ELECTRONIC SUPPLEMENTARY INFORMATION

Enhancement of ibuprofen solubility and skin permeation by conjugation with L-valine alkyl esters

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ESI contents

1. GENERAL ANALYTICAL METHODS

NMR

The NMR spectra were recorded in $CDCl_3$ on a BRUKER DPX-400 spectrometer (Billerica, MA, USA) operating at 400 MHz (^1H) and 100 MHz (^{13}C). TMS was used as the standard. Chemical shifts are given in δ (ppm) and coupling constants *J* are given in Hz.

FTIR

The FTIR spectra were measured on a spectrometer model 'Nicolet 380' (Thermo Electron Corporation, Waltham, MA, USA) with Diamond ATR in transmission mode, in the range of 4000 - 400 cm^{-1}. The resolution was 4 cm^{-1}.

UV-VIS

The UV-VIS absorption spectra were registered using a Spectroquant® Pharo 300 Spectrophotometer from Merck (Darmstadt, Germany) with the accuracy of ±1 nm in a 10 mm quartz cell. The concentration of compound was in the range of 10^{-4}-10^{-5} M in absolute ethanol.

Elemental analysis

The elemental analysis CHNS/O was performed by using Thermo Scientific™ FLASH 2000 CHNS/O Analyzer (Waltham, MA, USA). Compounds were weighed to an accuracy of ±0.000001 g in tin crucibles (2-3 mg) for analysis in CHNS mode, and in silver crucibles (1-2 mg) in oxygen mode, respectively. 2,5-(Bis(5-tert-butyl-2-benzo-oxazol-2-yl) thiophene (BBOT), sulphanilamide, L-cysteine and L-methionine were used as standards to calibrate the device in CHNS mode. In oxygen mode an acetanilide and benzoic acid were used.

Thermogravimetric analysis

Thermogravimetric (TG) analysis was carried out using thermomicrobalance TG 209 F1 Libra® from NETZSCH (Selb, Germany). Samples of 5-8 mg, loaded in Al_2O_3 crucible, were heated from 25°C to 1000°C, at the heating rate of 10°C min^{-1}, in an air atmosphere (25 cm^3 min^{-1}) with nitrogen flow (10 cm^3 min^{-1}) as the purge gas.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed using TA Instruments, model Q-100 DSC (New Castle, DE, USA). The sample was loaded on an aluminum pan with a pierced lid. The analysis was carried out in nitrogen atmosphere. The sample was first

cooled from 20°C to 0°C (without the collection of data) and then was heated from 0°C to specified temperature, again cooled to 0°C and heated to the specified temperature. The rate of heating/cooling/heating was 10°C min^{-1}. The specified temperature was the individual temperature for each compound, and it was at least 10°C lower than the onset decomposition temperature, determined from TG analysis. Indium and mercury were used as standards to calibrate the temperature. Heat calibration used indium.

Specific rotation

The specific rotation $[\alpha]_D^{20}$ was measured in ethanol solution using AUTOPOL IV Polarimeter (Rudolph Research Analytical, Hackettstown, NJ, USA) for the concentration of compound about 0.01 g cm^{-3}. A polarimeter precision was 0.001° of angular rotation, and accuracy of temperature determination was 0.1°C.

2. SYNTHESIS AND ANALYSIS OF L-VALINE ALKYL ESTERS HYDROCHLORIDES

General procedure for preparation of L-valine alkyl ester hydrochlorides (ValOR·HCl)

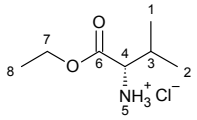
L-valine alkyl ester hydrochlorides (ValOR·HCl) were synthesized by modification of previous method[1]

First, 5 g of L-valine was dispersed into 50 mL of alkyl alcohol at room temperature. Then, two molar equivalents of TMSCl was added into the mixture. The solution was stirred thoroughly at 60ºC for 24 h. Then the excess of TMSCl and alcohol and formed by-products were removed by evaporation at 60°C under vacuum. The product was purified from the residue of unreacted TMSCl and secondary TMSOH or TMSR formed by washing with diethyl ether. The product was then dissolved in chloroform and filtered under reduced pressure to purify it from unreacted amino acid. The filtrate was distilled off under reduced pressure (60°C, 10 mbar). The obtained hydrochloride was dried in a vacuum dryer at 60°C, 5 mbar for 24 h. As a result, the L-valine alkyl ester hydrochloride (ValOR·HCl) was obtained with good yield (95-99%).

Table SD1. Amounts of substrates and yields of synthesis of L-valine alkyl ester hydrochlorides (L-ValOR·HCl)

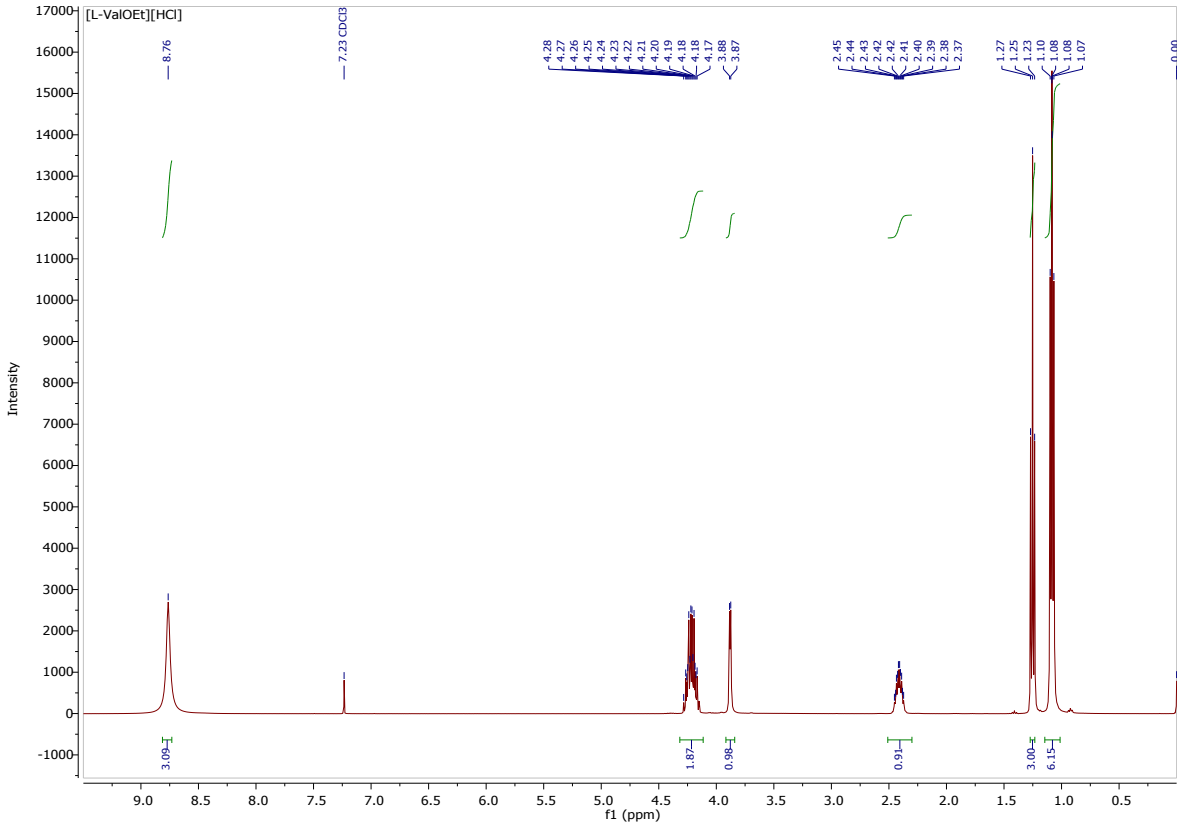
No.	Compound	Reactants		Product		
		Amino acid [g]	TMSCl [mL]	ValOR·HCl [g]	Yield [%]	State
1	ValOEt·HCl	5.21	11.29	7.68	95	white solid
2	ValOiPr·HCl	5.50	11.92	8.17	89	white solid
3	ValOPr·HCl	5.40	11.70	8.36	93	white solid
4	ValOBu·HCl	5.33	11.55	8.87	93	white solid
5	ValOAm·HCl	5.00	10.83	9.00	94	white solid
6	ValOHex·HCl	5.68	12.31	10.58	92	white solid

ValOEt·HCl – L-valine ethyl ester hydrochloride

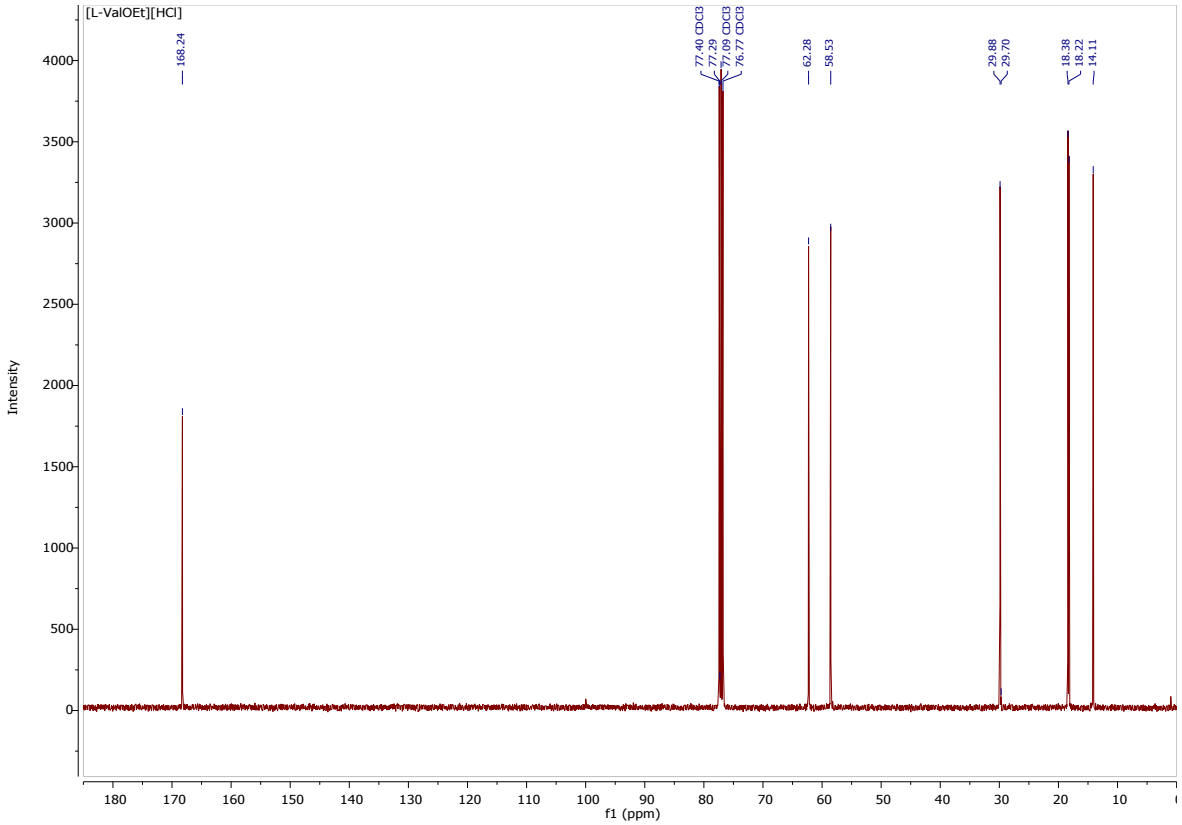


^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 8.76 (s, 3H, H5); 4.17-4.27 (m, 2H, H7); 3.87 (d, 1H, $J_{4,3}$=4.1 Hz, H4); 2.39-2.43 (m, 1H, H3); 1.23 (t, 3H, $J_{2,3}$=7.1 Hz, H8); 1.07 (dt, 6H, H1, H2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 168.25 (C6); 62.29 (C4); 58.55 (C7); 29.88 (C3); 18.39 (C8); 18.23 (C2) 14.12 (C1); **FT-IR**: ν (ATR): 2966; 2942; 2868; 2636; 2605; 2048; 1732; 1596; 1574; 1524; 1504; 1470; 1447; 1418; 1399; 1355; 1291; 1263; 1221; 1168; 1136; 1106; 1066; 1034; 1012; 931; 862; 837; 804; 772; 743; 680; 515; 422 cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 208.4 nm; **Elemental analysis:** calc. (%) for

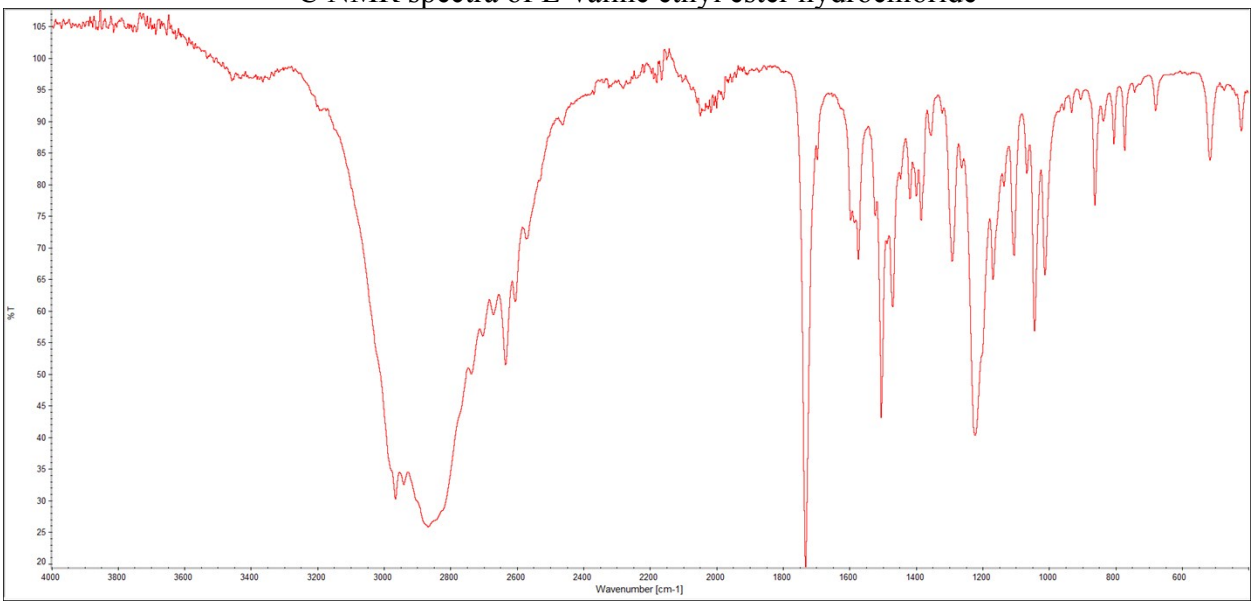
$C_7H_{16}NO_2Cl$ (181.662): C (46.28), H (8.88), N (7.71), O (17.61), found: C (46.15), H (8.88), N (7.72), O (17.52); $\mathbf{T_m}$=102.9-112.5^{0}C; $[\alpha]_D^{20}$ = +14.057 (c=1.059 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine ethyl ester hydrochloride

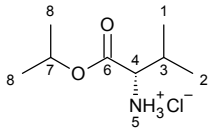


^{13}C NMR spectra of L-valine ethyl ester hydrochloride

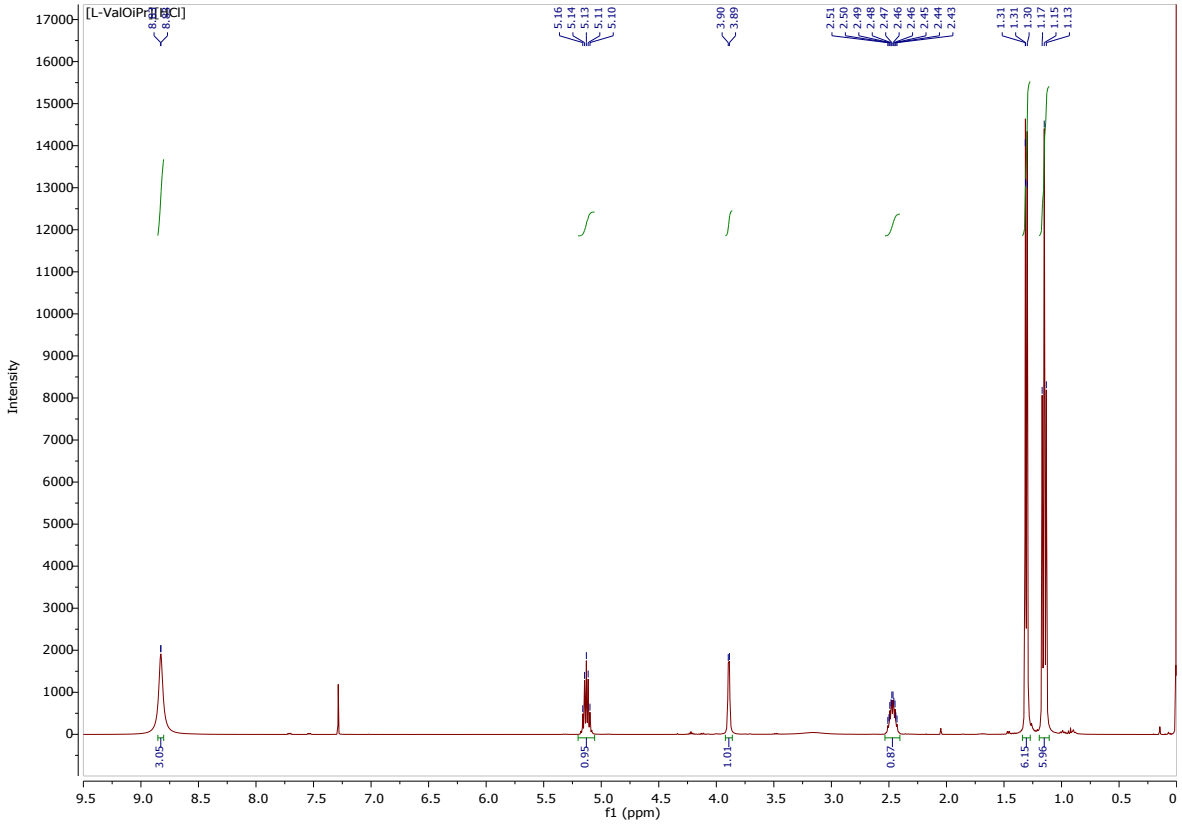


FTIR spectra of L-valine ethyl ester hydrochloride

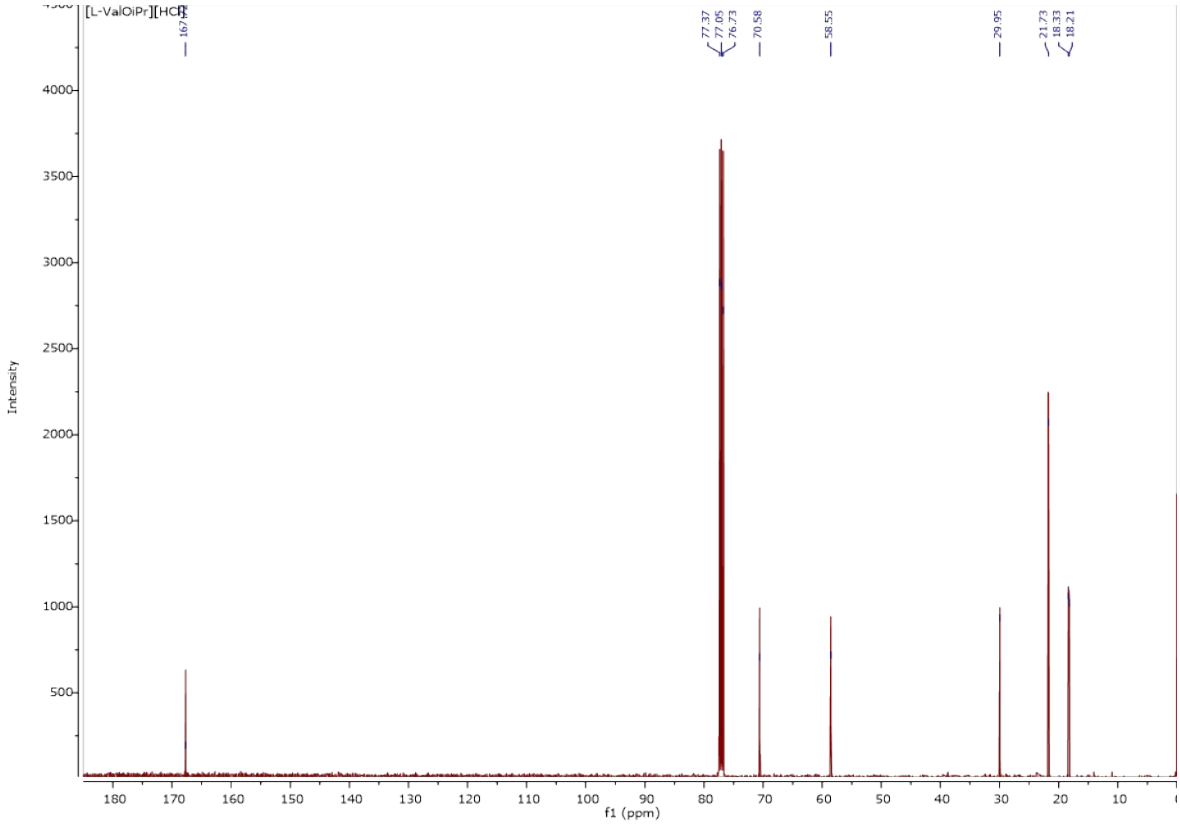
ValOiPr·HCl – L-valine isopropyl ester hydrochloride



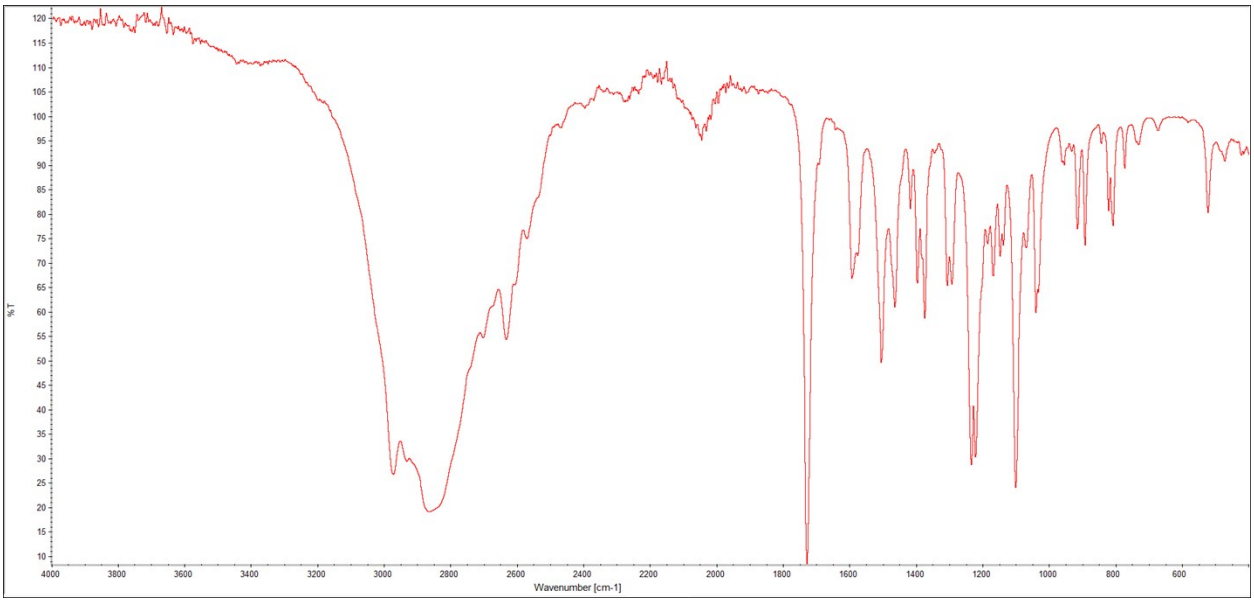
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 8.83 (s, 3H, H5); 5.10-5.16 (m, 1H, H7); 3.89 (d, 1H, $J_{4,3}$=3.9 Hz, H4); 2.44-2.49 (m, 1H, H3); 1.30 (d, 6H, $J_{8,7}$=6.1, H8); 1.15 (t, 6H, $J_{1,3}$=7.3 Hz, H2, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 167.72 (C6); 70.58 (C4); 58.55 (C7); 29.96 (C3); 21.73 (C8); 18.34 (C2) 18.34 (C1); **FT-IR**: ν (ATR): 2893; 2863; 2703; 2570; 2044; 1728; 1592; 1504; 1463; 1397; 1375; 1375; 1344; 1235; 1220; 1184; 1168; 1147; 1147; 1138; 1101; 1068; 955; 931; 914; 822; 843; 772; 730; 670; 521; 471; 422 cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 202.0 nm; **Elemental analysis:** calc. (%) for $C_8H_{18}NO_2Cl$ (195.689): C (49.10), H (9.27), N (7.16), O (16.35), found: C (49.17), H (9.28), N (7.16), O (16.47); **T_m**=116.7-126.4^{0}C; $[\alpha]_D^{20}$ = +17,872 (c=0.705 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine isopropyl ester hydrochloride

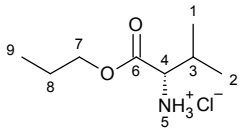


^{13}C NMR spectra of L-valine isopropyl ester hydrochloride

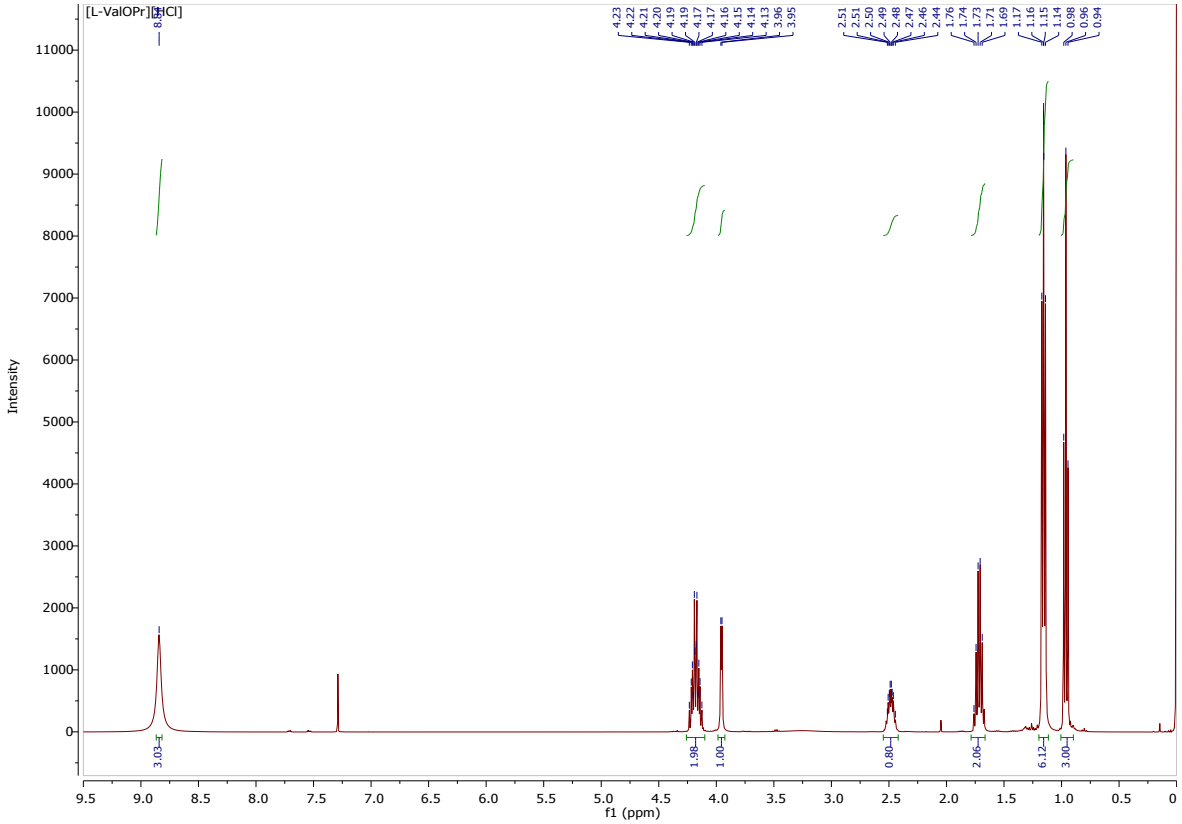


FTIR spectra of L-valine isopropyl ester hydrochloride

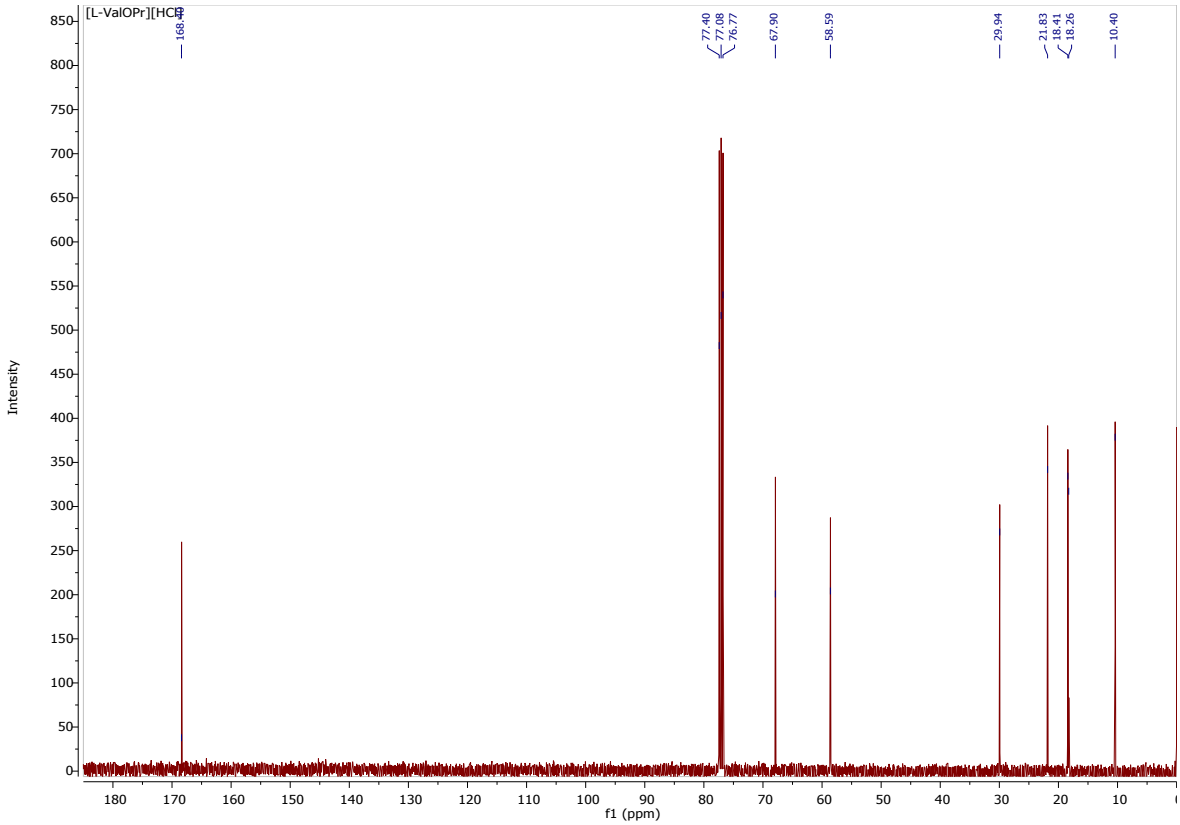
ValOPr·HCl – L-valine propyl ester hydrochloride



