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New hybrids between triterpenoid acids and nucleoside HIV-RT inhibitors

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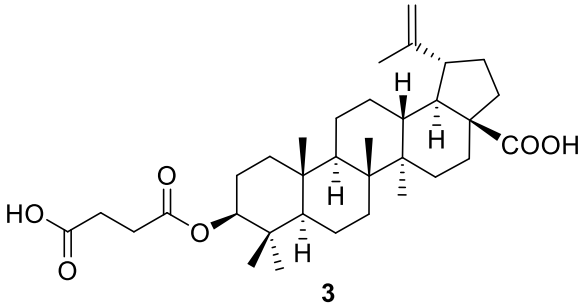
All new compounds gave satisfactory spectroscopic and analytical results. Their ^{1}H NMR and ^{13}C NMR spectra were consistent with the structures shown in Schemes 2-4.

Compound **6**. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 4.73 (1H, s, H-29a); 4.61(1H, s, H-29b); 4.31 (2H, q, C<u>H</u>$_2$ Et); 3.18 (1H, dd, *J*=4.5, 11.0 Hz, H-3); 2.94 (1H, ddd, *J*=5.0, 11.5, 16.0 Hz, H-19); 2.23 (2H, ddd, *J*=2.5, 12.5, 15.5 Hz, H-15a, H-16a); 1.91-2.05 (2H, m, H-12a, H-22a); 1.61-1.72 (3H, m, H-1a, H-2a, H-21a); 1.68 (3H, s, H-30); 1.54-1.62 (2H, m, H-15b, H-16b); 1.47-1.52 (4H, m, H-6, H-13a, H-22b); 1.39-1.46 (4H, m, H-7, H-11); 1.36 (3H, t, *J*=7.0 Hz, C<u>H</u>$_3$, Et); 1.21-1.28 (2H, H-9, H-21a); 0.96 (3H, s, H-27), 0.95 (3H, s, H-23), 0.94 (3H, s, H-26), 0.87 (1H, d, *J*=12Hz, H-5); 0.82 (3H, s, H-24); 0.75 (3H, s, H-25); 0.66-0.68 (1H, m, H-1a).^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm: 170.5 (C-28), 149.6 (C-20), 149.8 (C-20); 109.9 (C-29), 78.9 (C-3), 65.5 (<u>C</u>H$_2$ Et); 57.4 (C-17); 55.4 (C-5); 50.6 (C-9); 49.3 (C-18); 46.5 (C-19); 42.4 (C-14); 40.7 (C-8); 38.8 (C-4); 38.1 (C-1); 37.2 (C-13); 36.1 (C-10, C-22); 34.3 (C-7); 31.5 (C-16); 29.7 (C-21); 27.9 (C-15); 27.4 (C-23); 25.4 (C-2), 25.3 (C-12), 20.8 (C-11), 19.3 (C-30); 18.2 (C-6); 16.1 (C-25); 15.8 (C-26); 15.3 (C-24); 14.6 (C-27); 13.9 (<u>C</u>H$_3$ Et). HRMS calcd. for $C_{33}H_{53}O_5$ $[M+H]^+$: 529.3888, found: 529.3894.

