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N-difluoromethyl triazole as scaffold in peptidomimetic

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Topics

1. Experimental Section
1.1 General experimental methods

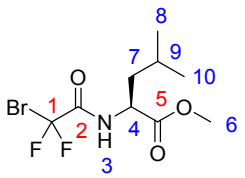
All experiments dealing with air and moisture-sensitive compounds were conducted under an atmosphere of dry argon. The usual solvents were purchased from commercial sources without further purification. Tetrahydrofuran (THF) was distilled on sodium/benzophenone and acetonitrile was distilled from CaH_2. Reagents were used without further purification as received from commercial.TLC was performed on silica gel, 60F-250 (0.26mm thickness) plates. The plates were visualized with UV light (254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol or with a solution of $KMnO_4$ in water. Flash chromatography (FC) was performed on Merck 60 silica gel (230 – 400 mesh). Melting points were determined on a Kofler melting point apparatus. NMR spectra were measured on an Ultrafield AVANCE300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) and BRUKER AMX 200 (^{1}H, 200 MHz; ^{19}F, 188 MHz) spectrometer. Unless otherwise stated, NMR data were obtained under ambient temperature conditions and $CDCl_3$ was used as solvent. Chemical shifts δ are in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet doublet (dd), triplet (t), q (quartet), quintuplet (quint), multiplet (m) and broad singlet (brs). High resolution mass spectra were recorded on a MicrotofQ Bruker Daltonics.

Conformations of reactants and products were fully optimized without constraint using the DFT method with the hybrid Becke3LYP functional and the 6-31G* base as implemented in the Gaussian 09 software package. Vibrational analysis within the harmonic approximation was performed at the same level of theory upon geometrical optimization convergence, and local minima were characterized by the absence of imaginary frequency. Thermodynamic quantities at 298.15 K were calculated using the zero-point and thermal energy corrections derived from unscaled frequencies

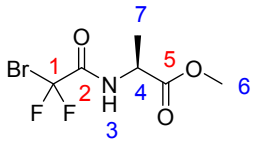
2. General procedure for the preparation of *N*-Bromodifluoroacetylated Amino Acids.

To a solution of bromodifluoro ethyl acetate (1 eq) in DMF (0.8M) was added the corresponding *O*-protected aminoacid (1 eq), and Et_3N (1.5 eq) on a scaled tube. The tube was put into an ultrasound bath and the reaction was performed under sonication for 4h without heating the bath. After completion, (monitored by ^{19}F NMR) the solution was diluted with water (10 mL) and extracted with DCM (3 × 10 mL). The organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography in appropriate solvents.

Methyl 2-(2-bromo-2,2-difluoroacetamido)-4-methylpentanoate 7a: The product was obtained following the general procedure (VII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **7a** as a colorless oil (1.28 g, 4.25 mmol, 90%).



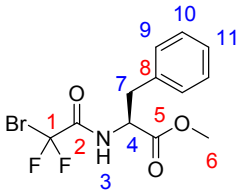
^{19}F NMR (188 MHz, $CDCl_3$): δ = -61.27 (s, 2F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.68 (d, ^3J(H,H) = 6.2 Hz, 1H, 3), 4.64 (td, ^3J(H,H) = 8.4 Hz, ^3J(H,H) = 5.1 Hz, 1H, 4), 3.78 (s, 3H, 6), 1.82 – 1.58 (m, 3H, 7 + 9), 0.97 (d, ^3J(H,H) = 6.3 Hz, 3H, 8), 0.96 (d, ^3J(H,H) = 6.2 Hz, 3H, 10). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.10 (5), 159.75 (t, ^2J(C,F) = 28.0 Hz, 2), 111.39 (t, ^1J(C,F) = 315.9 Hz, 1), 52.76 (6), 51.40 (4), 41.08 (7), 24.87 (9), 22.75 (8), 21.79 (10). **HRMS** (ESI-TOF) *m/z* $C_9H_{14}BrF_2NO_3$ $[M+Na]^+$ cal. 324.0023, found 324.0028. **$[\alpha]_D$** -107° (c 1.35, MeOH).



Methyl 2-(2-bromo-2,2-difluoroacetamido)propanoate 7b: The product was obtained following the general procedure (VII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **7b** as a colorless oil (910 mg, 3.51 mmol, 80%).

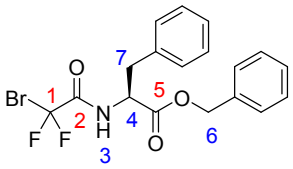
^{19}F NMR (188 MHz, $CDCl_3$): δ = -61.51 (s, 2F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.46 (d, ^{3}J(H,H) = 7.2 Hz, 1H, 3), 4.40 (p, ^{3}J(H,H) = 7.3 Hz, 1H, 4), 3.61 (s, 3H, 6), 1.33 (d, ^{3}J(H,H) = 7.3 Hz, 3H, 7). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 171.66 (5), 159.45 (t, ^{2}J(C,F) = 28.1 Hz, 2), 111.21 (t, ^{1}J(C,F) = 315.6 Hz, 1), 52.49 (6), 48.60 (4), 16.81 (7). **HRMS** (ESI-TOF) *m/z* $C_6H_8BrF_2NO_3$ $[M+Na]^+$ cal. 281.9553, found 281.9553. **$[\alpha]_D$** -136° (c 1.50, MeOH).

Methyl 2-(2-bromo-2,2-difluoroacetamido)-3-methylpentanoate 7c: The product was obtained following the general procedure (VII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **7c** as a white solid (1.51 g, 5.51 mmol, 90%).



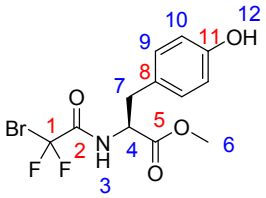
m. p.: 66°C. **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -61.21 (s, 2F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.38 – 7.25 (m, 3H, C_{ar}), 7.18 – 7.08 (m, 2H, C_{ar}), 6.70 (br d, ^{3}J(H,H) = 7.7 Hz, 1H, 3), 4.88 (dt, ^{3}J(H,H) = 7.9 Hz, ^{3}J(H,H) = 5.6 *Hz*, 1H, 4), 3.79 (s, 1H, 6), 3.28 (dd, ^{3}J(H,H) = 14.0 Hz, ^{3}J(H,H) = 5.5 Hz, 1H, 7a), 3.18 (dd, ^{3}J(H,H) = 14.0 Hz, ^{3}J(H,H) = 5.8 Hz, 1H, 7b). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 170.54 (5), 159.34 (t, ^{2}J(C,F) = 28.2 Hz, 2), 134.78 (8), 129.28 (9), 128.82 (10), 127.57 (11), 111.29 (t, ^{1}J(C,F) = 315.9 Hz, 1), 53.74 (4), 52.86 (6), 37.31 (7). **HRMS** (ESI-TOF) *m/z* $C_{12}H_{12}BrF_2NO_3$ $[M+Na]^+$ cal. 357.9866, found 357.9864. **$[\alpha]_D$** -55° (c 0.80, MeOH).

Benzyl 2-(2-bromo-2,2-difluoroacetamido)-3-phenylpropanoate 7d: The product was obtained following the general procedure (VII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **7d** as a white solid (700 mg, 1.70 mmol, 85%).



m. p.: 100°C. **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -61.16 (s, 2F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.41 – 7.29 (m, 5H, C_{ar}), 7.25 – 7.18 (m, 3H, C_{ar}), 7.00 – 6.93 (m, 2H, C_{ar}), 6.70 (d, ^{3}J(H,H) = 8.1 Hz, 1H, 3), 5.22 (d, ^{3}J(H,H) = 12.0 Hz, 1H, 6a), 5.15 (d, ^{3}J(H,H) = 12.0 Hz, 1H, 6b), 4.88 (dt, ^{3}J(H,H) = 7.7 Hz, ^{3}J(H,H) = 5.6 Hz, 1H, 4), 3.23 (dd, ^{3}J(H,H) = 14.0 Hz, ^{3}J(H,H) = 5.8 Hz, 1H, 7a), 3.15 (dd, ^{3}J(H,H) = 14.0 Hz, ^{3}J(H,H) = 5.4 Hz, 1H, 7b). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 170.01 (5), 159.34 (t, ^{2}J(C,F) = 28.1 Hz, 2), 136.88 – 125.84 (C_{ar}), 111.40 (t, ^{1}J(C,F) = 315.6 Hz, 1), 68.04 (6), 53.77 (4), 37.33 (7). **HRMS** (ESI-TOF) *m/z* $C_{18}H_{16}BrF_2NO_3$ $[M+Na]^+$ cal. 434.0179, found 434.0180. **$[\alpha]_D$** -59° (c 0.82, MeOH).

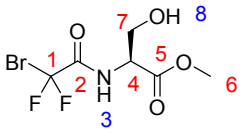
Methyl 2-(2-bromo-2,2-difluoroacetamido)-3-(4-hydroxyphenyl)pentanoate 7e: The product was obtained following the general procedure (VII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **7e** as a white solid (1.44 g, 4.54 mmol, 91%).



m. p.: 125°C. **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -61.68 (d, ^{2}J(F,F) = 162.0 Hz, 1F), -60.80 (d, ^{2}J(F,F) = 162.0 Hz, 1F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.01 – 6.90 (m, 2H, 9), 6.80 – 6.68 (m, 2H, 10), 5.26 (br s, 1H, 3), 4.83 (dt, ^{3}J(H,H) = 7.7 Hz, ^{3}J(H,H) = 5.4 *Hz*, 1H, 4), 3.79 (s, 1H, 6), 3.18 (dd, ^{3}J(H,H) = 14.2 Hz, ^{3}J(H,H) = 5.5 Hz, 1H, 7a), 3.10 (dd, ^{3}J(H,H) = 14.2 Hz, ^{3}J(H,H) = 5.4 Hz, 1H, 7b). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 170.80 (5), 159.49 (t, ^{2}J(C,F) = 28.2 Hz, 2), 155.27 (11), 130.59 (9), 126.60 (8),

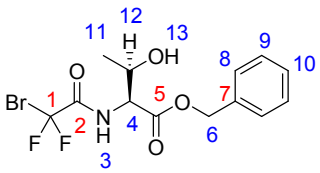
115.86 (10), 111.35 (t, ^{1}J(C,F) = 313.9 Hz, 1), 53.94 (4), 53.03 (6), 36.67 (7). **HRMS** (ESI-TOF) *m/z* $C_{12}H_{12}BrF_2NO_4$ $[M+Na]^+$ cal. 373.9815, found 373.9816. **$[\alpha]_D$** -78° (c 0.78, MeOH).

Methyl 2-(2-bromo-2,2-difluoroacetamido)-3-hydroxypentanoate 7f: The product was obtained following the general procedure (VII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 60/40) to provide **7f** as a colorless oil (1.22 g, 4.44 mmol, 84%).



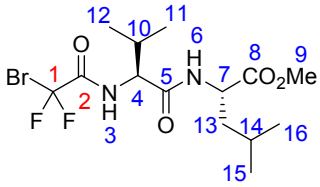
^{19}F NMR (188 MHz, $CDCl_3$): δ = -61.49 (s, 2F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.54 (d, ^{3}J(H,H) = 8.5 Hz, 1H, 3), 4.58 (dt, ^{3}J(H,H) = 7.3 Hz, ^{3}J(H,H) = 3.5 Hz, 1H, 4), 4.02 (dd, ^{3}J(H,H) = 11.5 Hz, ^{3}J(H,H) = 3.6 Hz, 1H, 7a), 3.88 (dd, ^{3}J(H,H) = 11.5 Hz, ^{3}J(H,H) = 3.4 Hz, 1H, 7b), 3.76 (s, 3H, 6), 3.45 (brs, 1H, 8). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.67 (5), 160.36 (t, ^{2}J(C,F) = 28.3 Hz, 2), 111.22 (t, ^{1}J(C,F) = 315.5 Hz, 1), 61.87 (7), 54.97 (4), 53.14 (6). **HRMS** (ESI-TOF) *m/z* $C_6H_8BrF_2NO_4$ $[M+H]^+$ cal. 297.9502, found 297.9510. **$[\alpha]_D$** -55° (c 0.80, MeOH).

Benzyl 2-(2-azido-2,2-difluoroacetamido)-3-hydroxybutanoate 7g: The product was obtained following the general procedure (VII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 60/40) to provide **7g** as a white solid (670 mg, 1.84 mmol, 73%).



^{19}F NMR (188 MHz, Acetone-d_6): δ = -59.33 (s, 2F). **^{1}H NMR** (300 MHz, Acetone-d_6): δ = 7.94 (d, ^{3}J(H,H) = 8.9 Hz, 1H, 3), 7.46 – 7.29 (m, 5H, 8 + 9 + 10), 5.22 (s, 2H, 6), 4.58 (dd, ^{3}J(H,H) = 8.8 Hz, ^{3}J(H,H) = 3.0 Hz, 1H, 4), 4.44 (ddq, ^{3}J(H,H) = 9.1 Hz, ^{3}J(H,H) = 6.1 Hz, ^{3}J(H,H) = 3.0 Hz, 1H, 12), 4.42 (d, ^{3}J(H,H) = 5.8 Hz, 1H, 13), 1.25 (d, ^{3}J(H,H) = 6.2 Hz, 3H, 11). **^{13}C NMR** (75 MHz, Acetone-d_6): δ = 169.87 (5), 161.03 (t, ^{2}J(C,F) = 27.7 Hz, 2), 136.75 (7), 129.27 (8), 128.96(9), 128.81 (10), 112.54 (t, ^{1}J(C,F) = 312.4 Hz, 1), 67.74 (6), 67.61 (12), 59.50 (4), 20.48 (11).

methyl (2-bromo-2,2-difluoroacetyl)-L-valyl-L-leucinate 7h: The product was obtained following the general procedure (VII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 60/40) to provide **7h** as a colorless oil (0.1 g, 0.25 mmol, 70%).



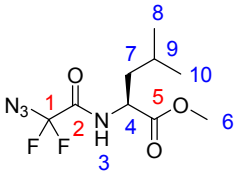
^{19}F NMR (188 MHz, $CDCl_3$): δ = -60.53 (s, 2F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.53 (d, ^{3}J(H,H) = 8.9 Hz, 1H, 3), 7.18 (d, ^{3}J(H,H) = 7.5 Hz, 1H, 6), 4.47 - 4.59 (m, 1 H, 4), 4.41 (t, ^{3}J(H,H) = 7.91 Hz, 1 H, 7), 3.69 (s, 3H, 9), 2.21-2.09 (m, 1H, 10), 1.44-1.71 (m, 3H, 13 + 14), 0.97 (d, ^{3}J(H,H) = 7.2 Hz, 3H, 12), 0.93 (d, ^{3}J(H,H) = 7.2 Hz, 3H, 11), 0.88 (d, ^{3}J(H,H) = 3.6 Hz, 6H, 15 + 16). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.89 (8), 169.80 (5), 159.94 (t, ^{2}J(C,F) = 28.5 Hz, 2), 111.27 (t, ^{1}J(C,F) = 316.1 Hz, 1), 58.64 (9), 52.13 (4), 50.99 (7), 40.66 (10), 31.70 (13), 24.69 (14), 22.57, 21.67 (12, 11), 18.85, 17.91 (15, 16). **HRMS** (ESI-TOF) *m/z* $C_{14}H_{23}BrF_2N_2O_4$ $[M+Na]^+$ cal. 400.0809, found 400.0805.

3. General procedure for the preparation of *N*-Azidodifluoroacetylated Amino Acids.

To a solution of corresponding bromodifluoroacetylated aminoacid (1 eq) in DMSO (0.2 M) was added NaN_3 (3 eq) and the mixture was stirred at 70°C one night. After completion,

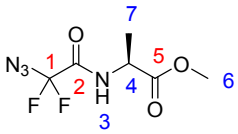
(monitored by ^{19}F NMR) the solution was diluted with water (10 mL) and extracted with DCM (2 × 10 mL). The organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography in appropriate solvents.

Methyl 2-(2-azido-2,2-difluoroacetamido)-4-methylpentanoate 3a: The product was obtained following the general procedure (VIII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **3a** as a colorless oil (370 mg, 1.4 mmol, 70%).



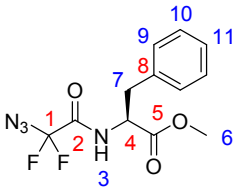
^{19}F NMR (188 MHz, $CDCl_3$): δ = -83.58 (d, ^2J(F,F) = 193.6 Hz, 1F), -84.79 (d, ^2J(F,F) = 193.6 Hz, 1F). **^1H NMR** (300 MHz, $CDCl_3$): δ = 7.06 (d, ^3J(H,H) = 8.7 Hz, 1H, 3), 4.57 (td, ^3J(H,H) = 8.6 Hz, ^3J(H,H) = 4.7 Hz, 1H, 4), 3.70 (s, 3H, 6), 1.73 – 1.51 (m, 3H, 7 + 9), 0.88 (d, ^3J(H,H) = 6.2 Hz, 6H, 8 + 10). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.05 (5), 159.55 (t, ^2J(C,F) = 34.8 Hz, 2), 113.57 (t, ^1J(C,F) = 269.0 Hz, 1), 52.71 (6), 51.24 (4), 41.17 (7) , 24.88 (9), 22.66 (8) , 21.80 (10). **HRMS** (ESI-TOF) *m/z* $C_9H_{14}F_2N_4O_3$ $[M+Na]^+$ cal. 287.0932, found 287.0934. **$[\alpha]_D$** -42° (c 1.01, MeOH).

Methyl 2-(2-azido-2,2-difluoroacetamido)propanoate 3b: The product was obtained following the general procedure (VIII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **3b** as a colorless oil (262 mg, 1.18 mmol, 59%).



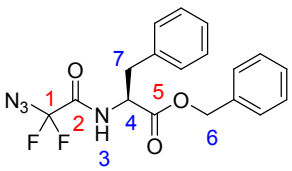
^{19}F NMR (188 MHz, $CDCl_3$): δ = -83.38 (d, ^2J(F,F) = 193.6 Hz, 1F), -84.47 (d, ^2J(F,F) = 193.6 Hz, 1F). **^1H NMR** (300 MHz, $CDCl_3$): δ = 6.96 (brs, 1H, 3), 4.58 (p, ^3J(H,H) = 7.2 Hz, 1H, 4), 3.80 (s, 3H, 6), 1.49 (d, ^3J(H,H) = 7.2 Hz, 3H, 7). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 171.95 (5), 159.29 (t, ^2J(C,F) = 34.9 Hz, 2), 113.42 (t, ^1J(C,F) = 268.9 Hz, 1), 52.75 (6), 48.53 (4), 17.44 (7). **HRMS** (ESI-TOF) *m/z* $C_6H_8F_2N_4O_3$ $[M+Na]^+$ cal. 245.0462, found 245.0468. **$[\alpha]_D$** -67° (c 1.05, MeOH).

Methyl 2-(2-azido-2,2-difluoroacetamido)-3-phenylpropanoate 3c: The product was obtained following the general procedure (VIII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **3c** as a white solid (387 mg, 1.3 mmol, 65%).



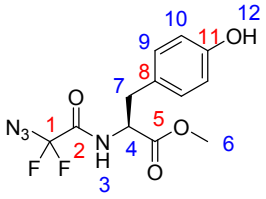
m. p.: <40°C. **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -83.36 (d, ^2J(F,F) = 194.6 Hz, 1F), -84.46 (d, ^2J(F,F) = 194.6 Hz, 1F). **^1H NMR** (300 MHz, $CDCl_3$): δ = 7.32 – 7.18 (m, 3H, 9 + 11), 7.08 – 6.99 (m, 2H, 10), 6.74 (d, ^3J(H,H) = 7.9 Hz, 1H, 3), 4.81(dt, ^3J(H,H) = 7.9 Hz, ^3J(H,H) = 5.7 *J* =, 1H, 4), 3.79 (s, 3H, 6), 3.19 (dd, ^1J(H,H) = 14.0 Hz, ^3J(H,H) = 5.7 Hz, 1H, 7a), 3.10 (dd, ^1J(H,H) = 13.9 Hz, ^3J(H,H) = 5.7 Hz, 1H, 7b). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 170.53 (5), 159.22 (t, ^2J(C,F) = 35.0 Hz, 2), 134.83 (8), 129.20 (9), 128.80 (10), 127.53 (11), 113.39 (t, ^1J(C,F) = 269.1 Hz, 1), 53.57 (4), 52.78 (6), 37.38 (7). **HRMS** (ESI-TOF) *m/z* $C_{12}H_{12}F_2N4O_3$ $[M+Na]^+$ cal. 321.0775, found 321.0772. **$[\alpha]_D$** +4° (c 1.00, MeOH).

Benzyl 2-(2-azido-2,2-difluoroacetamido)-3-phenylpropanoate 3d: The product was obtained following the general procedure (VIII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **3d** as a white solid (419 mg, 1.12 mmol, 50%).



m. p.: <40°C. **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -83.28 (d, ^2J(F,F) = 194.6 Hz, 1F), -84.39 (d, ^2J(F,F) = 194.6 Hz, 1F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.33 – 7.20 (m, 5H, C_{ar}), 7.20 – 7.08 (m, 3H, C_{ar}), 6.96 – 6.82 (m, 2H, C_{ar}), 6.74 (d, ^3J(H,H) = 7.3 Hz, 1H, 3), 5.13 (d, ^1J(H,H) = 12.0 Hz, 1H, 6a), 5.05 (d, ^1J(H,H) = 12.0 Hz, 1H, 6b), 4.79 (dt, *J* = 7.8 Hz, *J* = 5.7 *J* =, 1H, 4), 3.12 (dd, ^1J(H,H) = 14.0 Hz, ^3J(H,H) = 5.9 Hz, 1H, 7a), 3.04 (dd, ^1J(H,H) = 14.0 Hz, ^3J(H,H) = 5.6 Hz, 1H, 7b). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.99 (5), 159.23 (t, ^2J(C,F) = 35.0 Hz, 2), 135.15 – 126.60 (C_{ar}), 113.44 (t, ^1J(C,F) = 269.3 Hz, 1), 67.95 (6), 53.59 (4), 37.38 (7). **HRMS** (ESI-TOF) *m/z* $C_{18}H_{16}F_2N_4O_3$ $[M+Na]^+$ cal. 397.1088, found 397.1086. **$[\alpha]_D$** -6° (c 1.00, MeOH).

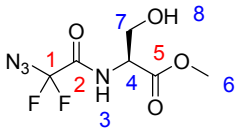
Methyl 2-(2-azido-2,2-difluoroacetamido))-3-(4-hydroxyphenyl)propanoate 3e: The



product was obtained following the general procedure (VIII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **3e** as a white solid (377 mg, 1.20 mmol, 60%).

m. p.: 124 - 126°C. **^{19}F NMR** (188 MHz, Acetone-d_6): δ = -82.86 (d, ^2J(F,F) = 195.5 Hz, 1F), -84.04 (d, ^2J(F,F) = 195.5 Hz, 1F). **^{1}H NMR** (300 MHz, Acetone-d_6): δ = 8.41 (d, ^3J(H,H) = 7.2 Hz, 1H, 3), 8.25 (s, 1H, 12), 7.14 – 7.05 (m, 2H, 9), 6.81 – 6.72 (m, 2H, 10), 4.70 (ddd, ^3J(H,H) = 9.5 Hz, ^3J(H,H) = 8.1 Hz, ^3J(H,H) = 5.1 Hz, 1H, 4), 3.71 (s, 3H, 6), 3.20 (dd, ^1J(H,H) = 14.1 Hz, ^3J(H,H) = 5.1 Hz, 1H, 7a), 3.01 (dd, ^1J(H,H) = 14.1 Hz, ^3J(H,H) = 9.5 Hz, 1H, 7b). **^{13}C NMR** (75 MHz, Acetone-d_6): δ = 171.36 (5), 160.40 (t, ^2J(C,F) = 35.2 Hz, 2), 157.22 (11), 131.02 (9), 127.96 (8), 116.12 (10), 114.56 (t, ^1J(C,F) = 265.9 Hz, 1), 55.23 (4), 52.71 (6), 36.52 (7). **HRMS** (ESI-TOF) *m/z* $C_{12}H_{12}F_2N_4O_4$ $[M+Na]^+$ cal. 337.0724, found 337.0717. **$[\alpha]_D$** +20° (c 1.00, MeOH).

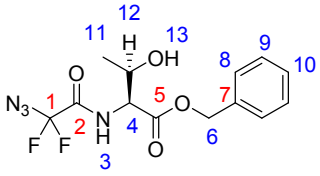
Methyl 2-(2-azido-2,2-difluoroacetamido)propanoate 3f: The product was obtained



following the general procedure (VIII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **3f** as a colorless oil (298 mg, 1.25 mmol, 63%).

^{19}F NMR (188 MHz, $CDCl_3$): δ = -83.46 (d, ^2J(F,F) = 194.6 Hz, 1F), -84.52 (d, ^2J(F,F) = 194.6 Hz, 1F). **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.62 (brs, 1H, 3), 4.65 (dt, ^3J(H,H) = 7.2 Hz, ^3J(H,H) = 3.2 Hz, 1H, 4), 4.10 (ddd, ^1J(H,H) = 11.4 Hz, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 3.3 Hz, 1H, 7a), 3.80 (ddd, ^1J(H,H) = 11.4 Hz, ^3J(H,H) = 5.2 Hz, ^3J(H,H) = 3.3 Hz, 1H, 7b), 3.82 (s, 3H, 6), 2.41 (brt, ^3J(H,H) = 5.6 Hz, 8). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.56 (5), 169.95 (t, ^2J(C,F) = 35.0 Hz, 2), 113.39 (t, ^1J(C,F) = 269.1 Hz, 1), 61.60 (7), 54.69 (4), 52.84 (6). **HRMS** (ESI-TOF) *m/z* $C_6H_8F_2N4O_4$ $[M+Na]^+$ cal. 261.0411, found 261.0401. **$[\alpha]_D$** -19° (c 1.09, MeOH).

Benzyl 2-(2-azido-2,2-difluoroacetamido)-3-hydroxybutanoate 3g: The product was



obtained following the general procedure (VIII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 60/40) to provide **3g** as a white solid (328 mg, 1.00 mmol, 50%).

m. p.: 56 - 58°C. **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -82.85 (d, ^2J(F,F) = 193.6 Hz, 1F), -84.11 (d, ^2J(F,F) = 193.6 Hz, 1F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.42 – 7.31 (m, 5H, 8 + 9 + 10), 7.27 (d, ^3J(H,H) = 8.4 Hz, 1H, 3), 5.23 (d, ^3J(H,H) = 13.5 Hz, 1H, 6a), 5.19 (d, ^3J(H,H) = 13.5 Hz, 1H, 6b), 4.60 (dd, ^3J(H,H) = 9.0 Hz, ^3J(H,H) = 2.3 Hz, 1H, 4), 4.44 (qd, ^3J(H,H) = 6.4 Hz, ^3J(H,H) = 2.3 Hz, 1H, 12), 2.48 (brs, 1H, 13), 1.21 (d, ^3J(H,H) = 6.4 Hz, 3H, 11). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.43 (5), 169.50 (t,

^2J(C,F) = 35.0 Hz, 2), 134.87 (7), 128.76 (8 + 9), 128.29 (10), 113.65 (t, ^1J(C,F) = 269.4 Hz, 1), 67.92 (6), 67.58 (12), 57.74 (4), 19.91 (11). **HRMS** (ESI-TOF) *m/z* $C_{13}H_{14}F_2N4O_4$ $[M+Na]^+$ cal. 351.0881, found 351.0876. **$[\alpha]_D$** -20° (c 1.00, MeOH).

Methyl 2-(2-azido-2,2-difluoroacetamido)-4-methylpentanoate 3h: The product was obtained following the general procedure (VIII). The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 90/10) to provide **3h** as a colorless oil (58 mg, 0.16 mmol, 64%). **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -82.85 (d, ^2J(F,F) = 194.3 Hz, 1F), -83.49 (d, ^2J(F,F) = 194.3 Hz, 1F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.18 (d, ^3J(H,H) = 8.5 Hz, 1H, 3), 6.43 (d, ^3J(H,H) = 8.1 Hz, 1H, 6), 4.65-4.53 (m, 1 H, 4), 4.34 (t, ^3J(H,H) = 7.6 Hz, 1 H, 7), 3.74 (s, 3H, 9), 2.20-2.08 (m, 1H, 10), 1.69-1.52 (m, 3H, 13 + 14), 0.95 (d, ^3J(H,H) = 6.3 Hz, 3H, 12), 0.94 (d, ^3J(H,H) = 6.3 Hz, 3H, 11), 0.92 (d, ^3J(H,H) = 4.5 Hz, 6H, 15 + 16). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.91 (8), 169.42 (5), 159.58 (t, ^2J(C,F) = 35.1 Hz, 2), 113.54 (t, ^1J(C,F) = 270.1 Hz, 1), 58.56 (9), 52.33 (4), 50.97 (7), 41.10 (13), 31.68 (10), 24.79 (14), 22.60, 21.76 (12, 11), 18.76, 17.92 (15, 16). **HRMS** (ESI-TOF) *m/z* C14H23F2N5O4 $[M+Na]^+$ cal. 363,1718, found 363,1716.

4. General procedure for the one pot reaction

To a solution of bromodifluoroethylacetate (1.1 eq) in DMF (0.5 M) was added NaN_3 (1.15 eq)d the mixture was stirred at 30°C one night. After completion (monitored by ^{19}F NMR) triethylamine (1.5eq) and aminoacid (1eq) was added and the mixture was heat in an ultrasound bath for 4h. The solution was diluted with water (10 mL) and extracted with Et_2O (2 × 10 mL). The organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography in appropriate solvents.

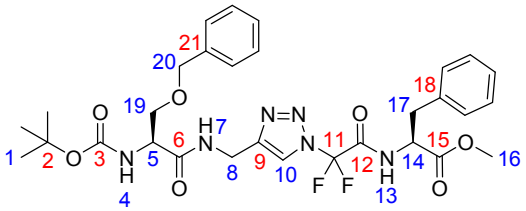
5. General procedure for the CuAAC reaction

To a solution of corresponding azidodifluoroacetylated aminoacid (1 eq) and propargylamide aminoacid (1eq) in tBuOH:H_2O (0.2 M) was added $CuSO_4$ (10mol%), sodium ascorbate (1eq) and 10% of TBTA. The mixture was stirred r.t. for several hours. After completion, (monitored by ^{19}F NMR) the solvents were evaporated under vacuum and the crude product was directly purified by column chromatography in appropriate solvents.

Ala-Ala Tetrapeptide 5a: The product was obtained following the general procedure in 2h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 40/60) to provide **5d** as a white solid (266 mg, 0.59 mmol, 93%). **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -87.51 (d, ^2J(F,F) = 208.5 Hz, 1F), -89.02 (d, ^2J(F,F) = 208.6 Hz, 1F). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.09 (d, ^3J(H,H) = 7.1 Hz, 1H, 13), 8.02 (s, 1H, 10), 7.51 (brt, ^3J(H,H) = 5.7 Hz, 1H, 7), 4.96 (brs, 1H, 4), 5.51 (m, 1H, 8), 4.57 (m, 2H, 14), 4.46 (brs, 1H, 5), 3.70 (s, 3H, 16), 1.45 (d, ^3J(H,H) = 7.1 Hz, 3H, 17), 1.32 (s, 9H, 1), 1.26 (d, ^3J(H,H) = 7.1 Hz, 3H, 18). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 173.64 (15),

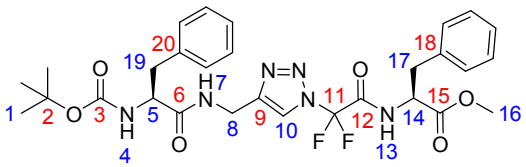
171.95 (6), 157.78 (t, ^2J(C,F) = 31.5 Hz, 12), 155.65 (3), 145.64 (9), 121.13 (10), 110.16 (t, ^1J(C,F) = 268.9 Hz, 11), 80.13 (2), 52.85 (16), 50.20 (5), 49.03 (14), 34.57 (8), 28.22 (1), 18.32 (17), 17.26 (18). **HRMS** (ESI-TOF) *m/z* $C_{17}H_{26}F_2N_6O_6$ $[M+Na]^+$ cal. 448.4278, found .448.4271.

Ser(OBn)-Phe Tetrapeptide 5b: The product was obtained following the general procedure in 5h40. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 40/60) to provide **5b** as a waste (265 mg, 0.42 mmol, 91%).



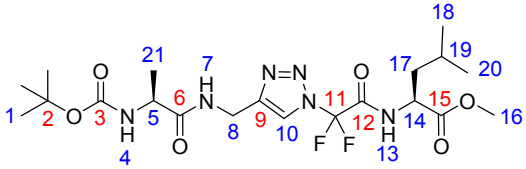
^{19}F NMR (188 MHz, $CDCl_3$): δ = -87.46 (d, ^2J(F,F) = 209.1 Hz, 1F), -89.03 (d, ^2J(F,F) = 209.1 Hz, 1F). **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.95 (s, 1H, 10), 7.51 – 7.09 (m, 12H, CH_{ar} + 13 +7), 5.45 (d, ^3J(H,H) = 7.2 Hz, 1H, 4), 4.94 (dt, ^3J(H,H) = 8.0 Hz, ^3J(H,H) = 5.8 Hz, 1H, 14), 4.67 – 4.42 (m, 4H, 8 + 20), 4.31 (brs, 1H, 5), 3.91 (dd, ^1J(H,H) = 9.3 Hz, ^3J(H,H) = 4.1 Hz, 1H, 4a), 3.77 (s, 3H, 16), 3.60 (dd, ^1J(H,H) = 9.4 Hz, ^3J(H,H) = 5.9 Hz, 1H, 4b), 3.27 (dd, ^1J(H,H) = 13.8 Hz, ^3J(H,H) = 5.4 Hz, 1H, 17a), 3.18 (dd, ^1J(H,H) = 13.4 Hz, ^3J(H,H) = 5.6 Hz, 1H, 17b), 1.44 (s, 9H, 1).). **^{13}C NMR** (75 MHz, Acetone-d_6): δ = 171.26 (15), 171.15 (6), 158.84 (t, ^2J(C,F) = 31.5 Hz, 11), 156.34 (3), 147.13 (9), 139.08 (21), 137.32 (18), 130.00-129.28 (C_{ortho}), 129.02 and 128.32 (C_{meta}), 128.24 and 127.71 (C_{para}), 121.88 (10), 111.18 (t, ^1J(C,F) = 269.2 Hz, 11), 79.67 (2), 73.46 (20), 70.84 (19), 55.62 (5), 55.31 (14), 53.79 (16), 37.26 (17), 35.27 (8), 28.48 (1). **HRMS** (ESI-TOF) *m/z* $C_{30}H_{36}F_2N_6O_7$ $[M+Na]^+$ cal. 630.2614, found .630.2601.

Phe-Phe Tetrapeptide 5c: The product was obtained following the general procedure in 4h45. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 50/50) to provide **5c** as a white solid (271 mg, 0.43 mmol, 90%).



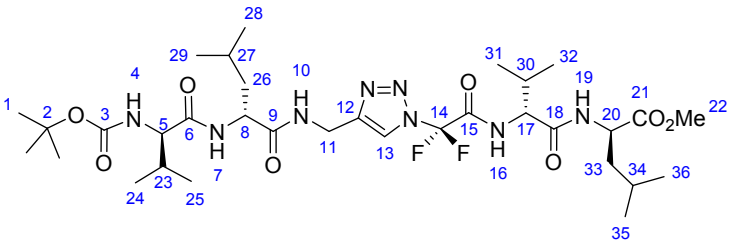
m. p.: 62 - 64°C. **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -87.33 (d, ^2J(F,F) = 208.7 Hz, 1F), -88.70 (d, ^2J(F,F) = 208.7 Hz, 1F). **^{1}H NMR** (400 MHz, $CDCl_3$): δ =7.68 (s, 1H, 10), 7.23 (d, ^3J(H,H) = 7.8 Hz, 1H, 13), 7.20 – 6.97 (m, 10H, CH_{ar}), 6.55 – 6.45 (m, 1H, 7), 4.96 (d, ^3J(H,H) = 8.0 Hz, 1H, 4), 4.81 (dt, ^3J(H,H) = 7.7 Hz, ^3J(H,H) = 5.6 Hz, 1H, 14), 4.37 (d, ^3J(H,H) = 5.9 Hz, 2H, 8), 4.31 – 4.16 (m, 1H, 5), 3.65 (s, 3H, 16), 3.13 (dd, ^3J(H,H) = 14.0 Hz, ^3J(H,H) = 5.6 Hz, 1H, 17a), 3.07 (dd, ^3J(H,H) = 14.0 Hz, ^3J(H,H) = 5.7 Hz, 1H, 17b), 2.93 (brd, ^3J(H,H) = 7.0 Hz, 2H, 19), 1.26 (s, 9H, 1). **^{13}C NMR** (75 MHz, Acetone-d_6): δ = 171.77 (15), 170.50 (6), 157.67 (t, ^2J(C,F) = 31.5 Hz, 12), 155.55 (3), 145.33 (9), 136.55 (20), 134.91 (18), 129.32 (C_{ortho}), 128.81 and 128.64 (C_{meta}), 127.51 and 127.04 (C_{para}), 121.01 (10), 110.22 (t, ^1J(C,F) = 269.2 Hz, 11), 80.34 (2), 55.87 (5), 54.14 (14), 52.84 (16), 38.64 (19), 37.37 (17), 34.58 (8), 28.29 (1). **HRMS** (ESI-TOF) *m/z* $C_{29}H_{34}F_2N_6O_6$ $[M+Na]^+$ cal. 623.2406, found 623.2401.

Ala-Leu Tetrapeptide 5d: The product was obtained following the general procedure in 5h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 40/60) to provide **5d** as a white solid (88 mg, 0.172 mmol, 95%).



m. p.: 110 - 112°C. **^{19}F NMR** (188 MHz, $CDCl_3$): δ = -87.09 (d, ^2J(F,F) = 208.3 Hz, 1F), -89.18 (d, ^2J(F,F) = 208.4 Hz, 1F). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.03 (s, 1H, 10), 7.49 (d, ^3J(H,H) = 8.2 Hz, 1H, 13), 7.09 (t, ^3J(H,H) = 5.3 Hz, 1H, 7), 5.13 (d, ^3J(H,H) = 7.6 Hz, 1H, 4), 4.75 – 4.64 (m, 1H, 14), 4.60 (dd, ^3J(H,H) = 15.4 Hz, ^3J(H,H) = 5.9 Hz, 2H, 8a), 4.51 (dd, ^3J(H,H) = 15.5 Hz, ^3J(H,H) = 5.9 Hz, 2H, 8b), 4.31 – 4.03 (m, 1H, 5), 3.77 (s, 3H, 16), 1.82 – 1.59 (m, 3H, 17 + 19), 1.40 (s, 9H, 1), 1.34 (d, ^3J(H,H) = 7.1 Hz, 3H, 21), 0.94 (brd, ^3J(H,H) = 5.8 Hz, 6H, 18 + 20). **^{13}C NMR** (75 MHz, Acetone-d_6): δ = 173.89 (15), 172.26 (6), 159.09 (t, ^2J(C,F) = 31.3 Hz, 12), 156.33 (3), 147.58 (9), 121.82 (10), 111.45 (t, ^1J(C,F) = 266.5 Hz, 11), 79.42 (2), 52.72 (16), 52.41 (14), 51.25 (5), 40.44 (17), 35.28 (8), 28.55 (1), 25.37 (19), 23.19 (18), 21.50 (20), 18.45 (21). **HRMS** (ESI-TOF) *m/z* $C_{20}H_{32}F_2N_6O_6$ $[M+Na]^+$ cal. 513.2249, found 513.2250.

