Heterocycle-fused Lupane Triterpenoids Inhibit *Leishmania donovani* Amastigotes

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SYNTHESIS

General experimental details

Commercially available reagents were used without further purification and all of the solvents were HPLC grade. THF was distilled over sodium/benzophenone ketyl. Other anhydrous solvents were purchased from Sigma-Aldrich and used without further drying. All reactions in anhydrous solvents were performed in oven dried glassware under an inert atmosphere of dry argon. Thin layer chromatography (TLC) was performed on E. Merck Silica Gel 60 aluminium packed plates, with visualization accomplished by UV illumination and staining with 5% H2SO4 in MeOH. Flash chromatography on a silica gel with a Biotage SP1 purification system (Uppsala, Sweden) using appropriate size cartridge. IR-spectra were recorded on a Bruker Vertex 70 FT-IR spectrometer (Ettlingen, Germany) with ATR technique. The 1H and 13C NMR spectra were measured on a Varian Mercury 300 MHz spectrometer (Varian, Palo Alto, CA) or Bruker Avance III 500 MHz spectrometer. 1H and 13C NMR were recorded as solutions in DMSO-d6, CDCl3, (CD3)2CO or CD3OD. Deuterated solvents were purchased from Aldrich. Chemical shifts (δ) are given as parts per million (ppm) relative to the NMR solvent signals (DMSO-d6 2.50 and 39.50 ppm, CDCl3 7.26 and 77.00 ppm, (CD3)2CO 2.05 and 29.84 ppm, CD3OD 3.31 and 49.00 ppm for 1H and 13C NMR respectively). High resolution mass spectra (HRMS) were measured on a Waters Acquity UPLC® system (Waters, Milford MA, USA) equipped with Synapt G2 HDMS mass spectrometer (Waters, Milford MA, USA).

Chemistry

Lup-20(29)-ene-3β,28-diol (betulin) (1)

Betulin was isolated (95% purity) from the bark of birch (Betula sp.) by extraction and was obtained from UPM Kymmene (Lappeenranta, Finland). The crude betulin was recrystallized from 2-propanol/H2O azeotrope to give betulin as a white solid.1 mp 252-253 °C; Rf 0.2 (1:4 EtOAc/n-hexane); 1H NMR (300 MHz, CDCl3) δ 4.68 (s, 1H), 4.57 (s, 1H), 3.79 (d, J = 10.8 Hz, 1H), 3.32 (d, J = 10.8 Hz, 1H), 3.18 (dd, J = 5.1, 10.8 Hz, 1H), 2.38 (m, 1H), 1.68 (s, 3H), 1.02 (s, 3H), 0.97 (s, 6H), 0.96 (s, 3H), 0.82 (s, 3H), 0.75 (s, 3H); 13C NMR (75 MHz, DMSO-d6) δ 150.4, 109.7, 79.0, 60.5, 55.2, 50.4, 48.7, 47.7, 42.7, 40.9, 38.8, 38.7, 37.3, 37.1, 34.2, 33.9, 29.7, 29.1, 27.9, 27.3, 27.0, 25.2, 20.8, 19.1, 18.3, 16.1, 15.9, 15.3, 14.7; FTIR (ν, cm⁻¹): 879, 1009, 1035, 1232, 1375, 1452, 1739, 2939, 3360; MS (direct, EI+): m/z 442; Anal. (C30H50O2) C, H.

3-Oxo-20(29)-lupen-28-oic acid (betulonic acid) (2)

To a solution of betulin (50.0 g, 113 mmol) in acetone (1500 mL) was added freshly prepared Jones reagent [Na2Cr2O7, (66.5 g, 226 mmol) and H2SO4 (60 mL) in water (500 mL)] during 1 h in an ice bath. The reaction mixture was allowed to warm to room temperature and stirring was continued for 21 h. First, MeOH (700 mL) was added and then water (1000 mL) to the reaction mixture. Precipitate was filtered off and washed with water (500 mL). The crude product was dried in a vacuum, dissolved to Et2O (600 mL) and washed with water (300 mL), 7.5% hydrochloric acid (200 mL), water (200 mL), a saturated aqueous solution of NaHCO3 (200 mL) and water (200 mL). Two thirds of Et2O was removed in vacuo, and the residue was treated with a 10% aqueous solution of NaOH (75 mL). The formed precipitate was filtered off by suction, and dried in vacuo. Precipitate was dissolved to boiling MeOH (100 mL), and acetic acid (10 mL) was added. The product was precipitated by adding water (200 mL) and then filtered by suction, washed with water (300 mL) and dried in vacuo to give betulonic acid (22.3 g, 44%) as a white solid. mp 230-235 °C; Rf 0.4 (1:4 EtOAc/n-hexane); 1H NMR (300 MHz, CDCl3) δ 4.74 (s, 1H), 4.62 (s, 1H), 3.01 (m, 1H), 2.44 (m, 2H), 2.27 (m, 2H), 1.96 (m, 3H),
1.70 (s, 3H), 1.07 (s, 3H), 1.02 (s, 6H), 0.99 (s, 3H), 0.93 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 218.4, 181.9, 150.3, 109.7, 56.3, 49.8, 49.1, 47.3, 46.9, 42.5, 40.6, 39.6, 38.5, 37.0, 36.9, 34.1, 33.6, 32.1, 30.5, 29.6, 26.6, 25.5, 21.3, 21.0, 19.6, 19.3, 15.9, 15.8, 14.6; FTIR (v, cm⁻¹): 883, 1692, 2944; MS (ESI+): m/z 455.3 [M+1]+; Anal. (C30H46O3) C, H: calcd, 79.25, 10.20; found, 78.32, 10.16. NMR spectral data is consistent with those previously reported.²

