Supporting Information

Functionally Optimized Neuritogenic Farinosone C Analogs: SAR-Study and Investigations on their Mode of Action

Patrick Burch[†,‡], Andrea Chicca[§], Jürg Gertsch[§] and Karl Gademann[†]*

[†]Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland.

[‡]Swiss Federal Institute of Technology (EPFL), Chemical Synthesis Laboratory (SB-ISIC-LSYNC), 1015 Lausanne, Switzerland.

[§]Institute of Biochemistry and Molecular Medicine, University of Bern, Bühlstrasse 28, CH-3012 Bern, Switzerland.

I. General Materials and Methods:

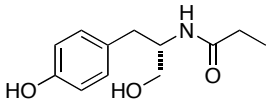
Synthesis. Nuclear magnetic resonance (NMR) spectra were performed using a Bruker Avance 400 MHz spectrometer. Coupling constants *J* are quoted in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), doublet of triplet (dt), triplet (t), quartet (q), quartet of triplet (qt), multiplet (m). Chemical shifts are reported in parts per million (ppm). NMR-solvents were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). Dry solvents were used from the Solvent System PS-MD5 (Innovative Technology, Inc., USA) or obtained from Sigma-Aldrich. Technical solvents used for extractions and purifications (pentane, Et_2O, EtOAc, MeOH and CH_2Cl_2) were distilled prior to use. Chemicals obtained from commercial suppliers were used without further purification, except Et_3N that was distilled prior to use. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F254 glass precoated plates. TLCs were analyzed by UV and $KMnO_4$-dip stain (1.50 g $KMnO_4$, 10 g K_2CO_3, 1.25 ml 10% NaOH in 200 ml dist. H_2O). Flash column chromatography (FC) was performed with the declared solvents using Silicycle SiliaFlash® P60 (230–400 mesh) silica.

Reactions were performed in flame-dried glassware under an argon atmosphere. Product purification was performed on an ultimate 3000 semi-preperative HPLC from Thermo Scientific applying a Gemini-NX5 10u C18 column. High-resolution mass spectra (HRMS) were recorded on a Bruker maXis 4G mass spectrometer using electrospray ionisation. Infrared spectroscopy and melting point measurements were performed on a Varian 800 FT-IR machine or on a Büchi melting point B-545 apparatus, respectably. The melting points are uncorrected. The optical rotation was measured on a JASCO P-2000 digital polarimeter (sodium D lamp) adding 1.0 mL of solution in a 3.5 x 100 mm glass cuvette. The concentration is referred as g/100 ml.

PC12 Cell Assay. Collagen coated 6- or 24-well plates (Becton Dickinson Labware, UK), Giemsa stain (modified solution), NGF-7S from murine submaxillary gland, penicillin-streptomycin solution, phosphate-buffered saline (PBS) (10X, 7.4 pH), culture flasks (Corning® cell culture flasks, 75 cm^2) were ordered from Sigma-Aldrich. Horse serum, MEM GlutaMAX™, fetal bovine serum (heat inactivated) and F-12K media were purchased from Invitrogen. Adherent PC12 cells were obtained from LTC Standards, Paris. The cells were cultured in growth media (GM) (F-12K media, 15% horse serum, 2.5% fetal bovine serum, 100 U/mL Penicillin, 100 mg/mL streptomycin). Cells were then scratched off the surface using a cell scraper (BD Falcon) and disaggregated by passage several times through a 21-gauge needle. The cell suspensions (35K cells/mL) was then subjected to the 24-well plates and incubated (36 °C, 5% CO_2) for 4 h. The GM was replaced by differentiation media (DM) (MEM GlutaMAX™, 1% horse serum, 0.5% fetal bovine serum) containing NGF 7S (20 ng mL^{-1}) and incubated for 16 h. After the media was replaced by DM without NGF the cells were incubated for 2 d with the compounds of interest. Thereafter, cells were fixed with 4% buffered formaldehyde solution for 2 h at 4 °C, then stained with Giemsa stain (modified solution), washed twice with PBS and pictured under a phase contrast microscope (Leica DMI 4000B). The ratio of differentiated cells (at least one neurite with a length equal to at least one cell diameter) to the total cell number per picture was evaluated by manual counting. At least six photographs were taken form three different wells with the same compound. On average 200-300 cells per picture were examined. Samples with DMSO (0.1%) and NGF 7S (10 ng mL^{-1}) were used as controls. All experiments were performed in triplicate and carried out under sterile conditions. Plots were made using the Prism software (GraphPad Software, Inc., USA).

II. Experimental Procedure:

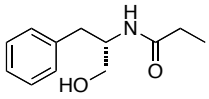
(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)propionamide (4)[1,2]



To a solution of L-tyrosinol hydrochloride (400 mg, 1.96 mmol, 1.00 equiv.) in THF (4.00 mL), K_2CO_3 (1.22 g, 8.84 mmol, 4.40 equiv.) dissolved in H_2O (3.50 mL) was added at once. The reaction mixture was stirred for 45 min at r.t. before propanoyl chloride (308 mg, 3.53 mmol, 1.80 equiv.) was added. The mixture was stirred for 15 h at r.t.. The organic solvent was then evaporated and brine was added before the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/EtOAc, 20:1) and yielded the products **4** (313 mg, 1.40 mmol, 71%), **7** (8.0 mg, 0.028 mmol, 1%) and **9** (13.4 mg, 0.048 mmol, 2%) as yellow oils.

$\mathbf{R}_f$ = 0.49 (CH_2Cl_2/MeOH, 8:2). **^{1}H-NMR** (400 MHz, MeOD) δ 7.03 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 4.09 - 3.93 (m, 1H), 3.63 - 3.39 (m, 2H), 2.80 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.60 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.14 (q, *J* = 7.6 Hz, 2H), 1.04 (t, *J* = 7.6 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ 176.87, 156.86, 131.23, 130.53, 116.05, 64.19, 54.22, 37.13, 30.29, 10.51. **HRMS ESI-TOF** calcd. for $C_{12}H_{17}NO_3$ (100%, $[M+H]^+$): 224.1287; found 224.1287. **FTIR** $\tilde{\nu}$ 3276*m*, 2940*w*, 2882*w*, 1616*s*, 1545*s*, 1514*s*, 1451*m*, 1373*m*, 1236*s*, 1042*m*, 823*m*, 634*s* cm^{-1}. **Optical rotation:** $[\alpha]_D^{25} = -3.7$ (c = 1.2, MeOH).

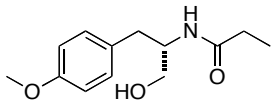
(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)propionamide (5)[5]



To a solution of (*S*)-(–)-2-Amino-3-phenyl-1-propanol (100 mg, 1.17 mmol, 1.00 equiv.) in H_2O/THF (1:1, 10.0 mL) was K_2CO_3 (647 mg, 4.68 mmol, 4.00 equiv.) added at r.t.. The mixture was stirred for 1 h before propionyl chlorid (204 μL, 2.34 mmol, 2.0 equiv.) was added. The reaction mixture was then stirred for 17 h under argon atmosphere. The organic solvent was evaporated and the aqueous layer was extracted with CH_2Cl_2 (3x), brine (1x), dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (EtOAc/CH_2Cl_2, 1:5) to yield the product **5** (200 mg, 0.97 mmol, 82%) as colorless solid.

R_f = 0.34 (MeOH/CH_2Cl_2, 1:20). **M.P.** = 77 - 78 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.42 - 7.15 (m, 5H), 5.89 (d, *J* = 6.7 Hz, 1H), 4.31 - 4.08 (m, 1H), 3.69 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.60 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.04 - 2.79 (m, 2H), 2.18 (q, *J* = 7.7 Hz, 2H), 1.11 (t, *J* = 7.7 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 174.68, 137.81, 129.33, 128.73, 126.77, 64.25, 52.92, 37.10, 29.88, 9.92. **HRMS ESI-TOF** calcd. for $C_{12}H_{18}NO_2^+$ (100%, $[M+H]^+$): 208.1332; found 208.1332. **FTIR** $\tilde{\nu}$ 3325*m br*, 2962*m*, 2361*m*, 2337*m*, 1634*m*, 1615*m*, 1515*s*, 1453*m*, 1367*m*, 1229*m*, 1043*m*, 826*w* cm^{-1}. **Optical rotation:** $[\alpha]_D^{23}$= –10.7 (c = 1.0, MeOH).

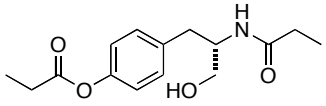
(*S*)-*N*-(1-hydroxy-3-(4-methoxyphenyl)propan-2-yl)propionamide (6)



To a solution of propionamide **4** (120 mg, 0.538 mmol, 1.00 equiv.) in MeCN (8.0 mL) was added $CsCO_3$ (193 mg, 0.592 mmol, 1.10 equiv.) and MeI (40 μL, 0.644 mmol, 1.20 equiv.). The reaction mixture was stirred at r.t. under an argon atmosphere. After 18 h additional MeI (30 μL, 0.482 mmol, 0.9 equiv.) and $CsCO_3$ (150 mg, 0.778 mmol, 0.85 equiv) were added and the mixture was stirred for another 32 h. The solvent was evaporated and the crude products were extracted using EtOAc (3x) and brine (1x). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 20:1) and yielded the products **6** (118 mg, 0.50 mmol, 52 %) and **10** (21 mg, 0.083 mmol, 9 %) as white solids.

R_f = 0.68 (MeOH/CH_2Cl_2, 1:10). **M.P.** = 80 - 82 °C. **^{1}H-NMR** (400 MHz, MeOD) δ 8.37 (dt, *J* = 8.3 Hz, 1H), 8.03 - 7.80 (m, 2H), 7.72 - 7.56 (m, 2H), 5.56 (t, *J* = 5.5 Hz, 1H), 4.74 - 4.57 (m, 2H), 4.51 (s, 3H), 4.14 ? 4.00 (m, 2H), 3.56 (dd, *J* = 13.7, 5.6 Hz, 1H), 3.38 - 3.25 (m, 2H), 2.82 (q, *J* = 7.6 Hz, 2H), 1.72 (t, *J* = 7.6 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ 182.10, 167.02, 140.63, 139.56, 123.00, 72.12, 64.46, 61.94, 45.21, 38.11, 19.54. **HRMS ESI-TOF** calcd. for $C_{13}H_{20}NO_3$ (100%, $[M+H]^+$): 238.1443; found 238.1451. **FTIR** $\tilde{\nu}$ 3494*w*, 3300*m*, 3080*w*, 2939*w*, 2922*w*, 1640*s*, 1540*s*, 1513*s*, 1463*m*, 1442*m*, 1247*s*, 1178*m*, 1075*m*, 1030*s*, 810*m*, 697*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= –4.0 (c = 0.68, MeOH).

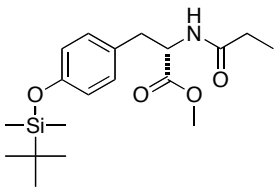
(*S*)-4-(3-hydroxy-2-propionamidopropyl)phenyl propionate (7)



For experimental please see compound **4**.

$\mathbf{R}_f$ = 0.27 (EtOAc/CH_2Cl_2, 4:6). **^{1}H-NMR** (400 MHz, DMSO) δ 7.36 – 7.11 (m, 1H), 7.10 - 6.81 (m, 2H), 7.11 - 6.89 (m, 2H), 4.22 - 4.02 (m, 1H), 3.61 - 3.43 (m, 2H), 2.93 (dd, *J* = 13.7, 5.3 Hz 1H), 2.72 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.65 - 2.53 (q, *J* = 7.6 Hz, 2H), 2.14 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.04 (t, *J* = 7.6 Hz, 3H). **^{13}C-NMR** (101 MHz, DMSO) δ 172.57, 172.52, 148.70, 136.70, 129.94, 121.25, 62.65, 52.11, 35.89, 28.56, 26.88, 9.97, 8.87. **HRMS ESI-TOF** calcd. for $C_{15}H_{21}NNaO_4^+$ (100%, $[M+Na]^+$): 302.1363; found 302.1366 **FTIR** $\tilde{\nu}$ 3454*w*, 3386*w*, 3339*w*, 3284*w*, 2976*w*, 2922*m*, 2877*w*, 2852*w*, 1753*s*, 1647*s*, 1617*s*, 1550*s*, 1510*s*, 1361*s*, 1196*s*, 1167*s*, 1074*s*, 1046*m*, 1021*m*, 900*s*, 825*m*, 667*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= –17.6 (c = 0.17, $CHCl_3$).

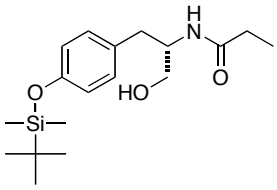
***(S)*-methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-propionamidopropanoate (I)**



To a solution of the methyl ester **11** (100 mg, 0.398 mmol, 1.00 equiv) in dry CH_2Cl_2 (5.00 mL) TBSCl (120 mg, 0.796 mmol, 2.00 equiv.), DMAP (9.72 mg, 80 μmol, 0.2 equiv.) and NEt_3 (168 mL, 1.19 mmol, 3.00 equiv.) were added. The reaction mixture was stirred for 5 h at r.t. under argon before sat. NH_4Cl-solution was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by gradiental flash chromatography on SiO_2 (first EtOAc/CH_2Cl_2, 1:4, then MeOH/CH_2Cl_2, 1:5) to yield the TBS-protected methyl ester **I** (140 mg, 0.383 mmol, 96%) as yellow oil.

$\mathbf{R}_f$ = 0.61 (CH_2Cl_2). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.12 - 7.04 (m, 2H), 6.80 - 6.73 (m, 2H), 4.63 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.68 (s, 3H), 3.09 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.89 (dd, *J* = 13.9, 9.0 Hz, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.05 (t, *J* = 7.6 Hz, 3H), 0.99 (s, 9H), 0.19 (s, 6H), **^{13}C-NMR** (101 MHz, MeOD) δ 176.74, 173.65, 155.79, 131.23, 131.01, 121.00, 55.19, 52.58, 37.71, 29.77, 26.17, 19.04, 10.34, –4.29. **HRMS ESI-TOF** calcd. for $C_{19}H_{31}NNaO_4Si^+$ (100%, $[M+Na]^+$): 388.1920; found 388.1912. **FTIR** $\tilde{\nu}$ 3290*w*, 2955*w*, 2933*w*, 2858*w*, 2361*w*, 2340*w*, 1745*m*, 1651*m*, 1510*s*, 1464*w*, 1439*w*, 1254*s*, 1212*m*, 1173*m*, 914*s*, 840*s*, 625*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= 20.4 (c = 2.13, MeOH).

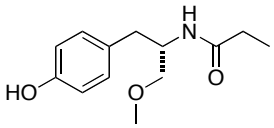
(*S*)-*N*-(1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-hydroxypropan-2-yl)propionamide (II)



The TBDMS-protected methyl ester **I** (170 mg, 0.465 mmol, 1.00 equiv.) was dissolved in dry DMF (5.00 mL). The solution was cooled to 0 °C before $LiAlH_4$ (176 mg, 4.65 mmol, 10.0 equiv.) was added in one portion. The reaction mixture was stirred for 1 h under an argon atmosphere. The reaction mixture was quenched using H_2O (5.00 mL) followed by NaOH-solution (5.00 mL, 1 M). The mixture was then stirred for an additional hour, filtered over celite and washed with H_2O and hot EtOAc. The mixture was then extracted using statured NH_4Cl-solution, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:40) to yield the product **II** (132 mg, 0.391 mmol, 84%) as colorless oil.

R_f = 0.36 (MeOH/CH_2Cl_2, 1:20). **^{1}H-NMR** (400 MHz, $CDCl_3$) 7.13 - 6.98 (m, 2H), 6.86 - 6.69 (m, 2H), 5.62 (d, *J* = 6.8 Hz, 1H), 4.19 - 4.03 (m, 1H), 3.76 - 3.65 (m, 1H), 3.63 - 3.49 (m, 1H), 2.95 - 2.70 (m, 2H), 2.17 (q, *J* = 7.4 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H), 0.97 (s, 9H), 0.18 (s, 6H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 174.78, 154.60, 130.23 (2C), 120.42, 77.48, 77.16, 76.84, 64.90, 53.24, 36.30, 29.90, 25.81, 18.34, 9.93, –4.29. **HRMS ESI-TOF** calcd. for $C_{18}H_{31}NNaO_3Si^+$ (100%, $[M+H]^+$): 360.1971; found: 360.1963. **FTIR** $\tilde{\nu}$ 3326*m*, 2946*w*, 2834*w*, 1651*w*, 1511*w*, 1451*w*, 1415*w*, 1259*w*, 1115*w*, 1025*s*, 638*s* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= 1.9 (c = 1.0 MeOH).

(*S*)-*N*-(1-(4-hydroxyphenyl)-3-methoxypropan-2-yl)propionamide (8)

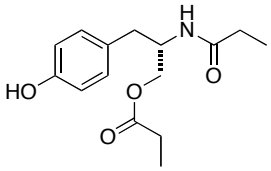


To a solution the TBS-protected alcohol **II** (500 mg, 1.48 mmol, 1.00 equiv.) in dry DMF (15.0 mL) at 0 °C was added NaH (60% in mineral oil, 89.0 mg, 2.22 mmol, 1.5 equiv.) in one portion. The mixture was allowed to reach r.t. before iodomethane (466 µL, 7.41 mmol, 5.00 equiv.) was added drop wise. The reaction mixture was stirred for 24 h under argon and then quenched using citric acid solution (5 %, 50 ml). The mixture was extracted using EtOAc (3x10 mL), brine (10mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude was filtered over a short plug of silica (EtOAc/CH_2Cl_2, 1:10) and concentrated again. The yellow residue was dissolved in dry THF (8.0 mL) and tetrabutylammonium fluoride (1 M solution

in THF, 1.01 mL, 3.41 mmol, 3.00 equiv.) was added. The mixture was stirred overnight under argon before MeOH (3.0 mL) was added. The solvents were removed and the crude was extracted with CH_2Cl_2 (3x10 ml), dried (Na_2SO_4) and concentrated. The crude product was purified first by flash chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:40) followed by preparative HPLC separation to yield the ether **8** (80 mg, 0.337 mmol, 23%) as white solid.

$\mathbf{R}_f$ = 0.54 (MeOH/CH_2Cl_2, 1:10). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.16 - 6.94 (m, 2H), 6.84 - 6.70 (m, 2H), 5.79 (d, *J* = 8.6 Hz, 1H), 4.10 - 4.19 (m, 1H), 3.47 - 3.24 (m, 4H), 2.77 (d, *J* = 7.4 Hz, 2H), 2.27 - 2.11 (m, 2H), 1.10 (t, *J* = 7.6 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.91, 155.01, 130.47, 129.61, 115.54, 77.48, 77.16, 76.84, 72.65, 59.19, 50.50, 36.84, 30.01, 9.98. **HRMS ESI-TOF** calcd. for $C_{13}H_{20}NO_3^+$ (100%, $[M+H]^+$): 238.1438; found: 238.1438. **FTIR** $\tilde{\nu}$ 3286*br*, 2938*w*, 2830*w*, 2362*m*, 2339*w*, 1644*m*, 1546*m*, 1515*s*, 1457*m*, 1239*m*, 1124*w*, 1025*w*, 770*m*, 634*s* cm^{-1}. **Optical rotation**: $[\alpha]_D^{21}$= –10.4 (c = 0.35 MeOH).

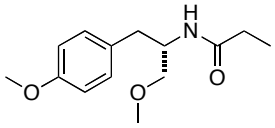
(*S*)-3-(4-hydroxyphenyl)-2-propionamidopropyl propionate (9)



For experimental procedure please see compound **4**

$\mathbf{R}_f$ = 0.43 (EtOAc/CH_2Cl_2, 4:6). **^{1}H-NMR** (400 MHz, DMSO) δ 9.17 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 4.13 - 4.02 (m, 1H), 3.99 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.86 (dd, *J* = 10.9, 6.6 Hz, 1H), 2.61 (m, 2H), 2.02 (q, *J* = 7.5 Hz, 3H), 2.02 (q, *J* = 7.4 Hz, 2H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H). **^{13}C-NMR** (101 MHz, DMSO) δ 173.49, 172.63, 155.64, 129.88, 128.21, 114.95, 64.77, 49.13, 35.82, 28.54, 26.76, 9.95, 8.96. **HRMS ESI-TOF** calcd. for $C_{14}H_{20}NO_4^-$ (100%, $[M]^-$): 279.1471; found 279.1392. **FTIR** $\tilde{\nu}$ 3365*m*, 3312*m*, 2986*w*, 2929*w*, 2853*w*, 1706*s*, 1650*s*, 1536*s*, 1515*s*, 1444*m*, 1363*m*, 1268*m*, 1209*s*, 1030*m*, 980*m*, 823*m*, 657*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= –12.1 (c = 0.14, $CHCl_3$).

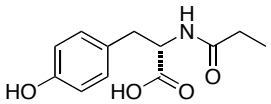
(*S*)-*N*-(1-methoxy-3-(4-methoxyphenyl)propan-2-yl)propionamide (10)



For experimental procedure please see compound **6**

R_f = 0.40 (EtOAc/CH_2Cl_2, 4:6). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.17 - 7.01 (m, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.71 (d, *J* = 6.0 Hz, 1H), 4.19-4.24 (m, 1H), 3.82 (s, 3H) 3.34 (s, 3H), 3.29 (d, *J* = 3.8 Hz, 2H), 2.79-2.85 (m, 2H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.12 (t, *J* = 7.7 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 173.27, 158.21, 130.37, 130.07, 113.88, 72.16, 59.00, 55.26, 50.13, 36.46, 29.86, 9.85. **HRMS ESI-TOF** calcd. for $C_{14}H_{22}NO_3^+$ (100%, $[M+H]^+$): 252.1600; found 252.1564. **FTIR** $\tilde{\nu}$ 3290*w*, 3072*w*, 2923*w*, 1743*w*, 1644*s*, 1512*s*, 1462*m*, 1444*m*, 1245*s*, 1179*m*, 1123*m*, 1083*m*, 1035*m*, 966*w*, 912*w*, 816*w*, 659*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22} = -7.2$ (c = 0.06, MeOH).

(*S*)-3-(4-hydroxyphenyl)-2-propionamidopropanoic acid (11)[6]

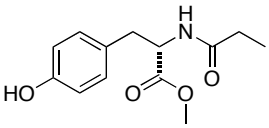


To a solution of L-tyrosine hydrochloride (3.00 g, 16.6 mmol, 1.00 equiv.) in H_2O/THF (1:1, 40.0 mL) was K_2CO_3 (9.15 g, 66.2 mmol, 4.00 equiv.) added at r.t. The mixture was stirred for 1 h before propionyl chlorid (1.59 mL, 18.2 mmol, 1.1 equiv.) was added. The reaction mixture was then stirred for 16 h under an argon atmosphere. The organic solvent was evaporated and HCl-soluiton (10 %, 50.0 mL) was added. The aqueous layer was extracted with EtOAc (3x), dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH, 15:1 + 2‰ TFA) to yield the acid **11** (3.42 g, 14.3 mmol, 87%) as viscous colorless oil.

R_f = 0.15 (MeOH/CH_2Cl_2, 1:15). **^{1}H-NMR** (400 MHz, D_2O) δ 7.18 - 7.11 (m, 2H), 6.88 - 6.81 (m, 2H), 4.57 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.15 (dd, *J* = 14.0, 5.4 Hz, 1H), 2.92 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.19 (q, *J* = 7.7 Hz, 2H), 0.99 (t, *J* = 7.7 Hz, 3H). **^{13}C-NMR** (101 MHz, D_2O) δ 177.72, 175.10, 173.85, 154.34, 130.50, 130.46, 128.38, 128.22, 115.34, 54.17, 54.00, 52.79, 35.77, 28.73, 9.27 (rotamer present) **HRMS ESI-TOF** calcd. for $C_{12}H_{16}NO_4^+$ (100%, $[M+H]^+$): 238.2625; found 238.1074. (100%, $[M]^+$). **FTIR** $\tilde{\nu}$ 3320*w br*, 2979*w*, 2941*w*, 1721*m*, 1638*m*, 1613*m*, 1514*s*, 1444*m*, 1377*w*, 1221*s*, 1125*m*, 1016*w*, 911*w*, 828*m*, 660*m* cm^{-}

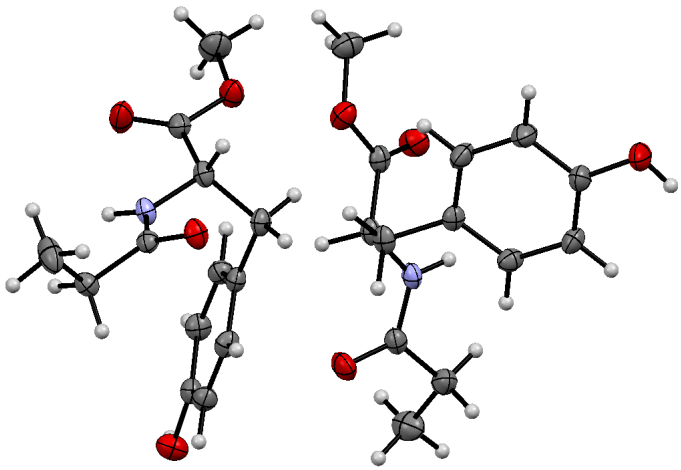
[1]. **Optical rotation:** $[\alpha]_D^{22}$= 34.9 (c = 0.35, H_2O). The reported data is in accordance with the literature.[6]

(*S*)-methyl 3-(4-hydroxyphenyl)-2-propionamidopropanoate (12)



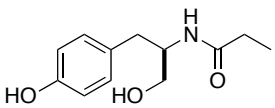
To a solution of L-tyrosinol methyl ester (1.01 g, 5.07 mmol, 1.00 equiv.) in H_2O/THF (1:1, 9.00 mL) was K_2CO_3 (2.10 g, 15.2 mmol, 3.00 equiv.) added at r.t.. The mixture was stirred for 1 h before propionyl chloride (0.531 μL, 6.08 mmol, 1.20 equiv.) was added. The reaction mixture was then stirred for 2 d under an argon atmosphere. The organic solvent was evaporated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 30:1) to yield the methyl ester **11** (1.24 g, 4.93 mmol, 97%) as white solid.

$\mathbf{R}_f$ = 0.43 (MeOH/CH_2Cl_2, 1:20). **M.P.** = 103 - 104 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.93 (m, 2H), 6.84 - 6.64 (m, 2H), 6.08 (m, 1H), 4.87 (dt, *J* = 8.0, 6.0 Hz, 1H), 3.74 (s, 3H), 3.09 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.97 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.21 (q, *J* = 7.8 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 174.25, 172.57, 155.76, 130.35, 126.97, 115.71, 77.48, 77.16, 76.84, 53.32, 52.57, 37.32, 29.68, 9.80. **HRMS ESI-TOF** calcd. for $C_{13}H_{18}NO_4^+$ (100%, $[M+H]^+$): 252.1230; found: 252.1230. **FTIR** $\tilde{\nu}$ 3300*m*, 3024*w*, 2981*w*, 2953*w*, 2361*m*, 2340*m*, 1736*m*, 1650*m*, 1516*s*, 1444*m*, 1373*m*, 1225*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= 19.1 (c = 1.6, MeOH).



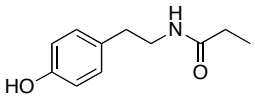
Crystal data for **11**: formula $C_{13}H_{17}NO_4$, M = 251.28, F(000) = 536, colourless plate, size 0.04 · 0.30 · 0.45 mm^3, monoclinic, space group P2(1), Z = 4, a = 9.4301(4) Å, b = 14.8968(6) Å, c = 10.0047(4) Å, α = 90.00°, β = 109.569(2)°, γ = 90.00°, V = 1324.26(9) $Å_3$, Dcalc. = 1.260 Mg · m-3. The crystal was measured on a Bruker APEX-II CCD diffractometer at 123(2)K using graphite-monochromated MoK_α-radiation with λ = 0.71073 Å, Θmax = 27.49°. Minimal/maximal transmission 0.9591/0.9963, μ = 0.094 mm-1. The Bruker APEX2 suite has been used for datacollection and integration. From a total of 30118 reflections, 6060 were independent (merging r = 0.0253). From these, 6060 were considered as observed (>2sigma(I)) and were used to refine 331 parameters. The structure was solved by direct methods using the program SHELXS-97. Least-squares refinement against Fsqd was carried out on all non-hydrogen atoms using the program SHELXL-97. R = 0.0280 (observed data), wR = 0.0726 (all data), GOF = 1.026. Minimal/maximal residual electron density = -0.153/0.194 e Å-3. Chebychev polynomial weights were used to complete the refinement. Plots were produced using Bruker SHELXTL. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center, the deposition number is **CCDC 955378**.

