SUPPLEMENTARY MATERIAL

Synthesis of new boswellic acid derivatives as potential antiproliferative agents

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ABSTRACT

In the current investigation, a series of heterocyclic derivatives of boswellic acids were prepared along with new monomers of 3-O-acetyl-11-keto-β-boswellic acid (AKBA, 1) 11-keto-β-boswellic acid (KBA, 2) and several new bis-AKBA and KBA homodimers and AKBA-KBA heterodimers. The effects of these compounds on the proliferation of different human cancer cell lines, viz., FaDu (pharynx carcinoma), A2780 (ovarian carcinoma), HT29 (colon adenocarcinoma), and A375 (malignant melanoma), have been evaluated. Thus, KBA homodimer 21 effectively inhibited the growth of FaDu, A2780, HT29 and A375 cells with EC<sub>50</sub> values below 9 μM. In addition, compounds 7, 8, 11, 12, 15, 16 and 17 also exhibited cytotoxic effects for A2780, HT29 and A375 cancer cells. In particular, the pyrazine analog 8 was highly cytotoxic for A375 cancer cells with an EC<sub>50</sub> value of 2.1 μM.

Keywords: Boswellic acid; AKBA-KBA heterodimers; cytotoxicity
Experimental Section

General

Multinuclear and multidimensional NMR spectra were recorded on a BRUKER NMR spectrometer operating at 600 MHz (150 MHz for $^{13}$C) with cryoprobe prodigy. The chemical shift values are reported in ppm ($\delta$) units, and the coupling constants ($J$) are given in Hz. ESI-MS spectra were recorded on a Waters Quattro Premier XE Mass Spectrometer (Waters, Milford, MA). For TLC, pre-coated aluminum sheets (silica gel 60F254, E. Merck) were used. Visualizations of the TLC plates were achieved under the UV light at 254 and 366 nm and also by spraying with the ceric sulfate reagent. Frankincense was provided by commercial supplier and compound 2 was prepared from frankincense according to Jauch's procedure (Jauch and Bergmann, 2003). The interconversion of compounds 1–4 followed our previously published procedures (Wolfram et al., 2017).

Synthesis

(3a,4β) Benzyl 3-hydroxy-11-oxours-12-en-24-oate (5)

Compound 5 was prepared as previously reported; mp: 201-204 °C (Csuk et al., 2015).

(4β) Benzyl 3,11-dioxours-12-en-24-oate (6)

Compound 6 was prepared as previously reported; mp: 94-97 °C (Csuk et al., 2015).

(4β)-Ursa-2,12-dieno-[2,3-b]-11-oxo-pyrazin (7) and (4β) Benzyl-ursa-2,12-dieno-[2,3-b]-11-oxo-pyrazin-24-oate (8)

Sulfur (0.02 g, 0.64 mmol) and ethylenediamine (0.021 g, 0.35 mmol) were added to a solution of 6 (0.04 g, 0.07 mmol) in morpholine (10 mL). The mixture was heated under reflux for overnight. Usual workup followed by column chromatography [silica gel, n-hexane $\rightarrow$ n-hexane/EtOAc (6:4)] gave compounds 7 and 8, respectively. Data for 7: White amorphous solid; yield: 0.017 g, 45%; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.33 (s, 1H, H-31), 8.30 (s, 1H, H-31), 8.30 (s, 1H, H-32), 5.62 (s, 1H, H-12), 4.03 (d, $J = 17.4$ Hz, 1H, H-1a), 2.59 (d, $J = 17.4$ Hz, 1H), 2.54 (s, 1H), 2.10 (m,1H), 1.87 (m, 2H), 1.70 (m, 1H), 1.64 (m, 1H), 1.52 (br d, $J = 11.2$ Hz, 1H), 1.45 (m, 1H),
1.42 (m, 3H), 1.40 (d, \( J = 6.6 \) Hz, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.28 (m, 1H), 1.23 (s, 3H), 1.21 (m, 2H), 1.07 (m, 3H), 0.93 (br s, 3H), 0.82 (s, 3H), 0.81 (d, \( J = 5.3 \) Hz, 3H) ppm; \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 198.8 (C-11), 165.3 (C-13), 155.4 (C-2), 152.1 (C-1), 141.9 (C-31), 141.6 (C-32), 130.3 (C-12), 59.0, 58.2, 50.1, 48.3, 44.6, 43.7, 40.9, 39.3, 39.2, 37.1, 33.9, 31.1, 30.9, 28.8, 27.5, 27.2, 21.5, 21.1, 20.5, 18.1, 17.9, 17.5, 14.2 ppm; ESIMS: \( m/z \) 461.2 ([M+H\(^{+}\)].

