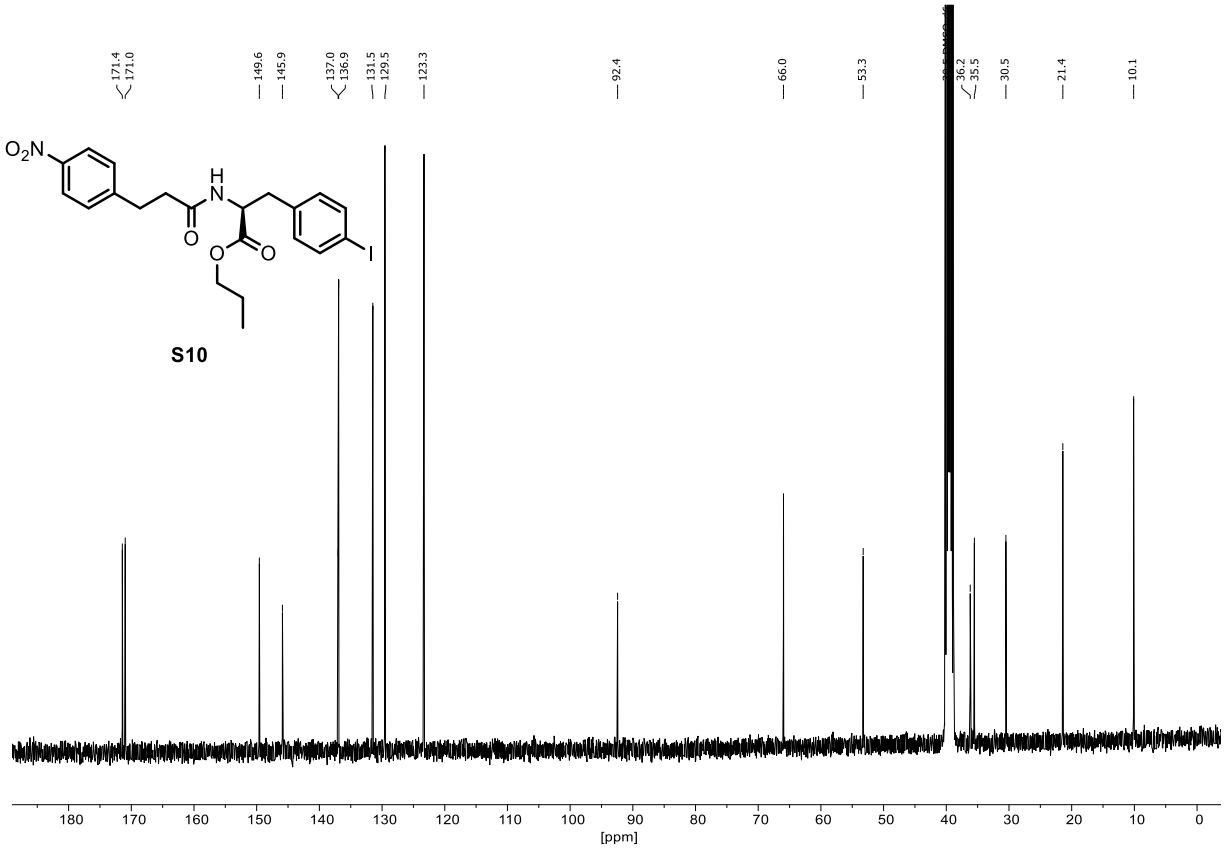
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35.5
30.5
21.4
10.1
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O
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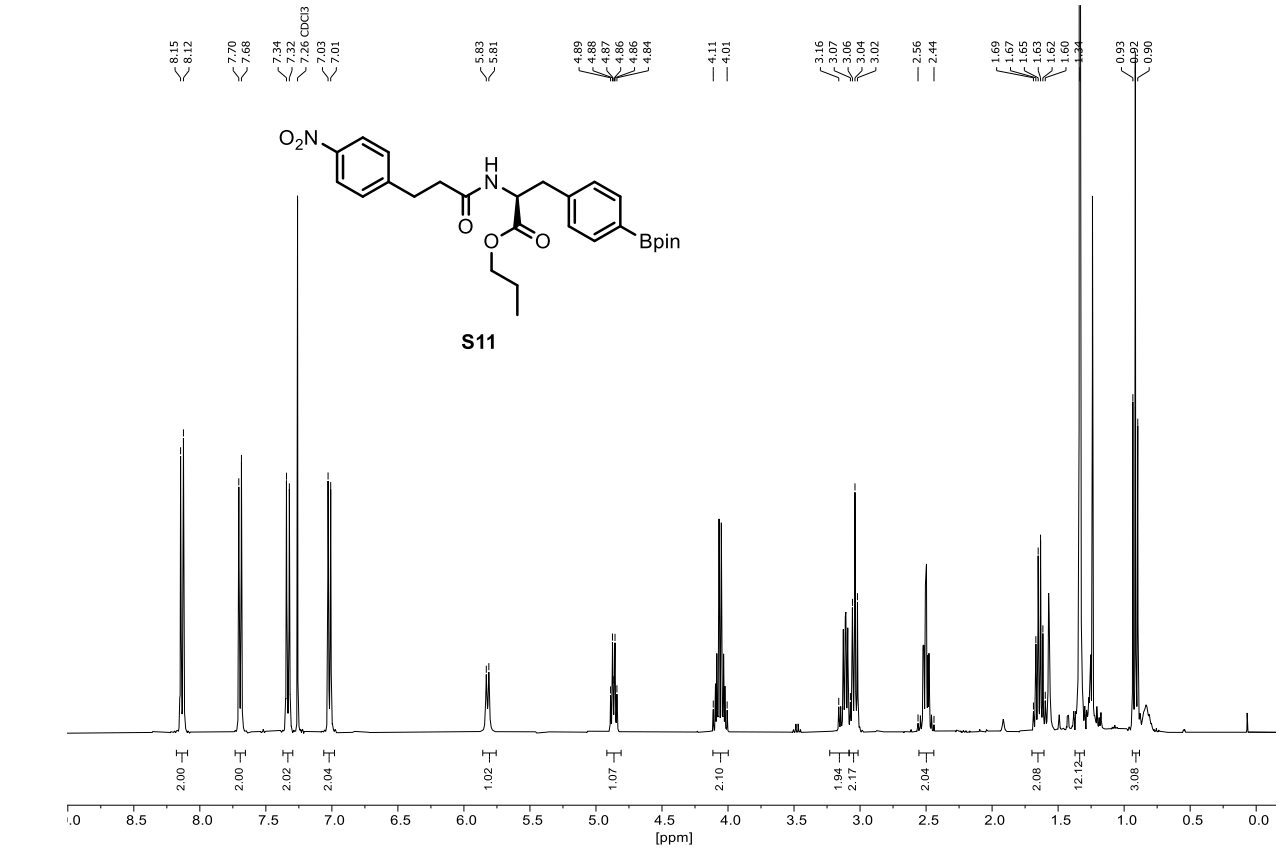
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4.87
4.86
4.86
4.84
4.11
4.01
3.16
3.07
3.06
3.04
3.02
2.56
2.44
1.69
1.67
1.65
1.63
1.62
1.60
1.34
0.93
0.92
0.90
O2N
H
N
O
O
O
Bpin
S11
2.00
2.00
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1.02
1.07
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1.94
2.17
2.04
2.08
12.12
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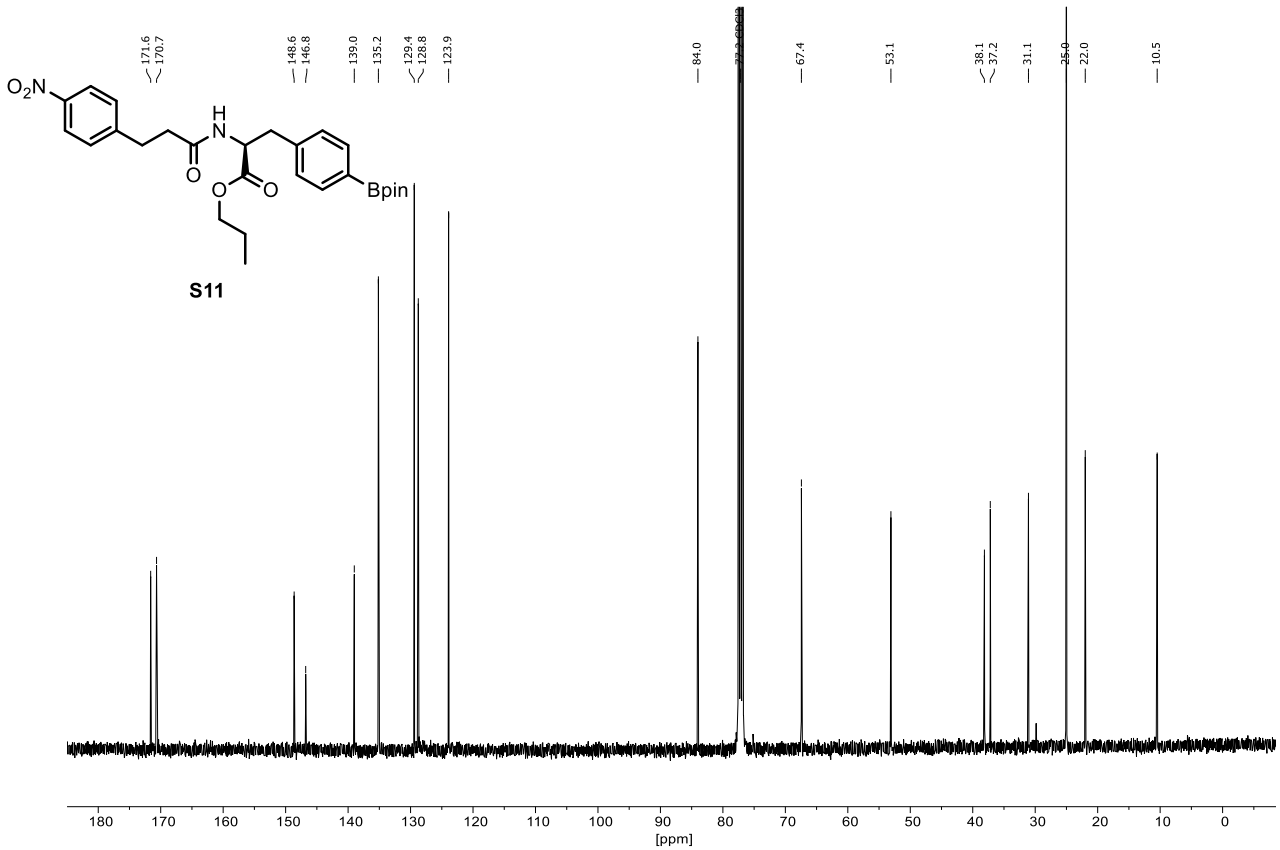
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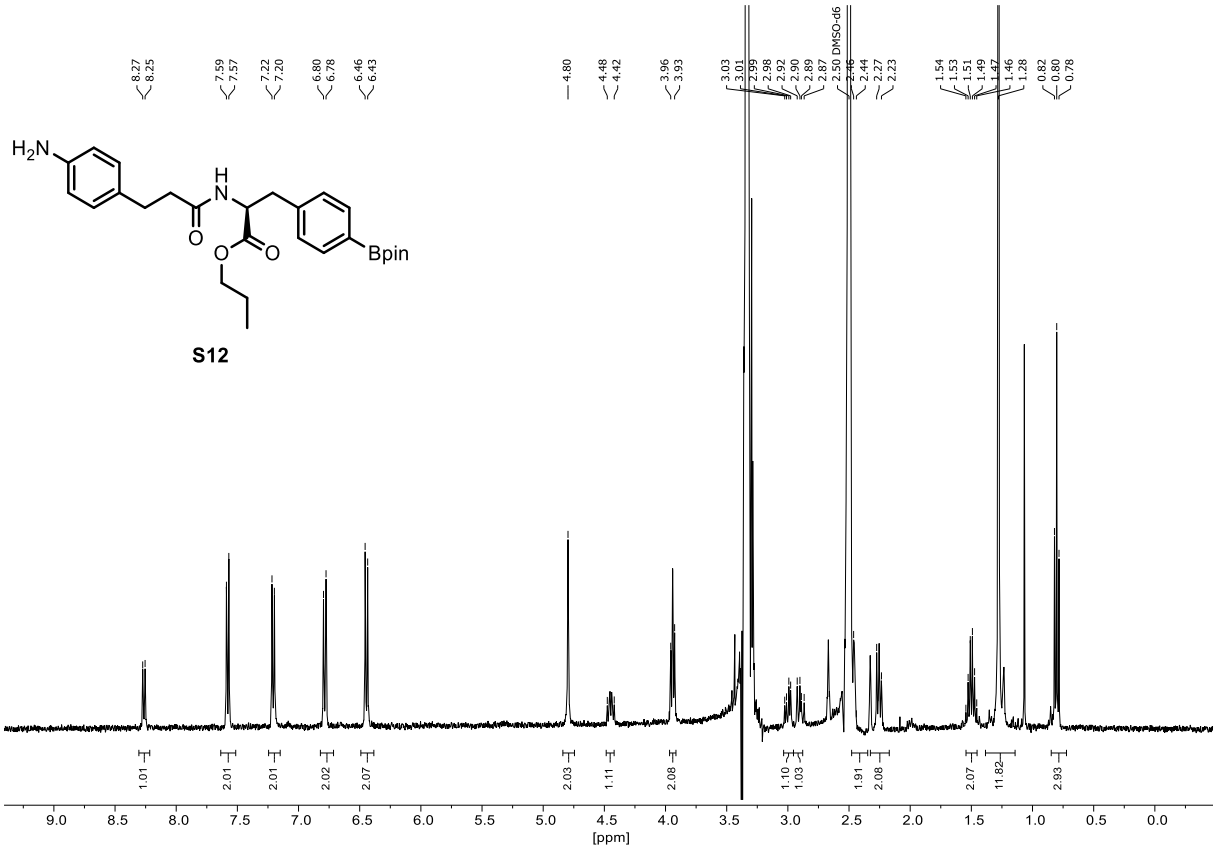
22.0
10.5
O2N
H
N
O
O
O
Bpin
S11
[ppm]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6.43
4.80
4.48
4.42
3.96
3.93
3.03
3.01
2.99
2.98
2.92
2.90
2.87
2.50 DMSO-d6
2.36
2.44
2.27
2.23
1.54
1.53
1.51
1.49
1.47
1.46
1.28
0.82
0.80
0.78
1.01
2.01
2.01
2.02
2.07
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1.11
2.08
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1.03