(*R*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)propionamide (13)



Amide **13** was prepared similar than **4** but D-tyrosinol hydrochloride was used as staring material instead. The analytical data is in accordance with the one of its enantiomer **4**. Yield: 92%, **Optical rotation:** $[\alpha]_D^{21}$= 1.8 (c = 0.25, MeOH).

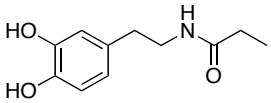
***N*-(4-hydroxyphenethyl)propionamide (14)**



Tryamine (300 mg, 2.19 mmol, 1.00 equiv.) was dissolved in H_2O/THF (1:1, 10.0 mL). To this solution K_2CO_3 (907 mg, 6.56 mmol, 3.00 equiv.) was added at r.t.. The mixture was stirred for 1 h before propionyl chlorid (263 μL, 2.19 mmol, 1.3 equiv.) was added. The reaction mixture was then stirred for 2 h under an argon atmosphere. The organic solvent was evaporated and the aqueous layer was extracted with EtOAc (3x), brine (1x), dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:30) to yield the product **14** (432 mg, quant.) as colorless solid.

R_f = 0.31 (MeOH/CH_2Cl_2, 1:20). **M.P.** = 109 - 110 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.05 - 6.98 (m, 2H), 6.74 - 6.67 (m, 2H), 3.33 (t, *J* = 7.3 Hz, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 2.15 (q, *J* = 7.6 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ 176.98, 156.88, 131.25, 130.71, 116.19, 42.26, 35.69, 30.22, 10.56. **HRMS ESI-TOF** calcd for $C_{11}H_{16}NO_2^+$ (100%, $[M+H]^+$): 194.1176; found 194.1176. (100%, $[M+H]^+$). **EA**: calc. (%) for $C_{11}H_{15}NO_2$: C 68.37, H 7.82, N 7.25; found C 68.16, H 7.65, N 7.25. **FTIR** $\tilde{\nu}$ 3393*m br*, 2978*m*, 2938*m*, 2360*m*, 2343*m*, 1638*s*, 1615*s*, 1546*m*, 1515*s*, 1454*m*, 1364*m*, 2337*m*, 829*w*, 632*s* cm^{-1}.

***N*-(3,4-dihydroxyphenethyl)propionamide (15)**

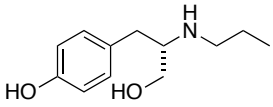


To a solution of dopamine hydrochloride (1.00 g, 5.27 mmol, 1.00 equiv.) in a mixture of H_2O/THF (1:1, 4.00 mL) was K_2CO_3 (2.19 g, 15.8 mmol, 3.00 equiv.) added. The mixture was stirred for 1 h under argon before propionyl chloride (24.7 μL, 0.223 mmol, 1.05 equiv.) was added. The mixture was then stirred overnight at r.t.. The solvent was removed and the dark residue was purified directly by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 20:1) to yield the amide **15** as brown oil (420 mg, 2.01 mmol, 38%).

R_f = 0.55 (MeOH/CH_2Cl_2, 1:20). **M.P.** = 112 - 113 °C. **^{1}H-NMR** (400 MHz, D_2O) δ 6.85 - 6.58 (m, 2H), 6.60 – 6.30 (m, 2H), 3.34 - 3.27 (m, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.14 (q, *J* = 7.6 Hz, 2H), 1.08 (t, *J* = 7.6 Hz, 3H). **^{13}C-NMR** (101 MHz, D_2O) δ 176.98, 146.16, 144.67, 132.02, 121.01, 116.84, 116.32, 42.22, 35.87, 30.20, 10.55. **HRMS ESI-TOF** calcd. for (100%, $[M+H]^+$): 210.1130; found: 210.1130. **FTIR** $\tilde{\nu}$ 3373*m*, 3100*m br*, 2974*w*, 2941*w*,

1631*m*, 1608*s*, 1545*s*, 1529*m*, 1440*s*, 1376*m*, 1276*m*, 1252*s*, 1192*s*, 1114*m*, 949*m*, 873*m*, 821*m*, 660*m* cm^{-1}.

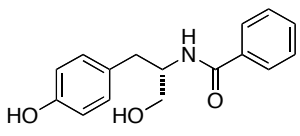
(*S*)-4-(3-hydroxy-2-(propylamino)propyl)phenol (16)



To a solution of L-tyrosinol hydrochloride (60 mg, 0.295 mmol, 2.00 equiv.) in a mixture of H_2O/THF (1:1, 2.00 mL) was K_2CO_3 (100 mg, 0.442 mmol, 3.00 equiv.) added. The mixture was stirred for 10 min at r.t. before prior to use distilled 1-bromopropane (9 μL, 0.73 mmol, 1.00 equiv.) was added. The mixture was then stirred overnight at 70 °C under an argon atmosphere. The organic solvent was removed and the residue was first directly purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH, 20:1) followed by reverse phase preparative HPLC separation to yield the amine **16** (12 mg, 57.3 μmol, 39%) as colorless fluffy solid.

$\mathbf{R}_f$ = 0.17 (MeOH/CH_2Cl_2, 1:5). **^{1}H-NMR** (400 MHz, D_2O) δ 7.24 - 7.17 (m, 2H), 6.93 - 6.86 (m, 2H), 3.81 (dd, *J* = 12.7, 3.5 Hz, 1H), 3.63 (dd, *J* = 12.7, 5.2 Hz, 1H), 3.56 - 3.45 (m, 1H), 3.11 - 2.88 (m, 4H), 1.68 (hept, *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). **^{13}C-NMR** (101 MHz, D_2O) δ 154.79, 130.65, 127.23, 115.79, 60.01, 57.96, 46.44, 32.51, 19.23, 10.15. **HRMS ESI-TOF** calcd. for $C_{12}H_{20}NO_2^+$ (100%, $[M+H]^+$): 210.1489; found 210.1489. **FTIR** $\tilde{\nu}$ 3365*w*, 3241*m*, 3098*w*, 2975*w*, 2822*w*, 1614*w*, 1573*m*, 1514*s*, 1458*s*, 1260*s*, 1224*s*, 1172*w*, 1094*m*, 1073*m*, 1031*m*, 968*s*, 844*m*, 828*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= -10.4 (c = 0.14, H_2O).

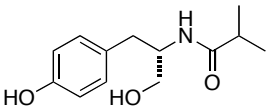
(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)benzamide (17)[3]



To a solution of L-tyrosinol hydrochloride (100 mg, 0.49 mmol, 1.00 equiv.) and benzyl chloride (60 mL, 0.51 mmol, 1.05 equiv.) in MeCN (4.00 mL) was added K_2CO_3 (311 mg, 2.25 mmol, 4.50 equiv.) dissolved in H_2O (3.00 mL) drop wise during 0.3 h at r.t.. The reaction mixture was then stirred for 3.5 h at r.t.. The organic solvent was evaporated and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH, 20:1) to yield the products **17** (98 mg, 0.361 mmol, 73%) as colorless solid.

$\mathbf{R}_f$ = 0.43 (EtOAc/ CH_2Cl_2, 4:6). **M.P.** = 37 - 41°C. **^{1}H-NMR** (400 MHz, MeOD) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.82 - 7.64 (m, 2H), 7.56 - 7.35 (m, 2H), 7.19 - 6.95 (m, 2H), 6.80 - 6.59 (m, 2H), 4.37 - 4.17 (m, 1H), 3.63 (d, *J* = 5.4 Hz, 2H), 2.91 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.77 (dd, *J* = 13.8, 8.2 Hz, 1H). **^{13}C-NMR** (101 MHz, DMSO) δ 165.98, 155.43, 134.84, 130.93, 129.93, 129.41, 128.11, 127.22, 114.90, 62.78, 53.54, 35.67. **FTIR** $\tilde{\nu}$ 3448*w*, 3308*m*, 2956*w*, 2928*w*, 1630*s*, 1602*m*, 1519*s*, 1488*m*, 1332*m*, 1239*s*, 1030*s*, 820*m*, 805*m*, 689*s*, 658*s* cm^{-1}. **HRMS ESI-TOF** calcd. for $C_{16}H_{18}NO_3$ (100%, $[M+H]^+$): 272.1287; found 272.1482. **Optical rotation:** $[\alpha]_D^{24}$= -67.7 (c = 0.26, MeOH).

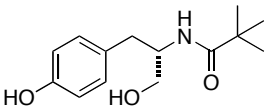
(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)isobutyramide (18)



To a solution of L-tyrosinol (3.00 g, 16.6 mmol, 1.00 equiv.) in H_2O/THF (1:1, 4.0 mL) was K_2CO_3 (61 mg, 0.442 mmol, 3.00 equiv.) added at r.t.. The mixture was stirred for 1 h before isobutyryl chloride (19 μL, 0.177 mmol, 1.20 equiv.) was added. The reaction mixture was then stirred for 15 h under argon atmosphere. The organic solvent was evaporated and sat. NH_4Cl-solution (5.0 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH, 30:1) to yield the product **18** (33 mg, 0.139 mmol, 94%) as colorless oil.

$\mathbf{R}_f$ = 0.21 (MeOH/CH_2Cl_2, 1:20). **^{1}H-NMR** (400 MHz, MeOD) δ 7.08 - 7.01 (m, 2 H), 6.79 - 6.56 (m, 2H), 4.13 - 3.94 (m, 1H), 3.51 (d, 5.4 Hz, 2H), 2.82 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.60 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.38 (hept, *J* = 6.9 Hz, 1H), 1.01 (dd, *J* = 27.9, 6.9 Hz, 6H). **^{13}C-NMR** (101 MHz, MeOD) δ 179.94, 156.82, 131.26, 130.56, 116.03, 64.33, 53.96, 37.12, 36.32, 20.04, 19.68. **HRMS ESI-TOF** calcd. for $C_{13}H_{20}NO_3^+$ (100%, $[M+H]^+$): 238.1438; found 238.1438. (100%, $[M]^+$). **FTIR** $\tilde{\nu}$ 3299*m br*, 2970*m*, 2932*m*, 2876*w*, 2357*w*, 2339*w*, 1639*s*, 1615*s*, 1542*s*, 1515*s*, 1456*m*, 1373*m*, 1241*s*, 1097*w*, 1041*m*, 771*m*, 630*s* cm^{-1}. **Optical rotation:** $[\alpha]_D^{23}$= -10.7 (c = 0.1, MeOH).

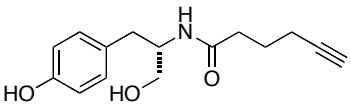
(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)pivalamide (19)



To a solution of L-tyrosinol (100 mg, 0.491 mmol, 1.00 equiv.) in H_2O/THF (1:1, 5.0 mL) was K_2CO_3 (204 mg, 1.470 mmol, 3.00 equiv.) added at r.t.. The mixture was stirred for 0.5 h before trimethylacetyl chloride (73 μL, 0.589 mmol, 1.20 equiv.) was added. The reaction mixture was then stirred overnight under argon atmosphere. The organic solvent was evaporated and sat. NH_4Cl-solution (10.0 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH, 30:1) to yield the product **19** (114 mg, 0.454 mmol, 92%) as colorless oil.

R_f = 0.26 (MeOH/CH_2Cl_2, 1:20). **M.P.** = 116 - 117 °C. **^{1}H-NMR** (400 MHz, MeOD) δ 7.11 - 7.00 (m, 2H), 6.75 - 6.57 (m, 2H), 4.13 - 4.02 (m, 1H), 3.61 - 3.45 (m, 2H), 2.83 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.65 (dd, *J* = 13.8, 8.6 Hz, 1H), 1.09 (s, 9H). **^{13}C-NMR** (101 MHz, MeOD) δ 180.99, 156.80, 131.27, 130.54, 116.03, 64.18, 54.14, 39.63, 36.94, 27.76. **HRMS ESI-TOF** calcd. for $C_{14}H_{22}NO_3^+$ (100%, $[M+H]^+$): 252.1594; found 252.1594. **FTIR** $\tilde{\nu}$ 3478*w*, 3441*w*, 3360*w*, 3335*w*, 3183*w broad*, 2962*w*, 2935*w*, 2868*w*, 2360*w*, 1706*w*, 1615*w*, 1530*s*, 1366*w*, 1227*s*, 1038*m*, 822*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$ = -8.8 (c = 1.0, MeOH).

(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)hex-5-ynamide (III)

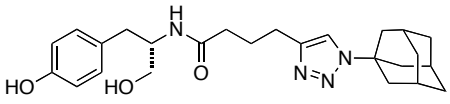


To a solution of L-tyrosinol hydrochloride (1.00 g, 4.91 mmol, 1.00 equiv.) in THF/H_2O (1:1, 16.0 mL) K_2CO_3 (1.69 g, 12.27 mmol, 4.40 equiv.) was added. The reaction mixture was stirred for 1 h at r.t. before hex-5-ynoyl chloride (770 mg, 5.89 mmol, 1.20 equiv.) was added. After stirring for 4 h additional hex-5-ynoyl chloride (150 mg, 1.15 mmol, 0.23 equiv) was added. The mixture was stirred for another 1.2 h. The organic solvent was evaporated and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by gradiental flash chromatography on SiO_2 (MeOH in CH_2Cl_2, 1-10%) to yield alkin **III** (1.03 g, 3.93 mmol, 85%) as white solid.

R_f = 0.51 (MeOH/CH_2Cl_2, 1:10). **M.P.** = 91 - 93 °C **^{1}H-NMR** (400 MHz, MeOD) δ 7.61 (d, *J* = 8.5 Hz, 1H), 7.13 - 6.89 (m, 2H), 6.78 - 6.57 (m, 2H), 4.14 - 3.91 (m, 1H), 3.57 -3.38 (m,

2H), 2.80 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.58 (dd, *J* = 13.8, 8.5 Hz, 1H), 2.31-2.15 (m, 3H), 2.13 - 1.97 (m, 2H), 1.76 - 1.56 (m, 2H). **^{13}C-NMR** (101 MHz, MeOD) δ 175.22, 156.86, 131.22, 130.51, 116.07, 84.25, 70.08, 64.38, 54.37, 54.27, 37.04, 36.01, 25.99, 18.54. **HRMS ESI-TOF** calcd. for $C_{15}H_{20}NO_3$ (100%, $[M+H]^+$): 262.1443; found 262.1443. **FTIR** $\tilde{\nu}$ 3483*w*, 3314*m*, 3300*m*, 3208*m*, 2690*w*, 2927*w*, 2881*w*, 1633*s*, 1615*m*, 1530*s*, 1517*s*, 1453*m*, 1247*m*, 1214*m*, 1031*s*, 821*m*, 744*m*, 681*m*, 650*s*, 627*s* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= -19.5 (c = 0.82, MeOH).

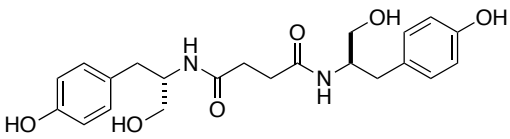
(*S*)-4-(1-(adamantan-1-yl)-1H-1,2,3-triazol-4-yl)-N-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)butanamide (20)



(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)hex-5-ynamide **III** (50 mg, 0.191 mmol, 1.00 equiv.), 1-azidoadamantane (37.3 mg, 0.210 mmol, 1.10 equiv.), L-Ascorbic acid sodium salt (37.9 mg, 0.191 mmol, 1.00 equiv.) Copper (II) sulfate pentahydrate (1.9 mg, 0.008 mmol, 0.04 equiv.) and tris-(benzyltriazolylmethyl)amine (4.2 mg, 0.008 mmol, 0.04 equiv.) were dissolved in DMSO (2.00 mL). The reaction mixture was stirred for 2 d at r.t. under an argon atmosphere. The organic solvent was removed and the crude was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by gradiental flash chromatography on SiO_2 (MeOH in EtOAc 2-5%) yielded the product **20** (64 mg, 0.146 mmol, 76%) as white solid.

R$_f$ = 0.15 (EtOAc/CH_2Cl_2, 4:6), **M.P.** = 76 - 77 °C, **^{1}H-NMR** (500 MHz, DMSO) δ 7.74 (s, 1H), 7.13 - 6.97 (m, 2H), 6.74 - 6.61 (m, 2H), 4.10 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.51 (h, *J* = 5.7 Hz, 2H), 2.83 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.67 - 2.44 (m, 3H), 2.25 (s, 10H), 2.18 (t, *J* = 7.3 Hz, 2H), 1.85 (d, *J* = 7.0 Hz, 8H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 175.51, 156.87, 131.25, 130.55, 119.94 (2C), 116.10, 64.48, 60.90, 54.16, 37.16, 36.94, 36.46, 31.00, 26.78, 25.58. **HRMS ESI-TOF** calcd. for $C_{25}H_{36}N_4O_3^+$ (100%, $[M+H]^+$): 439.2709; found 439.2709. (100%, $[M+H]^+$). **FTIR** $\tilde{\nu}$ 3263*m*, 2915*s*, 2854*m*, 1732*m*, 1640*s*, 1548*m*, 1515*s*, 1452*s*, 1233*s*, 1144*m*, 1103*m*, 1064*s*, 818*m*, 685*m*, 662*m*, 649*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= –7.8 (c = 0.12, MeOH).

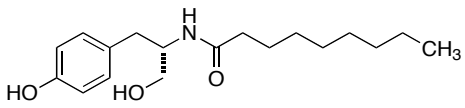
_N_-((_R_)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)-_N_-((_S_)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)succinamide (21)



To a solution of L-tyrosinol hydrochloride (100 mg, 0.491 mmol, 2.00 equiv.) in a mixture of H_2O/THF (1:1, 4.00 mL) was K_2CO_3 (154 mg, 1.120 mmol, 5.00 equiv.) added. The mixture was stirred for 1 h under argon before succinyl chloride (24.7 μL, 0.223 mmol, 1 equiv.), which was distilled prior to use, was added. The mixture was stirred for 2 d under an argon atmosphere at r.t.. The organic solvent was removed and the pale yellow residue was purified directly by flash chromatography on SiO_2 (CH_2Cl_2/MeOH, 40:1) to yield the dimer **21** as colorless solid (51 mg, 0.122 mmol, 55%).

R_f = 0.37 (MeOH/CH_2Cl_2, 1:20). **M.P.** = 167 - 169 °C. **^{1}H-NMR** (400 MHz, MeOD) 7.18 - 6.80 (m, 5H), 6.86 - 6.45 (m, 4H), 4.39 (td, *J* = 10.3, 9.8, 5.5 Hz, 2H), 4.06 (dd, *J* = 11.4, 9.4 Hz, 2H), 3.72 (dd, *J* = 11.4, 5.0 Hz, 2H), 3.00 (dd, *J* = 13.8, 10.3 Hz, 2H), 2.89 (dd, *J* = 13.8, 6.1 Hz, 2H), 2.63 - 2.41 (m, 4H). **^{13}C-NMR** (101 MHz, MeOD) δ 180.25, 157.14, 130.92, 129.64, 116.21, 61.85, 57.50, 33.81, 28.76. **FTIR** $\tilde{\nu}$ 3204*w*, 2995*w*, 2963*w*, 2946*w*, 2506*w*, 2383*m*, 1758*w*, 1676*s*, 1613*m*, 1517*m*, 1401*m*, 1372*m*, 1257*m*, 1172*s*, 1021*m*, 889*w*, 810*s*, 668*s,* 620*m* cm^{-1}.

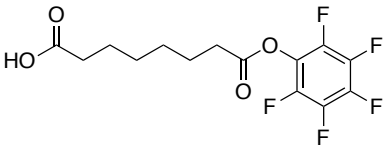
(_S_)-_N_-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)nonanamide (22)



To a solution of L-tyrosinol (200 mg, 0.982 mmol, 1.00 equiv.) in H_2O/THF (1:1, 8.0 mL) was K_2CO_3 (543 mg, 3.93 mmol, 4.00 equiv.) added at r.t. under an argon atmosphere. The mixture was stirred for 0.33 h before nonanoyl chloride (248 μL, 1.37 mmol, 1.40 equiv.) was added. The reaction mixture was then stirred overnight. The organic solvent was evaporated and sat. NH_4Cl-solution (10.0 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 30:1) to yield the product **22** (213 mg, 0.693 mmol, 71%) as slight yellow solid.

R_f = 0.25 ($MeOH/CH_2Cl_2$, 1:20). **M.P.** = 101 - 102 °C. **^{1}H-NMR** (400 MHz, MeOD) δ 7.14 - 6.98 (m, 2H), 6.77 - 6.62 (m, 2H), 4.17 - 3.98 (m, 1H), 3.52 (d, *J* = 5.4 Hz, 2H), 2.84 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.61 (dd, *J* = 13.9, 8.6 Hz, 1H), 2.14 (t, *J* = 7.5 Hz, 2H), 1.52 (p, *J* = 7.5 Hz, 2H), 1.44 - 1.15 (m, 10H), 0.92 (t, *J* = 6.9 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ 176.13, 156.88, 131.20, 130.51, 116.05, 64.38, 54.19, 37.27, 37.14, 33.02, 30.44, 30.27, 30.20, 27.06, 23.70, 14.44. **HRMS ESI-TOF** calcd. for $C_{18}H_{29}NNaO_3^+$ (100%, $[M+Na]^+$): 330.4232; found; 330.2042. **FTIR** $\tilde{\nu}$ 3300*m broad*, 2933*m*, 2859*w*, 2361*w*, 2338*w*, 1629*w*, 1550*w*, 1516*m*, 1452*w,* 1373*w*, 1243*s*, 1044*w*, 631*s* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$ = –13.7 (c = 1.00, MeOH).

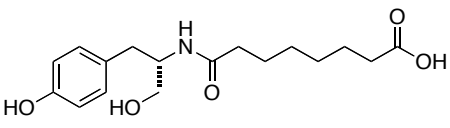
8-oxo-8-(perfluorophenoxy)octanoic acid (IV) [4]



Pentaflourobenzoic acid (1.32 g, 7.176 mmol, 1.00 equiv.), octanedioic acid (2.50 g, 14.352 mmol, 2.00 equiv.) and EDC (1.65 g, 8.61 mmol, 1.20 equiv.) were dissolved in DMF/THF (1:3, 135 mL). This reaction mixture was then stirred overnight under nitrogen. The solvents were removed, first under slightly reduced pressure then under high vacuum while heating. The residue was extracted with EtOAc (4x) and aqueous HCl-solution (10 %, v:v). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was first purified by flash chromatography on SiO_2 (CH_2Cl_2/EtOAc/TFA, 200:20:1) followed by recrystallization from pentane to yield the activated acid **IV** (680 mg, 0.361 mmol, 35%) as white crystals.

R_f = 0.59 (EtOAc). **M.P.** = 50 - 52 °C. **^{13}C-NMR** (101 MHz, MeOD) δ 34.78, 33.80, 29.73, 29.56, 25.83, 25.66, 14.46. **HRMS ESI-TOF** calcd. for $C_{14}H_{12}O_4F_5^-$ (100%, $[M]^-$): 339.0661; found 339.0656. The analytical data was in accordance with the literature. [4]

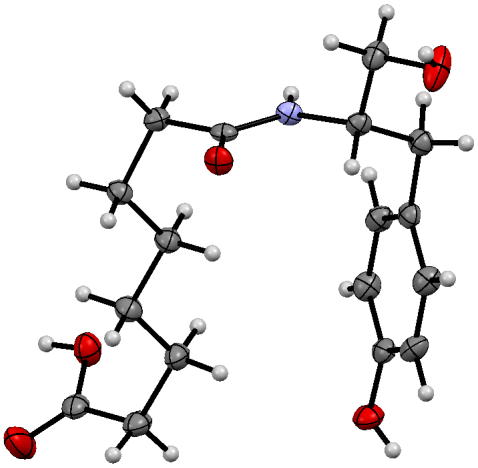
(*S*)-8-((1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)amino)-8-oxooctanoic acid (23)



To a solution of the mono-activated acid **IV** (350 mg, 1.03 mmol, 1.20 equiv.) in DMF/THF (1:3, 6.0 mL) was L-tyrosinol hydrochloride (175 mg, 0.857 mmol, 1.00 equiv.) and NEt_3 (631 μL, 2.57 mmol, 3.00 equiv.) added. The mixture was stirred for 16 h under an argon atmosphere at r.t.. Solvent removal was accomplished under high vacuum

while heating. The brown residue was extracted with EtOAc (4x) and aqueous HCl-solution (10 %, v:v). The crude product was first purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH/TFA, 100:10:1) followed by preparative HPLC separation to yield the acid **23** (70 mg, 0.216 mmol, 25%) as colourless solid.

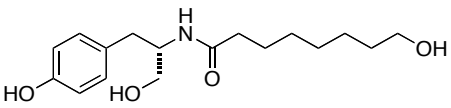
R_f = 0.46 (MeOH/CH_2Cl_2, 1:30). **M.P.** = 101 - 103 °C. **^{1}H-NMR** (400 MHz, MeOD) d 7.11 - 6.95 (m, 2H), 6.77 - 6.60 (m, 2H), 4.16 - 3.98 (m, 1H), 3.50 (d, *J* = 5.6 Hz, 2H), 2.82 (dd, *J* = 13.9, 5.9 Hz, 1H), 2.58 (dd, *J* = 13.9, 8.7 Hz, 1H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.54 (dt, *J* = 26.1, 7.5 Hz, 4H), 1.37 - 1.19 (m, 4H). **^{13}C-NMR** (126 MHz, MeOD) d 177.73, 176.01, 156.78, 131.18, 130.46, 116.04, 64.39, 54.13, 37.11(2C), 34.87, 29.85, 29.73, 26.84, 25.84. **HRMS ESI-TOF** calcd. for $C_{17}H_{24}NO_5^-$ (100%, $[M]^-$): 322.1660; found 322.1640. **FTIR** $\tilde{\nu}$ 3308*m*, 3064*w*, 3021*w*, 2923*m*, 2852*m*, 1702*s*, 1634*s*, 1536*s*, 1514*s*, 1444*w*, 1365*s*, 1232*s*, 1036*s*, 960*s*, 847*m*, 817*m*, 683*m* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= –29.0 (c = 0.05 MeOH).



Crystal data for **23**: formula $C_{17}H_{25}NO_5$, M = 323.38, F(000) = 348, colourless prismatic, size 0.10 · 0.24 · 0.30 mm^3, monoclinic, space group P 21, Z = 2, a = 5.0493(3) Å, b = 16.9091(8) Å, c = 10.1272 Å, α = 90.00°, β = 100.905(6)°, γ = 90.00°, V = 849.04(8) $Å_3$, Dcalc. = 1.265 Mg · m-3. The crystal was measured on a Oxford Diffraction, KM4/Sapphire CCD diffractometer at 140(2)K using graphite-monochromated MoK_α-radiation with λ = 0.71073 Å, Θmax = 26.37°. Minimal/maximal transmission 0.95248/1.00000, μ = 0.093 mm-1. The CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.33.66 suite has been used for datacollection and integration. From a total of 6522 reflections, 3336 were independent (merging r = 0.0142). From these, 3336 were considered as observed (>2sigma(I)) and were used to refine 308 parameters. The structure was solved by direct methods using the program

SHELXS-97. Least-squares refinement against Fsqd was carried out on all non-hydrogen atoms using the program SHELXL-97. R = 0.0260 (observed data), wR = 0.0616 (all data), GOF = 1.038. Minimal/maximal residual electron density = -0.138/0.129 e Å-3. Chebychev polynomial weights were used to complete the refinement. Plots were produced using Bruker SHELXTL. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center, the deposition number is **CCDC 955377**.

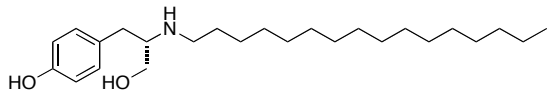
(*S*)-8-hydroxy-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)octanamide (24)



To a solution of L-tyrosinol (150 mg, 0.736 mmol, 1.00 equiv.) in MeCN (14.0 mL) was 8-hydroxyoctanoic acid (118 mg, 0.736 mmol, 1.00 equiv.), NEt_3 (311 μL, 2.21 mmol, 3.00 equiv.), EDC (282 mg, 1.47 mmol, 2.00 equiv.) and 1-hydroxybenzotriazole hydrate (149 mg, 1.1 mmol, 1.5 equiv.) added. The mixture was stirred at r.t. under argon for 12 h. The organic solvent was evaporated and sat. NH_4Cl-solution was added. The aqueous layer was extracted with CH_2Cl_2 (4x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/EtOAc 5:1) to yield the triol **24** (42 mg, 0.136 mmol, 19%) as slight yellow solid.