Hexapeptide 5f: The product was obtained following the general procedure in 5h30. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 60/40) to provide **5f** as a white solid (30 mg, 0.04 mmol, 60%).



^{19}F NMR (188 MHz, $CDCl_3$): δ = -86.69 (d, ^2J(F,F) = 207.3 Hz, 1F), -87.93 (d, ^2J(F,F) = 208.7 Hz, 1F). **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 8.03 (s, 1H, 13), 7.65 (d, ^3J(H,H) = 8.3 Hz, 1H, 19), 7.44 (t, ^3J(H,H) = 8.1 Hz, 1H, 16), 6.75 (d, ^3J(H,H) = 8.2 Hz, 1H, 10), 6.66 (d, ^3J(H,H) = 8.3 Hz, 1H, 7), 5.22 (d, ^3J(H,H) = 8.0 Hz, 1H, 4), 4.67-4.39 (m, 5H, 8, 11, 17, 20), 3.87 (t, ^3J(H,H) = 7.7 Hz, 5), 3.75 (s, 3H, 22), 2.22 (m, 1H, 23), 2.09 (m, 1H, 30), 1.75-1.49 (m, 6H, 26, 27, 33, 34), 1.42 (s, 9H, 1), 1.01, (t, ^3J(H,H) = 7.4 Hz, 12H, 24, 25, 31, 32), 0.92 (d, ^3J(H,H) = 7.6 Hz, 12H, 28, 29, 35, 36).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.02 (21), 172.35, 172.15, 169.68 (6, 9, 18), 158.04 (t, ^2J(C,F) = 30.7 Hz, 15), 156.03 (3), 145.71 (12), 120.63 (13), 110.39 (t, ^1J(C,F) = 267.9 Hz, 14), 79.85 (2), 60.26, 59.28 (5, 17), 52.25 (22), 51.66, 50.99 (8, 20), 40.90, 40.61 (26, 33), 34.68 (11), 31.30, 30.57 (23, 30), 28.28 (1), 24.79, 24.73 (27, 34), 22.75, 22.60, 21.99, 21.79 (24, 25, 31, 32), 19.08, 18.82, 18.15, 17.98 (28, 29, 35, 36). **HRMS** (ESI-TOF) *m/z* $C_{33}H_{56}F_2N_8O_8$ $[M+Na]^+$ cal. 730.4189, found 730.4175.

6. Computational methods

Using MCMM method[1] as implemented in MacroModel v10.9 software package,[2] 10,000 random conformations of compound **1** were generated, minimized with OPLS_2005 force field[2] and deduplicated.

The 12 resulting conformations were fully optimized without constraint using DFT[3,4] method with the hybrid Becke3LYP functional[5,6] and the 6-31G* basis set[7] as implemented in Gaussian 09 software package.[8] Vibrational analysis within the harmonic approximation was performed at the same level of theory upon geometrical optimization convergence and local minima were characterized by the absence of imaginary frequency.

Refinement of the unique conformations found at this stage was performed under the same conditions, using previously mentioned Becke3LYP functional or Minnesota 06 functional M06-2X [9] with 6-311++G(2d,2p) basis set[7]. PCM model was used in some calculations to take into account water solvation.[10]

The potential energy surface scan was conducted starting from conformation *a* by varying the ψ angle over 360° with an increment of approximately +10°. At every step, optimization of all but the constrained geometrical parameter was performed until convergence using the previously mentioned Becke3LYP functional and 6-31G* basis set.

Molecular graphics were designed and rendered with UCSF Chimera.[11,12]

Conformation	Gas		Water	
	ΔG^0_{rel}	Population	ΔG^0_{rel}	Population
a	0.00 kcal/mol	42%	0.00 kcal/mol	90%
b	0.00 kcal/mol	42%	2.94 kcal/mol	1%
c	0.60 kcal/mol	15%	1.37 kcal/mol	9%

Table 1. Free energies calculated for compound **1** at the B3LYP/6-311++G(2d,2p) level.

Conformation	Gas		Water	
	ΔG^0_{rel}	Population	ΔG^0_{rel}	Population
a	0.00 kcal/mol	67%	0.27 kcal/mol	39%
b	0.43 kcal/mol	33%	0.00 kcal/mol	61%

Table 2. Free energies calculated for compound **1** at the M06-2X/6-311++G(2d,2p) level.

Conformation	Functional	Angles (°)			
		Gas		Water	
		θ	Ψ	θ	Ψ
a	B3LYP	−75.6	137.6	−100.9	147.1
	M06-2X	−73.6	131.9	−77.0	146.1
b	B3LYP	79.3	126.1	98.2	117.1
	M06-2X	76.1	126.4	71.3	142.6
c	B3LYP	−77.5	128.4	−99.0	121.9

Table 3. Most significant dihedral angles measured on calculated conformations of compound **1**.

Machine-readable coordinates of the three gas phase conformations calculated at the B3LYP/6-311++G(2d,2p) level under the MDL Molfile file format.

7. Coordinates and energies

B3LYP/6-311++G(2d,2p) level / gas phase

Conformation *a*:
Electronic energy (RB3LYP): −935.656823066 Ha.
Lowest frequency: 15.5166 cm^{-1}.
Sum of electronic and thermal free energies: −935.497756 Ha.
Atomic nuclei coordinates:

```
N   0.47434  -1.84850  -0.78630
C   1.36626  -1.21534   0.03562
C   0.68036  -0.30382   0.79737
N  -0.60567  -0.43556   0.38348
N  -0.71513  -1.38442  -0.57981
C   2.83149  -1.52452  -0.00578
N   3.62596  -0.52349  -0.71197
C  -1.79378   0.21501   0.85790
C  -2.71894   0.65609  -0.31433
F  -1.42728   1.29746   1.57010
F  -2.44765  -0.62469   1.72395
N  -3.89189   0.00409  -0.38469
O  -2.34052   1.54749  -1.04329
C  -4.83882   0.24667  -1.46227
C   3.97396   0.65093  -0.11307
C   4.72583   1.64369  -0.97464
O   3.70396   0.88253   1.05672
H   1.00088   0.40222   1.53909
H   2.96755  -2.48162  -0.50437
H   3.22756  -1.60227   1.00413
H   3.74183  -0.61887  -1.70560
H  -4.04652  -0.76426   0.24490
H  -5.84933   0.07528  -1.09893
H  -4.74172   1.27822  -1.78750
```

H -4.64543 -0.40759 -2.31350
H 5.67240 1.87698 -0.48977
H 4.14789 2.56532 -1.02823
H 4.92034 1.28446 -1.98395

Conformation *b*:
Electronic energy (RB3LYP): −935.656133966 Ha.
Lowest frequency: 13.0827 cm^{-1}.
Sum of electronic and thermal free energies: −935.497751 Ha.
Atomic nuclei coordinates:
N -0.43894 1.85495 0.35204
C -1.24551 1.01953 -0.36533
C -0.58392 -0.17062 -0.54603
N 0.60567 0.01330 0.07893
N 0.67534 1.25347 0.62313
C -2.61468 1.43445 -0.81048
N -3.69005 0.92578 0.03506
C 1.70335 -0.92188 0.25462
C 3.11048 -0.42530 -0.23041
F 1.37708 -2.03718 -0.41057
F 1.78701 -1.23404 1.57795
N 3.47714 0.77597 0.24448
O 3.77821 -1.15564 -0.93080
C 4.76945 1.35628 -0.08903
C -4.12125 -0.36327 -0.07344
C -5.20363 -0.79124 0.89497
O -3.66537 -1.12353 -0.91526
H -0.86673 -1.08454 -1.03149
H -2.79834 1.08355 -1.82344
H -2.66506 2.52096 -0.80710
H -3.99629 1.48428 0.81202
H 2.77467 1.34193 0.70124
H 5.00424 2.12854 0.63876
H 5.53315 0.58376 -0.05497
H 4.76742 1.79402 -1.08848
H -4.84627 -1.65138 1.45907
H -6.07334 -1.11196 0.32343
H -5.50271 -0.00669 1.58824

Conformation *c*:
Electronic energy (RB3LYP): −935.656020475 Ha.
Lowest frequency: 14.5973 cm^{-1}.
Sum of electronic and thermal free energies: −935.496793 Ha.
Atomic nuclei coordinates:
N -0.48855 -2.01918 0.22098
C -1.35400 -1.15674 -0.38772
C -0.62994 -0.10985 -0.90375
N 0.65291 -0.39790 -0.57061
N 0.72055 -1.56934 0.10937
C -2.83173 -1.40433 -0.40879
N -3.57879 -0.61353 0.56481
C 1.86888 0.32270 -0.90547
C 2.81306 0.67399 0.29726
F 1.49634 1.45452 -1.51652

F 2.57197 -0.42338 -1.80293
N 3.11939 -0.36103 1.09572
O 3.23974 1.80471 0.39384
C 4.01559 -0.19507 2.23037
C -3.85307 0.70324 0.34183
C -4.58916 1.43055 1.44722
O -3.53123 1.25853 -0.69863
H -0.92375 0.77325 -1.43718
H -3.00788 -2.45677 -0.19845
H -3.23237 -1.17852 -1.39460
H -3.75226 -1.00618 1.47307
H 2.58896 -1.21572 0.99327
H 3.52388 0.31730 3.05863
H 4.34353 -1.17684 2.56122
H 4.88021 0.39184 1.93059
H -5.52417 1.81757 1.04489
H -3.98991 2.28331 1.76272
H -4.80546 0.80460 2.31158

B3LYP/6-311++G(2d,2p) level / water solvation model

Conformation *a*:
Electronic energy (RB3LYP): −935.677789040 Ha.
Lowest frequency: 4.9417 cm^{-1}.
Sum of electronic and thermal free energies: −935.520912 Ha.
Atomic nuclei coordinates:
N 0.61971 -0.33393 -1.74812
C 1.37189 -0.84902 -0.72692
C 0.55836 -1.00194 0.36496
N -0.65372 -0.55839 -0.05706
N -0.59996 -0.15921 -1.35053
C 2.83417 -1.13961 -0.88323
N 3.67672 0.04795 -0.80143
C -1.91411 -0.57354 0.63195
C -2.80184 0.64687 0.25574
F -1.66470 -0.54230 1.96018
F -2.54962 -1.75780 0.38341
N -3.95368 0.35341 -0.34383
O -2.40098 1.76154 0.55259
C -4.90010 1.39120 -0.73646
C 4.14018 0.53730 0.37288
C 4.97722 1.79365 0.28822
O 3.90040 -0.00989 1.45005
H 0.73609 -1.36544 1.35892
H 3.00627 -1.60539 -1.85111
H 3.15077 -1.83491 -0.11082
H 3.86496 0.55579 -1.64860
H -4.17941 -0.61060 -0.52335
H -5.73184 0.91935 -1.24857
H -5.27004 1.92271 0.13870
H -4.42227 2.10499 -1.40471
H 5.94027 1.60542 0.76038
H 4.48023 2.58287 0.85136
H 5.14028 2.13464 -0.73161

Conformation *b*:
Electronic energy (RB3LYP): −935.675211533 Ha.
Lowest frequency: 19.0723 cm^{-1}.
Sum of electronic and thermal free energies: −935.516221 Ha.
Atomic nuclei coordinates:

N	-0.54836	1.64520	0.44824
C	-1.21838	0.84877	-0.43560
C	-0.45472	-0.26793	-0.66767
N	0.64716	-0.08641	0.10174
N	0.57488	1.08663	0.77534
C	-2.56295	1.22299	-0.98333
N	-3.66603	0.91933	-0.07901
C	1.80947	-0.93835	0.25576
C	3.18276	-0.33748	-0.20136
F	1.57051	-2.06129	-0.43883
F	1.91578	-1.27883	1.57121
N	3.41285	0.91741	0.18106
O	3.95329	-1.05658	-0.81714
C	4.67518	1.58746	-0.11012
C	-4.26712	-0.29319	-0.04083
C	-5.37894	-0.45473	0.97094
O	-3.93397	-1.21187	-0.79064
H	-0.60291	-1.13263	-1.28488
H	-2.73531	0.69629	-1.91787
H	-2.58139	2.29138	-1.18631
H	-3.94450	1.62195	0.58409
H	2.67562	1.42662	0.64877
H	4.65502	2.56854	0.35285
H	5.50924	1.01634	0.29291
H	4.81387	1.69960	-1.18445
H	-5.11429	-1.25993	1.65525
H	-6.28800	-0.74900	0.44834
H	-5.57386	0.44904	1.54391

Conformation *c*:
Electronic energy (RB3LYP): −935.675159710 Ha.
Lowest frequency: 2.3227 cm^{-1}.
Sum of electronic and thermal free energies: −935.518733 Ha.
Atomic nuclei coordinates:

N	-0.62301	-0.51821	1.82215
C	-1.33787	-0.94162	0.73847
C	-0.46597	-1.11410	-0.30717
N	0.74443	-0.78152	0.20654
N	0.63054	-0.42087	1.50742
C	-2.82313	-1.13917	0.79048
N	-3.58076	0.09940	0.65469
C	2.04539	-0.80003	-0.43085
C	2.83464	0.55350	-0.47239
F	1.86014	-1.23400	-1.68748
F	2.82377	-1.71793	0.21120
N	2.79009	1.28381	0.64004
O	3.46795	0.81660	-1.48250
C	3.53778	2.52947	0.76700

C -3.91341 0.62313 -0.54874
C -4.68196 1.92477 -0.52139
O -3.61488 0.06881 -1.60743
H -0.60508 -1.43263 -1.32191
H -3.09080 -1.59261 1.74205
H -3.12797 -1.81365 -0.00490
H -3.81033 0.61056 1.48956
H 2.19843 0.97662 1.40003
H 3.18802 3.26427 0.04343
H 3.38922 2.91572 1.76989
H 4.59914 2.35392 0.60218
H -5.63215 1.78096 -1.03407
H -4.11770 2.67534 -1.07342
H -4.87242 2.29161 0.48463

M06-2X/6-311++G(2d,2p) level / gas phase

Conformation *a*:
Electronic energy (RM062X): −935.305088554 Ha.
Lowest frequency: 15.9166 cm^{-1}.
Sum of electronic and thermal free energies: −935.141214 Ha.
Atomic nuclei coordinates:
N -0.47031 -1.75976 1.01037
C -1.37622 -1.24464 0.13011
C -0.70619 -0.45699 -0.76850
N 0.58185 -0.55019 -0.36660
N 0.70825 -1.33975 0.70948
C -2.84033 -1.52059 0.25983
N -3.58543 -0.39567 0.80451
C 1.76225 0.04232 -0.92559
C 2.61478 0.71198 0.17607
F 1.38261 0.95303 -1.82274
F 2.46743 -0.90780 -1.58219
N 3.75328 0.07600 0.48090
O 2.21522 1.73664 0.67279
C 4.57409 0.55488 1.57843
C -3.78921 0.70861 0.03622
C -4.42570 1.89274 0.72130
O -3.47059 0.73187 -1.13837
H -1.03438 0.14327 -1.59609
H -2.97372 -2.37489 0.91897
H -3.26669 -1.75703 -0.71260
H -3.69280 -0.32340 1.80114
H 3.92950 -0.82482 0.07139
H 4.07302 0.40039 2.53359
H 5.51848 0.01978 1.56984
H 4.75788 1.61892 1.45191
H -5.17877 2.30974 0.05801
H -3.65839 2.65039 0.87692
H -4.87585 1.63823 1.67820

Conformation *b*:
Electronic energy (RM062X): −935.304823329 Ha.
Lowest frequency: 15.5454 cm^{-1}.

Sum of electronic and thermal free energies: −935.140533 Ha.
Atomic nuclei coordinates:

N	-0.45473	1.84342	0.46886
C	-1.29364	1.06953	-0.27776
C	-0.65739	-0.11026	-0.55997
N	0.54357	0.02971	0.04531
N	0.65376	1.21691	0.65811
C	-2.66767	1.53122	-0.64383
N	-3.71145	0.91675	0.16242
C	1.65175	-0.87986	0.10999
C	2.95323	-0.19928	-0.37167
F	1.37319	-1.92550	-0.66878
F	1.77402	-1.33098	1.37911
N	3.84077	0.07631	0.59381
O	3.08229	0.02705	-1.54975
C	5.04929	0.81664	0.27978
C	-4.02567	-0.39216	-0.02673
C	-5.03582	-0.98592	0.92476
O	-3.52022	-1.04335	-0.92243
H	-0.95561	-0.98508	-1.10616
H	-2.87494	1.29988	-1.68649
H	-2.71752	2.60872	-0.50768
H	-4.02016	1.38156	0.99769
H	3.56924	-0.06597	1.55123
H	5.77084	0.67408	1.07847
H	5.45913	0.43757	-0.65250
H	4.83867	1.87930	0.16066
H	-4.55022	-1.78407	1.48351
H	-5.83805	-1.43027	0.34004
H	-5.45062	-0.25826	1.61865

M06-2X/6-311++G(2d,2p) level / water solvation model

Conformation *a*:
Electronic energy (RM062X): −935.325330380 Ha.
Lowest frequency: 17.7861 cm^{-1}.
Sum of electronic and thermal free energies: −935.161221 Ha.
Atomic nuclei coordinates:

N	-0.49279	-1.91295	0.48424
C	-1.37939	-1.17871	-0.24893
C	-0.69536	-0.14817	-0.83571
N	0.57638	-0.32452	-0.40992
N	0.68419	-1.39820	0.38289
C	-2.83671	-1.51428	-0.29774
N	-3.64120	-0.66383	0.56363
C	1.75627	0.40894	-0.76532
C	2.73061	0.50744	0.42936
F	1.37864	1.63881	-1.13595
F	2.33795	-0.16845	-1.83821
N	3.89231	-0.11516	0.27363
O	2.37792	1.14443	1.40277
C	4.89055	-0.08717	1.33080
C	-3.91455	0.61079	0.21558
C	-4.72939	1.41907	1.19121

O -3.51979 1.08072 -0.84685
H -1.00160 0.66041 -1.47180
H -2.96911 -2.54437 0.02198
H -3.20531 -1.41714 -1.31661
H -3.92272 -1.00608 1.46605
H 4.08220 -0.60283 -0.58602
H 4.47153 -0.49612 2.24784
H 5.73938 -0.68543 1.01974
H 5.21294 0.93560 1.51605
H -5.62605 1.76948 0.68365
H -4.14808 2.29086 1.48585
H -5.01194 0.85620 2.07676

Conformation *b*:
Electronic energy (RM062X): −935.325209513 Ha.
Lowest frequency: 17.1252 cm^{-1}.
Sum of electronic and thermal free energies: −935.161655 Ha.
Atomic nuclei coordinates:
N -0.43954 1.91001 0.39658
C -1.33019 1.10368 -0.24981
C -0.69571 -0.07083 -0.55760
N 0.55484 0.10631 -0.07398
N 0.69505 1.30629 0.50088
C -2.73890 1.53326 -0.51716
N -3.71355 0.83445 0.30320
C 1.64926 -0.82054 -0.03560
C 2.99256 -0.10705 -0.30531
F 1.43608 -1.74386 -0.98052
F 1.65308 -1.45802 1.15405
N 3.85938 -0.11904 0.69935
O 3.16233 0.39330 -1.40017
C 5.15813 0.52122 0.56104
C -4.05220 -0.44382 0.03729
C -5.06715 -1.07870 0.95140
O -3.55968 -1.05083 -0.90873
H -1.02133 -0.96532 -1.05383
H -2.98558 1.36116 -1.56310
H -2.82156 2.59728 -0.31337
H -4.08761 1.29028 1.11738
H 3.60938 -0.56961 1.56383
H 5.69663 0.41158 1.49546
H 5.72216 0.05333 -0.24318
H 5.02985 1.57781 0.33484
H -4.64146 -1.99349 1.35875
H -5.94033 -1.34944 0.36026
H -5.37193 -0.42586 1.76478

7.2. Potential energy surface scan around the N−CF_2

A potential energy surface scan around the N−CF_2 bond was conducted at the B3LYP/6-31G* level, revealing indeed the existence of a single minimum associated with a significant population

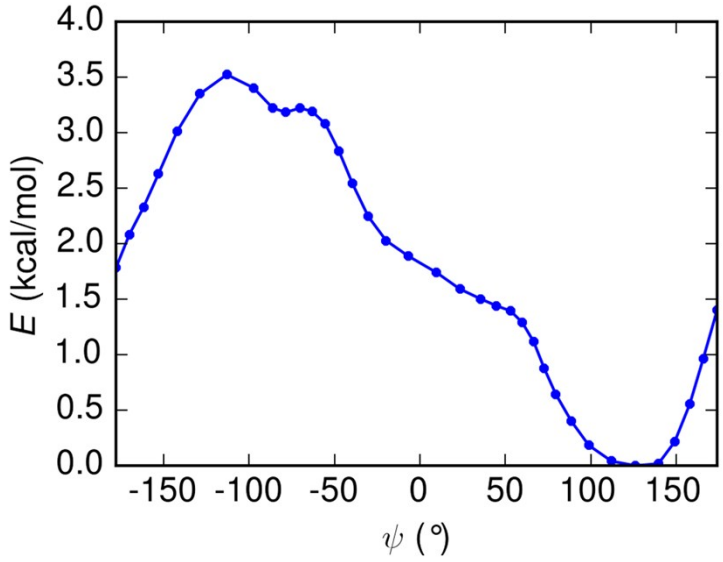


Fig.3 Energy profile of a relaxed PES scan at the B3LYP/6-31G* level starting from conformation *a*.

7.3.Dihedral angles

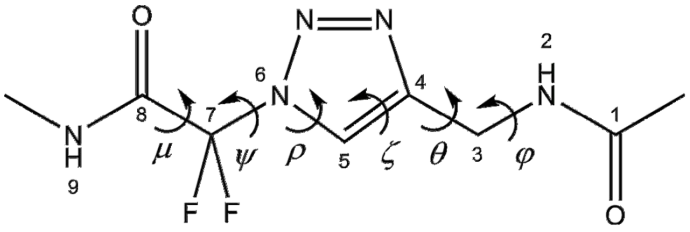


Figure S1. Location of the backbone dihedral angles in compound **1**.

Name	Definition	Value (°)									
		B3LYP						M06-2X			
		Gas			Water			Gas		Water	
		a	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*a*	*b*
φ	(C1,N2,C3,C4)	79.0	−78.4	77.6	86.8	−86.2	86.0	72.2	−72.1	75.0	−75.2
θ	(N2,C3,C4,C5)	−75.6	79.3	−77.5	−100.9	98.2	−99.0	−73.6	76.1	−77.0	71.3
ζ	(C3,C4,C5,N6)	178.1	−179.2	178.9	178.8	−179.1	179.4	177.6	−178.8	178.0	−179.9
ρ	(C4,C5,N6,C7)	177.0	177.8	176.8	174.9	−179.4	178.6	179.1	179.8	175.9	176.0
ψ	(C5,N6,C7,C8)	137.6	126.1	128.4	147.1	117.1	121.9	131.9	126.4	146.1	142.6
μ	(N6,C7,C8,N9)	113.0	51.4	51.0	117.3	44.5	41.5	108.2	108.1	114.9	116.0

Table S1. Values of the backbone dihedral angles in the various conformations of compound **1** found at the B3LYP/6-311++G(2d,2p) and M06-2X/6-311++G(2d,2p) level.

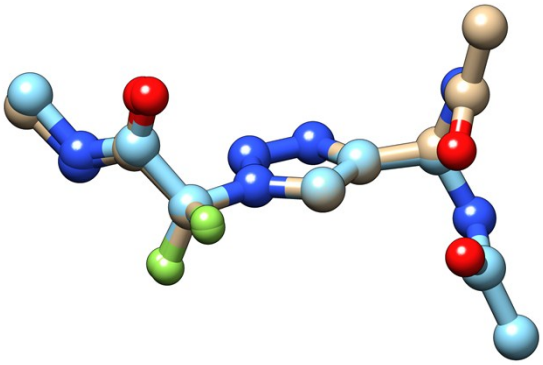


Figure S2. Superimposition of conformations *a* (brown color) and *b* (blue color) found at the M06-2X/6-311++G(2d,2p) level in gas phase. (Hydrogen atoms were removed in order to increase legibility.)

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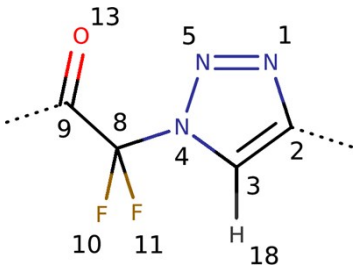
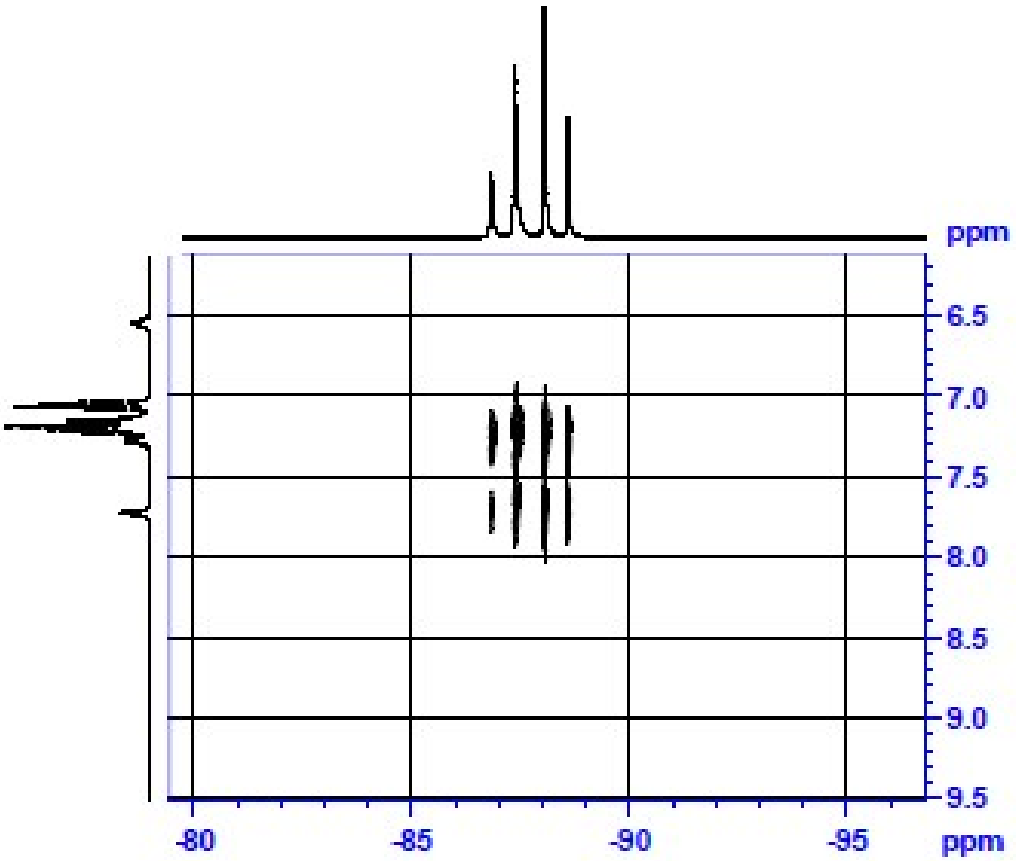
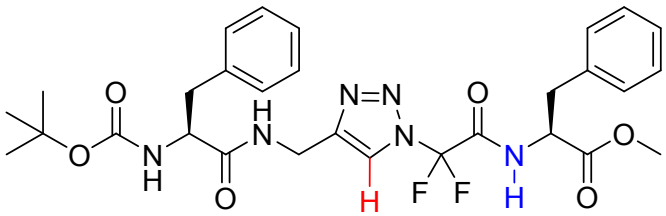
7.4. "Mulliken charges for the triazole moiety calculated at the B3LYP/6-311++G(2d,2p) level in gas phase"

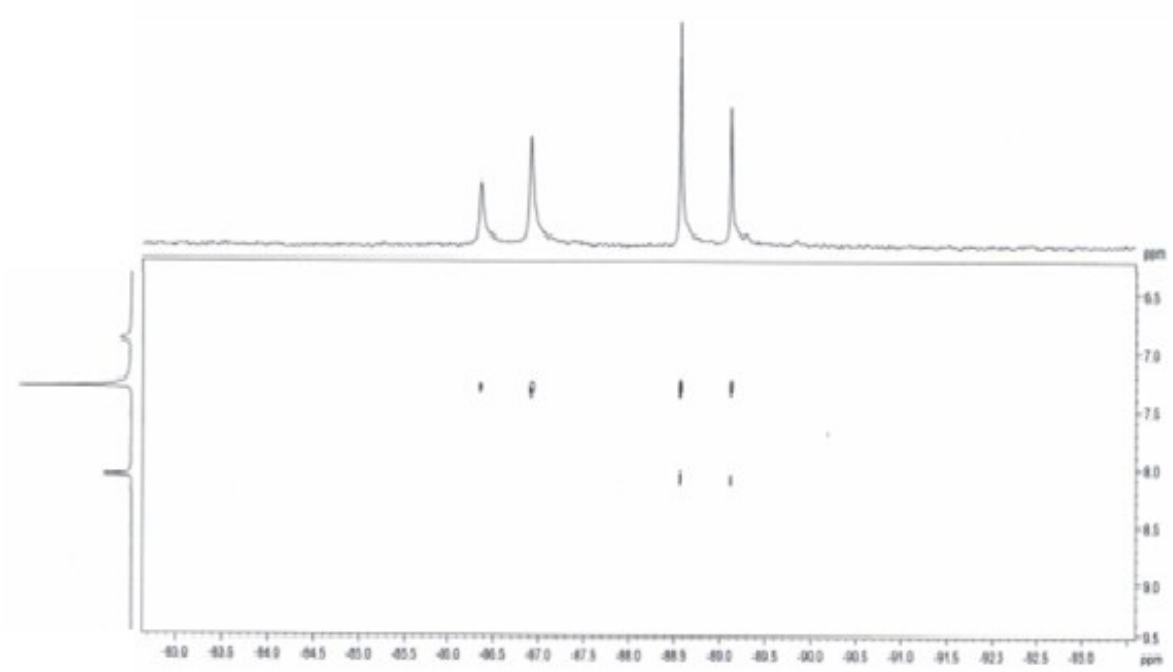


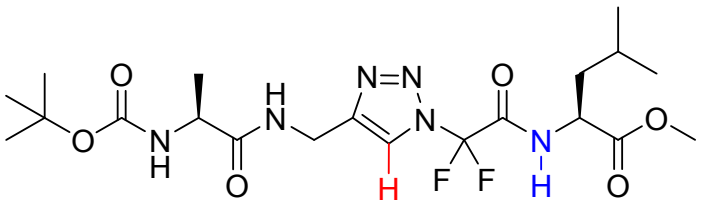
Atom type	Atom number	Conformation a	Conformation b	Conformation c	Standard deviation
N	1	-0,19	-0,19	-0,19	0,002
C	2	0,36	0,34	0,29	0,031
C	3	-0,32	-0,21	-0,21	0,002
N	4	0,39	0,30	0,31	0,010
N	5	-0,35	-0,35	-0,36	0,009
C	8	0,52	0,46	0,47	0,008
C	9	0,32	0,37	0,37	0,000
F	10	-0,26	-0,27	-0,27	0,002
F	11	-0,31	-0,27	-0,28	0,002
O	13	-0,47	-0,46	-0,46	0,001
H	18	0,20	0,22	0,22	0,001

8. NOESY of compounds 5c and 5a








O
O
N
H
H
N
O
N=N
N
H
F
F
O
N
H
O
O

9. X ray compound 5c

Crystal Data for $C_{29}H_{34}F_2N_6O_6$ (*M* =600.62 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 5.1466(2) Å, *b* = 22.4076(9) Å, *c* = 25.6853(18) Å, *V* = 2962.1(3) Å^3, *Z* = 4, *T* = 293 K, μ(CuKα) = 0.876 mm^{-1}, *Dcalc* = 1.347 g/cm^3, 25575 reflections measured (10.478° ≤ 2Θ ≤ 136.468°), 5393 unique (R_{int} = 0.0513, R_{sigma} = 0.0744) which were used in all calculations. The final R_1 was 0.0485 (I > 2σ(I)) and wR_2 was 0.1397 (all data).

Supporting info part :

Single crystals suitable for X-ray diffraction were obtained by recrystallization from cyclohexane/DCM. X-ray crystallographic data were collected at room temperature on a Rigaku Rapid II (IP area detector system) diffractometer equipped with a rotating anode mm007 HF generator and Osmic mirrors (Cu Kα radiation, λ = 1.54187 Å) using ω-scans.

Data were indexed, integrated and scaled using *FS_Process* from the *CrystalClear*[1] software suite. They were also corrected for polarization, Lorentz and absorption effects (*FS_Abscor*).

The structure was solved by direct methods with SHELXT[2], and refined with SHELXL-2014/7[3]. The model (Figure 1) was refined using full-matrix least-squares, all non-hydrogen atoms were refined with anisotropic displacement parameters. H atoms have been added geometrically and treated as riding on their parent atoms

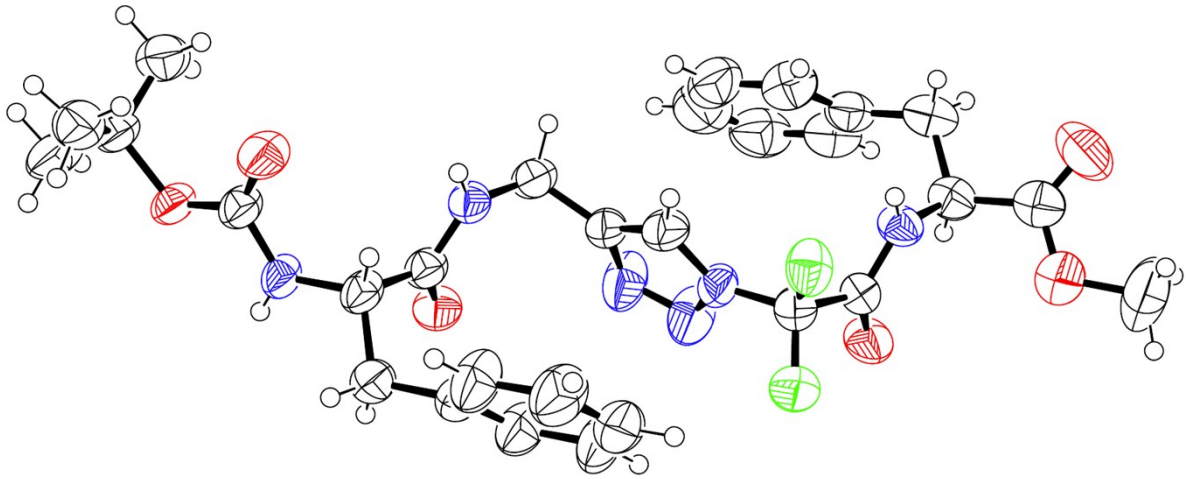


Figure 1 : Ortep view of compound 5c (*Color* scheme: C, gray; O, red; N, blue; F, green)

The absolute configuration was analysed by using Hooft methods[4,5], and the results indicated that absolute structure had been correctly assigned (Flack parameter is 0.04(10), 2346 Bijvoet pairs, Bijvoet coverage = 0.95. P2(true) = P3(true) = 1.00. P3(rac-twin) = 4.10^{-4} P3(false) = 2.10^{-15}. Correlation coefficient = 0.997).

Molecular graphics were computed with Ortep-3[6]. CCDC 1491960 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(1) Rigaku, CrystalClear-SM Expert 2.0 r4, **2009**.
(2) Sheldrick, G. M. *Acta Crystallogr. Sect. Found. Adv.* **2015**, *71* (1), 3.
(3) Sheldrick, G. M. *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71* (1), 3.
(4) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Crystallogr.* **2008**, *41* (1), 96.
(5) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Crystallogr.* **2010**, *43* (4), 665.
(6) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30* (5), 565.

