

Supporting Information

Structure Optimization of 12 β -O- γ -Glutamyl Oleanolic Acid Derivatives Resulting In FXR Antagonist/Modulator for NASH therapy

Hao Ma ^{1,†}, Yunyang Bao ^{2,†}, Shuaishuai Niu ¹, Shaorong Wang ¹, Yiming Li ²,

Hongwei He ², Na Zhang ², Weishuo Fang ^{1,*}

¹ State Key Laboratory of Bioactive Substances and Functions of Natural Medicines & Ministry of Health Key Laboratory of Biosynthesis of Natural Products, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, 2A Nan Wei Road, Beijing 100050, China

² Key Laboratory of Biotechnology of Antibiotics, the National Health and Family Planning Commission (NHFP), Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

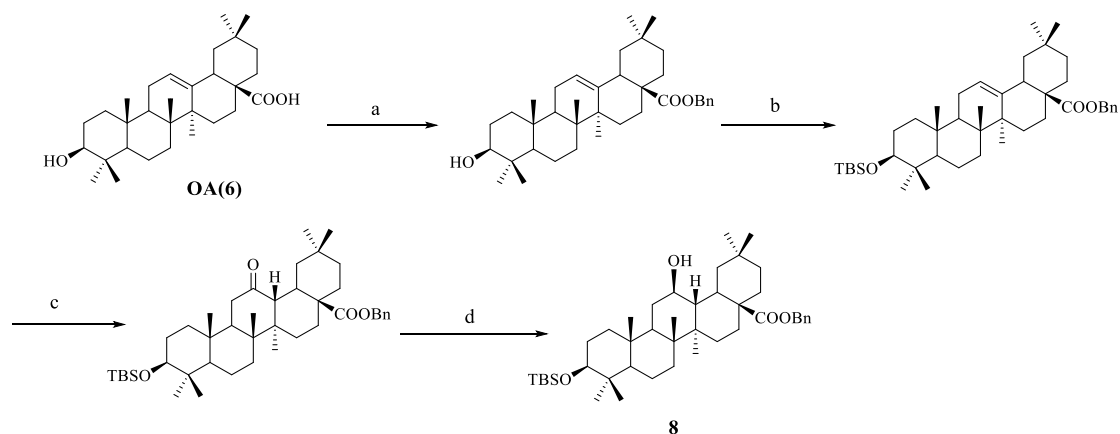
* Correspondence: wfang@imm.ac.cn

[†]: These authors contributed equally to this work.

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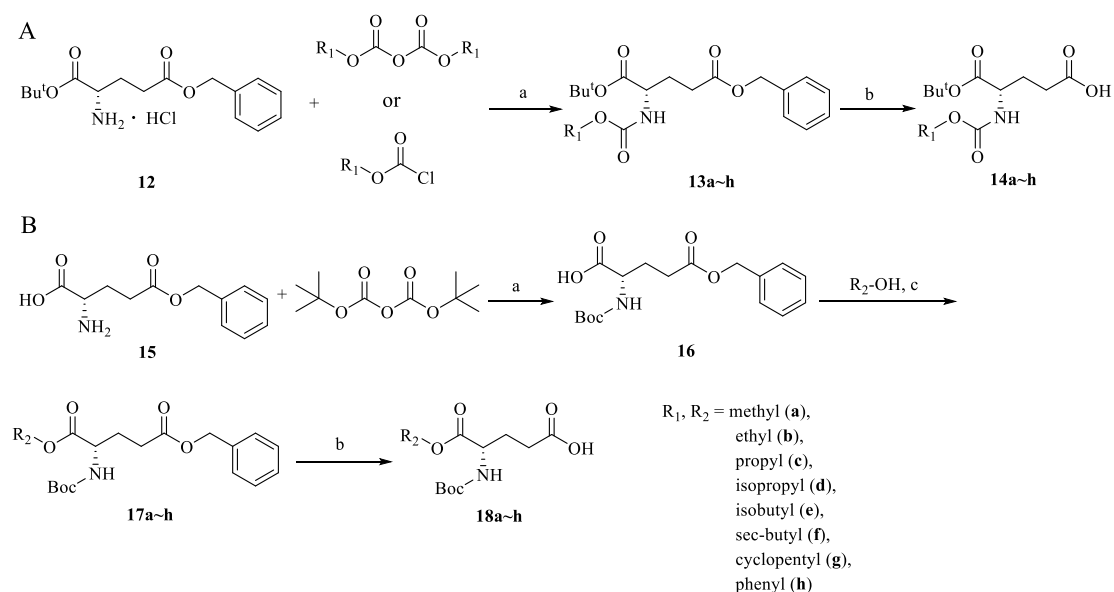
1. Preparation of key intermediate **8**

Starting with oleanolic acid (OA, **6**), the C-28 carboxyl group was protected with benzyl (Bn) to create benzyl 3 β -hydroxy-olean-28-oate (Scheme S1), which improved the solubility of the substrates and facilitated product purification in subsequent reactions. The t-butylmethylsilyl (TBS) was chosen to protect 3-OH group. This yielded the 3-*O*-TBS derivative in high yield (81%) upon treatment with t-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and imidazole. We prepared the 12-oxo derivative through *m*-CPBA oxidation of the olefin, followed by rearrangement of an epoxide intermediate. The newly formed chiral center (C-13) was assigned as β based on stereochemistry described previously, which was supported by an NOESY experiment. The C-12 carbonyl group was then reduced using NaBH₄ in tetrahydrofuran (THF) in the presence of trace water to produce the 12 β - and 12 α -hydroxyl derivatives in a ratio of approximately 2:1. The 12 β -hydroxy OA (**8**) was finally separated through chromatography on silica gel (Pe/EtOAc: 20:1-10:1).



Scheme S1. Synthesis route for key intermediate **8**. *Reagents and conditions:* (a) BnBr, K₂CO₃, tetrabutylammonium bromide (TBAB), THF, H₂O; (b) TBSOTf, imidazole, CH₂Cl₂; (c) *m*-CPBA, CH₂Cl₂; (d) NaBH₄, THF.

2. Preparation of γ -glutamic acids bearing different size of protecting groups.



Scheme S2. Preparation of the corresponding γ -glutamic acids. Reagents and conditions: (a) DIPEA, THF/H₂O 4:1, 23°C for 8 h, yield: > 98% (for anhydride), or DIPEA, DCM, 23°C for 4 h, yield: >98% (for acyl chloride); (b) Pd/C, hydrogen (1 atm.), MeOH, 23°C for 6 h, yield: 55.7~97.1%; (c) DIC, 4-DMAP, DCM, 23°C for 8 h, yield: >98%.

As shown in Scheme S2, For α -carboxyl terminal protected by *tert*-butyl ester, amino-terminal introduced different substituents of glutamic acid modification, the following method was prepared as follows: to a solution of *L*-glutamic acid-5-benzyl ester-1-*tert*-butyl ester hydrochloride (1 g, 3.0 mmol, 1.0 eq.) in 15 mL of THF/H₂O 4:1 mixture, DIPEA 1.3 mL (9.0 mmol, 3.0 eq.) and acid anhydrides containing different substituents (2.0 eq.) were slowly added. The reaction mixture was stirred at room temperature for 12 hours (if it is acid chlorides substituted by different substituents, the reaction solvent should be adjusted to dry DCM, and the reagent equivalent should be the same as above). Then the mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate and concentrated in vacuum to obtain crude product using to the next step without any purification. The obtained intermediates were dissolved in 15 mL of methanol, with 10% of the mass of palladium carbon. The hydrogen gas at 1 atmosphere was passed through, and the reaction mixture was stirred at room temperature. After 6 hours, the mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate and concentrated in vacuum to obtain crude products, and then directly subjected to flash chromatography on silica gel using PE/EtOAc (2:1) to obtain intermediates quantitatively.

5-(tert-butoxy)-4-((methoxycarbonyl)amino)-L-glutamic acid (14a).

White solid 441 mg, overall yield: 55.7%. $[\alpha]_{\text{D}}^{20} = +14.4^{\circ}$ (c 1.3, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.66 (br, 1H, COOH), 5.40 (d, 1H, $J = 6.8$ Hz, NH), 4.26-4.32 (m, 1H, 4-H), 3.68 (s, 3H, OCH₃), 2.37-2.53 (m, 2H, 2-2H), 2.17-2.20 (m, 1H, 3-H_a), 1.90-1.99 (m, 1H, 3-H_b), 1.47 (s, 9H, OBu^t). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 178.0, 171.1, 156.8, 82.7, 53.7, 52.4, 30.0, 28.0, 27.8. MS (ESI) m/z 284.2 (M+Na)⁺.

5-(tert-butoxy)-4-((ethoxycarbonyl)amino)-L-glutamic acid (14b).

White solid 792 mg, overall yield: 94.8%. $[\alpha]_{\text{D}}^{20} = +11.4^{\circ}$ (c 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.56 (br, 1H, COOH), 5.34 (d, 1H, $J = 7.6$ Hz, NH), 4.26-4.32 (m, 1H, 4-H), 4.12 (q, 2H, $J = 6.8$ Hz, OCH₂CH₃), 2.37-2.53 (m, 2H, 2-2H), 2.15-2.23 (m, 1H, 3-H_a), 1.89-1.99 (m, 1H, 3-H_b), 1.47 (s, 9H, OBu^t), 1.25 (t, 3H, $J = 7.2$ Hz, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 177.9, 171.1, 156.4, 82.6, 61.3, 53.5, 30.0, 28.0, 28.0, 14.5. MS (ESI) m/z 298.1 (M+Na)⁺.

5-(tert-butoxy)-4-((propoxycarbonyl)amino)-L-glutamic acid (14c).

White solid 758 mg, overall yield: 86.4%. $[\alpha]_{\text{D}}^{20} = +10.8^{\circ}$ (c 2.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.58 (br, 1H, COOH), 5.34 (d, 1H, $J = 7.2$ Hz, NH), 4.27-4.32 (m, 1H, 4-H), 4.12 (t, 2H, $J = 6.4$ Hz, OCH₂CH₂CH₃), 2.37-2.53 (m, 2H, 2-2H), 2.17-2.23 (m, 1H, 3-H_a), 1.89-1.99 (m, 1H, 3-H_b), 1.59-1.68 (m, 2H, OCH₂CH₂CH₃), 1.47 (s, 9H, OBu^t), 0.93 (t, 3H, $J = 7.2$ Hz, OCH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 177.8, 171.1, 156.5, 82.6, 66.9, 53.5, 30.0, 28.0, 28.0, 22.3, 10.3. MS (ESI) m/z 312.2 (M+Na)⁺.

5-(tert-butoxy)-4-((isopropoxycarbonyl)amino)-L-glutamic acid (14d).

White solid 836 mg, overall yield: 95.3%. $[\alpha]_{\text{D}}^{20} = +9.0^{\circ}$ (c 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.80 (br, 1H, COOH), 5.26 (d, 1H, $J = 7.6$ Hz, NH), 4.86-4.92 (m, 1H, OCHMe₂), 4.27-4.30 (m, 1H, 4-H), 2.37-2.52 (m, 2H, 2-2H), 2.16-2.21 (m, 1H, 3-H_a), 1.89-1.98 (m, 1H, 3-H_b), 1.47 (s, 9H, OBu^t), 1.23 (d, 6H, $J = 6.0$ Hz, OCHMe₂). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 177.9, 171.1, 156.0, 82.5, 68.7, 53.5, 30.0, 28.0, 28.0, 22.0. MS (ESI) m/z 312.3 (M+Na)⁺.

5-(tert-butoxy)-4-((isobutoxycarbonyl)amino)-L-glutamic acid (14e).

White solid 828 mg, overall yield: 90.1%. $[\alpha]_{\text{D}}^{20} = +8.9^{\circ}$ (c 1.3, CHCl₃). ¹H NMR

(400 MHz, CDCl₃) δ (ppm): 5.36 (br, 1H, NH), 4.26-4.31 (m, 1H, 4-H), 3.84 (d, 2H, J = 6.4 Hz, OCH₂CHMe₂), 2.37-2.52 (m, 2H, 2-2H), 2.15-2.23 (m, 1H, 3-H_a), 1.85-1.96 (m, 2H, 3-H_b, OCH₂CHMe₂), 1.47 (s, 9H, OBU^t), 0.92 (d, 6H, J = 6.4 Hz, OCH₂CHMe₂). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 177.7, 171.2, 156.5, 82.6, 71.4, 53.6, 30.0, 28.0, 28.0, 28.0, 19.0. MS (ESI) m/z 326.3 (M+Na)⁺.

5-(tert-butoxy)-4-((sec-butoxycarbonyl)amino)-L-glutamic acid (14f).

White solid 972 mg, overall yield: 97.1%. [α]_D²⁰ = +7.8° (c 1.9, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.29 (br, 1H, COOH), 5.26 (d, 1H, J = 7.6 Hz, NH), 4.70-4.74 (m, 1H, 1'-H), 4.26-4.31 (m, 1H, 4-H), 2.37-2.52 (m, 2H, 2-2H), 2.15-2.20 (m, 1H, 3-H_a), 1.89-1.98 (m, 1H, 3-H_b), 1.50-1.63 (m, 2H, 2'-2H), 1.47 (s, 9H, OBU^t), 1.20 (d, 3H, J = 6.0 Hz, 1'-CH₃), 0.90 (t, 3H, J = 7.6 Hz, 3'-3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 177.7, 171.1, 156.3, 82.5, 73.3, 53.5, 30.0, 29.0, 28.0, 28.0, 19.7, 9.6. MS (ESI) m/z 326.3 (M+Na)⁺.

5-(tert-butoxy)-4-(((cyclopentyloxy)carbonyl))amino)-L-glutamic acid (14g).

White solid 811 mg, overall yield: 84.8%. [α]_D²⁰ = +7.7° (c 1.7, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.28 (br, 1H, COOH), 5.24 (d, 1H, J = 7.6 Hz, NH), 5.08 (br, 1H, cyclopentyl-H), 4.26-4.31 (m, 1H, 4-H), 2.36-2.52 (m, 2H, 2-2H), 2.15-2.21 (m, 1H, 3-H_a), 1.90-1.97 (m, 1H, 3-H_b), 1.80-1.85 (m, cyclopentyl-2H), 1.68-1.70 (m, 4H, cyclopentyl-4H), 1.53-1.60 (m, 2H, cyclopentyl-2H), 1.47 (s, 9H, OBU^t). MS (ESI) m/z 338.3 (M+Na)⁺. Known compound.

5-(tert-butoxy)-4-((phenoxycarbonyl)amino)-L-glutamic acid (14h).

White solid 803 mg, overall yield: 81.9%. [α]_D²⁰ = +10.1° (c 2.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.35 (dd, 2H, J = 7.6, 8.4 Hz, Ph-2H), 7.20 (dd, 1H, J = 7.6, 8.4 Hz, Ph-H), 7.12 (d, 2H, J = 7.6 Hz, Ph-2H), 5.78 (d, 1H, J = 8.0 Hz, NH), 4.36 (ddd, 1H, J = 5.2, 8.0, 8.4 Hz, 4-H), 2.41-2.57 (m, 2H, 2-2H), 2.21-2.29 (m, 1H, 3-H_a), 1.97-2.06 (m, 1H, 3-H_b), 1.49 (s, 9H, OBU^t). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 177.9, 170.8, 154.4, 150.8, 129.3, 125.5, 121.6, 83.0, 53.8, 29.9, 28.0, 27.7. MS (ESI) m/z 346.2 (M+Na)⁺.

For α -carboxyl terminal modified with esters of different substituents and amino terminal protected by *tert*-butoxycarbonyl, the following method was prepared as follows: to a solution of *L*-glutamic acid- γ -benzyl (1 g, 4.2 mmol, 1.0 eq.) in 15 mL

THF/H₂O 4:1 mixture, DIPEA (1.3 mL, 9.0 mmol, 3.0 eq.) and (Boc)₂O (2.0 eq.) were added slowly, and the mixture was stirred at 23°C for 12 hours. Then the mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate and concentrated in vacuum to obtain crude product using to the next step directly. The intermediate in DCM 15 mL was added alcohols with different substituents (equivalent ratio 1:1). Then DIC (1.0 eq.) and 4-DMAP (0.2 eq.) were added slowly, and the mixture was stirred at room temperature for 12 hours. Then the mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate and concentrated in vacuum to obtain crude products using to the next step without any purification. The corresponding γ -glutamic acids were prepared under the same catalytic hydrogenation conditions as previously described, and were subsequently subjected to flash chromatography on silica gel using PE/EtOAc (2:1) as the solvent.

4-((tert-butoxycarbonyl)amino)-5-methoxy-L-glutamic acid (18a).

White solid 325 mg, overall yield: 98.8%. $[\alpha]_D^{20} = +13.9^\circ$ (c 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.28 (br, 1H, COOH), 5.19 (d, 1H, $J = 7.6$ Hz, NH), 4.34-4.40 (m, 1H, 4-H), 3.75 (s, 3H, OCH₃), 2.39-2.53 (m, 2H, 2-2H), 2.17-2.22 (m, 1H, 3-H_a), 1.92-1.97 (m, 1H, 3-H_b), 1.44 (s, 9H, Boc). MS (ESI) m/z 284.3 (M+Na)⁺. Known compound.

4-((tert-butoxycarbonyl)amino)-5-ethoxy-L-glutamic acid (18b).

White solid 314 mg, overall yield: 89.2%. $[\alpha]_D^{20} = +12.0^\circ$ (c 1.4, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.42 (br, 1H, COOH), 5.21 (d, 1H, $J = 7.6$ Hz, NH), 4.31-4.36 (m, 1H, 4-H), 4.20 (q, 2H, $J = 7.2$ Hz, OCH₂CH₃), 2.39-2.53 (m, 2H, 2-2H), 2.16-2.23 (m, 1H, 3-H_a), 1.90-2.01 (m, 1H, 3-H_b), 1.44 (s, 9H, Boc), 1.29 (t, 3H, $J = 7.2$ Hz, OCH₂CH₃). MS (ESI) m/z 298.2 (M+Na)⁺. Known compound.

4-((tert-butoxycarbonyl)amino)-5-propoxy-L-glutamic acid (18c).

White solid 286 mg, overall yield: 85.6%. $[\alpha]_D^{20} = +10.5^\circ$ (c 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 5.20 (d, 1H, $J = 7.6$ Hz, NH), 4.32-4.38 (m, 1H, 4-H), 4.10 (t, 3H, $J = 6.4$ Hz, OCH₂CH₂CH₃), 2.39-2.54 (m, 2H, 2-2H), 2.16-2.23 (m, 1H, 3-H_a), 1.92-1.99 (m, 1H, 3-H_b), 1.63-1.72 (m, 2H, OCH₂CH₂CH₃), 1.44 (s, 9H, Boc), 1.29 (t, 3H, $J = 7.6$ Hz, OCH₂CH₂CH₃). MS (ESI) m/z 312.3 (M+Na)⁺. Known compound.

4-((tert-butoxycarbonyl)amino)-5-isopropoxy-L-glutamic acid (18d).

White solid 300 mg, overall yield: 75.4%. $[\alpha]_{\text{D}}^{20} = +10.1^{\circ}$ (c 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 5.20 (d, 1H, $J = 7.6$ Hz, NH), 5.00-5.10 (m, 1H, OCHMe₂), 4.27-4.32 (m, 1H, 4-H), 2.38-2.53 (m, 2H, 2-2H), 2.15-2.20 (m, 1H, 3-H_a), 1.89-1.98 (m, 1H, 3-H_b), 1.44 (s, 9H, Boc), 1.23 (d, 6H, $J = 6.0$ Hz, OCHMe₂). MS (ESI) m/z 312.2 (M+Na)⁺. Known compound.

4-((tert-butoxycarbonyl)amino)-5-isobutoxy-L-glutamic acid (18e).

White solid 320 mg, overall yield: 81.0%. $[\alpha]_{\text{D}}^{20} = +8.7^{\circ}$ (c 1.8, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 11.21 (s, 1H, COOH), 5.20 (d, 1H, $J = 8.0$ Hz, NH), 4.34-4.39 (m, 1H, 4-H), 3.92 (d, 2H, $J = 6.8$ Hz, OCH₂CHMe₂), 2.39-2.54 (m, 2H, 2-2H), 2.18-2.23 (m, 1H, 3-H_a), 1.91-2.01 (m, 2H, 3-H_b, OCH₂CHMe₂), 1.44 (s, 9H, Boc), 0.94 (d, 6H, $J = 6.8$ Hz, OCH₂CHMe₂). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 178.0, 172.3, 155.5, 80.2, 71.6, 52.8, 30.1, 28.3, 27.8, 27.7, 19.0. MS (ESI) m/z 326.3 (M+Na)⁺.

4-((tert-butoxycarbonyl)amino)-5-(sec-butoxy)-L-glutamic acid (18f).

White solid 325 mg, overall yield: 62.4%. $[\alpha]_{\text{D}}^{20} = +8.2^{\circ}$ (c 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 5.22 (d, 1H, $J = 7.2$ Hz, NH), 4.89 (ddq, 1H, $J = 3.2, 6.4, 13.2$ Hz, 1'-H), 4.29-4.34 (m, 1H, 4-H), 2.37-2.53 (m, 2H, 2-2H), 2.15-2.22 (m, 1H, 3-H_a), 1.89-1.98 (m, 1H, 3-H_b), 1.52-1.67 (m, 2H, 2'-2H), 1.44 (s, 9H, Boc), 1.23 (d, 3H, $J = 5.6$ Hz, 1'-CH₃), 0.90 (t, 3H, $J = 7.6$ Hz, 3'-3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 177.9, 171.9, 155.6, 80.1, 74.0, 53.0, 30.1, 28.7, 28.3, 27.9, 19.4, 9.7. MS (ESI) m/z 326.3 (M+Na)⁺.

4-((tert-butoxycarbonyl)amino)-5-cyclopentyloxy-L-glutamic acid (18g).

White solid 344 mg, overall yield: 69.6%. $[\alpha]_{\text{D}}^{20} = +7.8^{\circ}$ (c 1.4, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 11.04 (br, 1H, COOH), 5.17-5.23 (m, 2H, NH, cyclopentyl-H), 4.26-4.31 (m, 1H, 4-H), 2.38-2.52 (m, 2H, 2-2H), 2.14-2.20 (m, 1H, 3-H_a), 1.84-1.97 (m, 3H, 3-H_b, cyclopentyl-2H), 1.68-1.76 (m, 4H, cyclopentyl-4H), 1.59-1.62 (m, 2H, cyclopentyl-2H), 1.44 (s, 9H, Boc). MS (ESI) m/z 338.3 (M+Na)⁺. Known compound.

4-((tert-butoxycarbonyl)amino)-5-phenoxy-L-glutamic acid (18h).

White solid 155 mg, overall yield: 30.9%. $[\alpha]_{\text{D}}^{20} = +10.4^{\circ}$ (c 1.8, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.38 (dd, 2H, $J = 8.0, 8.4$ Hz, Ph-2H), 7.23-7.26 (m, 1H,

Ph-H), 7.10 (d, 2H, $J = 8.0$ Hz, Ph-2H), 5.22 (d, 1H, $J = 8.0$ Hz, NH), 4.58-4.61 (m, 1H, 4-H), 2.51-2.65 (m, 2H, 2-2H), 2.36-2.39 (m, 1H, 3-H_a), 2.09-2.15 (m, 1H, 3-H_b), 1.47 (s, 9H, Boc). MS (ESI) m/z 346.3 (M+Na)⁺. Known compound.

3. Stability test of compound **10b**

To preliminarily determine the stability of compound **10b** in a biological environment, an in vitro experimental verification method was employed. The trace compound was dissolved in mouse plasma to simulate the biological environment. Samples were taken at different time intervals at 37°C, and the content of the compound was determined by HPLC C18 analytical column. The peak area of the absorption at 220 nm was utilized for content calculation.

The standard curve shown in Fig. S1 can be plotted using the peak area and the mass of compound **10b** in the corresponding volume of the solution. The relationship is $y = 23.253x + 100.67$ ($R^2 = 0.9994$), which meets linearity requirements and can be used for subsequent operations.

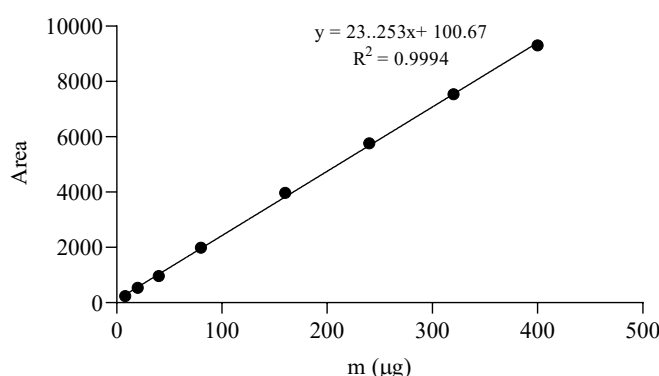


Fig. S1. The relationship curve between the absorption peak area and mass of compound **10b** at 220 nm.

Subsequently, a mouse with a body weight of 20 g and blood volume of 1 mL was calculated based on the subsequent in vivo experiment's dosage (100 mg·Kg⁻¹). Assuming 100% absorption, the converted plasma drug concentration is 2 mg·mL⁻¹. Based on the calculation, 0.5 mg of **10b** was added to 200 mL of mouse plasma to prepare a mixed solution. The plasma was then processed after 1h, 6h, 12 h, 24 h, and 48 h, respectively. The compound content in the sample was compared to the initial content with UV absorption and retention time ($t = 6.5$ min). As shown in Table S1, no significant decrease in the content of **10b** was observed between 0 to 48 hours, indicating that compound **10b** existed stably in mouse plasma.

Table S1. The contents of compound **10b** extracted from mouse plasma in different time periods.

Time (37°C)	Peak area	Mass of 10b (μg)	Theoretical mass of 10b (μg)	Recovery rate
0 h	710.1	26.2	38.5	68.0 %
1 h	743.3	27.3	38.5	70.9 %
6 h	781.0	29.2	38.5	75.8 %
12 h	667.1	24.4	38.5	63.4 %
24 h	714.8	26.4	38.5	68.5 %
48 h	786.8	29.5	38.5	76.6 %

4. Compound **10b** affects markers of liver injury and hepatic fibrosis in BDL rats

Table S2. Serum biochemical markers of BDL rats (n=8).

	Sham(n=8)	BDL(n=8)	10b 100mg·kg ⁻¹ (n=7)
Serum ALT (U·L ⁻¹)	27.75±3.86	102.38±41.49 ^{##}	84.83±18.11
Serum AST (U·L ⁻¹)	116±20.02	659.75±179.41 ^{##}	435.5±98.62 [*]
Serum ALP (U·L ⁻¹)	178.5±54.74	371.00±41.17 ^{##}	391.33±52.42
Serum γ-GT (U·L ⁻¹)	/	39.63±22.93 ^{##}	37.5±6.74
Serum CHO (mmol·L ⁻¹)	1.57±0.16	2.55±0.44 ^{##}	2.08±0.43
Serum LDL (mmol·L ⁻¹)	1.57±0.16	1.08±0.22 ^{##}	1.06±0.22
Serum HDL (mmol·L ⁻¹)	0.65±0.08	0.47±0.12 ^{##}	0.29±0.06 ^{**}
Serum TG (mmol·L ⁻¹)	0.27±0.12	0.74±0.24 ^{##}	0.67±0.19
Serum TBA (μmol·L ⁻¹)	8.53±2.65	228.45±31.99 ^{##}	202.60±30.80
Serum TBiL (μmol·L ⁻¹)	0.78±0.21	177.45±19.94 ^{##}	180.00±26.16
Bile TBA(μmol·L ⁻¹)	/	258.46±69.07	249.4±103.67
Bile TBiL (μmol·L ⁻¹)	/	5.63±1.51	5.8±2.46
Urine TBA(μmol·L ⁻¹)	-0.53±1.62	24.75±20.07 ^{##}	15.38±5.76
Urine TBiL (μmol·L ⁻¹)	2.93±4.72	6.65±4.09 ^{##}	5.33±1.50

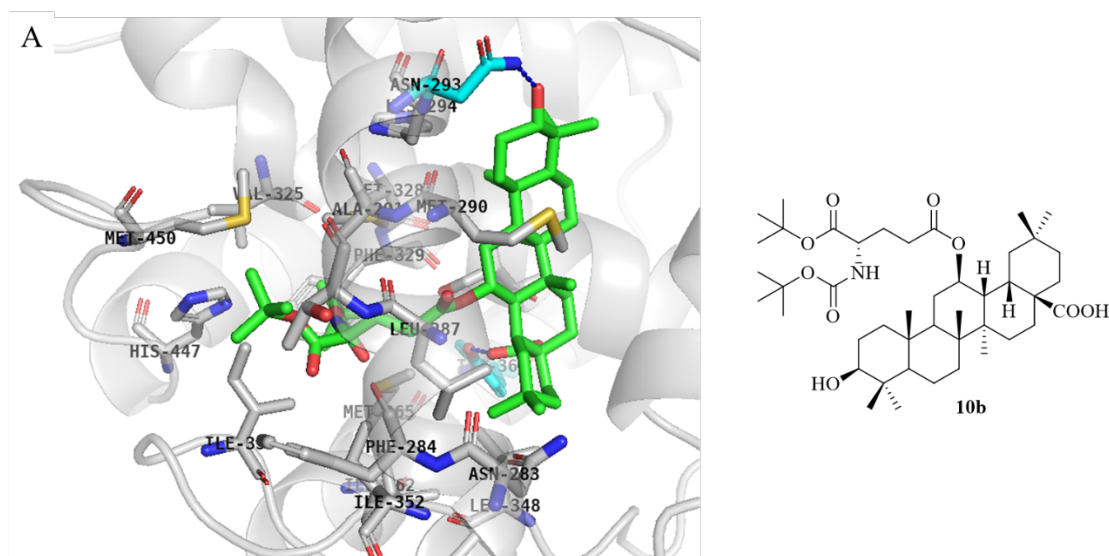
5. Compound **10b** affects serum biochemical markers in HFD mice

Table S3. Serum biochemical markers of HFD mice (n=7)

	Ctrl (n=7)	Model (n=7)	10b 100mg·kg ⁻¹ (n=7)
Serum ALT (U·L ⁻¹)	32.63±30.61	258.33±43.36 ^{##}	325.43±88.40
Serum AST (U·L ⁻¹)	114.88±32.21	326.83±43.41 ^{##}	401.86±91.05
Serum ALP (U·L ⁻¹)	59.00±8.30	128.83±9.50 ^{##}	189.71±29.41
Serum LDH (U·L ⁻¹)	474.00±188.43	1563.67±245.77 ^{##}	1326.57±264.54
Serum CHO (mmol·L ⁻¹)	2.79±0.32	2.13±0.42 ^{##}	2.36±0.44
Serum LDL (mmol·L ⁻¹)	0.14±0.02	0.33±0.13 ^{##}	0.23±0.04
Serum HDL (mmol·L ⁻¹)	1.89±0.32	1.03±0.20 ^{##}	1.22±0.33
Serum TG (mmol·L ⁻¹)	1.24±0.25	1.08±0.18	0.85±0.30
Serum Glu (mmol·L ⁻¹)	8.72±0.94	3.80±1.37 ^{##}	5.71±1.25
Serum TBA (μmol·L ⁻¹)	1.34±0.57	25.72±4.10 ^{##}	23.46±12.81
Serum TBiL (μmol·L ⁻¹)	1.48±1.21	3.80±1.13 ^{##}	3.81±0.92

Values are presented as the mean ± SD (n=7); ^{##} *p*<0.01, significantly different from the sham group.

6. Binding model of 12β-OA derivative interacting with FXR-LBD



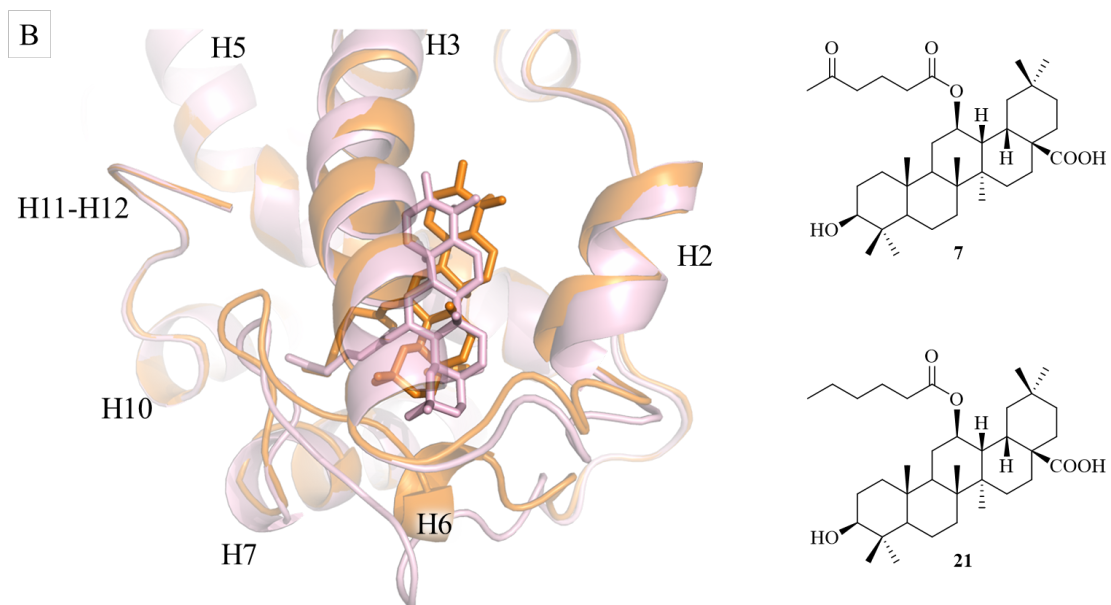


Fig. S2. (A) Binding model of compound **10b** (green) as ligand interacting with FXR-LBD. (B) Binding model of compound **7** (pink) and **21** (orange) as ligands interacting with FXR-LBD.