R_f = 0.17 (MeOH/CH_2Cl_2 1:20). **M.P.** = 124 - 125 °C. **^{1}H-NMR** (400 MHz, MeOD) δ 7.12 - 6.96 (m, 2H), 6.76 - 6.62 (m, 2H), 4.11 - 4.00 (m, 1H), 3.60 - 3.44 (m, 4H), 2.82 (dd, *J* = 13.9, 5.9 Hz, 1H), 2.59 (dd, *J* = 13.9, 8.7 Hz, 1H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.60 - 1.41 (m, 4H), 1.40 - 1.12 (m, 6H). **^{13}C-NMR** (101 MHz, MeOD) δ 176.11, 156.85, 131.20, 130.54, 116.08, 64.44, 62.98, 54.17, 37.22, 37.14, 33.60, 30.27, 30.11, 26.98, 26.75. **HRMS ESI-TOF** calcd. for $C_{17}H_{27}NNaO_4^+$ (100%, $[M+Na]^+$): 332.1832; found; 332.1832. **FTIR** $\tilde{\nu}$ 3293*m*, 2932*m*, 2858*w*, 2362*s*, 2338*s*, 1638*m*, 1560*w*, 1515*m*, 1459*w*, 1369*w*, 1243*w*, 1036*w*, 758*s*, 632*s* cm^{-1}. **Optical rotation:** $[\alpha]_D^{22}$= -12.0 (c = 0.50, MeOH).

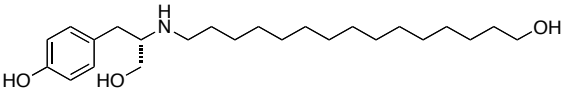
(*S*)-4-(2-(hexadecylamino)-3-hydroxypropyl)phenol (28)



Amide **32** (23.0 mg, 0.055 mmol, 1.00 equiv.), chlorotrimetyhlsilane (1.0 mg, 0.009 mmol, 0.17 equiv.) and 1,1,1,3,3,3-hexamethyldisilazane (28.3 mg, 0.175 mmol 3.20 equiv.) were dissolved in MeCN (1.5 mL) and refluxed (90 ºC) under argon for 2.5 h. The solvent was removed under reduced pressure and the residue was dissolved in dioxane (1.50 mL). Borane dimethyl sulfide complex solution in THF (2 M) (138 mL, 0.277 mmol, 5.00 equiv.) was added and the mixture was refluxed (100 ºC) under argon for 20 h. Then HCl-solution (10%, v:v, 1.0 mL) was added and the mixture was refluxed (100 ºC) for another hour. The mixture was then extracted using saturated $NaHCO_3$-solution (5.00 mL) and CH_2Cl_2 (3x). The combined organic layers were concentrated and the residue was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 4:1 + 0.1% TFA) to yield the product **28** (12.5 mg, 0.031 mmol, 56%) as white solid.

R_f = 0.28 (CH_2Cl_2/MeOH 10:1). **M.P.** = 75 - 78 °C. **^{1}H-NMR** (400 MHz, MeOH) δ 7.09 (m, 2H), 6.76 (m, 2H), 3.67 (dd, *J* = 11.8, 3.5 Hz, 1H), 3.50 (dd, *J* = 11.9, 4.9 Hz, 1H), 3.27 - 3.17 (m, 1H), 3.02 - 2.75 (m, 4H), 1.76 - 1.53 (m, 2H), 1.44 - 1.10 (m, 26H), 0.90 (t, *J* = 6.7 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOH) δ 157.70, 131.35 (2C), 128.28, 116.62 (2C), 62.15, 59.67, 46.82, 34.93, 33.07, 30.78 (2C), 30.77, 30.76, 30.71, 30.65, 30.54, 30.47, 30.28, 28.04, 27.77, 23.73, 14.43. **HRMS ESI-TOF** calcd. for $C_{25}H_{46}NO_2^+$ (100%, $[M+H]^+$): 392.3523; found; 392.3525. **FTIR** $\tilde{\nu}$ 3298*w*, 2956*w*, 2917*s*, 2850*s*, 1615*w*, 1600*w*, 1564*w*, 1516*m*, 1469*m*, 1368*w*, 1249*m*, 1175*w*, 1104*w*, 1069*w*, 1041*w*, 1018*w*, 991*w*, 965*w*, 839*w*, 818*m*, 777*w*, 719*w*, 649w. **Optical rotation:** $[\alpha]_D^{25}$ = –8.7 (c = 0.28, MeOH).

(*S*)-4-(3-hydroxy-2-((15-hydroxypentadecyl)amino)propyl)phenol (29)

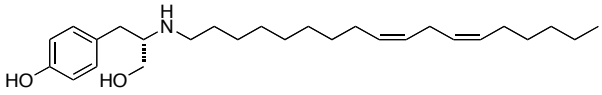


Amide **33** (28.0 mg, 0.069 mmol, 1.00 equiv.), chlorotrimetyhlsilane (3.6 mg, 0.033 mmol, 0.50 equiv.) and 1,1,1,3,3,3-hexamethyldisilazane (35.5 mg, 0.220 mmol 3.20 equiv.) were dissolved in MeCN (2.00 mL) and refluxed (90 ºC) under argon for 1h. The solvent was removed under reduced pressure and the residue was dissolved in dioxane (1.80 mL). Borane dimethyl sulfide complex solution in THF (2 M, 172 mL, 0.343 mmol, 5.00 equiv.) was added and the mixture was refluxed (100 ºC) under argon for 13 h. Then HCl-solution (10%, v:v,

1.00 mL) was added and the mixture was refluxed (100 °C) for another h. The mixture was extracted using saturated $NaHCO_3$-solution and CH_2Cl_2 (3x). The combined organic layers were concentrated and the residue was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 6:1 + 0.1% TEA) to yield the product **29** (11 mg, 0.028 mmol, 41%) as white solid.

R_f = 0.14 (CH_2Cl_2/MeOH 10:1 + TEA). **M.P.** = 133 - 135 °C. **^{1}H-NMR** (500 MHz, MeOD) δ 7.13-7.05 (m, 2H), 6.80 - 6.73 (m, 2H), 3.69 (dd, *J* = 11.9, 3.5 Hz, 1H), 3.57 - 3.48 (m, 3H), 3.24 (td, *J* = 9.2, 4.8 Hz, 1H), 3.05 - 2.78 (m, 4H), 1.74 - 1.61 (m, 2H), 1.57 - 1.48 (m, 2H), 1.43 - 1.24 (m, 22H). **^{13}C-NMR** (125 MHz, MeOD) δ 157.73, 131.36 (2C), 128.18, 116.63 (2C), 63.00, 62.13, 59.46, 46.75, 34.79, 33.66, 30.75 (2C), 30.73 (2C), 30.64, 30.61 (2C), 30.53, 30.26, 27.91, 27.74, 26.95. **HRMS ESI-TOF** calcd. for $C_{24}H_{44}NO_3^+$ (100%, $[M+H]^+$): 394.3316; found; 394.3316. **FTIR** $\tilde{\nu}$ 3310*w*, 2919*s*, 2849*s*, 2523*w*, 2458*m*, 1612*w*, 1515*s*, 1468*s*, 1372*w*, 1258*m*, 1171*w*, 1106*w*, 1096*w*, 1064*m*, 1011*w*, 940*w*, 820*w*. **Optical rotation:** $[\alpha]_D^{25} = -11.3$ (c = 0.26, MeOH).

4-((*S*)-3-hydroxy-2-((9*Z*,12*Z*)-octadeca-9,12-dien-1-ylamino)propyl)phenol (30)

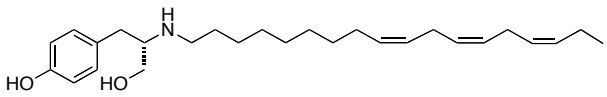


To a cooled (–78 °C) solution of ethyl linoleate (60 mg, 0.194 mmol, 1.00 equiv.) in toluene (3.00 mL) was added a precooled (–78 °C) DIBAL-H solution (1 M in *n*-hexane) (202 μL, 0.202 mmol, 1.05 equiv.) which was dissolved in toluene (1.00 mL). The mixture was stirred for 50 min at this temperature under argon before it was quenched using satured Rochelle salt-solution (3.00 mL) and extracted with Et_2O (3x). The combined organic layers were dried over $NaSO_4$ and concentrated.

The crude linolic aldehyde was dissolved in MeOH (2.00 mL). To this solution glacial acetic acid (0.10 mL), L-Tyrosinol hydrochloride (53.1 mg, 0.261 mmol, 1.35 equiv.) and sodium cyanoborohydride (18.2 mg, 0.290 mmol, 1.50 equiv.) were added. The mixture was stirred for 2.5 h at r.t. under argon before it was quenched with HCl-soltion (10%, v:v, 30 mL). The mixture was extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine, dried using $NaSO_4$ and concentrated. The residue was purified by flash chromatography on SiO_2 (MeOH/$CH_2Cl_2$1:15 + 0.1% TEA) to yield the product **30** (22 mg, 0.052 mmol, 27%) as colourless oil.

R_f = 0.50 (CH_2Cl_2/MeOH 10:1 + TEA). **^{1}H-NMR** (400 MHz, MeOH) δ 7.11 (m, 2H), 6.77 (m, 2H), 5.43 - 5.26 (m, 4H), 3.72 (dd, *J* = 12.1, 3.3 Hz, 1H), 3.53 (dd, *J* = 12.1, 4.5 Hz, 1H), 3.40 - 3.32 (m, 1H), 3.13 - 2.82 (m, 4H), 2.78 (t, *J* = 6.3 Hz, 2H), 2.15 - 2.00 (m, 4H), 1.76 - 1.59 (m, 2H), 1.60 - 1.23 (m, 18H), 0.91 (t, *J* = 6.9 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ 157.86, 131.39, 130.96, 130.84, 129.14, 129.03, 127.67, 116.68, 62.06, 58.61, 46.45, 34.25, 32.66, 30.75, 30.47, 30.42, 30.26, 30.20, 28.17, 27.67, 27.40, 26.53, 23.62, 14.43. **HRMS ESI-TOF** calcd. for $C_{27}H_{46}NO_2^+$ (100%, $[M+H]^+$): 416.3523; found; 416.3525. **FTIR** $\tilde{\nu}$ 3263*w*, 3010*w*, 2925*s*, 2854*s*, 1614*s*, 1603*w*, 1516s, 1453*m*, 1376*w*, 1260*m*, 1231*m*, 1174*w*, 1106*w*, 1044*m*, 966*w*, 840*w*, 778*w*, 660*s*, 618*s*. **Optical rotation:** $[\alpha]_D^{25}$= –5.5 (c = 0.19, MeOH).

4-((*S*)-3-hydroxy-2-((9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trien-1-ylamino)propyl)phenol (31)



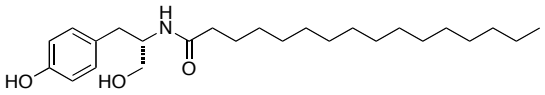
To a cooled (–78 ºC) solution of ethyl linolenate (150 mg, 0.489 mmol, 1.00 equiv.) in toluene (3.00 mL) was added a precooled (–78 ºC) DIBAL-H solution (1 M in *n*-hexane, 514 mL, 0.514 mmol, 1.05 equiv.) which was prior dissolved in toluene (1.00 mL). The mixture was stirred for 50 min at this temperature under argon before it was quenched using sat. rochelle-salt-solution (5.00 mL) and extracted with Et_2O (3x). The combined organic layers were dried over $NaSO_4$ and concentrated.

The crude linolenic aldehyde was dissolved in MeOH (4.00 mL). To this solution glacial acetic acid (0.15 mL), L-Tyrosinol hydrochloride (130 mg, 0.636 mmol, 1.30 equiv.) and sodium cyanoborohydride (46.1 mg, 0.734 mmol, 1.50 equiv.) were added. The mixture was stirred for 2 h at r.t. under argon before it was quenched with HCl-soltion (10%, v:v, 30 mL). The mixture was extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine, dried using $NaSO_4$ and concentrated. The residue was purified by flash chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:20 + 0.1% TEA) to yield the product **31** (90 mg, 0.218 mmol, 22%) as colorless oil.

R_f = 0.49 (CH_2Cl_2/MeOH 10:1). **^{1}H-NMR** (400 MHz, MeOD) δ 7.08 (m, 2H), 6.75 (m, 2H), 5.50-5.16 (m, 6H), 3.65 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.49 (dd, *J* = 11.7, 5.0 Hz, 1H), 3.15 (td, *J* = 9.2, 4.9 Hz, 1H), 3.05 - 2.63 (m, 8H), 2.22-2.01 (m, 4H), 1.71 - 1.55 (m, 2H), 1.34 (s, 10H), 0.97 (td, *J* = 7.5, 0.7 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ 157.54, 132.71, 131.31 (2C), 131.05, 129.18 (2C), 128.84, 128.66, 128.21, 116.55 (2C), 62.20, 60.29, 47.04, 35.32, 30.72,

30.45, 30.30, 30.26, 28.42, 28.17, 27.84, 26.52, 26.40, 21.48, 14.67. **HRMS ESI-TOF** calcd. for $C_{27}H_{44}NO_2^+$ (100%, $[M+H]^+$): 414.3367; found; 414.3367. **FTIR** $\tilde{\nu}$ 3283*w*, 3011*w*, 2962*w* 2926*m*, 2854*m*, 2361*w*, 2338*w*, 1614*w*, 1595*w*, 1516*m*, 1451*m*, 1393*w*, 1368*w*, 1233*m*, 1172*w*, 1106*w*, 1043*w*, 839*w*, 770*m*, 716*m*, 655*s*. **Optical rotation:** $[\alpha]_D^{25}$= –8.7 (c = 0.14, MeOH).

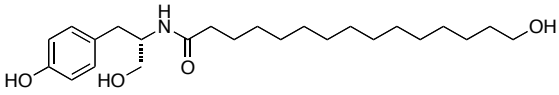
(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)palmitamide (32)



L-Tyrosinol hydrochloride (150 mg, 0.736 mmol, 1.00 equiv.), palmitic acid (189 mg, 0.736 mmol, 1.00 equiv.), EDC (283 mg, 1.472 mmol, 2.00 equiv.), 1H-benzotriazole (149 mg, 1.100 mmol, 1.50 equiv.) and TEA (311mL, 2.208 mmol, 3.00 equiv.) were suspended in MeCN (8.00 mL). The mixture was then stirred under argon at r.t. for 18 h. The solvent was evaporated and the white residue was directly purified by gradiental flash chromatography on SiO_2 (CH_2Cl_2/MeOH 10:1 to 4:1) to yield the product **32** (203 mg, 0.500 mmol, 68%) as white fluffy solid.

$\mathbf{R_f}$ = 0.44 (CH_2Cl_2/MeOH 10:1). **M.P.** = 52 - 55 °C. **^{1}H-NMR** (400 MHz, MeOH) δ 7.04 (m, 2H), 6.68 (m, 2H), 4.05 (dq, *J* = 11.4, 5.6 Hz, 1H), 4.05 (dq, *J* = 11.4, 5.6 Hz, 1H), 3.50 (d, *J* = 5.3 Hz, 2H), 3.40-3.27 (m, 3H), 2.82 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.59 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.68- 1.40 (m, 2H), 1.26 (d, *J* = 24.7 Hz, 25H), 0.90 (t, *J* = 6.8 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOH) δ 176.15, 156.90, 131.21, 130.50, 116.06, 64.36, 54.19, 37.27, 37.15, 33.08, 30.81, 30.77, 30.59, 30.48, 30.20, 27.06, 23.74, 14.44. **HRMS ESI-TOF** calcd. for $C_{25}H_{44}NO_3^+$ (100%, $[M+H]^+$): 406.3316; found; 406.3320. **FTIR** $\tilde{\nu}$ 3485*w*, 3314*w,* 3202*w,* 2918*s*, 2850*s,* 2390*w,* 1636*s,* 1614*w,* 1537*s,* 1515*m,* 1462*m,* 1451*m,* 1380*w,* 1366*w,* 1246*m,* 1224*w,* 1038*s,* 830*m,* 730*w,* 720*w,* 686*m*. **Optical rotation:** $[\alpha]_D^{25}$= –12.8 (c = 0.51, MeOH).

(*S*)-15-hydroxy-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)pentadecanamide (33)

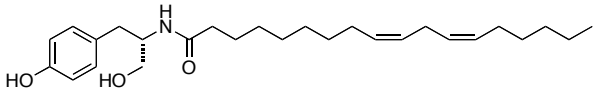


L-Tyrosinol hydrochloride (150 mg, 0.736 mmol, 1.00 equiv.), 15-hydroxypentadecanoic acid (196 mg, 0.736 mmol, 1.00 equiv.), EDC (283 mg, 1.472 mmol, 2.00 equiv.), 1H-benzotriazole (149 mg, 1.100 mmol, 1.50 equiv.) and TEA (311 μL, 2.208 mmol, 3.00 equiv.)

were suspended in MeCN (8.00 mL). The mixture was then stirred under argon at to r. t. for 16 h. The solvent was evaporated and the white residue was directly purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 2:1) followed by a recrystallization (pentane/acetone 4:1) to yield the product **33** (188 mg, 0.461 mmol, 63%) as white solid.

R_f = 0.43 (CH_2Cl_2/MeOH 10:1). **M.P.** = 40 - 43 °C. **^{1}H-NMR** (400 MHz, MeOD) δ 7.07 - 7.00 (m, 2H), 6.74 - 6.65 (m, 2H), 4.04 (dt, *J* = 11.3, 5.6 Hz, 1H), 3.58 - 3.46 (m, 4H), 2.82 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.59 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.12 (t, *J* = 7.5 Hz, 2H), 1.58 - 1.41 (m, 4H), 1.39 - 1.00 (m, 20H). **^{13}C-NMR** (101 MHz, MeOD) δ 176.14, 156.89, 131.20 (2C), 130.50, 116.06 (2C), 64.37, 63.02, 54.20, 37.27, 37.15, 33.68, 30.79, 30.77 (2C), 30.75 (2C), 30.62, 30.59, 30.48, 30.19, 27.07, 26.96. **HRMS ESI-TOF** calcd. for $C_{24}H_{42}NO_4^+$ (100%, $[M+H]^+$): 408.3108; found; 408.3108. **FTIR** $\tilde{\nu}$ 3451*w*, 3301*m*, 3027*w*, 2920*s*, 2848*s*, 1638*s*, 1556*s*, 1514*s*, 1459*s*, 1421*w*, 1377*m*, 1343*w*, 1313*w*, 1271*m*, 1238*s*, 1175*w*, 1083*w*, 1048*s*, 1026*w*, 952*w*, 852*w*, 816*w*, 778*w*, 726*m*. **Optical rotation:** $[\alpha]_D^{25}$= –13.3 (c = 0.26, MeOH).

(9*Z*,12*Z*)-*N*-((*S*)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)octadeca-9,12-dienamide (BSL34)

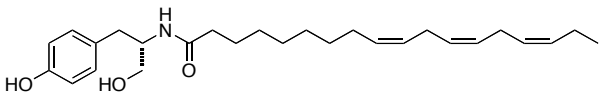


Linoleic acid (50 mg, 0.178 mmol, 1.00 equiv.), DCC (73.6 mg, 0.357 mmol, 2.00 equiv.) and pentafluorophenol (49.2 mg, 0.267 mmol, 1.50 equiv.) were suspended in DMF (4.00 mL). The mixture was stirred under argon at 60 °C for 18 h. Then L-tyrosinol hydrochloride (38.8 mg, 0.214 mmol, 1.20 equiv.) and TEA (75 mL, 0.535 mmol, 3.00 equiv.) were added and the mixture was stirred at room temperature for 30 h. The reaction mixture was concentrated and directly purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 20:1) without extraction to yield the product **BSL34** (22 mg, 0.461 mmol, 63%) as white solid.

R_f = 0.65 (MeOH/$CH_2Cl_2$1:20). **M.P.** = 52 - 55 °C. **^{1}H-NMR** (400 MHz, MeOD) δ 7.04 (m, 2H), 6.69 (m, 2H), 5.44 - 5.25 (m, 4H), 4.05 (tt, *J* = 11.3, 5.6 Hz, 1H), 3.50 (d, *J* = 5.4 Hz, 2H), 2.88 - 2.72 (m, 3H), 2.59 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.15 - 2.02 (m, 6H), 1.56 - 1.45 (m, 2H), 1.42 - 1.15 (m, 14H), 0.90 (t, *J* = 6.8 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ 176.12, 156.90, 131.21, 130.94, 130.50, 129.07, 129.06, 116.07, 64.36, 54.19, 37.26, 37.15, 32.66, 30.77, 30.48, 30.38, 30.23, 30.18, 28.18, 28.16, 27.06, 26.54, 23.63, 14.43. **HRMS ESI-TOF**

calcd. for $C_{27}H_{44}NO_3^+$ (100%, $[M+H]^+$): 430.3316; found; 430.3316. **FTIR** $\tilde{\nu}$ 3491*w,* 3317*m*, 3186*w*, 3010*w*, 2923*m*, 2853*m*, 1642*s*, 1614*w*, 1534*s*, 1515*s*, 1462*m*, 1447*m*, 1384*w*, 1363*w*, 1246*m*, 1220*s*, 1113*w*, 1053*m*, 1036*s*, 954*w*, 823*w*, 724*w*, 680*m*. **Optical rotation:** $[\alpha]_D^{25} = -12.8$ (c = 0.21, MeOH).

(9*Z*,12*Z*,15*Z*)-*N*-((*S*)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)octadeca-9,12,15-trienamide (35)



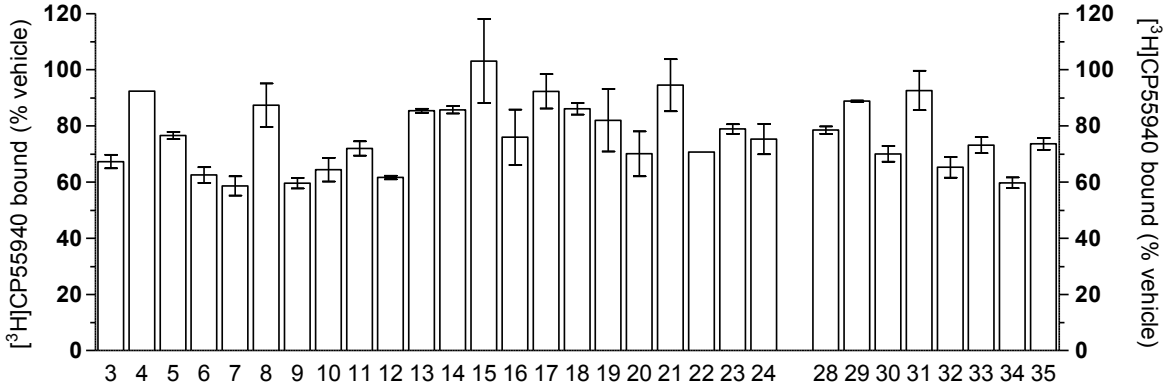
Linolenic acid (55 mg, 0.198 mmol, 1.00 equiv.), DCC (81.5 mg, 0.395 mmol, 2.00 equiv.) and pentafluorophenol (54.5 mg, 0.296 mmol, 1.50 equiv.) were suspended in DMF (4.00 mL). The mixture was stirred under argon at r.t. for 48 h. Then L-tyrosinol hydrochloride (50 mg, 0.277 mmol, 1.40 equiv.) and TEA (83 mL, 0.593 mmol, 3.00 equiv.) were added and the mixture was stirred at r.t. for 20 h. The reaction mixture was concentrated, diluted with water and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $NaSO_4$ and concentrated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 50:1) yielded the product **35** (49 mg, 0.111 mmol, 56%) as white solid.

$\mathbf{R_f}$ = 0.50 (CH_2Cl_2/EtOAc 8:2). **M.P.** = 70 - 72 °C. **^{1}H-NMR** (400 MHz, MeOD) δ 7.03 (m, 2H), 6.69 (m, 2H), 5.45 - 5.23 (m, 6H), 4.05 (tt, *J* = 11.3, 5.6 Hz, 1H), 3.50 (d, *J* = 5.4 Hz, 2H), 2.91 - 2.72 (m, 5H), 2.59 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.17 - 1.99 (m, 6H), 1.55 - 1.45 (m, 2H), 1.41 - 1.12 (m, 8H), 0.97 (t, *J* = 7.5 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ 176.09, 156.88, 132.71, 131.19, 131.12, 130.48, 129.21, 129.18, 128.79, 128.23, 116.06, 64.35, 54.18, 37.26, 37.15, 30.75, 30.37, 30.22, 30.18, 28.19, 27.06, 26.52, 26.40, 21.49, 14.66. **HRMS ESI-TOF** calcd. for $C_{27}H_{41}NNaO_3^+$ (100%, $[M+Na]^+$): 450.2979; found; 450.2979. **FTIR** $\tilde{\nu}$ 3491*w*, 3317*m*, 3182*w*, 3007*w*, 2927*m*, 2876*w*, 2852*w*, 1641*s*, 1614*w*, 1600*w*, 1533*s*, 1516*s*, 1448*m*, 1389*m*, 1363*m*, 1305*w*, 1248*m*, 1219*m*, 1114*w*, 1079*w*, 1054*m*, 1037*s*, 955*w*, 935*w*, 861*w*, 844*w*, 823*m*, 771*m*, 714*m*, 679*w*. **Optical rotation:** $[\alpha]_D^{25} = -12.9$ (c = 0.24, MeOH).