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2.08
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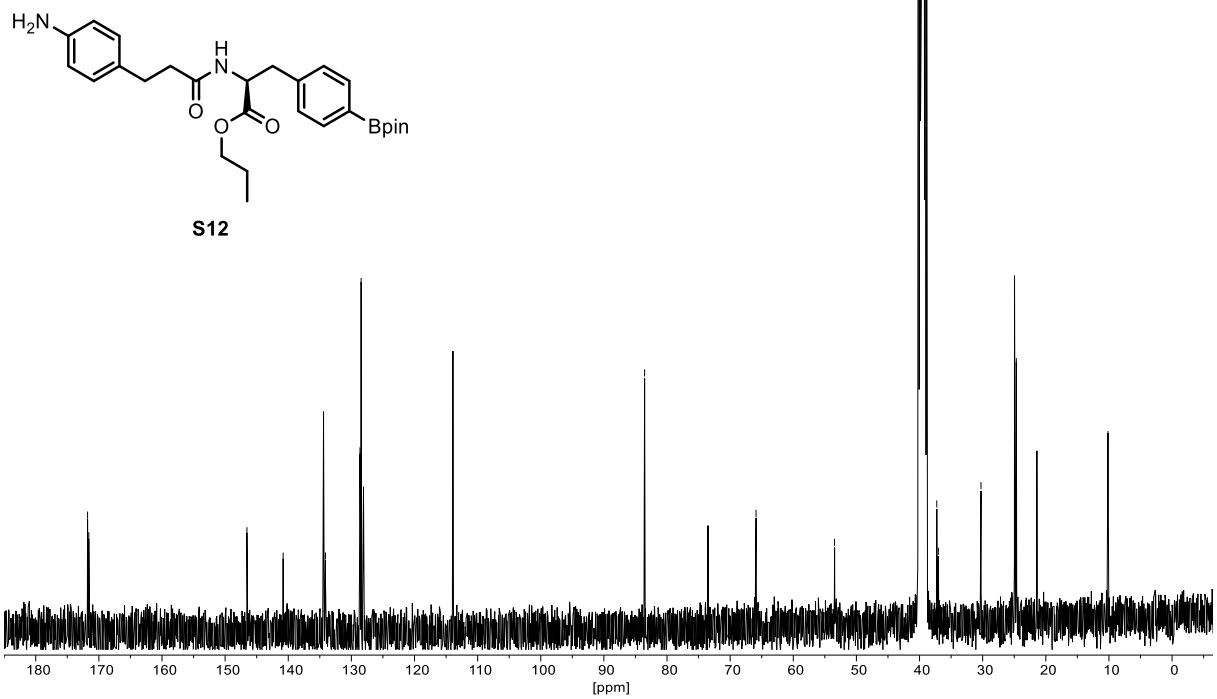
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134.1
128.6
128.5
128.1
113.9
83.6
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53.5
39.5 DMSO-d6
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10.2
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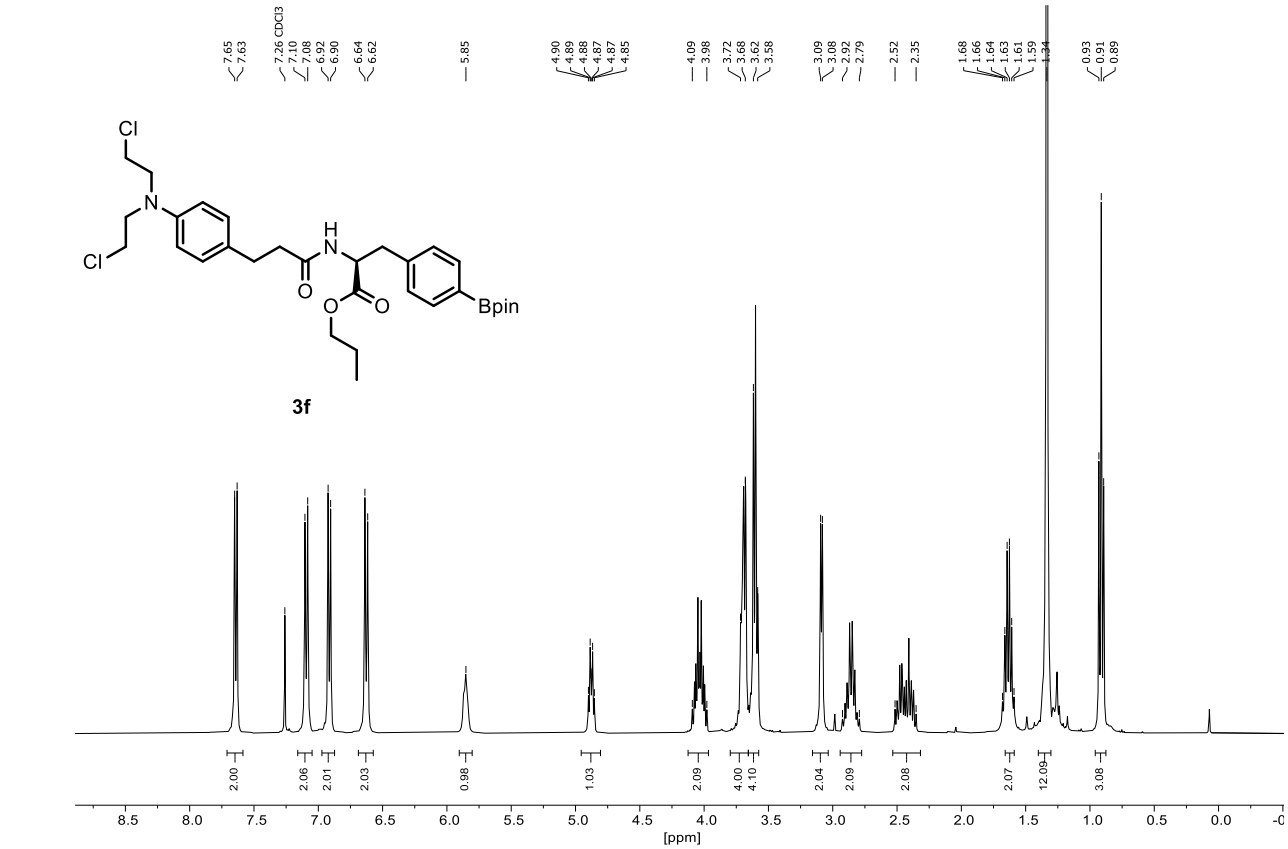
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7.63
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7.10
7.08
6.92
6.90
6.64
6.62
5.85
4.90
4.89
4.88
4.87
4.87
4.85
4.09
3.98
3.72
3.68
3.62
3.58
3.09
3.08
2.92
2.79
2.52
2.35
1.68
1.66
1.64
1.63
1.61
1.59
1.34
0.93
0.91
0.89
Cl
N
Cl
H
N
O
O
O
Bpin
2.00
2.06
2.01
2.03
0.98
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2.09
4.00
4.10
2.04
2.09
2.08
2.07
12.09
3.08
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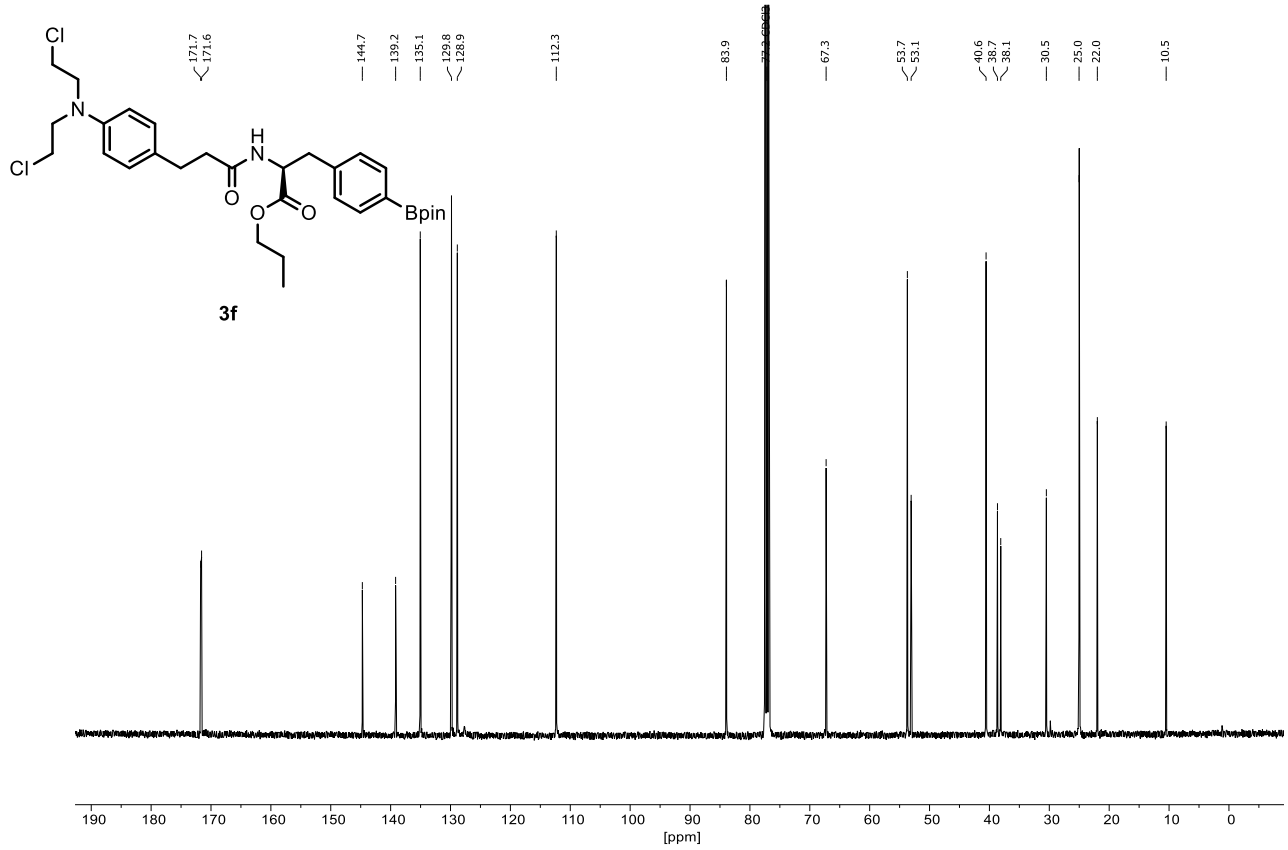
3f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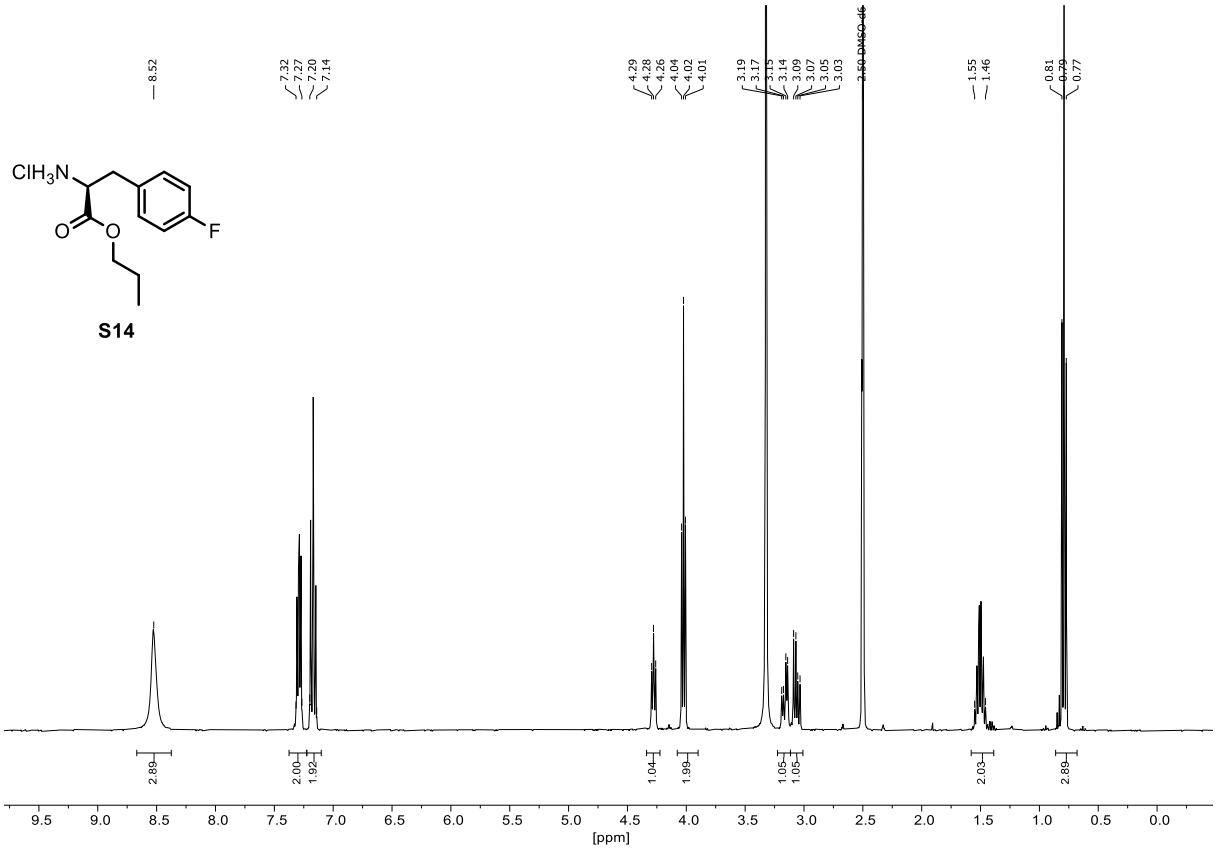
139.2
135.1
129.8
128.9
112.3
83.9
77.2
67.3
53.7
53.1
40.6
38.7
38.1
30.5
25.0
22.0
10.5
Cl
N
Cl
H
N
O
O
O
Bpin
[ppm]