7. NMR and HRMS spectra of all compounds

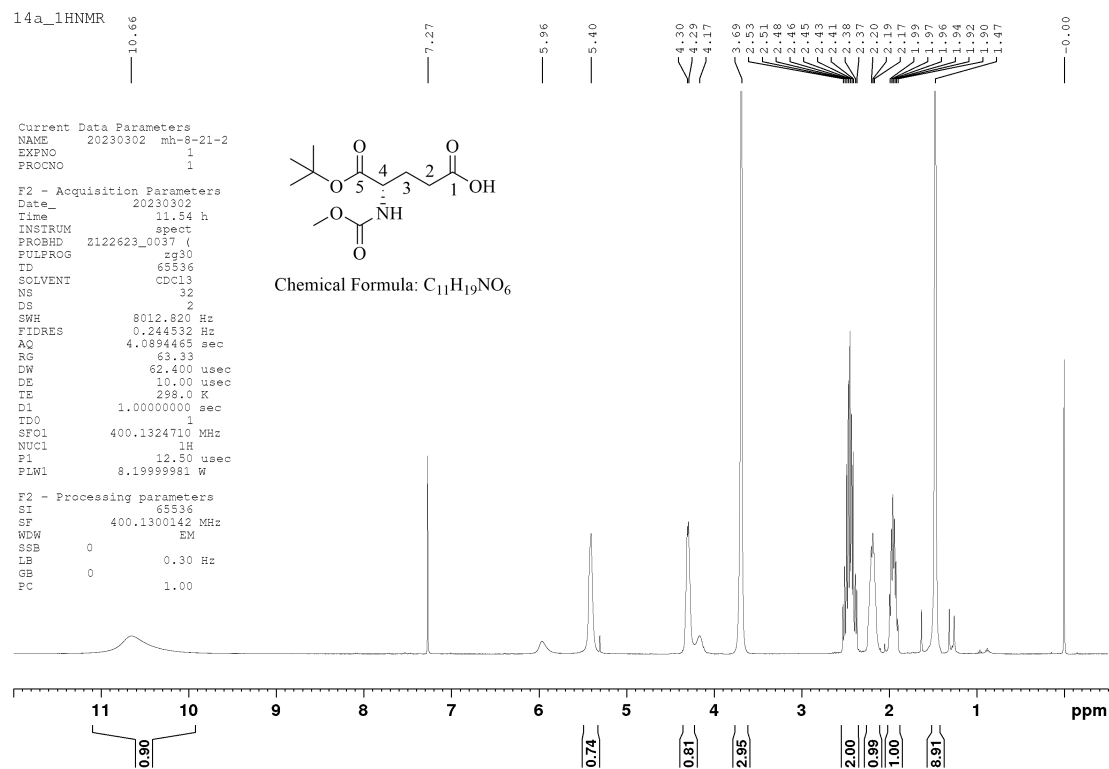


Fig. S3. ¹H NMR of intermediate 14a

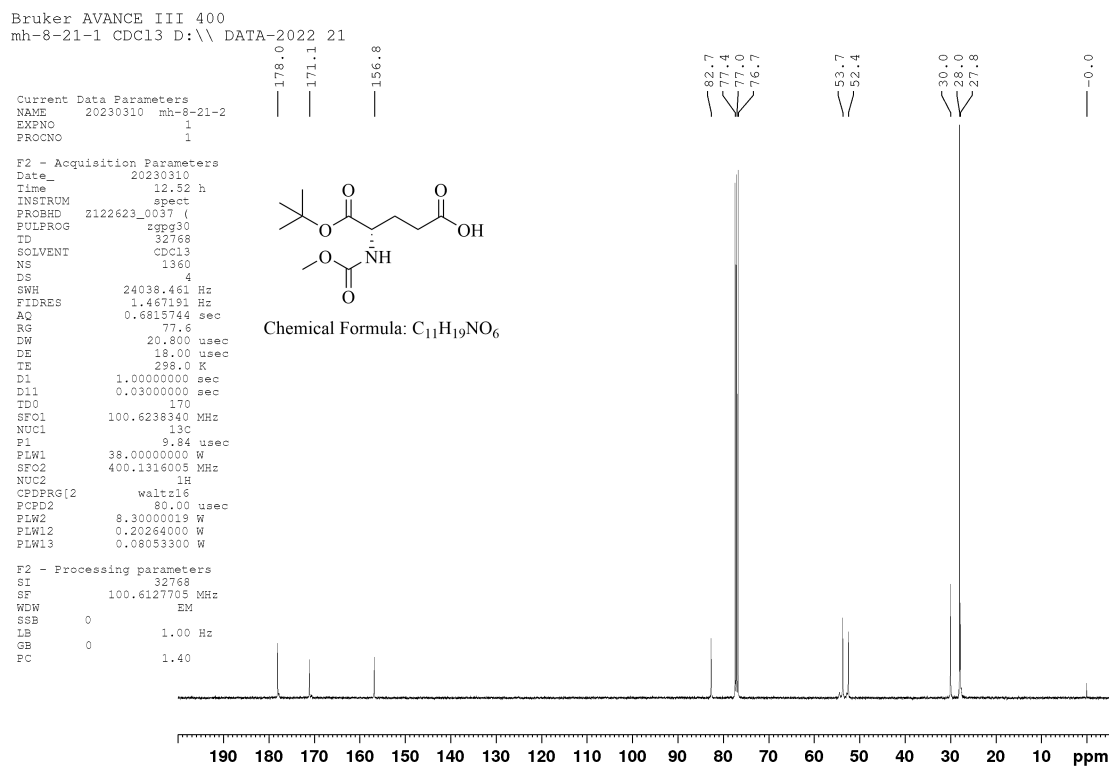


Fig. S4. ¹³C NMR of intermediate 14a

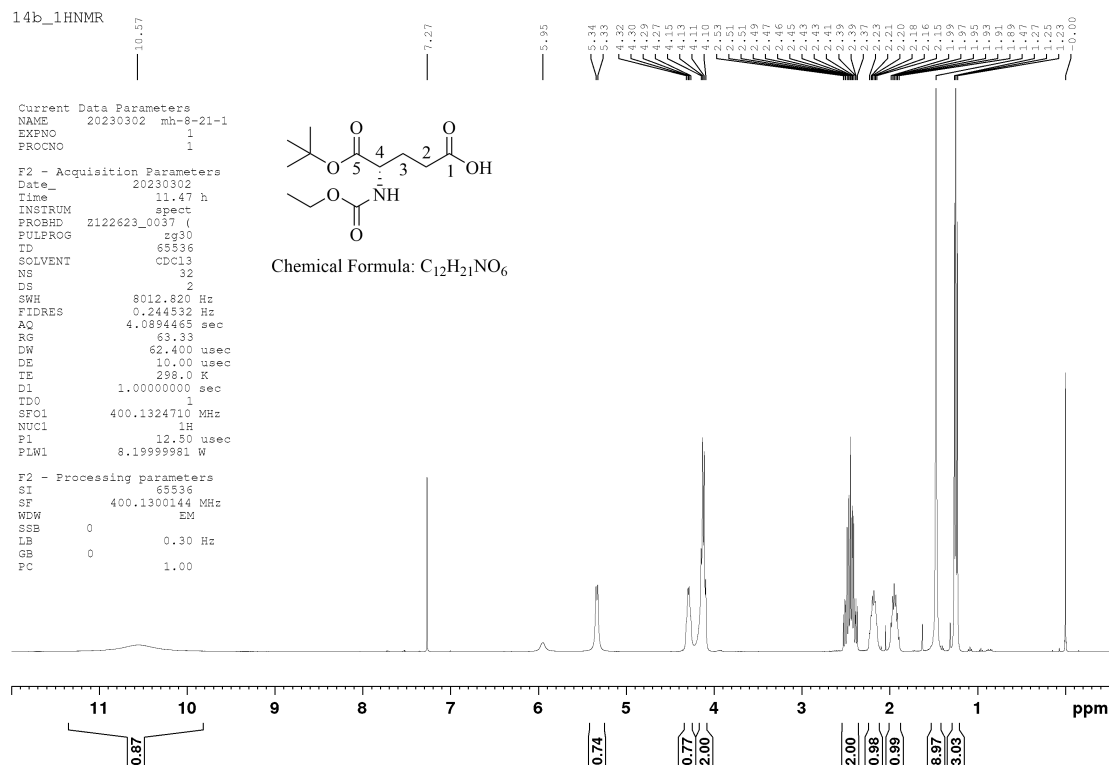


Fig. S5. ¹H NMR of intermediate 14b

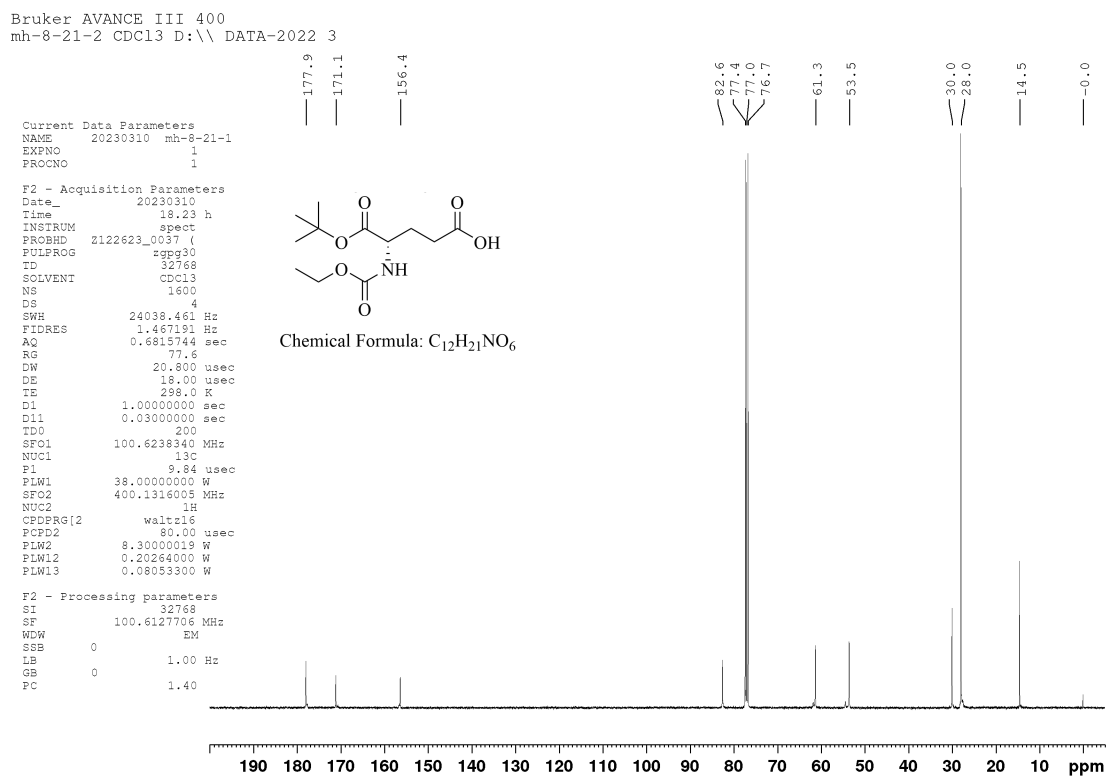


Fig. S6. ¹³C NMR of intermediate 14b

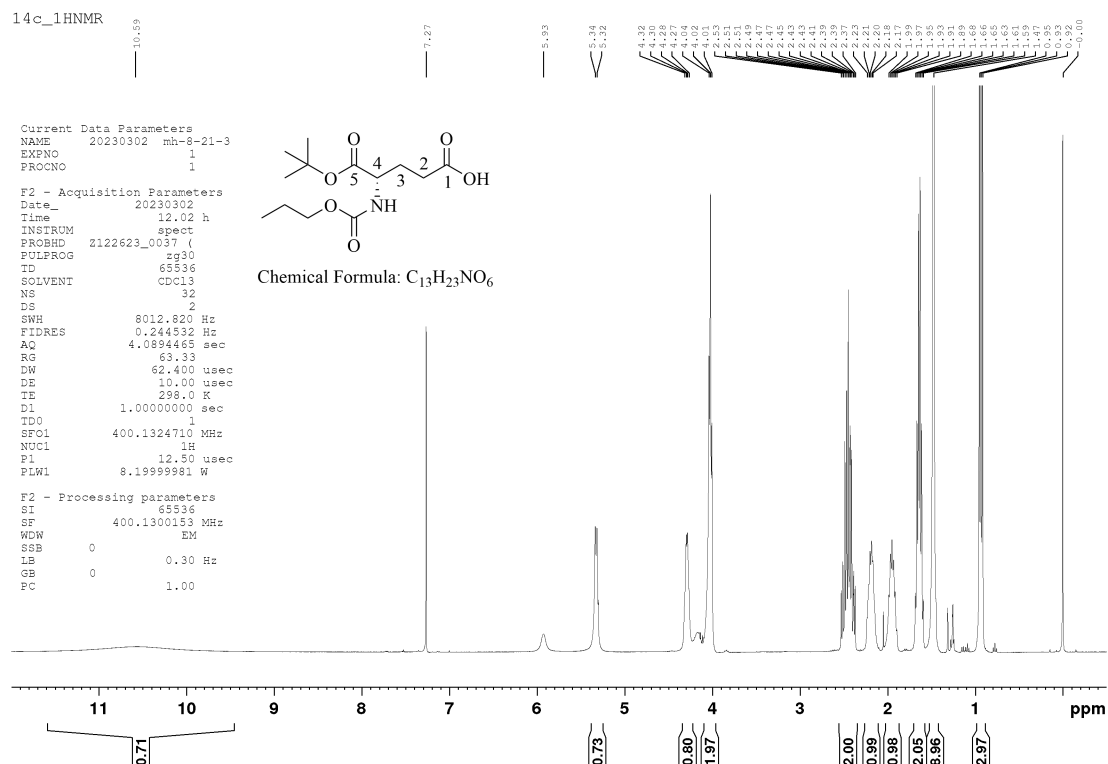


Fig. S7. ¹H NMR of intermediate 14c

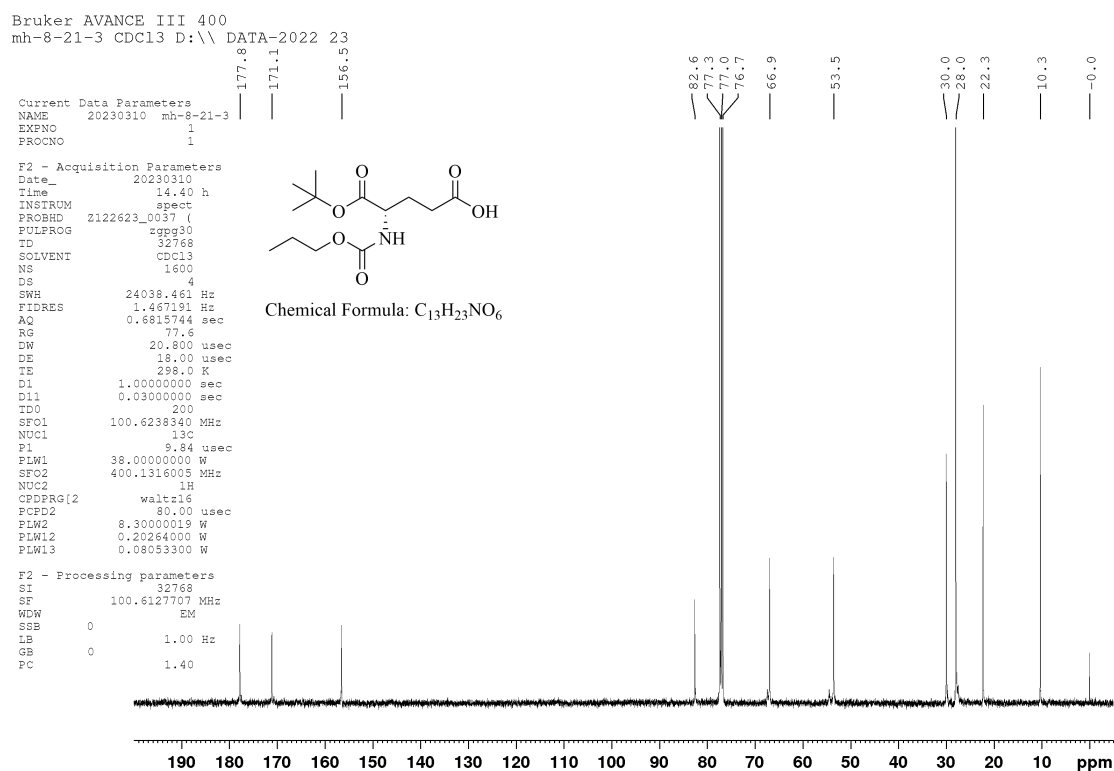


Fig. S8. ¹³C NMR of intermediate 14c

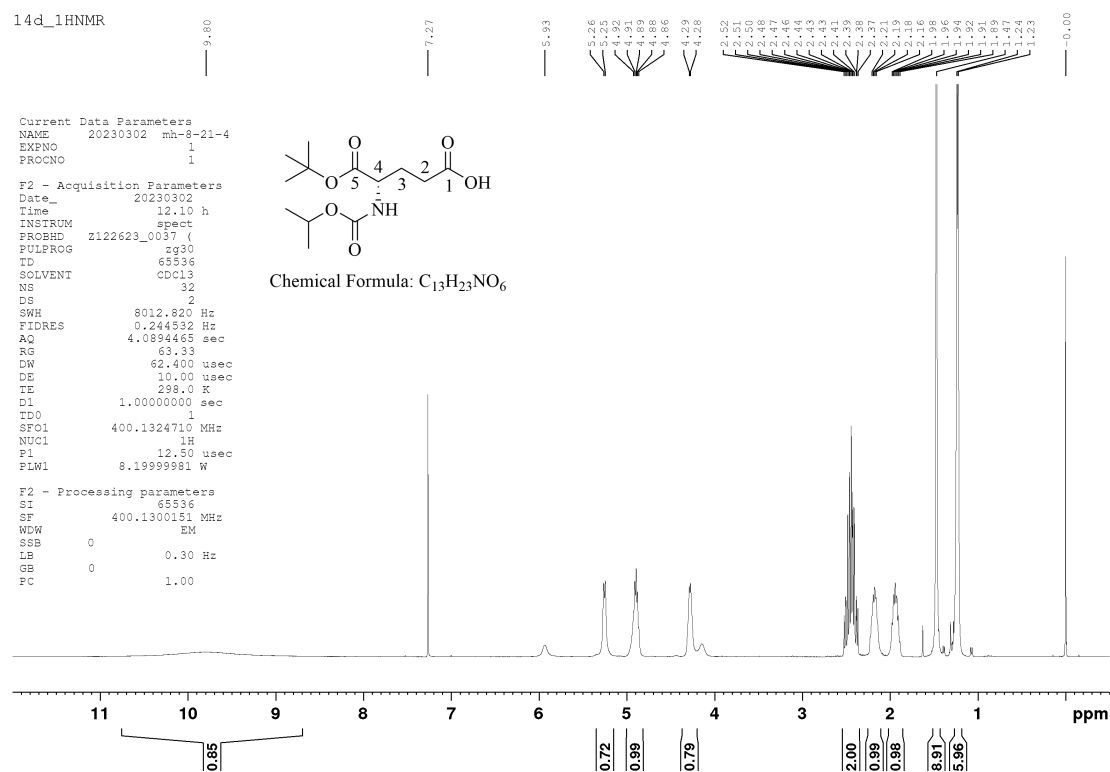


Fig. S9. ¹H NMR of intermediate 14d

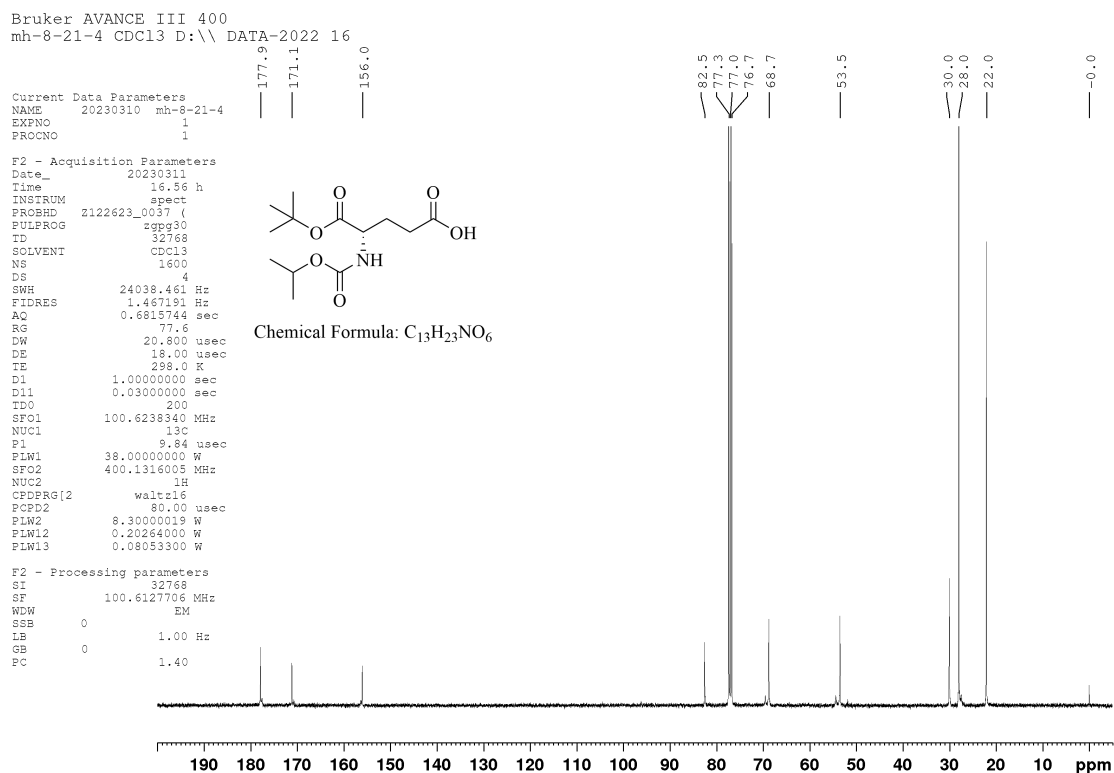


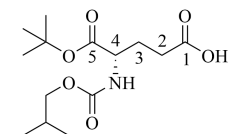
Fig. S10. ¹³C NMR of intermediate 14d

14e_1HNMR

Current Data Parameters
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EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230302
Time 12.18 h
INSTRUM spect
PROBHD Z122623_0037 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 63.33
DM 62.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324710 MHz
NUC1 1H
P1 12.50 usec
PLW1 8.19999981 W

F2 - Processing parameters
SI 65536
SF 400.1300148 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Chemical Formula: C₁₄H₂₅NO₆

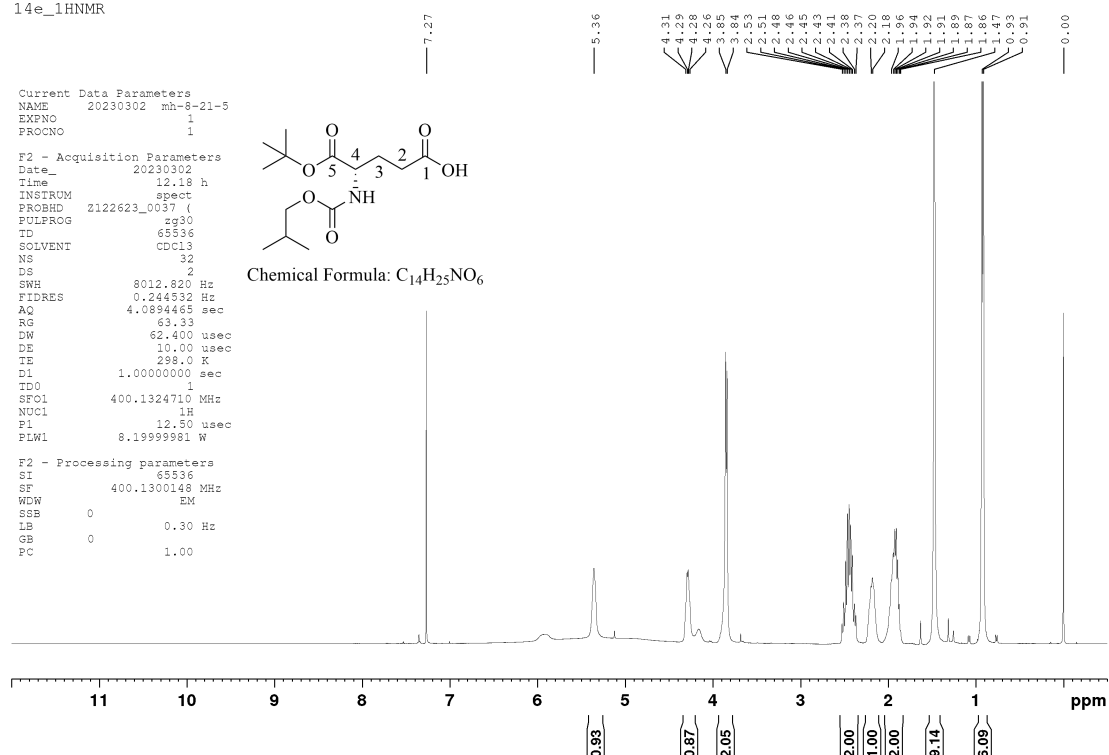


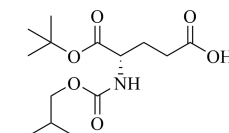
Fig. S11. ¹H NMR of intermediate 14e

Bruker AVANCE III 400
mh-8-21-5 CDCl3 D:\ DATA-2022 22

Current Data Parameters
NAME 20230310 mh-8-21-5
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230310
Time 13.47 h
INSTRUM spect
PROBHD Z122623_0037 (
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 1436
DS 4
SWH 24038.461 Hz
FIDRES 1.467191 Hz
AQ 0.6819744 sec
RG 77.6
DM 20.800 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 200
SFO1 100.6238340 MHz
NUC1 13C
P1 9.84 usec
PLW1 38.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 80.00 usec
PLW2 8.30000019 W
PLW12 0.20264000 W
PLW13 0.08053300 W

F2 - Processing parameters
SI 32768
SF 100.6127706 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Chemical Formula: C₁₄H₂₅NO₆

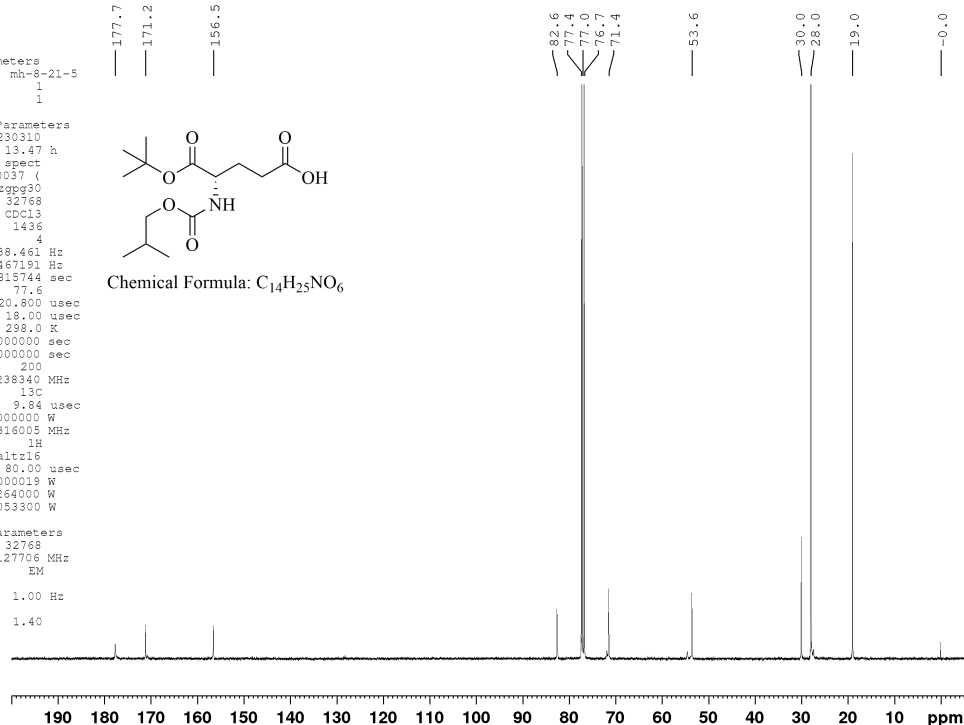


Fig. S12. ¹³C NMR of intermediate 14e

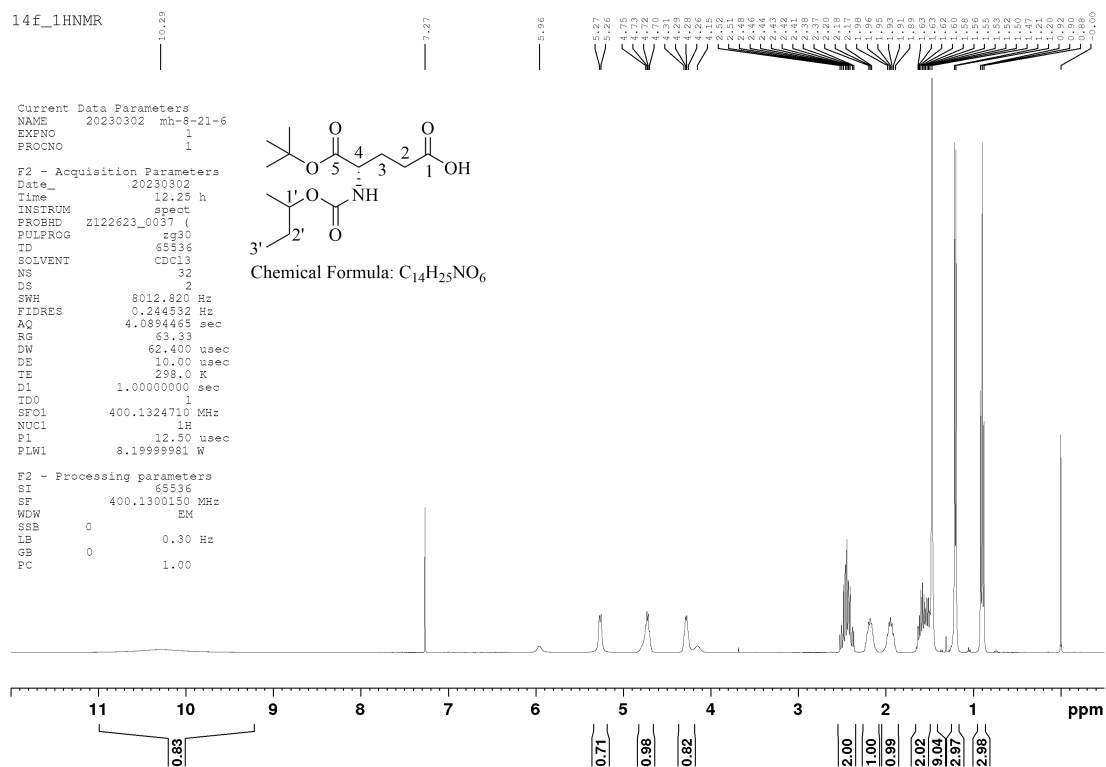


Fig. S13. ¹H NMR of intermediate 14f

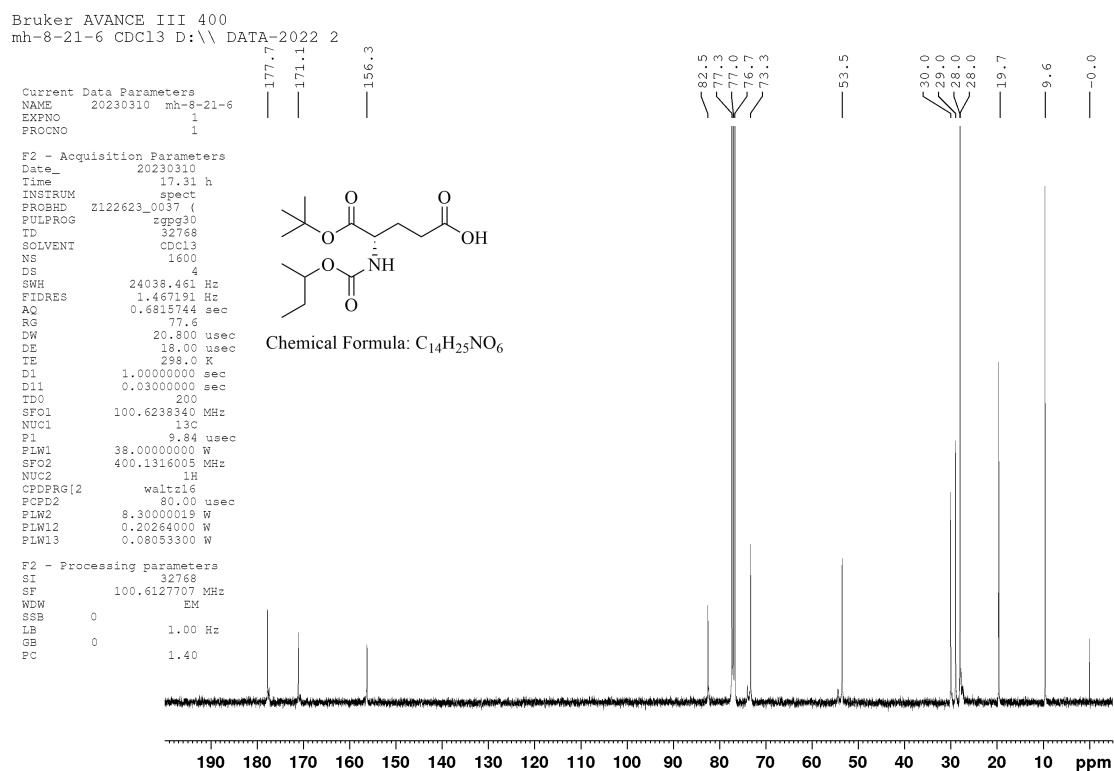


Fig. S14. ¹³C NMR of intermediate 14f

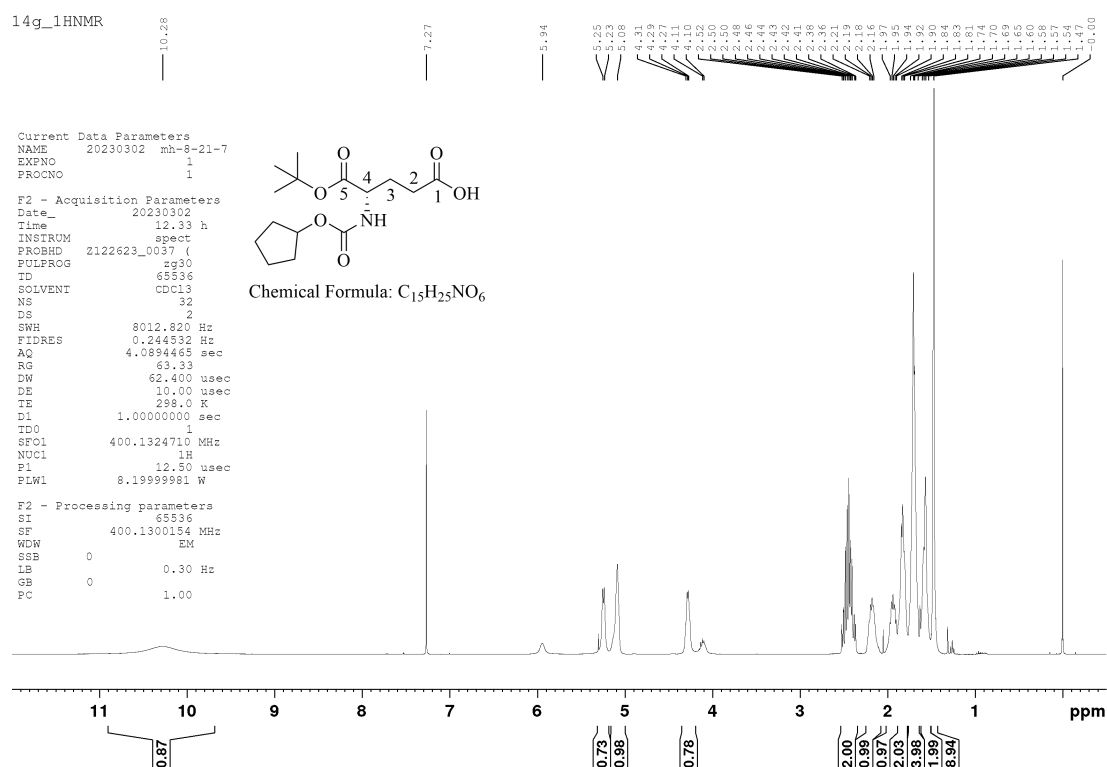


Fig. S15. ¹H NMR of intermediate 14g

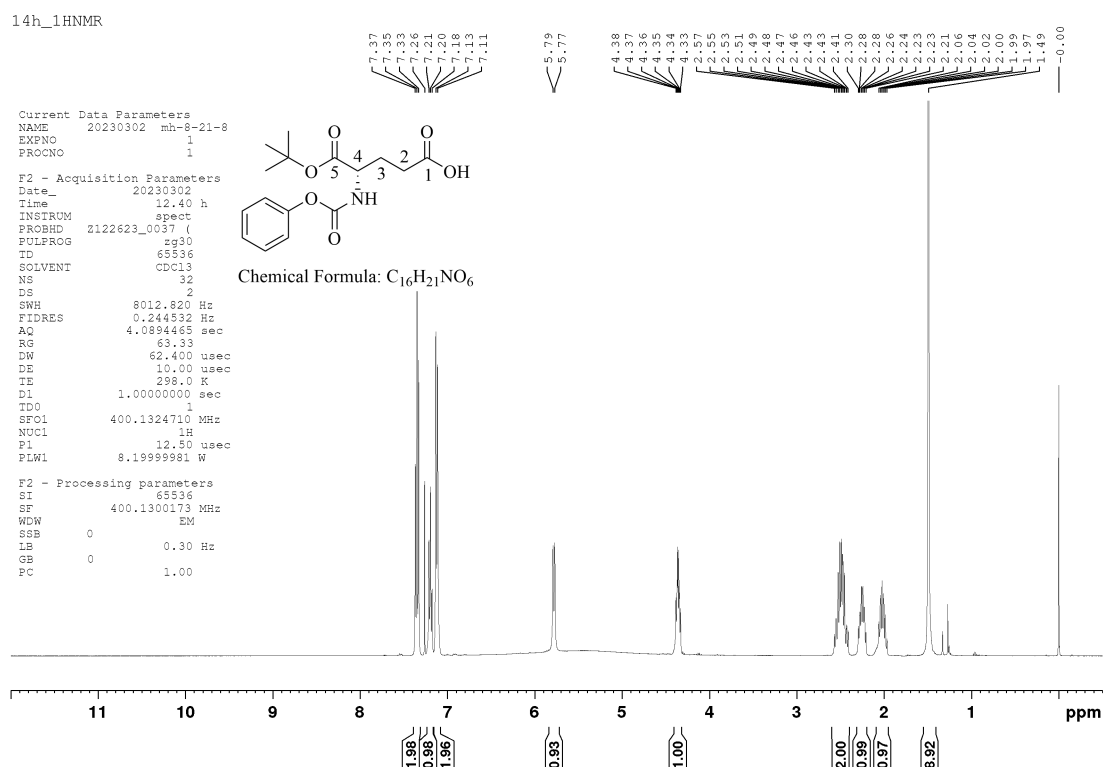


Fig. S16. ¹H NMR of intermediate 14h

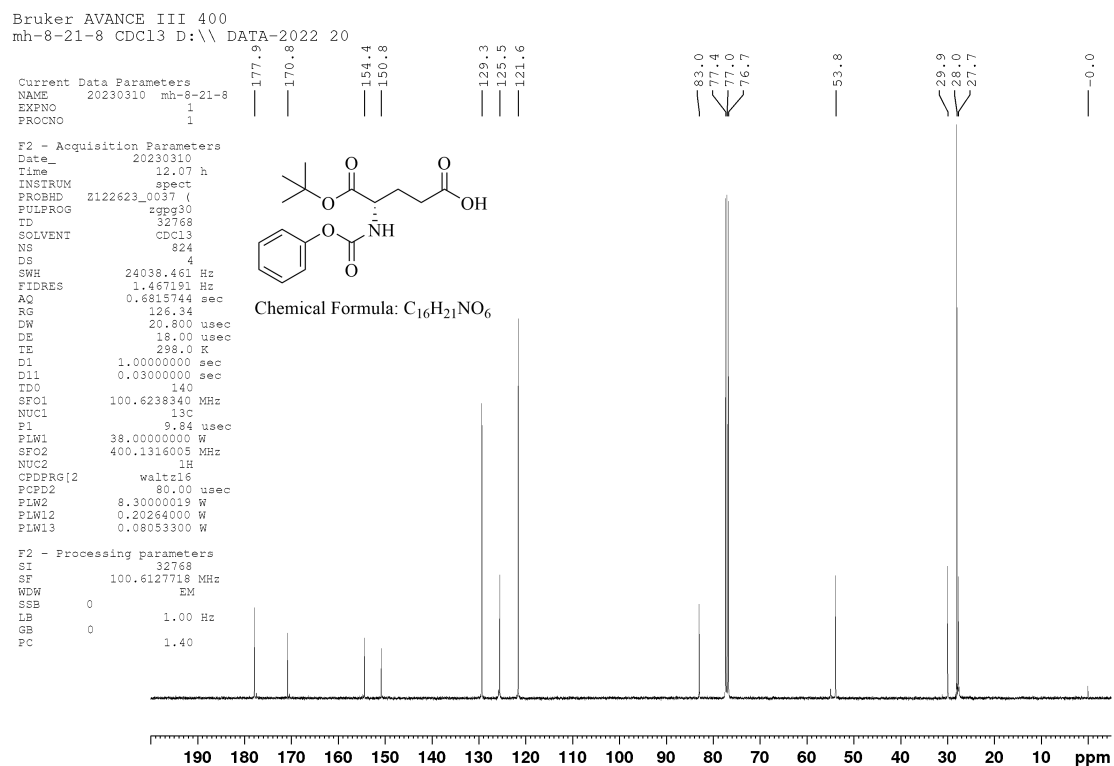


Fig. S17. ¹³C NMR of intermediate 14h

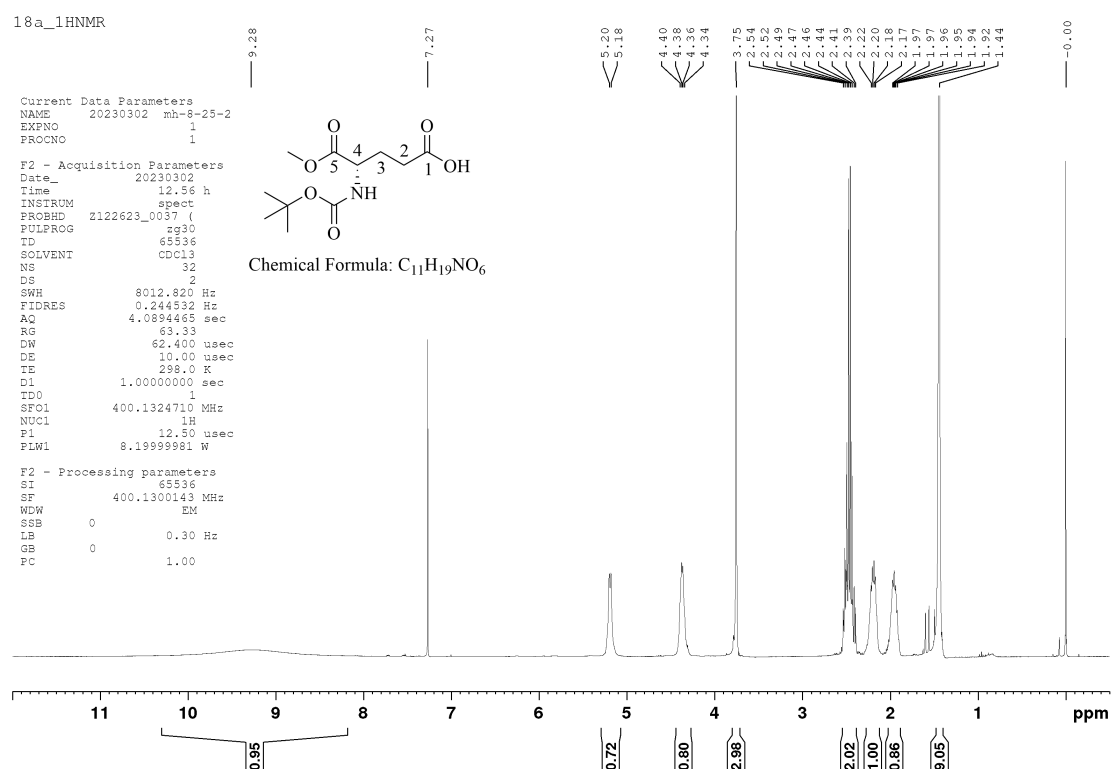


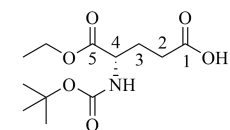
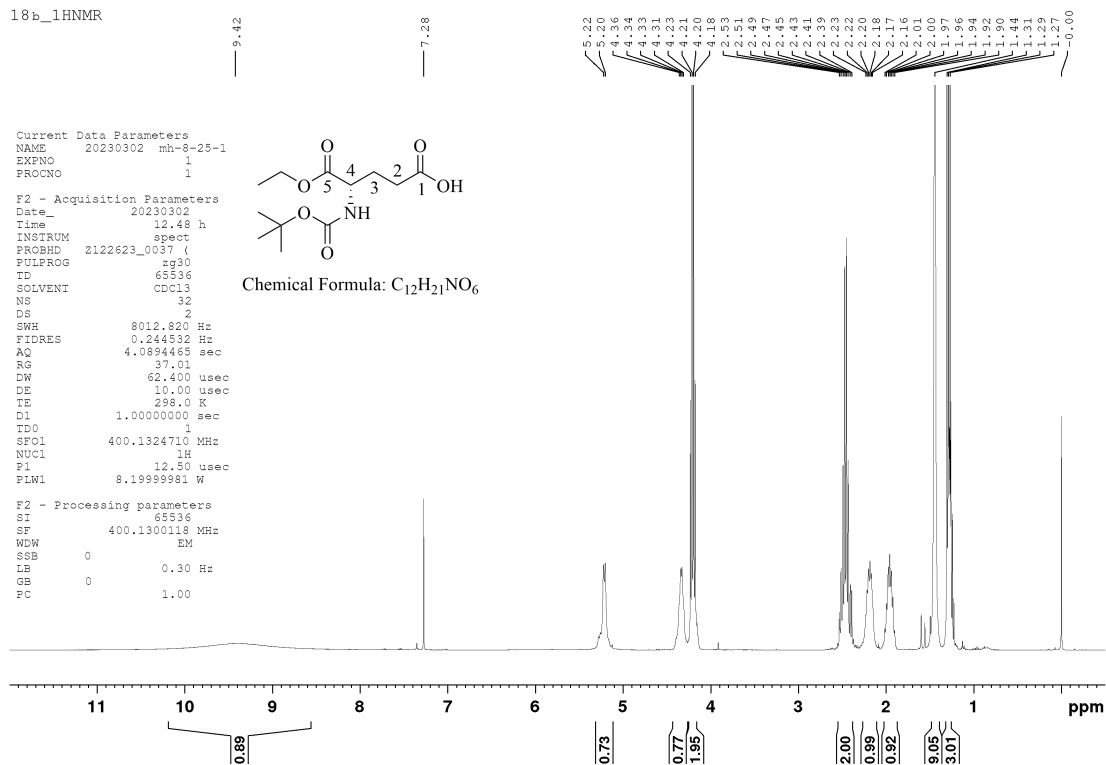
Fig. S18. ¹H NMR of intermediate 18a

18b_1HNMR

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 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20230302
 Time 12.48 h
 INSTRUM spect
 PROBHD Z122623_0037 (
 PULPROG zg30
 ID 65536
 SOLVENT CDCl3
 NS 32
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.244532 Hz
 AQ 4.0894465 sec
 RG 37.01
 DW 62.400 usec
 DE 10.00 usec
 TE 298.0 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1324710 MHz
 NUC1 1H
 P1 12.50 usec
 PLW1 8.19999981 W

