Supporting information

A Modular Approach towards Drug delivery Vehicles Using Oxanorbornane-based Non-ionic Amphiphiles

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S. No	Table of Contents	Page No.
1	Synthetic scheme	2
2	Experimental procedure & Spectral data	3-18
3	SEM images and DLS analysis results	19-21
4	CMC calculation	22
5	Results from PXRD analyses	23
6	Composition of Niosomal formulations	23
7	Niosomal formulations – particle size distribution and morphology	24
8	CTEM images of sample from **1c**	25
9	Drug-loading and drug-release studies	25-28
10	Stability of aggregates	29
11	^{1}H & ^{13}C NMR spectra of various compounds	30-84

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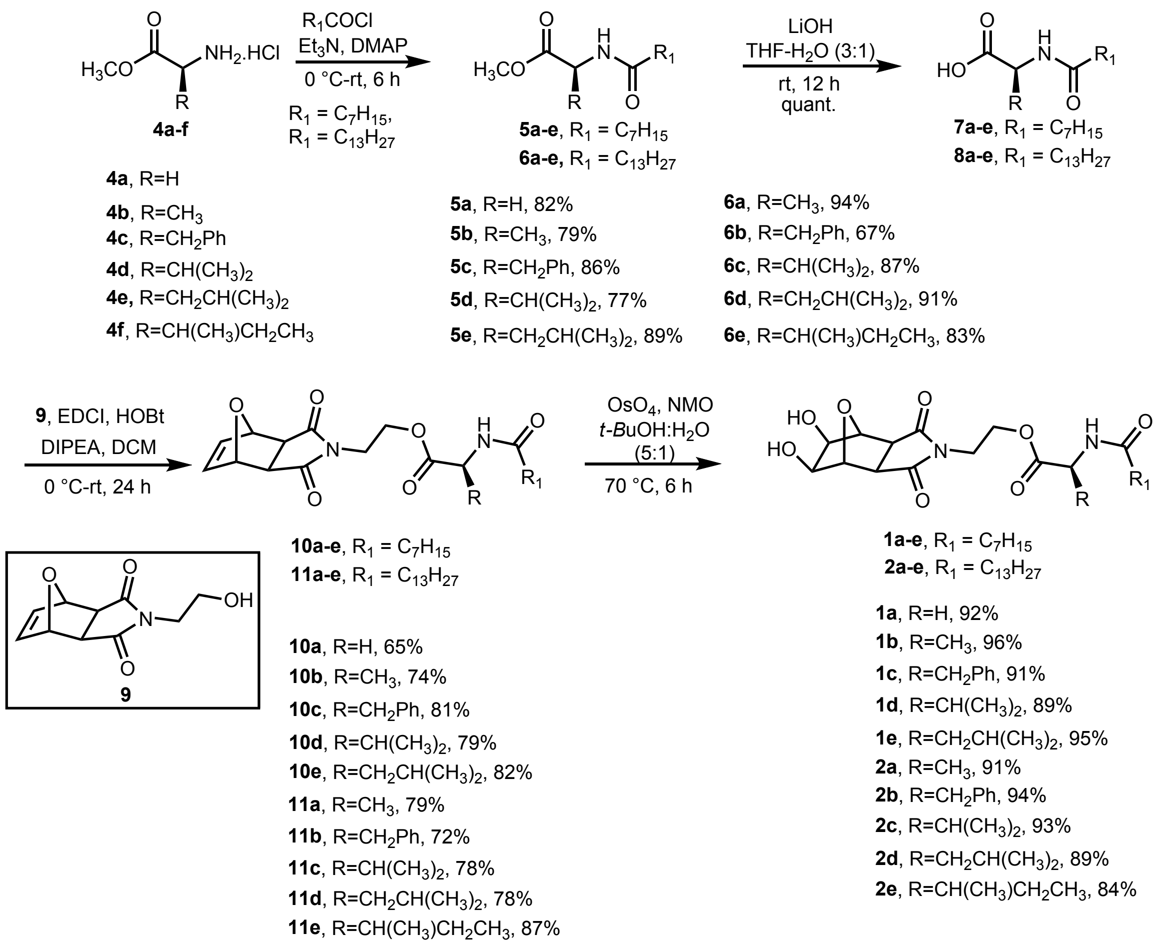
1. Synthetic scheme:

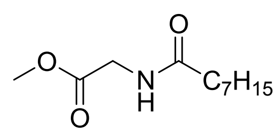


Scheme 1-SI. Syntheses of amphiphiles with C_7 and C_{13} chain lengths having amino acid units as spacers between head and tail.

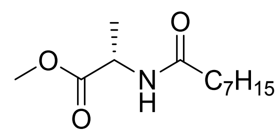
2. Experimental procedure & Spectral data:

General procedure for the preparation of compounds 5a-e, 6a-e (N-acylation):

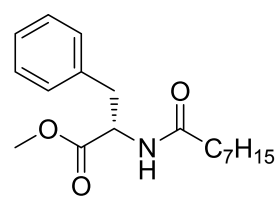
To a stirred solution of the amino acid methyl ester (1.0 equiv.) and Et_3N (2.2 equiv.) in dry dichloromethane was added the appropriate acid chloride (1.1 equiv.) at 0 ˚C under N_2 atmosphere. The reaction mixture was warmed to room temperature and allowed to stir for 3-4 h. After completion of the reaction, the mixture was washed with water and extracted with dichloromethane. The organic layer was dried using Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using 20-30% EtOAc/Hexane. Yields and spectroscopic details of various compounds are given below.



N-octanoyl Gly-methyl ester (5a): Yield, 82%; R_f (5% EtOAc/Hexane), 0.62; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.02 (bs, 1H), 4.04 (d, 2H, J = 4.4 Hz), 3.75 (s, 3H), 2.24 (t, 2H, J = 7.6 Hz), 1.70-1.59 (quin, 2H, J = 6.8 Hz), 1.35-1.23 (m, 8H), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5, 170.7, 52.4, 41.3, 36.5, 31.8, 29.1 (2C), 25.7, 22.6, 14.1; IR (KBr): 2927, 2858, 2364, 1752, 1656, 1547, 1446, 1371, 1208, 1033, 707 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{11}H_{22}NO_3$ $(M+H)^+$ 216.1600, found $(M+H)^+$ 216.1590.

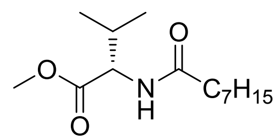


N-octanoyl Ala-methyl ester (5b): Yield, 79%; R_f (5% EtOAc/Hexane), 0.62; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.08 (bs, 1H), 4.58 (quin, 1H, J = 7.0 Hz), 3.73 (s, 3H), 2.18 (t, 2H, J = 7.5 Hz), 1.61 (quin, 2H, J = 7.0 Hz), 1.38 (d, 3H, J = 5.6 Hz), 1.35-1.20 (m, 8H), 0.85 (t, 3H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.8, 172.8, 52.5, 48.0, 36.6, 31.8, 29.3, 29.1, 25.7, 22.7, 18.6, 14.1; IR (KBr): 2864, 1744, 1651, 1538, 1453, 1374, 1266, 1204, 1154, 1014, 759 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{12}H_{24}NO_3$ $(M+H)^+$ 230.1756, found $(M+H)^+$ 230.1746.



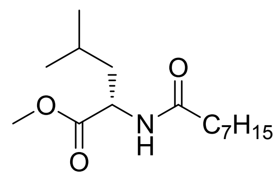
N-octanoyl Phe-methyl ester (5c): Yield, 86%; R_f (5% EtOAc/Hexane), 0.70; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.20 (m, 3H), 7.09 (d, 2H, J = 6.8 Hz), 5.90 (d, 1H, J = 7.6 Hz), 4.9-4.8 (m, 1H) 3.73 (s, 3H), 3.15 (dd, 1H, J = 14.0, 6.0 Hz), 3.09 (dd, 1H, J = 13.6, 5.6 Hz), 2.17 (t, 2H, J = 6.8 Hz), 1.58 (quin, 2H, J = 7.2 Hz), 1.32-1.23 (m, 8H), 0.88 (t, 3H, J = 6.8

Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8, 172.3, 136.0, 129.4 (2C), 128.7 (2C), 127.2, 53.0, 52.4, 36.7, 31.8, 29.3, 29.1 (2C), 25.7, 22.7, 14.2; IR (KBr): 2927, 2857, 1751, 1746, 1650, 1540, 1446, 1211, 1179, 743, 701, 697, 670 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{28}NO_3$ $(M+H)^+$ 306.2069, found $(M+H)^+$ 306.2079

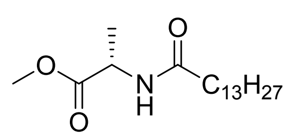


N-octanoyl Val-methyl ester (5d): Yield, 77%; R_f (5% EtOAc/Hexane), 0.66; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.96 (bs, 1H), 4.59-4.54 (m, 1H), 3.72 (s, 3H), 2.22 (t, 2H, *J* = 7.5 Hz), 2.13 (quin, 1H, *J* = 6.5 Hz), 1.62 (t, 2H, *J* = 6.5 Hz), 1.32-1.23 (m, 8H), 0.92 (d, 3H, *J* = 6.5 Hz), 0.88 (d, 3H, *J* = 6.5 Hz), 0.86 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.2, 172.9, 56.9, 52.2, 36.8, 31.8, 31.4, 29.3, 29.1, 25.8, 22.7, 19.0, 17.9, 14.2; IR (KBr): 3590, 3376, 3272, 3063, 2956, 2859, 1745, 1650, 1539, 1460, 1373, 1206, 1153, 1018 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{14}H_{28}NO_3$ $(M+H)^+$ 258.2069, found $(M+H)^+$ 258.2063.

N-octanoyl Leu-methyl ester (5e)

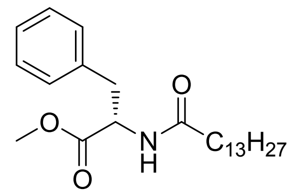


Yield, 89%; R_f (5% EtOAc/Hexane), 0.66; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.87 (bs, 1H), 4.63 (sext, 1H, *J* = 4.5 Hz), 3.71 (s, 3H), 2.19 (t, 2H, *J* = 7.0 Hz), 1.68-1.58 (m, 4H), 1.51 (quin, 1H, *J* = 9.0 Hz), 1.34-1.20 (m, 8H), 0.96-0.90 (m, 6H), 0.86 (t, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9, 173.1, 52.4, 50.6, 41.9, 36.7, 31.8, 29.3, 29.1, 25.7, 25.0, 22.9, 22.7, 22.1, 14.2; IR (KBr): 2954, 2861, 2345, 2338, 1747, 1650, 1543, 1457, 1371, 1273, 1207, 1160, 1024, 721, 667 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{15}H_{30}NO_3$ $(M+H)^+$ 272.2147, found $(M+H)^+$ 272.2154

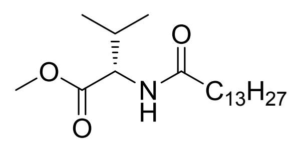


N-myristoyl Ala-methyl ester (6a): Yield, 94%; R_f (5% EtOAc/Hexane), 0.70; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.02 (bs, 1H), 4.60 (quin, 1H, *J* = 7.0 Hz), 3.74 (s, 3H), 2.19 (t, 2H, *J* = 7.5 Hz), 1.62 (quin, 2H, *J* = 7.5 Hz), 1.39 (d, 3H, *J* = 7.0 Hz), 1.32-1.22 (m, 20H), 0.87 (t, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9, 172.8, 52.6, 48.0, 36.7, 32.0, 29.8, 29.77 (3C), 29.74, 29.6, 29.5, 29.4, 25.7, 22.8, 18.7, 14.2; IR (KBr): 3053, 2988, 2932, 2923, 2854, 2309, 2301, 1747, 1742, 1736, 1671, 1509, 1439, 1266, 1215, 1166, 897 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{36}NO_3$ $(M+H)^+$ 314.2695, found $(M+H)^+$ 314.2686.

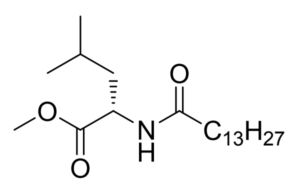
N-myristoyl Phe-methyl ester (6b): Yield, 67%; R_f (5% EtOAc/Hexane), 0.80; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.22 (m, 3H), 7.08 (d, 2H, *J* = 6.8 Hz), 5.86 (bs 1H), 4.90 (q, 1H, *J* = 5.6 Hz), 3.73 (s, 3H), 3.15 (dd, 1H, *J* = 14.0 Hz, 6.0 Hz), 3.09 (dd, 1H, *J* = 14.0 Hz, 6.0 Hz), 2.16 (t, 2H, *J* = 7.2 Hz), 1.58 (t, 2H, *J* = 6.8 Hz), 1.32-1.23 (m, 20 H), 0.88 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8, 172.3, 136.0, 129.4 (2C), 128.7 (2C), 127.2, 53.0, 52.4, 38.1, 36.7, 32.0, 29.8, 29.78 (3C), 29.75, 29.6, 29.5, 29.3, 25.7, 22.8, 14.2; IR (KBr): 3332, 3055, 2922, 2854, 2325, 1744, 1673, 1645, 1531, 1462, 1454, 1448, 1428, 1267, 745, 675, 659 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{40}NO_3$ $(M+H)^+$ 390.2930, found $(M+H)^+$ 390.2939



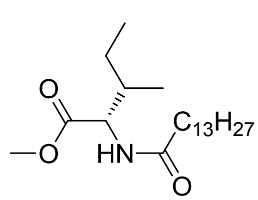
N-myristoyl Val-methyl ester (6c): Yield, 87%; R_f (5% EtOAc/Hexane), 0.75; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.90 (d, 1H, *J* = 8.0 Hz), 4.58 (dd, 1H, *J* = 8.8 Hz, 4.8 Hz), 3.74 (s, 3H), 2.23 (t, 2H, *J* = 7.2 Hz), 2.20-2.10 (m, 1H), 1.67-1.61 (m, 2H), 1.30-1.23 (bs, 20H), 0.95-0.80 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2, 172.9, 56.9, 52.2, 36.9, 32.0, 31.4, 29.8, 29.76 (3C), 29.72, 29.6, 29.5, 29.4, 25.8, 22.8, 19.0, 17.9, 14.2; IR (KBr): 3059, 3054, 2923, 2916, 2850, 1739, 1658, 1522, 1440, 1375, 1266, 1205, 1019, 739 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{40}NO_3$ $(M+H)^+$ 342.3008, found $(M+H)^+$ 342.2996.



N-myristoyl Leu-methyl ester (6d): Yield, 91%; R_f (5% EtOAc/Hexane), 0.75; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.90 (bs, 1H), 4.64 (td, 1H, *J* = 9.0 Hz, 4.0 Hz), 3.71 (s, 3H), 2.19 (t, 2H, *J* = 8.0 Hz), 1.68-1.58 (m, 4H), 1.51 (q, 1H, *J* = 9.0 Hz), 1.30-1.20 (m, 20H), 0.92 (t, 6H, *J* = 3.5 Hz), 0.86 (t, 3H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9, 173.1, 52.3, 50.6, 41.9, 36.7, 32.0, 29.8, 29.76 (3C), 29.72, 29.6, 29.5, 29.3, 25.7, 25.0, 22.9, 22.8, 22.1, 14.2; IR (KBr): 3348, 2918, 2852, 2359, 1751, 1644, 1529, 1462, 1375, 1271, 1239, 1201, 1156, 977, 729 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{42}NO_3$ $(M+H)^+$ 356.3165, found $(M+H)^+$ 356.3168.



N-myristoyl Ileu-methyl ester (6e): Yield, 83%; R_f (5% EtOAc/Hexane), 0.80; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.81 (bs, 1H), 4.65

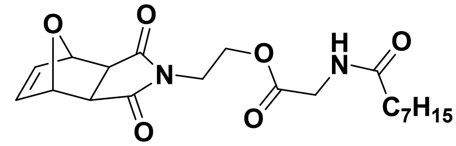


(td, 1H, J = 8.8 Hz, 5.2 Hz), 3.72 (s, 3H), 2.20(t, 2H, J = 7.6 Hz), 1.68-1.57 (m, 4H), 1.51 (quin, 1H, J = 9.2 Hz), 1.33-1.22 (m, 20H), 0.94 (d, 3H, J = 2.4 Hz), 0.93 (d, 3H, J = 2.8 Hz), 0.87 (t, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.9, 173.1, 52.4, 50.7, 41.9, 36.7, 32.1, 29.8, 29.77, 29.74, 29.6, 29.5, 29.4, 25.7, 25.0, 22.9, 22.8, 22.1, 14.2 (3C); IR (KBr): 3436, 3056, 2928, 2857, 2360, 2313, 1739, 1671, 1511, 1430, 1265, 896, 743 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{42}NO_3$ $(M+H)^+$ 356.3165, found $(M+H)^+$ 356.3178.

Procedure for the preparation of esters 10a-e, **11a-e**:

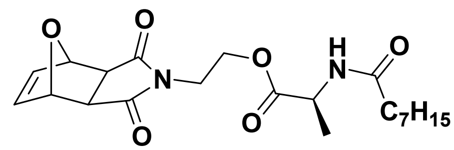
Step 1. Preparation of free acids **7a-e**, **8a-e**: Lithium hydroxide (2 equiv.) was added to a solution of the methyl esters **5a-e**/**6a-e** (1equiv.) in THF-H_2O (3:1) and the mixture was stirred overnight. The solvent was evaporated, diluted with water and washed with ethyl acetate to remove organic impurities. The aquoeous layer was then treated with 10% HCl to bring the pH to ~2, extracted with EtOAc twice, the organic layer washed with water and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave C_7 and C_{13} N-acylated amino acids in quantitative yield. These acids were then used for esterification with **9**.

Step 2. Preparation of esters **10a-e/11a-e, 12a-f**: To a stirred solution containing a mixture of N-acyl amino acid **7a-e/8a-e** (1 equiv.) and 1-hydroxybenzotriazole (HOBT, 1 equiv.) in dry DCM at 0 ˚C was added i-Pr_2NEt (1.2 equiv.) and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDCI, 1.1 equiv.). The reaction mixture was stirred at 0 ˚C for 10 min to which the alcohol **9** was added, allowed to stir at 0 ˚C for 30 min and then at room temperature for 24 h. After completion of the reaction, mixture was diluted with DCM and washed with water (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, solvent evaporated under reduced pressure, and the residue was purified by chromatography on silica gel column using EtOAc/Hexane to get compounds **10a-e, 11a-e** in 65-87% yields. Use of NBoc amino acids in esterification gave the corresponding esters **12a-f** (**12a** R = H; **12b** R=CH_3; **12c** R=CH_2Ph; **12d** R=$CH(CH_3)_2$; **12e** R = $CH_2CH(CH_3)_2$; **12f** R=$CH(CH_3)CH_2CH_3$ with R_1 = -OtBu 69-83% yields.

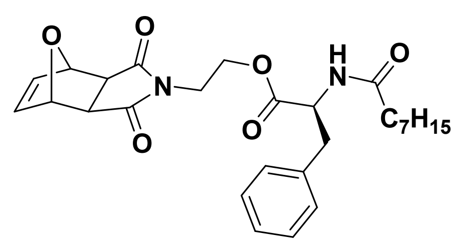


Compound 10a: Yield, 65%; R_f (50% EtOAc/Hexane), 0.38; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.52 (s, 2H), 5.96 (bs, 1H), 5.26 (s, 2H), 4.32 (t, 2H, J = 4.8 Hz), 3.99 (d, 2H, J = 5.2 Hz), 3.77 (t, 2H, J = 5.2 Hz), 2.88 (s, 2H), 2.22 (t,

2H, J = 7.6 Hz), 1.68-1.59 (m, 2H), 1.35-1.23 (m, 8H), 0.87 (t, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2 (2C), 173.4, 169.9, 136.7 (2C), 81.1 (2C), 61.5, 47.6 (2C), 41.4, 37.8, 36.5, 31.8, 29.4, 29.1, 25.7, 22.8, 14.2; IR (KBr): 3434, 3322, 3056, 2957, 2930, 2857, 1752, 1707, 1676, 1518, 1429, 1400, 1375, 1338, 1266, 1193, 1154, 1127, 1022, 992, 917, 896, 878, 854, 739 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{28}N_2O_6Na$ $(M+Na)^+$ 415.1845, found $(M+Na)^+$ 415.1834.

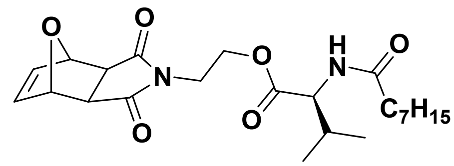


Compound 10b: Yield, 74%; R_f (50% EtOAc/Hexane), 0.40; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.51 (s, 2H), 6.02 (d, 1H, J = 9.0 Hz), 5.26 (s, 2H), 4.56 (quin, 1H, J = 9.5) 4.36-4.26 (m, 2H), 3.77 (t, 2H, J = 6.5 Hz), 2.88 (q, 2H, J = 8.0 Hz), 2.19 (t, 2H, J = 8.5 Hz), 1.61 (quin, 2H, J = 7.2 Hz), 1.35 (d, 3H, J = 9.0 Hz), 1.28 (t, 8H, J = 6.0 Hz), 0.87 (t, 3H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.2, 176.1, 172.7, 172.6, 136.6 (2C), 81.0 (2C), 61.5, 48.0, 47.6, 47.55, 37.8, 36.6, 31.8, 29.3, 29.1, 25.6, 22.7, 18.4, 14.1; IR (KBr): 3056, 2985, 2958, 2930, 2858, 1777, 1747, 1701, 1671, 1512, 1456, 1427, 1400, 1337, 1310, 1267, 1194, 1155, 1124, 1063, 1023, 917, 895, 879, 855, 751, 704 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{31}N_2O_6$ $(M+H)^+$ 407.2182, found $(M+H)^+$ 407.2187.

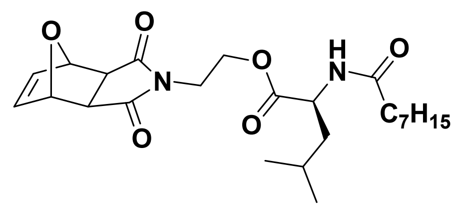


Compound 10c: Yield, 81%; R_f (50% EtOAc/Hexane), 0.5; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.18 (m, 3H), 7.13-7.07 (m, 2H), 6.50 (s, 2H), 5.88 (d, 1H, J = 8.0 Hz), 5.24 (d, 2H, J = 5.0 Hz), 4.86 (td, 1H, J = 8.0, 6.0 Hz), 4.33-4.20 (m, 2H), 3.75 (t, 2H, J = 5.5 Hz), 3.14 (dd, 1H, J = 16.0, 5.5 Hz), 3.02 (dd, 1H, J = 14, 6.5 Hz), 2.84 (d, 2H, J = 1.5 Hz), 2.20-2.10 (m, 2H), 1.56 (quin, 2H, J = 8.0 Hz), 1.32-1.20 (m, 8H), 0.86 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.1 (2C), 172.9, 171.2, 136.6 (2C), 136.2, 129.4 (2C), 128.6 (2C), 127.1, 81.0 (2C), 61.6, 53.1, 47.6, 47.58, 37.73, 37.69, 36.6, 31.8, 29.3, 29.1, 25.6, 22.7, 14.2; IR (KBr): 3427, 3055, 2985, 2958, 2929, 2857, 1746, 1704, 1672, 1510, 1454, 1425, 1399, 1337, 1264, 1193, 1155, 1126, 1023, 917, 896, 879, 701 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{27}H_{35}N_2O_6$ $(M+H)^+$ 483.2495, found $(M+H)^+$ 483.2485.

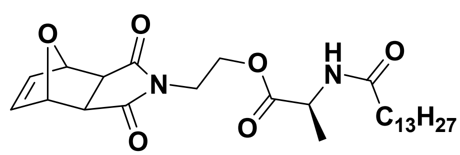
Compound 10d: Yield, 79%; R_f (50% EtOAc/Hexane), 0.44; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.49 (s, 2H), 6.00 (d, 1H, *J* = 8.8 Hz), 5.22 (s, 2H), 4.51 (dd, 1H, *J* = 8.4 Hz, 4.8 Hz), 4.31-4.19 (m, 2H), 3.74 (t, 2H, *J* = 5.2 Hz), 2.84 (s, 2H), 2.20 (t, 2H, *J* = 7.6 Hz), 2.09 (sext, 1H, *J* = 6.4 Hz), 1.59 (quin, 2H, *J* = 6.0 Hz), 1.33-1.18 (m, 8H), 0.88 (d, 3H, *J* = 6.4 Hz), 0.86-0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1, 176.0, 173.2, 171.6, 136.6, 136.5, 80.9 (2C), 61.3, 56.8, 47.5, 47.4, 37.7, 36.7, 31.7, 31.1, 29.3, 29.0, 25.7, 22.6, 19.0, 17.7, 14.5; IR (KBr): 3055, 2961, 2929, 2857, 2307, 1778, 1746, 1705, 1651, 1524, 1466, 1398, 1337, 1272, 1192, 1151, 1022, 999, 917, 879, 855, 749 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{35}N_2O_6$ $(M+H)^+$ 435.2495, found $(M+H)^+$ 435.2495.



Compound 10e: Yield, 82%; R_f (50% EtOAc/Hexane), 0.46; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.51 (s, 2H), 5.82 (d, 1H, *J* = 8.4 Hz), 5.26 (d, 2H, *J* = 2.8 Hz), 4.61 (td, 1H, *J* = 8.8, 4.4 Hz), 4.30-4.26 (m, 2H), 3.76 (t, 2H, *J* = 6.0 Hz), 2.87 (q, 2H, *J* = 6.4 Hz), 2.19 (t, 2H, *J* = 7.6 Hz), 1.66-1.56 (m, 4H), 1.46 (quin, 1H, *J* = 9.2 Hz), 1.33-1.22 (m, 8H), 0.92 (d, 6H, *J* = 6.0 Hz), 0.87 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2, 176.1, 173.1, 172.7, 136.7 (2C), 81.0 (2C), 61.4, 50.6, 47.6, 47.5, 41.6, 37.9, 36.7, 31.8, 29.3, 29.1, 25.7, 24.9, 23.0, 22.7, 21.9, 14.2; IR (KBr): 2957, 2929, 2858, 1748, 1704, 1650, 1541, 1399, 1336, 1275, 1193, 1154, 1022, 917, 879, 854, 750, 719 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{37}N_2O_6$ $(M+H)^+$ 449.5695, found $(M+H)^+$ 449.5688.

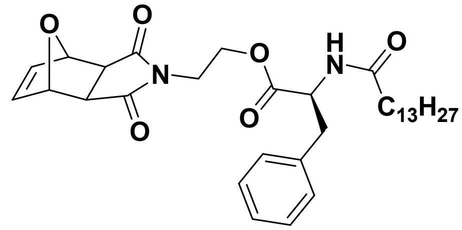


Compound 11a: Yield, 79%; R_f (50% EtOAc/Hexane), 0.50; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.52 (s, 2H), 6.02 (d, 1H, *J* = 7.0 Hz), 5.26 (d, 2H, *J* = 7.0 Hz), 4.56 (quin, 1H, *J* = 4.0 Hz), 4.31 (sext, 2H, *J* = 5.0), 3.78 (t, 2H, *J* = 5.0 Hz), 2.88 (q, 2H, *J* = 6.5 Hz), 2.19 (tq, 2H, *J* = 7.5 Hz, 1.6 Hz), 1.62 (sext, 2H, *J* = 6.0 Hz), 1.35 (d, 3H, *J* = 7.0 Hz), 1.30-1.23 (m, 20H), 0.88 (t, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (2C), 172.8, 172.7, 136.7 (2C), 81.1 (2C), 61.6, 48.1, 47.6, 47.5, 37.9, 36.7, 32.0, 29.8 (3C), 29.6, 29.5 (3C), 29.4, 25.7, 22.8, 18.4, 14.2; IR (KBr): 3431, 3055, 2986, 2926, 2855,

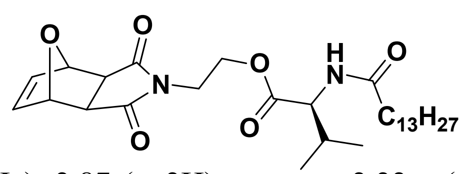


1777, 1746, 1705, 1672, 1510, 1455, 1426, 1400, 1337, 1264, 1194, 1156, 1022, 917, 896, 879, 855, 749 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{27}H_{43}N_2O_6$ $(M+H)^+$ 491.6504, found $(M+H)^+$ 491.6491.

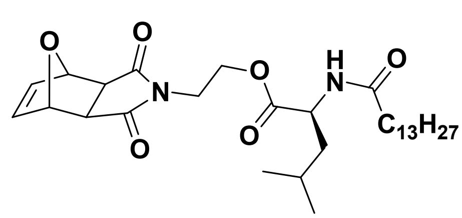
Compound 11b: Yield, 72%; R_f (50% EtOAc/Hexane), 0.60; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.20 (m, 3H), 7.09 (d, 2H, *J* = 7.6 Hz), 6.51 (s, 2H), 5.90 (d, 1H, *J* = 8.0 Hz), 5.24 (d, 2H, *J* = 4.0 Hz), 4.86 (q, 1H, *J* = 6.8 Hz), 4.32-4.20 (m, 2H), 3.75 (t, 2H, *J* = 5.2 Hz), 3.14 (dd, 1H, *J* = 14.0 Hz, 5.6 Hz), 3.02 (dd, 1H, *J* = 14.0 Hz, 6.4 Hz), 2.84 (s, 2H), 2.15 (td, 2H, *J* = 7.2 Hz, 3.6 Hz), 1.56 (quin, 2H, *J* = 6.4 Hz), 1.34-1.22 (m, 20H), 0.88 (t, 3H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (2C), 172.9, 171.2, 136.7, 136.6, 136.2, 129.5 (2C), 128.6 (2C), 127.1, 81.1 (2C), 61.7, 53.1, 47.6, 37.8, 37.7, 36.6, 32.1, 29.8 (4C), 29.6, 29.5 (3C), 29.4, 25.7, 22.8, 14.2; IR (KBr): 3431, 3055, 2986, 2928, 2855, 1777, 1745, 1707, 1673, 1510, 1455, 1424, 1399, 1337, 1265, 1193, 1154, 1126, 1023, 896, 879, 748, 705 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{33}H_{47}N_2O_6$ $(M+H)^+$ 567.3434, found $(M+H)^+$ 567.3448.



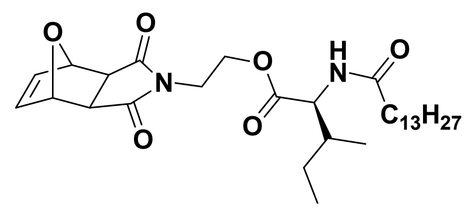
Compound 11c: Yield, 78%; R_f (50% EtOAc/Hexane), 0.50; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.51 (s, 2H), 5.95 (d, 1H, *J* = 8.8 Hz), 5.26 (d, 2H, *J* = 2.4 Hz), 4.55 (dd, 1H, *J* = 9.2 Hz, 5.2 Hz), 4.34-4.22 (m, 2H), 3.77 (t, 2H, *J* = 5.2 Hz), 2.87 (s, 2H), 2.22 (t, 2H, *J* = 7.2 Hz), 2.17-2.10 (m, 1H), 1.70-1.60 (m, 2H), 1.32-1.23 (m, 20H), 0.91 (d, 3H, *J* = 6.8 Hz), 0.87 (t, 3H, *J* = 6.4 Hz), 0.86 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ176.1, 176.0, 173.2, 171.7, 136.7, 136.6, 81.0 (2C), 61.4, 56.9, 47.6, 47.5, 37.8, 36.8, 32.1, 31.3, 29.8, 29.7 (3C), 29.6, 29.5 (2C), 29.4, 25.8, 22.8, 19.2, 17.8, 14.3; IR (KBr): 3565, 3325, 2958, 2925, 2854, 1744, 1705, 1650, 1537, 1466, 1429, 1398, 1336, 1271, 1192, 1152, 1124, 1022, 917, 878, 854, 748, 720 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{29}H_{46}N_2O_6Na$ $(M+Na)^+$ 541.3254, found $(M+H)^+$ 541.3231.



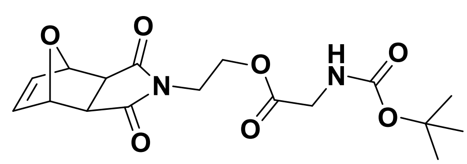
Compound 11d: Yield, 78%; R_f (50% EtOAc/Hexane), 0.50; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.52 (s, 2H), 5.80 (d, 1H, *J* = 8.8 Hz), 5.26 (d, 2H, *J* = 2.4 Hz), 4.62 (td, 1H, *J* = 9.2 Hz, 4.8 Hz),



4.28 (td, 2H, J = 5.2 Hz, 0.8 Hz), 3.77 (t, 2H, J = 5.6 Hz), 2.88 (q, 2H, J = 6.8 Hz), 2.19 (td, 2H, J = 7.6 Hz, 2.0 Hz), 1.65-1.58 (m, 4H), 1.47 (q, 1H, J = 9.2 Hz), 1.32-1.23 (m, 20H), 0.93 (d, 6H, J = 6.0 Hz), 0.88 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2, 176.1, 173.1, 172.7, 136.7 (2C), 81.0 (2C), 61.4, 50.6, 47.6, 47.5, 41.6, 37.9, 36.7, 32.0, 29.8, 29.7 (3C), 29.6, 29.5 (2C), 29.4, 25.7, 25.0, 23.0, 22.8, 21.9, 14.3; IR (KBr): 3312, 3056, 2956, 2925, 2854, 1776, 1746, 1704, 1651, 1541, 1469, 1399, 1366, 1337, 1275, 1193, 1154, 1125, 1023, 992, 917, 879, 855, 750, 719 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{30}H_{48}N_2O_6Na$ $(M+Na)^+$ 555.3410, found $(M+Na)^+$ 555.3417.

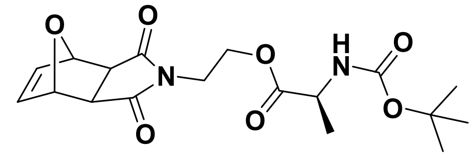


Compound 11e: Yield, 87%; R_f (50% EtOAc/Hexane), 0.60; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.50 (s, 2H), 6.03 (d, 1H, J = 8.4 Hz), 5.25 (s, 2H), 4.67 (dd, 1H, J = 8.8 Hz, 4.0 Hz), 4.21 (t, 2H, J = 5.2 Hz), 3.74 (t, 2H, J = 5.6 Hz), 2.85 (s, 2H), 2.24 (t, 2H, J = 7.2 Hz), 1.63 (quin, 2H, J = 6.8 Hz), 1.56 (quin, 2H, J = 7.2 Hz), 1.42 (quin, 1H, J = 7.2 Hz), 1.32-1.20 (m, 20H), 0.94 (quin, 3H, J = 4.4 Hz), 0.91 (d, 3H, J = 7.2 Hz) , 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2 (2C), 175.5, 173.7, 136.7 (2C), 81.1 (2C), 60.5, 56.5, 55.3, 47.6 (2C), 38.1, 34.2, 32.0, 29.8, 29.77 (3C), 29.73, 29.6, 29.59, 29.50, 29.38, 29.35, 29.26, 24.8, 22.7, 14.3; IR (KBr): 3365, 2920, 2851, 2361, 2341, 1746, 1718, 1649, 1555, 1541, 1510, 1468, 1397, 1338, 1196, 1153, 1024, 877, 749, 716 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{30}H_{48}N_2O_6Na$ $(M+Na)^+$ 555.7132, found $(M+H)^+$ 555.7137.

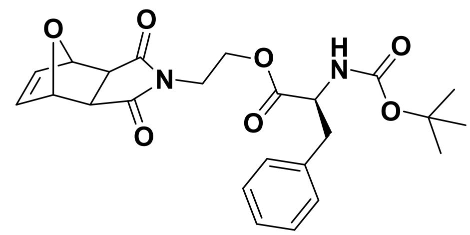


Compound 12a: Yield, 78%; R_f (60% EtOAc/Hexane), 0.30; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.51 (s, 2H), 5.26 (s, 2H), 5.02 (bs, 1H), 4.30 (t, 2H, J = 5.2 Hz), 3.85 (d, 2H, J = 5.6 Hz), 3.75 (t, 2H, J = 5.6 Hz), 2.87 (s, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2 (2C), 170.3, 155.8, 136.6 (2C), 81.1 (2C), 80.1, 61.3, 47.6 (2C), 42.4, 37.8, 28.4 (3C); IR (KBr): 3397, 3008, 2980, 2937, 1751, 1699, 1520, 1398, 1368, 1338, 1278, 1191, 1160, 1126, 1058, 1021, 991, 949, 916, 877, 854 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{17}H_{22}N_2O_7Na$ $(M+Na)^+$ 389.1325, found $(M+Na)^+$ 389.1331.

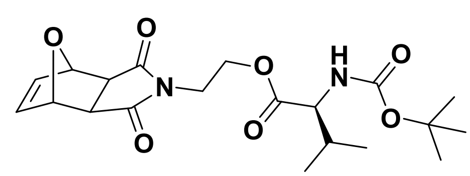
Compound 12b: Yield, 75%; R_f (60% EtOAc/Hexane), 0.30; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.50 (s, 2H), 5.26 (s, 2H), 5.04 (bs, 1H), 4.29 (t, 2H, *J* = 5.6 Hz), 3.81 (sext, 2H, *J* = 5.2 Hz), 2.86 (d, 2H, *J* = 4.0 Hz), 1.42 (s, 9H), 1.33 (d, 3H, *J* = 7.2 Hz); NH proton did not appear ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (2C), 172.9, 155.2, 136.6 (2C), 81.0 (2C), 79.9, 61.4, 49.3, 47.6, 47.5, 37.9, 28.4 (3C), 18.5; IR (KBr): 3438, 3055, 2986, 1777, 1746, 1708, 1651, 1506, 1423, 1399, 1367, 1338, 1265, 1163, 1068, 1023, 916, 896, 880, 855, 745 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{24}N_2O_7Na$ $(M+Na)^+$ 403.1481, found $(M+Na)^+$ 403.1479.



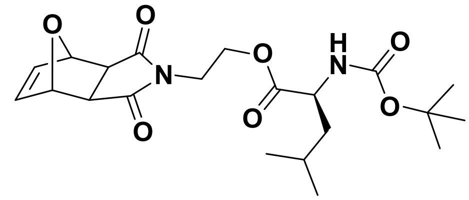
Compound 12c: Yield, 72%; R_f (60% EtOAc/Hexane), 0.48; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.26 (m, 2H), 7.24-7.17 (m, 1H), 7.13 (d, 2H, *J* = 7.2 Hz), 6.50 (s, 2H), 5.26 (d, 2H, *J* = 12.4 Hz), 4.97 (d, 1H, *J* = 8.0 Hz), 4.94 (d, 1H, *J* = 6.0 Hz), 4.37-4.27 (m, 1H), 4.26-4.18 (m, 1H), 3.83-3.69 (m, 2H), 3.11 (dd, 1H, *J* = 13.6 Hz, 4.8 Hz), 2.96 (dd, 1H, *J* = 13.2 Hz, 6.8 Hz), 2.85 (s, 2H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (2C), 171.6, 155.6, 136.7, 136.6, 136.4, 129.5 (2C), 128.6 (2C), 127.0, 81.1 (2C), 80.0, 61.4, 54.5, 47.6 (2C), 38.2, 37.7, 28.4 (3C); IR (KBr): 3433, 3056, 2983, 2934, 2307, 1777, 1747, 1704, 1505, 1454, 1428, 1397, 1367, 1338, 1264, 1167, 1126, 1080, 1057, 1023, 998, 917, 896, 879, 856, 802 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{28}N_2O_7Na$ $(M+Na)^+$ 479.1794, found $(M+Na)^+$ 479.1799.



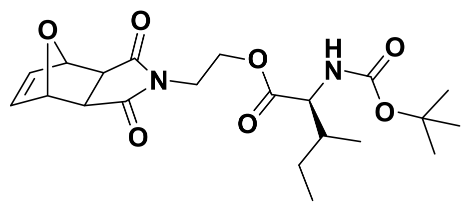
Compound 12d: Yield, 69%; R_f (60% EtOAc/Hexane), 0.40; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.49 (s, 2H), 5.28 (d, 2H, *J* = 4.0 Hz), 5.04 (d, 1H, *J* = 8.8 Hz), 4.36-4.27 (m, 1H), 4.26-4.14 (m, 2H), 3.81-3.69 (m, 2H), 2.86 (s, 2H), 2.14-1.93 (m, 1H), 1.42 (s, 9H), 0.92 (d, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0 (2C), 171.9, 155.8, 136.6 (2C), 81.06, 81.03, 79.8, 61.1, 58.6, 47.6 (2C), 37.8, 31.1, 28.4 (3C), 19.2, 17.5; IR (KBr): 3446, 3056, 2985, 1753, 1708, 1509, 1428, 1398, 1370, 1266, 1194, 1165, 1023, 896, 878, 741, 706 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{28}N_2O_7Na$ $(M+Na)^+$ 431.4426, found $(M+Na)^+$ 431.4431.



Compound 12e: Yield, 72%; R_f (60% EtOAc/Hexane), 0.44; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.51 (s, 2H), 5.27 (d, 2H, *J* = 3.2 Hz), 4.89 (d, 1H, *J* = 8.8 Hz), 4.35-4.20 (m, 3H), 3.76 (quin, 2H, *J* = 6.4 Hz), 2.87 (d, 2H, *J* = 3.6 Hz), 1.78-1.50 (m, 3H), 1.42 (s, 9H), 0.92 (d, 6H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (2C), 173.1, 155.5, 136.7 (2C), 81.0 (2C), 79.9, 61.2, 52.1, 47.6, 47.59, 41.6, 37.9, 28.4 (3C), 24.9, 23.1, 21.8; IR (KBr): 3437, 3056, 2964, 2872, 1776, 1745, 1708, 1651, 1507, 1397, 1368, 1336, 1266, 1162, 1123, 1050, 1023, 879, 748, 705 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{30}N_2O_7Na$ $(M+Na)^+$ 445.1951, found $(M+Na)^+$ 445.1938.



Compound 12f: Yield, 71%; R_f (60% EtOAc/Hexane), 0.44; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.47 (s, 2H), 5.23 (d, 2H, *J* = 10.0 Hz), 5.07 (d, 1H, *J* = 9.2 Hz), 4.34-4.25 (m, 1H), 4.23-4.13 (m, 2H), 3.78-3.67 (m, 2H), 2.84 (d, 2H, *J* = 2.0 Hz), 1.39 (s, 9H), 1.35-1.33 (m, 2H), 1.14-1.10 (m, 1H), 0.85 (t, 6H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0 (2C), 171.9, 155.6, 136.6, 136.5, 80.97, 80.94, 79.7, 60.9, 57.9, 47.5 (2C), 37.8, 37.7, 28.4 (3C), 24.9, 15.5, 11.7; IR (KBr): 3585, 3564, 3443, 3055, 2983, 2361, 1709, 1505, 1456, 1423, 1397, 1367, 1337, 1266, 1192, 1159, 1023, 742 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{30}N_2O_7Na$ $(M+Na)^+$ 445.4696, found $(M+Na)^+$ 445.4693.

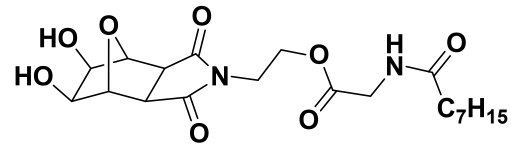


General procedure for the preparation of 1a-e, 2a-e, 3a-f:

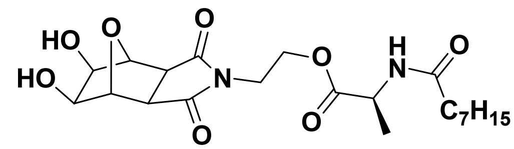
To a stirred solution containing a mixture of the oxanorbornene derivative (**10a-e/11a-e/12a-f**; 1.0 equiv.), N-methyl morpholine N-Oxide (2.4 equiv.) and pyridine (30 μL for 100 mg of the alkene) in *t*-BuOH-H_2O (3:1) was added osmium tetroxide (0.02 M solution in *t*-BuOH, 0.01 equiv.) and it was heated at 80 ˚C for 7-8 h. After completion of the reaction, the mixture was cooled to room temperature, treated with 15% aq. Na_2SO_3 solution (1 mL), allowed to stir for 5-10 min. *t*-BuOH was then removed under reduced pressure and the mixture was diluted with dichloromethane, dried using sodium sulfate, evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel using EtOAc/DCM/MeOH

(50:45:5) in a gradient mode to get the products as colorless solids. Yields and spectroscopic details of various compounds synthesized are given below.

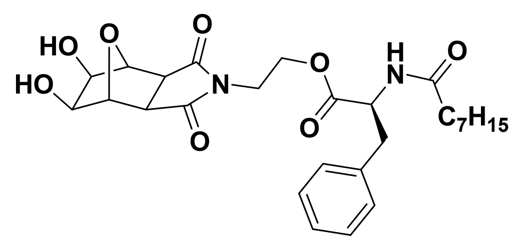
Compound 1a: Yield, 92%; R_f (EtOAc), 0.40; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.61 (s, 2H), 4.43 (bs, 1H), 4.30 (t, 2H, *J* = 5.5 Hz), 3.94 (s, 2H), 3.92 (s, 2H), 3.75 (t, 2H, *J* = 5.0 Hz), 3.40 (bs, 1H), 2.83 (s, 2H), 2.21 (t, 2H, *J* = 7.5 Hz), 1.60 (quin, 2H, *J* = 7.5 Hz), 1.29-1.23 (m, 8H), 0.86 (t, 3H, *J* = 7 Hz), -NH proton did not appear; ^{13}C NMR ($CDCl_3$+CD_3OD, 100 MHz): δ 176.5 (2C), 174.8, 169.8, 83.8 (2C), 72.2 (2C), 60.8, 45.3 (2C), 40.7, 37.7, 35.8, 31.4, 28.9, 28.7, 25.4, 22.3, 13.6; IR (KBr): 3322, 2921, 2850, 1751, 1705, 1642, 1522, 1438, 1405, 1326, 1190, 1119, 998, 879, 849, 828, 813, 769, 733, 653 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{31}N_2O_8$ $(M+H)^+$ 427.2080, found $(M+H)^+$ 427.2066.



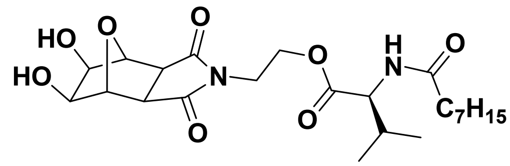
Compound 1b: Yield, 96%; R_f (EtOAc), 0.40; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.15 (d, 1H, *J* = 7.6 Hz), 4.65 (s, 1H), 4.62 (s, 1H), 4.52 (quin, 1H, *J* = 7.2 Hz), 4.38-4.33 (m, 1H), 4.26-4.20 (m, 1H), 4.04 (bs, 1H), 4.00-3.92 (m, 3H), 3.83-3.70 (m, 2H), 2.86 (d, 2H, *J* = 2.4 Hz), 2.22-2.18 (m, 2H), 1.60 (quin, 2H, *J* = 6.8 Hz), 1.34 (d, 3H, *J* = 7.2 Hz), 1.30-1.22 (m, 8H), 0.87 (t, 3H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2 (2C), 173.5, 172.7, 84.3, 84.2, 73.1 (2C), 61.3, 48.0, 45.6, 45.5, 38.2, 36.7, 31.8, 29.3, 29.1, 25.7, 22.7, 18.4, 14.2 ; IR (KBr): 3442, 3056, 2985, 1709, 1548, 1428, 1267, 897, 755 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{33}N_2O_8$ $(M+H)^+$ 441.2237, found $(M+H)^+$ 441.2233.