3f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7.32
7.27
7.20
7.14
4.29
4.28
4.26
4.04
4.02
4.01
3.19
3.17
3.15
3.14
3.09
3.07
3.05
3.03
3.50 DMSO 46
1.55
1.46
0.81
0.79
0.77
ClH3N
O
O
F
S14
2.89
2.00
1.92
1.04
1.99
1.05
1.05
2.03
2.89
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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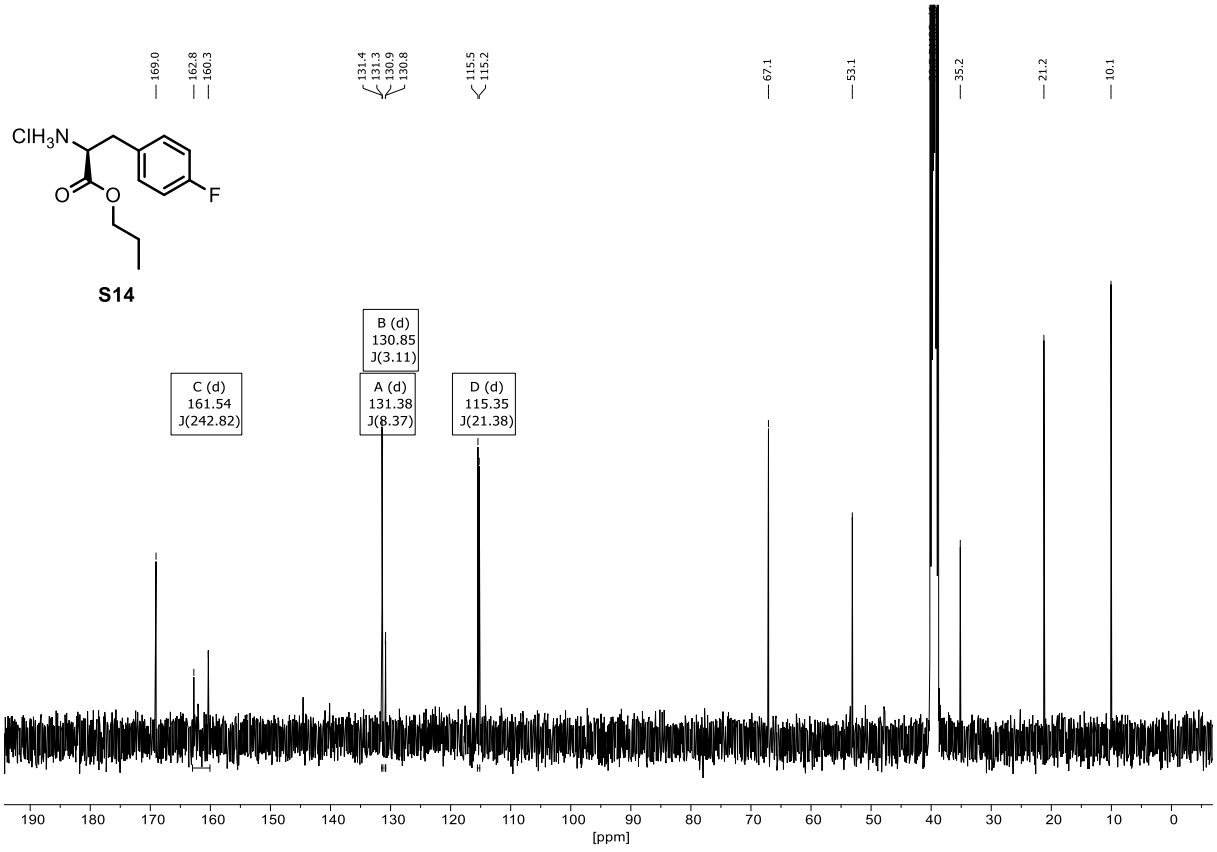
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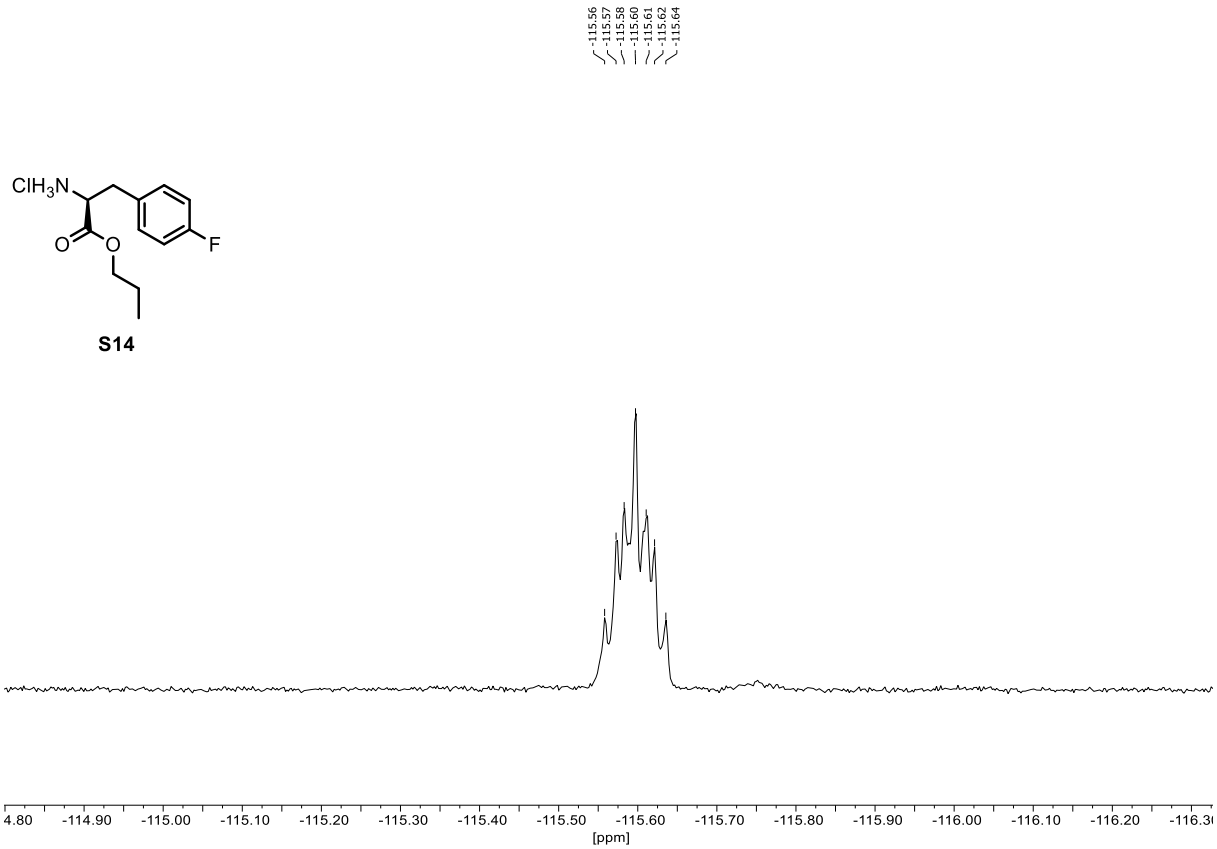
162.8
160.3
131.4
131.3
130.9
130.8
115.5
115.2
67.1
53.1
35.2
21.2
10.1
ClH3N
O
O
F
S14
B (d)
130.85
J(3.11)
C (d)
161.54
J(242.82)
A (d)
131.38
J(8.37)
D (d)
115.35
J(21.38)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
[ppm]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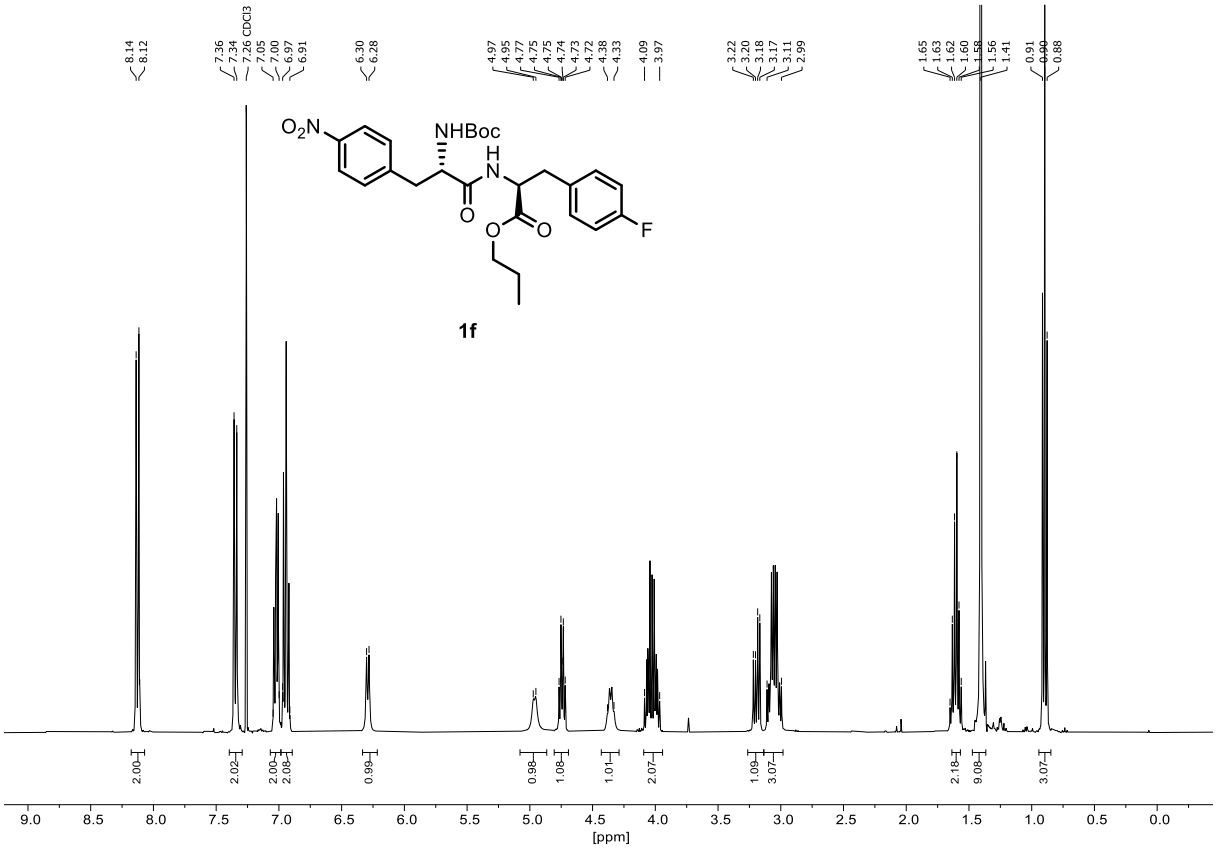
-115.58
-115.60
-115.61
-115.62
-115.64
ClH3N
O
O
F
S14
4.80
-114.90
-115.00
-115.10
-115.20
-115.30
-115.40
-115.50
-115.60
-115.70
-115.80
-115.90
-116.00
-116.10
-116.20
[ppm]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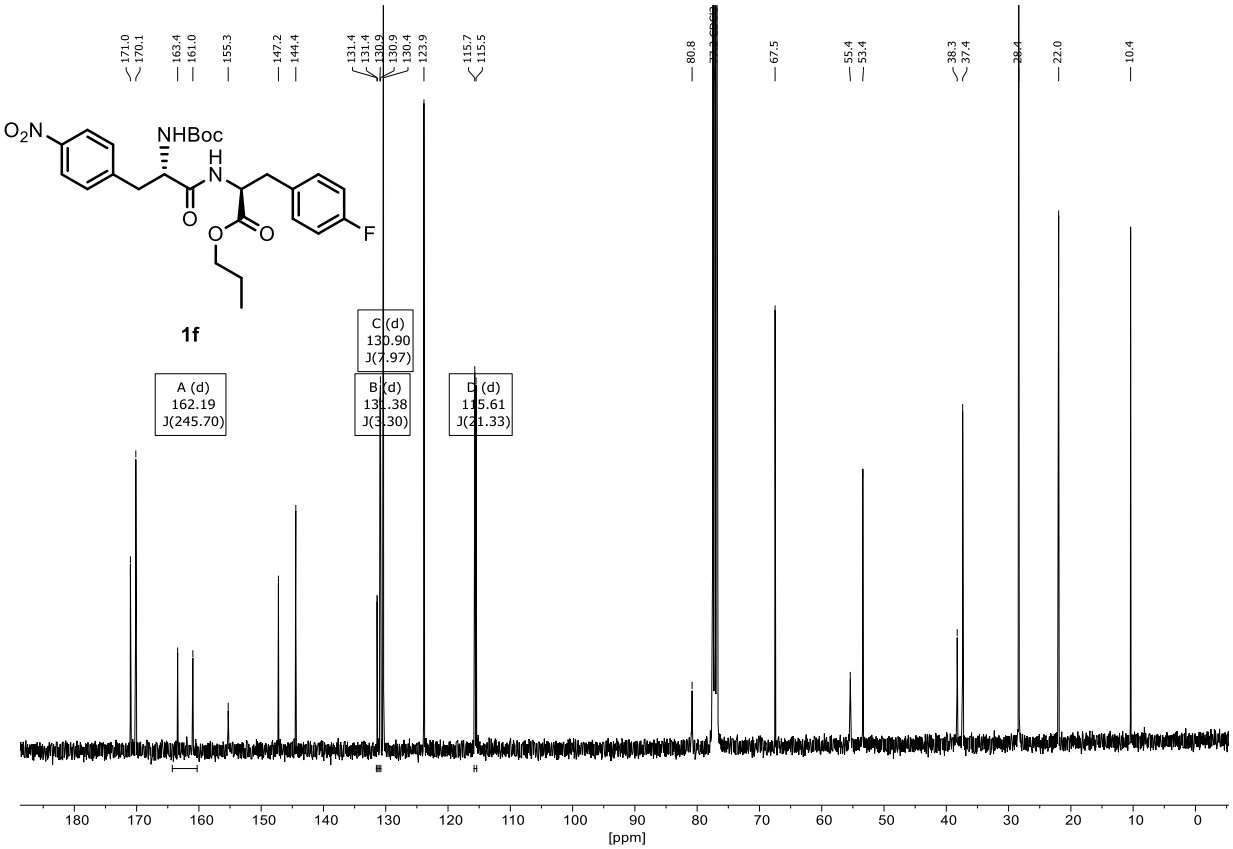
8.12
7.36
7.34
7.26 CDCl3
7.05
7.00
6.97
6.91
6.30
6.28
4.97
4.95
4.77
4.75
4.75
4.74
4.73
4.72
4.38
4.33
4.09
3.97
3.22
3.20
3.18
3.17
3.11
2.99
1.65
1.63
1.62
1.60
1.58
1.56
1.41
0.91
0.90
0.88
O2N
NHBoc
H
N
O
O
O
F
1f