F2 - Processing parameters
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 SF 400.1300118 MHz
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 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

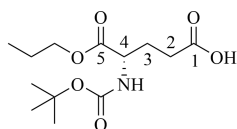
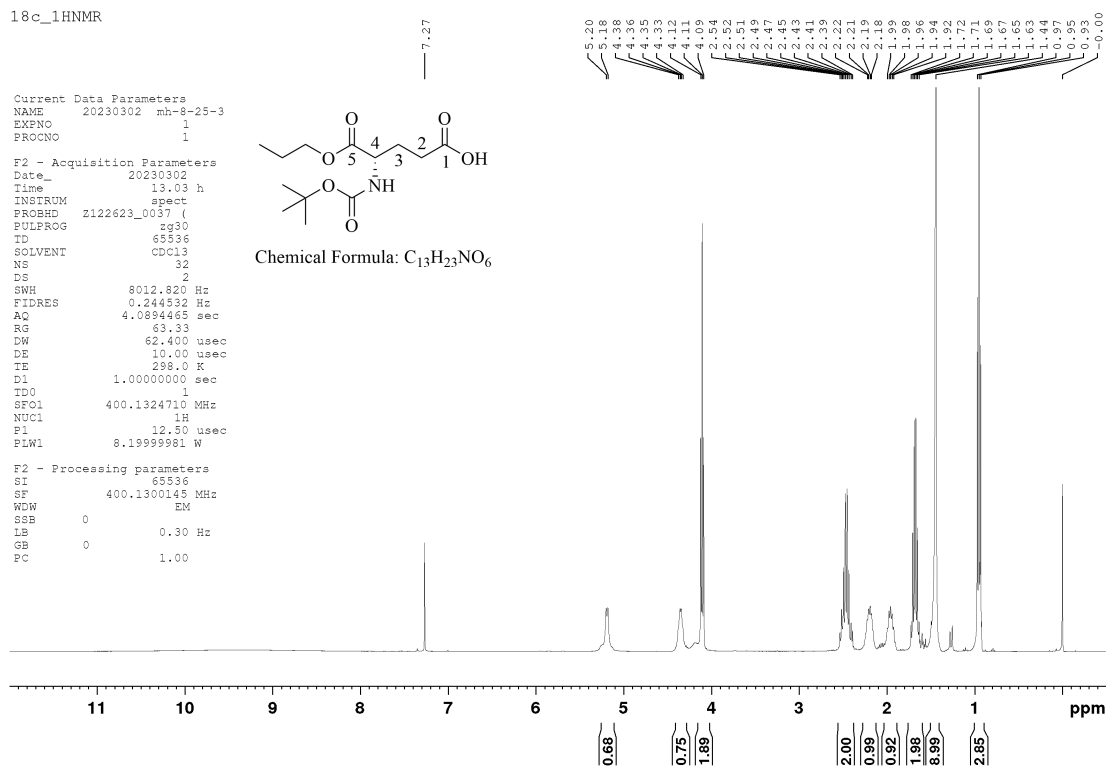
Chemical Formula: C₁₂H₂₁NO₆Fig. S19. ¹H NMR of intermediate 18b

18c_1HNMR

Current Data Parameters
 NAME 20230302 mh-8-25-3
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20230302
 Time 13.03 h
 INSTRUM spect
 PROBHD Z122623_0037 (
 PULPROG zg30
 ID 65536
 SOLVENT CDCl3
 NS 32
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.244532 Hz
 AQ 4.0894465 sec
 RG 63.33
 DW 62.400 usec
 DE 10.00 usec
 TE 298.0 K
 D1 1.00000000 sec
 TD0 1
 SFO1 400.1324710 MHz
 NUC1 1H
 P1 12.50 usec
 PLW1 8.19999981 W

F2 - Processing parameters
 SI 65536
 SF 400.1300145 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

Chemical Formula: C₁₃H₂₃NO₆Fig. S20. ¹H NMR of intermediate 18c

18d_1HNMR

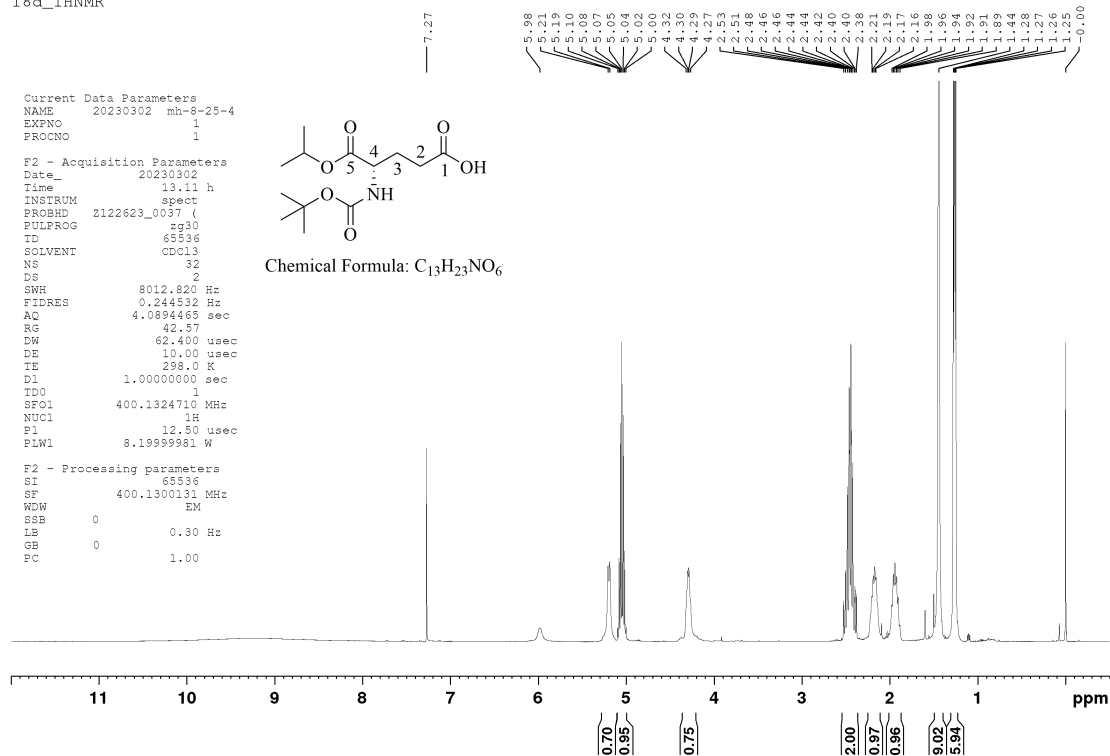


Fig. S21. 1H NMR of intermediate 18d

18e_1HNMR

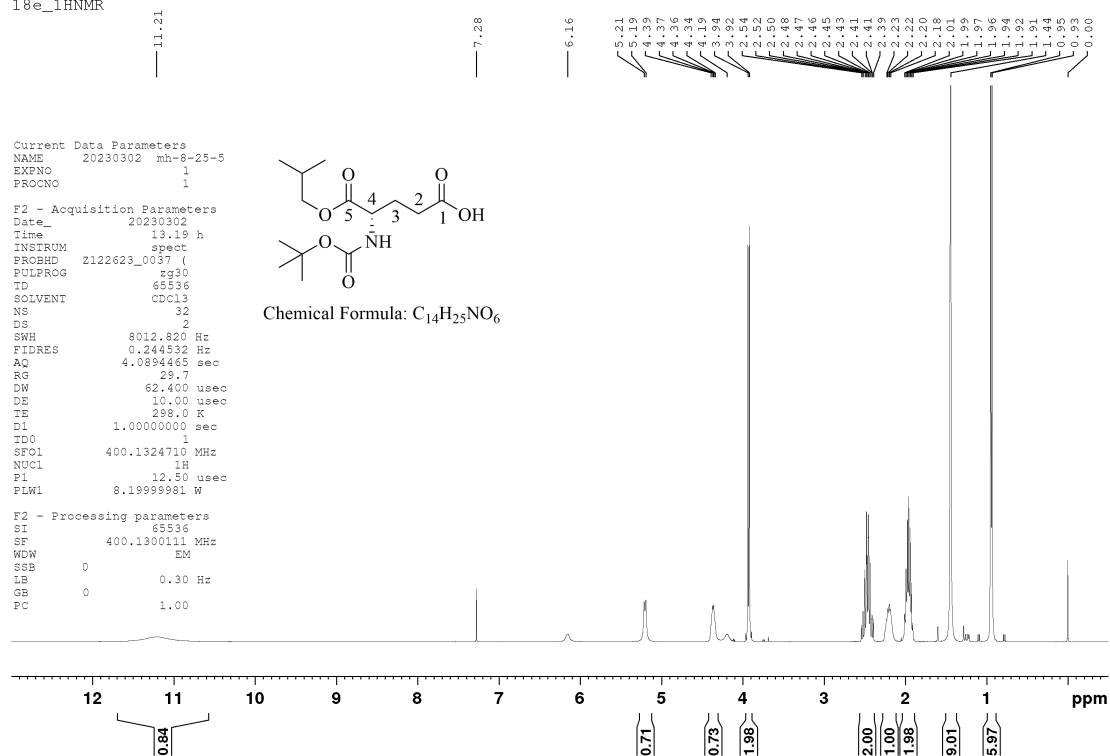


Fig. S22. 1H NMR of intermediate 18e

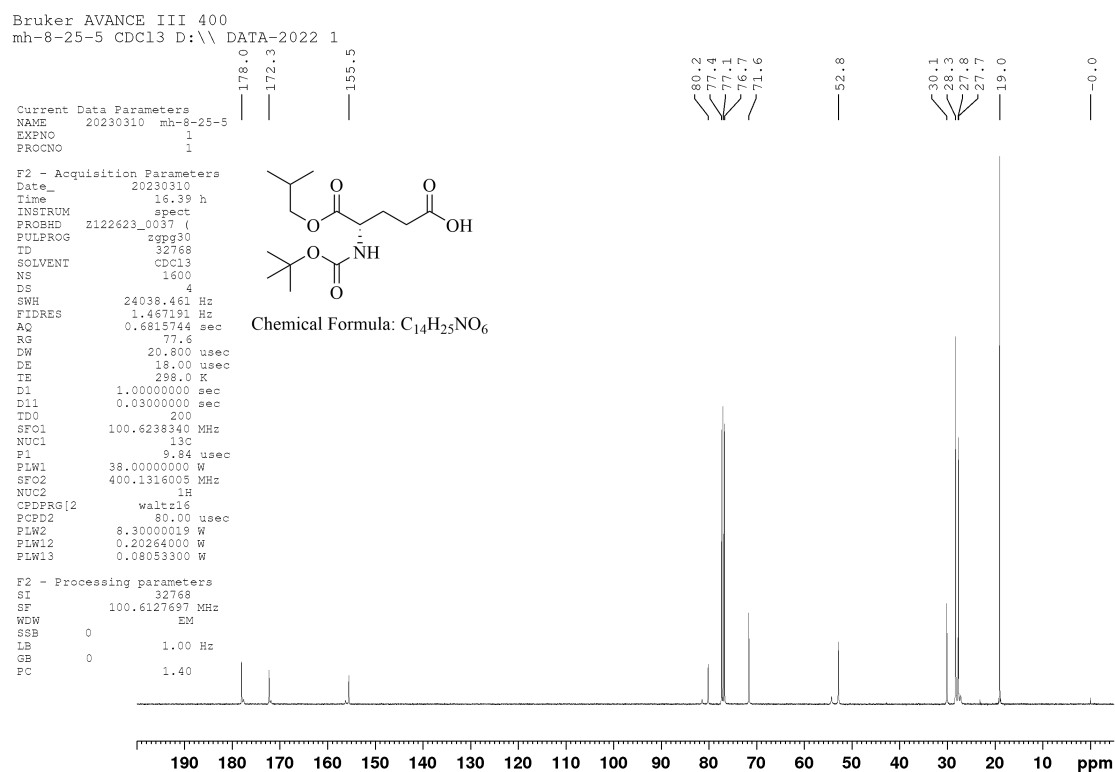


Fig. S23. ¹³C NMR of intermediate 18e

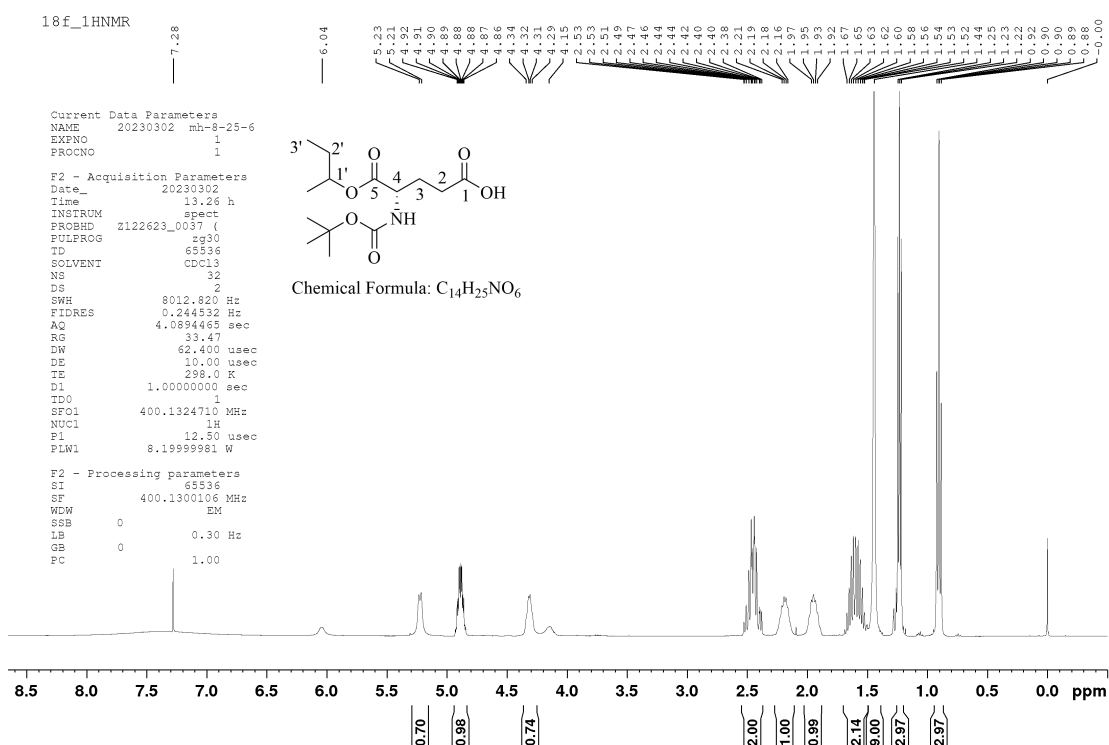


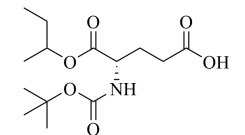
Fig. S24. ¹H NMR of intermediate 18f

Bruker AVANCE III 400
mh-8-25-6 CDCl3 D:\ DATA-2022 24

Current Data Parameters
NAME 20230310 mh-8-25-6
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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Time 15.47 h
INSTRUM spect
PROBHD Z122623_0037 (
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 1600
DS 4
SWH 24038.461 Hz
FIDRES 1.467191 Hz
AQ 0.6815744 sec
RG 77.6
DW 20.800 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 200
SFO1 100.6238340 MHz
NUC1 13C
P1 9.84 usec
PLW1 38.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG2 waltr16
PCPD2 80.00 usec
PLW2 8.30000019 W
PLW12 0.20264000 W
PLW13 0.08053300 W

F2 - Processing parameters
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SF 100.6127691 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Chemical Formula: C₁₄H₂₅NO₆

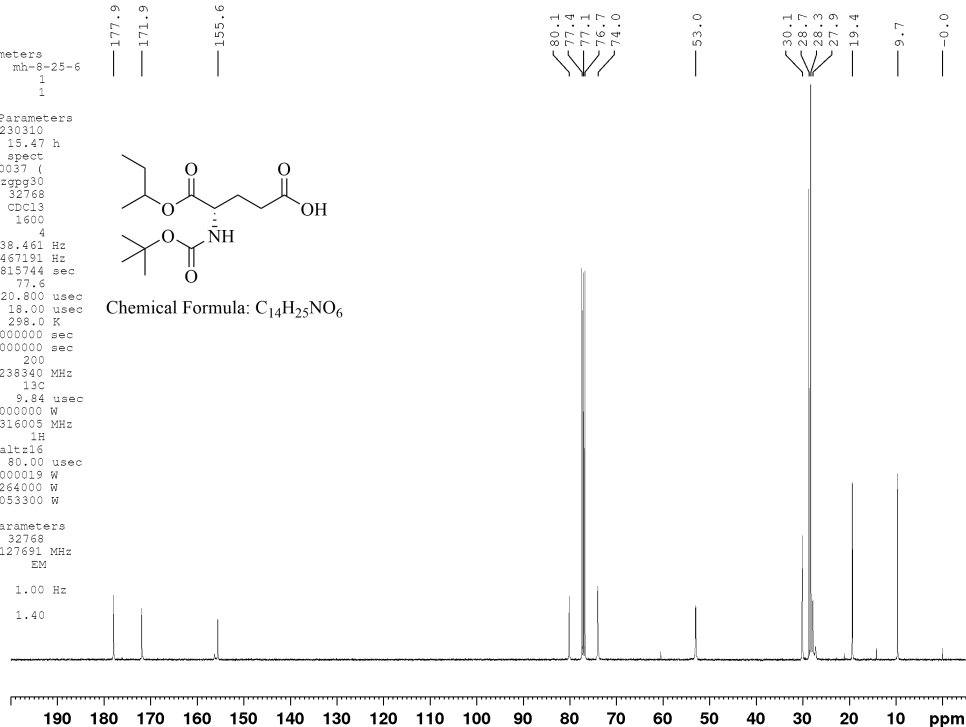


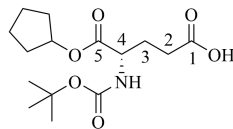
Fig. S25. ¹³C NMR of intermediate **18f**

18g_1HNMR

Current Data Parameters
NAME 20230302 mh-8-25-7
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230302
Time 13.34 h
INSTRUM spect
PROBHD Z122623_0037 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 42.57
DW 62.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 1
TD0 400.1324710 MHz
SFO1 1H
NUC1 1H
P1 12.50 usec
PLW1 8.19999981 W

F2 - Processing parameters
SI 65536
SF 400.1300129 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Chemical Formula: C₁₅H₂₅NO₆

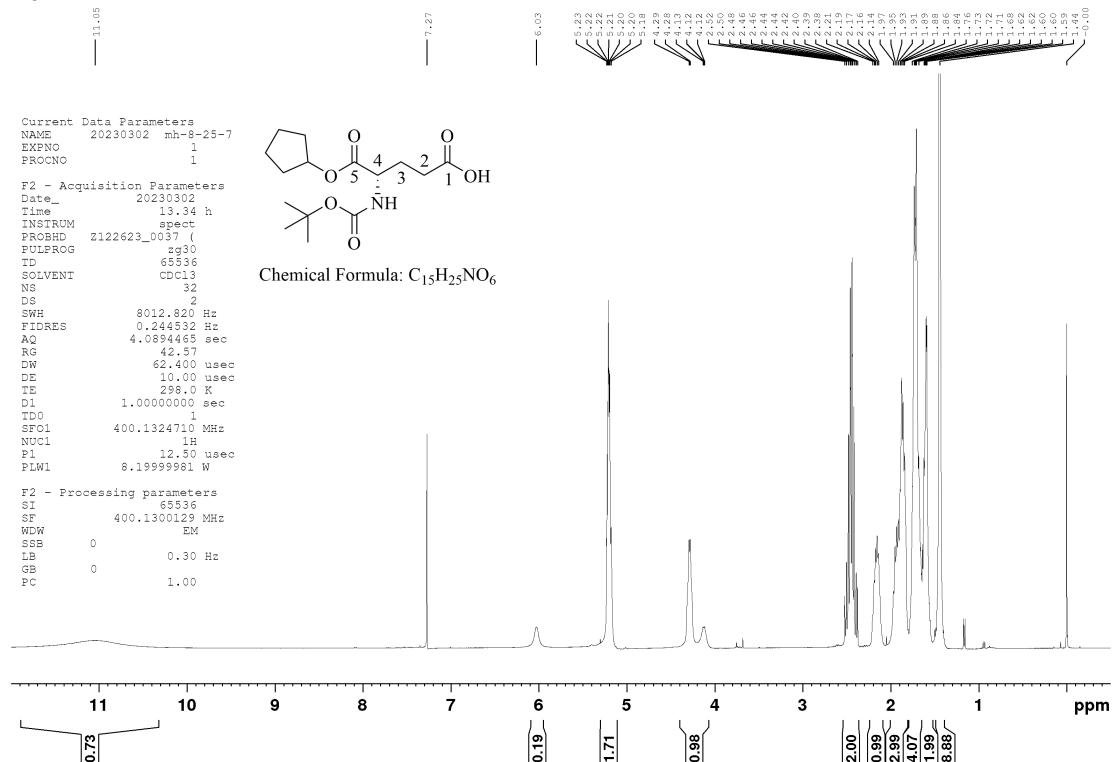


Fig. S26. ¹H NMR of intermediate **18g**

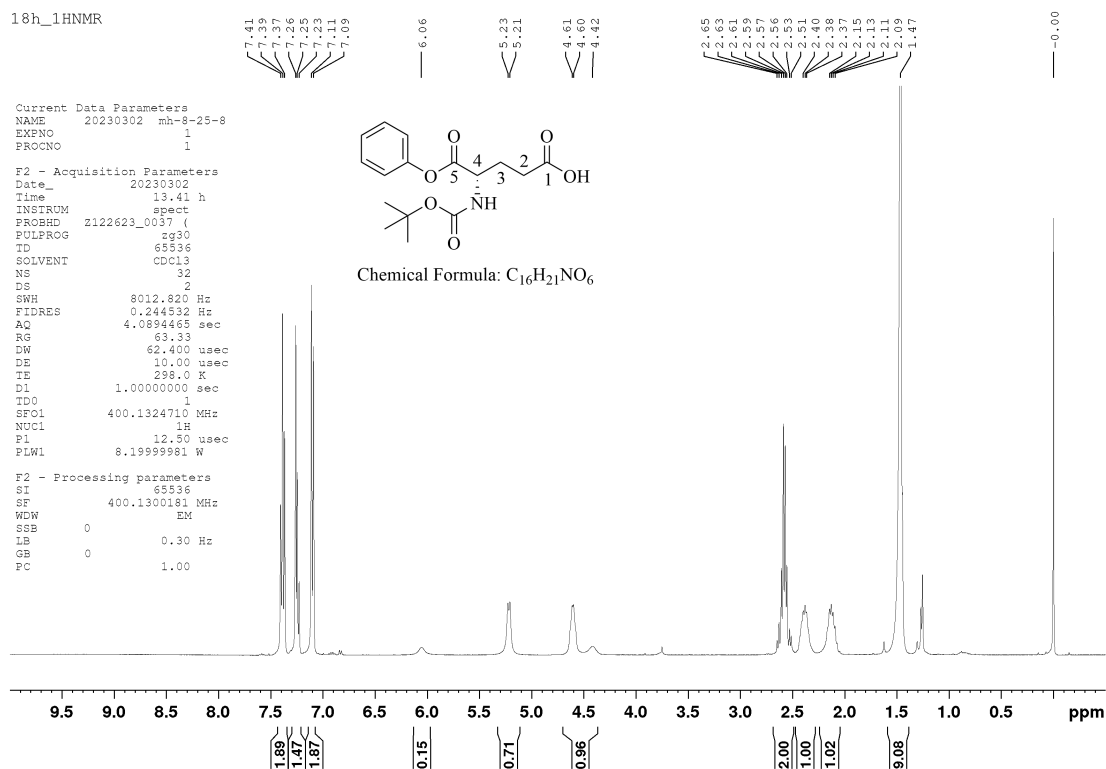


Fig. S27. ¹H NMR of intermediate 18h

Compound 63

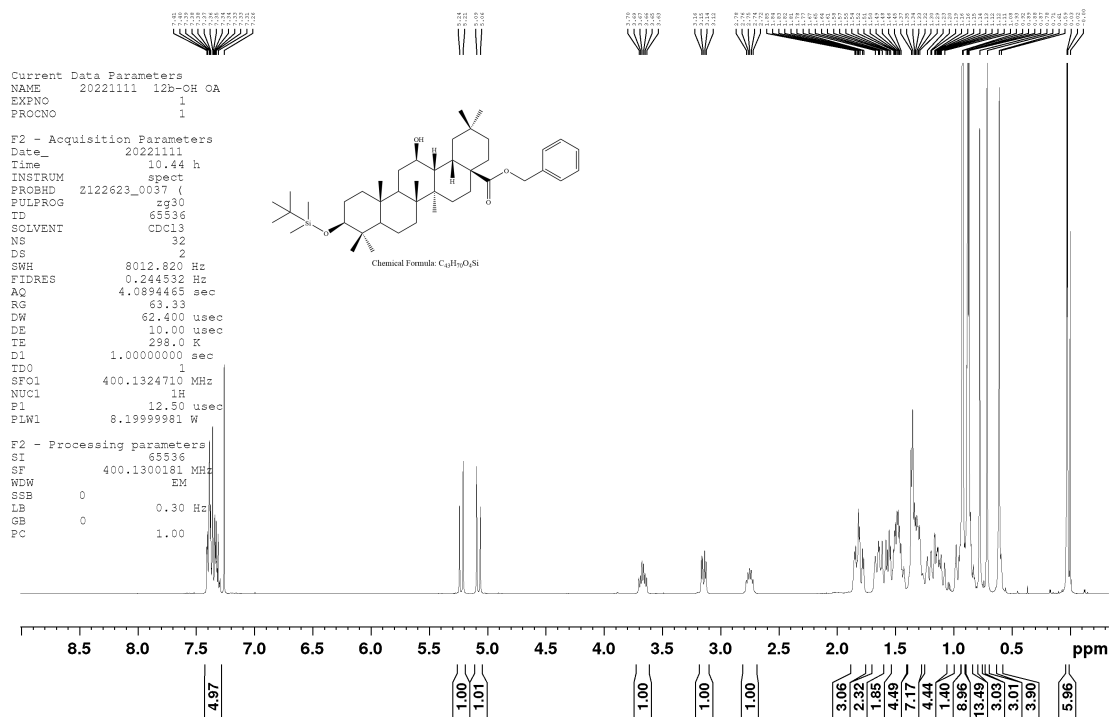


Fig. S28. ¹H NMR of compound 8

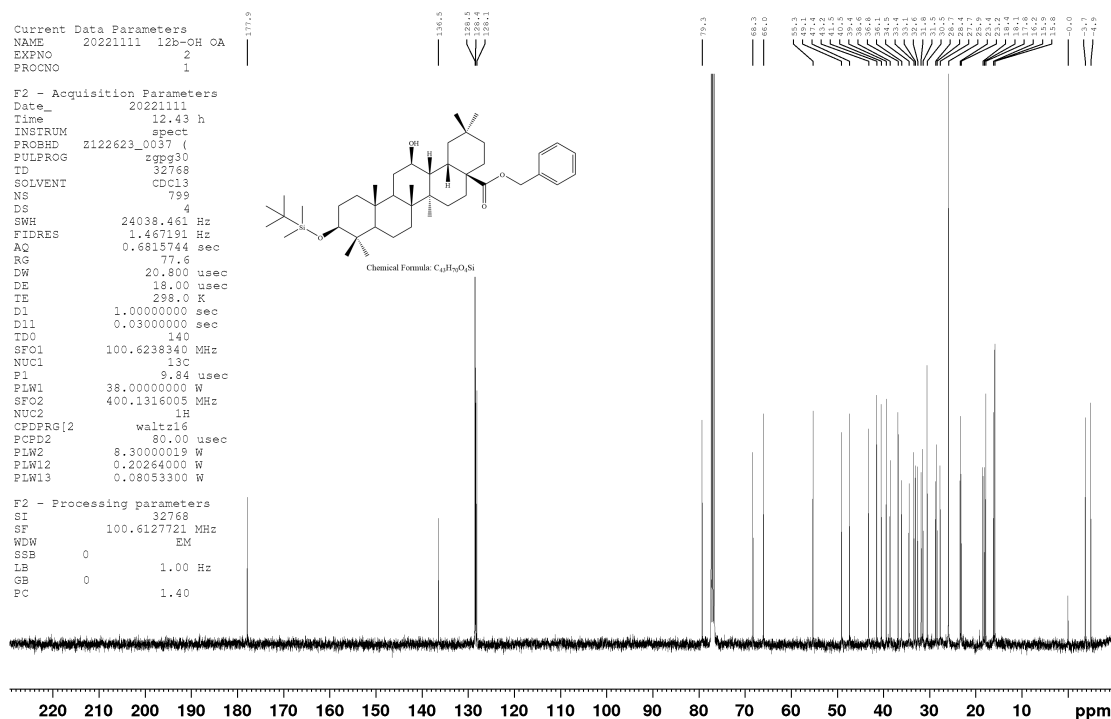
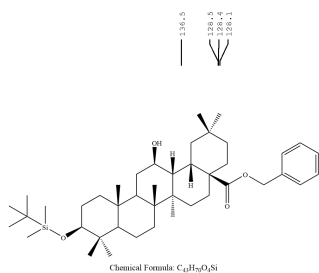
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EXPNO      2
PROCNO     1
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PULPROG    zgpg30
TD          32768
SOLVENT    CDCl3
NS          799
DS          4
SWH         24038.461 Hz
FIDRES      1.467191 Hz
AQ          0.6515744 sec
RG          77.6
WDW          20.800 usec
DE          18.800 usec
TE          298.0 K
D1          1.00000000 sec
D11         0.03000000 sec
D10         140
P2          100.6238340 MHz
NUC1        13C
P1          9.84 usec
PLW1        38.00000000 W
SFO2        400.1316050 MHz
NUC2        1H
PCPDPRG2    waltz12
PCPD2       80.00 usec
PLW2        8.30000019 W
SFO1        500.1360900 MHz
PLW13       0.08053300 W

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```
F2 - Processing parameters
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SF                      100.6127721 MHz
WDW                      EM
SSB                      0
LB                      1.00 Hz
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PC                      1.40
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Compound 70a

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Current Data Parameters
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EXPNO      1
PROCNO     1
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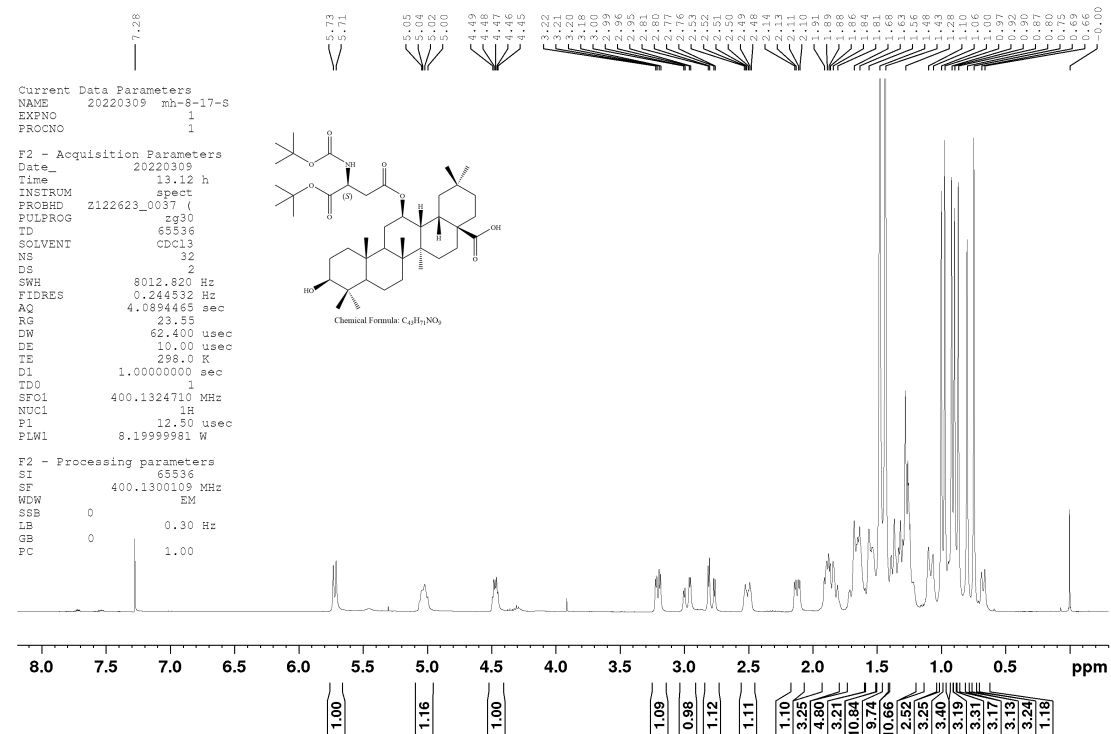
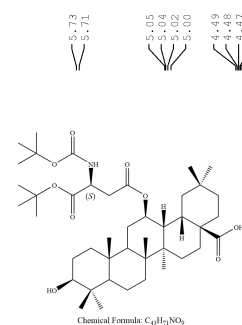
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TD          65536
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DS          2
SWH         8012.820 Hz
FIDRES     0.244532 Hz
AQ         0.40894456 sec
RG         23.55
WDW         62.4000 usec
DE         10.00 usec
TE          298.0 K
D1          1.00000000 sec
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NUC1       1H
P1          12.50 usec
PLM1       8.19999981 W

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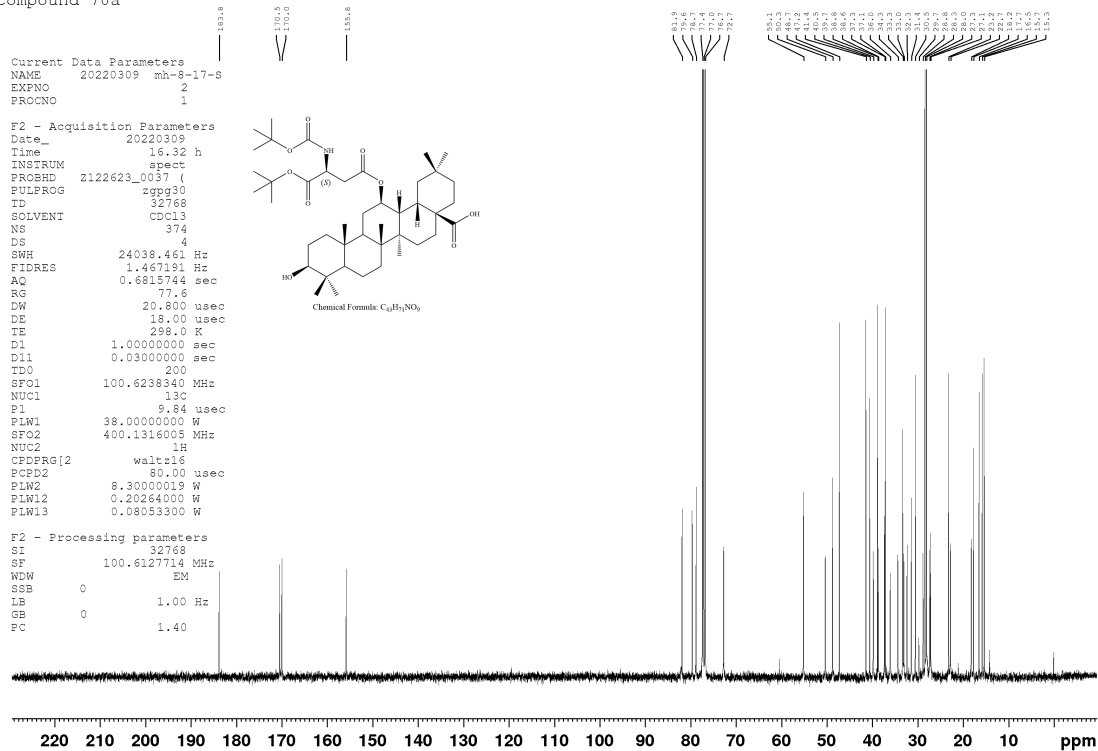
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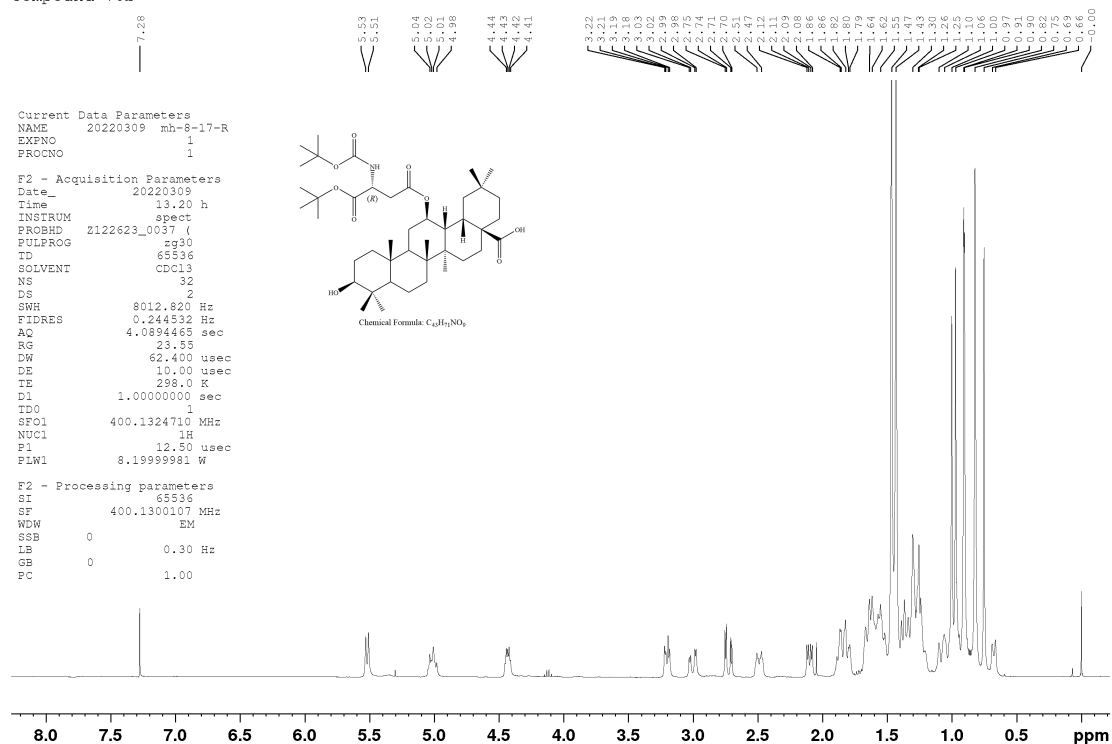