Table 1 Crystal data and structure refinement for 5c	
CCDC number	1491960
Empirical formula	$C_{29}H_{34}F_2N_6O_6$
Formula weight	600.62
Temperature/K	293
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.1466(2)
b/Å	22.4076(9)
c/Å	25.6853(18)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2962.1(3)
Z	4
ρ_{calc}g/cm^3	1.347
μ/mm^{-1}	0.876
F(000)	1264.0
Crystal size/mm^3	0.19 × 0.17 × 0.11
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	10.478 to 136.468
Index ranges	$-6 \le h \le 5$, $-22 \le k \le 26$, $-29 \le l \le 30$
Reflections collected	25575
Independent reflections	5393 [R_{int} = 0.0513, R_{sigma} = 0.0744]
Data/restraints/parameters	5393/0/392
Goodness-of-fit on F^2	0.988
Final R indexes [I>=2σ (I)]	R_1 = 0.0485, wR_2 = 0.0959
Final R indexes [all data]	R_1 = 0.1229, wR_2 = 0.1397
Largest diff. peak/hole / e Å^{-3}	0.18/-0.23
Flack parameter	0.04(10)

Table 2 Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters for 5c				
Atom	***x***	***y***	***z***	**U(eq)**
C1	0.3358(11)	0.1644(2)	0.6033(3)	0.094(2)
C2	-0.0146(11)	0.2232(2)	0.6464(2)	0.0765(18)
C3	0.1539(10)	0.2163(2)	0.5978(2)	0.0547(14)
C4	-0.0066(11)	0.2117(2)	0.5486(2)	0.0767(17)
C5	0.2418(10)	0.3237(3)	0.5893(2)	0.0572(16)
C6	0.3910(10)	0.4260(2)	0.5765(2)	0.0550(15)
C7	0.5652(10)	0.4664(2)	0.6088(2)	0.0622(15)
C8	0.5124(11)	0.5318(3)	0.5990(2)	0.0603(15)
C9	0.3034(13)	0.5594(3)	0.6225(3)	0.084(2)
C10	0.2497(14)	0.6192(3)	0.6125(3)	0.095(2)
C11	0.4007(14)	0.6514(3)	0.5797(3)	0.086(2)
C12	0.6087(14)	0.6249(3)	0.5558(3)	0.088(2)
C13	0.6624(12)	0.5651(3)	0.5651(3)	0.0767(19)
C14	0.4308(10)	0.4388(2)	0.5191(2)	0.0540(14)
C15	0.2267(10)	0.4678(2)	0.4370(2)	0.0598(15)
C16	0.3162(10)	0.5300(3)	0.4291(2)	0.0537(14)
C17	0.1889(10)	0.5829(2)	0.4362(2)	0.0616(16)
C18	0.3217(11)	0.6893(3)	0.4188(2)	0.0613(15)
C19	0.3684(11)	0.7123(2)	0.3634(2)	0.0548(14)
C20	0.1659(11)	0.7313(3)	0.2794(2)	0.0600(15)
C21	0.0850(14)	0.7952(3)	0.2675(2)	0.0698(18)
C22	0.2132(18)	0.8957(3)	0.2751(3)	0.135(3)
C23	0.0042(12)	0.6862(3)	0.2483(2)	0.0739(17)
C24	0.0958(13)	0.6239(3)	0.2561(3)	0.0693(17)
C25	0.3052(14)	0.6011(4)	0.2289(3)	0.086(2)
C26	0.3936(15)	0.5443(4)	0.2382(3)	0.105(3)

C27	0.270(2)	0.5086(4)	0.2735(4)	0.112(3)
C28	0.0591(17)	0.5293(4)	0.3006(3)	0.097(2)
C29	-0.0250(14)	0.5870(4)	0.2914(3)	0.086(2)
F1	0.0796(6)	0.70111(12)	0.43628(12)	0.0705(9)
F2	0.4904(7)	0.71661(13)	0.45134(12)	0.0824(10)
N1	0.4396(8)	0.36301(17)	0.58697(16)	0.0565(12)
N2	0.2157(8)	0.45027(17)	0.49129(18)	0.0554(12)
N3	0.5584(9)	0.5432(2)	0.4110(2)	0.0857(17)
N4	0.5851(9)	0.6010(2)	0.4067(2)	0.0873(18)
N5	0.3585(8)	0.6259(2)	0.42261(17)	0.0575(12)
N6	0.1536(8)	0.71899(17)	0.33474(17)	0.0557(12)
O1	0.3340(6)	0.26807(15)	0.59473(14)	0.0580(10)
O2	0.0140(6)	0.33820(15)	0.58720(16)	0.0755(12)
O3	0.6485(6)	0.44003(15)	0.49955(14)	0.0647(10)
O4	0.5893(7)	0.72032(17)	0.34849(14)	0.0730(12)
O5	-0.0972(11)	0.8101(2)	0.2432(2)	0.1224(19)
O6	0.2507(9)	0.8330(2)	0.28768(18)	0.1016(16)

Table 3 Anisotropic Displacement Parameters for 5c

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
C1	0.052(3)	0.051(4)	0.180(7)	0.006(4)	-0.006(4)	-0.002(3)
C2	0.070(4)	0.088(5)	0.072(4)	0.010(3)	-0.002(3)	-0.012(4)
C3	0.041(3)	0.042(3)	0.081(4)	0.003(3)	0.002(3)	-0.009(3)
C4	0.075(4)	0.082(4)	0.073(4)	-0.005(3)	-0.002(4)	-0.015(4)
C5	0.046(3)	0.047(4)	0.078(5)	0.006(3)	0.003(3)	-0.004(3)
C6	0.043(3)	0.045(4)	0.077(4)	0.005(3)	0.005(3)	-0.001(3)
C7	0.058(3)	0.053(4)	0.075(4)	0.001(3)	-0.006(3)	-0.001(3)
C8	0.061(3)	0.046(4)	0.073(4)	-0.003(3)	-0.005(3)	0.000(3)
C9	0.082(5)	0.054(4)	0.117(6)	0.008(4)	0.019(4)	0.004(4)
C10	0.084(5)	0.064(5)	0.137(7)	-0.004(5)	0.006(5)	0.007(4)
C11	0.095(5)	0.052(4)	0.113(6)	-0.005(4)	-0.025(5)	0.003(4)
C12	0.114(6)	0.048(5)	0.101(5)	0.007(4)	-0.003(5)	-0.004(4)
C13	0.080(4)	0.057(4)	0.094(5)	-0.001(4)	0.006(4)	-0.003(4)
C14	0.044(3)	0.050(4)	0.067(4)	0.001(3)	0.000(3)	-0.003(3)
C15	0.054(3)	0.052(4)	0.073(4)	-0.005(3)	-0.001(3)	-0.009(3)
C16	0.044(3)	0.053(4)	0.064(4)	0.006(3)	-0.002(3)	-0.003(3)
C17	0.044(3)	0.065(4)	0.077(4)	0.004(3)	0.003(3)	-0.008(3)
C18	0.057(4)	0.057(4)	0.071(4)	0.008(4)	-0.006(3)	-0.001(3)
C19	0.055(4)	0.054(4)	0.056(4)	0.004(3)	-0.007(3)	0.000(3)
C20	0.052(3)	0.074(5)	0.054(4)	0.000(3)	0.003(3)	0.001(3)
C21	0.065(4)	0.083(6)	0.062(4)	-0.002(4)	0.002(3)	-0.003(4)
C22	0.182(9)	0.062(5)	0.161(8)	0.021(5)	0.001(7)	-0.004(5)
C23	0.060(4)	0.094(5)	0.068(4)	-0.011(4)	-0.008(3)	-0.001(4)
C24	0.062(4)	0.075(5)	0.072(4)	-0.010(4)	-0.012(4)	-0.002(4)
C25	0.073(5)	0.100(6)	0.086(5)	-0.016(5)	-0.002(4)	-0.002(4)
C26	0.081(6)	0.108(8)	0.125(7)	-0.031(6)	-0.008(5)	0.009(5)
C27	0.119(8)	0.095(7)	0.123(8)	-0.032(6)	-0.032(6)	0.013(6)
C28	0.123(7)	0.087(6)	0.082(5)	0.001(5)	-0.014(5)	-0.031(5)
C29	0.085(5)	0.089(6)	0.084(5)	-0.008(5)	0.001(4)	-0.012(5)
F1	0.068(2)	0.064(2)	0.080(2)	0.0069(17)	0.0159(18)	0.0145(17)
F2	0.095(2)	0.075(2)	0.077(2)	0.0031(18)	-0.027(2)	-0.015(2)
N1	0.040(2)	0.039(3)	0.090(3)	0.011(2)	0.000(2)	0.003(2)
N2	0.043(2)	0.054(3)	0.069(3)	0.008(3)	0.002(2)	-0.003(2)
N3	0.068(3)	0.064(4)	0.125(5)	0.022(3)	0.027(3)	0.009(3)
N4	0.051(3)	0.067(4)	0.144(5)	0.021(4)	0.027(3)	0.012(3)
N5	0.048(3)	0.051(3)	0.073(3)	0.012(3)	0.001(3)	-0.004(2)
N6	0.042(2)	0.070(3)	0.055(3)	0.006(2)	0.001(2)	-0.002(2)

O1	0.0402(19)	0.042(2)	0.091(3)	0.005(2)	0.000(2)	-0.0038(17)
O2	0.039(2)	0.060(3)	0.128(4)	0.008(2)	-0.001(2)	0.0051(19)
O3	0.0394(19)	0.075(3)	0.080(3)	0.005(2)	0.009(2)	-0.0010(19)
O4	0.041(2)	0.094(3)	0.084(3)	0.020(2)	0.002(2)	-0.003(2)
O5	0.121(4)	0.115(4)	0.131(4)	0.003(3)	-0.059(4)	0.029(4)
O6	0.101(4)	0.073(4)	0.131(4)	0.009(3)	-0.024(3)	-0.003(3)

Table 4 Bond Lengths for 5c

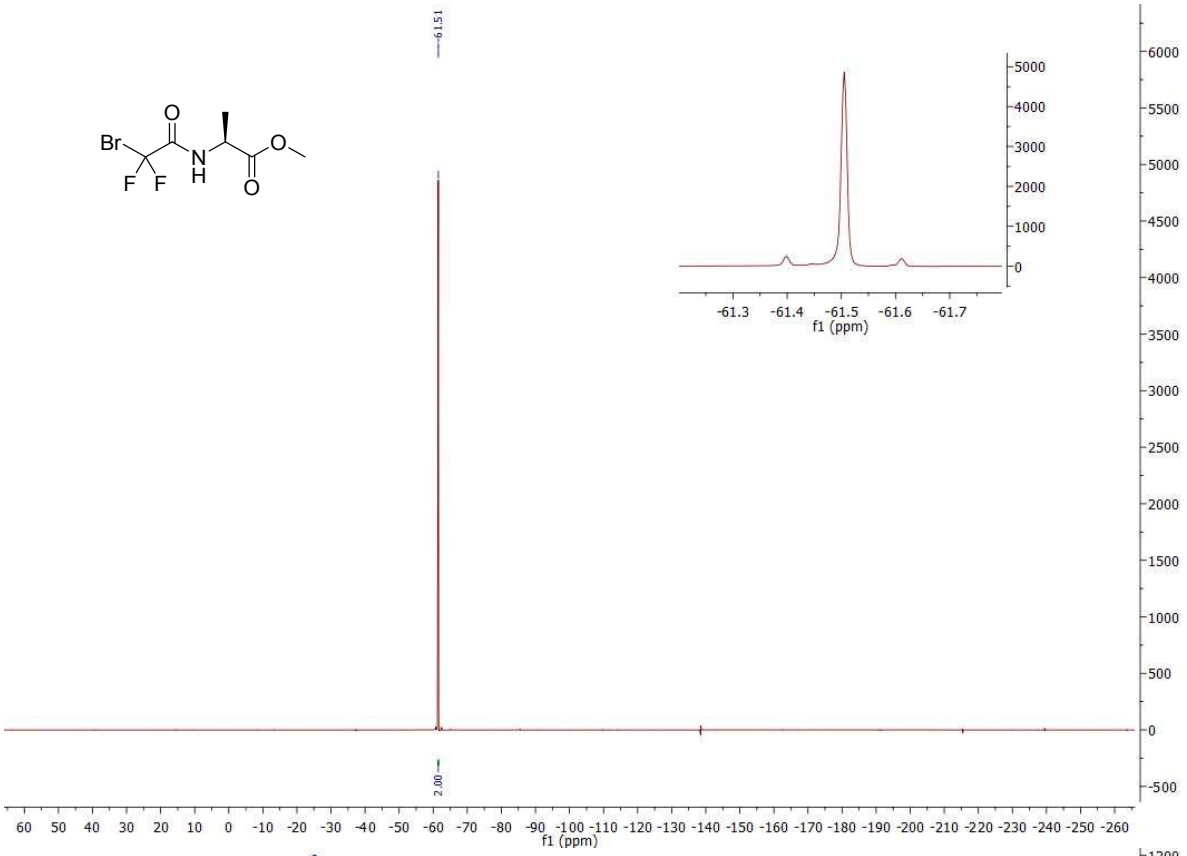
Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C3	1.500(6)	C17	N5	1.347(6)
C2	C3	1.527(7)	C18	C19	1.532(7)
C3	C4	1.515(7)	C18	F1	1.351(6)
C3	O1	1.486(5)	C18	F2	1.352(6)
C5	N1	1.347(6)	C18	N5	1.435(6)
C5	O1	1.342(6)	C19	N6	1.337(6)
C5	O2	1.217(5)	C19	O4	1.213(6)
C6	C7	1.521(6)	C20	C21	1.522(8)
C6	C14	1.515(7)	C20	C23	1.533(7)
C6	N1	1.460(5)	C20	N6	1.450(6)
C7	C8	1.512(7)	C21	O5	1.175(7)
C8	C9	1.380(7)	C21	O6	1.309(7)
C8	C13	1.382(7)	C22	O6	1.455(7)
C9	C10	1.392(8)	C23	C24	1.487(7)
C10	C11	1.354(9)	C24	C25	1.382(8)
C11	C12	1.370(8)	C24	C29	1.377(8)
C12	C13	1.388(7)	C25	C26	1.371(9)
C14	N2	1.342(6)	C26	C27	1.367(10)
C14	O3	1.228(5)	C27	C28	1.370(10)
C15	C16	1.483(7)	C28	C29	1.383(9)
C15	N2	1.450(6)	N3	N4	1.309(6)
C16	C17	1.365(6)	N4	N5	1.356(5)
C16	N3	1.363(6)			

Table 5 Bond Angles for 5c

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1	C3	C2	110.8(5)	F2	C18	C19	108.7(5)
C1	C3	C4	111.5(5)	F2	C18	N5	108.8(5)
C4	C3	C2	112.3(4)	N5	C18	C19	112.1(5)
O1	C3	C1	102.7(4)	N6	C19	C18	114.8(5)
O1	C3	C2	108.6(4)	O4	C19	C18	119.4(5)
O1	C3	C4	110.4(4)	O4	C19	N6	125.7(5)
O1	C5	N1	110.1(4)	C21	C20	C23	111.6(5)
O2	C5	N1	123.5(5)	N6	C20	C21	111.3(4)
O2	C5	O1	126.4(5)	N6	C20	C23	111.1(5)
C14	C6	C7	109.8(4)	O5	C21	C20	126.3(7)
N1	C6	C7	111.9(4)	O5	C21	O6	123.1(7)
N1	C6	C14	109.9(4)	O6	C21	C20	110.6(6)
C8	C7	C6	112.2(4)	C24	C23	C20	112.2(5)
C9	C8	C7	120.1(6)	C25	C24	C23	121.8(7)
C9	C8	C13	117.9(6)	C29	C24	C23	120.6(7)
C13	C8	C7	121.9(6)	C29	C24	C25	117.6(7)
C8	C9	C10	120.4(7)	C26	C25	C24	121.0(7)
C11	C10	C9	120.9(7)	C27	C26	C25	120.2(8)
C10	C11	C12	119.8(7)	C26	C27	C28	120.5(9)
C11	C12	C13	119.8(7)	C27	C28	C29	118.6(8)

C8	C13	C12	121.2(6)	C24	C29	C28	122.2(7)
N2	C14	C6	116.3(5)	C5	N1	C6	120.7(4)
O3	C14	C6	121.7(5)	C14	N2	C15	122.1(4)
O3	C14	N2	122.0(5)	N4	N3	C16	109.8(5)
N2	C15	C16	113.4(5)	N3	N4	N5	106.9(5)
C17	C16	C15	130.4(5)	C17	N5	C18	129.8(5)
N3	C16	C15	122.3(5)	C17	N5	N4	110.0(4)
N3	C16	C17	107.3(5)	N4	N5	C18	119.9(5)
N5	C17	C16	106.0(5)	C19	N6	C20	121.7(5)
F1	C18	C19	112.7(5)	C5	O1	C3	120.6(4)
F1	C18	F2	107.3(5)	C21	O6	C22	116.8(6)
F1	C18	N5	107.1(5)				

10. Copies of ^{1}H NMR, ^{19}FNMR, ^{13}C NMR spectra


Br
F F
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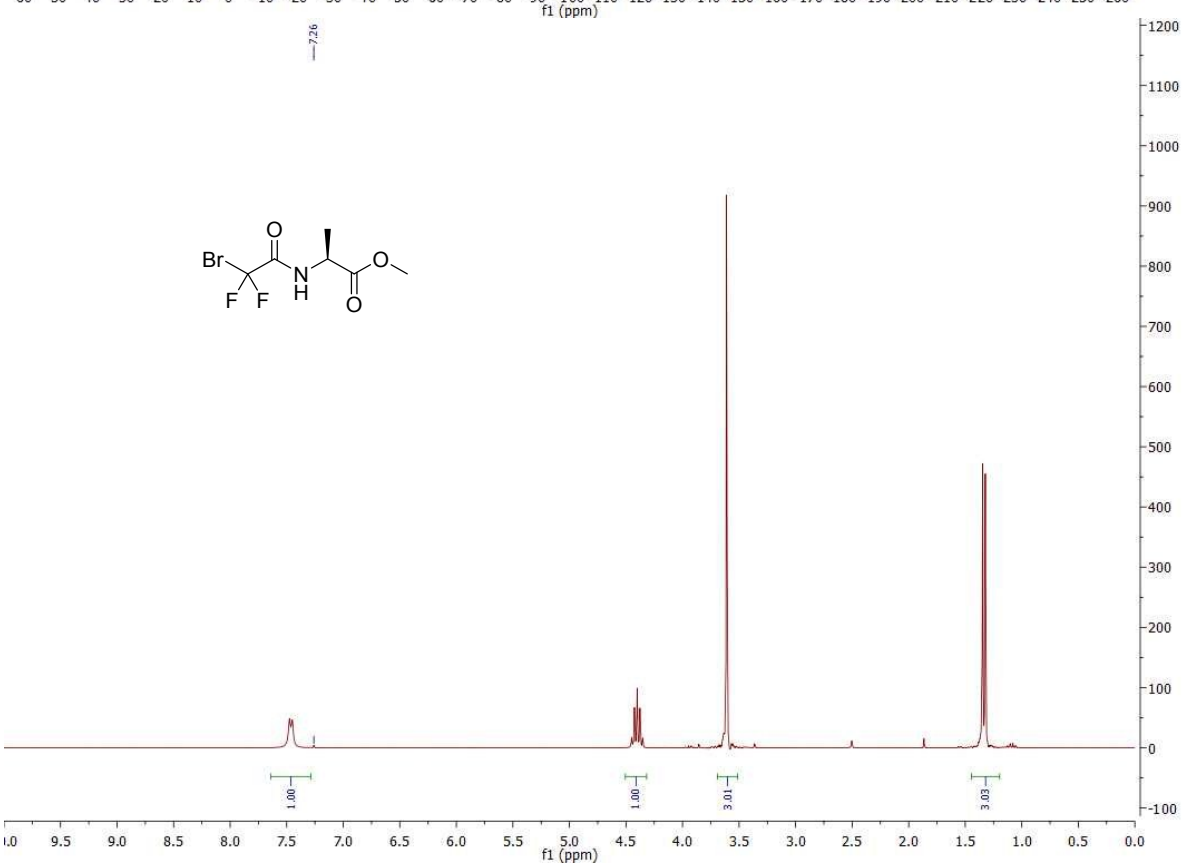
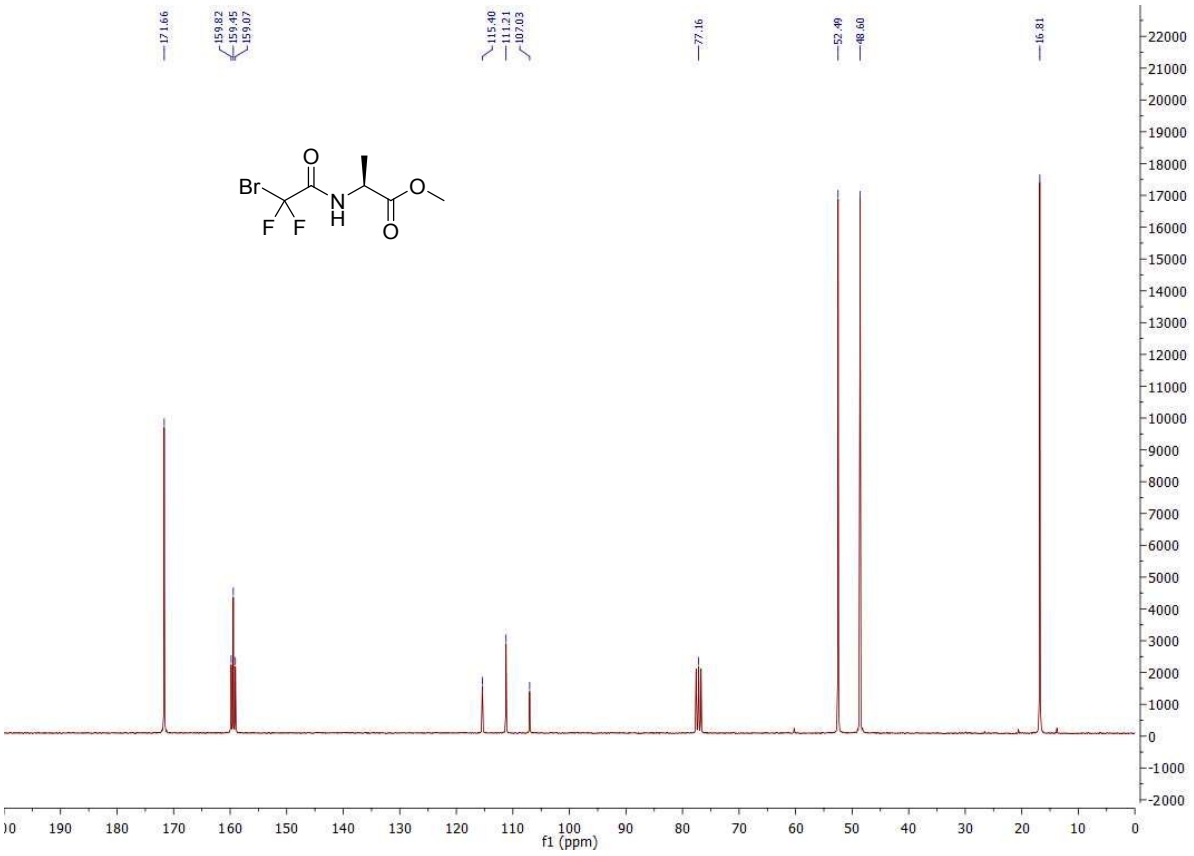
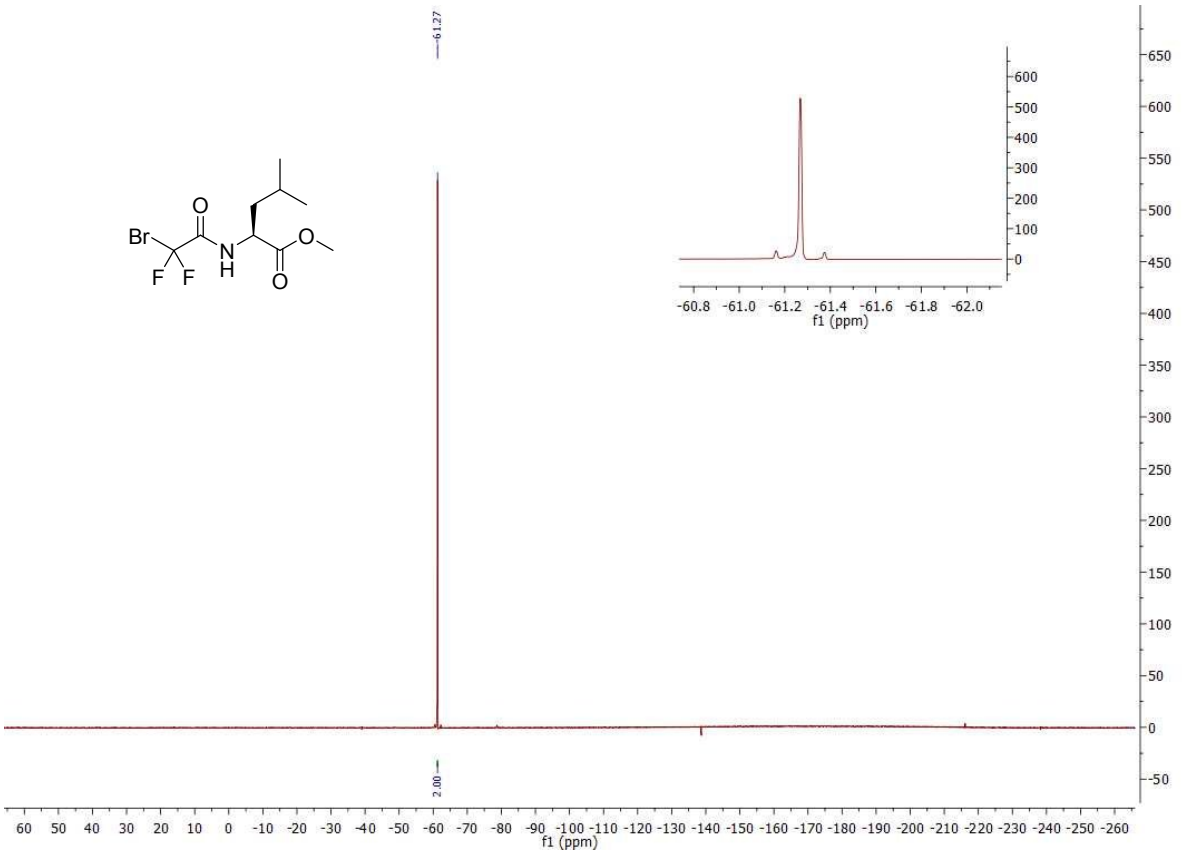
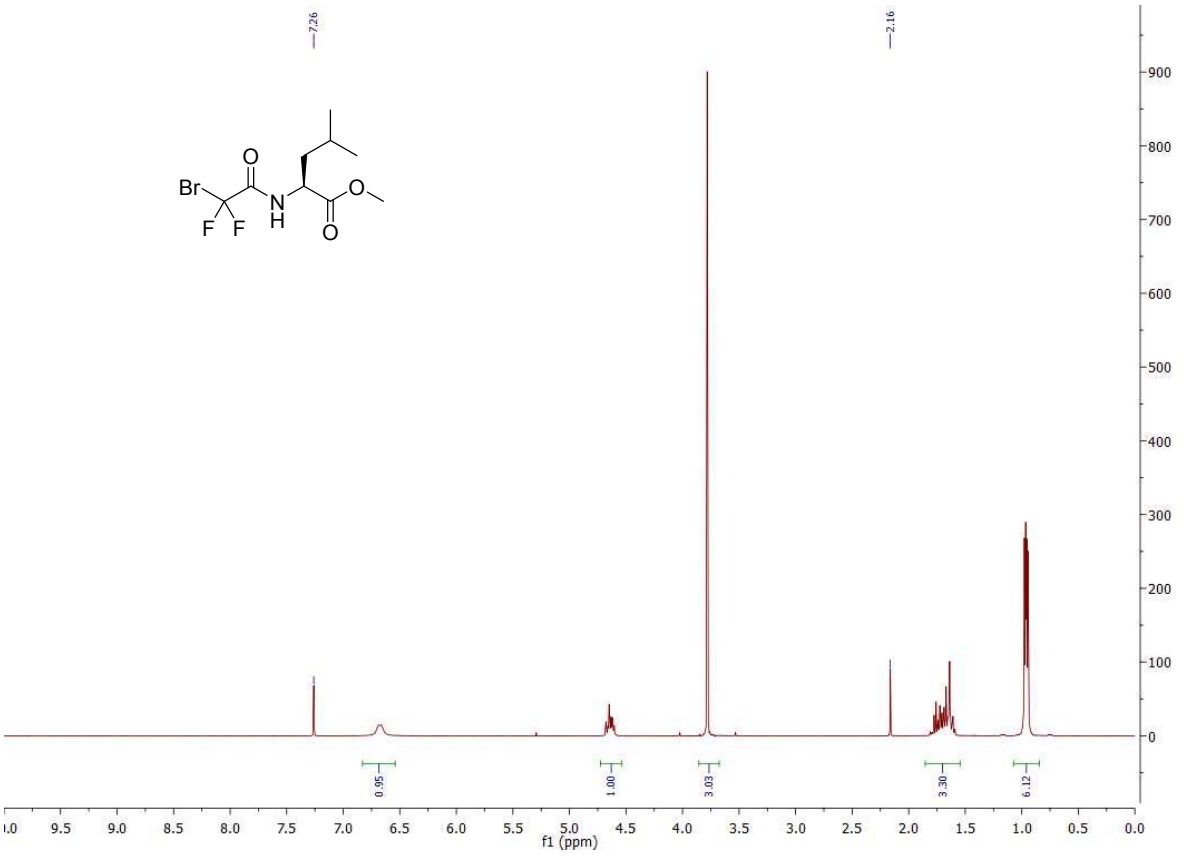
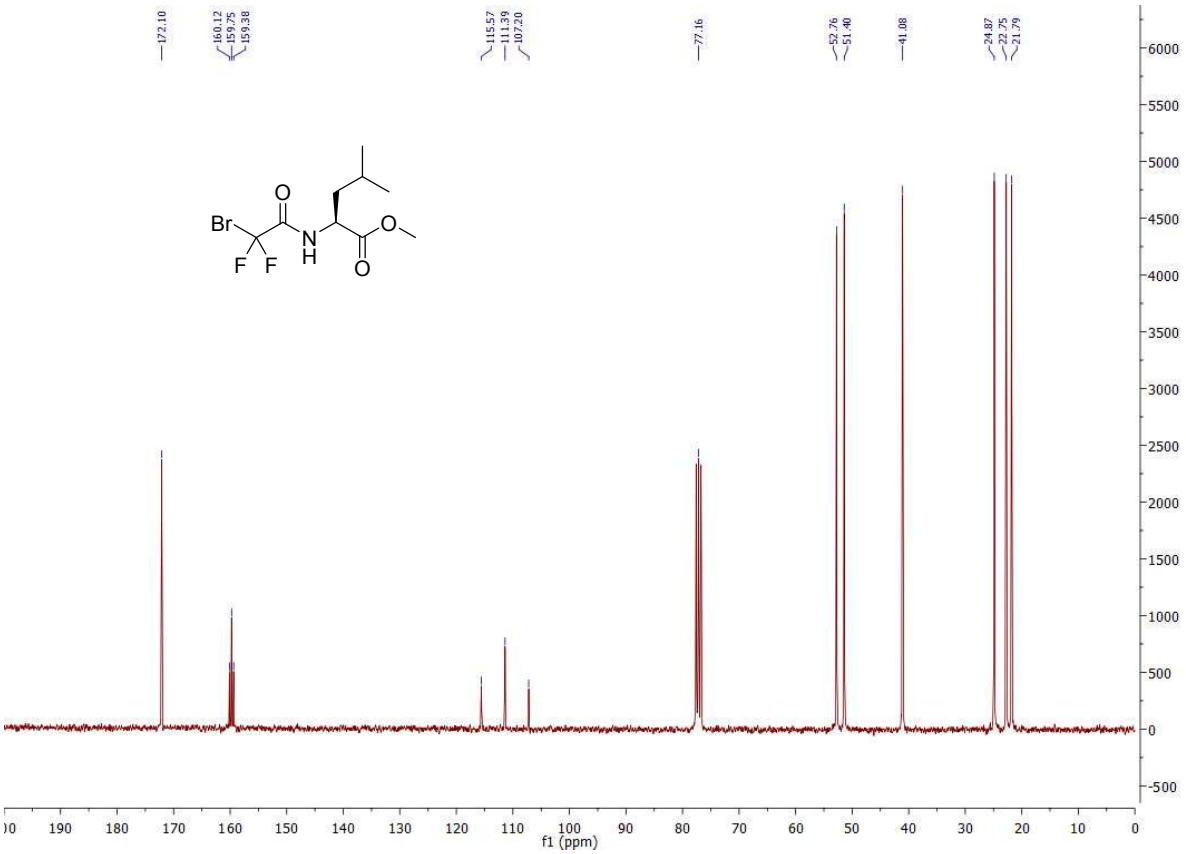
O
O
-61.51
2.00
f1 (ppm)

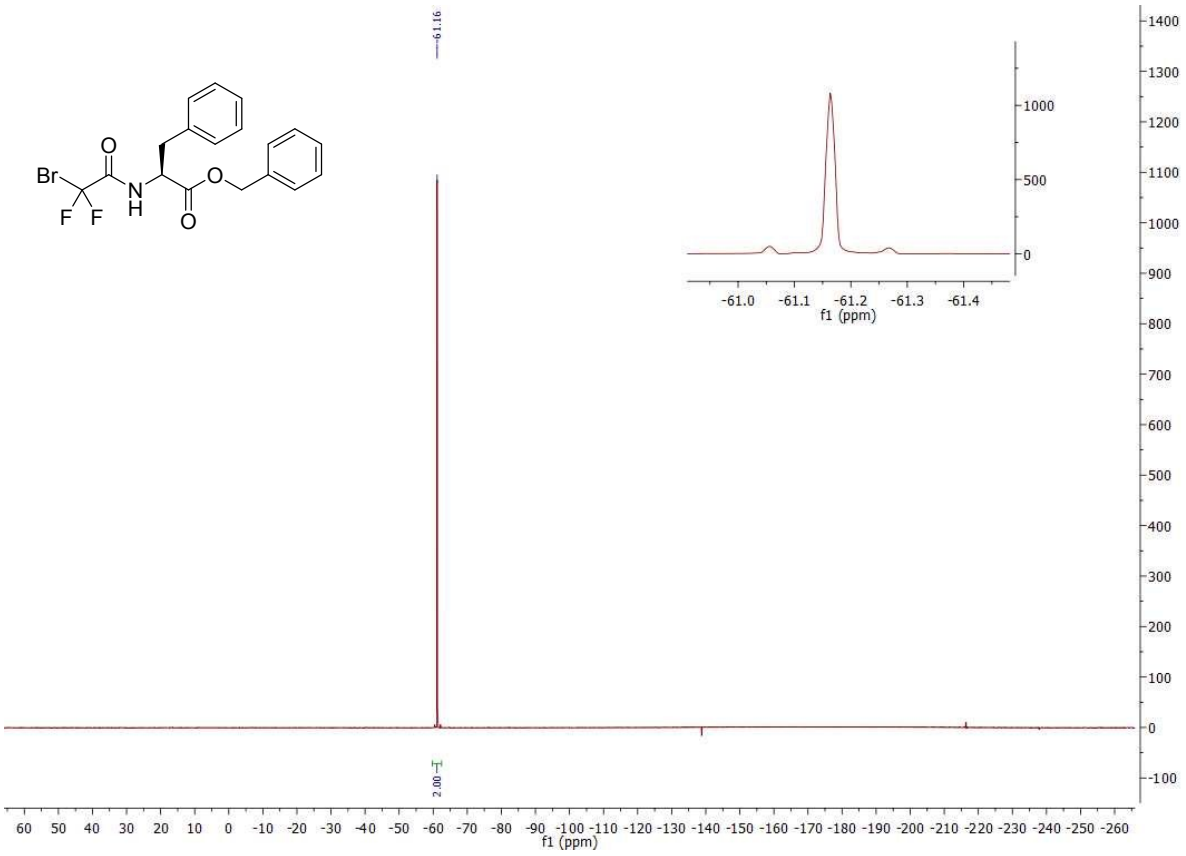

Br
F F
O
N
H
O
O
7.26
1.00
1.00
3.01
3.03
f1 (ppm)

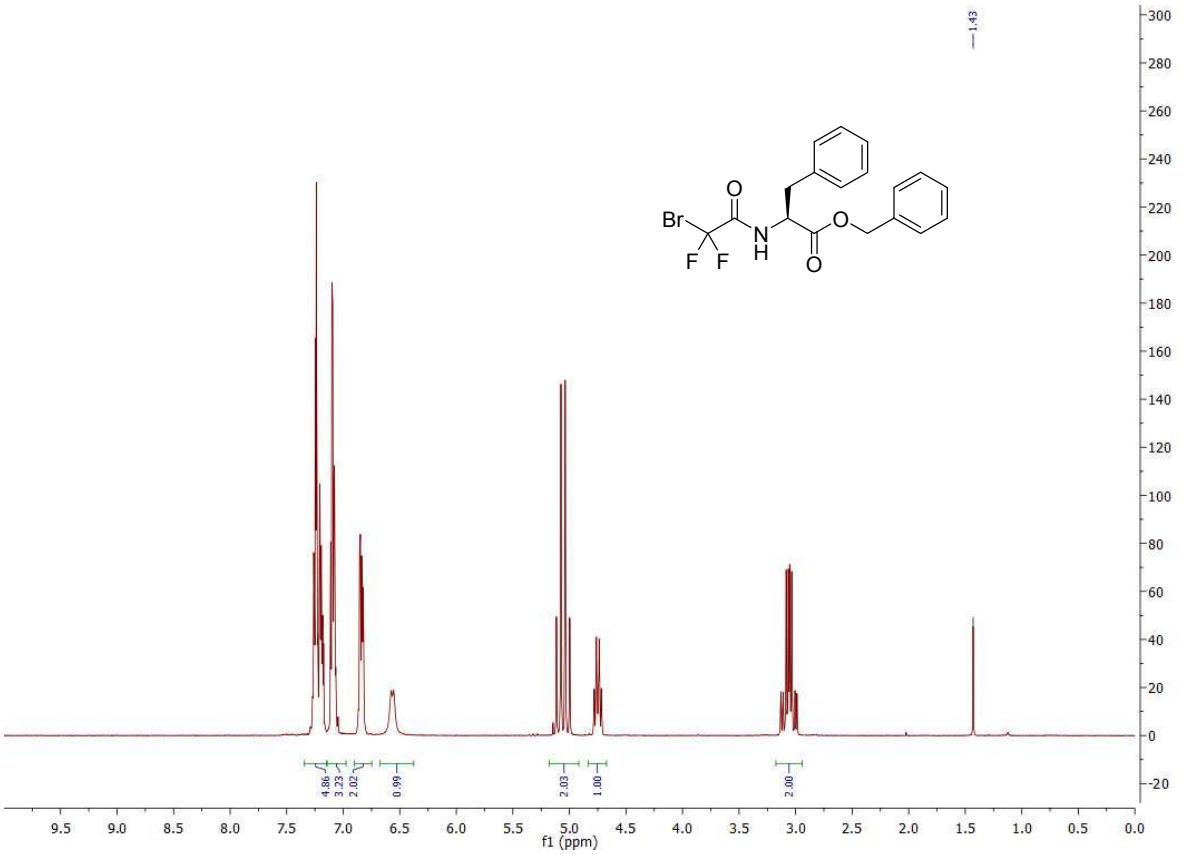

171.66
159.82
159.45
159.07
115.40
111.21
107.03
77.16
52.49
48.60
16.81
Br
F F
O
N
H
O
O
f1 (ppm)