2.00
2.02
2.00
2.08
0.99
0.98
1.08
1.01
2.07
1.09
3.07
2.18
9.08
3.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
[ppm]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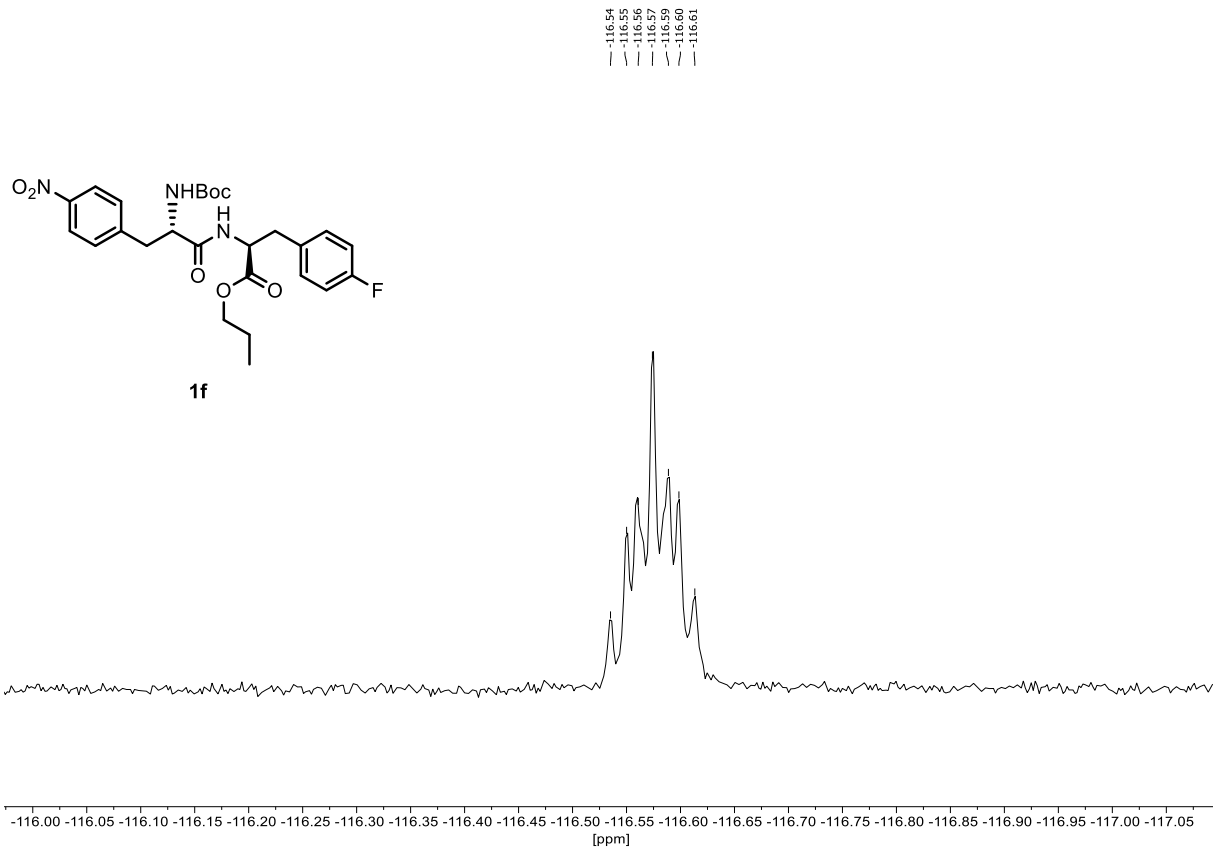
170.1
163.4
161.0
155.3
147.2
144.4
131.4
131.4
130.9
130.4
123.9
115.7
115.5
80.8
67.5
55.4
53.4
38.3
37.4
28.4
22.0
10.4
NHBoc
O2N
F
1f
A (d)
162.19
J(245.70)
C (d)
130.90
J(7.97)
B (d)
131.38
J(3.30)
D (d)
115.61
J(21.33)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
[ppm]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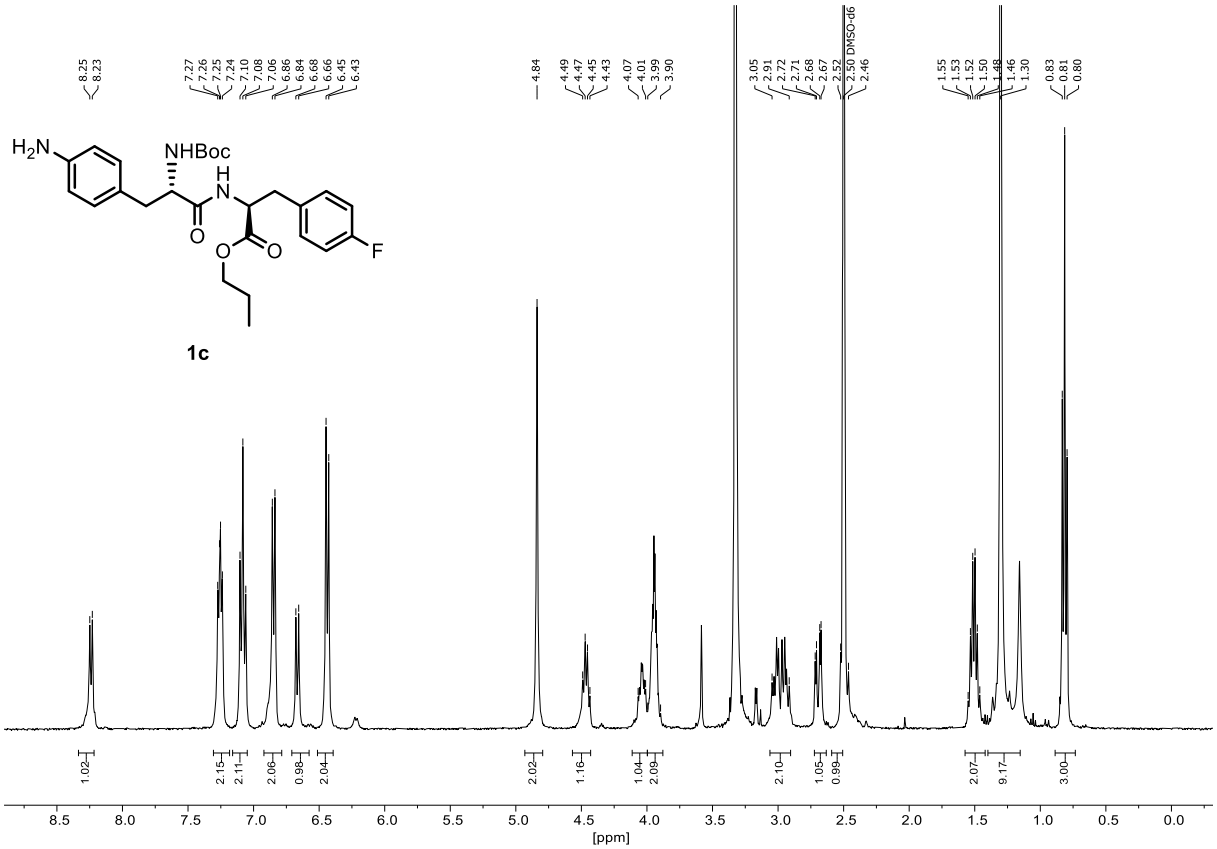
-116.55
-116.56
-116.57
-116.59
-116.60
-116.61
NHBoc
O2N
F
1f
-116.00 -116.05 -116.10 -116.15 -116.20 -116.25 -116.30 -116.35 -116.40 -116.45 -116.50 -116.55 -116.60 -116.65 -116.70 -116.75 -116.80 -116.85 -116.90 -116.95 -117.00 -117.05
[ppm]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7.24
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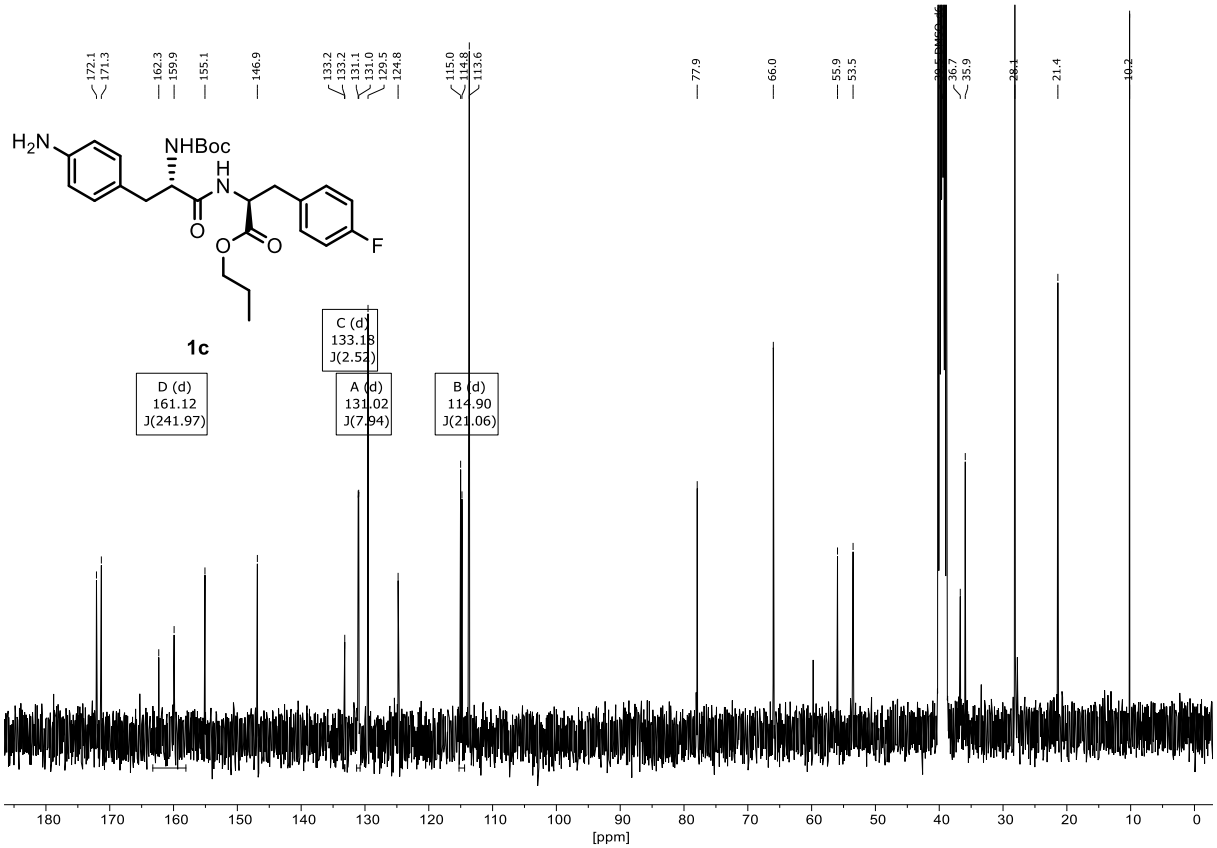
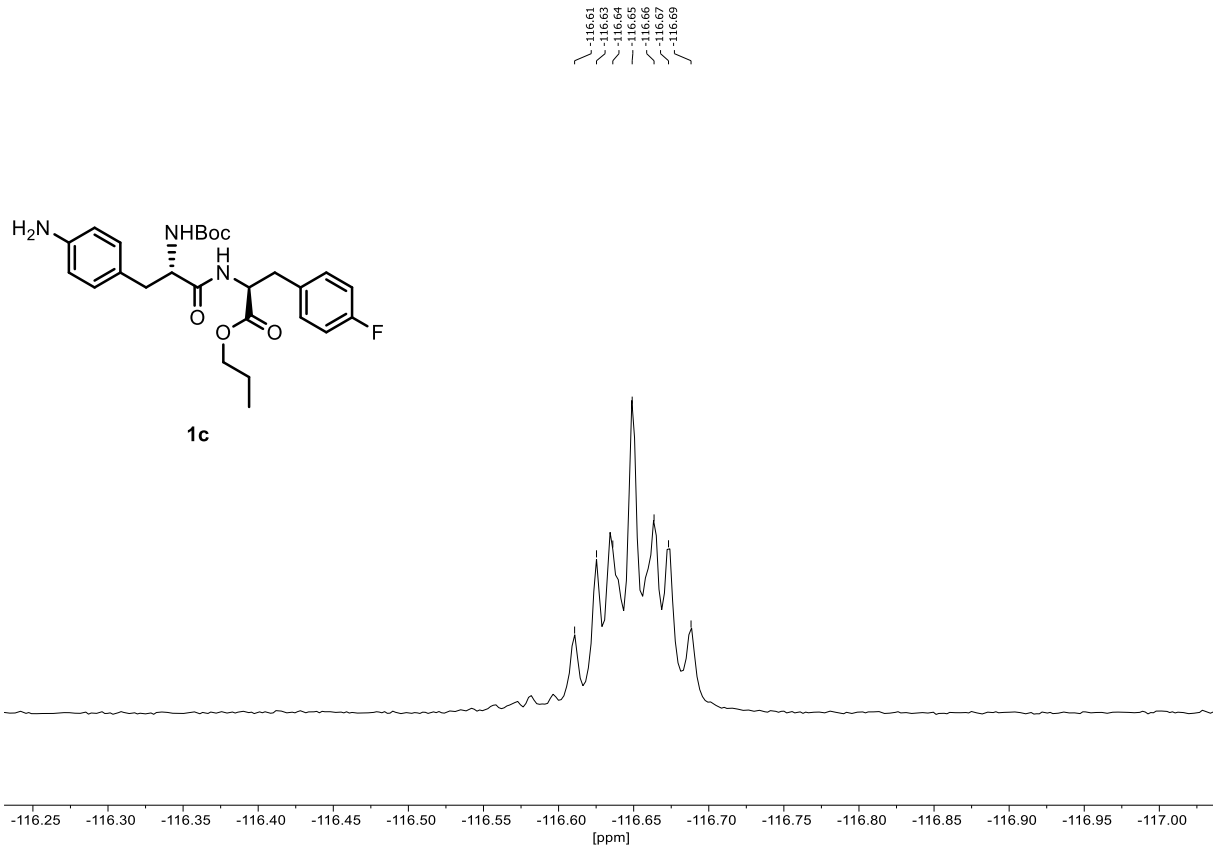
7.08
7.06
6.86
6.84
6.68
6.66
6.45
6.43
4.84
4.49
4.47
4.45
4.43
4.07
4.01
3.99
3.90
3.05
2.91
2.72
2.71
2.68
2.67
2.50 DMSO-d6
2.46
1.55
1.53
1.52
1.50
1.48
1.46
1.30
0.83
0.81
0.80
1.02
2.15
2.11
2.06
0.98
2.04
2.02
1.16
1.04
2.09
2.10
1.05
0.99
2.07
9.17
3.00
[ppm]
1c