Compound **11.**^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 7.40 (1H, s, H-6'); 6.21 (1H, t, *J*=6.5 Hz, H-1"); 5.27 (1H, t, *J*=3.5 Hz, H-12); 4.44 (1H, dd, *J*=3.0, 12.0 Hz, H-5"a); 4.35 (1H, dd, *J*=3.0, 12.0 Hz, H-5"b); 4.23-4.27 (2H, m, C<u>H</u>$_2$ Et); 4.25 (1H, d, *J*=2 Hz, H-3"); 4.06 (1H, dd, *J*=2.5, 7.5 Hz, H-4"); 3.20 (1H, dd, *J*=5.0, 11.0 Hz, H-3); 2.81 (1H, dd, *J*=4.0, 14.0 Hz, H-18); 2.47 (1H, ddd, *J*=1.5, 6.0, 12.5 Hz, H-2"a); 2.37 (1H, ddd, *J*=1.0, 6.0, 12.5 Hz, H-2"b); 1.93-1.94 (1H, m, H-16a); 1.84-1.88 (1H, m, H-11a); 1.86 (3H, s, C<u>H</u>$_3$ AZT); 1.72-1.77 (2H, m, H-22a, H-15a); 1.54-1.65 (8H, m, H-1b, H-2, H-6a, H-9, H-16b, H-19a, H-22b); 1.38-1.44 (2H, dd, *J*=3.5, 13.0 Hz, H-6b, H-7a); 1.27 (3H, t, *J*=7.0 Hz, C<u>H</u>$_3$ Et); 1.22-1.33 (3H, m, H-21, H-7b); 1.18 (3H, s, H-27); 1.13-1.17 (2H, m, H-15b, H-19b); 0.98 (3H, s, H-23); 0.97-0.99 (1H, m, H-1b); 0.86-0.88 (1H, m, H-11b); 0.87 (3H, s, H-29); 0.85 (3H, s, H-25); 0.84 (3H, s, H-30); 0.78 (3H, s, H-26); 0.77 (3H, s, H-24); 0.75-0.76 (1H, m, H-5b). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 183.2 (C-28); 163.7 (<u>C</u>O); 154.5 (C-4'); 150.1 (C-2'); 143.6 (C-5'); 135.3 (C-13); 122.3 (C-12); 111.3 (C-6'); 84.9 (C-10");

81.7 (C-4”); 79.0 (C-3); 66.0 (<u>C</u>H$_2$ Et); 64.7 (C-5”); 59.9 (C-3”); 55.2 (C-5); 47.6 (C-9); 46.5 (C-17); 45.9 (C-19); 41.6 (C-18); 41.0 (C-14); 39.3 (C-8); 38.7 (C-1); 38.4 (C-4); 37.7 (C-2”); 37.0 (C-10); 33.8 (C-21); 33.0 (C-29); 32.6 (C-22); 32.4 (C-7); 30.6 (C-20); 28.1 (C-23); 27.7 (C-15); 27.1 (C-2); 25.9 (C-27); 23.5 (C-11); 23.4 (C-30); 22.9 (C-16); 18.3 (C-6); 17.0 (C-26); 15.5 (C-24); 15.3 (C-25); 14.2 (<u>C</u>H$_3$ Et); 12.4 (<u>C</u>H$_3$ AZT).