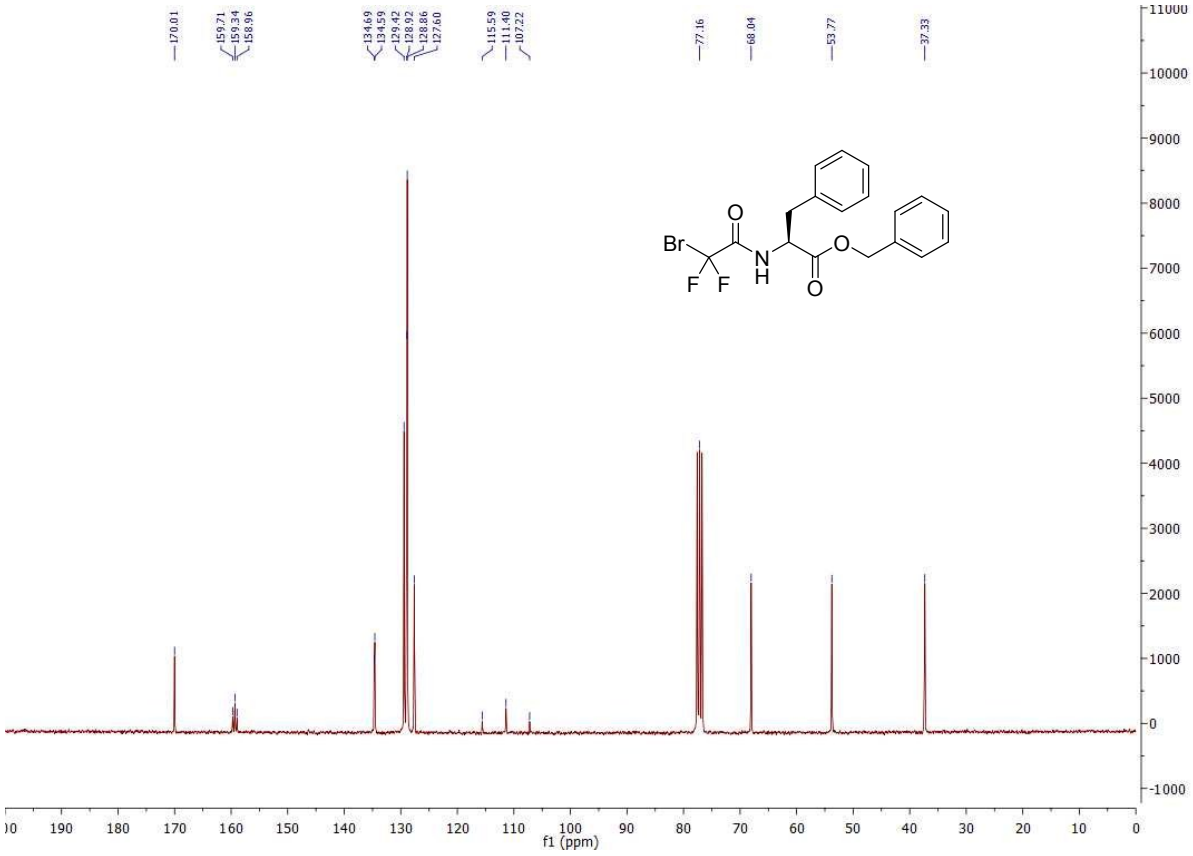

-61.27
Br
F F
O
N
H
O
O
2.00
-60.8 -61.0 -61.2 -61.4 -61.6 -61.8 -62.0
f1 (ppm)
f1 (ppm)

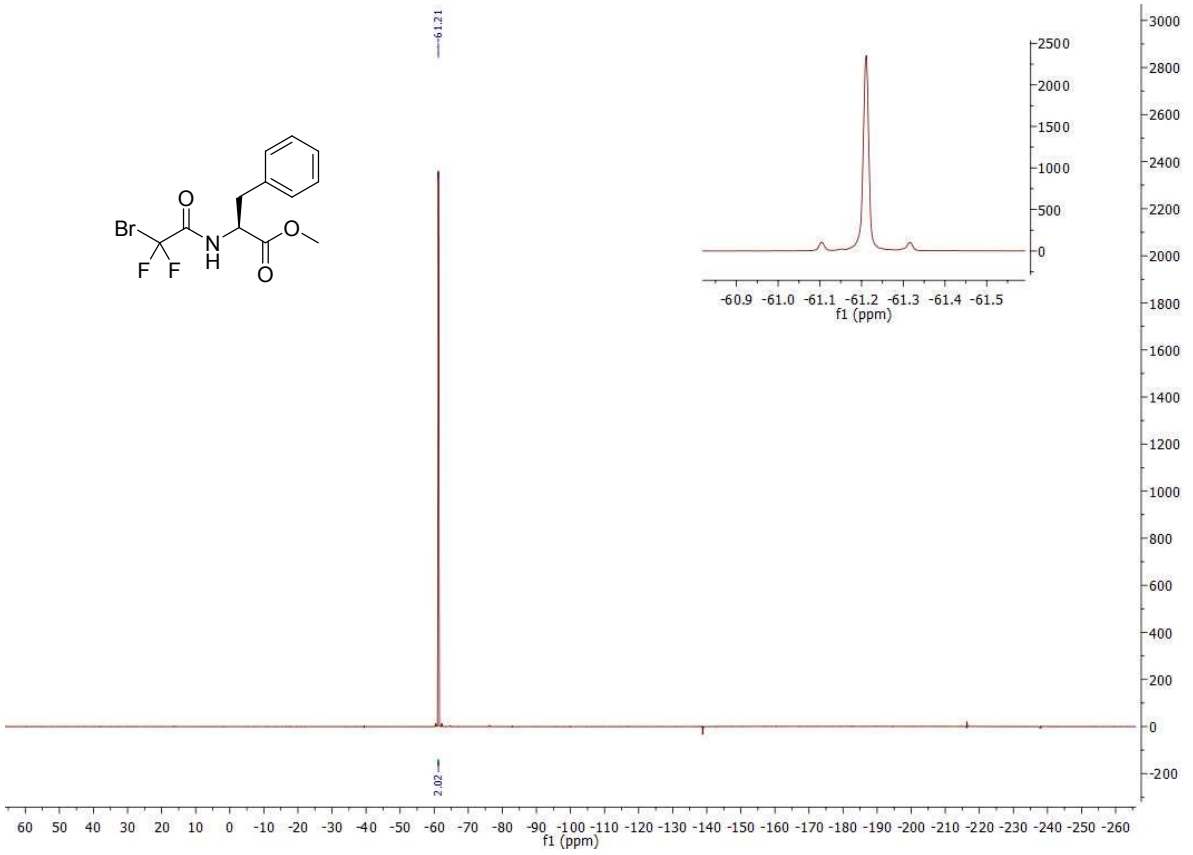

7.26
2.16
Br
F F
O
N
H
O
O
0.95
1.00
3.03
3.30
6.12
f1 (ppm)

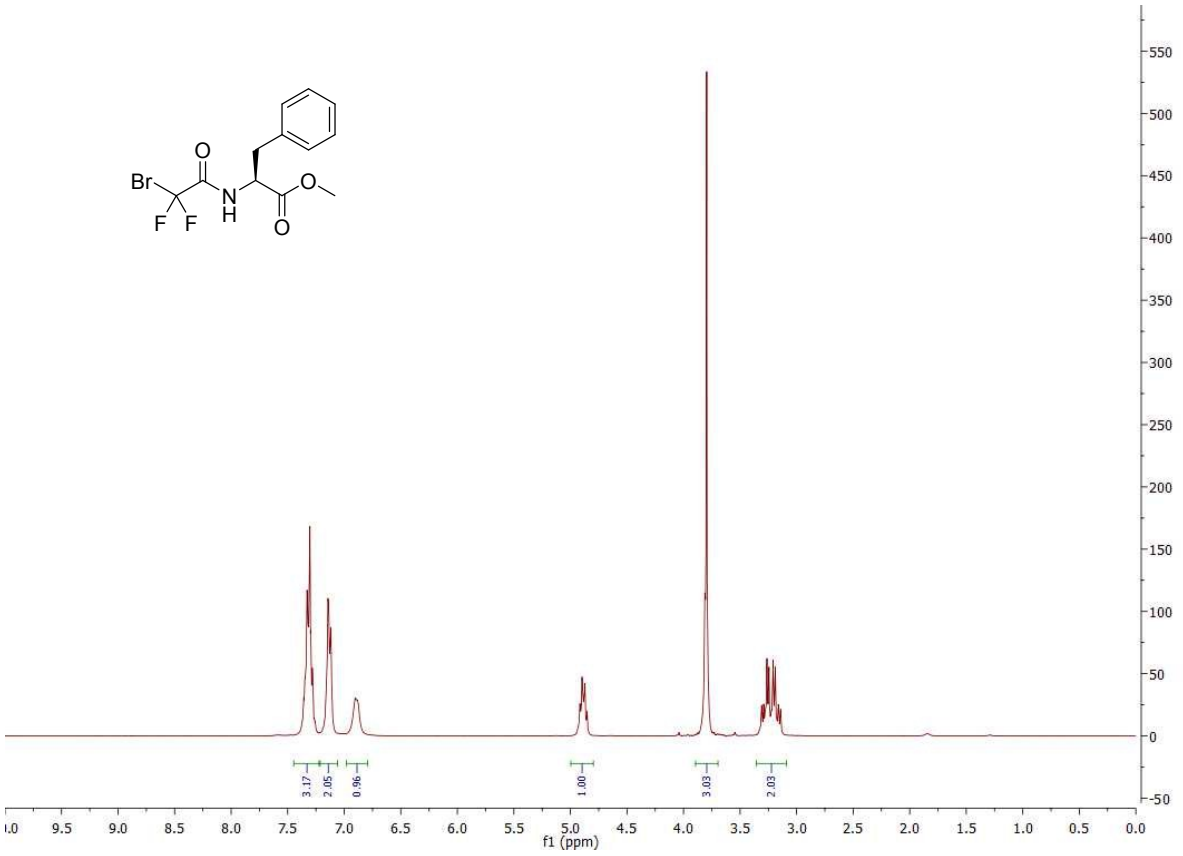

172.10
160.12
159.75
159.38
115.57
111.39
107.20
77.16
52.76
51.40
41.08
24.87
22.75
21.79
Br
F F
O
N
H
O
O
f1 (ppm)

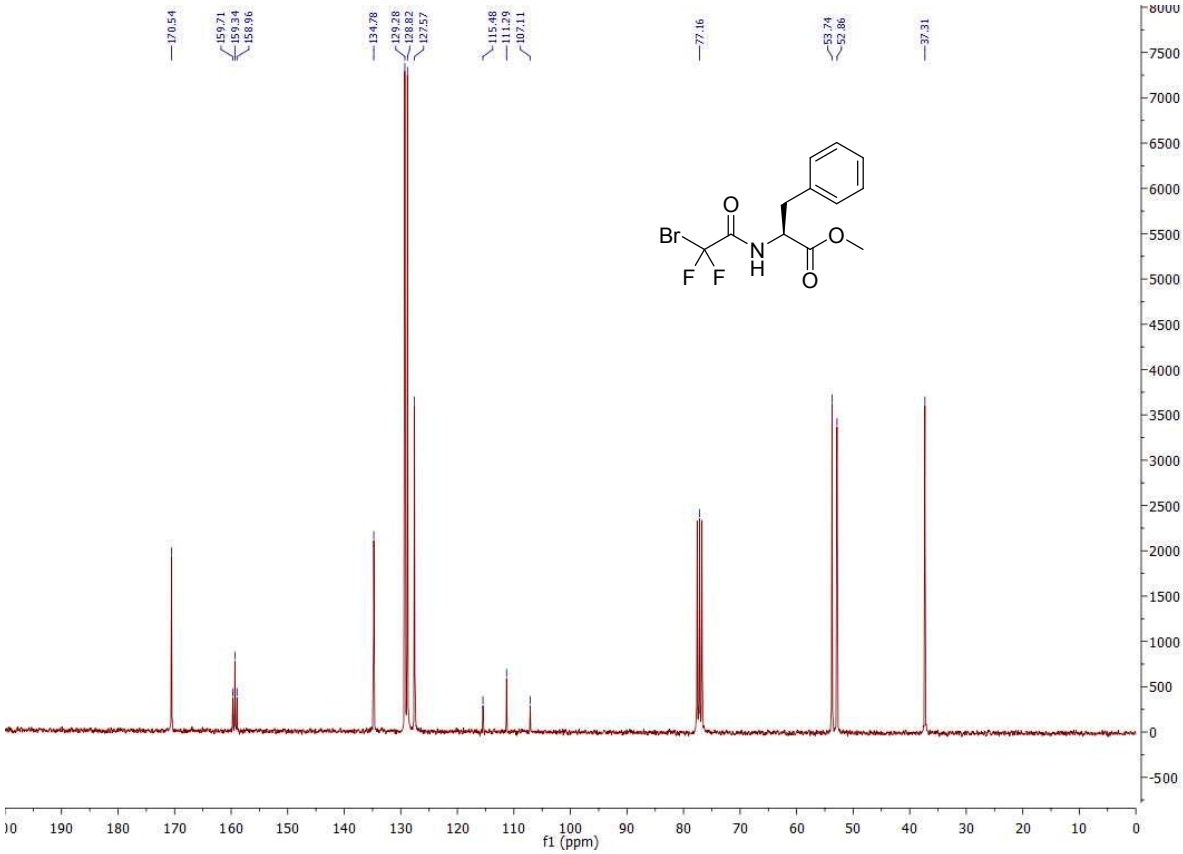

Br
F F
O
N
H
O
O
-61.16
2.00
f1 (ppm)

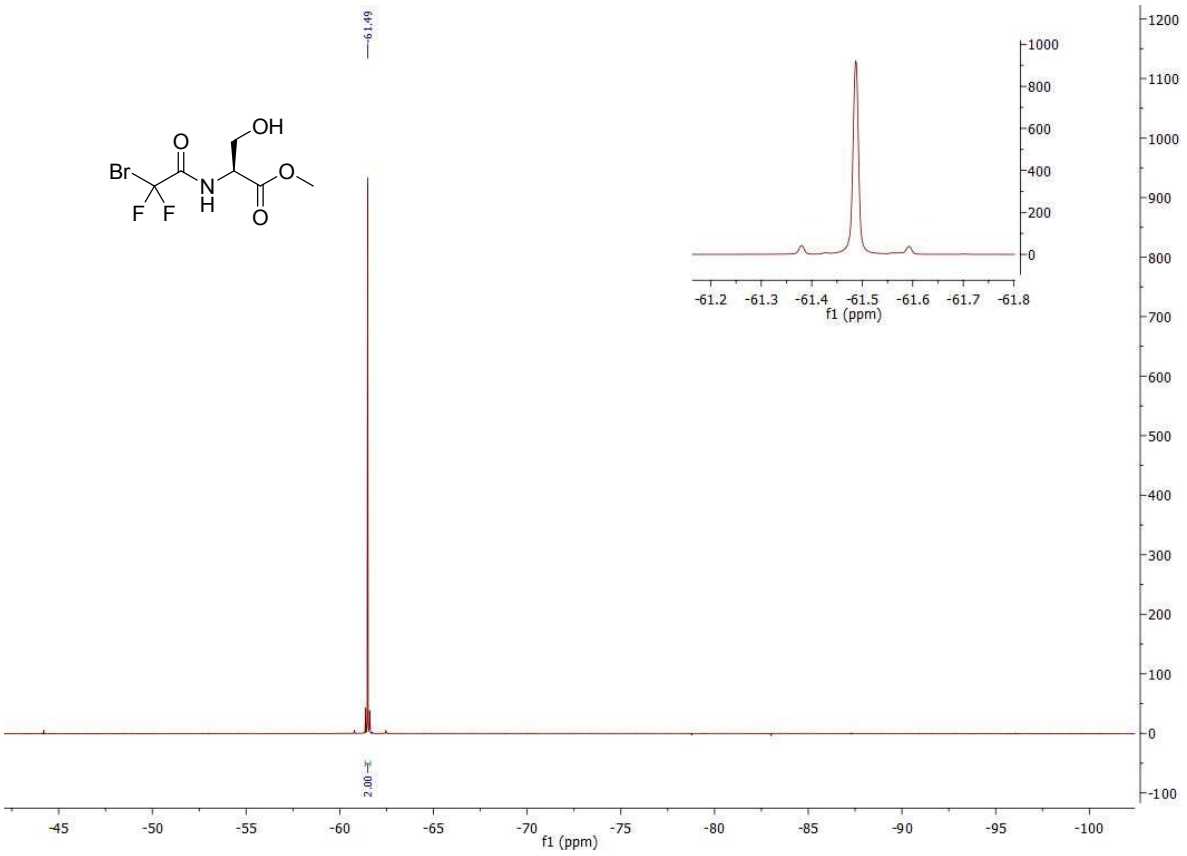

Br
F F
O
N
H
O
O
1.43
4.86
3.23
2.02
0.99
2.03
1.00
2.00
f1 (ppm)

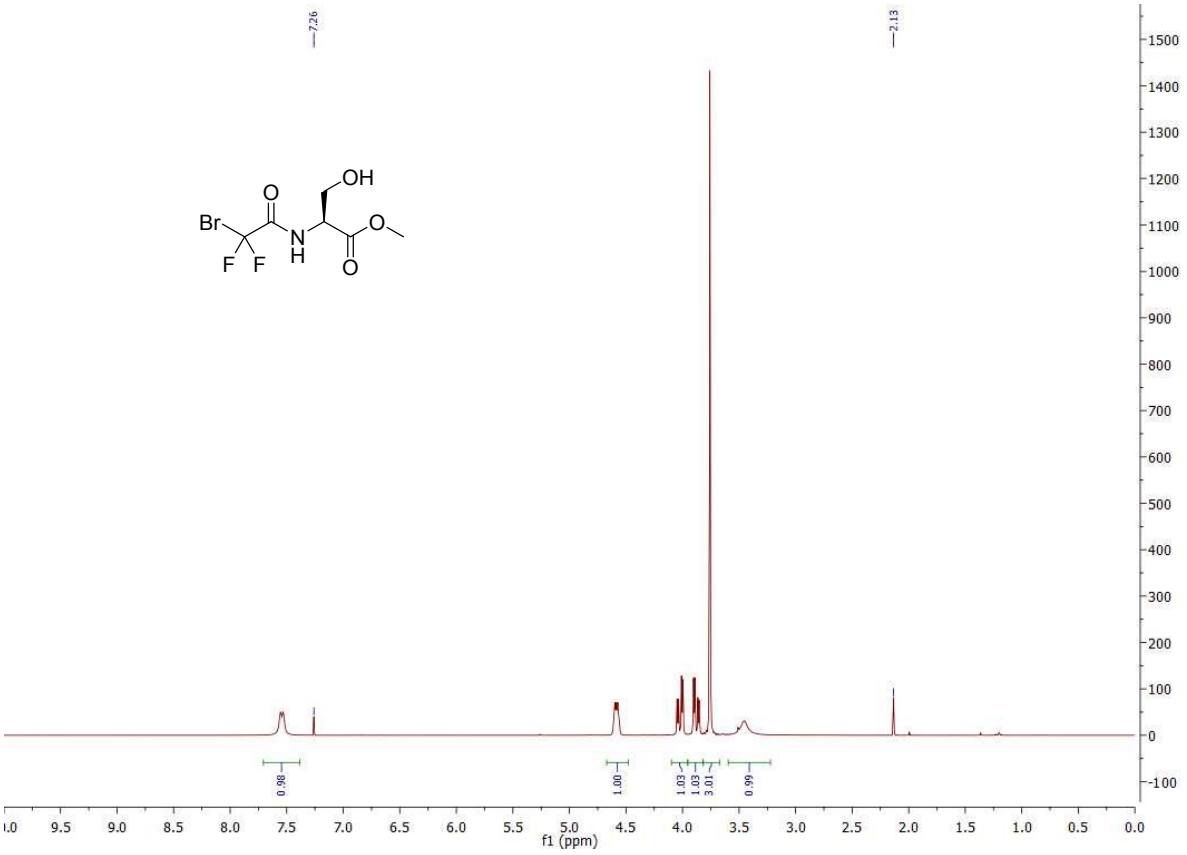

170.01
159.71
159.34
158.96
134.69
134.59
129.42
128.92
128.86
127.60
115.59
111.40
107.22
77.16
68.04
53.77
37.33
Br
F F
O
N
H
O
O
f1 (ppm)

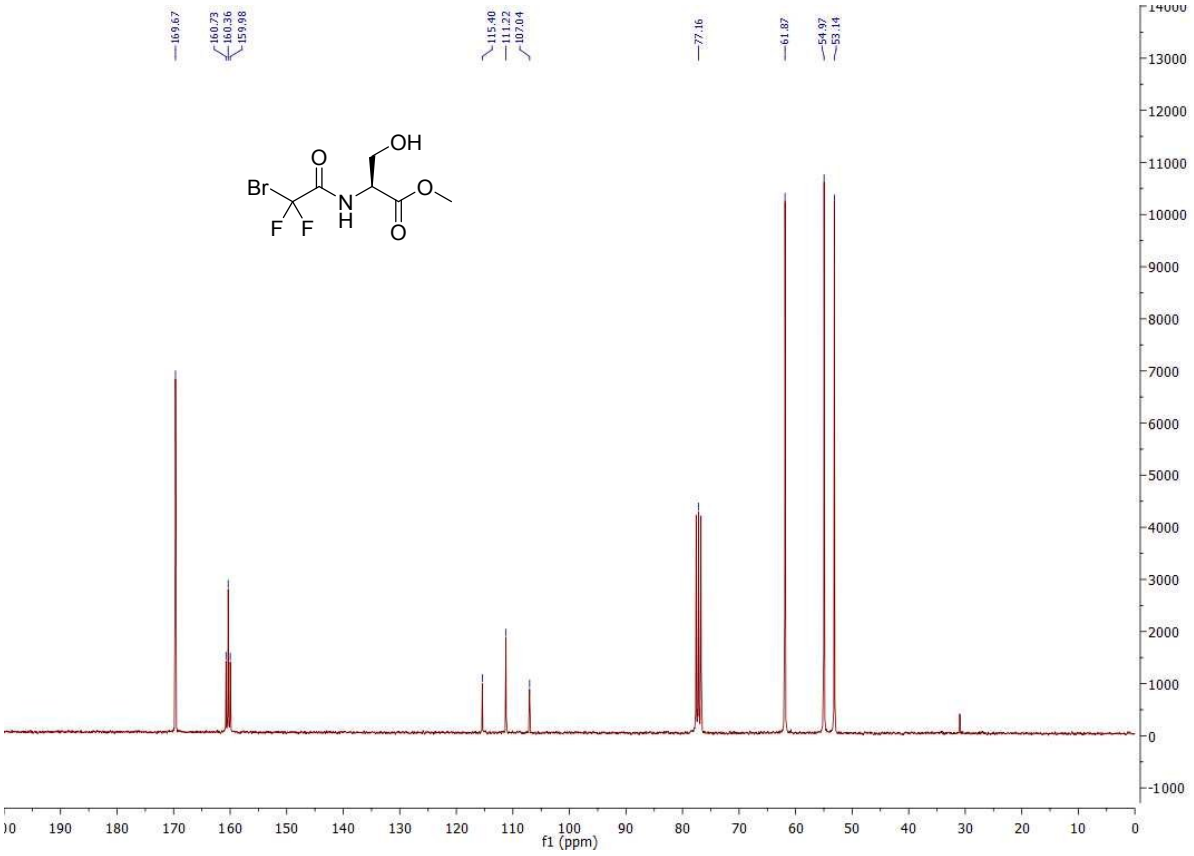

-61.21
2.02
Br
F F
O
N
H
O
O
-60.9 -61.0 -61.1 -61.2 -61.3 -61.4 -61.5
f1 (ppm)
f1 (ppm)

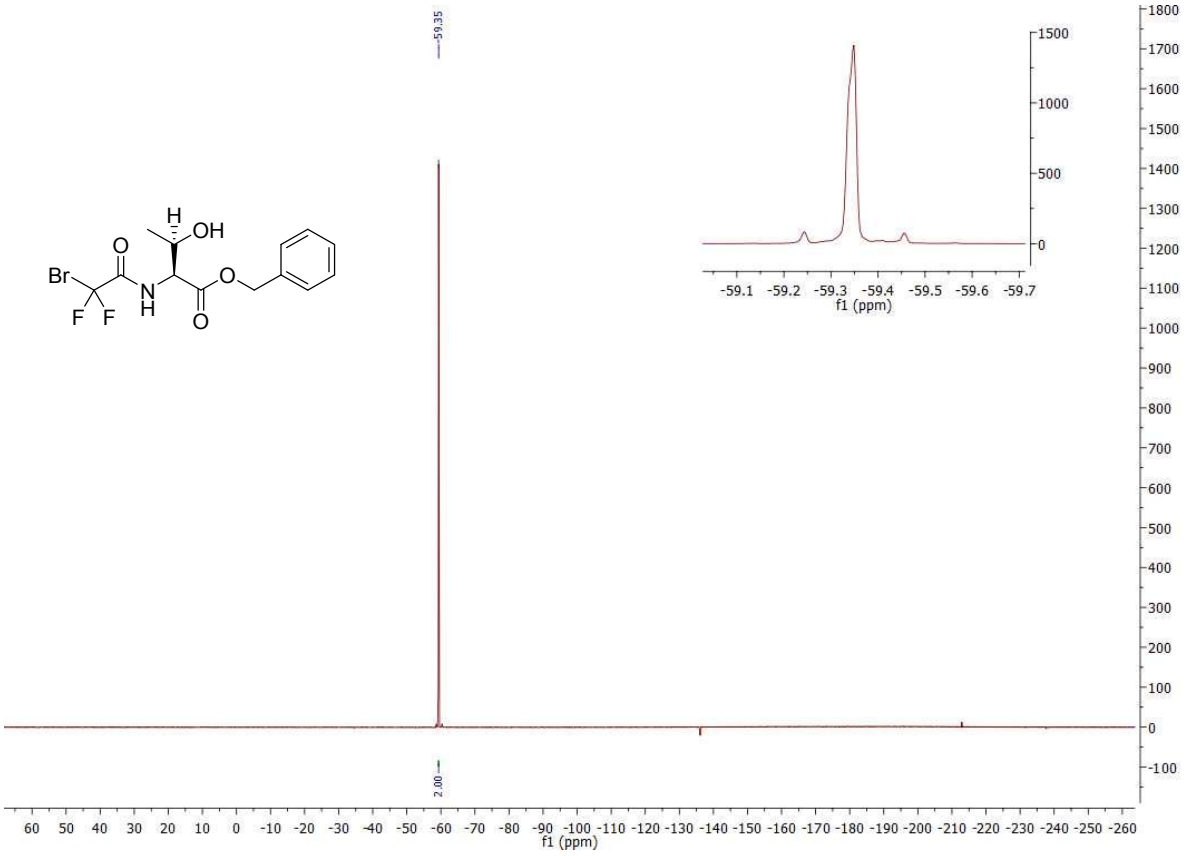

Br
F F
O
N
H
O
O
3.17
2.05
0.96
1.00
3.03
2.03
f1 (ppm)

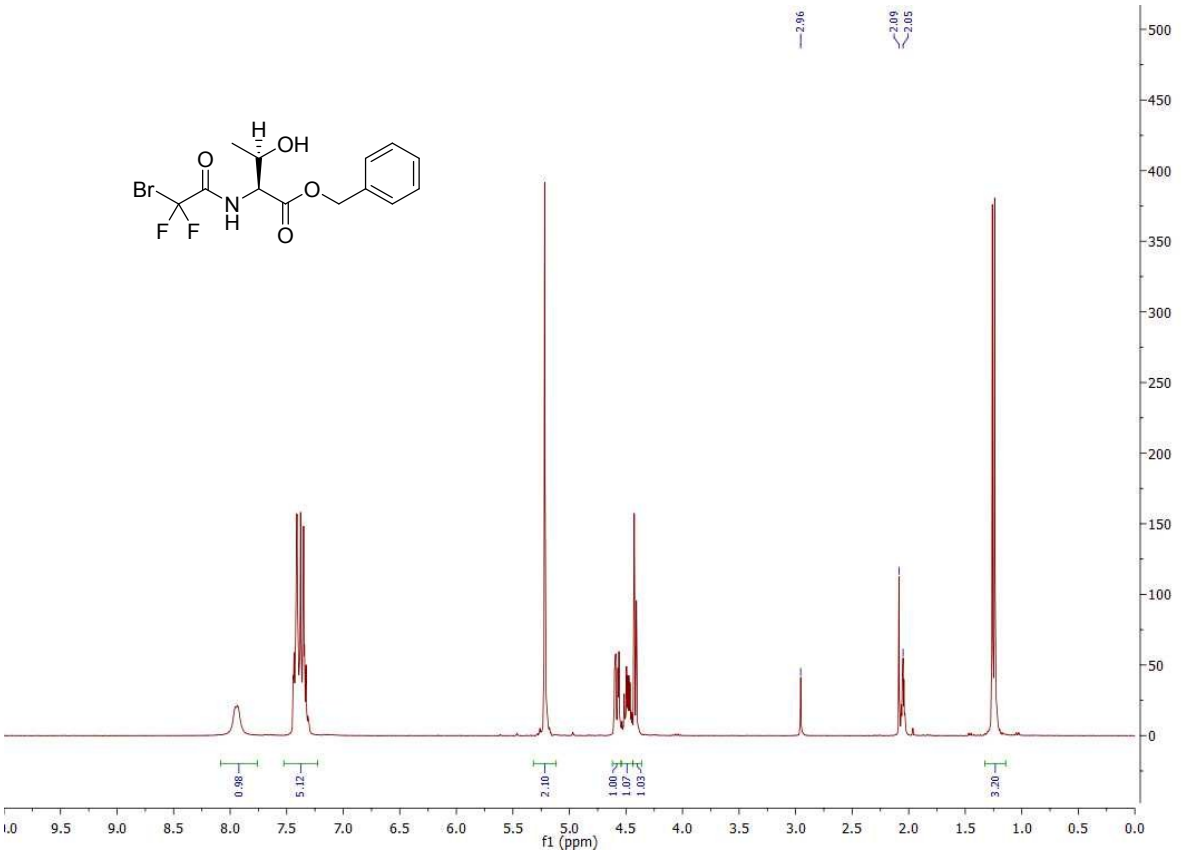

170.54
159.71
159.34
158.96
134.78
129.28
128.82
127.57
115.48
111.29
107.11
77.16
53.74
52.86
37.31
Br
F F
O
N
H
O
O
f1 (ppm)

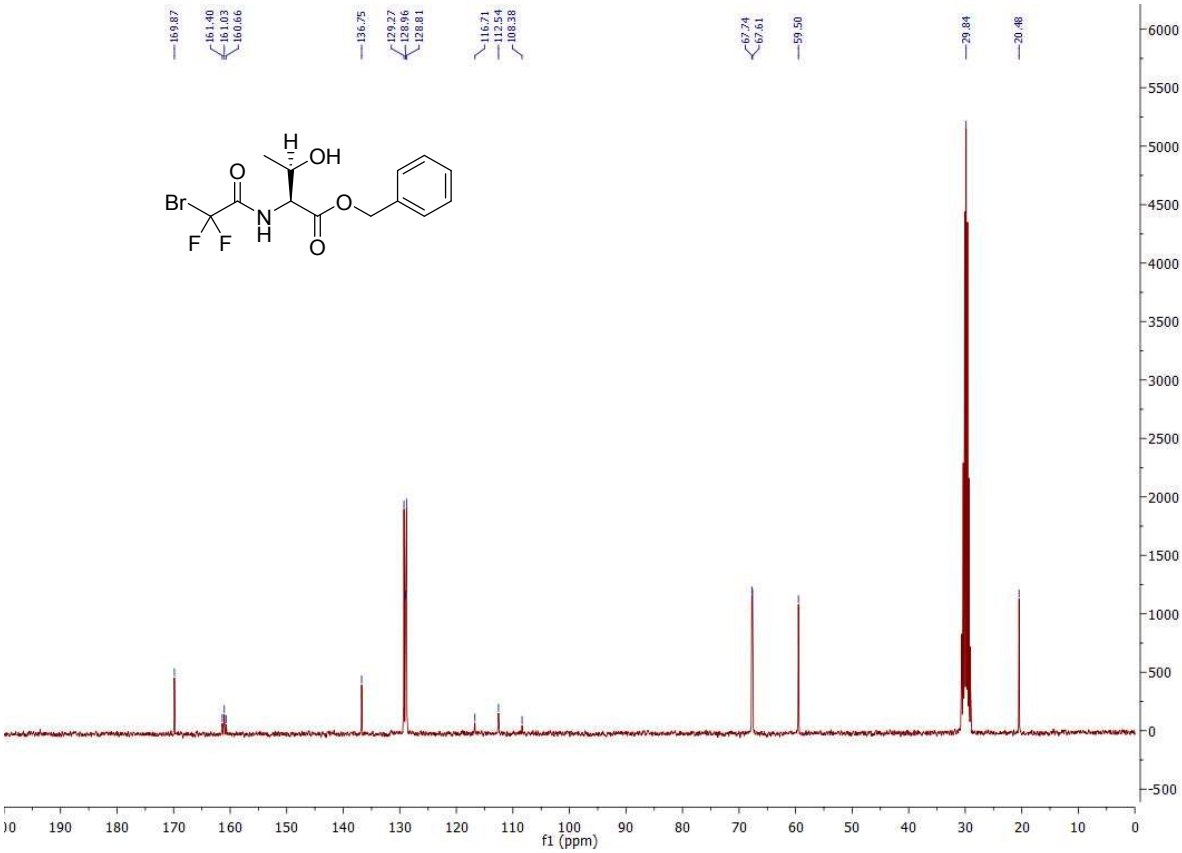

Br
F F
O
N
H
OH
O
O
-61.49
2.00
f1 (ppm)

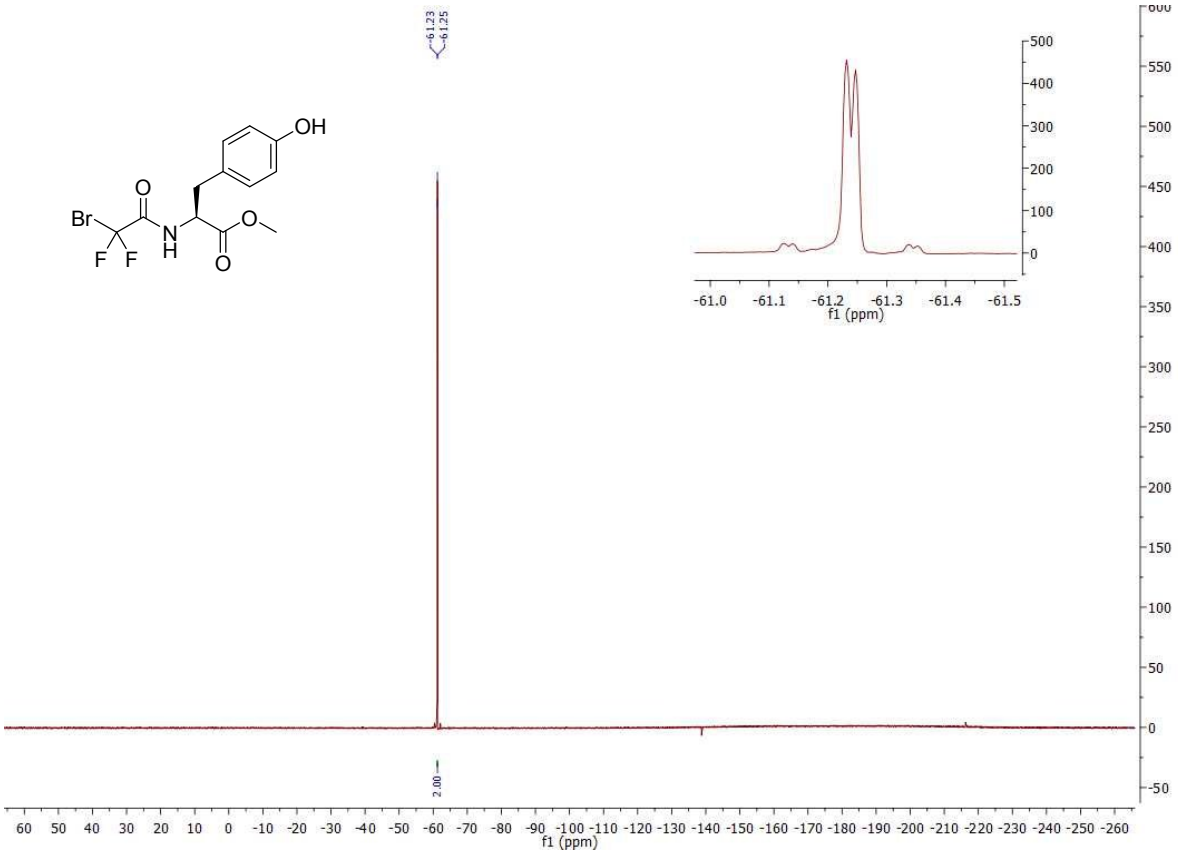

Br
F F
O
N
H
OH
O
O
7.26
2.13
0.98
1.00
1.03
1.03
3.01
0.99
f1 (ppm)

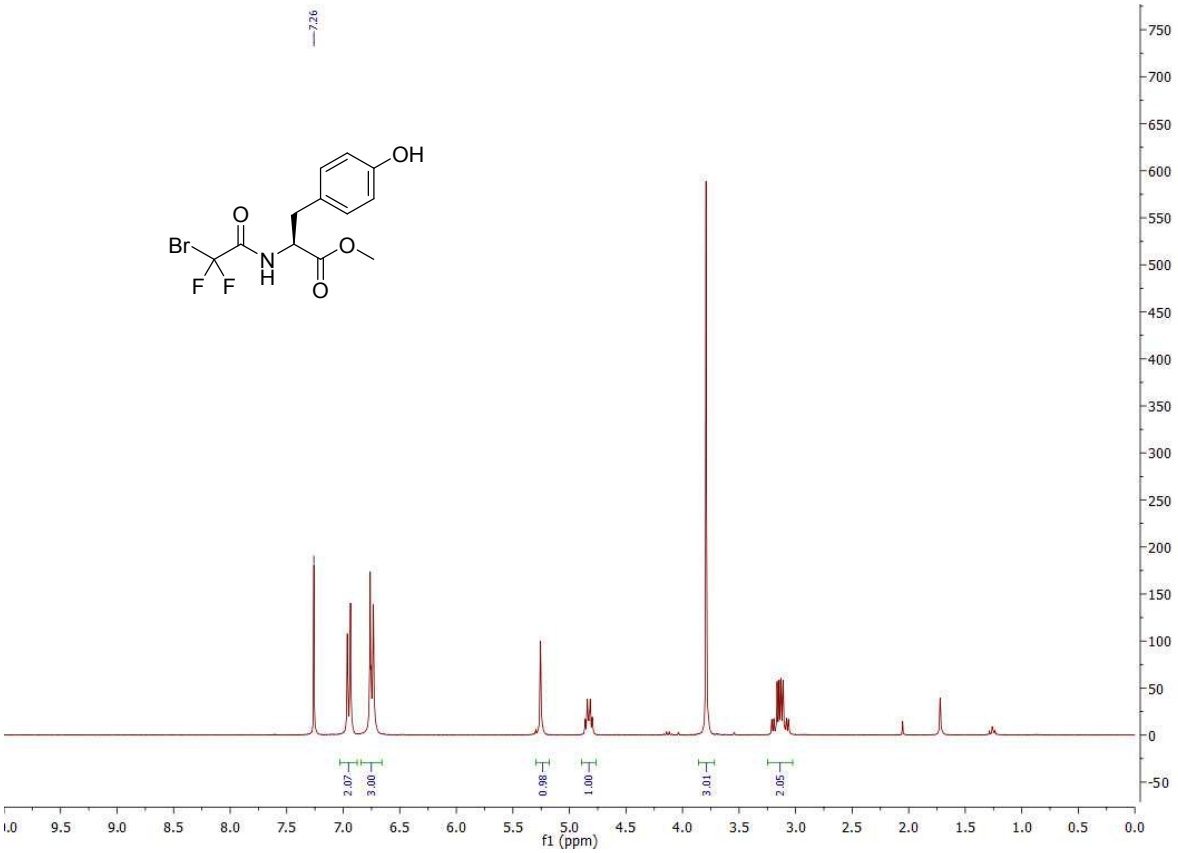

169.67
160.73
160.36
159.98
115.40
111.22
107.04
77.16
61.87
54.97
53.14
OH
O
Br
N
H
O
F F
O
f1 (ppm)