172.1
171.3
162.3
159.9
155.1
146.9
133.2
133.2
131.1
131.0
129.5
124.8
115.0
114.8
113.6
77.9
66.0
55.9
53.5
36.7
35.9
28.1
21.4
10.2
C (d)
133.18
J(2.52)
D (d)
161.12
J(241.97)
A (d)
131.02
J(7.94)
B (d)
114.90
J(21.06)
1c
[ppm]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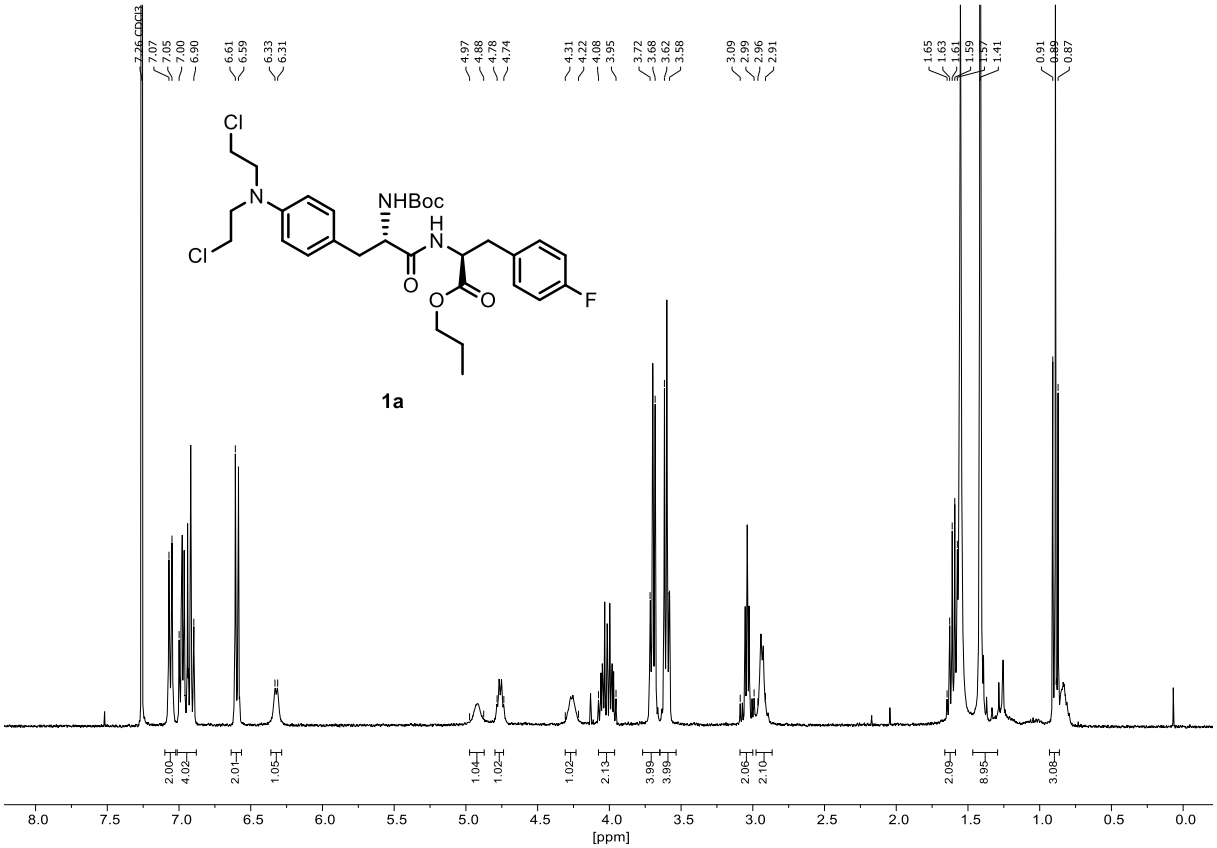
-116.63
-116.64
-116.65
-116.66
-116.67
-116.69
NHBoc
F
1c
-116.25 -116.30 -116.35 -116.40 -116.45 -116.50 -116.55 -116.60 -116.65 -116.70 -116.75 -116.80 -116.85 -116.90 -116.95 -117.00
[ppm]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7.07
7.05
7.00
6.90
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6.59
6.33
6.31
4.97
4.88
4.78
4.74
4.31
4.22
4.08
3.95
3.72
3.68
3.62
3.58
3.09
2.99
2.96
2.91
1.65
1.63
1.61
1.59
1.57
1.41
0.91
0.89
0.87
Cl
Cl
NHBoc
F
1a
2.00
4.02
2.01
1.05
1.04
1.02
1.02
2.13
3.99
3.99
2.06
2.10
2.09
8.95
3.08
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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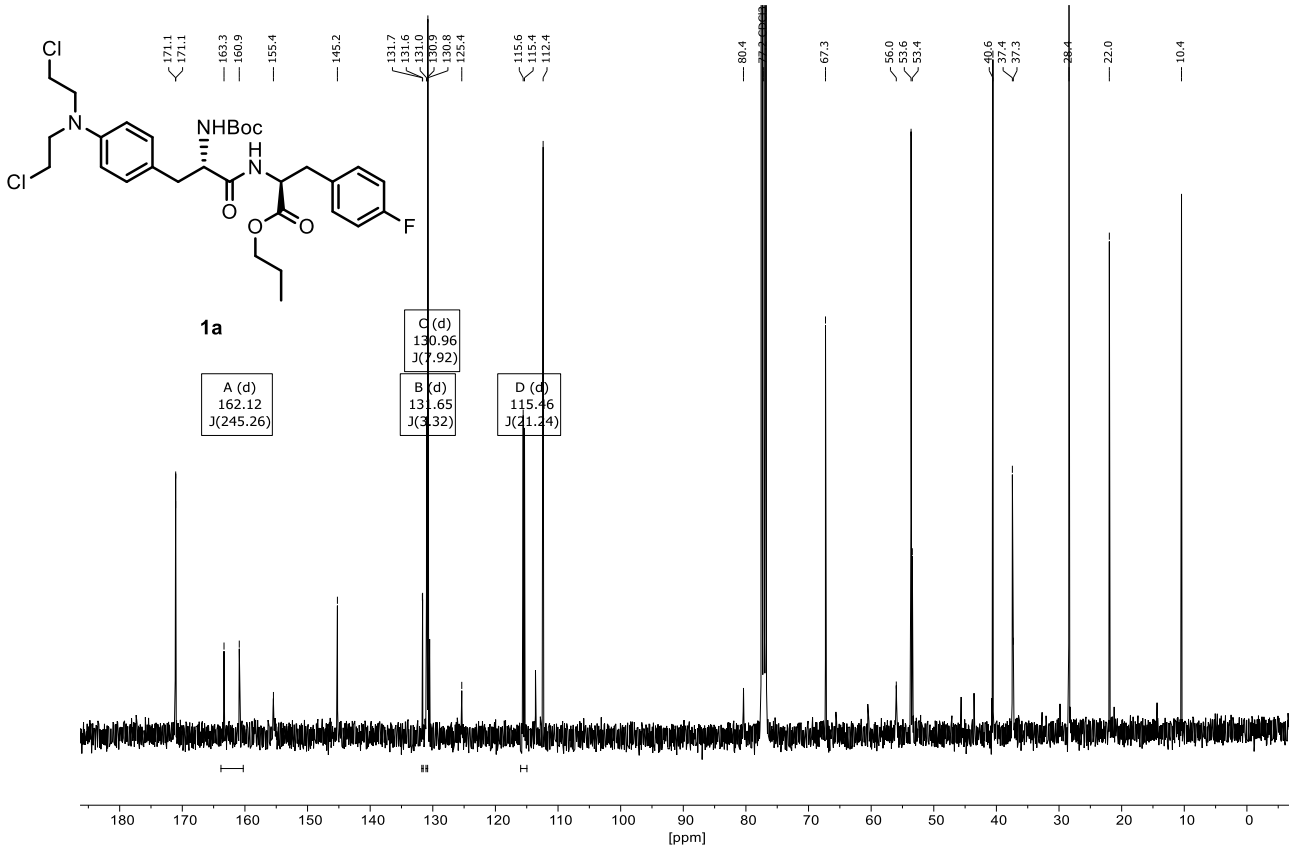
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171.1
163.3
160.9
155.4
145.2
131.7
131.6
131.0
130.9
130.8
125.4
115.6
115.4
112.4
80.4
67.3
56.0
53.6
53.4
40.6
37.4
37.3
28.4
22.0
10.4
NHBoc
H
N
Cl
Cl
N
O
O
O
O
F
1a
A (d)
162.12
J(245.26)
C (d)
130.96
J(7.92)
B (d)
131.65
J(3.32)
D (d)
115.46
J(21.24)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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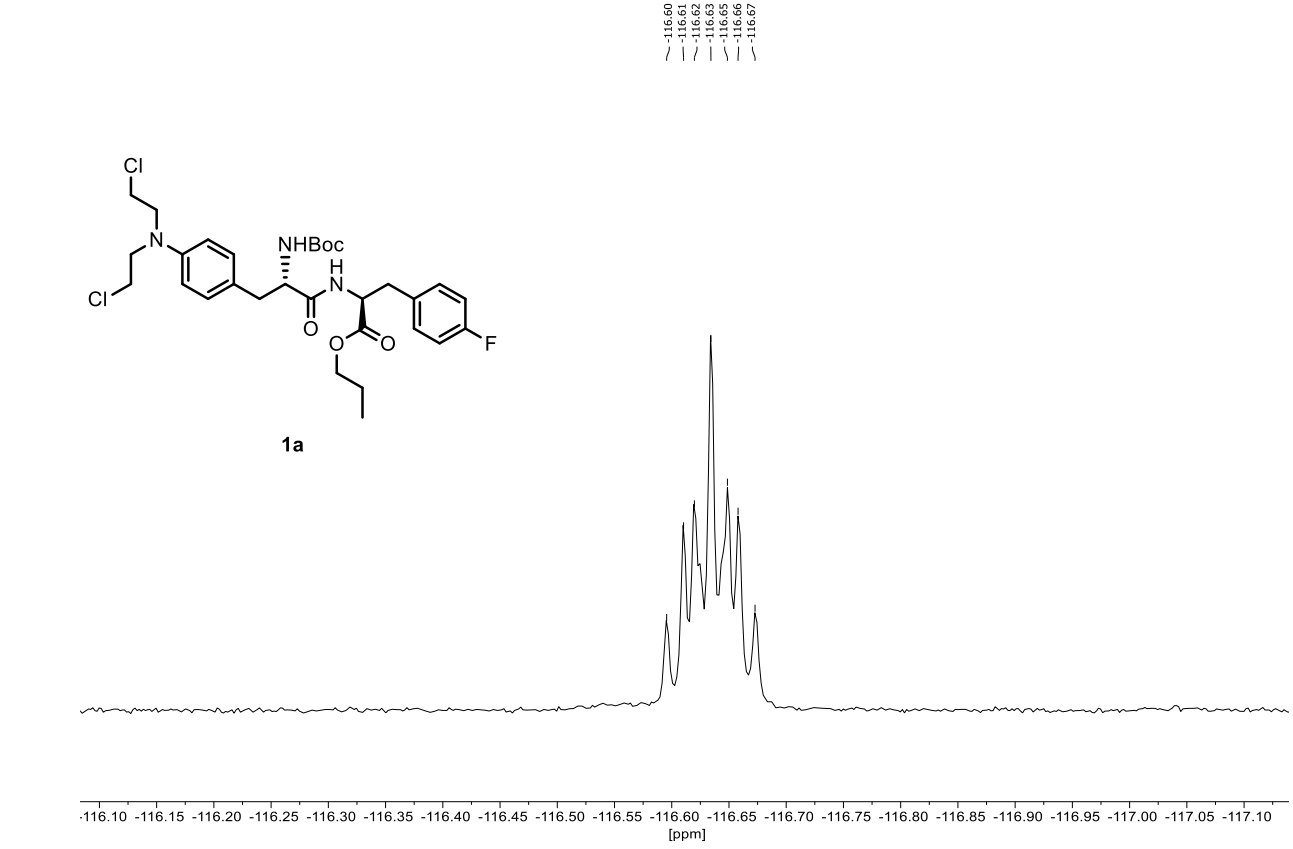
-116.60
-116.61
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-116.66
-116.67
Cl
Cl
N
NHBoc
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N
O
O
O
O
F
1a
-116.10
-116.15
-116.20
-116.25
-116.30
-116.35
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-116.60
-116.65
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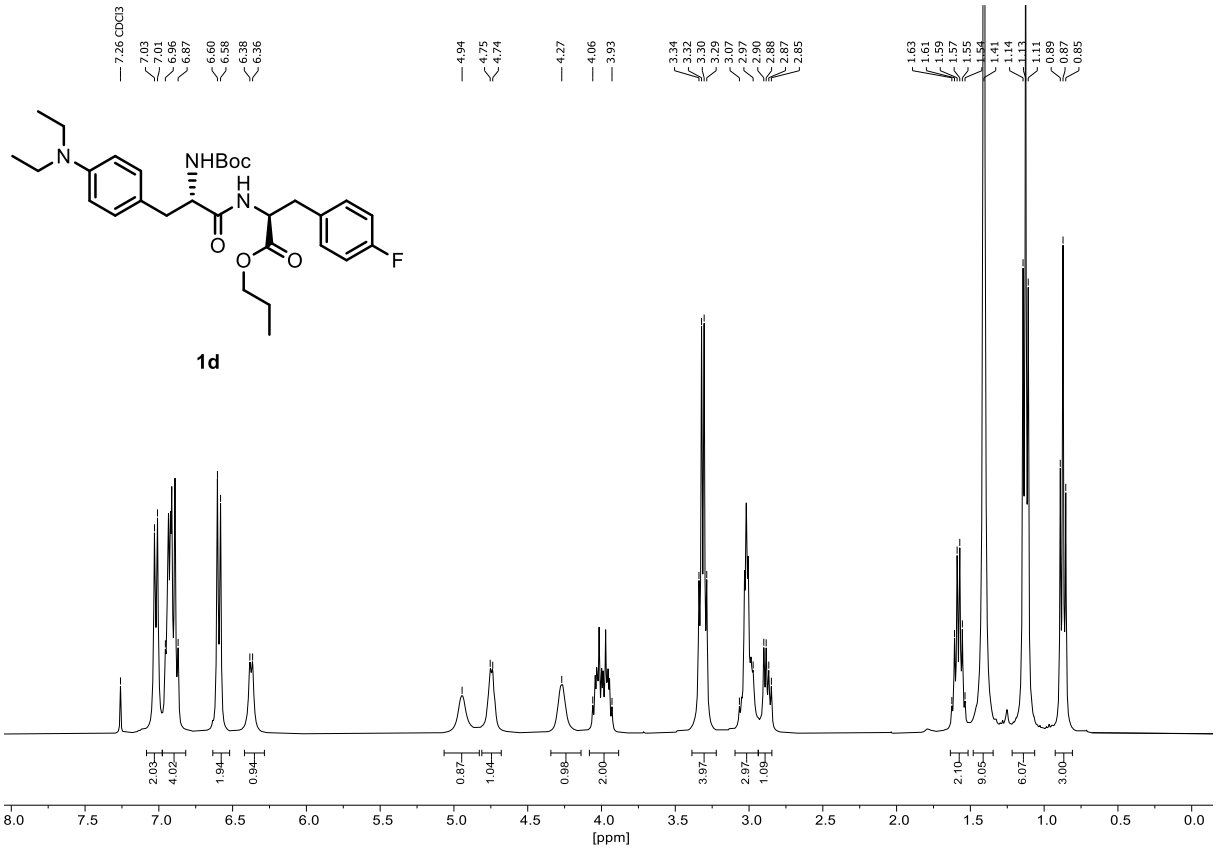
-116.80
-116.85
-116.90
-116.95
-117.00
-117.05
-117.10
[ppm]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6.58
6.38
6.36
4.94
4.75
4.74
4.27
4.06
3.93
3.34
3.32
3.30
3.29
3.07
2.97
2.90
2.88
2.87
2.85
1.63
1.61
1.59
1.57
1.55
1.54
1.41
1.14
1.13
1.11
0.89
0.87
0.85
NHBoc
H
N
O
O
O
O
F
N
1d
2.03
4.02
1.94
0.94
0.87
1.04
0.98
2.00
3.97
2.97
1.09
2.10
9.05
6.07
3.00
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
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2.5
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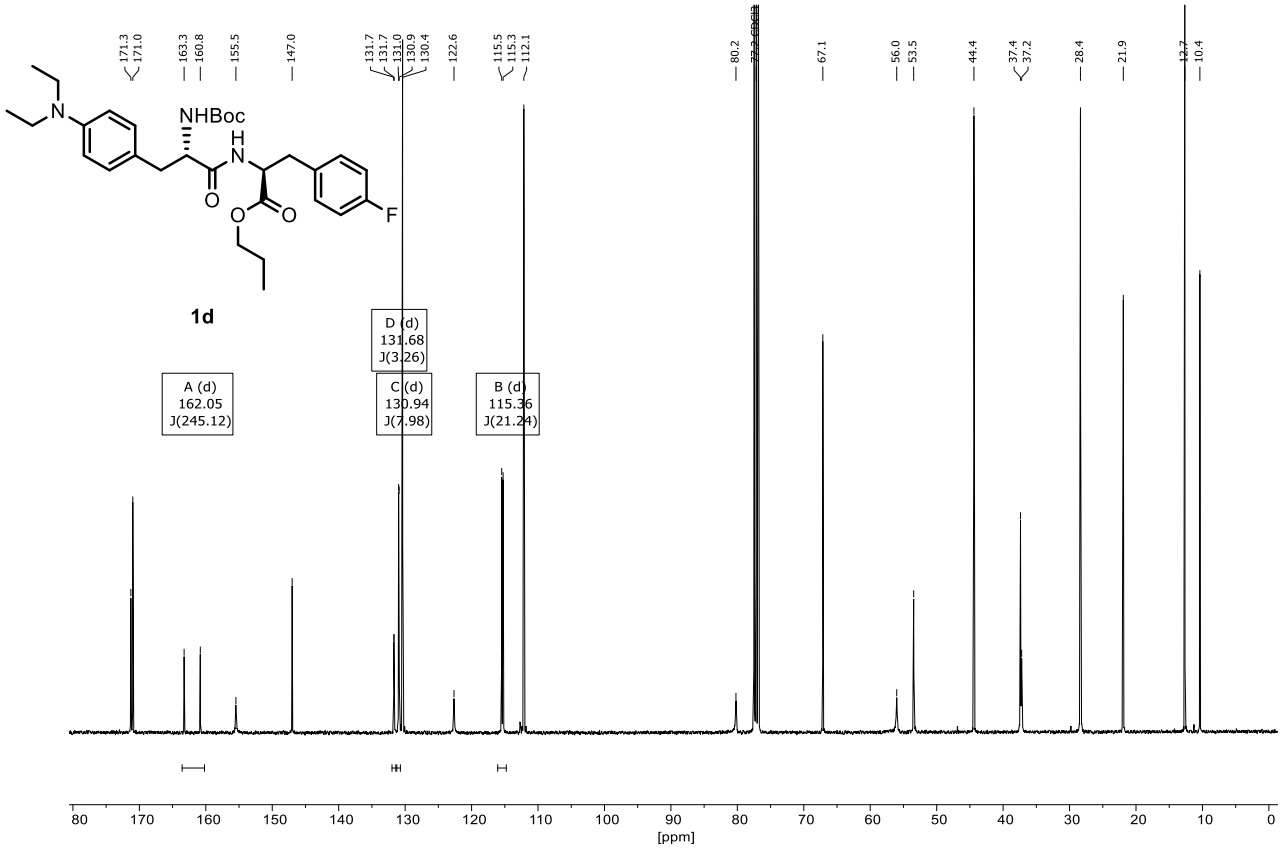
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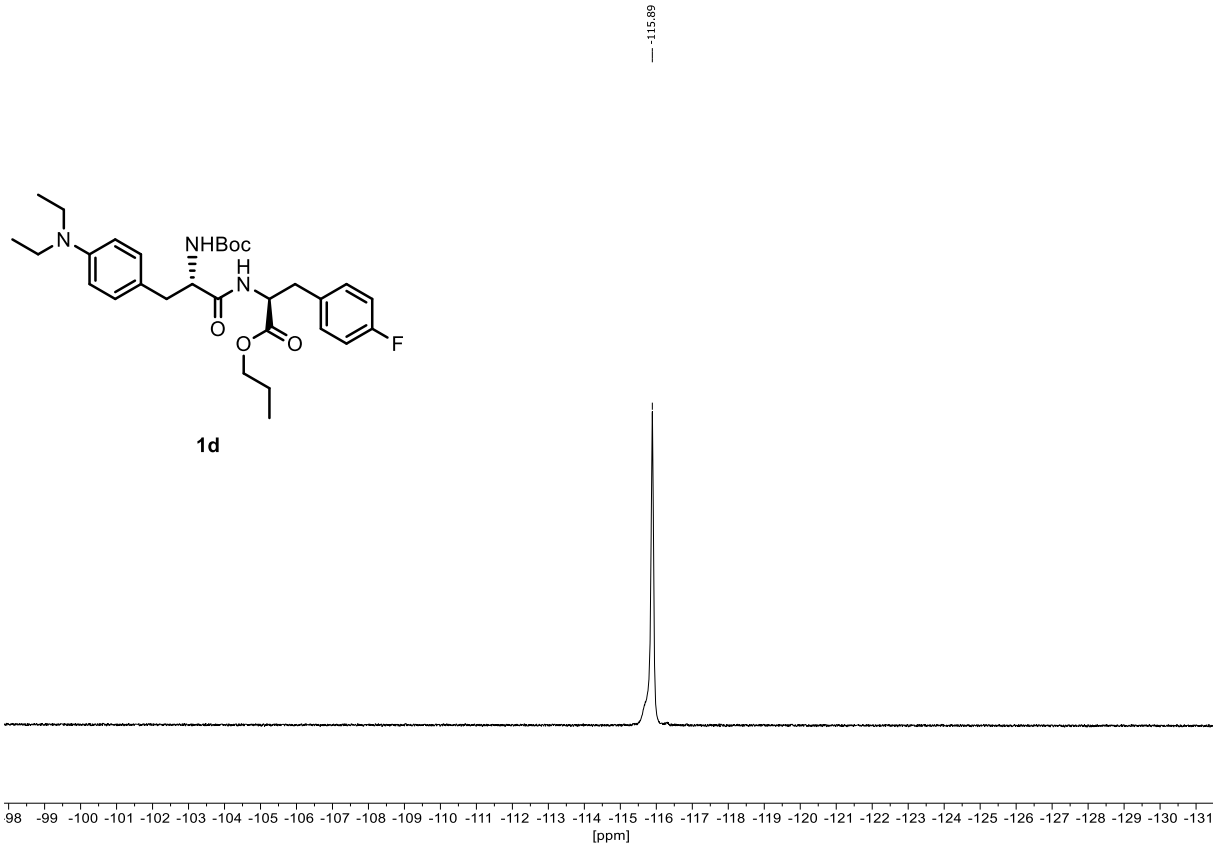
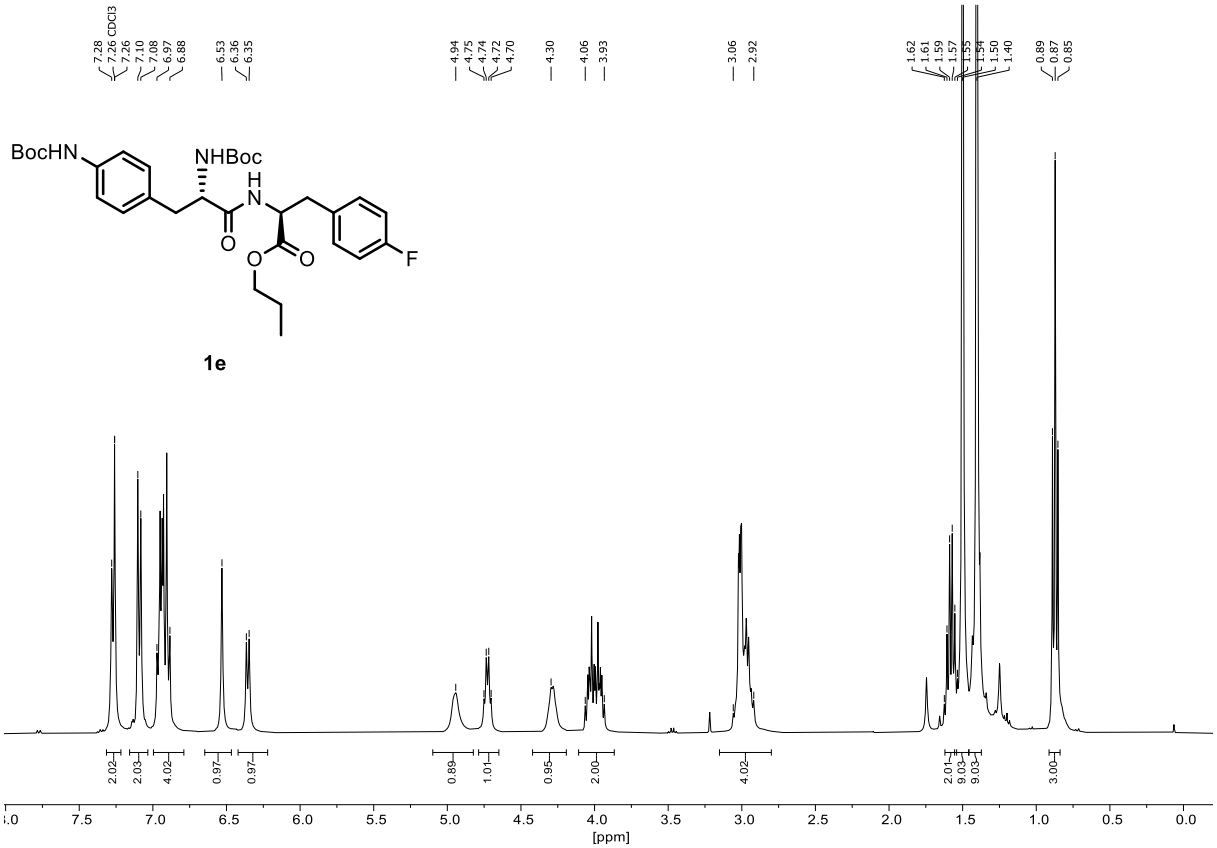
160.8
155.5
147.0
131.7
131.7
131.0
130.9
130.4
122.6
115.5
115.3
112.1
80.2
77.3 CDCl3
67.1
56.0
53.5
44.4
37.4
37.2
28.4
21.9
13.7
10.4
NHBoc
H
N
O
O
O
O
F
N
1d
D (d)
131.68
J(3.26)
A (d)
162.05
J(245.12)
C (d)
130.94
J(7.98)
B (d)
115.36
J(21.24)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
[ppm]