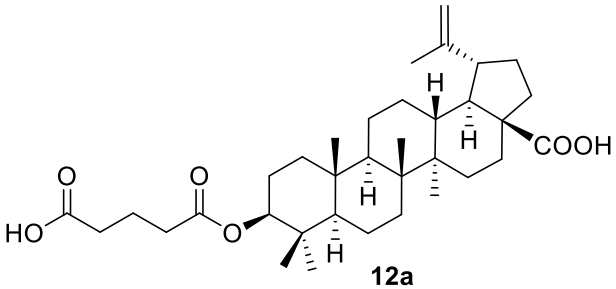
Compound **3**



3

^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 4.72 (1H, s, H-29a); 4.60 (1H, s, H-29b); 4.49 (1H, dd, *J*=6.0, 10.0 Hz, H-3); 2.97 (1H, ddd, *J*=5.0, 11.0, 15.5 Hz, H-19); 2.68 (2H, t, *J*=5.0 Hz, C<u>H</u>$_2$); 2.62 (2H, t, *J*=5.0 Hz, C<u>H</u>$_2$); 2.24-2.30 (1H, m, H-15a); 2.17 (1H, ddd, *J*=2.5, 12.5, 15.5 Hz, H-16a); 1.91-1.98 (2H, m, H-12a, H-22a); 1.68 (3H, s, H-30); 1.57-1.65 (3H, m, H-1a, H-2a, H-21a); 1.47-1.54 (4H, m, H-15b, H-16b, H-6); 1.33-1.42 (4H, m, H-7, H-13a, H-22b); 1.22-1.28 (2H, m, H-11); 1.08-1.15 (2H, H-9, H-21a); 0.96 (3H, s, H-27), 0.92 (3H, s, H-23), 0.86 (3H, s, H-26), 0.84 (1H, d, *J*=12Hz, H-5); 0.82 (3H, s, H-24); 0.81 (3H, s, H-25); 0.76-0.78 (1H, m, H-1a).^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm: 183.0 (C-28); 178.5 (C-1’), 171.8 (C-4’); 150.3 (C-20); 109.7 (C-29); 81.5 (C-3); 56.4 (C-17); 55.4 (C-5); 50.3 (C-9); 49.2 (C-18); 46.9 (C-19); 42.4 (C-14); 40.7 (C-8); 38.3 (C-4); 38.3 (C-1); 37.1 (C-13); 37.0 (C-10); 36.6 (C-22); 34.2 (C-7); 31.1 (C-16); 30.5 (C-21); 30.3 (C-15); 29.3 (<u>C</u>H$_2$); 29.1 (<u>C</u>H$_2$); 27.9 (C-23); 25.4 (C-2), 24.6 (C-12), 20.8 (C-11), 19.3 (C-30); 18.8 (C-6); 18.1 (C-25); 16.5 (C-26); 16.1 (C-24); 14.6 (C-27);. HRMS calcd. for $C_{34}H_{53}O_6$ $[M+H]^+$: 557.3837, found: 557.3843.

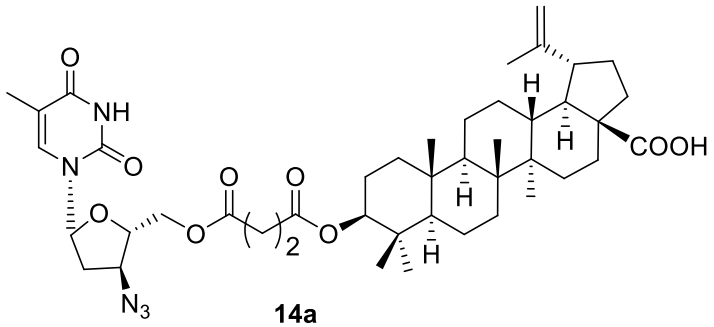
Compound **12a**



12a

^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 4.73 (1H, s, H-29a); 4.60 (1H, s, H-29b); 4.48 (1H, dd, *J*=5.5, 11.0 Hz, H-3); 2.98 (1H, ddd, *J*=4.5, 10.5, 15.5 Hz, H-19); 2.68 (4H, q, 2C$\underline{H}_2$); 2.27-2.30 (1H, m, H-15a); 2.17 (1H, ddd, *J*=2.5, 12.5, 15.5 Hz, H-16a); 1.93-2.01 (4H, m, H-12a, H-22a, C$\underline{H}_2$); 1.68 (3H, s, H-30); 1.59-1.65 (4H, m, H-1a, H-2a, H-6a, H-21a); 1.46-1.54 (3H, m, H-15b, H-6b, H-16b); 1.32-1.45 (4H, m, H-7, H-13a, H-22b); 1.22-1.28 (2H, m, H-11); 1.08-1.15 (2H, H-9, H-21a); 0.96 (3H, s, H-27), 0.92 (3H, s, H-23), 0.85 (3H, s, H-26), 0.84 (1H, d, *J*=12Hz, H-5); 0.82 (3H, s, H-24); 0.81 (3H, s, H-25); 0.78-0.80 (1H, m, H-1a). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm: 182.8 (C-28); 178.9 (C-1'), 172.5 (C-5'); 150.3 (C-20); 109.7 (C-29); 81.5 (C-3); 56.4 (C-17); 55.3 (C-5); 50.3 (C-9); 49.3 (C-18); 46.9 (C-19); 42.4 (C-14); 40.7 (C-8); 38.4 (C-4); 38.3 (C-1); 37.8 (C-13); 37.1 (C-10); 37.0 (C-22); 34.2 (C-7); 33.7 (C-2;); 33.0 (C-4'); 32.1 (C-16); 30.6 (C-21); 29.7 (C-15); 28.7 (C-3'); 25.4 (C-2), 24.6 (C-12), 20.8 (C-11), 20.8 (C-23); 19.3 (C-30); 18.2 (C-6); 16.5 (C-25); 16.2 (C-26); 16.1 (C-24); 14.6 (C-27). HRMS calcd. for $C_{35}H_{55}O_6$ $[M+H]^+$: 571.3993, found: 571.3998.