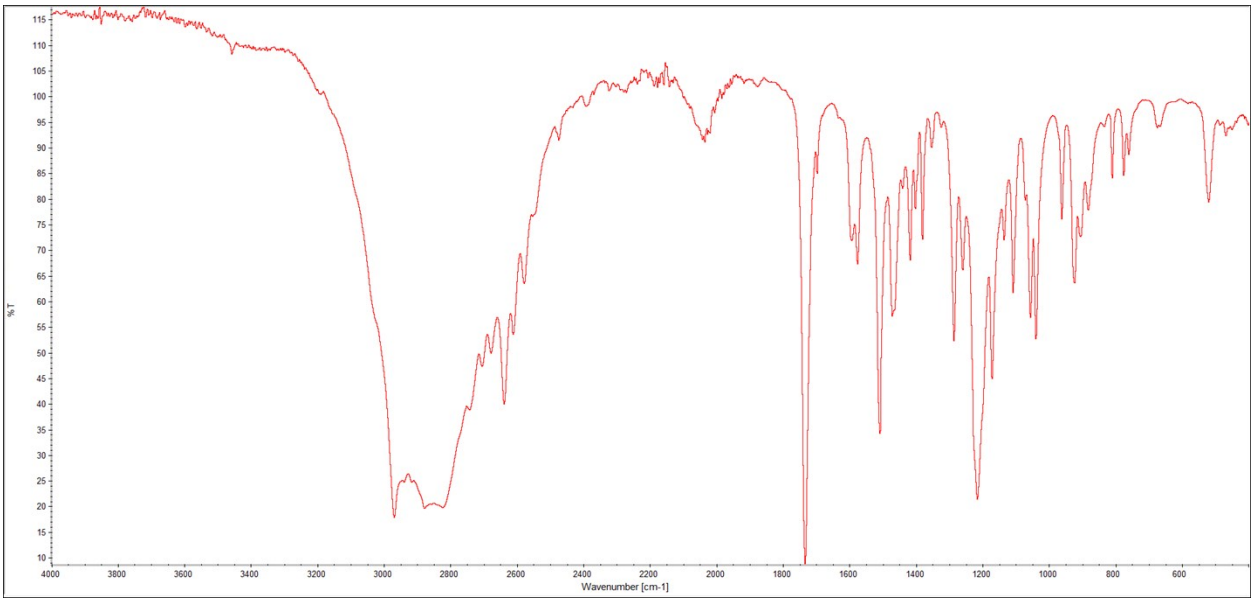
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 8.84 (s, 3H, H5); 4.17-4.22 (m, 2H, H7); 3.98 (d, 1H, $J_{4,3}$=4.2 Hz, H4); 2.46-2.51 (m, 1H, H3); 1.67-1.74 (m, 2H, H8); 1.14 (dt, 6H, H9, H2); 0.94 (t, 3H, $J_{2,3}$=7.5 Hz, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 168.40 (C6); 67.90 (C4); 58.59 (C7); 29.94 (C3); 20.84 (C8); 18.41 (C2); 18.26 (C1) 10.41 (C9); **FT-IR**: ν (ATR): 3389; 3323; 2963; 2935; 2877; 1728; 1605; 1466; 1387; 1368; 1338; 1223; 1175; 1057; 982; 957; 846; 758; cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 202.0 nm; **Elemental analysis:** calc. (%) for $C_8H_{18}NO_2Cl$ (195.689): C (49.10), H (9.27), N (7.16), O (16.35), found: C (49.09), H (9.29), N (7.17), O (16.34); **T_m**=76.7-85.0^{0}C; $[\alpha]_D^{20}$ = +16,288 (c=0.523 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine propyl ester hydrochloride

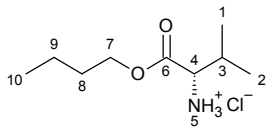


^{13}C NMR spectra of L-valine propyl ester hydrochloride

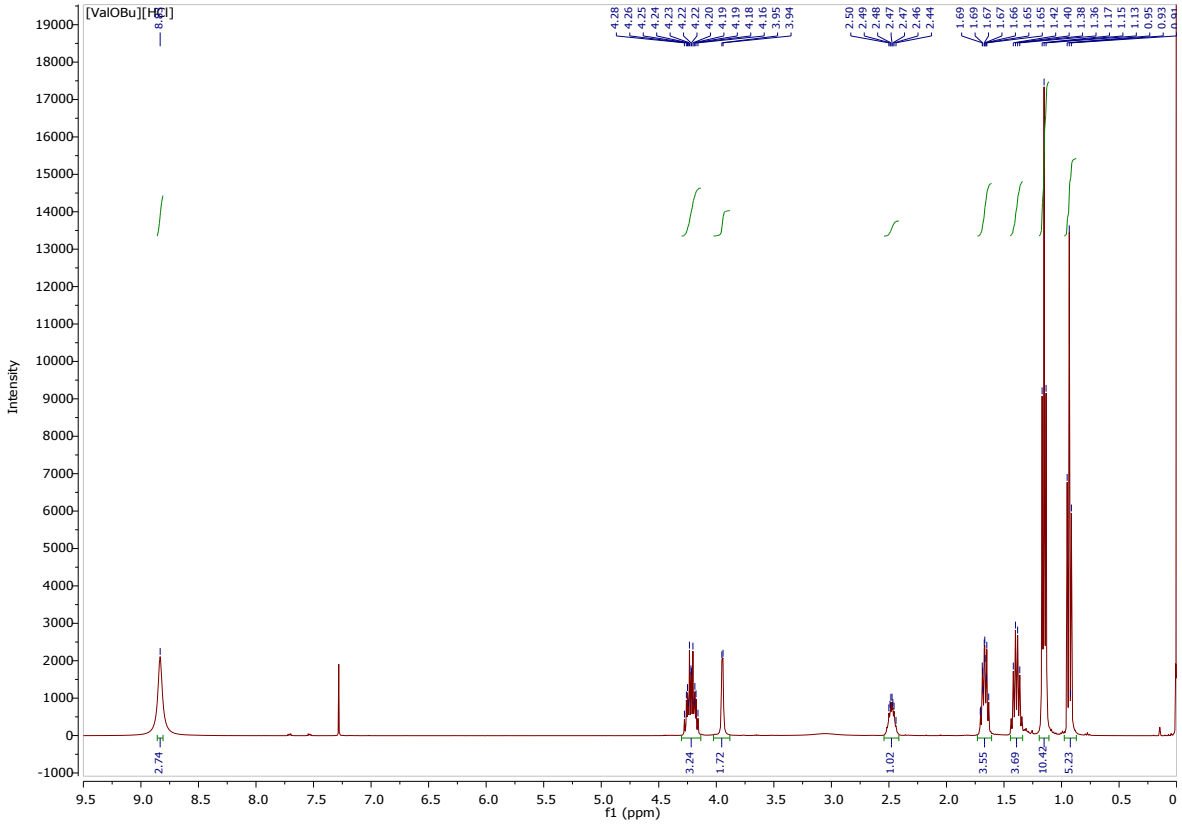


FTIR spectra of L-valine propyl ester hydrochloride

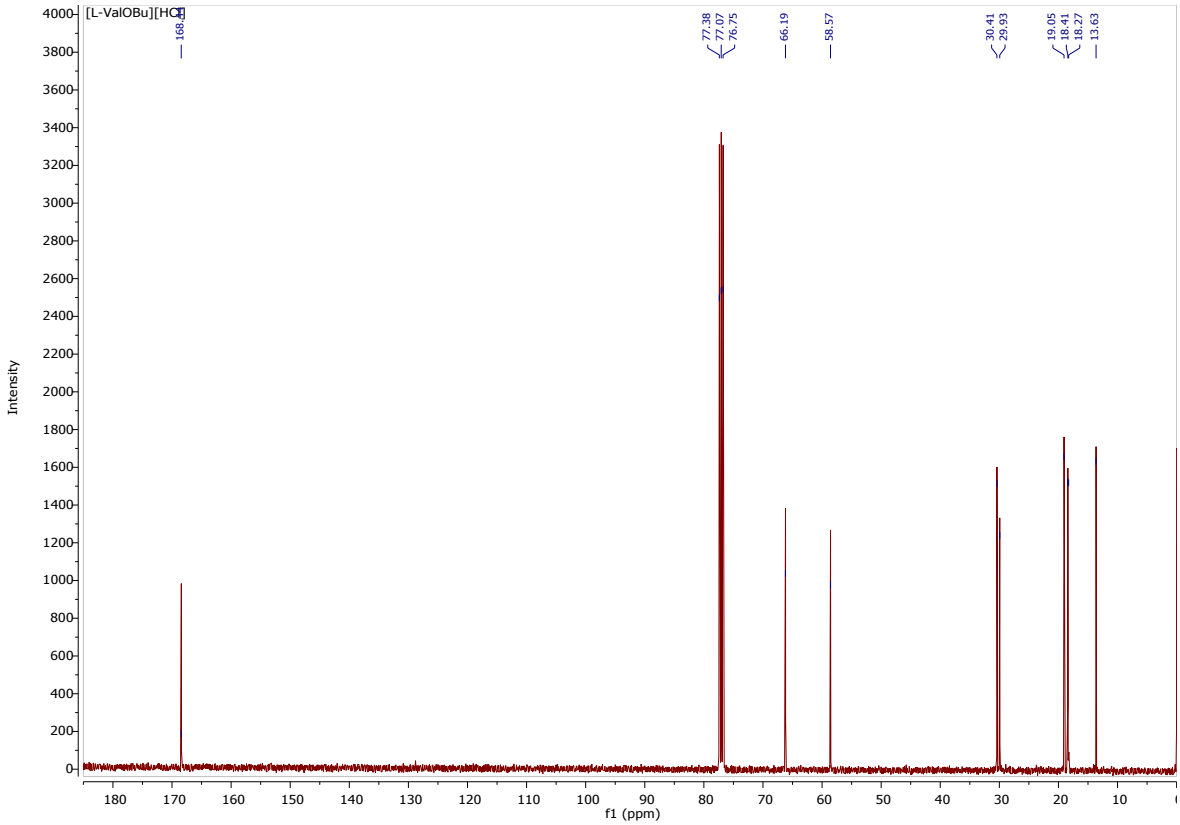
ValOBu·HCl – L-valine butyl ester hydrochloride



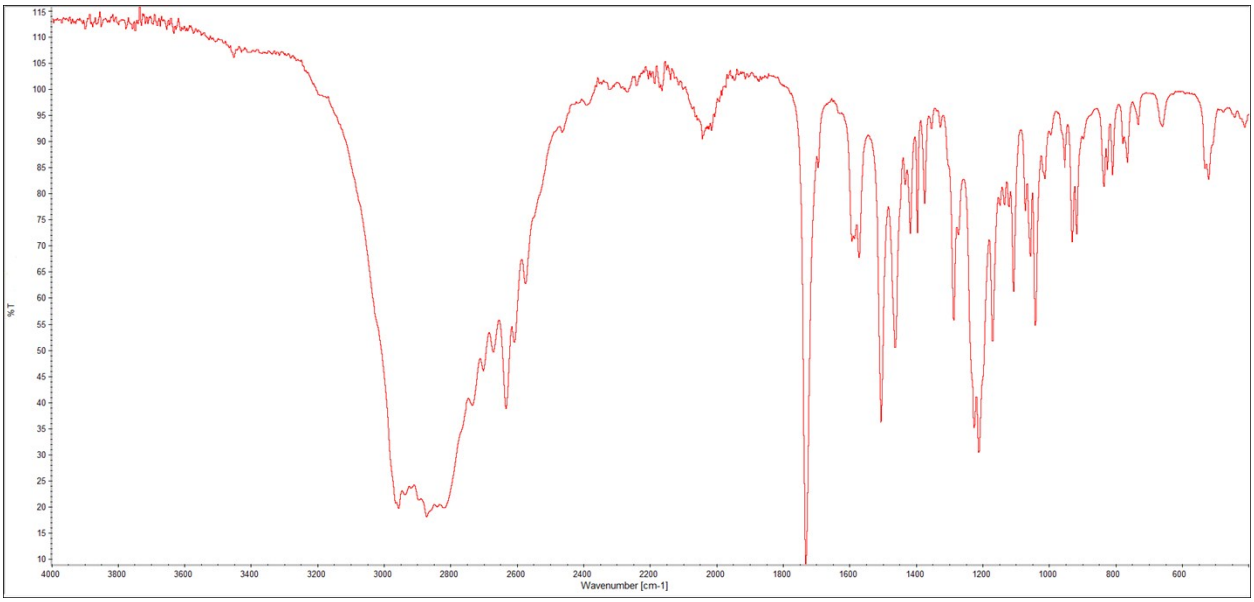
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 8.83 (s, 3H, H5); 4.18-4.28 (m, 2H, H7); 3.94 (d, 1H, $J_{4,3}$=3.9 Hz, H4); 2.46-2.50 (m, 1H, H3); 1.63-1.70 (m, 2H, H8); 1.35-1.44 (m, 2H, H9); 1.13 (dt, 6H, H10, H2); 0.91 (t, 3H, $J_{1,3}$=7.5 Hz; H1);**^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 168.44 (C6); 66.19 (C4); 58.58 (C7); 30.41 (C3); 29.93 (C8); 19.06 (C9); 18.41 (C2); 18.23 (C1); 13.63 (C10); **FT-IR**: ν (ATR): 2957; 2872; 2820; 2735; 2672; 2608; 2575; 2041; 1731; 1695; 1593; 1585; 1572; 1505; 1463; 1417; 1397; 1353; 1326; 1287; 1273; 1224; 1210; 1169; 1148; 1134; 1121; 1107; 11070; 1056; 1041; 1013; 995; 953; 930; 916; 835; 825; 777; 764; 731; 658; 529; 519' 412 cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 202.0 nm; **Elemental analysis:** calc. (%) for $C_9H_{20}NO_2Cl$ (209.716): C (51.55), H (9.61), N (6.68), O (15.26), found: C (51.87), H (9.64), N (6.72), O (15.17); **T_m**=72.4-88.3^{0}C; $[\alpha]_D^{20}$ = +14,266 (c=0.722 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine butyl ester hydrochloride

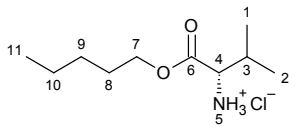


^{13}C NMR spectra of L-valine butyl ester hydrochloride



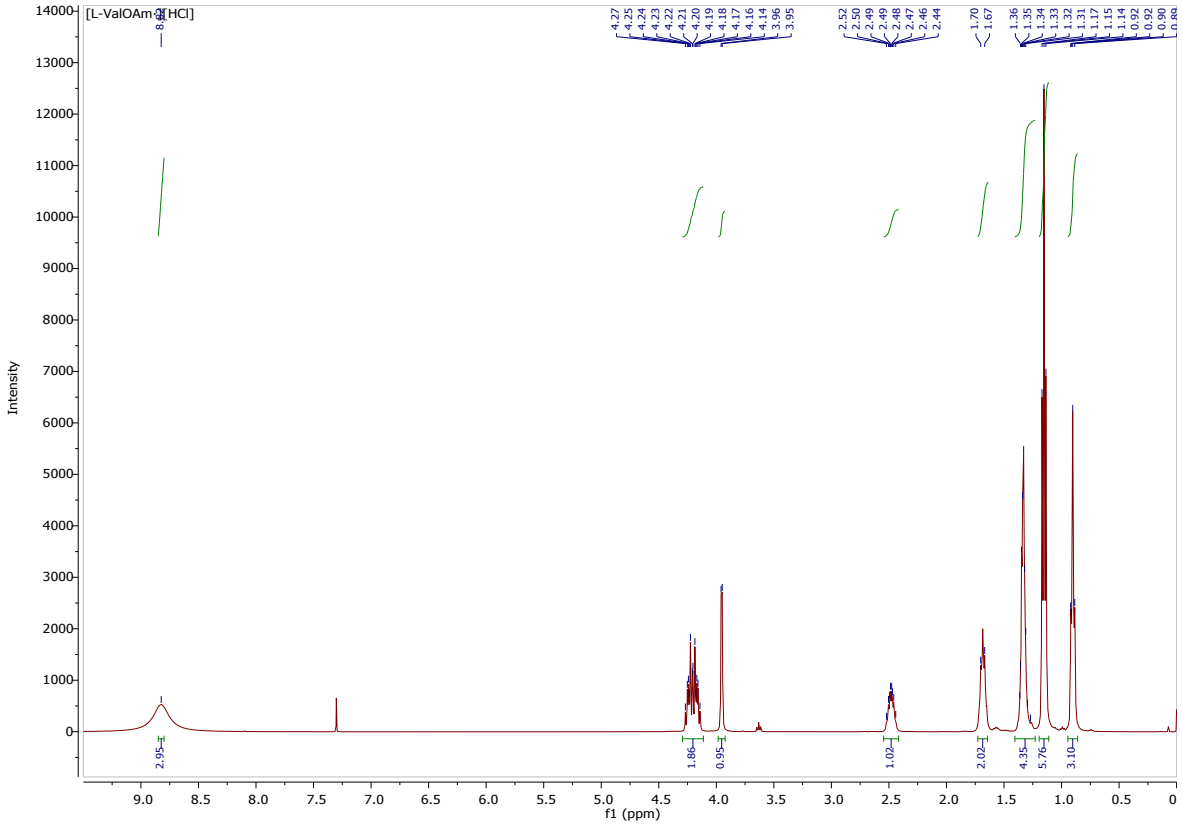
FTIR spectra of L-valine ethyl butyl ester hydrochloride

ValOAm·HCl – L-valine pentyl ester hydrochloride

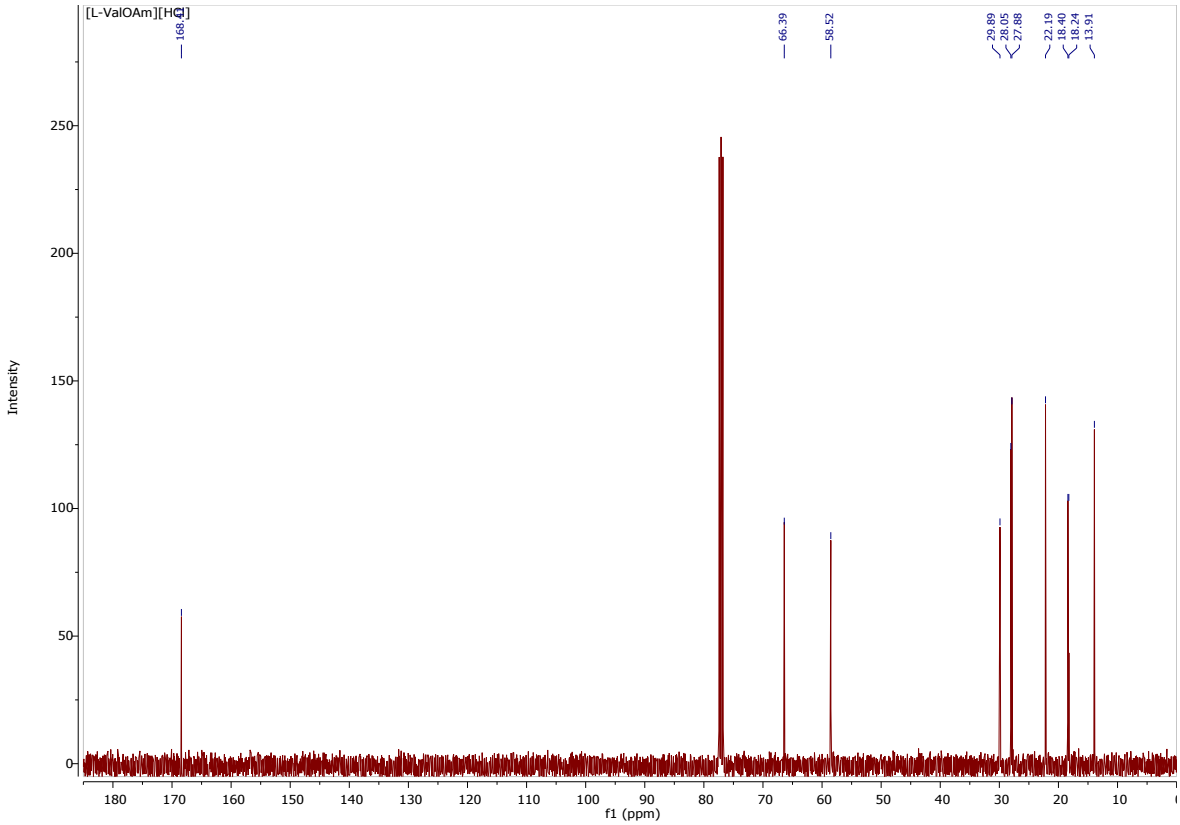


^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 8.82 (s, 3H, H5); 4.14-4.27 (m, 2H, H7); 3.95 (d, 1H, $J_{4,3}$=3.8 Hz, H4); 2.47-2.50 (m, 1H, H3); 1.65-1.70 (m, 2H, H8); 1.31-1.35 (m, 4H, H9, H10) 1.15 (t, 6H, H2, H11); 0.89 (t, 3H, $J_{1,3}$=6.9 Hz, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 168.43 (C6); 66.40 (C4); 58.53 (C7); 29.90 (C3); 28.06 (C8); 27.88 (C9); 22.20 (C10); 18.40 (C2); 18.25 (C1); 13.92 (C11);

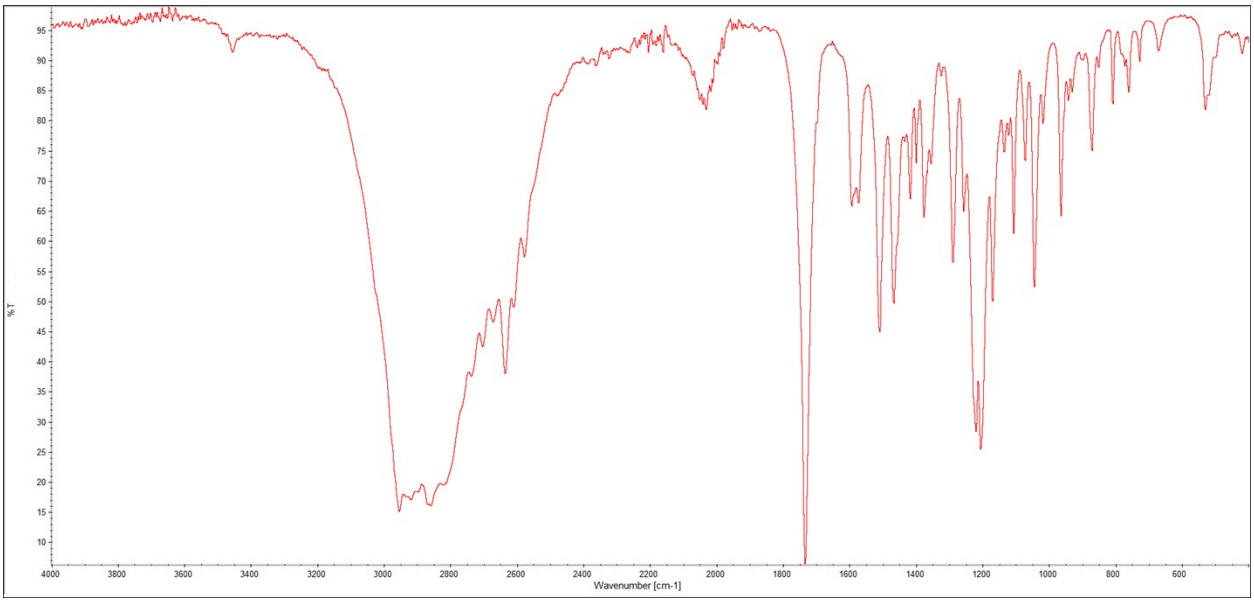
FT-IR: ν (ATR): 29955; 2920 2860; 2637; 2041; 1733; 1593; 1573; 1510; 1466; 1417; 1400; 1377; 1355; 1324; 1289; 1257; 1170; 1135; 1122; 1107; 1071; 1043; 1018; 965; 941; 898; 871; 851; 807; 771; 760; 669; 529; 419 cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 202.2 nm; **Elemental analysis:** calc. (%) for $C_{11}H_{22}NO_2Cl$ (223.742): C (53.83), H (9.93), N (6.26), O (14.30), found: C (53.73), H (9.93), N (6.28), O (14.26); **T_m**=55.1-68.3^{0}C; $[\alpha]_D^{20}$ = +14.189 (c=0.592 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine pentyl ester hydrochloride

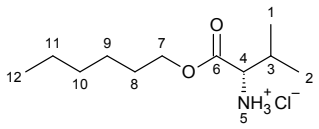


^{13}C NMR spectra of L-valine pentyl ester hydrochloride

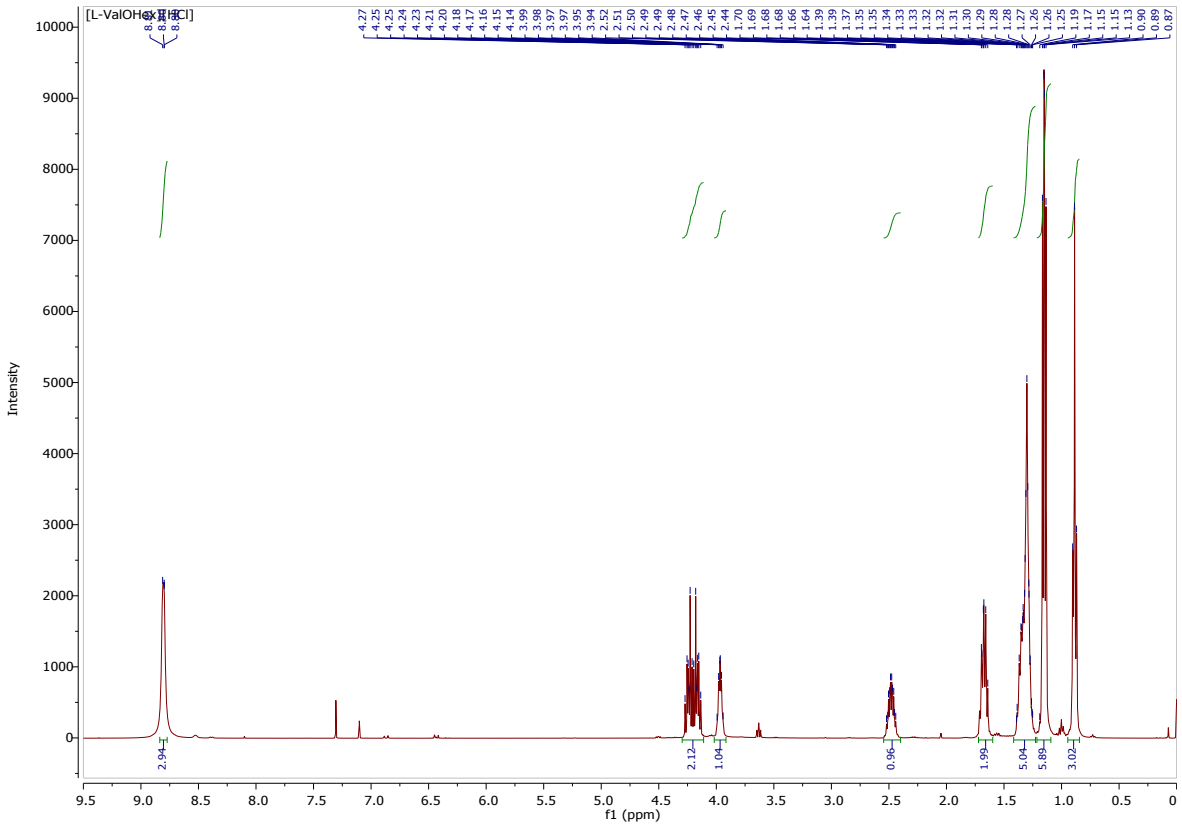


FTIR spectra of L-valine pentyl ester hydrochloride

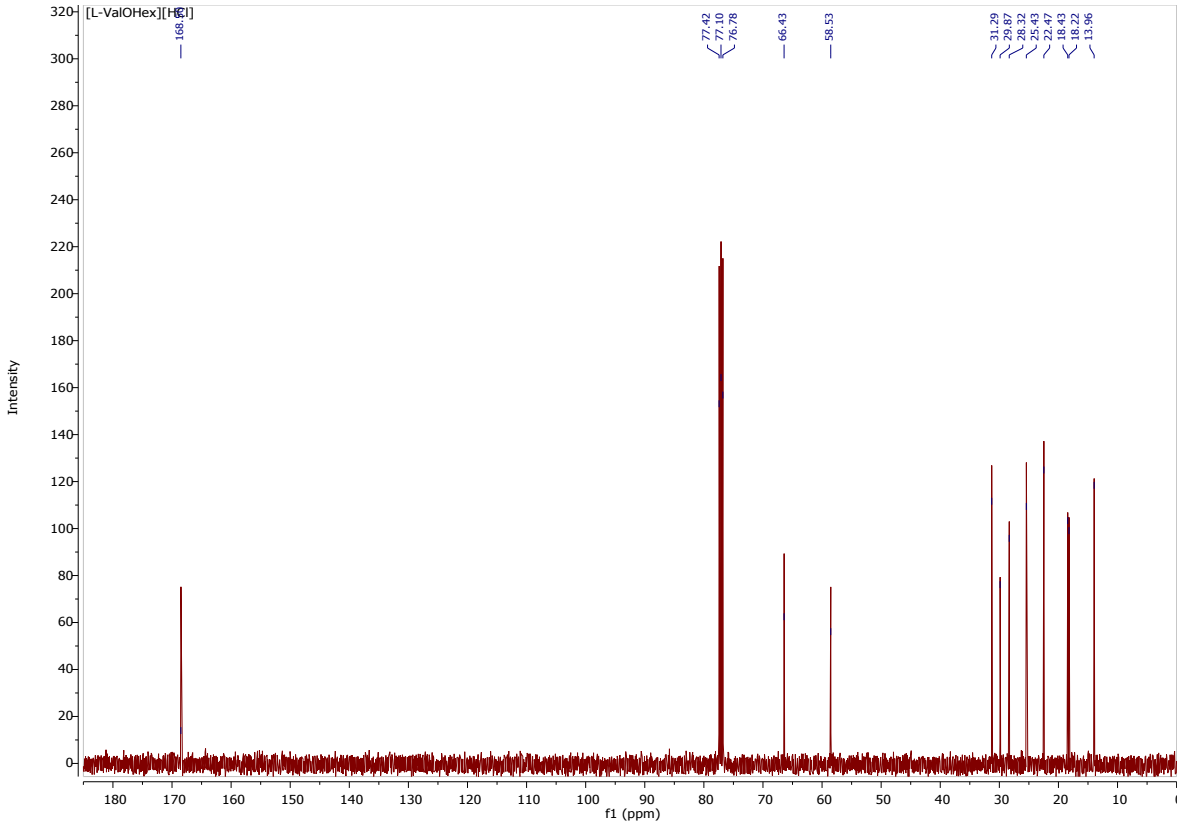
ValOHex·HCl – L-valine hexyl ester hydrochloride