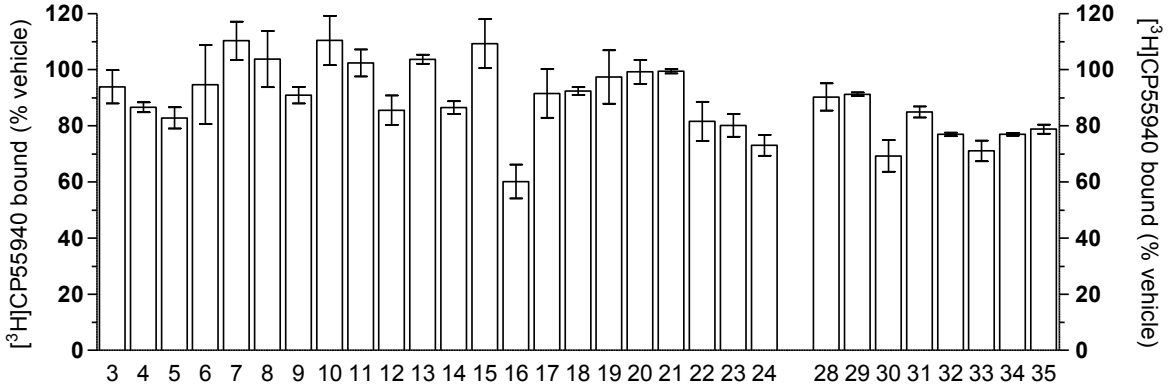
III. Additional Figure:

To obtain the biological data (see below) already established procedures were followed.[7]

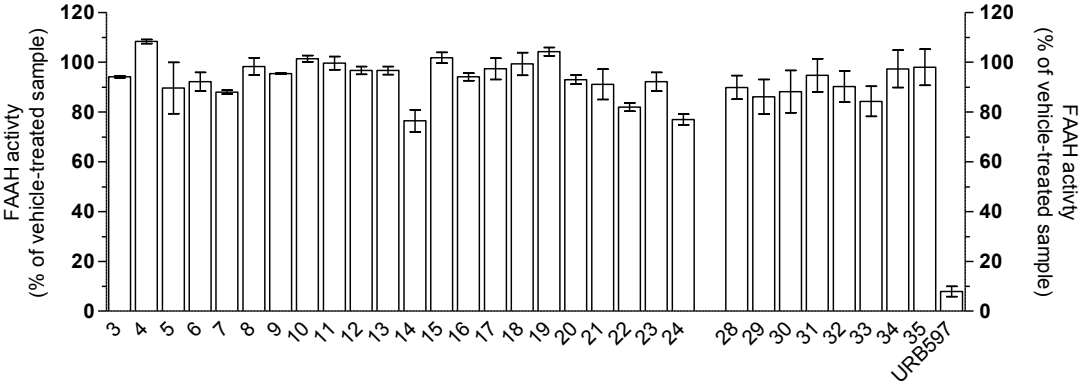
SI Figure 1A. CB_1 receptor binding at 1 μM, **34** = **BSL34**, n=2, each in triplicates, mean ± SD



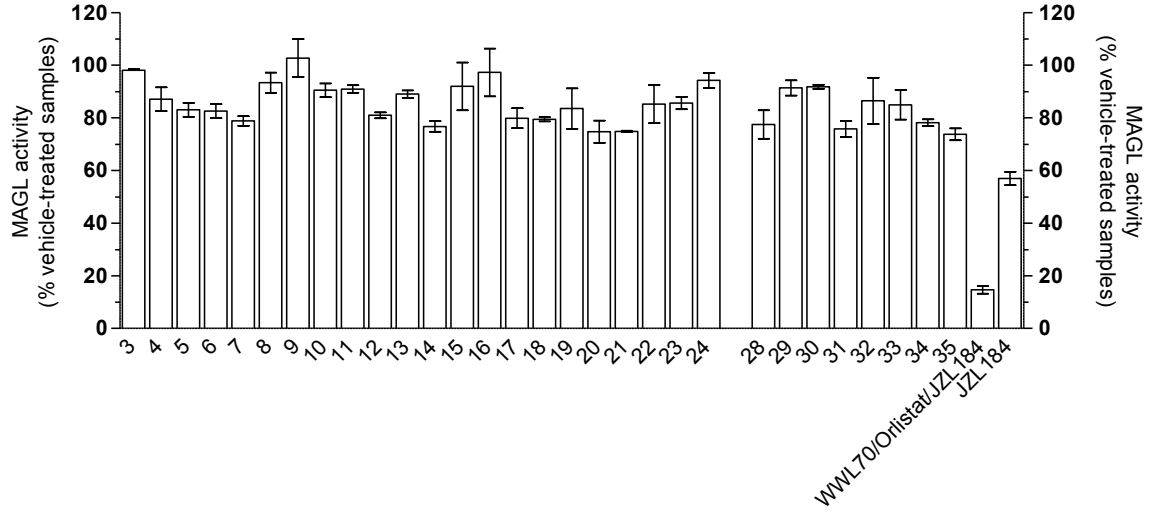
SI Figure 1B. CB_2 receptor binding at 1 μM, n=2, each in triplicates, mean ± SD



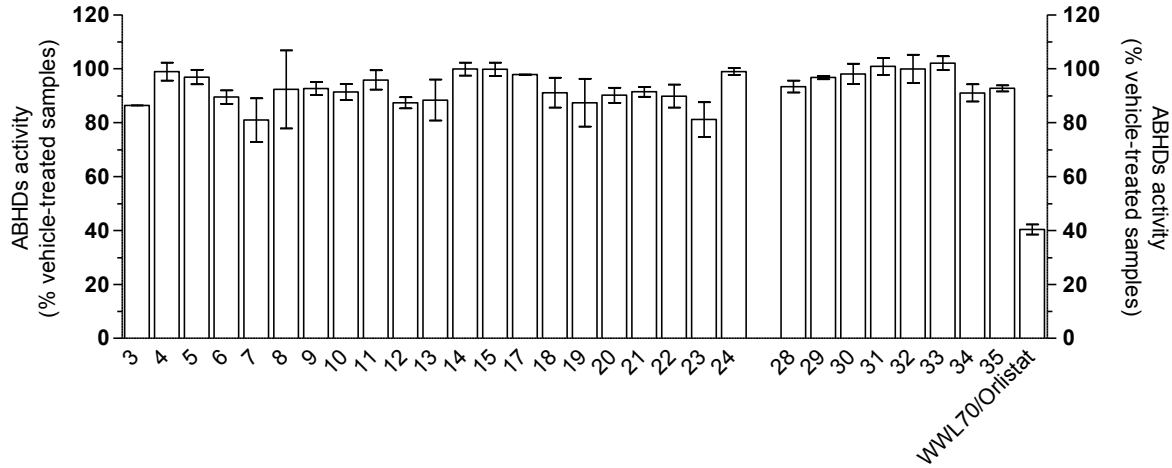
SI Figure 2. FAAH activity at 1 μM, positive control is URB597 1 μM. n=2, each in triplicates mean ± SD



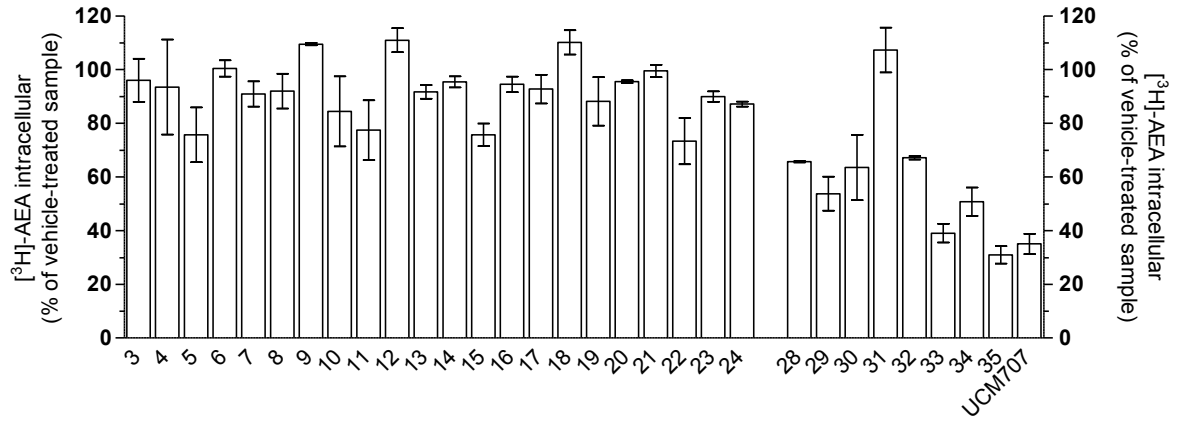
SI Figure 3A. MAGL activity at 1 μM, positive controls for ABHD-6, ABHD-12 and MAGL are WWL70 10 μM, Orlistat 20 μM, JZL184 10 μM, respectively. n=2, each in triplicates, mean ± SD



SI Figure 3B. ABHDs activity at 10 μM, positive controls for ABHD-6 and ABHD-12 WWL70 10 μM, Orlistat 20 μM, respectively. n=2, each in triplicates, mean ± SD



SI Figure 4. EMT activity at 10 μM, positive control UCM707 10 μM. n=2, each in triplicates, mean ± SD



IV. References

(1) Jessen, H. J.; Barbaras, D.; Hamburger, M.; Gademann, K. *Org. Lett.* **2009**, *11*, 3446–3449.

(2) Sellergren, B.; Anderson, L. *J. Org. Chem.* **1990**, *55*, 3381–3383.

(3) Gershon, H.; Rodin, R. *J. Med. Chem.* **1965**, *8*, 864–866.

(4) Imming, P.; Jung, M.-H. *Archiv der Pharmatie*, **1995**, *1*, 87–91.

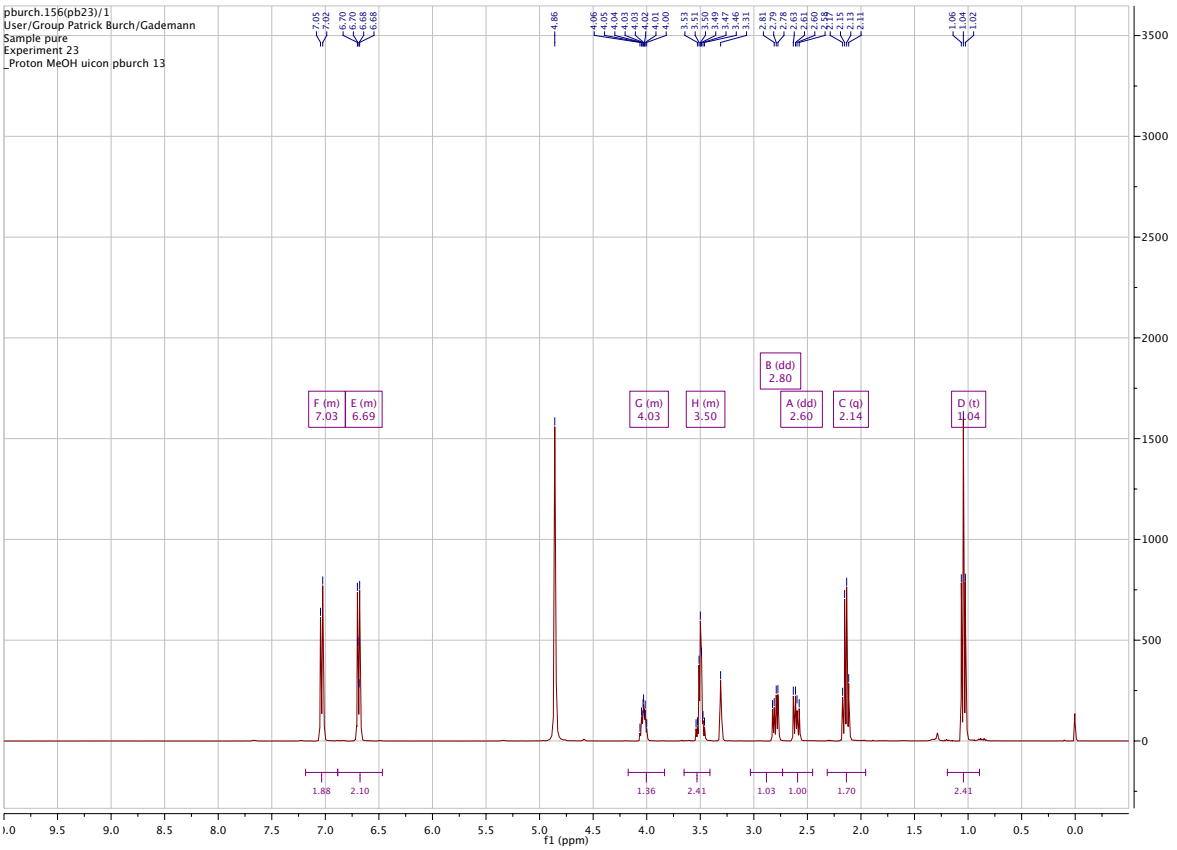
(5) Seki, H.; Koga, K.; Yamada, *Chem. Pharm. Bull.* **2013**, *12*, 1948–1954.

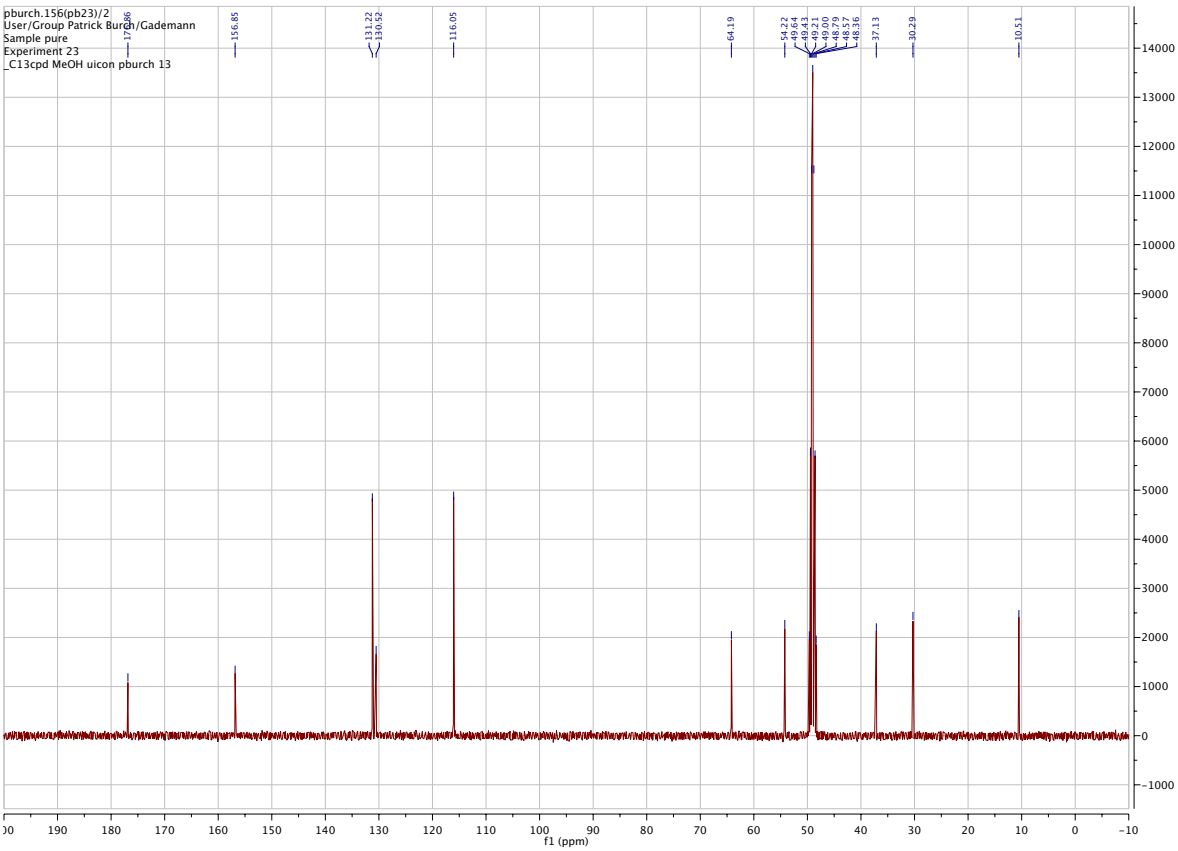
(6) Ueda, K.; Yoshihara, M.; Nakao, M.; Tanaka, T. *J. Agric. Food Chem.* **2010**, *58*, 6053–6063.

(7) Chicca, A.; Marazzi, J.; Nicolussi, S.; Gertsch, J. *J. Biological Chem.* **2012**, *287*, 34660–34682.

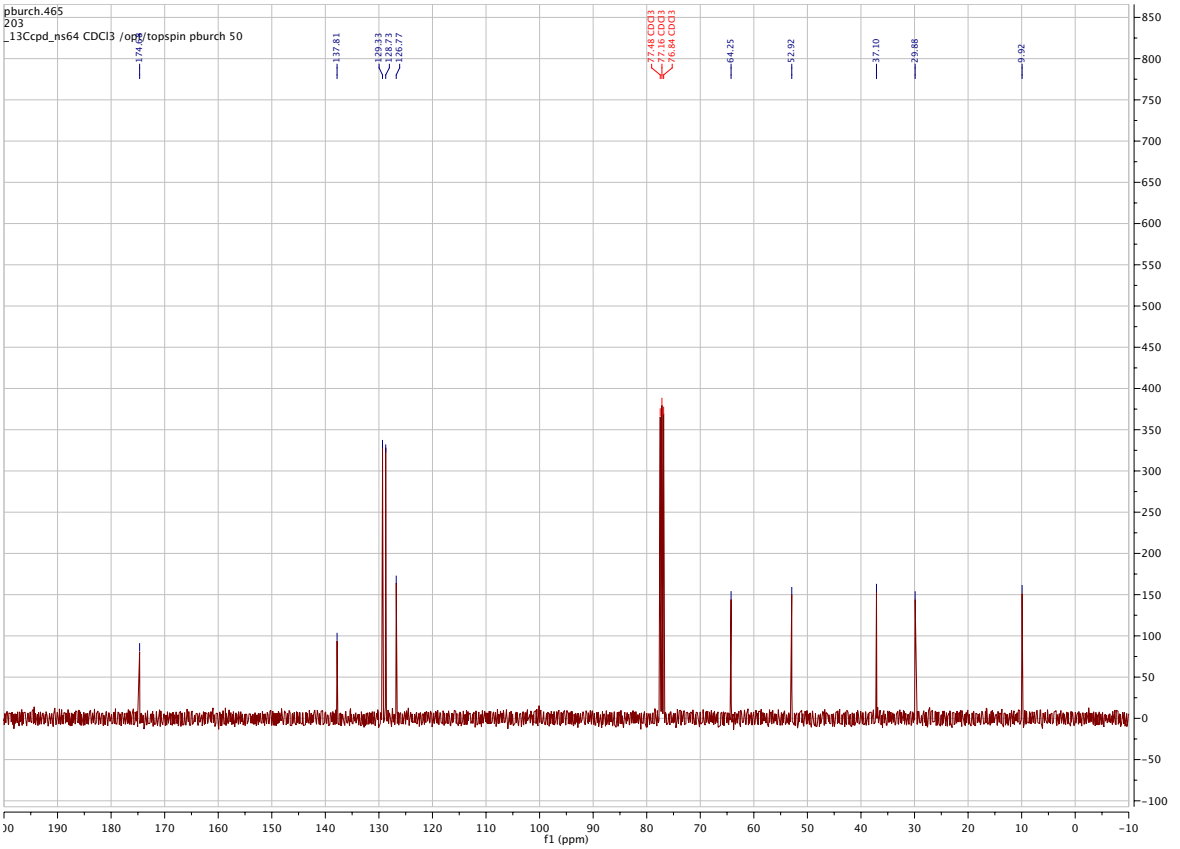
V. NMR Spectra

(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)propionamide (4)

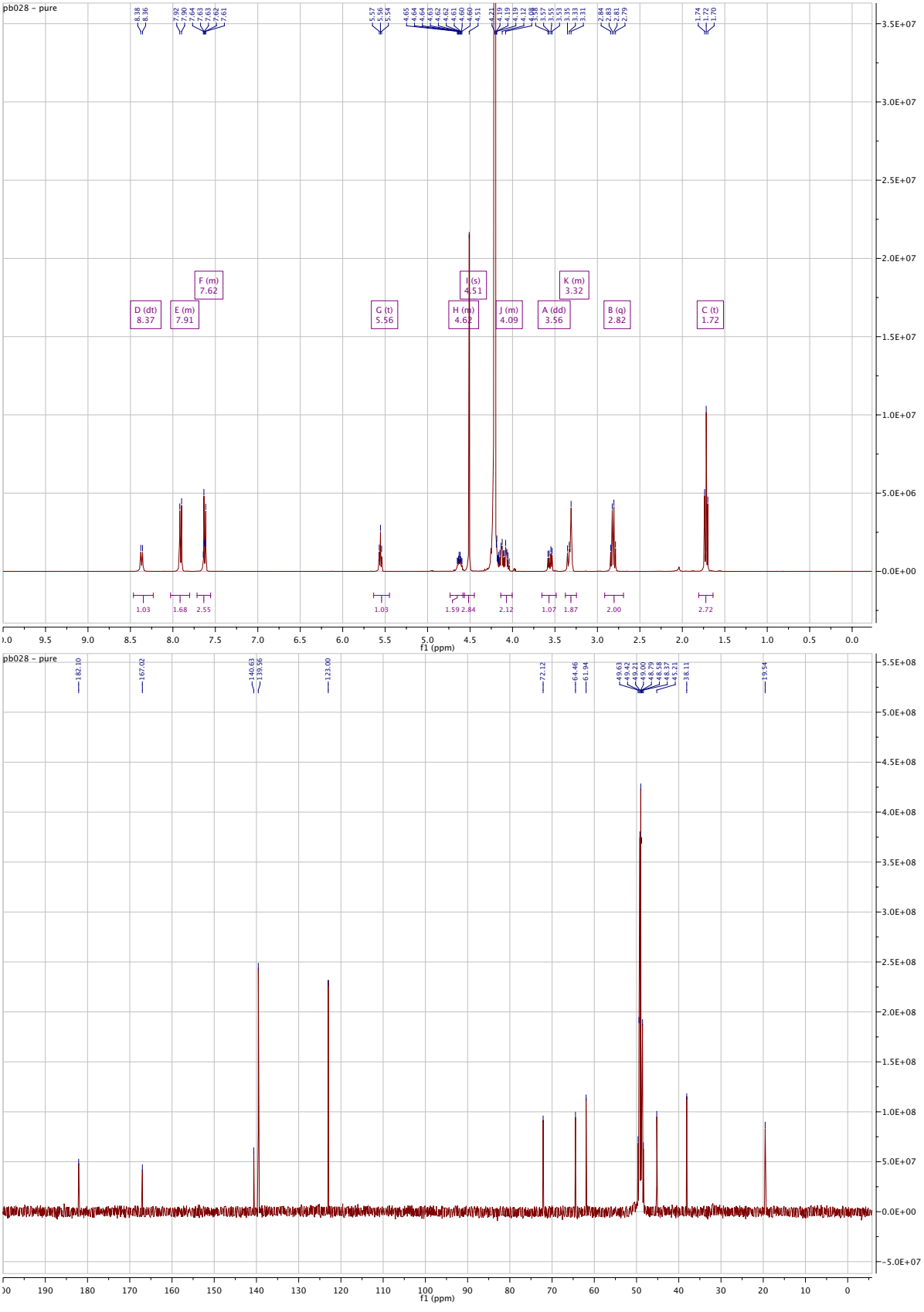




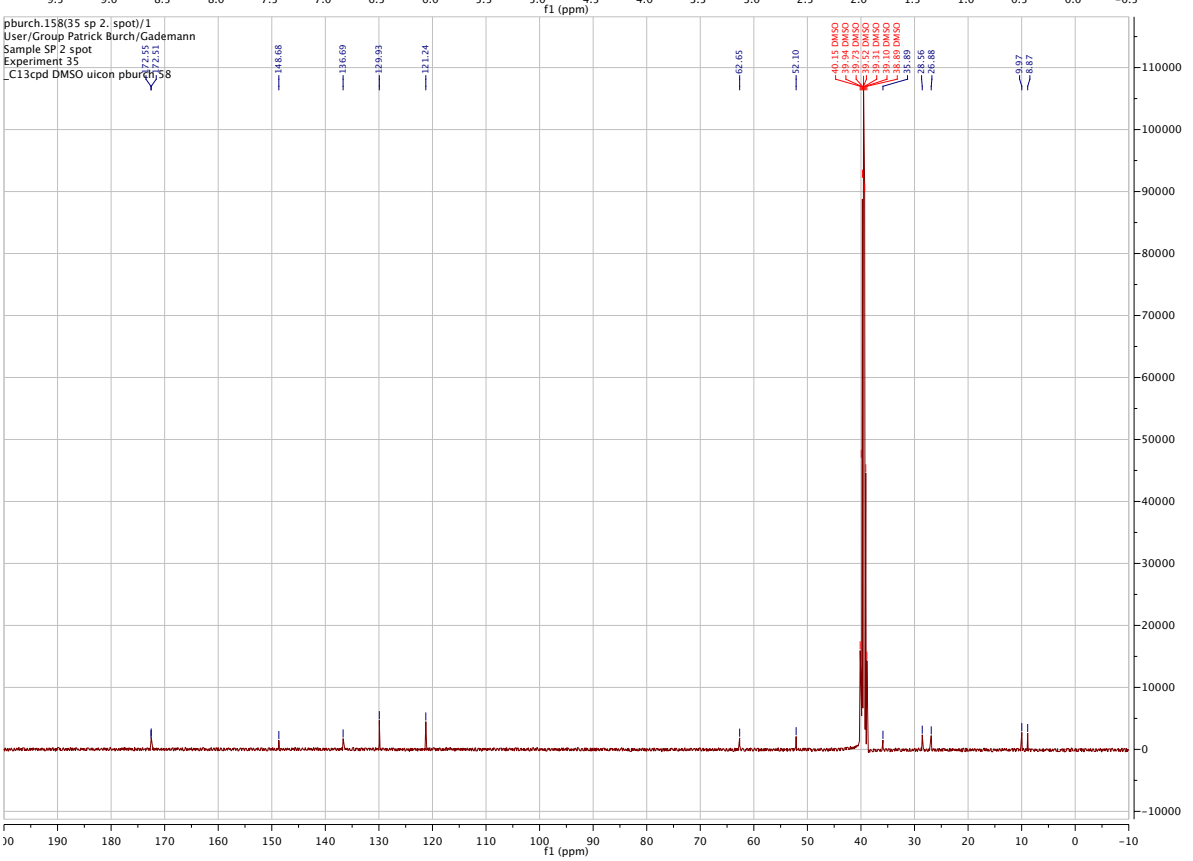
(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)propionamide (5)



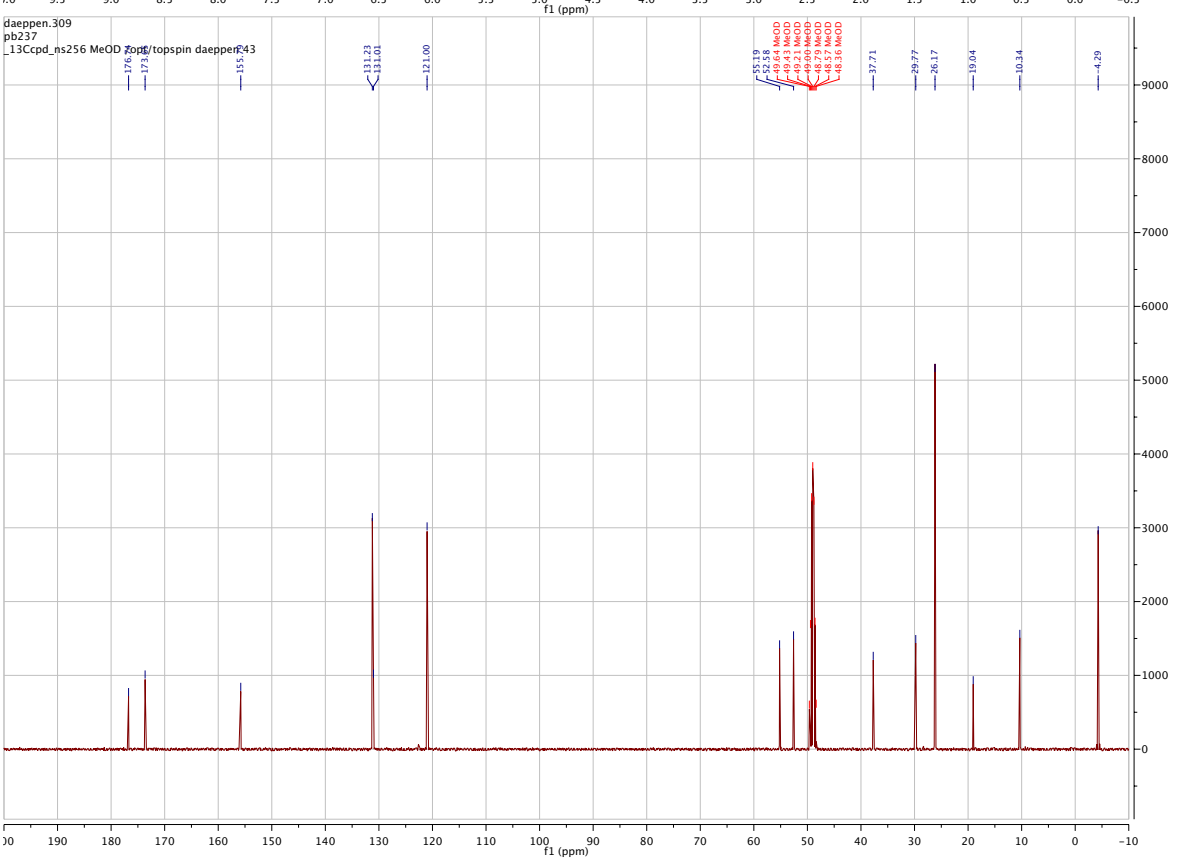
(*S*)-*N*-(1-hydroxy-3-(4-methoxyphenyl)propan-2-yl)propionamide (6)



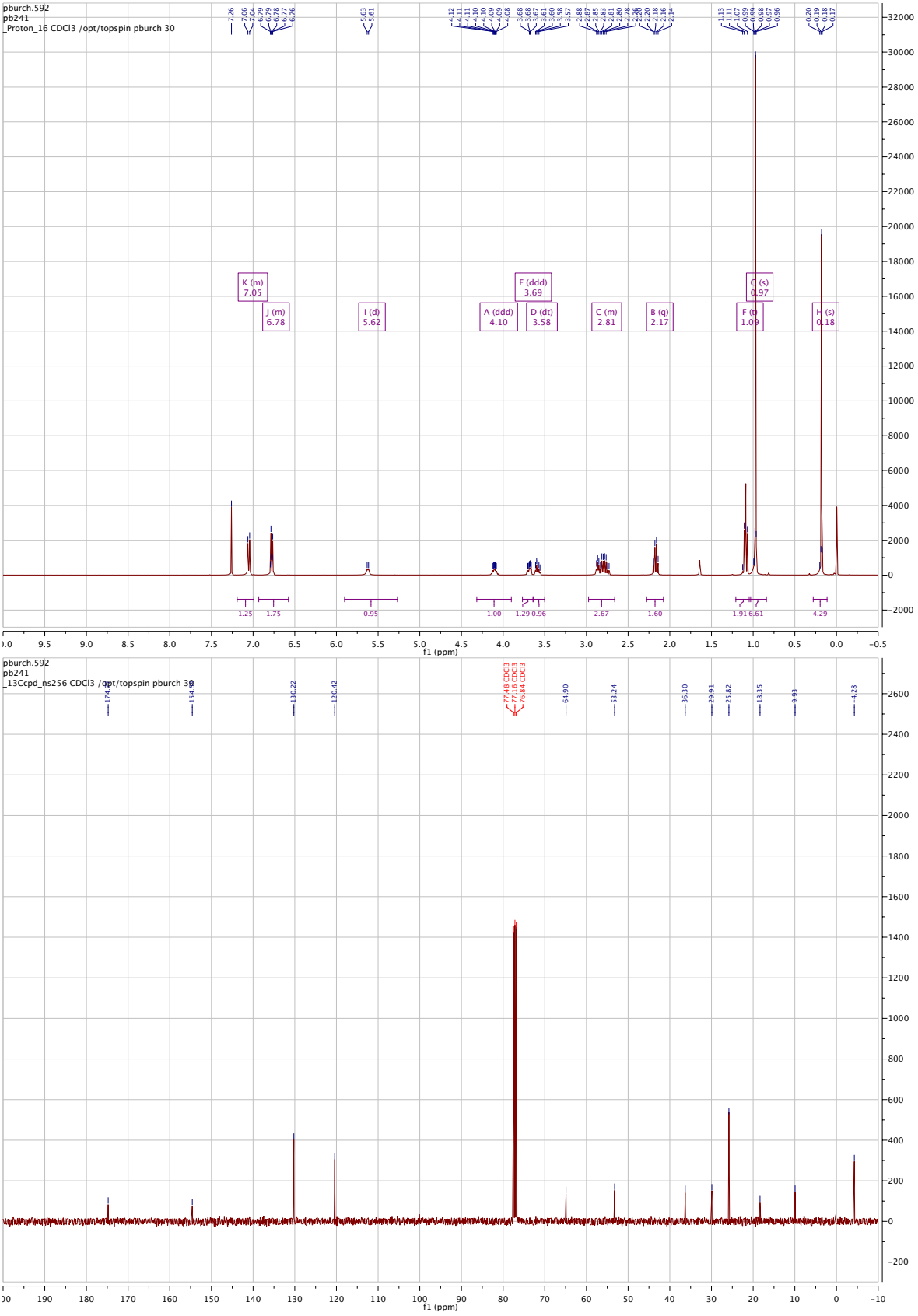
(*S*)-4-(3-hydroxy-2-propionamidopropyl)phenyl propionate (7)