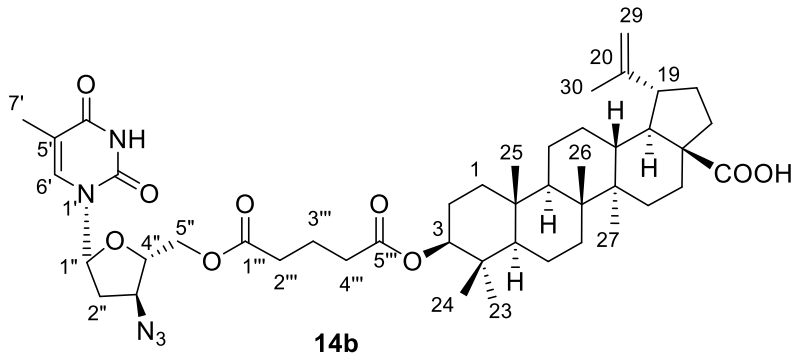
Compound **14a**



14a

^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm: 7.22 (1H, s, H-6'); 6.08 (1H, t, *J* = 6.0 Hz, H-1"); 4.73 (1H, s, H-29a); 4.60 (1H, s, H-29b); 4.50 (1H, t, *J* = 7.5 Hz, H-3); 4.47 (1H, dd, *J* = 3.5, 12 Hz, H-5"a); 4.30 (1H, dd,*J* = 4.0, 12.0 Hz, H-5"b); 4.22-4.19 (1H, m, H-3"); 4.06 (1H, m, H-4"); 3.02-2.98 (1H, m, H-19); 2.62-2.70 (4H, m, 2H-2''', 2H-3'''); 2.44-2.62 (1H, m, H-15a); 2.39 (1H, ddd, *J*=3.0, 12.5, 15.5 Hz, H-16a); 2.26-2.16 (2H, m, 2H-2''); 1.94-1.98 (4H, m, H-1a, H-2a, H-6a, H-21a); 1.93 (3H, s, H-7'); 1.71-1.78 (4H, m, H-1a, H-2a, H-6a, H-21a); 1.69 (3H, s, H-30); 1.57-1.61 (3H, m, H-15b, H-6b, H-16b); 1.42-1.51 (4H, m, H-7, H-13a, H-22b); 1.32-1.41 (2H, m, H-11); 1.17-1.27 (2H, H-9, H-21a); 0.97 (3H, s, H-27), 0.93 (3H, s, H-24), 0.84 (3H, s, H-23); 0.83 (3H, s, H-26), 0.82 (3H, s, H-25); 0.77-0.79 (1H, m, H-1a). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm: 180.7 (C-28), 172.0 (C-1'''), 171.9 (C-4'''), 163.5 (C-4'), 150.3 (C-2'); 149.9 (C-20); 135.5 (C-6'); 111.3 (C-5'); 109.7 (C-29); 85.1 (C-1"); 81.8 (C-4"); 81.7 (C-3); 63.0 (C-5''); 60.1 (C-3"); 56.2 (C-17); 55.3 (C-5); 50.3 (C-9); 49.2 (C-18); 46.8 (C-19); 42.4 (C-14); 40.6 (C-8); 38.4 (C-13); 38.3 (C-1); 37.8 (C-4); 37.8 (C-2''); 37.5 (C-10), 37.1 (C-22); 37.0 (C-2"'); 34.1 (C-7); 32.1 (C-3'''); 30.5 (C-16); 29.6 (C-21); 29.2 (C-15); 29.0 (C-23); 27.9 (C-2); 25.4 (C-12); 23.6 (C-11); 20.8 (C-30); 19.3 (C-6); 16.5 (C-25); 16.1 (C-26); 15.9 (C-24); 14.6 (C-27), 12.5 (C-7'). HRMS calcd. for $C_{44}H_{64}N_5O_9$ $[M+H]^+$: 806.4699, found: 806.4705.