25

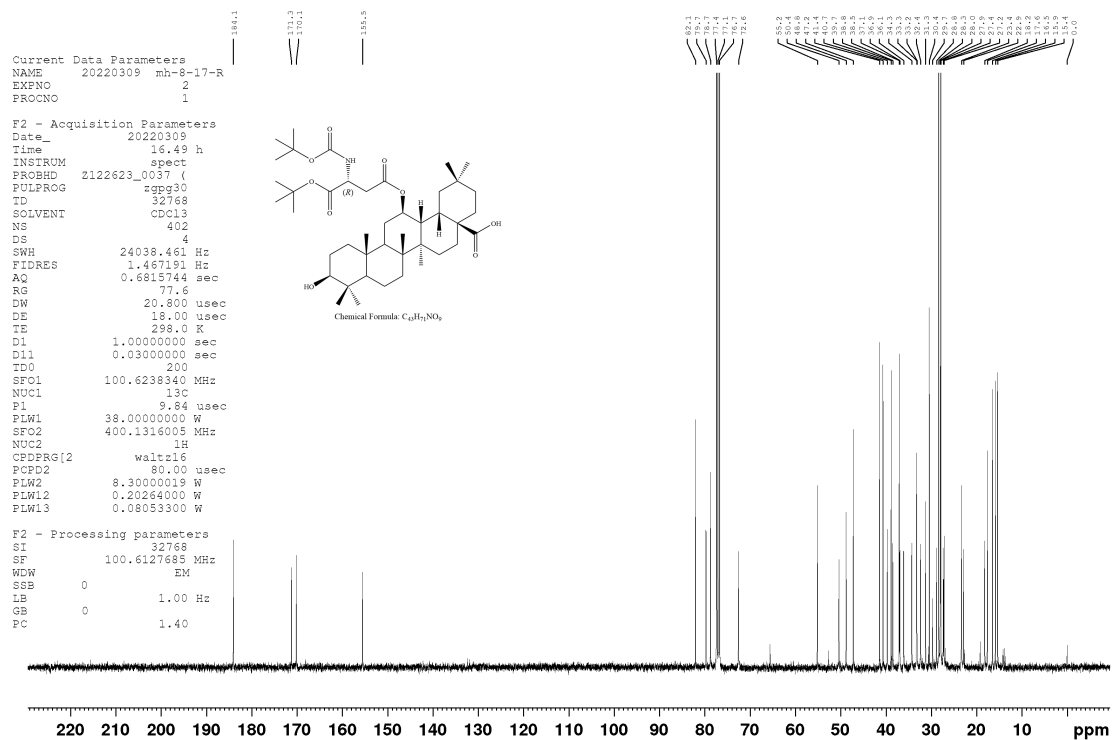
Compound 70a

Fig. S31. ^{13}C NMR of compound 9a

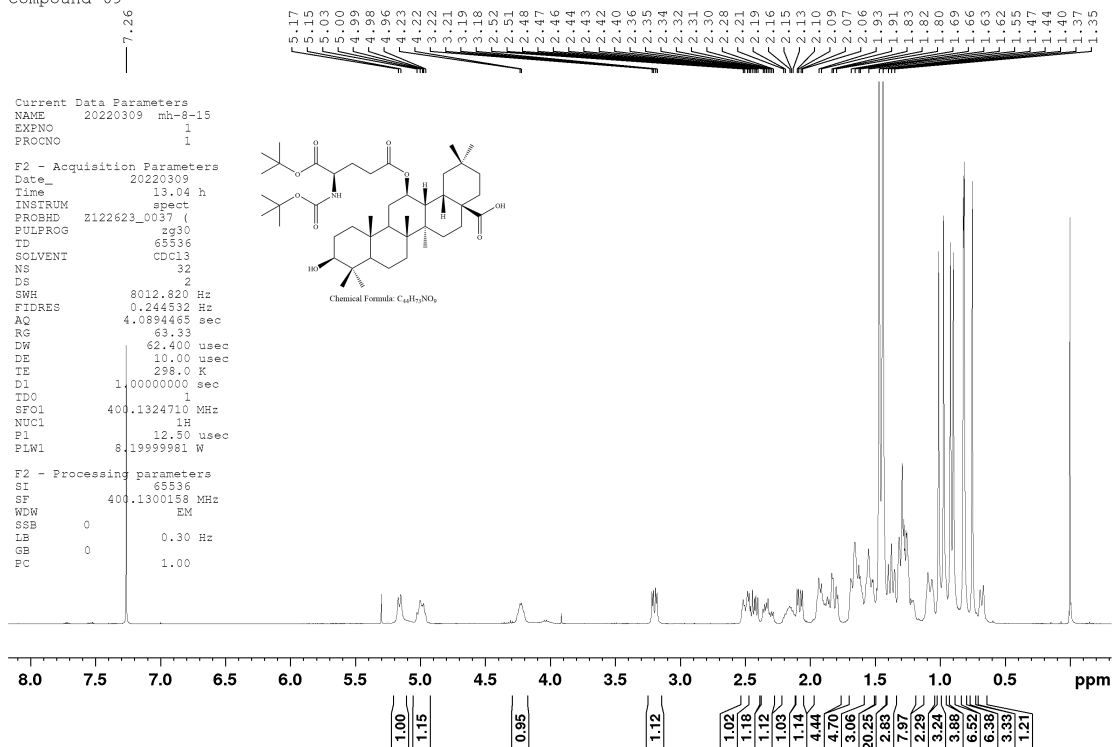
Compound 70b

Fig. S32. 1H NMR of compound 9b

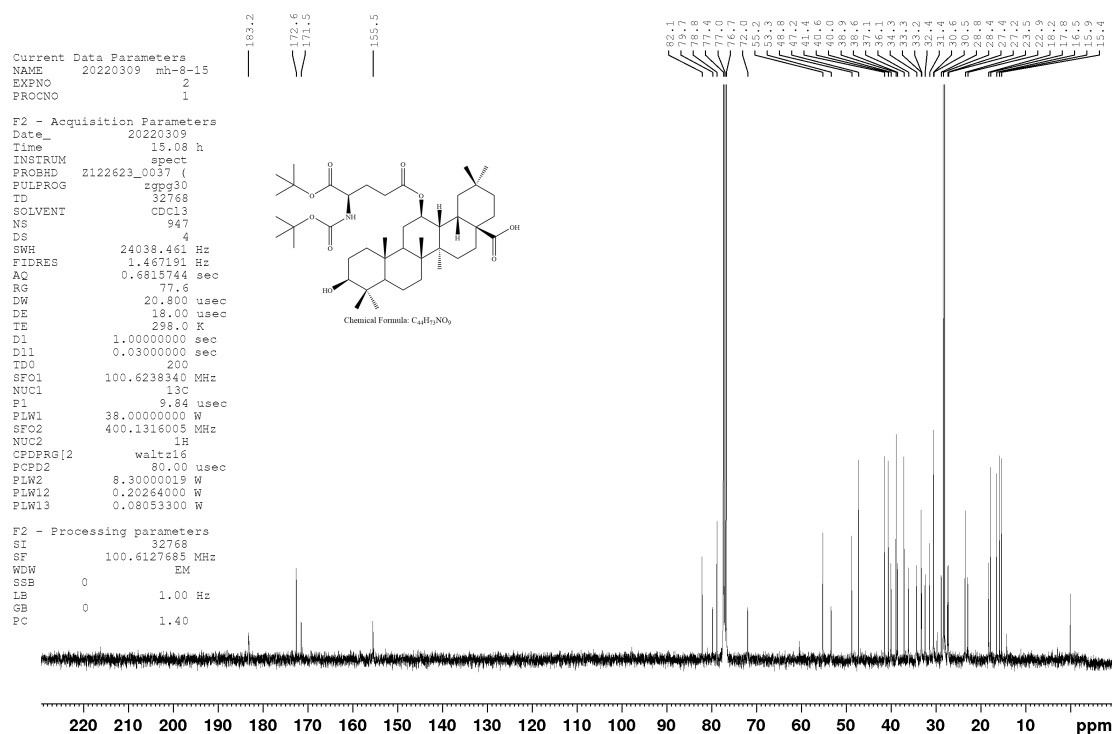
Compound 70b

Fig. S33. ^{13}C NMR of compound 9b

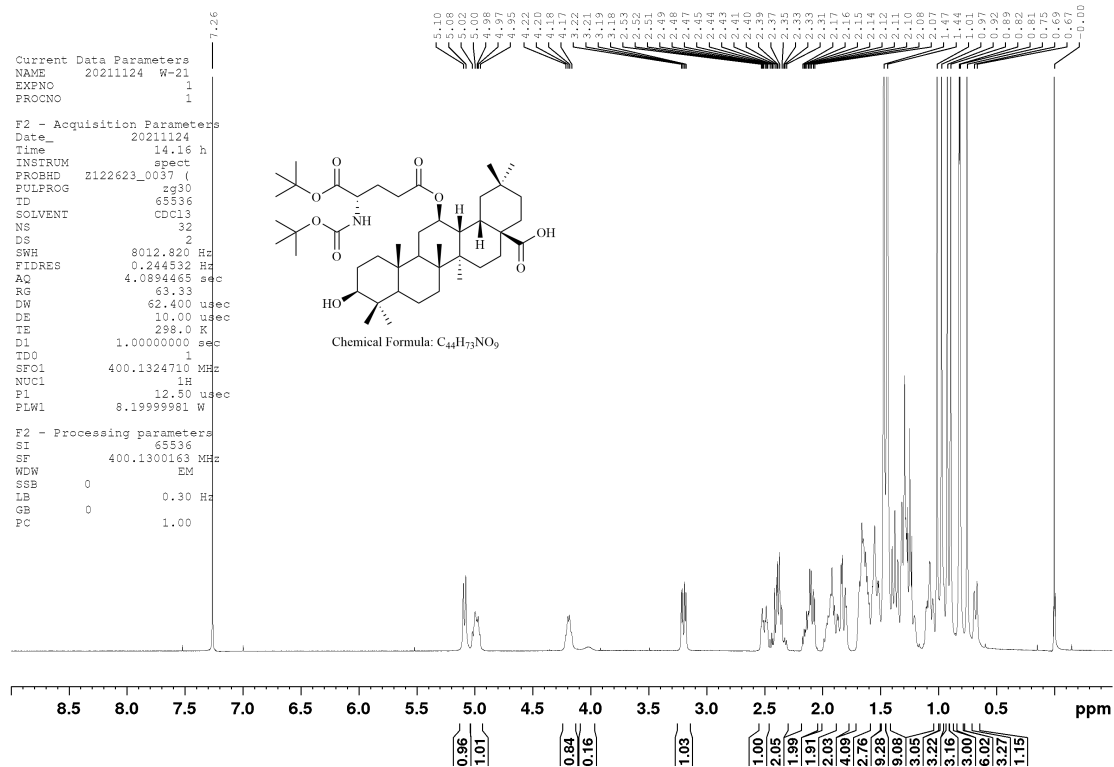
Compound 69

Fig. S34. ^1H NMR of compound 10a

Compound 69

Fig. S35. ^{13}C NMR of compound 10a

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 PROTON2 CDC13 D:\ DATA-2021 7

Fig. S36. ^1H NMR of compound 10b

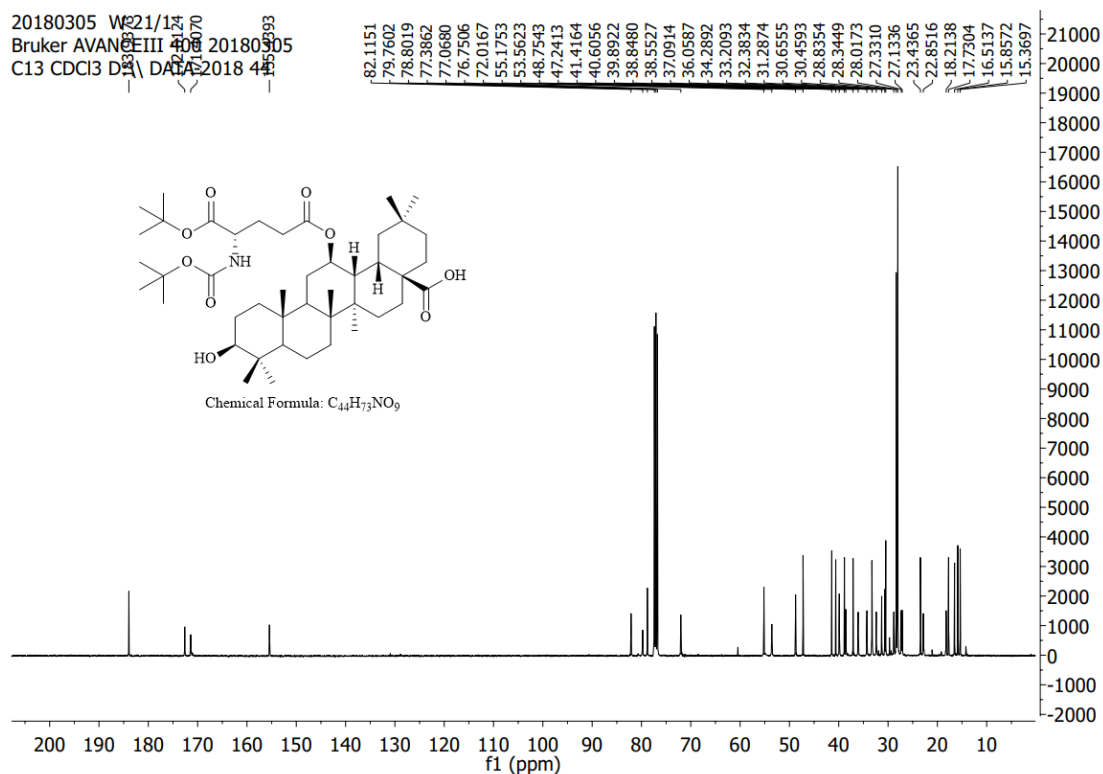


Fig. S37. ^{13}C NMR of compound 10b

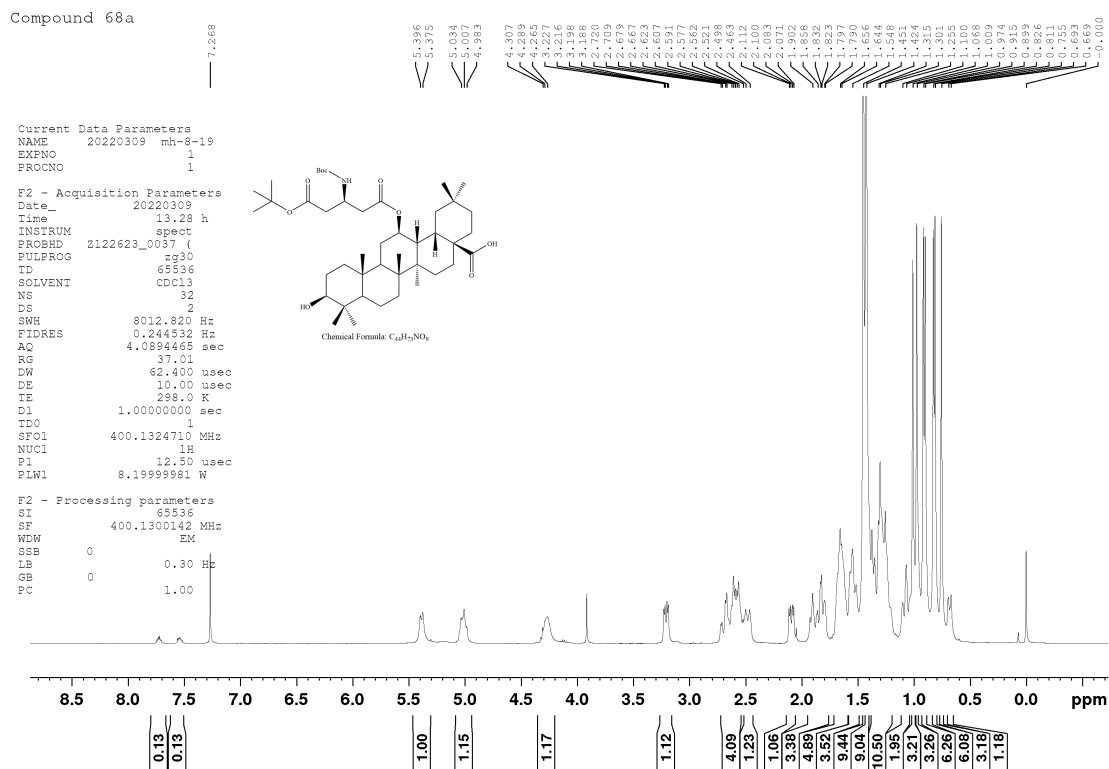


Fig. S38. 1H NMR of compound 10c

Current Data Parameters

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EXPNO 2
PROCNO 1

F2 - Acquisition Parameters

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PULPROG zgpg30
TD 32768
SOLVENT CDC13
NS 1600
DS 4
SWH 24038.461 Hz
FIDRES 1.467191 Hz
AQ 0.6815744 sec
RG 77.6
DW 20.800 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
d11 0.03000000 sec
TD0 200
SFO1 100.6238340 MHz
NUC1 13C
P1 9.84 usec
PL1 38.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 80.00 usec
PLM2 8.30000019 W
PLM12 0.20266000 W
PLM13 0.08053300 W

F2 - Processing parameters

SI 32768
SF 100.6127114 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Chemical Formula: $C_{24}H_{32}O_5$

183.56
171.35
159.45
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78.32
78.26
78.16
77.02
76.92
76.22
65.15
48.79
48.75
46.46
46.44
39.79
39.75
39.59
39.54
37.86
37.84
37.07
36.97
36.25
36.23
35.11
35.11
33.29
33.43
33.39
28.39
28.35
26.02
26.02
23.46
23.44
21.74
21.74
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21.18
18.47
18.47
15.83
11.83

Fig. S39. ^{13}C NMR of compound **10c**

Current Data Parameters

NAME	20220309 mh-8-16
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20220309
Time	12.57 h
INSTRUM	spect
PROBHD	Z122623_0037 (
FULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	32
DS	2
SWH	8012.820 Hz
FIDRES	0.244532 Hz
AQ	4.0894455 sec
RG	63.33
DW	62.400 usec
DE	10.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
SFO1	400.1324710 MHz
NUC1	1H
P1	12.50 usec
PLW1	8.19899981 W

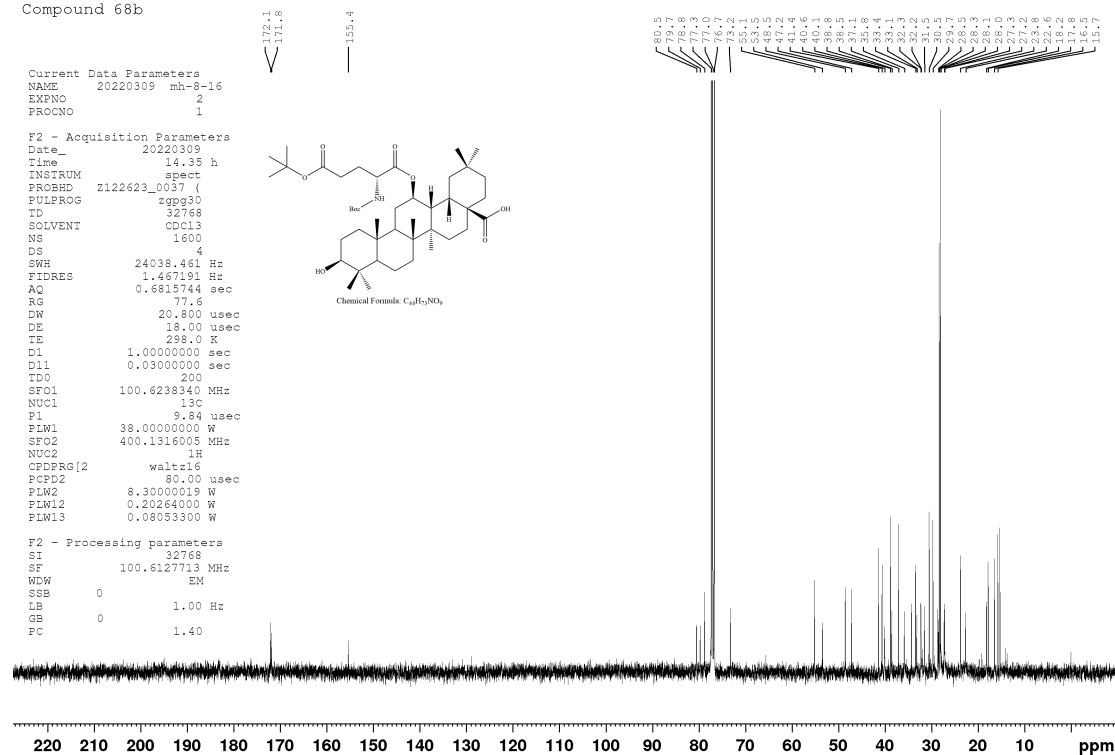
F2 - Processing parameters

SI	65536
SF	400.1300153 MHz
WDW	EM
SBB	0
LB	0.30 Hz
GB	0
PC	1.00

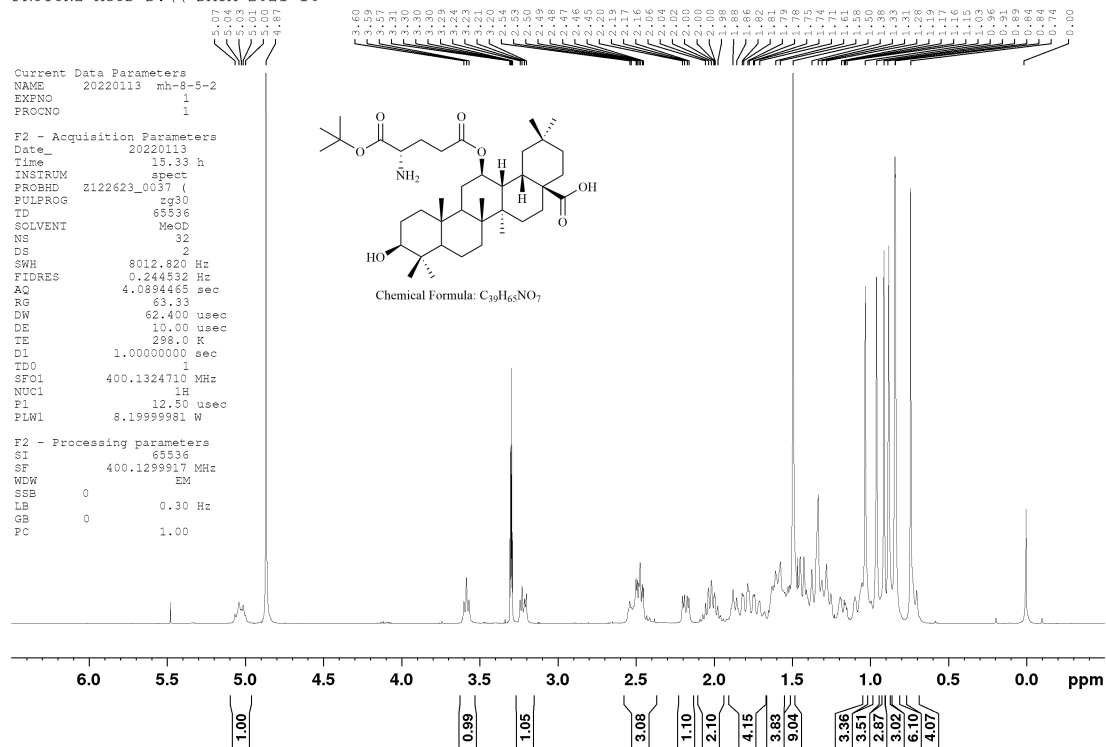
Chemical Formula: $C_{24}H_{37}NO_3$

Fig. S40. ^1H NMR of compound **10d**

Compound 68b

Fig. S41. ^{13}C NMR of compound 10d

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Fig. S42. ^1H NMR of compound 11a

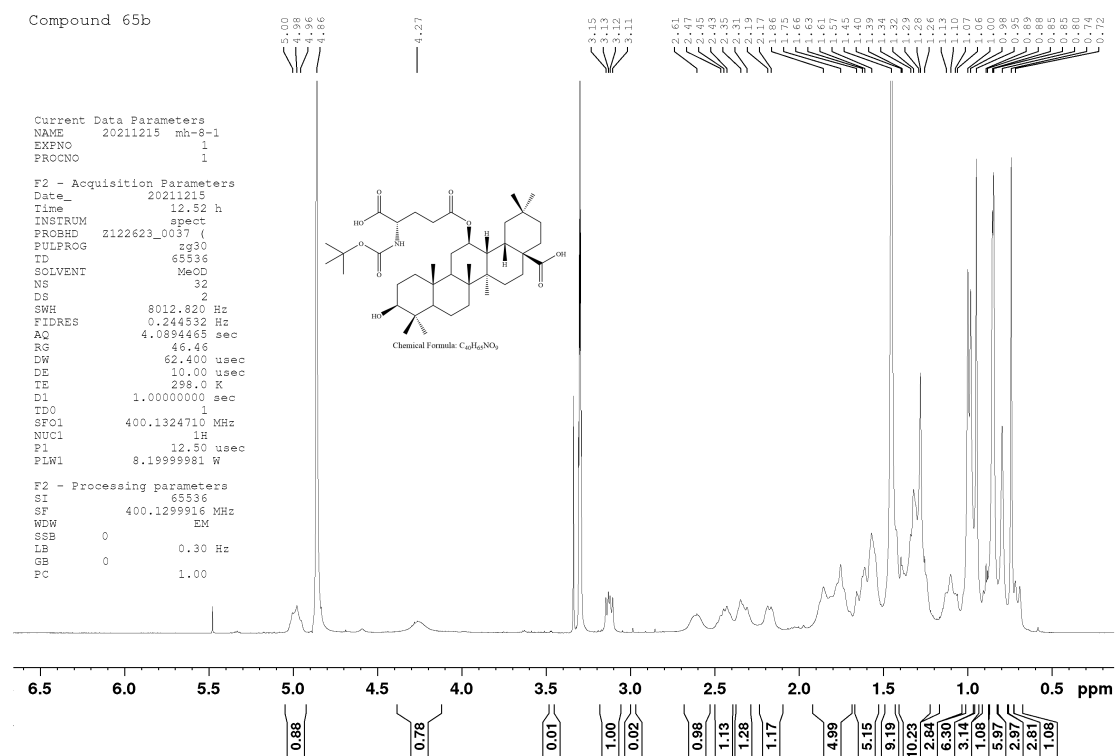


Fig. S43. ^1H NMR of compound 11b

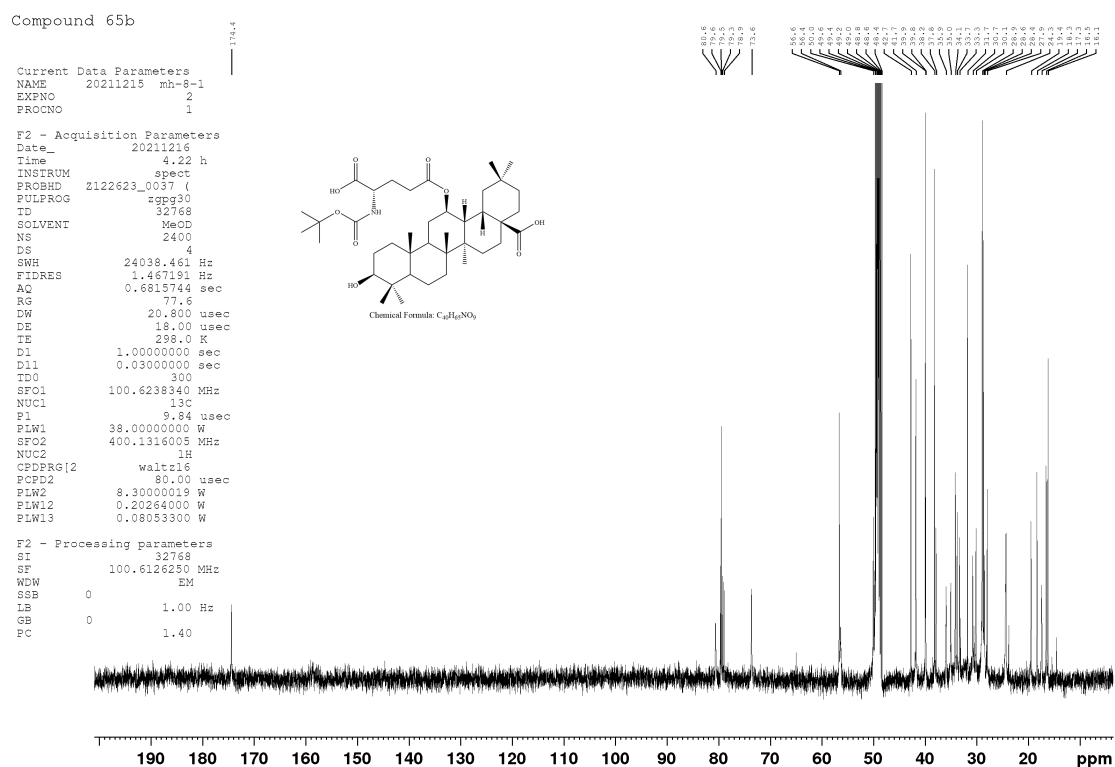


Fig. S44. ^{13}C NMR of compound 11b

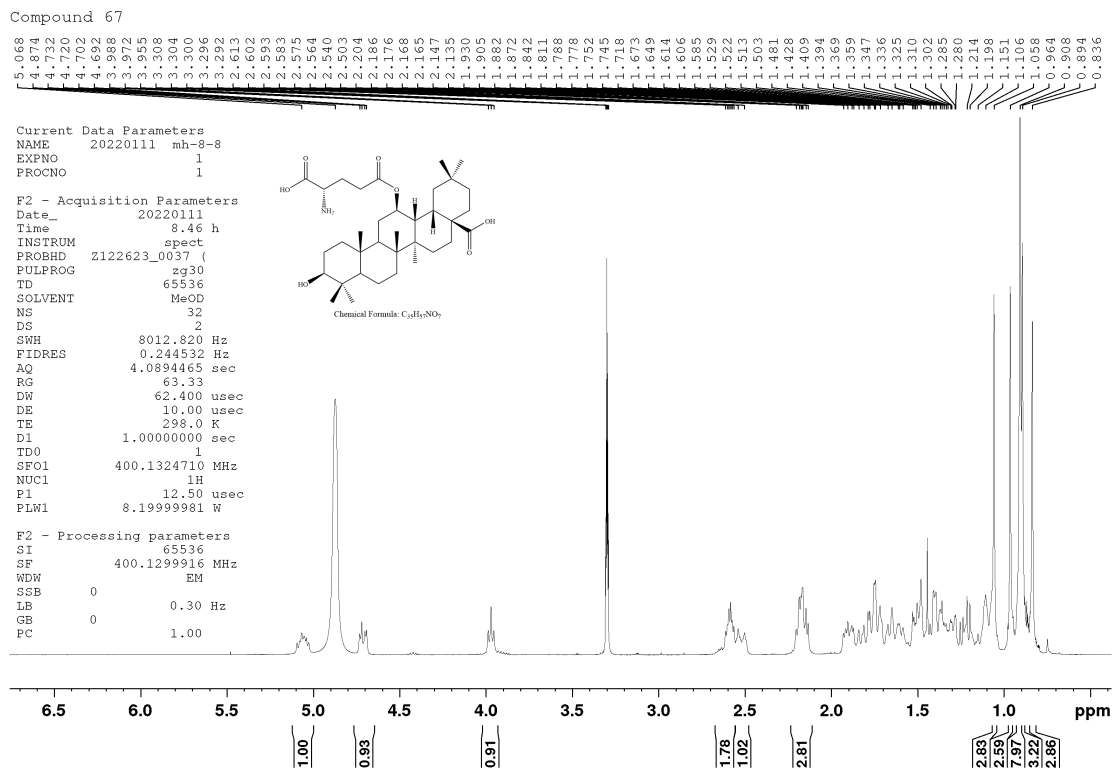


Fig. S45. ^1H NMR of compound 11c

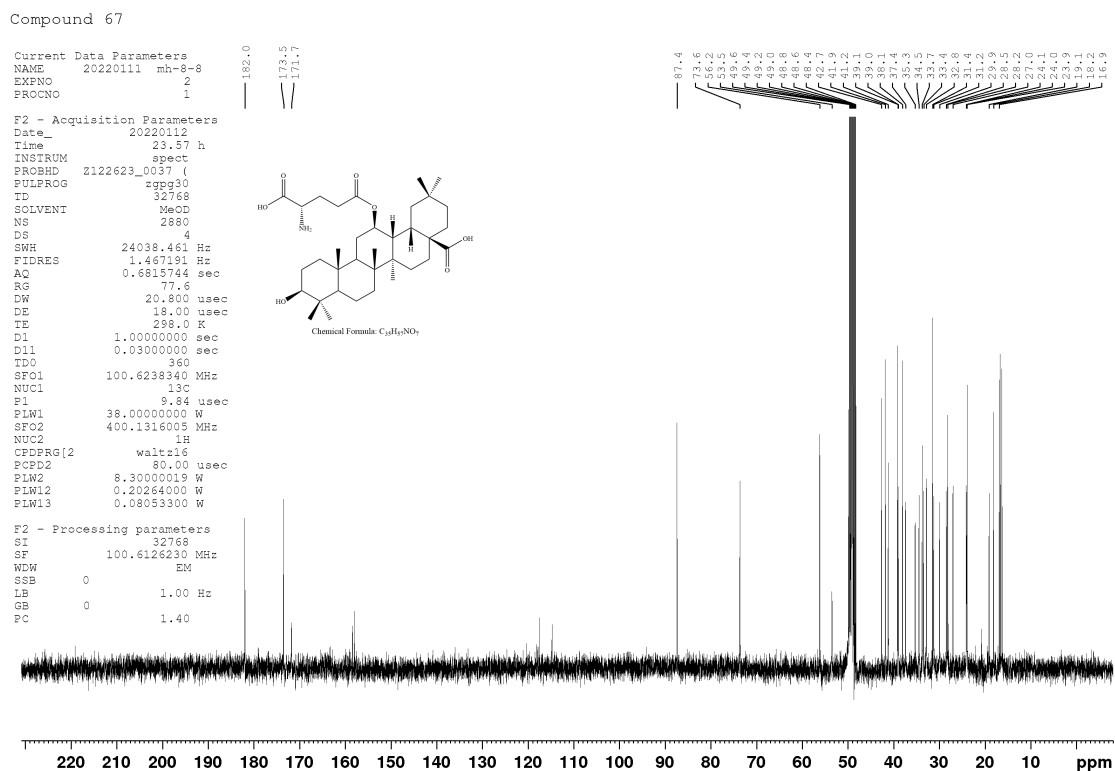


Fig. S46. ^{13}C NMR of compound 11c

Compound 74a

Current Data Parameters
NAME 20220628 mh-8-27-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220628
Time 14.21 h
INSTRUM spect
PROBHD z122623_0037
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 37.01
DW 62.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324710 MHz
NUC1 1H
P1 12.50 usec
PLW1 8.19999981 W

F2 - Processing parameters
SI 65536
SF 400.1300144 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

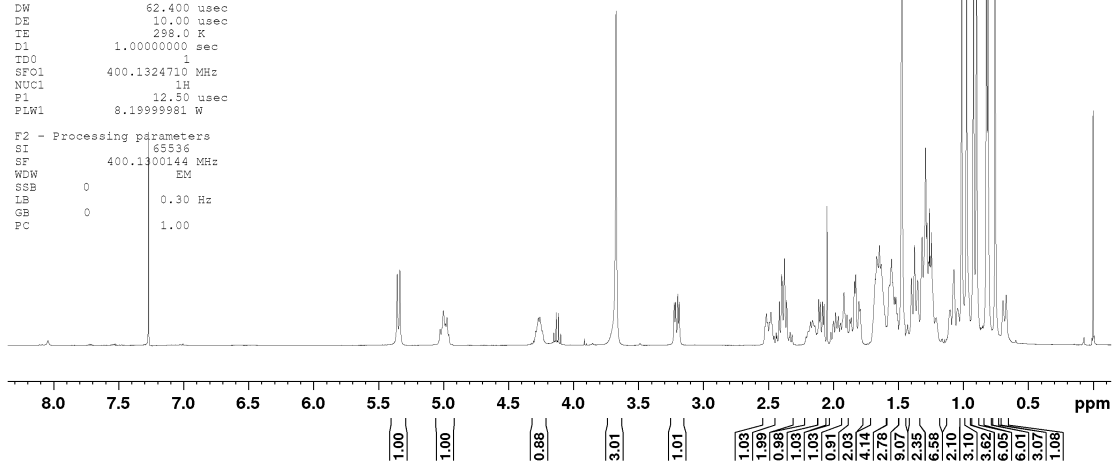
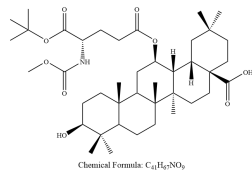


Fig. S47. ^1H NMR of compound 19a

Compound 74a

Current Data Parameters
NAME 20220628 mh-8-27-1
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220629
Time 8.20 h
INSTRUM spect
PROBHD z122623_0037
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 473
DS 4
SWH 24038.461 Hz
FIDRES 1.467191 Hz
AQ 0.6815744 sec
RG 77.6
DW 20.800 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 200
SFO1 100.6238340 MHz
NUC1 ^{13}C
P1 9.84 usec
PLW1 38.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2] waltz16
PCPD2 80.00 usec
PLW2 8.30000019 W
PLW12 0.20264000 W
PLW13 0.08053300 W

F2 - Processing parameters
SI 32768
SF 100.6127583 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

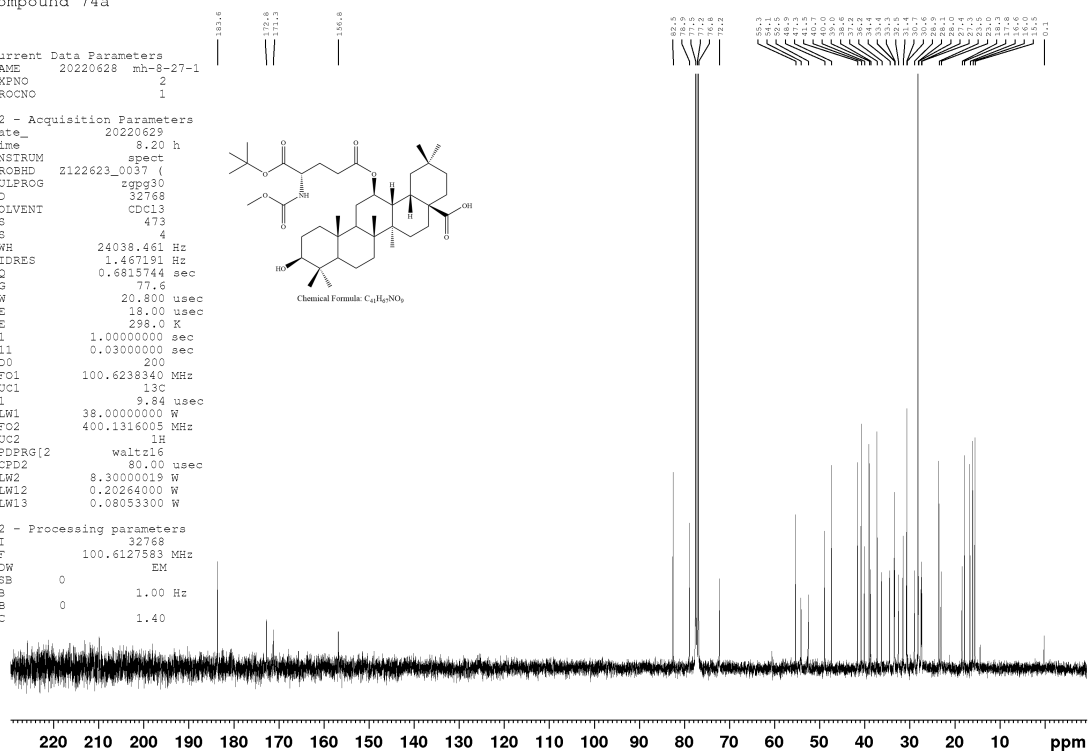
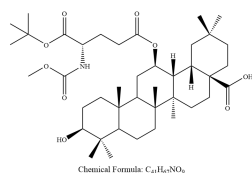


