Catalytic Enantioselective Acyl Transfer: The Case for 4-PPY with a C-3 Carboxamide Peptide Auxiliary based on Synthesis and Modelling Studies

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SUPPORTING INFORMATION

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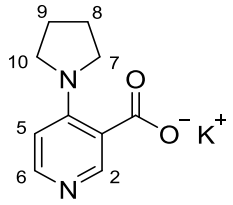
1) General Information

Column chromatography was performed using silica-gel 60 (Merck 7734). Thin layer chromatography was carried out on aluminium-backed Merck silica-gel 60 F_{254} plates. Compounds were visualised on TLC by using one or more of the following revealing techniques: UV lamp, iodine vapour or spraying with a 2.5% solution of anisaldehyde in a mixture of sulfuric acid and ethanol (1:10 v/v). Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 MHz (75.5 MHz for ^{13}C) or a Bruker 400 MHz (101 MHz for ^{13}C) instrument and were carried out in chloroform-d. Chemical shifts (δ) were recorded relative to residual chloroform (δ 7.26 in ^{1}H NMR and δ 77.00 in ^{13}C NMR). All chemical shifts are reported in ppm. Infra-Red (IR) absorptions were measured on a Perkin Elmer Spectrum 100 FT-IR Spectrometer. All mass spectra were recorded on a Waters Synapt G2 machine in ESI mode. Melting points were obtained using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHNS elemental analyser. The enantiomeric excess (ee) of the products were determined by HPLC on an Agilent 1220 Series using a Diacel Chiracel OD (250 × 4.6 mm) or Chiralpak AD (250 × 4.6 mm) column. Optical rotations were obtained using a Perkin Elmer 343 polarimeter at λ = 589 nm and 20 °C. The concentration *c* refers to g/100ml.

All solvents were freshly distilled. Dichloromethane was distilled from phosphorus pentoxide under nitrogen. Acetonitrile was distilled from calcium hydride under nitrogen. THF was distilled over sodium wire with benzophenone under nitrogen. All reagents were available by commercial sources (Sigma-Aldrich, Merck) and were used without further purification.

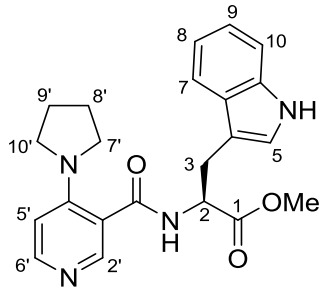
2) Synthesis Procedures and Characterisation Data

Potassium 4-(pyrrolidino) nicotinate (2)[1]



To as stirred suspension of 4-chloropyridine-3-carboxylic acid (153 mg, 0.97 mmol) in toluene (4 mL), was added pyrrolidine (0.35 mL, 4.2 mmol) and the resulting solution stirred at reflux temperature, After 2 hour, the temperature was lowered to r.t. and the reaction mixture concentrated on the rotary evaporator. Saturated K_2CO_3 (10 mL) was added and the mixture stirred for 30 minutes and concentrated. Ethanol was added to the residue, and the solution was filtered through Celite ® to remove potassium salts. The ethanol was removed and the residue was dissolved in ethanol and filtered through Celite ® again. The solvent was removed under reduced pressure to give **2** as a brown solid (211 mg, 95%). The salt was used in the next step without further purification. ^{1}H HMR (400 MHz, D_2O) δ 7.81 (s, 1H, *H-2*), 7.73 (d, *J* = 6.2 Hz, 1H, *H-6*), 6.37 (d, *J* = 6.2 Hz, 1H, *H-5*), 3.09 (s, 4H, *H-7*, *H-10*), 1.68 (s, 4H, *H-8*, *H-9*).

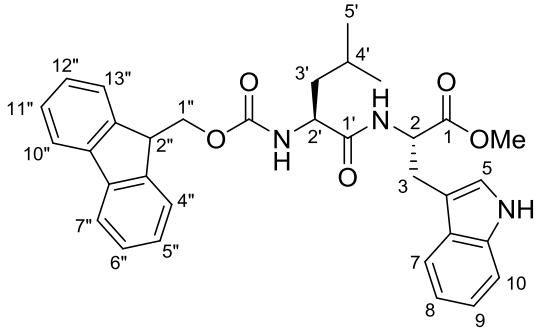
***N*-4-Pyrrolidinyl nicotinamido-L-tryptophan methyl ester (3)**



To a stirred solution of salt **2** (65.0 mg, 0.282 mmol) and HCl-L-Trp-OMe (107.8 mg, 0.423 mmol), at r.t. in pyridine (1.5 mL) and water (3 drops), were added EDC (108.1 mg, 0.564 mmol) and HOBt (15.2 mg, 0.112 mmol). After 18 hrs, (sat.) aq. $NaHCO_3$ (10 mL) was added and the aqueous layer extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent evaporated to afford a yellow oil that was purified by column chromatography using ethyl acetate/hexane (80/20) followed by MeOH/DCM (5/95) to provide **3** as a colourless solid (49.0 mg, 44%), mp 214–217 °C; $[\alpha]_D^{20}$ − 29.0 (*c* = 0.13, DCM); IR (DCM) 3289, 2957, 1740 (CO_2Me), 1617, 1588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H, *H-2'*), 8.15 (d, *J* = 6.1 Hz, 1H, *H-6'*), 8.09 (s, 1H, *N-H*$_{indole}$), 7.59 (d, *J* = 8.0 Hz, 1H, *Ar-H*), 7.35 (d, *J* = 8.0 Hz, 1H, *Ar-H*), 7.20 (t, *J* = 7.2 Hz, 1H, *Ar-H*), 7.13 (t, *J* = 7.2 Hz, 1H, *Ar-H*), 7.06 (d, *J* = 2.3 Hz, 1H, *Ar-H*), 6.42 (d, *J* = 6.1 Hz, 1H, *H-5'*), 6.32 (d, *J* = 7.4 Hz, 1H, *N-H*$_{Trp}$), 5.12 (d, *J* = 6.5 Hz, 1H, *H-2*), 3.76 (s, 3H, OMe), 3.46 (dd, *J* = 15.0, 6.0 Hz, 1H, *H-3*), 3.38 (dd, *J* = 15.0, 6.0 Hz, 1H, *H-3*), 3.29–3.14 (m, 4H, *H-7', H-10'*), 1.91–1.78 (m, 4H, *H-8', H-9'*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.4 , 171.4, 168.6, 150.4,149.6,136.5, 127.6, 122.7, 122.6, 120.0, 118.6, 117.7, 111.3, 110.4, 108.5 , 53.1, 52.3,

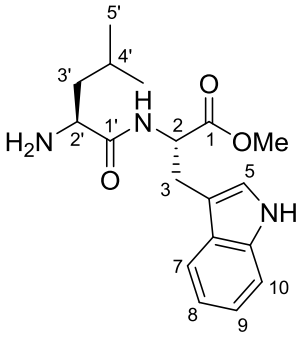
49.4, 27.8, 25.6; HRMS (ES): *m/z* 393.1928 $[M + H]^+$. Calculated for $C_{22}H_{25}N_4O_3$, 393.1927 $[M + H]^+$.

Fmoc-L-Leu-L-Trp-OMe[2]



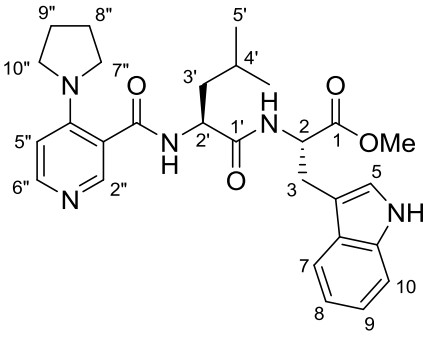
To a stirred solution of Fmoc-L-Leu-OH (606 mg, 1.72 mmol) and HCl-L-Trp-OMe (524 mg, 2.06 mmol) in pyridine (10 mL) at r.t., was added EDC (349 mg, 2.06 mmol) followed by HOBt (28 mg, 0.21 mmol). After 18 hrs 1M HCl (15 mL) was added followed by ethyl acetate (3 x 25 mL). The combined organic extracts was washed with 1 M HCl (3 x 50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed to give a yellow residue that was purified by ethyl acetate/hexane (40/60) to afford Fmoc-L-Leu-L-Trp-OMe as a colourless solid (927 mg, 97%), mp 146–148 °C; $[\alpha]_D^{20}$ − 4.5 (*c* 0.5, MeOH); IR (DCM) 3055, 2989, 2309, 1422, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H, *N-H*$_{indole}$), 7.77 (d, *J* = 7.5 Hz, 2H, *Ar-H*), 7.55 (m, 2H, *Ar-H*), 7.50 (m, 1H, *Ar-H*), 7.41 (m, 2H, *Ar-H*), 7.31 (m, 2H, *Ar-H*), 7.26 (m, 1H, *Ar-H*), 7.13 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, *Ar-H*), 7.07 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, *Ar-H*), 6.95 (br. s, 1H, *Ar-H*), 6.51 (d, *J* = 7.9 Hz, 1H, *N-H*$_{Trp}$), 5.10 (d, *J* = 8.6 Hz, 1H, *N-H*$_{Leu}$), 4.90 (m, 1H, *H-2*), 4.39 (m, 1H, *H-1"*), 4.26 (m, 1H, *H-1"*), 4.22 –4.13 (m, 2H, *H-2', H-2"*), 3.66 (s, 3H, *OMe*), 3.30 (d, *J* = 5.5 Hz, 2H, *H-3*), 1.60 (m, 2H, *H-3', H-4'*), 1.44 (m, 1H, *H-3'*), 0.89 (br. s, 6H, *H-5'*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 , 171.8, 143.8, 141.3, 136.1, 127.8, 127.1, 125.1, 125.0, 123.0, 122.2, 120.0, 119.6, 118.5, 111.7, 111.7, 109.7, 67.0, 53.5, 52.8, 52.4, 47.1, 41.5, 27.6, 24.6, 22.9, 21.9; Anal. Found C, 70.67; H, 6.67; N, 7.75 $C_{33}H_{35}N_3O_5$ requires C, 71.59; H, 6.37; N, 7.59; Chiralcel OD 20% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 13.452 min.

NH_2-L-Leu-L-Trp-OMe



To a stirred solution of Fmoc-L-Leu-L-Trp-OMe (150.3 mg, 0.2715 mmol) in DCM (2 mL) at 0 °C, was added piperidine (0.05 mL, 0.5 mmol). After 18 hrs, the solvent was removed *in vacuo* to give a crude product that was purified by column chromatography using MeOH/DCM (10/90) to afford NH_2-L-Leu-L-Trp-OMe as a clear oil (58.0 mg, 64%), $[\alpha]_D^{20}$ + 39.8 (*c* 1.0, DCM, 91% ee); IR (DCM) 3412 (NH), 2958, 1740 (CO_2Me), 1659 $(CO)_{amide}$, 1514, 1216 cm−1;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (br. s, 1H, *N-H*$_{indole}$), 7.71 (d, *J* = 8.3 Hz, 1H, *N-H*$_{Trp}$), 7.55 (m, 1H, *Ar-H*), 7.34 (m, 1H, *Ar-H*), 7.17 (m, 1H, *Ar-H*), 7.10 (m, 1H, *Ar-H*), 6.99 (s, 1H, *Ar-H*), 4.92 (m, 1H, *H-2*), 3.69 (s, 3H, *OMe*), 3.31 (m, 3H, *H-3*, *H-2'*), 1.63 (m, 2H, *H-4', H-3'*), 1.18 (m, 1H, *H-3'*), 0.91 (d, *J* = 6.4 Hz, 3H, *H-5'*), 0.87 (d, *J* = 6.4 Hz, 3H, *H-5'*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4,172.6, 136.1, 127.7, 122.6, 122.1, 119.5, 118.7, 111.2, 110.4, 53.4, 52.7, 52.2, 43.9, 27.8, 24.8, 23.4, 21.3; HRMS (ES): *m/z* 332.1962 $[M + H]^+$. Calculated for $C_{18}H_{26}N_3O_3$, 332.1974 $[M + H]^+$; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 6.63 min.

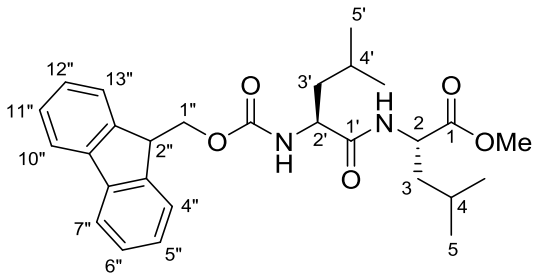
***N*-4-Pyrrolidinyl nicotinamido-L-leucine-L-tryptophan methyl ester (4)**



Salt **2** (98 mg, 0.426 mmol) and NH_2-L-Leu-L-Trp-OMe (127 mg, 0.384 mmol) were dissolved in pyridine (2.0 mL) and water (3 drops) at r.t. EDC (as its hydrochloride) (112 mg, 0.587 mmol) and HOBt (21 mg, 0.16 mmol) were then added. After 12 hrs, (sat.) aq. $NaHCO_3$ (10 mL) was added and the aqueous layer extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated to afford a yellow oil that was purified by column chromatography using ethyl acetate/hexane (80/20) followed by MeOH/DCM (5/95) to provide **4** as a pale-yellow solid (85 mg, 44%), mp 102–105 °C; $[\alpha]_D^{20}$ − 5.8 (*c* 0.12, DCM); IR (DCM) 3289, 2957, 1742 (CO_2Me), 1640, 1593, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H, *N-H*$_{indole}$), 8.14 (d, *J* = 6.1 Hz, 1H, *H-6''*),

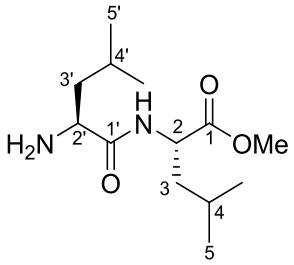
8.12 (s, 1H, *H-2"*), 7.53 (d, *J* = 7.9 Hz, 1H, *Ar-H*), 7.30 (d, *J* = 7.9 Hz, 1H, *Ar-H*), 7.20–7.02 (m, 3H, *Ar-H*), 6.73 (d, *J* = 7.8 Hz, 1H, *N-H*$_{Leu}$), 6.44 (m, 2H, *N-H*$_{Trp}$, *H-5"*), 4.91 (m, 1H, *H-2*), 4.57 (m, 1H, *H-2'*), 3.68 (s, 3H, *OMe*), 3.32 (d, *J* = 5.6 Hz, 2H, *H-3*), 3.25 (m, 4H, *H-7", H-10"*), 1.85 (m, 4H, *H-8", H-9"*), 1.77–1.54 (m, 3H, *H-3', H-4'*), 0.93 (m, 6H, *H-5'*); ^{13}C NMR (400 MHz, $CDCl_3$) δ ; 171.9, 171.4, 169.0, 150.5, 150.0, 149.1, 136.2, 127.5, 123.4, 122.1, 119.6, 118.4, 117.2, 111.4, 109.5, 108.6, 52.9, 52.4, 49.5, 40.9, 27.6, 25.5, 24.9, 22.9, 21.9; HRMS (ES); *m/z* 506.2767 [M + H]+. Calculated for $C_{28}H_{36}N_5O_4$, 506.2767 [M + H]+; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 7.072 min.

Fmoc-L-Leu-L-Leu-OMe



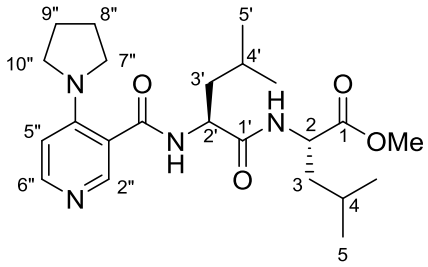
To a stirred solution of Fmoc-L-Leu-OH (748.6 mg, 2.12 mmol) and HCl-L-Leu-OMe (577.0 mg, 3.19 mmol) in pyridine (10 mL), at r.t., was added DCC (570.0 mg, 2.80 mmol) followed by HOBt (288.1 mg, 2.13 mmol). After 18 hrs, 1M HCl (20 mL) was added followed by an extraction with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with 1M HCl (3 x 60 mL), dried over anhydrous $MgSO_4$ and the solvent removed to give a yellow residue that was purified by ethyl acetate/hexane (40/60) to afford Fmoc-L-Leu-L-Leu-OMe as a colourless oily solid (818.2 mg, 80%), mp 111–113 °C; $[\alpha]_D^{20}$ − 39.2 (*c* 0.52, MeOH); IR ($CHCl_3$) 3321 (NH), 1742 (CO_2Me), 1674 (CO)$_{amide}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.6, 0.6 Hz, 2H, *Ar-H*), 7.58 (d, *J* = 7.5 Hz, 2H, *Ar-H*), 7.39 (t, *J* = 7.5 Hz, 2H, *Ar-H*), 7.29 (m, *J* = 7.4, 1.3 Hz, 2H, *Ar-H*), 6.54 (d, *J* = 6.7 Hz, 1H, *N-H*$_{Leu}$), 5.41 (d, *J* = 7.9 Hz, 1H, *N-H*$_{Leu}$), 4.61 (td, *J* = 8.6, 5.2 Hz, 1H, *H-2 or H-2'*), 4.41 (m, 2H, *H-1"*), 4.26 (m, 1H, *H-2 or H-2'*), 4.20 (m, 1H, *H-2"*), 3.71 (s, 3H, *OMe*), 1.63 (m, 6H, *H-3, H-3', H-4, H-4'*), 0.95 (m, 6H, *H-5 or H-5'*), 0.90 (d, *J* = 3.1 Hz, 3H, *H-5 or H-5'*), 0.89 (d, *J* = 3.3 Hz, 3H, *H-5 or H-5'*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 172.0, 156.2, 143.8, 143.7, 127.7, 127.0, 125.0, 119.9, 67.1, 53.4, 52.2, 50.7, 47.1, 41.5, 41.4, 24.8, 24.6, 22.8, 22.7, 22.0, 21.9; Anal. Found C, 69.58; H, 7.40; N, 5.53 $C_{28}H_{36}N_2O_5$ requires C, 69.98; H, 7.55; N, 5.83; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 3.78 min;

NH_2-L-Leu-L-Leu-OMe



To a stirred solution of Fmoc-L-Leu-L-Leu-OMe (1.163 g, 2.42 mol) in DCM (10 mL) was added piperidine (0.5 mL, 5.0 mmol) at 0 °C. After 18 hrs the solvent and piperidine were removed to give a crude residue that was purified column chromatography using MeOH/DCM (5/95) to afford NH_2-L-Leu-L-Leu-OMe as a clear oil (337.7 mg, 54%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 1H, *N-H*$_{Leu}$), 4.61 (m, 1H, *H-2*), 3.73 (s, 3H, *OMe*), 3.43 (m, 1H, *H-2'*), 1.79–1.54 (m, 5H, *H-3*, *H-4*, *H-3', H-4'*), 1.39–1.28 (m, 1H, *H-3'*), 0.98–0.90 (m, 12H, *H-5*, *H-5'*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 173.6, 53.5, 52.1, 50.3, 44.1, 41.5, 24.9, 24.8, 23.3, 22.8, 21.9, 21.4.

Methyl (4-(pyrrolidin-1-yl)nicotinoyl)-L-leucyl-L-leucinate (5)



Salt **2** (451.6 mg, 1.961 mmol) and NH_2-L-Leu-L-Leu-OMe (337.7 mg, 1.307 mmol) were dissolved in pyridine (5 mL) and water (0.5 mL) at r.t. EDC (326.0 mg, 1.700 mmol) followed by HOBt (212.0 mg, 1.569 mmol) were then added. After 18 hrs aq. $NaHCO_3$ (10 mL) was added and the organic material extracted into ethyl acetate (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed to give a yellow residue that was purified by column chromatography using MeOH/DCM (8/92) to afford **5** as a pale-yellow oil (151.2 mg, 27%), $[\alpha]_D^{20}$ − 25.3 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3420 (NH), 3022 (NH), 1742 (CO)$_{ester}$, 1644 (CO)$_{amide}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H, *H-2"*), 8.14 (d, *J* = 5.8 Hz, 1H, *H-6"*), 6.86 (d, *J* = 8.3 Hz, 1H, *N-H*$_{Leu}$), 6.80 (d, *J* = 8.3 Hz, 1H, *N-H*$_{Leu}$), 6.47 (d, *J* = 5.8 Hz, 1H, *H-5"*), 4.61 (m, 2H, *H-2*, *H-2'*), 3.72 (s, 3H, *OMe*), 3.30 (m, 4H, *H-7", H-10"*), 1.94 (m, 4H, *H-8", H-9"*), 1.52–1.80 (m, 6H, *H-3*, *H-4*, *H-3', H-4'*), 0.97 (d, *J* = 6.2 Hz, 3H, *H-5 or H-5'*), 0.95 (d, *J* = 6.2 Hz, 3H, *H-5 or H-5'*), 0.92 (d, *J* = 2.5 Hz, 3H, *H-5 or H-5'*), 0.91 (d, *J* = 2.5 Hz, 3H, *H-5 or H-5'*); ^{13}C NMR (101 MHz, $CDCl_3$) 173.1, 171.6, 168.8, 150.2, 149.3, 148.7, 117.4, 108.6, 52.4, 52.2, 50.8, 49.5, 41.5, 41.0, 25.5, 24.9, 24.8, 22.9, 22.8, 22.0, 21.9; HRMS (ES): *m/z* 433.2810 $[M + H]^+$. Calculated for $C_{23}H_{37}N_4O_4$,

433.2814 $[M + H]^+$; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 7.651 min;.

_N_-Methyl salts LeuTrp-N-Me ($4_{N\text{-}Me}$) and LeuLeu-N-Me ($5_{N\text{-}Me}$)

Each dipeptide (20 mg) was stirred in DCM (0.5 mL) with an excess of methyl iodide (0.2 ml) for 18 hr at room temperature until tlc indicated a consumption of starting material. In the case of LeuTrp (**4**) a gum was formed on evaporation whereas with LeuLeu (**5**) the salt precipitated and was collected.

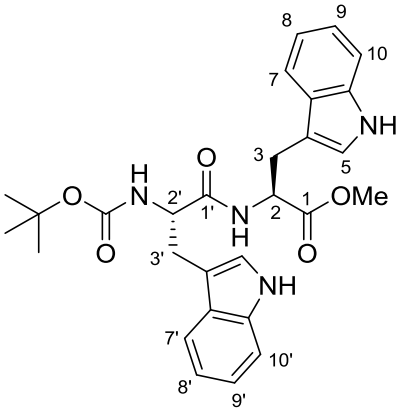
LeuTrp-N-Me ($4_{N\text{-}Me}$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H, *NH_{ind}*), 8.78 (d, *J* = 8.4 Hz, 1H, *NH_{Leu}*), 8.27 (s, 1H, *H-2"*), 7.67 (d, *J* = 7.2 Hz, 1H, *H-6"*), 7.50 (d, *J* = 7.2 Hz, 1H, *H-7 or H-10*), 7.35-7.31 (m, 2H, *H-5 + H-7 or H-10*), 7.21 (d, *J* = 8.4 Hz, *NH_{Trp}*), 7.08-6.98 (m, 2H, *H-8 + H-9*), 6.51 (d, *J* = 7.2 Hz, 1H, *H-5"*), 4.85 (m, 1H, *H-2*), 4.62 (m, 1H, *H-2'*), 3.78 (s, 3H, *NMe*), 3.63 (s, 3H, *OMe*), 3.45-3.20 (m, 6H, *H-3, H-7"/ H-10"*), 2.03-1.64 (m, 7H, *H-3', H-4', H-8"/H-9"*), 0.95 (d, *J* = 6.4 Hz, 3H, *H-5'*), 0.86 (d, *J* = 6.4 Hz, 3H, *H-5'*).

LeuLeu-N-Me ($5_{N\text{-}Me}$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (d, *J* = 9.0 Hz, 1H, *NH_{Leu}*), 8.87 (d, *J* = 1.5 Hz, 1H, *H-2"*), 7.77 (dd, *J* = 7.6, 1.5 Hz, 1H, *H-6"*), 7.56 (d, *J* = 8.7 Hz, 1H, *NH_{Trp}*), 6.66 (d, *J* = 7.6 Hz, 1H, *H-5"*), 4.77-4.67 (m, 2H, H-2, *H-2'*), 4.06 (s, 3H, *NMe*), 3.67 (s, 3H, *OMe*), 3.55-3.45 (m, 4H, *H-7"/H-10"*), 2.06-1.55 (m, 10H, *H-3, H-3', H-4, H-4', H-8"/H-9"*), 1.00-0.92 (m, 12H, *H-5, H-5'*).

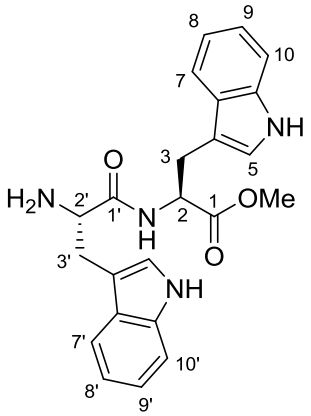
Boc-L-Trp-L-Trp-OMe[3]



To a stirred solution of HCl-L-Trp-OMe (460.1 mg, 1.807 mmol) and *N*-Boc-L-Trp-OH (500.3 mg, 1.664 mmol) in pyridine (6.5 mL), at r.t., was added EDC (347.6 mg, 1.813 mmol) followed by HOBt (91.0 mg, 0.673 mmol). After 18 hrs 1M HCl (15 mL) was added followed by ethyl acetate (3 x 15 mL). The combined organic extracts were washed with 1M HCl (3 x 45 mL) and dried over anhydrous $MgSO_4$. The solvent was removed to give a yellow residue that was purified by ethyl acetate/hexane (40/60) to afford Boc-L-Trp-L-Trp-OMe as a colourless solid (674 mg, 81%), $[\alpha]_D^{20}$ − 20.5 (*c* 1.0, MeOH) (lit.[1] $[\alpha]_D^{25}$ − 15 (*c* 0.9, MeOH);

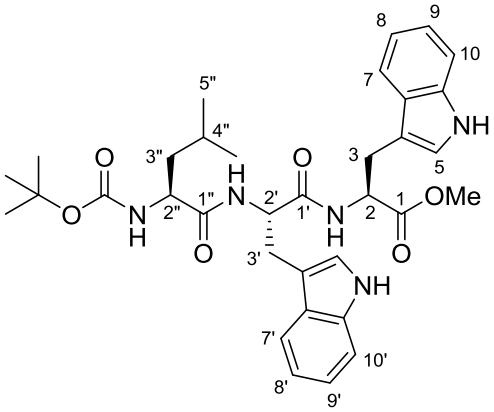
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H, *N-H$_{indole}$*), 7.86 (s, 1H, *N-H$_{indole}$*), 7.65 (d, *J* = 7.8 Hz, 1H, *Ar-H*), 7.30 (m, 3H, *Ar-H*), 7.22–7.09 (m, 3H, *Ar-H*), 6.97 (t, *J* = 7.5 Hz, 1H, *Ar-H*), 6.90 (s, 1H, *H-5 or H-5'*), 6.65 (s, 1H, *H-5 or H-5'*), 6.24 (d, *J* = 7.6 Hz, 1H, *N-H*), 5.01 (s, 1H, *N-H*), 4.82 (dd, *J* = 13.4, 5.6 Hz, 1H, *H-2 or H-2'*), 4.43 (dd, *J* = 12.8, 7.4 Hz, 1H, *H-2 or H-2'*), 3.60 (s, 3H, *OMe*), 3.32–3.08 (m, 4H, *H-3, H-3'*), 1.40 (s, 9H, *t*-Bu).

NH_2-L-Trp-L-Trp-OMe [4]



To a stirred suspension of Boc-L-Trp-L-Trp-OMe (358 mg, 0.710 mmol) and anisole (0.23 mL, 2.1 mmol) in DCM (5.5 mL), at 0 °C was added TFA (1.4 mL). After 2 hrs aqueous $NaHCO_3$ (15 mL) was added with cooling until a pH of 8 was reached. The organic layer was separated and the aqueous layer was washed with DCM (2 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed to give a yellow residue that was purified by MeOH/DCM (10/90) to afford NH_2-L-Trp-L-Trp-OMe as a colourless solid (286 mg, 99%), $[\alpha]_D^{20}$ − 15.2 (*c* 0.5, MeOH) (lit.[4] $[\alpha]_D^{25}$ − 11.0 (*c* 0.75, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H, *N-H$_{indole}$*), 8.25 (s, 1H, *N-H$_{indole}$*), 7.79 (d, *J* = 8.3 Hz, 1H, *Ar-H*), 7.58 (d, *J* = 7.9 Hz, 1H, *Ar-H*), 7.39 (d, *J* = 7.9 Hz, 1H, *Ar-H*), 7.31 (d, *J* = 4.3 Hz, 1H, *Ar-H*), 7.16 (m, 2H, *Ar-H*), 7.09 (m, 1H, *Ar-H*), 7.01 (m, 1H, *Ar-H*), 6.79 (m, 1H, *Ar-H*), 6.69 (d, 1H, *J* = 2.3 Hz, *Ar-H*), 4.95 (m, 1H, *H-2*), 3.64 (m, 4H, *H-2', OMe*), 3.30–2.85 (m, 4H, *H-3, H-3'*).

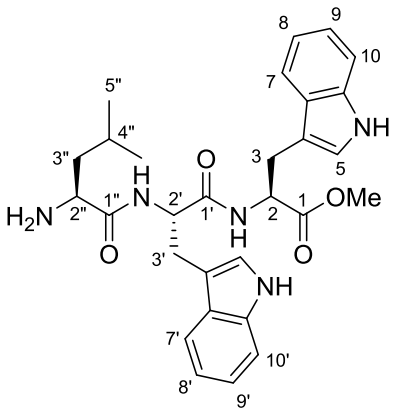
Boc-L-Leu-L-Trp-L-Trp-OMe



To a stirred solution of NH_2-L-Trp-L-Trp-OMe (233.5 mg, 0.577 mmol) and *N*-Boc-L-Leu-OH (200.1 mg, 0.8651 mmol) in pyridine (3.0 mL), at r.t., were added EDC (168.7 mg, 0.8800

mmol) and HOBt (36.0 mg, 0.266 mmol). After 18 hrs, 1M HCl (15 mL) was added and the aqueous layer extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with 1M HCl (3 x 50 mL), dried over anhydrous $MgSO_4$, and the solvent evaporated to afford a yellow oil that was purified by column chromatography using ethyl acetate/hexane (50/50) to provide Boc-L-Leu-L-Trp-L-Trp-OMe as a colourless solid (218.0 mg, 61%), mp 107–109 °C; $[\alpha]_D^{20}$ − 23.2 (*c* 1.0, MeOH); IR (DCM) 3313 (NH), 1741 (CO_2Me), 1649 (CO)*amide*, 1169 (C-N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H, *N-H*$_{indole}$), 7.90 (s, 1H, *N-H*$_{indole}$), 7.70 (d, *J* = 7.8 Hz, 1H, *Ar-H*), 7.31 (m, 3H, *Ar-H*), 7.19 (m, 1H, *Ar-H*), 7.13 (m, 2H, *Ar-H*), 7.01 (t, *J* = 7.5 Hz, 1H, *Ar-H*), 6.96 (s, 1H, *Ar-H*), 6.68 (d, *J* = 7.7 Hz, 1H, *N-H*$_{Trp}$), 6.66 (s, 1H, *Ar-H*), 6.26 (d, *J* = 7.4 Hz, 1H, *N-H*$_{Trp}$), 4.77 (m, 1H, *H-2 or H-2'*), 4.70 (m, 1H, *H-2 or H-2'*), 4.65 (d, *J* = 8.0 Hz, 1H, *N-H*$_{Leu}$), 4.05 (m, 1H, *H-2''*), 3.61 (s, 3H, *OMe*), 3.32 (dd, *J* = 14.6, 6.6 Hz, 1H, *H-3 or H-3'*), 3.15 (m, 2H, *H-3 or H-3'*), 3.10 (dd, *J* = 14.6, 6.6 Hz, 1H, *H-3 or H-3'*), 1.55 (m, 2H, *H-3'', H-4''*), 1.43 (s, 9H, *t-Bu*), 1.27 (m, 1H, *H-3''*), 0.86 (d, *J* = 6.3 Hz, 3H, *H-5''*), 0.85 (d, *J* = 6.3 Hz, 3H, *H-5''*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.4, 171.7, 170.6, 155.6, 136.4, 136.3, 127.7, 127.5, 123.6, 123.2, 122.3, 122.2, 119.9, 119.6, 119.1, 118.6, 111.2, 109.8, 80.3, 53.8, 53.8, 52.8, 52.1, 41.5, 28.4, 28.0, 27.6, 24.9, 22.9, 21.8; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 6.185 min; Anal. Found C, 65.94; H, 7.06; N, 11.01. $C_{34}H_{43}N_5O_6$ requires C, 66.11; H, 7.02; N, 11.34.

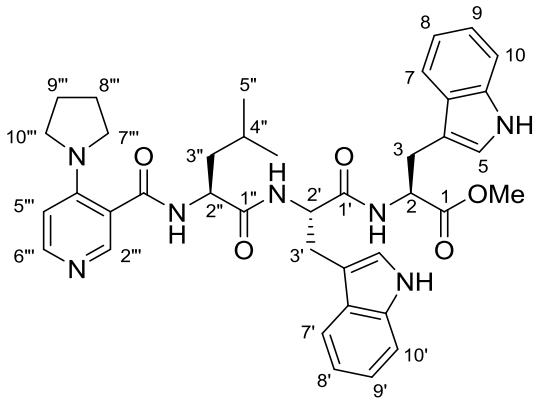
NH_2-L-Leu-L-Trp-L-Trp-OMe



To a stirred suspension of Boc-L-Leu-L-Trp-L-Trp-OMe (216 mg, 0.350 mmol) and anisole (0.11 mg, 1.0 mmol) in DCM (2.8 mL), at 0 °C, was added TFA (0.7 mL) dropwise over 1 minute. After 2 hrs, (sat.) $NaHCO_3$ (10 mL) was added, with cooling, until a pH of 8 was reached. The aqueous layer was extracted with DCM (3 x 10 mL), the combined organic extracts dried over anhydrous $MgSO_4$, and the solvent evaporated to afford an orange oil that was purified by column chromatography using ethyl acetate/hexane (50/50) followed by MeOH/DCM (10/90), to give NH_2-L-Leu-L-Trp-L-Trp-OMe as a pale-yellow oily-solid (180 mg, 99%), $[\alpha]_D^{20}$ + 3 (*c* 0.10, $CHCl_3$); IR 3308, 2956, 1739 (CO_2CH_3), 1657 (CO)*amide*,1458,

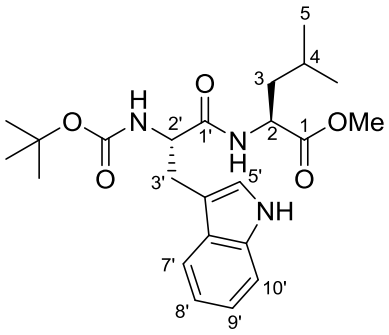
1343, 1216; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H, *N-H$_{indole}$*), 7.98 (s, 1H, *N-H$_{indole}$*), 7.72 (d, *J* = 8.0 Hz, 1H, *N-H$_{Trp}$*), 7.68 (d, *J* = 7.9 Hz, 1H, *Ar-H*), 7.30 (t, *J* = 7.9 Hz, 3H, *Ar-H*), 7.21–7.05 (m, 3H, *Ar-H*), 6.96 (m, 2H, *Ar-H*), 6.68 (d, *J* = 1.9 Hz, 1H, *Ar-H*), 6.43 (d, *J* = 7.5 Hz, 1H, *N-H$_{Trp}$*), 4.80 (m, 1H, *H-2 or H-2'*), 4.73 (m, 1H, *H-2 or H-2'*), 3.62 (s, 3H, *OMe*), 3.32–3.06 (m, *5*H, *H-3, H-3', H-2"*), 1.62 (br. s, 3H, *NH$_2$, H-4"*), 1.49 (m, 1H, *H-3"*), 1.11 (m, 1H, *H-3"*), 0.85 (d, *J* = 6.4 Hz, 3H, *H-5*), 0.80 (d, *J* = 6.4 Hz, 3H, *H-5*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.6, 171.9, 171.2, 136.2, 136.0, 127.6, 127.4, 123.4, 123.2, 122.1, 122.0, 119.6, 119.5, 119.1, 118.5, 111.2, 111.1, 110.8, 109.6, 53.4, 52.7, 52.7, 52.3, 43.6, 27.9, 27.4, 24.7, 23.3, 21.3; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 7.856 min.