Data for \( \mathbf{8} \): white amorphous solid; yield: 0.013 g, 42%; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 8.37 (s, 2H, H-31, H-32), 7.26-7.21 (m, 5H, CH\(_2\)Ph), 5.59 (s, 1H, H-12), 5.09 (br s, 2H, CH\(_2\)Ph), 4.16 (d, \( J = 17.4 \) Hz, 1H, H-1a), 2.52 (d, \( J = 17.4 \) Hz, 1H), 2.49 (s, 1H), 2.08 (m, 1H), 1.87 (m, 2H), 1.70 (m, 1H), 1.62 (s, 3H), 1.64 (m, 1H), 1.52 (br d, \( J = 11.2 \) Hz, 1H), 1.45 (m, 1H), 1.42 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.30 (s, 3H), 1.28 (m, 1H), 1.21 (m, 2H), 1.08 (s, 3H), 1.07 (m, 1H), 1.01 (s, 3H), 0.96 (br s, 3H), 0.80 (s, 3H), 0.79 (d, \( J = 5.3 \) Hz, 3H) ppm; \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 198.3 (C-11), 173.8 (C-24), 165.3 (C-13), 154.0 (C-2), 151.3 (C-1), 142.7 (C-31), 142.0 (C-32), 135.4 (CH\(_2\)Ph), 130.3 (C-12), 128.4 (CH\(_2\)Ph), 128.3 (CH\(_2\)Ph), 128.1 (CH\(_2\)Ph), 66.7 (CH\(_2\)Ph), 59.2, 59.0, 54.6, 51.4, 48.2, 44.5, 43.6, 40.8, 39.3, 39.2, 36.6, 33.9, 32.1, 30.8, 28.8, 28.4, 27.4, 27.2, 21.1, 20.5, 19.7, 17.9, 17.5, 15.7 ppm; ESIMS: \( m/z \) 617.1 ([M+Na\(^{+}\)], C\(_{39}\)H\(_{50}\)N\(_2\)NaO\(_3\)).

**Benzyl 2,3-dinor-1,11-dioxours-12-en-24-oate (9)**

Potassium tert-butoxide (0.03 g, 0.26 mmol) and aniline (0.01 g, 0.10 mmol) were added to a solution of \( \mathbf{6} \) (0.03 g, 0.053 mmol) in DMSO (8 mL). The reaction was stirred at 25 °C for 5 h. Usual workup followed by column chromatography [silica gel, \( n\)-hexane \( \rightarrow \) \( n\)-hexane/EtOAc (8:2)] gave \( \mathbf{9} \) (0.013 g, 48%) as an amorphous solid; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 9.90 (s, 1H, CHO), 7.33 (br s, 5H, CH\(_2\)Ph), 5.62 (br s, 1H, H-12), 5.08 (br s, 2H, CH\(_2\)Ph), 3.29 (s, 1H), 2.40 (m, 2H), 2.08 (m, 1H), 1.90 (m, 2H), 1.64 (m, 1H), 1.58 (m, 1H), 1.53 (m, 1H), 1.52 (br d, \( J = 11.2 \) Hz, 1H), 1.45 (m, 1H), 1.42 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.29 (s, 6H), 1.21 (m, 1H), 1.08 (s, 3H), 1.08 (m, 1H), 1.01 (d, \( J = 6.6 \) Hz, 3H), 0.92 (s, 3H), 0.79 (s, 3H), 0.75 (d, \( J = 6.6 \) Hz, 3H) ppm; \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 209.0 (CHO), 196.7 (C-11), 175.9 (C-24), 169.1 (C-13), 135.7 (CH\(_2\)Ph), 128.7 (C-12), 128.5 (CH\(_2\)Ph), 128.3 (CH\(_2\)Ph), 128.2 (CH\(_2\)Ph), 66.2 (CH\(_2\)Ph), 60.3, 58.3, 48.1, 42.2, 43.9, 43.3, 40.8, 39.5, 39.2, 34.0, 30.1, 30.8, 28.9, 27.3, 27.2, 19.1, 17.4, 21.1, 21.8, 17.5, 17.4, 14.5 ppm; ESIMS: \( m/z \) 555.1 ([M+Na\(^{+}\)], C\(_{35}\)H\(_{46}\)NaO\(_3\)).
Thiosemicarbazide (0.020 g, 0.026 mmol) was added to a solution of 6 (0.03 g, 0.053 mmol) in EtOH (10 mL). The reaction mixture was heated under reflux for 15 h. Usual workup followed by column chromatography [silica gel, n-hexane \( \rightarrow \) n-hexane-EtOAc (5:5)] gave 10 (0.027 g, 81%) as a white amorphous solid; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 8.73 (s, 1H, NH), 7.32-7.29 (m, 5H, CH\(_2\)Ph), 6.34 (s, 1H, NH), 5.52 (br s, 1H, H-12), 5.12 (d, \(J = 14.4\) Hz, 1H, CH\(_2\)Ph), 5.02 (d, \(J = 14.4\) Hz, 1H, CH\(_2\)Ph), 2.90 (m, 1H), 2.52 (m, 2H), 2.26 (s, 1H), 2.06 (m,1H), 1.83 (m, 2H), 1.58 (m, 1H), 1.53 (m, 1H), 1.52 (br d, \(J = 11.2\) Hz, 1H), 1.45 (m, 1H), 1.42 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.46 (s, 3H), 1.28 (m, 1H), 1.22 (s, 3H), 1.21 (m, 2H), 1.11 (s, 3H), 1.08 (m, 2H), 1.02 (s, 3H), 0.90 (s, 3H), 0.91 (m, 1H), 0.78 (s, 3H), 0.75 (d, \(J = 6.6\) Hz, 3H) ppm; \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 198.7 (C-11), 179.4 (C=S), 174.0 (C-24), 165.6 (C-13), 156.1 (C-3), 135.0 (CH\(_2\)Ph), 130.2 (C-12), 128.6 (CH\(_2\)Ph), 128.5 (CH\(_2\)Ph), 128.4 (CH\(_2\)Ph), 67.0 (CH\(_2\)Ph), 59.8, 58.9, 58.0, 52.3, 44.8, 43.7, 40.8, 39.3, 39.2, 37.0, 33.9, 32.6, 30.8, 28.8, 27.4, 27.2, 23.1, 21.5, 21.1, 20.3, 19.7, 18.2, 17.4, 13.3 ppm; ESIMS: \(m/\epsilon\) 654.1 ([M+Na]\(^+\), C\(_{38}\)H\(_{53}\)N\(_3\)NaO\(_3\)S).