-115.89
NHBoc
H
N
O
O
O
F
98 -99 -100 -101 -102 -103 -104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119 -120 -121 -122 -123 -124 -125 -126 -127 -128 -129 -130 -131
[ppm]

1d


7.28
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7.26
7.10
7.08
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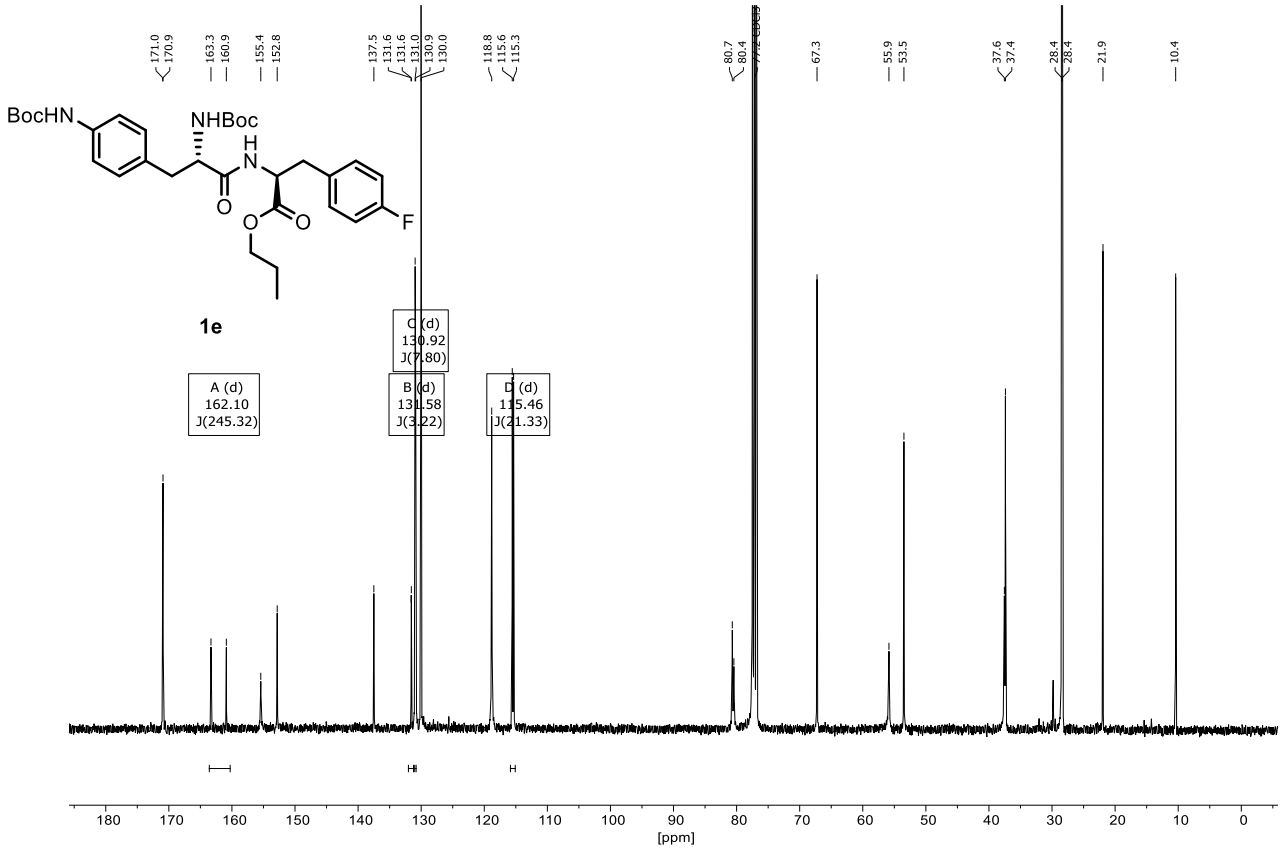
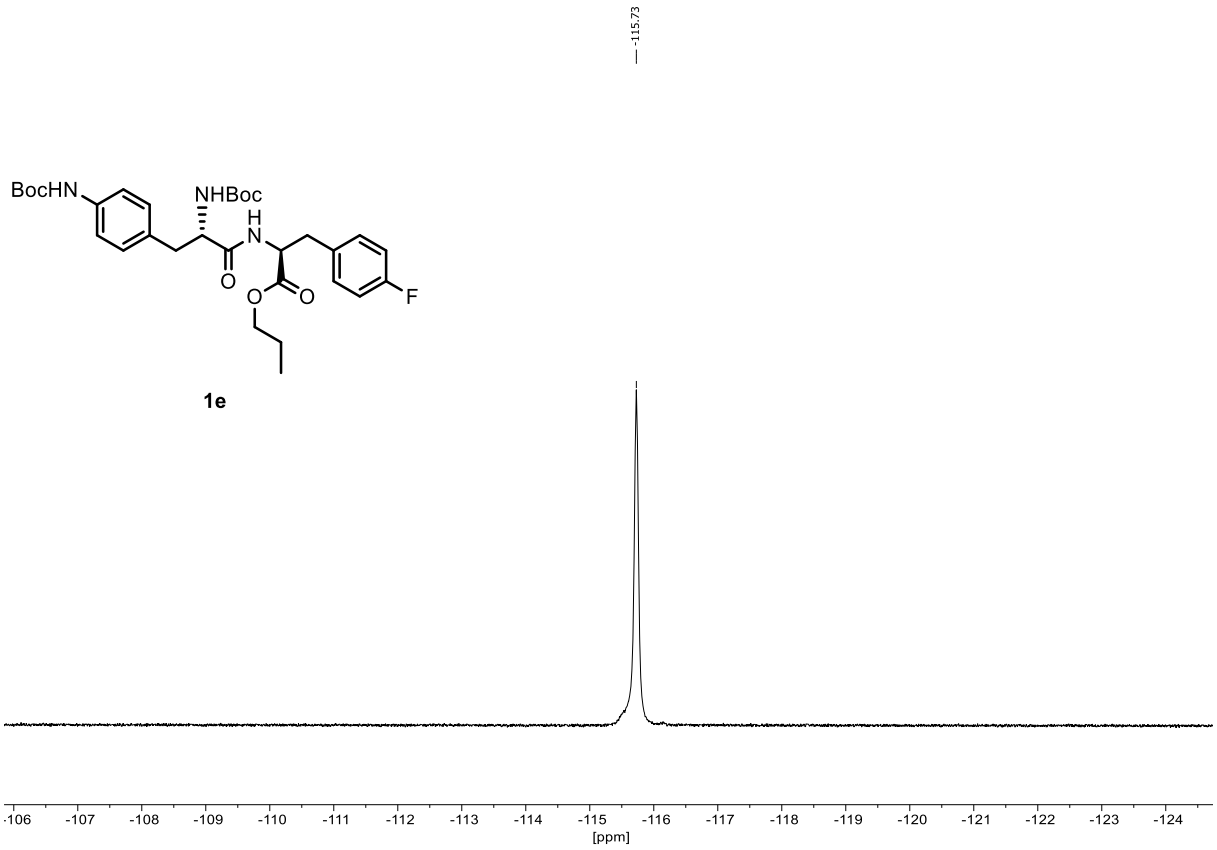
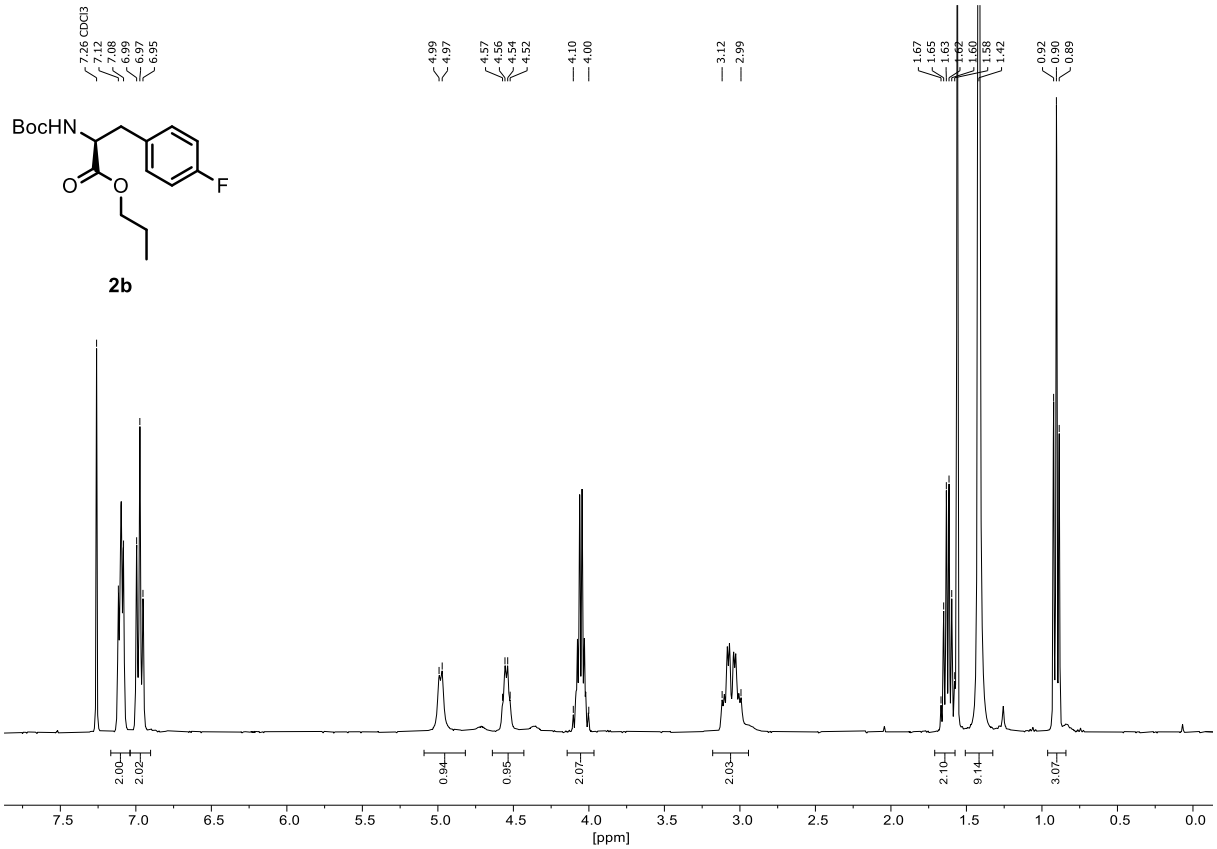
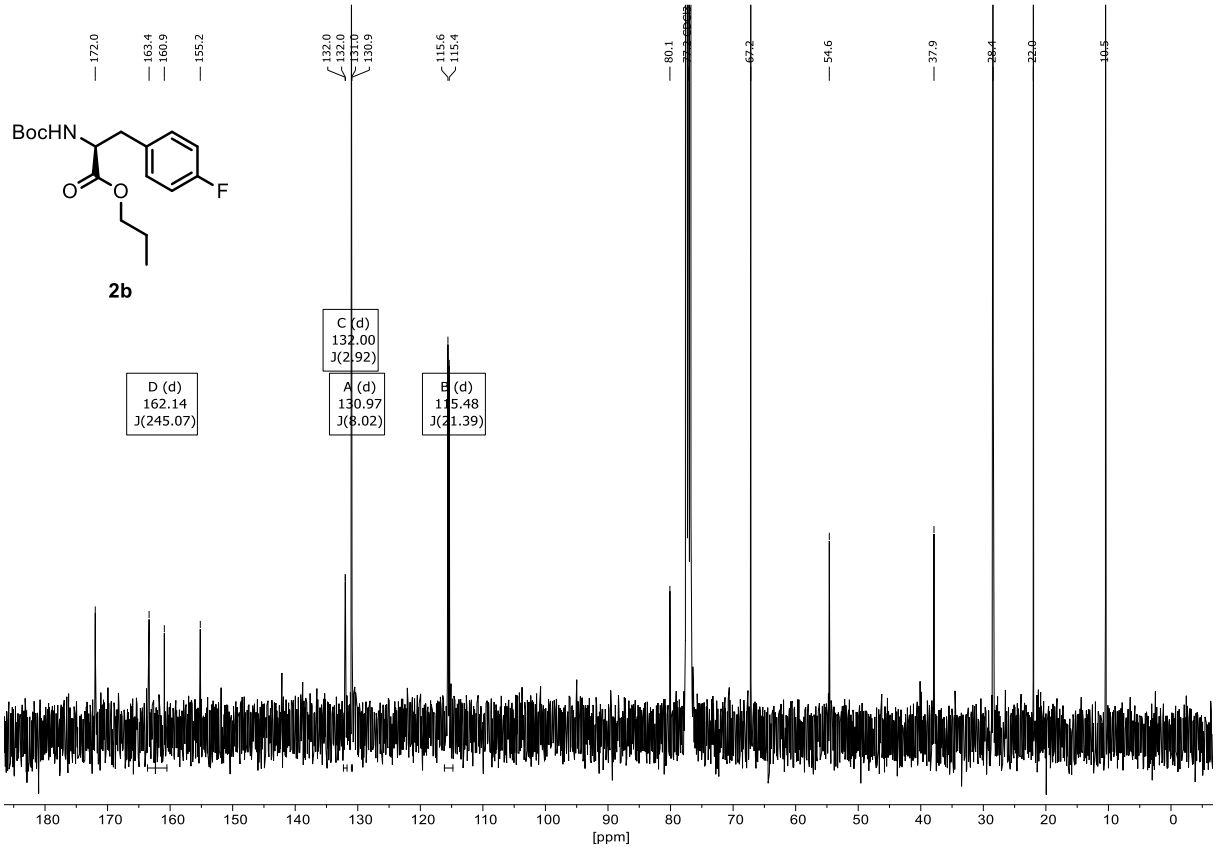
6.88
6.53
6.36
6.35
4.94
4.75
4.74
4.72
4.70
4.30
4.06
3.93
3.06
2.92
1.62
1.61
1.59
1.57
1.55
1.54
1.50
1.40
0.89
0.87
0.85
BocHN
NHBoc
H
N
O
O
O
F
2.02
2.03
4.02
0.97
0.97
0.89
1.01
0.95
2.00
4.02
2.01
9.03
9.03
3.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

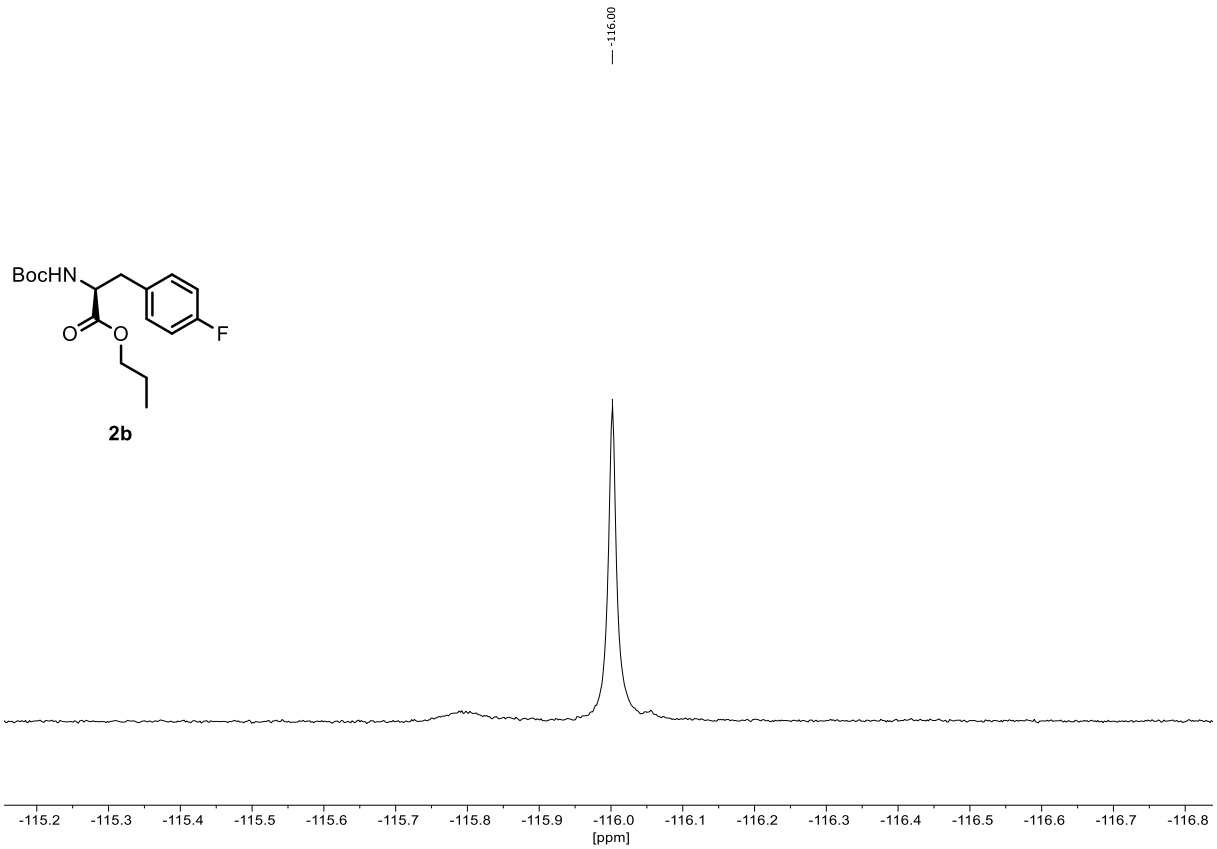
1e

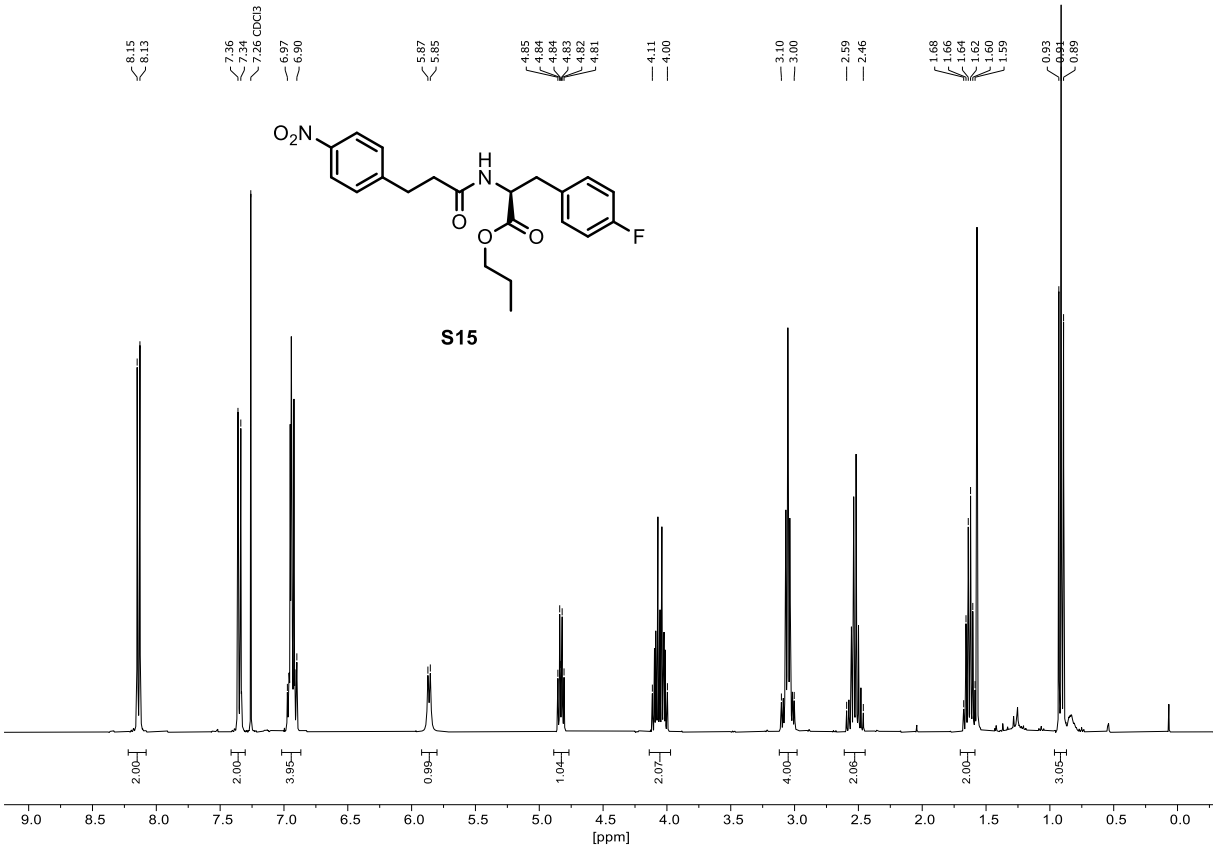

171.0
170.9
163.3
160.9
155.4
152.8
137.5
131.6
131.6
131.0
130.9
130.0
118.8
115.6
115.3
80.7
80.4
67.3
55.9
53.5
37.6
37.4
28.4
28.4
21.9
10.4
BocHN
NHBoc
H
N
O
O
O
O
F
1e
A (d)
162.10
J(245.32)
B (d)
131.58
J(3.22)
C (d)
130.92
J(7.80)
D (d)
115.46
J(21.33)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
[ppm]

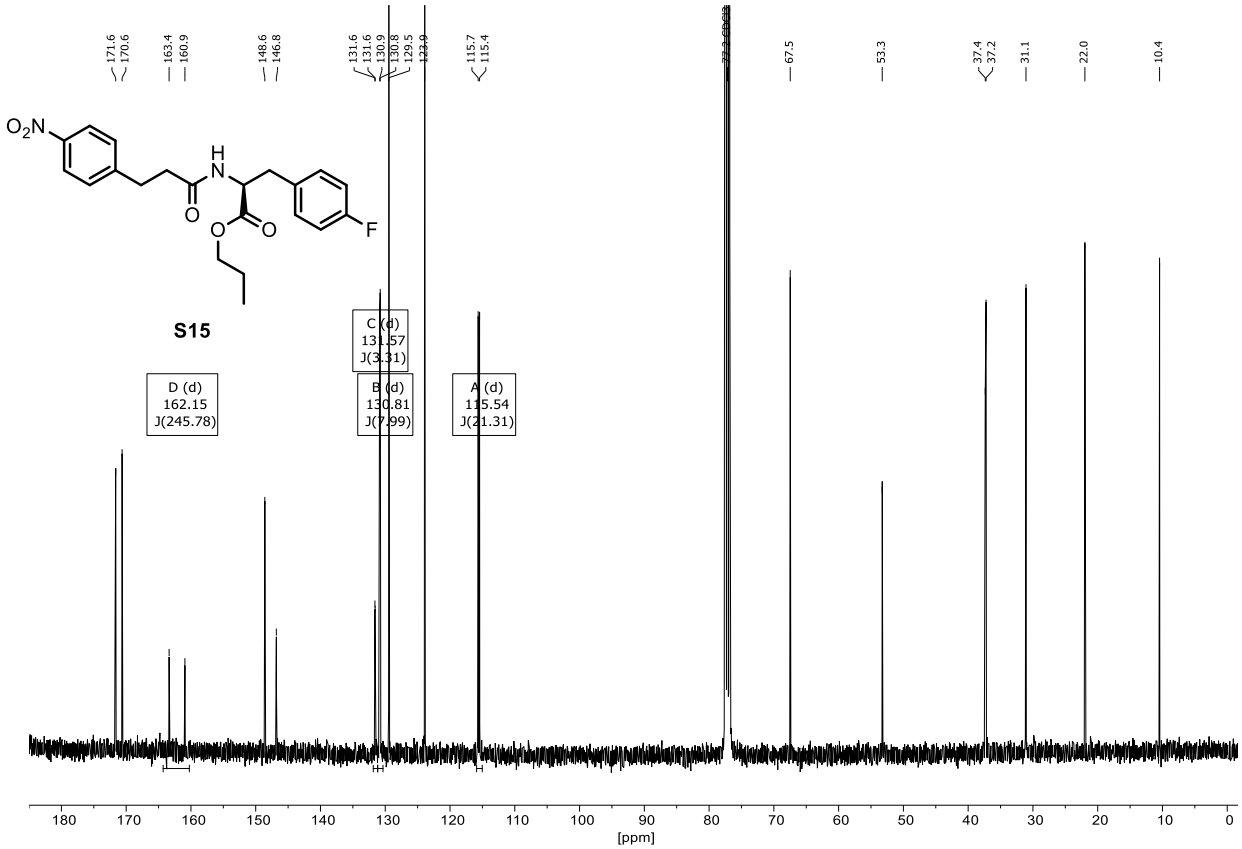

-115.73
BocHN
NHBoc
H
N
O
O
O
O
F
1e
-106
-107
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
-123
-124
[ppm]