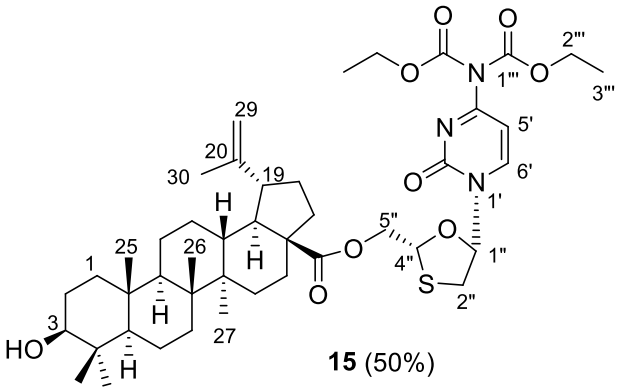
Compound **14b**



14b

^{1}H-NMR (500 MHz, $CDCl_3$) (typical signals for terpenoid structure were obmitted for clarification) δ ppm: 7.21 (1H, s, H-6'); 6.08 (1H, t, J = 6.5 Hz, H-1"); 4.74 (1H, s, H-29a); 4.60 (1H, s, H-29b); 4.47 (1H, t, J = 7.5 Hz, H-3); 4.39 (1H, dd, J = 4.5, 12 Hz, H-5"a); 4.30 (1H, dd, J = 4, 12 Hz, H-5"b); 4.22-4.19 (1H, m, H-3"); 4.06 (1H, m, H-4"); 3.02-2.98 (1H, m, H-19); 2.50-2.53 (6H, m, 2H-2''', 2H-3''', 2H-4'''); 2.24-2.26 (1H, m, H-15a); 2.19 (1H, ddd, J=3.0, 12.5, 15.5 Hz, H-16a); 2.26-2.16 (2H, m, 2H-2''); 1.94-1.98 (4H, m, H-1a, H-2a, H-6a, H-21a); 1.93 (3H, s, H-7'); 1.69 (3H, s, H-30); 1.58-1.62 (3H, m, H-15b, H-6b, H-16b); 1.42-1.54 (4H, m, H-7, H-13a, H-22b); 1.32-1.40 (2H, m, H-11); 1.21-1.27 (2H, H-9, H-21a); 0.97 (3H, s, H-27), 0.93 (3H, s, H-24), 0.86 (3H, s, H-23), 0.84 (3H, s, H-26), 0.84 (3H, s, H-25); 0.77-0.79 (1H, m, H-1a). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm: 181.3 (C-28); 172.5 (C-1'''); 172.4 (C-5'''); 163.8 (C-4'); 150.4 (C-2'); 150.0 (C-20); 135.5 (C-6'); 111.3 (C-5'); 109.7 (C-29); 85.7 (C-1"); 81.8 (C-4"); 81.2 (C-3); 63.3 (C-5''); 60.6 (C-3"); 56.3 (C-17); 55.4 (C-5); 50.4 (C-9); 49.3 (C-18); 46.9 (C-19); 42.4 (C-14); 40.7 (C-8); 38.4 (C-13); 38.3 (C-1); 37.8 (C-4); 37.5 (C-2''); 37.12 (C-10); 37.07 (C-22); 34.3 (C-7); 33.5 (C-2'''); 33.1 (C-4'''); 32.2 (C-16); 30.6 (C-21); 29.7 (C-15); 28.0 (C-23); 25.4 (C-2); 23.8 (C-12); 20.9 (C-11); 20.1 (C-3'''); 19.4 (C-30); 18.2 (C-6); 16.5 (C-25); 16.2 (C-26); 16.0 (C-24); 14.7 (C-27); 12.1 (C-7'). HRMS calcd. for $C_{45}H_{66}N_5O_9$ $[M+H]^+$: 820.4855, found: 820.4858. The structure of this compound was further confirmed through HSQC and HMBC spectra. HMBC spectrum showed interactions between H-16, H-18, and H-22 with the free carboxylic group at C-28 position, together with coupling interactions between H-2''', H-4''', and H-5'' with the two ester groups at C-1''' and C-5'''. Esterification of hydroxyl group at C-3 shifted the NMR signal of the proton H-3 downfield to 4.47 ppm.