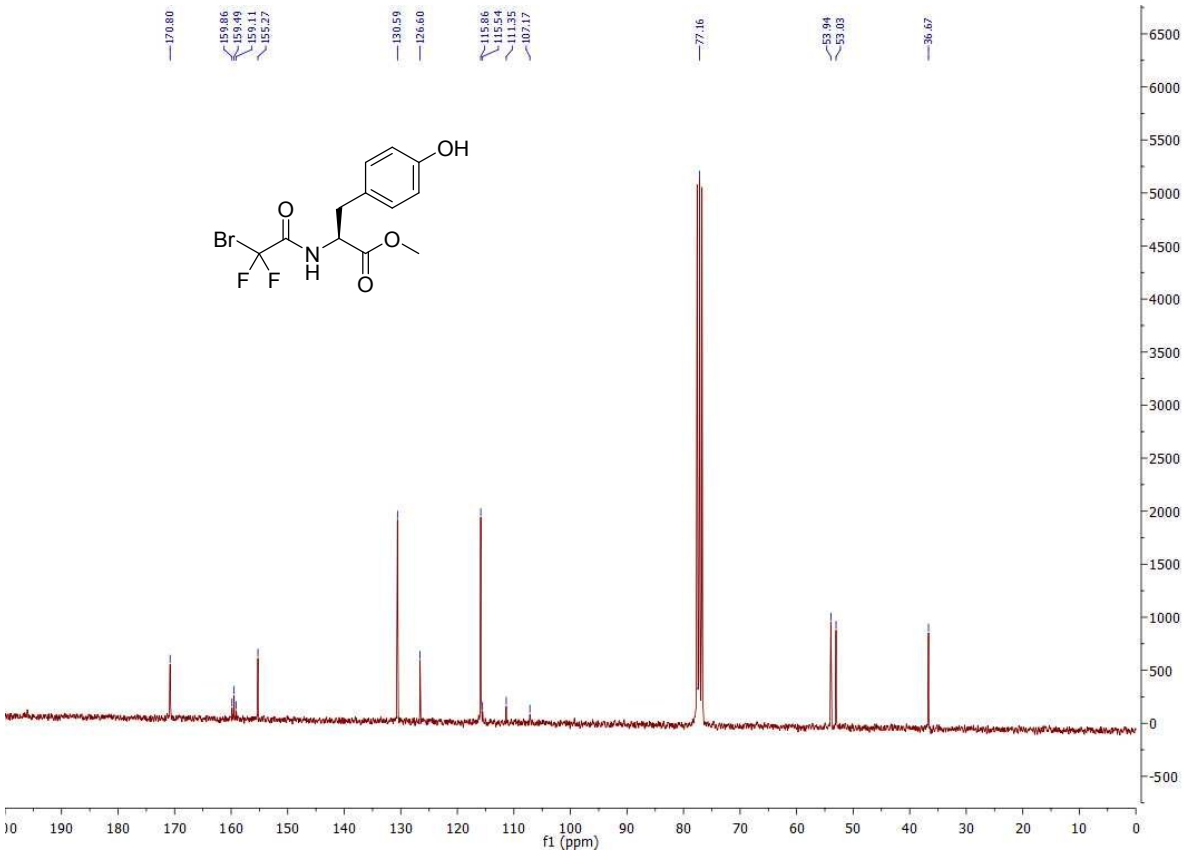

59.35
H
OH
O
Br
N
H
O
O
F F
2.00
f1 (ppm)
-59.1 -59.2 -59.3 -59.4 -59.5 -59.6 -59.7
f1 (ppm)

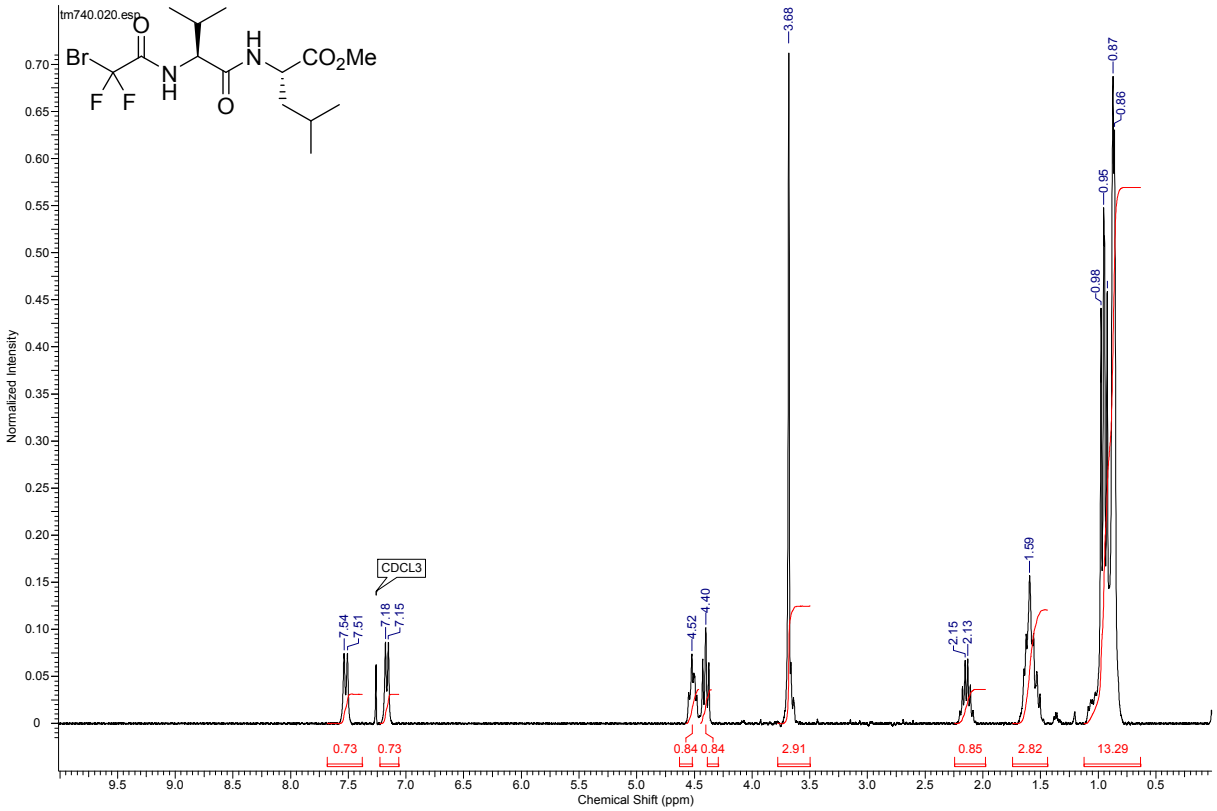

Br
F
F
O
N
H
H
OH
O
O
O
2.96
2.09
2.05
0.98
5.12
2.10
1.00
1.07
1.03
3.20
f1 (ppm)

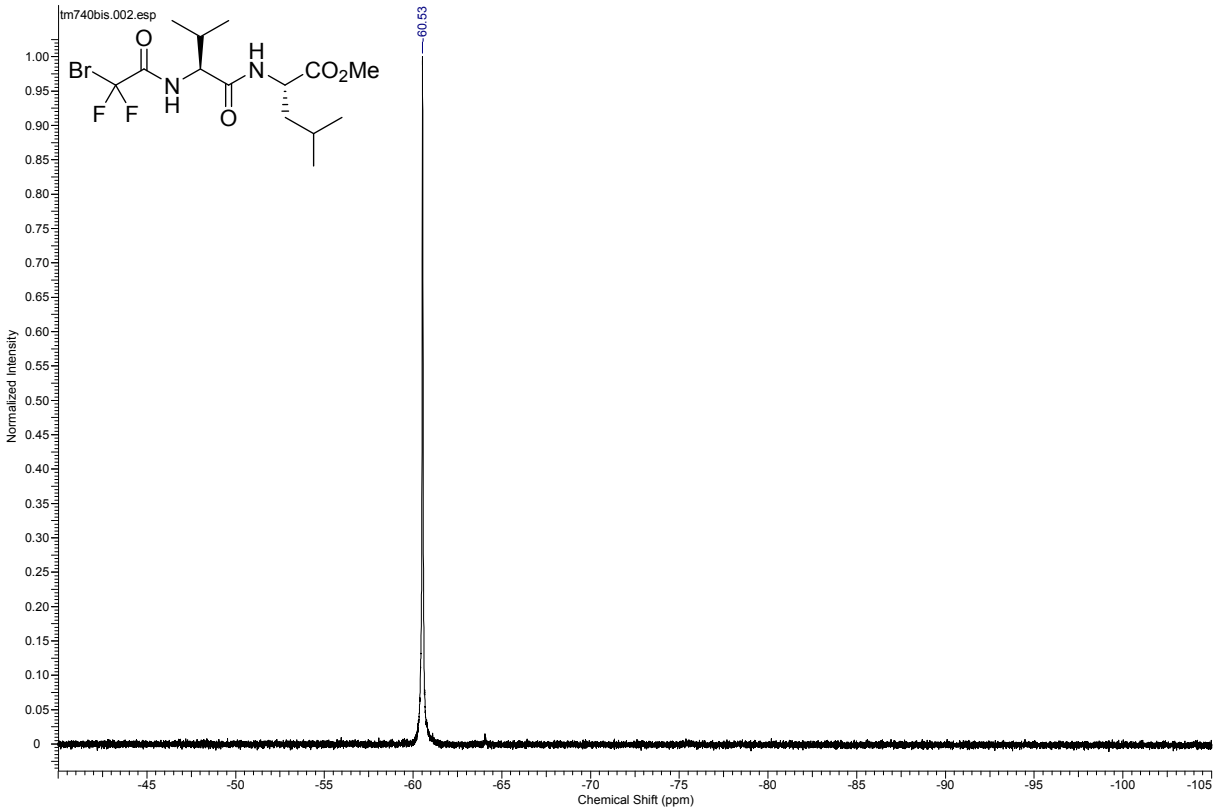

Br
F
F
O
N
H
H
OH
O
O
O
169.87
161.40
161.03
160.66
136.75
129.27
128.96
128.81
116.71
112.54
108.38
67.74
67.61
59.50
29.84
20.48
f1 (ppm)

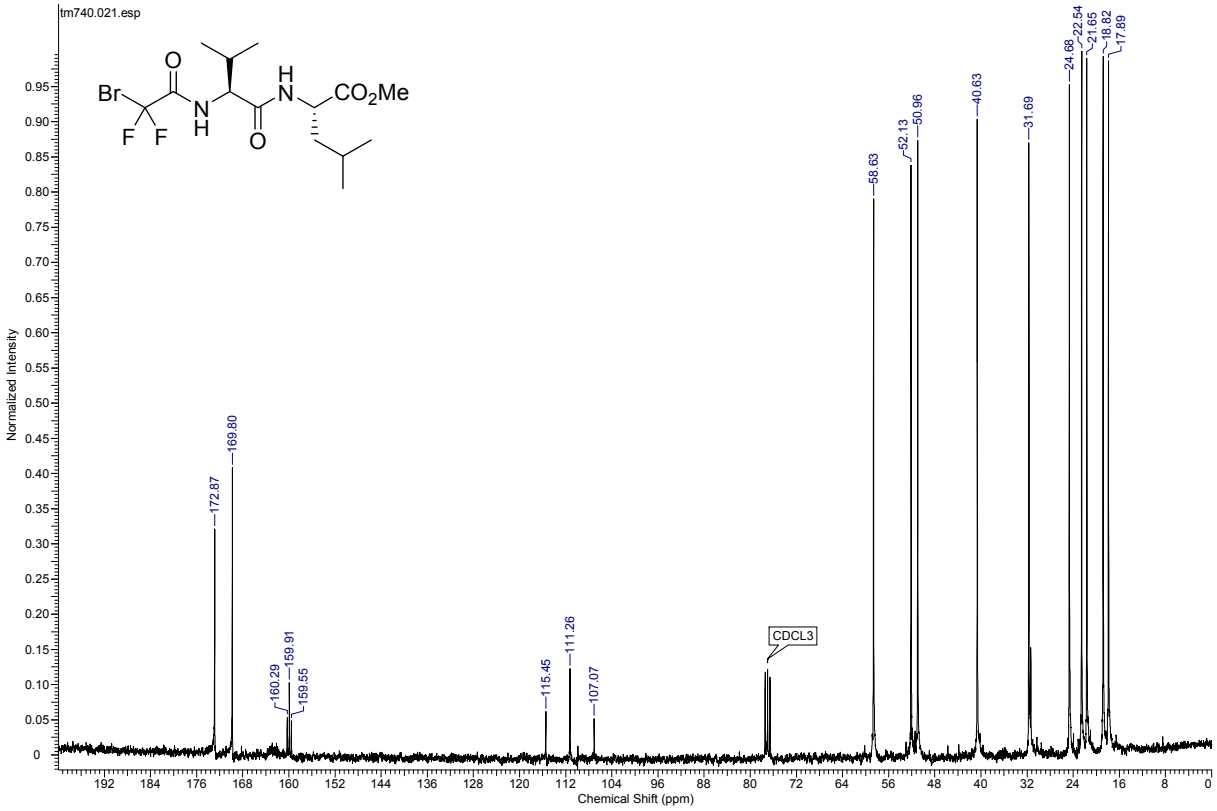

OH
O
Br
N
H
F F
O
O
-61.23
-61.25
2.00
f1 (ppm)

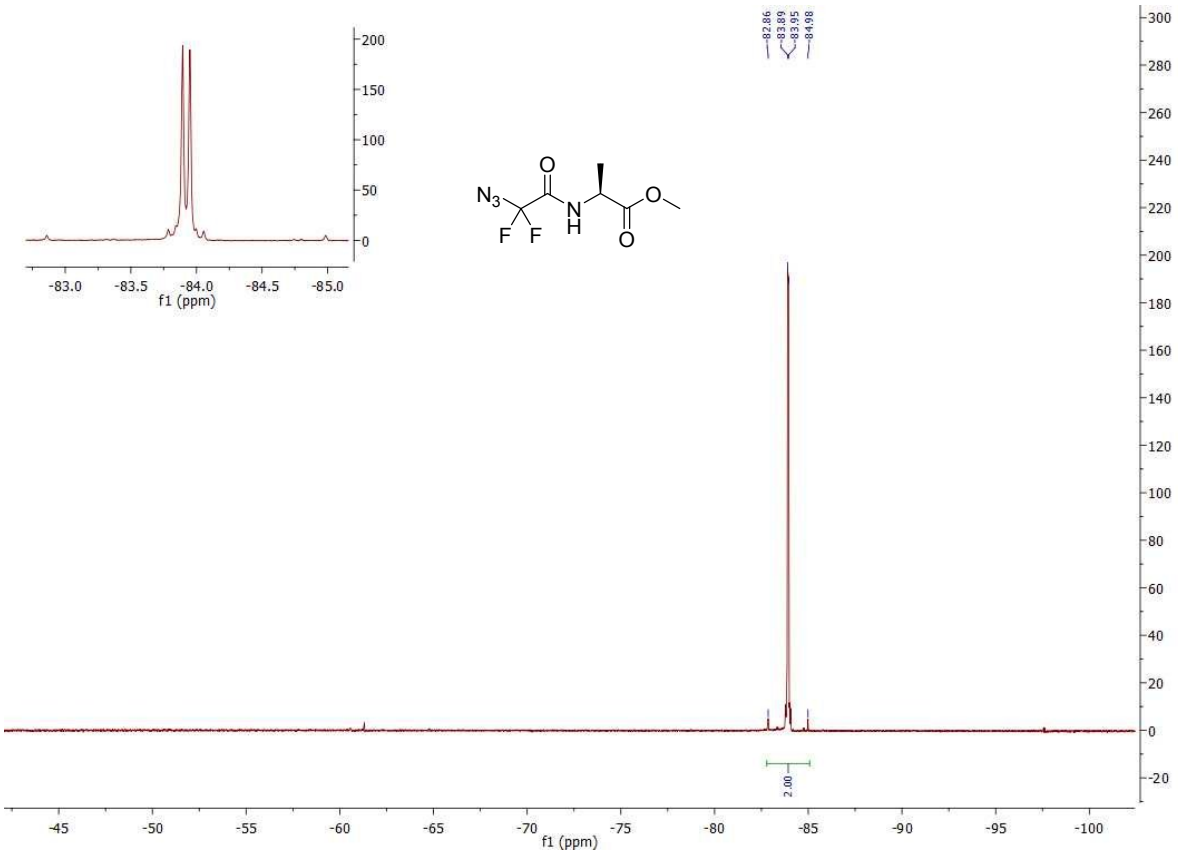

7.26
OH
O
Br
N
H
F F
O
O
2.07
3.00
0.98
1.00
3.01
2.05
f1 (ppm)

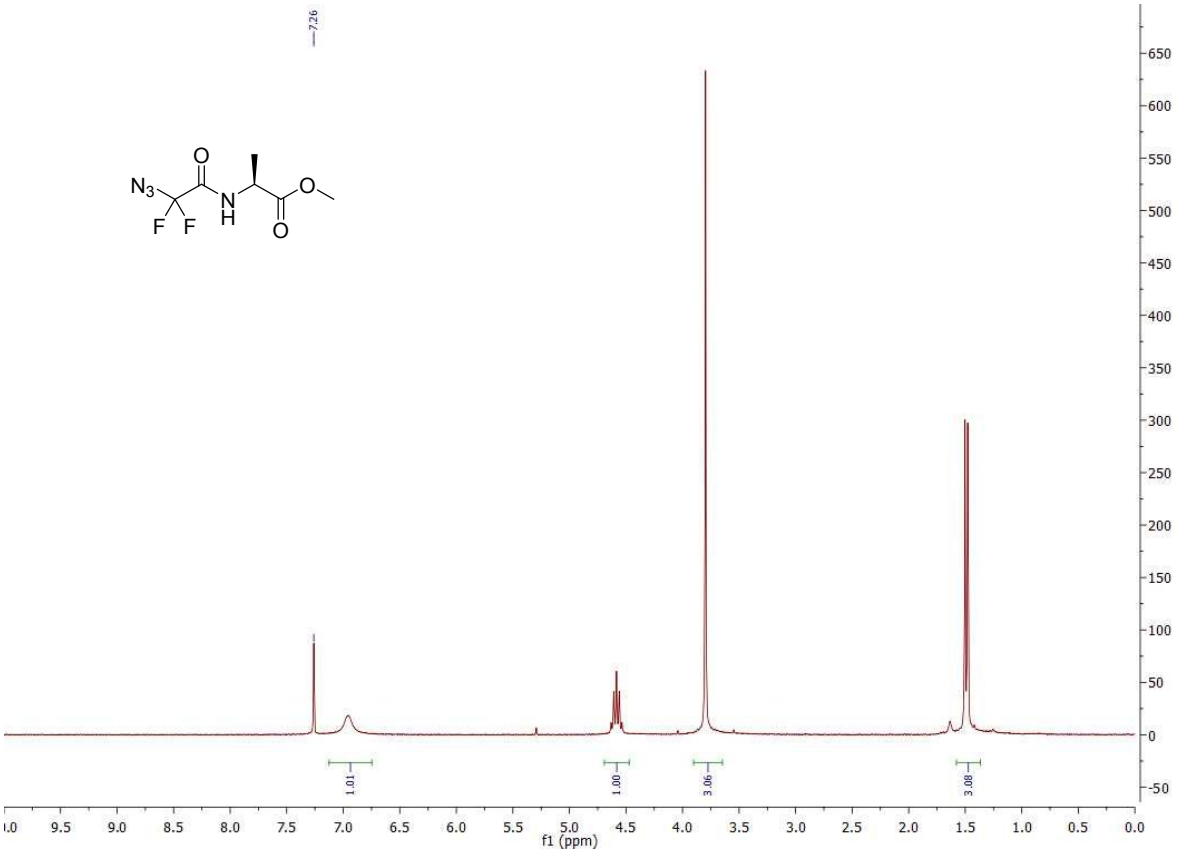

170.80
159.86
159.49
159.11
155.27
130.59
126.60
115.86
115.54
111.35
107.17
77.16
53.94
53.03
36.67
OH
Br
F F
O
N
H
O
O
f1 (ppm)

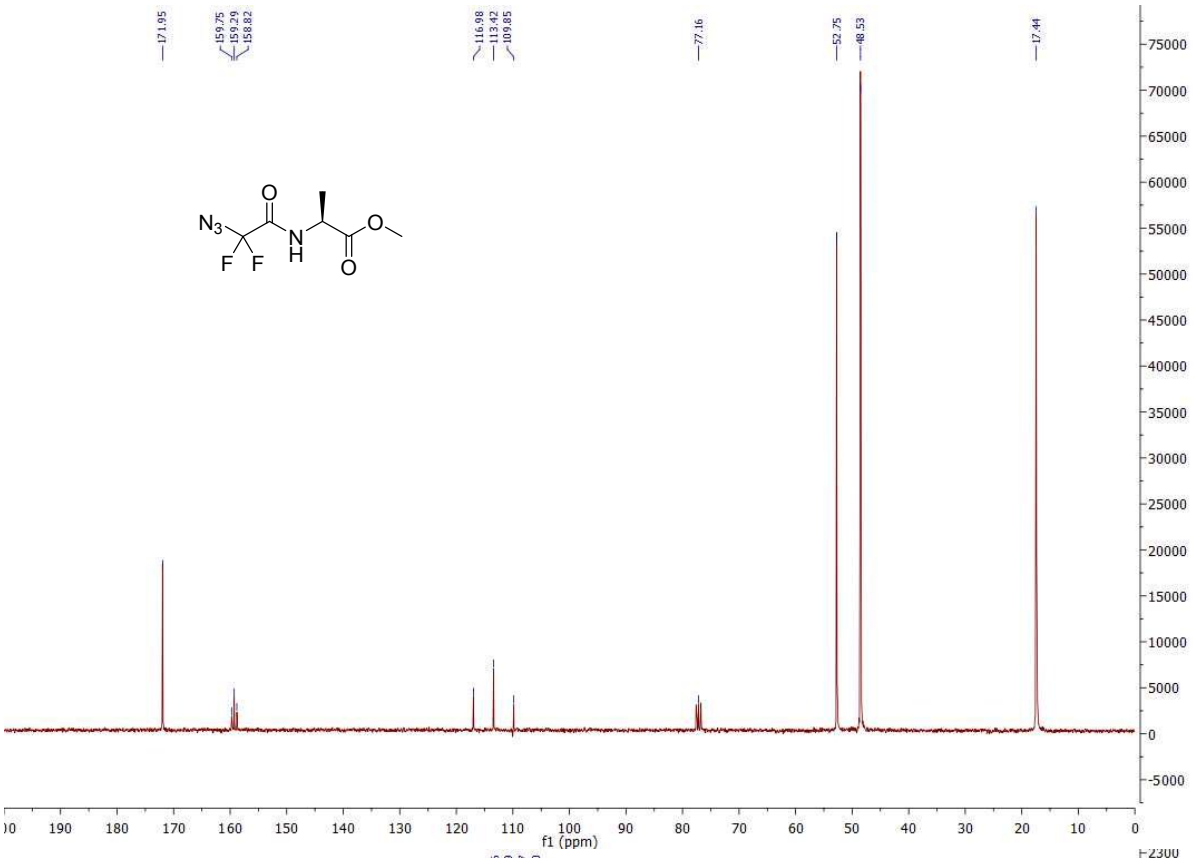

tm740.020.esp
Br
F F
O
N
H
O
H
N
CO2Me
Normalized Intensity
CDCL3
7.54
7.51
7.18
7.15
4.52
4.40
3.68
2.15
2.13
1.59
0.98
0.95
0.87
0.86
0.73
0.73
0.84
0.84
2.91
0.85
2.82
13.29
Chemical Shift (ppm)

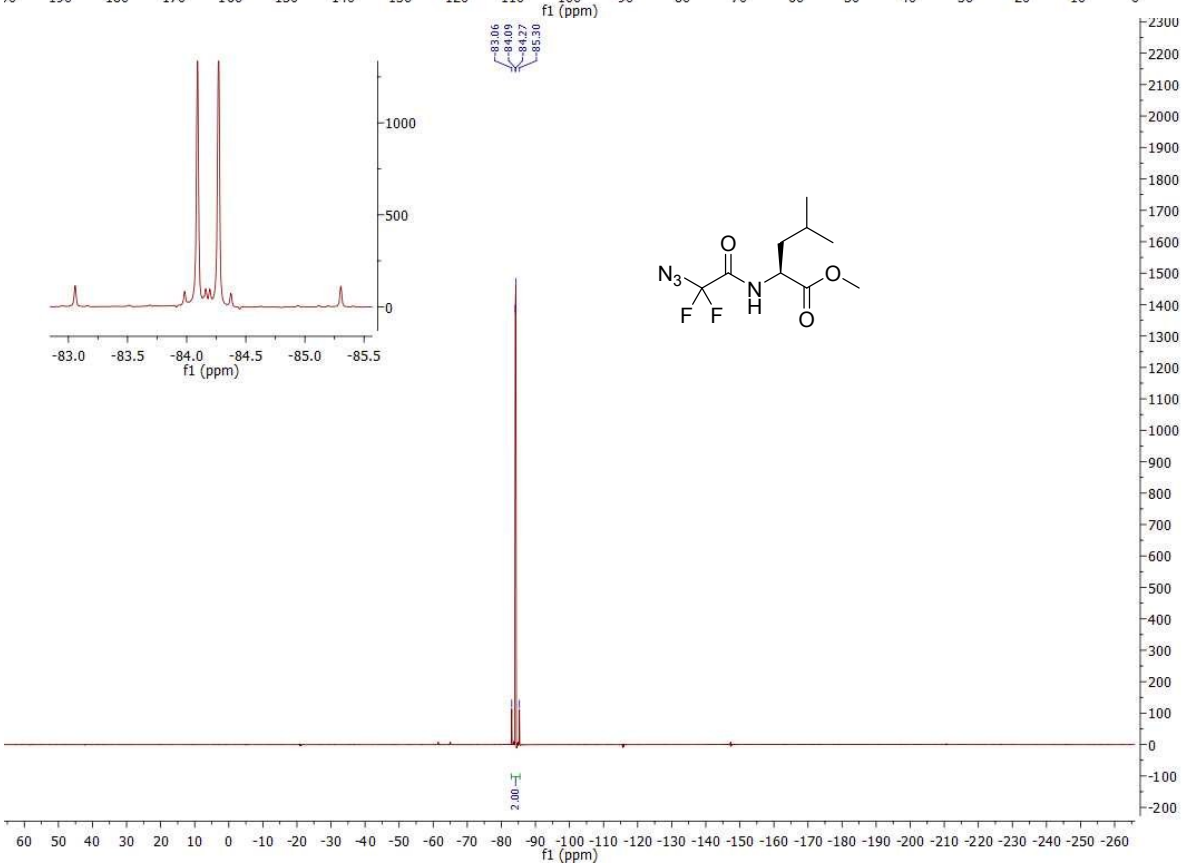

tm740bis.002.esp
Br
F F
O
N
H
O
H
N
CO2Me
60.53
Normalized Intensity
Chemical Shift (ppm)

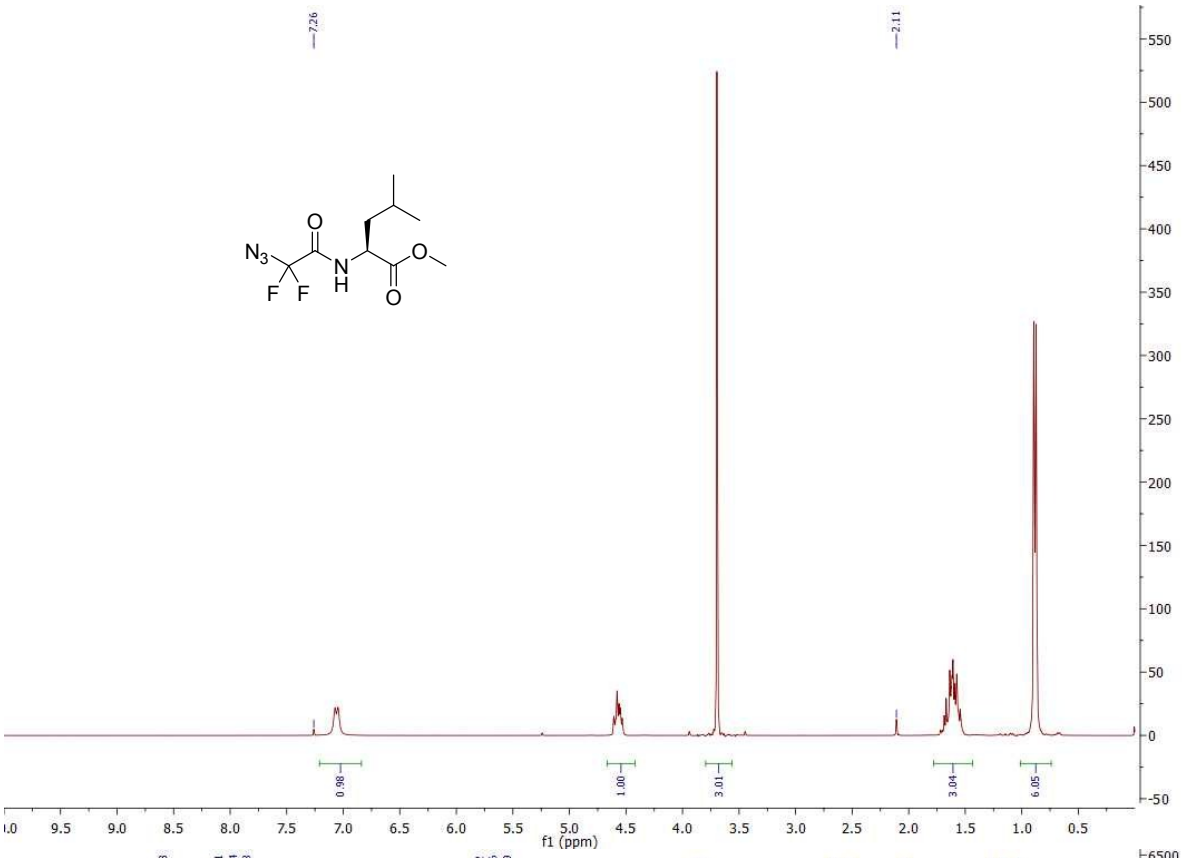

tm740.021.esp
Br
F F
O
N
H
O
H
N
CO2Me
172.87
169.80
160.29
159.91
159.55
115.45
111.26
107.07
CDCL3
58.63
52.13
50.96
40.63
31.69
24.68
22.54
21.65
18.82
17.89
Normalized Intensity
Chemical Shift (ppm)

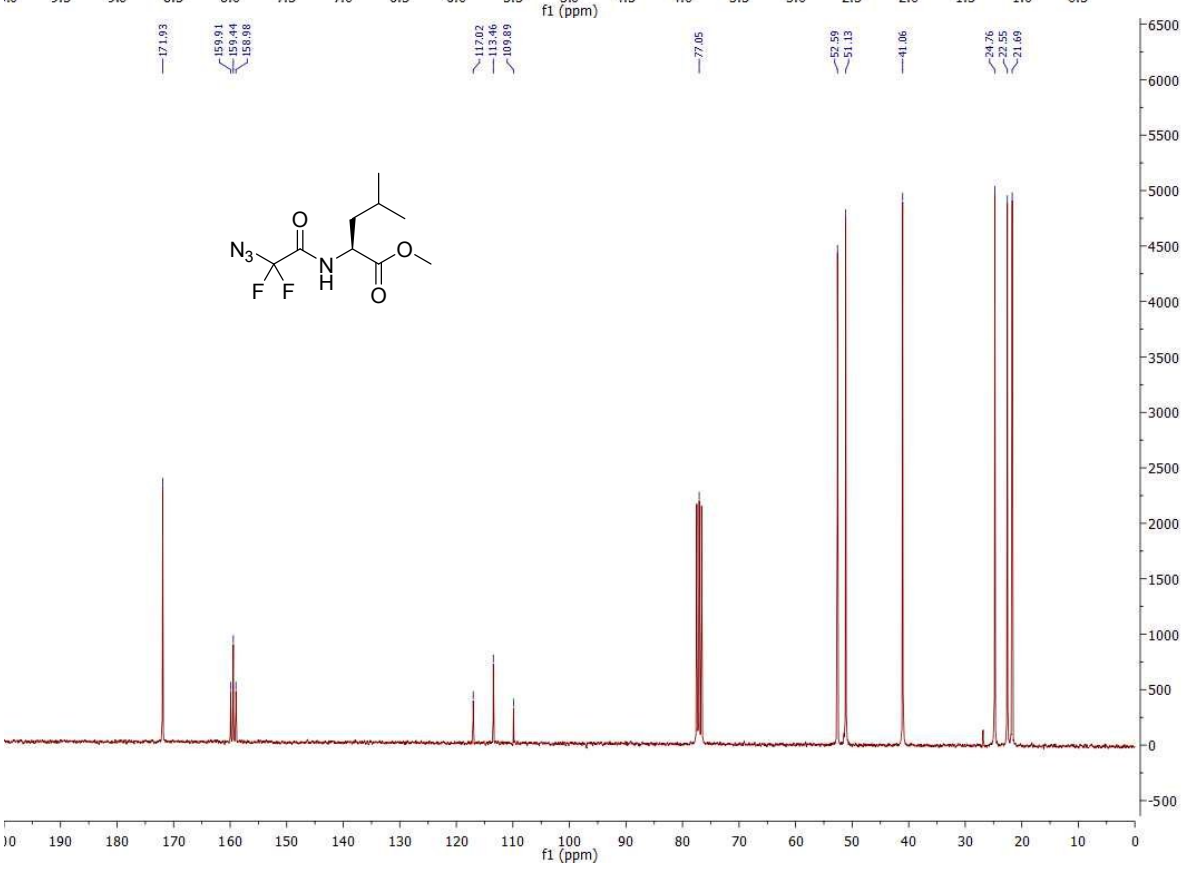

82.86
83.89
83.95
84.98
2.00
f1 (ppm)

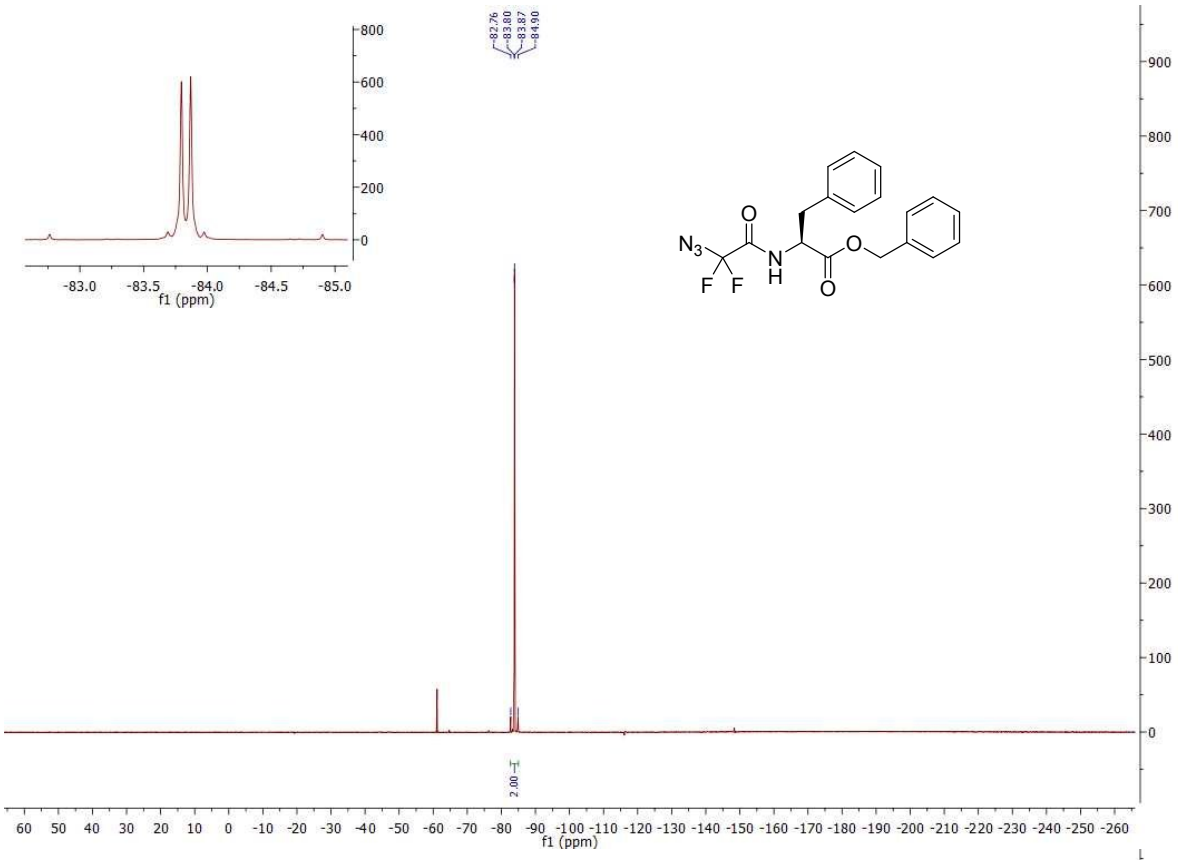

7.26
1.01
1.00
3.06
3.08
f1 (ppm)