Betulonic acid (26)
To a solution of betulonic acid 2 (10.0 g, 22.1 mmol) in 2-propanol (400 mL) was added NaBH₄ (1.76 g, 44.2 mmol) during 10 min, and the reaction mixture was stirred at room temperature for 2.5 h.² 10% Hydrochloric acid (600 mL) was added, and the precipitated product was filtered by suction, washed with water (200 mL) and dried in a vacuum oven. The crude product was crystallized from EtOH to give 26 (8.25 g, 82 %) as white crystals. mp 288-290 °C; Rf 0.3 (1:4 EtOAc/n-hexane); 1H NMR (300 MHz, CDCl3) δ 0.75 (s, 3H), 0.82 (s, 3H), 0.93 (s, 3H), 0.96 (s, 6H), 0.97 (s, 3H), 1.09 (s, 3H), 1.97 (m, 2H), 2.28 (m, 2H), 3.01 (m, 1H), 3.19 (dd, J = 5.5, 10.7 Hz, 1H), 4.60 (s, 1H), 4.74 (s, 1H); 13C NMR (75 MHz, DMSO) δ 14.4, 15.7, 15.8, 16.0, 18.0, 19.0, 20.5, 25.1, 27.2, 28.1, 30.1, 31.7, 34.0, 36.4, 36.7, 37.6, 38.3, 38.5, 40.3, 42.0, 46.6, 48.6, 50.0, 54.9, 55.4, 76.8, 109.7, 150.3, 177.3; FTIR (v, cm⁻¹): 884, 1034, 1236, 1689, 2942; MS (direct, EI+): m/z 456; Anal. (C 30H48O3) C, H. NMR spectral data is consistent with those previously reported.²

Betulonic aldehyde (22)
Betulin (2.0 g, 4.5 mmol) was stirred with pyridinium chlorochromate (5.8 g, 27 mmol) in CH₂Cl₂ (200 mL) for 1 h at room temperature. The reaction mixture was filtered through alumina pad, the resulting filtrate was concentrated, and purified with SiO₂ column chromatography (15-25% EtOAc/n-hexane) to yield a white crystalline product (533 mg, 27%). 1H NMR (300 MHz, CDCl3) δ 9.67 (s, 1H), 4.76 (s, 1H), 4.64 (s, 1H), 2.87 (m, 2H), 2.57–2.31 (m, 5H), 2.13–1.99 (m, 4H), 1.97–1.83 (m, 5H), 1.77 (m, 6H), 1.70 (s, 3H), 1.53–1.14 (m, 6H), 1.07 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H). NMR spectral data is consistent with those previously reported.²

1β-Lup-2,20(29)-diieno[3,2-b]indol-28-oic acid (3)
Betulonic acid (0.10 g, 0.22 mmol) and the corresponding phenylhydrazine hydrochloride (0.35 g, 0.24 mmol) were dissolved in acetic acid (10 mL) and refluxed (130 °C) for 3 h. Water was added and the resulting mixture was extracted with Et₂O. The organic phase was washed with water and brine, dried over anhydrous Na₂SO₄, and the solvents were evaporated. The crude product was purified with SiO₂ column chromatography (25-50% EtOAc/n-hexane) to give a yellowish solid (49 mg, 42%). 1H NMR (300 MHz, CDCl3) δ 7.71 (s, 1H), 7.37 (m, 1H), 7.29 (m, 1H), 7.08 (m, 2H), 4.79 (s, 1H), 4.65 (s, 1H), 3.08 (m, 1H), 2.83 (d, J = 15.0 Hz, 1H), 2.38–2.09 (m, 4H), 1.73 (s, 3H), 1.68–1.31 (m, 12H), 1.28 (s, 3H), 1.17 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 0.88 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 181.7, 150.4, 149.9, 136.2, 128.4, 121.0, 119.0, 117.9, 110.3, 109.8, 107.1, 56.5, 53.3, 49.4, 49.4, 47.0, 42.5, 40.8, 38.7, 38.3, 37.1, 34.1, 33.6, 32.2, 31.6, 30.9, 29.9, 25.7, 23.1, 22.6, 21.5, 19.4, 19.2, 16.3, 15.9, 14.8; FTIR (v, cm⁻¹): 738, 885, 907, 1459, 1693, 2873, 2843; HRMS: m/z calcd for C36H50NO2 528.3842, found 528.3838 [M+H]+. NMR spectral data is consistent with those previously reported.³
5'-Methoxy-1'-lupa-2,20(29)-dieno[3,2-b]indol-28-oic acid. (4)
Synthesized from 4-methoxyphenylhydrazine hydrochloride (0.47 g, 0.27 mmol) according to the above-mentioned procedure. A yellowish solid (25 mg, 21%) 1H NMR (300 MHz, CDCl3) δ 7.56 (s, 1H), 7.17 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 2.5 Hz, 1H), 6.76 (dd, J = 8.7, 2.5 Hz, 1H), 4.77 (s, 1H), 4.63 (s, 1H), 3.84 (s, 3H), 3.07 (m, 1H), 2.79 (d, J = 14.8 Hz, 1H), 2.21 (m, 4H), 2.00 (m, 3H), 1.70 (s, 3H), 1.67–1.35 (m, 12H), 1.27 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H), 0.88 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 181.9, 153.8, 150.4, 141.9, 131.2, 128.7, 111.0, 110.7, 109.8, 107.0, 100.3, 56.4, 55.9, 53.3, 49.4, 49.3, 47.0, 42.5, 40.8, 38.7, 38.3, 37.1, 34.2, 33.6, 32.1, 31.6, 30.9, 29.8, 25.7, 23.2, 21.4, 19.3, 19.2, 16.4, 15.8, 14.8; FTIR (ν, cm⁻¹): 795, 882, 1173, 1203, 1454, 1693, 2870, 2941; HRMS: m/z calcd for C37H52NO3 558.3947, found 558.3947 [M+H]+. NMR spectral data is consistent with those previously reported.3