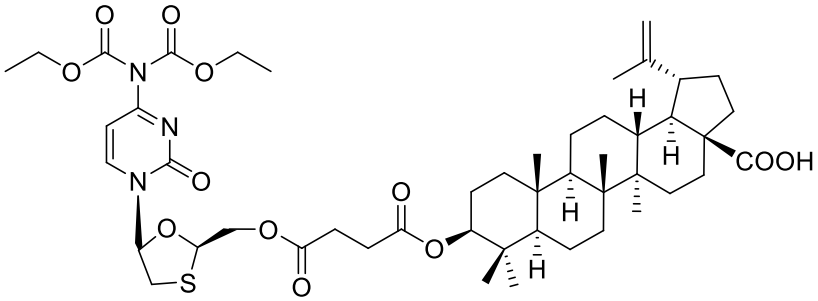
Compound **15**



15 (50%)

^{1}H-NMR ($CDCl_3$, 500 MHz) (typical signals for terpenoid structure were obmitted for clarification) δ ppm 8.20 (1H, d, *J* = 7.5 Hz, H-6'); 7.27 (1H, d, *J* = 5.5 Hz, H-5'); 6.33 (1H, dd, *J* = 3.5, 5 Hz, H-1''); 5.41 (1H, dd, *J* = 3, 5.5 Hz, H-4''); 4.73 (1H, s, H-29b); 4.62 (1H, dd, *J* = 3, 12.5 Hz, H-5''b); 4.59 (1H, s, H-29a); 4.53 (1H, dd, *J* = 3, 12.5 Hz, H-5''a); 4.26 (4H, q, H-2'''a,b); 3.62 (1H, dd, *J* = 5, 12.5 Hz, H-2''b); 3.23 (1H, dd, *J* = 5, 12.5 Hz, H-2''a); 3.19 (1H, d, *J* = 7 Hz, H-3); 3.00 (1H, m, H-19); 2.27-2.30 (1H, m, H-15a); 2.09 (1H, m, H-16a); 1.94-2.08 (4H, m, H-1a, H-2a, H-6a, H-21a); 1.69 (3H, s, H-30); 1.65-1.71 (3H, m, H-15b, H-6b, H-16b); 1.55-1.64 (4H, m, H-7, H-13a, H-22b); 1.45-1.54 (2H, m, H-11); 1.32 (6H, t, *J*=7Hz, H-3'''a,b); 1.18-1.22 (2H, H-9, H-21a); 0.97 (3H, s, H-24), 0.96 (3H, s, H-23), 0.94 (3H, s, H-27), 0.82 (3H, s, H-25), 0.75 (3H, s, H-26); 0.77-0.79 (1H, m, H-1a). ^{13}C-NMR (CDCl3, 125 MHz) δ ppm 179.7 (C-28), 163.2 (C-4'), 154.8 (C-2'), 150.8 (C-1'''a,b), 150.3 (C-20), 144.0 (C-6'), 109.4 (C-29), 95.2 (C-5'), 87.9 (C-1''), 84.3 (C-4''), 78.9 (C-3); 66.5 (C-2'''a,b), 64.8 (C-5''), 56.3 (C-17), 55.4 (C-5), 50.6 (C-9), 49.2 (C-18), 46.9 (C-19), 42.4 (C-14); 40.7 (C-8), 38.8 (C-4); 38.7 (C-1), 38.3 (C-13), 37.8 (C-2''), 37.2 (C-10), 37.1 (C-22), 34.3 (C-7), 32.3 (C-16), 30.6 (C-21), 29.7 (C-15), 27.9 (C-23), 27.2 (C-2), 25.6 (C-12), 20.8 (C-11), 19.3 (C-30), 18.2 (C-6), 16.2 (C-25), 15.9 (C-26), 15.3 (C-24), 14.7 (C-27), 14.2 (C-3'''a,b). HRMS calcd. for $C_{44}H_{66}N_3O_9S$ $[M+H]^+$: 812.4514, found: 812.4518.