Fig. S48. ^{13}C NMR of compound 19a

Compound 74b

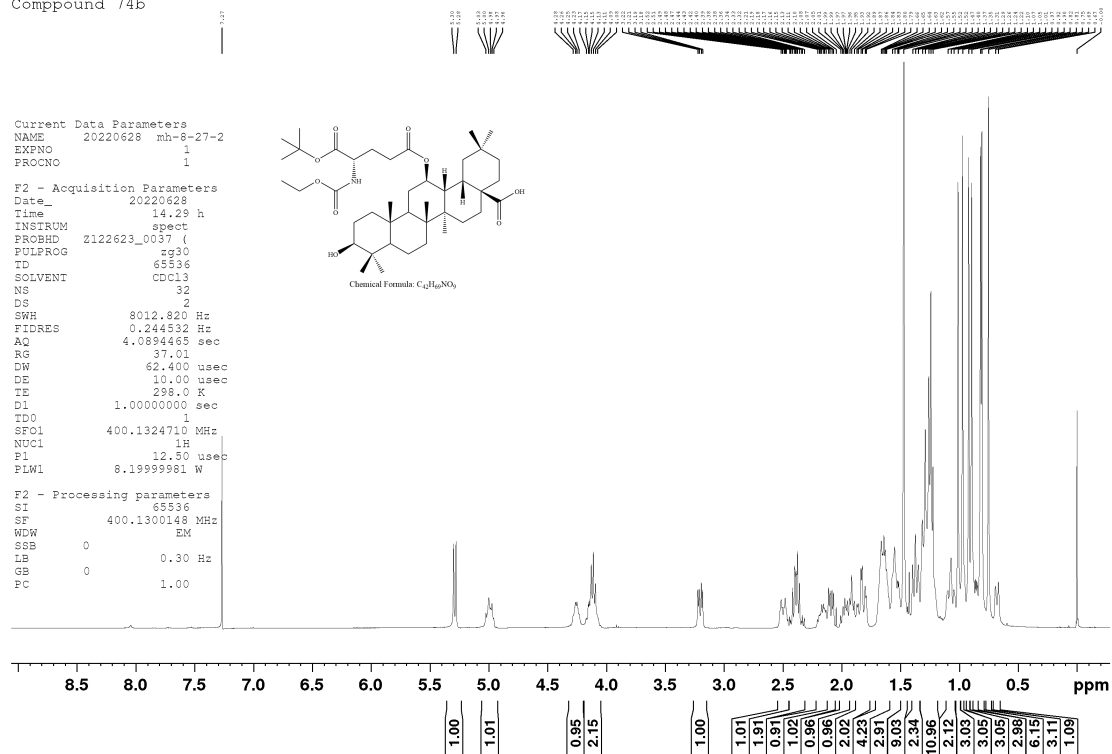


Fig. S49. ^1H NMR of compound 19b

Compound 74b

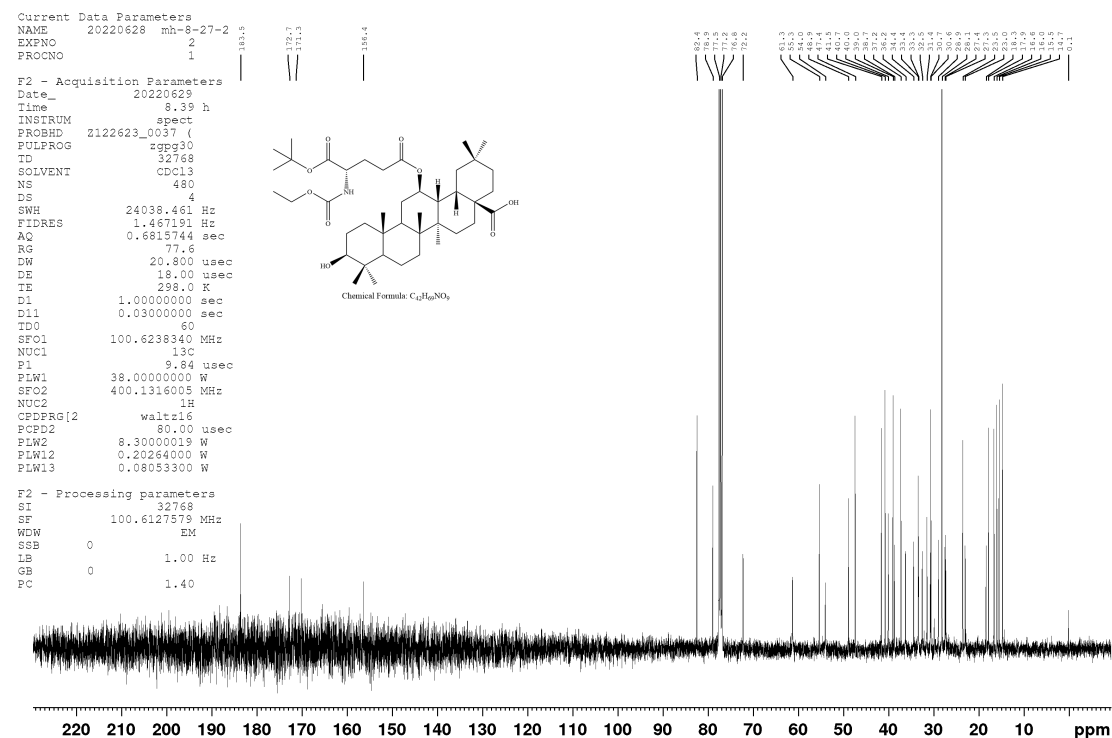
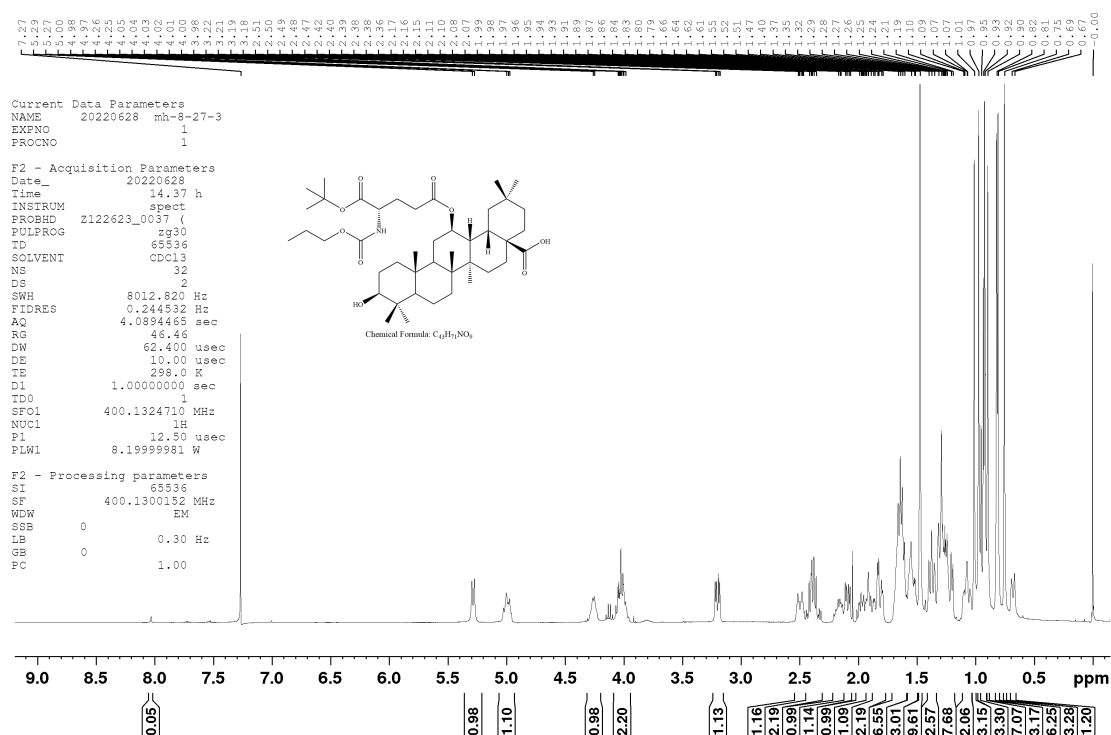
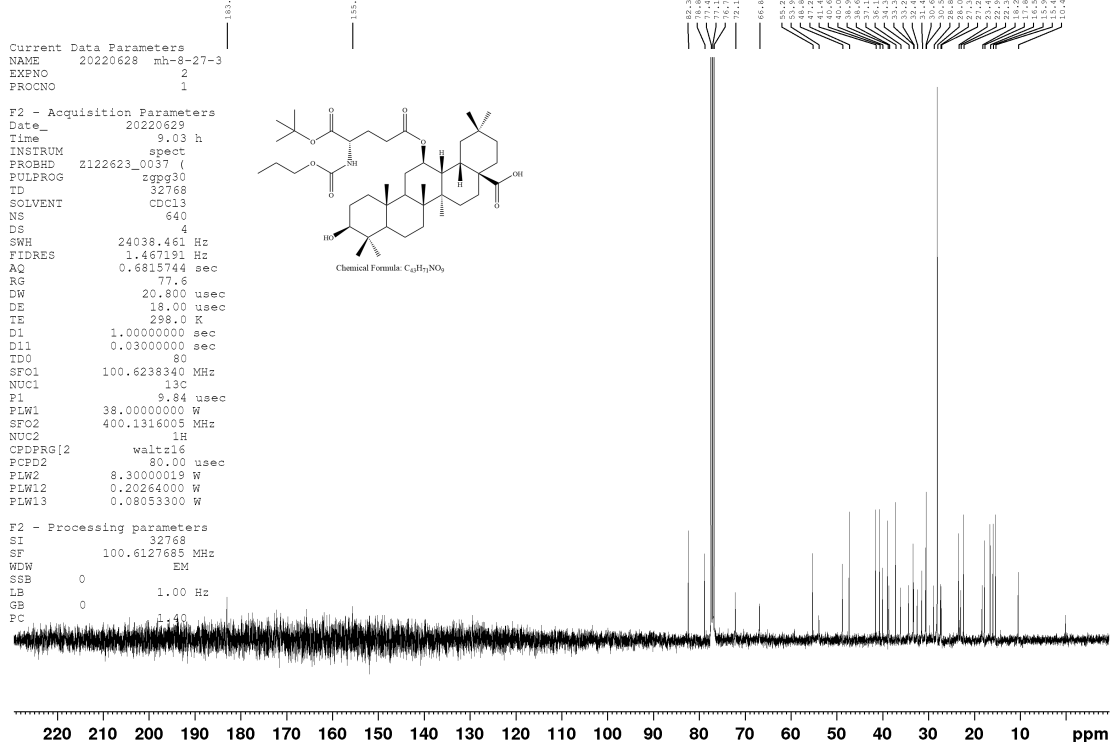


Fig. S50. ^{13}C NMR of compound 19b

Compound 74c

Fig. S51. ^1H NMR of compound 19c

Compound 74c

Fig. S52. ^{13}C NMR of compound 19c

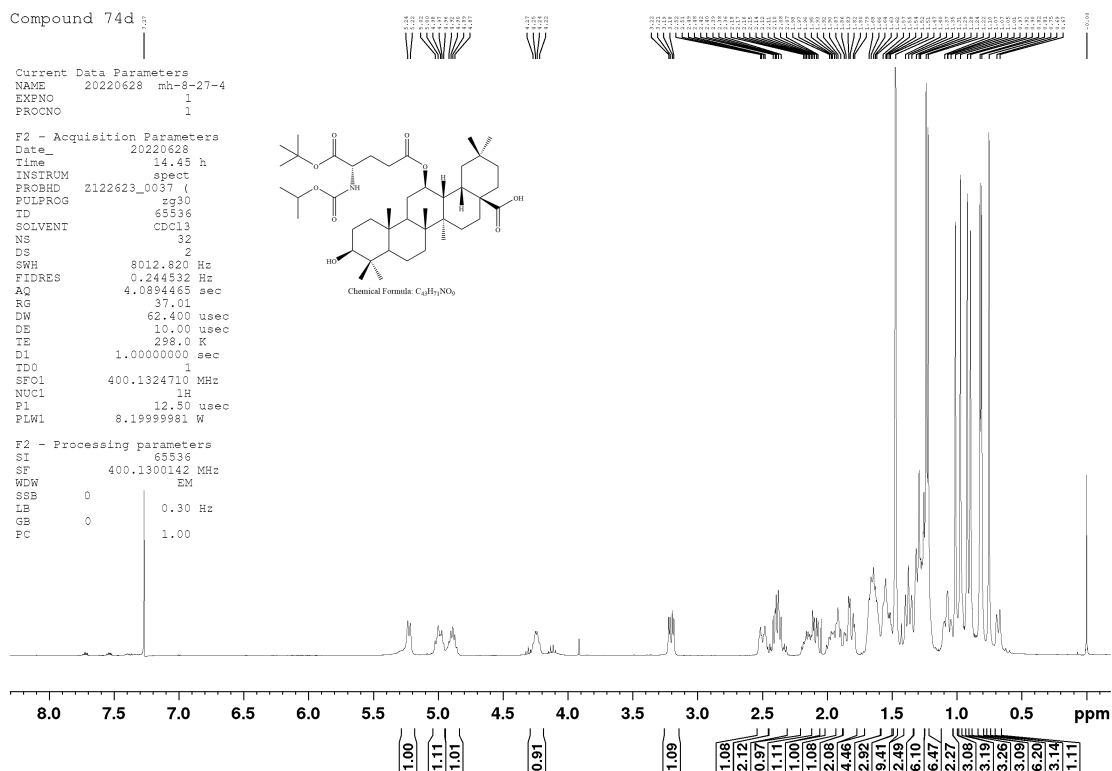


Fig. S53. ^1H NMR of compound 19d

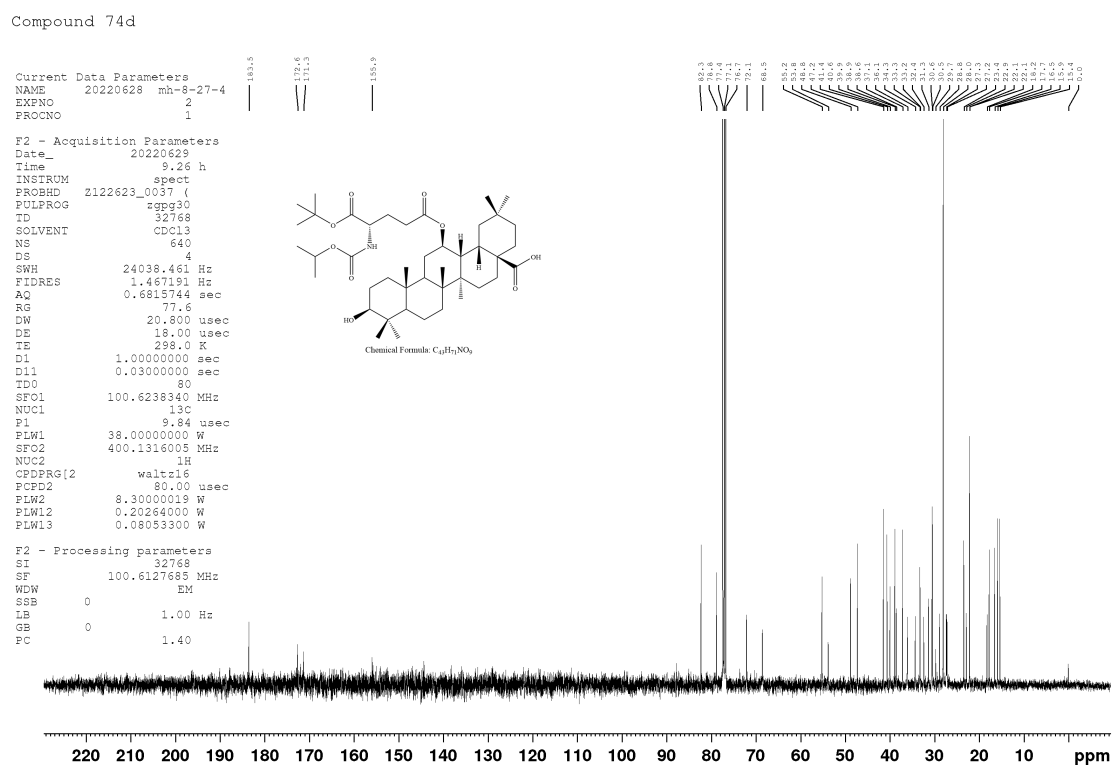
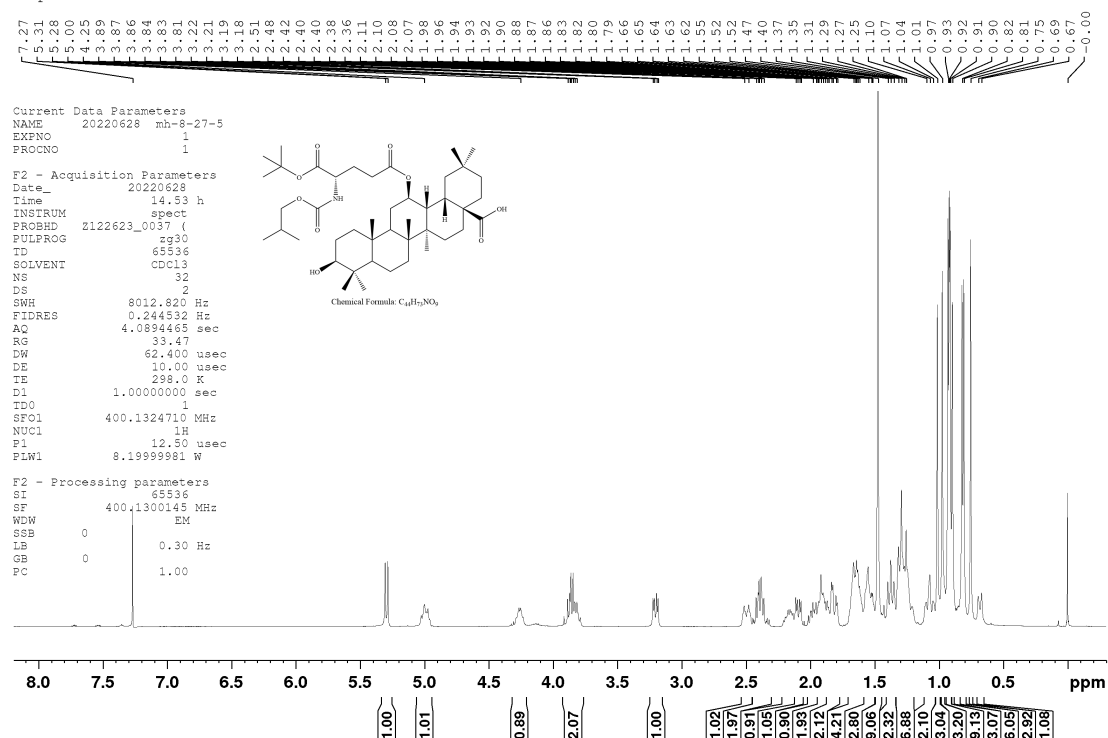
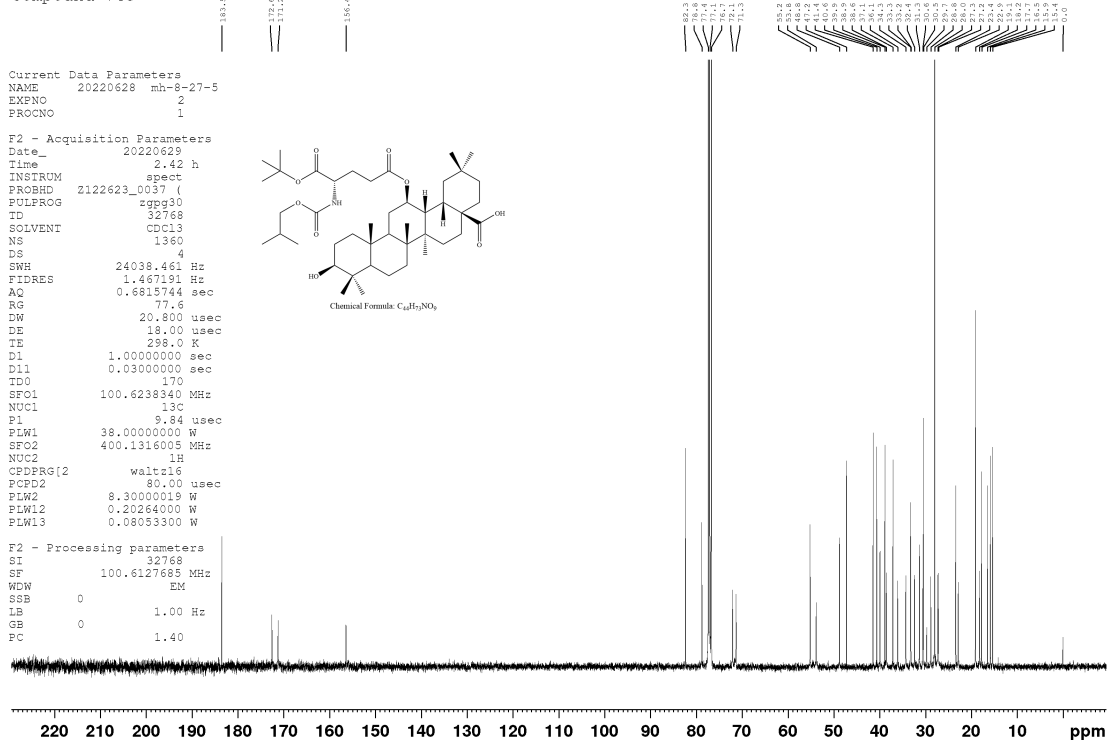


Fig. S54. ^{13}C NMR of compound 19d

Compound 74e

Fig. S55. 1H NMR of compound 19e

Compound 74e

Fig. S56. ^{13}C NMR of compound 19e

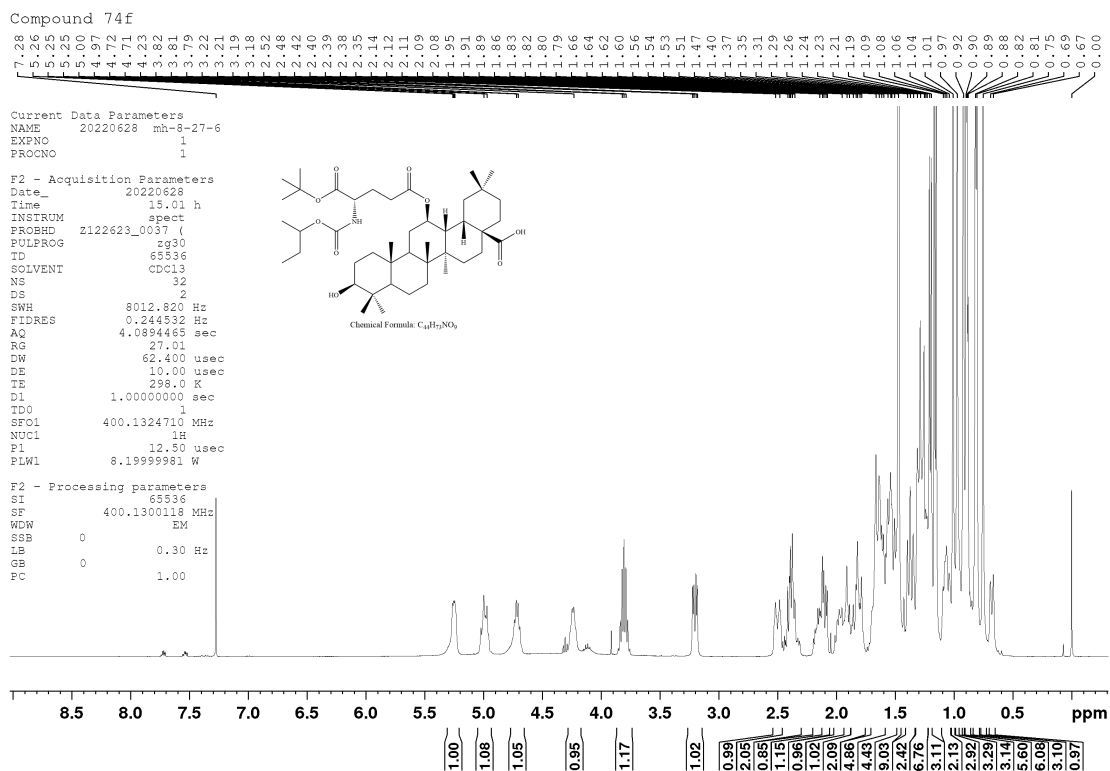


Fig. S57. ^1H NMR of compound 19f

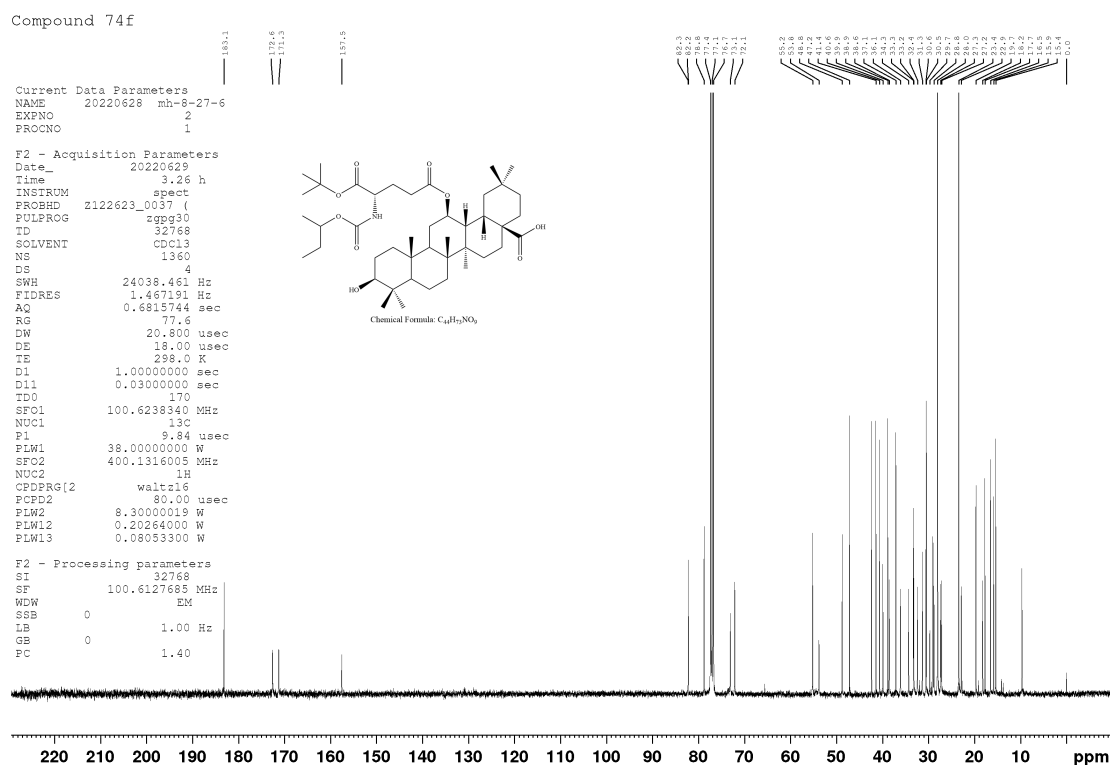
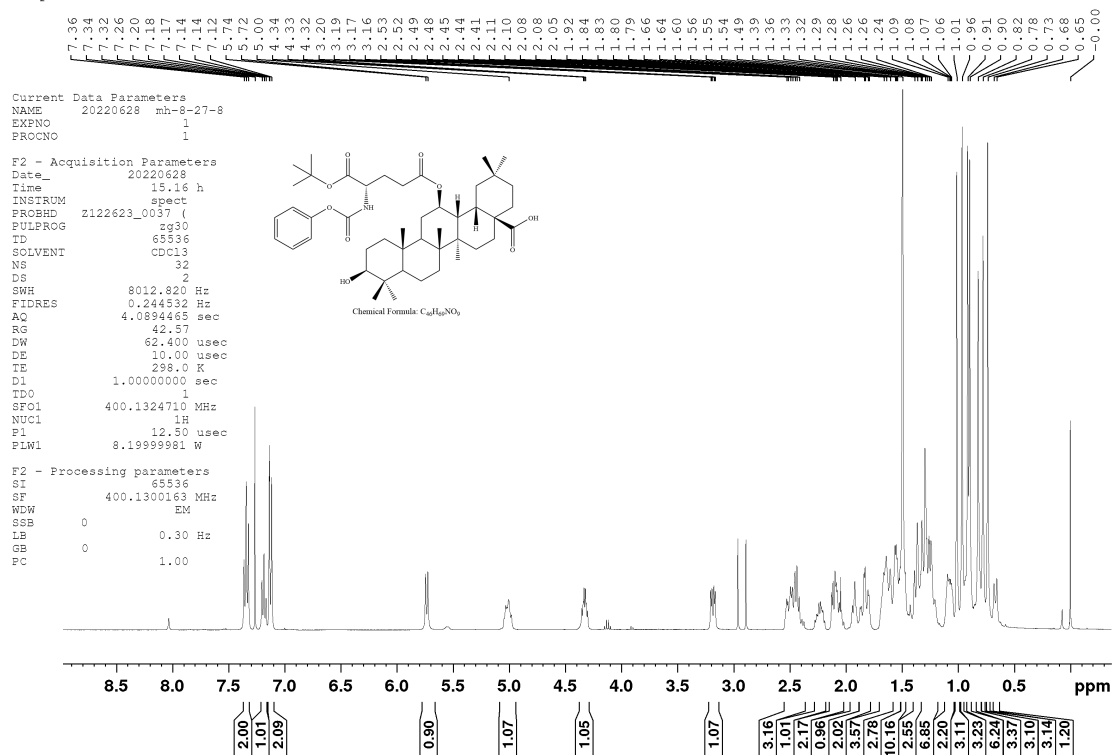
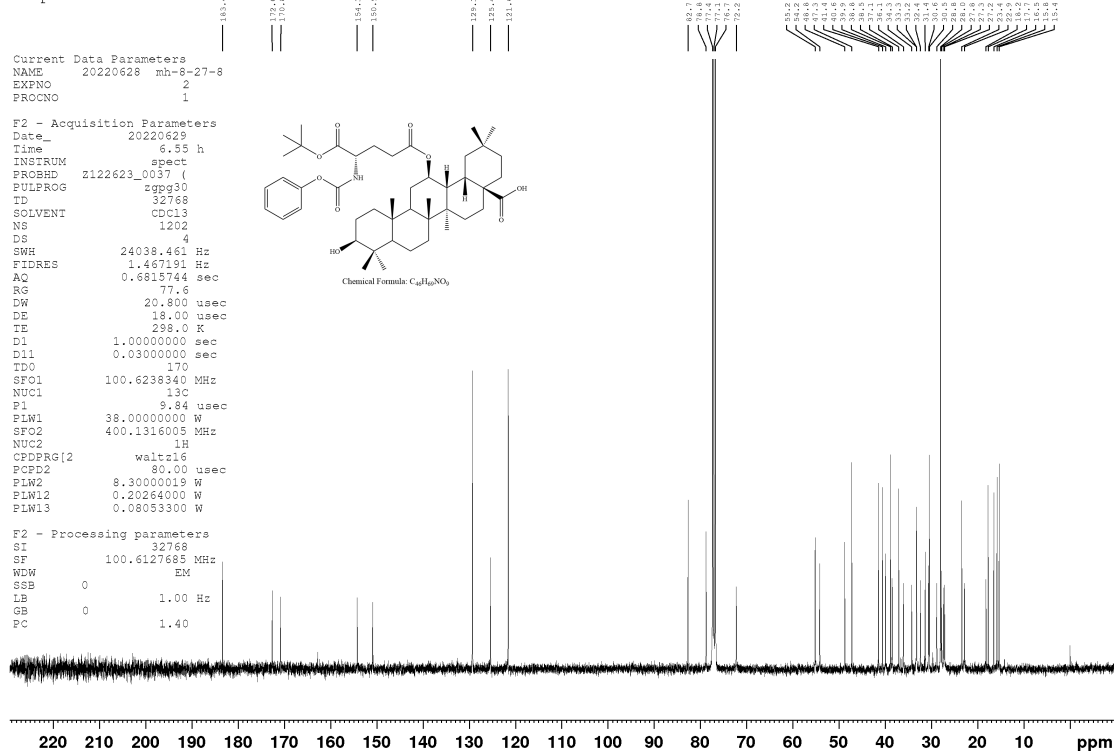


Fig. S58. ^{13}C NMR of compound 19f

Compound 74h

Fig. S61. ^1H NMR of compound 19h

Compound 74h

Fig. S62. ^{13}C NMR of compound 19h

Compound 79a

Current Data Parameters
NAME 20220713 mh-8-28-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220713
Time 13:37 h
INSTRUM spect
PROBHD Z122623_0037 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 27.01
DW 62.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.0000000 sec
TD0 1
SFO1 400.1324710 MHz
NUC1 1H
P1 12.50 usec
PLW1 8.19999981 W

F2 - Processing parameters
SI 65536
SF 400.1300107 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

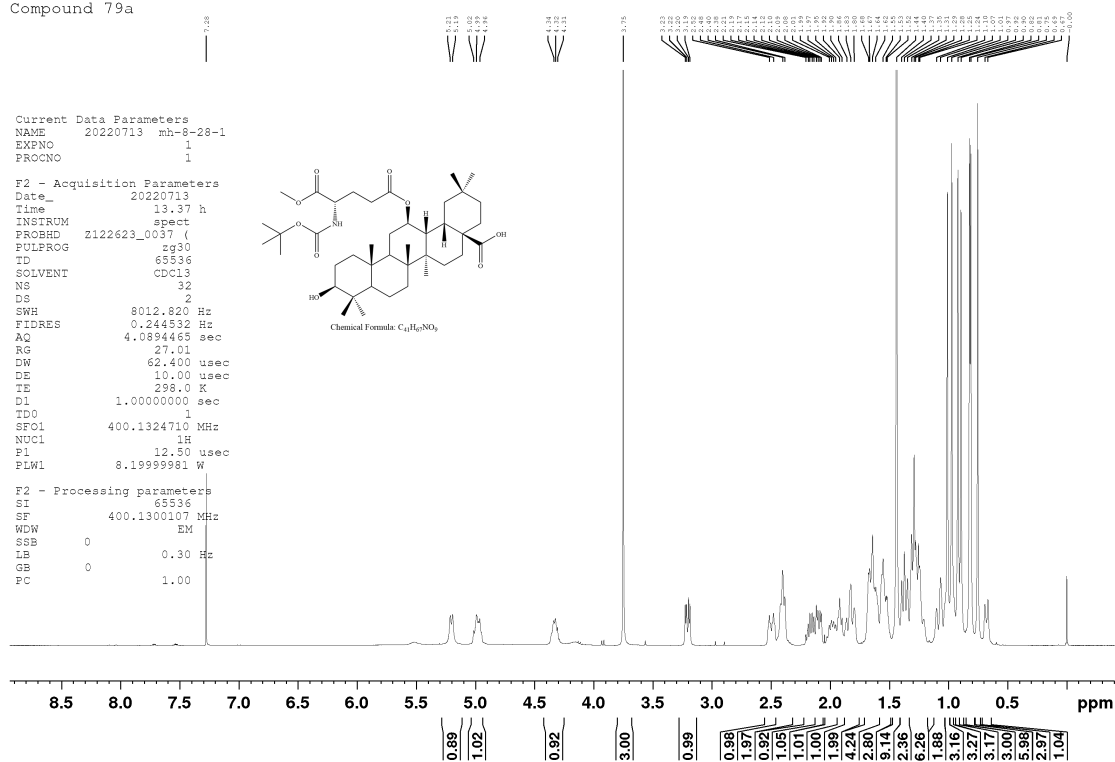
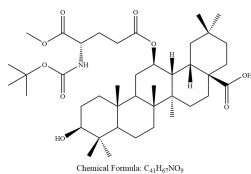


Fig. S63. ^1H NMR of compound 20a

Compound 79a

Current Data Parameters
NAME 20220713 mh-8-28-1
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20220714
Time 11:31 h
INSTRUM spect
PROBHD Z122623_0037 (
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 1120
DS 4
SWH 24038.461 Hz
FIDRES 1.467191 Hz
AQ 0.6815744 sec
RG 77.6
DW 20.800 usec
DE 18.00 usec
TE 298.0 K
D1 1.0000000 sec
D11 0.0300000 sec
TD0 140
SFO1 100.6238340 MHz
NUC1 13C
P1 9.84 usec
PLW1 38.0000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG12 waltz16
PCPD2 80.00 usec
PLW2 8.30000019 W
PLW12 0.20264000 W
PLW13 0.08053300 W

F2 - Processing parameters
SI 32768
SF 100.6127713 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

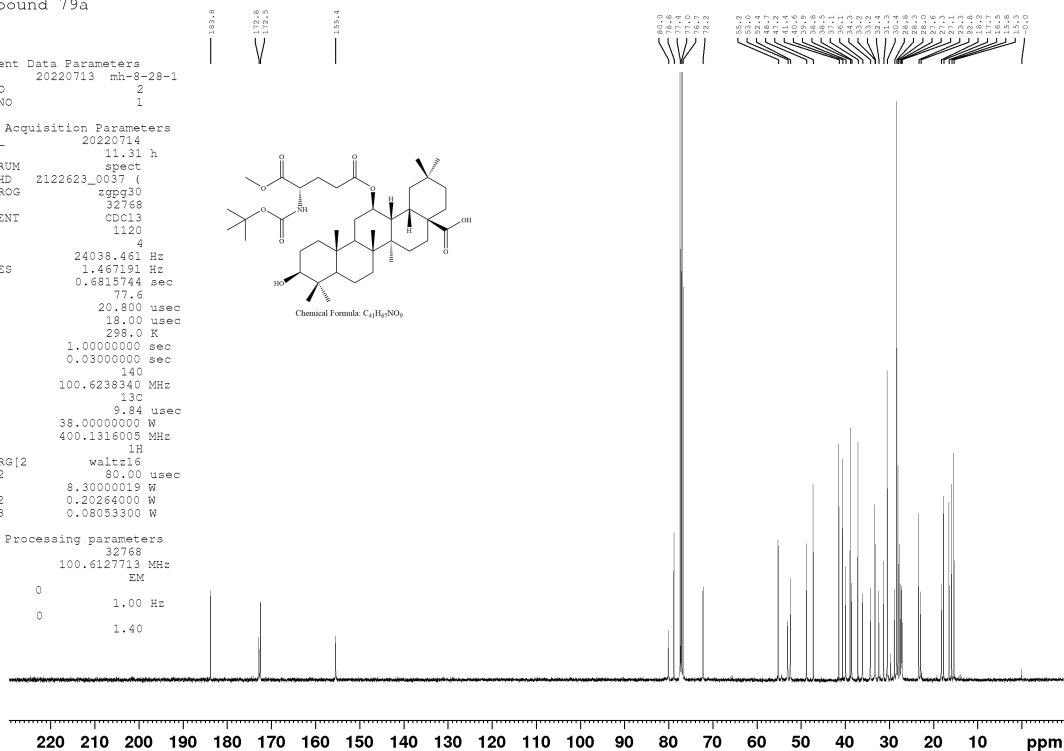
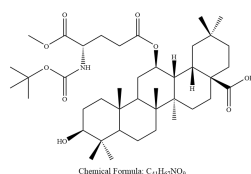