4-Aza-3-oxo-homolup-20(29)-en-28-oic acid (8)
A mixture of betulonic acid (0.20 g, 0.44 mmol), hydroxylamine hydrochloride (290 mg, 4.2 mmol), dry pyridine (5 mL) and methanol (8 mL) was refluxed for 16 h. Water was added, and the precipitated 3-oximinolup-20(29)-en-28-oic acid was filtered and collected (173 mg, 84%). 3-Oximinolup-20(29)-en-28-oic acid (86 mg, 0.18 mmol) was dissolved in CH2Cl2 (5 mL), and the resulting solution cooled to the ice-water bath temperature. Trifluoroacetic anhydride (1.0 mL, 7.1 mmol) was added to this solution and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was washed with water, a saturated aqueous solution of NaHCO3, and evaporated. The crude product was purified with SiO2 column chromatography (0-10% MeOH/CH2Cl2) to yield a white crystalline solid (28 mg, 33%). 1H NMR (300 MHz, CDCl3) δ 6.39 (s, 1H), 4.73 (s, 1H), 4.61 (s, 1H), 2.99 (m, 1H), 2.59–2.41 (m, 1H), 2.42–2.15 (m, 4H), 2.13–1.94 (m, 2H), 1.69 (s, 3H), 1.57–1.33 (m, 15H), 1.31 (s, 3H), 1.23 (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 181.1, 177.3, 150.3, 109.7, 56.3, 56.3, 53.0, 51.0, 49.1, 46.9, 42.6, 40.7, 40.3, 39.2, 38.6, 37.1, 33.6, 33.1, 32.1, 31.8, 30.6, 29.6, 27.0, 25.8, 22.5, 22.0, 19.4, 18.3, 15.9, 14.5; FTIR (ν, cm⁻¹): 731, 883, 1185, 1374, 1454, 1628, 1691, 2938, 3250; HRMS: m/z calcd for C30H48NO3 470.3634, found 470.3630 [M+H]+.

(3β,18α,19β)-19,28-Epoxyoleanan-3-ol (allobetulin) (19)
Betulin (2.0 g, 4.5 mmol) was refluxed in formic acid (40 mL) for 45 min. The reaction mixture was cooled to room temperature, filtered, washed with ethanol and recrystallized from benzene. The resulting crystals of allobetulin formate were refluxed in a mixture consisting of a 1 M ethanolic solution of KOH (15 mL) and benzene (2.5 mL) for 30 min. Solvents were evaporated, and the residue was washed with ether and water. Recrystallization from ethanol gave allobetulin (0.5 g, 25%). 1H NMR (300 MHz, CDCl3) δ 3.77 (d, J = 7.6 Hz, 1H), 3.52 (s, 1H), 3.43 (d, J = 7.8 Hz, 1H), 3.20 (m, 1H), 1.80–1.00 (m, 22H), 0.97 (s, 6H), 0.92 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H), 0.79 (s, 3H), 0.76 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 99.8, 87.9, 79.0, 71.3, 55.5, 51.1, 46.8, 41.5, 40.7, 40.6, 38.9, 38.9, 37.3, 36.8, 36.3, 34.1, 33.9, 32.7, 28.8, 28.0, 27.4, 26.4, 26.3, 24.6, 21.0, 18.3, 16.5, 15.7, 15.4, 13.5. NMR spectral data is consistent with those previously reported.5

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(18α,19β)-19,28-Epoxyoleanan-3-one (allobetulone)

To a solution of allobetulin (1.6 g, 3.7 mmol) in acetone (225 mL) was added freshly prepared Jones reagent [Na2Cr2O7, (0.9 g, 3.1 mmol) and H2SO4 (0.9 mL) in water (3.7 mL)] dropwise in an ice bath. The reaction mixture was allowed to warm to room temperature and stirring was continued for 21 h. First, MeOH (100 mL) and reaction mixture was poured into ice with HCl. Solids were filtered and dissolved with THF, organic phase was washed with water twice, dried over Na2SO4, and evaporated yielding white crystalline solid (1.4 g, 88%). 1H NMR (300 MHz, CDCl3) δ 3.78 (d, J = 7.8 Hz, 1H) 3.53 (s, 1H), 3.45 (d, J = 7.8 Hz, 1H), 2.45 (m, 2H), 1.94 (m, 1H), 1.11–1.71 (m, 15H), 1.08 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.80 (s, 3H). NMR spectral data is consistent with those previously reported.

19β,28-Epoxy[3,2-b]indole-18α-oleanan (20)

A mixture of allobetulone (0.10 g, 0.23 mmol) and phenylhydrazine hydrochloride (0.034 g, 0.24 mmol) in acetic acid (10 mL) was refluxed (130 °C) for 3 h. Water was added and the resulting mixture was extracted with Et2O. The organic phase was washed with water and brine, dried over anhydrous Na2SO4 and evaporated to dryness. The crude product was purified with SiO2 column chromatography (5-50% EtOAc/n-hexane) to yield 19β,28-epoxy[3,2-b]indole-18α-oleanan as a yellowish crystalline solid (67 mg, 57%). mp 303 °C; 1H NMR (300 MHz, CDCl3) δ 7.80 (s, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.30 (m, 1H), 7.21–7.08 (m, 2H), 3.84 (d, J = 7.7 Hz, 1H), 3.62 (s, 1H), 3.50 (d, J = 7.7 Hz, 1H), 2.89 (d, J = 15.0 Hz, 1H), 2.38 (s, 2H), 2.19 (d, J = 15.0 Hz, 1H), 1.34-1.79 (m, 15H), 1.31 (s, 3H), 1.22 (s, 3H), 1.08 (s, 3H), (s, 1H) 0.98 (s, 3H), 0.99 (s, 3H), 0.85 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 140.9, 136.1, 120.9, 118.9, 117.9, 110.3, 107.0, 87.9, 71.3, 55.0, 53.4, 50.4, 49.9, 46.8, 41.5, 40.8, 39.8, 36.7, 36.3, 34.3, 34.1, 33.1, 32.7, 31.6, 30.9, 28.8, 26.4, 24.5, 23.1, 22.7, 21.5, 19.6, 19.2, 15.5, 14.1, 13.6. FTIR (ν, cm-1): 739, 1457, 2912; HRMS: m/z calcd for C36H52NO: 514.4049, found 514.4048 [M+H]+.