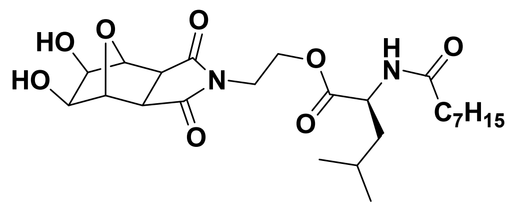
Compound 1c: Yield, 91%; R_f (EtOAc), 0.50; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.20 (m, 3H), 7.09 (d, 2H, *J* = 7.5 Hz), 6.00 (bs, 1H), 4.81 (quin, 1H, *J* = 7.5 Hz), 4.66 (d, 1H, *J* = 9.0 Hz), 4.61 (s, 1H), 4.42-4.30 (m, 1H), 4.20-4.14 (m, 1H), 4.00-3.92 (m, 2H), 3.81-3.68 (m, 2H), 3.10 (dd, 1H, *J* = 14 Hz, 5.5 Hz), 2.99 (ddd, 1H, *J* = 14 Hz, 6.5 Hz, 2 Hz), 2.82 (s, 2H), 2.15 (sext, 2H, *J* = 7 Hz), 1.57-1.49 (m, 2H), 1.32-1.20 (m, 8H), 0.87 (t, 3H, *J* = 5.5 Hz), -OH protons did not appear; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.2, 173.6, 171.2 (2C),



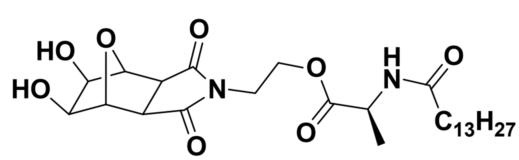
136.0, 129.4 (2C), 128.7 (2C), 127.2, 84.24, 84.20, 73.1, 61.3, 52.9, 45.6, 45.5, 38.0, 37.8, 36.6, 31.8, 29.8, 29.2, 29.1, 25.7, 22.7, 14.2; IR (KBr): 3426, 3057, 2930, 2861, 1780, 1746, 1708, 1663, 1516, 1429, 1337, 1266, 1190, 1115, 1010, 898, 820, 744 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{27}H_{37}N_2O_8$ $(M+H)^+$ 517.2550, found $(M+H)^+$ 517.2561.



Compound 1d: Yield, 89%; R_f (EtOAc), 0.44; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.04 (d, 1H, *J* = 8.8 Hz), 4.66 (s, 1H), 4.60 (s, 1H), 4.48-4.41 (m, 2H), 4.14-4.10 (m, 1H), 3.98 (d, 1H, *J* = 6.0 Hz), 3.94 (d, 1H, *J* = 5.6 Hz), 3.86-3.79 (m, 1H), 3.75-3.70 (m, 1H), 2.85 (s, 2H), 2.24 (sext, 2H, *J* = 4 Hz), 2.10 (sext, 1H, *J* = 6.4 Hz), 1.65-1.55 (m, 2H), 1.35-1.20 (m, 8H), 0.91 (d, 3H, *J* = 6.8 Hz), 0.88-0.84 (m, 6H), -2 OH protons did not appear; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (2C), 174.1, 171.7, 84.3, 84.2, 73.1, 73.0, 60.9, 56.9, 45.6, 45.5, 38.0, 36.9, 31.8, 31.2, 29.8, 29.3, 29.1, 25.8, 22.7, 19.2, 17.7, 14.2 ; IR (KBr): 3681, 3299, 3056, 2928, 2860, 2360, 2312, 1709, 1518, 1429, 1266, 1193, 1009, 897, 746 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{23}H_{37}N_2O_8$ $(M+H)^+$ 469.2550, found $(M+H)^+$ 469.2570.



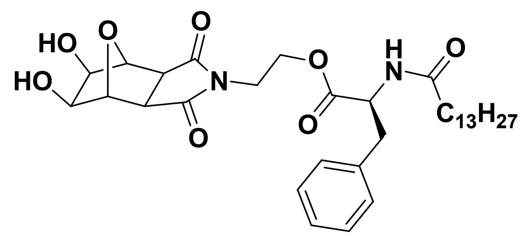
Compound 1e: Yield, 95%; R_f (EtOAc), 0.5; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.95 (d, 1H, *J* = 8.8 Hz), 4.66 (s, 1H), 4.60 (s, 1H), 4.55 (dt, 1H, *J* = 9.2, 4.8 Hz), 4.41-4.35 (m, 1H), 4.19-4.14 (m, 1H), 3.97 (q, 2H, *J* = 6 Hz), 3.84-3.61 (m, 2H), 2.85 (d, 2H, J = 1.6 Hz), 2.21 (dt, 2H, *J* = 7.2, 4.0 Hz), 1.65-1.55 (m, 4H), 1.44 (sext, 2H, *J* = 9.2 Hz), 1.35-1.20 (m, 8H), 0.93 (d, 6H, *J* = 6.8 Hz), 0.87 (t, 3H, *J* = 6.5 Hz) -OH proton did not appears; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2 (2C), 173.8, 172.7, 84.3, 84.2, 73.1 (2C), 61.1, 50.6, 45.6, 45.5, 41.6, 38.1, 36.7, 31.8, 29.3, 29.1, 25.7, 25.0, 23.0, 22.7, 21.8, 14.2; IR (KBr): 3659, 3430, 3057, 2930, 2863, 1708, 1519, 1430, 1400, 1335, 1267, 1194, 1111, 1010, 898, 818, 742, 611 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{39}N_2O_8$ $(M+H)^+$ 483.2628, found $(M+H)^+$ 483.2644.



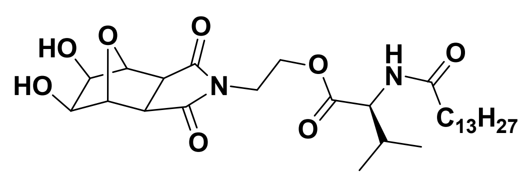
Compound 2a: Yield, 91%; R_f (EtOAc) 0.50; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.26 (d, 1H, *J* = 8 Hz), 4.55 (d, 2H, *J* = 6.0 Hz), 4.49-4.41 (m, 1H), 4.29-

4.17 (m, 2H), 3.89 (s, 2H), 3.72-3.68 (m, 2H), 2.79 (d, 2H, J = 3.6 Hz), 2.13 (td, 2H, J = 7.6 Hz, 3.2 Hz), 1.53 (quin, 2H, J = 7.2 Hz), 1.27 (d, 3H, J = 7.2 Hz), 1.25-1.15 (m, 20H), 0.81 (t, 3H, J = 6.8 Hz), -2 OH proton did not appear; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 176.3 (2C), 173.6, 172.7, 84.1 84.0, 72.8, 61.2 (2C), 47.9, 47.8, 45.6, 45.5, 38.1, 36.6, 32.0, 29.8, 29.7 (2C), 29.6, 29.5 (2C), 29.3, 25.7, 22.8, 18.2, 14.2; IR (KBr): 3313, 2923, 1705, 1532, 1190, 1108, 1012, 514 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{27}H_{44}N_2O_8Na$ (M+Na)$^+$ 547.6468, found (M+Na)$^+$ 547.6461.

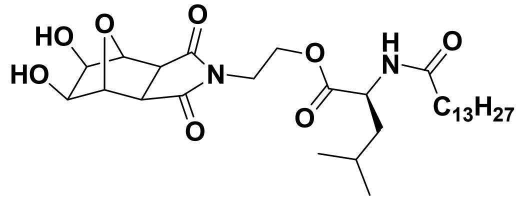
Compound 2b: Yield, 94%; R$_f$ (EtOAc/Hexane), 0.50; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.30-7.20 (m, 3H), 7.08 (d, 2H, J = 6.8 Hz), 5.98 (d, 1H, J = 8.0 Hz), 4.84-4.78 (m, 1H), 4.66 (s, 1H), 4.61 (s, 1H), 4.38-4.34 (m, 1H), 4.19-4.14 (m, 1H), 3.95 (q, 2H, J = 6.0 Hz), 3.82-3.69 (m, 2H), 3.11 (dd, 1H, J = 14.0 Hz, 5.6 Hz), 2.99 (dd, 1H, J = 14.0 Hz, 6.4 Hz), 2.82 (s, 2H), 2.20-2.09 (m, 2H), 1.58-1.48 (m, 2H), 1.32-1.18 (m, 20H), 0.87 (t, 3H, J = 6.4 Hz), -NH, -OH protons did not appear; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 176.2 (2C), 173.5, 171.2, 135.9, 129.4 (2C), 128.7 (2C), 127.2, 84.3, 84.2, 73.1, 61.3, 52.9, 45.6, 45.5, 37.9, 37.8, 36.6, 32.0, 29.8 (4C), 29.6, 29.5 (2C), 29.3, 25.7, 22.8, 14.3; IR (KBr): 3365, 3057, 2927, 2856, 1741, 1707, 1518, 1429, 1266, 1191, 1009, 897, 742 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{33}H_{49}N_2O_8$ (M+H)$^+$ 601.7632, found (M+H)$^+$ 601.7624.



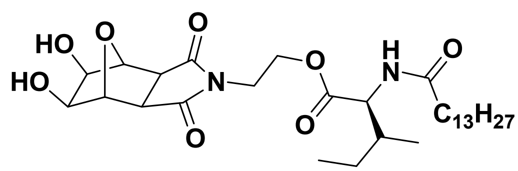
Compound 2c: Yield, 93%; R$_f$ (EtOAc), 0.50; ^{1}H NMR (CDCl$_3$, 400 MHz):δ 6.03 (d, 1H, J = 9.2 Hz), 4.68 (s, 1H), 4.60 (s, 1H), 4.50-4.46 (m, 2H), 4.20 (bs, 1H), 4.13-4.01 (m, 1H), 3.98 (d, 1H, J = 6.0 Hz), 3.93 (d, 1H, J = 6.0 Hz), 3.88-3.81 (m, 1H), 3.75-3.69 (m, 1H), 2.85 (s, 2H), 2.28-2.20 (m, 2H), 2.14-2.06 (m, 1H), 1.67-1.55 (m, 2H), 1.30-1.23 (m, 20H), 0.91 (d, 3H, J = 6.8 Hz), 0.87 (t, 3H, J = 6.8 Hz), 0.85 (d, 3H, J = 6.8 Hz), -OH protons did not appear; ^{13}C NMR (CDCl$_3$, 100 MHz): δ 176.1 (2C), 174.1, 171.7, 84.2 (2C), 73.0 (2C), 60.8, 56.9, 45.6, 45.1, 37.9, 32.0, 31.3, 29.8 (2C), 29.7 (3C), 29.6, 29.5 (2C), 29.4, 25.8, 22.8, 19.2, 17.7, 14.2; IR (KBr): 3305, 3056, 2984, 2925, 2854, 1709, 1547, 1429, 1267, 897, 755 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{29}H_{49}N_2O_8$ (M+H)$^+$ 553.3489, found (M+H)$^+$ 553.3481.



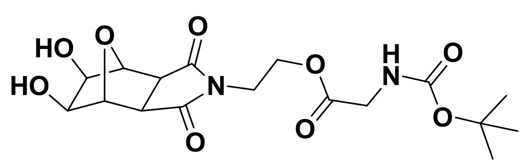
Compound 2d: Yield, 89%; R_f (EtOAc), 0.50; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.86 (d, 1H, J = 8.4 Hz), 4.70 (s, 1H), 4.60 (s, 1H), 4.59-4.54 (m, 1H), 4.52-4.44 (m, 1H), 4.10 (dt, 1H, J = 9.6 Hz, 4.4 Hz), 4.02-3.97 (m, 1H), 3.93 (d, 1H, J = 6.0 Hz), 3.92-3.83 (m, 1H), 3.77-3.67 (m, 1H), 2.85 (s, 2H), 2.27-2.16 (m, 2H), 1.66-1.55 (m, 6H), 1.45 (quin, 1H, J = 9.6 Hz), 1.31-1.23 (m, 20H), 0.97-0.91 (m, 6H), 0.88 (t, 3H, J = 6.8 Hz) -OH proton did not appear ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.3 (2C), 173.9, 172.8, 84.1 (2C), 72.7 (2C), 61.1, 50.6, 50.5, 45.6, 45.5, 41.3, 38.1, 36.5, 32.0, 29.7 (2C), 29.6 (2C), 29.4 (2C), 29.3, 25.7, 24.9, 22.9, 22.7, 21.8, 14.2; IR (KBr): 3430, 3056, 2928, 2858, 1710, 1518, 1429, 1335, 1266, 1194, 1010, 897, 741 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{30}H_{51}N_2O_8$ $(M+H)^+$ 567.3645, found $(M+H)^+$ 567.3625.



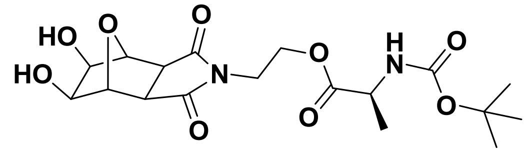
Compound 2e: Yield, 84%; R_f (EtOAc), 0.50; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.49 (s, 2H), 4.10 (bs, 2H), 3.85-3.83 (m, 2H), 3.64 (bs, 2H), 3.27 (bs, 1H), 2.76-2.73 (m, 2H), 2.15 (bs, 2H), 1.60-1.41 (m, 2H), 1.31-1.28 (m, 1H), 1.27-1.12 (m, 25H), 0.88 (bs, 6H), -OH, -NH protons did not appear; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.5 (2C), 174.4, 174.1, 84.0 (2C), 72.5, 60.4, 55.2, 45.5 (2C), 38.3, 37.5, 34.0, 31.9, 29.7, 29.62 (2C), 29.58, 29.5, 29.3, 29.2, 29.1, 26.3, 24.7, 22.7, 15.3, 14.4, 14.0 ; IR (KBr): 3315, 2953, 2921, 2851, 2474, 2362, 2342, 1737, 1703, 1464, 1434, 1400, 1328, 1193, 1157, 1005, 992, 885, 733 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{30}H_{51}N_2O_8$ $(M+H)^+$ 567.3645, found $(M+H)^+$ 567.3657.



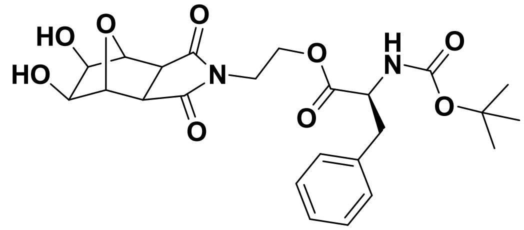
Compound 3a: Yield, 89%; R_f (EtOAc), 0.30; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.21 (bs, 1H), 4.66 (s, 2H), 4.30 (bs, 2H), 3.98 (s, 2H), 3.89 (bs, 1H), 3.83 (d, 2H, J = 4.8 Hz), 3.76 (bs, 2H), 2.88 (s, 2H), 1.44 (s, 9H) -OH protan did not appear; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.2 (2C), 170.5, 156.1, 84.2 (2C), 80.4, 73.2 (2C), 61.1, 45.5 (2C), 42.3, 38.2, 28.5 (3C); IR (KBr): 3350, 2980, 2929, 1770, 1694, 1528, 1406, 1268, 1165, 1015, 900, 757 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{17}H_{24}N_2O_9Na$ $(M+Na)^+$ 423.3763, found $(M+Na)^+$ 423.3772.



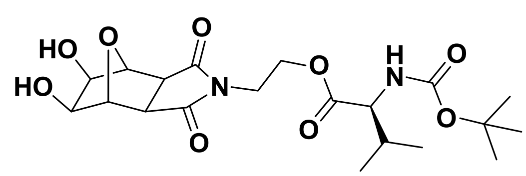
Compound 3b: Yield, 91%; R_f (EtOAc), 0.30; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.59 (s, 2H), 4.27 (t, 2H, *J* = 4.8 Hz), 4.24-4.14 (m, 1H), 3.91 (s, 2H), 3.78-3.68 (m, 2H), 2.82 (q, 2H, *J* = 6.8 Hz), 1.40 (s, 9H), 1.30 (d, 3H, *J* = 7.2 Hz), -NH, -OH protons did not appear; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.4 (2C), 173.1, 155.5, 83.9 (2C), 80.0, 72.7 (2C), 61.1, 49.1, 45.6, 45.5, 38.1, 28.3 (3C), 17.9; IR (KBr): 3510, 3371, 3056, 2980, 2931, 2860, 2595, 2505, 1743, 1696, 1519, 1441, 1343, 1266, 1166, 1109, 1065, 897, 746 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{18}H_{26}N_2O_9Na$ $(M+Na)^+$ 437.4033, found $(M+Na)^+$ 437.4041



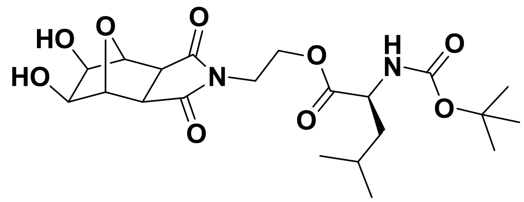
Compound 3c: Yield, 93%; R_f (EtOAc), 0.40; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.28 (m, 2H), 7.26-7.18 (m, 1H), 7.15 (d, 2H, *J* = 7.2 Hz), 5.26 (d, 2H, *J* = 12.4 Hz), 5.16 (s, 2H), 4.97 (d, 1H, *J* = 8.0 Hz), 4.94 (d, 1H, *J* = 6.0 Hz), 4.38-4.28 (m, 1H), 4.29-4.19 (m, 1H), 3.85-3.71 (m, 2H), 3.15 (dd, 1H, *J* = 13.6, 4.8 Hz), 2.98 (dd, 2H, *J* = 13.2, 6.8 Hz), 2.88 (s, 2H), 1.42 (s, 9H), -OH protan did not appear;(spectra and expansion not there) ^{13}C NMR ($CDCl_3$+CD_3OD, 100 MHz): δ 176.4 (2C), 171.7, 155.5, 136.2, 129.4, 129.2 , 128.5 (2C), 126.9, 83.9 (2C), 80.2, 72.6(2C), 61.1, 54.4, 45.5 (2C), 38.0, 37.8, 28.2 (3C); IR (KBr): 3516, 3371, 2924, 1700, 1519, 1448, 1345, 1294, 1176, 984, 746 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{24}H_{30}N_2O_9Na$ $(M+Na)^+$ 513.5014, found $(M+Na)^+$ 513.5028.



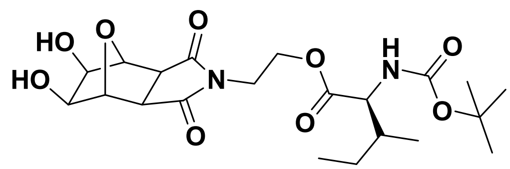
Compound 3d: Yield, 93%; R_f (EtOAc), 0.33; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.07 (d, 1H, *J* = 7.2 Hz), 4.67 (s, 1H), 4.65 (s, 1H), 4.40-4.30 (m, 1H), 4.24-4.10 (m, 2H), 3.98 (d, 2H, *J* = 2.8 Hz), 3.82-3.70 (m, 2H), 2.86 (s, 2H), 2.12-2.02 (m, 1H), 1.44 (s, 9H), 0.93 (d, 3H, *J* = 7.2 Hz), 0.85 (d, 3H, *J* = 6.4 Hz), -OH protons did not appear; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.9 (2C), 172.2, 156.0, 84.3, 84.2, 80.2, 73.3 (2C), 61.0, 58.6, 45.6 (2C), 38.2, 31.1, 28.5 (3C), 19.2, 17.5; IR (KBr): 3437, 3057, 2977, 2929, 2860, 1710, 1508, 1399, 1265, 1165, 1103, 1010, 898, 739 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{20}H_{30}N_2O_9Na$ $(M+Na)^+$ 465.4572, found $(M+Na)^+$ 465.4572.



Compound 3e: Yield, 92%; R_f (EtOAc), 0.33; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.03-4.93 (m, 1H), 4.66 (s, 2H), 4.65 (s, 1H), 4.37-4.27 (m, 2H), 4.26-4.17 (m, 2H), 3.98 (d, 2H, *J* = 2.8 Hz), 3.81-3.70 (m, 2H), 2.86 (q, 2H, *J* = 7.2 Hz), 1.67 (sep, 1H, *J* = 6.8 Hz), 1.60-1.52 (m, 1H), 1.51-1.44 (m, 1H), 1.43 (s, 9H), 0.93 (d, 6H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0 (2C), 173.3, 155.8, 84.2 (2C), 80.2, 73.3, 73.2, 61.1, 52.2, 45.6, 45.5, 41.5, 38.3, 28.5 (3C), 24.9, 23.1, 21.8; IR (KBr): 3364, 2949, 1705, 1634, 1519, 1445, 1397, 1167, 1112, 1012, 899, 727, 600 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{32}N_2O_9Na$ $(M+Na)^+$ 479.4842, found $(M+Na)^+$ 479.4818.



Compound 3f: Yield, 97%; R_f (EtOAc), 0.33; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.10 (d, 1H, *J* = 9.2 Hz), 4.64 (s, 2H), 4.40-4.30 (m, 1H), 4.24-4.12 (m, 2H), 3.96 (s, 2H), 3.82-3.69 (m, 2H), 3.43 (bs, 2H), 2.87 (s, 2H), 1.86-1.77 (m, 1H), 1.42 (s, 9H), 1.39-1.30 (m, 1H), 1.19-1.06 (m, 1H), 0.88 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1 (2C), 172.2, 155.9, 84.2, 84.1, 80.2, 73.2, 73.1, 60.9, 58.1, 45.6 (2C), 38.1, 37.8, 28.4 (3C), 24.9, 15.6, 11.7; IR (KBr): 3476, 2967, 2930, 1780, 1696, 1527, 1398, 1164, 1111, 1008, 902, 858, 831, 780, 734, 697 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{21}H_{32}N_2O_9Na$ $(M+Na)^+$ 479.4842, found $(M+Na)^+$ 479.4855.



3. SEM images and DLS analysis results of samples prepared under various conditions:

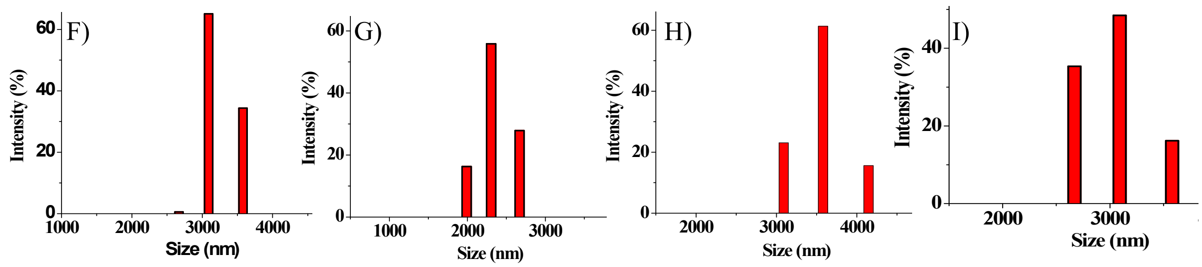


Figure SI-1. DLS histograms of **1b** (F), **1c** (G), 1**d** (H) and 1**e** (I) are shown.

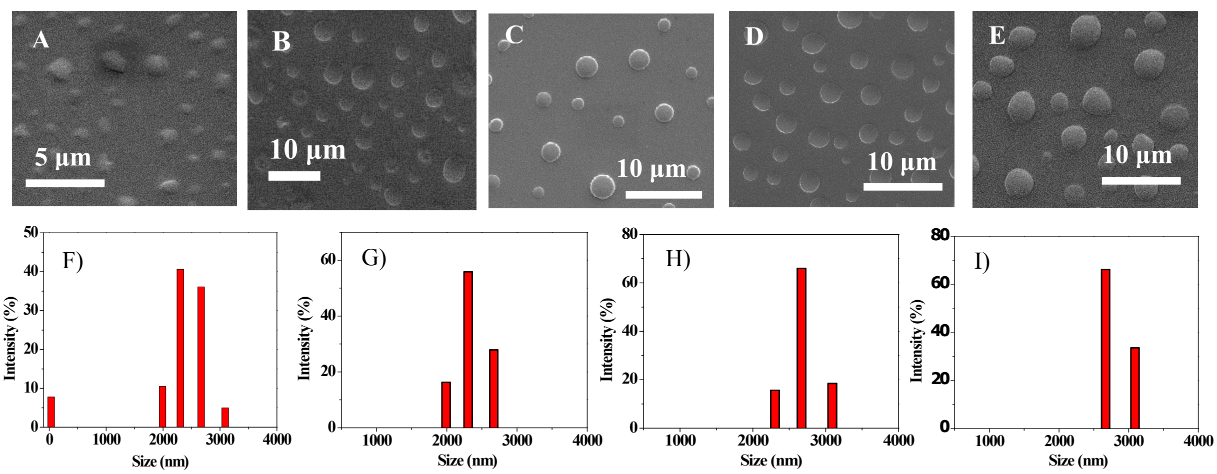


Figure SI-2. SEM images of samples of **1c** made from acetone solutions of different concentrations A) 0.1 mg/1.5 mL, B) 0.5 mg/1.5 mL, C) 1.0 mg/1.5 mL, D) 1.5 mg/1.5 mL, and E) 2.0 mg/1.5 mL; Samples were prepared by directly drop-casting their acetone solutions on silica substrate. DLS histograms of solutions of **1c** at various concentrations: F) 0.5 mg/1.5 ml, G) 1.0 mg/1.5 mL, H) 1.5 mg/1.5 mL, and I) 2.0 mg/1.5 mL.

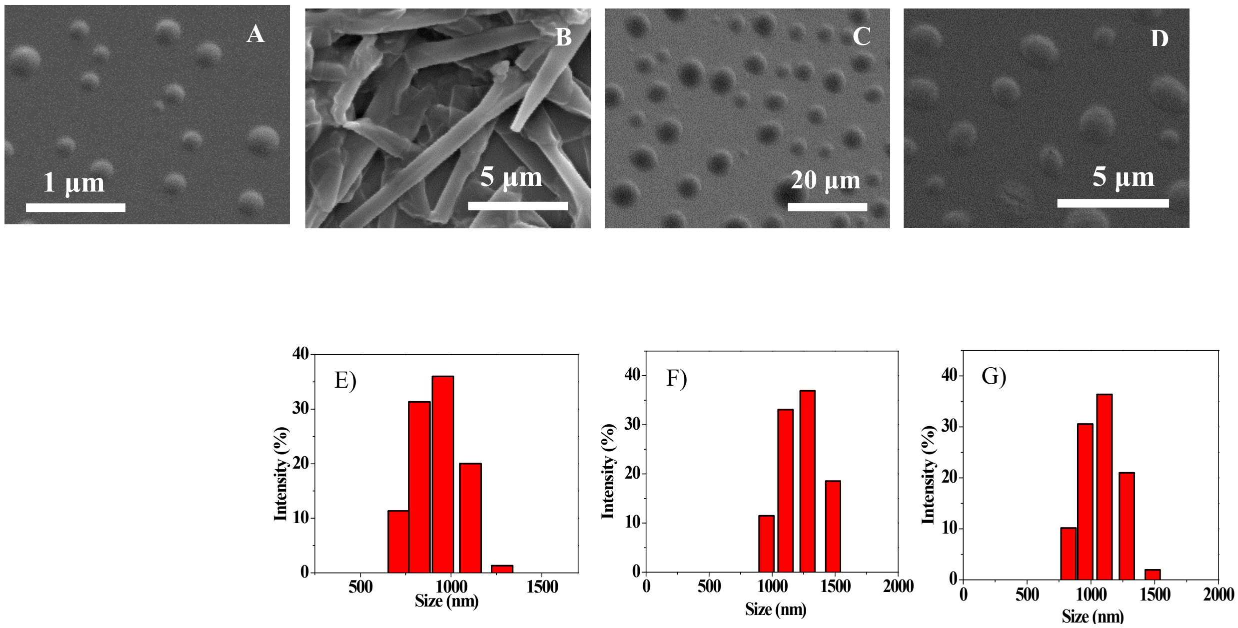


Figure SI-3. SEM images of samples of **1a** (A), **1b** (B), **1d** (C), and **1e** (D) prepared by directly drop-casting their methanol solution (1 mg/1.5 mL) on silica substrate. DLS of histogram of **1a** (E), **1d** (F), and **1e** (G) are also shown; image of sample of 1c in MeOH is given in Fig. SI-9.

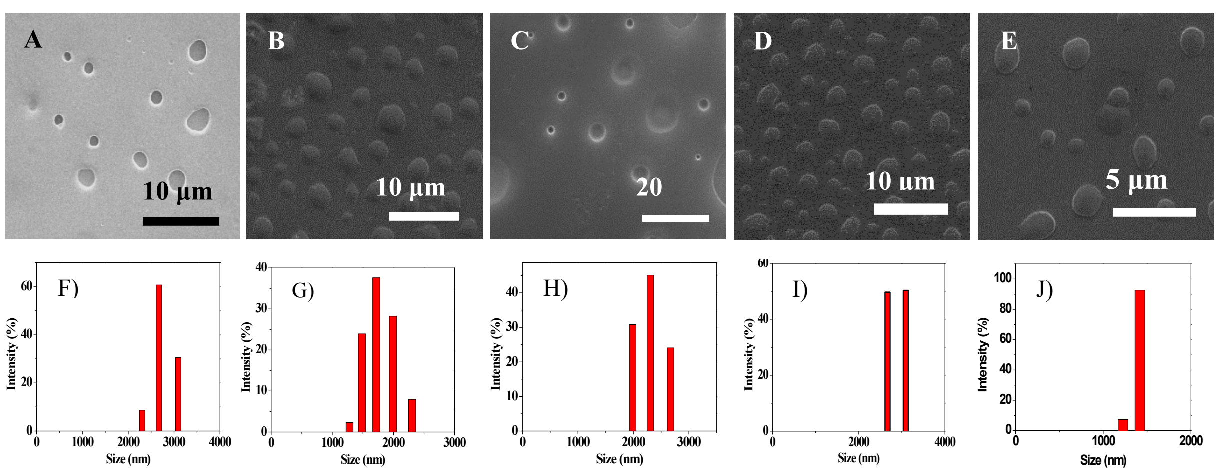


Figure SI-4. SEM images of samples of **3a** (A), **3b** (B), **3d** (C), **3e** (D) and **3f** (E), prepared by directly drop-casting their acetone solutions (1 mg/1.5 mL) on silica substrate; DLS histograms of samples of **3a** (F), **3b** (G), **3d** (H), **3e** (I) and **3f** (J) in this solvent (1 mg/1.5 mL) are also shown .

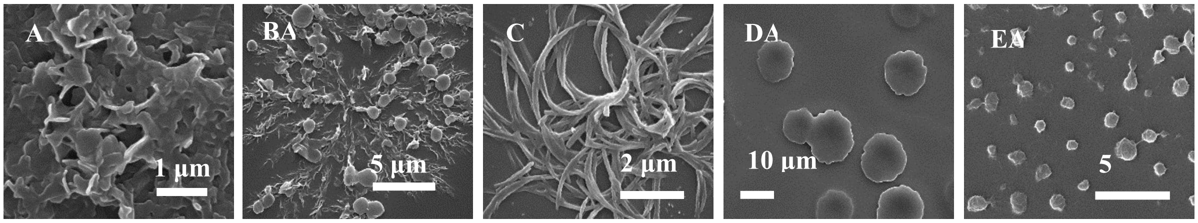


Figure SI-5. SEM images of samples of **2a** (A), **2b** (B), **2c** (C) and **2d** (D) and **2e** (E) prepared by directly drop-casting their acetone solutions (1 mg/1.5 mL) on silica substrate.

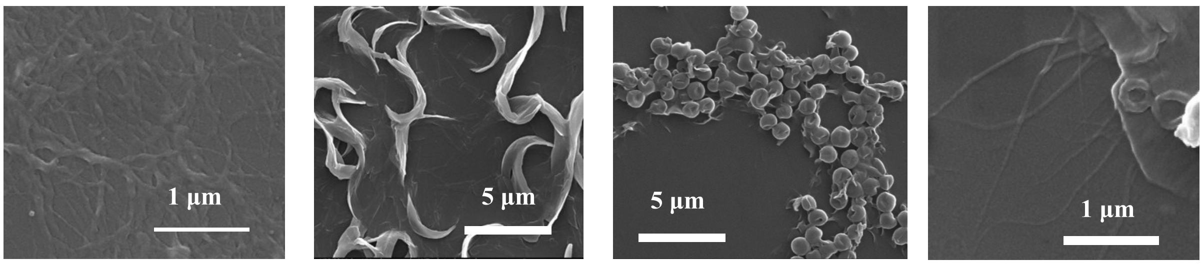


Figure SI-6. SEM images of samples of **2a** (A), **2b** (B), **2c** (C) and **2e** (E) prepared by directly drop-casting their methanol solutions (1 mg/1.5 mL) on silica substrate.

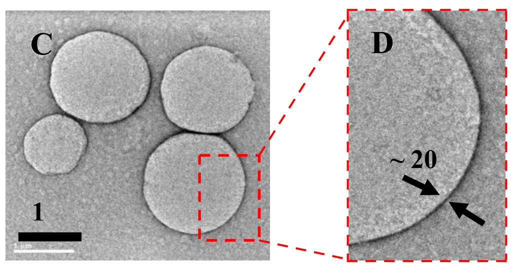


Figure SI-7. TEM images of sample of **1d** (C&D) prepared by directly drop-casting its acetone solution (1 mg/1.5 mL) on carbon coated copper grid.

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4. Critical micellar concentration

Critical micellar concentration (cmc) was calculated by fluorescent probe-based method using pyrene in water. Solutions of **1a-e** in water with concentrations ranging from 0.3 mM to 5.0 mM were admixed with 0.125 mM solution (50 µL) of pyrene in methanol in a quartz fluorescence cell and made up to a final volume of 3 mL. After exciting pyrene at 334 nm, its emission at 373 and 384 nm, corresponding to the first and third vibrational bands (I_1, I_3) respectively were noted. From the plots of I_3/I_1 vs. concentration of the lipid (Figure 8), the cmcs were measured

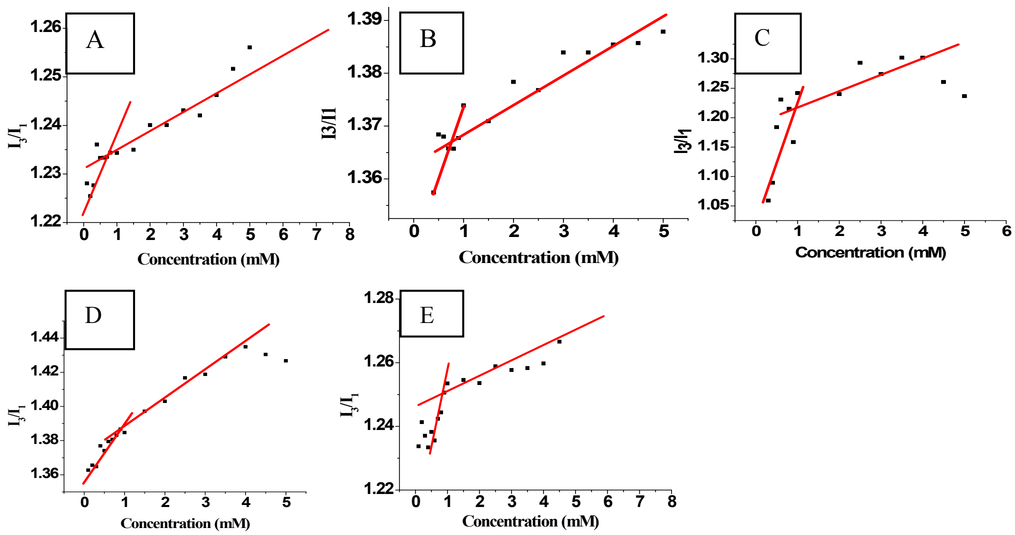


Figure SI-8. Plots of intensity of fluorescene emission I_3/I_1 vs concentration of the lipids A) **1a**, B) **1b**, C) **1c**, D) **1d**, E) **1e**

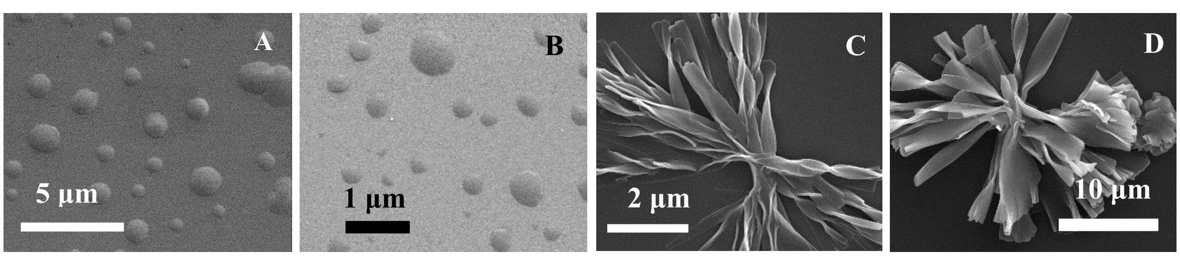


Figure SI-9. SEM images of samples of **1c** from A) MeOH, B) THF, C) $CHCl_3$ and D) Water; prepared by directly drop-casting their methanol solution (1 mg/1.5 mL) on silica substrate.

5. Results from PXRD analysis:

Table SI-1. Results from PXRD analysis of **1a-e**

Compound	d values (Å)			Arrangement	Lattice parameter (Å)
	d_1	d_2	d_3		
1a	32.7	17.2	11.5	Lamellar	a=32.7
1b	116.1	48.4	37.1	Lamellar	a=116.1
1c	26.4	13.2	9.7	Lamellar	a=26.4
1d	32.5	16.7	11.1	Lamellar	a=32.5
1e	24.3	12.3	9.3	Lamellar	a=24.3

6. Composition of Niosomal formulations:

Table SI-2. Composition of different formulations (lipid/methanol = 1 (mg)/1.5 mL)

amphiphiles	Amount of lipid (mg)	Cholesterol (mg)	Ibuprofen (mg)	Methanol (mL)
LCPC	15	7.5	15	22.5
NC1b	10	5	10	15
N1b	10	_	10	15
NC1c	10	5	10	15
N1c	10	_	10	15
NC1a	20	10	20	30
N1a	20	_	20	30
NC1e	15	7.5	15	22.5
N1e	15	_	15	22.5
NC1d	15	7.5	15	22.5
N1d	15	_	15	22.5

7. Niosomal formulations – particle size distribution and morphology:

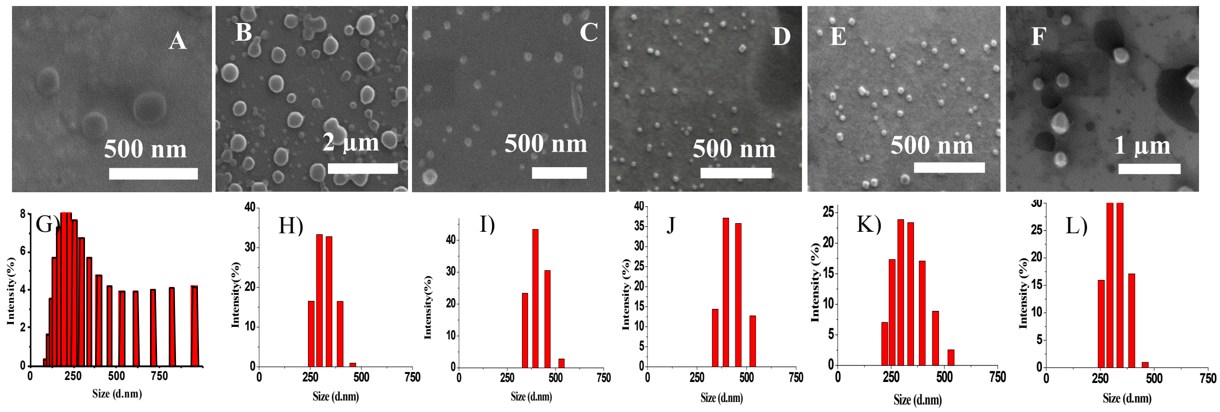


Figure SI-10. SEM images of samples of **LCPC** (A), **NC1a** (B), **NC1b** (C), **NC1c** (D), **NC1d** (E) and **NC1e** (F) prepared by directly drop-casting these formulations on silica substrate. DLS histogram of **LCPC** (G), **NC1a** (H), **NC1b** (I), **NC1c** (J), **NC1d** (K) and **NC1e** (L) in phosphate buffer (Amphiphile: Drug: Cholesterol = 1: 1: 0.5, concentration 1mg of amphiphile/1.5 mL of buffer)

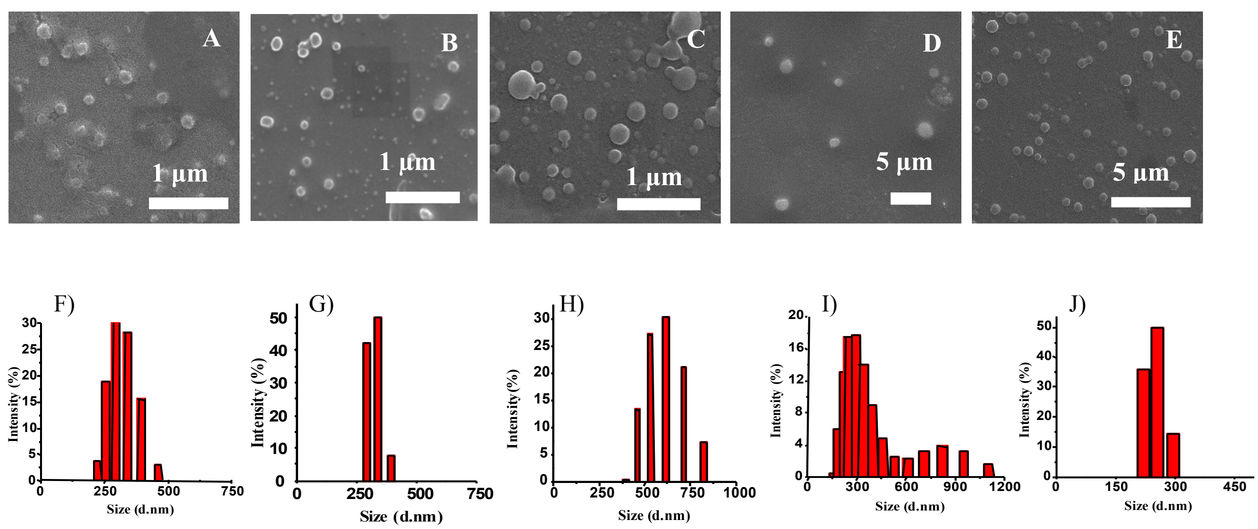


Figure SI-11. SEM images of samples of **N1a** (A), **N1b** (B), **N1c** (C), **N1d** (D) and **N1e** (E) prepared by directly drop-casting the liposomes without cholesterol, on silica substrate. DLS histogram of **N1a** (F), **N1b** (G), **N1c** (H), **N1d** (I) and **N1e** (J) in phosphate buffer (Amphiphile: Drug = 1:1, concentration 1mg of amphiphile/1.5 mL of buffer).

8. CryoTEM Images of 1c

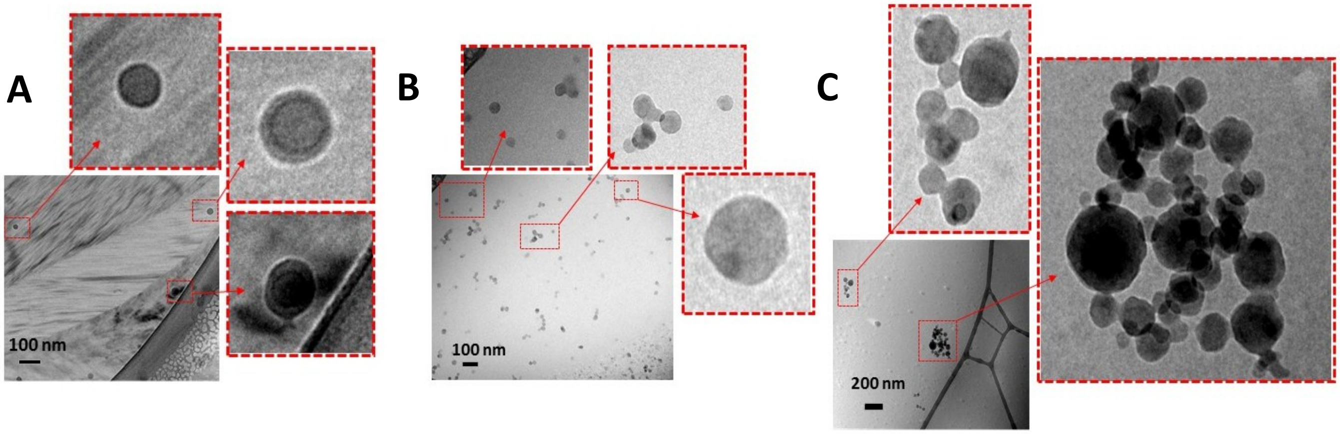


Figure SI-12. A.Cryo TEM image of Amphiphile **1c** in water after thin film hydration method **B.** Cryo TEM image of Amphiphile **1c** alone entrapped with Ibuprofen in water. **C.** Cryo TEM image of **NC1c** in water

9. Drug loading and drug release studies:

λ_{max} of Ibuprofen was determined in phosphate buffer at pH 7.2 and was found to be 223 nm. To make the calibration curve, different concentrations (5 to 30µg/mL) of this drug in phosphate buffer (pH 7.2) were prepared and their absorbances at 223 nm were measured using a UV spectrophotometer. The absorbance was plotted against concentration (µg/ml) to obtain the standard graph which is given below.

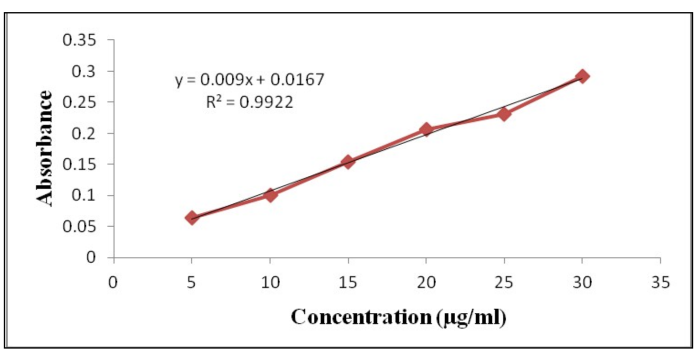


Figure SI-13. Calibration Curve of Ibuprofen in phosphate buffer of pH 7.2

Drug encapsulation efficiency: Ibuprofen-loaded vesicles were separated from un-entrapped drug by centrifuging at 10,000 rpm at 4 ^{0}C for 2 hr. The supernatant was taken and diluted three times with phosphate buffer of pH 7.2. The concentration of Ibuprofen in the solution (supernatant) was determined by a UV spectrophotometer by noting the absorption at 223 nm. The absorbance was then converted to concentration/mL using standard calibration curve. The percentage of drug encapsulated was then calculated using the following equation:

Encapsulation efficiency = (Drug.encapsulated / Total drug) x 100

Table 3-SI. Drug encapsulation efficiency of various formulations (in triplicate)

Name	Trial 1	Trial 2	Trial 3	Mean encapsulation efficiency (%)
LCPC	78.9	78.8	78.2	78.6±0.3
NC1a	49.1	49.6	48.1	48.9±0.8
NC1b	57.3	56.5	56.6	56.8±0.4
NC1c	**66.2**	**65.7**	**66.2**	**66.1±0.3**
NC1d	65.8	64.9	65.4	65.4±0.4
NC1e	65.7	64.7	64.8	65.1±0.6
N1a	32.9	32.7	32.6	32.8±0.2
N1b	31.1	32.9	31.9	31.9±0.9
N1c	31.9	33.4	32.4	32.6±0.7
N1d	27.0	26.7	26.4	26.7±0.3
N1e	33.1	32.7	41.2	35.7±0.8

Table 4-SI. Results from drug-release studies (procedure discussed in the main text).

