Supporting Information

Exploring structural motifs necessary for substrate binding in the active site of *Escherichia coli* pantothenate kinase

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General information

All reagents and buffer components were purchased from Sigma-Aldrich or Fisher Scientific and used without further purification. TLC analyses (F-254) were performed with 60 Å silica gel from Silicycle. Flash chromatography of compounds was performed using a Redisep Isoco Companion system or a Biotage purification system. ^{1}H and ^{13}C NMR spectra were measured on either a Varian 300, 400, or 500 MHz instrument with the solvent peaks used as internal standard. HRMS spectra were acquired at the McGill University Mass Spectral Facility on an EXACTIVE instrument in orbitrap mode. Microwave reactions were performed using Biotage microwave system.

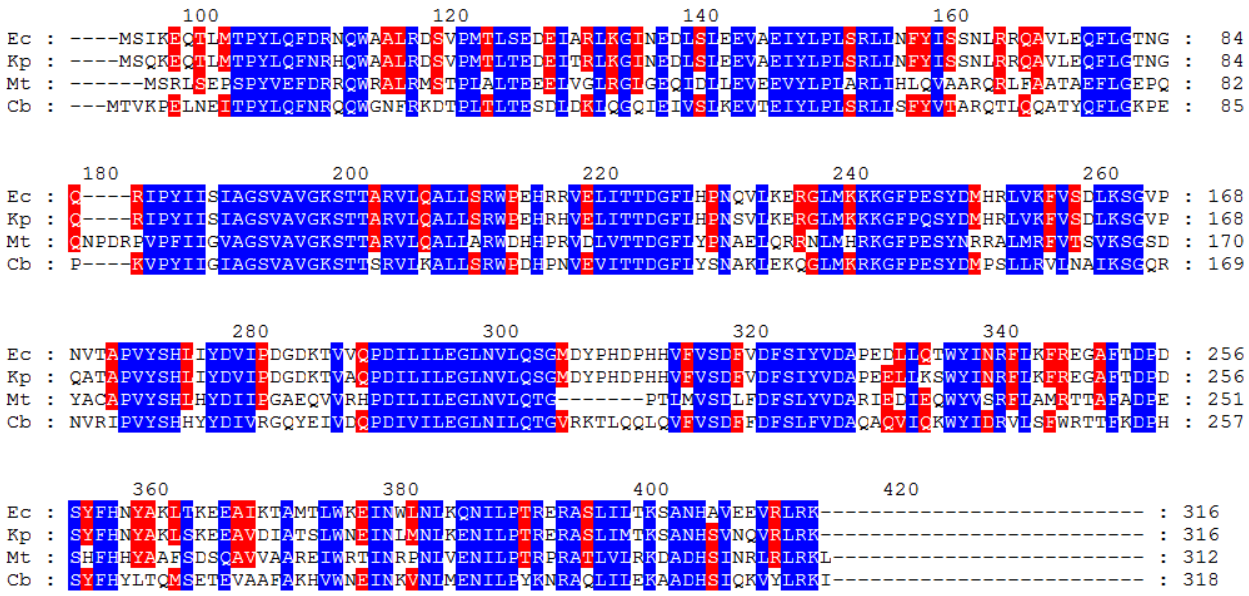


Figure S1. Sequence alignment of type I PanK isoforms from *E. coli* (Ec; P0A6I3), *M. tuberculosis* (Mt; P63810), *C. burnetii* (Cb; Q83EV9), and *K. pneumoniae* (Kp; B5XYG3). Conservation by more than 60% and 80% is represented by red and blue, respectively.

General procedure A: Oxidation of the protected alcohol to acid (to produce 20, 72a-f). (1)

To a solution of the protected alcohol (**71a-f**) (1 mmol) in DCM (5 ml) was added Dess-Martin Periodinane (2 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with diethyl ether (30 ml) and washed with a 1:1 (v/v) mixture of saturated sodium thiosulfate and saturated sodium bicarbonate (3 × 6 ml). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to yield the aldehyde as an oily product which was pure enough for the next reaction. The aldehyde was dissolved in a mixture of acetone and DCM (8 mL, 3:1 v/v). To this mixture was added a freshly prepared solution of NaH_2PO_4 (10 mmol) and $NaClO_2$ (5 mmol) in H_2O (2.7 mL). The reaction mixture was stirred at room temperature for 15 min. The organic solvents were removed under vacuum and the remaining aqueous layer was quenched with saturated sodium sulfite (1 ml per mol equivalent of $NaClO_2$), and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and concentrated under vacuum.

General procedure B: Amide coupling. (1)

If necessary, Fmoc-deprotection was carried out by the addition of piperidine (1.5 ml per 200 mg) to a solution of Fmoc-amine (200 mg) in DMF (10 ml per 200 mg) at room temperature for 30 min. Solvent was then removed under reduced pressure and the crude residue was used in the subsequent coupling without further purification.

If necessary, Boc-deprotection was carried out by dissolving the protected amine in TFA/DCM (1:1 v/v, 1 ml per 100 mg) and stirring at room temperature for 30 min. Solvent was then removed under reduced pressure and the crude residue was used the subsequent coupling without further purification.

A mixture of the amine (2.0 mmol), EDC (2.6 mmol), and HOBt (3.3 mmol) were purged with nitrogen before the addition of the acid (2.6 mmol) and THF (10 ml). DIPEA (11.0 mmol) was then added and the reaction was stirred at room temperature for 16 h. The reaction mixture was poured into a separatory funnel containing saturated NH_4Cl (10 ml) and extracted with ethyl acetate (3 × 30 ml). The combined organic layers were dried over Na_2SO_4, concentrated under vacuum. Purification on silica gel yielded the desired product.

General procedure C: Deprotection of PMB-protected *N*-substituted pantothenamides (to form NpPan (34), 35-39, 41-42, 44-48, 51-52, and 62-67).

To the PMB-protected pantothenamide (0.2 mmol) was added 90% aqueous AcOH (8 ml). The reaction mixture was stirred at room temperature for 16 h. Evaporation of the solvent under vacuum and purification of the crude product on silica gel yielded the desired product.

General procedure D: Synthesis of PMP-protected *N*-substituted pantothenamides to generate 55a-d, f-j, l,).

NHS ester **54** (143 mg, 0.33 mmol) was dissolved in DCM (5 ml). The appropriate amine (0.66 mmol) was added and the reaction mixture was stirred at room temperature for 6-16 h depending on the amine. Evaporation of the solvent under vacuum and purification of the crude product on silica gel yielded the desired product.

General procedure E: Synthesis of PMP-protected *N*-substituted pantothenamides *via* microwave amide coupling (to form 55e, k, m).

To a mixture of **53** (84 mg, 0.25 mmol) and HATU (190 mg, 0.5 mmol) in DMF (3 ml) was added the amine (0.5 mmol) and DIPEA (87 µl, 0.5 mmol). The mixture was microwaved at 60^{o}C for 30 min. The reaction mixture was then poured into a separatory funnel containing saturated NH_4Cl and extracted with EtOAc (3 × 15 ml). The organic layer was dried over Na_2SO_4, concentrated under vacuum, and purification of the crude product on silica gel yielded the desired product.

General procedure F: Reduction and 1,3 protection of triol to yield **71a-f**. (1)

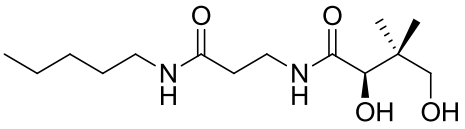
To a solution of $LiAlH_4$ (3 mmol) in THF (5 ml) under argon at 0^{o}C was added drop wise a solution of the diester **70a-f** (1 mmol) in THF (15 ml). The reaction mixture was refluxed at 60^{o}C for 16 h, cooled to 0^{o}C and quenched with saturated NH_4Cl (10 ml). The mixture was extracted in ethyl acetate (4 × 10 ml) until there was no product in the aqueous layer (monitored by TLC). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to yield the triol which was used without further purification. To the dried triol dissolved in anhydrous DCM (15 ml) was added *p*-anisaldehyde dimethyl acetal (1.5 mmol) and camphor sulfonic acid (CSA) (0.1 mmol). The reaction mixture was stirred at room temperature for 4 h and quenched with excess triethylamine (1 ml). Evaporation of the solvent and triethylamine under vacuum and purification of the oily product on silica gel yielded the desired product.

General procedure G: Installation of the pantoyl moiety through the ring opening of D-pantolactone (**4**, **7**, **8**-**12**, , **40**, **43**, **49**-**50**). (2)

The Boc-protected amine (0.3 mmol) was first dissolved in TFA/DCM (1 ml, 1:1) and stirred at room temperature for 30 min to yield the crude deprotected amine. Upon evaporation to dryness, the free amine and D-pantolactone (0.8 mmol) were dissolved in anhydrous EtOH (5 ml). Triethylamine (1.4 mmol) was added, and the reaction was refluxed at 75°C for 24 h. The reaction was evaporated to dryness and the product purified by silica gel chromatography.

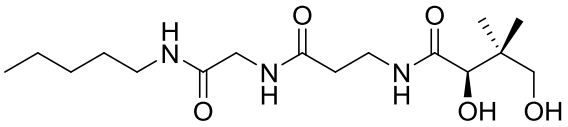
General procedure for Boc-protections:

The amine (14.5 mmol) was dissolved in H_2O/dioxane (30 ml, 1:1). $NaHCO_3$ (29 mmol) was added, and the mixture was cooled to 0°C on ice. Boc anhydride (19 mmol) was dissolved in dioxane (15 ml) and added slowly. The reaction was stirred overnight, and allowed to warm to room temperature. Upon reaction completion, H_2O (80 ml) was added and the product was extracted in EtOAc (3 × 80 ml). The combined organic layers were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The product was purified by flash chromatography.



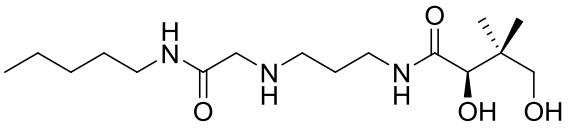
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-(pentylamino)propyl)butanamide (N5-Pan, (3)).

Synthesized according to the general protocol C and D and characterization followed standard literature protocol. (3)



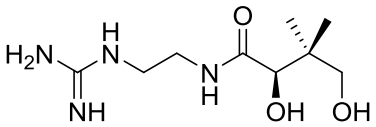
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-((2-oxo-2-(pentylamino)ethyl)amino)propyl) butanamide (4)

Compound **4** was synthesized according to the general protocol G. The amine of compound **15** (230 mg, 0.74 mmol) was deprotected and used directly in the nucleophilic ring opening of D-pantolactone (290 mg, 2.2 mmol) in the presence of triethylamine (460 µl, 3.3 mmol). The product was purified by flash chromatography using a 0-15% gradient of MeOH in EtOAc. Yield: 97 mg, 38% over two steps. R_f = 0.54 (20% MeOH/EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 3.89 (s, 1H), 3.81 (s, 2H), 3.58 – 3.26 (m, 4H), 3.24 – 3.13 (m, 2H), 2.49 (t, *J* = 6.5 Hz, 2H), 1.59 – 1.43 (m, 2H), 1.40 – 1.20 (m, 4H), 0.97 – 0.85 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.7, 173.0, 170.0, 76.0, 69.0, 42.2, 39.1, 39.0, 35.1, 34.9, 28.8, 28.7, 22.1, 20.1, 19.7, 13.1; HRMS for $C_{16}H_{31}N_3O_5$ $[M+Na]^+$ calcd. 368.2162, found 368.2150.



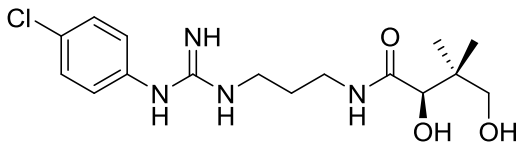
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-(2-oxo-2(pentylamino)ethylamino)propyl)butanamide (5)

To a solution of **17** (100.0 mg, 0.33 mmol) in DCM (2 ml), TFA (1 ml) was added at room temperature and the mixture was stirred for 1 h. The solvent was then evaporated to yield the deprotected amine as an oily residue. To this crude product (100.0 mg, 0.33 mmol) in anhydrous EtOH (5 ml), D-pantolactone (129 mg, 0.99 mmol) and triethylamine (208 µl, 1.49 mmol) were added. The reaction mixture was refluxed at 75^{o}C for 24 h. The solvent was then removed and the crude product was purified on silica gel with 30% MeOH/DCM to yield the desired product (45 mg, 0.136 mmol) in 41% yield over three steps. R_f = 0.21; ^{1}H NMR (500 MHz, CD_3OD) δ 3.90 (s, 1H), 3.47 (d, *J* = 11.0 Hz, 1H), 3.43 (s, 2H), 3.39 (d, *J* = 11.0 Hz, 1H), 3.30 (m, 2H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.76 (t, *J* = 7.0 Hz, 2H), 1.78 (m, 2H), 1.52 (m, 2H), 1.33 (m, 4H), 0.90-0.93 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.1, 169.6, 75.9, 68.9, 50.1, 46.1, 39.0, 38.9, 36.0, 28.8, 28.0, 22.0, 20.0, 19.6, 12.9; HRMS-ESI for $C_{16}H_{34}N_3O_4$ $[M+1]^+$ Calcd 332.2544 found 332.2557.



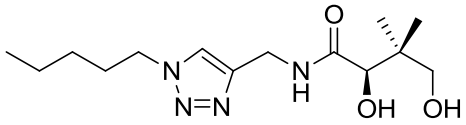
(*R*)-*N*-(2-Guanidinoethyl)-2,4-dihydroxy-3,3-dimethylbutanamide ((6)

To solution of **21** (100 mg, 0.182 mmol) in DCM (2 ml), TFA (1 ml) was added at room temperature and the mixture was stirred for 3 h. The solvent was evaporated and 80% aqueous AcOH (2 ml) was added to the oily residue. The mixture was stirred at room temperature for 1 h. After removal of the solvent under vacuum, the crude product was purified on silica gel with 20% MeOH/DCM to yield the product (40 mg, 0.12 mmol) in 66% yield. R_f = 0.14; ^{1}H NMR (300 MHz, D_2O) δ 3.83 (s, 1H), 3.36-3.19 (m, 6H), 0.75 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 157.5, 75.8, 68.7, 40.8, 39.0, 37.4, 19.5, 19.4; HRMS-ESI for $C_9H_{22}N_4O_3$ $[M+1]^+$ Calcd 233.1607 found 233.1607.



(*R*)-*N*-(3-(3-(4-Chlorophenyl)guanidino)propyl)-2,4-dihydroxy-3,3-dimethylbutanamide ((7)

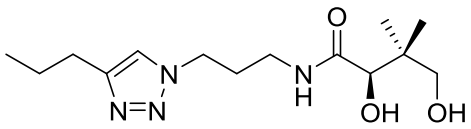
To a solution of **24** (84 mg, 0.26 mmol) in DCM (2 ml), TFA (1 ml) was added at room temperature and the mixture was stirred for 1 h. The solvent was then evaporated to yield the deprotected amine as an oily residue. To the crude amine (40 mg, 0.18 mmol) in anhydrous EtOH (5 ml), D-pantolactone (100 mg, 0.77 mmol) and triethylamine (104 µl, 0.78 mmol) were added. The reaction mixture was refluxed at 75^{o}C for 24 h. The solvent was then removed and the product was purified on silica gel with 20%/5%/75% MeOH/NH_4OH/DCM. The product (211 mg, 0.11 mmol) was generated in 59% yield over two steps. R_f = 0.33; ^{1}H NMR (400 MHz, D_2O) δ 7.34 (d, *J* = 9.0 Hz, 2H), 7.13 (d, *J* = 9.0 Hz, 2H), 4.84 (s, 1H), 3.46 (d, *J* = 10.8 Hz, , 1H), 3.38 (d, *J* = 10.8 Hz, 1H), 3.14-3.17 (m, 4H), 1.71 (t, *J* = 6.8 Hz, 2H), 0.77 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.2, 155.5, 133.9, 129.7, 126.6, 75.9, 68.9, 39.0, 38.4, 35.5, 28.6, 20.0, 19.6; HRMS-ESI for $C_{16}H_{26}ClN_4O_3$ $[M+1]^+$ Calcd 357.1690 found 357.1688.



(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-((4-pentyl-1H-1,2,3-triazol-1-yl)methyl)butanamide (8)

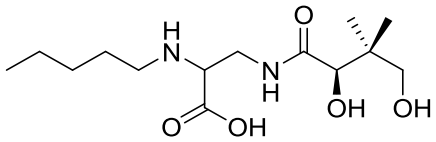
Compound **8** was synthesized according to general protocol G. The amine of compound **26** (400 mg, 1.50 mmol) was deprotected and used directly in the nucleophilic ring opening of D-pantolactone (880 mg, 6.75 mmol) in the presence of triethylamine (940 µl, 6.75 mmol). The product was purified by flash chromatography using a 0-15% gradient of MeOH in EtOAc. Yield: 206 mg, 46% over two steps. R_f = 0.56 (10% MeOH/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (bs, NH), 7.52 (s, 1H), 4.41 (d, *J* = 5.8 Hz, 2H), 4.22 (t, *J* = 7.2 Hz, 2H), 3.98 (s, 1H), 3.36 (dd, *J* = 24.8, 11.1 Hz, 2H), 1.87 – 1.71 (m, 2H), 1.31 – 1.11 (m, 4H), 0.94 – 0.67 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 144.5, 122.3, 77.6, 70.6,

50.4, 39.3, 34.2, 29.8, 28.4, 22.0, 21.0, 20.5, 13.8; HRMS for $C_{14}H_{26}N_4O_3$ $[M+Na]^+$ calcd. 321.1903, found 321.1894.



(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-(4-propyl-1H-1,2,3-triazol-1-yl)propyl)butanamide (9)

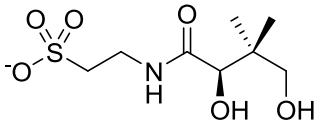
Compound **9** was synthesized according to general protocol B. The amine of compound **28** (60 mg, 0.22 mmol) was deprotected and used directly in the nucleophilic ring opening of D-pantolactone (130 mg, 1.00 mmol) in the presence of triethylamine (140 µl, 1.00 mmol). The product was purified by flash chromatography using a 0-10% gradient of MeOH in EtOAc. Yield: 9 mg, 14% over two steps. R_f = 0.51 (10% MeOH/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (bs, NH), 7.25 (s, 1H), 4.37 (t, *J* = 6.3 Hz, 2H), 4.05 (s, 1H), 3.51 (s, 2H), 3.30 (d, *J* = 6.0 Hz, 2H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.21 – 2.02 (m, 2H), 1.76 – 1.60 (m, 2H), 1.05 – 0.88 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 151.8, 122.5, 77.6, 71.2, 47.7, 39.3, 36.0, 30.2, 27.5, 22.6, 21.5, 20.4, 13.8; HRMS for $C_{14}H_{26}N_4O_3$ $[M+Na]^+$ calcd. 321.1903, found 321.1891.



3-((*R*)-2,4-Dihydroxy-3,3-dimethylbutanamido)-2-(pentylamino)propanoic acid (10)

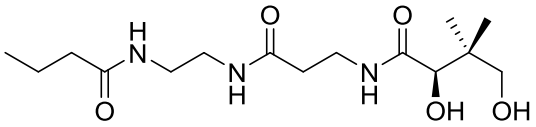
To a solution of **30** (41 mg, 0.24 mmol) in DCM (2 ml), TFA (1 ml) was added at room temperature and the mixture was stirred for 1 h. The solvent was then evaporated to yield the deprotected amine as an oily residue. To a solution of the crude amine (41 mg, 0.24 mmol) in anhydrous EtOH (5 ml), D-pantolactone (93 mg, 0.72 mmol) and triethylamine (150 µl, 1.08 mmol) were added. The reaction mixture was refluxed at 75^{o}C for 24 h. The solvent was then removed *in vacuo* and the product was purified on silica gel with 30% MeOH/DCM to yield the desired compound (38 mg, 0.126 mmol) in 52% yield over two steps. R_f = 0.32; ^{1}H NMR (400 MHz, D_2O) δ 4.0 (s, 1H), 3.65-3.85 (m, 3H), 3.43

(dd, *J* = 11.3 Hz, 15.4 Hz, 2H), 3.05-3.11 (m, 2H), 1.70 (q, *J* = 6.2 Hz, 2H), 1.35 (m, 4H), 0.86-0.92 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 177.0, 176.9, 75.6, 67.8, 67.6, 63.3, 39.4, 38.8, 28.3, 25.7, 21.8, 20.8, 20.1, 12.7; HRMS-ESI $C_{14}H_{28}N_2NaO_5$ $[M+Na]^+$ Calcd 327.1890 found 327.1896.



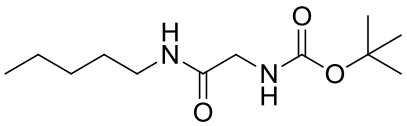
(*R*)-2-(2,4-Dihydroxy-3,3-dimethylbutanamido)ethane-1-sulfonate (11)

Synthesis and characterization followed standard literature protocol. (4)



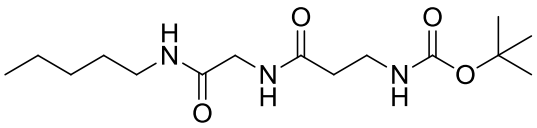
(*R*)-*N*-(3-((2-Butyramidoethyl)amino)-3-oxopropyl)-2,4-dihydroxy-3,3-dimethylbutanamide (12)

Compound **12** was synthesized according to general protocol G. The amine of compound **33** (163 mg, 0.54 mmol) was deprotected and used directly in the nucleophilic ring opening of D-pantolactone (210 mg, 1.6 mmol) in the presence of triethylamine (340 µl, 2.4 mmol). The product was purified by flash chromatography using a gradient of 0-20% MeOH in DCM. Yield: 20 mg, 11% over two steps. R_f = 0.29 (15% MeOH/DCM); ^{1}H NMR (300 MHz, CD_3OD) δ 3.88 (s, 1H), 3.53 – 3.42 (m, 3H), 3.38 (d, *J* = 10.9 Hz, 1H), 3.32 – 3.25 (m, 4H), 2.41 (t, *J* = 6.6 Hz, 2H), 2.16 (t, *J* = 7.5 Hz, 2H), 1.71 – 1.53 (m, 2H), 0.99 – 0.87 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.0, 174.6, 172.7, 75.8, 68.9, 38.9, 38.7, 38.5, 37.6, 35.2, 35.0, 19.9, 19.5, 18.9, 12.6; HRMS for $C_{15}H_{29}N_3O_5$ $[M+Na]^+$ calcd. 354.2005, found 354.2008.



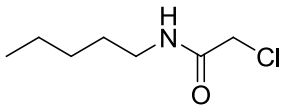
***tert*-Butyl (2-oxo-2-(pentylamino)ethyl)carbamate (14)**

Compound **14** was synthesized according to general procedure B. Thus, pentylamine (80 µl, 0.68 mmol) was coupled to Boc-β-glycine (100 mg, 0.57 mmol), using EDC (142 mg, 0.74 mmol), HOBt (123 mg, 0.91 mmol), and DIPEA (546 µl, 3.13 mmol) in THF (6 ml). The product was purified by flash chromatography using a gradient of 0-10% MeOH in DCM. Yield: 130 mg, 94%. R_f = 0.38 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (bs, NH), 5.58 (bs, NH), 3.71 (d, *J* = 5.5 Hz, 2H), 3.17 (dd, *J* = 13.4, 6.8 Hz, 2H), 1.51 – 1.34 (m, 11H), 1.32 – 1.14 (m, 4H), 0.82 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 156.2, 79.9, 44.2, 39.4, 29.1, 28.9, 28.2, 22.3, 13.9; HRMS for $C_{12}H_{24}N_2O_3$ $[M+Na]^+$ calcd. 267.1685, found 267.1679.



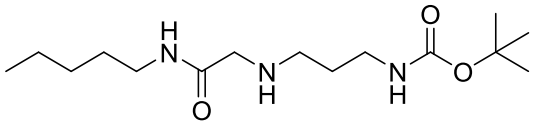
***tert*-Butyl (3-oxo-3-((2-oxo-2-(pentylamino)ethyl)amino)propyl)carbamate (15)**

Compound **15** was synthesized using general procedure B. Thus, compound **14** (130 mg, 0.53 mmol) was Boc-deprotected and coupled to Boc-β-alanine (121 mg, 0.64 mmol) using EDC (133 mg, 0.69 mmol), DMAP (cat. 5 mg), and DIPEA (510 µl, 2.93 mmol) in THF (6 ml). The product was purified by flash chromatography using a gradient of 0-20% MeOH in DCM. Yield: 100 mg, 60% over two steps. R_f = 0.56 (10% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (bs, NH), 7.00 (bs, NH), 5.39 (bs, NH), 3.86 (d, *J* = 5.1 Hz, 2H), 3.44 – 3.27 (m, 2H), 3.16 (dd, *J* = 13.0, 6.8 Hz, 2H), 2.42 (t, *J* = 5.9 Hz, 2H), 1.51 – 1.32 (m, 11H), 1.31 – 1.10 (m, 4H), 0.82 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 169.0, 156.1, 79.2, 43.2, 39.6, 36.8, 36.0, 29.0, 29.0, 28.3, 22.3, 13.9; HRMS for $C_{15}H_{29}N_3O_4$ $[M+Na]^+$ calcd. 338.2056, found 338.2051.



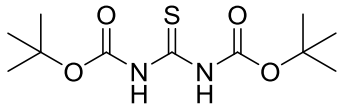
2-Chloro-*N*-pentylacetamide (16)

To a solution of *N*-pentylamine **(13)** (1.5 ml, 12.6 mmol) in anhydrous THF (10 ml) was added chloro acetyl chloride (500 µl, 6.28 mmol). The reaction mixture was stirred at room temperature for 16 h. The white precipitate was filtered off and the solvent was removed under vacuum. The crude product was purified on silica gel using 30% EtOAc/Hex to yield the product (912 mg, 5.6 mmol) in 89% yield. R_f = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (bs, 1H), 4.06 (s, 2H), 3.30 (q, *J* = 6.0 Hz, 2H), 1.56-1.51 (m, 2H), 1.32-1.23 (m, 4H), 0.90 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 42.6, 39.8, 28.9, 22.2, 13.8; LRMS-ESI for $C_7H_{15}ClNO$ $[M+1]^+$ calcd. 164.08, found 164.08.



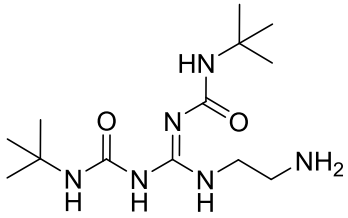
***tert*-Butyl 3-(2-oxo-2-(pentylamino)ethylamino)propylcarbamate (17)**

To a solution of **16** (100 mg, 0.61 mmol) and *tert*-butyl 3-aminopropylcarbamate (160 mg, 0.92 mmol) in DMF (6 ml) was added K_2CO_3 (126 mg, 0.92 mmol). The mixture was heated at 50^{o}C for 16 h. DMF was then removed under vacuum and the residue was passed through a short pad of silica gel using 10% MeOH/DCM to remove excess reagent. The solvent was removed under vacuum and was used for the next reaction without further purification.



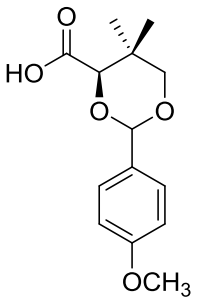
***N,N-tert*-Butoxycarbonylthiourea (18)**

Synthesis and characterization followed a standard literature protocol (5) to yield the product (883.6 mg, 3.20 mmol) in 85% yield which was used without further purification.



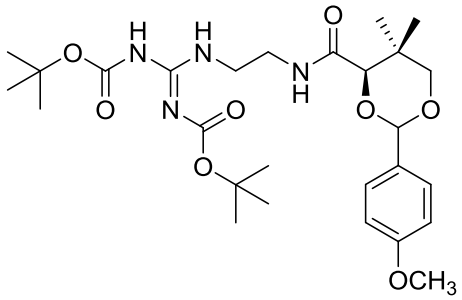
Boc-1-(2-aminoethyl)guanidine (19)

Synthesis and characterization followed a standard literature protocol. (5) The product was obtained 356 mg, 1.18 mmol) in 82% yield and used without purification.



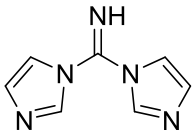
((*4R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxan-4-carboxylic acid (20)

Synthesis and characterization follows standard literature protocol. (6)



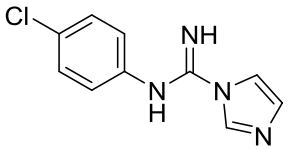
***tert*-Butyl-1-((*4R*)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxan-4-yl)-10,10-dimethyl-1,8-dioxo-9-oxa-2,5,7-triazaundecan-6-ylidenecarbamate (21)**

Experimental details are outlined in Procedure B to describe the coupling of**19** (267.3 mg, 0.89 mmol) and **20** (162 mg, 0.59 mmol). Purification on silica gel with 50% EtOAc/Hex yielded the product (256 mg, 0.465 mmol) in 79% yield. R_f = 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.47 (b, 1H), 8.56 (b, 1H), 6.71 (b, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.46 (s, 1H), 4.10 (s, 1H), 3.82 (s, 3H), 3.74-3.57 (m, 6H), 1.49 (s, 18H), 1.12 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 160.2, 156.5, 153.0, 130.2, 127.5, 113.7, 101.4, 83.9, 83.2, 79.4, 78.5, 55.3, 40.2, 37.9, 33.1, 28.3, 28.0, 21.3, 19.1; LRMS-ESI for $C_{27}H_{43}N_4O_8$ $[M+1]^+$ calcd. 551.03, found 551.24.



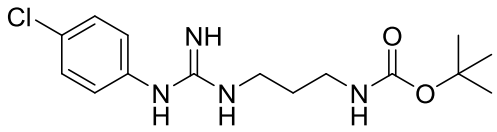
Di(1H-imidazol-1-yl)methanimine (22)

Synthesis and characterization followed a standard literature protocol. (7)



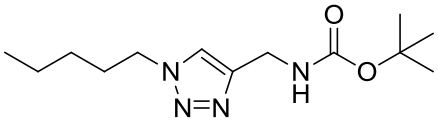
***N*-(4-Chlorophenyl)-*1H*-imidazole-1-carboximidamide (23)**

To a solution of **22** (200 mg, 1.24 mmol) in freshly distilled THF (8 ml), was added 4-chloro-aniline (208 mg, 1.64 mmol). The mixture was stirred at room temperature for 24 h. The solvent was then removed under vacuum and the residue was purified on silica with 10% MeOH/DCM to yield the product as a white solid (240 mg, 1.09 mmol) in 88% yield. R_f = 0.34; ^{1}H NMR (300 MHz, CD_3OD) δ 8.29 (s, 1H), 7.67 (s, 1H), 7.32 (d, *J* =8.6 Hz, 2H), 7.08 (s, 1H), 6.99 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 145.7, 145.2, 135.8, 129.2, 128.5, 128.3, 123.6, 117.3. LRMS-ESI for $C_{10}H_{10}ClN_4$ $[M+1]^+$ calcd. 221.05, found 221.66.



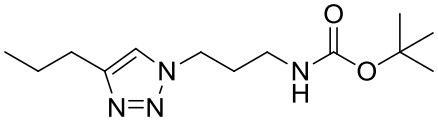
***tert*-Butyl 3-(3-(4-chlorophenyl)guanidino)propylcarbamate (24)**

To a stirred solution of **23** (110 mg, 0.5 mmol) in anhydrous THF (5 ml) was added *tert*-butyl 3-aminopropylcarbamate (174 mg, 1.0 mmol) in anhydrous THF (2 ml). The mixture was refluxed at 70^{o}C for 24 h. The solvent was removed under vacuum and the oily, crude product was purified on silica gel with a gradient of 5-20% MeOH/DCM, followed by 26%/4%/70% MeOH/NH_4OH/DCM, to yield the product (140 mg, 0.43 mmol) in 86% yield. R_f = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.34 (b, 1H), 4.35 (b, 3H), 3.31 (t, *J* = 6.0 Hz, 2H), 3.18 (q, *J* = 5.6 2H), 1.67-1.64 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 152.3, 147.5, 129.2, 127.2, 124.9, 79.3, 37.9, 37.3, 30.4, 28.4. LRMS-ESI for $C_{15}H_{24}ClN_4O_2$ $[M+1]^+$ calcd. 327.16, found 327.05.



***tert*-Butyl ((4-pentyl-1H-1,2,3-triazol-1-yl)methyl)carbamate (26)**

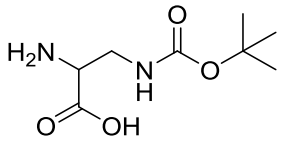
A protocol described by Feldman *et al.* was used for the following one-pot 1,3-dipolar cycloaddition. (8) 1-Bromopentane (410 µl, 3.3 mmol), Boc-protected propargylamine (428 mg, 2.8 mmol), and NaN_3 (270 mg, 4.1 mmol) were dissolved in DMF/H_2O (15 ml, 4:1). Sodium ascorbate (220 mg, 1.1 mmol, 40 mol%) was dissolved in H_2O (0.5 ml) and added. $CuSO_4$•$5H_2O$ (137 mg, 0.55 mmol, 20 mol%) was dissolved in H_2O (0.5 ml) and added as well. The reaction was refluxed at 100°C overnight. Upon reaction completion, NH_4OH (60 ml, 20% aq.) was added, and the product was extracted in EtOAc (3 × 80 ml). The organic layer was dried over anhydrous sodium sulfate, and evaporated to dryness. The product was purified by flash chromatography using a gradient of 30-80% EtOAc in hexanes. Yield: 601 mg, 81%. R_f = 0.56 (70% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 5.70 (bs, NH), 4.20 – 3.99 (m, 4H), 1.71 – 1.56 (m, 2H), 1.18 (s, 9H), 1.13 – 0.97 (m, 4H), 0.63 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 145.3, 121.8, 79.0, 50.0, 35.9, 29.7, 28.3, 28.1, 21.8, 13.6; HRMS for $C_{13}H_{24}N_4O_2$ $[M+Na]^+$ calcd. 291.1797, found 291.1795.



***tert*-Butyl (3-(4-propyl-1H-1,2,3-triazol-1-yl)propyl)carbamate ((28)**

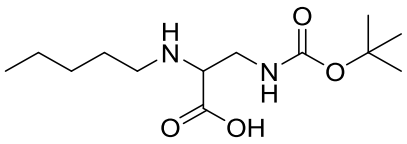
A protocol described by Feldman *et al.* was used for the following one-pot 1,3-dipolar cycloaddition. (8) 1-Pentyne (140 µl, 1.40 mmol), Boc-protected bromopropylamine (400 mg, 1.7 mmol), and NaN_3 (136 mg, 2.1 mmol) were dissolved in DMF/H_2O (10 ml, 4:1). Sodium ascorbate (110 mg, 0.56 mmol, 40 mol%) was dissolved in H_2O (0.5 ml) and added. $CuSO_4$•$5H_2O$ (70 mg, 0.28 mmol, 20 mol%) was dissolved in H_2O (0.5 ml) and added as well. The reaction was refluxed at 100°C overnight. Upon reaction completion, NH_4OH (60 ml, 20% aq.) was added, and the product was extracted in EtOAc (3 ×

60 ml). The organic layer was dried over anhydrous sodium sulfate, and evaporated to dryness. The product was purified by flash chromatography using a gradient of 30-80% EtOAc in hexanes. Yield: 97 mg, 26%. R_f = 0.42 (70% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 5.08 (bs, NH), 4.30 (t, *J* = 6.8 Hz, 2H), 3.11 – 2.98 (m, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.06 – 1.93 (m, 2H), 1.68 – 1.53 (m, 2H), 1.35 (s, 9H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 148.2, 121.0, 79.2, 47.3, 37.3, 30.7, 28.3, 27.6, 22.6, 13.7; HRMS for $C_{13}H_{24}N_4O_2$ $[M+Na]^+$ calcd. 291.1797, found 291.1796.



2-Amino-3-(*tert*-butoxycarbonylamino)propanoic acid (29)

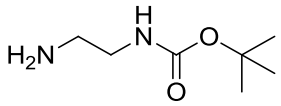
To a solution of 2,3-diaminopropanoic acid (100 mg, 0.7 mmol) in dioxane (5 ml) and H_2O (5 ml) was added NaOH (56 mg, 1.4 mmol). The reaction mixture was cooled to 0^{o}C and a solution of Boc anhydride (126 mg, 0.58 mmol) in dioxane (10 ml) was added drop wise. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 16 h. The solvent was removed under vacuum and the residue was purified with 20%/10%/70% MeOH/NH_4OH/DCM to afford the desired product (70 mg, 57% yield).



3-(*tert*-Butoxycarbonylamino)-2-(pentylamino)propanoic acid (30)

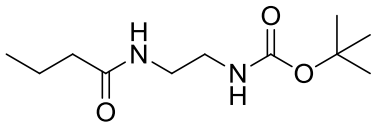
To a solution of **29** (136 mg, 0.66 mmol) in anhydrous MeOH (10 ml) was added 1% v/v AcOH in MeOH (100 µl) and pentanal (91 µl, 0.86 mmol). The mixture was stirred at room temperature for 5 h. The reaction mixture was cooled to 0^{o}C before addition of a first portion of $NaBH_4$ (37.4 mg, 0.99 mmol) and stirred at 0^{o}C for an additional 30 min. A second portion of $NaBH_4$ (37.4 mg, 0.99 mmol) was added and the mixture was stirred at 0^{o}C for an additional 30 min before stirring at room

temperature for 1 h. The excess $NaBH_4$ was quenched with saturated NH_4Cl (aq). The solvent was removed under vacuum and the residue was purified with 20% MeOH/DCM to yield the desired product which was used for further reaction.



***tert*-Butyl (2-aminoethyl)carbamate (31)**

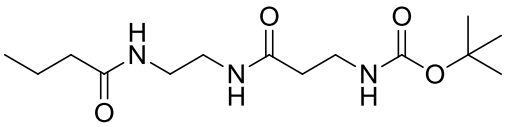
To a mixture of ethylenediamine (3.0 ml, 45.9 mmol) in anhydrous DCM (20 ml) cooled at 0^oC was added drop wise Boc anhydride (1.0 g, 4.6 mmol) in DCM (5 ml). The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was diluted in DCM (100 ml) and washed with H_2O (5 × 10 ml). The organic layer was dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The final product was purified by flash chromatography using a gradient of 20-40% EtOAc in hexanes. Yield: 604 mg, 82%. Characterization matched previous report of this known compound. (9) R_f = 0.53 (5% NH_4OH / 20% MeOH / 75% DCM); ^1H NMR (300 MHz, CD_3OD) δ 3.10 (t, *J* = 6.3 Hz, 2H), 2.68 (t, *J* = 6.3 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 157.1, 78.6, 42.5, 41.0, 27.4; HRMS for $C_7H_{16}N_2O_2$ $[M+H]^+$ calcd. 161.1290, found 161.1284.



***tert*-Butyl (2-butyramidoethyl)carbamate (32)**

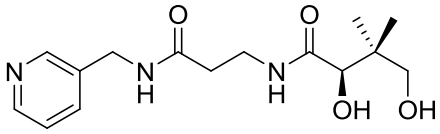
Compound **32** was synthesized according to general procedure B. Thus, compound **31** (400 ml, 2.5 mmol) was coupled to butyric acid (270 µl, 3.0 mmol), using EDC (623 mg, 3.3 mmol), DMAP (cat. 10 mg), and DIPEA (2.4 ml, 13.8 mmol). The product was purified by flash chromatography using a gradient of 0-15% MeOH in DCM. Yield: 306 mg, 53%. R_f = 0.68 (10% MeOH/DCM); ^1H NMR (300 MHz, $CDCl_3$) δ 6.55 (bs, NH), 5.25 (bs, NH), 3.36 – 3.26 (m, 2H), 3.27 – 3.15 (m, 2H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.68 – 1.53 (m, 2H), 1.39 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

173.9, 156.9, 79.5, 40.5, 40.2, 38.5, 28.3, 19.1, 13.7; HRMS for $C_{11}H_{22}N_2O_3$ $[M+Na]^+$ calcd. 253.1528, found 253.1524.



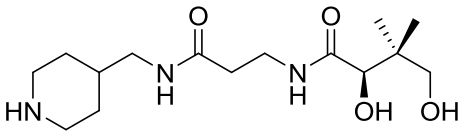
***tert*-Butyl (3-((2-butyramidoethyl)amino)-3-oxopropyl)carbamate (33)**

Compound **33** was synthesized using general procedure B. Thus, compound **32** (57 mg, 0.25 mmol) was Boc-deprotected and coupled to Boc-β-alanine (56 mg, 0.30 mmol) using EDC (62 mg, 0.33 mmol), DMAP (cat. 5 mg), and DIPEA (240 µl, 1.38 mmol) in THF (4 ml). The product was purified by flash chromatography using a gradient of 0-20% MeOH in DCM. Yield: 48 mg, 64% over 2 steps. R_f = 0.38 (10% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (bs, NH), 6.87 (bs, NH), 5.37 (bs, NH), 3.41 – 3.24 (m, 6H), 2.36 (t, *J* = 6.1 Hz, 2H), 2.13 (t, *J* = 7.5 Hz, 2H), 1.67 – 1.51 (m, 2H), 1.38 (s, 9H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 172.6, 156.2, 79.3, 39.8, 39.6, 38.4, 36.8, 36.3, 28.3, 19.1, 13.7; HRMS for $C_{14}H_{27}N_3O_4$ $[M+Na]^+$ calcd. 324.1900, found 324.1889.



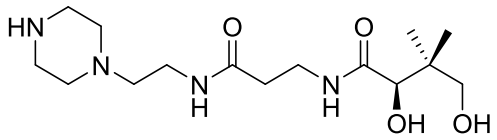
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-(pyridin-3-ylmethylamino)propyl)butanamide (Np-Pan) (34)

Experimental details are outlined in Procedure C to describe the deprotection of **55a** (125 mg, 0.29 mmol). Purification was carried out on silica gel with 20% MeOH/DCM to yield the product (84.7 mg, 0.274 mmol) in 94% yield. R_f = 0.33; ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.43 (d, *J* = 4.0 Hz, 1H), 7.78 (d, *J* = 4.0 Hz, 1H), 7.40 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.40 (s, 2H), 3.88 (s, 1H), 3.48-3.53 (m, 2H), 3.45 (d, *J* = 11.0 Hz, 1H), 3.38 (d, *J* = 11.0 Hz, 1H), 2.48 (t, *J* = 6.6 Hz, 2H), 0.89 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.7, 172.4, 148.0, 147.4, 136.3, 135.2, 123.9, 75.8, 68.9, 40.2, 39.0, 35.0, 34.9, 20.0, 19.5; HRMS-ESI for $C_{15}H_{23}N_3NaO_4$ $[M+Na]^+$ calcd. 332.1581, found 332.1592.



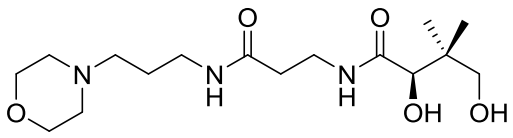
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-(piperidin-4-ylmethylamino)propyl)butanamide (35)

Experimental details are outlined in Procedure C to describe the deprotection of **55b** (99 mg, 0.23 mmol). Purification was carried out on silica gel with 30%/5%/65% MeOH/NH_4OH/DCM to yield the product (66 mg, 0.21 mmol) in 91% yield. R_f = 0.15; ^{1}H NMR (400 MHz, CD_3OD) δ 3.88 (s, 1H), 3.59-3.44 (m, 3H), 3.39-3.34 (m, 3H), 3.12 (d, *J* = 6.7 Hz, 2H), 2.94 (t, *J* = 10.1 Hz, 2H), 2.45 (t, *J* = 6.7 Hz, 2H), 1.93-1.89 (m, 2H), 1.82-1.78 (m, 1H), 1.47-1.38 (m, 2H), 0.91 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.6, 172.6, 75.6, 68.9, 43.6, 39.0, 35.2, 35.0, 34.0, 26.4, 20.1, 19.5; HRMS-ESI for $C_{15}H_{30}N_3O_4$ $[M+1]^+$ calcd. 316.2231, found 316.2225.



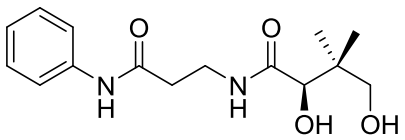
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-(2-(piperazin-1-yl)ethylamino)propyl)butanamide (36)

Experimental details are outlined in Procedure C to describe the deprotection of **55c** (120 mg, 0.268 mmol). Purification was carried out on silica gel with 30%/5%/65% MeOH/NH_4Cl/DCM to yield the product (79 mg, 0.24 mmol) in 90% yield. R_f, = 0.28; ^{1}H NMR (400 MHz, CD_3OD) δ 3.88 (s, 1H), 3.49-3.44 (m, 3H), 3.49-3.44 (m, 3H), 3.06 (t, *J* = 4.8 Hz, 4H), 2.62 (t, *J* = 4.8 Hz, 4H), 2.51 (t, *J* = 6.6 Hz, 2H), 2.43 (t, *J* = 6.6 Hz, 2H), 0.91 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.6, 172.4, 75.8, 68.9, 56.8, 51.0, 43.9, 39.0, 35.8, 35.1, 35.0, 20.0, 19.5; HRMS-ESI for $C_{15}H_{31}N_4O_4$ $[M+1]^+$ calcd. 331.2231, found 331.2342.



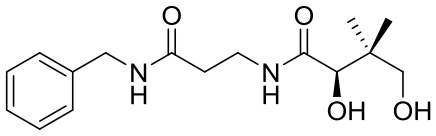
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-(3-morpholinopropylamino)-3-oxopropyl)butanamide (37)

Experimental details are outlined in Procedure C to describe the deprotection of **55d** (140 mg, 0.3 mmol). Purification was carried out on silica gel with 20%/2%/78% MeOH/NH_4Cl/DCM by column chromatography to yield the product (98 mg, 0.283 mmol) in 94% yield. R_f = 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (t, *J* = 5.9 Hz, 1H), 7.46 (t, *J* = 5.9 Hz, 1H), 3.92 (s, 1H), 3.65 (t, *J* = 4.4 Hz, 4H), 3.47 (m, 2H) 3.41 (dd, *J* = 11.1, 5.1 Hz, 2H), 3.29-3.14 (m, 2H), 2.35-2.41 (m, 8H), 1.67-1.58 (m, 2H), 0.91 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 171.5, 76.9, 70.5, 66.7, 57.0, 53.5, 39.3, 38.6, 35.8, 35.3, 25.2, 21.3, 20.5; HRMS-ESI for $C_{16}H_{32}N_3O_5$ $[M+1]^+$ Calcd 346.2329 found 346.2336.



(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-(phenylamino)propyl)butanamide (38)

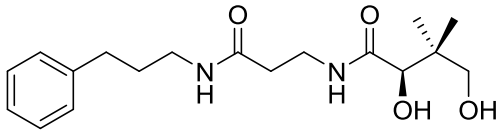
Experimental details are outlined in Procedure C to describe the deprotection of **55e**. Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (60 mg, 0.204 mmol) in 82% yield over two steps. R_f = 0.30; ^{1}H NMR (300 MHz, CD_3OD) δ 8.03 (t, *J* = 5.1 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 3.90 (s, 1H), 3.59-3.51 (m, 2H), 3.40 (d, *J* =12.0 Hz, 1H), 3.36 (d, *J* =12.0 Hz, 1H), 2.61 (t, *J* = 6.2 Hz, 2H) 0.91 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.7, 170.7, 138.3, 128.4, 123.8, 119.8, 75.8, 68.9, 39.0, 35.9, 35.0, 34.9, 19.9, 19.5; HRMS-ESI for $C_{15}H_{22}N_2NaO_4$ $[M+Na]^+$ calcd. 317.1472, found 317.1481.



***(R)*-*N*-(3-(Benzylamino)-3-oxopropyl)-2,4-dihydroxy-3,3-dimethylbutanamide (39)**

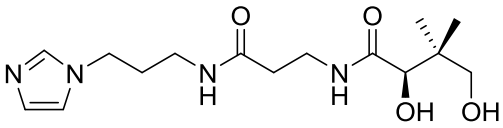
Experimental details are outlined in Procedure C to describe the deprotection of **55f** (98 mg, 0.23 mmol). Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (60 mg, 0.194 mmol) in 84% yield over two steps. R_f = 0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (t, *J* = 5.4 Hz, 1H), 7.31-7.21 (m, 5H), 6.66 (b, 1H), 4.36 (d, *J* = 5.4 Hz, 2H), 3.95 (s, 1H), 3.54 (dd, *J* = 12.0, 6.0 Hz,

2H), 3.45 (t, *J* = 6.0 Hz, 2H), 2.44 (t, *J* = 6.0 Hz, 2H), 0.95 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.9, 171.4, 137.8, 128.7, 127.8, 127.6, 70.7, 43.6, 39.3, 35.7, 35.3, 21.4, 20.4; HRMS-ESI for $C_{16}H_{24}N_2NaO_4$ $[M+Na]^+$ calcd. 331.1628, found 331.1634.



(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-((3-phenylpropyl)amino)propyl)butanamide (40)

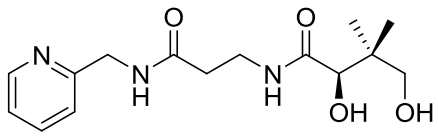
Compound **40** was synthesized according to general procedure G. The amine of compound **57a** (150 mg, 0.5 mmol) was deprotected and used directly in the nucleophilic ring opening of D-pantolactone (190 mg, 1.5 mmol) in the presence of triethylamine (340 µl, 2.5 mmol). The product was purified by flash chromatography using a gradient of 0-10% MeOH in EtOAc. Yield: 87 mg, 53% over two steps. R_f = 0.25 (10% MeOH/EtOAc); ^{1}H NMR (500 MHz, CD_3OD) δ 7.32 – 7.10 (m, 5H), 3.89 (s, 1H), 3.53 – 3.29 (m, 4H), 3.17 (t, *J* = 7.0 Hz, 2H), 2.68 – 2.57 (m, 2H), 2.41 (t, *J* = 6.7 Hz, 2H), 1.85 – 1.74 (m, 2H), 0.91 (s, 6H); ^{13}C NMR (126 MHz, CD_3OD) δ 174.6, 172.2, 141.5, 128.0, 128.0, 125.5, 75.8, 69.0, 39.0, 38.7, 35.1, 35.0, 32.8, 30.8, 19.9, 19.5; HRMS for $C_{18}H_{28}N_2O_4$ $[M+H]^+$ calcd. 337.2127, found 337.2199.



(*R*)-*N*-(3-(3-(1H-Imidazol-1-yl)propylamino)-3-oxopropyl)-2,4-dihydroxy-3,3-dimethylbutanamide (41)

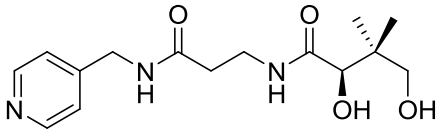
Experimental details are outlined in Procedure C to describe the deprotection of **55g** (126 mg, 0.28 mmol). Purification was carried out on silica gel with 20%/4%/76% MeOH/NH_4OH/DCM by column chromatography to yield the product (84 mg, 0.256 mmol) in 91% yield. R_f = 0.36; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70 (s, 1H), 7.17 (s, 1H), 6.98 (s, 1H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.88 (s, 1H), 3.51-3.36 (m, 4H), 3.16 (t, *J* = 6.9, 2H), 2.42 (t, *J* = 6.9 Hz, 2H), 1.99-1.94 (m, 2H), 0.91 (s, 6H); ^{13}C NMR (75 MHz,

CD_3OD) δ 174.6, 172.5, 137.1, 127.9, 119.3, 75.8, 68.9, 44.1, 39.0, 36.1, 35.0, 34.9, 30.5, 19.9, 19.5; HRMS-ESI for $C_{15}H_{27}N_4O_4$ $[M+1]^+$ calcd. 327.2027, found 327.2020.



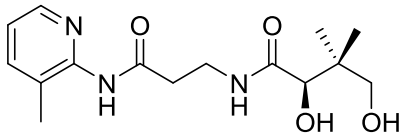
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-(pyridin-2-ylmethylamino)propyl)butanamide (42)

Experimental details are outlined in Procedure C to describe the deprotection of **55h** (115 mg, 0.27 mmol). Purification was carried out on silica gel with 20% MeOH/DCM to yield the product (76 mg, 0.25 mmol) in 91% yield. R_f = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.5 Hz, 1H), 7.61-7.63 (m, 3H), 7.23 (d, *J* = 7.8, 1H), 7.17, (t, *J* = 6.6 Hz, 1H), 4.44 (d, *J* = 5.3 Hz, 2H) 3.92 (s, 1H), 3.50 (m, 2H), 3.38 (dd, *J* = 12.1, 5.4 Hz, 2H), 2.47 (t, *J* = 5.8 Hz, 2H), 0.89 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 171.9, 156.6, 148.8, 137.3, 122.6, 122.4, 76.0, 70.0, 44.5, 39.2, 35.7, 35.3, 21.3, 20.5; HRMS-ESI for $C_{15}H_{23}N_3NaO_4$ $[M+Na]^+$ calcd. 332.1581, found 332.1589.