5'-Fluoro-19β,28-epoxy[3,2-b]indole-18α-oleanan (21)

Synthesized from allobetulone (0.10 g, 0.23 mmol) and 4-fluorophenylhydrazine hydrochloride (0.034 g, 0.24 mmol) in acetic acid (10 mL) was refluxed (130 °C) for 3 h. Water was added and the resulting mixture was extracted with Et2O. The organic phase was washed with water and brine, dried over anhydrous Na2SO4 and evaporated to dryness. The crude product was purified with SiO2 column chromatography (5-50% EtOAc/n-hexane) to yield 5'-fluoro-19β,28-epoxy[3,2-b]indole-18α-oleanan as a yellowish crystalline solid (77 mg, 63%). 1H NMR (300 MHz, CDCl3) δ 7.71 (s, 1H), 7.18 (dd, J = 8.7, 4.3 Hz, 1H), 6.84 (m, 1H), 3.81 (d, J = 7.7 Hz, 1H), 3.59 (s, 1H), 3.47 (d, J = 7.7 Hz, 1H), 2.79 (d, J = 15.0 Hz, 1H), 2.14 (d, J = 15.0 Hz, 1H), 1.81–1.33 (m, 16H), 1.30 (s, 3H), 1.25 (m, 4H) 1.20 (s, 3H) 0.97 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 143.0, 132.6, 110.7, 110.6, 109.0, 108.7, 103.2, 102.9, 88.0, 71.3, 53.5, 49.9, 46.9, 41.6, 40.8, 40.7, 38.4, 37.4, 36.8, 36.3, 34.4, 34.3, 33.2, 32.8, 30.9, 28.8, 26.6, 26.3, 24.6, 23.2, 21.6, 19.2, 16.7, 15.6, 13.6. FTIR (ν, cm-1): 791, 1170, 1457, 2912; HRMS: m/z calcd for C36H51NOF: 532.3955, found 532.3953 [M+H]+.
Lupa-2,20(29)-dieno[2,3-b]pyrazin-28-oic acid (5)
A mixture of betulonic acid (0.20 g, 0.44 mmol), 1,2-diaminoethane (130 mg, 2.0 mmol), sulfur (130 mg, 4.1 mmol) and morpholine (4 mL) was refluxed for 21 h. Water was added and the resulting mixture was extracted with CH$_2$Cl$_2$. The organic phase was washed with 1 M hydrochloric acid, water, a saturated aqueous solution of NaHCO$_3$, water and brine, dried over anhydrous Na$_2$SO$_4$ and evaporated. The crude product was purified with SiO$_2$ column chromatography (20-50% EtOAc/n-hexane) to give a white crystalline solid (147 mg, 68%).

1H NMR (300 MHz, CDCl$_3$) $\delta$ 8.42 (d, $J = 2.4$ Hz, 1H), 8.29 (d, $J = 2.4$ Hz, 1H), 4.76 (s, 1H), 4.64 (s, 1H), 3.05 (m, 2H), 2.46 (d, $J = 16.5$ Hz, 1H), 2.29 (m, 2H), 1.30 (s, 3H), 1.72 (s, 3H), 1.27 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H), 0.81 (s, 3H); 13C NMR (75 MHz, CDCl$_3$) $\delta$ 181.5, 160.0, 151.0, 150.5, 142.6, 141.5, 110.0, 56.6, 53.2, 49.4, 49.0, 48.7, 47.1, 42.7, 40.8, 39.7, 38.7, 37.3, 37.0, 33.6, 32.4, 31.7, 30.8, 30.0, 25.7, 24.2, 21.6, 20.3, 19.7, 16.4, 15.9, 14.9; FTIR (v, cm$^{-1}$): 878, 1107, 1381, 1408, 1686, 2869, 2943; HRMS: m/z calcd for C$_{32}$H$_{47}$N$_2$O$_2$ 491.3638, found 491.3637 [M+H]$^+$. 1H NMR spectral data is consistent with those previously reported.

1'H-Lup-20(29)-eno[2,3-b]pyridin-28-oic acid (9)
A mixture of betulonic acid (100 mg, 0.22 mmol), propargylamine (24 mg, 0.44 mmol), Cu(I)Cl (5.0 mg, 0.050 mmol) and ethanol (5 mL) was refluxed for 17 h. The resulting solution was filtered, evaporated, and the crude product was purified with SiO$_2$ column chromatography (10-20% EtOAc/n-hexane) to yield a crystalline solid (12 mg, 11%).

1H NMR (300 MHz, CDCl$_3$) $\delta$ 8.47 (m, 1H), 7.27 (m, 1H), 7.02 (dd, $J = 7.6$, 4.8 Hz, 1H), 4.75 (s, 1H), 4.62 (s, 1H), 3.10 (m, 1H), 2.74 (d, $J = 15.9$ Hz, 1H), 2.32 (m, 3H), 2.03 (m, 2H), 1.70 (s, 3H), 1.67–1.36 (m, 15H), 1.32 (s, 3H), 1.27 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.78 (s, 3H). 13C NMR (75 MHz, CDCl$_3$) $\delta$ 180.3, 163.6, 150.8, 146.8, 138.3, 130.1, 121.1, 109.7, 56.6, 53.8, 49.5, 49.0, 47.12 46.1, 42.7, 40.8, 39.6, 38.7, 37.2, 36.4 , 33.7, 32.5, 31.6, 30.9, 30.0, 25.8, 24.2, 21.7, 20.4, 19.6, 16.0, 15.9, 14.8; FTIR (v, cm$^{-1}$): 1012, 1045, 1110, 1132, 1184, 1457, 1457, 2856, 2927, 2959; HRMS: m/z calcd for C$_{33}$H$_{48}$NO$_2$ 490.3685, found 490.3683 [M+H]$^+$. 1H NMR spectral data is consistent with those previously reported.