Time (h)	Drug release (%)			
	LCPC	**NC1c**	**NC1d**	**NC1e**
0	0.9±0.4	0.7±0.3	0.5±0.9	0.0±0.8
1	6.6±3.6	8.0±0.5	9.0±1.5	3.4±0.7
2	9.8±0.2	13.9±0.9	10.6±0.5	6.8±0.6
3	13.2±0.8	15.9±0.6	13.0±0.6	7.5±0.4
4	16.8±0.3	17.9±0.3	13.8±0.4	8.0±0.1
5	19.7±0.6	19.2±0.6	14.2±1.8	8.7±0.3
6	22.3±0.9	20.1±0.8	14.6±2.1	9.2±0.2
8	27.3±0.4	22.8±0.5	16.7±0.8	10.4±0.0
10	30.8±0.5	25.4±0.8	18.8±0.6	13.0±0.6
12	33.2±0.0	28.4±0.8	20.6±1.8	15.5±0.5
24	**49.6±0.8**	**46.0±0.9**	34.8±0.5	23.5±0.5

Loading Content: Niosomes were prepared by thin film hydration method. Towards this, the lipid (**1a-e**) alone or in combination with cholesterol and Ibuprofen in 1:0.5:1 ratio was dissolved in methanol. Solvent was then removed by rotary evaporation under reduced pressure to get a thin film which was subsequently hydrated using phosphate buffer (pH 7.2). The resulting suspension was sonicated and then extruded through 1000 nm filters to get more-or-less uniformly-sized niosomes. 1 mL of suspension was centrifuged and the supernatant containing unentrapped drug was removed. To the resulting pellet, 0.5% solution of TritonX-100 was added and diluted to 1ml using phosphate buffer (pH 7.2). The solution was again centrifuged and supernatant was assessed to get the loading content by UV-Vis spectrophotometer. The absorbance was converted to concentration per mL using standard calibration curve. The percentage of drug encapsulated in the original aggregate was calculated by the following equation.

$$\text{Loading content} = (\text{Drug loaded} / \text{Total drug}) \times 100$$

Table 5-SI. Loading contents of different formulations

Formulation code	Percent loading content	Formulation code	Percent loading content
NC1a	19.6566±0.0096	**N1a**	10.3456±0.0456
NC1b	27.6683±0.0263	**N1b**	19.0654±0.0345
NC1c	43.4216±0.0223	**N1c**	30.0567±0.1123
NC1d	37.31±0.0456	**N1d**	21.0678±0.0243
NC1e	34.5283±0.0210	**N1e**	20.0341±0.8765

Stability Studies:

The suspensions of aggregates (**NC1a-NC1e**) prepared through the procedure give above (under loading content) were stored at 4^{0}C for 12 days and the loading content was calculated again to know their stability, especially to see whether there is any leakage of drug from the aggregates.

Table 6-SI. Variation in loading content on storage

Formulation code	Percent loading efficiency
NC1a	18.3909±0.7227
NC1b	23.6090±1.4072
NC1c	41.3636±0.9608
NC1d	33.2181±0.3818
NC1e	26.5363±0.6883

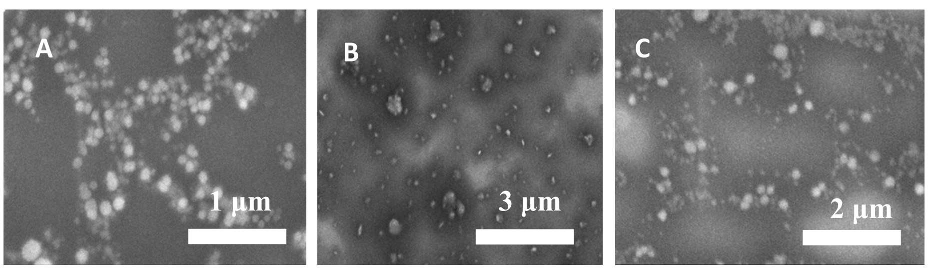
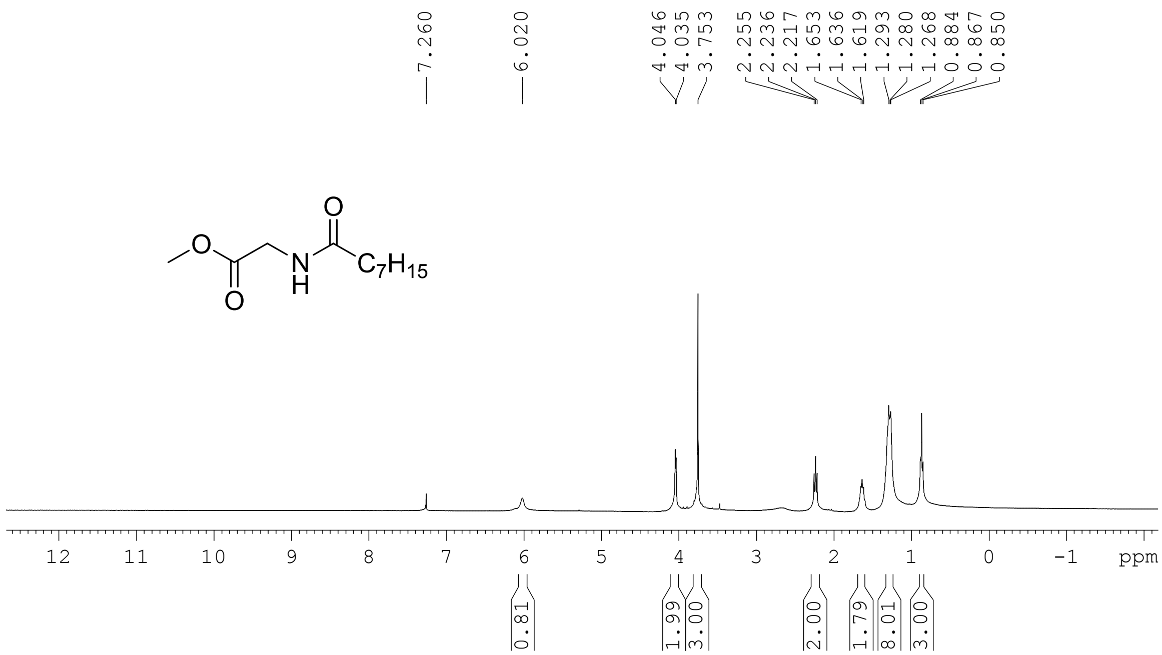
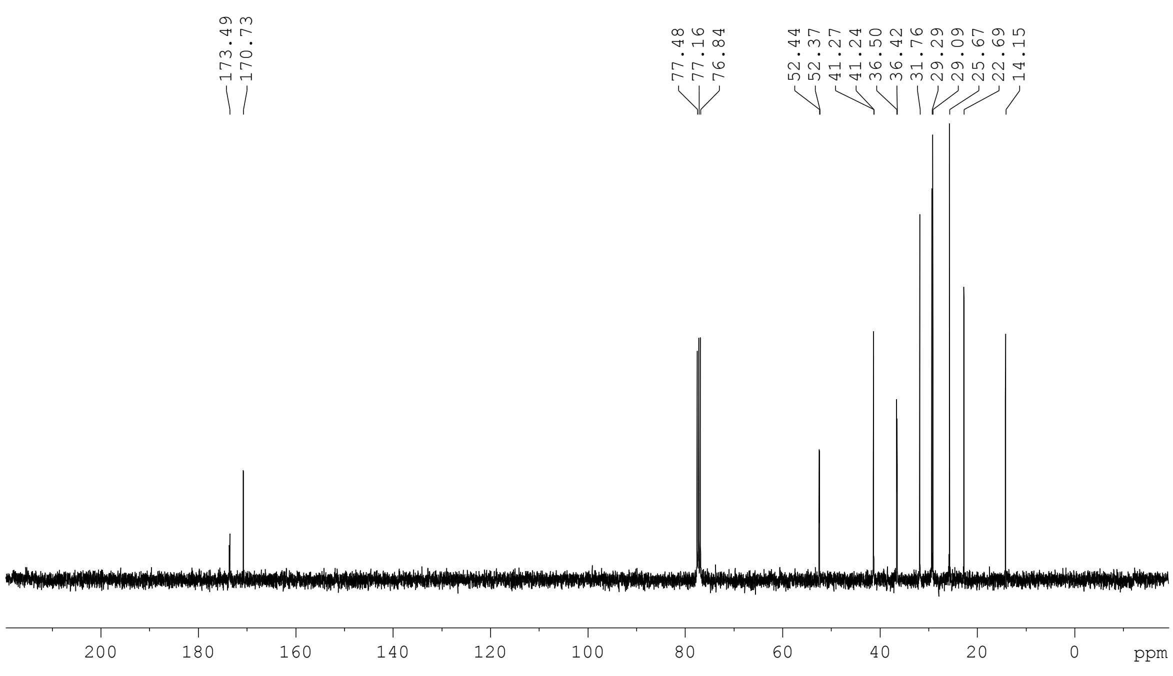


Figure SI-14. (A) SEM images of samples of **NC1c**, (B) **NC1c** after adding Triton X 100,(C) **NC1c** after storing for 12 days in phosphate buffer

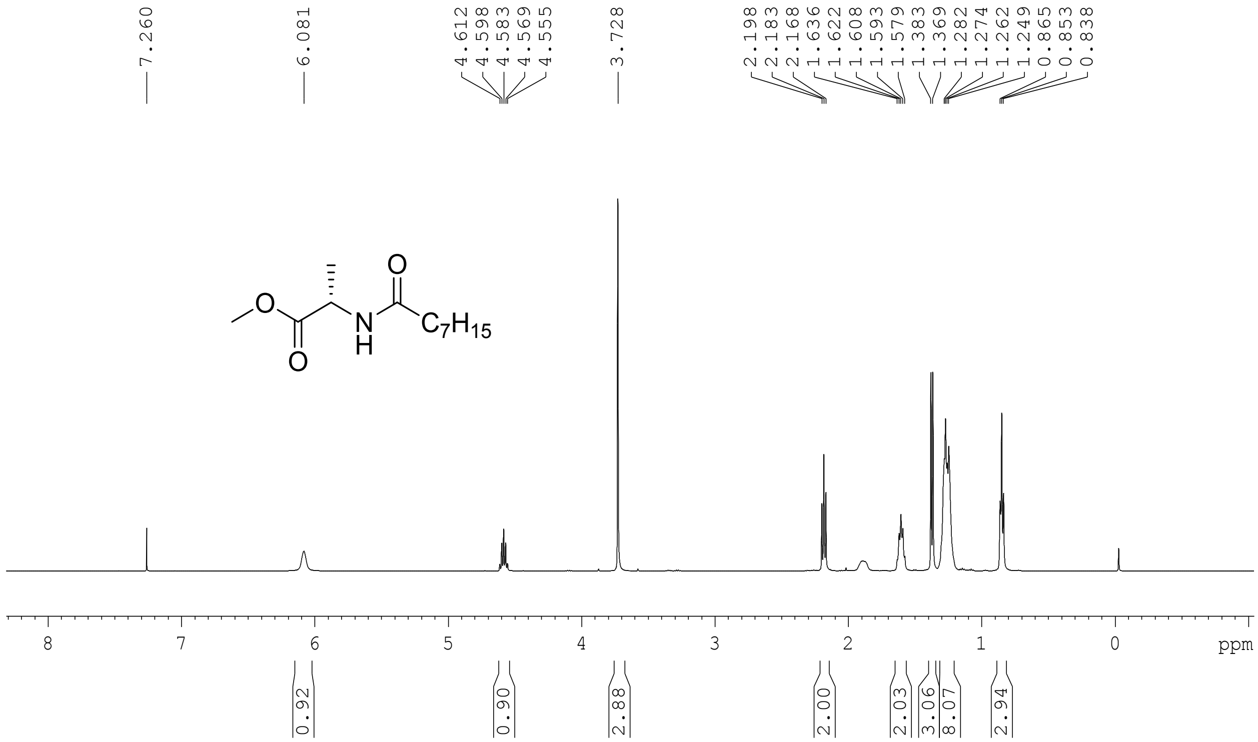
10. ^{1}H & ^{13}C NMR spectra of various compounds:



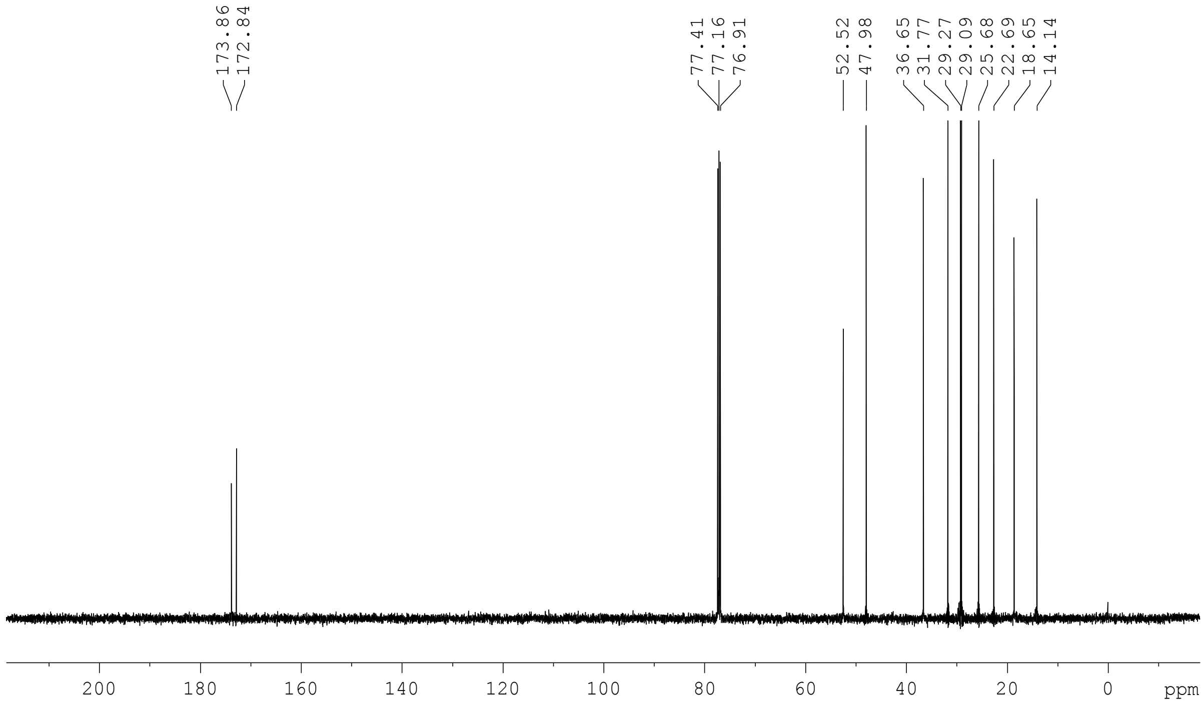
^{1}H NMR spectrum of compound **5a**



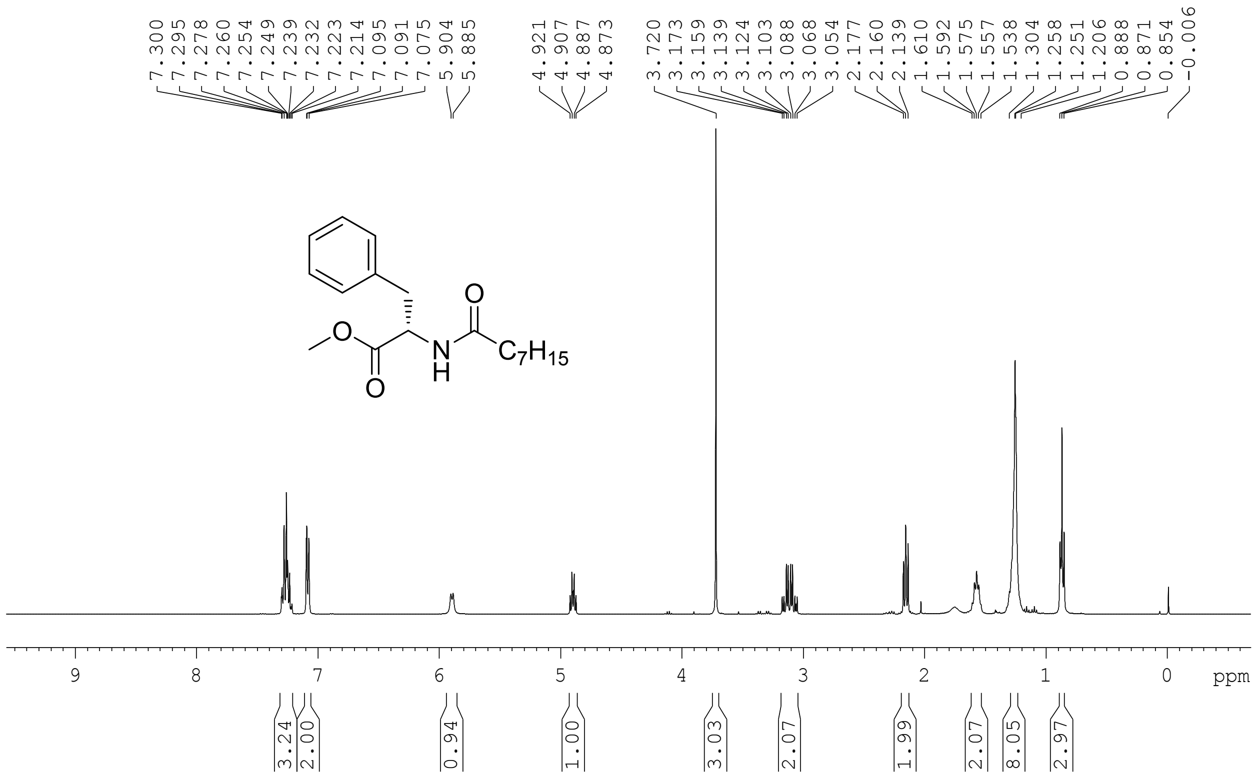
^{13}C NMR spectrum of compound **5a**



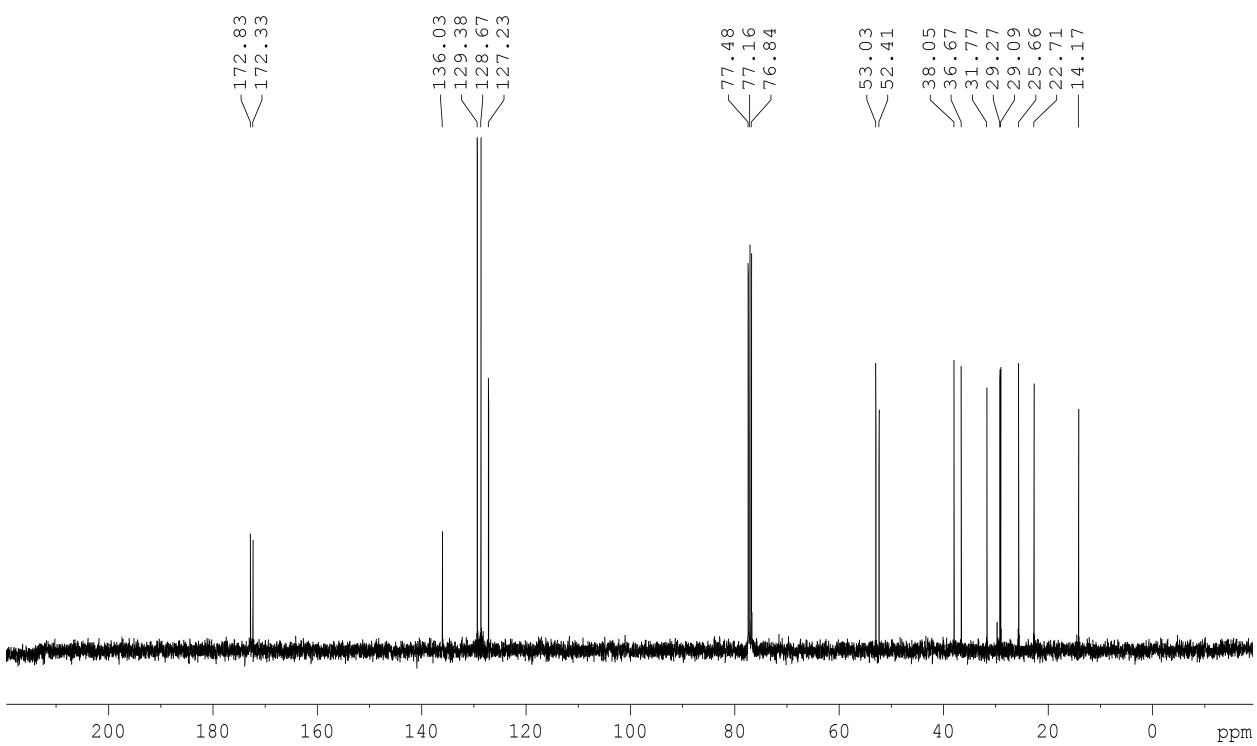
¹H NMR spectrum of compound **5b**



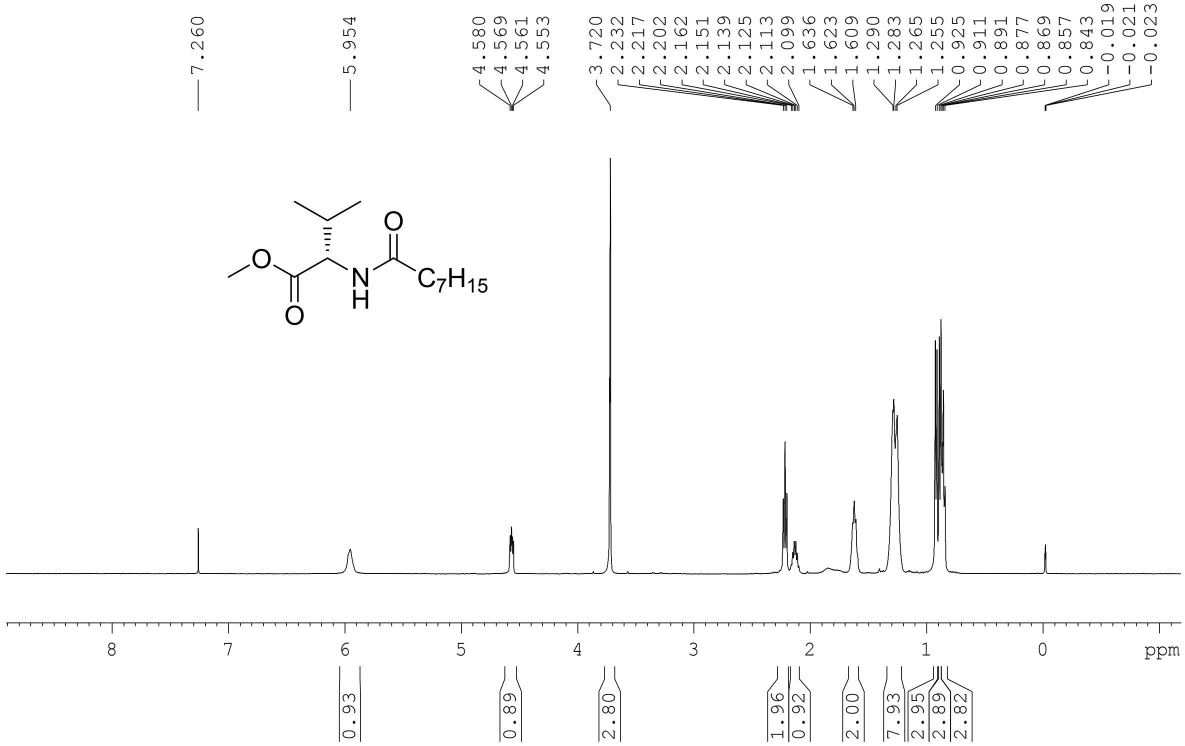
¹³C NMR spectrum of compound **5b**



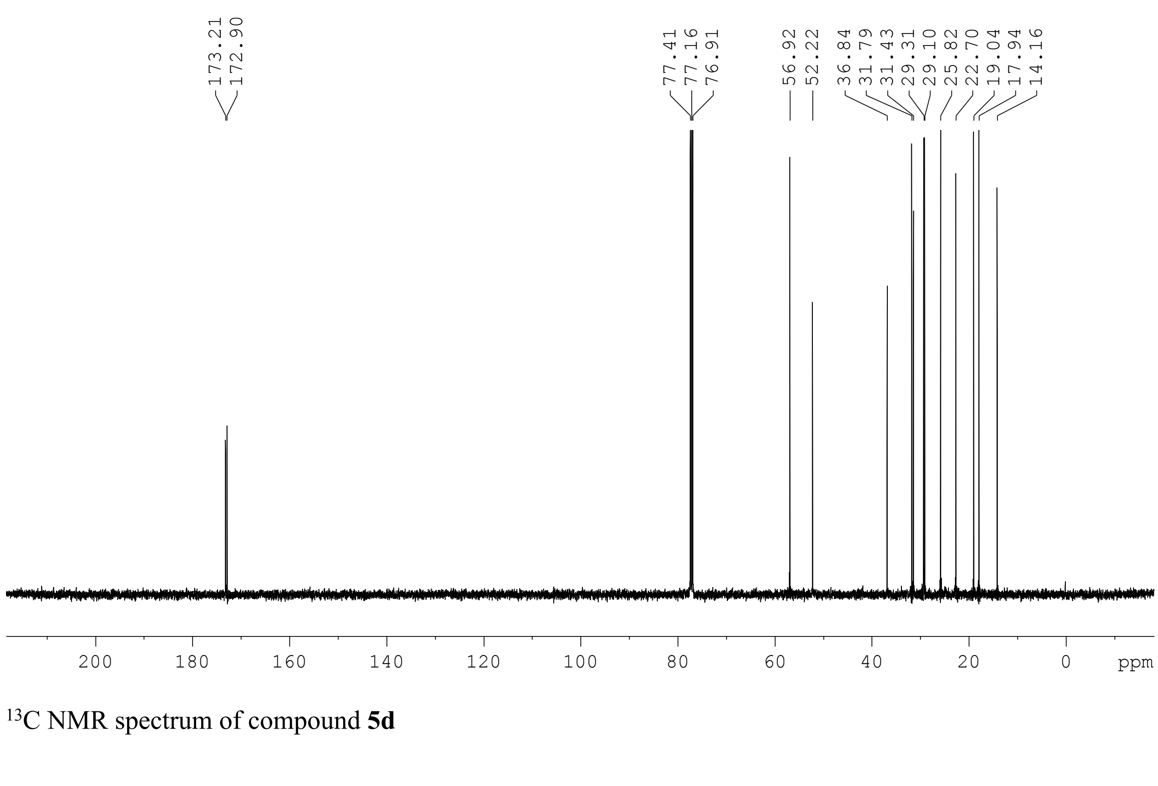
[1]H NMR spectrum of compound **5c**



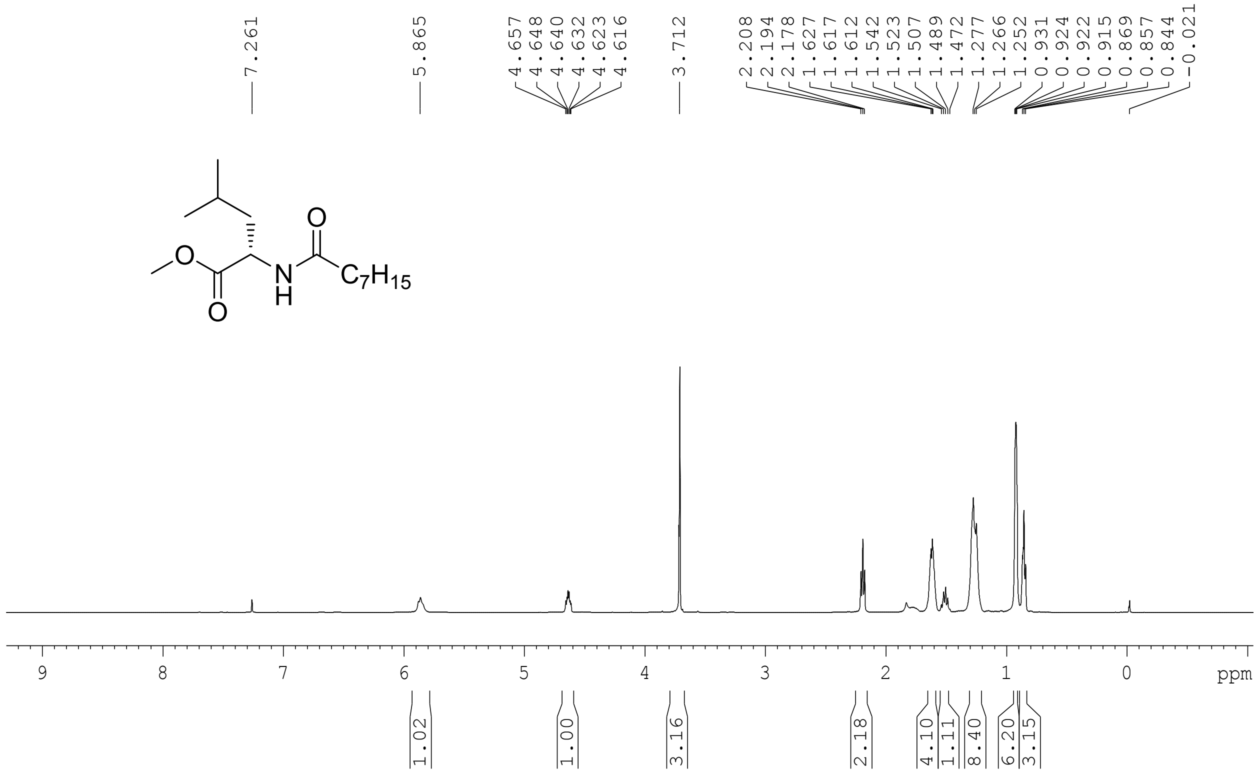
[13]C NMR spectrum of compound **5c**



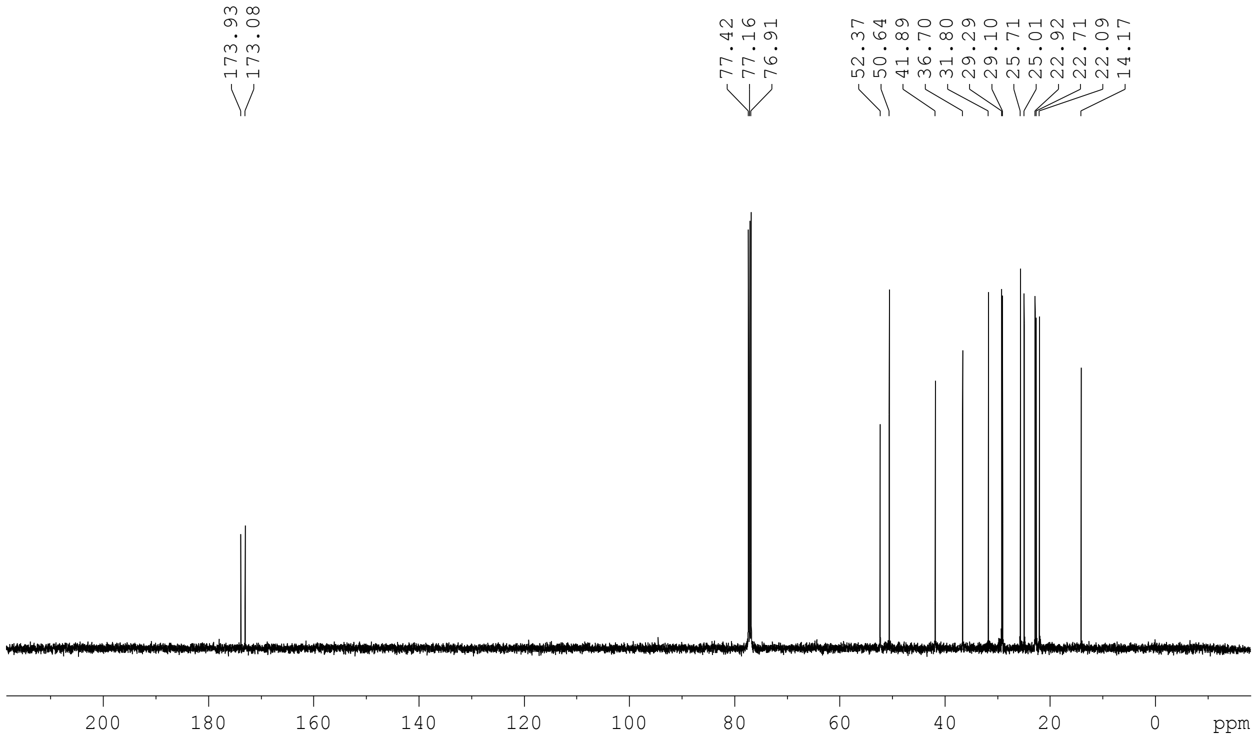
[1]H NMR spectrum of compound **5d**



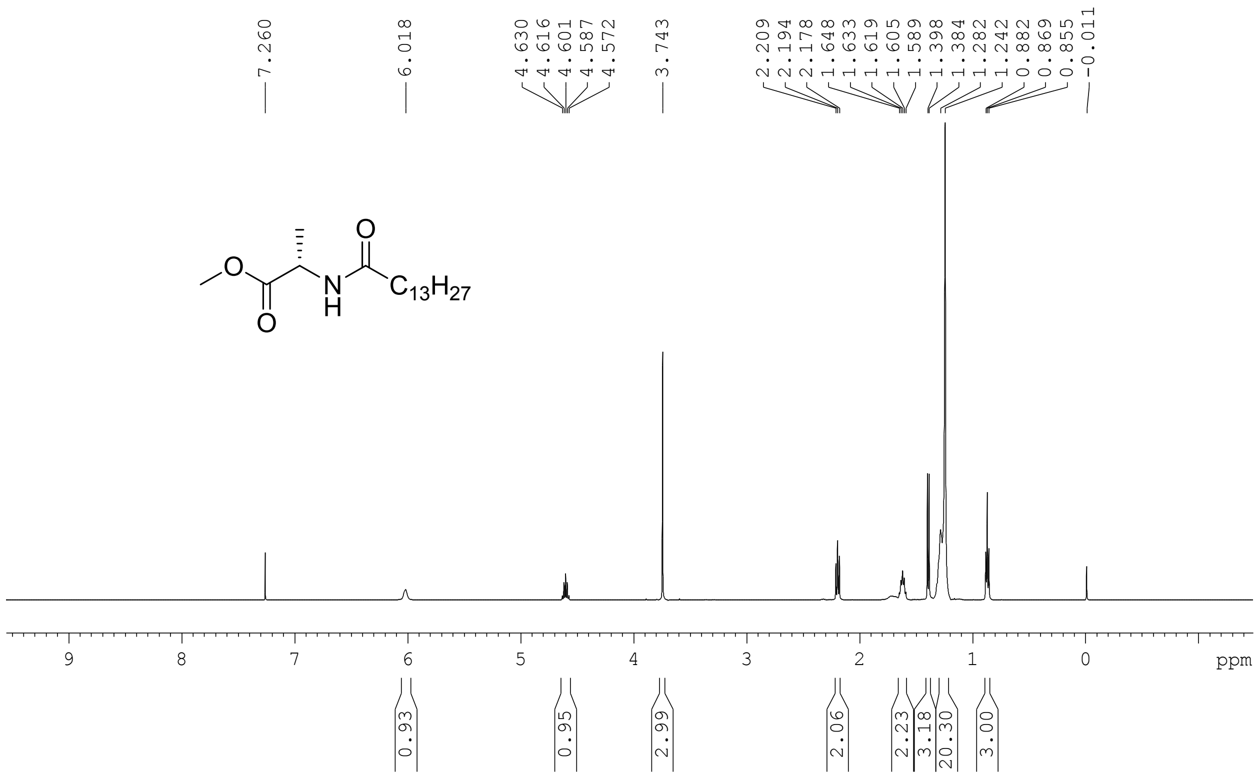
[13]C NMR spectrum of compound **5d**



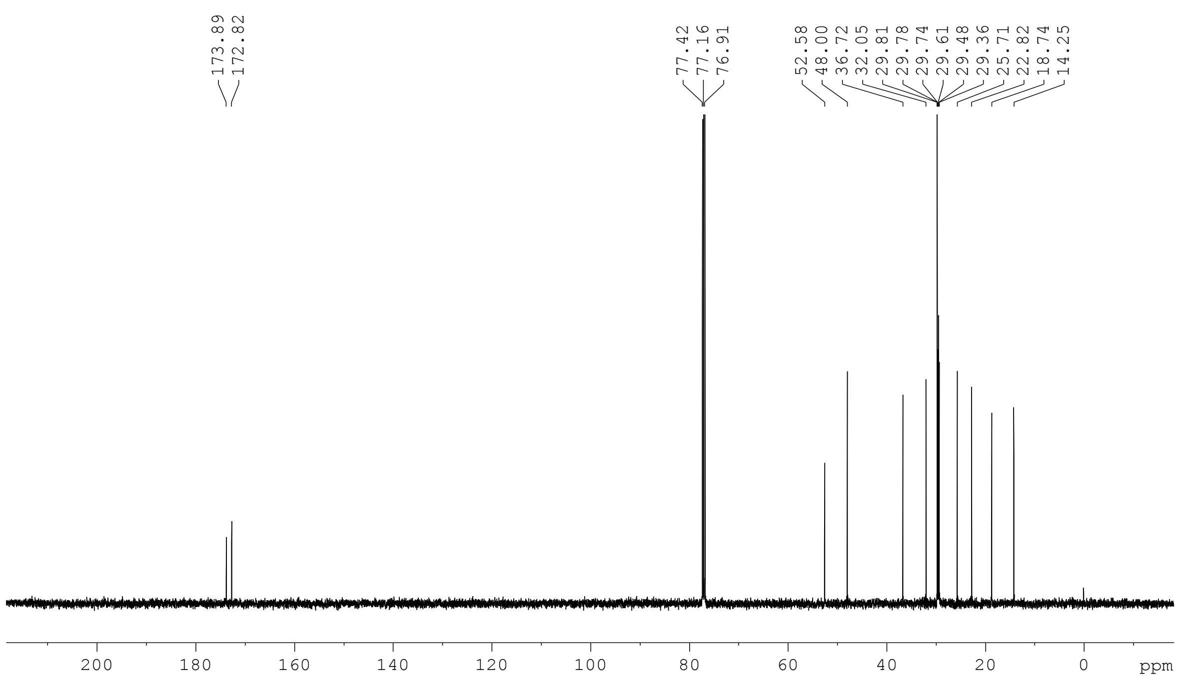
[1]H NMR spectrum of compound **5e**



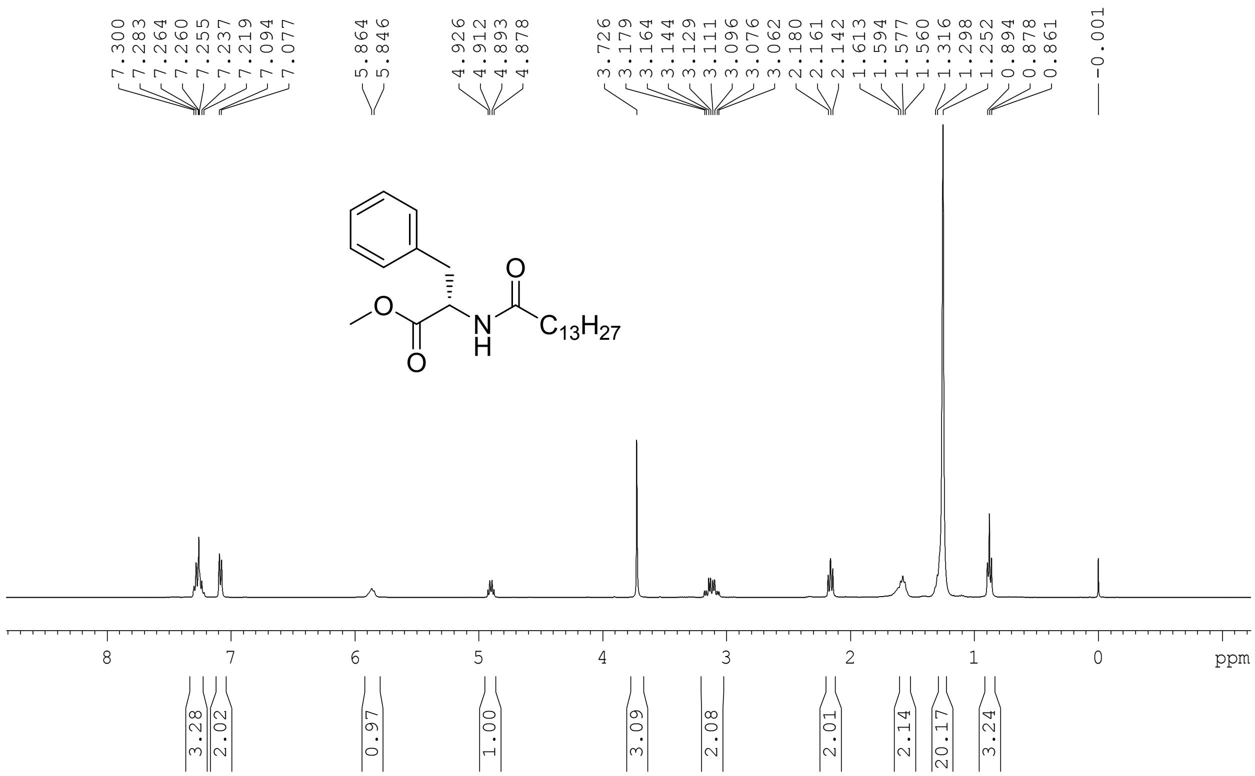
[13]C NMR spectrum of compound **5e**



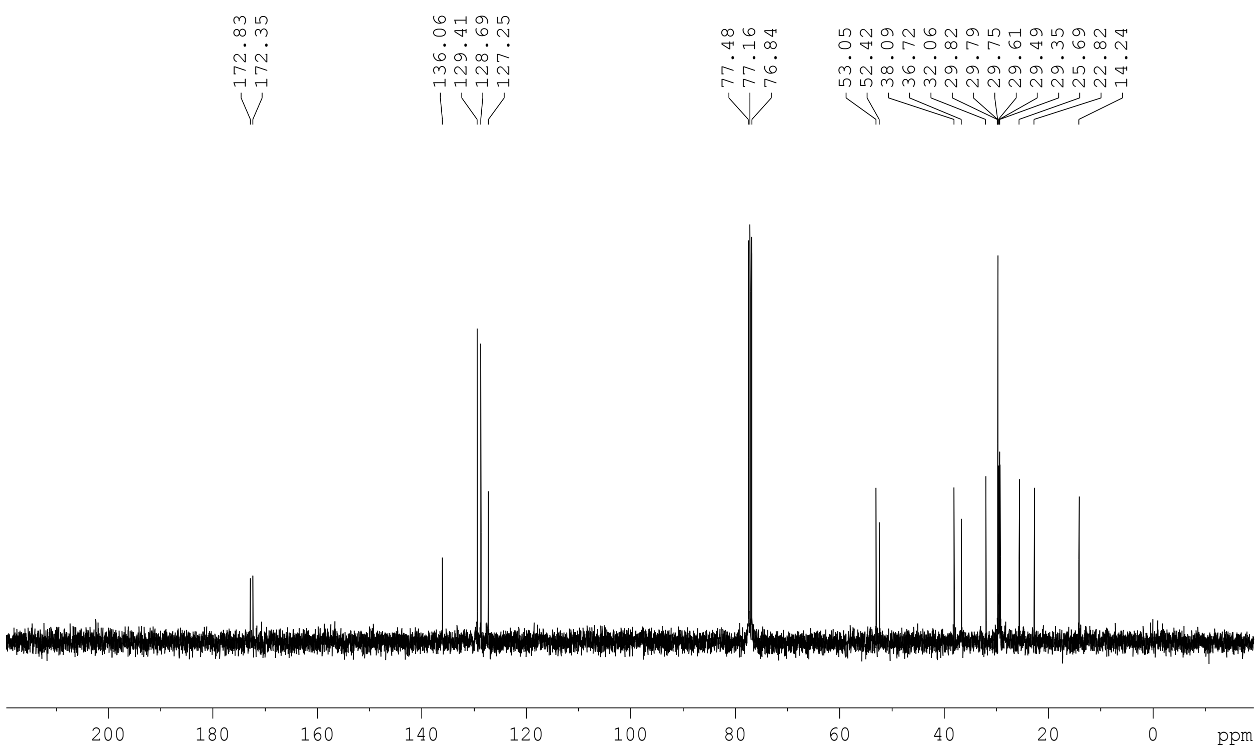
[1]H NMR spectrum of compound **6a**



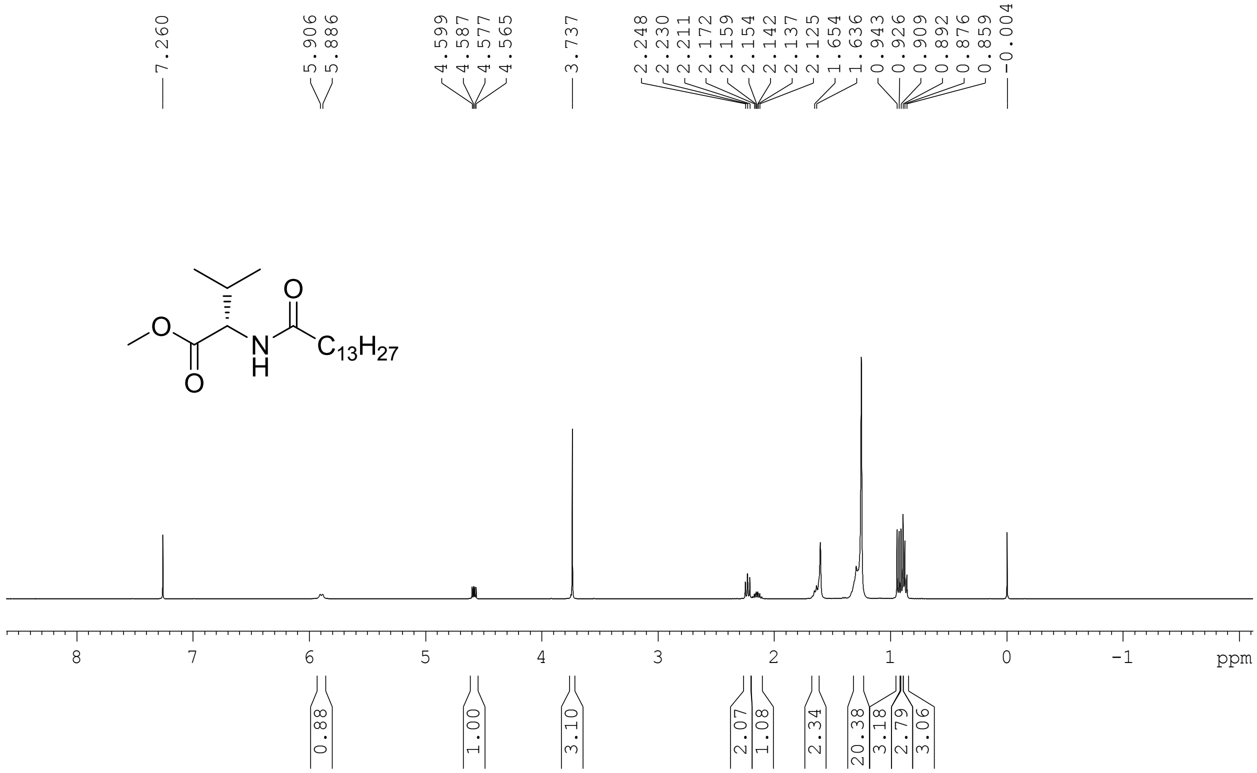
[13]C NMR spectrum of compound **6a**



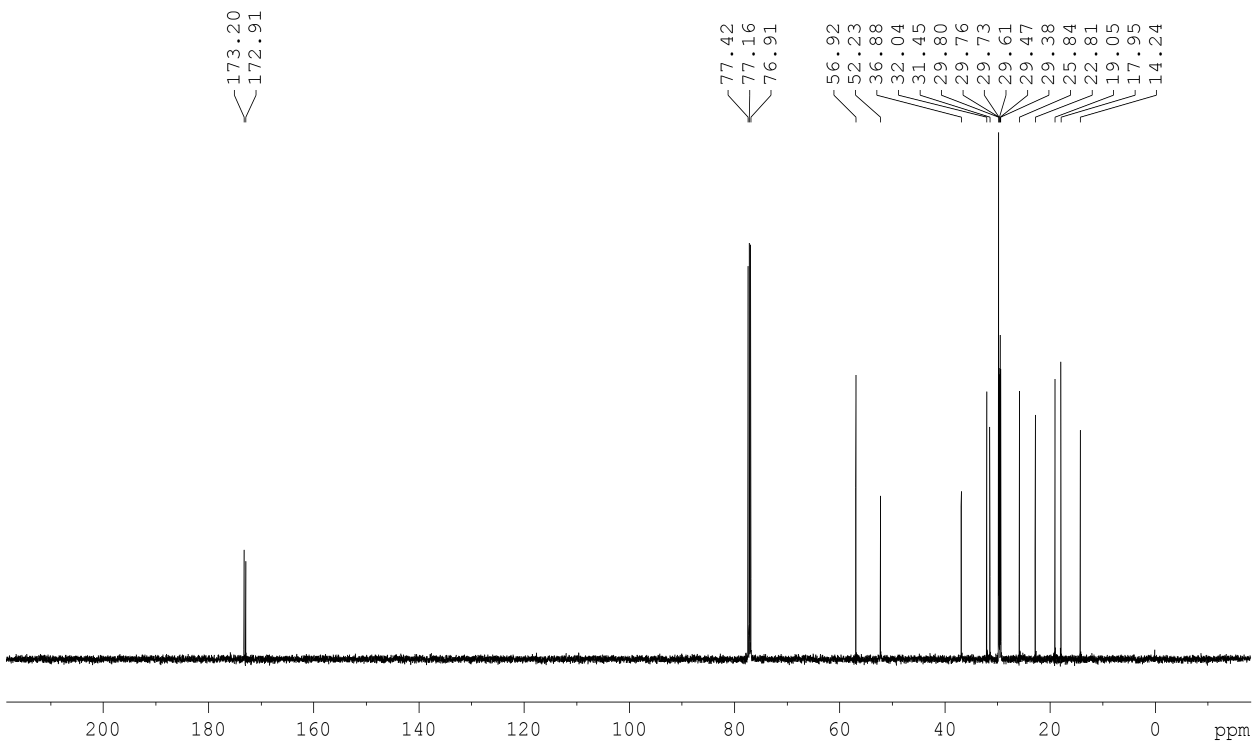
[1]H NMR spectrum of compound **6b**



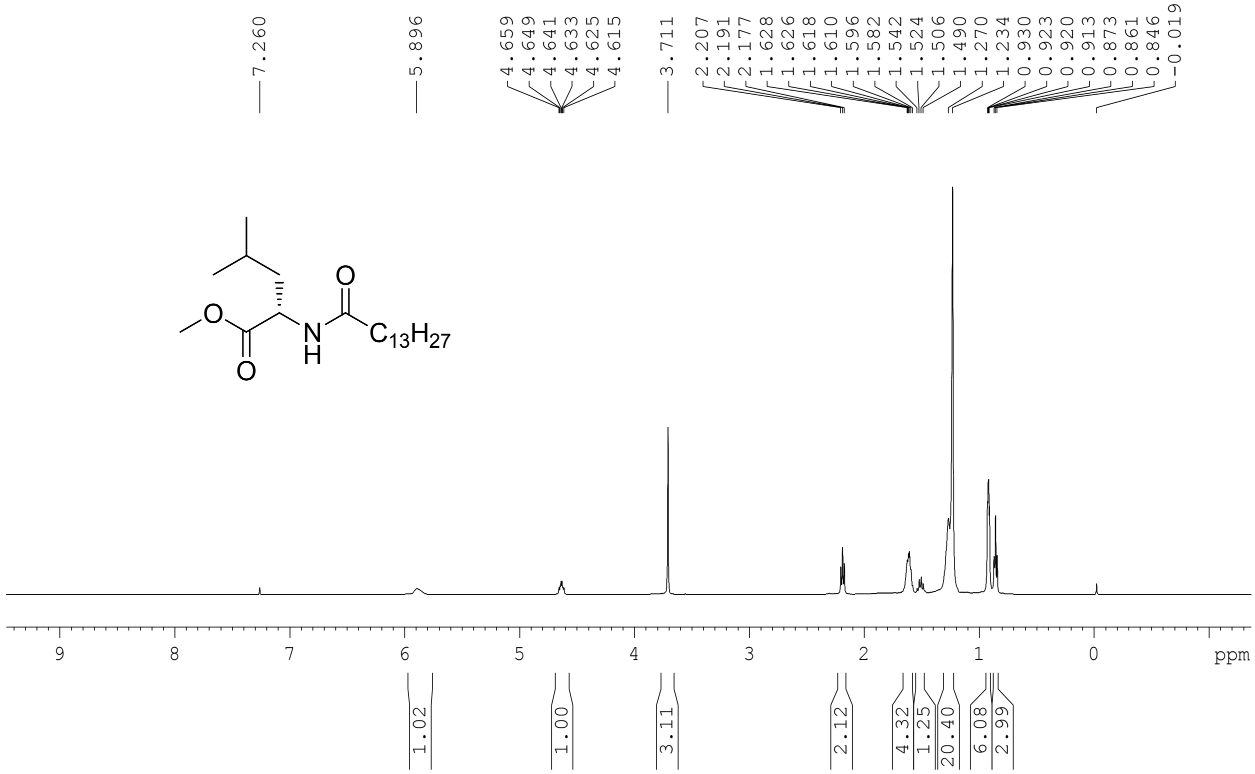
[13]C NMR spectrum of compound **6b**



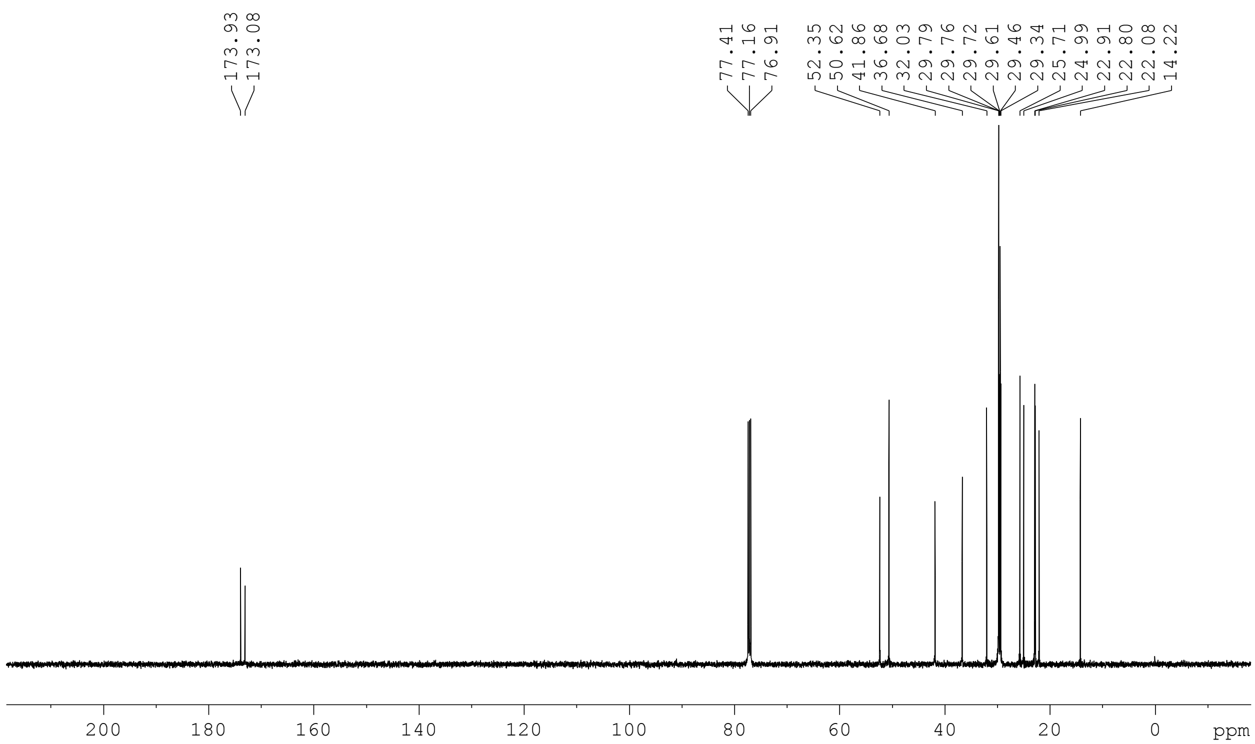
^{1}H NMR spectrum of compound **6c**



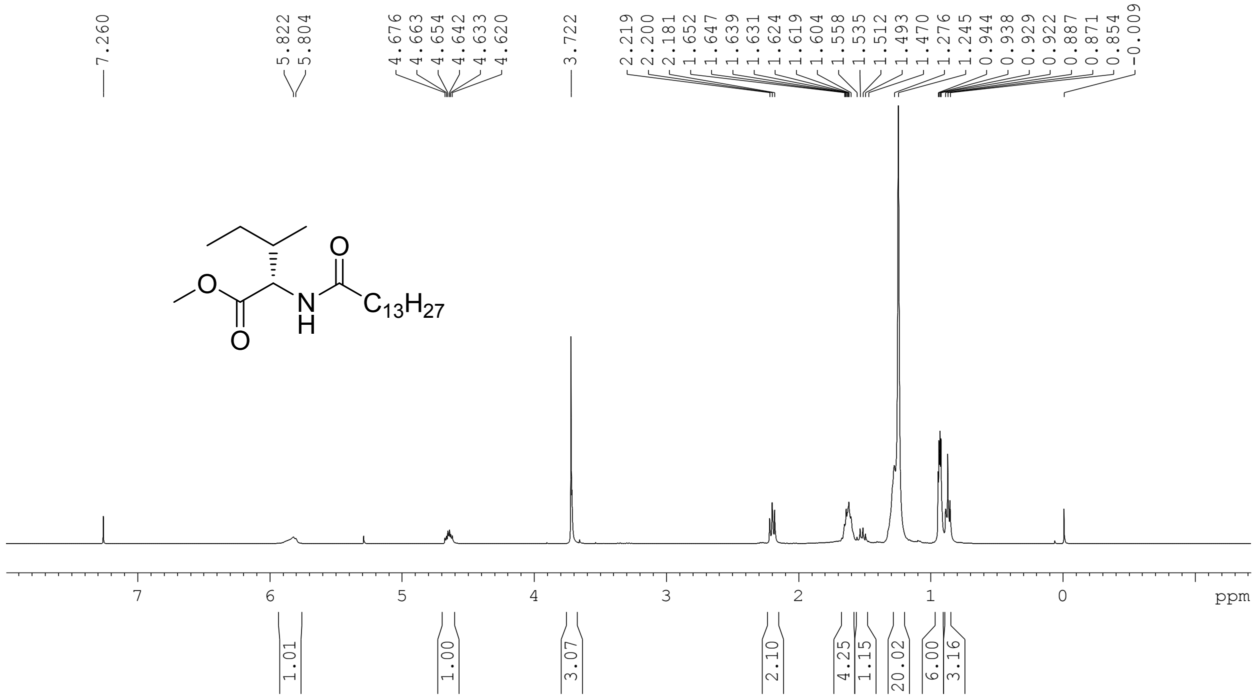
^{13}C NMR spectrum of compound **6c**



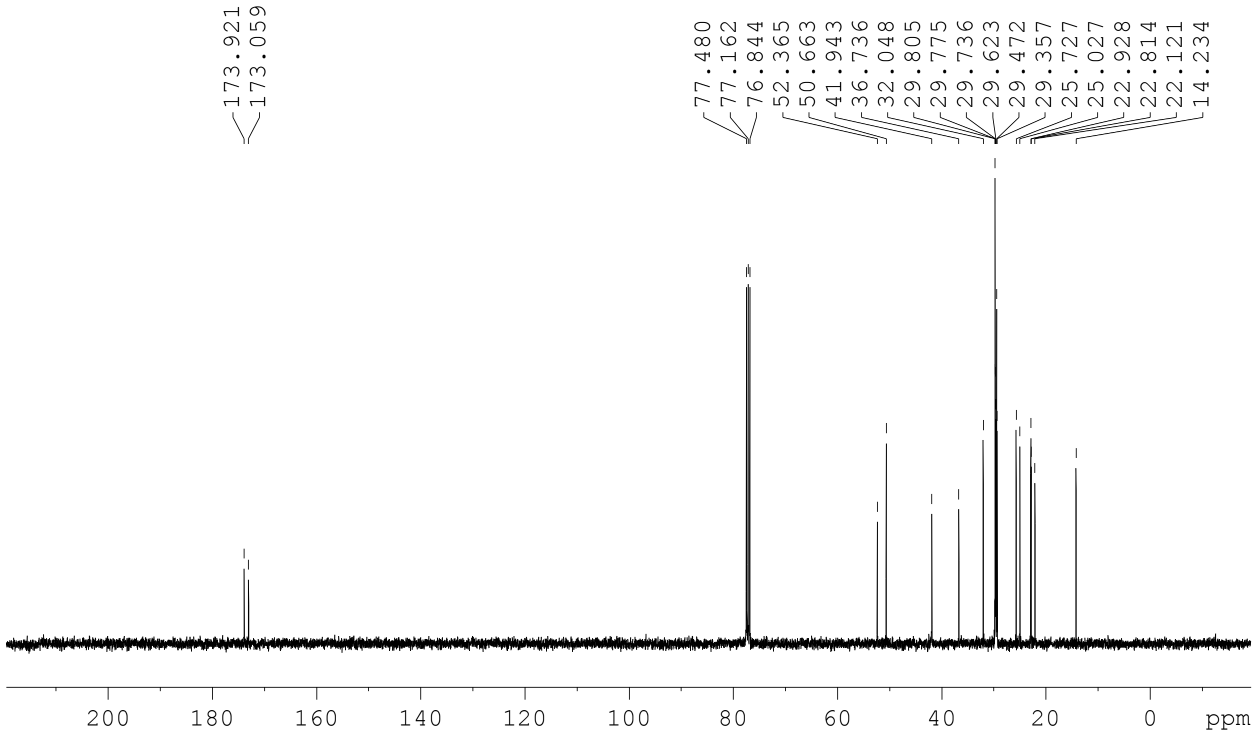
[1]H NMR spectrum of compound **6d**



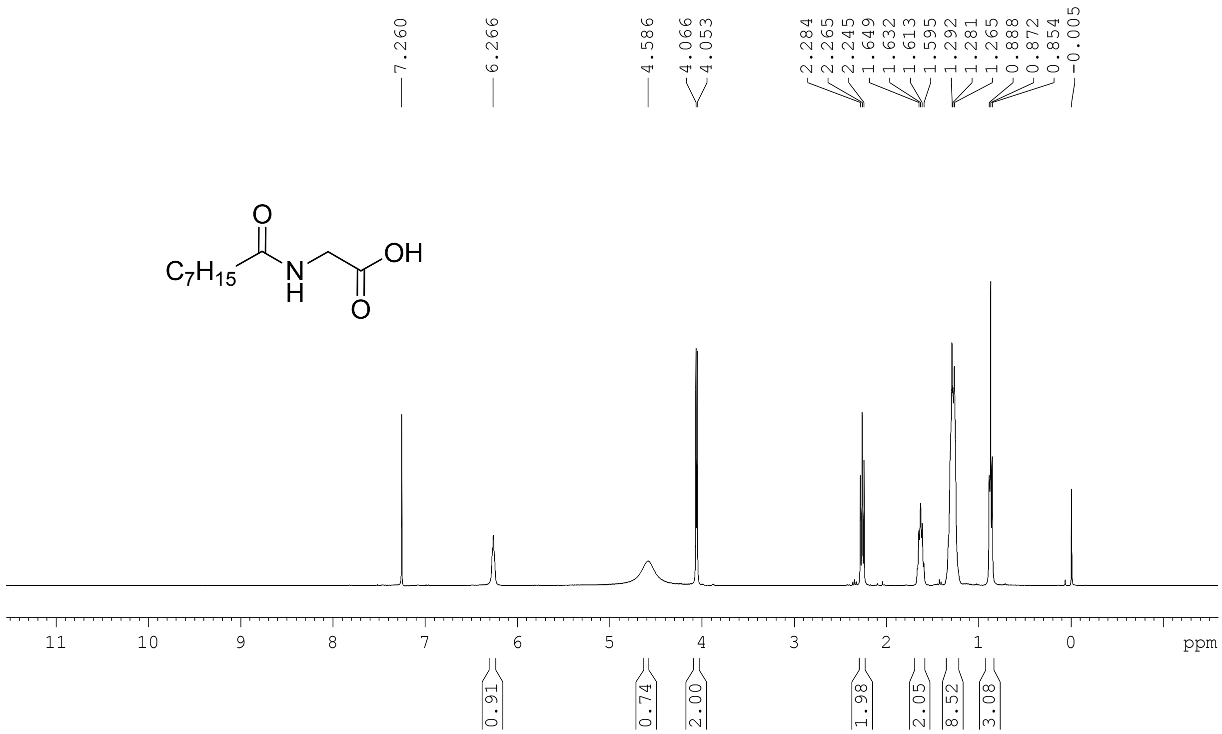
[13]C NMR spectrum of compound **6d**



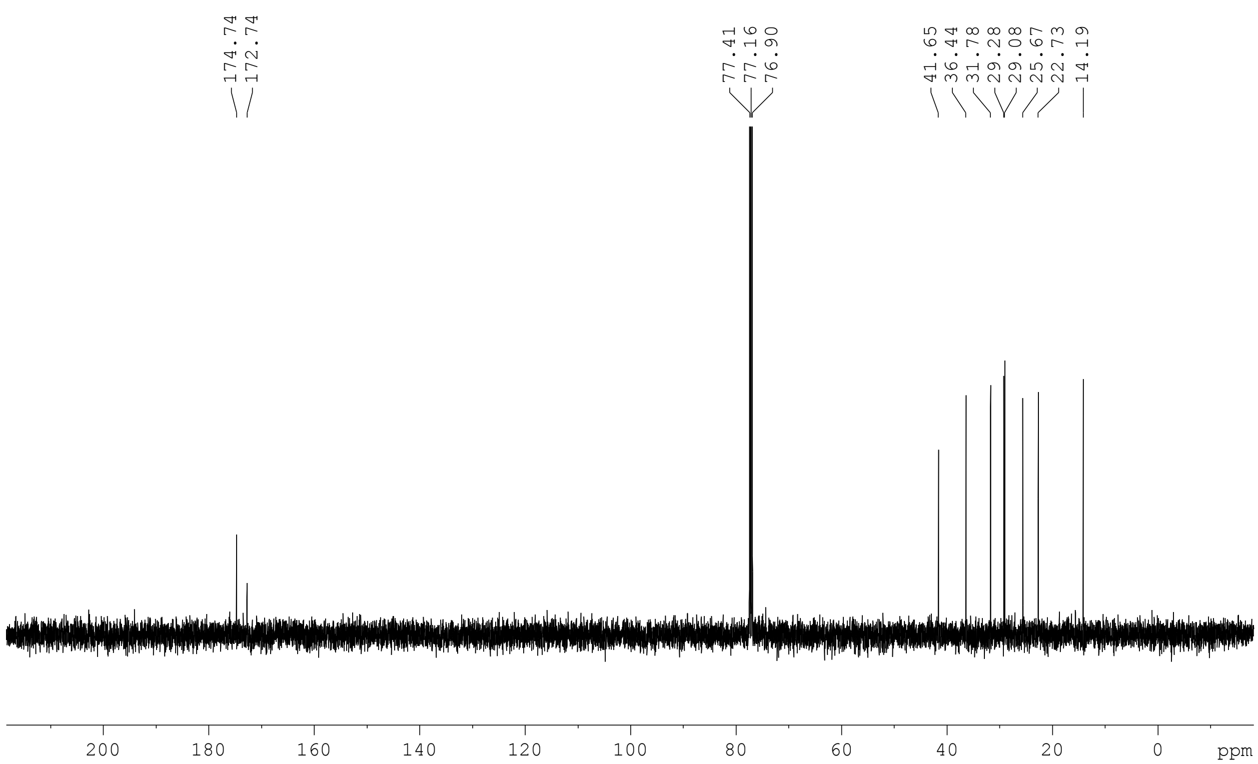
[1]H NMR spectrum of compound **6e**



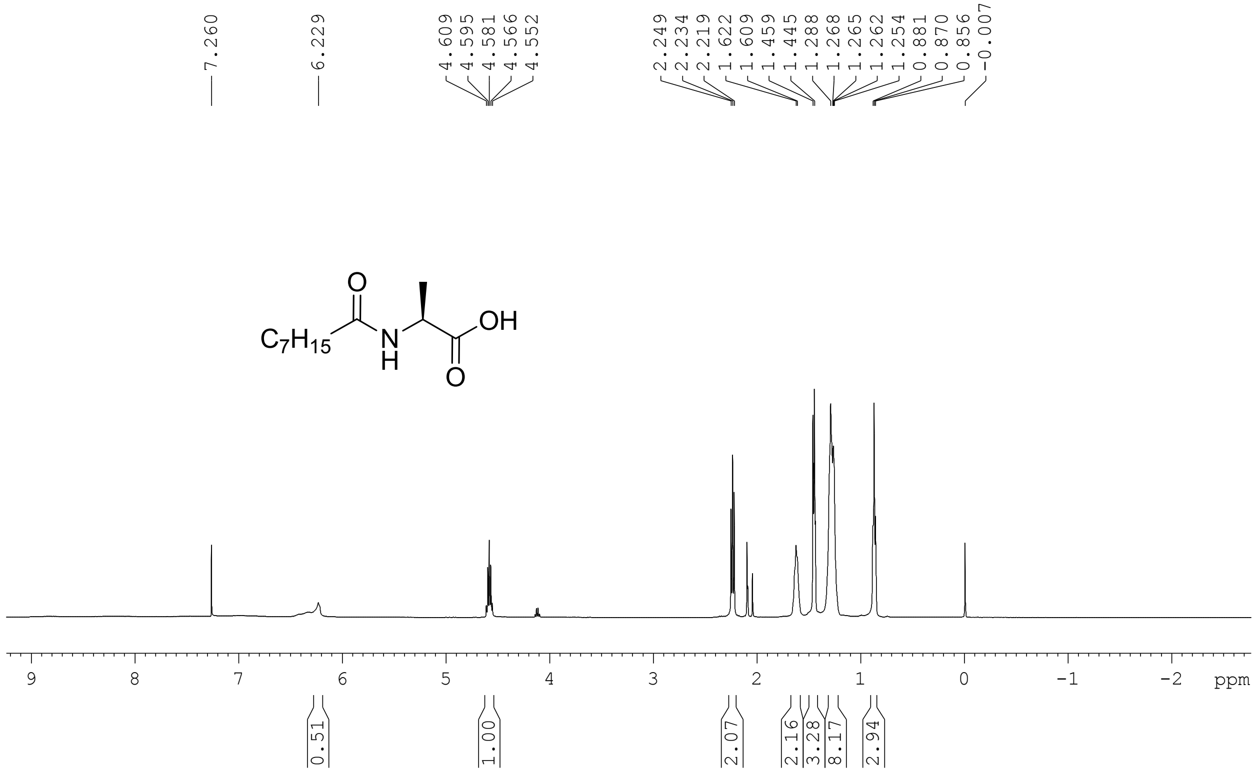
[13]C NMR spectrum of compound **6e**



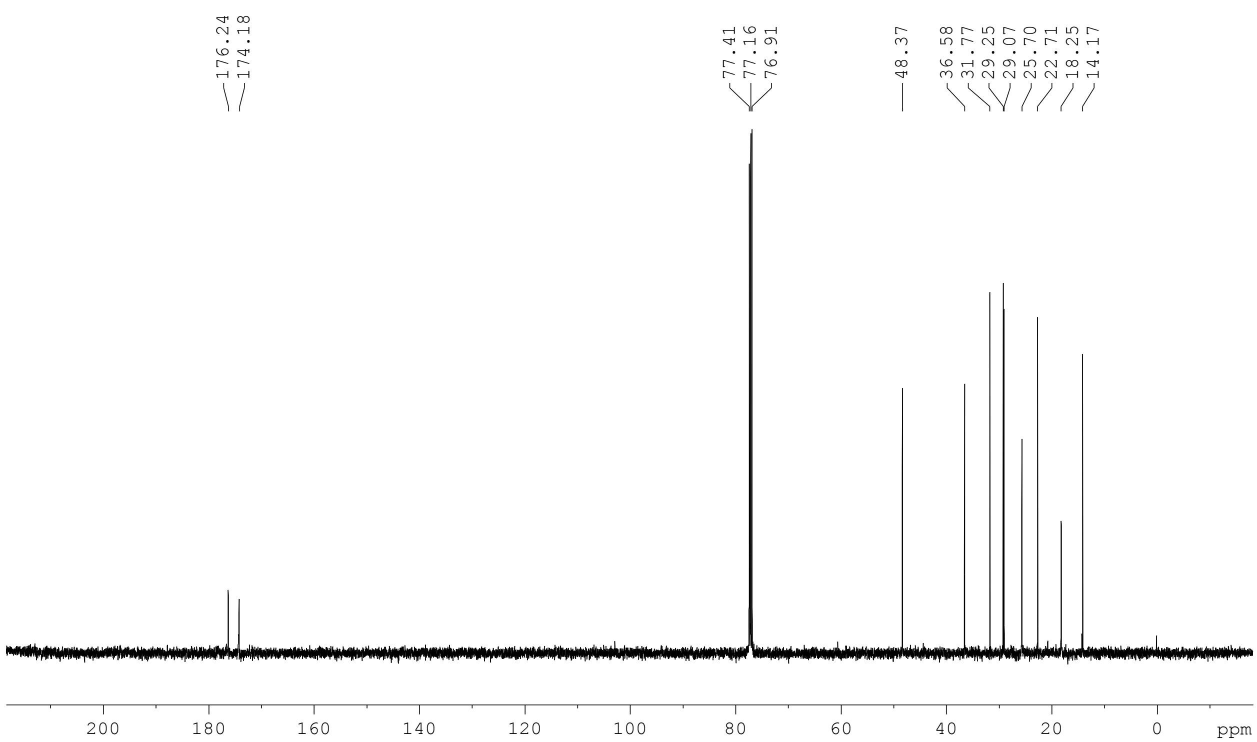
[1]H NMR spectrum of compound **7a**