Methyl (4-(pyrrolidin-1-yl)nicotinoyl)-L-leucyl-L-tryptophyl-L-tryptophanate (6)



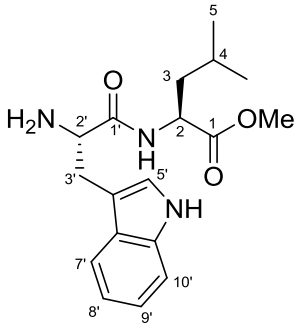
Salt **2** (78.0 mg, 0.339 mmol), and NH_2-L-Leu-L-Trp-L-Trp-OMe (160 mg, 0.309 mmol) were dissolved in pyridine (5 mL) and water (5 drops) at r.t. EDC (71 mg, 0.37 mmol) and HOBt (20 mg, 0.15 mmol) were then added. After 12 hrs, (sat.) $NaHCO_3$ (20 mL) was added and the aqueous layer extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated to afford a yellow oil that was purified by column chromatography using ethyl acetate/hexane (20/80) followed by MeOH/DCM (8/92) to provide **6** as a pale-yellow solid (113 mg, 53%), mp 136–138 °C; $[\alpha]_D^{20}$ − 46.0 (*c* 0.28, DCM); IR (DCM) 1738, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H, *N-H$_{indole}$*), 8.49 (s, 1H, *N-H$_{indole}$*), 8.03 (d, *J* = 6.2 Hz, 1H, *H-6"'*), 7.98 (s, 1H, *H-2"'*), 7.63 (d, *J* = 7.9 Hz, 1H, *Ar-H*), 7.30 (t, *J* = 7.3 Hz, 2H, *Ar-H*), 7.22 (d, *J* = 8.0 Hz, 1H, *Ar-H*), 7.04 (m, 6H, *5 x Ar-H, N-H$_{Trp}$*,), 6.80 (s, 1H, *N-H$_{Leu}$*), 6.71 (s, 1H, *N-H$_{Trp}$*), 6.56 (s, 1H, *Ar-H*), 6.37 (d, *J* = 6.2 Hz, 1H, *H-5"'*), 4.82 (m, 1H, *H-2 or H-2'*), 4.73 (m, 1H, *H-2 or H-2'*), 4.55 (m, 1H, *H-2"*), 3.59 (s, 3H, *OMe*), 3.19 (m, 8H, *H-3, H-3', H-7"', H-10"'*), 1.81 (m, 4H, *H-8"', H-9"'*), 1.66–1.42 (m, 3H, *H-3", H-4"*), 0.87–0.80 (2 x d, *J* = 6.0 Hz, 6H, *H-5"*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.9, 171.8, 170.8, 168.8, 150.2, 148.9 148.3 136.2, 136.1, 127.4, 127.2, 123.8, 123.2, 122.0, 121.9, 119.6, 119.3, 118.8, 118.3, 117.2, 111.5, 111.3, 109.9, 109.4, 108.6, 53.5, 52.9, 52.8, 52.3, 49.5, 40.8, 28.0, 27.4, 25.4, 25.0, 22.9, 21.6; HRMS (ES): *m/z* Found 692.3580 $[M+H]^+$. Calculated for $C_{39}H_{46}N_7O_5$, 692.3560

Boc-L-Trp-L-Leu-OMe[5]



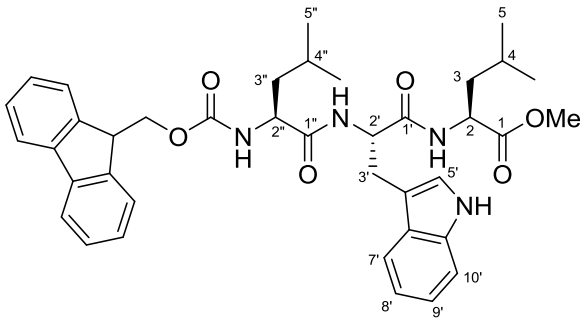
To a stirred solution of HCl-L-Leu-OMe (575 mg, 3.17 mmol) and Boc-L-Trp-OH (800 mg, 2.63 mmol), in pyridine (10 mL) at r.t., were added EDC (756 mg, 3.94 mmol) and HOBt (180 mg, 1.33 mmol). After 18 hrs, 1M HCl (5 mL) was added and the aqueous extracted with ethyl acetate. The combined organic extracts were washed with 1M HCl and dried over anhydrous $MgSO_4$ to give a crude product that was purified by column chromatography using ethyl acetate/hexane to yield Boc-L-Trp-L-Leu-OMe as a colourless solid (966 mg, 85%); $[\alpha]_D^{20}$ − 29.4 (*c* 0.49, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H, *N-H*$_{indole}$), 7.67 (m, 1H, *Ar-H*), 7.35 (m, 1H, *Ar-H*), 7.24–7.06 (m, 3H, *Ar-H*), 6.18 (d, *J* = 8.0 Hz, 1H, *N-H*), 5.14 (s, 1H, *N-H*), 4.52 (m, 1H, *H-2'*), 4.42 (m, 1H, *H-2*), 3.64 (s, 3H, *OMe*), 3.30–3.19 (m, 2H, H-3'), 1.54–1.36 (m, 12H, *H-3*, *H-4*, *t*-Bu) 0.86 (d, *J* = 4.3 Hz, 3H, *H-5*), 0.84 (d, *J* = 4.4 Hz, 3H, *H-5*).

NH_2-L-Trp-L-Leu-OMe[6]



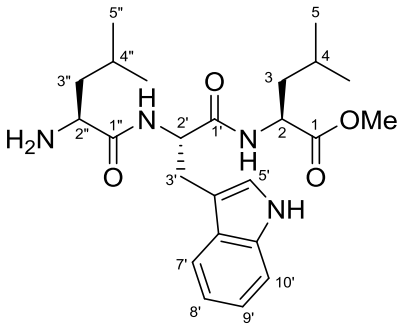
To a stirred solution of anisole (0.27 mL, 2.5 mmol), in 30% TFA/DCM (10 mL) at 0 °C was added Boc-L-Trp-L-Leu-OMe (533.8 mg, 1.237 mmol). After 2 hrs, sat. $NaHCO_3$ (25 mL) was added until a pH of approximately 9 was reached. The aqueous layer was washed with DCM (3 x 25 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure to give a crude oil that was purified by column chromatography using MeOH/DCM (10/90) to afford NH_2-L-Trp-L-Leu-OMe as a clear oil (238 mg, 58%); $[\alpha]_D^{20}$ − 6.0 (*c* 0.50, MeOH) (lit.[3] $[\alpha]_D^{20}$ − 1.2 (*c* 0.50, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H, *N-H*$_{indole}$), 7.70 (d, *J* = 8.4 Hz, 1H, *N-H*$_{Trp}$), 7.64 (d, *J* = 8.0 Hz, 1H, *Ar-H*), 7.36 (d, *J* = 8.0 Hz, 1H, *Ar-H*), 7.18 (m, 1H, *Ar-H*), 7.09 (m, 1H, *Ar-H*), 7.05 (d, *J* = 2.4 Hz, 1H, *Ar-H*), 4.62 (m, 1H, *H-2'*), 3.71 (m, 4H, *H-2*, *OMe*), 3.37 (dd, *J* = 14.5, 4.1Hz, 1H, *H-3'*), 2.92 (dd, *J* = 14.5, 9.0 Hz, 1H, *H-3'*), 1.65–1.49 (m, 3H, *H-3*, *H-4*), 0.91 (m, 6H, *H-5*).

Fmoc-L-Leu-L-Trp-L-Leu-OMe



To a stirred solution of NH_2-L-Trp-L-Leu-OMe (482.0 mg, 1.454 mmol) and Fmoc-L-Leu-OMe (666.2 mg, 1.885 mmol), in pyridine (6 mL), at r.t., were added EDC (408.3 mg, 2.130 mmol) and HOBt (196.0 mg, 1.450 mmol). After 18 hrs, 1M HCl (10 mL) was added followed by ethyl acetate (3 x 10 mL). The combined organic extracts were washed with 1M HCl (3 x 50 mL) and dried over anhydrous $MgSO_4$ to give a crude product that was purified by column chromatography using ethyl acetate/hexane (40/60) to afford Fmoc-L-Leu-L-Trp-L-Leu-OMe as a pale-yellow solid (584.2 mg, 60%), mp 170–172 °C; $[\alpha]_D^{20}$ − 39.5 (*c* 0.57, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H, *N-H*$_{indole}$), 7.78-7.04 (m, 13H, *Ar-H*), 6.62 (br s, 1H, *N-H*), 6.20 (d, *J* = 7.9 Hz, 1H, *N-H*), 4.98 (d, *J* = 8.0 Hz, 1H, *N-H*), 4.72-4.13 (m, 6H, Fmoc + *H-2, H-2', H-2"*), 3.66 (s, 3H, *OMe*), 3.30 (dd, *J* = 14.7, 7.5 Hz, 1H, *H-3'*), 3.18 (dd, *J* = 14.7, 7.5 Hz, 1H, *H-3'*), 1.59–1.34 (m, 6H, *H-3, H-3" and H-4, H-4"*), 0.89 (m, 6H, *H-5 or H-5"*), 0.82 (m, 6H, *H-5 or H-5"*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.7, 172.0, 170.7, 156.2, 143.9, 141.4, 136.4, 127.8, 127.2, 127.1, 125.0, 123.3, 122.4, 120.0, 119.9, 118.9, 111.2, 110.7, 67.1, 53.9, 53.8, 52.1, 51.1, 51.1, 47.3, 41.5, 27.9, 24.8, 24.8, 22.9, 22.6, 22.0, 21.9; HRMS (ES): *m/z* Found 667.3508 $[M + H]^+$. Calculated for $C_{39}H_{47}N_6O_6$, 667.3496; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 4.701 min;

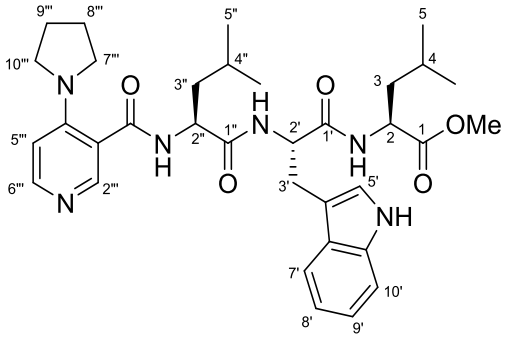
NH_2-L-Leu-L-Trp-L-Leu-OMe



To a stirred solution of Fmoc-L-Leu-L-Trp-L-Leu-OMe (173.6 mg, 0.261 mmol) in DCM (2 mL) at 0 °C, was added piperidine (0.06 mL, 0.6 mmol). After 18 hrs, the solvent was removed *in vacuo* to give a crude product that was purified by column chromatography using MeOH/DCM (10/90) to afford NH_2-L-Leu-L-Trp-L-Leu-OMe as a colourless solid (84.3 mg, 73% 61%), mp 118–120 °C; $[\alpha]_D^{20}$ − 37.8 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3020 (NH_2), 1772

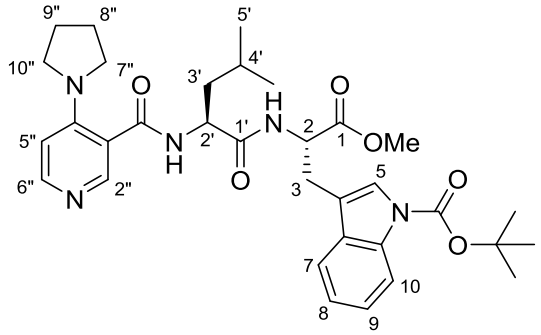
(CO_2Me), 1659 $(CO)_{amide}$, 1516 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H, *N-H*$_{indole}$), 7.83 (d, *J* = 8.1 Hz, 1H, *N-H*$_{Trp}$), 7.73–7.68 (d, *J* = 8.1 Hz, 1H, *Ar-H*), 7.34 (d, *J* = 8.1 Hz, 1H, *Ar-H*), 7.17 (m, 1H, *Ar-H*), 7.14–7.07 (m, 2H, *Ar-H*), 6.39 (d, *J* = 7.9 Hz, 1H, *N-H*$_{Leu}$), 4.76 (m, 1H, *H-2'*), 4.49 (m, 1H, *H-2*), 3.65 (s, 3H, *OMe*), 3.34 (dd, *J* = 9.6, 4.1 Hz, *H-2"*), 3.30–3.17 (m, 2H, *H-3'*), 1.59–1.18 (m, 6H, *H-3*, *H-3", H-4*, *H-4"*), 0.89 (d, *J* = 6.4 Hz, 3H, *H-5 or H-5"*), 0.87 (d, *J* = 6.4 Hz, 3H, *H-5*, *H-5"*), 0.84 (m, 6H, *H-5*, *H-5"*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.7, 172.9, 171.2, 136.2, 127.6, 123.3, 122.1, 119.6, 119.0, 111.1, 110.9, 53.6, 53.5, 52.2, 51.0, 51.0 43.8, 41.4, 27.9, 24.8, 23.3, 22.6, 22.0, 21.4; HRMS (ES): *m/z* 445.2815 $[M + H]^+$. Calculated for $C_{24}H_{37}N_4O_4$, 445.2815; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 5.163 min.

Methyl (4-(pyrrolidin-1-yl)nicotinoyl)-L-leucyl-L-tryptophyl-L-leucinate (7)



Salt **2** (160 mg, 0.694 mmol) and NH_2-L-Leu-L-Trp-L-Leu-OMe (365 mg, 0.821 mmol) were dissolved in pyridine (5 mL) and DCM (4 mL), at r.t. EDC (200 mg, 1.04 mmol) was added followed by HOBt (47 mg, 0.35 mmol). After 12 hrs, (sat.) aq. $NaHCO_3$ (20 mL) was added and the aqueous layer extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated to afford a yellow oil that was purified by column chromatography using ethyl acetate/hexane (80/20), followed by MeOH/DCM (5/95) to provide **7** as a pale-yellow solid (188 mg, 44 %), mp 186–189 °C; $[\alpha]_D^{20}$ − 54.7 (*c* 0.5, CH_3OH); IR (DCM) 1741 (CO_2Me), 1641 $(CO)_{amide}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H, *N-H*$_{indole}$), 8.11 (d, *J* = 6.2 Hz, 1H, *H-6"'*), 8.05 (s, 1H, *H-2"'*), 7.62 (d, *J* = 8.1 Hz, 1H, *Ar-H*), 7.30 (d, *J* = 8.1 Hz, 1H, *Ar-H*), 7.13 (t, *J* = 7.1 Hz, 1H, *Ar-H*), 7.09 (d, *J* = 2.2 Hz, 1H, *Ar-H*), 7.05 (t, *J* = 7.1 Hz, 1H, *Ar-H*), 6.93 (d, *J* = 7.9 Hz, 1H, *N-H*$_{Trp}$), 6.84 (d, *J* = 7.9 Hz, 1H, *N-H*$_{Leu}$), 6.73 (d, *J* = 7.9 Hz, 1H, *N-H*$_{Leu}$), 6.40 (d, *J* = 6.2 Hz, 1H, *H-5"'*), 4.81 (m, 1H, *H-2'*), 4.60 (m, 1H, *H-2 or H-2"*), 4.47 (m, 1 H, *H-2 or H-2"*), 3.63 (s, 1H, *OMe*), 3.21 (m, 6H, *H-3', H-7"', H-10"'*), 1.84 (m, 4H, *H-8"', H-9"'*), 1.65 (m, 3H, *H-3*, *H-3", H-4 or H-4"*), 1.44 (m, 3H, *H-3*, *H-3", H-4 or H-4"*), 0.93 (m, 6H, *H-5 or H-5"*), 0.82 (d, *J* = 6.1 Hz, 3H, *H-5 or H-5"*), 0.79 (d, *J* = 6.1 Hz, 3H, *H-5 or H-5"*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.9, 171.7, 170.9, 168.8, 150.1, 149.4, 148.7, 136.3, 127.4, 123.6, 122.0, 119.5, 118.7, 117.2, 111.4, 110.1, 108.6, 53.4, 52.5, 52.1, 51.0, 49.5, 41.2, 41.1, 29.7, 28.1, 25.5, 25.0, 24.8, 23.0, 22.6, 21.8; HRMS (ES): *m/z* Found 619.3606 $[M + H]^+$. Calculated for $C_{34}H_{47}N_6O_5$, 619.3608; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 4.588 min.

tert-Butyl-3-((S)-3-methoxy-2-((S)-4-methyl-2-(4-(pyrrolidin-1-yl)nicotinamido)pentanamido)-3-oxopropyl)-1H-indole-1-carboxylate (8)



To a stirred solution of **4** (70 mg, 0.14 mmol) in THF (4 mL), was added di-*tert*-butyl dicarbonate (90 mg, 0.42 mmol, 3 eq). After 4 hrs, at room temperature (sat.) $NaHCO_3$ (10 mL) was added and the THF removed *in vacuo*. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated to afford a yellow oil that was purified by column chromatography using MeOH/DCM (5/95) to provide **8** as a pale-yellow solid (74 mg, 89%), mp 108-110°C; $[\alpha]_D^{20}$ +8.6 (*c* 0.5, $CHCl_3$, 98% ee); IR (DCM) 3420 (NH), 1736 (CO_2Me), 167 $(CO)_{amide}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, *H-2"*), 8.14 (d, *J* = 6.1 Hz, 1H, *H-6"*), 8.08 (d, *J* = 8.2 Hz, 1H, *Ar-H*), 7.51 (d, *J* = 8.2 Hz, 1H, *Ar-H*), 7.46 (s, 1H, *Ar-H*), 7.26 (m, 1H, *Ar-H*), 7.21 (m, 1H, *Ar-H*), 6.79 (d, *J* = 6.1 Hz, 1H, *N-H*$_{Trp}$), 6.49 (d, *J* = 6.1 Hz, 1H, *N-H*$_{Leu}$), 6.44 (d, *J* = 6.1 Hz, 1H, *H-5"*), 4.92 (m, 1H, *H-2*), 4.58 (m, 1H, *H-2'*), 3.67 (s, 3H, *OMe*), 3.35-3.15 (m, 6H, *H-3, H-7", H-10"*), 1.86 (m, 4H, *H-8", H-9"*), 1.71 (m, 2H, *H-3', H-4'*), 1.64 (m, 10H, *H-3', t-Bu*), 0.95 (m, 6H, *H-5'*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.7, 171.6, 168.8, 150.1, 150.0, 149.5, 149.2, 135.4, 130.4, 124.6, 124.3, 122.6, 118.8 , 117.3, 115.3, 114.7, 108.6, 83.8, 52.8, 52.4, 52.4, 49.5, 41.2, 28.2, 27.6, 25.5, 25.0, 23.0, 21.9; Chiralpak AD 30% isopropyl alcohol/hexane, 1.0 mL/min, 254 nm, 7.526 min; HRMS (ES): *m/z* 606.3290 $[M + H]^+$. Calculated for $C_{33}H_{44}N_5O_6$, 606.3291.

References

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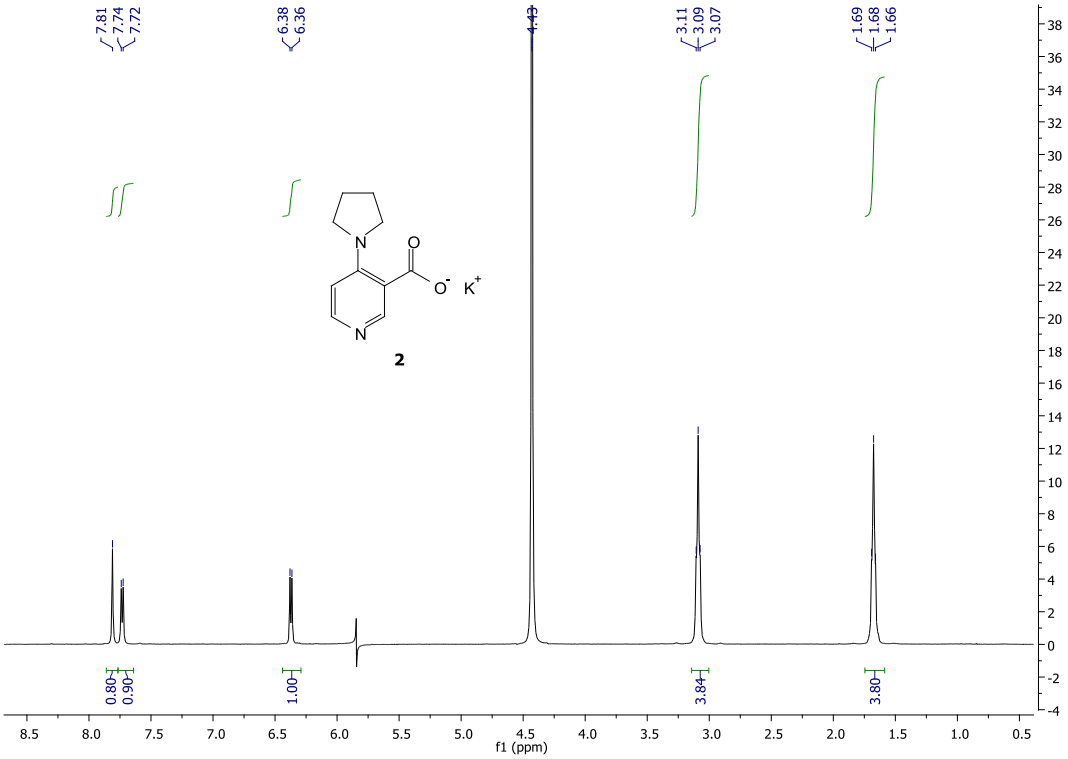
3) ^{1}H NMR and ^{13}C NMR spectra



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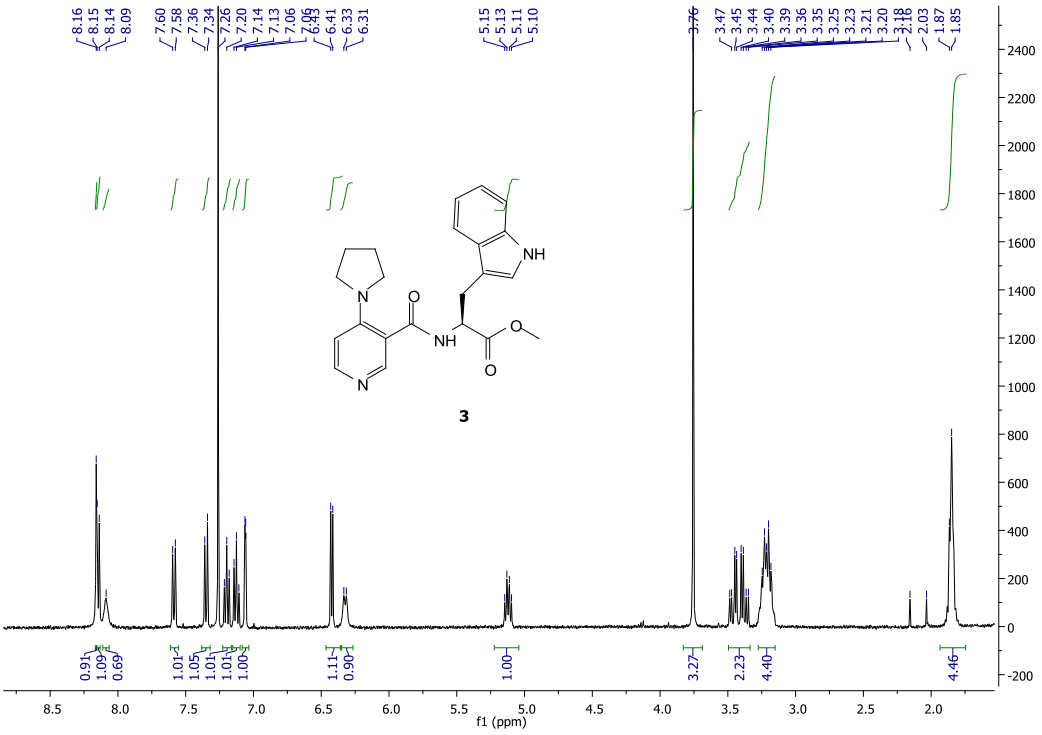