**General procedure for the synthesis of compounds 11-16** (Saeed et al., 2018)

To a solution of AKBA (1, 0.2 mmol) or KBA (2, 0.2 mmol) in DMF (10 mL), K\(_2\)CO\(_3\) (0.24 mmol) and the appropriate dibromoalkane (0.500 mmol) were added. After stirring at room temperature for 12 h, the mixture was diluted with H\(_2\)O (45 mL) and extracted with EtOAc (3 x 35 mL). The combined organic layers were washed successively with H\(_2\)O, saturated aqueous NaHCO\(_3\) and brine, dried (MgSO\(_4\)), filtered, and concentrated. The residue was purified by column chromatography.

**\((3\alpha, 4\beta)\) 3-O-Acetyl-(2-bromoethyl -11-oxours-12-en-24-oate (11)**

White amorphous solid; yield: 81%; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 5.52 (s, 1H, H-12), 5.30 (br s, 1H, H-3), 4.43 (m, 1H, H-31a), 4.36 (m, 1H, H-31b), 3.52 (t, \(J = 5.4\) Hz, 2H, H-32), 2.52 (m, 1H), 2.39 (s, 1H), 2.21 (m, 1H), 2.08 (m,1H), 2.06 (s, 3H), 1.90 (m, 2H, H-6a), 1.72 (m, 1H), 1.64 (m, 1H), 1.58 (m, 1H), 1.52 (br d, \(J = 11.2\) Hz, 1H), 1.46 (m, 1H), 1.42 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.28 (m, 1H), 1.21 (m, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 1.00 (m, 1H), 0.92 (s, 3H), 0.91 (m, 1H), 0.80 (s, 3H), 0.78 (d, \(J = 6.6\) Hz, 3H) ppm; \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 199.2 (C-11), 175.4 (C-24), 170.1 (CH\(_3\)CO), 164.9 (C-13), 130.5
(3α, 4β) (3-Bromopropyl) 3-O-acetyl-11-oxours-12-en-24-oate (12)
White amorphous solid; yield: 78%; $^1$H NMR (600 MHz, CDCl$_3$): δ 5.53 (s, 1H, H-12), 5.29 (br s, 1H), 4.25 (m, 1H, H-31a), 4.15 (m, 1H, H-31b), 3.46 (t, $J$ = 5.4 Hz, 2H), 2.52 (m, 1H), 2.39 (s, 1H), 2.17 (m, 1H), 2.07 (m, 1H), 2.06 (s, 3H), 1.88 (m, 2H), 1.80 (m, 2H), 1.72 (m, 1H), 1.65 (m, 1H), 1.60 (m, 1H), 1.52 (br d, $J$ = 11.2 Hz, 1H), 1.46 (m, 1H), 1.42 (m, 3H), 1.37 (m, 1H, H-19), 1.36 (m, 1H, H-5), 1.32 (s, 3H), 1.29 (m, 1H), 1.21 (m, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 1.04 (s, 3H), 1.00 (m, 1H), 0.92 (s, 3H), 0.80 (s, 3H), 0.77 (d, $J$ = 6.6 Hz, 3H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): δ 199.2 (C-11), 175.5 (C-24), 170.1 (CH$_3$CO), 164.9 (C-13), 130.5 (C-12), 73.1 (C-3), 62.3 (C-31), 60.2, 59.0, 50.4, 46.7, 45.0, 43.7, 40.9, 39.3, 39.2, 37.2, 34.6, 33.9, 32.9, 32.8, 32.1, 30.9, 29.4, 28.8, 27.5, 27.2, 23.9, 23.6, 21.3, 21.1, 20.5, 18.8, 18.3, 17.4, 17.4, 13.3 ppm; ESIMS: m/z 669.0 ([$^{79}$BrM+Na]$^+$), 671.0 ([$^{81}$BrM+Na]$^+$, C$_{36}$H$_{35}$BrNaO$_5$).