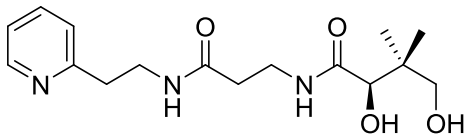
(*R*)-2,4-Dihydroxy-3,3-dimethyl-N-(3-oxo-3-((pyridin-4-ylmethyl)amino)propyl)butanamide (43)

Compound **43** was synthesized according to general procedure G. The amine of compound **57b** (80 mg, 0.29 mmol) was deprotected and used directly in the nucleophilic ring opening of D-pantolactone (112 mg, 0.86 mmol) in the presence of triethylamine (200 µl, 1.5 mmol). The product was purified by flash chromatography using a gradient of 0-20% MeOH in DCM. Yield: 28 mg, 31% over two steps. R_f = 0.34 (20% MeOH/DCM); ^{1}H NMR (300 MHz, CD_3OD) δ 8.46 (s, 2H), 7.35 (d, *J* = 5.2 Hz, 2H), 4.42 (s, 2H), 3.89 (s, 1H), 3.62 – 3.13 (m, 4H), 2.53 (t, *J* = 6.6 Hz, 2H), 0.90 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.7, 172.6, 149.4, 148.6, 122.5, 75.8, 68.9, 41.5, 39.0, 34.9, 34.9, 19.9, 19.5; HRMS for $C_{15}H_{23}N_3O_4$ $[M+H]^+$ calcd. 310.1767, found 310.1760.



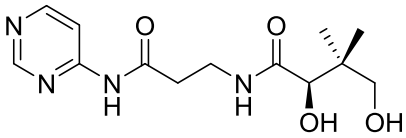
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-(3-methylpyridin-2-ylamino)-3-oxopropyl)butanamide (44)

Experimental details are outlined in Procedure C to describe the deprotection of **55k**. Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (55 mg, 0.178 mmol) in 71% yield over two steps. R_f = 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (b, 1H), 8.18 (d, *J* = 6.0 Hz, 1H), 7.59 (m, 2H), 7.13 (dd, *J* = 5.0, 2.3 Hz, 1H), 3.97 (s, 1H), 3.71-3.64 (m, 1H), 3.59-3.53 (m, 1H), 3.47-3.40 (m, 2H), 2.74-2.63 (m, 2H), 2.25 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 149.1, 145.5, 140.3, 122.3, 77.3, 70.4, 39.2, 35.7, 35.3, 21.7, 20.8, 17.9; HRMS-ESI for $C_{15}H_{23}N_3NaO_4$ $[M+Na]^+$ calcd. 332.1581, found 332.1589.



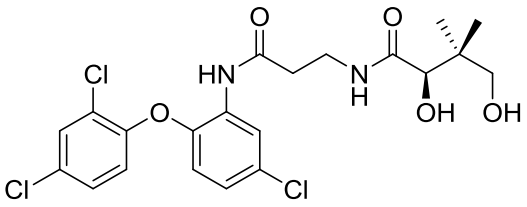
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-(2-(pyridin-2-yl)ethylamino)propyl)butanamide (45)

Experimental details are outlined in Procedure C to describe the deprotection of **55i** (110 mg, 0.25 mmol). Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (71 mg, 0.22 mmol) in 88% yield. R_f = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.65 (td, *J* = 7.7, 6.2 Hz, 1H), 7.53 (t, *J* = 6.2 Hz, 1H), 7.24-7.09 (m, 2H), 6.91 (t, *J* = 5.5 Hz, 1H), 3.99 (s, 1H), 3.69-3.62 (m, 2H), 3.61-3.42 (m, 4H), 2.94 (t, *J* = 6.5 Hz, 2H), 2.37 (t, *J* = 6.5 Hz, 2H), 0.99 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 171.7, 159.2, 148.7, 137.3, 123.7, 122.0, 73.1, 70.6, 39.3, 37.1, 35.9, 35.4 21.5, 20.5; HRMS-ESI for $C_{16}H_{25}N_3NaO_4$ $[M+Na]^+$ calcd. 346.1737, found 346.1738.



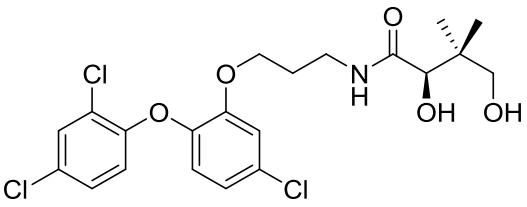
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-oxo-3-(pyrimidin-4-ylamino)propyl)butanamide (46)

Experimental details are outlined in Procedure C to describe the deprotection of **55m** (80 mg, 0.19 mmol). Purification was carried out on silica gel with 20% MeOH/DCM to yield the product (54 mg, 0.18 mmol) in 93% yield. R_f = 0.32; ^{1}H NMR (300 MHz, CD_3OD) δ 8.79 (s, 1H), 8.77 (d, *J* = 6.0 Hz, 1H), 8.16 (d, *J* = 6.0 Hz, 1H), 3.90 (s, 1H), 3.60-3.56 (m, 2H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.35 (d, *J* = 12.0 Hz, 1H), 2.72 (t, *J* = 6.0 Hz, 2H), 0.89 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.7, 172.2, 158.1, 157.8, 157.2, 110.1, 75.8, 68.9, 39.0, 36.0, 34.3, 19.9, 19.4; HRMS-ESI for $C_{13}H_{20}N_4NaO_4$ $[M+Na]^+$ calcd. 319.1377, found 319.1384.



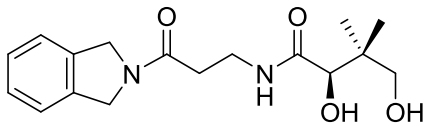
(*R*)-*N*-(3-((5-Chloro-2-(2,4-dichlorophenoxy)phenyl)amino)-3-oxopropyl)-2,4-dihydroxy-3,3-dimethylbutanamide (47)

Experimental details are outlined in Procedure C to describe the deprotection of **59** (60 mg, 0.10 mmol). Purification was carried out on silica gel with 100% EtOAc to yield the product (44 mg, 0.09 mmol) in 90% yield. R_f = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H) 7.92 (s, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.37(t, *J* = 5.2 Hz, 1H), 7.24 (d, *J* = 9 Hz, 1H), 6.95-6.99 (m, 2H), 6.58 (d, *J* = 9 Hz, 1H), 4.00 (s, 1H), 3.65 (q, *J* = 4.8 Hz, 2H), 3.49 (q, *J* = 4.4 Hz, 2H), 2.69 (t, *J* = 4.8 Hz, 2H) 1.00 (s, 3H), 0.9 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 169.9, 149.7, 143.8, 130.8, 129.3, 128.5, 126.8, 122.1, 121.2, 116.7, 77.6, 71.1, 69.6, 39.3, 36.8, 35.0, 21.3, 20.3; HRMS-ESI for $C_{21}H_{23}Cl_3N_2NaO_5$ $[M+Na]^+$ calcd. 511.0565, found 511.0568.



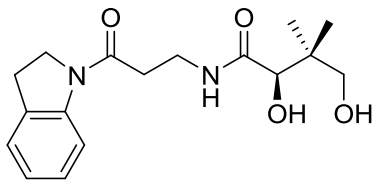
(*R*)-*N*-(3-(5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)propyl)-2,4-dihydroxy-3,3-dimethylbutanamide (48)

Experimental details are outlined in Procedure C to describe the deprotection of**61**. Purification was carried out on silica gel with 50% EtOAc/Hex to yield the product (90 mg, 0.19 mmol) in 50% yield over two steps. R_f = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.87-6.96 (m, 3H), 6.70 (d, *J* = 8.8 Hz, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.95 (s, 1H), 3.45 (q, *J* = 6.4 Hz, 2H), 3.26 (t, *J* = 6.0 Hz, 2H), 1.90 (q, *J* = 6.4 Hz, 2H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 152.1, 150.4, 143.4, 130.4, 130.4, 130.3, 128.3, 127.8, 124.7, 121.4, 118.6, 114.9, 71.2, 67.1, 39.3, 36.2, 28.8, 21.3, 20.2; HRMS-ESI for $C_{21}H_{24}Cl_3NNaO_5$ $[M+Na]^+$ calcd. 498.0612, found 498.0615.



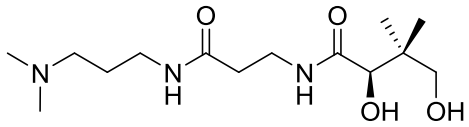
(*R*)-2,4-Dihydroxy-*N*-(3-(isoindolin-2-yl)-3-oxopropyl)-3,3-dimethylbutanamide (49)

Compound **49** was synthesized according to general Procedure G. The amine of compound **57c** (80 mg, 0.28 mmol) was deprotected and used directly in the nucleophilic ring opening of D-pantolactone (108 mg, 0.83 mmol) in the presence of triethylamine (195 µl, 1.4 mmol). The product was purified by flash chromatography using a gradient of 0-10% MeOH in EtOAc. Yield: 13 mg, 15% over two steps. R_f = 0.33 (10% MeOH/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (bs, NH), 7.33 – 7.21 (m, 4H), 4.76 (s, 4H), 4.02 (s, 1H), 3.65 (dd, *J* = 11.6, 5.8 Hz, 1H), 3.48 (s, 2H), 2.63 (t, *J* = 5.6 Hz, 2H), 1.00 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 170.6, 135.9, 135.7, 128.0, 127.7, 123.0, 122.7, 77.5, 71.0, 52.5, 52.1, 39.4, 34.5, 33.8, 21.5, 20.3; HRMS for $C_{17}H_{24}N_2O_4$ $[M+Na]^+$ calcd. 343.1634, found 343.1636.



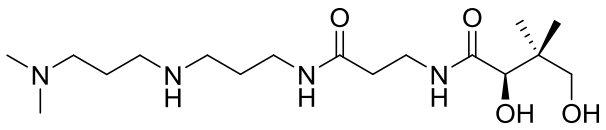
(*R*)-2,4-Dihydroxy-*N*-(3-(indolin-1-yl)-3-oxopropyl)-3,3-dimethylbutanamide (50)

Compound **50** was synthesized according to general Procedure G. The amine of compound **57d** (80 mg, 0.28 mmol) was deprotected and used directly in the nucleophilic ring opening of D-pantolactone (108 mg, 0.83 mmol) in the presence of triethylamine (195 µl, 1.4 mmol). The product was purified by flash chromatography using a gradient of 0-10% MeOH in EtOAc. Yield: 9 mg, 10% over two steps. R_f = 0.32 (10% MeOH/EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.01 (t, *J* = 8.4 Hz, 2H), 3.89 (s, 1H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.39 (s, 2H), 3.17 (t, *J* = 8.4 Hz, 2H), 2.65 (t, *J* = 6.0 Hz, 2H), 0.89 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.3, 169.8, 142.3, 131.4, 127.3, 124.7, 124.1, 116.8, 76.9, 70.5, 47.9, 39.0, 35.2, 34.3, 27.8, 20.6, 20.2; HRMS for $C_{17}H_{24}N_2O_4$ $[M+H]^+$ calcd. 321.1814, found 321.1806.



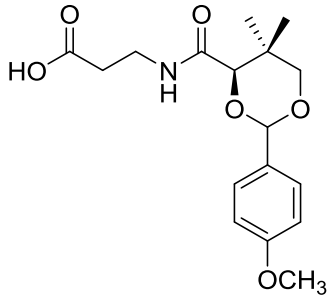
(*R*)-*N*-(3-(3-(Dimethylamino)propylamino)-3-oxopropyl)-2,4-dihydroxy-3,3-dimethylbutanamide (51)

Experimental details are outlined in Procedure C to describe the deprotection of **55j** (120 mg, 0.29 mmol). Purification was carried out on silica gel with 20%/5%/75% MeOH/NH_4OH/DCM to yield the product (78 mg, 0.258 mmol) in 89% yield. R_f = 0.31; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 1H), 3.44-3.49 (m, 4H), 3.22 (t, *J* = 7.7 Hz, 2H), 2.75 (q, *J* = 7.7 Hz, 2H), 2.58 (s, 6H), 2.45 (t, *J* = 6.6 Hz, 2H), 1.77-1.83 (m, 2H), 0.91 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 172.8, 75.6, 68.9, 55.6, 42.9, 39.0, 36.3, 35.2, 35.0, 25.5, 20.0, 19.5; HRMS-ESI for $C_{14}H_{30}N_3O_4$ $[M+1]^+$ calcd. 304.2231 found, 304.2236.



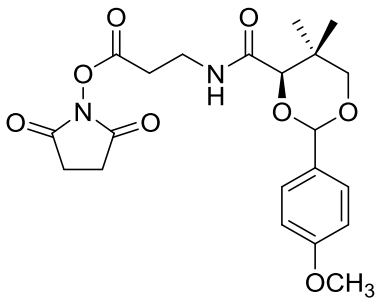
(*R*)-*N*-(3-(3-(3-(Dimethylamino)propylamino)propylamino)-3-oxopropyl)-2,4-dihydroxy-3,3-dimethylbutanamide (52)

Experimental details are outlined in Procedure C to describe the deprotection of **55l** (131 mg, 0.273 mmol). Purification was carried out on silica gel with 30%/10%/60% MeOH/NH_4OH/DCM to yield the product (83 mg, 0.23 mmol) in 84% yield. R_f = 0.36; ^{1}HNMR (300 MHz, CD_3OD) δ 3.89 (s, 1H), 3.36-3.52 (m, 4H), 3.25-3.31 (m, 4H), 3.01 (t, *J* = 7.1 Hz, 2H), 2.94, (t, *J* = 7.1 Hz, 2H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.46 (s, 6H), 1.91 (t, *J* = 6.6 Hz, 2H), 1.84 (t, *J* = 6.6 Hz, 2H), 0.91 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.6, 173.3, 75.8, 68.8, 56.0, 46.1, 45.0, 43.3, 39.0, 35.6, 35.1, 35.0, 26.6, 22.8, 20.0, 19.5; HRMS-ESI for $C_{17}H_{37}N_4O_4$ $[M+1]^+$ calcd. 361.2821, found 361.2809.



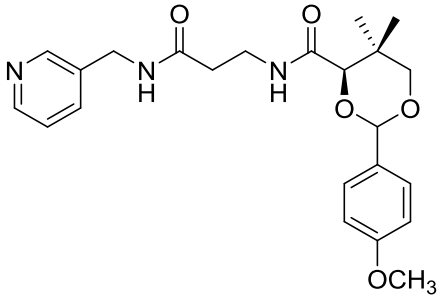
3-((*4R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamido)propanoic acid (53)

Synthesis and characterization followed a standard literature protocol. (10) The desired product was obtained as a white crystalline solid (5.3 g, 15.7 mmol) in 75% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.63 (bs, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.52 (s, 1H), 4.13 (s, 1H), 3.79 (s, 3H), 3.68 (dd, *J* = 11.7, 4.8 Hz, 2H), 3.58-3.43 (m, 2H), 2.51 (t, *J* = 6.6 Hz, 2H), 1.09 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.0, 170.2, 160.3, 130.4, 127.4, 113.1, 101.2, 83.6, 77.9, 54.3, 34.3, 33.1, 32.5, 20.7, 18.2; LRMS-ESI for $C_{17}H_{24}NO_6$ $[M+1]^+$ calcd. 338.16, found 338.36.



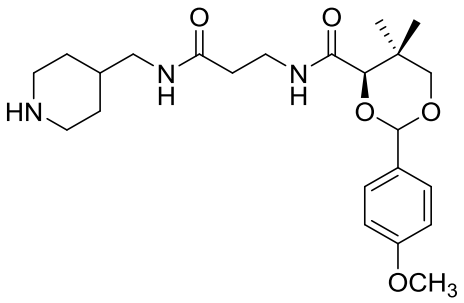
2,5-Dioxopyrrolidin-1-yl-3-((4*R*)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamido)propanoate (NHS ester) (54)

Synthesis and characterization followed a standard literature protocol. (10) From **53** (750 mg, 2.10 mmol) and *N*-hydroxysuccinimide (242 mg, 2.10 mmol) the desired product was obtained as a viscous, clear oil (824 mg, 1.9 mmol) in 90% yield, which was used in subsequent reactions without further purification.



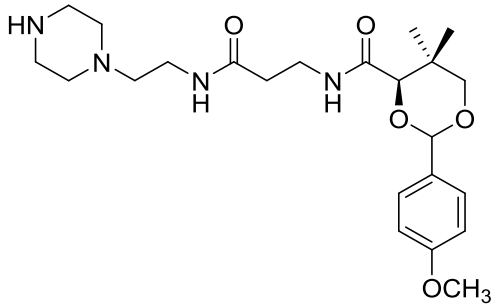
(*4R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-oxo-3-(pyridin-3-ylmethylamino)propyl)-1,3-dioxane-4-carboxamide (55a)

Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **50** (143 mg, 0.33 mmol) and 3-picolylamine (67 µl, 0.66 mmol). Purification was carried out on silica gel with 5% MeOH/DCM to yield the product (R_f = 0.27), which was used in subsequent reactions without further purification.



(*4R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-oxo-3-(piperidin-4-ylmethylamino)propyl)-1,3-dioxane-4-carboxamide (55b)

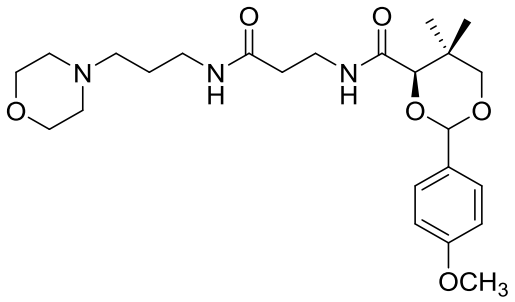
Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **54** (143 mg, 0.33 mmol) and 4-aminomethylpiperidine (50 µl, 0.66 mmol). Purification was carried out on silica gel with 25%/5%/70% MeOH/NH_4OH/DCM to yield the product (99 mg, 0.229 mmol) in 69% yield. $R_f = 0.15$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 3H), 7.13 (t, *J* = 6.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.44 (s, 1H), 4.04 (s, 1H), 3.79 (s, 3H), 3.70-3.58 (m, 2H), 3.51-3.38 (m, 4H), 3.12-3.08 (m, 2H), 2.81 (t, *J* = 11.8 Hz, 2H), 2.45 (t, *J* = 6.4 Hz, 2H), 1.85-1.77 (m. 3H), 1.59-1.56 (m, 2H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 169.7, 160.2, 130.1, 127.6, 113.8, 101.3, 83.8, 78.3, 63.6, 55.4, 43.9, 35.9, 35.3, 33.9, 33.1, 26.4, 21.9, 19.2; LRMS-ESI for $C_{23}H_{36}N_3O_5$ $[M+1]^+$ Calcd 434.26 found 434.33.



(*4R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-oxo-3-(2-(piperazin-1-yl)ethylamino)propyl)-1,3-dioxane-4-carboxamide (55c)

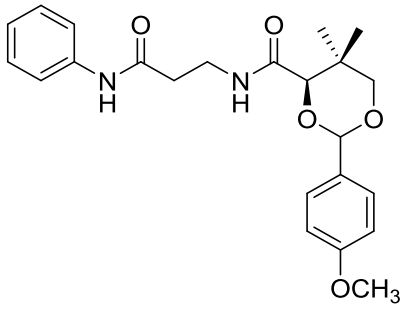
Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **54** (143 mg, 0.33 mmol) and 2-(piperazin-1-yl)ethanamine

(87 µl, 0.66 mmol). Purification was carried out on silica gel with 25%/5%/70% MeOH/NH_4OH/DCM to yield the product (121 mg, 0.27 mmol) in 82% yield. R_f = 0.28; ^{1}H NMR (300 MHz, $(CD_3)_3CO$) δ 7.47 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.56 (s, 1H), 4.11 (s, 1H), 3.81 (s, 3H), 3.63 (dd, *J* = 11.1, 6.9 Hz, 2H), 3.58-3.33 (m, 2H), 3.27 (t, *J* = 6.3 Hz, 2H), 2.85 (t, *J* = 4.8 Hz, 4H), 2.41-2.36 (m, 8H), 1.08 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $(CD_3)_3CO$) δ 170.7, 168.5, 160.1, 130.9, 127.7, 113.3, 101.0, 83.6, 77.9, 74.4, 57.6, 54.7, 53.3, 45.2, 36.0, 35.2, 32.7, 21.3, 18.7; LRMS-ESI for $C_{23}H_{37}N_4O_5$ $[M+1]^+$ calcd. 449.27, found 449.17.



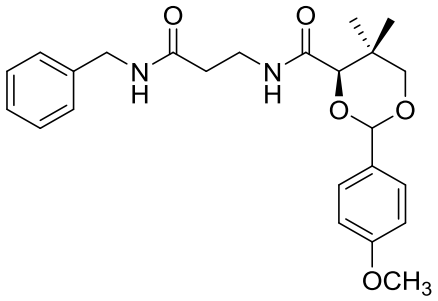
(*4R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-(3-morpholinopropylamino)-3-oxopropyl)-1,3-dioxane-4-carboxamide (55d)

Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **54** (143 mg, 0.33 mmol) and *N*-(3-aminopropyl)morpholine (97 µl, 0.66 mmol). Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (144 mg, 0.31 mmol) in 94% yield. R_f = 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 2H), 7.02 (bs, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.45 (s, 1H), 4.05 (s, 1H), 3.81 (s, 3H), 3.72-3.62 (m, 6H), 3.58-3.50 (m, 2H), 3.31-3.28 (m, 2H), 2.43-2.36 (m, 8H), 1.65-1.60 (m, 2H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.4, 160.2, 130.1, 127.5, 113.7, 101.3, 83.8, 78.4, 66.8, 57.2, 55.3, 53.5, 38.9, 36.1, 35.0, 33.0, 24.9, 21.8, 19.1; LRMS-ESI for $C_{24}H_{38}N_3O_6$ $[M+1]^+$ calcd. 464.27, found 464.22.



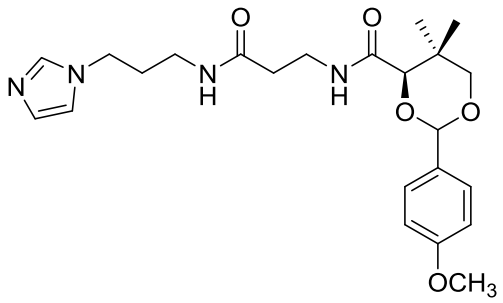
(*4R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-oxo-3-(phenylamino)propyl)-1,3-dioxane-4-carboxamide. **(55e)**

Experimental details are outlined in Procedure E to describe the synthesis of PMP protected *N*-substituted pantothenamides from **53** (84 mg, 0.25 mmol) and aniline (45 µl, 0.5 mmol). Purification was carried out on silica gel with 5% MeOH/DCM to yield the product (R_f = 0.35) and used for the deprotection step.



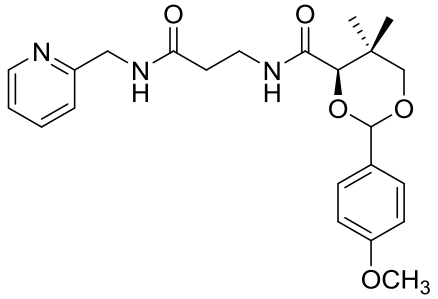
(*4R*)-*N*-(3-(Benzylamino)-3-oxopropyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamide (55f)

Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **54** (84 mg 0.25 mmol) and benzylamine (60 µl, 0.5 mmol). Purification was carried out on silica gel with 5% MeOH/DCM to yield the product (R_f = 0.34) which was used for the deprotection step.



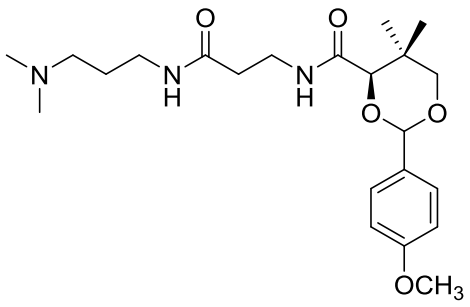
(*4R*)-*N*-(3-(3-(*1H*-Imidazol-1-yl)propylamino)-3-oxopropyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamide (55g)

Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **50** (143 mg, 0.33 mmol) and *N*-(3-(aminopropyl)-imidazole (79 µl, 0.66 mmol). Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (R_f = 0.31) which was used for the deprotection step.



(*4R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-oxo-3-(pyridin-2-ylmethylamino)propyl)-1,3-dioxane-4-carboxamide (55h)

Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **50** (143 mg, 0.33 mmol) and 2-picolylamine (68.0 µl, 0.66 mmol). The crude product was passed through a short pad of silica gel using 5% MeOH/DCM to afford the product (R_f = 0.28) which was used for the deprotection step.



(4*R*)-*N*-(3-(3-(Dimethylamino)propylamino)-3-oxopropyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamide (55i)

Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **54** (143 mg, 0.33 mmol) and 3-(dimethylamino)-1-propylamine (83 µl, 0.66 mmol). Purification was achieved on silica gel with 25%/10%/65% MeOH/NH_4OH/DCM to yield the product (124 mg, 0.295 mmol) in 89% yield. R_f = 0.31; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.7 Hz, 2H), 7.26 (t, *J* = 1.7 Hz, 1H), 7.06 (t, *J* = 1.7 Hz, 1H) 6.85 (d, *J* = 8.7 Hz, 2H), 5.40 (s, 1H), 4.01 (s, 1H), 3.75 (s, 3H), 3.61 (dd, *J* = 11.3, 5.6 Hz, 2H), 3.48 (m, 2H), 3.20 (q, *J* = 6.0 Hz, 2H), 2.35 (q, *J* = 6.8 Hz, 4H), 2.20 (s, 6H), 1.59 (m, 2H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 169.3, 160.1, 130.1, 127.5, 113.7, 101.2, 83.8, 78.4, 57.4, 55.3, 44.7, 38.3, 35.8, 35.0, 33.0, 25.8, 21.8, 19.1; LRMS-ESI for $C_{22}H_{36}N_3O_5$ $[M+1]^+$ calcd. 422.26, found 422.25.

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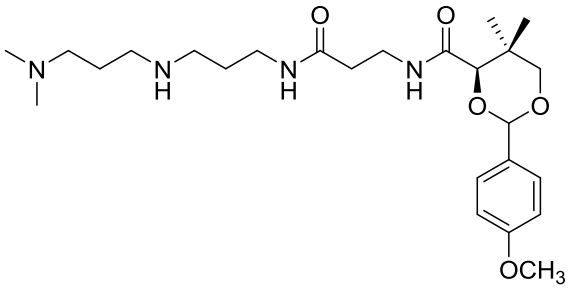
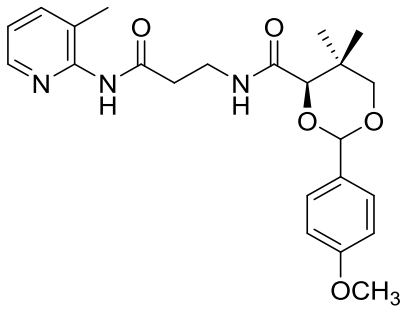


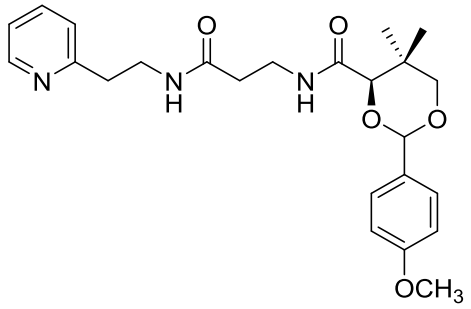
(4*R*)-*N*-(3-(3-(3-(Dimethylamino)propylamino)propylamino)-3-oxopropyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamide (55j)

Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **54** (143 mg, 0.33 mmol) and 1,3-propanediamine-*N*3-(3-aminopropyl)-*N1*-*N1*-dimethyl (118 µl, 0.66 mmol). Purification was achieved on silica gel with 25%/10%/65% MeOH/NH_4OH/DCM to yield the product (134 mg, 0.28 mmol) in 85% yield. R_f = 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.8 Hz, 2H), 7.28 (t, *J* = 3.9 Hz, 1H) 7.05 (t, *J* = 3.9 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.44 (s, 1H), 4.05 (s, 1H), 3.80 (s, 3H), 3.65 (q, *J* = 5.9, 2H), 3.47-3.55 (m, 2H), 3.26 (q, *J* = 6.5 Hz, 2H), 2.65 (q, *J* = 6.8 Hz, 4H), 2.29-2.39 (m, 4H), 2.20 (s, 6H), 1.62 (m, 4H), 1.08 (s, 3H), 1.07, (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.3, 160.2, 130.2, 127.5, 113.7, 113.6, 101.3, 83.8, 78.5, 58.1, 55.3, 48.4, 47.6, 45.4, 38.3, 36.0, 35.1, 33.0, 28.1, 26.7, 21.8, 19.1; LRMS-ESI for $C_{25}H_{43}N_4O_5$ $[M+1]^+$ calcd. 479.31, found 479.23.



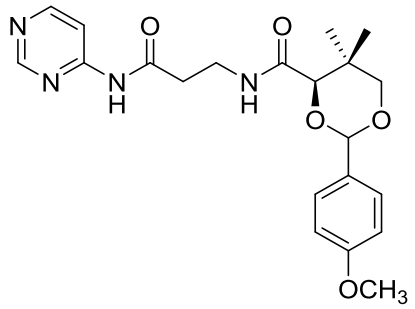
(4*R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-(3-methylpyridin-2-ylamino)-3-oxopropyl)-1,3-dioxane-4-carboxamide (55k)

Experimental details are outlined in Procedure E to describe the synthesis of PMP protected *N*-substituted pantothenamides from **53** (84 mg 0.25 mmol) and 2-amino-3-picoline (50 µl, 0.5 mmol). Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (R_f = 0.31). which was used for the deprotection step.



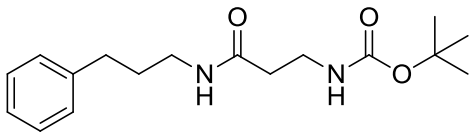
(4*R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-oxo-3-(2-(pyridin-2-yl)ethylamino)propyl)-1,3-dioxane-4-carboxamide (55l)

Experimental details are outlined in Procedure D to describe the synthesis of PMP protected *N*-substituted pantothenamides from NHS ester **54** (143. mg, 0.33 mmol) and 2-pyridylethylamine (53 µl, 0.66 mmol). Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (119 mg, 0.27 mmoL) in 82% yield. R_f = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.0 Hz, 1H), 7.58 (td, *J* = 8.0, 4.0 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.21-7.03 (m, 3H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.74 (t, *J* = 5.4 Hz, 1H), 5.42 (s, 1H), 4.03 (s, 1H), 3.78 (s, 3H), 3.73-3.36 (m, 6H), 2.90 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 6.4Hz, 2H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.3, 160.1, 159.4, 149.1, 136.7, 130.2, 127.5, 123.4, 121.6, 113.7, 101.3, 83.8, 78.5, 55.3, 38.7, 36.8, 36.0, 35.0, 33.0, 21.8, 19.1; LRMS-ESI for $C_{24}H_{32}N_3O_5$ $[M+1]^+$ calcd. for 442.23, found 422.19.



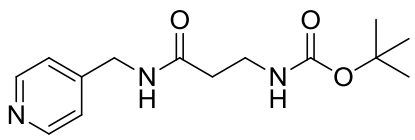
(4*R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-*N*-(3-oxo-3-(pyrimidin-4-ylamino)propyl)-1,3-dioxane-4-carboxamide (55m)

Experimental details are outlined in Procedure E to describe the synthesis of PMP protected *N*-substituted pantothenamides from **53** (84 mg 0.25 mmol) and 4-aminopyridine (47 mg, 0.5 mmol). Purification was achieved on silica gel with 10% MeOH/DCM to yield the product (89 mg, 0.215 mmol) in 86% yield. R_f = 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.85 (s, 1H), 8.60 (d, *J* = 5.7 Hz, 1H), 8.10 (d, *J* = 5.7 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 2H) 7.11 (t, *J* = 5.1 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.4 (s, 1H), 4.10 (s, 1H), 3.79 (s, 3H), 3.60-3.79 (m, 4H), 2.73 (t, *J* = 5.7 Hz, 2H), 1.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 169.8, 160.2, 158.3, 158.3, 157.1, 130.1, 127.5, 113.7, 110.4, 101.3, 83.8, 78.4, 55.3, 37.0, 34.5, 33.1, 21.8, 19.1; LRMS-ESI for $C_{21}H_{26}N_4NaO_5$ $[M+Na]^+$ calcd. 437.18, found 437.28



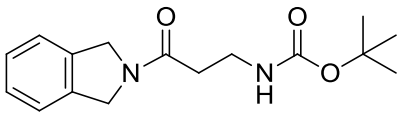
***tert*-Butyl (3-oxo-3-((3-phenylpropyl)amino)propyl)carbamate (57a)**

Compound **53g** was synthesized according to general Procedure B. Thus, 3-phenyl-1-propylamine (290 µl, 2.0 mmol) was coupled to Boc-β-alanine **(56)** (500 mg, 2.6 mmol), using EDC (506 mg, 2.6 mmol), HOBt (438 mg, 3.3 mmol), and DIPEA (1.9 ml, 11.0 mmol). The product was purified by flash chromatography using a gradient of 0-5% MeOH in DCM. Yield: 609 mg, 98%. R_f = 0.39 (5% MeOH/DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.20 – 7.14 (m, 3H), 5.86 (bs, NH), 5.19 (bs, NH), 3.37 (m, 2H), 3.27 (m, 2H), 2.68 – 2.61 (m, 2H), 2.34 (t, *J* = 5.9 Hz, 2H), 1.87 – 1.79 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 156.2, 141.3, 128.5, 128.3, 126.0, 79.3, 39.2, 36.6, 36.3, 33.3, 31.1, 28.4; HRMS for $C_{17}H_{26}N_2O_3$ $[M+Na]^+$ calcd. 329.1841, found 329.1826.



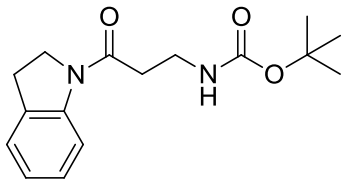
***tert*-Butyl (3-oxo-3-((pyridin-4-ylmethyl)amino)propyl)carbamate (57b)**

Compound **57b** was synthesized according to general procedure B. Thus, 4-(aminomethyl) pyridine (213 µl, 1.9 mmol) was coupled to Boc-β-alanine **(56)** (291 mg, 1.5 mmol), using EDC (384 mg, 2.0 mmol), HOBt (335 mg, 2.5 mmol), and DIPEA (1.5 ml, 8.5 mmol). The product was purified by flash chromatography using a gradient of 0-5% MeOH in $CHCl_3$. Yield: 361 mg, 70%. R_f = 0.36 (10% MeOH/ $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 2H), 7.57 (bs, NH), 7.09 (d, *J* = 5.2 Hz, 2H), 5.46 (bs, NH), 4.32 (d, *J* = 5.9 Hz, 2H), 3.31 (d, *J* = 6.1 Hz, 2H), 2.40 (t, *J* = 6.1 Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.3, 149.5, 147.9, 122.2, 79.3, 42.1, 36.7, 36.1, 28.3; HRMS for $C_{14}H_{21}N_3O_3$ $[M+Na]^+$ calcd. 302.1481, found 302.1474.



***tert*-Butyl (3-(isoindolin-2-yl)-3-oxopropyl)carbamate (57c)**

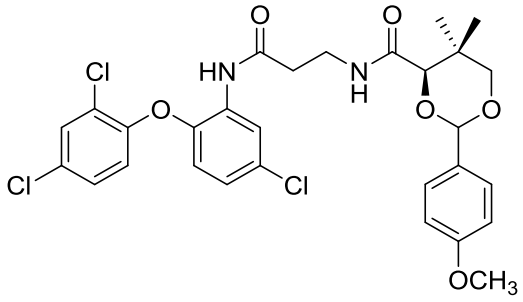
Compound **57c** was synthesized according to general procedure B. Thus, isoindoline (210 µl, 1.9 mmol) was coupled to Boc-β-alanine **(56)** (291 mg, 1.5 mmol), using EDC (384 mg, 2.0 mmol), HOBt (335 mg, 2.5 mmol), and DIPEA (1.5 ml, 8.5 mmol). The product was purified by flash chromatography using a gradient of 0-5% MeOH in $CHCl_3$. Yield: 280 mg, 63%. R_f = 0.54 (10% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.12 (m, 4H), 4.76 (t, *J* = 8.0 Hz, 4H), 3.46 (t, *J* = 5.7 Hz, 2H), 2.55 (t, *J* = 5.7 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 156.0, 136.2, 136.0, 127.9, 127.6, 123.0, 122.6, 79.1, 52.4, 52.0, 36.0, 34.4, 28.4; HRMS for $C_{16}H_{22}N_2O_3$ $[M+Na]^+$ calcd. 313.1528, found 313.1526.



***tert*-Butyl (3-(indolin-1-yl)-3-oxopropyl)carbamate (57d)**

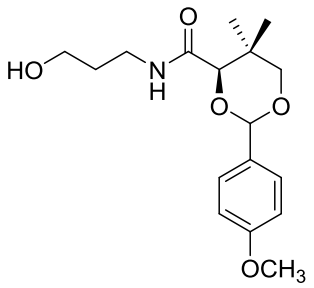
Compound **53o** was synthesized according to general procedure B. Thus, indoline (207 µl, 1.9 mmol) was coupled to Boc-β-alanine **(56)** (291 mg, 1.5 mmol), using EDC (384 mg, 2.0 mmol), HOBt (335

mg, 2.5 mmol), and DIPEA (1.5 ml, 8.5 mmol). The product was purified by flash chromatography using a gradient of 0-5% MeOH in $CHCl_3$. Yield: 306 mg, 60%. R_f = 0.53 (10% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.08 (m, 2H), 7.04 – 6.95 (m, 1H), 3.97 (t, *J* = 8.5 Hz, 2H), 3.48 (t, *J* = 5.6 Hz, 2H), 3.16 (t, *J* = 8.4 Hz, 2H), 2.59 (t, *J* = 6.0 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 156.0, 142.7, 131.1, 127.5, 124.6, 123.8, 116.8, 79.2, 47.8, 36.1, 36.0, 28.4, 27.9; HRMS for $C_{16}H_{22}N_2O_3$ $[M+Na]^+$ calcd. 313.1528, found 313.1536.



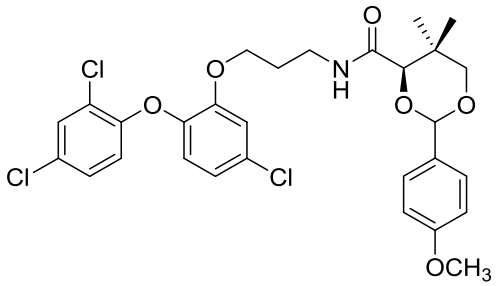
(4*R*)-*N*-(3-(5-Chloro-2-(2,4-dichlorophenoxy)phenylamino)-3-oxopropyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamide (59)

To a mixture of**58** (80 mg, 0.28 mmol), **53** (118 mg, 0.35 mmol), and HATU (160 mg, 0.42 mmol) in DMF (4 ml) was added DIPEA (175 µl, 0.99 mmol) and the mixture was stirred at 80^{o}C for 16 h. The reaction mixture was poured in a separatory funnel containing saturated aqueous NH_4Cl (10 ml) and extracted with DCM (3 × 15 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification of the oily residue was achieved on silica gel with 50% EtOAc/Hex to yield the product (122 mg, 0.20 mmol) in 72% yield. R_f = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.88 (s, 1H), 7.49 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.22-7.25 (m, 1H), 6.90- 6.98 (m, 4H), 6.58 (d, *J* = 8.6 Hz, 2H), 5.45 (s, 1H), 4.06 (s, 1H), 3.82 (s, 3H), 3.62-3.68 (m, 4H), 2.67 (t, *J* = 5.9 Hz, 2H), 1.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 169.5, 160.2, 149.8, 143.8, 130.8, 130.7, 130.1, 129.5, 129.3, 128.5, 127.4, 126.8, 123.7, 122.0, 121.0, 116.7, 113.8, 101.1, 83.7, 78.4, 55.3, 37.0, 34.6, 33.1, 21.8, 19.1; HRMS-ESI for $C_{29}H_{29}Cl_3N_2NaO_6$ $[M+Na]^+$ calcd. 629.10, found 629.37.



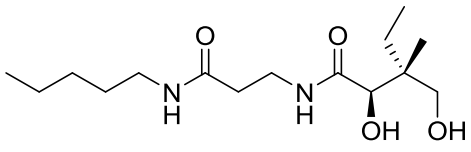
(4*R*)-*N*-(3-Hydroxypropyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamide (60)

Synthesis and characterization followed a standard literature protocol. (11)



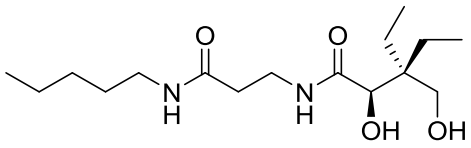
(4*R*)-*N*-(3-(5-Chloro-2-(2,4-dichlorophenoxy)phenoxy)propyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane-4-carboxamide (61)

A mixture of triclosan (135 mg, 0.48 mmol) and **60** (122 mg, 0.38 mmol) in anhydrous THF (5 ml) was cooled to 0^{o}C before addition of PPh_3 (125 mg, 0.48 mmol) in anhydrous THF (2.5 ml). The mixture was stirred for 10 min after which DIAD (93 µl, 0.48 mmol) was added drop wise. The reaction mixture was allowed to warm to room temperature and stirred for an additional 24 h under nitrogen. The solvent was removed under vacuum and purification was achievedon silica gel with 30% EtOAc/hexanes. The product, which was contaminated with Ph_3PO, was used in subsequent steps without further purification.



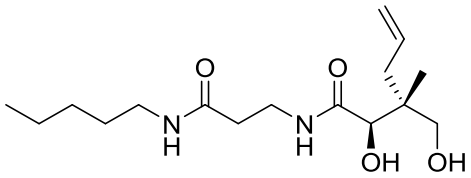
(2*R*,3*R*)-2-Hydroxy-3-(hydroxymethyl)-3-methyl-*N*-(3-oxo-3-(pentylamino)propyl)pentanamide (62) from **75a**

Synthesis and characterization followed a standard literature protocol. (1)



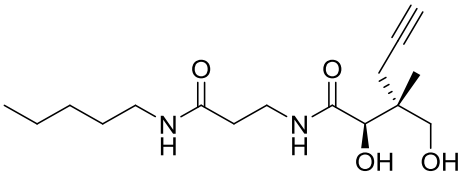
(*R*)-3-Ethyl-2-hydroxy-3-(hydroxymethyl)-*N*-(3-oxo-3-(pentylamino)propyl)pentanamide (63)

Experimental details are outlined in Procedure C to describe the deprotection of **75b**. Purification was achieved on silica gel with 5% MeOH/DCM to yield the product (30 mg, 0.10 mmol) in 64% yield over 4 steps. R_f = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (bs, 1H), 7.25 (bs, 1H), 4.01 (s, 1H), 3.56 (s, 2H), 3.53-3.46 (m, 2H), 3.20 (q, *J* = 6.8 Hz, 2H), 2.42 (t, *J* = 5.8 Hz, 2H), 1.52-1.38 (m, 5H), 1.33-1.22 (m, 5H), 0.90-0.82 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 171.6, 76.2, 66.5, 43.8, 39.7, 35.7, 35.4, 29.1, 23.9, 22.9, 22.3, 14.0, 7.7, 7.5; HRMS-ESI for $C_{16}H_{32}N_2NaO_4$ $[M+Na]^+$ calcd. 339.2254, found 339.2263.



(2*R*,3*R*)-2-Hydroxy-3-(hydroxymethyl)-3-methyl-*N*-(3-oxo-3-(pentylamino)propyl)hex-5-enamide (64) from **75c**

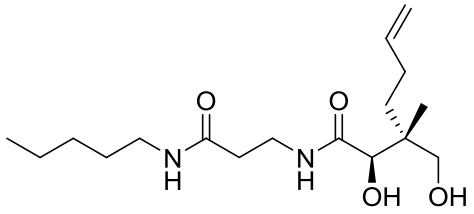
Synthesis and characterization followed a standard literature protocol. (1)



(2*R*,3*R*)-2-Hydroxy-3-(hydroxymethyl)-3-methyl-*N*-(3-oxo-3-(pentylamino)propyl)hex-5-ynamide (65) from **75d**

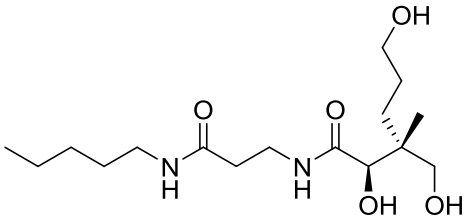
Experimental details are outlined in Procedure C to describe the deprotection of **75d** (170 mg, 0.40 mmol). Purification was achieved on silica gel with 10% MeOH/DCM to yield the product (100 mg, 0.32 mmol) in 81% yield. R_f = 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, *J* = 6.1 Hz, 1H), 6.51 (t, *J* = 5.6 Hz, 1H), 4.09 (s, 1H), 3.62 (dd, *J* = 11.4, 9.1 Hz, 2H), 3.58-3.44 (m, 2H), 3.18 (q, *J* = 6.8 Hz, 2H),

2.47-2.28 (m, 4H), 2.01 (t, *J* = 4.0 Hz, 1H), 1.51-1.1.43 (m, 2H), 1.33-1.22 (m, 4H), 1.00 (s, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 171.6, 81.2, 75.8, 70.9, 67.4, 41.8, 39.7, 35.7, 35.4, 29.1, 23.8, 22.3, 18.1, 14.0; HRMS-ESI for $C_{16}H_{28}N_2NaO_4$ $[M+Na]^+$ calcd. 335.1941, found 335.1947.



(2*R*,3*R*)-2-Hydroxy-3-(hydroxymethyl)-3-methyl-*N*-(3-oxo-3-(pentylamino)propyl)hept-6-enamide (66)

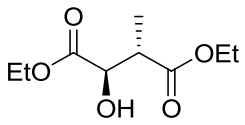
Experimental details are outlined in Procedure C to describe the deprotection of **75e**. Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (90 mg, 0.27 mmoL) in 44% yield over 4 steps. R_f = 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (t, *J* = 6.0 Hz, 1H), 6.22 (t, *J* = 5.3 Hz, 1H), 5.80-5.74 (m, 1H), 4.98 (dd, *J* = 11.9, 8.8 Hz, 2H), 4.0 (s, 1H), 3.62-3.42 (m, 4H), 3.18 (q, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 2.02 (q, *J* = 8.1 Hz, 2H), 1.66-1.56 (m, 1H), 1.49-1.24 (m, 7H), 0.95 (s, 3H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 171.6, 139.0, 114.3, 68.4, 41.7, 39.7, 35.8, 35.3, 32.6, 29.1, 29.0, 27.8, 22.3, 18.9, 14.0; HRMS-ESI for $C_{17}H_{32}N_2NaO_4$ $[M+Na]^+$ calcd. 351.2254, found 351.2268.



(2*R*,3*R*)-2,6-Dihydroxy-3-(hydroxymethyl)-3-methyl-*N*-(3-oxo-3-(pentylamino)propyl)hexanamide (67)

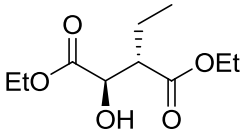
Experimental details are outlined in Procedure C to describe the deprotection of **75f** (50 mg, 0.094 mmol). Purification was carried out on silica gel with 10% MeOH/DCM to yield the product (20 mg,

0.06 mmol) in 64% yield. R_f = 0.25; ^{1}H NMR (300 MHz, CD_3OD) δ 3.94 (s, 1H), 3.51-3.44 (m, 6H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.51-1.48 (m, 5H), 1.33-1.30 (m, 5H), 0.93-0.89 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.8, 172.2, 75.5, 66.3, 62.4, 41.2, 39.0, 35.1, 35.0, 29.2, 28.8, 28.7, 26.2, 22.0, 17.1, 12.9; HRMS-ESI for $C_{16}H_{32}N_2NaO_4$ $[M+Na]^+$ calcd. 355.2203, found 355.2214.



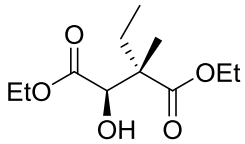
Diethyl (2*R, 3S*)-2-hydroxy-3-methylsuccinate 69a

Synthesis and characterization followed a standard literature protocol. (1)



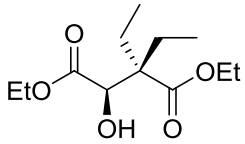
Diethyl (*2S,* 3*R*)-2-ethyl-3-hydroxysuccinate (69b)

Synthesis and characterization followed a standard literature protocol. (1)



Diethyl (2*S*,3*R*)-2-ethyl-3-hydroxy-2-methylsuccinate (70a)

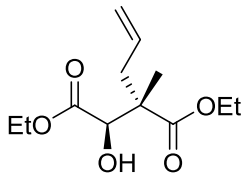
Synthesis and characterization followed a standard literature protocol. (1)



(*R*)-Diethyl 2,2-diethyl-3-hydroxysuccinate (70b)

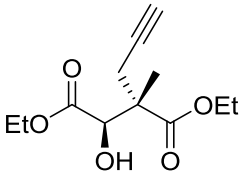
Synthesis followed a standard literature protocol (1), starting with the alkylation of **69b** (540 mg, 2.5 mmol). Purification was carried out on silica gel with 40% Et_2O/Hex to yield the product which was

used in the reduction step as the product was always contaminated with the starting material.



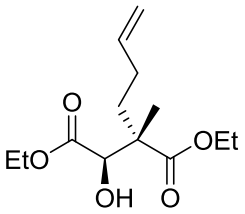
Diethyl (2*S*,3*R*)-2-allyl-3-hydroxy-2-methylsuccinate (70c)

Synthesis and characterization followed a standard literature protocol. (1)



(*2S,3R*)-Diethyl 3-hydroxy-2-methyl-2-(prop-2-yn-1-yl)succinate (70d)

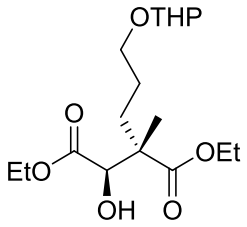
Synthesis followed a standard literature protocol (1), starting with the alkylation of **69a** (668 mg, 3.27 mmol). Purification was carried out on silica gel with 40% Et_2O/Hex to yield the product (455 mg, 1.88 mmol) in 58% yield. R_f = 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (m, 5H), 3.33 (d, *J* = 7.2 Hz, 1H), 2.64 (d, *J* = 2.7 Hz, 2H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.33 (s, 3H), 1.31-1.71 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 172.5, 79.9, 74.3. 71.2, 62.0, 61.3, 49.6, 25.0, 18.8, 14.1, 14.0; LRMS-ESI for$C_{12}H_{18}NaO_5$ $[M+Na]^+$ calcd. 265.11, found 265.16.



(*2S,3R*)-Diethyl 2-(but-3-en-1-yl)-3-hydroxy-2-methylsuccinate (70e)

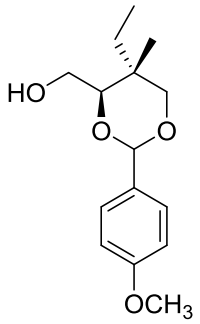
Synthesis followed a standard literature protocol (1), starting with the alkylation of **69a** (813 mg, 3.99 mmol). Purification was carried out on silica gel with 40% Et_2O/hexanes to yield the product (460 mg, 1.78 mmol) in 45% yield. R_f = 0.37; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80-5.69 (m, 1H), 5.02-4.91 (m, 2H), 4.26-4.12 (m, 5H), 3.37 (d, *J* = 7.2 Hz, 1H), 2.08-1.80 (m, 2H), 1.84 (td, *J* = 7.1, 4.7 Hz, 1H), 1.66-1.56 (td, *J* = 7.1, 4.7 Hz, 1H), 1.30-1.22 (m, 6H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5,

172.6, 138.0, 114.8, 75.6, 61.8, 60.9, 49.8, 34.4, 28.6, 17.3, 14.1; LRMS-ESI for $C_{13}H_{22}NaO_5$ $[M+Na]^+$ calcd. 281.14, found 281.16.



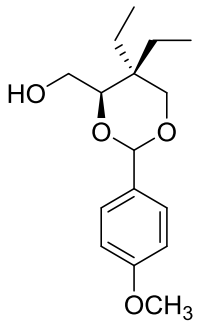
(*2S,3R*)-Diethyl 3-hydroxy-2-methyl-2-(3-((tetrahydro-*2H*-pyran-2-yl)oxy)propyl)succinate (70f)

Synthesis followed a standard literature protocol,(1) starting with the alkylation of **69a** (670 mg, 3.27 mmol). Purification was carried out on silica gel with 30% EtOAc/hexanes to yield the product (500 mg, 1.45 mmol) in 44% yield. R_f = 0.31; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (t, *J* = 2.9 Hz, 1H), 4.24-4.03 (m, 5H), 3.82-3.76 (m, 1H), 3.68-3.63 (m, 1H), 3.47-3.29 (m, 3H), 1.80-1.41 (m, 10H), 1.27-1.17 (m, 6H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 171.8, 98.7, 75.6, 67.4, 62.2, 61.7, 60.9, 49.8, 31.8, 30.6, 25.4, 24.7, 19.5, 17.2, 14.1. LRMS-ESI for $C_{17}H_{30}NaO_7$ $[M+Na]^+$ calcd. 369.19, found 369.40.



