Supplementary Information

A Straightforward Click-Approach towards Pretubulysin-Analogues

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Experimental

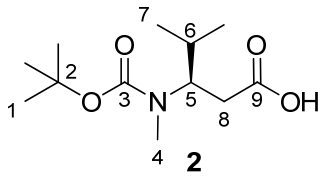
General remarks

All reactions were carried out in oven-dried glassware (70 °C) under an atmosphere of nitrogen. Dried solvents were distilled before use: THF was distilled from $LiAlH_4$, DCM from CaH_2, dry DMF and MeOH was purchased from Sigma-Aldrich. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel 60, 0.063–0.2 mm). Mixtures of ethyl acetate/petroleum ether and DCM/MeOH were generally used as eluents. Analytical TLC was performed on precoated silica gel plates (Macherey-Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV-light, $KMnO_4$ solution or Ninhydrine solution. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$ or MeOH-d^4. Chemical shifts are reported in ppm (δ) with respect to TMS, $CHCl_3$ and MeOH-d^4 was used as the internal

standard. Optical rotation measurements were performed on a Perkin-Elmer 341 polarimeter, with concentrations given in g/100 mL. Melting points were determined with a MEL-TEMP II apparatus and are uncorrected. Mass spectra were recorded with a Finnigan MAT 95 spectrometer using the CI or EI technique. Elemental analyses were performed at the Saarland University.

(*R*)-3-(*tert*-Butoxycarbonyl(methyl)amino)-4-methylpentanoic acid (2)

Boc-β-L-Valin **1**[1] (440 mg, 1.90 mmol) and methyl iodide (900 µl, 14.5 mmol) were dissolved in dry THF (20 mL) and the solution was cooled to 0 °C. NaH (230 mg, 5.75 mmol, 60 % in oil) was added carefully and the suspension was stirred at room temperature for 24 h. Ethyl acetate (10 mL) and water (10 mL) were added and the solvents were removed under reduced pressure. The residue was partitioned between ether and water (100 mL). The ether layer was washed with saturated aqueous $NaHCO_3$ (2 x 50 mL), and the combined aqueous extracts were acidified to pH 1 with aqueous HCl (1 M). The product was extracted with ethyl acetate (3 x 50 mL). The extract was washed with water, 5% aqueous sodium thiosulfate, water, brine and dried over Na_2SO_4. The solvent was evaporated to yield acid **2** (431 mg, 1.80 mmol, 95%) as a colourless resin and a mixture of rotamers.



2

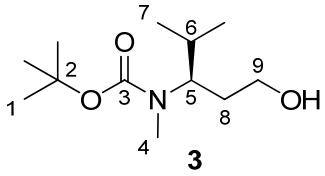
$[\alpha]_D^{20}$ = –6.0° (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.92 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7'-H), 1.43 (s, 9 H, 1-H), 1.80 (m, 1 H, 6-H), 2.50 (m, 1 H, 8-H_a), 2.62 (m, 1 H, 8-H_b), 2.74 (s, 3 H, 4-H), 4.01 (m, 1 H, 5-H), 10.38 (bs, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6 (q, C-7), 20.1 (q, C-7'), 28.3 (q, C-1), 30.5 (q, C-4), 30.9 (d, C-6), 36.2 (t, C-8), 59.3 (d, C-5), 79.8 (s, C-2), 156.0 (s, C-3), 177.3 (s, C-9) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (s, 3 H, 4-H), 3.92 (bs, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (q, C-7), 19.9 (q, C-7'), 30.5 (d, C-6), 35.9 (t, C-8), 60.0 (d, C-5), 79.5 (s, C-2), 156.1 (s, C-3), 177.1 (s, C-9) ppm. HRMS (CI) *m/z* calcd for $C_{12}H_{24}NO_4$ $[M+H]^+$: 246.1705; found 246.1714. Anal. calcd for $C_{12}H_{23}NO_4$ (245.31): C 58.75, H 9.45, N 5.71; found C 58.33, H 9.10, N 5.78.

(*R*)-*tert*-Butyl 1-hydroxy-4-methylpentan-3-yl(methyl)carbamate (3)[2]

A solution of acid **2** (290 mg, 1.18 mmol) in dry THF (6 mL) was cooled to 0 °C and triethylamine (182 µL, 1.31 mmol) was added, followed by ethyl chloroformate (125 µL, 1.31 mmol) dropwise. After stirring at this temperature for 15 min the suspension was filtered under nitrogen and the filtrate was added to an ice cooled solution of sodium borohydride

(1) D. Seebach, M. Overhand, F. N. M. Kuehnle, B. Martinoni, B. *Helv. Chim. Acta* **1996**, *79*, 913–941.
(2) P. Wipf, Z. Wang, *Org. Lett.* **2007,** *9*, 1605–1607.

(73 mg, 1.93 mmol) in water (3 mL). The clear solution was stirred one hour at 0 °C and two hours at room temperature. The reaction mixture was hydrolyzed with aqueous HCl (1 M) and extracted thrice with ethyl acetate. The combined extracts were washed with saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (SiO_2, hexanes/ethyl acetate = 1:1) to yield alcohol **3** (213 mg, 0.92 mmol, 78%) as a colourless oil and a mixture of rotamers.

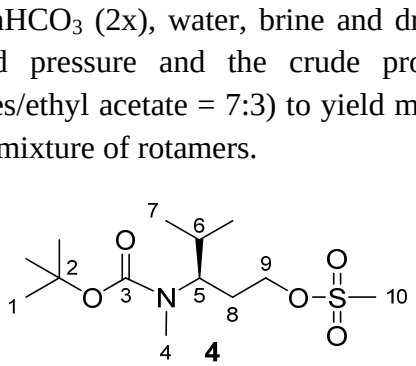


3

R_f = 0.27 (hexanes/EtOAc, 1:1). $[\alpha]_D^{20}$ = –20.3° (*c* = 1.3, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, $^3J_{7,6}$ = 6.4 Hz, 3 H, 7-H), 0.96 (d, $^3J_{7',6}$ = 6.8 Hz, 3 H, 7'-H), 1.33 (m, 1 H, 8-H_a), 1.46 (s, 9 H, 1-H), 1.67 (m, 1 H, 6-H), 1.92 (m, 1 H, 8-H_b), 2.61 (s, 3 H, 4-H), 3.35 (ddd, $^3J_{9a,8a}$ = $^3J_{9a,8b}$ = 11.6 Hz, $^2J_{9a,9b}$ = 2.8 Hz, 1 H, 9-H_a), 3.48–3.70 (sh, 2 H, 9-H_b, OH), 3.83 (ddd, $^3J_{5,8a}$ = 12.0 Hz, $^3J_{5,6}$ = 10.8 Hz, $^3J_{5,8b}$ = 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (q, C-7), 27.9 (q, C-4), 28.4 (q, C-1), 30.0 (d, C-6), 31.7 (t, C-8), 57.3 (d, C-5), 59.8 (t, C-9), 80.0 (s, C-2), 158.0 (s, C-3) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (d, $^3J_{7,6}$ = 6.4 Hz, 3 H, 7-H), 0.94 (d, $^3J_{7',6}$ = 6.4 Hz, 3 H, 7'-H), 2.66 (s, 3 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 (q, C-7), 28.5 (q, C-1), 30.5 (d, C-6), 32.1 (t, C-8), 59.8 (d, C-5), 80.1 (s, C-2), 156.2 (s, C-3) ppm.

(*R*)-3-(*tert*-Butoxycarbonyl(methyl)amino)-4-methylpentyl methanesulfonate (4)

A solution of alcohol **3** (268 mg, 1.16 mmol) and triethylamine (0.50 mL, 3.60 mmol) in dry dichloromethane (6 mL) was cooled to 0 °C and treated dropwise with methanesulfonyl chloride (135 µL, 1.74 mmol) followed by stirring for additional 3 h at 0 °C. The reaction mixture was diluted with dichloromethane and successfully washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ (2x), water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (SiO_2, hexanes/ethyl acetate = 7:3) to yield mesylate **4** (290 mg, 0.94 mmol, 81%) as a colourless oil and a mixture of rotamers.



4

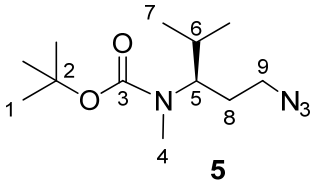
The mesylate is very unstable and decomposes very fast.

R_f = 0.14 (hexanes/EtOAc, 7:3). $[\alpha]_D^{20}$ = +6.1° (*c* = 1.5, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.95 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7'-H), 1.45 (s, 9 H, 1-H), 1.70 (m, 1 H, 6-H), 1.80 (m, 1 H, 8-H_a), 2.07 (m, 1 H, 8-H_b), 2.65 (s, 3 H, 4-H), 3.01 (s, 3 H, 10-H), 3.82 (ddd, $^3J_{5,6}$ = $^3J_{5,8a}$ = 11.0 Hz, $^3J_{5,8b}$ = 3.0 Hz, 1 H, 5-H), 4.10

(m, 1 H, 9-H_a), 4.19 (m, 1 H, 9-H_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (q, C-7), 19.7 (q, C-7'), 28.4 (q, C-1), 28.8 (q, C-4), 28.9 (t, C-8) 30.4 (d, C-6), 37.3 (q, C-10), 57.8 (d, C-5), 67.5 (t, C-9), 79.5 (s, C-2), 156.5 (s, C-3) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (d, $^3J_{7,6}$ = 6.5 Hz, 3 H, 7-H), 0.94 (d, $^3J_{7',6}$ = 6.5 Hz, 3 H, 7'-H), 1.46 (s, 9 H, 1-H), 2.69 (s, 3 H, 4-H), 2.99 (s, 3 H, 10-H), 3.65 (bs, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 (q, C-7), 20.2 (q, C-7'), 28.4 (q, C-1), 29.5 (t, C-8), 30.7 (d, C-6), 37.3 (q, C-10), 67.6 (t, C-9), 79.9 (s, C-2), 156.3 (s, C-3) ppm. HRMS (CI) *m/z* calcd for $C_{13}H_{28}NO_5S$ $[M+H]^+$: 310.1688; found 310.1690.

(*R*)-*tert*-Butyl 1-azido-4-methylpentan-3-yl(methyl)carbamate (5)

To a solution of mesylate **5** (280 mg, 0.90 mmol) in dry DMF (9 mL) was added sodium azide (454 mg, 7.00 mmol), and the reaction mixture was heated to 60 °C for 20 h. After being cooled to room temperature, the reaction mixture was portioned between water and ethyl acetate (40 mL), and the aqueous layer was extracted with ethyl acetate (3x). The combined extracts were washed with water (3x) and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (SiO_2, hexanes/ethyl acetate = 8:2) to yield azide **5** (218 mg, 0.58 mmol, 94%) as a colourless liquid and a mixture of rotamers.



5

The azide is very stable and can be stored at room temperature.

R_f = 0.36 (hexanes/EtOAc, 8:2). $[\alpha]_D^{20}$ = –3.4° (*c* = 1.3, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.93 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7'-H), 1.46 (s, 9 H, 1-H), 1.57–1.73 (m, 2 H, 6-H, 8-H_a), 1.84 (m, 1 H, 8-H_b), 2.64 (s, 3 H, 4-H), 3.20 (m, 2 H, 9-H), 3.76 (ddd, $^3J_{4,6}$ = $^3J_{5,8a}$ = 11.0 Hz, $^3J_{5,8b}$ = 2.9 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 (q, C-7), 20.2 (q, C-7'), 28.4 (2 q, C-1, C-4), 28.9 (d, C-6), 30.6 (t, C-8), 48.7 (t, C-9), 59.0 (d, C-5), 79.7 (s, C-2), 156.4, (s, C-3) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, 7-H), 0.95 (d, $^3J_{7',6}$ = 6.6 Hz, 3 H, 7'-H), 1.45 (s, 9 H, 1-H), 2.67 (s, 3 H, 4-H), 3.13 (m, 1 H, 9-H_a), 3.31 (m, 1 H, 9-H_b), 3.62 (bs, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (q, C-7), 19.8 (q, C-7'), 28.8 (d, C-6), 30.7 (t, C-8), 49.1 (t, C-9), 79.3 (s, C-2) ppm. HRMS (CI) *m/z* calcd for $C_{12}H_{25}N_4O_2$ $[M+H]^+$: 257.1977; found 257.2000.

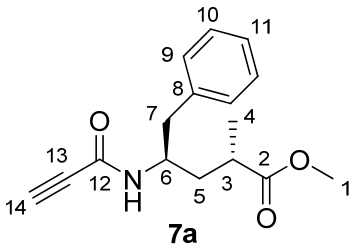
General procedure for amide coupling with propane phosphonic acid anhydride (T3P)

To an ice cooled solution of the amine (1.0 mmol) and diisopropyl ethylamine (1.1 mmol) in dry DCM (10 mL) was added dropwise propiolic acid (1.0 mmol) and T3P (1.5 mmol). The reaction mixture was stirred at room temperature overnight, diluted with DCM and successfully washed with aqueous HCl (1 M), saturated aqueous $NaHCO_3$, water (3x) and

brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate) to yield the pure product.

(2*S*,4*R*)-Methyl 2-methyl-5-phenyl-4-propiolamidopentanoate (7a)

Following the general procedure for amide coupling with T3P, **7a** was obtained from Tup-OMe (338 mg, 1.53 mmol), diisopropyl ethylamine (0.29 mL, 1.68 mmol), propiolic acid (97 µL, 1.53 mmol) and T3P (1.4 mL, 2.35 mmol, 50% in ethyl acetate). After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 7:3), alkyne **7a** (403 mg, 1.31 mmol, 86%) could be isolated as a white solid and a mixture of rotamers; m.p. 81–83 °C.



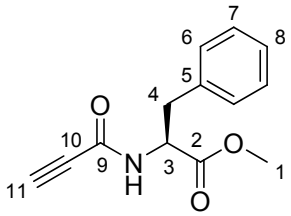
7a

R_f = 0.13 (petroleum ether/EtOAc, 7:3). $[\alpha]_D^{21}$ = +30.5° (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, $^3J_{4,3}$ = 7.1 Hz, 1 H, 4-H), 1.53 (ddd, $^2J_{5a,5b}$ = 14.2 Hz, $^3J_{5a,3/6}$ = 9.9 Hz, $^3J_{5a,6/3}$ = 4.2 Hz, 1 H, 5-Ha), 1.92 (ddd, $^2J_{5b,5a}$ = 13.8 Hz, $^3J_{5b,3/6}$ = 9.8 Hz, $^3J_{5b,6/3}$ = 4.0 Hz, 1 H, 5-H_b), 2.58 (m, 1 H, 3-H), 2.74 (s, 3 H, 14-H), 2.80 (dd, $^2J_{7a,7b}$ = 14.2 Hz, $^3J_{7a,6}$ = 6.8 Hz, 1 H, 7-H_a), 2.85 (dd, $^2J_{7b,7a}$ = 14.0 Hz, $^3J_{7b,6}$ = 6.5 Hz, 1 H, 7-H_b), 3.67 (s, 3 H, 1-H), 4.24 (m, 1 H, 6-H), 5.93 (d, $^3J_{NH,6}$ = 8.7 Hz, 1 H, NH), 7.16 (m, 2 H, 10-H), 7.22 (m, 1 H, 11-H), 7.30 (m, 2 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5 (q, C-4), 36.2 (d, C-3), 37.1 (t, C-5), 40.5 (t, C-7), 49.1 (d, C-6), 51.8 (q, C-1), 73.0 (d, C-14), 77.3 (s, C-13), 126.7 (d, C-11), 128.5 (d, C-9), 129.3 (d, C-10), 137.0 (s, C-8), 151.6 (s, C-12), 176.5 (s, C-2) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, $^3J_{4,3}$ = 7.3 Hz, 1 H, 4-H), 1.45 (ddd, $^2J_{5a,5b}$ = 14.3 Hz, $^3J_{5a,3/6}$ = 10.5 Hz, $^3J_{5a,6/3}$ = 3.9 Hz, 1 H, 5-Ha), 1.99 (ddd, $^2J_{5b,5a}$ = 14.0 Hz, $^3J_{5b,3/6}$ = 10.3 Hz, $^3J_{5b,6/3}$ = 3.5 Hz, 1 H, 5-H_b), 2.98 (s, 3 H, 14-H), 3.65 (s, 3 H, 1-H), 4.15 (m, 1 H, 6-H), 6.12 (d, $^3J_{NH,6}$ = 10.5 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9 (q, C-4), 36.0 (d, C-3), 38.5 (t, C-5), 42.9 (t, C-7), 51.7 (d, C-1), 53.6 (q, C-6), 74.9 (d, C-14), 78.8 (s, C-13), 126.8 (d, C-11), 128.5 (d, C-9), 129.5 (d, C-10), 136.6 (s, C-8), 154.5 (s, C-12), 176.3 (s, C-2) ppm. HRMS (CI) *m/z* calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1443; found 274.1470. Anal. calcd for $C_{16}H_{19}NO_3$ (273.32): C 70.31, H 7.01, N 5.12; found C 70.15, H 6.94, N 5.06.

(*S*)-Methyl 3-phenyl-2-propiolamidopropanoate (7b)

To a solution of L-phenylalanine methylester (2.85 g, 15.9 mmol) in dry DCM (80 mL) was added propiolic acid (1.1 mL, 17.4 mmol) followed by DCC (3.59 g, 17.4 mmol). After stirring for 3 h at room temperature the urea was filtered off and the filtrate was successfully washed with aqueous HCl (1 M), saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash

chromatography (SiO_2, petroleum ether/ethyl acetate = 7:3) to yield alkyne **7b** (3.65 g, 15.8 mmol, 99%) as a white solid and a mixture of rotamers; m. p. 78–80 °C.

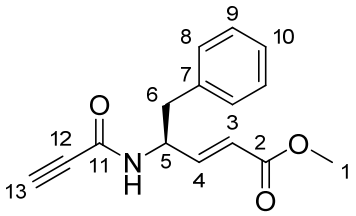


7b

R_f = 0.17 (petroleum ether/EtOAc, 7:3). $[\alpha]_D^{21}$ = +121.7° (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.83 (s, 1 H, 11-H), 3.14 (dd, $^2J_{4a,4b}$ = 14.0 Hz, $^3J_{4a,3}$ = 5.6 Hz, 1 H, 4-H_a), 3.20 (dd, $^2J_{4b,4a}$ = 13.9 Hz, $^3J_{4b,3}$ = 5.8 Hz, 1 H, 4-H_b), 3.76 (s, 3 H, 1-H), 4.93 (td, $^3J_{3,NH}$ = 7.9 Hz, $^3J_{3,4}$ = 5.7 Hz, 1 H, 3-H), 6.41 (d, $^3J_{NH,3}$ = 6.8 Hz, 1 H, NH), 7.14 (m, 2 H, 7-H), 7.26–7.35 (m, 3 H, 6-H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.5 (t, C-4), 52.5 (q, C-1), 53.4 (d, C-3), 74.0 (d, C-11), 79.3 (s, C-10), 127.3 (d, C-8), 128.6 (d, C-6), 129.2 (d, C-7), 135.2 (s, C-5), 151.4 (s, C-9), 171.0 (s, C-2) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.07 (s, 1 H, 11-H), 3.78 (s, 3 H, 1-H), 4.85 (ddd, $^3J_{3,NH}$ = 9.7 Hz, $^3J_{3,4a}$ = 6.6 Hz, $^3J_{3,4b}$ = 5.6 Hz, 1 H, 3-H), 6.14 (d, $^3J_{NH,3}$ = 10.0 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.6 (t, C-4), 52.6 (q, C-1), 57.1 (d, C-3), 74.5 (d, C-11), 76.7 (s, C-10), 127.5 (d, C-8), 128.8 (d, C-6), 129.4 (d, C-7) ppm. HRMS (CI) *m/z* calcd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0973; found 232.0972.

(*S*,*E*)-methyl 5-phenyl-4-propiolamidopent-2-enoate (7c)

Following the general procedure for amide coupling with T3P, **7c** was obtained from (*S*,*E*)-methyl 4-amino-5-phenylpent-2-enoate (133 mg, 0.65 mmol), diisopropyl ethylamine (0.12 mL, 0.71 mmol), propiolic acid (41 µL, 0.65 mmol) and T3P (0.58 mL, 0.97 mmol, 50% in ethyl acetate). After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 1:1), alkyne **7c** (144 mg, 0.56 mmol, 86%) could be isolated as a white solid and a mixture of rotamers; m.p. 152–154 °C.



7c

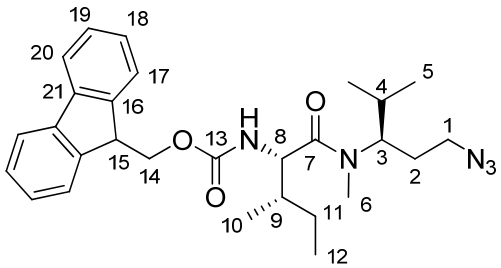
R_f = 0.33 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{21}$ = +2.1° (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79 (s, 1 H, 13-H), 2.95 (d, $^3J_{6,5}$ = 6.7 Hz, 2 H, 6-H), 3.73 (s, 3 H, 1-H), 4.97 (m, 1 H, 5-H), 5.87 (dd, $^3J_{3,4}$ = 15.7 Hz, $^4J_{3,5}$ = 1.6 Hz, 1 H, 3-H), 5.94 (d, $^3J_{NH,5}$ = 8.0 Hz, 1 H, NH), 6.88 (dd, $^3J_{4,3}$ = 15.7 Hz, $^4J_{4,5}$ = 5.4 Hz, 1 H, 4-H), 7.17 (m, 2 H, 7-H), 7.26–7.34 (m, 3 H, 6-H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.1 (t, C-6), 51.2 (d, C-5), 51.7 (q, C-1), 73.9 (d, C-13), 76.8 (s, C-12), 121.7 (d, C-3), 127.2 (d, C-10), 128.8 (d,

C-8), 129.3 (d, C-9), 135.5 (s, C-7), 145.6 (d, C-4), 151.3 (s, C-11), 166.2 (s, C-2) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99 (d, $^{3}J_{6,5}$ = 6.7 Hz, 2 H, 6-H), 3.01 (s, 1 H, 13-H), 3.75 (s, 3 H, 1-H), 4.88 (m, 1 H, 5-H), 6.95 (dd, $^{3}J_{4,3}$ = 15.8 Hz, $^{4}J_{4,5}$ = 5.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.8 (d, C-3), 128.9 (d, C-8), 129.4 (d, C-9) ppm. HRMS (CI) *m/z* calcd for $C_{15}H_{16}NO_3$ $[M+H]^+$: 258.1130; found 258.1129. Anal. calcd for $C_{15}H_{15}NO_3$ (257.29): C 70.02, H 5.88, N 5.44; found C 69.44, H 5.84, N 5.12.

(9H-Fluoren-9-yl)methyl(2*S*,3*S*)-1-(((*R*)-1-azido-4-methylpentan-3-yl)(methyl) amino)3-methyl-1-oxopentan-2-ylcarbamate (9)

HCl in dioxane (5.0 mL, 20 mmol, 4 M) was added at 0 °C to azide **5** (492 mg, 1.92 mmol). The solvent was evaporated in vacuum after complete deprotection (30 min, TLC monitoring) and the hydrochloride salt was dried in high vacuum.

N-Deprotected **5**, Fmoc-protected L-isoleucine (732 mg, 2.07 mmol) and BEP (567 mg, 2.07 mmol) were dissolved in dry DCM (11 mL) and diisopropyl ethylamine (0.96 mL, 5.64 mmol) was added dropwise to this solution at –10 °C. The cooling bath was removed after 20 min and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with DCM and washed with aqueous HCl (1 M), saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 9:1, 8:2) to yield azide **9** (803 mg, 1.64 mmol, 87% over 2 steps) as a colorless resin and a mixture of rotamers.



9

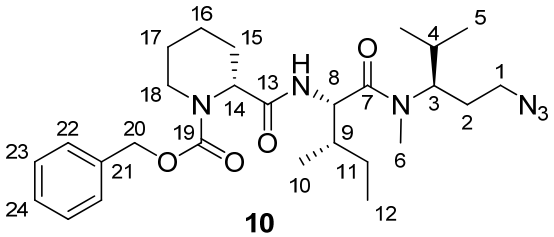
R_f = 0.20 (petroleum ether/EtOAc, 8:2). $[\alpha]_D^{21}$ = –22.0° (*c* = 1.1, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, $^{3}J_{5,4}$ = 6.6 Hz, 3 H, 5-H), 0.93 (t, $^{3}J_{12,11}$ = 7.4 Hz, 3 H, 12-H), 0.94–1.02 (m, 6 H, 5'-H, 10-H), 1.15 (m, 1 H, 11-H_a), 1.58 (m, 1 H, 11-H_b), 1.64–1.86 (m, 3 H, 2-H_a, 4-H, 9-H), 1.94 (m, 1 H, 2-H_b), 2.92 (s, 3 H, 6-H), 3.17 (t, $^{3}J_{1,2}$ = 7.1 Hz, 2 H, 1-H), 4.21 (t, $^{3}J_{15,14}$ = 6.9 Hz, 1 H, 15-H), 4.27 (m, 1 H, 3-H), 4.36 (dd, $^{2}J_{14a,14b}$ = 6.6 Hz, $^{3}J_{14,15}$ = 5.4 Hz, 2 H, 14-H), 4.53 (dd, $^{3}J_{8,NH}$ = 9.4 Hz, $^{3}J_{8,9}$ = 7.0 Hz, 1 H, 8-H), 5.48 (d, $^{3}J_{NH,8}$ = 9.1 Hz, 1 H, NH), 7.30 (dd, $^{3}J_{18,17}$ = $^{3}J_{18,17}$ = 7.4 Hz, 2 H, 18-H), 7.39 (dd, $^{3}J_{19,18}$ = $^{3}J_{19,20}$ = 7.4 Hz, 2 H, 19-H), 7.58 (d, $^{3}J_{17,18}$ = 7.5 Hz, 2 H, 17-H), 7.76 (d, $^{3}J_{20,19}$ = 7.5 Hz, 2 H, 20-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1 (q, C-12), 15.8 (q, C-10), 19.4 (q, C-5), 19.9 (q, C-5'), 23.7 (t, C-11), 28.3 (t, C-2), 29.7 (q, C-6), 29.9 (d, C-4), 37.4 (d, C-9), 47.1 (d, C-15), 48.7 (t, C-1), 55.6 (d, C-8), 57.5 (d, C-3), 66.8 (t, C-14), 119.8 (d, C-20), 125.0 (d, C-17), 126.9 (d, C-18), 127.5 (d, C-19), 141.1 (s, C-21), 143.6 (s, C-16), 156.3 (s, C-13), 173.0 (s, C-7) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $^{3}J_{12,11}$ = 7.4

Hz, 3 H, 12-H), 1.05 (d, $^{3}J_{5,4}$ = 6.6 Hz, 3 H, 5-H), 2.76 (s, 3 H, 6-H), 3.03 (m, 1 H, 1-H_a), 3.23 (1 H, 1-H_b), 3.53 (m, 1 H, 3-H), 4.63 (dd, $^{3}J_{8,NH}$ = 9.5 Hz, $^{3}J_{8,9}$ = 6.0 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3 (q, C-12), 16.1 (q, C-10), 20.1 (q, C-5), 23.3 (t, C-11), 27.4 (q, C-6), 29.5 (t, C-2), 31.2 (d, C-4), 37.8 (d, C-9), 47.1 (d, C-15), 47.9 (t, C-1), 55.2 (d, C-8), 60.4 (d, C-3), 119.8 (d, C-20), 141.2 (s, C-21), 143.8 (s, C-16), 172.5 (s, C-7) ppm. HRMS (CI) *m/z* calcd for $C_{28}H_{38}N_5O_3$ $[M+H]^+$: 492.2974; found 492.3001. Anal. calcd for $C_{28}H_{37}N_5O_3$ (491.63): C 68.41, H 7.59, N 14.25; found C 68.51, H 7.69, N 14.48.

(*R*)-Benzyl-2-((2*S*,3*S*)-1-(((*R*)-1-azido-4-methylpentan-3-yl)(methyl)amino)-3-methyl-1-oxopentan-2-ylcarbamoyl)piperidine-1-carboxylate (10)

To a solution of azide **9** (1.1 g, 2.24 mmol) in dry DCM (20 mL) was added *tris*(amino ethyl)amine (4.6 mL, 31.0 mmol). After stirring for 30 min at room temperature the reaction mixture was diluted with ethyl acetate and washed twice with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated.

Isobutyl chloroformate (0.33 mL, 2.48 mmol) was added dropwise at –20 °C to a solution of *Z*-protected (*R*)-pipecolic acid (653 mg, 2.47 mmol) and NMM (0.28 mL, 2.54 mmol) in dry THF (15 mL). After 20 min, the free amine in dry THF (10 mL) was added and the mixture was allowed to warm to room temperature overnight. Water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were washed with aqueous HCl (1 M), water, saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 8:2, 7:3) to yield azide **10** (986 mg, 1.92 mmol, 86% over 2 steps) as a white solid and a mixture of rotamers; m. p. 57–58 °C.



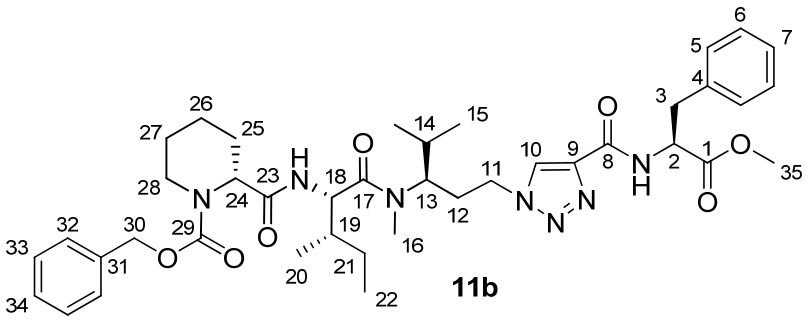
10

R_f = 0.18 (petroleum ether/EtOAc, 7:3). $[\alpha]_D^{21}$ = +14.1° (*c* = 1.1, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (d, $^{3}J_{5,4}$ = 6.6 Hz, 3 H, 5-H), 0.85 (bs, 3 H, 12-H), 0.92 (m, 3 H, 10-H), 0.96 (d, $^{3}J_{5',4}$ = 6.6 Hz, 3 H, 5'-H), 1.03 (m, 1 H, 11-Ha), 1.28–1.44 (m, 2 H, 16-H_a, 17-H_a), 1.44–1.58 (m, 2 H, 11-H_b, 15-H_a), 1.58–1.84 (m, 5 H, 2-H_a, 4-H, 9-H, 16-H_b, 17-H_b), 1.93 (m, 2-H_b), 2.30 (m, 15-H_b), 2.86 (m, 1 H, 18-H_a), 2.94 (s, 3 H, 6-H), 3.15 (t, $^{3}J_{1,2}$ = 7.2 Hz, 2 H, 1-H), 4.09 (m, 1 H, 18-H_b), 4.27 (m, 1 H, 3-H), 4.77 (m, 1 H, 8-H), 4.88 (m, 1 H, 14-H), 5.17 (m, 2 H, 20-H), 6.61 (bs, 1 H, NH), 7.28–7.43 (m, 5 H, 22-H, 23-H, 24-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0 (q, C-12), 16.1 (q, C-10), 19.4 (q, C-5), 19.8 (q, C-5'), 20.3 (t, C-16), 24.0 (t, C-2), 24.7 (d, t, C-11, C-17), 25.5 (t, C-15), 28.4 (t, C-16), 29.6 (q, C-6), 29.9 (d, C-4), 37.0 (d, C-9), 42.2 (t, C-18), 48.8 (t, C-1), 53.5 (d, C-8), 54.9 (d, C-14), 57.3 (d, C-3), 67.5 (t, C-20), 127.8, 128.0, 128.4 (3 d, C-22, C-23, C-24), 136.3 (s, C-21), 156.3 (s, C-19), 170.4 (s, C-13), 173.0 (s, C-7) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, $^{3}J_{5,4}$ = 7.1 Hz, 3 H, 5-H), (d, $^{3}J_{5',4}$ = 6.5 Hz, 3 H, 5'-H), 2.74 (s, 3 H,

6-H), 3.51 (m, 1 H, 3-H), 6.50 (bs, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3 (q, C-12), 15.8 (q, C-10), 20.2 (q, C-5), 20.2 (q, C-5'), 23.2 (t, C-2), 26.1 (t, C-15), 27.4 (q, C-6), 31.2 (d, C-4), 37.6 (d, C-9), 41.9 (t, C-18), 47.9 (t, C-1), 53.2 (d, C-8), 55.3 (d, C-14), 60.5 (d, C-3), 67.5 (t, C-20), 155.3 (s, C-19) ppm. HRMS (CI) *m/z* calcd for $C_{27}H_{43}N_6O_4$ $[M+H]^+$: 515.3346; found 515.3361. Anal. calcd for $C_{27}H_{42}N_6O_4$ (514.66): C 63.01, H 8.23, N 16.33; found C 62.80, H 8.20, N 16.58.

(*R*)-Benzyl 2-((2*S*,3*S*)-1-(((*R*)-1-(4-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbamoyl)-1H-1,2,3-triazol-1-yl)-4-methylpentan-3-yl)(methyl)amino)-3-methyl-1-oxopentan-2-ylcarbamoyl)piperidine-1-carboxylate (11b).

Following the general procedure for Click-reaction **11b** was obtained from azide **10** (200 mg, 0.39 mmol), alkyne **7b** (136 mg, 0.59 mmol), $CuSO_4$ solution (80 µL, 80 µmol, 1 M) and sodium ascorbate solution (80 µL, 80 µmol, 1 M) in *tert*-butanol/water after 3 d. After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 4:6), triazole **11b** (270 mg, 0.36 mmol, 93%) could be isolated as a white solid and a mixture of rotamers; m. p. 94–96 °C.

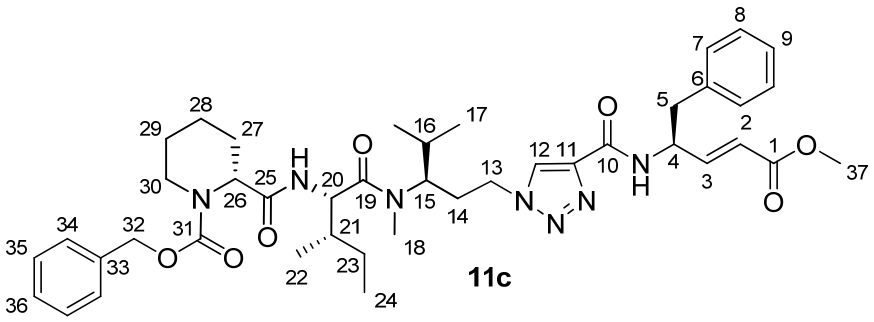


R_f = 0.16 (petroleum ether/EtOAc, 3:7). $[\alpha]_D^{20}$ = +19.7° (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, $^3J_{15,14}$ = 6.4 Hz, 3 H, 15-H), 0.80–0.98 (sh, 9 H, 15'-H, 20-H, 22-H), 1.18 (m, 1 H, 21-H_a), 1.32–1.78 (sh, 7 H, 14-H, 21-H_b, 25-H_{ax}, 26-H, 27-H), 1.84 (m, 1 H, 19-H), 2.00 (m, 1 H, 12-H_a), 2.08–2.38 (sh, 2 H, 12-H_b, 25-H_{eq}), 3.05 (s, 3 H, 16-H), 3.12–3.38 (sh, 3 H, 3-H, 28-H_{ax}), 3.71 (s, 3 H, 35-H), 3.97 (m, 1 H, 28-H_{eq}), 4.12–4.34 (3 H, 11-H, 13-H), 4.64 (m, 1 H, 18-H), 4.78 (m, 1 H, 24-H), 4.98–5.18 (sh, 3 H, 2-H, 30-H), 7.12–7.30 (sh, 11 H, 5-H, 6-H, 7-H, 32-H, 33-H, 34-H, NH), 7.60 (m, 1 H, NH), 8.21 (s, 1 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8 (q, C-22), 15.8 (q, C-20), 19.2 (q, C-15), 19.5 (q, C-15'), 20.0 (t, C-26), 24.4 (t, C-27), 24.5 (t, C-21), 26.3 (t, C-25), 29.8 (d, C-14), 30.2 (q, C-16), 30.6 (t, C-12), 36.2 (d, C-19), 38.0 (t, C-3), 42.2 (t, C-28), 48.1 (t, C-11), 50.6 (q, C-35), 53.0 (d, C-2), 54.2 (d, C-18), 54.5 (d, C-24), 58.2 (d, C-13), 67.9 (t, C-30), 126.3 (d, C-10), 127.0 (d, C-7), 127.8, 128.1, 128.4, 128.6, 129.1 (5 d, C-5, C-6, C-32, C-33, C-34), 135.6, 135.8 (2 s, C-4, C-31), 156.8 (s, C-29), 159.8 (s, C-8), 171.3 (s, C-1), 172.5 (s, C-17), 174.6 (s, C-23) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (d, $^3J_{15,14}$ = 6.3 Hz, 3 H, 15-H), 2.58 (s, 3 H, 16-H), 2.86 (m, 1 H, 28-H_{ax}), 3.67 (s, 3 H, 35-H), 3.75 (m, 1 H, 13-H), 4.46 (m, 1 H, 11-H), 6.62 (bs, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1 (q, C-22), 16.1 (q, C-20), 20.1 (q, C-15), 20.0 (t, C-26), 27.4 (q, C-16), 31.2 (d, C-14), 42.0 (t, C-28), 47.4 (t, C-11), 53.1 (d, C-2), 61.3 (d, C-13), 67.5 (t, C-30), 157.2 (s,

C-29), 160.0 (s, C-8) ppm. HRMS (CI) *m/z* calcd for $C_{40}H_{55}N_7O_7$ $[M+H]^+$: 745.4163; found 788.4163.

(*R*)-Benzyl 2-((2*S*,3*S*)-1-(((*R*)-1-(4-((*S*,*E*)-5-methoxy-5-oxo-1-phenylpent-3-en-2-ylcarbamoyl)-1H-1,2,3-triazol-1-yl)-4-methylpentan-3-yl)(methyl)amino)-3-methyl-1-oxopentan-2-ylcarbamoyl)piperidine-1-carboxylate (11c).

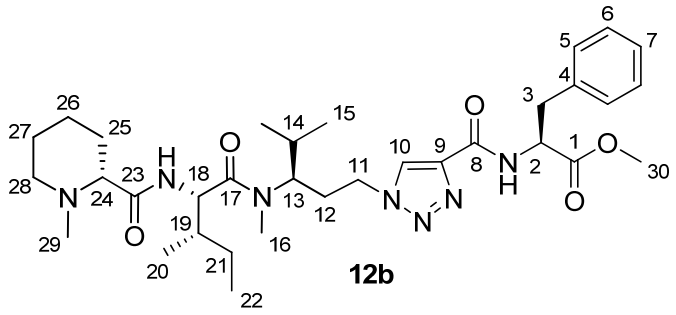
Following the general procedure for Click-reaction **11c** was obtained from azide **10** (165 mg, 0.32 mmol), alkyne **7c** (124 mg, 0.48 mmol), $CuSO_4$ solution (80 µL, 80 µmol, 1 M) and sodium ascorbate solution (80 µL, 80 µmol, 1 M) in DMSO/water after 3 d. After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 4:6, 3:7), triazole **11c** (197 mg, 0.26 mmol, 81%) could be isolated as a white solid and a mixture of rotamers; m. p. 132–134 °C.