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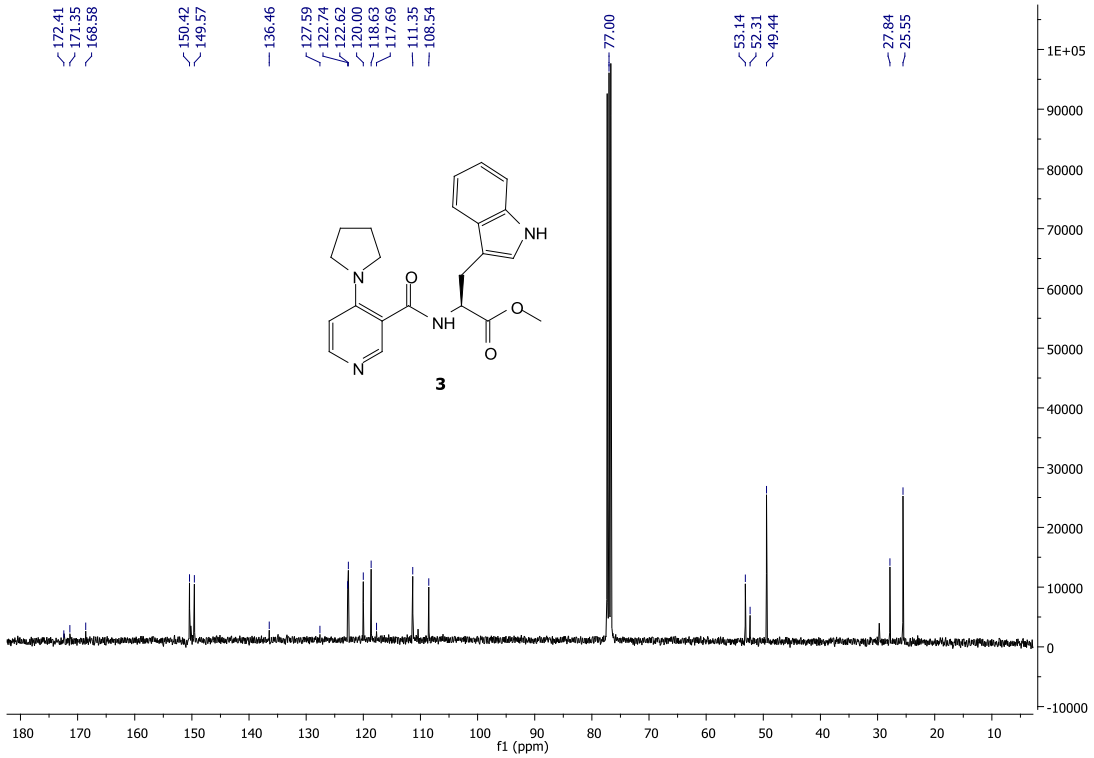
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NH
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N
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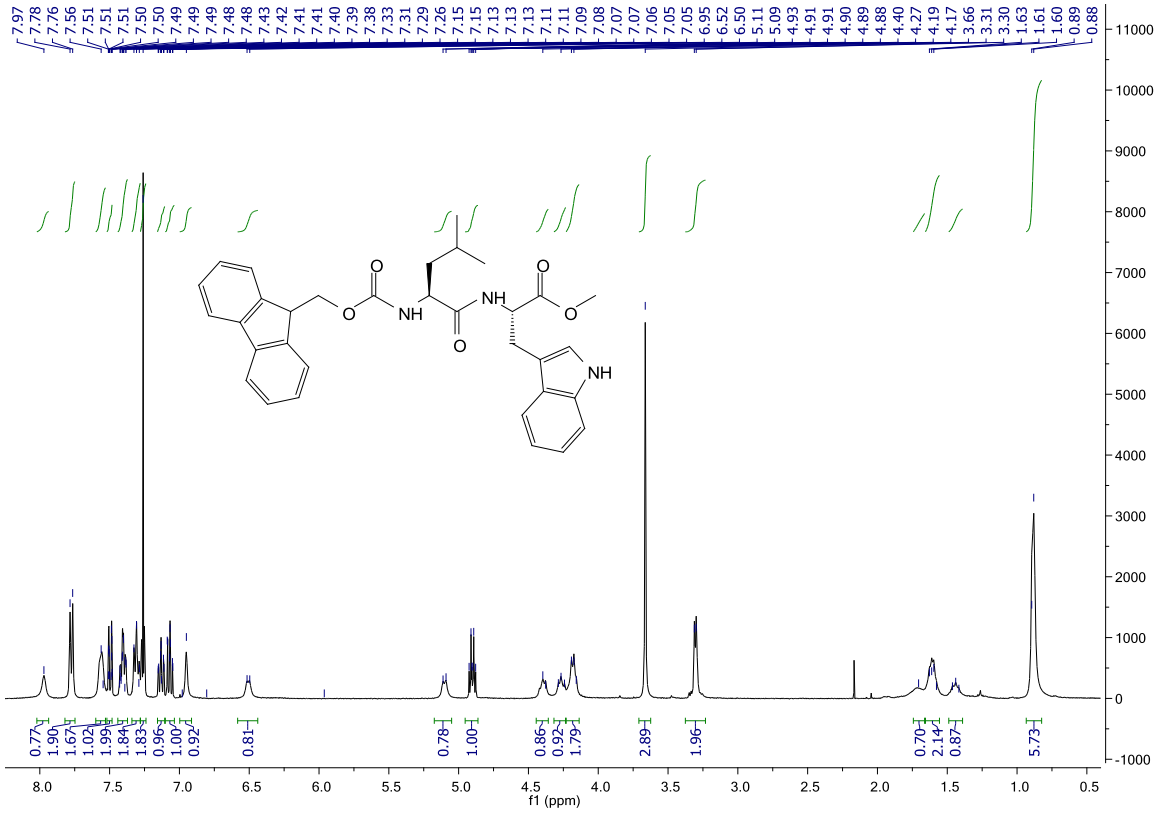
f1 (ppm)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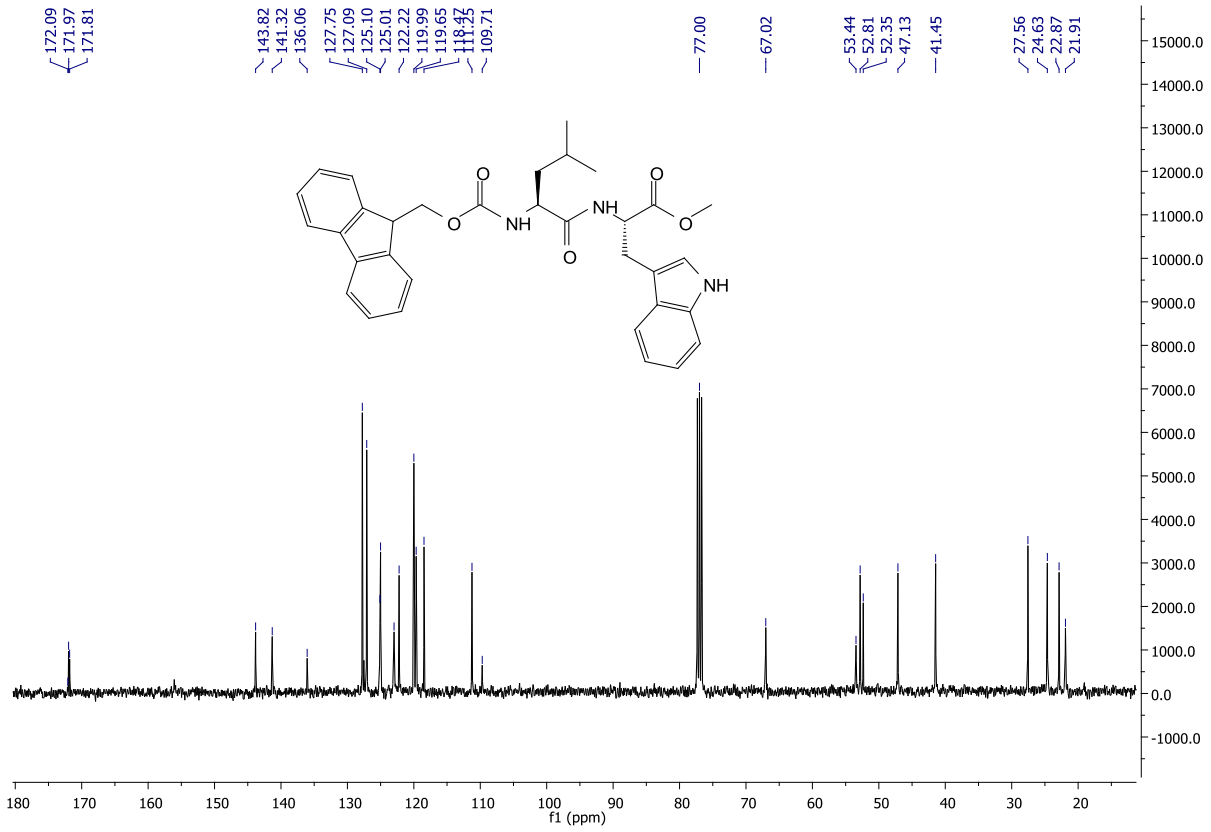
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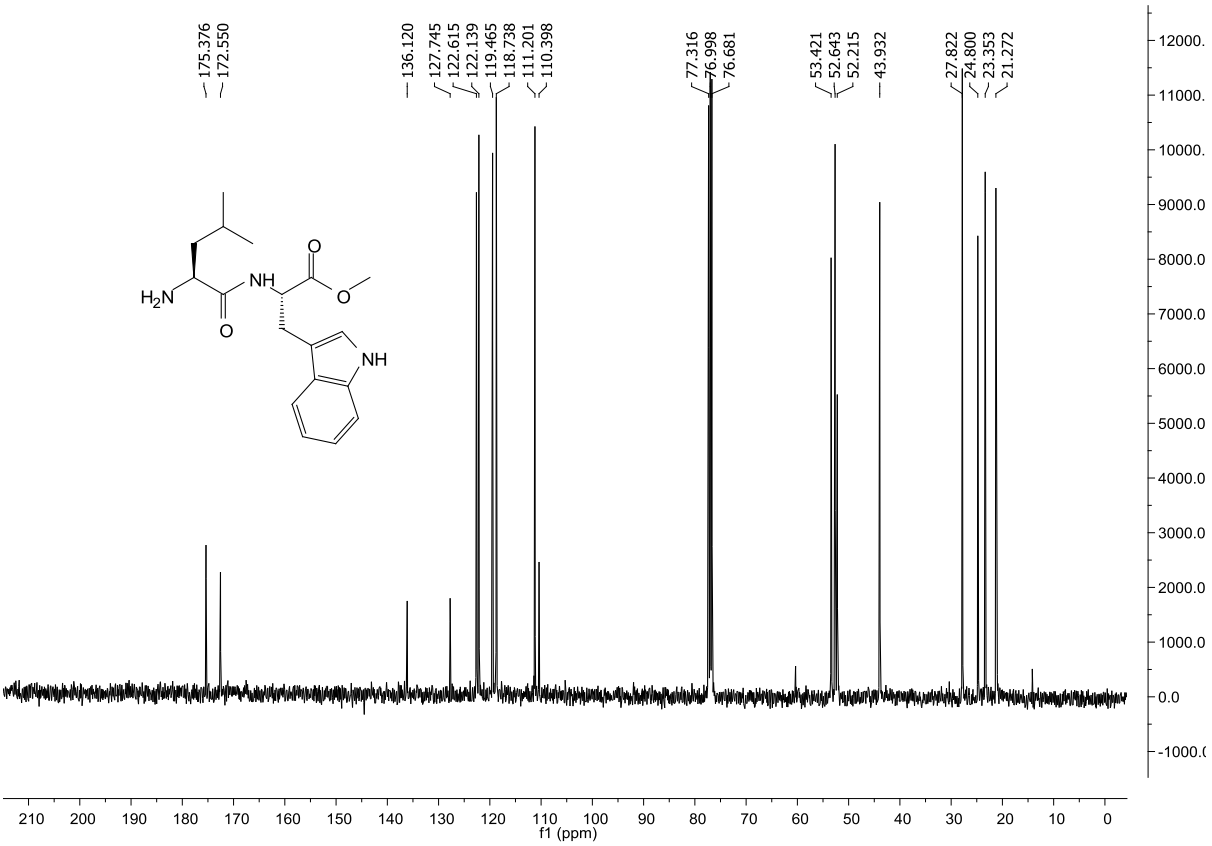
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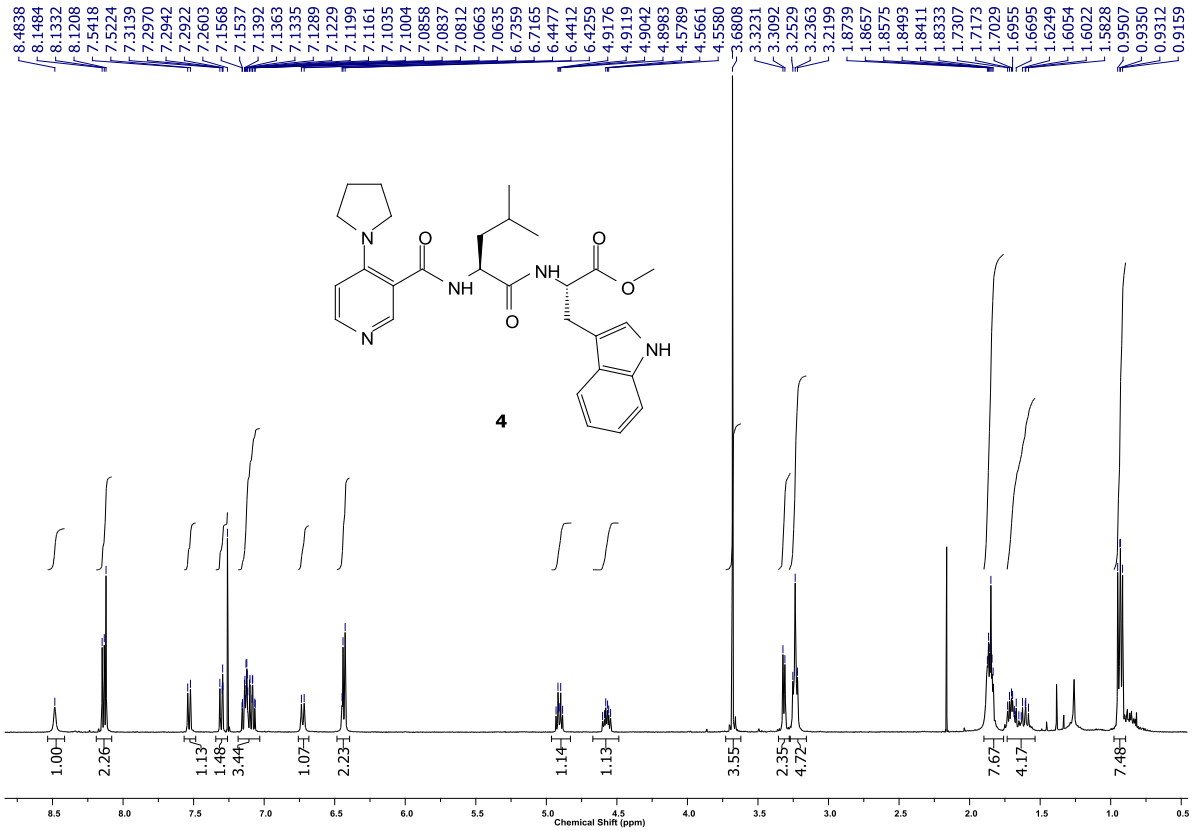
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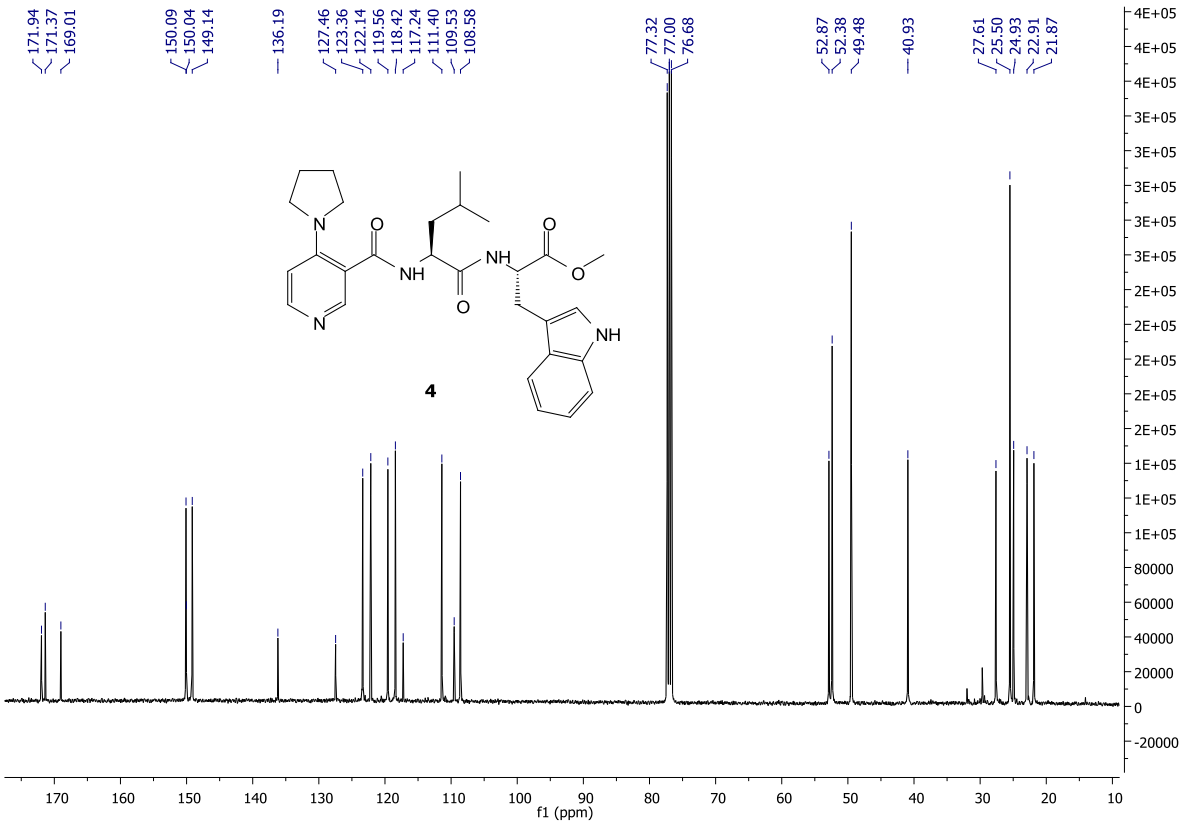
Chemical Shift (ppm)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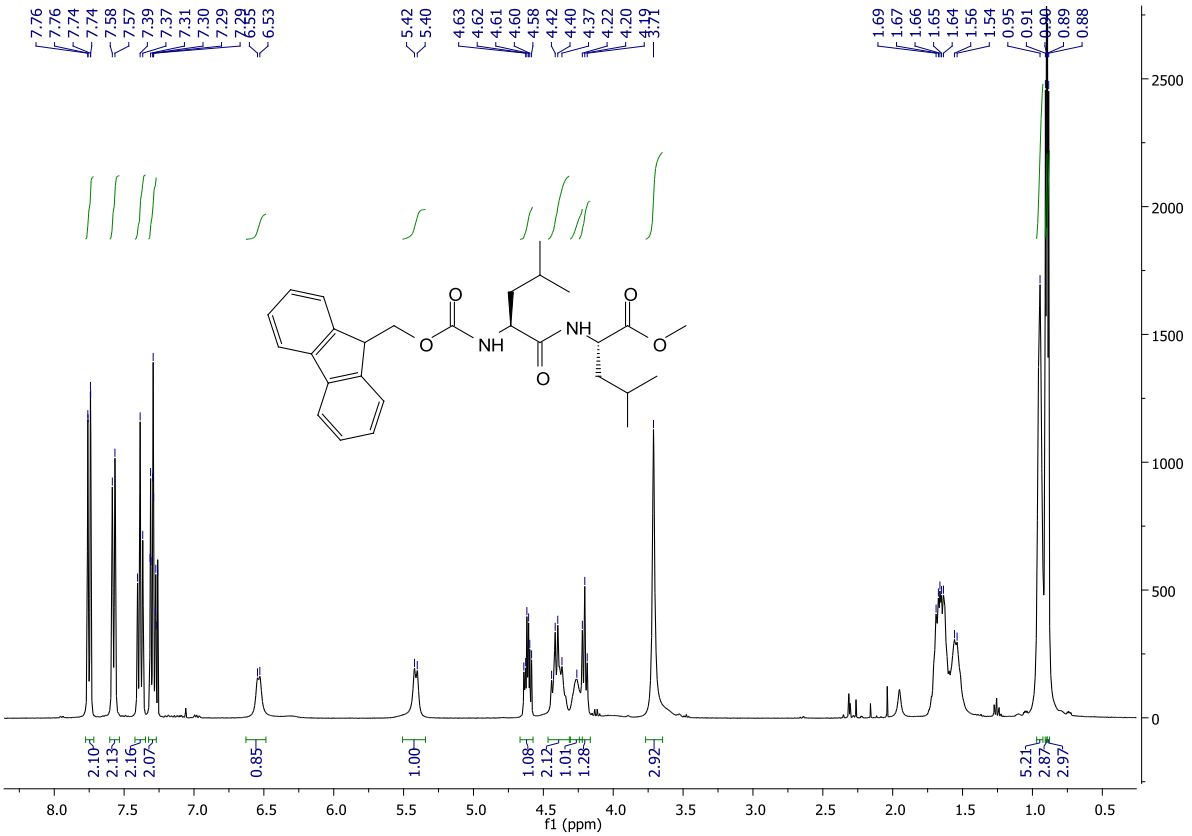
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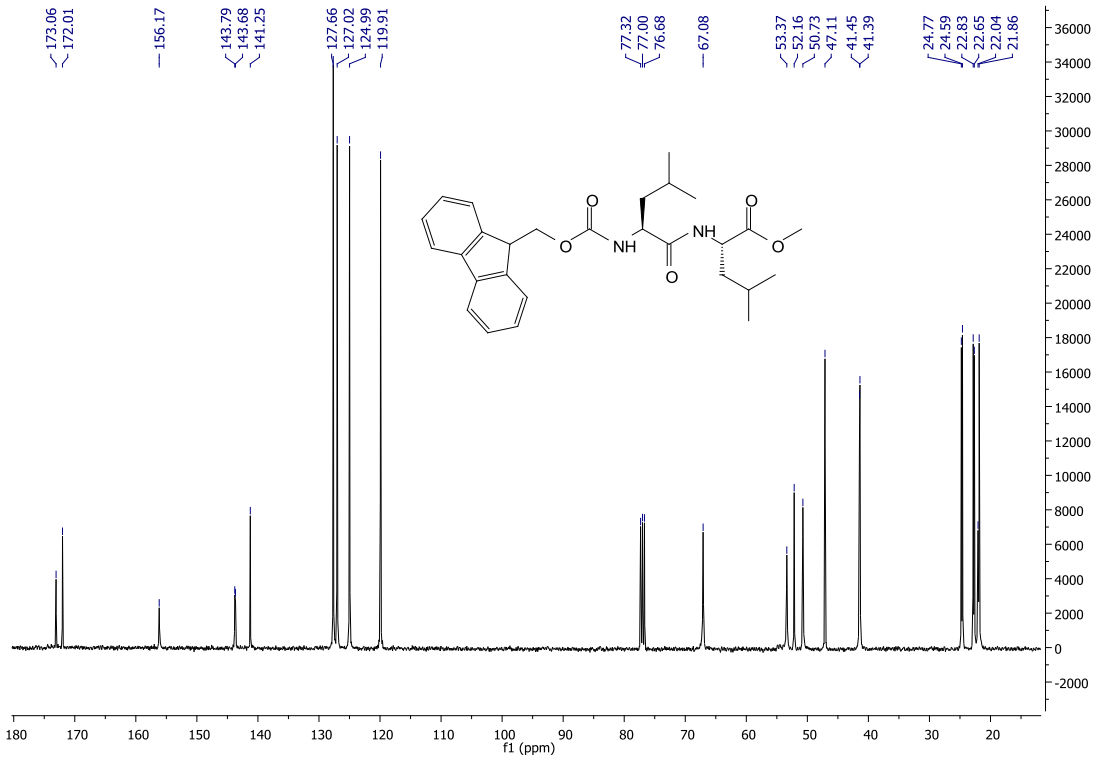
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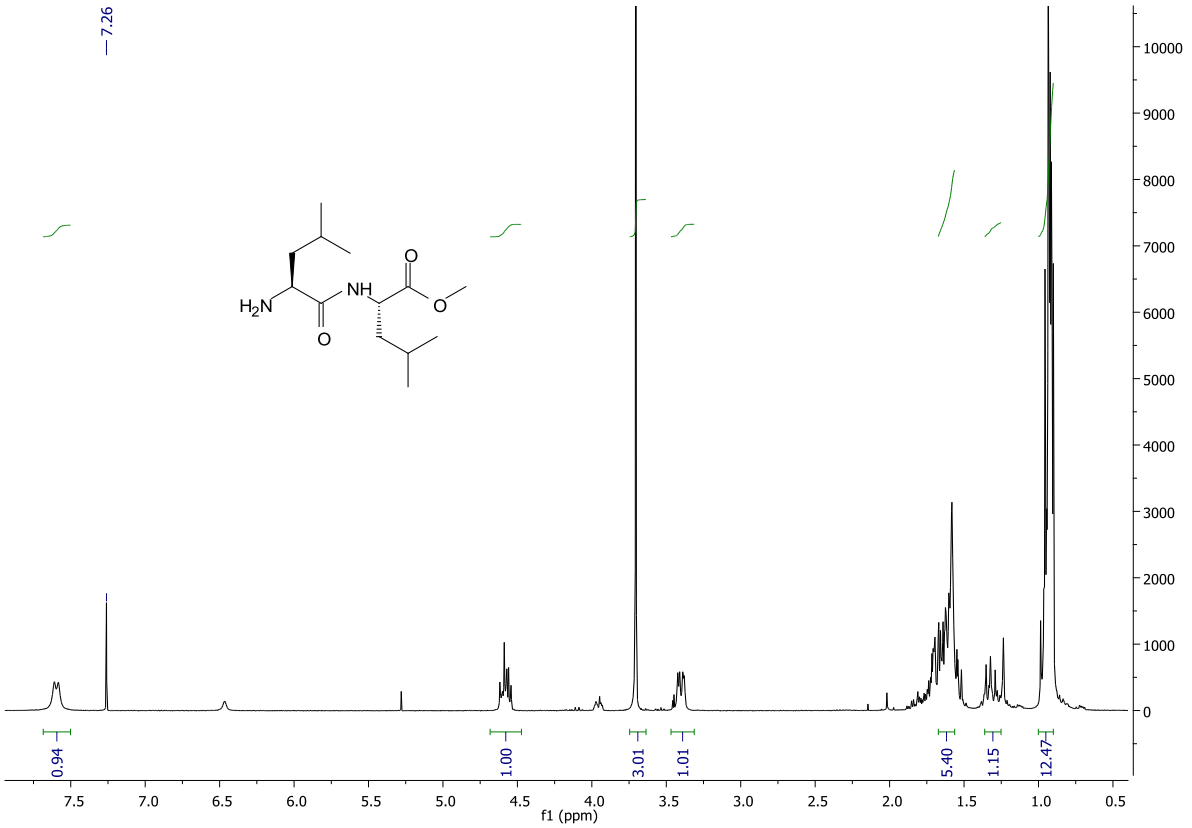
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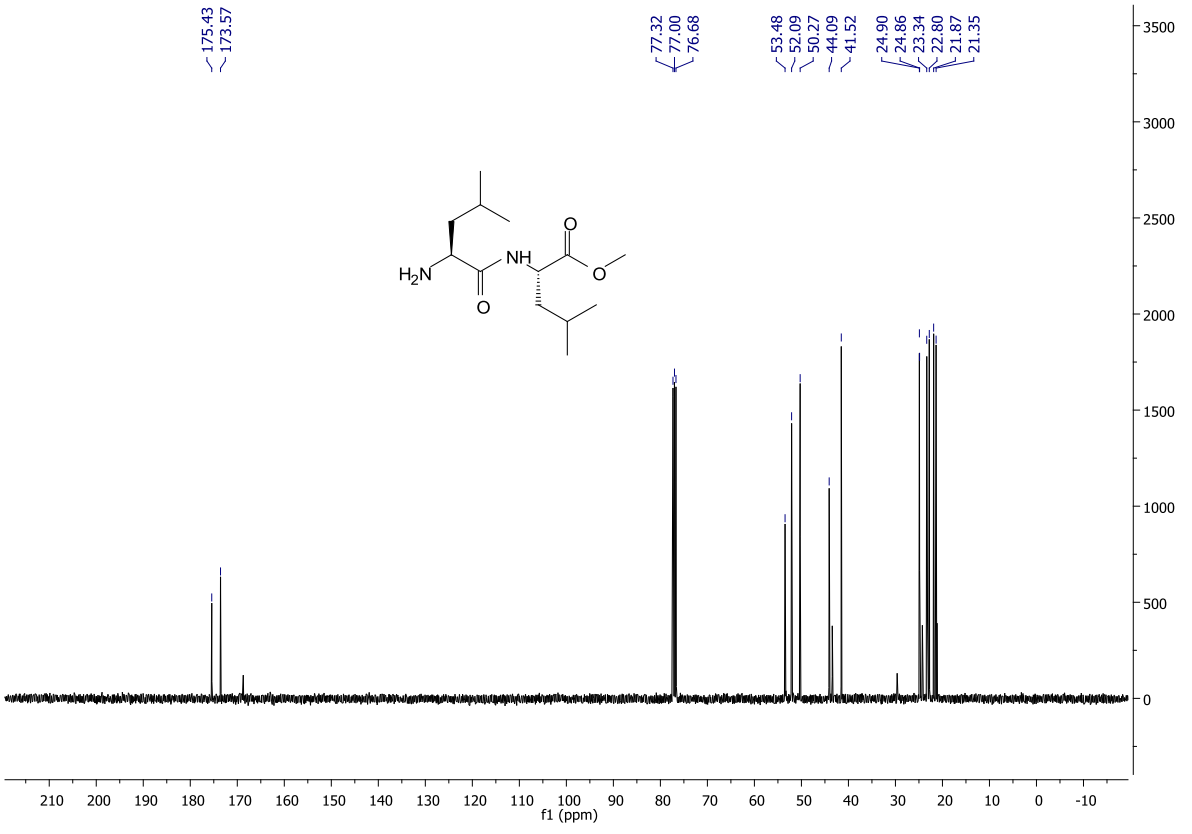
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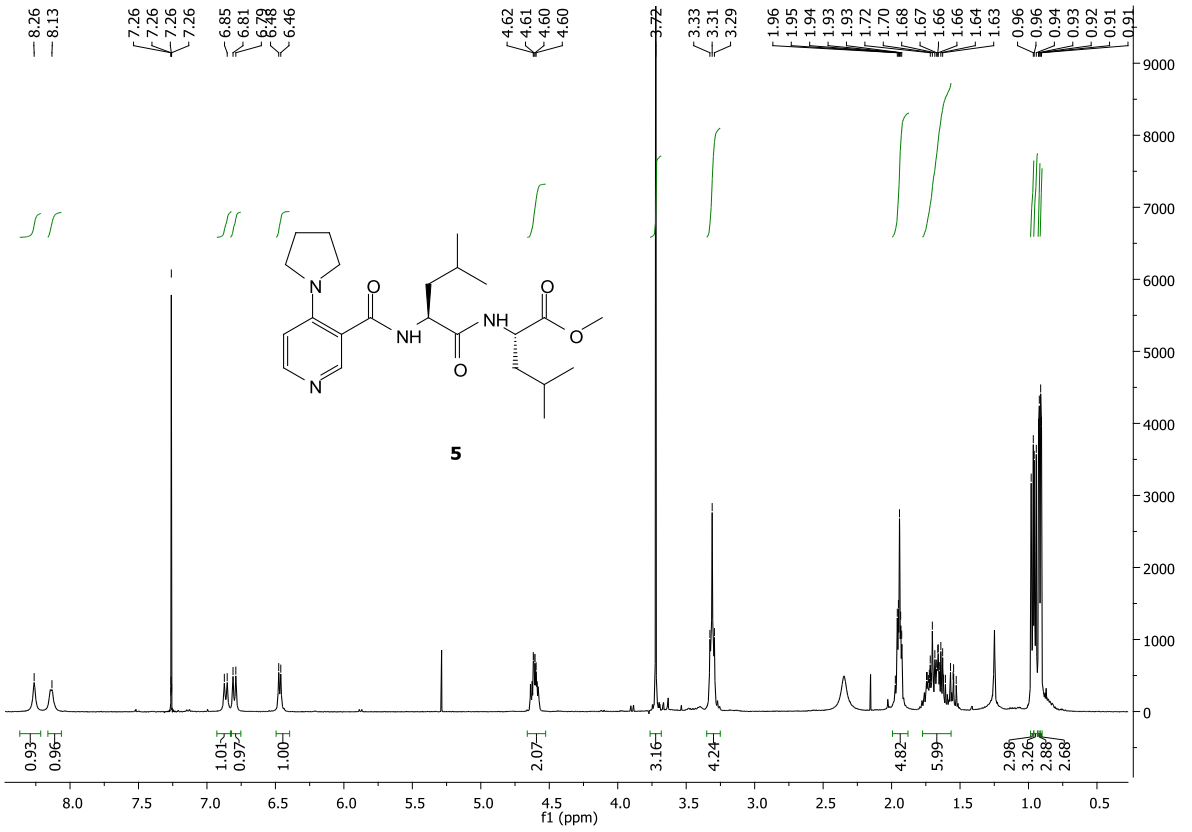
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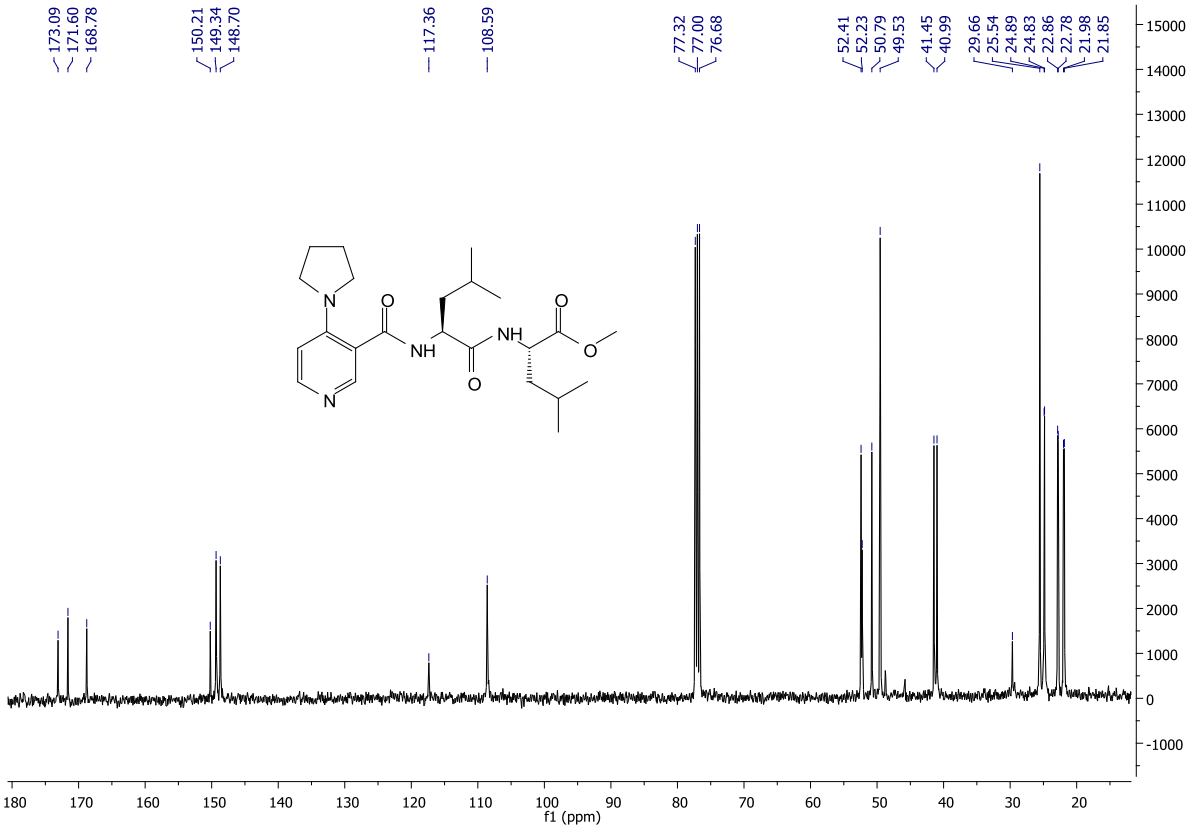
5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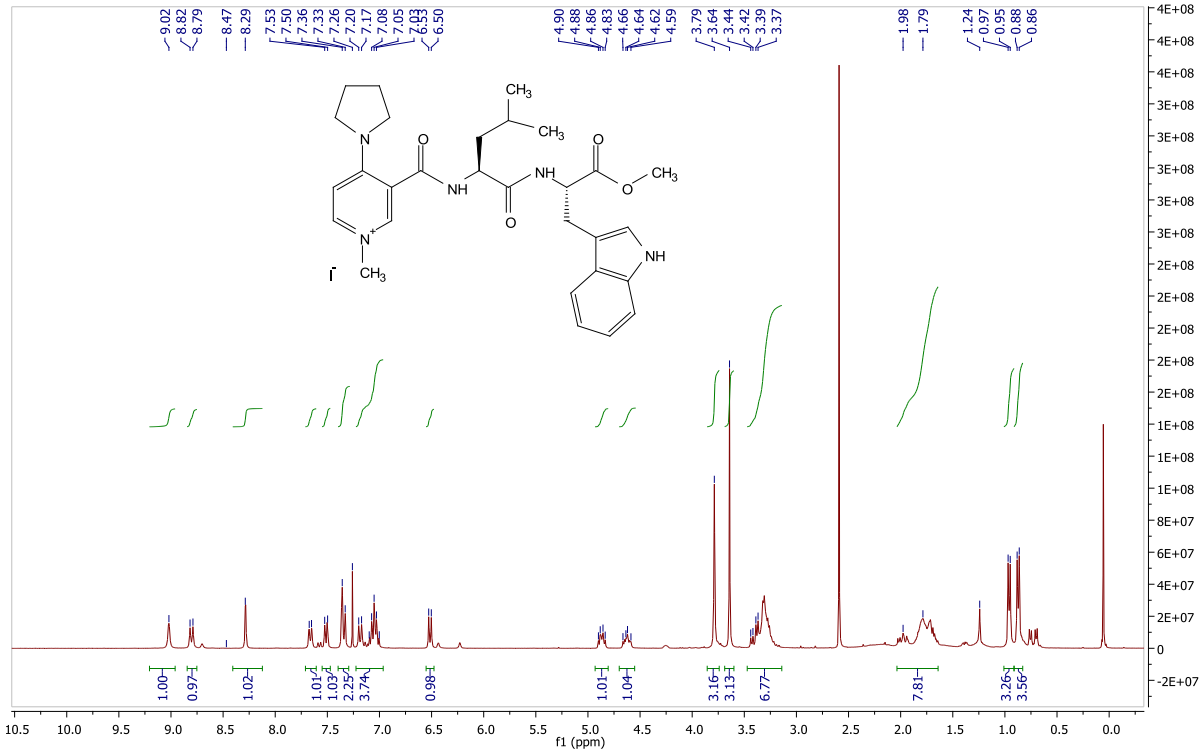
f1 (ppm)

4 $_{N\text{-}Me}$ salt



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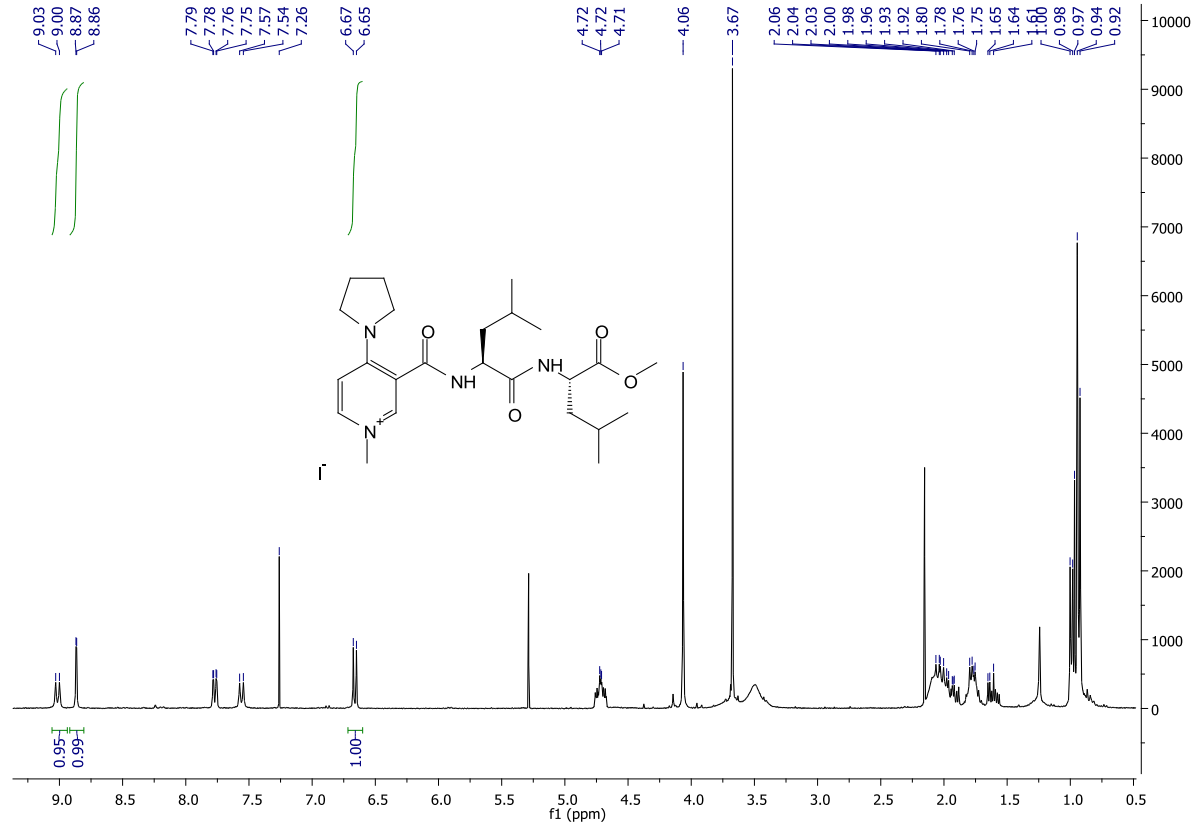

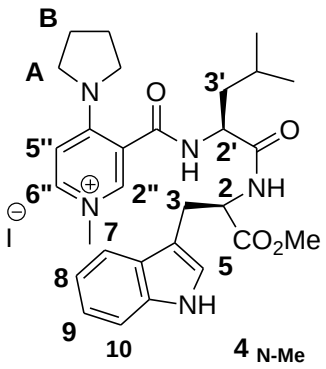
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6''
2''
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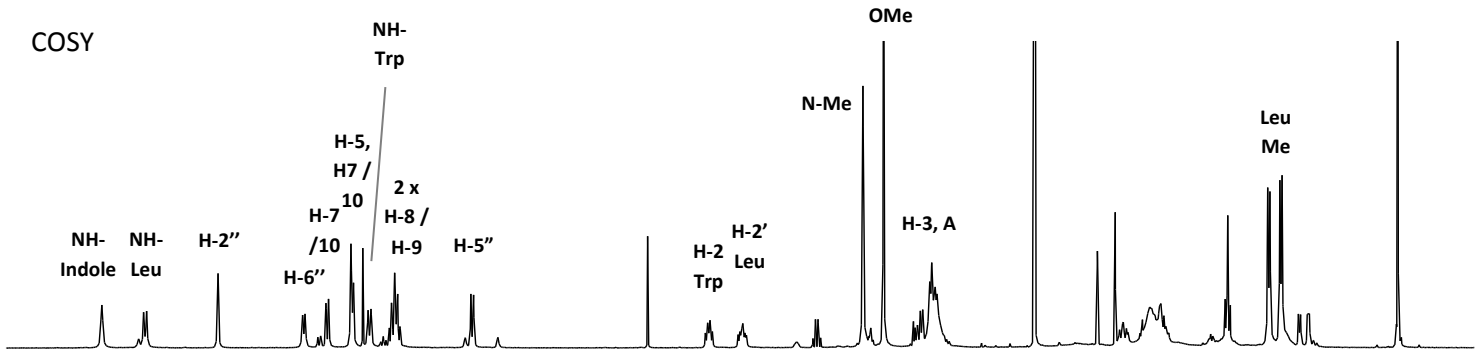
7
CO2Me
8
5
NH
9
10
4 N-Me

COSY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OMe
N-Me
Leu
Me
H-5,
H7 /
10
2 x
H-8 /
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H-7
/10
H-2''
H-6''
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Trp
H-2'
Leu
H-3, A
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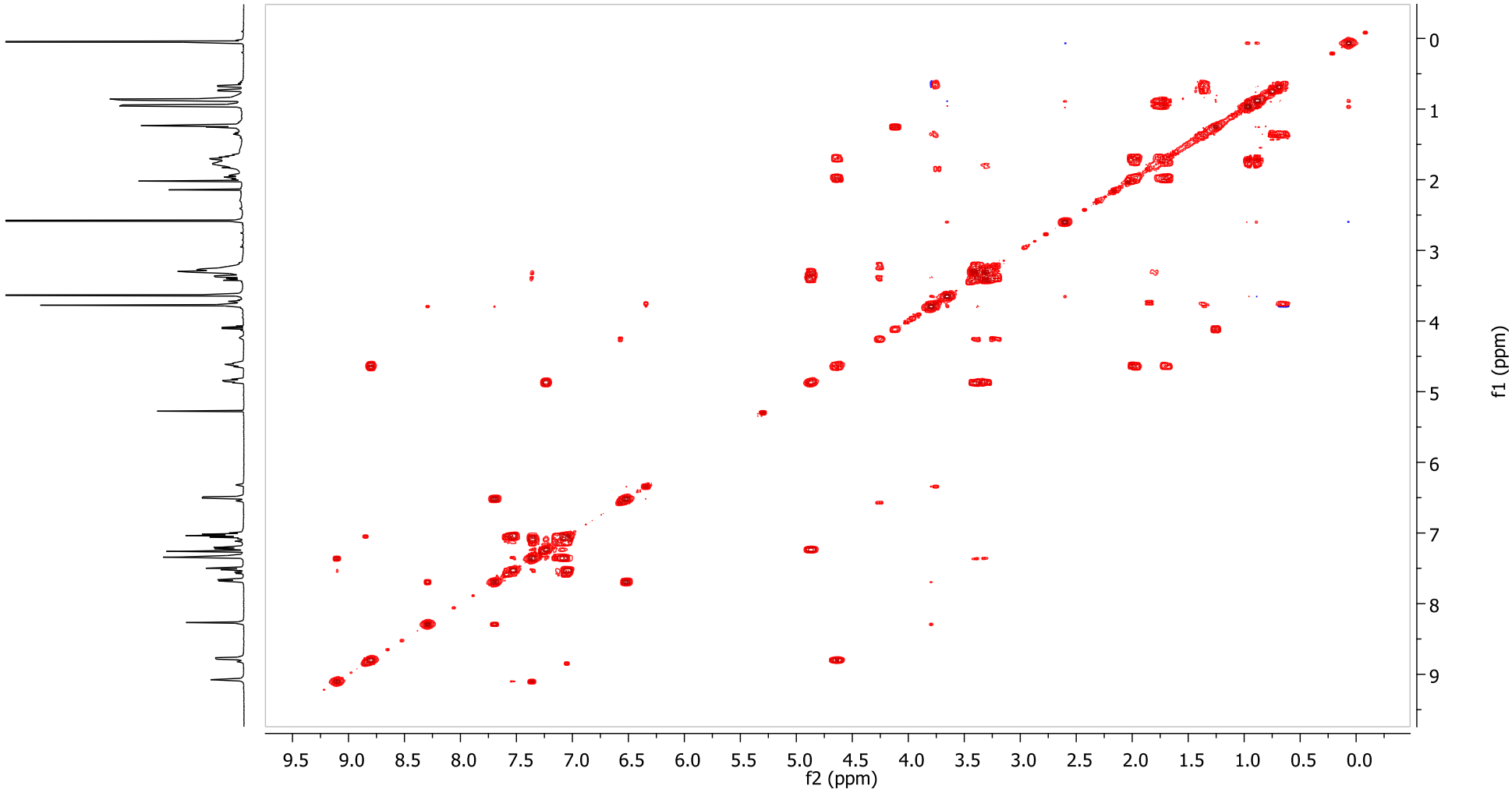
Indole
NH-
Leu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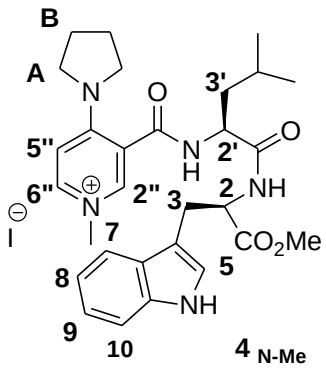
2
3
4
5
6
7
8
9
f1 (ppm)



NOESY

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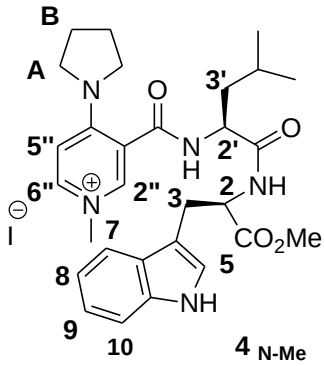
NH-Leu
H-2''
H-7 /10
H-6''
H-5, H7 / 10
NH-Trp
2 x H-8 / H-9
H-5''
H-2 Trp
H-2' Leu
N-Me
OMe
H-3, A
H-3', B
Leu Me

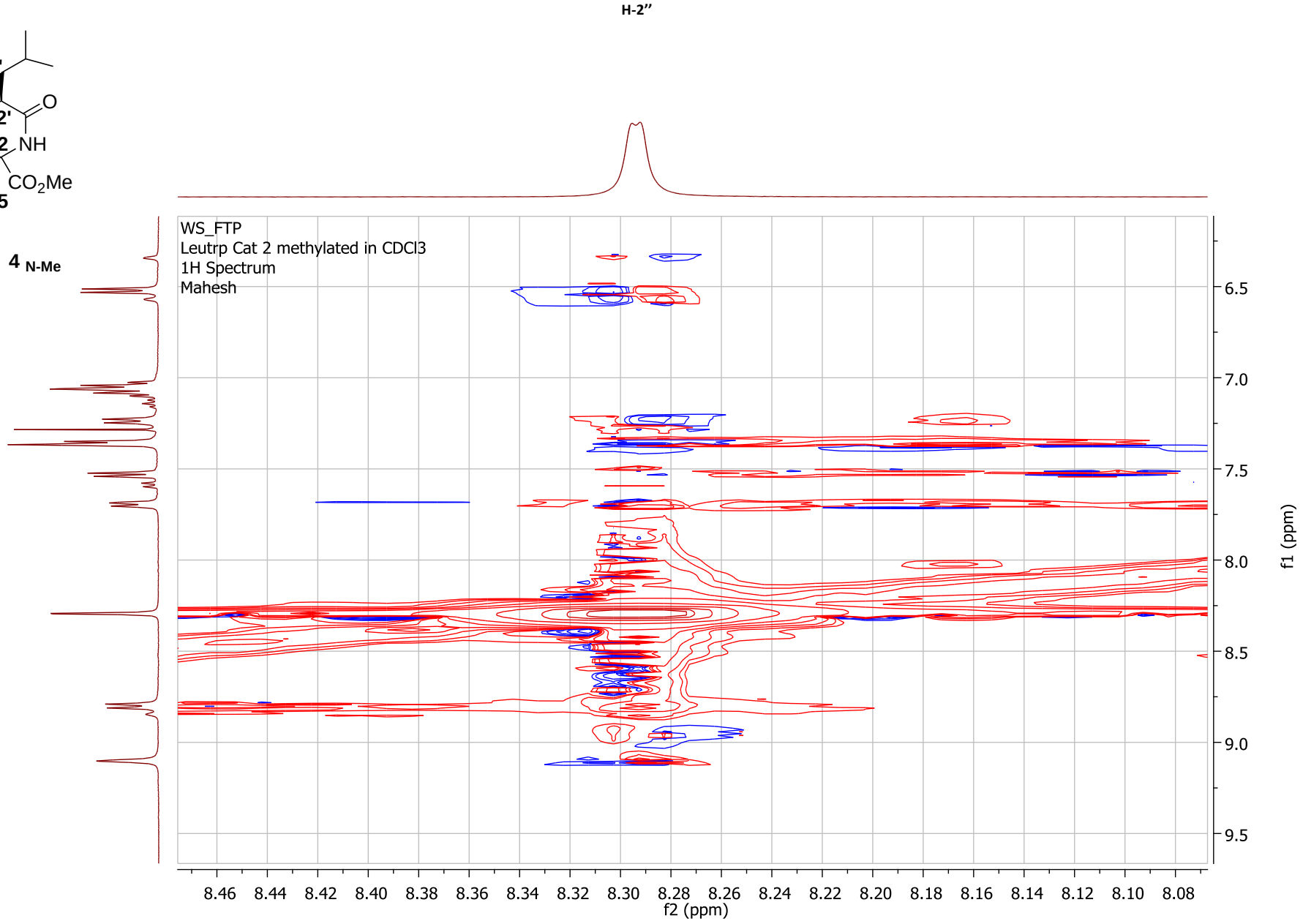
Leu Me
H-3', B
H-3, A
OMe
N-Me
H-2' Leu
H-2 Trp
H-5''
2 x H-8 / H-9
NH-Trp
H-5, H7 / 10
H7 / 10
H-6''
H-2''
NH-Leu
NH-Indole

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)

0 1 2 3 4 5 6 7 8 9
f1 (ppm)

H-2” expansion NOESY (in blue)