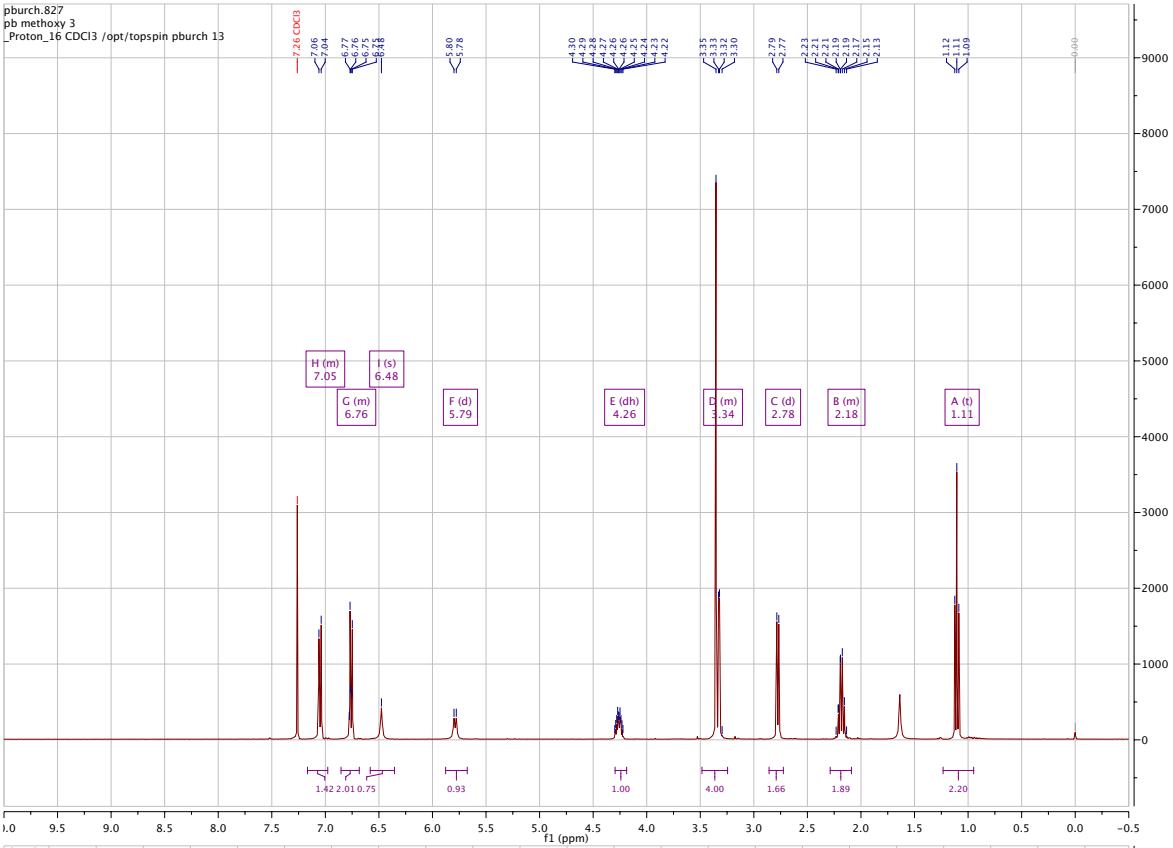
(*S*)-*N*-(1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-3-hydroxypropan-2-yl)propionamide (I)

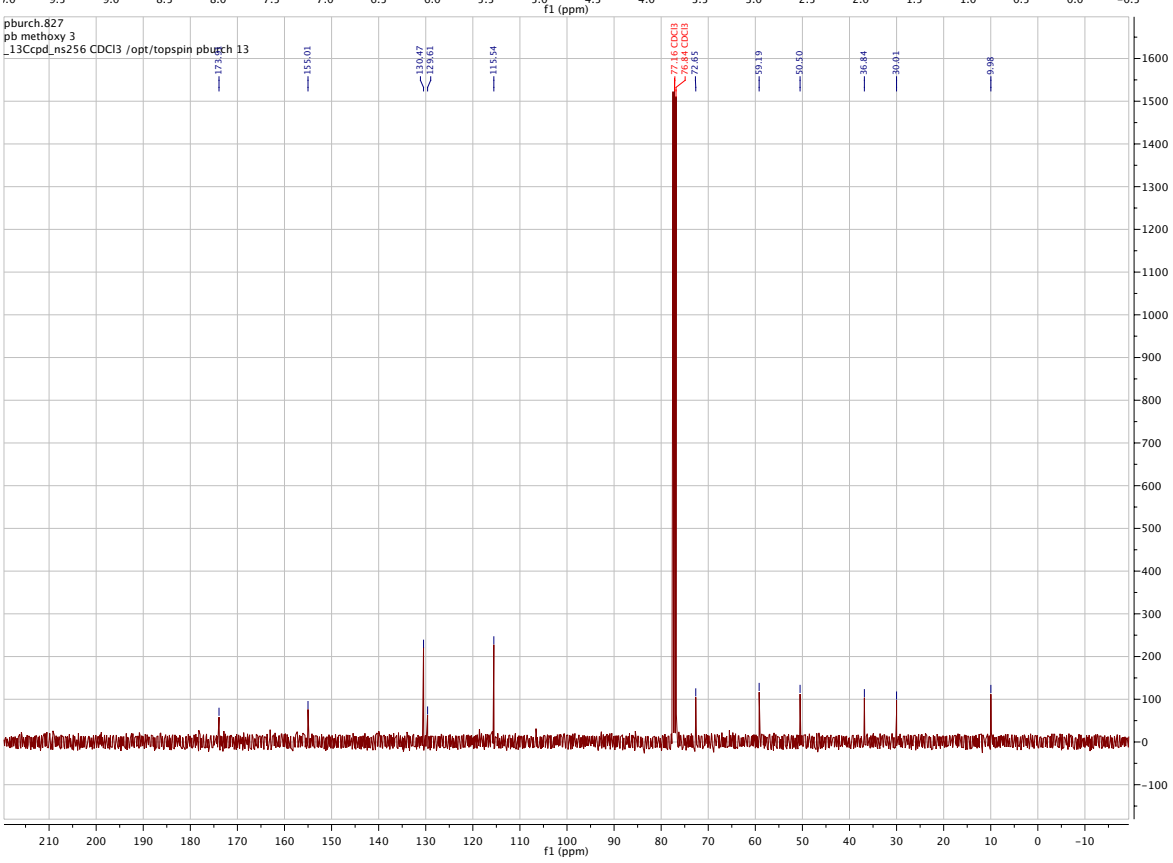


(*S*)-methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-propionamidopropanoate (II)

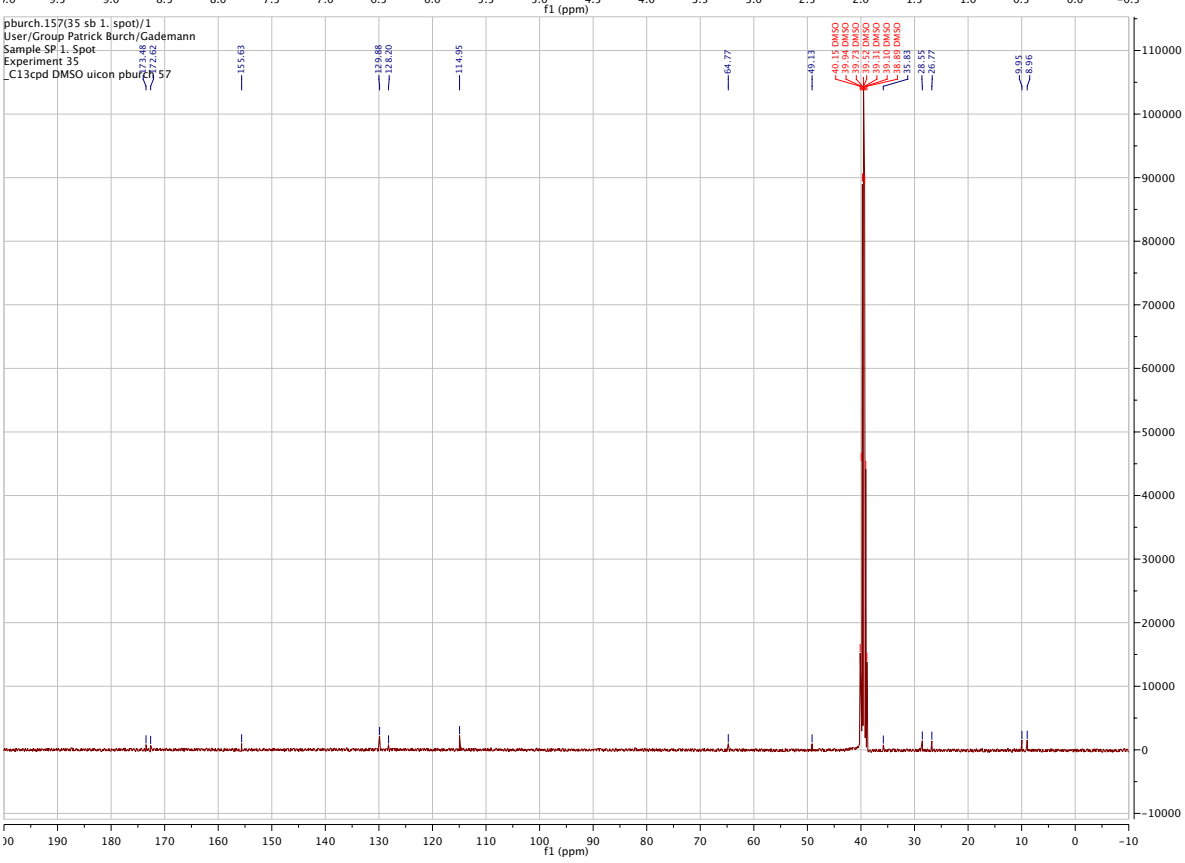


(*S*)-*N*-(1-(4-hydroxyphenyl)-3-methoxypropan-2-yl)propionamide (8)

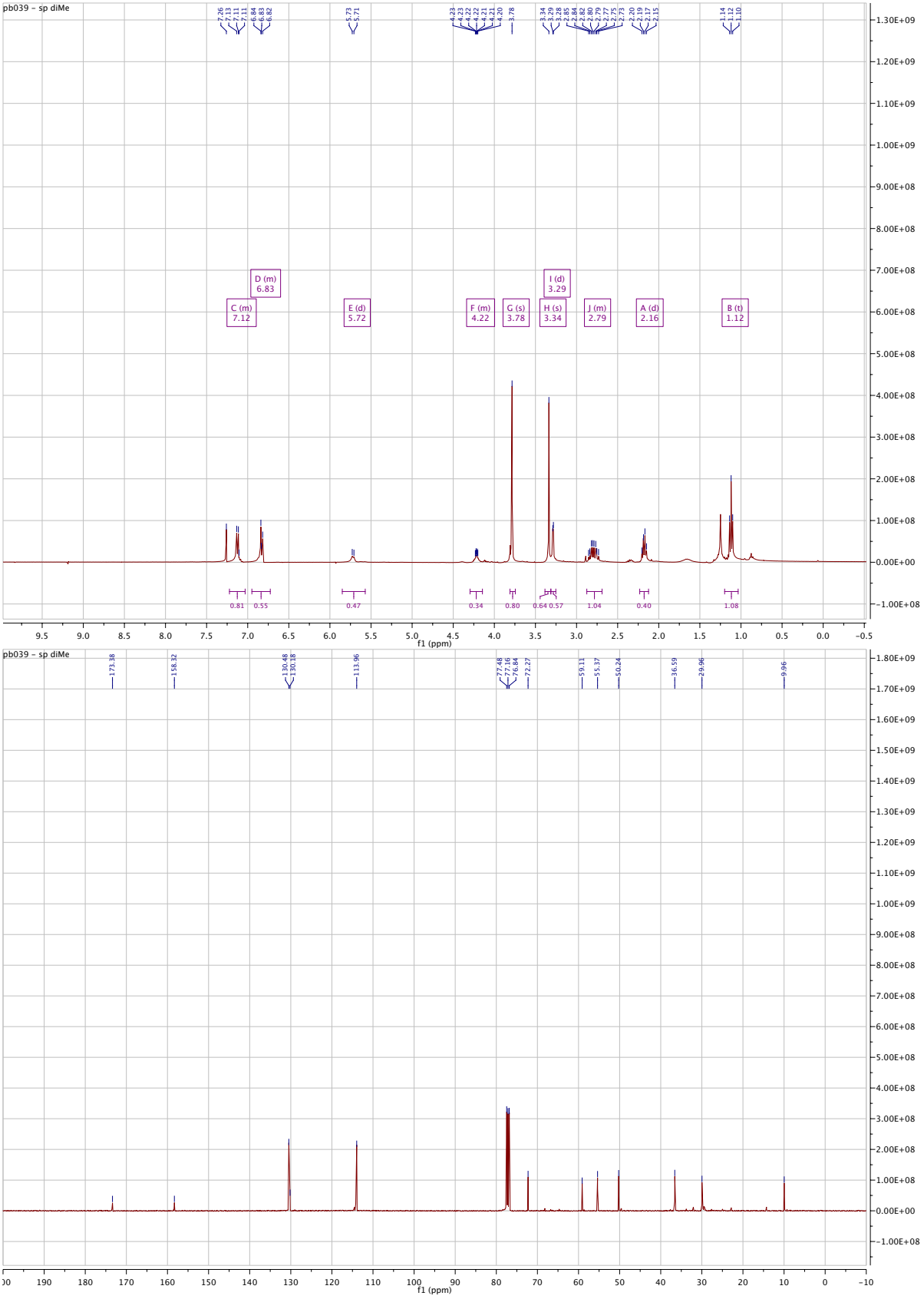




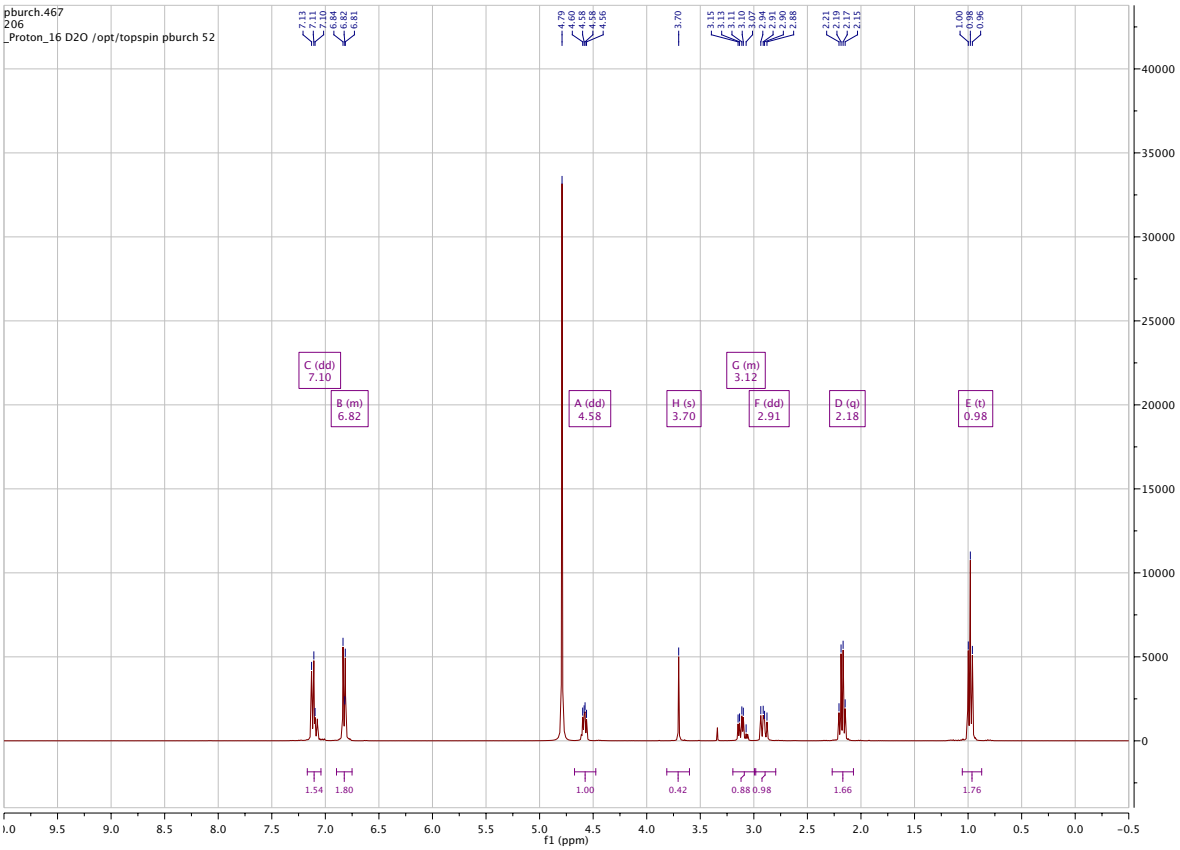
(*S*)-3-(4-hydroxyphenyl)-2-propionamidopropyl propionate (9)

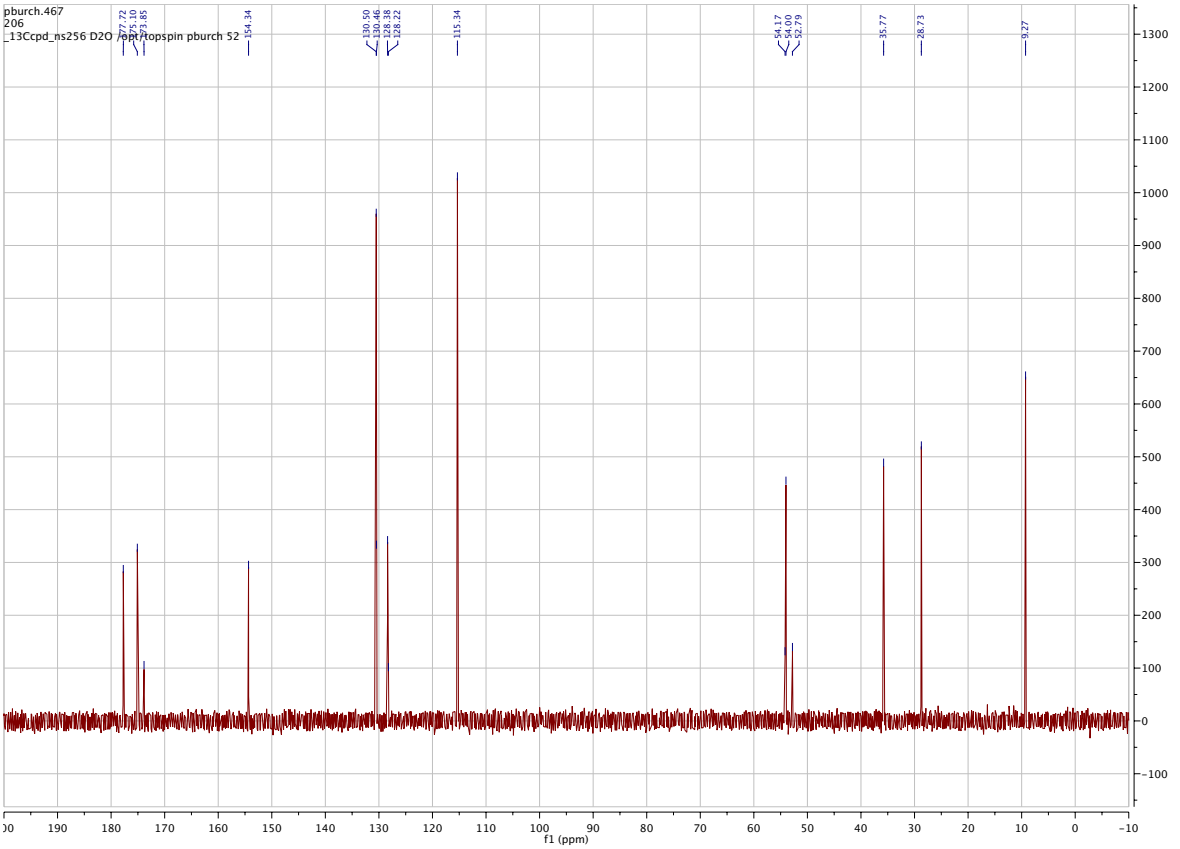


(*S*)-*N*-(1-methoxy-3-(4-methoxyphenyl)propan-2-yl)propionamide (10)

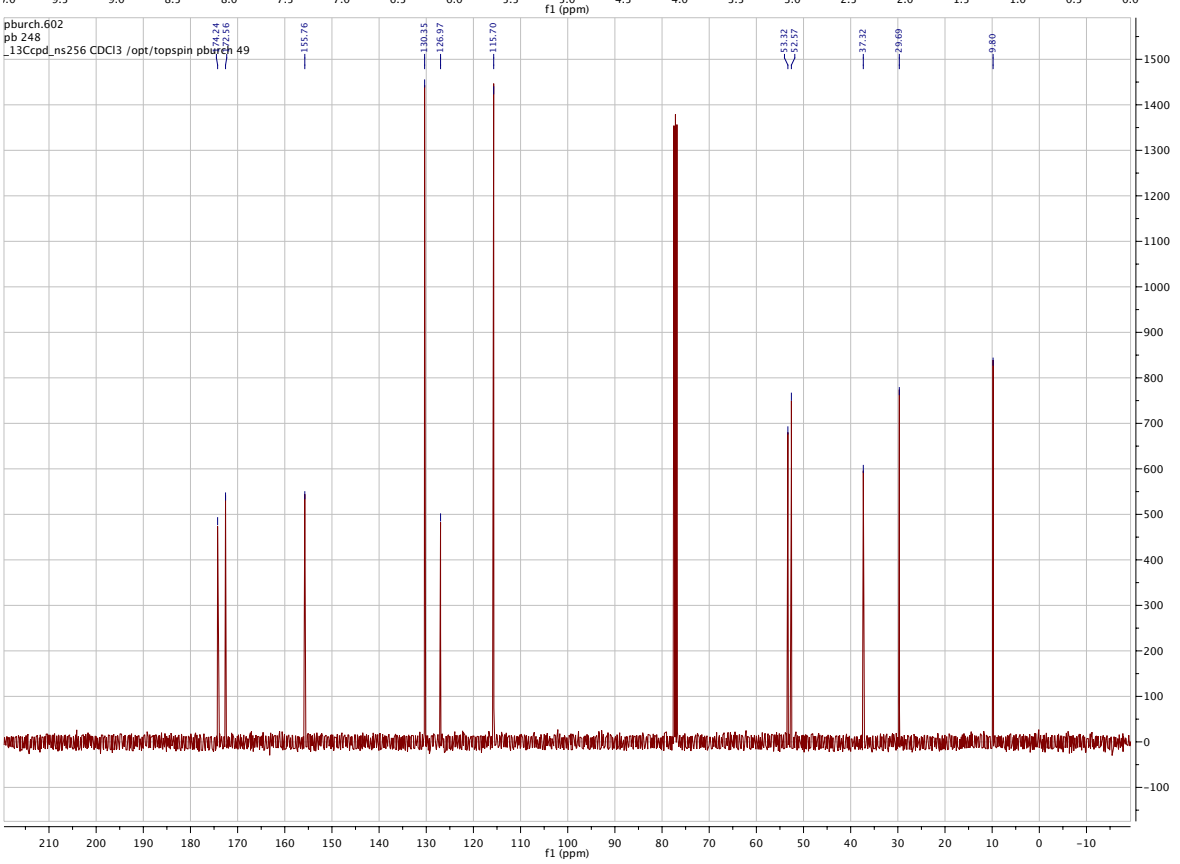


(*S*)-3-(4-hydroxyphenyl)-2-propionamidopropanoic acid (11)

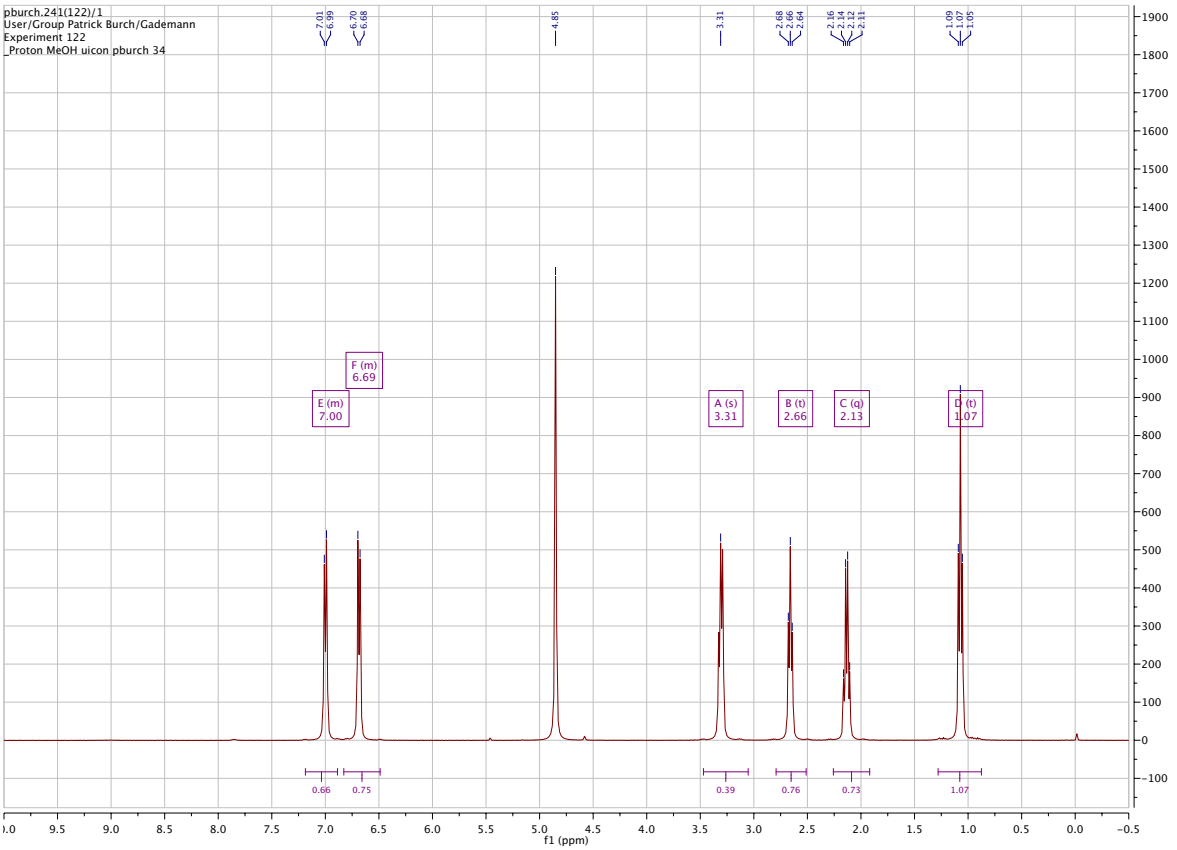


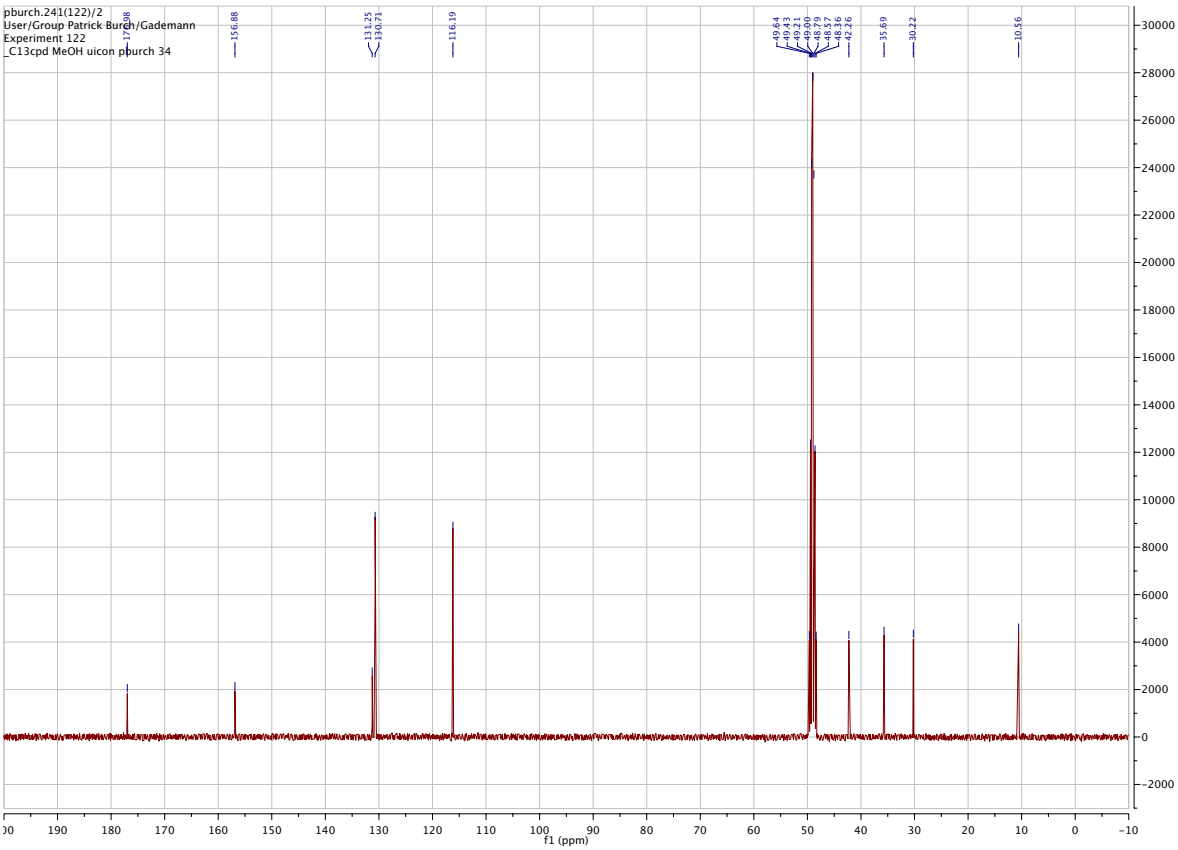


(*S*)-methyl 3-(4-hydroxyphenyl)-2-propionamidopropanoate (12)