R_f = 0.30 (petroleum ether/EtOAc, 3:7). $[\alpha]_D^{21}$ = –28.1° (*c* = 0.8, MeOH). Major rotamer: ^{1}H NMR (400 MHz, MeOH-d^4): δ = 0.60 (m, 3 H, 17-H), 0.72–0.82 (sh, 6 H, 17‘-H, 24-H), 0.86 (d, $^3J_{22,21}$ = 6.7 Hz, 3 H, 22-H), 1.04 (m, 1 H, 23-H$_a$), 1.22–1.34 (sh, 2 H, 28-H$_{ax}$, 29-H$_{ax}$), 1.40–1.55 (sh, 5 H, 16-H, 23-H$_b$, 27-H$_{ax}$, 28-H$_{eq}$, 29-H$_{eq}$), 1.83 (m, 1 H, 21-H), 1.97 (m, 1 H, 14-H$_a$), 2.08 (m, 1 H, 27-H$_{eq}$), 2.18 (m, 1 H, 14-H$_b$), 2.88–3.06 (sh, 5 H, 5-H, 18-H, 30-H$_{ax}$), 3.58 (s, 3 H, 37-H), 3.86–4.08 (sh, 2 H, 15-H, 30-H$_{eq}$), 4.17 (m, 2 H, 13-H), 4.64 (d, $^3J_{20,21}$ = 8.9 Hz, 1 H, 20-H), 4.07 (m, 1 H, 26-H), 4.92 (m, 1 H, 4-H), 4.99 (m, 2 H, 32-H), 5.83 (dd, $^3J_{2,3}$ = 15.7 Hz, $^4J_{2,4}$ = 1.5 Hz, 1 H, 2-H), 6.92 (dd, $^3J_{3,2}$ = 15.7 Hz, $^3J_{3,4}$ = 5.7 Hz, 1 H, 3-H), 7.02–7.22 (sh, 10 H, 7-H, 8-H, 9-H, 34-H, 35-H, 36-H), 8.27 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, MeOH-d^4): δ 11.1 (q, C-24), 16.3 (q, C-22), 20.2 (q, C-17), 20.4 (q, C-17’), 21.2 (t, C-28), 25.6 (2 t, C-23, C-29), 28.0 (t, C-27), 30.7, 31.1 (t, d, q, C-14, C-16, C-18), 37.4 (d, C-21), 40.9 (t, C-5), 43.3 (t, C-30), 49.2 (t, C-13), 52.2 (q, C-37), 53.1 (d, C-4), 55.5 (d, C-20), 56.2 (d, C-26), 59.1 (d, C-15), 68.5 (t, C-32), 122.1 (d, C-2), 127.8 (d, C-12), 128.7, 129.1, 129.5, 129.6, 130.4 (6 d, C-7, C-8, C-9, C-34, C-35, C-36), 138.0, 138.6 (2 s, C-6, C-33), 143.5 (s, C-11), 148.6 (d, C-3), 158.1 (s, C-31), 162.0 (s, C-10), 168.2 (s, C-1), 173.2 (s, C-19), 175.1 (s, C-25) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, MeOH-d^4): δ 0.92 (d, $^3J_{17,16}$ = 6.5 Hz, 3 H, 17-H), 2.65 (s, 3 H, 18-H), 3.79 (m, 1 H, 15-H), 4.82 (m, 2 H, 32-H) ppm. ^{13}C NMR (100 MHz, MeOH-d^4): δ 11.2 (q, C-24), 16.7 (q, C-22), 20.3 (q, C-17), 21.0 (q, C-17’), 21.1 (t, C-28), 28.4 (t, C-27), 29.1 (q, C-18), 32.4, 32.5 (t, d, C-14, C-16), 38.6 (d, C-21), 53.0 (d, C-4), 54.3 (d, C-20), 62.0 (d, C-15), 127.6 (d, C-12), 157.6 (s, C-31) ppm. HRMS (CI) *m/z* calcd for $C_{42}H_{58}N_7O_7$ $[M+H]^+$: 772.4397; found 772.4348.

(*S*)-Methyl 2-(1-((*R*)-3-((2*S*,3*S*)-*N*,3-dimethyl-2-((*R*)-1-methylpiperidine-2-carboxamido)pentanamido)-4-methylpentyl)-1H-1,2,3-triazole-4-carboxamido)-3-phenylpropanoate (12b).

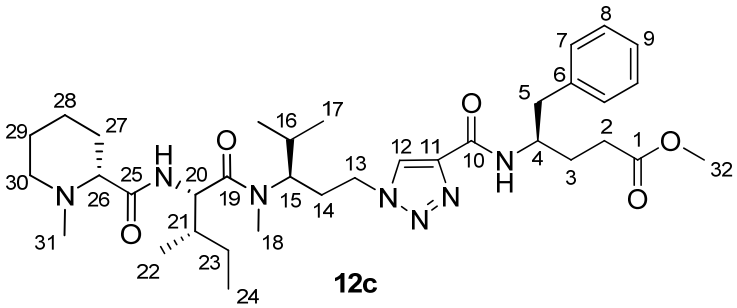
According to the general procedure for Cbz-deprotection **11b** (168 mg, 0.21 mmol) was hydrogenated. Following the general procedure for reductive methylation **12b** was obtained from the crude amine, paraformaldehyde (21 mg, 0.22 mmol) and sodium cyanoborohydride (16 mg, 0.24 mmol). After purification by flash chromatography (SiO_2, DCM/MeOH = 93:7), **12b** (106 mg, 0.17 mmol, 79% over 2 steps) could be isolated as a white solid and a mixture of rotamers; m. p. 58–60 °C.



R_f = 0.19 (DCM/MeOH, 93:7). $[\alpha]_D^{20}$ = +30.2° (*c* = 0.7, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, $^3J_{15,14}$ = 6.6 Hz, 3 H, 15-H), 0.87–0.94 (sh, 6 H, 15‘-H, 22-H), 0.98 (d, $^3J_{20,19}$ = 6.7 Hz, 3 H, 20-H), 1.13–1.25 (sh, 2 H, 21-H_a, 26-H_{ax}), 1.35 (m, 1 H, 25-H_{ax}), 1.45–1.79 (sh, 6 H, 14-H, 21-H_b, 25-H_{eq}, 26-H_{eq}, 27-H_{eq}), 1.89 (m, 1 H, 19-H), 1.95–2.05 (sh, 2 H, 12-H_a, 28-H_{ax}), 2.22 (s, 3 H, 29-H), 2.28 (m, 1 H, 12-H_b), 2.48 (m, 1 H, 24-H), 2.89 (m, 1 H, 28-H_{eq}), 3.03 (s, 3 H, 16-H), 3.18 (dd, $^2J_{3a,3b}$ = 13.9 Hz, $^3J_{3a,2}$ = 5.9 Hz, 1 H, 3-H_a), 3.23 (dd, $^2J_{3b,3a}$ = 14.0 Hz, $^3J_{3b,4}$ = 5.9 Hz, 1 H, 3-H_b), 3.71 (s, 3 H, 30-H), 4.15–4.30 (sh, 2 H, 11-H, 13-H), 4.75 (dd, $^3J_{18,19}$ = $^3J_{18,NH}$ = 8.9 Hz, 1 H, 18-H), 5.04 (ddd, $^3J_{2,NH}$ = 8.2 Hz, $^3J_{2,5a}$ = $^3J_{2,5b}$ = 6.2 Hz, 1 H, 2-H), 7.03 (d, $^3J_{NH,18}$ = 9.1 Hz, 1 H, NH), 7.17 (m, 2 H, 6-H), 7.20–7.29 (sh, 3 H, 5-H, 7-H), 7.53 (d, $^3J_{NH,2}$ = 8.2 Hz, 1 H, NH), 8.16 (s, 1 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8 (q, C-22), 16.0 (q, C-20), 19.4 (q, C-15), 19.9 (q, C-15’), 23.1 (t, C-26), 24.6 (t, C-21), 25.0 (t, C-27), 29.6 (t, C-12), 29.8 (q, C-16), 30.2 (d, C-14), 30.3 (t, C-25), 36.8 (d, C-19), 38.1 (t, C-3), 44.8 (q, C-29), 48.0 (t, C-11), 52.2 (q, C-30), 52.9, 53.0 (2 d, C-2, C-18), 55.3 (t, C-28), 57.4 (d, C-13), 69.5 (d, C-24), 125.8 (d, C-10), 127.0 (d, C-7), 128.5 (d, C-5), 129.1 (d, C-6), 135.8 (s, C-4), 142.6 (s, C-9), 159.5 (s, C-8), 171.4 (s, C-1), 173.5 (s, C-179, 174.2 (s, C-23) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, $^3J_{15,14}$ = 6.6 Hz, 3 H, 15-H), 2.80 (s, 3 H, 16-H), 4.09 (m, 1 H, 13-H), 4.48 (m, 1 H, 11-H), 4.85 (dd, $^3J_{18,NH}$ = 9.6 Hz, $^3J_{18,19}$ = 6.3 Hz, 1 H, 18-H), 8.09 (s, 1 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3 (q, C-22), 16.5 (q, C-20), 20.0 (q, C-15), 20.4 (q, C-15’), 27.2 (q, C-16), 47.5 (t, C-11) ppm. HRMS (CI) *m/z* calcd for $C_{33}H_{52}N_7O_5$ $[M+H]^+$: 626.4030; found 626.4060. Anal. calcd for $C_{33}H_{51}N_7O_5$ (625.80): C 63.34, H 8.21, N 15.67; found C 63.09, H 8.34, N 15.29.

(*R*)-Methyl 4-(1-((*R*)-3-((2*S*,3*S*)-*N*,3-dimethyl-2-((*R*)-1-methyl piperidine-2-carboxamido)pentanamido)-4-methylpentyl)-1H-1,2,3-triazole-4-carboxamido)-5-phenylpentanoate (12c).

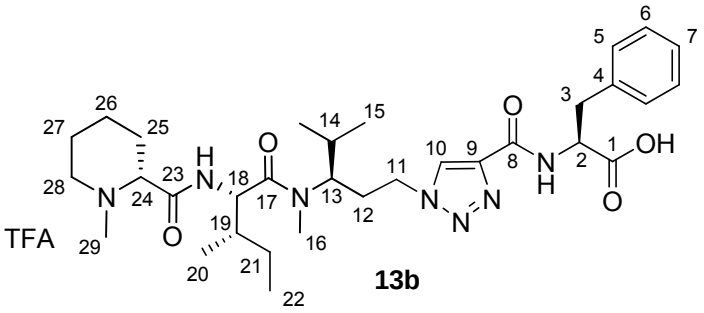
According to the general procedure for Cbz-deprotection **11c** (43 mg, 56 µmol) was hydrogenated. Following the general procedure for reductive methylation **12c** was obtained from the crude amine, paraformaldehyde (6 mg, 64 µmol) and sodium cyanoborohydride (4 mg, 60 µmol). After purification by flash chromatography (SiO_2, DCM/MeOH = 93:7), **12c** (28 mg, 43 µmol, 77% over 2 steps) could be isolated as a white solid and a mixture of rotamers; m. p. 62–64 °C.



R_f = 0.19 (DCM/MeOH, 93:7). $[\alpha]_D^{20}$ = –0.8° (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, $^3J_{17,16}$ = 6.5 Hz, 3 H, 17-H), 0.87–0.94 (sh, 6 H, 17‘-H, 24-H), 1.00 (d, $^3J_{22,21}$ = 6.7 Hz, 3 H, 22-H), 1.13–1.25 (sh, 2 H, 23-H_a, 28-H_{ax}), 1.35 (m, 1 H, 27-H_{ax}), 1.53–1.84 (sh, 7 H, 3-H_a, 16-H, 23-H_b, 27-H_{eq}, 28-H_{eq}, 29-H), 1.95 (m, 1 H, 21-H), 1.97–2.10 (sh, 3 H, 3-H_b, 14-H_a, 30-H_{ax}), 2.24 (s, 3 H, 31-H), 2.30 (m, 1 H, 14-H_b), 2.41 (t, $^3J_{2,3}$ = 7.5 Hz, 2 H, 2-H), 2.48 (m, 1 H, 26-H), 2.85–2.99 (sh, 3 H, 5-H, 30-H_{eq}), 3.05 (s, 3 H, 18-H), 3.63 (s, 3 H, 32-H), 4.18–4.32 (sh, 2 H, 15-H, 13-H), 4.41 (m, 1 H, 4-H), 4.77 (dd, $^3J_{20,21}$ = $^3J_{20,NH}$ = 8.8 Hz, 1 H, 20-H), 7.00–7.10 (sh, 2 H, NH, NH), 7.19–7.31 (sh, 5 H, 7-H, 8-H, 9-H), 8.14 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 (q, C-24), 15.8 (q, C-22), 19.2 (q, C-17), 19.7 (q, C-17’), 23.0 (t, C-28), 24.4 (t, C-23), 24.7 (t, C-29), 29.0 (t, C-3), 29.5 (t, C-14), 29.6 (q, C-18), 30.0 (d, C-16), 30.1 (t, C-27), 30.7 (t, C-2), 36.6 (d, C-21), 41.2 (t, C-5), 44.6 (q, C-31), 47.9 (t, C-13), 49.5 (d, C-4), 51.4 (q, C-32), 52.7 (d, C-20), 55.1 (t, C-30), 57.3 (d, C-15), 69.3 (d, C-26), 125.4 (d, C-12), 126.3 (d, C-9), 128.2 (d, C-7), 129.1 (d, C-8), 137.2 (s, C-6), 142.9 (s, C-11), 159.5 (s, C-10), 173.3 (2 s, C-1, C-19), 174.1 (s, C-25) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (d, $^3J_{17,16}$ = 6.6 Hz, 3 H, 17-H), 2.82 (s, 3 H, 18-H), 3.48 (m, 1 H, 4-H), 3.73 (m, 1 H, 15-H), 8.07 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1 (q, C-24), 16.3 (q, C-22), 19.8 (q, C-17), 20.2 (q, C-17’), 41.1 (t, C-5), 135.2 (s, C-6) ppm. HRMS (CI) *m/z* calcd for $C_{35}H_{56}N_7O_5$ $[M+H]^+$: 654.4343; found 654.4336.

(*S*)-2-(1-((*R*)-3-((2*S*,3*S*)-*N*,3-Dimethyl-2-((*R*)-1-methylpiperidine-2-carboxamido)pentanamido)-4-methylpentyl)-1H-1,2,3-triazole-4-carboxamido)-3-phenylpropanoicacid (13b).

According to **13a** derivative **13b** was obtained from **12b** (53 mg, 0.13 mmol) and aqueous NaOH solution (270 µL, 270 µmol, 1 M) after 16 h at room temperature. After purification by flash chromatography (SiO_2, DCM/MeOH = 85:15), TFA-salt **13b** (86 mg, 0.12 mmol, 89%) could be isolated as a white solid and a mixture of rotamers; m. p. 128–130 °C.

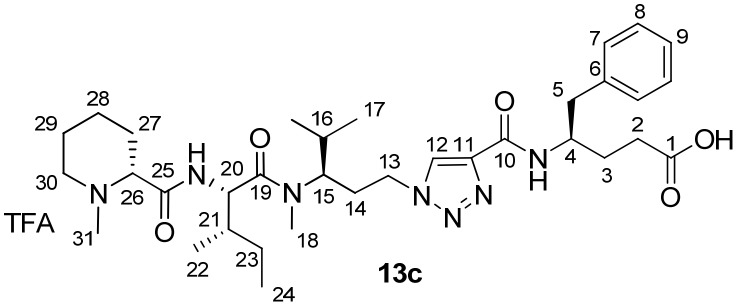


13b

R_f = 0.13 (DCM/MeOH, 85:15). $[\alpha]_D^{21}$ = –6.1° (*c* = 1.1, MeOH). Major rotamer: ^{1}H NMR (400 MHz, MeOH-d^4): δ = 0.78 (d, $^3J_{15,14}$ = 6.5 Hz, 3 H, 15-H), 0.88–0.99 (sh, 6 H, 15‘-H, 22-H), 1.03 (d, $^3J_{20,19}$ = 6.7 Hz, 3 H, 20-H), 1.24 (m, 1 H, 21-H$_a$), 1.52–1.68 (sh, 2 H, 21-H$_b$, 26-H$_{ax}$), 1.73–1.96 (sh, 6 H, 14-H, 19-H, 25-H$_{ax}$, 26-H$_{eq}$, 27-H), 2.08–2.20 (sh, 2 H, 12-H$_a$, 25-H$_{eq}$), 2.33 (m, 1 H, 12-H$_b$), 2.73 (s, 3 H, 29-H), 3.08 (m, 1 H, 28-H$_{ax}$), 3.10 (s, 3 H, 16-H), 3.17 (dd, $^2J_{3a,3b}$ = 13.9 Hz, $^3J_{3a,2}$ = 8.2 Hz, 1 H, 3-H$_a$), 3.35 (m, 1 H, 3-H$_b$), 3.49 (m, 1 H, 28-H$_{eq}$), 3.78 (m, 1 H, 24-H), 4.11 (m, 1 H, 13-H), 4.32 (m, 2 H, 11-H), 4.69 (d, $^3J_{18,19}$ = 7.8 Hz, 1 H, 18-H), 4.88 (m, 1 H, 2-H), 7.13–7.38 (sh, 5 H, 5-H, 6-H, 7-H), 8.39 (s, 1 H, 10-H) ppm. ^{13}C NMR (100 MHz, MeOH-d^4): δ 11.3 (q, C-22), 16.2 (q, C-20), 20.2 (q, C-15), 20.4 (q, C-15’), 22.3 (t, C-26), 24.0 (t, C-27), 25.5 (t, C-21), 30.2 (d, C-14), 30.9 (t, C-25), 31.0 (t, q, C-12, C-16), 37.4 (d, C-19), 38.4 (q, C-29), 49.3 (t, C-11), 54.8 (d, C-2), 56.1 (d, C-18), 56.2 (t, C-28), 59.6 (d, C-13), 68.1 (d, C-24), 118.3 (q, $^2J_{C,F}$ = 289 Hz, $\underline{C}F_3COOH$), 127.5 (d, C-10), 127.9 (d, C-7), 129.5 (d, C-5), 130.4 (d, C-6), 138.2 (s, C-4), 143.5 (s, C-9), 162.0 (s, C-8), 163.0 (q, $^3J_{C,F}$ = 34.0 Hz, $CF_3\underline{C}OOH$), 169.2 (s, C-17), 174.3 (s, C-23), 174.7 (s, C-1) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, MeOH-d^4): δ 2.77 (s, 3 H, 16-H), 4.78 (d, $^3J_{18,19}$ = 4.5 Hz, 1 H, 18-H), 8.38 (s, 1 H, 10-H) ppm. ^{13}C NMR (100 MHz, MeOH-d^4): δ 11.9 (q, C-22), 16.3 (q, C-20), 20.6 (q, C-15), 24.1 (t, C-27), 28.4 (d, C-14), 37.5 (t, C-19), 43.3 (q, C-29), 62.3 (d, C-13), 169.9 (s, C-17), 173.3 (s, C-23) ppm. HRMS (CI) *m/z* calcd for $C_{32}H_{50}N_7O_5$ $[M+H]^+$: 612.3873; found 612.3884.

(*R*)-4-(1-((*R*)-3-((2*S*,3*S*)-*N*,3-dimethyl-2-((*R*)-1-methylpiperidine-2-carboxamido)pentanamido)-4-methylpentyl)-1H-1,2,3-triazole-4-carboxamido)-5-phenylpentanoic acid (13c).

According to **13a** derivative **13c** was obtained from **12c** (78 mg, 0.12 mmol) and aqueous NaOH solution (240 µL, 240 µmol, 1 M) after 16 h at room temperature. After purification by flash chromatography (SiO_2, DCM/MeOH = 85:15), TFA-salt **13c** (93 mg, 0.12 mmol, 99%) could be isolated as a white solid and a mixture of rotamers; m. p. 122–124 °C.

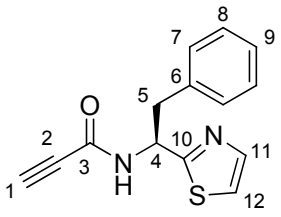


13c

R_f = 0.33 (DCM/MeOH, 85:15). $[\alpha]_D^{21}$ = –27.4° (*c* = 1.0, MeOH). Major rotamer: ^{1}H NMR (400 MHz, MeOH-d^4): δ = 0.79 (d, $^3J_{17,16}$ = 6.5 Hz, 3 H, 17-H), 0.89–0.99 (sh, 6 H, 17'-H, 24-H), 1.04 (d, $^3J_{22,21}$ = 6.8 Hz, 3 H, 22-H), 1.25 (m, 1 H, 23-H$_a$), 1.54–1.64 (sh, 2 H, 23-H$_b$, 28-H$_{ax}$), 1.73–2.03 (sh, 8 H, 3-H, 16-H, 21-H, 27-H$_{ax}$, 28-H$_{eq}$, 29-H), 2.08–2.20 (sh, 2 H, 14-H$_a$, 27-H$_{eq}$), 2.30–2.44 (sh, 3 H, 2-H, 14-H$_b$), 2.72 (s, 3 H, 31-H), 2.91 (d, $^3J_{5,4}$ = 7.0 Hz, 2 H, 5-H), 3.08 (m, 1 H, 30-H$_{ax}$), 3.11 (s, 3 H, 18-H), 3.49 (m, 1 H, 30-H$_{eq}$), 3.78 (m, 1 H, 26-H), 4.11 (m, 1 H, 15-H), 4.26–4.47 (sh, 3 H, 4-H, 13-H), 4.69 (d, $^3J_{20,21}$ = 7.9 Hz, 1 H, 20-H), 7.13–7.28 (sh, 5 H, 7-H, 8-H, 9-H), 8.34 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, MeOH-d^4): δ 11.3 (q, C-24), 16.2 (q, C-22), 20.2 (q, C-17), 20.4 (q, C-17'), 22.3 (t, C-28), 24.0 (t, C-29), 25.5 (t, C-23), 30.2 (t, C-3), 30.7 (t, C-14), 30.8 (q, C-18), 30.9 (d, C-16), 31.0 (t, C-27), 31.9 (t, C-2), 37.4 (d, C-21), 42.1 (t, C-5), 42.9 (q, C-31), 49.2 (t, C-13), 51.8 (d, C-4), 56.1 (d, C-20), 56.2 (t, C-30), 59.6 (d, C-15), 68.1 (d, C-26), 118.3 (q, $^2J_{C,F}$ = 296 Hz, $\underline{C}F_3COOH$), 127.3 (d, C-12), 127.4 (d, C-9), 129.4 (d, C-7), 130.4 (d, C-8), 139.7 (s, C-6), 143.9 (s, C-11), 162.3 (s, C-10), 163.0 (q, $^3J_{C,F}$ = 34.0 Hz, $CF_3\underline{C}OOH$), 169.3 (s, C-19), 174.7 (s, C-25), 176.7 (s, C-1) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, MeOH-d^4): δ 2.72 (s, 3 H, 31-H), 2.79 (s, 3 H, 18-H), 4.79 (d, $^3J_{20,21}$ = 4.6 Hz, 1 H, 20-H), 8.32 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, MeOH-d^4): δ 11.3 (q, C-24), 16.3 (q, C-22), 20.6 (q, C-17), 28.4 (q, C-18), 62.3 (d, C-15), 143.9 (s, C-11), 169.9 (s, C-19), 173.4 (s, C-25) ppm. HRMS (CI) *m/z* calcd for $C_{34}H_{54}N_7O_5$ $[M+H]^+$: 640.4186; found 640.4193.

(*S*)-*N*-(2-phenyl-1-(thiazol-2-yl)ethyl)propiolamide (14)

Following the general procedure for amide coupling with T3P, **14** was obtained from (*S*)-2-phenyl-1-(thiazol-2-yl)ethanamine (225 mg, 1.1 mmol, 93% ee), diisopropyl ethylamine (0.19 mL, 1.1 mmol), propiolic acid (70 µL, 1.1 mmol) and T3P (0.98 mL, 1.65 mmol, 50% in ethyl acetate). After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 1:1), alkyne **14** (246 mg, 0.96 mmol, 87%) could be isolated as a yellowish solid and a mixture of rotamers; m.p. 106–108 °C.



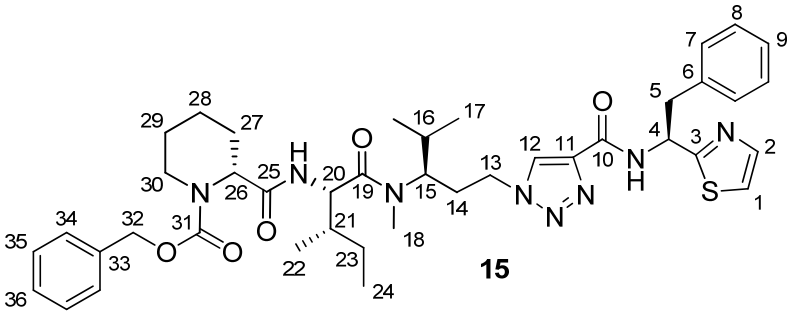
14

R_f = 0.30 (petroleum ether/EtOAc, 1:1). $[\alpha]_D^{21}$ = +2.1° (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (s, 1 H, 1-H), 3.27 (dd, $^2J_{5a,5b}$ = 13.6 Hz, $^3J_{5a,4}$ = 7.4 Hz, 1 H, 5-H$_a$), 3.34 (dd, $^2J_{5b,5a}$ = 13.7 Hz, $^3J_{5b,4}$ = 6.4 Hz, 1 H, 5-H$_b$), 5.63 (m, 1 H, 4-H), 7.07 (m, 2 H, 8-H), 7.19–7.29 (m, 5 H, 7-H, 9-H, 12-H), 7.72 (d, $^3J_{11,12}$ = 3.3 Hz, 1 H, 11-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.7 (t, C-5), 52.5 (d, C-4), 74.1 (d, C-1), 76.8 (s, C-2), 119.3 (d, C-12), 127.1 (d, C-9), 128.6 (d, C-7), 129.4 (d, C-8), 135.9 (s, C-6), 142.4 (d, C-11), 151.4 (s, C-3), 168.6 (s, C-10) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (s, 1 H, 1-H), 3.44 (dd, $^2J_{5b,5a}$ = 13.8 Hz, $^3J_{5b,4}$ = 6.0 Hz, 1 H, 5-H$_b$), 5.63 (m, 1 H, 4-H), 7.80 (d, $^3J_{11,12}$ = 3.3 Hz, 1 H, 11-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.6 (t, C-5), 56.9

(d, C-4), 74.6 (d, C-1), 79.8 (s, C-2), 119.4 (d, C-12), 127.3 (d, C-9), 128.7 (d, C-7), 129.6 (d, C-8), 135.5 (s, C-6), 143.1 (d, C-11) ppm. HRMS (CI) *m/z* calcd for $C_{14}H_{13}N_2OS$ $[M+H]^+$: 257.0748; found 257.0752. Anal. calcd for $C_{14}H_{12}N_2OS$ (256.32): C 65.50, H 4.72, N 10.93; found C 65.58, H 4.58, N 10.84.

(*R*)-Benzyl 2-((2*S*,3*S*)-3-methyl-1-(methyl((*R*)-4-methyl-1-(4-((*S*)-2-phenyl-1-(thiazol-2-yl)ethylcarbamoyl)-1H-1,2,3-triazol-1-yl)pentan-3-yl)amino)-1-oxopentan-2-ylcarbamoyl)piperidine-1-carboxylate (15).

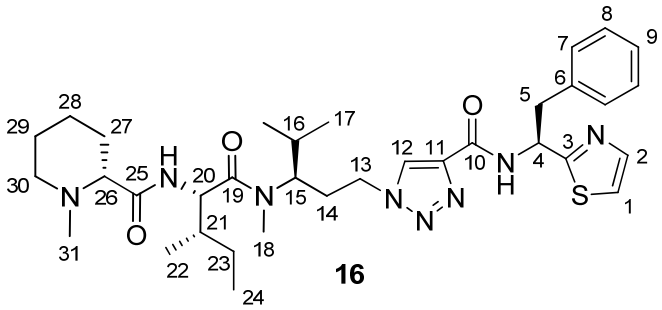
Following the general procedure for Click-reaction **15** was obtained from azide **10** (215 mg, 0.42 mmol), alkyne **14** (161 mg, 0.48 mmol, 93% ee), $CuSO_4$ solution (130 µL, 130 µmol, 1 M) and sodium ascorbate solution (130 µL, 130 µmol, 1 M) in *tert*-butanol/water after 3 d. After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 2:8), triazole **15** (320 mg, 0.42 mmol, 99%, >95% ds) could be isolated as a white solid and a mixture of rotamers; m. p. 150–152 °C.



R_f = 0.18 (petroleum ether/EtOAc, 2:8). $[\alpha]_D^{21}$ = –21.9° (*c* = 1.0, MeOH, >95% ds). Major rotamer: ^{1}H NMR (400 MHz, MeOH-d^4): δ = 0.70 (m, 3 H, 17-H), 0.82–0.93 (sh, 6 H, 17‘-H, 24-H), 0.96 (d, $^3J_{22,21}$ = 6.6 Hz, 3 H, 22-H), 1.14 (m, 1 H, 23-H$_a$), 1.33–1.44 (sh, 2 H, 28-H$_{ax}$, 29-H$_{ax}$), 1.50–1.80 (sh, 5 H, 16 H, 23-H$_b$, 27-H$_{ax}$, 28-H$_{eq}$, 29-H$_{eq}$), 1.94 (m, 1 H, 21-H), 2.09 (m, 1 H, 14-H$_a$), 2.18 (m, 1 H, 27-H$_{eq}$), 2.28 (m, 1 H, 14-H$_b$), 3.04 (s, 3 H, 18-H), 3.13 (m, 1 H, 30-H$_{ax}$), 3.34 (dd, $^2J_{5a,5b}$ = 14.0 Hz, $^3J_{5a,4}$ = 9.2 Hz, 1 H, 5-H$_a$), 3.50 (dd, $^2J_{5b,5a}$ = 13.8 Hz, $^3J_{5b,4}$ = 5.7 Hz, 1 H, 5-H$_b$), 3.96–4.14 (sh, 15-H, 30-H$_{eq}$), 4.27 (m, 2 H, 13-H), 4.73 (d, $^3J_{20,21}$ = 8.9 Hz, 1 H, 20-H), 4.80 (bs, 1 H, 26-H), 5.10 (m, 2 H, 32-H), 5.75 (dd, $^3J_{4,5a}$ = 9.1 Hz, $^3J_{4,5b}$ = 5.7 Hz, 1 H, 4-H), 7.11–7.32 (sh, 10 H, 7-H, 8-H, 9-H, 34-H, 35-H, 36-H), 7.50 (d, $^3J_{1,2}$ = 3.2 Hz, 1 H, 1-H), 7.77 (d, $^3J_{2,1}$ = 3.2 Hz, 1 H, 2-H), 8.41 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, MeOH-d^4): δ 11.0 (q, C-24), 16.2 (q, C-22), 20.3 (q, C-17), 21.2 (t, C-28), 25.6 (2 t, C-23, C-29), 28.1 (t, C-27), 30.7, 31.0 (t, d, q, C-14, C-16, C-18), 37.4 (d, C-21), 41.8 (t, C-5), 43.4 (t, C-30), 54.0 (d, C-4), 55.6 (d, C-20), 56.2 (d, C-26), 62.1 (d, C-15), 68.5 (t, C-32), 120.9 (d, C-1), 127.9 (d, C-12), 128.7, 129.1, 129.5, 129.6 130.4 (6 d, C-7, C-8, C-9, C-34, C-35, C-36), 137.9 (s, C-33), 138.4 (s, C-6), 143.0 (s, C-11), 143.4 (d, C-2), 162.1 (s, C-10), 173.4 (2 s, C-3, C-19), 175.1 (s, C-25) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, MeOH-d^4): δ 1.03 (d, $^3J_{17,16}$ = 6.5 Hz, 3 H, 17-H), 2.74 (s, 3 H, 18-H), 4.92 (s, 2 H, 32-H), 7.47 (m, 1 H, 1-H), 8.37 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, MeOH-d^4): δ 11.2 (q, C-24), 16.7 (q, C-22), 20.1 (q, C-17), 20.9 (q, C-17’), 21.1 (t, C-28), 29.0 (q, C-18), 32.3, 32.4 (t, d, C-14, C-16), 54.3 (d, C-4), 55.5 (d, C-20), 56.1 (d, C-26), 68.2 (t, C-32), 127.7 (d, C-12) ppm. HRMS (CI) *m/z* calcd for $C_{34}H_{47}N_8O_4S$ $[M+H]^+$: 663.3441; found 663.3430.

(*R*)-1-Methyl-*N*-((2*S*,3*S*)-3-methyl-1-(methyl((*R*)-4-methyl-1-(4-((*S*)-2-phenyl-1-(thiazol-2-yl)ethylcarbamoyl)-1H-1,2,3-triazol-1-yl)pentan-3-yl)amino)-1-oxopentan-2-yl)piperidine-2-carboxamide (16).

Compound **15** (210 mg, 0.27 mmol, >95% ds) was treated with HBr in acetic acid (0.46 ml, 2.66 mmol, 33%) under nitrogen at room temperature for 30 min. The reaction mixture was diluted with diethyl ether and the HBr salt was filtrated and washed with diethyl ether. Saturated aqueous $NaHCO_3$ was added to the HBr-salt and the free amine was extrated with DCM. The combined organic layer was dried over Na_2SO_4 and the solvent was removed in vacuum to obtain the crude amine. Following the general procedure for reductive methylation **16** was obtained from the crude amine, paraformaldehyde (26 mg, 0.28 mmol) and sodium cyanoborohydride (19 mg, 0.29 mmol). The crude product was purified by flash chromatography (SiO_2, DCM:MeOH 95:5) to yield **16** [a.) 74 mg, 114 µmol, 78% ds, b.) 22 mg, 34 µmol, >95% ds] as a white solid (60% over 2 steps) and a mixture of rotamers; m. p. 70–72 °C (>95% ds).



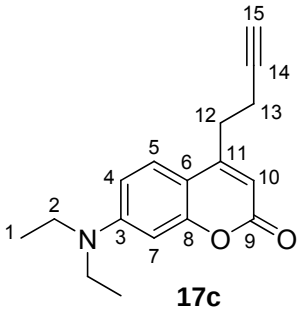
16

Major diastereomer: R_f = 0.16 (DCM/MeOH, 95:5). $[\alpha]_D^{21}$ = –22.5° (*c* = 0.9, $CHCl_3$, >95% ds). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, $^3J_{17,16}$ = 6.6 Hz, 3 H, 17-H), 0.88–0.92 (sh, 6 H, 17‘-H, 24-H), 0.97 (d, $^3J_{22,21}$ = 6.7 Hz, 3 H, 22-H), 1.13–1.25 (sh, 2 H, 23-H_a, 28-H_{ax}), 1.33 (m, 1 H, 27-H_{ax}), 1.64–1.79 (sh, 6 H, 16-H, 23-H_b, 27-H_{eq}, 28-H_{eq}, 29-H), 1.88 (m, 1 H, 21-H), 1.94–2.03 (sh, 2 H, 14-H_a, 30-H_{ax}), 2.22 (s, 3 H, 31-H), 2.26 (m, 1 H, 14-H_b), 2.47 (dd, $^3J_{26,27eq}$ = 10.9 Hz, $^3J_{26,27ax}$ = 2.6 Hz, 1 H, 26-H), 2.89 (m, 1 H, 30-H_{eq}), 3.03 (s, 3 H, 18-H), 3.42 (dd, $^3J_{5a,5b}$ = $^3J_{5,4}$ = 6.6 Hz, 2 H, 5-H), 4.15–4.31 (sh, 3 H, 13-H, 15-H), 4.75 (dd, $^3J_{20,21}$ = $^3J_{20,NH}$ = 8.9 Hz, 1 H, 20-H), 5.79 (m, 1 H, 4-H), 7.02 (d, $^3J_{NH,20}$ = 9.3 Hz, 1 H, NH), 7.11–7.25 (sh, 6 H, 1-H, 7-H, 8-H, 9-H), 7.77 (d, $^3J_{2,1}$ = 3.2 Hz, 1 H, 2-H), 7.82 (d, $^3J_{NH,4}$ = 8.6 Hz, 1 H, NH), 8.15 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.9 (q, C-24), 16.0 (q, C-22), 19.4 (q, C-17), 19.9 (q, C-17’), 23.2 (t, C-28), 24.6 (t, C-23), 25.0 (t, C-27), 29.7 (t, C-14), 29.9 (q, C-18), 30.2 (d, C-16), 30.4 (t, C-27), 36.8 (d, C-21), 41.6 (t, C-5), 44.9 (q, C-31), 48.1 (t, C-13), 51.9 (d, C-4), 53.0 (d, C-20), 55.3 (t, C-30), 57.5 (d, C-15), 69.5 (d, C-26), 118.9 (d, C-1), 126.0 (d, C-12), 126.8 (d, C-9), 128.5 (d, C-7), 129.4 (d, C-8), 136.4 (s, C-6), 143.0 (d, C-2), 159.4 (s, C-10), 170.2 (s, C-3), 173.6 (s, C-19), 174.4 (s, C-25) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, $^3J_{17,16}$ = 6.5 Hz, 3 H, 17-H), 3.03 (s, 3 H, 18-H), 3.39 (m, 1 H, 5-H_a), 3.45 (m, 1 H, 5-H_b), 3.73 (m, 1 H, 15-H), 4.09 (m, 1 H, 13-H_a), 4.48 (m, 1 H, 13-H_b), 8.08 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2 (q, C-24), 16.5 (q, C-22), 20.0 (q, C-17), 20.3 (q, C-17’), 37.6 (d, C-21), 44.8 (q, C-31), 47.5 (t, C-13), 60.7 (d, C-15), 69.3 (d, C-26), 142.4 (d, C-2), 159.3 (s, C-10) ppm. Minor diastereomer (selected signals): R_f = 0.19 (DCM/MeOH, 95:5). Major rotamer: ^{1}H

NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, 31-H), 8.13 (s, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.9 (q, C-24), 19.4 (q, C-17), 37.1 (d, C-21), 44.5 (q, C-31), 52.7 (d, C-20), 55.3 (t, C-30), 69.7 (d, C-26), 172.4 (s, C-19), 174.4 (s, C-25) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.77 (s, 3 H, 18-H), 8.09 (s, 1 H, 12-H) ppm. HRMS (CI) *m/z* calcd for $C_{34}H_{51}N_8O_3S$ $[M+H]^+$: 651.3805; found 651.3769. Anal. calcd for $C_{33}H_{51}N_7O_5$ (650.88): C 62.74, H 7.74, N 17.22; found C 62.68, H 7.63, N 17.08.

4-(But-3-ynyl)-7-(diethylamino)-2H-chromen-2-one (17c)

Chlorotitanium triisopropoxide (20 mL, 20 mmol, 1 M in hexanes) was added to a solution of 2-diethyl aminophenol (1.65 g, 10 mmol) and methyl 3-oxohept-6-ynoate (1.59 g, 10.3 mmol) in dry toluene (30 mL), and the reaction mixture was refluxed for 18 h. After cooling to room temperature the mixture was diluted with DCM and poured into saturated aqueous Na/K tartrate solution. The layer ware separated and the aqueous layer was extracted thrice with DCM. The combined extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (SiO_2, DCM, DCM/MeOH = 9:1) to yield coumarin **17c** (682 mg, 2.53 mmol, 25%) as a red solid; m. p. 74–76 °C.

