Synthesis, Anticancer and Antibacterial Evaluation of Novel Spiramycin-Acylated Derivatives

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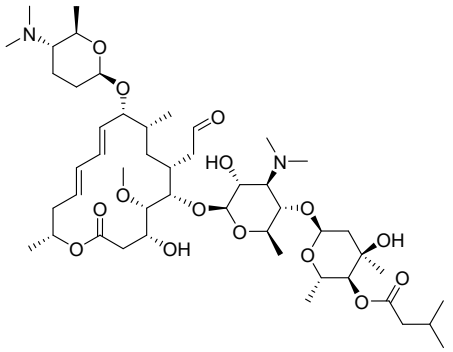
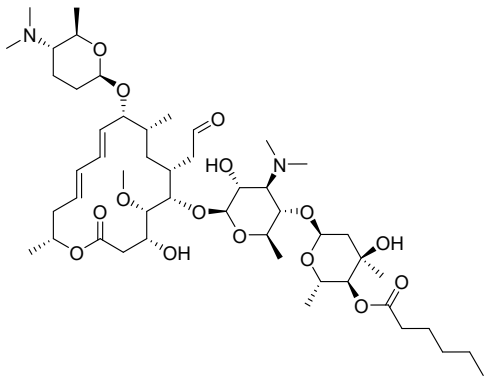
Characterization data of synthetic compounds **1-20**

*4''-isovaleryl-Spiramycin I (**1**).*



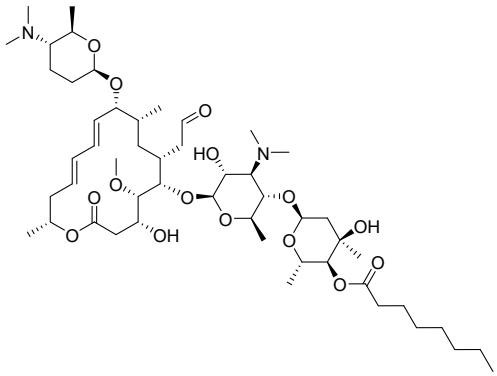
According to the method A, compound **1** could be obtained with 27% yield as white solid using spiramycin I and isovaleryl chloride as substrates. HRMS (ESI) for $C_{48}H_{82}N_2O_{15}$: calculated, $[M+H]^+$ = 927.5788, found 927.5870; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.83 (s, 1H), 6.25 (dd, J = 15.0, 10.8 Hz, 1H), 6.06 – 5.98 (m, 1H), 5.69 (dd, J = 15.0, 9.6 Hz, 1H), 5.57 (t, J = 12.0 Hz, 1H), 5.29 (s, 1H), 5.07 (s, 1H), 4.62 (d, J = 10.2 Hz, 1H), 4.47 (dd, J = 19.2, 8.4 Hz, 2H), 4.38 (d, J = 9.0 Hz, 1H), 4.12 (d, J = 8.4 Hz, 1H), 4.05 (d, J = 6.4 Hz, 2H), 3.81 (d, J = 10.8 Hz, 1H), 3.52 (d, J = 15.2 Hz, 4H), 3.46 – 3.39 (m, 1H), 3.29 (t, J = 8.0 Hz, 2H), 3.08 (d, J = 8.4 Hz, 1H), 2.79 (dd, J = 17.6, 9.2 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.51 (s, 6H), 2.50 – 2.44 (m, 2H), 2.36 (d, J = 17.8 Hz, 1H), 2.30 (d, J = 7.2 Hz, 3H), 2.25 (d, J = 14.8 Hz, 2H), 2.18 – 2.07 (m, 3H), 2.03 – 1.99 (m, 1H), 1.94 (s, 1H), 1.87 – 1.80 (m, 3H), 1.47 (dt, J = 36.0, 12.0 Hz, 3H), 1.30 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 4.8 Hz, 6H), 1.14 (d, J = 6.0 Hz, 3H), 1.12 (s, 3H), 1.00 (s, 1H), 0.98 (d, J = 6.0 Hz, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.82, 174.23, 172.96, 134.64, 132.82, 131.02, 128.60, 103.89, 100.31, 97.03, 85.25, 79.34, 78.78, 75.97, 73.88, 73.08, 71.69, 69.37, 69.21, 68.72, 68.24, 64.86, 63.49, 61.82, 43.32, 43.25, 42.00, 41.71, 40.71, 37.68, 31.78, 31.29, 30.73, 30.54, 25.55, 25.35, 22.45, 22.40, 20.10, 18.96, 18.86, 18.41, 17.85, 15.31.

*4''-n-hexanoyl-Spiramycin I (**2**).*



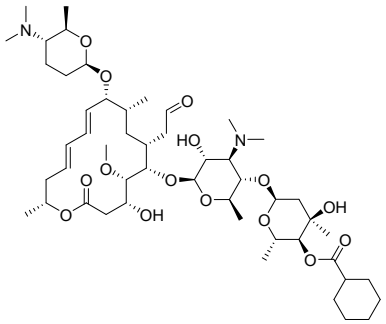
According to the method A, compound **2** could be obtained with 50% yield as white solid using spiramycin I and n-hexanoyl chloride as substrates. HRMS (ESI) for $C_{49}H_{84}N_2O_{15}$: calculated, $[M+2H]^{2+}/2$ = 471.3009, found 471.3022; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 6.24 (dd, *J* = 15.1, 10.6 Hz, 1H), 6.02 (dd, *J* = 14.8, 10.9 Hz, 1H), 5.68 (dd, *J* = 15.1, 9.6 Hz, 1H), 5.58 (ddd, *J* = 15.1, 11.1, 4.0 Hz, 1H), 5.30 (ddd, *J* = 11.2, 6.3, 3.0 Hz, 1H), 5.08 (d, *J* = 3.5 Hz, 1H), 4.62 (d, *J* = 10.2 Hz, 1H), 4.51 (d, *J* = 7.5 Hz, 1H), 4.43 (dd, *J* = 10.5, 5.9 Hz, 3H), 4.11 (d, *J* = 8.7 Hz, 1H), 4.04 (dd, *J* = 9.5, 4.0 Hz, 2H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.62 – 3.42 (m, 6H), 3.39 – 3.24 (m, 3H), 3.08 (d, *J* = 8.6 Hz, 1H), 2.93 (dd, *J* = 28.9, 19.3 Hz, 1H), 2.84 – 2.74 (m, 2H), 2.74 – 2.65 (m, 2H), 2.55 (s, 6H), 2.43 (s, 2H), 2.42 (s, 6H), 2.39 (dd, *J* = 6.5, 4.5 Hz, 3H), 2.33 (s, 2H), 2.27 (t, *J* = 5.3 Hz, 2H), 2.23 (s, 1H), 2.17 – 2.07 (m, 2H), 2.07 – 2.02 (m, 1H), 2.01 (d, *J* = 5.6 Hz, 2H), 1.94 – 1.89 (m, 2H), 1.86 – 1.81 (m, 1H), 1.67 (dd, *J* = 14.8, 7.4 Hz, 2H), 1.53 (t, *J* = 10.9 Hz, 3H), 1.37 – 1.29 (m, 12H), 1.24 (d, *J* = 5.3 Hz, 3H), 1.13 (d, *J* = 7.8 Hz, 6H), 0.98 (d, *J* = 6.6 Hz, 4H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, CDCl3) δ 202.81, 174.23, 173.75, 134.64, 132.82, 131.02, 103.89, 100.31, 97.02, 85.25, 79.35, 78.78, 75.95, 73.88, 73.08, 71.70, 69.37, 69.21, 68.72, 68.25, 64.86, 63.48, 61.82, 43.25, 42.00, 41.70, 40.71, 37.68, 34.26, 31.78, 31.34, 31.29, 30.73, 30.54, 25.31, 24.75, 22.30, 20.10, 18.96, 18.86, 18.41, 17.80, 15.31, 13.89.

*4''-n-octanoyl-Spiramycin I (**3**)*.



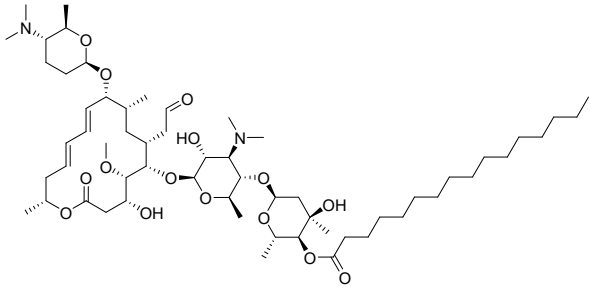
According to the method B, compound **3** could be obtained with 19% yield as white solid using spiramycin I and n-octanoyl acid as substrates. HRMS (ESI) for $C_{54}H_{88}N_2O_{15}$: calculated, $[M+H]^+$ = 969.6257, found 969.6240; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.23 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.08 (dd, *J* = 14.8, 10.8 Hz, 1H), 5.67 (dd, *J* = 14.8, 9.6 Hz, 1H), 5.61 – 5.52 (m, 1H), 5.34 – 5.21 (m, 1H), 5.11 (s, 1H), 4.53 (d, *J* = 6.8 Hz, 1H), 4.43 (d, *J* = 6.8 Hz, 1H), 4.11(s, 1H), 4.10 – 4.01 (m, 2H), 3.78 (d, *J* = 10.8 Hz, 2H), 3.61 (s, 1H), 3.56 – 3.52 (m, 1H), 3.50 (s, 3H), 3.32 (s, 2H), 3.09 (d, *J* = 8.4 Hz, 1H), 2.97 (s, 2H), 2.91 – 2.84 (m, 1H), 2.79 (dd, *J* = 17.6, 9.2 Hz, 2H), 2.71 – 2.62 (m, 2H), 2.50 (s, 2H), 2.48 (s, 6H), 2.46 – 2.40 (m, 3H), 2.37 (s, 1H), 2.33 – 2.23 (m, 3H), 2.15 – 2.06 (m, 1H), 2.03 – 2.00 (m, 2H), 1.92 – 1.90 (m, 2H), 1.75 – 1.70 (m, 1H), 1.68 – 1.61 (m, 2H), 1.59 – 1.54 (m, 2H), 1.52 – 1.45 (m, 1H), 1.37 – 1.36 (m , 4H), 1.32 – 1.23 (m, 22H), 1.00 – 2.62 (m, 1H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.87 (t, *J* = 5.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.95, 174.24, 169.64, 134.84, 132.56, 131.49, 128.15, 103.36, 99.77, 85.01, 79.58, 77.30, 72.64, 71.77, 70.40, 70.06, 69.26, 68.21, 67.16, 65.14, 61.89, 61.47, 43.54, 41.94, 40.80, 40.40, 37.64, 35.26, 31.85, 31.55, 30.76, 30.38, 29.13, 29.01, 28.95, 28.81, 28.79, 25.82, 25.00, 24.56, 22.64, 22.58, 22.54, 20.09, 20.00, 19.65, 19.12, 18.25, 15.23, 14.14, 14.07, 14.03.

*4''-cyclohexanecarbonyl-Spiramycin I (**4**)*.



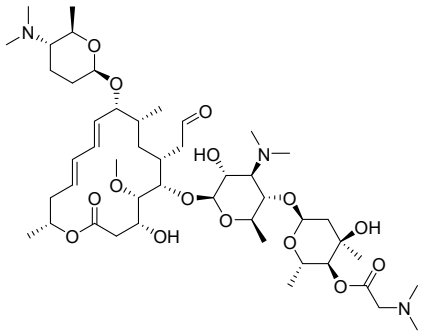
According to the method A, compound **4** could be obtained with 46% yield as white solid using spiramycin I and cyclohexanecarbonyl chloride as substrates. HRMS (ESI) for $C_{50}H_{84}N_2O_{15}$: calculated, $[M+H]^+$ = 953.5944, found 953.5965; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.83 (s, 1H), 6.28-6.20 (m, 1H), 6.05-5.99 (m, 1H), 5.72-5.66 (m, 1H), 5.60-5.53 (m, 1H), 5.34 – 5.25 (m, 1H), 5.07 (d, *J* =6 Hz, 1H), 4.60 (d, *J* = 18.0 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.47 – 4.42 (m, 1H), 4.41 – 4.35 (m, 1H), 4.14-4.10 (m, 1H), 4.07-4.03 (m, 2H), 3.81 (d, *J* = 12.0 Hz, 1H), 3.54 – 3.49 (m, 4H), 3.45-3.40 (m, 1H), 3.34 – 3.26 (m, 2H), 3.08 (d, *J* = 12.0 Hz, 1H), 2.82 – 2.76 (m, 1H), 2.72-2.65 (m, 1H), 2.51 (s, 6H), 2.50 – 2.45 (m, 2H), 2.48-2.40 (m, 1H), 2.40-2.34 (m, 1H), 2.33-2.28 (m, 1H), 2.25 (d, *J* = 12.0 Hz, 2H), 2.22 (s, 6H), 2.21-2.17(m, 1H), 2.14 – 2.07 (m, 1H), 2.02 – 1.98 (m, 1H), 1.97-1.91 (m, 3H), 1.87-1.81(m, 3H), 1.79 – 1.74 (m, 2H), 1.68-1.64(m, 1H), 1.56 – 1.39 (m, 6H), 1.35 – 1.31 (m, 1H), 1.30 (d, *J* = 6.0 Hz, 4H), 1.28 – 1.25 (m, 2H), 1.23 (t, *J* = 6.0 Hz, 6H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.10 (s, 2H), 0.99 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.94, 176.05, 174.35, 134.76, 132.94, 131.14, 128.71, 104.00, 100.43, 97.16, 85.37, 79.46, 78.90, 76.79, 76.08, 74.00, 73.20, 71.80, 69.48, 69.33, 68.86, 68.36, 64.98, 63.60, 61.95, 43.36, 43.33, 42.12, 41.83, 40.83, 37.80, 31.90, 31.41, 30.85, 30.65, 29.41, 29.19, 25.82, 25.59, 25.44, 25.41, 20.23, 19.08, 18.98, 18.53, 17.88, 15.43.

*4''-n-hexadecyl-Spiramycin I (**5**)*.



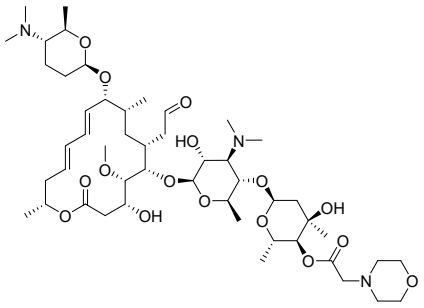
According to the method B, compound **5** could be obtained with 12% yield as white solid using spiramycin I and hexadecanoic acid as substrates. HRMS (ESI) for $C_{59}H_{104}N_2O_{15}$: calculated, $[M+H]^+$ =1081.7509, found 1081.7509; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 6.66 – 6.50 (m, 1H), 6.16 – 6.03 (m, 1H), 5.85 – 5.70 (m, 1H), 5.64 (dd, *J* = 14.4, 9.6 Hz, 1H), 5.16 (d, *J* = 6.8 Hz, 1H), 5.08 (s, 1H), 5.07 – 4.98 (m, 1H), 4.87 (s, 1H), 4.61 (dd, *J* = 15.2, 10.0 Hz, 1H), 4.54 – 4.48 (m, 1H), 4.44 (dd, *J* = 16.0, 8.8 Hz, 2H), 4.00 – 3.92 (m, 1H), 3.92 – 3.83 (m, 1H), 3.65 – 3.51 (m, 4H), 3.43 (td, *J* = 6.8, 1.6 Hz, 5H), 3.32 (dd, *J* = 16.4, 6.4 Hz, 2H), 3.25 (d, *J* = 14.4 Hz, 3H), 2.90 – 2.82 (m, 1H), 2.77 (dd, *J* = 21.6, 9.6 Hz, 2H), 2.60 (s, 1H), 2.55 (d, *J* = 15.2 Hz, 7H), 2.50 – 2.43 (m, 3H), 2.42 – 2.33 (m, 3H), 2.30 (s, 3H), 2.26 (s, 1H), 2.23 (s, 7H), 2.17 (s, 5H), 2.12 (s, 1H), 2.06 (d, *J* = 6.0 Hz, 1H), 2.03 (s, 2H), 1.94 – 1.83 (m, 7H), 1.71 (dd, *J* = 14.8, 3.2 Hz, 1H), 1.49 (d, *J* = 1.6 Hz, 6H), 1.44 (s, 3H), 1.35 (d, *J* = 5.6 Hz, 1H), 1.28 (d, *J* = 6.0 Hz, 4H), 1.23 (d, *J* = 6.0 Hz, 5H), 1.15 (s, 4H), 1.12 (d, *J* = 5.6 Hz, 2H), 1.00 (t, *J* = 5.6 Hz, 4H), 0.92 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.90 , 178.35 , 174.25 , 132.74 , 131.17 , 103.87 , 100.23 , 96.28 , 85.24 , 79.35, 79.03, 74.61, 73.39, 73.12, 71.73, 69.69, 69.25, 68.79, 68.22, 66.12, 64.57, 61.84, 43.31, 42.00, 40.88, 40.34, 37.66, 34.32, 31.93, 31.05, 30.76, 30.46, 29.69, 29.66, 29.62, 29.48, 29.36, 29.30, 29.18, 25.34, 24.94, 22.70, 20.11, 19.11, 18.98, 18.26, 15.32, 14.13.

*4''-(N,N-dimethylaminoacetyl)-Spiramycin I (**6**)*.



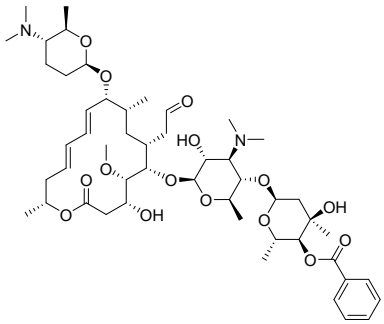
According to the method B, compound **6** could be obtained with 13% yield as white solid using spiramycin I and N,N-dimethylglycine as substrates. HRMS (ESI) for $C_{47}H_{81}N_3O_{15}$: calculated, $[M+H]^+$ = 928.5740, found 928.5753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 6.27 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.04 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.71 (dd, *J* = 15.2, 9.6 Hz, 1H), 5.62 – 5.55 (m, 1H), 5.33 – 5.28 (m, 1H), 5.10 (d, *J* = 3.2 Hz, 1H), 4.50 (d, *J* = 7.6 Hz, 1H), 4.41 (d, *J* = 8.8 Hz, 1H), 4.13 (d, *J* = 8.8 Hz, 1H), 4.07 (dd, *J* = 9.6, 4.4 Hz, 2H), 3.82 (d, *J* = 11.2 Hz, 1H), 3.59 – 3.54 (m, 2H), 3.52 (s, 3H), 3.46 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.30 (dd, *J* = 6.0, 3.2 Hz, 2H), 3.10 (dd, *J* = 8.8, 1.2 Hz, 1H), 2.97 (d, *J* = 9.6 Hz, 2H), 2.90 (s, 2H), 2.85 – 2.76 (m, 2H), 2.70 (dd, *J* = 14.8, 11.2 Hz, 2H), 2.52 (d, *J* = 12.4 Hz, 9H), 2.42 – 2.34 (m, 2H), 2.27 (d, *J* = 11.2 Hz, 9H), 2.12 (d, *J* = 13.6 Hz, 1H), 2.05 (d, *J* = 14.0 Hz, 1H), 1.99 – 1.94 (m, 1H), 1.88 (d, *J* = 9.6 Hz, 2H), 1.77 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.50 (d, *J* = 9.2 Hz, 2H), 1.32 (d, *J* = 6.0 Hz, 7H), 1.27 (d, *J* = 5.2 Hz, 9H), 1.04 – 0.96 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.83, 174.27, 134.69, 132.79, 131.12, 103.88, 100.25, 96.35, 85.26, 78.86, 77.23, 76.44, 73.65, 73.13, 71.72, 69.49, 69.23, 68.83, 68.22, 66.14, 64.87, 61.85, 60.65, 44.15, 43.28, 42.02（2C）, 40.88, 40.67（2C）, 37.65, 31.18, 30.74, 30.48, 25.43, 20.11, 19.09, 19.05, 18.29, 15.31.

4''-(2-morpholineacetyl)-Spiramycin I (7).



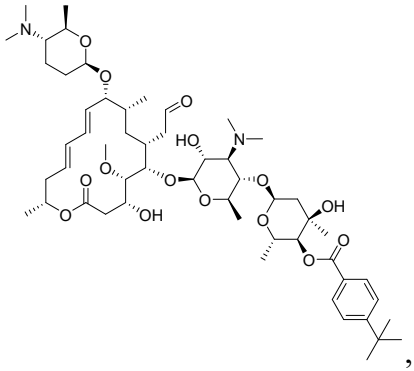
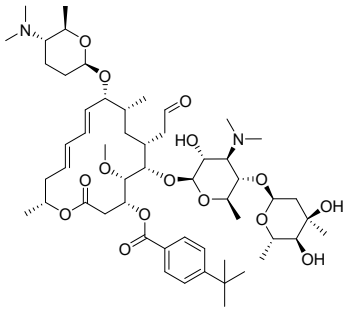
According to the method B, compound **7** could be obtained with 13% yield as white solid using spiramycin I and 2-morpholineacetic acid as substrates. HRMS (ESI) for $C_{49}H_{83}N_3O_{16}$: calculated, $[M+2H]^{2+}/2$ = 485.7960, found 485.7987; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 6.26 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.04 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.70 (dd, *J* = 15.2, 9.6 Hz, 1H), 5.59 (m, 1H), 5.31 (m, 1H), 5.10 (d, *J* = 3.2 Hz, 1H), 4.50 (d, *J* = 7.6 Hz, 1H), 4.44 – 4.38 (m, 1H), 4.17 – 4.09 (m, 1H), 4.07 (dd, *J* = 9.6, 4.4 Hz, 2H), 3.88 – 3.84 (m, 3H), 3.82 (d, *J* = 11.2 Hz, 1H), 3.59 – 3.53 (m, 2H), 3.52 (s, 3H), 3.47 (dd, *J* = 9.3, 6.2 Hz, 2H), 3.31 (d, *J* = 2.6 Hz, 2H), 3.28 (s, 3H), 3.10 (dd, *J* = 8.7, 1.1 Hz, 1H), 2.97 (d, *J* = 9.8 Hz, 1H), 2.88 – 2.83 (m, 3H), 2.83 – 2.76 (m, 1H), 2.70 (dd, *J* = 14.6, 11.0 Hz, 1H), 2.53 (s, 6H), 2.49 (d, *J* = 9.8 Hz, 1H), 2.42 – 2.34 (m, 1H), 2.33 – 2.24 (m, 7H), 2.18 – 2.09 (m, 1H), 2.05 (d, *J* = 14.0 Hz, 1H), 1.77 (dd, *J* = 14.4, 3.8 Hz, 1H), 1.50 (td, *J* = 11.6, 2.7 Hz, 3H), 1.32 (d, *J* = 6.1 Hz, 6H), 1.29 – 1.24 (m, 19H), 1.06 – 0.95 (m, 4H). ^{13}C NMR (101 MHz, CDCl3) δ 202.84, 174.26, 134.72, 132.76, 131.17, 128.47, 103.86, 100.21, 96.32, 85.26, 79.38, 78.95, 77.24, 76.43, 74.63, 73.44, 73.13, 71.68, 69.52, 69.24, 68.86, 68.22, 66.16, 66.03, 64.73, 61.85, 60.08, 53.24, 43.32, 42.02, 40.89, 40.51, 37.65, 31.78, 31.09, 30.76, 30.47, 25.42, 20.11, 19.10, 18.81, 18.29, 15.31.

*4''-benzoyl-Spiramycin I (**8**)*.



According to the method B, compound **8** could be obtained with 37% yield as white solid using spiramycin I and benzoic acid as substrates. HRMS (ESI) for $C_{50}H_{78}N_2O_{15}$: calculated, $[M+H]^+$ =947.5475 , found 947.5479; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.09 (d, *J* = 6.8 Hz, 2H), 7.44 (d, *J* = 6.8 Hz, 2H), 6.32 – 6.19 (m, 1H), 6.10 – 5.94 (m, 1H), 5.70 (dd, *J* = 14.4, 9.6 Hz, 1H), 5.63 – 5.51 (m, 1H), 5.35 – 5.24 (m, 1H), 5.10 (s, 1H), 4.54 – 4.47 (m, 1H), 4.42 (d, *J* = 7.6 Hz, 1H), 4.12 (d, *J* = 8.4 Hz, 1H), 4.06 (dd, *J* = 6.0, 3.2 Hz, 2H), 3.81 (d, *J* = 10.8 Hz, 1H), 3.30 (d, *J* = 4.8 Hz, 2H), 3.09 (d, *J* = 8.4 Hz, 1H), 2.97 (dd, *J* = 9.6, 2.4 Hz, 1H), 2.84 – 2.77 (m, 1H), 2.74 – 2.64 (m, 2H), 2.54 (d, *J* = 2.0 Hz, 9H), 2.41 (d, *J* = 2.4 Hz, 7H), 2.37 – 2.26 (m, 3H), 2.24 (s, 1H), 2.18 – 2.09 (m, 1H), 2.05 (d, *J* = 13.6 Hz, 2H), 1.94 (dd, *J* = 25.4, 8.8 Hz, 3H), 1.77 (d, *J* = 14.4 Hz, 1H), 1.61 – 1.45 (m, 4H), 1.32 (s, 9H), 1.27 (d, *J* = 2.0 Hz, 6H), 1.00 (d, *J* = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.89, 174.25, 170.77, 134.72, 132.70, 132.37, 132.00, 131.24, 129.86, 128.17, 103.85, 100.19, 96.25, 85.22, 79.40, 74.49, 73.11, 73.02, 71.63, 69.72, 69.24, 68.87, 68.22, 66.21, 64.40, 61.84, 43.38, 42.00, 40.91, 40.12, 37.65, 31.88, 30.89, 30.78, 30.46, 25.37, 15.32.

*4''-(4-tert-butylbenzoyl)-Spiramycin I (**9a**) and 3-(4-tert-butylbenzoyl)-Spiramycin I (**9b**).*

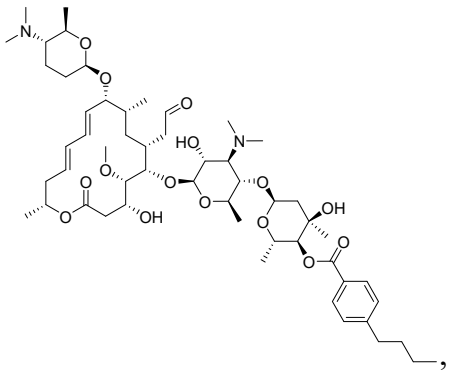
According to the method B, compound **9a**，**9b** could be obtained with 20% and 20% yield as white solid using spiramycin I and 4-tert-butylbenzoic acid as substrates. HRMS (ESI) for $C_{54}H_{86}N_2O_{15}$: calculated, $[M+H]^+$ =1003.6101, found **9a** 1003.5997, **9b** 1003.5993;

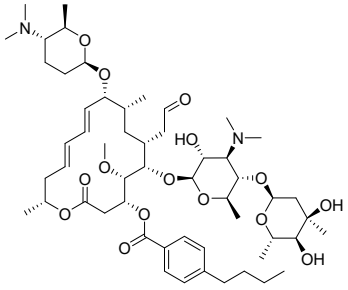
9a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.08 – 8.00 (m, 2H), 7.54 – 7.45 (m, 2H), 6.28-6.22 (m, 1H), 6.05-6.00 (m, 1H), 5.72-5.66(m, 1H), 5.60-5.53 (m, 1H), 5.30 – 5.26 (m, 1H), 5.13 (d, *J* = 6.0 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.63-4.57 (m, 1H), 4.51 (d, *J* = 6.0 Hz, 1H), 4.41 – 4.36 (m, 1H), 4.15-4.12(m , 1H), 4.09 – 4.03 (m, 2H), 3.81 (d, *J* = 12.0 Hz, 1H), 3.56-3.52(m, 1H), 3.52 (s, 3H), 3.45 – 3.40 (m, 1H), 3.36 – 3.27 (m, 2H), 3.09 (d, *J* = 8.8 Hz, 1H), 2.85-2.75 (m, 1H), 2.72-2.60 (m, 1H), 2.54 (s, 6H), 2.53-2.48 (m, 2H), 2.39 – 2.33 (m, 1H), 2.28-2.23 (m, 1H), 2.22 (s, 6H), 2.21-2.17 (m, 1H), 2.16 – 2.09 (m, 1H), 2.08 – 2.04 (m, 1H), 1.97-1.92 (m, 1H), 1.89 (dd, *J* = 12.0, 6.0 Hz, 1H), 1.87-1.81 (m, 2H), 1.56 – 1.47 (m, 2H), 1.47 – 1.41 (m, 1H), 1.34 (s, 9H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.16 (s, 3H), 0.99 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.84, 174.27, 166.39, 156.87, 134.68, 132.82, 131.04, 129.84, 128.54, 127.08, 125.41, 103.90, 100.30, 96.87, 85.27, 79.32, 78.77, 77.56, 75.50, 73.88, 73.12, 71.78, 69.52, 69.22, 68.77, 68.23, 64.86, 63.57, 61.86, 53.43, 43.24, 42.02, 41.69, 40.73, 37.66, 35.12, 31.74, 31.29, 31.12, 30.73, 30.49, 29.71, 25.44, 20.11, 18.97, 18.96, 18.38, 17.90, 15.31.

9b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.00 (d, *J* = 4.0 Hz, 2H), 7.46 (d, *J* =

4.0 Hz, 2H), 6.65-6.55(m, 1H), 6.15 – 6.02 (m, 1H), 5.78 – 5.63 (m, 2H), 5.42 (d, *J* = 12.0 Hz, 1H), 5.15-5.00 (m, 2H), 4.44 (d, *J* = 8.0 Hz, 1H), 4.33 (d, *J* = 4.0 Hz, 1H), 4.17 – 3.99 (m, 2H), 3.75 (d, *J* = 4.0 Hz, 1H), 3.60-3.53(m, 4H), 3.50 – 3.40 (m, 1H), 3.32 (d, *J* = 8.0 Hz, 1H), 3.27 – 3.17 (m, 2H), 2.97 – 2.85 (m, 3H), 2.80-2.70 (m, 2H), 2.49 (s, 6H), 2.45-2.43 (m, 1H), 2.42-2.39 (m, 1H), 2.38-2.34 (m, 1H), 2.33-2.28 (m, 1H), 2.25 (s, 6H), 2.18 – 2.10 (m, 1H), 2.02 (d, *J* = 8.0 Hz, 1H), 1.97 (s, 1H), 1.92-1.82(m, 2H), 1.77 – 1.69 (m, 1H), 1.54 – 1.41 (m, 3H), 1.33 (s, 9H), 1.28 (d, J = 6.0 Hz, 3H), 1.26 – 1.22 (m, 10H), 1.16 (d, *J* = 4.0 Hz, 3H), 1.01 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.15, 170.12, 166.15, 156.40, 134.91, 132.38, 131.74, 129.74, 127.48, 125.38, 104.81, 100.27, 96.30, 84.08, 79.87, 79.32, 77.25, 76.40, 74.58, 73.71, 73.19, 71.82, 69.56, 69.45, 69.26, 68.78, 66.05, 64.85, 62.09, 43.22, 42.08, 41.32, 40.90, 40.65, 37.42, 35.07, 32.13, 31.25, 31.15, 30.19, 25.41, 20.30, 19.10, 19.05, 18.58, 18.27, 15.50.

*4''-(4-n-butylbenzoyl)-Spiramycin I (**10a**) and 3-(4-n-butylbenzoyl)-Spiramycin I (**10b**).*





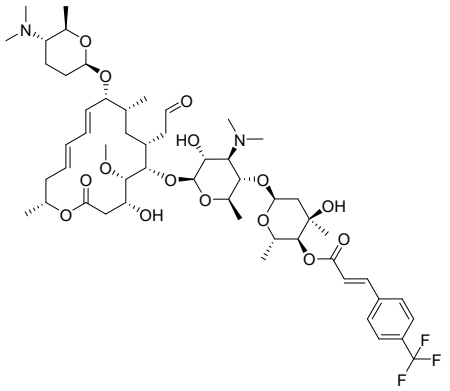
According to the method B, compound **10a**，**10b** could be obtained with 25% and 13% yield as white solid using spiramycin I and 4-butylbenzoic acid as substrates. HRMS (ESI) for $C_{54}H_{86}N_2O_{15}$: calculated, $[M+H]^+$ = 1003.6101, found **10a** 1003.6126，**10b** 1003.6111;

10a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.02 – 7.94 (m, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.25 (dd, J = 15.2, 10.4 Hz, 1H), 6.02 (dd, J = 15.2, 10.8 Hz, 1H), 5.69 (dd, J = 15.2, 9.6 Hz, 1H), 5.57 (m, 1H), 5.29 (m, 1H), 5.08 (d, J = 3.2 Hz, 1H), 4.48 (d, J = 7.6 Hz, 1H), 4.40 (dd, J = 11.2, 3.6 Hz, 1H), 4.11 (d, J = 8.8 Hz, 1H), 4.06 (dt, J = 10.0, 5.2 Hz, 2H), 3.80 (d, J = 10.8 Hz, 1H), 3.57 – 3.49 (m, 5H), 3.49 – 3.41 (m, 2H), 3.28 (dd, J = 6.0, 3.2 Hz, 3H), 3.10 – 3.05 (m, 1H), 2.95 (d, J = 9.6 Hz, 1H), 2.84 – 2.74 (m, 1H), 2.73 – 2.63 (m, 2H), 2.11 (dd, J = 18.4, 6.8 Hz, 1H), 2.04 (d, J = 15.2 Hz, 1H), 1.97 – 1.84 (m, 3H), 1.76 (dd, J = 14.4,4.0 Hz, 1H), 1.61 (m, 1H), 1.55 – 1.44 (m, 3H), 1.36 (dd, J = 15.2, 7.2 Hz, 1H), 1.30 (d, J = 6.0 Hz, 6H), 1.24 (t, J = 6.4 Hz, 9H), 0.99 (d, J = 6.4 Hz, 4H), 0.93 (t, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.88, 174.26, 170.32, 148.14, 134.70, 132.76, 131.15, 129.96, 128.76, 128.94 – 128.14 (m), 128.47, 103.88, 100.25, 96.33, 85.25, 79.34, 78.96, 74.69, 73.52, 73.13, 71.75, 69.58, 69.24, 68.78, 68.22, 66.11, 64.67, 61.85, 43.29, 42.01, 40.88, 40.46, 37.66, 35.71, 33.33, 31.79, 31.12, 30.75, 30.47, 25.38, 22.32, 20.11, 19.10, 18.85, 18.28, 15.32, 13.92.

