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Supporting Information

for

Efficient synthesis of piperazinyl amides of 18β-glycyrrhetinic acid

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Preparation procedures and analytical data of compounds 1, 4–9, 11, 13, 15–18

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Experimental

Materials and methods

Unless otherwise required, all reagents used in the experiment were purchased as commercial analytical grade and used without further purification. Melting points were obtained in open capillary tubes with a WRS-1B melting point apparatus and were uncorrected (Shen Guang Electric Appliances Co., Ltd., Shanghai, CHN). The structures of the synthetic compounds were confirmed by ^{1}H NMR and ^{13}C NMR spectra on 400/54Premium Shielded NMR Magnet System (Agilent Technologies, Santa Clara, CA, USA) with tetramethylsilane (TMS) as an internal standard. HRMS spectral data were collected from an Agilent 6200 Series TOF and 6500 Series Q-TOF LC/MS System B.05.01. (B5125) and Thermo Scientific LTQ-Orbitrap XL in positive ion modes (Agilent Technologies, Santa Clara, CA, USA). X-ray single-crystal structure determinations were carried out on a Bruker SMART APEX II CCD diffractometer (Bruker AXS GMBH, Karlsruhe, GER).

Synthesis of 18β–GA analogs

3β-Acetoxy-11-oxo-18β-olean-12-en-30-oic acid (**2**)

18β-Glycyrrhetinic acid (0.47 g, 1.0 mmol) was heated at 130 °C with acetic anhydride (2.04 g, 20 mmol) for 1 h. Then, H_2O was added to the cool solution. The product was filtered off and washed with cold H_2O.

A white solid; yield, 99.2%; m.p. 304.4.0-306.1 °C (literature [1]: 312.0-313.0 °C); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.69 (d, *J* = 1.7 Hz, 1H, CH-12), 4.50 (dt, *J* = 11.7, 2.8 Hz, 1H, CH-3), 2.77 (dd, *J* = 14.0, 4.0 Hz, 1H, CH-1), 2.35 (s, 1H, CH-9), 2.03 (s, 2H, acetyloxy CH_3), 1.35 (m, 3H, CH_3-27), 1.21 (s, 3H, CH_3-25), 1.14 (s, 3H, CH_3-26), 1.10 (s, 3H, CH_3-29), 0.86 (s, 6H, CH_3-23/24), 0.85 (s, 3H, CH_3-28), 0.77 (m, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.41 (C11), 181.77 (30), 171.08 (acetyloxy C=O), 169.55 (C13), 128.37 (C12), 80.61 (C3), 61.66 (C9), 54.97 (C5), 48.21 (C18), 45.44 (C14), 43.79 (C20), 43.17 (C8), 40.78 (C19), 38.73 (C1), 38.02 (C4), 37.67 (C22), 36.89 (C10), 32.66 (C7), 31.84 (C17), 30.86 (C21), 28.52 (C29), 28.44 (C28), 28.02 (C23), 26.43 (C2), 26.35 (C15), 23.54 (C16), 23.32 (C27), 21.32 (acetyloxy CH_3), 18.64 (C26), 17.33 (C6), 16.67 (C25), 16.39 (C24). HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{32}H_{49}O_5$: 513.3580, found: 513.3580.

General procedure for the preparation of compounds (**4**) and (**5**)

The compound **3** (0.44 g, 0.90 mmol) was dissolved in CH_2Cl_2 (30 mL) at 0 °C under stirring, then triethylamine (0.3 g, 3.00 mmol) and anhydrous piperazine (0.23 g, 2.70 mmol) were added. The reaction was stirred at 0 °C for 30 min. After reaction, the mixture was removed, and the residue was subjected to column chromatography (silica gel, CH_2Cl_2-methanol, 5:1) to yield compounds (**4**) and (**5**).

3β-Acetoxy-11-oxo-18β-olean-12-en-30-carbonyl piperazine (**4**) A white solid; yield, 36.1%; m.p. 237.2-239.0 °C (literature [2]: 160 °C-decomp.); ^{1}H NMR (400

MHz, Chloroform-*d*) δ 5.67 (s, 1H, CH-12), 4.49 (dd, *J* = 11.7, 4.8 Hz, 1H, CH-3), 3.61 (q, *J* = 4.7 Hz, 4H, piperazine CH_2×2), 2.85 (t, *J* = 5.0 Hz, 4H, piperazine CH_2×2), 2.77 (dt, *J* = 13.7, 3.6 Hz, 1H, CH-1), 2.33 (s, 1H, CH-9), 2.29 – 2.23 (m, 1H, CH-16), 2.16 (s, 3H, acetyloxy CH_3), 1.33 (s, 3H, CH_3-27), 1.20 (s, 3H, CH_3-25), 1.13 (s, 3H, CH_3-26), 1.10 (s, 3H, CH_3-29), 0.85 (s, 6H, CH_3-23/24), 0.79 (s, 3H, CH_3-28), 0.76 (m, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.01 (C11), 173.86 (C30), 171.03 (acetyloxy C=O), 169.67 (C13), 128.46 (C12), 80.59 (C3), 61.67 (C9), 54.99 (C5), 48.21(C18), 46.13 (piperazine C×2), 45.27 (C14), 43.77 (C20), 43.71 (C8), 43.26 (piperazine C×2), 38.78 (C19), 38.01 (C1/4), 37.73 (C22), 36.91 (C10), 33.38 (C7), 32.72 (C17), 31.76 (C21), 28.41 (C29), 28.02 (C28), 27.02 (C23), 26.69 (C2), 26.41 (C15), 23.54 (C16), 23.07 (C27), 21.32 (acetyloxy CH_3), 18.65 (C26), 17.35 (C6), 16.66 (C25), 16.41 (C24); HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{36}H_{57}N_2O_4$: 581.4318, found: 581.4316.

Bisamide (**5**) A white solid; yield, 64.6%; m.p. 211.4-212.0 °C. HRMS (*m*/*z*): $[M + Na]^+$ calcd. for $C_{68}H_{102}N_2NaO_8$: 1097.7534, found: 1097.7535.

3β-Acetyloxy -11-oxo-18β-olean-12-en-30-carbonyl piperazine (**4**)

Compound **8** (0.68 g, 1.0 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C under stirring. Trifluoroacetic acid (5 mL) was added, and the reaction was stirred at 0 °C for 3 h. After reaction, the mixture was made basic with a saturated Na_2CO_3 solution. This mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to give the desired product.

A white solid; yield, 94.1%; the chemical structures were characterized as above.

1H-Benzo[d][1,2,3]triazol-1-yl-3β-acetoxy-11-oxo-olean-12-en-30-oate (**6**)

Compound **2** (0.51 g, 1.0 mmol) was dissolved in acetonitrile (20 mL), then EDCl (0.23 g, 1.2 mmol), triethylamine (0.13 g, 1.2 mmol) and HOBt (0.16 g, 1.2 mmol) were added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give a residue which was treated with a mixture of ethanol and water. The solution was stirred at room temperature for 30 min, and a solid was obtained by filtration while washing with H_2O.

A white solid; yield, 97.8%; m.p. 208.7 °C - decomp. (literature [3]: 192-195 °C, decomp.); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 8.4 Hz, 1H, phenyl), 7.56 (t, *J* = 7.6 Hz, 1H, phenyl), 7.44 (t, *J* = 7.7 Hz, 1H, phenyl), 7.34 (d, *J* = 8.3 Hz, 1H, phenyl), 5.71 (s, 1H, CH-12), 3.22 (dd, *J* = 10.7, 5.5 Hz, 1H, OH-3), 2.77 (dt, *J* = 13.5, 3.6 Hz, 1H, CH-1), 2.39 – 2.23 (m, 2H, CH-9/16), 1.41 (s, 3H, CH_3-27), 1.15 (s, 3H, CH_3-25), 1.13 (s, 3H, CH_3-26), 1.00 (s, 3H, CH_3-29), 0.93 (s, 3H, CH_3-23), 0.80 (s, 3H, CH_3-24), 0.72 (d, *J* = 11.6 Hz, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.91 (C11), 172.51 (C30), 167.60 (C13), 143.54 (phenyl), 129.02 (phenyl), 128.83 (phenyl), 128.54 (C12), 124.82 (phenyl), 120.66, (phenyl) 107.81 (phenyl), 78.70 (C3), 61.83 (C9), 54.89 (C5), 48.20 (C18), 45.36 (C20), 44.36(C8), 43.15(C19), 40.85 (C1), 39.11 (C4), 37.75 (C22), 37.06 (C10), 32.72 (C7), 31.97 (C17),

31.16 (C21), 28.54 (C29), 28.08 (C28), 28.02 (C23), 27.25 (C2), 26.34 (C15/16), 23.48 (C27), 18.67 (C26), 17.45 (C6), 16.34 (C25), 15.57 (C24); HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{36}H_{50}N_3O_4$: 588.3801, found: 588.3801.

1H-Benzo[d][1,2,3]triazol-1-yl-3β-hydroxy-11-oxo-olean-12-en-30-oate (**7**)

18β-Glycyrrhetinic acid (0.47 g, 1.0 mmol) was dissolved in acetonitrile (20 mL), then EDCl (0.23 g, 1.2 mmol), triethylamine (0.13 g, 1.2 mmol) and HOBt (0.16 g, 1.2 mmol) were added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give a residue which was treated with a mixture of ethanol and water. The solution was stirred at room temperature for 30 min, and a solid was obtained by filtration while washing with H_2O.

A white solid; yield, 97.2%; m.p. 263.4-264.4 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.4 Hz, 1H, phenyl), 7.57 (t, *J* = 7.6 Hz, 1H, phenyl), 7.44 (t, *J* = 7.7 Hz, 1H, phenyl), 7.35 (d, *J* = 8.3 Hz, 1H, phenyl), 5.72 (s, 1H, CH-12), 4.52 (dd, *J* = 11.6, 4.8 Hz, 1H, CH-3), 2.78 (dt, *J* = 13.8, 3.7 Hz, 1H, CH-1), 2.37 (s, 1H, CH-9), 2.05 (s, 3H, acetyloxy CH_3), 1.41 (s, 3H, CH_3-27), 1.21 (s, 3H, CH_3-25), 1.16 (s, 6H, CH_3-26/29), 0.94 (s, 3H, CH_3-23), 0.88 (s, 6H, CH_3-24/28), 0.80 (m, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.76 (C11), 172.51 (30), 171.01 (acetyloxy C=O), 167.60 (C13), 143.55 (phenyl), 128.99 (phenyl), 128.81 (phenyl), 128.54 (C12), 124.80 (phenyl), 120.67 (phenyl), 107.80 (phenyl), 80.53 (C3), 61.74 (C9), 54.98 (C5), 48.19 (C18), 45.37 (C14), 44.35 (C20), 43.14 (C8), 40.84 (C19), 38.74 (C1), 38.02

(C4), 37.74 (C22), 36.91 (C10), 32.67 (C7), 31.97 (C17), 31.17 (C21), 28.53 (C29), 28.02 (C28/23), 26.33 (C2/15), 23.52 (C16), 23.42 (C27), 21.32 (acetyloxy CH_3), 18.67 (C26), 17.34 (C6), 16.66 (C25), 16.38 (C24); HRMS (*m*/*z*): ($M + H^+$) calcd. for $C_{38}H_{52}N_3O_5$: 630.3907, found: 630.3904.

tert-Butyl 4-(3β-acetoxy-11-oxo-18β-olean-12-en-30-carbonyl)piperazine-1-carboxylate (**8**)

Method A: Compound **2** (0.51 g, 1.0 mmol) was dissolved in acetonitrile (20 mL), then EDCl (0.23 g, 1.2 mmol), triethylamine (0.13 g, 1.2 mmol) and HOBt (0.16 g, 1.2 mmol) were added.The mixture was stirred at room temperature for 20 min. The 1-Boc-piperazine (0.46 g, 2.5 mmol) was added, and the mixture was stirred under reflux for 10 h. The solvent was removed under vacuum to give a residue which was treated with a mixture of ethanol and water. The solution was stirred at room temperature for 30 min, and a solid was obtained by filtration while washing with H_2O.

Method B: Compound **9** (0.64 g, 1.0 mmol) was heated at 130 °C with acetic anhydride (2.04 g, 20 mmol) for 1 h. Then, H_2O was added to the cool solution. The product was filtered off and washed with cold H_2O.

A white solid; yield, 95.7%; m.p. 221.6-223.0 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.66 (s, 1H, CH-12), 4.50 (dd, *J* = 11.7, 4.7 Hz, 1H, CH-3), 3.66 – 3.50 (m, 4H, piperazine CH_2×2), 3.40 (d, *J* = 5.1 Hz, 4H, piperazine CH_2×2), 2.79-2.74 (m, 1H, CH-1), 2.33 (s, 1H, CH-9), 2.30 – 2.22 (m, 1H, CH-16), 2.03 (s, 3H, acetyloxy CH_3), 1.45 (s, 9H, tert-butyl CH_3×3), 1.33 (s, 3H, CH_3-27), 1.20 (s, 3H,

CH_3-25), 1.14 (s, 3H, CH_3-26), 1.09 (s, 3H, CH_3-29), 0.85 (s, 6H, CH_3-23/24), 0.79 (s, 3H, CH_3-28), 0.76 (m, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.95 (C11), 174.12 (C30), 171.03 (acetyloxy C=O), 169.46 (C13), 154.52 (Boc C=O), 128.50 (C12), 80.58 (tert-butyl C), 80.24 (C3), 61.67 (C9), 54.99 (C5), 48.12 (C18), 45.27 (C14), 43.87 (piperazine C×2), 43.75 (C20), 43.25 (C8/19), 38.77 (C1/C4), 38.01 (piperazine C×2), 37.70 (C22), 36.90 (C10), 33.22 (C7), 32.72 (C17), 31.75 (C21), 28.40 (C29), 28.35 (tert-butyl CH_3×3), 28.02 (C28), 27.05 (C23), 26.68 (C2), 26.38 (C15), 23.54 (C16), 23.08 (C27), 21.31 (acetyloxy CH_3), 18.65 (C26), 17.35 (C6), 16.66 (C25), 16.40 (C24); HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{41}H_{65}N_2O_6$: 681.4843, found: 681.4841.

tert-Butyl 4-(3β-hydroxyl-11-oxo-18β-olean-12-en-30-carbonyl)piperazine-1-carboxylate (**9**)

18*β*-Glycyrrhetinic acid (0.47 g, 1.0 mmol) was dissolved in acetonitrile (20 mL), then EDCl (0.23 g, 1.2 mmol), triethylamine (0.13 g, 1.2 mmol) and HOBt (0.16 g, 1.2 mmol) were added. The mixture was stirred at room temperature for 20 min. The 1-Boc-piperazine (0.46 g, 2.5 mmol) was added, and the mixture was stirred under reflux for 10 h. The solvent was removed under vacuum to give a residue which was treated with a mixture of ethanol and water. The solution was stirred at room temperature for 30 min, and a solid was obtained by filtration while washing with H_2O.

A white solid; yield, 94.3%; m.p. 224.3-225.7 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.66 (s, 1H, CH-12), 3.63-3.52 (m, 4H, piperazine CH_2×2), 3.39 (t, *J* = 5.2

Hz, 4H, piperazine CH_2×2), 3.22-3.18 (m, 1H, OH-3), 2.79-2.74 (m, 1H, CH-1), 2.31 (s, 1H, CH-9), 2.30-2.23 (m, 1H, CH-16), 1.45 (s, 9H, tert-butyl CH_3×3), 1.34 (s, 3H, CH_3-27), 1.20 (s, 3H, CH_3-25), 1.11 (s, 3H, CH_3-26), 1.10 (s, 3H, CH_3-29), 0.98 (s, 3H, CH_3-23), 0.79 (s, 3H, CH_3-24), 0.78 (s, 3H, CH_3-28), 0.68 (d, *J* = 11.6 Hz, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.10 (C11), 174.13 (C30), 169.40 (C13), 154.53 (Boc C=O), 128.56 (C12), 80.25 (C3), 78.75 (tert-butyl C), 61.77 (C9), 54.92 (C5), 48.08 (C18), 45.26 (C14), 43.88 (C20), 43.82 (piperazine C×2), 43.26 (C8/C19), 39.12 (C1/C4), 39.10 (piperazine C×2), 37.70 (C22), 37.06 (C10), 33.16 (C7), 32.79 (C17), 31.75 (C21), 28.40 (C29), 28.36 (tert-butyl CH_3×3), 28.07 (C28), 27.28 (C23), 27.05 (C2), 26.69 (C15), 26.39 (C16), 23.14 (C27), 18.66 (C26), 17.46 (C6), 16.36 (C25), 15.56 (C24); HRMS (*m*/*z*): $[M + H]^+$ calcd. For $C_{39}H_{63}N_2O_5$: 639.4737, found: 639.4736.

N-(2-chloroacetyl) piperazinyl 3β-(2-chloroacetoxy)-11-oxo-18β-olean-12-en-29-amide (**11**)

Compound **9** (0.64 g, 1.0 mmol) was heated at 130 ºC with chloroacetic anhydride (3.42 g, 20 mmol) for 1 h. Then, H_2O was added to the cool solution. The product was filtered, washed with cold H_2O and dried.

A white solid; yield, 99%; m.p. 177.4-175.7 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.67 (s, 1H, CH-12), 4.60 (dd, *J* = 11.8, 4.7 Hz, 1H, CH-3), 4.14 – 3.99 (m, 4H, piperazine CH_2×2), 3.73 – 3.66 (m, 4H, piperazine CH_2×2), 3.66 – 3.55 (m, 2H, CH_2-Cl), 3.53 (d, *J* = 5.4 Hz, 2H, CH_2-Cl), 2.81 (dt, *J* = 13.8, 3.7 Hz, 1H, CH-1), 2.35 (s, 1H, CH-9), 2.30 (dd, *J* = 13.4, 3.8 Hz,

1H, CH-16), 1.35 (m, 3H, CH_3-27), 1.23 (s, 3H, CH_3-25), 1.15 (s, 3H, CH_3-26), 1.11 (s, 3H, CH_3-29), 0.89 (s, 6H, CH_3-23/24), 0.81 (s, 3H, CH_3-28), 0.79 (m, 1H, CH-5); ^{13}C NMR (101 MHz, chloroform-*d*) δ 199.81 (C11), 174.25 (C30), 169.44 (C13), 167.12 (chloroacetoxy C=O), 165.32 (chloroacetoxy C=O), 128.50 (C12), 82.97 (C3), 61.60 (C9), 54.93 (C5), 48.04 (C18), 46.27 (C14), 45.25 (piperazine C), 43.92 (piperazine C), 43.83 (C20), 43.26 (C8), 42.20 (C19), 41.24 (C1), 40.67 (C-Cl), 38.66 (C4), 38.21(piperazine C×2), 37.67 (C22), 36.86 (C10), 32.98 (C7), 32.66 (C17), 31.75 (C21), 28.39 (C29), 28.00 (C28), 27.02 (C23), 26.63 (C2), 26.34 (C15), 23.39 (C16), 23.10 (C27), 22.63, 18.64 (C26), 17.30 (C6), 16.60 (C25), 16.40 (C24); HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{38}H_{57}Cl_2N_2O_5$: 691.3645, found: 691.3641.

