Initial Efforts Toward the Optimization of Arylomycins For Antibiotic Activity Supplemental Information

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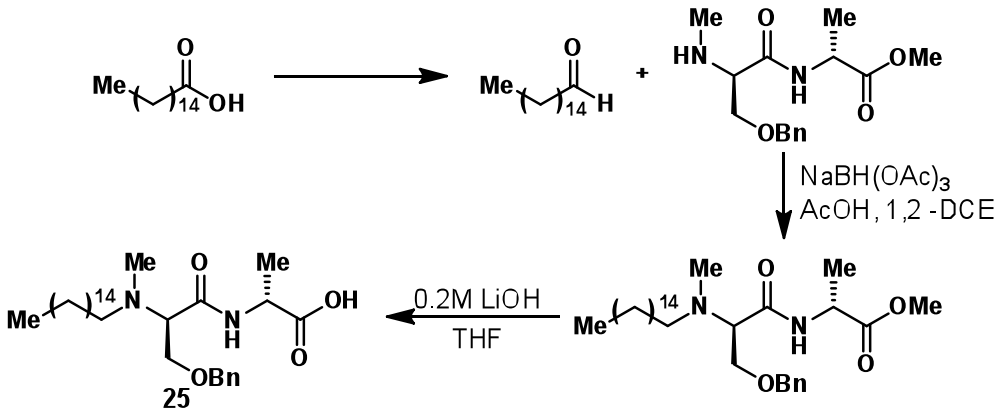
Synthetic Methods

General Procedure D - Methyl Ester Saponification

The starting material (1 eq) was taken up in THF and treated with a 0.2 N aqueous solution of LiOH (2.5 eq) and monitored via TLC. When all the starting material had been consumed the reaction was acidified with 5% aqueous citric acid (pH 3) and the THF was evaporated under a stream of nitrogen. Water and EtOAc were then added and the aqueous phase was extracted 3x with EtOAc. The combined organic layers were then washed with brine, dried over sodium sulfate and concentrated by rotary evaporation.

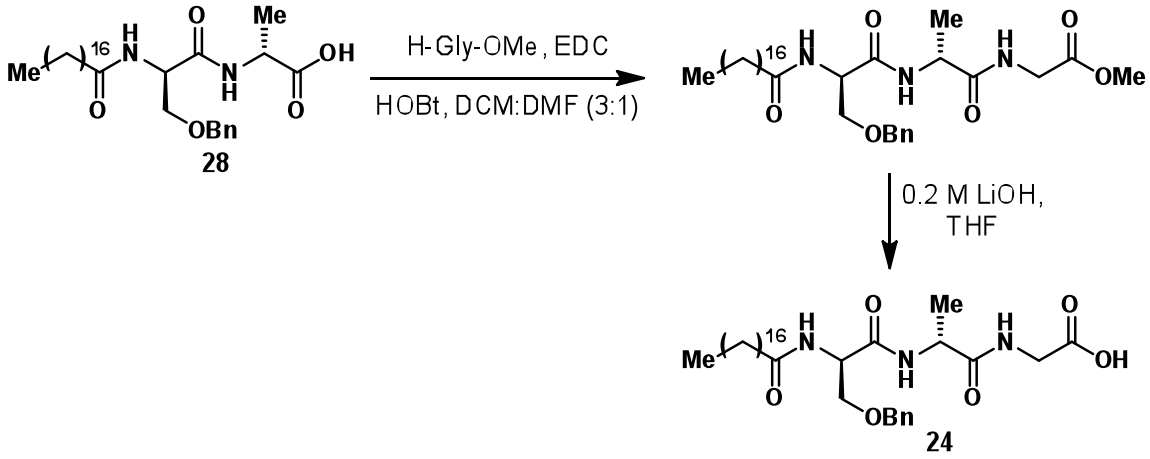
Compound 1 Tail Synthesis Scheme:



Palmitoyl chloride was reduced to the aldehyde via a previously reported method.[1] The aldehyde (26 mg, 3 eq, 0.10 mmol) was then coupled reductively to the dipeptide[2] (10 mg, 1.0 eq, 0.034 mmol) via a modification of a reported method,[3] The dipeptide and aldehyde were dissolved in 1,2-dichloroethane (1.0 mL) to which was added sodium triacetoxyborohydride (14.4 mg, 2.0 eq) and one drop of glacial acetic acid. The reaction was stirred for 27 h then the reaction was quenched with a small amount of water, the solvent was evaporated under a stream of nitrogen and the reaction was taken up in EtOAc and dilute sodium bicarbonate solution was added. The aqueous phase was extracted 3x, dried over sodium sulfate and concentrated. Silica gel column chromatography (2% MeOH in DCM) yielded two products of similar polarity which were taken forward without further purification. The resulting mixture (13.1 mg) was dissolved in THF and treated with 0.2 M $LiOH_{(aq)}$ (126 µL, ~1.5 eq). The reaction was monitored by TLC and treated with a 5% citric acid solution upon consumption of the starting material. The volatiles were evaporated under a stream of nitrogen, the aqueous phase was extracted 3x with EtOAc, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (7% MeOH in DCM w/ trace AcOH) to yield **25** as a residue (5.8 mg, 34%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.25 (s, 1H), 7.32-7.28 (m, 5H), 4.51 (dd, J = 30, 12Hz, 2H), 4.38 (s, 1H), 3.89 (m, 2H), 2.87-2.81 (m, 1H), 2.59 (s, 2H), 1.57 (s, 1H), 1.40 (s, 2H), 1.29-1.23 (m, 22H), 0.88 (t, *J* = 6.6Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) .5, 127.9, 127.8, 73.5, 32.1, 29.9 (3C), 29.8 (3C), 29.7, 29.6, 29.5, 27.3, 22.9, 14.3. ESI MS calcd for $C_{30}H_{52}N_2O_4$ [$(M + H)^+$]: 505.4, found: 505.6

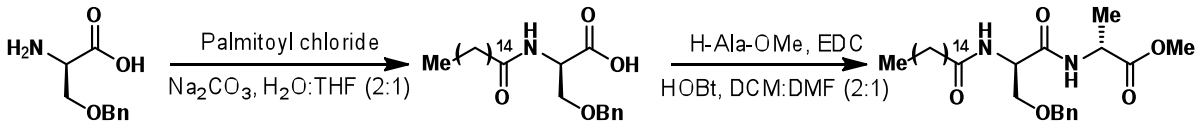
The tails for compounds **2** – **4** and **6** – **15** were synthesized as described previously.[2]

Compound 5 Tail Synthesis Scheme:



To a solution of compound **28** (103 mg, 0.19 mmol, 1 eq) in DCM (3.7 mL) and DMF (1.3 mL), under N_2, was added HOBt (83 mg, 3.3 eq), H-Gly-OMe HCl (71 mg, 3 eq), EDC (108 mg, 3 eq) and TEA (86 µL, 3.3 eq). The reaction was allowed to stir overnight, after which DCM and saturated $NaHCO_3$ were added. The aqueous phase was extracted 3x with DCM, washed with 0.1 N HCl and brine, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (70% EtOAc in Hex) to give the methyl ester (71.9 mg, 62%). ^{1}H NMR (CDCl3, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.36-7.28 (m, 5H), 7.05-6.99 (m, 2H), 5.01-4.96 (m, 1H), 4.60-4.45 (m, 3H), 4.05-3.95 (m, 2H), 3.88-3.87 (m, 0.5H), 3.82-3.71 (m, 4.5H), 3.01 (s, 3H), 2.36-2.31 (m, 2H), 1.98 (s, 1H), 1.62-1.57 (m, 2H), 1.36-1.24 (m, 33H), 0.87 (t, *J* = 6.6 Hz). ESI MS calcd for $C_{31}H_{51}N_3O_6$ [(M + Na)$^+$]: 599.4, found: 585.3. This material was then subjected to general procedure D to give compound **24** as a solid which was taken forward without purification or characterization.

Compound 16 Tail Synthesis Scheme:



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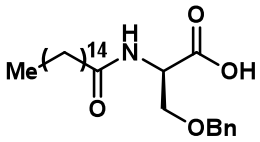
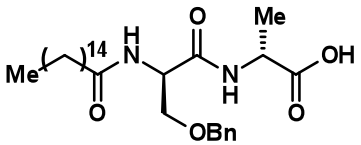


26

Compound **26** was synthesized using a modification of a reported procedure,[4] H-Ser(OBn)-OH (50 mg, 0.26 mmol, 1 eq) and Na_2CO_3 (81 mg, 3 eq) were dissolved in H_2O (2 mL) and added dropwise at room temperature to palmitoyl chloride (86 µL, 1.1 eq) in THF (1 mL) with vigorous stirring. The mixture was stirred for 2.5 h then acidified slowly with 5% citric acid (pH 3), and extracted 3x with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (2% MeOH in DCM then 7.5% MeOH in DCM) to give compound **26** (49 mg, 44% yield). ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.79 (br s, 1H), 7.30-7.26 (m, 5H), 6.58 (br s, 1H), 4.71 (br s, 1H), 4.53-4.47 (m, 2H), 3.90 (m, 1H), 3.69-3.68 (m, 1H), 2.21 (m, 2H), 1.59 (m, 2H), 1.25-1.24 (m, 24H), 0.88 (t, *J* = 7.2Hz, 3H) ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 174.3,137.5, 128.6, 128.0, 127.8, 73.5, 69.6, 52.9, 36.5, 32.1, 29.9, 29.8 (3C), 29.7, 29.5, 29.5, 29.4, 25.7, 22.8, 14.3. ESI MS calcd for $C_{26}H_{43}NO_4$ [(M + H)$^+$]: 434.3, found:434.5.

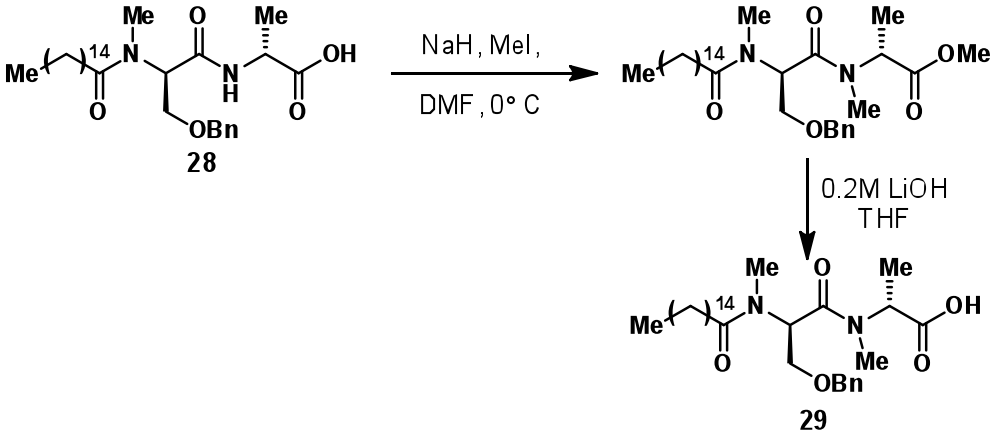


27

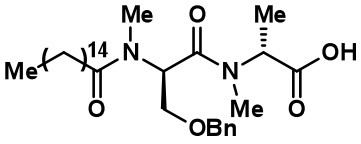
Compound **26** (99 mg, 0.23 mmol, 1 eq) was dissolved in a 2:1 mixture of DCM:DMF (3 mL). The solution was then treated sequentially with HOBt (124 mg, 4 eq), H-D-Ala-OMe HCl (35 mg, 1.1 eq), EDC HCl (176 mg, 4 eq) and DIEA (48 µL, 1.2 eq) and stirred for 20 h under Ar. The DCM was evaporated under a stream of nitrogen and to the reaction was then added water, 5% citric acid (pH 3) and EtOAc. The aqueous phase was extracted 3x with EtOAc, the combined organic layers were washed with

saturated $NaHCO_3$, water and brine, dried over sodium sulfate and concentrated. The residue was then subjected to general procedure D and the crude was purified via column chromatography (7% MeOH in DCM w/ trace AcOH) to give **27** (75 mg, 65%). R_f – 0.31 (7% MeOH in DCM w/1 drop AcOH/10 mL). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.34-7.24 (m, 5H), 4.65-4.62 (m, 1H), 4.56-4.51 (m, 2H), 4.33-4.29 (m, 1H), 3.78-3.68 (m, 2H), 2.29-2.26 (m, 2H), 1.62-1.60 (m, 2H), 1.38-1.28 (m, 26H), 0.90 (t, *J* = 8.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 176.5, 171.5, 139.3, 129.4, 128.8, 128.8, 128.7, 74.2, 70.8, 70.7, 54.7, 50.7, 36.9, 33.1, 30.8, 30.8, 30.7, 30.6, 30.5, 30.3, 30.3, 26.9, 23.7, 18.5, 14.5. ESI MS calcd for $C_{29}H_{48}N_2O_5$ [(M + H)$^+$]: 505.4, found:505.6 (M + H$^+$).

Compound 17 Tail Synthesis Scheme



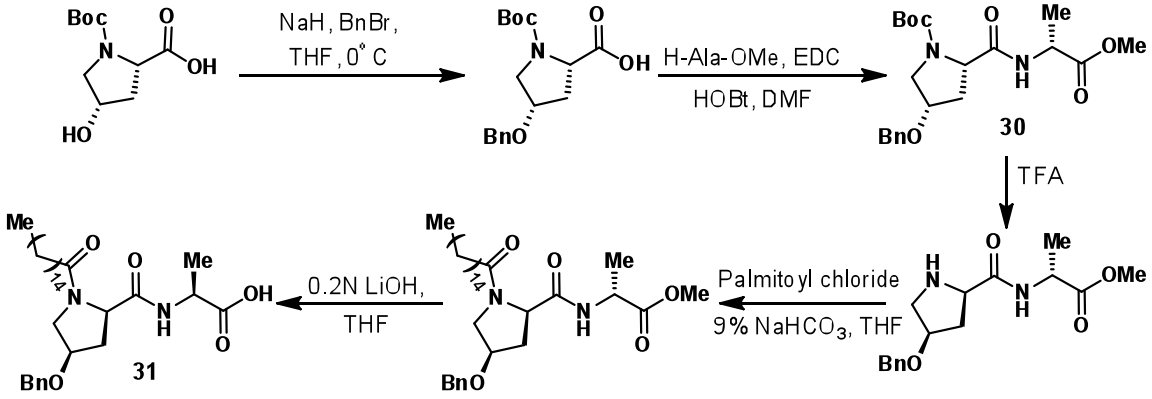
28 29

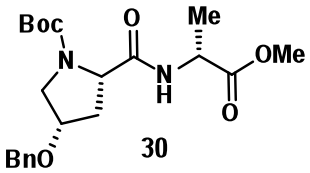


29

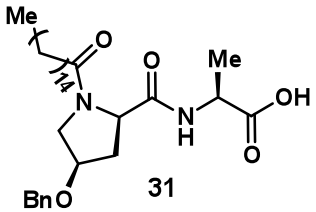
Compound **29** was synthesized as follows via a modification of a reported procedure.[5] Compound **28** was dissolved in DMF and cooled to 0° C in an ice bath under Ar. The solution was then treated with a 60% dispersion of NaH in mineral oil (15.4 mg, 10 eq) and allowed to stir for 1 h before MeI (24 µL, 10 eq) was added. The mixture was allowed to stir for 1 h then quenched by the addition of water. To the mixture was added saturated $NaHCO_3$ and EtOAc, the aqueous phase was extracted 3x with EtOAc, and the combined organic fractions were washed with brine. The solution was dried over sodium sulfate and concentrated to give a residue. This residue was then subjected to general procedure D and purified via column chromatography (7% MeOH in DCM w/ trace AcOH) to give compound **29** (10 mg, 49%) R_f – 0.32 (7% MeOH in DCM w/ trace AcOH). For ^{1}H NMR see page 42. ESI MS calcd for $C_{31}H_{52}N_2O_5$ [(M + Na)$^+$]: 555.4, found: 555.7.

Compound 18 Tail Synthesis Scheme:





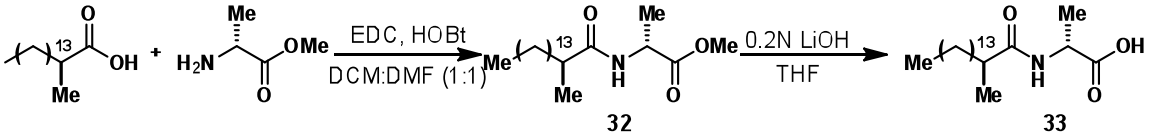
Boc-cis-4-hydroxy-D-proline (200mg, 0.86 mmol, 1 eq) was dissolved in THF (3 mL) and treated with a 60% dispersion of NaH in mineral oil (103 mg, 3 eq) at 0°C and allowed to stir until the evolution of H_2 had ceased. BnBr (226 µL, 2.2 eq) was then added to the mixture and it was allowed to warm to room temp and then stirred overnight. The reaction was quenched by the addition of water and a small amount of 5% citric acid (pH 3) then basified with saturated $NaHCO_3$. The aqueous layer was extracted 3x with EtOAc then acidified with 5% citric acid (pH 3) and extracted 2x with EtOAc. The combined layers of the extraction of the acidified aqueous phase were then washed with water and brine, dried over sodium sulfate and concentrated. The crude acid (167 mg (Rf – 0.38 in 7% MeOH in DCM)) was taken forward without further purification. This material was dissolved in DMF and treated sequentially with HOBt (240mg, 3.5 eq), H-D-Ala-OMe HCl (85 mg, 1.2 eq), EDC HCl (340 mg, 3.5 eq) and triethylamine (85 µL, 1.2 eq) and the mixture was allowed to stir overnight. Then, to the reaction was added water, saturated $NaHCO_3$ and EtOAc, and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were then washed with 5% citric acid (pH 3) and brine, dried over sodium sulfate and concentrated. Column chromatography (2% MeOH in DCM) yielded **30** as an oil (181 mg, 52%). R_f – 0.33 (2% MeOH in DCM). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.33-7.24 (m, 5H), 6.72 (s, 1H), 4.50-4.30 (m, 4H), 4.12 (m, 1H), 3.70-3.55 (m, 5H), 2.73-2.51 (m, 1H), 2.29-2.08 (m, 1H), 1.47 (s, 9H), 1.20-1.07 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 172.8, 172.0, 154.8, 137.5, 128.3, 127.8, 127.7, 80.9, 76.3, 70.5, 60.2, 59.6, 53.7, 52.9, 52.2, 47.8, 35.5, 33.0, 28.1, 17.8. . ESI MS calcd for $C_{21}H_{30}N_2O_6$ [$(M + H)^+$]: 407.3, found: 407.4.



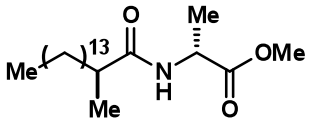
A solution of compound **30** (180 mg, 0.45 mmol) in DCM (2.0 mL) was treated with TFA (0.5mL) and stirred until the starting material had been consumed as determined by TLC analysis. The volatiles were then evaporated under a stream of nitrogen and the residue was dried under vacuum. The crude product was then taken up in a 9% $NaHCO_{3(aq)}$ solution and to it was added palmitoyl chloride (204 µL, 1.5 eq) in DCM (2 mL). This mixture was stirred vigorously overnight, then water and DCM were added and the aqueous phase was extracted 3× with DCM. The combined organic layers were dried over sodium sulfate and concentrated to give the crude product (Rf – 0.35 (3% MeOH in DCM). The crude product was then subjected to general

procedure D and purified via column chromatography (7.5%-8% MeOH in DCM) to give **31** as an amorphous solid (100.3 mg, 42% yield). Rf – 0.34 in 7.5% MeOH in DCM. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 8.62 (br s, 1H), 7.32-7.26 (m, 5H), 7.07-7.06 (m, 0.5H), 4.61-4.59 (m, 1H), 4.45-4.37 (m, 3H), 4.17-4.13 (m, 1H), 3.90-3.87 (m, 0.5H), 3.67-3.62 (m, 3H), 2.77-2.75 (m, 0.5H), 2.60-2.58 (m, 0.5H), 2.35-2.24 (m, 2H), 2.07 (m, 0.5H), 1.62-1.61 (m, 2H), 1.29-1.06 (m, 27H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (CD3OD, 150 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 175.3, 175.2, 174.7, 171.5, 171.2, 137.5, 137.3, 128.5, 128.5, 128.0 (3C), 127.9, 127.9, 76.7, 75.5, 70.7, 60.8, 59.6, 54.0, 53.1, 48.7, 48.2, 36.6, 34.8, 34.4, 32.5, 32.0, 29.8(2C), 29.7(3C), 29.6, 29.6, 29.5(2C), 29.4(2C), 24.9, 24.7, 22.8, 17.6, 17.2. ESI MS calcd for $C_{31}H_{50}N_2O_5$ [(M + H)$^+$]: 531.4, found: 531.7.

Compound 19 Tail Derivative Scheme:

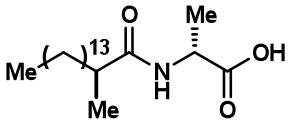


32 33



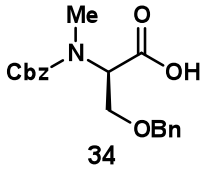
32

H-D-Ala-OMe HCl (50 mg, 0.36 mmol, 1 eq) was dissolved in DCM:DMF (1:1, 4 mL) and treated sequentially with HOBt (146 mg, 3 eq), racemic 2-methylpalmitic acid (107 mg, 1.1 eq), EDC (207 mg, 3 eq), and DIEA (101 µL, 1.6 eq). The reaction was allowed to stir overnight then water, 5% citric acid and EtOAc were added. The aqueous layer was extracted 3x with EtOAc, the combined organic layers were washed with saturated $NaHCO_{3(aq)}$, water and brine, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (1.25% MeOH in DCM) to give compound **32** (101 mg, 79%). ESI MS calcd for $C_{21}H_{41}NO_3$ [(M + H)$^+$]: 356.3, found: 356.3.