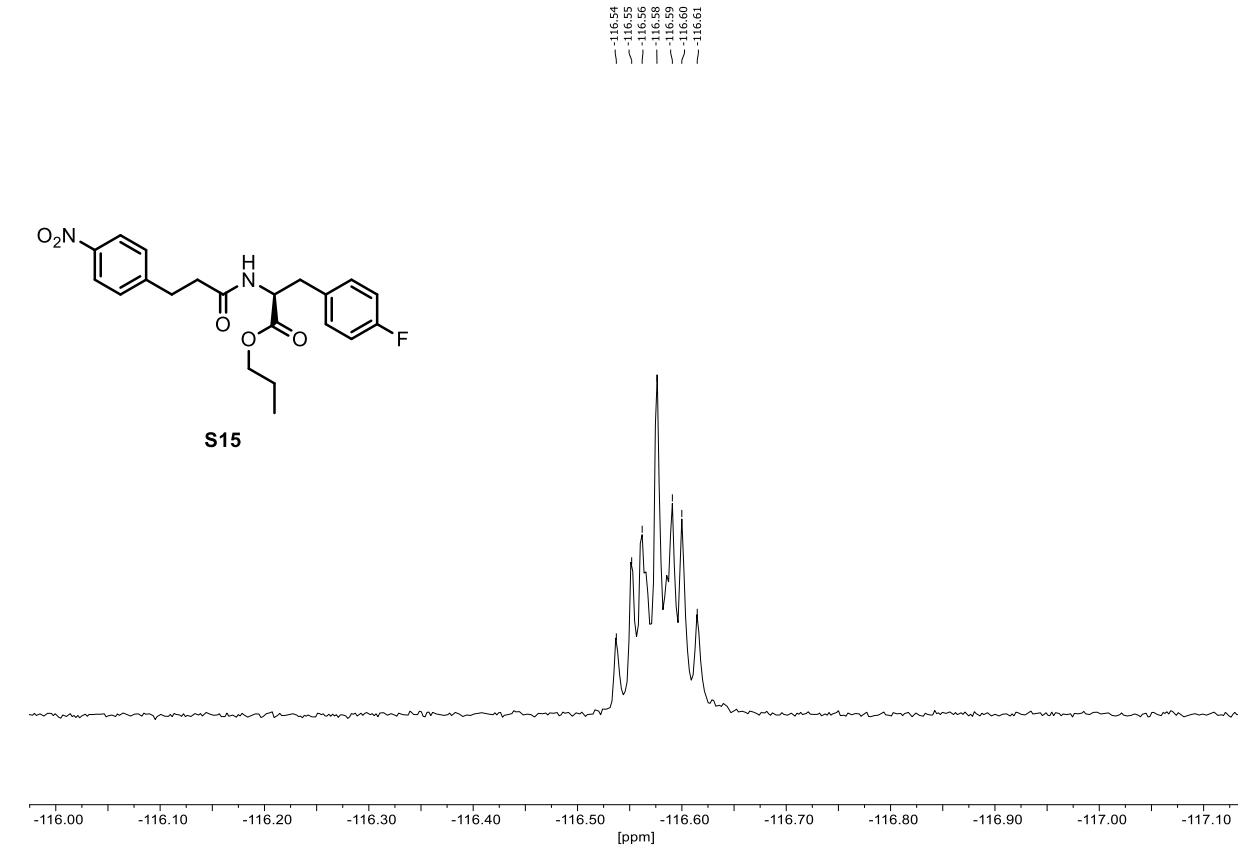

7.26 CDCl3
7.12
7.08
6.99
6.97
6.95
4.99
4.97
4.57
4.56
4.54
4.52
4.10
4.00
3.12
2.99
1.67
1.65
1.63
1.62
1.60
1.58
1.42
0.92
0.90
0.89
BocHN
O
O
F
2b
2.00
2.02
0.94
0.95
2.07
2.03
2.10
9.14
3.07
[ppm]

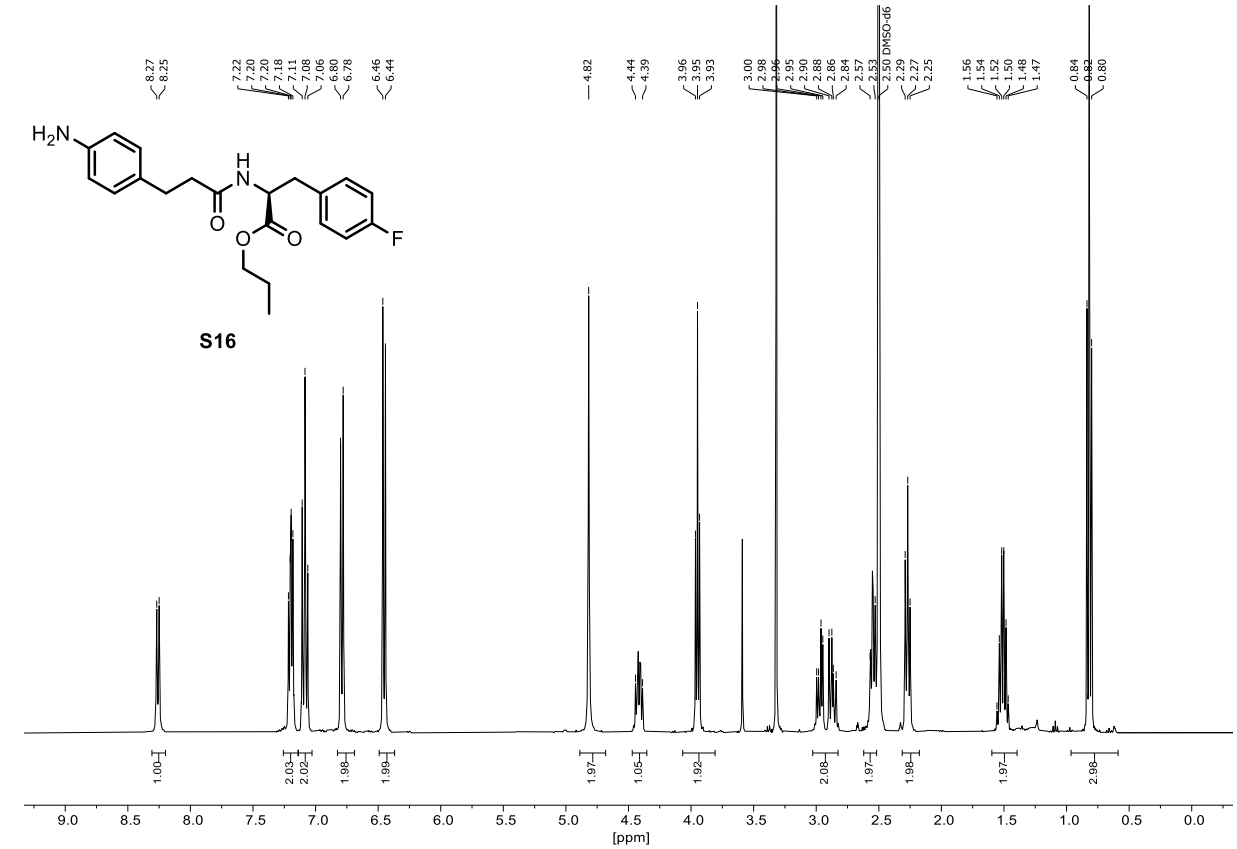

172.0
163.4
160.9
155.2
132.0
132.0
131.0
130.9
115.6
115.4
80.1
67.2
54.6
37.9
28.4
22.0
10.5
BocHN
O
O
F
2b
C (d)
132.00
J(2.92)
D (d)
162.14
J(245.07)
A (d)
130.97
J(8.02)
B (d)
115.48
J(21.39)
[ppm]

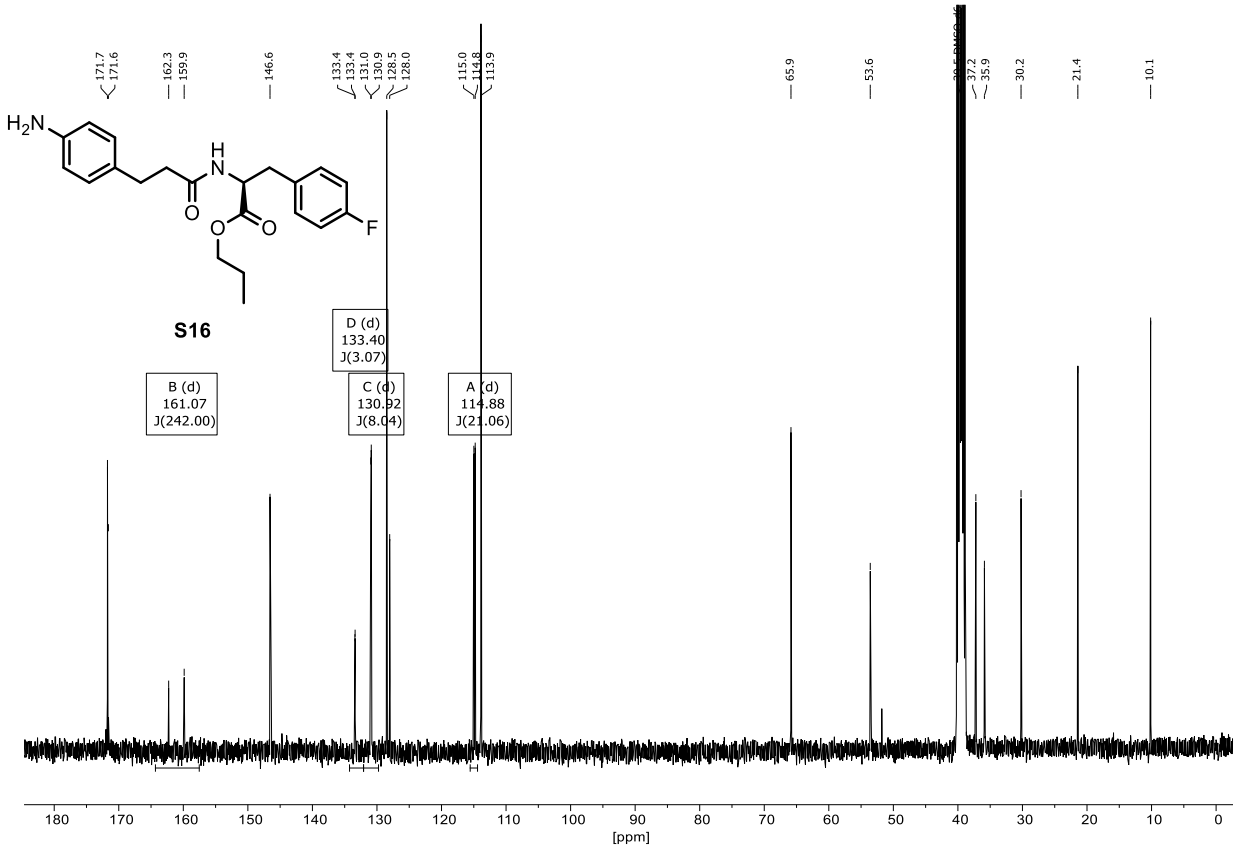

-116.00
BocHN
O
O
F
2b
-115.2
-115.3
-115.4
-115.5
-115.6
-115.7
-115.8
-115.9
-116.0
-116.1
-116.2
-116.3
-116.4
-116.5
-116.6
-116.7
-116.8
[ppm]

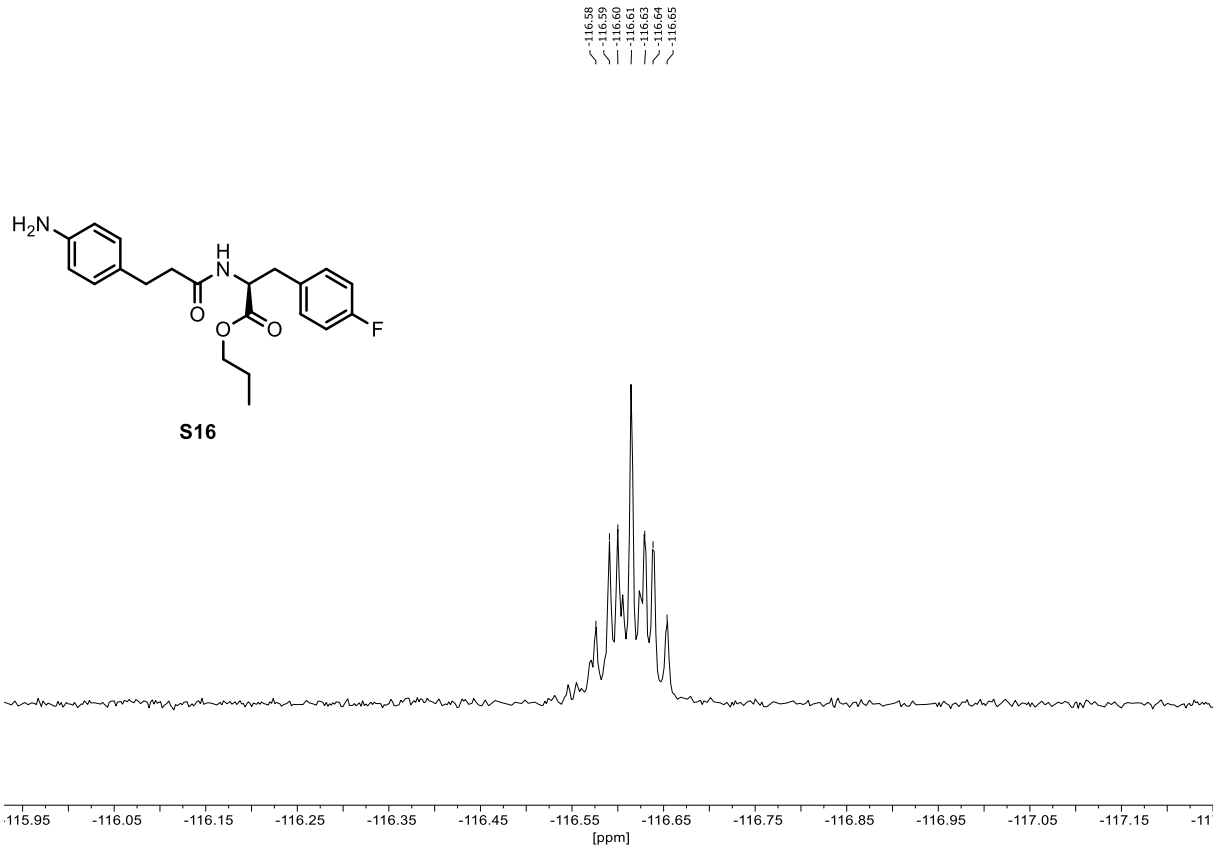

8.15
8.13
7.36
7.34
7.26 CDCl3
6.97
6.90
5.87
5.85
4.85
4.84
4.84
4.83
4.82
4.81
4.11
4.00
3.10
3.00
2.59
2.46
1.68
1.66
1.64
1.62
1.60
1.59
0.93
0.91
0.89
O2N
H
N
O
O
O
F
S15
2.00
2.00
3.95
0.99
1.04
2.07
4.00
2.06
2.00
3.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
[ppm]

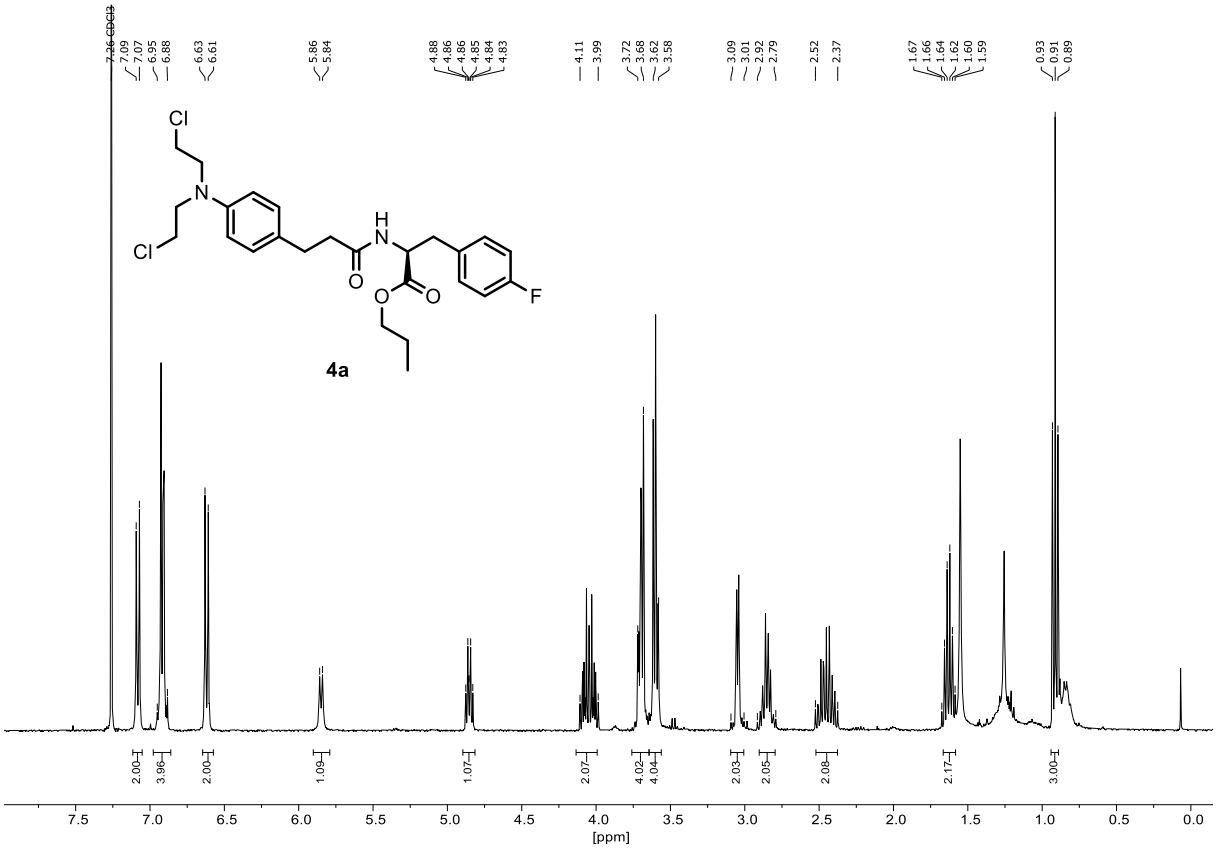

171.6
170.6
163.4
160.9
148.6
146.8
131.6
131.6
130.9
130.8
129.5
123.9
115.7
115.4
67.5
53.3
37.4
37.2
31.1
22.0
10.4
O2N
H
N
O
O
O
F
S15
C (d)
131.57
J(3.31)
D (d)
162.15
J(245.78)
B (d)
130.81
J(7.99)
A (d)
115.54
J(21.31)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
[ppm]