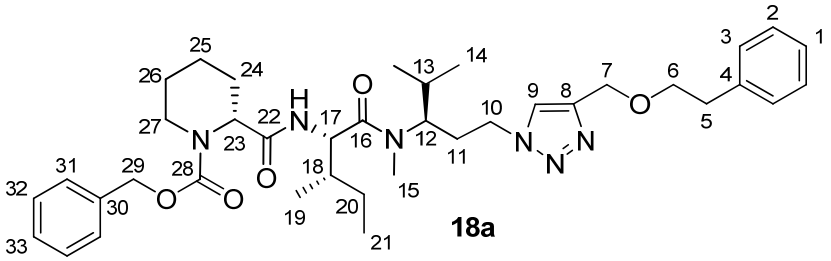


17c

R_f = 0.18 (DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, $^3J_{1,2}$ = 7.1 Hz, 6 H, 1-H), 2.04 (t, $^4J_{15,14}$ = 2.6 Hz, 1 H, 15-H), 2.57 (dt, $^3J_{13,15}$ = 7.5 Hz, $^4J_{13,15}$ = 2.6 Hz, 2 H, 13-H), 2.92 (t, $^3J_{12,13}$ = 7.3 Hz, 2 H, 12-H), 3.41 (q, $^3J_{2,1}$ = 7.1 Hz, 4 H, 2-H), 5.99 (s, 1 H, 10-H), 6.50 (d, $^4J_{7,4}$ = 2.6 Hz, 1 H, 7-H), 6.58 (dd, $^3J_{4,5}$ = 9.0 Hz, $^4J_{4,7}$ = 2.6 Hz, 1 H, 4-H), 7.38 (d, $^3J_{5,4}$ = 9.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4 (q, C-1), 17.6 (t, C-13), 30.4 (t, C-12), 44.6 (t, C-2), 70.0 (d, C-15), 82.2 (s, C-14), 97.8 (d, C-7), 107.7 (d, C-10), 107.9 (s, C-6), 108.4 (d, C-4), 124.9 (d, C-5), 150.4 (s, C-3), 154.0 (s, C-9), 156.2 (s, C-11), 162.0 (s, C-8) ppm. HRMS (CI) *m/z* calcd for $C_{17}H_{19}NO_2$ $[M]^+$: 269.1416; found 269.1434.

(*R*)-Benzyl 2-((2*S*,3*S*)-3-methyl-1-(methyl((*R*)-4-methyl-1-(4-(phenethoxymethyl)-1H-1,2,3-triazol-1-yl)pentan-3-yl)amino) -1-oxopentan-2-ylcarbamoyl)piperidine-1-carboxylate (18a).

Following the general procedure for Click-reaction **18a** was obtained from azide **10** (99 mg, 0.19 mmol), alkyne **17a** (54 mg, 0.34 mmol), $CuSO_4$ solution (38 µL, 38 µmol, 1 M) and sodium ascorbate solution (38 µL, 38 µmol, 1 M) in *tert*-butanol/water after 1 d. After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 4:6), triazole **18a** (109 mg, 0.16 mmol, 85%) could be isolated as colourless resin and a mixture of rotamers.

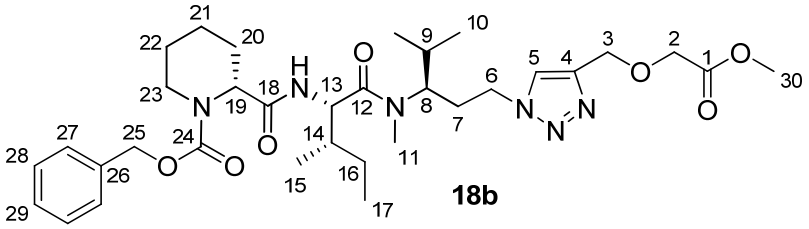


18a

R_f = 0.12 (petroleum ether/EtOAc, 4:6). $[\alpha]_D^{20}$ = +6.2° (*c* = 0.6, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (d, $^3J_{14,13}$ = 6.5 Hz, 3 H, 14-H), 0.79 (m, 3 H, 21-H), 0.84 (d, $^3J_{14',13}$ = 6.5 Hz, 3 H, 14'-H), 0.88 (m, 3 H, 19-H), 1.00 (m, 1 H, 20-H_a), 1.24–1.60 (sh, 6 H, 20-H_b, 24-H_{ax}, 25-H, 26-H), 1.66 (m, 1 H, 13-H), 1.74 (m, 1 H, 18-H), 1.92 (m, 1 H, 11-H_a), 2.15 (m, 1 H, 11-H_b), 2.23 (m, 1 H, 24-H_{eq}), 2.78 (m, 1 H, 27-H_{ax}), 2.83 (t, $^3J_{5,6}$ = 7.1 Hz, 2 H, 5-H), 2.95 (s, 3 H, 15-H), 3.67 (t, $^3J_{6,5}$ = 7.1 Hz, 2 H, 6-H), 3.98–4.05 (sh, 2 H, 10-H_a, 27-H_{eq}), 4.13–4.22 (sh, 2 H, 10-H_b, 12-H), 4.57 (s, 2 H, 7-H), 4.74 (dd, $^3J_{17,NH}$ = $^3J_{17,18}$ = 8.4 Hz, 1 H, 17-H), 4.81 (m, 1 H, 23-H), 5.07 (d, $^2J_{29a,29b}$ = 12.3 Hz, 1 H, 29-H_a), 5.12 (d, $^2J_{29b,29a}$ = 12.3 Hz, 1 H, 29-H_b), 6.48 (m, 1 H, NH), 7.11–7.14 (sh, 2 H, 1-H, 3-H), 7.18–7.34 (sh, 7 H, 2-H, 31-H, 32-H, 33-H), 7.42 (s, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.9 (q, C-21), 15.9 (q, C-19), 19.4 (q, C-14), 19.8 (q, C-14'), 20.4 (t, C-25), 24.2 (t, C-26), 24.7 (t, C-20), 25.6 (t, C-24), 29.6 (q, C-15), 29.8 (d, C-13), 30.2 (t, C-11), 36.1 (t, C-5), 36.9 (d, C-18), 42.2 (t, C-27), 47.6 (t, C-10), 53.5 (d, C-17), 54.9 (d, C-23), 57.5 (d, C-12), 64.3 (t, C-7), 67.6 (t, C-29), 71.4 (t, C-6), 122.7 (d, C-9), 126.1 (d, C-1), 127.8, 128.1, 128.2, 128.5, 128.8 (5 d, C-2, C-3, C-31, C-32, C-33), 136.3 (s, C-30), 138.7 (s, C-4), 145.2 (s, C-8), 156.1 (s, C-28), 170.5 (s, C-16), 173.5 (s, C-22) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (s, 3 H, 15-H), 3.63 (m, 2 H, 6-H), 4.53 (s, 2 H, 7-H), 5.01 (d, $^2J_{29a,29b}$ = 5.7 Hz, 1 H, 29-H_a), 6.94 (m, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1 (q, C-21), 16.2 (q, C-19), 20.1 (t, C-14), 24.5 (t, C-20), 26.0 (t, C-24), 27.4 (q, C-15), 42.0 (t, C-27), 47.0 (t, C-19), 55.3 (d, C-23), 60.8 (d, C-12) ppm. HRMS (CI) *m/z* calcd for $C_{38}H_{55}N_6O_5$ $[M+H]^+$: 675.4234; found 675.4219.

(*R*)-Benzyl 2-((2*S*,3*S*)-1-(((*R*)-1-(4-((2-methoxy-2-oxoethoxy) methyl)-1H-1,2,3-triazol-1-yl)-4-methylpentan-3-yl)(methyl) amino)-3-methyl-1-oxopentan-2-ylcarbamoyl)piperidine-1-carboxylate (18b).

Following the general procedure for Click-reaction **18b** was obtained from azide **10** (203 mg, 0.39 mmol), alkyne **17b** (117 mg, 0.91 mmol), $CuSO_4$ solution (80 µL, 80 µmol, 1 M) and sodium ascorbate solution (80 µL, 80 µmol, 1 M) in *tert*-butanol/water after 1 d. After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 2:8), triazole **18b** (209 mg, 0.33 mmol, 85%) could be isolated as colourless resin and a mixture of rotamers.

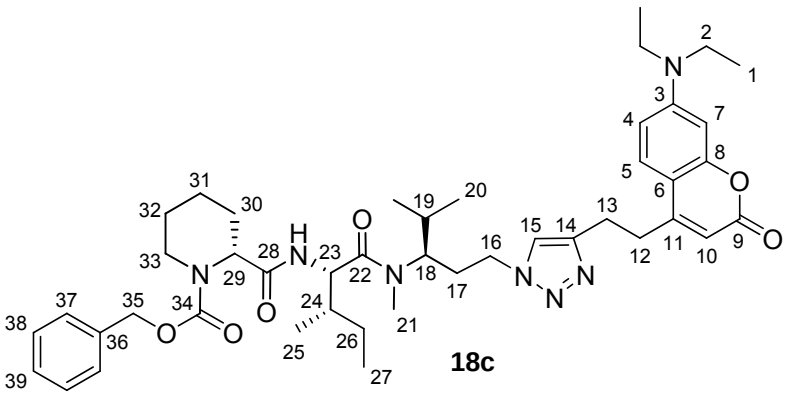


18b

R_f = 0.15 (petroleum ether/EtOAc, 2:8). $[\alpha]_D^{20}$ = +8.0° (*c* = 0.6, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75 (d, $^3J_{10,9}$ = 6.6 Hz, 3 H, 10-H), 0.84 (m, 3 H, 17-H), 0.89 (d, $^3J_{10',9}$ = 6.5 Hz, 3 H, 10'-H), 0.93 (m, 3 H, 15-H), 1.06 (m, 1 H, 16-H_a), 1.30–1.66 (sh, 6 H, 16-H_b, 20-H_{ax}, 21-H, 22-H), 1.72 (m, 1 H, 9-H), 1.80 (m, 1 H, 14-H), 2.01 (m, 1 H, 7-H_a), 2.23 (m, 1 H, 7-H_b), 2.28 (m, 1 H, 20-H_{eq}), 2.82 (m, 1 H, 23-H_{ax}), 3.01 (s, 3 H, 11-H), 3.74 (s, 3 H, 30-H), 4.05–4.14 (sh, 2 H, 6-H_a, 23-H_{eq}), 4.17 (s, 2 H, 2-H), 4.22–4.28 (sh, 2 H, 6-H_b, 8-H), 4.74 (s, 2 H, 3-H), 4.80 (dd, $^3J_{13,NH}$ = $^3J_{13,14}$ = 8.6 Hz, 1 H, 13-H), 4.87 (m, 1 H, 19-H), 5.13 (d, $^2J_{25a,25b}$ = 12.2 Hz, 1 H, 25-H_a), 5.18 (d, $^2J_{25b,25a}$ = 12.2 Hz, 1 H, 25-H_b), 7.27–7.38 (sh, 5 H, 27-H, 28-H, 29-H), 7.69 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.9 (q, C-17), 15.9 (q, C-15), 19.4 (q, C-10), 19.8 (q, C-10'), 20.4 (t, C-21), 24.2 (t, C-22), 24.8 (t, C-16), 25.6 (t, C-20), 29.7 (q, C-11), 29.8 (d, C-9), 30.2 (t, C-7), 36.9 (d, C-14), 42.3 (t, C-23), 47.6 (t, C-6), 51.8 (q, C-30), 53.5 (d, C-13), 54.9 (d, C-19), 57.5 (d, C-8), 64.5 (t, C-3), 67.2 (t, C-2), 67.6 (t, C-25), 123.4 (d, C-5), 127.8, 128.1, 128.5 (3 d, C-27, C-28, C-29), 136.3 (s, C-26), 144.1 (s, C-8), 156.4 (s, C-24), 170.5, 170.5 (2 s, C-1, C-12), 173.5 (s, C-18) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75 (s, 3 H, 11-H), 3.72 (s, 3 H, 30-H), 4.70 (s, 2 H, 3-H), 5.08 (d, $^2J_{25a,25b}$ = 4.2 Hz, 1 H, 25-H_a) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2 (q, C-15), 20.8 (t, C-10), 24.5 (t, C-16), 26.0 (t, C-20), 27.4 (q, C-11), 42.0 (t, C-23), 47.1 (t, C-6), 55.4 (d, C-19), 60.8 (d, C-8), 64.4 (t, C-3), 67.0 (t, C-2), 67.4 (t, C-25) ppm. HRMS (CI) *m/z* calcd for $C_{33}H_{51}N_6O_7$ $[M+H]^+$: 643.3819; found 643.3813.

(*R*)-Benzyl 2-((2*S*,3*S*)-1-(((*R*)-1-(4-(2-(7-(diethylamino)-2-oxo-2H-chromen-4-yl)ethyl)-1H-1,2,3-triazol-1-yl)-4-methylpentan-3-yl)(methyl)amino)-3-methyl-1-oxopentan-2-ylcarbamoyl)piperidine-1-carboxylate (18c).

Following the general procedure for Click-reaction **18c** was obtained from azide **10** (126 mg, 0.24 mmol), alkyne **17c** (97 mg, 0.36 mmol), $CuSO_4$ solution (50 µL, 50 µmol, 1 M) and sodium ascorbate solution (50 µL, 50 µmol, 1 M) in *tert*-butanol/water after 3 d. After purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate = 2:8), triazole **18c** (181 mg, 0.23 mmol, 99%) could be isolated as colourless resin and a mixture of rotamers; m. p. 82–84 °C.

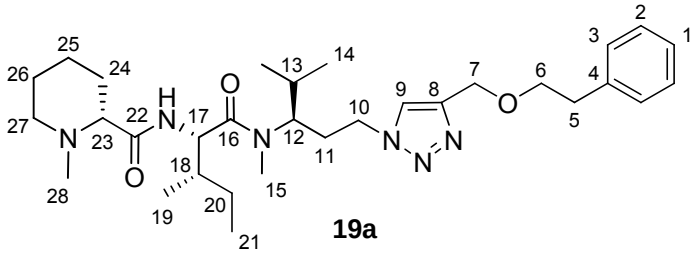


R_f = 0.11 (petroleum ether/EtOAc, 2:8). $[\alpha]_D^{20}$ = +9.0° (*c* = 1.2, $CHCl_3$). Major rotamer**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, $^3J_{20,19}$ = 6.5 Hz, 3 H, 20-H), 0.83 (m, 3 H, 27-H), 0.88 (d, $^3J_{20',19}$ = 6.5 Hz, 3 H, 20'-H), 0.93 (m, 3 H, 25-H), 1.05 (m, 1 H, 26-H_a), 1.17 (t, $^3J_{1,2}$ = 7.1 Hz, 3 H, 1-H), 1.30–1.40 (sh, 2 H, 31-H_{ax}, 32-H_{ax}), 1.46–1.64 (sh, 4 H, 20-H_a, 26-H_b, 31-H_{eq},

32-H_{eq}), 1.71 (m 1 H, 19-H), 1.79 (m, 1 H, 24-H), 1.96 (m, 1 H, 17-H_a), 2.20 (m, 1 H, 17-H_b), 2.28 (m, 1 H, 30-H_{eq}), 2.83 (m, 33-H_{ax}), 3.00 (s, 3 H, 21-H), 3.04–3.10 (sh, 4 H, 12-H, 13-H), 3.38 (q, $^3J_{2,1}$ = 7.0 Hz, 4 H, 2-H), 4.01–4.08 (sh, 2 H, 16-H_a, 33-H_{eq}), 4.14–4.27 (sh, 2 H, 16-H_b, 18-H), 4.79 (dd, $^3J_{23,NH}$ = $^3J_{23,24}$ = 8.6 Hz, 1 H, 23-H), 4.86 (m, 1 H, 29-H), 5.12 (d, $^2J_{35a,35b}$ = 12.8 Hz, 1 H, 35-H_a), 5.16 ($^2J_{35b,35a}$ = 12.2 Hz, 1 H, 35-H_b), 5.89 (s, 1 H, 10-H), 6.46 (d, $^4J_{7,4}$ = 2.4 Hz, 1 H, 7-H), 6.55 (dd, $^3J_{4,5}$ = 9.0 Hz, $^4J_{4,7}$ = 2.3 Hz, 1 H, 4-H), 6.58 (bs, 1 H, NH), 7.28–7.36 (sh, 5 H, 36-H, 37-H, 38-H), 7.41 (s, 1 H, 15-H), 7.44 (d, $^3J_{5,4}$ = 9.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.9 (q, C-27), 12.4 (q, C-1), 15.9 (q, C-25), 19.4 (q, C-20), 19.8 (q, C-20‘), 20.3 (t, C-31), 24.2 (t, C-26), 24.4 (d, C-19), 24.8 (t, C-32), 25.5 (t, C-30), 29.6 (q, C-21), 29.7 (d, C-19), 30.2 (t, C-17), 31.1 (t, C-12), 36.9 (d, C-24), 42.2 (t, C-33), 44.6 (t, C-2), 47.4 (t, C-16), 53.5 (d, C-23), 54.9 (d, C-29), 57.6 (d, C-18), 67.6 (t, C-35), 97.7 (d, C-7), 107.6 (d, C-10), 107.9 (s, C-6), 108.4 (d, C-4), 121.6 (d, C-15), 125.2 (d, C-5), 127.7, 128.0, 128.4 (3 d, C-37, C-38, C-39), 136.3 (s, C-36), 146.0 (s, C-14), 150.3 (s, C-3), 155.3 (s, C-9), 155.4 (s, C-34), 156.2 (s, C-11), 162.1 (s, C-8), 170.5 (s, C-22), 173.4 (s, C-28) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, $^3J_{25,24}$ = 6.5 Hz, 3 H, 25-H), 2.71 (s, 3 H, 21-H), 5.04 (s, 2 H, 35-H), 5.92 (s, 1 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1 (q, C-27), 16.2 (q, C-25), 20.1 (q, C-20), 31.3 (t, C-12), 55.3 (d, C-29), 60.8 (d, C-18) ppm. HRMS (CI) *m/z* calcd for $C_{44}H_{62}N_7O_6$ $[M+H]^+$: 784.4761; found 784.4790.

(*R*)-1-Methyl-*N*-((2*S*,3*S*)-3-methyl-1-(methyl((*R*)-4-methyl-1-(4-(phenethoxymethyl)-1H-1,2,3-triazol-1-yl)pentan-3-yl) amino)-1-oxopentan-2-yl)piperidine-2-carboxamide (19a).

According to the general procedure for Cbz-deprotection **18a** (74 mg, 0.11 mmol) was hydrogenated. Following the general procedure for reductive methylation **19a** was obtained from the crude amine, paraformaldehyde (12 mg, 0.12 mmol) and sodium cyanoborohydride (9 mg, 0.13 mmol). After purification by flash chromatography (SiO_2, DCM/MeOH = 9:1), **19a** (56 mg, 0.10 mmol, 87% over 2 steps) could be isolated as a colourless resin and a mixture of rotamers.



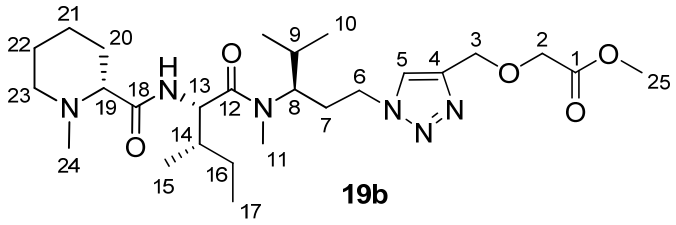
19a

R_f = 0.32 (DCM/MeOH, 9:1). $[\alpha]_D^{20}$ = +9.2° (*c* = 0.8, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (d, $^3J_{14,13}$ = 6.6 Hz, 3 H, 14-H), 0.83 (d, $^3J_{14',13}$ = 6.6 Hz, 3 H, 14’-H), 0.85 (t, $^3J_{21,20}$ = 7.5 Hz, 3 H, 21-H), 0.91 (d, $^3J_{19,18}$ = 6.8 Hz, 3 H, 19-H), 1.08–1.18 (sh, 2 H, 20-H_a, 25-H_{ax}), 1.28 (m, 1 H, 24-H_{ax}), 1.34–1.68 (sh, 5 H, 20-H_b, 24-H_{eq}, 25-H_{eq}, 26-H), 1.72 (m, 1 H, 13-H), 1.84 (m, 1 H, 18-H), 1.89–1.98 (sh, 2 H, 11-H_a, 27-H_{ax}), 2.11–2.19 (sh, 4 H, 11-H_b, 28-H), 2.41 (dd, $^3J_{23,24eq}$ = 10.7 Hz, $^3J_{23,24ax}$ = 2.2 Hz, 1 H, 23-H), 2.81 (m, 1 H, 27-H_{eq}), 2.84 (t, $^3J_{5,6}$ = 2.84 Hz, 2 H, 5-H), 2.96 (s, 3 H, 15-H), 3.67 (t, $^3J_{6,5}$ = 7.2 Hz, 2 H, 6-H), 4.02 (dt, $^2J_{10a,10b}$ = 13.8 Hz, $^3J_{10,11}$ = 7.9 Hz, 1 H, 10-H_a), 4.16–4.23 (sh, 2 H, 10-H_b, 12-H),

4.57 (s, 2 H, 7-H), 4.81 (dd, $^3J_{17,NH}$ = $^3J_{17,18}$ = 8.9 Hz, 1 H, 17-H), 6.96 (d, $^3J_{NH,17}$ = 9.1 Hz, 1 H, NH), 7.11–7.17 (sh, 3 H, 1-H, 3-H), 7.21 (m, 2 H, 2-H), 7.46 (s, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8 (q, C-21), 16.0 (q, C-19), 19.4 (q, C-14), 19.9 (q, C-14'), 23.2 (t, C-25), 24.6 (t, C-20), 25.0 (t, C-26), 29.7 (t, q, C-11, C-15), 30.3, 30.4 (d, t, C-13, C-24), 36.1 (t, C-5), 36.8 (d, C-18), 44.8 (q, C-28), 47.6 (t, C-10), 52.9 (d, C-17), 55.3 (t, C-27), 57.4 (d, C-12), 64.3 (t, C-7), 69.5 (d, C-23), 71.4 (t, C-6), 122.8 (d, C-9), 126.1 (d, C-1), 128.2 (d, C-2), 128.9 (d, C-3), 138.7 (s, C-4), 145.1 (s, C-8), 173.5 (s, C-16), 174.3 (s, C-22) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, $^3J_{19,18}$ = 6.6 Hz, 3 H, 19-H), 2.72 (s, 3 H, 15-H), 3.64 (t, $^3J_{6,5}$ = 7.3 Hz, 2 H, 6-H), 4.55 (s, 2 H, 7-H), 4.81 (dd, $^3J_{17,NH}$ = 9.7 Hz, $^3J_{17,18}$ = 5.9 Hz, 1 H, 17-H), 7.44 (s, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3 (q, C-21), 16.5 (q, C-19), 20.3 (q, C-14), 47.0 (t, C-10) ppm. HRMS (CI) *m/z* calcd for $C_{31}H_{51}N_6O_3$ $[M+H]^+$: 555.4022; found 555.4015.

Methyl 2-((1-((*R*)-3-((2*S*,3*S*)-*N*,3-dimethyl-2-((*R*)-1-methyl-piperidine-2-carboxamido)-pentanamido)-4-methylpentyl)-1H-1,2,3-triazol-4-yl)methoxy)acetate (19b).

According to the general procedure for Cbz-deprotection **18b** (170 mg, 0.26 mmol) was hydrogenated. Following the general procedure for reductive methylation **19b** was obtained from the crude amine, paraformaldehyde (25 mg, 0.27 mmol) and sodium cyanoborohydride (18 mg, 0.27 mmol). After purification by flash chromatography (SiO_2, DCM/MeOH = 9:1), **19b** (91 mg, 0.18 mmol, 69% over 2 steps) could be isolated as a colourless resin and a mixture of rotamers.



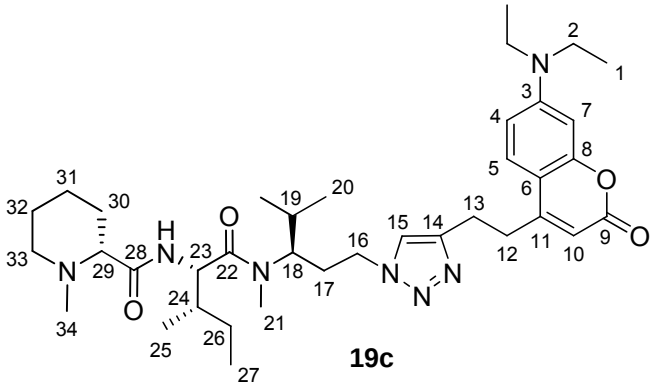
19b

R_f = 0.23 (DCM/MeOH, 9:1). $[\alpha]_D^{20}$ = +5.4° (*c* = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, $^3J_{10,9}$ = 6.6 Hz, 3 H, 10-H), 0.88 (d, $^3J_{10',9}$ = 6.6 Hz, 3 H, 10'-H), 0.90 (t, $^3J_{17,16}$ = 7.5 Hz, 3 H, 17-H), 0.96 (d, $^3J_{15,14}$ = 6.8 Hz, 3 H, 15-H), 1.12–1.23 (sh, 2 H, 16-H_a, 21-H_{ax}), 1.32 (m, 1 H, 20-H_{ax}), 1.44–1.80 (sh, 6 H, 9-H, 16-H_b, 20-H_{eq}, 21-H_{eq}, 22-H), 1.72 (m, 1 H, 13-H), 1.88 (m, 1 H, 14-H), 1.94–2.05 (sh, 2 H, 7-H_a, 23-H_{ax}), 2.18–2.27 (sh, 4 H, 7-H_b, 24-H), 2.46 (dd, $^3J_{19,20eq}$ = 10.9 Hz, $^3J_{19,20ax}$ = 2.6 Hz, 1 H, 19-H), 2.88 (m, 1 H, 23-H_{eq}), 3.02 (s, 3 H, 11-H), 3.74 (s, 3 H, 25-H), 4.10 (m, 1 H, 6-H_a), 4.16 (s, 2 H, 2-H), 4.20–4.30 (sh, 2 H, 6-H_b, 8-H), 4.70–4.76 (sh, 3 H, 3-H, 13-H), 7.00 ($^3J_{NH,13}$ = 9.3 Hz, 1 H, NH), 7.72 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3 (q, C-17), 16.0 (q, C-15), 19.4 (q, C-10), 19.9 (q, C-10'), 23.2 (t, C-21), 24.6 (t, C-16), 25.0 (t, C-22), 29.7 (t, C-7), 29.8 (q, C-11), 30.4, 30.5 (d, t, C-9, C-20), 36.8 (d, C-14), 44.9 (q, C-24), 47.7 (t, C-6), 51.8 (q, C-25), 53.0 (d, C-13), 55.3 (t, C-23), 57.4 (d, C-8), 64.5 (t, C-3), 67.2 (t, C-2), 69.5 (d, C-19), 123.5 (d, C-5), 144.0 (s, C-4), 170.5 (s, C-1), 173.6 (s, C-12), 174.3 (s, C-18) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, $^3J_{10,9}$ = 6.6 Hz, 3 H, 10-H), 2.77 (s, 3 H, 11-H), 4.84 (dd, $^3J_{13,NH}$ = 9.7 Hz, $^3J_{13,14}$ = 5.9 Hz, 1 H, 13-H), 7.12 ($^3J_{NH,13}$ = 9.8 Hz, 1 H, NH), 7.66 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3 (q, C-17), 16.5 (q, C-15),

20.1 (q, C-10), 20.4 (q, C-10‘), 37.6 (d, C-14), 47.1 (t, C-6), 64.4 (t, C-3), 67.1 (t, C-2) ppm. HRMS (CI) *m/z* calcd for $C_{26}H_{47}N_6O_5$ $[M+H]^+$: 523.3608; found 523.3607.

(*R*)-*N*-((2*S*,3*S*)-1-(((*R*)-1-(4-(2-(7-(diethylamino)-2-oxo-2H-chromen-4-yl)ethyl)-1H-1,2,3-triazol-1-yl)-4-methylpentan-3-yl)(methyl)amino)-3-methyl-1-oxopentan-2-yl)-1-methylpiperidine-2-carboxamide (19c).

According to the general procedure for Cbz-deprotection **18c** (58 mg, 74 µmol) was hydrogenated. Following the general procedure for reductive methylation **19c** was obtained from the crude amine, paraformaldehyde (7 mg, 75 µmol) and sodium cyanoborohydride (5 mg, 82 µmol). After purification by flash chromatography (SiO_2, DCM/MeOH = 9:1), **19c** (35 mg, 53 µmol, 72% over 2 steps) could be isolated as a yellow solid and a mixture of rotamers; m. p. 81–82 °C.

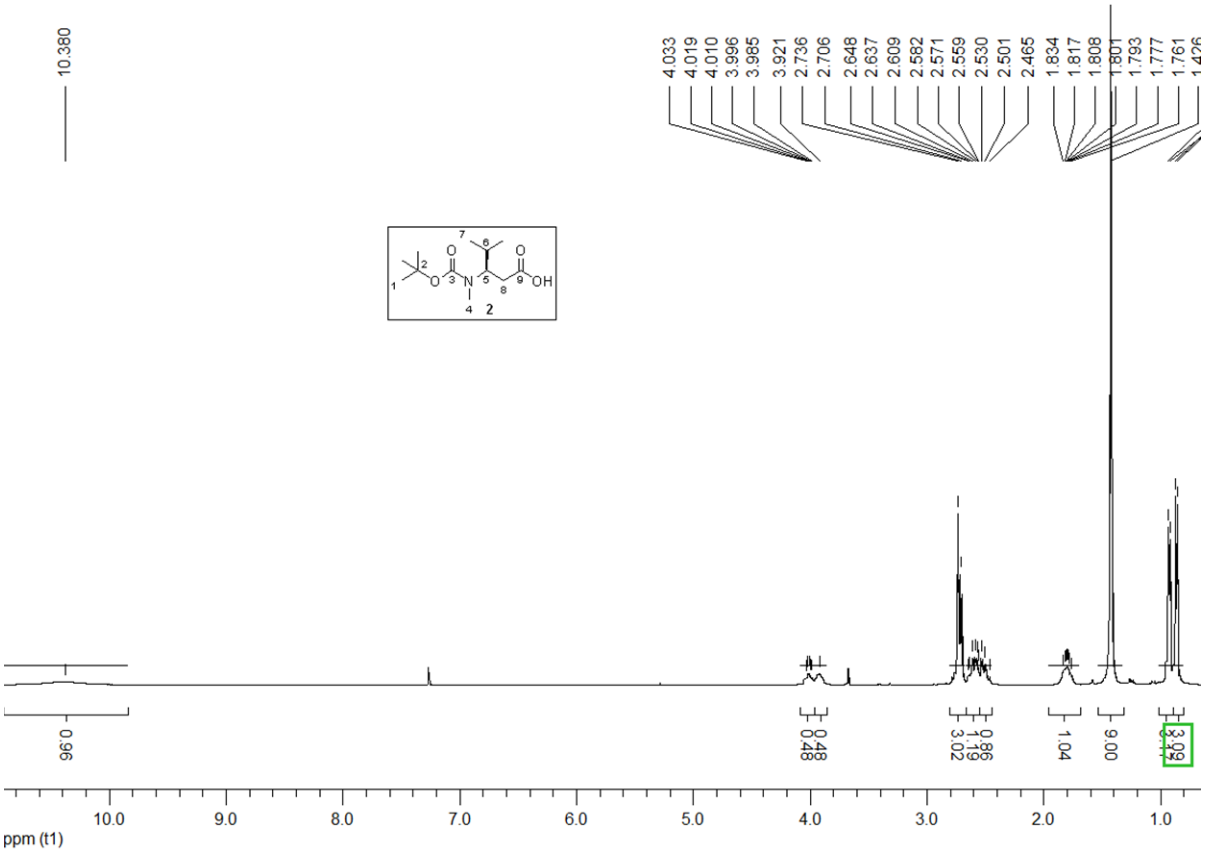


19c

R_f = 0.21 (DCM/MeOH, 9:1). $[\alpha]_D^{20}$ = +14.1° (*c* = 0.5, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, $^3J_{20,19}$ = 6.6 Hz, 3 H, 20-H), 0.88 (d, $^3J_{20',19}$ = 6.5 Hz, 3 H, 20‘-H), 0.91 (t, $^3J_{27,26}$ = 7.4 Hz, 3 H, 27-H), 0.97 (d, $^3J_{25,24}$ = 6.7 Hz, 3 H, 25-H), 1.19 (t, $^3J_{1,2}$ = 7.1 Hz, 6 H, 1-H), 1.15–1.23 (sh, 2 H, 26-H_a, 31-H_{ax}), 1.34 (m, 1 H, 30-H_{ax}), 1.46–1.79 (sh, 6 H, 19-H, 26-H_b, 30-H_{eq}, 31-H_{eq}, 32-H), 1.89 (m, 1 H, 24-H), 1.95–2.03 (sh, 2 H, 17-H_a, 33-H_{ax}), 2.16–2.25 (sh, 4 H, 17-H_b, 34-H), 2.47 (dd, $^3J_{29,30eq}$ = 10.9 Hz, $^3J_{29,30ax}$ = 2.7 Hz, 1 H, 29-H), 2.88 (m, 1 H, 33-H_{eq}), 3.02 (s, 3 H, 21-H), 3.04–3.12 (sh, 4 H, 12-H, 13-H), 3.39 (q, $^3J_{2,1}$ = 7.1 Hz, 4 H, 2-H), 4.06 (dt, $^2J_{16a,16b}$ = 13.9 Hz, $^3J_{16,17}$ = 7.9 Hz, 1 H, 16-H_a), 4.19–4.30 (sh, 2 H, 16-H_b, 18-H), 4.75 (dd, $^3J_{23,NH}$ = $^3J_{23,24}$ = 8.9 Hz, 1 H, 23-H), 5.91 (s, 1 H, 10-H), 6.48 (d, $^4J_{7,4}$ = 2.5 Hz, 1 H, 7-H), 6.56 (dd, $^3J_{4,5}$ = 9.0 Hz, $^4J_{4,7}$ = 2.6 Hz, 1 H, 7-H), 7.02 (d, $^3J_{NH,23}$ = 9.3 Hz, 1 H, NH), 7.44 (s, 1 H, 15-H), 7.46 (d, $^3J_{5,4}$ = 9.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8 (q, C-27), 12.4 (q, C-1), 16.0 (q, C-25), 19.4 (q, C-20), 19.9 (q, C-20‘), 23.2 (t, C-31), 24.5, 24.6 (2 t, C-13, C-26), 25.0 (t, C-32), 29.6 (d, C-19), 29.9 (q, C-21), 30.3, 30.4 (2 t, C-17, C-30), 31.2 (t, C-12), 36.8 (d, C-24), 44.7 (t, C-2), 44.9 (q, C-34), 47.5 (t, C-16), 53.0 (d, C-23), 55.3 (t, C-33), 57.6 (d, C-18), 69.6 (d, C-29), 97.7 (d, C-7), 107.6 (d, C-10), 107.9 (s, C-6), 108.5 (d, C-4), 121.7 (d, C-15), 125.3 (d, C-5), 146.0 (s, C-14), 150.4 (s, C-3), 155.4 (s, C-9), 156.3 (s, C-11), 162.2 (s, C-8), 173.6 (s, C-22), 174.3 (s, C-28) ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, $^3J_{25,24}$ = 6.5 Hz, 3 H, 25-H), 2.76 (s, 3 H, 21-H), 4.37 (m, 1 H, 16-H_b), 4.85 (dd, $^3J_{23,NH}$ = 9.7 Hz, $^3J_{23,24}$ = 5.7 Hz, 1 H, 23-H), 5.90 (s, 1 H, 10-H), 7.14 (d, $^3J_{NH,23}$ = 9.5 Hz, 1 H, NH), 7.43 (s, 1 H, 15-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4 (q, C-27), 16.5 (q, C-25), 20.1 (q, C-20), 20.3 (q, C-20‘),

27.4 (q, C-21), 29.6 (d, C-19), 31.5 (t, C-12), 60.9 (d, C-18), 121.8 (d, C-15) ppm. HRMS (CI) *m/z* calcd for $C_{44}H_{62}N_7O_6$ $[M+H]^+$: 664.4550; found 664.4563.