33

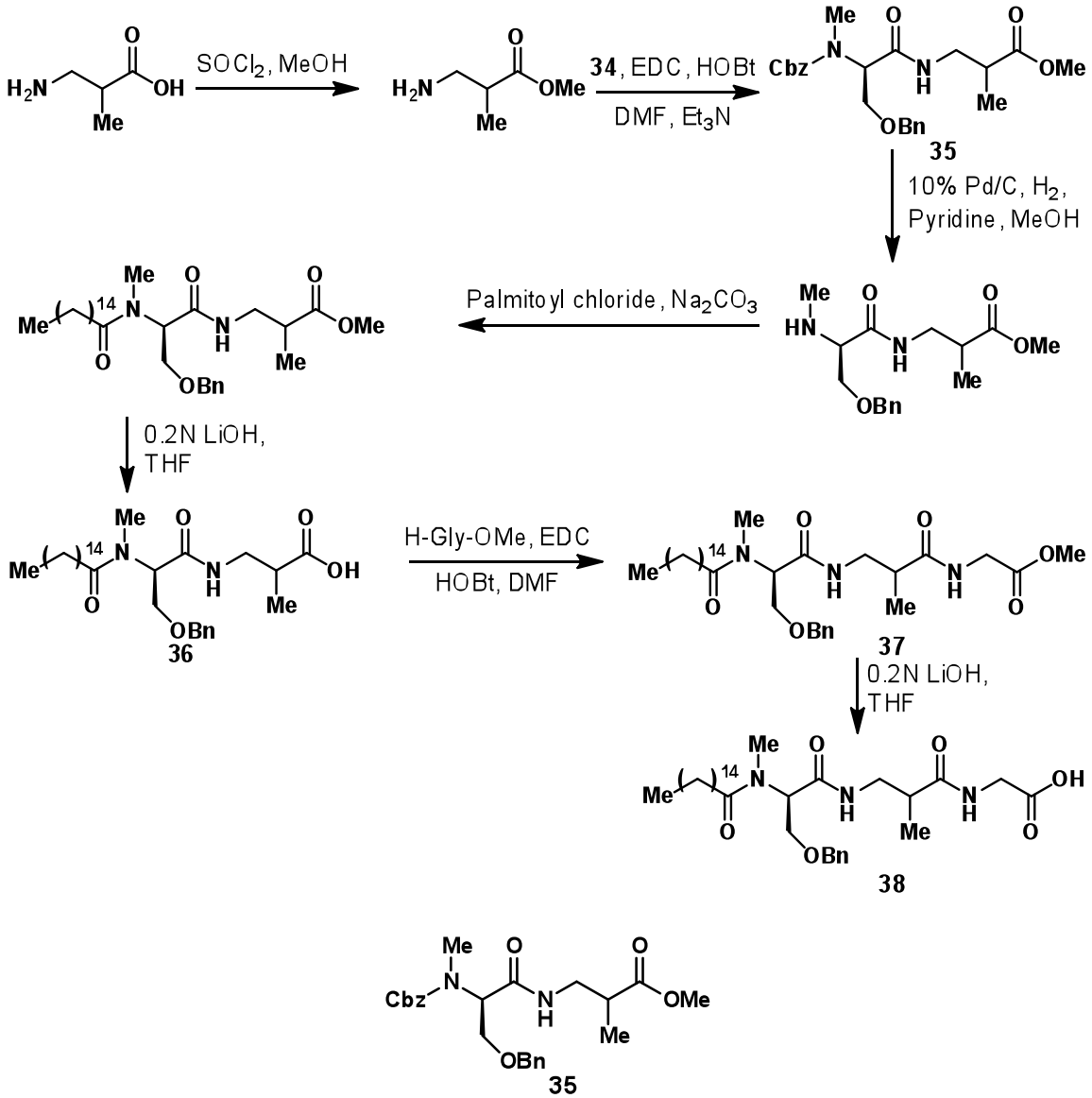
Compound **32** was subjected to general procedure D, then the crude material was purified, and the two diastereomers were separated by column chromatography (6% MeOH in DCM w/ trace AcOH) to give two diastereomers of **33** as products ((Diastereomer A (less polar) - 23.8 mg, 70%), (Diastereomer B (more polar) – 12.5 mg, 37%)). Diastereomer A - ^{1}H NMR (CD3OD, 600 MHz) δ (ppm) 4.38-4.35 (m, 5H), 2.36-2.35 (m, 1H), 1.62-1.59 (m, 1H), 1.39-1.28 (m, 29H), 1.09 (d, J = 3 Hz, 3H), 0.90 (t, J = 6 Hz, 3H). ^{13}C NMR (CD3OD, 600 MHz) δ (ppm) 179.5, 176.1, 41.7, 35.5, 33.1, 30.8, 30.8, 30.8, 30.8, 30.8, 30.7, 30.5, 28.4, 23.7, 18.3, 17.6, 14.5. MS (ESI) m/z 342.5 (M + H$^+$). Diastereomer B - ^{1}H NMR (CD3OD, 600 MHz) δ (ppm) 4.40-4.36 (m, 1H), 2.39-2.33 (m, 1H), 1.60-1.58 (m, 1H), 1.39-1.29 (m, 29H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 6 Hz, 3H). ^{13}C NMR (CD3OD, 150 MHz) δ (ppm) 179.4, 176.2, 41.7, 35.3, 33.1, 30.8, 30.8, 30.8, 30.8, 30.7, 30.7, 30.5, 28.6, 23.7, 18.3, 17.8, 14.5. ESI MS calcd for $C_{20}H_{39}NO_3$ [(M + H)$^+$]: 342.3, found: 342.5.



34

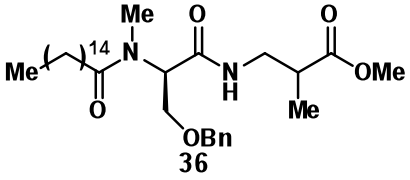
Compound **34** was synthesized by a modification of a reported procedure.[6] Cbz-D-Ser-OH (1.4 g, 4.25 mmol, 1 eq) was dissolved in THF and cooled to 0 °C. The solution was treated with a 60% dispersion of NaH in mineral oil (561 mg, 3.3 eq) and allowed to stir for 30 min. MeI (2.38 mL, 9 eq) was then added and the reaction was allowed to warm to room temperature. The reaction was allowed to stir overnight, then 5% citric acid (pH 3), water, and EtOAc were added. The aqueous phase was extracted 3x with EtOAc, the combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude material was purified via column chromatography (5% MeOH in DCM w/trace AcOH) to yield the product (640 mg, 44%). ^{1}H NMR (CDCl3, 400 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.37-7.29 (m, 10H), 5.17-5.12 (m, 2H), 5.01-4.98 (m, 0.5H), 4.84 (m, 0.5H), 4.60-4.51 (m, 2H), 3.96-3.82 (m, 2H), 3.18 (s, 0.5H), 3.00 (s, 2.5H). ESI MS calcd for $C_{19}H_{21}NO_5$ [(M + H)$^+$]: 344.1, found: 344.3.

Compound 20 Tail Synthesis Scheme:



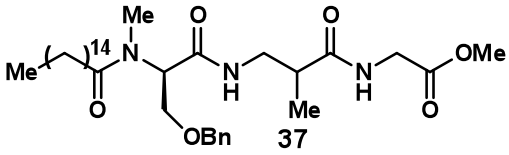
To a solution of DL-3-aminoisobutyric acid hydrate (206 mg, 2.0 mmol, 1 eq) in MeOH (20mL) was added thionyl chloride (0.32 mL, 2.2 eq), and the solution was refluxed in a sealed vial for 3 h. The solution was then concentrated under a stream of nitrogen and dried under vacuum. A portion of the crude material (154 mg, 1 mmol, 1.6 eq) was then taken up in DMF (8 mL) under Ar and to it was added HOBt (135 mg, 1 eq), compound **34** (215 mg, 1 eq), EDC (288 mg, 2.4 eq), and TEA (0.18 mL, 2.1 eq) at 0 °C. The reaction was allowed to warm to room temperature and then stirred overnight. Water was added, the aqueous

layer was extracted 3× with EtOAc, the combined organic layers were dried with sodium sulfate and concentrated. The crude product was purified by column chromatography (20-25% EtOAc in Hex) to give **35** (208 mg, 75% yield). ^{1}H NMR (CDCl3, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.36-7.28 (m, 10H), 6.77-6.62 (m, 1H), 5.17-5.14 (m, 2H), 4.88-4.73 (m, 1H), 4.60-4.48 (m, 2H), 3.94-3.90 (m, 1H), 3.82-3.71 (m, 1H), 3.63-3.62 (m, 3H), 3.54-3.24 (m, 2H), 2.88-2.87 (m, 3H), 2.69-2.60 (m, 1H), 1.14-1.13 (m, 3H). ^{13}C NMR (CDCl3, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 175.6 (2C), 169.4, 157.4, 157.1, 137.8, 136.8, 136.5, 128.6(2C), 128.2, 127.9 (2C), 73.3, 67.8, 67.2, 66.8, 59.5, 58.8, 52.0, 41.7, 41.6, 39.5, 31.3, 27.7, 14.9. ESI MS calcd for $C_{24}H_{30}N2O_6$ [(M + H)$^{+}$]: 443, found: 443.



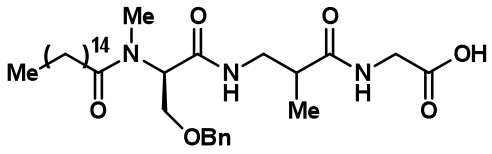
36

To a solution of compound **35** (86 mg, 0.2 mmol, 1 eq) in MeOH (10 mL) was added pyridine (8 µL, 0.5 eq), and 10% Pd/C (1/3 w/w) and the reaction was placed under an atmosphere of H_2. After all of the starting material had been consumed the reaction was filtered over Celite and concentrated. The crude material was then taken up in a 9% solution of $NaHCO_3$ (2.5 mL), treated with palmitoyl chloride (710 µL, 12 eq) in DCM (2.5 mL) and stirred vigorously for 4 h. The organic layer was then removed and the aqueous layer was extracted 2× with DCM. The combined organic layers were dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (5% EtOAc in Hex then 50% EtOAc in Hex) to give **36** (60 mg, 56% yield). ^{1}H NMR (CDCl3, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.33-7.26 (m, 5H), 6.82-6.76 (m, 1H), 5.26-5.22 (m, 2H), 4.56-4.45 (m, 2H), 3.87-3.77 (m, 2H), 3.64-3.63 (m, 3H), 3.51-3.35 (m, 1.5H), 3.26-3.20 (m, 0.5H), 2.92-2.90 (m, 2.5H), 2.77-2.74 (m, 0.5H), 2.68-2.61 (m, 1H), 2.35-2.32 (m, 2H), 1.65-1.59 (m, 2H), 1.28-1.24 (m, 26H), 1.15-1.11 (m, 3H), 0.88-0.85 (m, 3H). ^{13}C NMR (CDCl3, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 175.4 (2C), 174.8, 174.8, 169.5, 169.5, 137.7, 128.5, 127.8, 66.9, 66.8, 56.1, 56.0, 51.9, 51.8, 41.6, 41.5, 39.5, 39.5, 33.8, 32.0 (2C), 29.7(2C), 29.6, 29.5 (2C), 29.4, 25.0(2C), 22.7, 14.8, 14.7, 14.2. ESI MS calcd for $C_{31}H_{52}N_2O_5$ [(M + H)$^{+}$]: 547, found: 548.



37

Compound **36** (60 mg, 0.11 mmol) was subjected to general procedure A to give the crude acid. This material was then dissolved in DCM (3 mL) and DMF (1 mL), treated with TEA (20 µL, 1.1 eq), H-Gly-OMe HCl (18 mg, 1.25 eq), HOBt (51 mg, 3.3 eq) and EDC (66 mg, 3 eq) and allowed to stir overnight. The volatiles were then evaporated, DCM was added, the organic layer was washed with saturated $NaHCO_3$, 0.1 N HCl and brine, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (EtOAc) to give **37** (36 mg, 51%).

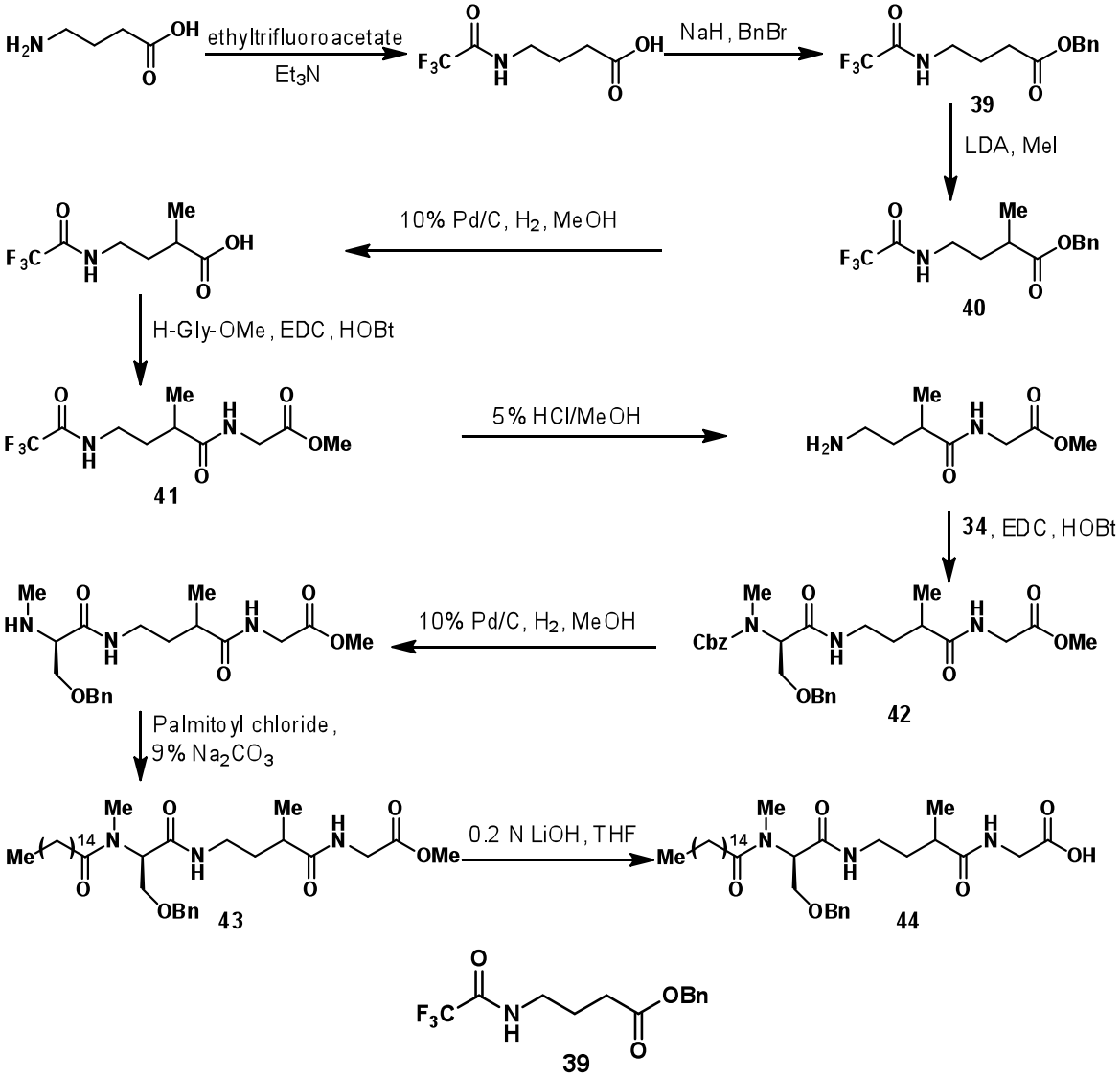


38

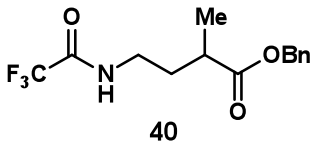
Compound **37** (36 mg, 60 µmol) was then subjected to general procedure D and purified by column chromatography (10% MeOH in DCM w/ trace AcOH) to give **38** (29 mg, 84%). ^{1}H NMR (CDCl3, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.43-7.23 (m, 6H), 7.15-6.94 (m, 1H), 5.12-5.03 (m, 1H), 4.55-4.42 (m, 1.5H), 4.09-4.01 (m, 0.5H), 3.93-3.89 (m, 0.5H), 3.84-3.61 (m, 1.5H), 3.52-3.46 (m, 0.5H), 3.12-3.07 (m, 0.5H), 3.00-2.98 (m,

1.75H), 2.79-2.73 (m, 0.25H), 2.61-2.55 (m, 0.5H), 2.33-2.30 (m, 1.25H), 2.05 (s, 1.25H), 1.60-1.53 (m, 1.5H), 1.30-1.24 (m, 21H), 1.12-1.06 (m, 3H), 0.87 (t, *J* = 7Hz, 3H). ^{13}C NMR (CDCl3, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 176.2 (2C), 175.7, 170.1, 169.7, 137.6 (2C), 128.8, 128.6, 128.5, 128.1, 128.0 (4C), 73.3, 73.2, 67.3, 67.2, 57.8, 57.2, 43.0, 40.7, 40.6, 34.0, 33.9, 32.9, 32.8, 32.0, 29.8 (2C), 29.7, 29.6, 29.5(2C), 25.0, 22.8, 14.7(2C), 14.2. ESI MS calcd for $C_{33}H_{55}N_3O_6$ [(M + H)$^+$]: 589, found: 589.

Compound 21 Tail Synthesis Scheme:

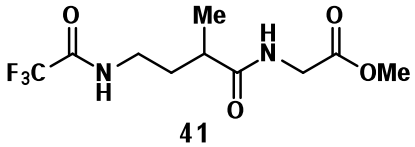


To a solution of racemic γ-aminobutyric acid (4.12 g, 40 mmol, 1 eq.) in MeOH (80 mL) under Ar was added ethyl trifluoroacetate (5.95 mL, 1.25 eq) and triethylamine (5.55 mL, 1 eq). The solution was stirred overnight then concentrated, taken up in DCM, concentrated and dried under vacuum. The crude product was then taken up in DCM (26.7 mL) and DMF (50 mL) under Ar, treated with BnBr (4.78 mL, 1.1 eq) and K_2CO_3 (4.97 g, 0.9 eq) and stirred at 35 °C overnight. To the solution was then added DCM and water. The organic phase was separated, then washed with saturated $NaHCO_3$ and 0.1 N HCl, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (20% EtOAc in Hex) to give **39** as a white solid (4.6 g, 40% yield) ^{1}H NMR (CDCl3, 400 MHz) δ (ppm) 7.37-7.33 (m, 5H), 7.14 (br s, 1H), 5.13 (s, 2H), 3.43-3.38 (m, 2H), 2.46 (t, *J* = 6.8 Hz, 2H), 2.04-1.85 (m, 2H). ^{13}C NMR (CDCl3, 100 MHz) δ (ppm) 173.4, 157.7, 157.4, 135.6, 128.7, 128.5, 128.4, 66.8, 39.7, 31.8, 23.7. ESI MS calcd for $C_{13}H_{14}F_3NO_3$ [(M + Na)$^+$]: 312.1, found:312.1.



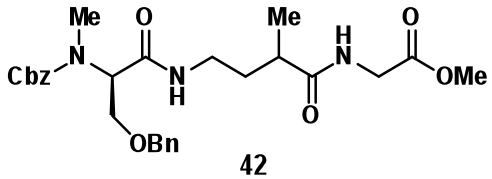
40

To a solution of LDA (2 M in heptane/THF/ethylbenzene, 5.0 mL, 2.5 eq) at -78 °C under N_2 was slowly added compound **38** (1.16 g, 4.0 mmol, 1 eq) in THF (25 mL) via syringe. The solution was stirred for 45 min then MeI (1.25 mL, 5 eq) was added and the solution was stirred for 2 h. The reaction was then quenched with 1.0 N HCl and allowed to warm to room temp. The volatiles were evaporated under N_2, the aqueous phase was extracted 3x with DCM, and the combined organic phases were washed with brine dried over sodium sulfate and concentrated. The crude product was purified via column chromatography (20% EtOAc in Hex) to give **40** (846 mg, 70%). ^{1}H NMR (CDCl3, 400 MHz) δ (ppm) 7.39-7.33 (m, 5H), 6.92 (br s, 1H), 5.13 (s, 2H), 3.40-3.35 (m, 2H), 2.60-2.55 (m, 1H), 1.97-1.91 (m, 1H), 1.81-1.72 (m, 1H), 1.23 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (CDCl3, 100 MHz) δ (ppm) 176.1, 157.6, 157.2, 135.8, 128.8, 128.5, 128.3, 117.4, 114.5, 100.1, 66.7, 38.1, 37.5, 32.2, 17.2. ESI MS calcd for $C_{14}H_{16}F_3NO_3$ [$(M + Na)^+$]: 326.2, found: 326.3.



41

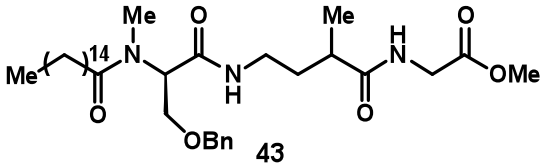
A solution of compound **40** (146 mg, 0.65 mmol, 1 eq) in THF (4.3 mL) was treated with 10% Pd/C (65 mg, 1/3 w/w) and the mixture was put under an atmosphere of H_2. The reaction was allowed to stir overnight then filtered through Celite and concentrated. The crude was taken up in DCM (13 mL) and DMF (4.6 mL) and treated with EDC (371 mg, 3 eq), HOBt (287 mg, 3.3 eq), TEA (184 µL, 2.05 eq) and H-Gly-OMe-HCl (101 mg, 1.25 eq) under Ar. The reaction was stirred overnight then the volatiles were evaporated under a stream of N_2. Next, EtOAc was added and the organic phase was washed with saturated $NaHCO_3$, 0.1 N HCl, and brine. The organics were dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (3% MeOH in DCM) to give **41** (81.0 mg, 44%). 1H NMR (CDCl3, 500 MHz) δ (ppm) 7.72 (s, 1H), 6.66 (m, 1H), 4.07 (dd, *J* = 18 Hz, *J* = 6 Hz, 1H), 3.92 (dd, *J* = 18 Hz, *J* = 5 Hz, 1H), 3.73 (s, 3H), 3.49-3.42 (m, 1H), 3.38-3.31 (m, 1H), 2.46-2.39 (m, 1H), 1.93-1.86 (m, 1H), 1.77-1.70 (m, 1H), 1.18 (d, *J* = 7Hz, 3H). ^{13}C NMR (CDCl3, 125 MHz) δ (ppm) 176.7, 170.7, 117.2, 114.9, 52.5, 41.2, 38.8, 38.1, 32.7, 18.0. ESI MS calcd for $C_{10}H_{15}F_3N_2O_4$ [$(M + H)^+$]: 285.1, found: 285.2.



42

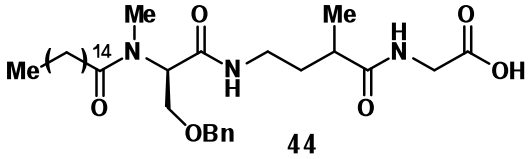
A solution of HCl in MeOH (5-10%, 10 mL) was added to compound **41** (200 mg, 0.7 mmol) in a vial. The vial was sealed, heated to 65 °C and stirred overnight. The reaction was cooled to room temperature and the volatiles were evaporated. The crude product was then taken up in DCM (14.0 mL), and DMF (5.0 mL), and to it was added compound **34** (207 mg, 0.85 eq), HOBt (313 mg, 3.3 eq), EDC (403 mg, 3 eq) and TEA (127 µL, 1.3 eq). The reaction was allowed to stir overnight under Ar then DCM was added, the organic layer was washed with saturated $NaHCO_{3(aq)}$, 0.1 N HCl, and brine, and finally dried over sodium sulfate and concentrated. The crude was purified by column chromatography (50% EtOAc in Hex) to give **42** (144 mg, 54%). ^{1}H NMR (CDCl3, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.33-7.28 (m, 10H), 7.14-6.85 (m, 1H), 5.18-5.07 (m, 2H), 4.85 (m, 0.25H), 4.72-4.69 (m, 0.5H), 4.55-4.48 (m, 2H), 4.19-4.09 (m, 1H), 3.96-3.69 (m, 6H), 3.43-3.06 (m, 2H), 2.96-2.86 (m, 3H), 2.25-2.21 (m, 1H), 2.03-2.12 (m, 0.5H), 1.71-1.70 (m, 2H), 1.07 (d, *J* = 3H, 3H). ^{13}C NMR (CDCl3, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled

resonances) 176.7, 176.5, 171.4, 171.2, 169.9, 169.8, 157.6, 157.5, 137.7, 137.6, 136.4, 136.3, 128.7, 128.6, 128.3, 128.0, 127.9, 127.8, 73.3, 67.7, 67.2, 59.4, 52.4, 41.0, 38.0, 37.8, 37.5, 37.5, 33.8, 31.7, 31.5, 18.0, 18.0. ESI MS calcd for $C_{27}H_{35}N_3O_7$ [(M + H)$^+$]: 514, found: 514.