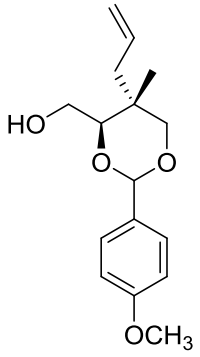
((4*R*,5*R*)-5-Ethyl-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)methanol (71a)

Synthesis and characterization followed a standard literature protocol. (1)



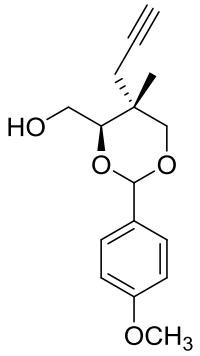
((*4R*)-5,5-Diethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)methanol (71b)

Experimental details are outlined in Procedure F to describe the reduction and 1,3 protection of triols. Crude (*R*)-3,3-diethylbutane-1,2,4-triol (100 mg, 0.62 mmol) was obtained. Purification of protected triol was carried out on silica gel with 30% EtOAc/hexanes to yield the product (100 mg, 0.36 mmol) in 58% yield over two steps. R_f = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H) 5.44 (s, 1H), 4.00-3.58 (m, 8H), 1.34-1.23 (m, 4H), 1.01-0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 130.9, 127.6, 113.7, 101.9, 85.3, 72.6, 61.3, 55.3, 36.2, 25.4, 23.1, 8.37, 8.05; LRMS-ESI for $C_{16}H_{24}NaO_4$ $[M+Na]^+$ calcd. 303.16, found 303.34.



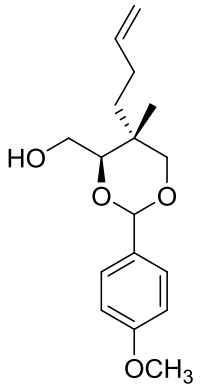
((4*R*,5*R*)-5-Allyl-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)methanol (71c)

Synthesis and characterization followed a standard literature protocol. (1)



((*4R,5R*)-2-(4-Methoxyphenyl)-5-methyl-5-(prop-2-ynyl)-1,3-dioxan-4-yl)methanol (71d)

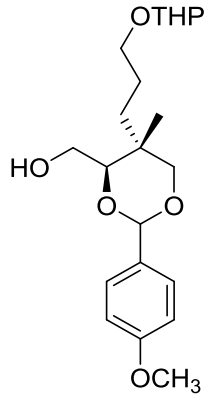
Experimental details are outlined in Procedure F to describe the reduction and 1,3 protection of triols. Crude (*2R,3R*)-3-methyl-3-(prop-2-yn-1-yl)butane-1,2,4-triol (170 mg, 1.08 mmol) was obtained. Purification of protected triol was carried out on silica gel with 30% EtOAc/hexanes to yield the product (256 mg, 0.93 mmol) in 86% yield. R_f = 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.47 (s, 1H), 3.89-3.85 (m, 8H), 2.20 (b, 1H), 2.14-2.10 (m, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 130.6, 127.8, 113.7, 101.9, 83.6, 79.1, 76.6, 71.9, 61.4, 55.3, 33.8, 25.1, 17.5; LRMS-ESI for $C_{16}H_{20}NaO_4$ $[M+Na]^+$ calcd. 299.13, found 299.31.



((*4R,5R*)-5-(But-3-enyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)methanol (71e)

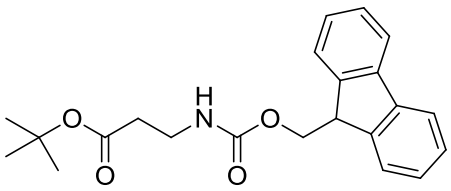
Experimental details are outlined in Procedure F to describe the reduction and 1,3 protection of triols. Crude (*2R,3R*)-3-(but-3-en-1-yl)-3-methylbutane-1,2,4-triol (143 mg, 0.87 mmol) was obtained. Purification of protected triol was carried out on silica gel with 30% EtOcA/hexanes to yield the product (180 mg, 0.62 mmol) in 71% yield. R_f = 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.82-5.73 (m, 1H), 5.45 (s, 1H), 5.07-4.95 (m, 2H), 3.85-3.62 (m, 9H), 2.08-

1.94 (m, 2H), 1.43-1.23 (m, 2H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 138.3, 130.8, 127.6, 114.9, 113.7, 101.8, 85.2, 77.5, 61.3, 55.3, 35.0, 34.0, 27.1, 17.2; LRMS-ESI for $C_{17}H_{24}NaO_4$ $[M+Na]^+$ calcd. 315.15, found 315.35.



((*4R,5R*)-2-(4-Methoxyphenyl)-5-methyl-5-(3-(tetrahydro-2H-pyran-2-yloxy)propyl)-1,3-dioxan-4-yl)methanol (71f)

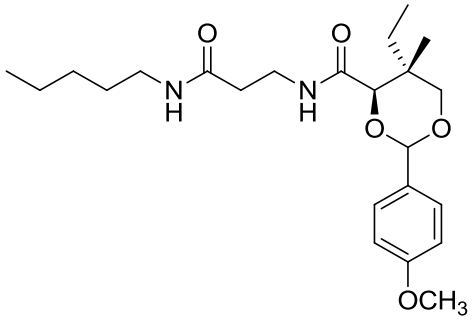
Experimental details are outlined in Procedure F to describe the reduction and 1,3 protection of triols. Crude (*2R,3R*)-3-methyl-3-(3-((tetrahydro-*2H*-pyran-2-yl)oxy)propyl)butane-1,2,4-triol (308 mg, 1.18 mmol) was obtained. Purification of protected triol was carried out on silica gel with 30% EtOAc/hexanes to yield the product (225 mg, 0.59 mmol) which was used for further reaction.



***tert*-Butyl 3-(((9H-fluoren-9-yl)methoxy)carbonylamino)propanoate (73)**

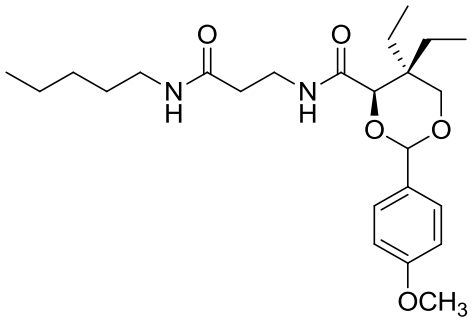
To a solution of Fmoc *β*-alanine (400 mg, 1.29 mmol) in anhydrous DCM (8 ml) was added *tert*-butanol (190 ul, 1.93 mmol), EDC (369 mg, 1.93 mmol) and DMAP (78 mg, 0.65 mmol). The mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with DCM (20 ml) and washed with a saturated aqueous solution of NH_4Cl (3 × 5 ml). Purification was carried out on silica gel with 10% EtOAc/hexanes to yield the product (294 mg, 0.80 mmol) in 62% yield. R_f = 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H) 7.31 (d, *J* =

8.5, 7.4 Hz, 2H), 5.38 (b, 1H), 4.38 (d, *J* = 7.1 Hz, 2H), 4.23 (t, *J* = 7.0 Hz, 1H), 3.45 (q, *J* = 5.7 Hz, 2H), 2.47 (q, *J* = 5.7 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 156.3, 144.0, 141.3, 127.7, 127.0, 125.1, 120.0, 81.1, 66.7, 47.2, 36.7, 35.5, 28.1; LRMS-ESI for $C_{22}H_{26}NO_4$ $[M+1]^+$ calcd. 368.19, found 368.55.



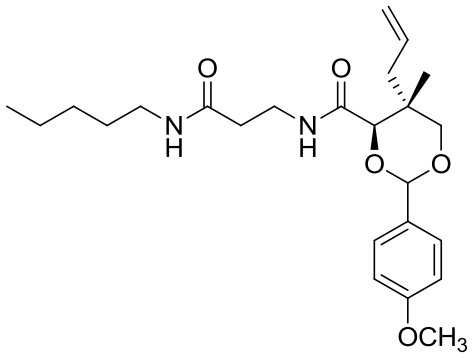
(4*R*,5*R*)-5-Ethyl-2-(4-methoxyphenyl)-5-methyl-*N*-(3-oxo-3-(pentylamino)propyl)-1,3-dioxane-4-carboxamide (75a)

Synthesis and characterization followed a standard literature protocol. (1)



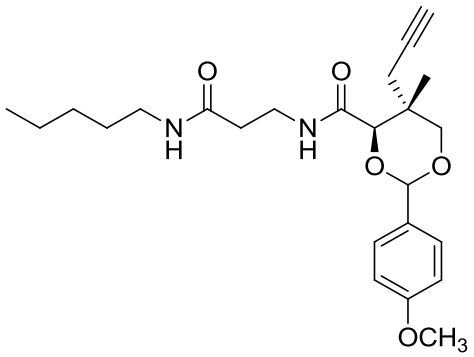
(4*R*)-5,5-Diethyl-2-(4-methoxyphenyl)-*N*-(3-oxo-3-(pentylamino)propyl)-1,3-dioxane-4-carboxamide (75b)

Experimental details are outlined in Procedure A for the oxidation of alcohol **71b** (85 mg, 0.30 mmol), and in Procedure B for amide coupling with **73** (54 mg, 0.14 mmol). Purification was carried out on silica gel with 100% EtOAc to yield the product. (R_f = 0.43) which was used in the deprotection step without further characterization.



(4*R*,5*R*)-5-Allyl-2-(4-methoxyphenyl)-5-methyl-*N*-(3-oxo-3-(pentylamino)propyl)-1,3-dioxane-4-carboxamide (75c)

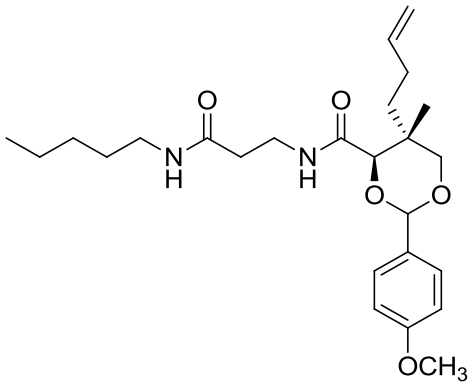
Synthesis and characterization followed a standard literature protocol. (1)



(*4R,5R*)-2-(4-Methoxyphenyl)-5-methyl-*N*-(3-oxo-3-(pentylamino)propyl)-5-(prop-2-ynyl)-1,3-dioxane-4-carboxamide (75d)

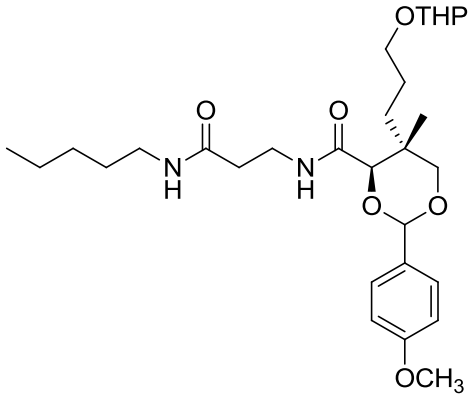
Experimental details are outlined in Procedure A for the oxidation of alcohol **71d** (253 mg, 0.93 mmol), and in Procedure B for amide coupling with **73** (524 mg, 1.38 mmol). Purification was carried out on silica gel with 80% EtOAc/hexanes to yield the product (200 mg, 0.47 mmol) in 51% yield over 3 steps. R_f = 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.09 (t, *J* = 5.9 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.82 (t, *J* = 5.0 Hz, 1H), 5.46 (s, 1H), 4.35 (s, 1H), 3.93 (dd, *J* = 11.4, 7.2 Hz, 2H), 3.81 (s, 3H), 3.53-3.44 (m, 2H), 3.15 (q, *J* = 5.8 Hz, 2H), 2.53 (d, *J* = 7.2 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 1H), 2.36 (t, *J* = 6.2 Hz, 2H), 2.05 (t, *J* = 2.6 Hz, 1H), 1.47-1.40 (m, 2H), 1.29-1.15 (m, 4H), 1.15 (s, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.3, 160.2, 129.9, 127.5, 113.7, 101.2, 81.0,

79.9, 75.9, 71.4, 55.3, 39.5, 35.9, 35.0, 34.9, 29.2, 29.0, 25.2, 22.3, 17.3, 14.0; LRMS-ESI for $C_{24}H_{34}N_2O_5$ $[M-1]^-$ calcd. 429.24, found 429.26.



(*4R,5R*)-5-(But-3-en-1-yl)-2-(4-Methoxyphenyl)-5-methyl-*N*-(3-oxo-3-(pentylamino)propyl)-1,3-dioxane-4-carboxamide (75e)

Experimental details are outlined in Procedure A for the oxidation of alcohol **71e** (180 mg, 0.62 mmol), and in Procedure B for amide coupling with **73** (336 mg, 0.89 mmol). Purification was carried out on silica gel with 70% EtOAc/hexanes to yield the product (R_f = 0.40) yielded the product which was always contaminated with the coupling agent and was used in the deprotection step.

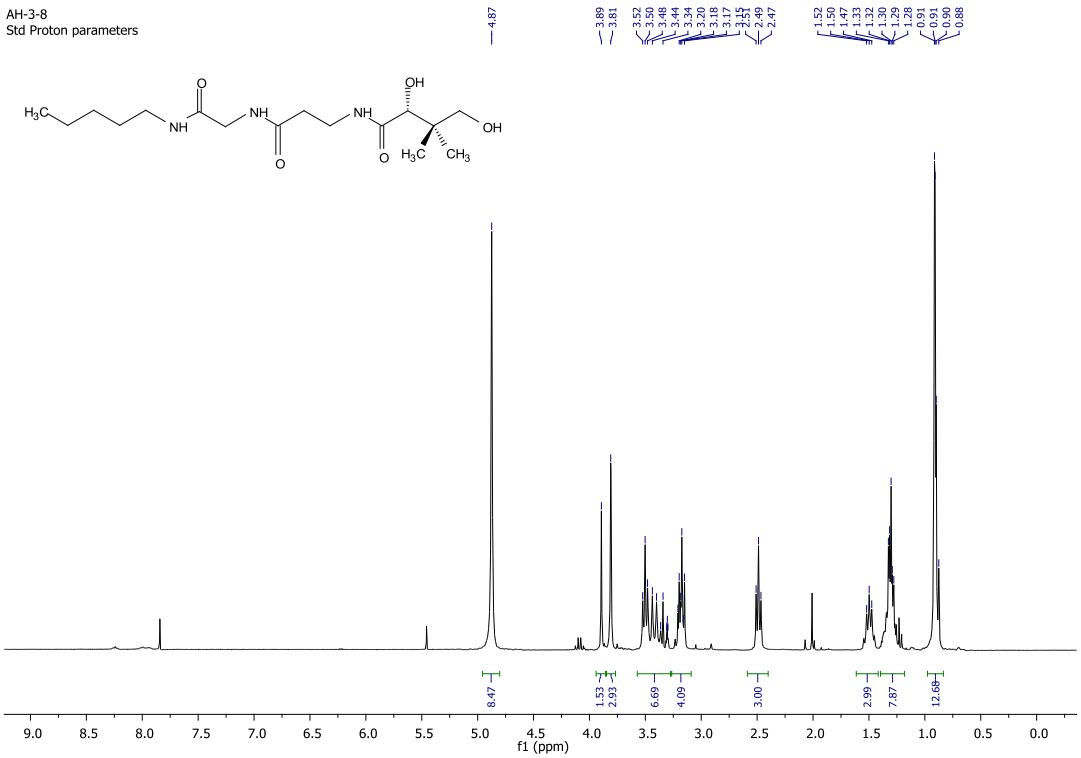


(*4R,5R*)-2-(4-Methoxyphenyl)-5-methyl-*N*-(3-oxo-3-(pentylamino)propyl)-5-(3-(tetrahydro-*2H*-pyran-2-yloxy)propyl)-1,3-dioxane-4-carboxamide (75f)

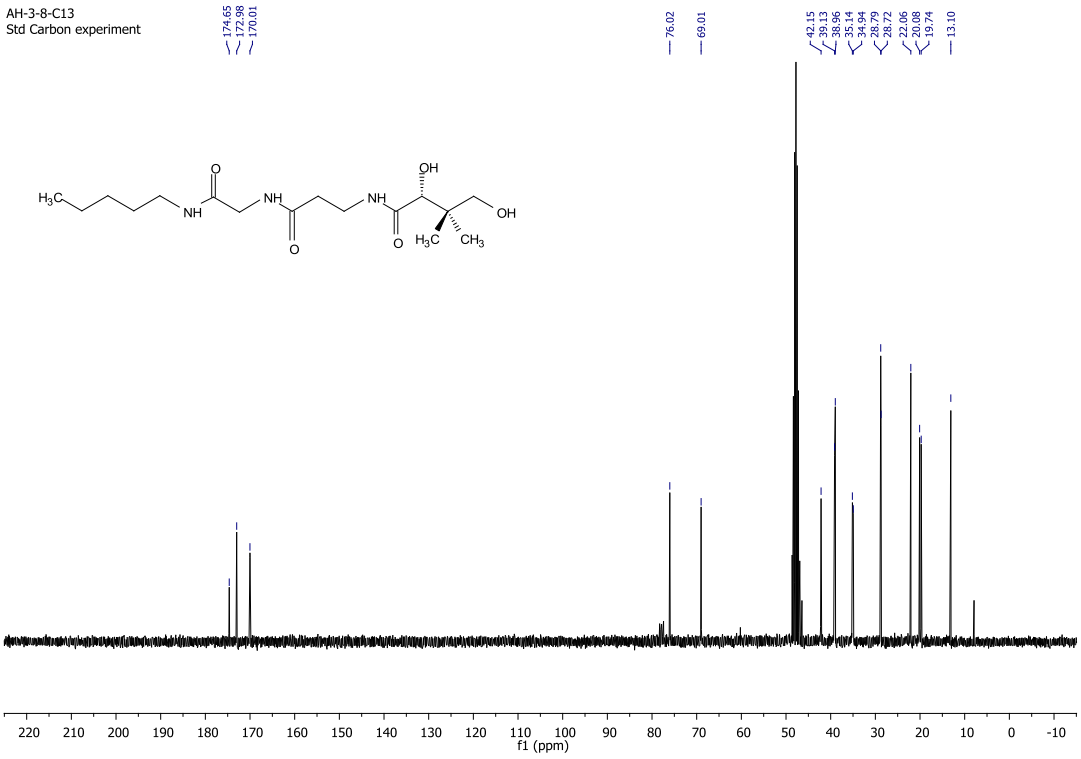
Experimental details are outlined in Procedure A for the oxidation of alcohol **71f** (260 mg. 0.68 mmol), and in Procedure B for amide coupling with **73** (202 mg, 0.53 mmol). Purification was carried out on

silica gel with 80% EtOAc/hexanes to yield the product (80 mg, 0.15 mmol) in 42% yield. (R_f = 0.26) and was used in the deprotection

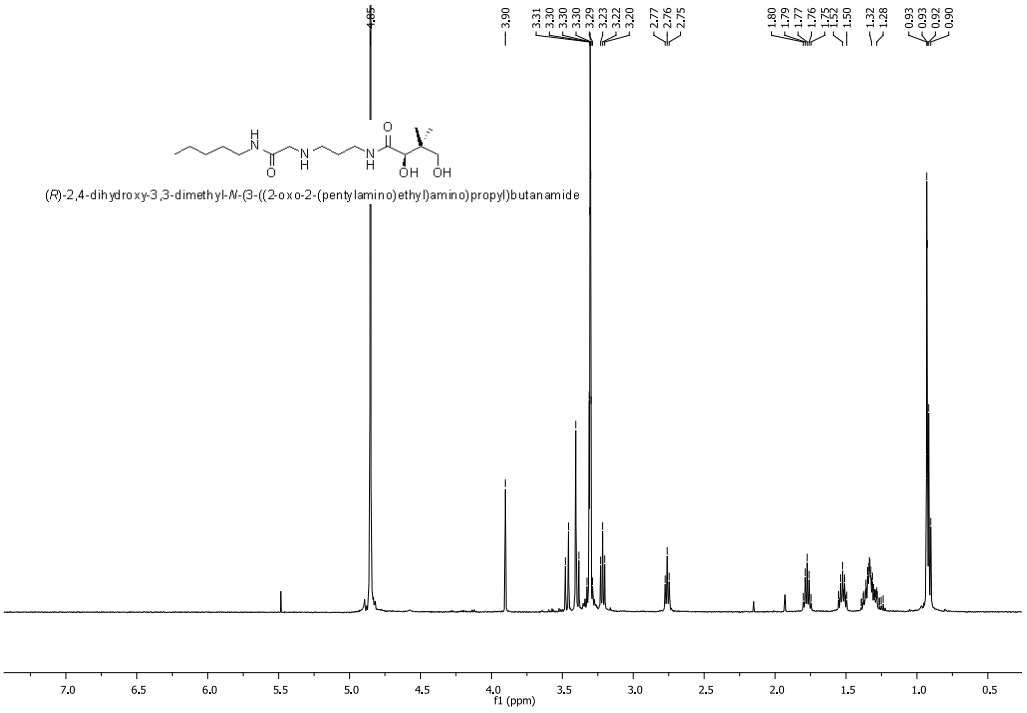
^{1}H-NMR spectrum in CD_3OD of compound **4**



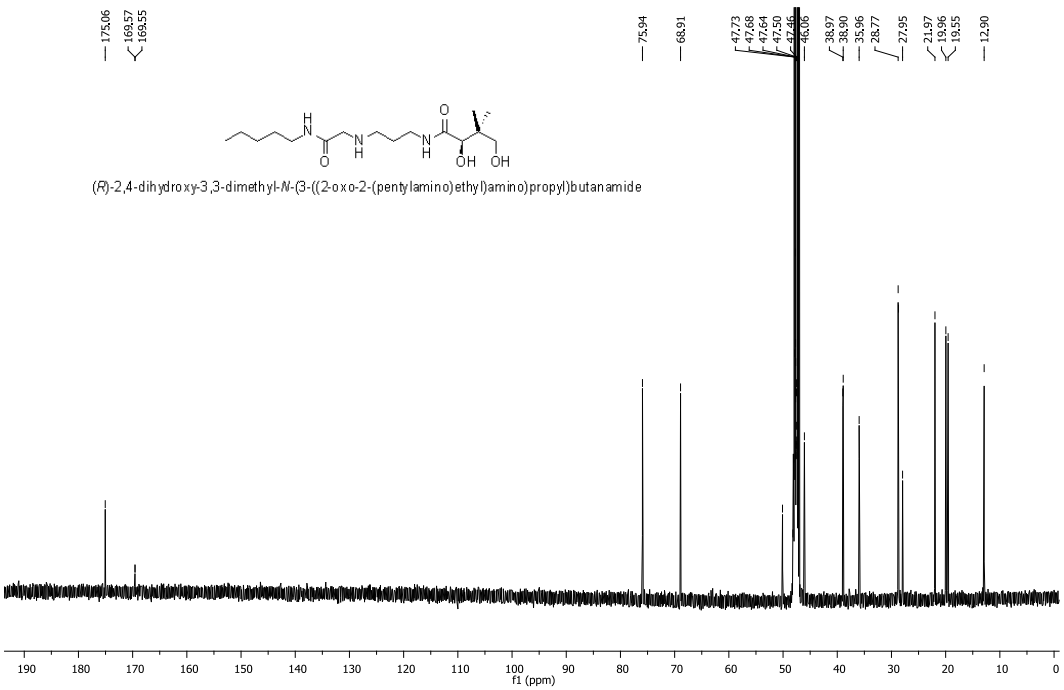
^{13}C-NMR spectrum CD_3OD of compound **4**



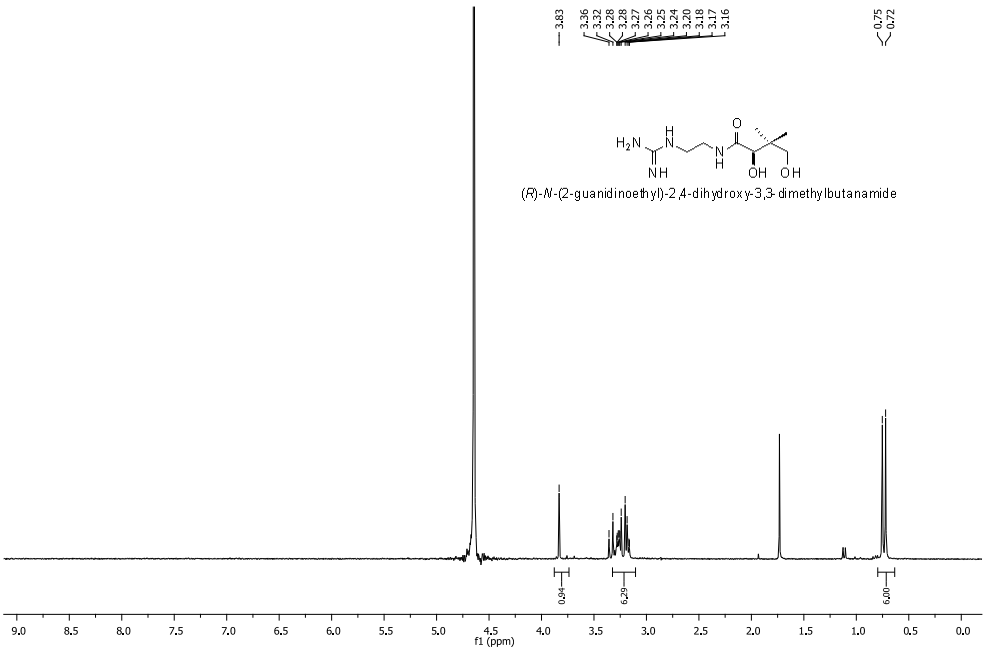
^{1}H-NMR spectrum in CD_3OD of compound **5**



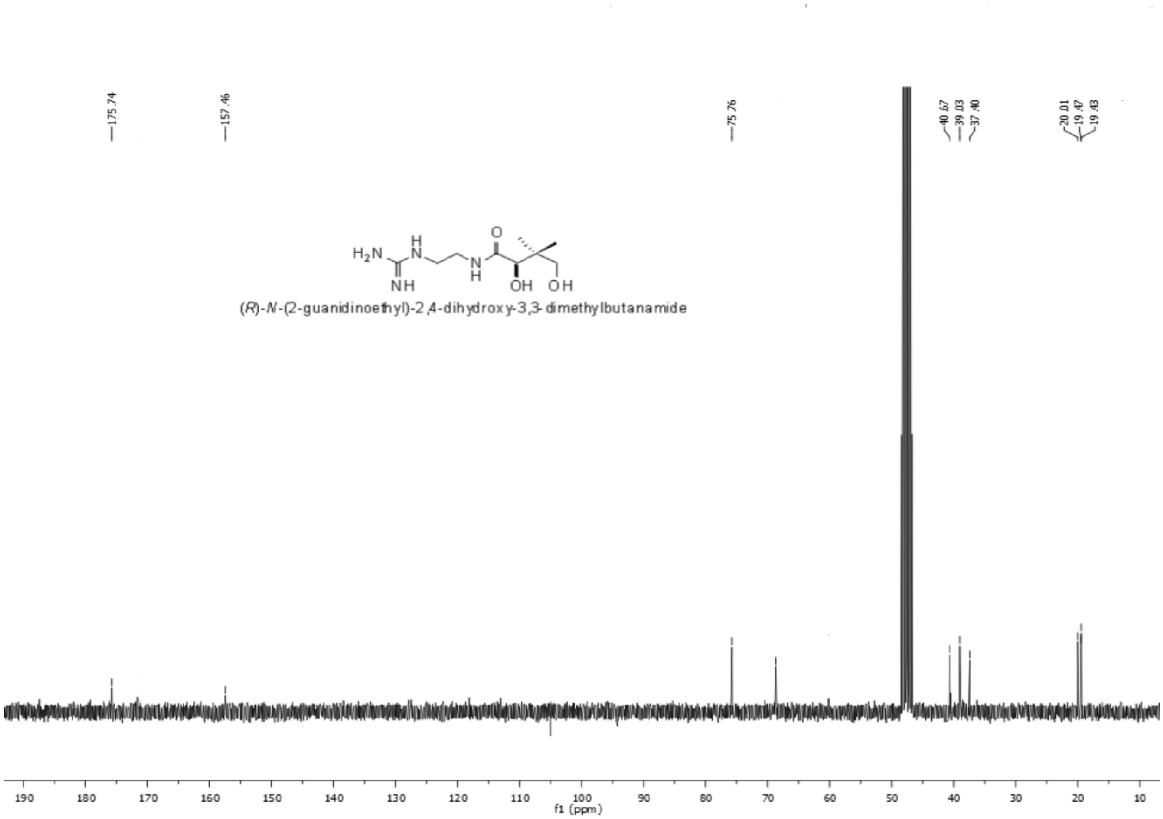
^{13}C-NMR spectrum CD_3OD of compound **5**



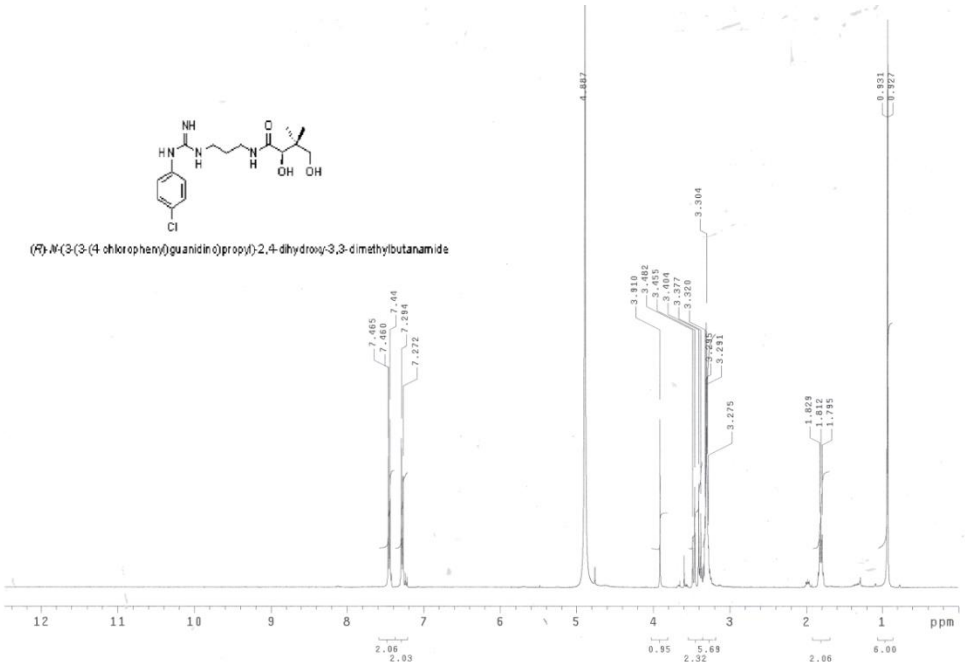
^{1}H-NMR spectrum in D_2O of compound **6**



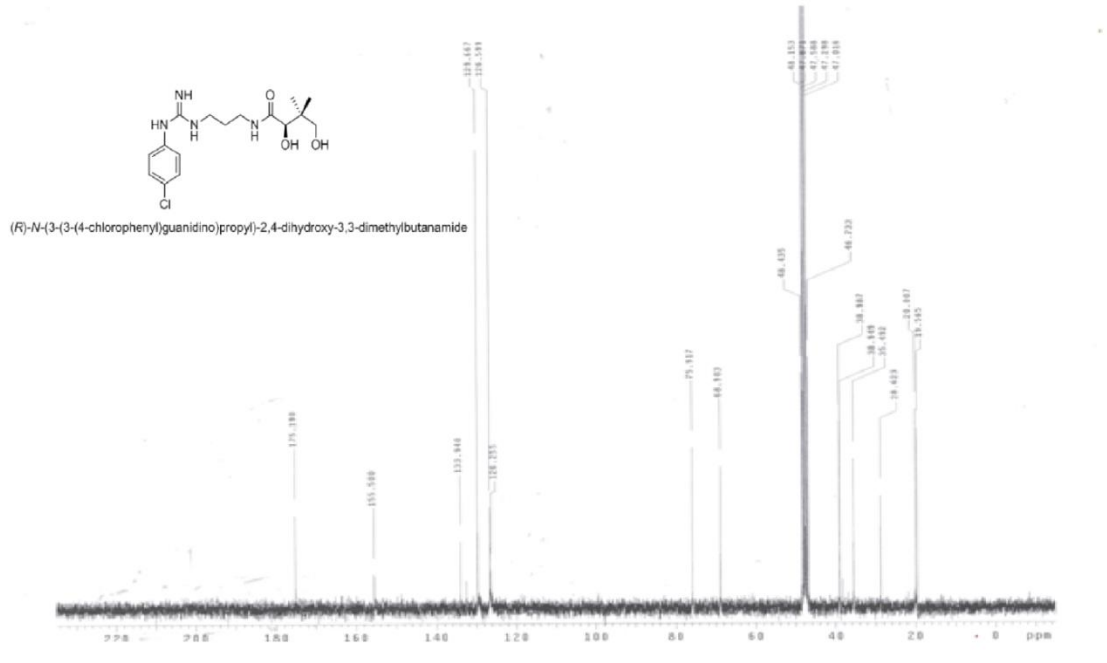
^{13}C-NMR spectrum CD_3OD of compound **6**



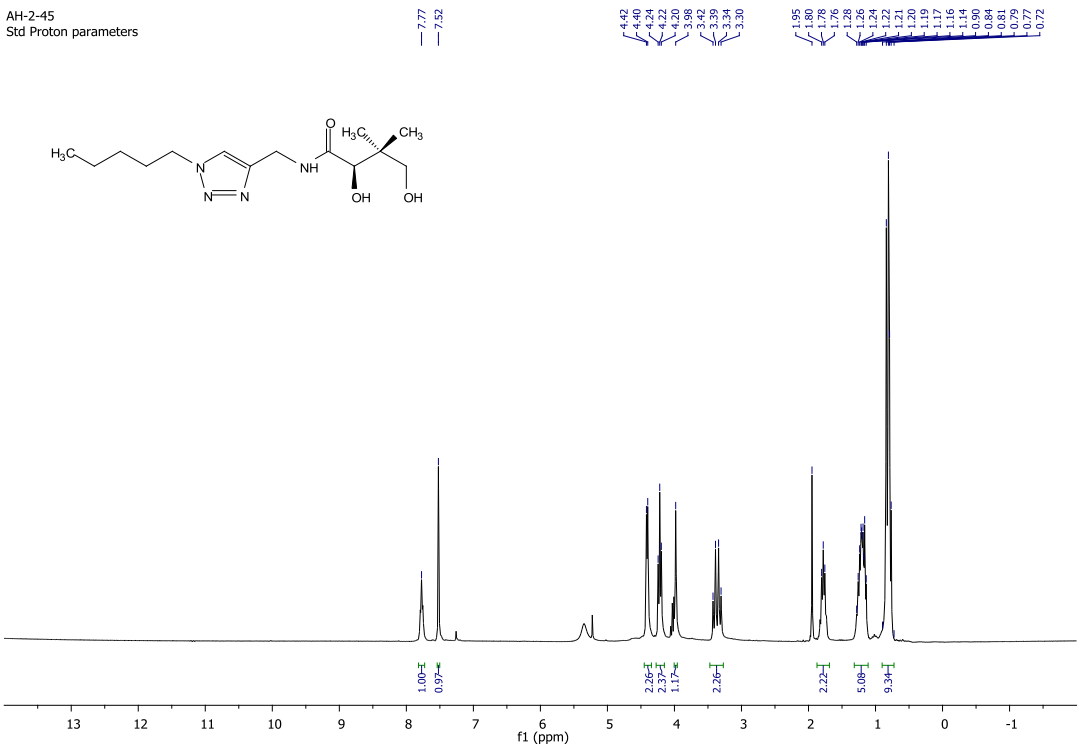
^{1}H-NMR spectrum in D_2O of compound **7**



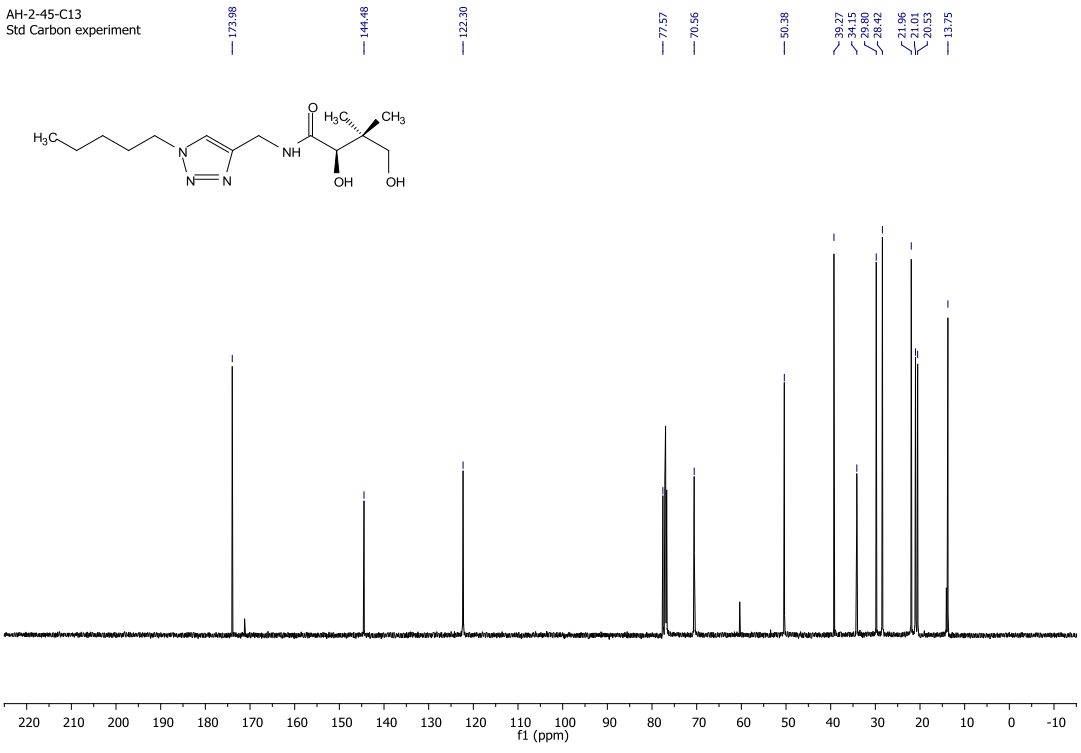
^{13}C-NMR spectrum in CD_3OD of compound **7**



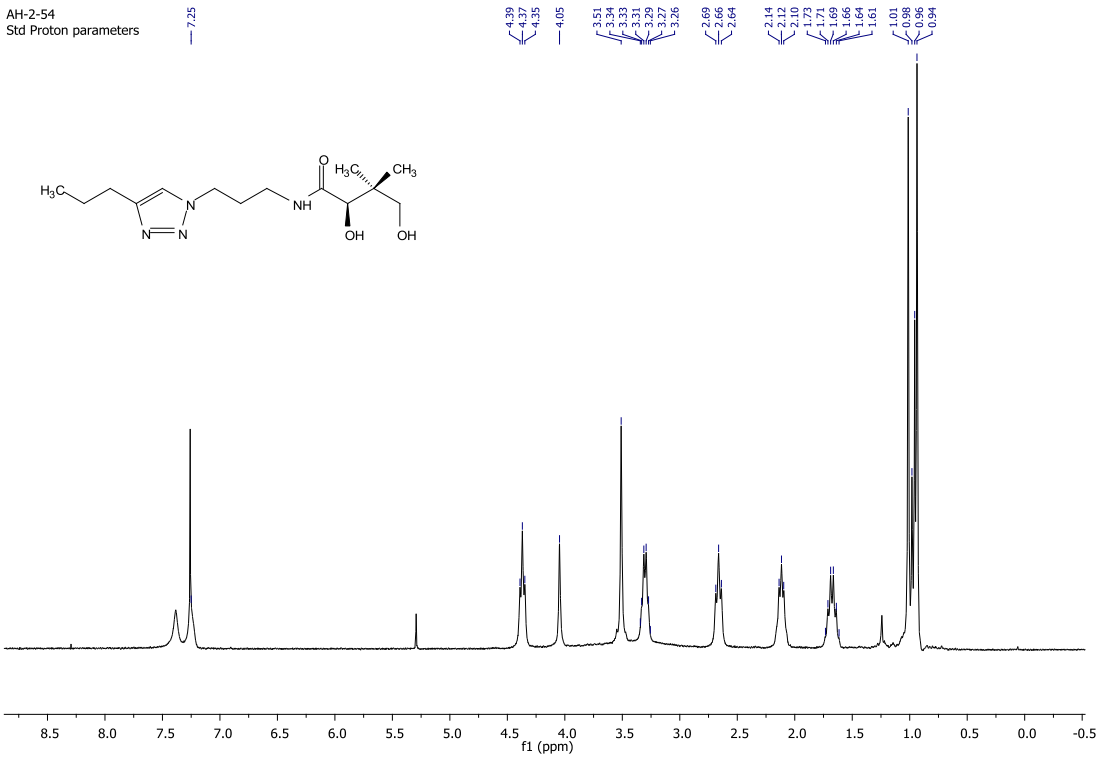
^{1}H-NMR spectrum in $CDCl_3$ of compound **8**



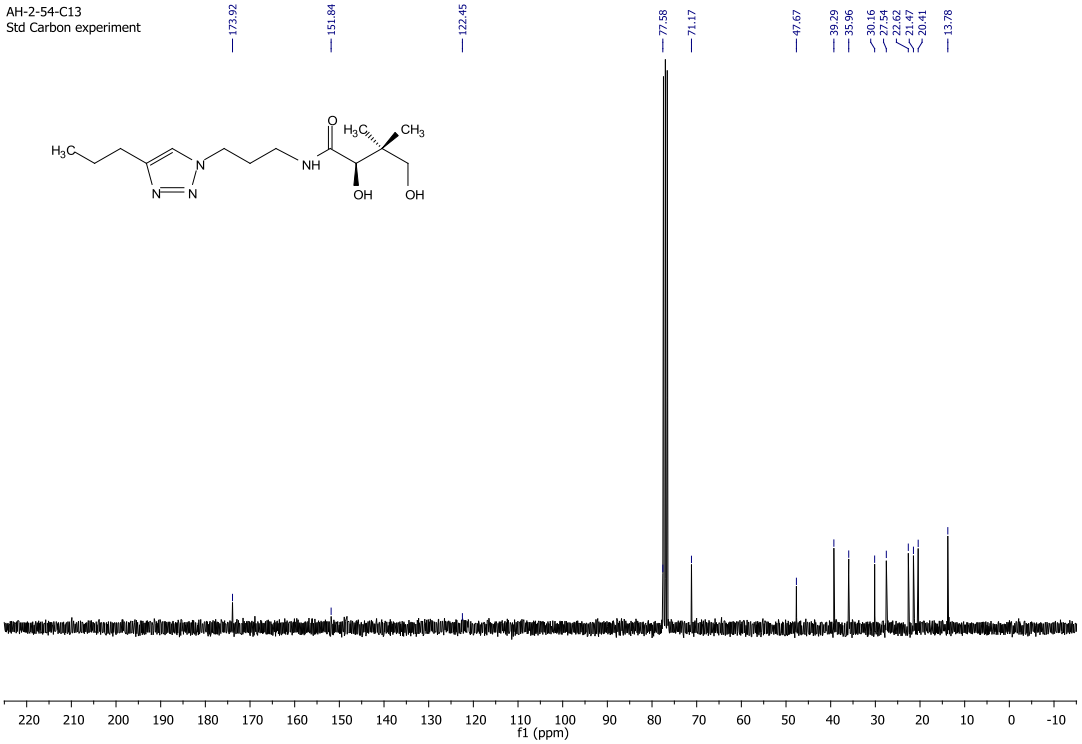
^{13}C-NMR spectrum in $CDCl_3$ of compound **8**



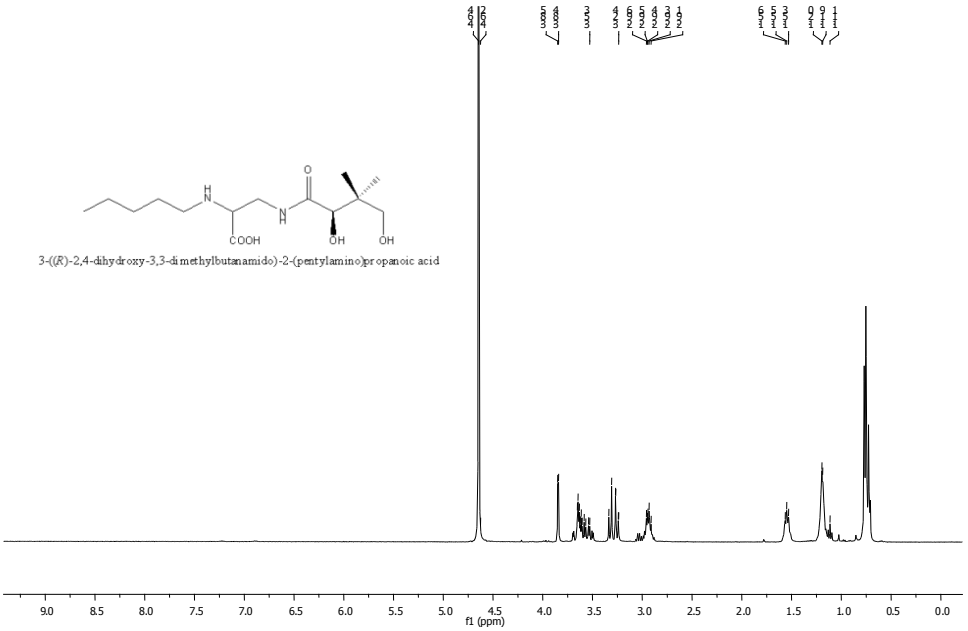
^{1}H-NMR spectrum in $CDCl_3$ of compound **9**



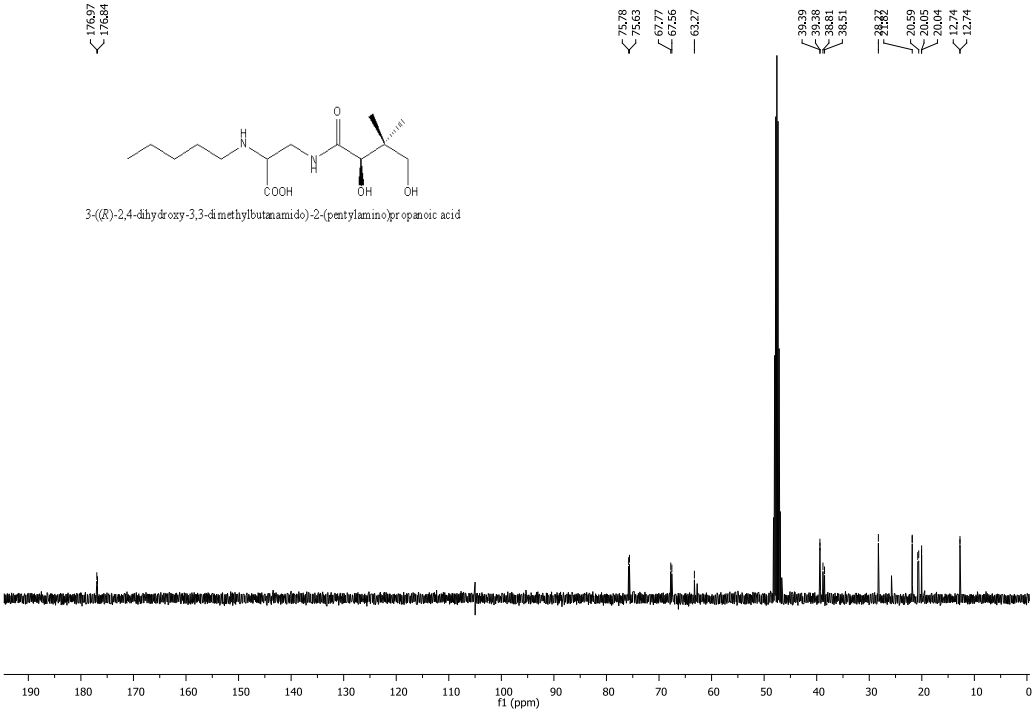
^{13}C-NMR spectrum in $CDCl_3$ of compound **9**



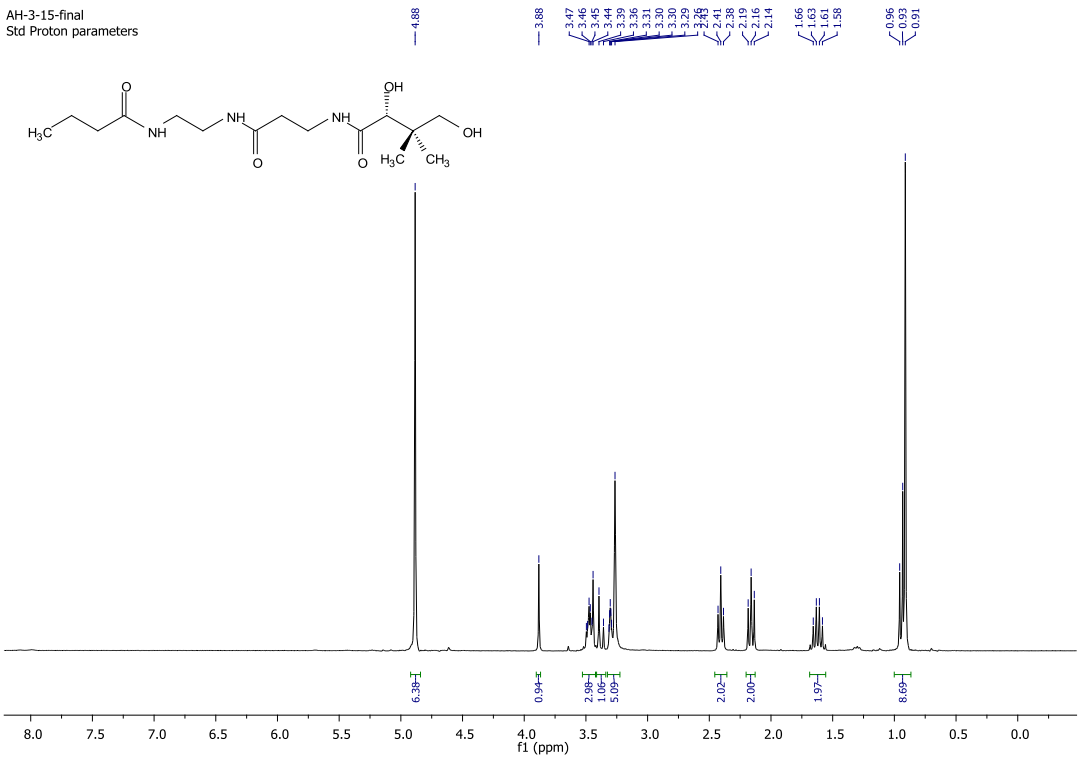
^{1}H-NMR spectrum in D_2O of compound **10**



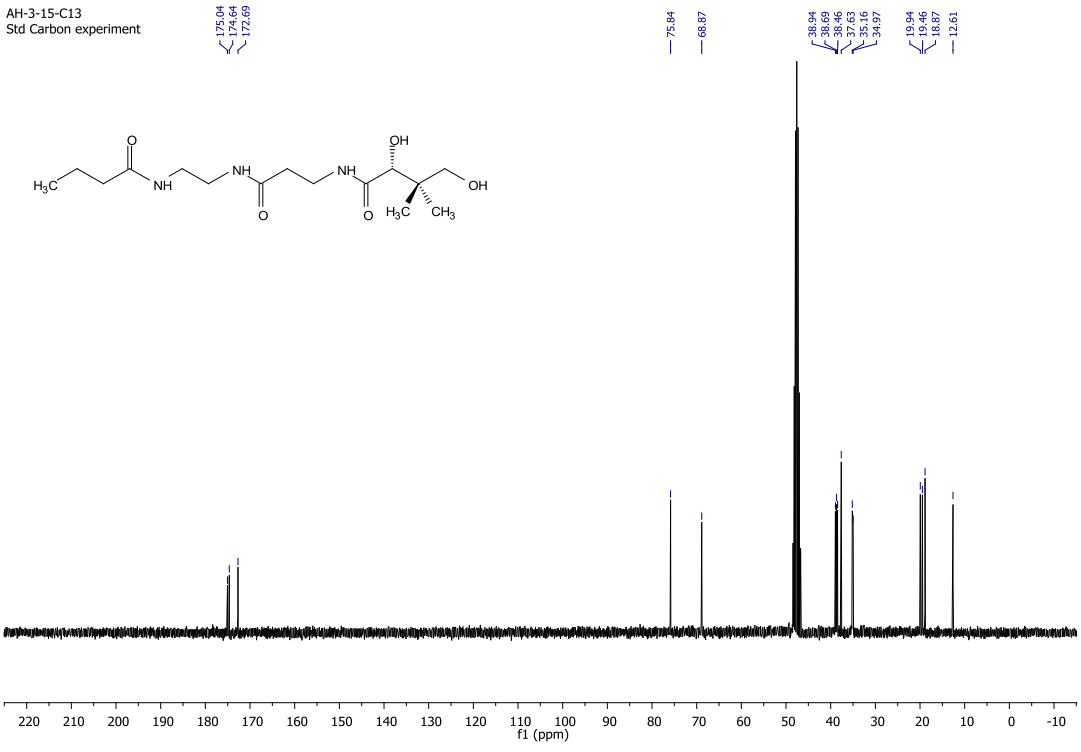
^{13}C-NMR spectrum CD_3OD of compound **10**