Compound **16**



16 (43%)

^{1}H-NMR ($CDCl_3$, 500 MHz) δ ppm: 8.13 (1H, d, *J* = 7.5 Hz, H-6'); 7.30 (1H, d, *J* = 5.5 Hz, H-5'); 6.31 (1H, dd, *J* = 3.5, 5 Hz, H-1''); 5.40 (1H, dd, *J* = 3, 5.5 Hz, H-4''); 4.72 (1H, s, H-29b); 4.61 (1H, dd, *J* = 2.5, 12.5 Hz, H-5''b); 4.59 (1H, s, H-29a); 4.53 (1H, dd, *J* = 3.5, 12.5 Hz, H-5''a); 4.26 (4H, q, H-2'''a,b); 3.62 (1H, dd, *J* = 5.0, 12.5 Hz, H-2''); 3.23 (1H, dd, *J* = 5.0, 12.5 Hz, H-2''a); 3.19 (1H, d, *J* = 7 Hz, H-3); 3.00 (1H, m, H-19); 2.51-2.53 (4H, m, H-2''', H-3'''); 2.20-2.30 (2H, m, H-15a, H-16a); 1.94-2.97 (4H, m, H-1a, H-2a, H-6a, H-21a); 1.68 (3H, s, H-30); 1.62-1.71 (3H, m, H-15b, H-6b, H-16b); 1.50-1.60 (4H, m, H-7, H-13a, H-22b); 1.45-1.49 (2H, m, H-11); 1.32 (6H, t, *J*=7Hz, H-3'''a,b); 1.10-1.25 (2H, H-9, H-21a); 0.97 (3H, s, H-24), 0.96 (3H, s, H-23), 0.94 (3H, s, H-27), 0.83 (3H, s, H-25), 0.76 (3H, s, H-26); 0.76-0.79 (1H, m, H-1a). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ ppm: 181.1 (C-28); 171.8 (C-1'''); 171.6 (C-4'''); 163.8 (C-4'); 154.8 (C-2'); 150.8 (C-1'''a,b); 150.5 (C-20); 144.3 (C-6'); 109.6 (C-29); 95.2 (C-5'); 88.0 (C-1''); 84.4 (C-4''); 81.6 (C-3); 66.3 (C-2'''a,b); 64.8 (C-5''); 56.3 (C-17); 55.4 (C-5); 50.4 (C-9); 49.3 (C-18); 46.9 (C-19); 42.4 (C-14); 40.7 (C-8); 38.8 (C-4); 38.4 (C-1), 38.3 (C-13); 37.8 (C-2''); 37.1 (C-10); 37.0 (C-22); 34.2 (C-7); 32.1 (C-16); 30.6 (C-21); 29.7 (C-15); 29.3 (C-2'''); 29.0 (C-2'''); 27.9 (C-23); 27.2 (C-2); 25.4 (C-12); 20.9 (C-11); 19.3 (C-30); 18.3 (C-6); 16.2 (C-25); 15.9 (C-26); 15.4 (C-24); 14.7 (C-27); 14.1 (C-3'''a,b). HRMS calcd. for $C_{48}H_{70}N_3O_{12}S$ $[M+H]^+$: 912.4675, found: 912.4681.