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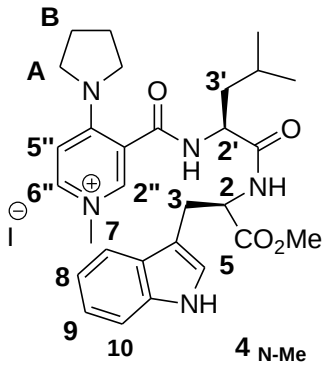
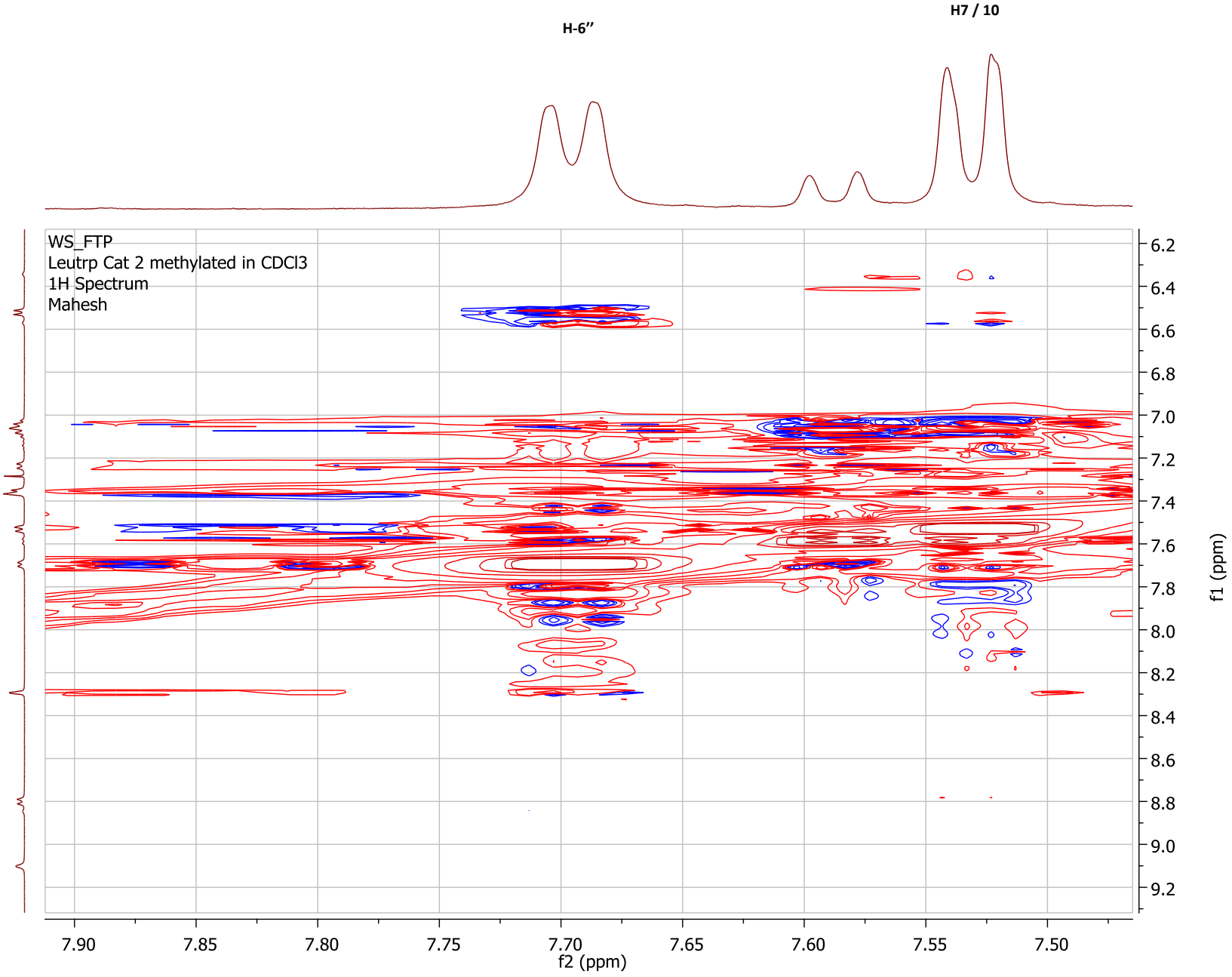
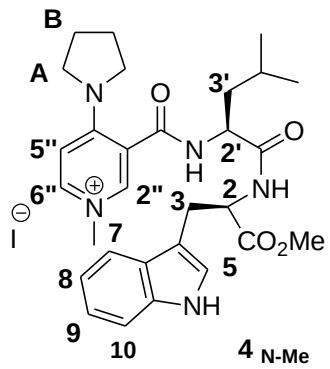
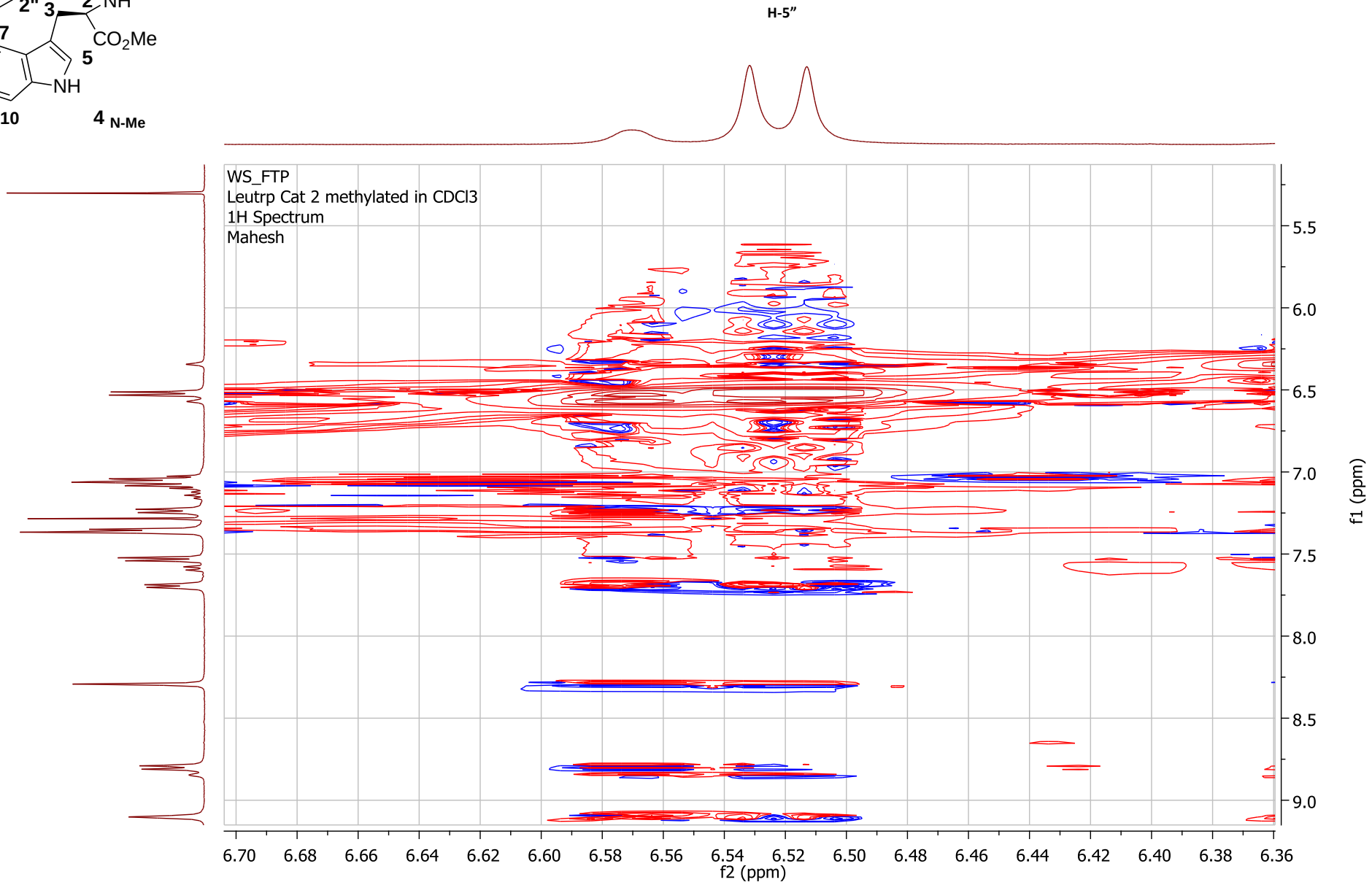
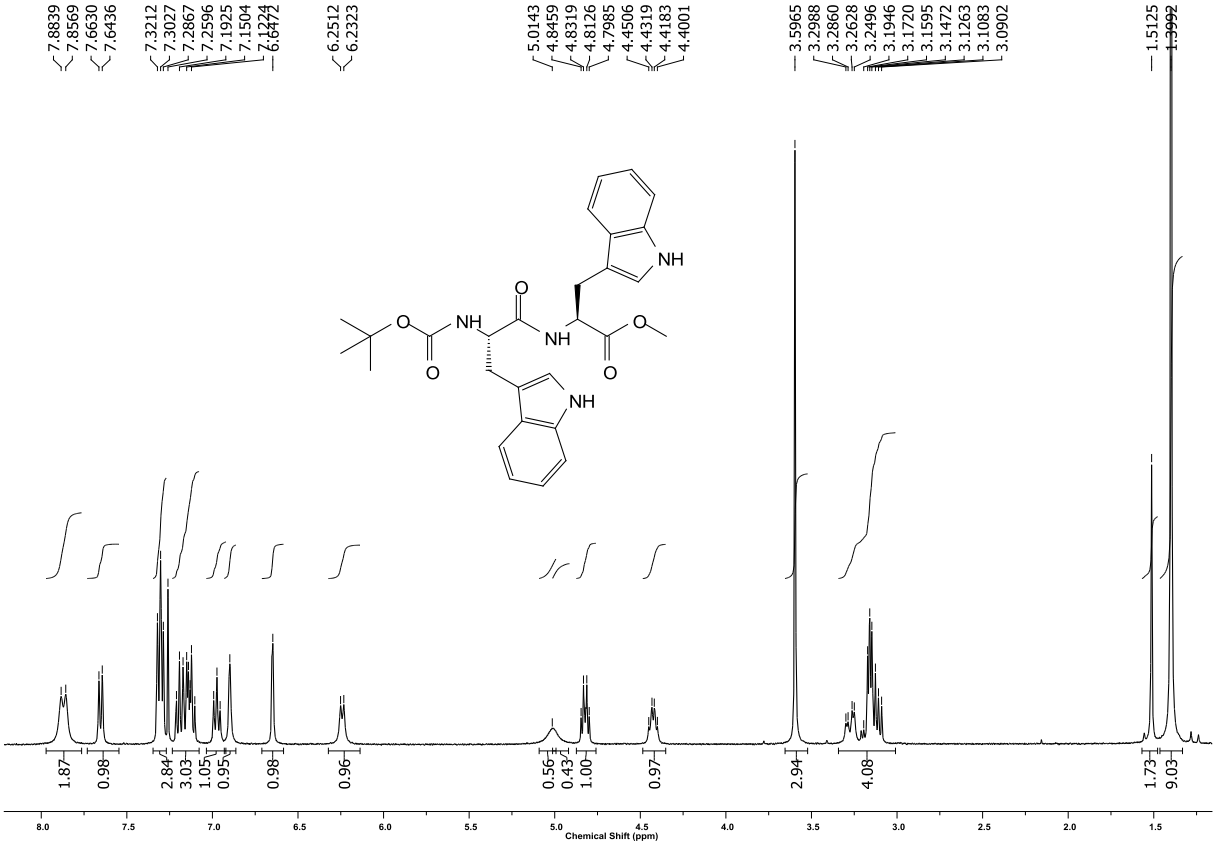






H-5” expansion NOESY (in blue)

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7.1224
6.6472
6.2512
6.2323
5.0143
4.8459
4.8319
4.8126
4.7985
4.4506
4.4319
4.4183
4.4001
3.5965
3.2988
3.2860
3.2628
3.2496
3.1946
3.1720
3.1595
3.1472
3.1263
3.1083
3.0902
1.5125
1.3992
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O
NH
NH
O
O
O
NH
1.87
0.98
2.84
3.03
1.05
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1.00
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4.08
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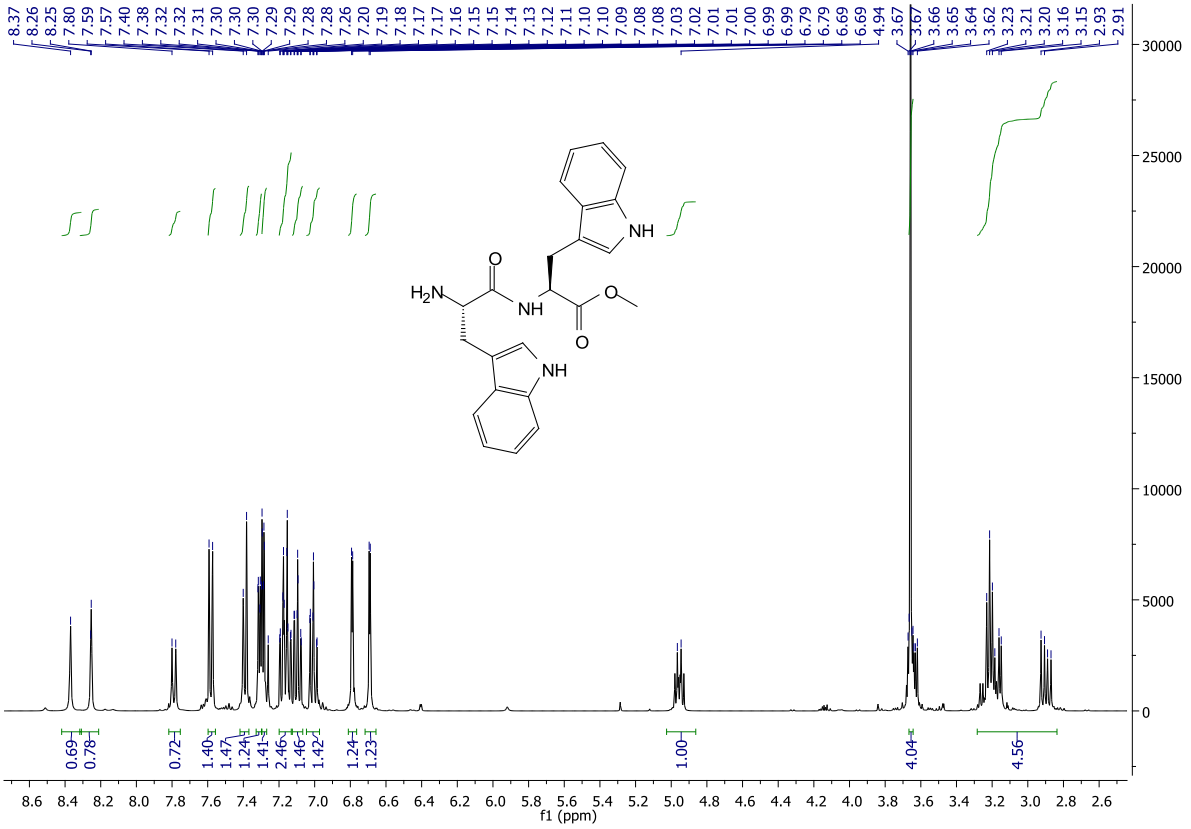
9.03
Chemical Shift (ppm)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7.30
7.29
7.29
7.28
7.28
7.26
7.20
7.19
7.18
7.17
7.17
7.16
7.15
7.15
7.14
7.13
7.12
7.11
7.10
7.10
7.09
7.08
7.08
7.03
7.02
7.01
7.01
7.00
6.99
6.99
6.79
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6.69
6.69
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3.67
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3.64
3.62
3.23
3.21
3.20
3.16
3.15
2.93
2.91
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O
O
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0.72
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1.24
1.23
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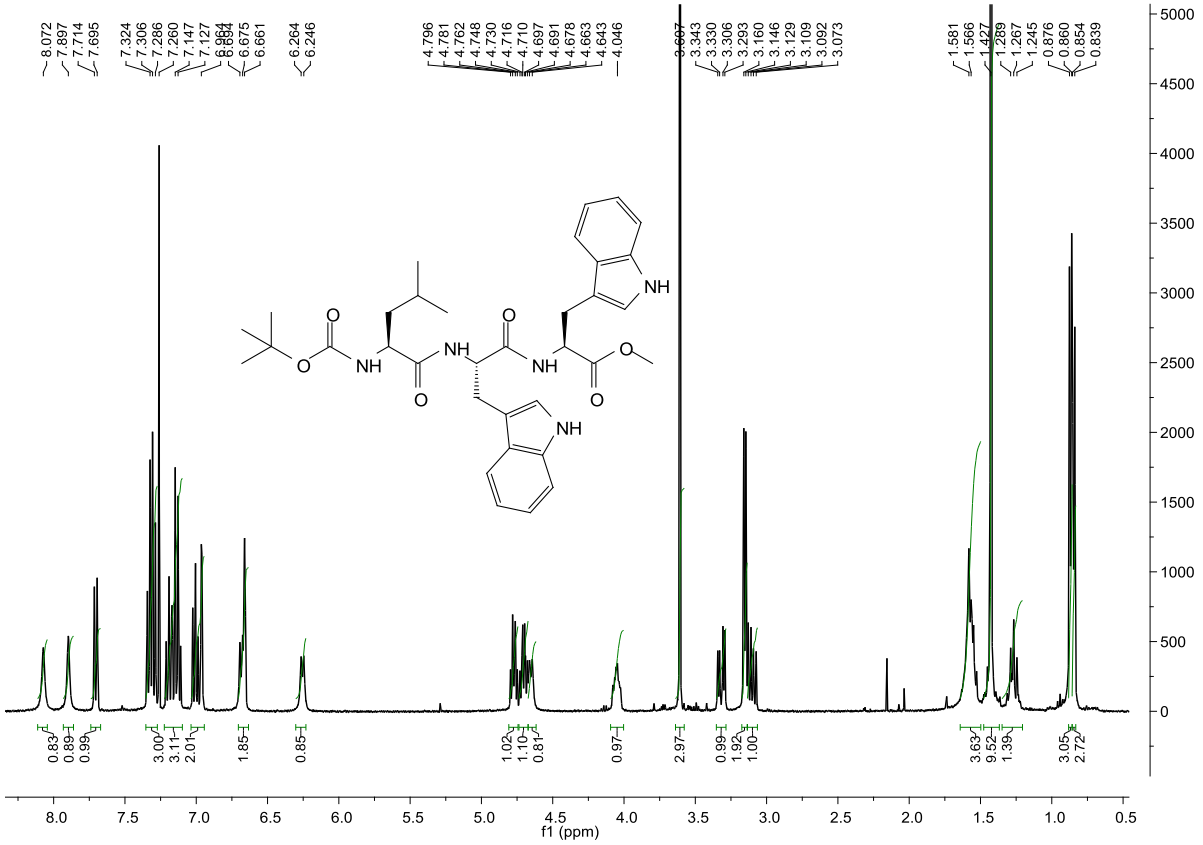
4.56
f1 (ppm)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4.762
4.748
4.730
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4.710
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4.691
4.678
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3.129
3.109
3.092
3.073
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1.566
1.427
1.289
1.267
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0.860
0.854
0.839
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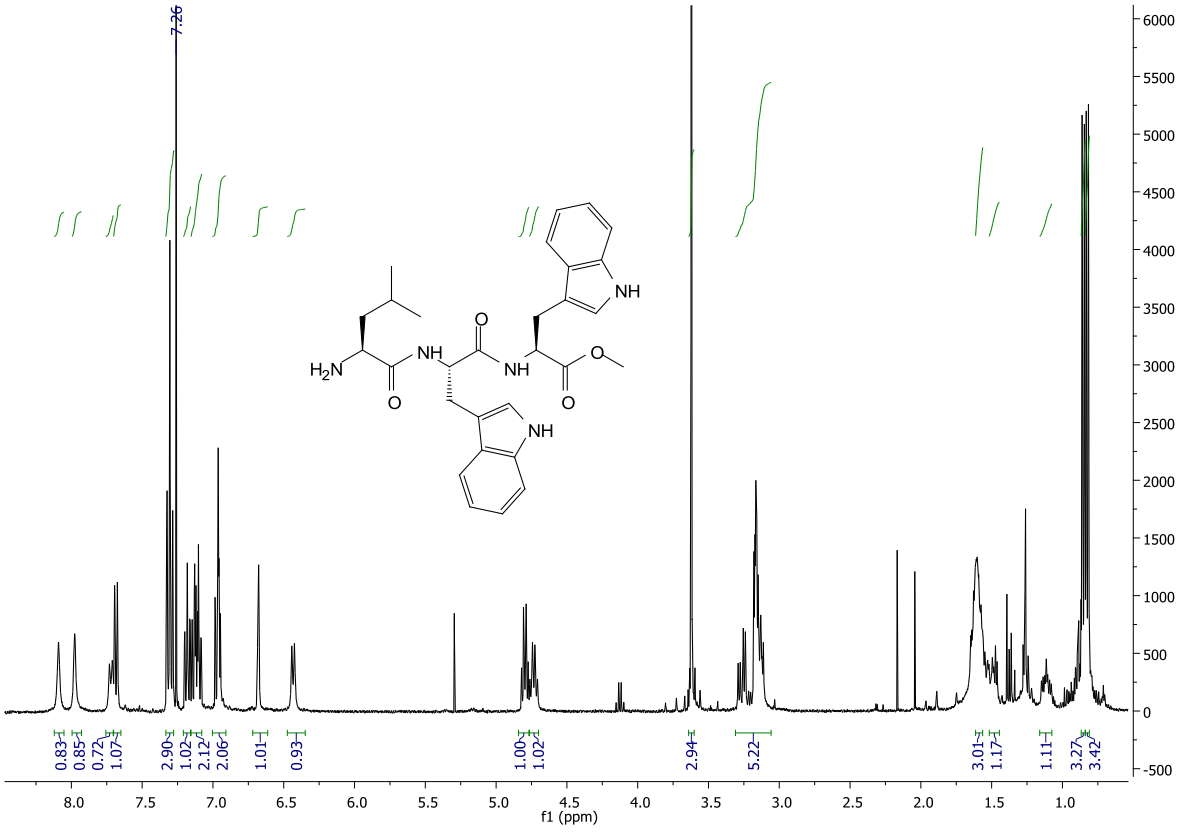
NH
NH
O
O
O
NH
f1 (ppm)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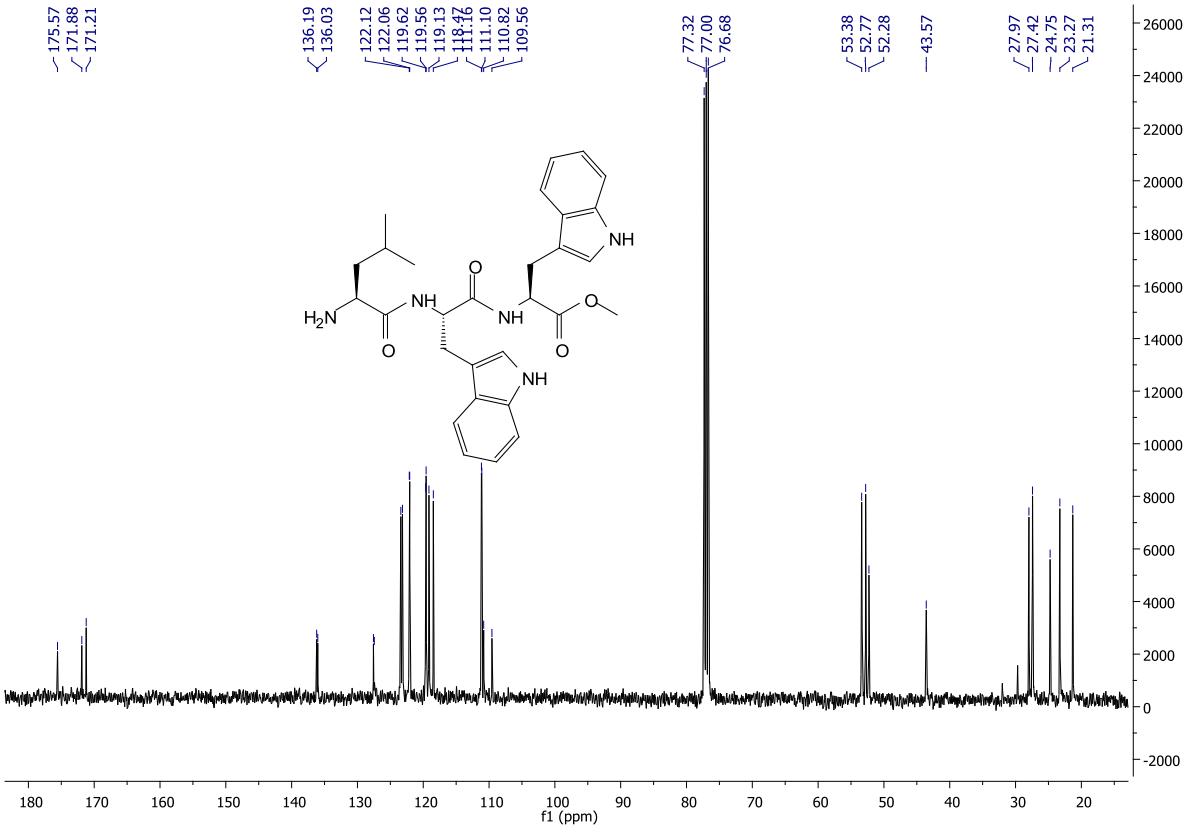
NH
NH
O
O
O
NH
f1 (ppm)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122.06
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111.10
110.82
109.56
77.32
77.00
76.68
53.38
52.77
52.28
43.57
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23.27
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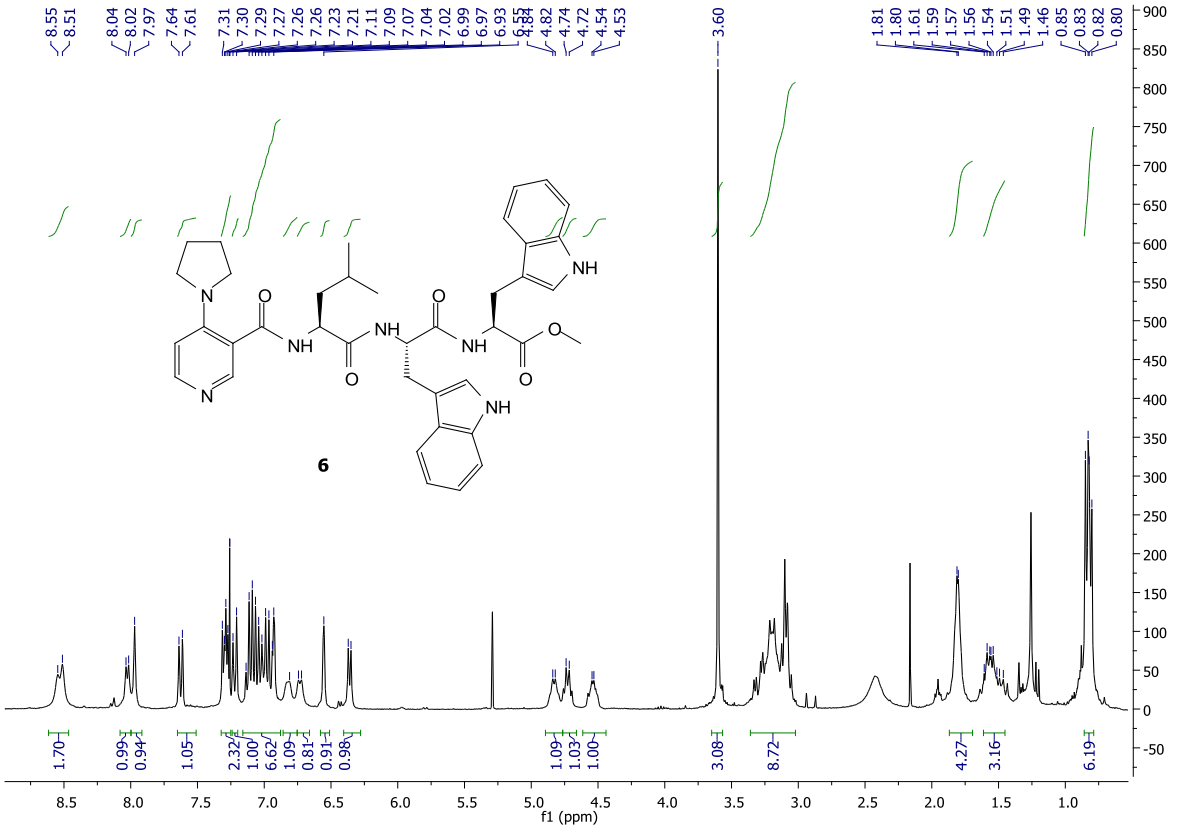
NH
O
O
O
O
H_2N
f1 (ppm)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7.26
7.23
7.21
7.11
7.09
7.07
7.04
7.02
6.99
6.97
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4.72
4.54
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3.60
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1.80
1.61
1.59
1.57
1.56
1.54
1.51
1.49
1.46
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0.83
0.82
0.80
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NH
NH
N
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O
O
O
O
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0.99
0.94
1.05
2.32
1.00
6.62
1.09
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1.00
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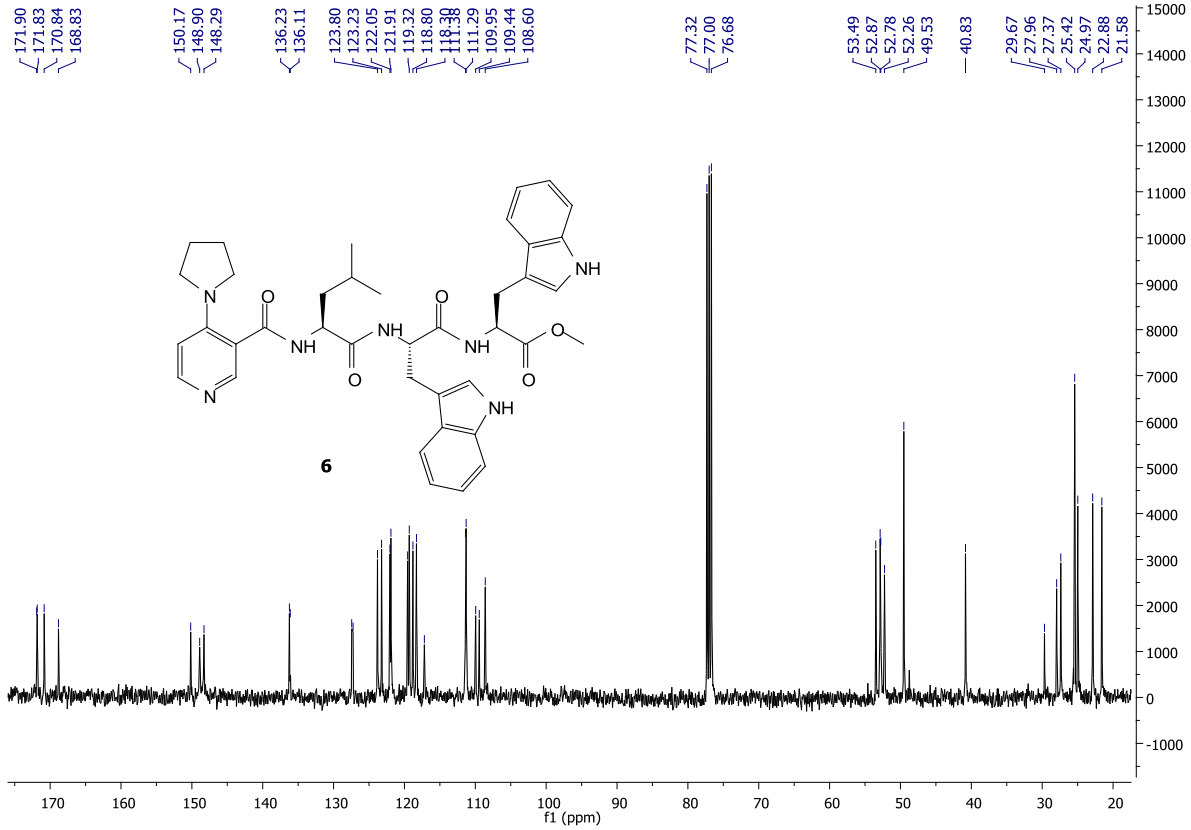
4.27
3.16
6.19
f1 (ppm)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148.29
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123.23
122.05
121.91
119.32
118.80
118.30
111.38
111.29
109.95
109.44
108.60
77.32
77.00
76.68
53.49
52.87
52.78
52.26
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29.67
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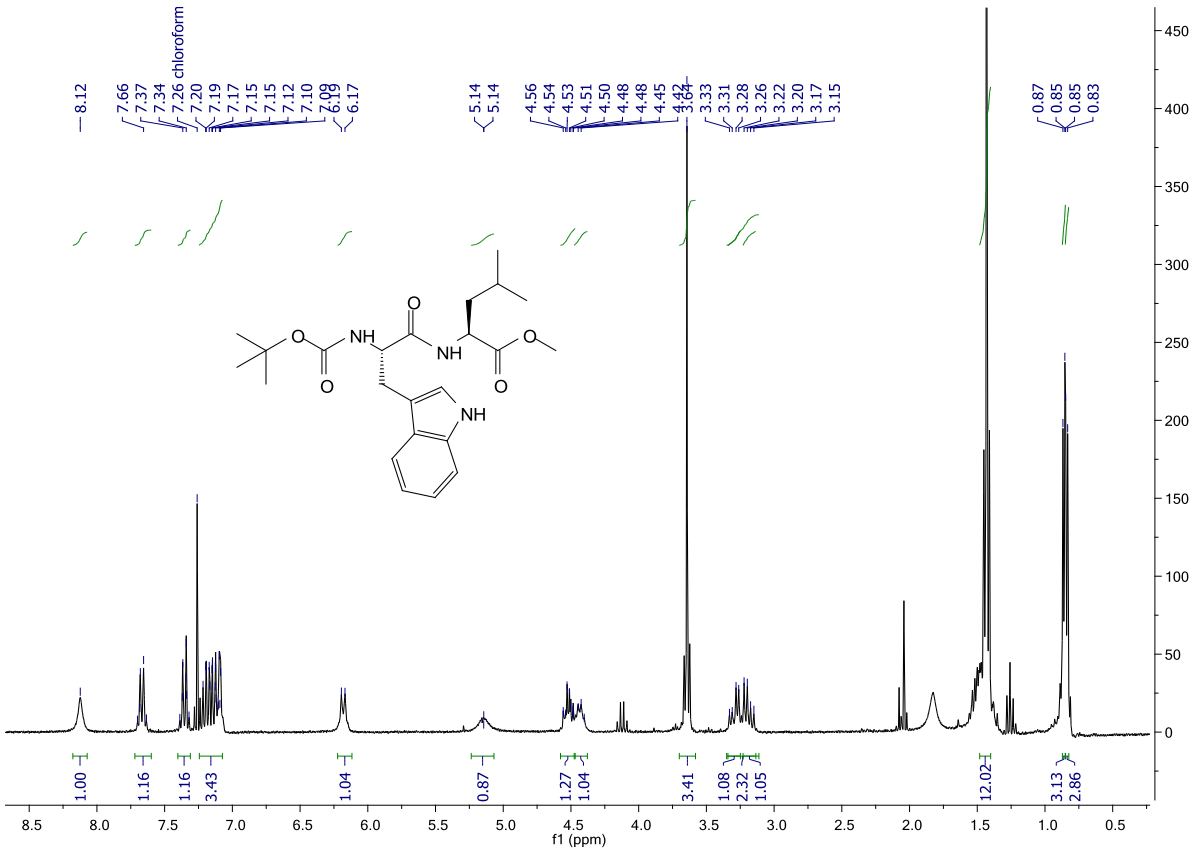
25.42
24.97
22.88
21.58
f1 (ppm)