43

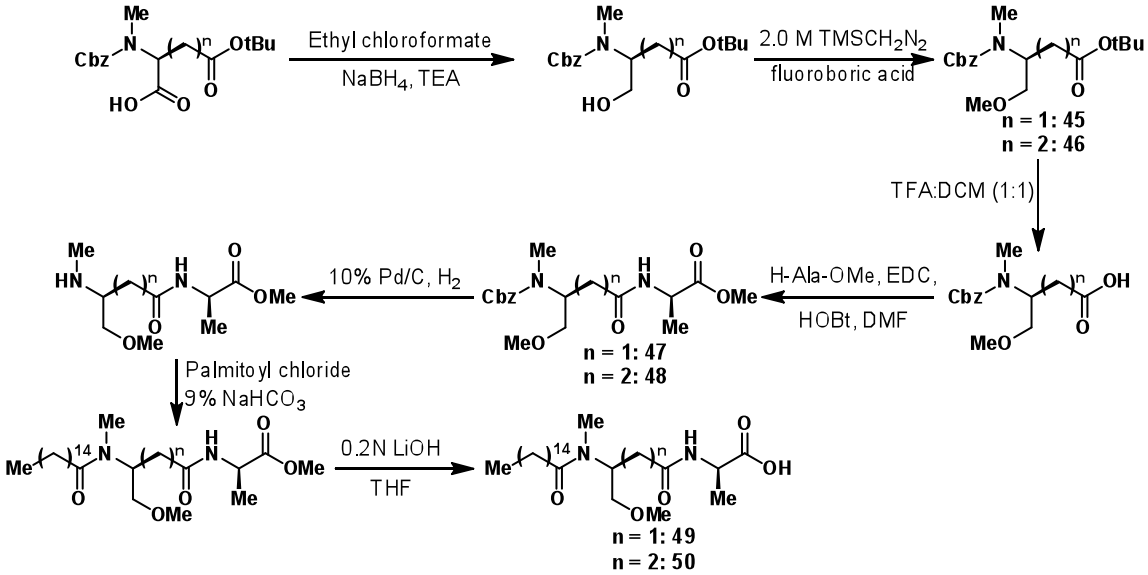
To a solution of compound **42** (63 mg, 0.12 mmol) in MeOH (3 mL) and THF (3 mL) was added pyridine (5 µL, 0.5 eq) and 10% Pd/C (1/3 w/w) and the mixture was put under an atmosphere of H_2. After the starting material had been consumed, as determined by TLC, the reaction was filtered through Celite and concentrated. The crude product was then dissolved in a 9% $NaHCO_3$ solution (2 mL) and treated with palmitoyl chloride (450 µL, 12 eq) in DCM (2 mL) and stirred vigorously for 5 hrs. The organic layer was then removed and the aqueous layer was extracted with 2 additional portions of DCM. The combined organic layers were then dried over sodium sulfate, concentrated and purified by column chromatography (20% EtOAc in Hex then 100% EtOAc to elute) to give compound **43** (37 mg, 49%).

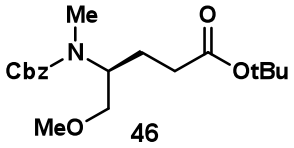


44

Compound **43** (37 mg, 1 eq) was then subjected to general procedure D to give **44** (26 mg, 69%). ^{1}H NMR (CDCl3, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.33-7.28 (m, 4H), 7.17-7.07 (m, 1H), 5.22 (m, 0.5H), 4.99 (m, 0.5H), 4.56-4.48 (m, 1.5H), 4.22-4.10 (m, 0.5H), 3.93-3.73 (m, 2H), 3.30-3.15 (m ,1H), 3.01-2.96 (m, 2H), 2.37-2.30 (m, 2H), 2.07 (s, 1H), 1.77-1.55 (m, 3H), 1.31-1.17 (m, 20H), 1.09 (d, *J* = 7 Hz, 3H), 0.89-0.86 (t, *J* = 7 Hz). ^{13}C NMR (CDCl3, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 177.4, 177.3, 175.7, 169.9, 169.7, 137.7, 137.6, 128.7, 128.6, 128.1 (2C), 128.0, 73.3, 67.0, 57.6, 56.8, 41.7, 38.2, 38.0, 37.6, 37.5, 34.1, 34.0, 33.7, 33.5, 33.0, 32.3, 32.1, 29.8, 29.7, 29.7, 29.6(2C), 29.5, 25.1, 25.1, 22.8, 20.8, 18.1, 14.3. ESI MS calcd for $C_{34}H_{57}N_3O_6$ [(M + H)$^+$]: 604, found: 604.

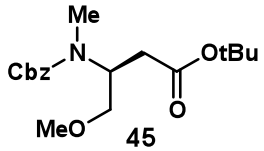
Compounds 22 and 23 tail synthesis scheme:





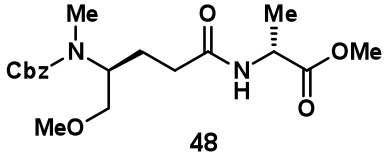
46

Compound **46** was synthesized by a modification of a reported procedure.[7] Cbz-N-Me-Glu(OtBu)-OH (200 mg, 0.57 mmol, 1 eq) was dissolved in THF and treated with ethyl chloroformate (54 µL, 0.99 eq), and TEA (79 µL, 0.99 eq) at 0° C. The reaction was allowed to stir for approximately 10 min. at which time it was filtered through glass wool to remove precipitates. To the filtrate was then added ice, water and $NaBH_4$ at 0° C and the mixture was stirred for an additional 10 min. Next, saturated $NaHCO_3$, water and EtOAc were added and the aqueous phase was extracted 3x with EtOAc. The combined organic layers were washed with 5% citric acid and brine then dried over sodium sulfate and concentrated. A portion of the crude material (132 mg, 0.39 mmol (theoretical)(Rf – 0.42 – 4% MeOH in DCM)) was taken up in DCM and subjected to a modification of a reported procedure.[8] The solution was cooled to 0° C on an ice bath and treated with a 50% solution of fluoroboric acid in water (49 µL, 1 eq) followed by 2.0 M $TMSCH_2N_2$ in Et_2O (488 µL, 2.5 eq) in five portions (1 eq, 0.5 eq, 0.25 eq, 0.25 eq, and 0.5 eq) at 20 min intervals. The solution was allowed to stir for an additional 20 min then was poured into water. The aqueous phase was extracted 3x with DCM then washed with water, dried over sodium sulfate and concentrated. The crude material was purified via column chromatography (1.75% MeOH in DCM) to give **46** as an oil (64.3 mg, 46% yield). Rf – 0.32 in 1.75% MeOH in DCM. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.36-7.27 (m, 5H), 5.18-5.11 (m, 2H), 4.37-4.34 (m, 0.5H), 4.28-4.25 (m, 0.5H), 3.48-3.42 (m, 1H), 3.37-3.28 (m, 3H), 2.80 (s, 3H), 2.24-2.18 (m, 2H), 1.78-1.72 (m, 2H), 1.43-1.41 (m, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 172.5, 172.4, 156.9, 156.9, 137.0, 137.0, 128.5, 127.9, 127.9, 80.5, 80.4, 73.1, 73.0, 67.3, 67.1, 58.9, 54.5, 32.2, 32.1, 29.0, 28.2, 24.0, 23.8. ESI MS calcd for $C_{19}H_{29}NO_5$ [$(M + Na)^+$]: 374.2, found: 374.4.



45

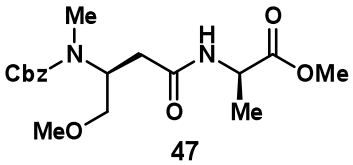
Compound **45** was synthesized and purified in an identical manner as compound **46** giving an oil (52.1 mg, 39% yield) ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.37-7.27 (m, 5H), 5.20-5.11 (m, 2H), 4.65-4.59 (m, 1H), 3.69-3.53 (m, 1H), 3.45-3.41 (m, 1H), 3.33-3.28 (m, 3H), 2.88 (s, 3H), 2.52-2.45 (m, 2H), 1.43-1.40 (m, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 169.1, 158.2, 128.5, 127.5, 127.0, 82.1, 67.4, 65.2, 54.1, 38.5, 38.5, 29.2, 28.0 ESI MS calcd for $C_{18}H_{27}NO_5$ [$(M + H)^+$]: 338.2, found: 338.4.



48

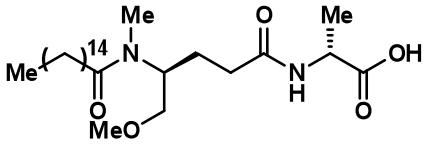
A solution of compound **46** (64 mg, 0.18 mmol, 1 eq) in DCM (1 mL) was treated with TFA (1 mL) and allowed to stir for 3 h. At this point TLC analysis showed no remaining starting material and the volatiles were evaporated under a stream of nitrogen, the residue was taken up again in DCM and was again evaporated under a stream of nitrogen. The residue was then dried under vacuum. This material was then taken up in DMF under Ar, and treated sequentially with HOBt (73 mg, 3 eq), H-D-Ala-OMe HCl (30 mg, 1.2 eq), EDC (104 mg, 3 eq), and DIEA (47 µL, 1.5 eq). The mixture was allowed to stir overnight, then water, 5% citric acid and EtOAc were added. The aqueous layer was extracted 4x with EtOAc and the combined organic layers were washed with saturated $NaHCO_3$, water and brine, dried over sodium sulfate and concentrated. The crude material was purified

by column chromatography (3.25% MeOH in DCM) to give **48** as an oil (45 mg, 65% yield). Rf – 0.33 in 3.25% MeOH in DCM. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.35-7.30 (m, 5H), 6.68-6.67 (m, 0.5H), 5.91 (m, 0.5H), 5.18-5.11 (m, 2H), 4.53-4.51 (m, 2H), 3.72-3.70 (m, 3H), 3.48-3.27 (m, 5H), 2.79 (s, 3H), 2.18-2.10 (m, 2H), 1.79-1.75 (m, 2H), 1.38-1.31 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 173.6, 172.3, 171.5, 157.5, 137.0, 136.9, 128.6, 128.1, 128.0, 127.8, 73.1, 72.8, 67.3, 67.2, 58.9, 58.8, 54.6, 54.2, 52.5, 52.4, 48.2, 48.0, 33.0, 32.7, 28.5, 24.5, 18.5, 18.1 ESI MS calcd for $C_{19}H_{28}N_2O_6$ [(M + H)$^+$]: 381.2, found: 381.4.



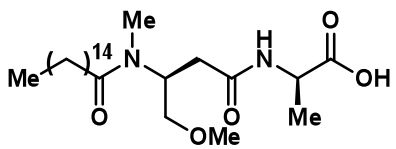
47

Compound **47** was synthesized and purified in an identical manner as compound **48** giving an oil (38 mg, 66%). Rf – 0.33 in 3.25% MeOH in DCM. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 7.34-7.29 (m, 5H), 6.58 (br s, 0.5H), 6.14 (br s, 0.5H), 5.18-5.09 (m, 2H), 4.52-4.50 (m, 2H), 3.70 (s, 3H), 3.61-3.43 (m, 2H), 3.33-3.29 (m, 3H), 2.89 (s, 3H), 2.66-2.46 (m, 2H), 1.31-1.30 (m ,3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 173.4, 169.9, 156.7, 136.8, 128.6, 128.0, 127.8, 73.0, 72.5, 67.4, 67.2, 58.9, 54.1, 53.1, 52.5, 48.2, 37.0, 36.6, 31.9, 18.4, 18.0. ESI MS calcd for $C_{18}H_{26}N_2O_6$ [(M + H)$^+$]: 367.2, found: 367.4.



50

To a solution of compound **48** (42 mg, 0.11 mmol, 1eq) in 95% EtOH was added 10% Pd/C (14 mg, 1/3 w/w) and the mixture was placed under an atmosphere of H_2. When all of the starting material had been consumed by TLC analysis, the mixture was filtered through Celite and concentrated by rotary evaporation. The crude residue was taken up in a 9% solution of $NaHCO_3$ (1.5 mL) and stirred vigorously while treated with a solution of palmitoyl chloride (50 µL, 1.5 eq) in DCM (1 mL). The mixture was allowed to stir overnight, then water and additional DCM were added and the aqueous layer was extracted 3x with DCM. The combined organic layers were dried over sodium sulfate and concentrated. The crude product was then taken up in THF and treated with 0.2 N $LiOH_{(aq)}$ (1.38 mL, 2.5 eq) and monitored by TLC (3% MeOH in DCM). When all of the starting material had been consumed, the reaction was acidified by the addition of 5% citric acid (pH 3) and the THF was evaporated under a stream of nitrogen. Approximately one half of the crude material was taken up in DMSO and purified by HPLC (linear gradient, 1% B/ min., product eluted at 98% B) to yield **50** as an oil. (17.5 mg, 69% yield). ^{1}H NMR (CD3OD, 600 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 4.79 (br s, 1H), 4.38-4.33 (m, 1H), 4.14-4.10 (m, 0.5H), 3.52-3.31 (m, 5H) 2.89 (s, 1.5H), 2.75 (s, 1H), 2.48-2.35 (m, 2H), 2.25-2.11 (m, 2H), 1.87-1.74 (m, 2H), 1.62-1.58 (m, 2H), 1.38-1.29 (m, 27H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 177.0, 176.9, 175.1, 174.5, 73.5, 73.4, 59.3, 58.9, 57.5, 53.4, 34.9, 34.3, 33.4, 33.1, 32.4, 30.8 (5C), 30.7 (2C), 30.6 (2C), 30.5 (2C), 30.3, 27.0, 26.5, 26.3, 25.4, 25.2, 23.7, 17.7, 17.6, 14.5. ESI MS calcd for $C_{26}H_{50}N_2O_5$ [(M + H)$^+$]: 471.4, found: 471.6.



49

Compound **49** was synthesized in the same manner as compound **50** yielding the product as an oil after HPLC purification (linear gradient, 1% B/ min, eluted at 97% B, 66% yield). ^{1}H NMR (CD3OD, 600 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 4.99 (br s, 1H), 4.56-4.55 (m, 0.5H), 4.37-4.34 (m, 1H), 3.58-3.40 (m, 2H), 3.34-3.30 (m, 4H), 2.96 (s, 1.5H), 2.80 (s, 1.5H), 2.56-2.43 (m, 3H), 2.43-2.34 (m, 1H), 1.57 (m, 2H), 1.38-1.30 (m, 27H), 0.90 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (CD3OD, 150 MHz) δ (ppm) (interconverting conformational isomers resulted in broadened or doubled resonances) 178.0, 176.7, 176.5, 172.6, 172.0, 73.2, 59.3, 59.0, 55.3, 52.6, 36.6, 36.3, 35.0, 34.0, 33.1, 30.8 (4C), 30.7 (2C),30.6, 30.5, 30.4, 27.6, 26.4, 26.2, 23.7, 17.7, 17.6, 14.5. ESI MS calcd for $C_{25}H_{48}N_2O_5$ [$(M + H)^+$]: 457.4, found: 457.6.

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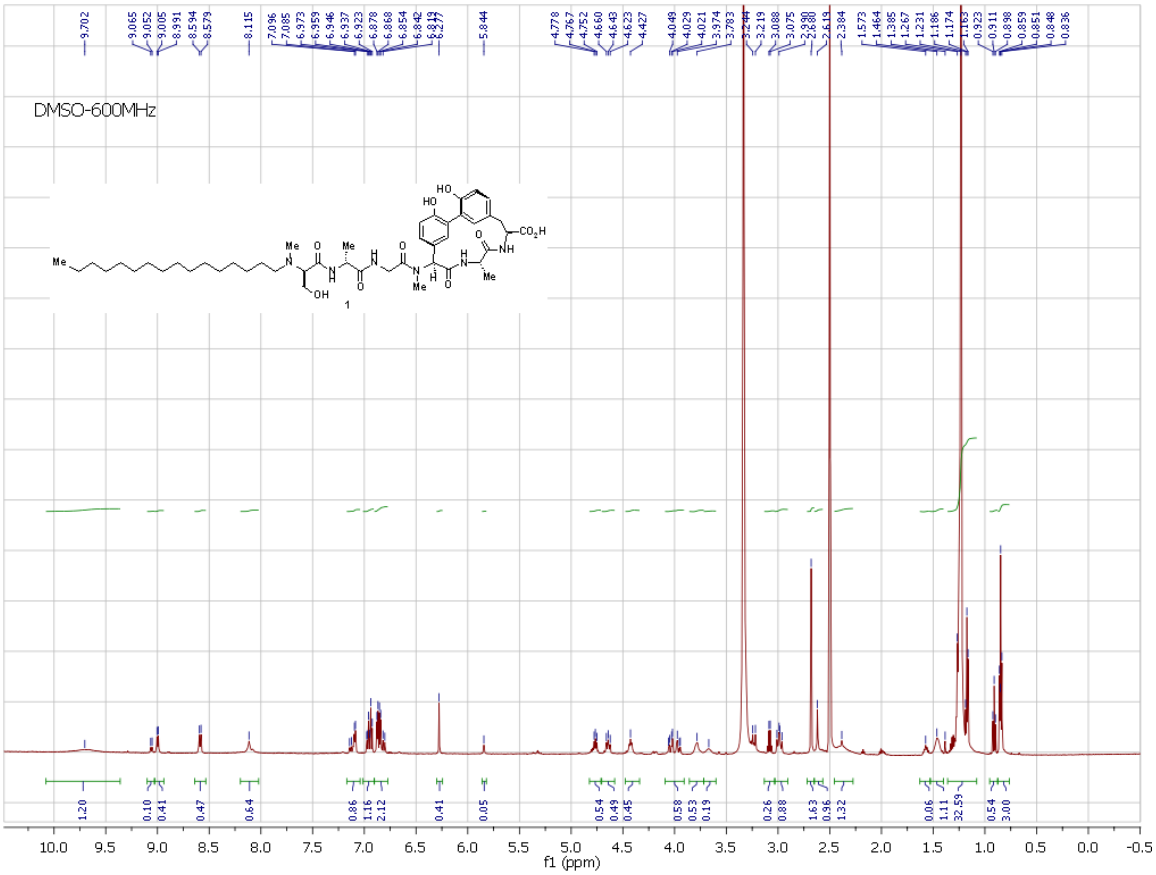
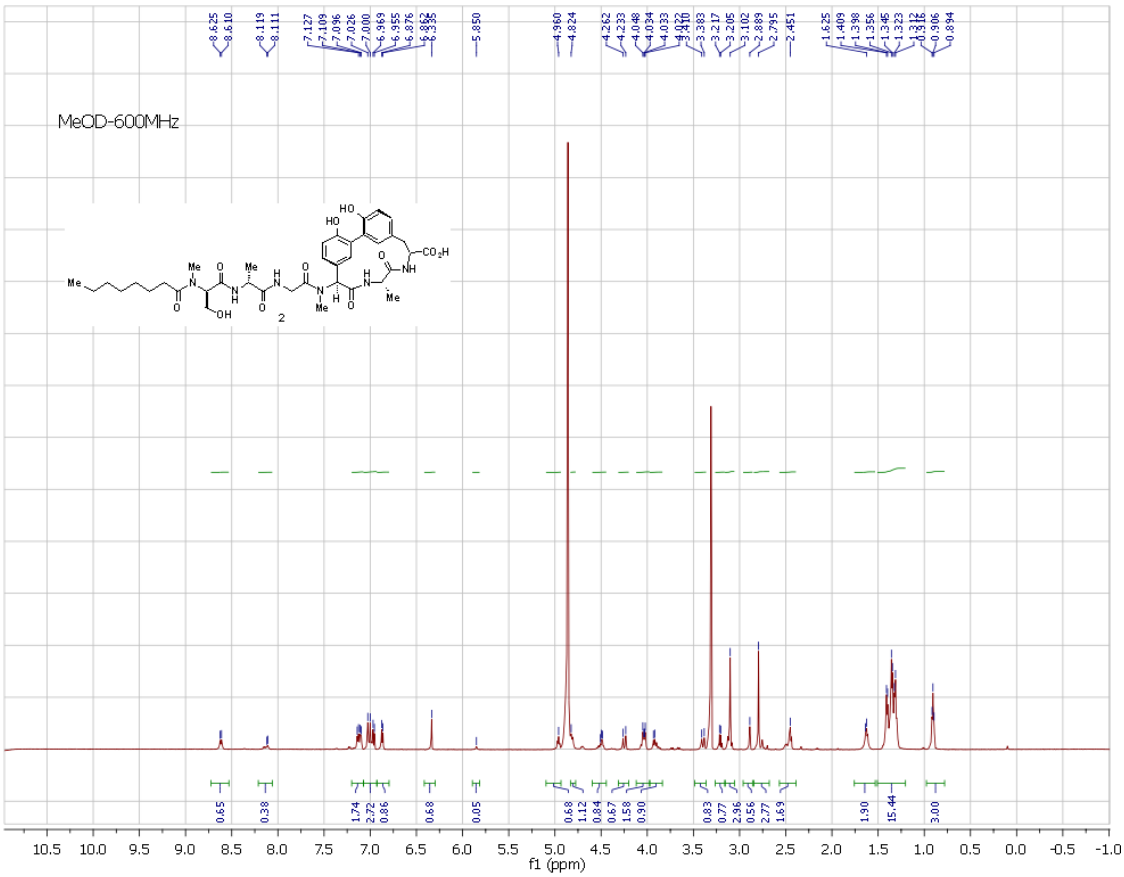
Spectra