10b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.63-6.50 (m, 1H), 6.14-6.05 (m, 1H), 5.79 – 5.72 (m, 1H), 5.70-5.65 (m,

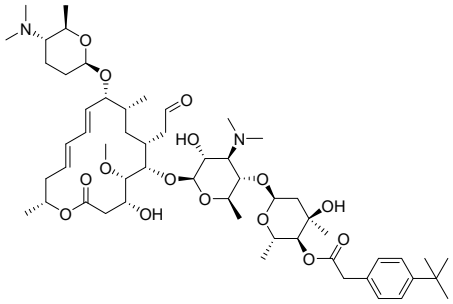
1H), 5.41 (d, *J* =8.0 Hz, 1H), 5.04 (d, *J* =4.0 Hz, 1H), 4.46-4.40(m, 1H), 4.34 (d, *J* = 8.0 Hz, 1H), 4.13 – 4.09 (m, 1H), 4.08 – 4.04 (m, 1H), 3.76 (d, *J* = 8.0 Hz, 1H), 3.58 (d, *J* = 8.0 Hz, 1H), 3.56 (s, 3H), 3.55 – 3.48 (m, 1H), 3.47-3.43 (m, 1H), 3.32 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.25 – 3.18 (m, 2H), 2.95-2.92 (m, 1H), 2.92 – 2.87 (m, 1H), 2.79-2.72 (m, 1H), 2.70 – 2.62 (m, 3H), 2.54 (s, 1H), 2.48 (s, 6H), 2.46-2.42 (m, 2H), 2.41-2.39 (m, 1H), 2.37 – 2.34 (m, 1H), 2.30 (d, *J* = 4.0 Hz, 1H), 2.24 (s, 6H), 2.19-2.14 (m, 1H), 2.13 – 2.08 (m, 1H), 2.06-1.96(m, 3H), 1.94-1.81 (m, 3H), 1.74 (dd, *J* = 12.0, 4.0 Hz, 1H), 1.66-1.56 (m, 3H), 1.54 – 1.43 (m, 3H), 1.36 (dd, *J* = 12.0, 8.0 Hz, 3H), 1.28 (d, *J* = 4.0 Hz, 3H), 1.24 (s, 3H), 1.23 (s, 6H), 1.18-1.14(m, 3H), 1.00 (d, *J* = 8.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.89, 174.27, 134.71, 132.79, 131.11, 130.01, 128.52, 103.89, 100.27, 96.87, 85.26, 79.32, 77.56, 75.52, 73.68, 73.11, 71.74, 69.56, 69.23, 68.78, 68.24, 64.84, 63.60, 61.86, 43.28, 42.02, 41.69, 40.65, 37.66, 35.73, 33.29, 31.20, 30.76, 30.48, 25.43, 22.29, 20.12, 19.05, 18.96, 18.59, 17.90, 15.31, 13.90.

*4''-(4-trifluoromethylcinnamyl)-Spiramycin I (**11**).*



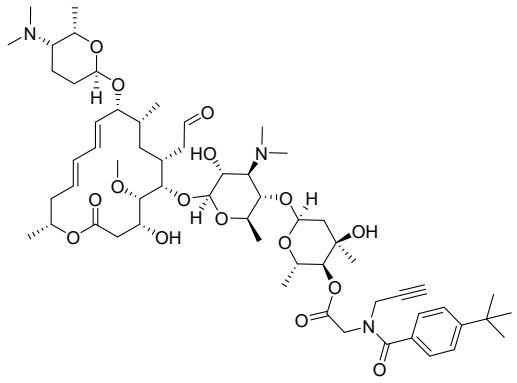
According to the method B, compound **11** could be obtained with 33% yield as white solid using spiramycin I and 4-trifluoromethyl cinnamic acid as substrates. HRMS (ESI) for $C_{53}H_{79}F_3N_2O_{15}$: calculated, $[M+2H]^{2+}/2$ = 521.2789, found 521.2803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.76 (d, *J* = 16.0 Hz, 1H), 7.65 (s, 4H), 6.67 (d, *J* = 16.0 Hz, 1H), 6.2-6.21 (m, 1H), 6.09 – 5.94 (m, 1H), 5.73-5.65 (m, 1H), 5.63-5.50(m, 1H), 5.34-5.25 (m, 1H), 5.12 (s, 1H), 4.75 (d, *J* = 8.0 Hz, 1H), 4.61 – 4.53 (m, 1H), 4.50 (d, *J* = 7.4 Hz, 1H), 4.39 (d, *J* = 8.0 Hz, 1H), 4.09 (dd, *J* = 28.0, 8.0 Hz, 3H), 3.81 (d, *J* = 12.0 Hz, 1H), 3.58 – 3.49 (m, 4H), 3.46 – 3.40 (m, 1H), 3.36 – 3.26 (m, 2H), 3.09 (d, *J* = 8.0 Hz, 1H), 2.80 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.71 (d, *J* = 12.0 Hz, 1H), 2.66-2.51 (m, 8H), 2.49 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 1H), 2.36 – 2.26 (m, 3H), 2.26-2.17 (m, 8H), 2.14 (d, *J* = 12.0 Hz, 1H), 2.10 – 2.06 (m, 1H), 2.02 (d, *J* = 12.0 Hz, 1H), 2.00-1.90(m, 2H), 1.87-1.83 (m, 1H), 1.54-1.38(m,3H), 1.30 (d, *J* = 4.0 Hz, 3H), 1.28 – 1.22 (m, 6H), 1.18 (d, *J* = 4.0 Hz, 6H), 0.99 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.86, 174.27, 166.41, 143.81, 137.69, 132.81, 131.07, 128.32, 125.92, 120.28, 103.91, 100.30, 96.92, 85.26, 79.35, 77.76, 77.24, 75.79, 73.84, 73.08, 71.76, 69.52, 69.23, 68.69, 68.24, 64.84, 63.53, 61.86, 43.25, 42.02, 41.62, 40.69, 37.66, 31.27, 30.73, 25.28, 20.11, 18.99, 18.91, 18.44, 17.85, 15.32.

*4''-(4-tert-butylphenylacetyl)-Spiramycin I (**12**)*.



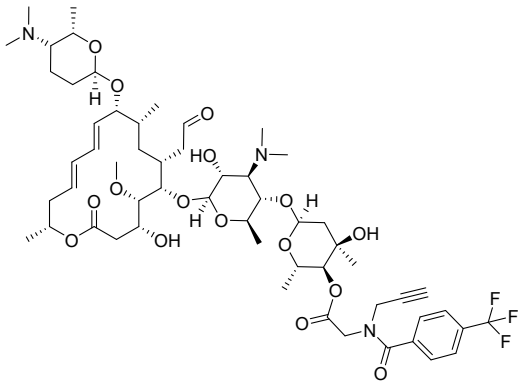
According to the method B, compound **12** could be obtained with 10% yield as white solid using spiramycin I and 4-tert-butyl-phenylacetic acid as substrates. HRMS (ESI) for $C_{55}H_{88}N_2O_{15}$: calculated, $[M+2H]^{2+}/2$ = 509.3165, found 509.3182; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.74 (d, *J* = 16.0 Hz, 1H), 7.51-7.39 (m, 3H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.30-6.18 (m, 1H), 6.07-5.98 (m, 1H), 5.73-5.65 (m, 1H), 5.62-5.52 (m, 1H), 5.33-5.25 (m, 1H), 5.11 (d, *J* = 4.0 Hz, 1H), 4.75 (d, *J* = 8.0 Hz, 1H), 4.59-4.46 (m, 2H), 4.41-4.35 (m, 1H), 4.16-4.11 (m, 1H), 4.10-4.00 (m, 2H), 3.81 (d, *J* = 8.0 Hz, 1H), 3.57 – 3.52 (m, 1H), 3.50 (d, *J* = 8.0 Hz, 3H), 3.47 – 3.42 (m, 1H), 3.35-3.29 (m, 2H), 3.12-3.05 (m, 1H), 2.96 – 2.80 (m, 1H), 2.80 – 2.71 (m, 1H), 2.70-2.64 (m, 1H), 2.54 (s, 6H), 2.50-2.47 (m, 1H), 2.42-2.39 (m, 1H), 2.34 (brs, 1H), 2.28-2.26 (m, 1H), 2.25 (s, 6H), 2.23 – 2.20 (m, 1H), 2.17 – 2.11 (m, 1H), 2.10-2.06 (m, 1H), 2.05-2.03 (m, 1H), 1.98-1.93 (m, 1H), 1.90 (d, *J* = 4.0 Hz, 1H), 1.88-1.86 (m, 1H), 1.86-1.84 (m, 1H), 1.56-1.45 (m, 3H), 1.33 (s, 9H), 1.32 – 1.29 (m, 3H), 1.26 – 1.23 (m, 6H), 1.17 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.86, 175.99, 174.27, 149.62, 134.71, 132.71, 131.73, 131.24, 129.00, 125.43, 103.85, 100.17, 96.24, 85.23, 79.43, 76.44, 74.44, 73.11, 71.62, 69.66, 69.26, 68.88, 68.22, 66.22, 64.48, 61.84, 43.38, 42.01, 41.33, 40.89, 40.22, 37.65, 34.43, 31.86, 31.37, 30.91, 30.78, 30.46, 25.39, 20.11, 19.23, 19.15, 19.10, 18.27, 15.32.

*4''-(N-(4-tert-butylbenzoyl)-N-(propargyl)-aminoacetyl)-Spiramycin I (**13**)*.



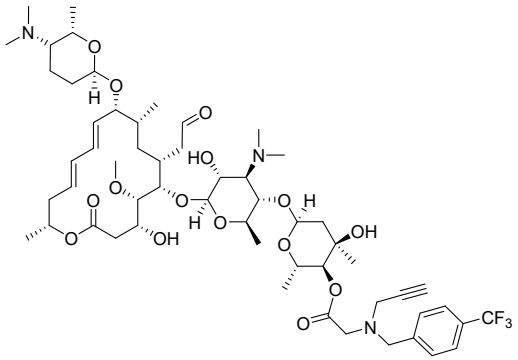
According to the method B, compound **13** could be obtained with 50% yield as white solid using spiramycin I and N-(4-tert-butylbenzoyl)-N-(propargyl)-aminoacetic acid as substrates. HRMS (ESI) for $C_{59}H_{91}N_3O_{16}$: calculated, $[M+2H]^{2+}/2$ = 549.8273, found 549.8283; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.54 – 7.33 (m, 4H), 6.28-6.21 (m, 1H), 6.08 – 5.96 (m, 1H), 5.73-5.65 (m, 1H), 5.61-5.50 (m, 1H), 5.35-5.23 (m, 1H), 5.12-5.05 (m, 1H), 4.73-4.59 (m, 1H), 4.54-4.46 (s, 2H), 4.43 (s, 1H), 4.41-4.32 (m, 2H), 4.30-4.16 (m, 2H), 4.25-4.11 (m, 1H), 4.08-4.12 (m, 2H), 3.80 (d, *J* = 12.0 Hz, 1H), 3.61 – 3.48 (m, 4H), 3.47 – 3.40 (m, 1H), 3.33-3.24 (m, 2H), 3.08 (d, *J* = 8.0 Hz, 1H), 2.98-2.79 (m, 1H), 2.78 – 2.61 (m, 2H), 2.60-2.40 (m, 9H), 2.37 (s, 1H), 2.35-2.27 (m, 3H), 2.24 (s, 6 H), 2.14 (d, *J* = 12.0 Hz, 1H), 2.08 (d, *J* = 12.0 Hz, 1H), 2.01 (s, 1H), 1.90-1.83 (m, 3H), 1.53 – 1.42 (m, 3H), 1.32 (s, 6H), 1.30 (d, *J* = 4.0Hz, 9H), 1.20 (d, *J* = 20.0 Hz, 9H), 0.99 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.87, 174.27, 134.71, 132.77, 131.14, 128.46, 127.20, 125.51, 124.83, 103.86, 100.24, 96.77, 85.25, 79.31, 75.63, 73.56, 73.04, 71.71, 69.55, 69.28, 69.24, 68.68, 68.23, 64.87, 61.85, 43.29, 42.02, 41.59, 40.64, 37.64, 34.88, 31.17, 30.75, 30.46, 29.70, 20.11, 19.09, 18.91, 15.31.

*4''-(N-(4-trifluoromethylbenzoyl)-N-(propargyl)-aminoacetyl)-Spiramycin I (**14**)*.



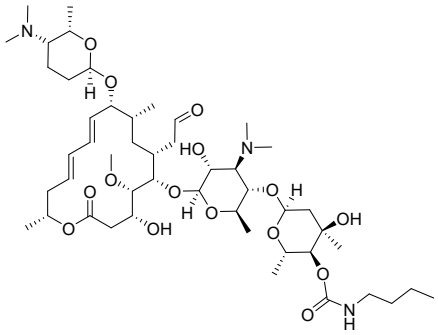
According to the method B, compound **14** could be obtained with 21% yield as white solid using spiramycin I and N-(4-trifluoromethylbenzoyl)-N-(propargyl)-aminoacetic acid as substrates. HRMS (ESI) for $C_{56}H_{82}F_3N_3O_{16}$: calculated, $[M+H]^+$ = 1110.5720, found 1110.5704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.74 – 7.56 (m, 4H), 6.30-6.22 (m, 1H), 6.11 – 5.93 (m, 1H), 5.73-5.65 (m, 1H), 5.61-5.53 (m, 1H), 5.30 – 5.24 (m, 1H), 5.10-5.06(m, 1H), 4.70-4.55 (m, 1H), 4.51-4.45 (m, 2H), 4.44 – 4.35 (m, 2H), 4.15 – 4.05 (m, 4H), 3.81 (d, J = 8.0 Hz, 1H), 3.58 – 3.52 (m, 1H), 3.50 (s, 3H), 3.45 – 3.40 (m, 1H), 3.36-3.27(m, 2H), 3.25-3.11 (m, 1H), 3.08(d, J = 4.0 Hz, 1H), 2.96-2.78 (m, 1H), 2.78 – 2.54 (m, 3H), 2.49 (s, 6H), 2.46-2.45 (m, 1H), 2.41-2.37 (m, 1H), 2.3-2.26 (m, 3H), 2.22 (s, 6H), 2.21-2.18 (m, 1H), 2.17-2.12 (m, 1H), 2.07 (d, J = 12.0 Hz, 1H), 2.03-1.96 (d, J = 12.0 Hz, 1H), 1.905-1.85(m, 2H), 1.84-1.82 (m, 1H), 1.53-1.41 (m, 3H), 1.30 (d, J = 8.0 Hz, 6H), 1.24 – 1.17 (m, 9H), 0.99 (d, J =8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.84, 174.27, 134.68, 132.82, 131.06, 128.54, 127.65, 125.74, 103.89, 100.30, 96.77, 85.27, 79.34, 77.43, 77.24, 77.03, 76.72, 75.66, 73.88, 73.05, 71.76, 69.23, 68.23, 64.85, 63.31, 61.85, 53.44, 46.34, 43.22, 42.02, 40.72, 37.64, 31.29, 30.72, 30.50, 25.40, 20.11, 18.97, 18.91, 18.38, 17.87, 15.32.

*4''-(N-(4-trifluoromethylbenzyl)-N-(propargyl)-aminoacetyl)-Spiramycin I (**15**)*.



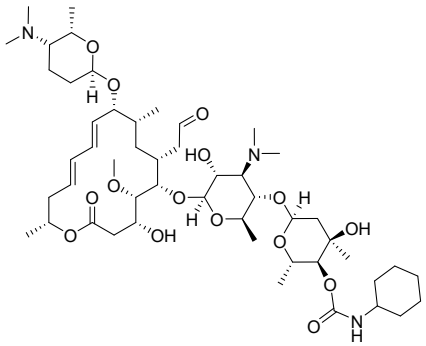
According to the method B, compound **15** could be obtained with 24% yield as white solid using spiramycin I and N-(4-trifluoromethylbenzyl)-N-(propargyl)-aminoacetic acid as substrates. HRMS (ESI) for $C_{56}H_{84}F_3N_3O_{15}$: calculated, $[M+2H]^{2+}/2$ = 548.8000, found 548.8023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.55 (dd, *J* = 18.8, 8.4 Hz, 4H), 6.24 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.01 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.68 (dd, *J* = 15.2, 9.6 Hz, 1H), 5.53-5.60 (m, 1H), 5.33 – 5.26 (m, 1H), 5.08 (d, *J* = 3.2 Hz, 1H), 4.66 (d, *J* = 10.0 Hz, 1H), 4.49 (d, *J* = 7.6 Hz, 1H), 4.43-4.47 (m, 1H), 4.41 – 4.37 (m, 1H), 4.11 (d, *J* = 8.8 Hz, 1H), 4.04 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.83 (s, 2H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.58 (s, 1H), 3.52 – 3.54 (m, 1H), 3.50 (s, 3H), 3.48 – 3.49 (m, 2H), 3.25 – 3.30 (m, 2H), 3.07 (d, *J* = 8.8 Hz, 1H), 2.83 – 2.74 (m, 1H), 2.68 (dd, *J* = 14.4, 10.8 Hz, 1H), 2.50 (s, 6H), 2.45 – 2.48 (m, 1H), 2.37 (s, 1H), 2.33 (s, 1H), 2.30 (s, 6H), 2.26 – 2.28 (m, 2H), 2.20 – 2.24 (m, 1H), 2.10 (dd, *J* = 24.8, 11.2 Hz, 1H), 2.04 – 1.98 (m, 1H), 1.82-1.93 (m, 4H), 1.54 – 1.44 (m, 3H), 1.33 – 1.25 (m, 9H), 1.23 (d, *J* = 5.6 Hz, 3H), 1.15 – 1.10 (m, 6H), 1.02 – 0.92 (m, 1H), 0.98(d, 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.84, 174.28, 170.66, 142.06, 142.04, 134.74, 132.74, 131.20, 129.31(4C), 128.44, 125.38, 125.35, 103.85, 100.21, 96.87, 85.25, 79.38, 79.03, 77.96, 77.72, 77.23, 75.77, 73.93, 73.32, 73.04, 71.70, 69.30, 69.23, 68.70, 68.23, 64.84, 63.31, 61.86, 57.04, 54.01, 43.35, 42.19, 42.02, 41.99, 41.61, 37.63, 31.05, 30.79, 30.48, 25.37, 20.11, 19.16, 18.90, 17.84, 15.31.

*4''-(butylaminoformyl)-Spiramycin I (**16**)*.



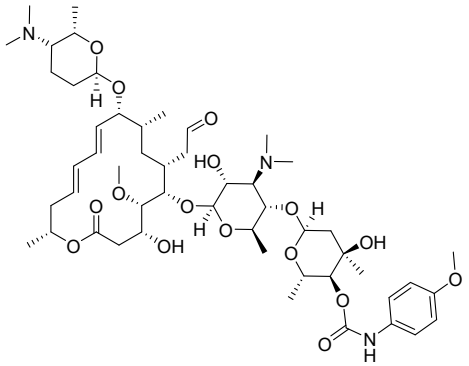
According to the method C, compound **16** could be obtained with 13% yield as white solid using spiramycin I and butyl isocyanate as substrates. HRMS (ESI) for $C_{48}H_{83}N_3O_{15}$: calculated, $[M+2H]^{2+}/2$ = 471.7985, found 471.8002; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 6.25 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.02 (dd, *J* = 14.8, 10.4 Hz, 1H), 5.69 (dd, *J* = 15.2, 9.6 Hz, 1H), 5.54 – 5.60 (m, 1H), 5.27 – 5.31 (m, 1H), 5.07 (d, *J* = 3.2 Hz, 1H), 4.48 (d, *J* = 7.6 Hz, 1H), 4.38 (d, *J* = 9.2 Hz, 1H), 4.14 – 4.01 (m, 4H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.51 – 3.56 (m, 1H), 3.50 (s, 3H), 3.40 – 3.47 (m, 1H), 3.28 – 3.31 (m, 3H), 3.24 – 3.26 (m, 1H), 3.07 (d, *J* = 8.8 Hz, 1H), 2.94 (d, *J* = 10.0 Hz, 1H), 2.79 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.68 (dd, *J* = 14.4, 10.8 Hz, 2H), 2.49 (s, 7H), 2.23 (s, 6H), 2.16 – 2.08 (m, 1H), 2.03 (d, *J* = 14.4 Hz, 2H), 1.91 – 1.97 (m, 1H), 1.80 – 1.89 (m, 3H), 1.77 (d, *J* = 4.0 Hz, 1H), 1.73 (d, *J* = 4.0 Hz, 1H), 1.57 – 1.64 (m, 3H), 1.54 – 1.46 (m, 2H), 1.45 – 1.38 (m, 3H), 1.29 – 1.31 (m, 5H), 1.23 – 1.25 (m, 10H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.92 – 0.96 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.84, 174.26, 136.00, 134.69, 132.80, 131.09, 129.06, 128.51, 103.89, 100.27, 96.39, 85.27, 79.33, 78.78, 77.24, 76.42, 74.82, 73.77, 73.14, 71.79, 69.46, 69.23, 68.77, 68.23, 66.07, 64.87, 61.85, 43.25, 42.68, 42.02, 40.88, 40.70, 37.65, 33.29, 31.74, 31.24, 30.73, 30.48, 25.41, 20.11, 19.69, 19.09, 19.01, 18.48, 18.29, 15.31, 13.40.

*4''-cyclohexylaminoformyl-Spiramycin I (**17**)*.



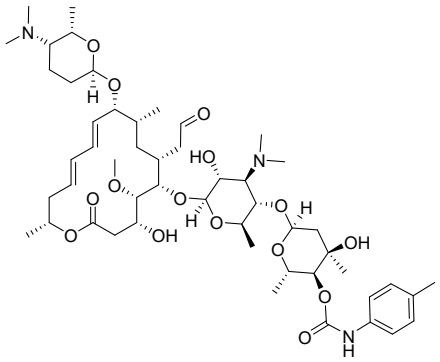
According to the method C, compound **17** could be obtained with 13% yield as white solid using spiramycin I and cyclohexyl isocyanate as substrates. HRMS (ESI) for $C_{50}H_{85}N_3O_{15}$: calculated, $[M+2H]^{2+}/2$ = 484.8063, found 484.8038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 6.25 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.02 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.68 (dd, *J* = 15.2, 9.6 Hz, 1H), 5.60 – 5.53 (m, 1H), 5.33 – 5.25 (m, 1H), 5.07 (d, *J* = 2.8 Hz, 1H), 4.47 (d, *J* = 7.6 Hz, 1H), 4.38 (d, *J* = 8.0 Hz, 1H), 4.11 – 4.03 (m, 4H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.55 – 3.52 (m, 2H), 3.50 (s, 3H), 3.46 – 3.38 (m, 2H), 3.32 – 3.22 (m, 2H), 3.07 (d, *J* = 8.8 Hz, 1H), 2.94 (d, *J* = 10.0 Hz, 1H), 2.79 (dd, *J* = 13.6, 10.0 Hz, 2H), 2.68 (dd, *J* = 14.8, 11.2 Hz, 2H), 2.54 – 2.42 (m, 7H), 2.40 – 2.25 (m, 3H), 2.21 (s, 6H), 2.10 (d, *J* = 13.6 Hz, 2H), 2.03 (d, *J* = 14.4 Hz, 2H), 1.98 – 1.80 (m, 5H), 1.76 (d, *J* = 3.6 Hz, 1H), 1.74 – 1.68 (m, 3H), 1.53 – 1.43 (m, 5H), 1.35 – 1.26 (m, 6H), 1.26 – 1.18 (m, 9H), 0.99 (t, *J* = 6.3 Hz, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 202.88, 174.21, 134.66, 132.78, 131.06, 128.49, 103.88, 100.24, 96.37, 85.24, 79.25, 78.75, 77.28, 76.40, 74.85, 73.82, 73.10, 71.76, 69.45, 69.22, 68.73, 68.21, 66.01, 64.82, 61.82, 53.33, 43.20, 41.97, 40.86, 40.68, 37.67, 34.76, 31.71, 31.25, 30.70, 30.46, 25.38, 25.19, 23.76, 20.10, 19.06, 18.97, 18.40, 18.26, 15.29.

*4''-(4-methoxyphenylaminoformyl)-Spiramycin I (**18**)*.



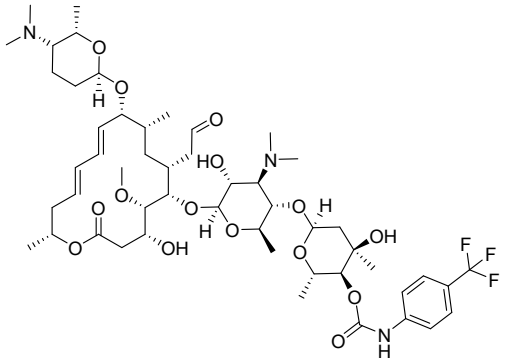
According to the method C, compound **18** could be obtained with 21% yield as white solid using spiramycin I and 4-methoxyphenyl isocyanate as substrates. HRMS (ESI) for $C_{51}H_{81}N_3O_{15}$: calculated, $[M+H]^+$ = 992.5690, found 992.5684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 6.24 (dd, *J* = 14.8, 10.4 Hz, 1H), 6.03 – 5.93 (m, 1H), 5.65 (dd, *J* = 15.6, 9.6 Hz, 1H), 5.61 – 5.51 (m, 1H), 5.36 – 5.23 (m, 1H), 5.10 (d, *J* = 3.2 Hz, 1H), 5.00 – 4.93 (m, 1H), 4.73 (d, *J* = 7.6 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 1H), 4.14 (d, *J* = 8.0 Hz, 1H), 4.08 – 4.03 (m, 2H), 3.82 (s, 3H), 3.77 (d, *J* = 11.2 Hz, 1H), 3.59 – 3.51 (m, 2H), 3.48 (s, 2H), 3.39 – 3.29 (m, 3H), 2.99 (dd, *J* = 14.8, 9.2 Hz, 3H), 2.84 (dd, *J* = 18.0, 8.4 Hz, 2H), 2.74 – 2.61 (m, 3H), 2.47 (s, 3H), 2.39 – 2.27 (m, 2H), 2.25 – 2.13 (m, 1H), 2.13 – 2.00 (m, 4H), 1.93 (s, 3H), 1.79 (dd, *J* = 14.4, 3.6 Hz, 2H), 1.59 (dd, *J* = 13.6, 7.6 Hz, 4H), 1.38 (s, 4H), 1.35 – 1.29 (m, 9H), 1.27 (d, *J* = 5.6 Hz, 6H), 1.06 – 0.96 (m, 4H), 0.89 (t, *J* = 12.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.90, 174.26, 170.09, 163.22, 134.71, 132.75, 131.96, 131.16, 128.45, 123.62, 113.49, 103.87, 100.23, 96.31, 85.24, 79.33, 78.97, 76.43, 74.66, 73.49, 73.12, 71.73, 69.60, 69.24, 68.79, 68.22, 66.12, 64.68, 61.85, 55.42, 43.29, 42.00, 40.88, 40.45, 37.66, 31.79, 31.10, 30.75, 30.45, 25.38, 20.11, 19.11, 18.87, 18.28, 15.31.

*4''-(4-methyl-phenylaminoformyl)-Spiramycin I (**19**)*.

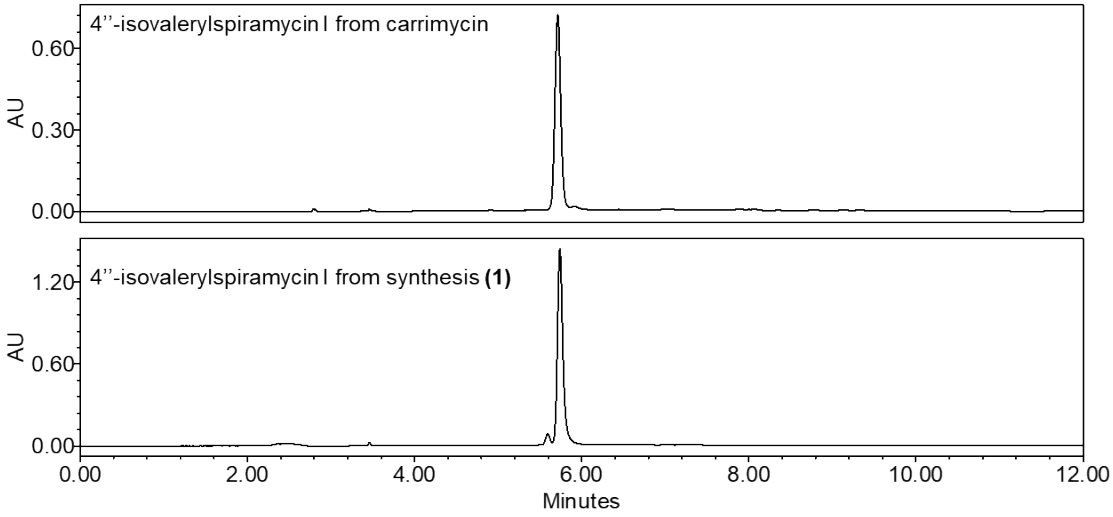


According to the method C, compound **19** could be obtained with 18% yield as white solid using spiramycin I and 4-methyl phenyl isocyanate as substrates. HRMS (ESI) for $C_{51}H_{81}N_3O_{15}$: calculated, $[M+H]^+$ = 976.5740, found 976.5748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.94 (s, 1H), 6.24 (dd, *J* = 14.8, 10.4 Hz, 1H), 6.01 (dd, *J* = 14.0, 11.2 Hz, 1H), 5.68 (dd, *J* = 14.8, 9.6 Hz, 1H), 5.62 – 5.48 (m, 1H), 5.28 (s, 1H), 5.09 (s, 1H), 4.54 (d, *J* = 10.0 Hz, 1H), 4.48 (d, *J* = 7.2 Hz, 1H), 4.37 (d, *J* = 8.0 Hz, 1H), 4.11 (d, *J* = 8.4 Hz, 1H), 4.05 (d, *J* = 9.2 Hz, 2H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.55 – 3.48 (m, 4H), 3.45 – 3.36 (m, 2H), 3.29 (d, *J* = 6.8 Hz, 2H), 3.07 (d, *J* = 8.4 Hz, 1H), 3.00 – 2.90 (m, 1H), 2.79 (dd, *J* = 17.2, 9.2 Hz, 1H), 2.72 – 2.63 (m, 1H), 2.52 (s, 5H), 2.48 – 2.43 (d, *J* = 19.0 Hz, 3H), 2.29 (s, 3H), 2.21 (s, 6H), 2.10 (d, *J* = 12.8 Hz, 1H), 2.03 (d, *J* = 14.4 Hz, 2H), 1.93 (s, 1H), 1.87 – 1.87 (m, 3H), 1.54 – 1.37 (m, 3H), 1.29 (d, *J* = 6.0 Hz, 6H), 1.22 (d, *J* = 7.3 Hz, 9H), 0.98 (d, *J* = 6.2 Hz, 4H), 0.86 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.97, 174.27, 171.64, 143.98, 134.73, 132.65, 131.32, 130.14, 129.10, 128.37, 127.59, 103.80, 100.17, 96.11, 85.19, 79.46, 76.46, 74.14, 73.08, 72.64, 71.48, 69.98, 69.27, 68.98, 68.24, 66.37, 64.23, 61.84, 43.46, 41.99, 40.93, 39.93, 37.65, 31.96, 30.71, 30.45, 25.35, 21.72, 20.10, 19.81, 19.24, 19.13, 18.26, 15.33.

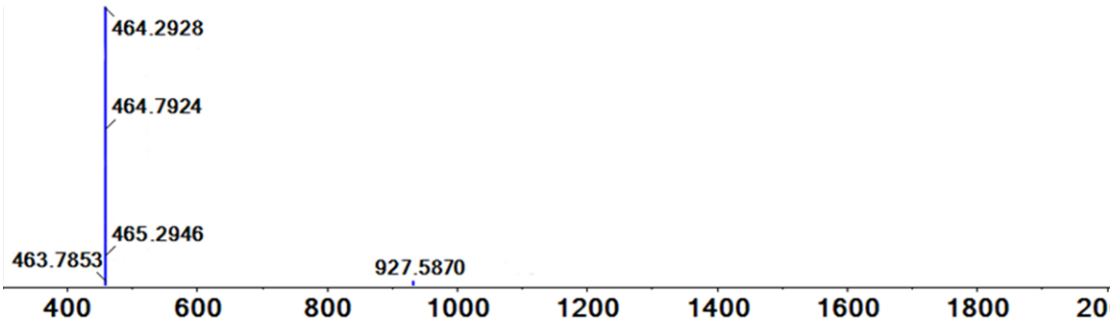
*4''-(4-methoxyphenylaminoformyl)-Spiramycin I (**20**)*.