Spectra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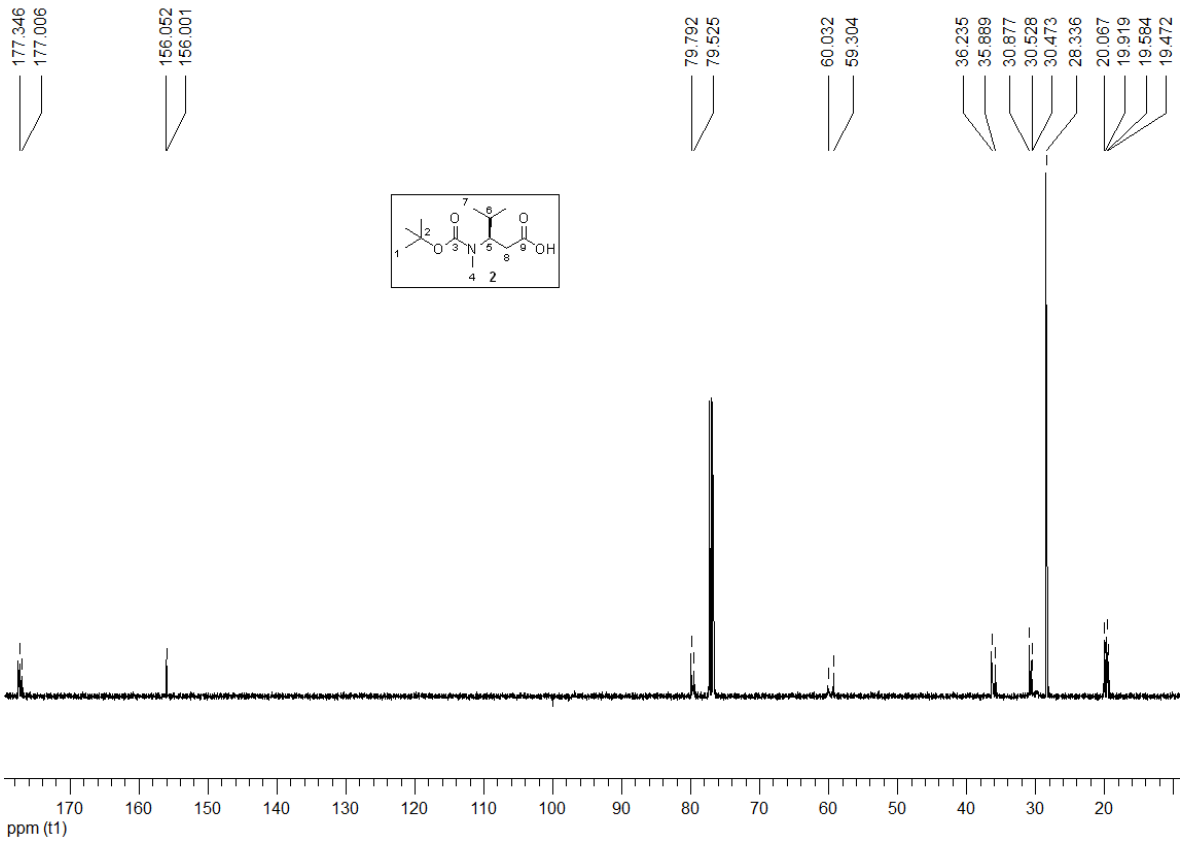
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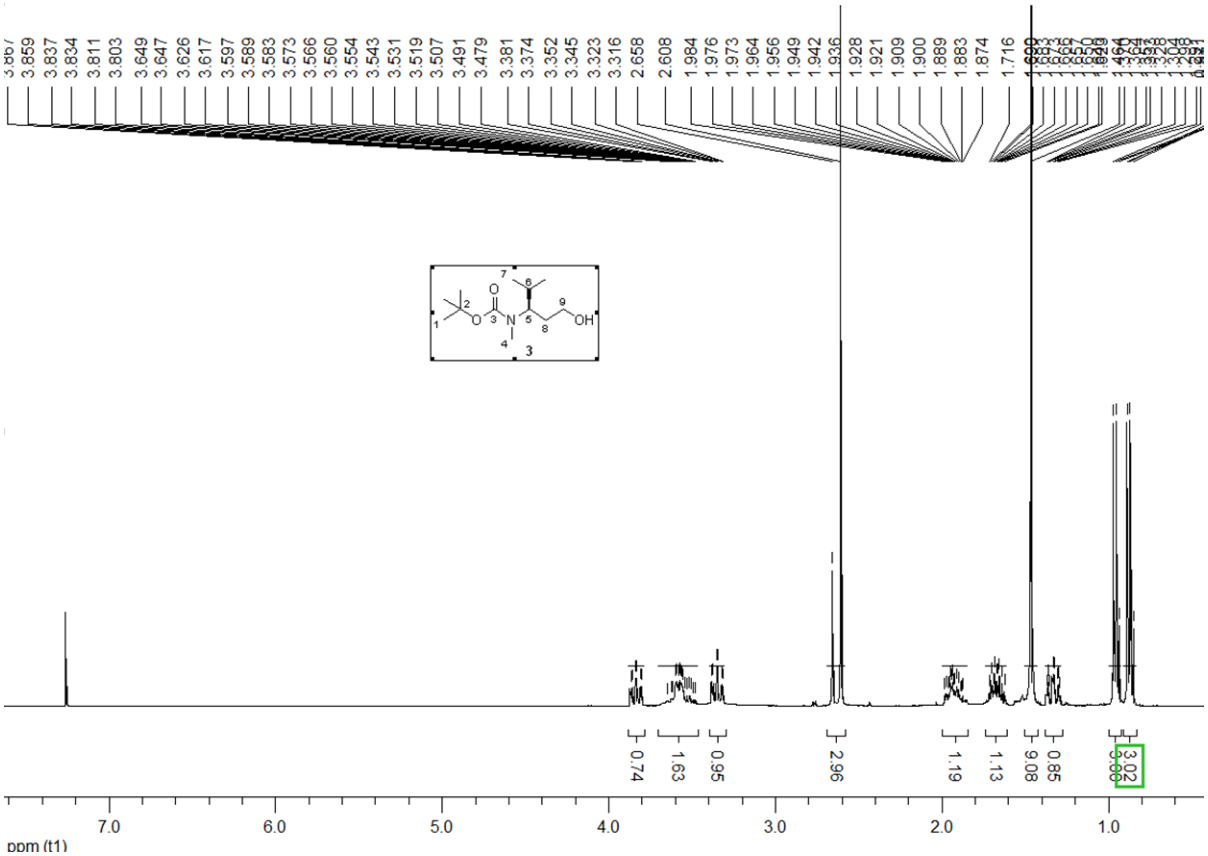
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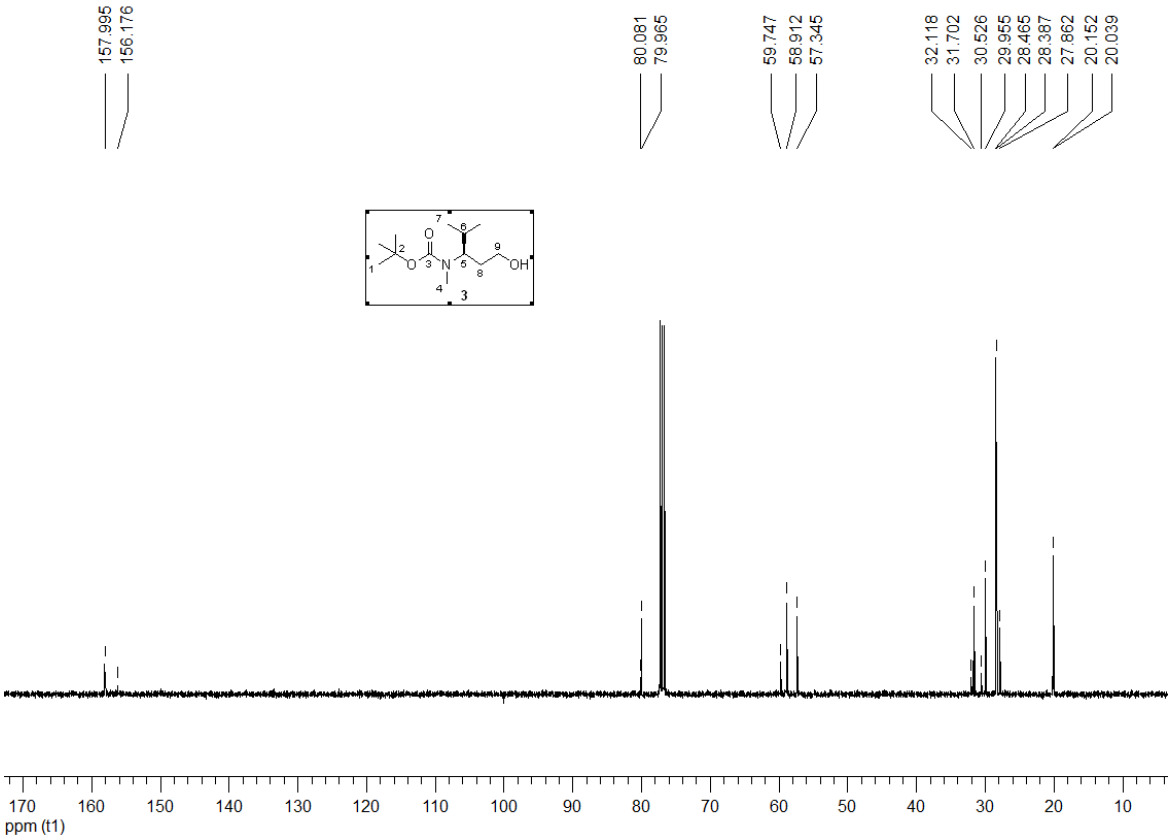
ppm (t1)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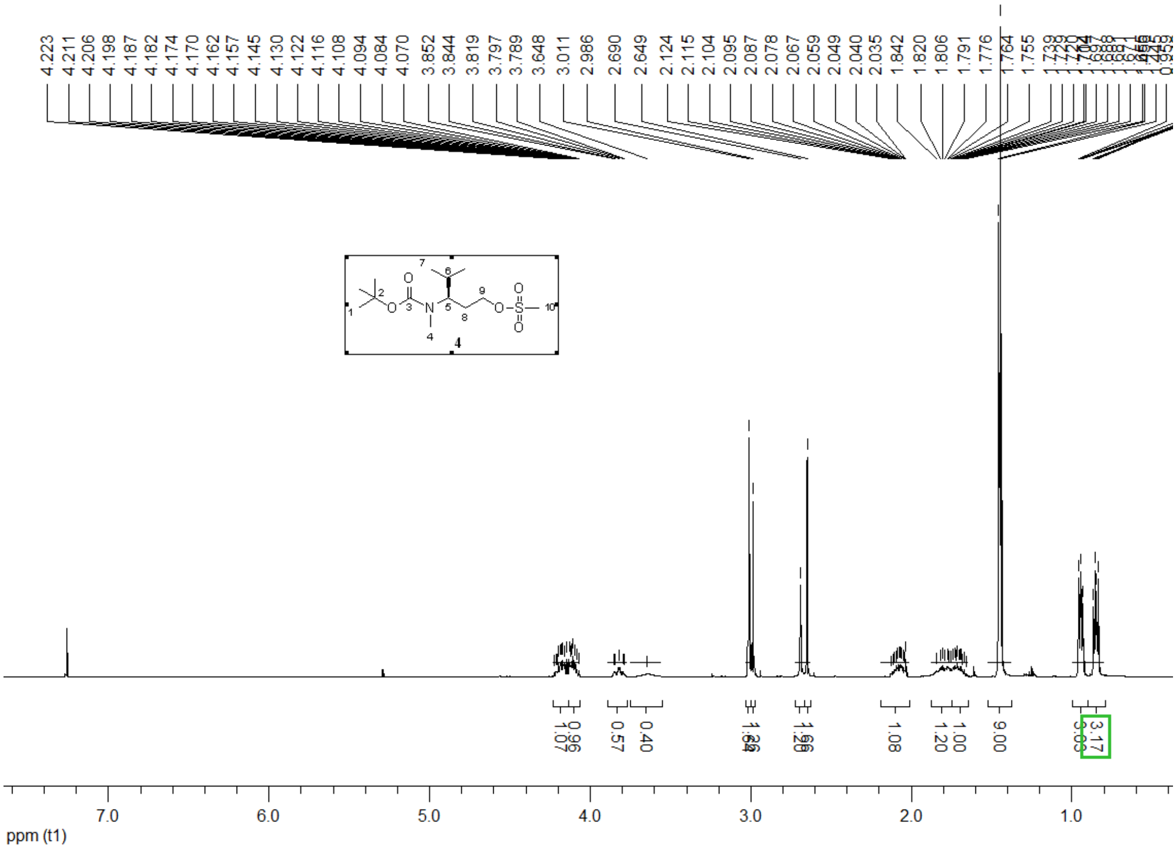
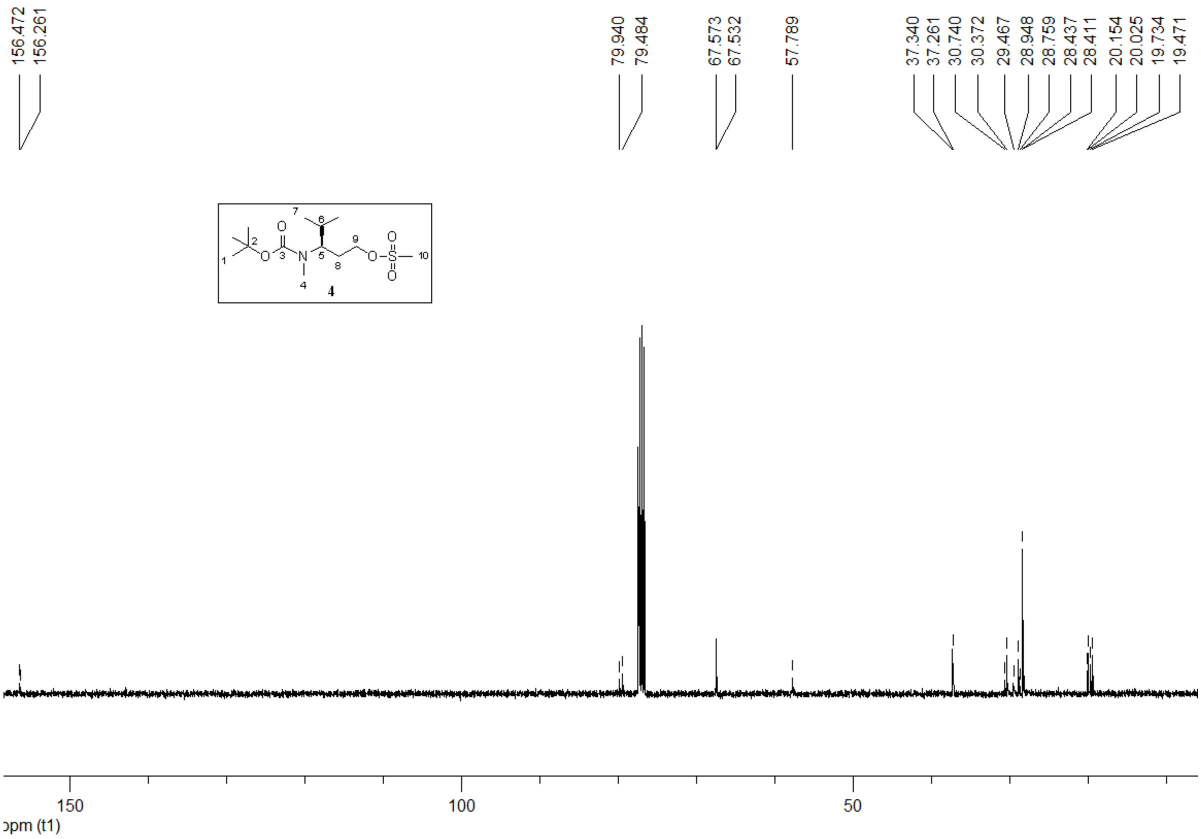
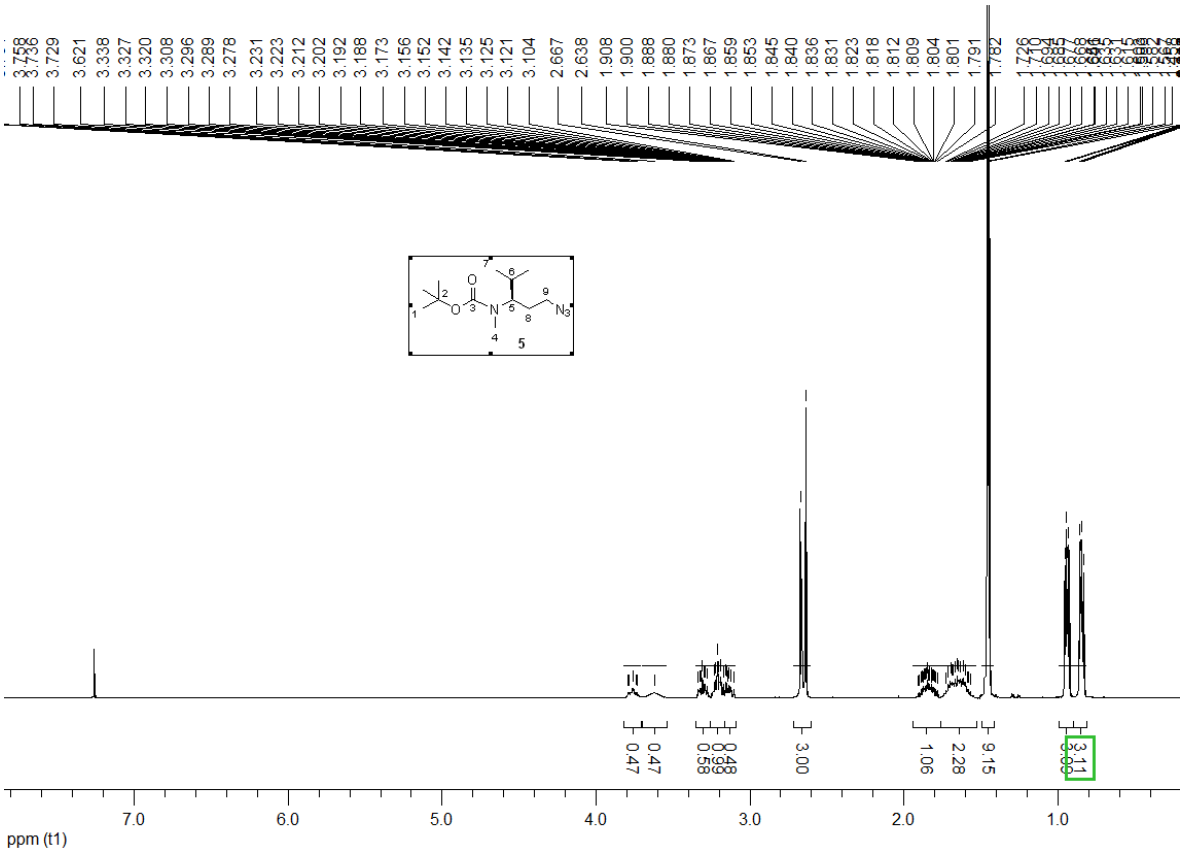
ppm (t1)



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3.308
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3.231
3.223
3.212
3.202
3.192
3.188
3.173
3.156
3.152
3.142
3.135
3.125
3.121
3.104
2.667
2.638
1.908
1.900
1.888
1.880
1.873
1.867
1.859
1.853
1.845
1.840
1.836
1.831
1.823
1.818
1.812
1.809
1.804
1.801
1.791
1.782
1.726
0.47
0.47
0.88
0.98
0.98
3.00
1.06
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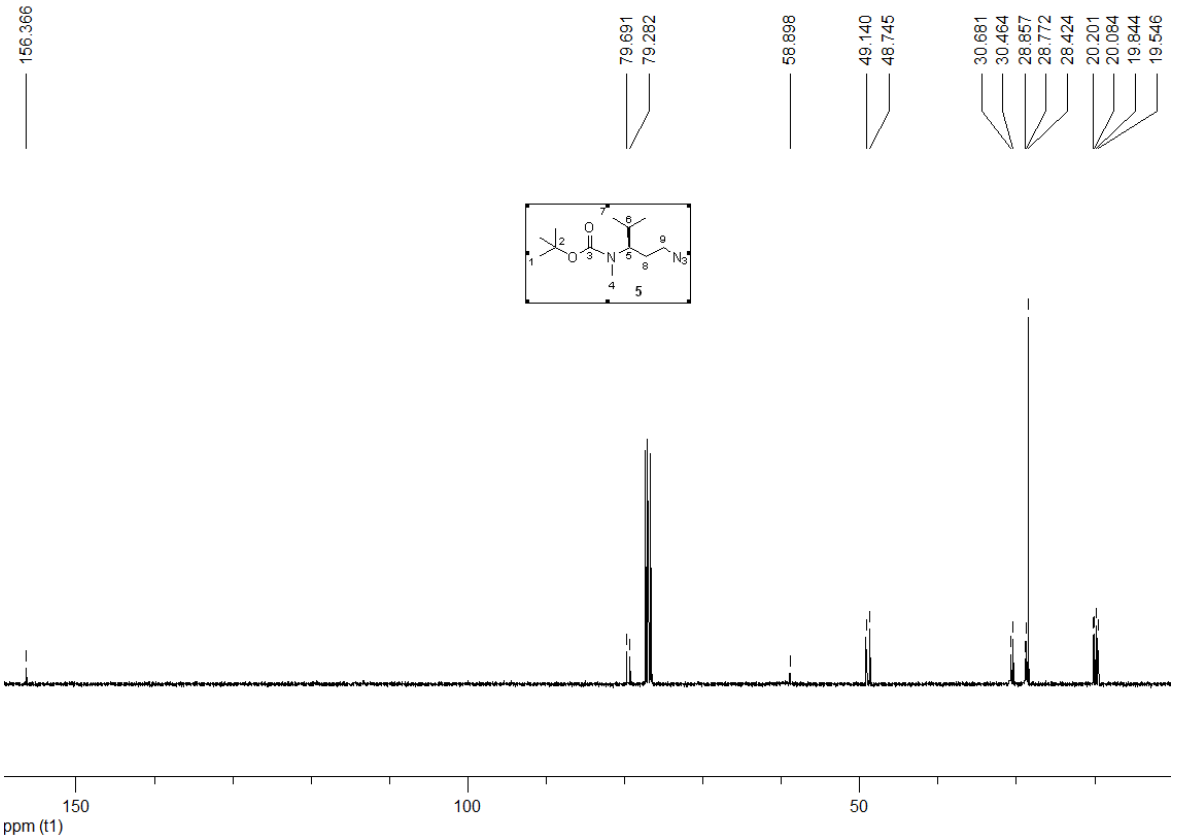
3.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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48.745
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28.424
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20.084
19.844
19.546
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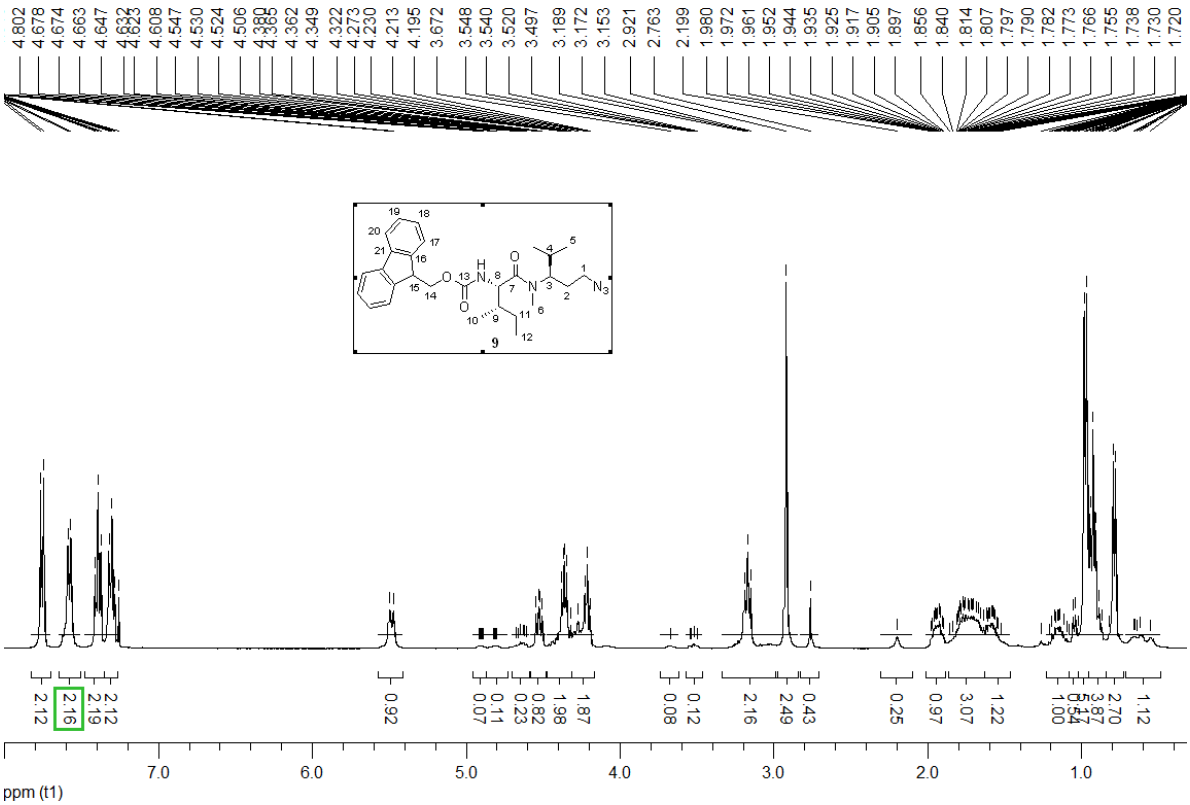
100
50
ppm (t1)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4.608
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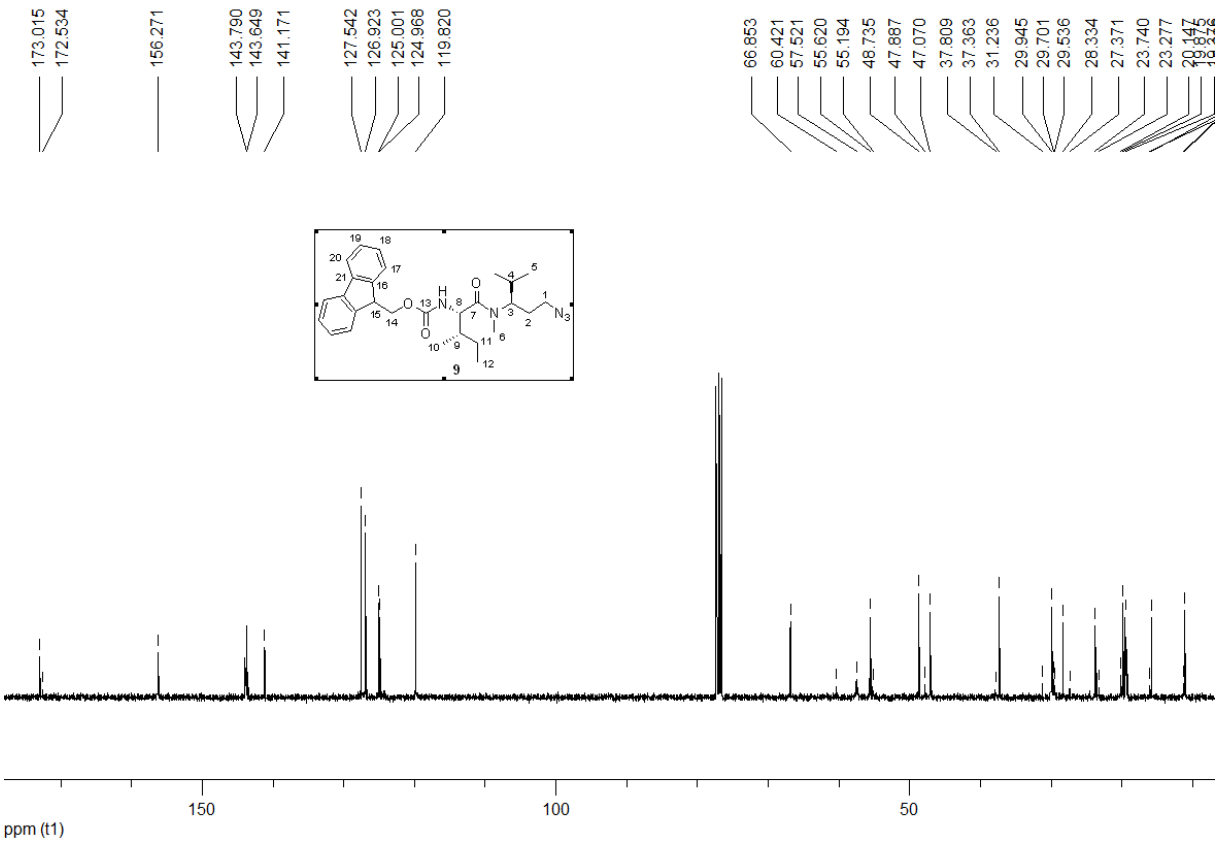
4.524
4.506
4.380
4.365
4.362
4.349
4.322
4.273
4.230
4.213
4.195
3.672
3.548
3.540
3.520
3.497
3.189
3.172
3.153
2.921
2.763
2.199
1.980
1.972
1.961
1.952
1.944
1.935
1.925
1.917
1.905
1.897
1.856
1.840
1.814
1.807
1.797
1.790
1.782
1.773
1.766
1.755
1.738
1.730
1.720
9
2.12
2.16
2.19
2.12
0.92
0.07
0.11
0.23
0.82
1.98
1.87
0.08
0.12
2.16
2.46
0.43
0.25
0.97
3.07
1.22
1.00
0.96
0.47
3.87
2.70
1.12
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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126.923
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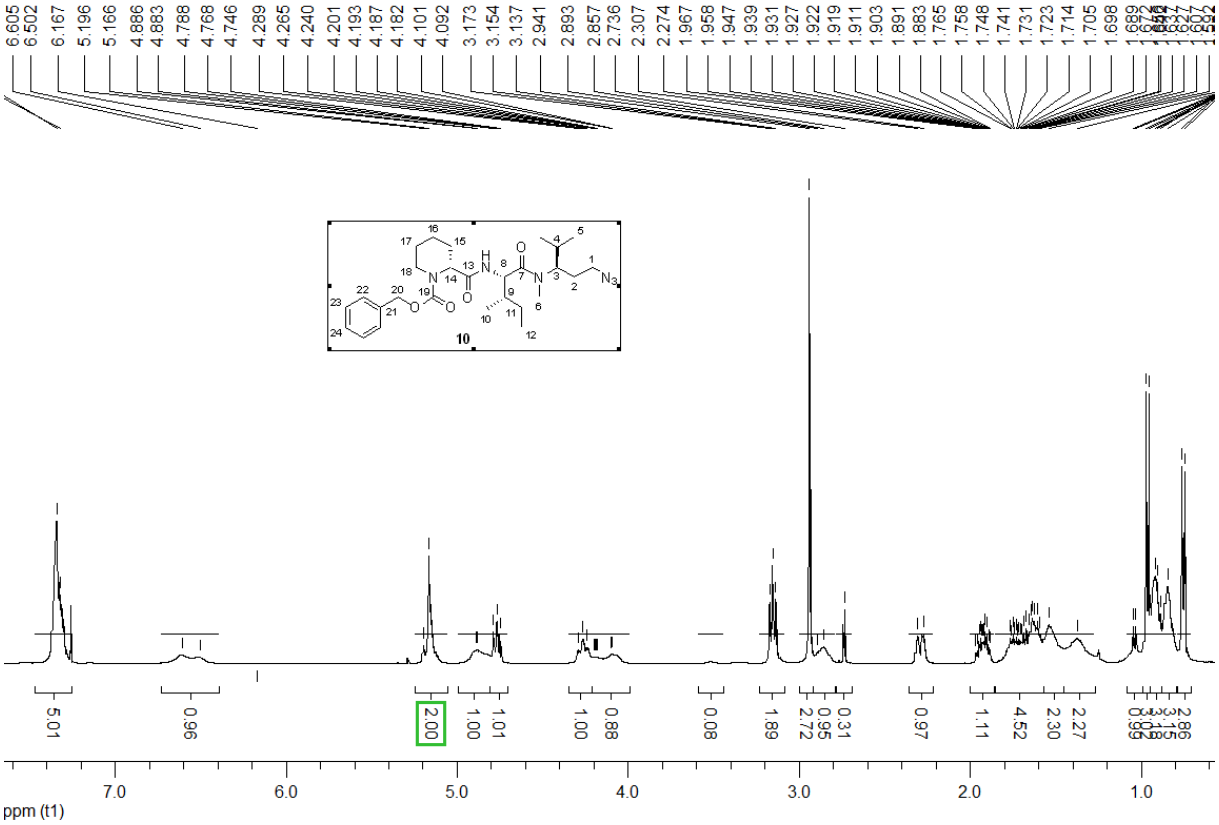
60.421
57.521
55.620
55.194
48.735
47.887
47.070
37.809
37.363
31.236
29.945
29.701
29.536
28.334
27.371
23.740
23.277
9
150
100
50
ppm (t1)