Benzyl 3-oxolup-20(29)-en-28-oate (benzyl betulanate)
A mixture of betulonic acid (0.50 g, 1.1 mmol), K$_2$CO$_3$ (0.76 g, 5.5 mmol) and DMF (7 mL) was warmed to 55 °C, and benzyl bromide (0.28 mg, 1.7 mmol) was added dropwise to the mixture. After stirring the reaction mixture at 55 °C overnight, water was added and the resulting solution was extracted with EtOAc. The organic phase was washed several times with water and subsequently with brine, dried over anhydrous Na$_2$SO$_4$ and evaporated. The crude product was purified with SiO$_2$ column chromatography (20-50% EtOAc/n-hexane) to give a white crystalline solid (230 mg, 43%).

1H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35 (m, 5H), 5.12 (q, $J = 12.3$ Hz, 2H), 4.72 (s, 1H), 4.60 (s, 1H), 3.16–2.93 (m, 1H), 2.35 (m, 4H), 1.97–1.79 (m, 3H), 1.66 (s, 3H), 1.49–1.19 (m, 15H), 1.06 (s, 3H), 1.01 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H), 0.79 (s, 3H). NMR spectral data is consistent with those previously reported.
3-Oxolupan-28-oic acid (dihydrobetulonic acid)
To a solution of benzyl 3-oxolup-20(29)-en-28-oate (260 mg, 0.48 mmol) in EtOAc (10 mL), 10% Pd on carbon (30 mg) was added under argon. The argon atmosphere was replaced with H₂ and the reaction mixture was stirred at room temperature for 3 d. The reaction mixture was filtered through a thin layer of Celite, and the resulting filtrate was evaporated to yield a white crystalline solid (170 mg, 77%). ¹H NMR (300 MHz, CDCl₃) δ 2.58–2.34 (m, 2H), 2.33–2.16 (m, 3H), 1.98–1.56 (m, 5H), 1.42 (s, 5H), 1.36–1.12 (m, 7H), 1.07 (s, 3H), 0.96 (s, 6H), 0.93 (s, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H). NMR spectral data is consistent with those previously reported.¹⁰

A mixture of betulin (1.0 g, 2.3 mmol), pyridine p-toluenesulfonate (3.20 g, 12.7 mmol), 3,4-dihydro-2H-pyran (0.26 g, 3.1 mmol) and CH₂Cl₂ (30 mL) was stirred at room temperature for 20 h. The resulting solution was washed with a saturated aqueous solution of NaHCO₃, water, and brine, dried over Na₂SO₄ and evaporated. The crude product was purified with SiO₂ column chromatography (10% EtOAc/n-hexane) to yield a white crystalline product (956 mg, 80%). ¹H NMR (300 MHz, CDCl₃) δ 4.73 (s, 1H), 4.67 (s, 1H), 4.57 (m, 3H), 3.88 (m, 3H), 3.62–3.32 (m, 3H), 3.11 (m, 2H), 2.44 (m, 1H), 1.92 (m, 5H), 1.68 (s, 3H), 1.51 (m, 9H), 1.40 (m, 5H), 1.32–1.21 (m, 4H), 1.03 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.89 (s, 3H), 0.83 (s, 3H), 0.78 (s, 3H).

28-[(Tetrahydro-2H-pyran-2-yl)oxy]lup-20(29)-en-3-one
A mixture of 3-hydroxy-28-[(tetrahydro-2H-pyran-2-yl)oxy]lup-20(29)-ene (0.62 g, 1.2 mmol), PCC (0.76 g, 3.5 mmol) and CH₂Cl₂ (10 mL) was stirred at room temperature overnight. The reaction mixture was poured into a saturated aqueous solution of NaHCO₃, water, and brine, dried over Na₂SO₄ and evaporated. The crude product was purified with SiO₂ column chromatography (10-25% EtOAc/n-hexane) to yield a crystalline product (0.28 g, 46%). ¹H NMR (300 MHz, CDCl₃) δ 4.67 (s, 1H), 4.60–4.49 (m, 2H), 3.85 (m, 1H), 3.52 (d, J = 9.8 Hz, 1H), 3.37 (d, J = 9.4 Hz, 1H), 2.99 (d, J = 9.4 Hz, 1H), 2.57–2.25 (m, 3H), 2.11–1.71 (m, 6H), 1.71–1.64 (m, 6H), 1.57–1.15 (m, 19H), 1.06 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.91 (s, 3H).
2-(Hydroxymethylene)-3-oxo-20(29)-dihydrolup-28-oic acid\textsuperscript{12}

A mixture of dihydrobetulonic acid (0.227 g, 0.497 mmol), NaH (60\% dispersion in mineral oil, 0.580 g, 14.5 mmol) and dry THF (20 mL) was cooled to the ice-water bath temperature. To this solution ethyl formate (0.845 g, 11.4 mmol) was added, the resulting mixture was warmed to room temperature and stirred overnight. A saturated aqueous solution of NH\textsubscript{4}Cl was added, and the resulting mixture was extracted with EtOAc, washed with water and brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, and evaporated. The crude product was purified with SiO\textsubscript{2} column chromatography (15\% EtOAc/\textit{n}-hexane) to yield a white crystalline solid (136 mg, 56\%). \textsuperscript{13} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 14.85 (s, 1H), 8.61 (d, \(J = 2.9\) Hz, 1H), 2.28 (m, 4H), 1.97–1.46 (m, 9H), 1.45–1.21 (m, 12H), 1.18 (s, 3H), 1.10 (s, 3H), 0.98 (s, 6H), 0.87 (d, \(J = 6.8\) Hz, 3H), 0.83 (s, 3H), 0.76 (d, \(J = 6.8\) Hz, 3H).

2-(Hydroxymethylene)-3-oxolup-20(29)-en-28-oic acid\textsuperscript{12} (12)

Synthesized from betulonic acid (0.20 g, 0.44 mmol) according to the above-mentioned procedure. A white crystalline solid (50 mg, 24\%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 14.85 (d, \(J = 2.6\) Hz, 1H), 9.88 (br s, 1H), 8.58 (d, \(J = 2.6\) Hz, 1H), 2.28 (m, 3H), 2.09–1.80 (m, 3H), 1.70 (s, 3H), 1.46 (m, 16H), 1.18 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.83 (s, 3H).