3β-(2-Chloroacetoxy)-11-oxo-18β-olean-12-en-30-oic acid (**12**)

18β-Glycyrrhetinic acid (0.47 g, 1.0 mmol) was heated at 130 °C with chloroacetic anhydride (3.42 g, 20 mmol) for 1 h. Then, H_2O was added to the cool solution. The product was filtered off and washed with cold H_2O.

A white solid; yield, 98.0%; m.p. 259.0 °C - decomp. (literature [1]: 260.8–261.8 °C); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.70 (s, 1H, CH-12), 4.59 (dd, *J* = 11.8, 4.8 Hz, 1H, CH-3), 4.05 (d, *J* = 2.3 Hz, 2H, CH_2-Cl), 2.81 (m, 1H, CH-1), 2.35 (s, 1H, CH-9), 2.17 (dd, *J* = 13.6, 4.1 Hz, 1H, CH-16), 1.36 (m, 3H, CH_3-27), 1.21 (s, 3H, CH_3-25), 1.15 (s, 3H, CH_3-26), 1.11 (s, 3H, CH_3-29), 0.88 (s, 6H, CH_3-23/24), 0.82 (s, 3H, CH_3-28) , 0.78 (m, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.26 (C11), 181.51(C30), 169.59 (C13), 167.12 (acetyloxy

C=O), 128.37 (C12), 83.00 (C3), 61.60 (C9), 54.94 (C5), 48.21 (C18), 45.43 (C14), 43.78 (C20), 43.18 (C8), 41.24 (C19), 40.80 (C-Cl), 38.64 (C1), 38.23 (C4), 37.67 (C22), 36.87 (C10), 32.62 (C7), 31.84 (C17), 30.87 (C21), 28.52 (C29), 28.43 (C28), 28.00 (C23), 26.43 (C2), 26.34 (C15), 23.41 (C16), 23.35 (C27), 18.64 (C26), 17.30 (C6), 16.61 (C25), 16.39 (C24); HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{32}H_{48}ClO_5$: 547.3190, found: 547.3188.

3*β-(2-Morpholinoacetoxy)-11-oxo-olean-12-ene-30-oic acid* (**13**)

Compound **12** (0.55 g, 1.0 mmol), morpholine (0.13 g, 1.5 mmol), K_2CO_3 (0.69 g, 5.0 mmol) and a catalytic amount of I_2 in absolute ethanol (15 mL) was stirred under reflux for 12 h. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in ethanol/H_2O mixture and the white precipitate was collected by filtration.

A white solid; yield, 92.0%; m.p.275.3-276.4 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.72 (t, *J* = 3.0 Hz, 1H, CH-12), 4.60 (dd, *J* = 11.2, 5.5 Hz, 1H, CH-3), 3.76 (d, *J* = 4.9 Hz, 4H, morpholine), 3.26 – 3.20 (m, 2H, CH_2), 2.80 (d, *J* = 12.9 Hz, 1H, CH-1), 2.63 (s, 4H, morpholine), 2.37 (t, *J* = 3.0 Hz, 1H, CH-9), 2.19 (d, *J* = 13.5 Hz, 1H, CH-16), 2.05 – 1.01 (m, 17H), 1.37 (s, 3H, CH_3-27), 1.27 (s, 3H, CH_3-25), 1.16 (s, 3H, CH_3-26), 1.13 (s, 3H, CH_3-29), 0.87 (s, 3H, CH_3-23/24), 0.83 (s, 3H, CH_3-28), 0.80 (s, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.25 (C11), 181.03 (C30), 169.70 (C13), 169.51 (acetoxy, C=O), 128.40 (C12), 81.09 (C3), 66.67 (morpholine C×2), 61.64 (C9), 59.53 (acetoxy, CH_2), 54.93 (C5), 53.14 (morpholine C×2), 48.25 (C18), 45.43 (C14), 43.75 (C20), 43.19

(C8), 40.90 (C19), 38.68 (C1), 38.07 (C4), 37.70 (C22), 36.89 (C10), 32.65 (C7), 31.86 (C17), 30.93 (C21), 28.55 (C29), 28.44 (C28), 28.13 (C23), 26.46 (C2), 26.37 (C15), 23.66 (C16), 23.36 (C27), 18.66 (C26), 17.36 (C6), 16.78 (C25), 16.42 (C24); HRMS (*m*/*z*): $[M + Na]^+$ calcd. For $C_{36}H_{56}NO_6$: 598.4108, found: 598.4150.

tert-Butyl 4-(3β-(2-morpholinoacetoxy)-11-oxo-18β-olean-12-en-30-carbonyl)-piperazine-1-carboxylate (**14**)

Compound **13** (0.60 g, 1.0 mmol) was dissolved in acetonitrile (20 mL), then EDCl (0.23 g, 1.2 mmol), triethylamine (0.13 g, 1.2 mmol) and HOBt (0.16 g, 1.2 mmol) were added.The mixture was stirred at room temperature for 20 min. The 1-Boc-piperazine (0.46 g, 2.5 mmol) was added, and the mixture was stirred under reflux for 10 h. The solvent was removed under vacuum to give a residue which was treated with a mixture of ethanol and water. The solution was stirred at room temperature for 30 min, and a solid was obtained by filtration while washing with H_2O.

A white solid; yield, 93.9%; m.p. 204.3-205.3 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.72 (t, *J* = 3.4 Hz, 1H, CH-12), 4.69 – 4.58 (m, 1H, CH-3), 3.79 (dt, *J* = 6.5, 3.3 Hz, 4H, morpholine CH_2×2), 3.72 – 3.59 (m, 4H, piperazine CH_2×2), 3.45 (d, *J* = 5.4 Hz, 4H, piperazine CH_2×2), 3.25 (q, *J* = 2.2 Hz, 2H, Morpholinoacetoxy CH_2), 2.84 (d, *J* = 13.6 Hz, 1H, CH-1), 2.64 (q, *J* = 5.1, 4.6 Hz, 4H, morpholine CH_2×2), 2.39 (d, *J* = 3.3 Hz, 1H, CH-9), 2.33 (d, *J* = 13.5 Hz, 1H, CH-16), 1.56 (s, 9H, tert-butyl CH_3×3),1.36 (s, 3H, CH_3-27),

1.27 (s, 3H, CH_3-25), 1.19 (s, 3H, CH_3-26), 1.15 (s, 3H, CH_3-29), 0.91 (s, 6H, CH_3-23/24), 0.84 (s, 3H, CH_3-28), 0.82(m, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.88 (C11), 174.10 (C30), 169.96 (acetyloxy C=O), 169.49 (C13), 154.51 (Boc C=O), 128.49 (C12), 81.01 (tert-butyl C), 80.23 (C3), 66.80 (morpholine C×2), 61.63 (C9), 59.75 (acetoxy CH_2), 54.93 (C5), 53.27 **(**morpholine C×2), 48.10 (C18), 45.26 (C14), 43.86 (piperazine C×2), 43.78 (C20), 43.26 (C8/19), 38.71(C1/C4), 38.04 (piperazine C×2), 37.70 (C22), 36.88 (C10), 33.18 (C7), 32.70 (C17), 31.75 (C21), 28.40 (C29), 28.35 (tert-butyl CH_3×3), 28.12 (C28), 27.05 (C23), 26.67 (C2), 26.38 (C15), 23.65 (C16), 23.09 (C27), 18.65 (C26), 17.35 (C6), 16.75 (C25), 16.40 (C24); HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{45}H_{72}N_3O_7$: 766.5370, found: 766.5301.

4-(3β-(2-Chloroacetoxy)-11-oxo-18β-olean-12-en-30-carbonyl)piperazine-1-carboxylic acid (**15**)

Chloroacetic anhydride (1.37 g, 8.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) was heated at 130 ºC in toluene for 20 min with a constant water separator. Then, compound **9** (0.64 g, 1.0 mmol) was added to the hot stirred suspension and the reaction mixture was stirred for another 1 h at 130 ºC. On removal of the toluene, the H_2O (50 ml) was added to the cool residue, After stirring for 1 h at room temperature, the white product was filtered, washed with cold H_2O and dried.

A white solid; yield, 96.3%; m.p.205.7.0-206.6 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.66 (s, 1H, CH-12), 4.59 (dd, *J* = 11.8, 4.7 Hz, 1H, CH-3), 4.15 – 3.97 (m, 4H, piperazine CH_2×2), 3.65 (s, 4H, piperazine CH_2×2), 3.52 (s, 2H,

CH_2-Cl), 2.85 – 2.75 (m, 1H, CH-1), 2.34 (s, 1H, CH-9), 2.28 (d, *J* = 12.1 Hz, 1H, CH-16), 1.34 (m, 3H, CH_3-27), 1.22 (s, 3H, CH_3-25), 1.14 (s, 3H, CH_3-26), 1.10 (s, 3H, CH_3-29), 0.88 (s, 6H, CH_3-23/24), 0.80 (s, 3H, CH_3-28), 0.78 (m, 1H, CH-5); ^{13}C NMR (101 MHz, chloroform-*d*) δ 199.83 (C11), 174.27 (C30), 169.43 (C13), 167.13 (chloroacetoxy C=O), 165.34 (-COOH), 128.51 (C12), 82.99 (C3), 61.62 (C9), 54.95 (C5), 48.06 (C18), 46.28 (C14), 45.26 (piperazine C), 43.93 (piperazine C), 43.83 (C20), 43.27 (C8), 42.21 (C19), 41.23 (C1), 40.65 (C-Cl), 38.67(C4), 38.22 (piperazine C×2), 37.67(C22), 36.88 (C10), 33.01 (C7), 32.68 (C17), 31.76 (C21), 28.39 (C29), 28.00 (C28), 27.03 (C23), 26.65 (C2), 26.35 (C15), 23.40 (C16), 23.11 (C27), 18.65 (C26), 17.31 (C6), 16.60 (C25), 16.40 (C24); HRMS (*m*/*z*): [M + H] $^+$ calcd. for $C_{37}H_{56}ClN_2O_6$: 659.3827, found: 659.3873.

4-(3β-(2-Morpholinoacetoxy)-11-oxo-18β-olean-12-en-30-carbonyl)piperazine-1-carboxylic acid (**16**)

Compound **15** (0.66 g, 1.0 mmol), morpholine (0.13 g, 1.5 mmol), K_2CO_3 (0.69 g, 5.0 mmol) and a catalytic amount of I_2 in absolute ethanol (15 mL) was stirred under reflux for 12 h. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in ethanol/H_2O mixture and the white precipitate was collected by filtration.

A white solid; yield, 91.2%; m.p. 196.0-196.9 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.66 (d, *J* = 2.9 Hz, 1H, CH-12), 4.58 (dd, *J* = 11.7, 4.3 Hz, 1H, CH-3), 3.70 (t, *J* = 4.5 Hz, 4H, morpholine CH_2×2), 3.60 (s, 8H, piperazine CH_2×4), 3.26 –

3.16 (m, 2H, morpholinoacetoxy CH_2), 2.86 – 2.74 (m, 1H, CH-1), 2.52 (d, *J* = 5.2 Hz, 4H, morpholine CH_2×2), 2.33 (s, 1H, CH-9), 2.27 (d, *J* = 13.2 Hz, 1H, CH-16),1.34 (s, 3H, CH_3-27), 1.21 (s, 3H, CH_3-25), 1.14 (s, 3H, CH_3-26), 1.09 (s, 3H, CH_3-29), 0.87 (s, 6H, CH_3-23/24), 0.79 (s, 3H, CH_3-28), 0.77(m, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.84 (C11), 174.27 (C30), 169.52 (C13), 167.71 (acetyloxy C=O), 167.13 (COOH), 128.48 (C12), 82.98 (C3), 66.76 (morpholine C×2), 61.62 (C9), 61.45 (acetoxy CH_2), 54.95 (C5), 53.44 (morpholine C×2), 48.10 (C18), 45.26 (C14), 43.91 (piperazine C×2), 43.79 (C20), 43.27 (C8), 41.86 (19), 41.23 (C1), 38.66 (C4), 38.22 (piperazine C×2), 37.68 (C22), 36.87 (C10), 33.09 (C7), 32.67 (C17), 31.76 (C21), 28.40 (C29), 28.00 (C28), 27.04 (C23), 26.66 (C2), 26.36 (C15), 23.40 (C16), 23.11 (C27), 18.64 (C26), 17.31 (C6), 16.60 (C25), 16.40 (C24); HRMS (Methanol as solvent, *m*/*z*): $[M_{Methyl\ ester} + H]^+$ calcd. for $C_{42}H_{66}N_3O_7$: 724.4901, found: 724.9726.

3β-(2-Morpholinoacetoxy)-11-oxo-18β-olean-12-en-30-carbonyl piperazine (**17**)

Compound **14** (0.77g, 1.0 mmol) or compound **16** (0.71 g, 1.0 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C under stirring. Trifluoroacetic acid (5 mL) was added, and the reaction was stirred at 0 °C for 3 h. After reaction, the mixture was made basic with a saturated Na_2CO_3 solution. This mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to give the desired product. A white solid; yield, 91.7%; m.p. 215.9-216.7 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.70 (t, *J* = 3.2 Hz, 1H, CH-12), 4.60 (dt, *J* = 11.2, 4.7 Hz, 1H, CH-3), 3.76 (dt, *J* = 6.7, 3.3 Hz, 4H, morpholine CH_2×2), 3.62 (t, *J* = 5.5 Hz, 4H, piperazine

CH_2×2), 3.21 (dd, *J* = 4.5, 2.4 Hz, 2H, morpholinoacetoxy CH_2), 2.91 – 2.84 (m, 4H, piperazine CH_2×2), 2.81 (d, *J* = 13.0 Hz, 1H, CH-1), 2.60 (t, *J* = 5.2 Hz, 4H, morpholine CH_2×2), 2.36 (t, *J* = 3.3 Hz, 1H, CH-9), 2.30 (d, *J* = 13.5 Hz, 1H, CH-16), 1.36 (s, 3H, CH_3-27), 1.23 (s, 3H, CH_3-25), 1.16 (s, 3H, CH_3-26), 1.12 (s, 3H, CH_3-29), 0.88 (s, 6H, CH_3-23/24), 0.82 (s, 3H, CH_3-28), 0.79 (s, 1H, CH-5); ^{13}C NMR (101 MHz, cdcl$_3$) δ 199.95 (C11), 173.84 (C30), 170.01 (acetyloxy C=O), 169.73 (C13), 128.47 (C12), 81.03 (C3), 66.83 (morpholine C×2), 61.65 (C9), 59.78 (morpholinoacetoxy CH_2), 54.95 (C5), 53.30 (morpholine C×2), 48.23(C18), 46.30 (piperazine C×2), 45.28 (C14), 43.79 (C20), 43.75 (C8), 43.28 (piperazine C×2), 38.75 (C19), 38.06 (C1/4), 37.75 (C22), 36.91 (C10), 33.40 (C7), 32.71 (C17), 31.77 (C21), 28.43 (C29), 28.13 (C28), 27.05 (C23), 26.71 (C2), 26.44 (C15), 23.66 (C16), 23.11 (C27), 18.67 (C26), 17.37 (C6), 16.77 (C25), 16.42 (C24) ; HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{40}H_{64}N_3O_5$: 666.4846, found: 666.4795.

3β-Acetoxy-30-(4-(3-fluorobenzoyl)-1-piperazinyl)-olean-12-ene-11,30-dione (**18**)

Compound **4** (0.58 g, 1.0 mmol) and triethylamine (0.13 g, 1.2 mmol) were dissolved in CH_2Cl_2 (20 mL) at 0 °C under stirring. 3-fluorobenzoyl chloride (0.158 g, 1.0 mmol) was added, and the reaction was stirred at room temperature for 3 h. After reaction, the mixture was washed twice with water. The organic layer was dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The crude product was then chromatographed on silica

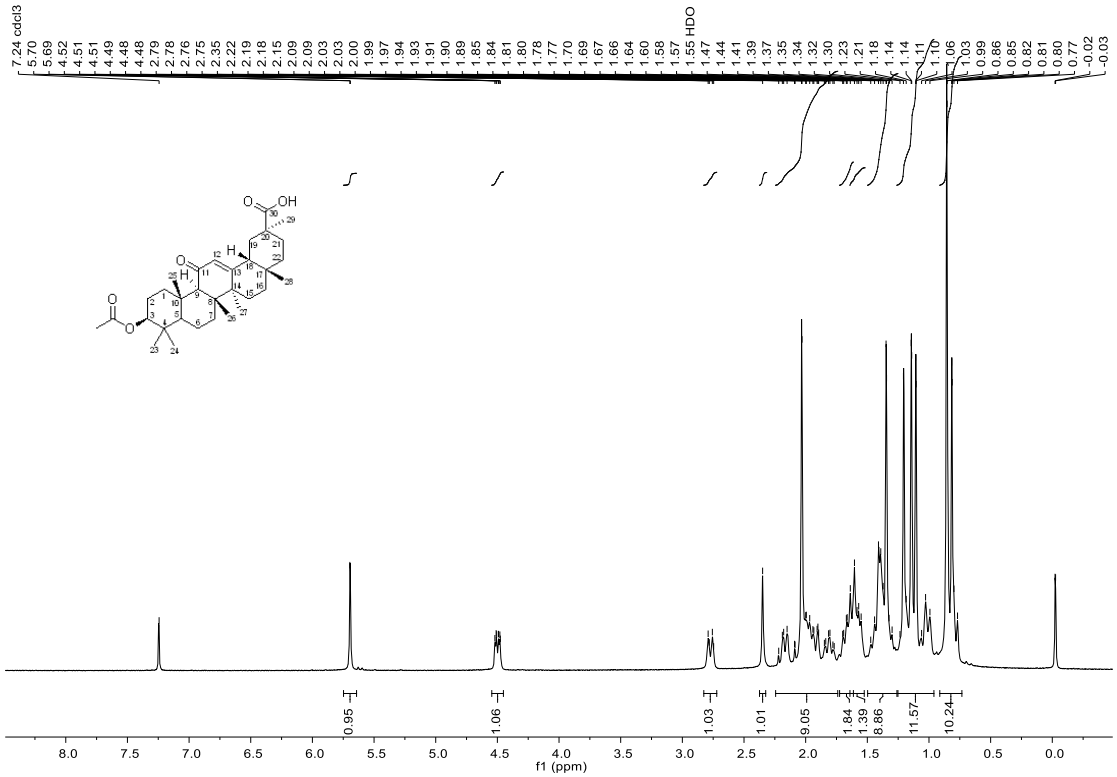
(DCM-methanol, 20:1).