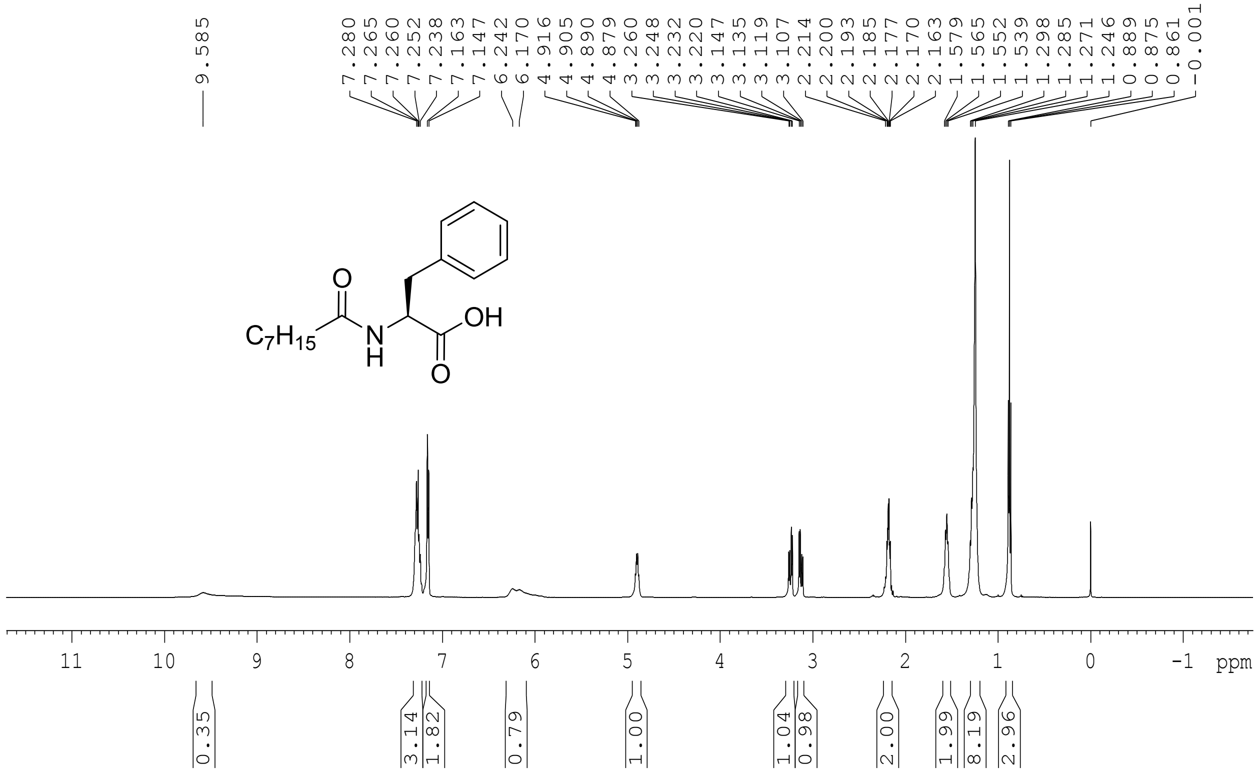
[13]C NMR spectrum of compound **7a**



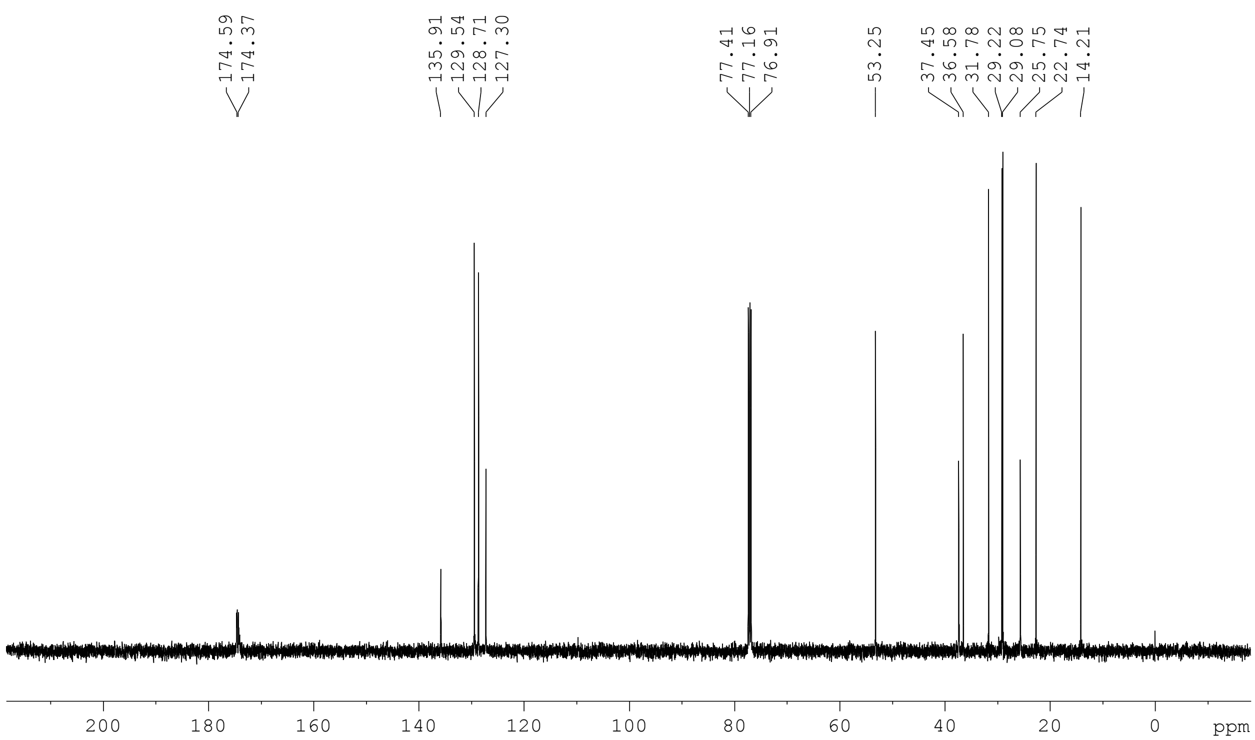
[1]H NMR spectrum of compound **7b**



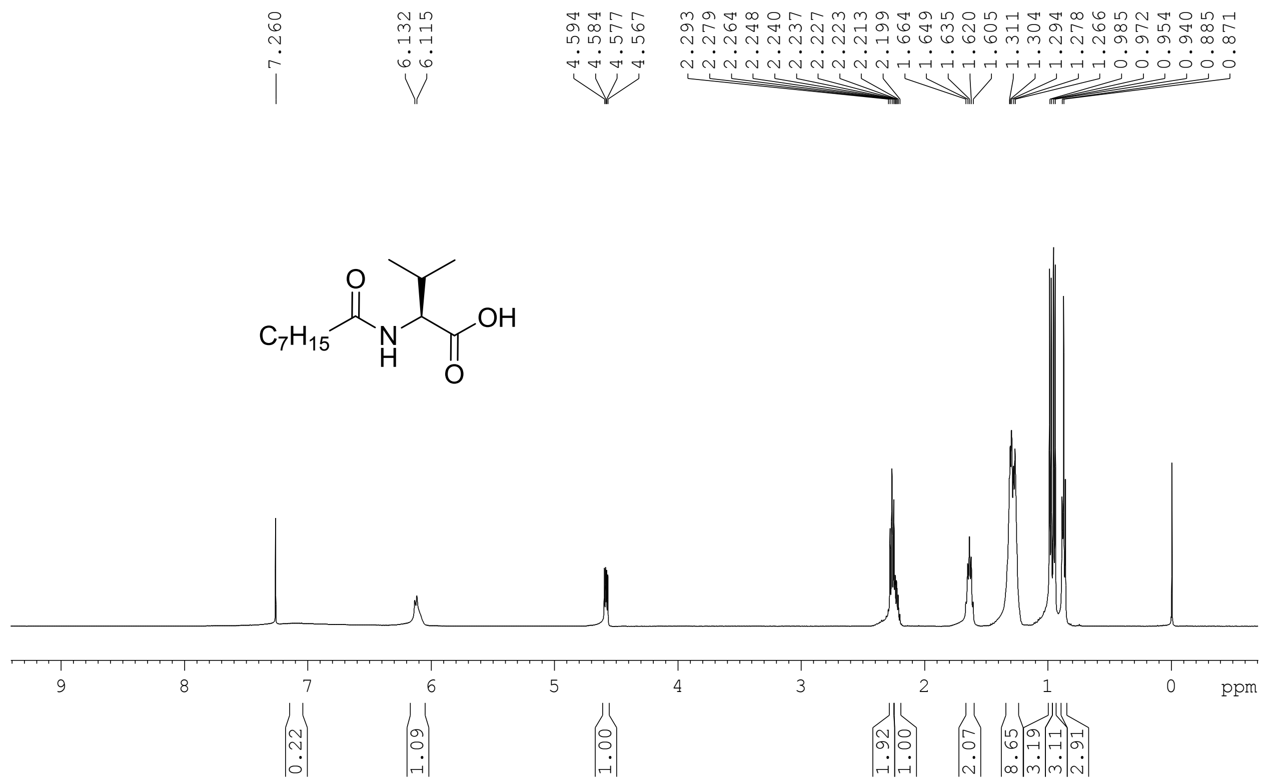
[13]C NMR spectrum of compound **7b**



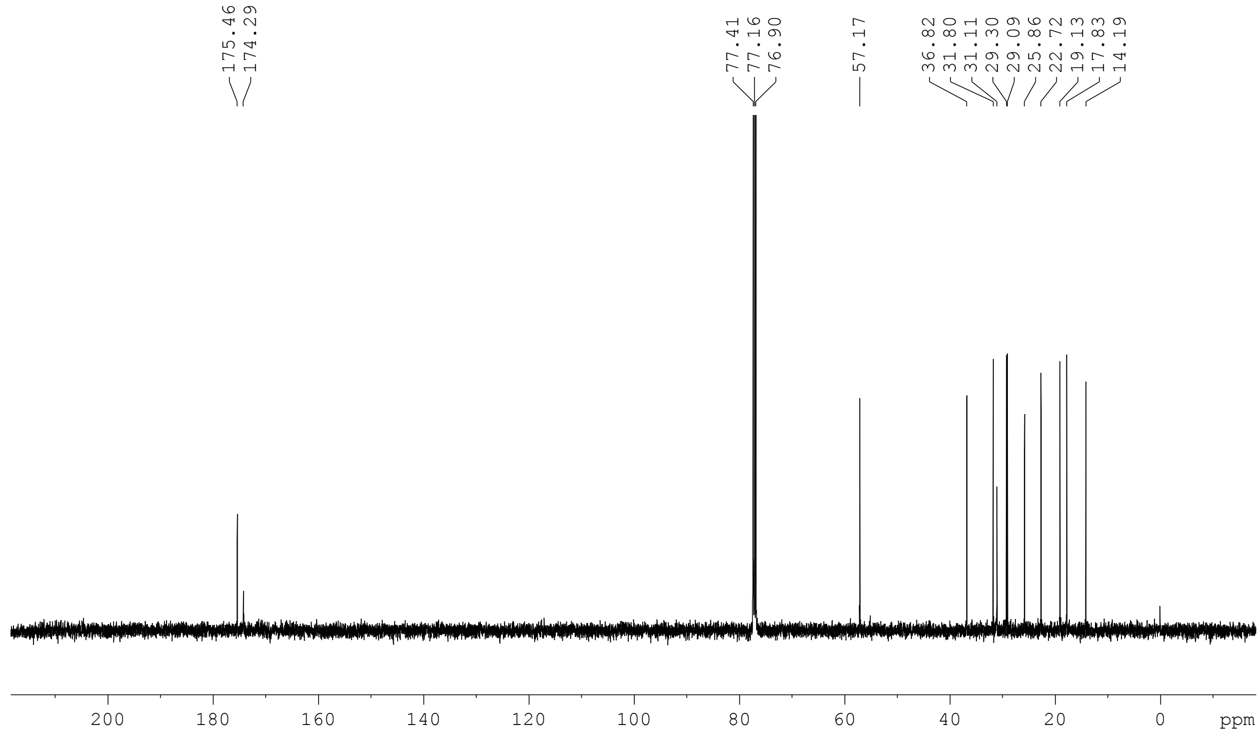
[1]H NMR spectrum of compound **7c**



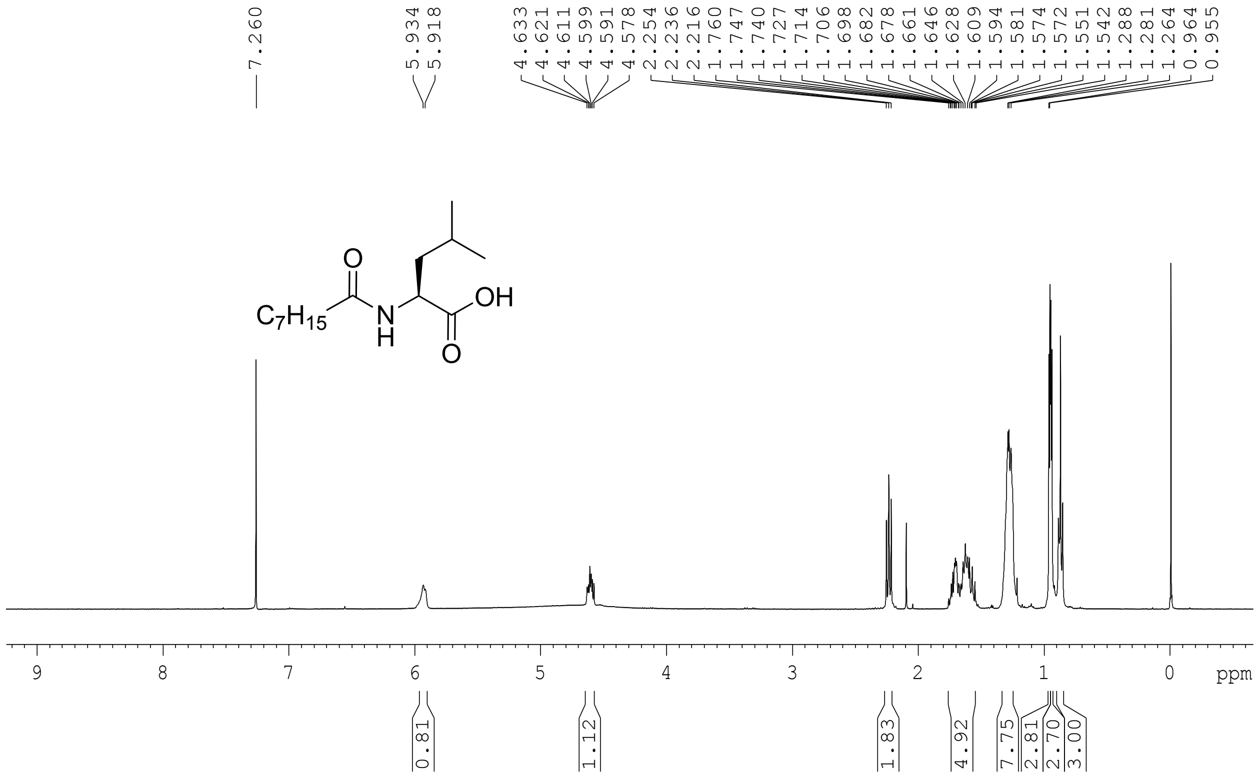
[13]C NMR spectrum of compound **7c**



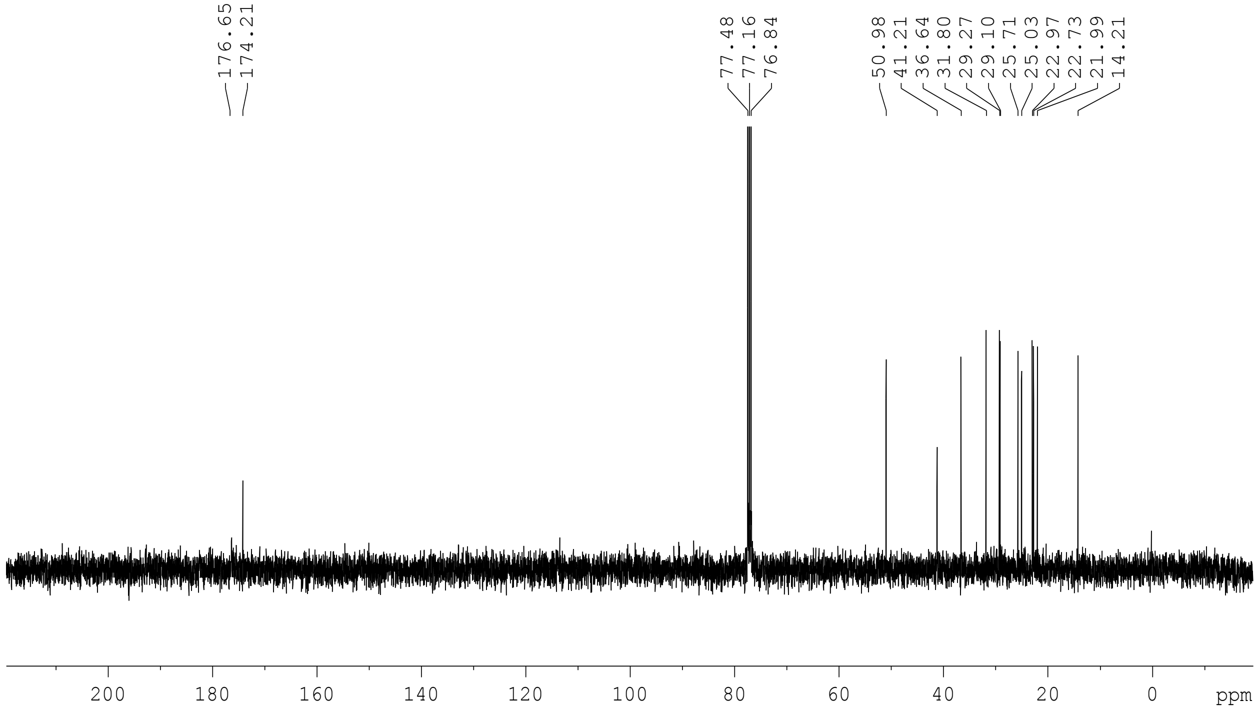
[1]H NMR spectrum of compound **7d**



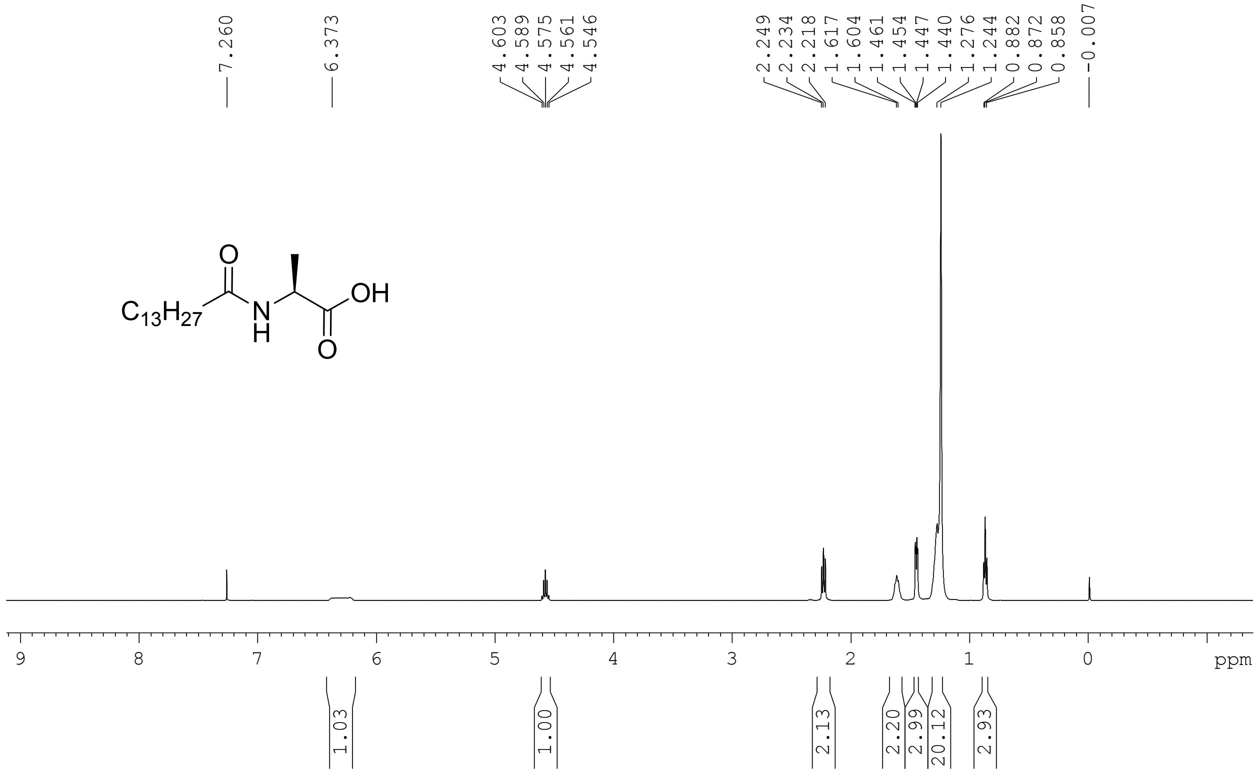
[13]C NMR spectrum of compound **7d**



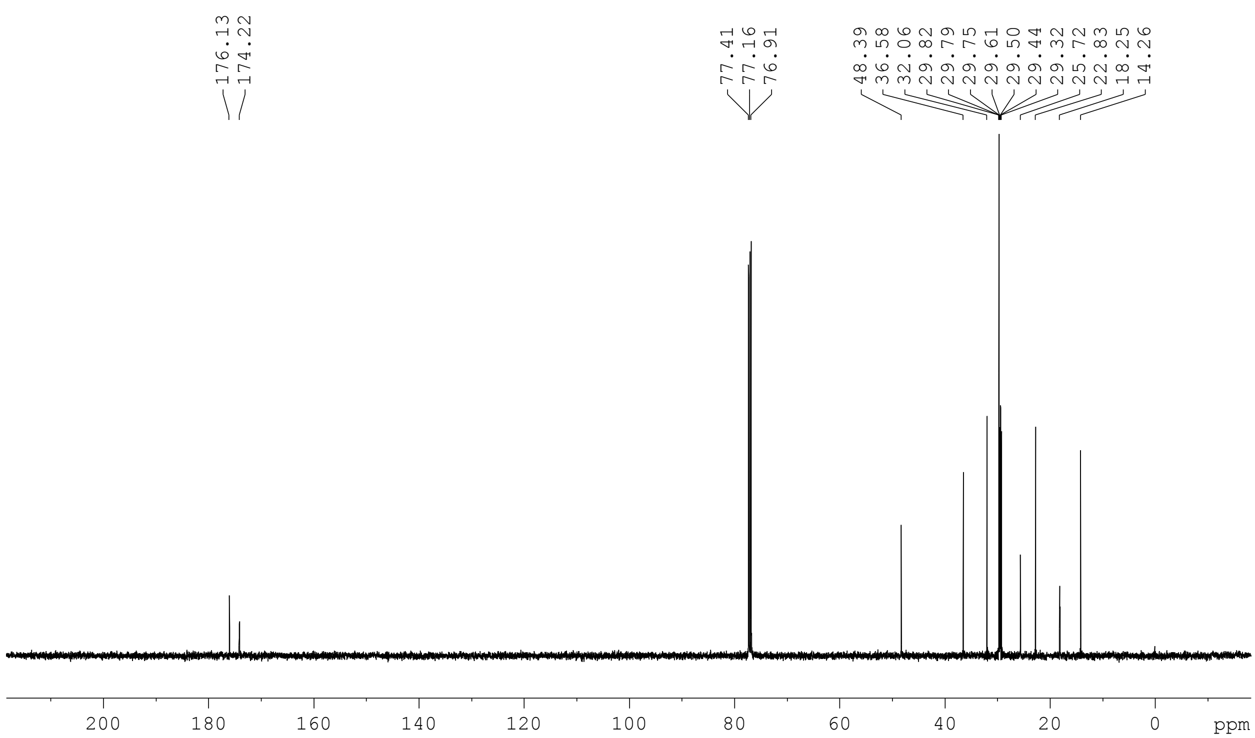
[1]H NMR spectrum of compound **7e**



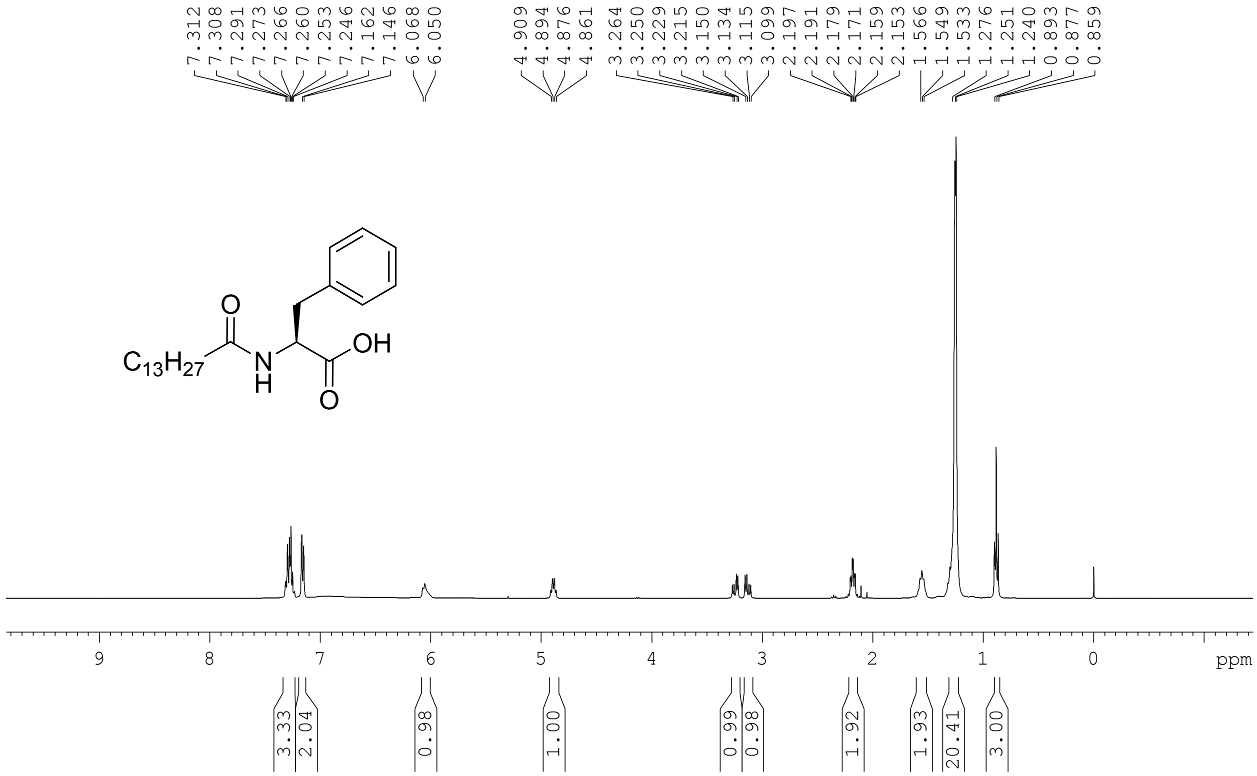
[13]C NMR spectrum of compound **7e**



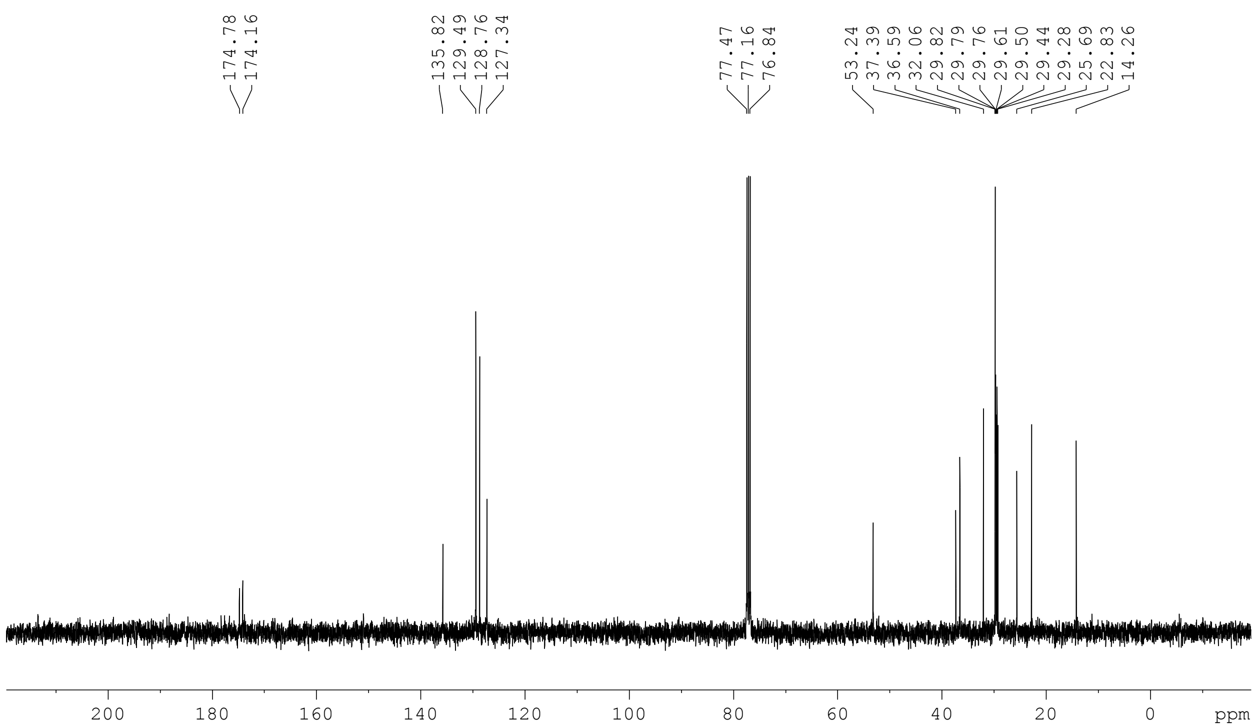
^{1}H NMR spectrum of compound **8a**



^{13}C NMR spectrum of compound **8a**

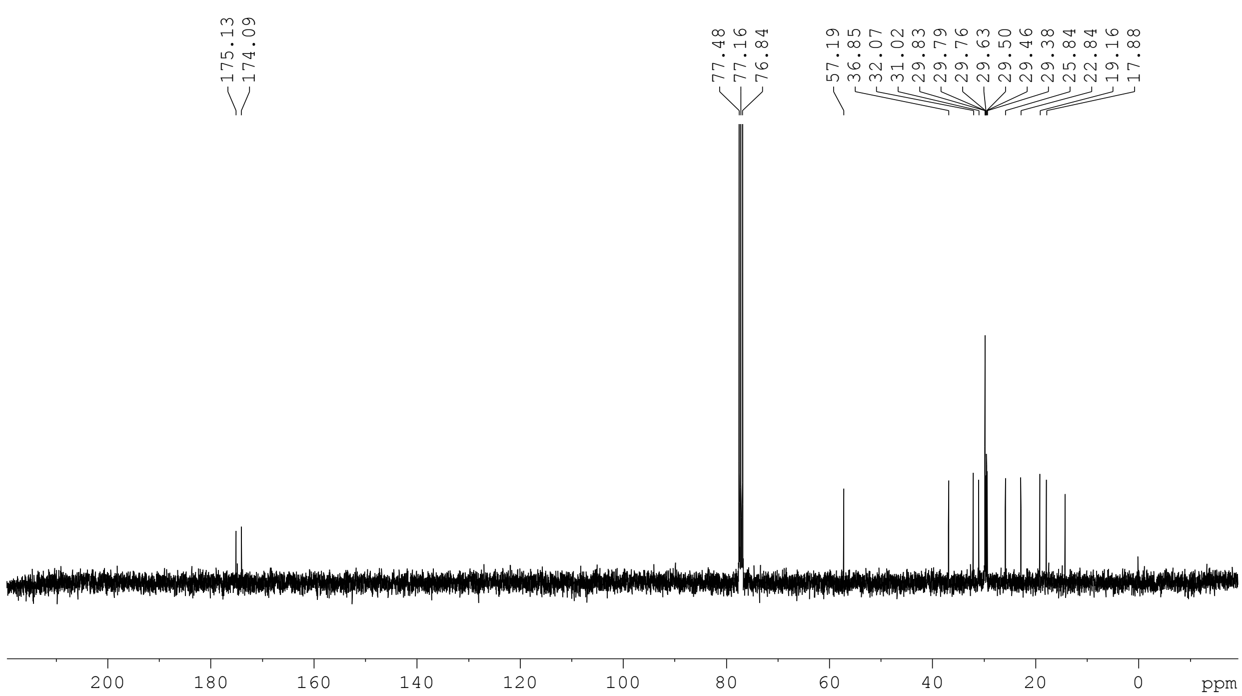


[1]H NMR spectrum of compound **8b**

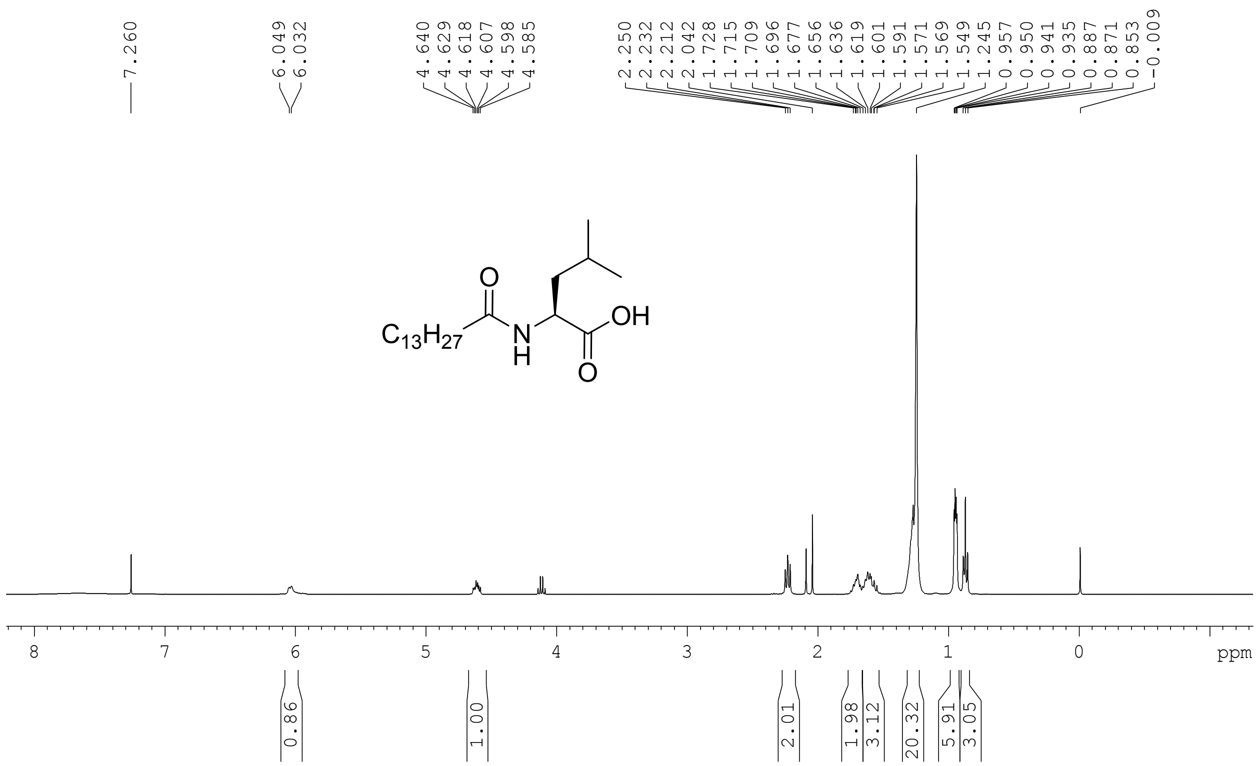


[13]C NMR spectrum of compound **8b**

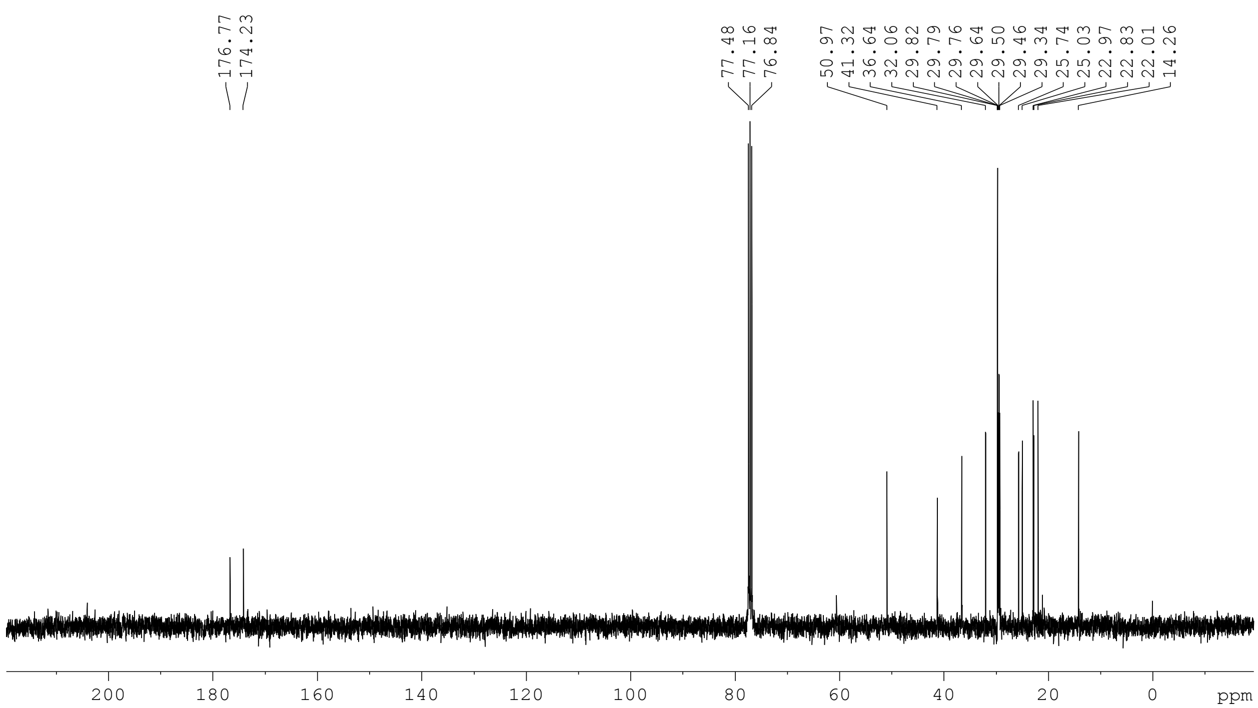
^{1}H NMR spectrum of compound **8c**



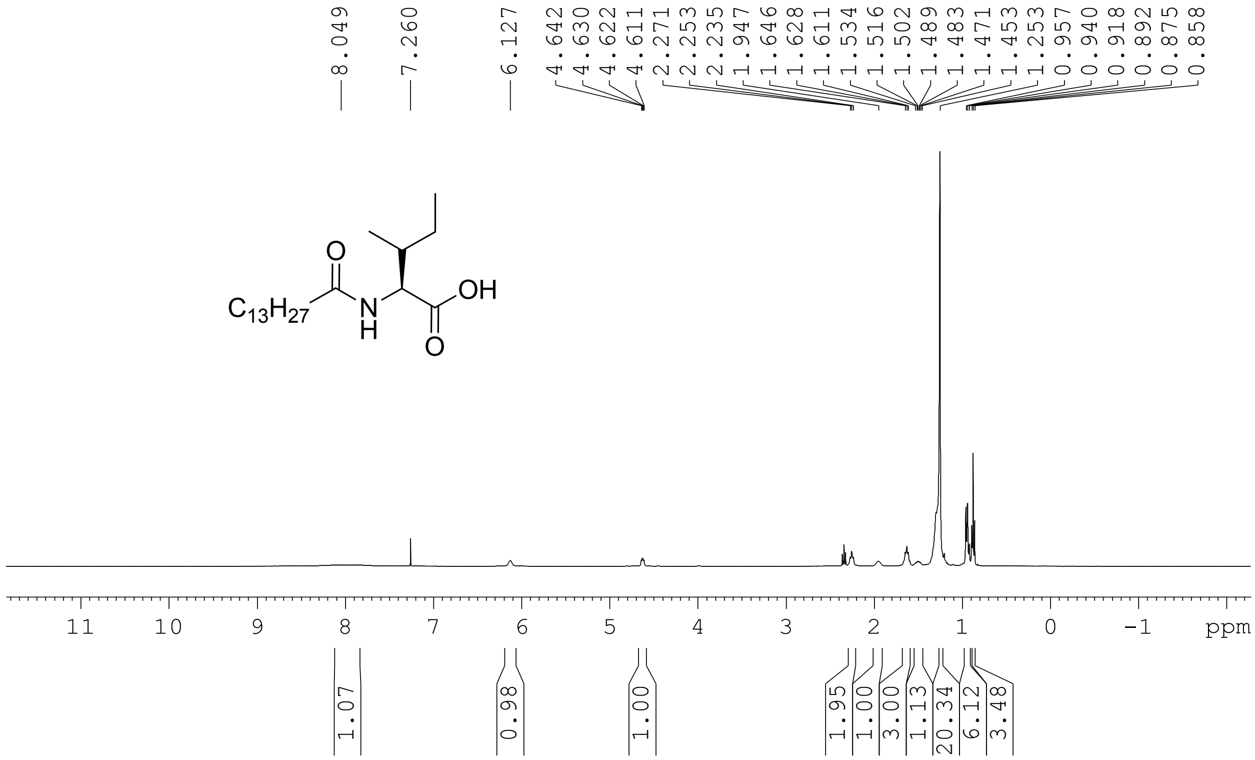
^{13}C NMR spectrum of compound **8c**



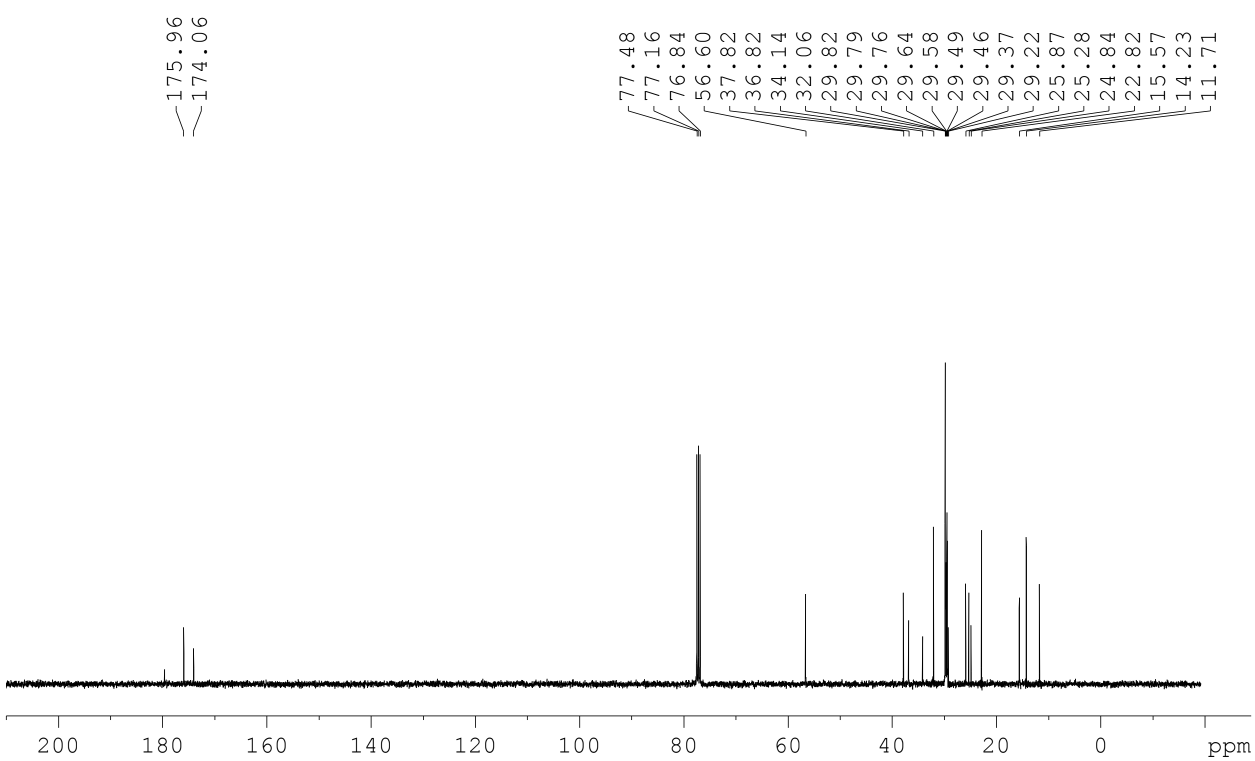
[1]H NMR spectrum of compound **8d**



[13]C NMR spectrum of compound **8d**

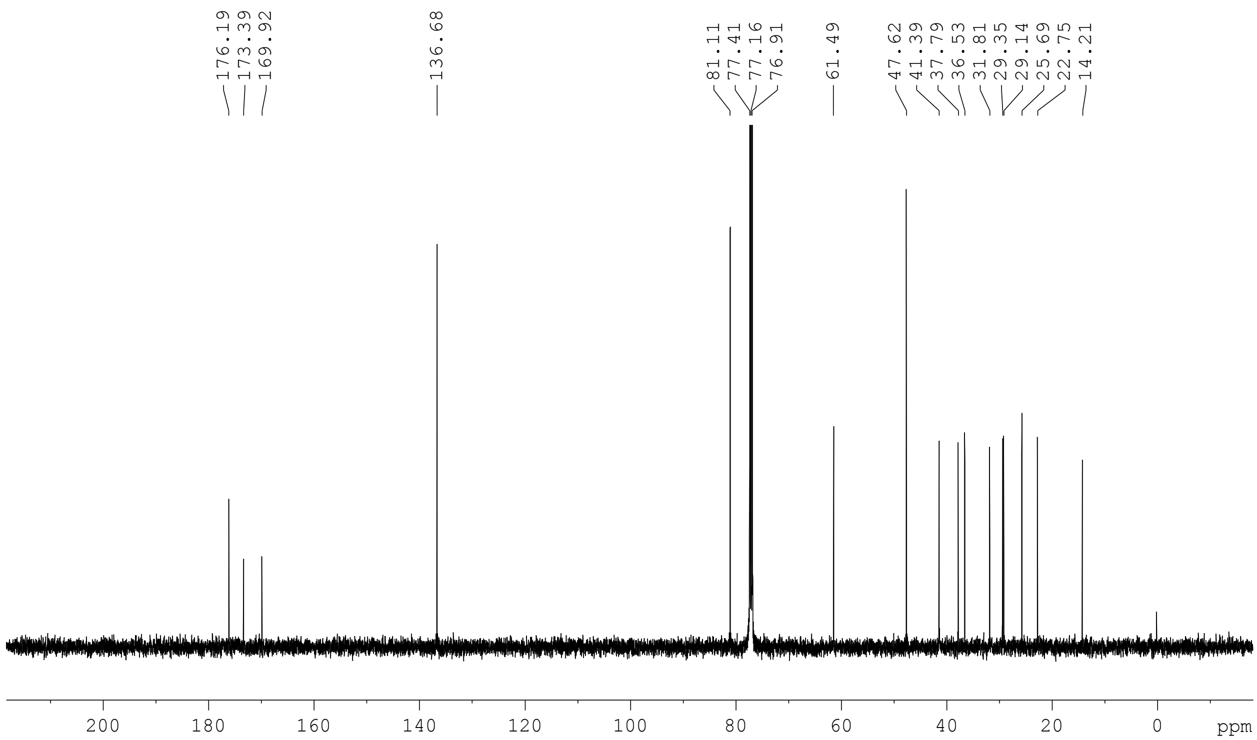


[1]H NMR spectrum of compound **8e**

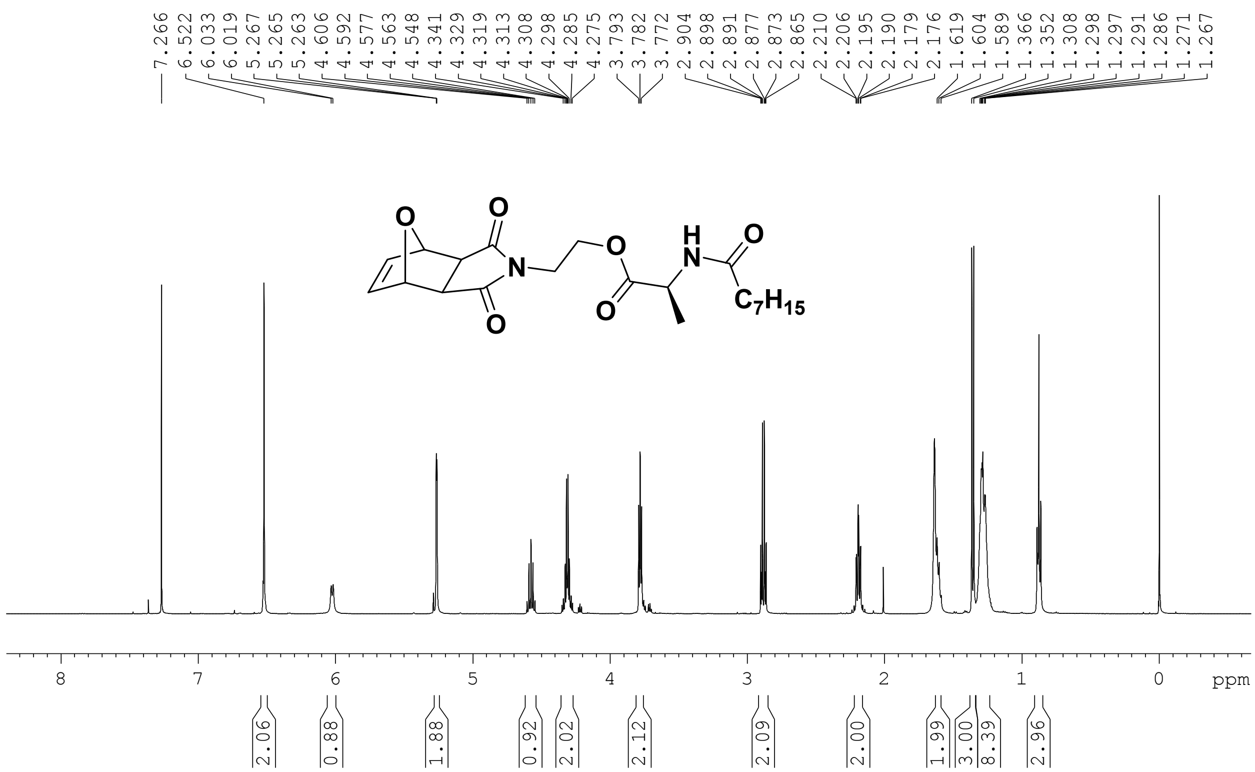


[13]C NMR spectrum of compound **8e**

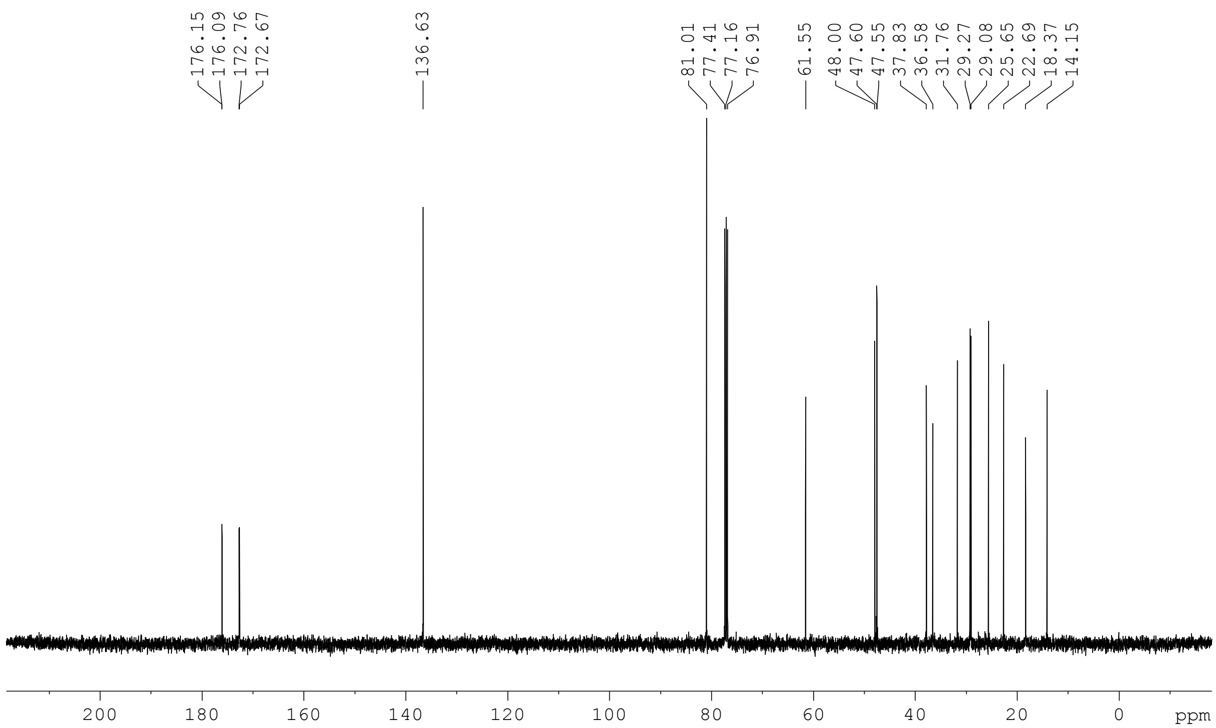
[1]H NMR spectrum of compound **10a**



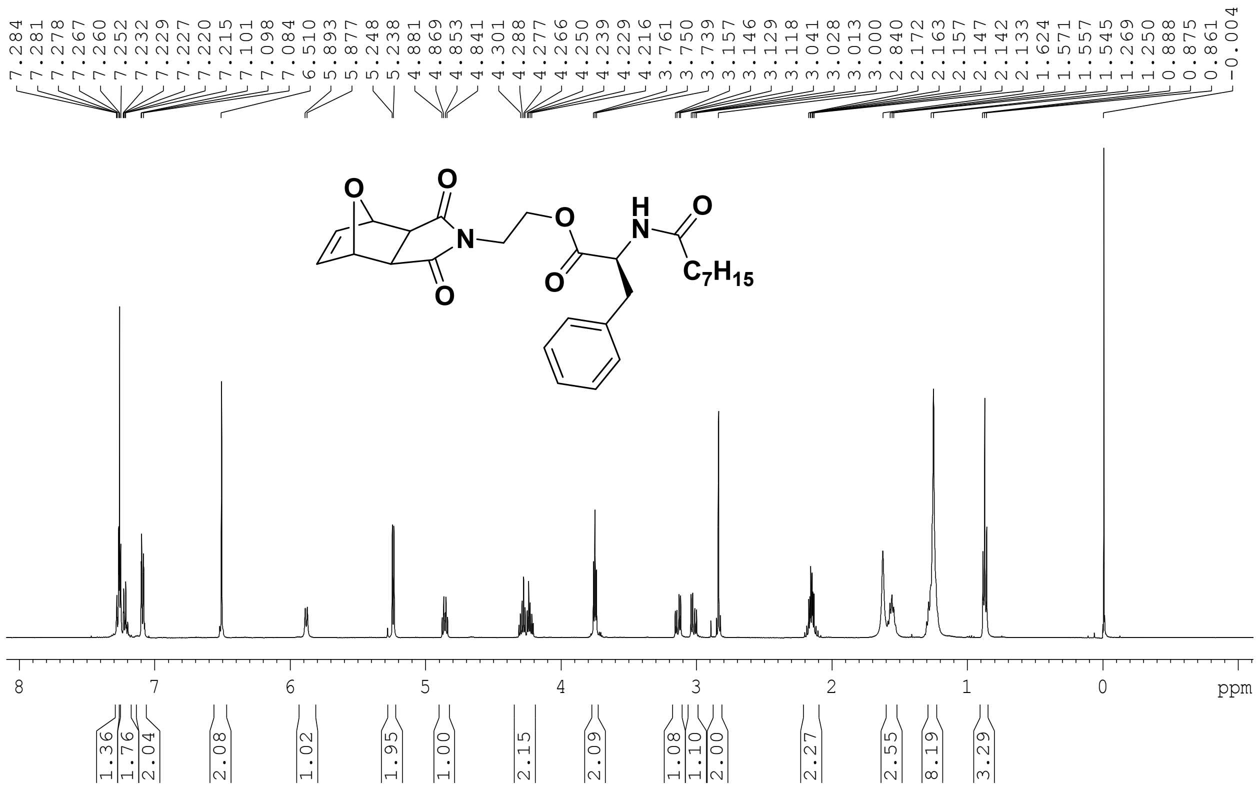
[13]C NMR spectrum of compound **10a**



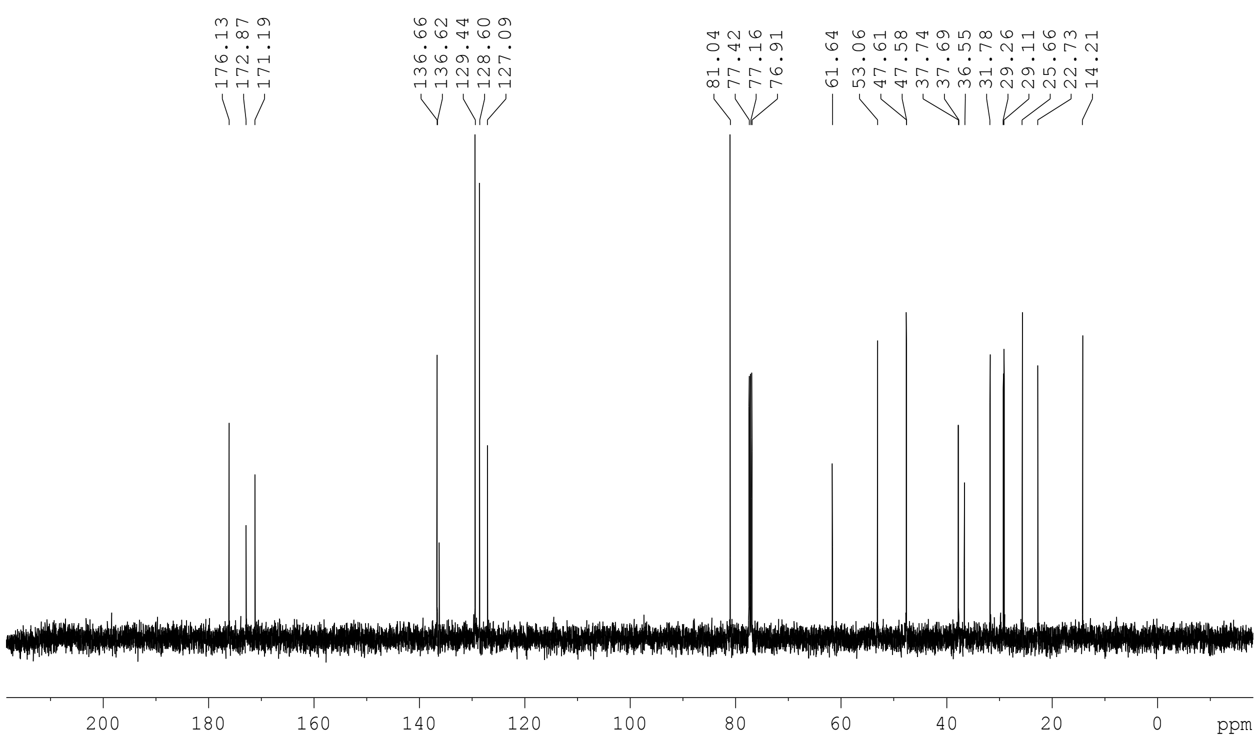
[1]H NMR spectrum of compound **10b**