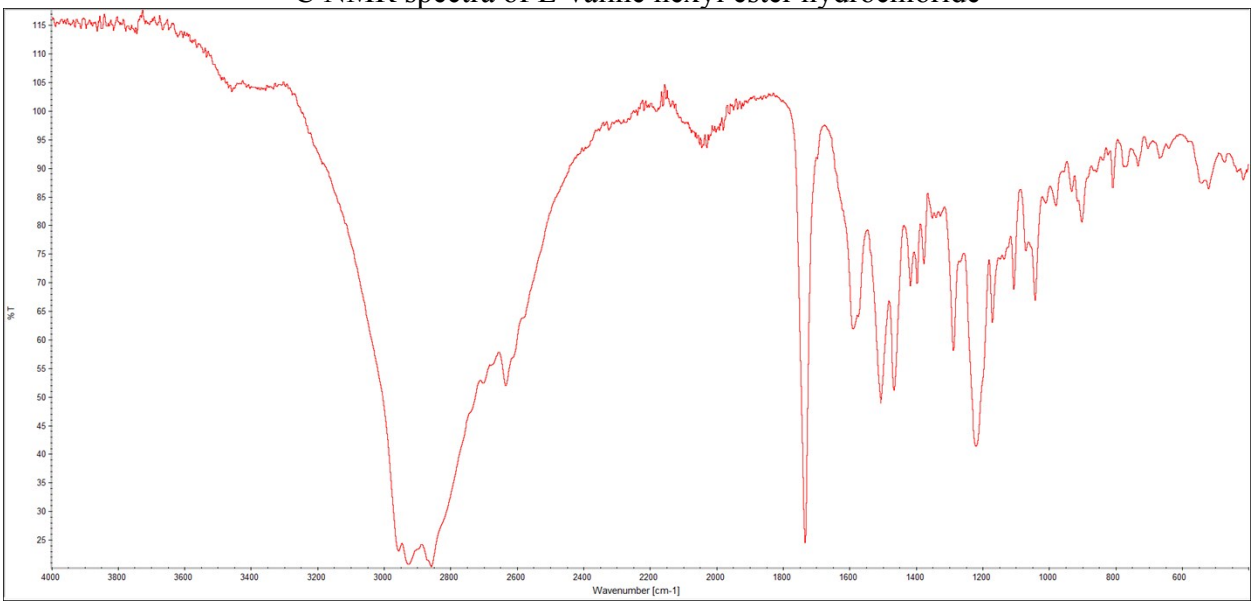
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 8.81 (s, 3H, H5); 4.14-4.27 (m, 2H, H7); 3.96 (d, 1H, $J_{4,3}$=4.8 Hz, H4); 2.44-2. 52 (m, 1H, H3); 1.25-1.39 (m, 6H, H9, H10, H11); 1.14 (dt, 6H, H12, H2); 0.87 (t, 3H, H1, $J_{1,3}$=7.1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 168.50 (C6); 66.43 (C4); 58.53 (C7); 31.29 (C3); 29.87 (C8); 28.32 (C9); 25.43 (C10); 22.47 (C11); 18.43 (C2); 18.22 (C1); 13.96 (C12); **FT-IR**: ν (ATR): 2957; 2927; 2858; 2635; 2043; 1733; 1589; 1505; 1466; 1417; 1397; 1377; 1350; 1288; 1219; 1170; 1107; 1069; 1042; 1010; 980; 931; 901; 858; 807; 769; 732; 702; 667; 519; 472; 416 cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 207.6 nm; **Elemental analysis:** calc. (%) for $C_{11}H_{24}NO_2Cl$ (237. 769): C (55.57), H (10.17), N (5.89), O (13.46), found: C (55.76), H (10.25), N (5.88), O (14.59); $[\alpha]_D^{20}$ = +11.446 (c=0.664 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine hexyl ester hydrochloride



^{13}C NMR spectra of L-valine hexyl ester hydrochloride



FTIR spectra of L-valine hexyl ester hydrochloride

3. SYNTHESIS AND ANALYSIS OF L-VALINE ALKYL ESTERS

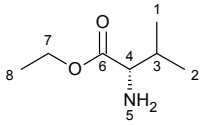
General procedure for preparation of L-valine alkyl esters (ValOR)

The obtained in the first step ValOR·HCl was added to small amount of distilled water and neutralized by the addition of one to three molar equivalents of 25% ammonium hydroxide aqueous solution. The solution was intensively mixed and then, the product was extracted with diethyl ether. The organic layer was dried using anhydrous Na_2SO_4 and then concentrated under vacuum to receive L-ValOR.

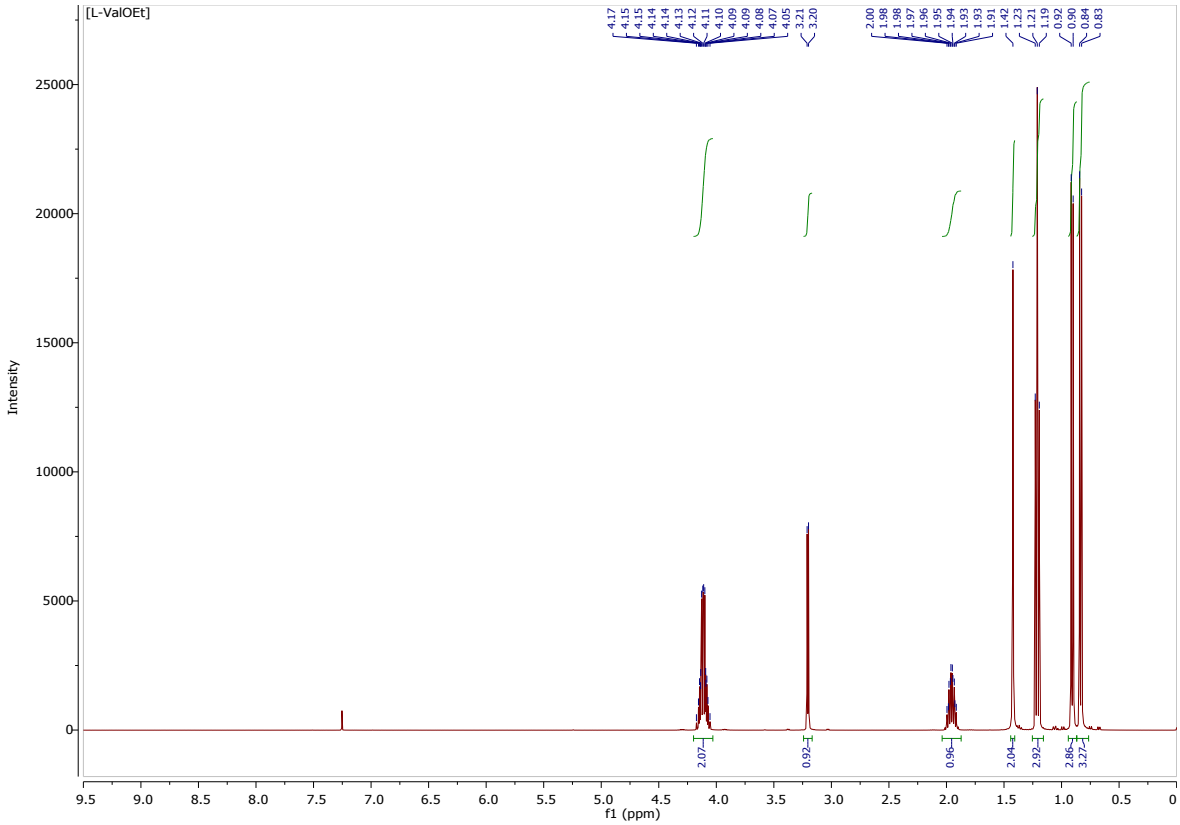
Table SD2. Amounts of substrates and yields of synthesis of L-valine alkyl esters (L-ValOR)

No.	Compound	Substrate		Product		
		ValOR·HCl [g]	25% $NH_3 \cdot H_2O$ [mL]	ValOR [g]	Yield [%]	State
1	ValOEt	1.00	2.55	0.67	84	yellow liquid
2	ValOiPr	1.00	2.35	0.64	79	yellow liquid
3	ValOPr	1.23	2.91	0.76	76	yellow liquid
4	ValOBu	1.06	2.33	0.73	83	yellow liquid
5	ValOAm	1.15	2.37	0.78	82	yellow liquid
6	ValOHex	0.99	1.93	0.68	80	yellow liquid

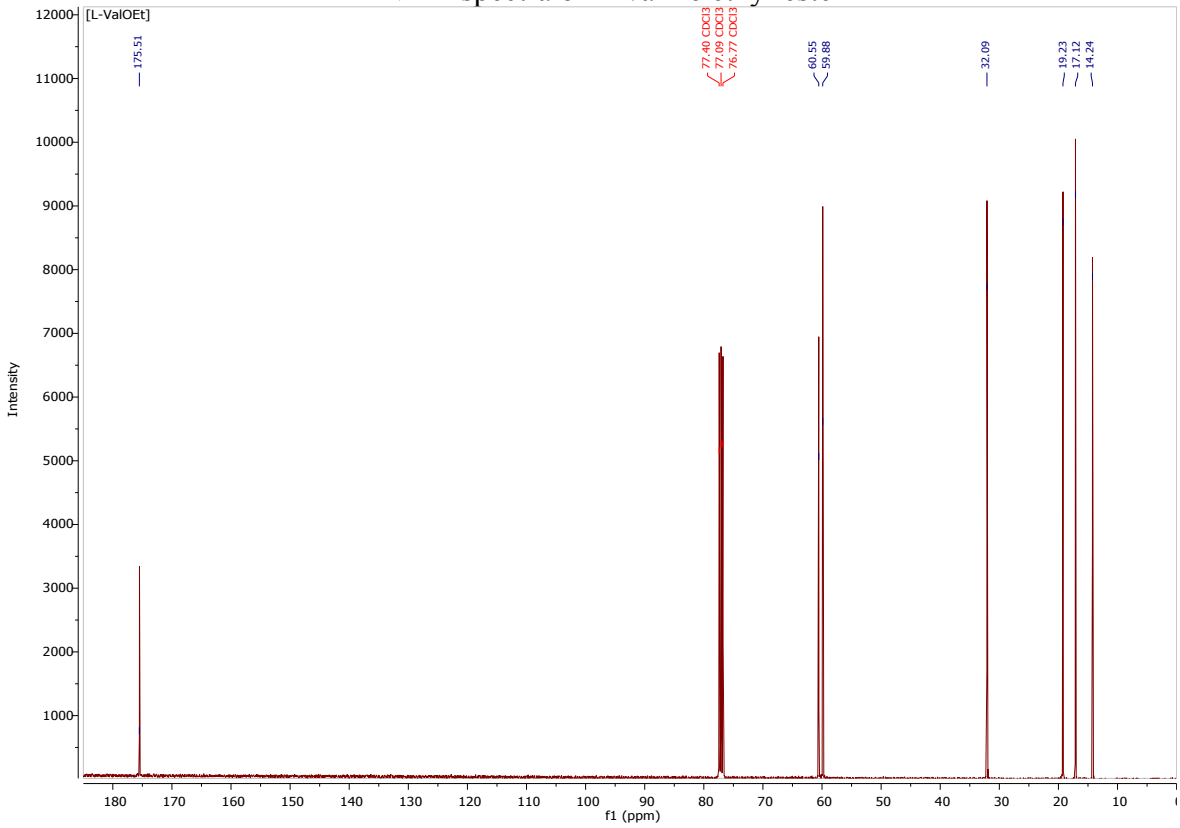
ValOEt – L-valine ethyl ester



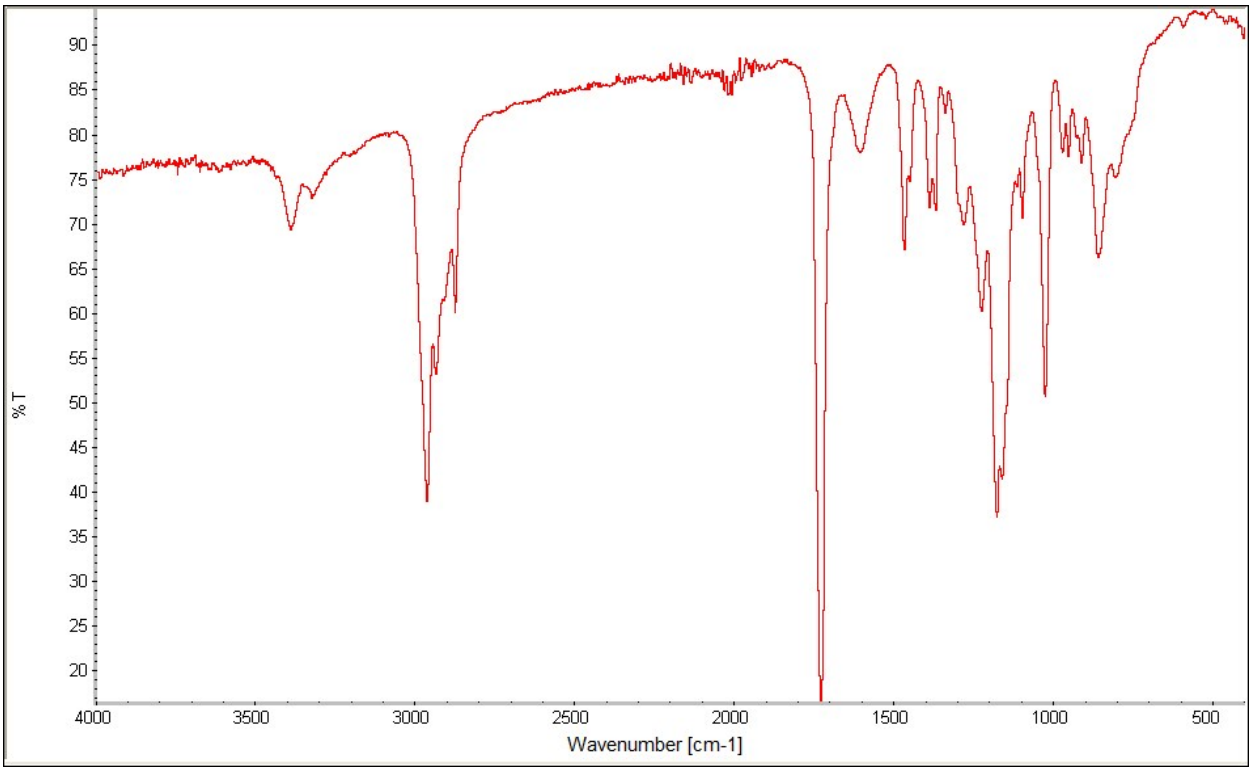
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 4.07-4.19 (m, 2H, H7); 3.23 (d, 1H, $J_{4,3}$=4.9 Hz, H4); 1.94-2.01 (m, 1H, H3); 1.44 (s, 2H, H5); 1.23 (t, 3H, $J_{2,3}$=7.1 Hz, H8); 0.92 (d, 3H, $J_{2,3}$=6.8 Hz, H2); 0.84 (d, 3H, $J_{1,3}$=6.9 Hz, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 175.51 (C6); 60.56 (C4); 59.89 (C7); 32.10 (C3); 19.24 (C8); 17.12 (C2) 14.24 (C1); **FT-IR**: ν (ATR): 3388; 3324; 2962; 2933; 2874; 1728; 1605; 1467; 1448; 1387; 1368; 1338; 1280; 1223; 1176; 1159; 1114; 1024; 969; 952; 858; 804; 593; 403 cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 202.3 nm; $[\alpha]_D^{20}$ = +28.141 (c=0.590 g/100 cm^3 EtOH)



^{1}H NMR spectra of L-valine ethyl ester

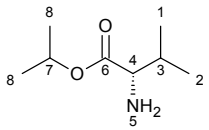


^{13}C NMR spectra of L-valine ethyl ester

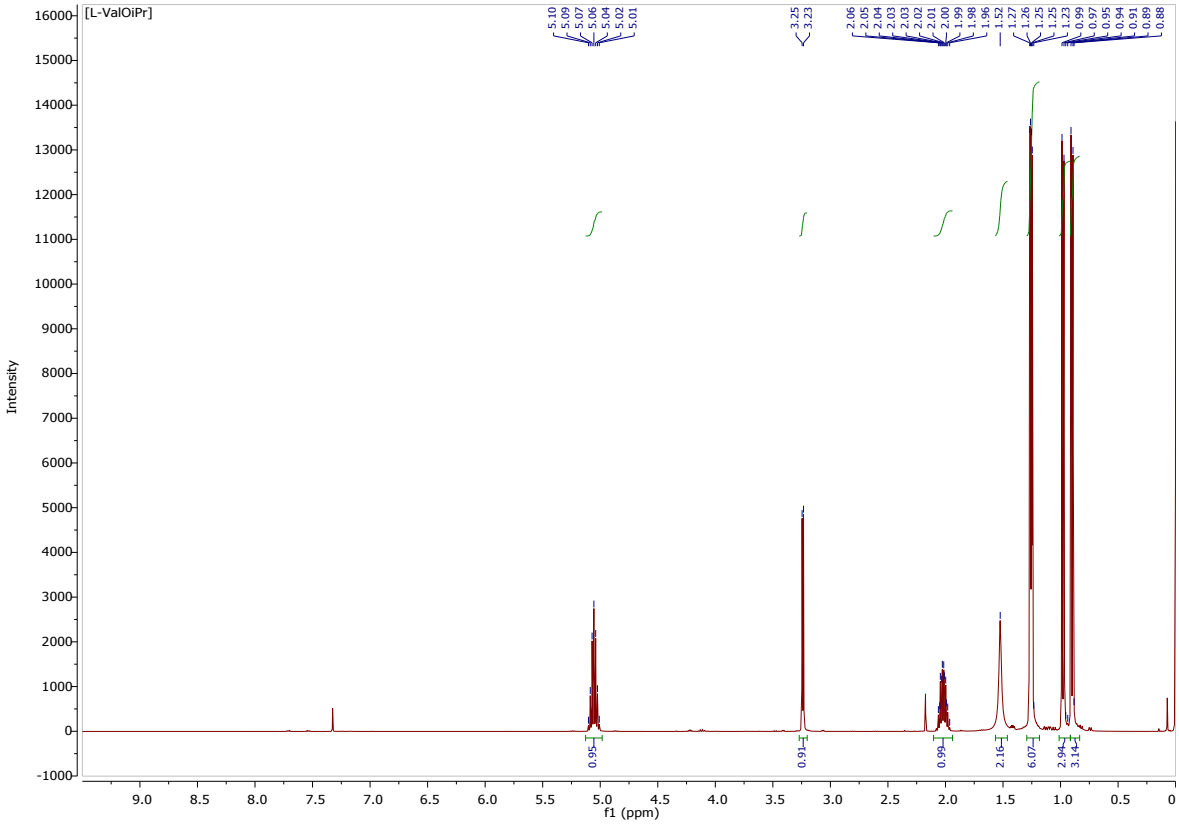


FTIR spectra of L-valine ethyl ester

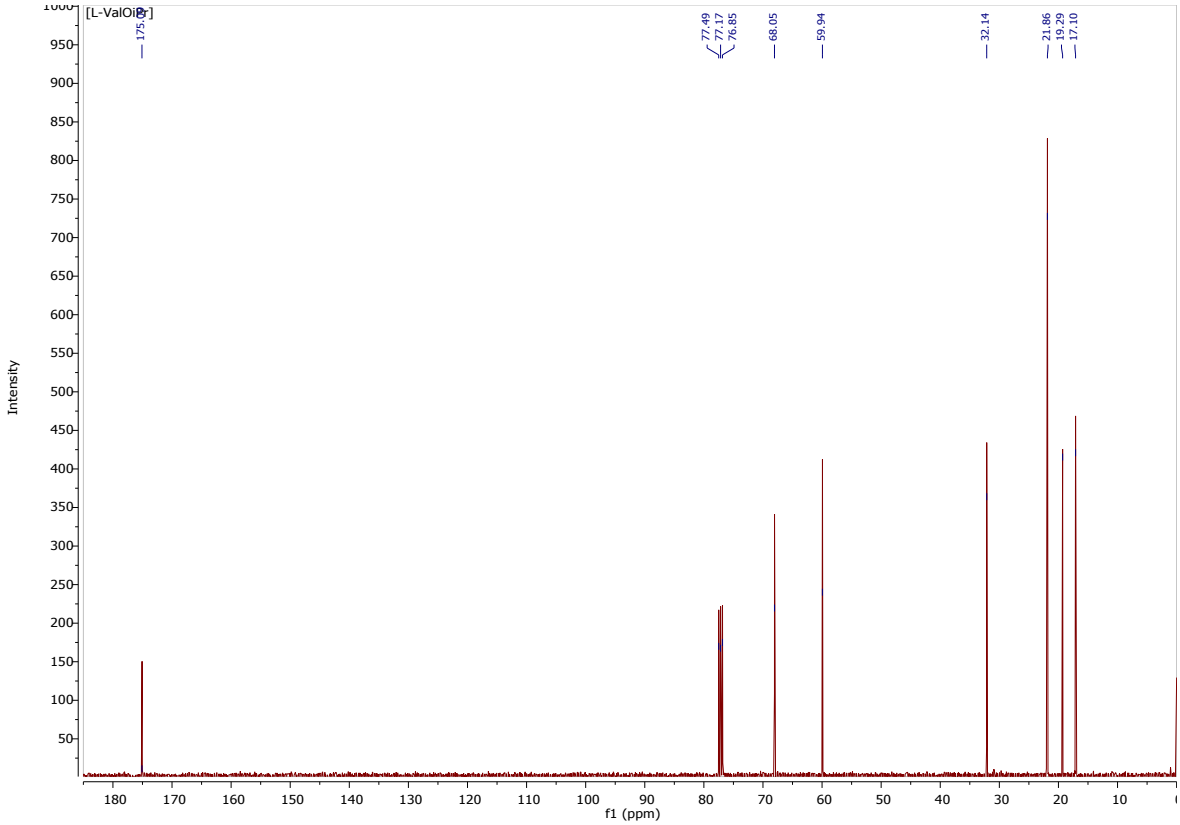
ValOiPr – L-valine isopropyl ester



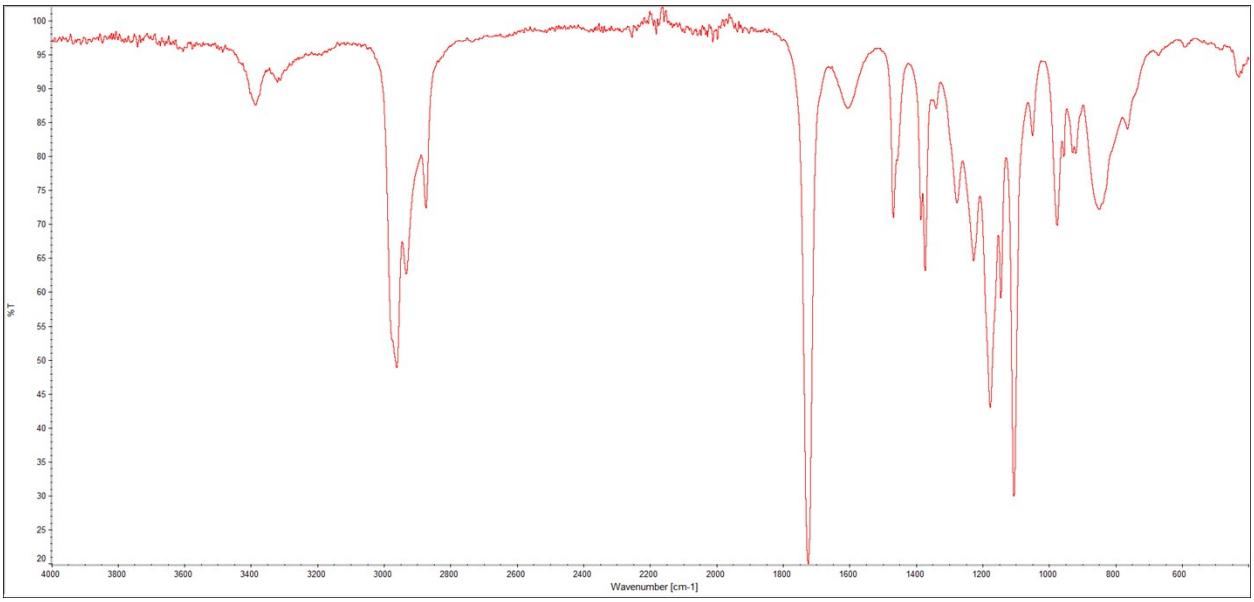
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 4.97-5.03 (m, 1H, H7); 3.18 (d, 1H, $J_{4,3}$=4.9 $J_{2,3}$=7.1 Hz, H2); 0.84 (d, 3H, $J_{1,3}$=6.9 Hz, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 175.09 (C6); 68.05 (C4); 59.94 (C7); 32.14 (C3); 21.86 (C8); 19.30 (C2) 17.10 (C1); **FT-IR**: ν (ATR): 3388; 3323; 2963; 2934; 2874; 1724; 1606; 1468; 1456; 1386; 1373; 1339; 1277; 1226; 1177; 1145; 1049; 977; 956; 928; 919; 850; 434; 429; cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 202.6 nm; $[\alpha]_D^{20}$ = +30.759 (c=0.790 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine isopropyl ester