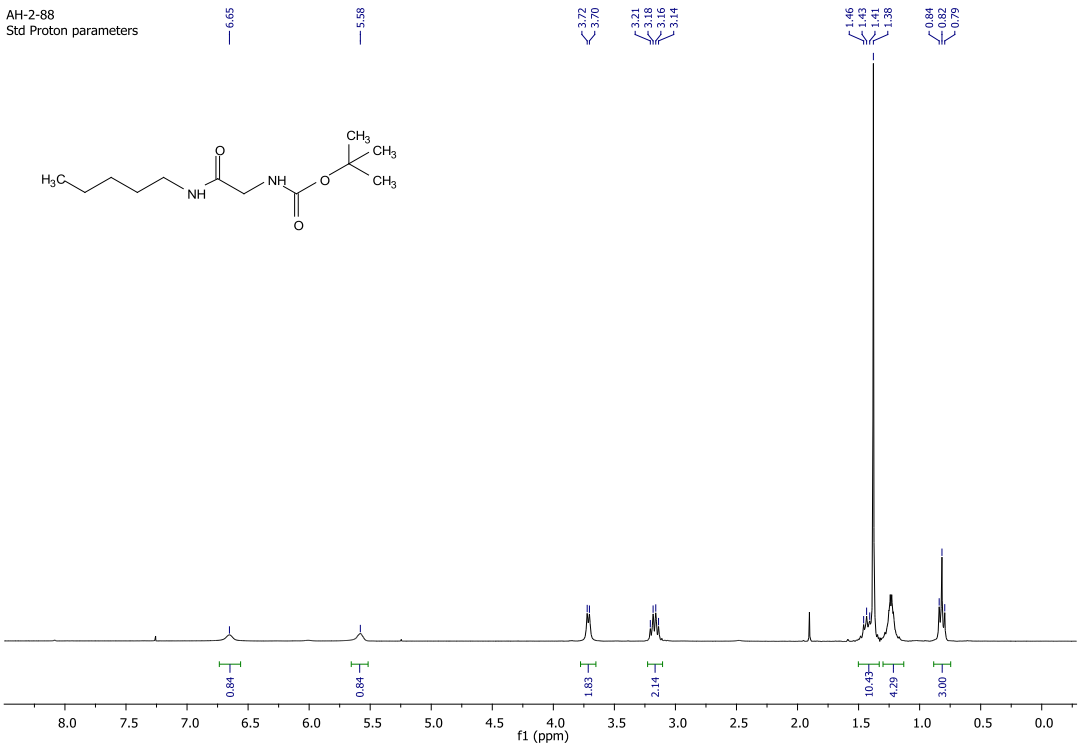
^{1}H-NMR spectrum in $CDCl_3$ of compound **12**



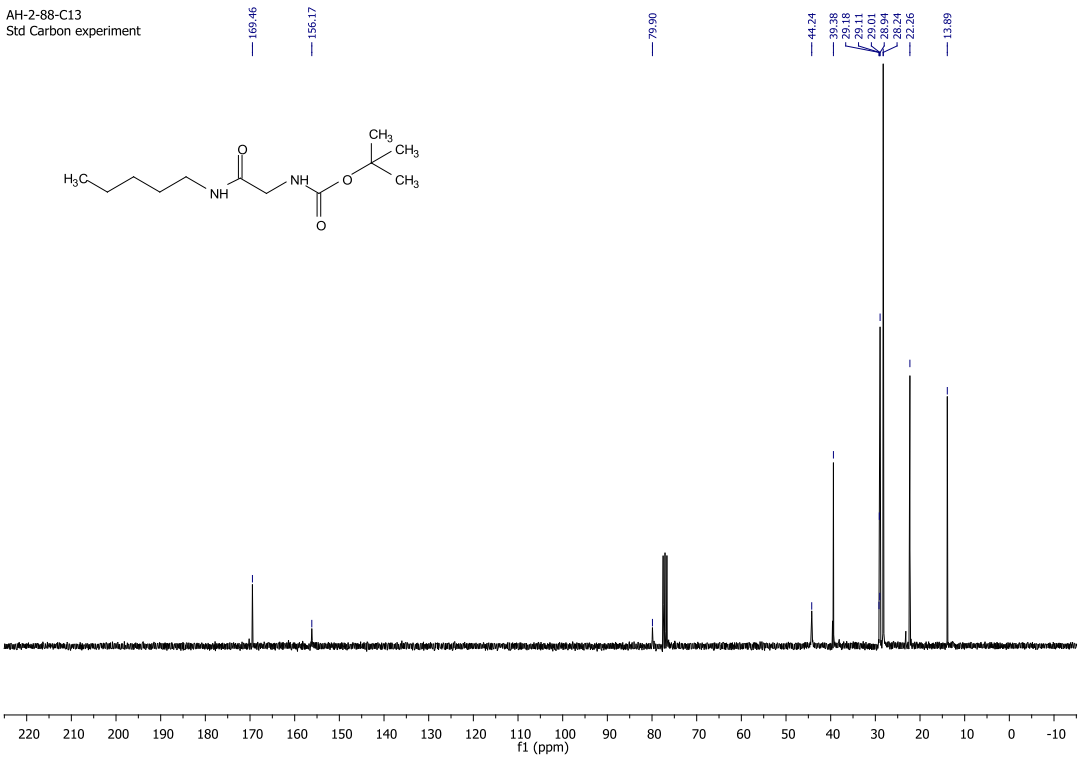
^{13}C-NMR spectrum in $CDCl_3$ of compound **12**



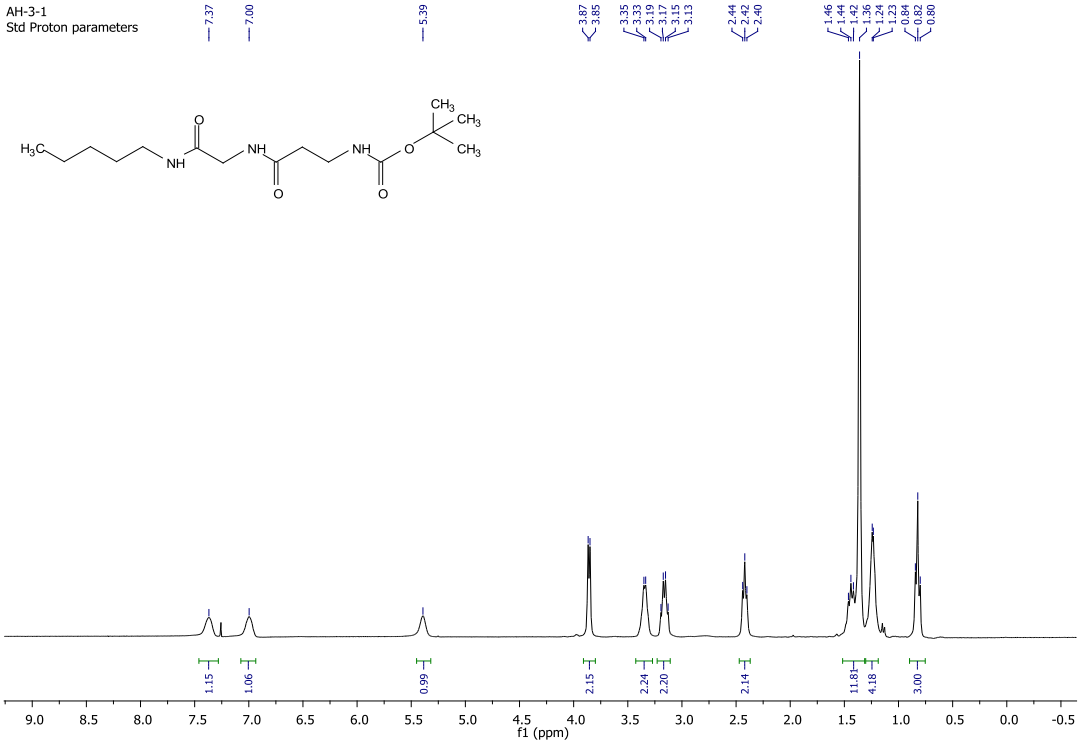
^{1}H-NMR spectrum in $CDCl_3$ of compound **14**



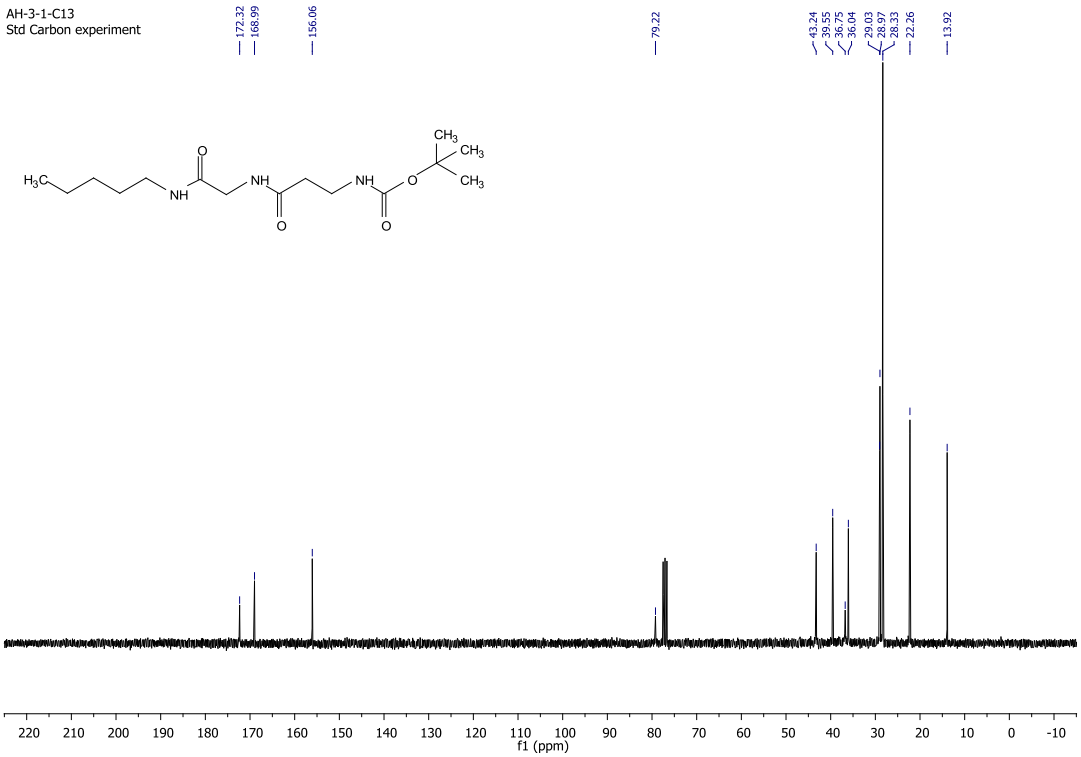
^{13}C-NMR spectrum in $CDCl_3$ of compound **14**



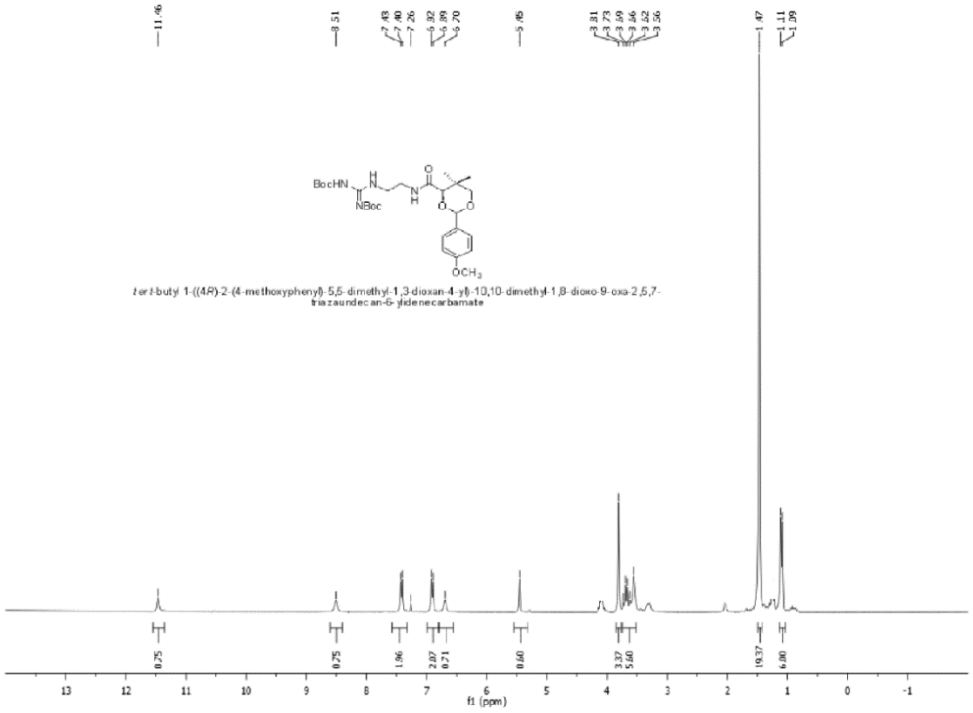
^{1}H-NMR spectrum in $CDCl_3$ of compound **15**



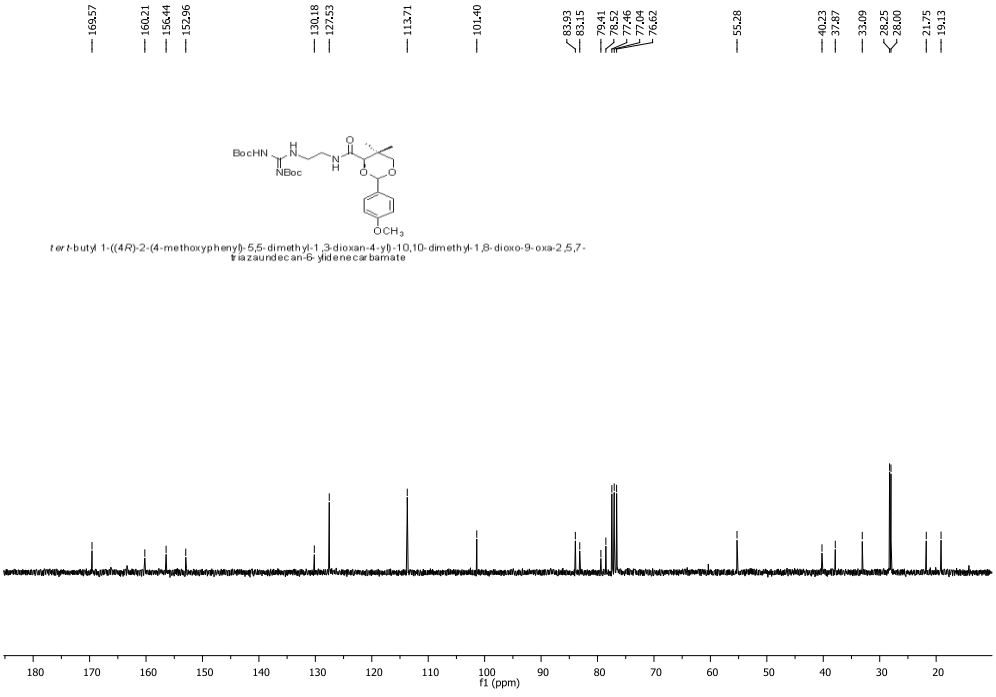
^{13}C-NMR spectrum in $CDCl_3$ of compound **15**



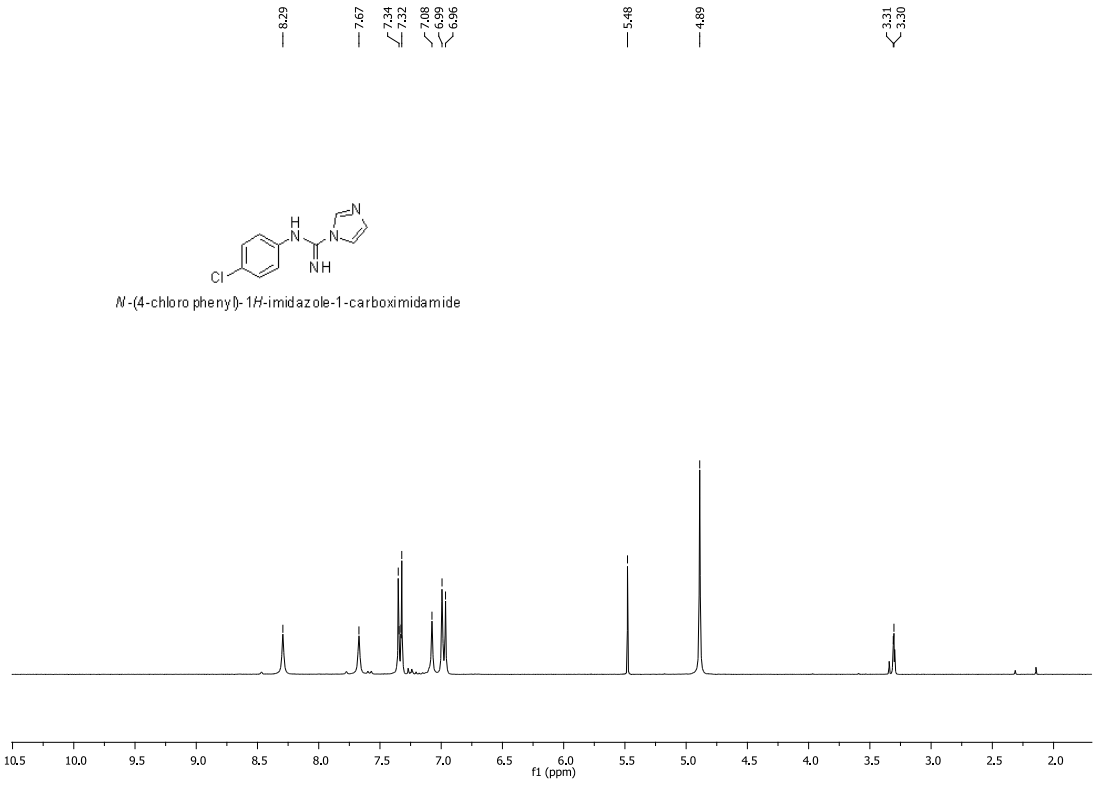
^{1}H-NMR spectrum in $CDCl_3$ of compound **21**



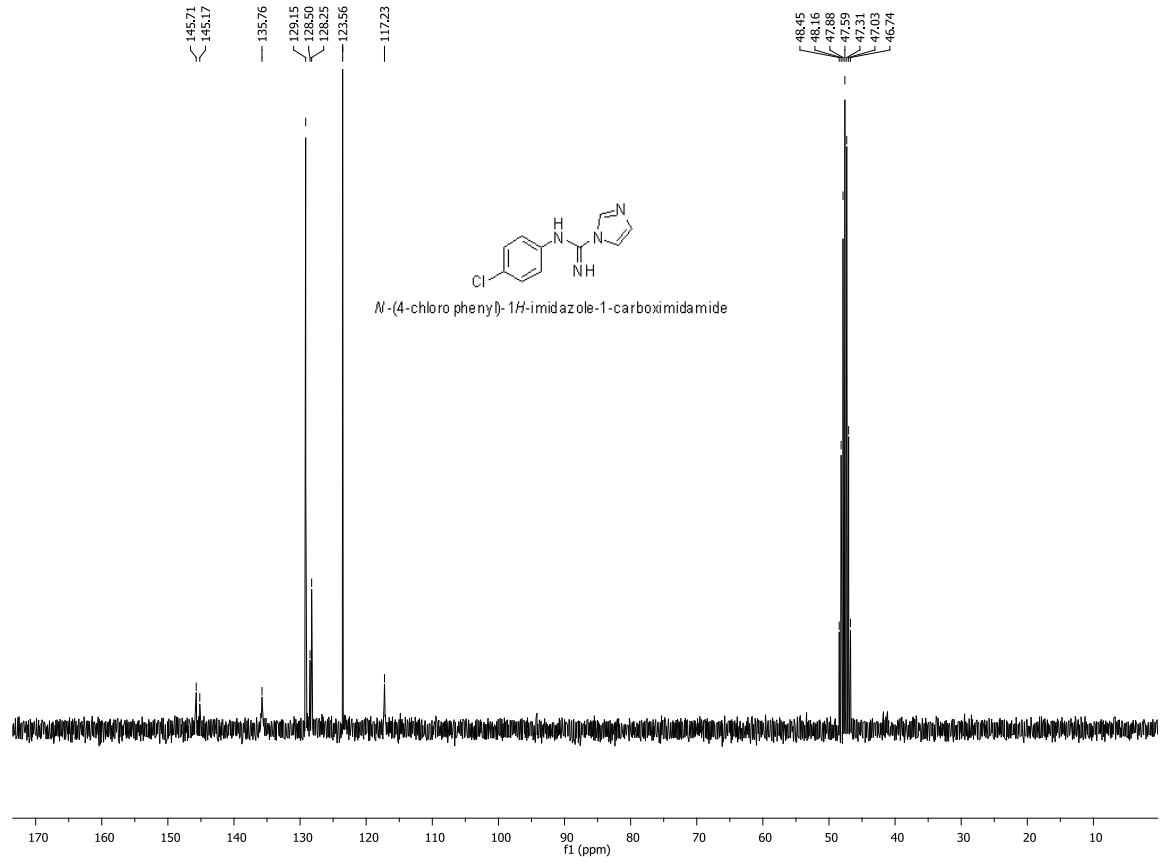
^{13}C-NMR spectrum in $CDCl_3$ of compound **21**



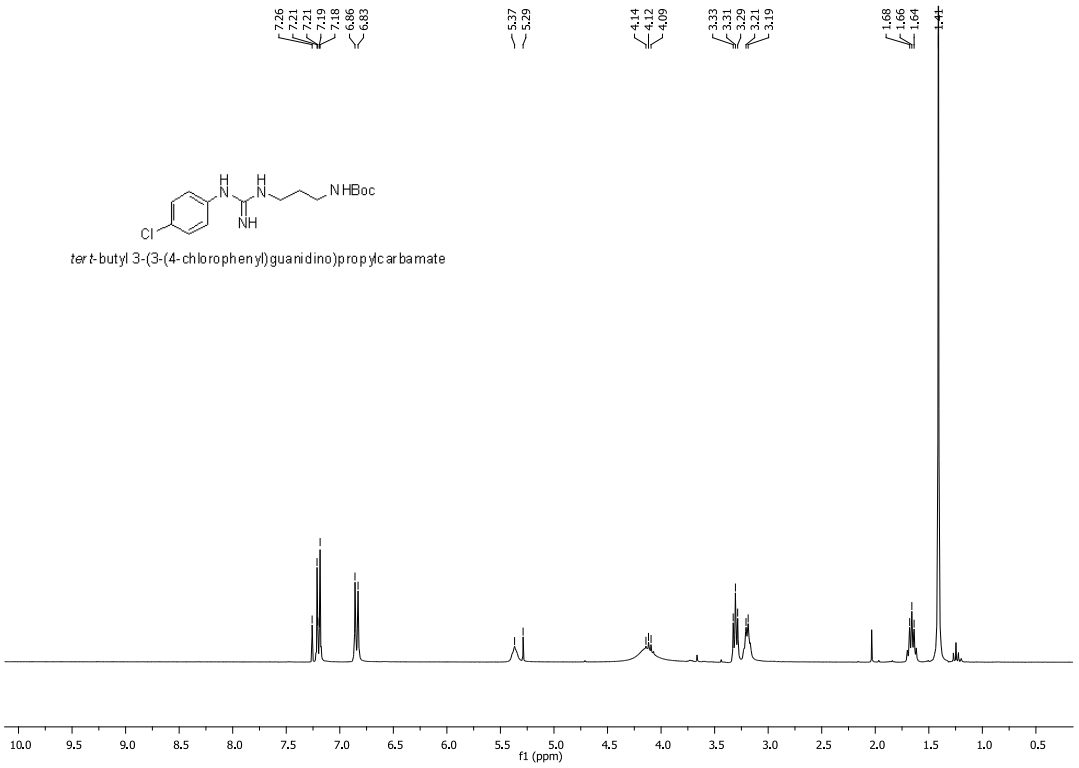
^{1}H-NMR spectrum in $CDCl_3$ of compound **23**



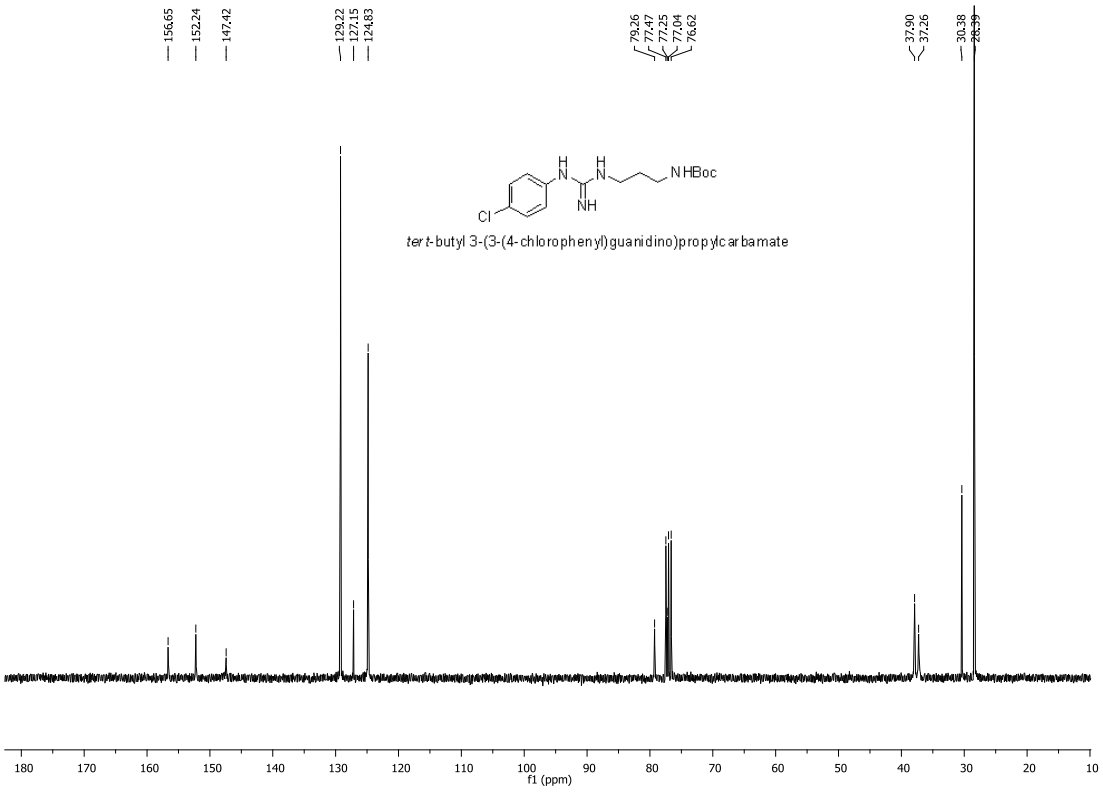
^{13}C-NMR spectrum in $CDCl_3$ of compound **23**



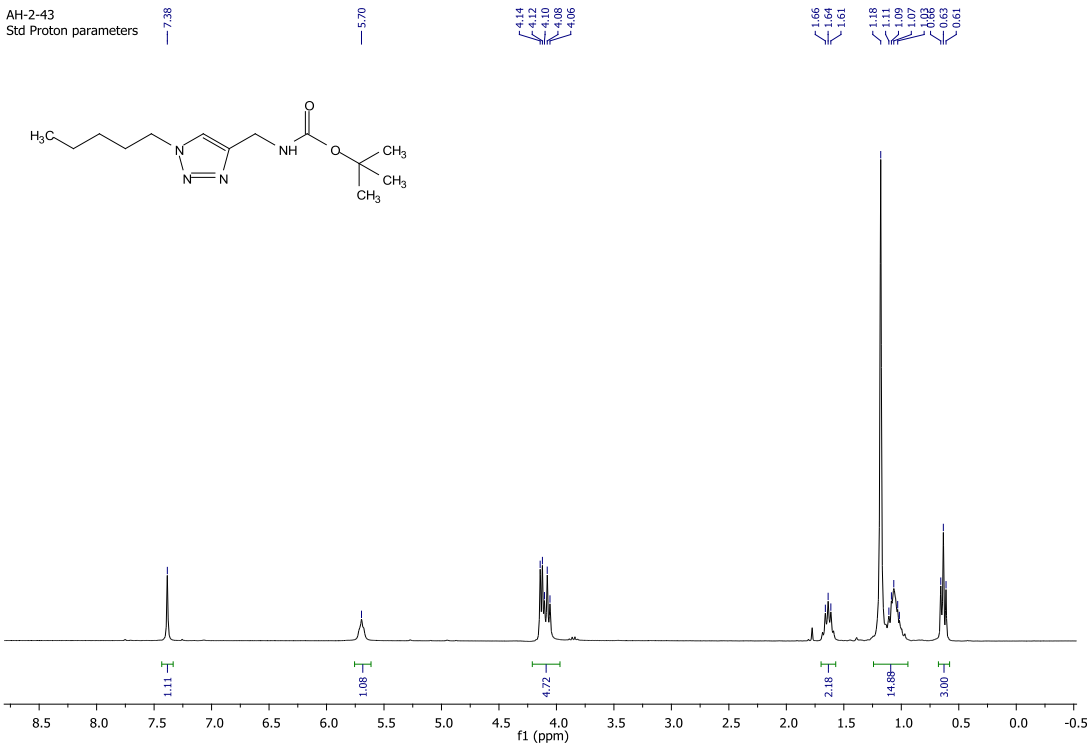
^{1}H-NMR spectrum in $CDCl_3$ of compound **24**



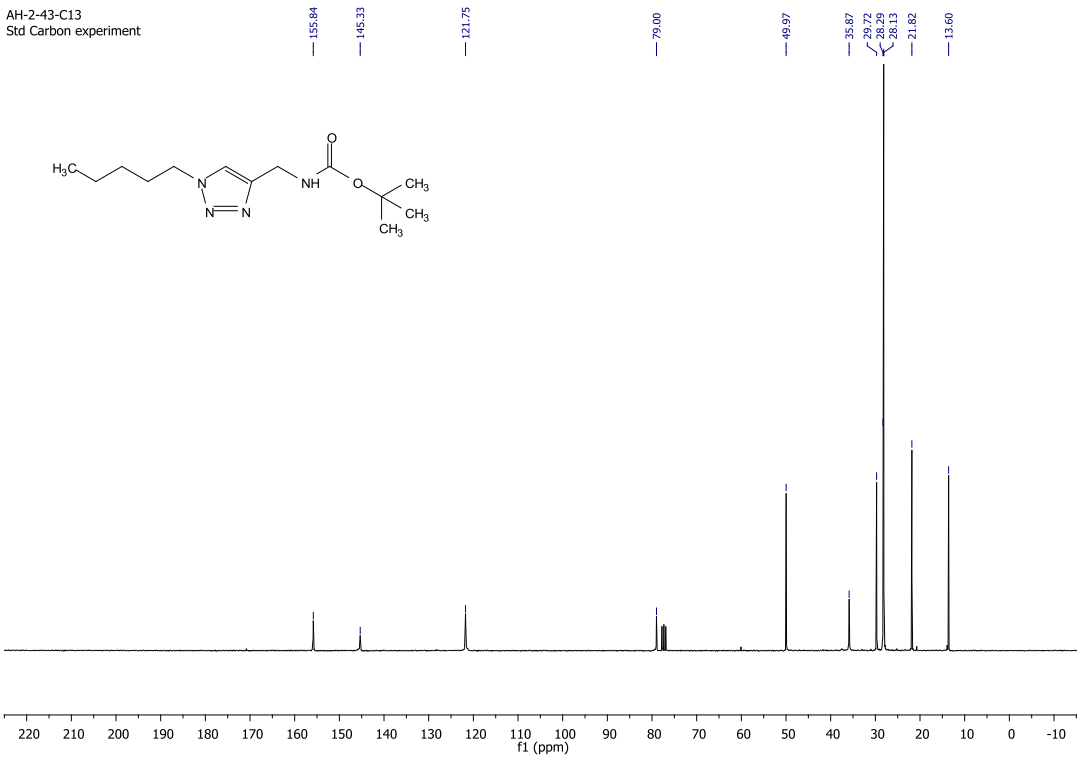
^{13}C-NMR spectrum in $CDCl_3$ of compound **24**



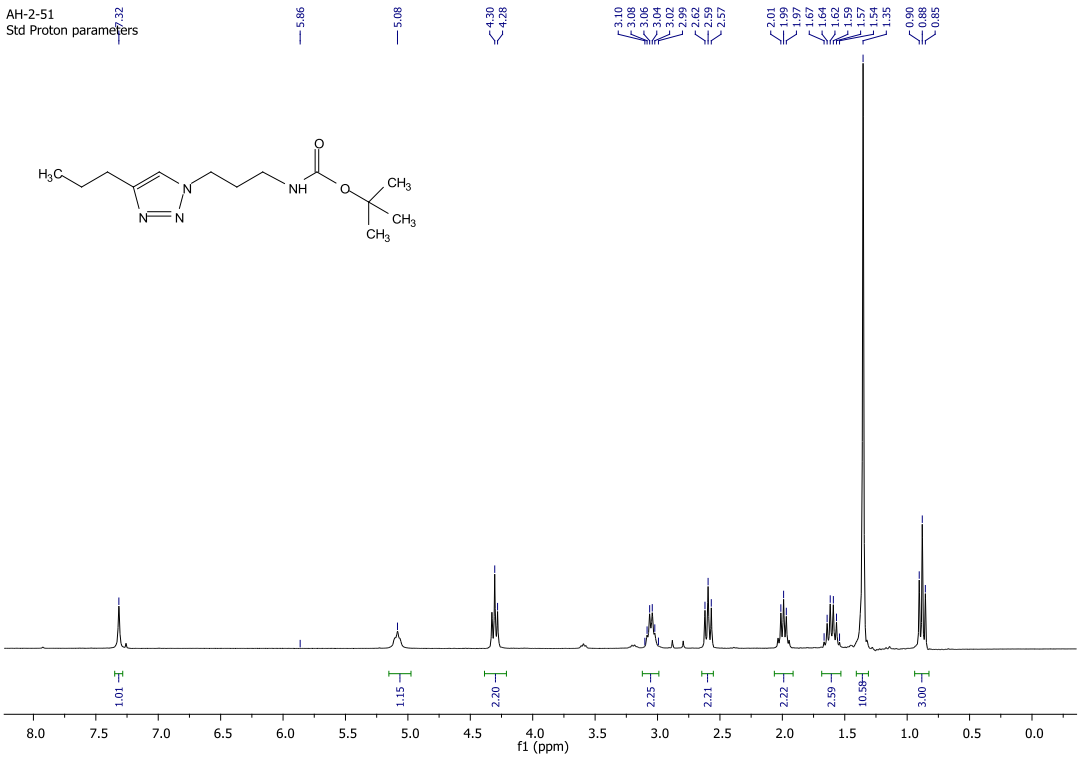
^{1}H-NMR spectrum in CD_3OD of **26**



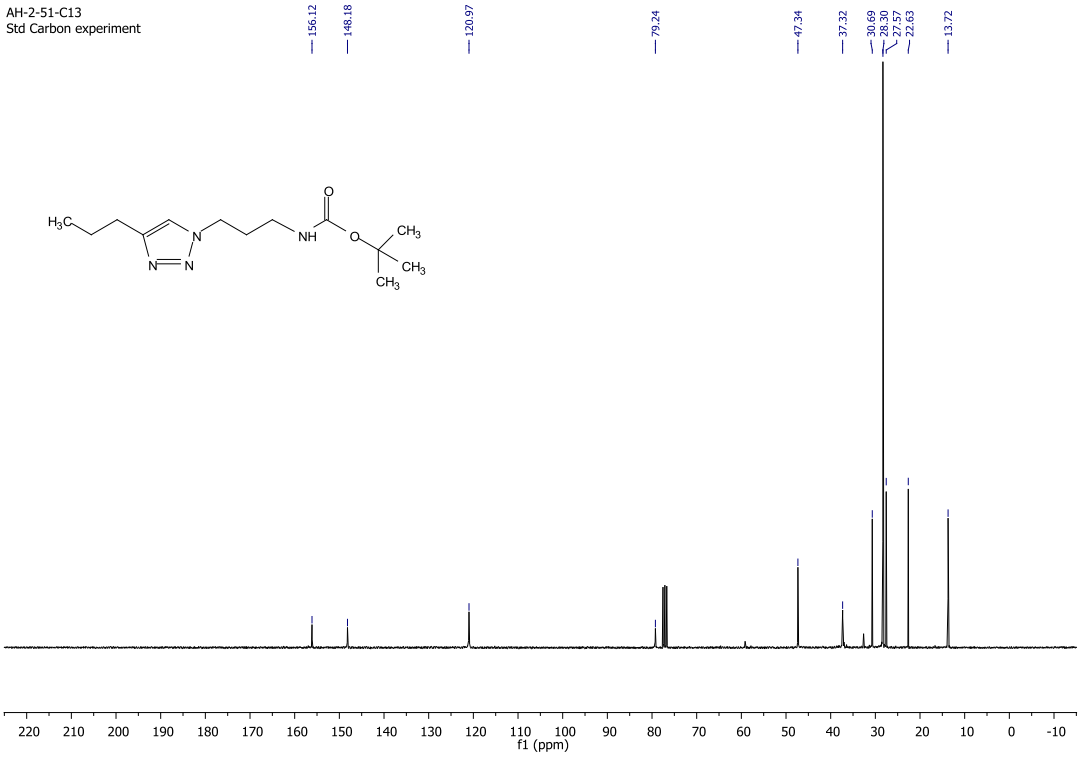
^{13}C-NMR spectrum in CD_3OD of **26**



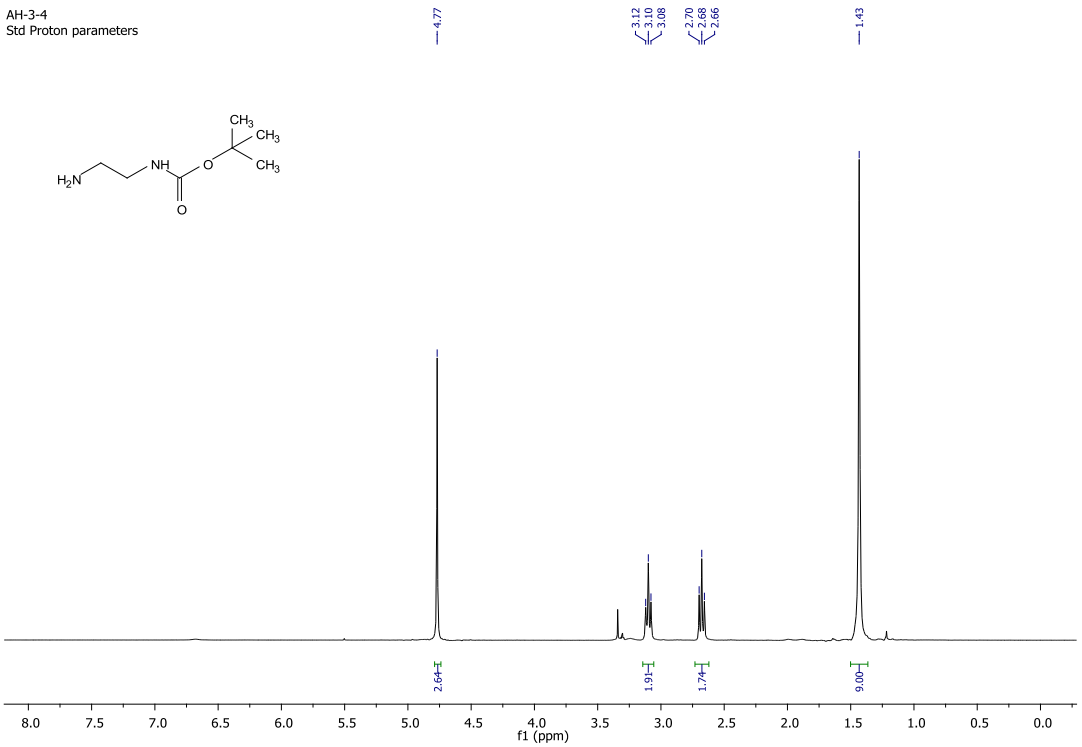
^{13}C-NMR spectrum in CD_3OD of **28**



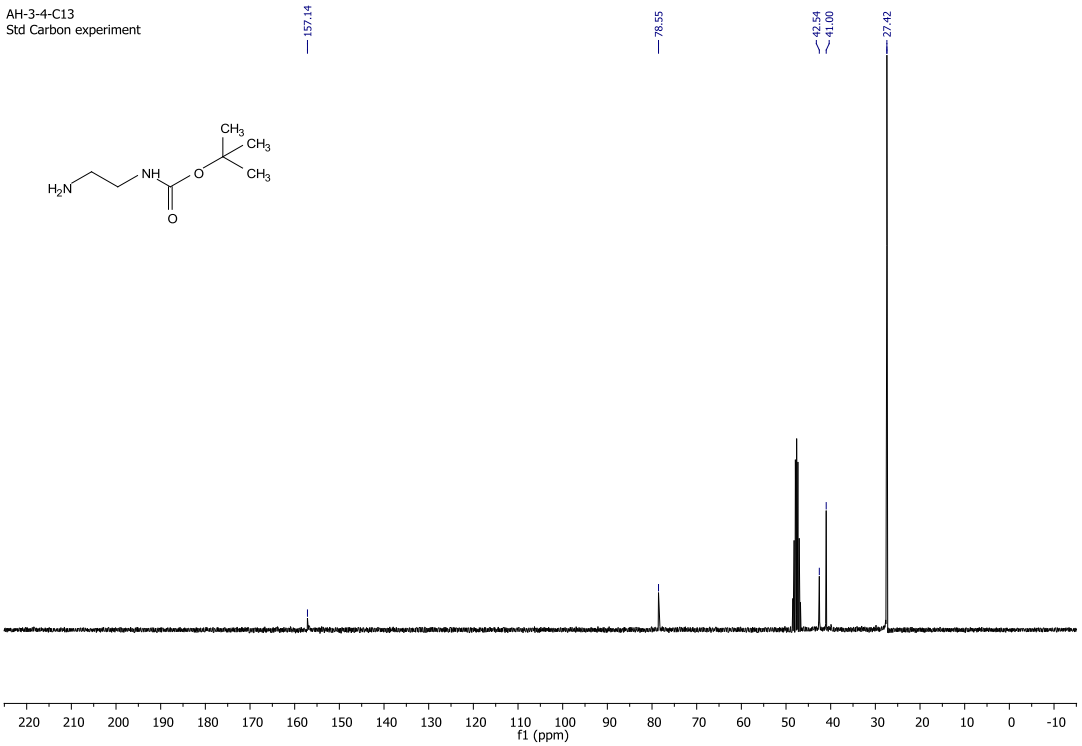
^{13}C-NMR spectrum in CD_3OD of **28**



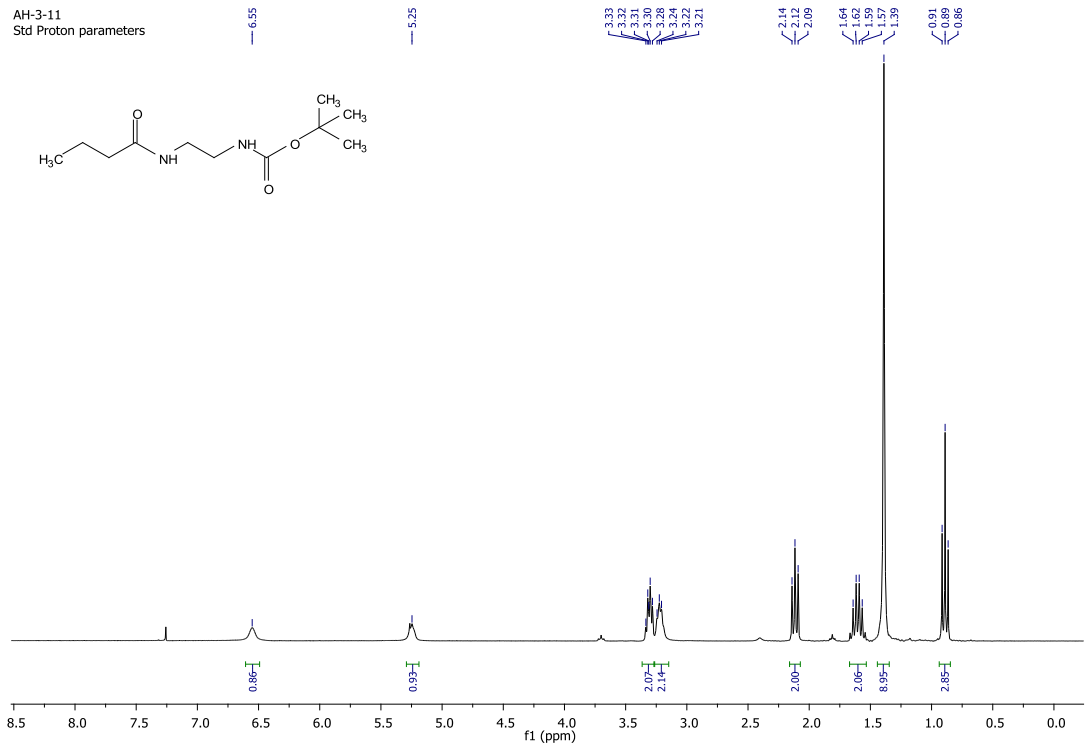
^{1}H-NMR spectrum in $CDCl_3$ of compound **31**



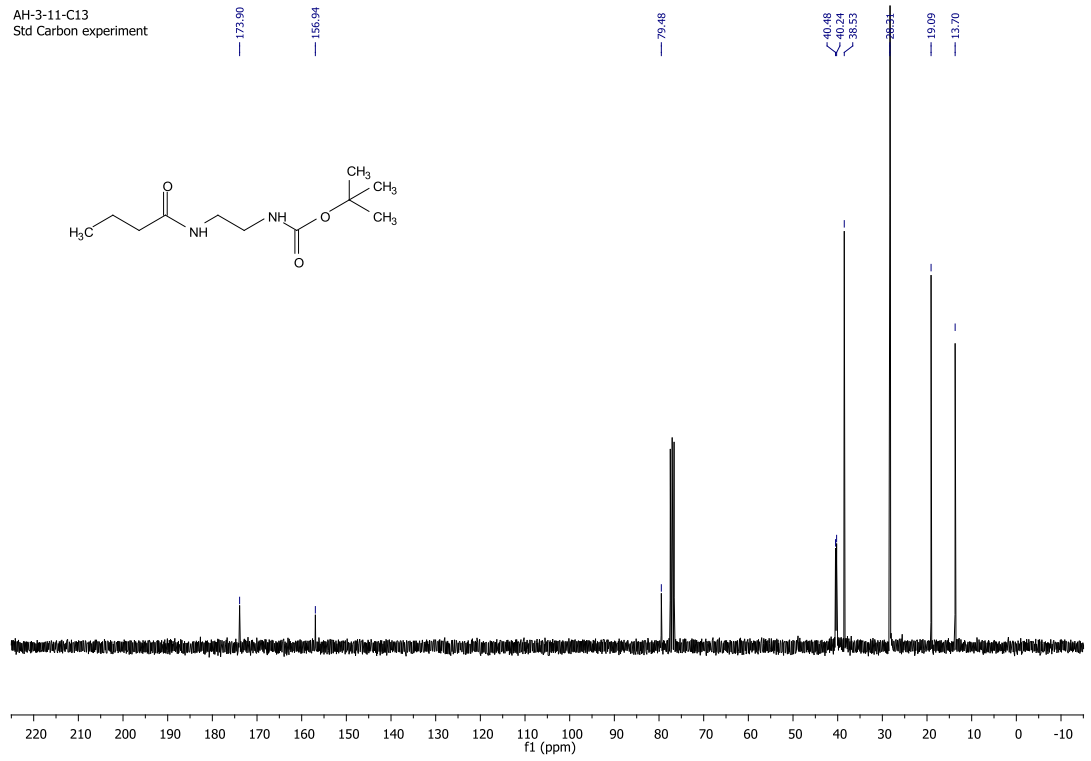
^{13}C-NMR spectrum in $CDCl_3$ of compound **31**



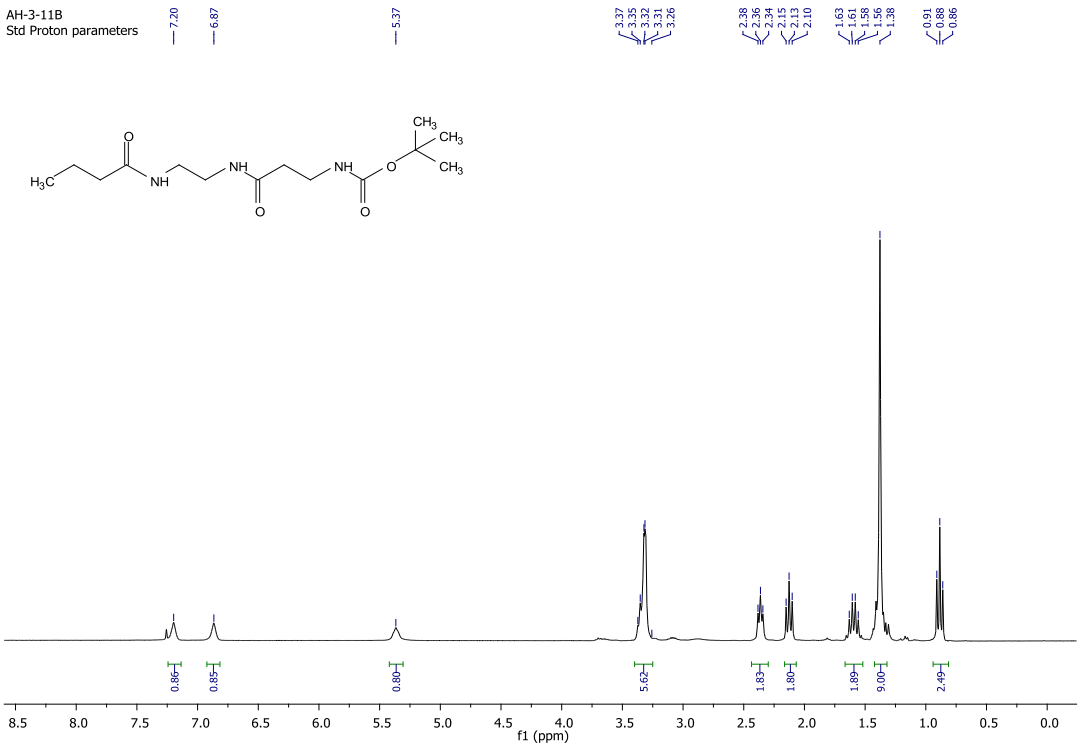
^{1}H-NMR spectrum in $CDCl_3$ of compound **32**



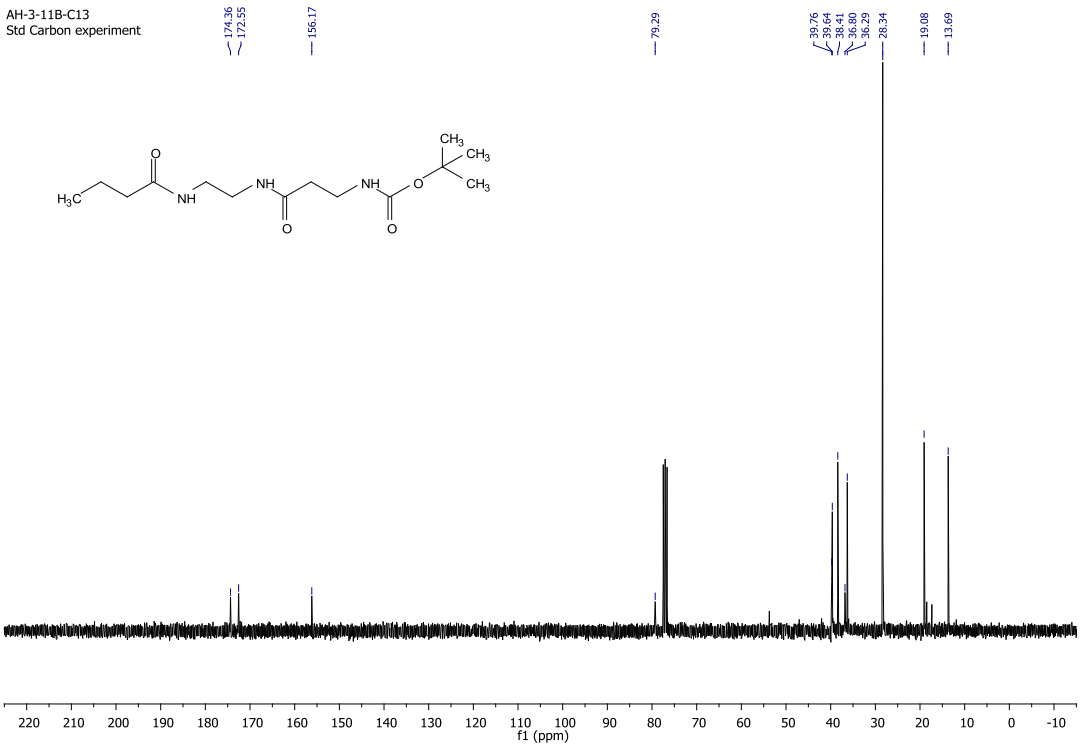
^{13}C-NMR spectrum in $CDCl_3$ of compound **32**