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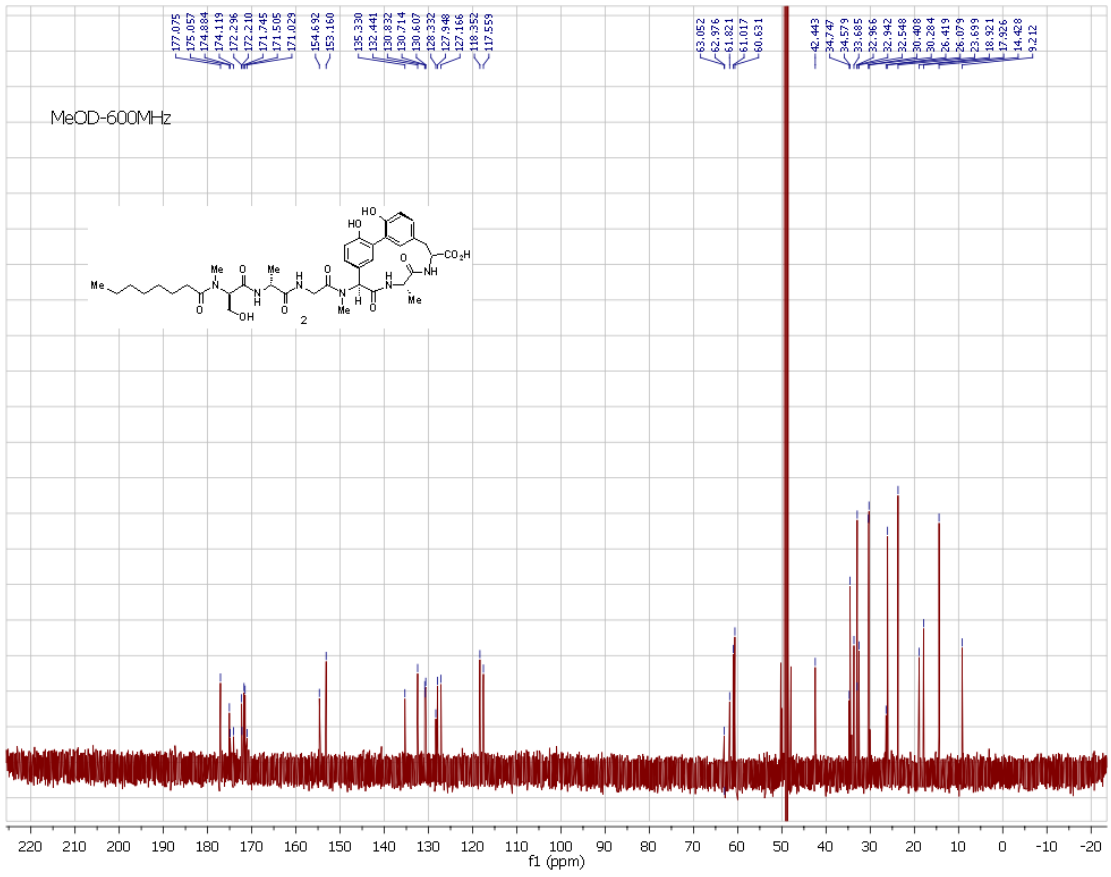
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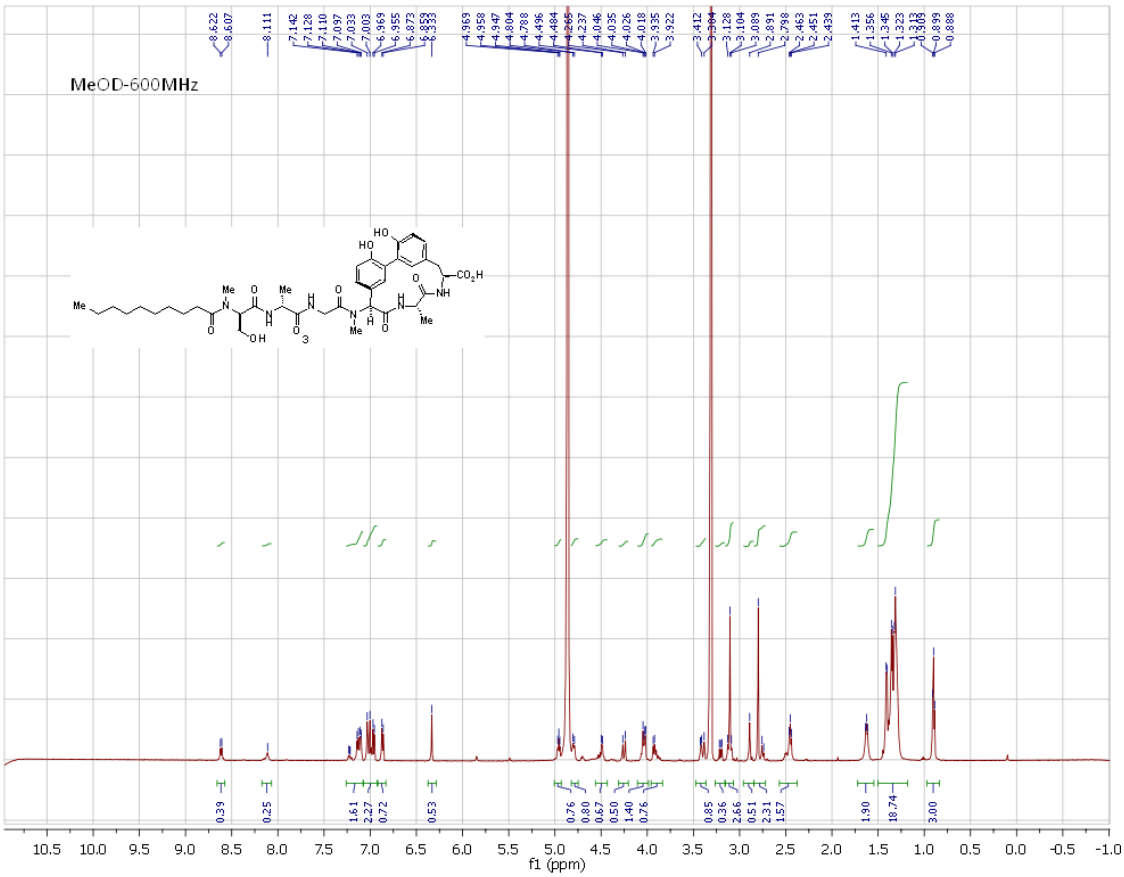
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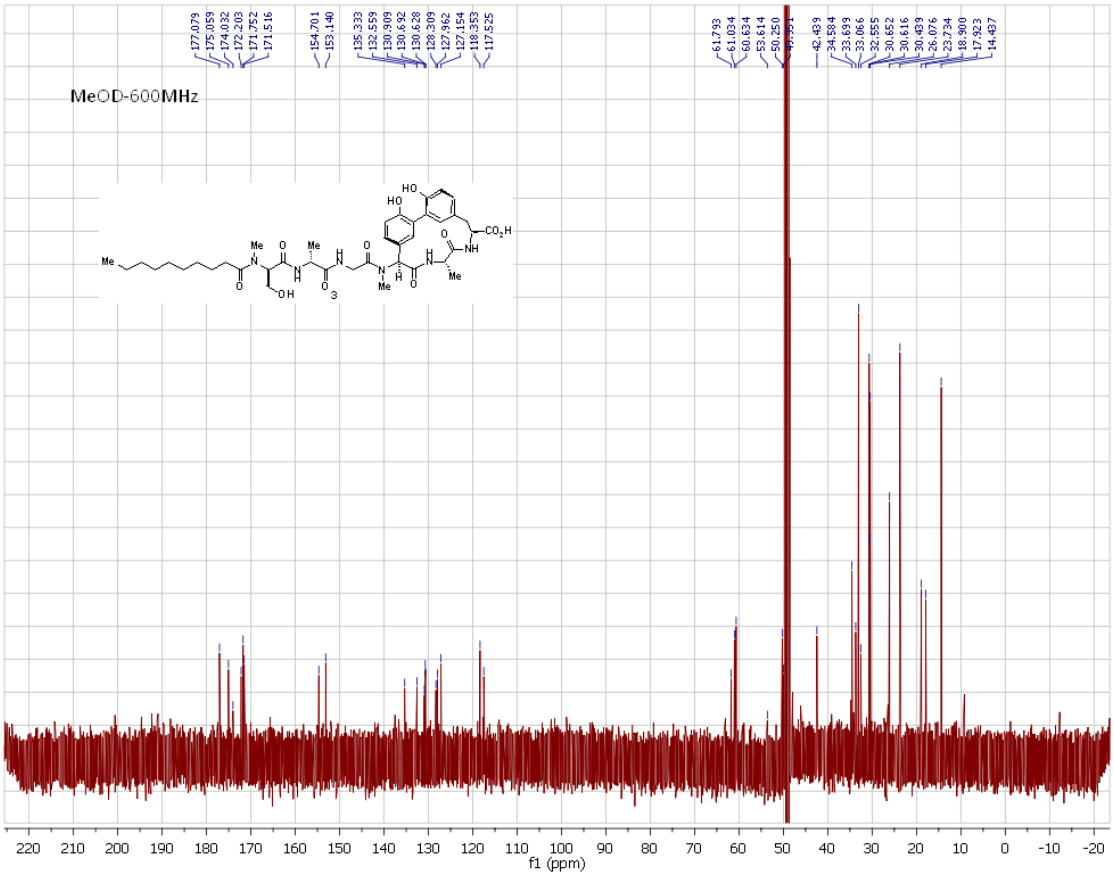
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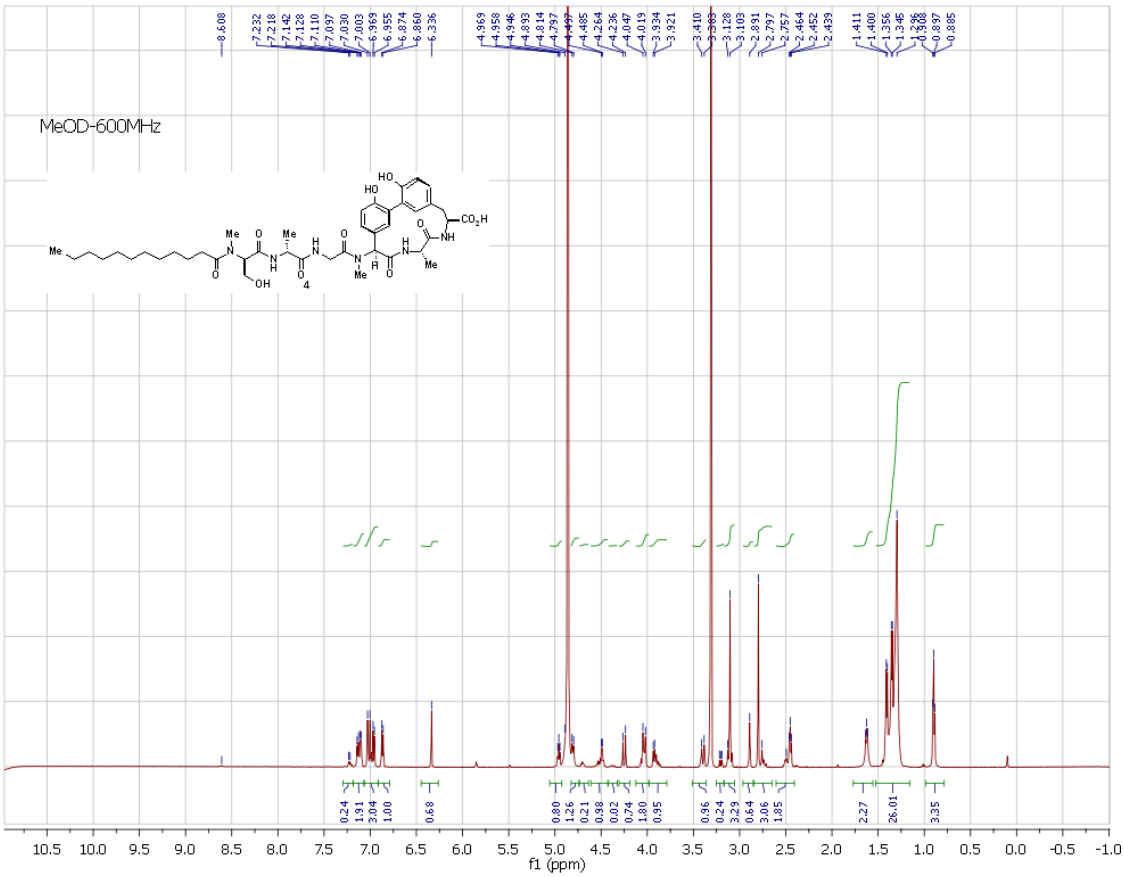
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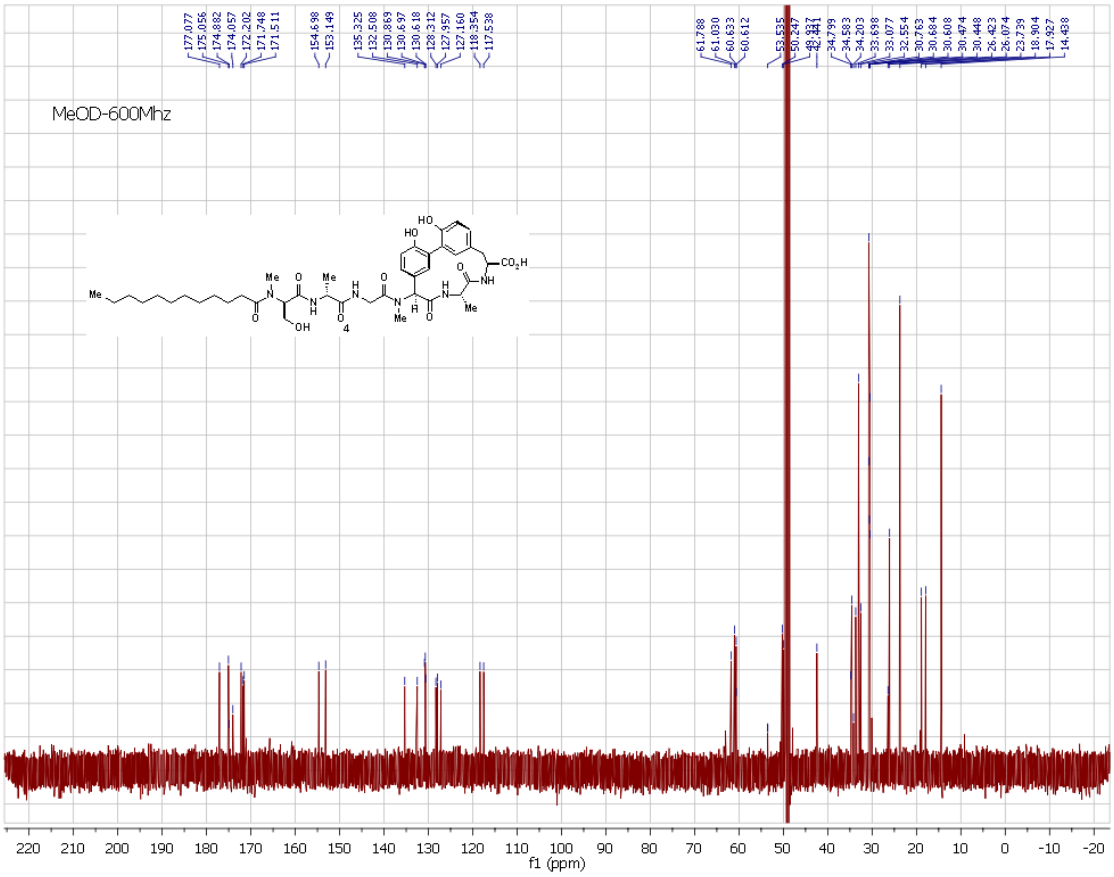
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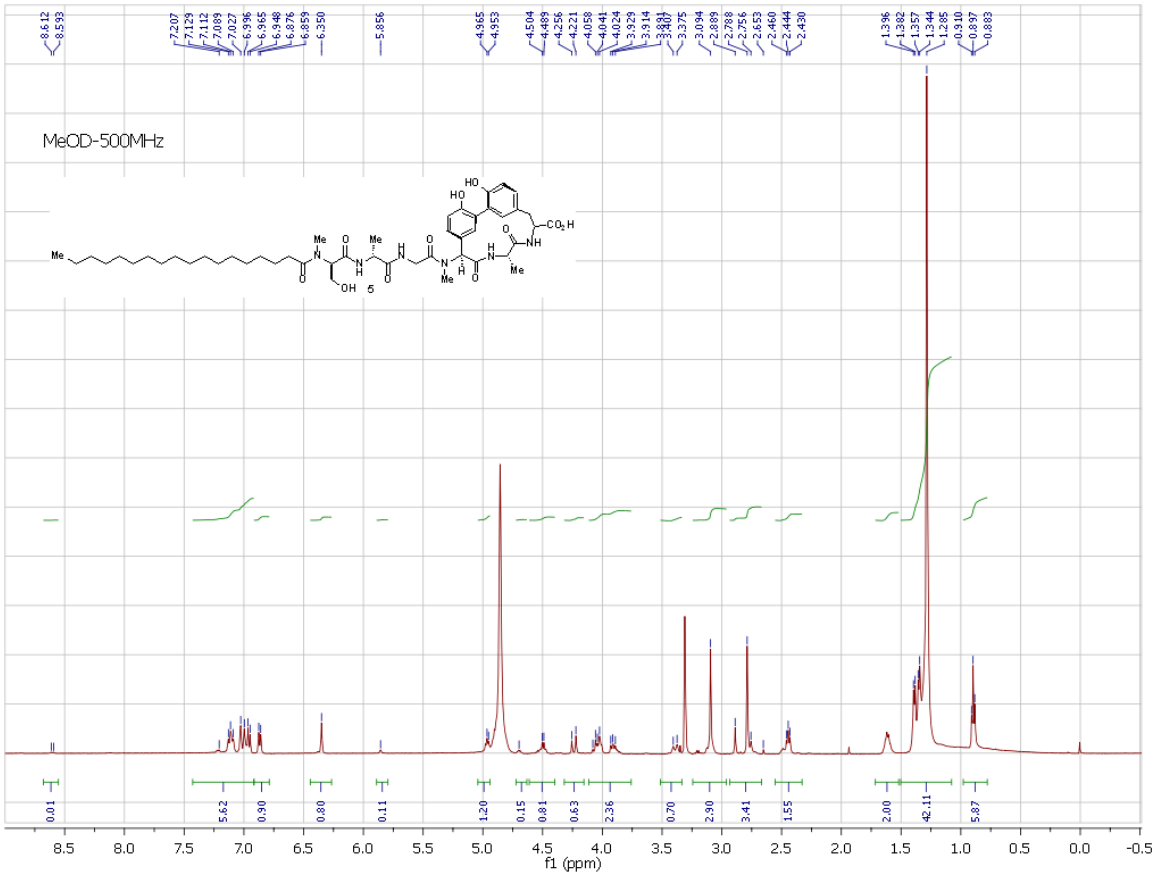
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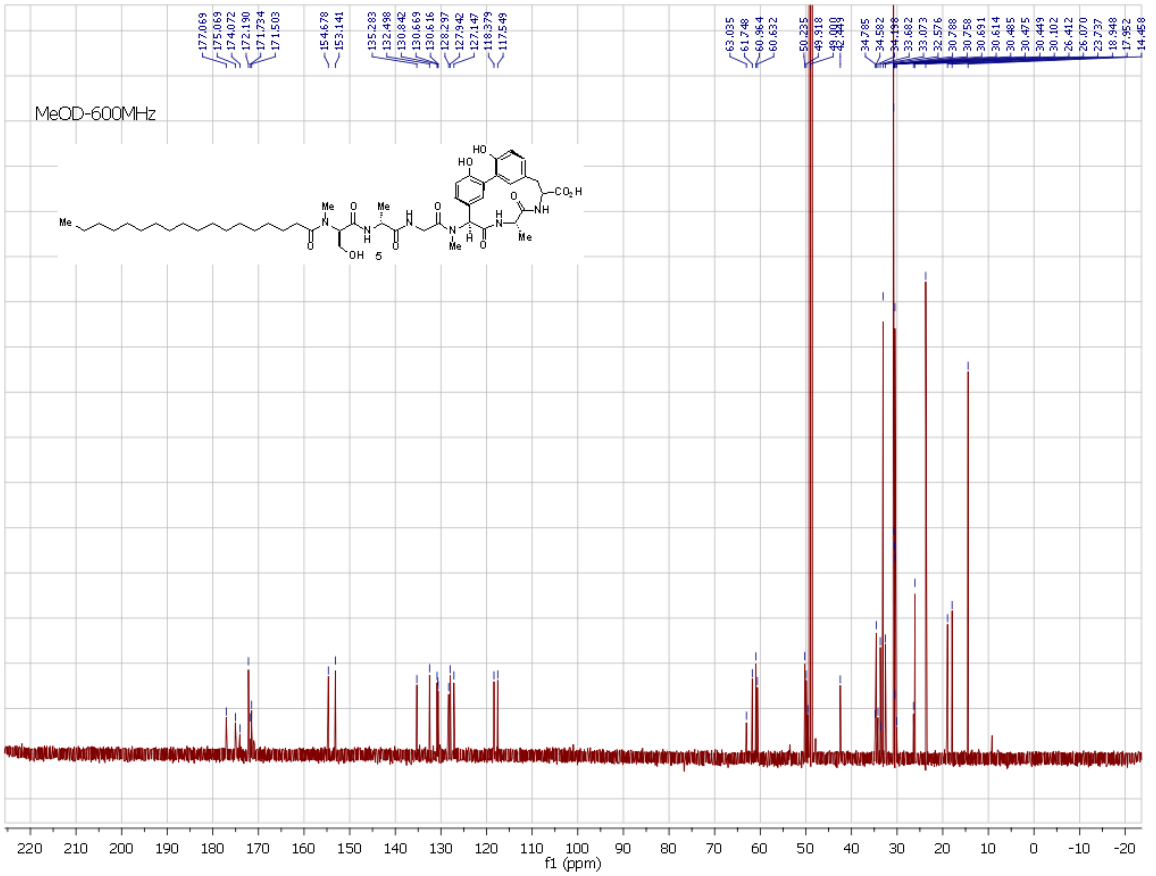
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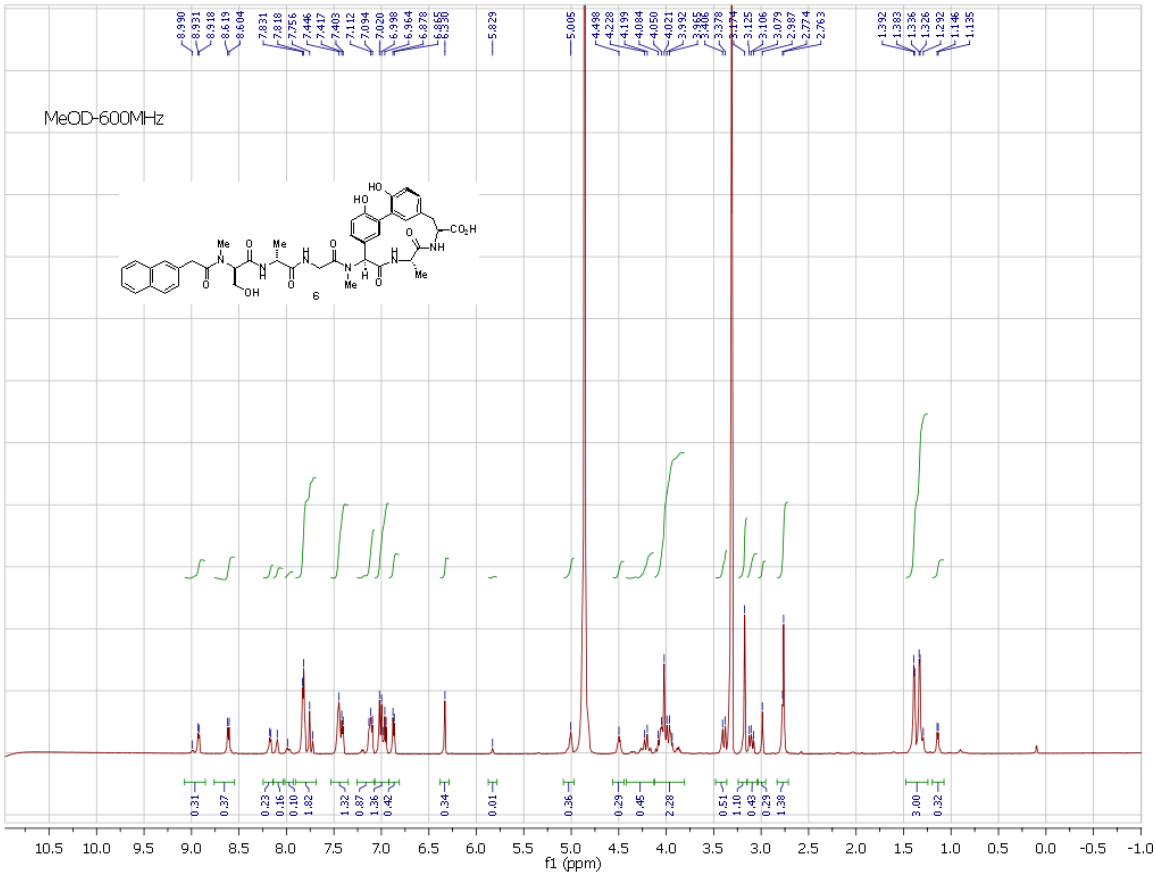