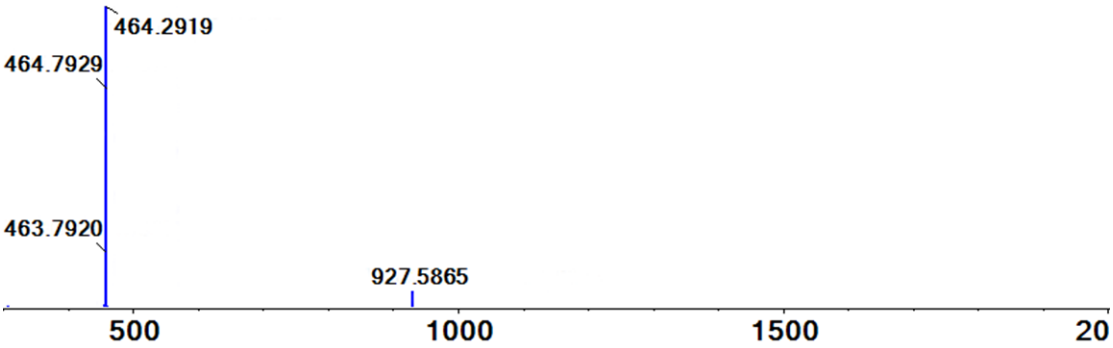
According to the method C, compound **20** could be obtained with 13% yield as white solid using spiramycin I and 4-trifluoromethyl phenyl isocyanate as substrates. HRMS (ESI) for $C_{51}H_{78}F_3N_3O_{15}$: calculated, $[M+H]^+$ = 1030.5458, found 1030.5465; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.26 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.03 (dd, *J* = 14.8, 10.8 Hz, 1H), 5.70 (dd, *J* = 15.2, 9.6 Hz, 1H), 5.54 – 5.61 (m, 1H), 5.28 – 5.33 (m, 1H), 5.09 (d, *J* = 3.2 Hz, 1H), 4.49 (d, *J* = 7.6 Hz, 1H), 4.42 – 4.37 (m, 1H), 4.12 (d, *J* = 8.4 Hz, 1H), 4.11 – 4.03 (m, 3H), 3.82 (d, *J* = 10.8 Hz, 1H), 3.58 – 3.52 (m, 2H), 3.52 (s, 3H), 3.41 – 3.48 (m, 1H), 3.27 – 3.30 (m, 2H), 3.09 (d, *J* = 8.4 Hz, 1H), 2.96 (d, *J* = 9.6 Hz, 1H), 2.85 – 2.77 (m, 1H), 2.70 (dd, *J* = 14.8, 11.2 Hz, 2H), 2.50 (s, 6H), 2.24 (s, 6H), 2.07 – 2.16 (m, 2H), 2.05 (d, *J* = 14.4 Hz, 2H), 1.92 – 1.99 (m, 1H), 1.89 – 1.83 (m, 2H), 1.77 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.56 – 1.41 (m, 4H), 1.30 – 1.99(m, 7H), 1.24 – 1.26(m, 10H), 1.0(d, *J* = 6.4 Hz, 3H), 1.03 – 0.96 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.87, 174.23, 152.44, 142.17, 134.78, 132.70, 131.24, 128.36, 126.16 (t, *J* = 7.2, 3.4 Hz), 125.67 (t, *J* = 127.4, 32.7 Hz), 118.63 (2C), 114.16, 103.85, 100.36, 96.33, 85.25, 79.28, 79.09, 77.26, 76.44, 74.73, 73.98, 73.11, 71.71, 69.55, 69.28, 68.75, 68.28, 66.02, 64.84, 61.87, 43.34, 41.94 (2C), 40.78 (2C), 37.67, 31.91, 31.29, 30.67, 30.49, 25.40, 20.09, 19.08, 18.99, 18.40, 18.28, 15.39.



4''-isovalerylspiramycin I from carrimycin



4''-isovalerylspiramycin I from synthesis (1)



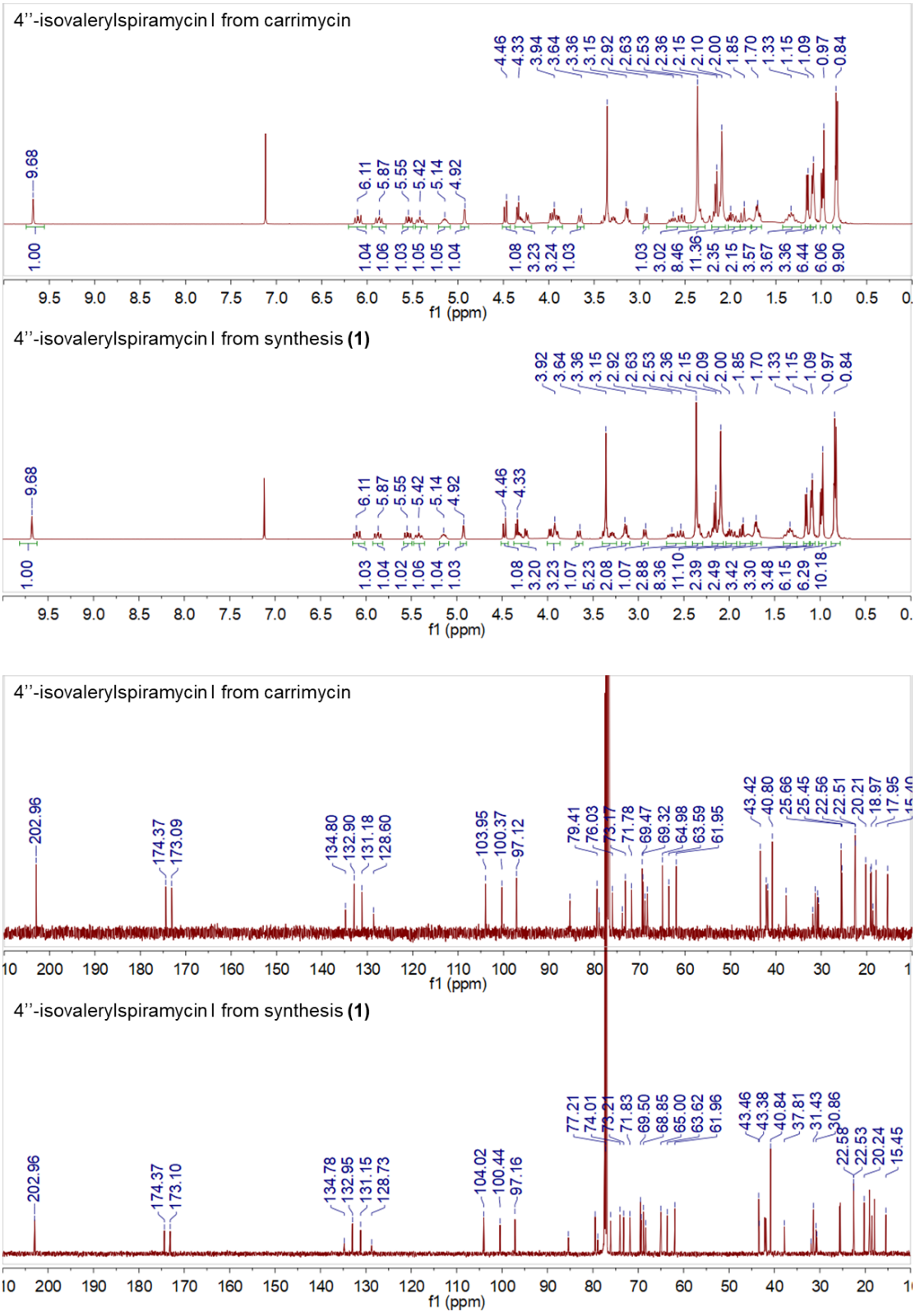


Figure S1. The HPLC, HR-ESI-MS and NMRs studies of 4''-isovalerylspiramycin I and compound **1** from carrimycin and synthesis, respectively.

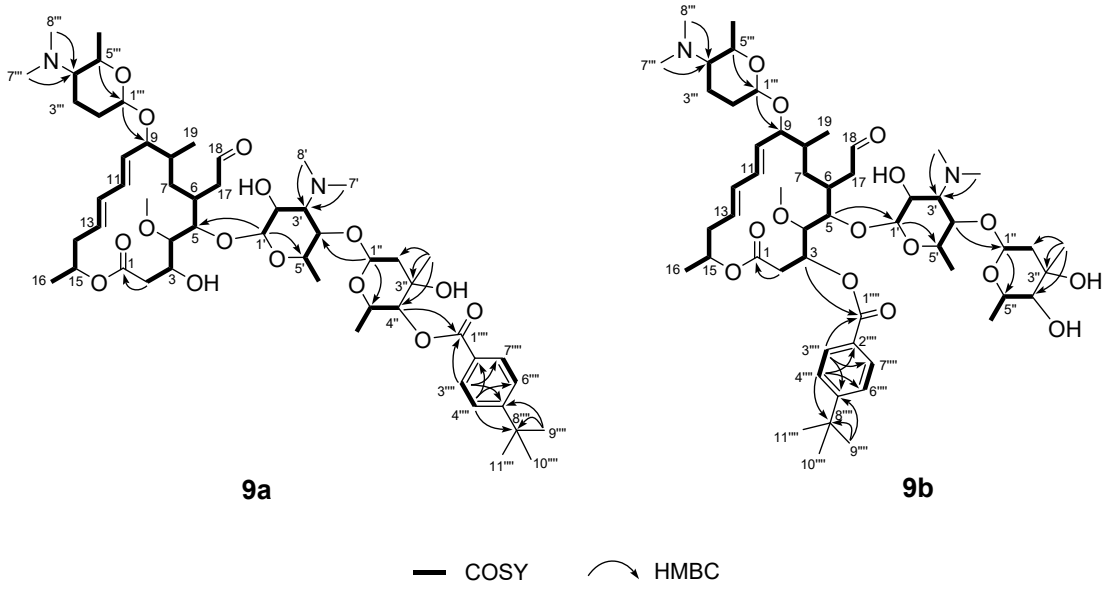
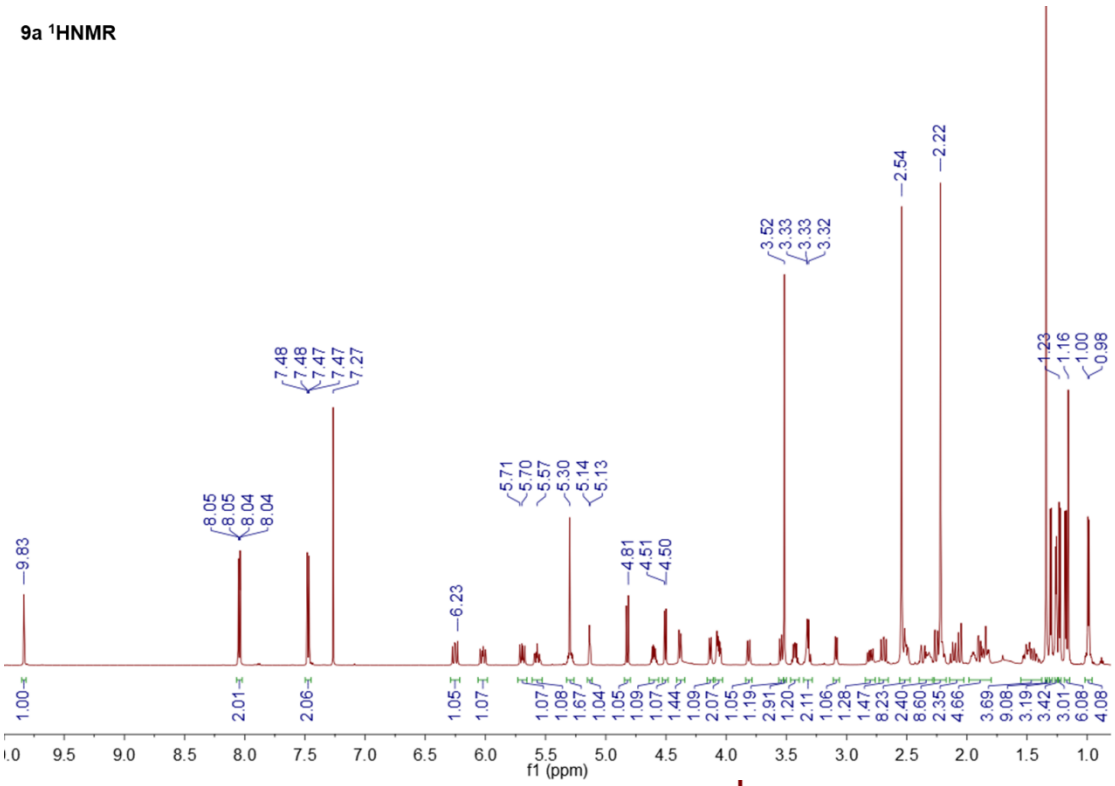


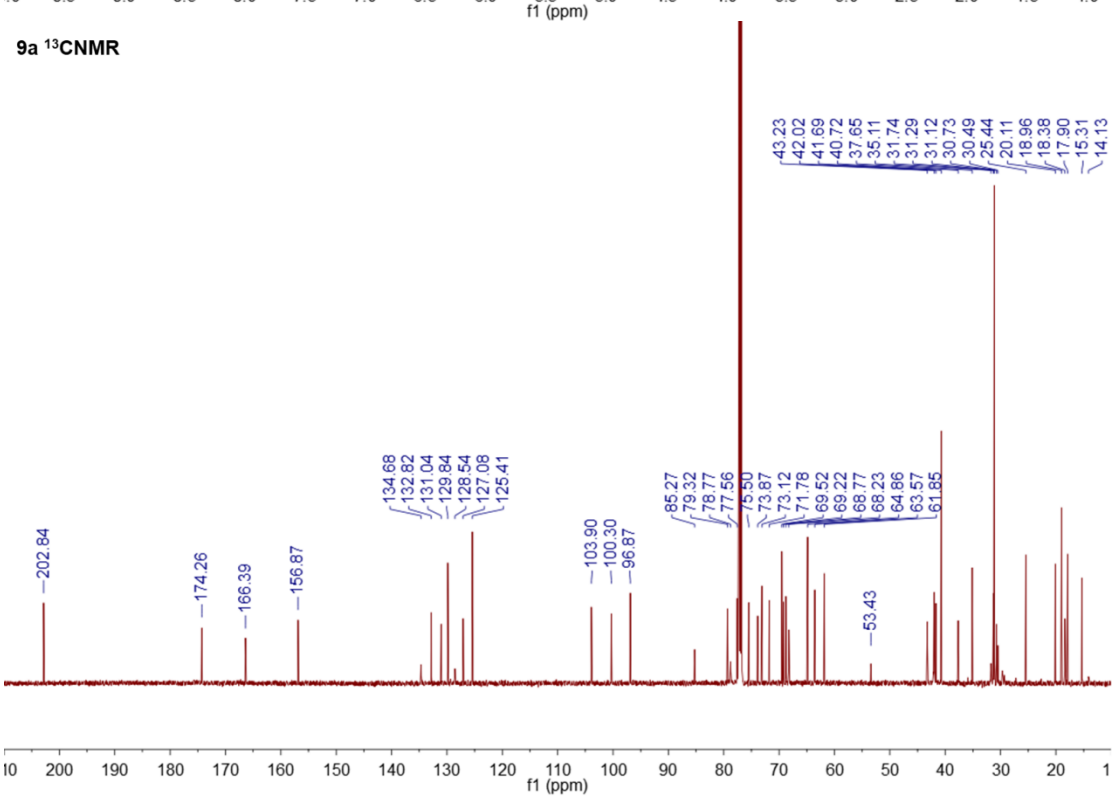
Figure S2. Key ^{1}H-^{1}H COSY and HMBC correlations of compounds **9a** and **9b**.

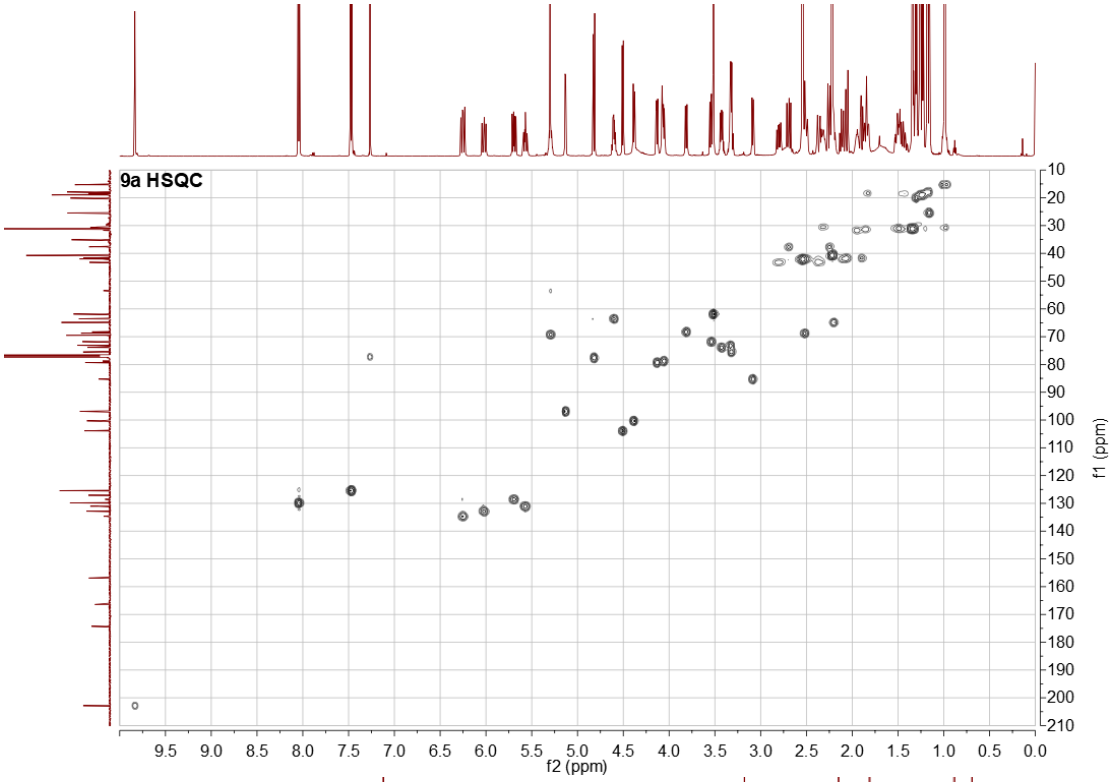
The 1D NMR data of **9a** were almost identical to those of **9b**. The main difference between them was that the 4-(*tert*-butyl)benzoyl was bonded to the 4’’-OH of **9a** and the 3-OH of **9b**, respectively. The structures of **9a** and **9b** could be verified by detailed analysis of their ^{1}H-^{1}H COSY, HSQC and HMBC correlations (**Figure S3** and **S4**). The 4-(*tert*-butyl)benzoyl moiety of **9a** and **9b** were clearly assigned by the key HMBC correlations from H-3‴′ to C-1‴′, C-5‴′ and C-7‴′; H-4‴′ to C-2‴′, C-6‴′ and C-8‴′; H-9‴′ (or H-10‴′, H-11‴′) to C-5‴′ and C-8‴′. In the HMBC spectrum of **9a**, the correlation between H-4″ (δ_H 4.82) and C-1‴′ (δ_C 166.4) supported that C-1‴′ was attached to C-4″ via an ether bridge. Similarly, according to the HMBC correlation, H-3 (δ_H 5.40) of **9b** was bonded to C-1‴′ (δ_C 166.3). Therefore, the structures of **9a** and **9b** were finally identified as shown in **Figure S3**.

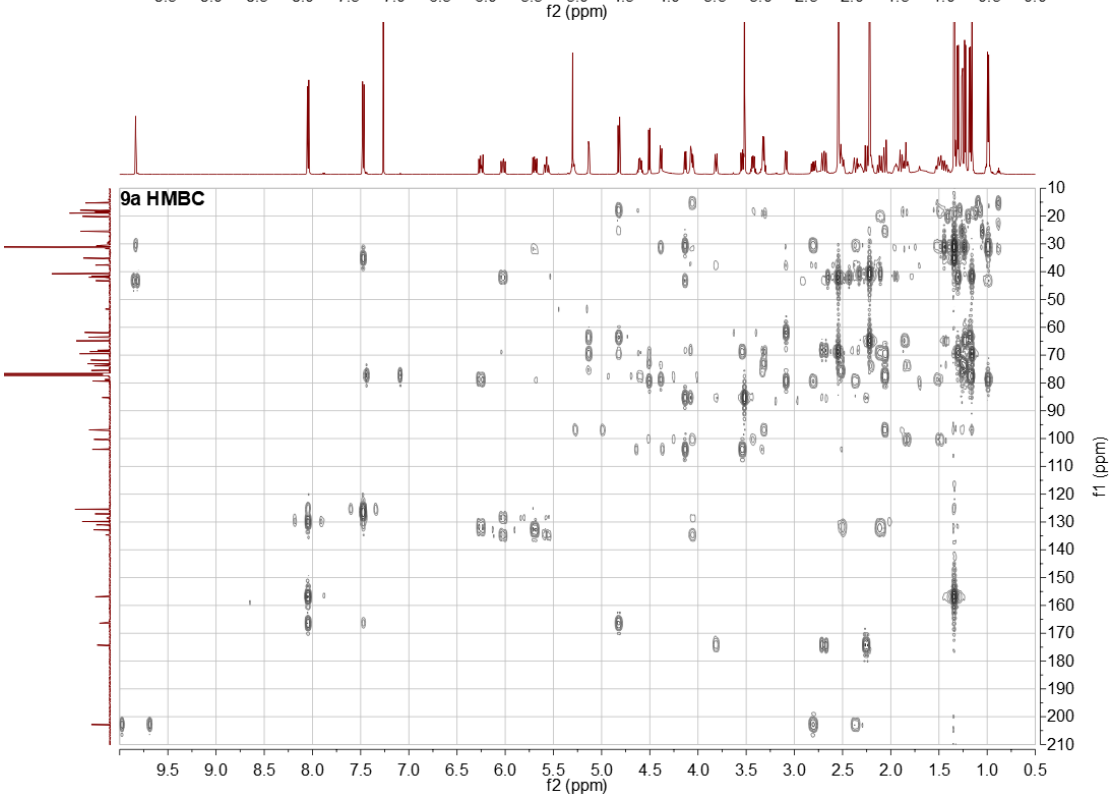
9a ^{1}HNMR



9a ^{13}CNMR




9a HSQC
f2 (ppm)
f1 (ppm)


9a HMBC
f2 (ppm)
f1 (ppm)

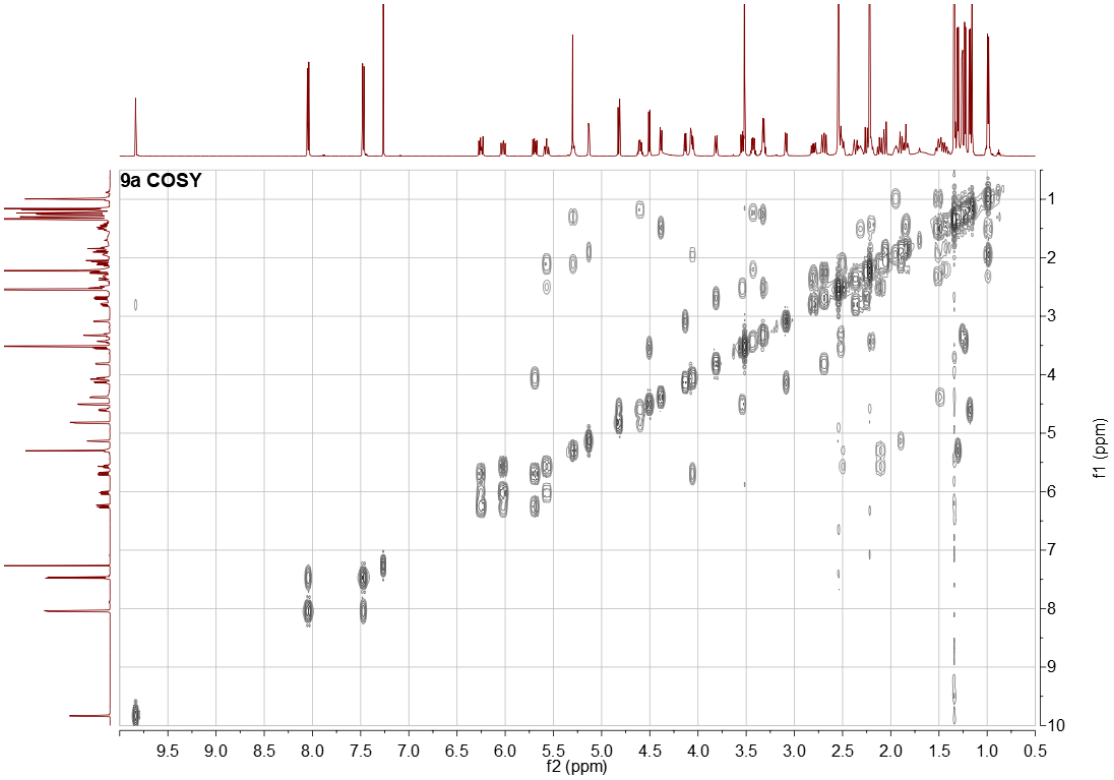
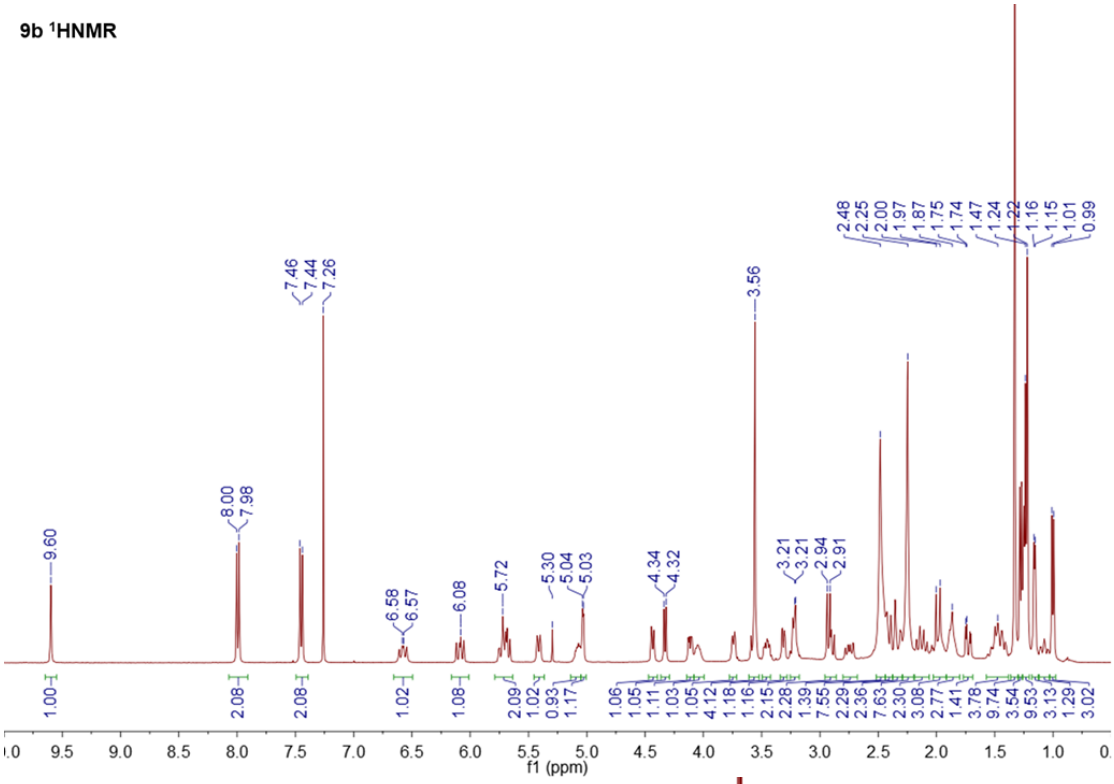
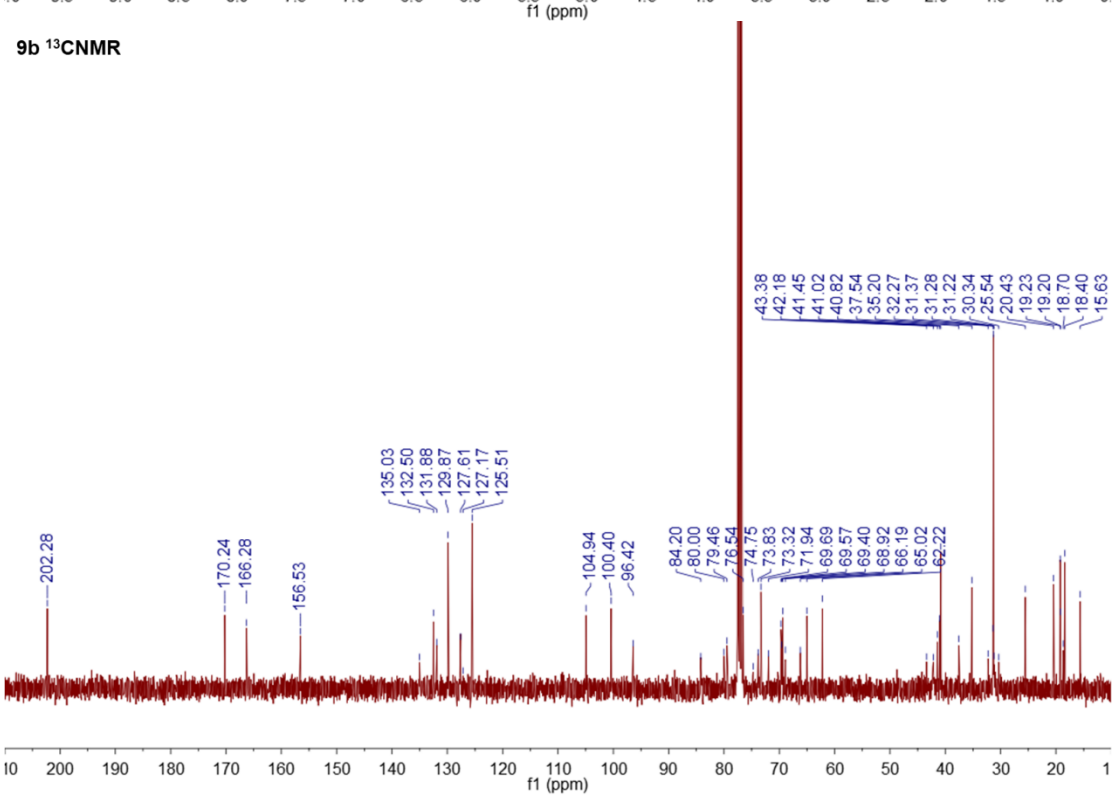


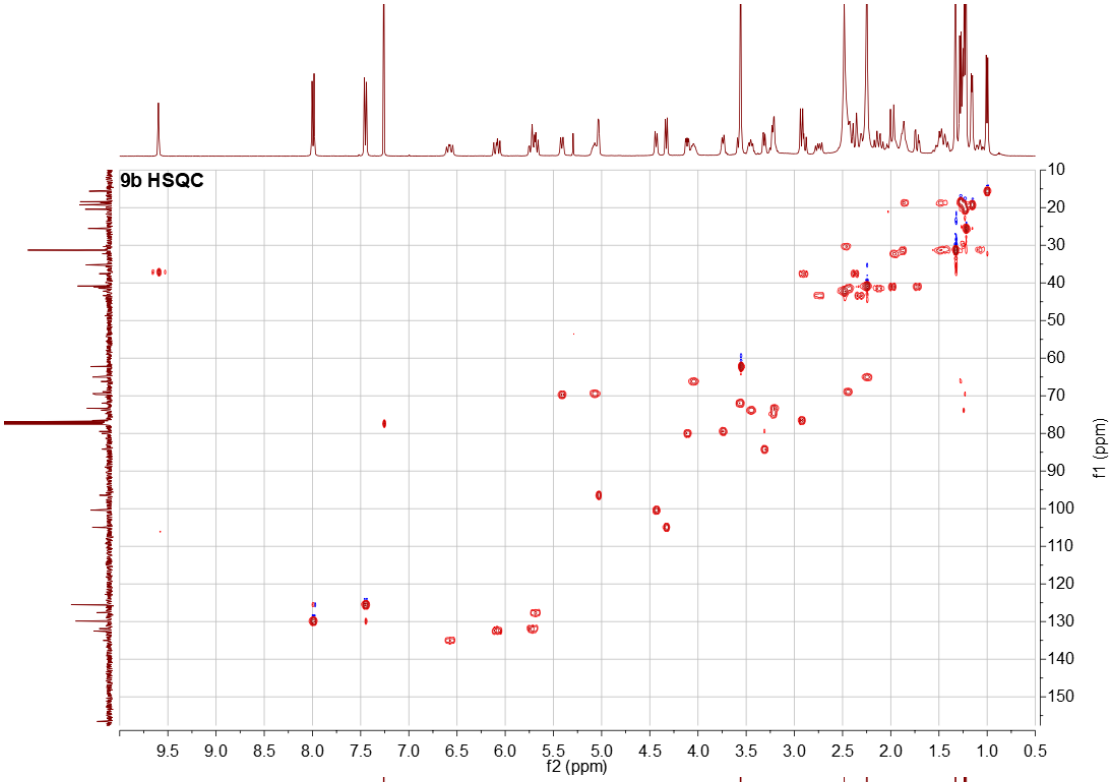
Figure S3. 1D and 2D NMR spectra of compound **9a**.