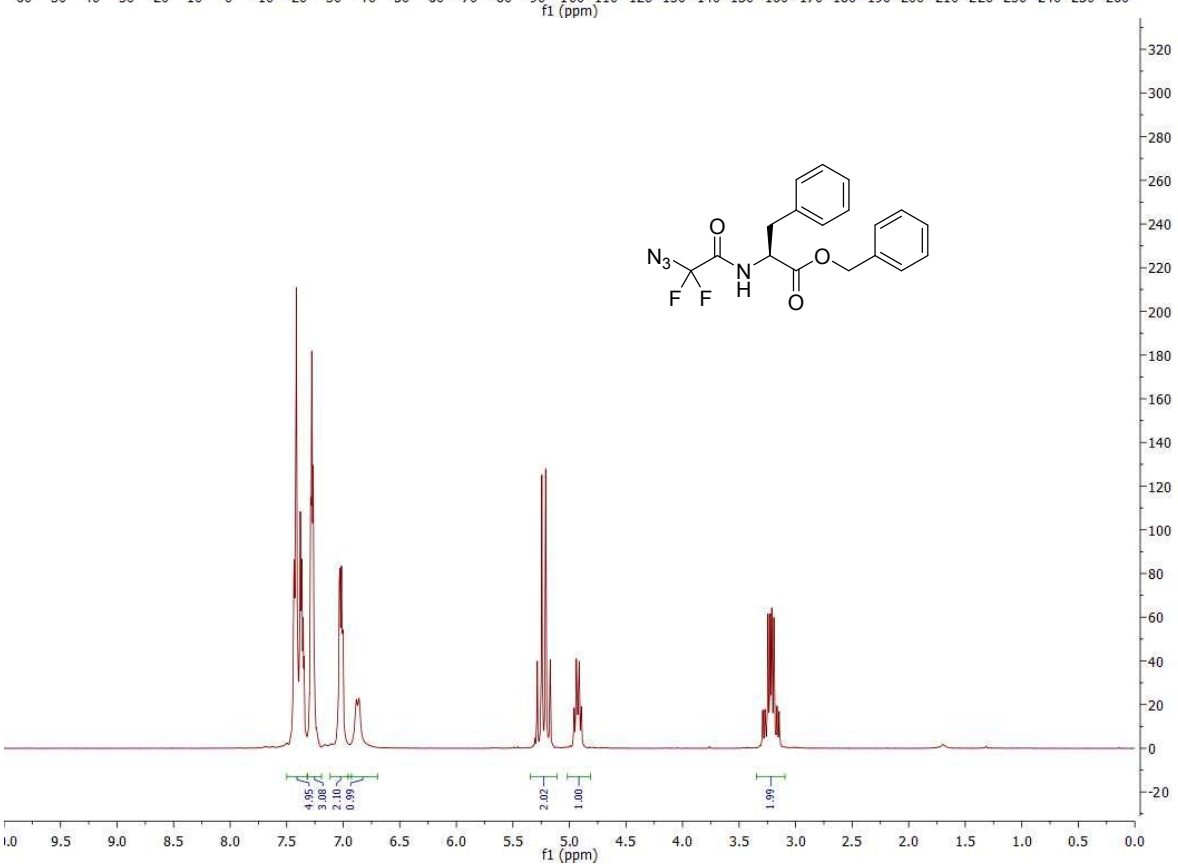

171.95
159.75
159.29
158.82
116.98
113.42
109.85
77.16
52.75
48.53
17.44
f1 (ppm)

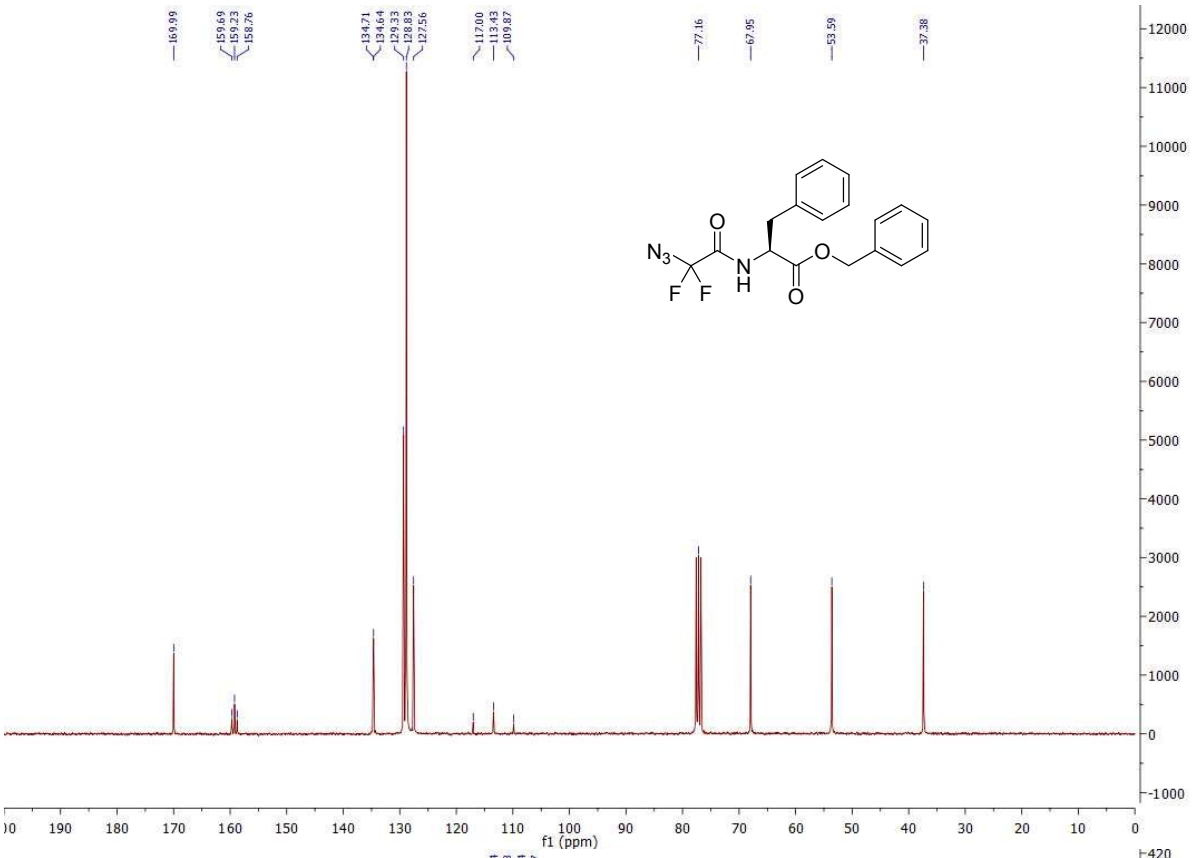

83.06
84.09
84.27
85.30
2.00
f1 (ppm)

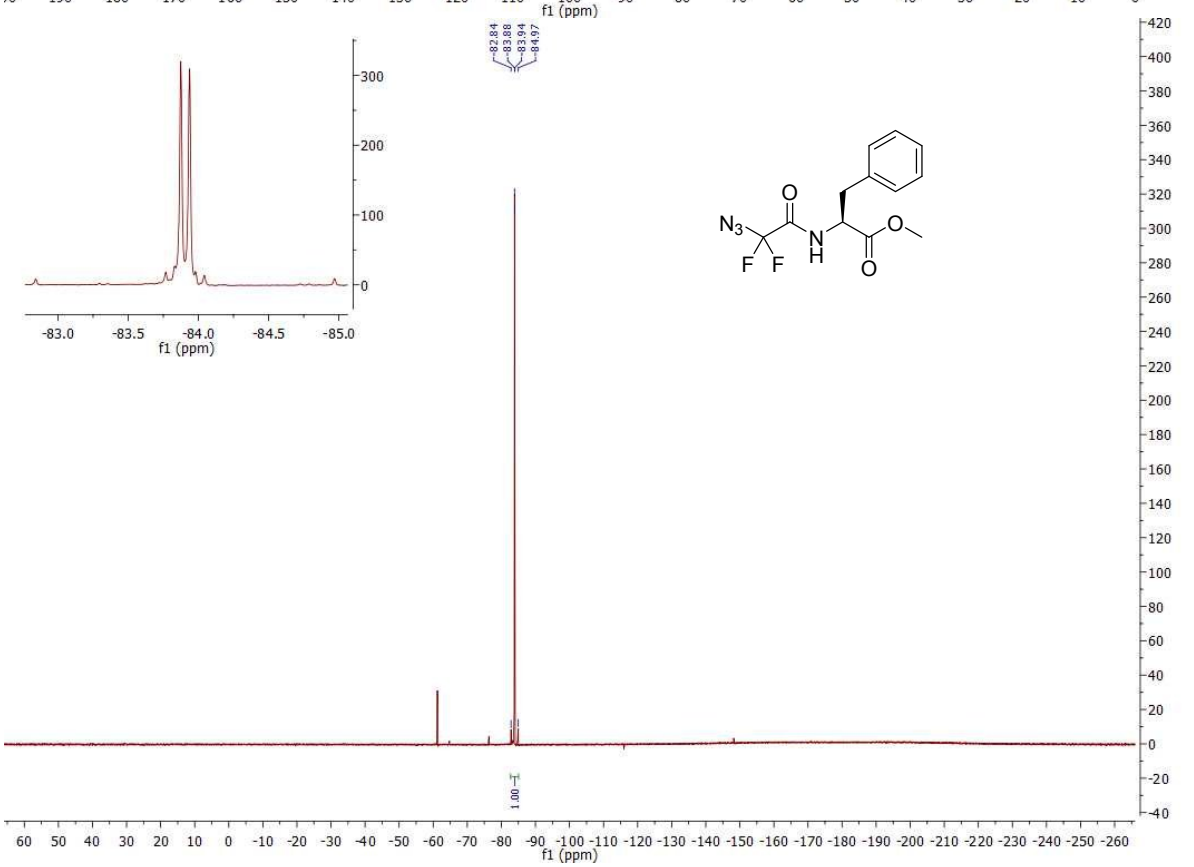

7.26
2.11
0.98
1.00
3.01
3.04
6.05
f1 (ppm)

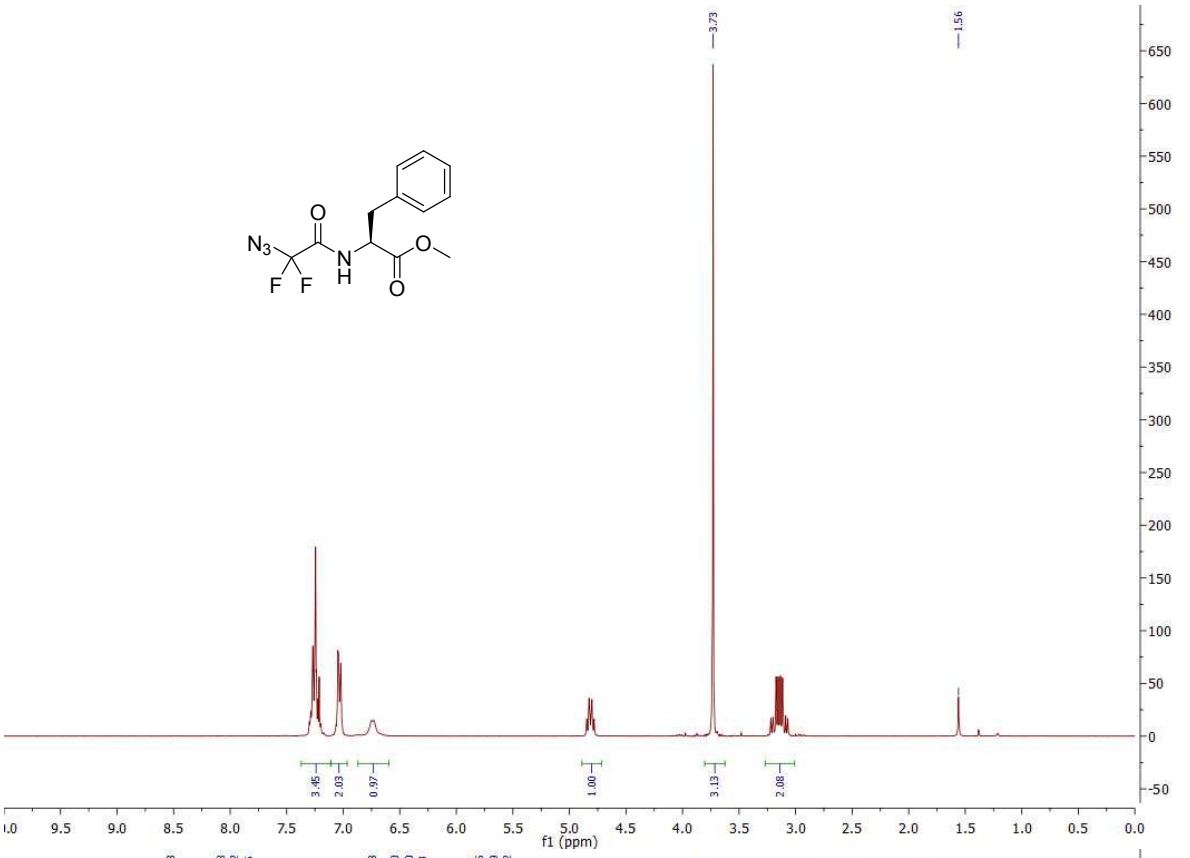

171.93
159.91
159.44
158.98
117.02
113.46
109.89
77.05
52.59
51.13
41.06
24.76
22.55
21.69
f1 (ppm)

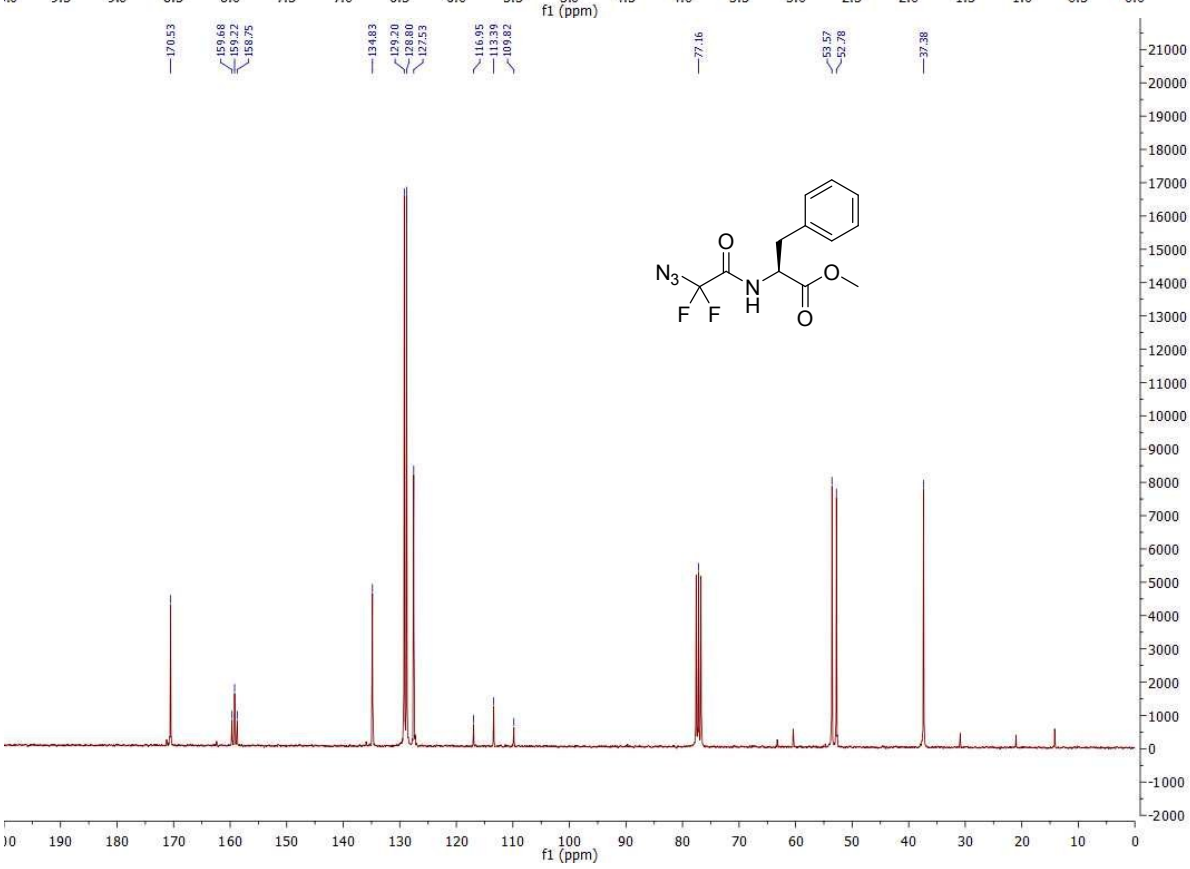

-82.76
-83.80
-83.87
-84.90
f1 (ppm)
2.00
f1 (ppm)

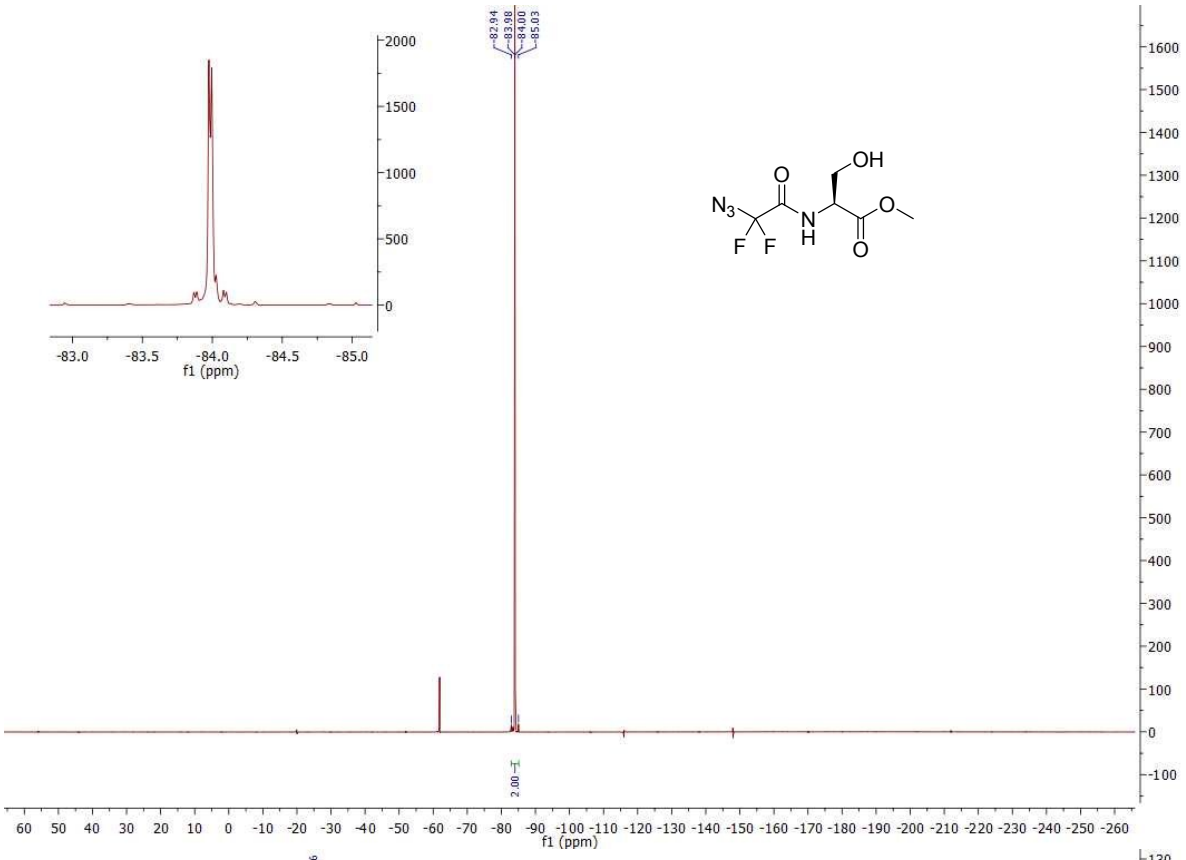

4.95
3.08
2.10
0.99
2.02
1.00
1.99
f1 (ppm)

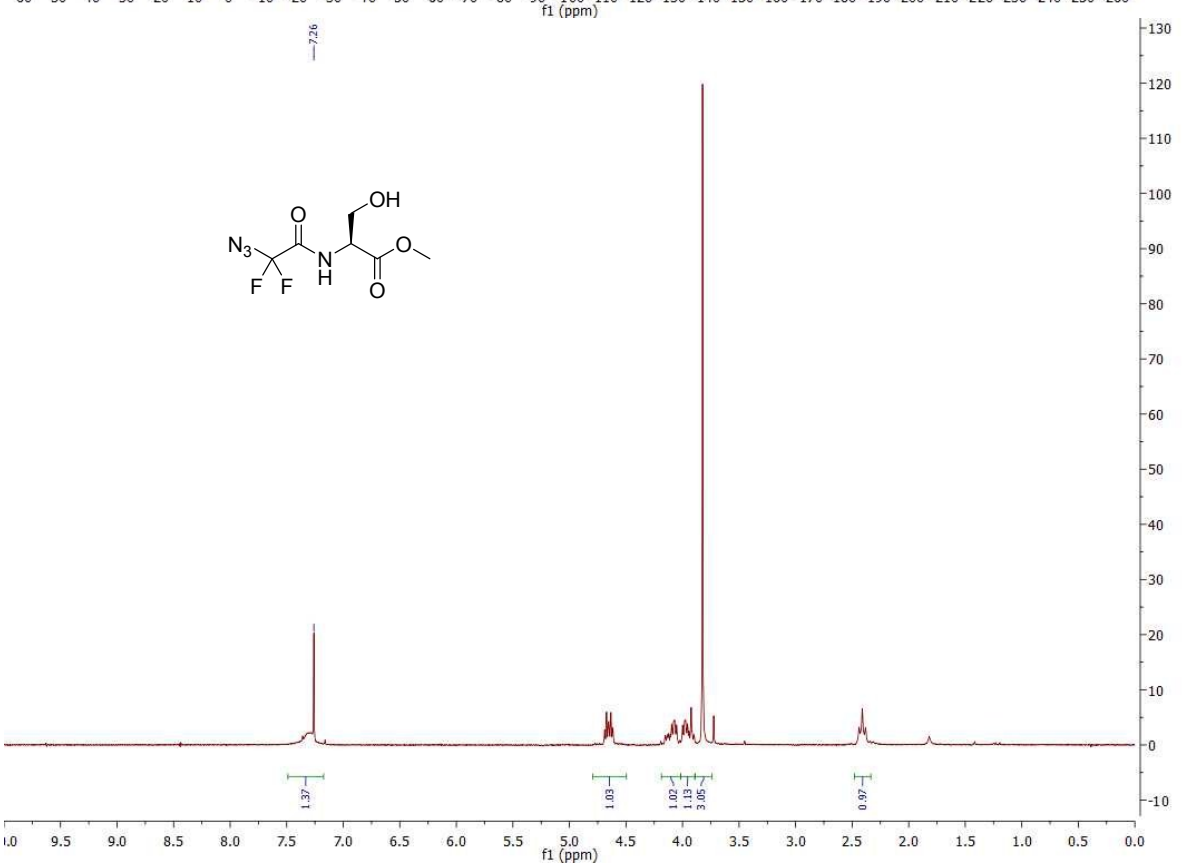

169.99
159.69
159.23
158.76
134.71
134.64
129.33
128.83
127.56
117.00
113.43
109.87
77.16
67.95
53.59
37.38
f1 (ppm)

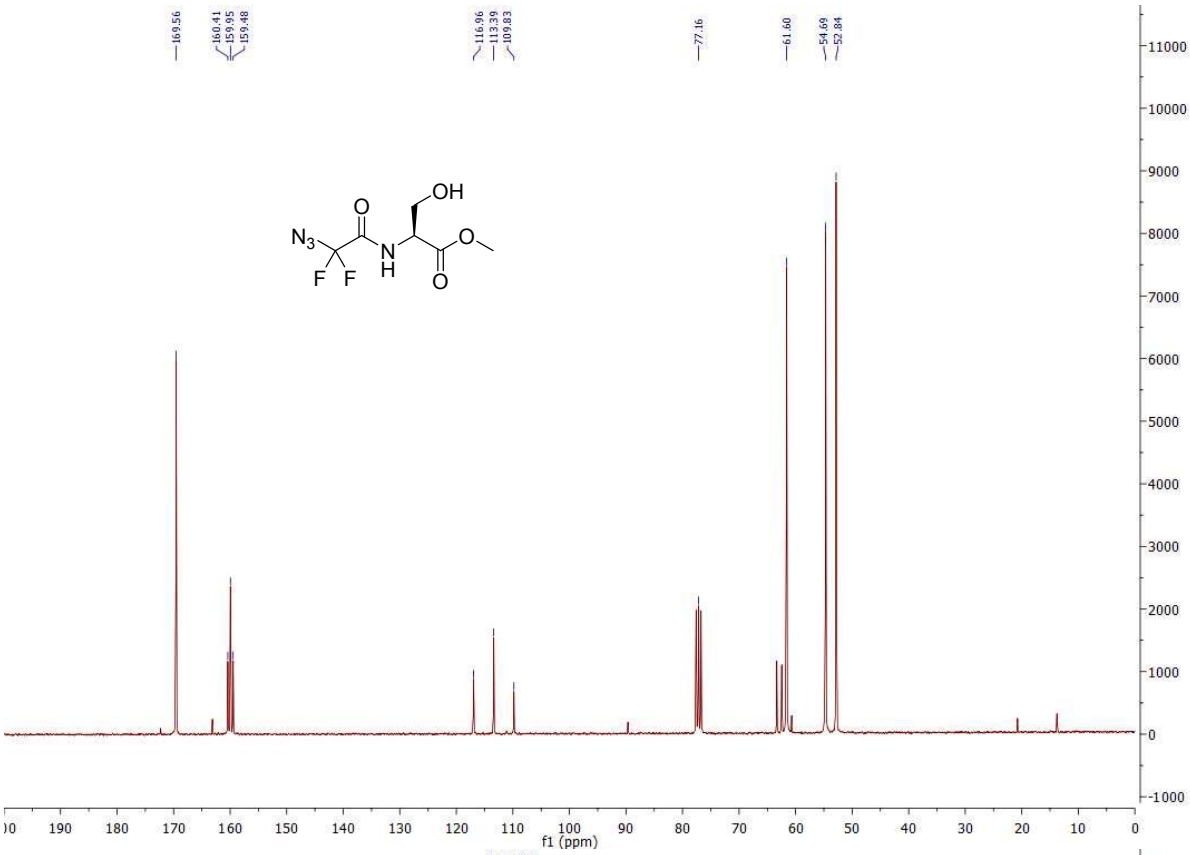

82.84
83.88
83.94
84.97
1.00
f1 (ppm)

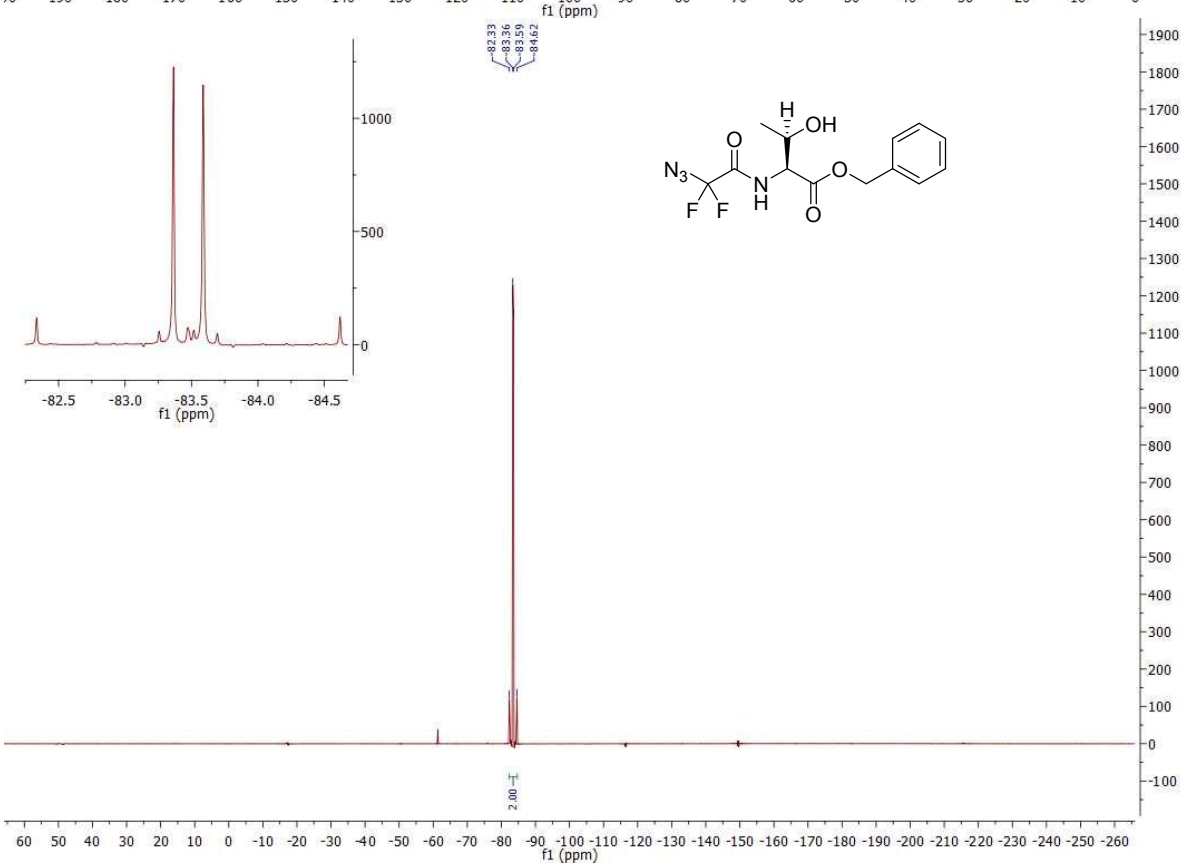

3.73
1.56
3.46
2.03
0.97
1.00
3.13
2.08
f1 (ppm)

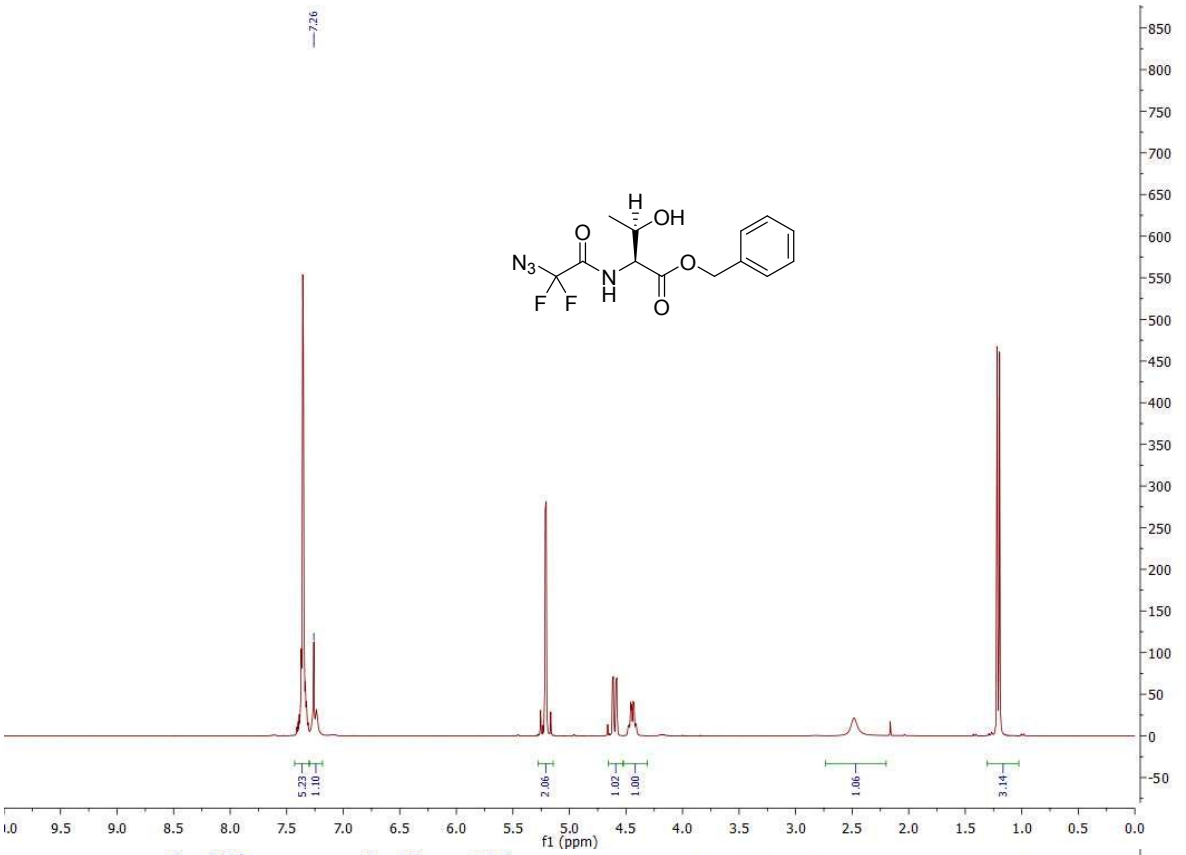

170.53
159.68
159.22
158.75
134.83
129.20
128.80
127.53
116.95
113.39
109.82
77.16
53.57
52.78
37.38
f1 (ppm)

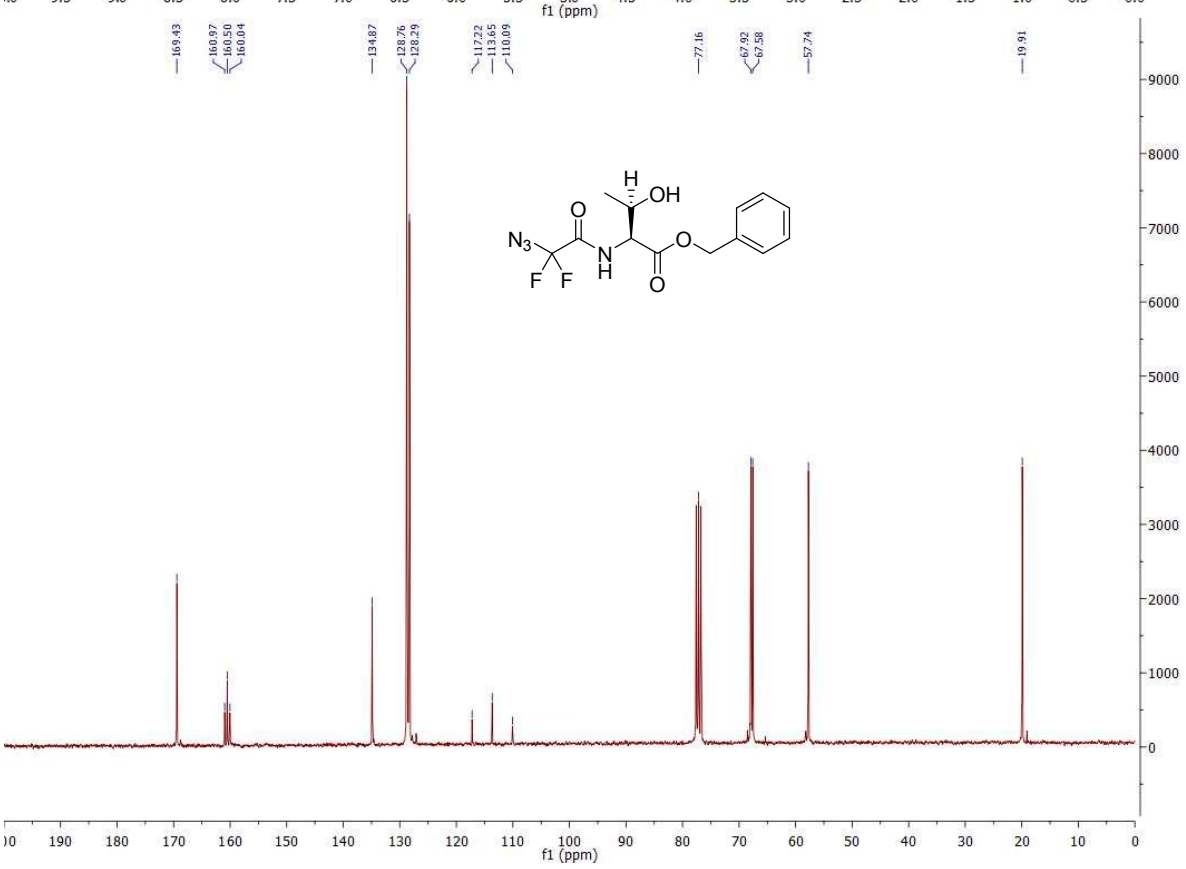

82.94
83.98
84.00
85.03
2.00
f1 (ppm)

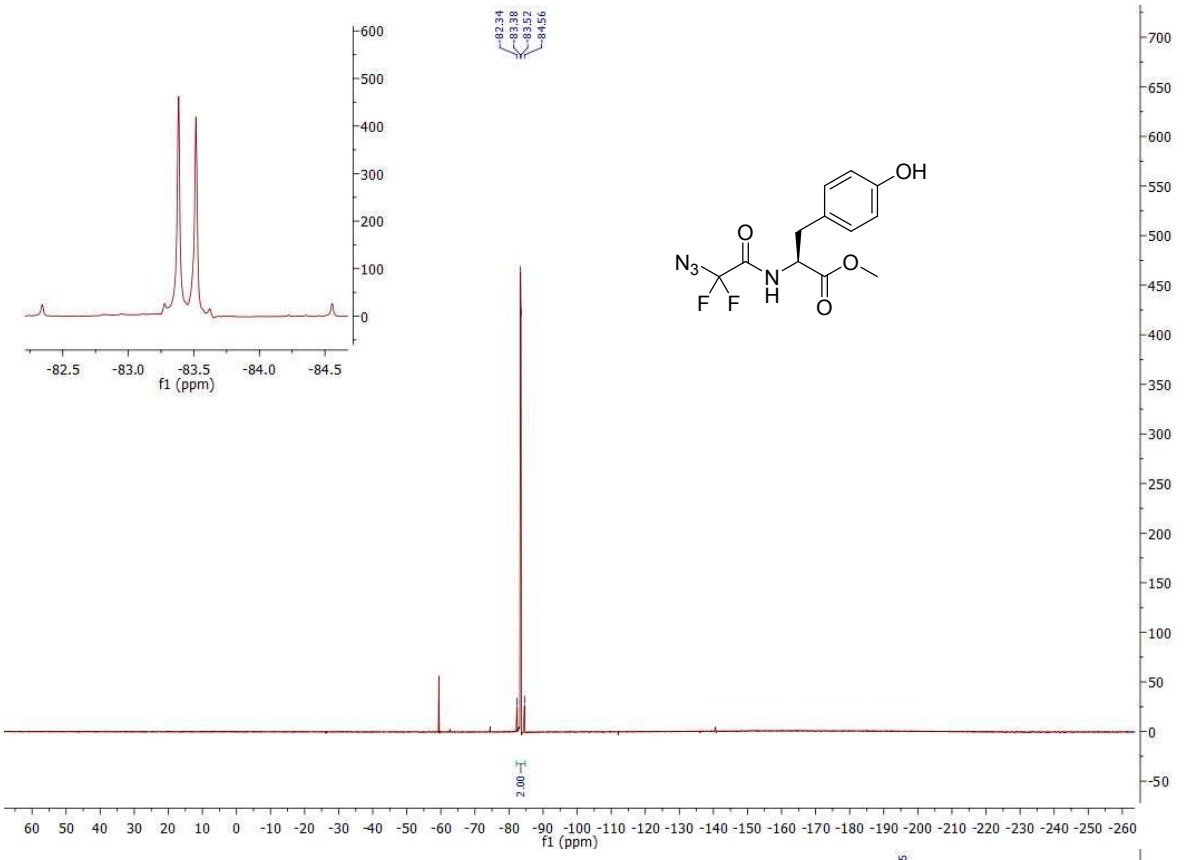

7.26
1.37
1.03
1.02
1.13
3.05
0.97
f1 (ppm)