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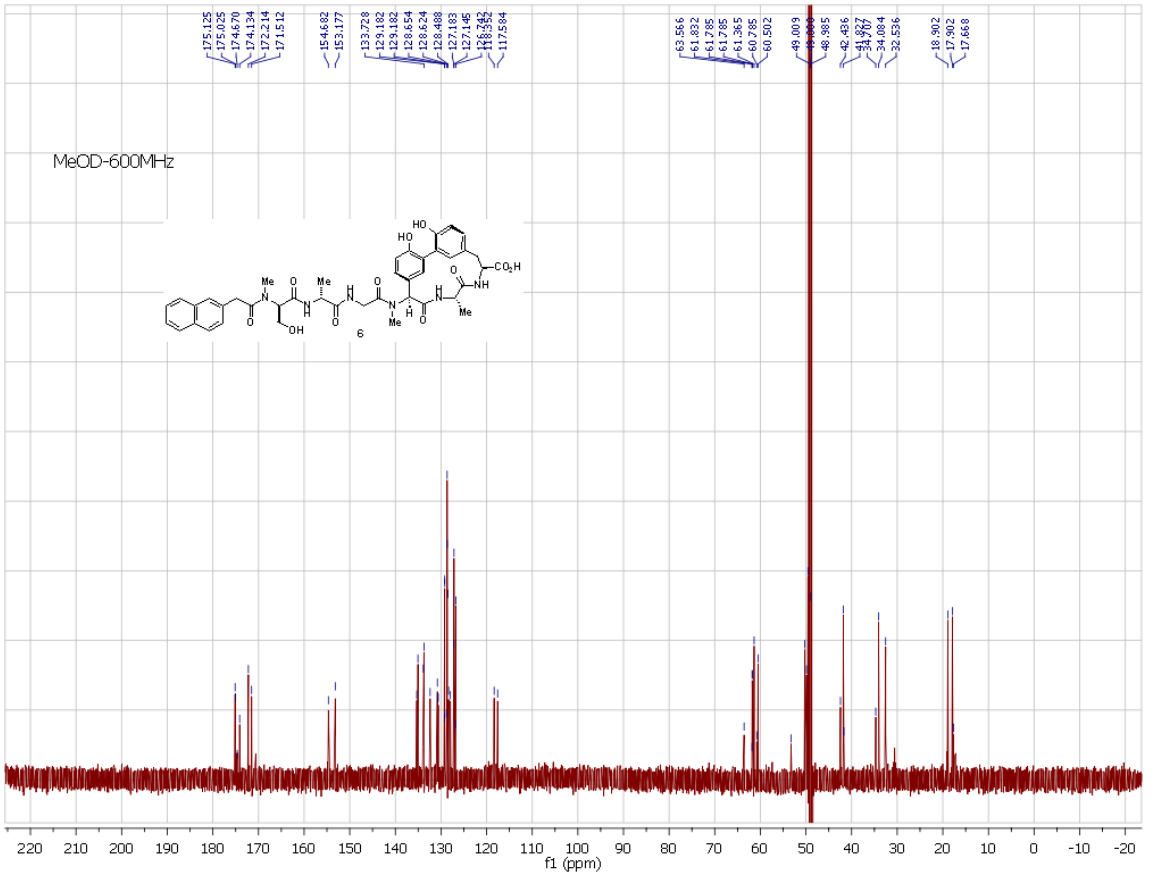
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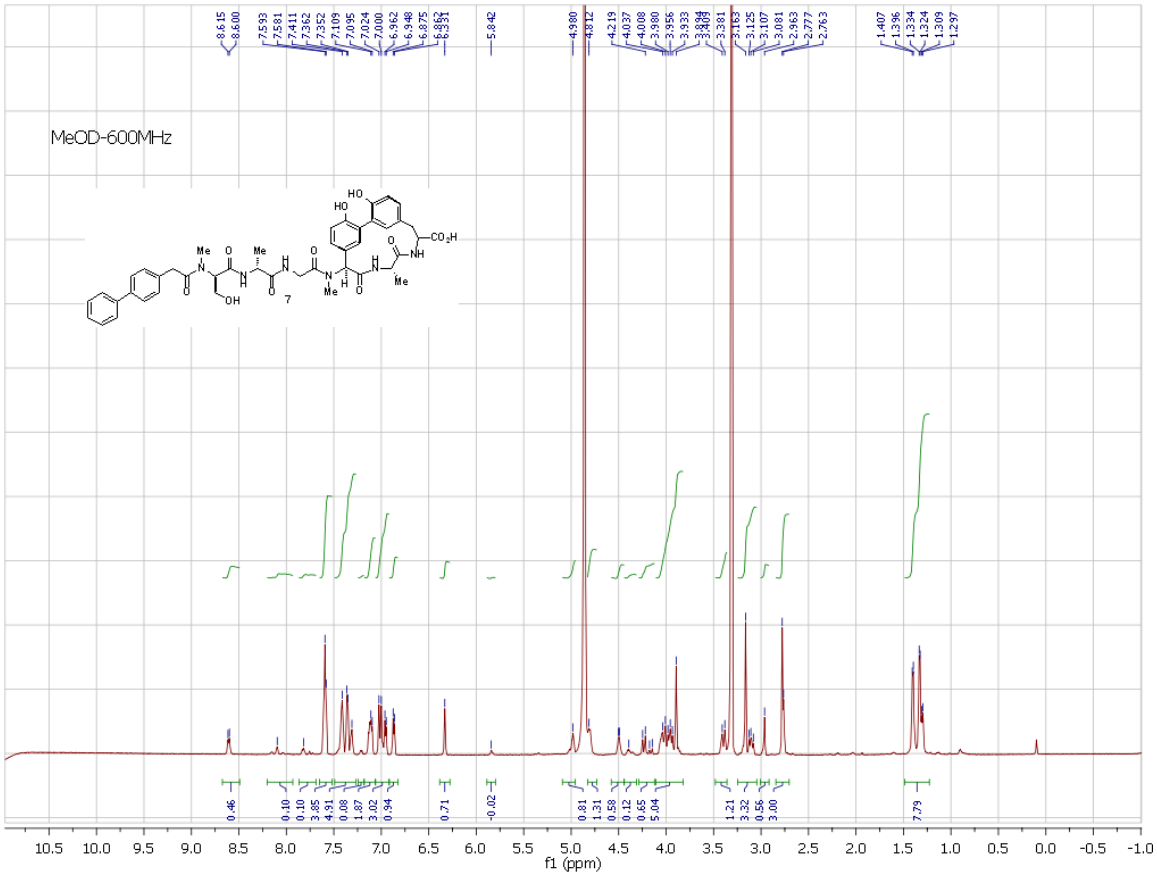
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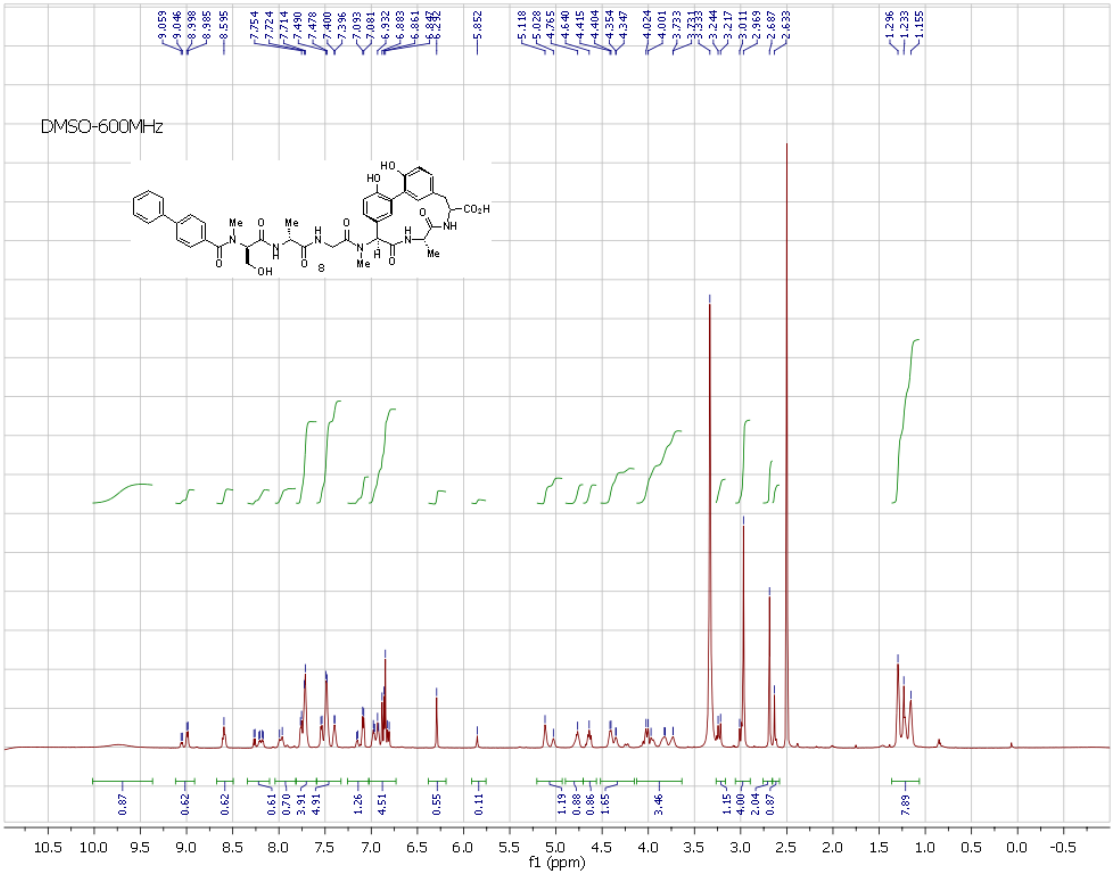
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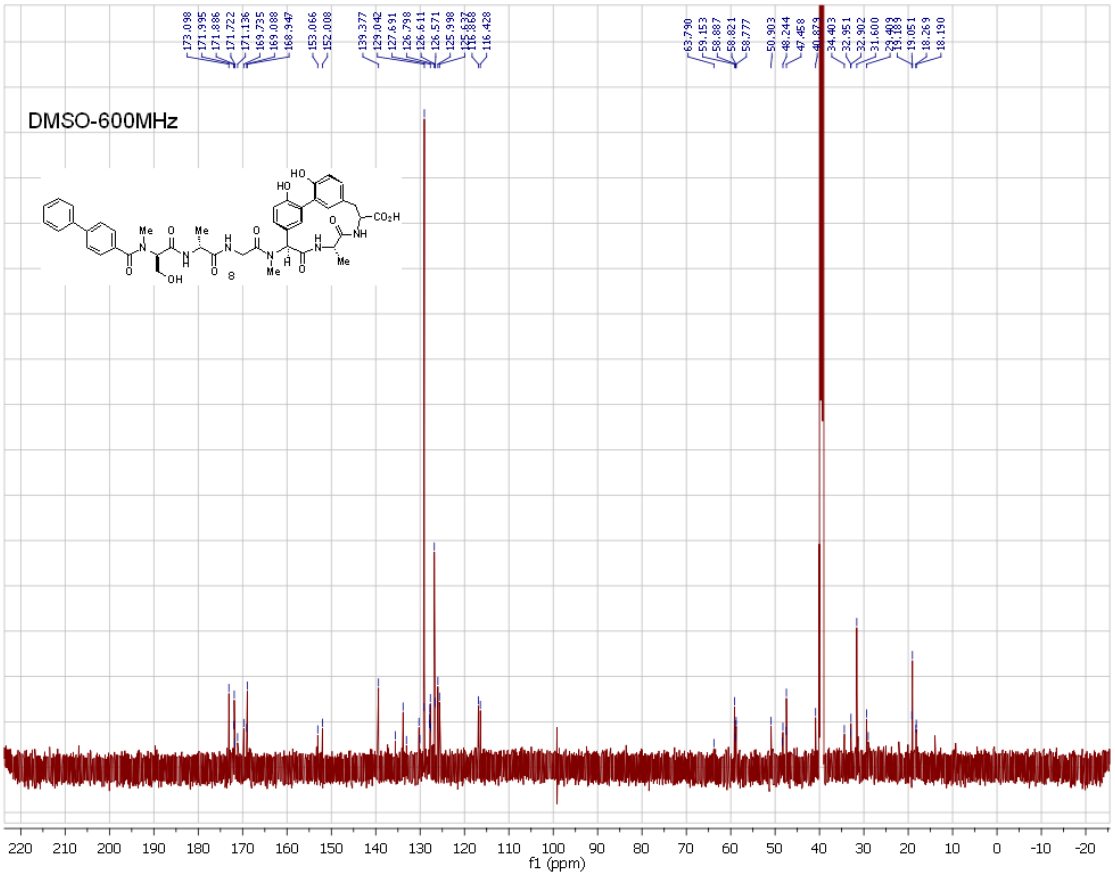
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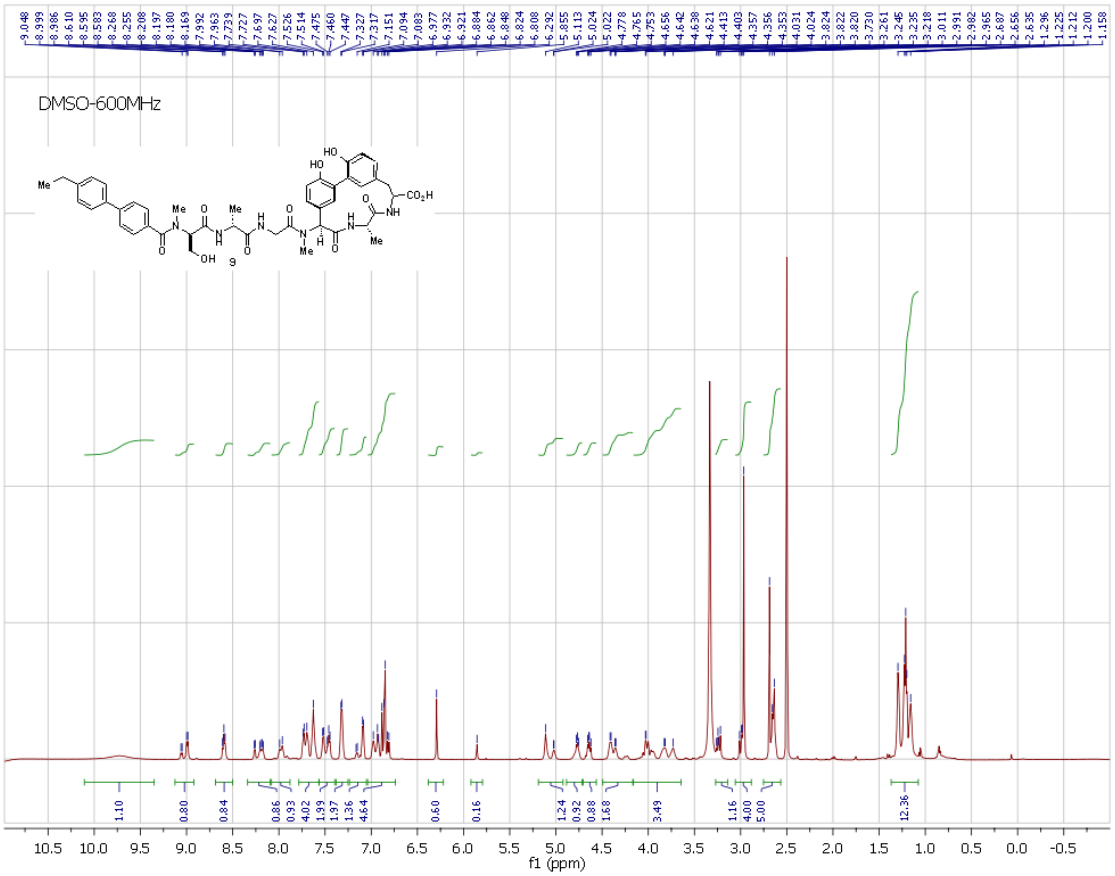
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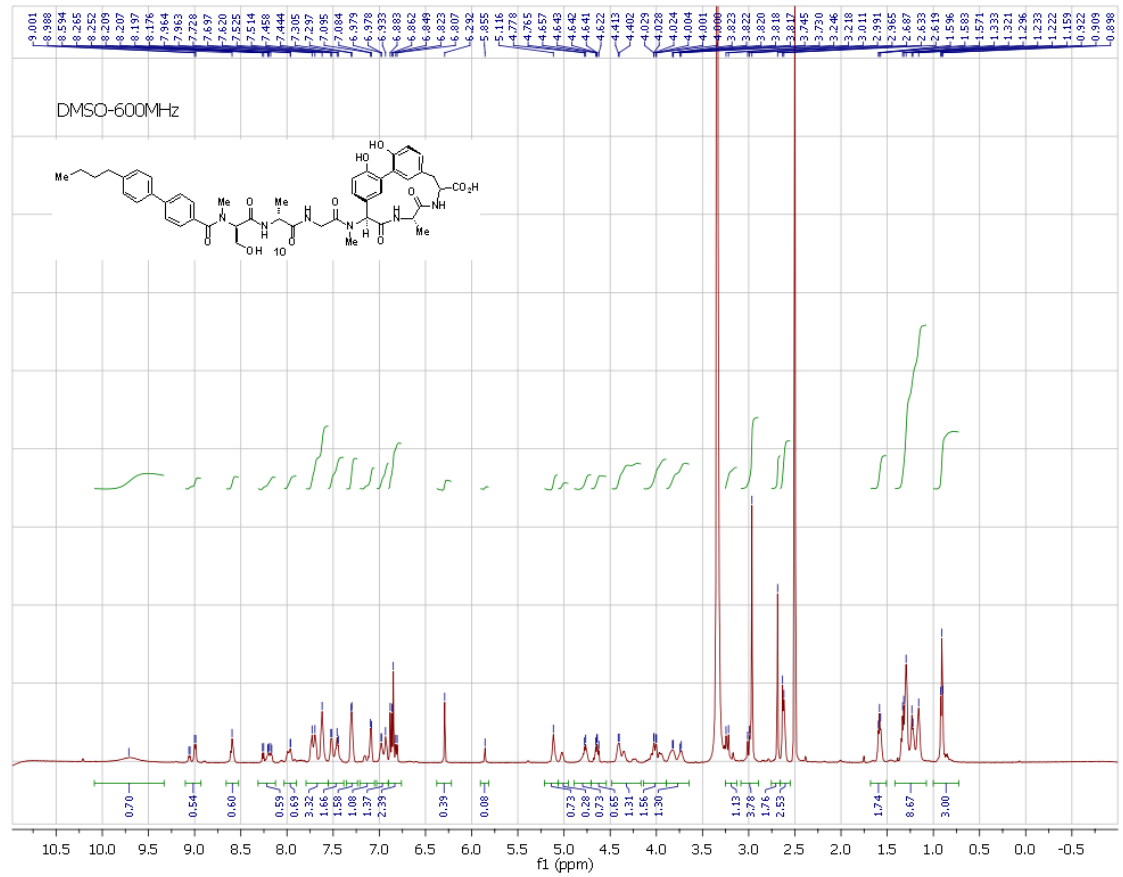
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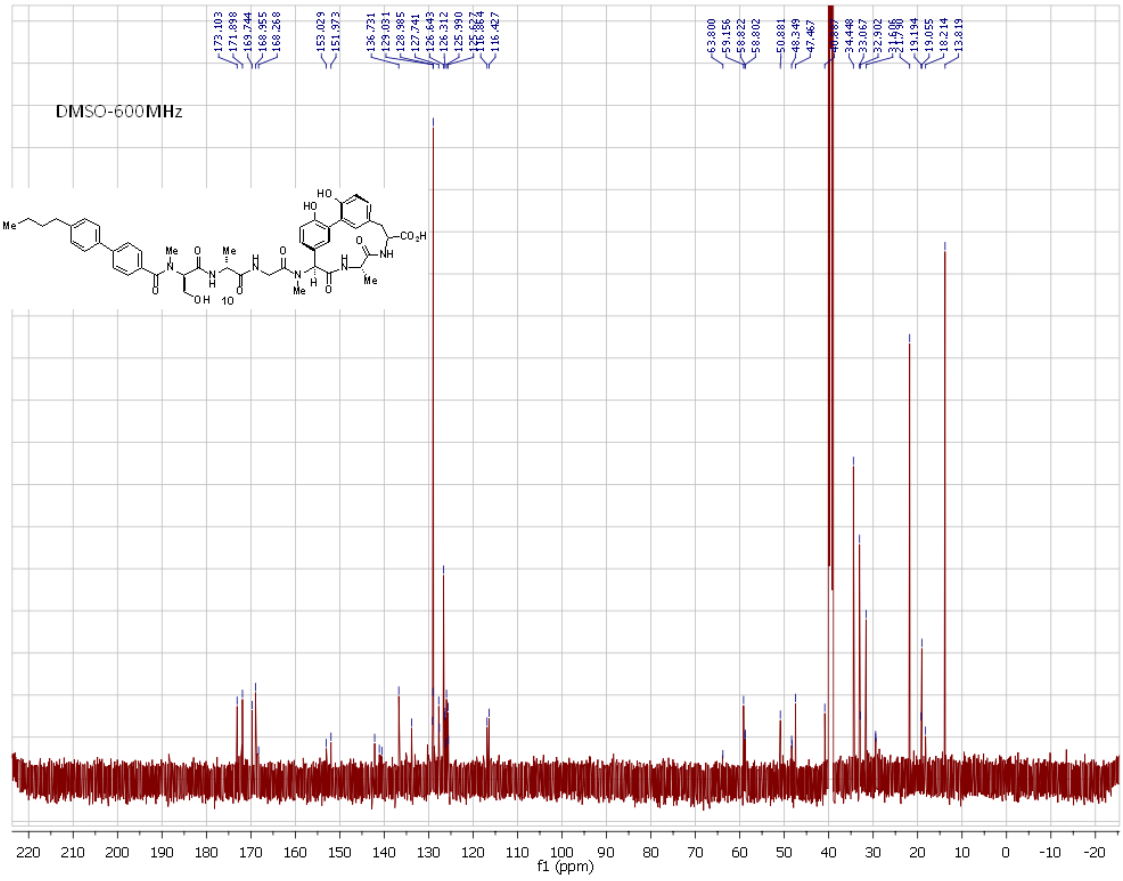
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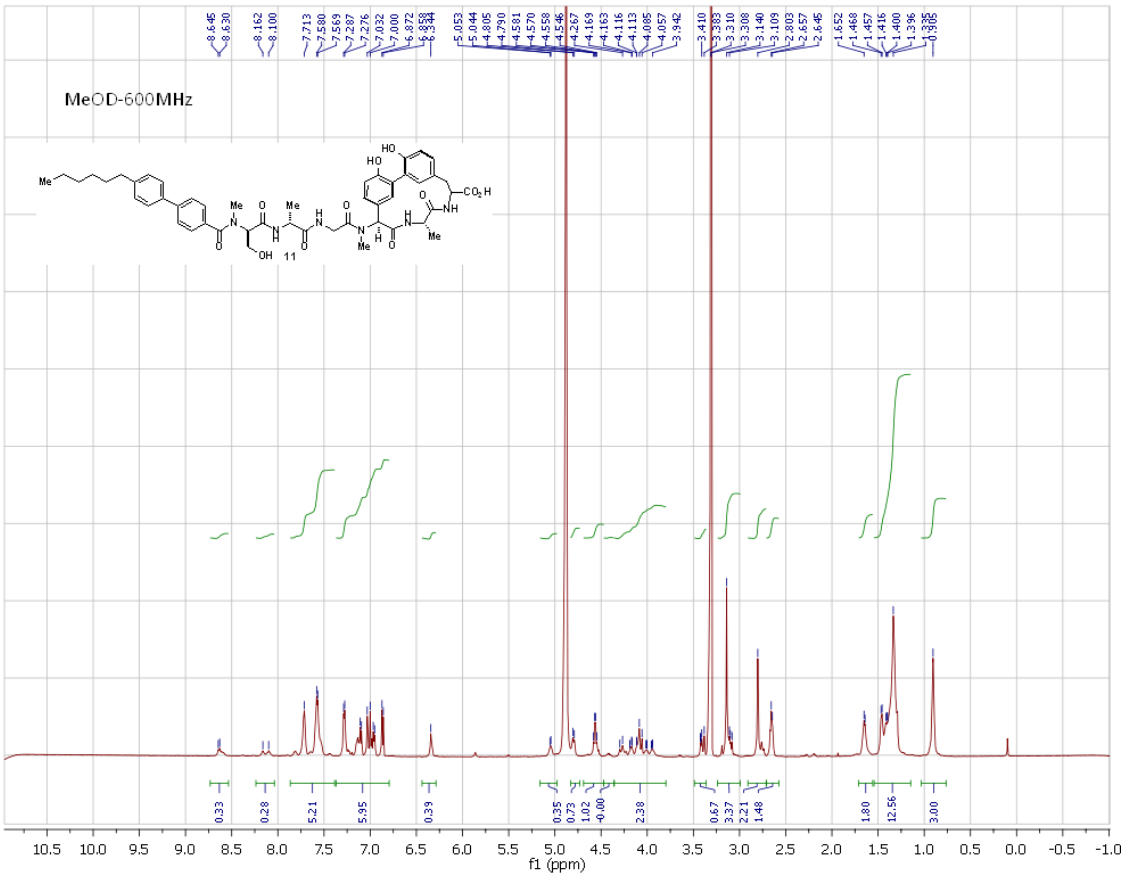