Synthesized from 28-[(tetrahydro-2\textit{H}-pyran-2-yl)oxy]lup-20(29)-en-3-one (0.28 g, 0.54 mmol) according to the above-mentioned procedure. A white crystalline solid (156 mg, 52\%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 14.84 (s, 1H), 8.58 (s, 1H), 4.75 (d, \(J = 2.1\) Hz, 1H), 4.62 (s, 1H), 3.03 (m, 1H), 2.28 (m, 3H), 1.96 (m, 2H), 1.72 (s, 3H), 1.59–1.32 (m, 11H), 1.18 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.83 (s, 3H).
1'H-Lup-20(29)-en[3,2-c]pyrazol-28-oic acid (11)

A mixture of 2-(hydroxymethylene)-3-oxolup-20(29)-en-28-oic acid (53 mg, 0.11 mmol), hydrazine hydrate (16 mg, 0.31 mmol) and toluene (20 mL) was refluxed at 150 °C under the Dean-Stark conditions overnight. After cooling the reaction mixture to room temperature, solvent was evaporated, and the resulting crude product was purified with SiO₂ column chromatography (1-10% EtOAc/n-hexane) to give a white crystalline solid (42 mg, 80%).  

$\text{^1H NMR (300 MHz, CD}_3\text{OD)} \delta 7.16 (s, 1H), 4.72 (s, 1H), 4.60 (s, 1H), 3.04 (m, 1H), 2.64 (d, J = 14.8 Hz, 1H), 1.91 (m, 2H), 1.70 (s, 3H), 1.65–1.33 (m, 11H), 1.26 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H), 0.80 (s, 3H); \text{^13C NMR (75 MHz, CD}_3\text{OD)} \delta 178.8, 150.8, 149.9, 133.2, 112.4, 110.9, 56.3, 53.8, 49.4, 49.2, 47.3, 42.5, 40.8, 38.6, 36.9, 36.5, 33.6, 33.4, 32.1, 30.6, 30.1, 29.8, 25.8, 22.8, 21.4, 19.1, 18.4, 15.3, 15.2, 14.0; FTIR (ν, cm⁻¹): 883, 960, 1086, 1184, 1370, 1452, 1643, 1695, 2869, 2943; m/z calcd for C₃₁H₄₇N₂O₂: 479.3638; found 479.3638 [M+H]^+.

NMR spectral data is consistent with those previously reported.¹²

Lupa-2,20(29)-dieno[2,3-d]isoxazol-28-oic acid (10)

A mixture of 2-(hydroxymethylene)-3-oxolup-20(29)-en-28-oic acid (0.091 g, 0.18 mmol), hydroxylamine hydrochloride (0.036 g, 0.52 mmol) and acetic acid (10 mL) was refluxed for 3 h. Water was added, and the resulting mixture was extracted with EtOAc, washed with a saturated aqueous solution of NaHCO₃, water, and brine, dried over anhydrous Na₂SO₄, and evaporated to give a white crystalline (59 mg, 68%).

$\text{^1H NMR (300 MHz, CDCl}_3\text{)} \delta 10.92 (br s, 1H), 7.97 (s, 1H), 4.75 (s, 1H), 4.63 (s, 1H), 3.06–2.92 (m, 1H), 2.47 (d, J = 15.1 Hz, 1H), 2.36–2.19 (m, 3H), 2.06–1.88 (m, 3H), 1.70 (s, 3H), 1.60–1.33 (m, 15H), 1.28 (s, 3H), 1.19 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.81 (s, 3H); \text{^13C NMR (75 MHz, CDCl}_3\text{)} \delta 181.3, 173.0, 150.3, 150.3, 109.8, 108.9, 56.4, 53.6, 49.1, 49.1, 47.3, 42.5, 40.8, 39.0, 38.5, 37.0, 35.9, 34.8, 33.4, 32.1, 30.6, 29.8, 28.7, 25.5, 21.4, 21.2, 19.4, 18.8, 16.1, 15.8, 14.7; FTIR (ν, cm⁻¹): 791, 1170, 1454, 1484, 2866, 2924; HRMS: m/z calcd for C₃₁H₄₆NO₃ 480.3478, found 480.3478 [M+H]^+. NMR spectral data is consistent with those previously reported.¹²

20(29)-Dihydrolup-2-en[2,3-d]isoxazol-28-oic acid (14)

Synthesized from 2-(hydroxymethylene)-3-oxolupan-28-oic acid (0.136 g, 0.281 mmol) according to the above-mentioned procedure. A white crystalline solid (121 mg, 90%). $\text{^1H NMR (300 MHz, CDCl}_3\text{)} \delta 7.98 (s, 1H), 2.50 (d, J = 15.1 Hz, 1H), 2.28 (m, 3H), 1.99–1.65 (m, 5H), 1.64–1.34 (m, 13H), 1.28 (s, 3H), 1.19 (s, 3H), 0.98 (s, 6H), 0.87 (d, J = 6.8 Hz, 3H), 0.81 (s, 3H), 0.77 (d, J = 6.8 Hz, 3H); \text{^13C NMR (75 MHz, CDCl}_3\text{)} \delta 181.7, 173.2, 150.5, 109.1, 57.0, 53.8, 49.1, 48.9, 44.4, 42.9, 41.0, 39.1, 38.5, 37.6, 36.1, 35.0, 33.6, 32.2, 30.0, 30.0, 28.9, 27.1, 23.2, 23.0, 21.6, 21.4, 19.0, 16.2, 16.0, 14.9, 14.8; FTIR (ν, cm⁻¹): 791, 1170, 1454, 1484, 2866, 2924; HRMS: m/z calcd for C₃₁H₄₆NO₃ 482.3634, found 482.3635 [M+H]^+. NMR spectral data is consistent with those previously reported.¹²
28-Acetoxylupa-2,20(29)-dieno[2,3-d]isoxazole (17)
Synthesized from 2-(hydroxymethylene)-3-oxo-28-[(tetrahydro-2H-pyran-2-yl)oxy]lup-20(29)-ene (0.68 g, 0.12 mmol) according to the above-mentioned procedure. A white crystalline solid (66 mg, quant.). 1H NMR (300 MHz, CDCl 3) δ 7.97 (s, 1H), 4.71 (s, 1H), 4.61 (s, 1H), 4.28 (d, J = 10.9 Hz, 1H), 3.83 (d, J = 10.9, 1H), 2.57–2.37 (m, 3H), 2.07 (s, 3H), 2.03–1.76 (m, 6H), 1.68 (s, 3H), 1.61–1.38 (m, 14H), 1.30 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 0.99 (s, 3H), 0.81 (s, 3H); 13C NMR (126 MHz, CDCl 3) δ 173.0, 171.6, 150.3, 150.1, 109.9, 108.9, 62.8, 53.5, 49.0, 48.7, 46.3, 42.8, 40.9, 38.9, 37.7, 35.8, 34.6, 33.2, 29.7, 29.6, 28.7, 27.2, 25.2, 21.3, 21.3, 21.1, 18.8, 16.1, 15.8, 14.7; FTIR (ν, cm⁻¹): 731, 1034, 1233, 1367, 1457, 1738, 2866, 2946. HRMS: m/z calcd for C 33H50NO3 508.3791, found 508.3794 [M+H].