Fig. S64. ^{13}C NMR of compound 20a

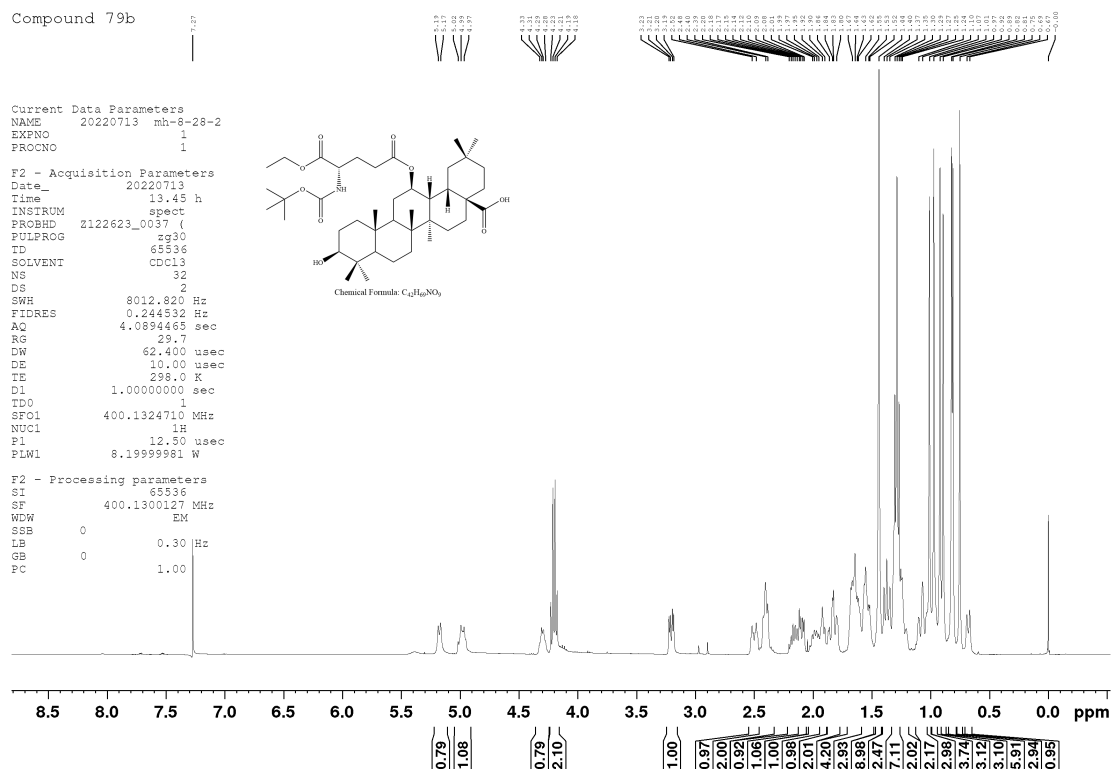


Fig. S65. ^1H NMR of compound 20b

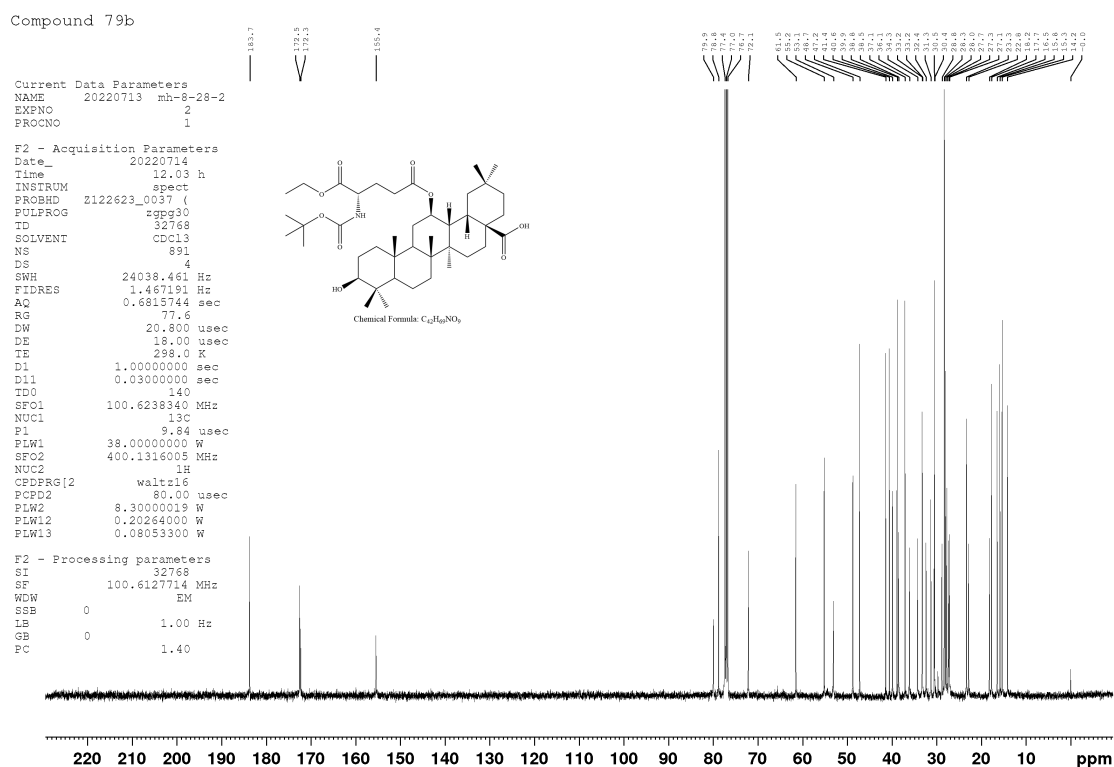
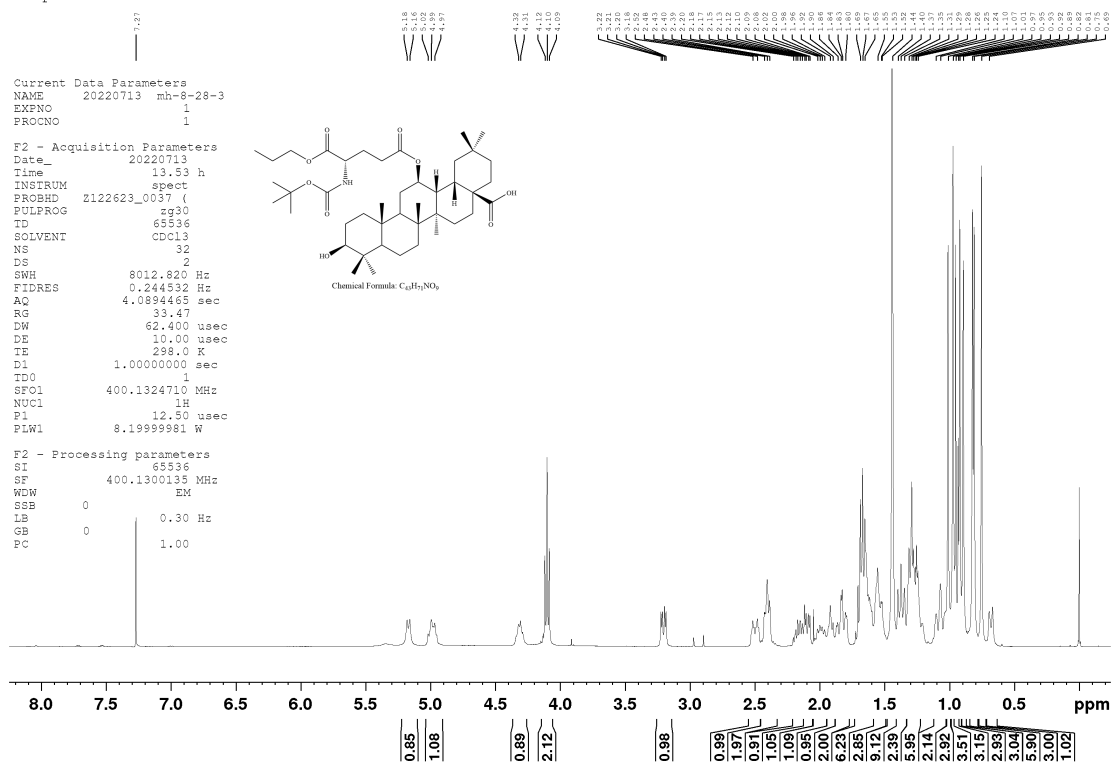
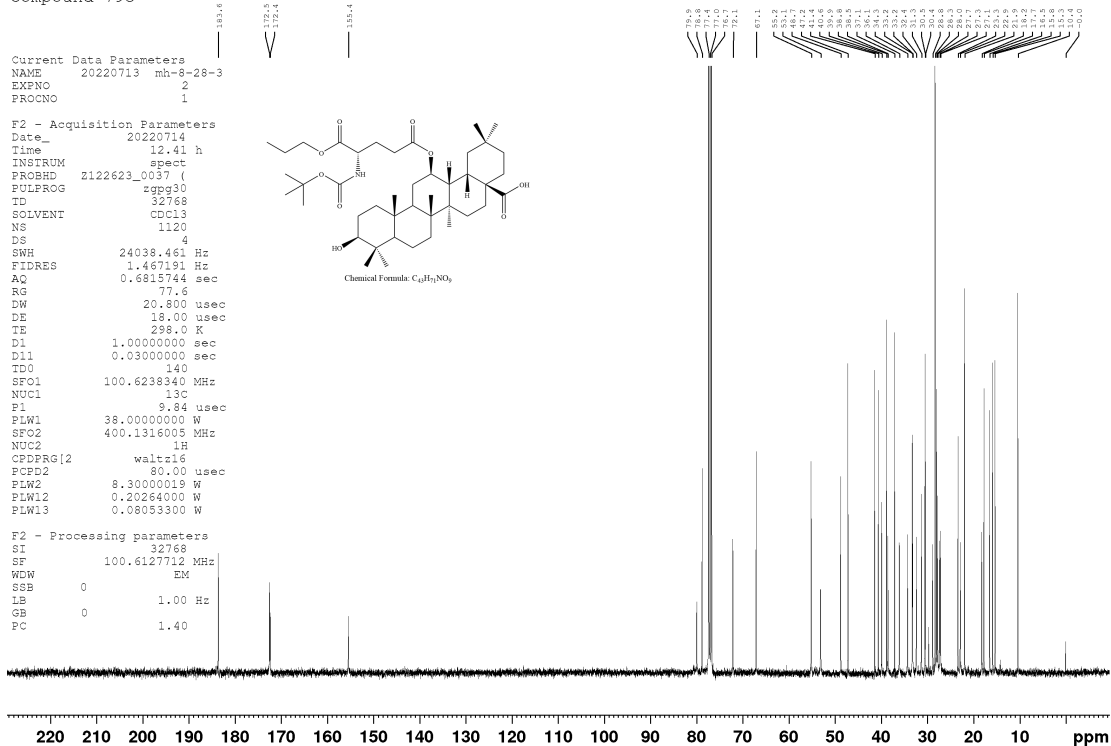


Fig. S66. ^{13}C NMR of compound 20b

Compound 79c

Fig. S67. ^1H NMR of compound 20c

Compound 79c

Fig. S68. ^{13}C NMR of compound 20c

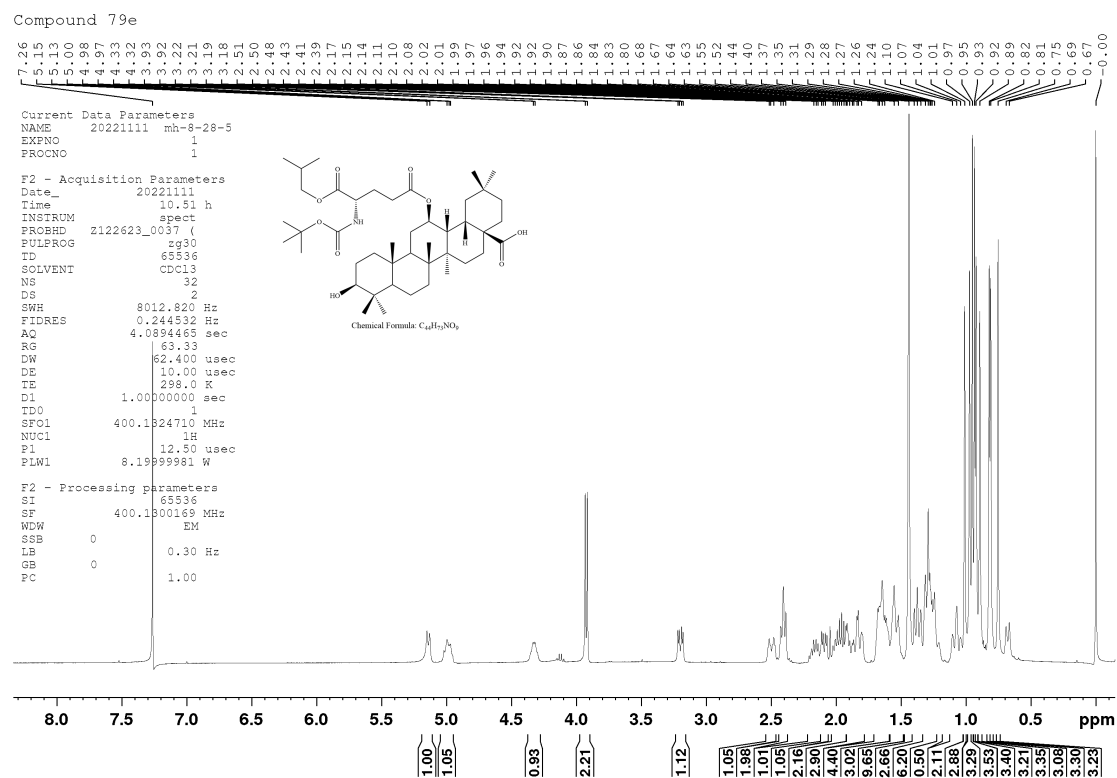


Fig. S71. ^1H NMR of compound 20e

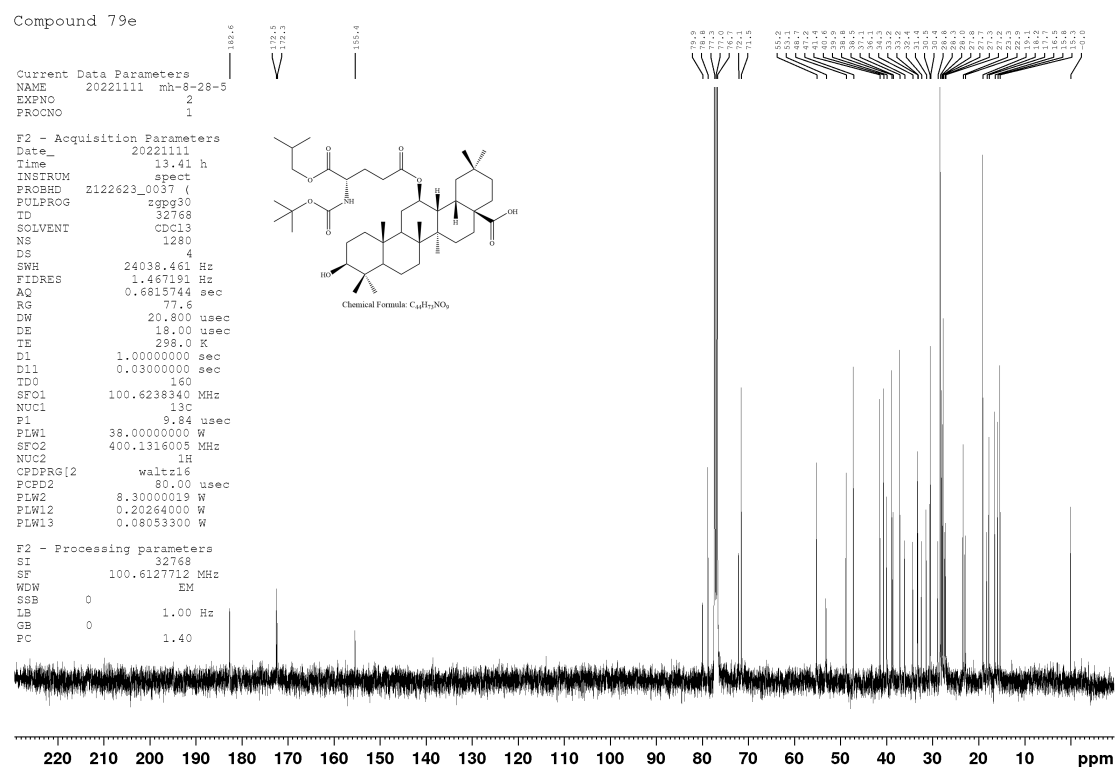
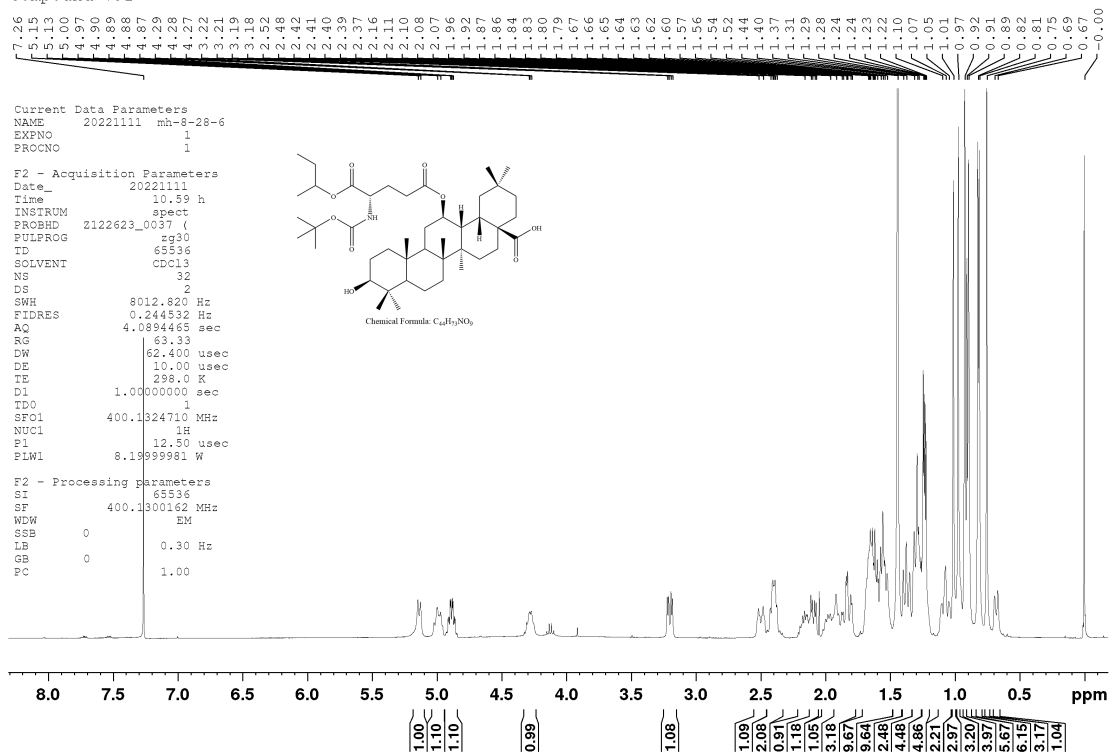
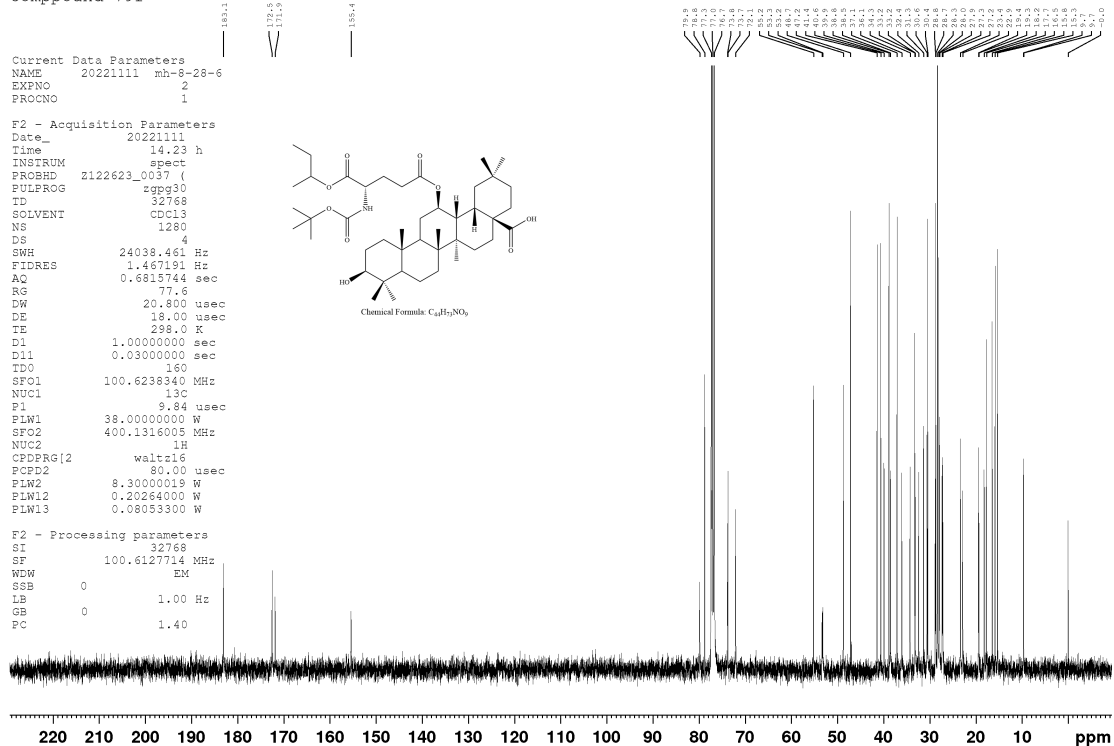