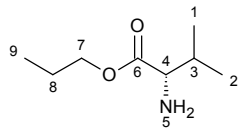


^{13}C NMR spectra of L-valine isopropyl ester

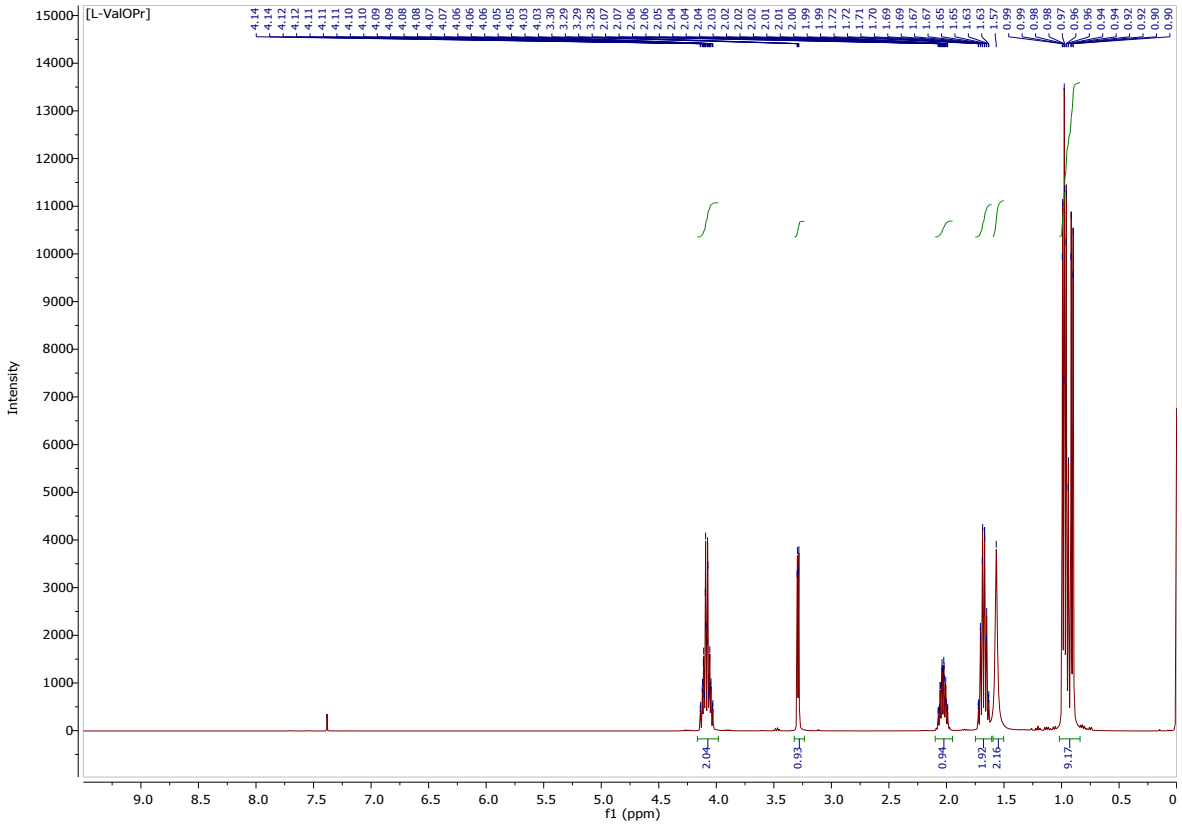


FTIR spectra of L-valine isopropyl ester

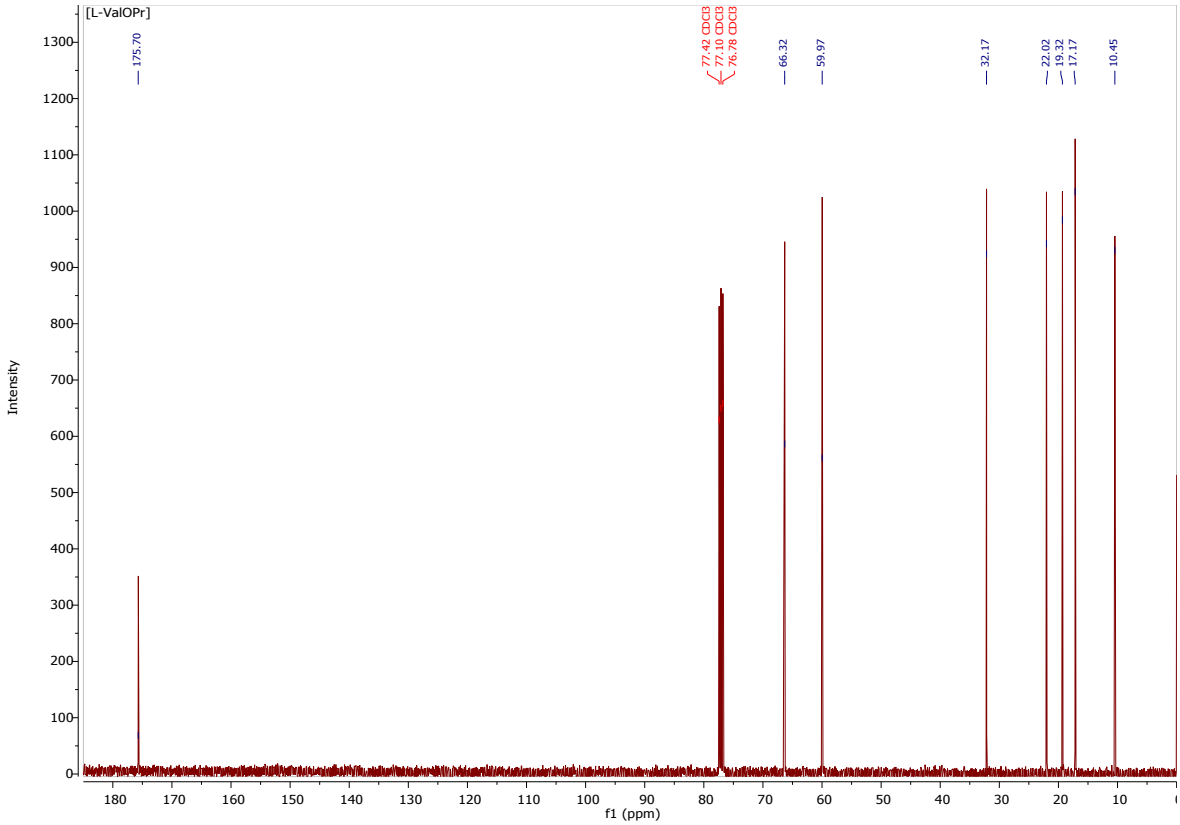
ValOPr – L-valine propyl ester



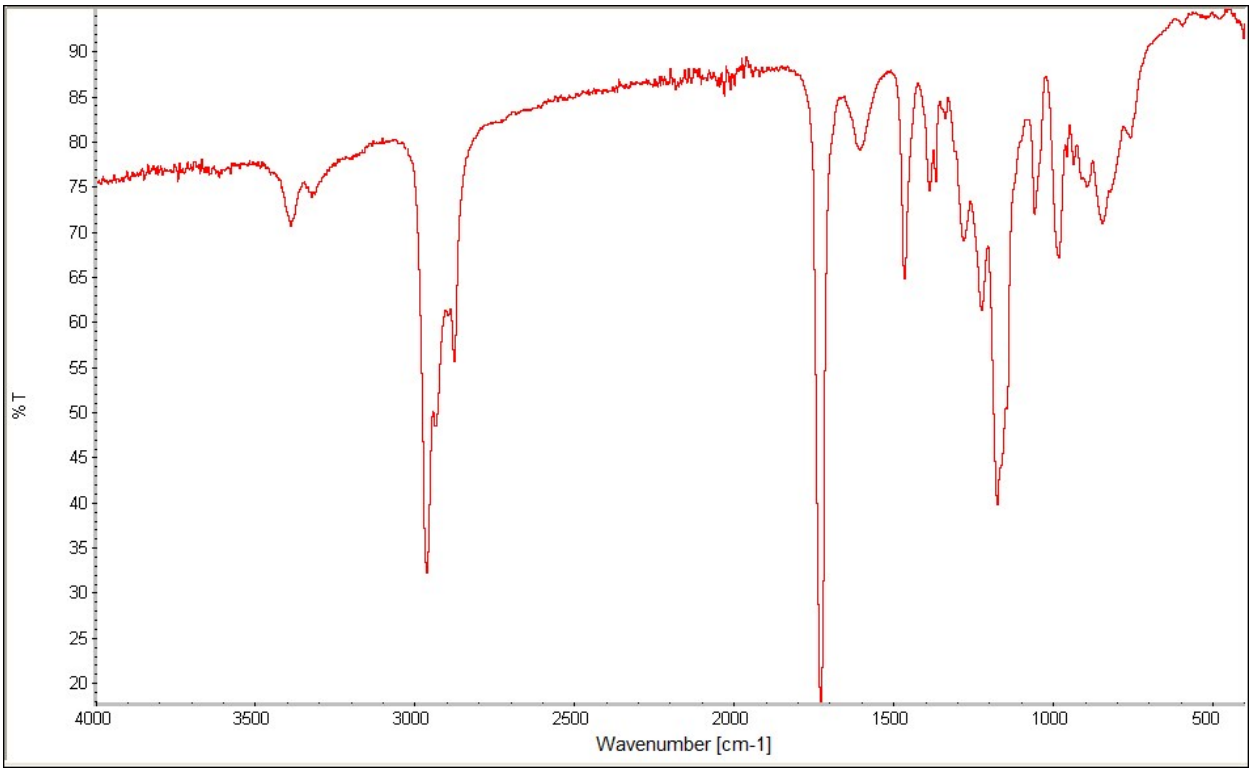
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 4.05-4.12 (m, 2H, H7); 3.28 (d, 1H, $J_{4,3}$=5.2 Hz, H4); 1.99-2.06 (m, 1H, H3); 1.63-1.72 (m, 2H, H8); 1.57 (s, 2H, H5); 0.96 (dt, 6H, H9, H2); 0.90 (d, 3H, $J_{2,3}$=6.9 Hz, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 175.70 (C6); 66.32 (C4); 59.97 (C7); 32.17 (C3); 22.03 (C8); 19.32 (C2); 17.17 (C1) 10.46 (C9); **FT-IR**: ν (ATR): 3389; 3323; 2963; 2935; 2877; 1728; 1605; 1466; 1387; 1368; 1338; 1223; 1175; 1057; 982; 957; 846; 758; cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 202.7 nm; $[\alpha]_D^{20}$ = +55.684 (c=0.517 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine propyl ester

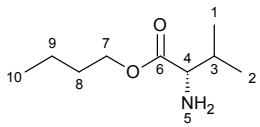


^{13}C NMR spectra of L-valine propyl ester

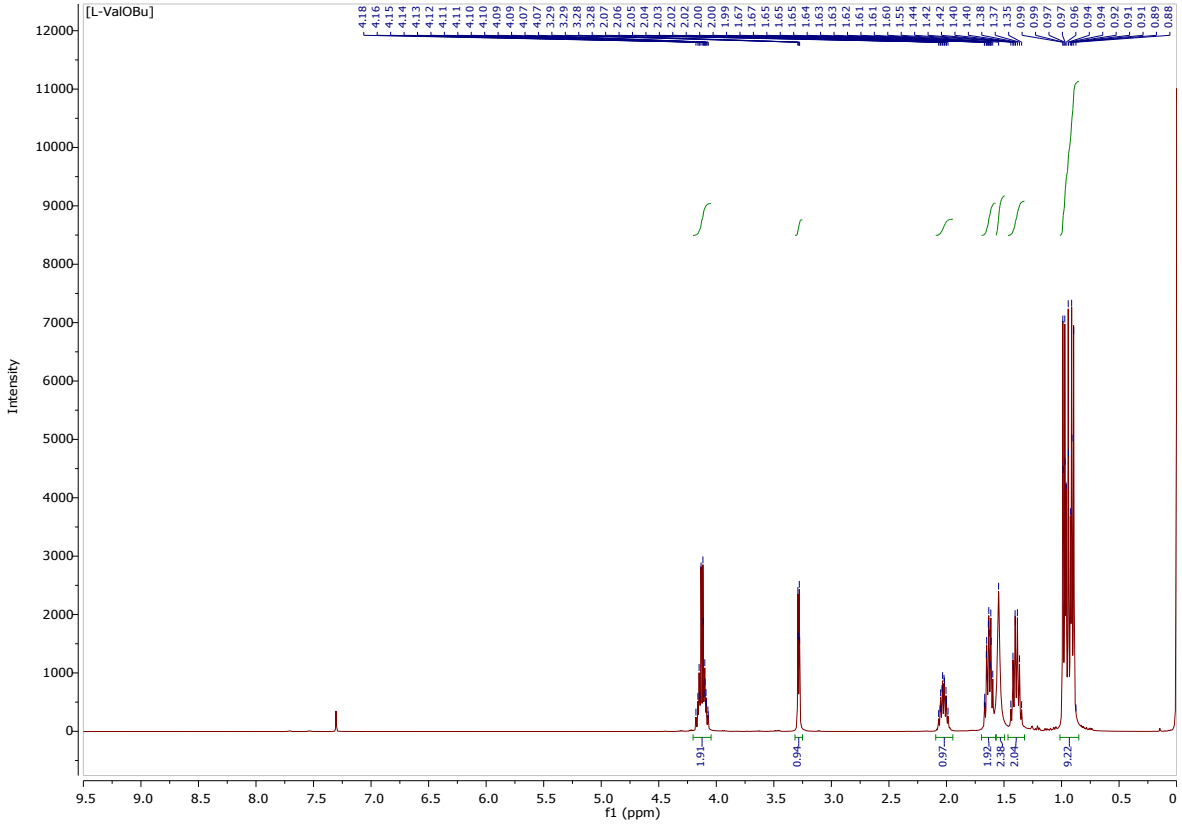


FTIR spectra of L-valine propyl ester

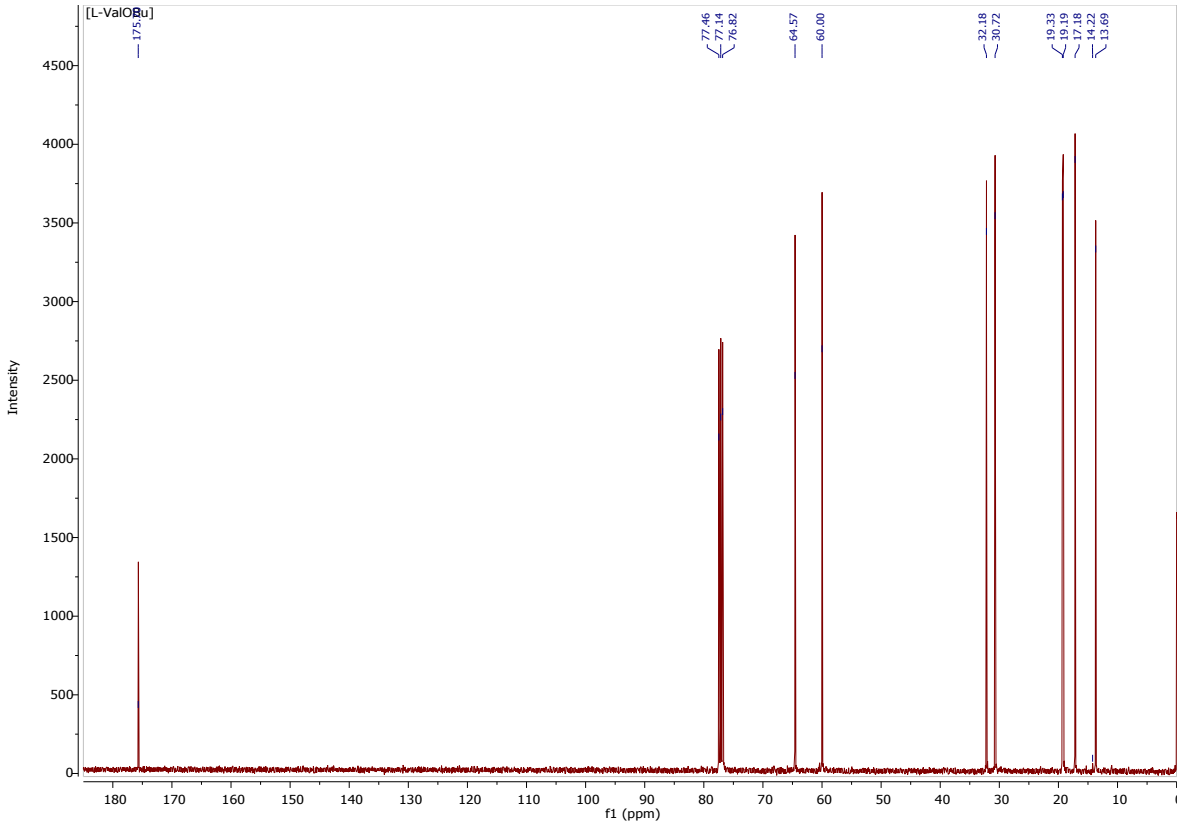
ValOBu – L-valine butyl ester



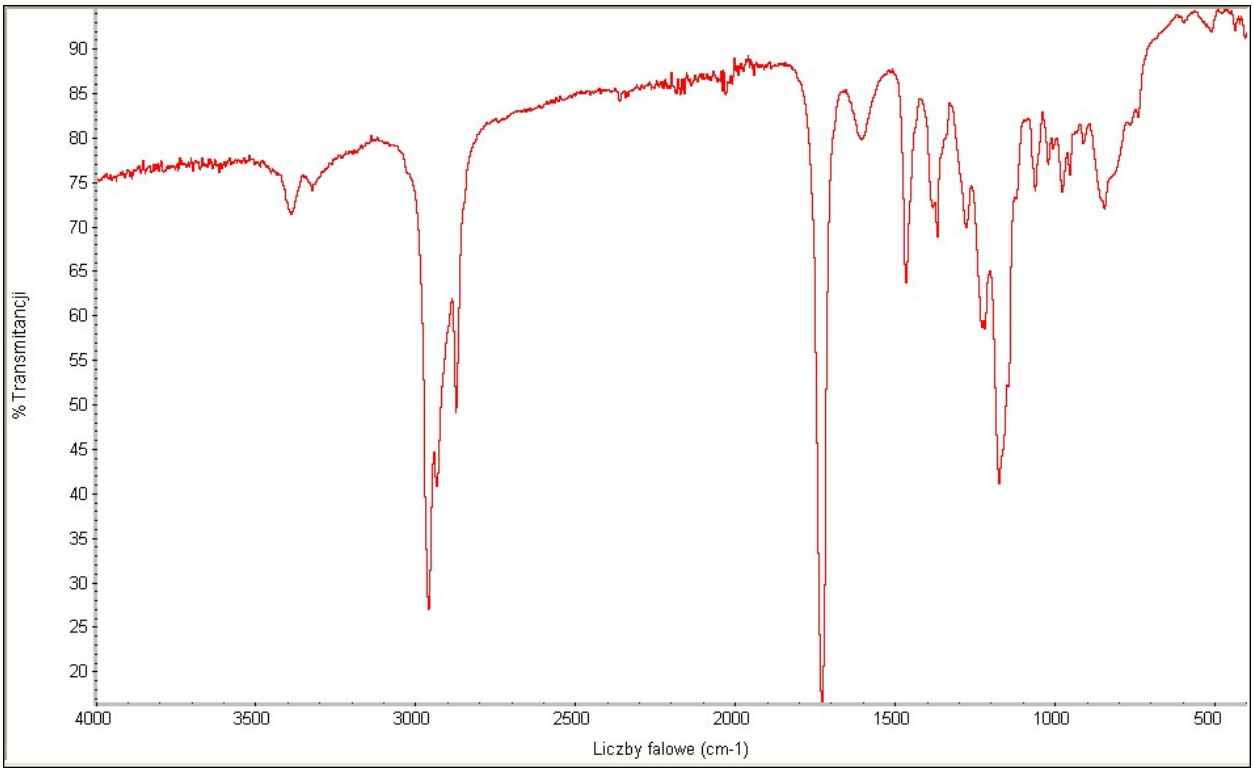
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 4.07-4.18 (m, 2H, H7); 3.28 (d, 1H, $J_{4,3}$=5.2 Hz, H4); 1.99-2.07 (m, 1H, H3); 1.60-1.67 (m, 2H, H8); 1.55 (s, 2H, H5); 1.35-1.44 (m, 2H, H9) 0.90 (m, 9H, H10, H2, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 175.70 (C6); 64.57 (C4); 60.00 (C7); 32.18 (C3); 30.72 (C8); 19.33 (C9); 19.19 (C2); 17.18 (C1); 13.69 (C10); **FT-IR**: ν (ATR): 3388; 3323; 2959; 2933; 2874; 1729; 1604; 1466; 1381; 1367; 1278; 1226; 1218; 1174; 1060; 1021; 1004; 976; 953; 843; 738; cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 202.6 nm; $[\alpha]_D^{20}$ = +26.510 (c=0.811 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine butyl ester

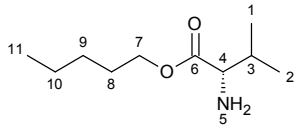


^{13}C NMR spectra of L-valine butyl ester

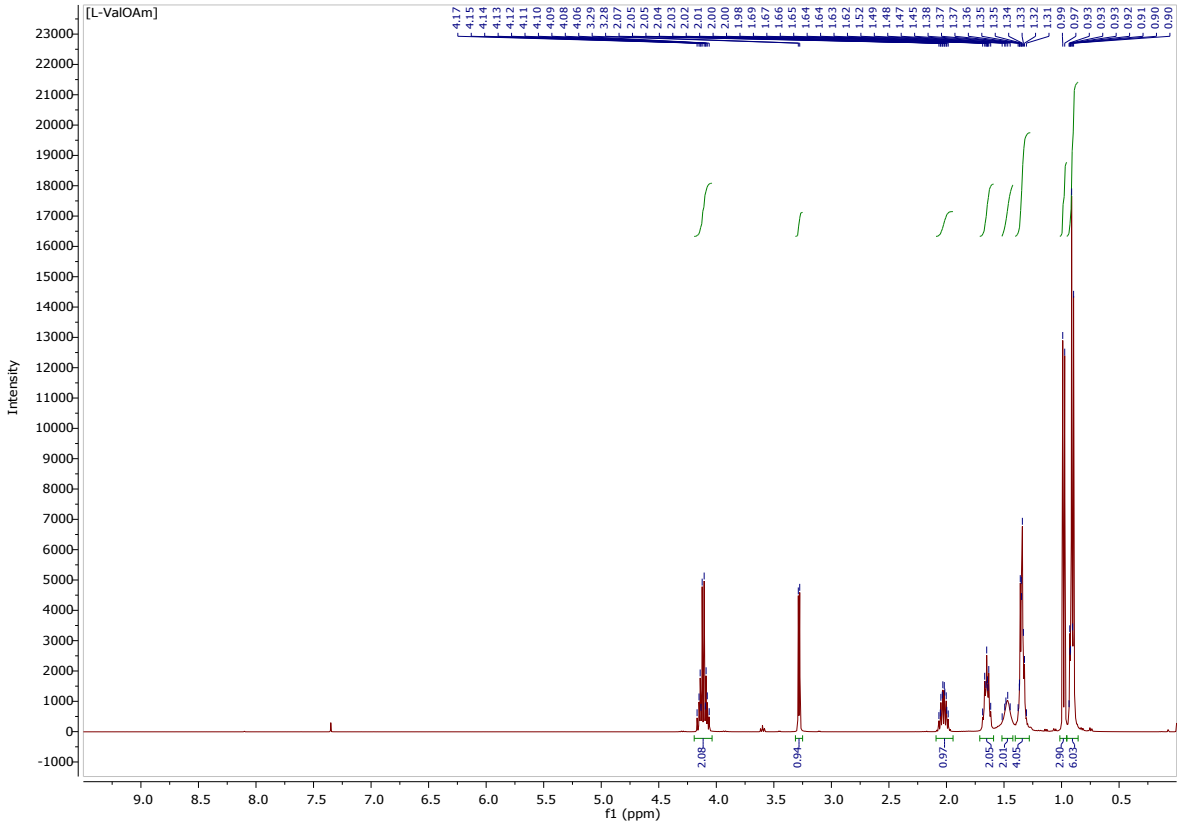


FTIR spectra of L-valine butyl ester

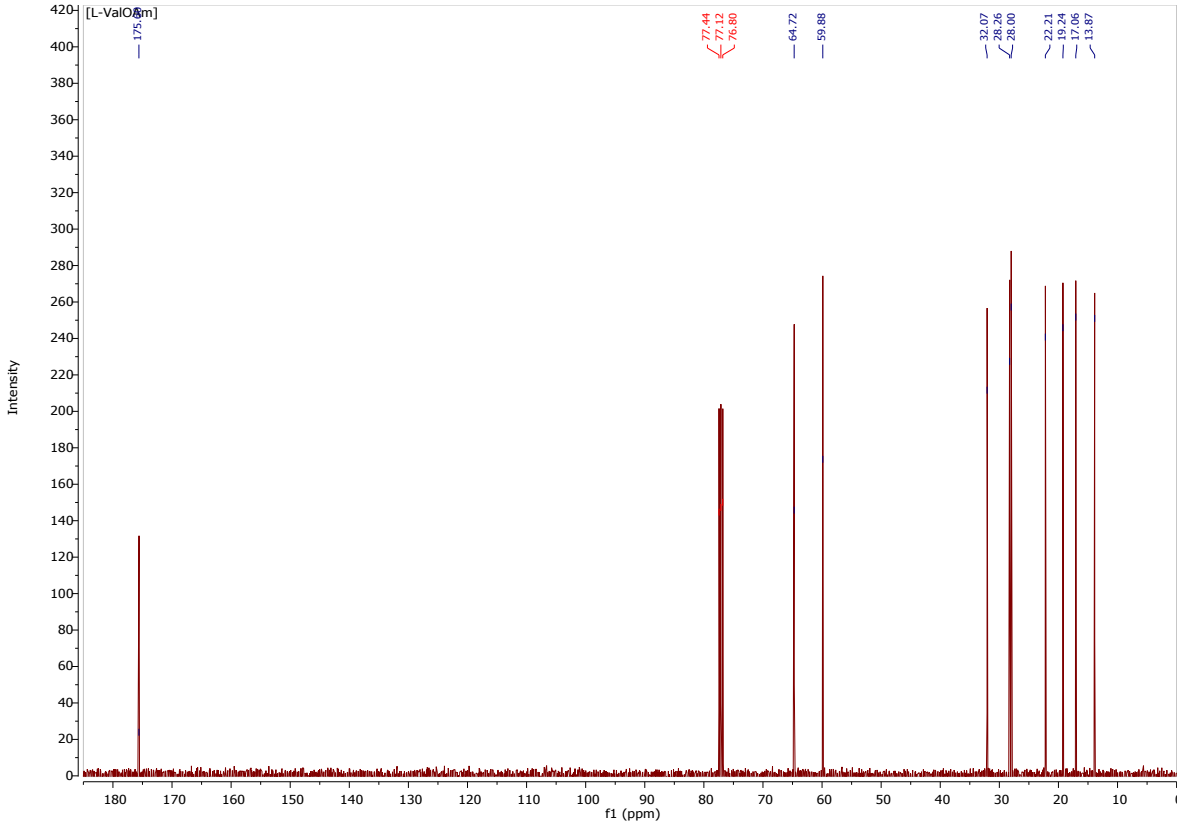
ValOAm – L-valine pentyl ester



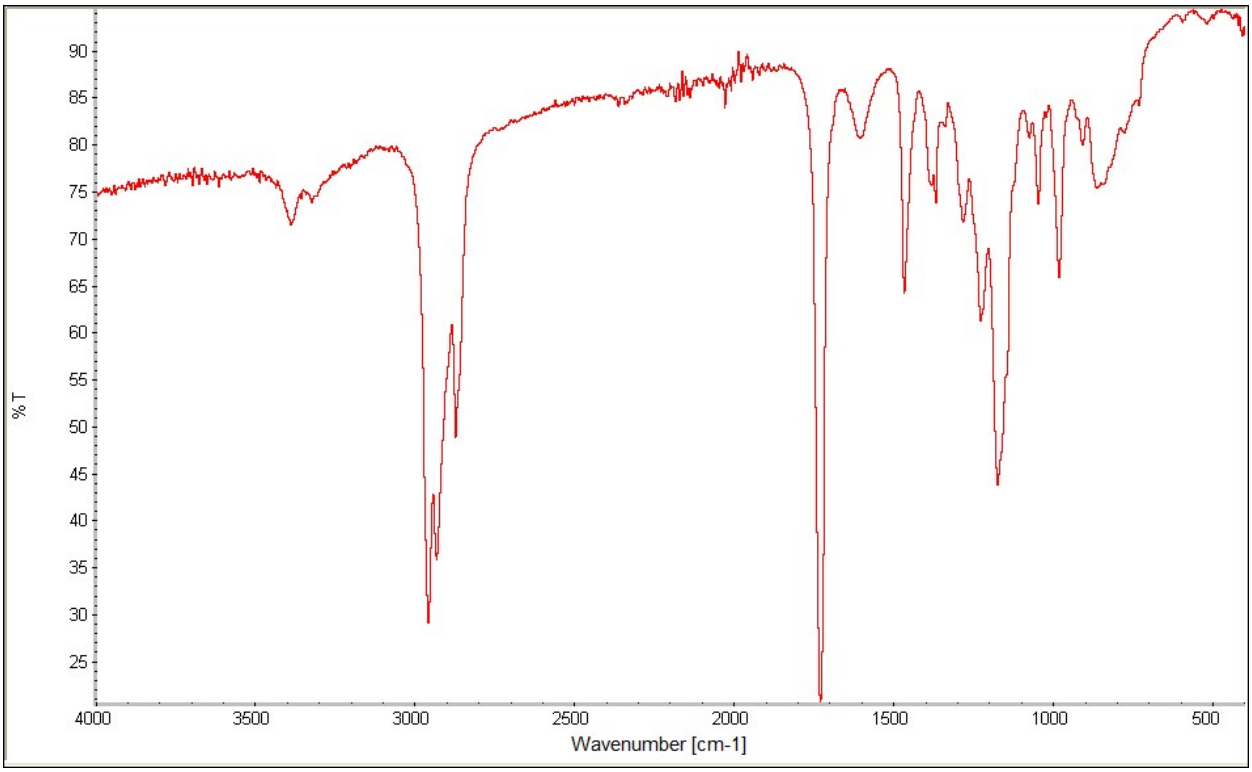
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 4.06-4.17 (m, 2H, H7); 3.28 (d, 1H, $J_{4,3}$=4.8 Hz, H4); 2.00-2.05 (m, 1H, H3); 1.62-1.67 (m, 2H, H8); 1.47 (s, 2H, H5); 1.31-1.37 (m, 4H, H9, H10) 0.93 (d, 3H, H2, $J_{1,3}$=7.2); 0.90 (m, 6H, H11, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 175.61 (C6); 64.72 (C4); 59.88 (C7); 32.08 (C3); 28.26 (C8); 28.00 (C9); 22.21 (C10); 19.25 (C2); 17.01 (C1); 13.87 (C11); **FT-IR**: ν (ATR): 3388; 3321; 2956; 2932; 2873; 1729; 1605; 1467; 1381; 1368; 1282; 1226; 1734; 1074; 1047; 1021; 980; 980; 906; 861; 730; cm^{-1}; **UV-Vis** (EtOH): λ_{max}= 203.0 nm; $[\alpha]_D^{20}$ = +23.894 (c=0.674 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine pentyl ester