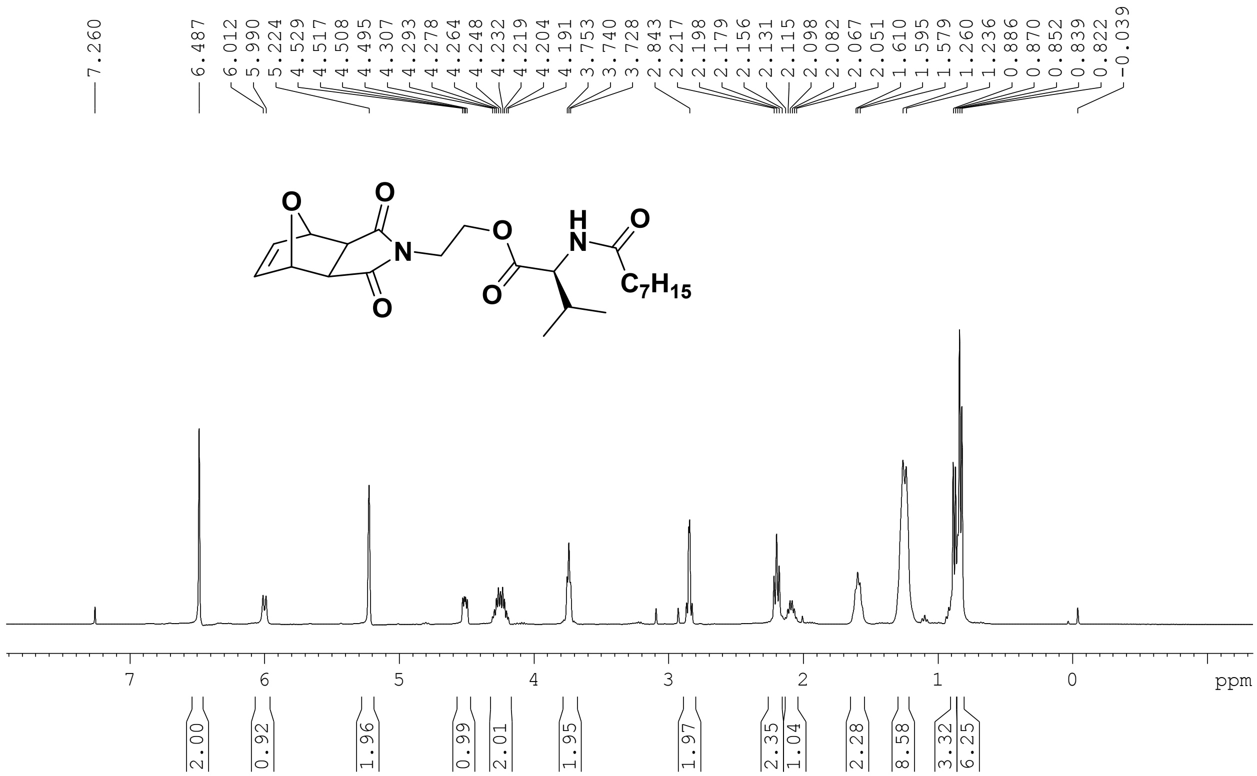
[13]C NMR spectrum of compound **10b**



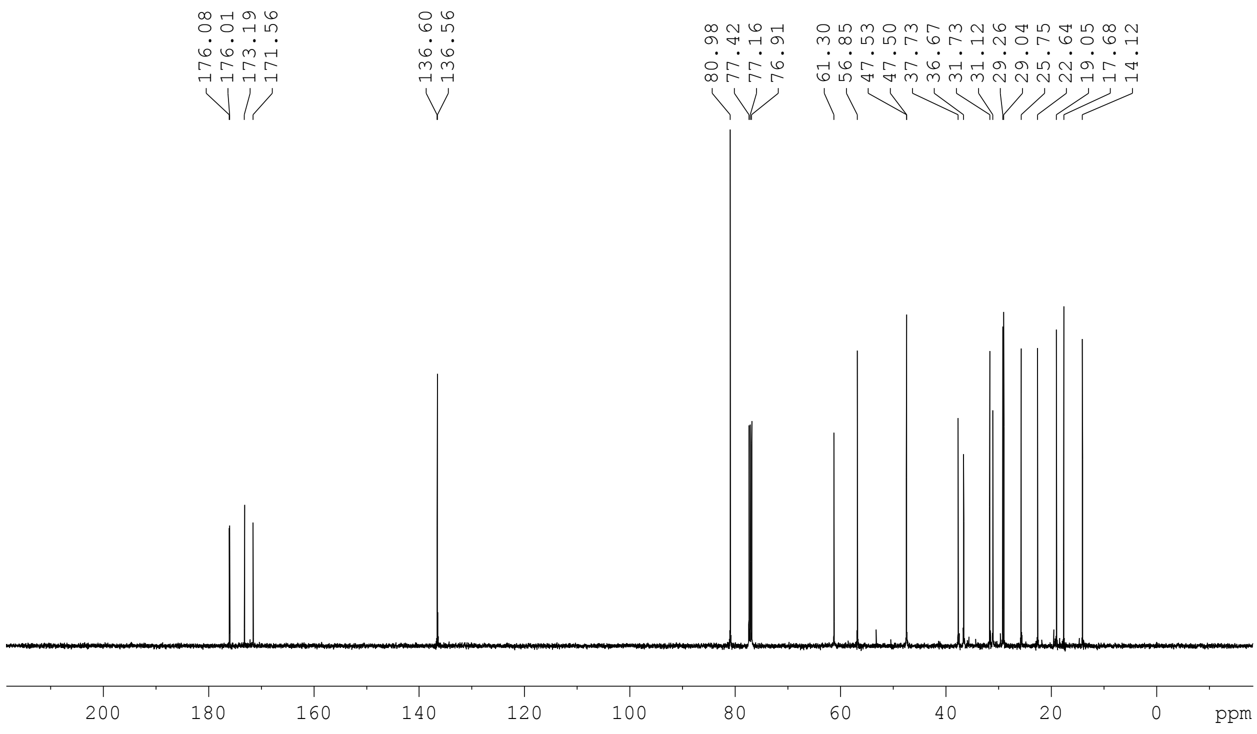
^{1}H NMR spectrum of compound **10c**



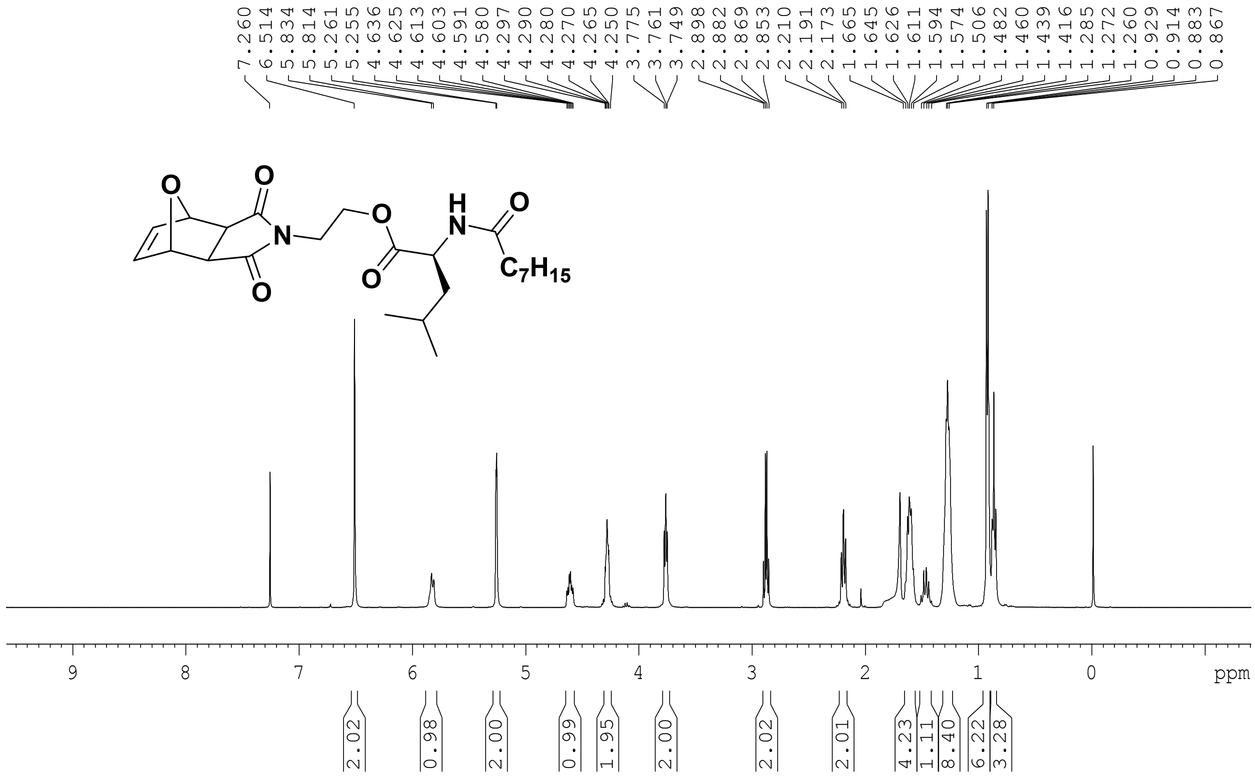
^{13}C NMR spectrum of compound **10c**



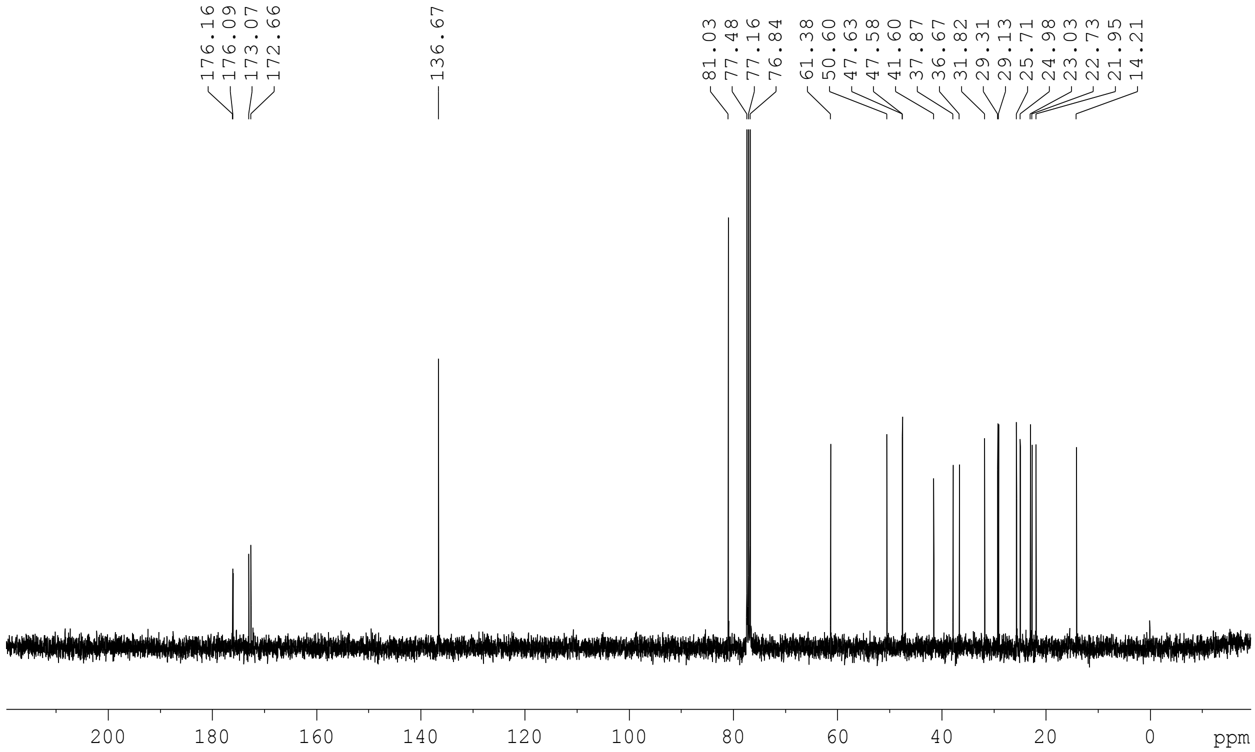
^{1}H NMR spectrum of compound **10d**



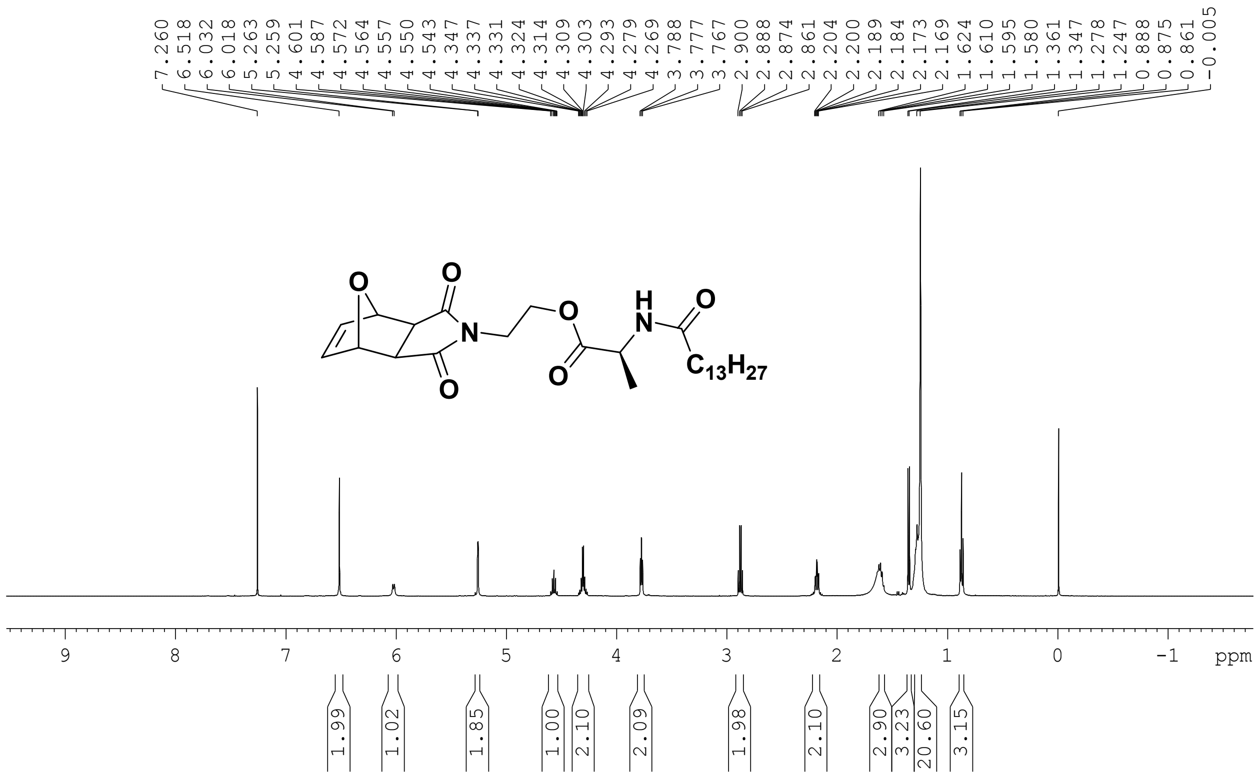
^{13}C NMR spectrum of compound **10d**



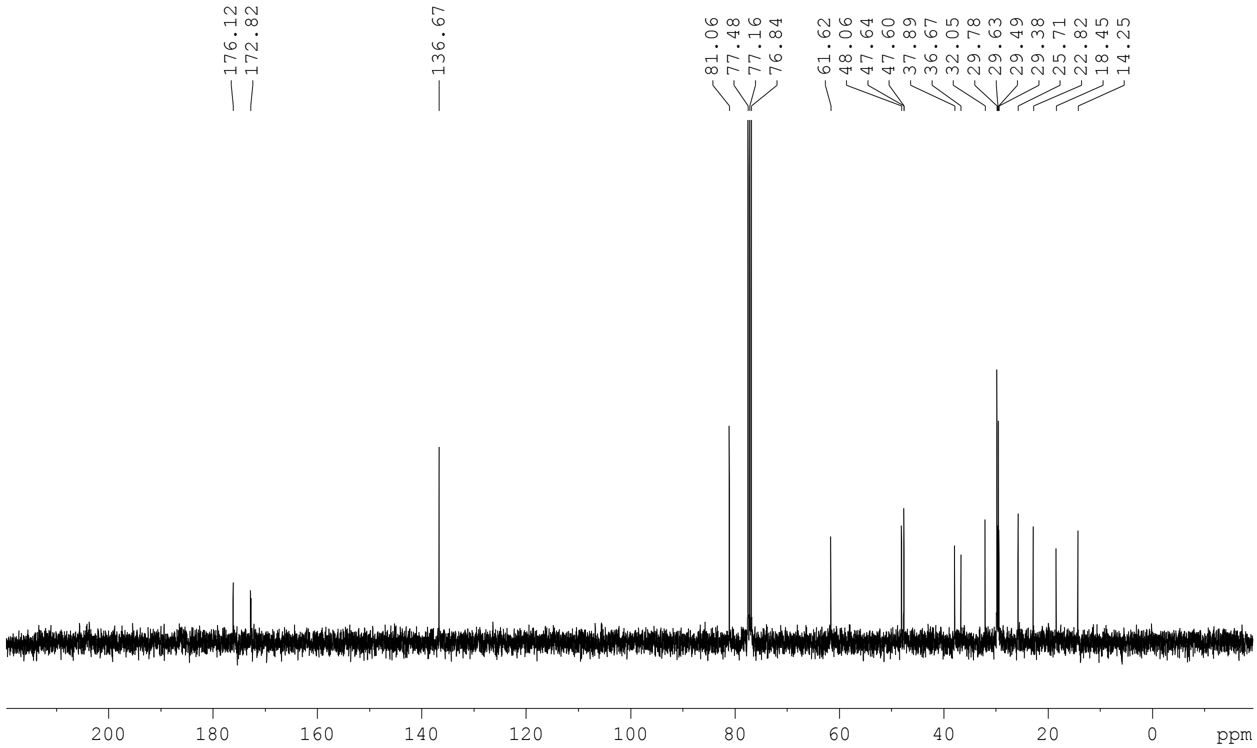
[1]H NMR spectrum of compound **10e**



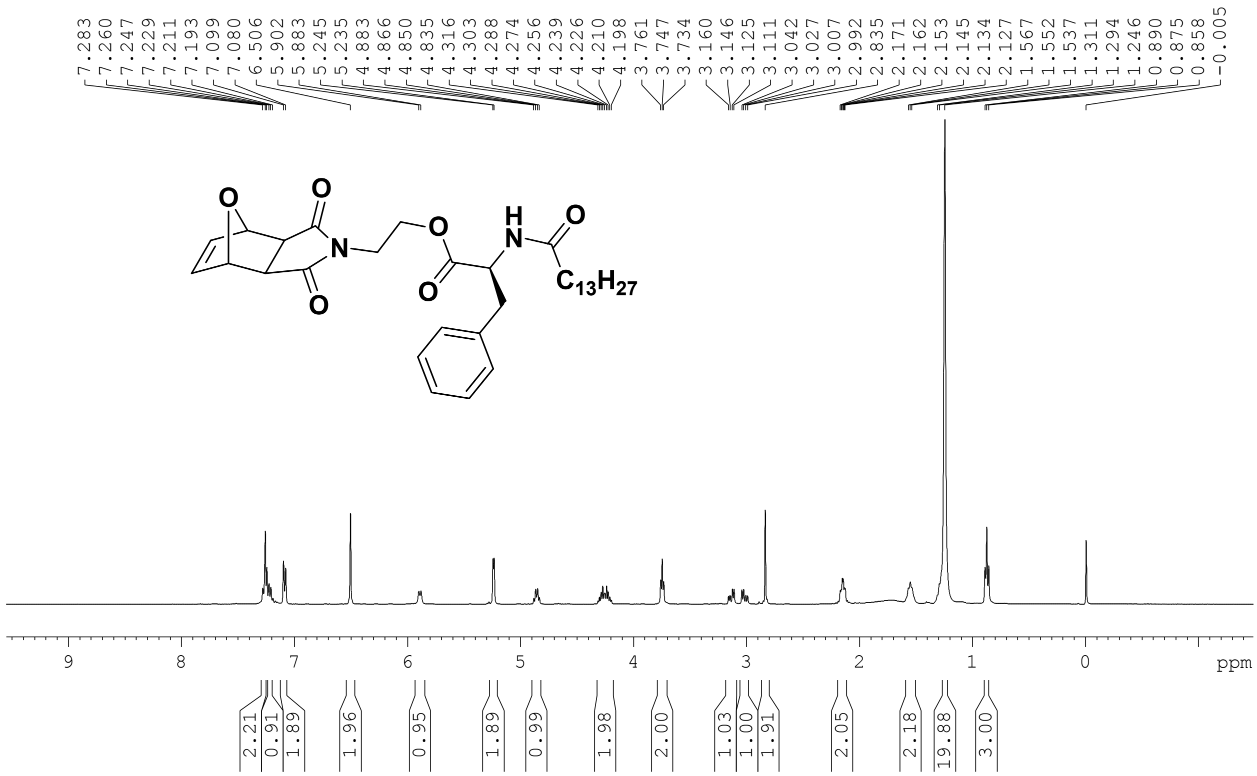
[13]C NMR spectrum of compound **10e**



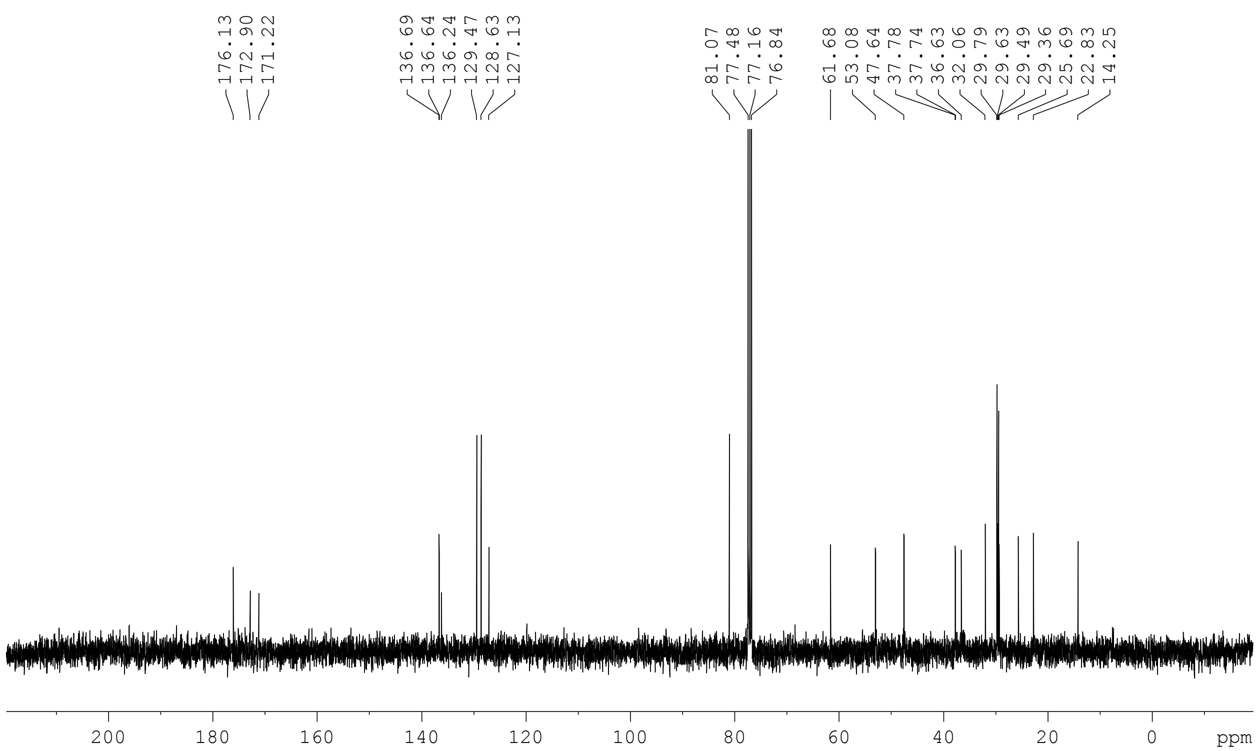
[1]H NMR spectrum of compound **11a**



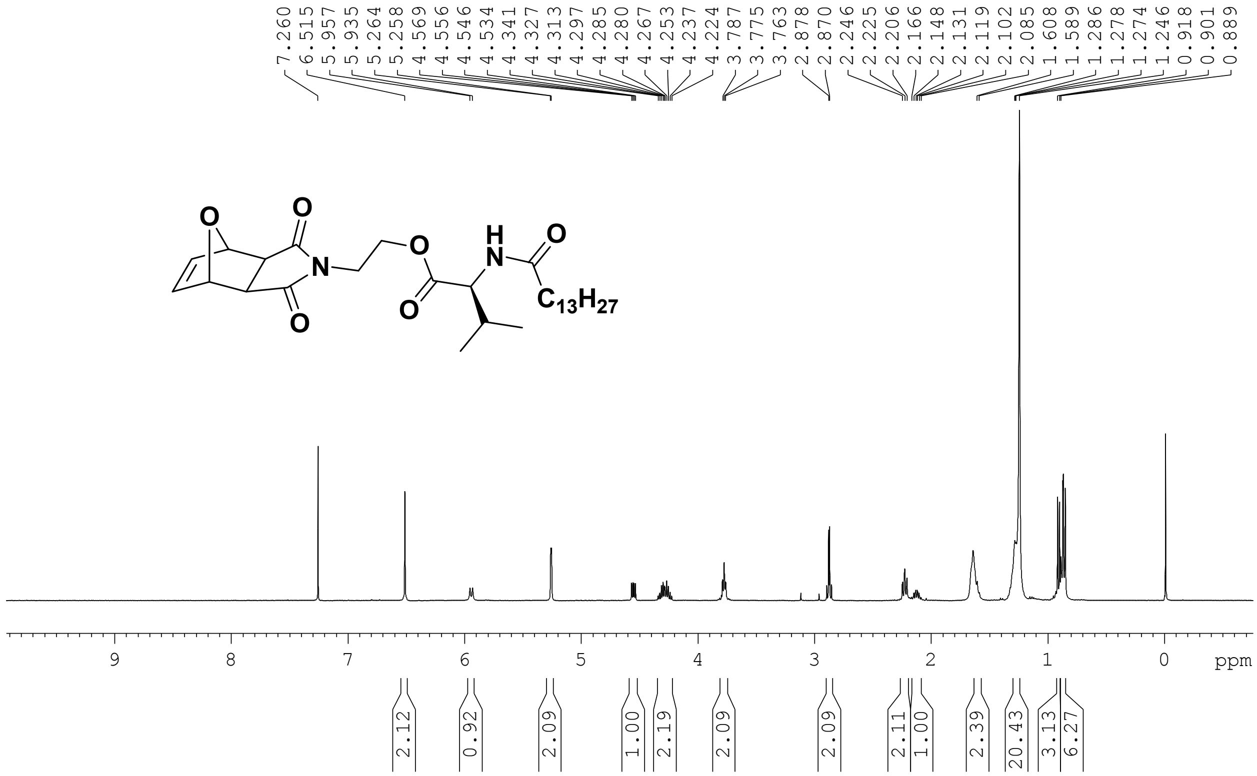
[13]C NMR spectrum of compound **11a**



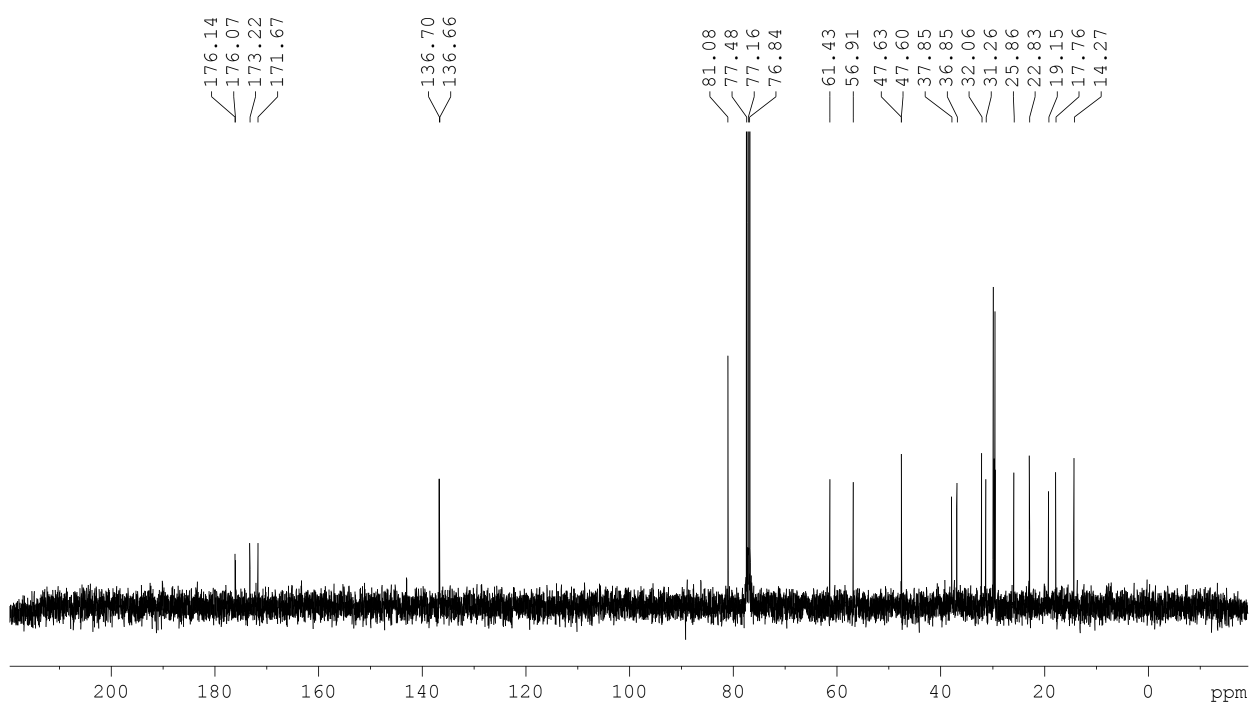
[1]H NMR spectrum of compound **11b**



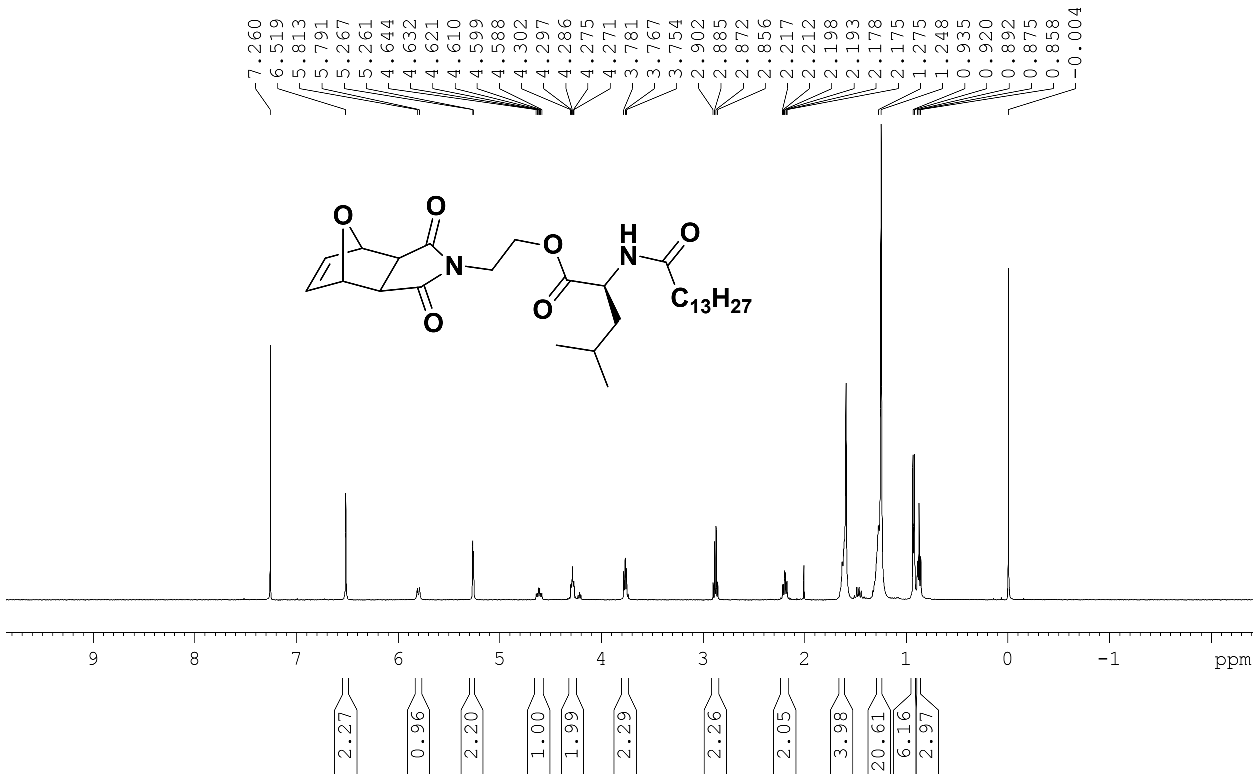
[13]C NMR spectrum of compound **11b**



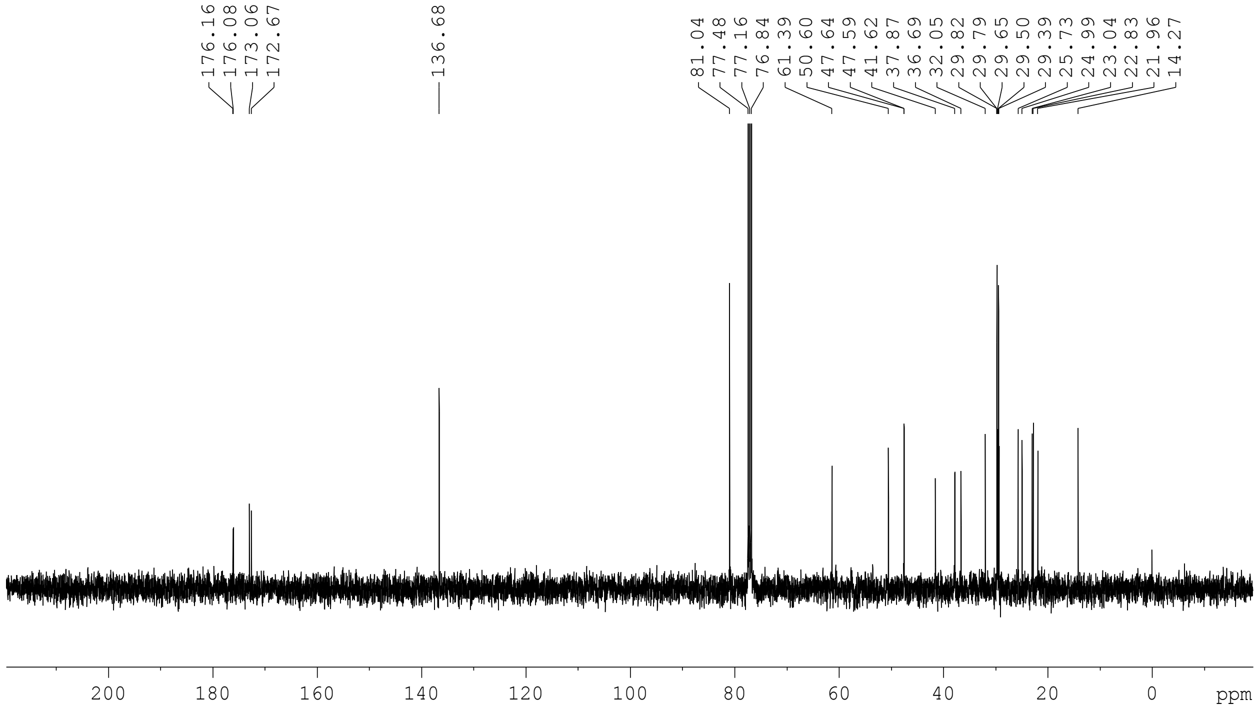
[1]H NMR spectrum of compound **11c**



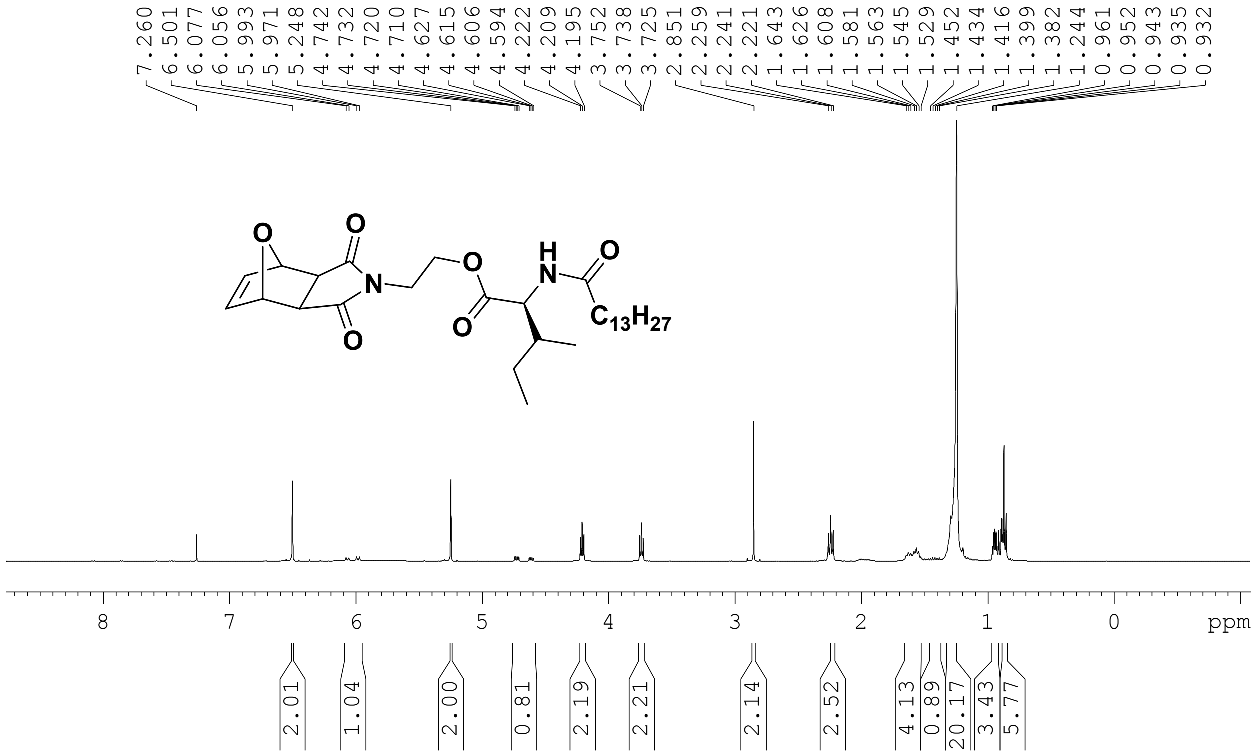
[13]C NMR spectrum of compound **11c**



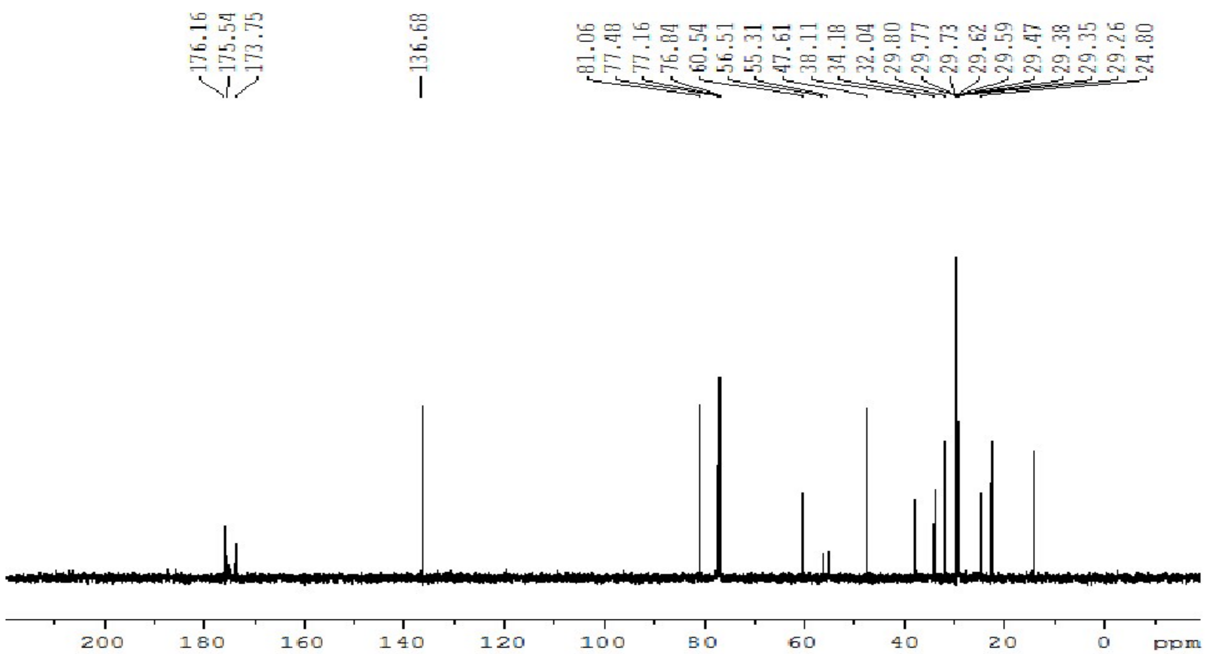
[1]H NMR spectrum of compound **11d**



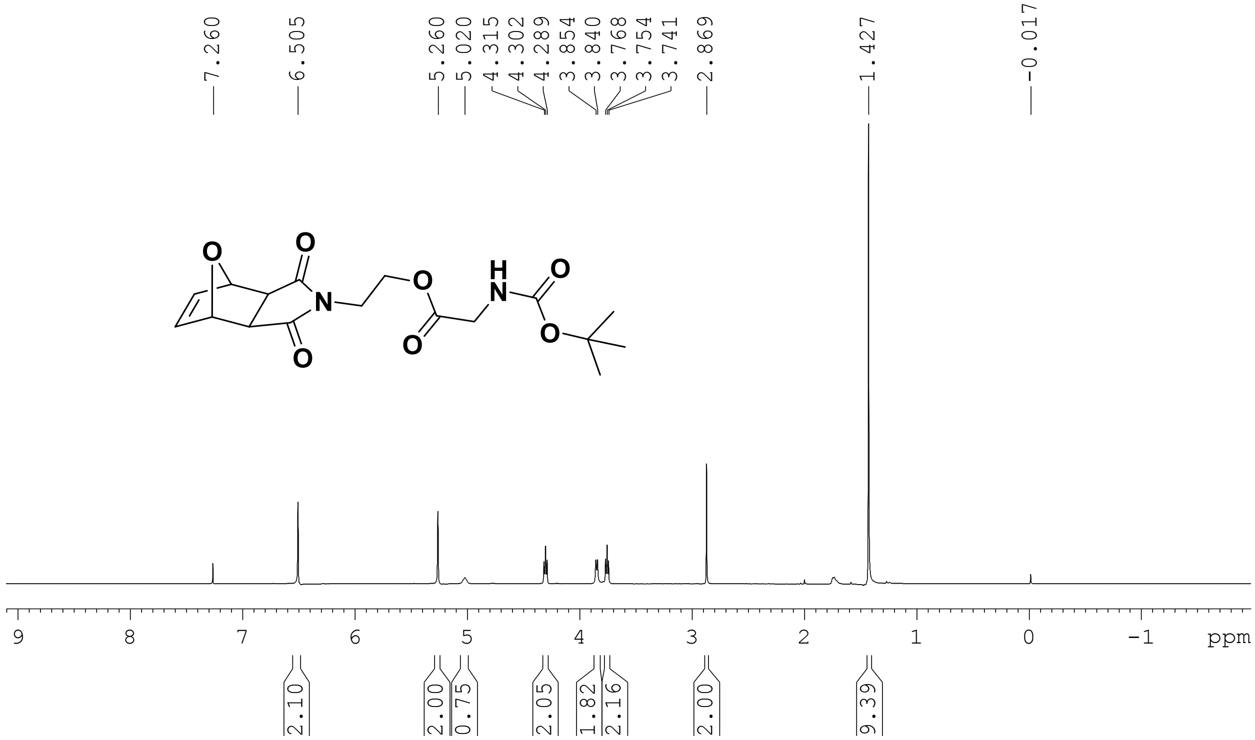
[13]C NMR spectrum of compound **11d**



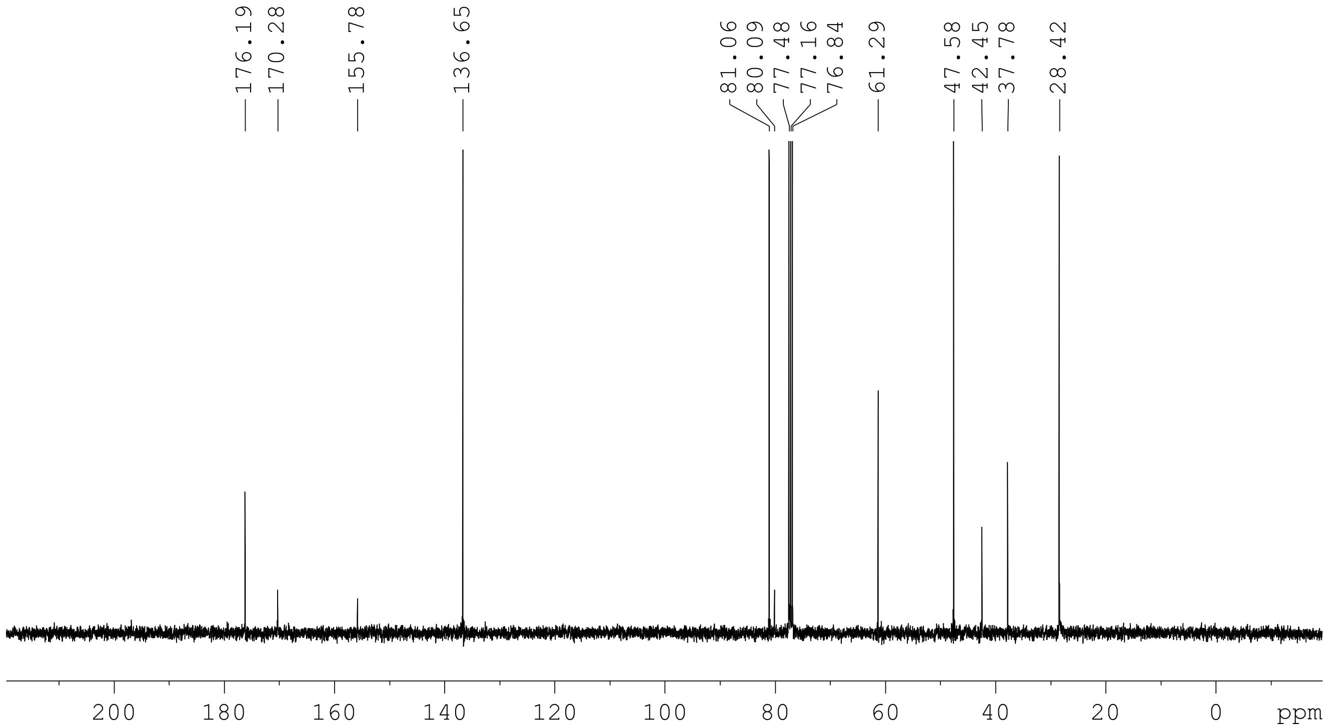
^{1}H NMR spectrum of compound **11e**



^{13}C NMR spectrum of compound **11e**

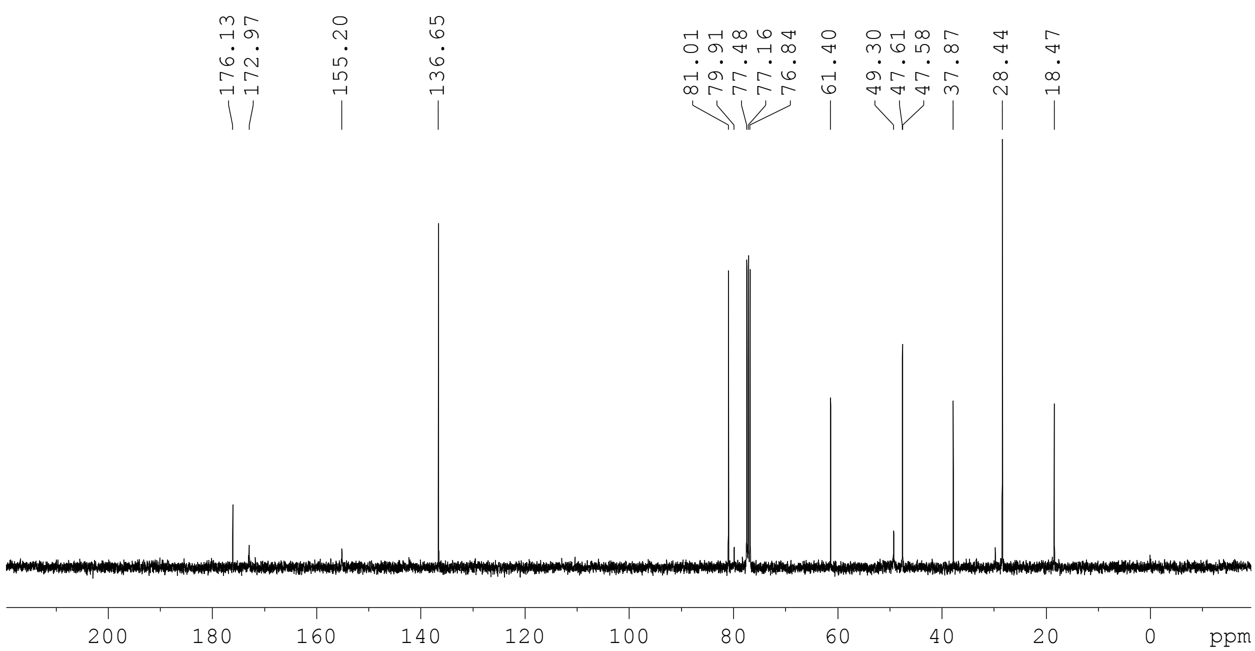


[1]H NMR spectrum of compound **12a**



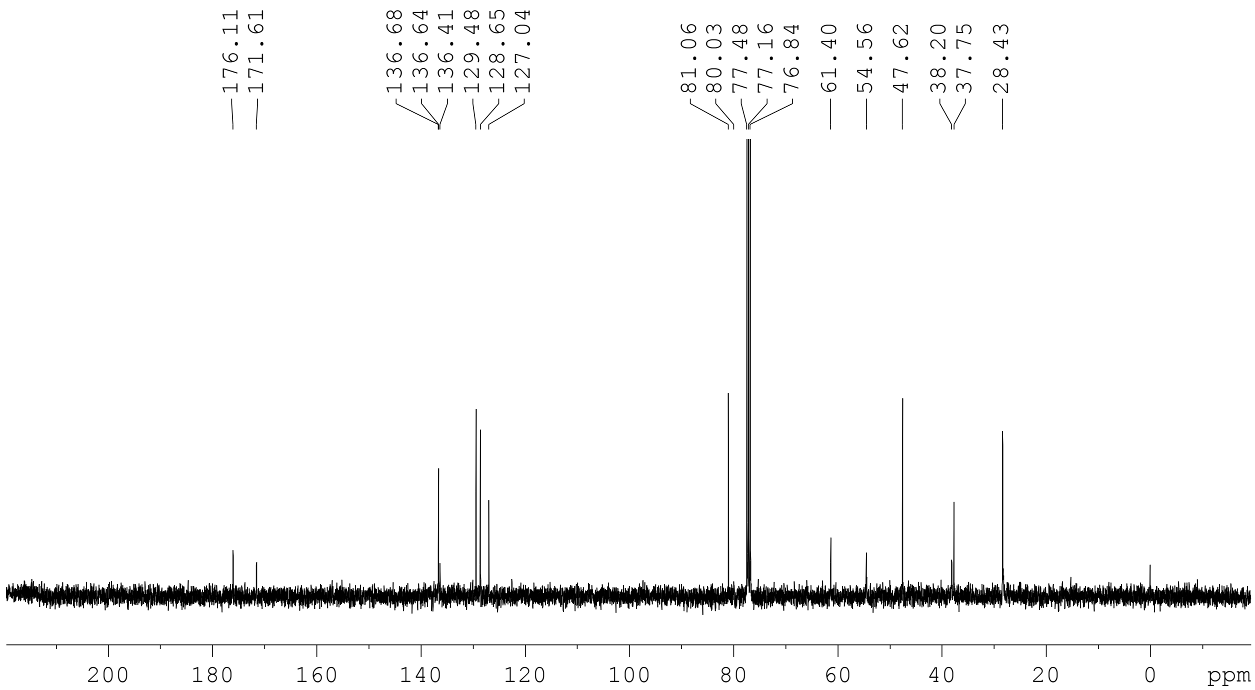
[13]C NMR spectrum of compound **12a**

[1]H NMR spectrum of compound **12b**

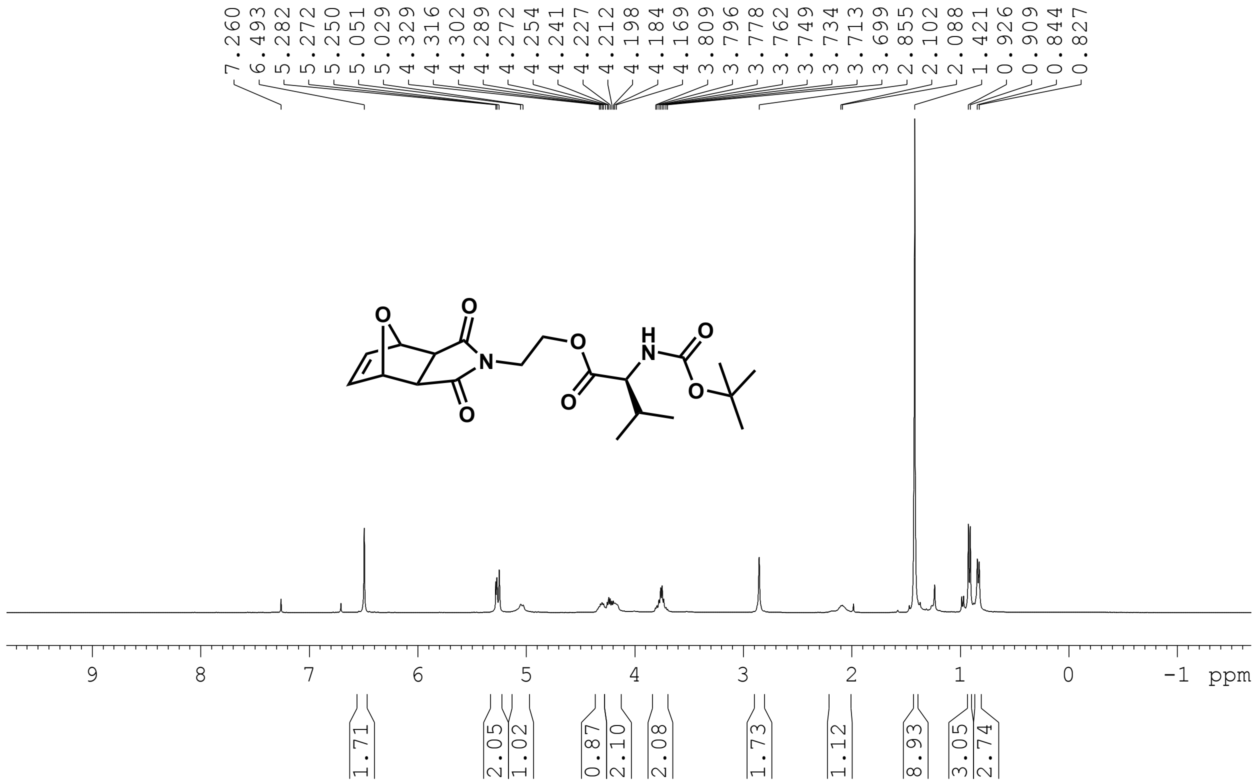


[13]C NMR spectrum of compound **12b**

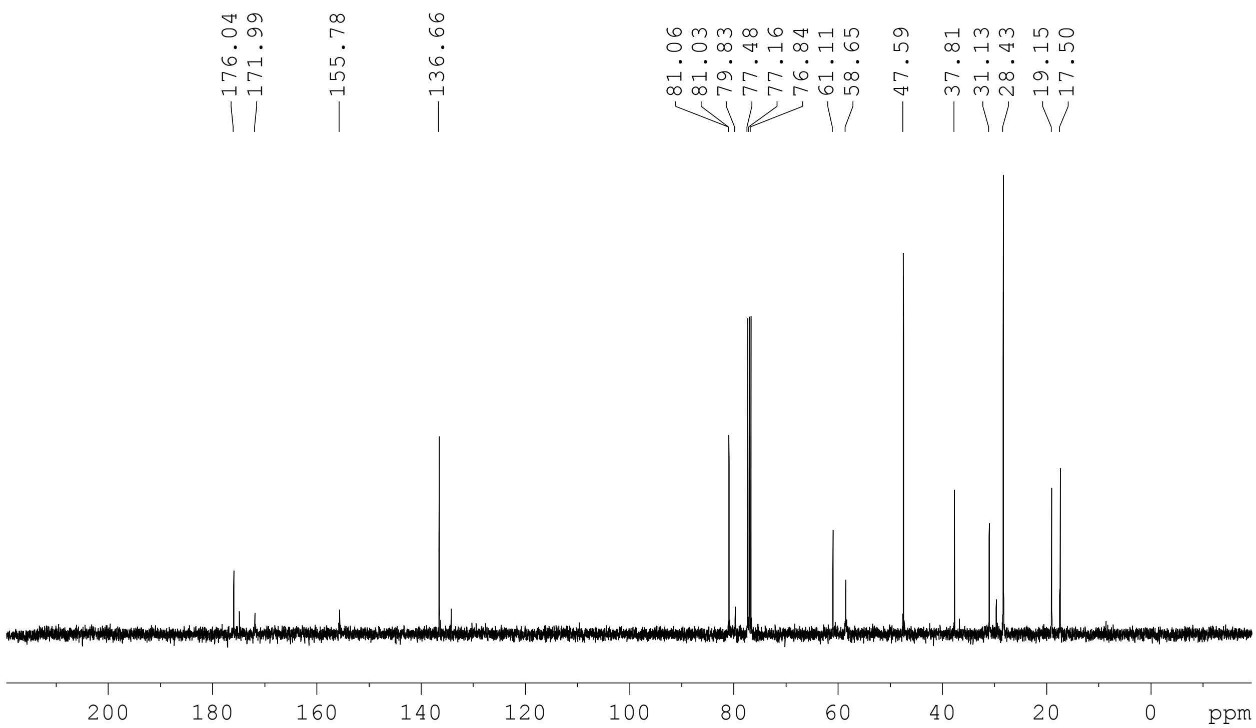