(3α, 4β) (2-Bromoethyl) 3-O-acetyl-11-oxours-12-en-24-oate (13)
White amorphous solid; yield: 77%; $^1$H NMR (600 MHz, CDCl$_3$): δ 5.52 (s, 1H, H-12), 5.28 (br s, 1H, H-3), 4.12 (m, 1H, H-31a), 4.05 (m, 1H, H-31b), 3.42 (t, $J$ = 5.4 Hz, 2H), 2.52 (m, 1H), 2.39 (s, 1H), 2.17 (m, 1H), 2.07 (m, 1H), 2.06 (s, 3H), 1.91 (m, 2H), 1.90 (m, 2H), 1.80 (m, 2H), 1.72 (m, 1H), 1.64 (m, 1H), 1.59 (m, 1H), 1.52 (br d, $J$ = 11.2 Hz, 1H), 1.46 (m, 1H), 1.42 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.28 (m, 1H), 1.21 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H), 0.98 (m, 1H), 0.92 (s, 3H), 0.87 (m, 1H), 0.79 (s, 3H), 0.77 (d, $J$ = 6.6 Hz, 3H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): δ 199.2 (C-11), 175.6 (C-24), 170.2 (CH$_3$CO), 164.9 (C-13), 130.5 (C-12), 73.2 (C-3), 63.7 (C-31), 60.2, 59.0, 50.4, 46.7, 45.0, 43.7, 40.9, 39.3, 39.2, 37.2, 34.6, 33.9, 32.9, 32.8, 30.9, 29.4, 28.8, 27.5, 27.2, 27.1, 23.9, 23.6, 21.3, 21.1, 20.5, 18.8, 18.3, 17.4, 17.4, 13.3 ppm; ESIMS: m/z 669.0 ([$^{79}$BrM+Na]$^+$), 671.0 ([$^{81}$BrM+Na]$^+$, C$_{36}$H$_{35}$BrNaO$_5$).

(3α, 4β) (2-Bromoethyl) 3-hydroxy-11-oxours-12-en-24-oate (14)
White amorphous solid; yield: 77%; $^1$H NMR (600 MHz, CDCl$_3$): δ 5.52 (s, 1H, H-12), 4.43 (m, 1H, H-31a), 4.36 (m, 1H, H-31b), 4.30 (br s, 1H), 3.52 (t, $J$ = 5.4 Hz, 2H), 2.52 (m, 1H), 2.39 (s, 3H).
$^1$H), 2.21 (m, 1H), 2.08 (m, 1H), 1.90 (m, 2H), 1.72 (m, 1H), 1.64 (m, 1H), 1.58 (m, 1H), 1.52 (br d, J = 11.2 Hz, 1H), 1.46 (m, 1H), 1.42 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.28 (m, 1H), 1.21 (m, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 1.00 (m, 2H), 0.92 (s, 3H), 0.91 (m, 1H), 0.80 (s, 3H), 0.78 (d, J = 6.6 Hz, 3H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 199.2 (C-11), 175.4 (C-24), 164.9 (C-13), 130.5 (C-12), 73.1 (C-3), 64.3 (C-31), 60.2, 59.0, 50.5, 46.7, 45.0, 43.8, 40.9, 39.3, 39.2, 37.4, 34.6, 33.9, 32.8, 30.9, 28.8, 28.6, 27.5, 27.2, 23.8, 23.6, 21.3, 20.5, 18.8, 18.3, 17.4, 13.3 ppm; ESIMS: m/z 599.0 ($[^{79}$BrM+Na]$^+$), 601.0 ($[^{81}$BrM+Na]$^+$, C$_{32}$H$_{49}$BrNaO$_4$).

(3$\alpha$, 4$\beta$) (2-Bromopropyl) 3-hydroxy-11-oxours-12-en-24-oate (15)
White amorphous solid; yield: 80%; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.51 (s, 1H, H-12), 4.43 (m, 1H, H-31a), 4.36 (br s, 1H, H-31b), 4.35 (m, 1H, H-3), 3.50 (t, J = 5.4 Hz, 2H), 2.52 (m, 1H), 2.39 (s, 1H), 2.21 (m, 1H), 2.08 (m, 1H), 1.90 (m, 2H), 1.72 (m, 1H), 1.64 (m, 1H), 1.57 (m, 1H), 1.52 (br d, J = 11.2 Hz, 1H), 1.46 (m, 2H), 1.42 (m, 3H), 1.37 (m, 2H), 1.36 (m, 1H), 1.32 (s, 3H), 1.28 (m, 2H), 1.21 (m, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 1.00 (m, 1H), 0.92 (s, 3H), 0.91 (m, 1H), 0.80 (s, 3H), 0.78 (d, J = 6.6 Hz, 3H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 199.2 (C-11), 175.1 (C-24), 164.8 (C-13), 130.1 (C-12), 73.1 (C-3), 64.1 (C-31), 60.1, 59.0, 50.1, 46.7, 45.0, 43.1, 40.9, 39.3, 39.2, 37.4, 34.6, 33.9, 32.8, 30.9, 28.8, 28.6, 27.5, 27.2, 23.8, 23.6, 21.1, 20.5, 18.8, 18.1, 17.4, 13.2 ppm; ESIMS: m/z 613.0 ($[^{79}$BrM+Na]$^+$), 615.0 ($[^{81}$BrM+Na]$^+$, C$_{33}$H$_{51}$BrNaO$_4$).