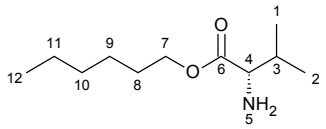


^{13}C NMR spectra of L-valine pentyl ester

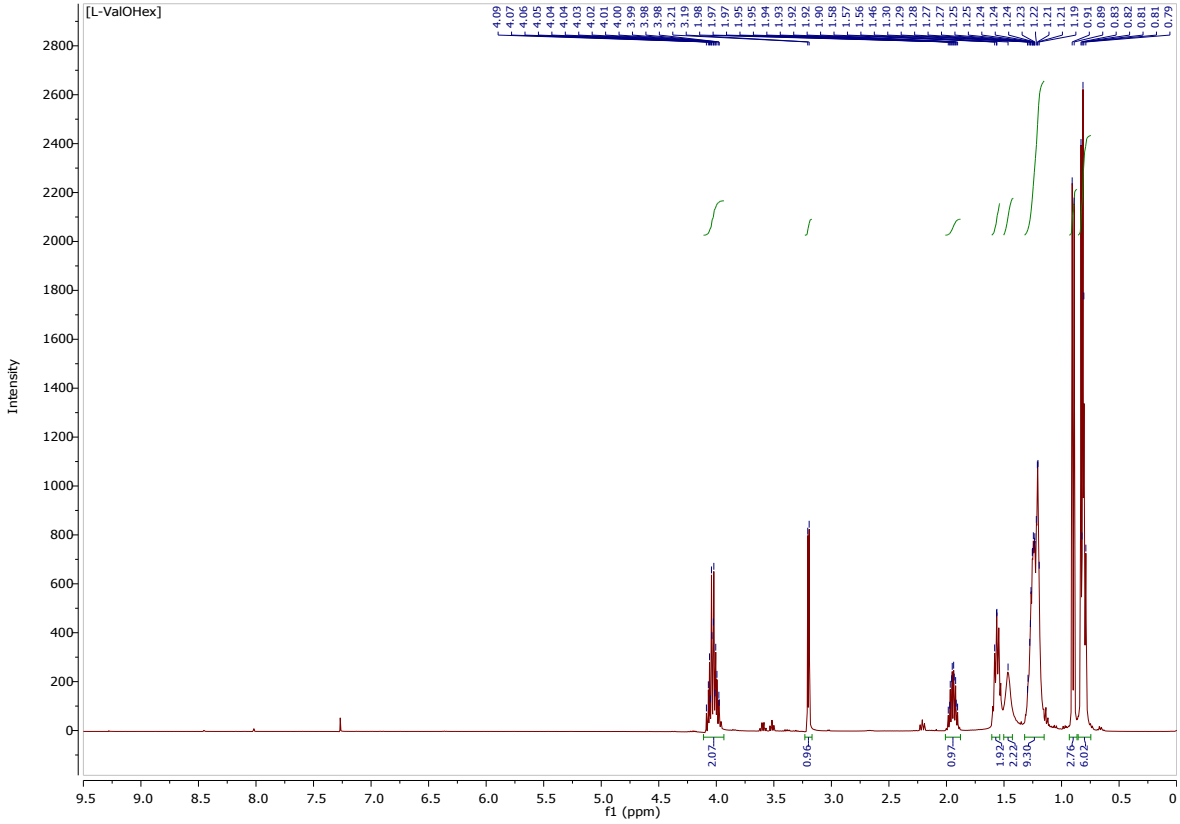


FTIR spectra of L-valine pentyl ester

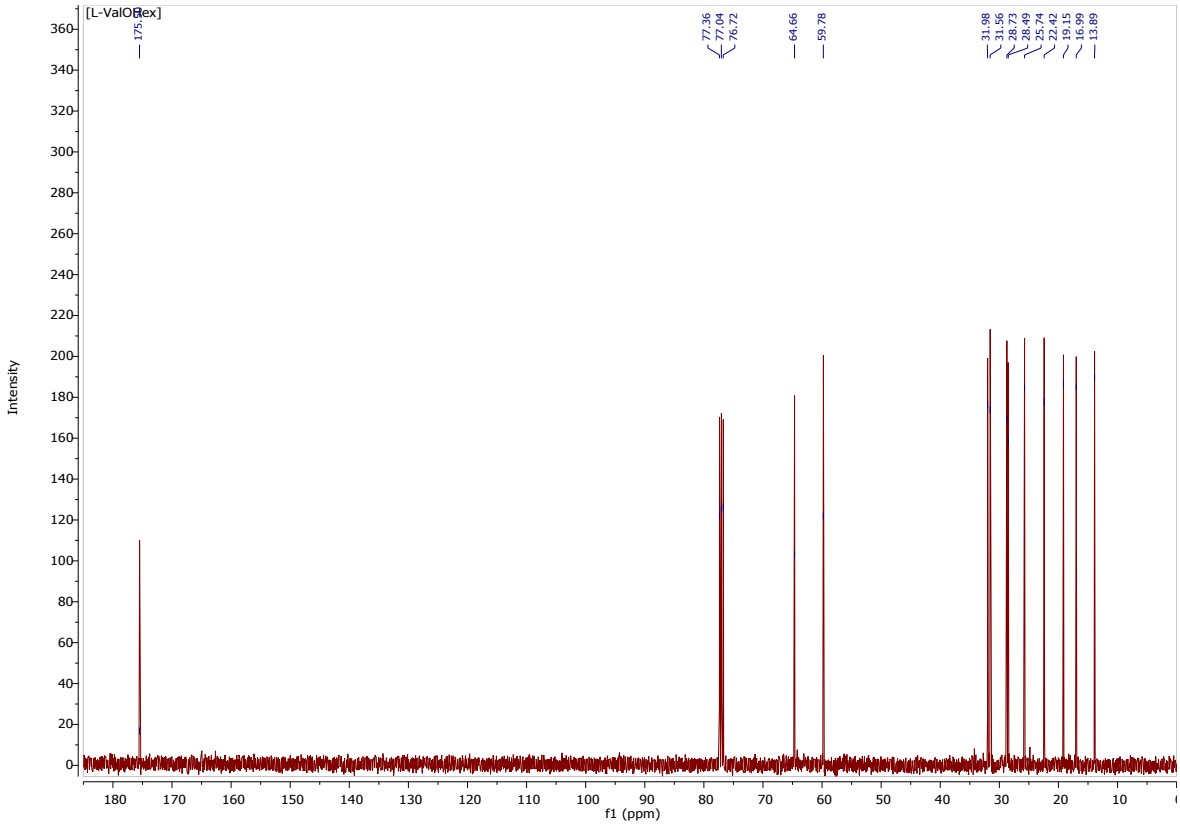
ValOHex– L-valine hexyl ester



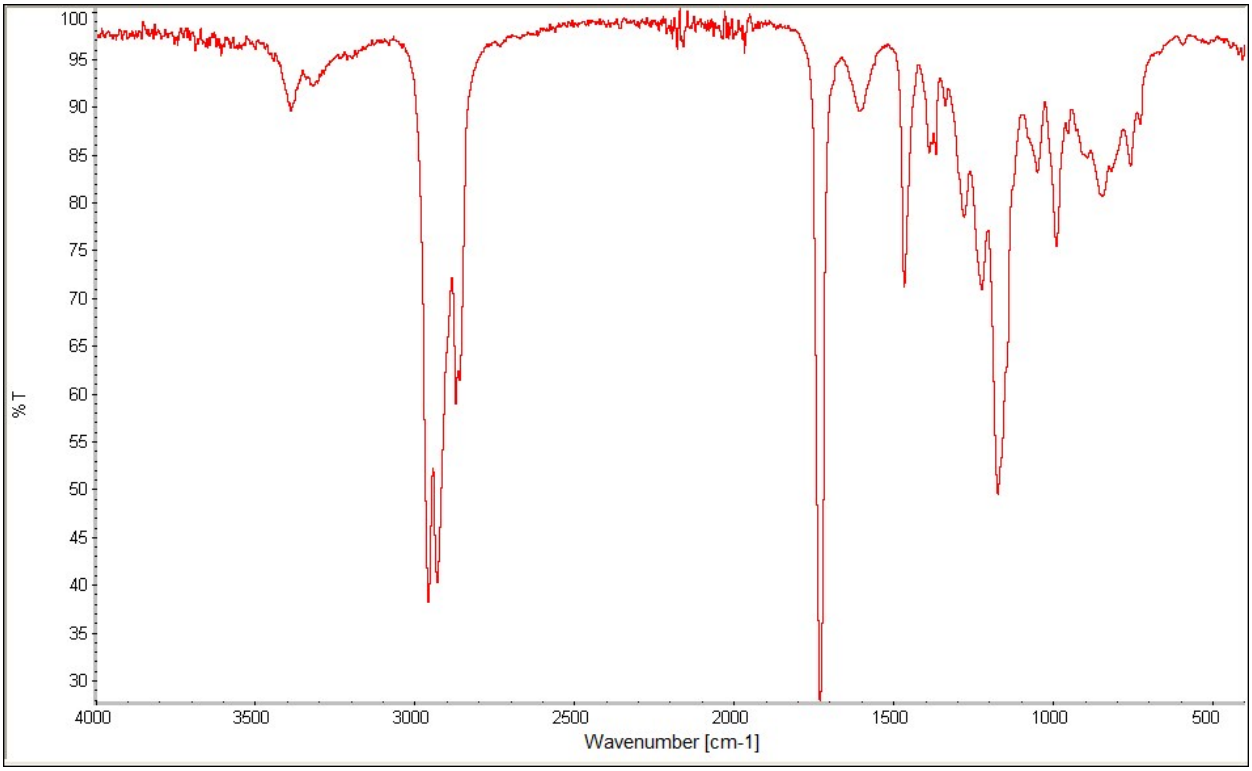
^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 3.98-4.09 (m, 2H, H7); 3.17 (d, 1H, $J_{4,3}$=5.0 Hz, H4); 1.88-1.95 (m, 1H, H3); 1.51-1.58 (m, 2H, H8); 1.42 (s, 2H, H5); 1.17-1.29 (m, 6H, H9, H10, H11) 0.87 (d, 3H, H2, $J_{1,3}$=6.8); 0.77 (dt, 6H, H12, H1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ in ppm: 175.48 (C6); 64.62 (C4); 59.76 (C7); 31.96 (C3); 31.22 (C8); 28.44 (C9); 25.43 (C10); 22.35 (C2); 19.13 (C1); 16.97 (C11); 13.80 (C12); **FT-IR**: ν (ATR): 3388; 3326; 2958; 2930; 2872; 1730; 1607; 1467; 1387; 1369; 1338; 1277; 1225; 1172; 1071; 1051; 990; 954; 844; 765; 727; **UV-Vis** (EtOH): λ_{max}= 203.6 nm; $[\alpha]_D^{20}$ = +20.235 (c=0.766 g/100 cm^3 EtOH).



^{1}H NMR spectra of L-valine hexyl ester



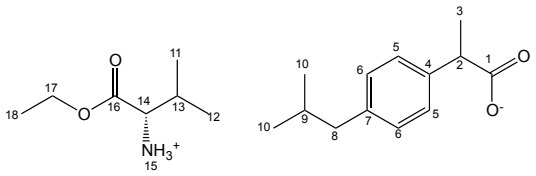
^{13}C NMR spectra of L-valine hexyl ester



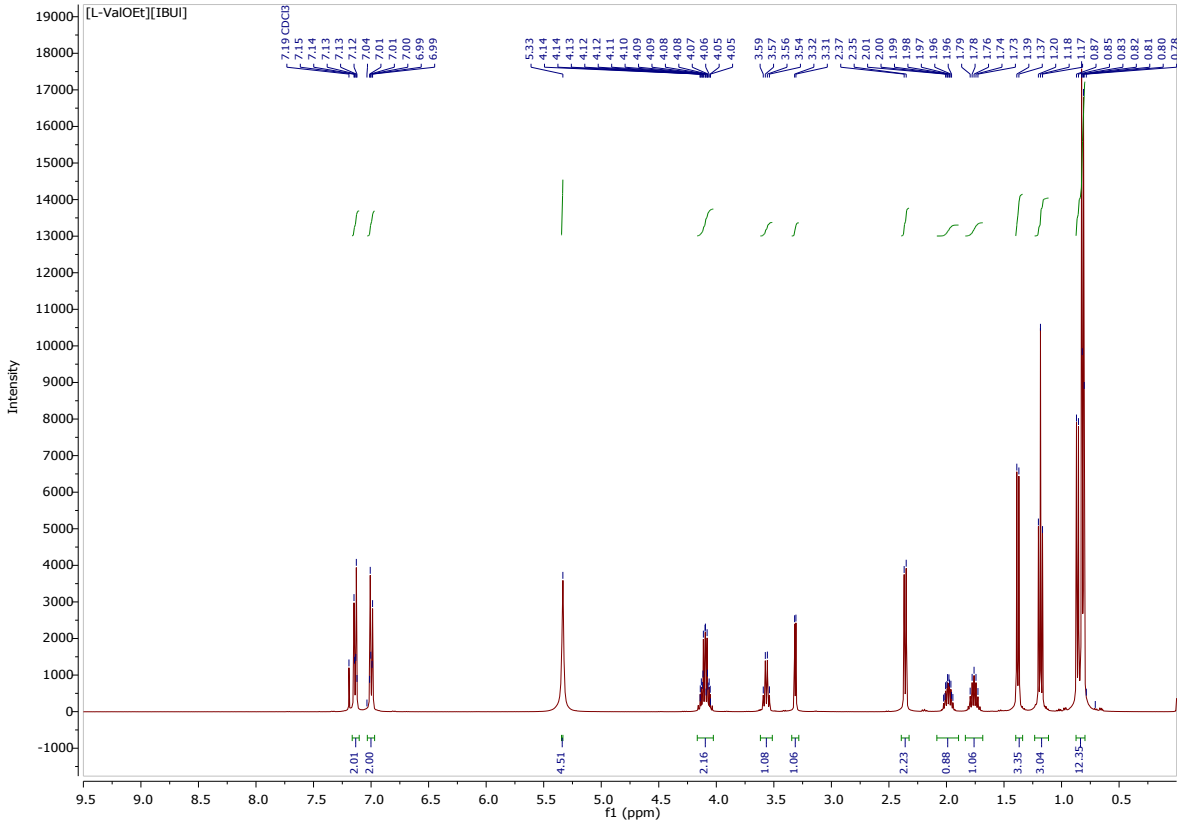
FTIR spectra of L-valine hexyl ester

4. COPIES OF ^{1}H, ^{13}C NMR AND FTIR SPECTRA, CURVES OF TG AND DSC ANALYSIS OF L-VALINE ALKYL ESTERS IBUPROFENATES

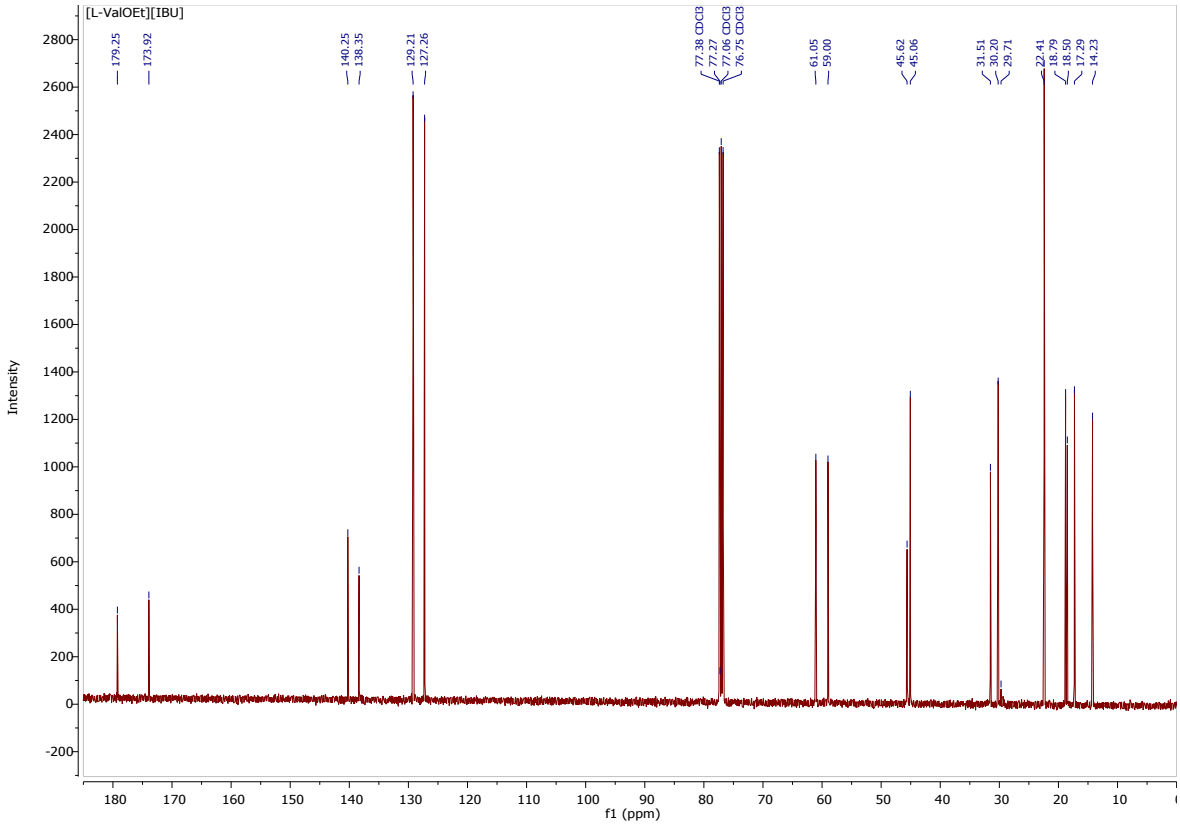
[ValOEt][IBU] – L-valine ethyl ester ibuprofenate



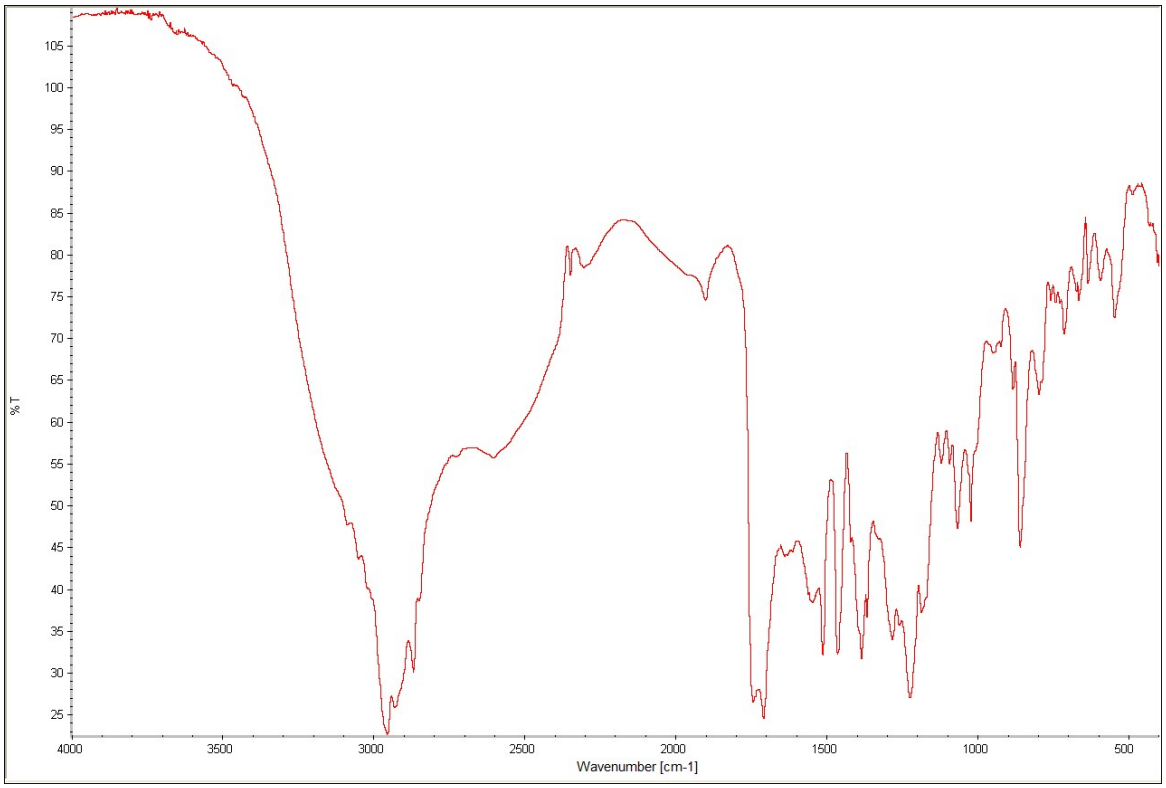
UV-Vis (EtOH): λ_{max}=229.0 nm; $\mathbf{T_m}$=75.7-79.8^{0}C; $[\alpha]_D^{20}$ = +8.867 (c=1.015 g/100 cm^3 EtOH).



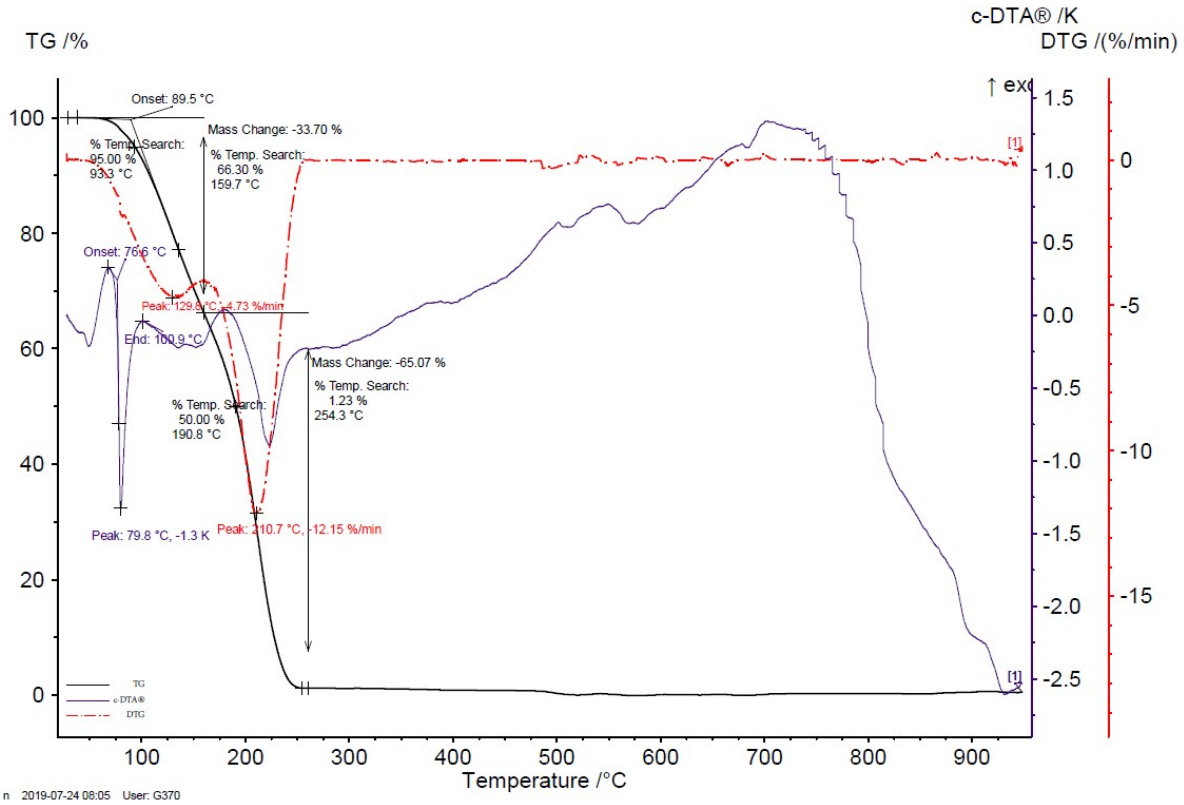
^{1}H NMR spectra of L-valine ethyl ester ibuprofenate



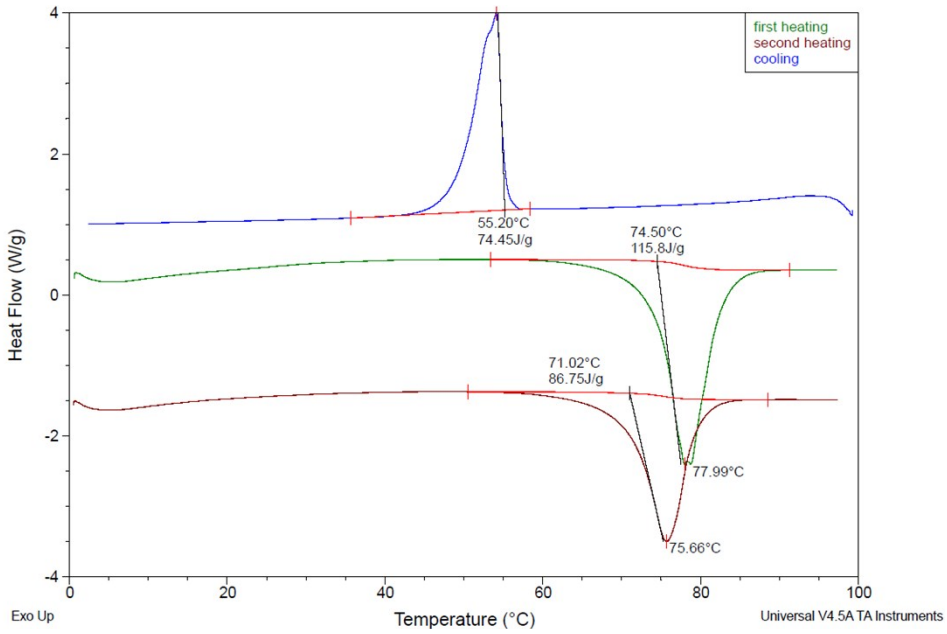
^{13}C NMR spectra of L-valine ethyl ester ibuprofenate



FTIR spectra of L-valine ethyl ester ibuprofenate

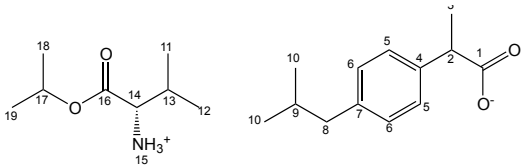


The TG, DTG and c-DTA curves of L-valine ethyl ester ibuprofenate

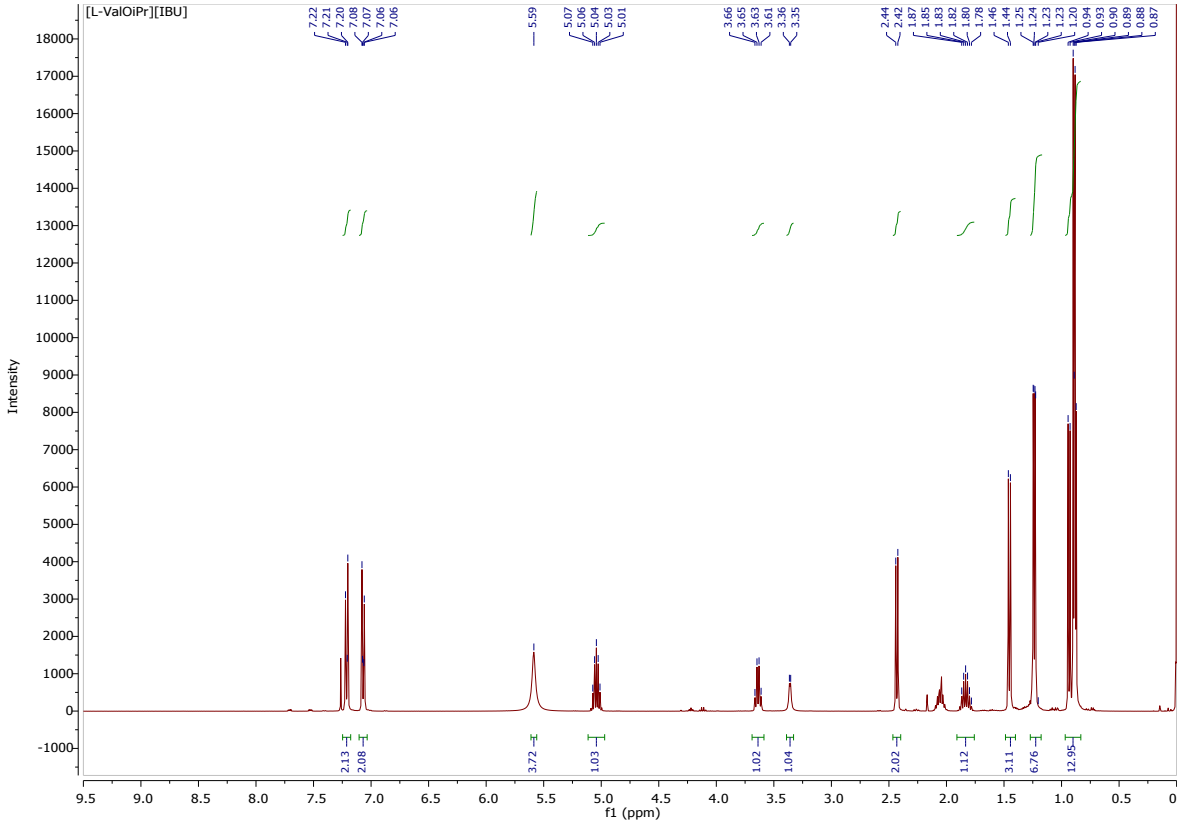


The DSC curves of L-valine ethyl ester ibuprofenate

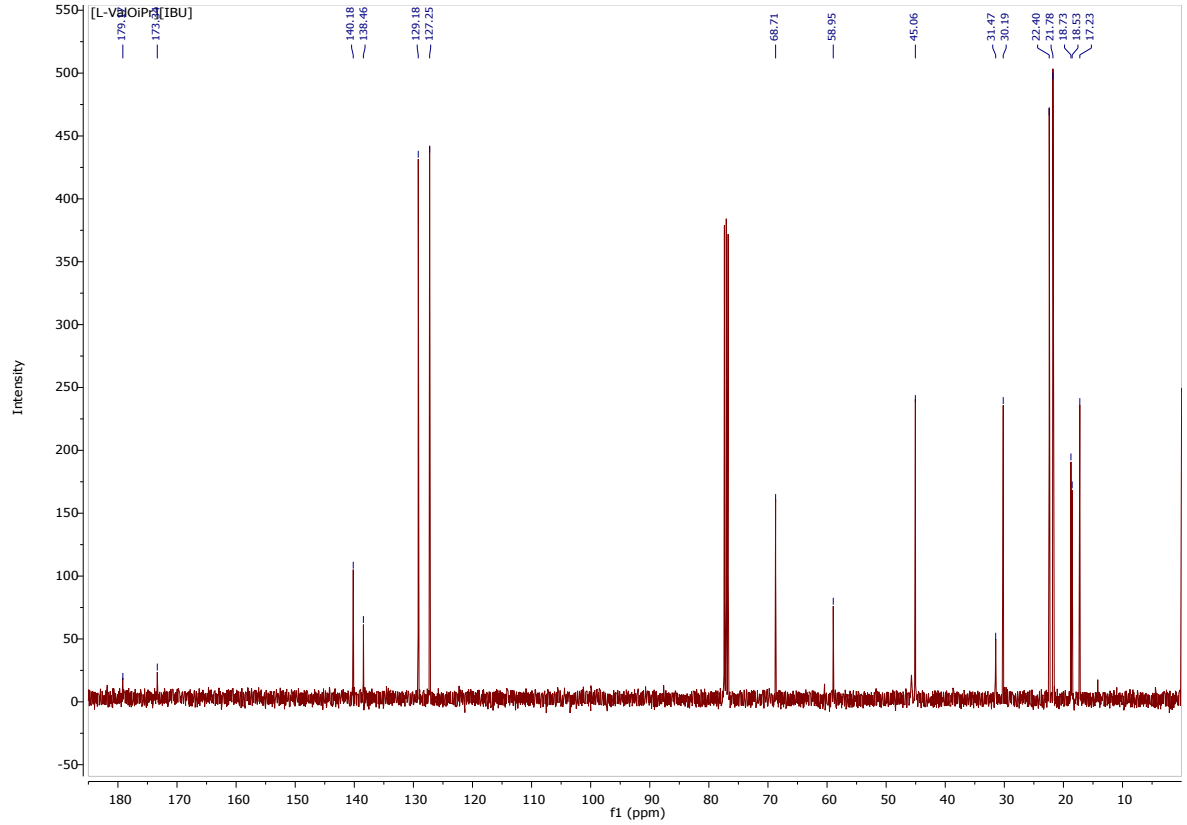
[ValOiPr][IBU] – L-valine isopropyl ester ibuprofenate



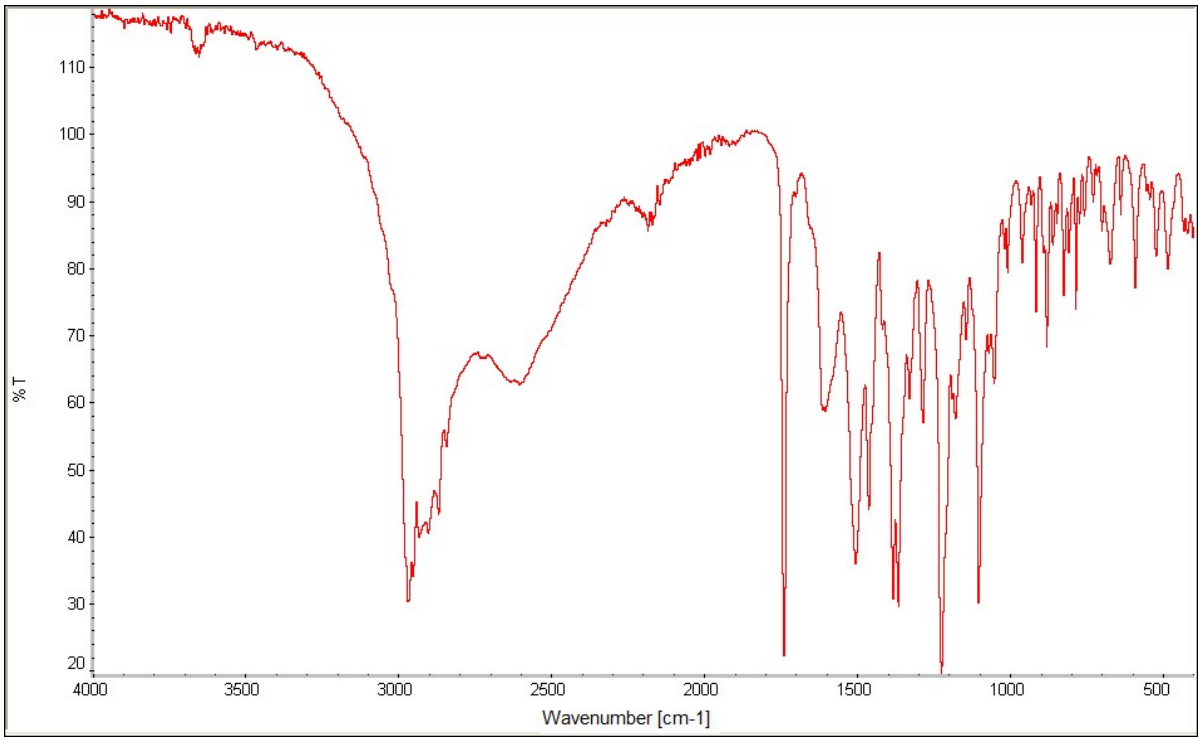
UV-Vis (EtOH): λ_{max}= 229.0 nm; $\mathbf{T_m}$=75.2-79.4^{0}C; $[\alpha]_D^{20}$ = +11.852 (c=0.539 g/100 cm^3 EtOH).