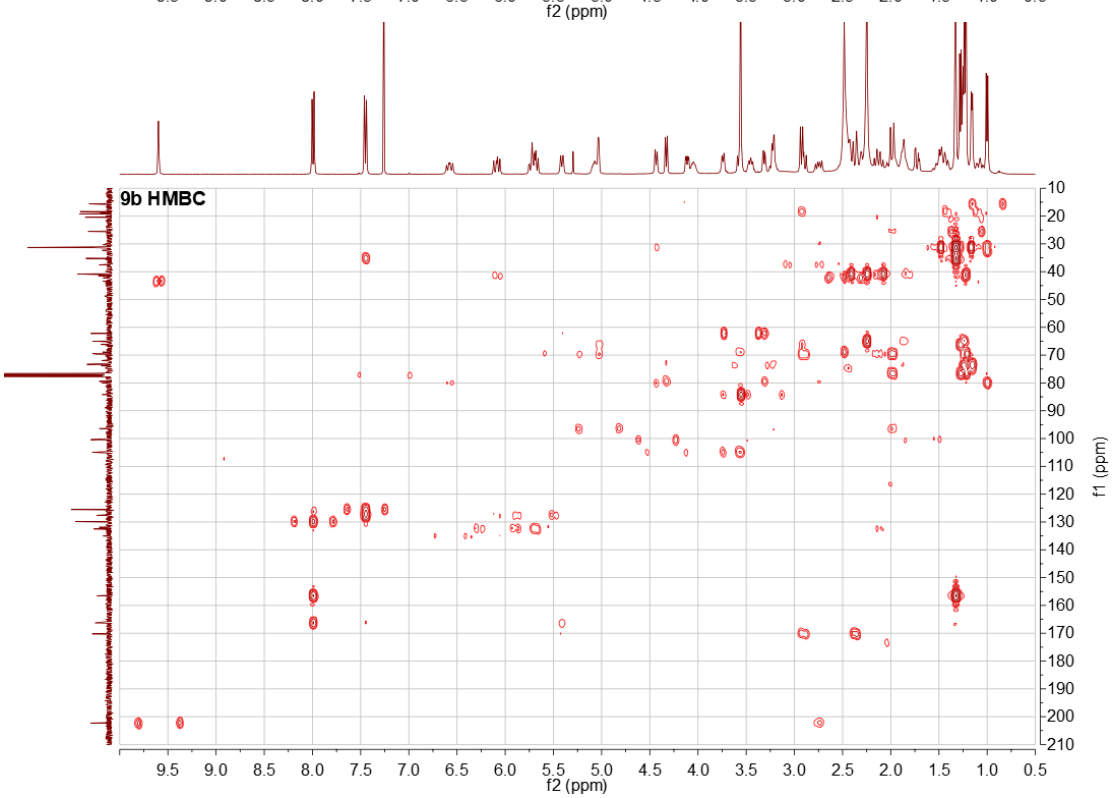
9b ^{1}HNMR



9b ^{13}CNMR




9b HSQC
f2 (ppm)
f1 (ppm)


9b HMBC
f2 (ppm)
f1 (ppm)

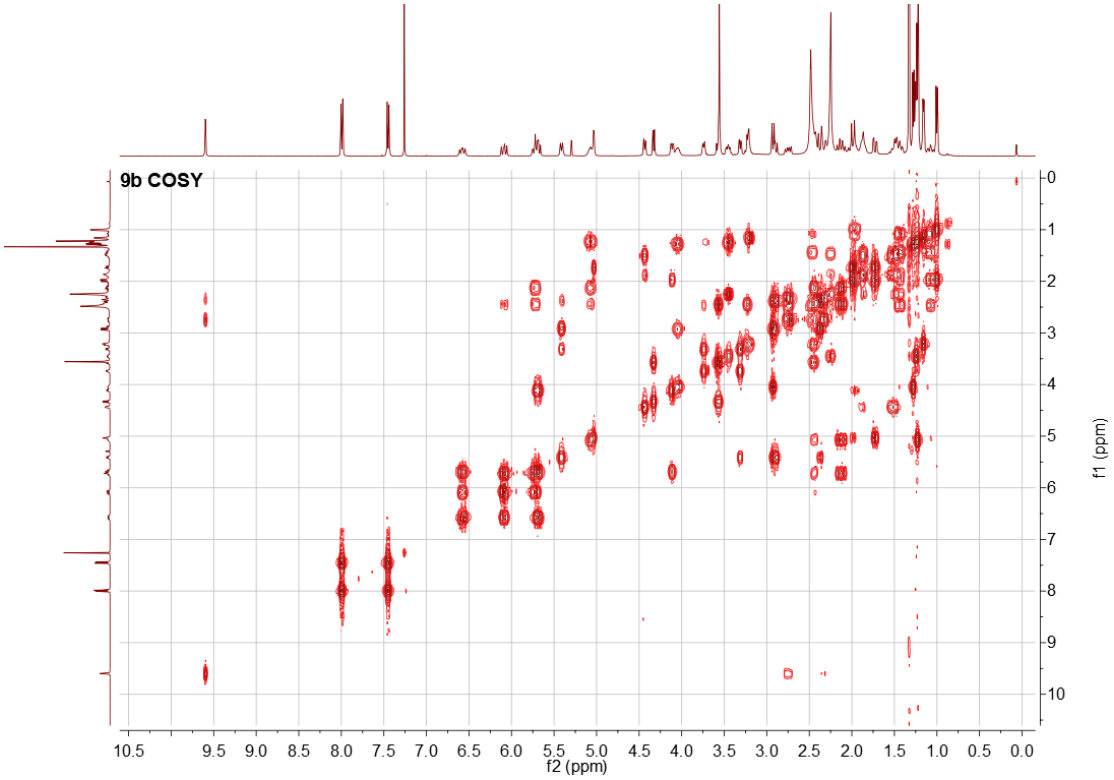


Figure S4. 1D and 2D NMR spectra of compound **9b**.

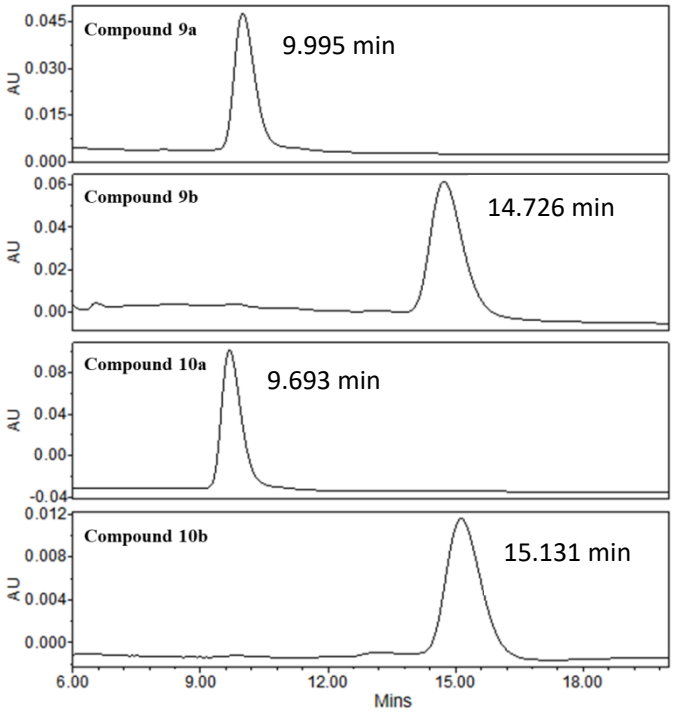


Figure S5. HPLC analysis of compounds **9a, 9b, 10a** and **10b**. The analysis was performed on C18YE column (4.6 mm × 250 mm) with a UV detection wavelength of 230 nm; the mobile phase consisted of (A) acetonitrile and (B) 0.1% formic acid in water (v/v); the flow rate was 0.6 mL/min at 25℃.

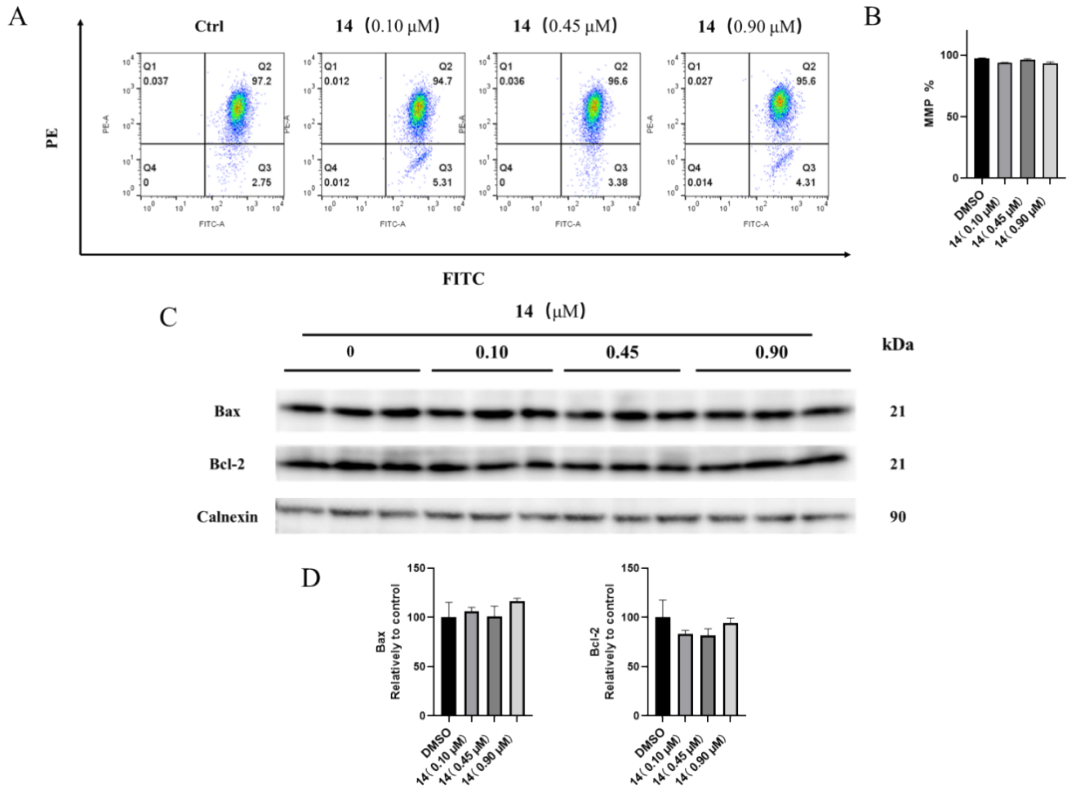
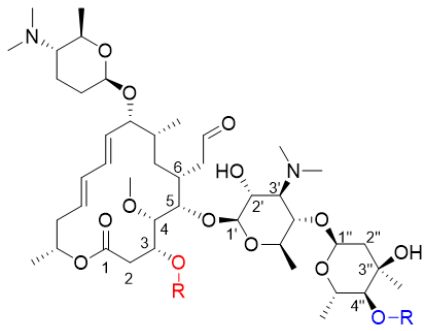


Figure S6. The effect of **14** on HGC-27 mitochondrion. (A) Flow cytometry and (B)bar graph analysis of mitochondrial membrane potential, (C) Western blot images and (D) bar graph analysis of Bax, and Bcl-2 protein expressions in HGC-27 after treatment with 14 (0, 0.10, 0.45, 0.90 μM) for 24 h.



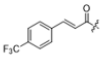
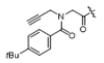
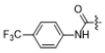
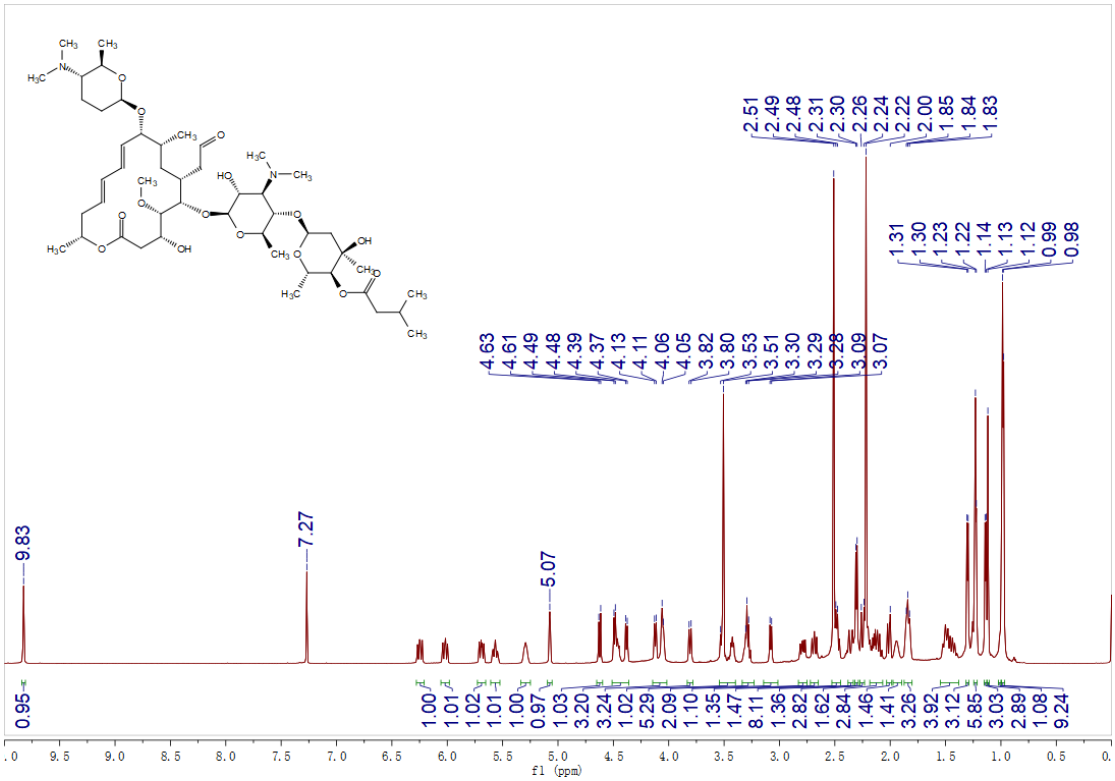
	R	MIC [μM]		R	MIC [μM]
1		4-16	2		2-8
3		2-16	4		4-16
5		4-32	6		2-16
9a		4->128	10a		4-32
10b		2-16	11		4->128
12		4-16	13		4-32
14		4-16	16		1-8
17		8-64	20		2-32

Figure S7. Antibacterial SAR of spiramycin I derivatives.

Compound 1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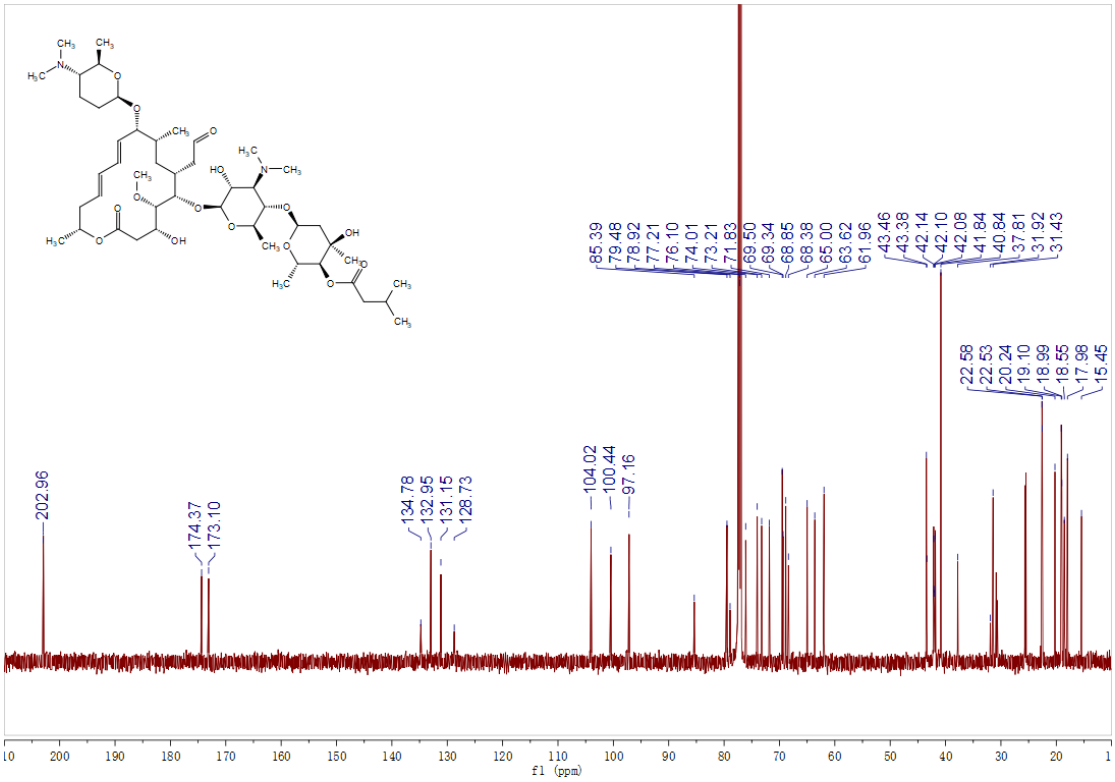
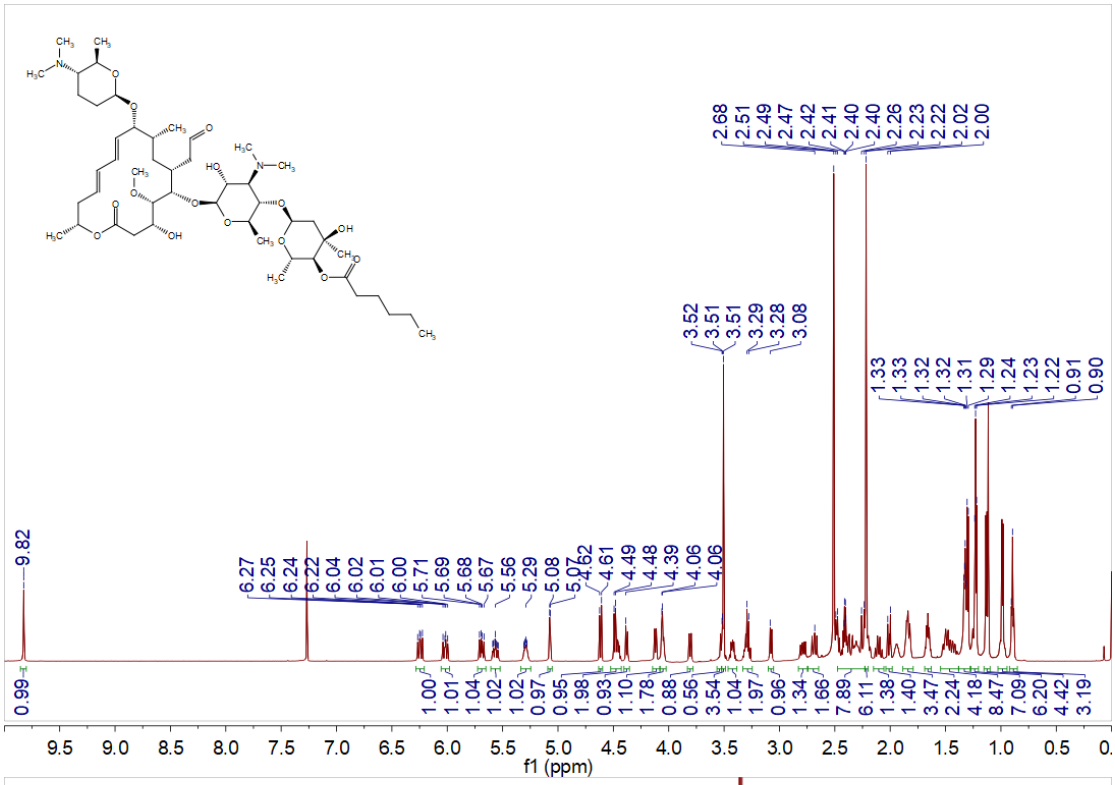
7.27
5.07
f1 (ppm)


202.96
174.37
173.10
134.78
132.95
131.15
128.73
104.02
100.44
97.16
f1 (ppm)

Compound 2


9.82
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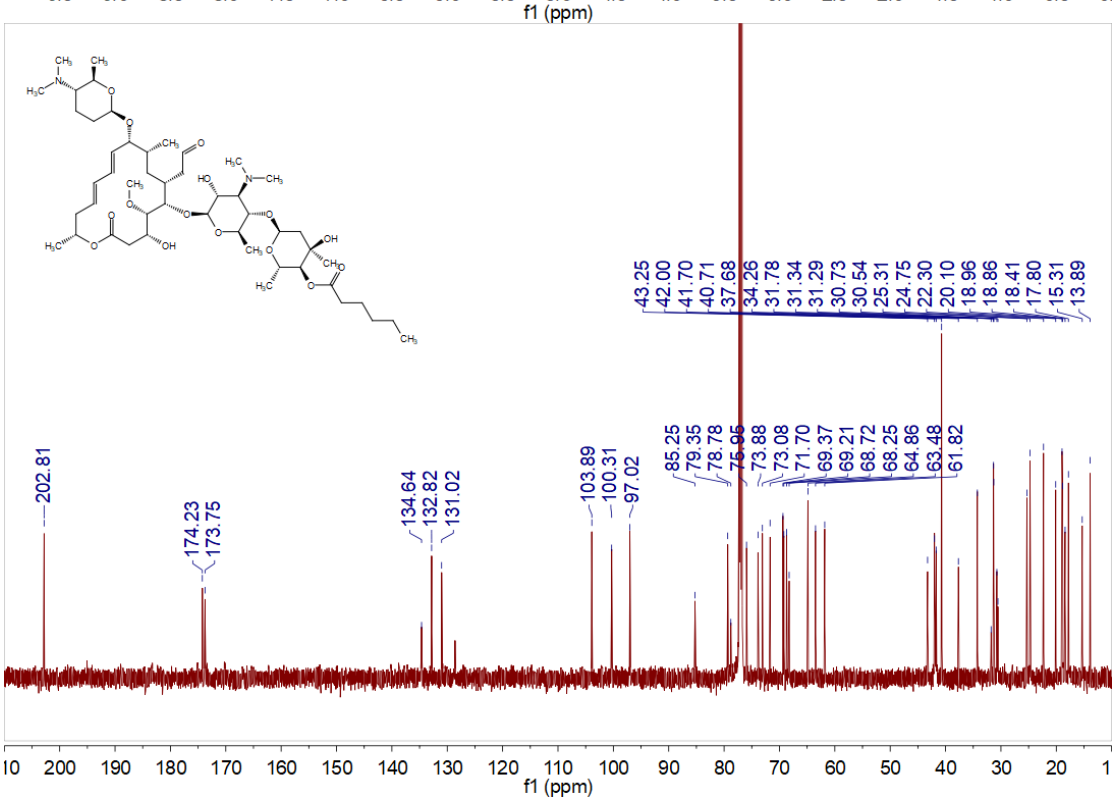
6.25
6.24
6.22
6.04
6.02
6.01
6.00
5.71
5.69
5.68
5.67
5.56
5.29
5.08
5.07
4.62
4.61
4.49
4.48
4.39
4.06
4.06
3.52
3.51
3.51
3.29
3.28
3.08
2.68
2.51
2.49
2.47
2.42
2.41
2.40
2.40
2.26
2.23
2.22
2.02
2.00
1.33
1.33
1.32
1.32
1.31
1.29
1.24
1.23
1.22
0.91
0.90
0.99
1.00
1.01
1.04
1.02
1.02
0.97
0.95
1.98
0.93
1.10
1.78
0.88
0.56
3.54
1.04
1.97
0.96
1.34
1.66
7.89
6.11
1.38
1.40
3.47
2.24
4.18
8.47
7.09
6.20
4.42
3.19
f1 (ppm)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174.23
173.75
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132.82
131.02
103.89
100.31
97.02
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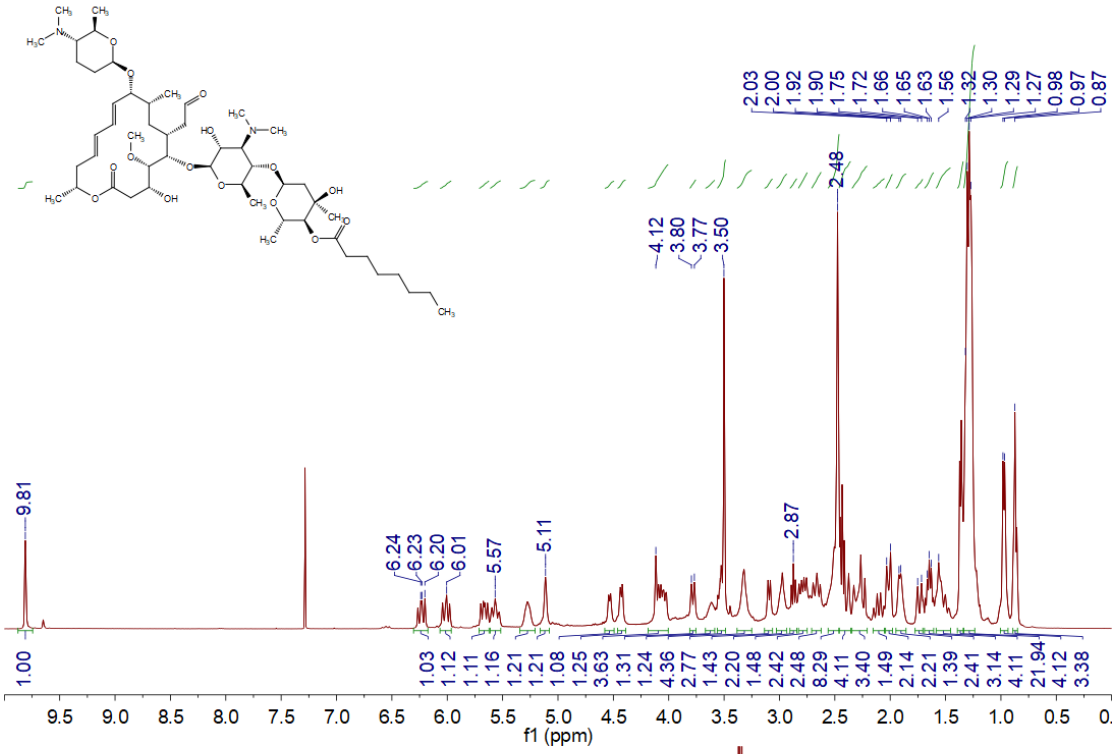
79.35
78.78
76.95
73.88
73.08
71.70
69.37
69.21
68.72
68.25
64.86
63.48
61.82
43.25
42.00
41.70
40.71
37.68
34.26
31.78
31.34
31.29
30.73
30.54
25.31
24.75
22.30
20.10
18.96
18.86
18.41
17.80
15.31
13.89
f1 (ppm)

Compound 3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2.00
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1.90
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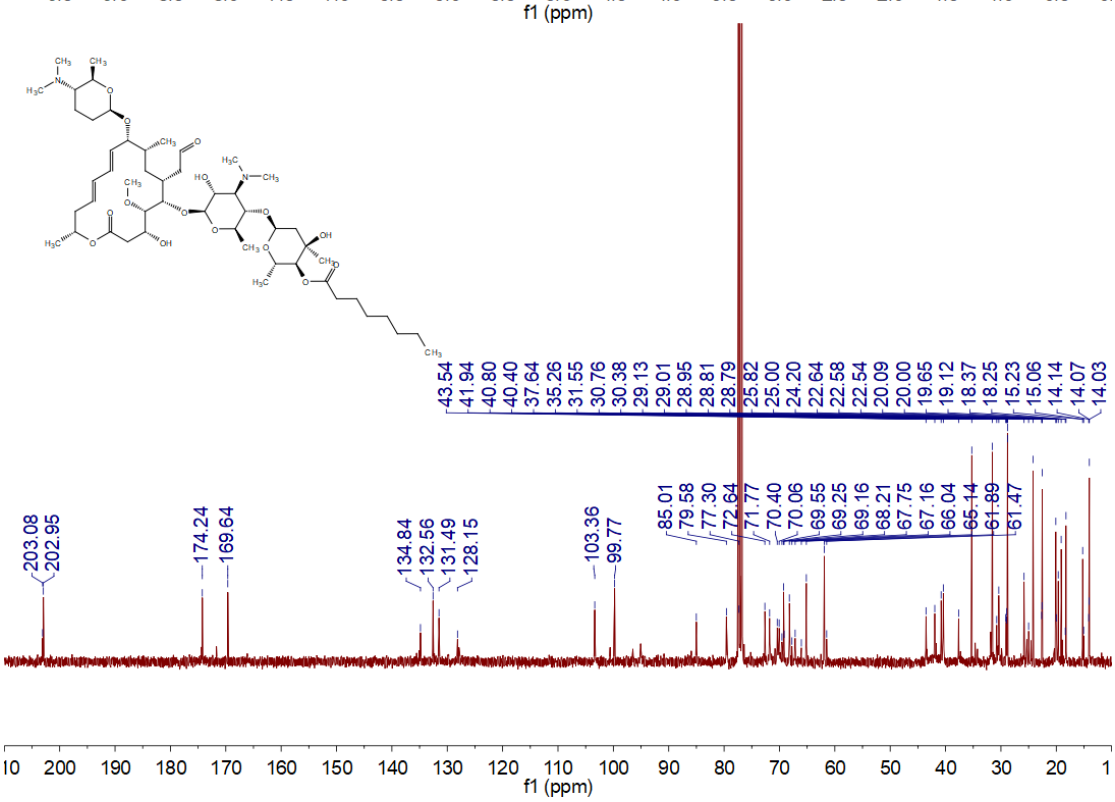
1.72
1.66
1.65
1.63
1.56
1.32
1.30
1.29
1.27
0.98
0.97
0.87
2.48
4.12
3.80
3.77
3.50
9.81
6.24
6.23
6.20
6.01
5.57
5.11
2.87
1.00
1.03
1.12
1.11
1.16
1.21
1.21
1.08
1.25
3.63
1.31
1.24
4.36
2.77
1.43
2.20
1.48
2.42
2.48
8.29
4.11
3.40
1.49
2.14
2.21
1.39
2.41
3.14
4.11
21.94
4.12
3.38
f1 (ppm)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29.01
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28.81
28.79
25.82
25.00
24.20
22.64
22.58
22.54
20.09
20.00
19.65
19.12
18.37
18.25
15.23
15.06
14.14
14.07
14.03
85.01
79.58
77.30
72.64
71.77
70.40
70.06
69.55
69.25
69.16
68.21
67.75
67.16
66.04
65.14
61.89
61.47
203.08
202.95
174.24
169.64
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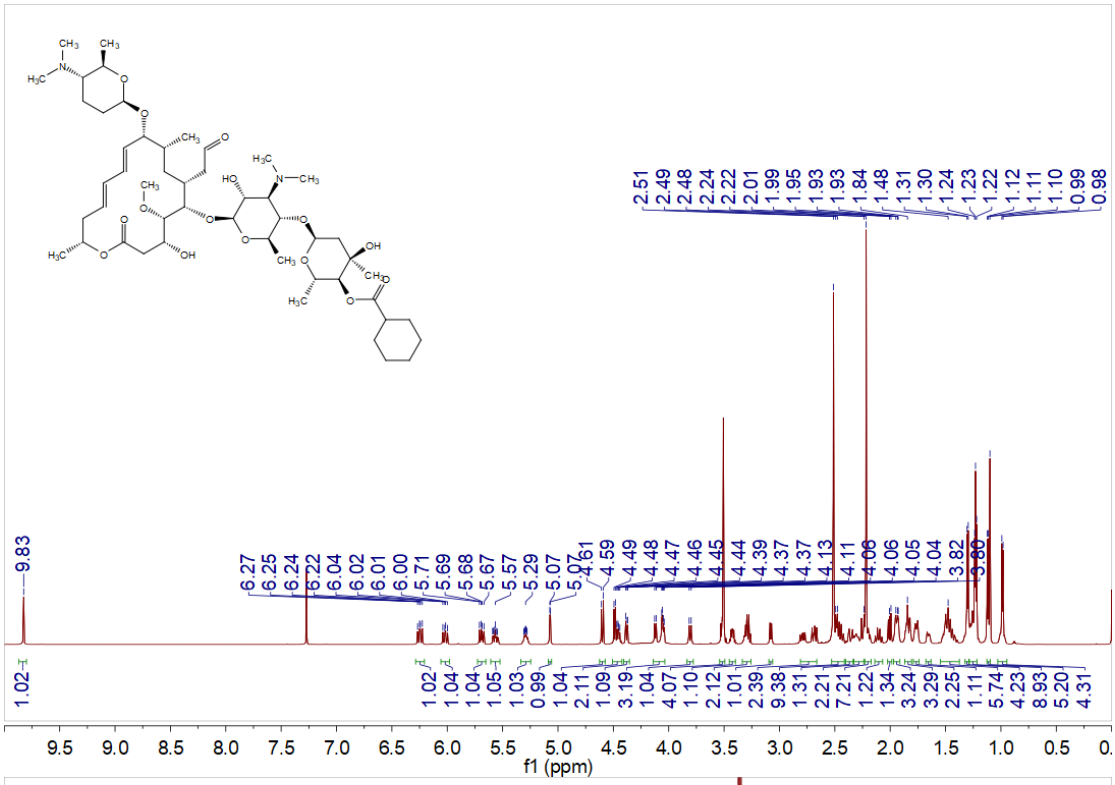
132.56
131.49
128.15
103.36
99.77
f1 (ppm)