(3$\alpha$, 4$\beta$) (2-Bromobutyl) 3-hydroxy-11-oxours-12-en-24-oate (16)
White amorphous solid; yield: 75%; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.51 (s, 1H, H-12), 4.41 (m, 1H, H-31a), 4.35 (m, 1H, H-31b), 4.33 (br s, 1H, H-3), 3.50 (t, J = 5.4 Hz, 2H), 2.75 (m, 1H), 2.51 (m, 1H), 2.39 (s, 1H), 2.22 (m, 1H), 2.08 (m, 1H), 1.90 (m, 2H), 1.72 (m, 2H), 1.64 (m, 2H), 1.57 (m, 2H), 1.52 (br d, J = 11.2 Hz, 1H), 1.46 (m, 1H), 1.42 (m, 3H), 1.38 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.28 (m, 2H), 1.21 (m, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 1.00 (m, 1H), 0.92 (s, 3H), 0.91 (m, 1H), 0.80 (s, 3H), 0.78 (d, J = 6.6 Hz, 3H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 199.3 (C-11), 175.1 (C-24), 164.8 (C-13), 130.3 (C-12), 73.1 (C-3), 64.4 (C-31), 60.2, 59.1, 50.1, 46.3, 45.1, 43.1, 40.9, 39.3, 39.2, 37.4, 34.6, 33.9, 32.8, 30.9, 28.8, 28.6, 27.5, 27.2, 23.8, 23.6, 21.1, 20.1, 18.7, 18.1, 17.2, 13.2 ppm; ESIMS: m/z 627.0 ($[^{79}$BrM+Na]$^+$); 629.0
General procedure for the synthesis of the dimers 17-24 (Saeed et al., 2018).

To a solution of monomers 12-17 (0.051 mmol) in DMF (5 mL), K₂CO₃ (0.062 mmol) and boswellic acids 1 or 2 (0.051 mmol) were added. After stirring at room temperature for 12 h, the mixture was diluted with H₂O (45 mL) and extracted with EtOAc (3 x 35 mL). The combined organic layers were washed successively with H₂O, saturated aqueous NaHCO₃, and brine, dried (MgSO₄), filtered, and concentrated. The residue was purified by column chromatography.

1,2-Ethanediyl-bis[(3α, 4β) 3-O-acetyl-11-oxours-12-en-24-oate] (17)

White amorphous solid; yield: 77%; ¹H NMR (600 MHz, CDCl₃): δ 5.52 (s, 1H, H-12), 5.30 (br s, 1H, H-3), 4.40 (br d, J = 9.0 Hz, 1H, H-31a), 4.22 (br d, J = 9.0 Hz, 1H, H-31b), 2.52 (m, 1H), 2.39 (s, 1H), 2.21 (m, 1H), 2.08 (m, 1H), 2.06 (s, 3H), 1.83 (ddd, J = 4.6, 13.9, 13.7 Hz, 1H), 1.76 (m, 2H), 1.64 (m, 1H), 1.58 (m, 1H), 1.52 (br d, J = 11.2 Hz, 1H), 1.47 (m, 1H), 1.43 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.29 (m, 1H), 1.20 (m, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 1.00 (m, 1H), 0.92 (s, 3H), 0.91 (m, 1H), 0.80 (s, 3H), 0.78 (d, J = 6.6 Hz, 3H) ppm; ¹³C NMR (150 MHz, CDCl₃): δ 199.2 (C-11), 175.6 (C-24), 170.1 (CH₃CO), 164.9 (C-13), 130.4 (C-12), 73.2 (C-3), 61.1 (C-31), 60.2, 59.0, 50.3, 46.7, 45.0, 43.8, 40.9, 39.3, 39.2, 37.2, 34.6, 33.9, 32.8, 30.9, 28.8, 27.5, 27.2, 23.8, 23.5, 21.3, 21.1, 20.5, 18.8, 18.3, 17.4, 13.3 ppm; ESIMS: m/z 1073.4 ([M+Na]+, C₆₆H₉₈NaO₁₀).

1,2-Propanediyl-bis[(3α, 4β) 3-O-acetyl-11-oxours-12-en-24-oate] (18)

White amorphous solid; yield: 79%; ¹H NMR (600 MHz, CDCl₃): δ 5.51 (s, 1H, H-12), 5.28 (br s, 1H, H-3), 4.18 (m, 1H, H-31a), 4.10 (m, 1H, H-31b), 2.50 (m, 1H), 2.38 (s, 1H), 2.17 (m, 1H), 2.08 (m, 1H), 2.06 (s, 3H), 2.00 (m, 2H), 1.86 (m, 1H), 1.76 (m, 2H), 1.64 (m, 1H), 1.58 (m, 1H), 1.52 (br d, J = 11.2 Hz, 1H), 1.47 (m, 1H), 1.43 (m, 3H), 1.37 (m, 1H), 1.31 (s, 3H), 1.28 (m, 1H), 1.22 (m, 2H), 1.14 (s, 3H), 1.13 (s, 3H), 1.02 (s, 3H), 0.99 (m, 1H), 0.91 (s, 3H), 0.87 (m, 1H), 0.79 (s, 3H), 0.77 (d, J = 6.6 Hz, 3H) ppm; ¹³C NMR (150 MHz, CDCl₃): δ 199.2 (C-11), 175.6 (C-24), 170.1 (CH₃CO), 164.9 (C-13), 130.4 (C-12), 73.2 (C-3), 61.1 (C-31), 60.2, 59.0, 50.3, 46.7, 45.0, 43.8, 40.9, 39.3, 39.2, 37.2, 34.6, 33.9, 32.8, 30.9, 28.8, 27.6, 27.5, 27.2, 23.8, 23.5, 21.3, 21.1, 20.5, 18.8, 18.3, 17.4, 13.3 ppm; ESIMS: m/z 1087.3 ([M+Na]+, C₆₇H₁₀₀NaO₁₀).
1,2-Butanediyl-bis[(3α, 4β) 3-O-acetyl-11-oxours-12-en-24-oate] (19)