6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7.15
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7.10
7.09
6.19
6.17
5.14
5.14
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4.53
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4.50
4.48
4.48
4.45
4.42
3.64
3.33
3.31
3.28
3.26
3.22
3.20
3.17
3.15
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0.85
0.85
0.83
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1.16
1.16
3.43
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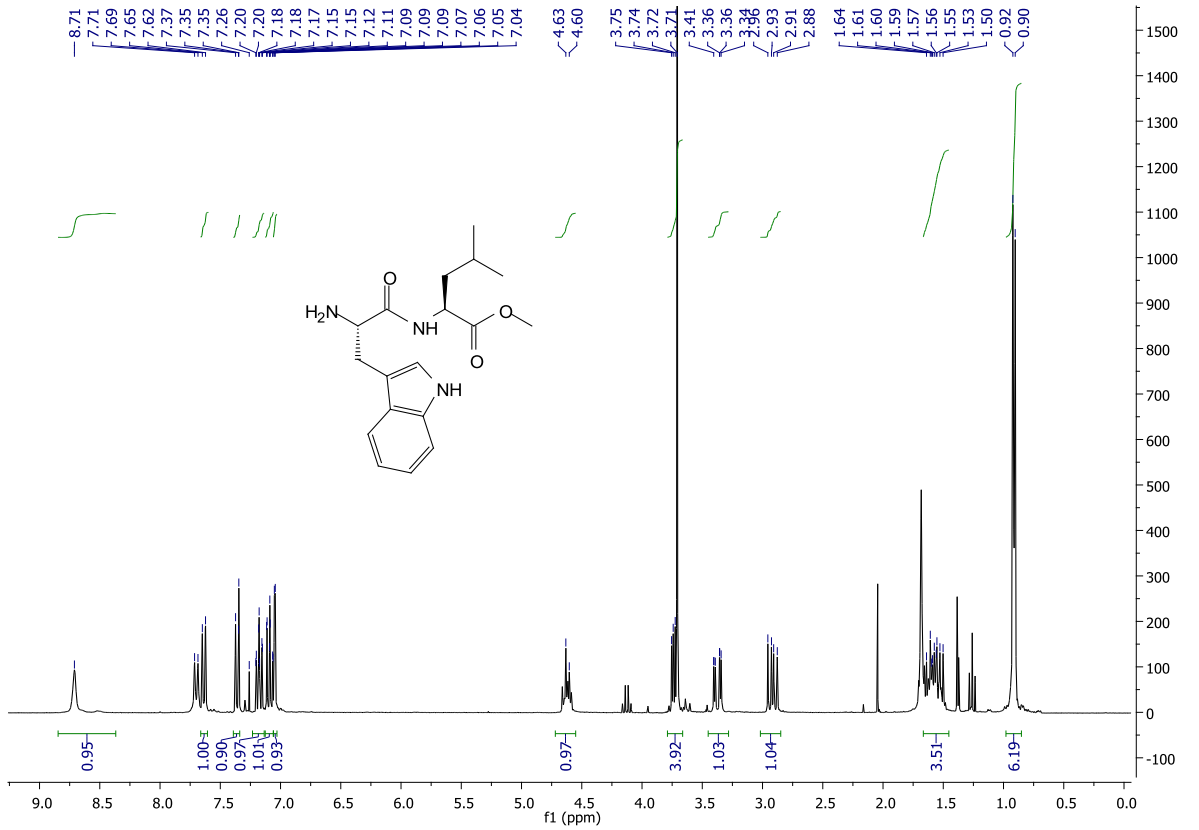
2.86
f1 (ppm)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7.17
7.15
7.15
7.12
7.11
7.09
7.09
7.09
7.07
7.06
7.05
7.04
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NH
O
O
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1.04
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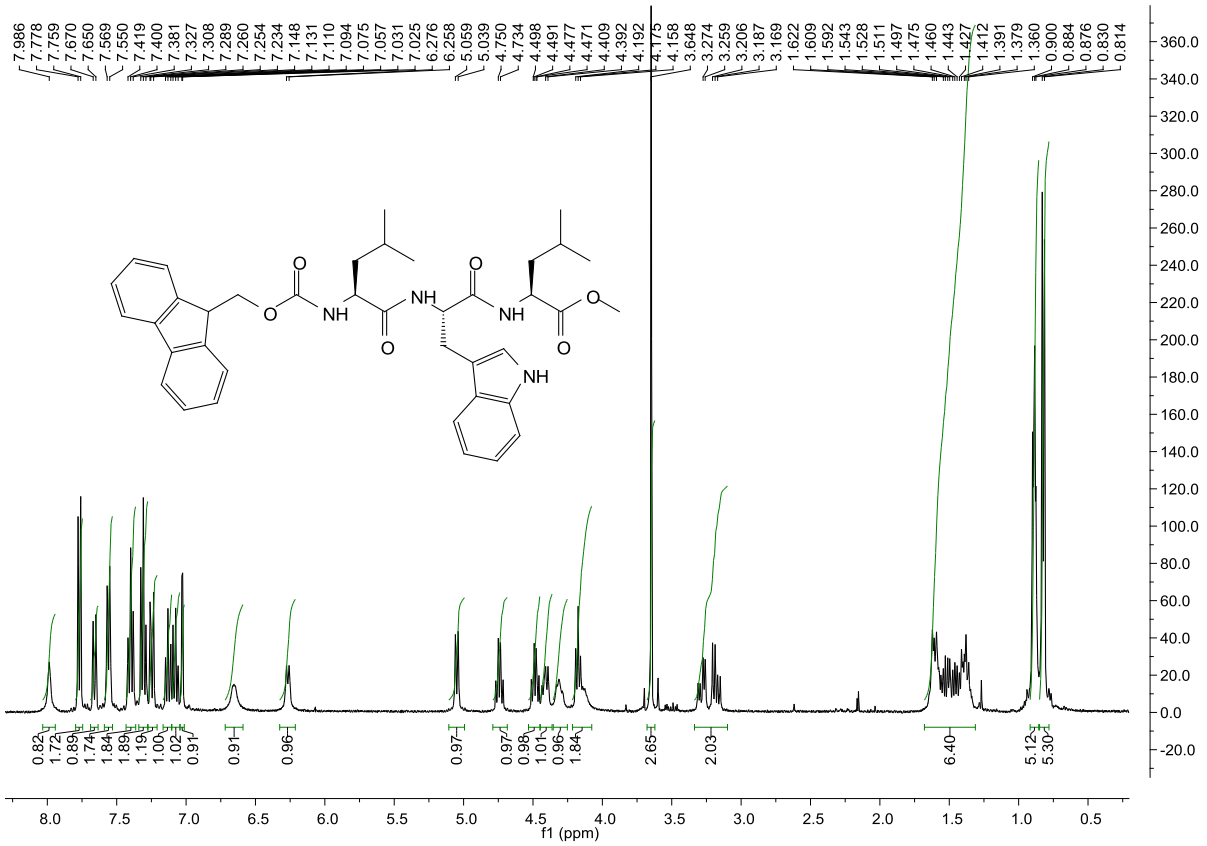
f1 (ppm)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7.260
7.254
7.234
7.148
7.131
7.110
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7.057
7.031
7.025
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4.158
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3.169
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1.543
1.528
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1.497
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1.460
1.443
1.427
1.412
1.391
1.379
1.360
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0.876
0.830
0.814
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O
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NH
O
NH
O
O
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1.74
1.84
1.89
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1.02
0.91
0.91
0.96
0.97
0.97
0.98
1.01
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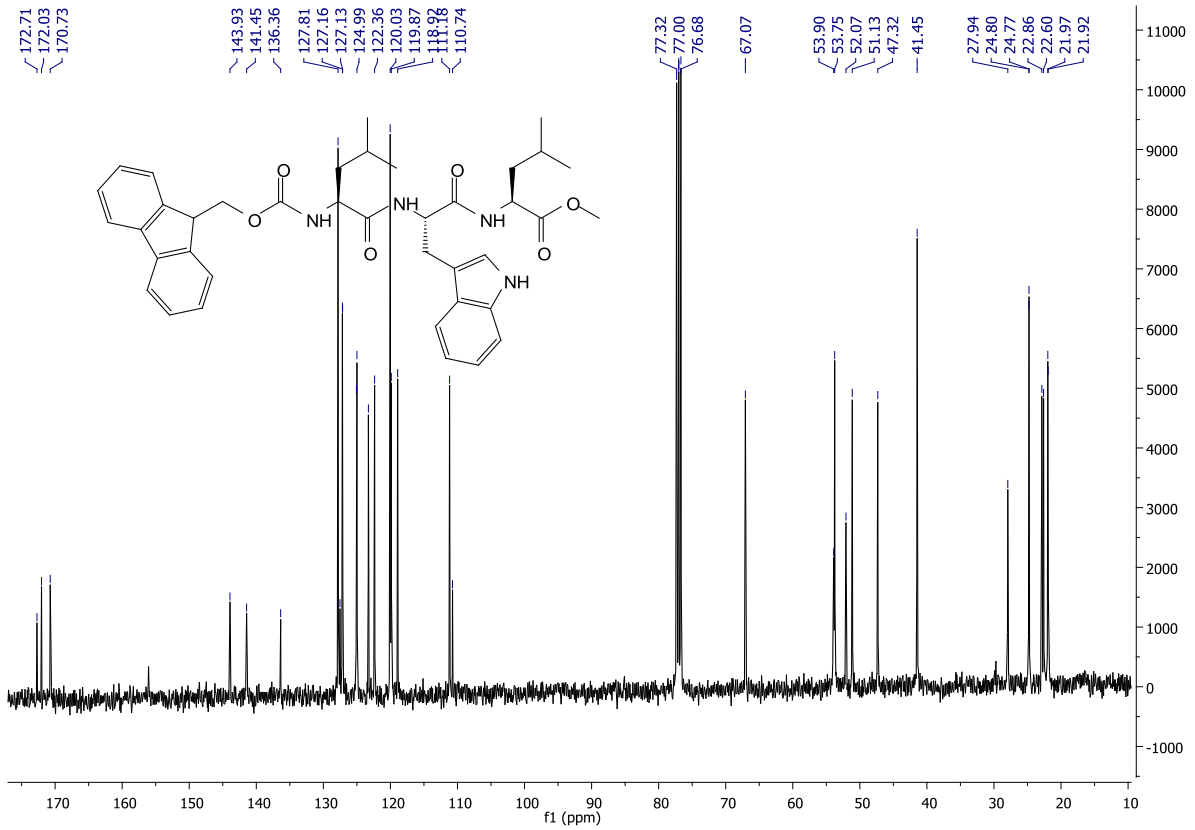
2.65
2.03
6.40
5.12
5.30
f1 (ppm)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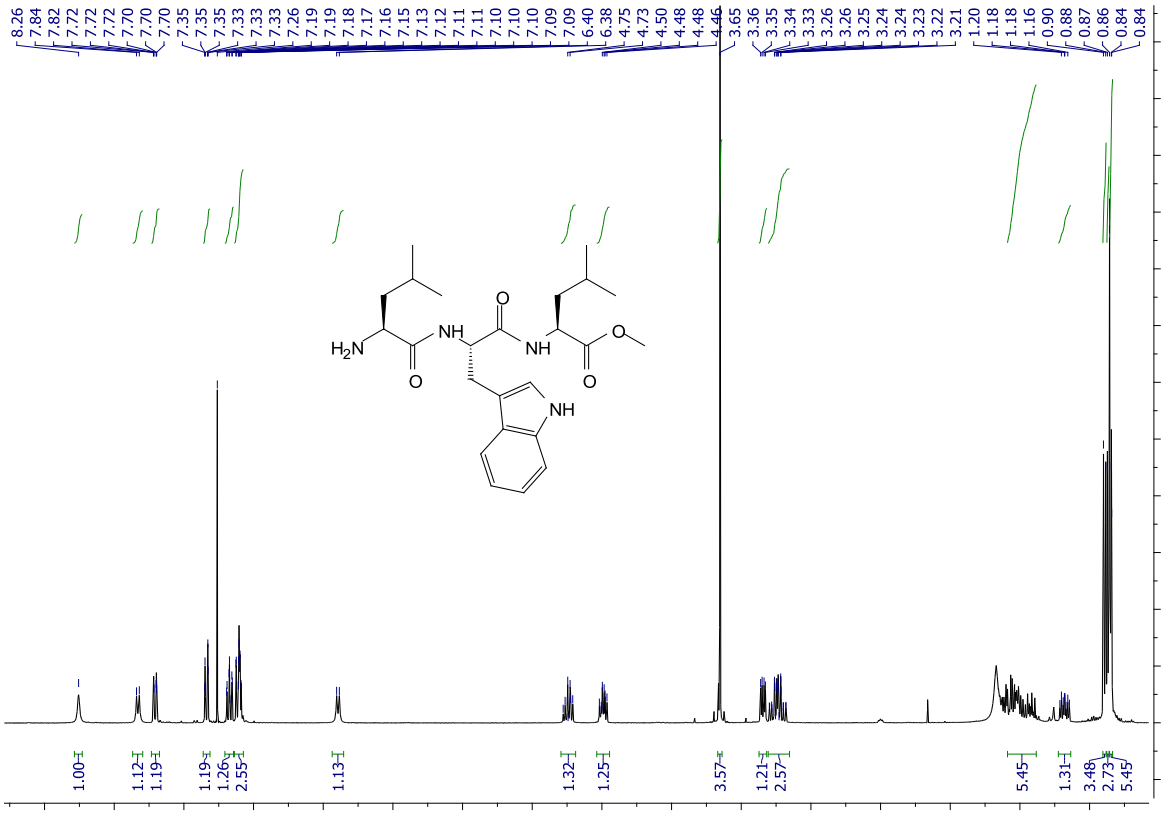
22.86
22.60
21.97
21.92
f1 (ppm)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3.25
3.24
3.24
3.23
3.22
3.21
1.20
1.18
1.18
1.16
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0.87
0.86
0.84
0.84
1.00
1.12
1.19
1.19
1.26
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1.32
1.25
3.57
1.21
2.57
5.45
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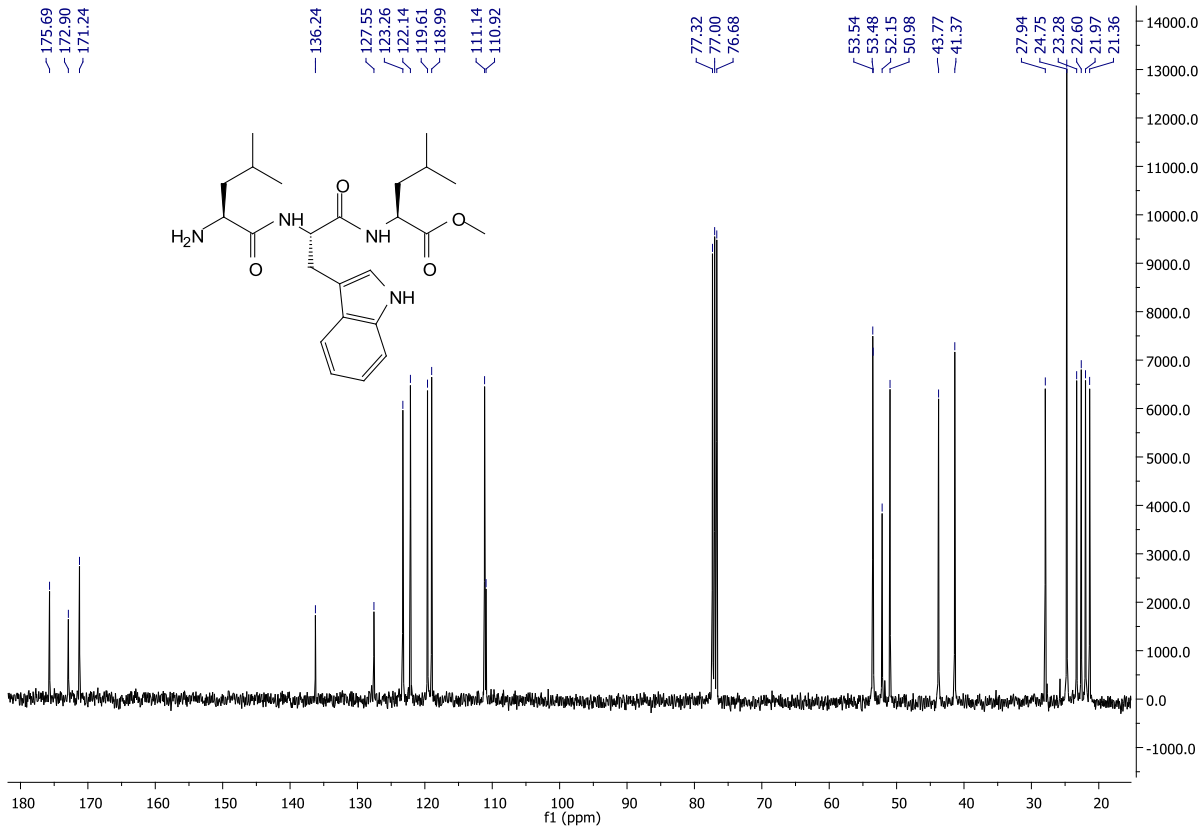
3.48
2.73
5.45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123.26
122.14
119.61
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111.14
110.92
77.32
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76.68
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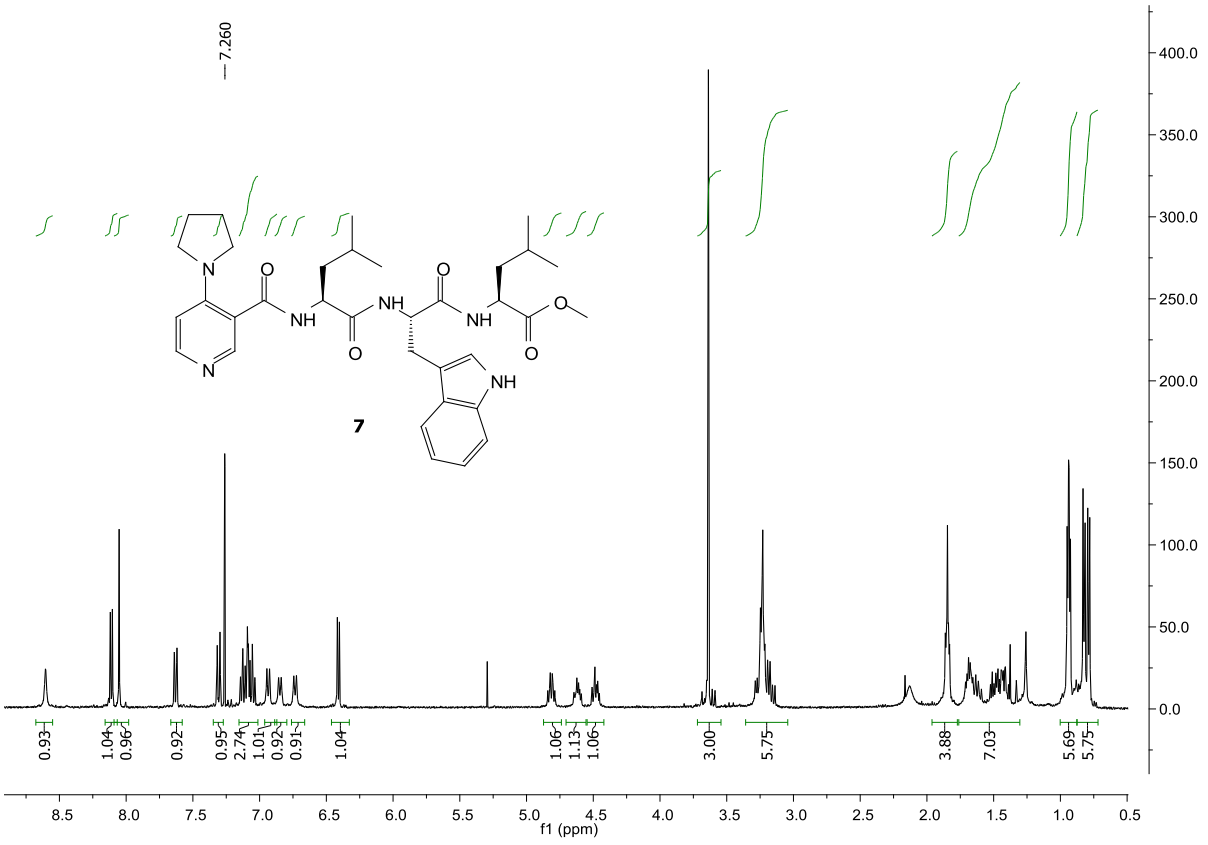
23.28
22.60
21.97
21.36
f1 (ppm)


7.260
7
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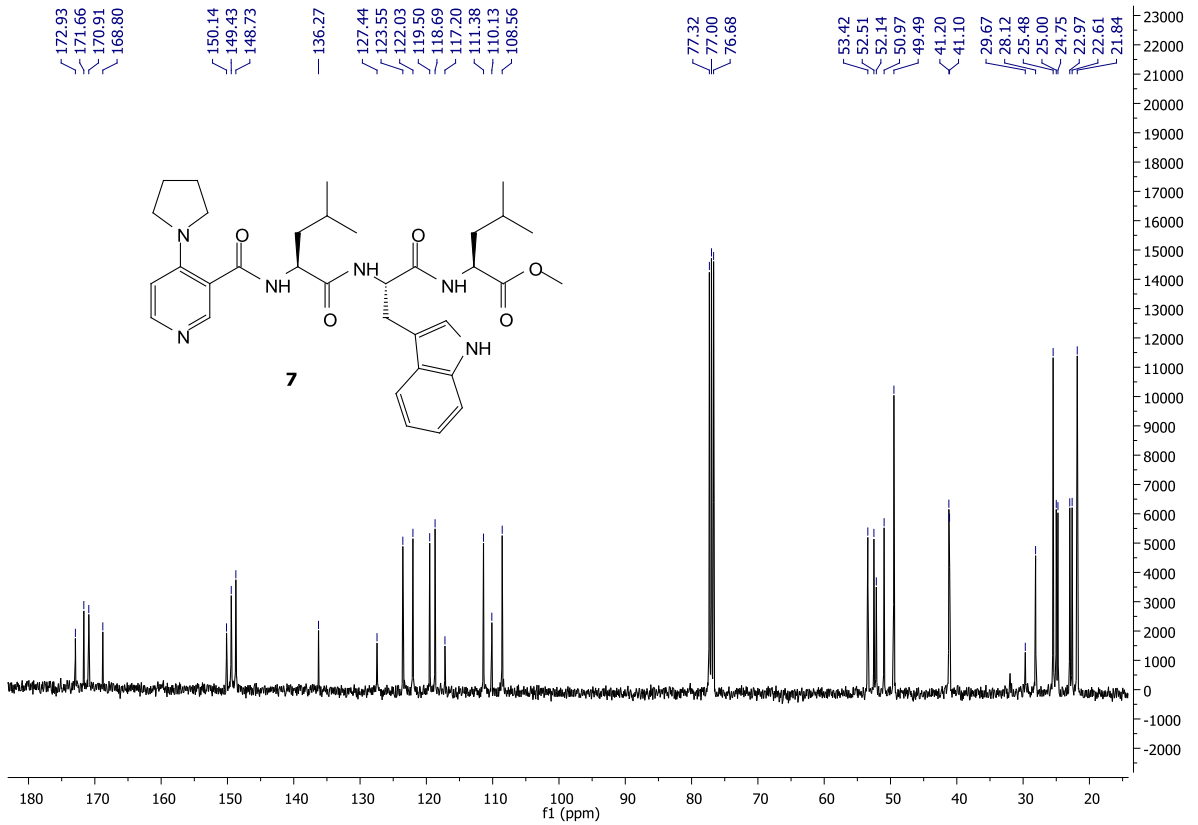
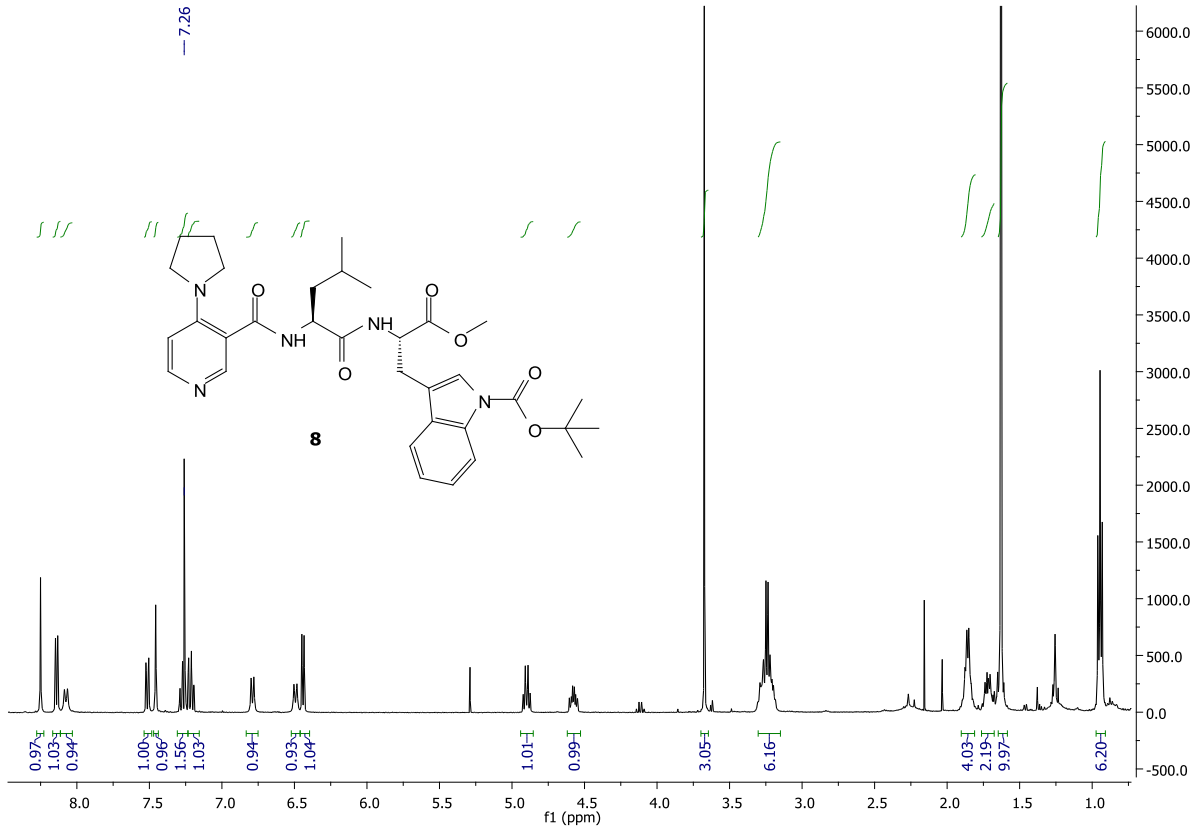
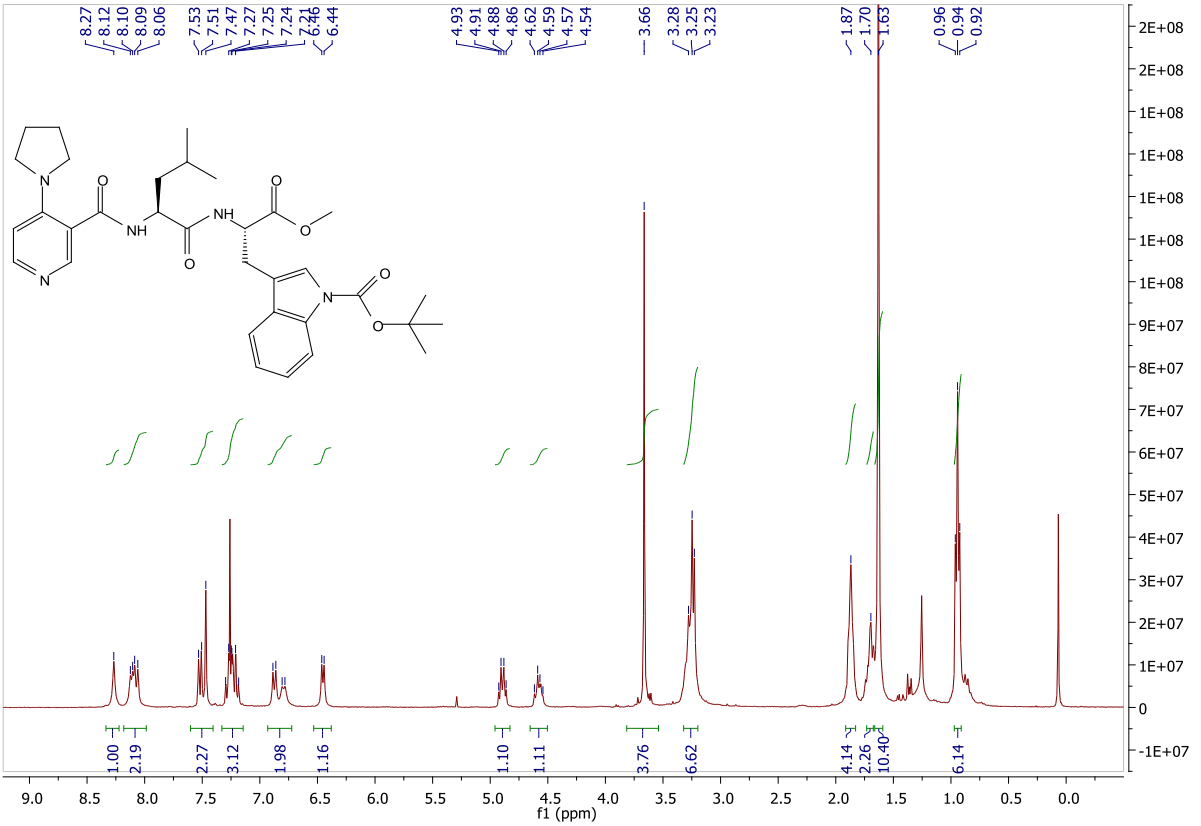


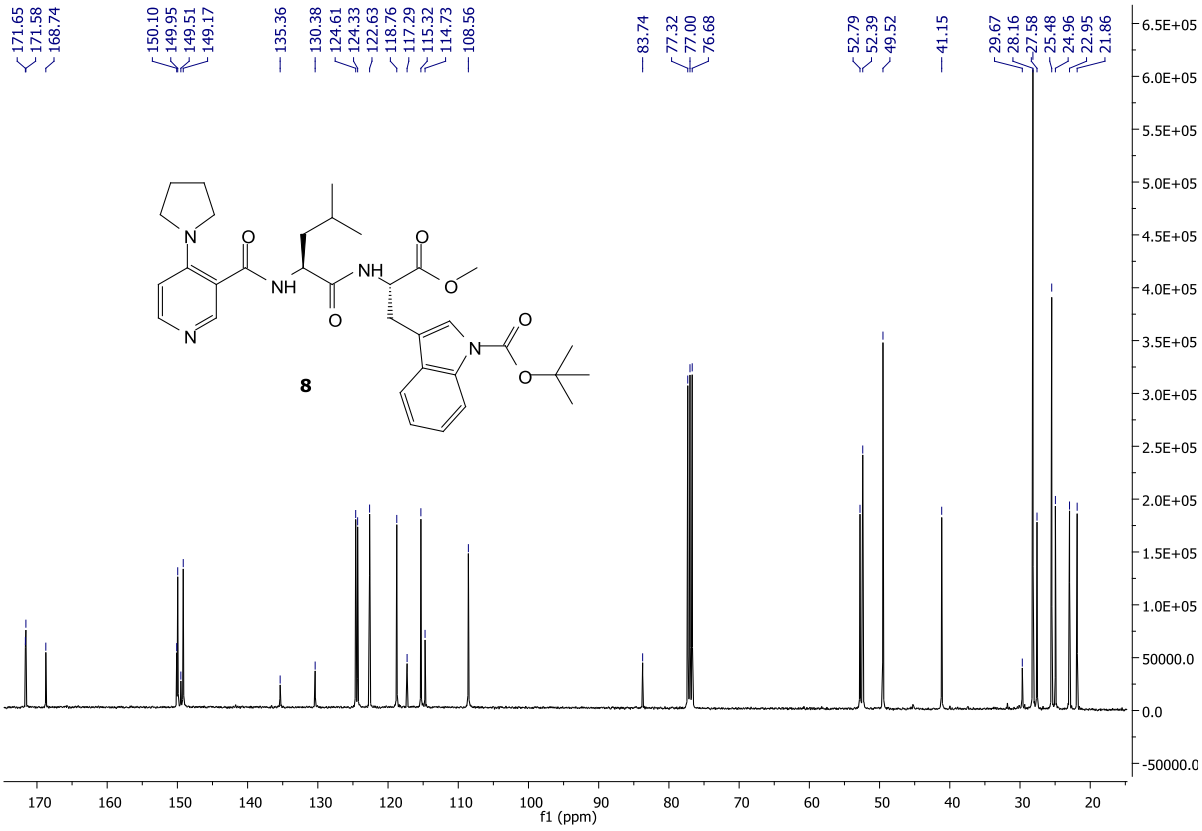
Sample 1: used for ^{1}H NMR data (400 MHz) in $CDCl_3$



Sample 2 of compound 8: ^{1}H NMR (300 MHz) in $CDCl_3$



Sample 1 of compound 8: ^{13}C NMR (100.6 MHz)



4) Kinetic Resolution (KR) Experiments and HPLC Data

General procedure for the catalytic kinetic resolution of *sec*-alcohols:

To a stirred solution of the *sec*-alcohol (0.5 mmol), catalyst (0.025 mmol), and triethylamine (0.45 mmol) in DCM (2 mL) at −78 °C, was added *iso*-butyric anhydride (0.35 mmol). After 3 hrs, the reaction was quenched with MeOH (1 mL), which was followed by the addition of sat. $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer extracted with DCM (2 x 5 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The alcohol and ester mixture was purified by column chromatography using ethyl acetate/hexane (20/80). The isolated ester was hydrolysed using 1M NaOH in MeOH (2 mL). After 6 hrs, the solvent was removed *in vacuo* and the residue purified by column chromatography using ethyl acetate/hexane (50/50). Each sample was then subjected to HPLC analysis.

Determination of enantiomeric excesses, conversion and selectivities:

All unreacted alcohols recovered from kinetic resolutions using catalyst were found to be enriched in the (*R*)-enantiomer, as determined by the signs of the optical rotations, while esters were enriched in the (*S*)-enantiomer (also determined by measuring optical rotations). The enantiomeric excess of the unreacted alcohol and the ester (after hydrolysis) were determined by analytical chiral HPLC (Chiracel OD, Chiralpak AD, or Chiralpak IC).

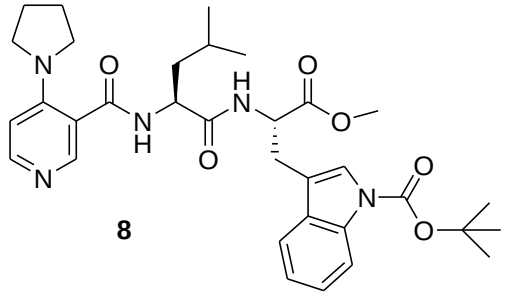
Selectivity was calculated according to:

$$S = \frac{\ln\left((1 - C_{HPLC})(1 - ee_A\right)}{\ln\left((1 - C_{HPLC})(1 + ee_A)\right)}$$

Where ee_A refers to the ee of unreacted alcohol and C_{HPLC} calculated according to:

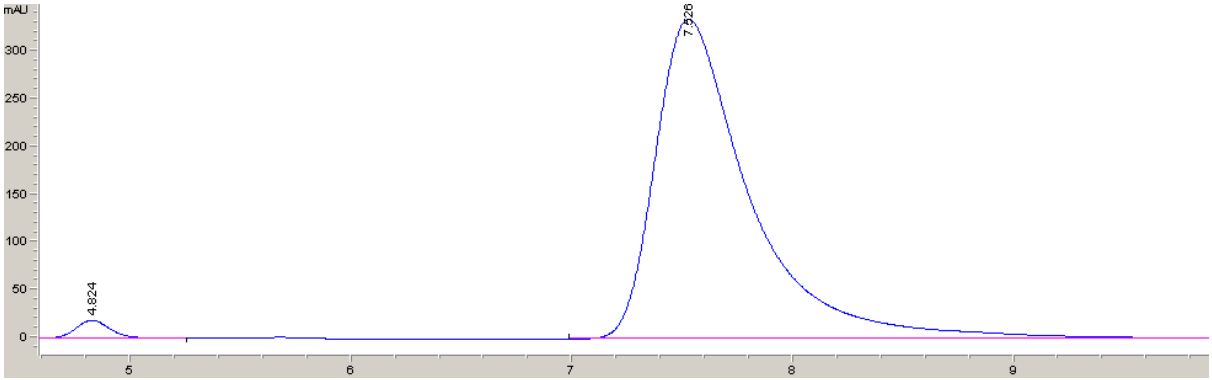
$$C_{HPLC} = \frac{ee_A}{ee_A + ee_E}$$

Now follows the data for the Tables in the text + the HPLC data:



8

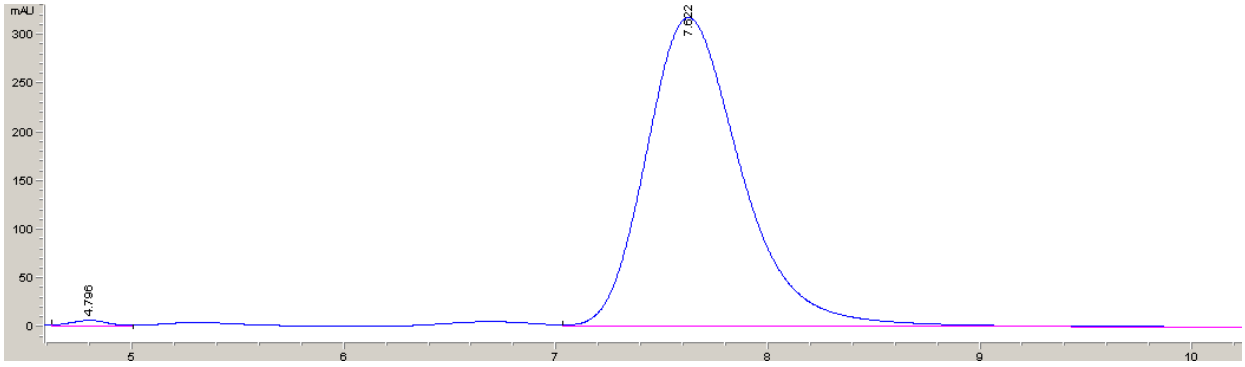
Sample 1



30% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
4.824	203.38611	1.9552
7.526	1.01990e4	**98.0448**

Sample 2



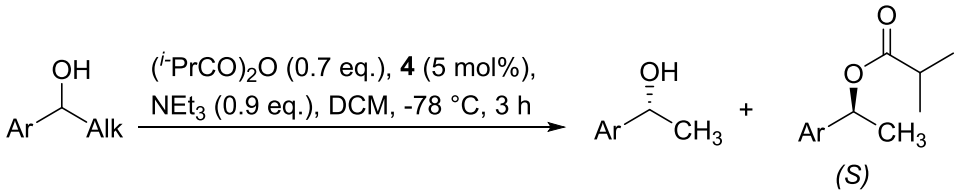
30% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

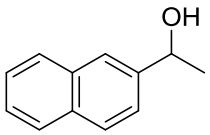
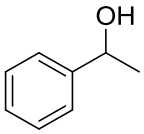
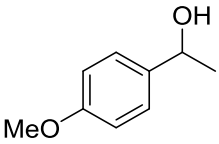
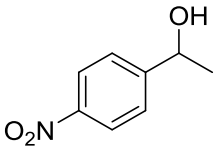
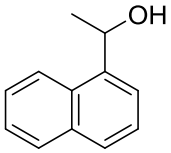
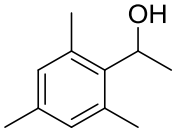
Retention time (min)	Area (mAU*s)	Area %
4.796	77.18579	0.7713

7.622	9930.67676	**99.2287**

HPLC Data

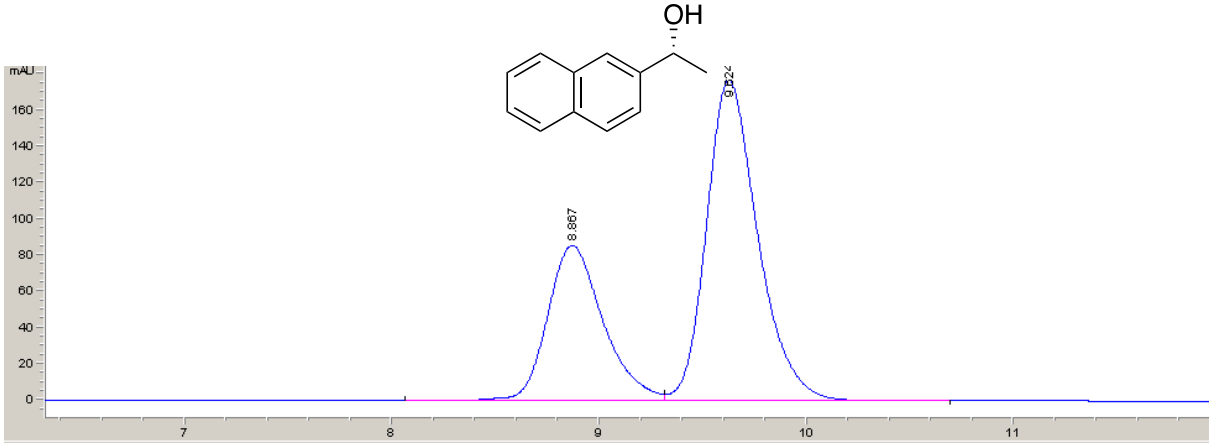
Table 1. The kinetic resolution of various racemic *sec*-alcohols catalysed by **4**.



Entry	Substrate	C[a]	ee[b] alcohol	ee[c] Ester	s[d]	Configuration[e]
1		34	31.1	59.4	5.3	(*S*)
2		49	38.6	40.1	3.3	(*S*)
3		42	21.9	30.3	2.3	(*S*)
4		63	12.4	7.1	1.3	(*S*)
5		60	48.4	32.2	3.0	(*S*)
6		27	17.3	46.3	3.2	(*S*)

[a] Conversion C = 100 x (ee of recovered alcohol)/(ee of recovered alcohol + ee of ester).
[b] ee of recovered alcohol as measured by chiral HPLC on an AD, OD, or IC column.
[c] ee of the hydrolysed ester (2M NaOH in MeOH/H_2O as measured on AD, OD, or IC column.
[d] Selectivity factor $s = \frac{\ln(1-C)(1-ee)}{\ln(1-C)(1+ee)}$ where ee refers to the recovered alcohol.
[e] The absolute configuration of the faster-reacting enantiomer (ester) and determined by a comparison of $[\alpha]_D^{20}$ values with those reported in the literature.