Fig. S72. ^{13}C NMR of compound 20e

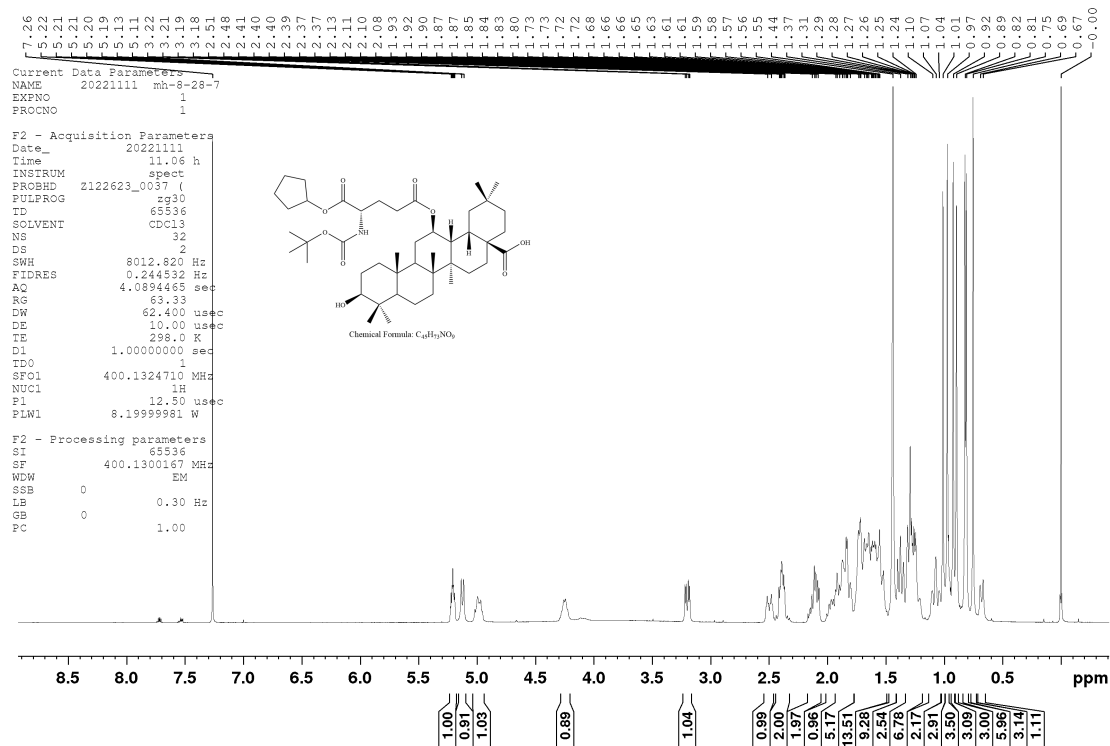
Compound 79f

Fig. S73. ^1H NMR of compound 20f

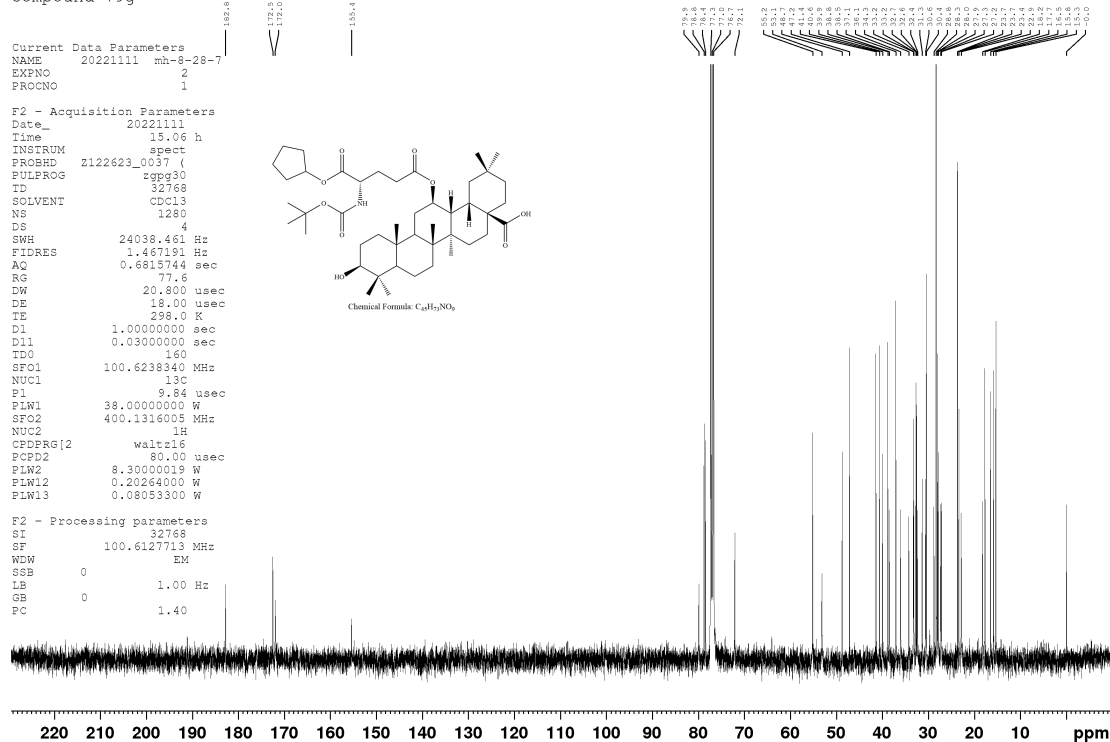
Compound 79f

Fig. S74. ^{13}C NMR of compound 20f

Compound 79g

Fig. S75. ^1H NMR of compound 20g

Compound 79g

Fig. S76. ^{13}C NMR of compound 20g

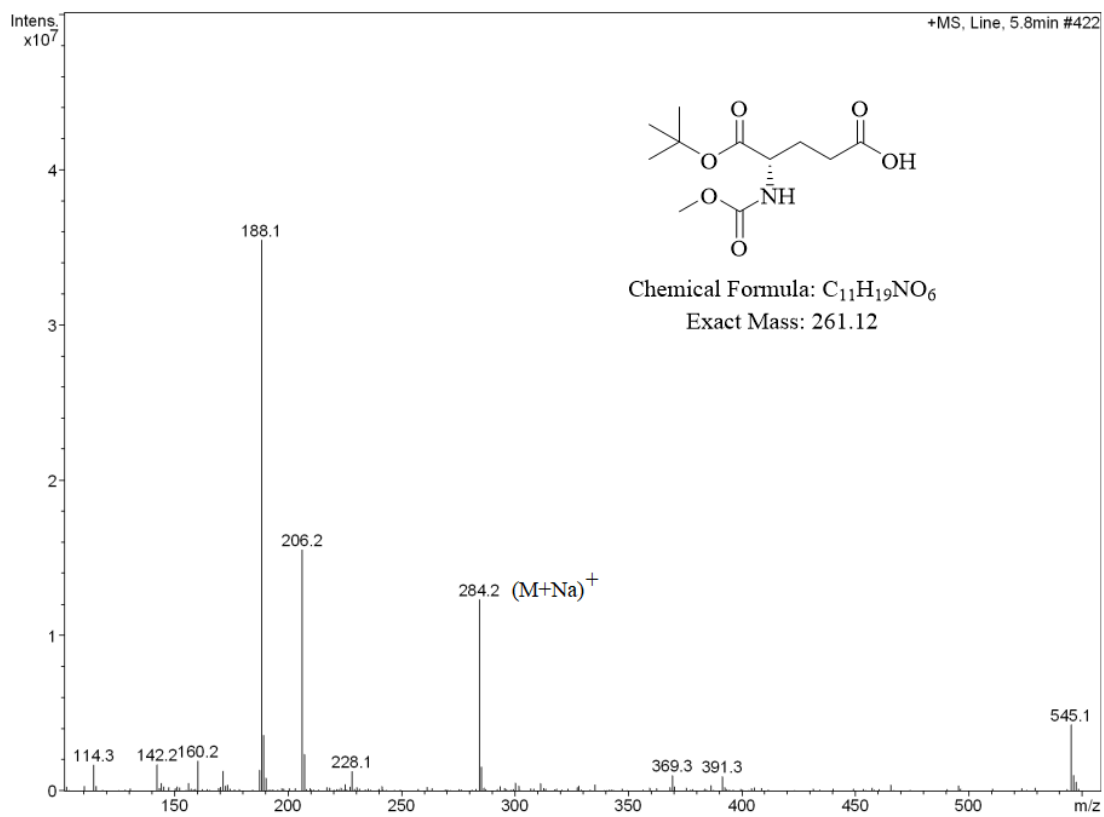


Fig. S77. MS of intermediate **14a**

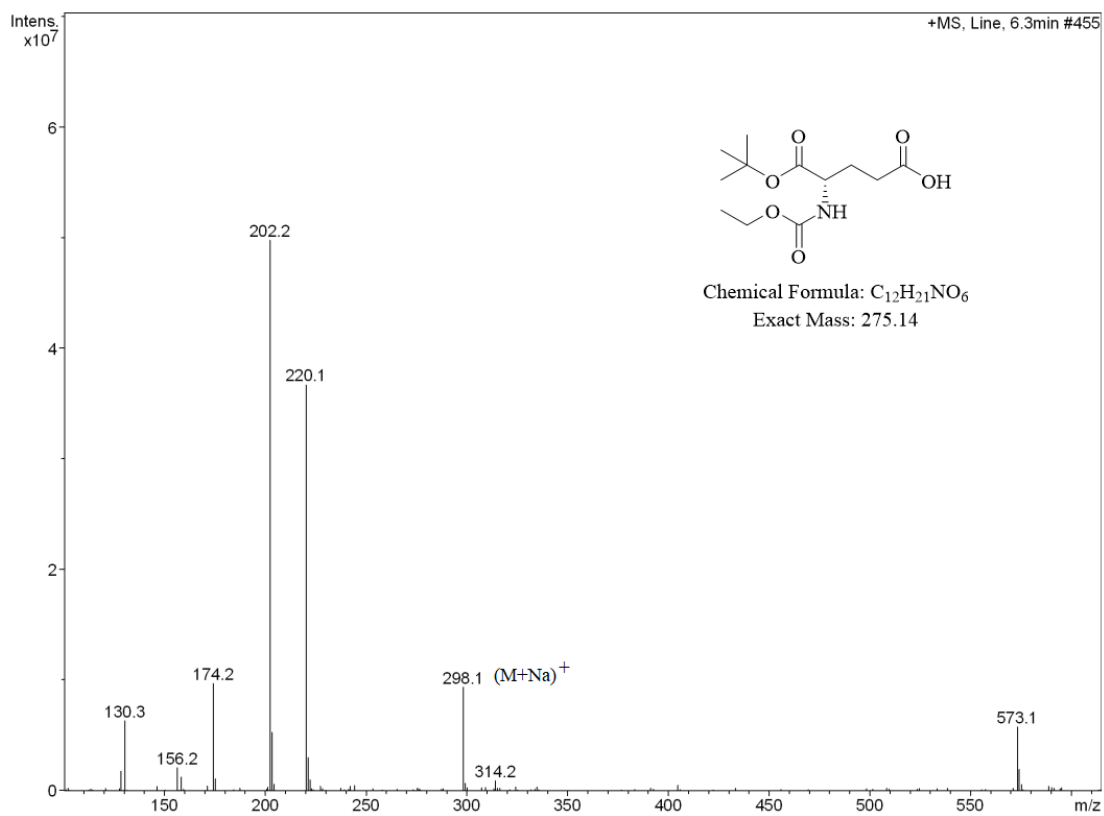


Fig. S78. MS of intermediate **14b**

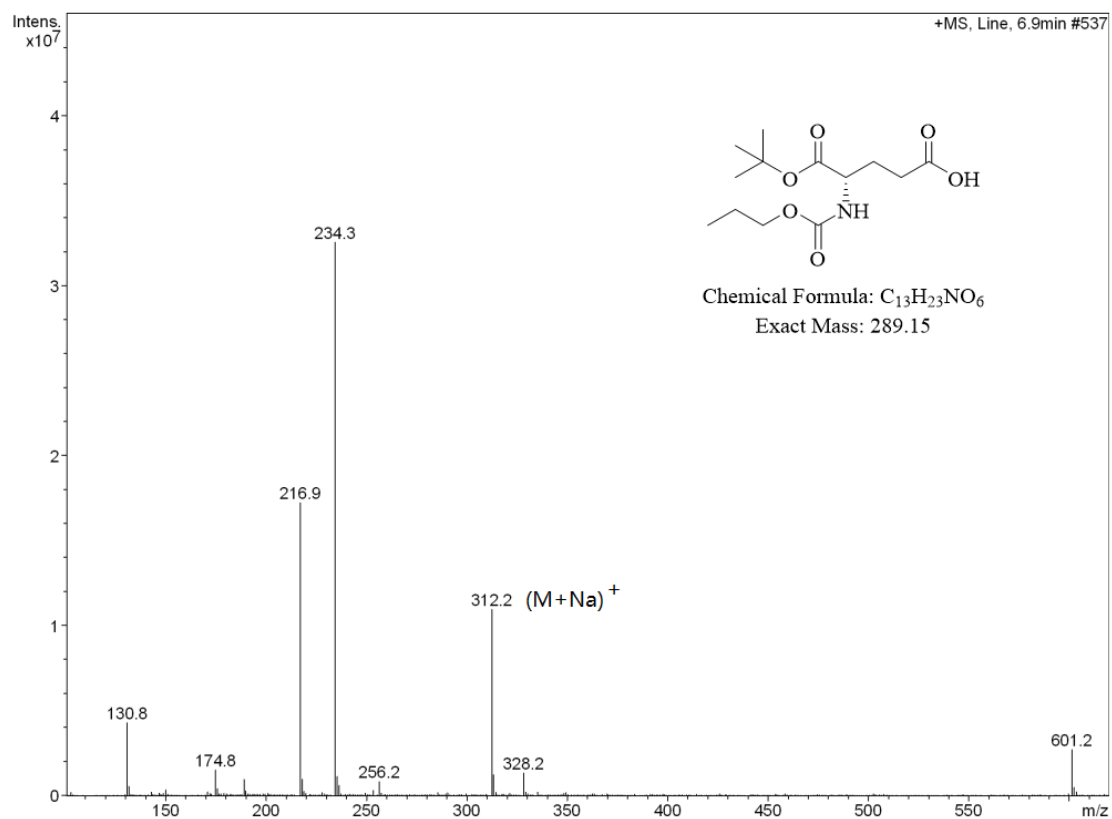


Fig. S79. MS of intermediate 14c

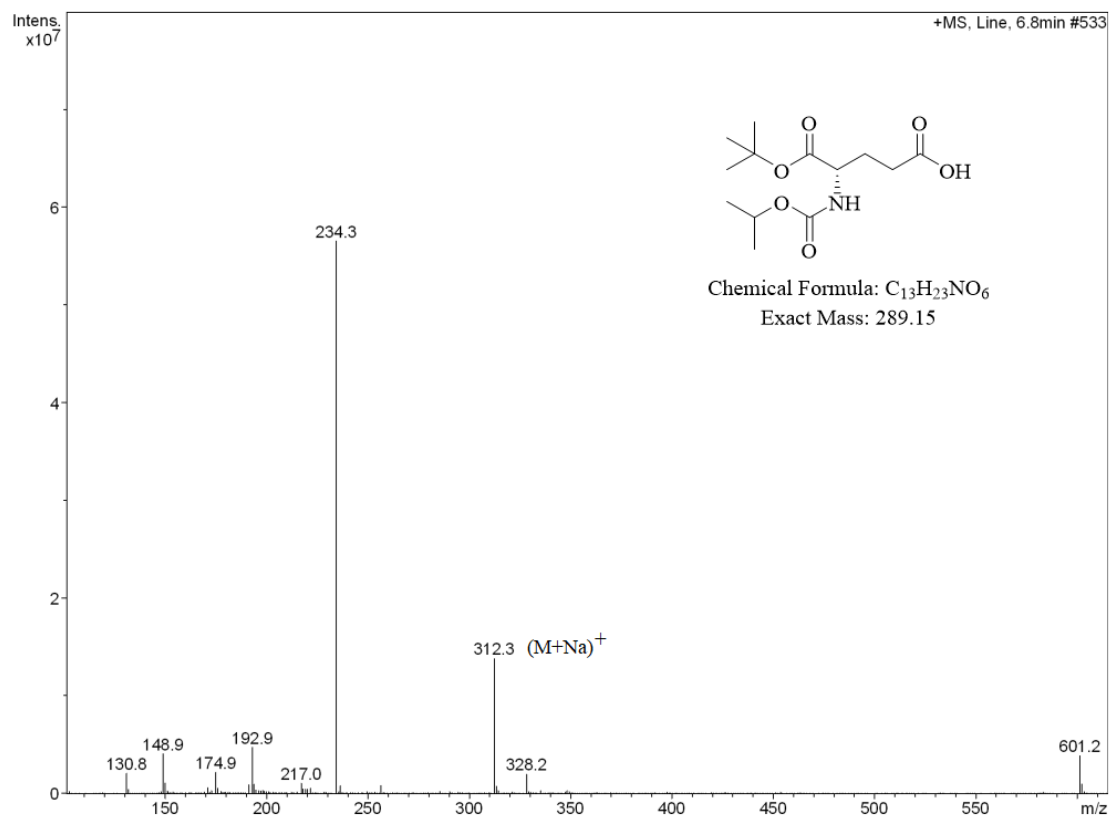


Fig. S80. MS of intermediate 14d

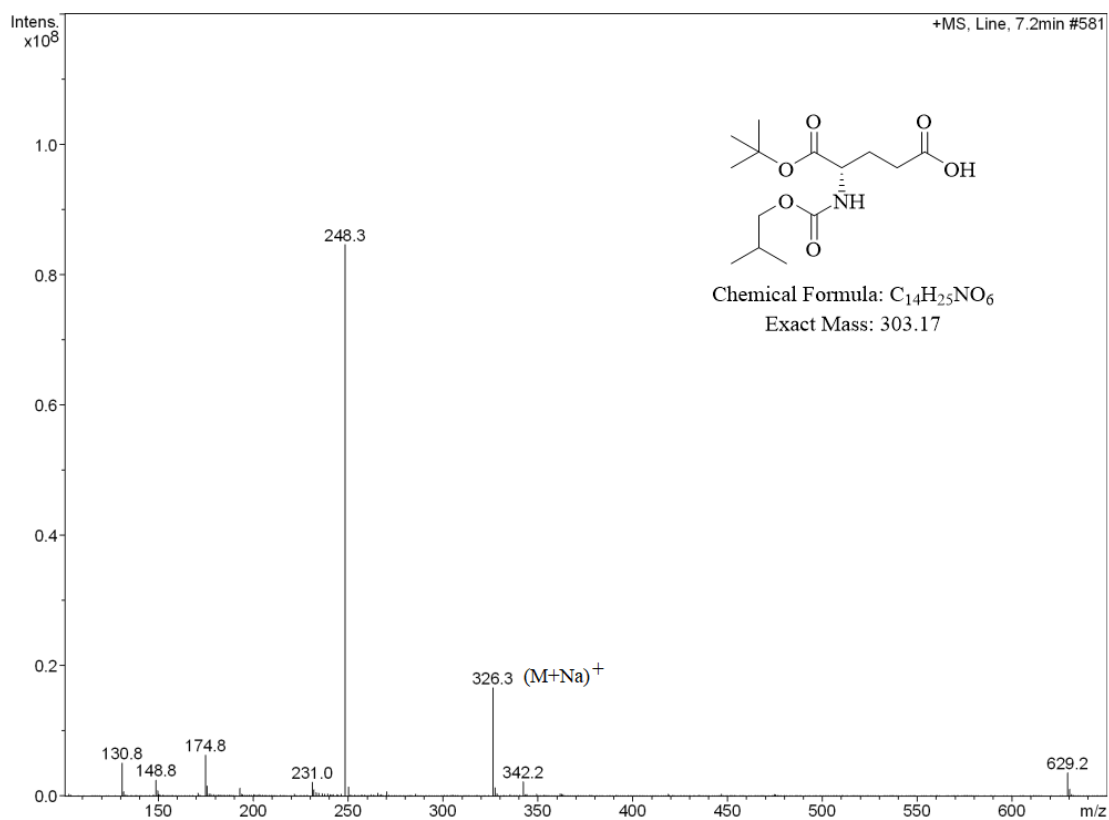


Fig. S81. MS of intermediate **14e**

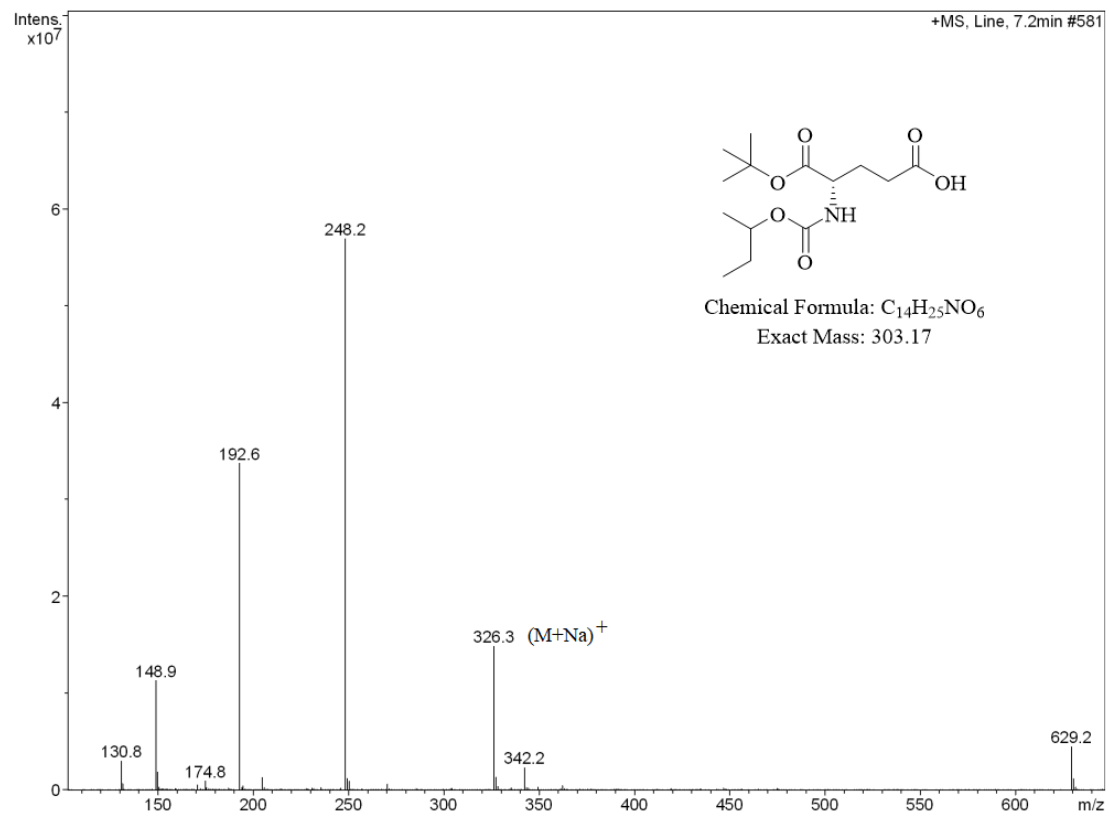


Fig. S82. MS of intermediate **14f**

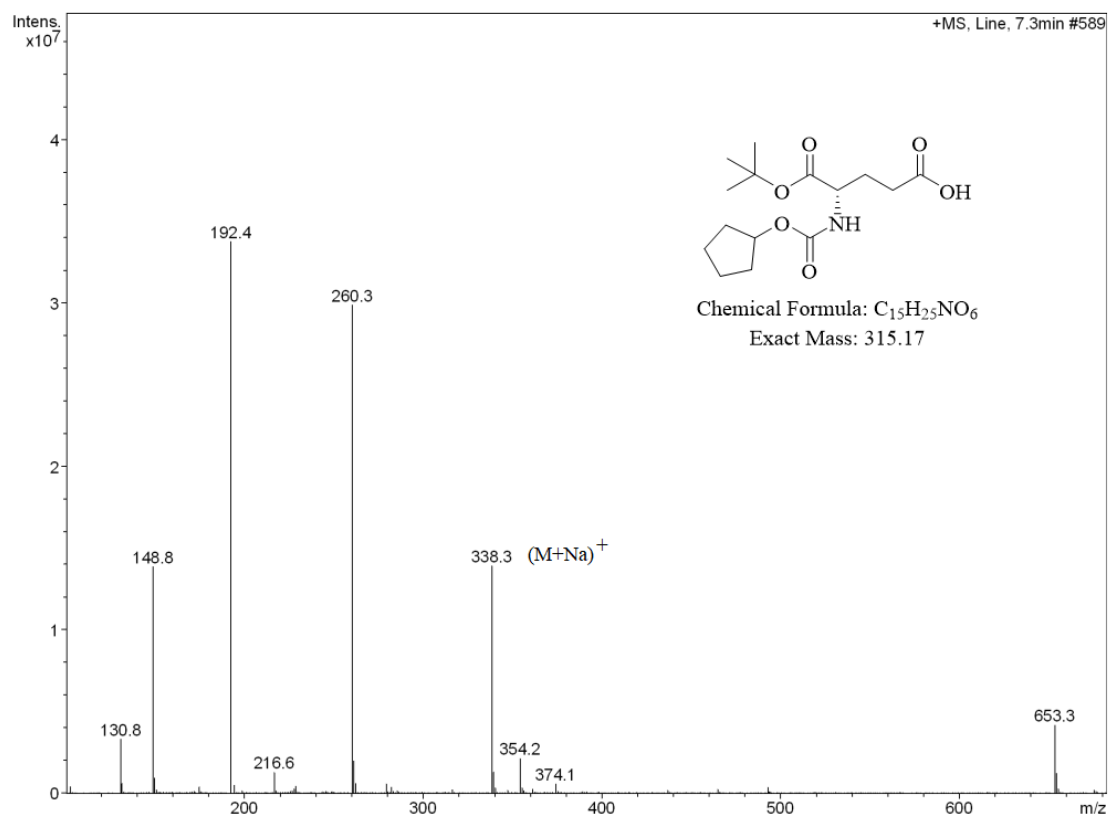


Fig. S83. MS of intermediate **14g**

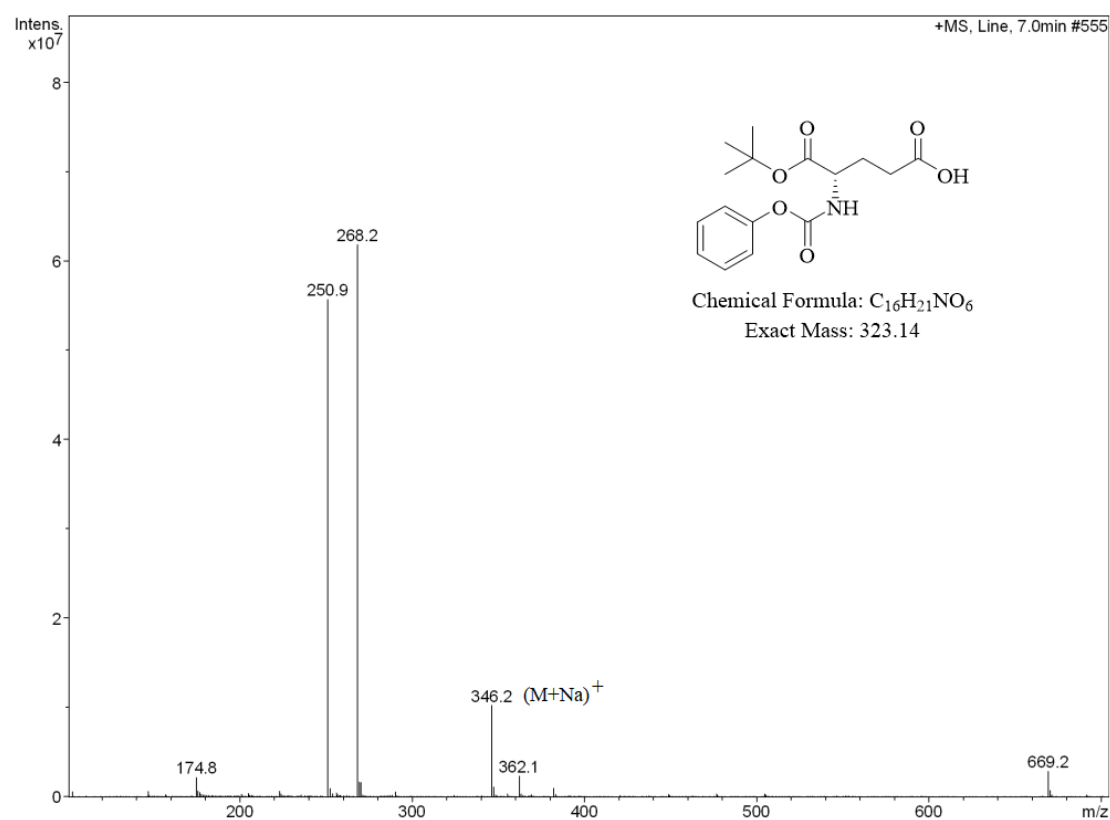


Fig. S84. MS of intermediate **14h**

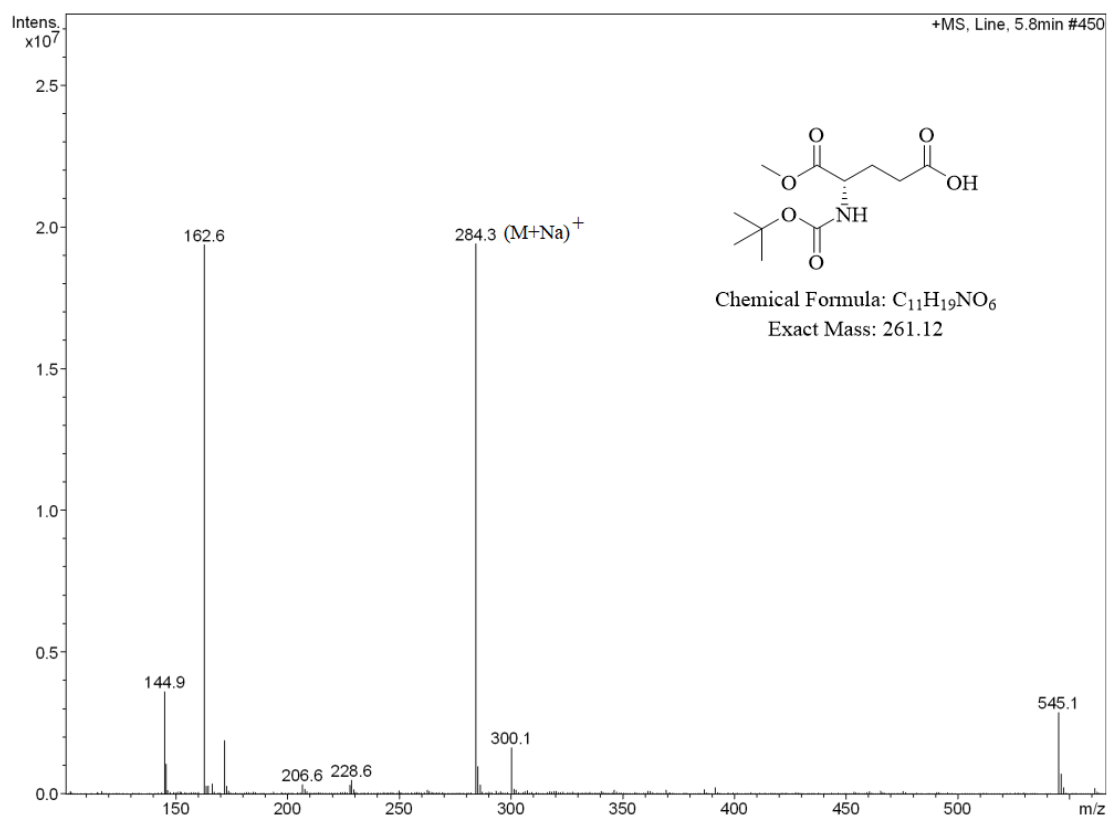


Fig. S85. MS of intermediate **18a**

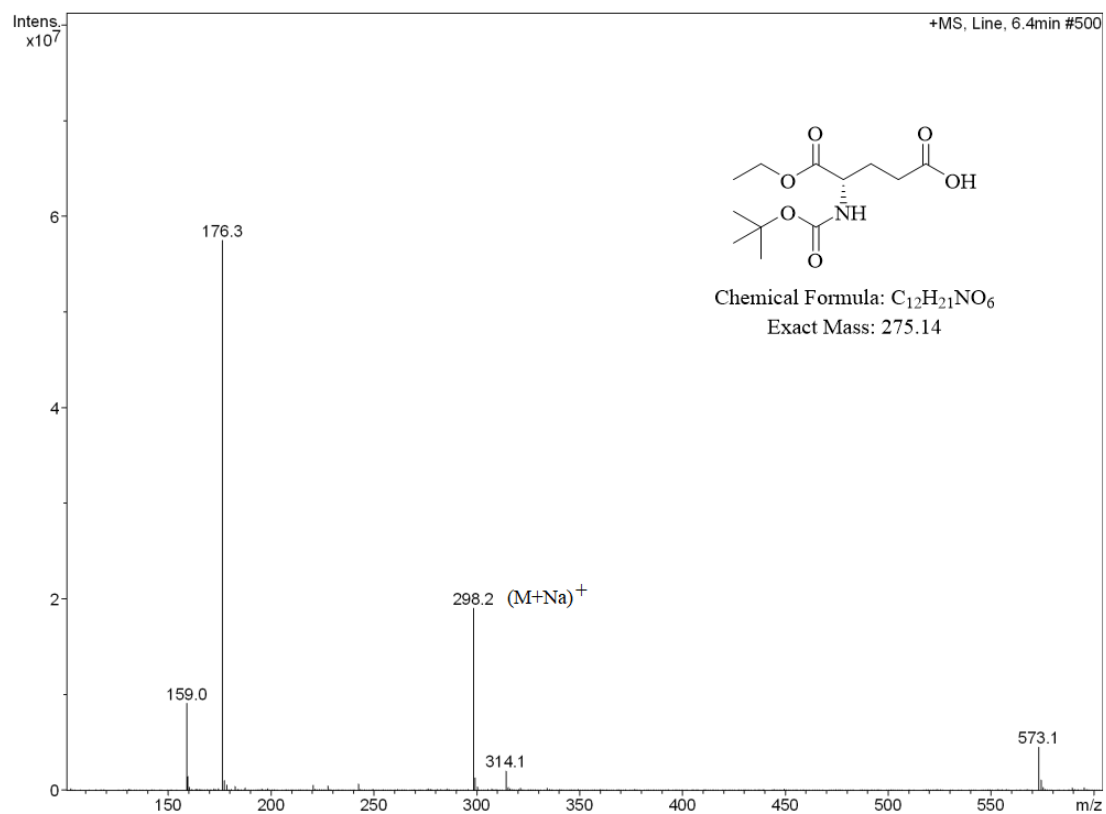


Fig. S86. MS of intermediate **18b**

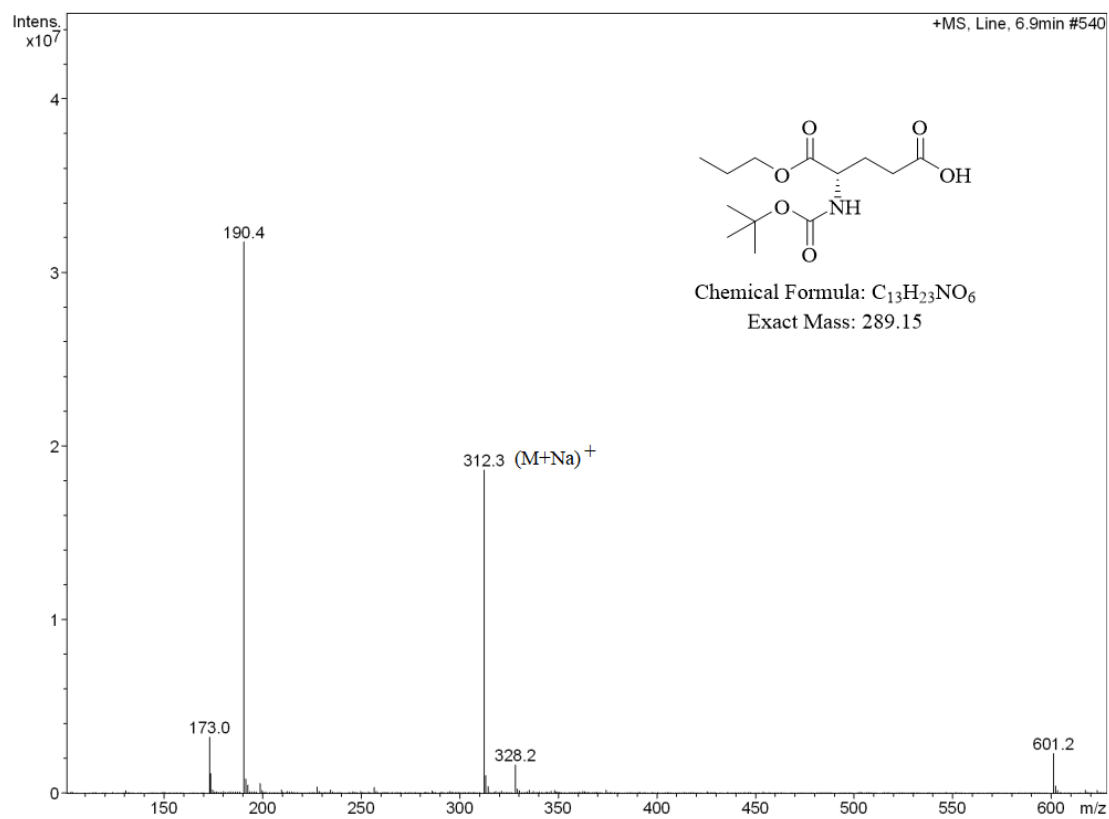


Fig. S87. MS of intermediate **18c**

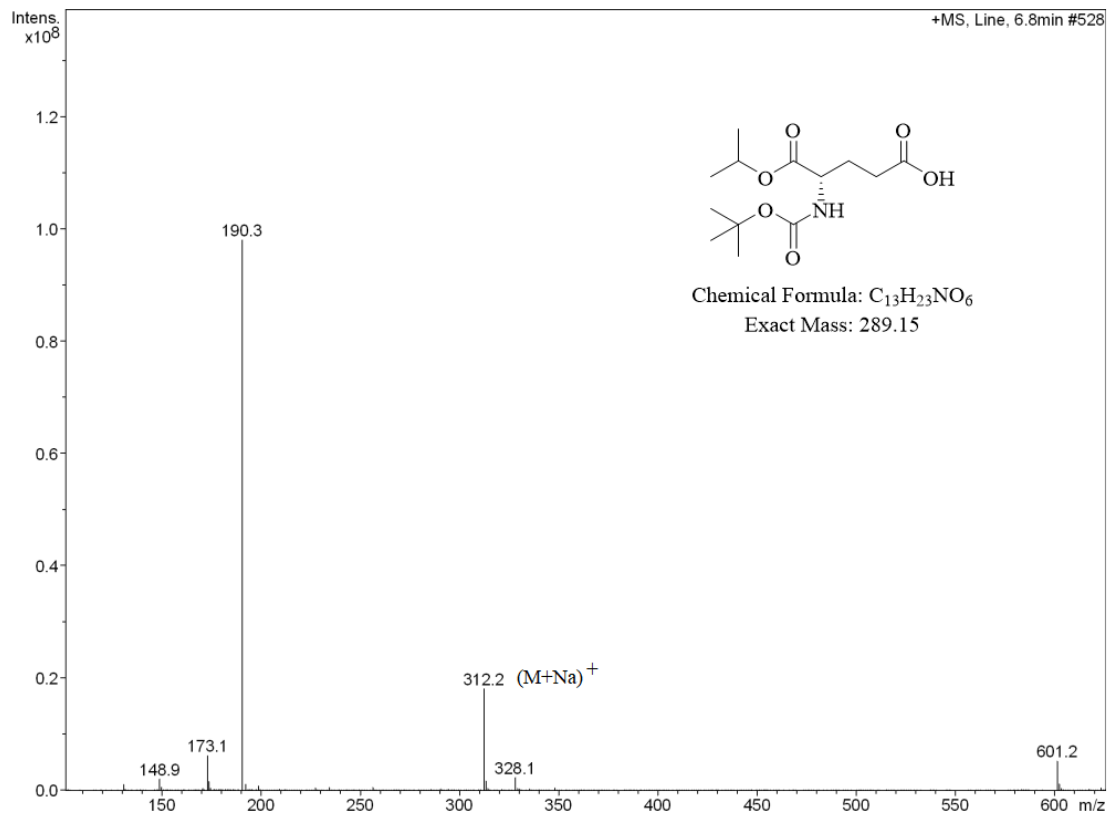


Fig. S88. MS of intermediate **18d**

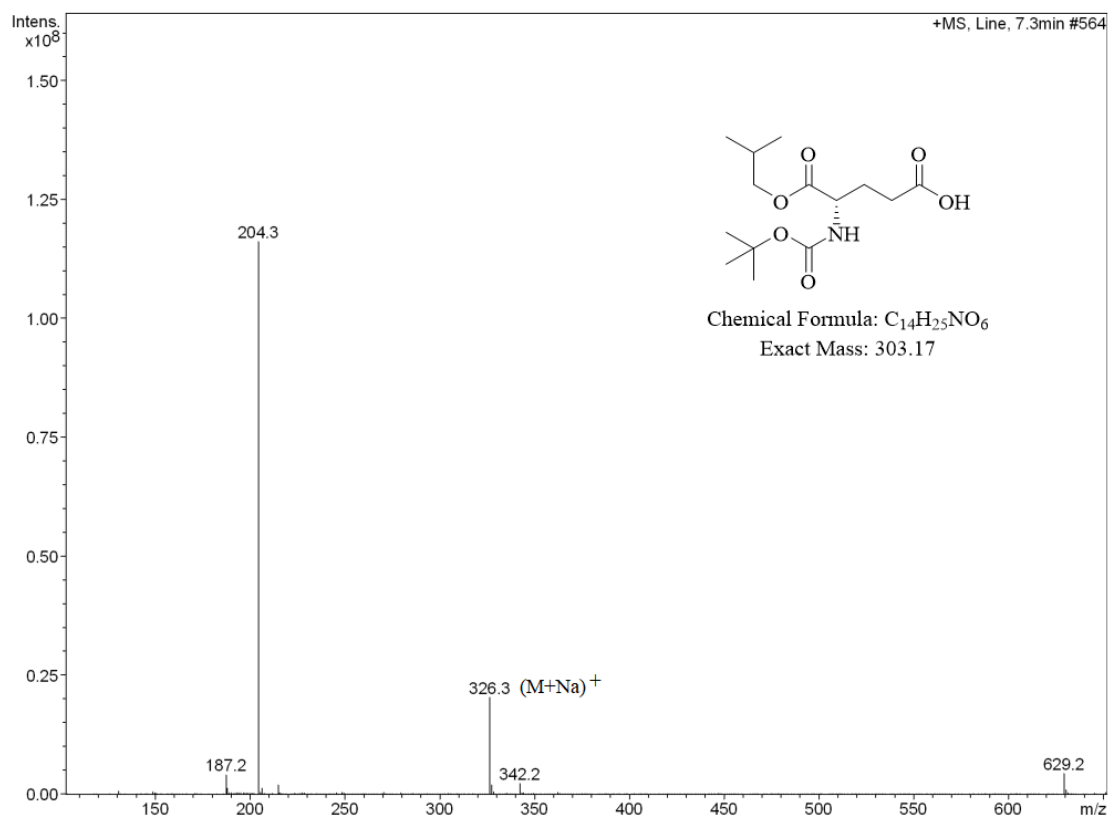


Fig. S89. MS of intermediate **18e**

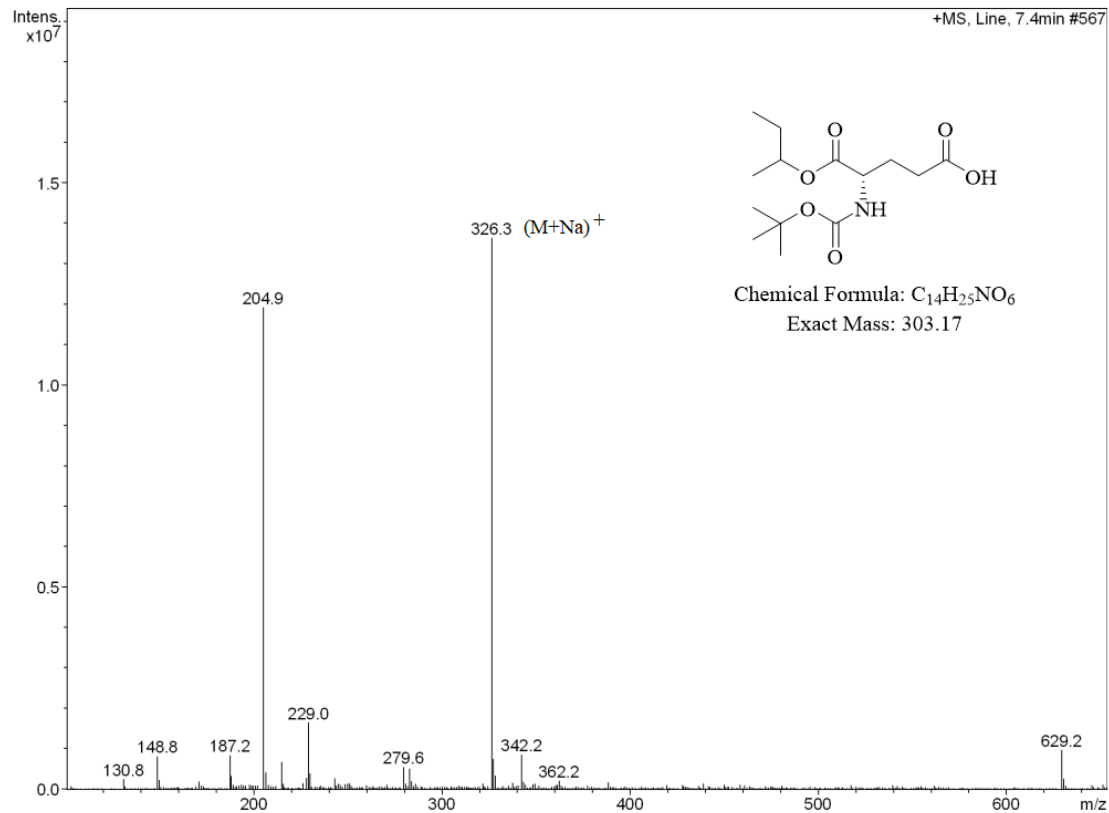


Fig. S90. MS of intermediate **18f**

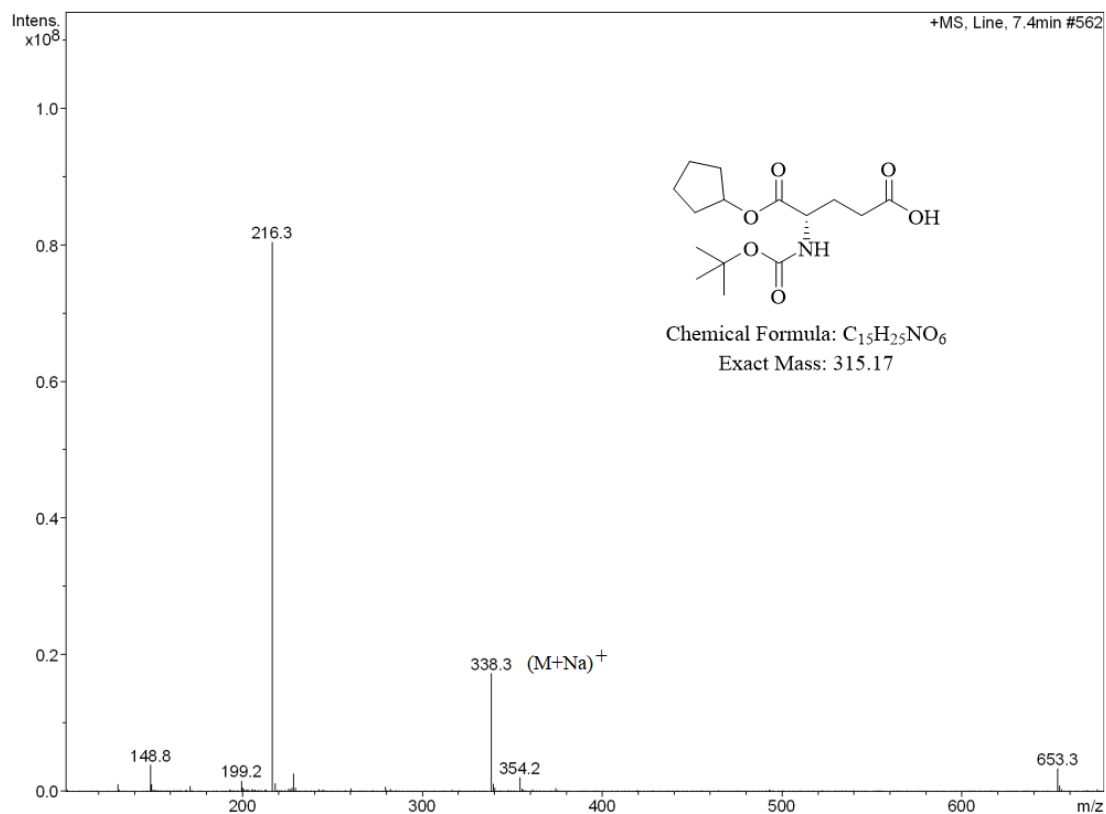


Fig. S91. MS of intermediate **18g**

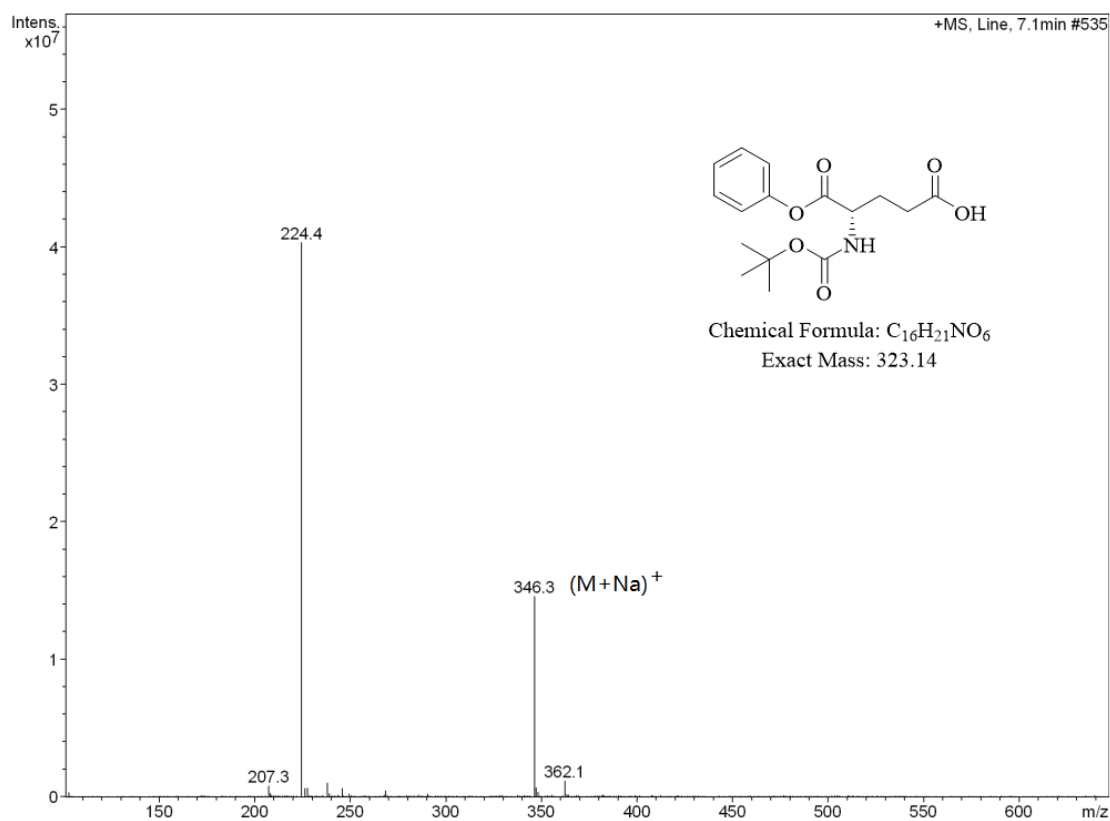
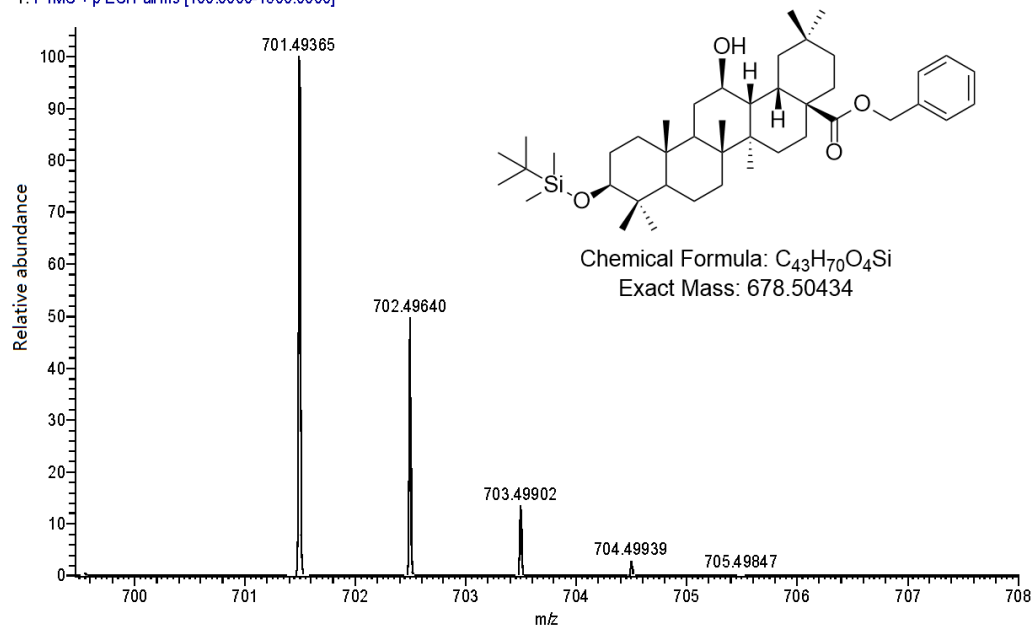


Fig. S92. MS of intermediate **18h**

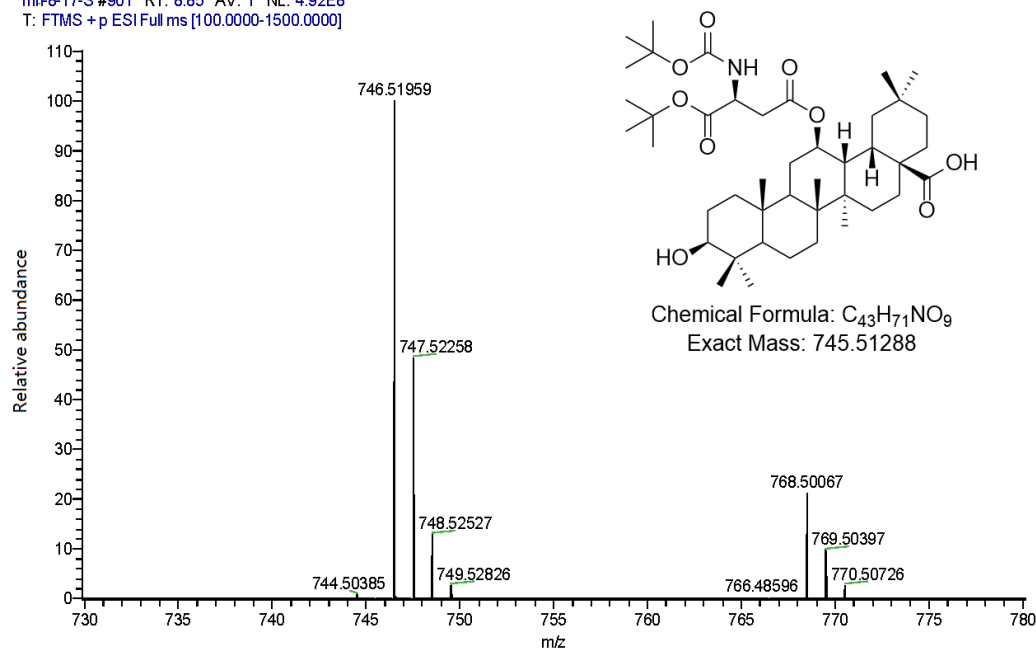
12B-OHOA #1341 RT: 13.44 AV: 1 NL: 4.16E7
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
701.49365	701.49356	0.092	9.5	C43 H70 O4 Na Si	M+Na

Fig. S93. HRMS of compound **8**

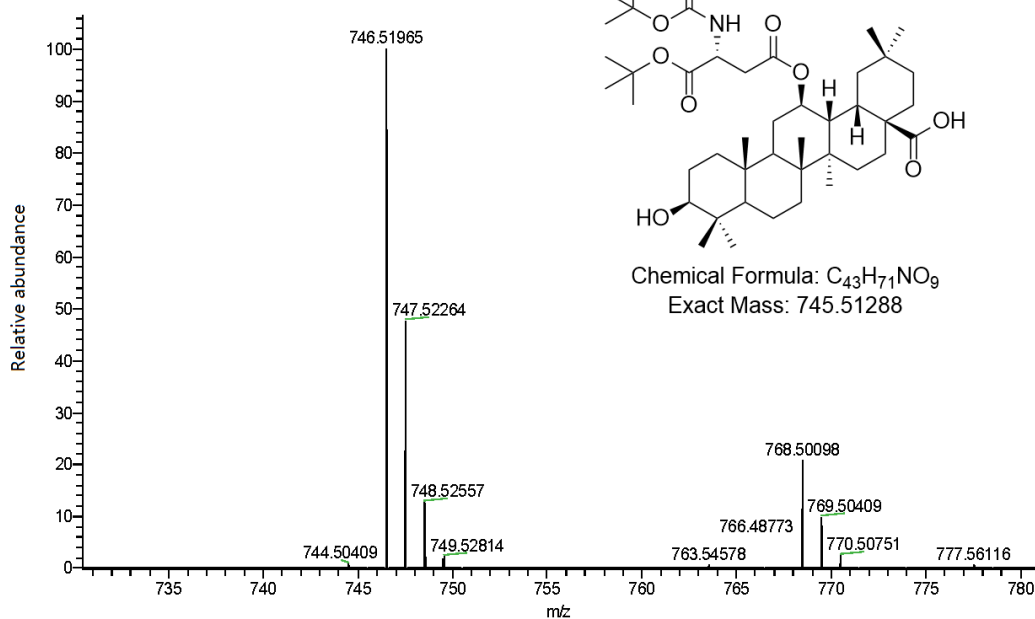
mh-8-17-S #901 RT: 8.85 AV: 1 NL: 4.92E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
746.51959	746.52016	-0.569	8.5	C43 H72 O9 N	M+H

Fig. S94. HRMS of compound **9a**

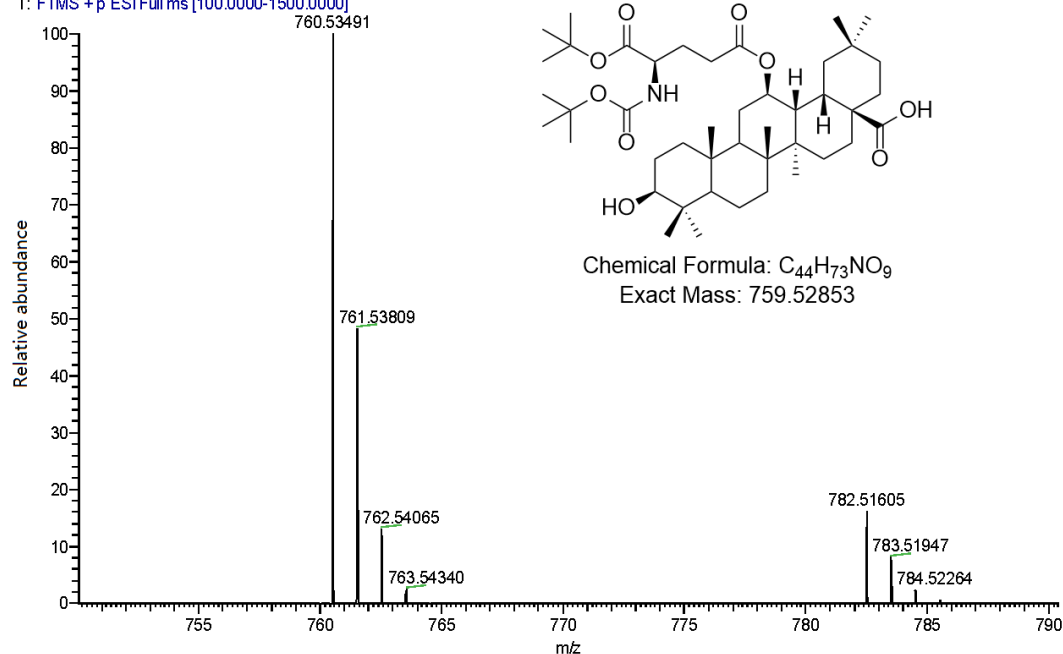
mh-8-17-R #901 RT: 8.84 AV: 1 NL: 4.31E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
746.51965	746.52016	-0.509	8.5	C43 H72 O9 N	M+H

Fig. S95. HRMS of compound **9b**

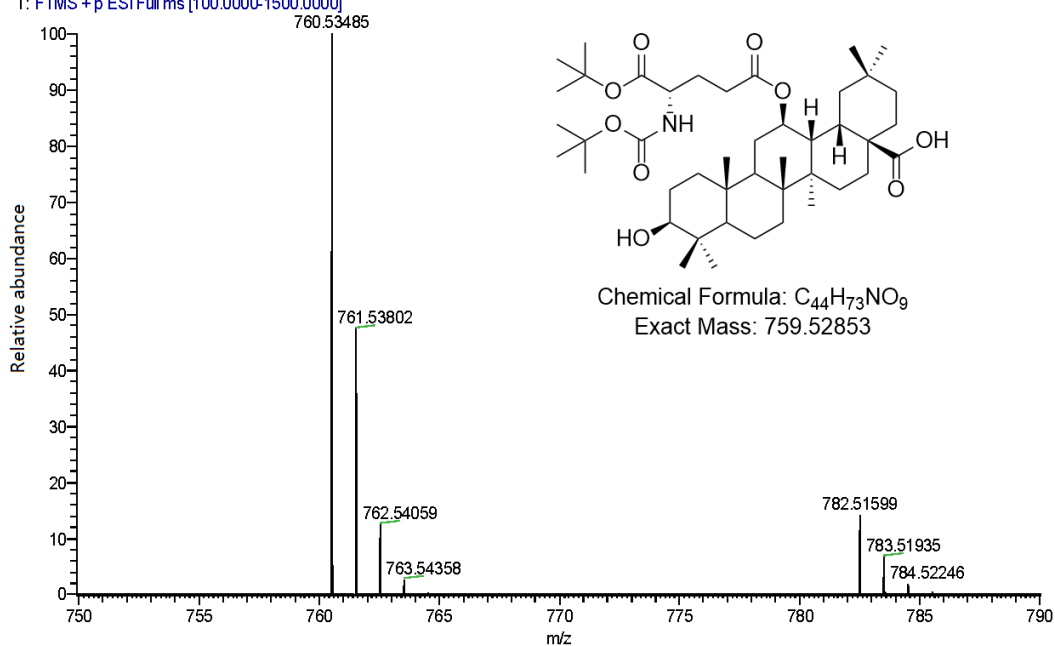
mh-8-15#885 RT: 8.70 AV: 1 NL: 1.04E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
760.53491	760.53581	-0.899	8.5	C44 H74 O9 N	M+H

Fig. S96. HRMS of compound **10a**

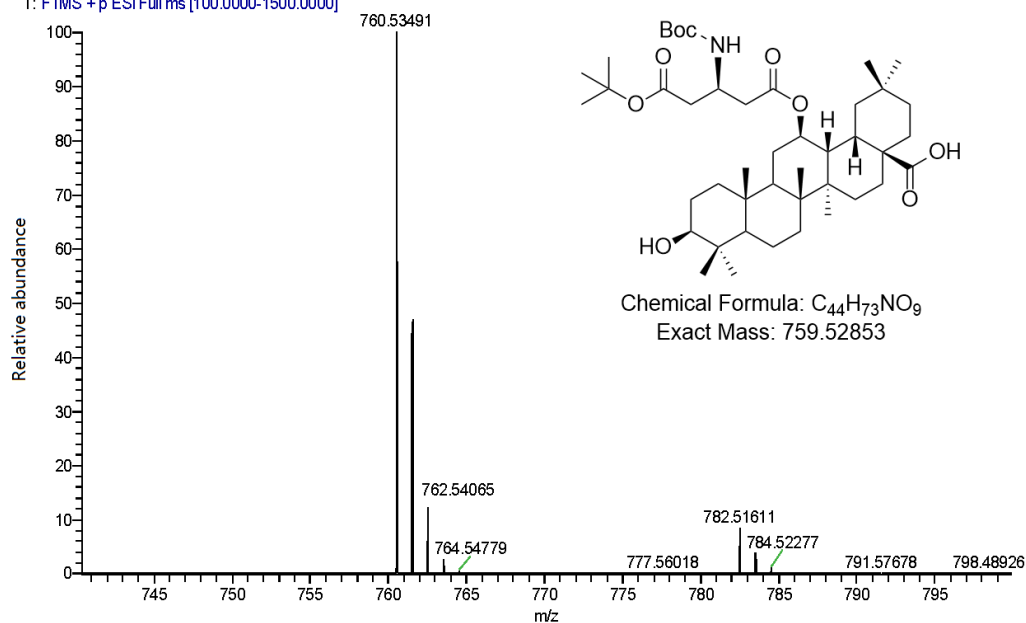
YMY-3-46 #883 RT: 8.68 AV: 1 NL: 9.84E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
760.53485	760.53581	-0.959	8.5	C ₄₄ H ₇₄ O ₉ N	M+H