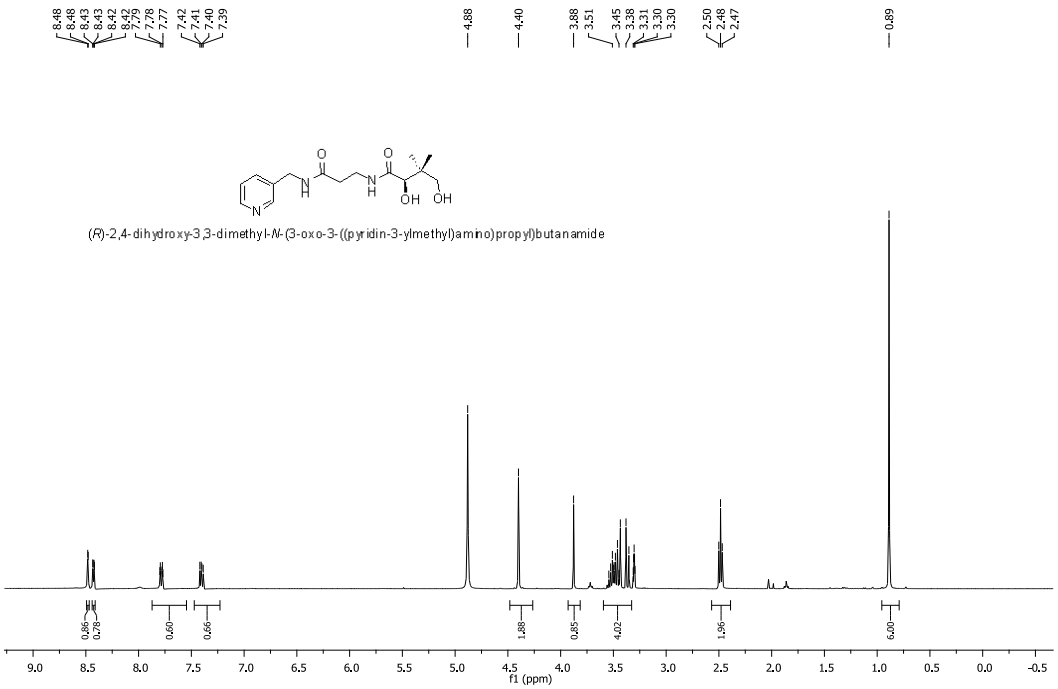
^{1}H-NMR spectrum in $CDCl_3$ of compound **33**



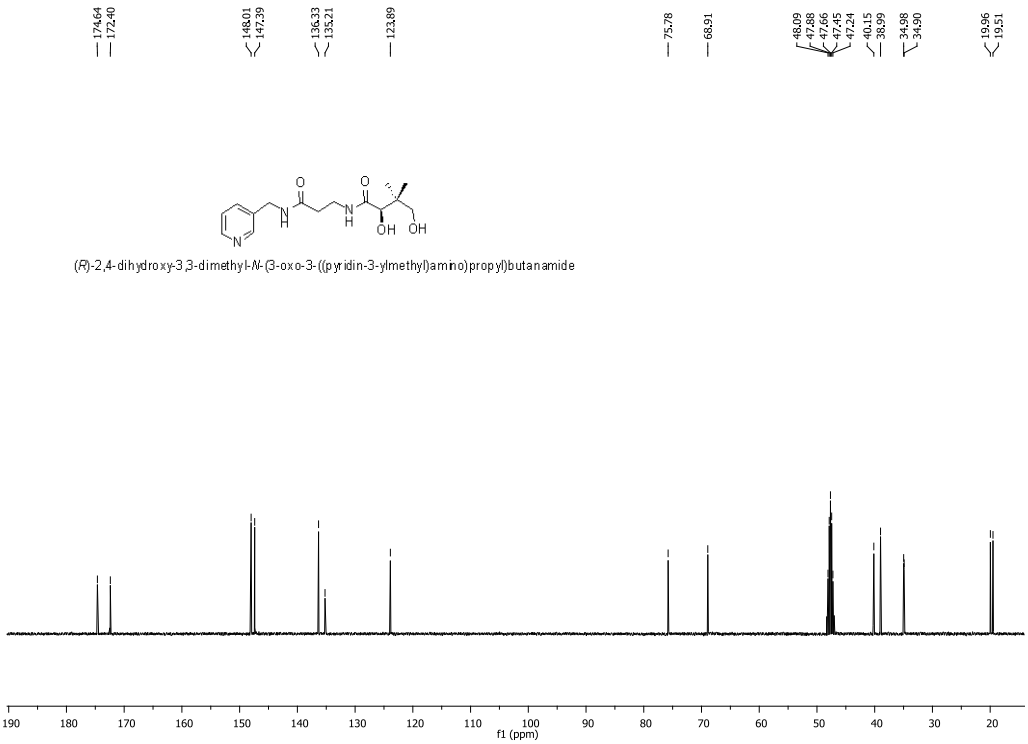
^{13}C-NMR spectrum in $CDCl_3$ of compound **33**



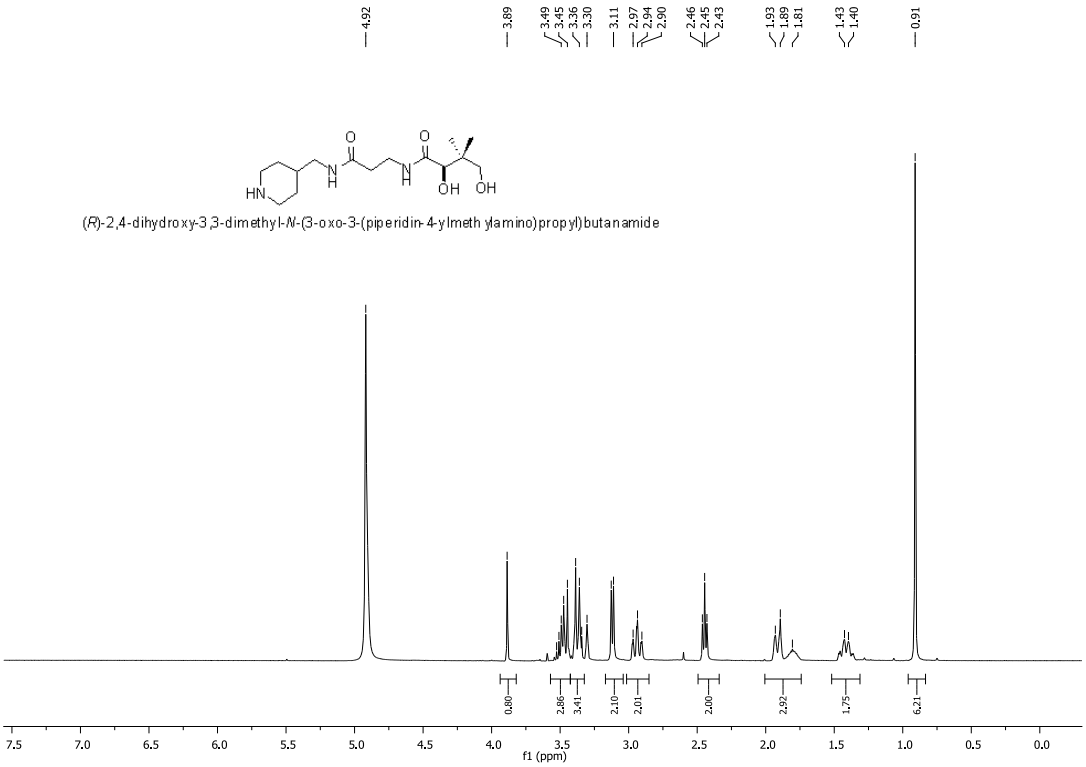
^{1}H-NMR spectrum in CD_3OD of **34**



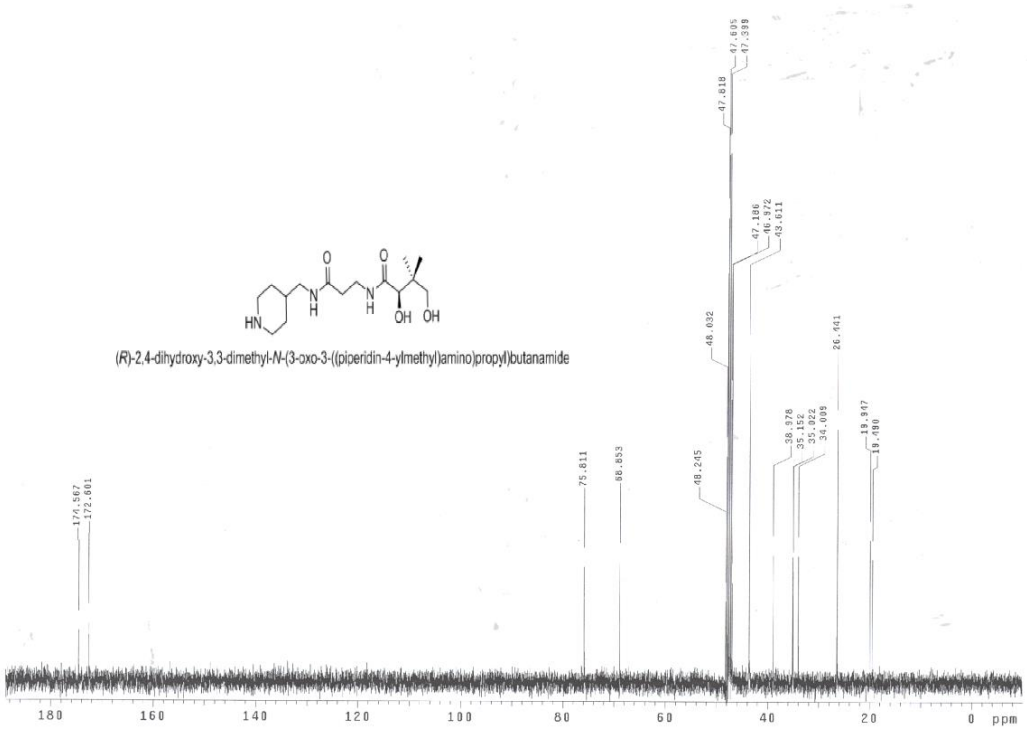
^{13}C-NMR spectrum in CD_3OD of **34**



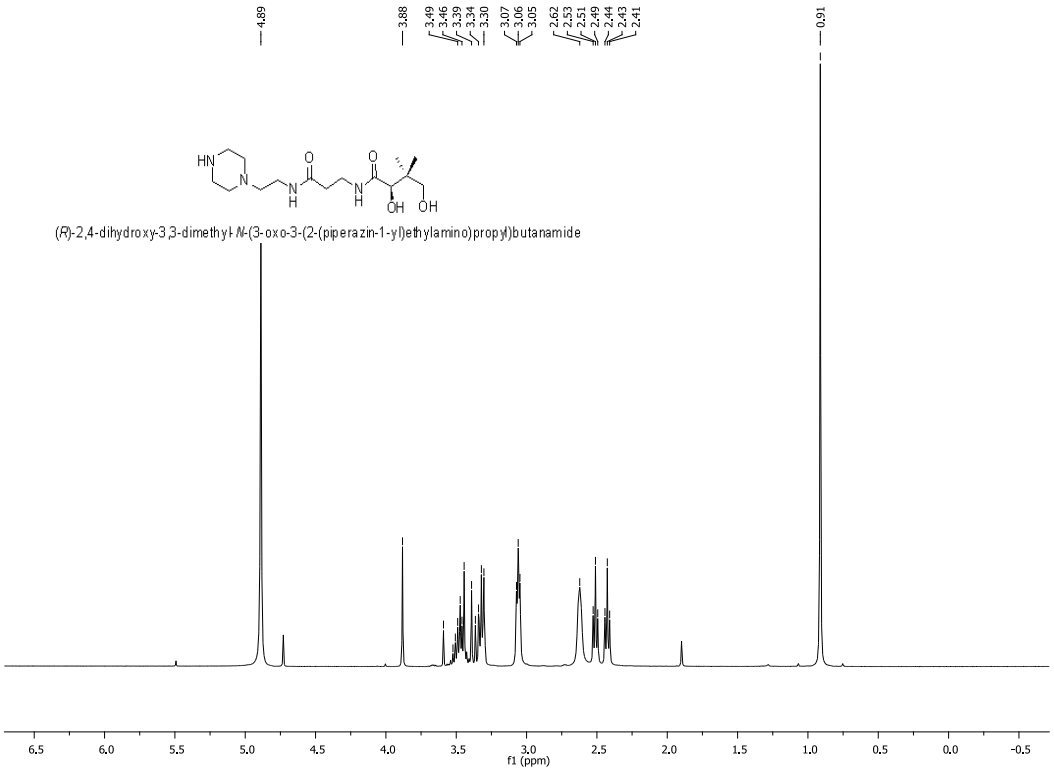
^{1}H-NMR spectrum in CD_3OD of compound **35**



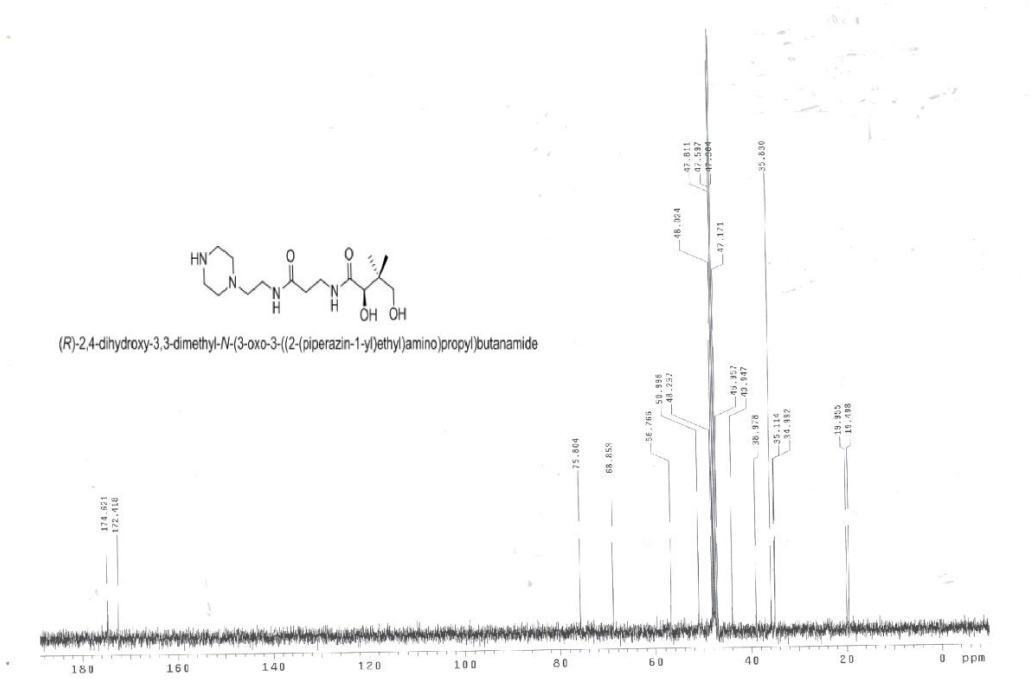
^{13}C-NMR spectrum in CD_3OD of compound **35**



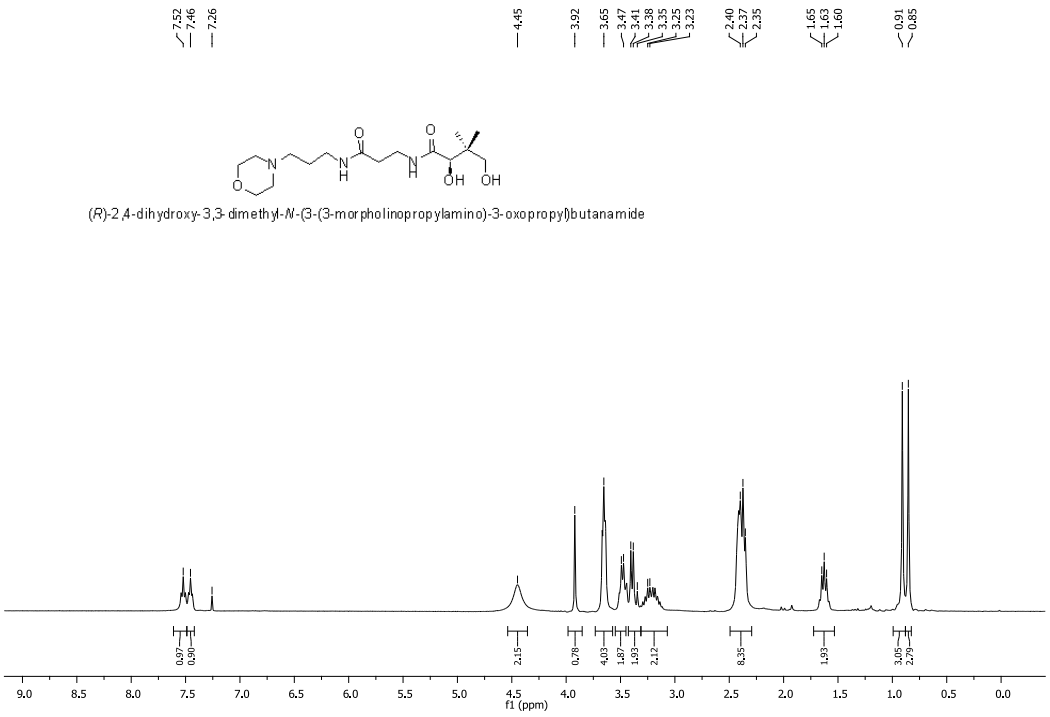
^{1}H-NMR spectrum in CD_3OD compound **36**



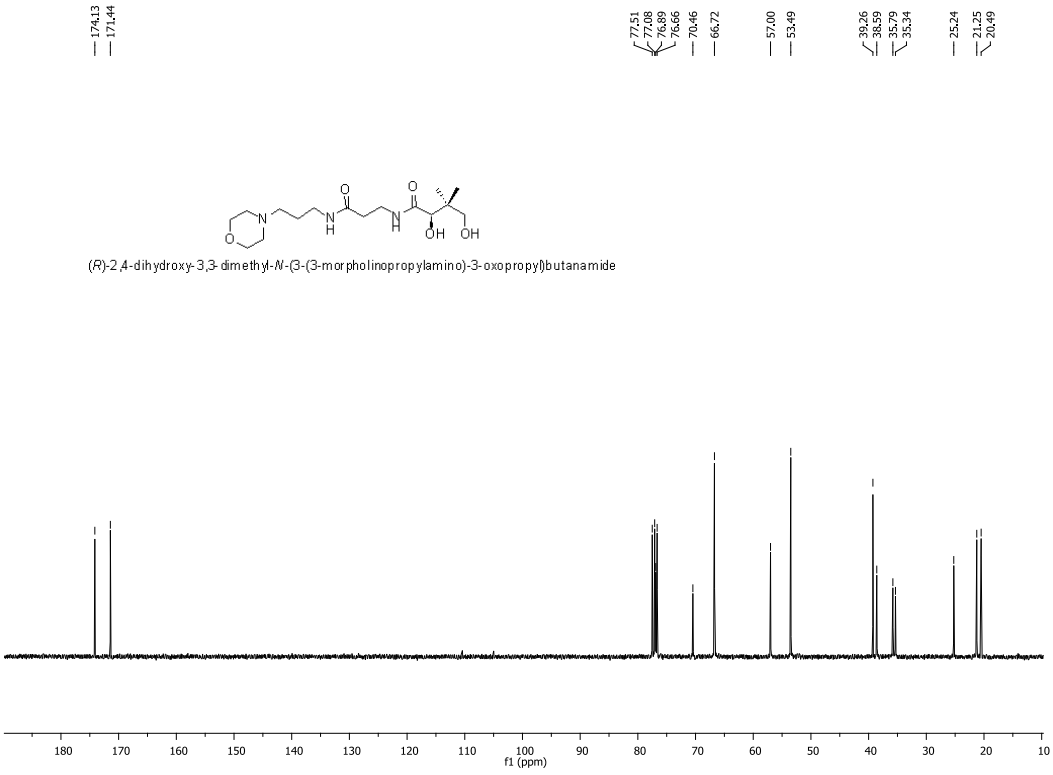
^{13}C-NMR spectrum in CD_3OD of compound **36**



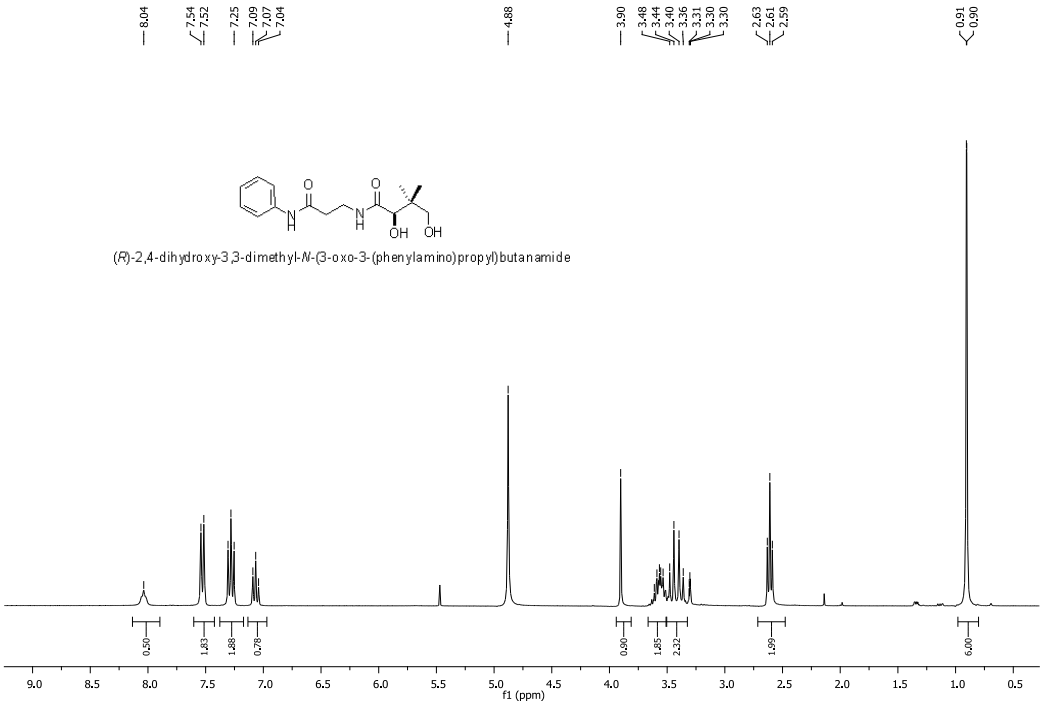
^{1}H-NMR spectrum in $CDCl_3$ of compound **37**



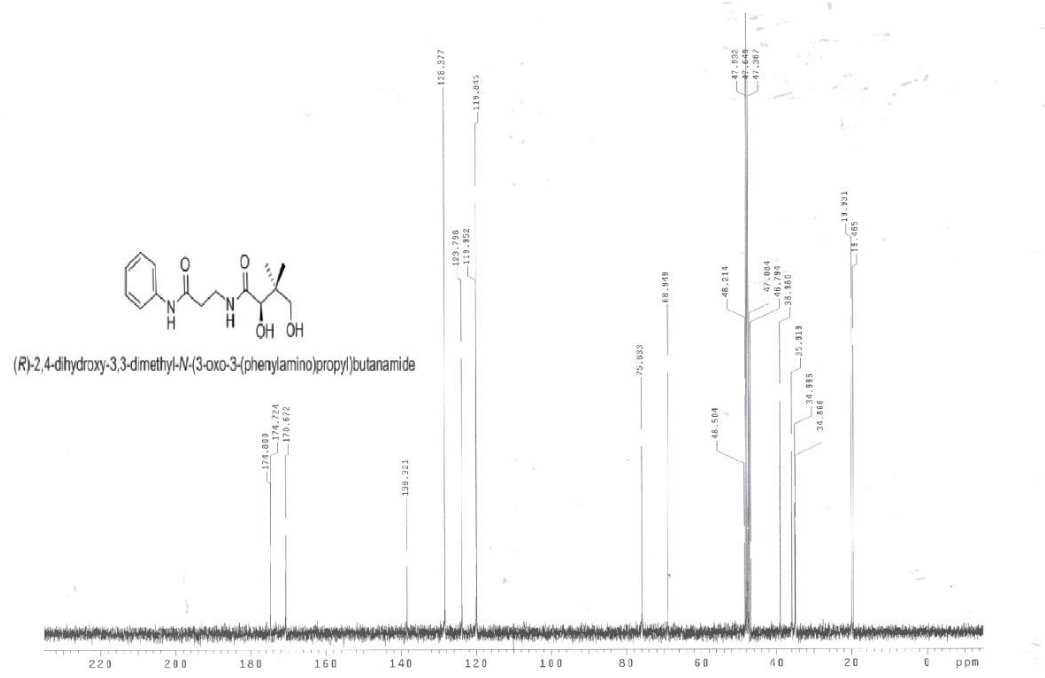
^{13}C-NMR spectrum in $CDCl_3$ of compound **37**



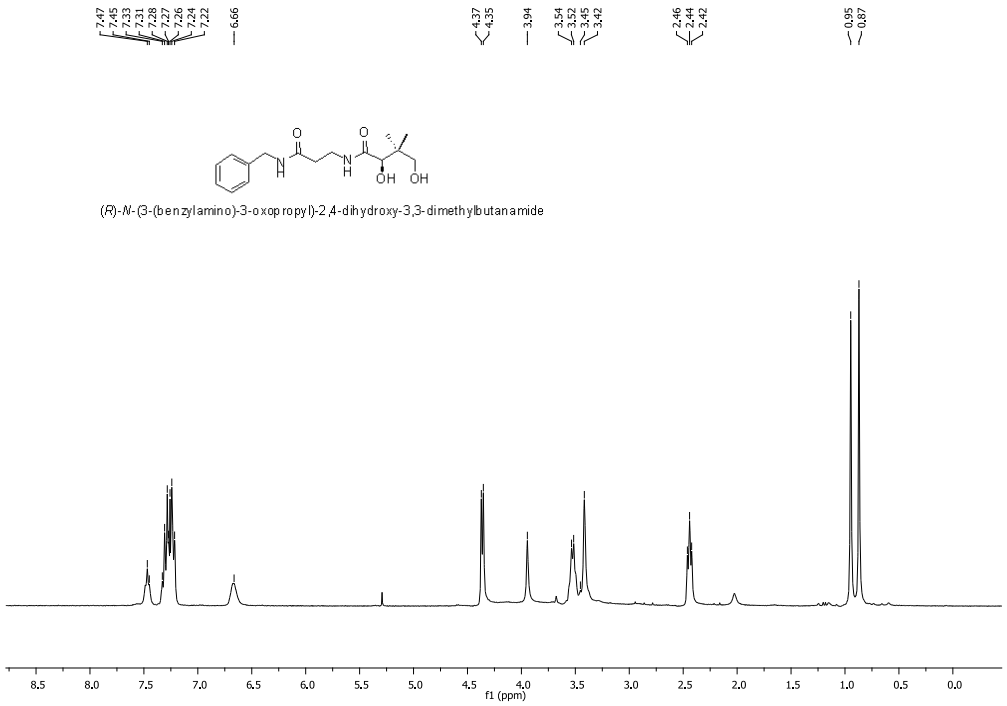
^{1}H-NMR spectrum in $CDCl_3$ of compound **38**



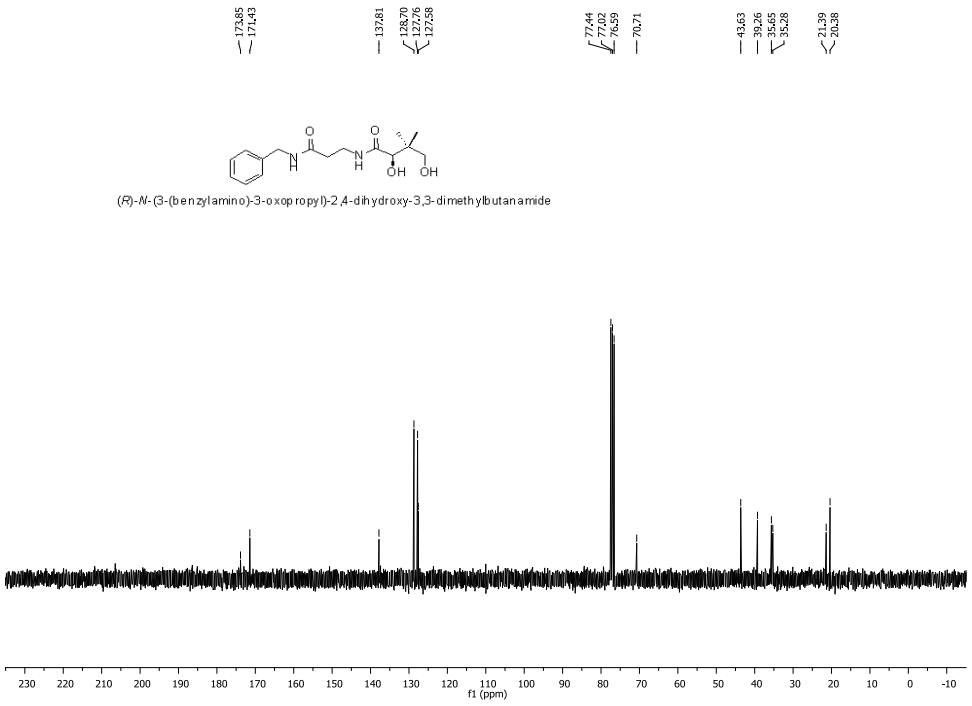
^{13}C-NMR spectrum in $CDCl_3$ of compound **38**



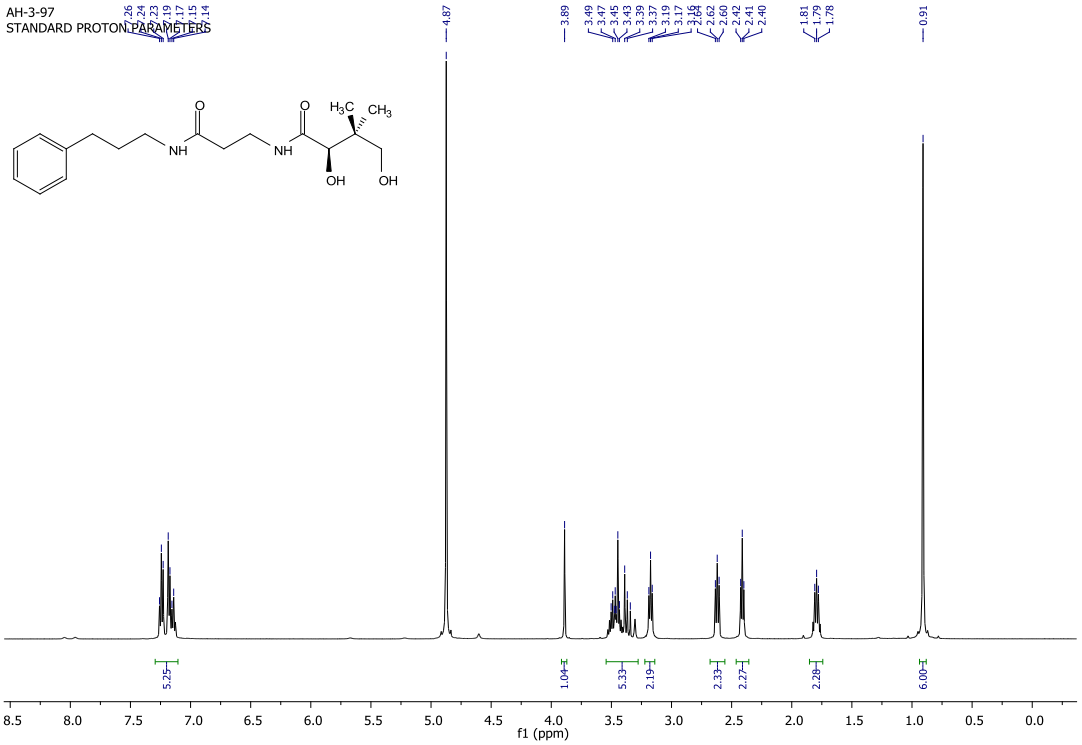
^{1}H-NMR spectrum in $CDCl_3$ of compound **39**.



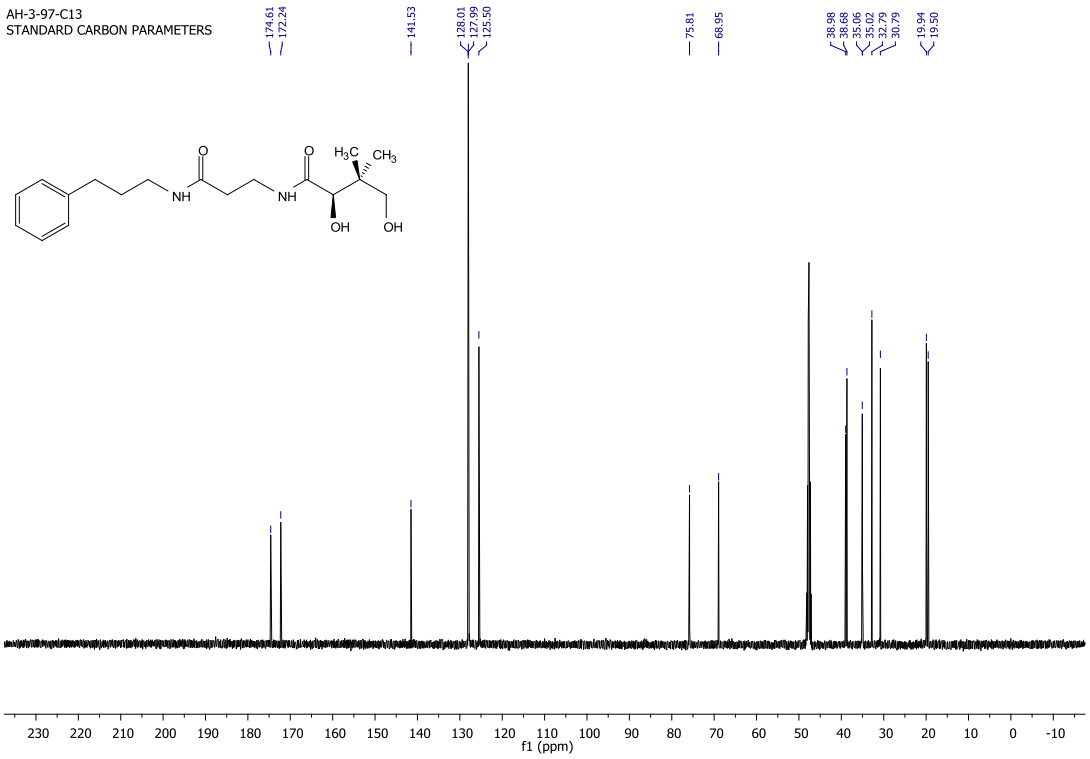
^{13}C-NMR spectrum in $CDCl_3$ of compound **39**



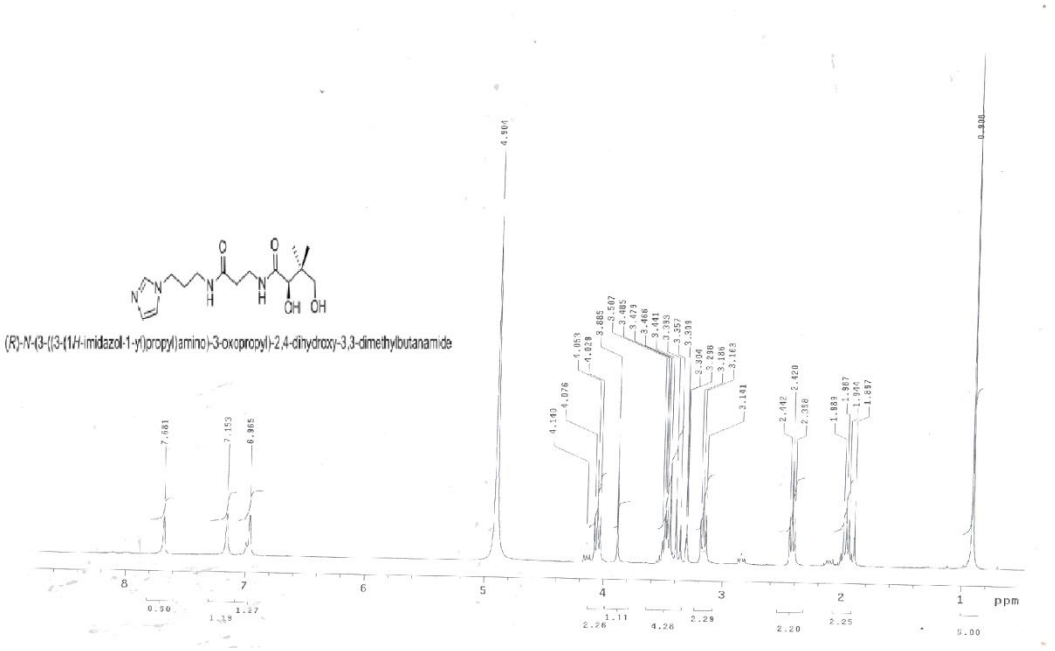
^{1}H-NMR spectrum in $CDCl_3$ of compound **40**



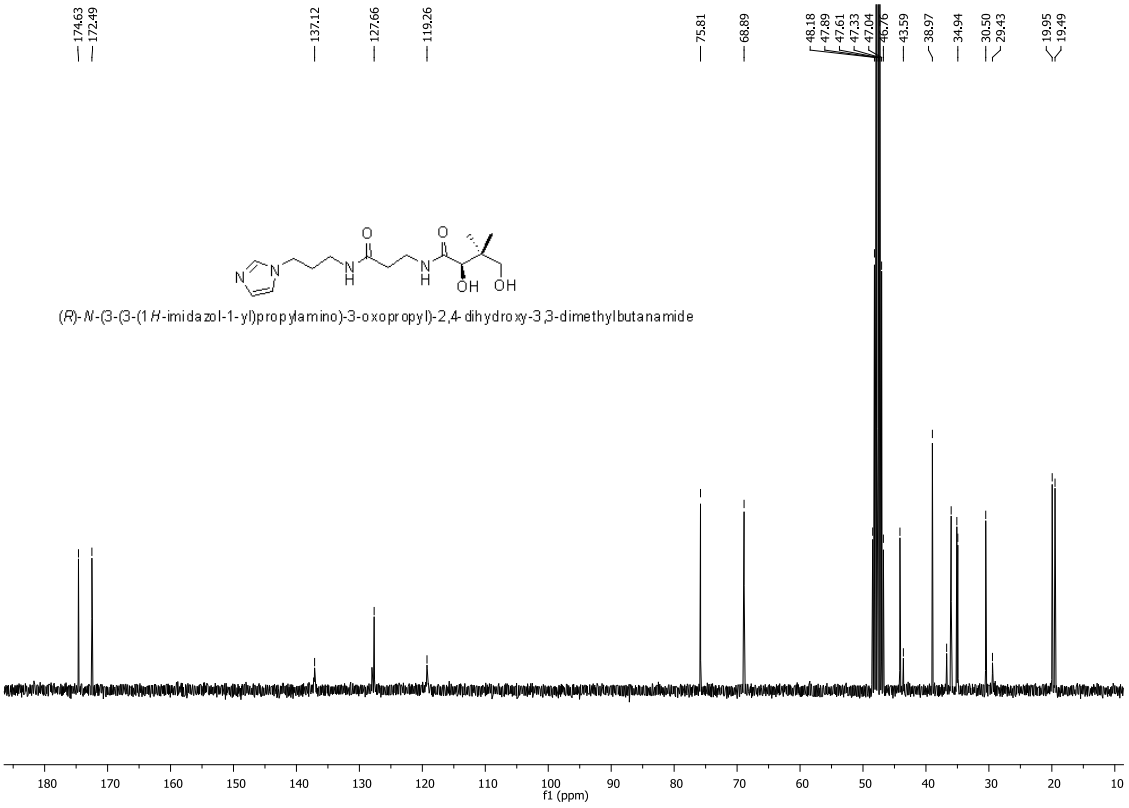
^{13}C-NMR spectrum in $CDCl_3$ of compound **40**



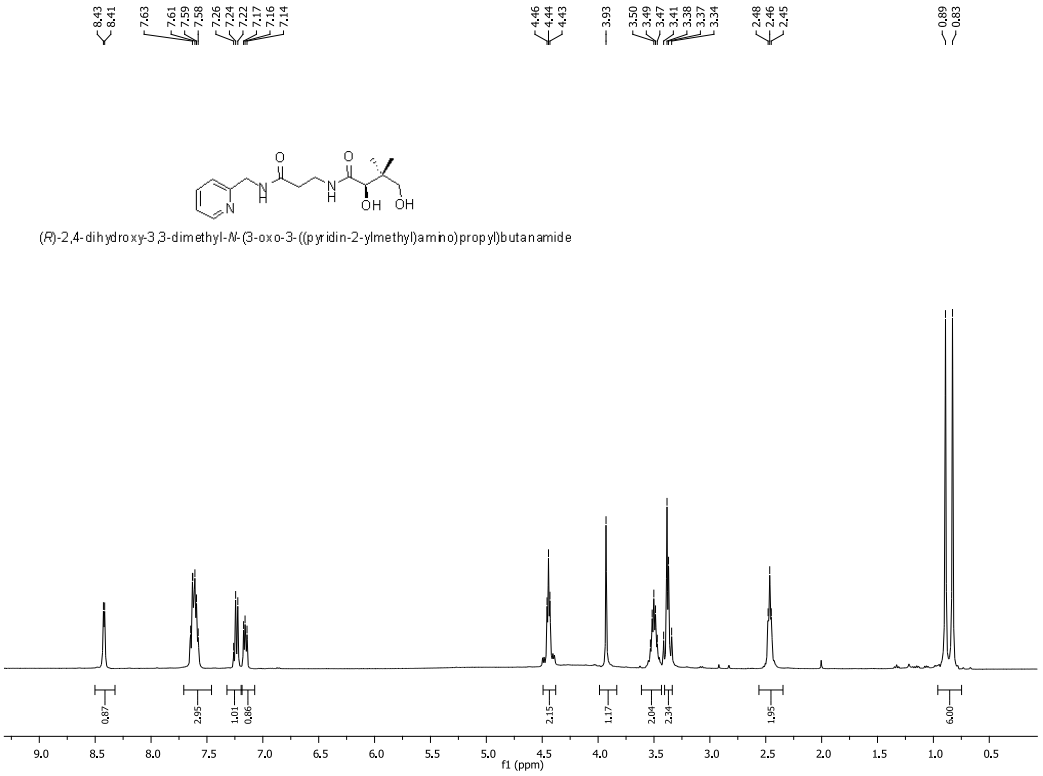
^{1}H-NMR spectrum in CD_3OD of compound **41**



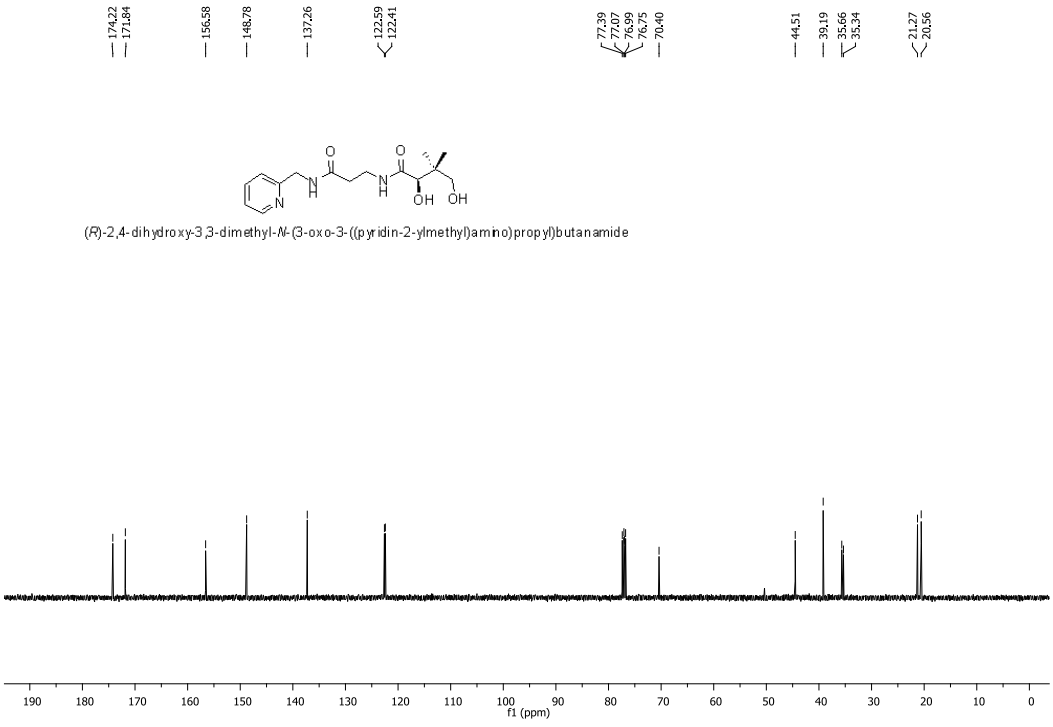
^{13}C-NMR spectrum in CD_3OD of compound **41**



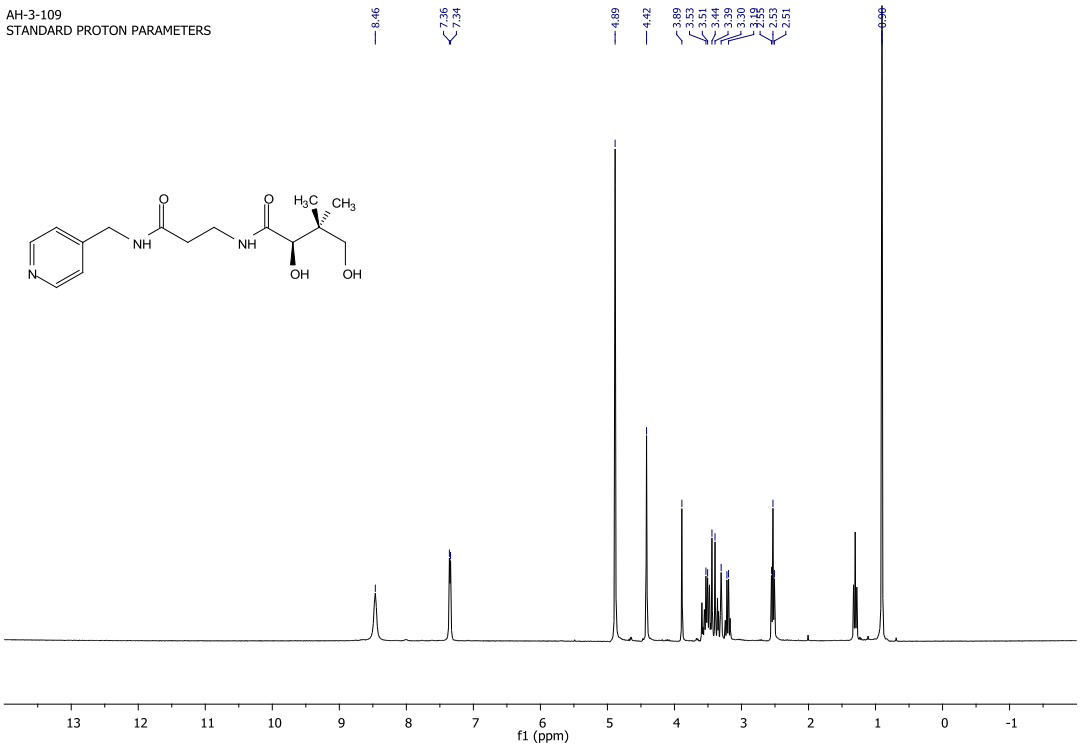
^{1}H-NMR spectrum in $CDCl_3$ for compound **42**



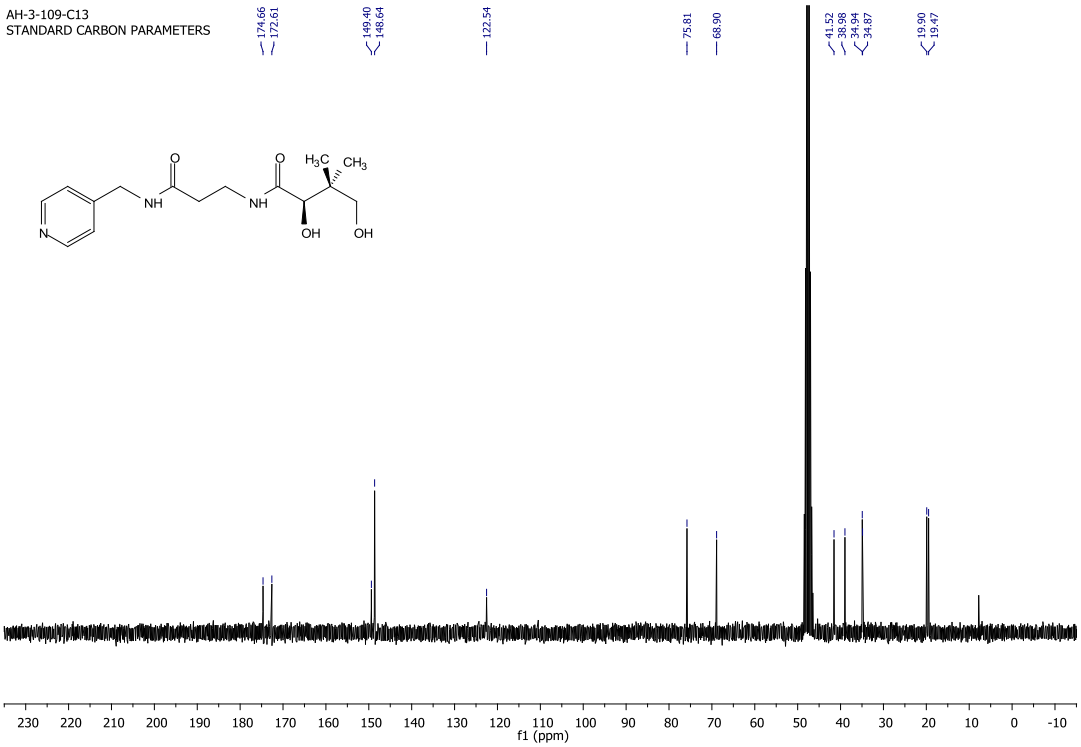
^{13}C-NMR spectrum in $CDCl_3$ of compound **42**



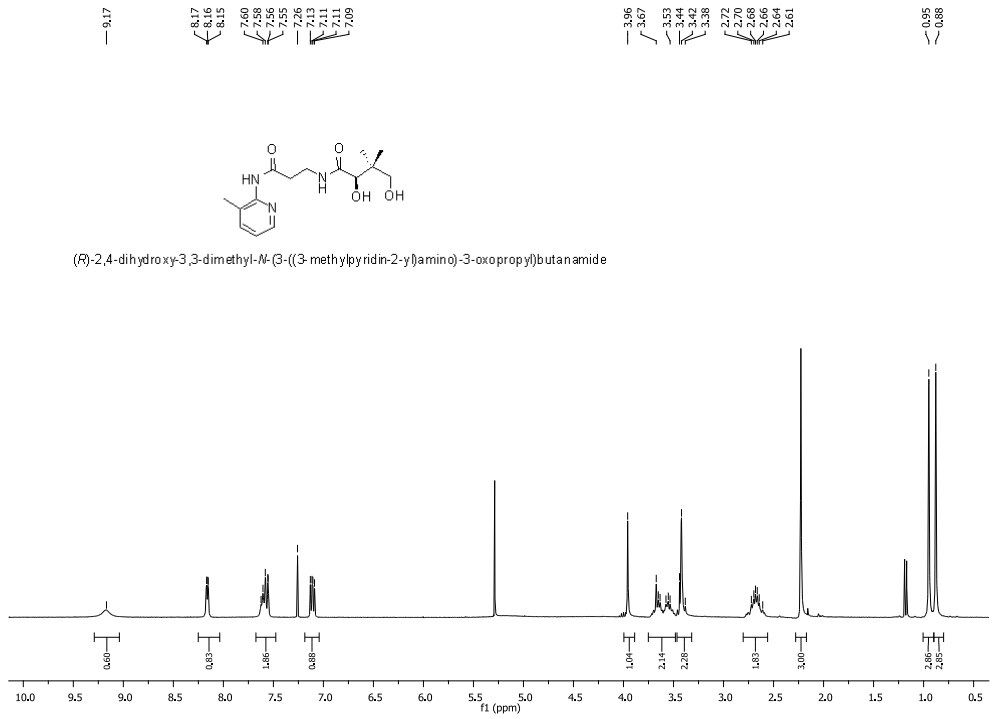
^{1}H-NMR spectrum in $CDCl_3$ of compound **43**



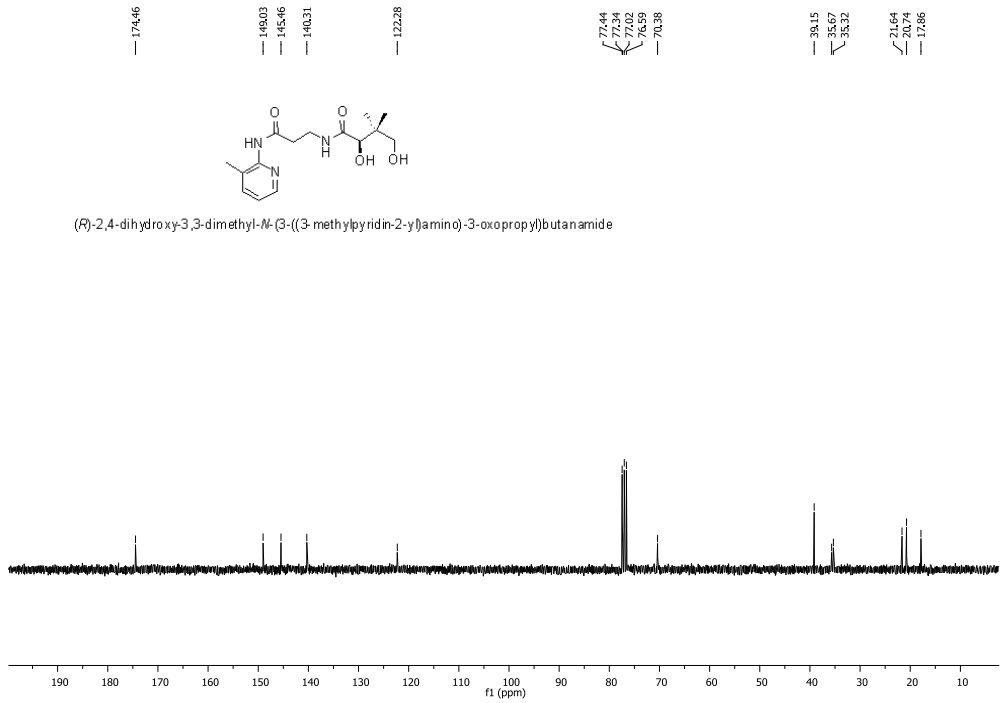
^{13}C-NMR spectrum in $CDCl_3$ of compound **43**