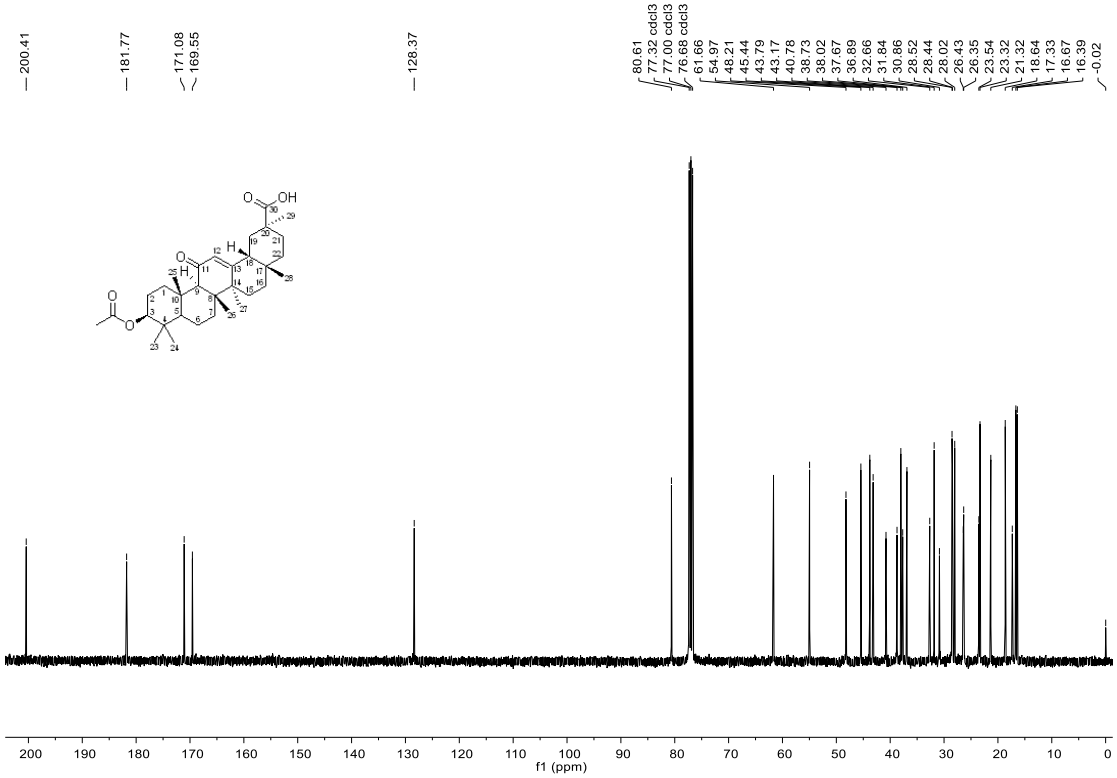
A white solid; yield, 88.2%; m.p. 234.1-225.9 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (td, *J* = 7.8, 5.6 Hz, 1H, phenyl), 7.23 – 7.09 (m, 3H, phenyl), 5.68 (s, 1H, CH-12), 4.52 (dd, *J* = 11.6, 4.7 Hz, 1H, CH-3), 3.71 – 3.45 (m, 8H, morpholine CH_2×4), 2.79 (dt, *J* = 13.5, 3.6 Hz, 1H, CH-1), 2.35 (s, 1H, CH-9), 2.32 – 2.23 (m, 1H, CH-16), 2.05 (s, 3H, acetyloxy CH_3), 1.35 (s, 3H, CH_3-27), 1.25 (s, 3H, CH_3-25), 1.24 (s, 3H, CH_3-26), 1.16 (s, 3H, CH_3-29), 1.12 (s, 3H, CH_3-23), 0.88 (s, 3H, CH_3-24), 0.82 (s, 3H, CH_3-28), 0.79 (m, 1H, CH-5); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.92 (C11), 174.25 (C30) – acetyloxy C=O), 169.31 (C13), 169.06 (benzoyl), 169.04 (benzoyl), 163.78 (C-F), 161.31 (C-F), 137.17 (phenyl), 137.10 (phenyl), 130.52 (phenyl), 130.44 (phenyl), 128.53 (C12), 122.73 (phenyl), 122.70 (phenyl), 117.21 (phenyl), 117.01 (phenyl), 114.56 (phenyl), 114.33 (phenyl), 80.56 (C3), 61.69 (C9), 55.00 (C5), – (C18), 45.28 (C14), 43.91 (C20), 43.70 (morpholine), 43.26 (C8), 38.78 (C19), 38.02 (C1/4), 37.67 (C22), 36.91 (C10) – (C7), 32.72 (C17), 31.78 (C21), 28.39 (C29), 28.02 (C28), 27.04 (C23), 26.66 (C2), 26.37 (C15), 23.54 (C16), 23.08 (C27), 21.32 (acetoxy CH_3), 18.65 (C26), 17.35 (C6), 16.67 (C25), 16.41 (C24); HRMS (*m*/*z*): $[M + H]^+$ calcd. for $C_{43}H_{60}FN_2O_5$: 703.4486, found: 703.4486.

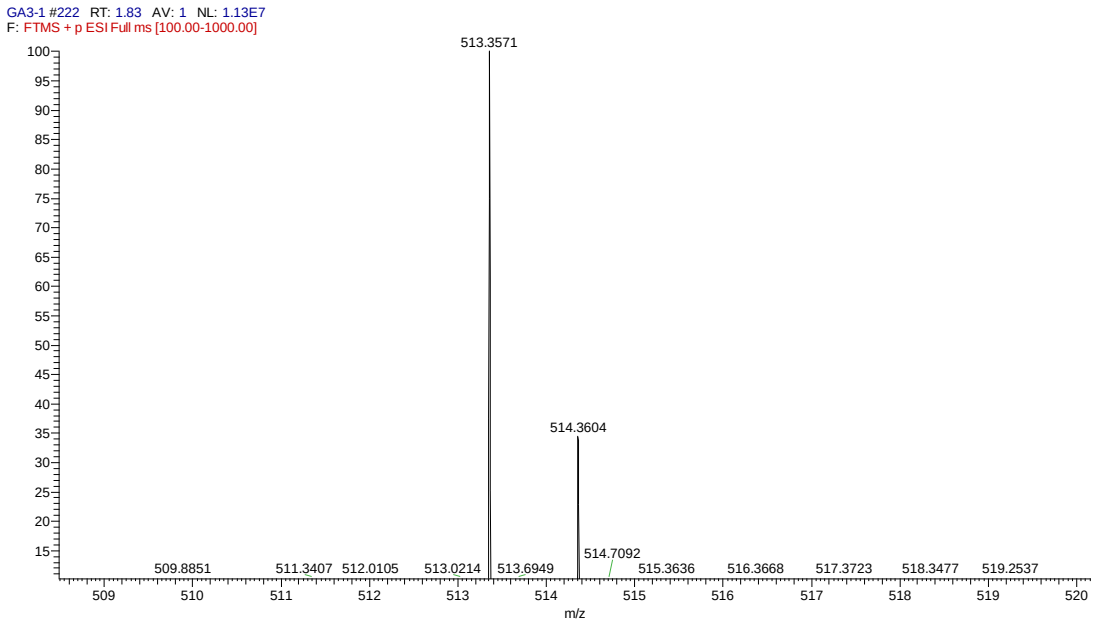
*Crystal structure analysis of compound (**18**)*

The single crystal X-ray diffraction data of compound **18** was collected on a Bruker SMART APEX II CCD detector employing graphitemonochromated Cu Kα radiation (λ = 1.54178 Å) at 273 (2) K. The structures were solved by direct methods using SHELXL-97 and refined using full-matrix least-squares calculation on F2 using SHELXL-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atom positions were geometrically idealized and allowed to ride on their parent atoms. Crystallographic data for compound **18** has been deposited at the Cambridge Crystallographic Data Centre. CCDC 1904891. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

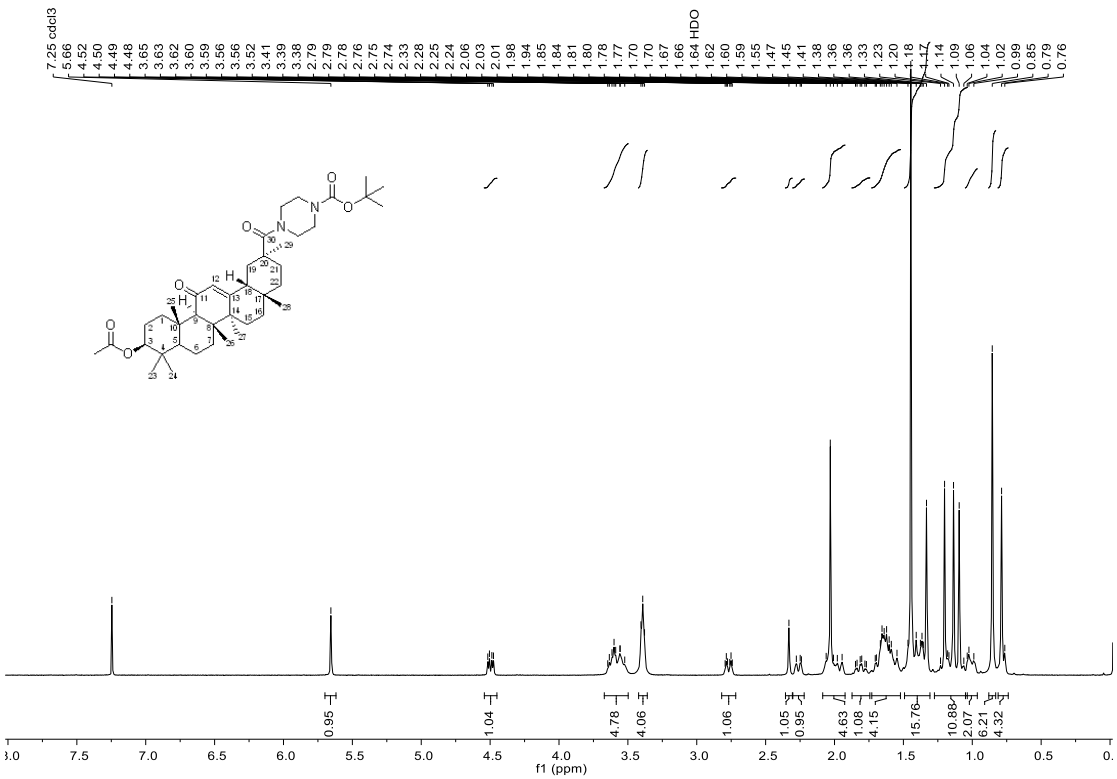
3β-Acetoxy-11-oxo-18β-olean-12-en-30-oic acid (**2**)

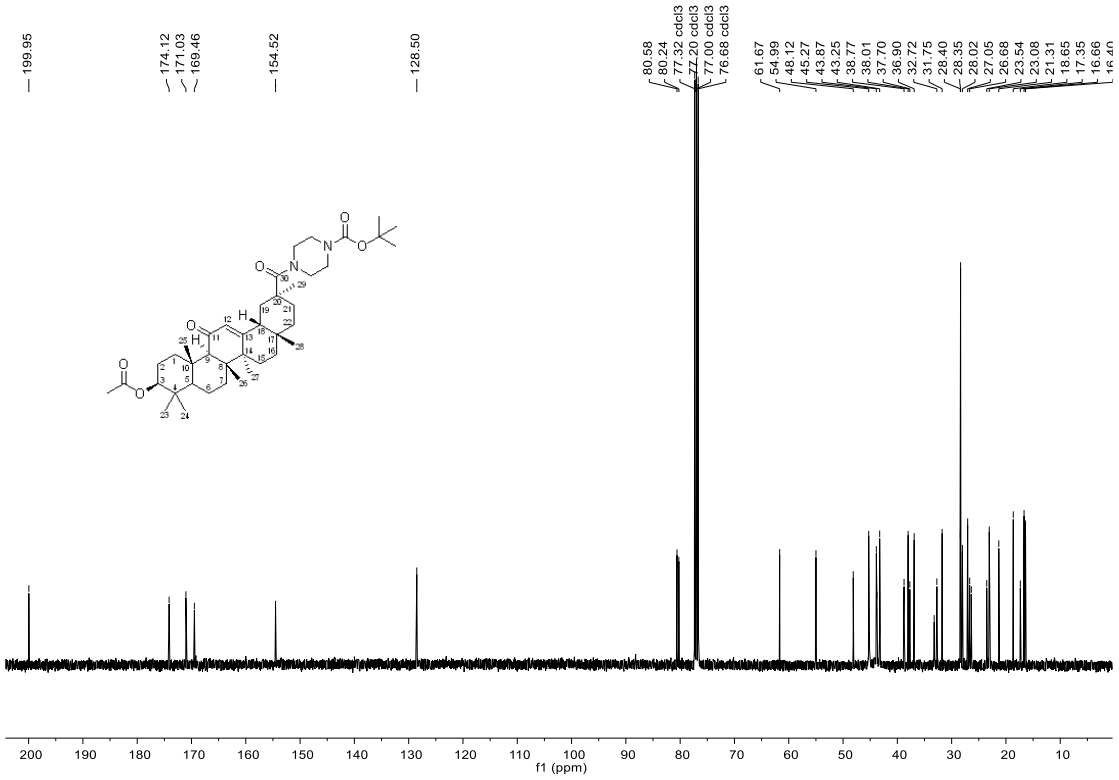






tert-Butyl 4-(3*β*-acetoxy-*11*-oxo-18*β*-olean-12-en-30-carbonyl)piperazine-1-carboxylate (**8**)