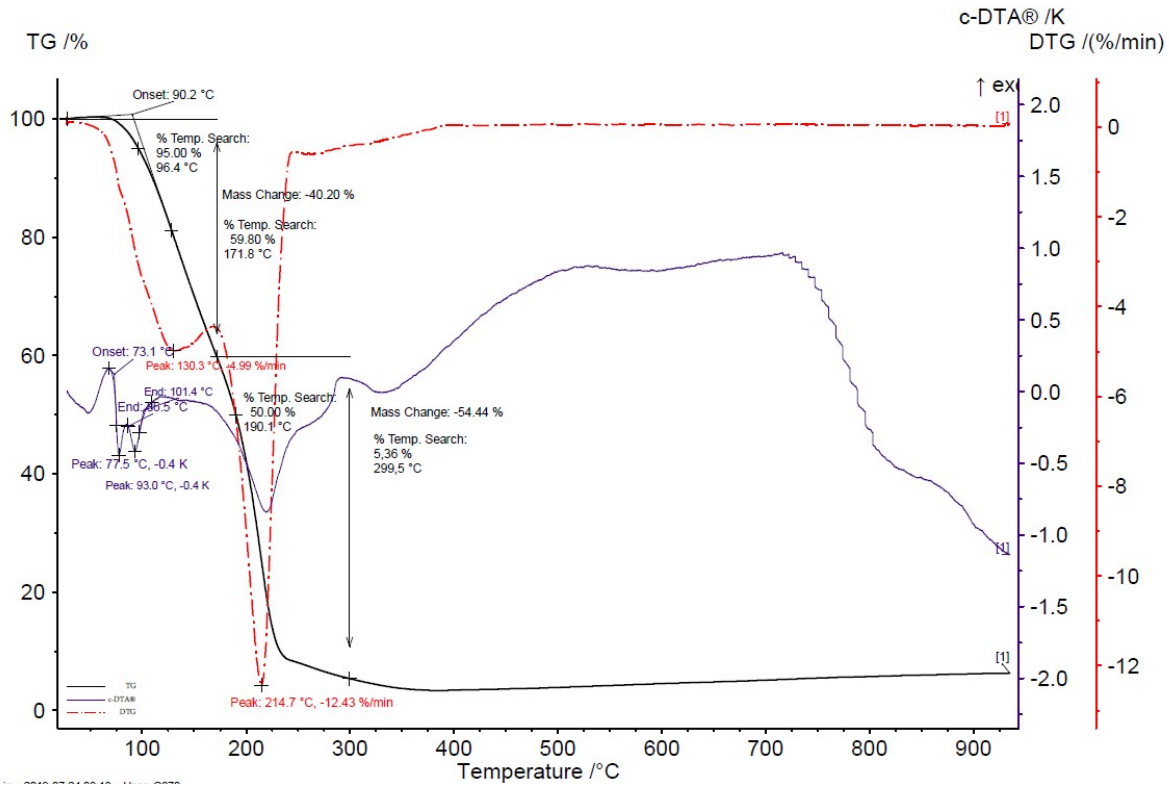
^{1}H NMR spectra of L-valine isopropyl ester ibuprofenate



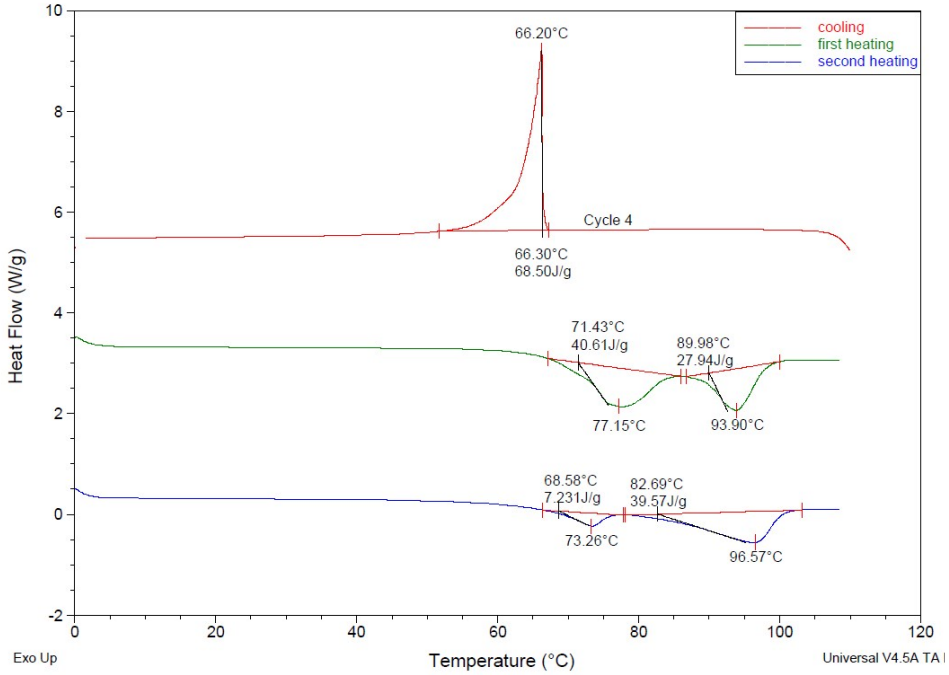
^{13}C NMR spectra of L-valine isopropyl ester ibuprofenate



FTIR spectra of L-valine isopropyl ester ibuprofenate

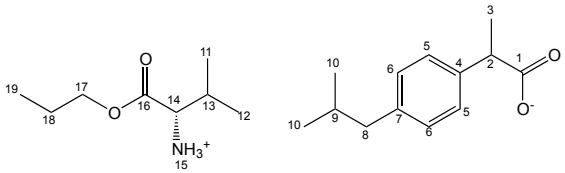


The TG, DTG and c-DTA curves of L-valine isopropyl ester ibuprofenate

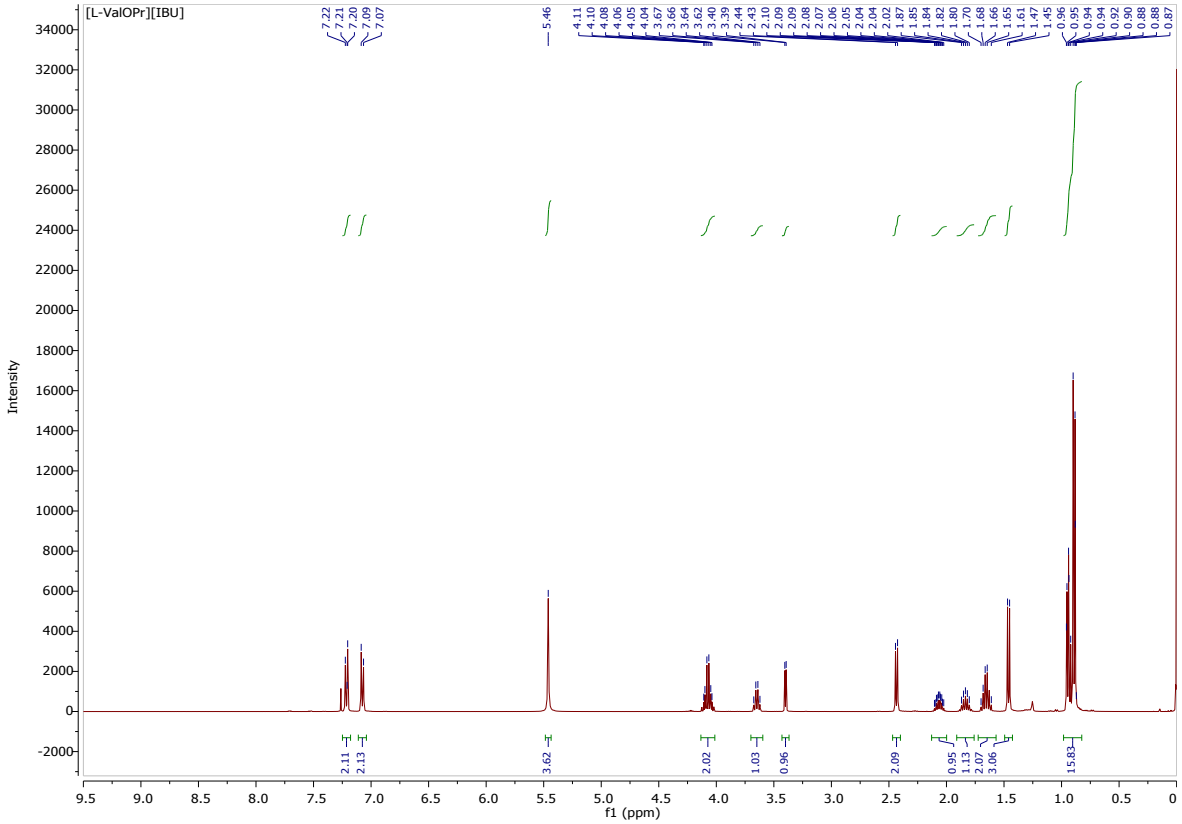


The DSC curves of L-valine isopropyl ester ibuprofenate

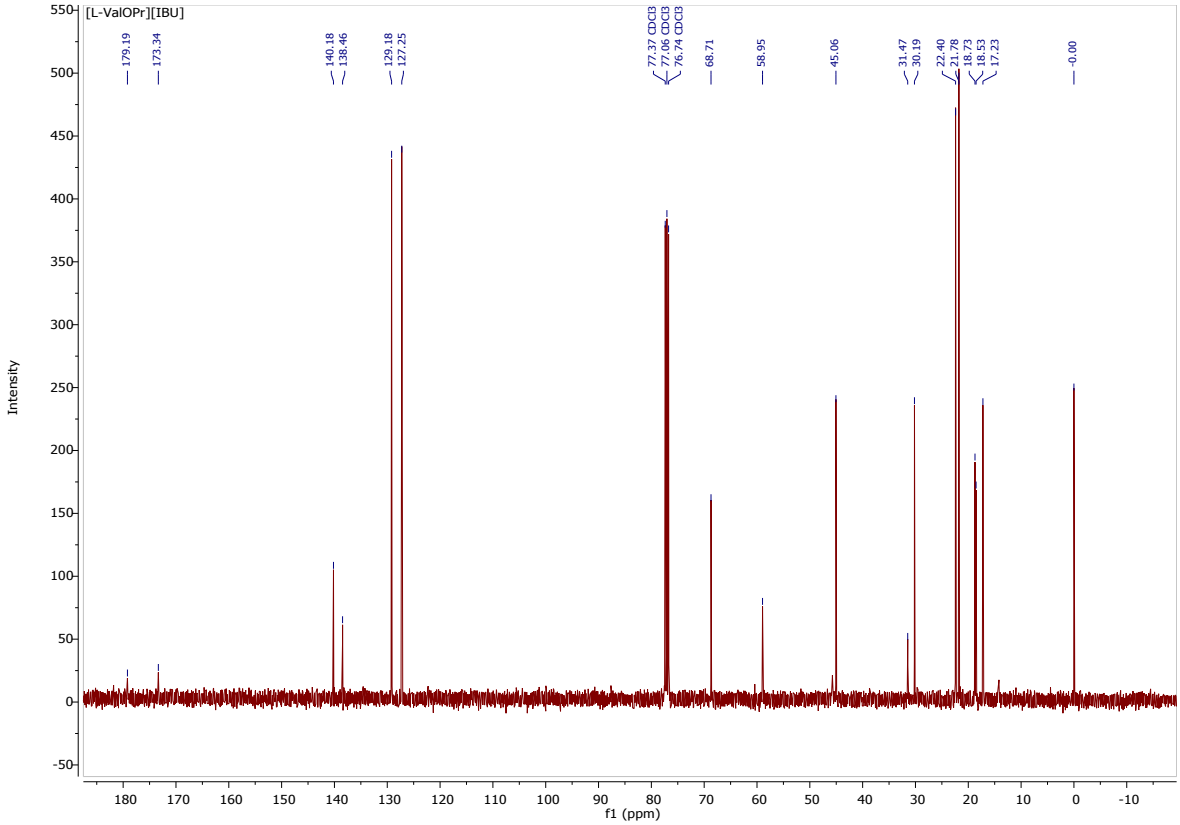
[ValOPr][IBU] – L-valine propyl ester ibuprofenate



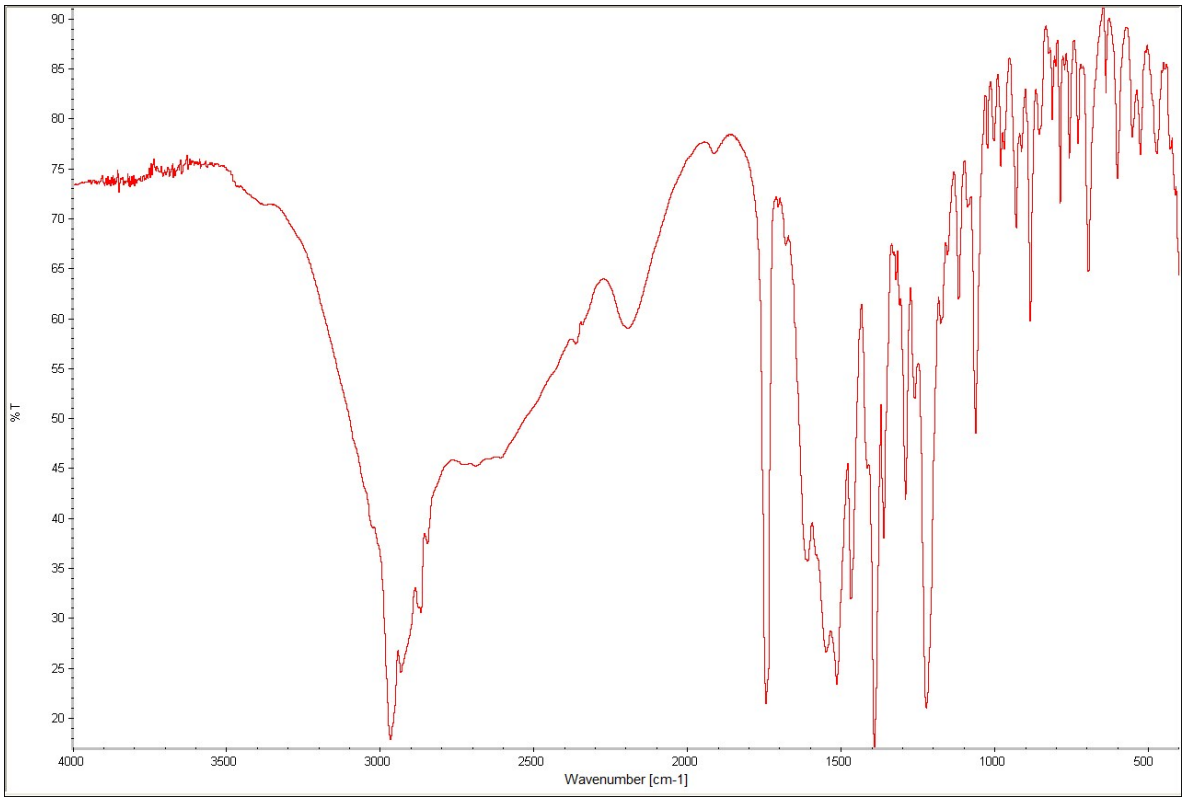
UV-Vis (EtOH): λ_{max}= 229.0 nm; $\mathbf{T_m}$=77.0-80.2^{0}C; $[\alpha]_D^{20}$ = +9.760 (c=0.584 g/100 cm^{3}EtOH).



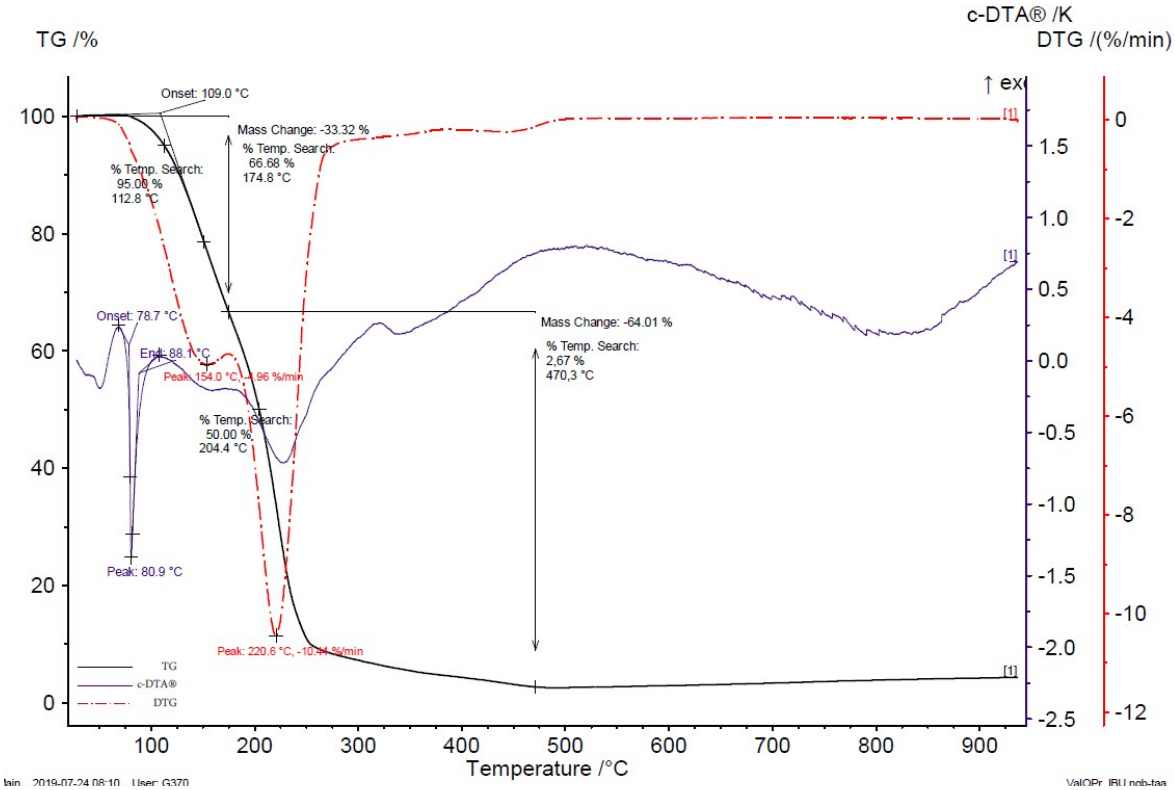
^{1}H NMR spectra of L-valine propyl ester ibuprofenate



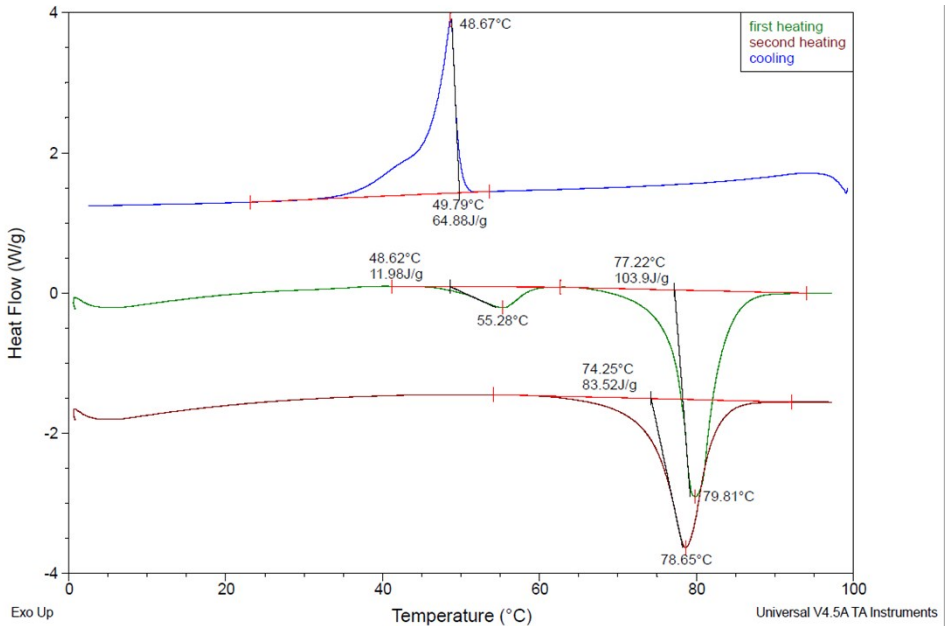
^{13}C NMR spectra of L-valine propyl ester ibuprofenate



FTIR spectra of L-valine propyl ester ibuprofenate

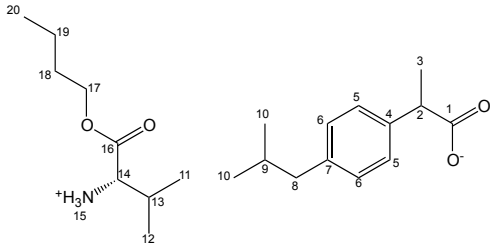


The TG, DTG and c-DTA curves of L-valine propyl ester ibuprofenate

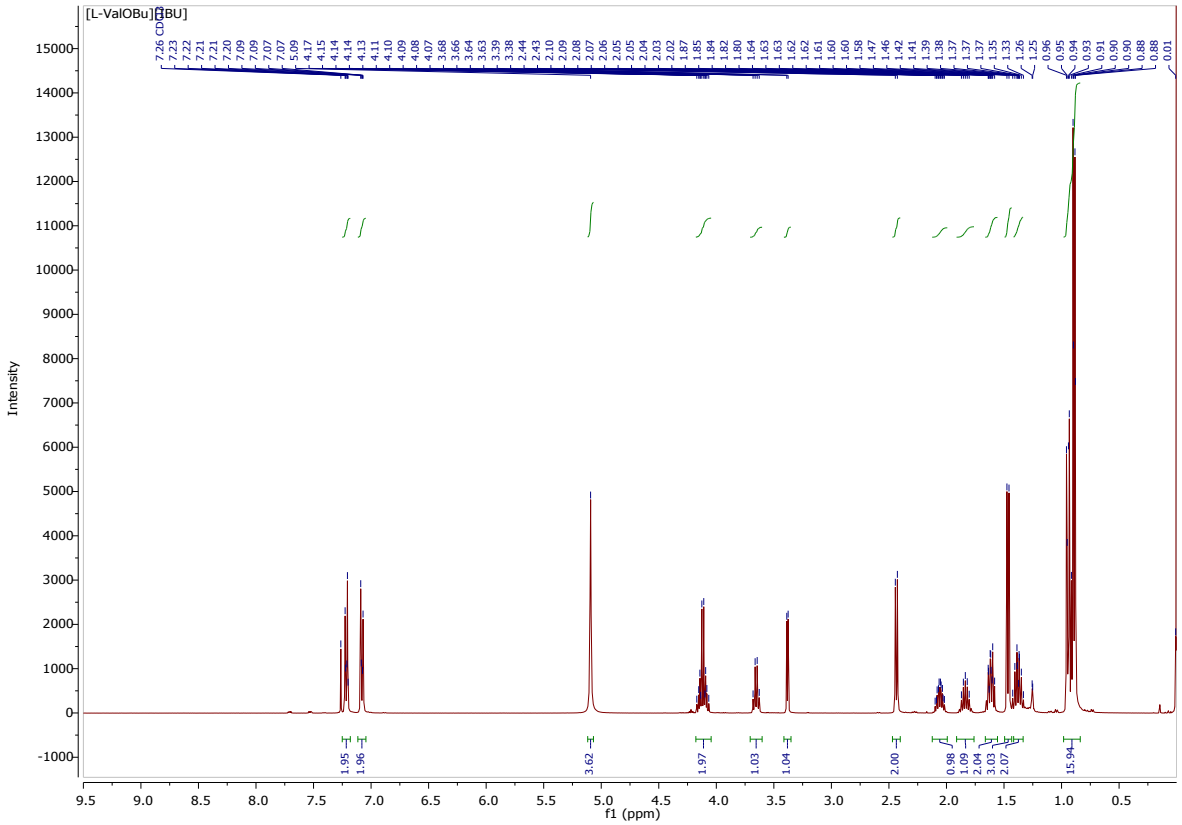


The DSC curves of L-valine propyl ester ibuprofenate

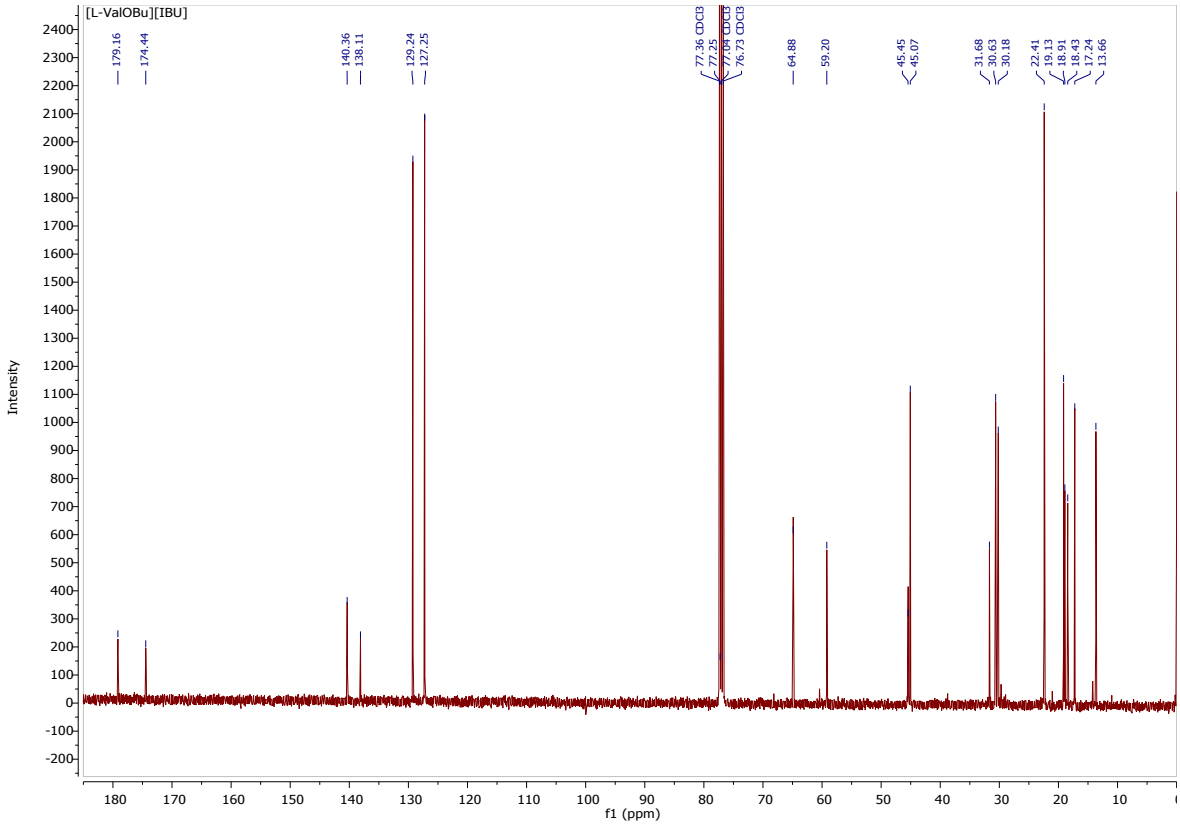
[ValOBu][IBU] – L-valine butyl ester ibuprofenate



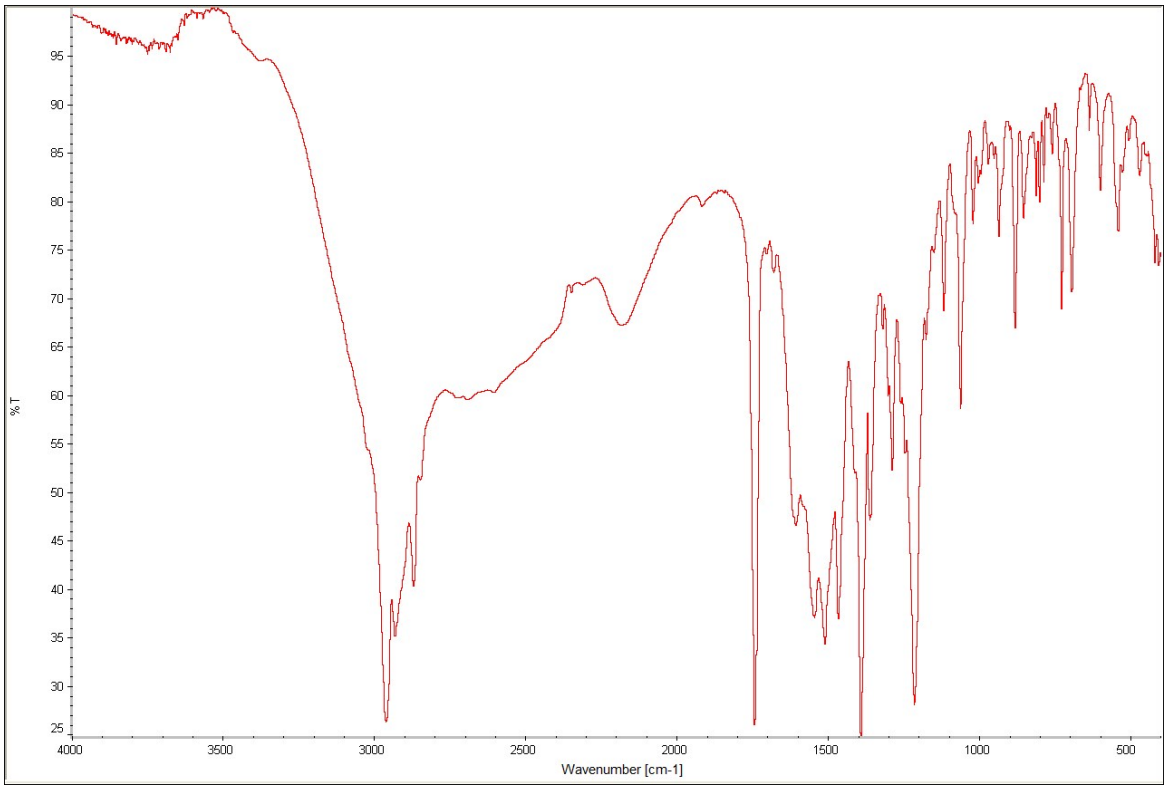
UV-Vis (EtOH): λ_{max}= 228.0 nm; $\mathbf{T_m}$=72.0-76.1^{0}C; $[\alpha]_D^{20}$ = +11.094 (c=0.658 g/100 cm^3 EtOH).