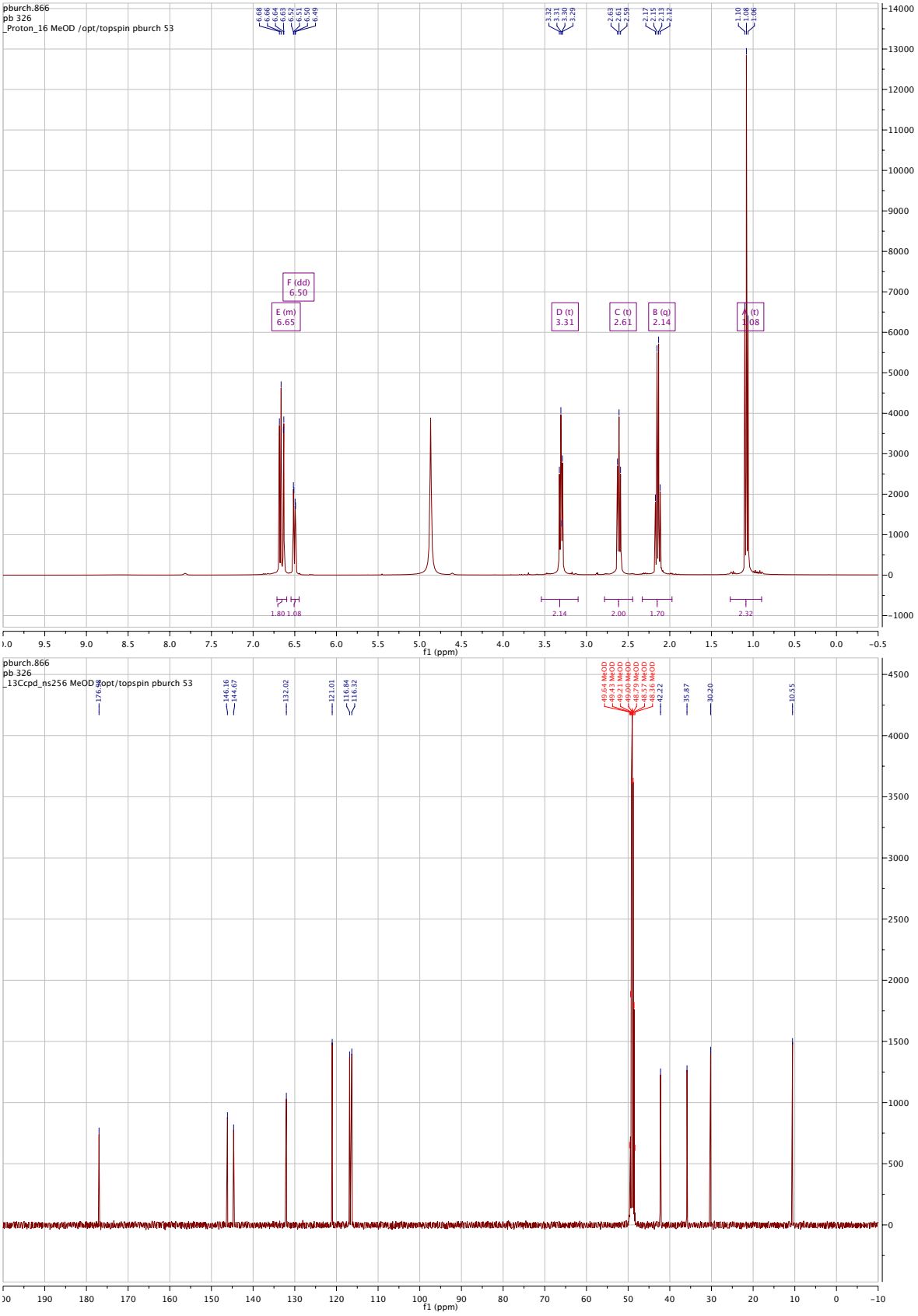


N-(4-hydroxyphenethyl)propionamide (14)

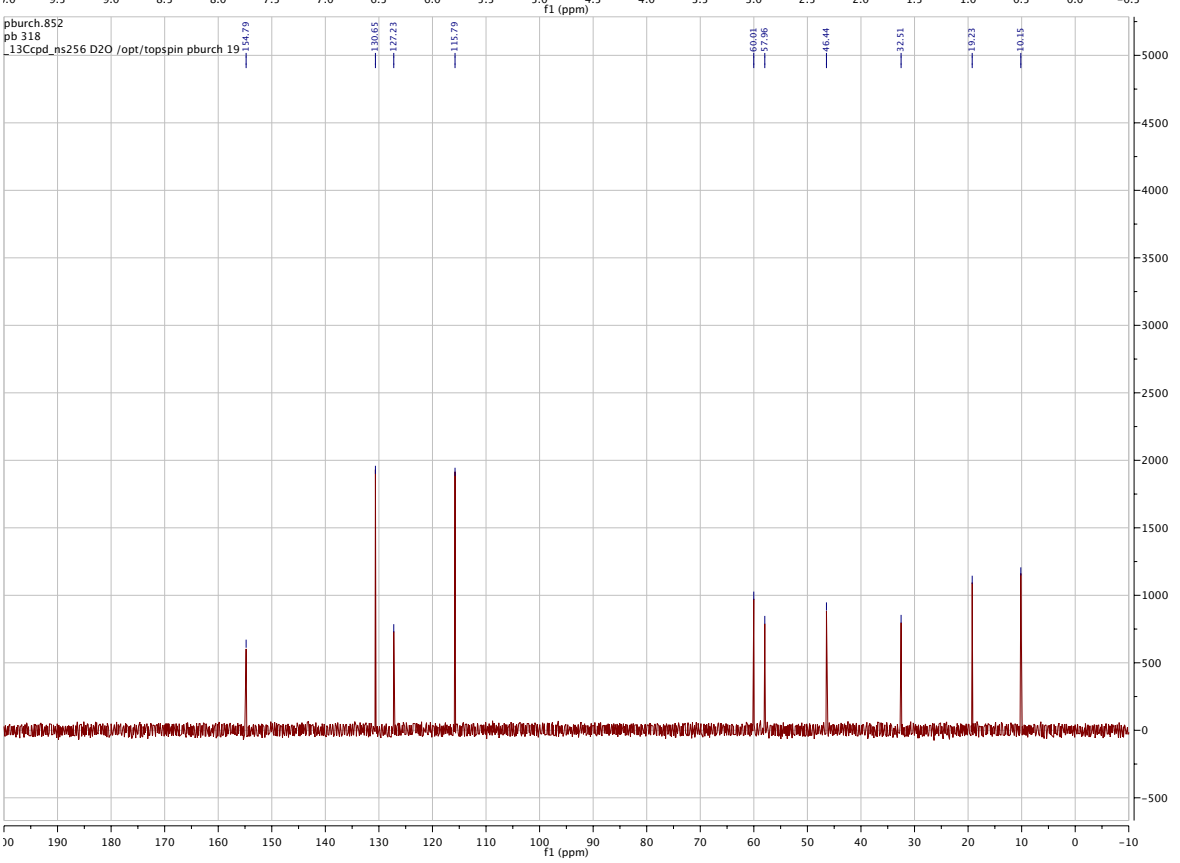




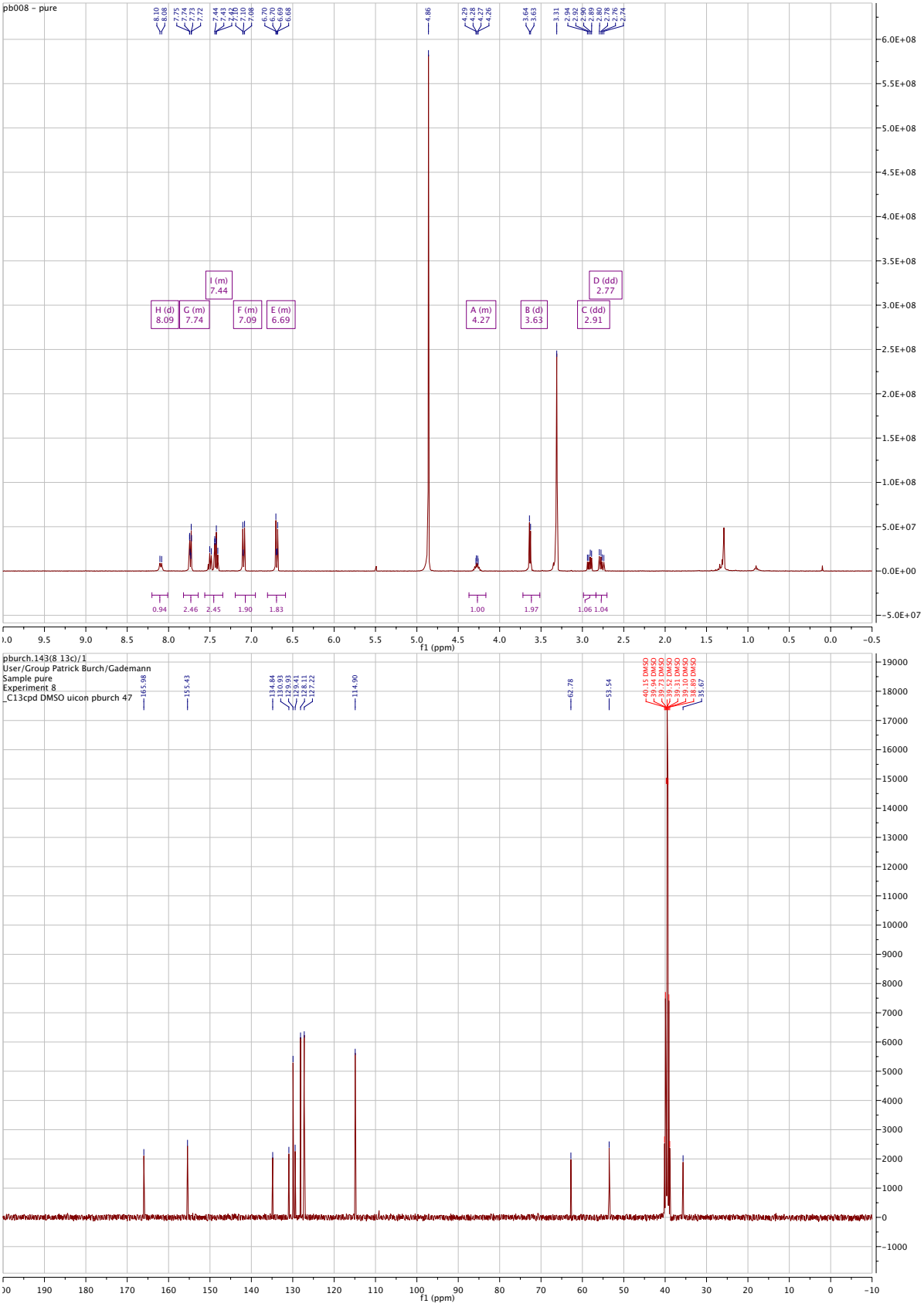
N-(3,4-dihydroxyphenethyl)propionamide (15)



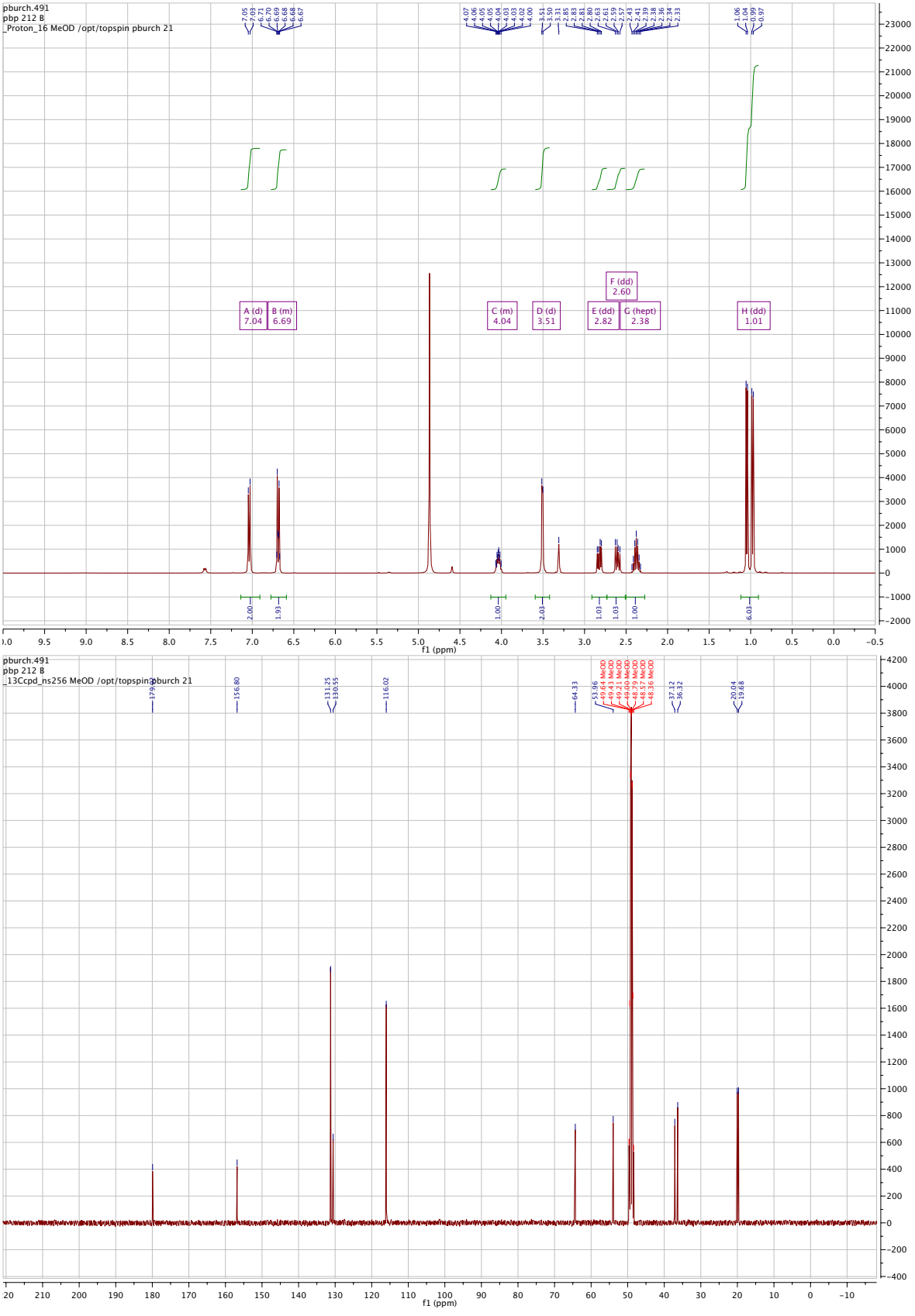
(*S*)-4-(3-hydroxy-2-(propylamino)propyl)phenol (16)



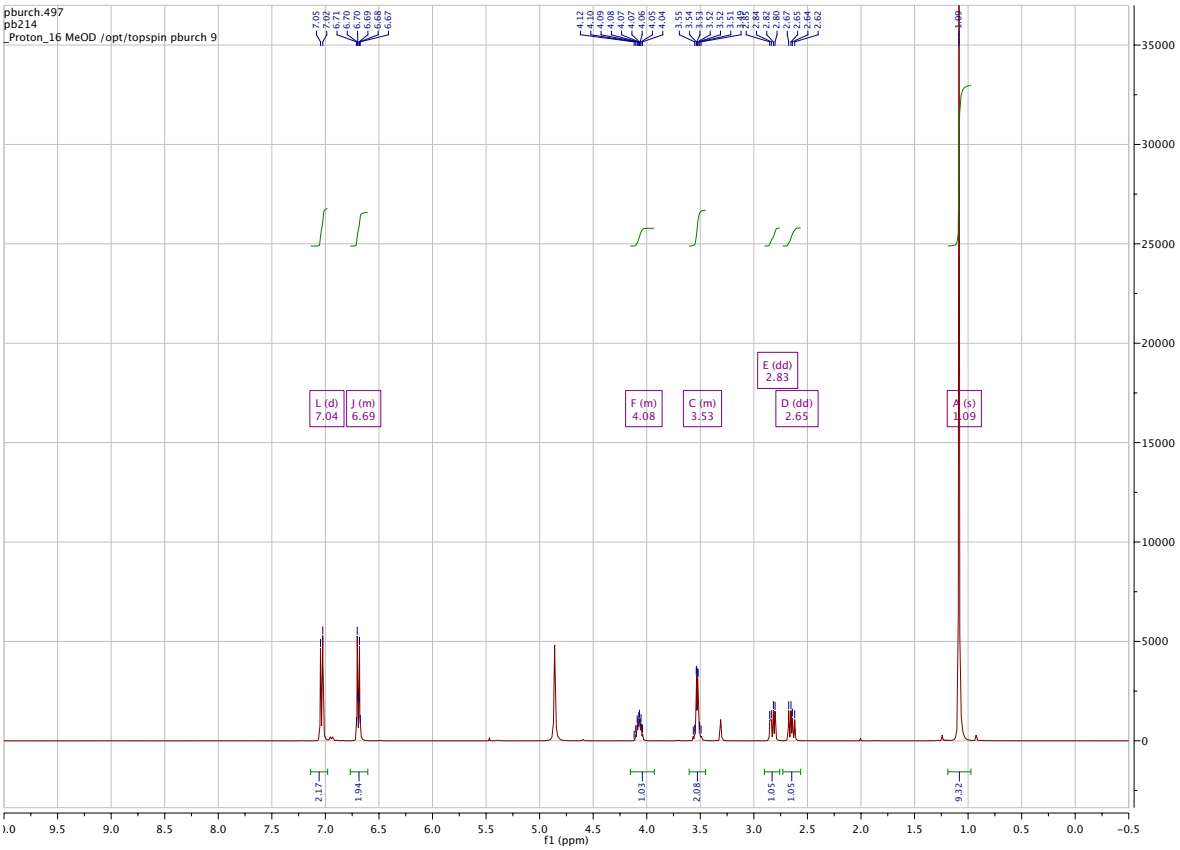
(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)benzamide (17)

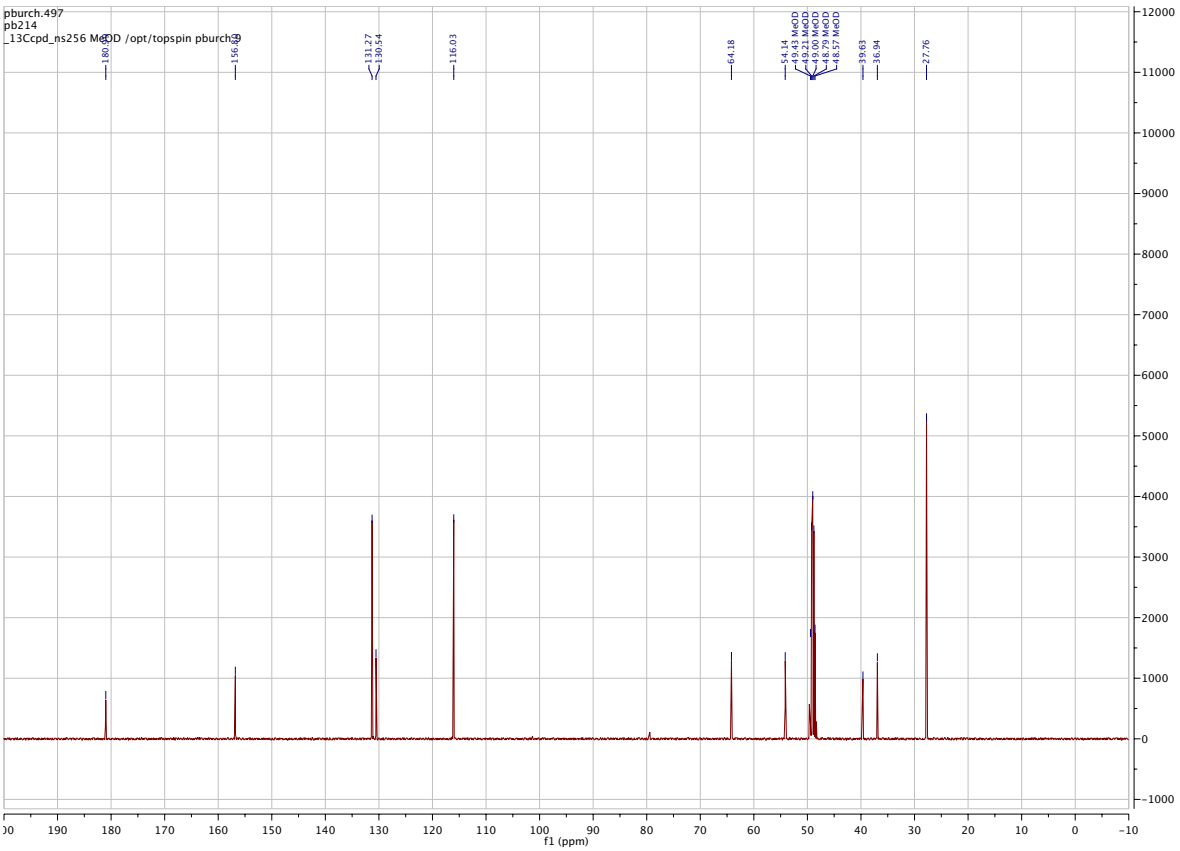


(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)isobutyramide (18)

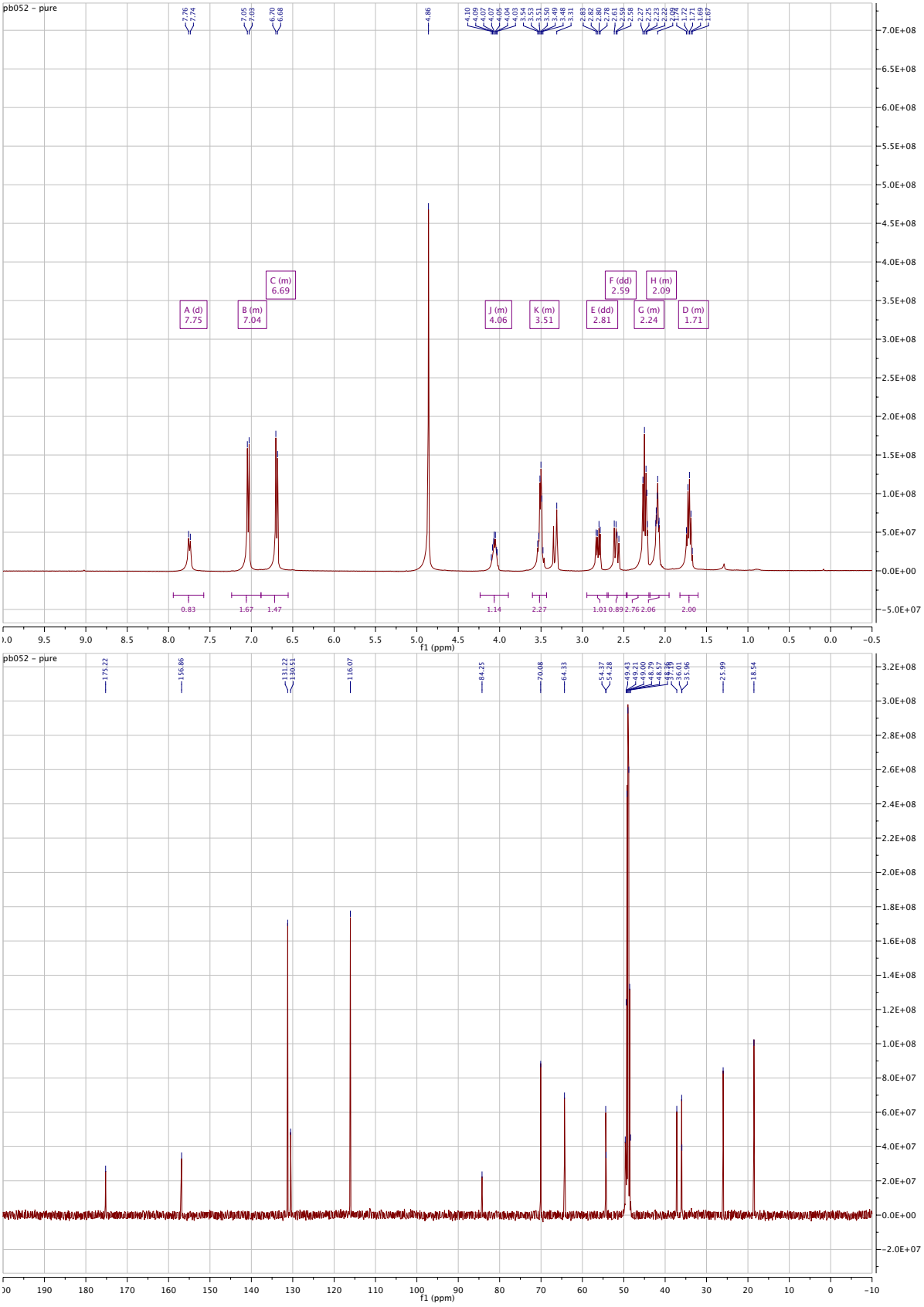


(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)pivalamide (19)