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80.24
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61.67
54.99
48.12
45.27
43.87
43.25
38.77
38.01
37.70
36.90
32.72
31.75
28.40
28.35
28.02
27.05
26.68
23.54
23.08
21.31
18.65
17.35
16.66
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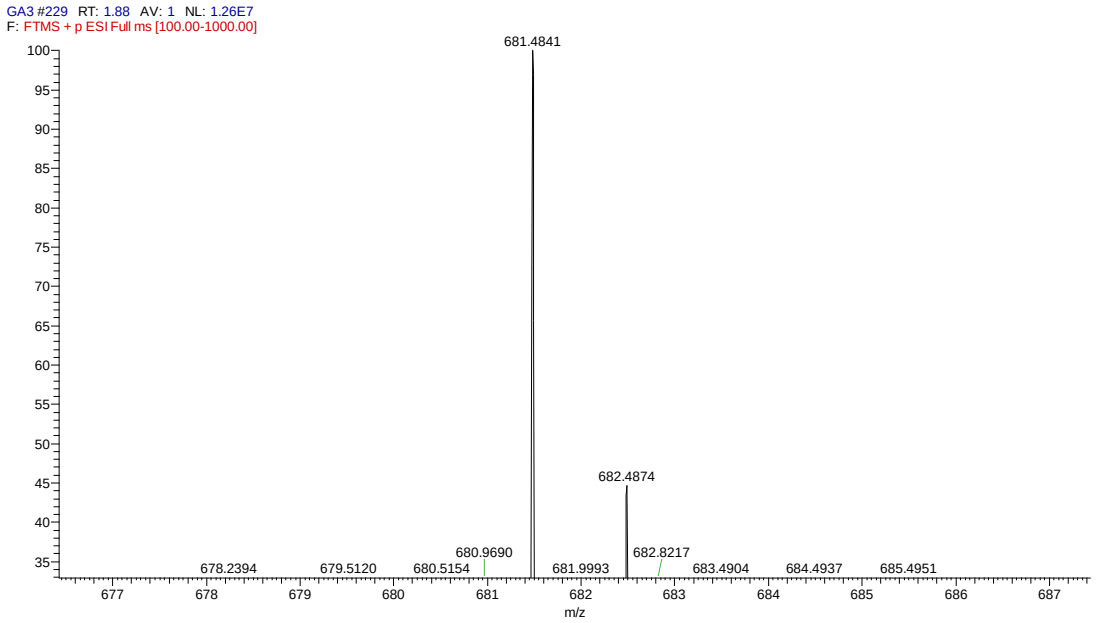
f1 (ppm)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684.4937
685.4951
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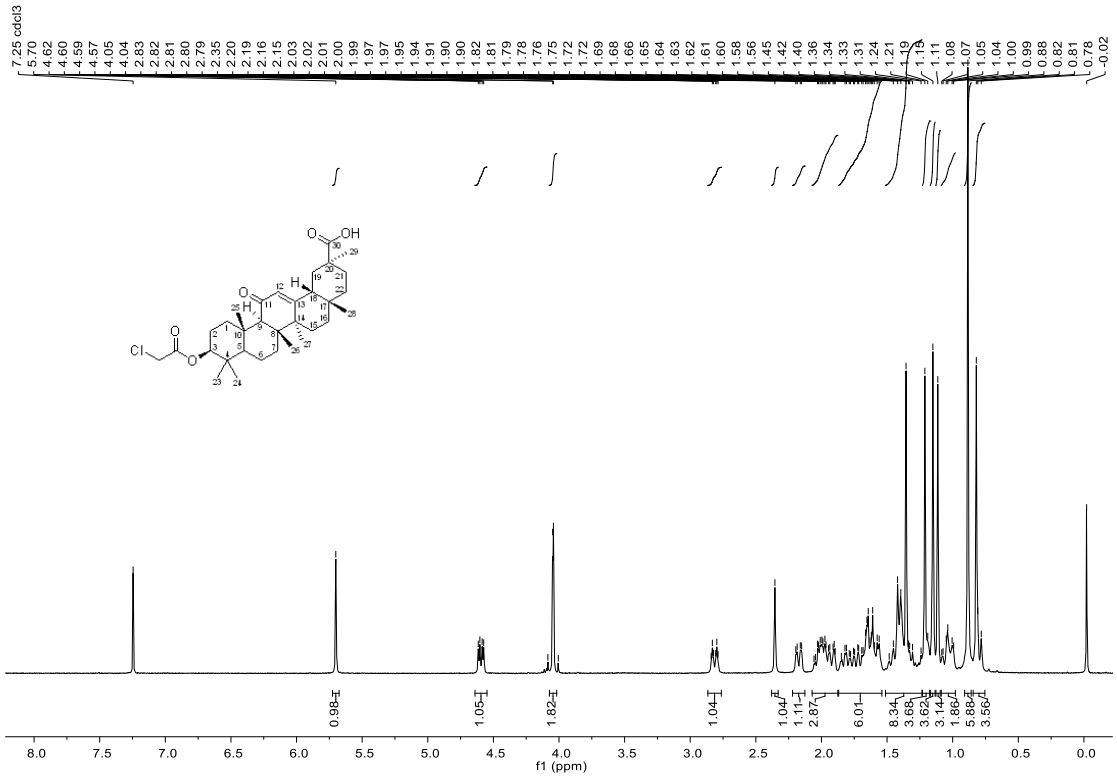
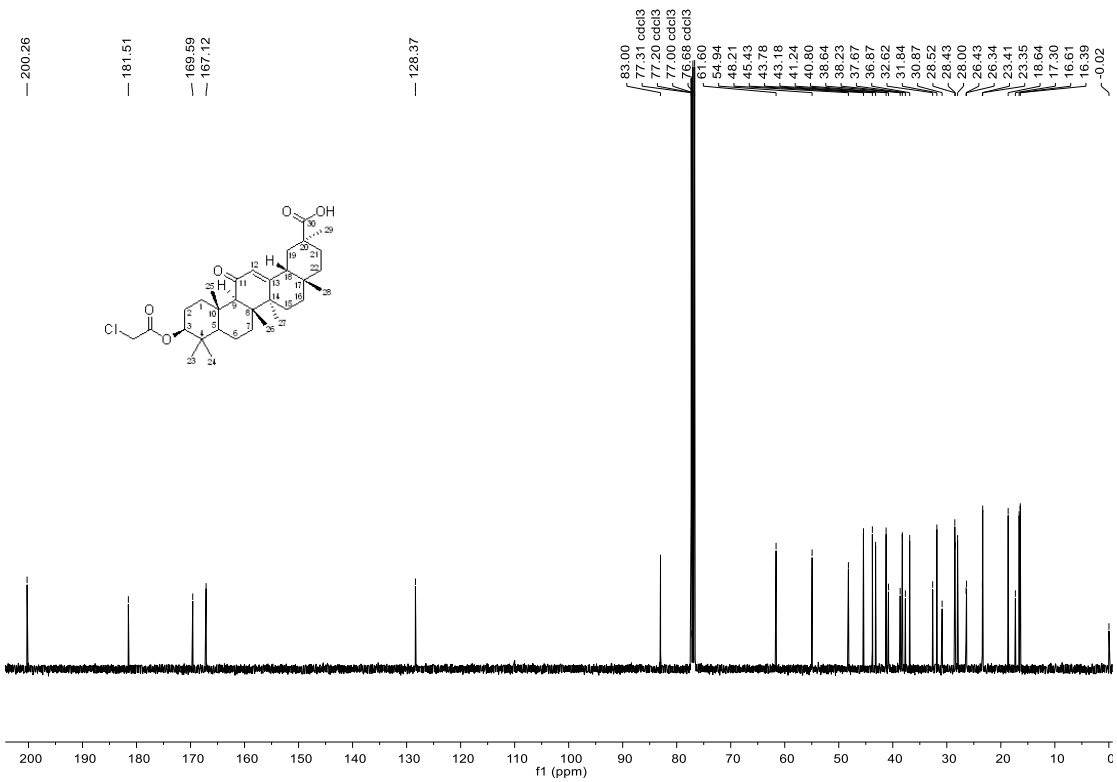
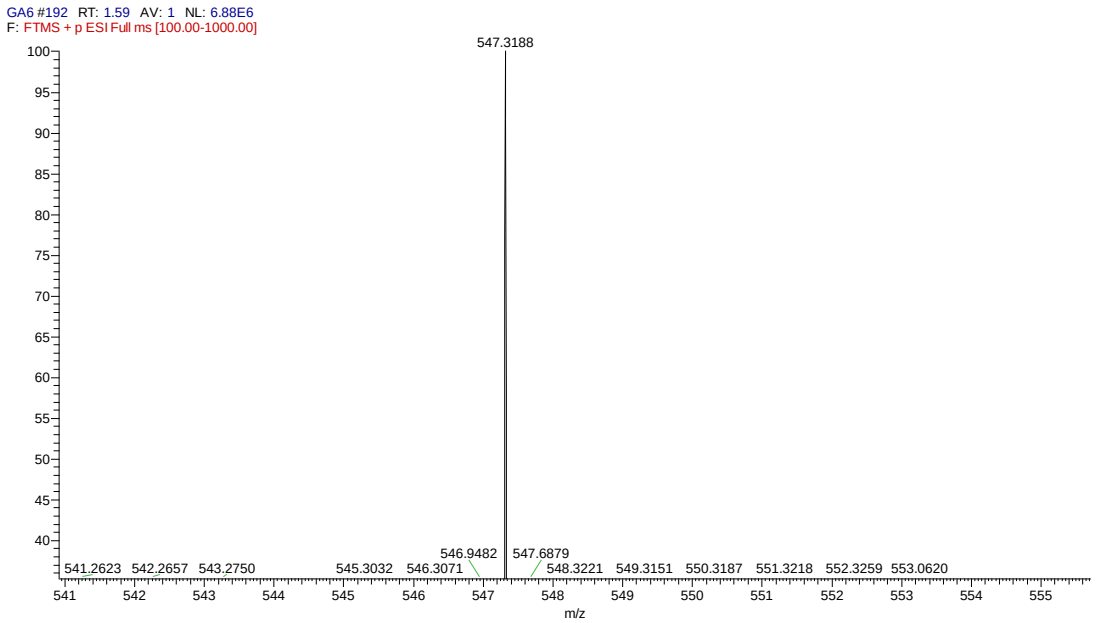
m/z

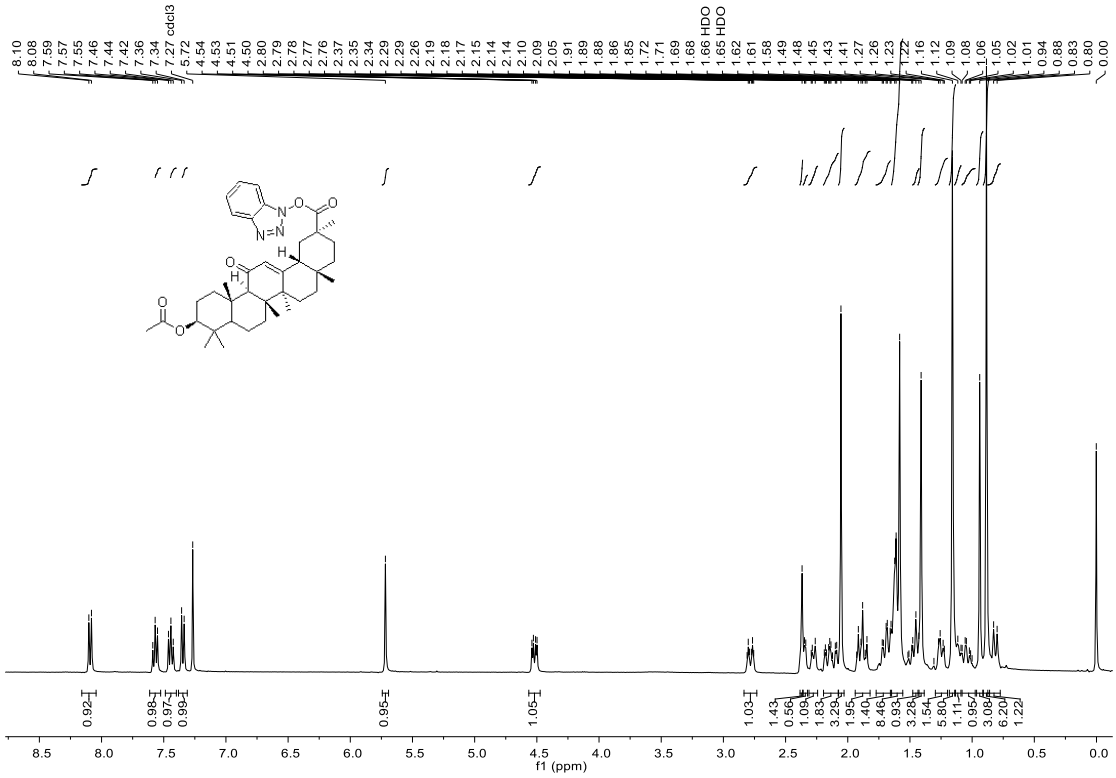
3β-(2-Chloroacetoxy)-11-oxo-18β-olean-12-en-30-oic acid (**12**)

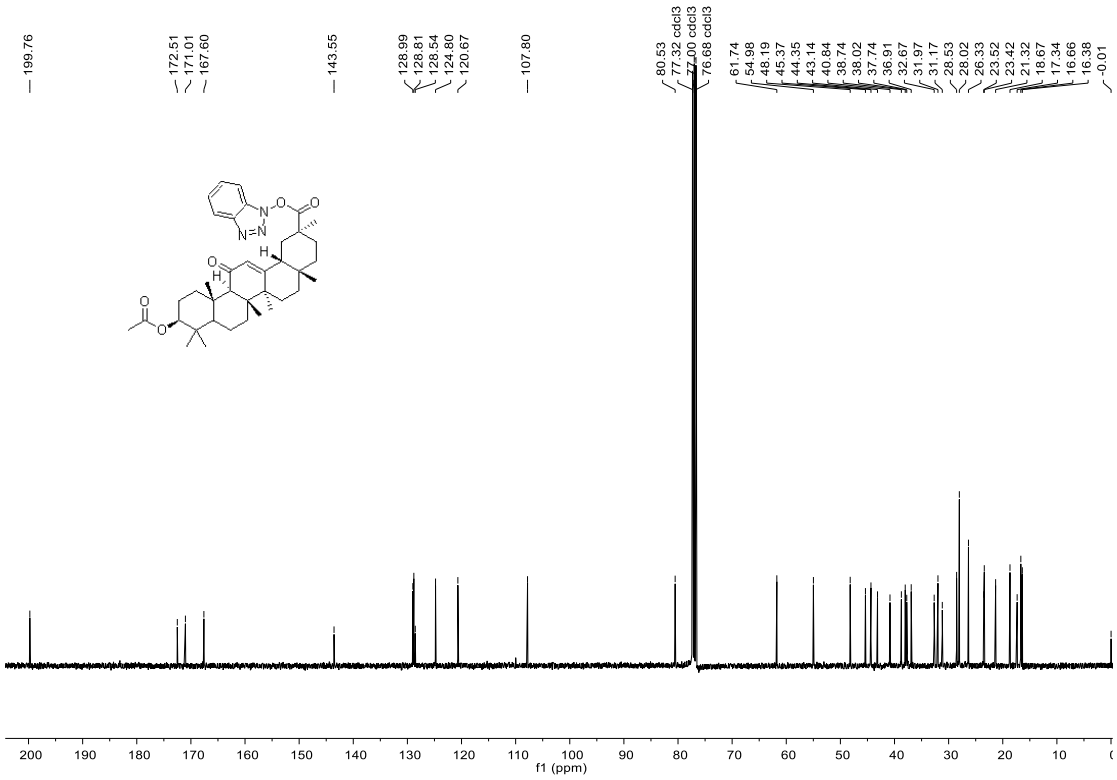






1H-Benzo[d][1,2,3]triazol-1-yl-3β-acetoxy-11-oxo-olean-12-en-30-oate (**6**)

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38.02
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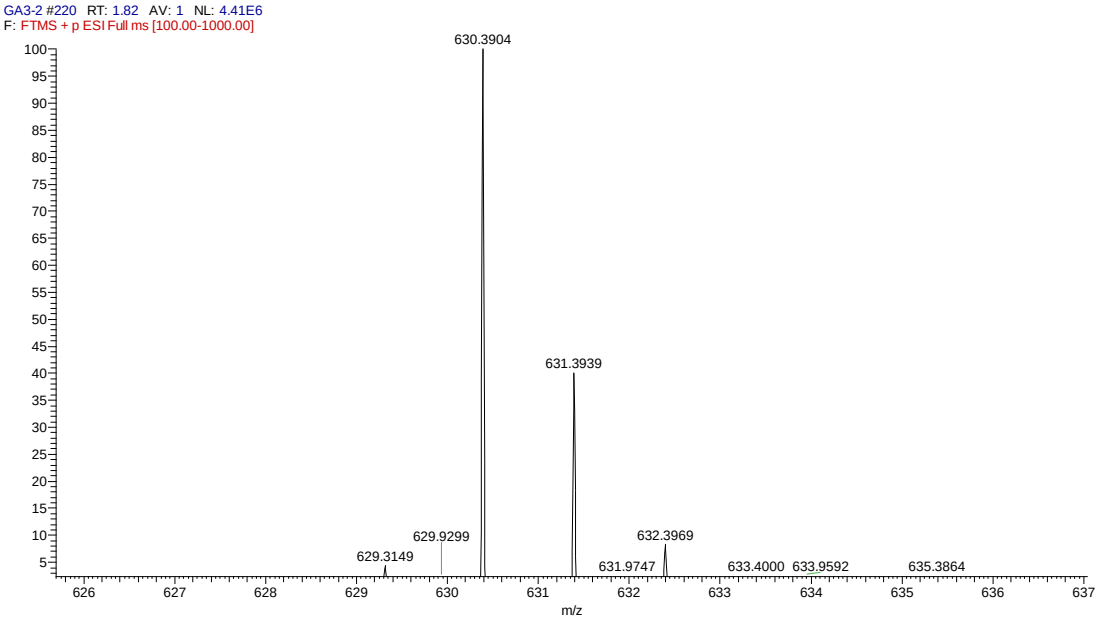
f1 (ppm)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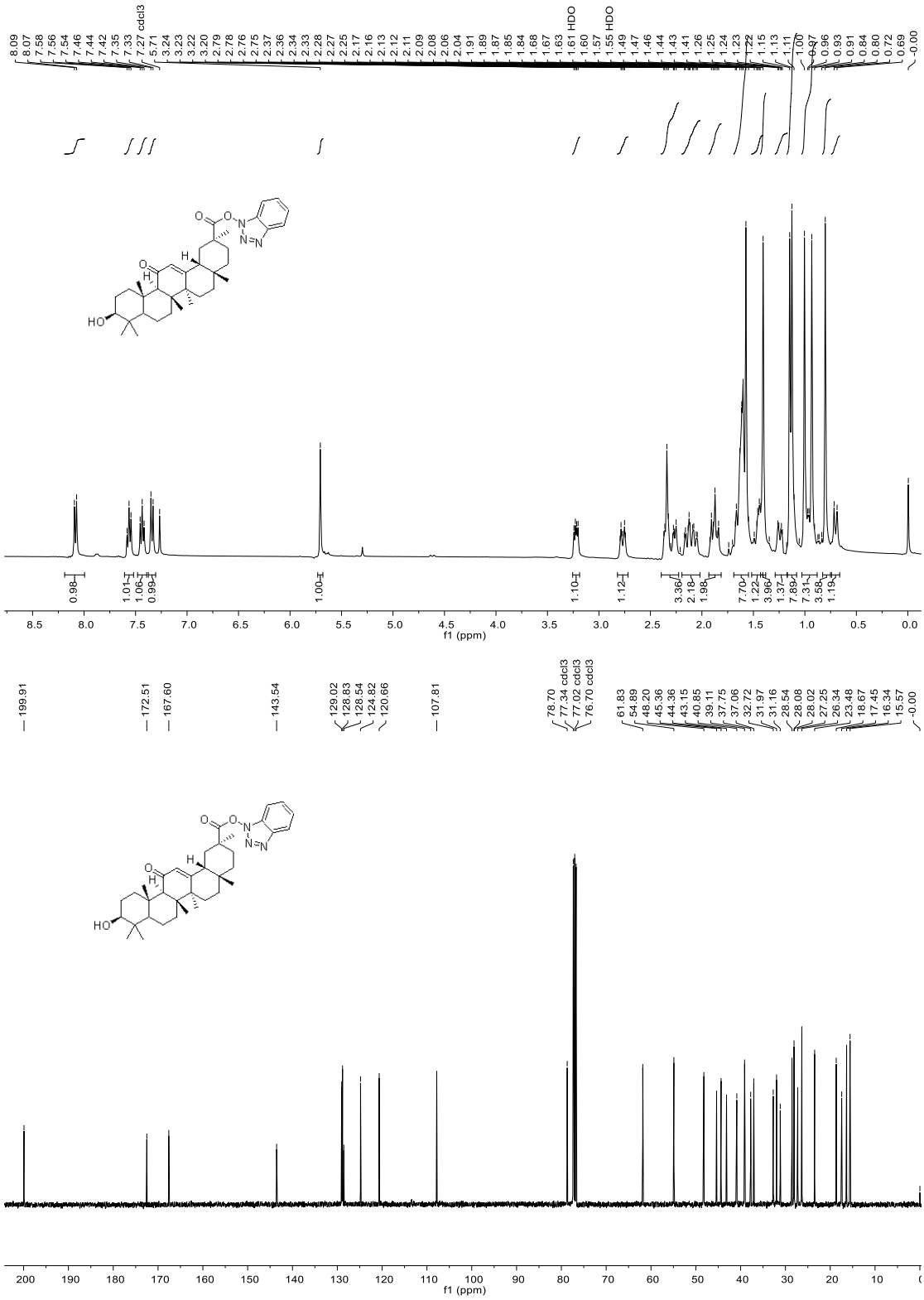
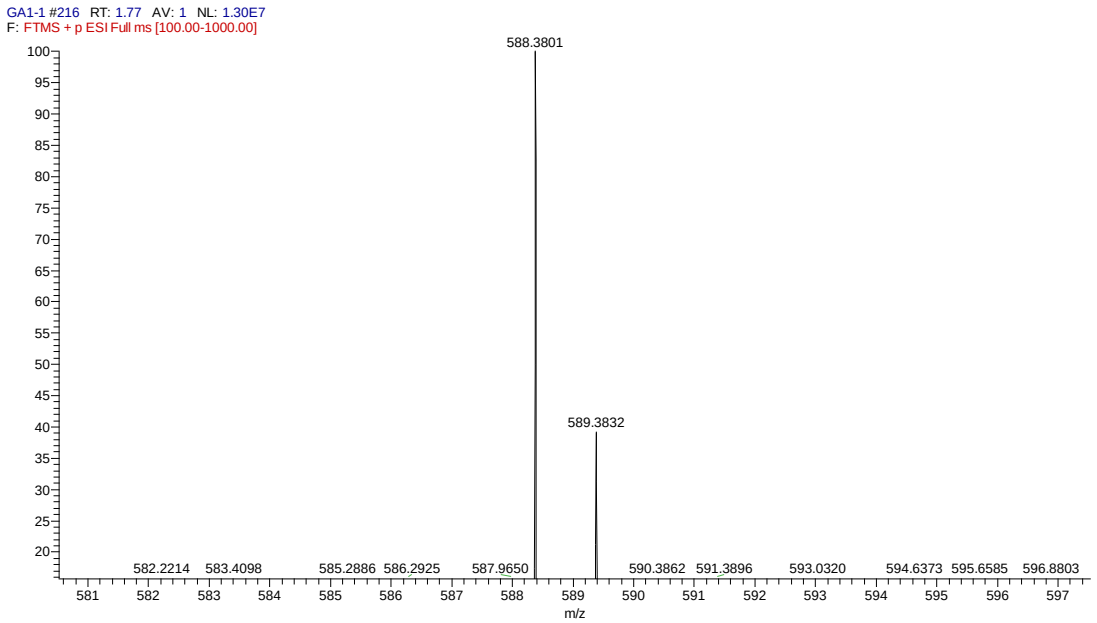
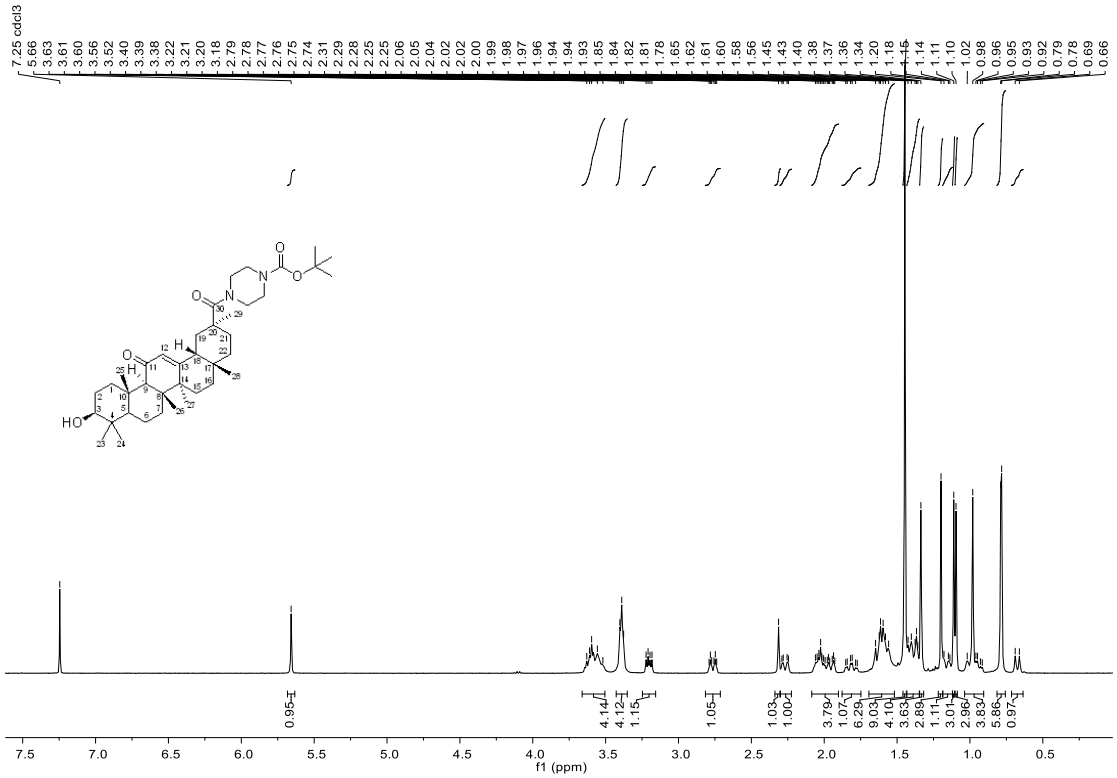
635.3864
m/z