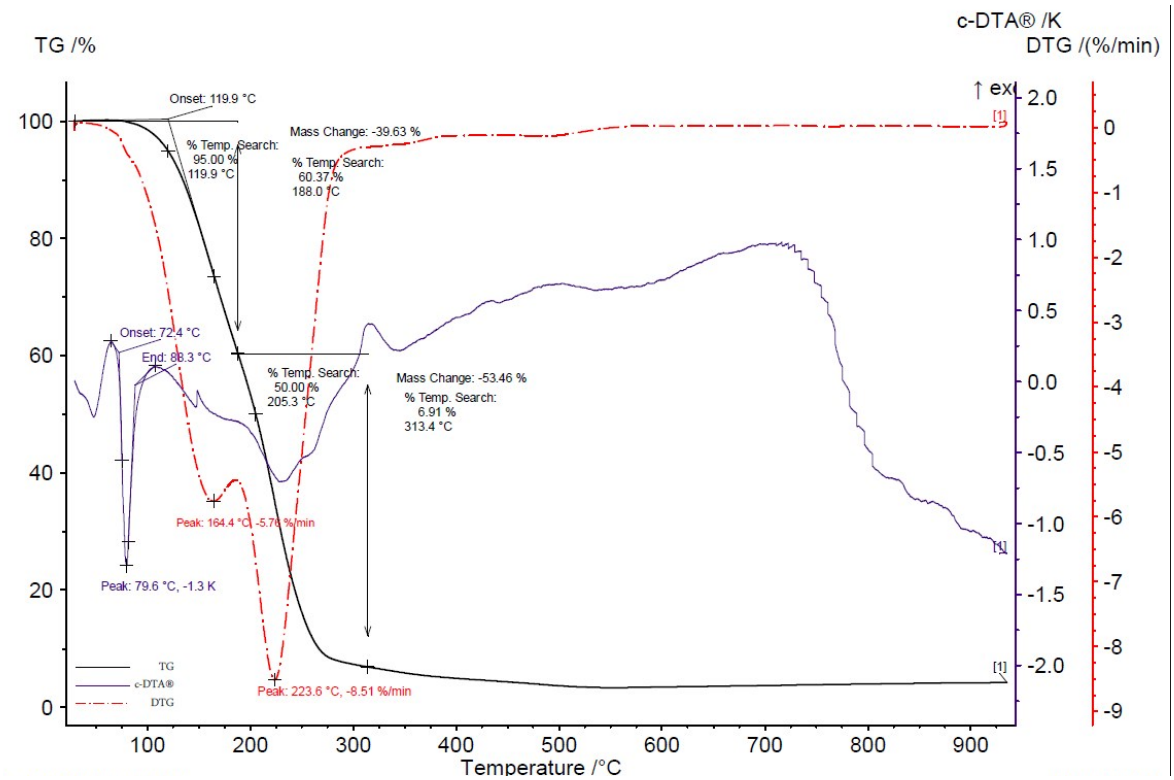
^{1}H NMR spectra of L-valine butyl ester ibuprofenate



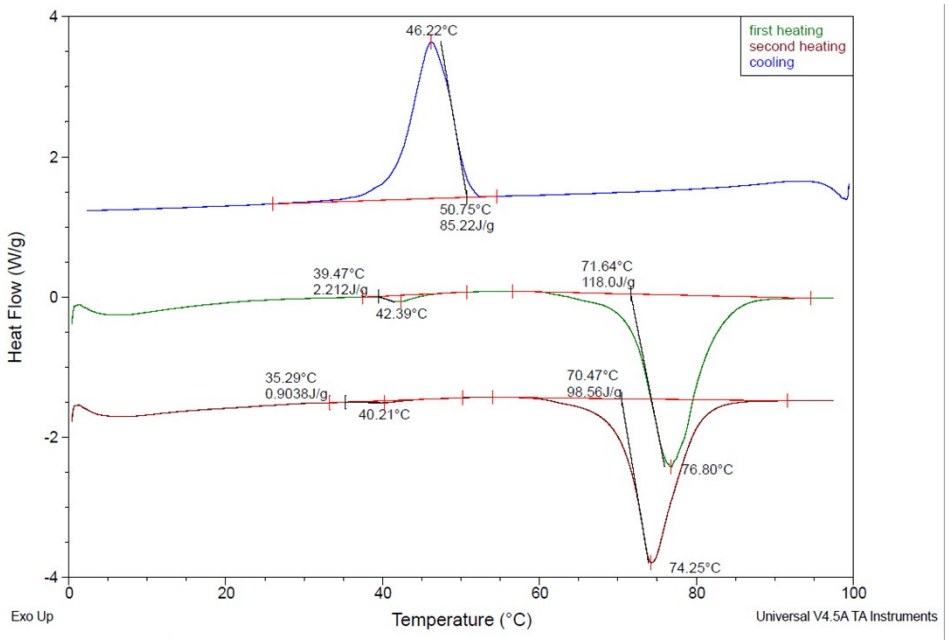
^{13}C NMR spectra of L-valine butyl ester ibuprofenate



FTIR spectra of L-valine butyl ester ibuprofenate

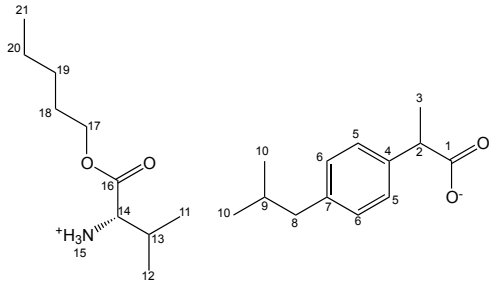


The TG, DTG and c-DTA curves of L-valine butyl ester ibuprofenate

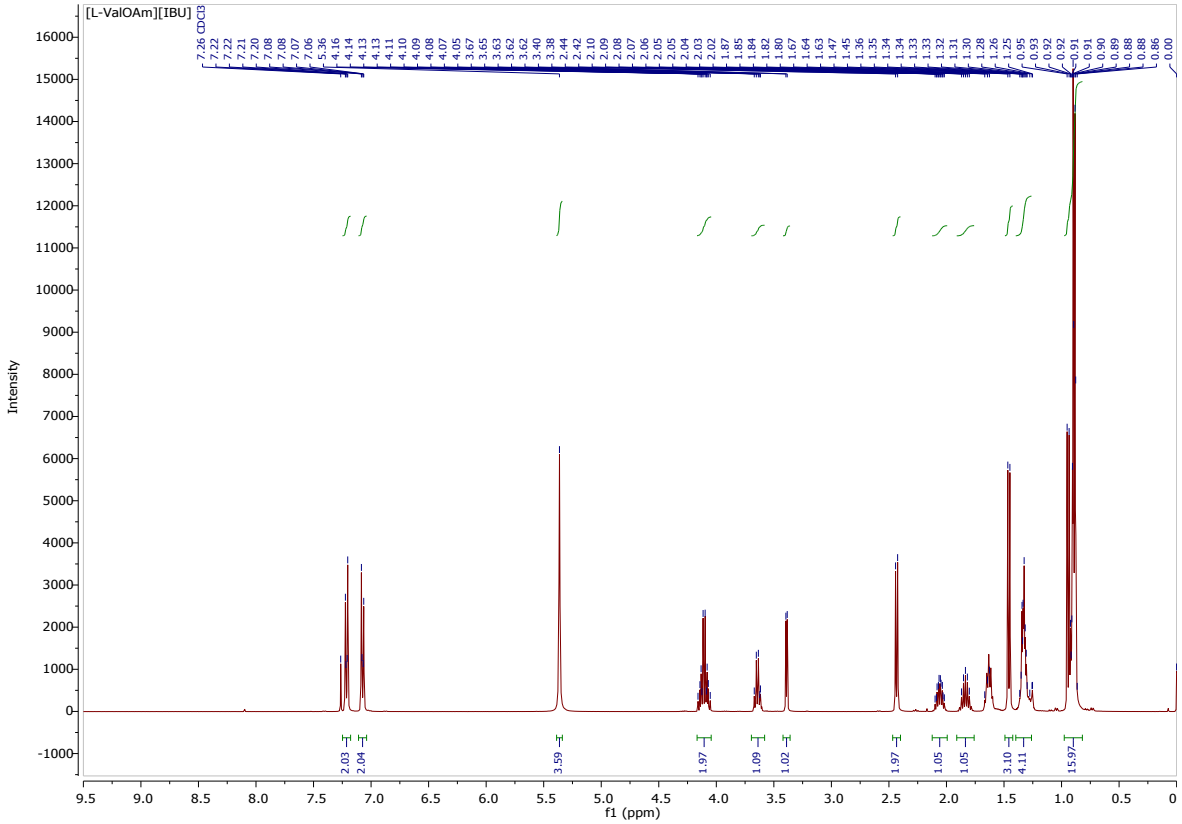


The DSC curves of L-valine butyl ester ibuprofenate

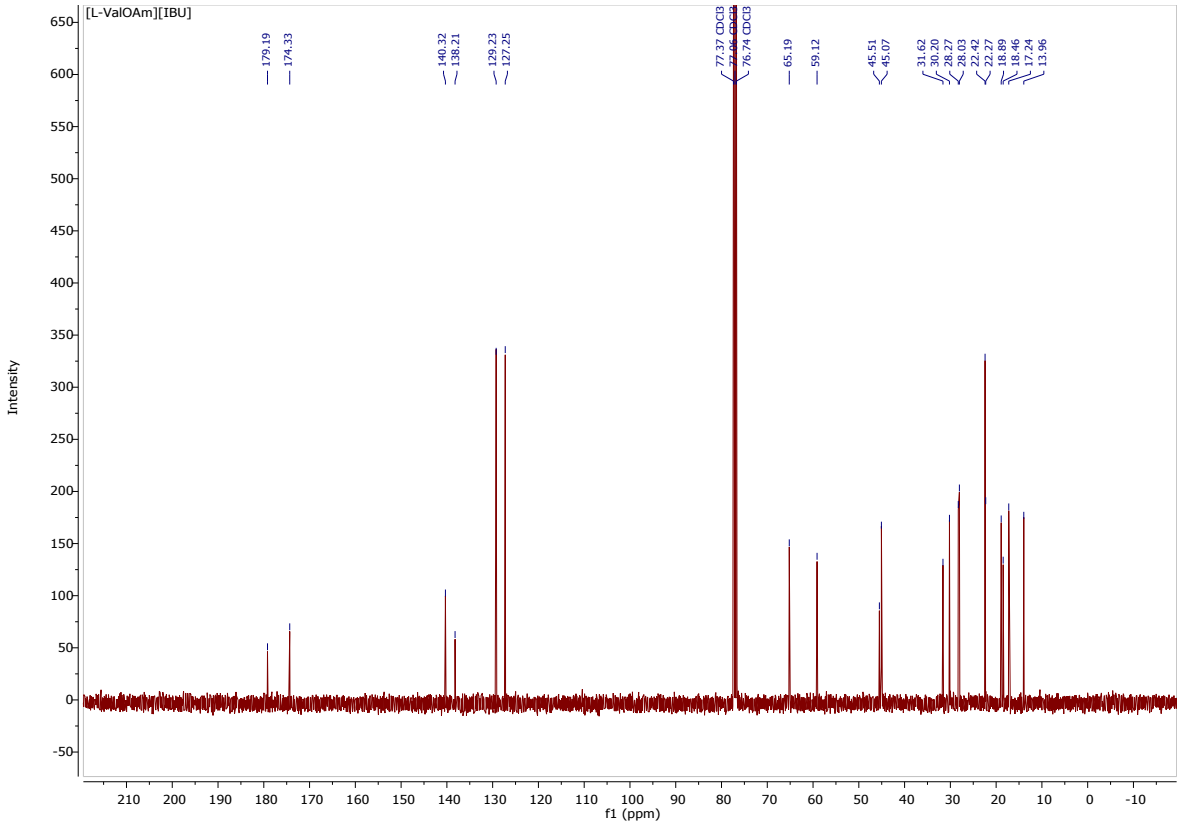
[ValOAm][IBU] – L-valine pentyl ester ibuprofenate



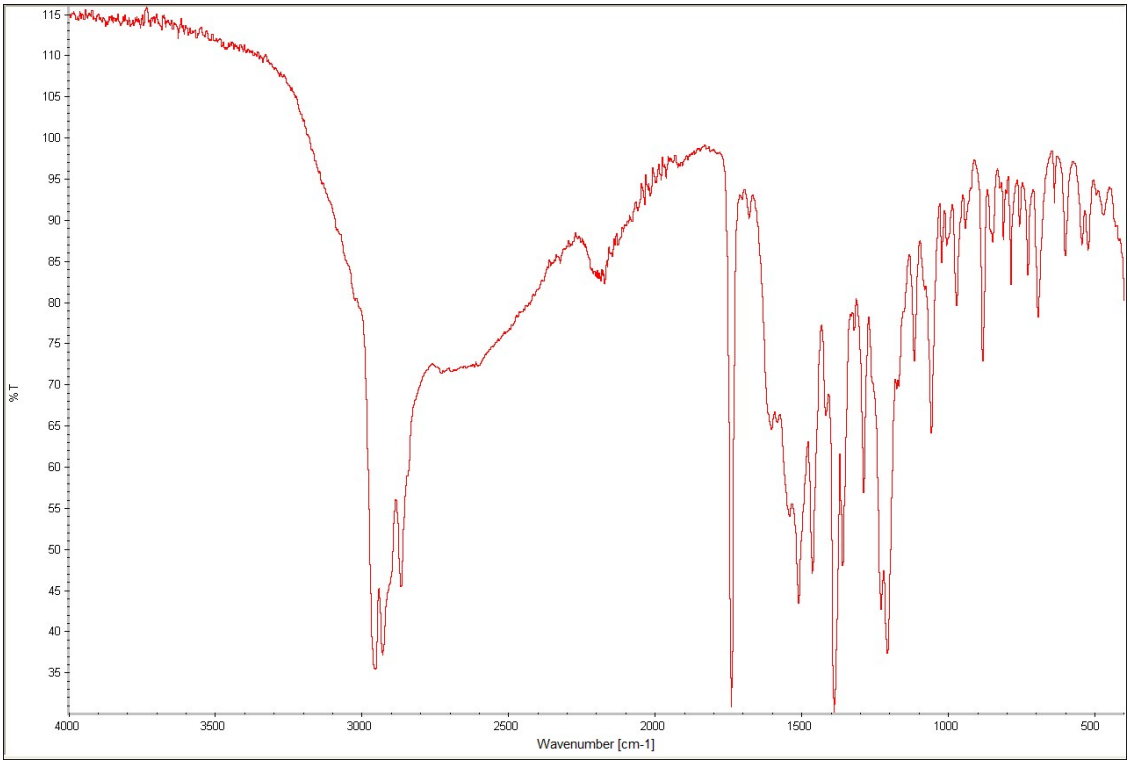
UV-Vis (EtOH): λ_{max}=228.7 nm; $\mathbf{T_m}$=67.9-71.4^{0}C; $[\alpha]_D^{20}$= +10.076 (c=0.526 g/100 cm^3 EtOH).



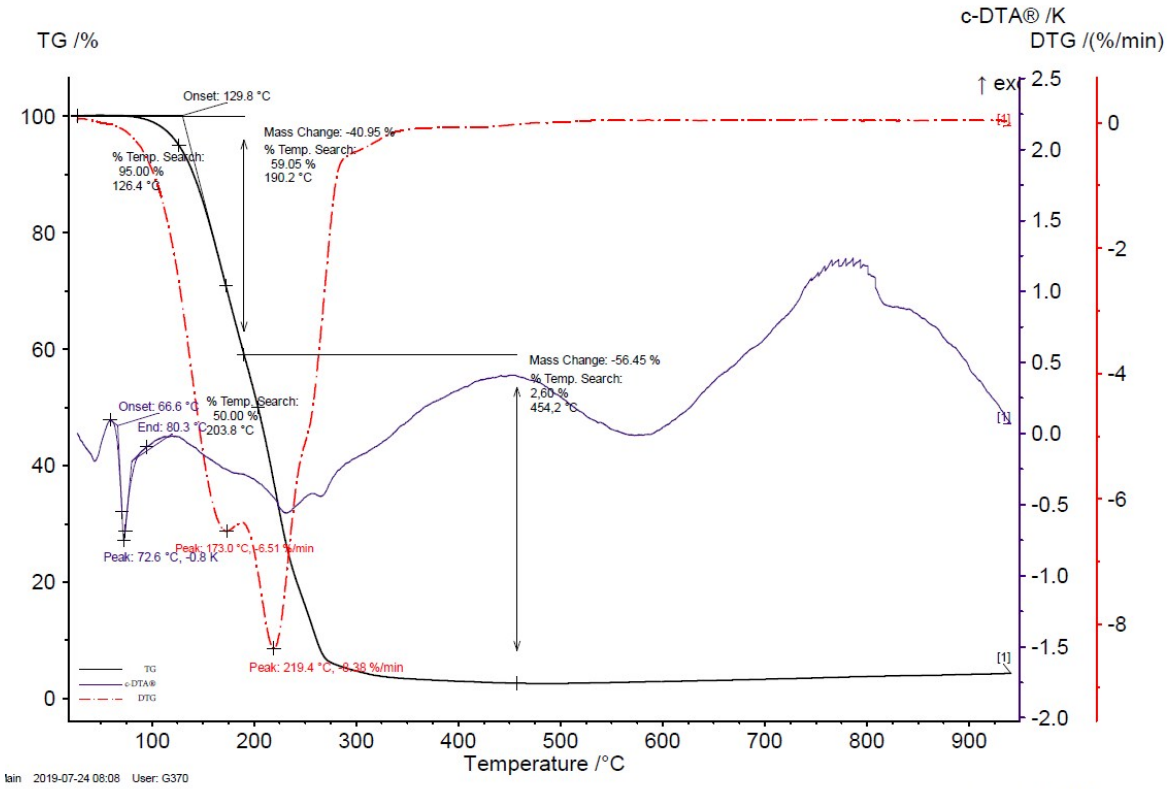
^{1}H NMR spectra of L-valine pentyl ester ibuprofenate



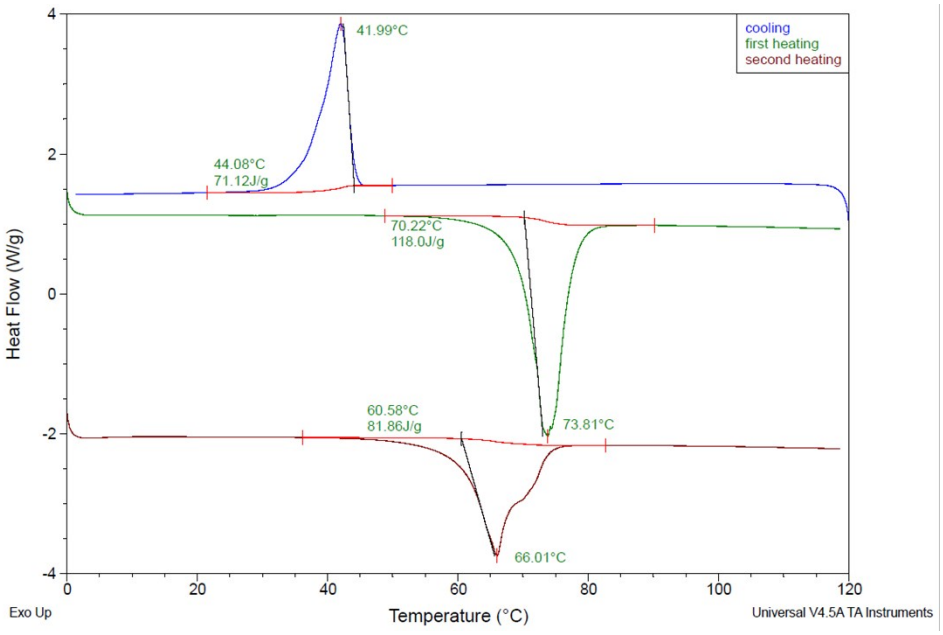
^{13}C NMR spectra of L-valine pentyl ester ibuprofenate



FTIR spectra of L-valine pentyl ester ibuprofenate

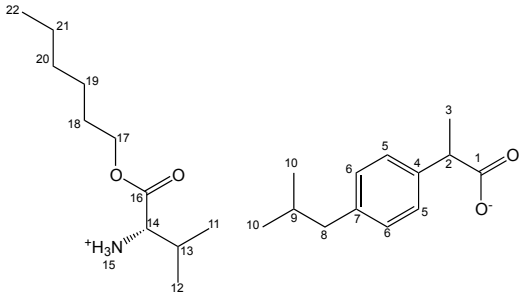


The TG, DTG and c-DTA curves of L-valine pentyl ester ibuprofenate

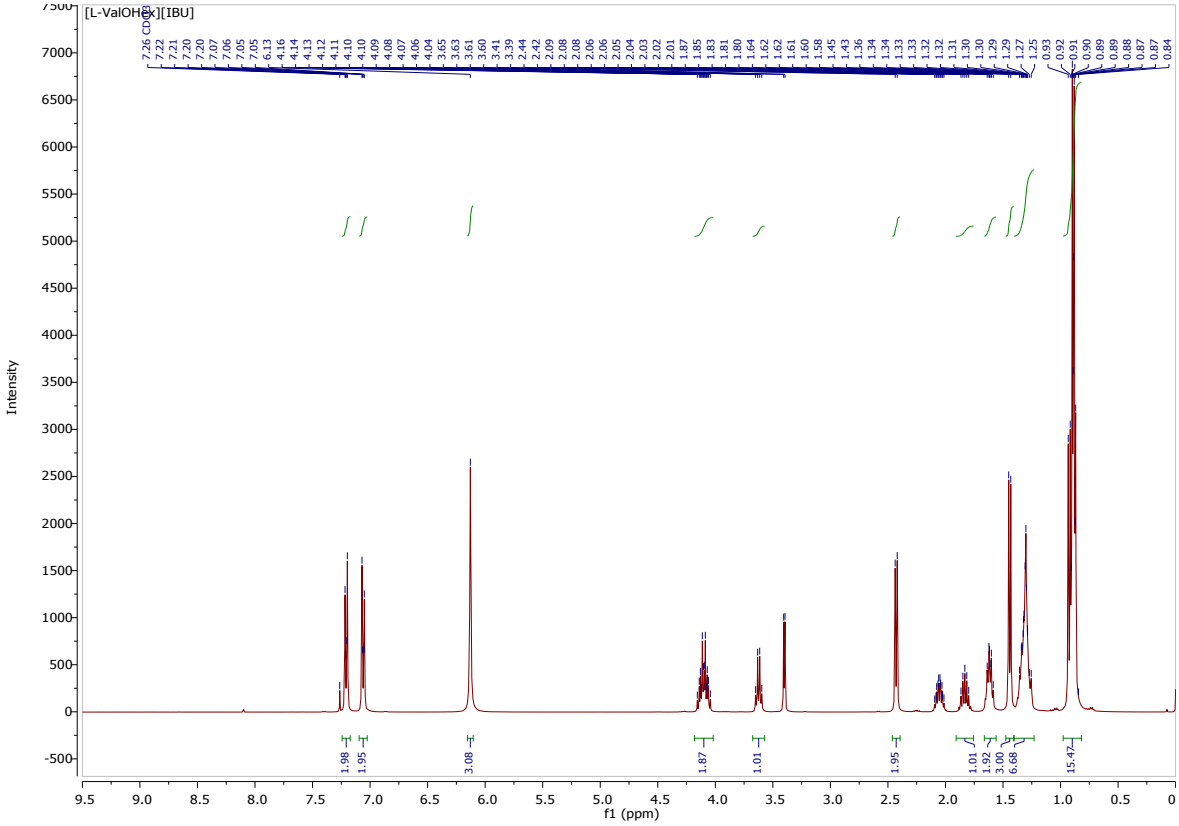


The DSC curves of L-valine pentyl ester ibuprofenate

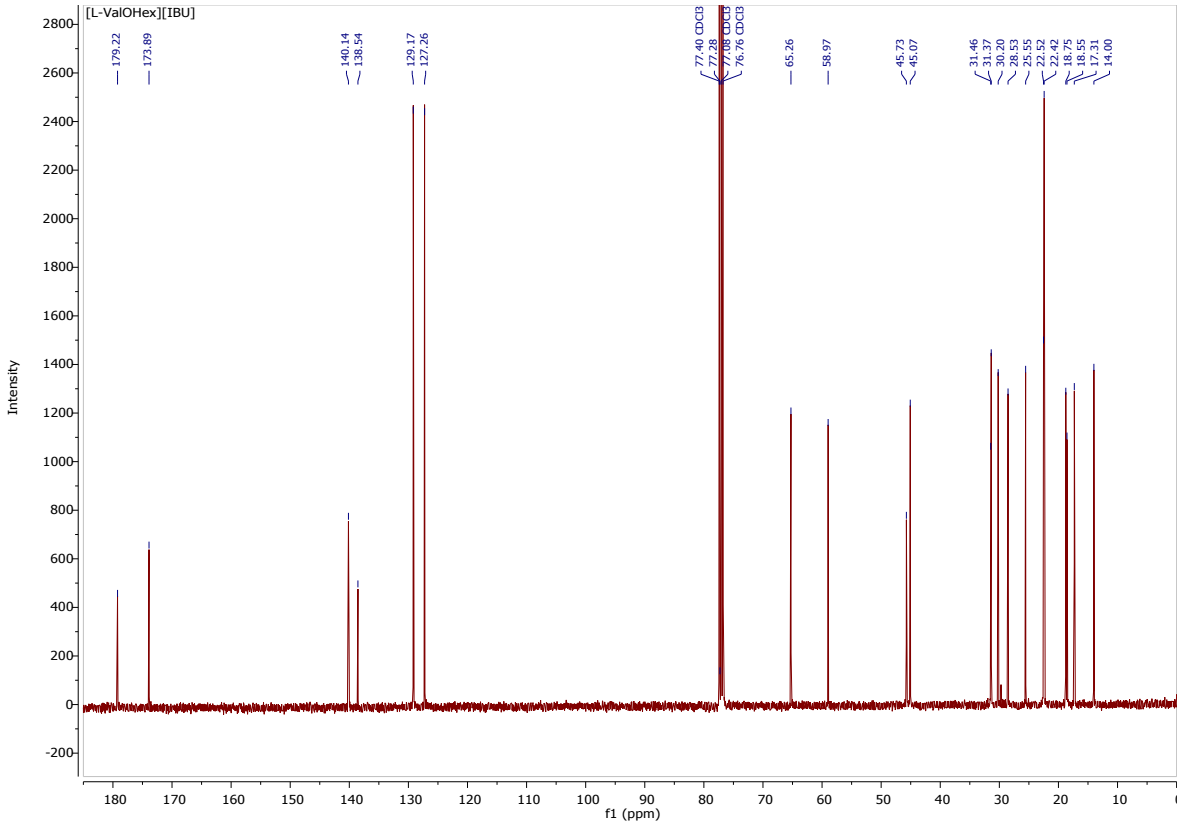
[ValOHex][IBU] – L-valine hexyl ester ibuprofenate



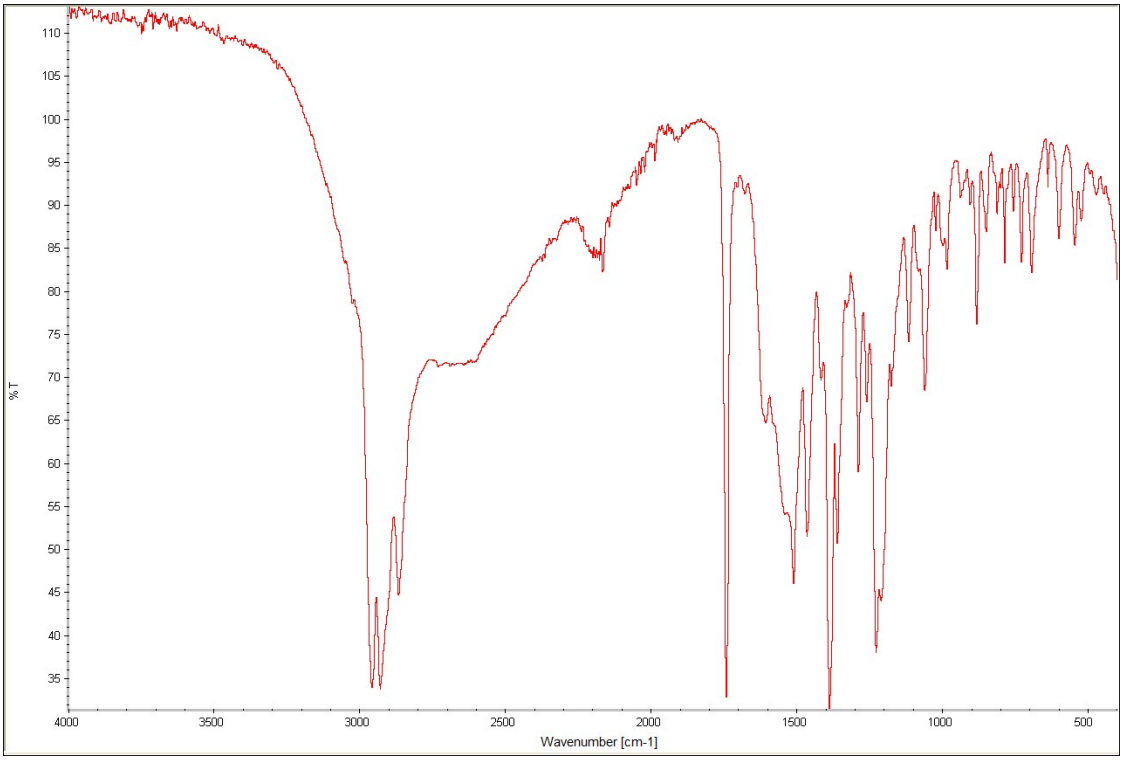
(**UV-Vis** (EtOH): λ_{max}=219.0 nm; $\mathbf{T_m}$=60.8-62.9^{0}C; $[\alpha]_D^{20}$ = +8.987 (c=0.523 g/100 cm^3 EtOH).