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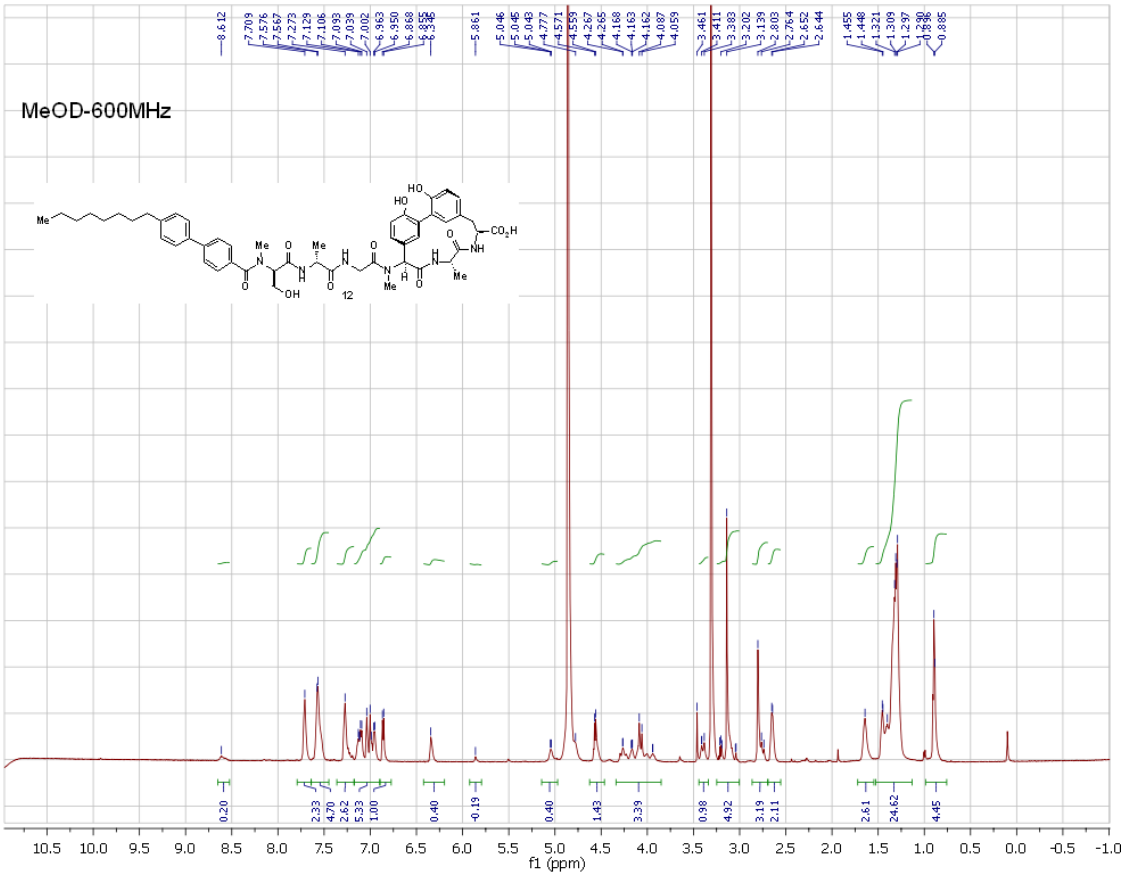
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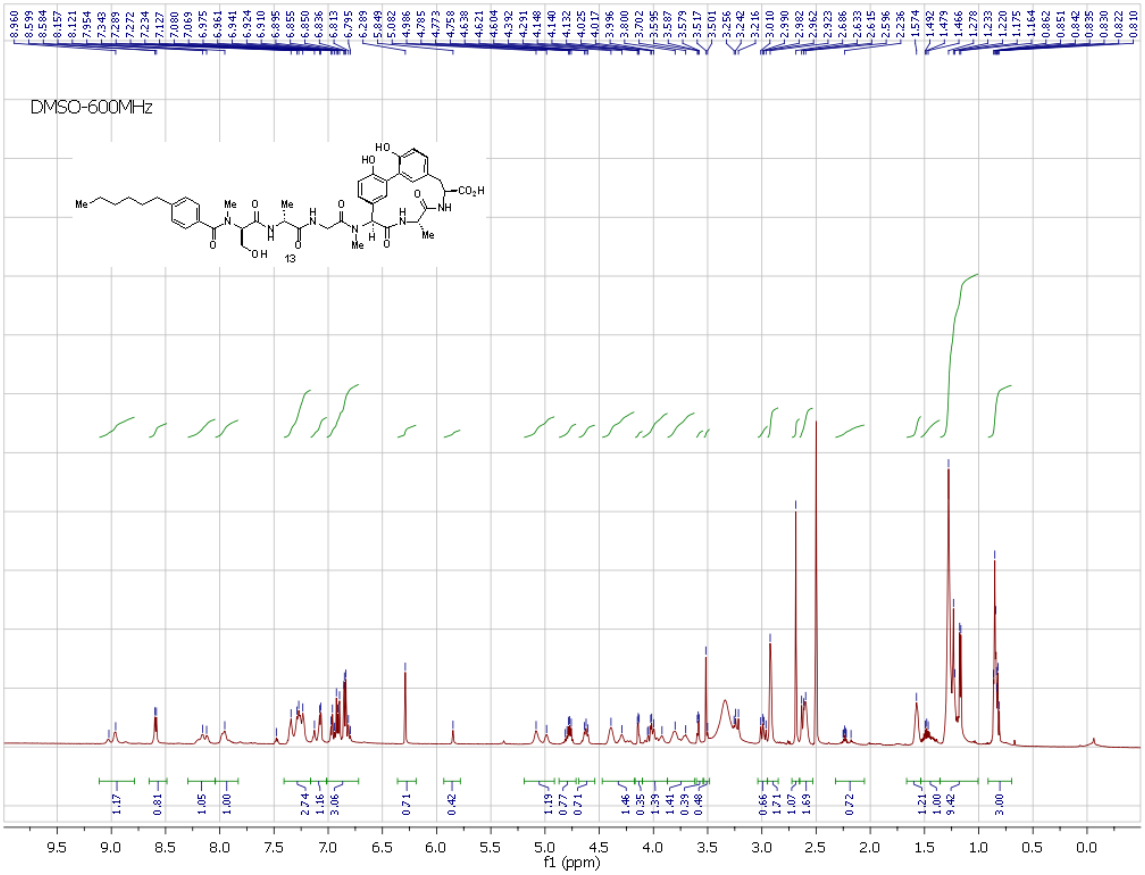
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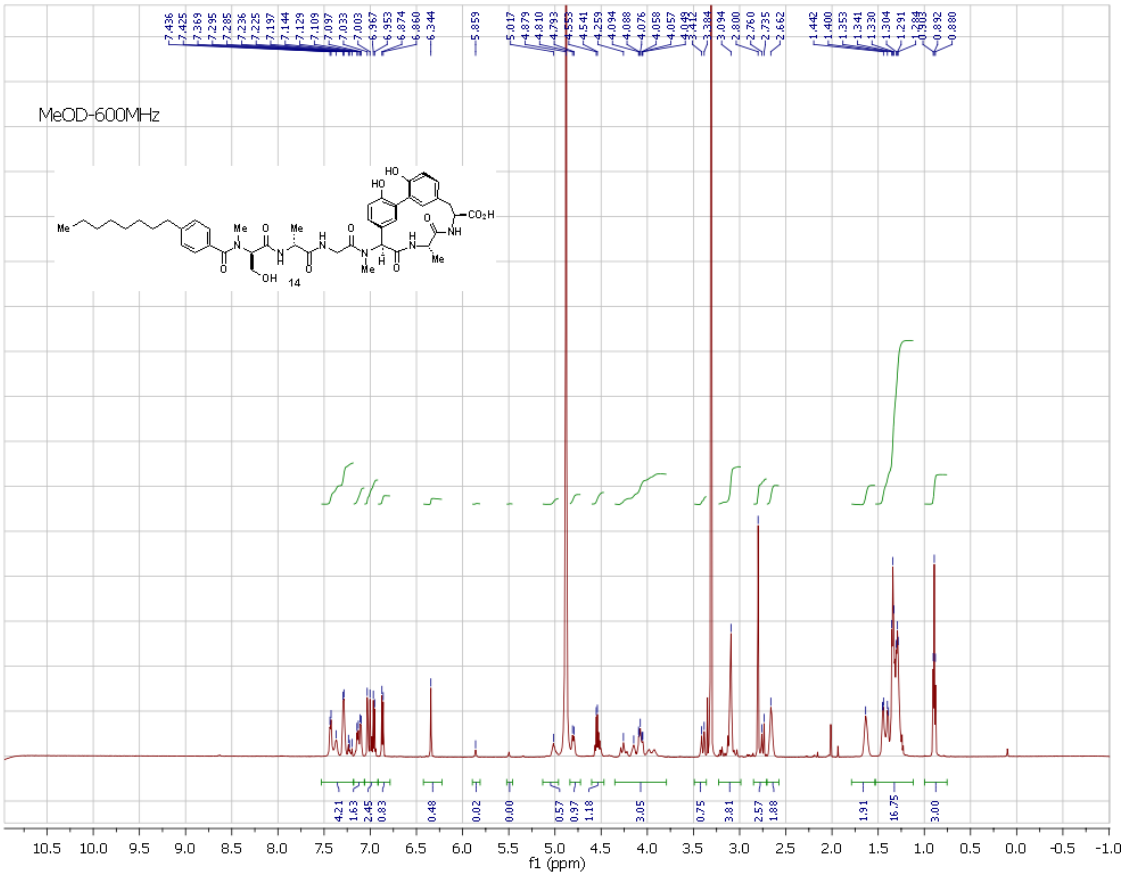
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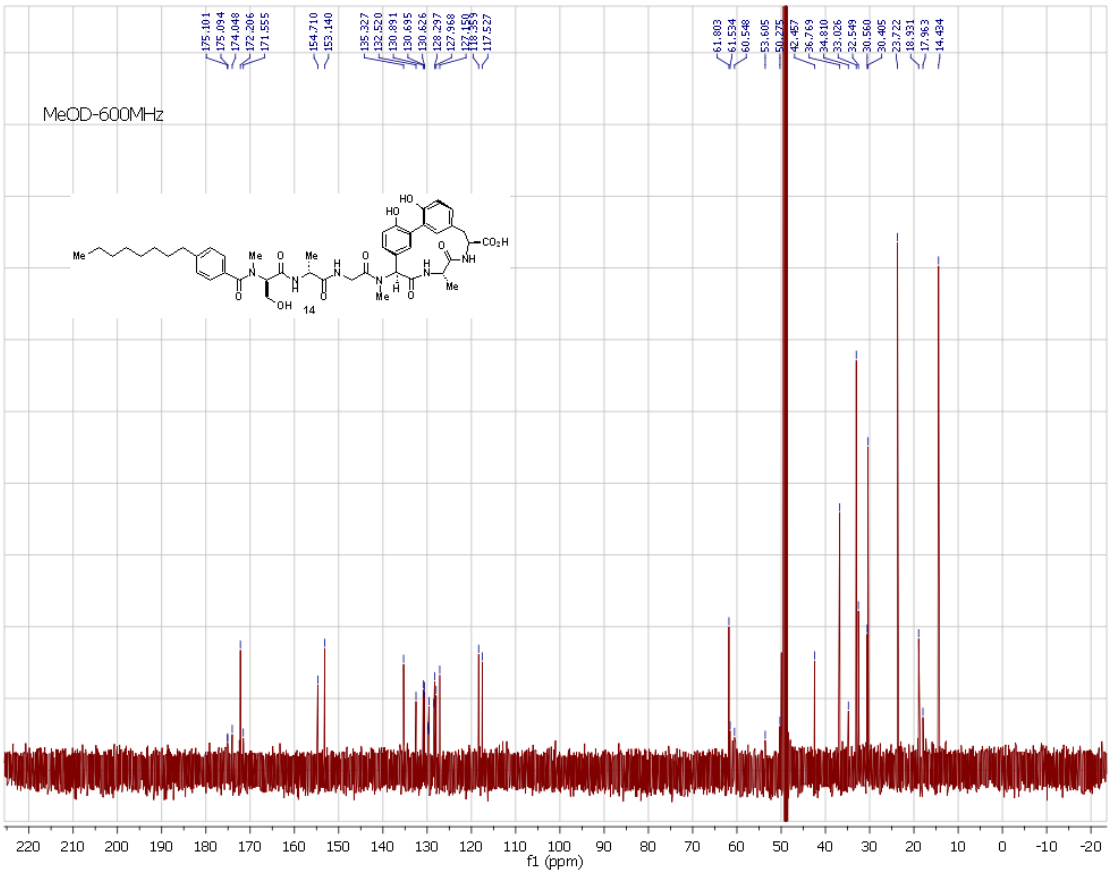
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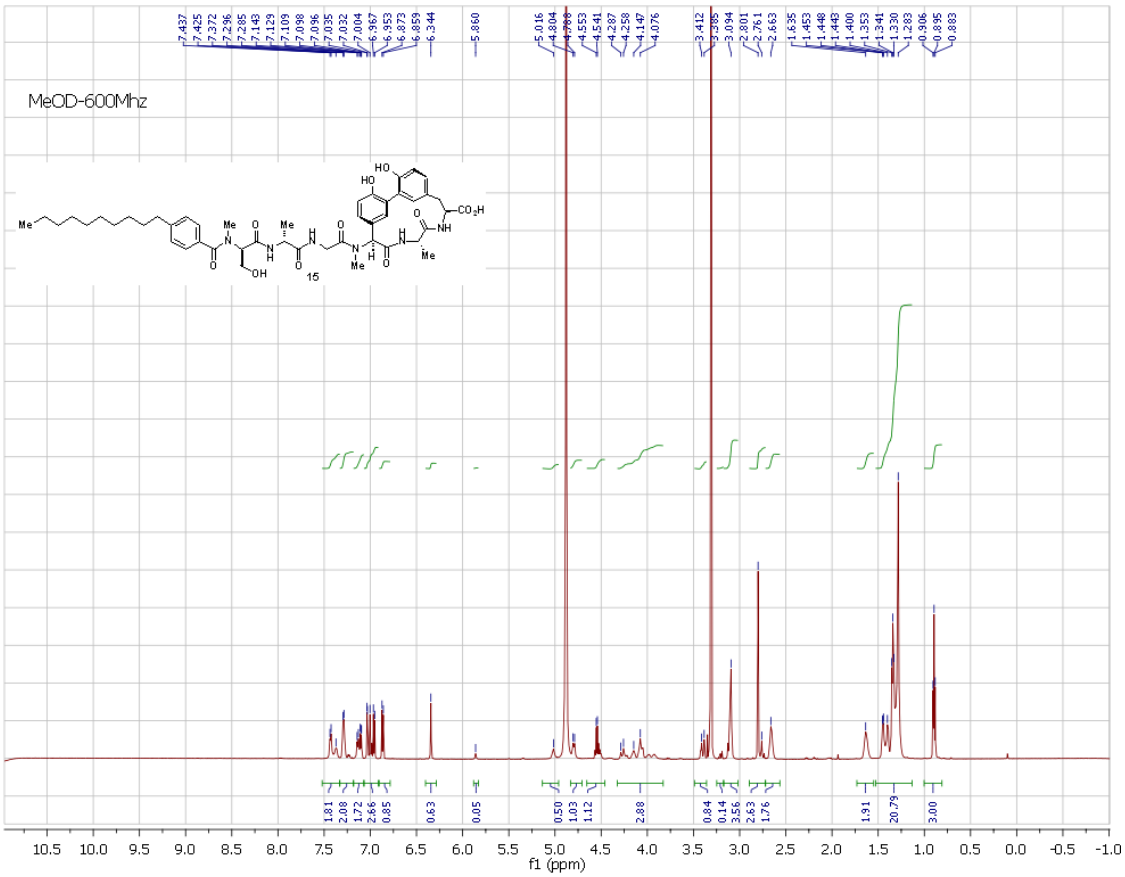
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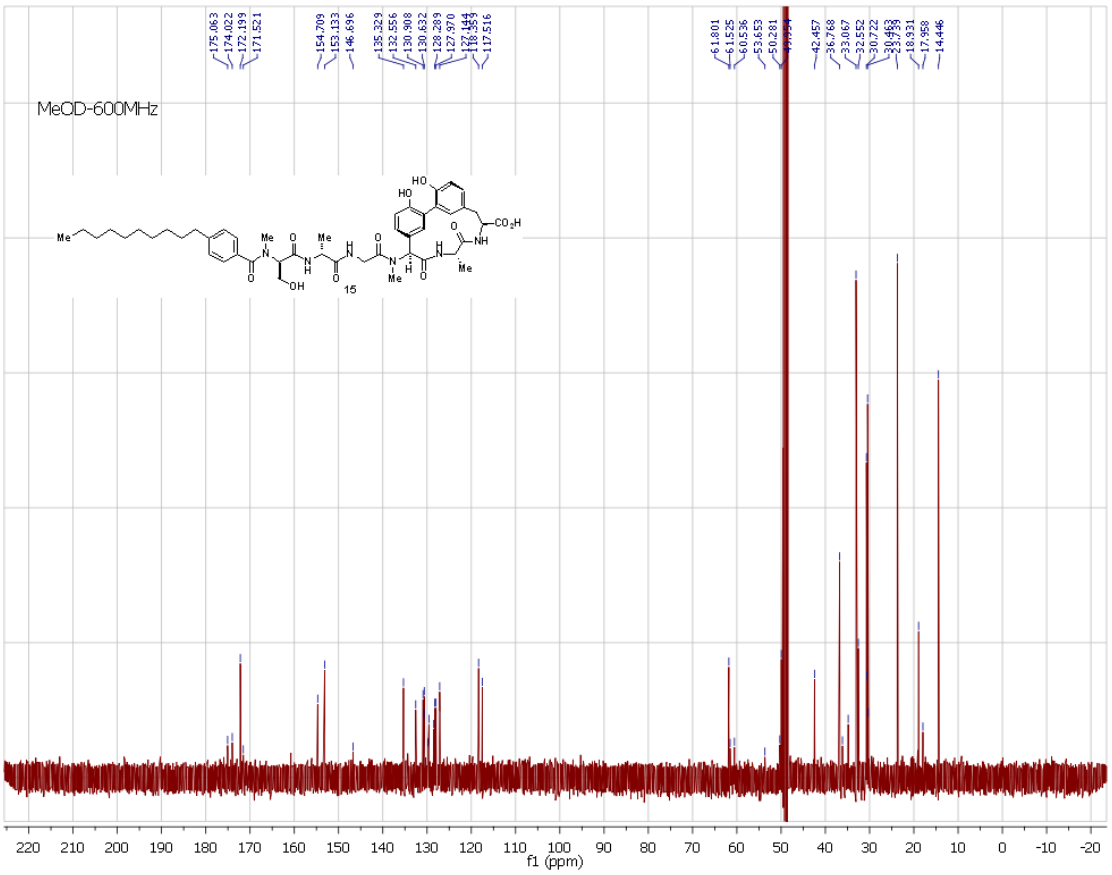
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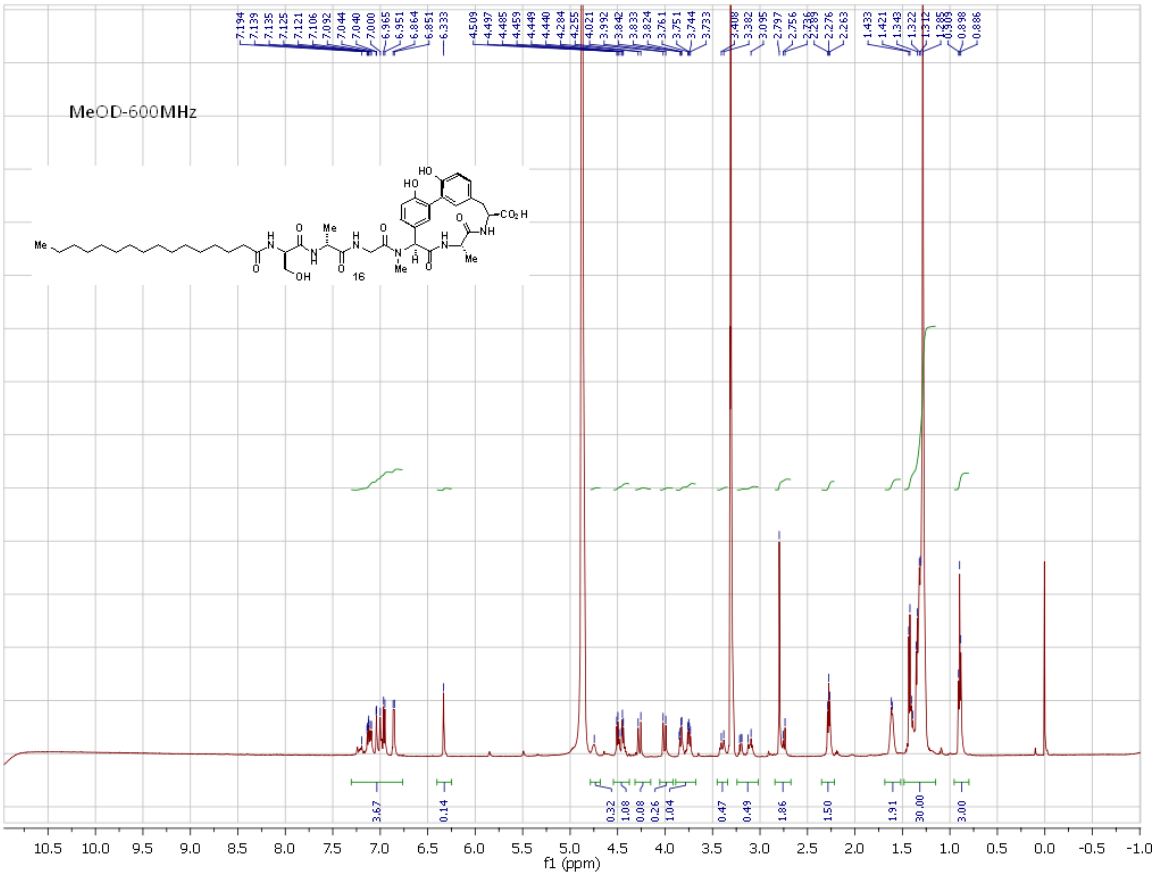
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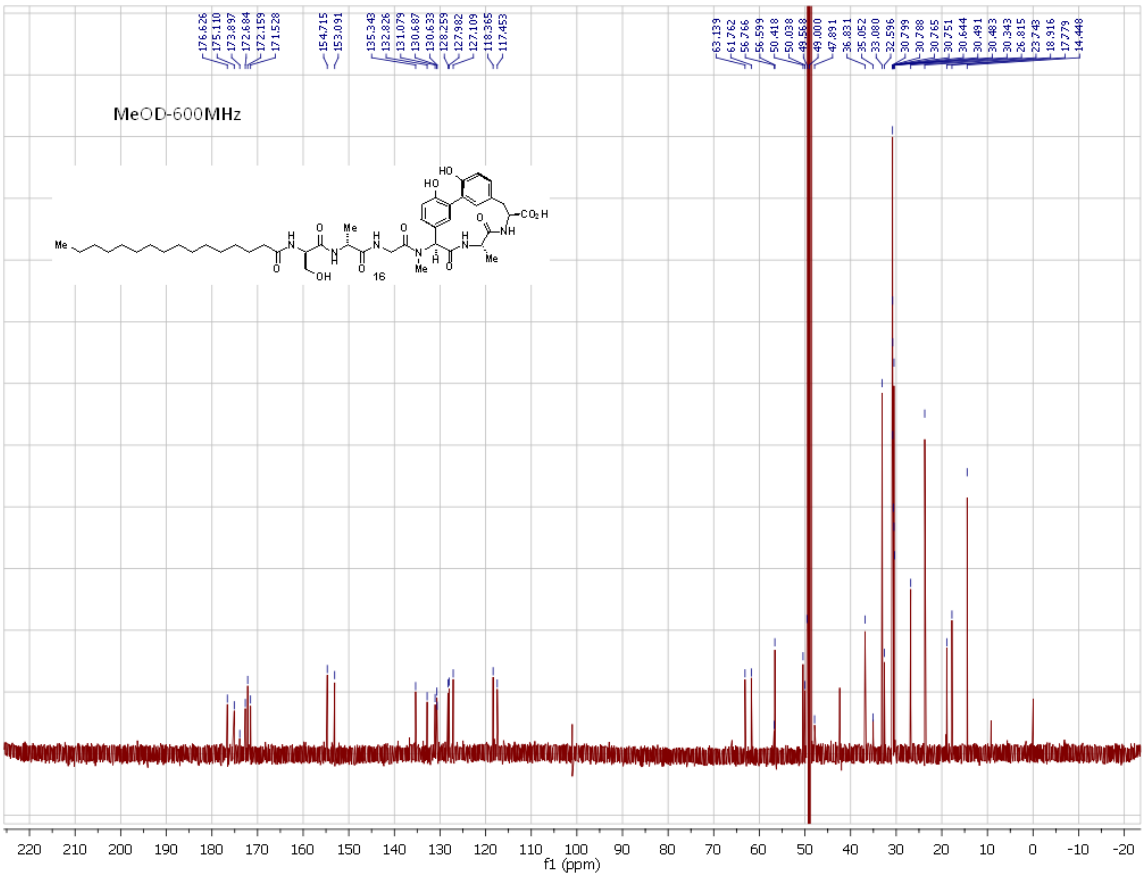