Compound 4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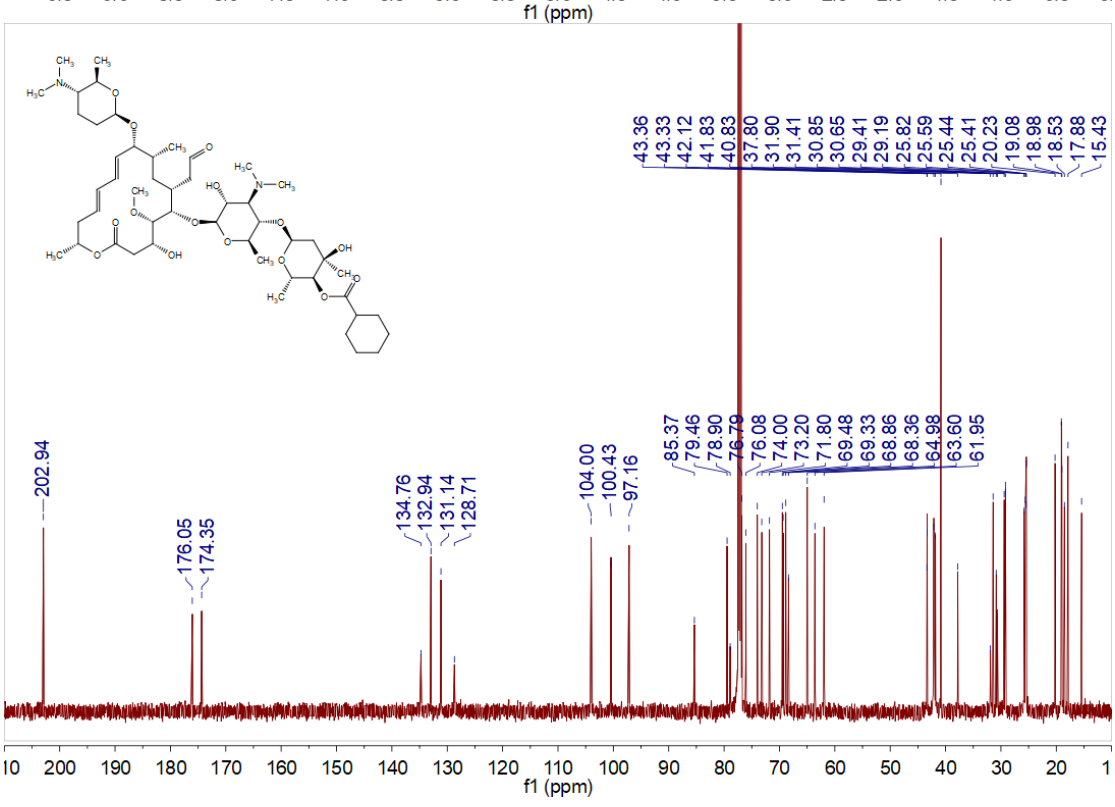
6.02
6.01
6.00
5.71
5.69
5.68
5.67
5.57
5.29
5.07
4.61
4.59
4.49
4.48
4.47
4.46
4.45
4.44
4.39
4.37
4.13
4.11
4.06
4.05
4.04
3.82
3.80
2.51
2.49
2.48
2.24
2.22
2.01
1.99
1.95
1.93
1.93
1.84
1.48
1.31
1.30
1.24
1.23
1.22
1.12
1.11
1.10
0.99
0.98
1.02
1.02
1.04
1.04
1.05
1.03
0.99
1.04
2.11
1.09
3.19
1.04
4.07
1.10
2.12
1.01
2.39
9.38
1.31
2.21
7.21
1.22
1.34
3.24
3.29
2.25
1.11
5.74
4.23
8.93
5.20
4.31
f1 (ppm)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76.79
76.08
74.00
73.20
71.80
69.48
69.33
68.86
68.36
64.98
63.60
61.95
43.36
43.33
42.12
41.83
40.83
37.80
31.90
31.41
30.85
30.65
29.41
29.19
25.82
25.59
25.44
25.41
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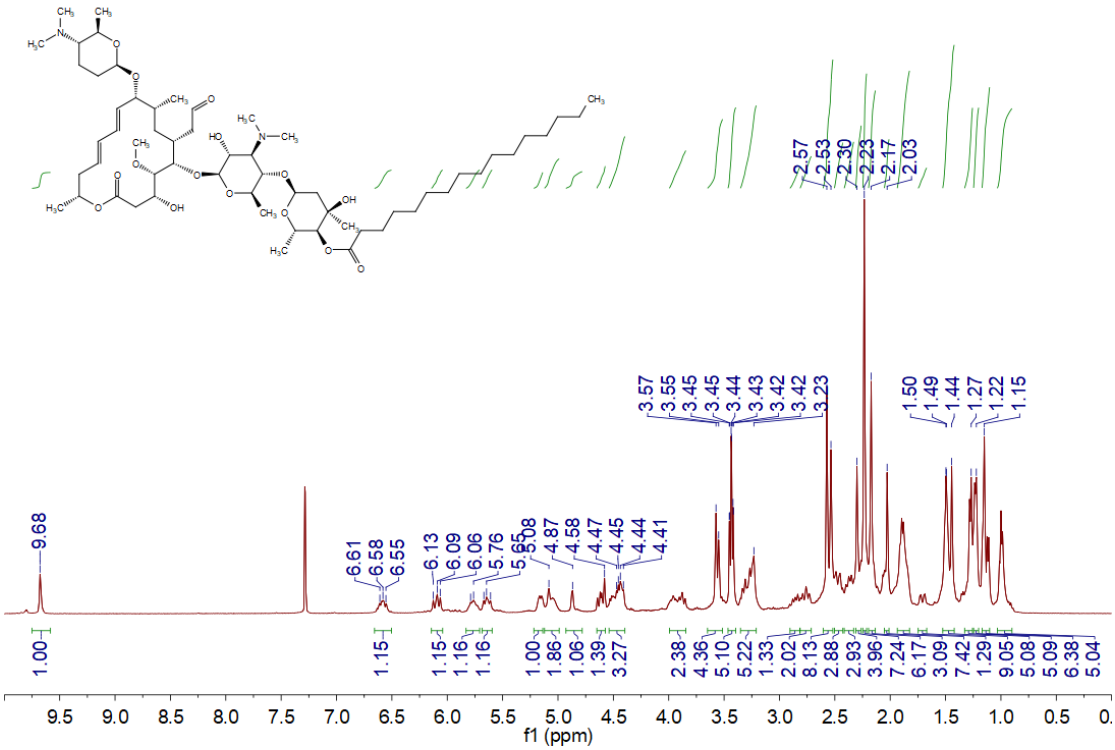
19.08
18.98
18.53
17.88
15.43
f1 (ppm)

Compound 5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4.58
4.47
4.45
4.44
4.41
3.57
3.55
3.45
3.45
3.44
3.43
3.42
3.42
3.23
2.57
2.53
2.30
2.23
2.17
2.03
1.50
1.49
1.44
1.27
1.22
1.15
1.00
1.15
1.15
1.16
1.16
1.00
1.86
1.06
1.39
3.27
2.38
4.36
5.10
5.22
1.33
2.02
8.13
2.88
2.93
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3.09
7.42
1.29
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5.08
5.09
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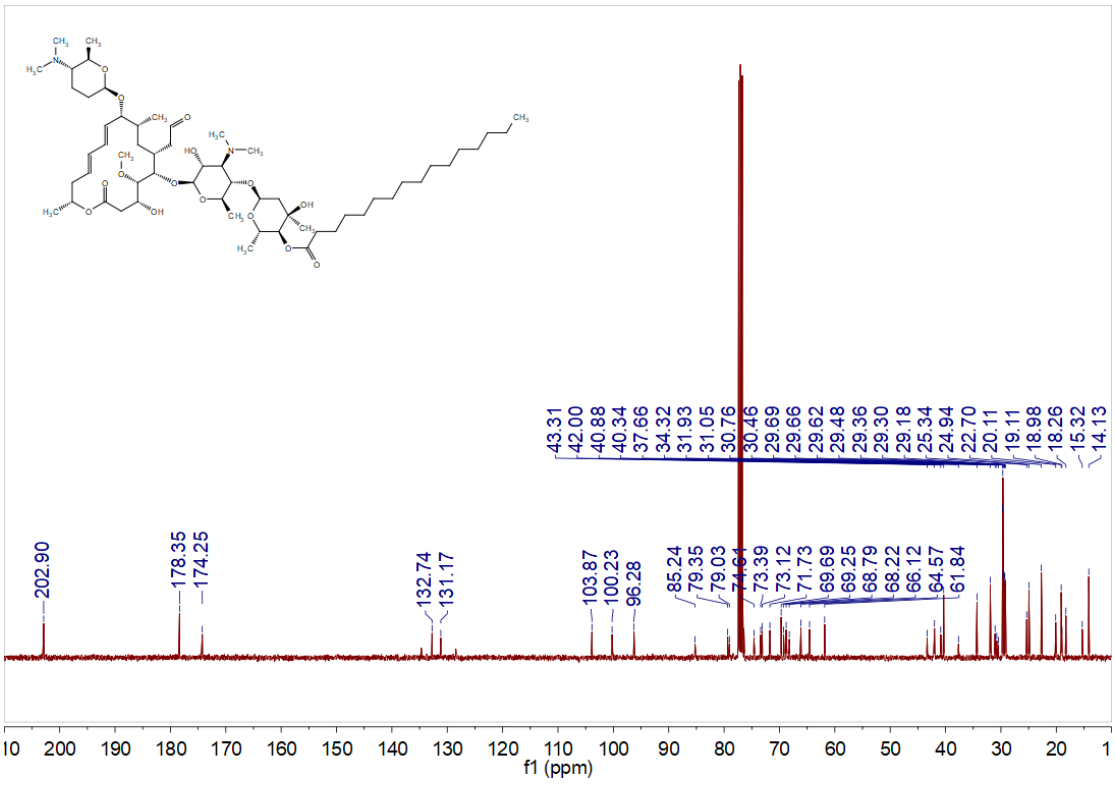
5.04
f1 (ppm)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103.87
100.23
96.28
85.24
79.35
79.03
74.61
73.39
73.12
71.73
69.69
69.25
68.79
68.22
66.12
64.57
61.84
43.31
42.00
40.88
40.34
37.66
34.32
31.93
31.05
30.76
30.46
29.69
29.66
29.62
29.48
29.36
29.30
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19.11
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15.32
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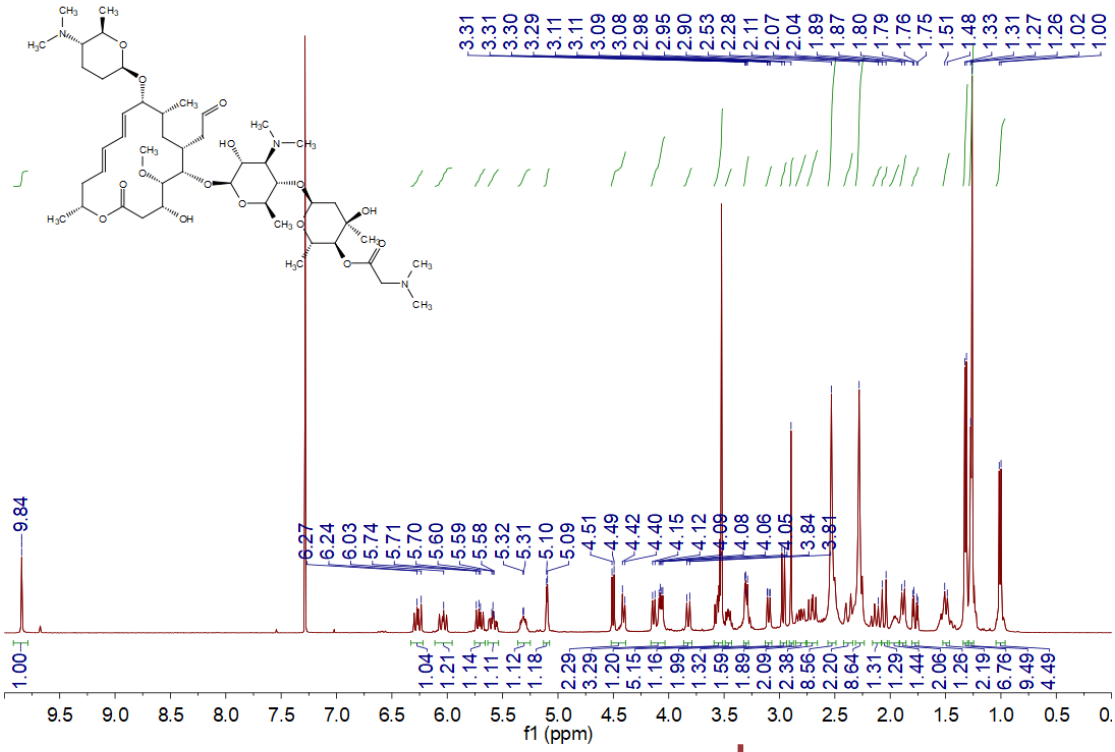
f1 (ppm)

Compound 6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3.11
3.11
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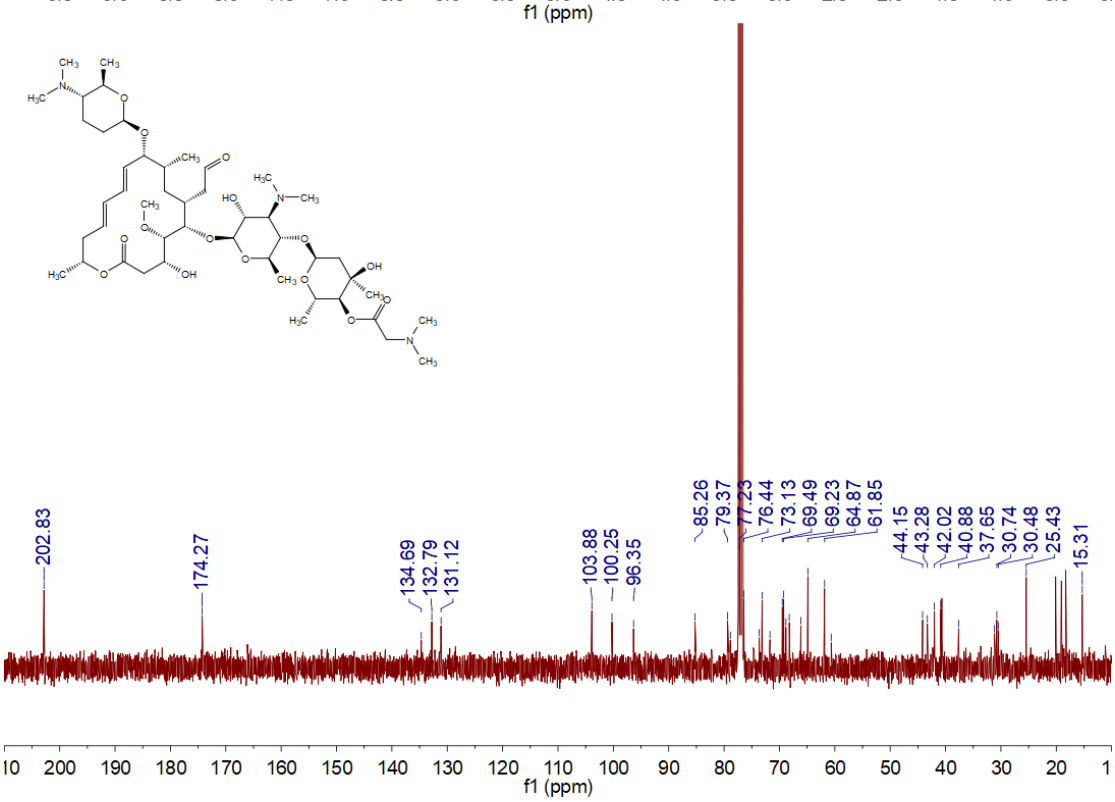
2.28
2.11
2.07
2.04
1.89
1.87
1.80
1.79
1.76
1.75
1.51
1.48
1.33
1.31
1.27
1.26
1.02
1.00
9.84
6.27
6.24
6.03
5.74
5.71
5.70
5.60
5.59
5.58
5.32
5.31
5.10
5.09
4.51
4.49
4.42
4.40
4.15
4.12
4.08
4.06
4.05
3.84
3.81
1.00
1.04
1.21
1.14
1.11
1.12
1.18
2.29
3.29
1.20
5.15
1.16
1.99
1.32
1.59
1.89
2.09
2.38
8.56
2.20
8.64
1.31
1.29
1.44
2.06
1.26
2.19
6.76
9.49
4.49
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)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77.23
76.44
73.13
69.49
69.23
64.87
61.85
44.15
43.28
42.02
40.88
37.65
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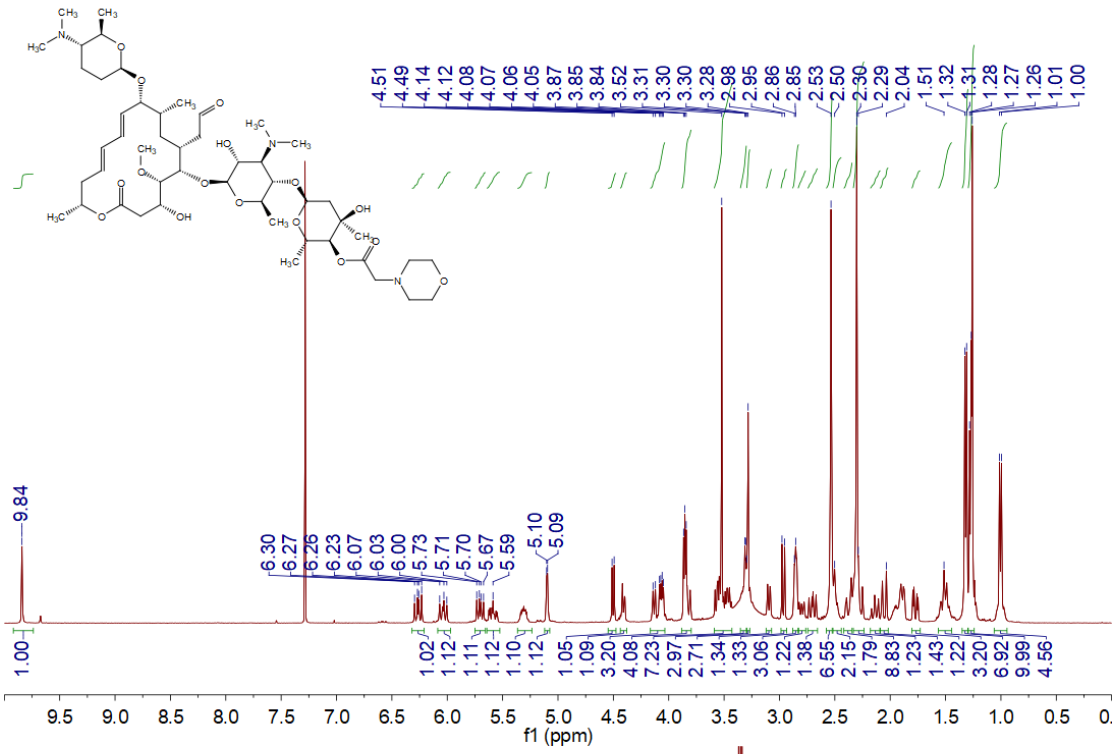
30.48
25.43
15.31
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 1
f1 (ppm)

Compound 7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4.08
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4.06
4.05
3.87
3.85
3.84
3.52
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3.30
3.30
3.28
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2.95
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2.53
2.50
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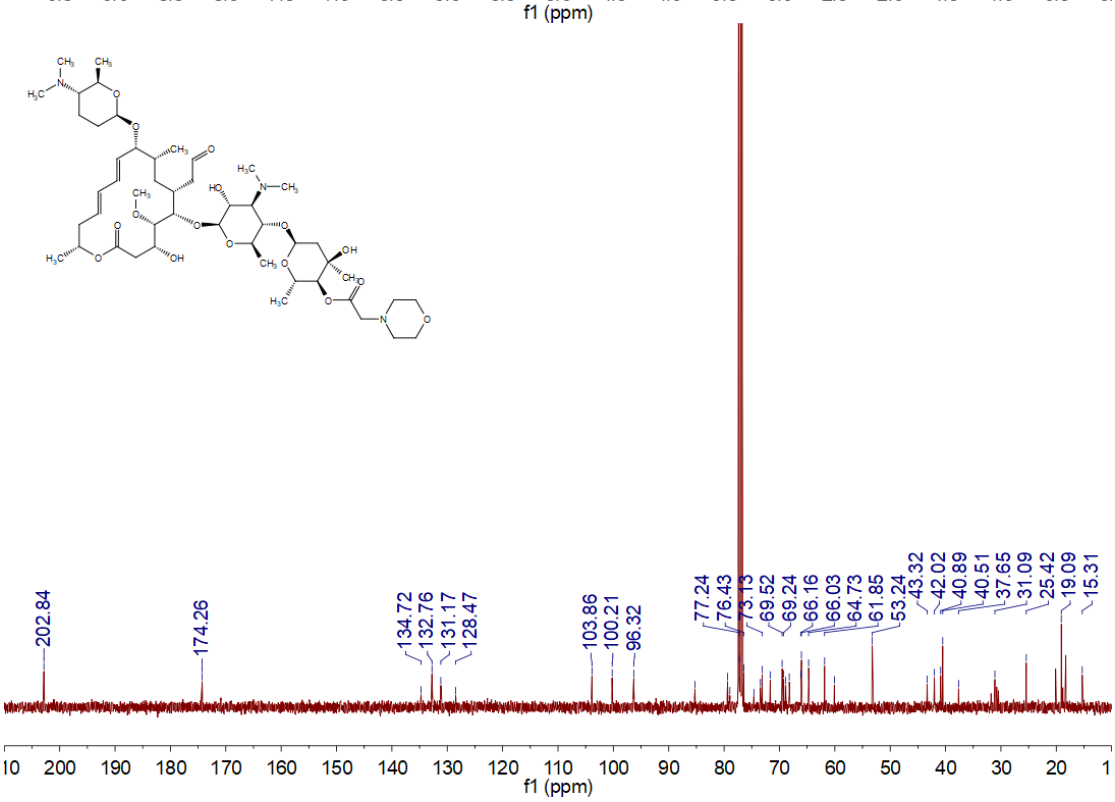
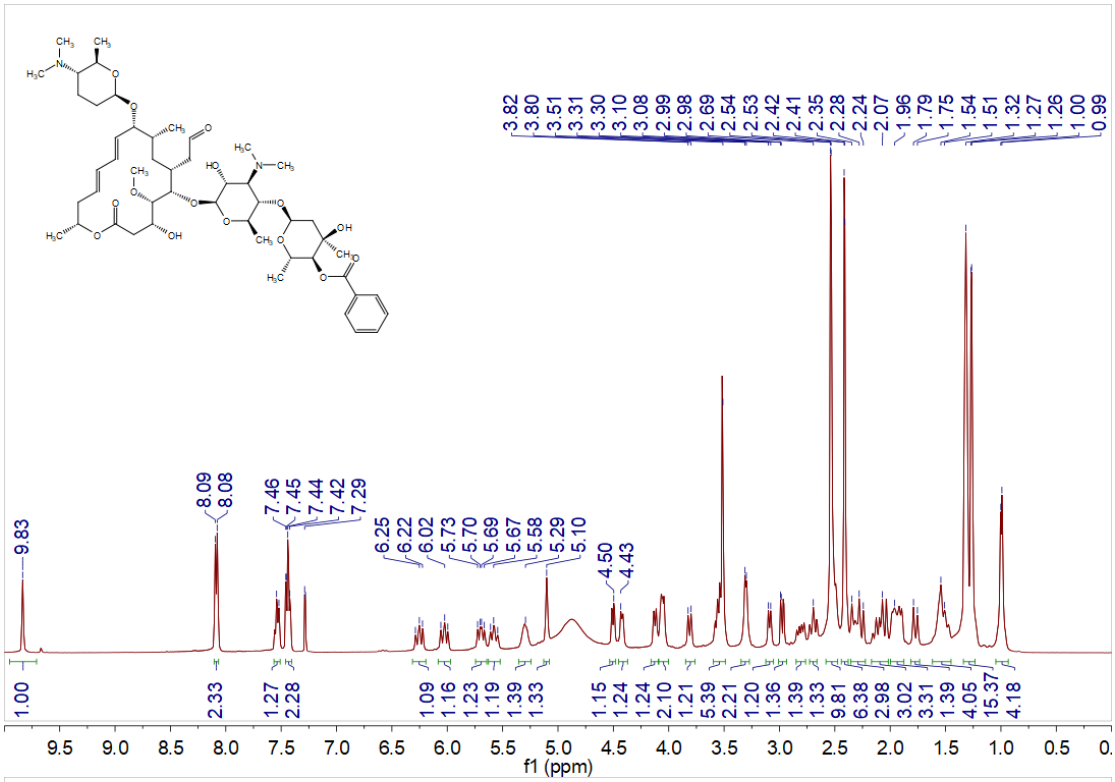
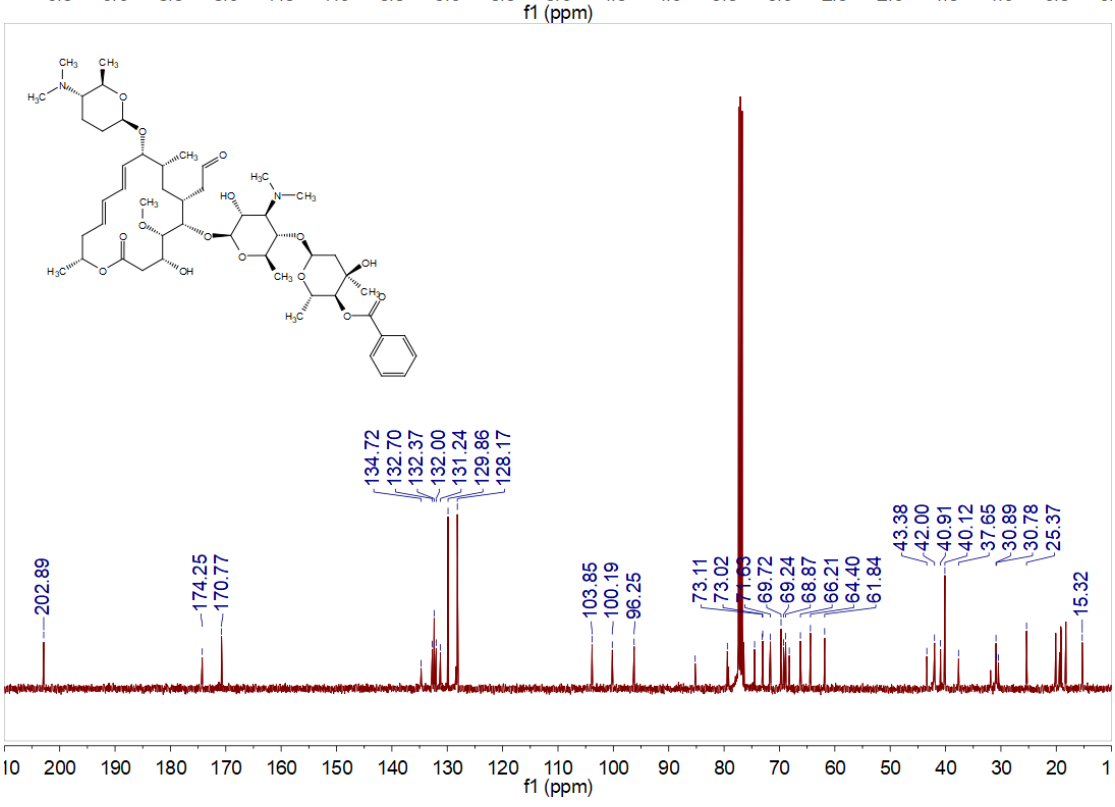
2.29
2.04
1.51
1.32
1.31
1.28
1.27
1.26
1.01
1.00
9.84
6.30
6.27
6.26
6.23
6.07
6.03
6.00
5.73
5.71
5.70
5.67
5.59
5.10
5.09
1.00
1.02
1.12
1.11
1.12
1.10
1.12
1.05
1.09
3.20
4.08
7.23
2.97
2.71
1.34
1.33
3.06
1.22
1.38
6.55
2.15
1.79
8.83
1.23
1.43
1.22
3.20
6.92
9.99
4.56
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

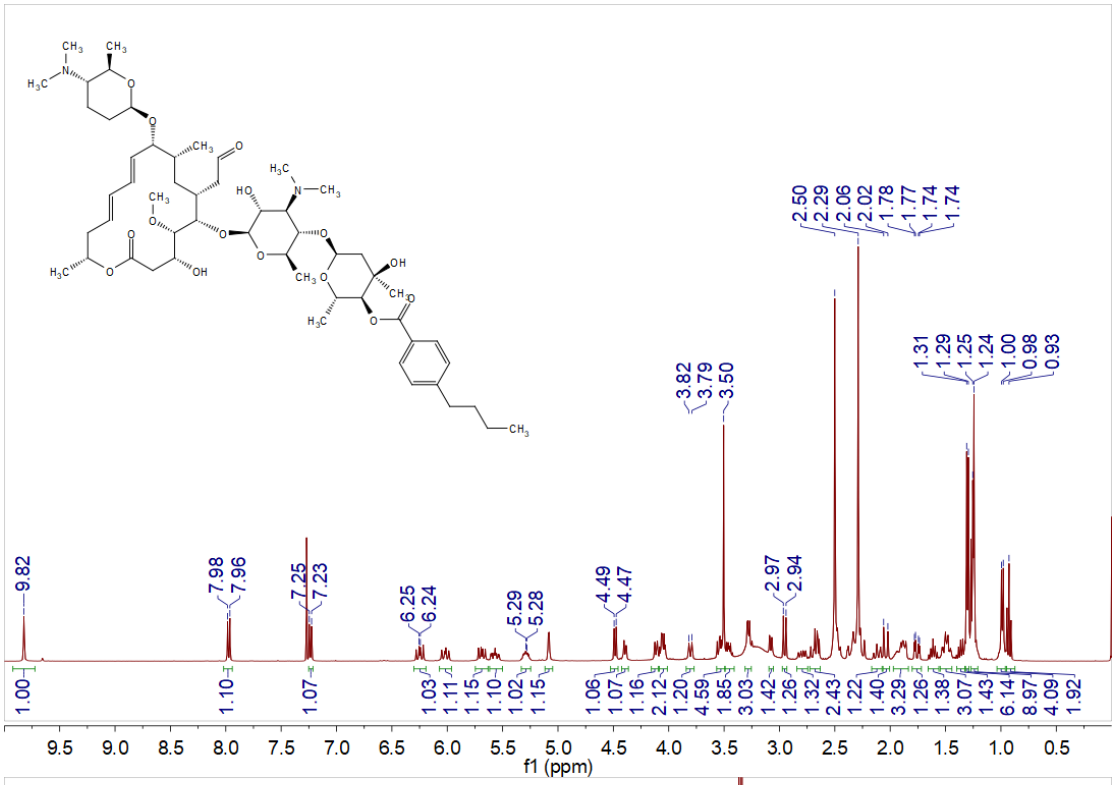

202.84
174.26
134.72
132.76
131.17
128.47
103.86
100.21
96.32
77.24
76.43
73.13
69.52
69.24
66.16
66.03
64.73
61.85
53.24
43.32
42.02
40.89
40.51
37.65
31.09
25.42
19.09
15.31
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 1
f1 (ppm)

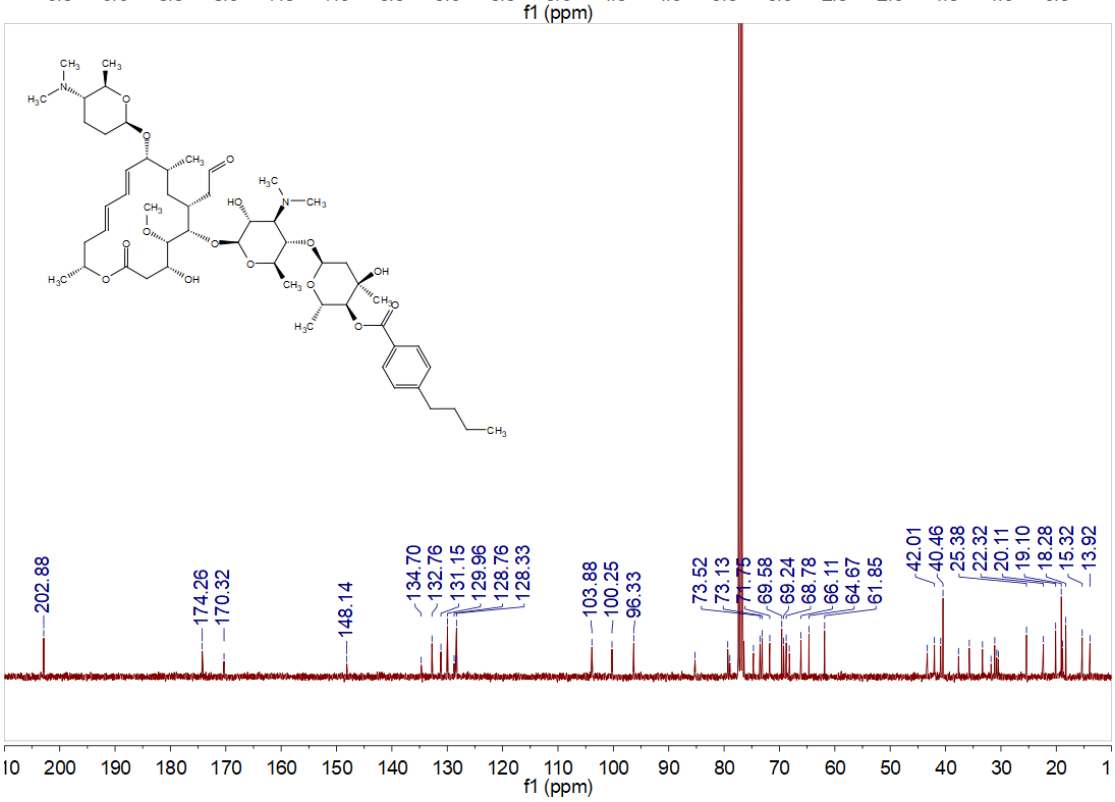
Compound 8


3.82
3.80
3.51
3.31
3.30
3.10
3.08
2.99
2.98
2.69
2.54
2.53
2.42
2.41
2.35
2.28
2.24
2.07
1.96
1.79
1.75
1.54
1.51
1.32
1.27
1.26
1.00
0.99
9.83
8.09
8.08
7.46
7.45
7.44
7.42
7.29
6.25
6.22
6.02
5.73
5.70
5.69
5.67
5.58
5.29
5.10
4.50
4.43
1.00
2.33
1.27
2.28
1.09
1.16
1.23
1.19
1.39
1.33
1.15
1.24
1.24
2.10
1.21
5.39
2.21
1.20
1.36
1.39
1.33
9.81
6.38
2.98
3.02
3.31
1.39
4.05
15.37
4.18
f1 (ppm)