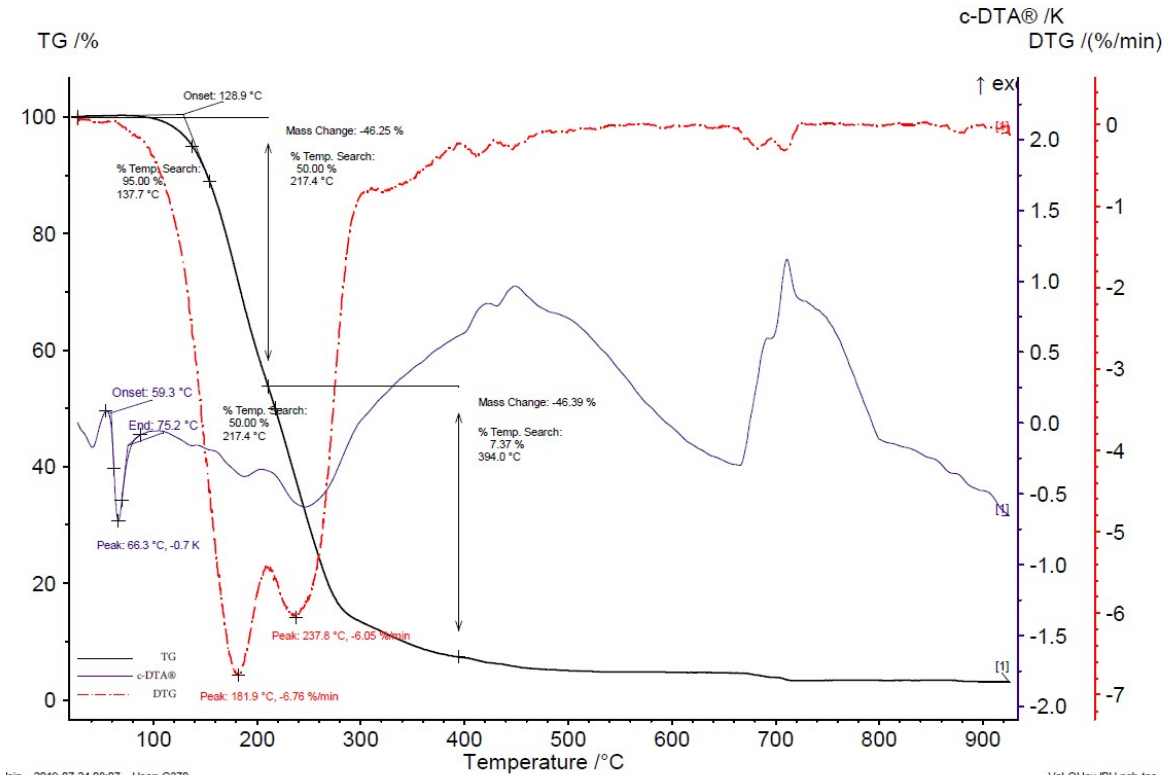
^{1}H NMR spectra of L-valine hexyl ester ibuprofenate



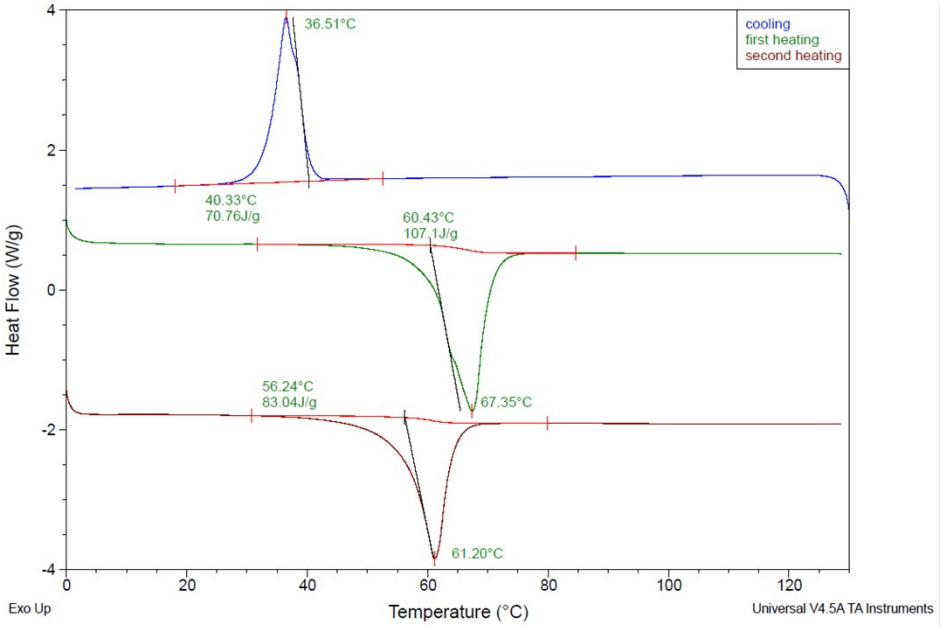
^{13}C NMR spectra of L-valine hexyl ester ibuprofenate



FTIR spectra of L-valine hexyl ester ibuprofenate

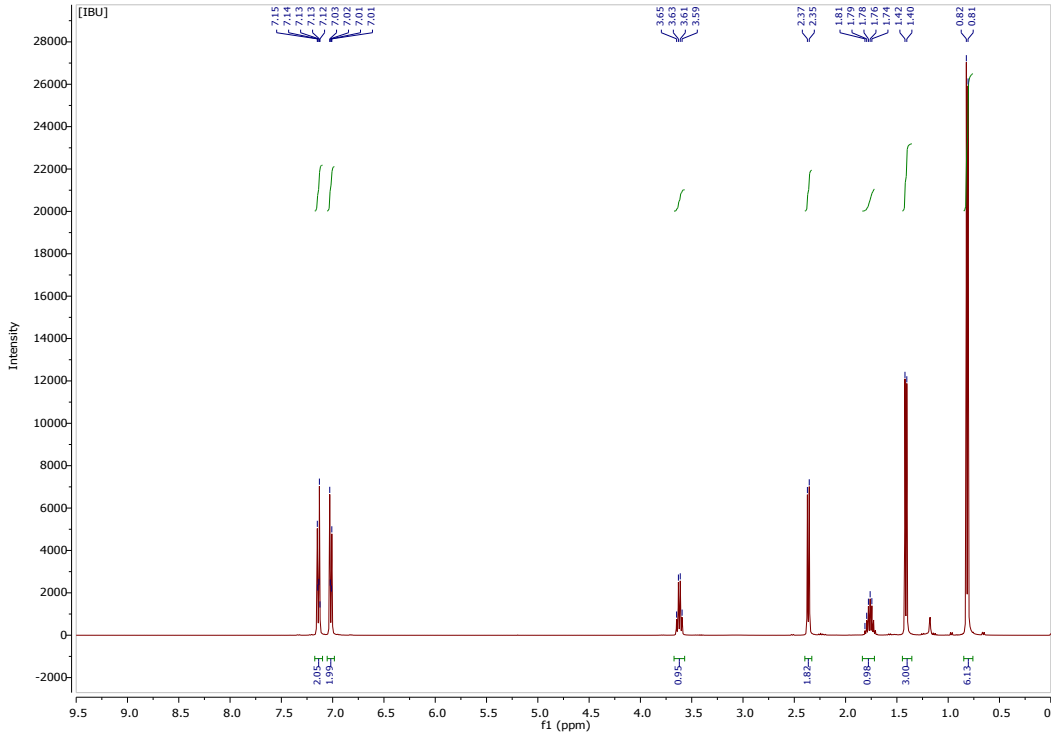


The TG, DTG and c-DTA curves of L-valine hexyl ester ibuprofenate

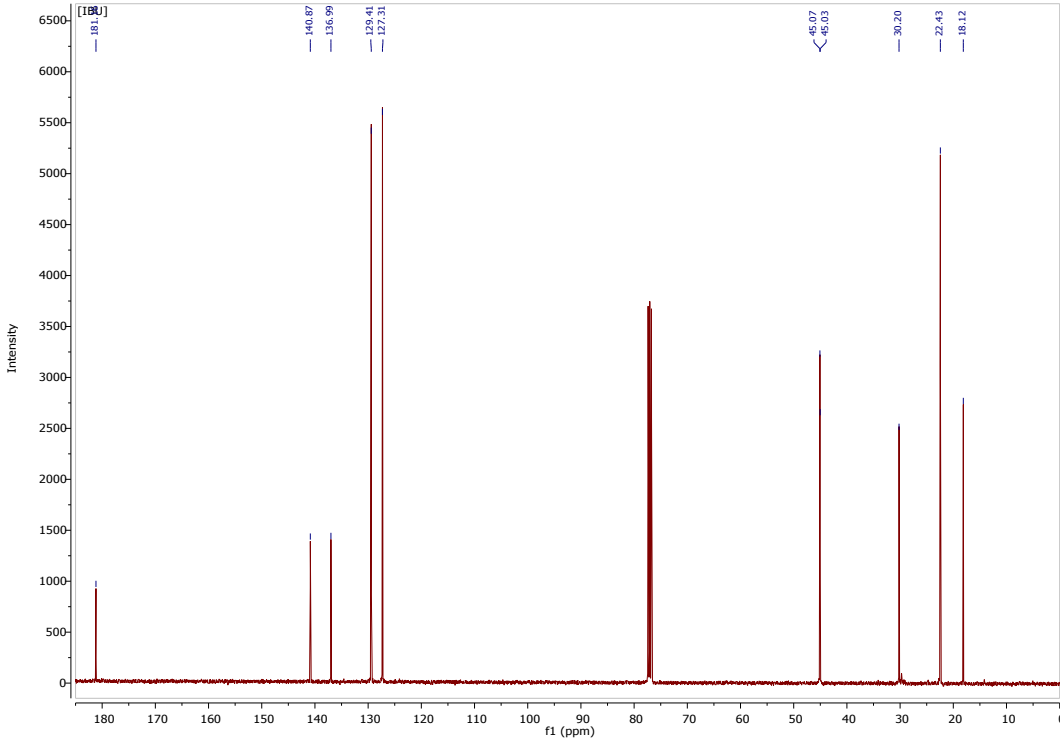


The DSC curves of L-valine hexyl ester ibuprofenate

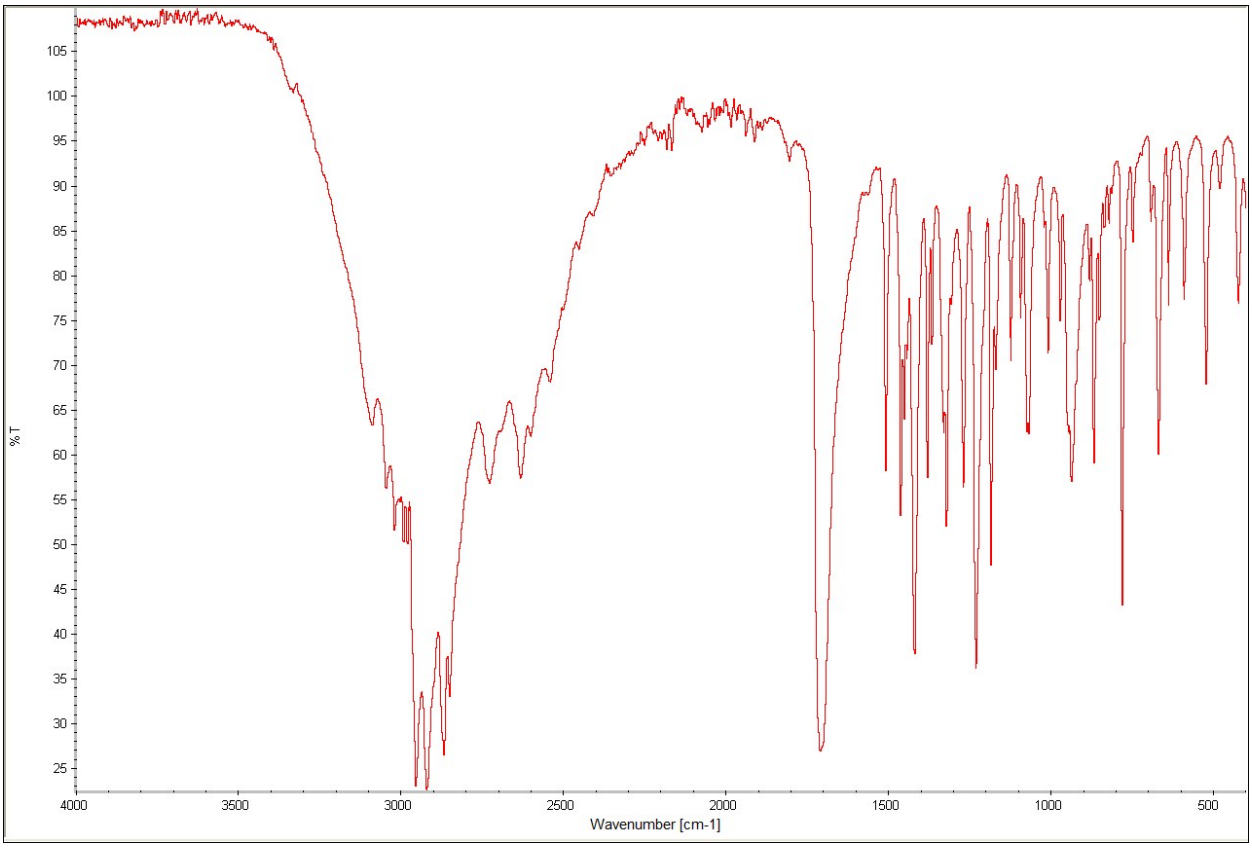
5. COPIES OF ^{1}H, ^{13}C NMR AND FTIR SPECTRA, CURVES OF TG AND DSC ANALYSIS OF IBUPROFEN



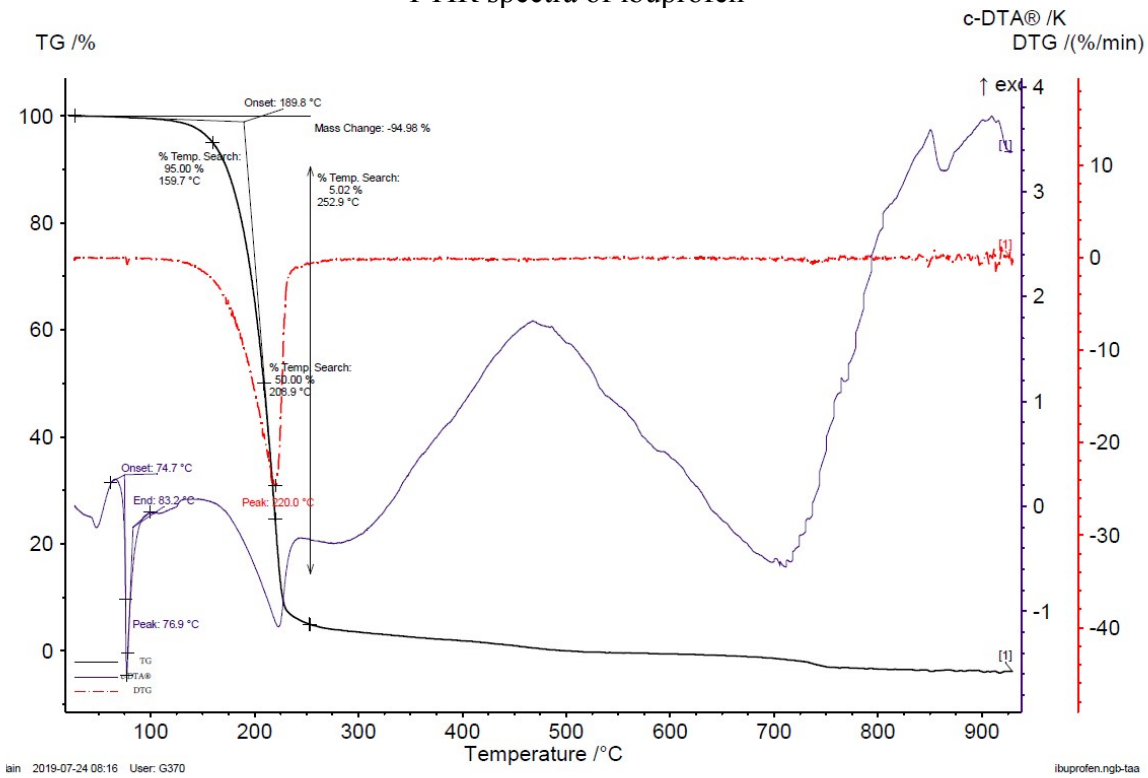
^{1}H NMR spectra of ibuprofen



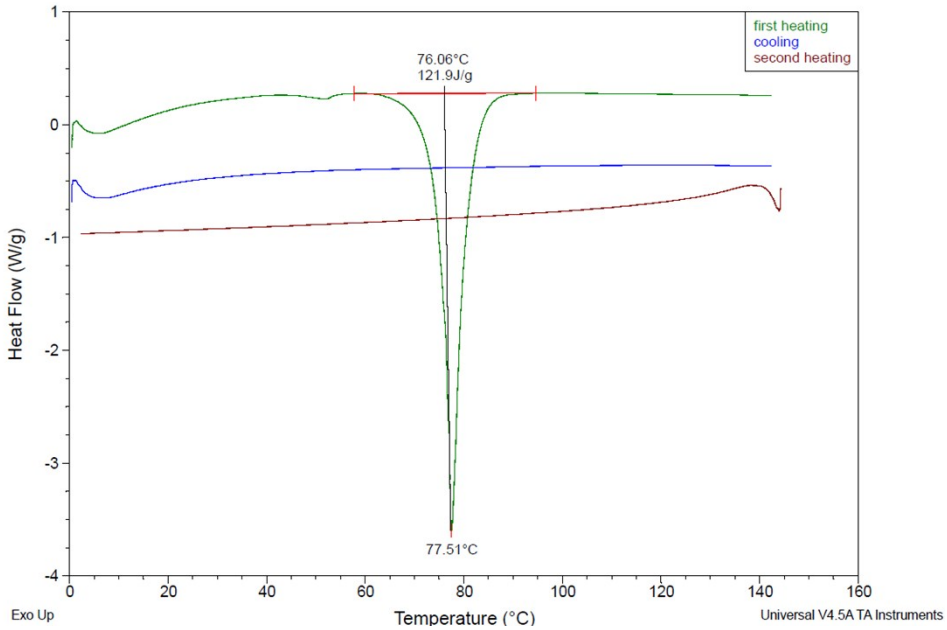
^{13}C NMR spectra of ibuprofen



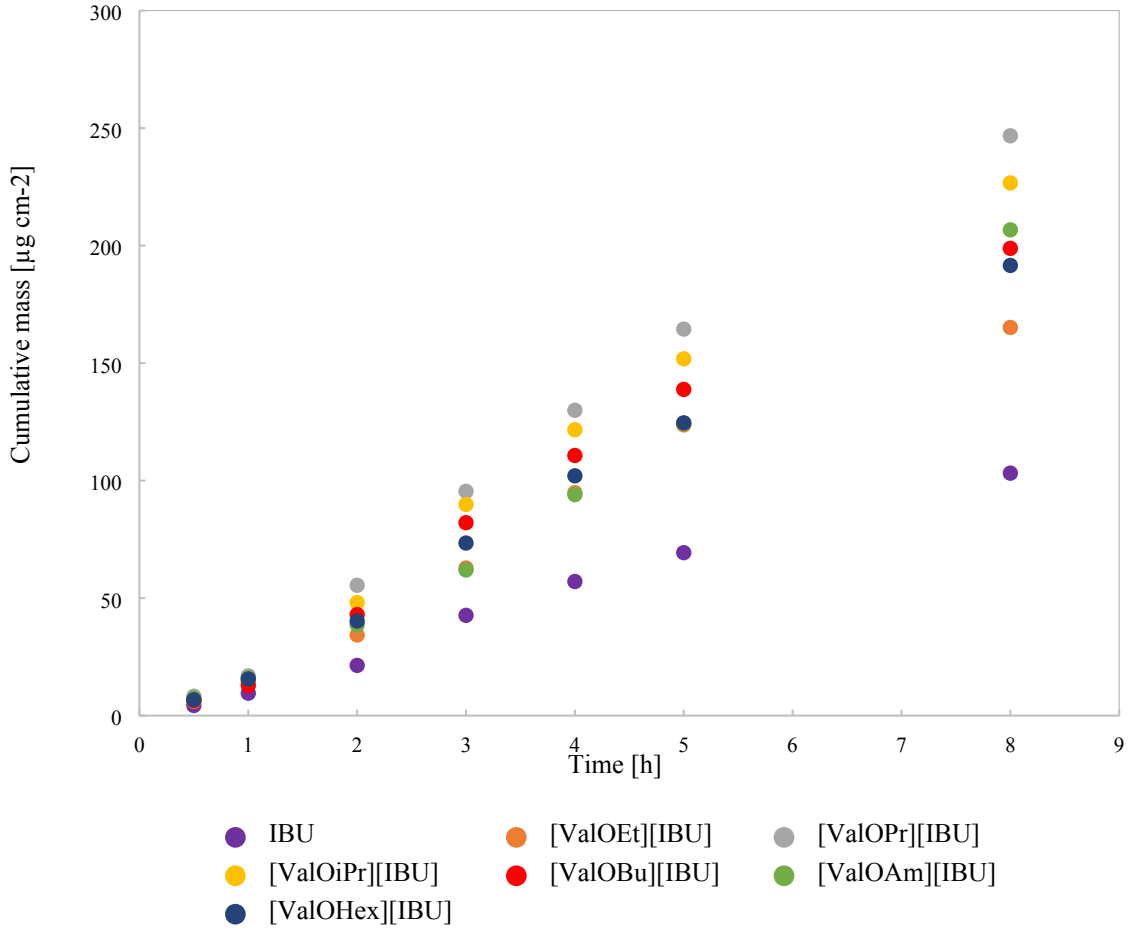
FTIR spectra of ibuprofen



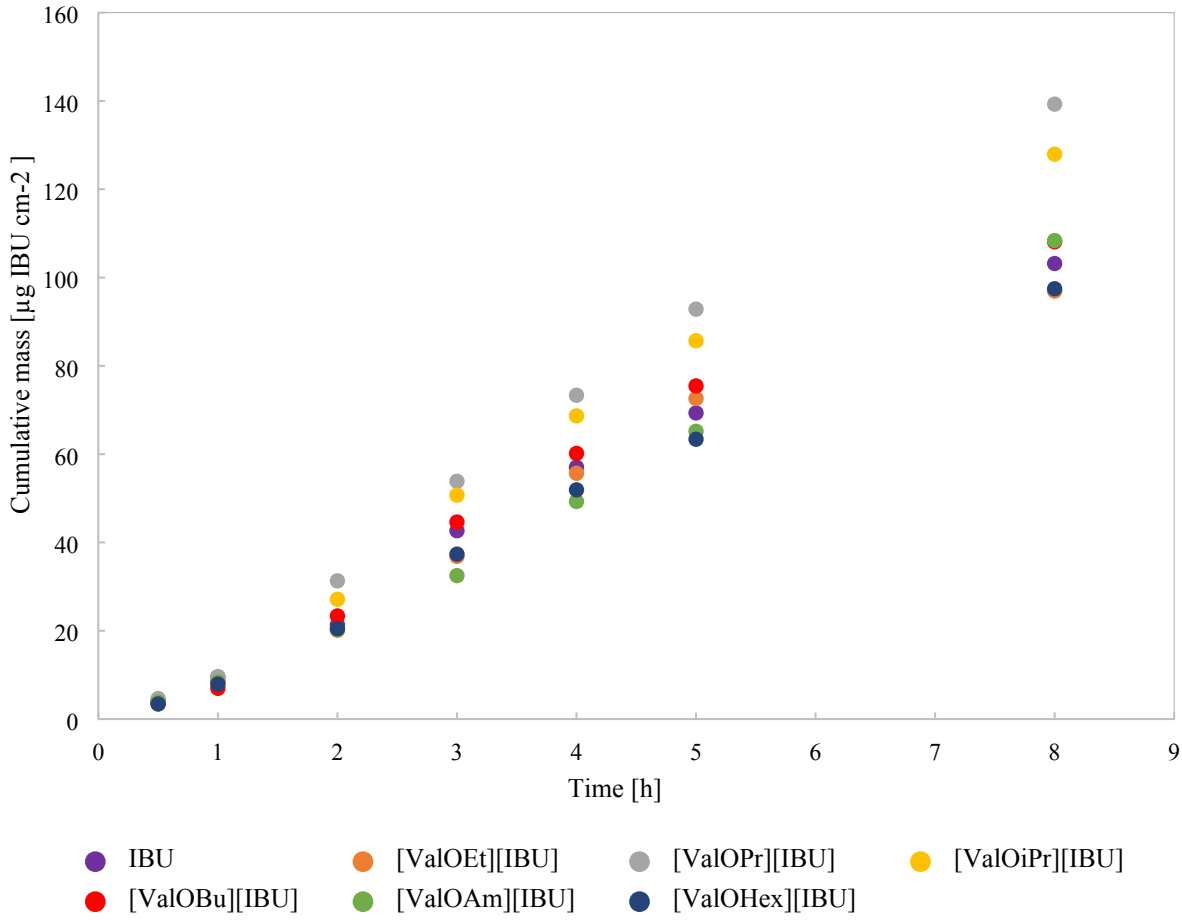
The TG, DTG and c-DTA curves of ibuprofen



The DSC curves of ibuprofen



Permeation as the cumulative mass of compound in the acceptor phase, in µg of compound per skin area, *vs.* time. *In vitro* permeation experiments through porcine skin for 1% (m/v) ethanolic solution of ibuprofen and its L-valine derivatives in donor phase



Permeation as the cumulative mass of ibuprofen in the acceptor phase, in µg of ibuprofen per skin area, *vs.* time. *In vitro* permeation experiments through porcine skin for 1% (m/v) ethanolic solution of ibuprofen and its L-valine derivatives in donor phase

References

1 J. Li, Y. Sha, A convenient synthesis of amino acid methyl esters, Molecules, 2008, **13**(5), 1111-1119, DOI:org/10.3390/molecules13051111.