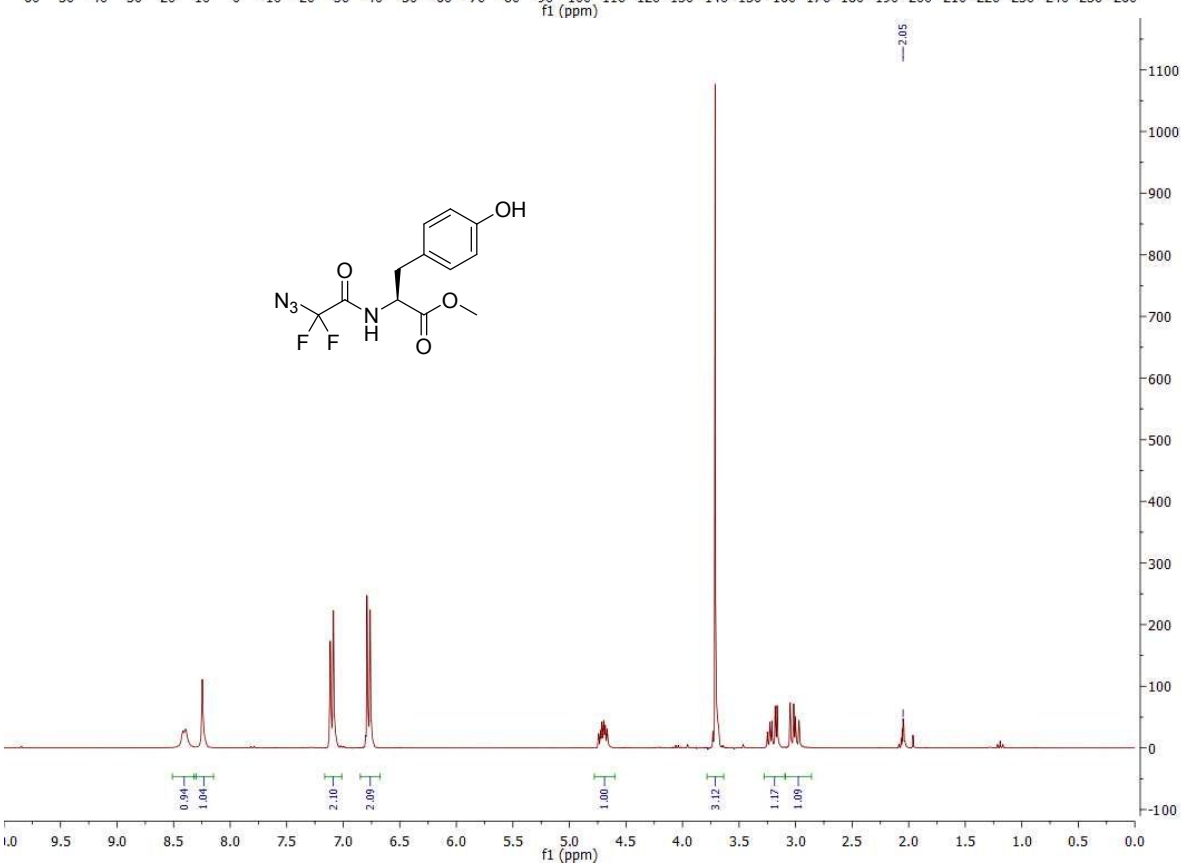

169.56
160.41
159.95
159.48
116.96
113.39
109.83
77.16
61.60
54.69
52.84
OH
O
N3
N
H
F F
O
O
f1 (ppm)

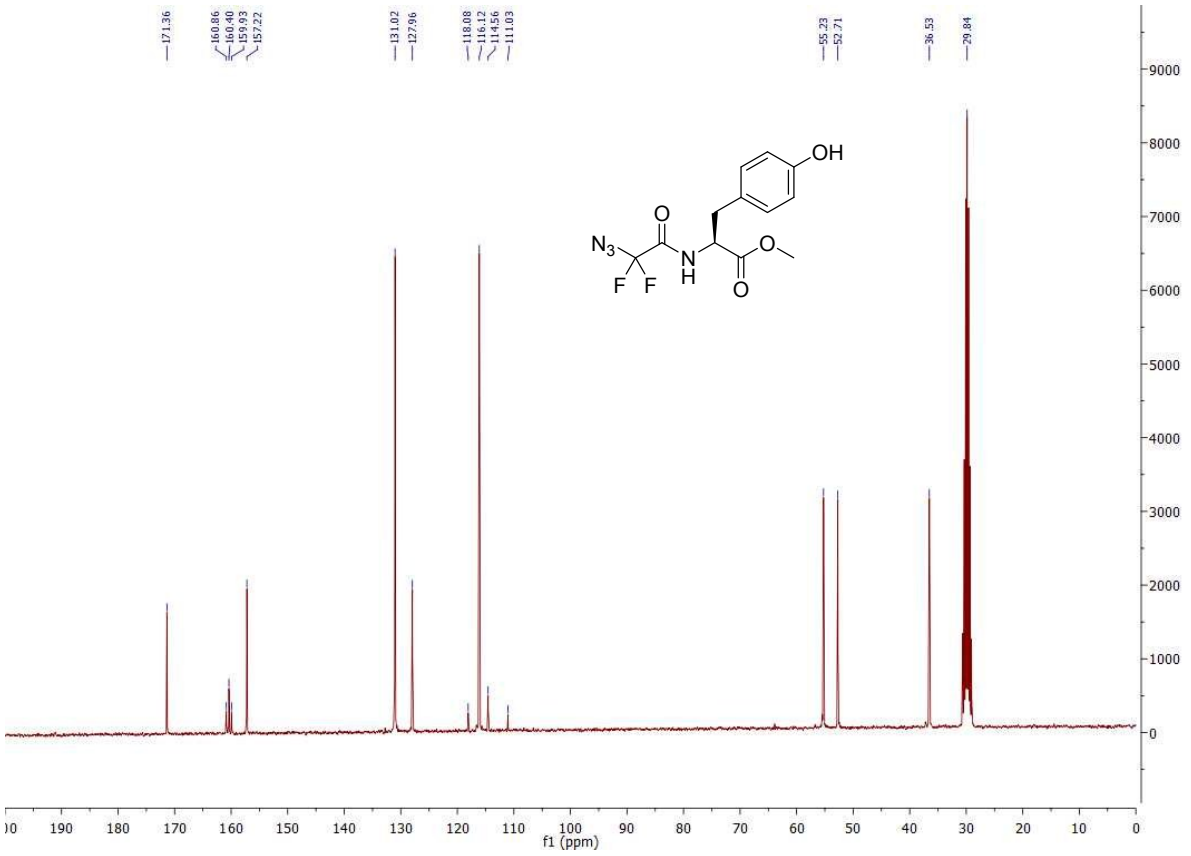

82.33
83.36
83.59
84.62
H
OH
O
N3
N
H
F F
O
O
f1 (ppm)
2.00
f1 (ppm)

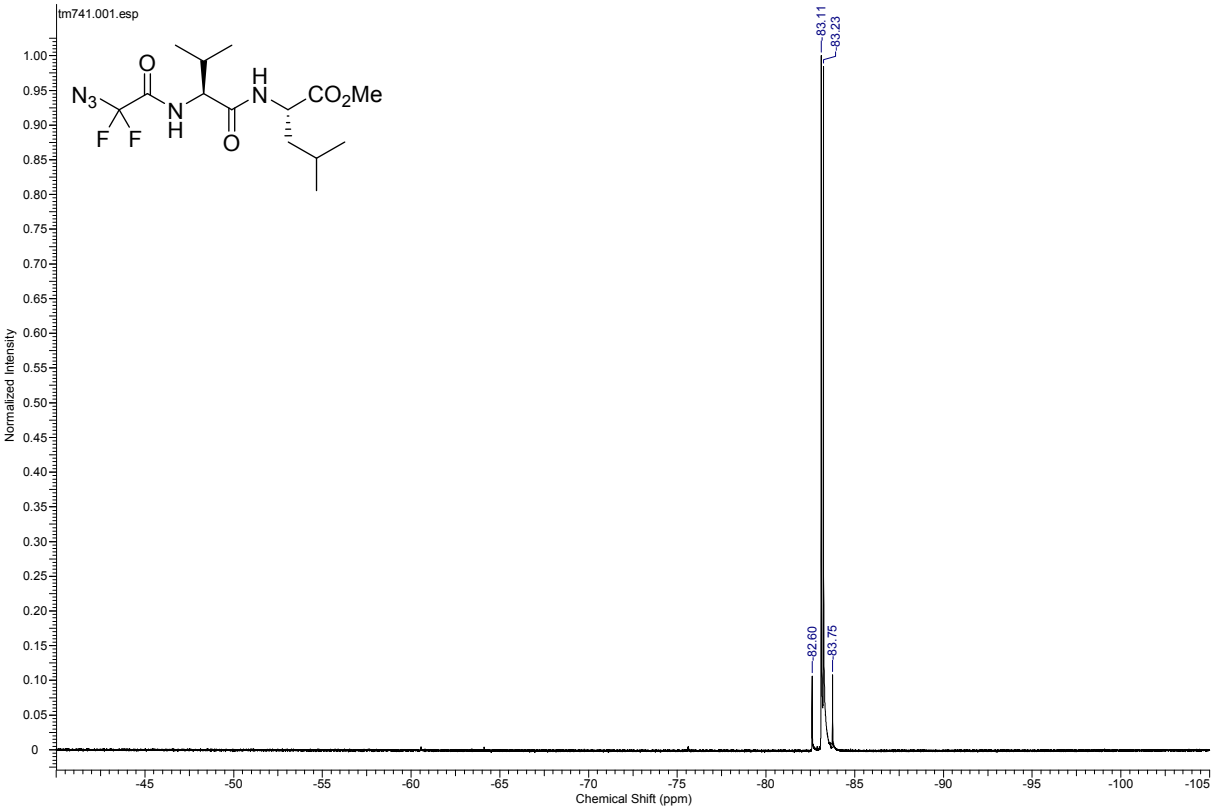

7.26
5.23
1.10
2.06
1.02
1.00
1.06
3.14
f1 (ppm)

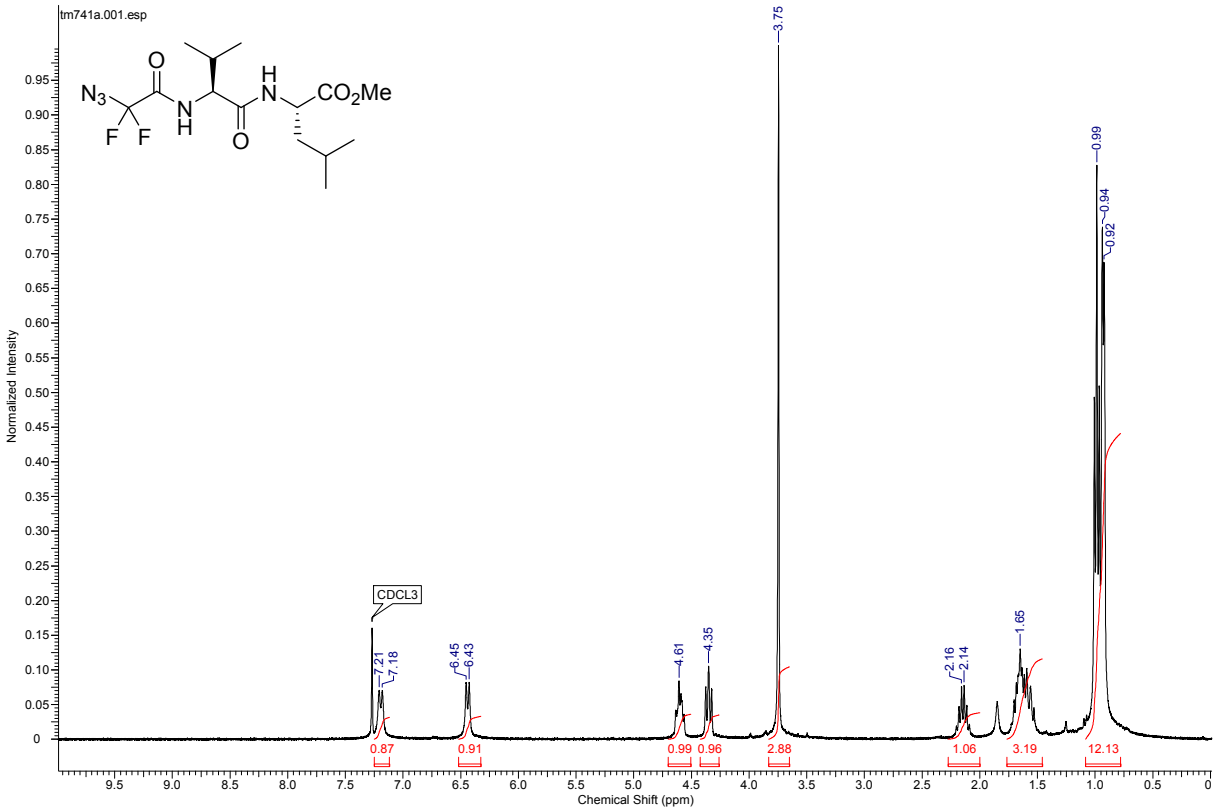

169.43
160.97
160.50
160.04
134.87
128.76
128.29
117.22
113.65
110.09
77.16
67.92
67.58
57.74
19.91
f1 (ppm)

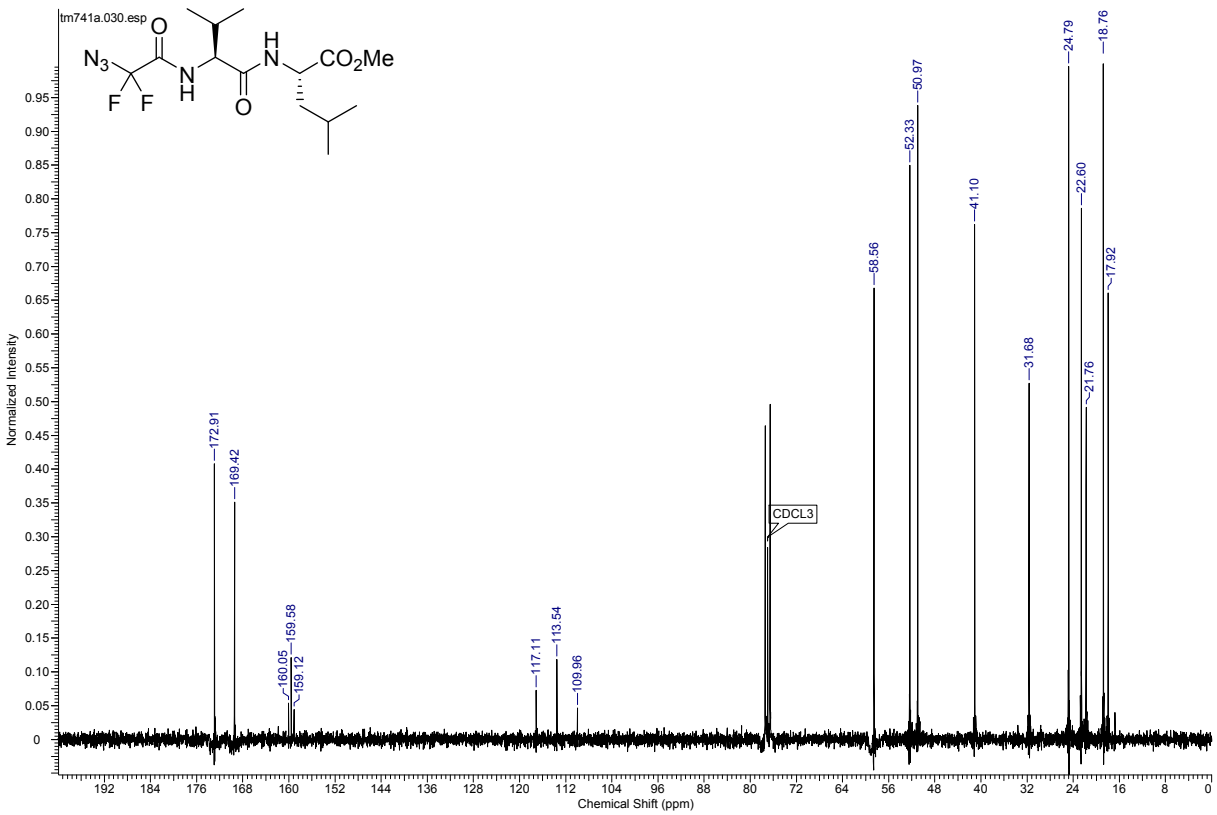

-82.34
-83.38
-83.52
-84.56
f1 (ppm)
OH
N3
F F
O
N
H
O
O
2.00
f1 (ppm)

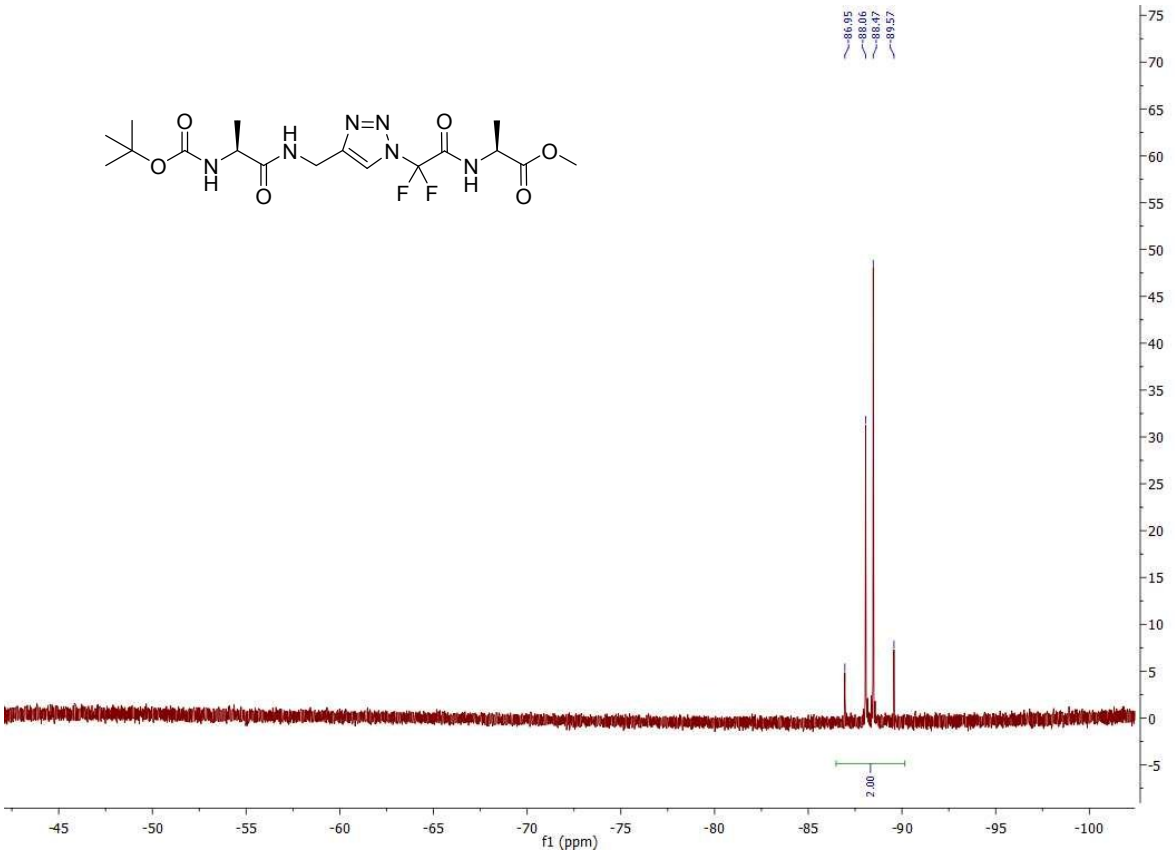

2.05
OH
N3
F F
O
N
H
O
O
0.94
1.04
2.10
2.09
1.00
3.12
1.17
1.09
f1 (ppm)

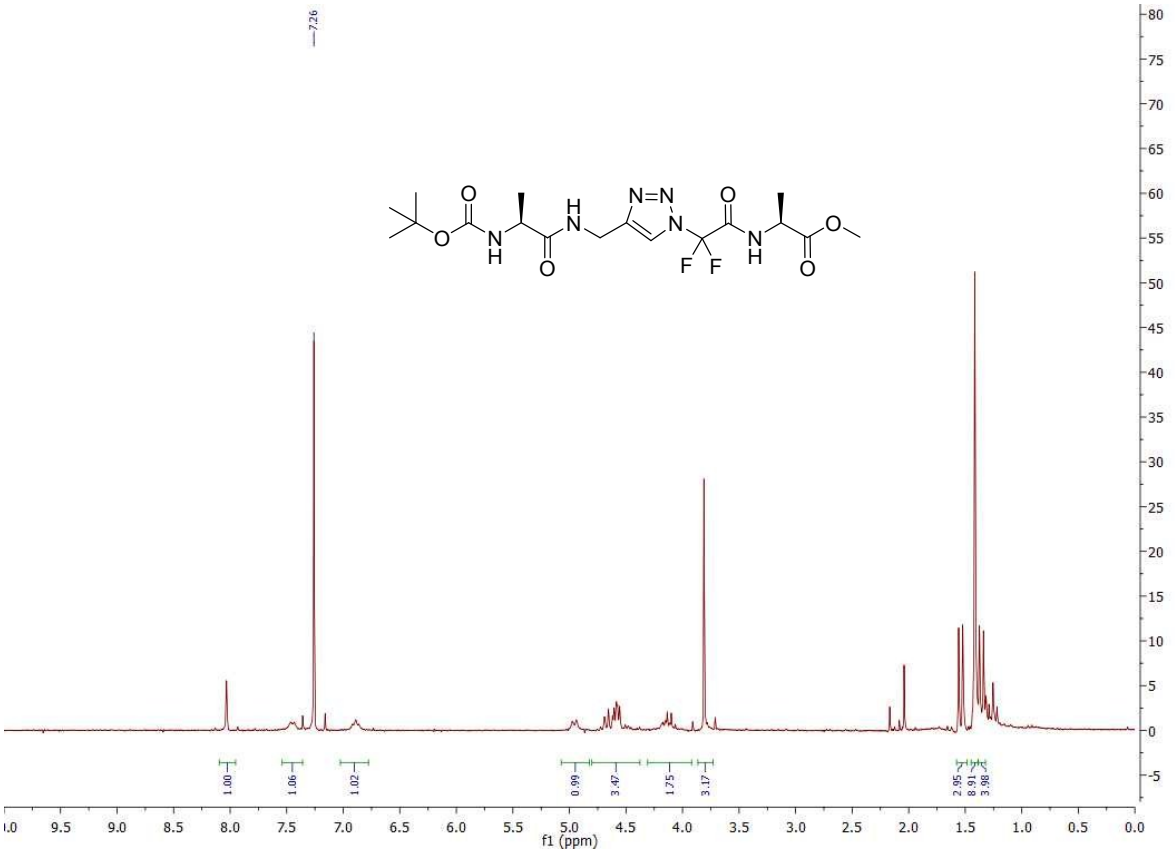

171.36
160.86
160.40
159.93
157.22
131.02
127.96
118.08
116.12
114.56
111.03
55.23
52.71
36.53
29.84
OH
O
N3
N
H
O
F F
O
f1 (ppm)

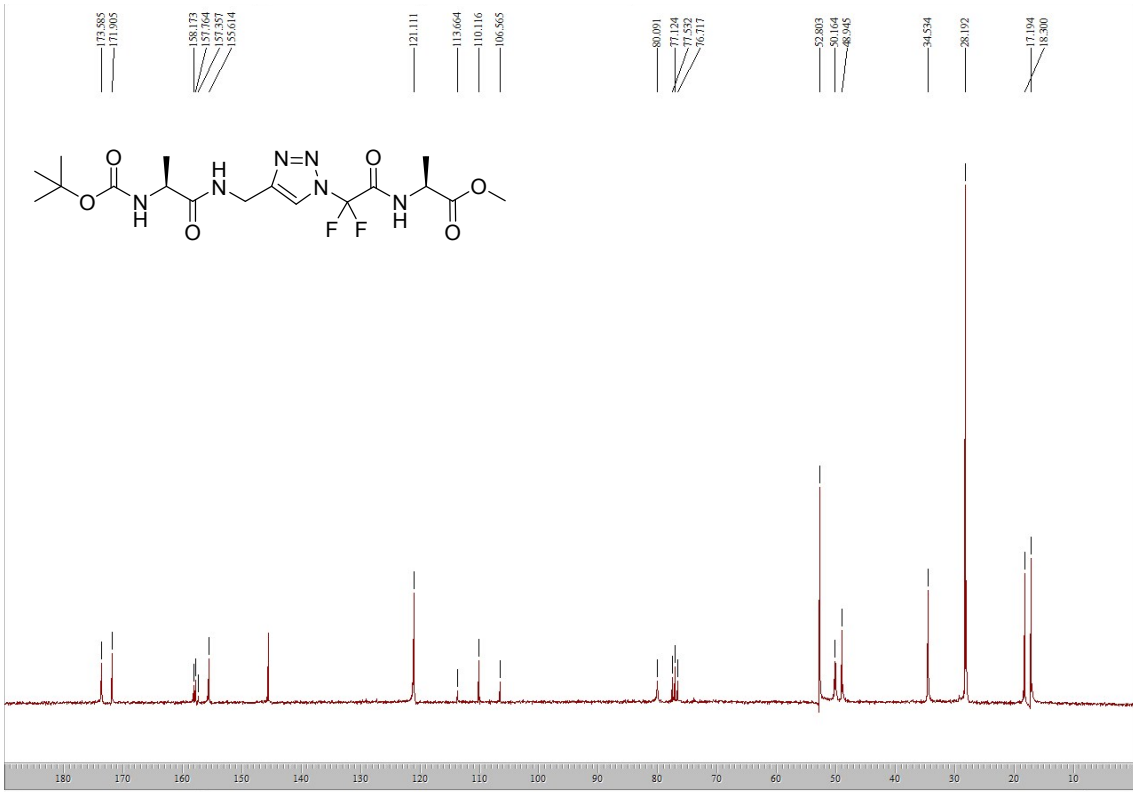

tm741.001.esp
O
N3
N
H
F F
H
N
CO2Me
O
83.11
83.23
82.60
83.75
Normalized Intensity
Chemical Shift (ppm)

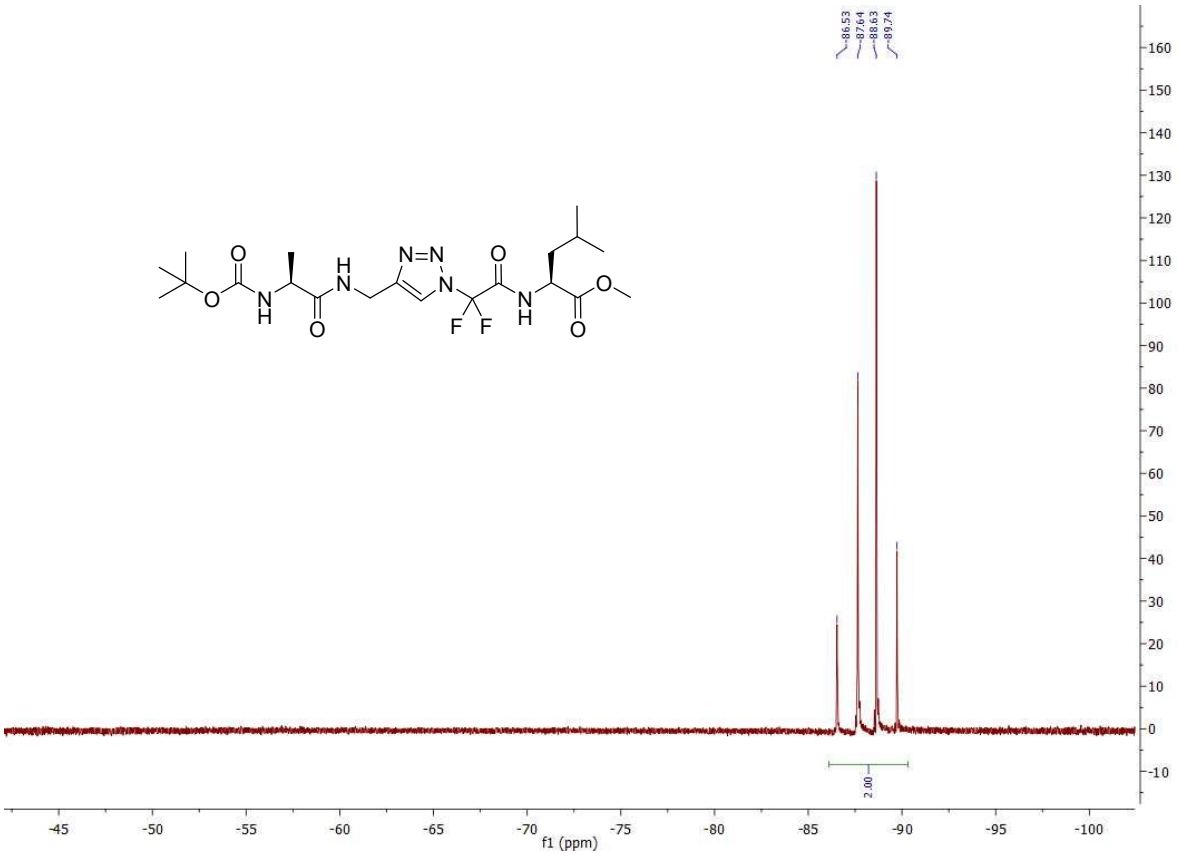

tm741a.001.esp
Normalized Intensity
Chemical Shift (ppm)
CDCL3
7.21
7.18
6.45
6.43
4.61
4.35
3.75
2.16
2.14
1.65
0.99
0.94
0.92
0.87
0.91
0.99
0.96
2.88
1.06
3.19
12.13

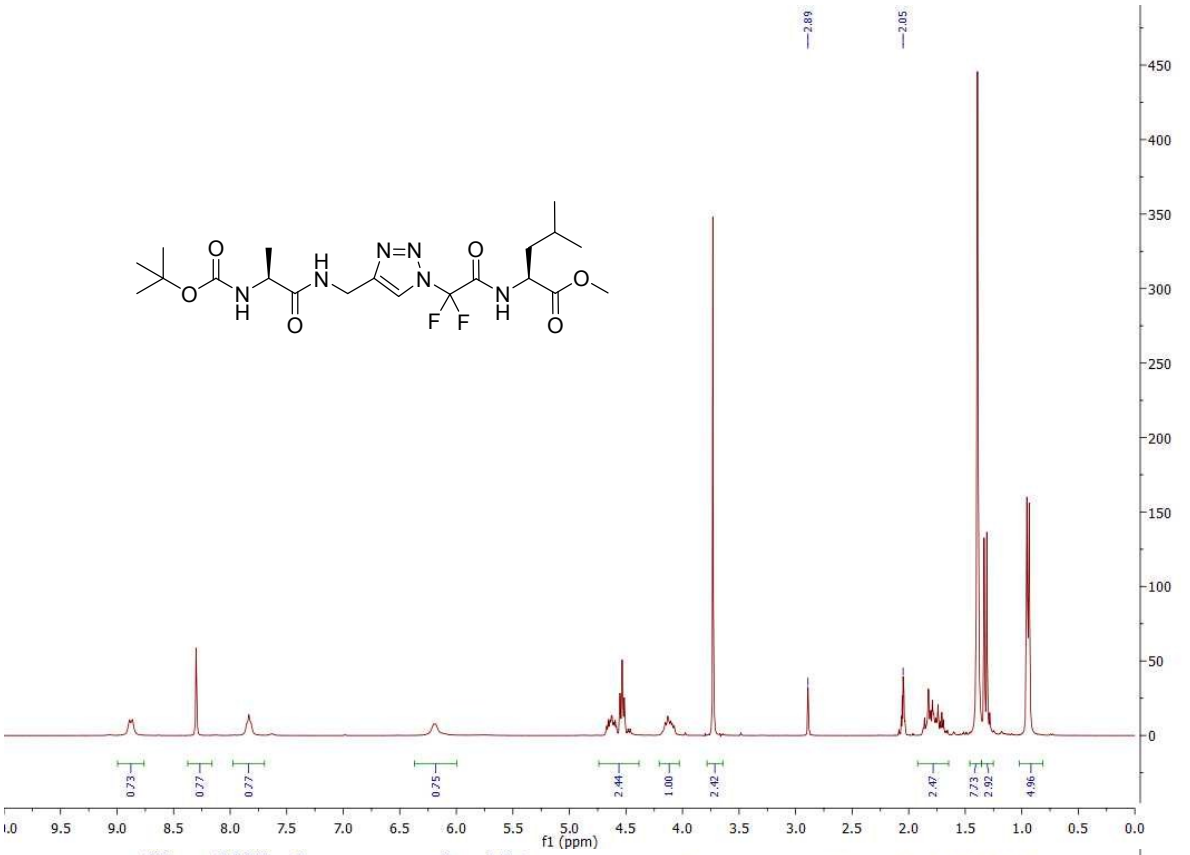

tm741a.030.esp
Normalized Intensity
Chemical Shift (ppm)
CDCL3
172.91
169.42
160.05
159.58
159.12
117.11
113.54
109.96
58.56
52.33
50.97
41.10
31.68
24.79
22.60
21.76
18.76
17.92

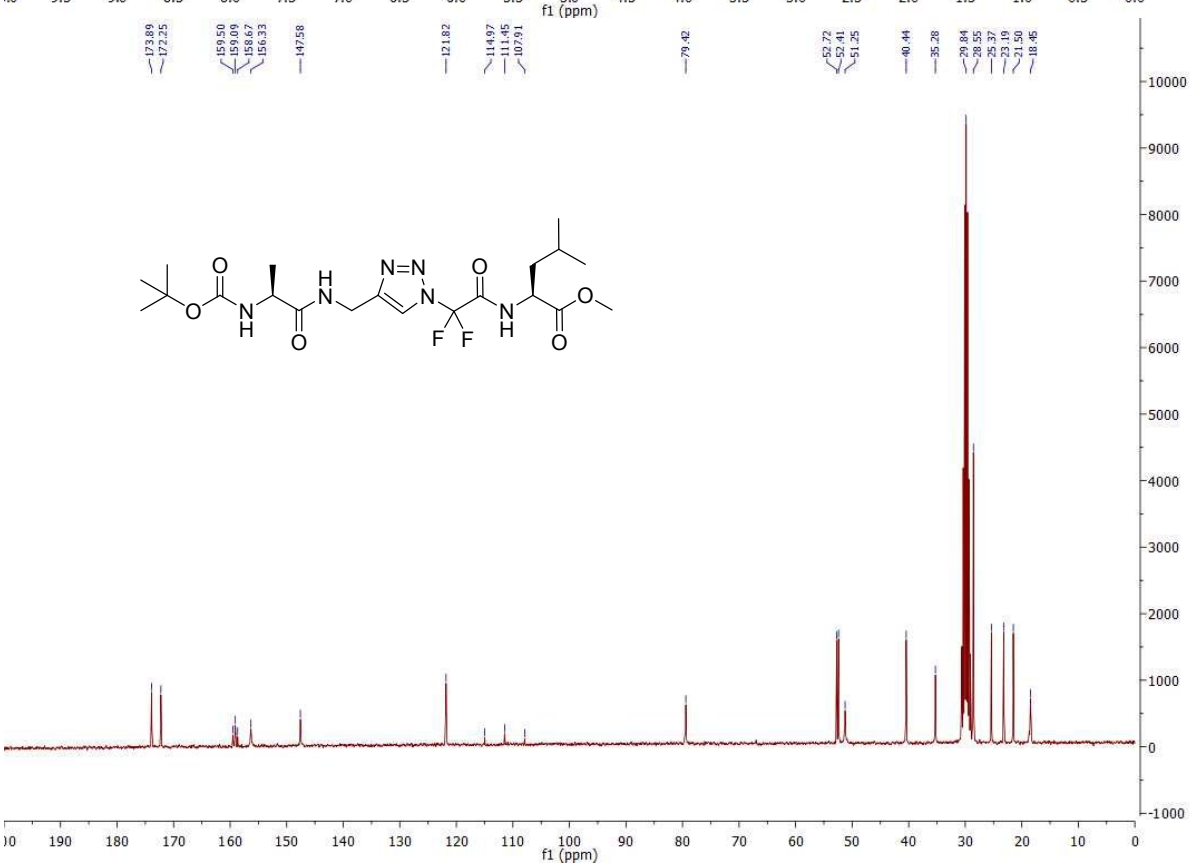

-86.95
-88.06
-88.47
-89.57
2.00
f1 (ppm)

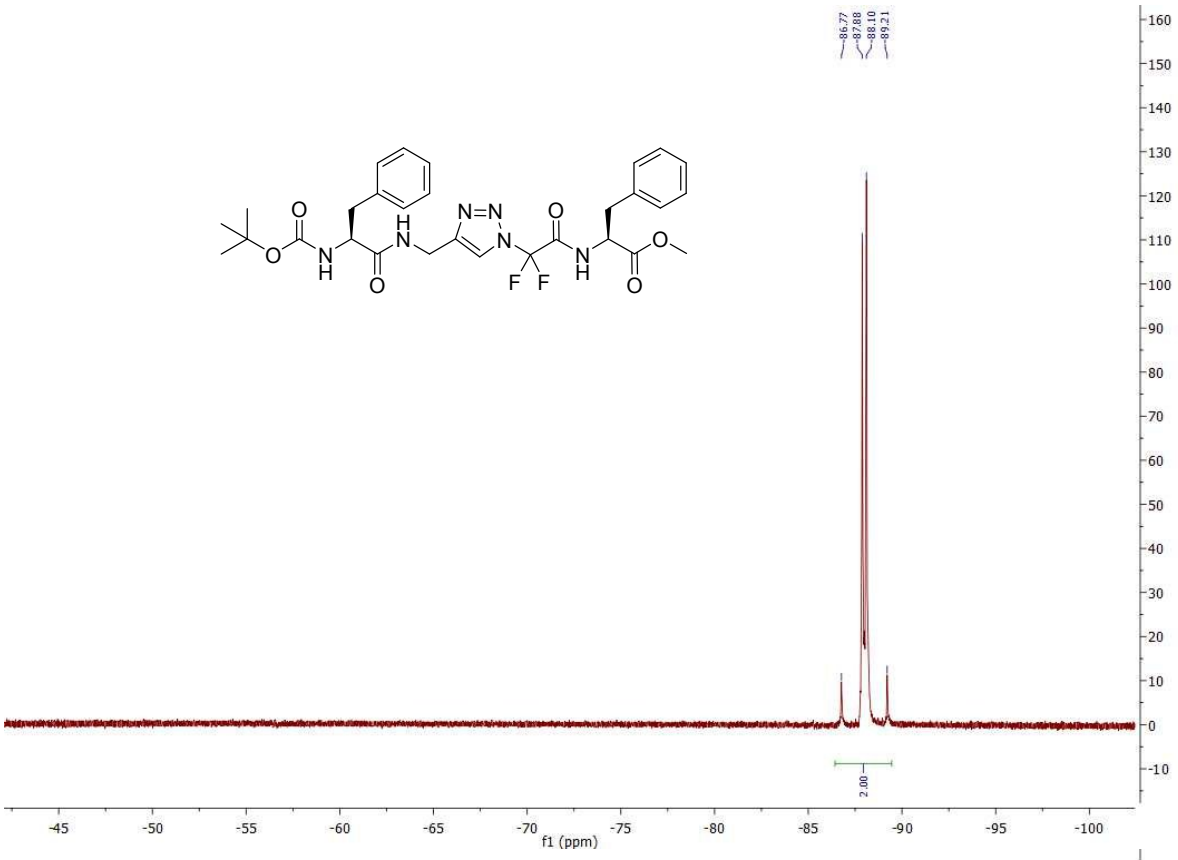

7.26
1.00
1.06
1.02
0.99
3.47
1.75
3.17
2.95
8.91
3.98
f1 (ppm)