6.605
6.502
6.167
5.196
5.166
4.886
4.883
4.788
4.768
4.746
4.289
4.265
4.240
4.201
4.193
4.187
4.182
4.101
4.092
3.173
3.154
3.137
2.941
2.893
2.857
2.736
2.307
2.274
1.967
1.958
1.947
1.939
1.931
1.927
1.922
1.919
1.911
1.903
1.891
1.883
1.765
1.758
1.748
1.741
1.731
1.723
1.714
1.705
1.698
10
5.01
0.96
2.00
1.00
1.01
1.00
0.88
0.08
1.89
2.72
0.95
0.91
0.97
1.11
4.52
2.30
2.27
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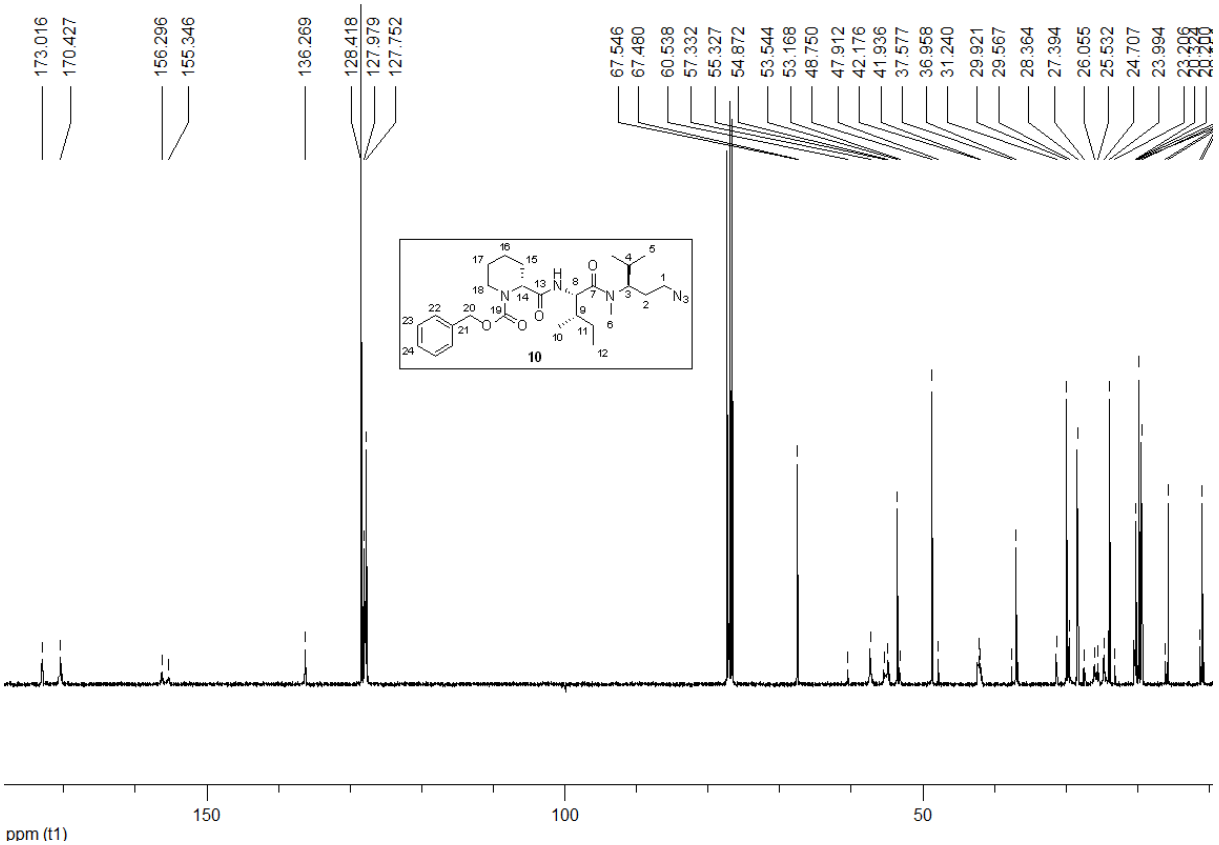
2.86
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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127.752
67.546
67.480
60.538
57.332
55.327
54.872
53.544
53.168
48.750
47.912
42.176
41.936
37.577
36.958
31.240
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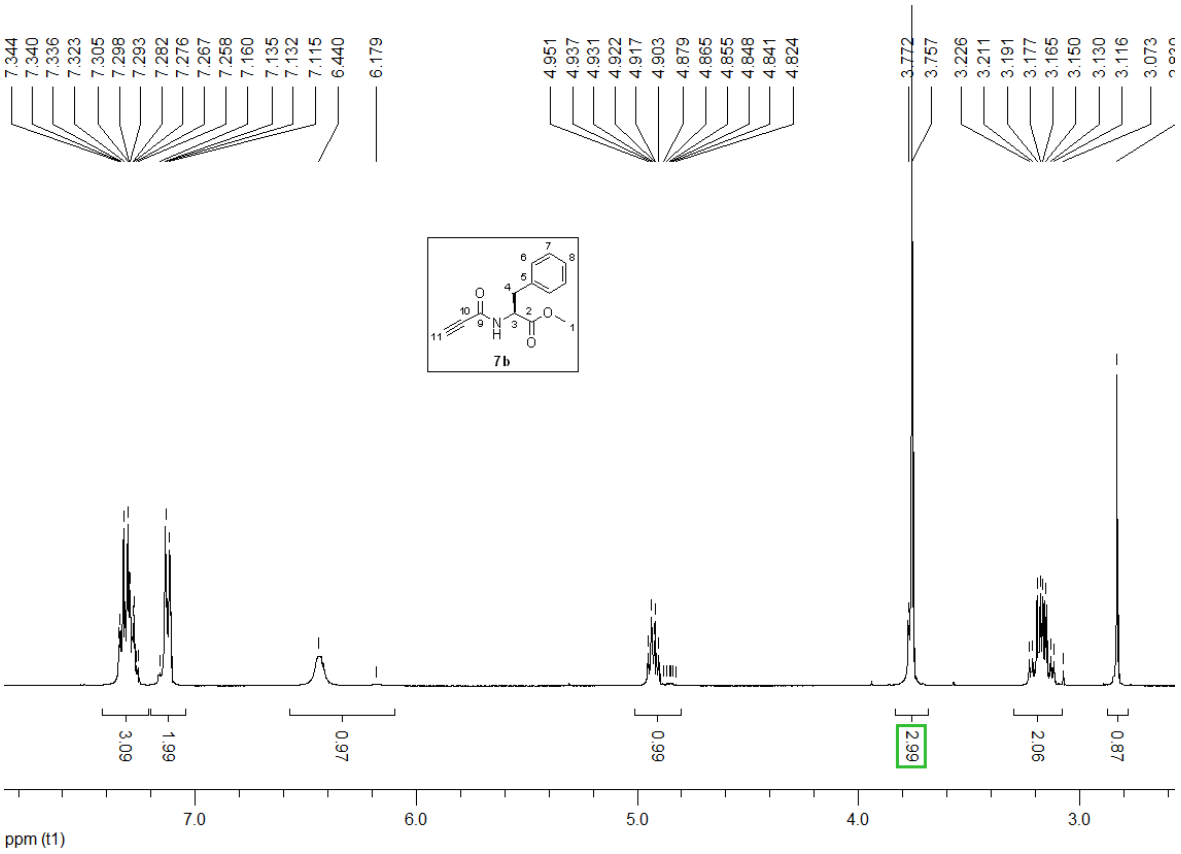
28.364
27.394
26.055
25.532
24.707
23.994
10
150
100
50
ppm (t1)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7.298
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7.282
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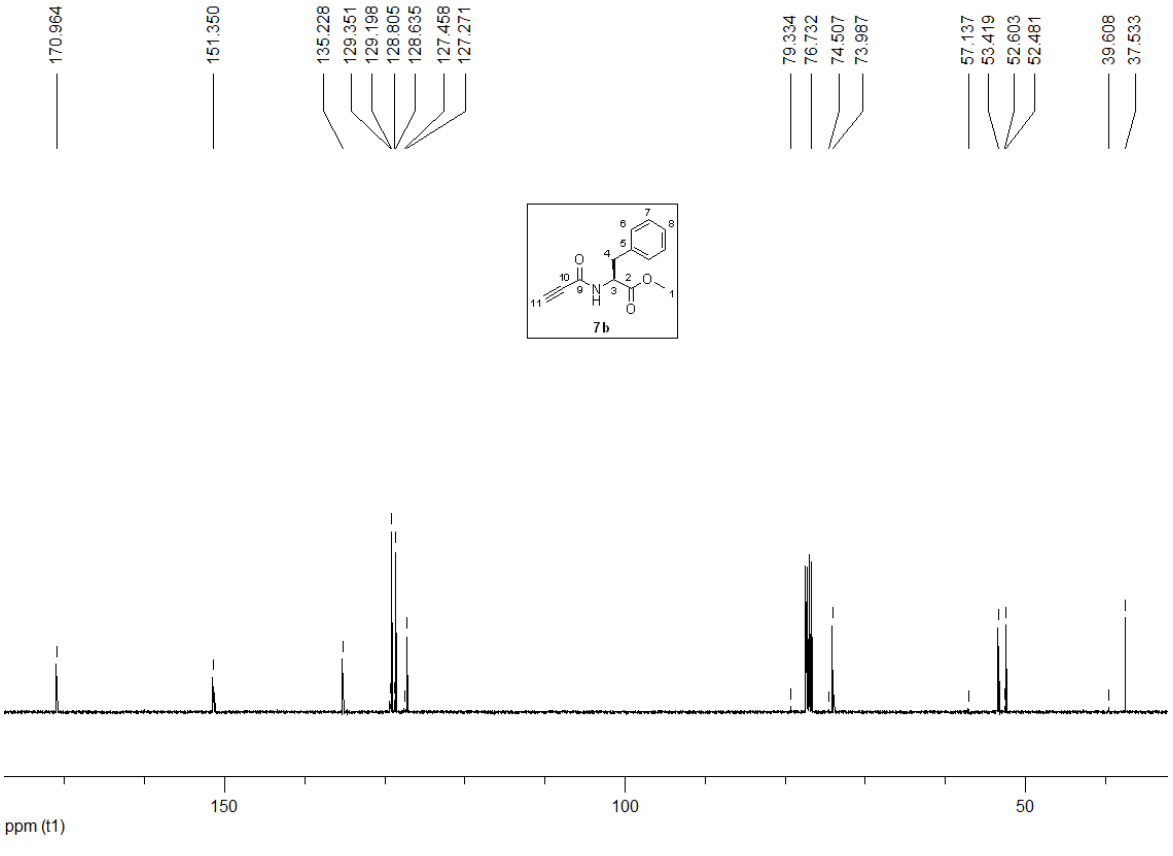
7.267
7.258
7.160
7.135
7.132
7.115
6.440
6.179
4.951
4.937
4.931
4.922
4.917
4.903
4.879
4.865
4.855
4.848
4.841
4.824
3.772
3.757
3.226
3.211
3.191
3.177
3.165
3.150
3.130
3.116
3.073
7b
3.09
1.99
0.97
0.99
2.99
2.06
0.87
7.0
6.0
5.0
4.0
3.0
ppm (t1)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135.228
129.351
129.198
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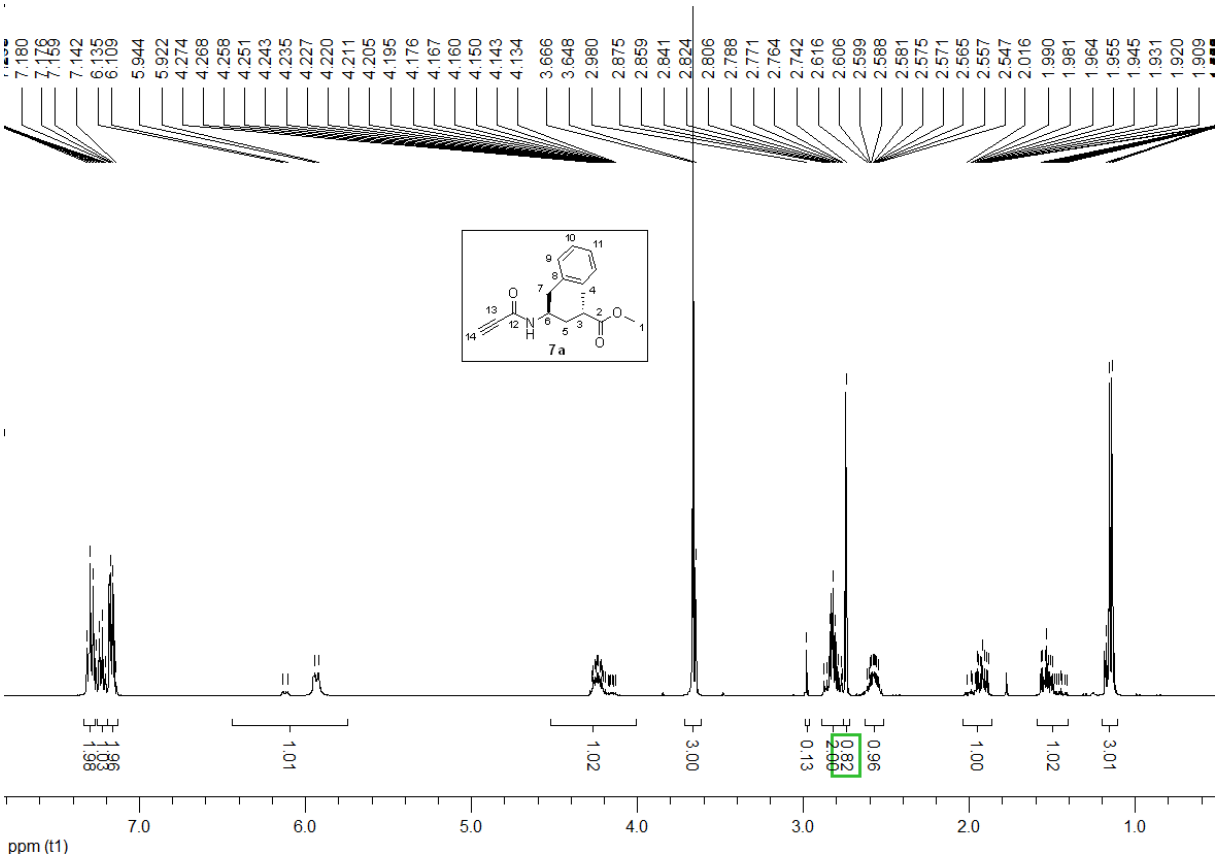
128.635
127.458
127.271
79.334
76.732
74.507
73.987
57.137
53.419
52.603
52.481
39.608
37.533
7b
150
100
50
ppm (t1)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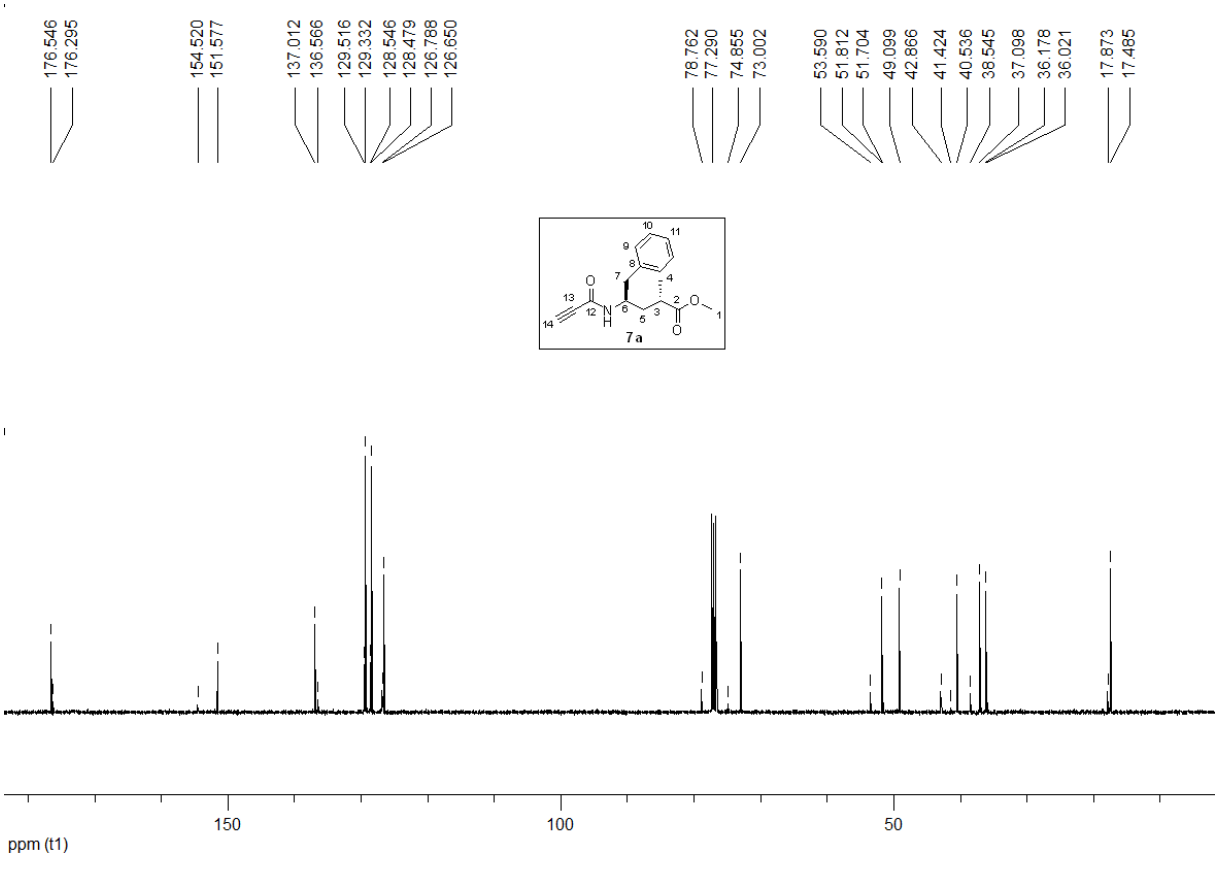
7.142
6.135
6.109
5.944
5.922
4.274
4.268
4.258
4.251
4.243
4.235
4.227
4.220
4.211
4.205
4.195
4.176
4.167
4.160
4.150
4.143
4.134
3.666
3.648
2.980
2.875
2.859
2.841
2.824
2.806
2.788
2.771
2.764
2.742
2.616
2.606
2.599
2.588
2.581
2.575
2.571
2.565
2.557
2.547
2.016
1.990
1.981
1.964
1.955
1.945
1.931
1.920
1.909
7a
1.98
1.03
0.96
1.01
1.02
3.00
0.13
2.00
0.82
0.96
1.00
1.02
3.01
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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129.332
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126.788
126.650
78.762
77.290
74.855
73.002
53.590
51.812
51.704
49.099
42.866
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40.536
38.545
37.098
36.178
36.021
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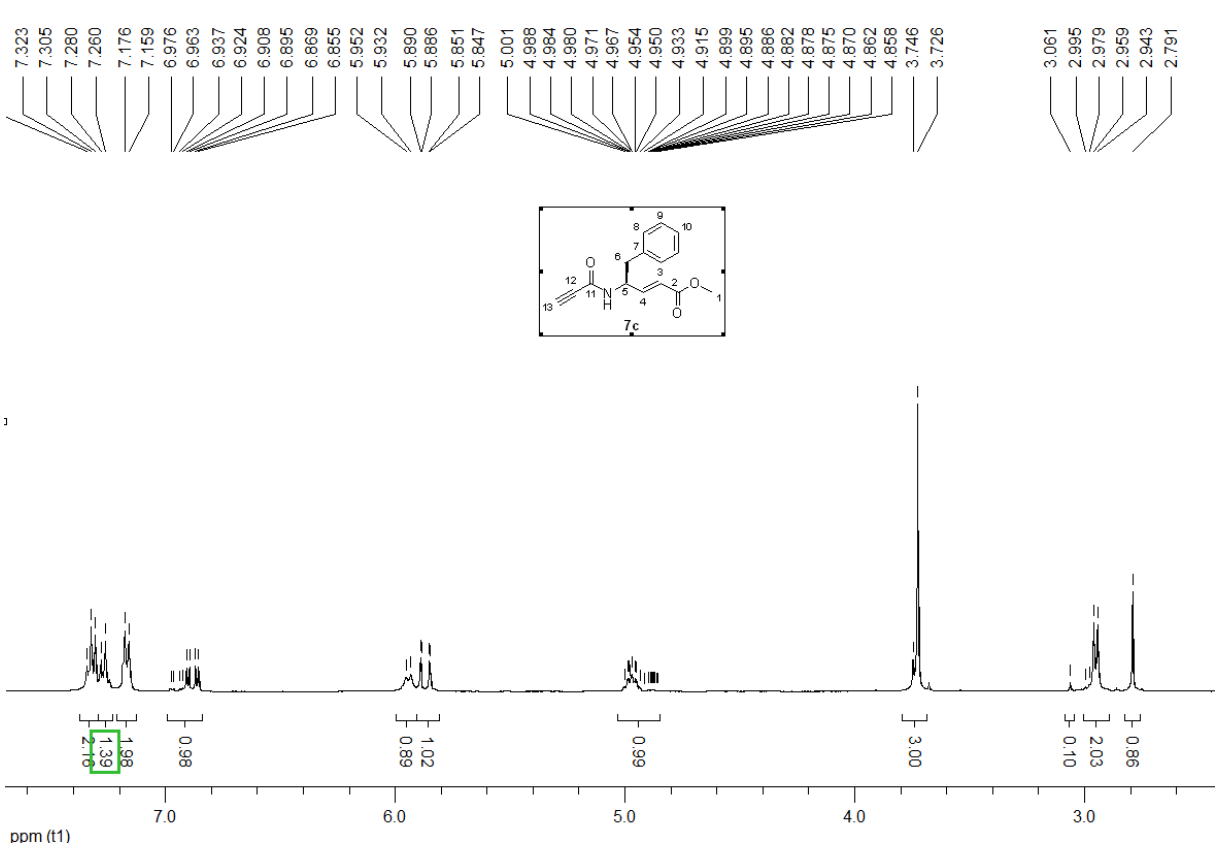
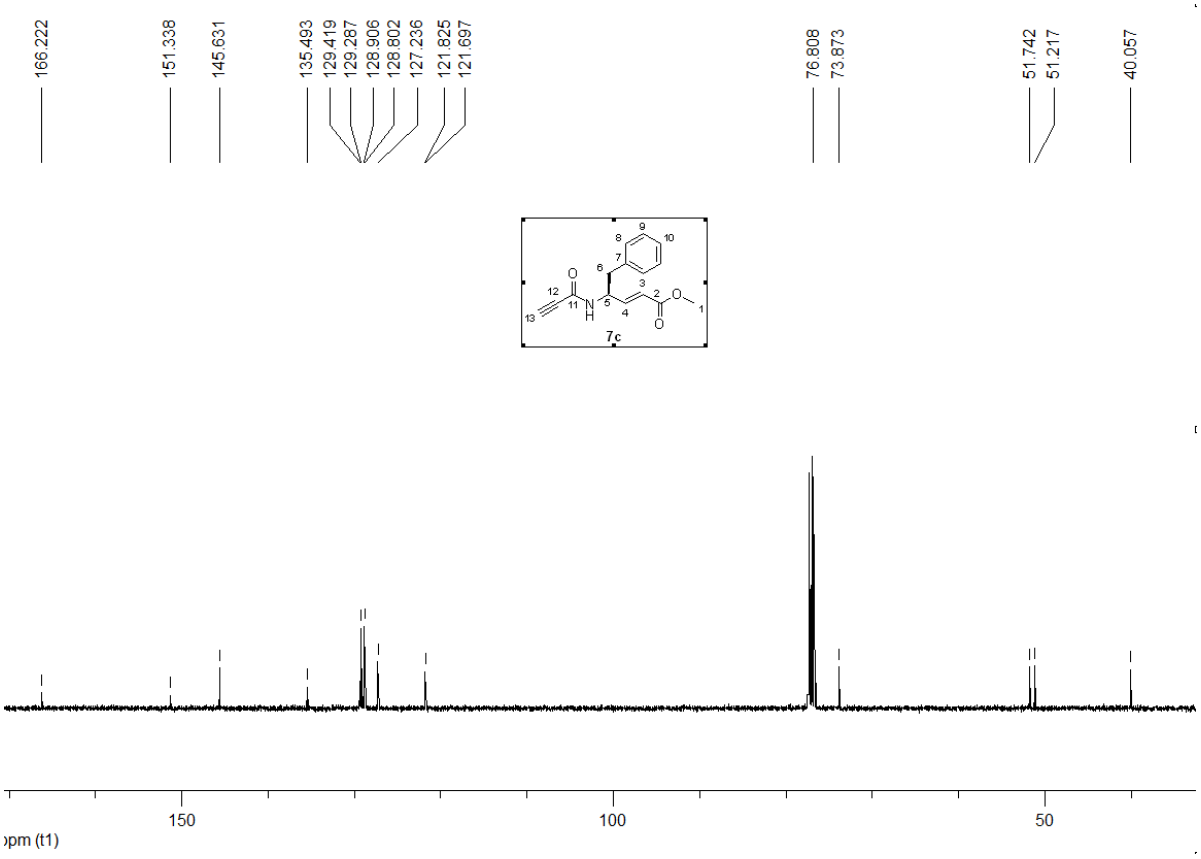
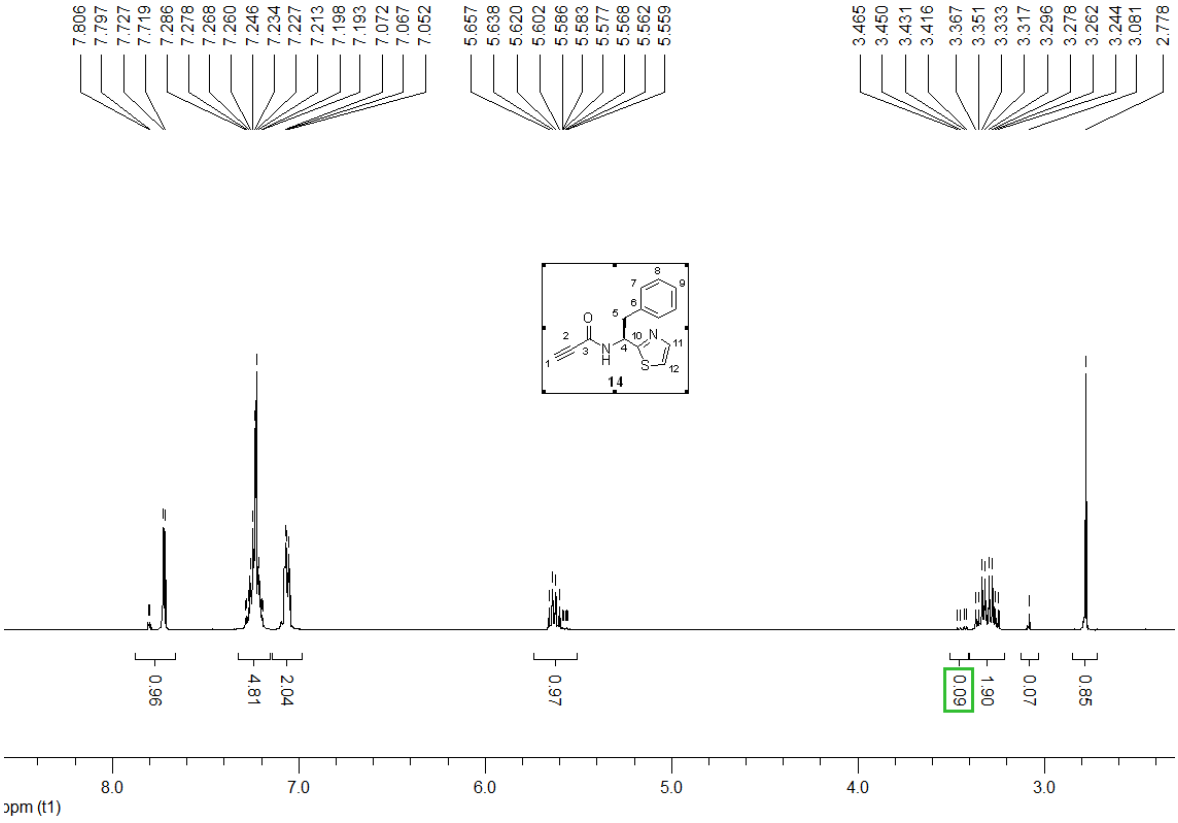
17.485
7a
150
100
50
ppm (t1)



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7.719
7.286
7.278
7.268
7.260
7.246
7.234
7.227
7.213
7.198
7.193
7.072
7.067
7.052
5.657
5.638
5.620
5.602
5.586
5.583
5.577
5.568
5.562
5.559
3.465
3.450
3.431
3.416
3.367
3.351
3.333
3.317
3.296
3.278
3.262
3.244
3.081
2.778
14
0.96
4.81
2.04
0.97
60.00
1.90
0.07
0.86
8.0
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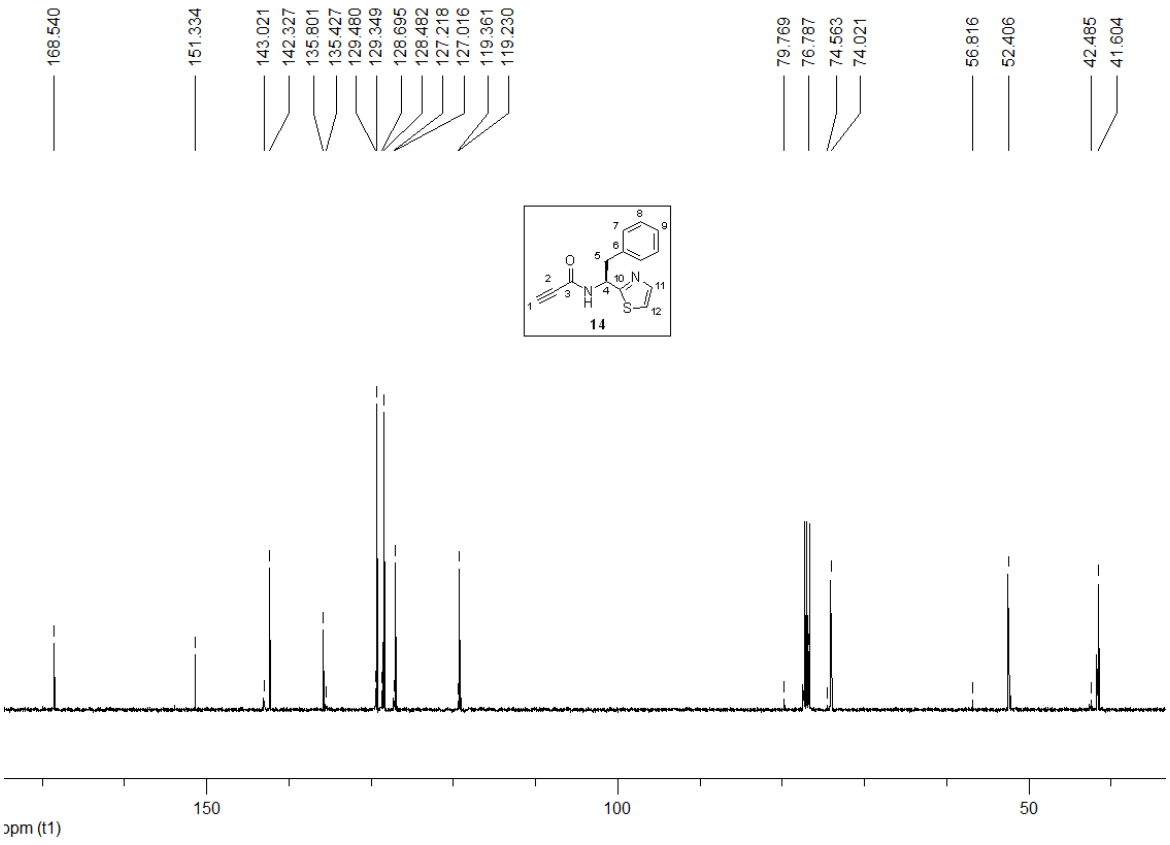
6.0
5.0
4.0
3.0
ppm (t1)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135.427
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129.349
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128.482
127.218
127.016
119.361
119.230
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76.787
74.563
74.021
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41.604
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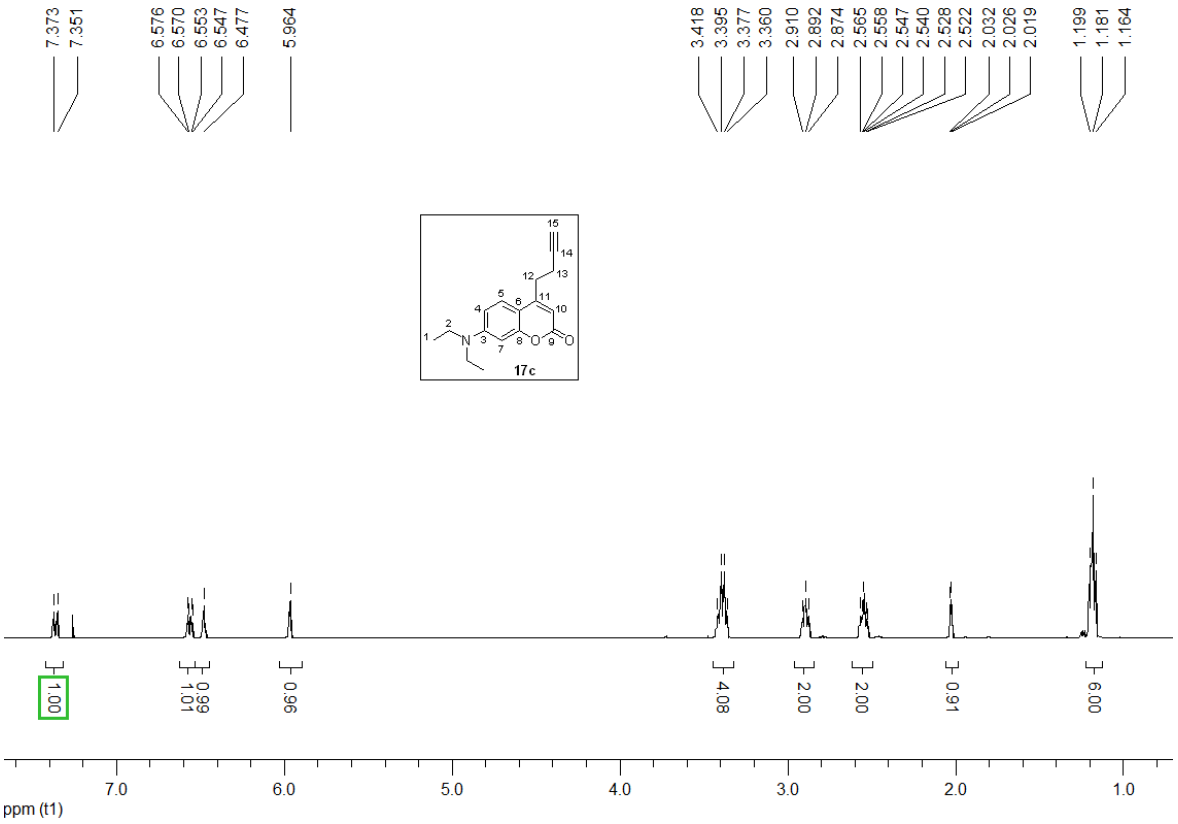
100
50
ppm (t1)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6.547
6.477
5.964
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3.395
3.377
3.360
2.910
2.892
2.874
2.565
2.558
2.547
2.540
2.528
2.522
2.032
2.026
2.019
1.199
1.181
1.164
17c
1.00
1.01
0.99
0.96
4.08
2.00
2.00
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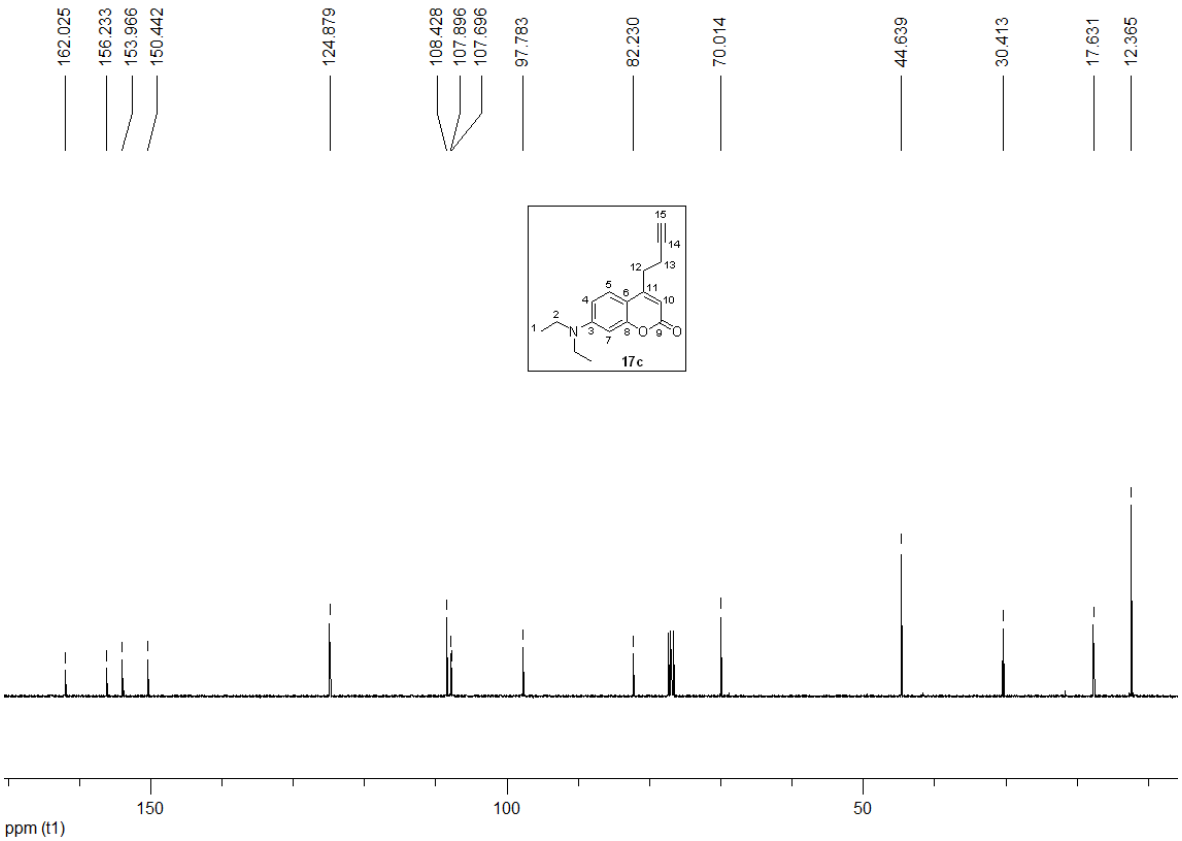
6.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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107.896
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70.014
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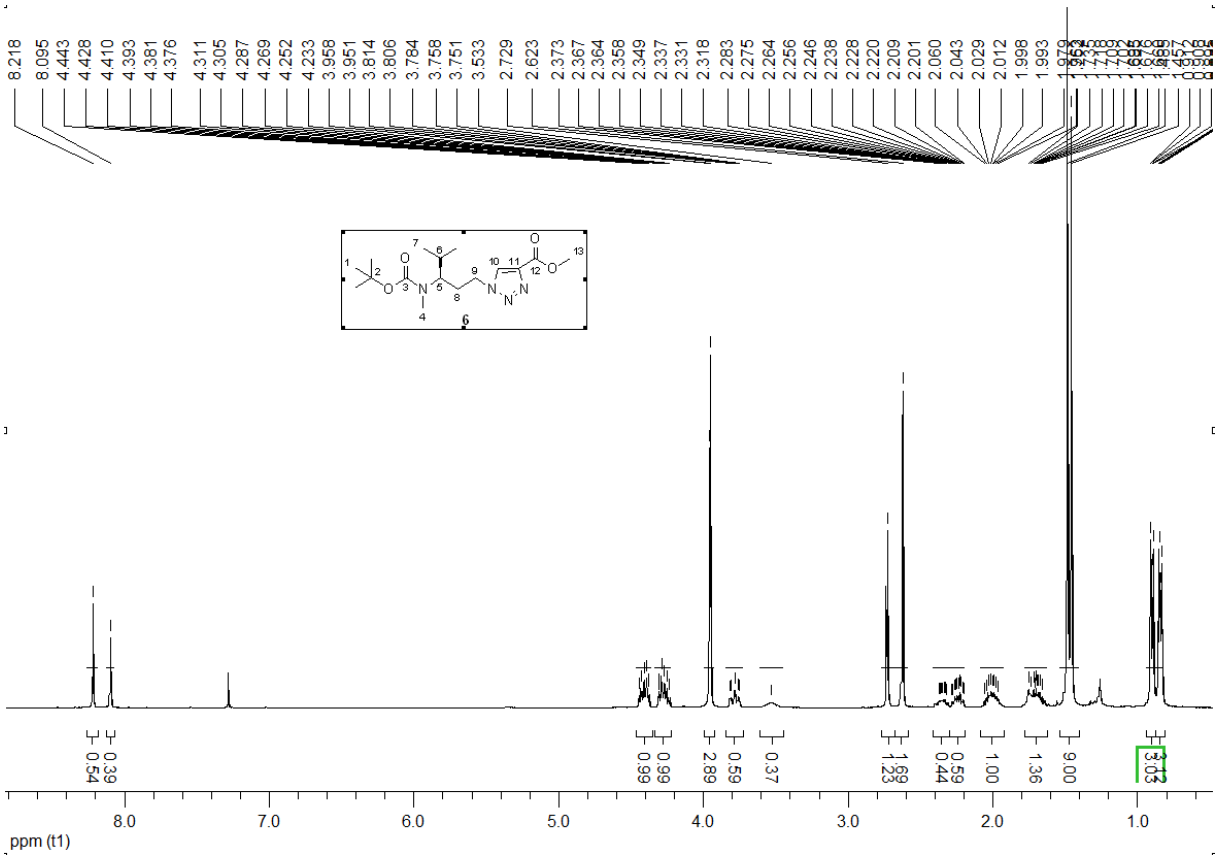
12.365
17c
150
100
50
ppm (t1)