28-Hydroxylupa-2,20(29)-dieno[2,3-d]isoxazole (15)
A mixture of lupa-2,20(29)-dieno-28-[(tetrahydro-2H-pyran-2-yl)oxy][2,3-d]isoxazole (0.066 g, 0.12 mmol), p-toluenesulfonic acid (0.009 mg, 0.048 mmol) and MeOH (5 mL) was stirred at 60 °C overnight. Solvent was evaporated, and the crude product was purified with SiO2 column chromatography (10% EtOAc/n-hexane) to yield a white crystalline solid (56 mg, quant.). 1H NMR (300 MHz, CDCl 3) δ 7.96 (s, 1H), 4.70 (d, J = 2.2 Hz, 1H), 4.60 (d, J = 2.2, 1H), 3.80 (d, 9.6 Hz, 1H), 3.36 (d, J = 9.6 Hz, 1H), 2.43 (m, 2H), 2.02–1.79 (m, 5H), 1.70 (s, 3H), 1.47 (m, 1H), 1.30 (s, 3H), 1.27 (m, 5H), 1.20 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 0.81 (s, 3H); 13C NMR (75 MHz, CDCl 3) δ 173.0, 150.4, 150.2, 109.7, 108.9, 60.5, 53.5, 49.0, 48.7, 47.8, 42.8, 41.0, 38.9, 37.4, 35.8, 34.8, 34.0, 33.2, 29.8, 29.1, 28.7, 27.2, 25.2, 21.4, 21.2, 19.1, 18.8, 16.0, 15.7, 14.7; FTIR (ν, cm⁻¹): 878, 1028, 1457, 2943; HRMS: m/z calcd for C31H48NO2 466.3685, found 466.3688 [M+H]+. NMR spectral data is consistent with those previously reported. 

28-Oxolupa-2,20(29)-dieno[2,3-d]isoxazole (18)
28-Hydroxylupa-2,20(29)-dieno[2,3-d]isoxazole (0.056 g, 0.12 mmol) was dissolved with THF (2 mL), DMSO (2 mL) was added following with IBX (0.047 g, 0.17 mmol) in DMSO (5 mL) and mixture was stirred at room temperature for 3.5 h. Solvent was evaporated, and the crude product was purified with SiO2 column chromatography (10% EtOAc/n-hexane) to yield a crystalline product (31 mg, 51%). 1H NMR (300 MHz, CDCl 3) δ 9.66 (d, J = 9.6 Hz, 1H), 7.96 (m, 1H), 4.77 (m, 1H), 4.65 (m, 1H), 2.88 (td, J = 11.1, 5.7 Hz, 1H), 2.47 (m, 1H), 2.59–2.36 (m, 1H), 2.18–1.73 (m, 8H), 1.70 (s, 3H), 1.60–1.39 (m, 12H), 1.28 (s, 3H), 1.18 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.80 (s, 3H); 13C NMR (75 MHz, CDCl 3) δ 206.4, 150.3, 149.7, 110.2, 109.7, 108.9, 60.5, 53.5, 49.0, 48.7, 47.8, 42.8, 41.0, 38.9, 37.4, 35.8, 34.8, 34.0, 33.2, 29.8, 29.1, 28.7, 27.2, 25.2, 21.4, 21.2, 19.1, 18.8, 16.0, 15.7, 14.7; FTIR (ν, cm⁻¹): 731, 908, 1069, 1178, 1271, 1378, 1457, 1719, 2937; HRMS: m/z calcd for C31H46NO2: 464.3529, found 464.3527 [M+H]+. NMR spectral data is consistent with those previously reported.
Lupa-2,20(29)-dieno[2,3-b]pyrazin-28-amide (6)
A mixture of lupa-2,20(29)-dieno[2,3-b]pyrazin-28-oic acid (141 mg, 0.28 mmol), oxalyl chloride (44 mg, 0.34 mmol), and a drop of DMF in dry THF (10 mL) was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was dissolved in EtOAc. The organic phase was washed with a saturated aqueous solution of NaHCO3, water and brine, dried over anhydrous Na2SO4 and evaporated. The resulting crude lupa-2,20(29)-dieno[2,3-b]pyrazin-28-oyl chloride was dissolved in chloroform (5 mL), and a water solution of 25% ammonia (2 mL) was added to the mixture. The resulting solution was stirred at room temperature for 30 min and evaporated to dryness to give a white crystalline solid (137 mg, quant). 1H NMR (300 MHz, CD3OD) δ 8.44 (d, J = 2.5 Hz, 1H), 8.26 (d, J = 2.5 Hz, 1H), 4.73 (d, J = 2.3 Hz, 1H), 4.61 (dd, J = 2.3, 1.4 Hz, 1H), 3.17 – 3.06 (m, 1H), 3.01 (d, J = 16.6 Hz, 1H), 2.73 – 2.59 (m, 1H), 2.51 (d, J = 16.6 Hz, 1H), 2.20 – 2.05 (m, 1H), 2.04 – 1.74 (m, 4H), 1.71 (s, 3H), 1.70 – 1.33 (m, 16H), 1.31 (s, 3H), 1.29 (s, 3H), 1.07 (s, 3H), 1.07 (s, 3H), 0.83 (s, 3H).; 13C NMR (75 MHz, CD3OD) δ 182.4, 161.4, 152.3, 152.0, 143.8, 142.3, 110.0, 57.1, 54.3, 51.2, 50.1, 48.1, 43.7, 41.9, 40.6, 39.4, 39.1, 37.9, 34.6, 34.3, 31.9, 31.8, 30.7, 27.0, 24.4, 22.8, 21.2, 19.6, 16.6, 16.3, 15.0; FTIR (ν, cm-1): 886, 1107, 1184, 1402, 1665, 2869, 2948, 3044, 3129; HRMS: m/z calcd for C32H48N3O 489.3797, found 490.3796 [M+H]+.