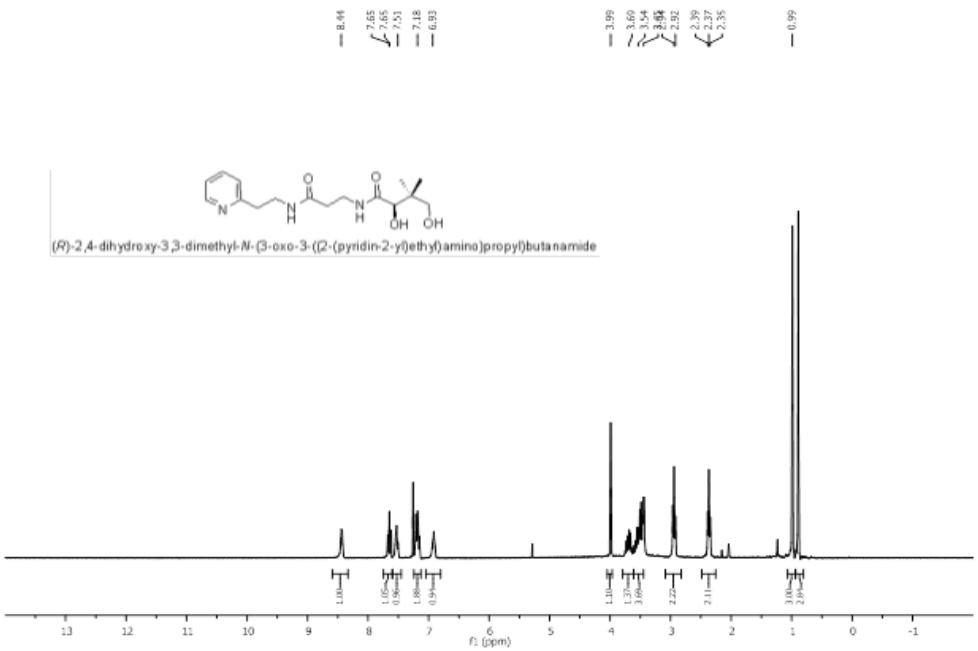
^{1}H-NMR spectrum of in $CDCl_3$ compound **44**



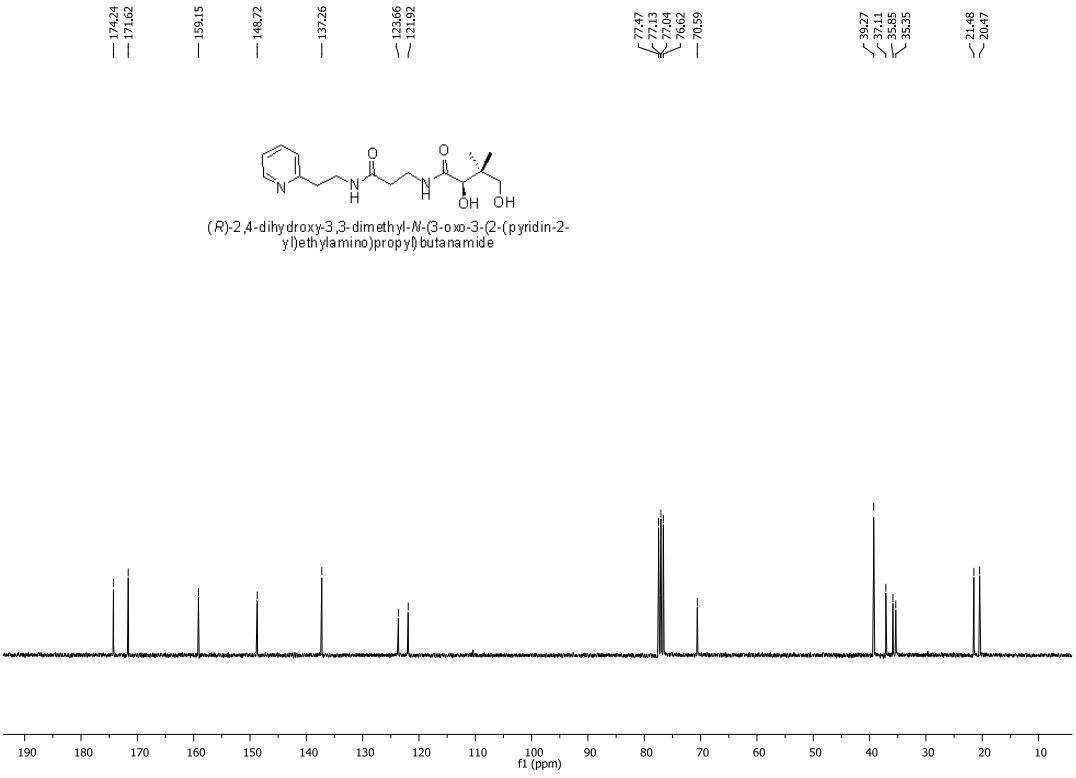
^{13}C-NMR spectrum in $CDCl_3$ of compound **44**



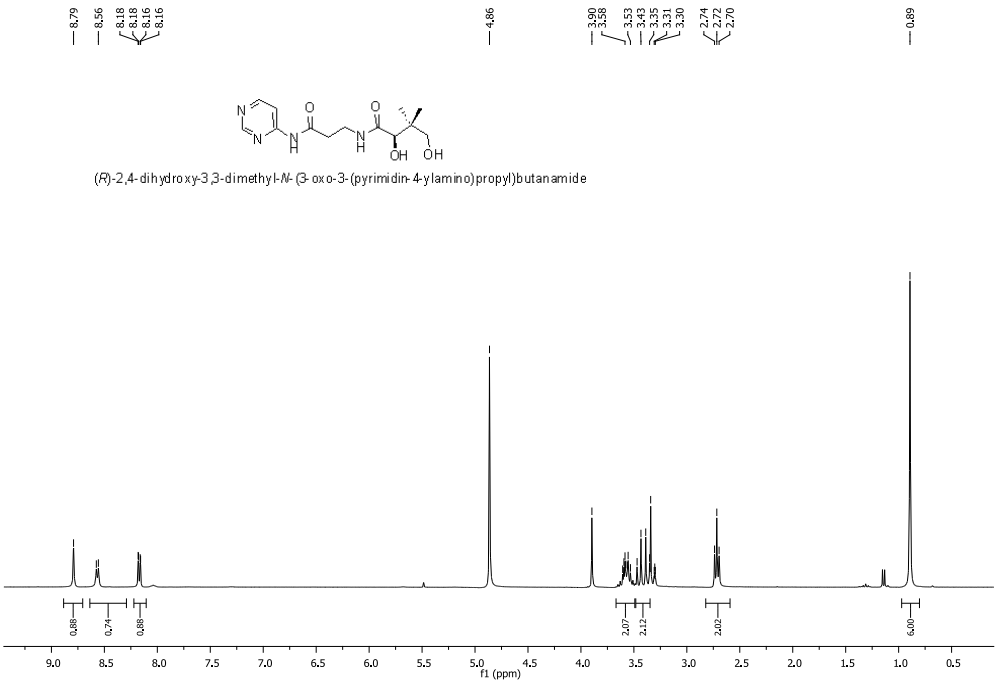
^{1}H-NMR spectrum in $CDCl_3$ of compound **45**



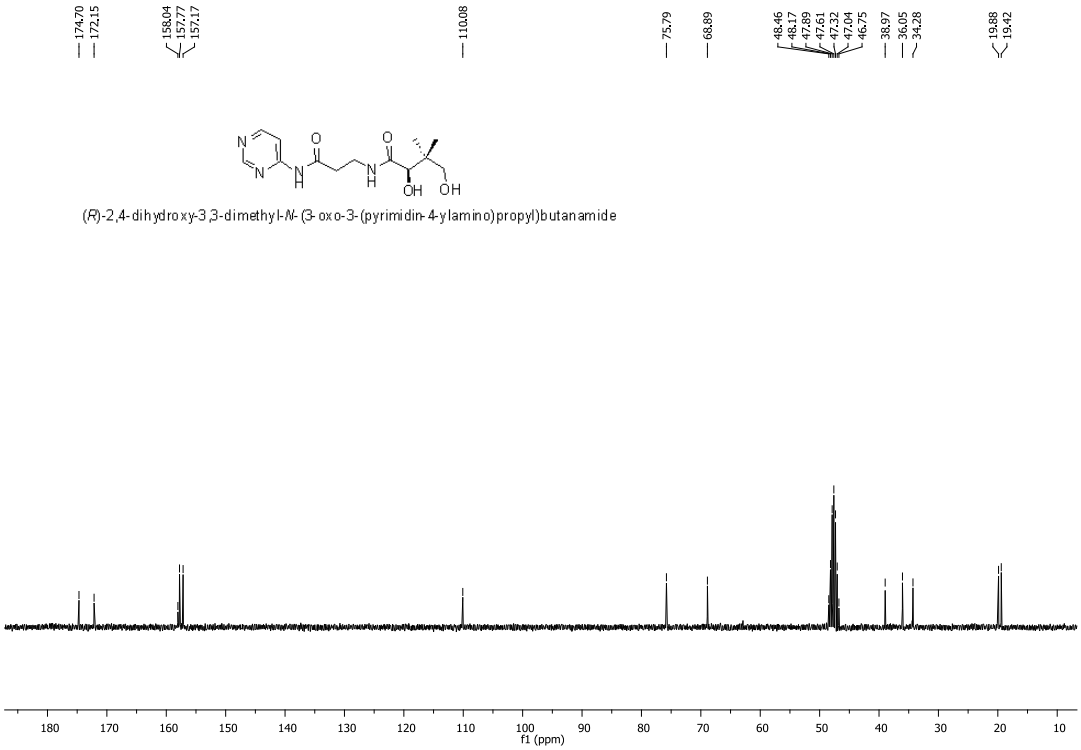
^{13}C-NMR spectrum in $CDCl_3$ of compound**45**



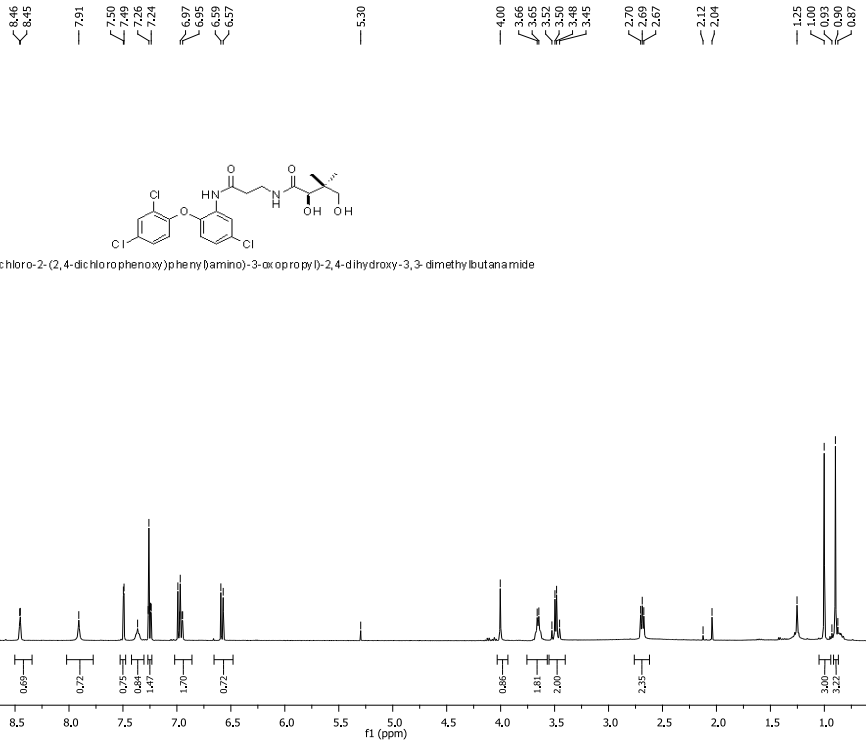
^{1}H-NMR spectrum in CD_3OD of compound **46**



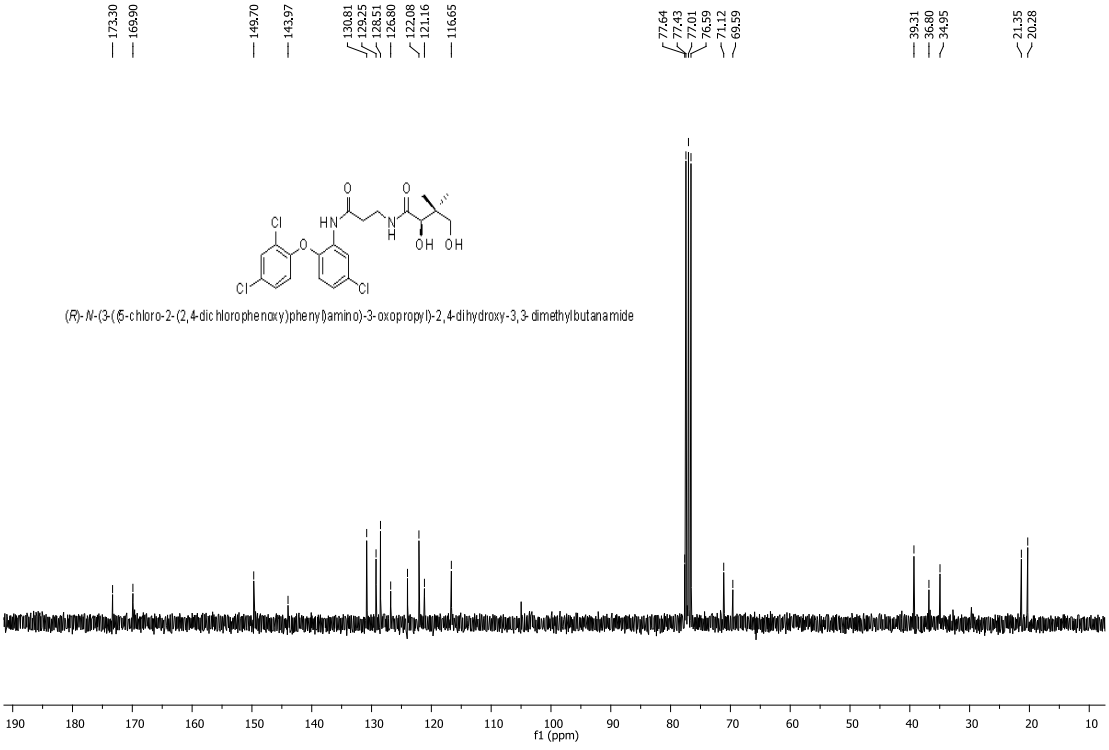
^{13}C-NMR spectrum in CD_3OD of compound **46**



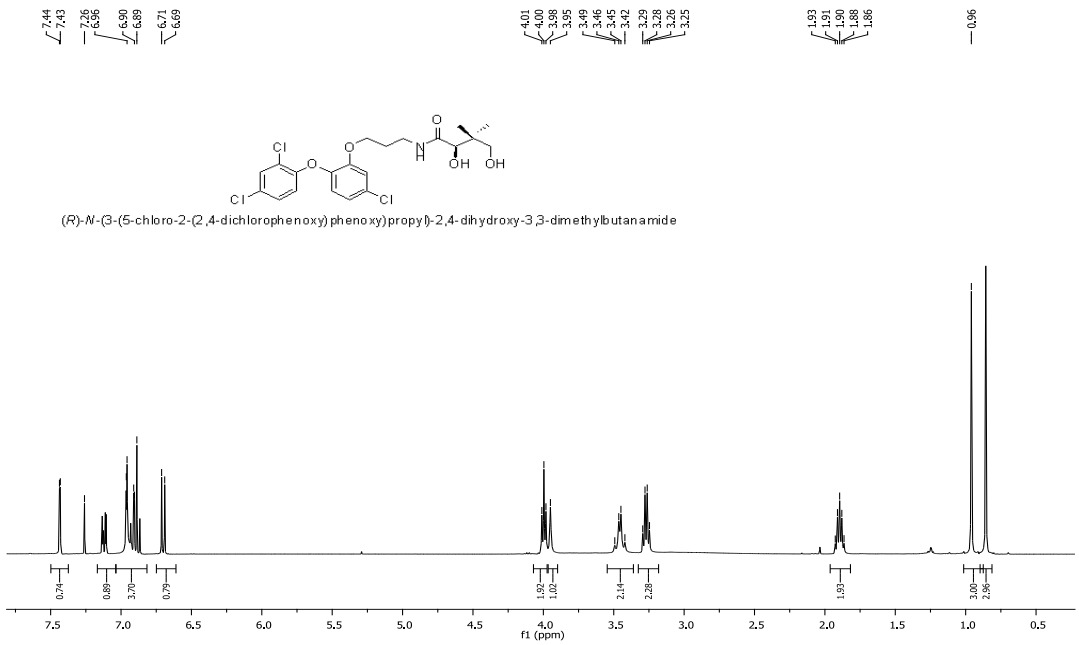
^{1}H-NMR spectrum in $CDCl_3$ of compound **47**



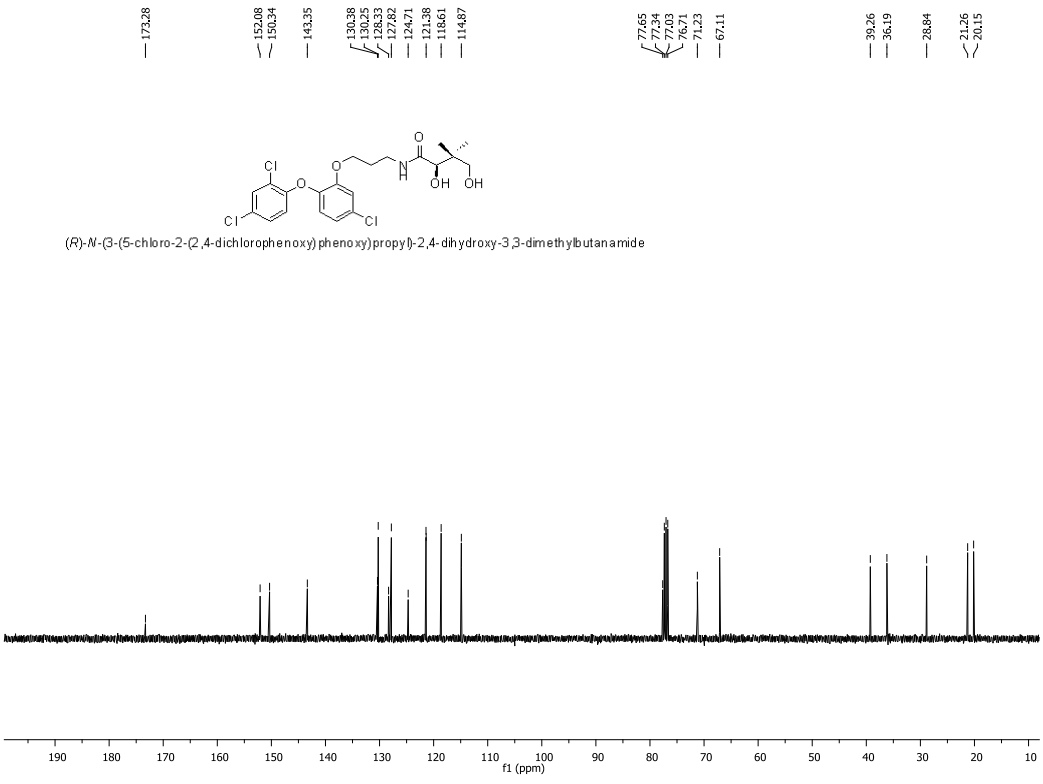
^{13}C-NMR spectrum in $CDCl_3$ of compound **47**



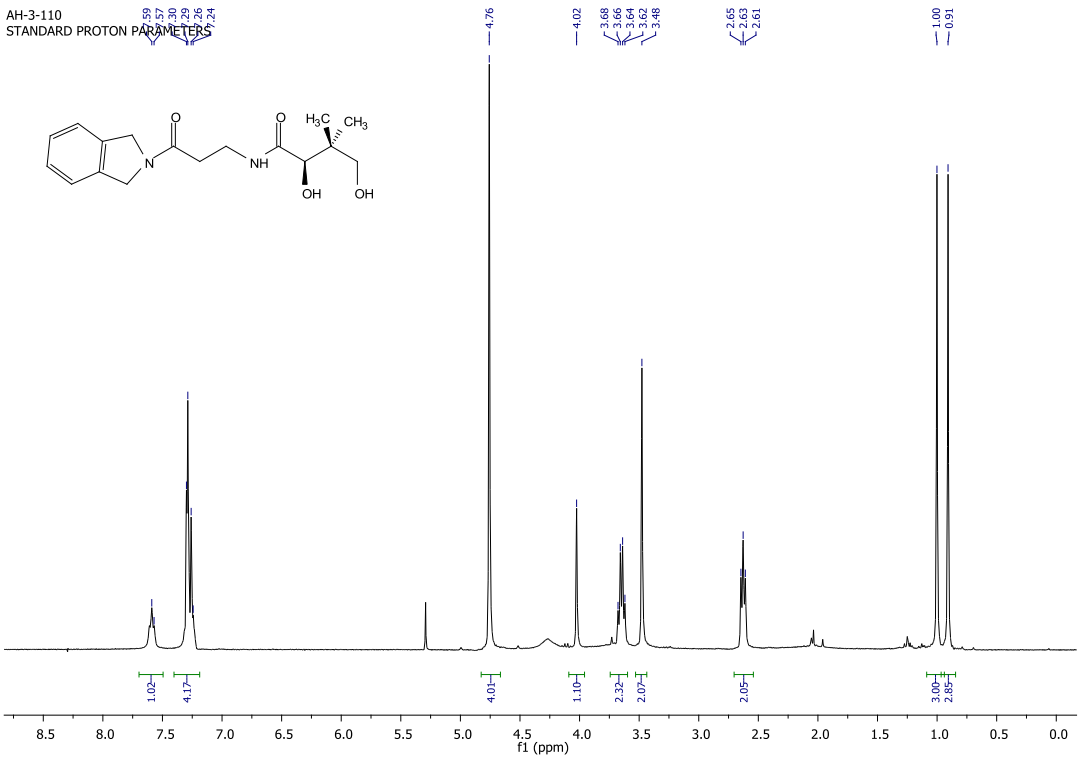
^{1}H-NMR spectrum in $CDCl_3$ of compound **48**



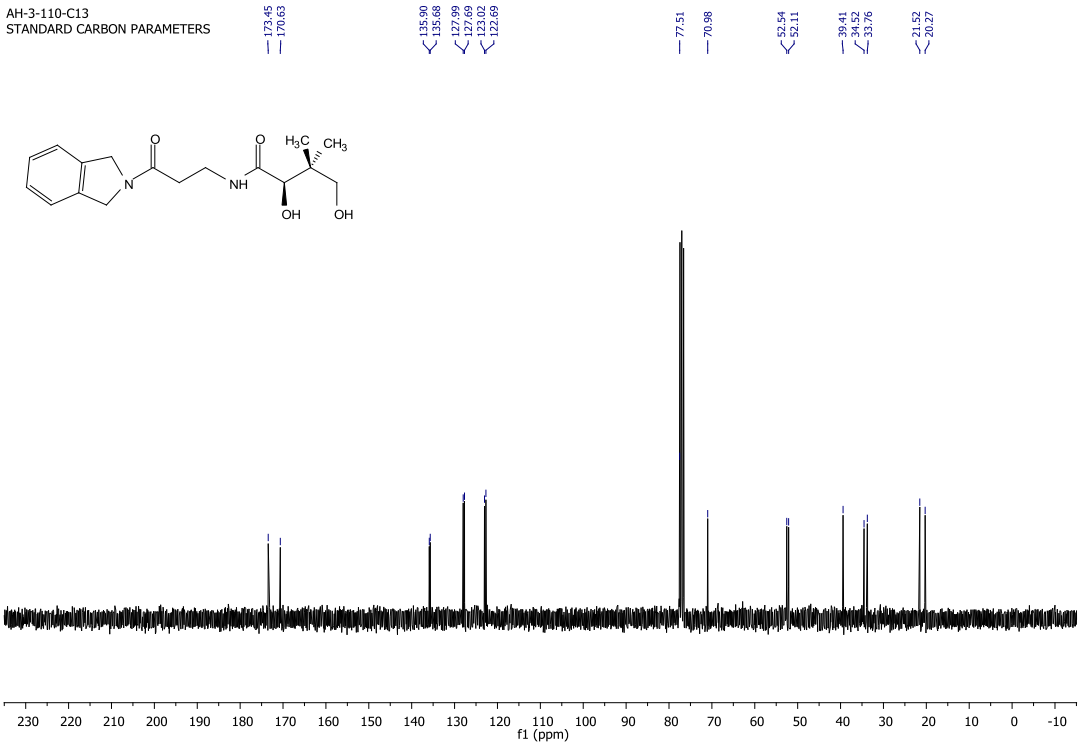
^{13}C-NMR spectrum in $CDCl_3$ of compound **48**



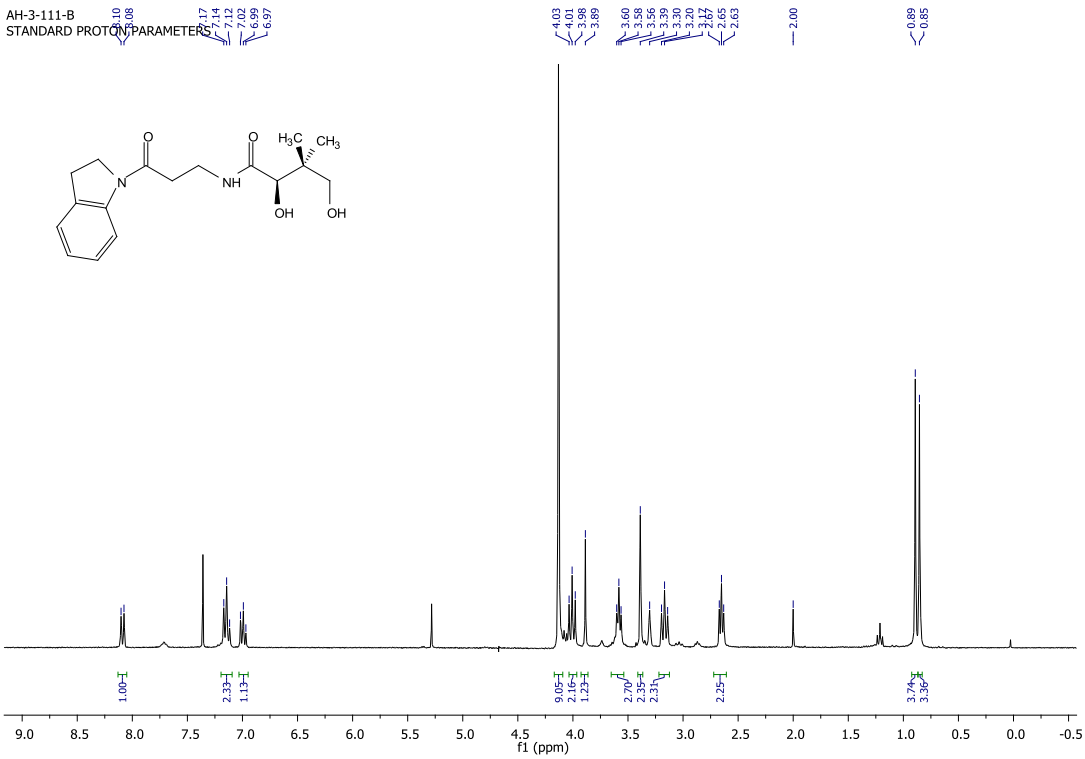
^{1}H-NMR spectrum in $CDCl_3$ of compound **49**



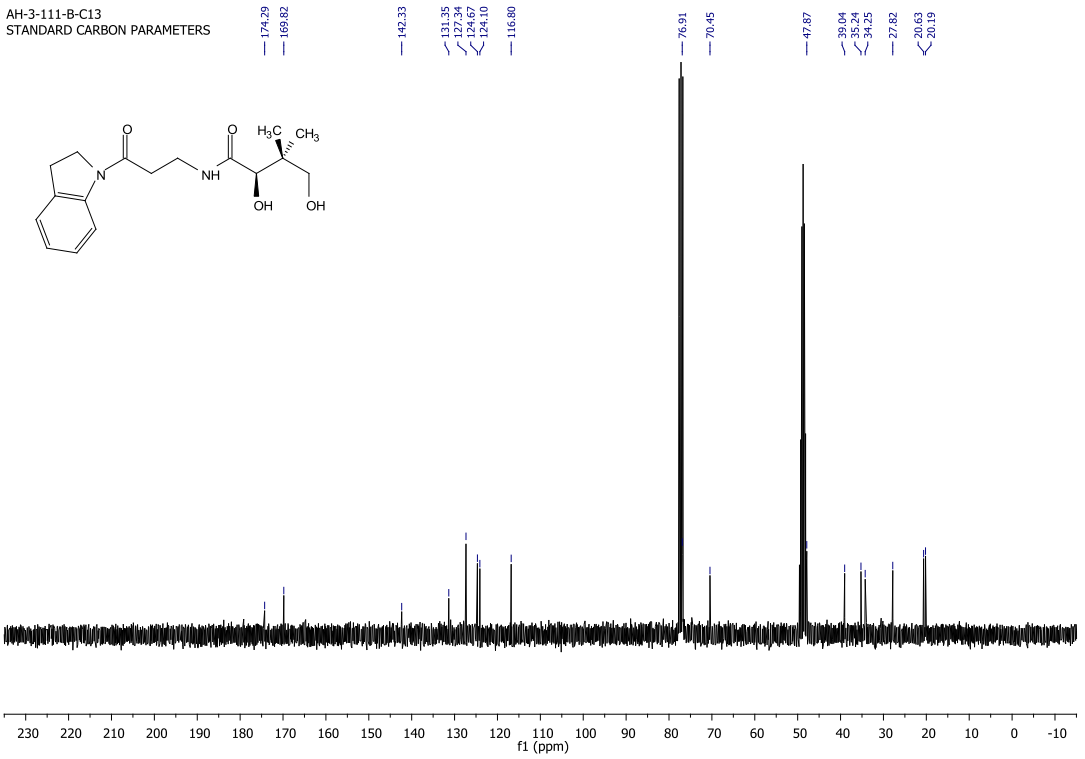
^{13}C-NMR spectrum in $CDCl_3$ of compound **49**



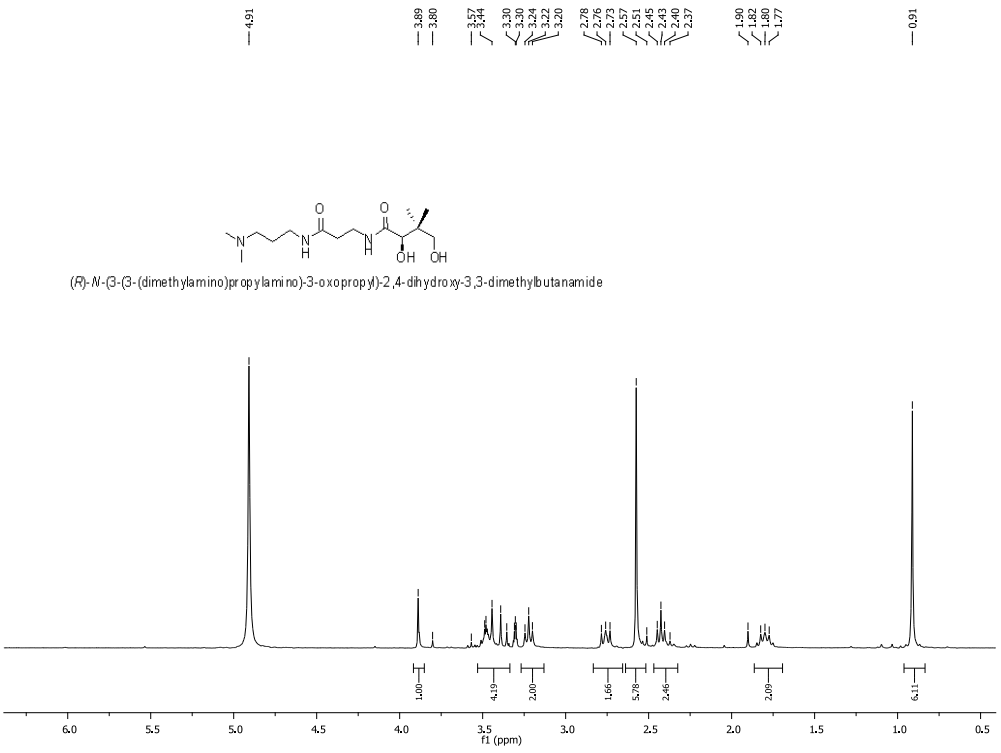
^{1}H-NMR spectrum in $CDCl_3$ of compound **50**



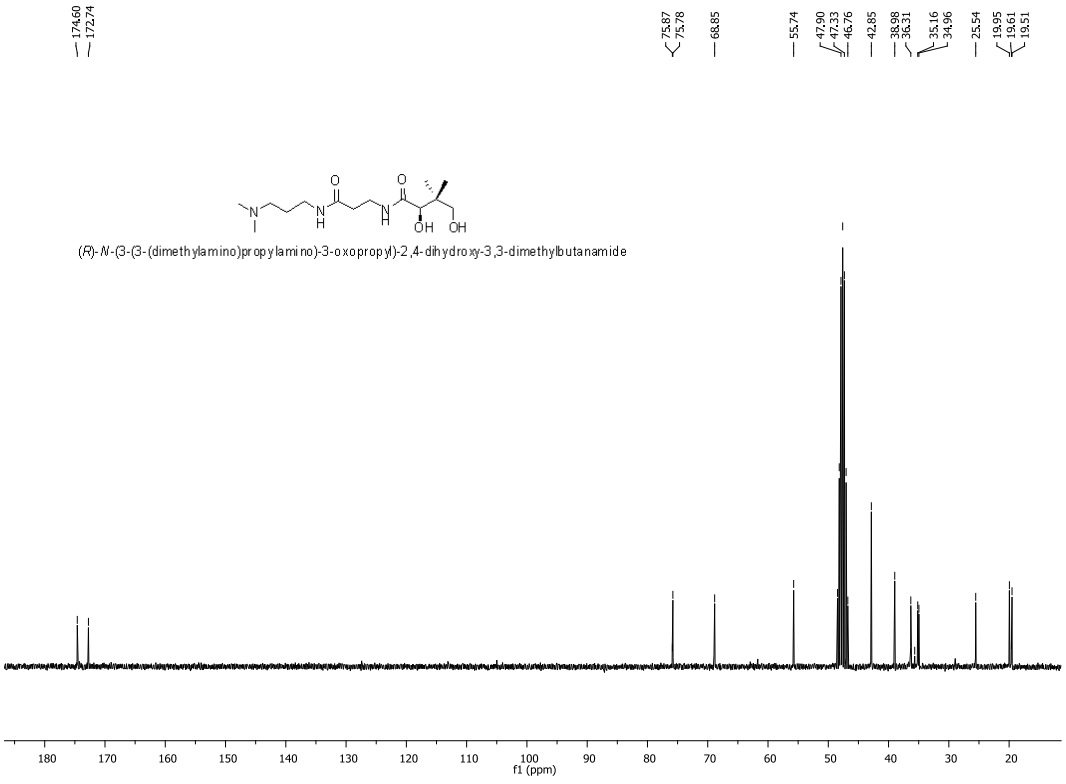
^{13}C-NMR spectrum in $CDCl_3$ of compound **50**



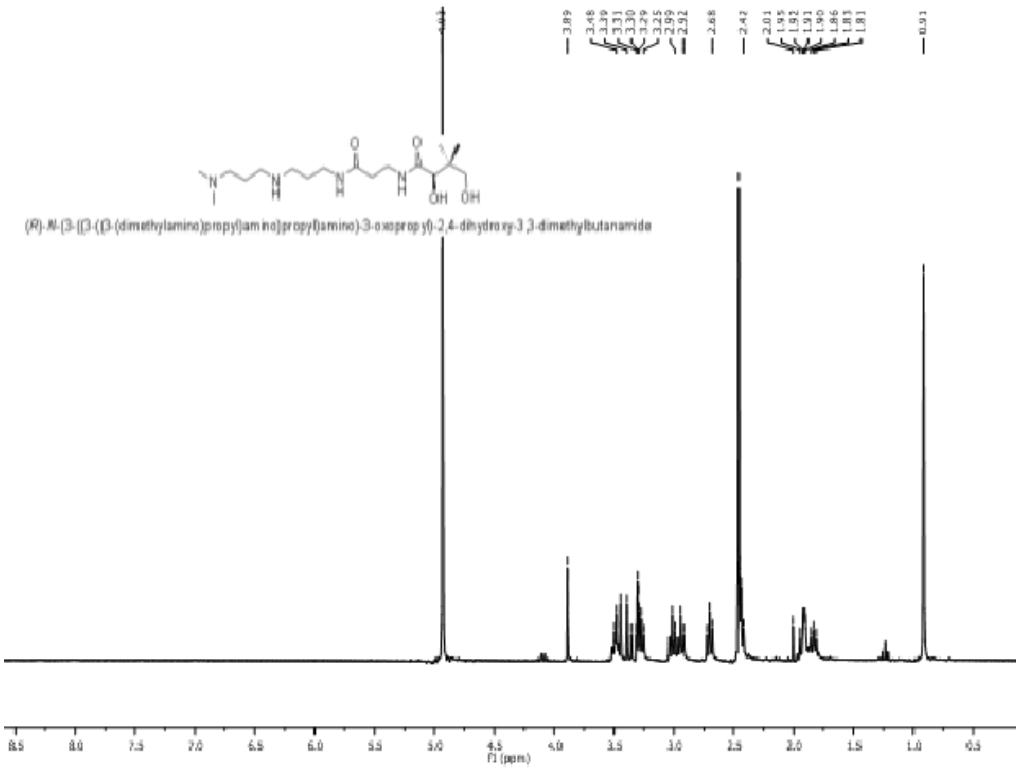
^{1}H-NMR spectrum in $CDCl_3$ of compound **51**



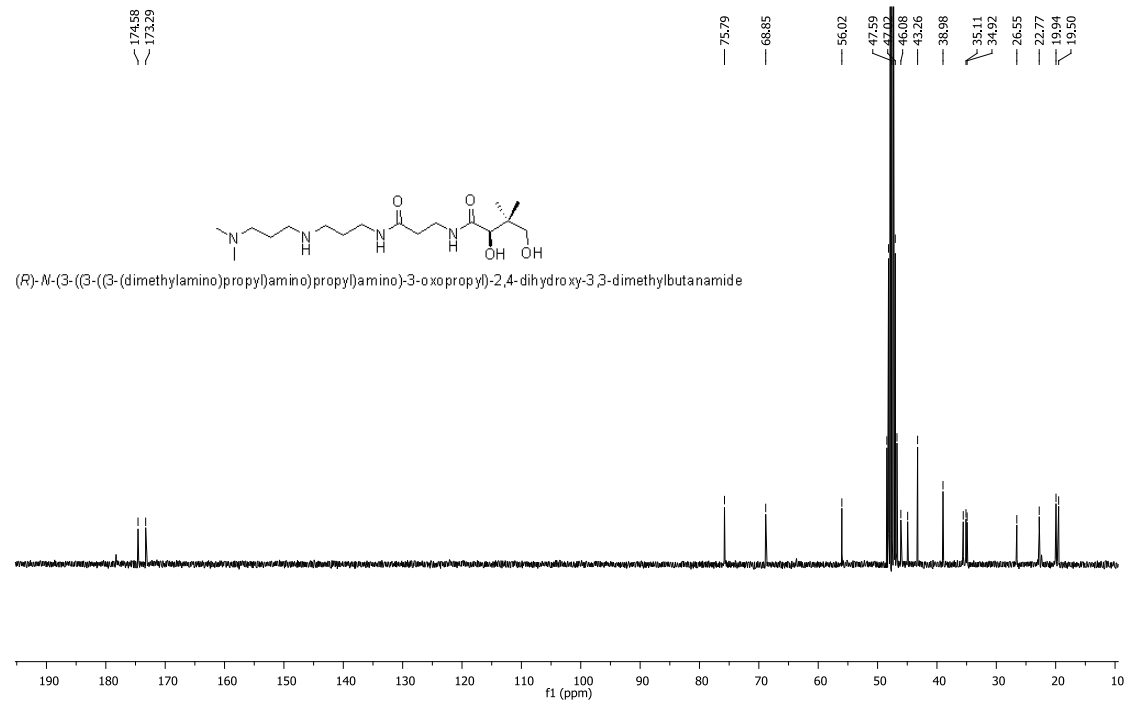
^{13}C-NMR spectrum in $CDCl_3$ of compound **51**



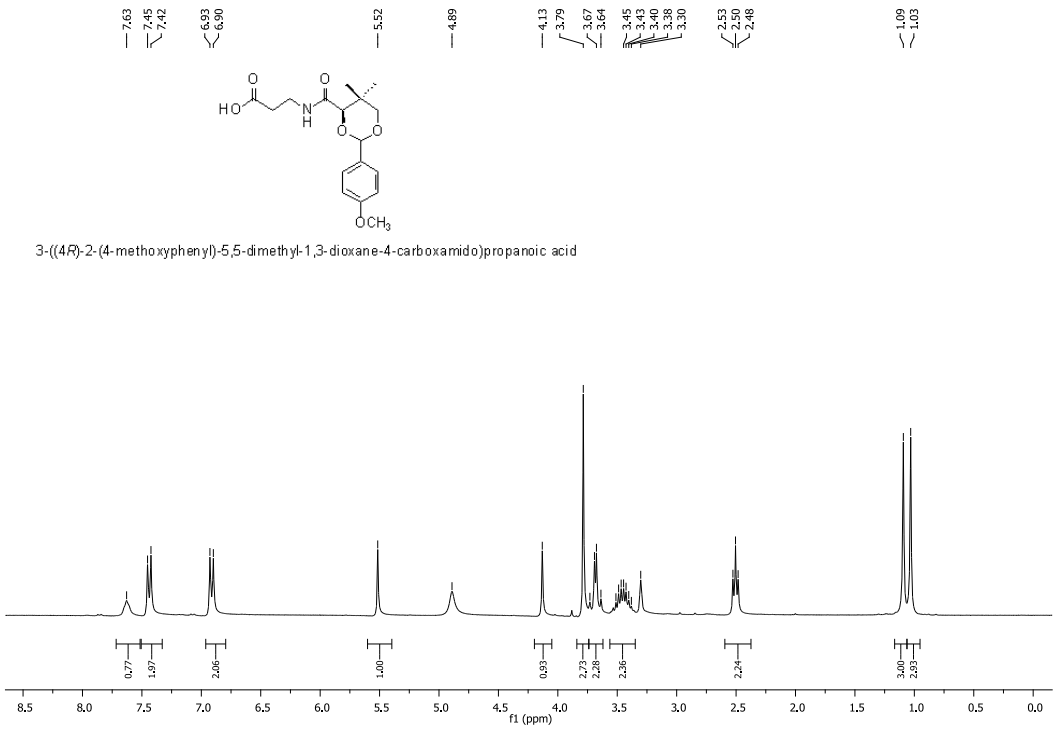
^{1}H-NMR spectrum in $CDCl_3$ of compound **52**



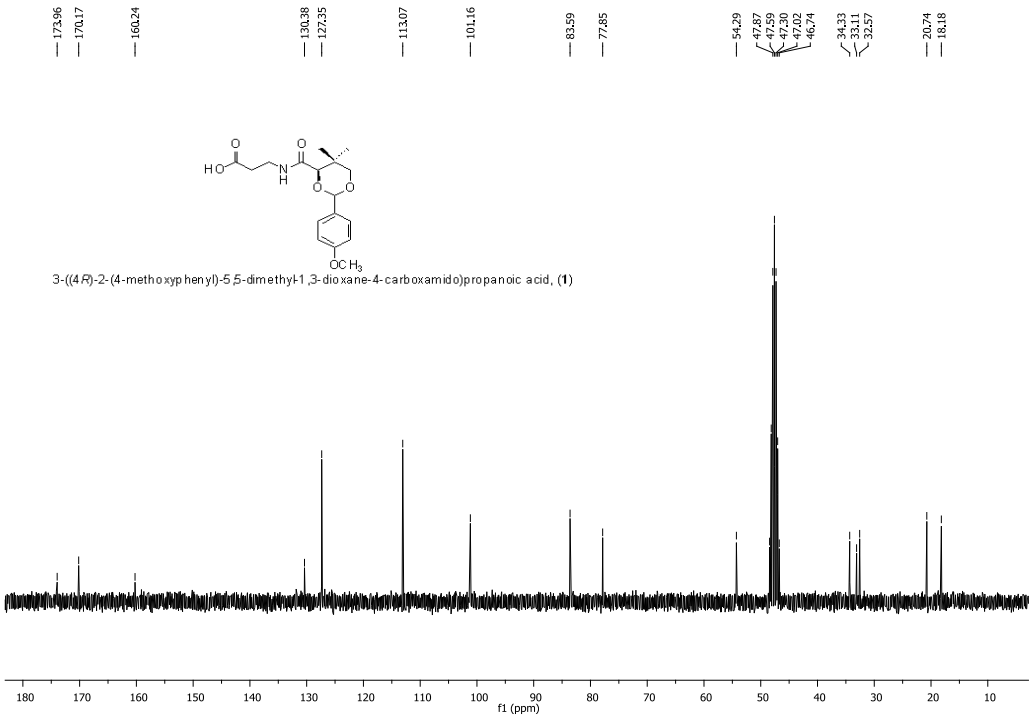
^{13}C-NMR spectrum in $CDCl_3$ of compound **52**



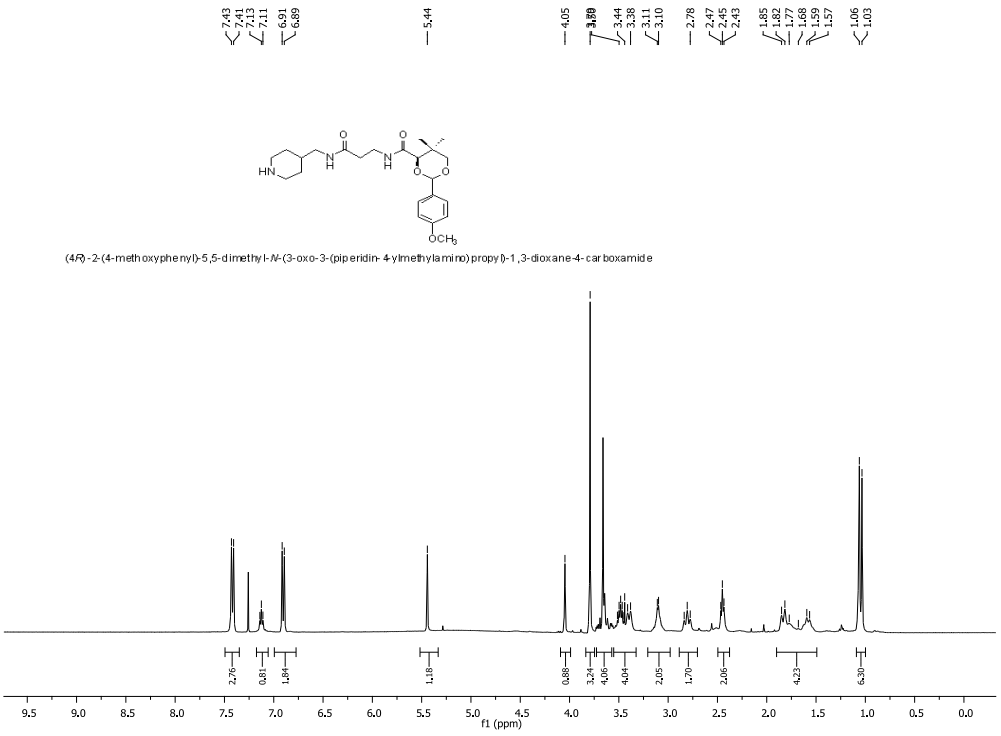
^{1}H-NMR spectrum in CD_3OD of compound **53**



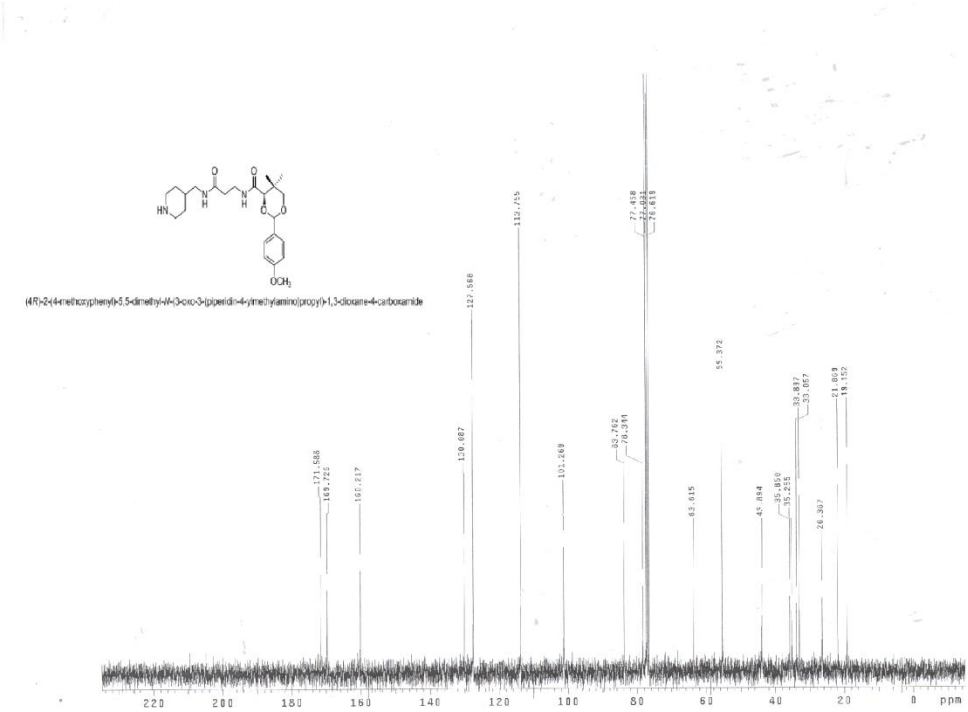
^{13}C-NMR spectrum in CD_3OD of compound **53**



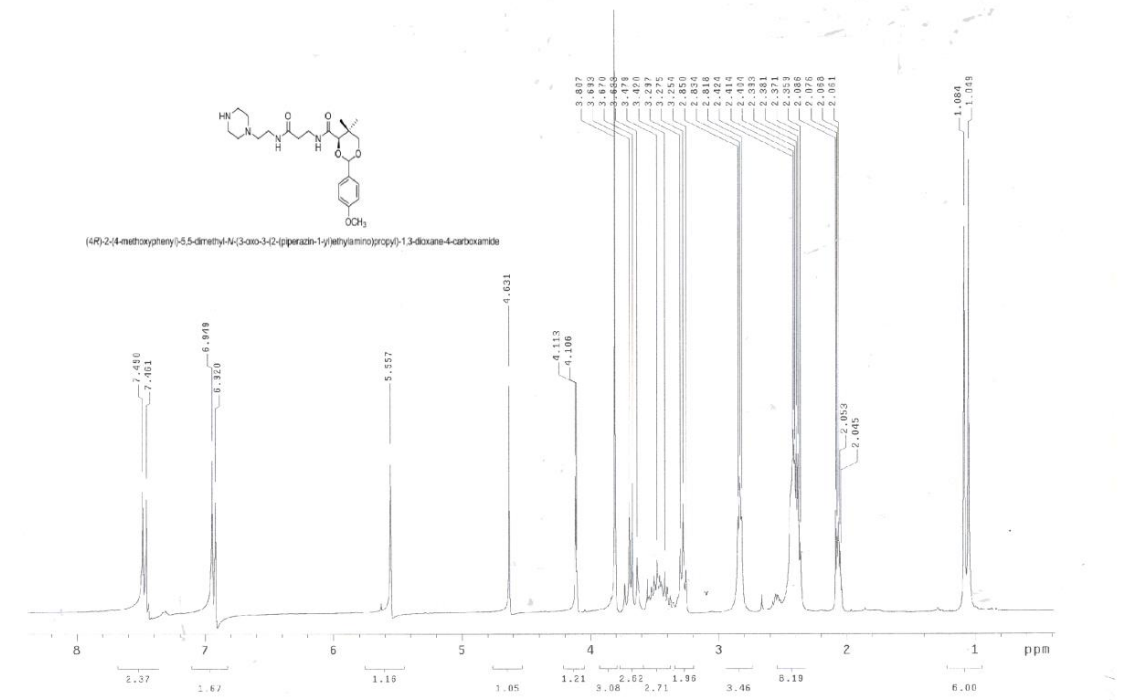
^{1}H-NMR spectrum in $CDCl_3$ of compound **55b**