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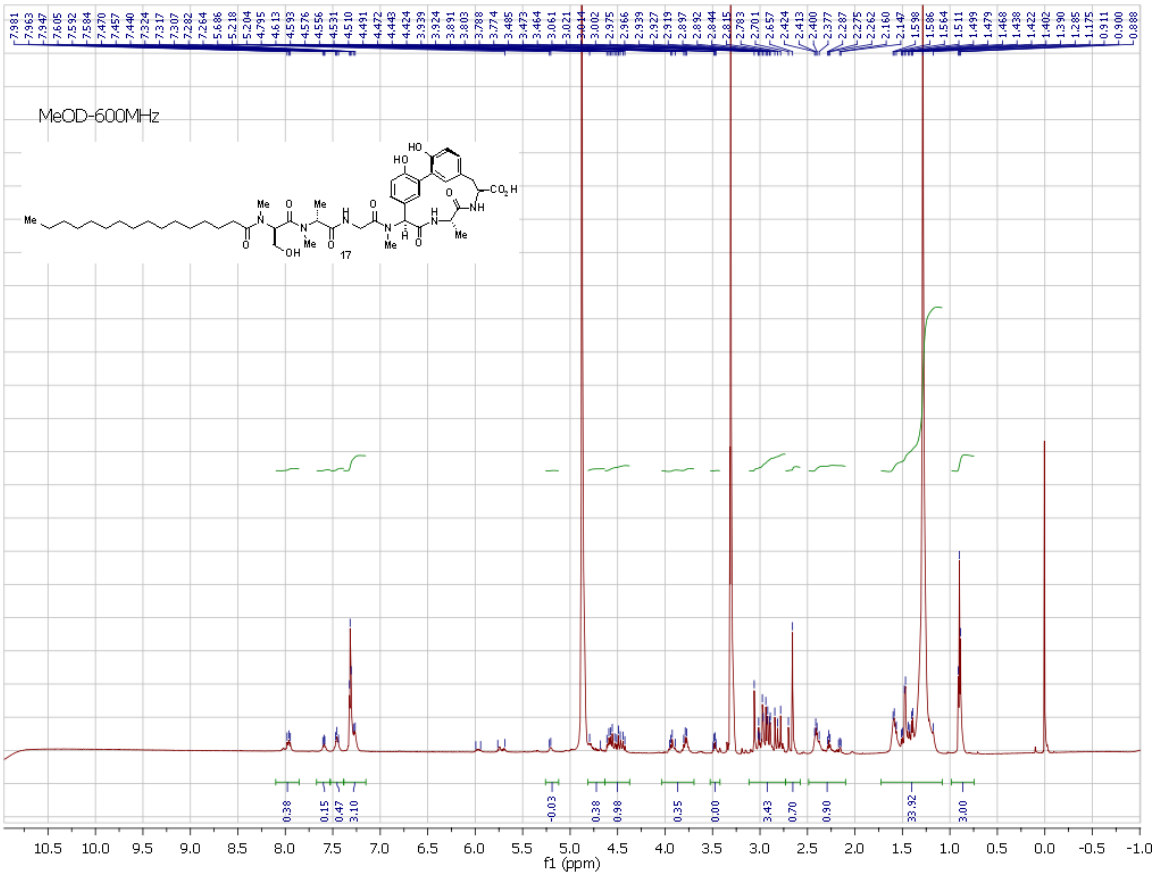
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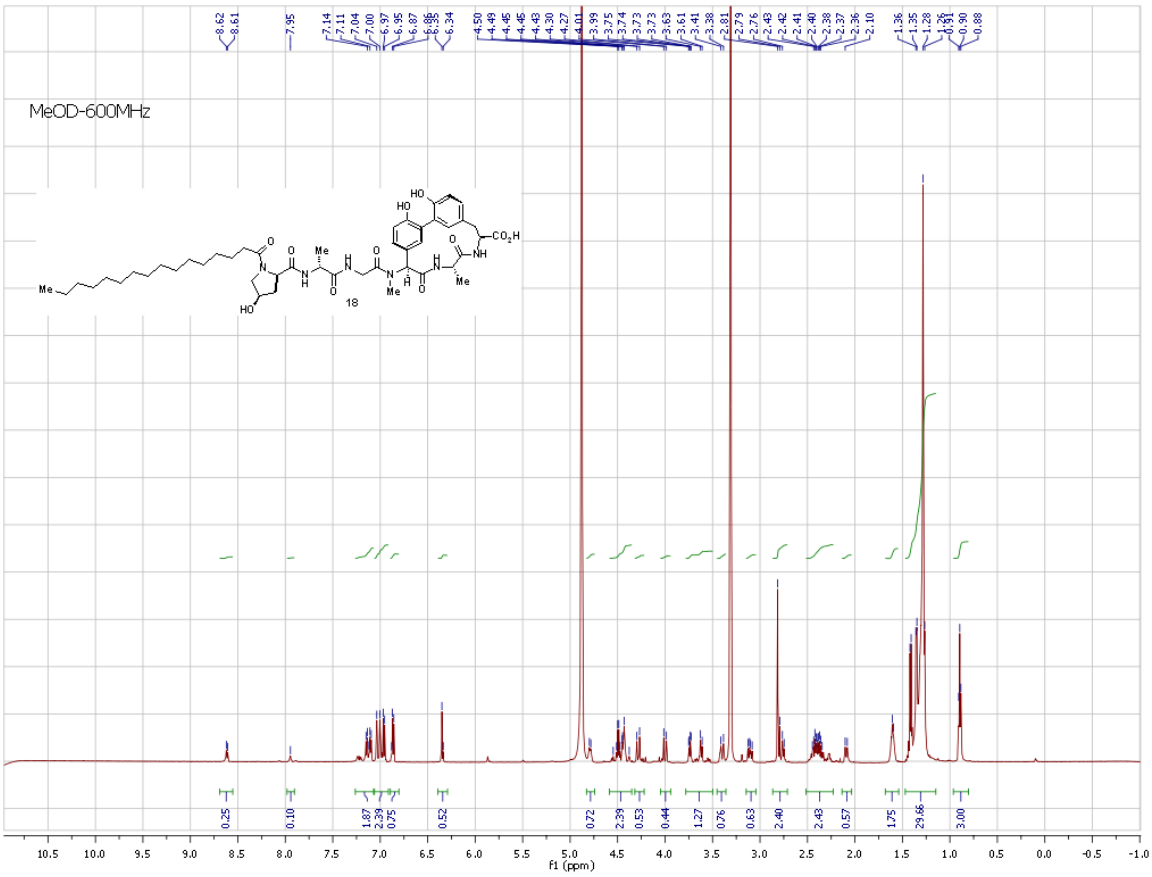
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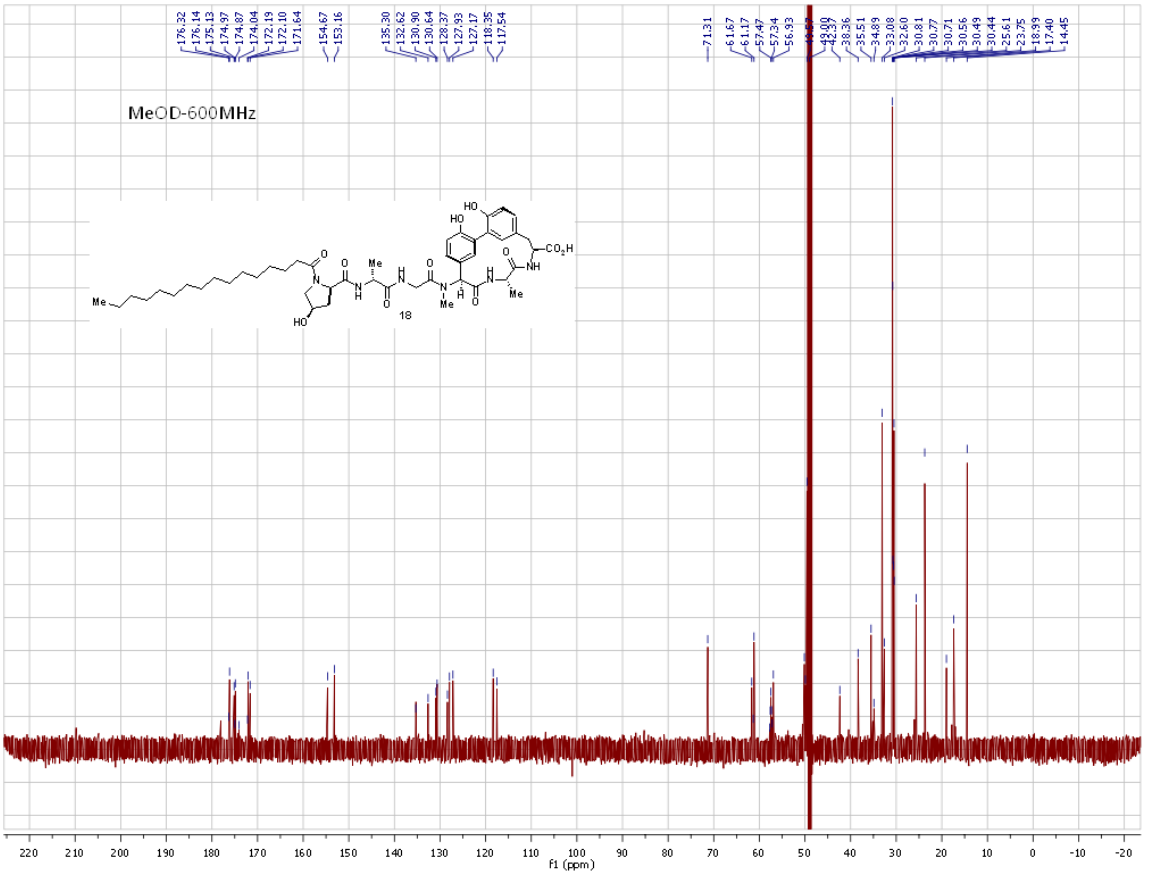
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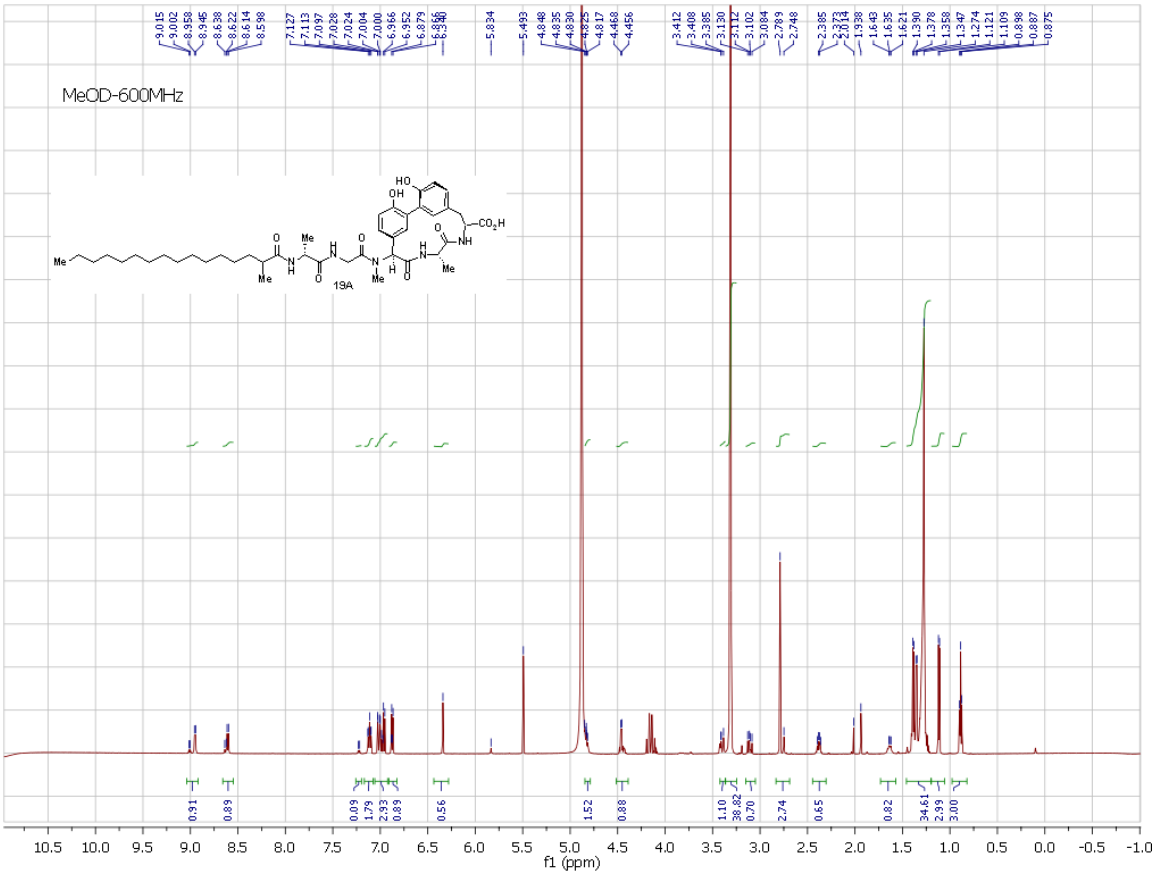
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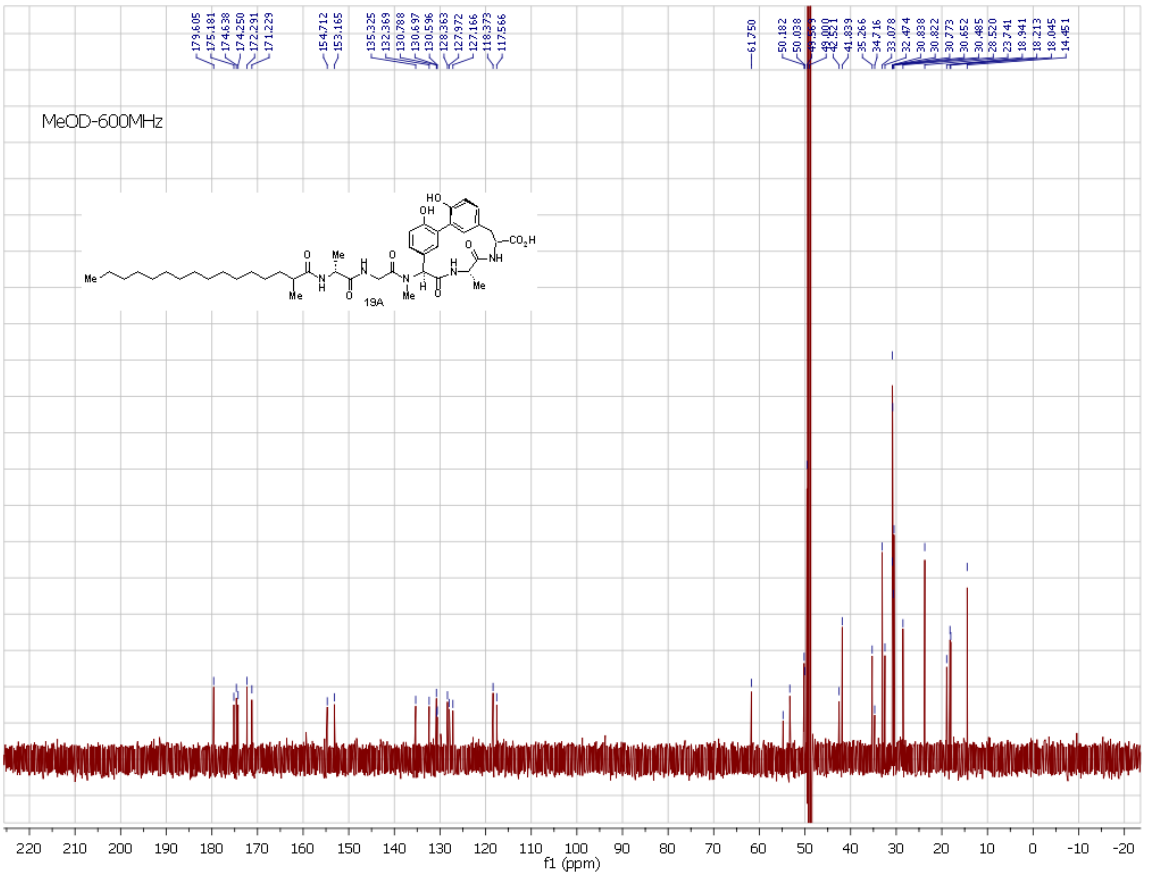
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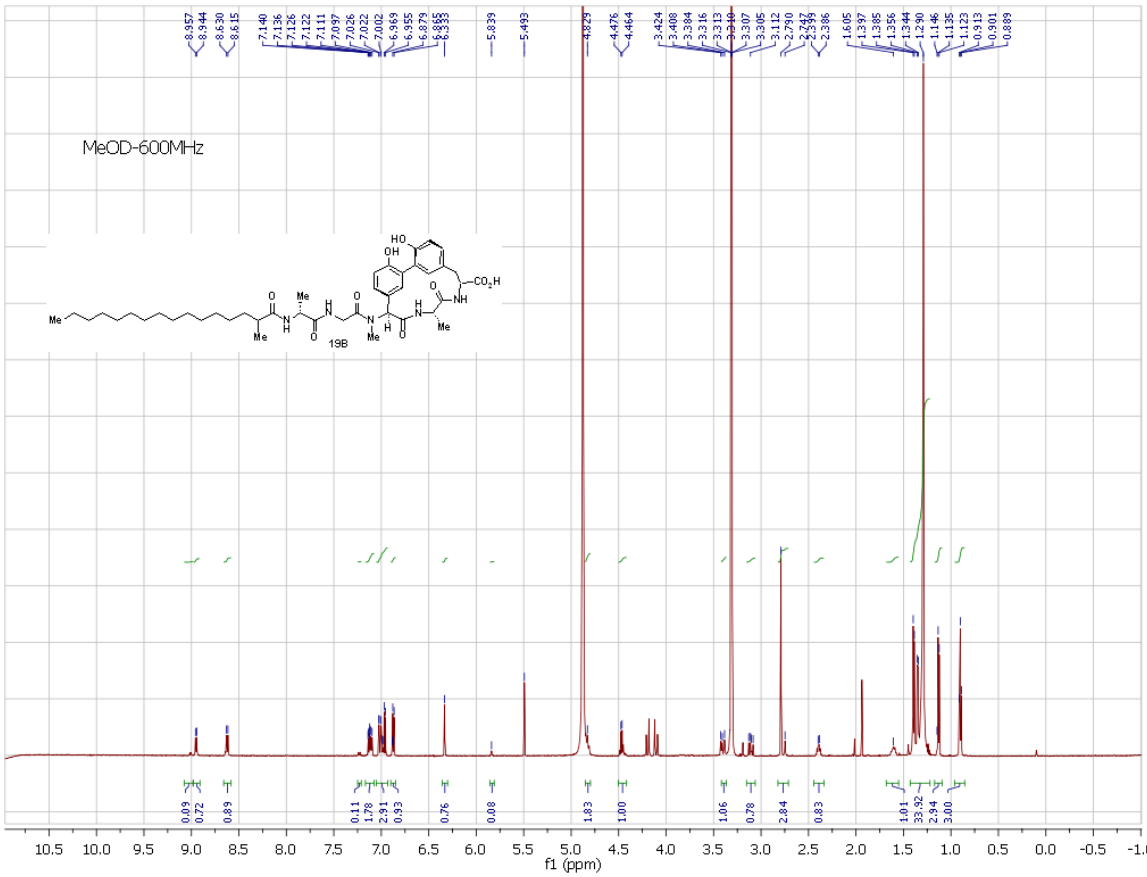
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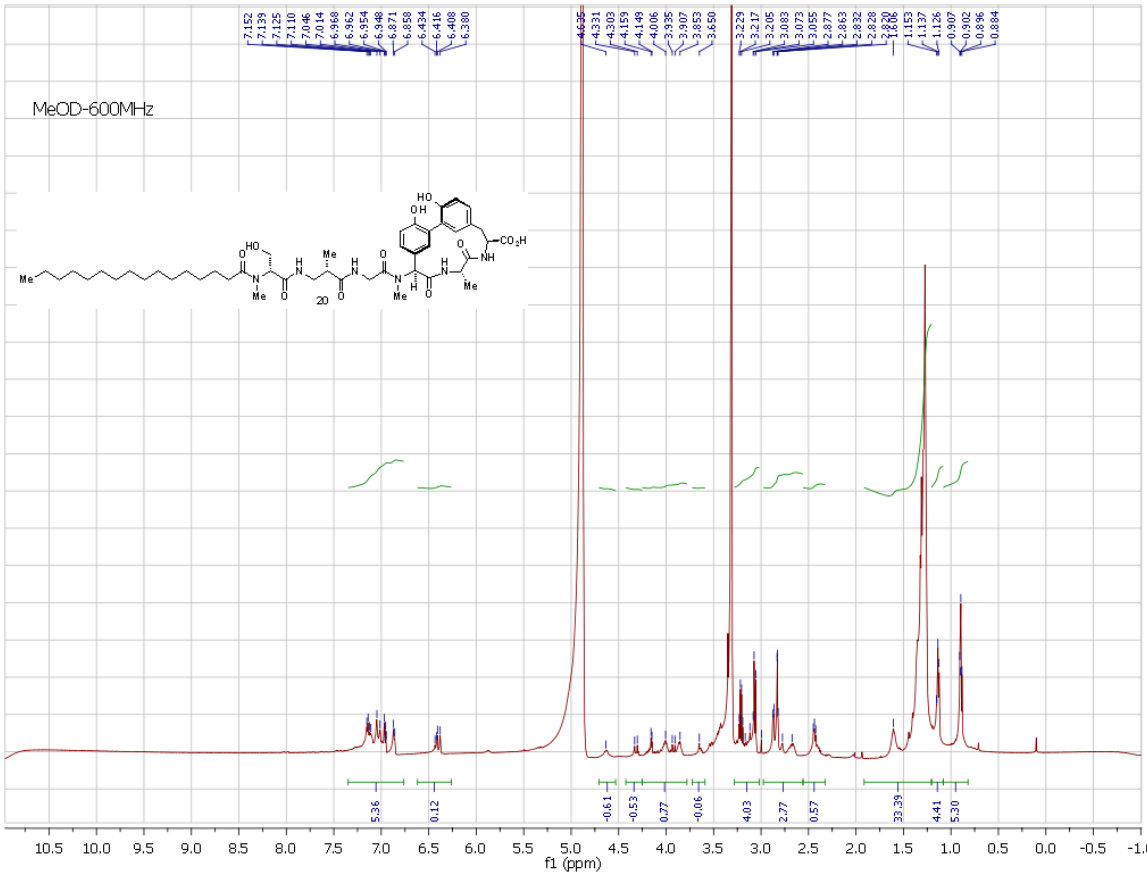
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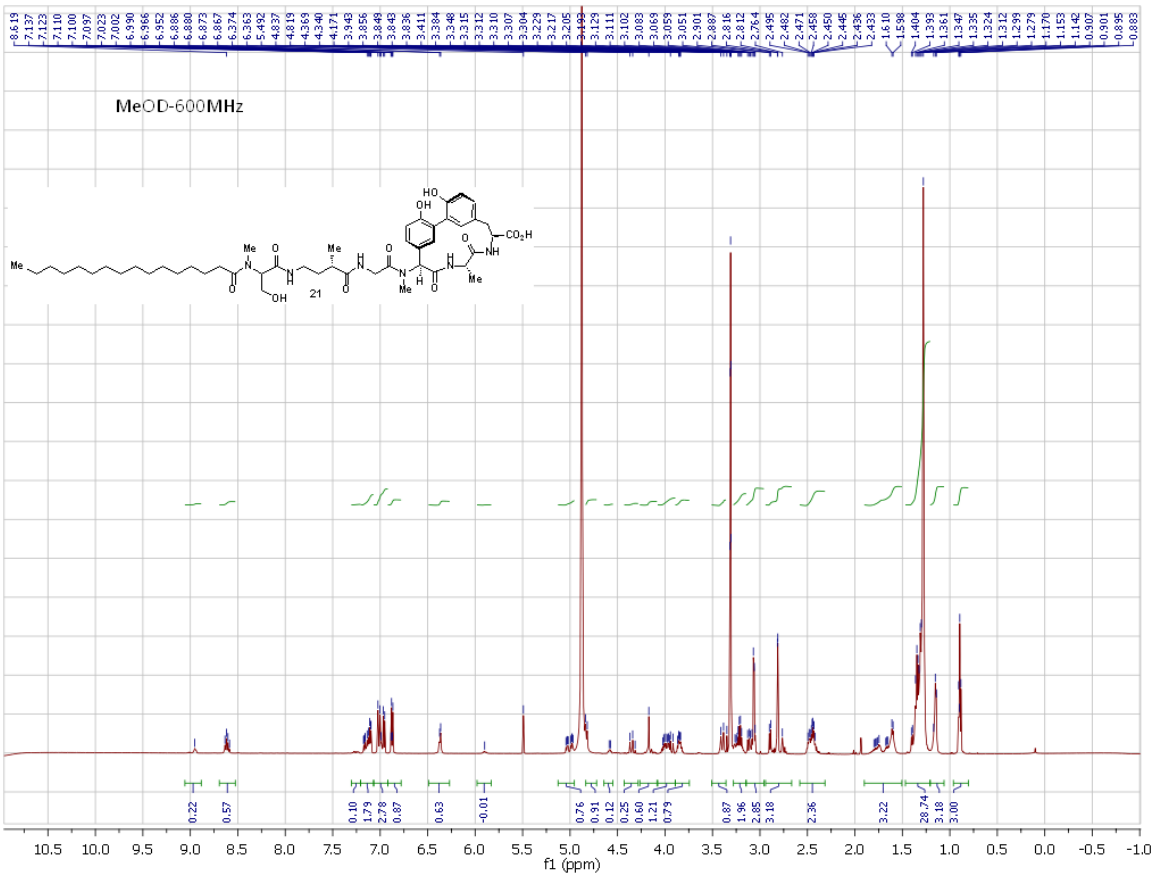