8.218
8.095
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4.428
4.410
4.393
4.381
4.376
4.311
4.305
4.287
4.269
4.252
4.233
3.958
3.951
3.814
3.806
3.784
3.758
3.751
3.533
2.729
2.623
2.373
2.367
2.364
2.358
2.349
2.337
2.331
2.318
2.283
2.275
2.264
2.256
2.246
2.238
2.228
2.220
2.209
2.201
2.060
2.043
2.029
2.012
1.998
1.993
6
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0.39
0.99
0.99
2.89
0.59
0.37
1.23
1.69
0.74
0.59
1.00
1.36
9.00
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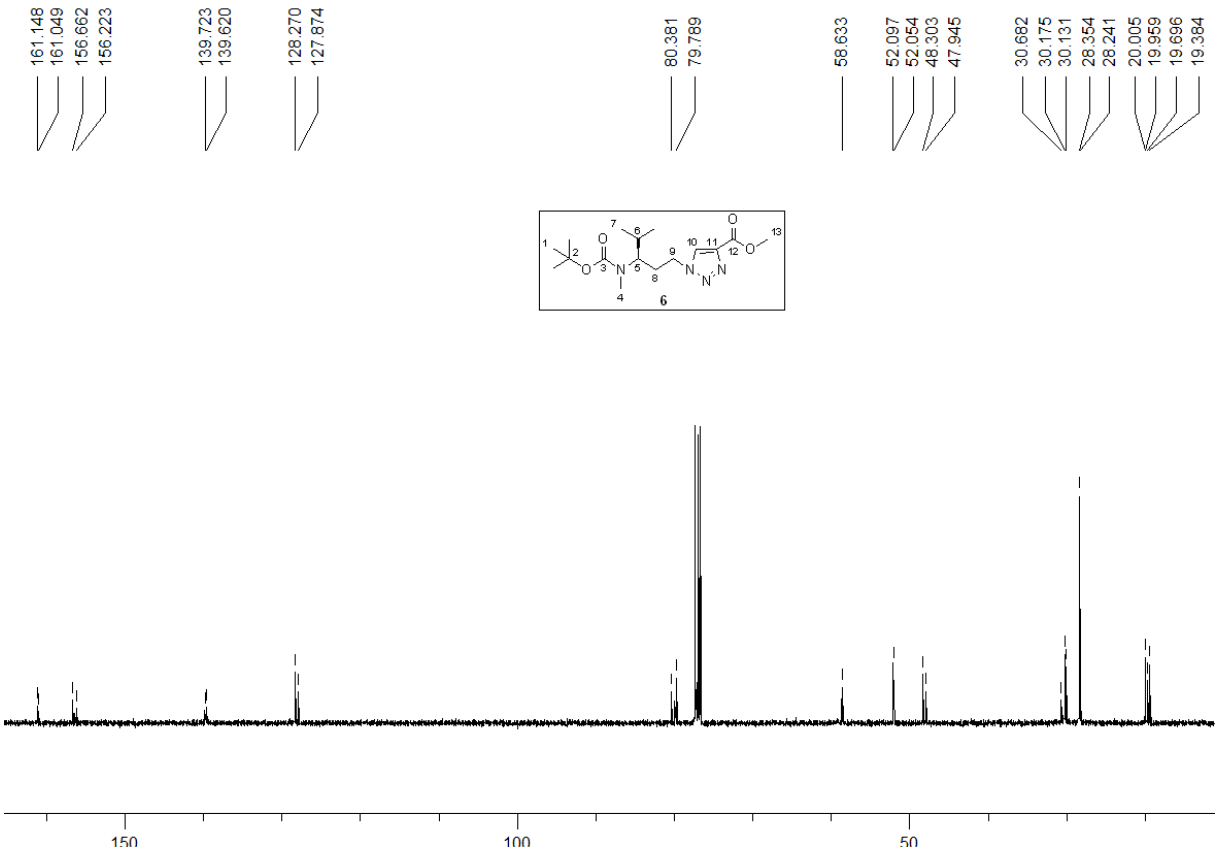
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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156.662
156.223
139.723
139.620
128.270
127.874
80.381
79.789
58.633
52.097
52.054
48.303
47.945
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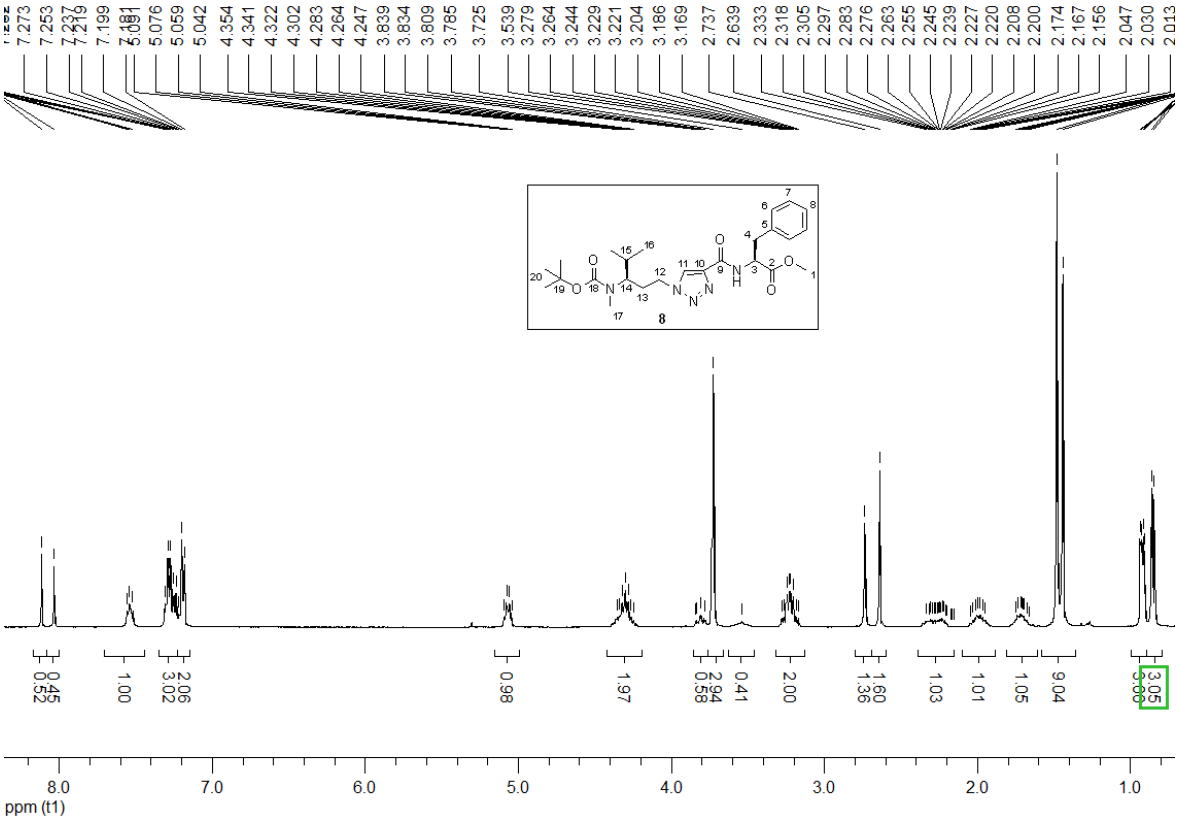
30.131
28.354
28.241
20.005
19.959
19.696
19.384
6
150
100
50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5.076
5.059
5.042
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4.341
4.322
4.302
4.283
4.264
4.247
3.839
3.834
3.809
3.785
3.725
3.539
3.279
3.264
3.244
3.229
3.221
3.204
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3.169
2.737
2.639
2.333
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2.305
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2.276
2.263
2.255
2.245
2.239
2.227
2.220
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2.200
2.174
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2.156
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2.013
8
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0.45
1.00
2.02
2.06
0.98
1.97
0.98
2.94
0.41
2.00
1.36
1.90
1.03
1.01
1.05
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3.00
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8.0
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6.0
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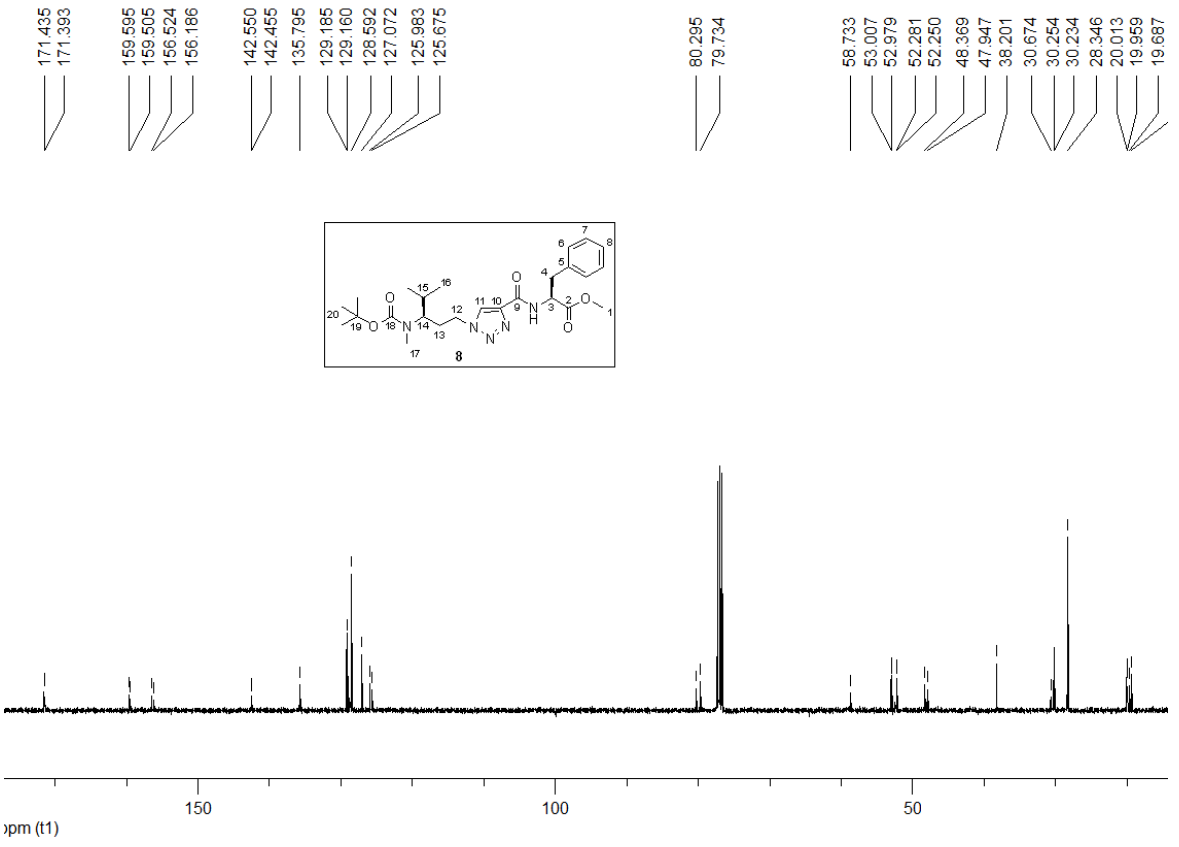
3.0
2.0
1.0
ppm (t1)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142.455
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129.160
128.592
127.072
125.983
125.675
80.295
79.734
58.733
53.007
52.979
52.281
52.250
48.369
47.947
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30.234
28.346
20.013
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19.687
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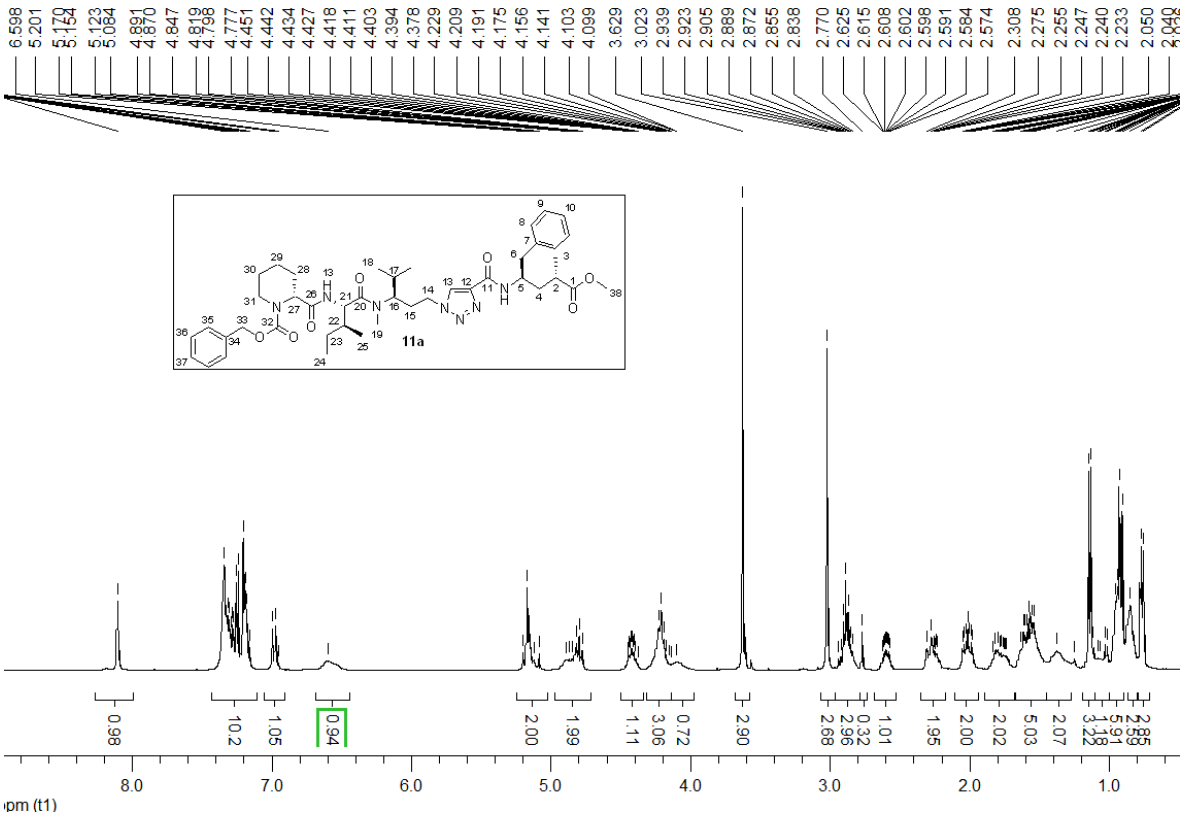
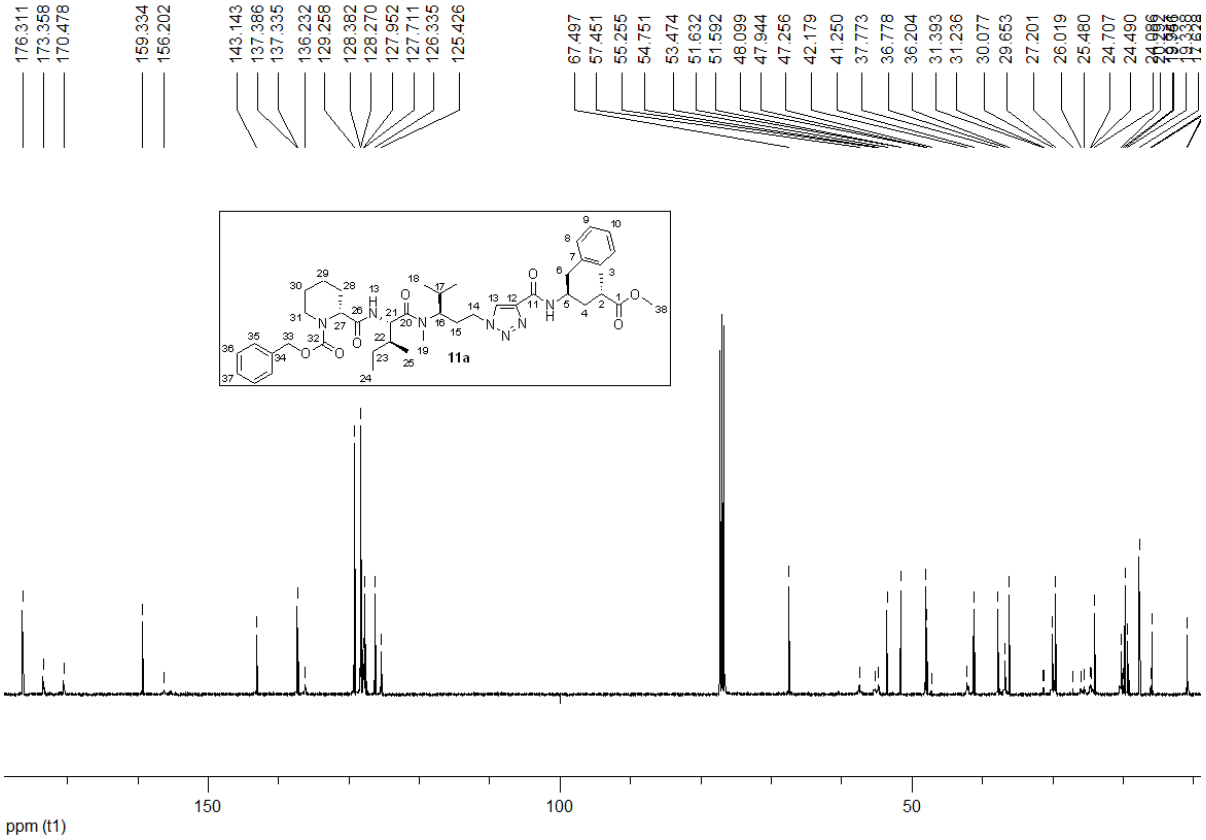
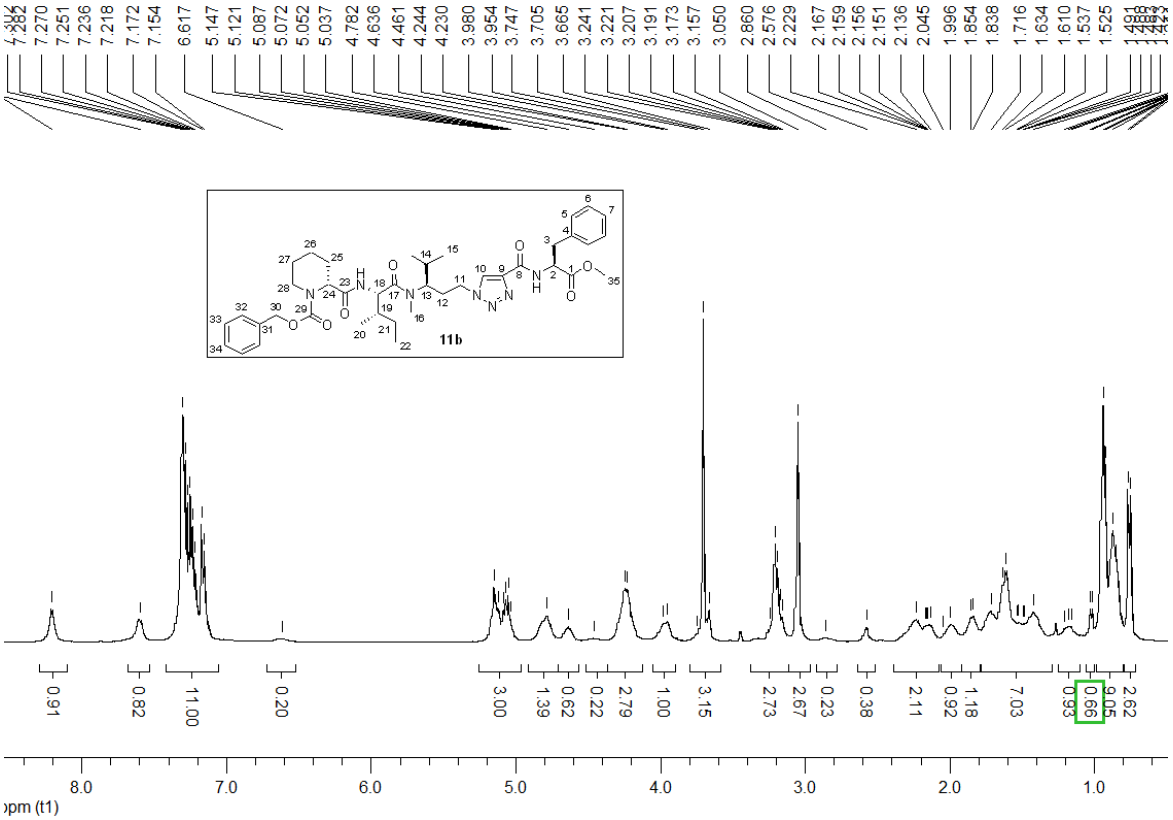
150
100
50
ppm (t1)


11a
ppm (t1)


11a
ppm (t1)


11b
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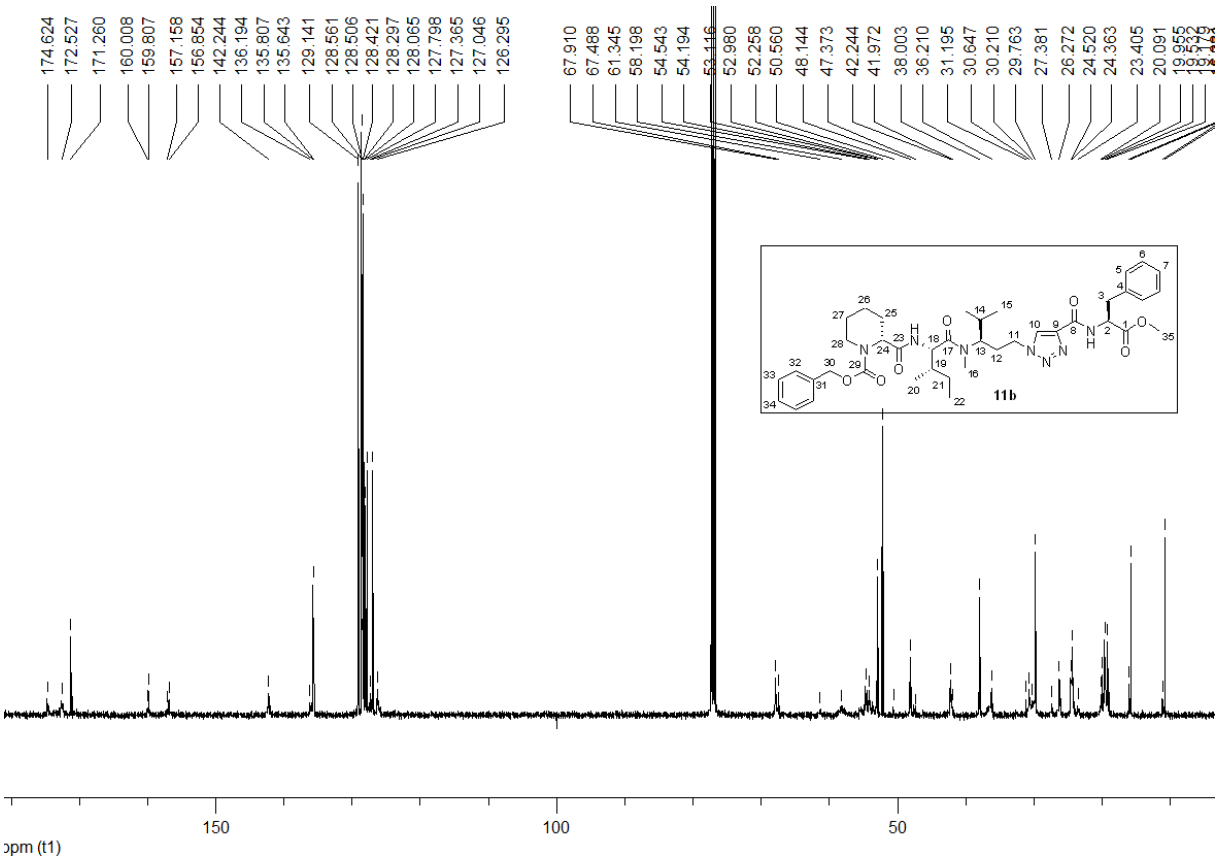
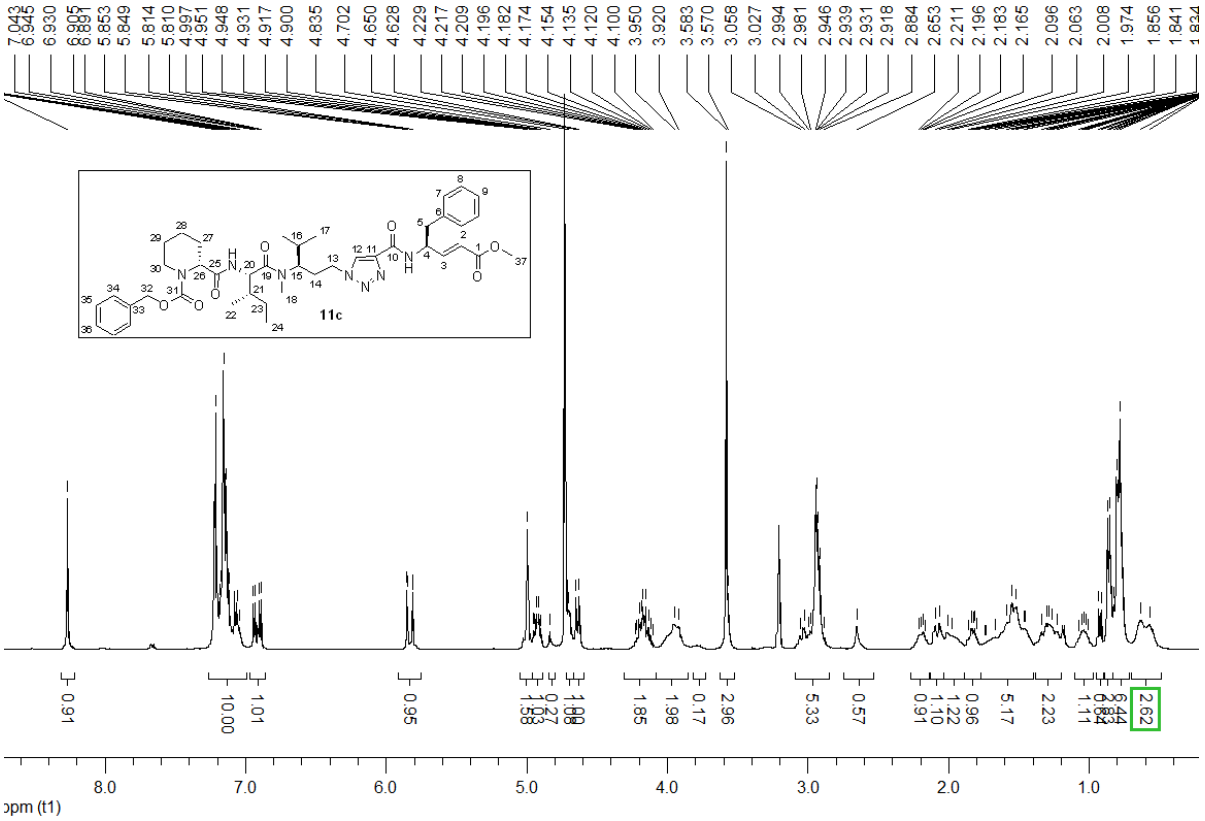
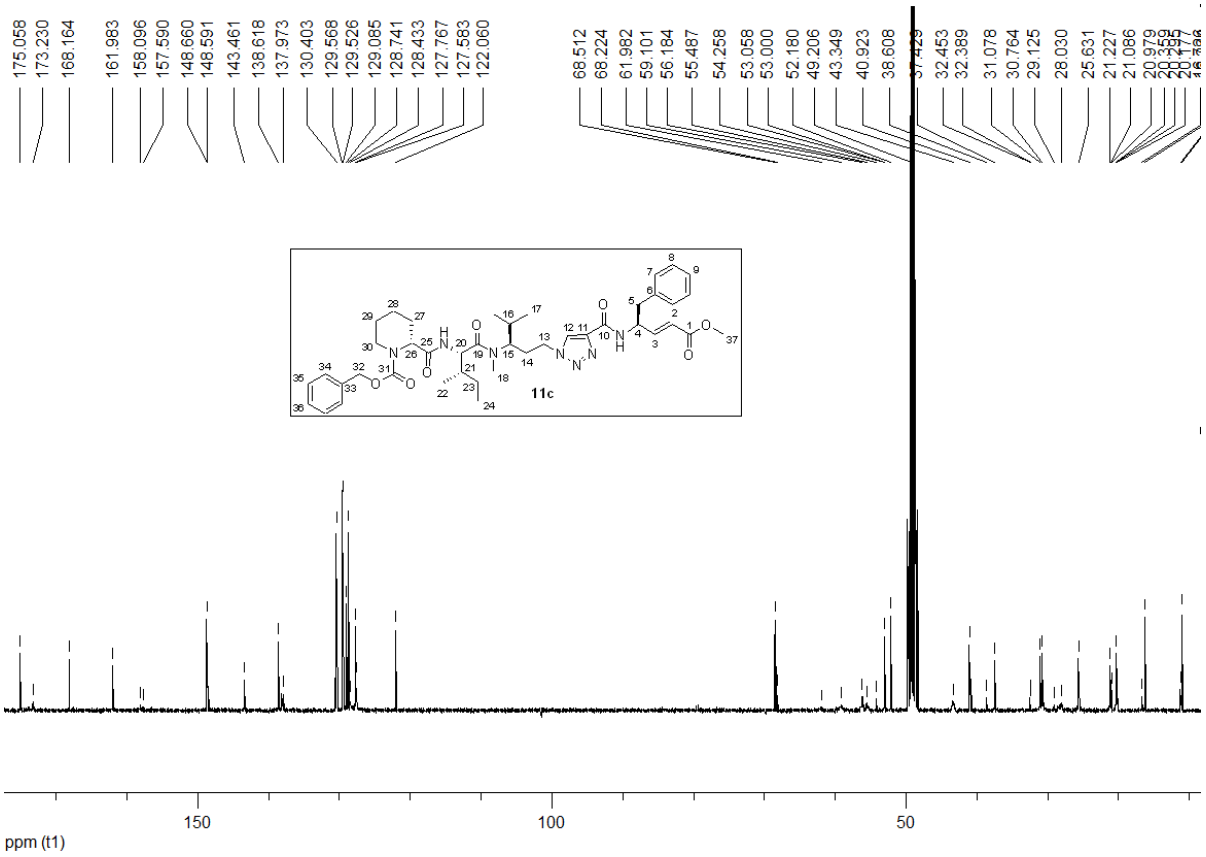
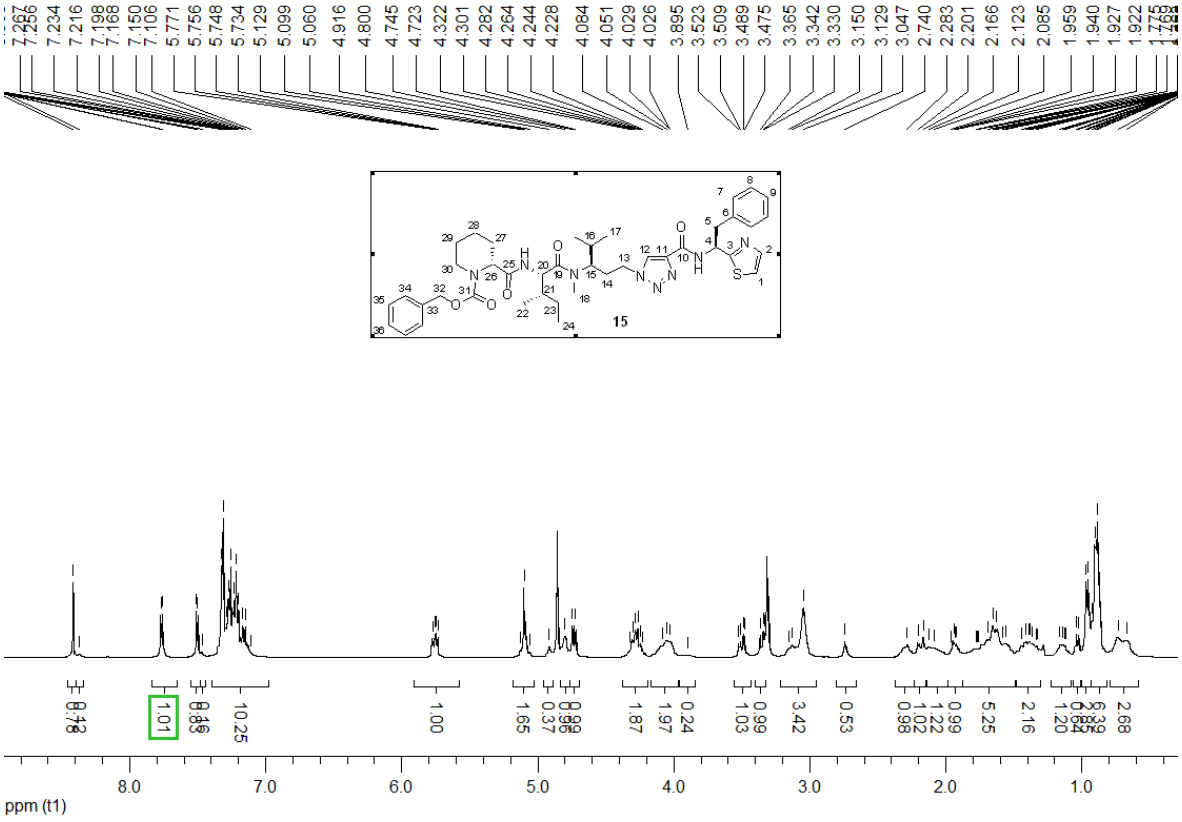
11.00
0.20
3.00
1.39
0.62
0.22
2.79
1.00
3.15
2.73
2.67
0.23
0.38
2.11
0.92
1.18
7.03
0.93
0.66
2.62
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


11b
150
100
50
ppm (t1)


11c
ppm (t1)


11c
ppm (t1)


7.267
7.256
7.234
7.216
7.198
7.168
7.150
7.106
5.771
5.756
5.748
5.734
5.129
5.099
5.060
4.916
4.800
4.745
4.723
4.322
4.301
4.282
4.264
4.244
4.228
4.084
4.051
4.029
4.026
3.895
3.523
3.509
3.489
3.475
3.365
3.342
3.330
3.150
3.129
3.047
2.740
2.283
2.201
2.166
2.123
2.085
1.959
1.940
1.927
1.922
15
0.76
1.01
0.85
10.25
1.00
1.65
0.37
1.87
1.97
0.24
1.03
0.99
2.42
0.53
0.98
1.02
1.22
0.99
5.25
2.16
1.20
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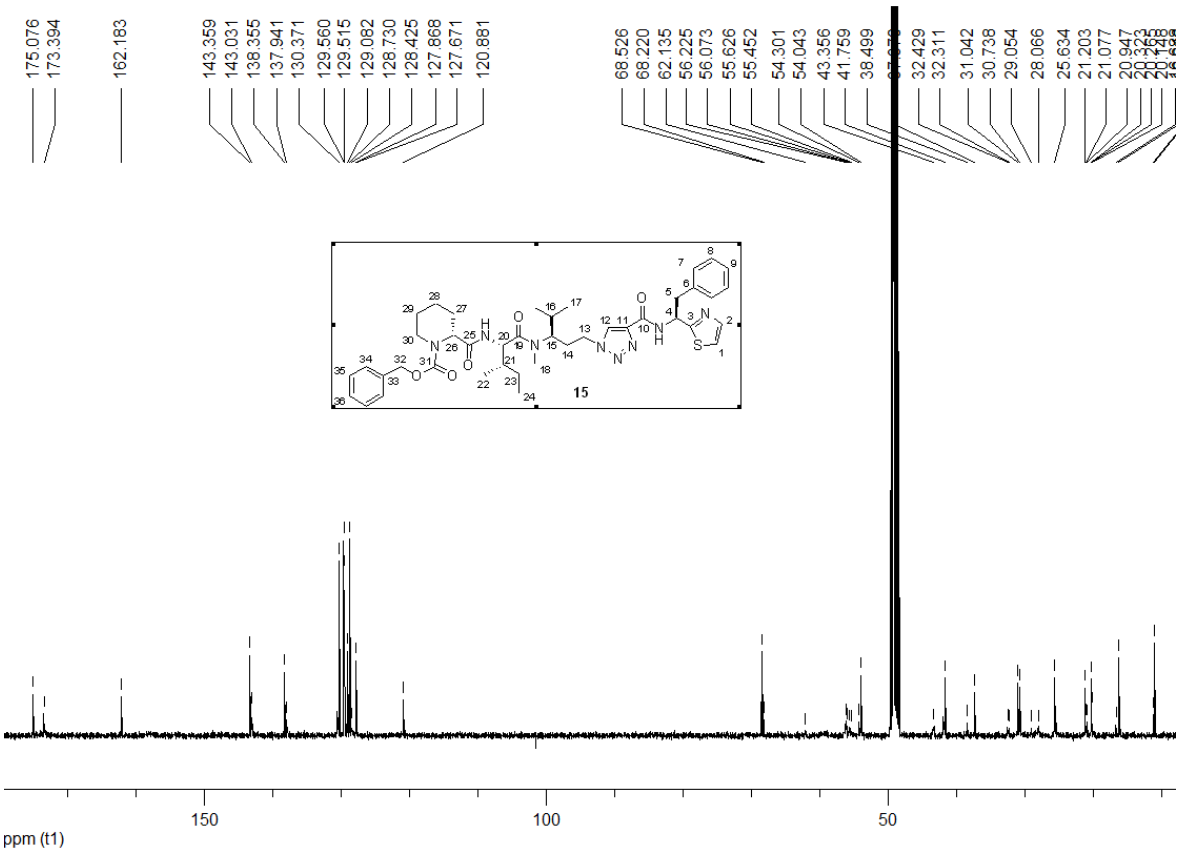
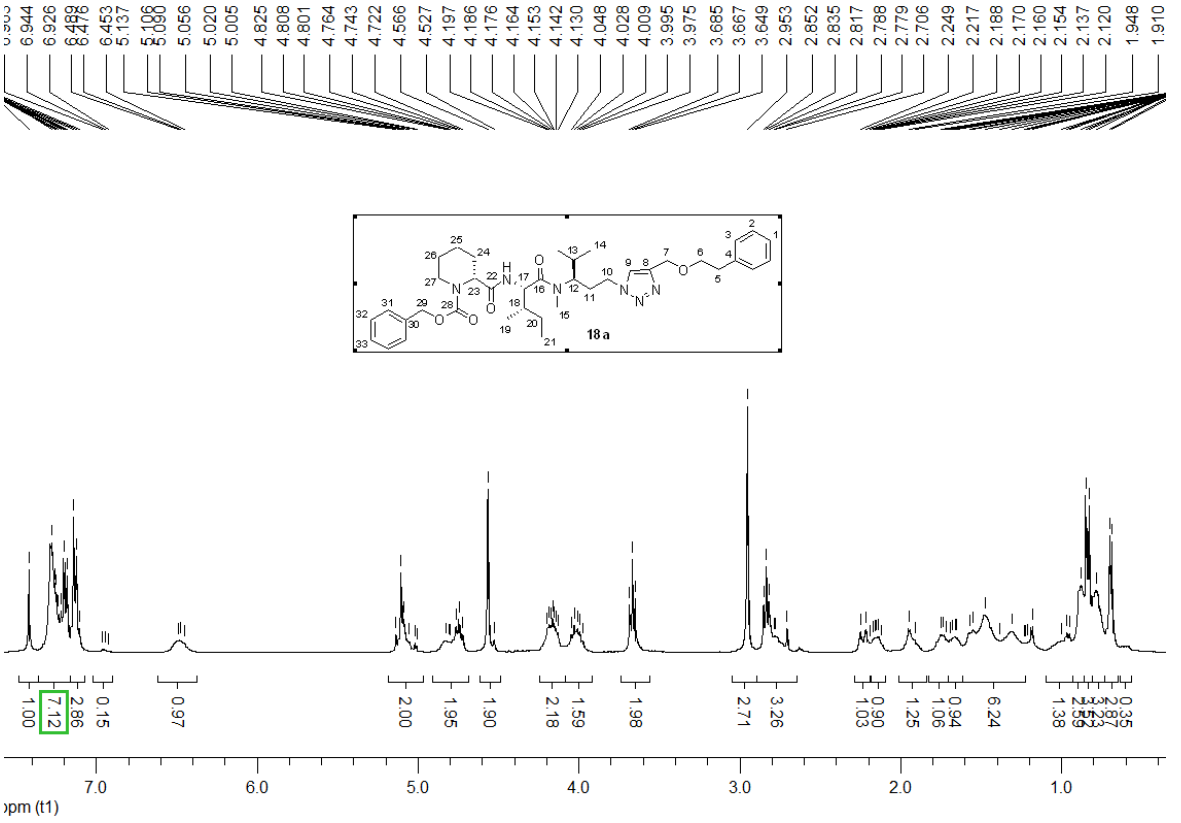
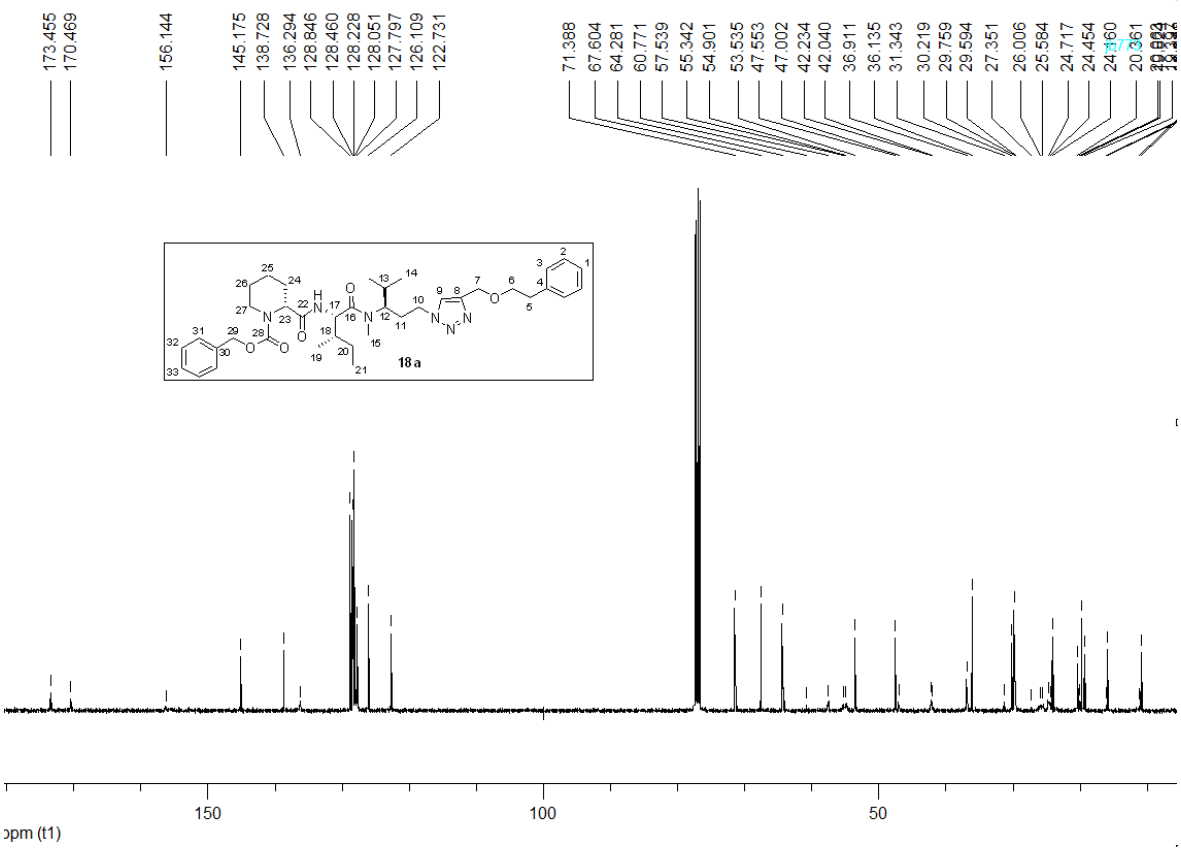
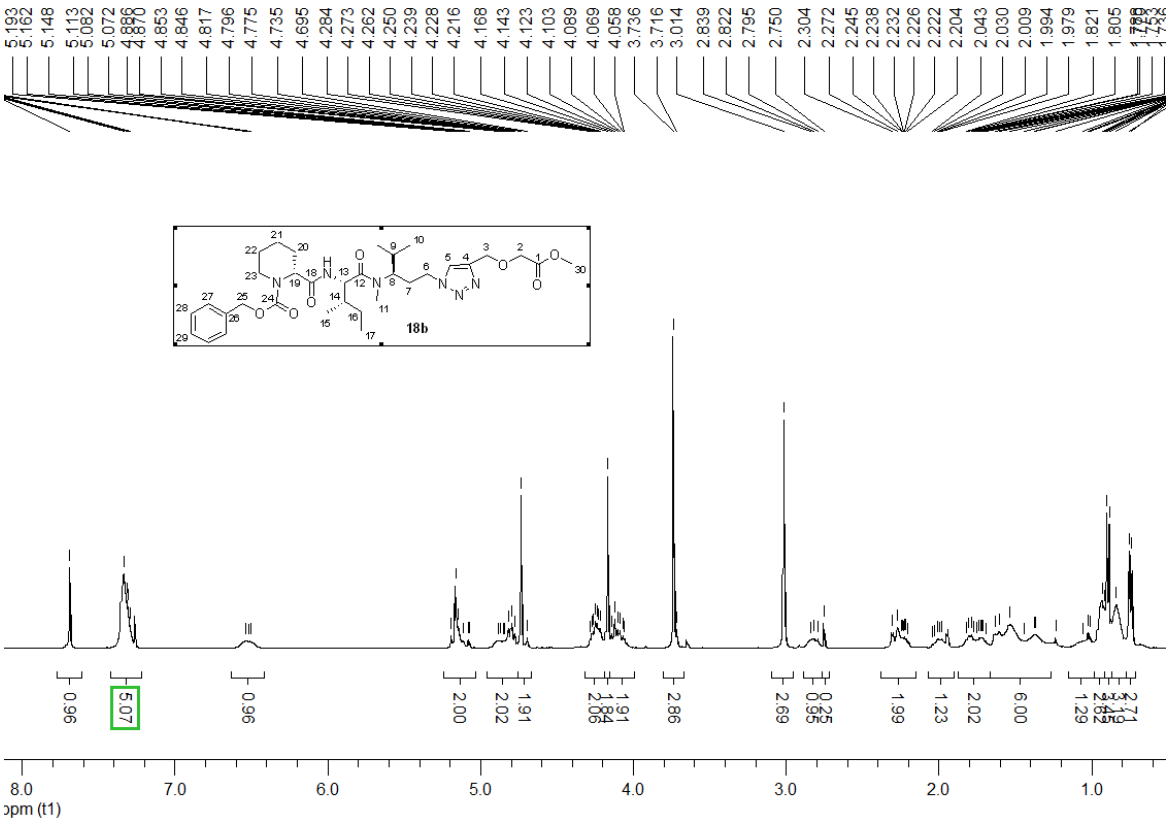
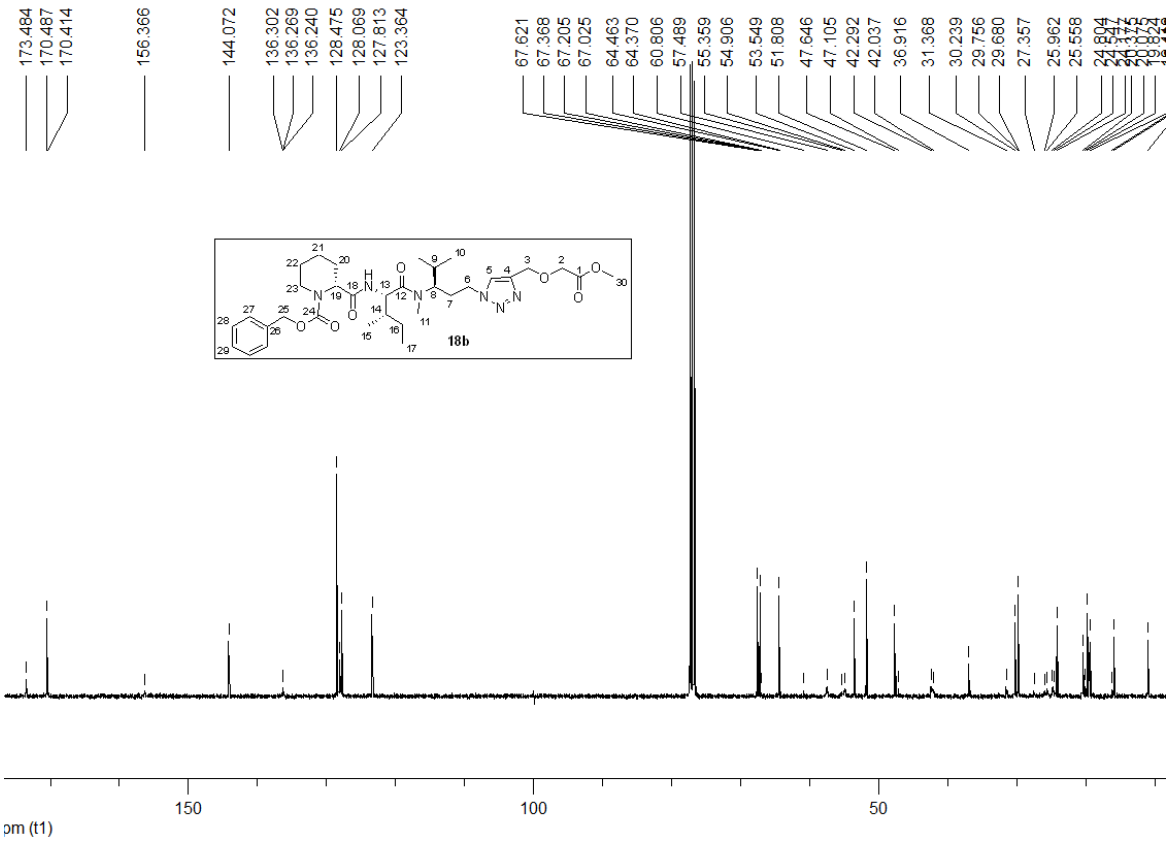
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