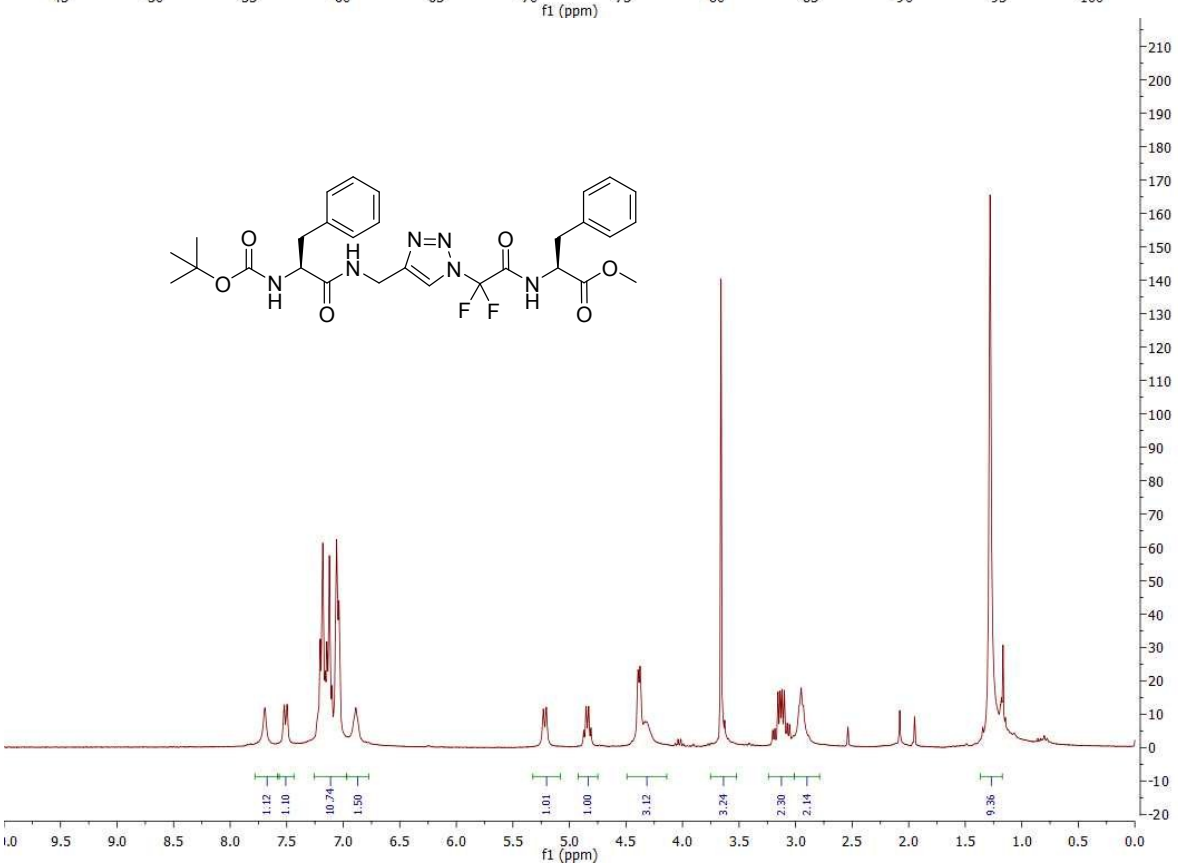

173.585
171.905
158.173
157.864
157.557
155.614
121.111
113.664
110.116
106.565
80.091
77.124
77.532
76.717
52.803
50.164
46.945
34.534
28.192
17.194
18.300

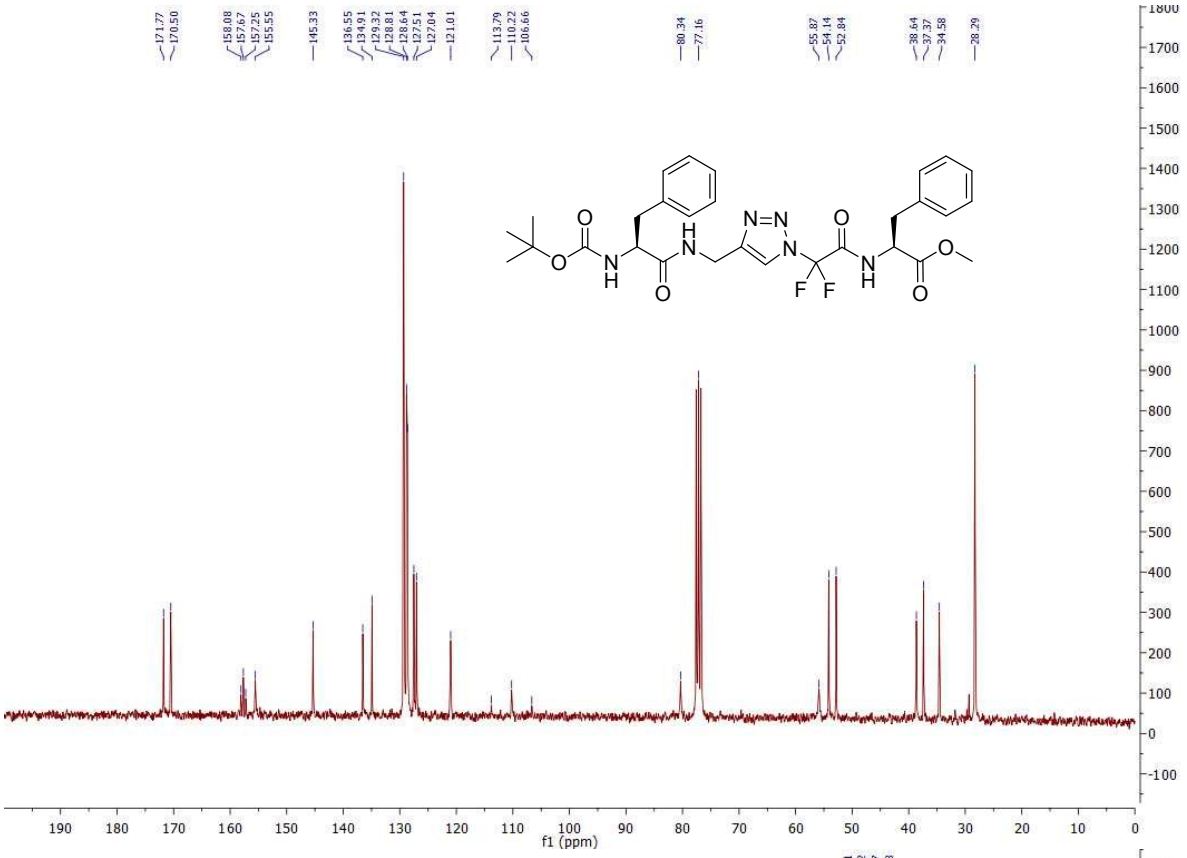

-86.53
-87.64
-88.63
-89.74
2.00
f1 (ppm)

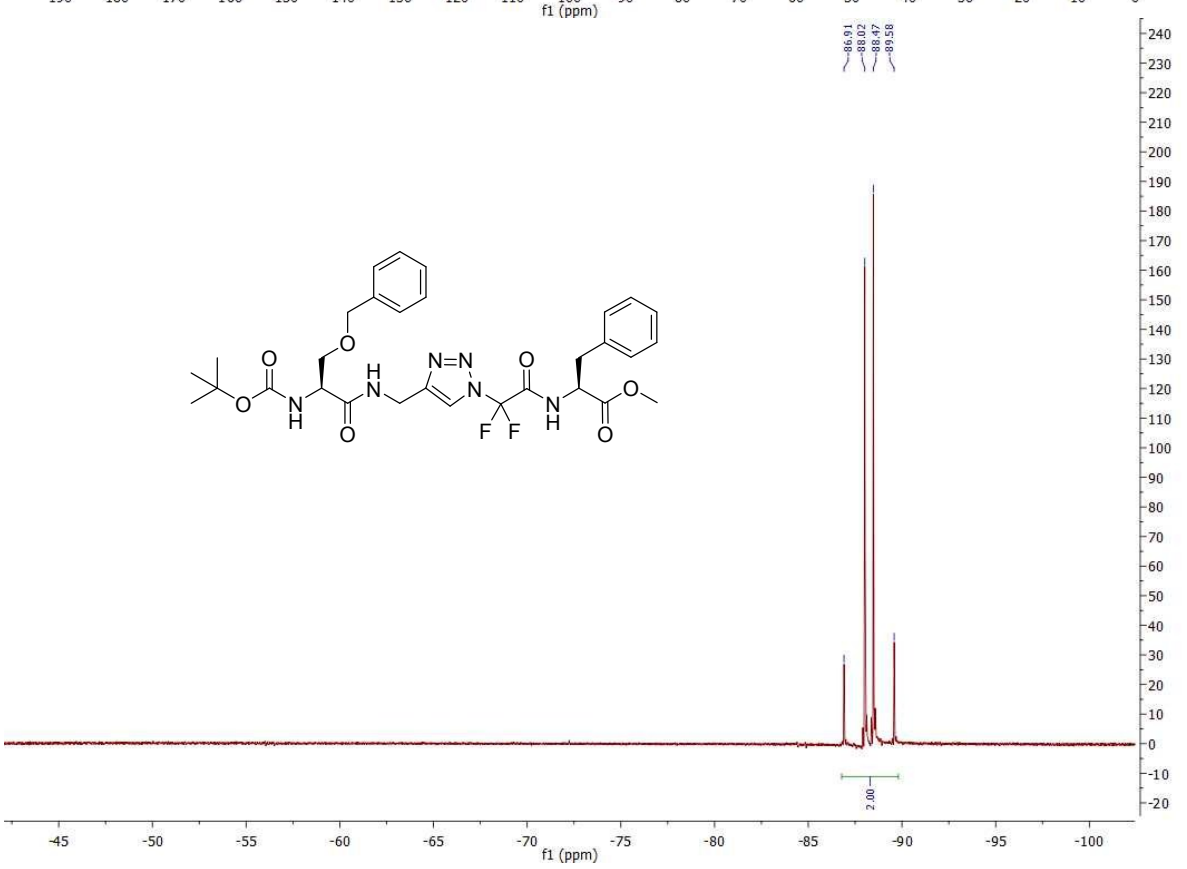

2.89
2.05
0.73
0.77
0.77
0.75
2.44
1.00
2.42
2.47
7.73
2.92
4.96
f1 (ppm)

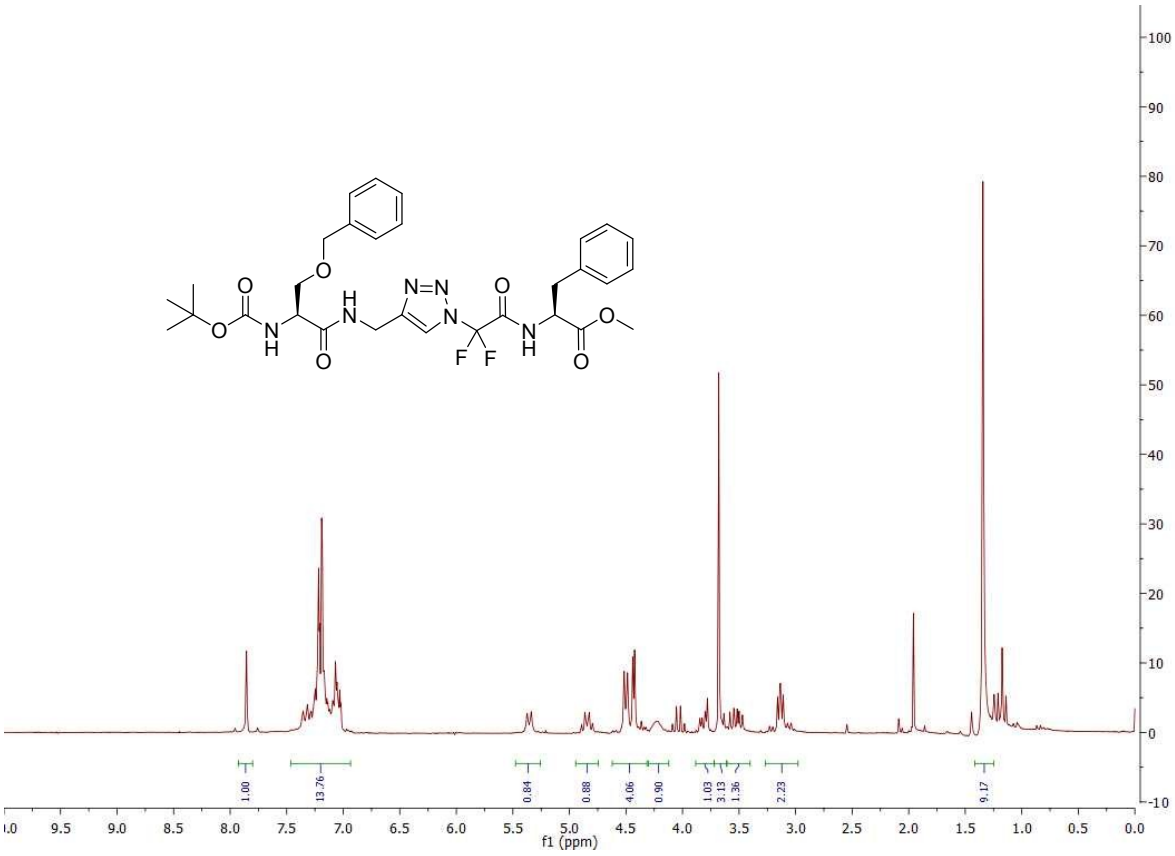

173.89
172.25
159.50
159.09
158.67
156.33
147.58
121.82
114.97
111.45
107.91
79.42
52.72
52.41
51.25
40.44
35.28
29.84
28.55
25.37
23.19
21.50
18.45
f1 (ppm)

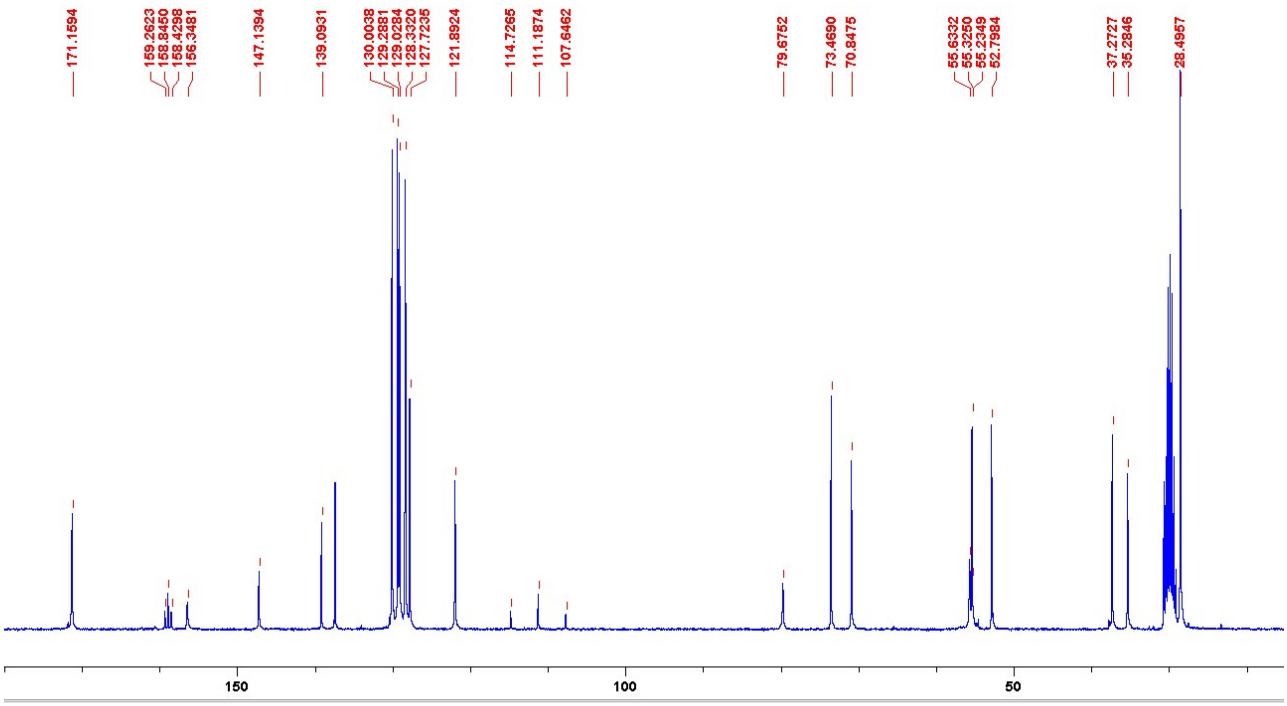

-86.77
-87.88
-88.10
-89.21
2.00
f1 (ppm)

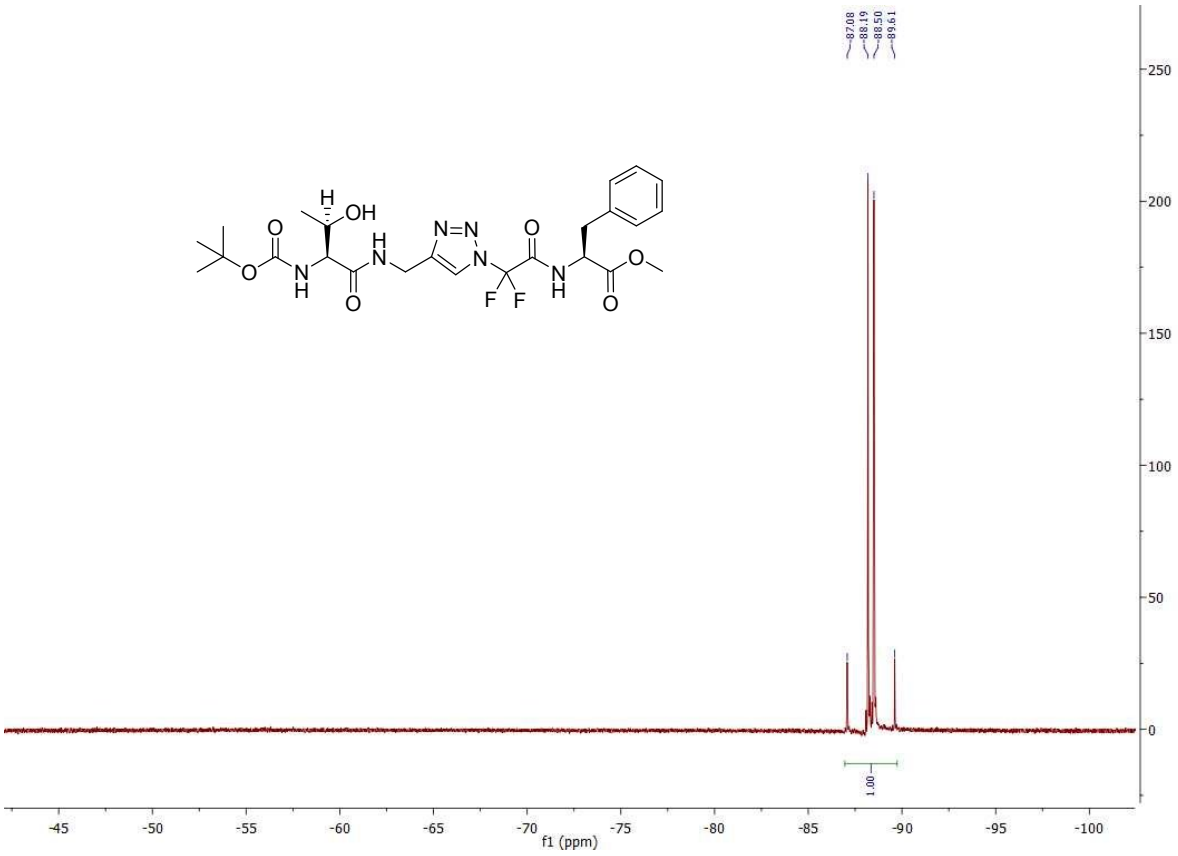

1.12
1.10
10.74
1.50
1.01
1.00
3.12
3.24
2.30
2.14
9.36
f1 (ppm)

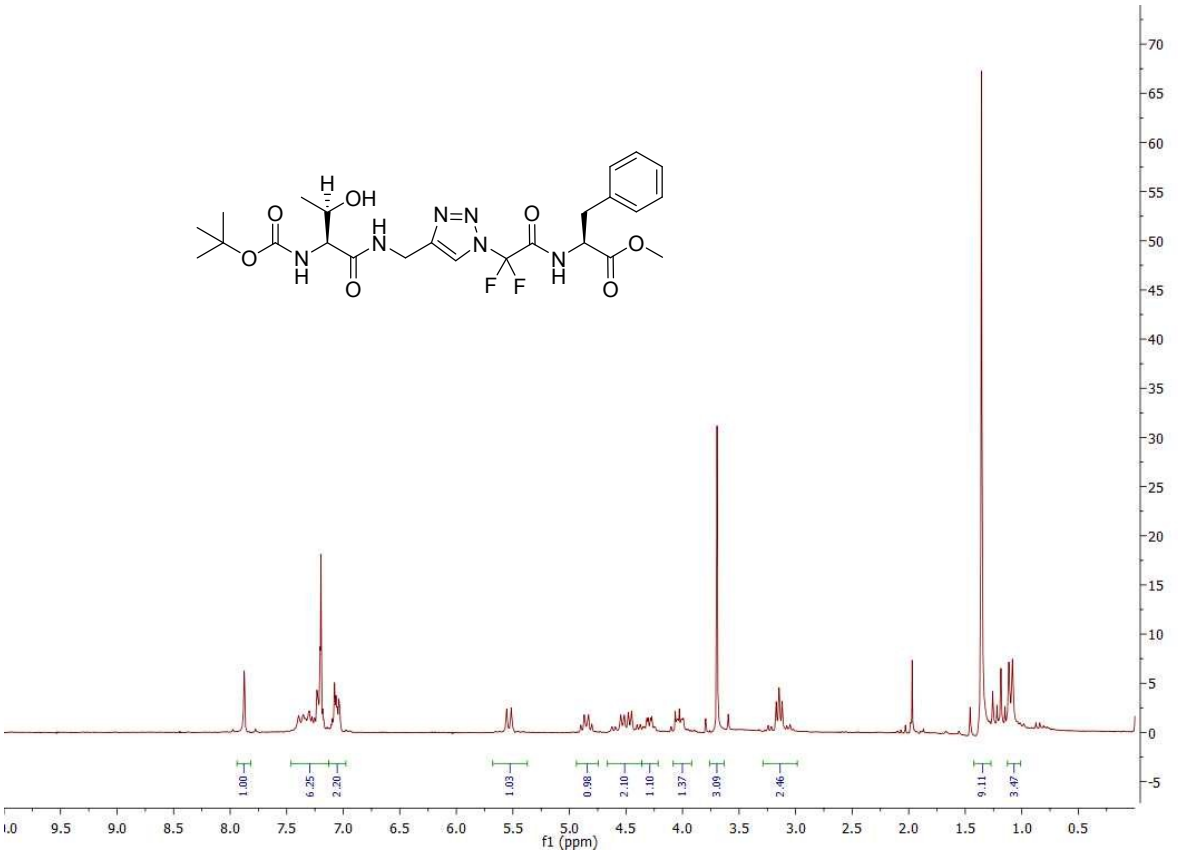

171.77
170.50
158.08
157.67
157.25
155.55
145.33
136.55
134.91
129.32
128.81
128.64
127.51
127.04
121.01
113.79
110.22
106.66
80.34
77.16
55.87
54.14
52.84
38.64
37.37
34.58
28.29
f1 (ppm)

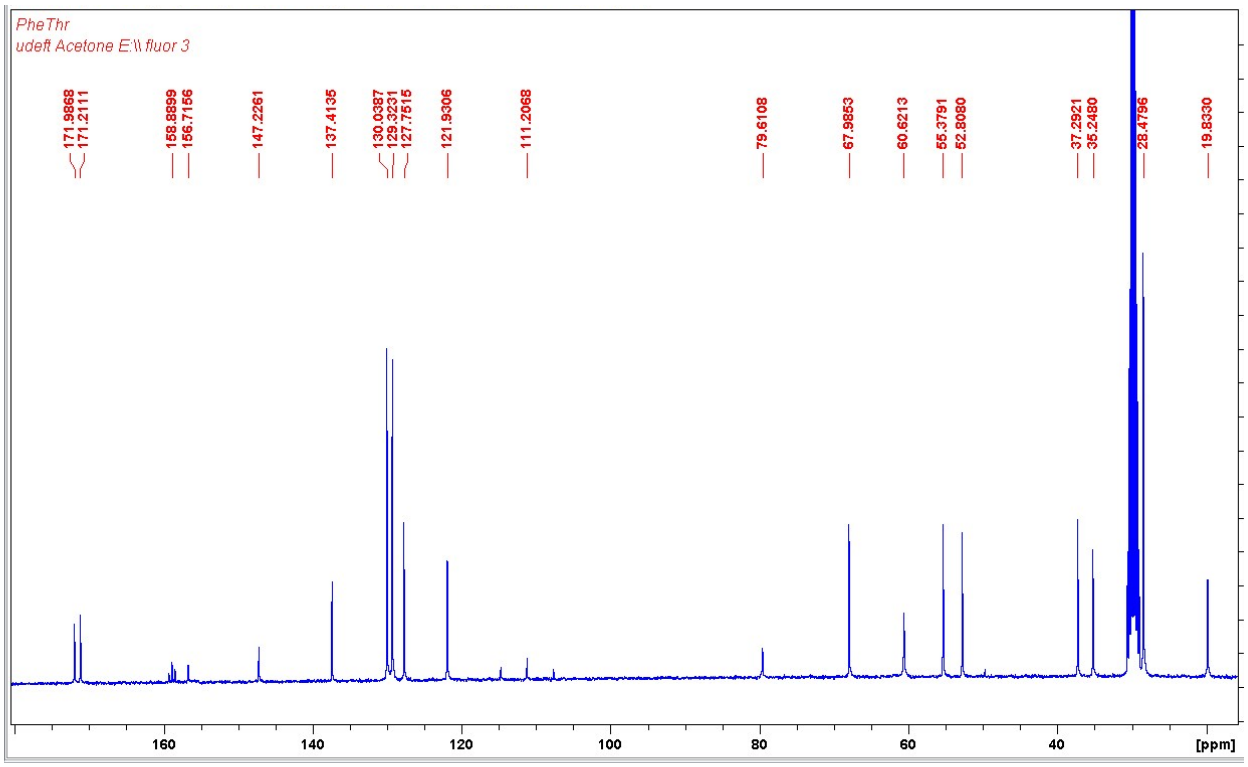

86.91
88.02
88.47
89.58
2.00
f1 (ppm)

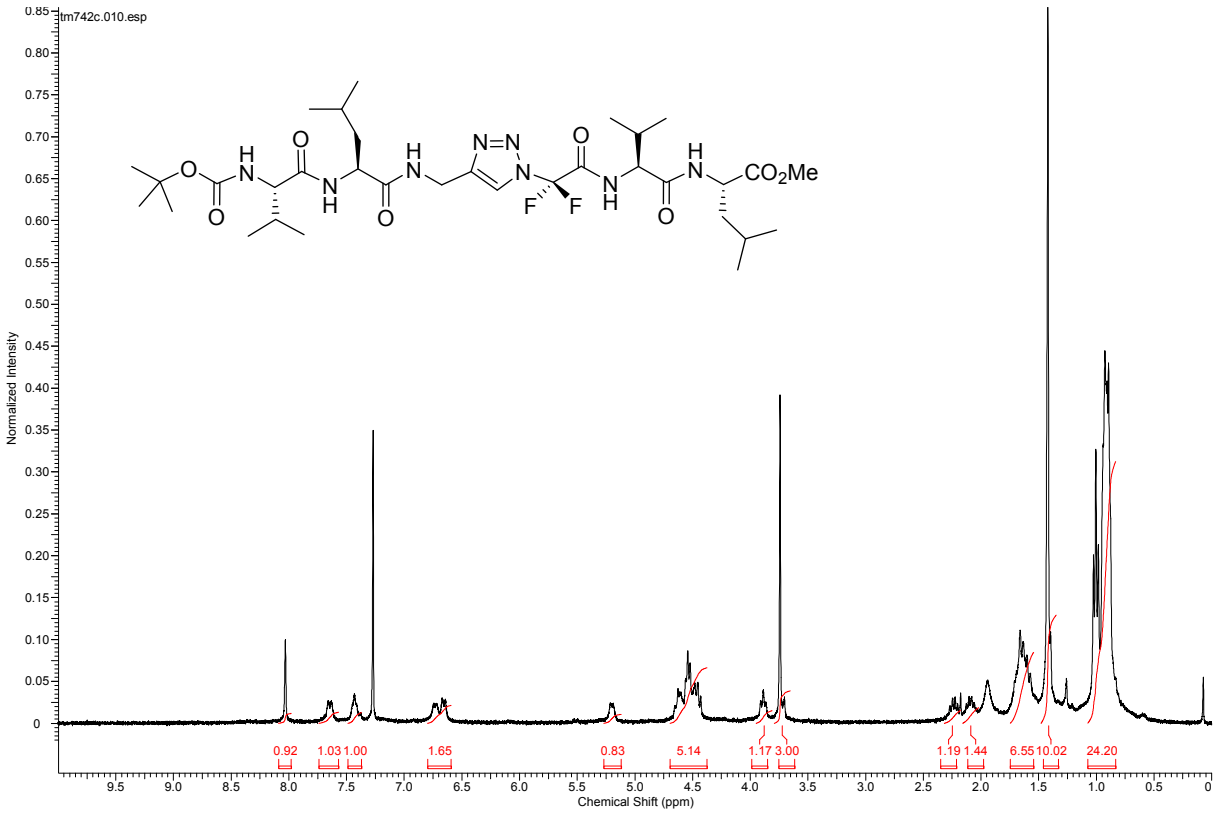

1.00
13.76
0.84
0.88
4.06
0.90
1.03
3.13
1.36
2.23
9.17
f1 (ppm)

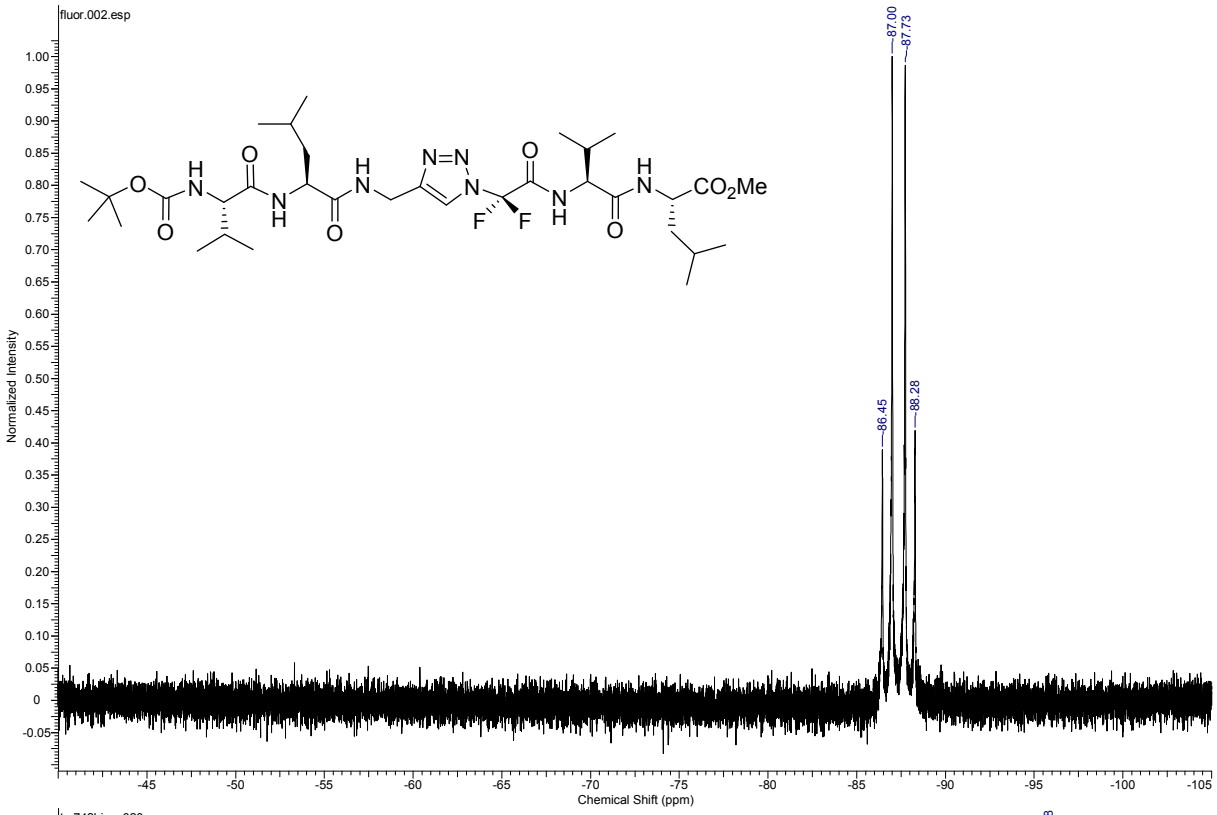

171.1594
159.2623
158.8450
158.4298
158.3481
147.1394
139.0931
130.0038
129.2881
129.0284
128.3320
127.7235
121.8924
114.7265
111.1874
107.6462
79.6752
73.4690
70.8475
55.6332
55.3250
55.2349
52.7984
37.2727
35.2846
28.4957

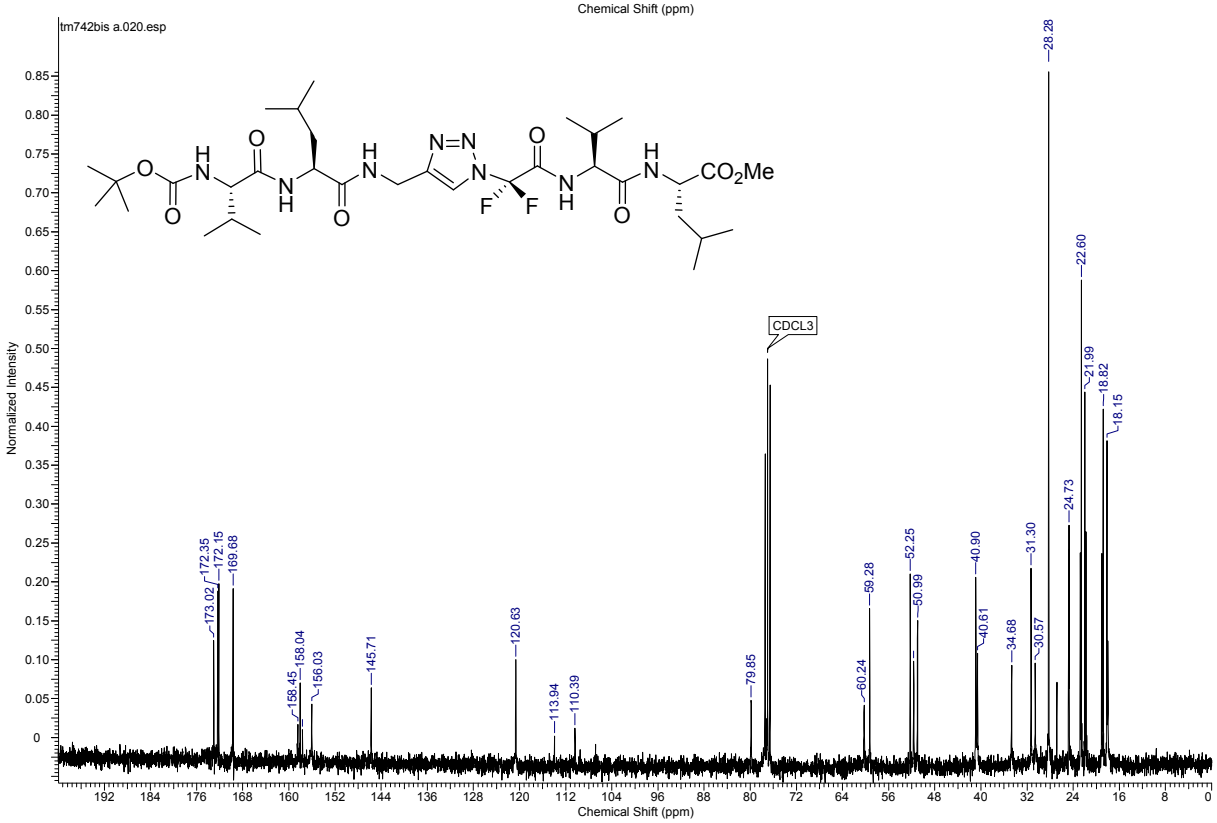

-87.08
-88.19
-88.50
-89.61
1.00
f1 (ppm)


1.00
6.25
2.20
1.03
0.98
2.10
1.10
1.37
3.09
2.46
9.11
3.47
f1 (ppm)


PheThr
udeft Acetone E:\\ fluor 3
171.9868
171.2111
158.8899
156.7156
147.2261
137.4135
130.0387
129.3231
127.7515
121.9306
111.2068
79.6108
67.9853
60.6213
55.3791
52.8080
37.2921
35.2480
28.4796
19.8330
160
140
120
100
80
60
40
[ppm]


tm742c.010.esp
Normalized Intensity
Chemical Shift (ppm)
0.92
1.03
1.00
1.65
0.83
5.14
1.17
3.00
1.19
1.44
6.55
10.02
24.20
CO2Me


fluor.002.esp
Normalized Intensity
Chemical Shift (ppm)
87.00
87.73
86.45
88.28


tm742bis a.020.esp
Normalized Intensity
Chemical Shift (ppm)
CDCL3
28.28
22.60
21.99
18.82
18.15
24.73
31.30
40.90
52.25
50.99
59.28
60.24
79.85
120.63
113.94
110.39
145.71
158.45
158.04
156.03
172.35
172.15
169.68
173.02
40.61
34.68
30.57