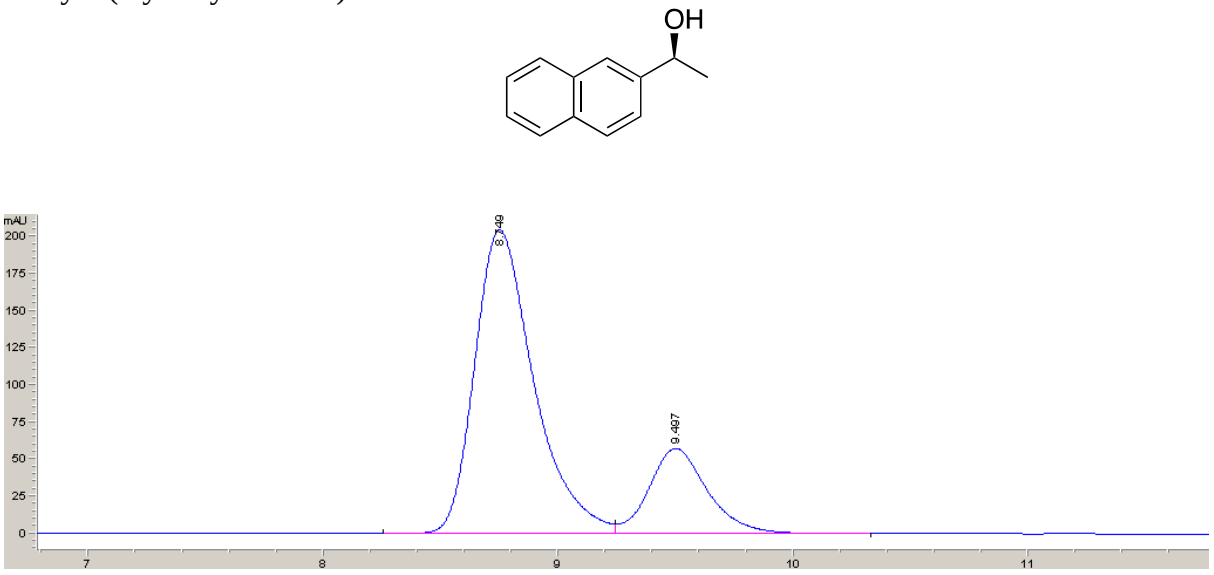
Entry 1 (Recovered alcohol)



9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
8.867	1596.50647	34.4301
9.624	3040.43677	65.5699

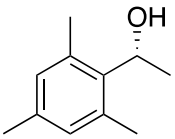
Entry 1 (Hydrolysed ester)

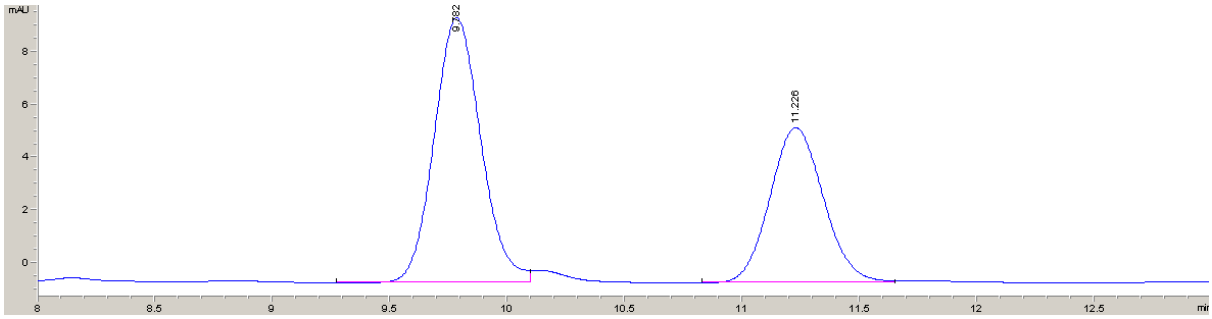


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
8.749	3600.12500	78.3763
9.497	993.25702	21.6237

Entry 6 (Recovered alcohol)

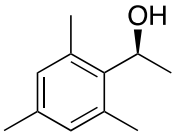


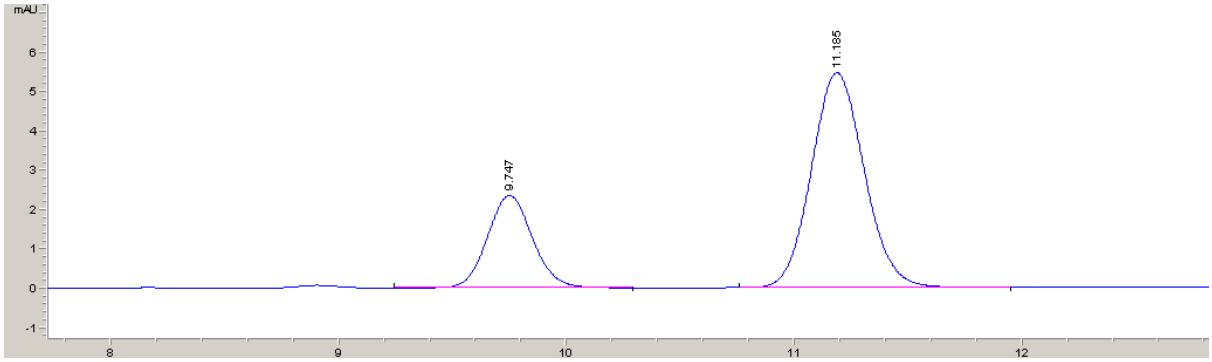


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
9.782	139.53105	59.8342
11.226	93.66512	40.1658

Entry 6 (Hydrolysed ester)

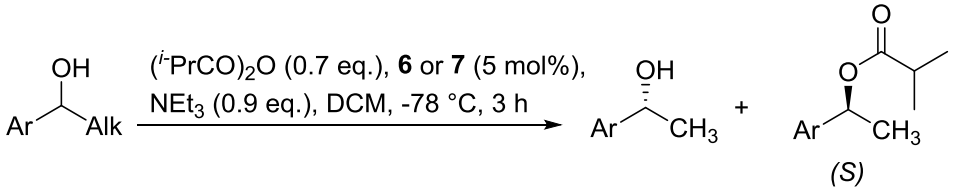


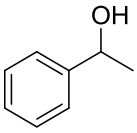
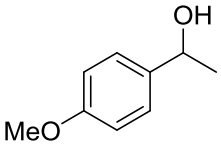
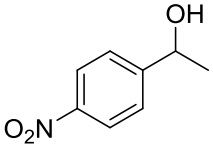
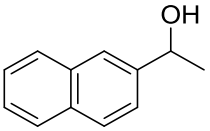
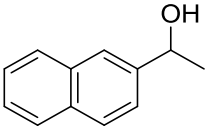
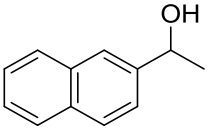


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
9.747	32.47028	26.9310
11.185	88.09808	73.0690

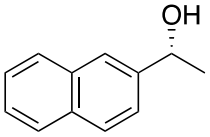
Table 3 The kinetic resolution of various racemic *sec*-alcohols catalysed by **6** or **7**.

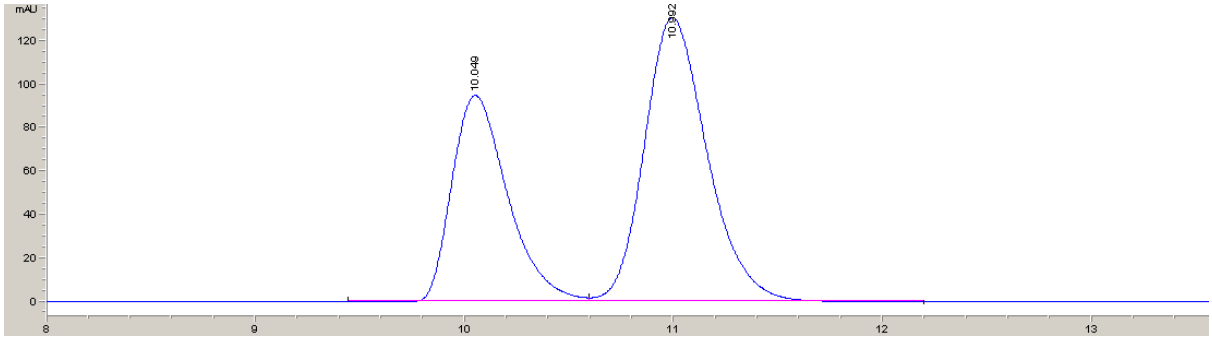


Entry	Cat	Substrate	C	ee[b] alcohol	ee[c] Ester	S[d]	Configuration[e]
1	**6**		28	10.7	28.2	2.0	(*S*)
2	**6**		35	12.1	22.3	1.8	(*S*)
3	**6**		53	7.6	6.7	1.2	(*S*)
4	**6**		51	21.6	21.1	1.9	(*S*)
5	**7**		5.8	3.2	52.5	3.3	(*S*)
6	**7**		46[f]	26.4	30.4	2.4	(*S*)

[a] Conditions = Alcohol (1.0 eq), cat (5 mol %), (*i*-PrCO)$_2$O(0.7 eq), NEt$_3$ (0.9 eq), −78 °C, DCM, 3 h.
[b] ee of recovered alcohol as measured by chiral HPLC on a AD, OD, or IC column.
[c] ee of the hydrolysed ester (2M NaOH in MeOH/H_2O as measured on an AD, OD, or IC column..
[d] Selectivity factor $s = \frac{\ln(1-C)(1-ee)}{\ln(1-C)(1+ee)}$ where ee refers to the recovered alcohol.
[e] The absolute configuration of the faster-reacting enantiomer (ester) and determined by a comparison of $[\alpha]_D^{20}$ values with those reported in the literature.
[f] T = 12 h

Entry 4 (Recovered alcohol)

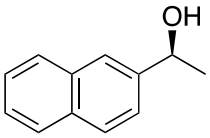


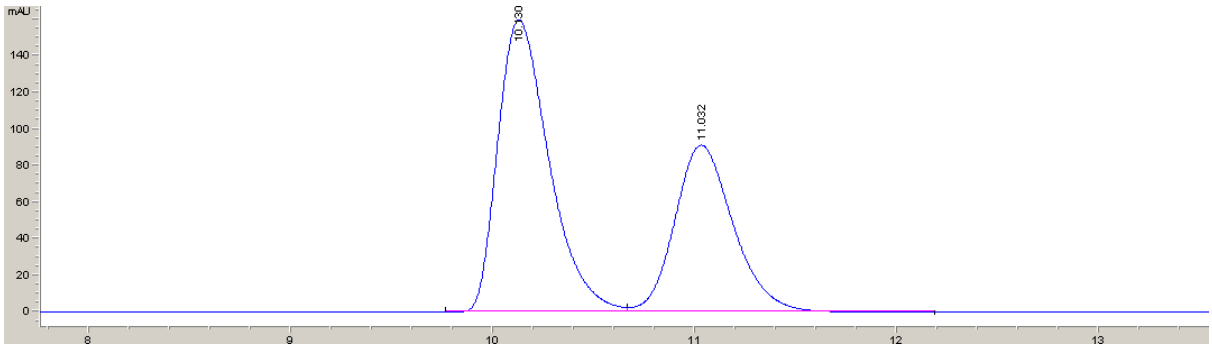


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.049	1759.00317	39.1974
10.992	2728.54565	60.8026

Entry 4 (Hydrolysed ester)

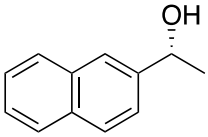


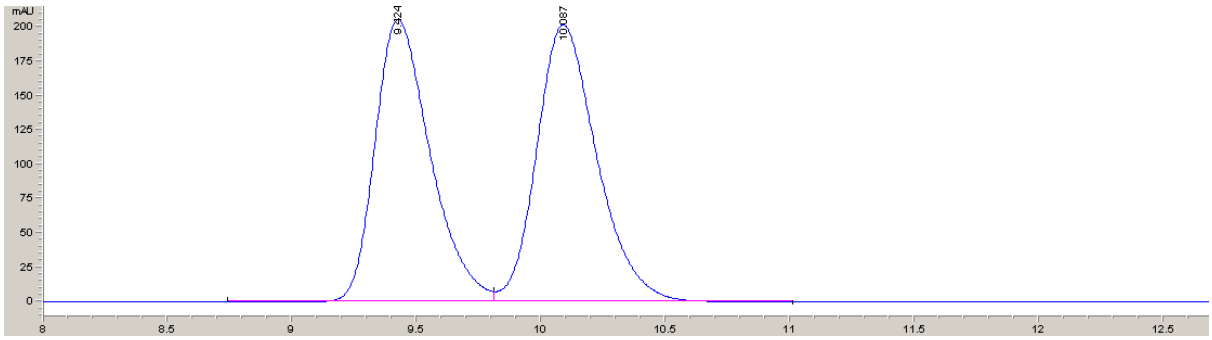


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.130	2819.36963	60.5382
11.032	1837.80481	39.4618

Entry 5 (Recovered alcohol)

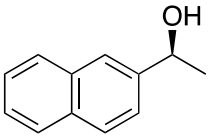


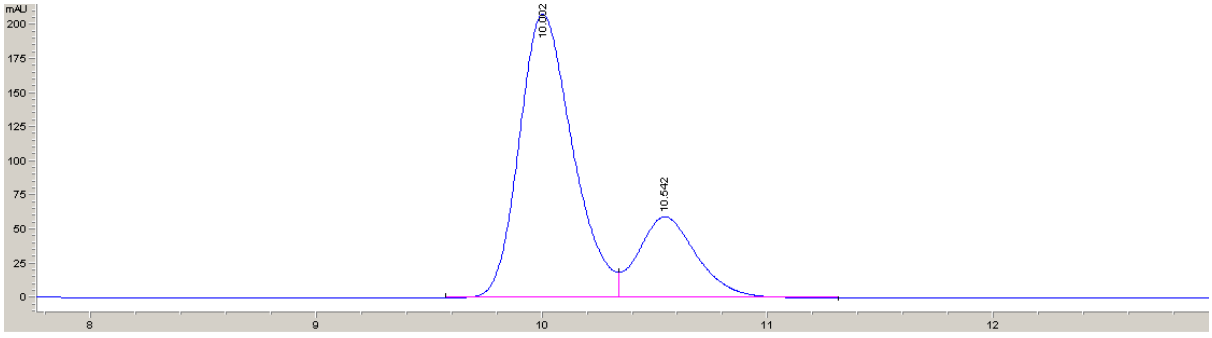


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
9.424	3172.42944	48.3537
10.087	3388.44897	51.6463

Entry 5 (Hydrolysed ester)

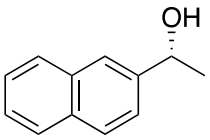


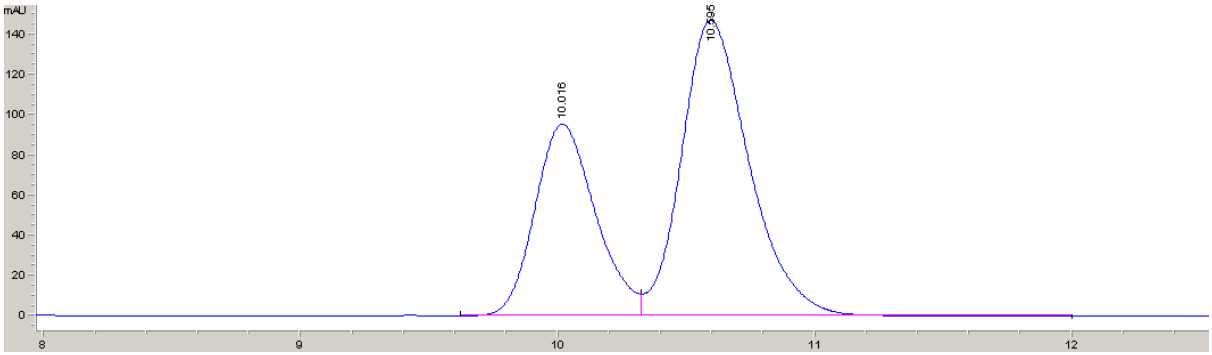


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.002	3410.65039	76.2492
10.542	1062.38318	23.7508

Entry 6 (Recovered alcohol)

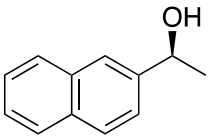


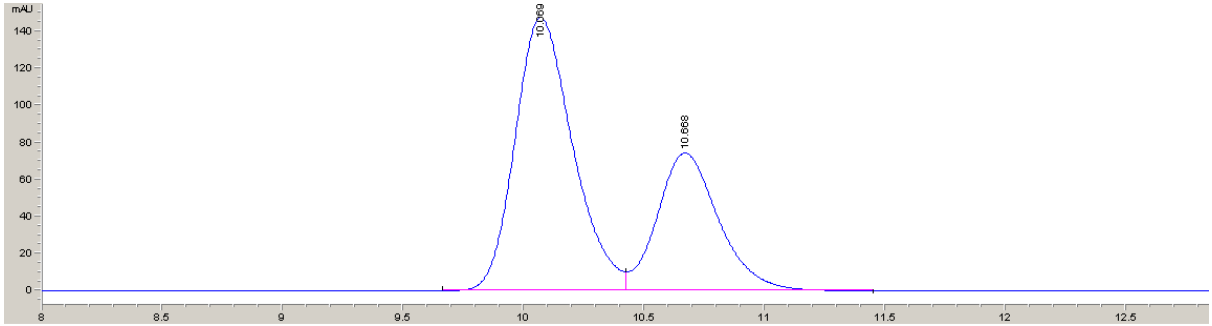


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.016	1564.62598	36.7764
10.595	2689.79956	63.2236

Entry 6 (Hydrolysed ester)

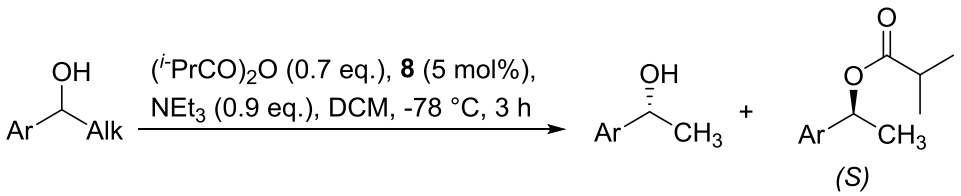


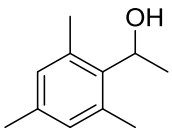
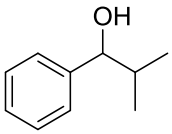
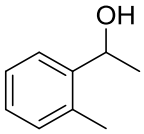
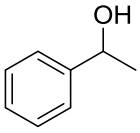
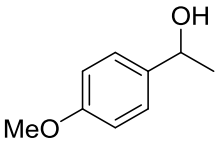
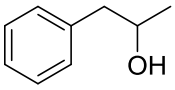
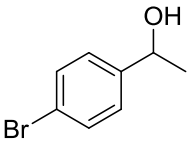
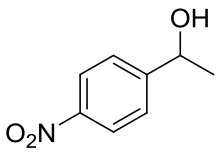


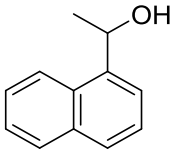
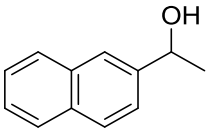
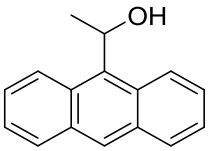
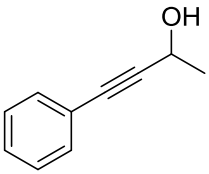
9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.069	2457.36670	65.1995
10.668	1311.62744	34.8005

Table 4 The kinetic resolution of racemic *sec*-alcohols catalysed by **8**.

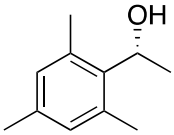


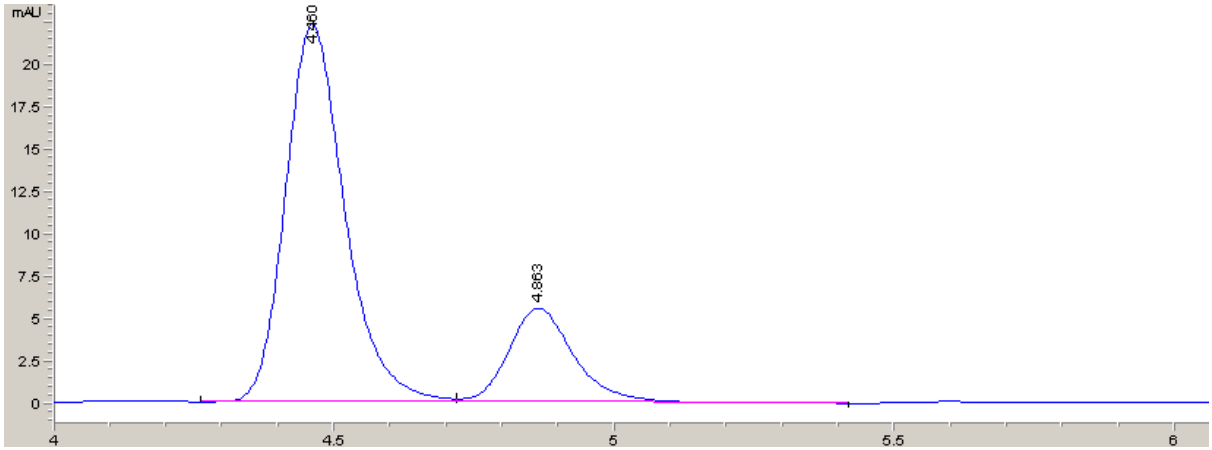
entry[a]	Substrate	C_{HPLC}[b]	Ee (alcohol)[c]	ee (ester)	s-value[d]	Configuration[e]
1		44	57.1	72.0	10.8	S
2		50	68.5	68.8	10.9	S
3		44	53.8	69.9	9.6	S
4		42	50.2	69.1	8.9	S
5		30	29.4	68.0	7.0	S
6		20	16.2	65.3	5.6	S
7		45	35.7	43.1	3.5	S
8		36	13.9	24.6	1.9	S

9		45	59.3	71.1	10.7	S
10		50	63.2	62.4	8.1	S
11		56	50.6	39.8[f]	3.7	S
12		11	3.6	30.6	1.9	S

[a] Conditions = Alcohol (1.0 eq), cat (5 mol %), (*i*-PrCO)$_2$O(0.7 eq), NEt$_3$ (0.9 eq), −78 °C, DCM, 3 h.
[b] ee of recovered alcohol as measured by chiral HPLC on a AD, OD, or IC column.
[c] ee of the hydrolysed ester (2M NaOH in MeOH/H_2O as measured on a AD, OD, or IC column.
[d] Selectivity factor $s = \frac{\ln(1-C)(1-ee)}{\ln(1-C)(1+ee)}$ where ee refers to the recovered alcohol.
[e] The absolute configuration of the faster-reacting enantiomer (ester) and determined by a comparison of $[\alpha]_D^{20}$ values with those reported in the literature.
[f] Ester not hydrolysed but measured directly.

Entry 1 (Recovered alcohol)

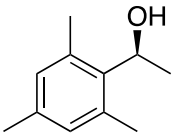


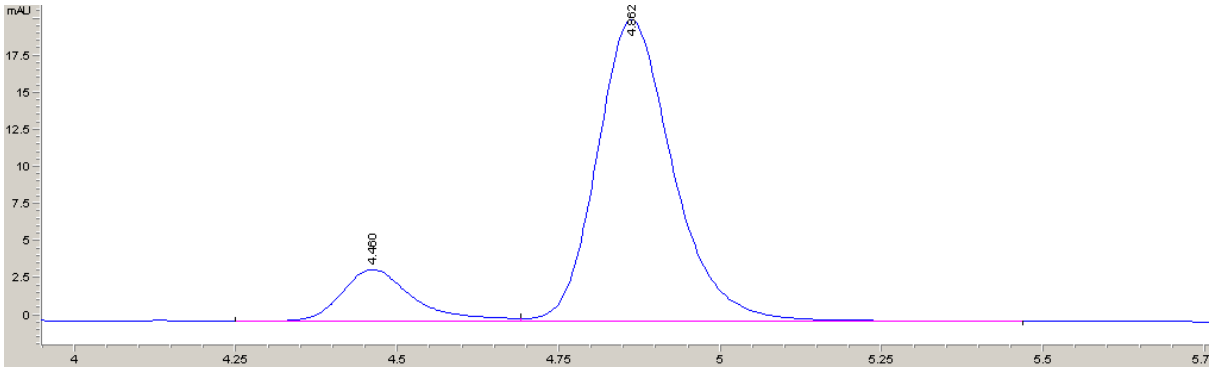


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
4.460	164.16508	78.2677
4.863	45.58303	21.7323

Entry 1 (Hydrolysed ester)

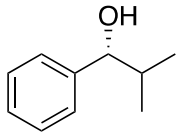


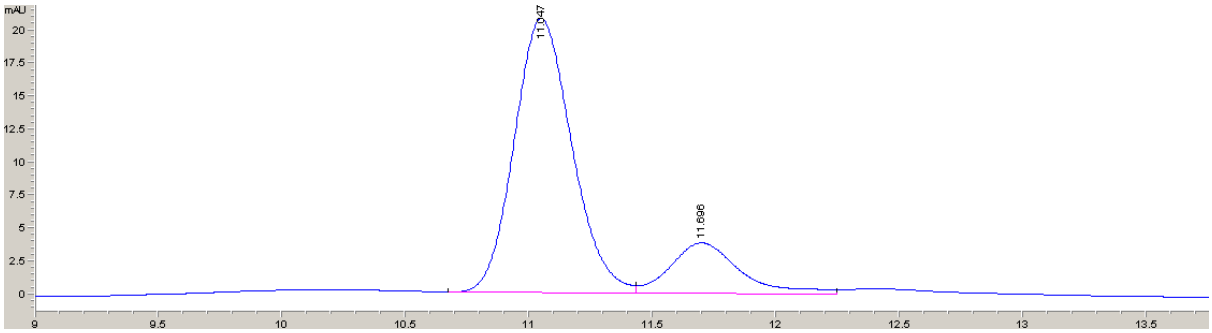


2.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
4.460	27.16413	13.9750
4.862	167.21220	86.0250

Entry 2 (Recovered alcohol)

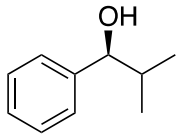


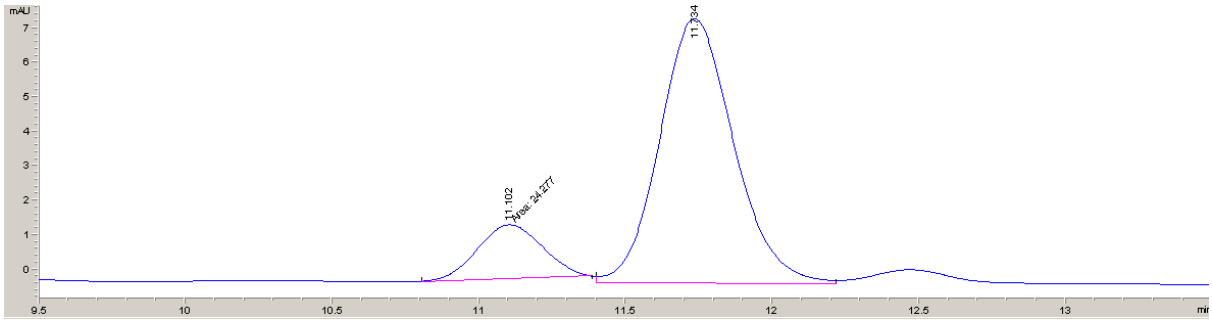


2.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
11.047	337.32312	81.5421
11.696	76.35664	18.4579

Entry 2 (Hydrolysed ester)

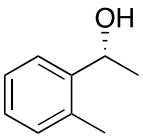


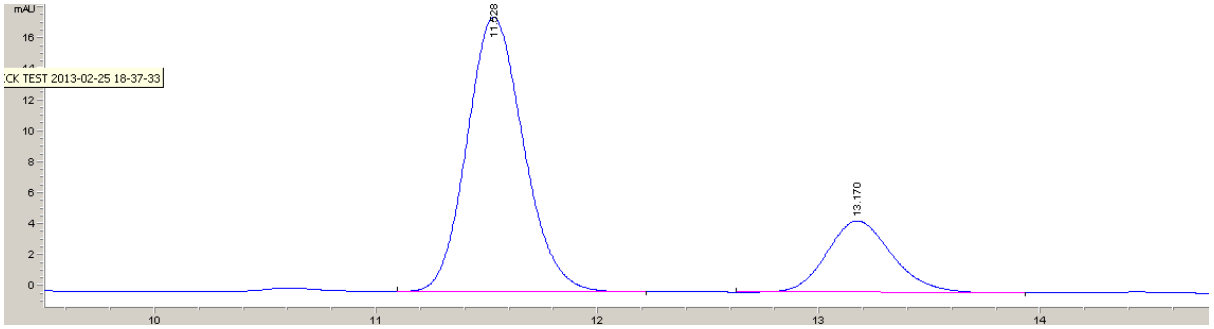


2.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
11.102	24.27703	15.2270
11.734	135.15681	84.7730

Entry 3 (Recovered alcohol)

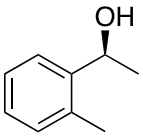


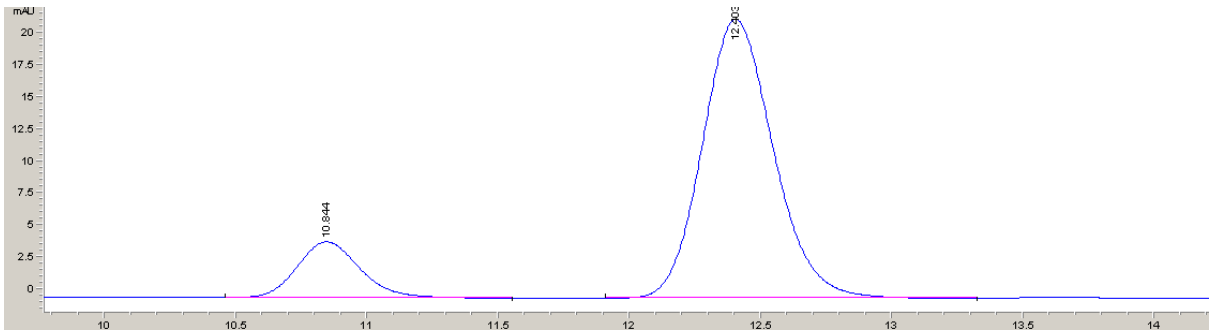


2.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
11.528	314.66922	76.9083
13.170	94.47910	23.0917

Entry 3 (Hydrolysed ester)

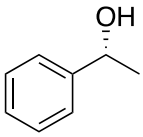


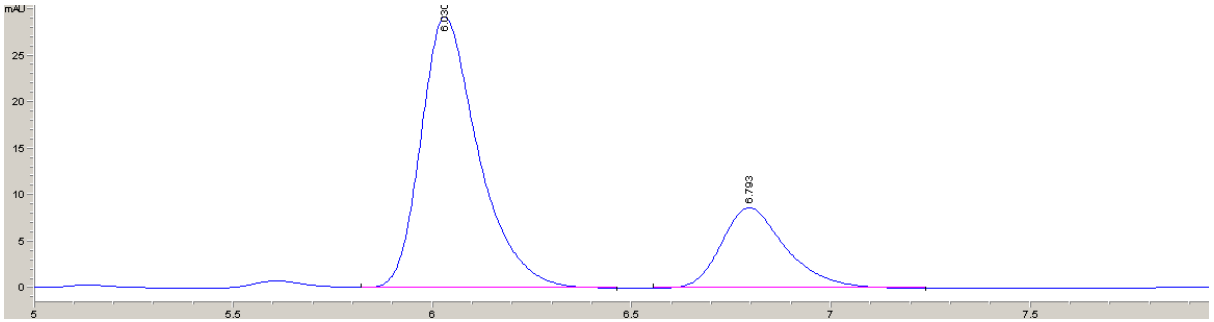


2.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.844	72.71805	15.0618
12.403	410.07892	84.9382

Entry 4 (Recovered alcohol) Sample 1

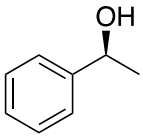


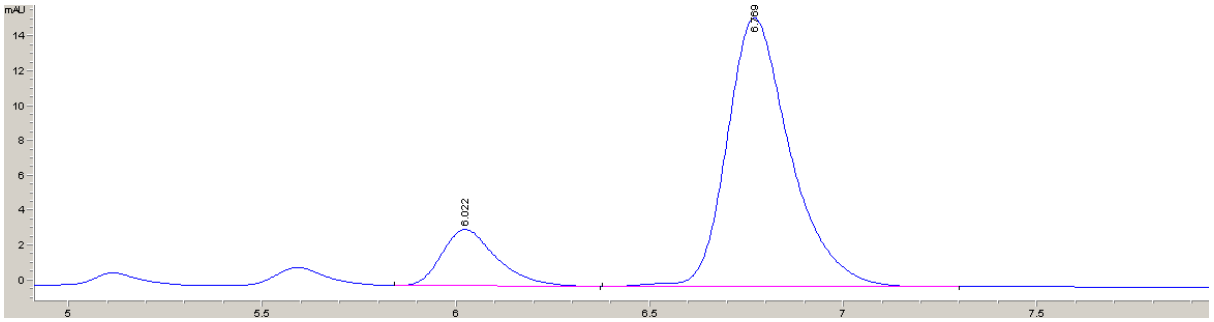


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
6.030	292.20432	75.1039
6.793	96.86226	24.8961

Entry 4 (Hydrolysed ester) Sample 1

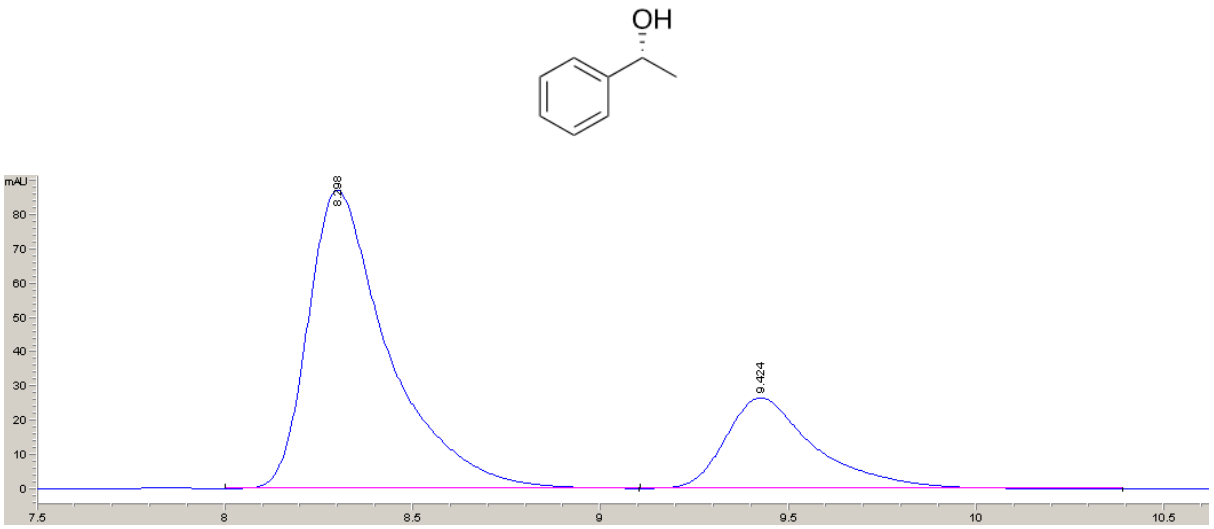




9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
6.022	32.02635	15.4692
6.769	175.00685	84.5308

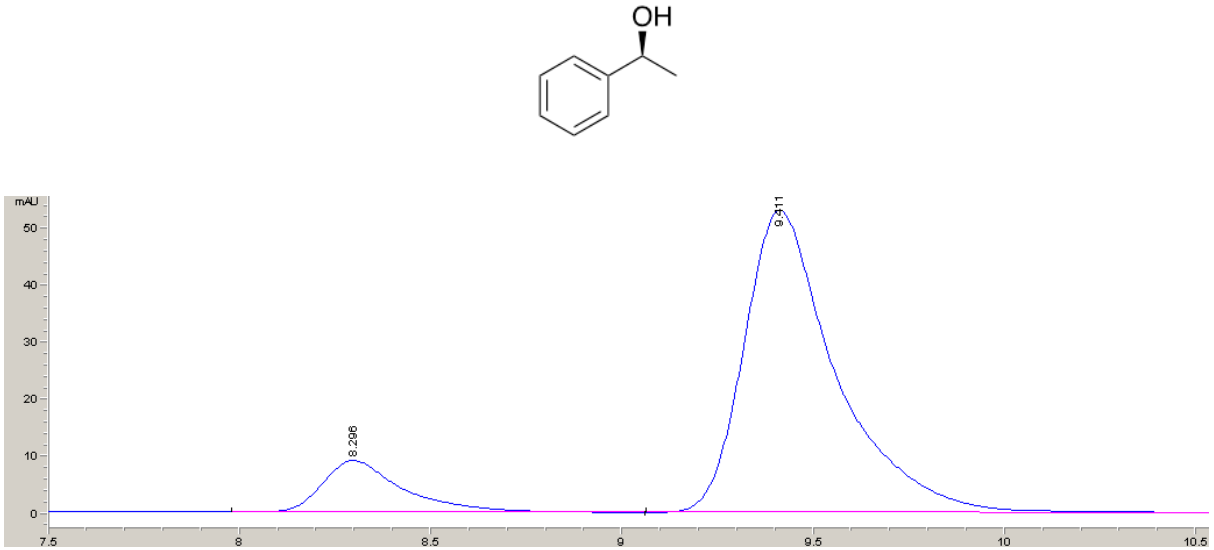
Entry 4 (Recovered alcohol) Sample 2



8% *i*-propanol in *n*-hexane, 0.75ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
8.298	1294.79944	74.7873
9.424	436.50912	25.2127

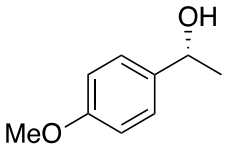
Entry 4 (Hydrolysed ester) Sample 2

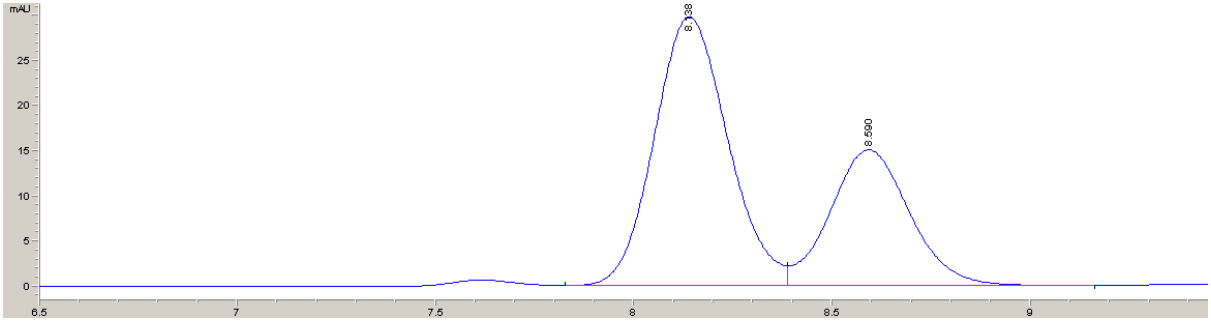


8% *i*-propanol in *n*-hexane, 0.75ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
8.296	132.42097	12.9680
9.411	888.71497	87.0320

Entry 5 (Recovered alcohol)