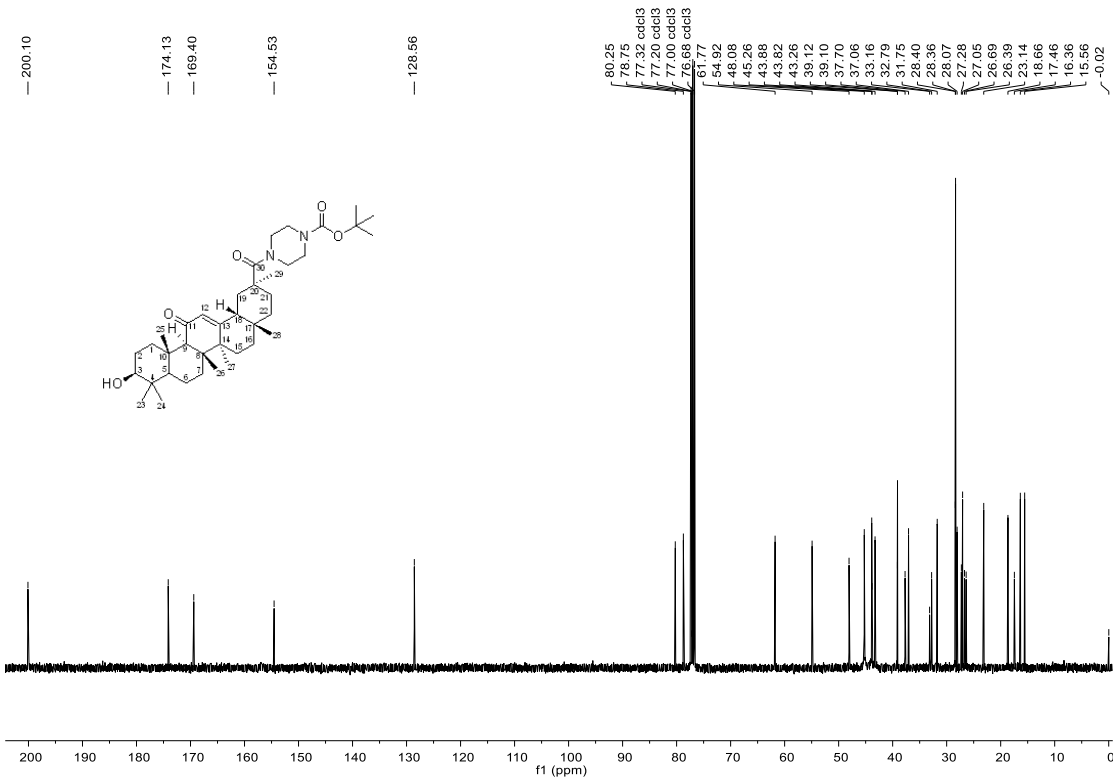
1H-Benzo[d][1,2,3]triazol-1-yl-3β-hydroxy-11-oxo-olean-12-en-30-oate (**7**)





tert-Butyl 4-(3β-hydroxyl-11-oxo-18β-olean-12-en-30-carbonyl)piperazine-1-carboxylate (**9**)

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61.77
54.92
48.08
45.26
43.88
43.82
43.26
39.12
39.10
37.70
37.06
33.16
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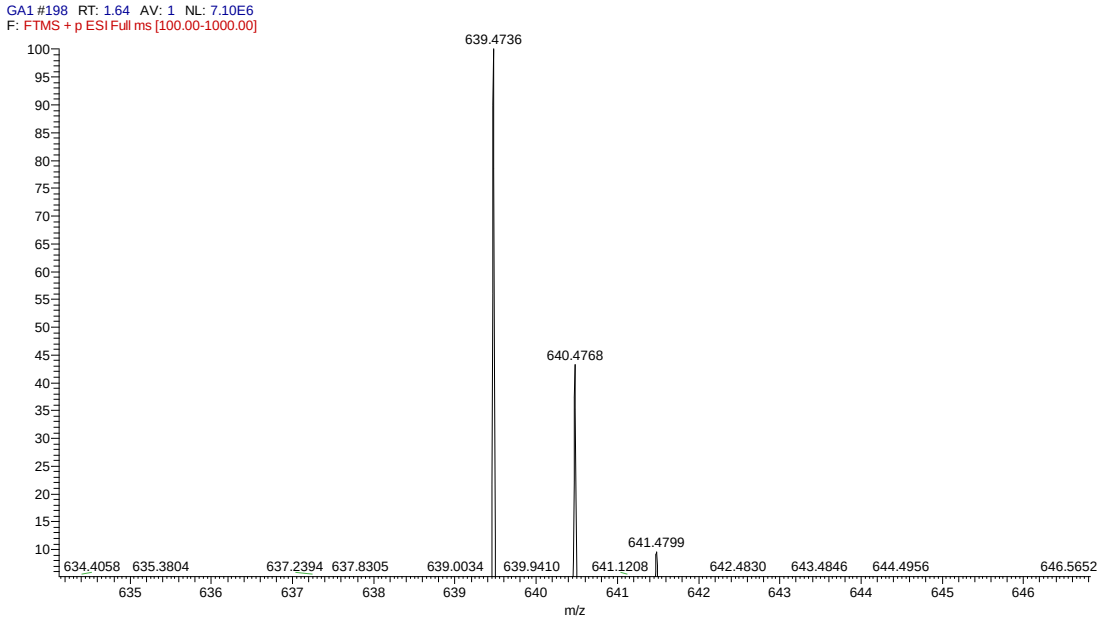
f1 (ppm)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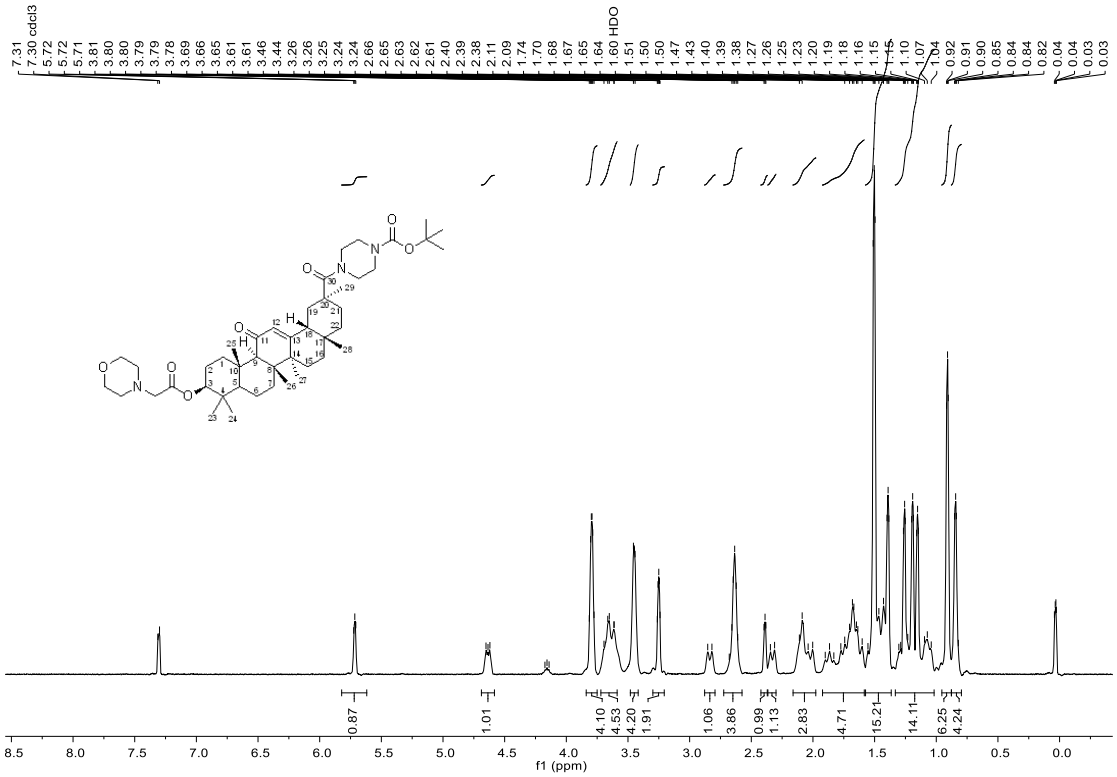
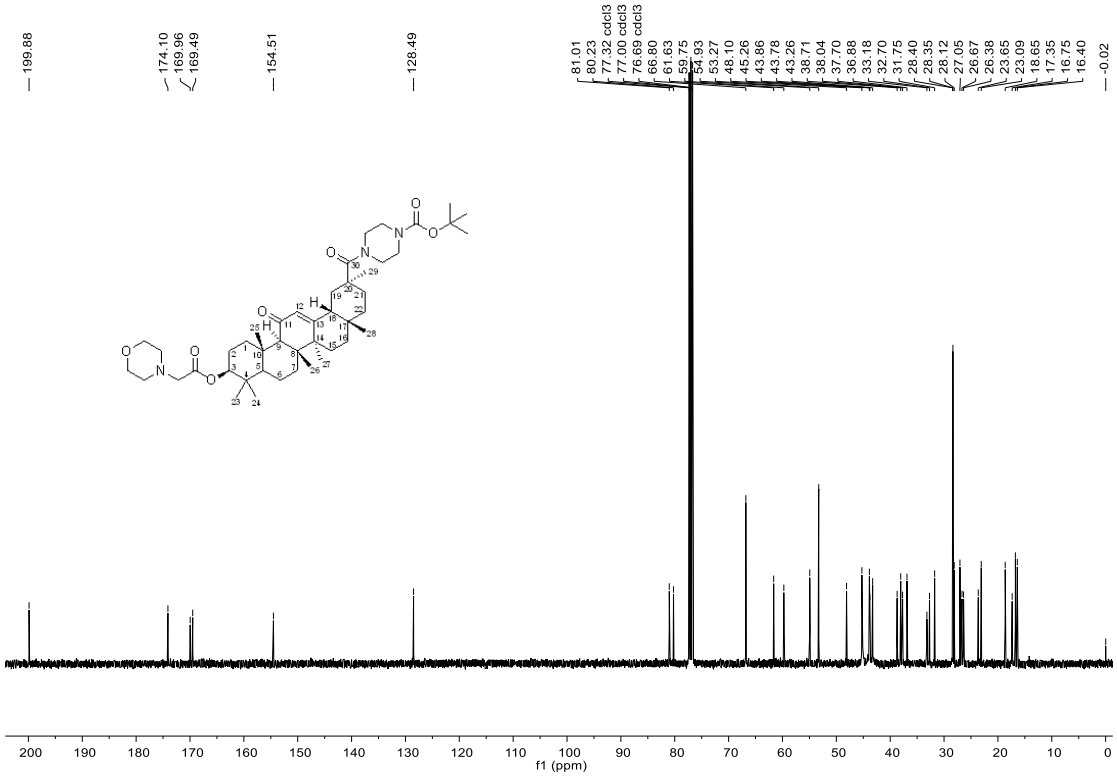
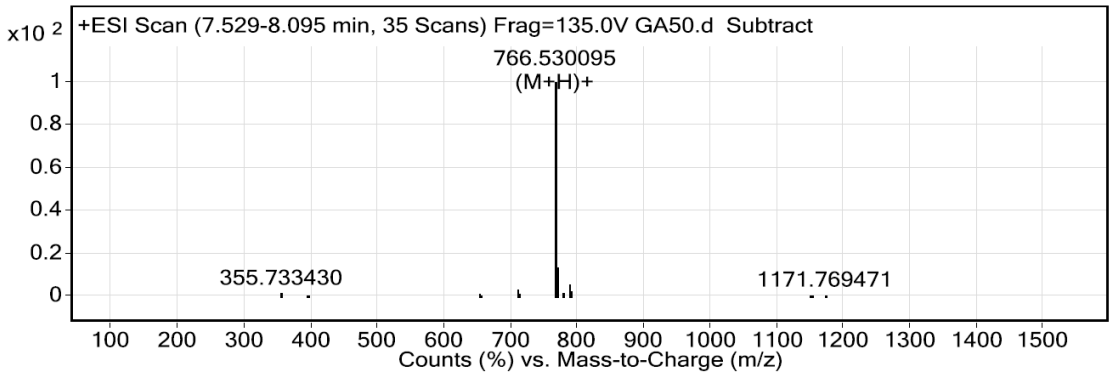
646.5652
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
635 636 637 638 639 640 641 642 643 644 645 646
m/z