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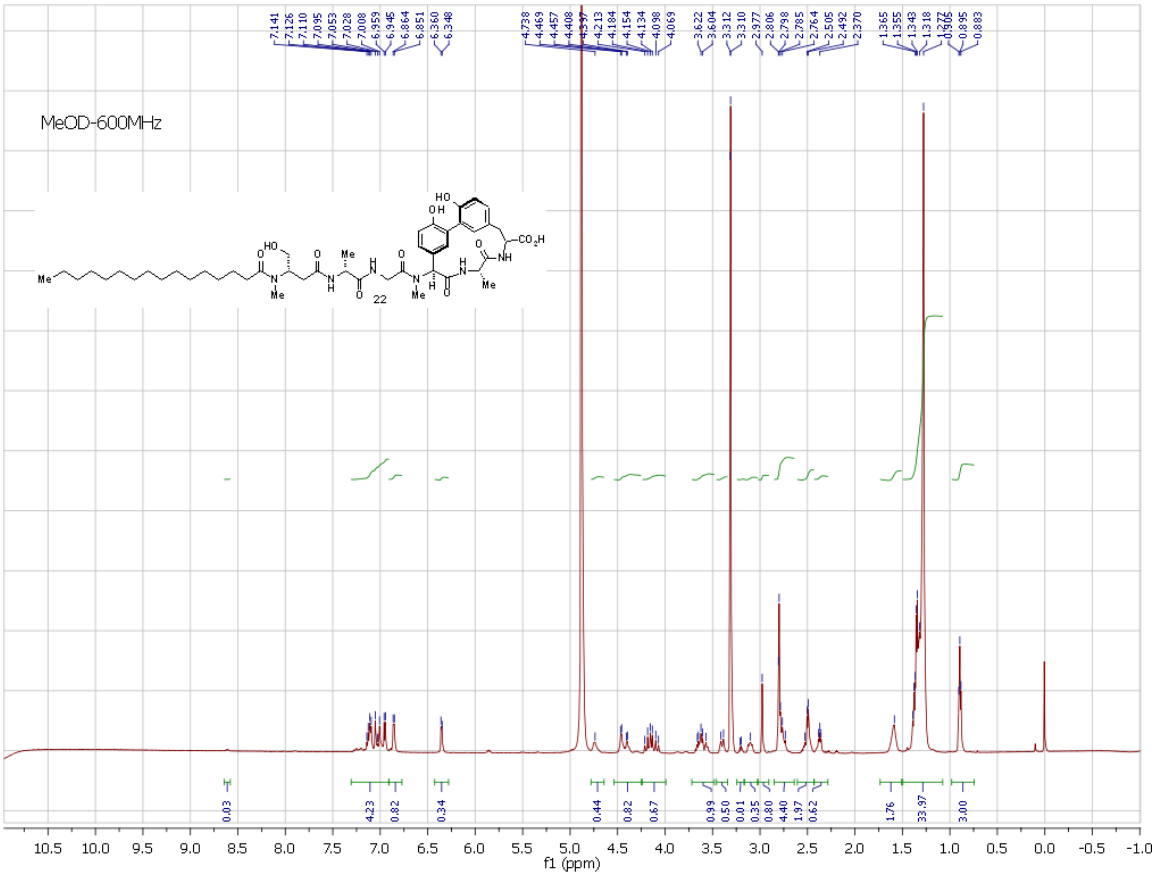
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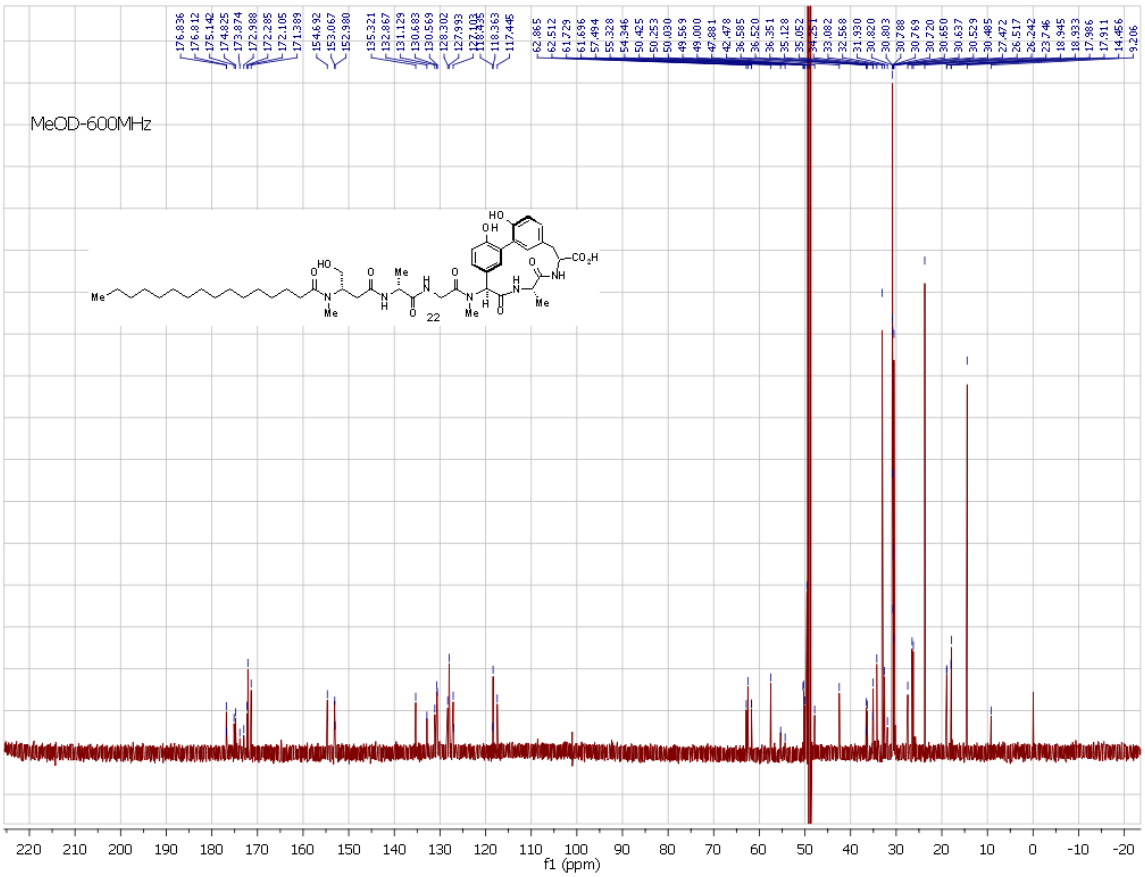
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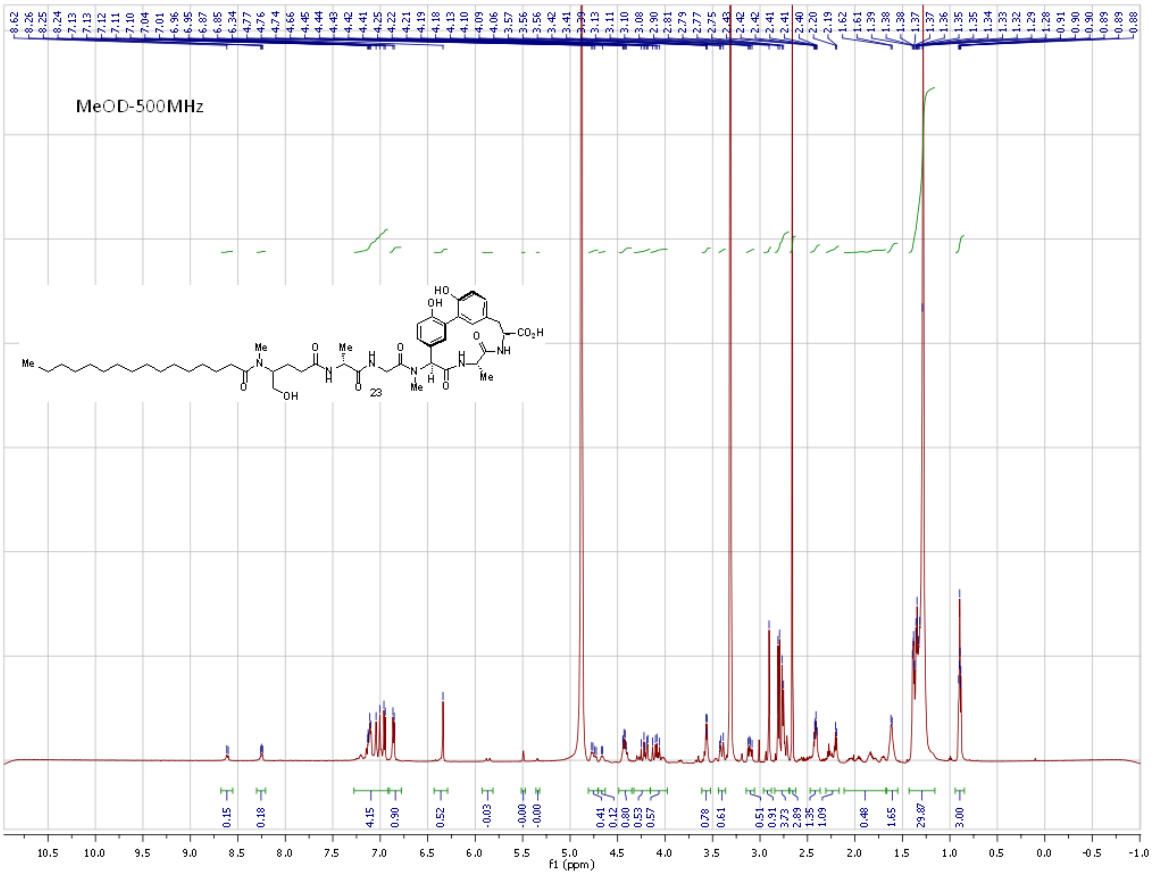
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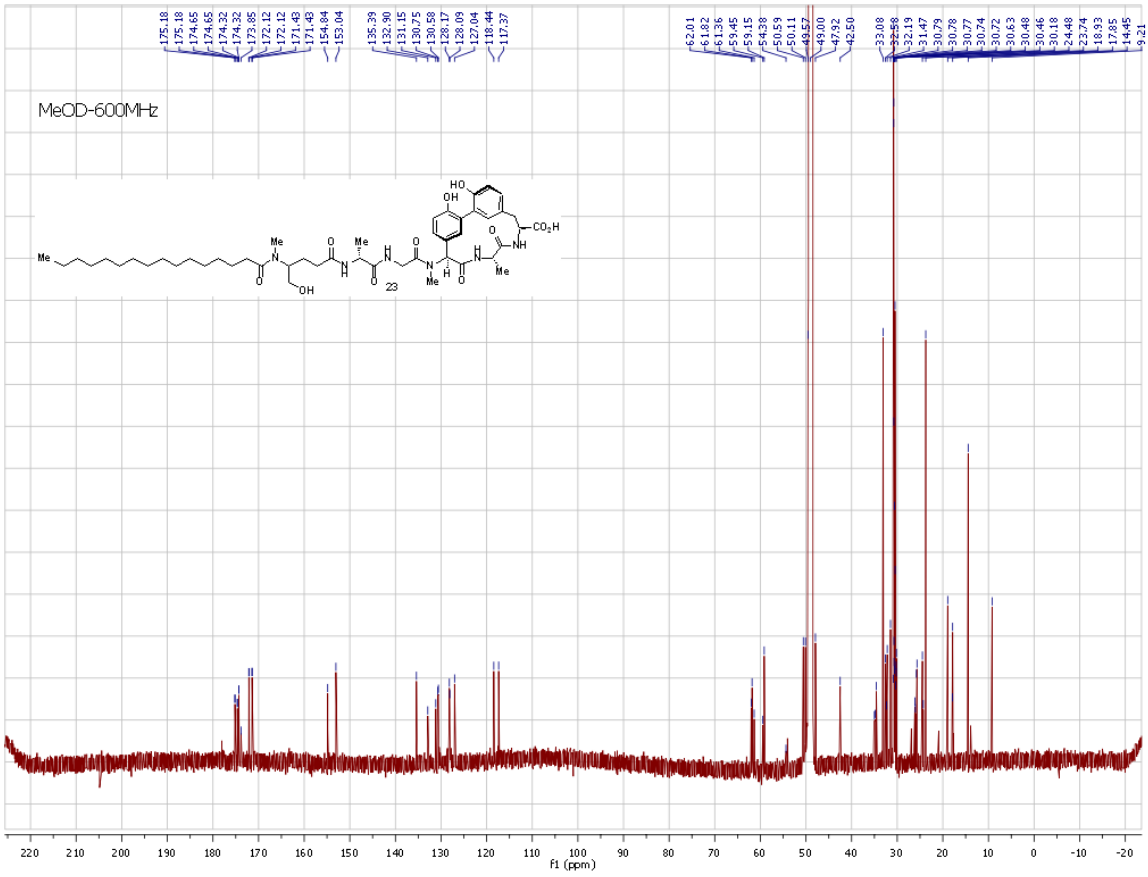
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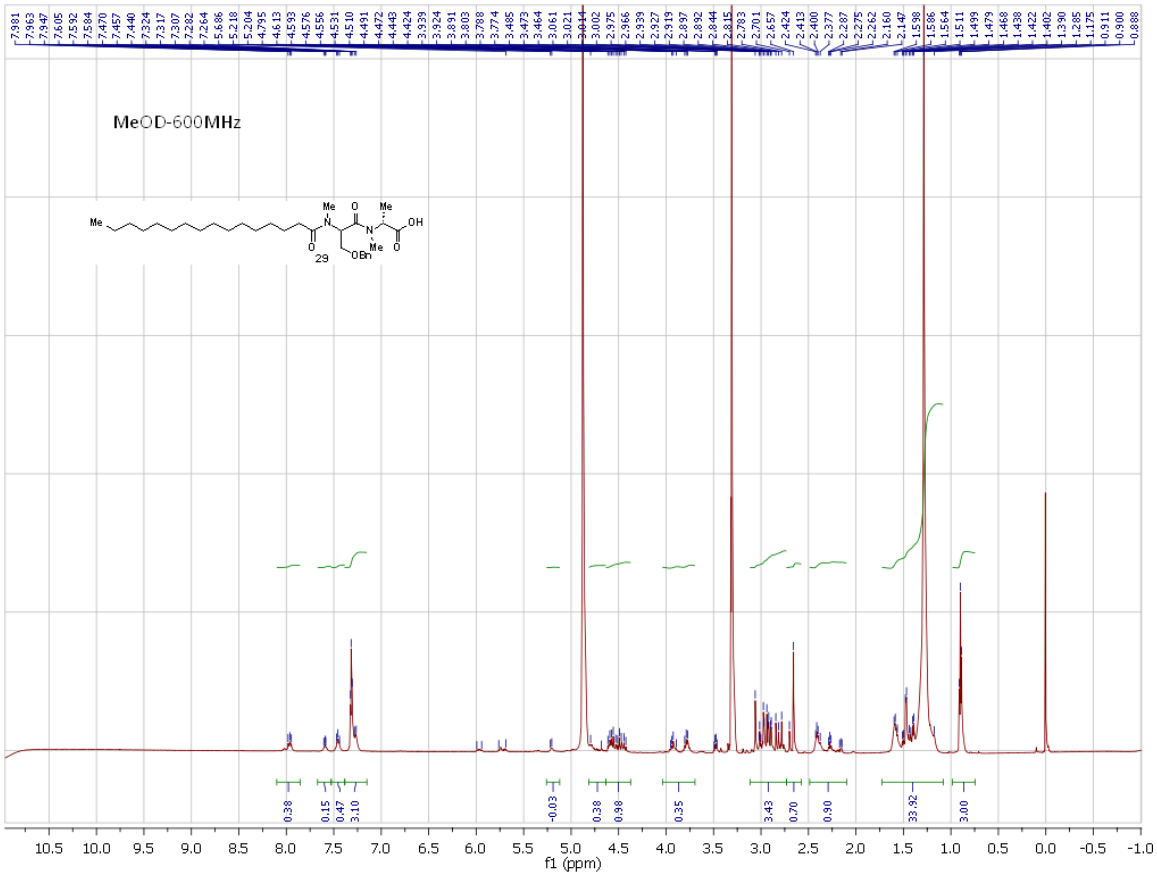
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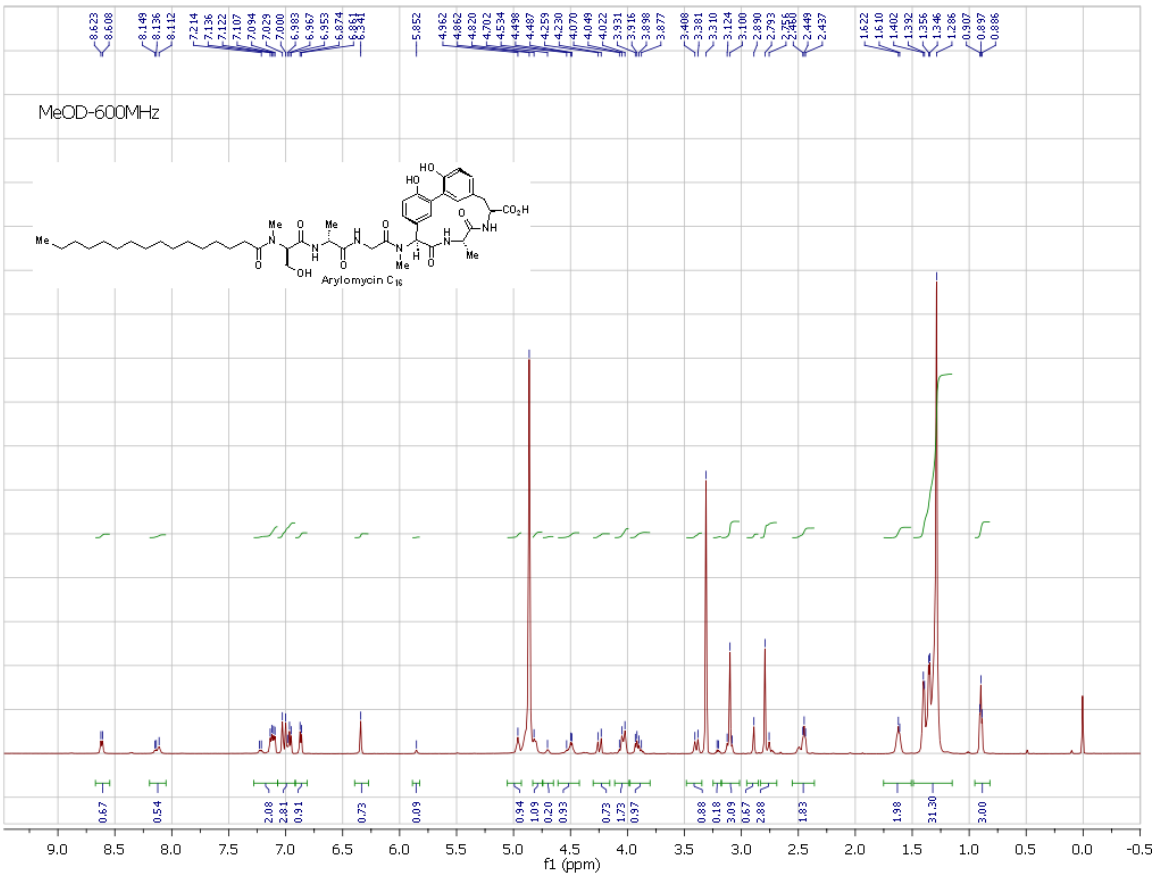
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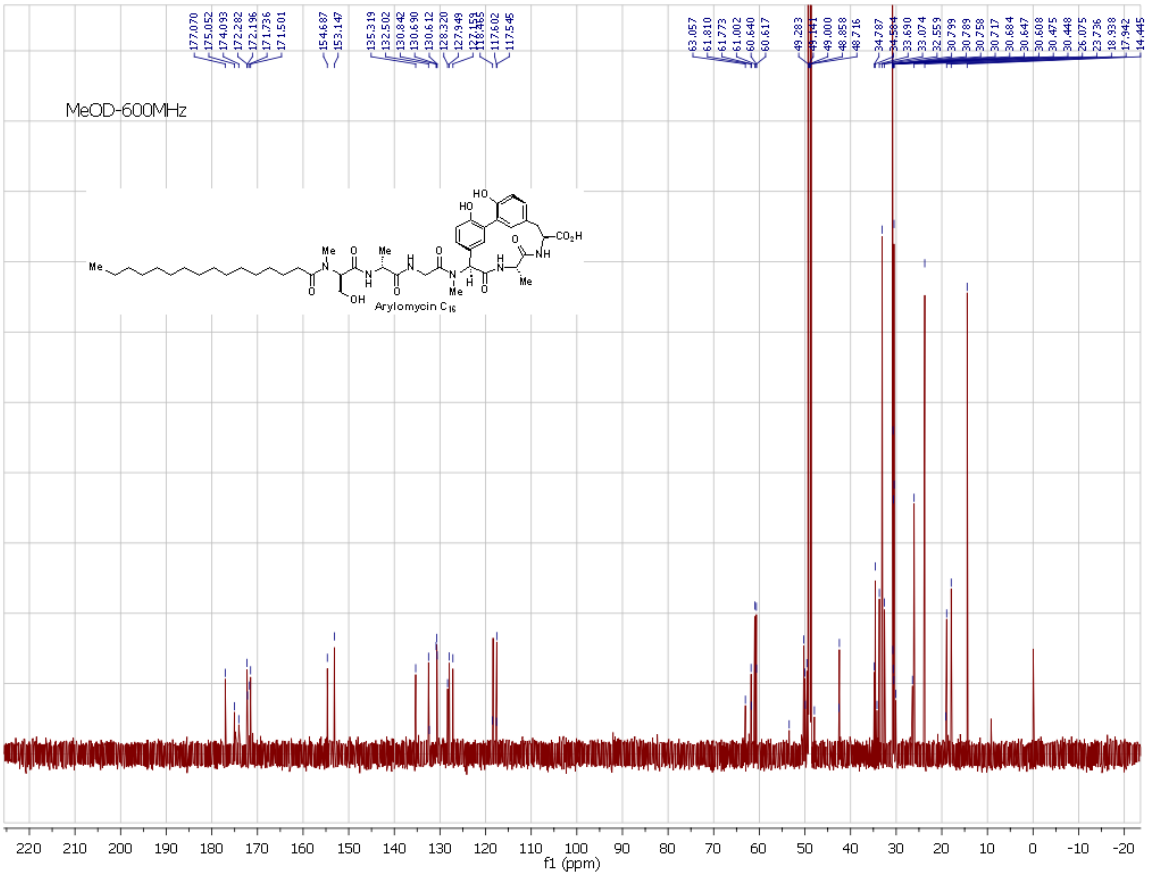
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