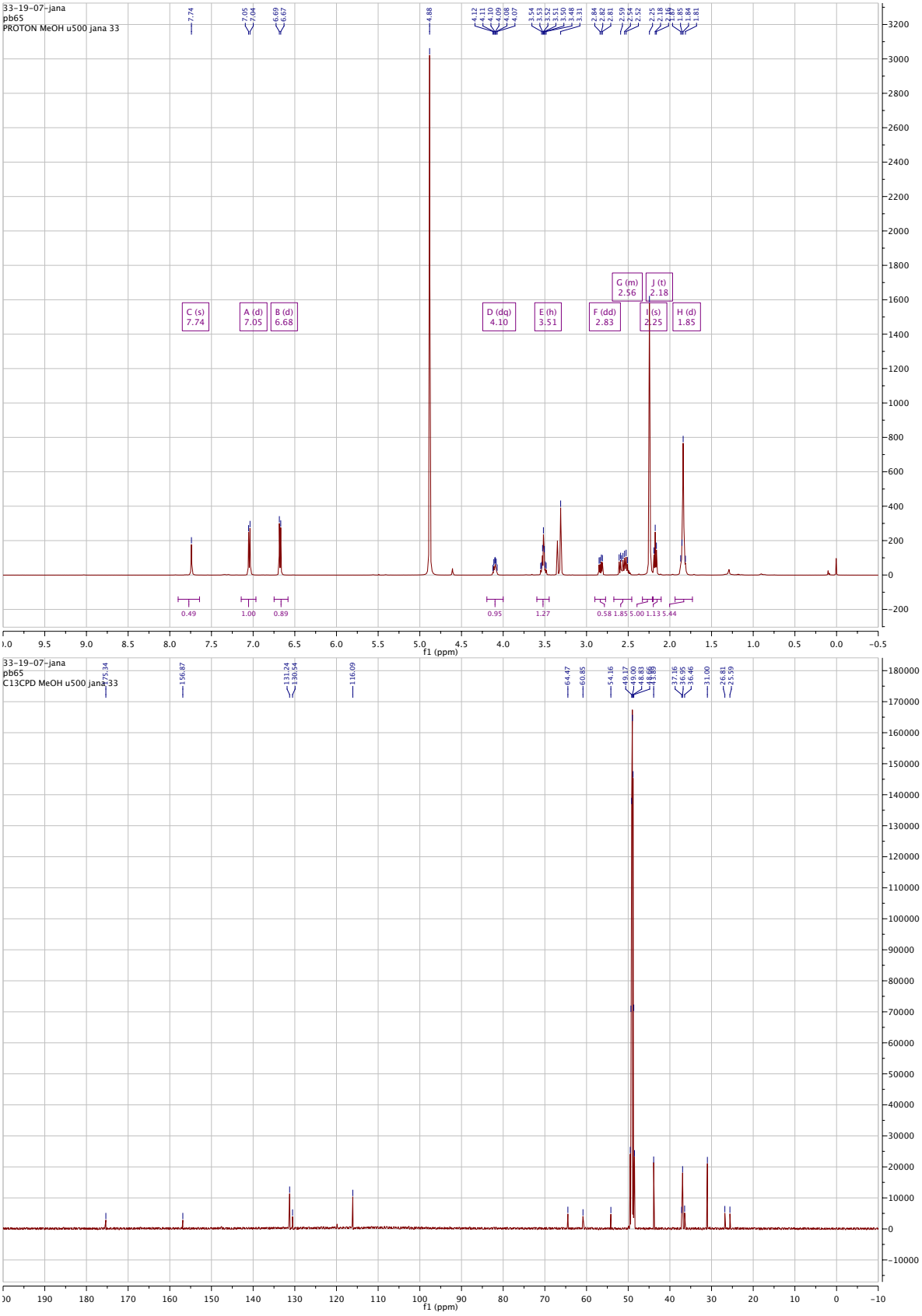




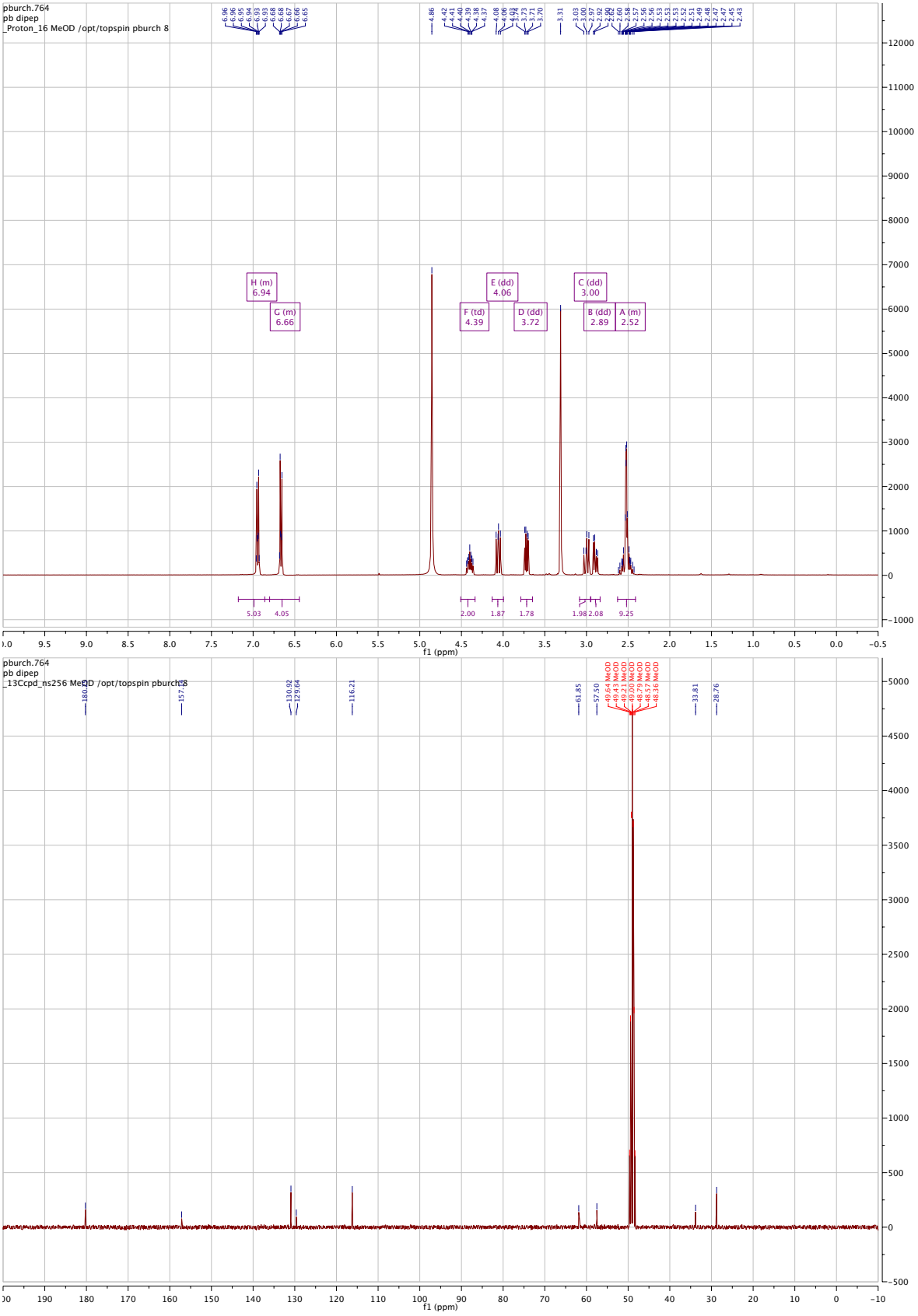
(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)hex-5-ynamide (III)



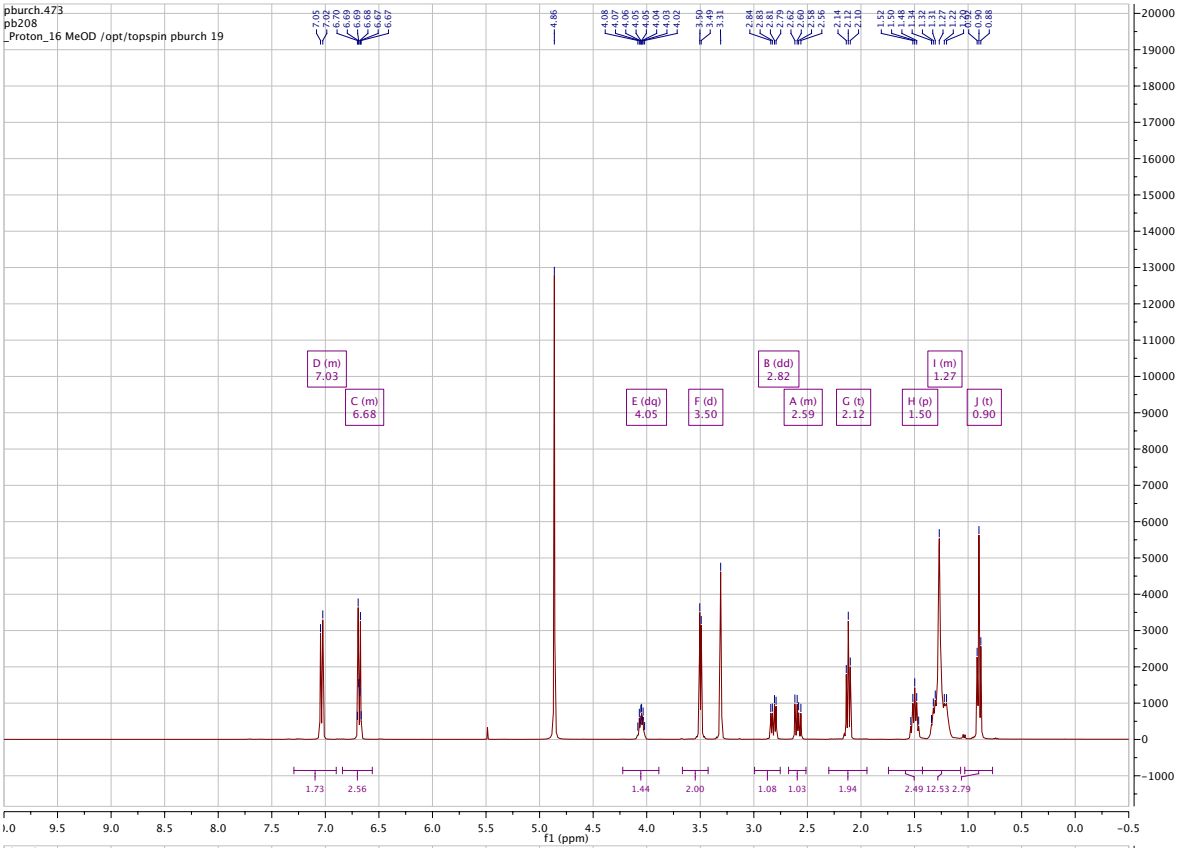
(*S*)-4-(1-(adamantan-1-yl)-1H-1,2,3-triazol-4-yl)-N-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)butanamide (20)

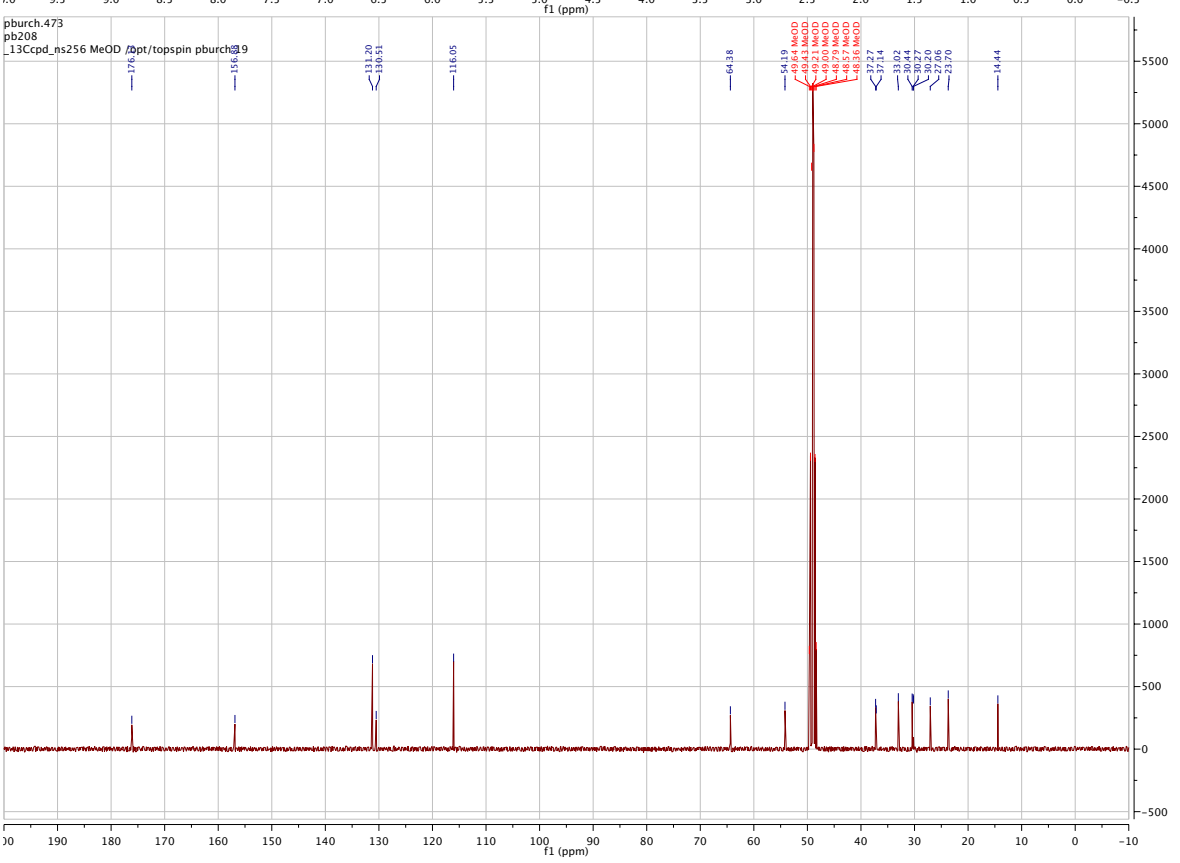


***N*-((*R*)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)-*N*-((*S*)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)succinamide (21)**

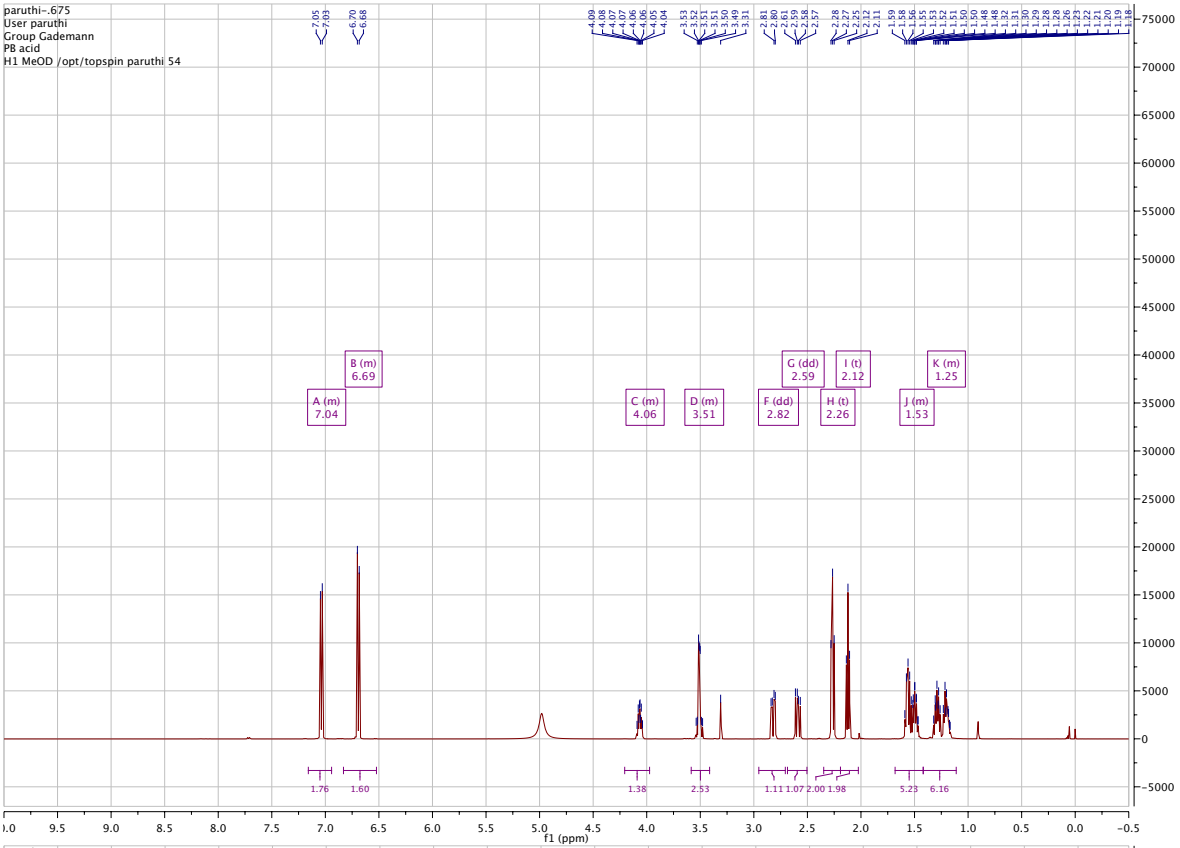


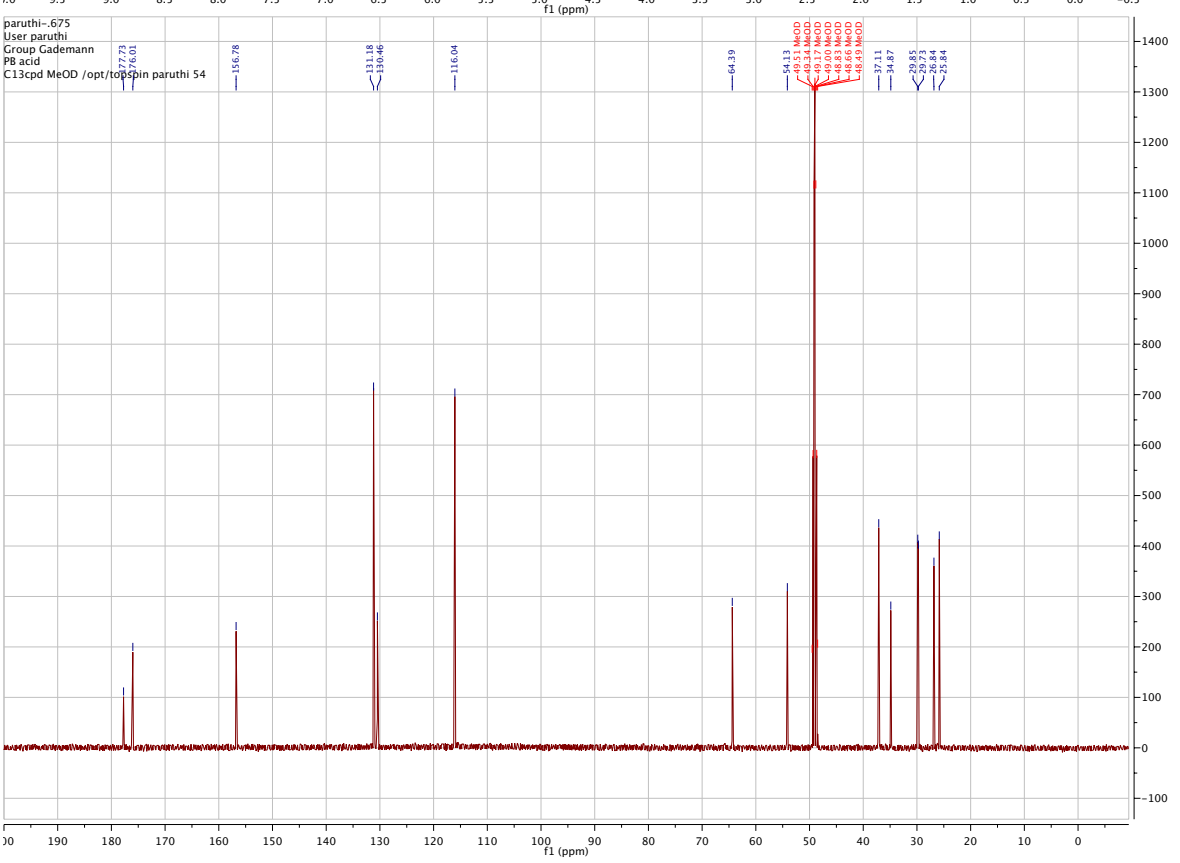
(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)nonanamide (22)



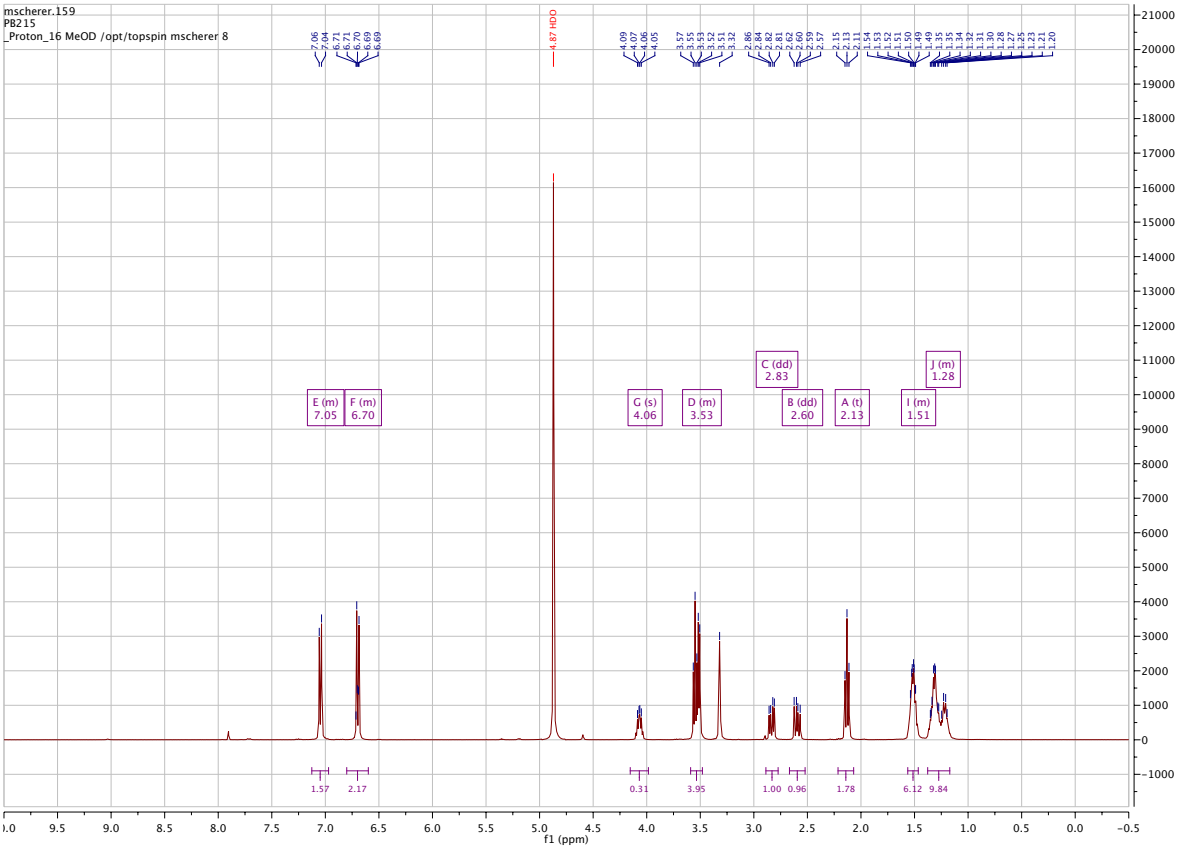


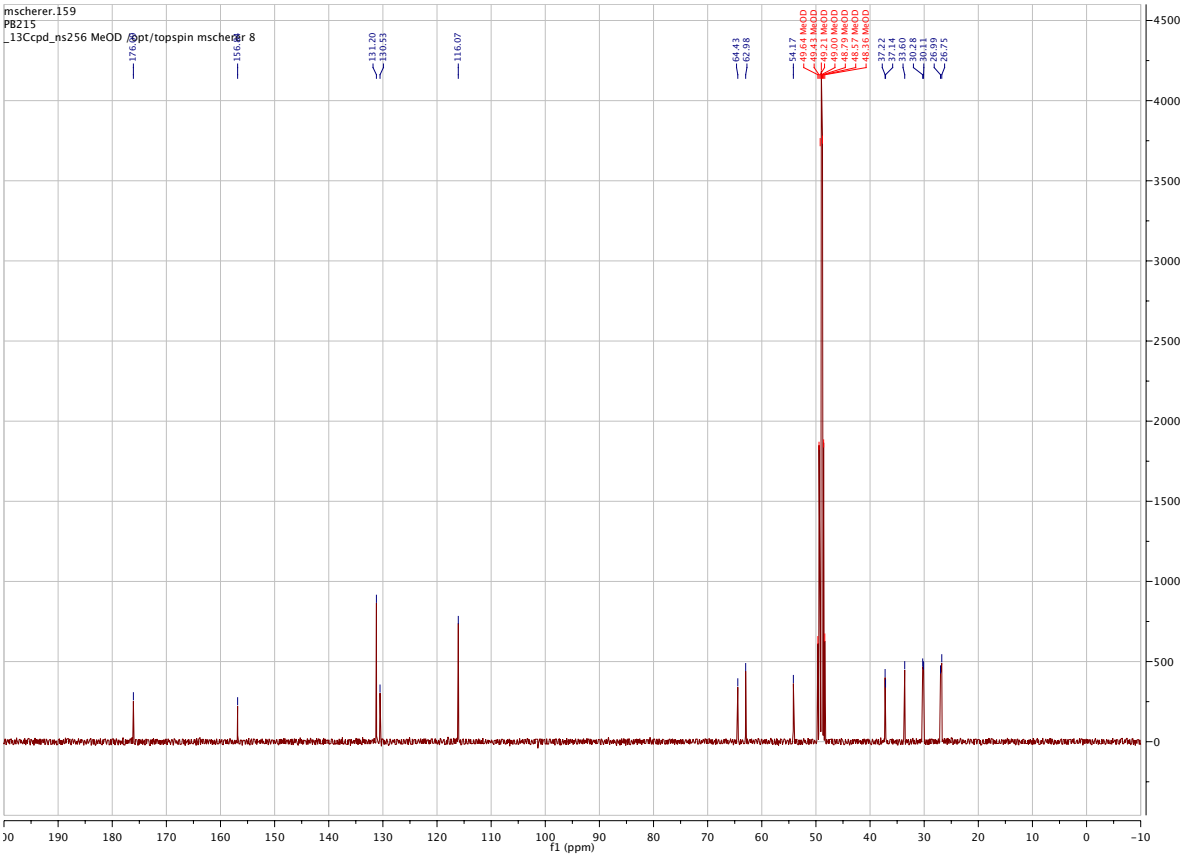
(*S*)-8-((1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)amino)-8-oxooctanoic acid (23)



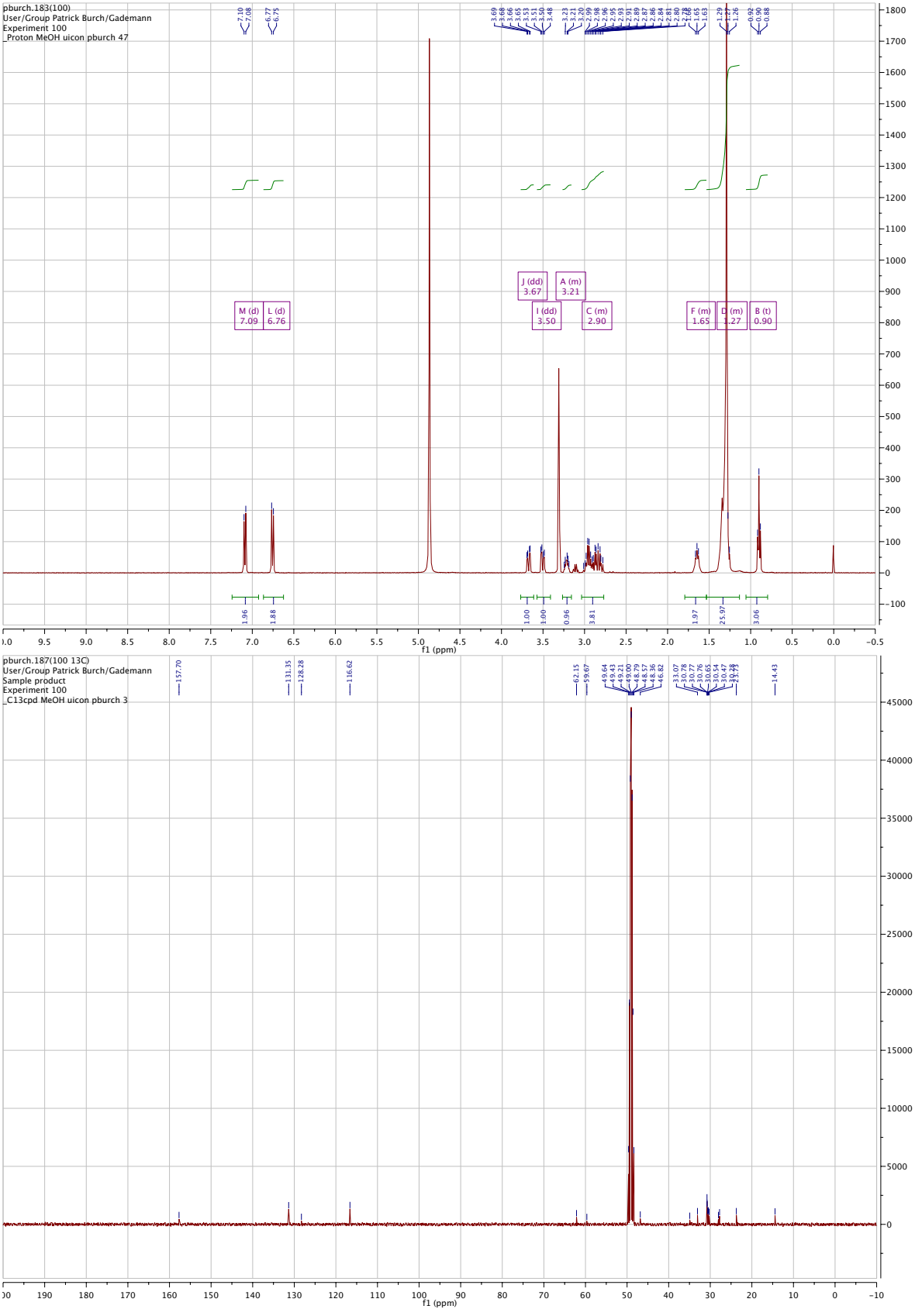


(*S*)-8-hydroxy-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)octanamide (24)