^{1}H NMR spectrum of compound **12c**



^{13}C NMR spectrum of compound **12c**

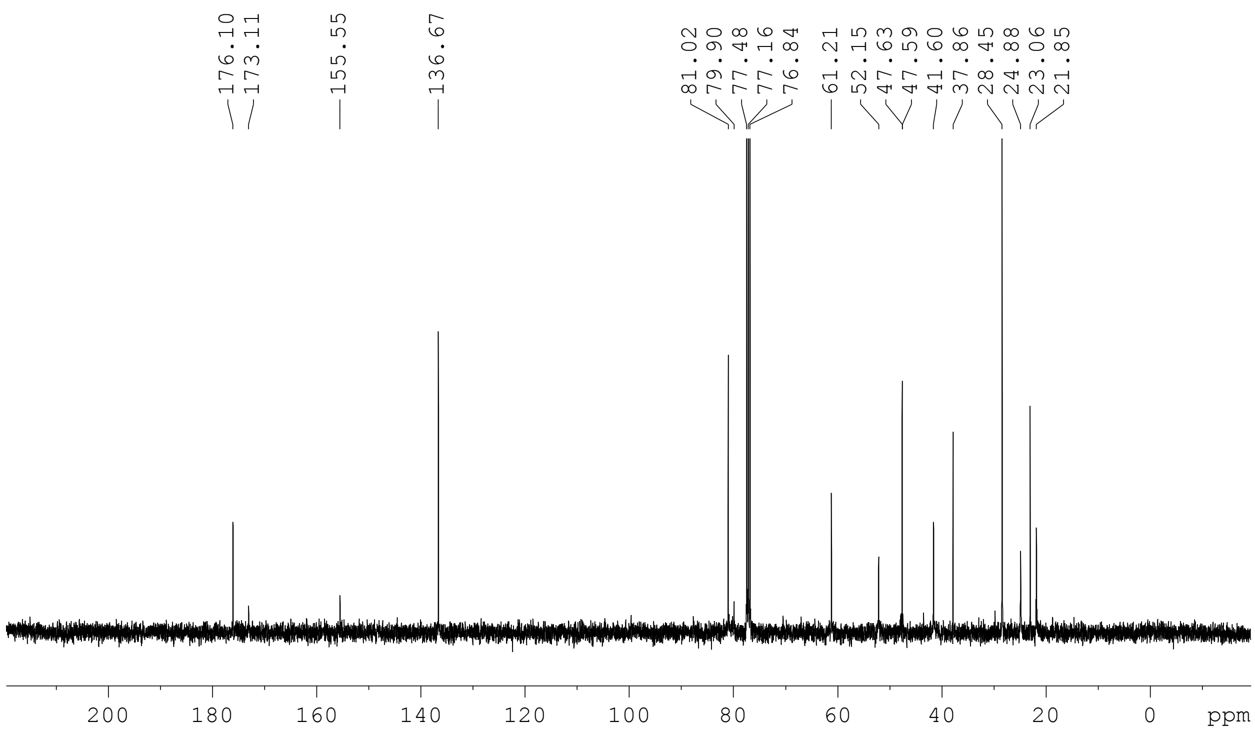


[1]H NMR spectrum of compound **12d**

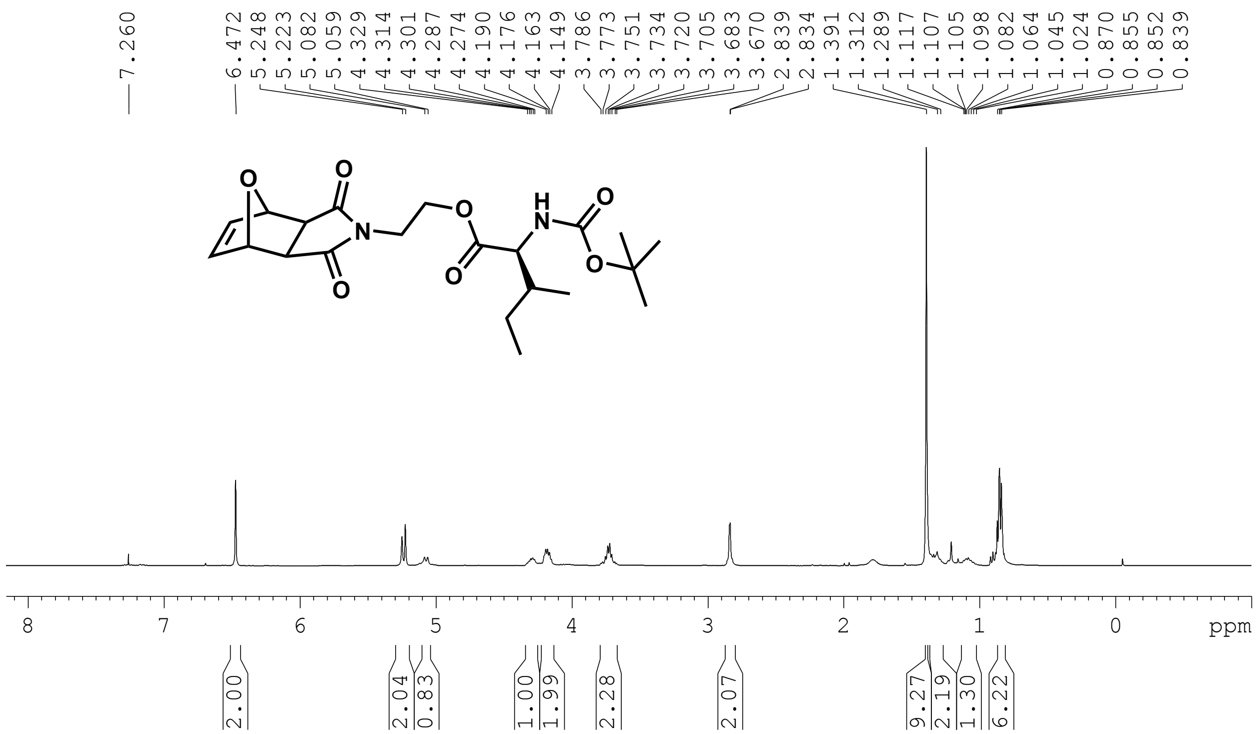


[1]H NMR spectrum of compound **12d**

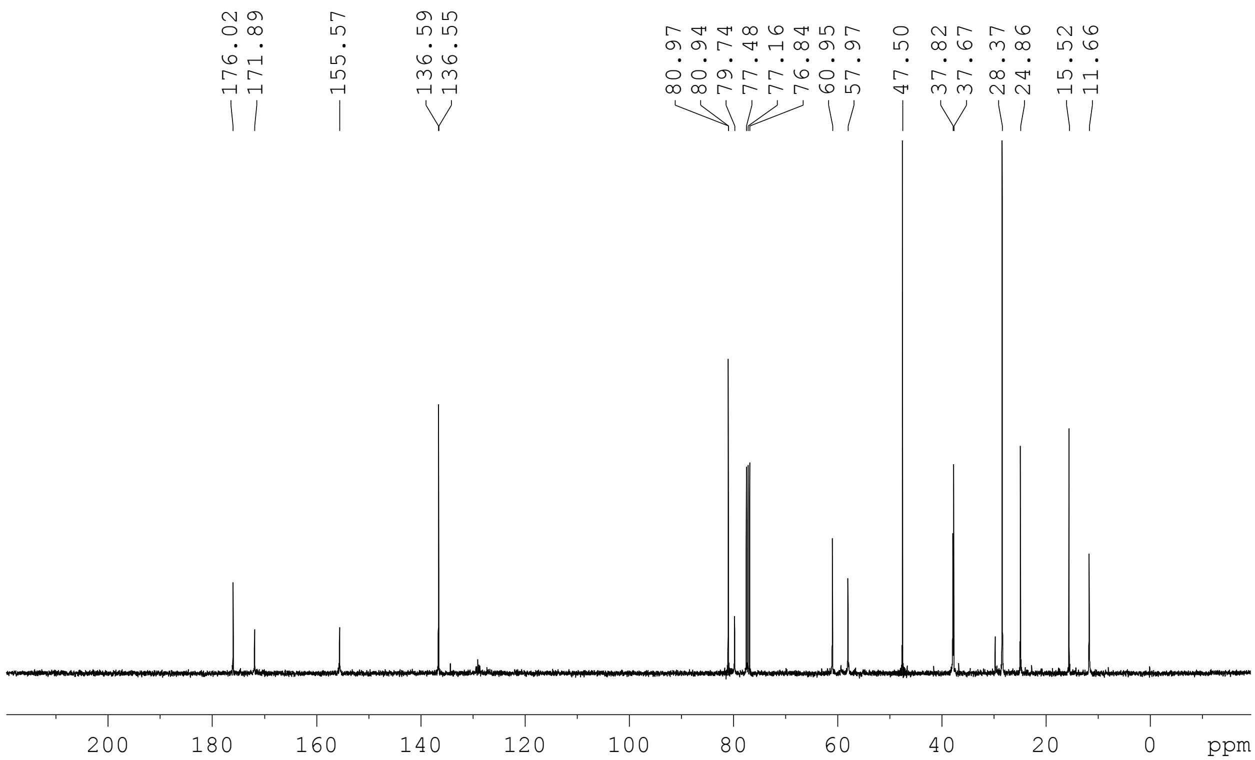
^{1}H NMR spectrum of compound **12e**



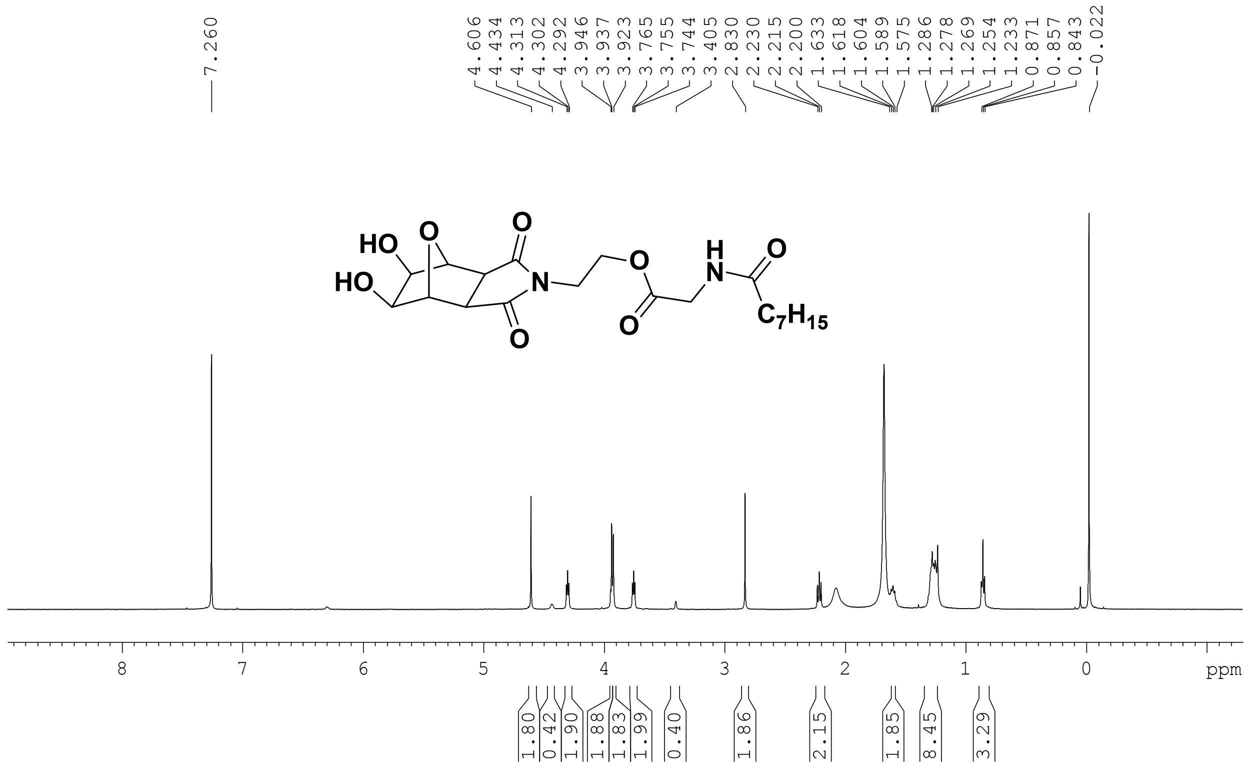
^{13}C NMR spectrum of compound **12e**



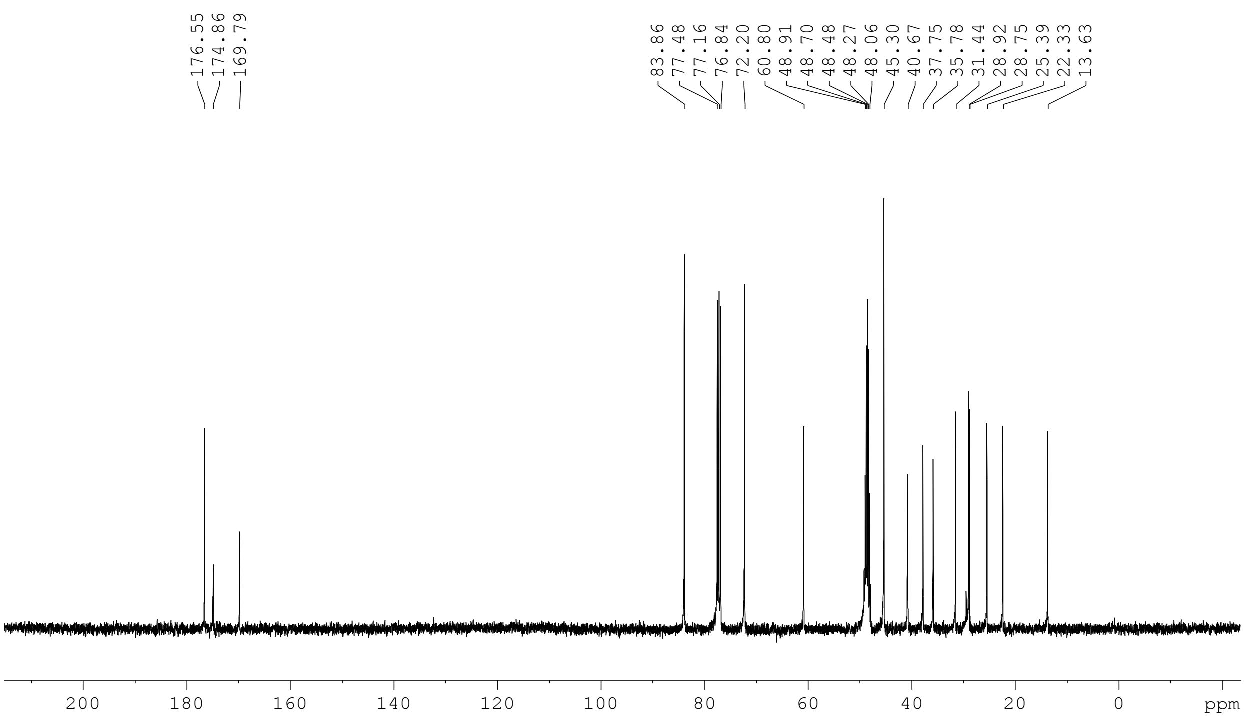
[1]H NMR spectrum of compound **12f**



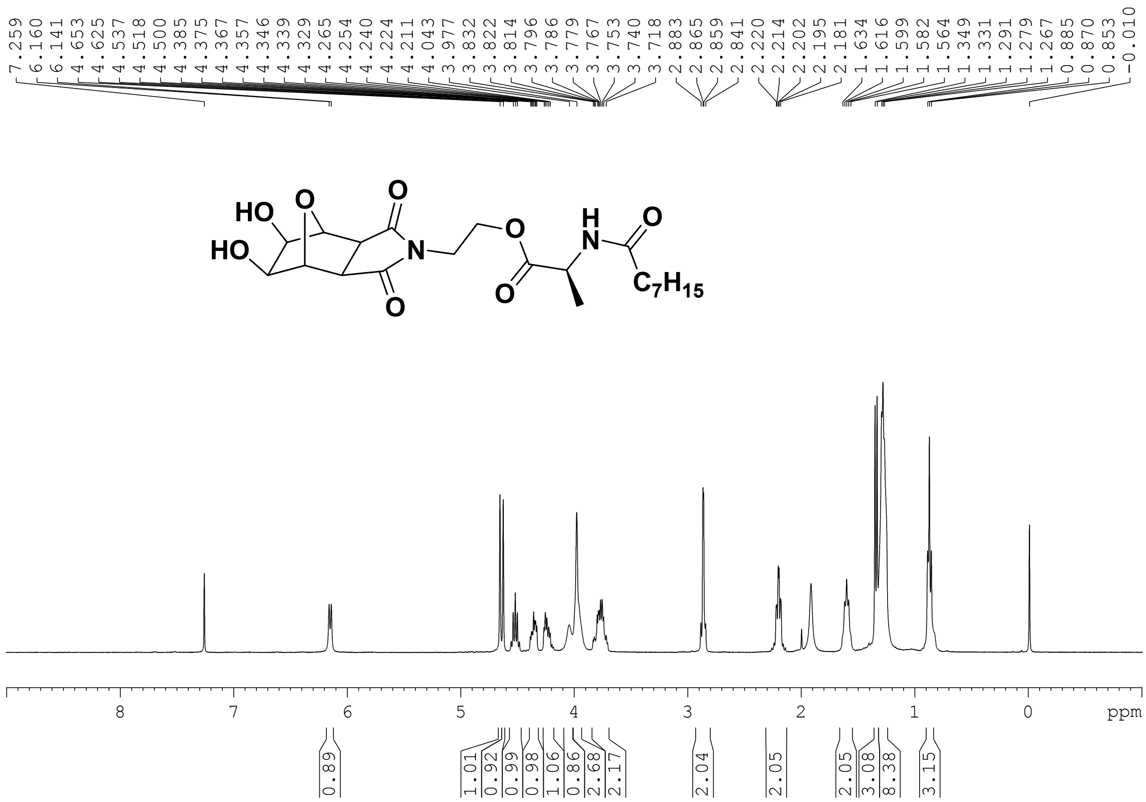
[13]C NMR spectrum of compound **12f**



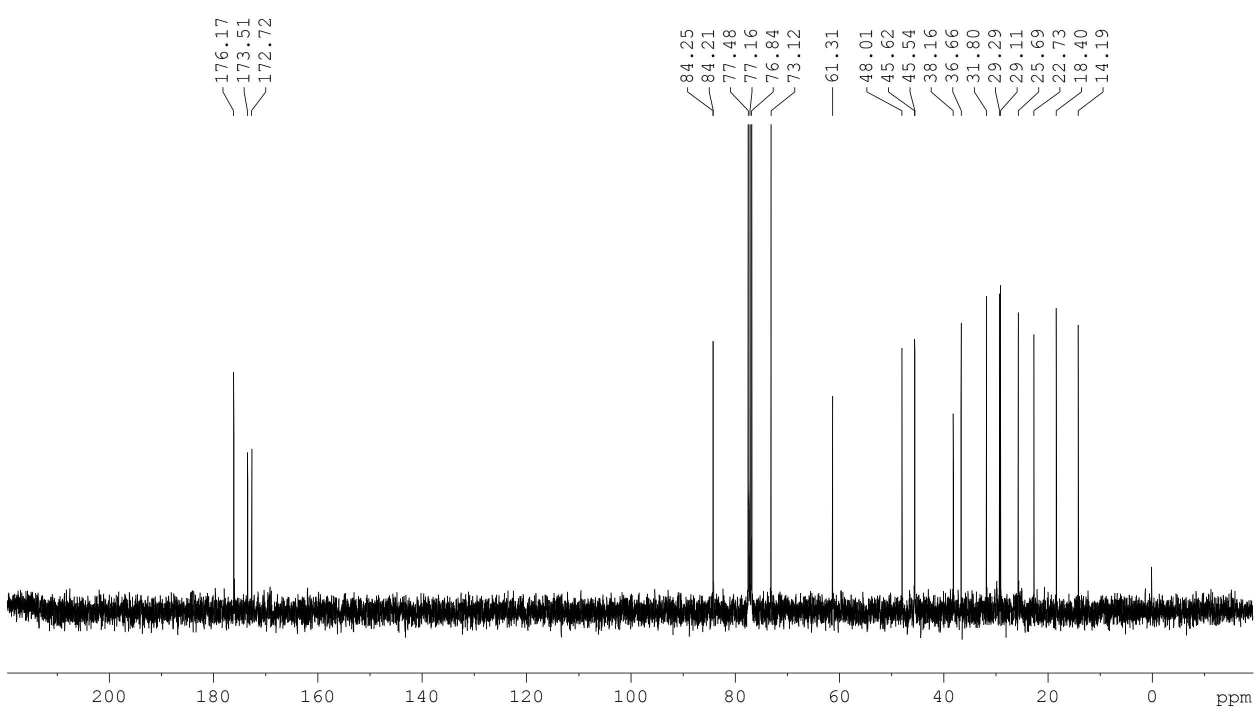
[1]H NMR spectrum of compound **1a**



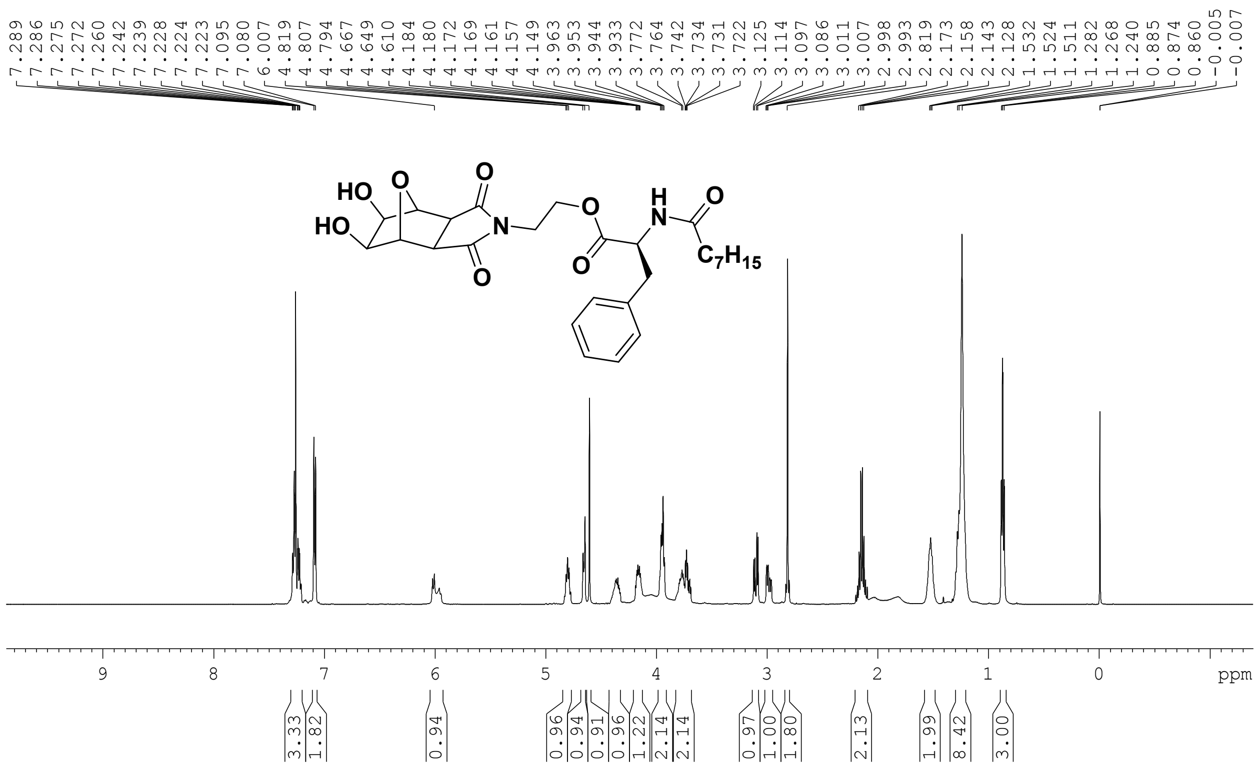
[13]C NMR spectrum of compound **1a**



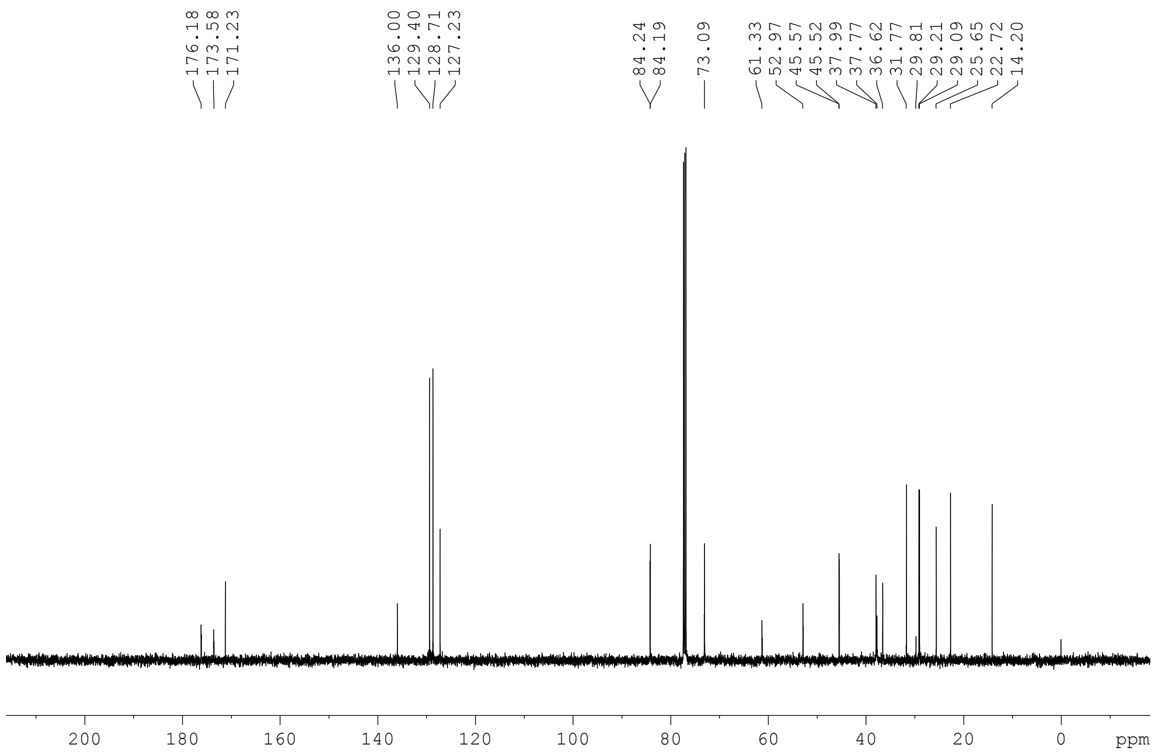
[1]H NMR spectrum of compound **1b**



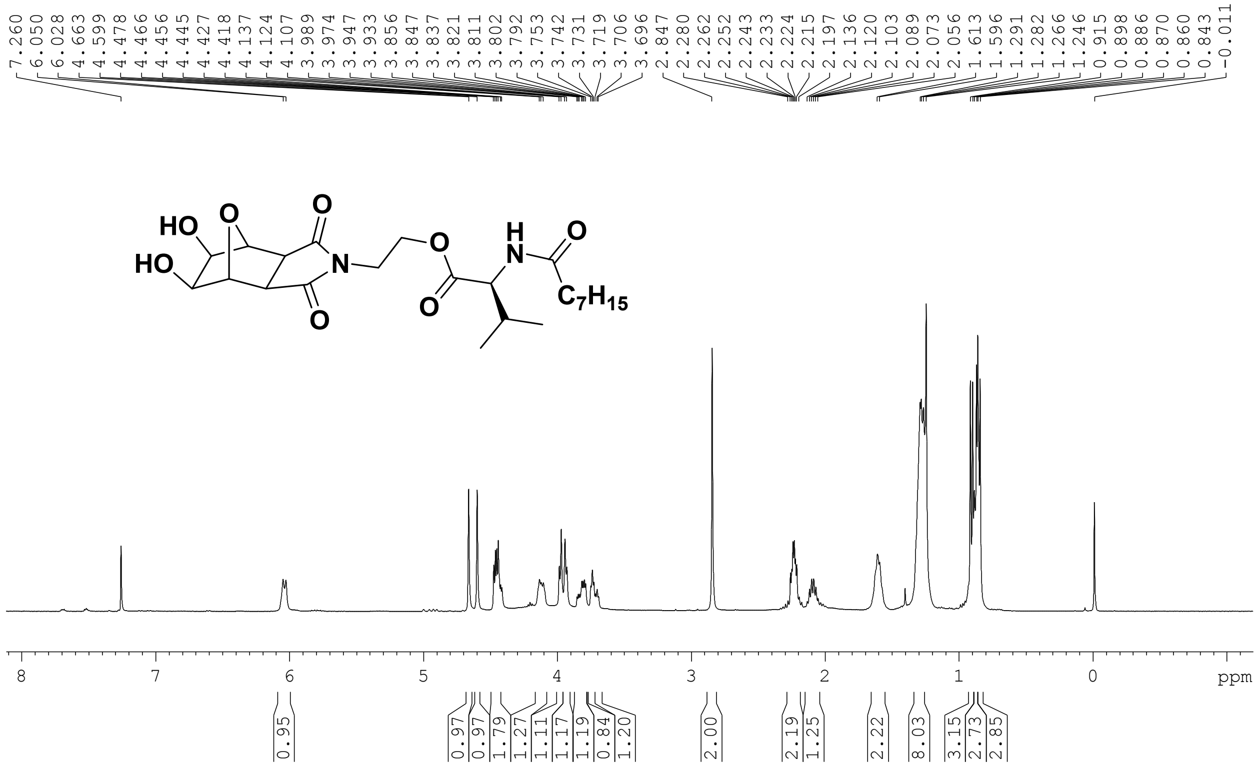
[13]C NMR spectrum of compound **1b**



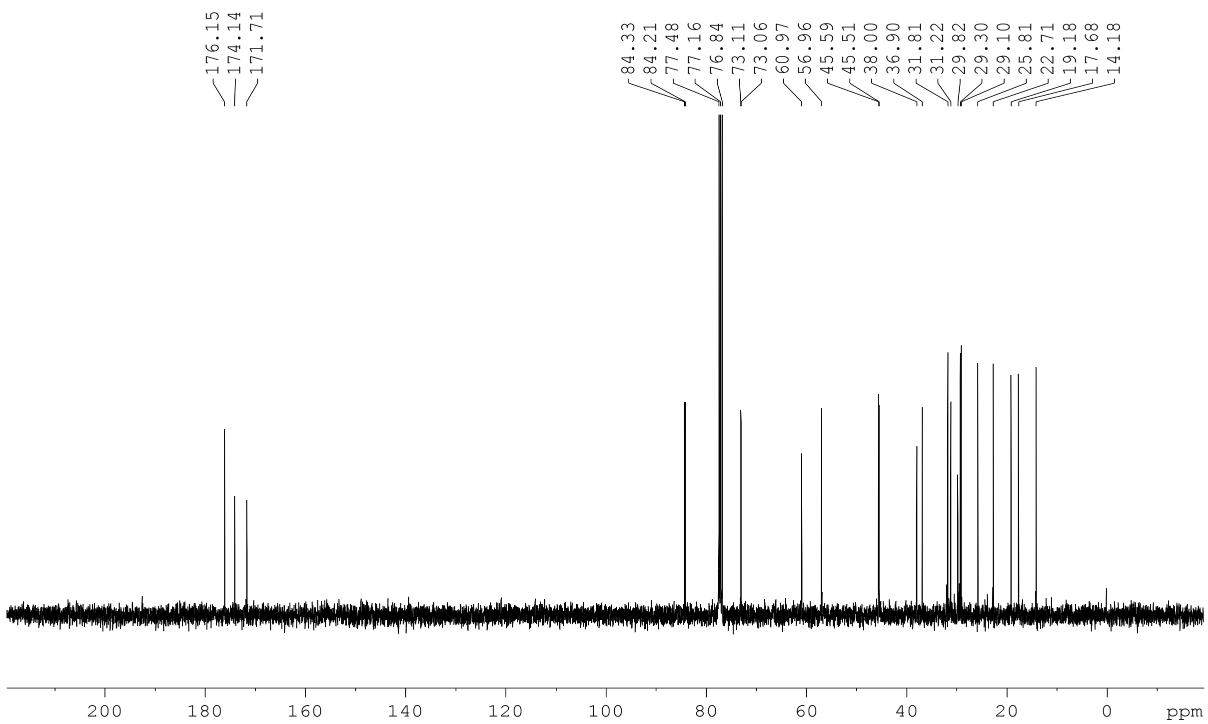
[1]H NMR spectrum of compound **1c**



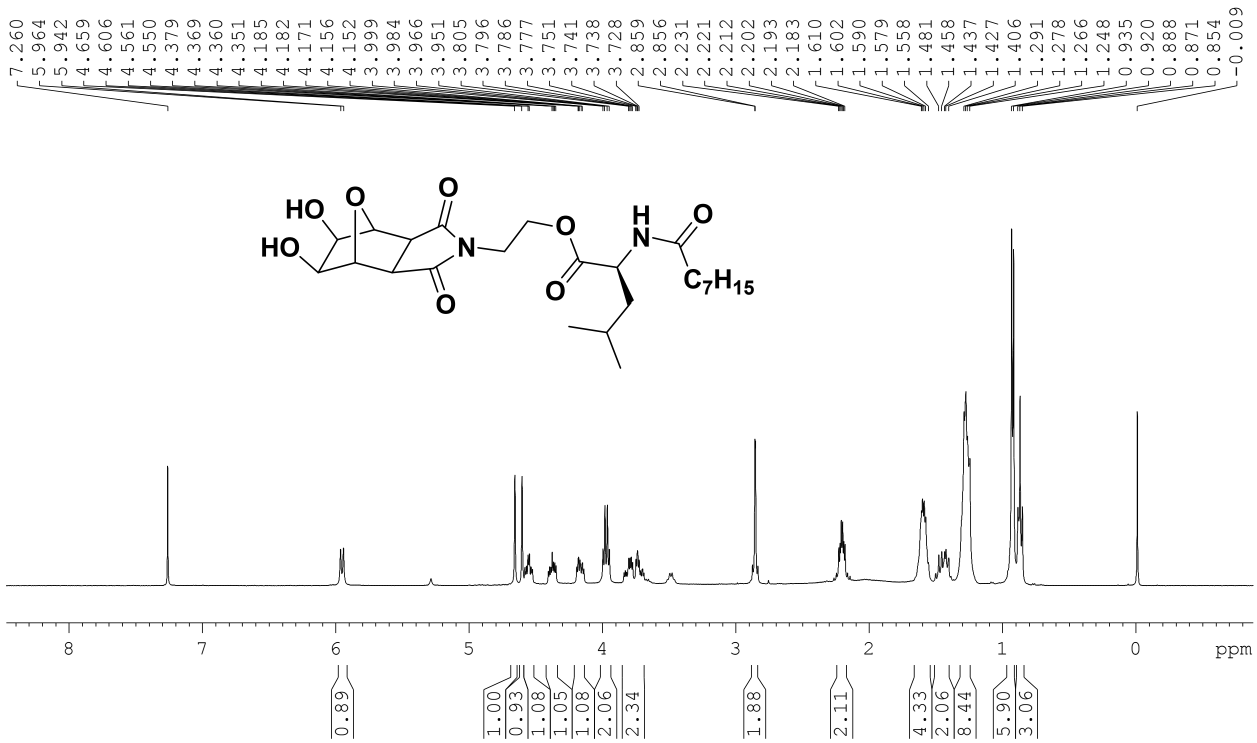
[13]C NMR spectrum of compound **1c**



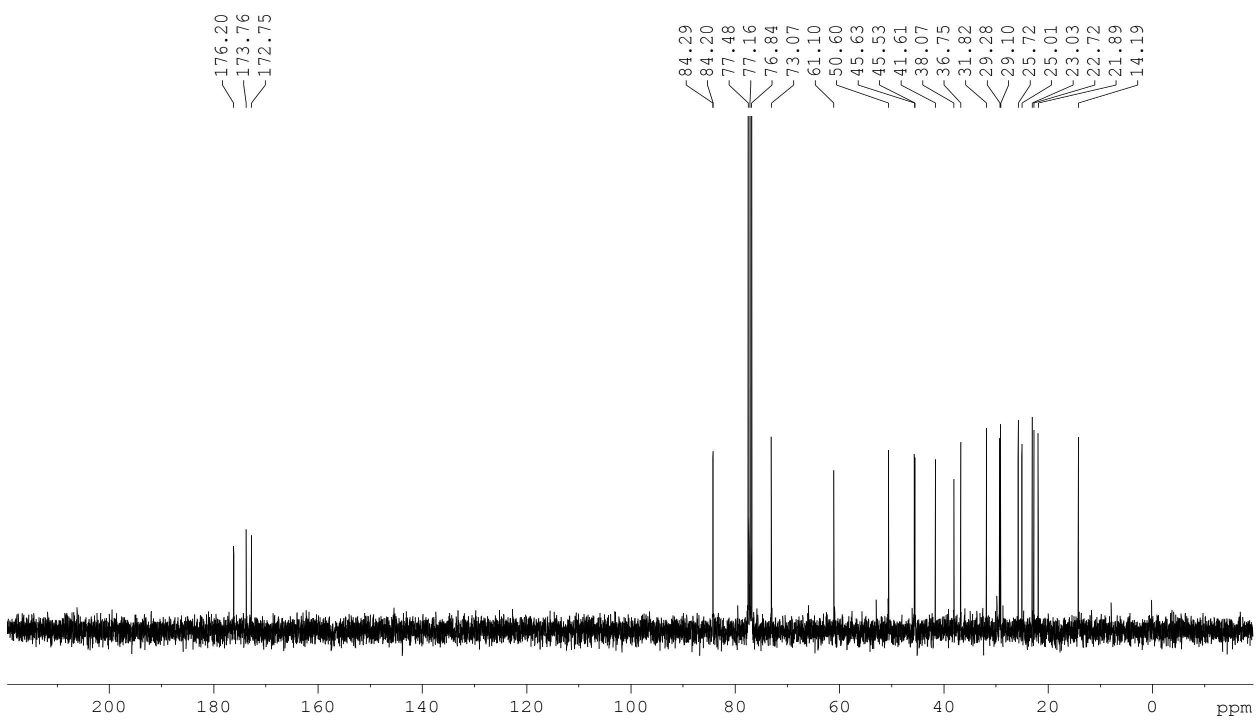
[1]H NMR spectrum of compound **1d**



[13]C NMR spectrum of compound **1d**

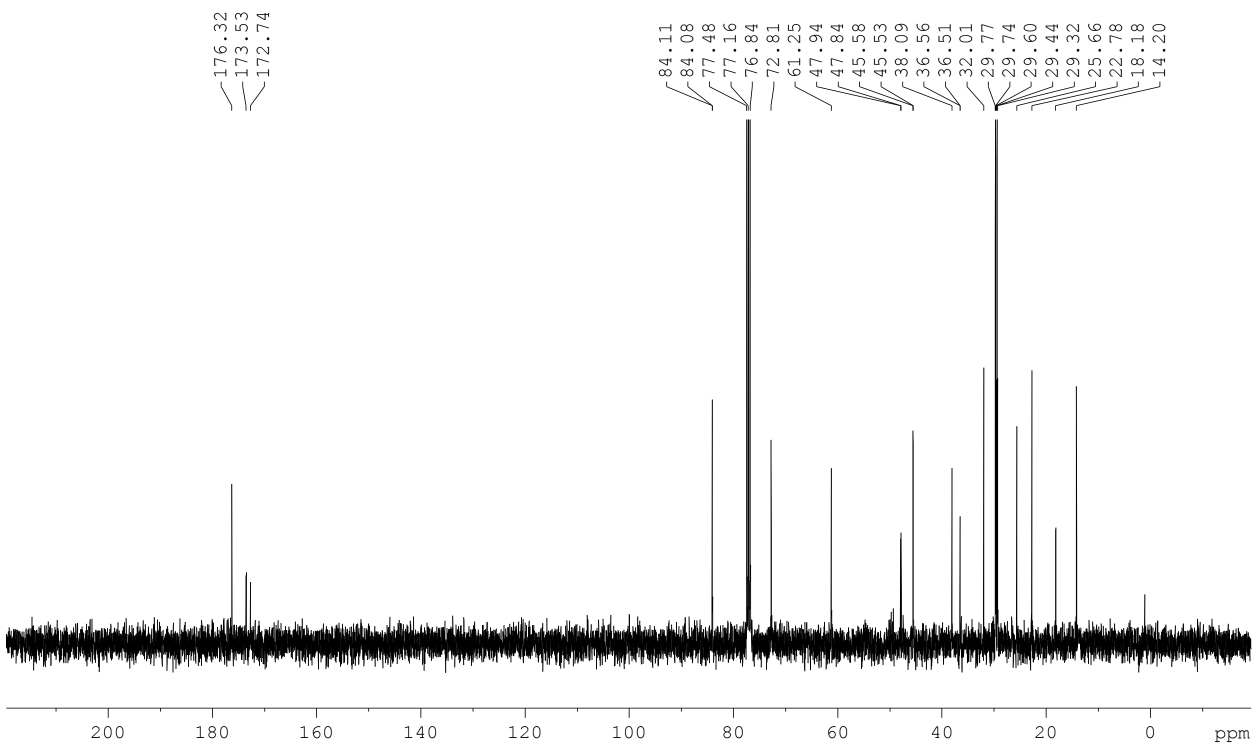


[1]H NMR spectrum of compound **1e**



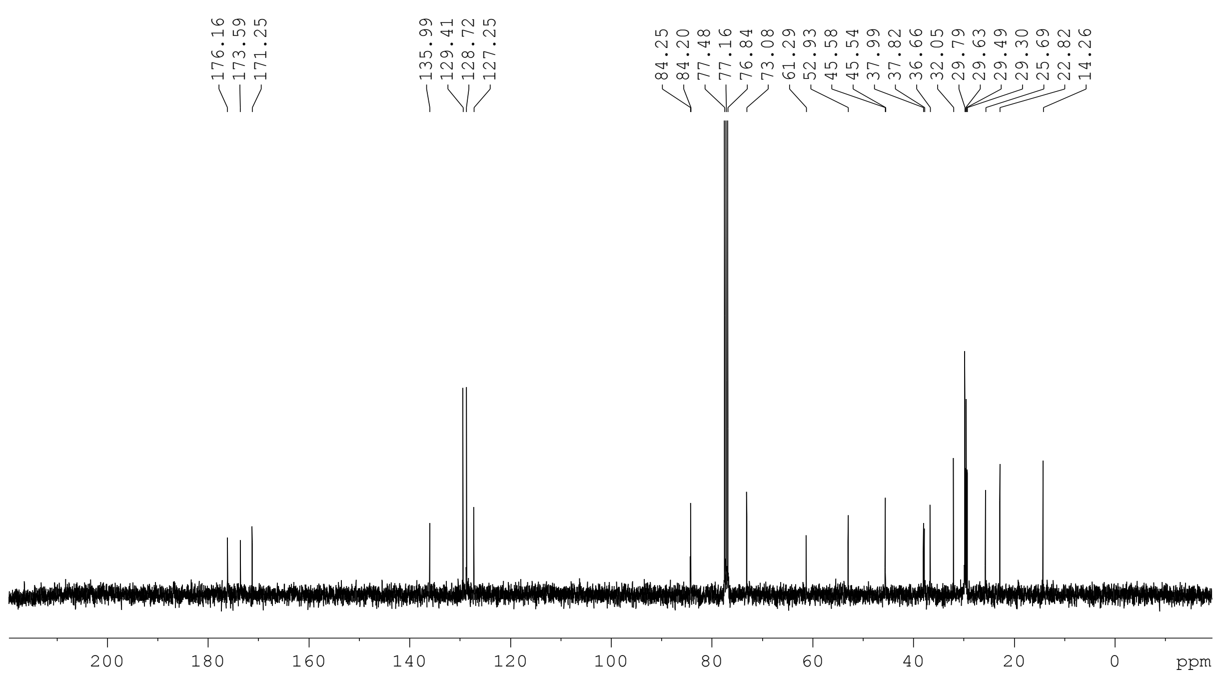
[13]C NMR spectrum of compound **1e**

[1]H NMR spectrum of compound **2a**

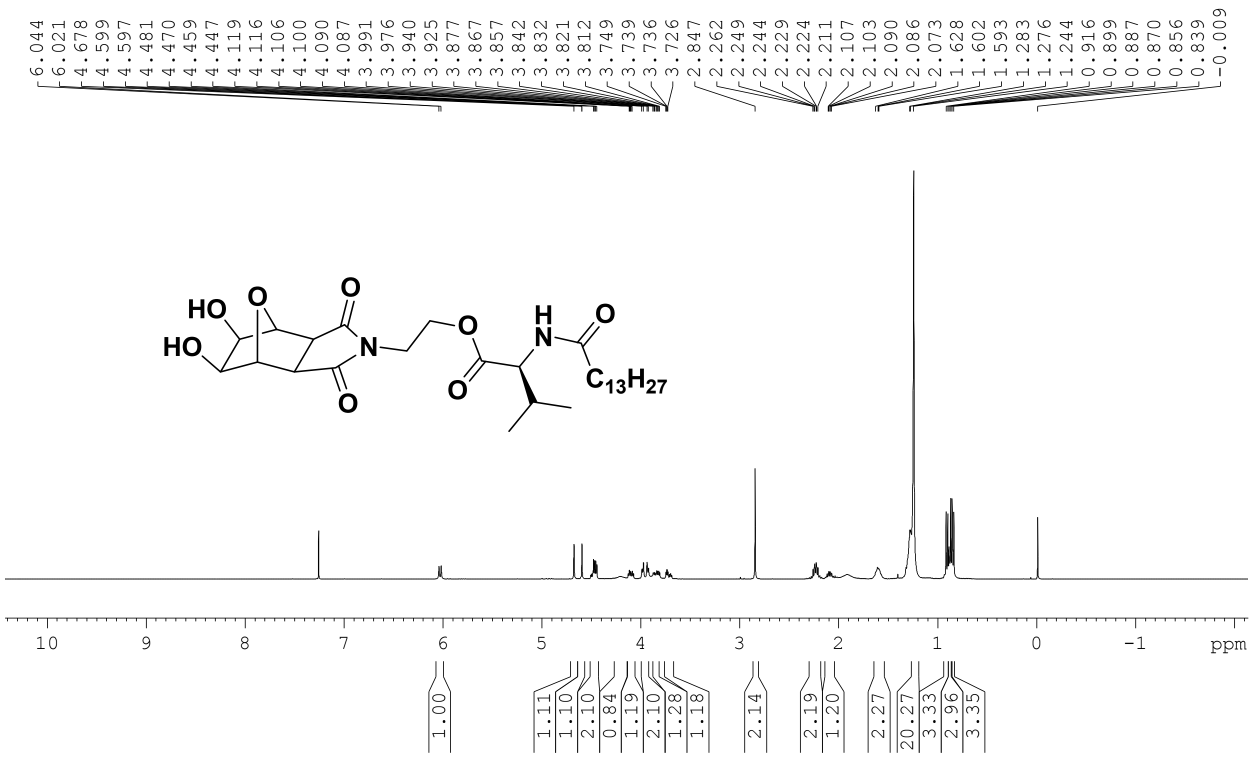


[13]C NMR spectrum of compound **2a**

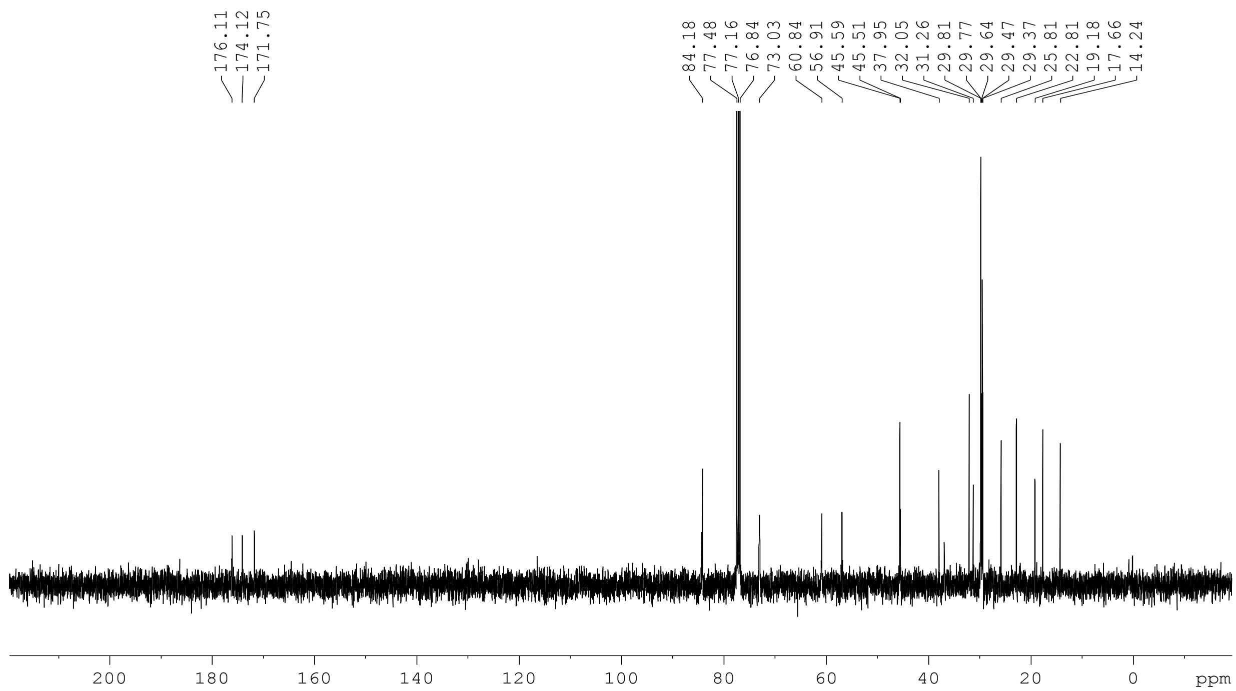
[1]H NMR spectrum of compound **2b**



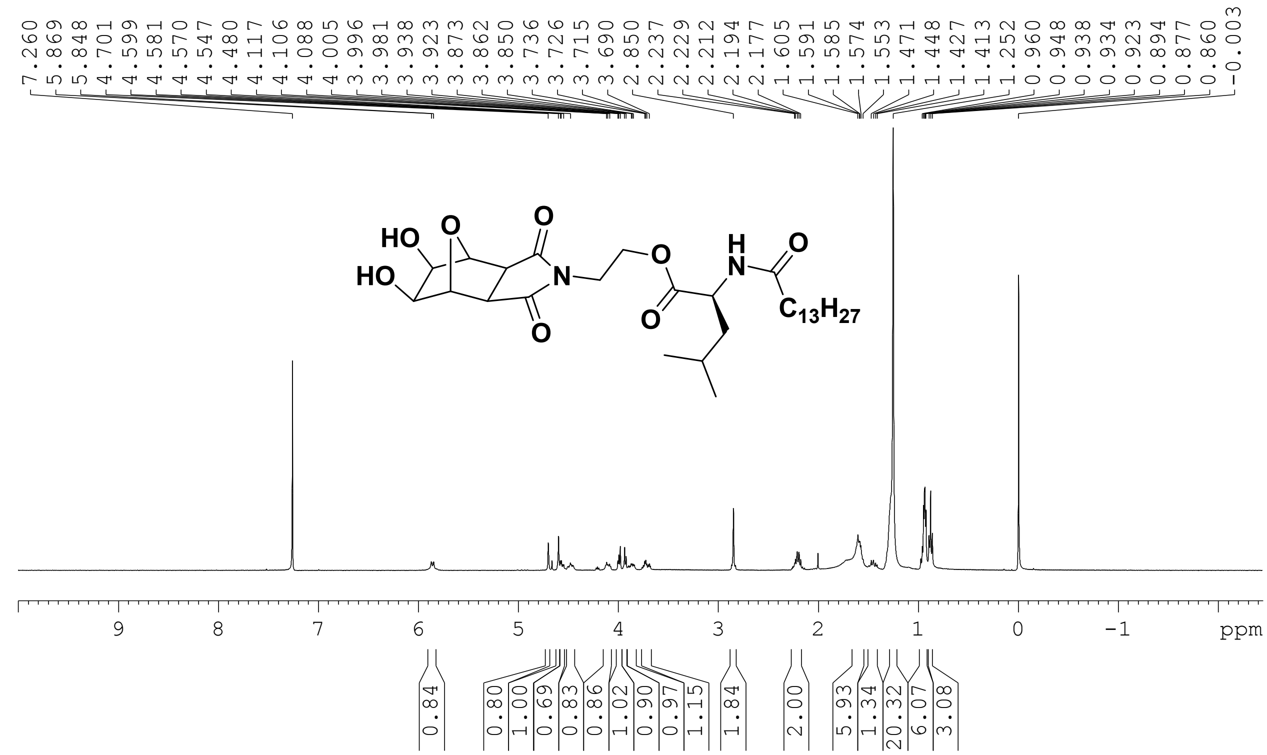
[13]C NMR spectrum of compound **2b**



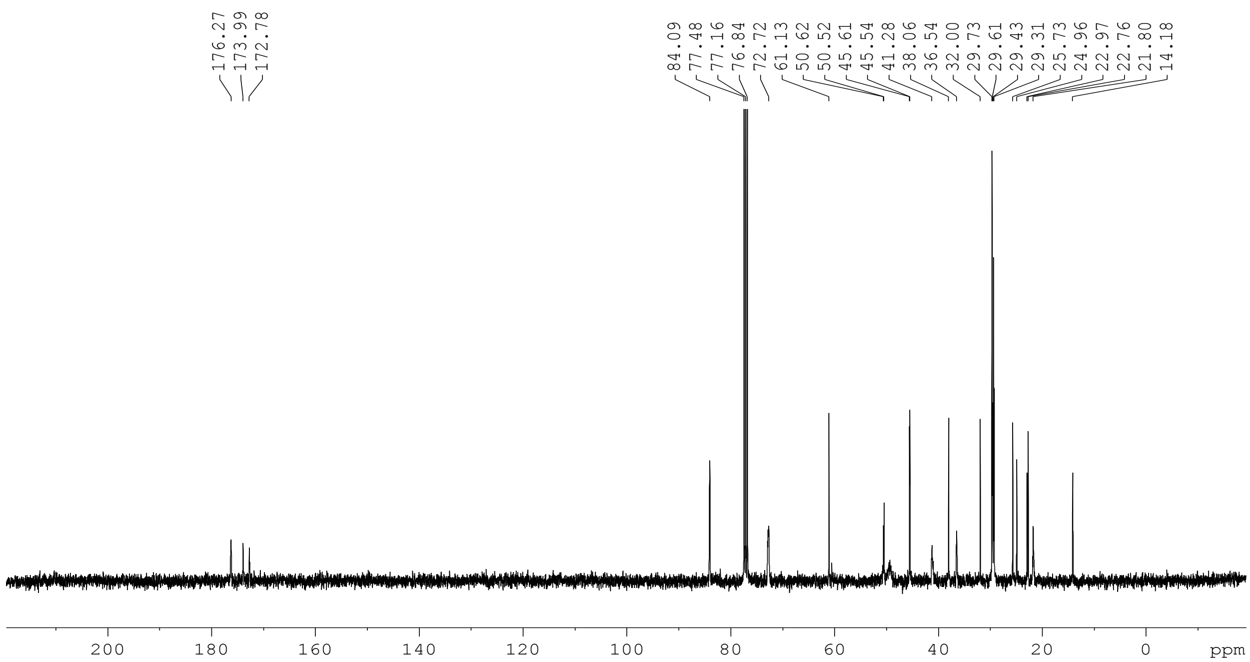
[1]H NMR spectrum of compound **2c**