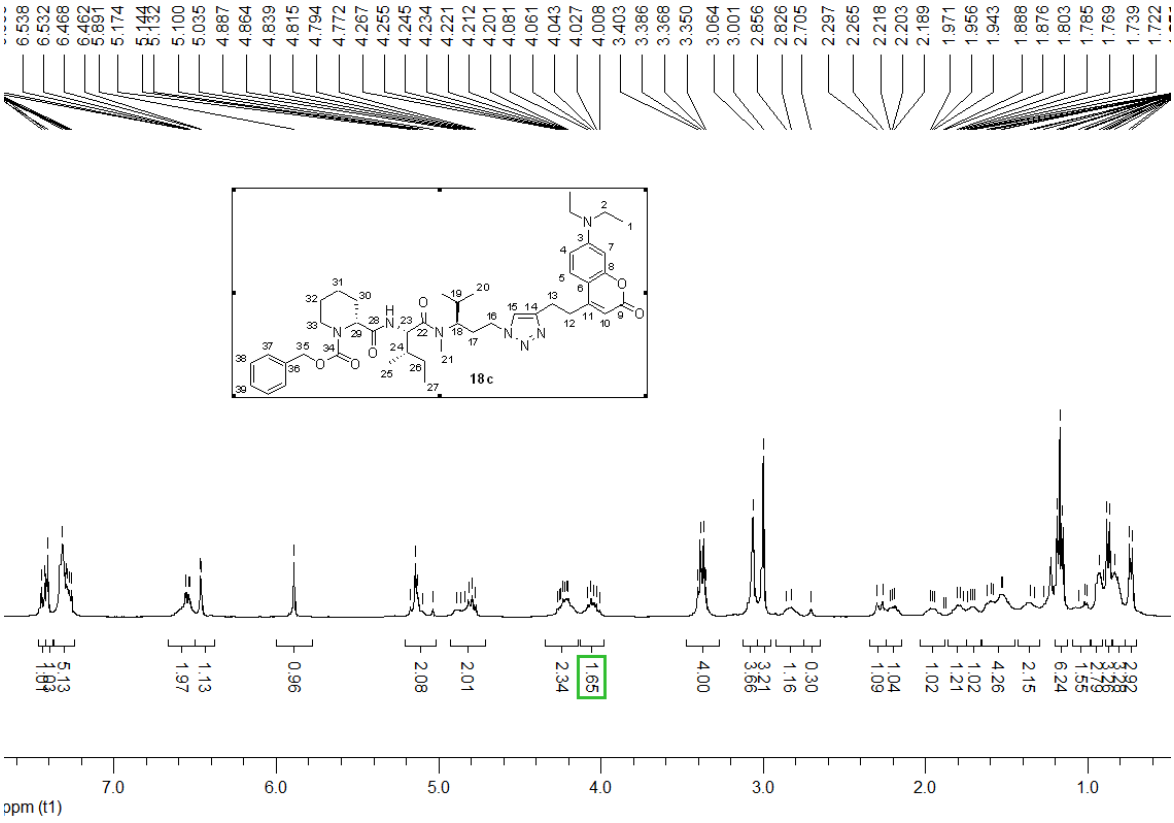

175.076
173.394
162.183
143.359
143.031
138.355
137.941
130.371
129.560
129.515
129.082
128.730
128.425
127.868
127.671
120.881
68.526
68.220
62.135
56.225
56.073
55.626
55.452
54.301
54.043
43.356
41.759
38.499
32.429
32.311
31.042
30.738
29.054
28.066
25.634
21.203
21.077
20.947
15
150
100
50
ppm (t1)

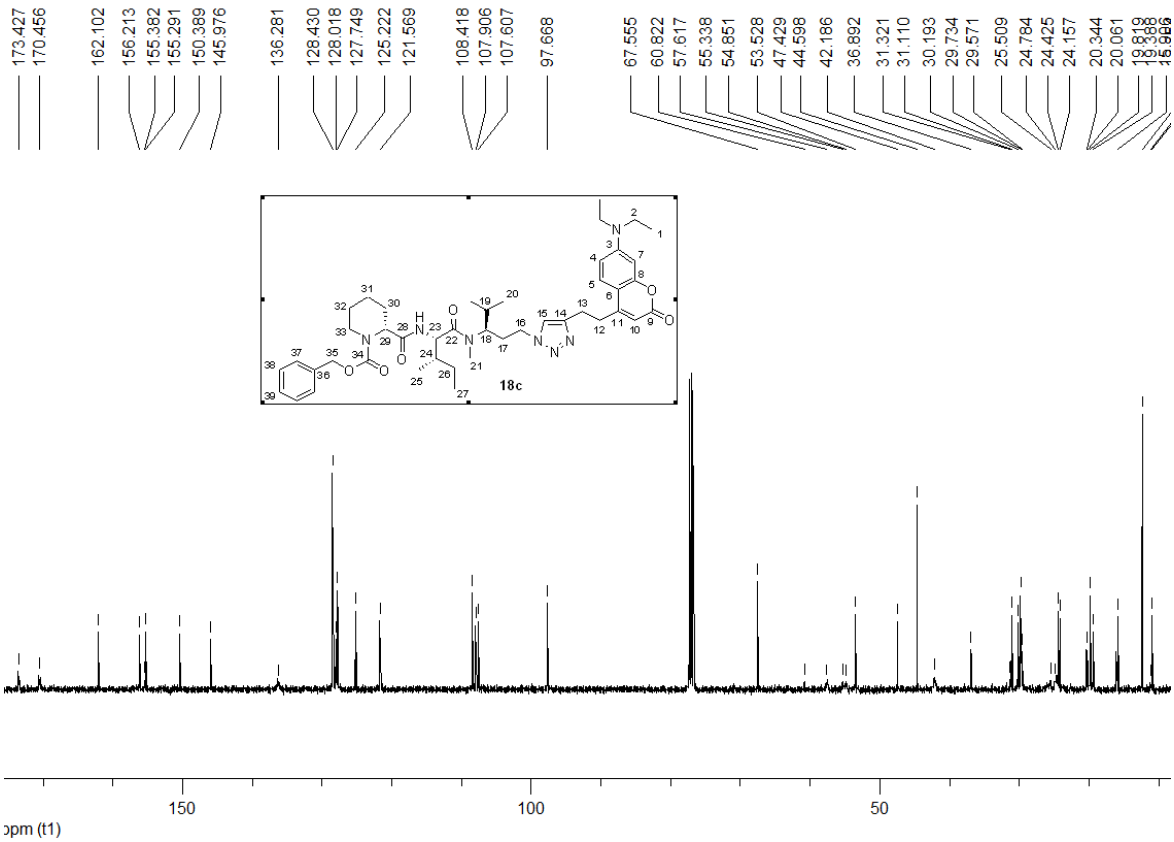

18 a
1.00
7.12
2.86
0.15
0.97
2.00
1.95
1.90
2.18
1.59
1.98
2.71
3.26
1.03
0.90
1.25
1.06
0.94
9.24
1.38
0.35
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

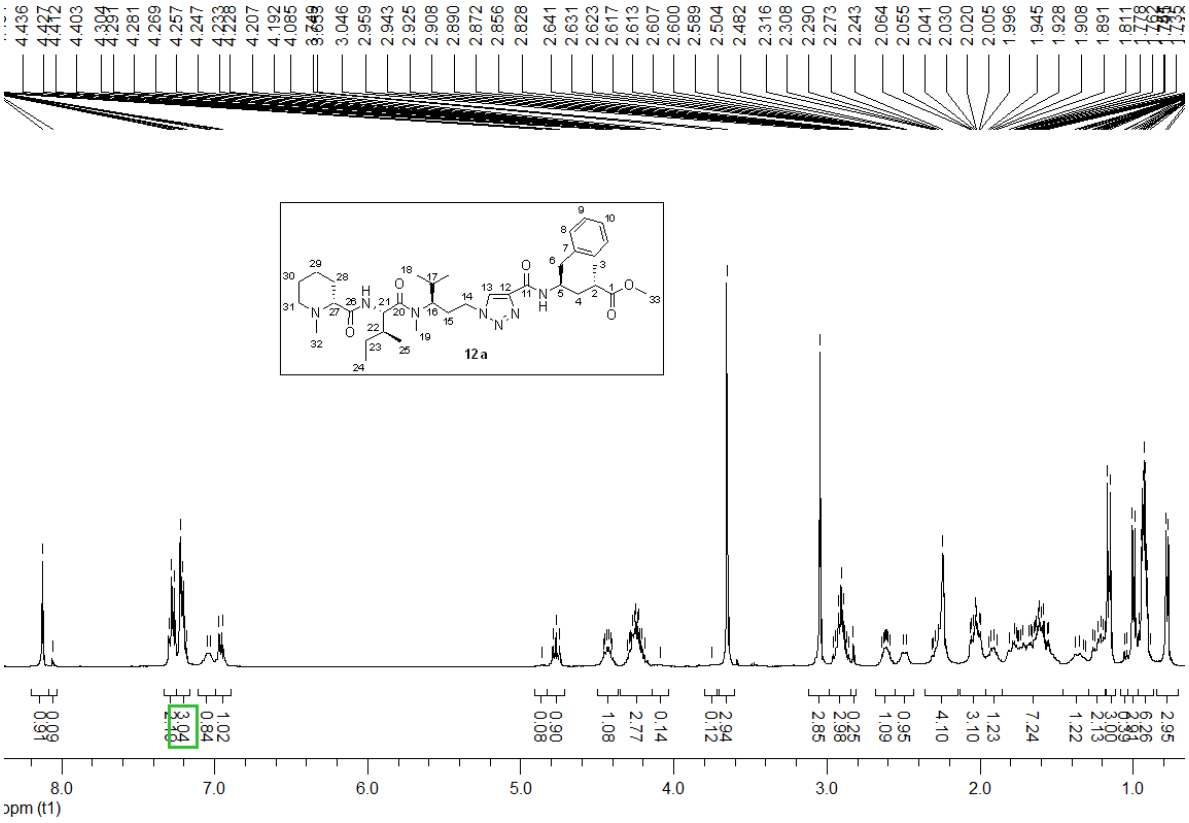

18 a
150
100
50
ppm (t1)

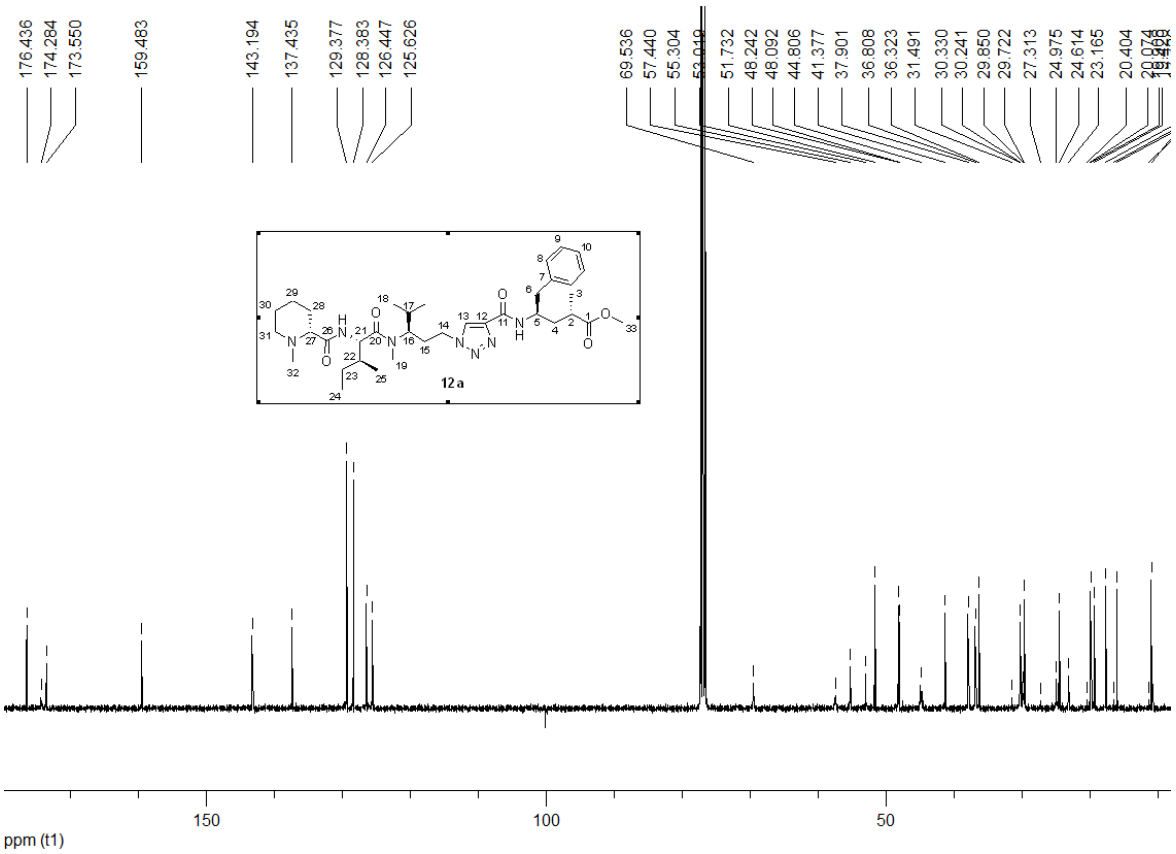

18b
0.96
5.07
0.96
2.00
2.02
1.91
2.06
1.84
1.91
2.86
2.69
0.95
0.95
1.99
1.23
2.02
6.00
1.29
2.71
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

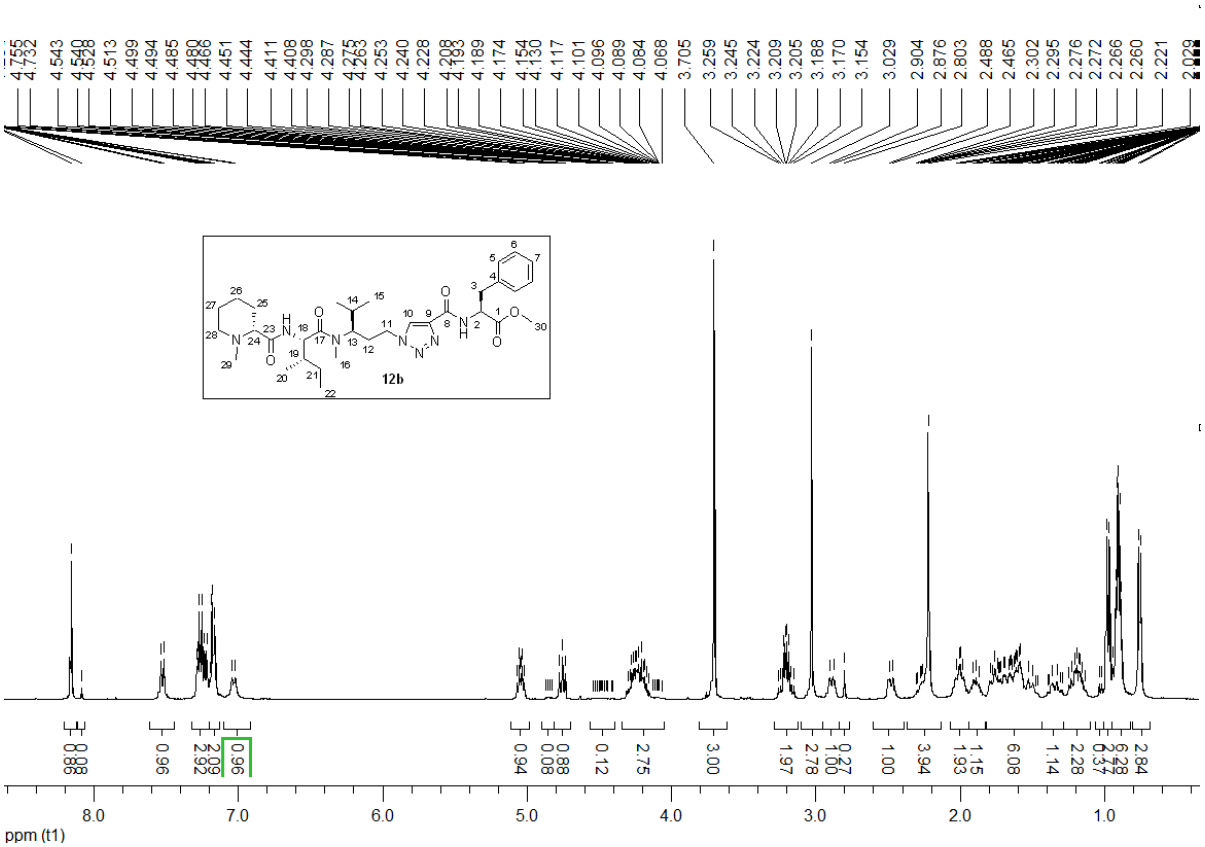

18b
150
100
50
ppm (t1)

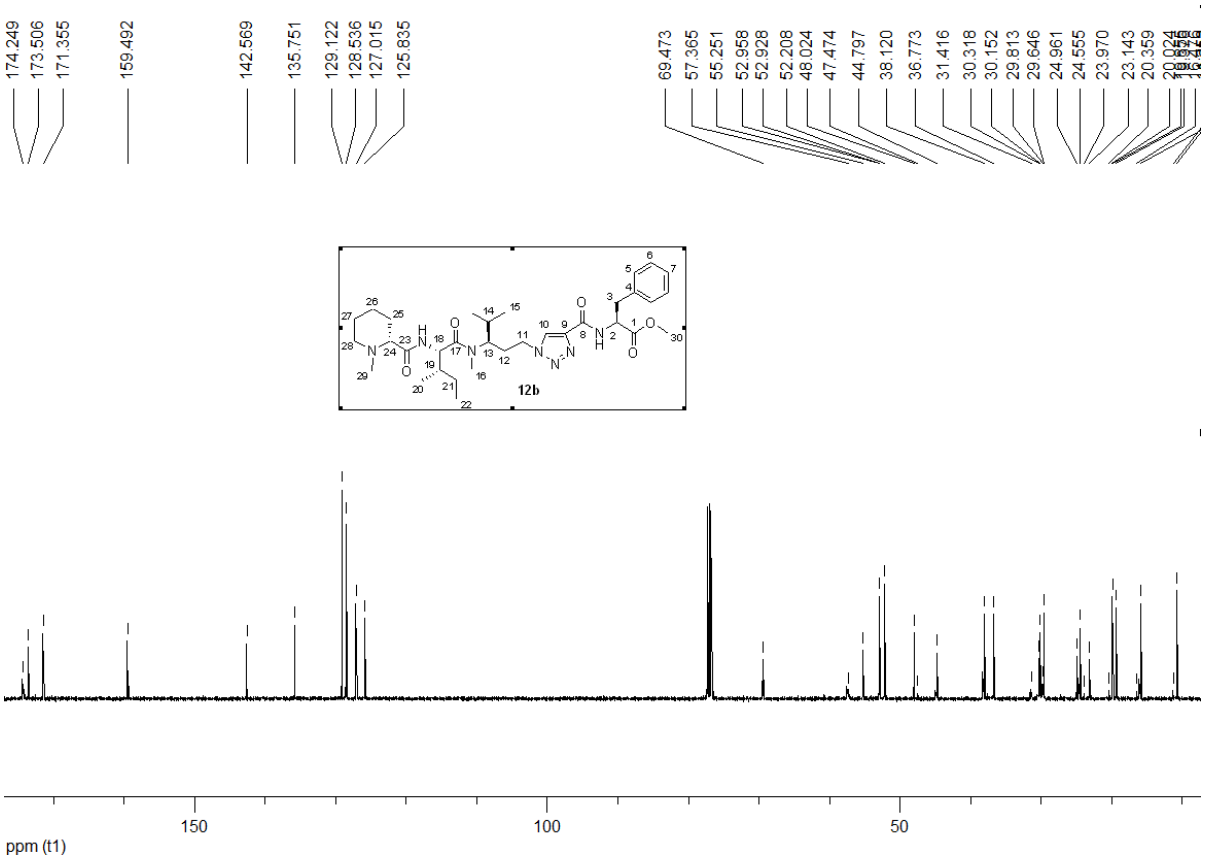

18c
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

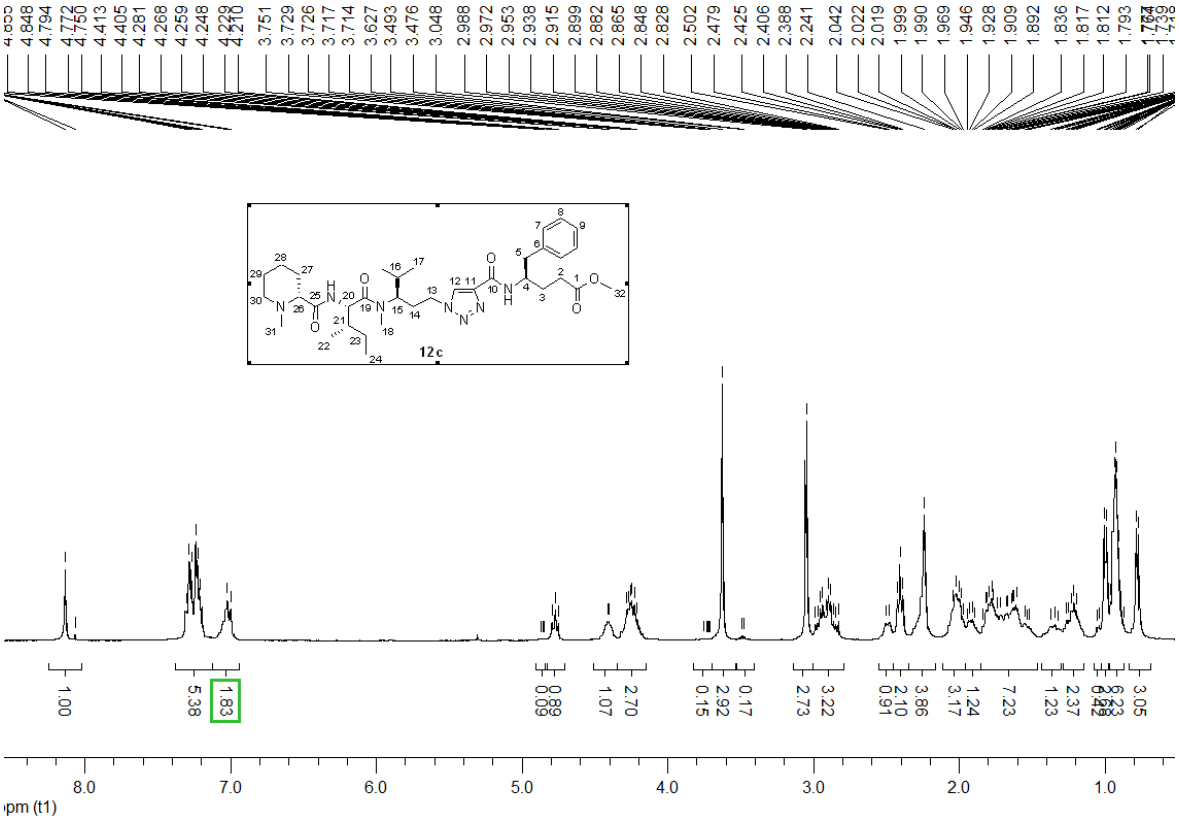

18c
150
100
50
ppm (t1)

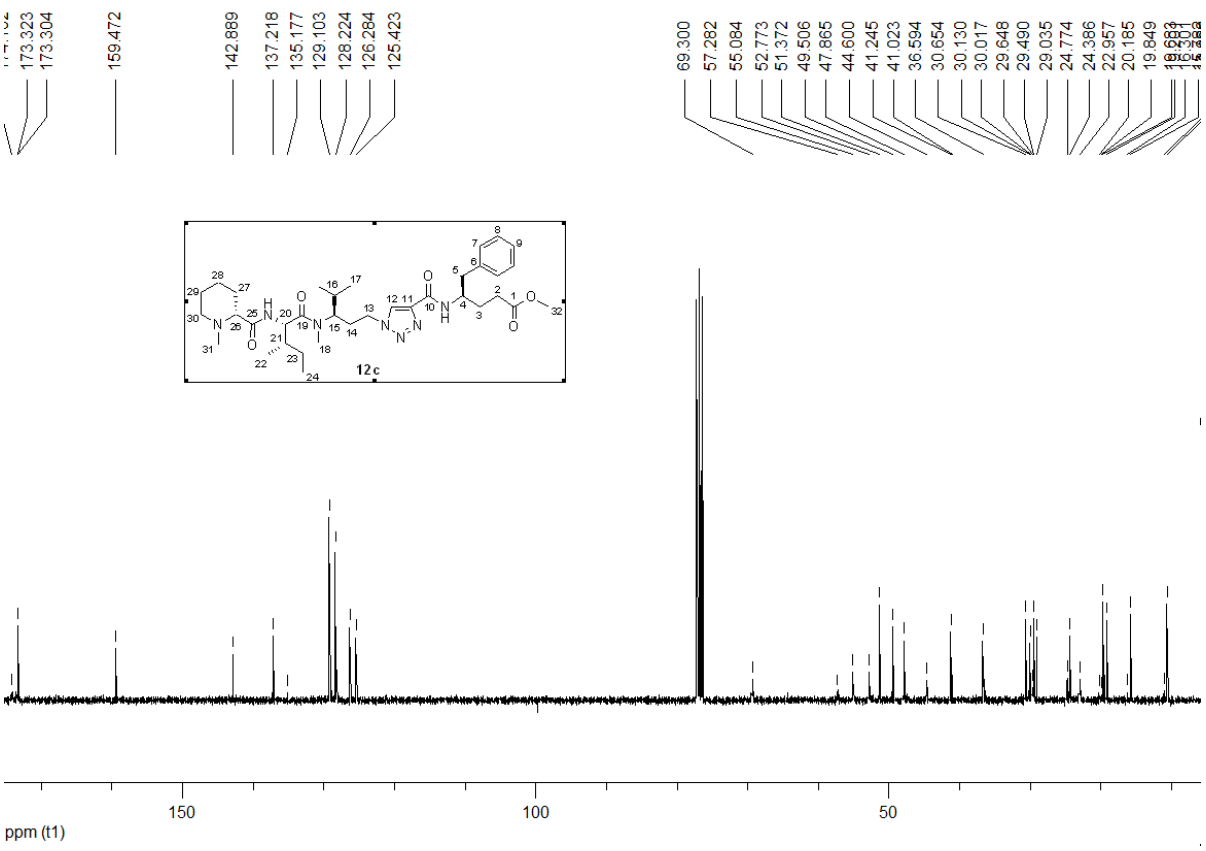

12a
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

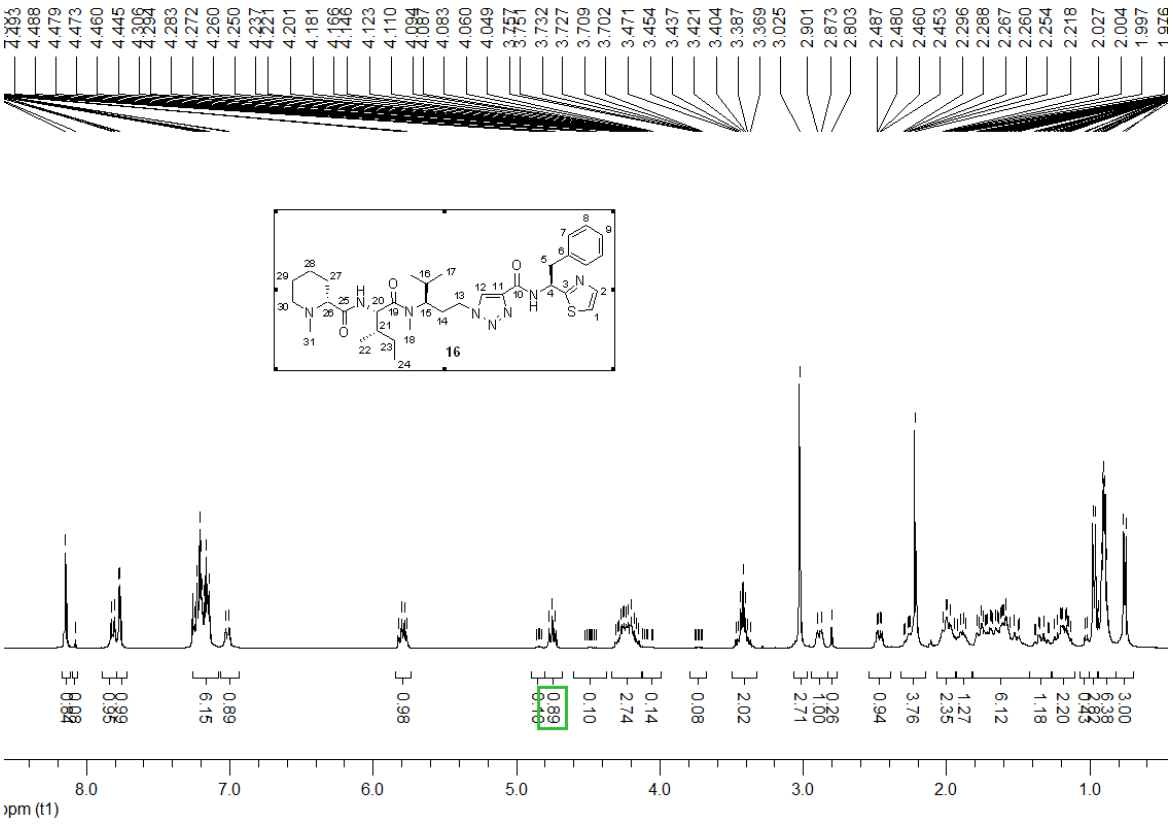

12a
150
100
50
ppm (t1)

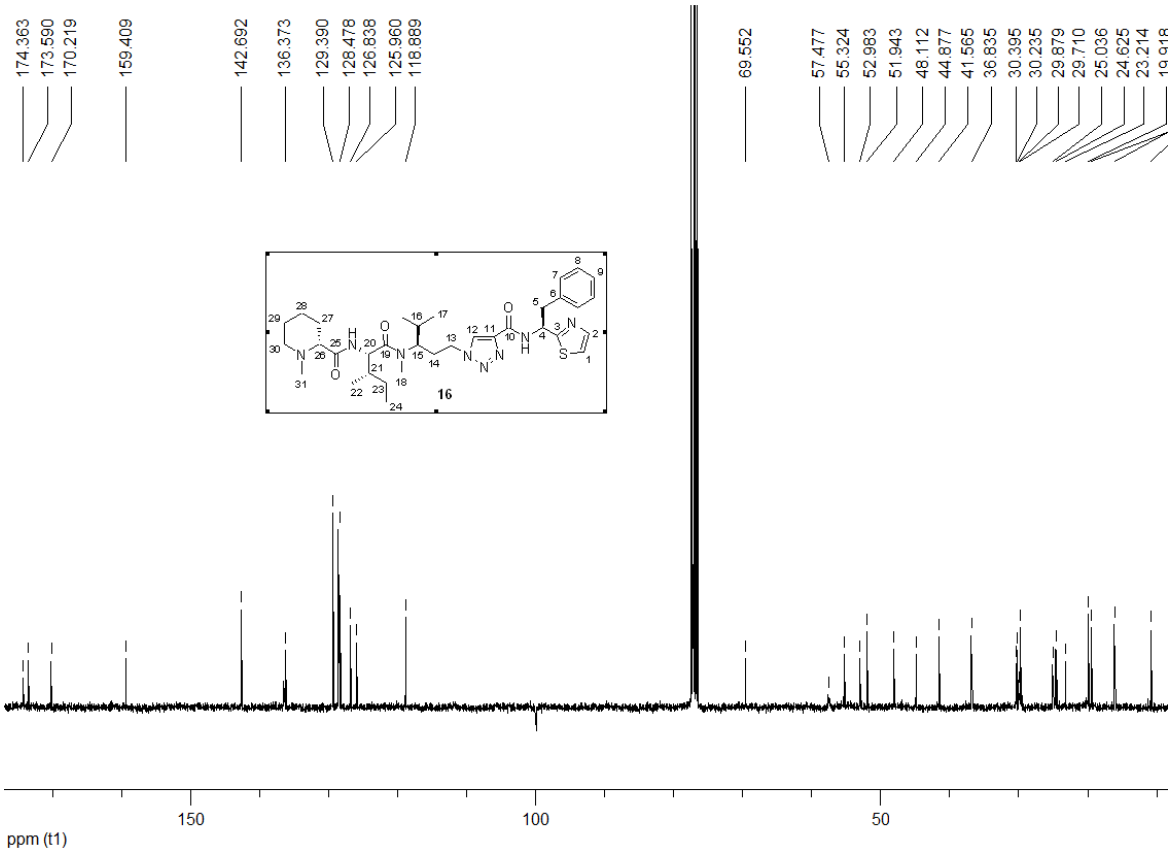

12b
ppm (t1)

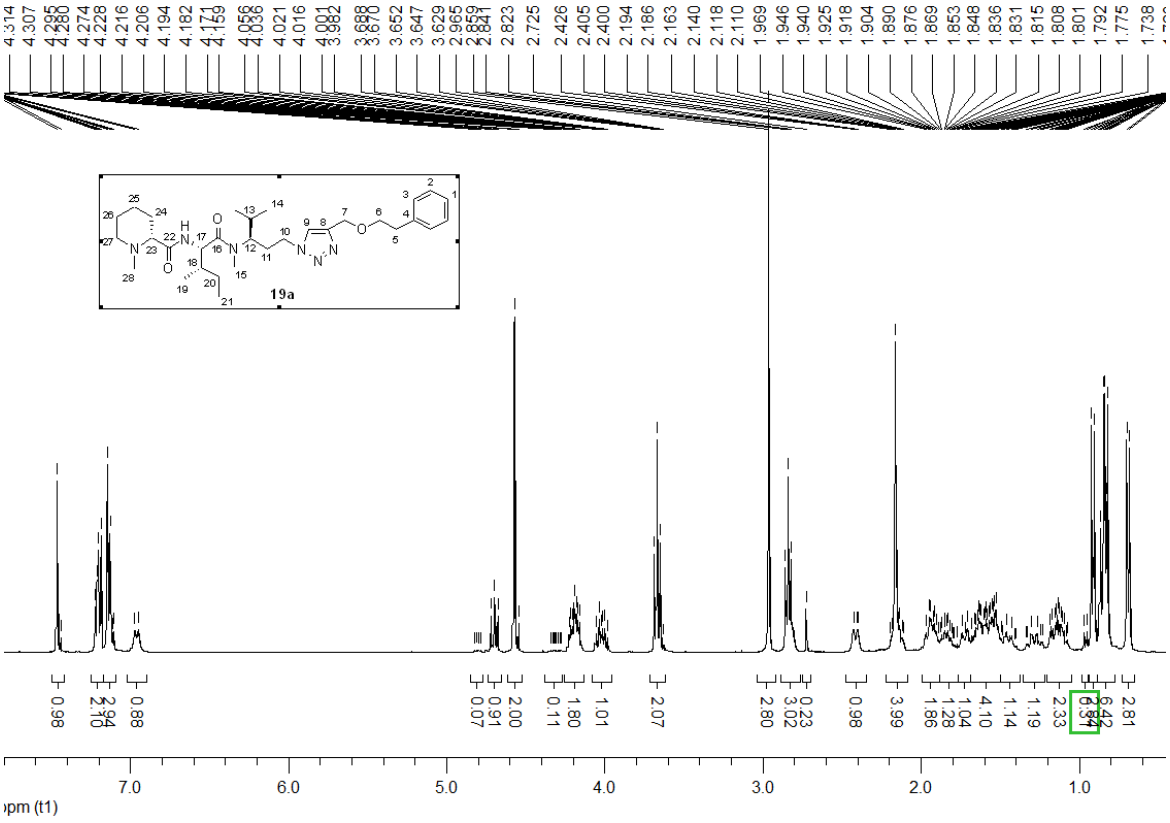

12b
ppm (t1)