White amorphous solid; yield: 76%; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.52 (s, 1H, H-12), 5.28 (br s, 1H, H-3), 4.14 (m, 1H, H-31a), 4.03 (m, 1H, H-31b), 2.50 (m, 1H), 2.38 (s, 1H), 2.19 (m, 1H), 2.08 (m, 1H), 2.06 (s, 3H), 1.86 (m, 1H), 1.76 (m, 2H), 1.73 (m, 2H), 1.64 (m, 1H), 1.58 (m, 1H), 1.52 (br d, $J = 11.2$ Hz, 1H), 1.47 (m, 1H), 1.43 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.29 (m, 1H), 1.22 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 0.99 (m, 1H), 0.91 (m, 3H), 0.87 (m, 1H), 0.79 (s, 3H), 0.77 (d, $J = 6.6$ Hz, 3H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 199.2 (C-11), 175.6 (C-24), 170.1 (CH$_3$CO), 164.9 (C-13), 130.4 (C-12), 73.2 (C-3), 64.0 (C-31), 60.3, 59.0, 50.4, 46.7, 45.0, 43.8, 40.9, 39.3, 39.2, 37.2, 34.6, 33.9, 32.8, 30.9, 28.8, 27.5 (C-16), 27.2, 25.4, 23.8, 23.6, 21.3, 21.1, 20.5, 18.8, 18.3, 17.4, 13.3 ppm; ESIMS: m/z 1101.3 ([M+Na]$^+$, C$_{68}$H$_{102}$NaO$_{10}$).

1,2-Ethanediyl-bis[(3α, 4β) 3-hydroxy-11-oxours-12-en-24-oate] (20)

White amorphous solid; yield: 81%; $^1$H NMR (600 MHz, acetone-$d_6$): $\delta$ 5.52 (s, 1H, H-12), 4.40 (br d, $J = 9.0$ Hz, 1H, H-31a), 4.30 (br s, 1H, H-3), 4.22 (br d, $J = 9.0$ Hz, 1H, H-31b), 2.52 (m, 1H), 2.39 (s, 1H), 2.21 (m, 1H), 2.08 (m, 1H), 1.83 (ddd, $J = 4.6$, 13.9, 13.7 Hz, 1H), 1.76 (m, 2H), 1.64 (m, 1H), 1.58 (m, 1H), 1.52 (br d, $J = 11.2$ Hz, 1H), 1.47 (m, 1H), 1.43 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.30 (m, 1H), 1.29 (s, 3H), 1.20 (m, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 1.00 (m, 1H), 0.92 (s, 3H), 0.91 (m, 1H), 0.80 (s, 3H), 0.78 (d, $J = 6.6$ Hz, 3H) ppm; $^{13}$C NMR (150 MHz, acetone-$d_6$): $\delta$ 199.2 (C-11), 175.4 (C-24), 164.9 (C-13), 130.4 (C-12), 73.1 (C-3), 62.1 (C-31), 60.3, 59.0, 50.3, 46.7, 45.0, 43.8, 40.9, 39.3, 39.2, 37.1, 34.6, 33.9, 32.8, 30.9, 28.8, 27.5, 27.2, 23.8, 23.6, 21.3, 21.1, 20.5, 18.8, 18.3, 17.4, 13.3 ppm; ESIMS: m/z 989.4 ([M+Na]$^+$, C$_{62}$H$_{94}$NaO$_{8}$).

1,2-Propanediyl-bis[(3α, 4β) 3-hydroxy-11-oxours-12-en-24-oate] (21)

White amorphous solid; yield: 77%; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.51 (s, 1H, H-12), 4.41 (br d, $J = 9.0$ Hz, 1H, H-31a), 4.32 (br s, 1H, H-3), 4.20 (br d, $J = 9.0$ Hz, 1H, H-31b), 2.52 (m, 1H), 2.39 (s, 1H), 2.21 (m, 1H), 2.08 (m, 1H), 1.83 (ddd, $J = 4.6$, 13.9, 13.7 Hz, 1H), 1.76 (m, 2H), 1.64 (m, 1H), 1.58 (m, 1H), 1.52 (br d, $J = 11.2$ Hz, 1H), 1.47 (m, 1H), 1.43 (m, 3H), 1.37 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.29 (m, 2H), 1.20 (m, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 1.04
(s, 3H), 1.00 (m, 2H), 0.92 (s, 3H), 0.92 (m, 1H), 0.81 (s, 3H), 0.78 (d, $J = 6.6$ Hz, 3H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 199.0 (C-11), 175.4 (C-24), 164.9 (C-13), 130.4 (C-12), 73.1 (C-3), 62.1 (C-31), 60.3, 59.0, 50.3, 46.7, 45.0, 43.8, 40.9, 39.3, 39.2, 37.1, 34.6, 33.9, 33.6, 32.8, 30.9, 28.8, 27.5, 27.2, 23.8, 23.5, 21.3, 20.5, 18.8, 18.3, 17.4, 13.3 ppm; ESIMS: $m/z$ 1003.3 ([M+Na]$^+$, C$_{63}$H$_{96}$NaO$_8$).