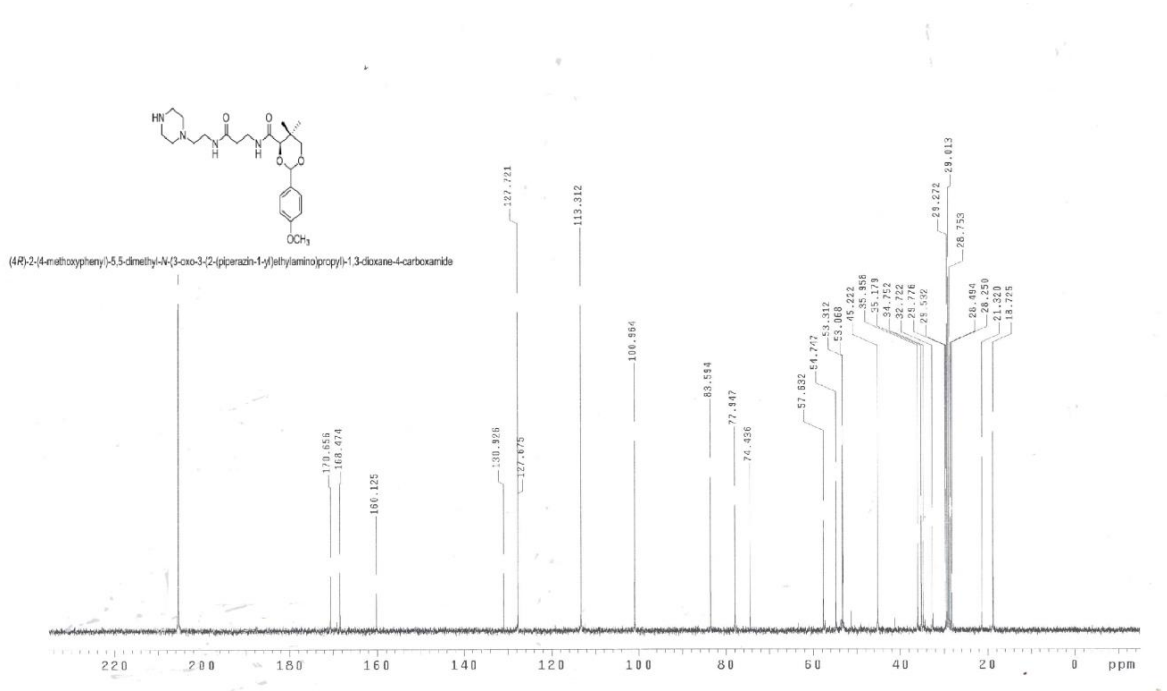
^{13}C-NMR spectrum in $CDCl_3$ of compound **55b**



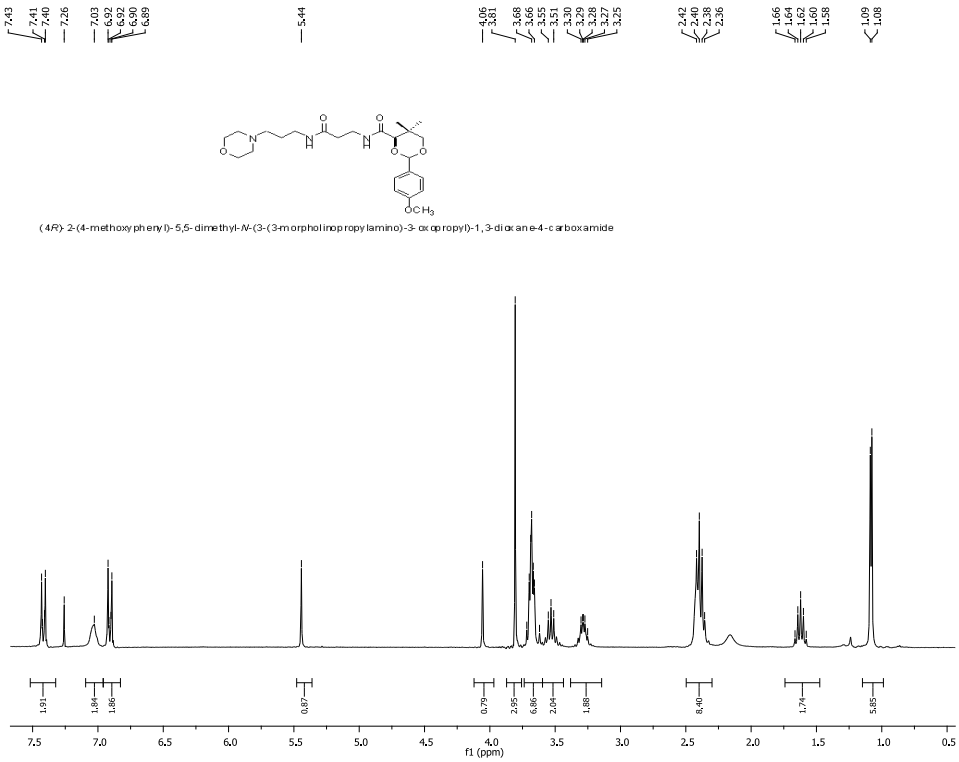
^{1}H-NMR spectrum in CD_3CO of compound **55c**



^{13}C-NMR spectrum in CD_3CO of compound **55c**

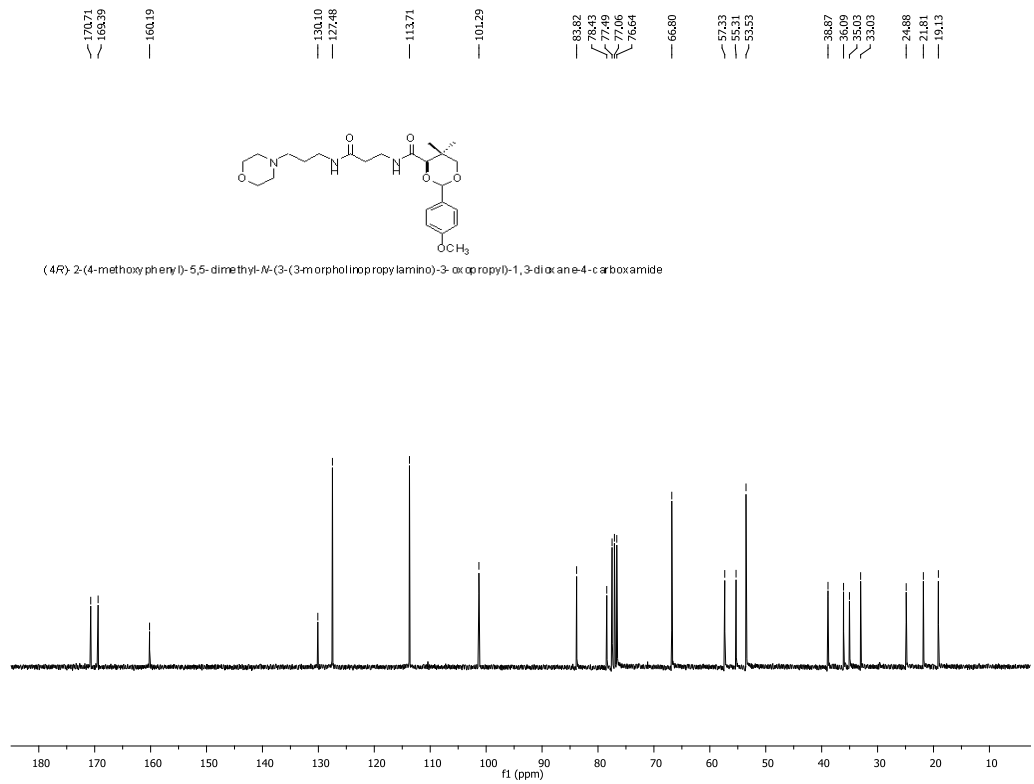


^{1}H-NMR spectrum in $CDCl_3$ of compound **55d**

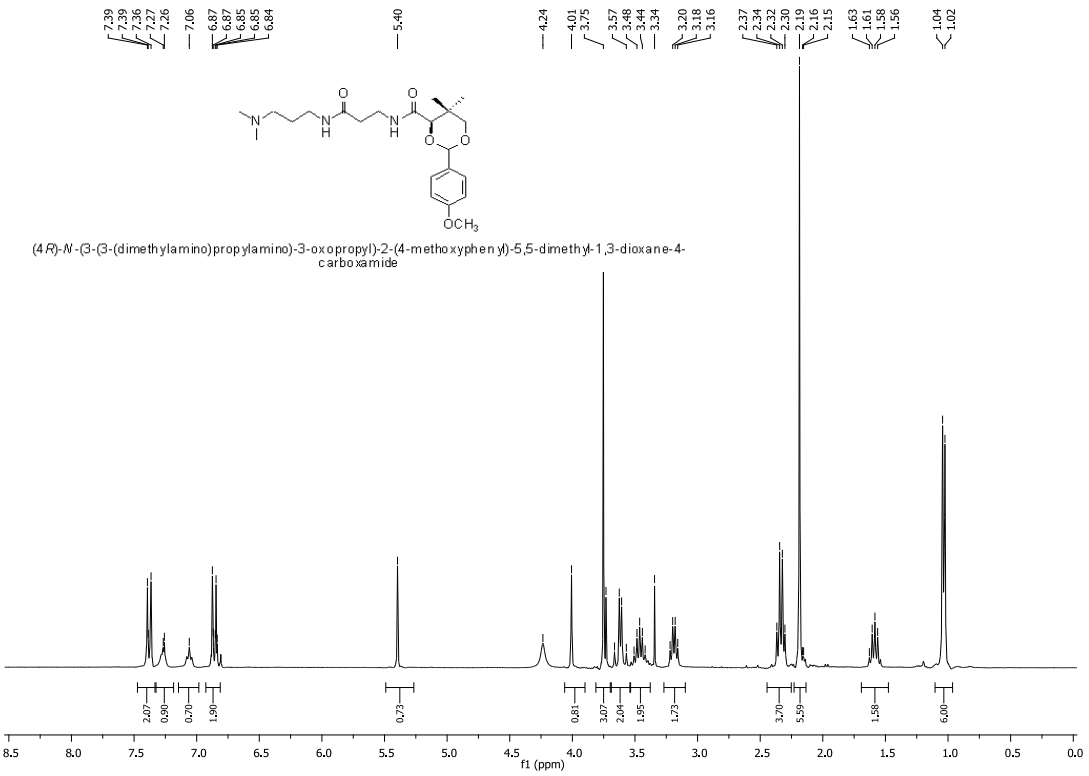


^{13}C-NMR spectrum in $CDCl_3$ of compound **55d**

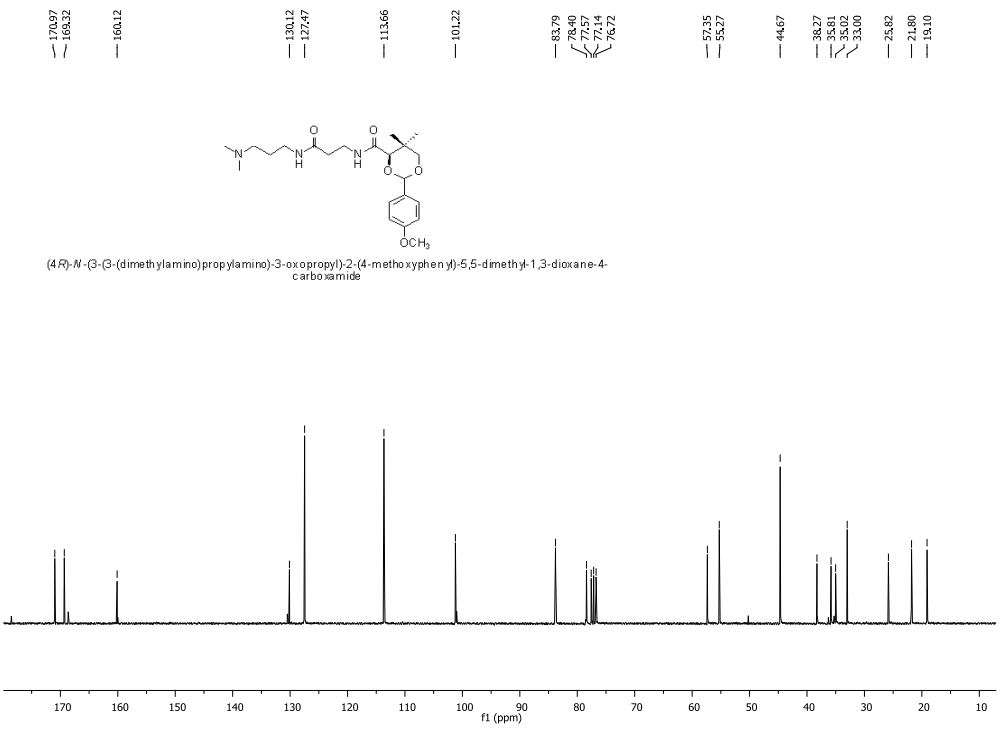
4



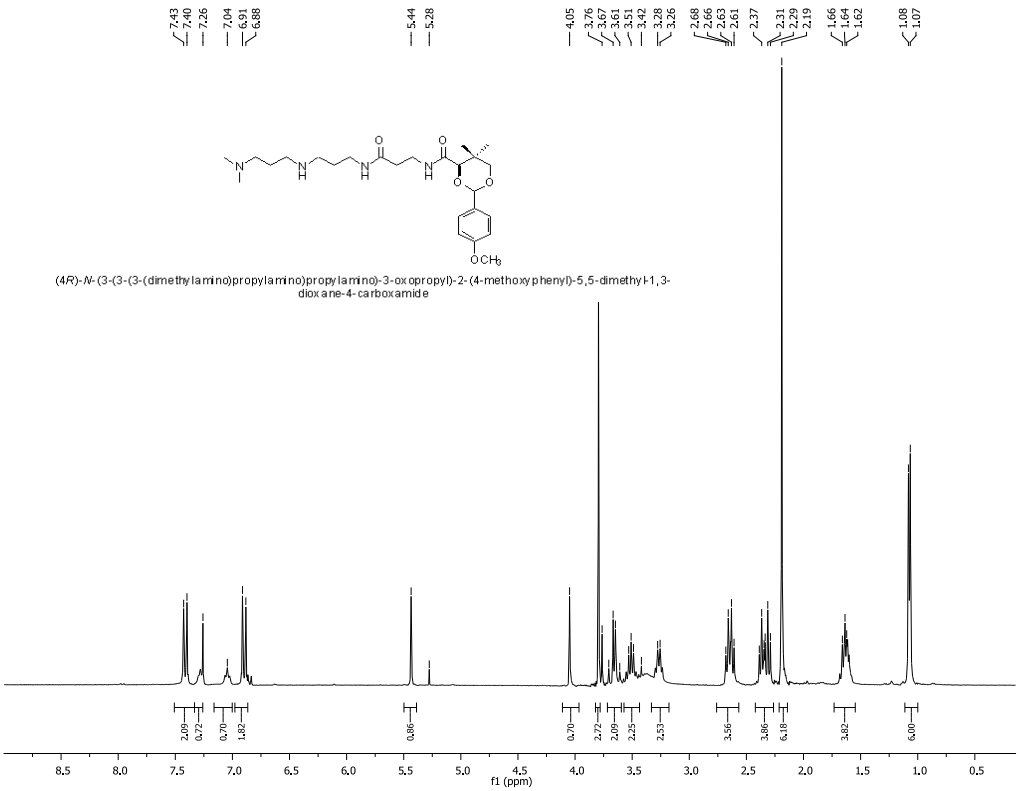
^{1}H-NMR spectrum in $CDCl_3$ of compound **55i**



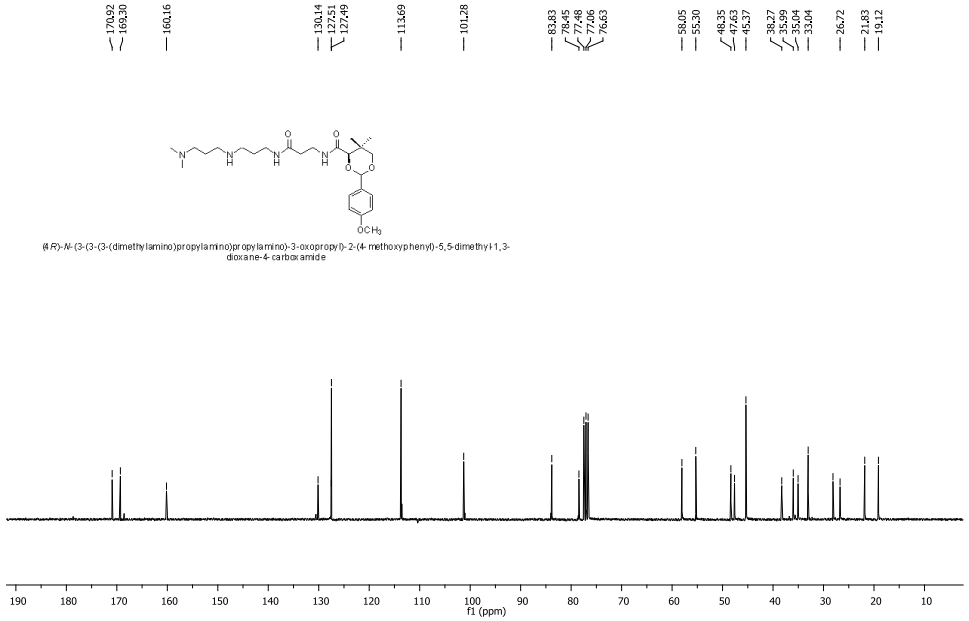
^{13}C-NMR spectrum in $CDCl_3$ of compound **55i**



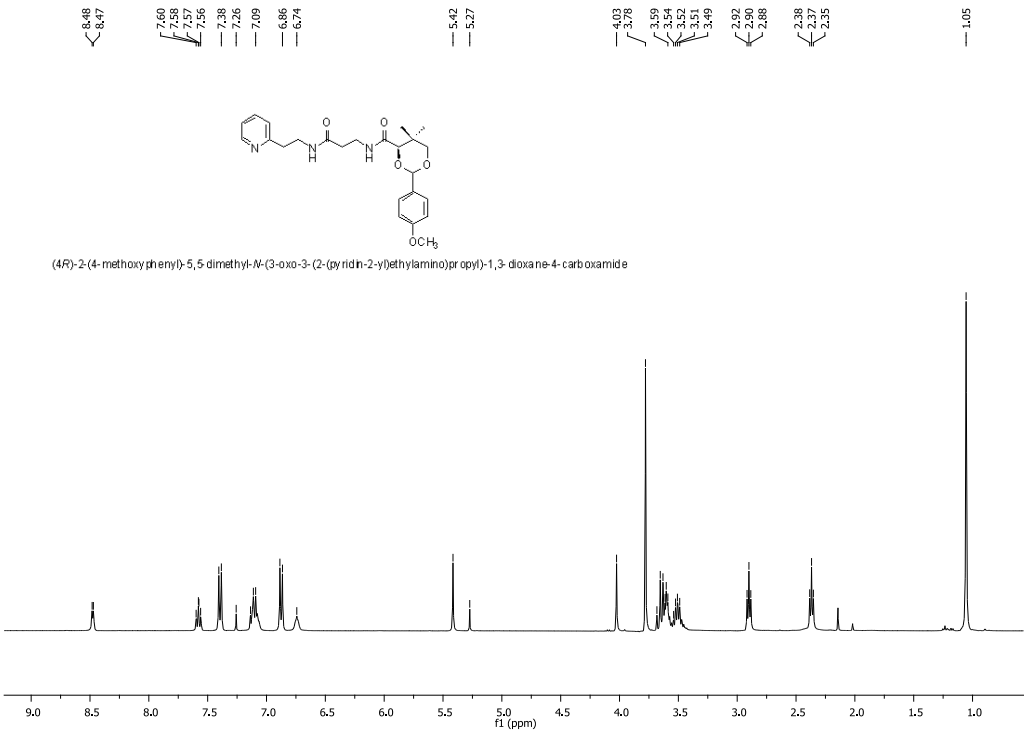
^{13}C-NMR spectrum in $CDCl_3$ of compound **55j**



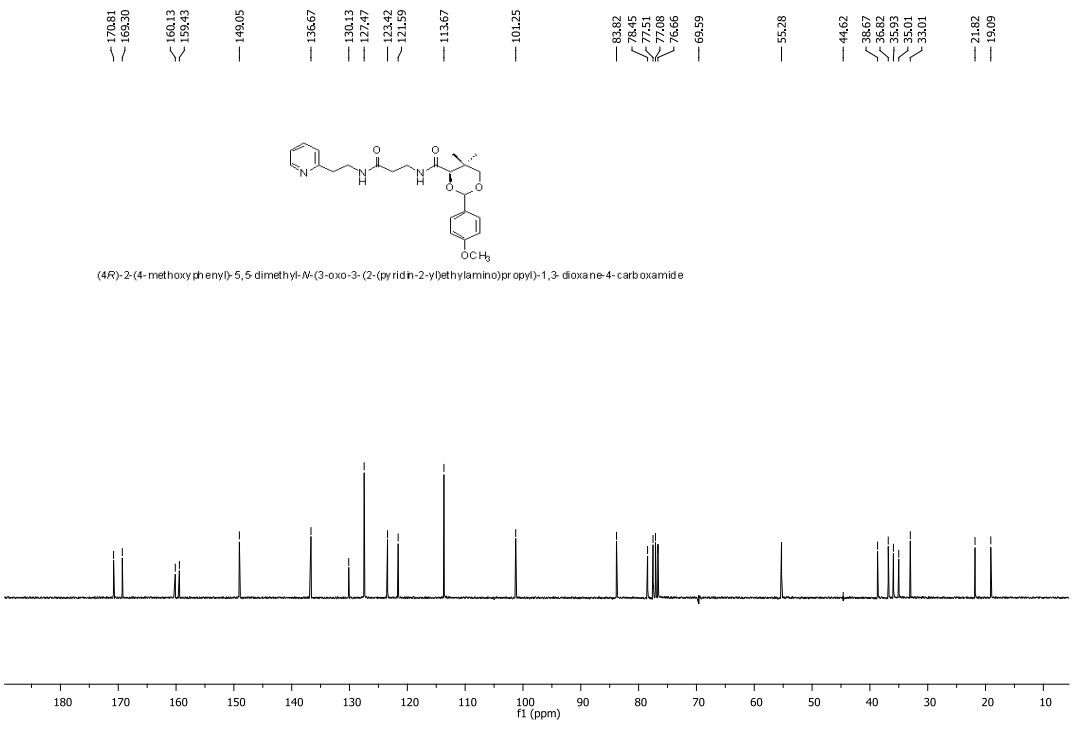
^{1}H-NMR spectrum in $CDCl_3$ of compound **55j**



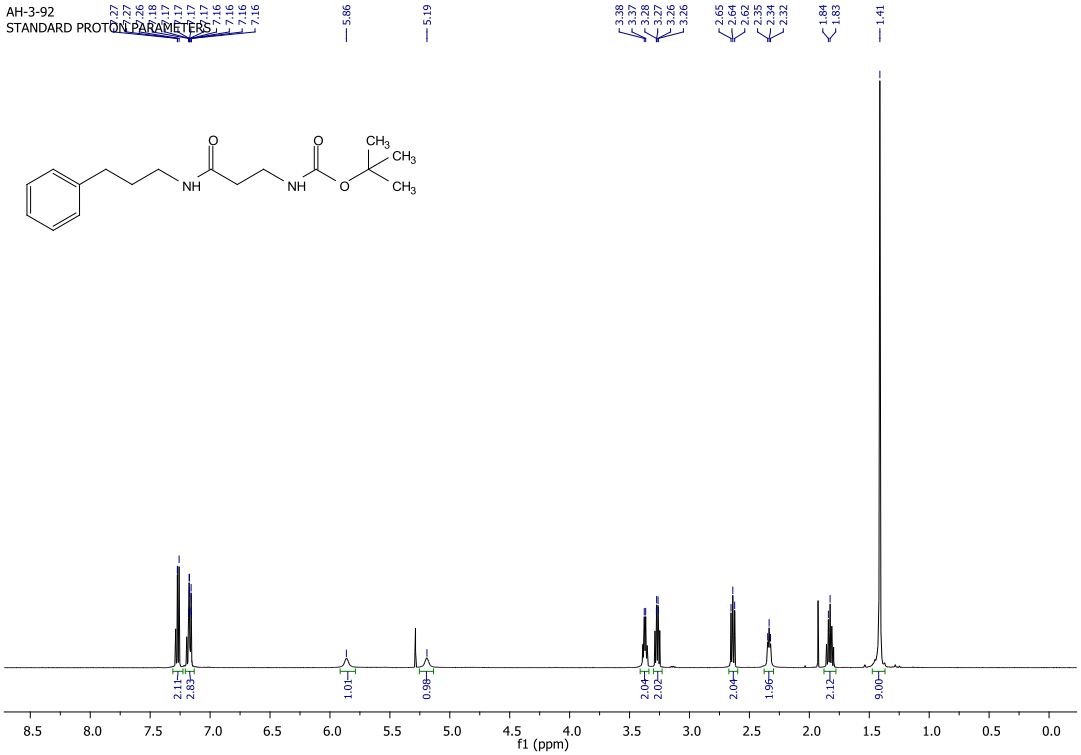
^{1}H-NMR spectrum in $CDCl_3$ of compound **55l**



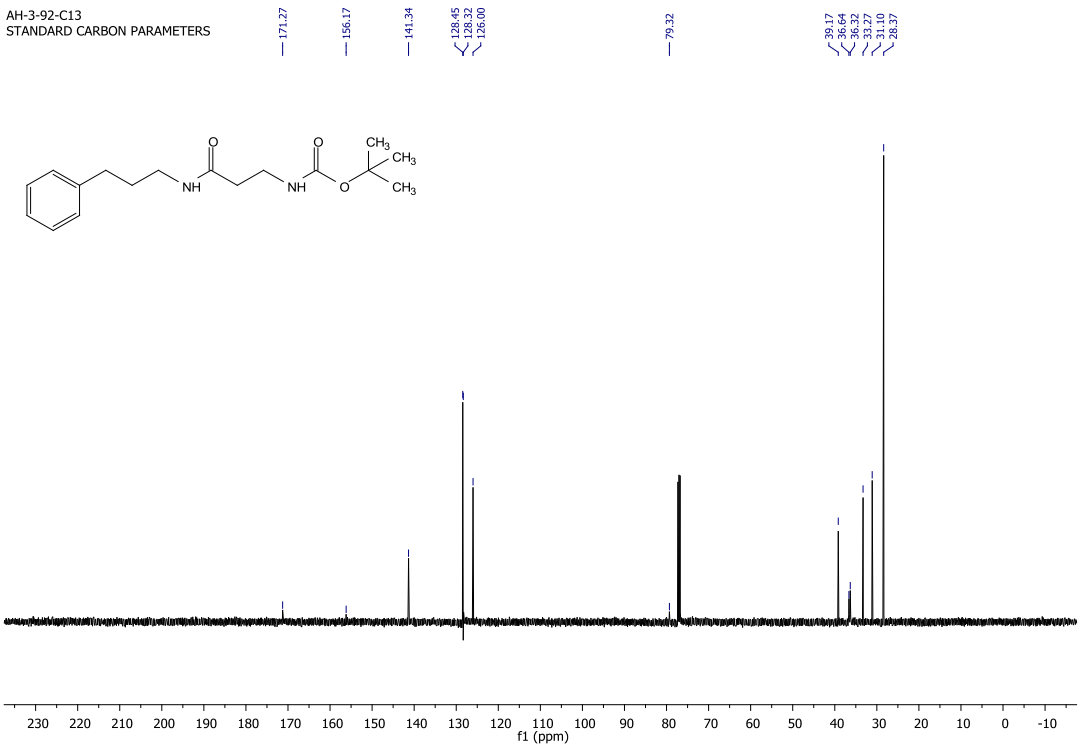
^{13}C-NMR spectrum in $CDCl_3$ of compound **55l**



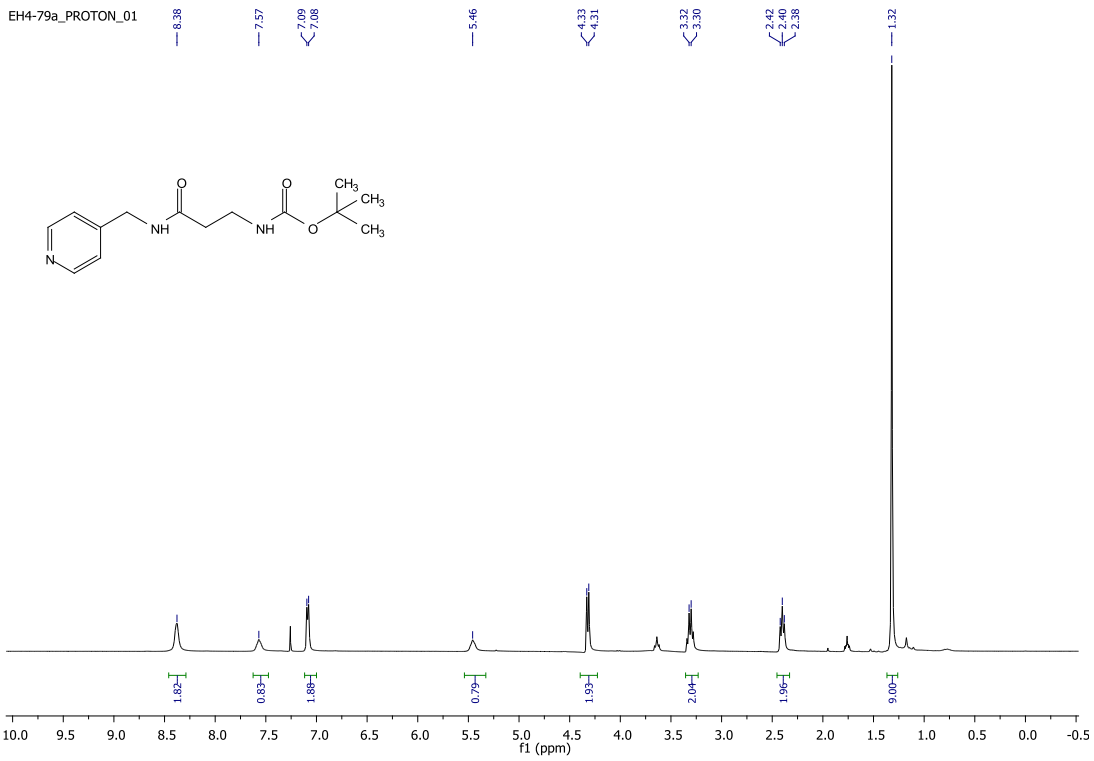
^{1}H-NMR spectrum in $CDCl_3$ of compound **57a**



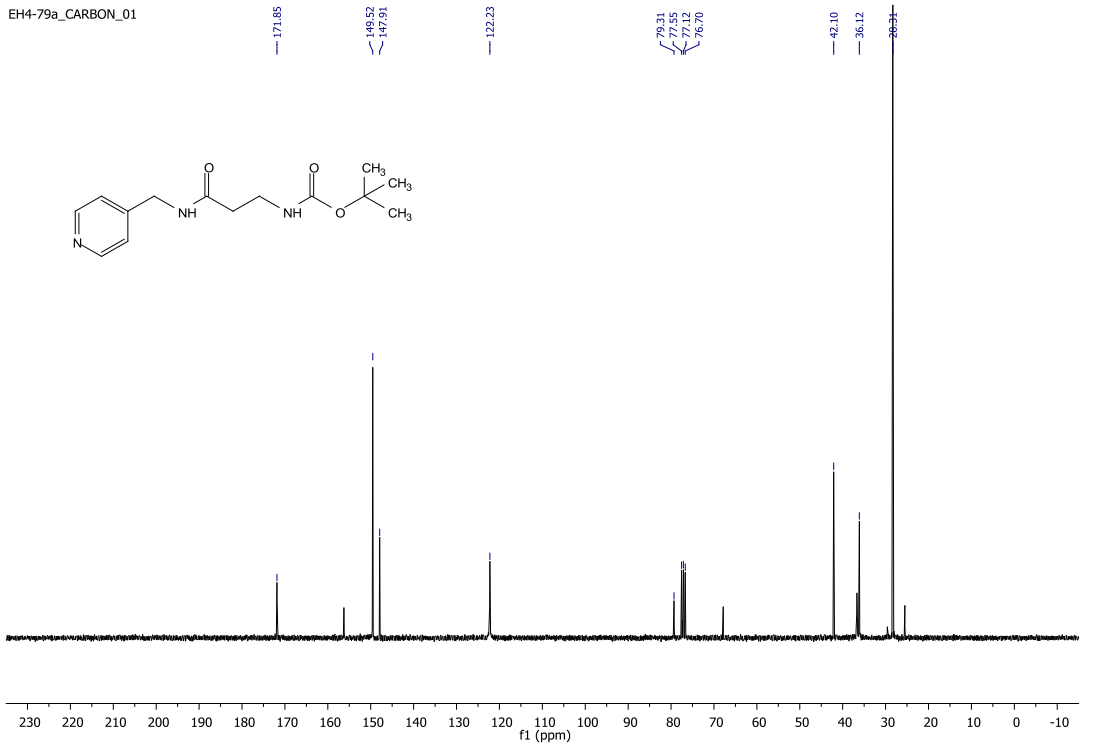
^{13}C-NMR spectrum in $CDCl_3$ of compound **57a**



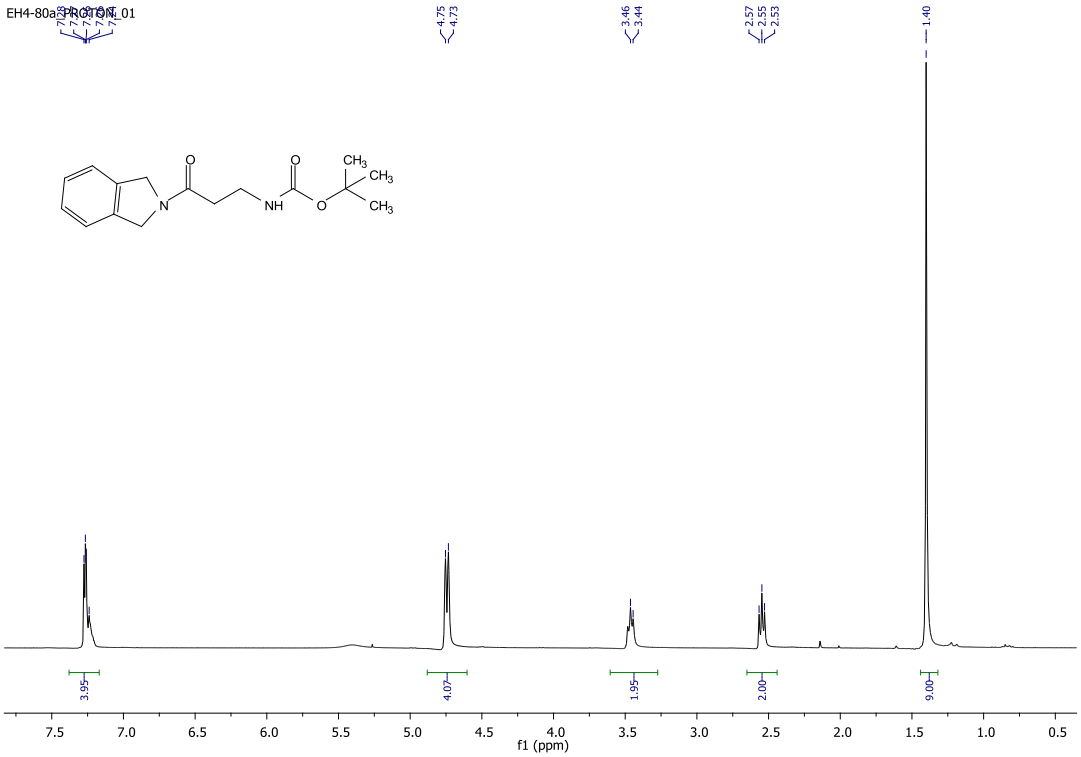
^{1}H-NMR spectrum in $CDCl_3$ of compound **57b**



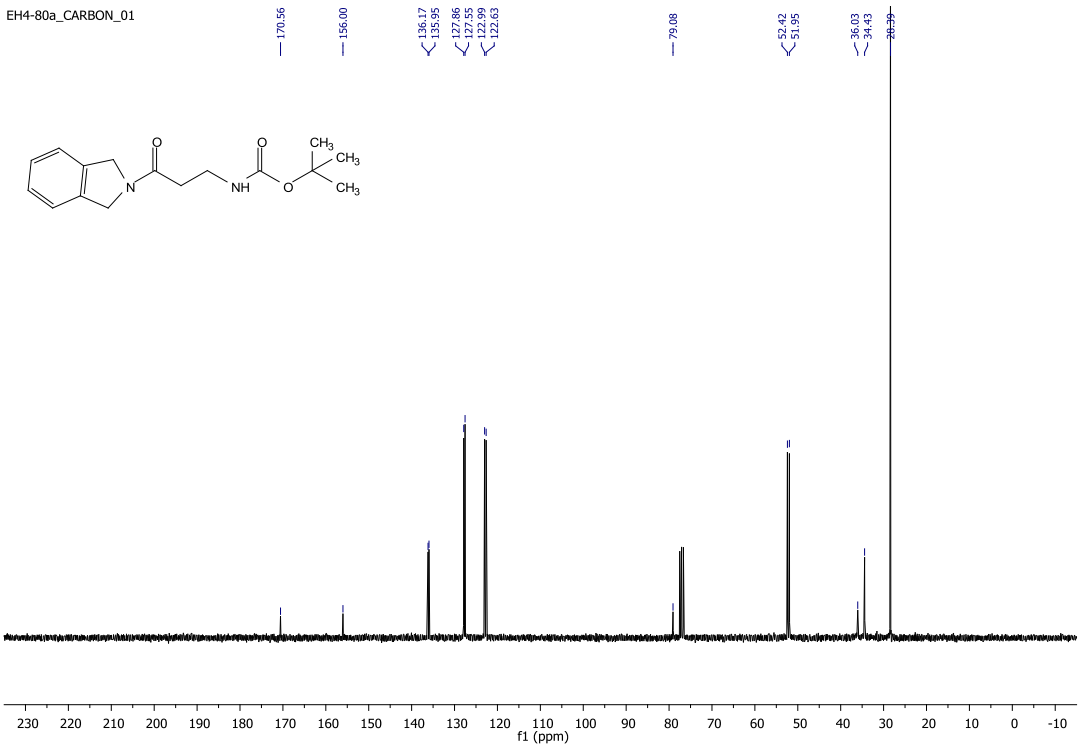
^{13}C-NMR spectrum in $CDCl_3$ of compound **57b**



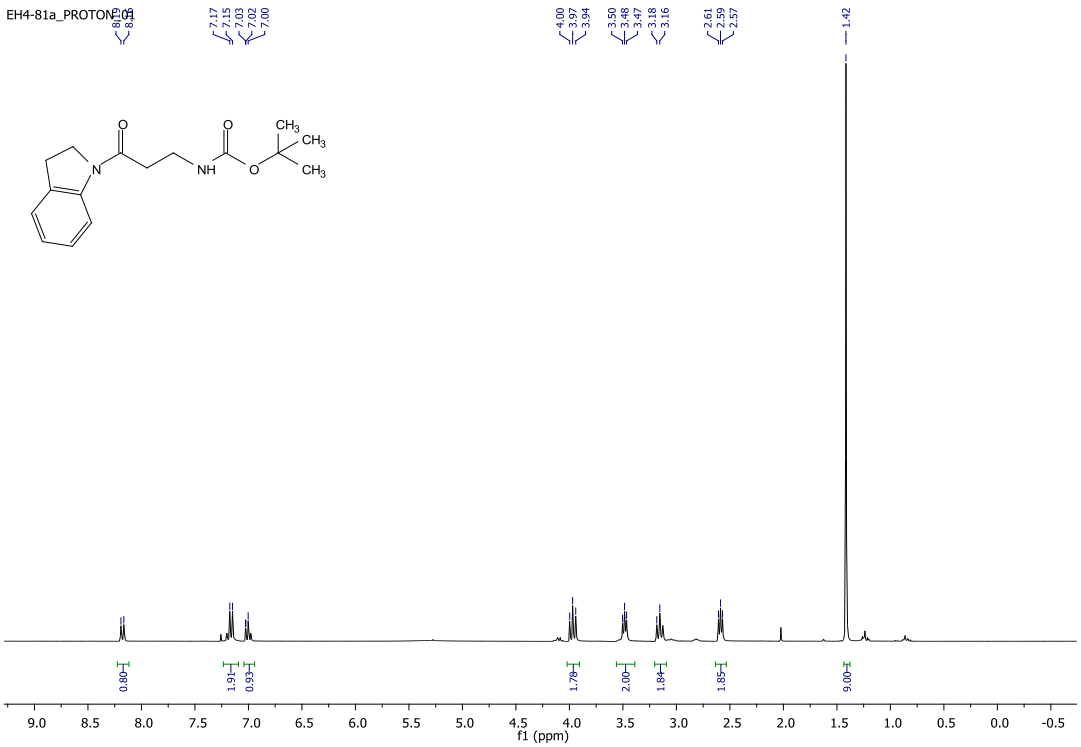
^{1}H-NMR spectrum in $CDCl_3$ of compound **57c**



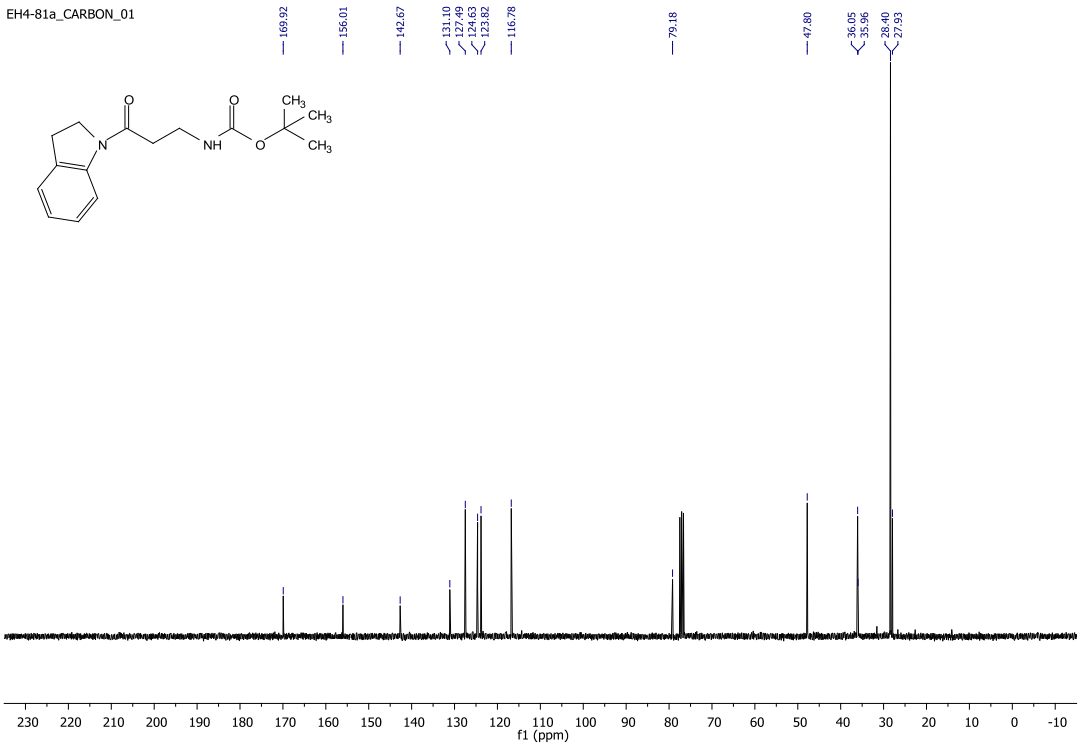
^{13}C-NMR spectrum in $CDCl_3$ of compound **57c**



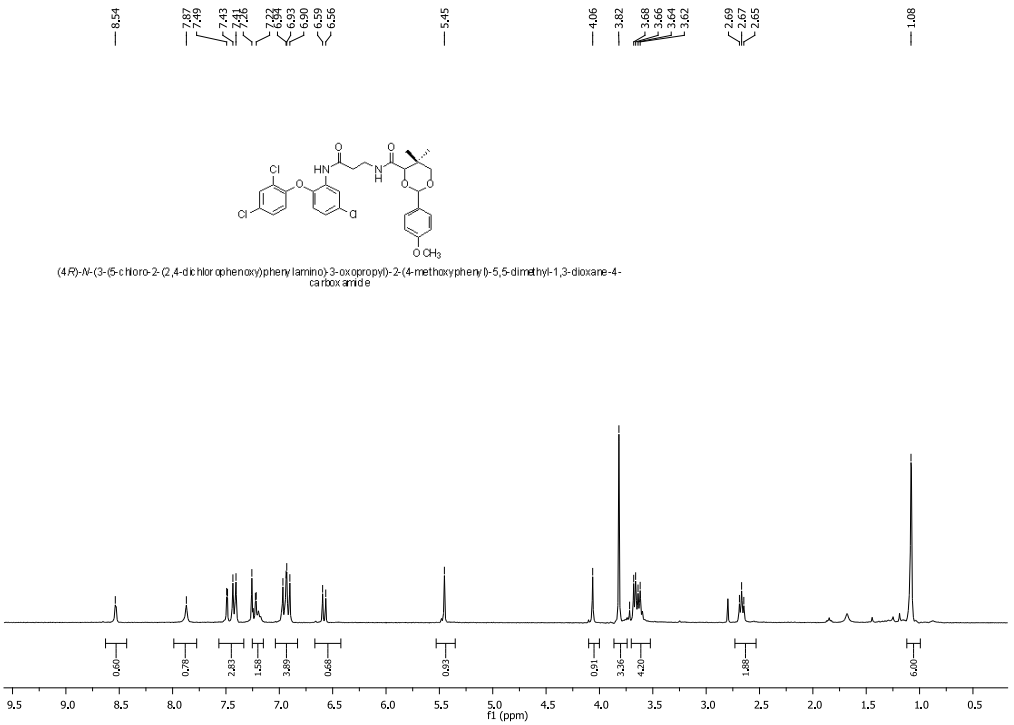
^{1}H-NMR spectrum in $CDCl_3$ of compound **57d**



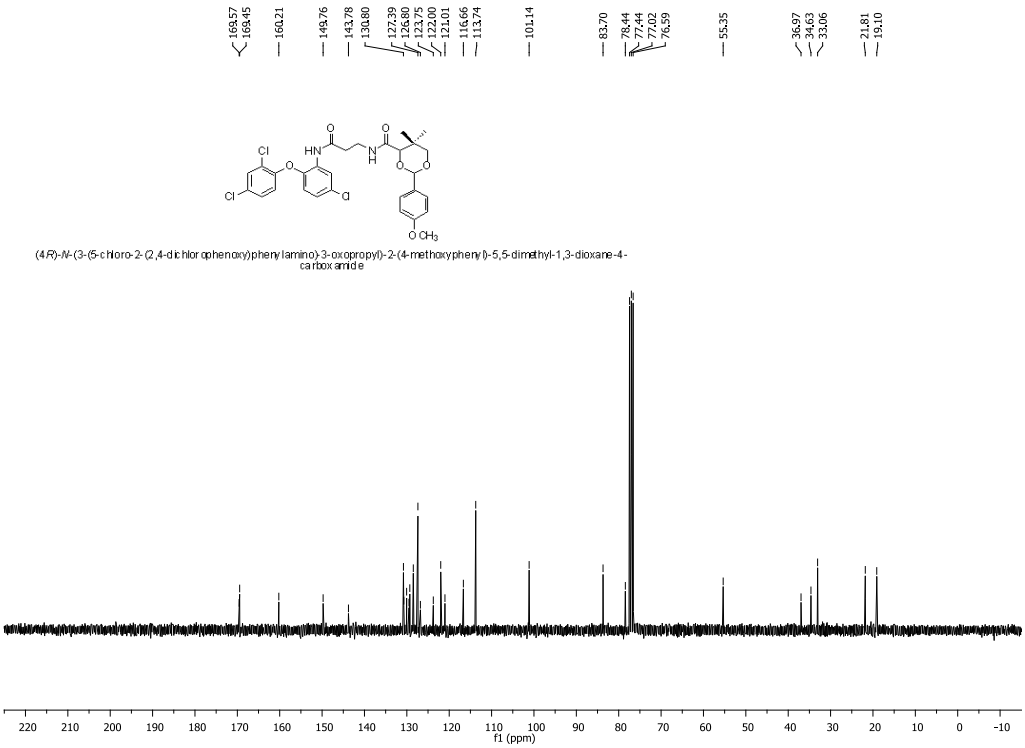
^{13}C-NMR spectrum in $CDCl_3$ of compound **57d**



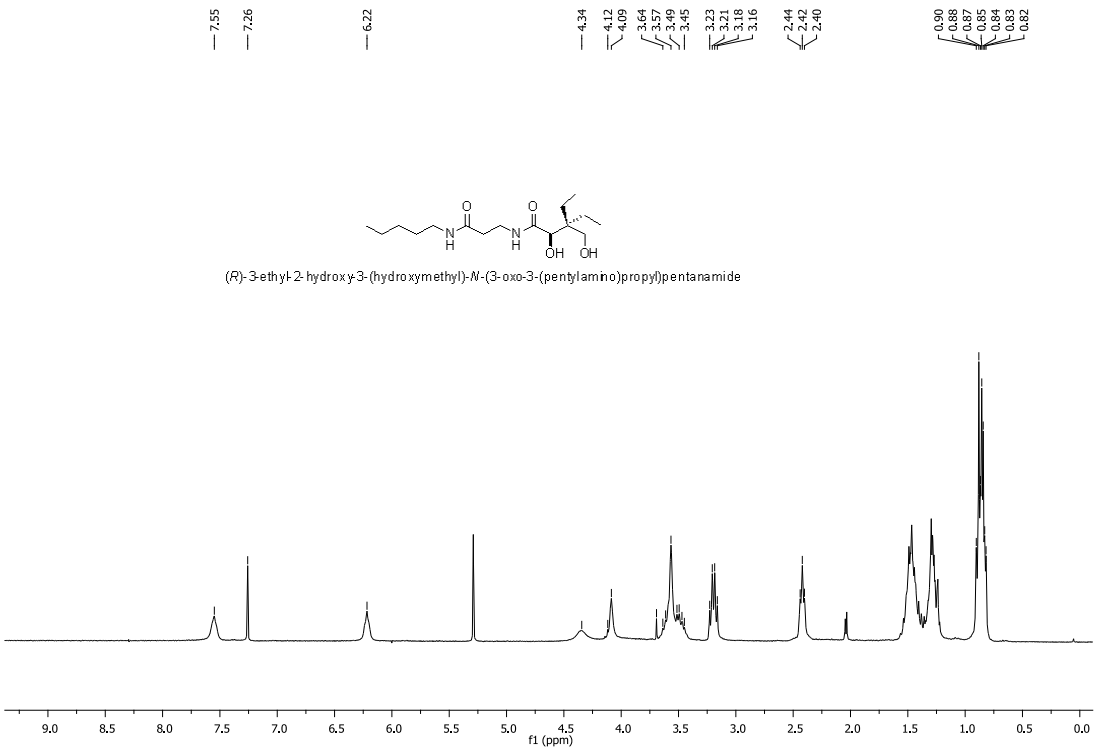
^{1}H-NMR spectrum in $CDCl_3$ of compound **59**



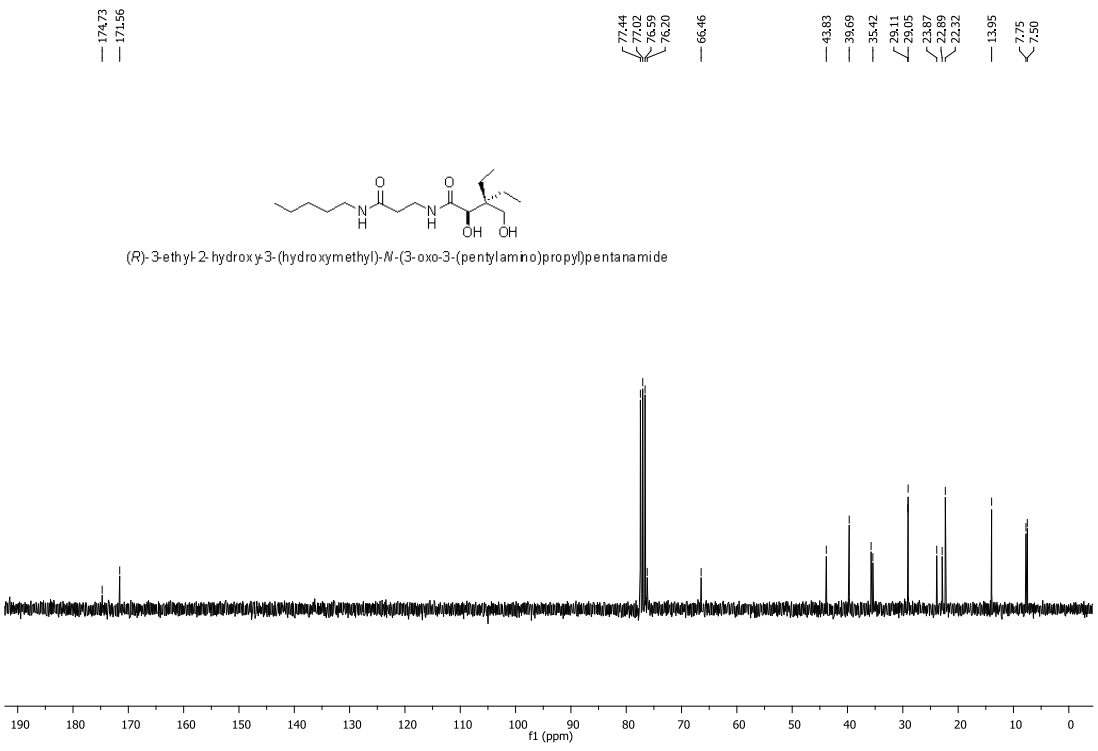
^{13}C-NMR spectrum in $CDCl_3$ of compound **59**