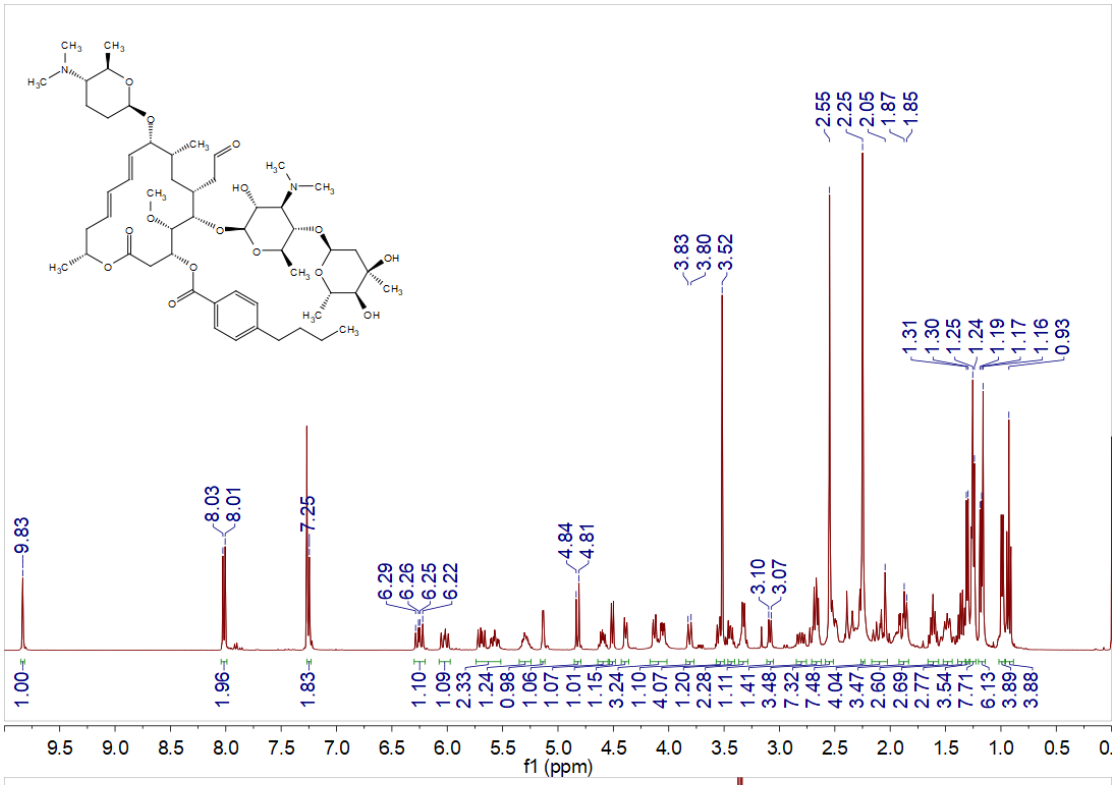

134.72
132.70
132.37
132.00
131.24
129.86
128.17
202.89
174.25
170.77
103.85
100.19
96.25
73.11
73.02
71.83
69.72
69.24
68.87
66.21
64.40
61.84
43.38
42.00
40.91
40.12
37.65
30.89
30.78
25.37
15.32
f1 (ppm)

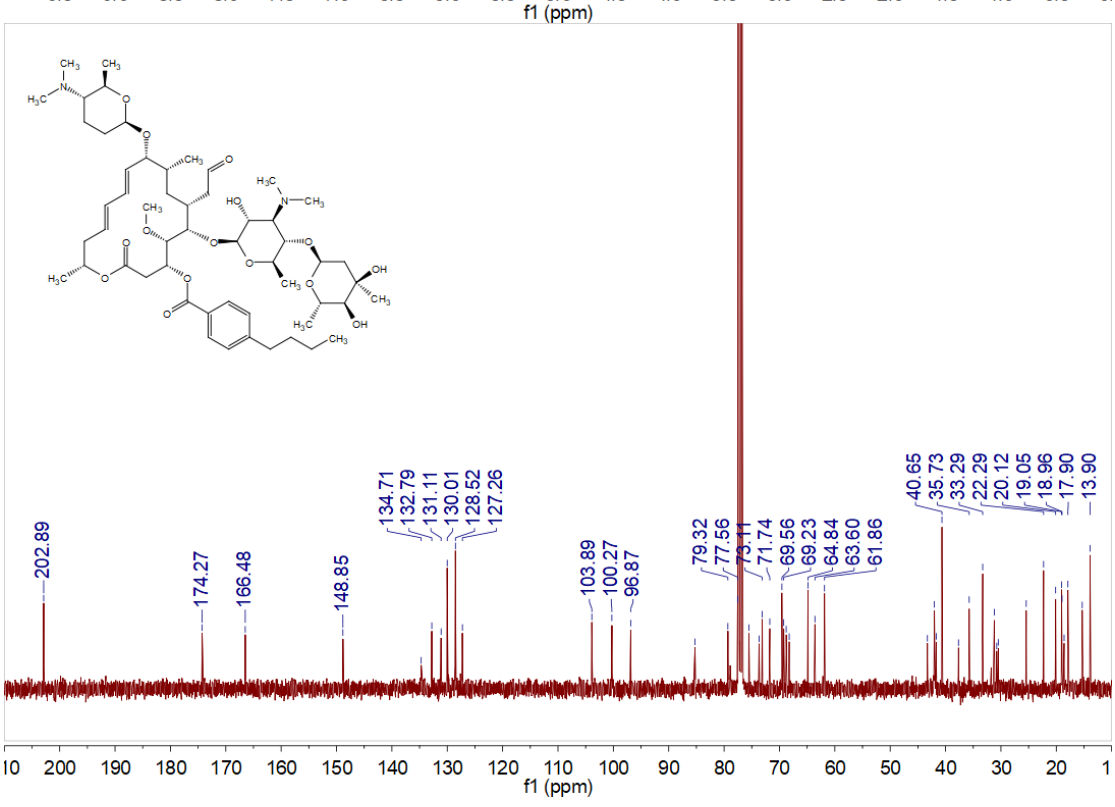
Compound 10a



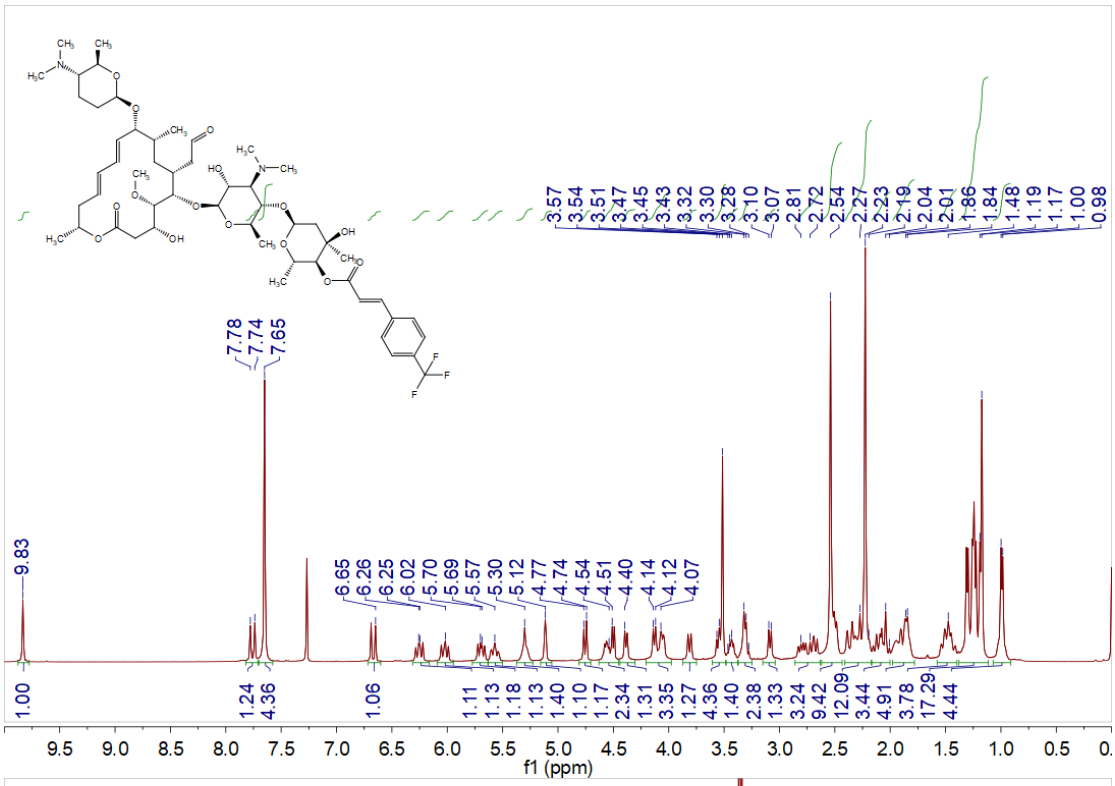


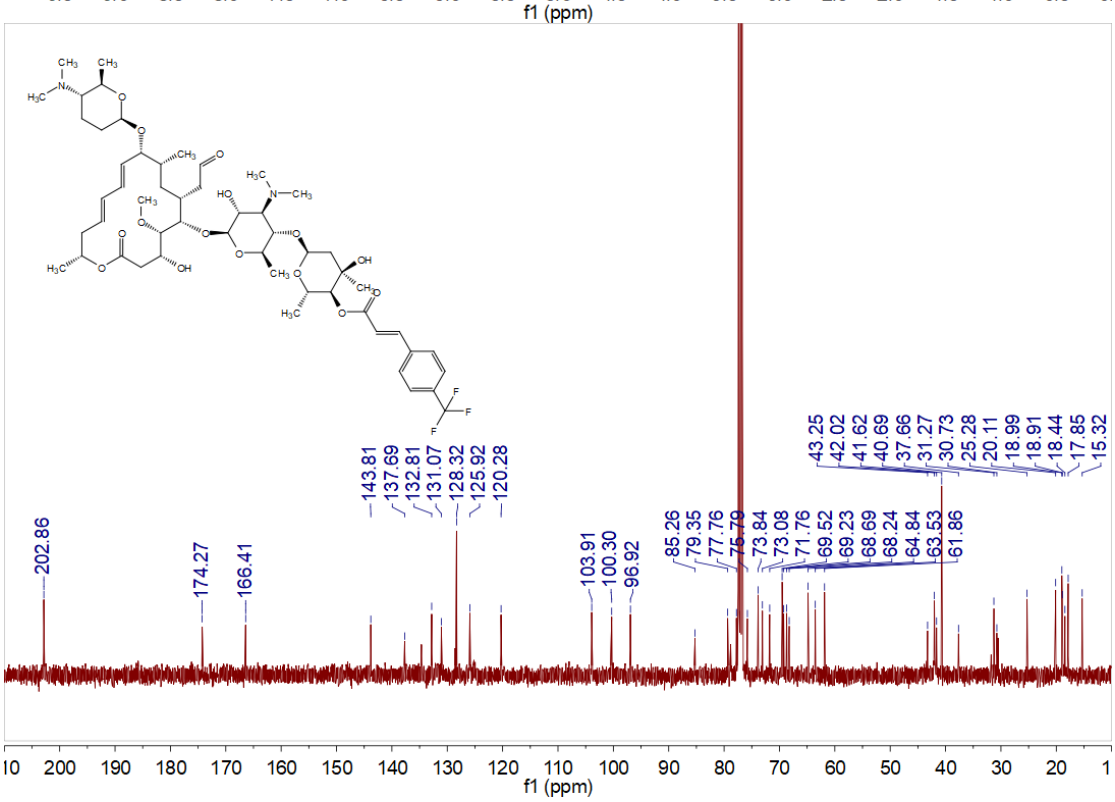
Compound 10b



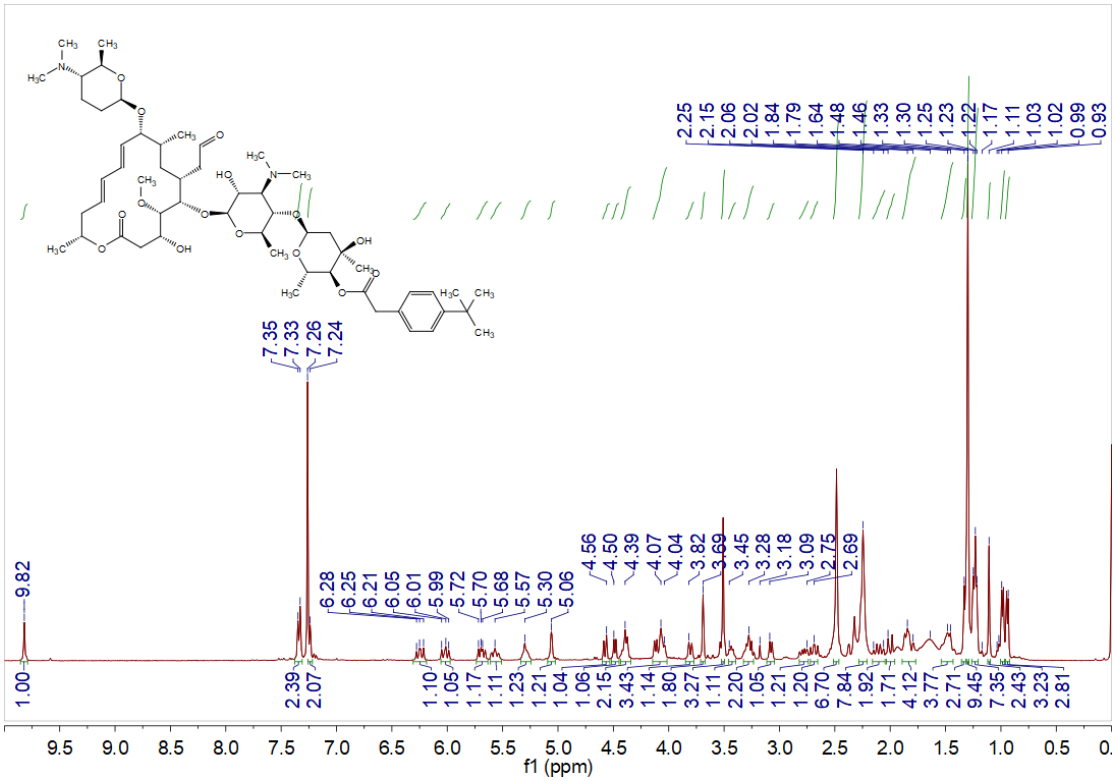


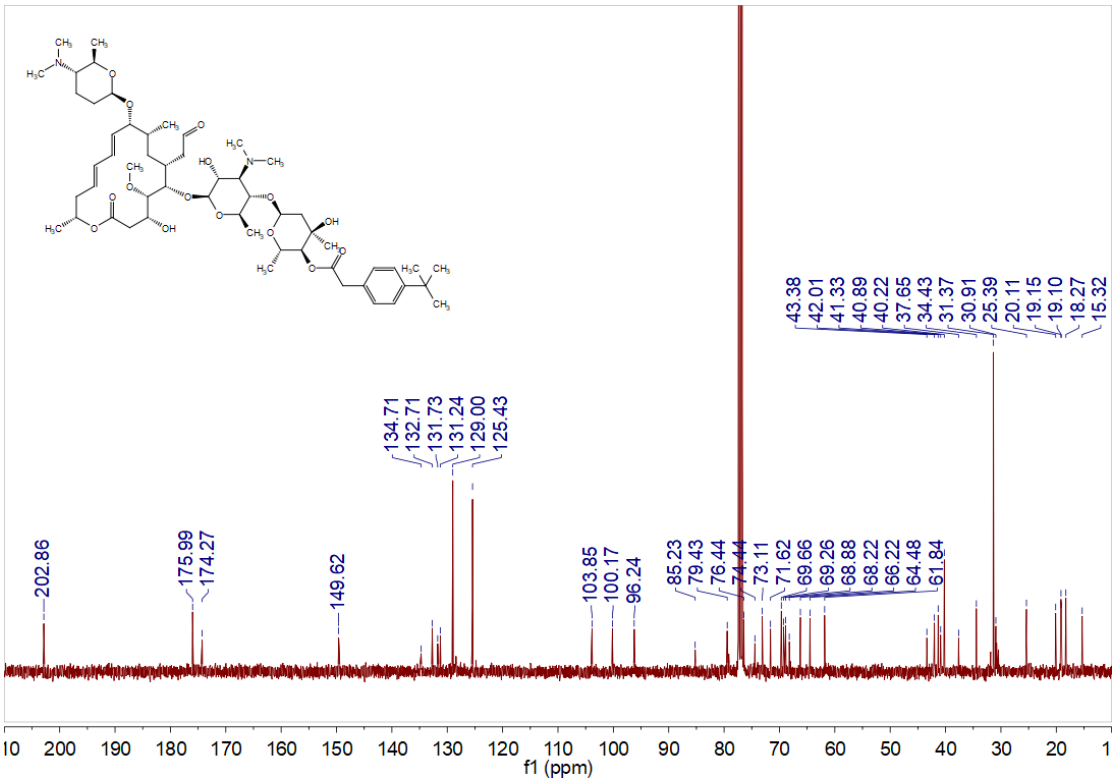
Compound 11


9.83
7.78
7.74
7.65
6.65
6.26
6.25
6.02
5.70
5.69
5.57
5.30
5.12
4.77
4.74
4.54
4.51
4.40
4.14
4.12
4.07
3.57
3.54
3.51
3.47
3.45
3.43
3.32
3.30
3.28
3.10
3.07
2.81
2.72
2.54
2.27
2.23
2.19
2.04
2.01
1.86
1.84
1.48
1.19
1.17
1.00
0.98
1.00
1.24
4.36
1.06
1.11
1.13
1.18
1.13
1.40
1.10
1.17
2.34
1.31
3.35
1.27
4.36
1.40
2.38
1.33
3.24
9.42
12.09
3.44
4.91
3.78
17.29
4.44
f1 (ppm)

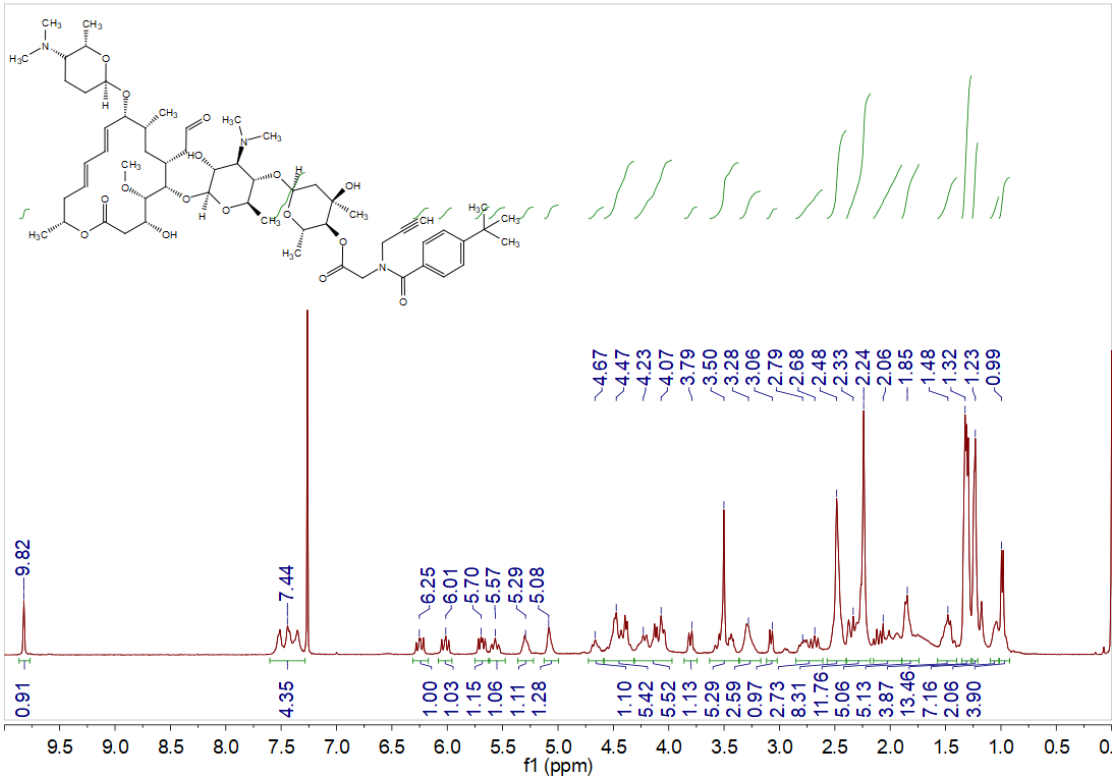

202.86
174.27
166.41
143.81
137.69
132.81
131.07
128.32
125.92
120.28
103.91
100.30
96.92
85.26
79.35
77.76
75.79
73.84
73.08
71.76
69.52
69.23
68.69
68.24
64.84
63.53
61.86
43.25
42.02
41.62
40.69
37.66
31.27
30.73
25.28
20.11
18.99
18.91
18.44
17.85
15.32
f1 (ppm)

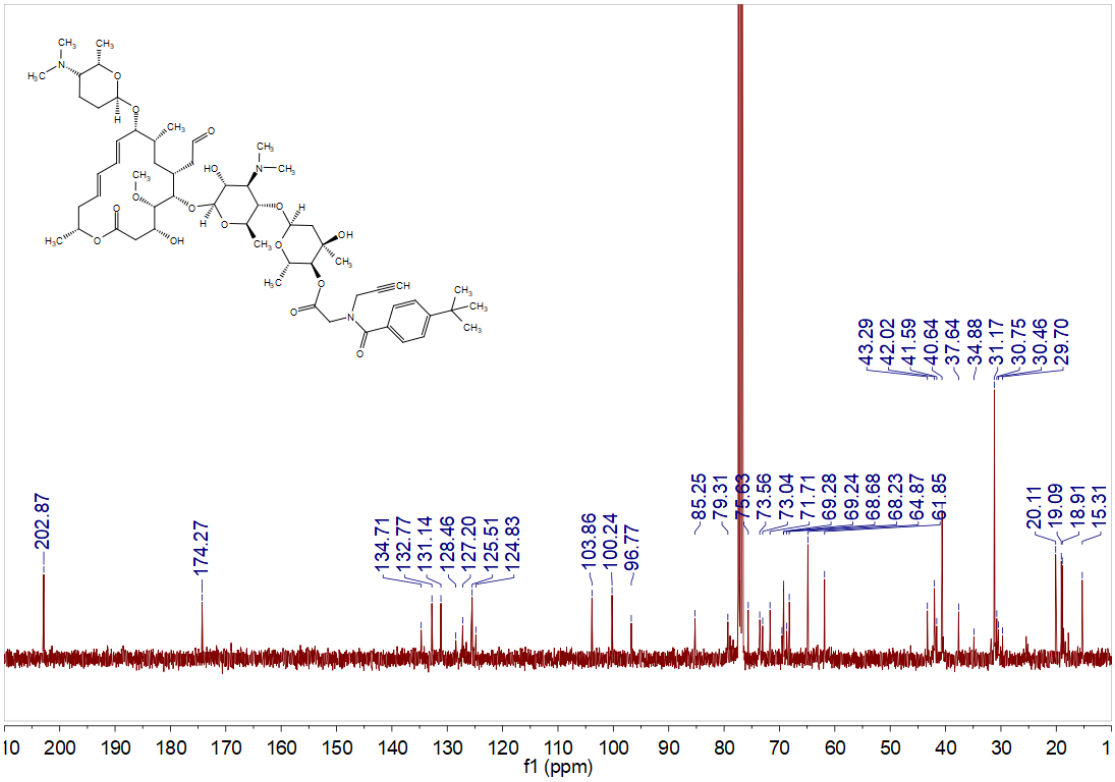
Compound 12


9.82
7.35
7.33
7.26
7.24
6.28
6.25
6.21
6.05
6.01
5.99
5.72
5.70
5.68
5.57
5.30
5.06
4.56
4.50
4.39
4.07
4.04
3.82
3.69
3.45
3.28
3.18
3.09
2.75
2.69
2.25
2.15
2.06
2.02
1.84
1.79
1.64
1.48
1.46
1.33
1.30
1.25
1.23
1.22
1.17
1.11
1.03
1.02
0.99
0.93
f1 (ppm)

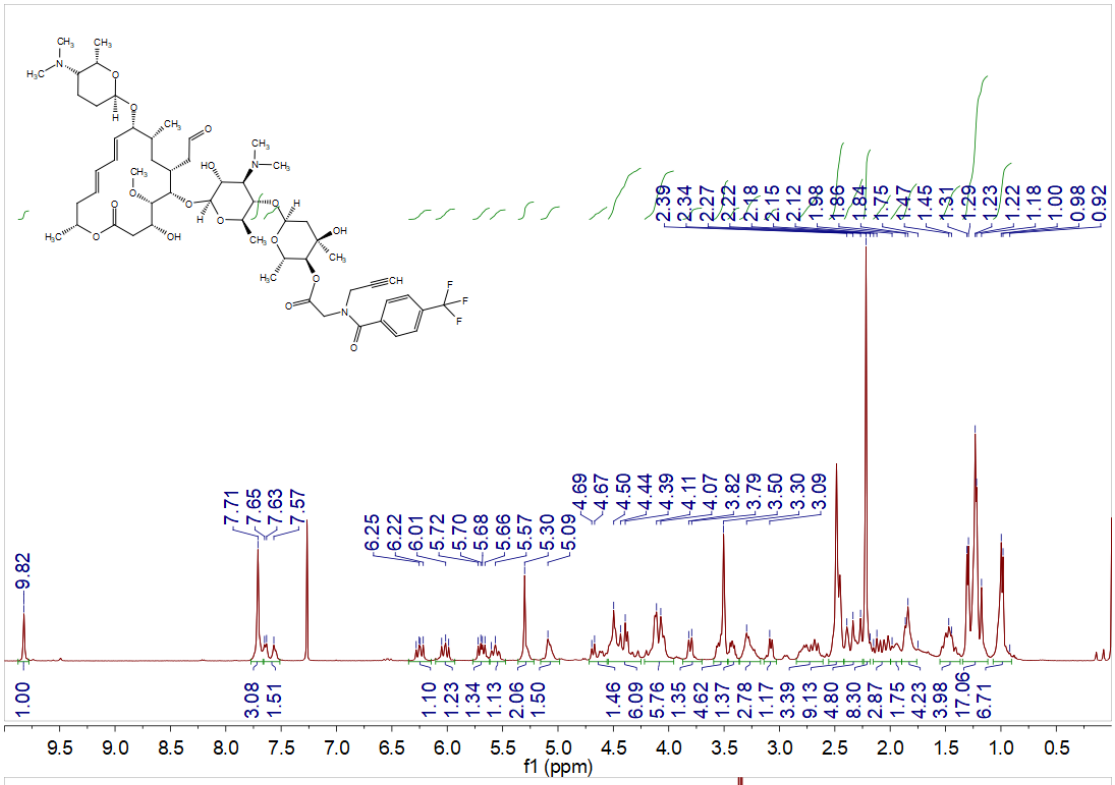

202.86
175.99
174.27
149.62
134.71
132.71
131.73
131.24
129.00
125.43
103.85
100.17
96.24
85.23
79.43
76.44
74.44
73.11
71.62
69.66
69.26
68.88
68.22
66.22
64.48
61.84
43.38
42.01
41.33
40.89
40.22
37.65
34.43
31.37
30.91
25.39
20.11
19.15
19.10
18.27
15.32
f1 (ppm)

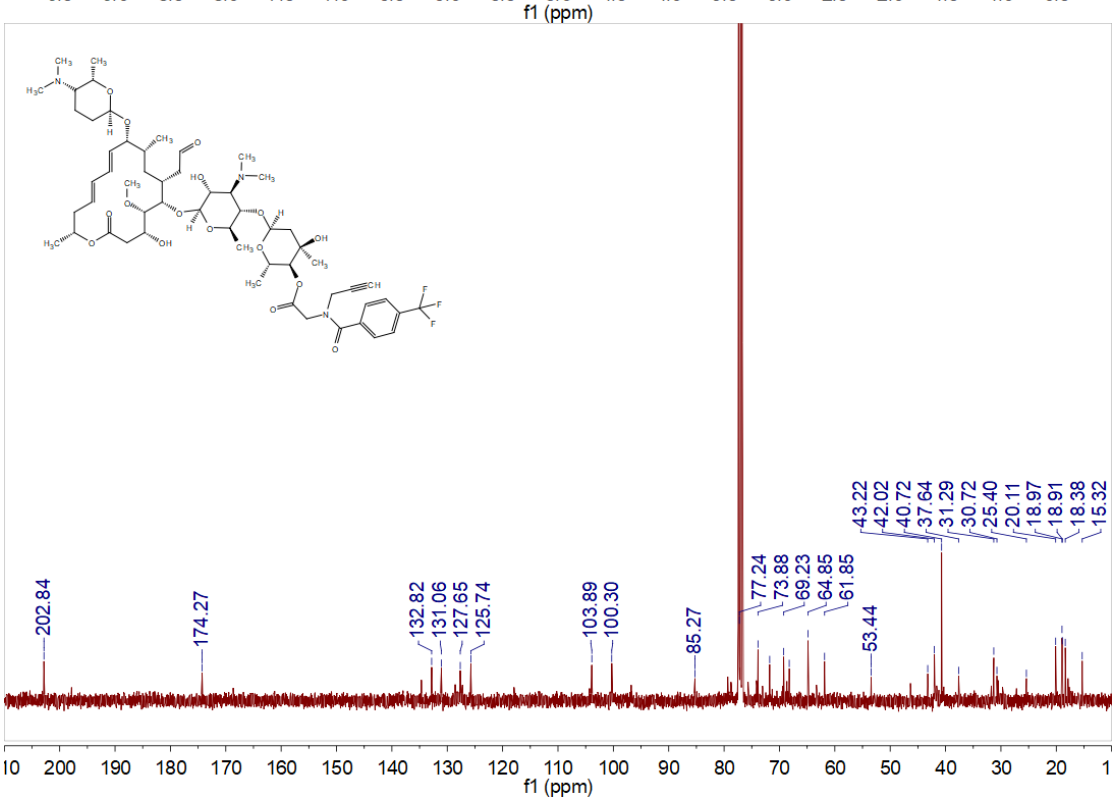
Compound 13


9.82
7.44
6.25
6.01
5.70
5.57
5.29
5.08
4.67
4.47
4.23
4.07
3.79
3.50
3.28
3.06
2.79
2.68
2.48
2.33
2.24
2.06
1.85
1.48
1.32
1.23
0.99
0.91
4.35
1.00
1.03
1.15
1.06
1.11
1.28
1.10
5.42
5.52
1.13
5.29
2.59
0.97
2.73
8.31
11.76
5.06
5.13
3.87
13.46
7.16
2.06
3.90
f1 (ppm)

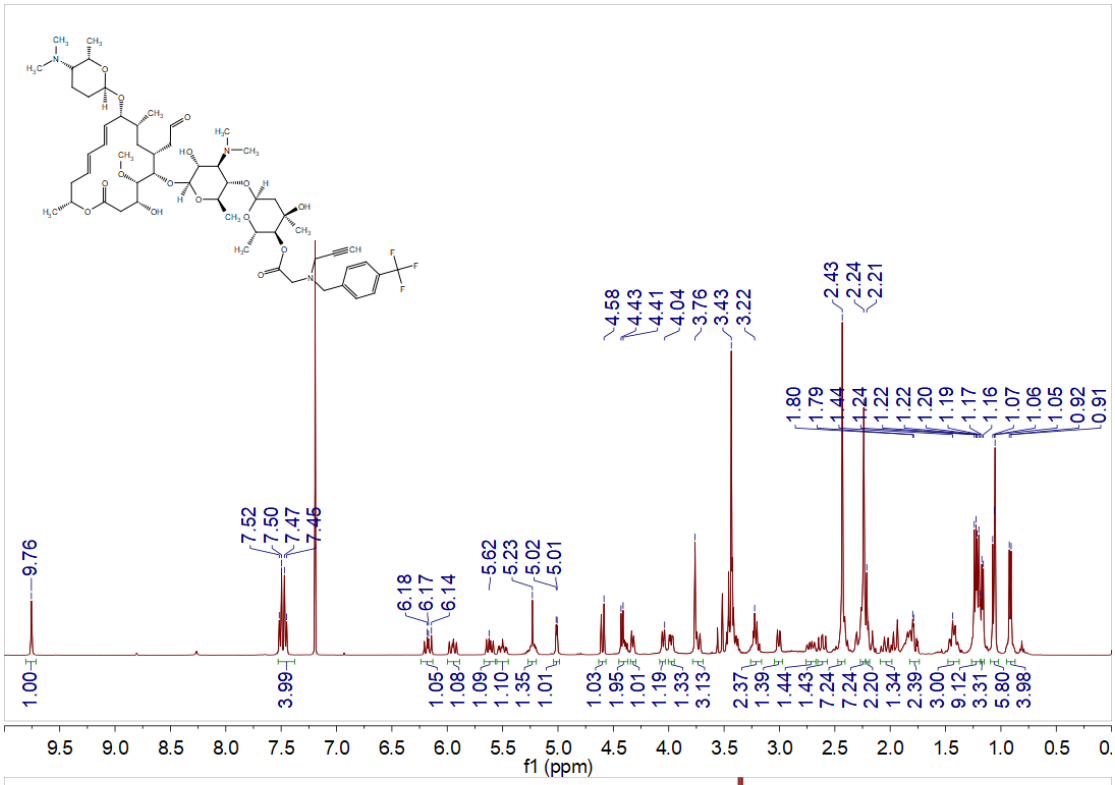

202.87
174.27
134.71
132.77
131.14
128.46
127.20
125.51
124.83
103.86
100.24
96.77
85.25
79.31
75.63
73.56
73.04
71.71
69.28
69.24
68.68
68.23
64.87
61.85
43.29
42.02
41.59
40.64
37.64
34.88
31.17
30.75
30.46
29.70
20.11
19.09
18.91
15.31
f1 (ppm)