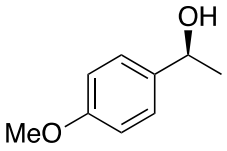


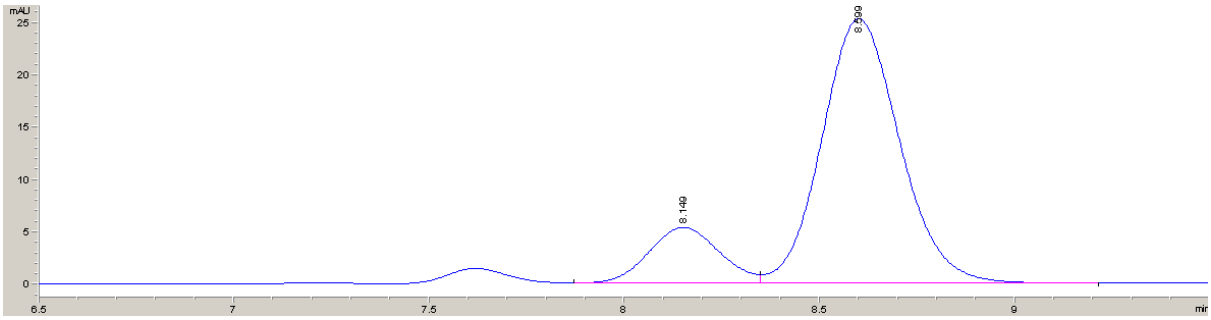


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
8.138	383.52814	64.6916
8.590	209.32780	35.3084

Entry 5 (Hydrolysed ester)

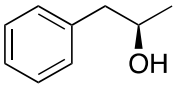


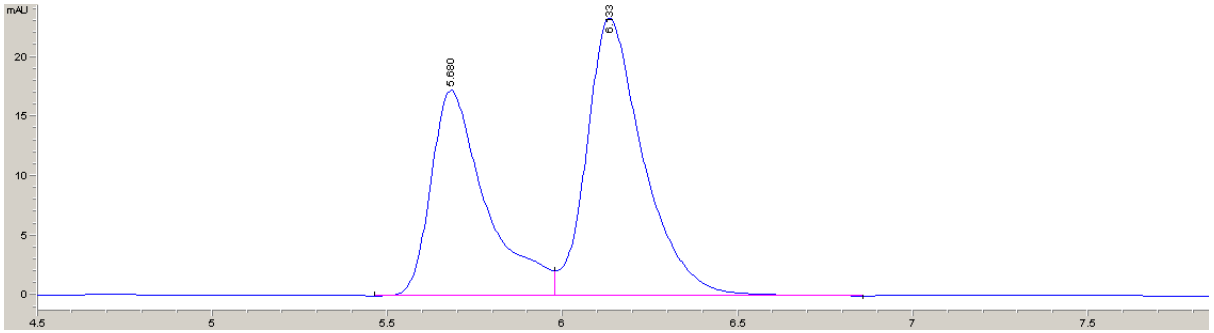


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
8.149	66.48589	15.9899
8.599	349.31271	84.0101

Entry 6 (Recovered alcohol)

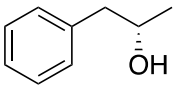


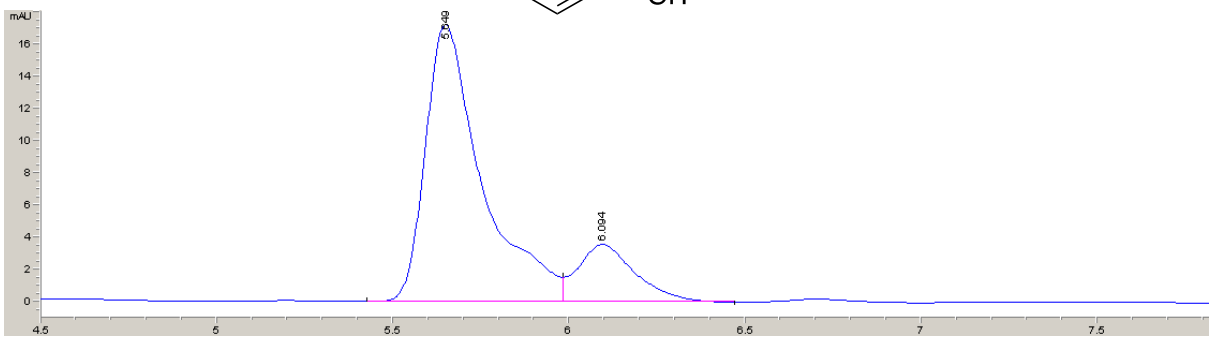


8% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
5.680	189.30516	41.8985
6.133	262.51315	58.1015

Entry 6 (Hydrolysed ester)

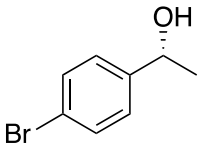


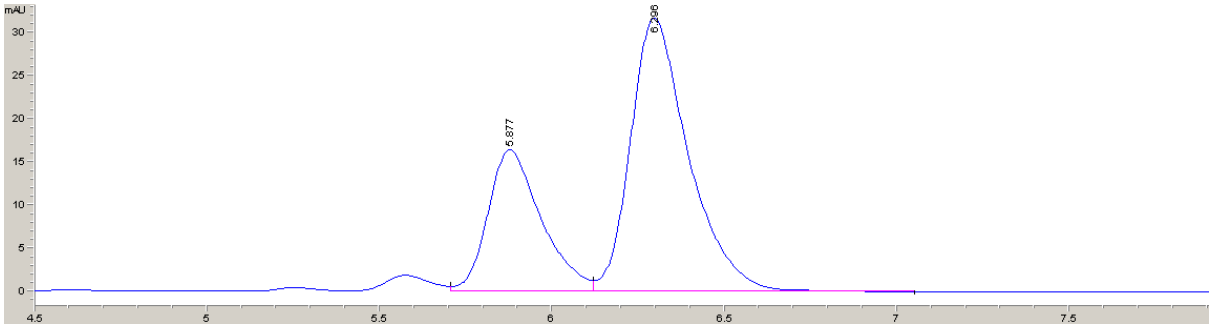


8% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
5.649	192.18741	82.6681
6.094	40.29322	17.3319

Entry 7 (Recovered alcohol)

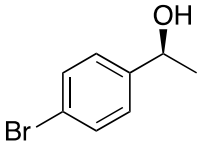


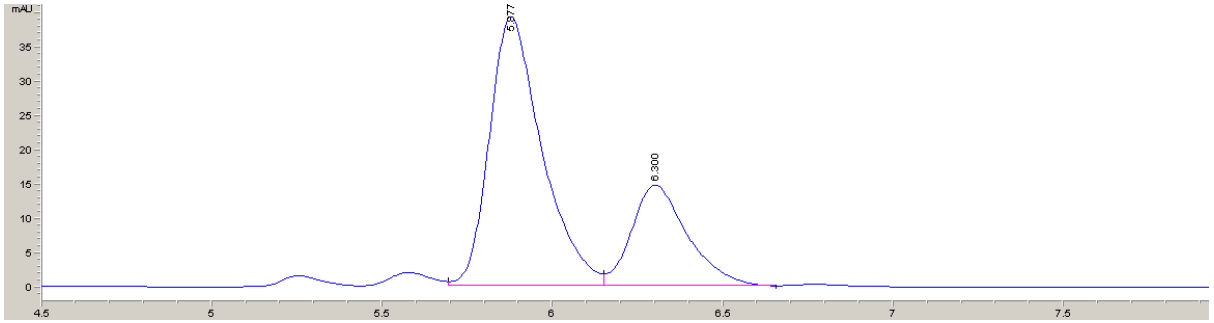


7% *i*-propanol in *n*-hexane, 0.8ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
5.877	176.31158	32.1657
6.296	371.82336	67.8343

Entry 7 (Hydrolysed ester)

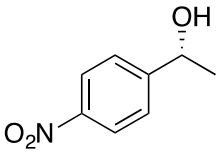


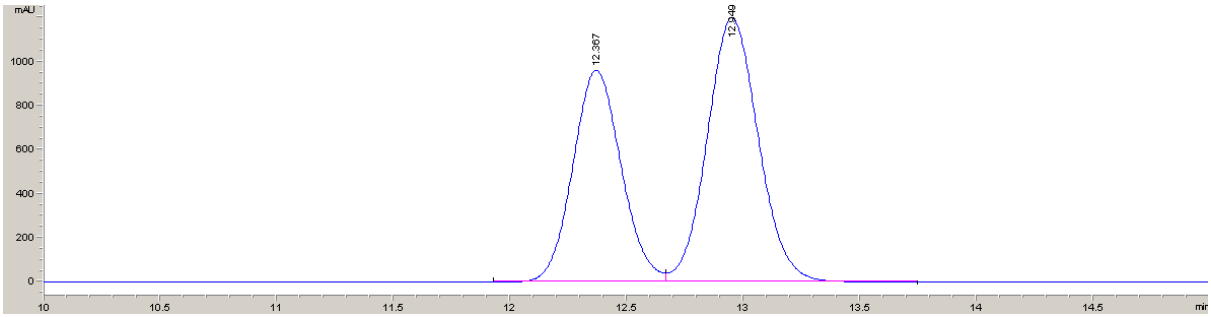


7% *i*-propanol in *n*-hexane, 0.8ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
5.877	421.71747	71.5734
6.300	167.49255	28.4266

Entry 8 (Recovered alcohol)

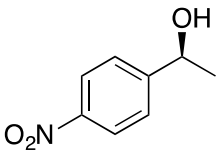


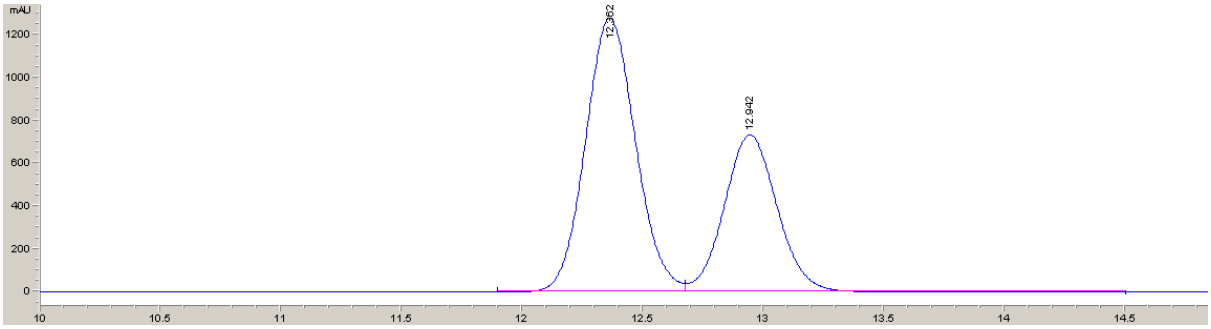


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	**Area (mAU*s)**	**Area %**
12.367	1.38354e4	43.0333
12.949	1.83150e4	56.9667

Entry 8 (Hydrolysed ester)

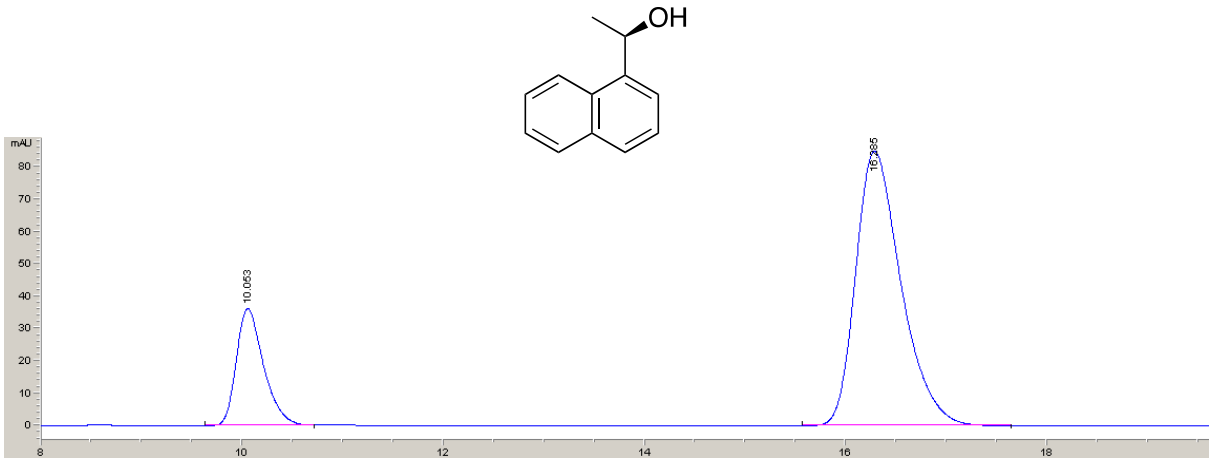




9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	**Area (mAU*s)**	**Area %**
12.362	1.84697e4	62.2952
12.942	1.11790e4	37.7048

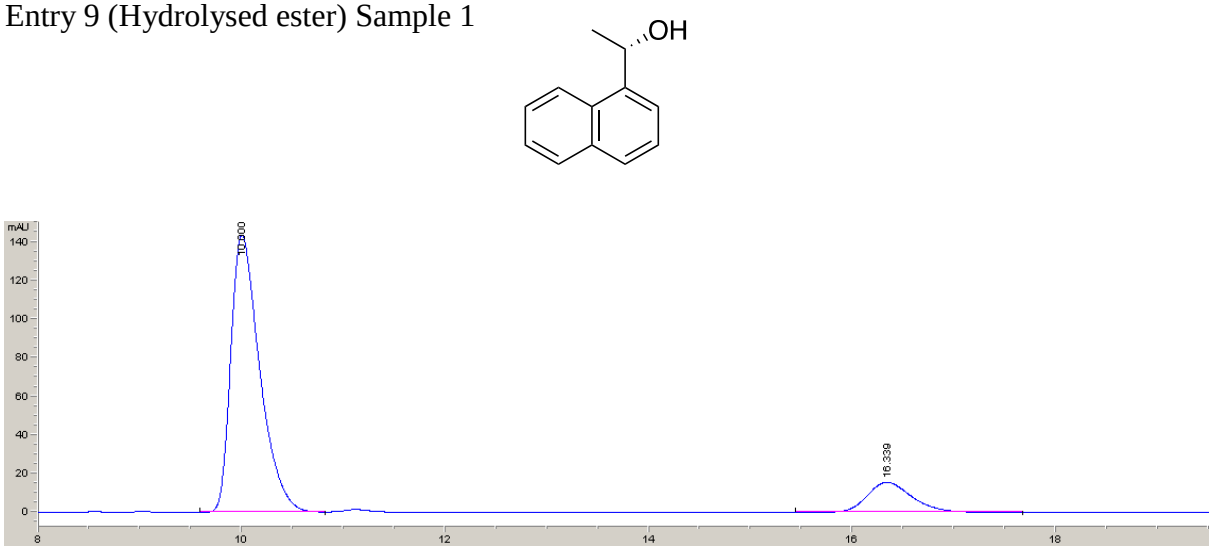
Entry 9 (Recovered alcohol) Sample 1



9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.053	679.49359	20.3230
16.285	2663.98462	79.6770

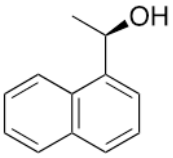
Entry 9 (Hydrolysed ester) Sample 1

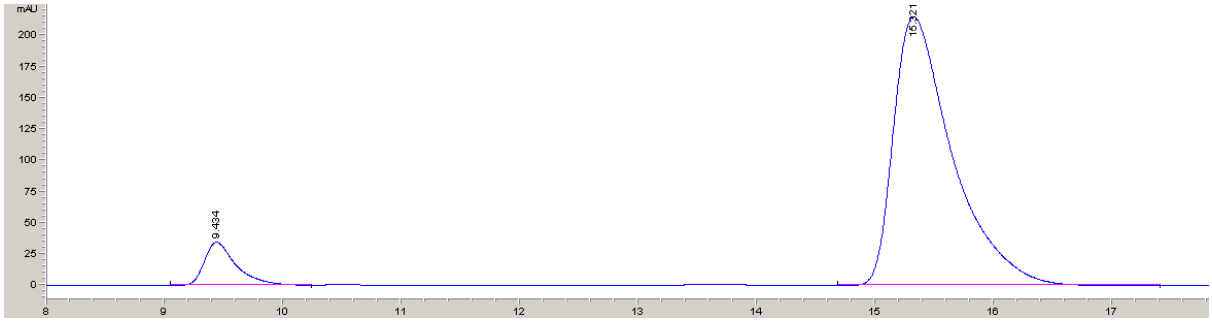


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.000	2829.48975	85.5625
16.339	477.43771	14.4375

Entry 9 (Recovered alcohol) Sample 2

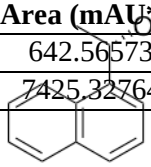


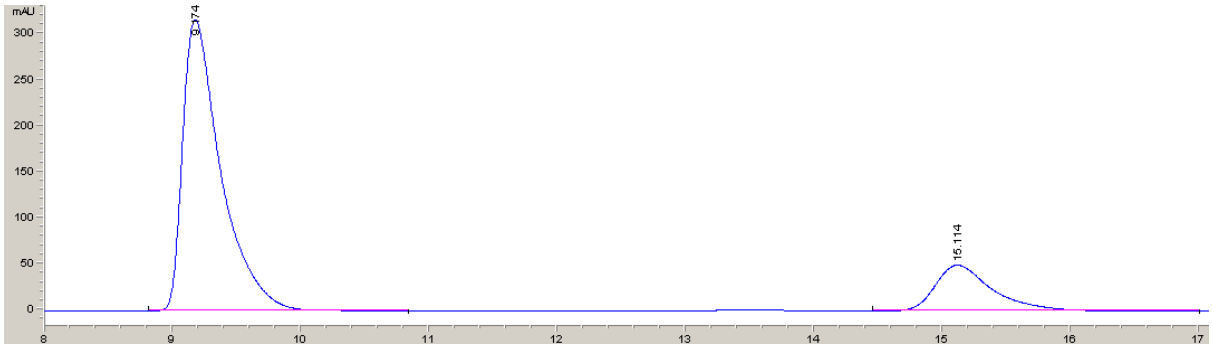


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
9.434	642.56573	7.9645
15.321	7425.32764	92.0355

Entry 9 (Hydrolysed ester) Sample 2

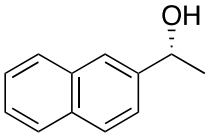


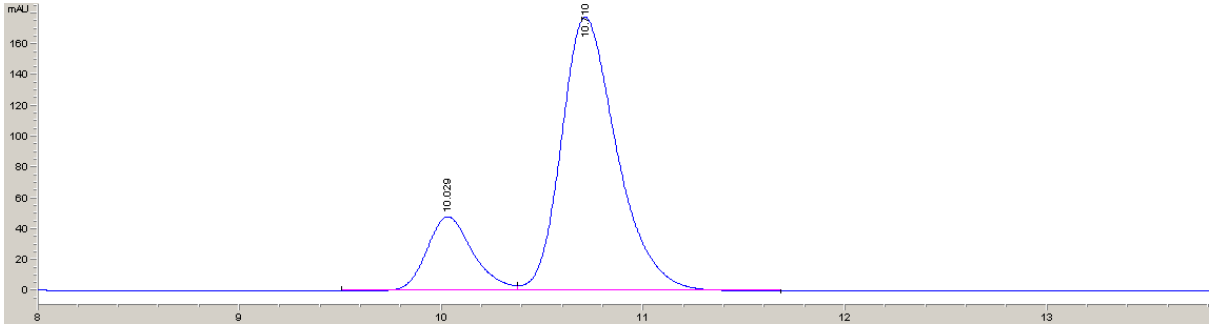


9.5% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
9.174	6538.41992	81.0650
15.114	1527.23486	18.9350

Entry 10 (Recovered alcohol)

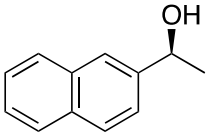


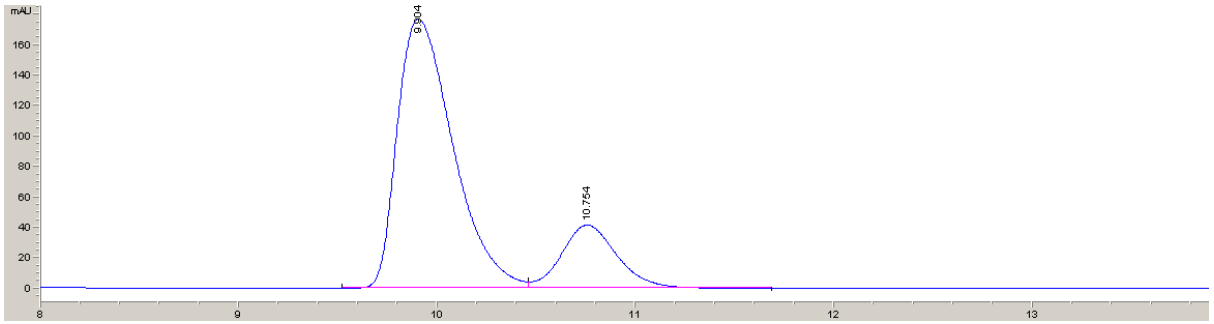


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
10.029	764.02173	18.4097
10.710	3386.07690	81.5903

Entry 10 (Hydrolysed ester)

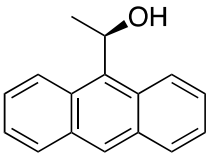


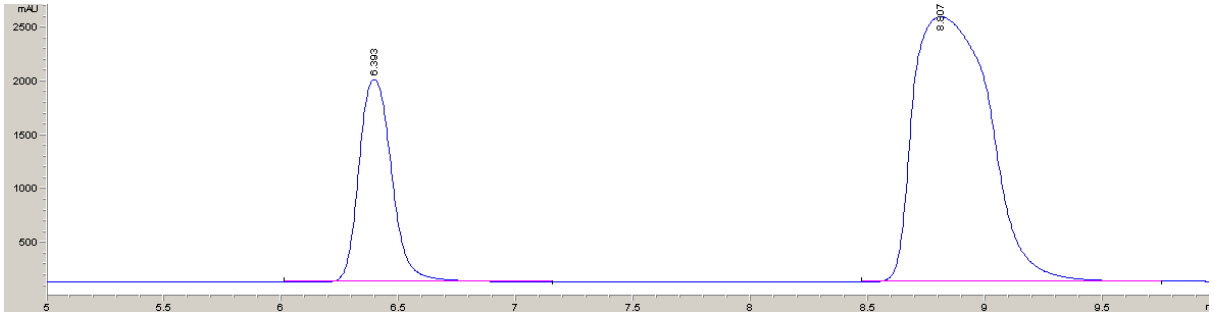


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
9.904	3454.07935	81.1769
10.754	800.92242	18.8231

Entry 11 (Recovered alcohol)

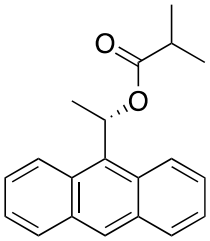


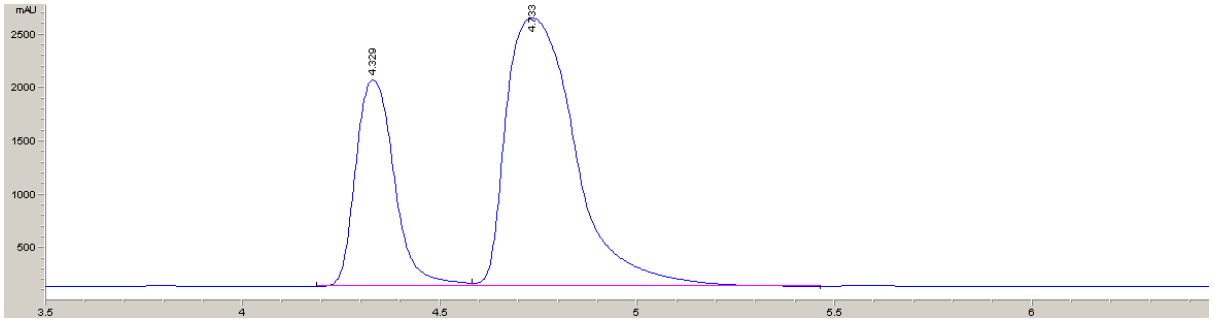


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
6.393	1.82284e4	24.6883
8.807	5.56057e4	75.3117

Entry 11 (recovered ester)

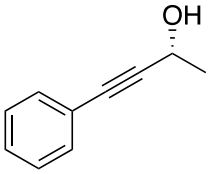


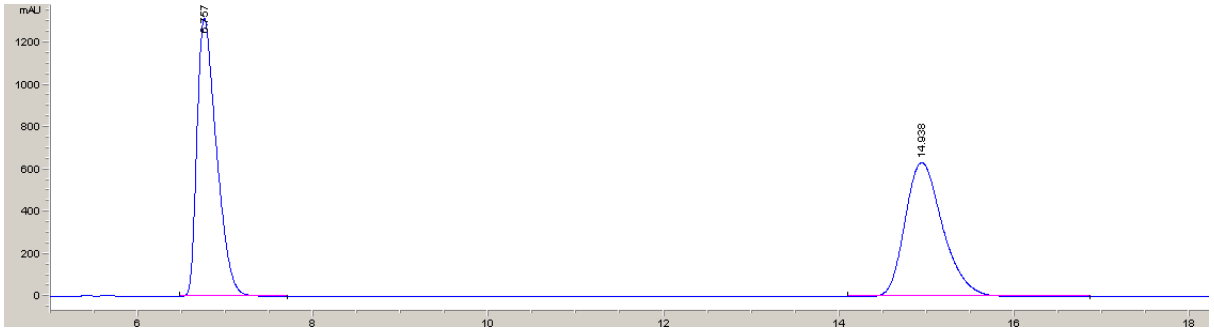


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
4.329	1.32012e4	30.0881
4.733	3.06738e4	69.9119

Entry 12 (Recovered alcohol)

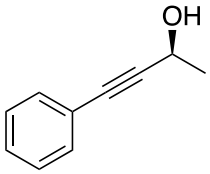


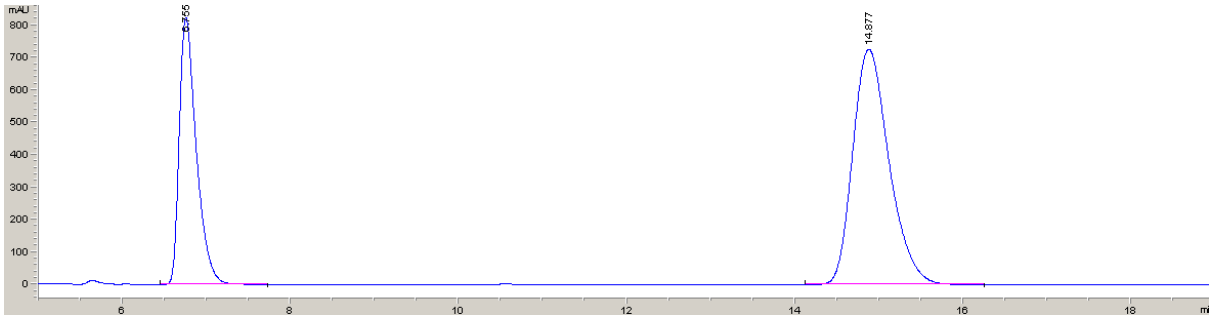


10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
6.757	2.02338e4	51.7967
14.938	1.88301e4	48.2033

Entry 12 (Hydrolysed ester)





10% *i*-propanol in *n*-hexane, 1ml/min at 254 nm

Retention time (min)	Area (mAU*s)	Area %
6.755	1.15722e4	34.7195
14.877	2.17583e4	65.2805

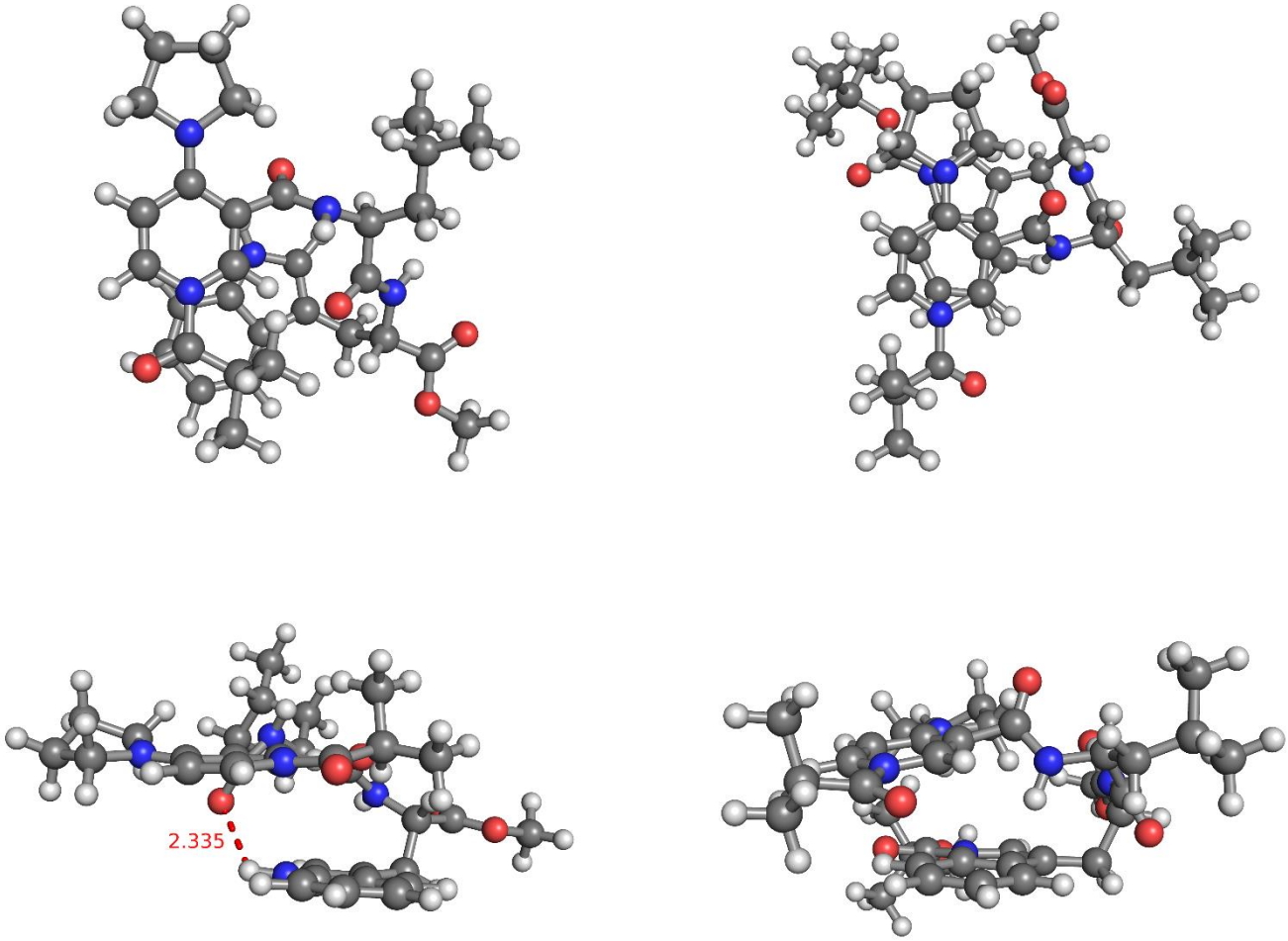
5) Modelling Data

5.1) Computational Details

Low energy conformers of $\mathbf{4}_{\mathbf{N\text{-}Ac}}$ and $\mathbf{8}_{\mathbf{N\text{-}Ac}}$ were investigated using molecular modelling. The computational procedure, described below, was applied to both $\mathbf{4}_{\mathbf{N\text{-}Ac}}$ and $\mathbf{8}_{\mathbf{N\text{-}Ac}}$. Given the large number of degrees of freedom (rotatable bonds) of these two ions, an exhaustive, systematic conformational search was not attempted in order to identify low energy conformers. Instead, an initial set of 1000 diverse conformers, based on a root–mean–square deviation (RMSD) criterion to assure effective spanning of conformational space, was first generated using the Open Babel 2.3 toolkit,[1] which employs a genetic algorithm for this task. Each conformer was then optimized using the MMFF94 force field.[2] A subset of the 100 lowest energy structures was then extracted and further optimized using the HF–3c method.[3] HF–3c is a fast quantum mechanical (QM) method that employs a minimal basis set with three corrections: (1) dispersion (D3–BJ), (2) geometrical counterpoise (gCP) and (3) an additional term correcting for basis set inefficiencies. This method is intended for pre–screening applications of large molecules.

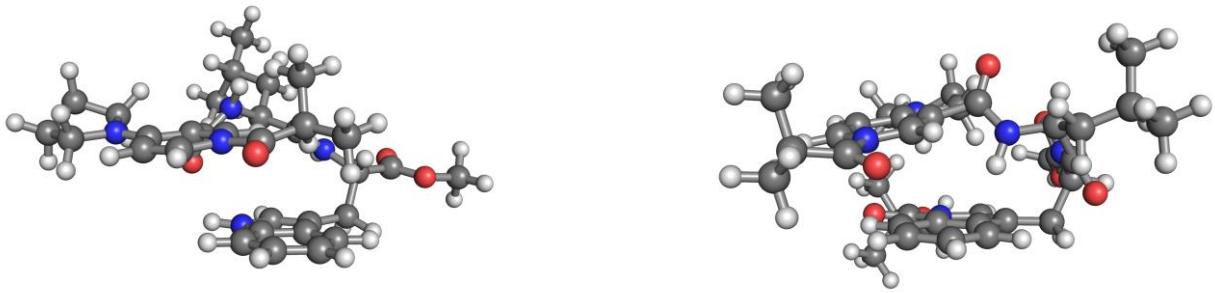
Subsequently, from these 100 structures, ten with the lowest energy were further refined using DFT. The ORCA 3.0.2 software package was used for the DFT calculations.[4] The B3LYP functional[5-7] and def2–SVP basis set[8] was used for these calculations. Given the importance of π–π interactions in these conformations, dispersion was taken into account by using the D3 dispersion correction of Grimme, with Becke–Johnson damping to assure the correct asymptotic behaviour.[9,10] To speed up the QM calculations, the resolution of identity (RI) approximation[11] was used to approximate Coulomb integrals and a chain of states method (RIJCOSX) for numerical integration of the exchange contribution to the hybrid functional.[12] Finally, since the dipeptides are charged, a further correction was made for solvation effects during the geometry optimizations, using the conductor–like screening polarizable continuum model (COSMO) with dichloromethane (CH_2Cl_2) selected as solvent, as implemented in the ORCA package.[13] All geometry optimizations were performed with tight convergence criteria. This level of QM theory is given the shorthand, B3LYP–D3(BJ)/def2–SVP.

Figure 1 shows the lowest energy structures of $\mathbf{4}_{\mathbf{N\text{-}Ac}}$ and $\mathbf{8}_{\mathbf{N\text{-}Ac}}$, on which our analysis was focused. Table 5 gives the relative energies of all ten conformers used in the DFT calculations and the associated Boltzmann distributions, at 298.15 K. Figure 2 gives three–dimensional representations of all ten of these conformers. Table 6 gives the Cartesian coordinates of the two lowest energy structures for each, shown in Figure 1.

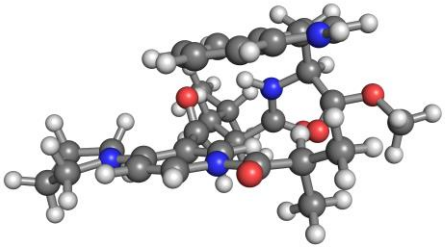


(a) (b)

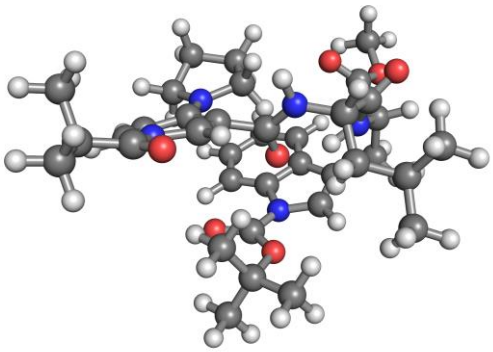
Figure 1. Three–dimensional representations of the lowest energy structures of (a) $\mathbf{4}_{\text{N-Ac}}$ and (b) $\mathbf{8}_{\text{N-Ac}}$. Two different views are shown for each. Structures were optimized at the B3LYP–D3(BJ)/def2–SVP level of theory with COSMO (CH_2Cl_2) solvent corrections.