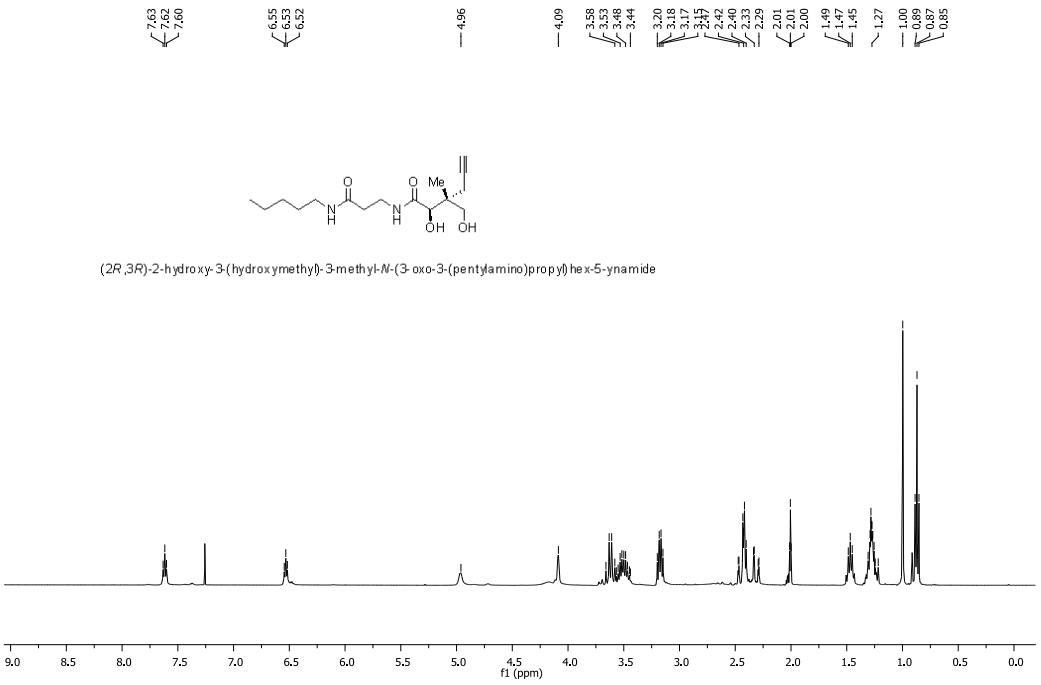
^{1}H NMR spectrum in $CDCl_3$ of compound **63**



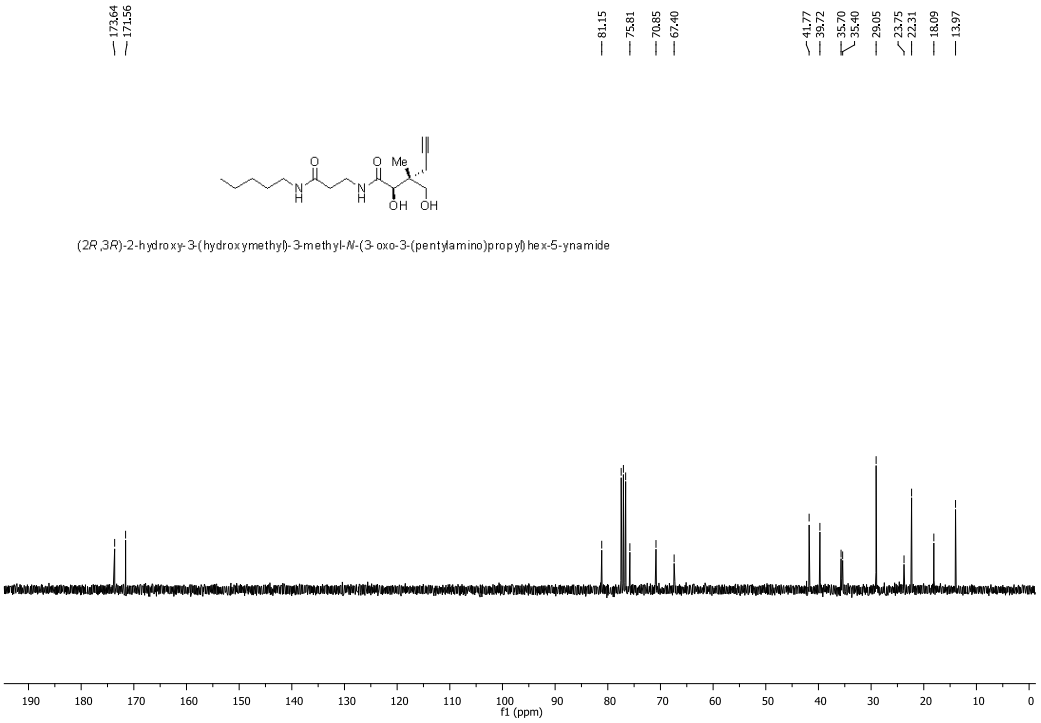
^{13}C-NMR spectrum in $CDCl_3$ of compound **63**



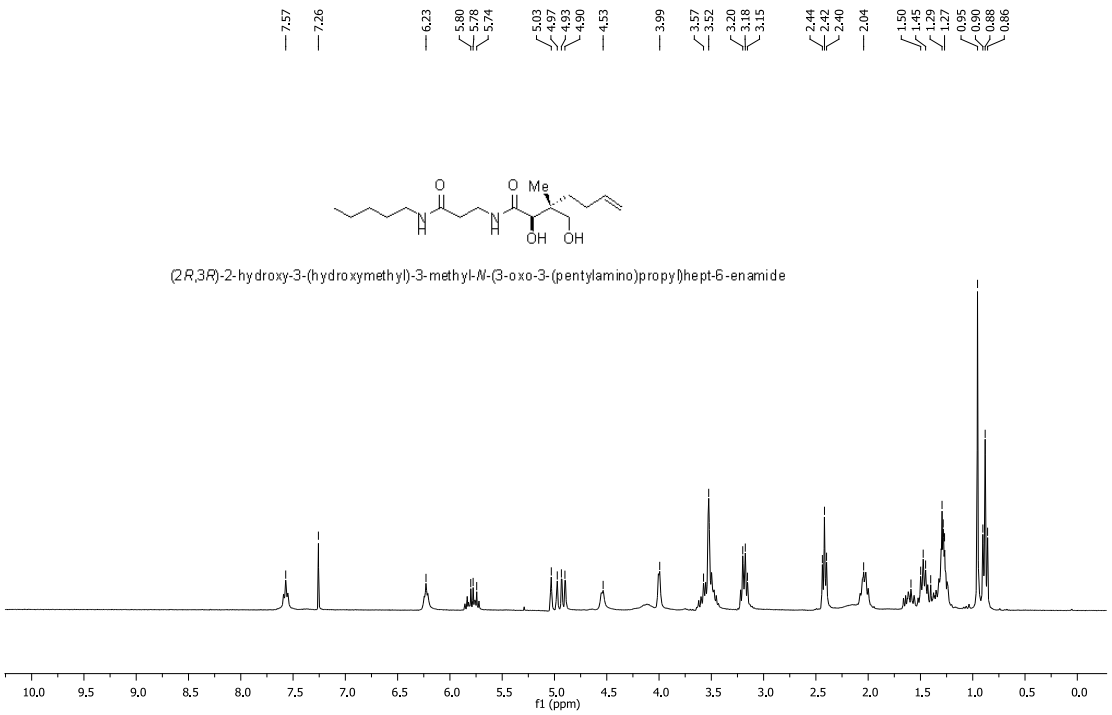
^{1}H-NMR spectrum in $CDCl_3$ of compound **65**



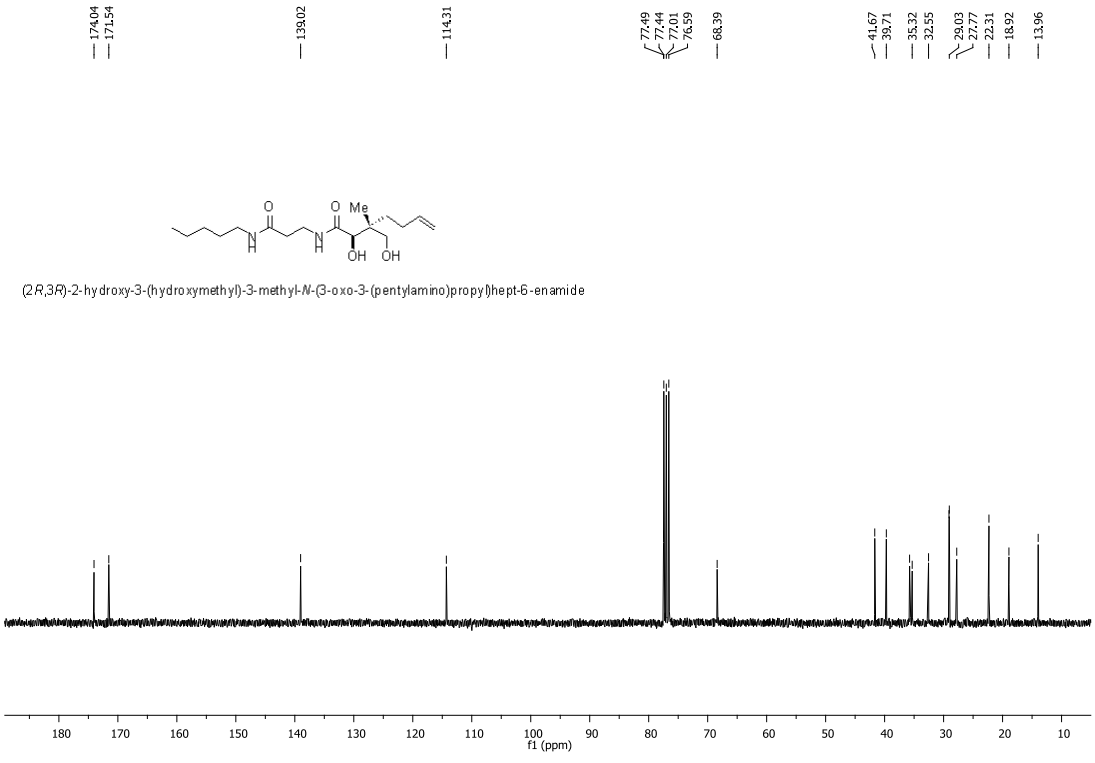
^{13}C-NMR spectrum in $CDCl_3$ of compound **65**



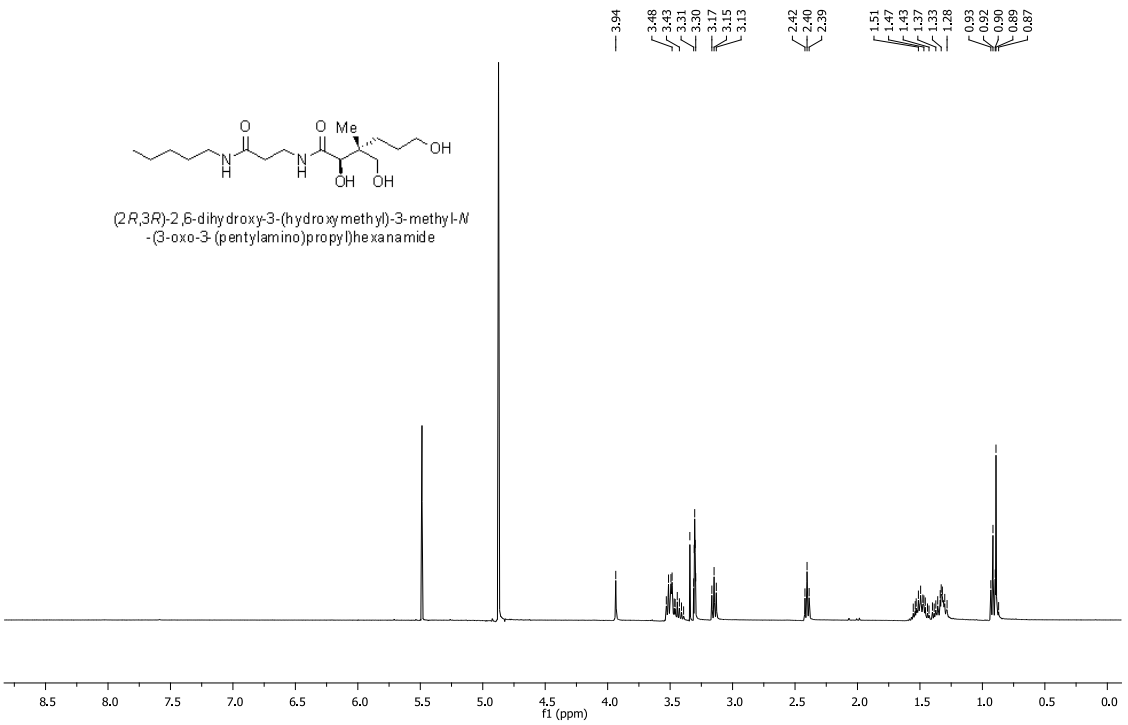
^{1}H-NMR spectrum in $CDCl_3$ of compound **66**



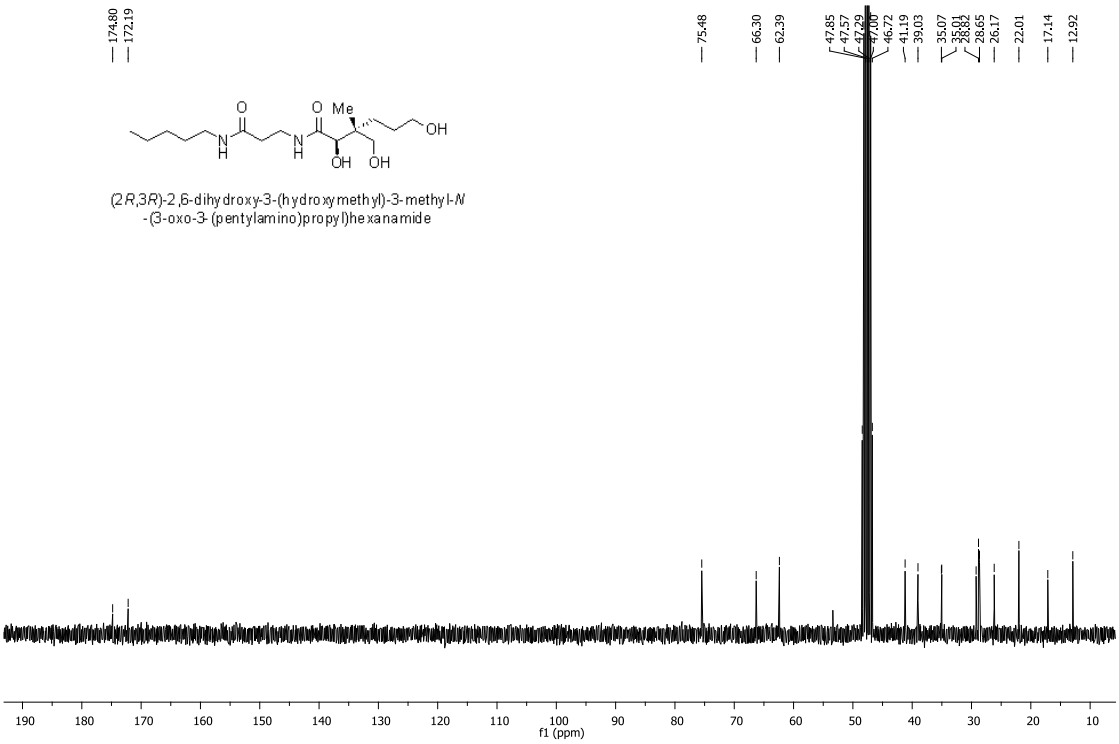
^{13}C-NMR spectrum in $CDCl_3$ of compound **66**



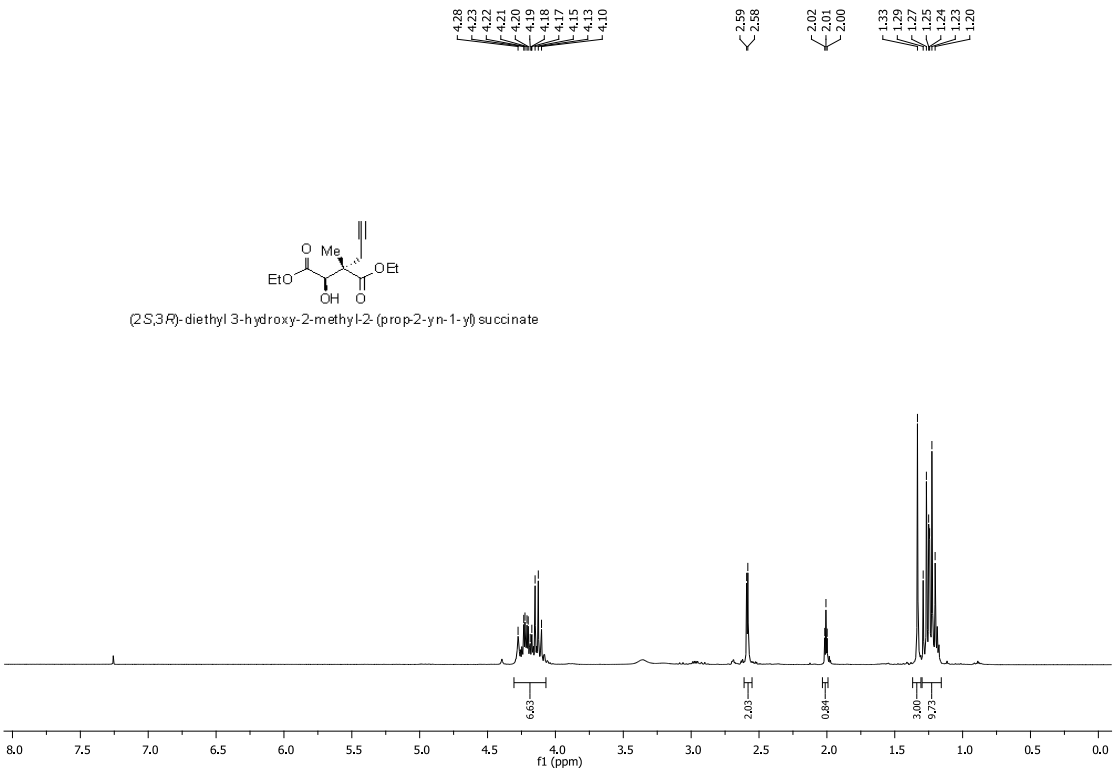
^{1}H-NMR spectrum in $CDCl_3$ of compound **67**



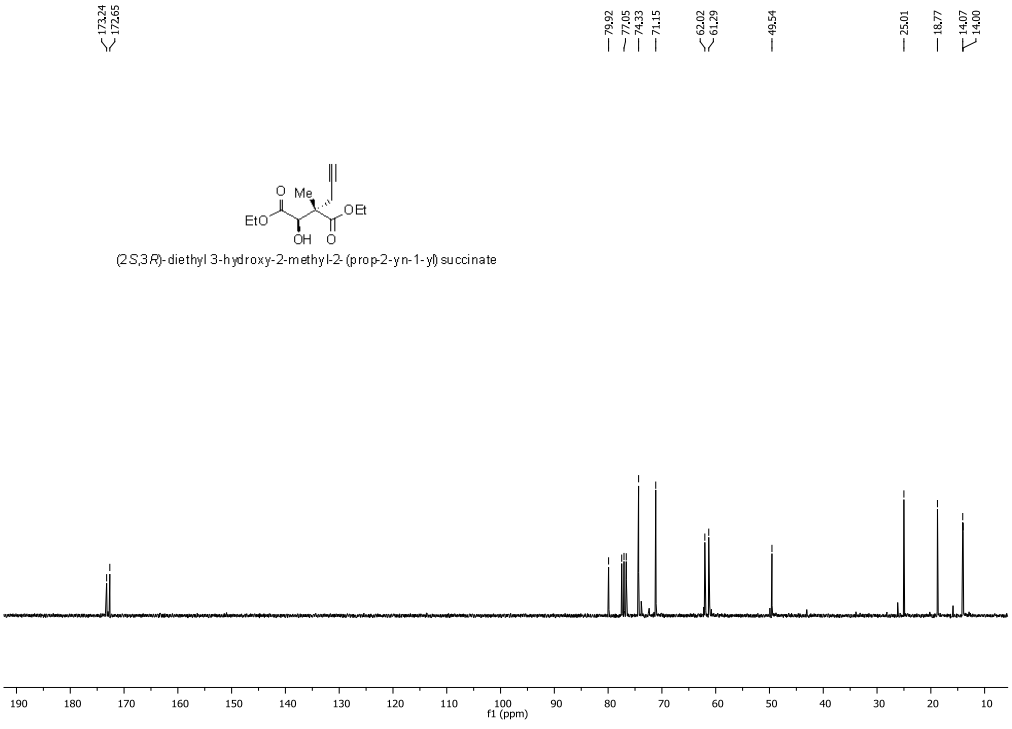
^{13}V-NMR spectrum in $CDCl_3$ of compound **67**



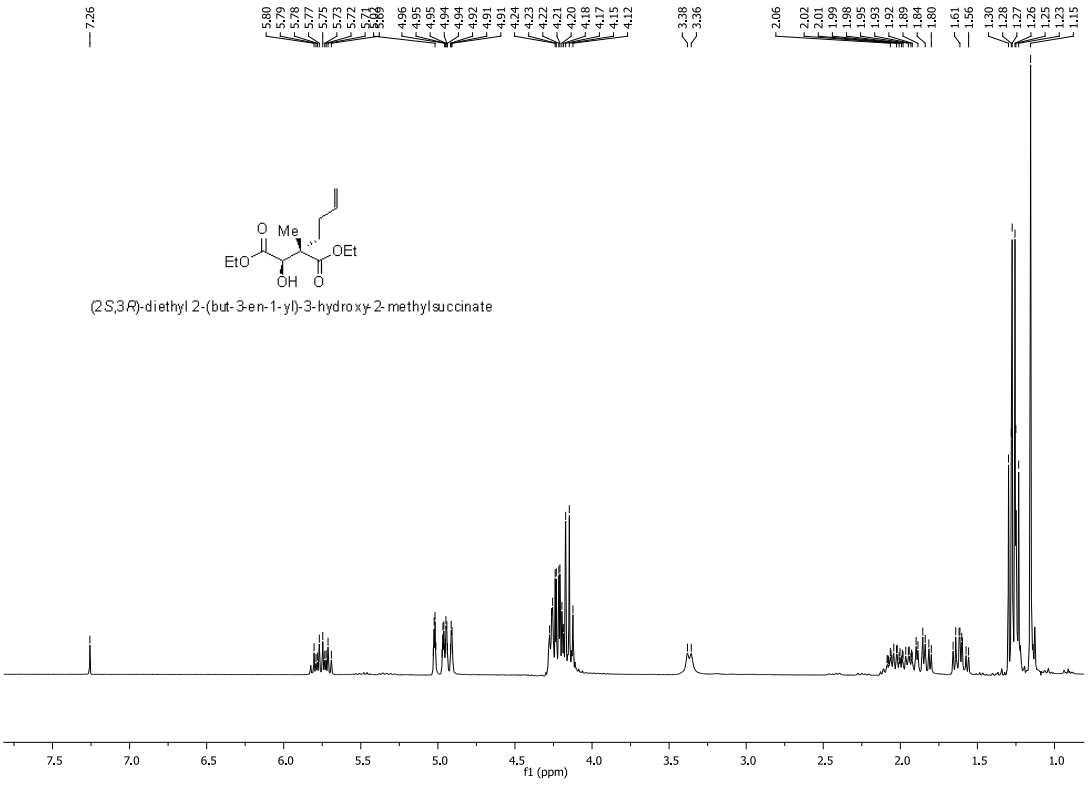
^{1}H-NMR spectrum in $CDCl_3$ of compound **70d**



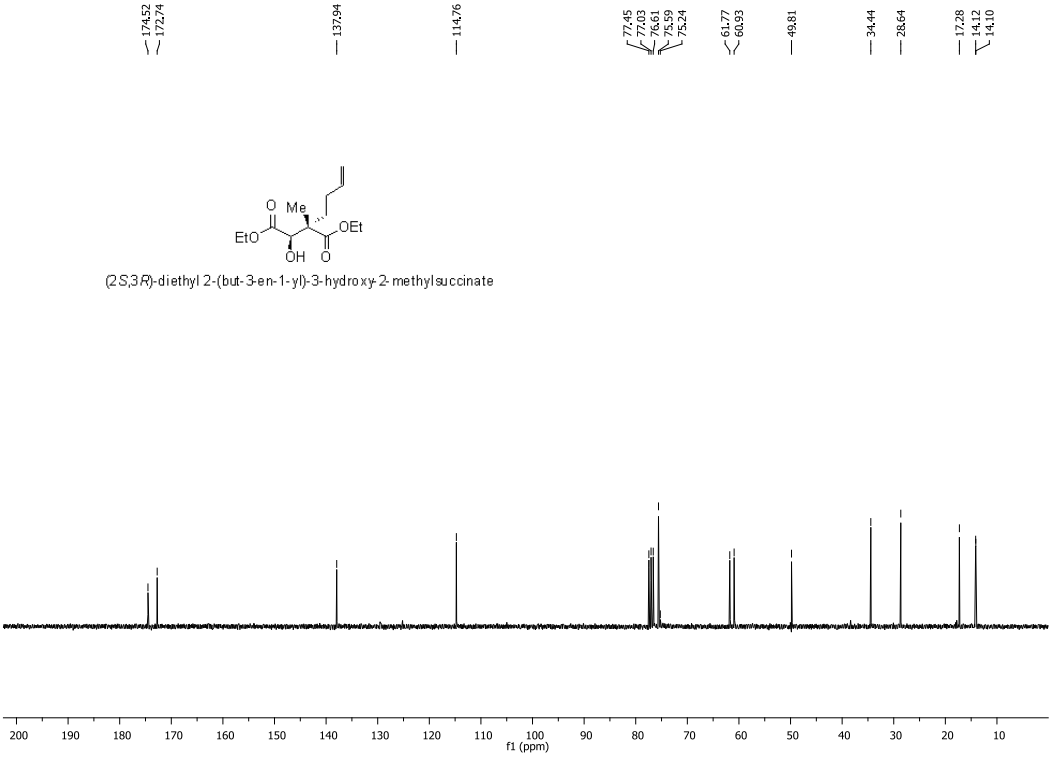
^{13}C-NMR spectrum in $CDCl_3$ of compound **70d**



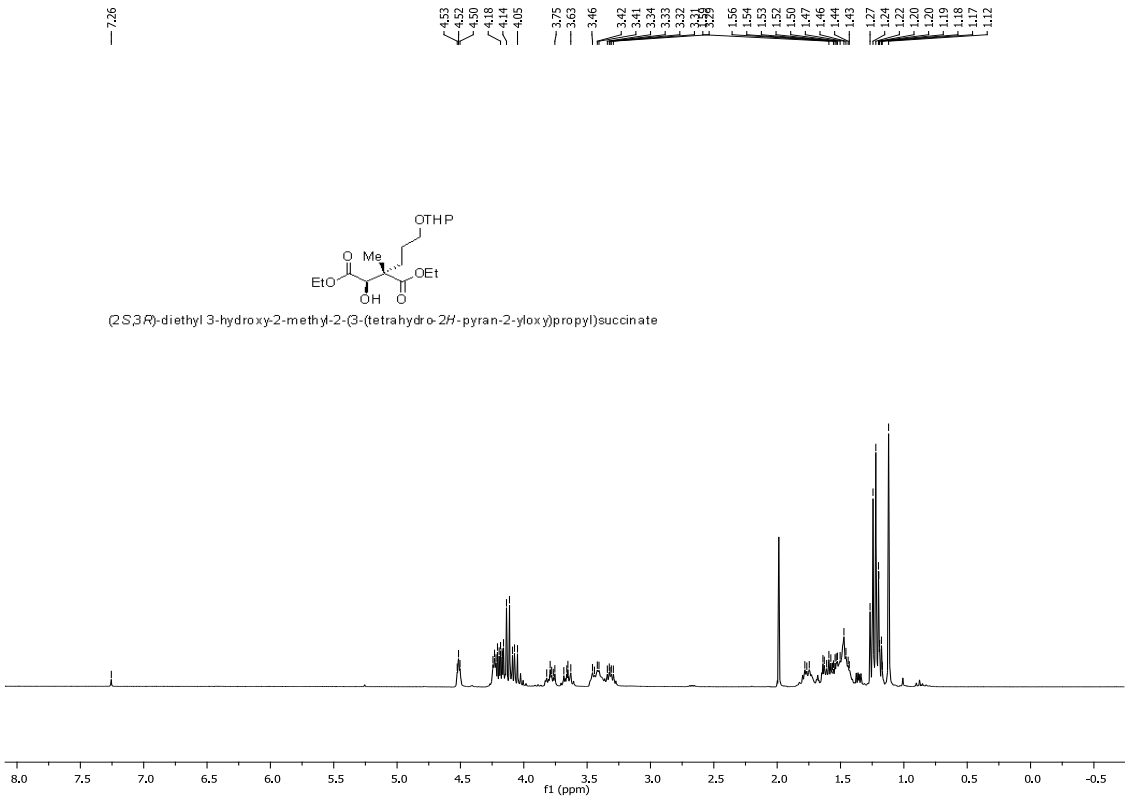
^{1}H-NMR spectrum in $CDCl_3$ of compound **70e**



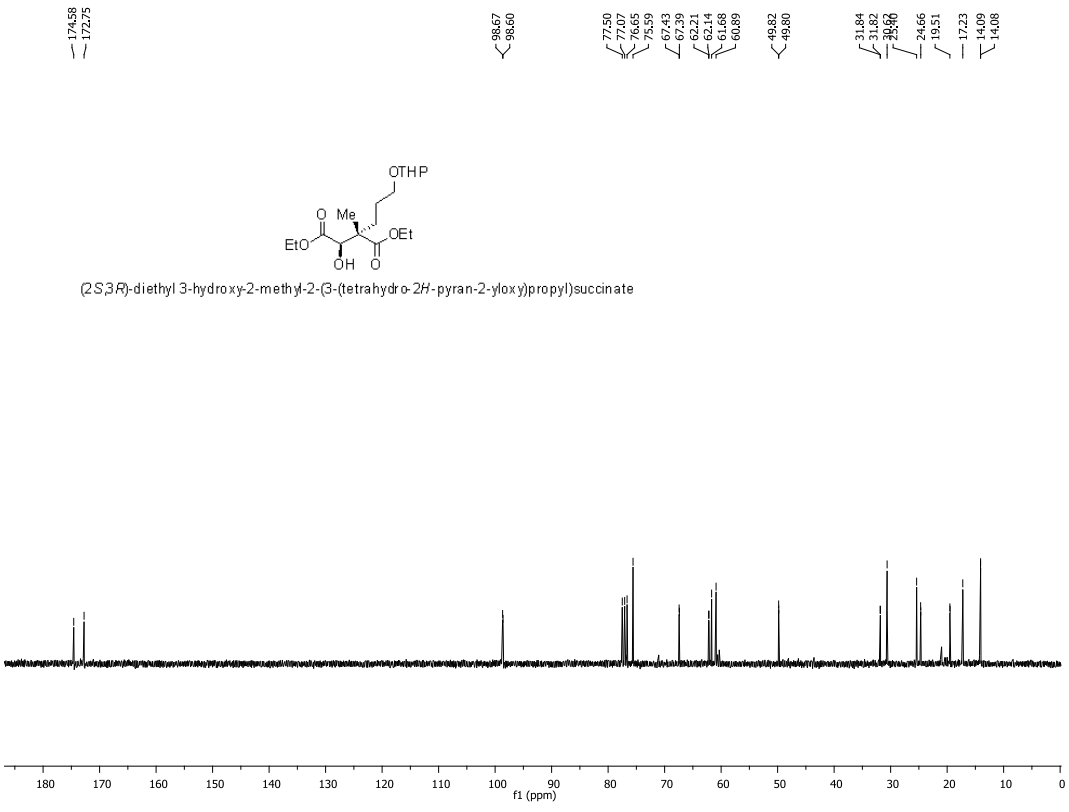
^{13}C-NMR spectrum in $CDCl_3$ of compound **70e**



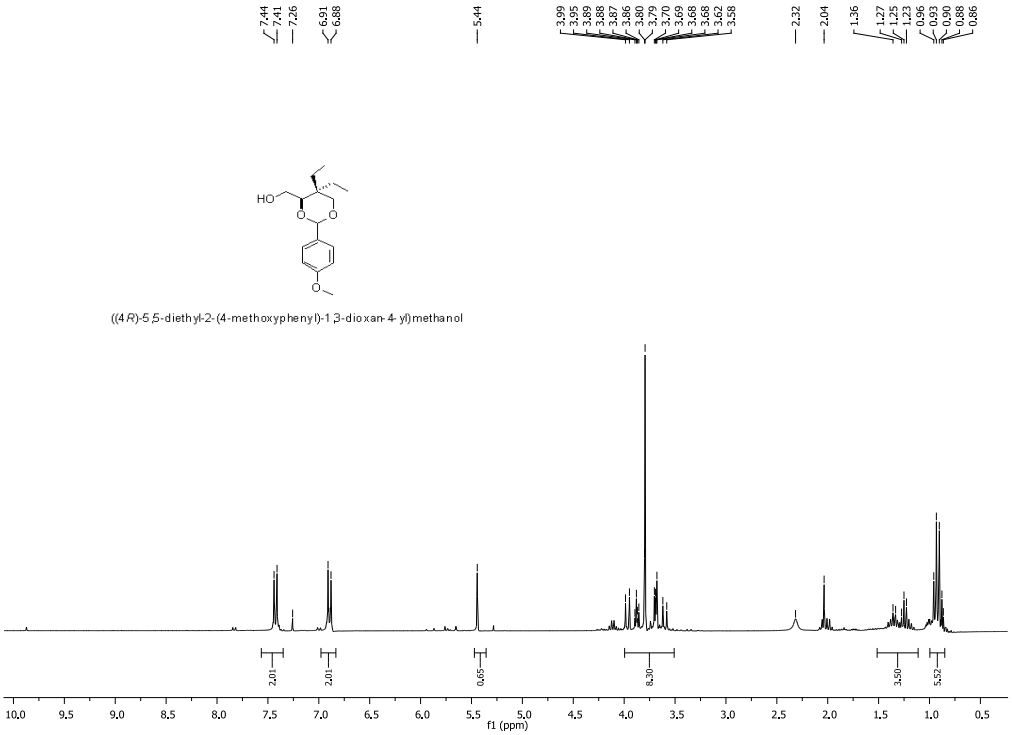
^{1}H-NMR spectrum in $CDCl_3$ of compound **70f**



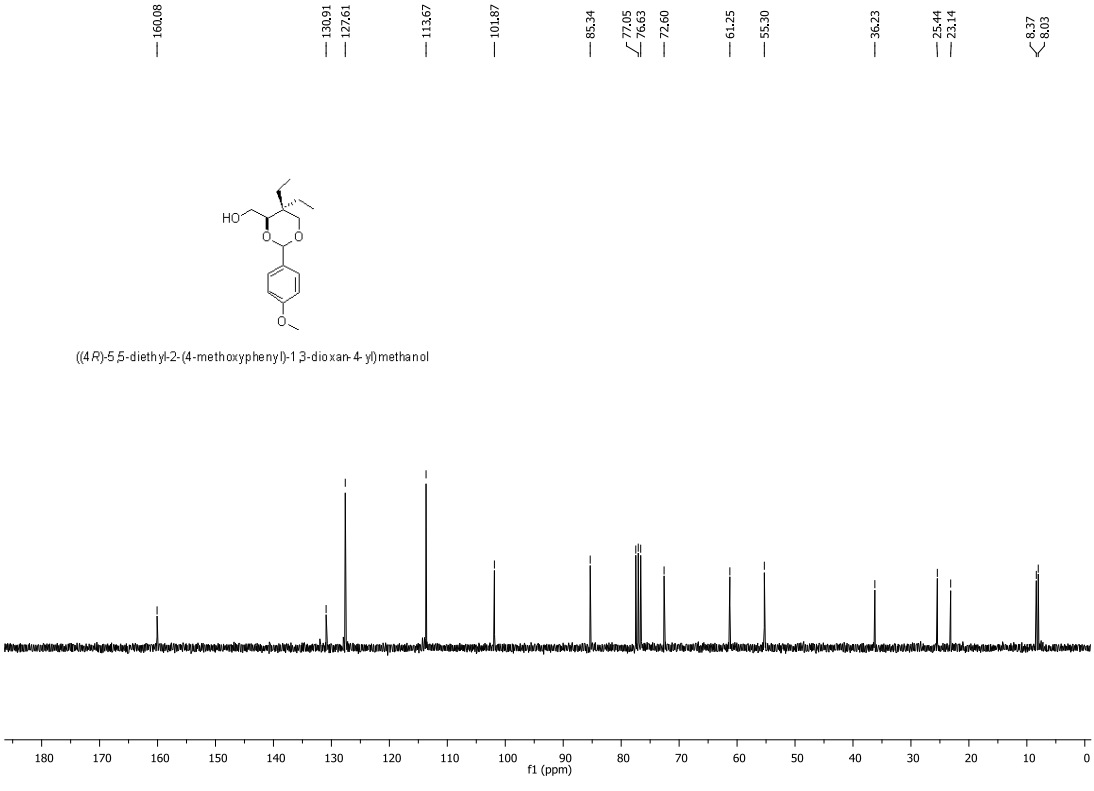
^{13}C-NMR spectrum in $CDCl_3$ of compound **70f**



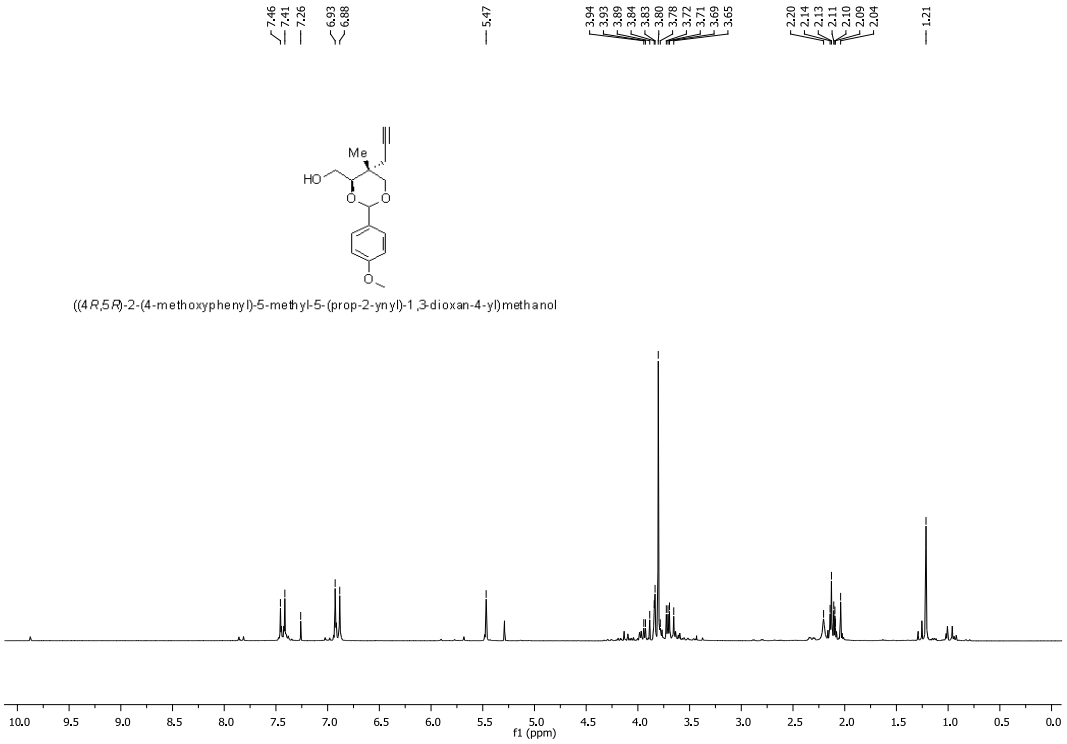
^{1}H-NMR spectrum in $CDCl_3$ of compound **71b**



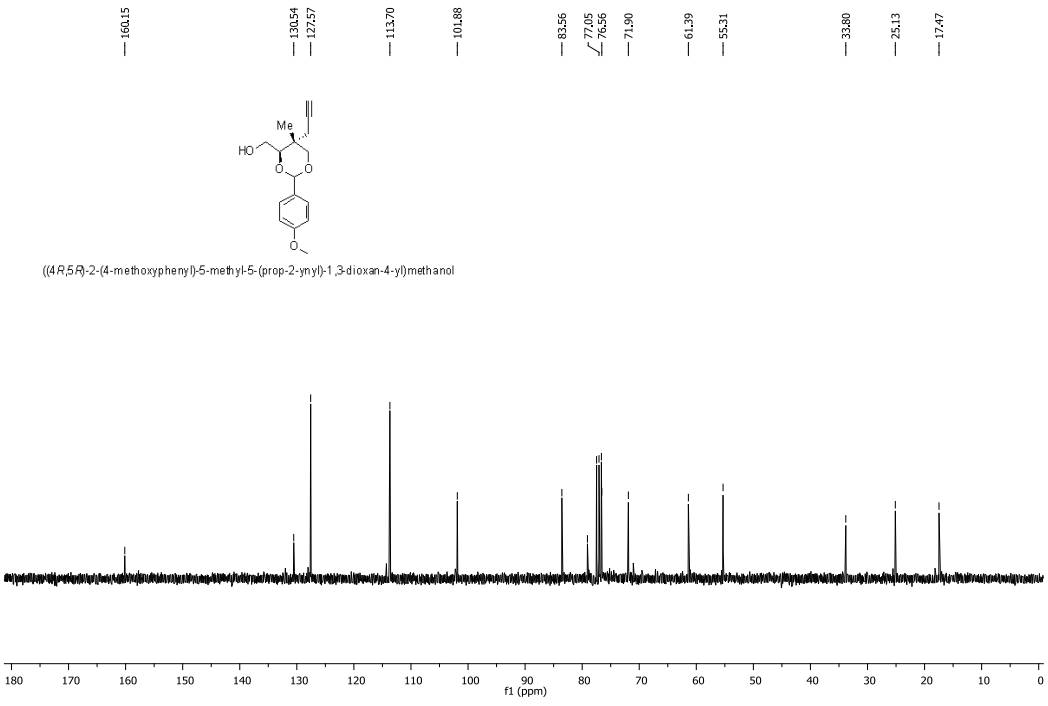
^{13}C-NMR spectrum in $CDCl_3$ of compound **71b**



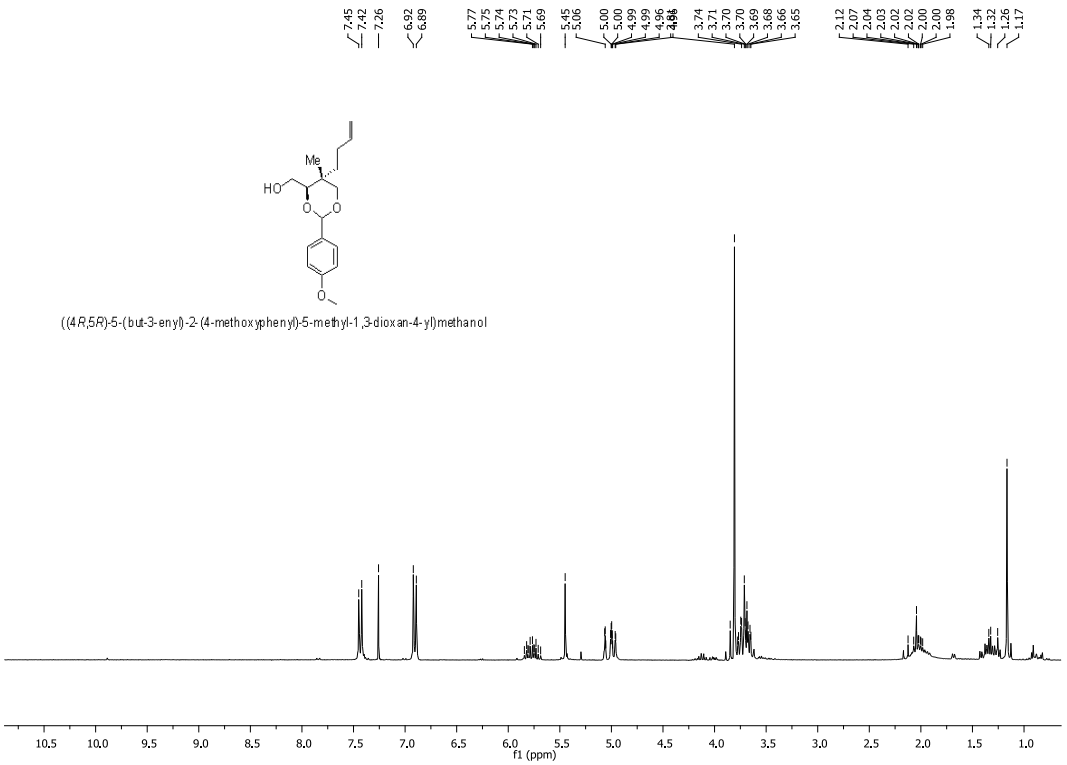
^{1}H-NMR spectrum in $CDCl_3$ of compound **71d**



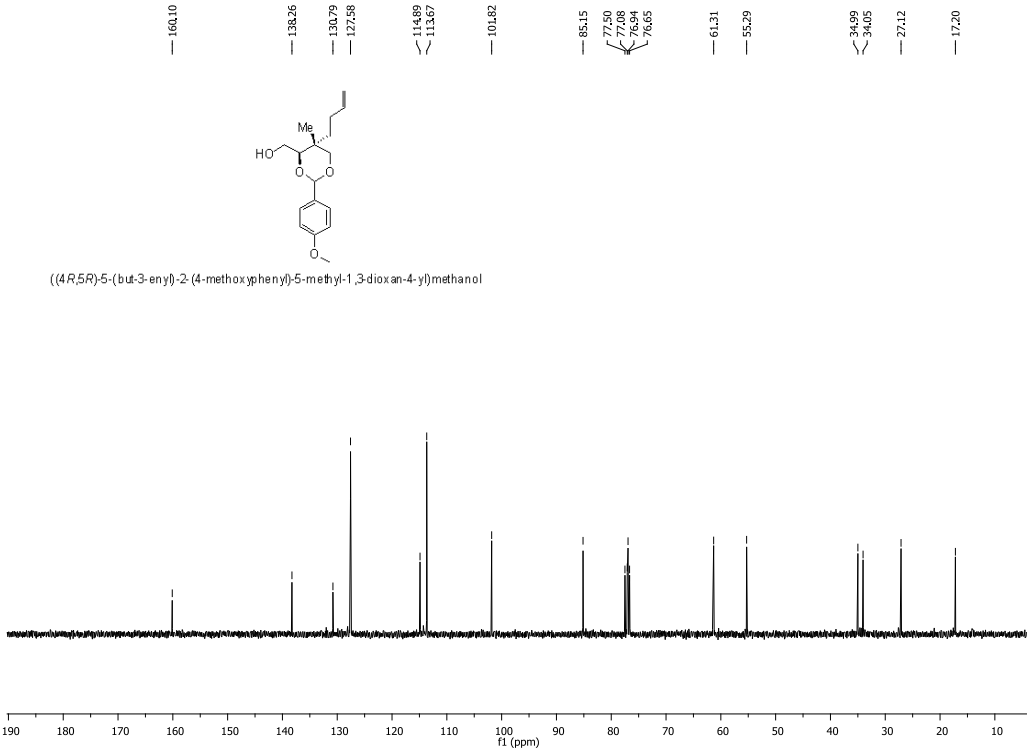
^{13}C-NMR spectrum in $CDCl_3$ of compound **71d**



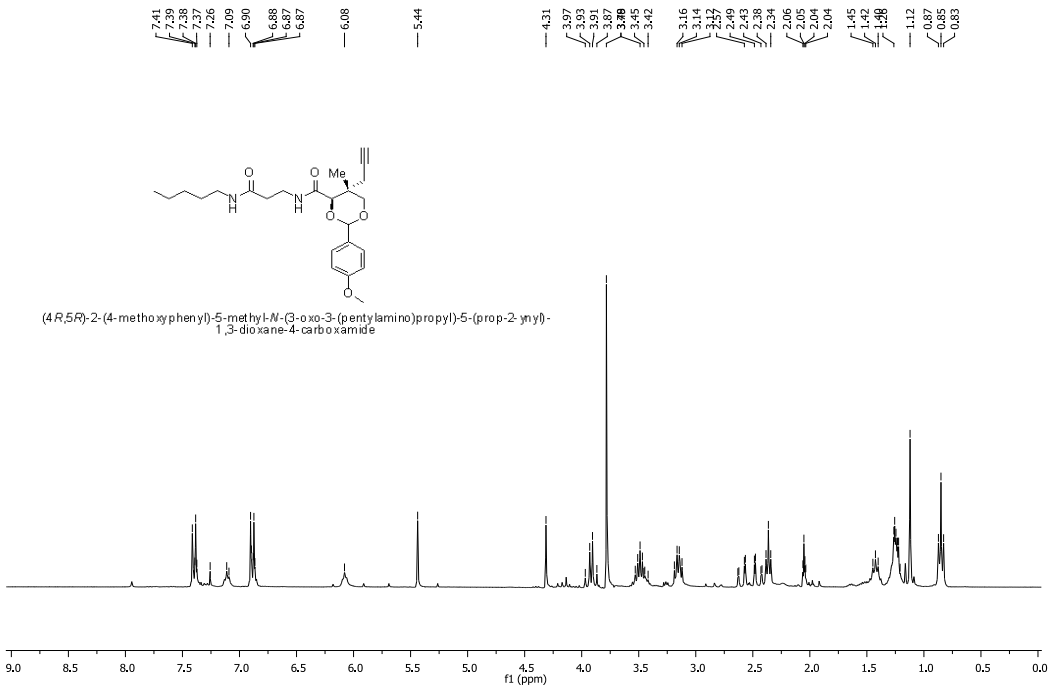
^{1}H-NMR spectrum in $CDCl_3$ of compound **71e**



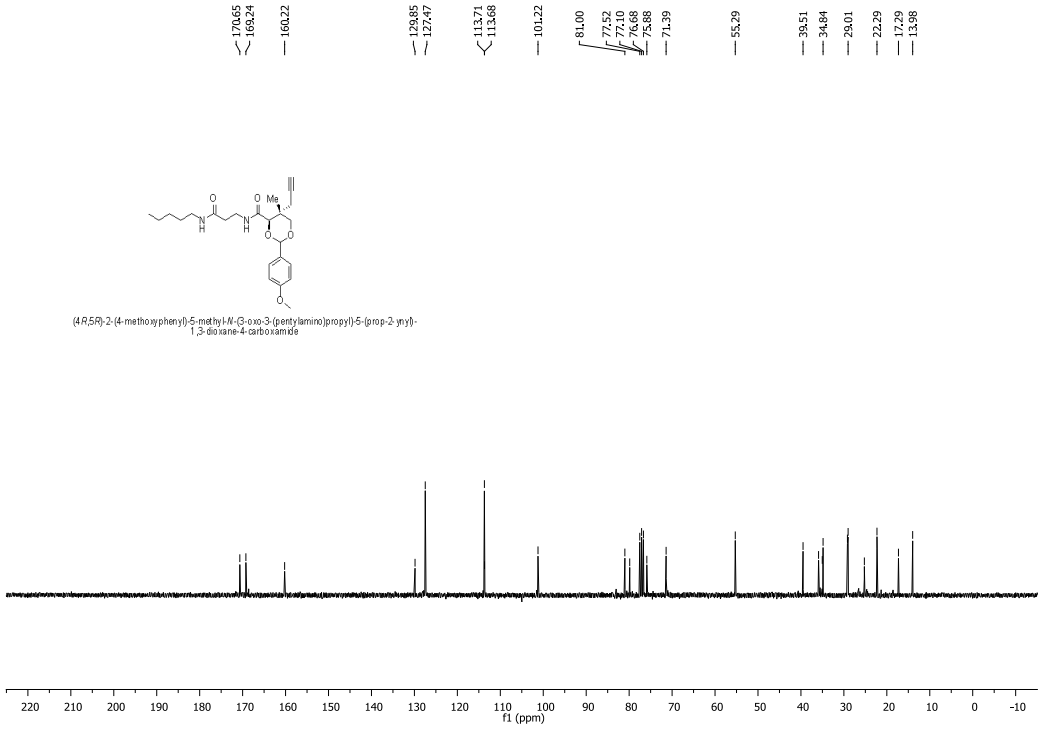
^{13C}-NMR spectrum in $CDCl_3$ of compound **71e**



^{1}H-NMR spectrum in $CDCl_3$ of compound **75d**



^{13}C-NMR spectrum in $CDCl_3$ of compound **75d**



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