Lupa-2,20(29)-dieno[2,3-b]isoxazol-28-oic amide (13)
Synthesized from lupa-2,20(29)-dieno[2,3-b]isoxazol-28-oic acid (0.029 g, 0.06 mmol) according to the above-mentioned procedure. A white crystalline product (28 mg, quant.) 1H NMR (300 MHz, CD3OD) δ 8.10 (s, 1H), 4.70 (m, 1H), 4.62 (m, 1H), 2.55 (d, J = 12.2 Hz, 1H), 2.02-1.82 (m, 4H) 1.70 (s, 3H), 1.63–1.33 (m, 15H), 1.29 (s, 3H), 1.20 (s, 3H), 1.4 (s, 6H), 0.83 (s, 3H); 13C NMR (75 MHz, CD3OD) δ 173.2, 152.2, 154.0, 110.0, 109.7, 54.4, 50.8, 50.1, 47.5, 43.3, 41.6, 39.7, 38.8, 38.3, 36.5, 35.5, 34.3, 33.9, 31.6, 30.4, 29.0, 26.6, 22.4, 21.6, 19.7, 19.6, 16.5, 16.4, 15.0; FTIR (ν, cm-1): 881, 1066, 1181, 1263, 1370, 1454, 1651, 2869, 2937; HRMS: m/z calcd for C31H46N2O2: 478.3638, found 479.3631 [M+H]+.

28-Oximinolupa-2,20(29)-dien[2,3-b]pyrazine (24)
A mixture of 28-oxolupadi-2,20(29)-en[2,3-b]pyrazine (38 mg, 0.080 mmol), hydroxylamine hydrochloride (56 mg, 0.80 mmol), pyridine (1 mL) and ethanol (3 mL) was refluxed for 16 h. Solvents were evaporated, and the crude product was purified with SiO2 column chromatography (16% EtOAc/n-hexane) to yield a white crystalline solid (30 mg, 77%). 1H NMR (300 MHz, CDCl3) δ 8.52 (br s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 7.57 (s, 1H), 4.74 (d, J = 2.1 Hz, 1H), 4.63 (dd, J = 2.1, 1.4 Hz, 1H), 3.04 (d, J = 16.6 Hz, 1H), 2.66–2.34 (m, 2H), 2.03–1.74 (m, 4H), 1.71 (s, 3H), 1.48 (m, 12H), 1.31 (s, 3H), 1.27 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.81 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 159.9, 155.4, 150.9, 149.8, 142.5, 141.5, 110.3, 53.1, 49.9, 49.4, 48.8, 48.0, 43.1, 40.9, 39.6, 38.8, 36.9, 33.5, 32.5, 31.6, 29.9, 28.1, 25.4, 24.2, 22.8, 21.5, 20.2, 19.4, 16.3, 15.8, 14.9, 14; FTIR (ν, cm-1): 885, 1108, 1379, 1404, 1452, 1644, 2871, 2939; HRMS: m/z calcd for C32H33N2O: 490.3797; found 490.3799 [M+H]+.
3β-(3-Carboxy-3-methylbutanoyloxy)lup-20(29)-en-28-oic acid (bevirimat) (25)

A mixture of betulinic acid (0.10 g, 0.22 mmol), 2,2-dimethylsuccinic anhydride (36 mg, 0.28 mmol), N,N-diisopropylethylamine (37 mg, 0.28 mmol) and DMF (5 mL) was stirred at 170 °C for 2 d. Solvent was evaporated, and the crude product was purified with SiO₂ column chromatography (20-100% EtOAc/n-hexane) to yield a white crystalline product (7.0 mg, 5%).¹⁷ ¹H NMR (300 MHz, CDCl₃) δ 4.73 (s, 1H), 4.60 (s, 1H), 4.48 (m, 1H), 3.06–2.87 (m, 1H), 2.81 (m, 1H), 2.63 (d, J = 3.3 Hz, 1H), 2.49 (m, 1H), 2.33–2.09 (m, 3H), 1.96 (m, 2H), 1.67 (s, 3H), 1.47 (m, 14H), 1.30 (s, 3H), 1.30 (s, 3H), 1.25 (m, 6H), 0.97 (s, 3H), 0.93 (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H); FTIR (v, cm⁻¹): 866, 979, 1135, 1192, 1703, 1733, 2877, 2943; HRMS: m/z calcd for C₃₆H₅₆O₆Na: 607.3975; found 607.3999 [M+Na⁺]. NMR spectral data is consistent with those previously reported.¹⁸
\(^1\text{H}\)- and \(^{13}\text{C}\)-NMR spectra of the new compounds

**Compound 6**
Compound 9
Compound 17
Compound 21
Compound 24
REFERENCES