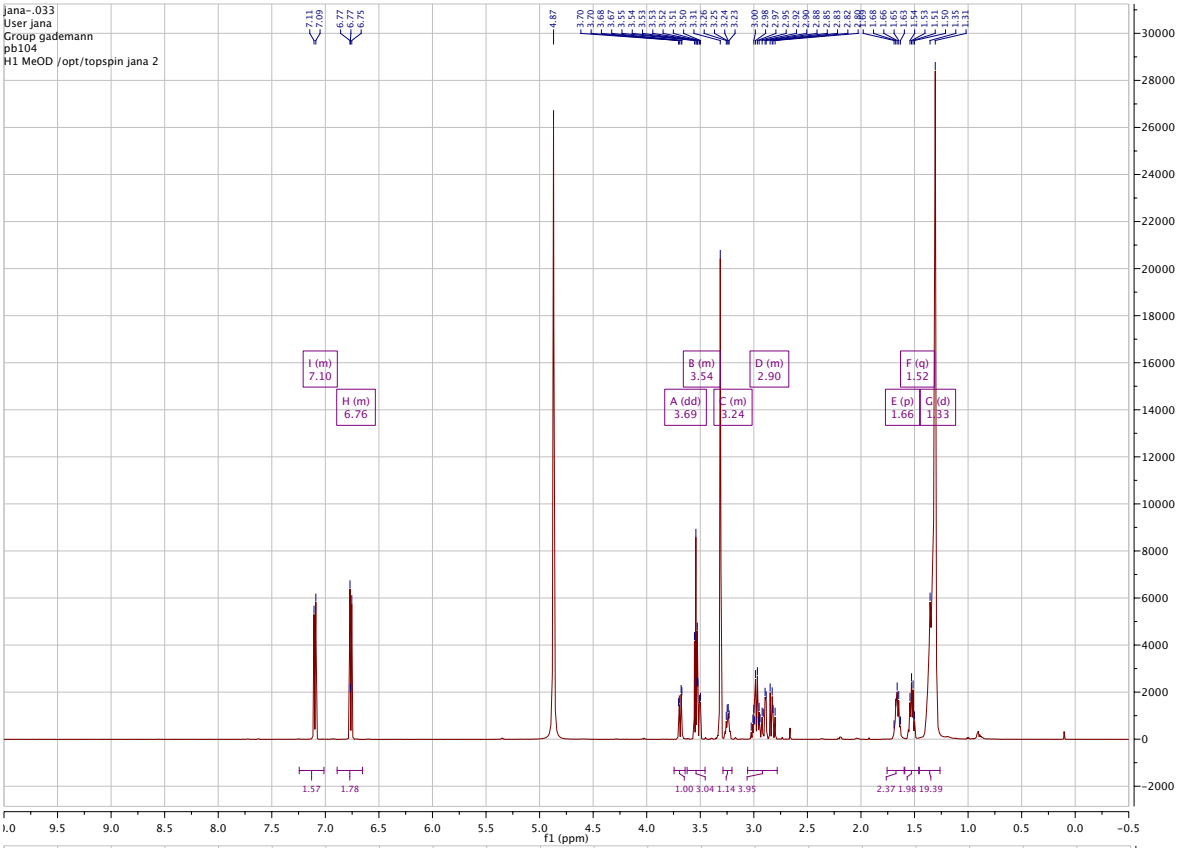


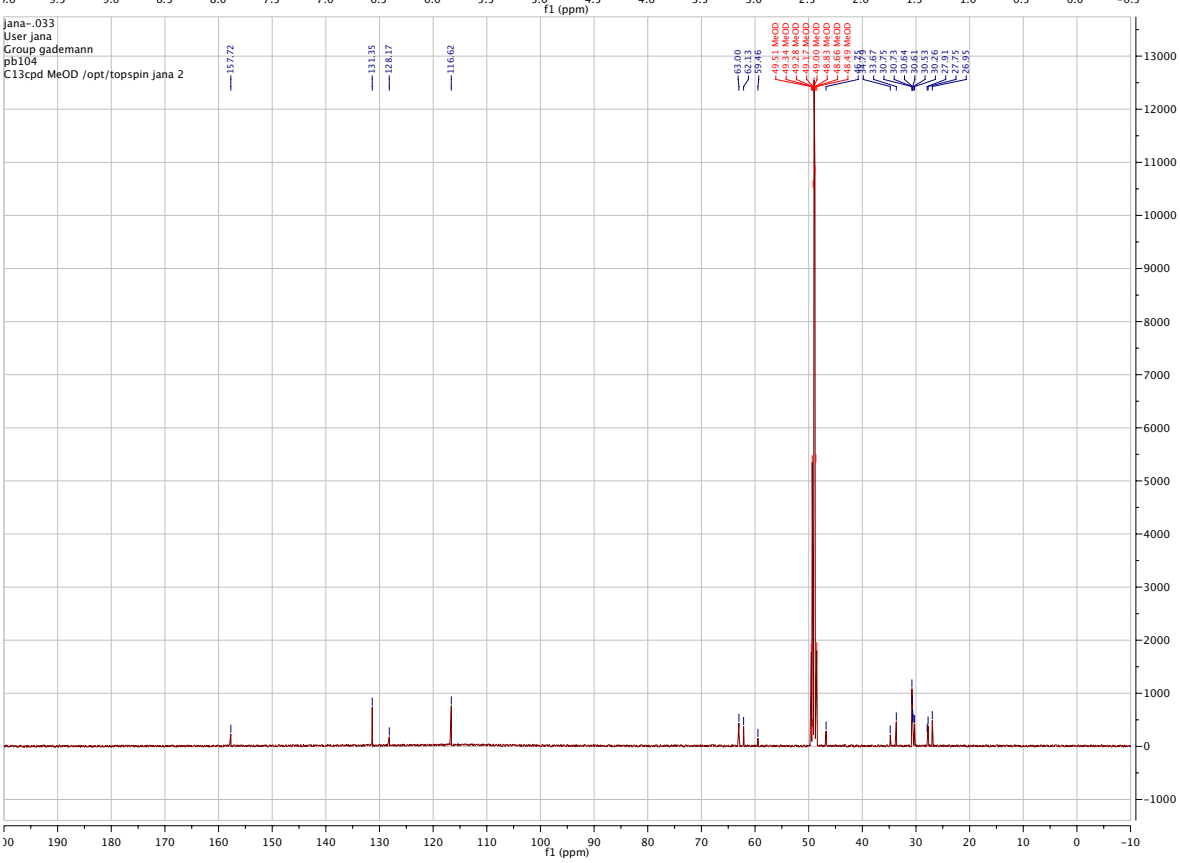


(*S*)-4-(2-(hexadecylamino)-3-hydroxypropyl)phenol (28)

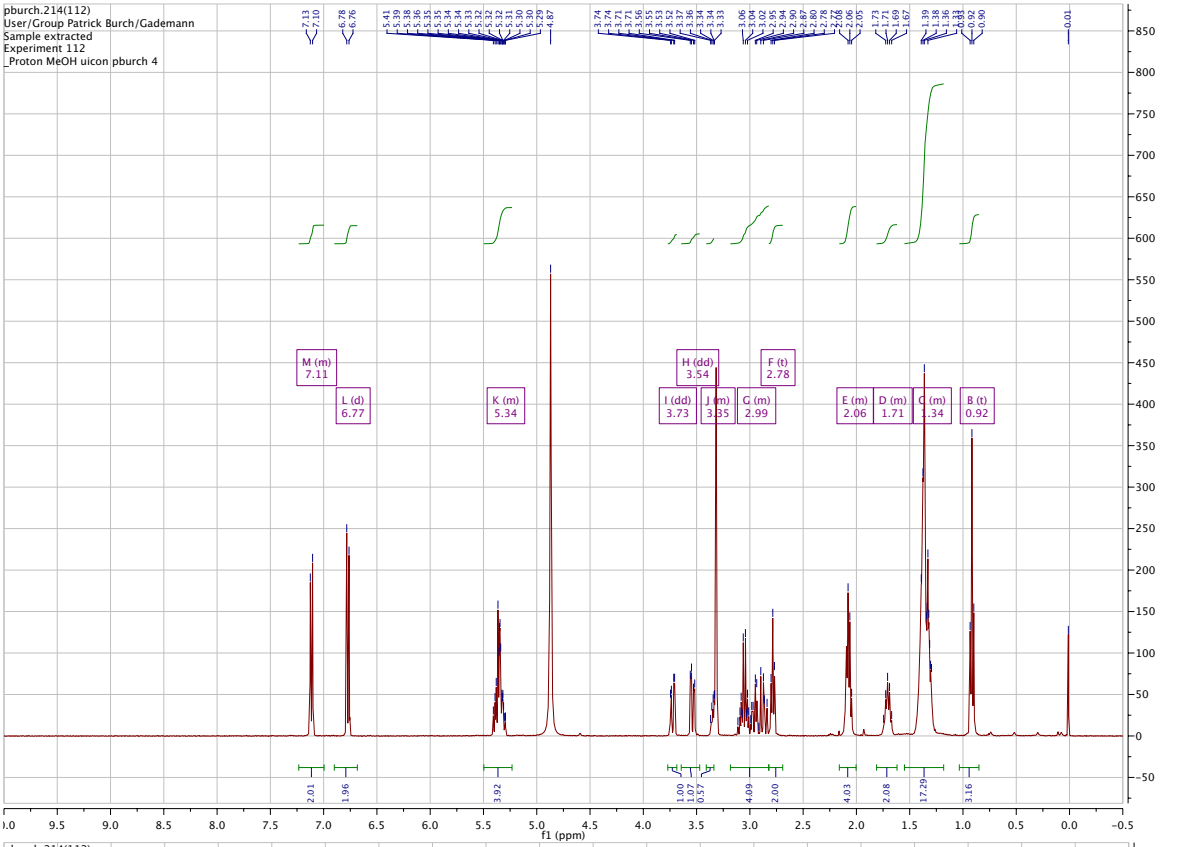


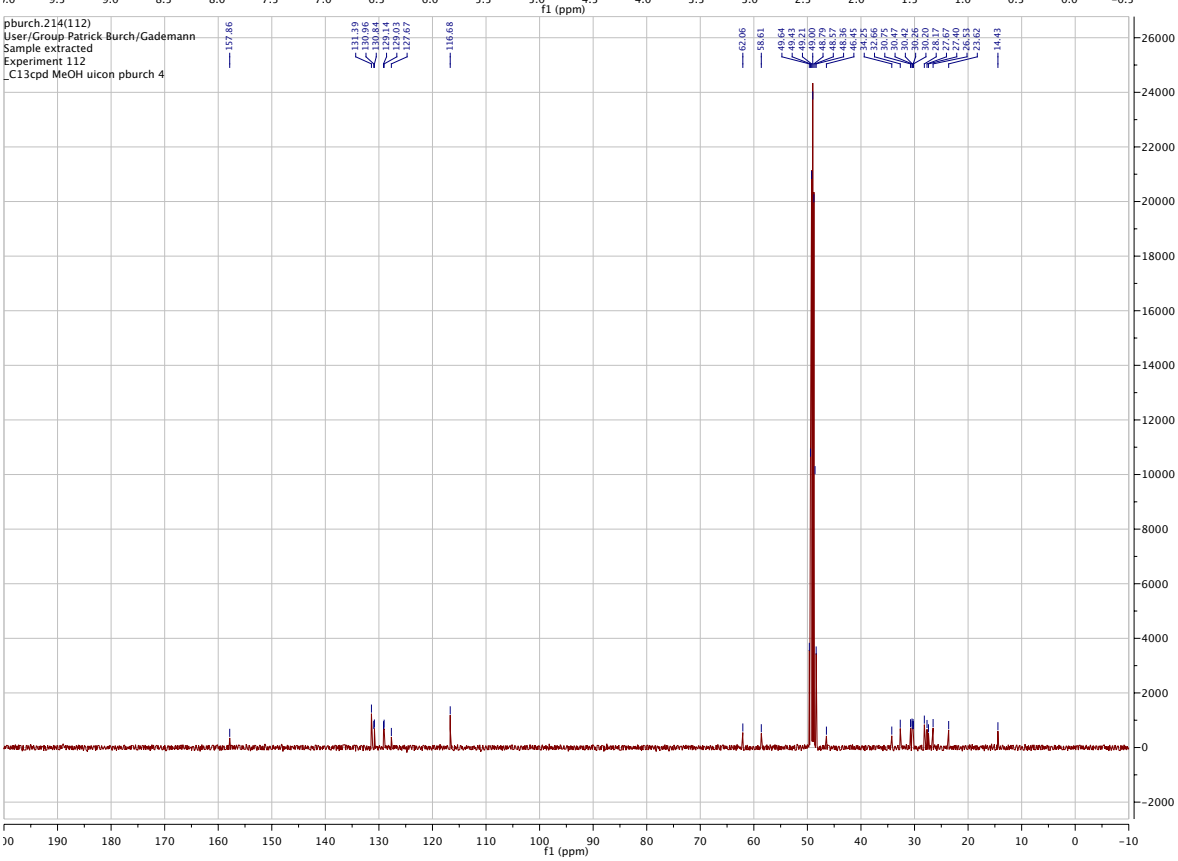
(*S*)-4-(3-hydroxy-2-((15-hydroxypentadecyl)amino)propyl)phenol (29)



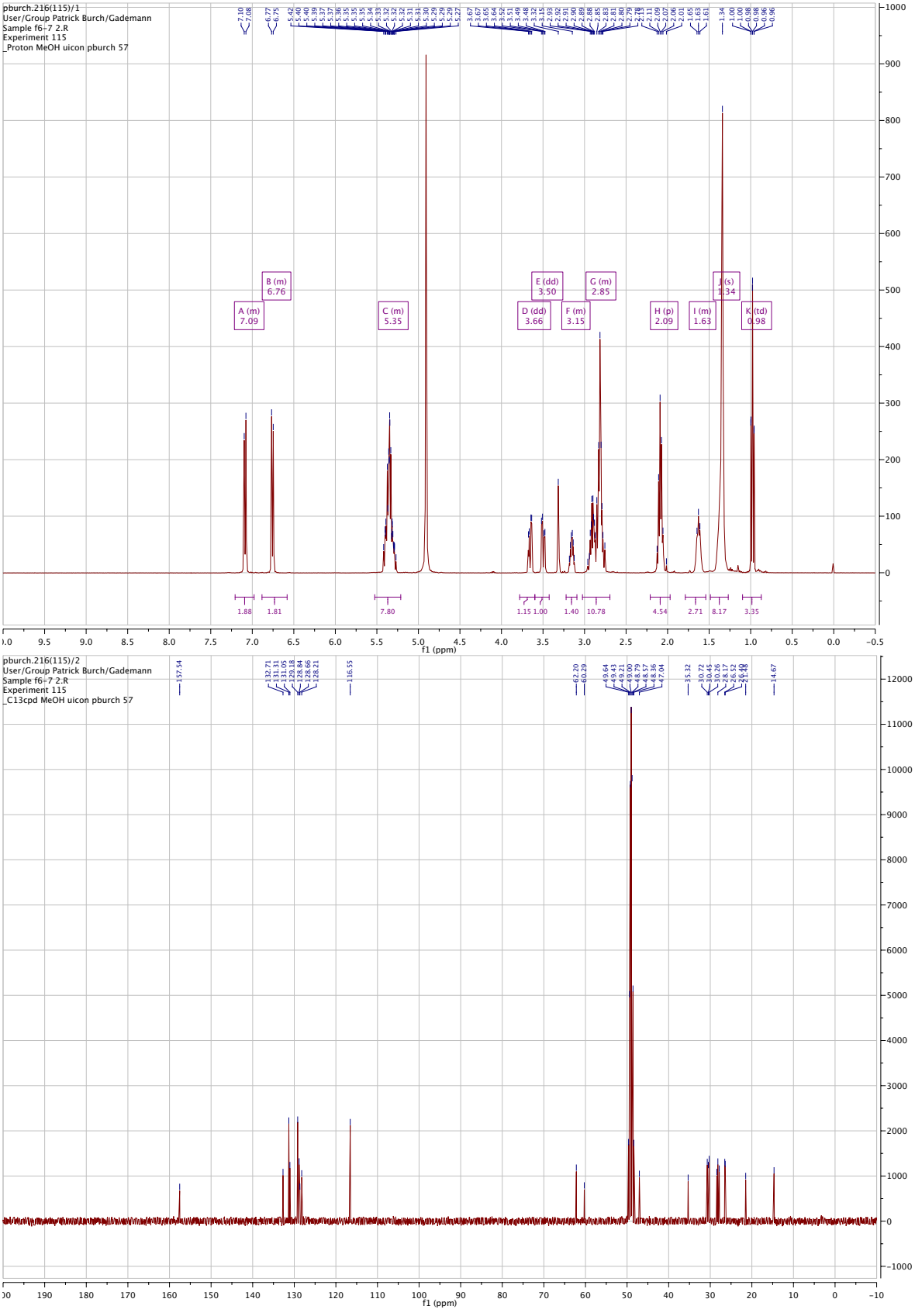


4-((*S*)-3-hydroxy-2-((9*Z*,12*Z*)-octadeca-9,12-dien-1-ylamino)propyl)phenol (30)

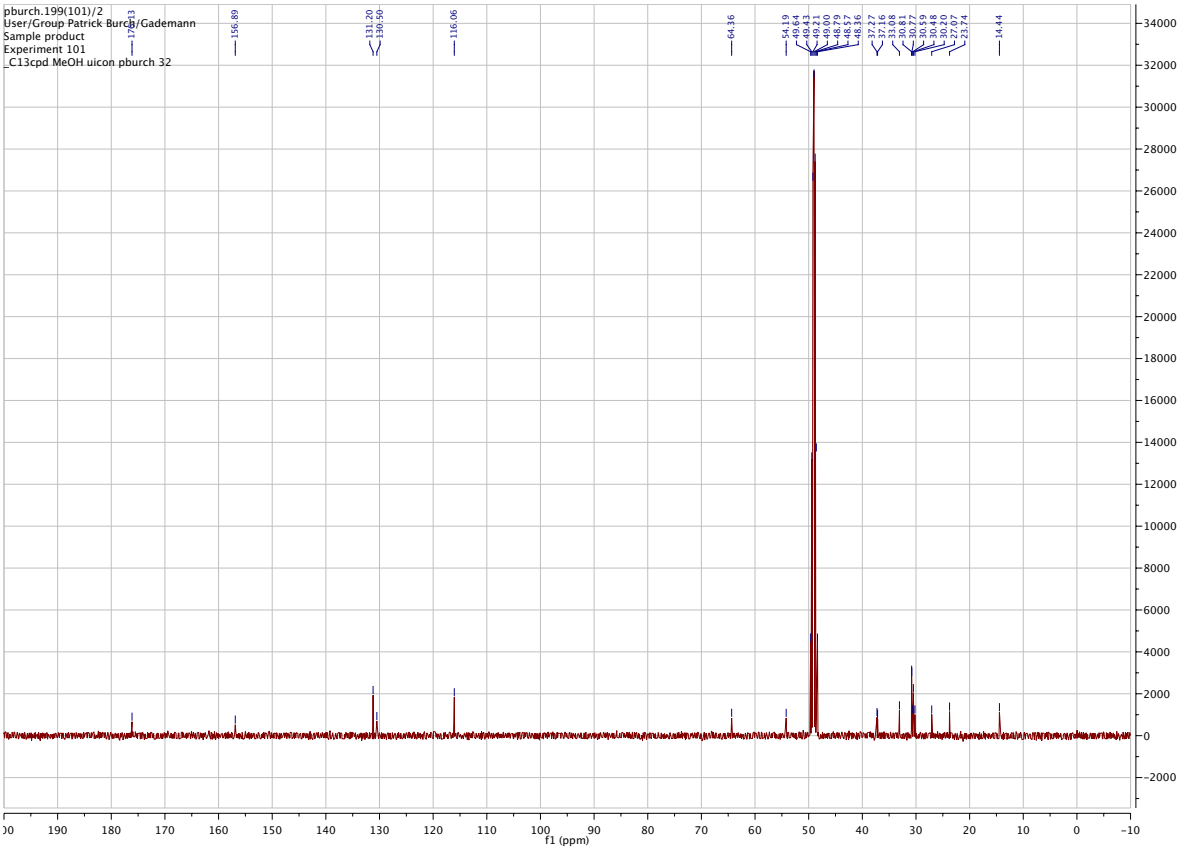




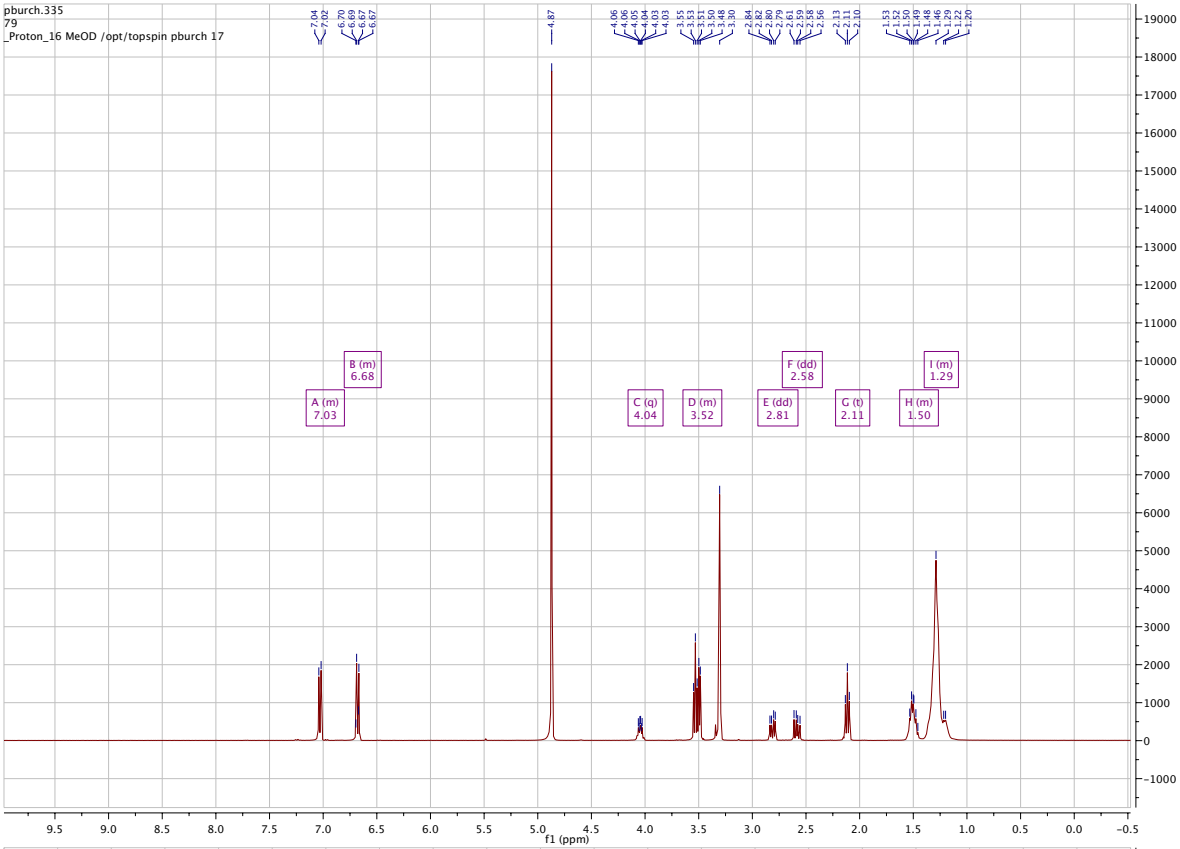
4-((*S*)-3-hydroxy-2-((9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trien-1-ylamino)propyl)phenol (31)

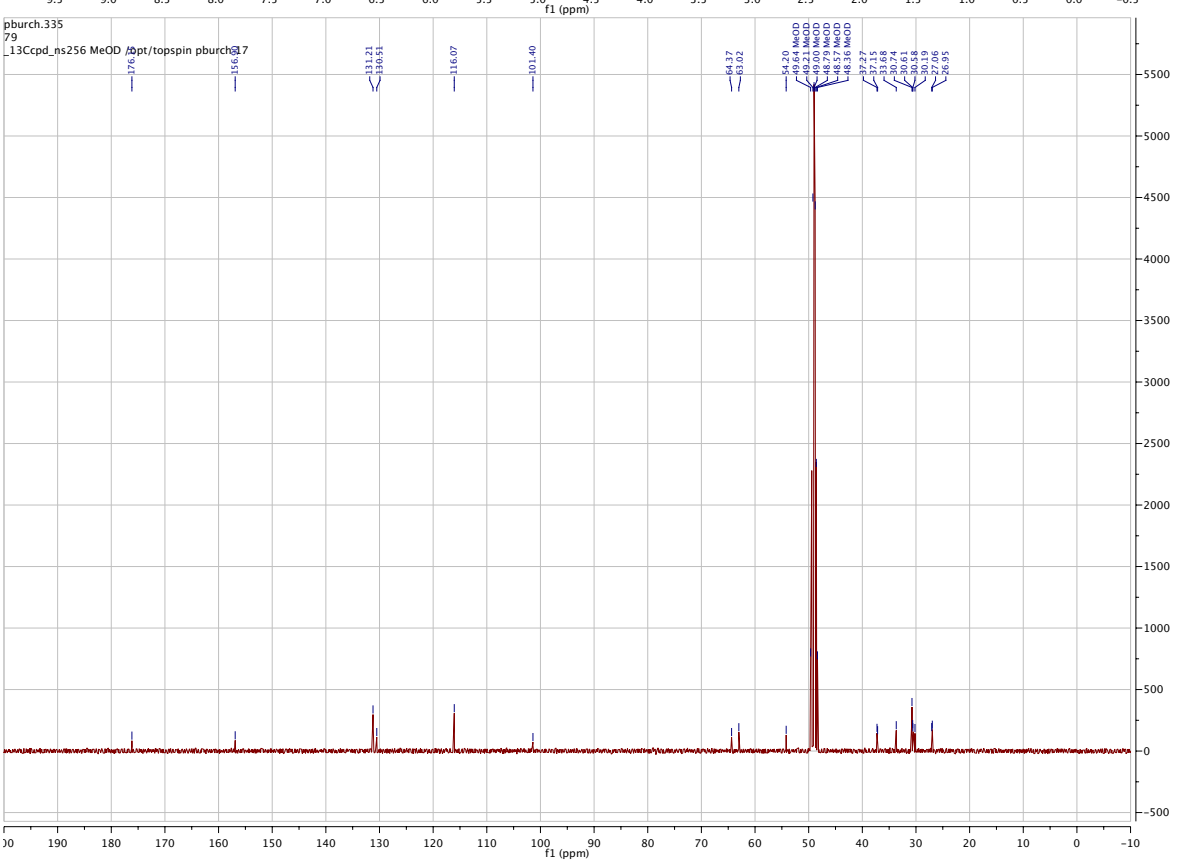


(*S*)-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)palmitamide (32)



(*S*)-15-hydroxy-*N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)pentadecanamide (33)





(9*Z*,12*Z*)-*N*-((*S*)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)octadeca-9,12-dienamide (BSL34)

(9*Z*,12*Z*,15*Z*)-*N*-((*S*)-1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)octadeca-9,12,15-trienamide (35)