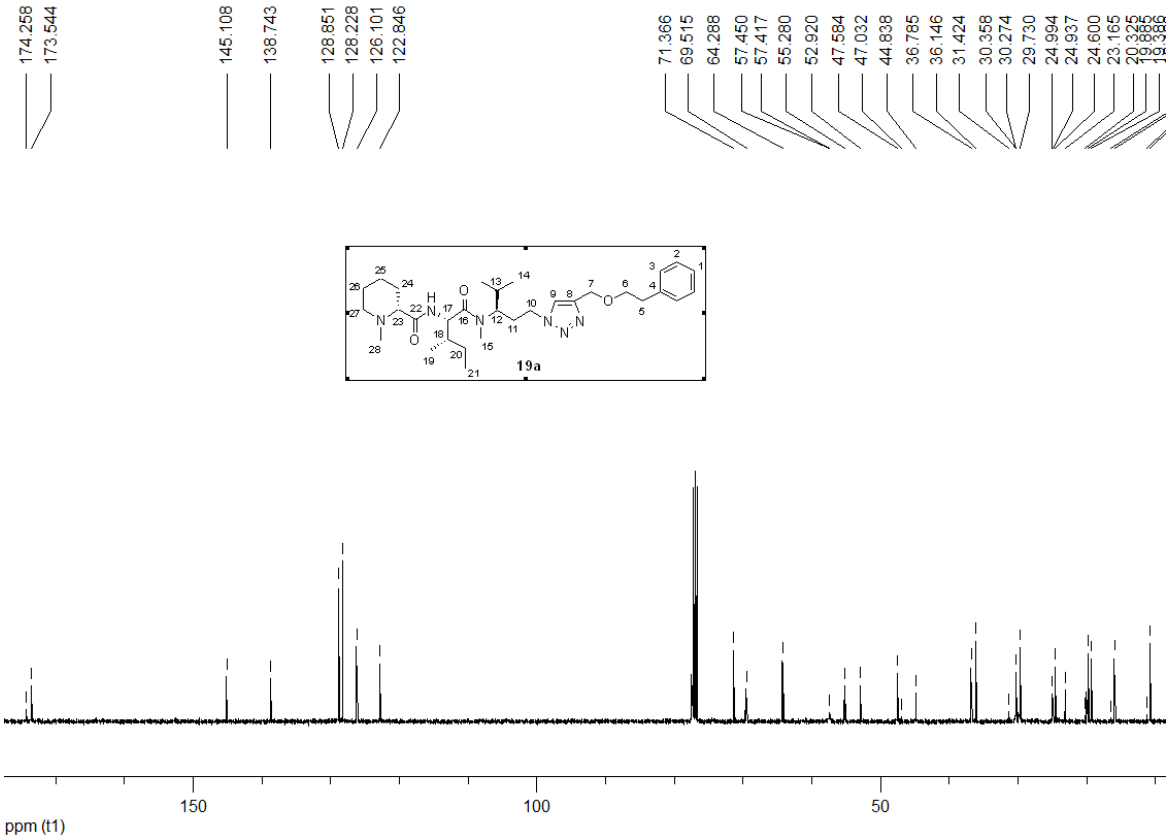

12c
1.00
5.38
1.83
0.89
0.09
1.07
2.70
0.15
2.62
0.17
2.73
3.22
0.91
2.10
3.86
3.17
1.24
7.23
1.23
2.37
3.05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

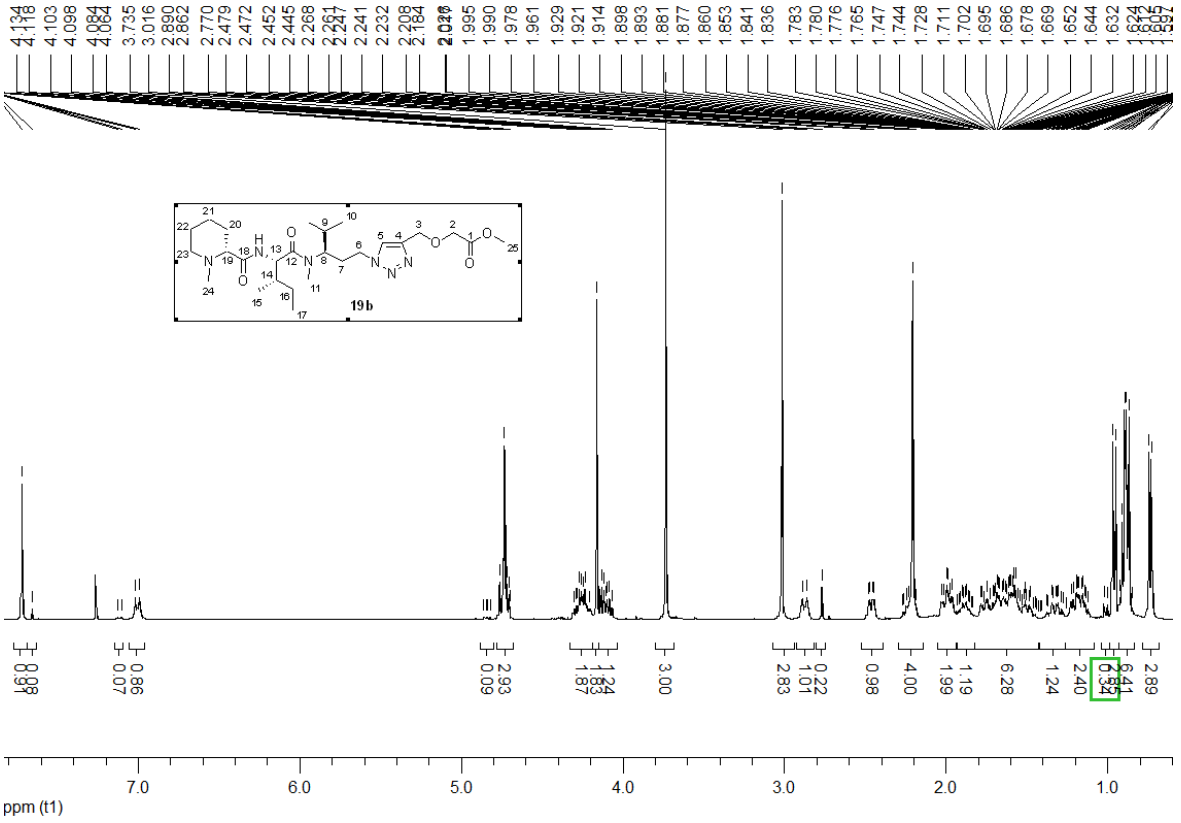

173.323
173.304
159.472
142.889
137.218
135.177
129.103
128.224
126.284
125.423
69.300
57.282
55.084
52.773
51.372
49.506
47.865
44.600
41.245
41.023
36.594
30.654
30.130
30.017
29.648
29.490
29.035
24.774
24.386
22.957
20.185
19.849
12c
150
100
50
ppm (t1)

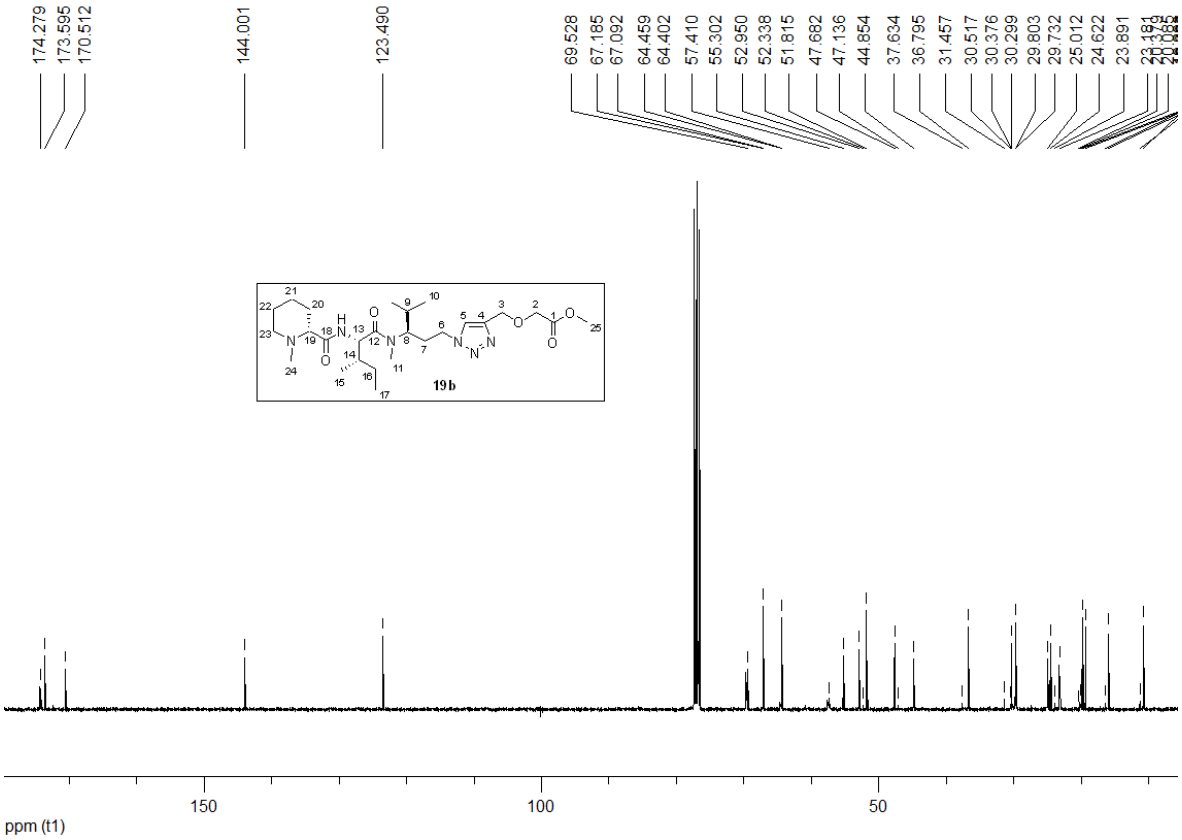

16
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

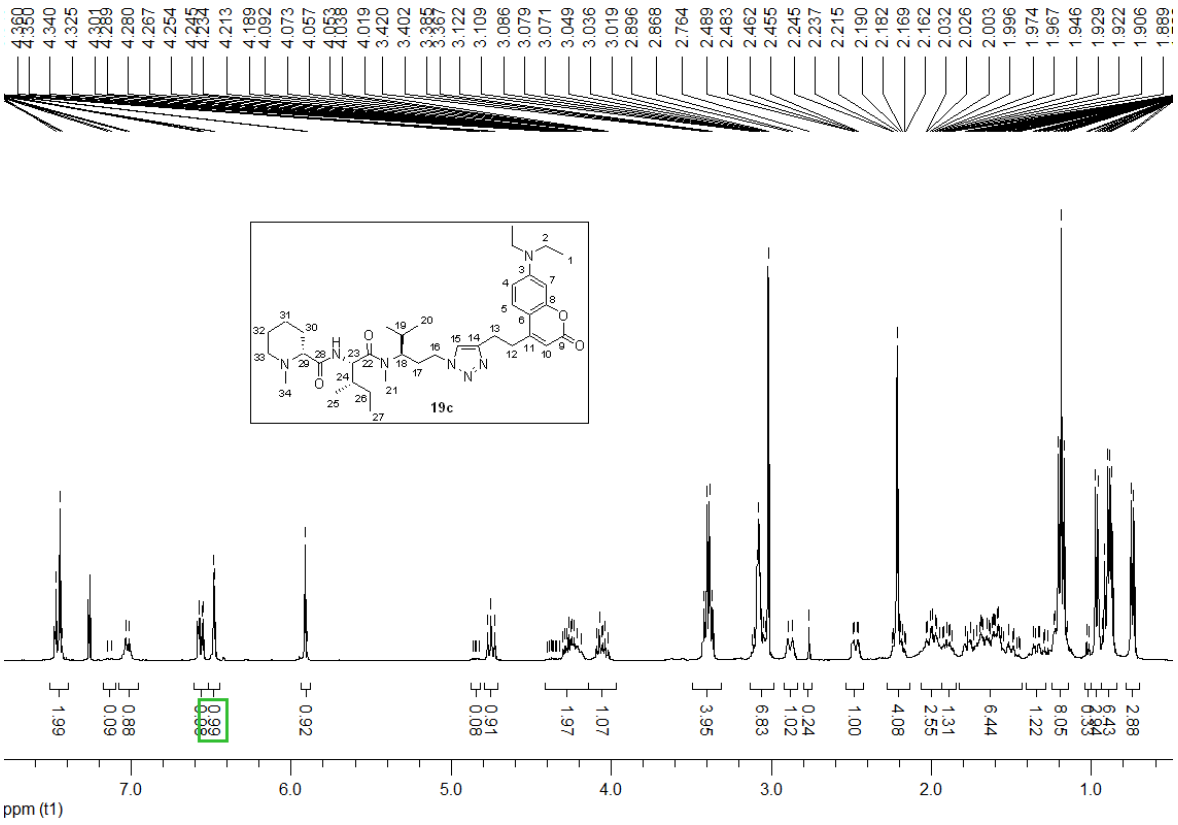

174.363
173.590
170.219
159.409
142.692
136.373
129.390
128.478
126.838
125.960
118.889
69.552
57.477
55.324
52.983
51.943
48.112
44.877
41.565
36.835
30.395
30.235
29.879
29.710
25.036
24.625
23.214
16
150
100
50
ppm (t1)

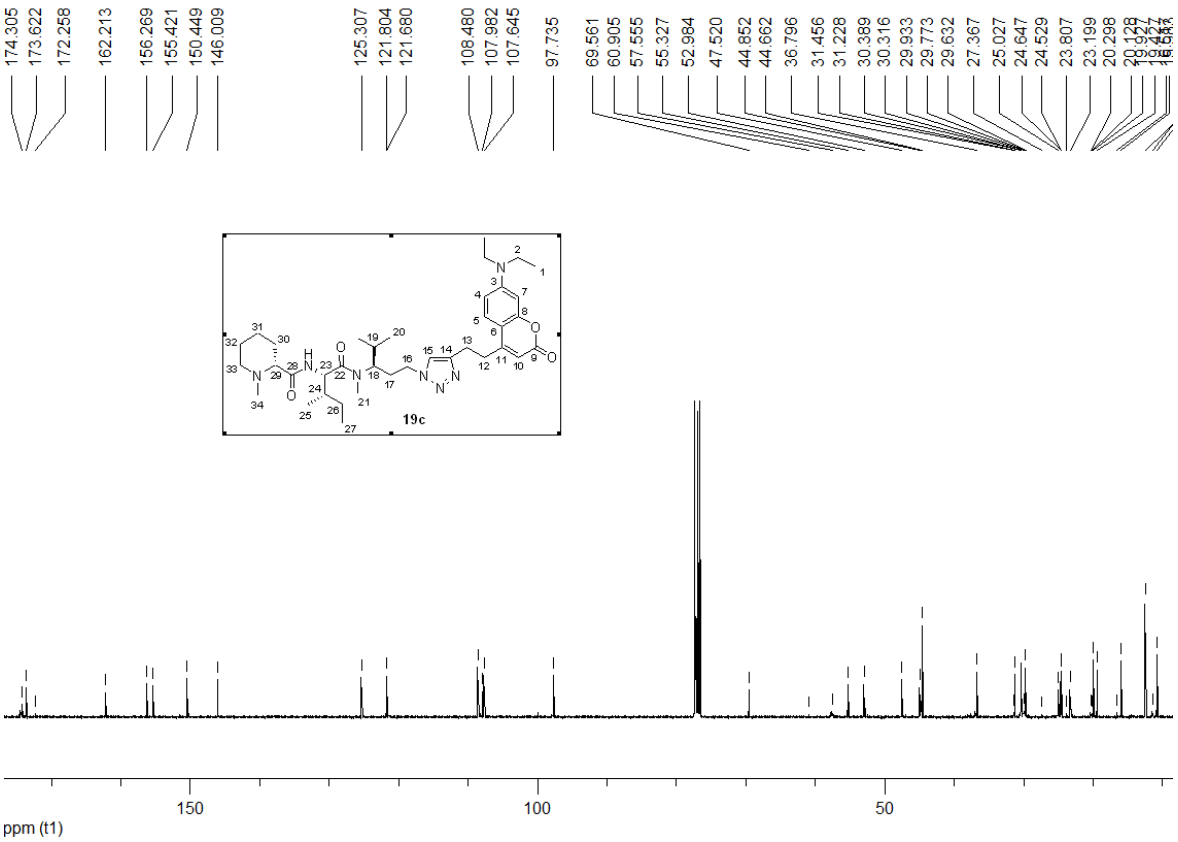

19a
0.98
2.94
3.10
0.88
0.07
1.61
2.00
0.11
1.80
1.01
2.07
2.80
3.02
0.23
0.98
3.69
1.86
1.28
1.04
4.10
1.14
1.19
2.33
6.37
6.42
2.81
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

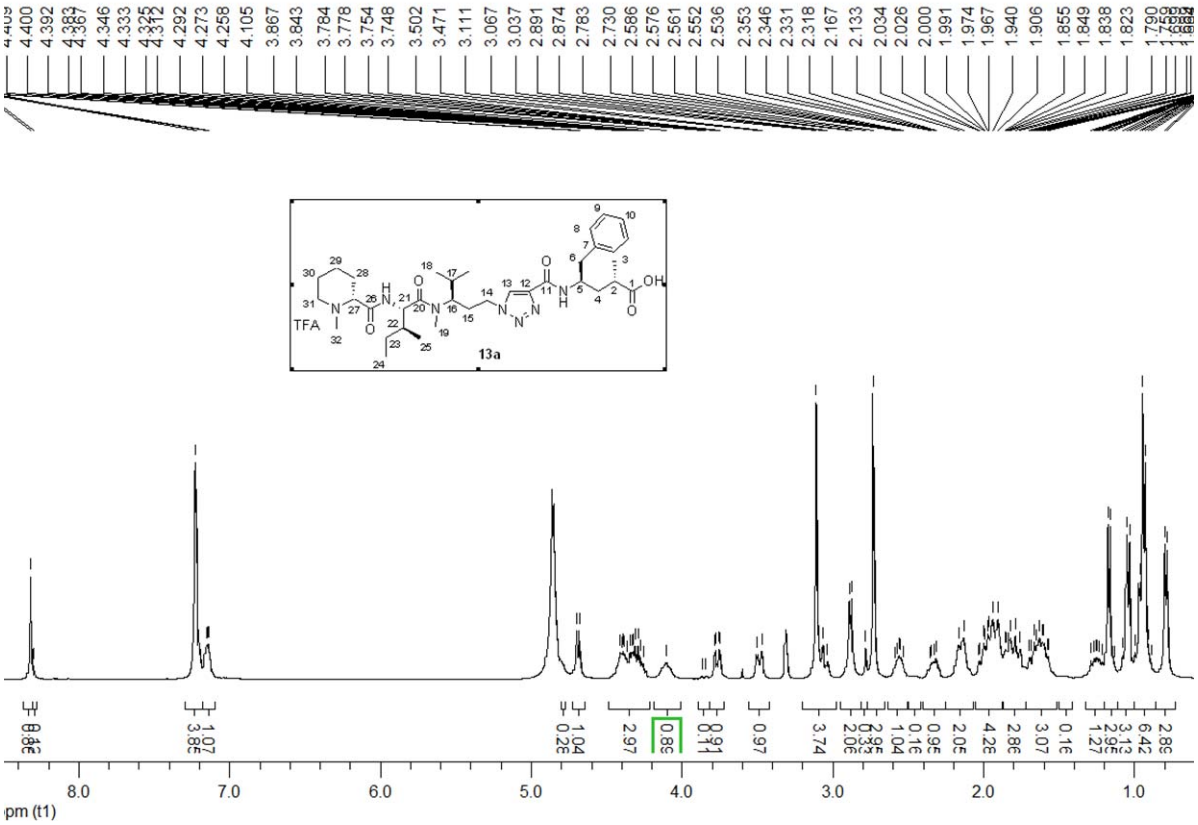

174.258
173.544
145.108
138.743
128.851
128.228
126.101
122.846
71.366
69.515
64.288
57.450
57.417
55.280
52.920
47.584
47.032
44.838
36.785
36.146
31.424
30.358
30.274
29.730
24.994
24.937
24.600
23.165
19.385
19.336
19a
150
100
50
ppm (t1)

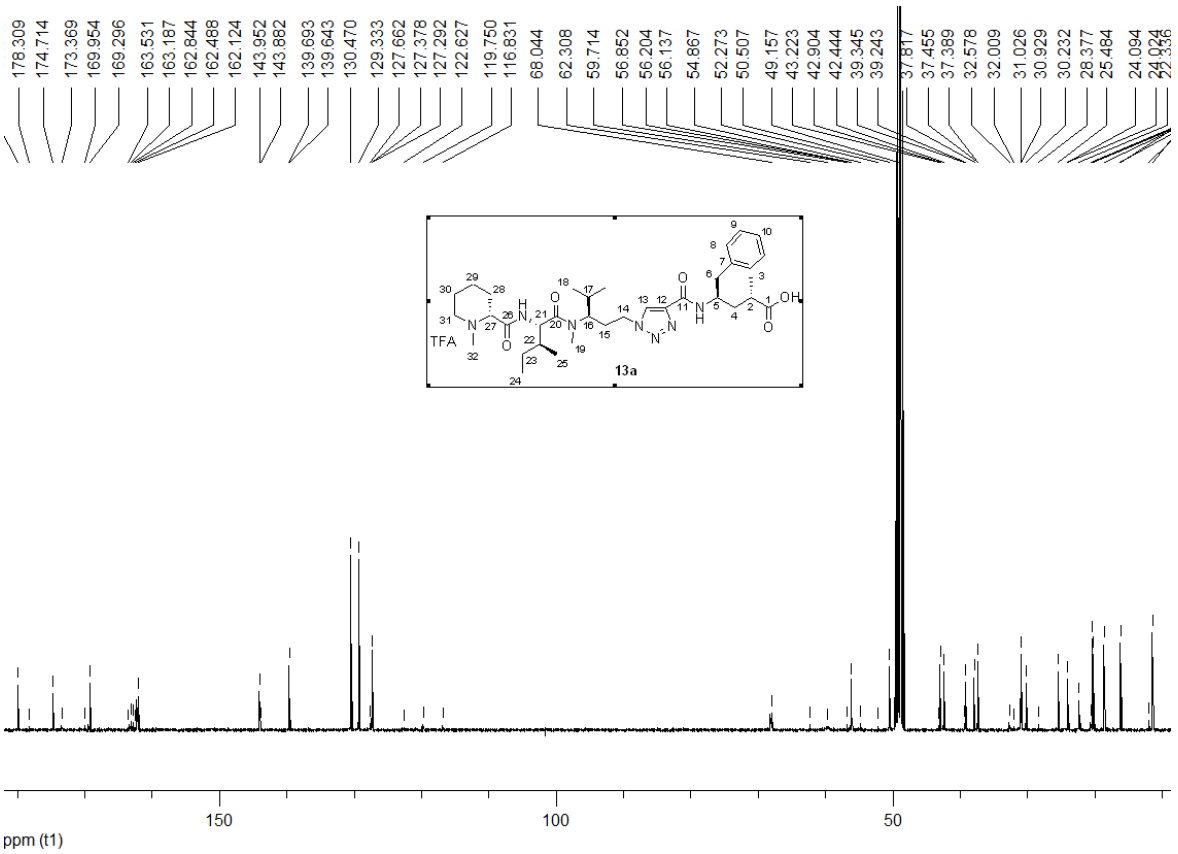

19b
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

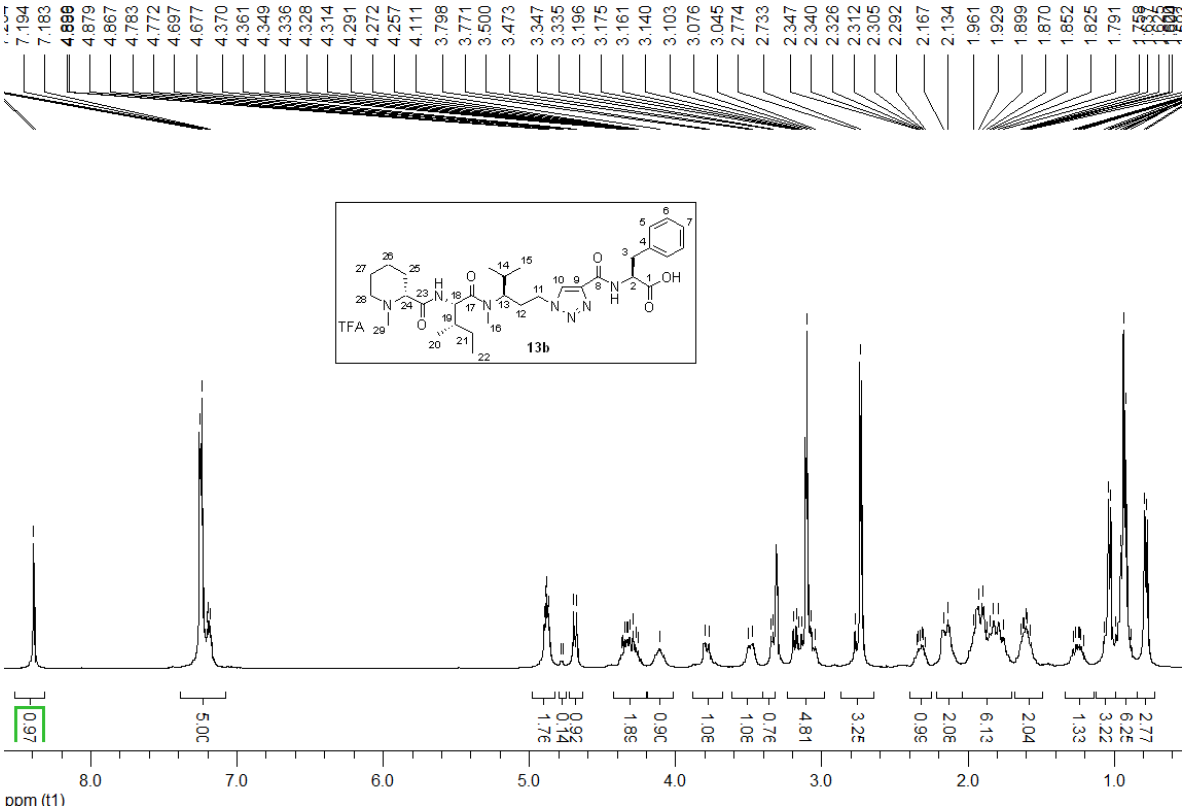

19b
150
100
50
ppm (t1)

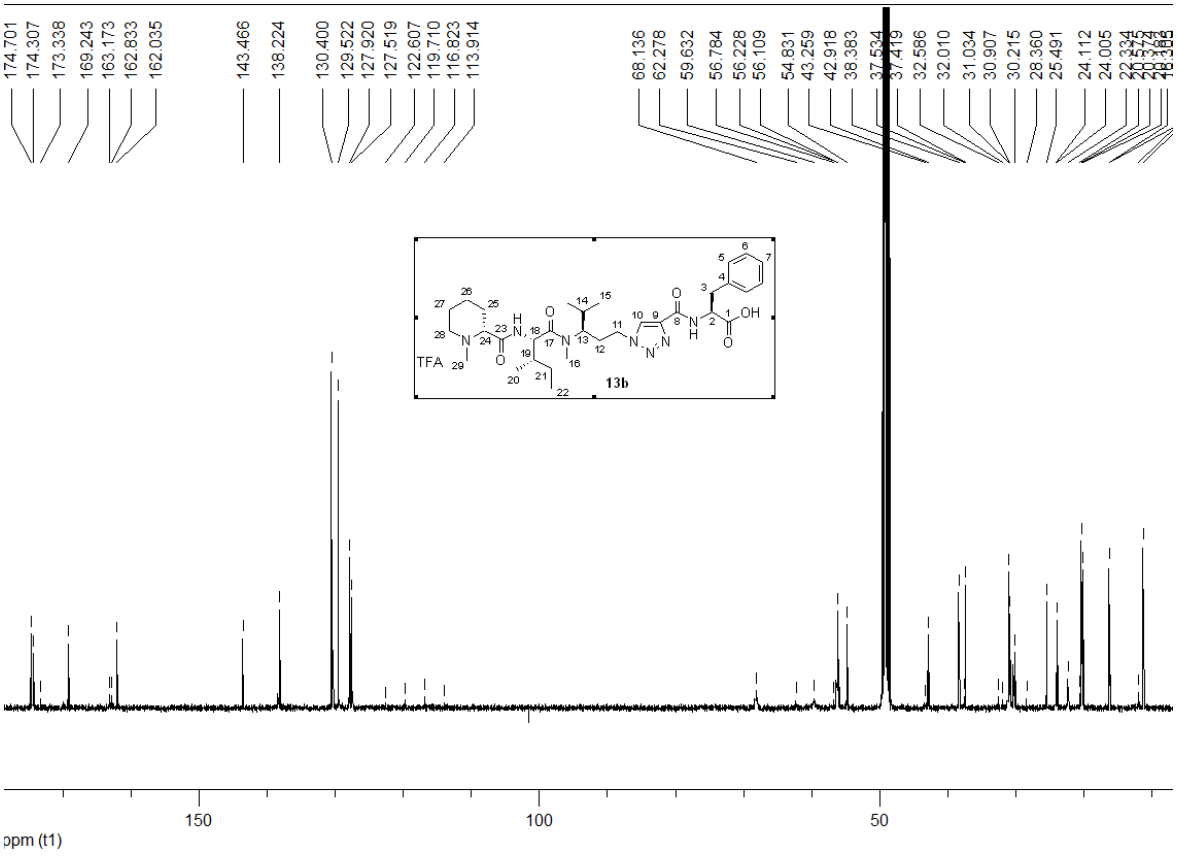

19c
ppm (t1)


19c
ppm (t1)


13a
TFA
ppm (t1)


13a
TFA
ppm (t1)


7.194
7.183
4.879
4.867
4.783
4.772
4.697
4.677
4.370
4.361
4.349
4.336
4.328
4.314
4.291
4.272
4.257
4.111
3.798
3.771
3.500
3.473
3.347
3.335
3.196
3.175
3.161
3.140
3.103
3.076
3.045
2.774
2.733
2.347
2.340
2.326
2.312
2.305
2.292
2.167
2.134
1.961
1.929
1.899
1.870
1.852
1.825
1.791
TFA
13b
0.97
5.00
1.76
0.96
1.86
0.90
1.00
1.00
0.76
4.81
3.25
0.99
2.00
6.12
2.04
1.31
3.22
6.26
2.77
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


174.701
174.307
173.338
169.243
163.173
162.833
162.035
143.466
138.224
130.400
129.522
127.920
127.519
122.607
119.710
116.823
113.914
68.136
62.278
59.632
56.784
56.228
56.109
54.831
43.259
42.918
38.383
37.534
37.419
32.586
32.010
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25.491
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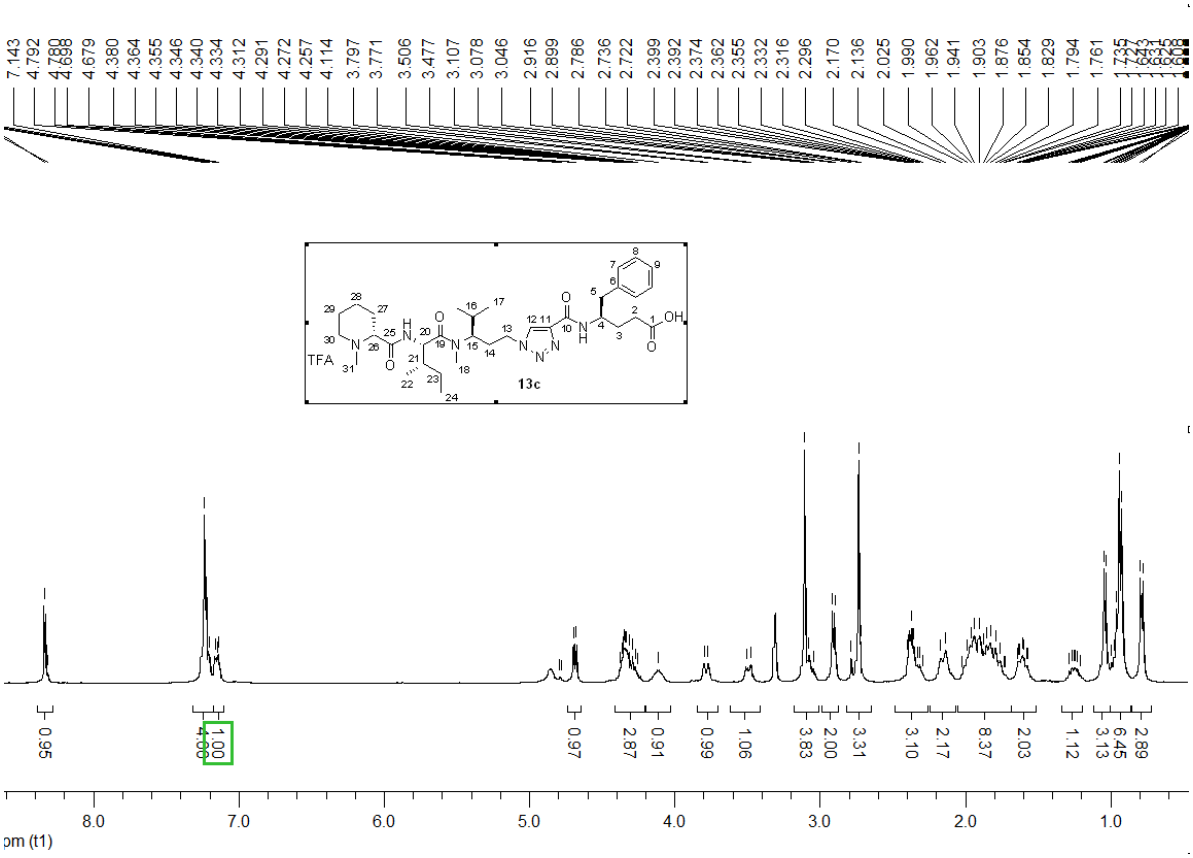
24.005
TFA
13b
150
100
50
ppm (t1)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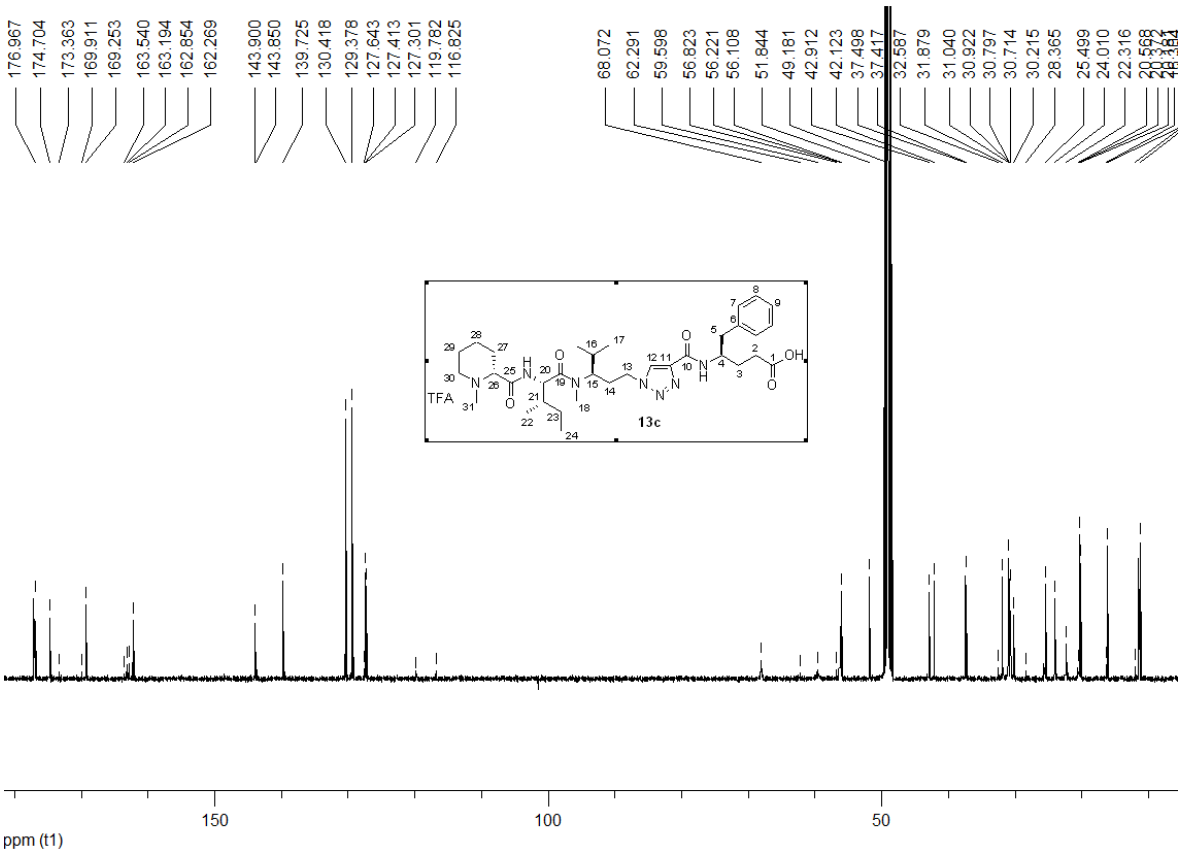
4.792
4.679
4.380
4.364
4.355
4.346
4.340
4.334
4.312
4.291
4.272
4.257
4.114
3.797
3.771
3.506
3.477
3.107
3.078
3.046
2.916
2.899
2.786
2.736
2.722
2.399
2.392
2.374
2.362
2.355
2.332
2.316
2.296
2.170
2.136
2.025
1.990
1.962
1.941
1.903
1.876
1.854
1.829
1.794
1.761
TFA
13c
0.95
4.00
1.00
0.97
2.87
0.91
0.99
1.06
3.83
2.00
3.31
3.10
2.17
8.37
2.03
1.12
3.13
6.45
2.89
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


176.967
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173.363
169.911
169.253
163.540
163.194
162.854
162.269
143.900
143.850
139.725
130.418
129.378
127.643
127.413
127.301
119.782
116.825
68.072
62.291
59.598
56.823
56.221
56.108
51.844
49.181
42.912
42.123
37.498
37.417
32.587
31.879
31.040
30.922
30.797
30.714
30.215
28.365
25.499
24.010
22.316
TFA
13c
150
100
50
ppm (t1)