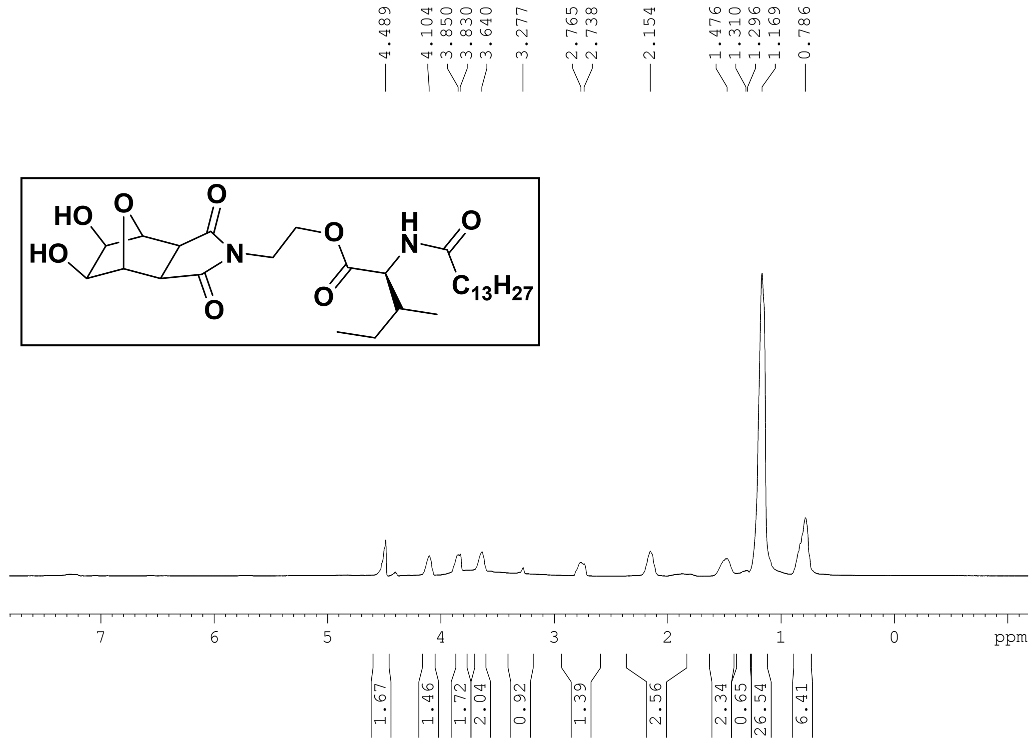
[13]C NMR spectrum of compound **2c**



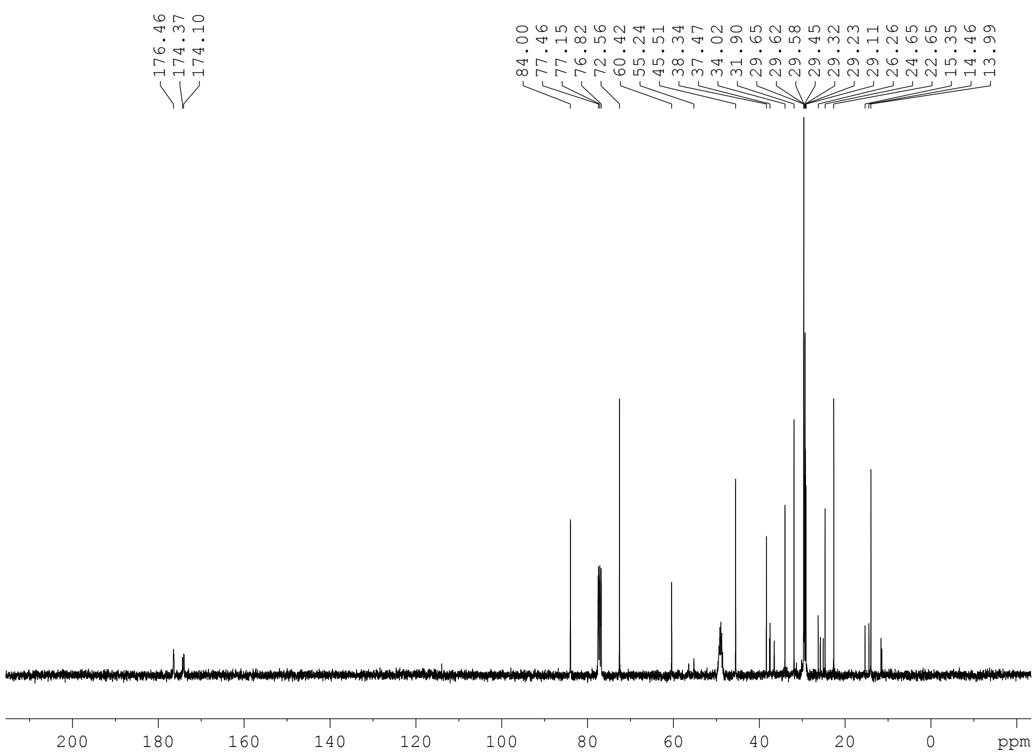
[1]H NMR spectrum of compound **2d**



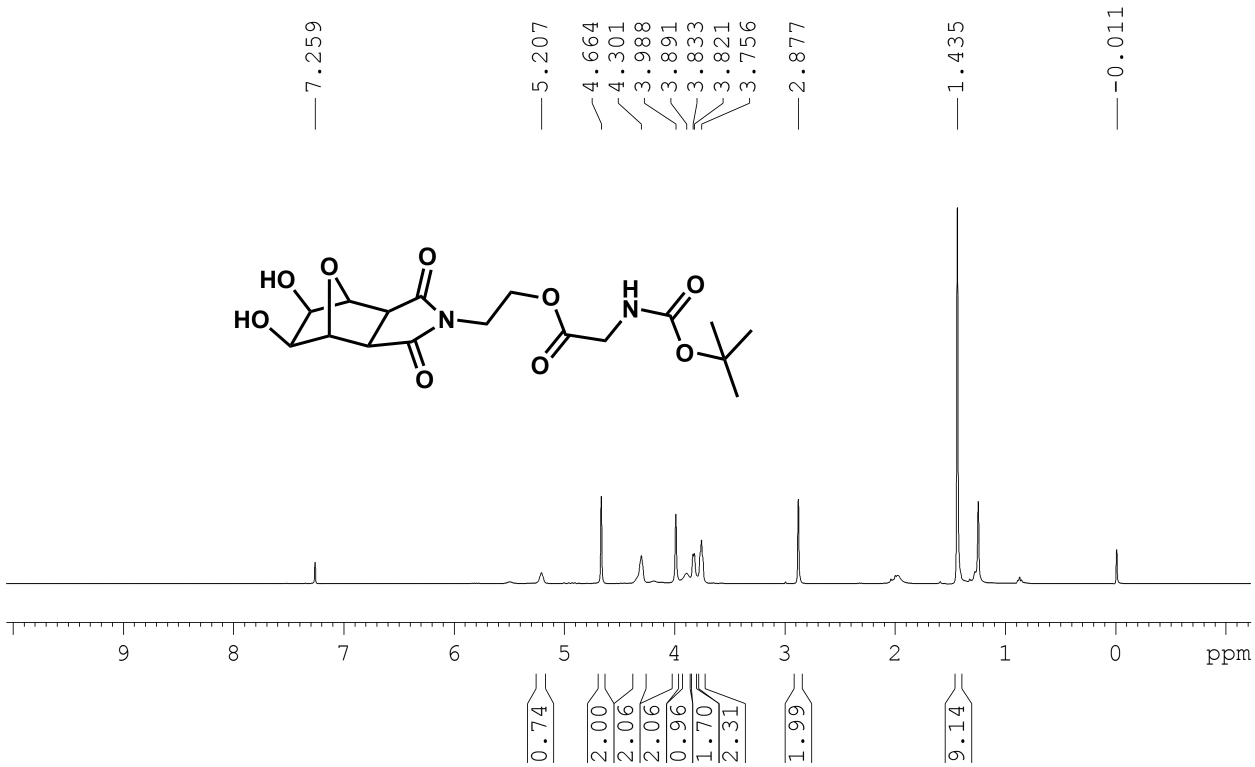
[13]C NMR spectrum of compound **2d**



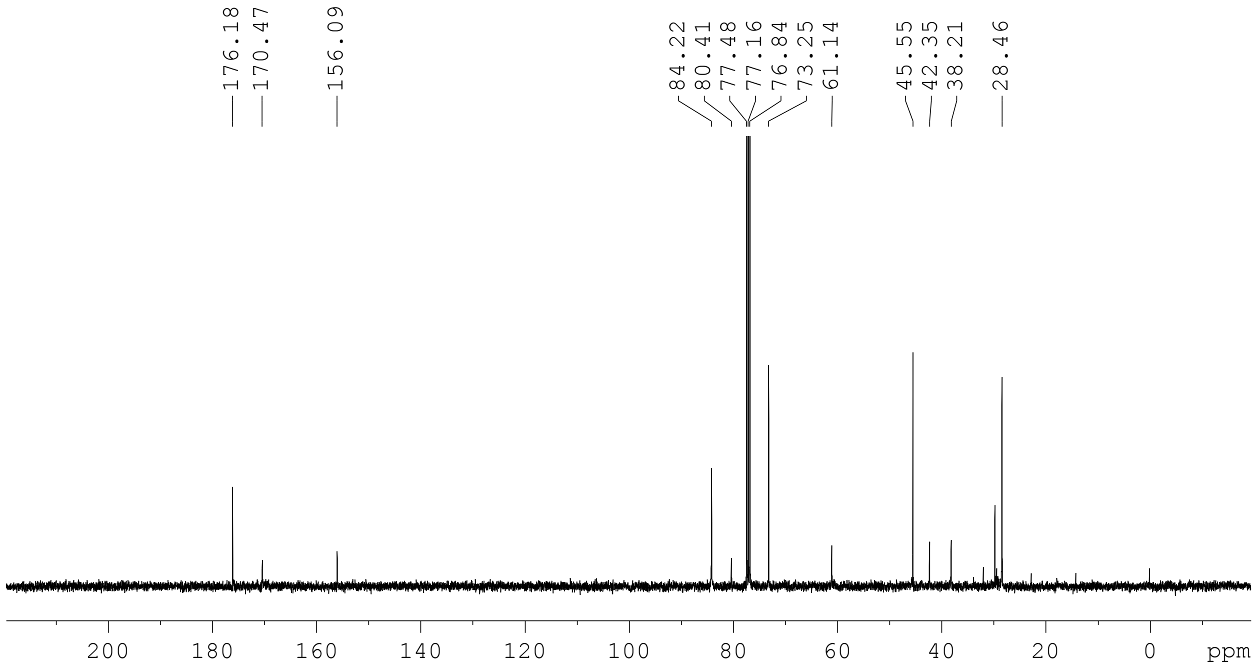
^{1}H NMR spectrum of compound **2e**



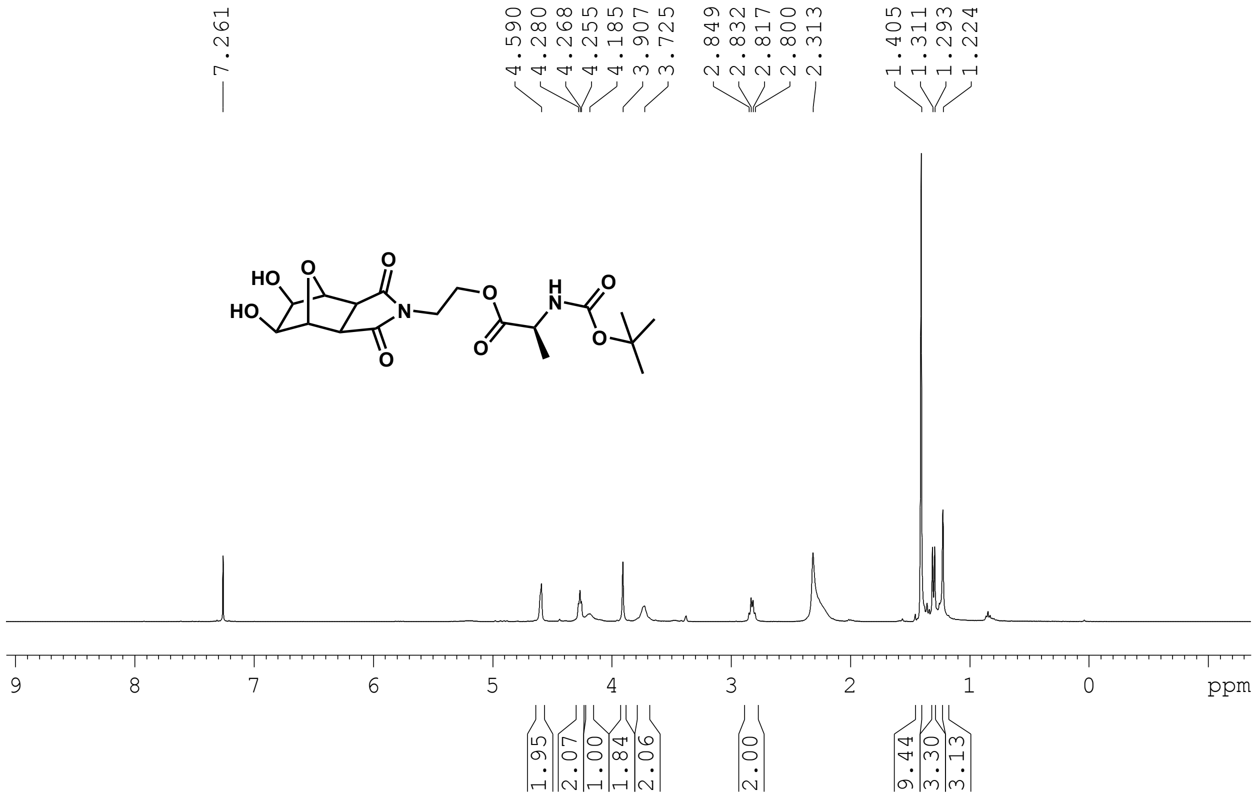
^{13}C NMR spectrum of compound **2e**



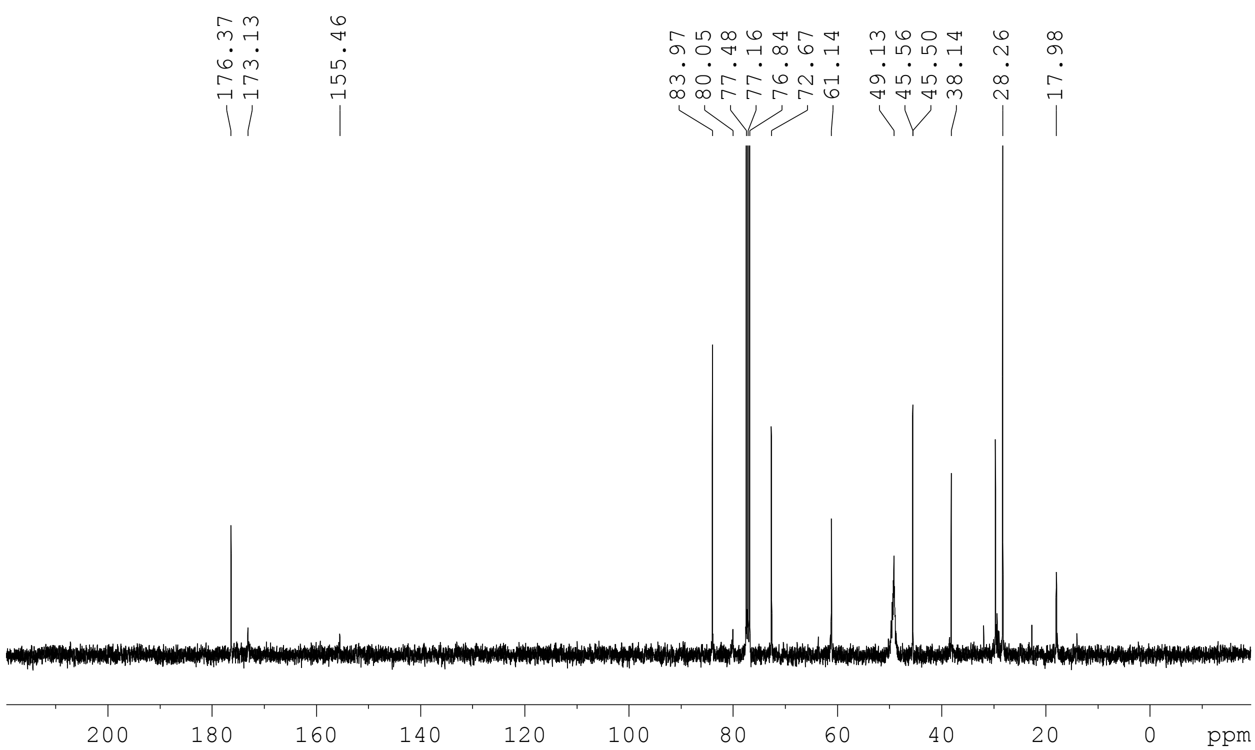
[1]H NMR spectrum of compound **3a**



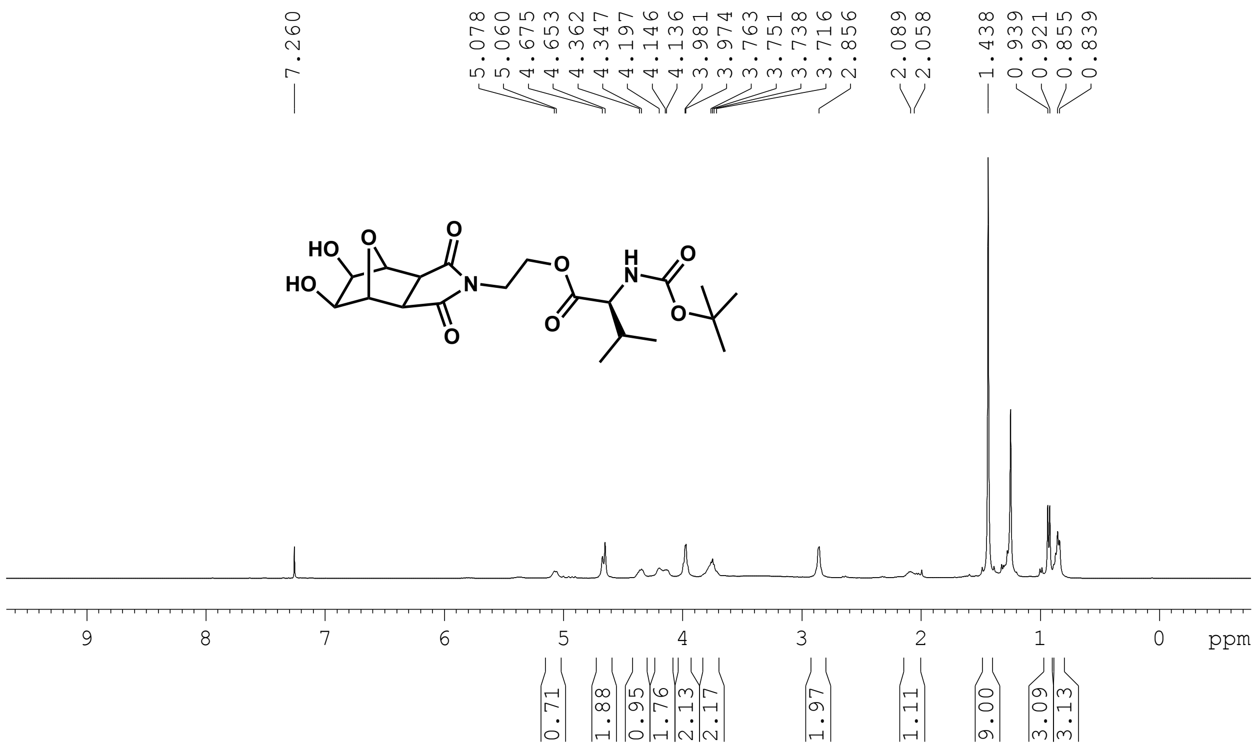
[13]C NMR spectrum of compound **3a**



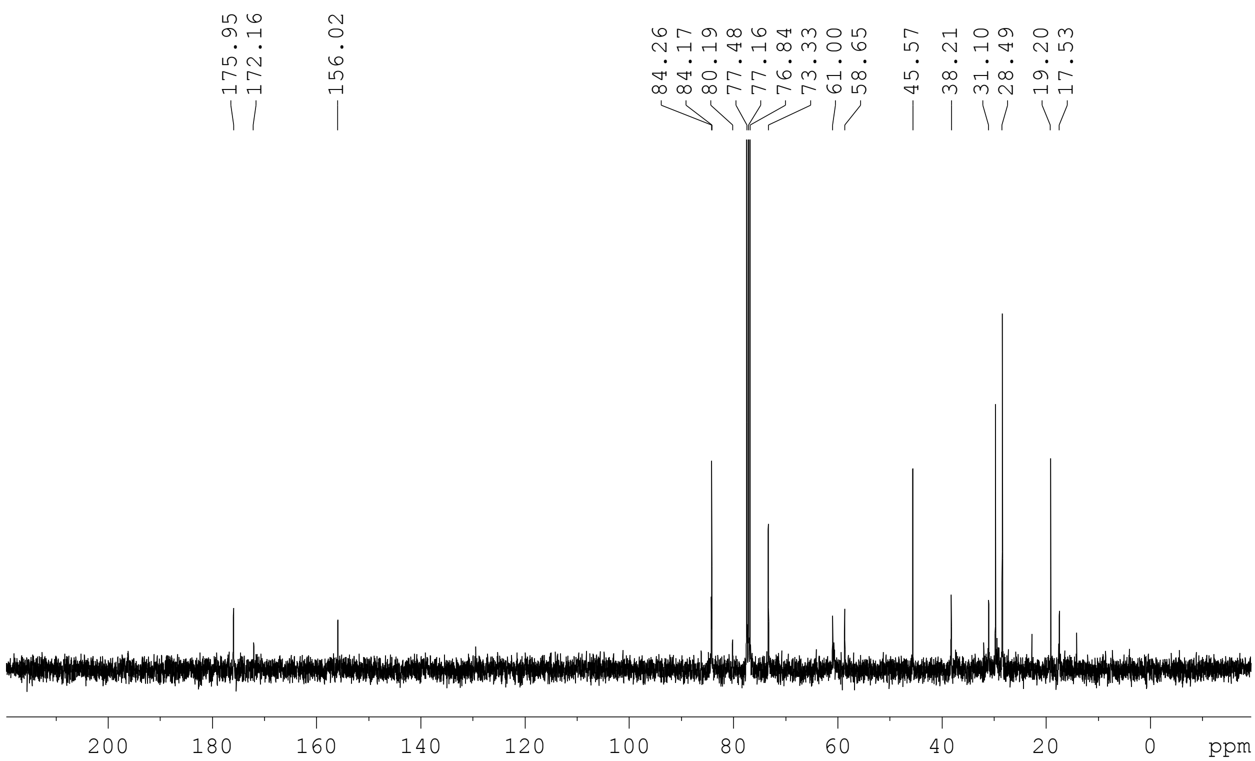
[1]H NMR spectrum of compound **3b**



[13]C NMR spectrum of compound **3b**

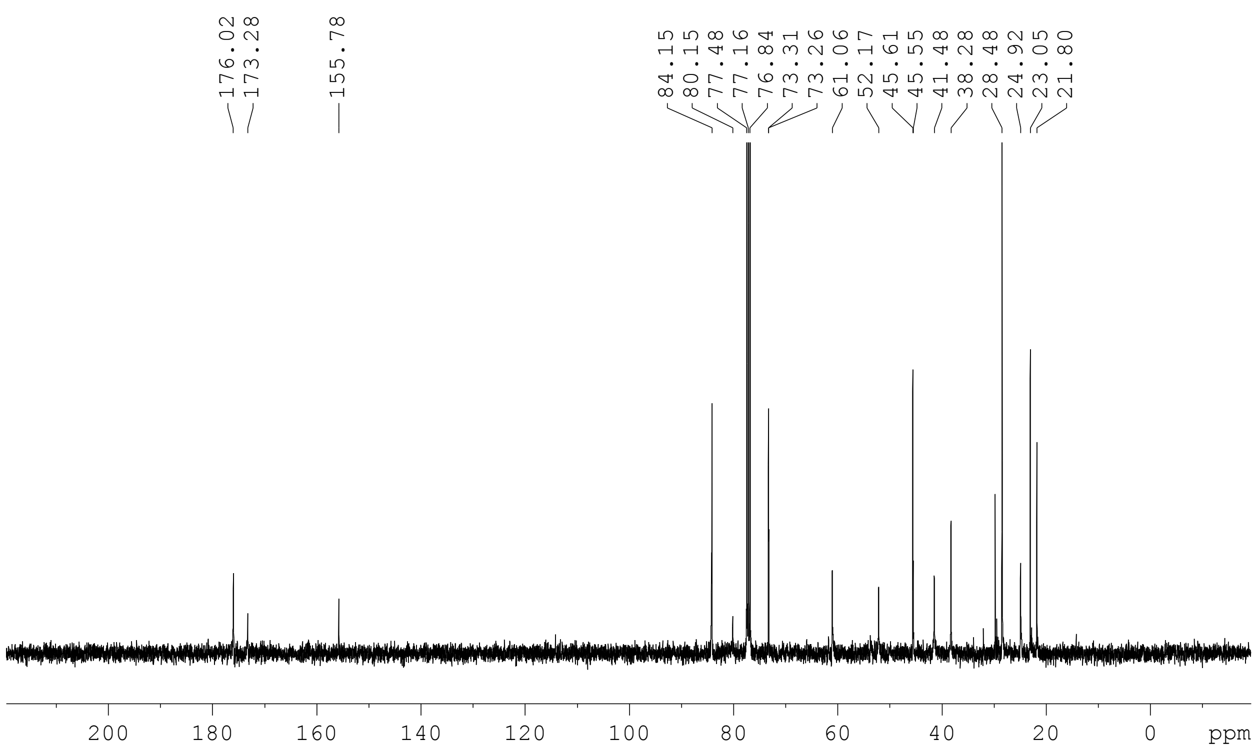


[1]H NMR spectrum of compound **3d**



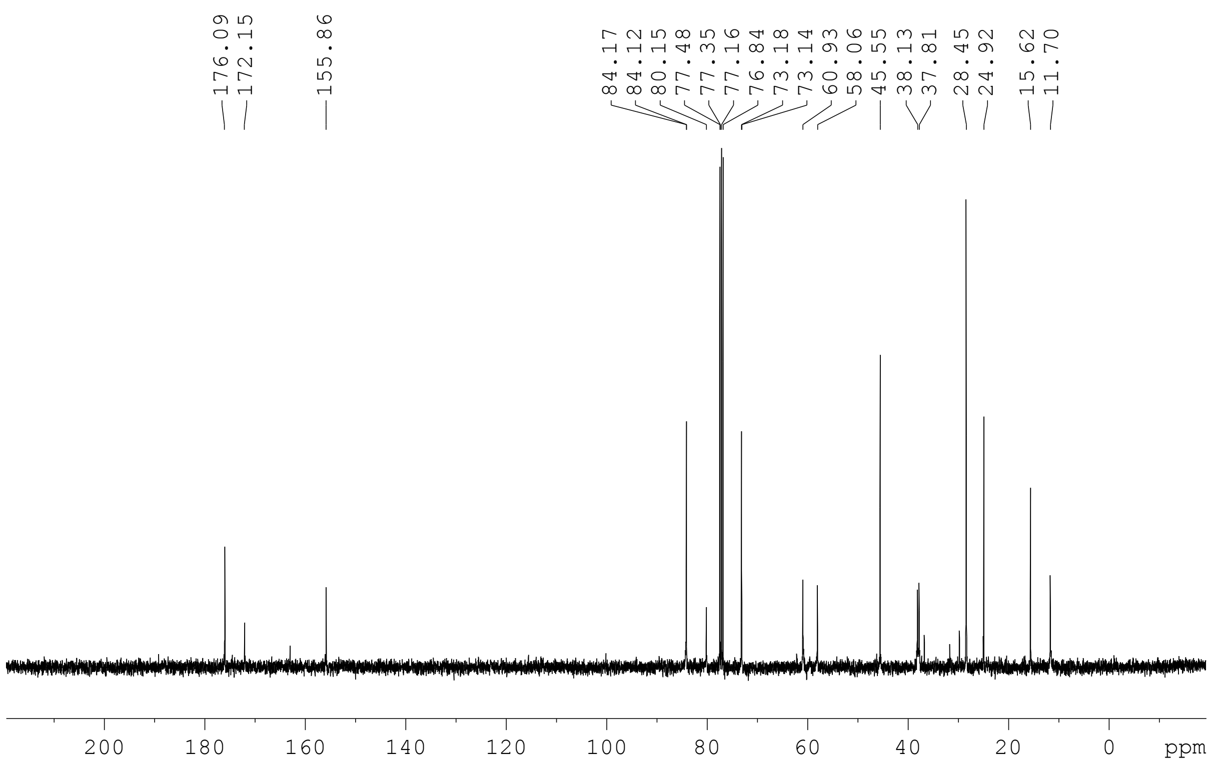
[13]C NMR spectrum of compound **3d**

[1]H NMR spectrum of compound **3e**

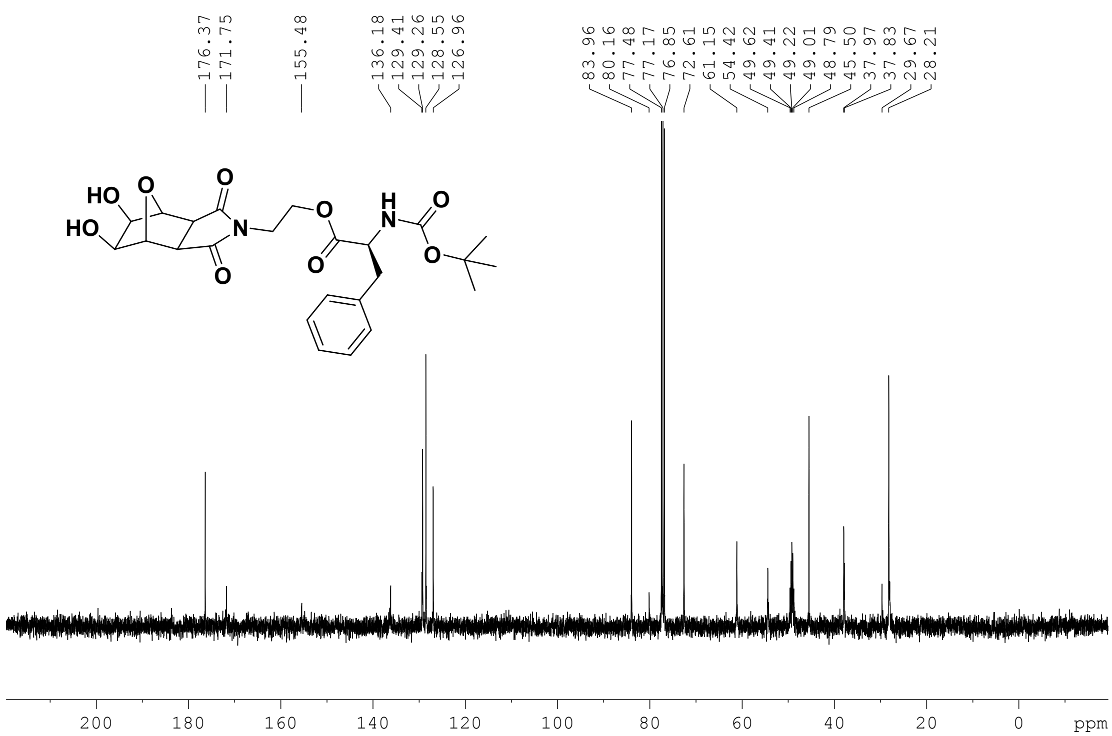


[13]C NMR spectrum of compound **3e**

[1]H NMR spectrum of compound **3f**

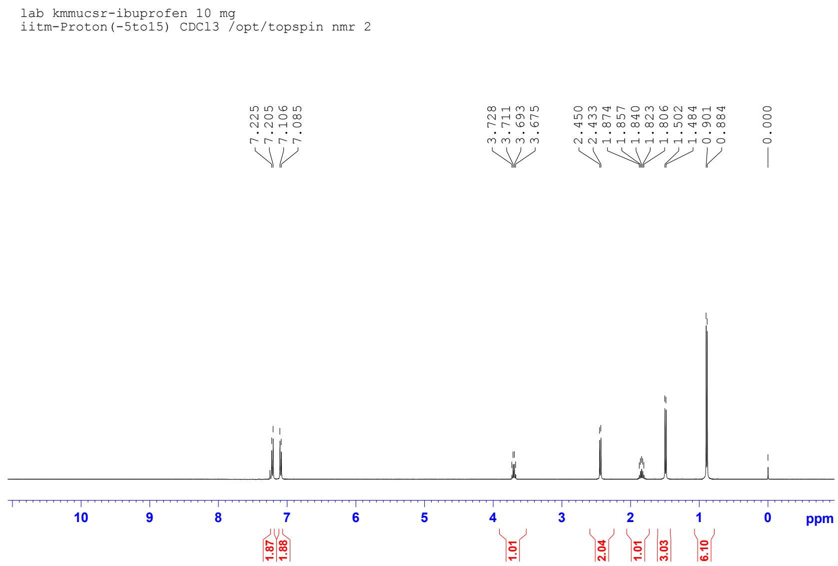


[13]C NMR spectrum of compound **3f**

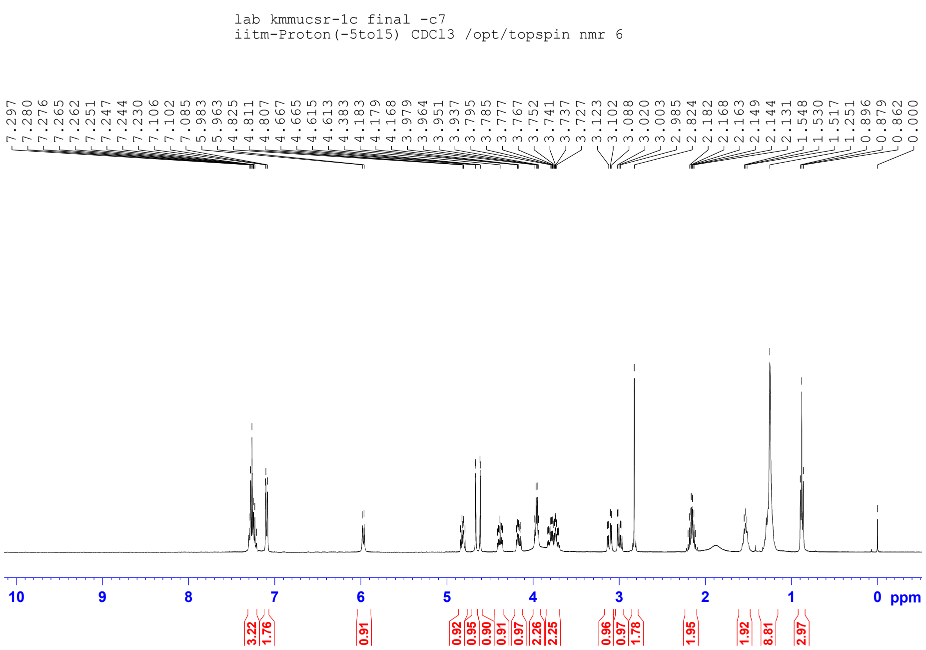


^{13}C NMR spectrum of compound **3c**

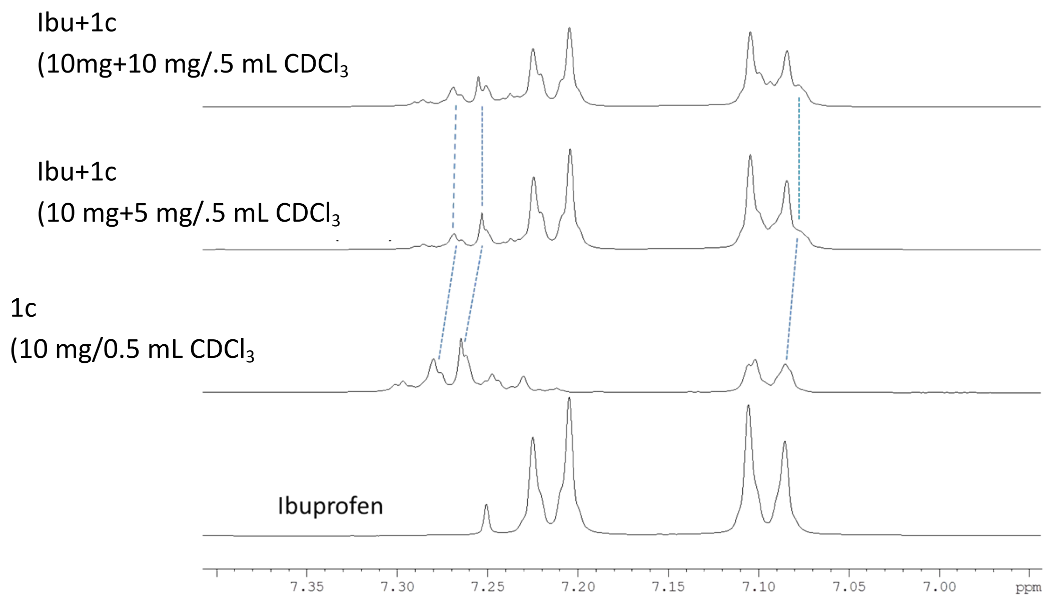
Evidence of H-bonded association in a mixture of Ibuprofen and 1c in $CDCl_3$



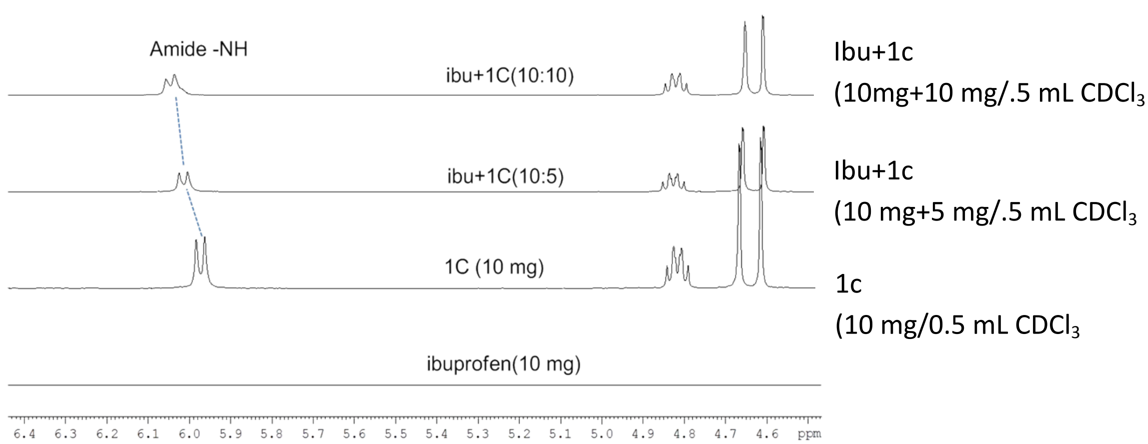
^{1}H NMR spectrum of Ibuprofen



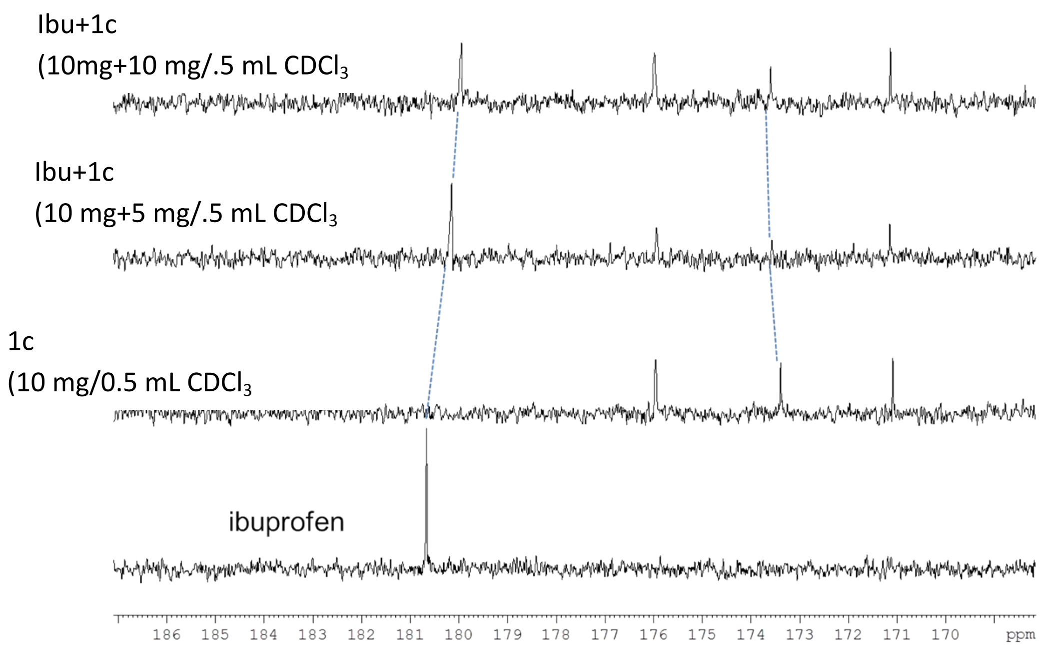
^{1}H NMR of compound 1c



Upfield shifting of aromatic signals on addition of Ibuprofen to its $CDCl_3$ solution



Downfield shift NH signal in 1c on addition of Ibuprofen



Upfield shifting carboxyl carbon in Ibuprofen and down-field shifting of amide carbonyl in 1c in their mixture in $CDCl_3$