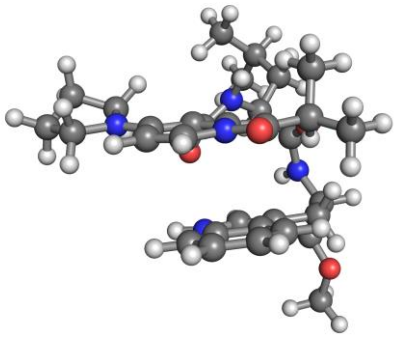
$\mathbf{4}_{\text{N-Ac}}$ **(1)** $\mathbf{8}_{\text{N-Ac}}$ **(1)**



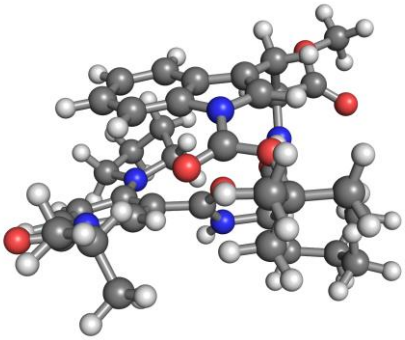
4N-Ac (2)



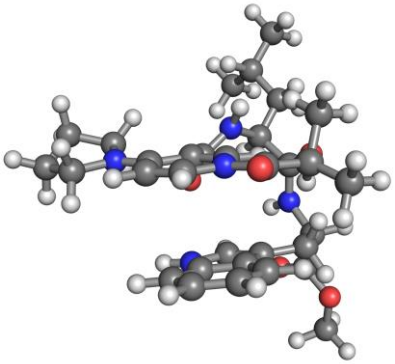
8N-Ac (2)



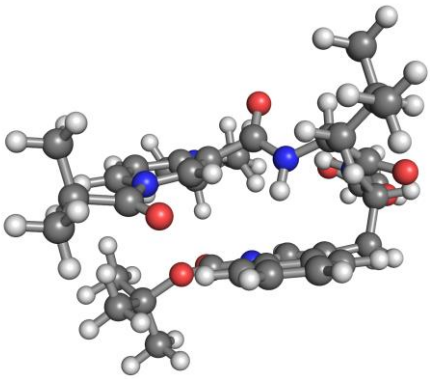
4N-Ac (3)



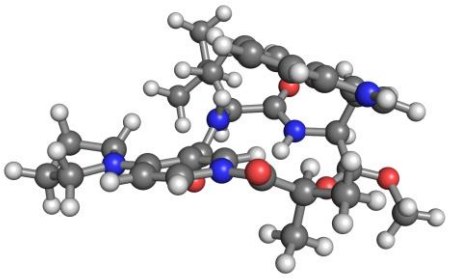
8N-Ac (3)



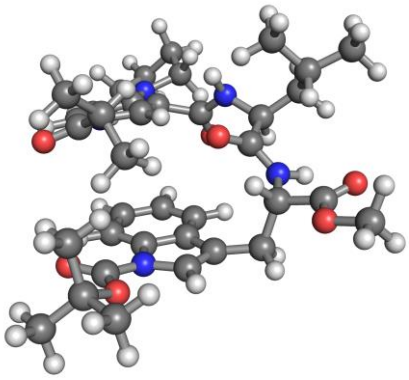
4N-Ac (4)



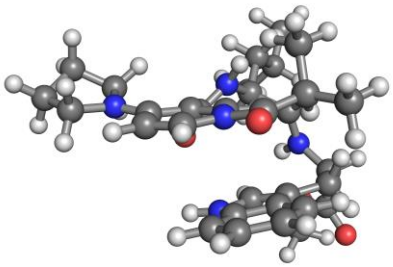
8N-Ac (4)



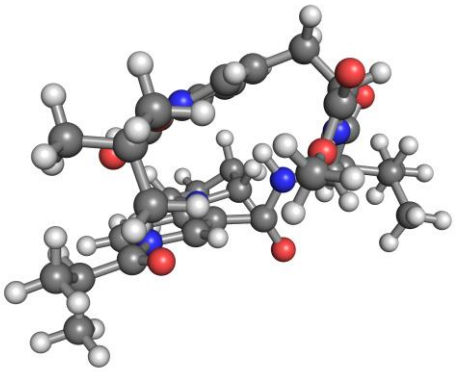
4N-Ac (5)



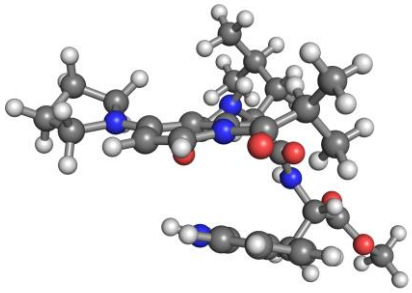
8N-Ac (5)



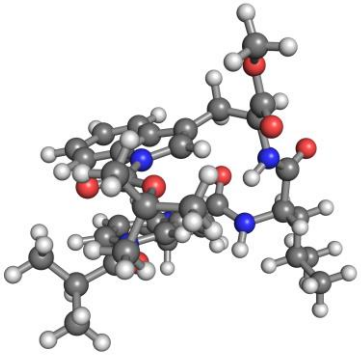
4$_{N\text{-}Ac}$ (6)



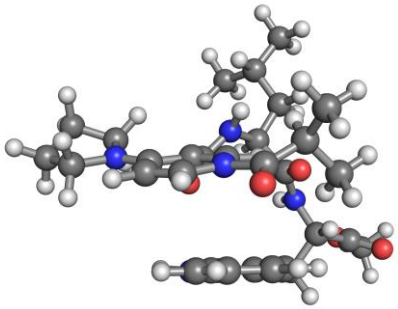
8$_{N\text{-}Ac}$ (6)



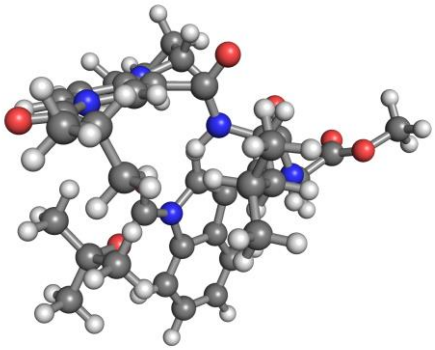
4$_{N\text{-}Ac}$ (7)



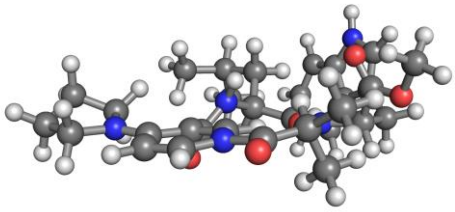
8$_{N\text{-}Ac}$ (7)



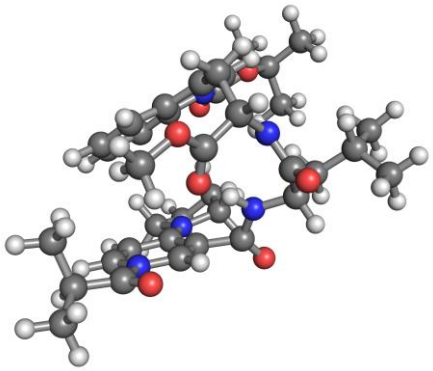
4$_{N\text{-}Ac}$ (8)



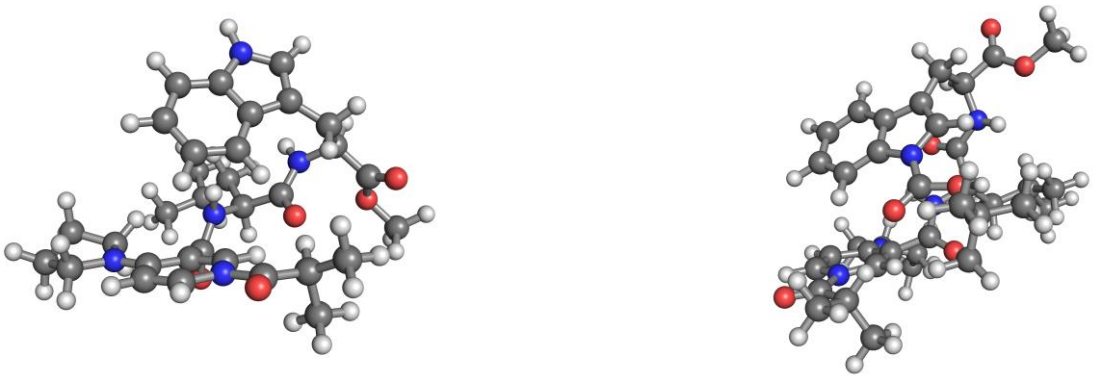
8$_{N\text{-}Ac}$ (8)



4$_{N\text{-}Ac}$ (9)



8$_{N\text{-}Ac}$ (9)



$4_{N\text{-}Ac}$ (10) **$8_{N\text{-}Ac}$ (10)**

Figure 2. Three–dimensional representations of the ten **$4_{N\text{-}Ac}$** and **$8_{N\text{-}Ac}$** conformers optimized at the B3LYP–D3(BJ)/def2–SVP level of theory with COSMO (CH_2Cl_2) solvent corrections. The relative energies are also given.

Table 5. Relative energies and associated weights (p_i) of ten low energy conformers of **$4_{N\text{-}Ac}$** and **$8_{N\text{-}Ac}$**, based on a Boltzmann distribution of the energies at 298.15 K.

	$4_{N\text{-}Ac}$			**$8_{N\text{-}Ac}$**	
	E_{rel} (kJ mol^{-1})	$p_i^{298.15}$		**E_{rel} (kJ mol^{-1})**	$p_i^{298.15}$
$4_{N\text{-}Ac}$ (1)	0.0	90.1	**$8_{N\text{-}Ac}$ (1)**	0.0	96.6
$4_{N\text{-}Ac}$ (2)	+6.2	7.4	**$8_{N\text{-}Ac}$ (2)**	+8.9	2.7
$4_{N\text{-}Ac}$ (3)	+11.6	0.8	**$8_{N\text{-}Ac}$ (3)**	+13.0	0.5
$4_{N\text{-}Ac}$ (4)	+11.5	0.9	**$8_{N\text{-}Ac}$ (4)**	+16.6	0.1
$4_{N\text{-}Ac}$ (5)	+11.5	0.9	**$8_{N\text{-}Ac}$ (5)**	+19.9	0.0
$4_{N\text{-}Ac}$ (6)	+20.4	0.0	**$8_{N\text{-}Ac}$ (6)**	+22.3	0.0
$4_{N\text{-}Ac}$ (7)	+23.3	0.0	**$8_{N\text{-}Ac}$ (7)**	+23.1	0.0
$4_{N\text{-}Ac}$ (8)	+25.2	0.0	**$8_{N\text{-}Ac}$ (8)**	+23.2	0.0
$4_{N\text{-}Ac}$ (9)	+35.7	0.0	**$8_{N\text{-}Ac}$ (9)**	+27.1	0.0
$4_{N\text{-}Ac}$ (10)	+45.5	0.0	**$8_{N\text{-}Ac}$ (10)**	+31.6	0.0

Table 6. Cartesian coordinates of the lowest energy conformers **$4_{N\text{-}Ac}$ (1)** and **$8_{N\text{-}Ac}$ (1)**.

		$4_{N\text{-}Ac}$ (1)		
#	**Atom**	***x* (Å)**	***y* (Å)**	***z* (Å)**
1	C	−1.28491	−1.93284	−1.37662
2	H	−2.10331	−2.45035	−1.87545
3	C	−0.50983	−2.51480	−0.41997
4	H	−0.72865	−3.54440	−0.14496
5	C	0.59649	−1.80960	0.17413
6	C	0.72055	−0.42090	−0.20154
7	C	−0.10704	0.09548	−1.16904
8	H	−0.03569	1.15236	−1.43170

9	N	−1.06758	−0.64237	−1.79065
10	N	1.45313	−2.43191	0.97365
11	C	2.74336	−1.88542	1.44605
12	H	3.22682	−1.32065	0.63619
13	H	2.56626	−1.19798	2.28551
14	C	1.29285	−3.84343	1.39107
15	H	1.41380	−4.49756	0.51097
16	H	0.29104	−4.00772	1.81273
17	C	2.41841	−4.04660	2.40474
18	H	2.08625	−3.71321	3.40146
19	H	2.72360	−5.09947	2.47846
20	C	3.52290	−3.12527	1.87879
21	H	4.02665	−3.58331	1.01251
22	H	4.28627	−2.88202	2.63037
23	C	−1.92173	−0.09069	−2.84952
24	C	−1.52708	1.25807	−3.41157
25	H	−1.38250	1.95706	−2.57206
26	C	−0.19631	1.13495	−4.18606
27	H	0.63145	0.75952	−3.56823
28	H	−0.31562	0.45879	−5.04681
29	H	0.09297	2.12709	−4.56069
30	C	−2.63554	1.79873	−4.31321
31	H	−3.56883	1.94134	−3.75322
32	H	−2.83220	1.11239	−5.15009
33	H	−2.32674	2.76990	−4.72801
34	O	−2.83275	−0.76974	−3.23897
35	C	1.50730	0.61827	0.55462
36	O	1.39342	0.73501	1.77151
37	N	2.23141	1.46141	−0.22565
38	H	2.23705	1.26103	−1.22104
39	C	2.37857	2.87000	0.09930
40	H	2.22061	2.96816	1.18151
41	C	1.23516	3.61396	−0.62570
42	O	0.60252	3.06470	−1.52879
43	N	0.97352	4.86705	−0.20704
44	H	1.52404	5.28354	0.53801
45	C	−0.23814	5.55467	−0.59889
46	H	−0.56959	5.13674	−1.55751
47	C	0.04626	7.03505	−0.76426
48	O	0.98602	7.60778	−0.26010
49	O	−0.90718	7.62602	−1.48133
50	C	−0.82576	9.05139	−1.63862
51	H	−1.63597	9.32669	−2.32259
52	H	0.14764	9.33671	−2.06189
53	H	−0.96214	9.54913	−0.66738
54	C	3.76565	3.40295	−0.27807
55	H	3.80724	4.47695	−0.02746
56	H	3.87930	3.33000	−1.37358
57	C	4.92203	2.66423	0.41248
58	H	4.82914	1.59647	0.14298

59	C	4.85133	2.77757	1.93832
60	H	3.92655	2.34110	2.34696
61	H	5.69415	2.24574	2.40609
62	H	4.90379	3.83300	2.25794
63	C	−1.37316	5.35825	0.45649
64	H	−1.07654	5.89962	1.36941
65	H	−2.27966	5.84527	0.06657
66	C	6.27084	3.16426	−0.11290
67	H	6.35470	3.02592	−1.20319
68	H	7.10155	2.61897	0.36285
69	H	6.40487	4.23772	0.10698
70	C	−1.62776	3.91733	0.76586
71	C	−0.90181	3.13012	1.63825
72	H	−0.08928	3.40323	2.30811
73	N	−1.34169	1.82587	1.57929
74	C	−2.57971	3.03867	0.12740
75	C	−4.13892	0.84346	−0.67379
76	C	−2.36588	1.73036	0.66447
77	C	−3.60459	3.22451	−0.82123
78	C	−4.37724	2.13151	−1.20571
79	C	−3.13459	0.62695	0.26796
80	H	−3.80018	4.21234	−1.24645
81	H	−5.18209	2.26864	−1.93206
82	H	−2.95240	−0.36439	0.68989
83	H	−4.75162	0.00445	−1.01065
84	H	−0.89876	1.05929	2.07324

8_{N-Ac} (1)

#	Atom	*x* (Å)	*y* (Å)	*z* (Å)
1	C	−5.68603	−0.38257	−5.45018
2	H	−5.5814	−0.33941	−6.53063
3	C	−6.93229	−0.21048	−4.93491
4	H	−7.79111	−0.05315	−5.58238
5	C	−4.54259	−0.6437	−4.61477
6	C	−4.8026	−0.59249	−3.18762
7	C	−6.09155	−0.44566	−2.74953
8	H	−6.34092	−0.43078	−1.68955
9	N	−7.15883	−0.26193	−3.58296
10	N	−3.37935	−0.9407	−5.18454
11	C	−2.11609	−1.29102	−4.50372
12	H	−2.20693	−2.31332	−4.10056
13	H	−1.9181	−0.60225	−3.68088
14	C	−3.21996	−1.02579	−6.65815
15	H	−4.00471	−1.66209	−7.08811
16	H	−3.31134	−0.01549	−7.08765
17	C	−1.8201	−1.60843	−6.86269
18	H	−1.36191	−1.23746	−7.78953
19	H	−1.86726	−2.70362	−6.93335
20	C	−1.06187	−1.19766	−5.60114
21	H	−0.19667	−1.83161	−5.37212
22	H	−0.70779	−0.15781	−5.68515

23	C	−8.48111	−0.12047	−2.9679
24	O	−8.59519	−0.44103	−1.81469
25	C	−9.57852	0.48241	−3.81773
26	H	−9.61346	−0.06322	−4.77508
27	C	−10.9299	0.32392	−3.11952
28	H	−11.1508	−0.73064	−2.89833
29	H	−11.7244	0.72049	−3.7681
30	H	−10.9458	0.88081	−2.17067
31	C	−9.25919	1.96551	−4.10364
32	H	−8.31706	2.10491	−4.65328
33	H	−9.19566	2.52996	−3.16054
34	H	−10.0689	2.39734	−4.70927
35	C	−3.75481	−0.57942	−2.09888
36	O	−2.85622	0.25593	−2.08259
37	N	−3.93621	−1.51622	−1.14118
38	H	−4.62933	−2.24179	−1.31141
39	C	−3.00266	−1.71496	−0.03567
40	H	−2.21707	−0.95859	−0.17407
41	C	−2.38757	−3.12209	−0.22981
42	O	−2.71241	−4.08401	0.45641
43	N	−1.54437	−3.20831	−1.28346
44	H	−1.21992	−2.36008	−1.74227
45	C	−0.91721	−4.43604	−1.7338
46	H	−0.32432	−4.88356	−0.91551
47	C	0.06355	−4.04137	−2.83291
48	O	0.28979	−2.89104	−3.14418
49	O	0.62295	−5.09353	−3.41854
50	C	1.54723	−4.82203	−4.48601
51	H	1.93324	−5.79522	−4.8091
52	H	2.364	−4.17883	−4.13084
53	H	1.02609	−4.32118	−5.31536
54	C	−3.67218	−1.54597	1.328
55	H	−4.31375	−2.42308	1.50651
56	H	−4.32981	−0.66231	1.27585
57	C	−2.68113	−1.38071	2.4946
58	H	−1.90453	−2.15976	2.38742
59	C	−3.38491	−1.60078	3.83798
60	H	−3.81273	−2.6138	3.91176
61	H	−4.20959	−0.87931	3.96878
62	H	−2.68409	−1.45767	4.67652
63	C	−1.99723	−0.00762	2.47478
64	H	−1.53136	0.2193	1.50212
65	H	−1.20599	0.05387	3.23876
66	H	−2.73037	0.7888	2.6915
67	C	−1.91308	−5.51687	−2.22365
68	H	−2.52319	−5.81549	−1.36156
69	H	−1.31858	−6.39047	−2.52349
70	C	−2.79434	−5.07481	−3.35382
71	C	−2.4865	−5.08664	−4.68701
72	H	−1.59369	−5.43368	−5.19731

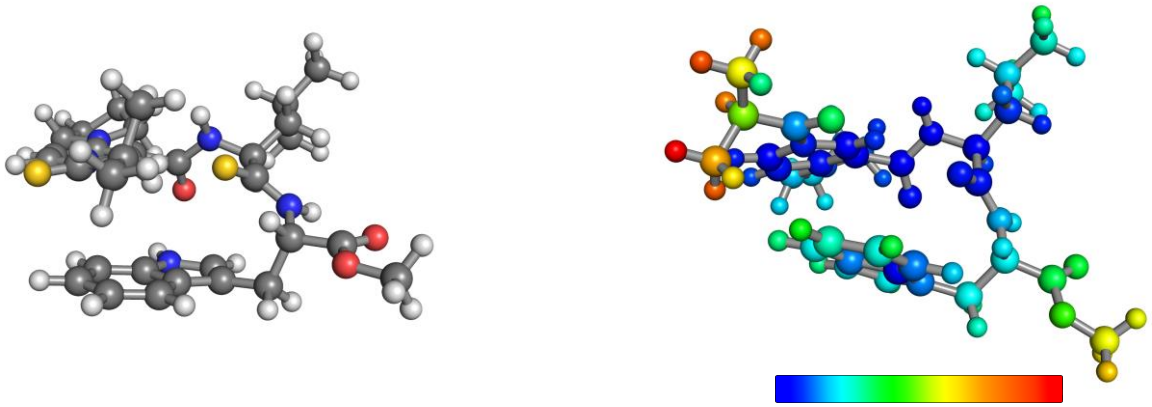
73	N	−3.56087	−4.58134	−5.43713
74	C	−4.14656	−4.55582	−3.24289
75	C	−6.73472	−3.60554	−3.69812
76	C	−5.02058	−4.39708	−2.15235
77	C	−4.60005	−4.24722	−4.55461
78	C	−5.89277	−3.76884	−4.79868
79	C	−6.31016	−3.9182	−2.3904
80	H	−4.69672	−4.66463	−1.14332
81	H	−6.2281	−3.5506	−5.81005
82	H	−7.00645	−3.7972	−1.55735
83	H	−7.75264	−3.24353	−3.85988
84	C	−3.63626	−4.55852	−6.83686
85	O	−4.55626	−4.03723	−7.43145
86	O	−2.57502	−5.15837	−7.35392
87	C	−2.40698	−5.43109	−8.80339
88	C	−1.14211	−6.28333	−8.82432
89	H	−1.29085	−7.21038	−8.25099
90	H	−0.29873	−5.72892	−8.38519
91	H	−0.88621	−6.54931	−9.86048
92	C	−2.19661	−4.11489	−9.54642
93	H	−3.09051	−3.47831	−9.49658
94	H	−1.97903	−4.33261	−10.6034
95	H	−1.33824	−3.56779	−9.13029
96	C	−3.61425	−6.21208	−9.3172
97	H	−3.80297	−7.08845	−8.67841
98	H	−3.40363	−6.57259	−10.3356
99	H	−4.51609	−5.58738	−9.34533

5.2) Comparison of the *s–trans*/*s-cis* N–acylpyridinium conformations

The lowest energy structure of $\mathbf{4}_{\mathbf{N\text{-}Ac}}$ has the N–acylpyridinium in the *s-trans* conformation, whereas for $\mathbf{8}_{\mathbf{N\text{-}Ac}}$, the N–acylpyridinium group is in the *s-cis* conformation. To investigate this observation further, we also generated the corresponding *s-cis* (for $\mathbf{4}_{\mathbf{N\text{-}Ac}}$) and *s-trans* (for $\mathbf{8}_{\mathbf{N\text{-}Ac}}$) conformations by adjusting the dihedral angle and optimized the corresponding geometries at the B3LYP–D3(BJ)/def2–SVP level of theory. Note that these alternate conformations did not appear in the list of 10 low energy conformations referred to earlier. We emphasize that this list is representative of the conformational space of the ions and given the stochastic procedure by which the generation happened, no claim can be made that these are necessarily *all* possible low energy structures. Figures 3 and 4 show the results.

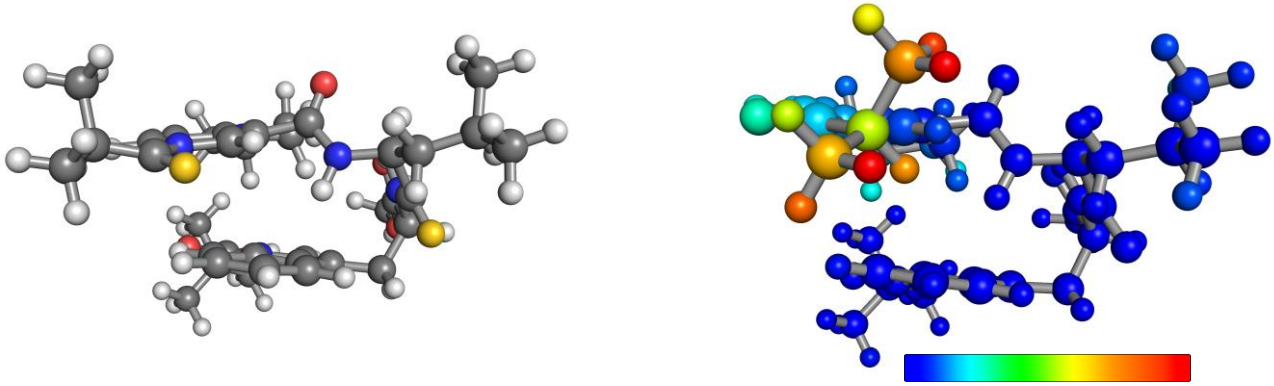
$\mathbf{4}_{\mathbf{N\text{-}Ac}}$ *s-trans* has τ(C-2^{pyri}, N-1^{pyri}, C$^{N–acyl}$, O$^{N–acyl}$) = −172.2° and the *s-cis* conformer has τ(C-2^{pyri}, N-1^{pyri}, C$^{N–acyl}$, O$^{N–acyl}$) = −8.6°. This latter conformer is 41.1 kJ mol^{-1} higher in energy than the former. $\mathbf{8}_{\mathbf{N\text{-}Ac}}$ *s-trans* has τ(C-2^{pyri}, N-1^{pyri}, C$^{N–acyl}$, O$^{N–acyl}$) = 179.0°, with the *s-cis* conformer having τ(C-2^{pyri}, N-1^{pyri}, C$^{N–acyl}$, O$^{N–acyl}$) = −14.8°, but interestingly is only 14.0 kJ mol^{-1} higher in energy. Whereas the geometry around the pyridinium–N–acyl bonds are therefore similar, there is a much greater difference in energy in the case of $\mathbf{4}_{\mathbf{N\text{-}Ac}}$. Factors contributing to this are likely to be the close proximity of the N–acyl oxygen atom and carbonyl

oxygen atom of the 2nd peptide (Leu···Trp) bond in **4**$_{\text{N-Ac}}$ *s-cis*, that is absent in **8**$_{\text{N-Ac}}$ *s-cis* (atoms shown coloured in gold in Fig. 3(a) and Fig. 4(a)), as well as concomitant changes in other secondary intramolecular interactions/close contacts when the conformations change. The $O_{N-acyl}\cdots O_{peptide}$ distance is 4.24 Å in **4**$_{\text{N-Ac}}$ *s-cis* and 7.28 Å in **8**$_{\text{N-Ac}}$ *s-cis*. The second effect is illustrated in Figures 3 and 4 where atoms are coloured according to RMSD between the two conformers. Dark blue atoms stay in a similar relative position and it is clear that the *s-cis*/*s-trans* switch in **4**$_{\text{N-Ac}}$ results in a greater extent of change. Crucially, the orientation of the 2nd peptide carbonyl oxygen changes; although the change is slight, it is enough to weaken two intramolecular O···H interactions. Two illustrate this, we turn to the noncovalent index, introduced by Johnson et al.[14]



(a) (b)

Figure 3. (a) **4**$_{\text{N-Ac}}$ **(1)** with τ(C-2^{pyri}, N-1^{pyri}, C^{N-acyl}, O^{N-acyl}) = −172.2°, giving the *s–trans* conformation. The oxygen atoms of the N–acyl group and the 2nd carbonyl of the side-chain are shown in gold. (b) **4**$_{\text{N-Ac}}$ with τ(C-2^{pyri}, N-1^{pyri}, C^{N-acyl}, O^{N-acyl}) = −8.6°, giving the *s–cis* conformation. This latter conformation is 41.1 kJ mol^{-1} higher in energy. Atoms are coloured according to RMSD. The colour spectrum ranges from blue (0.08 Å) to red (6.30 Å).



(a) (b)

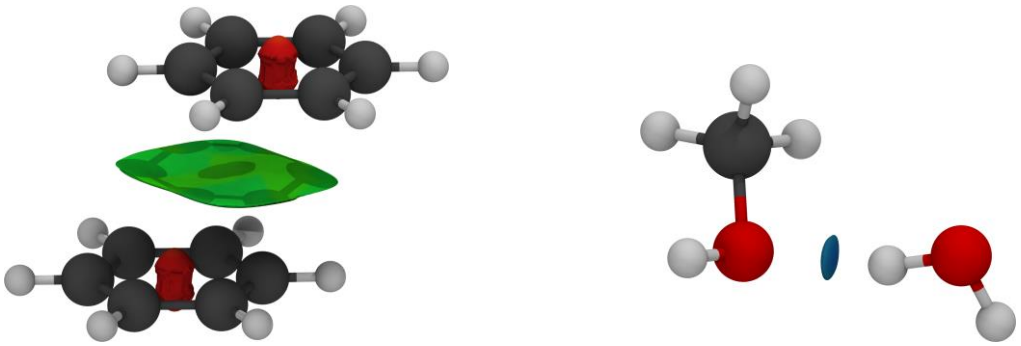
Figure 4. (a) $\mathbf{8}_{\mathbf{N\text{-}Ac}}$ **(1)** with τ(C-2^{pyri}, N-1^{pyri}, C$^{N–acyl}$, O$^{N–acyl}$) = −14.8°, giving the *s–cis* conformation. The oxygen atoms of the N–acyl group and the 2nd carbonyl of the side-chain are shown in gold. Note that here the 3rd peptide carbonyl oxygen points away from the N–acyl group, avoiding oxygen–oxygen close contact. (b) $\mathbf{8}_{\mathbf{N\text{-}Ac}}$ with τ(C-2^{pyri}, N-1^{pyri}, C$^{N–acyl}$, O$^{N–acyl}$) = 179.0°, giving the *s–trans* conformation. This latter conformation is 14.0 kJ mol^{-1} higher in energy and would have contributed with a weight of 0.3%, if included in the population of 10 low energy conformations, references earlier. Atoms are coloured according to RMSD. The colour spectrum ranges from blue (0.06 Å) to red (6.51 Å).

The noncovalent index (NCI) provides a qualitative measure of the strength and location of inter– and intramolecular interactions in molecules and can conveniently be used to display this information in a single three–dimensional representation.[14, 15] NCI operates by making use of features present in the reduced density gradient (RDG), *s*,

$$s = \frac{1}{2\left(3\pi^2\right)^{1/3}} \frac{|\nabla\rho|}{\rho^{4/3}}$$

In low density regions, where orbital overlap and inter/intramolecular interaction occur between molecules and atoms, a critical point ($\nabla\rho = 0$) appears in the electron density (ρ) and the RDG approaches zero. Based on conclusions similar to those typically used when applying the Quantum Theory of Atoms in Molecules (QTAIM),[16] the nature of this interaction can be further quantified as bonding (attractive) or antibonding (repulsive) by analysis of the sign of the second eigenvalue of the Laplacian ($\nabla^2\rho$) of the electron density, λ_2, where $\nabla^2\rho = \lambda_1 + \lambda_2 + \lambda_3$ and the eigenvalues are arranged in increasing order, $\lambda_1 < \lambda_2 < \lambda_3$. If $\lambda_2 < 0$, the interaction is attractive (e.g. hydrogen bonding) and if $\lambda_2 > 0$, the interaction is repulsive (e.g. steric repulsion). Weak attraction (e.g. van der Waals interaction) occurs where $\lambda_2 \leq 0$. A 2D NCI plot can be constructed by mapping the RDG against the electron density, multiplied by the sign of λ_2. Alternatively, this information can be visualized as regions in space in a 3D molecular representation by constructing arbitrary isosurfaces of the RDG, colored according to the sign of λ_2. The electron density can be calculated directly from the wavefunction, or alternatively for large molecules, from a promolecular electron density built from precalculated atomic densities. We use promolecular densities here. Further details can be found in the original literature.[14, 15] For illustrative purposes, we replicate the results of a 3D NCI plot for benzene dimers and a water–methanol complex, showing van der Waals/dispersion interaction

(as the green shape) and ring strain (red ellipsoid) as well as a hydrogen bond (blue disk), respectively, in Figure 5, below.

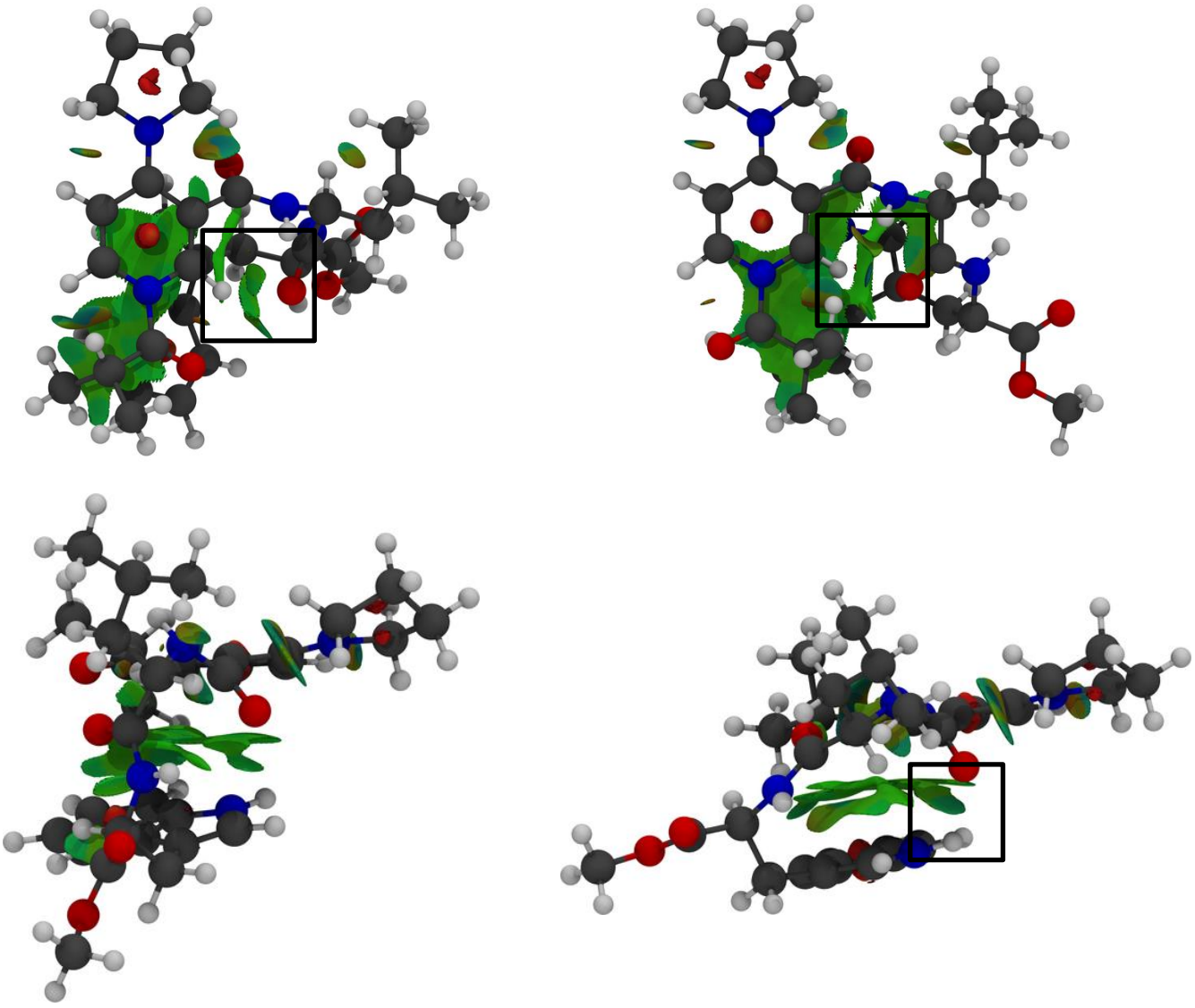


(a) (b)

Figure 5. Promolecular 3D noncovalent index (NCI) isosurfaces for (a) a benzene dimer and
(b) a water–methanol complex. Isosurfaces are drawn at $s = 0.3$ and coloured from attractive (blue, $\lambda_2 < 0$) through weak (green, $\lambda_2 \approx 0$) to repulsive (red, $\lambda_2 > 0$).

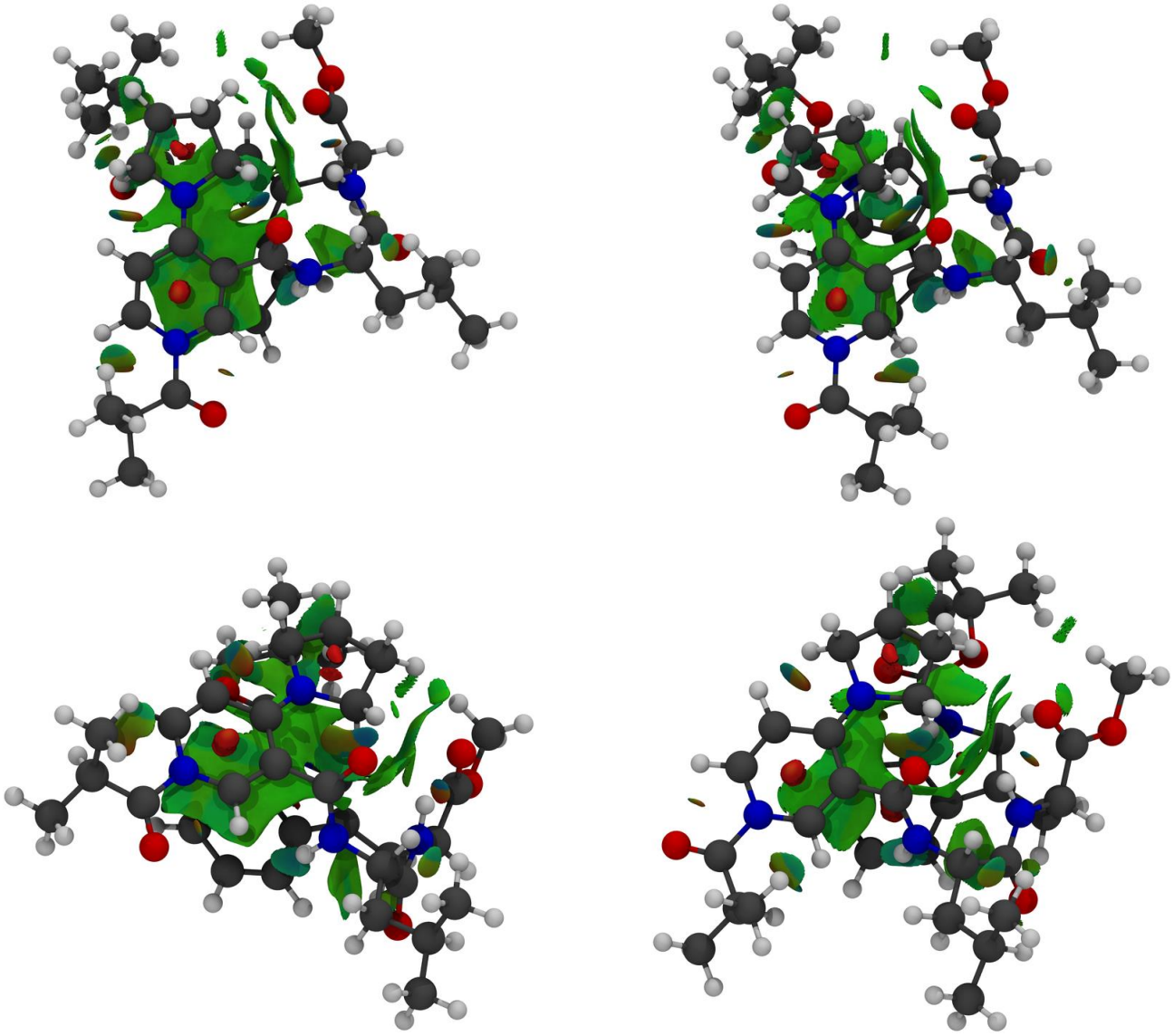
Looking at Figure 6, the top row shows that although the *s-cis/s-trans* switch in $\mathbf{4}_{\mathbf{N\text{-}Ac}}$ keeps several intramolecular interactions intact, the stabilising interaction between the 2nd peptide carbonyl group and the pyridinium C-2 hydrogen atom is strengthened (C-2^{pyri}–H$\cdots$ O), as evidenced by the more intense blue colour of the isosurface. In addition, the bottom row shows that the hydrogen bond between the 1st peptide carbonyl group and the indole NH is established and that this interaction is in fact missing in the *s-cis* conformation, due to the change in orientation of the indole ring. These interactions are blocked in Figure 6. The figure also suggests a change in the strength of van der Waals interaction between the aromatic groups, by virtue of the change in the isosurface shape and size. It is however, not possible to express this change quantitatively using NCI.

Similarly, Figure 7 shows that most of the intramolecular interactions stay intact for $\mathbf{8}_{\mathbf{N\text{-}Ac}}$ with the switch in conformation, as could also have been inferred from the observation that there is very little change in the relative position of the atoms not involved in the switch.



(a) (b)

Figure 6. Two views of the promolecular 3D noncovalent index (NCI) for (a) $\mathbf{4}_{\mathbf{N\text{-}Ac}}$ *s-cis* (ΔE = 41.1 kJ mol^{-1}) and (b) $\mathbf{4}_{\mathbf{N\text{-}Ac}}$ *s-trans*. Isosurfaces are drawn at s = 0.3 and coloured from attractive (blue, $\lambda_2 < 0$) through weak (green, $\lambda_2 \approx 0$) to repulsive (red, $\lambda_2 > 0$).



(a) (b)

Figure 7. Two views of the promolecular 3D noncovalent index (NCI) for (a) **8**$_{\text{N-Ac}}$ *s-cis* and (b) **8**$_{\text{N-Ac}}$ *s-trans* (ΔE = 14.0 kJ mol^{-1}). Isosurfaces are drawn at s = 0.3 and coloured from attractive (blue, $\lambda_2 < 0$) through weak (green, $\lambda_2 \approx 0$) to repulsive (red, $\lambda_2 > 0$).

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