Fig. S97. HRMS of compound 10b

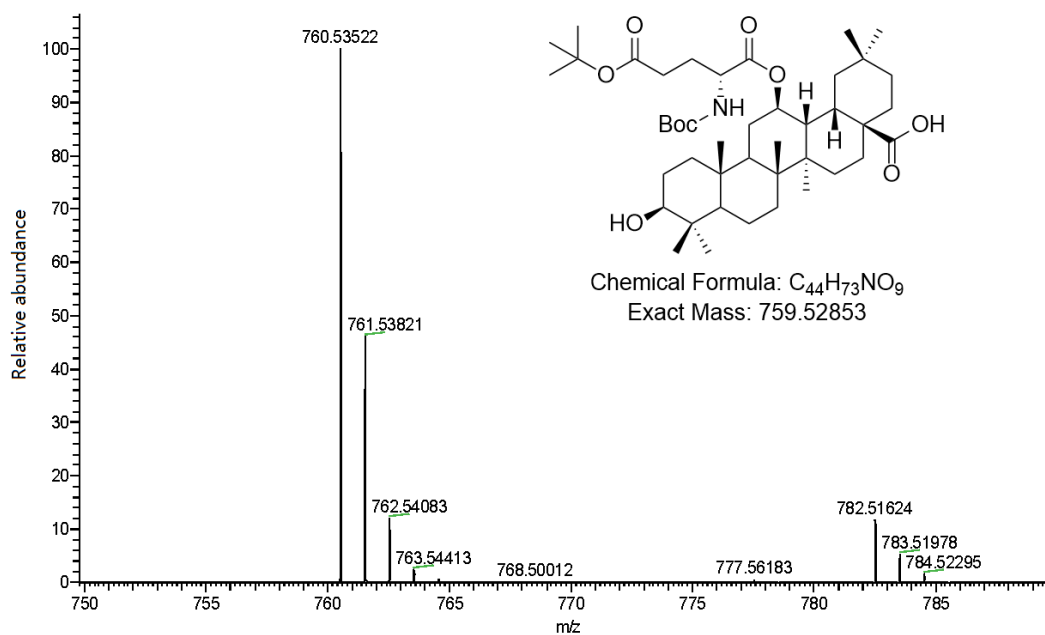
mh-8-19 #891 RT: 8.75 AV: 1 NL: 8.12E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
760.53491	760.53581	-0.899	8.5	C ₄₄ H ₇₄ O ₉ N	M+H

Fig. S98. HRMS of compound 10c

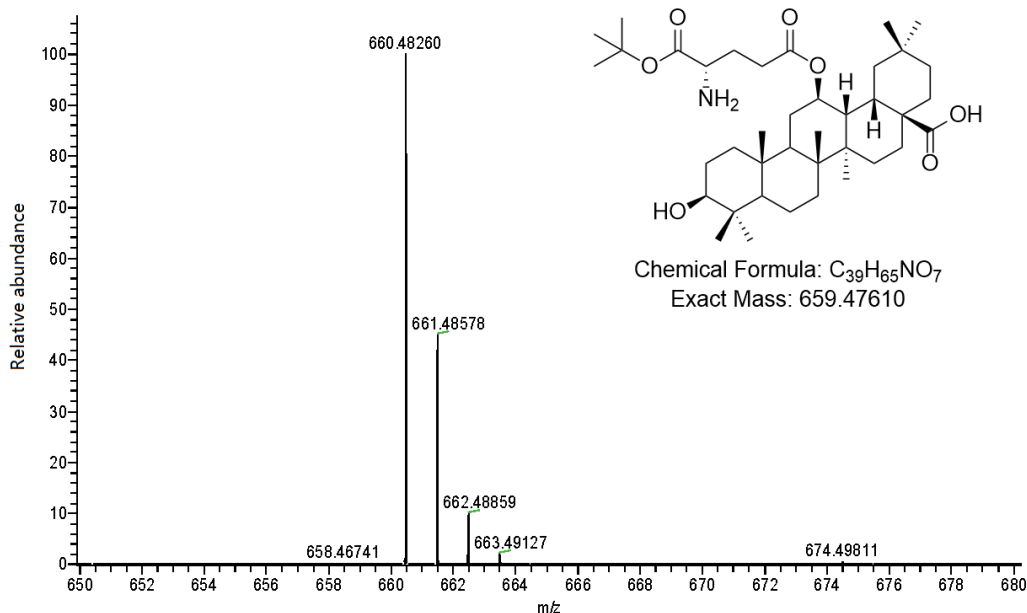
mh-8-16 #887 RT: 8.72 AV: 1 NL: 6.60E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
760.53522	760.53581	-0.589	8.5	C44 H74 O9 N	M+H

Fig. S99. HRMS of compound 10d

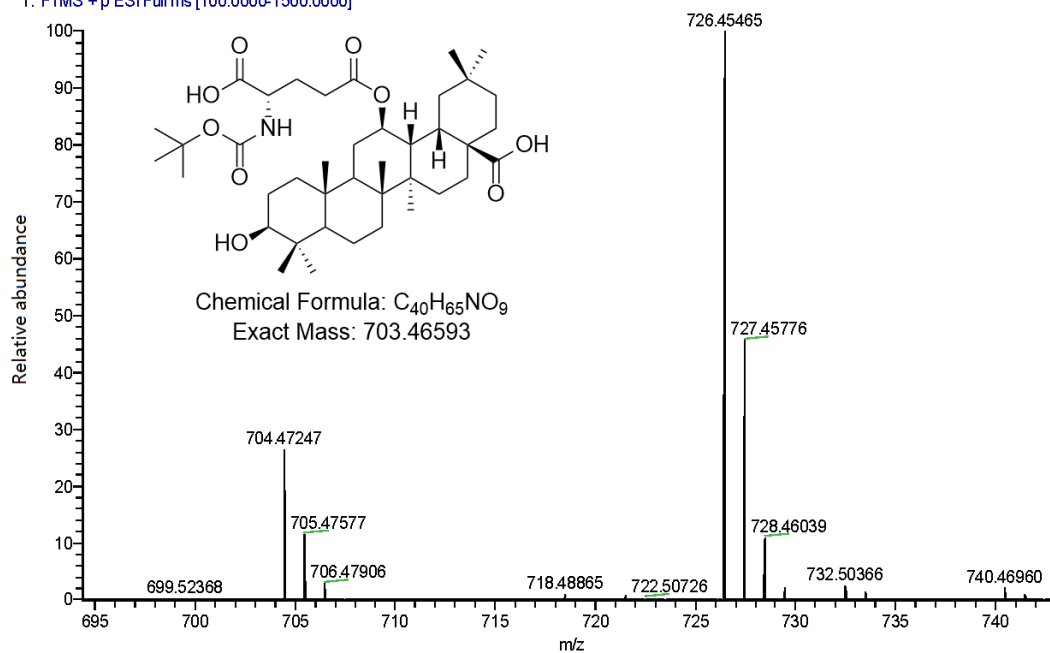
mh-8-5 #883 RT: 8.68 AV: 1 NL: 8.70E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
660.48260	660.48338	-0.78	7.5	C39 H66 O7 N	M+H

Fig. S100. HRMS of compound 11a

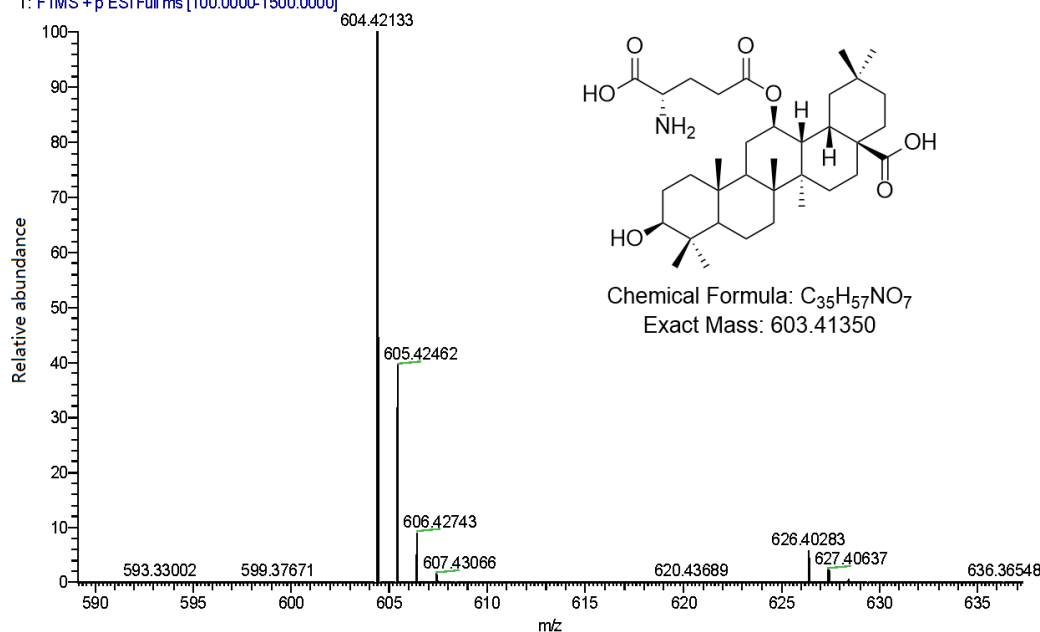
mh-8-1 #901 RT: 8.83 AV: 1 NL: 1.95E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
726.45465	726.45515	-0.504	8.5	C40 H65 O9 N Na	M+Na

Fig. S101. HRMS of compound 11b

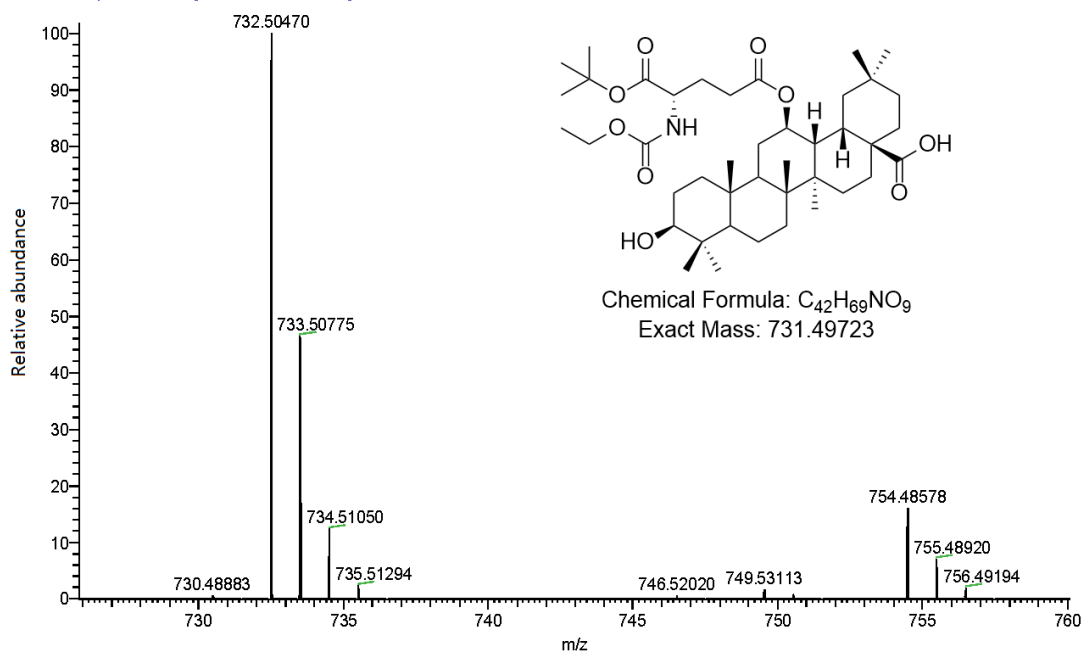
mh-8-8 #795 RT: 7.91 AV: 1 NL: 6.19E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
604.42133	604.42078	0.55	7.5	C35 H58 O7 N	M+H

Fig. S102. HRMS of compound 11c

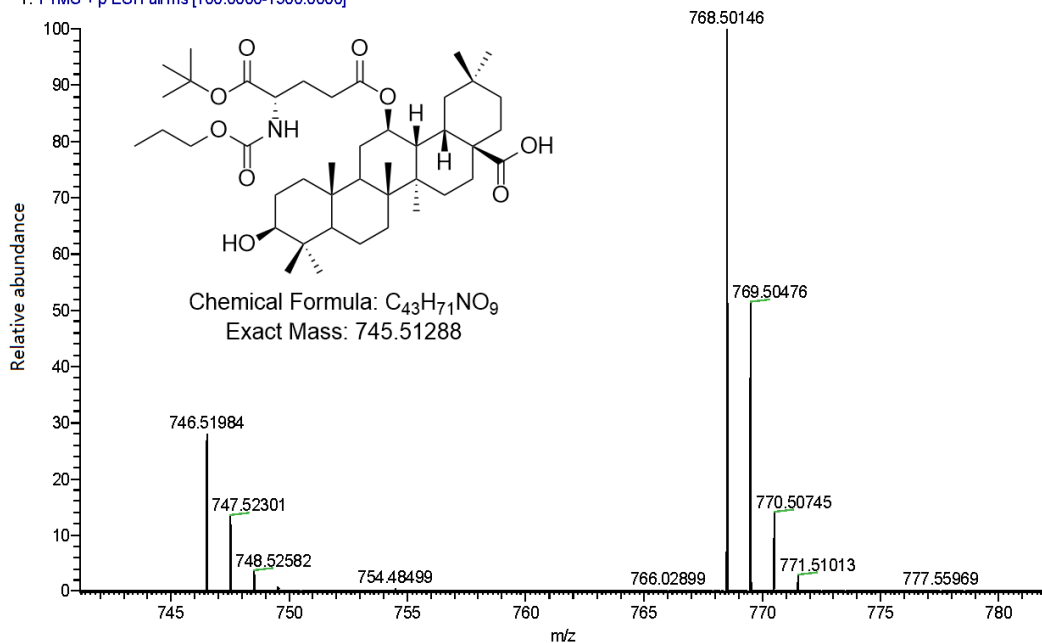
mh-8-27-2 #851 RT: 8.50 AV: 1 NL: 8.66E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
732.50470	732.50451	0.191	8.5	C42 H70 O9 N	M+H

Fig. S103. HRMS of compound **19b**

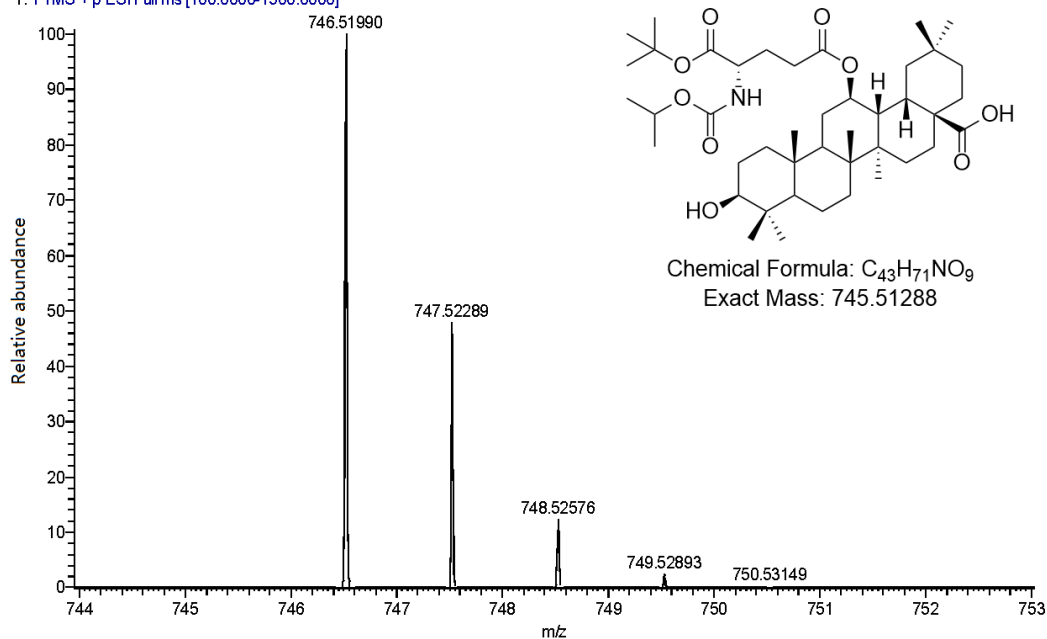
mh-8-27-3 #859 RT: 8.51 AV: 1 NL: 1.04E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
768.50146	768.50210	-0.644	8.5	C43 H71 O9 N Na	M+Na

Fig. S104. HRMS of compound **19c**

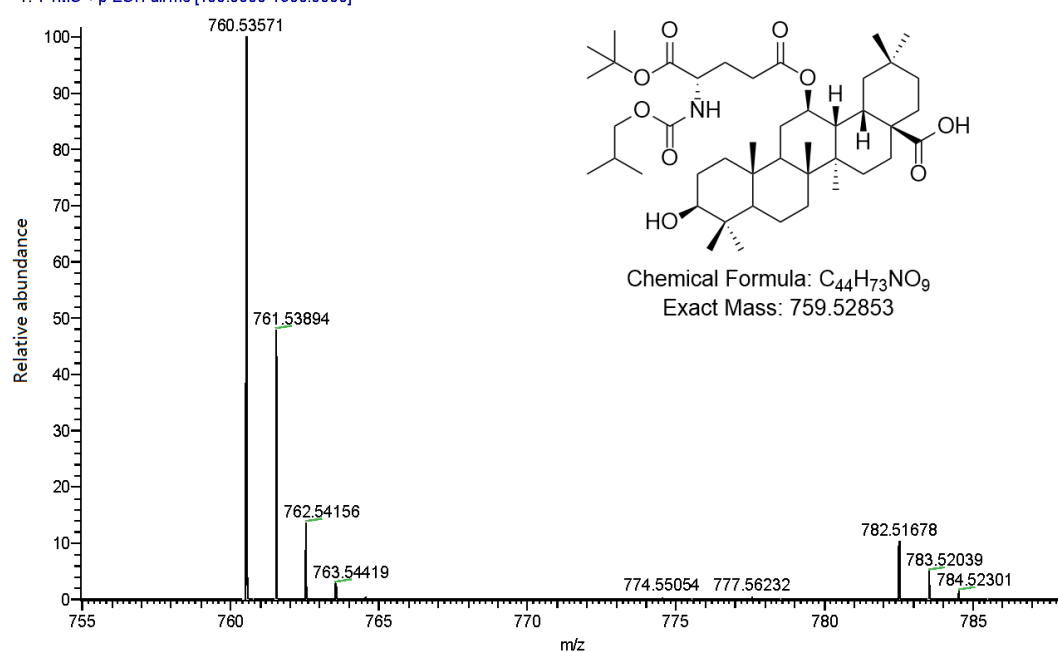
mh-8-27-4 #863 RT: 8.56 AV: 1 NL: 4.33E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
746.51990	746.52016	-0.259	8.5	C43 H72 O9 N	M+H

Fig. S105. HRMS of compound 19d

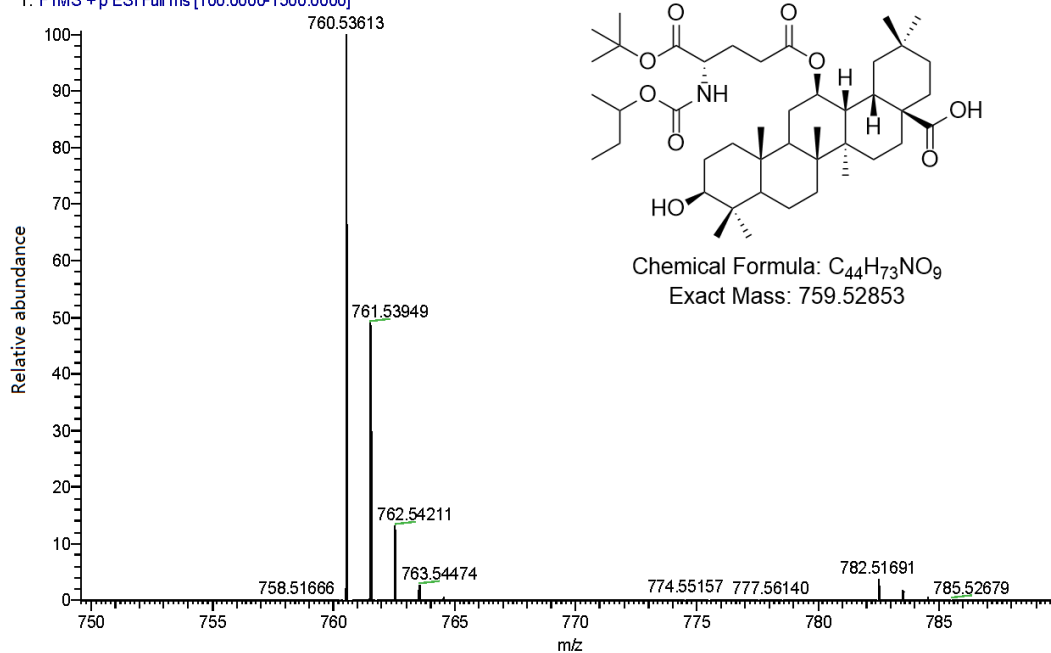
mh-8-27-5 #865 RT: 8.63 AV: 1 NL: 9.15E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
760.53571	760.53581	-0.099	8.5	C44 H74 O9 N	M+H

Fig. S106. HRMS of compound 19e

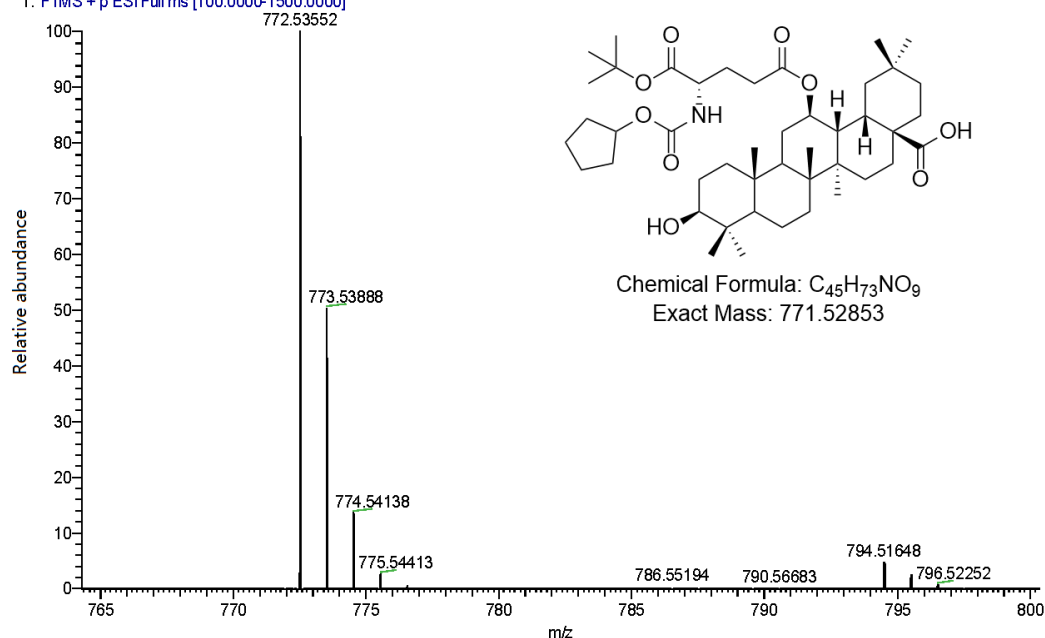
mh-8-27-6 #875 RT: 8.68 AV: 1 NL: 1.43E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
760.53613	760.53581	0.321	8.5	C ₄₄ H ₇₄ O ₉ N	M+H

Fig. S107. HRMS of compound 19f

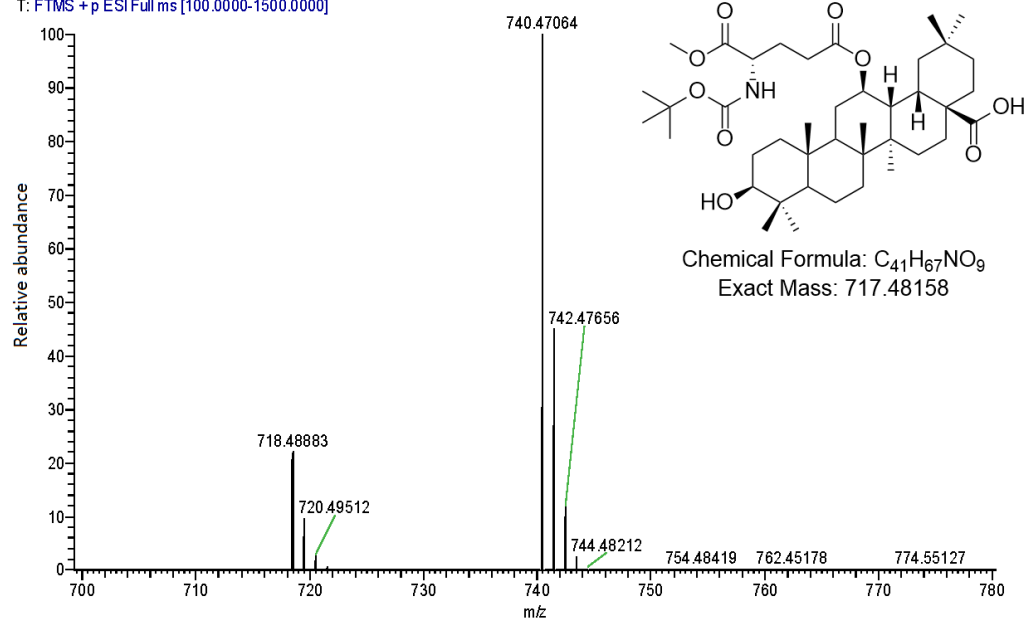
mh-8-27-7 #875 RT: 8.68 AV: 1 NL: 1.27E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
772.53552	772.53581	-0.289	9.5	C ₄₅ H ₇₄ O ₉ N	M+H

Fig. S108. HRMS of compound 19g

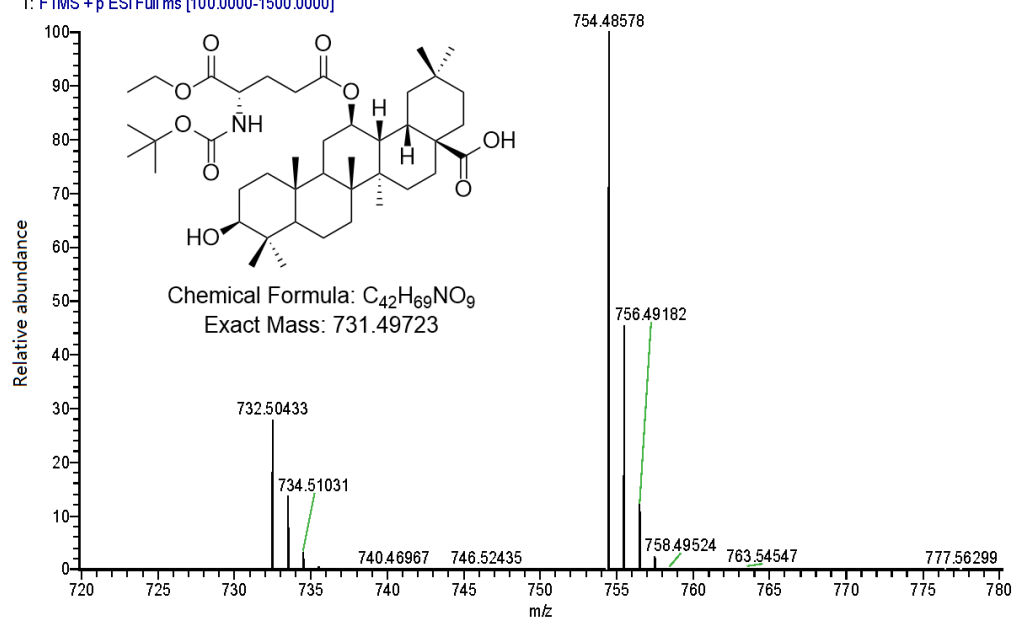
mh-8-28-1 #847 RT: 8.40 AV: 1 NL: 1.40E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
740.47064	740.47080	-0.164	8.5	C41 H67 O9 N Na	M+Na

Fig. S109. HRMS of compound **20a**

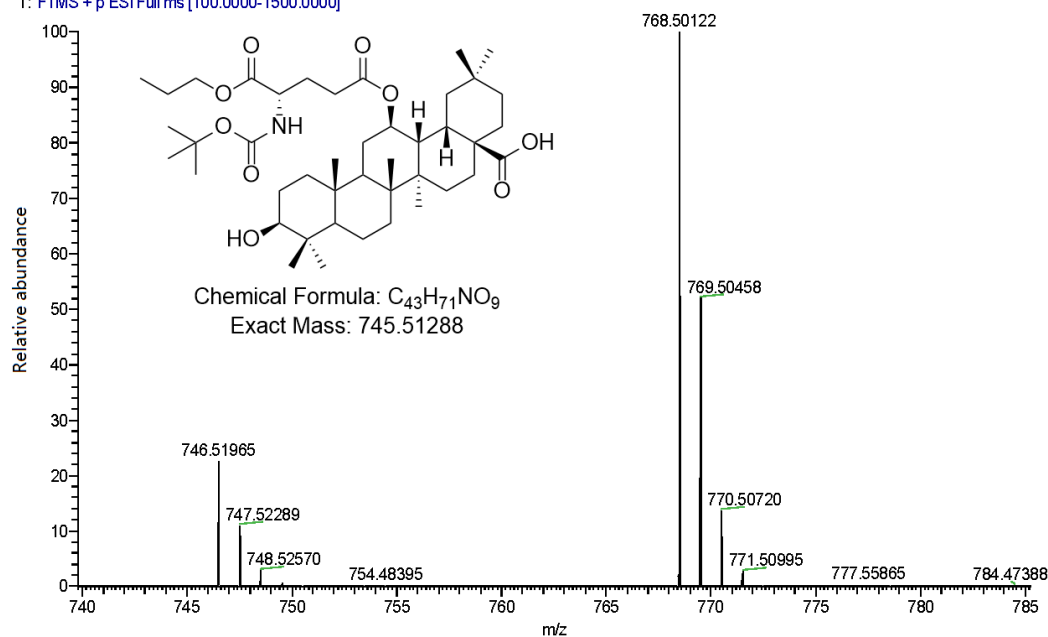
mh-8-28-2 #855 RT: 8.47 AV: 1 NL: 1.35E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
754.48578	754.48645	-0.674	8.5	C42 H69 O9 N Na	M+Na

Fig. S110. HRMS of compound **20b**

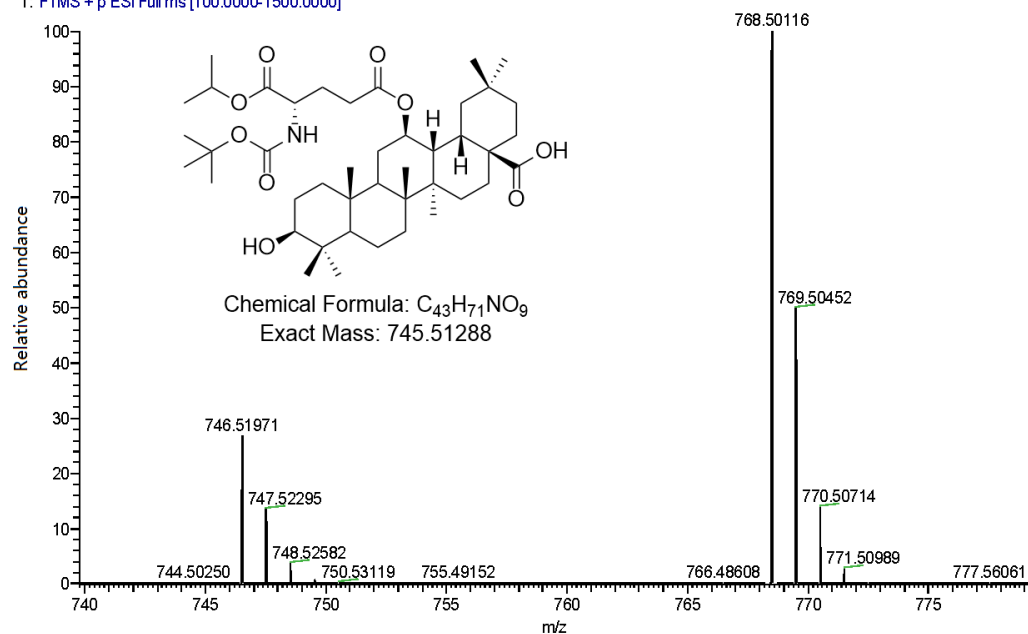
mh-8-28-3 #867 RT: 8.59 AV: 1 NL: 1.24E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
768.50122	768.50210	-0.884	8.5	C43 H71 O9 N Na	M+Na

Fig. S111. HRMS of compound **20c**

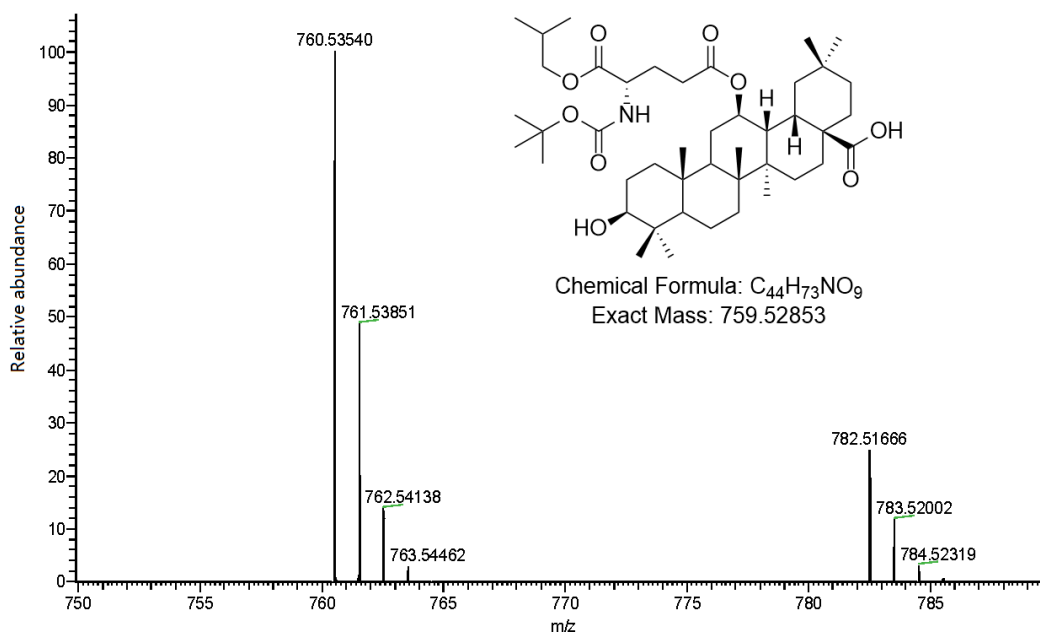
mh-8-28-4 #869 RT: 8.62 AV: 1 NL: 1.18E9
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
768.50116	768.50210	-0.944	8.5	C43 H71 O9 N Na	M+Na

Fig. S112. HRMS of compound **20d**

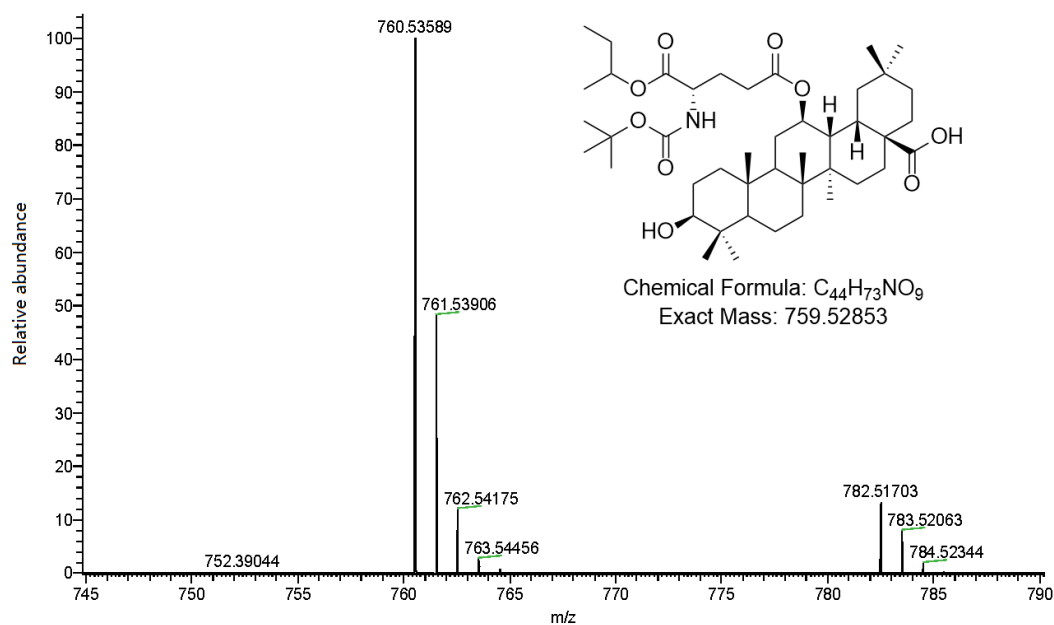
mh-8-28-5 #869 RT: 8.65 AV: 1 NL: 6.26E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
760.53540	760.53581	-0.409	8.5	C44 H74 O9 N	M+H

Fig. S113. HRMS of compound 20e

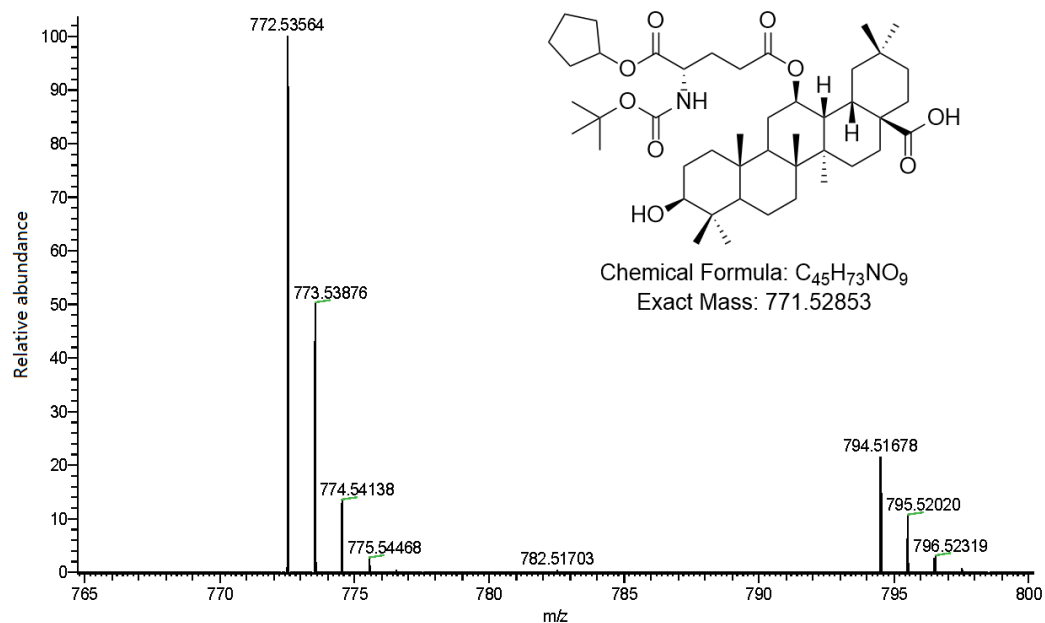
mh-8-28-6 #867 RT: 8.65 AV: 1 NL: 8.08E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
760.53589	760.53581	0.081	8.5	C44 H74 O9 N	M+H

Fig. S114. HRMS of compound 20f

mh-8-28-7 #871 RT: 8.68 AV: 1 NL: 6.44E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
772.53564	772.53581	-0.169	9.5	C45 H74 O9 N	M+H

Fig. S115. HRMS of compound **20g**