1,2-Butanediyl-bis[(3$\alpha$, 4$\beta$)-3-hydroxy-11-oxours-12-en-24-oate] (22)
White amorphous solid; yield: 75%; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.52 (s, 1H, H-12), 4.40 (br d, $J = 9.0$ Hz, 1H, H-31a), 4.30 (br s, 1H, H-3), 4.23 (br d, $J = 9.0$ Hz, 1H, H-31b), 2.50 (m, 1H), 2.39 (s, 1H), 2.21 (m, 1H), 2.08 (m, 1H), 1.83 (ddd, $J = 4.6$, 13.9, 13.7 Hz, 1H), 1.76 (m, 2H), 1.64 (m, 2H), 1.58 (m, 1H), 1.52 (br d, $J = 11.2$ Hz, 1H), 1.47 (m, 1H), 1.43 (m, 3H), 1.37 (m, 1H), 1.36 (m, 2H), 1.32 (s, 3H), 1.29 (m, 2H), 1.20 (m, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 1.00 (m, 1H), 0.92 (s, 3H), 0.92 (m, 1H), 0.80 (s, 3H), 0.77 (d, $J = 6.6$ Hz, 3H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 199.1, 175.1, 164.7, 130.3 (C-12), 73.1 (C-3), 62.3 (C-31), 60.1, 59.0, 50.3, 46.7, 45.0, 43.7, 40.9, 39.3, 39.2, 37.1, 34.6, 33.9, 33.6, 32.8, 30.9, 28.8, 27.5, 27.2, 23.8, 23.5, 21.3, 20.5, 18.8, 18.3, 17.1, 13.4 ppm; ESIMS: $m/z$ 1018.4 ([M+Na]$^+$, C$_{64}$H$_{98}$NaO$_8$).

(3$\alpha$, 4$\beta$) {[(3-Hydroxy-11-oxours-12-en-23)carbonyl]oxy}propyl (3$\alpha$, 4$\beta$) 3-O-acetyl-11-oxours-12-en-24-oate (23)
White amorphous solid; yield: 78%; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.52 (s, 1H), 5.51 (s, 1H), 5.29 (s, 1H), 4.21 (m, 2H), 4.11 (m, 5H), 2.51 (m, 3H), 2.39 (m, 3H), 2.25-2.14 (m, 6H), 2.07-2.00 (m, 3H), 2.05 (m, 3H), 1.85 (m, 4H), 1.73 (m, 4H), 1.64 (m, 4H), 1.58 (m, 4H), 1.46 (m, 2H), 1.37 (m, 4H), 1.32 (s, 6H), 1.29 (m, 3H), 1.28 (s, 6H), 1.20 (m, 2H), 1.15 (s, 3H), 1.13 (s, 6H), 1.02 (s, 3H), 1.01 (s, 3H), 0.92 (s, 6H), 0.90 (m, 1H), 0.78-0.78 (m, 9H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 199.1, 199.0, 176.7, 175.6, 170.1, 164.9, 130.4, 73.2, 70.6, 61.2, 60.8, 60.3, 60.2, 59.0, 50.3, 48.7, 47.7, 46.7, 45.1, 45.0, 43.8, 43.7, 41.0, 40.9, 39.3, 39.2, 37.3, 37.2, 34.0, 33.9, 32.9, 32.8, 30.9, 28.8, 27.9, 27.5, 27.2, 27.1, 24.2, 23.8, 23.5, 21.3, 21.1, 20.5, 19.0, 18.8, 18.3, 17.4, 13.3, 13.2 ppm; ESIMS: $m/z$ 1046.1 ([M+Na]$^+$, C$_{65}$H$_{98}$NaO$_9$).
White amorphous solid; yield: 78%; $^1$H NMR (600 MHz, CDCl$_3$): δ 5.52 (s, 1H), 5.51 (s, 1H), 5.30 (s, 1H), 4.17 (m, 2H), 4.10-4.02 (m, 5H), 2.52 (m, 3H), 2.40 (m, 3H), 2.25-2.15 (m, 6H), 2.07-2.00 (m, 3H), 2.06 (s, 3H), 1.85 (m, 4H), 1.73 (m, 4H), 1.64 (m, 4H), 1.55 (m, 4H), 1.45-1.41 (m, 4H), 1.37 (m, 4H), 1.32 (s, 6H), 1.29 (m, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.20 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.92 (s, 6H), 0.90 (m, 1H), 0.79-0.78 (m, 9H) ppm; $^{13}$C NMR (150 MHz, CDCl$_3$): δ 199.4, 199.2, 176.6, 175.5, 170.2, 164.9, 164.8, 130.6, 130.5, 73.2, 70.5, 64.1, 63.7, 60.3, 60.2, 59.0, 50.4, 48.8, 47.5, 46.7, 45.1, 45.0, 43.8, 43.7, 41.0, 40.9, 39.3, 39.2, 37.3, 37.2, 34.6, 34.0, 33.9, 32.9, 32.8, 30.9, 28.8, 27.5, 27.2, 27.1, 26.3, 24.3, 23.9, 23.6, 21.3, 21.1, 20.6, 20.5, 18.9, 18.7, 18.3, 17.5, 17.4, 13.4, 13.3 ppm; ESIMS: m/z 1060.2 [M+Na]$^+$, C$_{66}$H$_{100}$NaO$_9$.