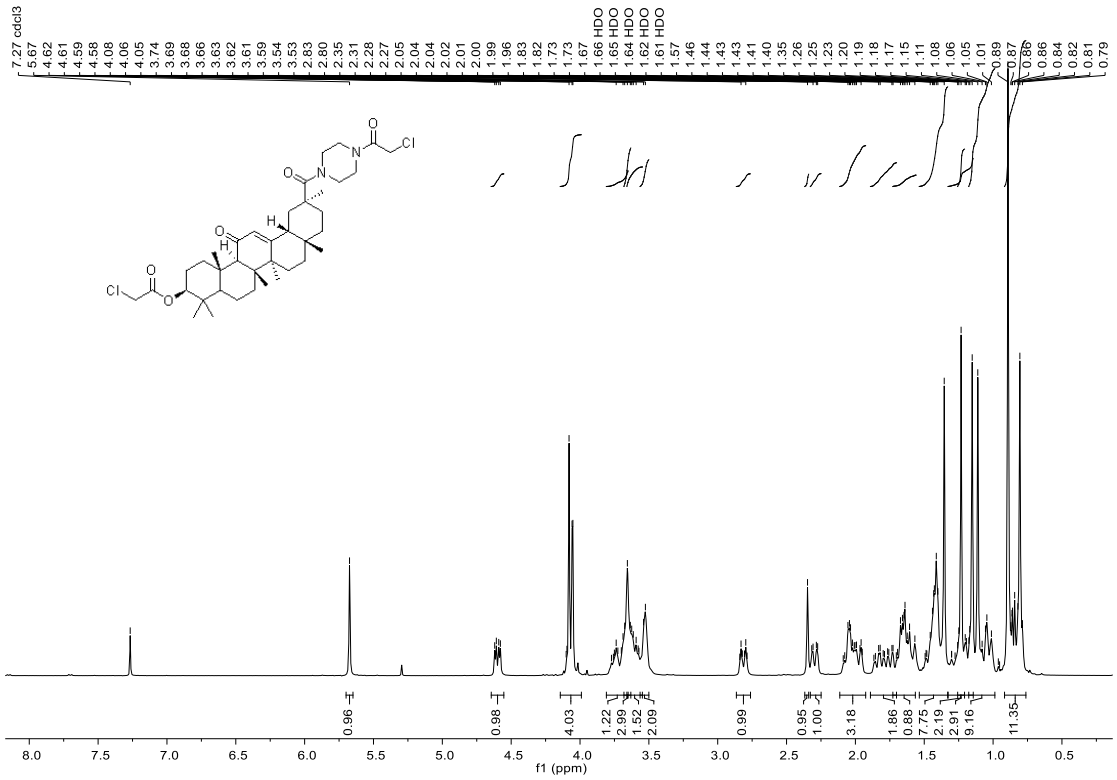
tert-Butyl 4-(3β- (2-morpholinoacetoxy)-11-oxo-18β-olean-12-en-30-carbonyl)piperazine-1-carboxylate (**14**)

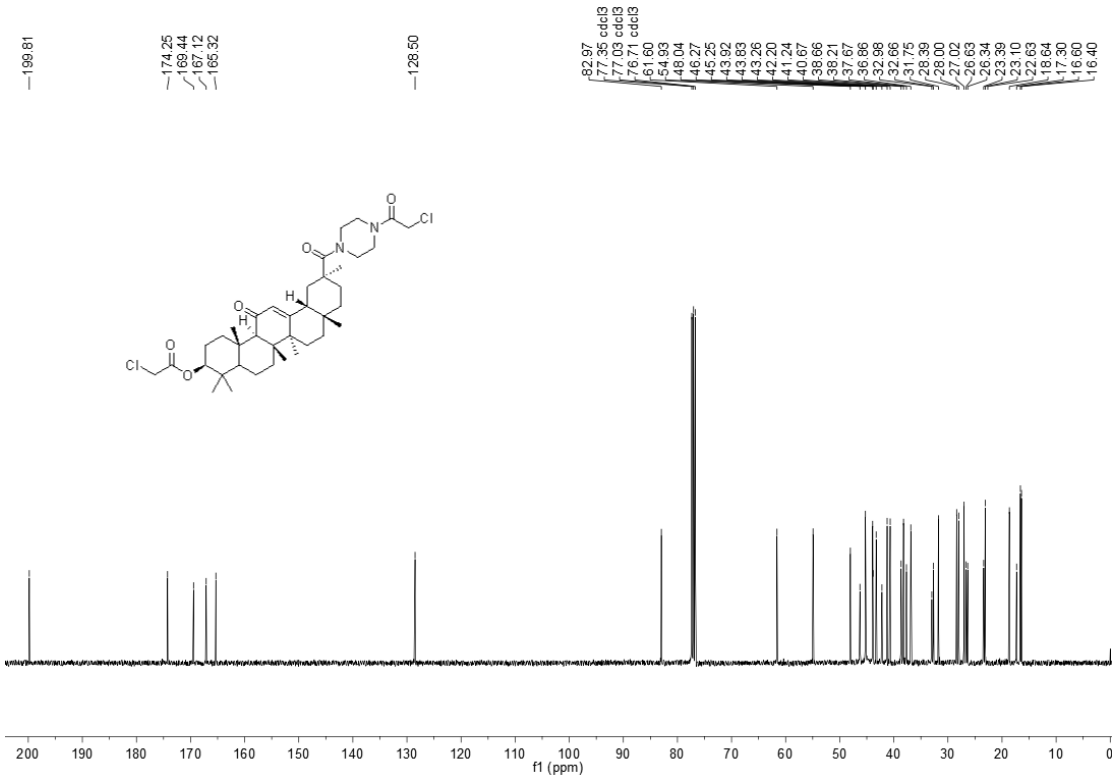


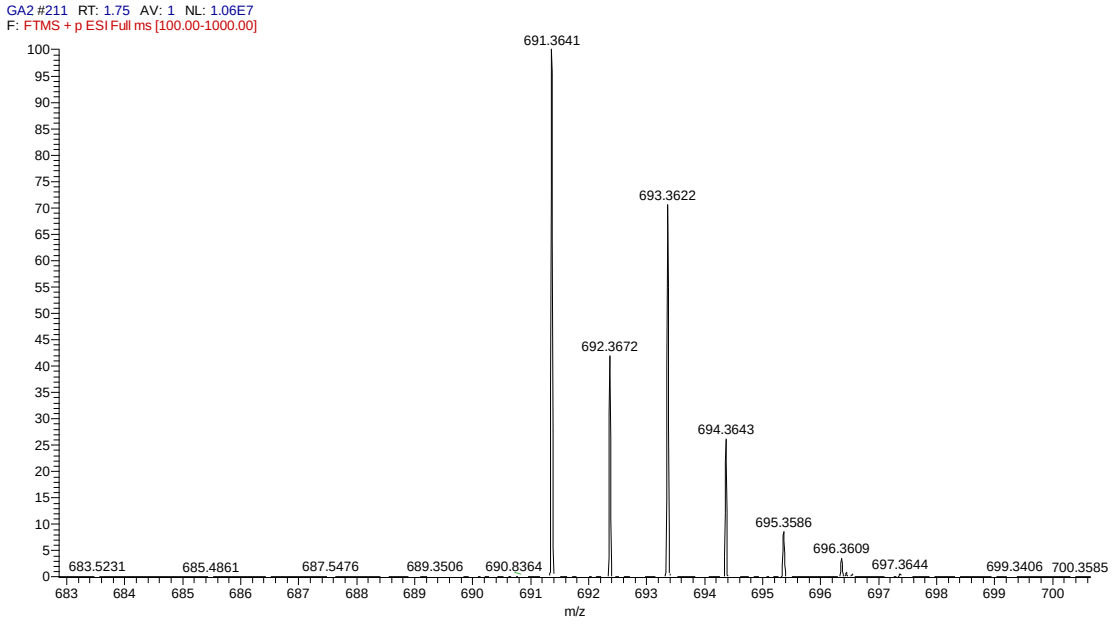




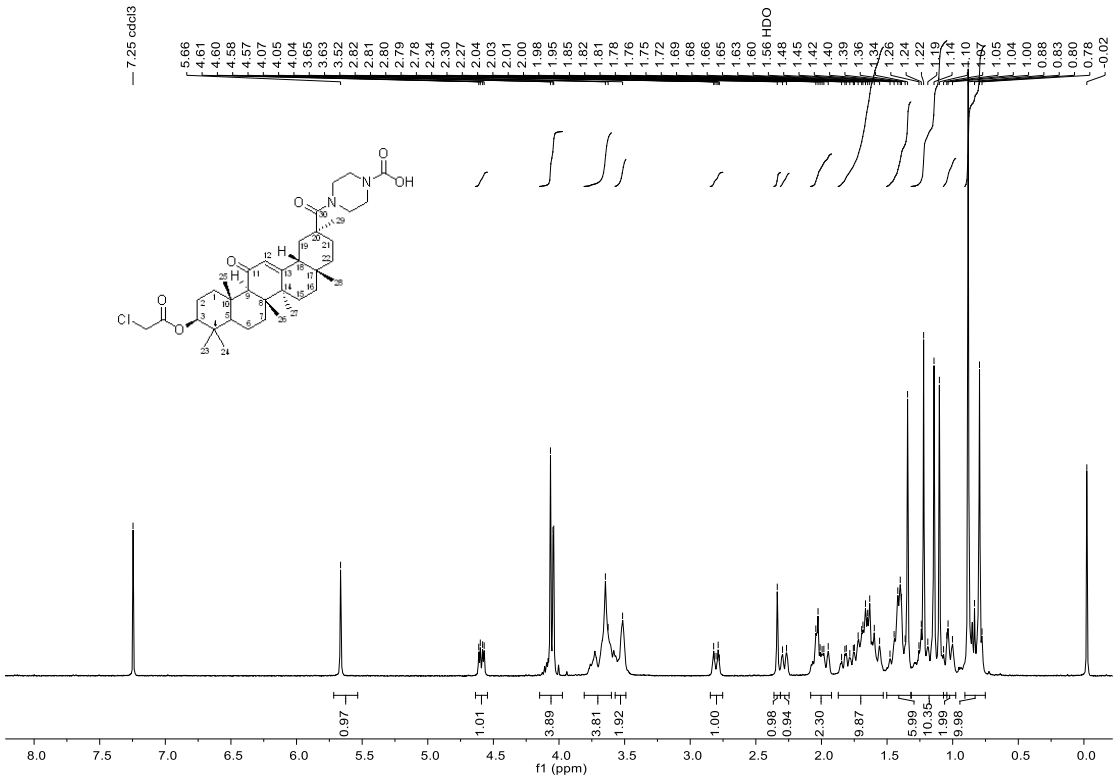
N-(2-Chloroacetyl)piperazinyl 3β-(2-chloroacetoxy)-11-oxo-18β-olean-12-en-30-amide (**11**)

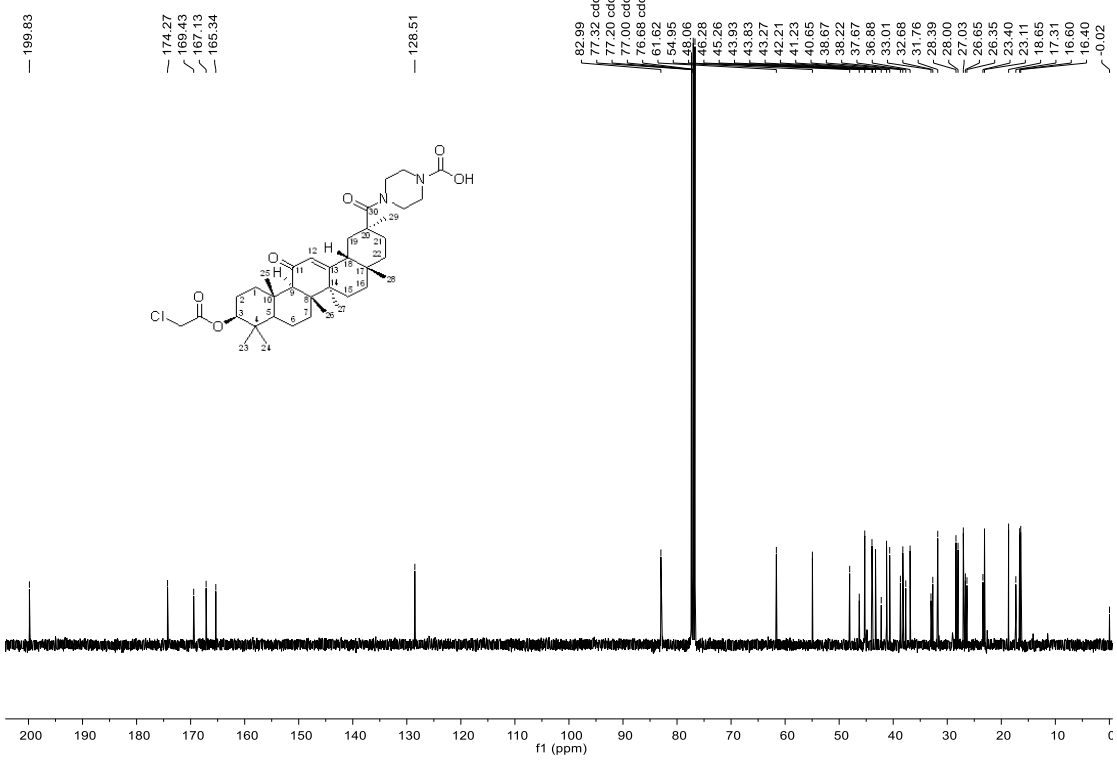


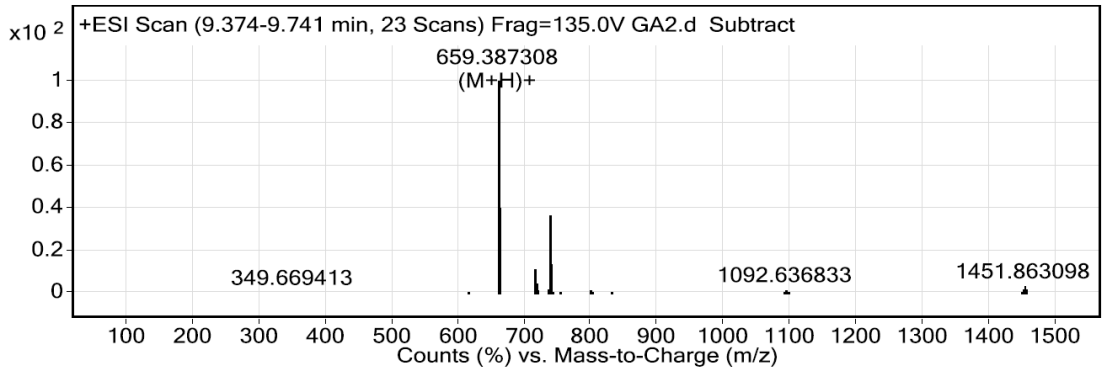

199.81
174.25
169.44
167.12
165.32
128.50
82.97
77.35 cdcl3
77.03 cdcl3
76.71 cdcl3
61.60
54.93
48.04
46.27
45.25
43.92
43.63
43.26
42.20
41.24
40.67
38.66
38.21
37.67
36.86
32.98
32.66
31.75
28.39
28.00
27.02
26.63
26.34
23.39
23.10
22.63
18.64
17.30
16.60
16.40
f1 (ppm)


GA2 #211 RT: 1.75 AV: 1 NL: 1.06E7
F: FTMS + p ESI Full ms [100.00-1000.00]
691.3641
693.3622
692.3672
694.3643
695.3586
696.3609
697.3644
683.5231
685.4861
687.5476
689.3506
690.8364
699.3406
700.3585
m/z

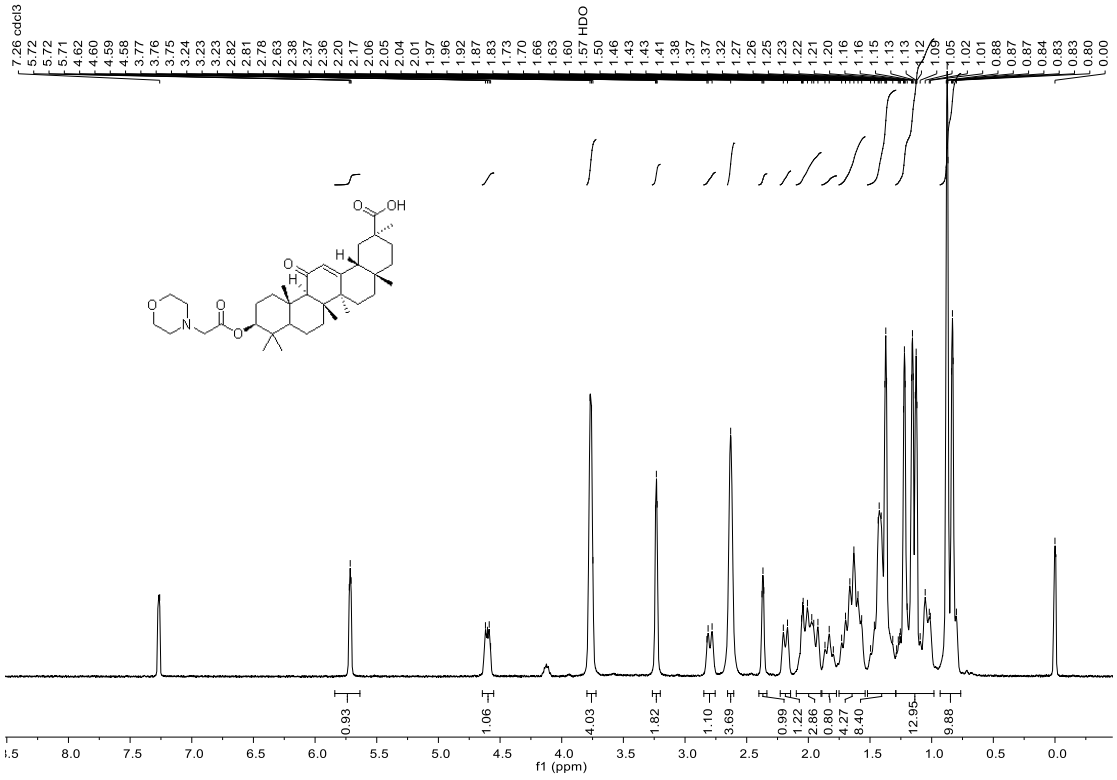
4-(3β-(2-Chloroacetoxy)-11-oxo-18β-olean-12-en-30-carbonyl)piperazine-1-carboxylic acid (**15**)