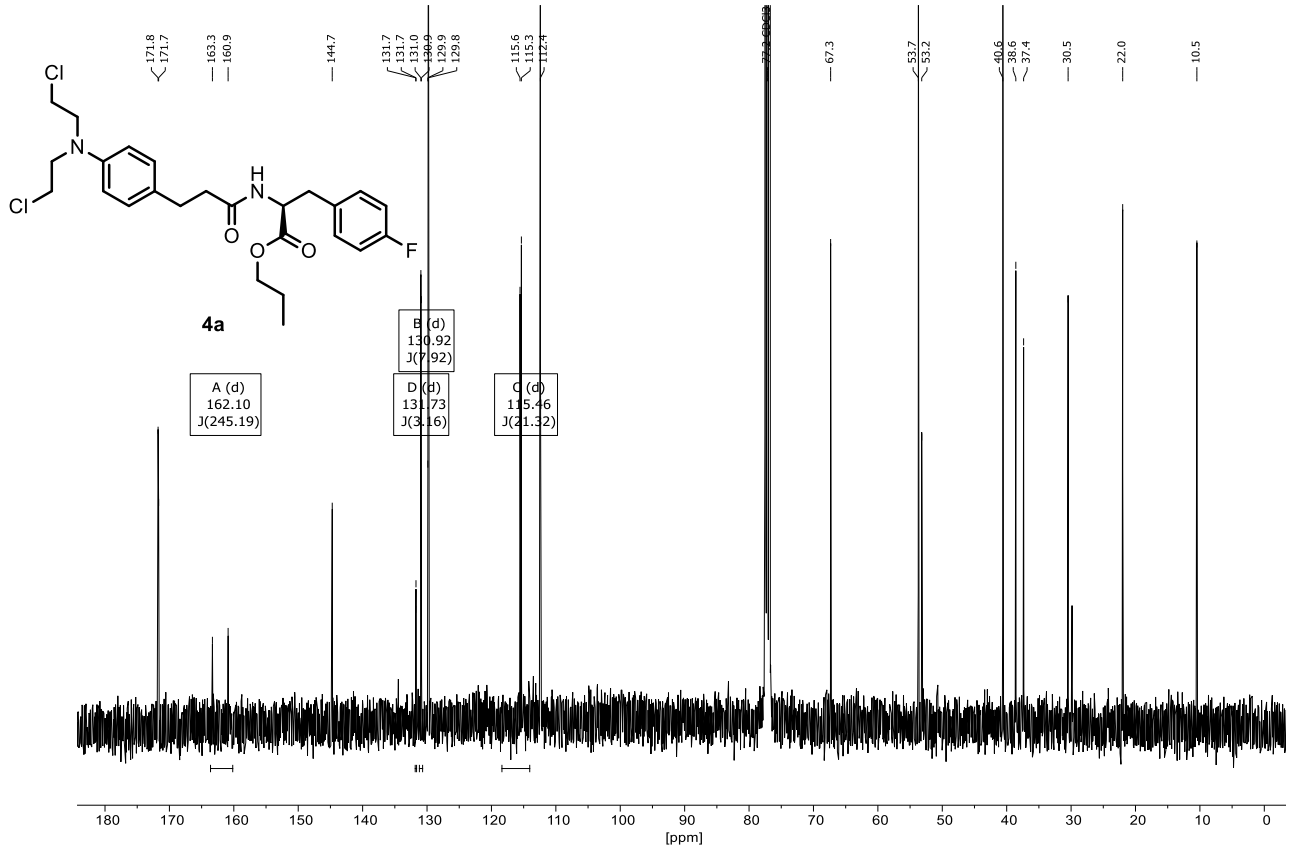

-116.54
-116.55
-116.56
-116.58
-116.59
-116.60
-116.61
O2N
H
N
O
O
O
F
S15
-116.00
-116.10
-116.20
-116.30
-116.40
-116.50
-116.60
-116.70
-116.80
-116.90
-117.00
-117.10
[ppm]

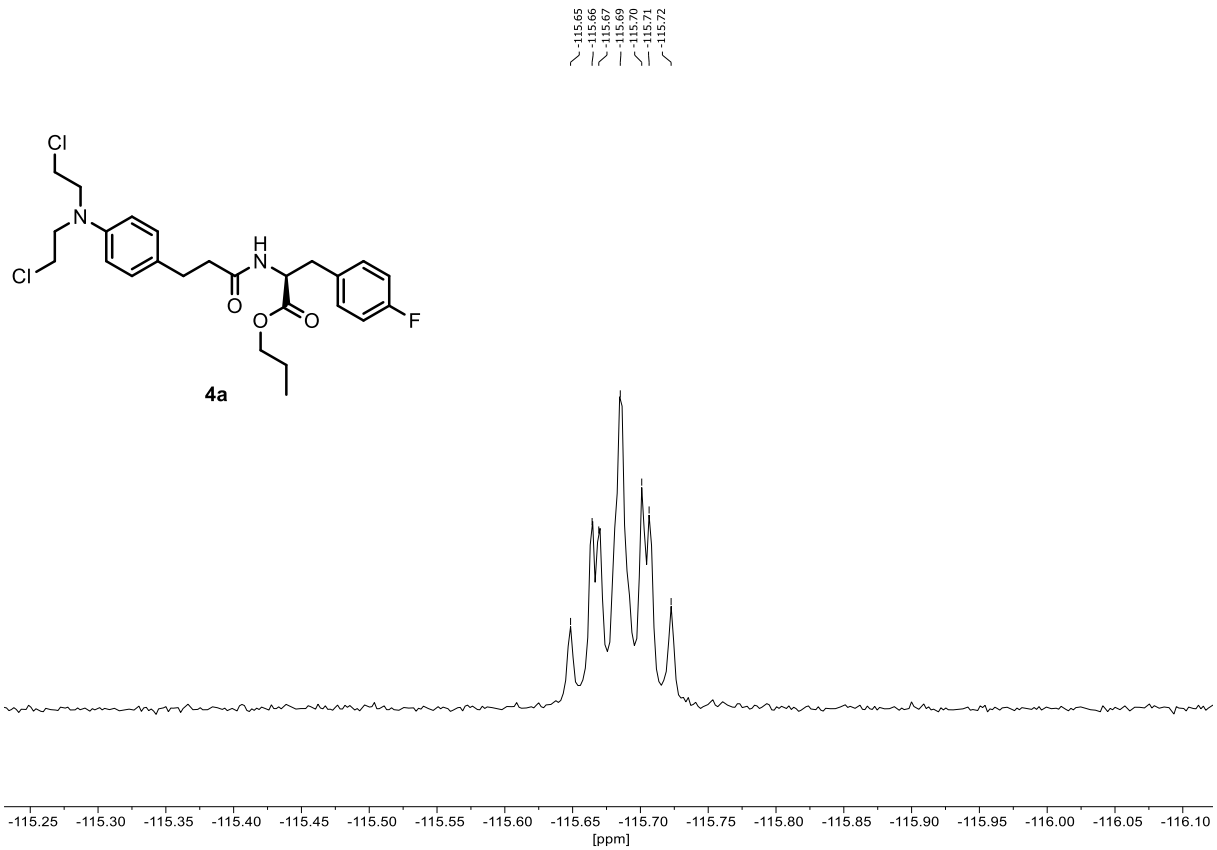

S16
[ppm]


S16
D (d)
133.40
J(3.07)
B (d)
161.07
J(242.00)
C (d)
130.92
J(8.04)
A (d)
114.88
J(21.06)
[ppm]

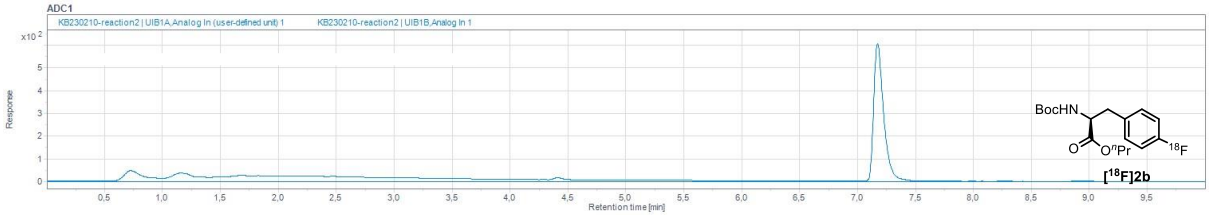

-116.58
-116.59
-116.60
-116.61
-116.63
-116.64
-116.65
S16
-115.95
-116.05
-116.15
-116.25
-116.35
-116.45
-116.55
-116.65
-116.75
-116.85
-116.95
-117.05
-117.15
[ppm]

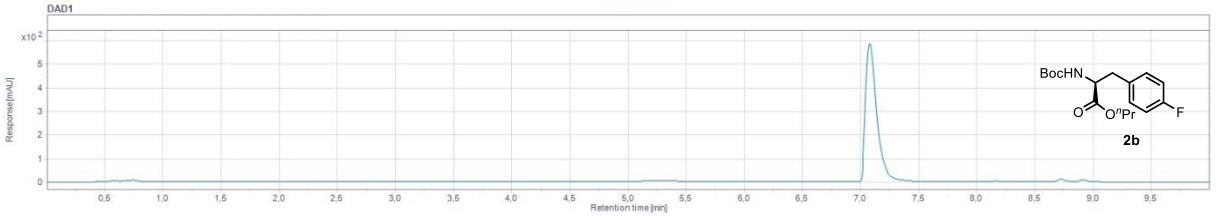

7.26 CDCl3
7.09
7.07
6.95
6.88
6.63
6.61
5.86
5.84
4.88
4.86
4.86
4.85
4.84
4.83
4.11
3.99
3.72
3.68
3.62
3.58
3.09
3.01
2.92
2.79
2.52
2.37
1.67
1.66
1.64
1.62
1.60
1.59
0.93
0.91
0.89
4a
2.00
3.96
2.00
1.09
1.07
2.07
4.02
4.04
2.03
2.05
2.08
2.17
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
[ppm]

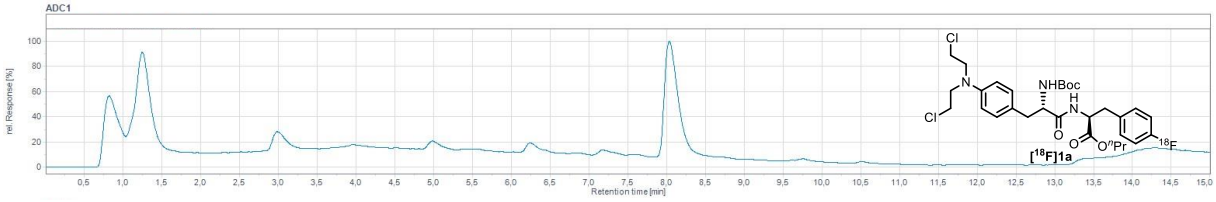

171.8
171.7
163.3
160.9
144.7
131.7
131.7
131.0
130.9
129.9
129.8
115.6
115.3
112.4
77.3
67.3
53.7
53.2
40.6
38.6
37.4
30.5
22.0
10.5
4a
A (d)
162.10
J(245.19)
B (d)
130.92
J(7.92)
D (d)
131.73
J(3.16)
C (d)
115.46
J(21.32)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
[ppm]

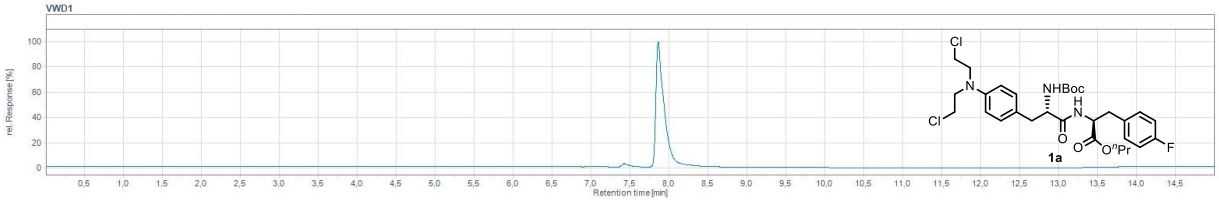

-115.65
-115.66
-115.67
-115.69
-115.70
-115.71
-115.72
4a
-115.25
-115.30
-115.35
-115.40
-115.45
-115.50
-115.55
-115.60
-115.65
-115.70
-115.75
-115.80
-115.85
-115.90
-115.95
-116.00
-116.05
-116.10
[ppm]

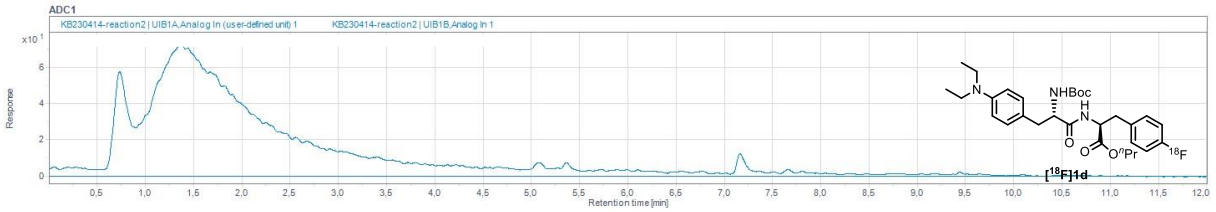
7.2. Radio/UV Analytical HPLC Chromatograms

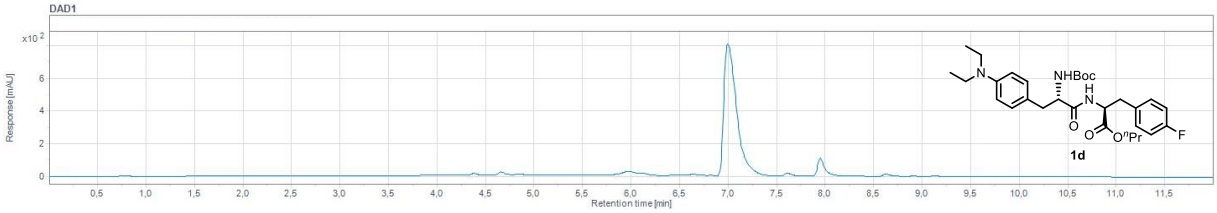


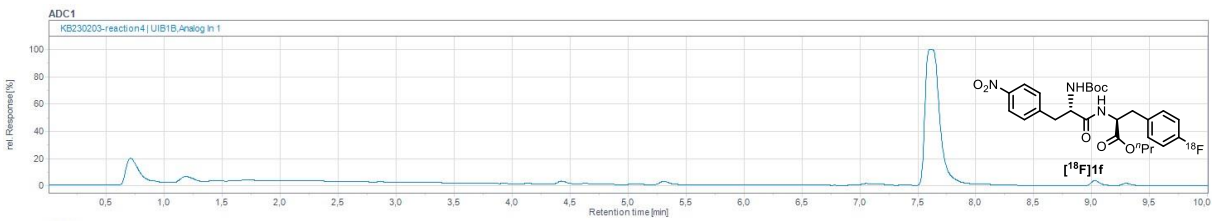


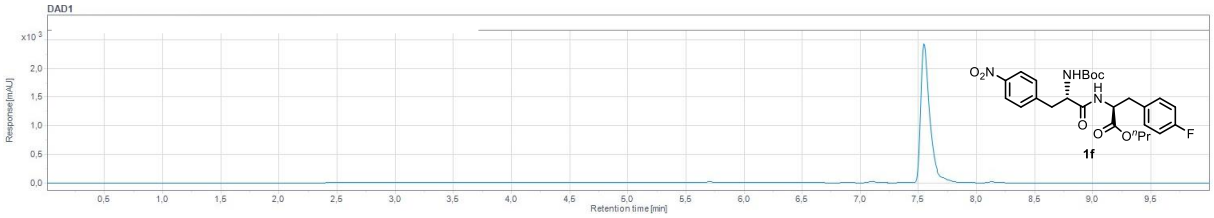


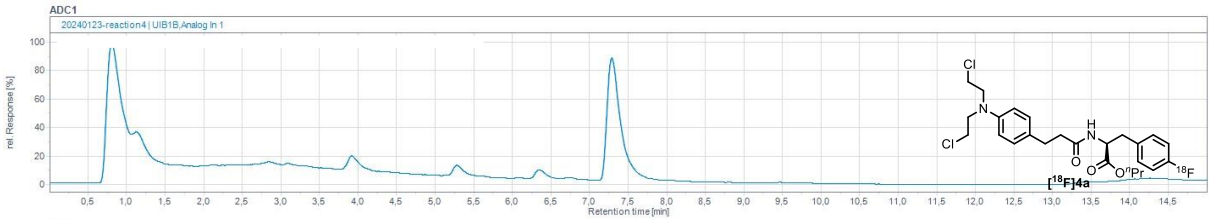


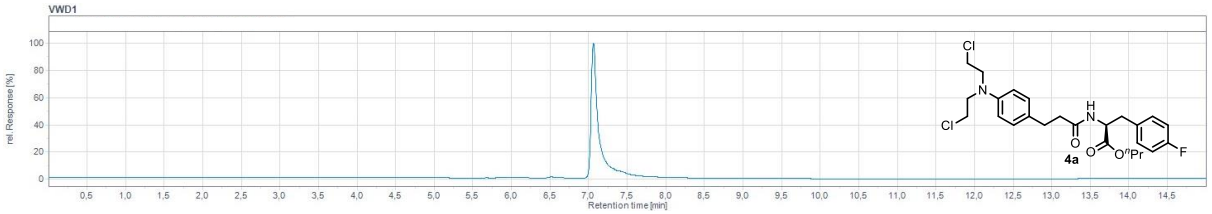







DAD1
x10 3
Response [mAU]
Retention time [min]
1f


ADC1
20240123-reaction4 | UIB1B,Analog In 1
rel. Response [%]
Retention time [min]
[18F]4a


VWD1
rel. Response [%]
Retention time [min]
4a