**Cytotoxic activity**

The cytotoxicity of the compounds was evaluated using the sulforhodamine-B (Kiton-Red S, ABCR) micro culture colorimetric assay. Cells were seeded into 96-well plates on day 0 at appropriate cell densities to prevent confluence of the cells during the period of experiment. After 24 h, the cells were treated with six different concentrations (1, 3, 7, 12, 20 and 30 mM) minimum. The final concentration of DMSO/DMF never exceeded 0.5%, which was nontoxic to the cells. After a 96 h treatment, the supernatant medium from the 96-well plates was discarded; the cells were fixed with 10% trichloroacetic acid (TCA) and allowed to rest at 4 °C. After 24 h fixation, the cells were washed in a strip washer and dyed with SRB solution (100 ml, 0.4% in 1% acetic acid) for about 20 min. After dying, the plates were washed four times with 1% acetic acid to remove the excess of the dye and allowed to air dry overnight. Tris base solution (200 ml, 10 mM) was added to each well and absorbance was measured at $\lambda = 570$ nm using a 96 well plate reader (Tecan Spectra, Crailsheim, Germany). The EC$_{50}$ values were averaged from three independent experiments performed each in triplicate calculated from semi logarithmic dose response curves applying a non-linear 4P Hills-slope equation (GraphPad Prism5; variables top and bottom were set to 100 and 0, respectively).
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Captions of Figures

Figure S1: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7
Figure S2: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7
Figure S3: ESI spectrum of compound 7
Figure S4: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 8
Figure S5: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 8
Figure S6: ESI spectrum of compound 8
Figure S7: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 9
Figure S8: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 9
Figure S9: ESI spectrum of compound 9
Figure S10: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 10
Figure S11: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 10
Figure S12: ESI spectrum of compound 10
Figure S13: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 11
Figure S14: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 11
Figure S15: ESI spectrum of compound 11
Figure S16: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 12
Figure S17: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 12
Figure S18: ESI spectrum of compound 12
Figure S19: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 13
Figure S20: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 13
Figure S21: ESI spectrum of compound 13
Figure S22: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 14
Figure S23: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 14
Figure S24: ESI spectrum of compound 14
Figure S25: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 15
Figure S26: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 15
Figure S27: ESI spectrum of compound 15
Figure S28: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 16
Figure S29: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 16
Figure S30: ESI spectrum of compound 16
Figure S31: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 17
Figure S32: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 17
Figure S33: ESI spectrum of compound 17
Figure S34: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 18
Figure S35: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 18
Figure S36: ESI spectrum of compound 18
Figure S37: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 19
Figure S38: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 19
Figure S39: ESI spectrum of compound 19
Figure S40: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 20
Figure S41: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 20
Figure S42: ESI spectrum of compound 20
Figure S43: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 21
Figure S44: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 21
Figure S45: ESI spectrum of compound 21
Figure S46: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 22
Figure S47: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 22
Figure S48: ESI spectrum of compound 22
Figure S49: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 23
Figure S50: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 23
Figure S51: ESI spectrum of compound 23
Figure S52: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 24
Figure S53: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 24
Figure S54: ESI spectrum of compound 24
Figure S1: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7.

Figure S2: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7.
Figure S3: ESI spectrum of compound 7.

Figure S4: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 8.
**Figure S5**: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 8.

**Figure S6**: ESI spectrum of compound 8.
Figure S7: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 9.

Figure S8: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 9.
**Figure S9:** ESI spectrum of compound 9.

**Figure S10:** $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 10.
Figure S11: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 10.

Figure S12: ESI spectrum of compound 10.
Figure S13: $^1$H-NMR spectrum (600 MHz, CDCl₃) of compound 11.

Figure S14: $^{13}$C-NMR spectrum (150 MHz, CDCl₃) of compound 11.
Figure S15: ESI spectrum of compound 11.

Figure S16: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 12.
Figure S17: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 12.

Figure S18: ESI spectrum of compound 12.
Figure S19: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 13.

Figure S20: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 13.
Figure S21: ESI spectrum of compound 13.

Figure S22: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 14.
**Figure S23:** $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 14.

**Figure S24:** ESI spectrum of compound 14.
Figure S25: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 15.

Figure S26: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 15.
Figure S27: ESI spectrum of compound 15.

Figure S28: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 16.
Figure S29: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 16.

Figure S30: ESI spectrum of compound 16.
Figure S31: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 17.

Figure S32: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 17.
Figure S33: ESI spectrum of compound 17.

Figure S34: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 18.
Figure S35: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 18.

Figure S36: ESI spectrum of compound 18.
Figure S37: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 19.

Figure S38: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 19.
Figure S39: ESI spectrum of compound 19.

Figure S40: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 20.
Figure S41: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 20.

Figure S42: ESI spectrum of compound 20.
Figure S43: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 21.

Figure S44: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 21.
Figure S45: ESI spectrum of compound 21.

Figure S46: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 22.
Figure S47: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 22.

Figure S48: ESI spectrum of compound 22.
Figure S49: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 23.

Figure S50: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 23.
Figure S51: ESI spectrum of compound 23.

Figure S52: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 24.
Figure S53: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 24.

Figure S54: ESI spectrum of compound 24.