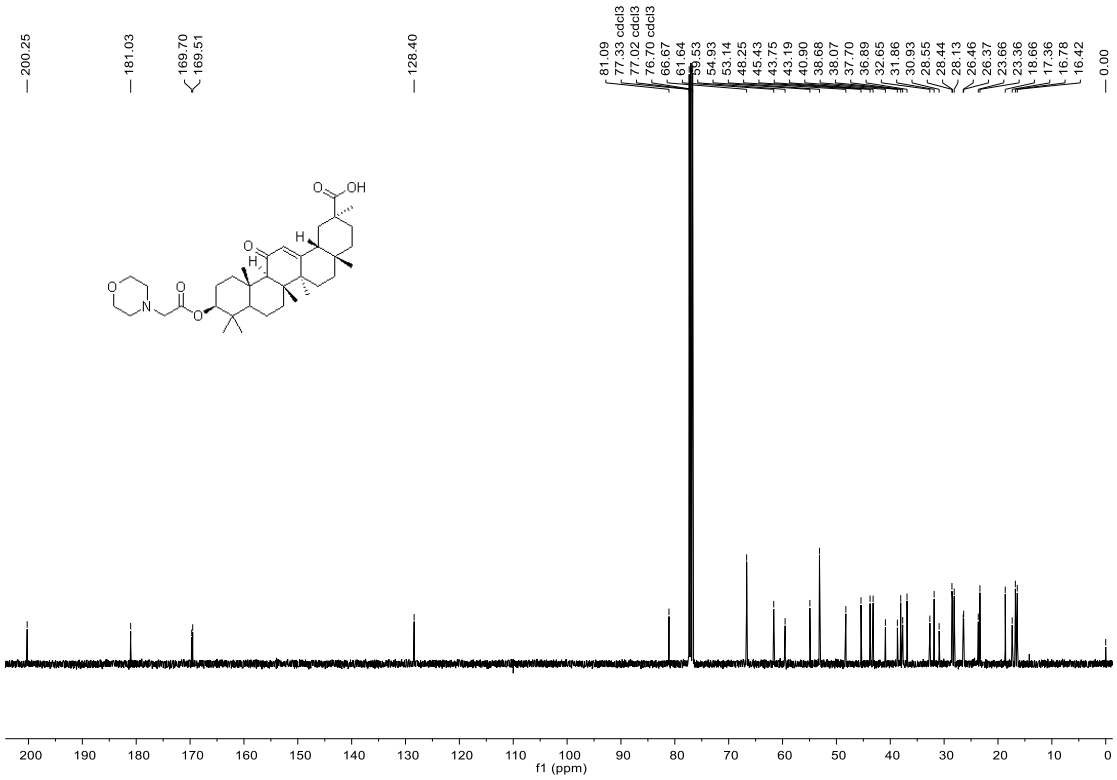


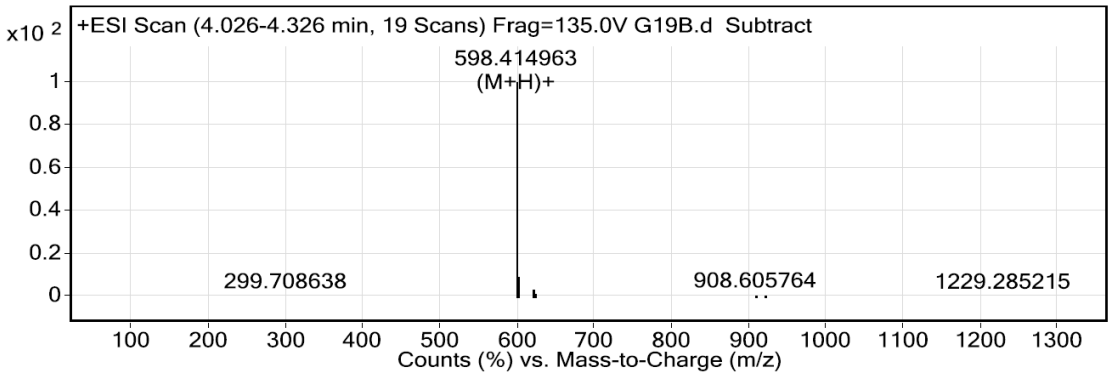




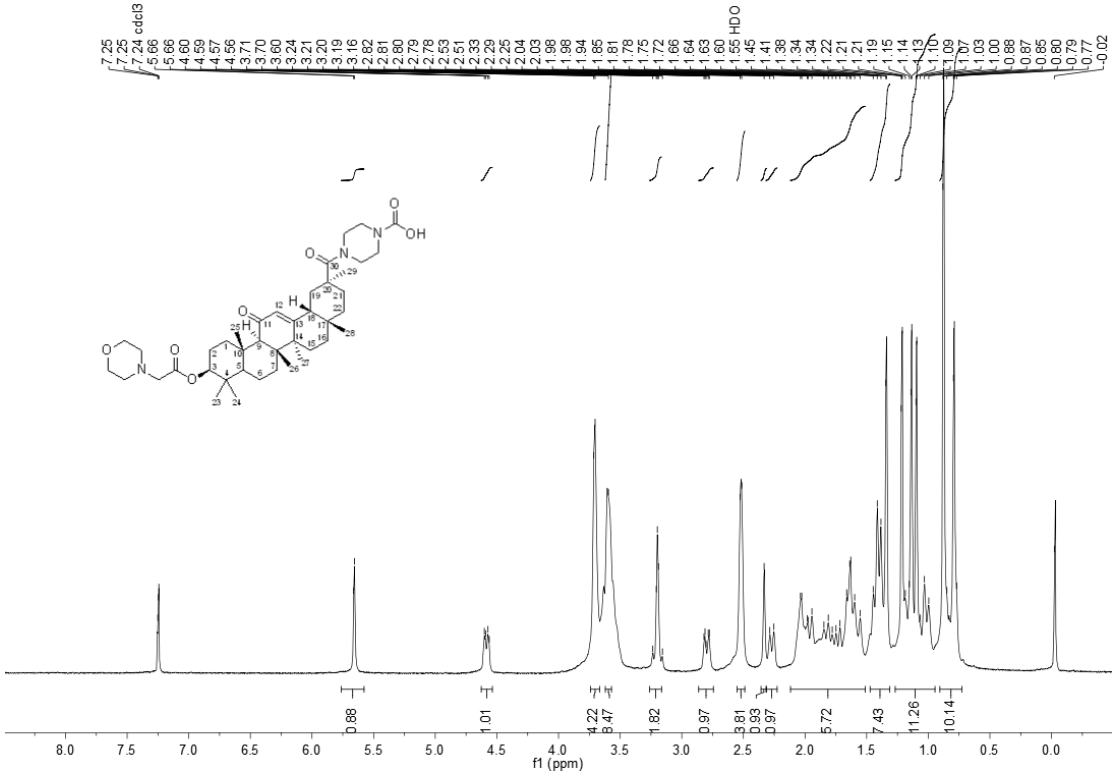
3β-(2-Morpholinoacetoxy)-11-oxo-olean-12-ene-30-oic acid (**13**)

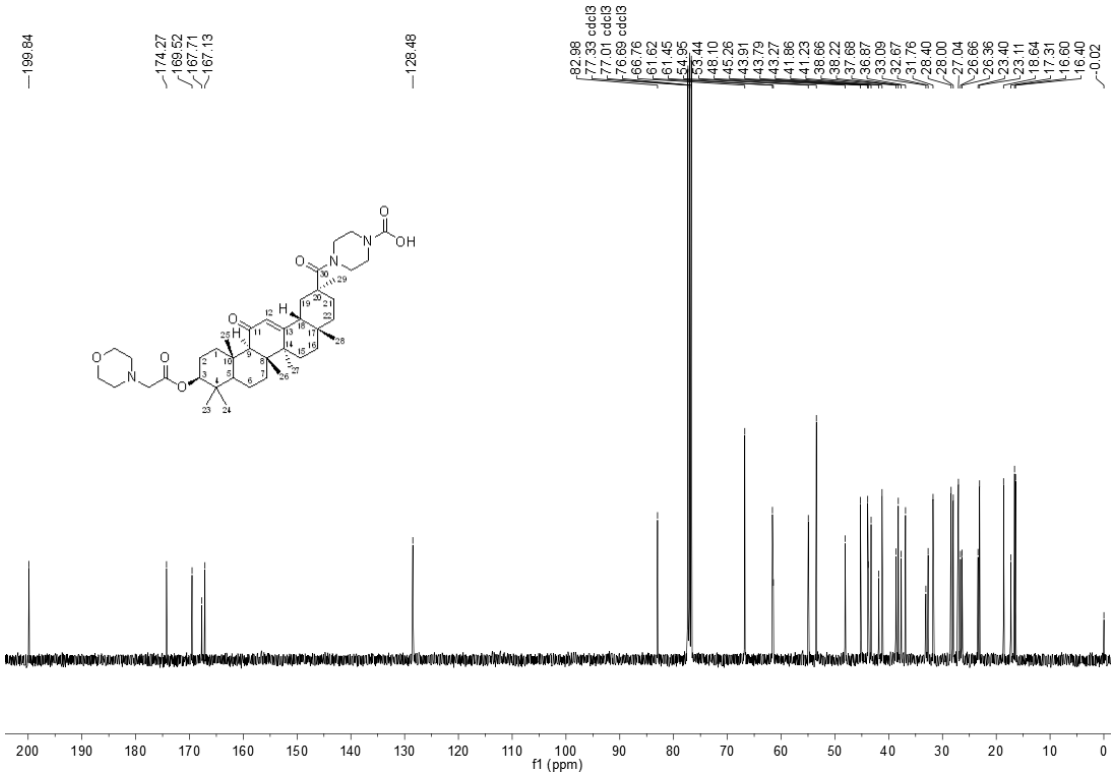


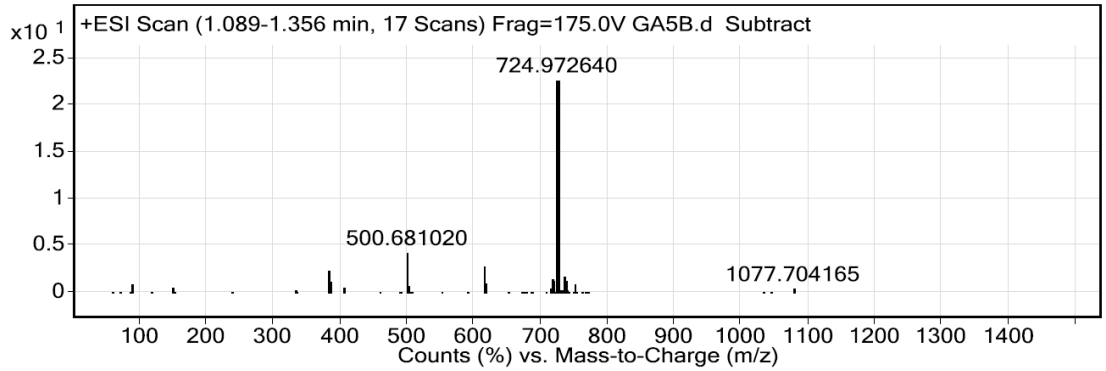

200.25
181.03
169.70
169.51
128.40
81.09
77.33 cdcl3
77.02 cdcl3
76.70 cdcl3
66.67
61.64
55.53
54.93
53.14
48.25
45.43
43.75
43.19
40.90
38.68
38.07
37.70
36.89
32.65
31.86
30.93
28.55
28.44
28.13
26.46
26.37
23.66
23.36
18.66
17.36
16.78
16.42
0.00
OH
O
H
O
H
O
N
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


x10 2
+ESI Scan (4.026-4.326 min, 19 Scans) Frag=135.0V G19B.d Subtract
598.414963
(M+H)+
1
0.8
0.6
0.4
0.2
0
299.708638
908.605764
1229.285215
100 200 300 400 500 600 700 800 900 1000 1100 1200 1300
Counts (%) vs. Mass-to-Charge (m/z)

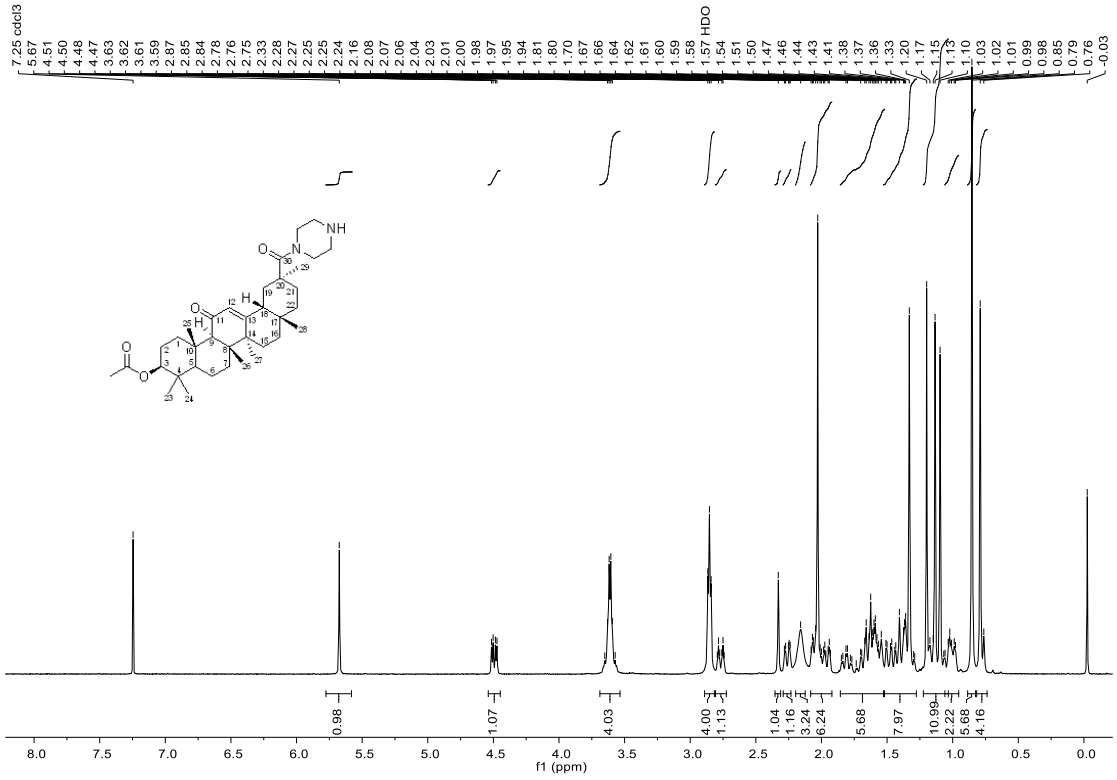
4-(3β-(2-Morpholinoacetoxy)-11-oxo-18β-olean-12-en-30-carbonyl)piperazine-1-carboxylic acid (**16**)

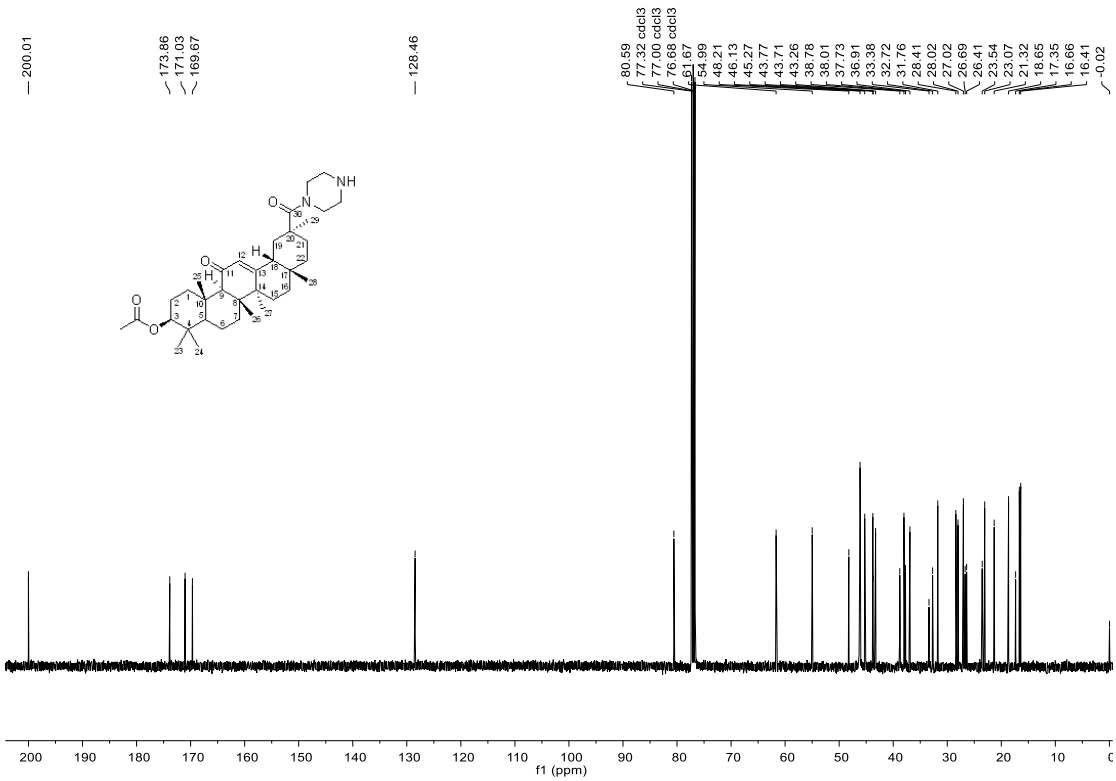


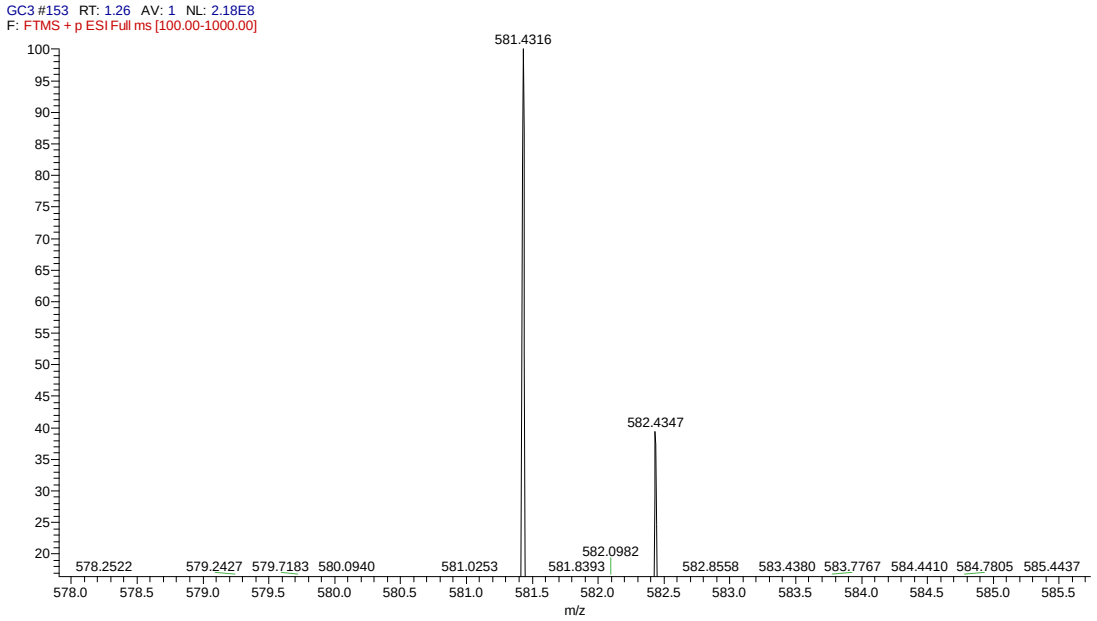




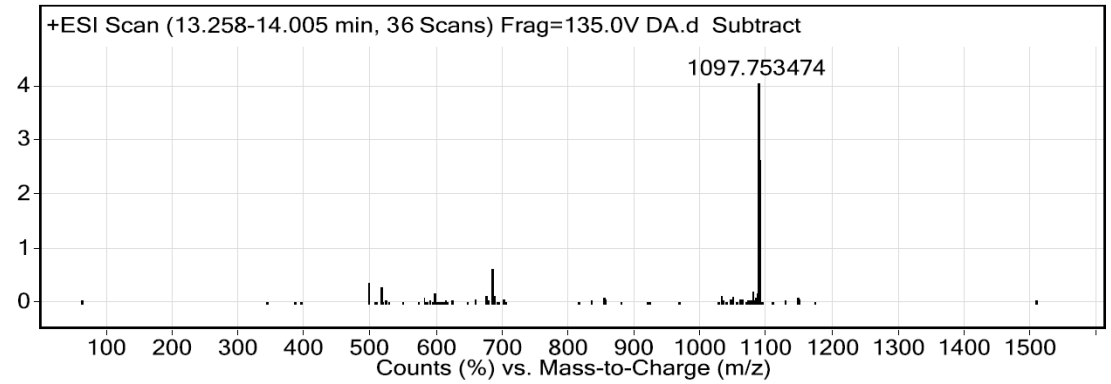
3β-Acetoxy-11-oxo-18β-olean-12-en-30-carbonyl piperazine (**4**)