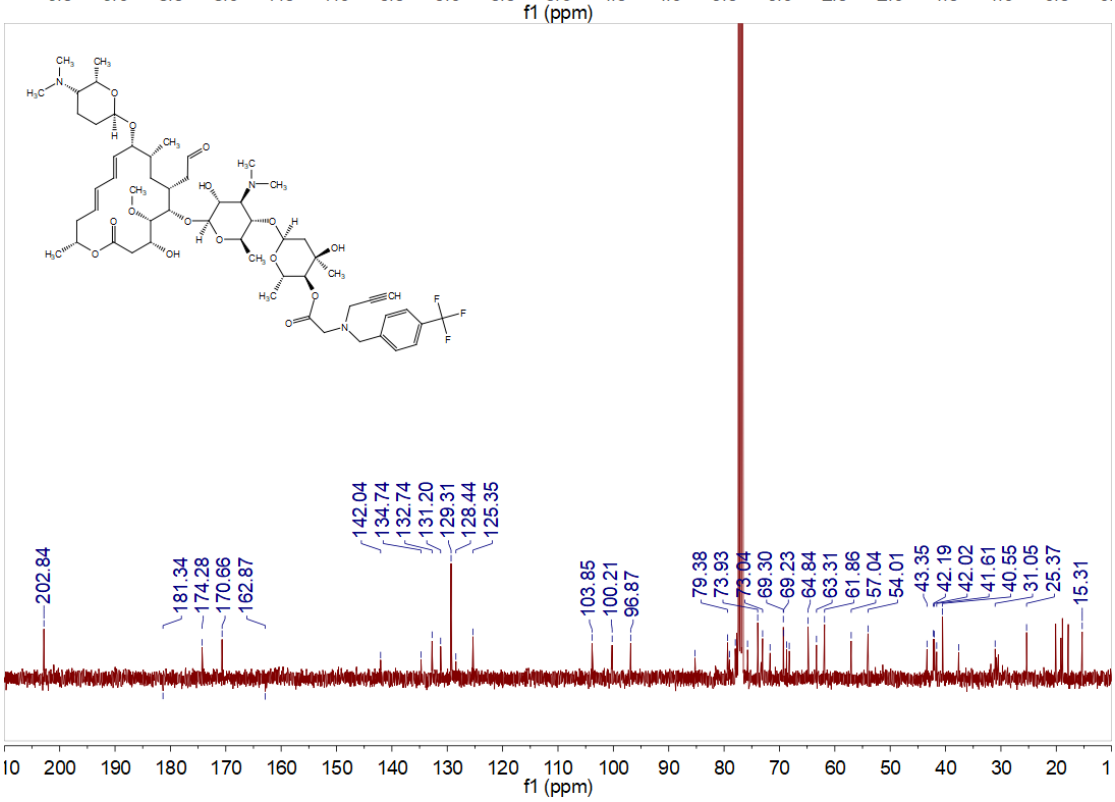
Compound 14


9.82
7.71
7.65
7.63
7.57
6.25
6.22
6.01
5.72
5.70
5.68
5.66
5.57
5.30
5.09
4.69
4.67
4.50
4.44
4.39
4.11
4.07
3.82
3.79
3.50
3.30
3.09
2.39
2.34
2.27
2.22
2.18
2.15
2.12
1.98
1.86
1.84
1.75
1.47
1.45
1.31
1.29
1.23
1.22
1.18
1.00
0.98
0.92
1.00
3.08
1.51
1.10
1.23
1.34
1.13
2.06
1.50
1.46
6.09
5.76
1.35
4.62
1.37
2.78
1.17
3.39
9.13
4.80
8.30
2.87
1.75
4.23
3.98
17.06
6.71
f1 (ppm)

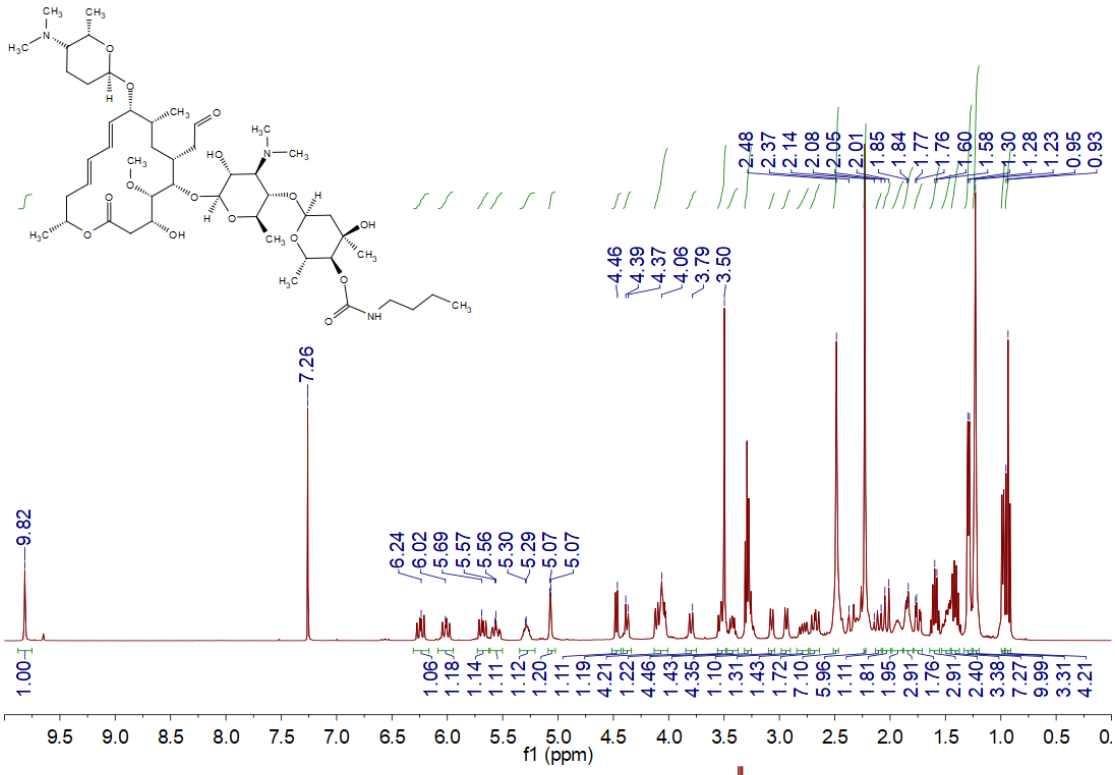

202.84
174.27
132.82
131.06
127.65
125.74
103.89
100.30
85.27
77.24
73.88
69.23
64.85
61.85
53.44
43.22
42.02
40.72
37.64
31.29
30.72
25.40
20.11
18.97
18.91
18.38
15.32
f1 (ppm)

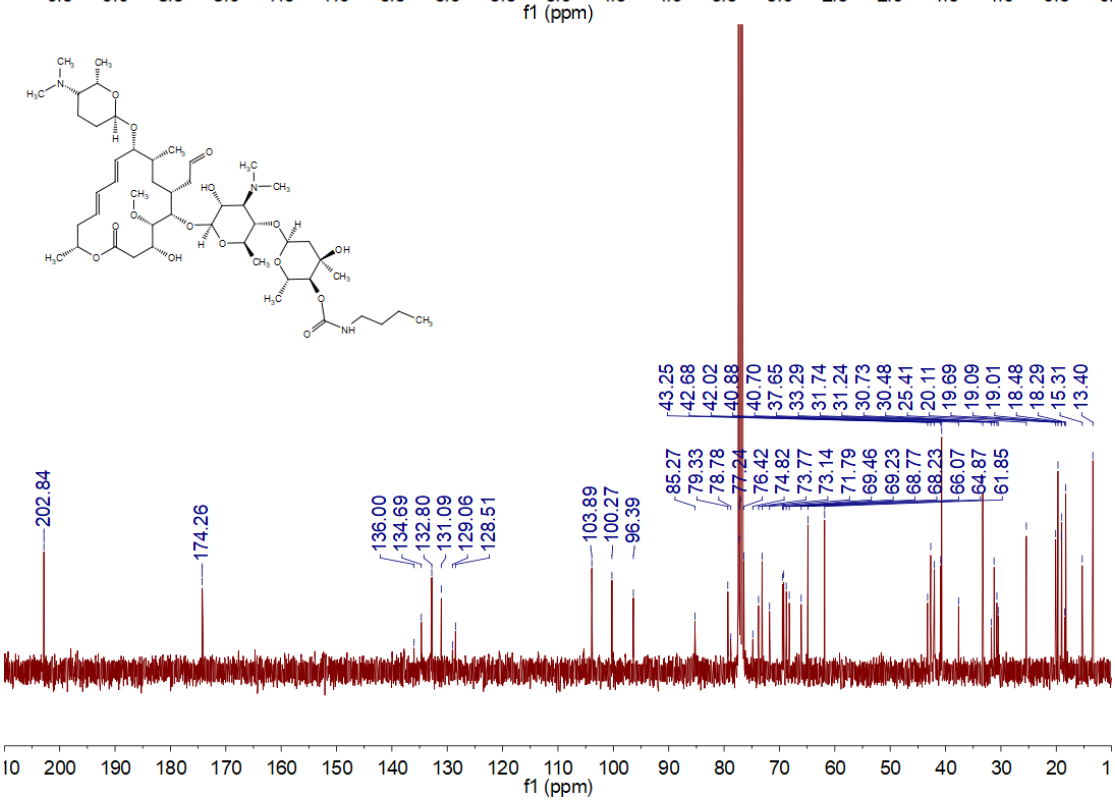
Compound 15


9.76
7.52
7.50
7.47
7.46
6.18
6.17
6.14
5.62
5.23
5.02
5.01
4.58
4.43
4.41
4.04
3.76
3.43
3.22
2.43
2.24
2.21
1.80
1.79
1.44
1.24
1.22
1.22
1.20
1.19
1.17
1.16
1.07
1.06
1.05
0.92
0.91
1.00
3.99
1.05
1.08
1.09
1.10
1.35
1.01
1.03
1.95
1.01
1.19
1.33
3.13
2.37
1.39
1.44
1.43
7.24
7.24
2.20
1.34
2.39
3.00
9.12
3.31
5.80
3.98
f1 (ppm)

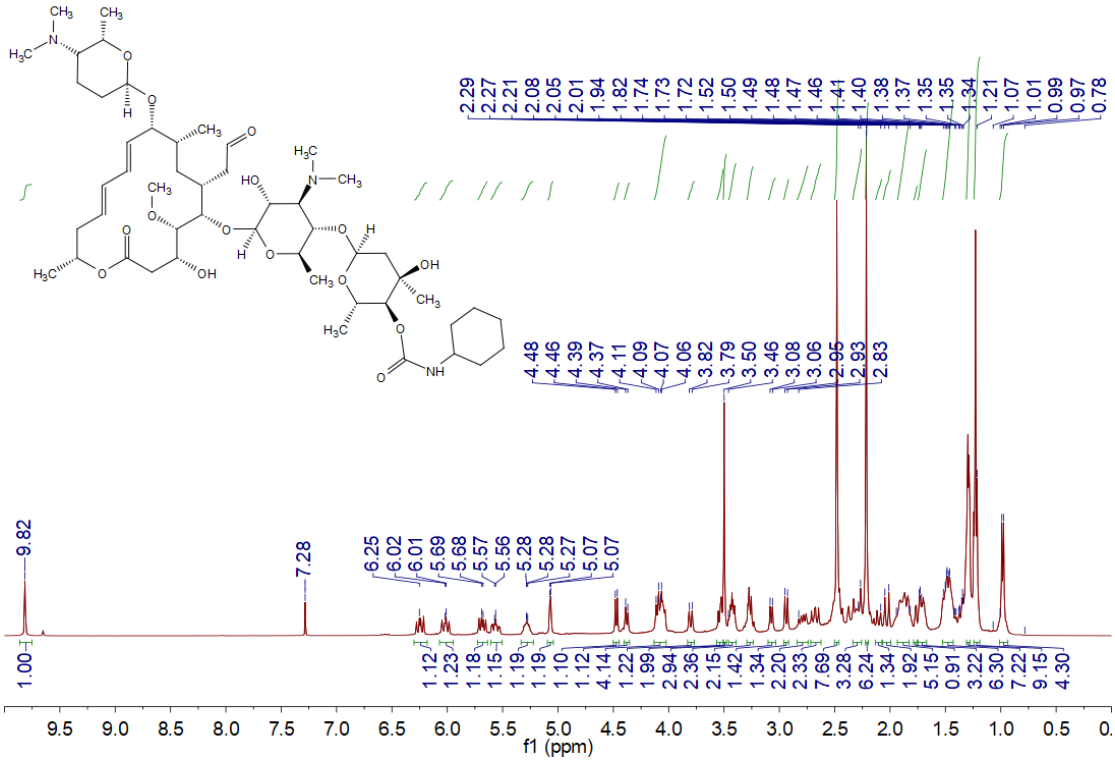

202.84
181.34
174.28
170.66
162.87
142.04
134.74
132.74
131.20
129.31
128.44
125.35
103.85
100.21
96.87
79.38
73.93
73.04
69.30
69.23
64.84
63.31
61.86
57.04
54.01
43.35
42.19
42.02
41.61
40.55
31.05
25.37
15.31
f1 (ppm)

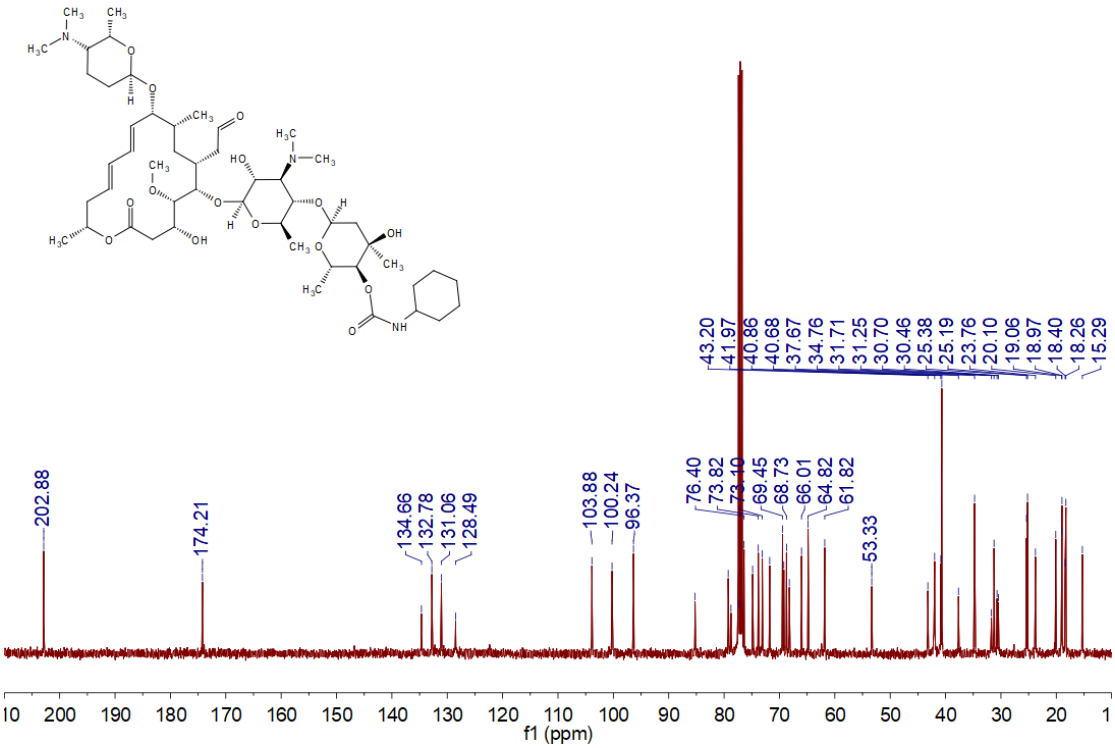
Compound 16


9.82
7.26
6.24
6.02
5.69
5.57
5.56
5.30
5.29
5.07
5.07
4.46
4.39
4.37
4.06
3.79
3.50
2.48
2.37
2.14
2.08
2.05
2.01
1.85
1.84
1.77
1.76
1.60
1.58
1.30
1.28
1.23
0.95
0.93
f1 (ppm)

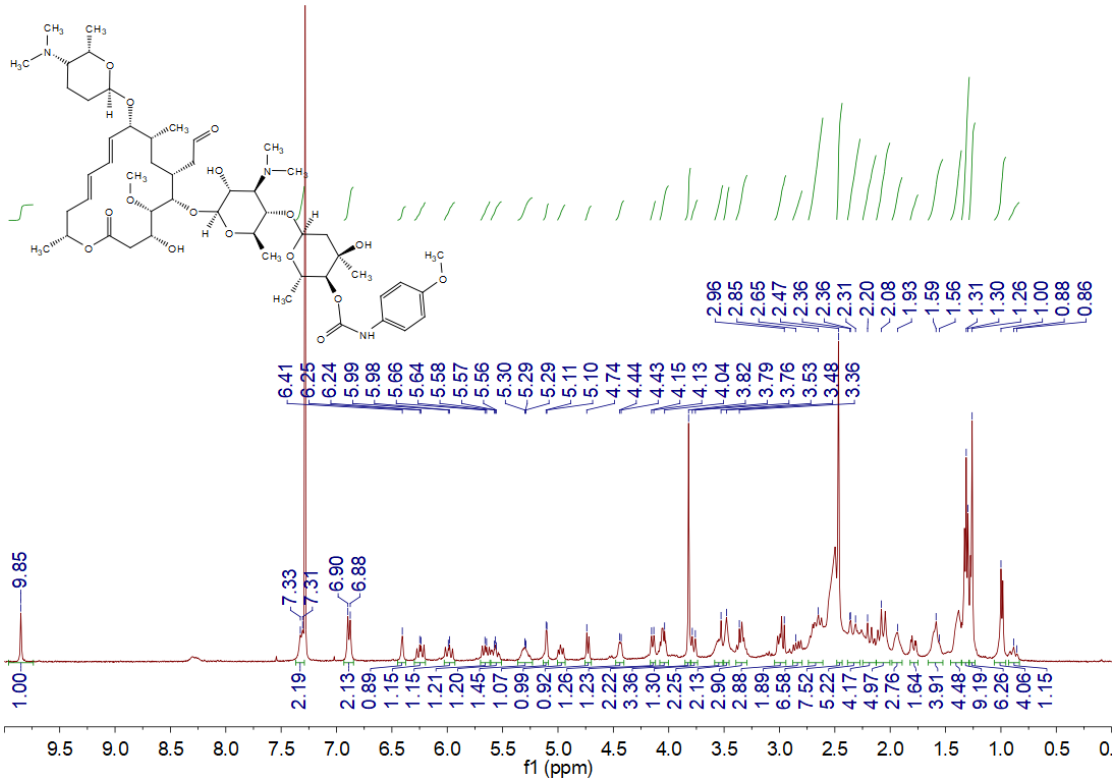

202.84
174.26
136.00
134.69
132.80
131.09
129.06
128.51
103.89
100.27
96.39
85.27
79.33
78.78
77.24
76.42
74.82
73.77
73.14
71.79
69.46
69.23
68.77
68.23
66.07
64.87
61.85
43.25
42.68
42.02
40.88
40.70
37.65
33.29
31.74
31.24
30.73
30.48
25.41
20.11
19.69
19.09
19.01
18.48
18.29
15.31
13.40
f1 (ppm)

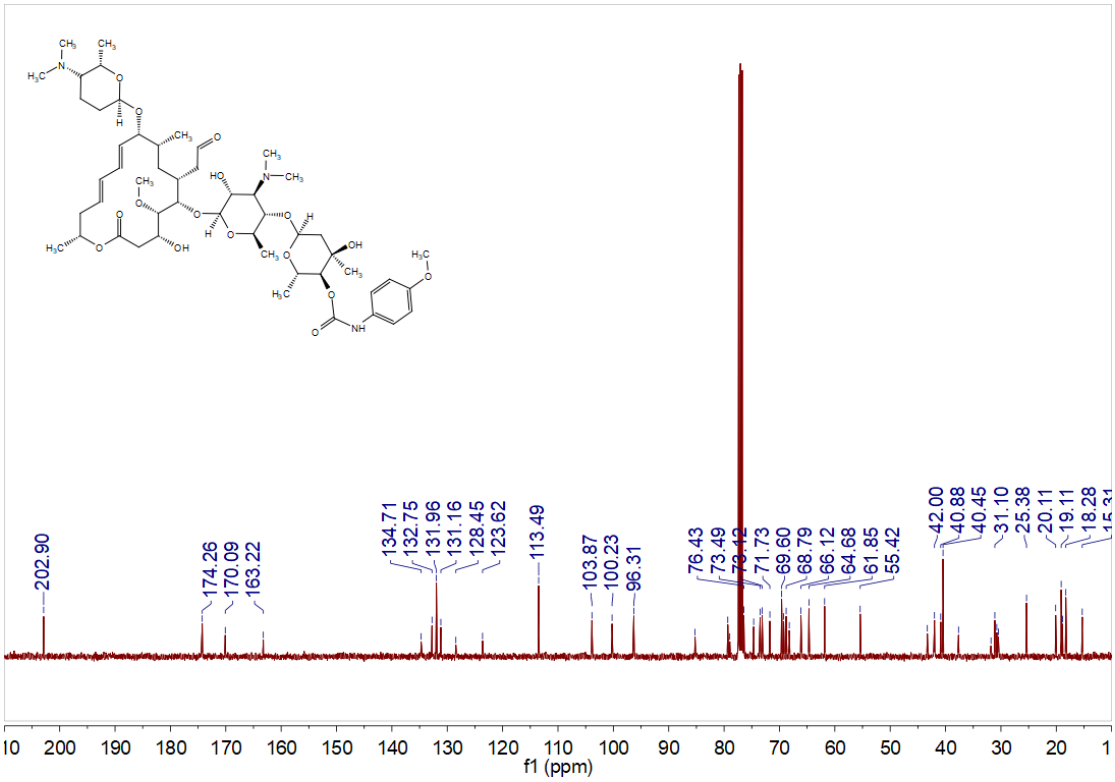
Compound 17


2.29
2.27
2.21
2.08
2.05
2.01
1.94
1.82
1.74
1.73
1.72
1.52
1.50
1.49
1.48
1.47
1.46
1.41
1.40
1.38
1.37
1.35
1.35
1.34
1.21
1.07
1.01
0.99
0.97
0.78
4.48
4.46
4.39
4.37
4.11
4.09
4.07
4.06
3.82
3.79
3.50
3.46
3.08
3.06
2.95
2.93
2.83
9.82
7.28
6.25
6.02
6.01
5.69
5.68
5.57
5.56
5.28
5.28
5.27
5.07
5.07
1.00
1.12
1.23
1.18
1.15
1.19
1.19
1.10
1.12
4.14
1.22
1.99
2.94
2.36
2.15
1.42
1.34
2.20
2.33
7.69
3.28
6.24
1.34
1.92
5.15
0.91
3.22
6.30
7.22
9.15
4.30
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

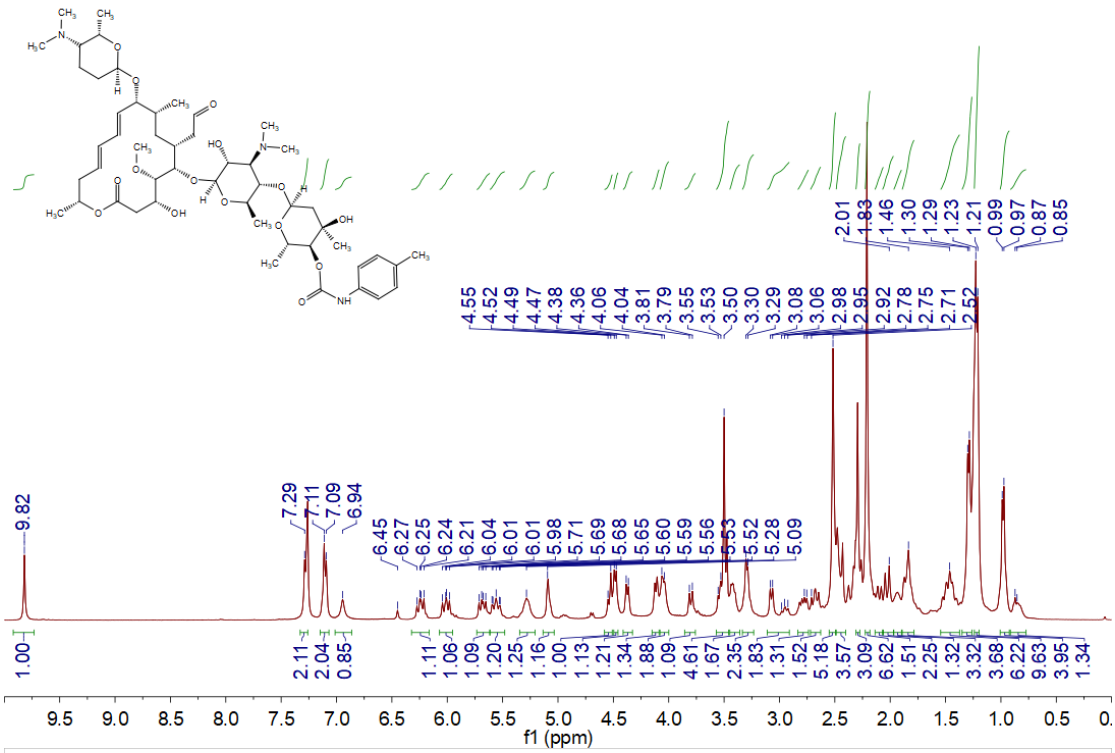

43.20
41.97
40.86
40.68
37.67
34.76
31.71
31.25
30.70
30.46
25.38
25.19
23.76
20.10
19.06
18.97
18.40
18.26
15.29
202.88
174.21
134.66
132.78
131.06
128.49
103.88
100.24
96.37
76.40
73.82
73.10
69.45
68.73
66.01
64.82
61.82
53.33
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 1
f1 (ppm)

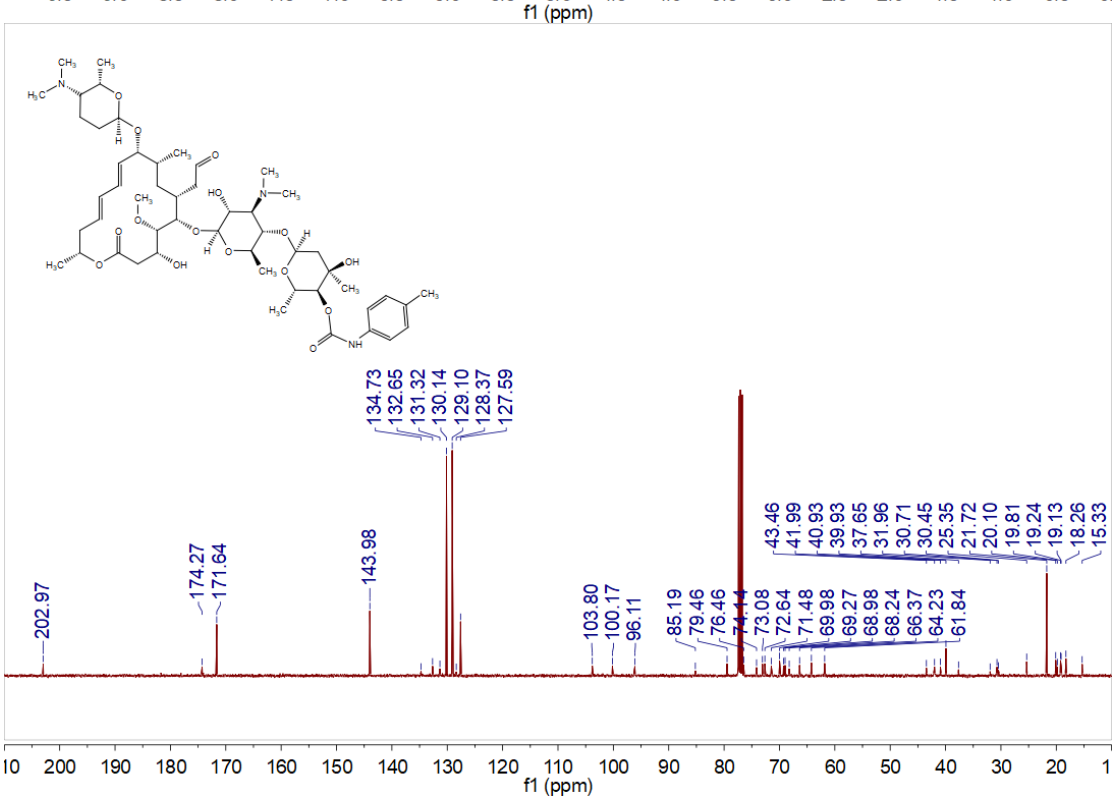
Compound 18


9.85
7.33
7.31
6.90
6.88
f1 (ppm)


202.90
174.26
170.09
163.22
134.71
132.75
131.96
131.16
128.45
123.62
113.49
103.87
100.23
96.31
76.43
73.49
71.73
69.60
68.79
66.12
64.68
61.85
55.42
42.00
40.88
40.45
31.10
25.38
20.11
19.11
18.28
f1 (ppm)

Compound 19


9.82
7.29
7.11
7.09
6.94
6.45
6.27
6.25
6.24
6.21
6.04
6.01
6.01
5.98
5.71
5.69
5.68
5.65
5.60
5.59
5.56
5.53
5.52
5.28
5.09
4.55
4.52
4.49
4.47
4.38
4.36
4.06
4.04
3.81
3.79
3.55
3.53
3.50
3.30
3.29
3.08
3.06
2.98
2.95
2.92
2.78
2.75
2.71
2.52
2.01
1.83
1.46
1.30
1.29
1.23
1.21
0.99
0.97
0.87
0.85
1.00
2.11
2.04
0.85
1.11
1.06
1.09
1.20
1.25
1.16
1.00
1.13
1.21
1.34
1.88
1.09
4.61
1.67
2.35
1.83
1.31
1.52
5.18
3.57
3.09
6.62
1.51
2.25
1.32
3.32
3.68
6.22
9.63
3.95
1.34
f1 (ppm)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100.17
96.11
85.19
79.46
76.46
74.14
73.08
72.64
71.48
69.98
69.27
68.98
68.24
66.37
64.23
61.84
43.46
41.99
40.93
39.93
37.65
31.96
30.71
30.45
25.35
21.72
20.10
19.81
19.24
19.13
18.26
15.33
f1 (ppm)

Compound 20

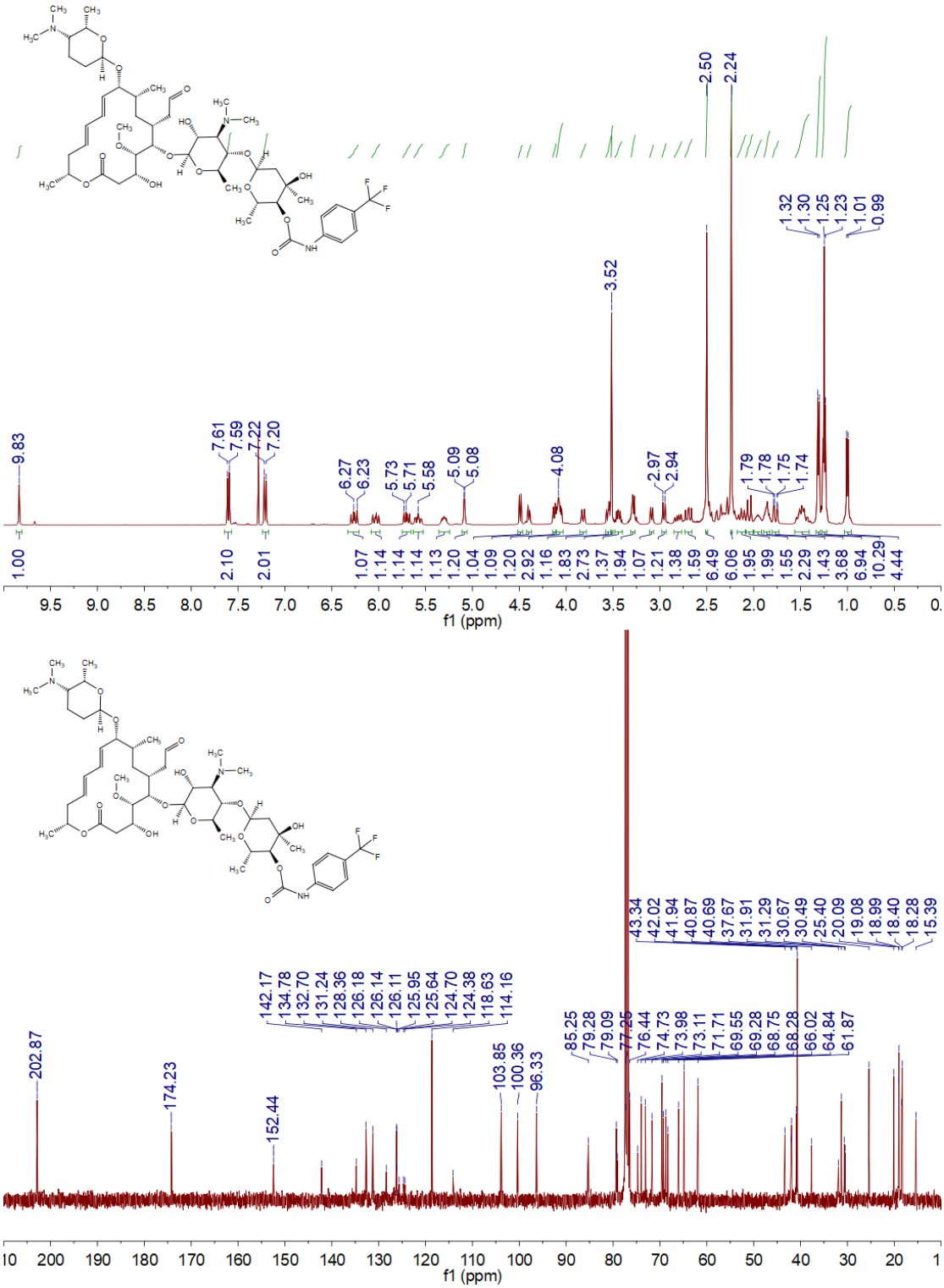
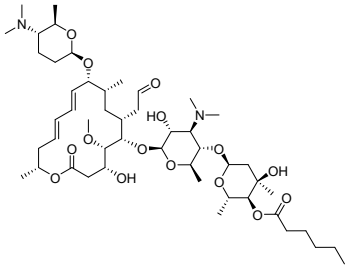
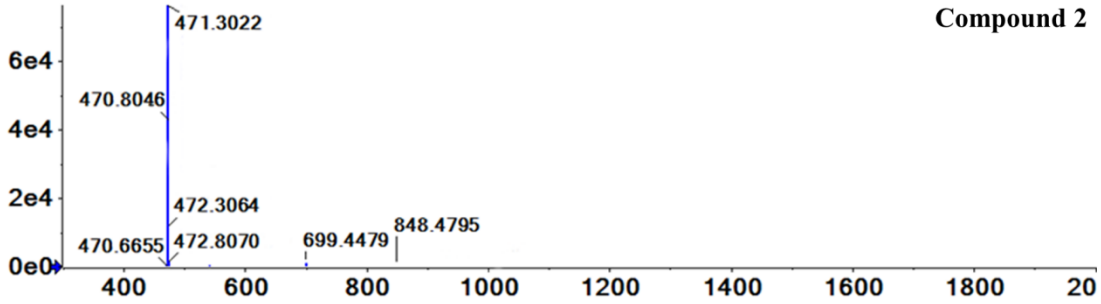
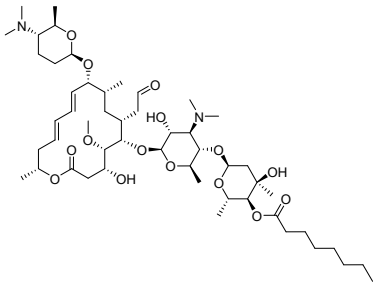


Figure S8. ^{1}H and ^{13}C NMR spectra of compounds **2-8**, **10-20**.

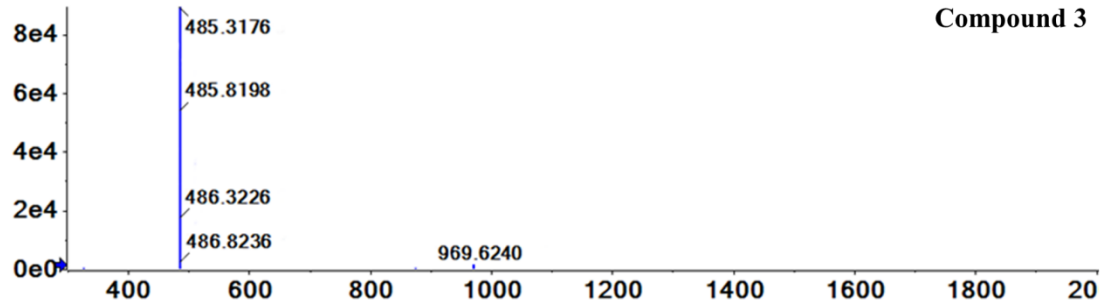


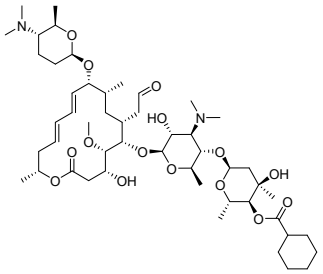
Chemical Formula: $C_{49}H_{84}N_2O_{15}$
Exact Mass: 940.5872



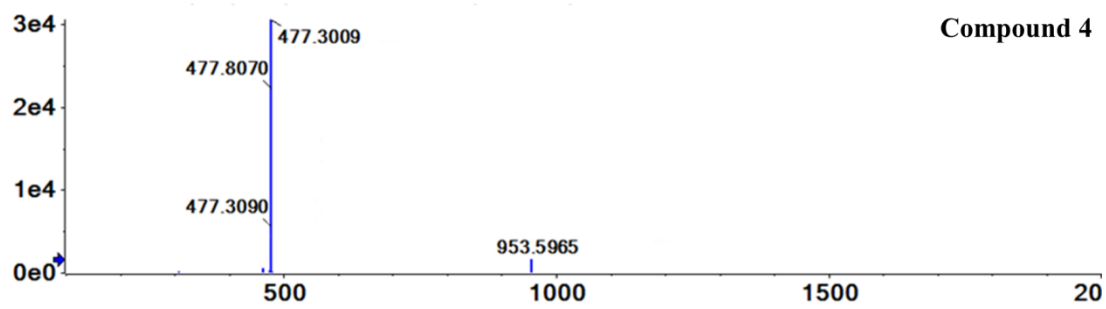


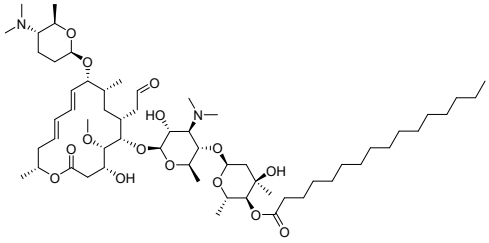
Chemical Formula: $C_{51}H_{88}N_2O_{15}$
Exact Mass: 968.6185



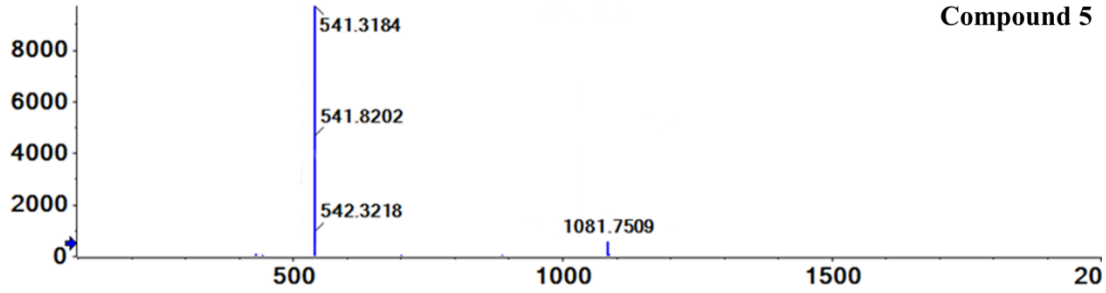


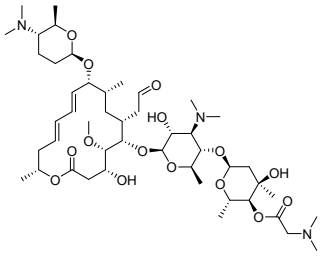
Chemical Formula: $C_{50}H_{84}N_2O_{15}$
Exact Mass: 952.5872



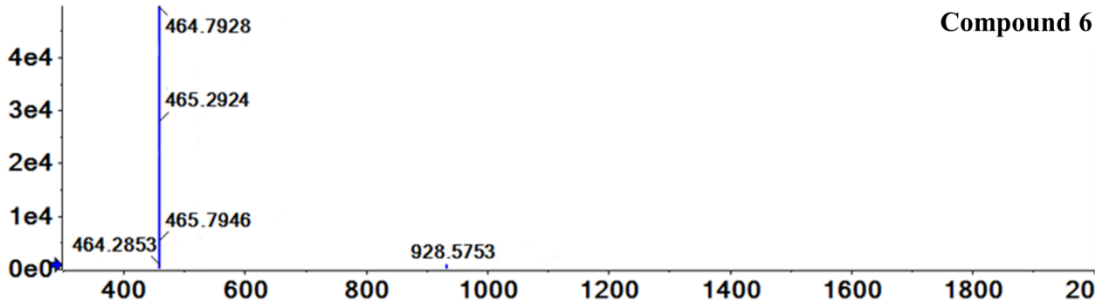


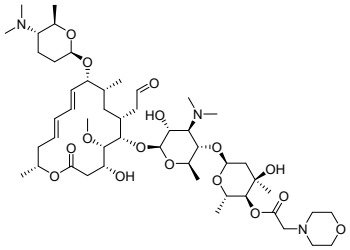
Chemical Formula: $C_{59}H_{104}N_2O_{15}$
Exact Mass: 1080.7437



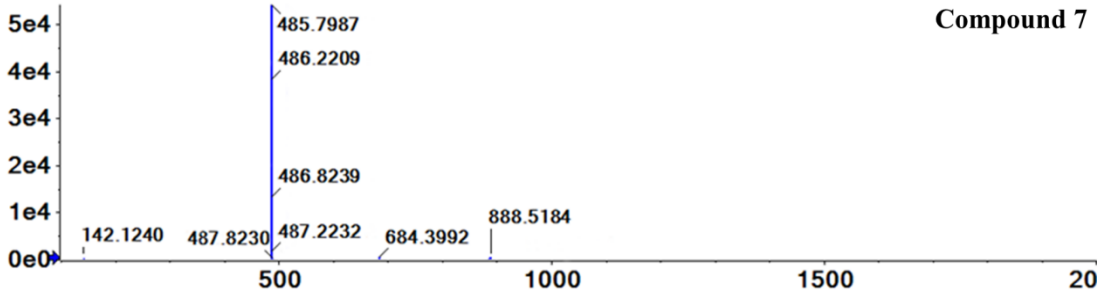


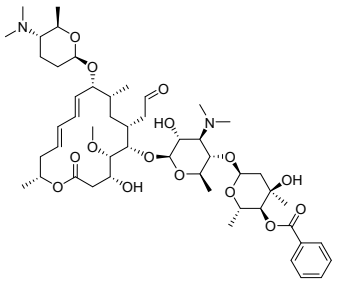
Chemical Formula: $C_{47}H_{81}N_3O_{15}$
Exact Mass: 927.5668



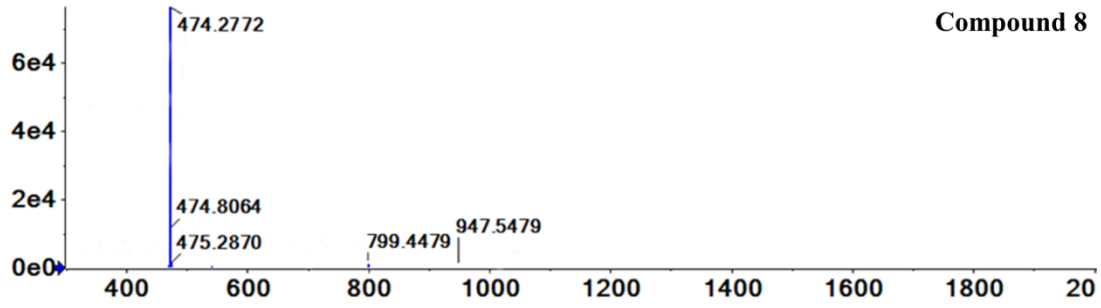


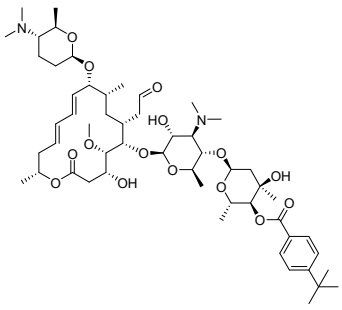
Chemical Formula: $C_{49}H_{83}N_3O_{16}$
Exact Mass: 969.5773



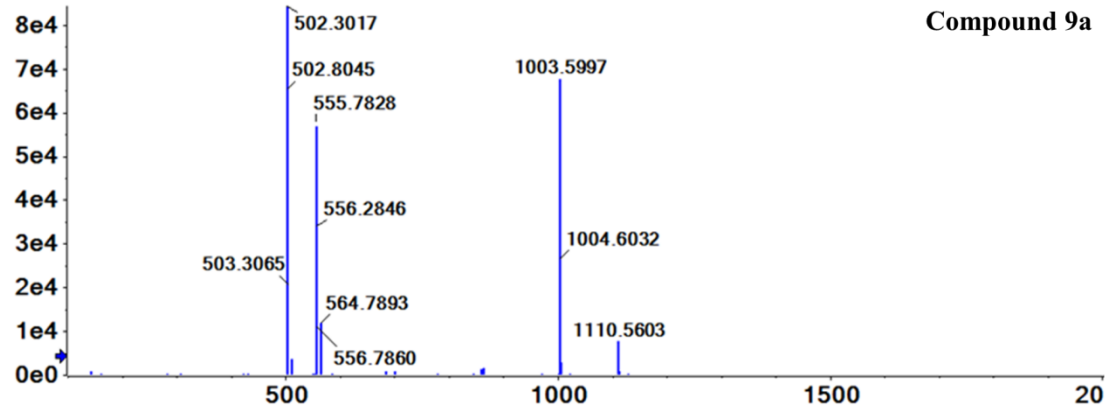


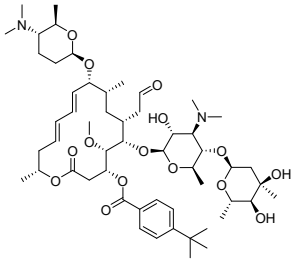
Chemical Formula: $C_{50}H_{78}N_2O_{15}$
Exact Mass: 946.5402



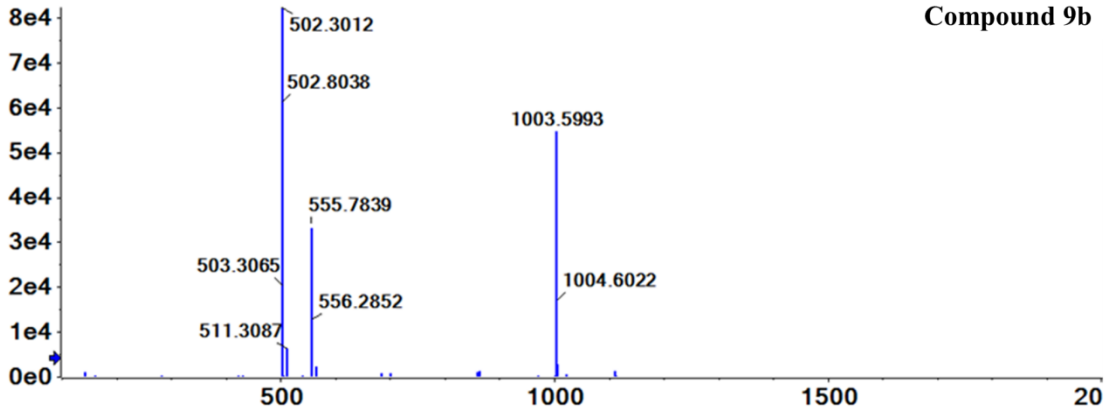


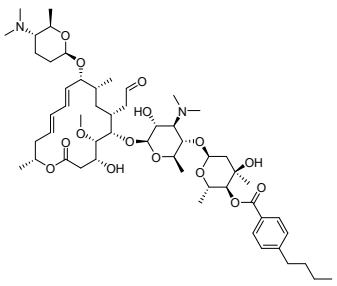
Chemical Formula: $C_{54}H_{86}N_2O_{15}$
Exact Mass: 1002.6028





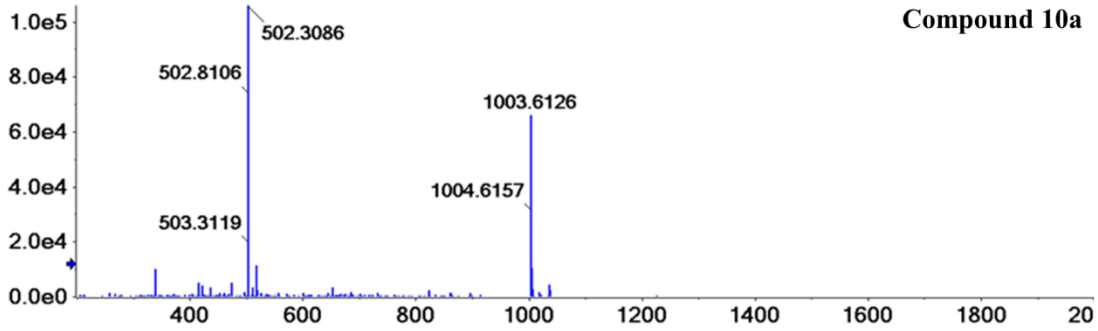
Chemical Formula: $C_{54}H_{86}N_2O_{15}$
Exact Mass: 1002.6028

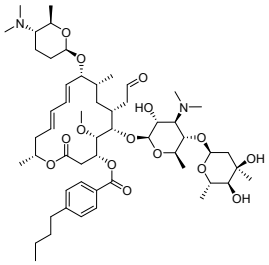




Chemical Formula: $C_{54}H_{86}N_2O_{15}$
Exact Mass: 1002.6028

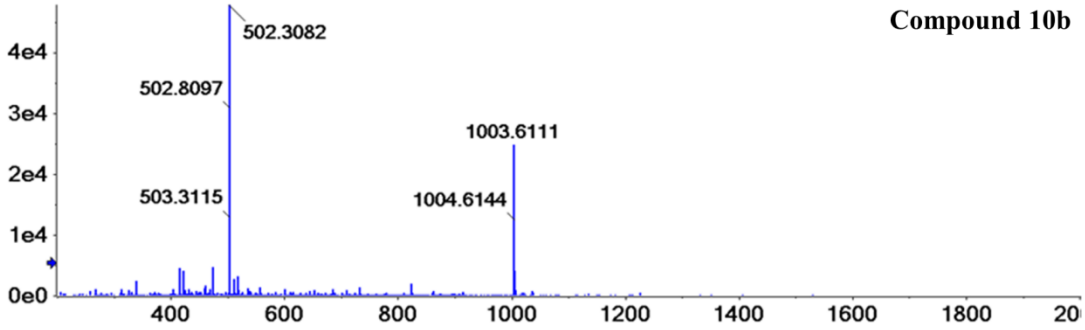
Compound 10a

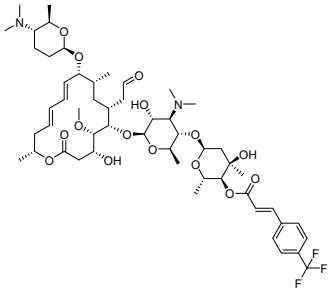




Chemical Formula: $C_{54}H_{86}N_2O_{15}$
Exact Mass: 1002.6028

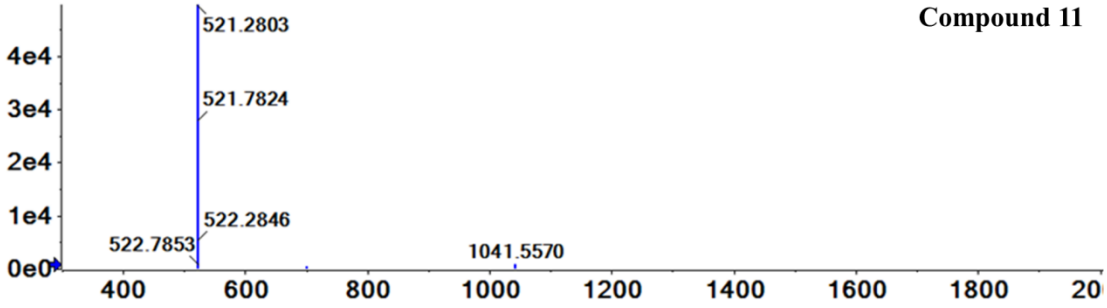
Compound 10b

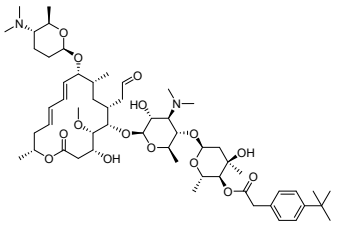




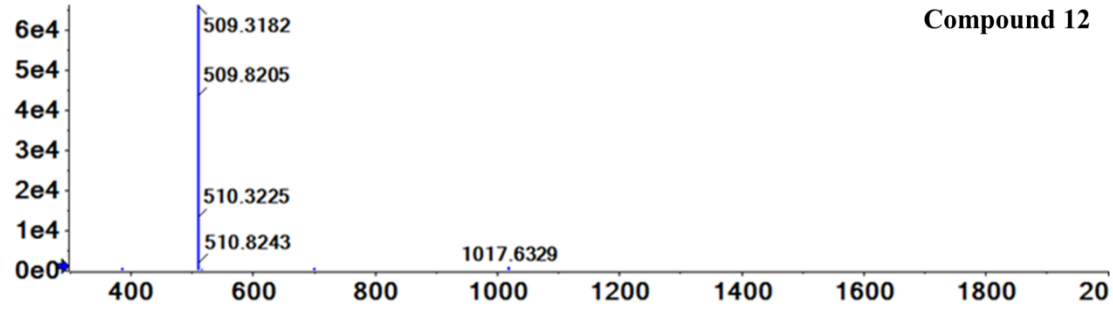
Chemical Formula: $C_{53}H_{79}F_3N_2O_{15}$
Exact Mass: 1040.5433

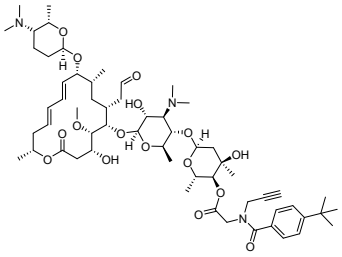
Compound 11



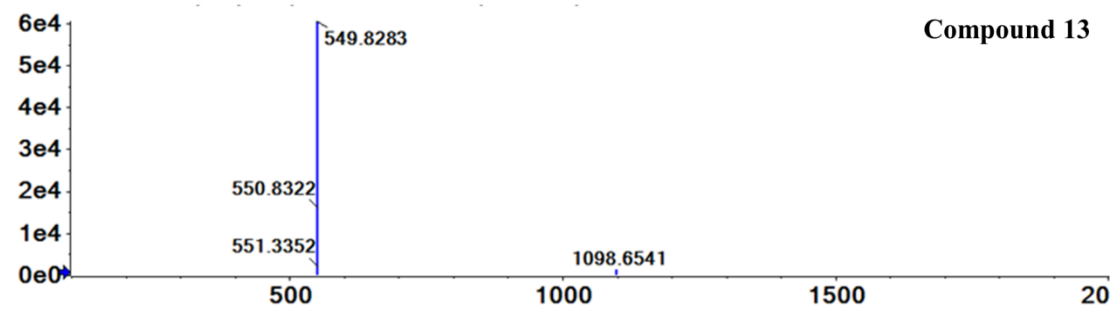


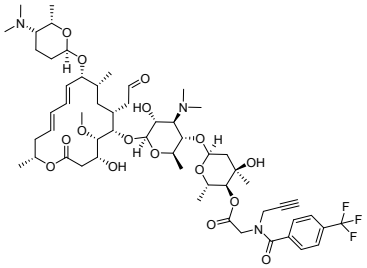
Chemical Formula: $C_{55}H_{88}N_2O_{15}$
Exact Mass: 1016.6185





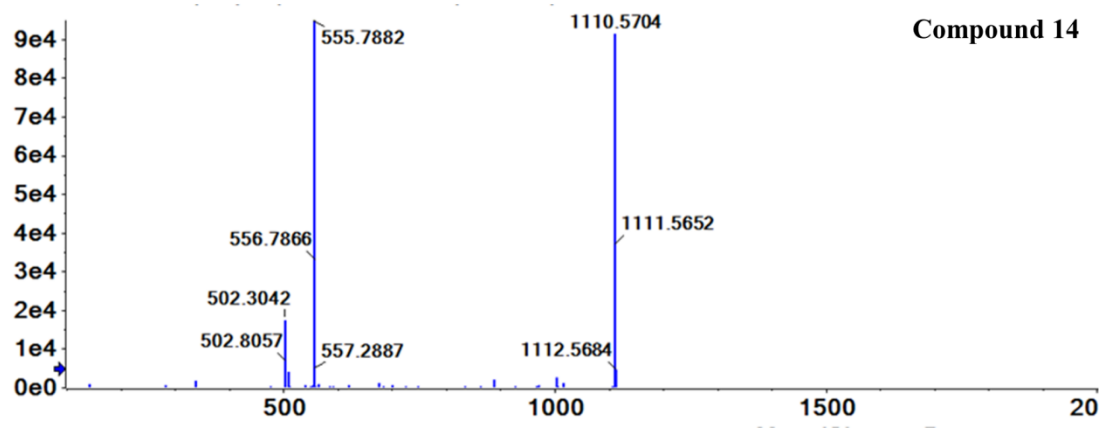
Chemical Formula: $C_{59}H_{91}N_3O_{16}$
Exact Mass: 1097.6399

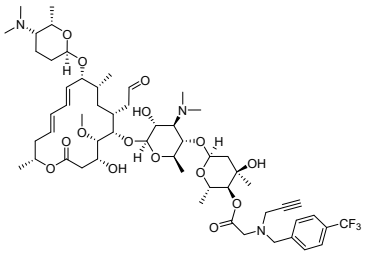




Chemical Formula: $C_{56}H_{82}F_3N_3O_{16}$
Exact Mass: 1109.5647

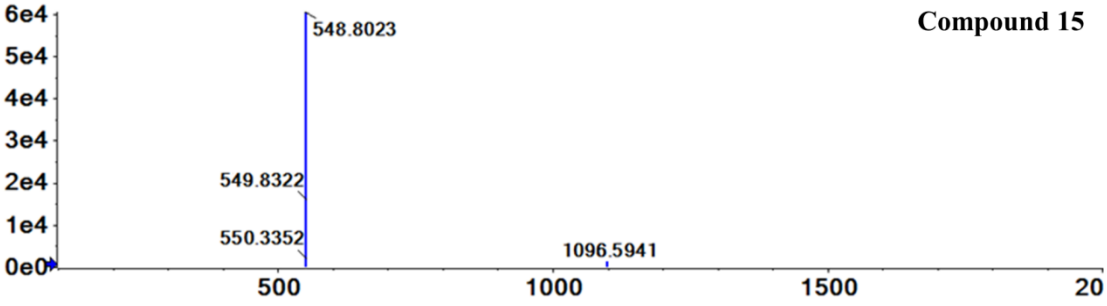
Compound 14

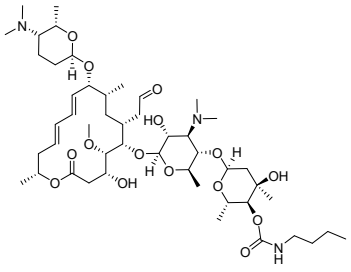




Chemical Formula: $C_{56}H_{84}F_3N_3O_{15}$
Exact Mass: 1095.5855

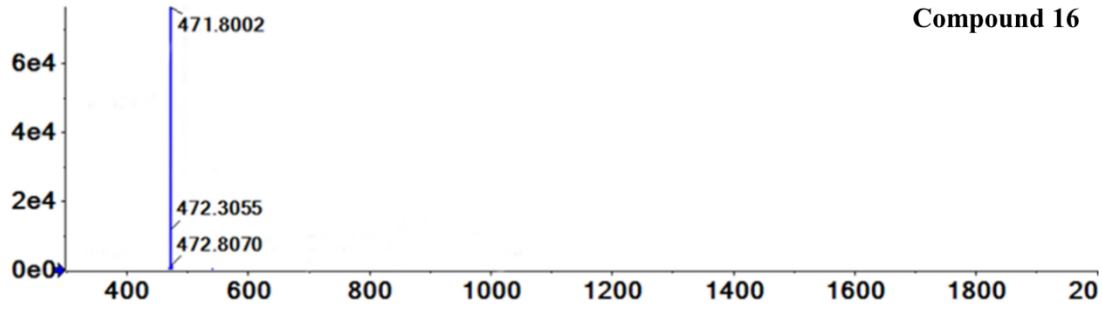
Compound 15

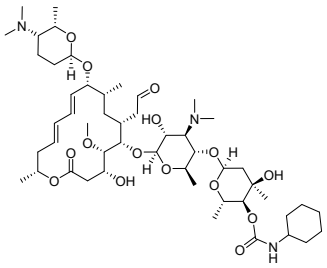




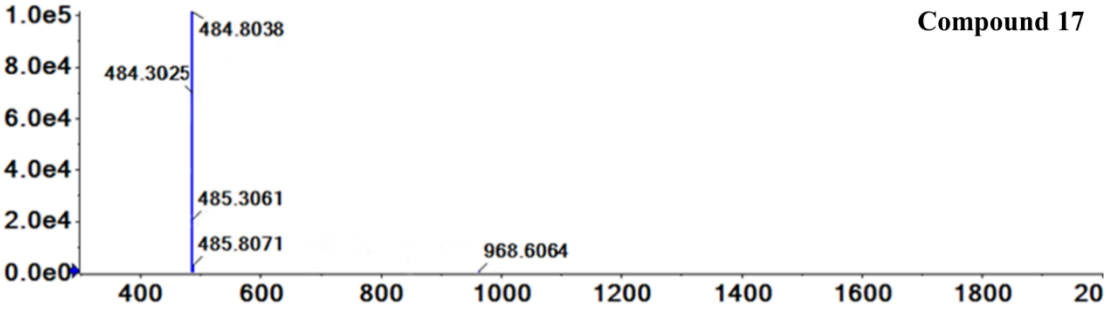
Chemical Formula: $C_{48}H_{83}N_3O_{15}$
Exact Mass: 941.5824

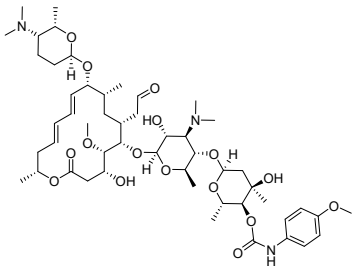
Compound 16



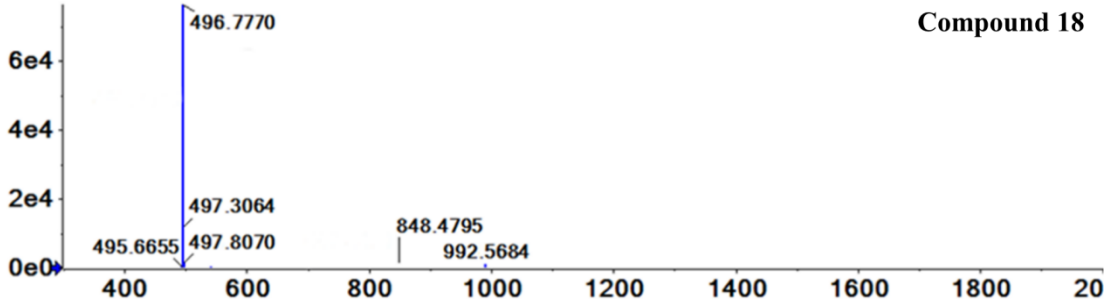


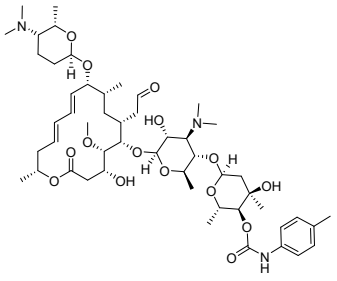
Chemical Formula: $C_{50}H_{85}N_3O_{15}$
Exact Mass: 967.5981





Chemical Formula: $C_{51}H_{81}N_3O_{16}$
Exact Mass: 991.5617





Chemical Formula: $C_{51}H_{81}N_3O_{15}$
Exact Mass: 975.5668

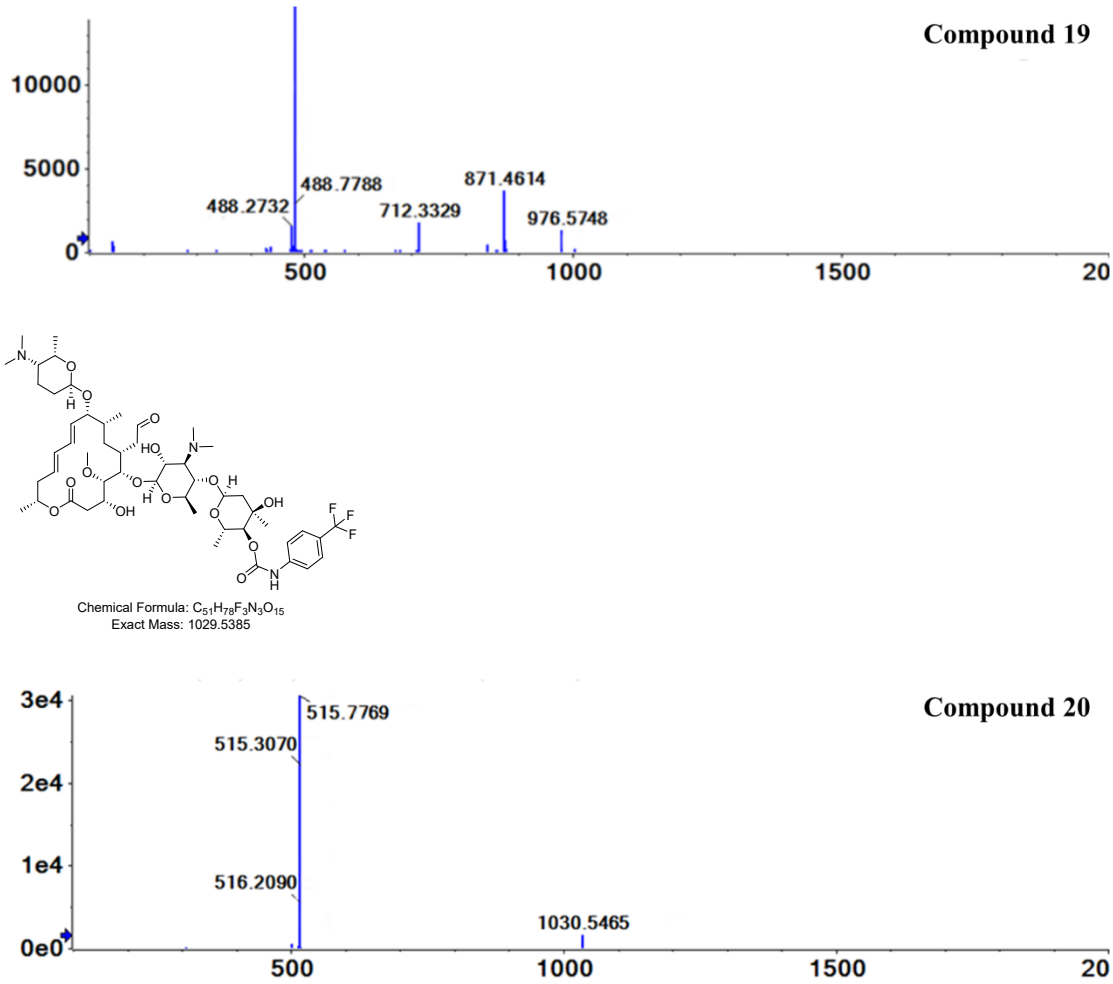


Figure S9. HRMS-ESI spectra of compounds **2-20.**