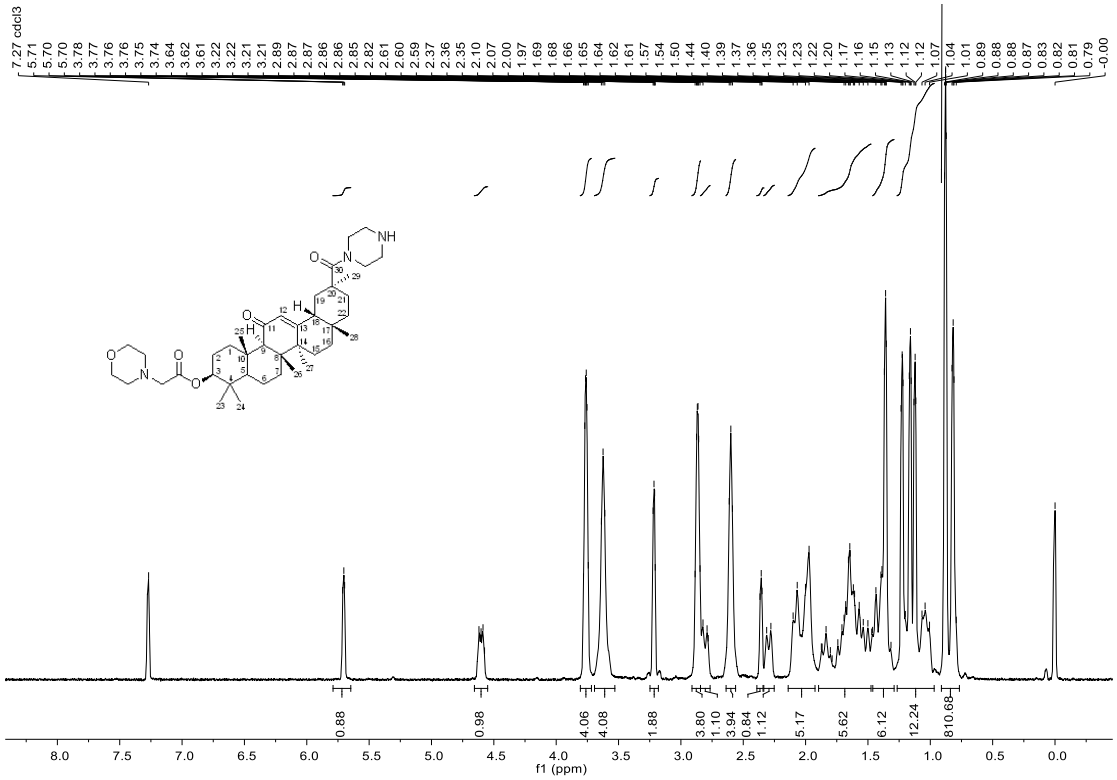


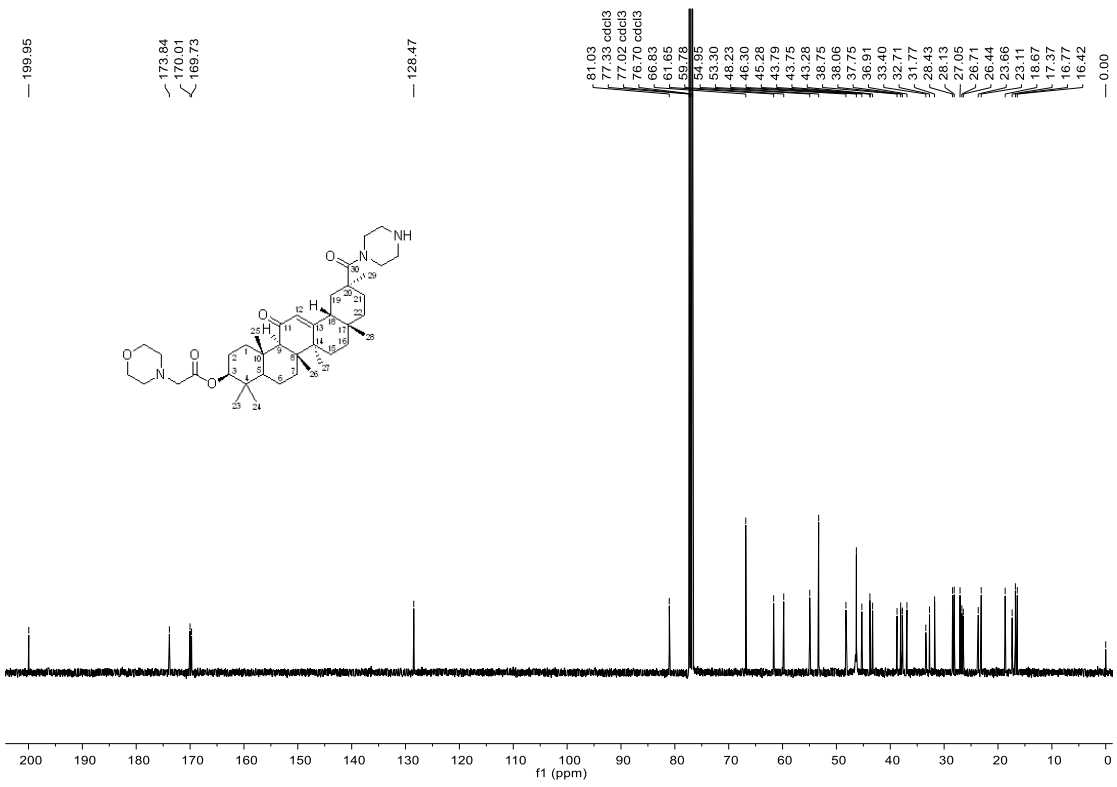


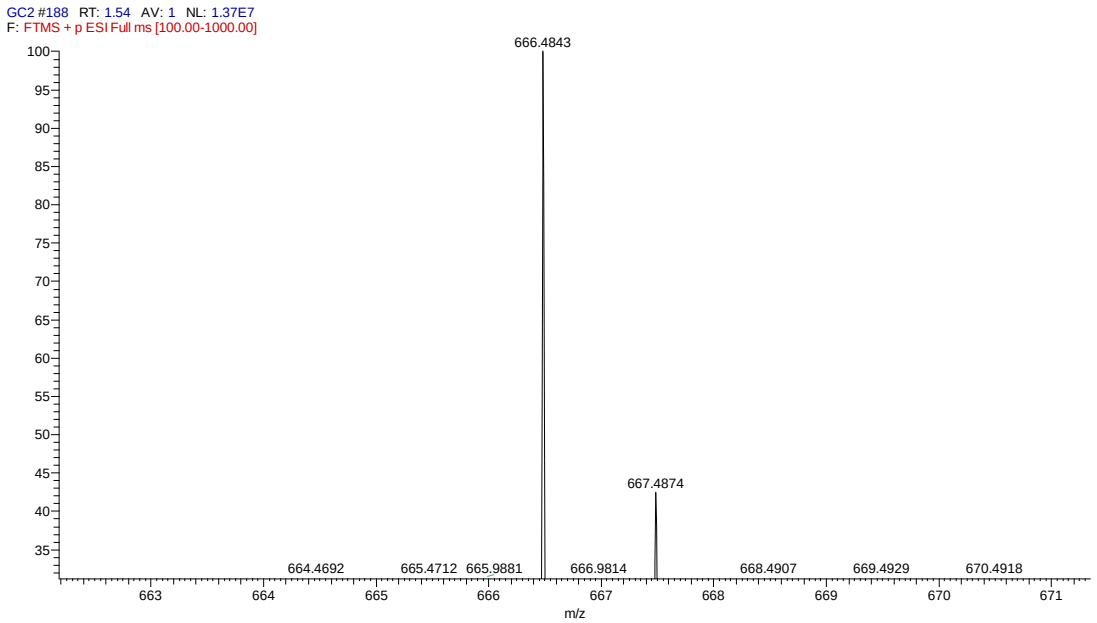
Bisamide product **5**



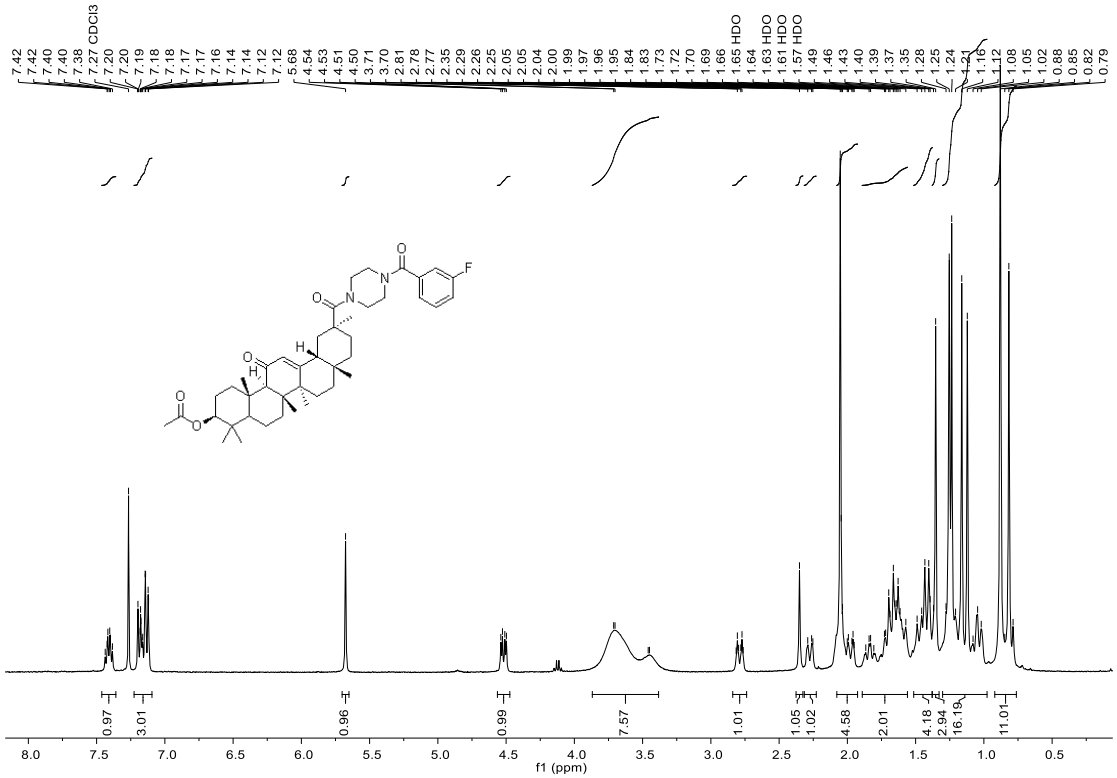
3β-(2-Morpholinoacetoxy)-11-oxo-18β-olean-12-en-30-carbonyl piperazine (**17**)

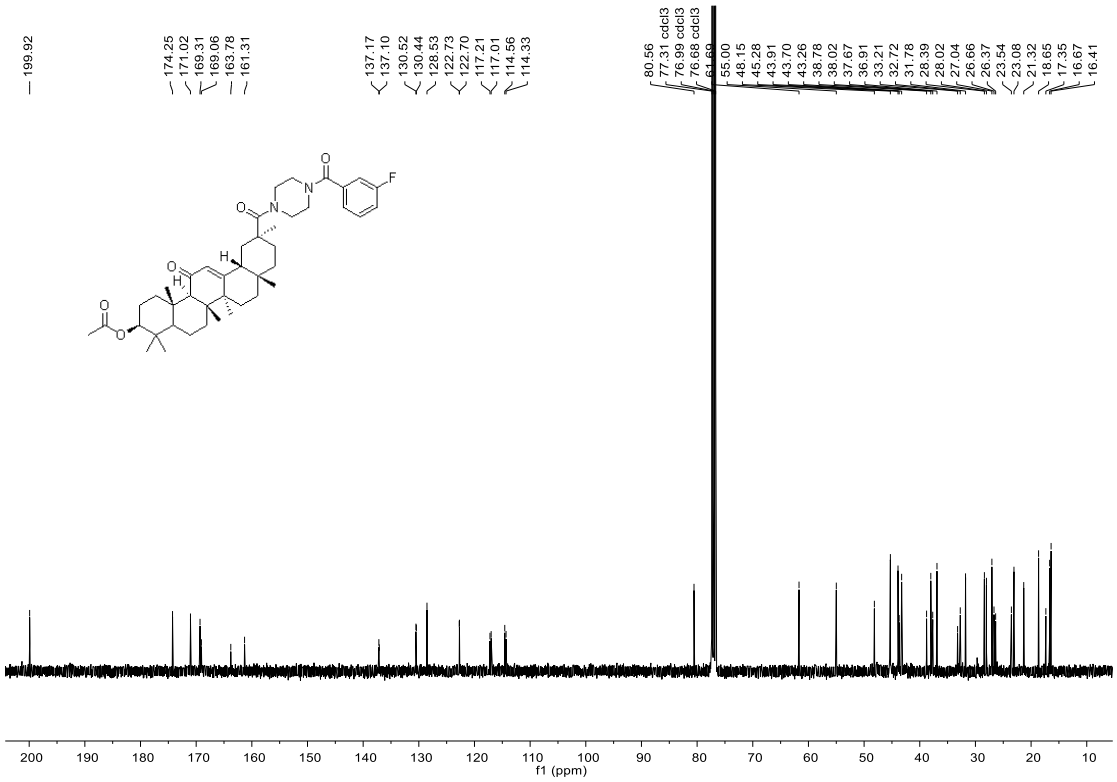


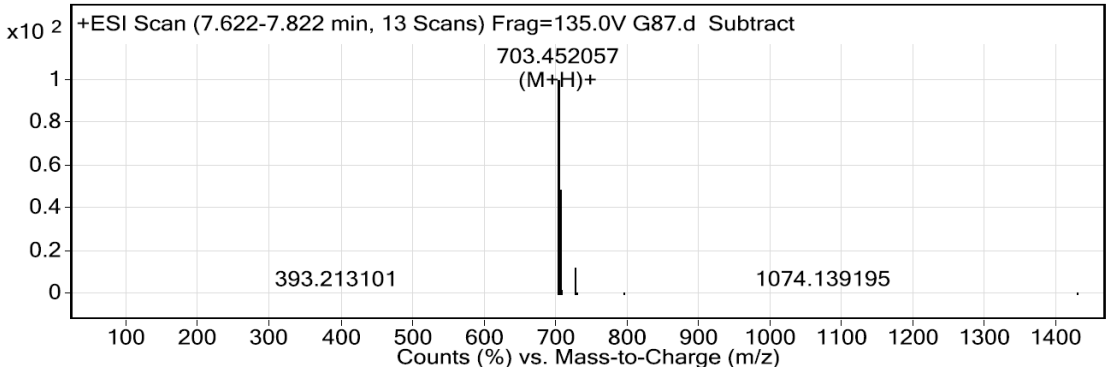




3β-Acetoxy-30-(4-(3-fluorobenzoyl)-1-piperazinyl)-olean-12-ene-11,30-dione (**18**)







1. Song, H.; Sun, Y.; Xu, G.; Hou, B.; Ao, G. Synthesis and biological evaluation of novel hydrogen sulfide releasing glycyrrhetic acid derivatives. *J. Enzyme Inhib. Med. Chem.* **2016,** *31* (6), 1457-1463.

2. Sommerwerk, S.; Heller, L.; Kerzig, C.; Kramell, A. E.; Csuk, R. Rhodamine B conjugates of triterpenoic acids are cytotoxic mitocans even at nanomolar concentrations. *Eur. J. Med. Chem.* **2017,** *127*, 1-9.