Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Synthesis and antiproliferative activity of novel erythromycin derivatives

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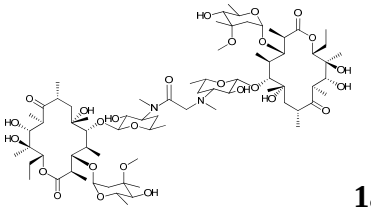
Contents include synthetic procedures, analytical data for final compounds in Figure 1, experimental details for in vitro assays presented in Table 1.

Chemistry General Methods

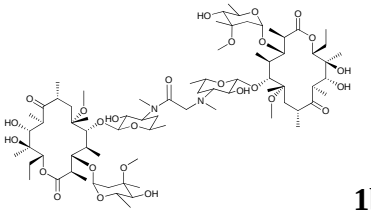
Unless otherwise noted, all the materials were obtained from commercially available sources and were used without purification. Thin-layer chromatography was performed on GF254 silica gel plates to monitor the reaction and the plates were examined under UV light or detected with a solution of phosphomolybdic acid in ethanol (5%). The purification of the products was performed using column chromatography (60 Å, 200-300 mesh, Qingdao Ocean Chemicals) or silica gel plates (0.25mm layer, Qingdao Ocean Chemicals) with the designated solvents. Melting points were measured on a hot-stage microscope (X-4, Beijing Taike Ltd.) and are uncorrected. Mass spectra were obtained on a Waters Quattro Micro API or Agilent 1100 series MSD TRAP using ESI. Elemental analyses were conducted by the Analytical Centre of Jilin University, China. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ solution on Bruker ARX-300 or Bruker AV-600 spectrometers with TMS as the internal reference. Chemical shifts were reported in ppm downfield from tetramethylsilane.



1a

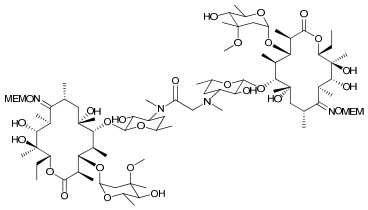
Chloroacetyl chloride (5.3 μL, 0.07 mmol) was added dropwise to a solution of compound **5a** (0.10 g, 0.14 mmol) and *N*,*N*-diisopropylethylamine (58.0 μL, 0.35 mmol) in anhydrous dichloromethane (5.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 48 h, then poured into water and extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography with chloroform-methanol-ammonium hydroxide solution (20:1:0.1) to yield **1a** (0.08 g, 76%) as a white solid. Mp 167–170 ^{o}C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 222.6 (C-9), 178.2 (C-1), 101.4 (C-1'), 94.7 (C-1"), 85.4 (C-5), 80.6 (C-3), 78.3 (C-4"), 75.3 (C-13), 74.9 (C-6), 74.6 (C-12), 73.0 (C-3"), 70.9 (C-2'), 68.9 (C-11), 68.1 (C-5'), 65.8 (C-5"), 65.6 (C-3'), 57.2 (NCH_2), 49.4 (3"-OMe), 44.8 (C-8), 44.7 (C-2), 39.1 (C-4), 38.7 (C-7), 38.0 (C-10), 37.2 (NMe), 34.6 (C-2"), 30.5/30.3 (C-4'), 26.8/26.2 (C-6 Me), 21.6 (C-5' Me), 21.4 (C-3" Me), 21.0 (C-14), 18.3 (C-5" Me), 18.1 (C-8 Me), 16.2 (C-2 Me), 16.1 (C-12 Me), 12.0 (C-10 Me), 10.9/10.6 (C-15), 9.5/9.0 (C-4 Me),

170.0 (CONMe); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (H-13), 4.87 (H-1"), 4.45 (H-1'), 3.29 (3"-OMe), 2.93 (NMe), 3.82 ($NCOCH_2$); MS (ESI, *m/z*): 1480.4 [$M+H^+$], 1503.6 [$M+Na^+$], 1479.4 [$M-H^+$]. Anal. Calcd. for $C_{74}H_{130}N_2O_{27}$: C, 60.06; H, 8.85; N, 1.89. Found: C, 59.95; H, 8.81; N, 1.87.



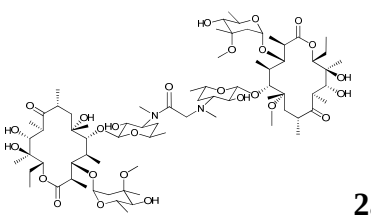
1b

White solid, yield 74%, mp 171–174°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.1/220.8 (C-9), 175.8/175.7 (C-1), 103.5/103.2 (C-1'), 96.4 (C-1"), 82.4 (C-5), 81.5 (C-3), 78.7/78.3 (C-6), 77.7 (C-4"), 77.2 (C-13), 74.2 (C-12), 72.8/72.6 (C-3"), 71.6/71.2 (C-2'), 69.0 (C-11), 68.6/68.1 (C-5'), 66.1 (C-3'), 65.3/64.2 (C-5"), 56.2 (NCH_2), 50.6 (6-OMe), 49.4 (3"-OMe), 45.1 (C-2), 45.0 (C-8), 39.4/39.0 (C-7), 39.2 (C-4), 37.2 (C-10), 37.1 (NMe), 35.6/34.9 (C-2"), 30.9/30.3 (C-4'), 21.5 (C-5' Me), 21.4/21.3 (C-3" Me), 21.1/21.0 (C-14), 19.7/19.5 (C-6 Me), 18.7/18.6 (C-5" Me), 18.0 (C-8 Me), 16.0 (C-2 Me/C-12 Me), 12.3 (C-10 Me), 10.6 (C-15), 9.4/9.0 (C-4 Me), 171.8 (CONMe); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07/5.04 (H-13), 4.91 (H-1"), 4.41 (H-1'), 3.32/3.31 (3"-OMe), 3.04 (6-OMe), 3.03 (NMe), 3.75 ($NCOCH_2$); MS (ESI, *m/z*): 1508.1 [$M+H^+$], 1542.1 [$M+Cl^-$]. Anal. Calcd. for $C_{76}H_{134}N_2O_{27}$: C, 60.54; H, 8.96; N, 1.86. Found: C, 65.50; H, 8.89; N, 1.93.



1c

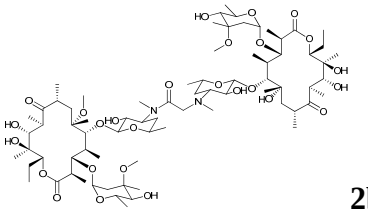
White solid, yield 68%, mp 136–139°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1 (C-1), 172.8/172.5 (C-9), 103.5 (C-1'), 96.6 (C-1"), 83.7 (C-5), 81.0 (C-3), 77.2 (C-4"), 76.8 (C-13), 74.8 (C-6), 74.3 (C-12), 72.6 (C-3"), 71.2 (C-2'), 70.4 (C-11), 68.3 (C-5'), 65.6 (C-3'), 65.4 (C-5"), 57.1 (NCH_2), 49.4 (3"-OMe), 44.7 (C-2), 38.7 (C-4), 37.5 (C-7), 37.1 (NMe), 35.2 (C-2"), 33.0 (C-10), 30.9/30.3 (C-4'), 26.9 (C-6 Me), 26.7 (C-8), 23.7 (C-5' Me), 23.0 (C-3" Me), 21.5/21.1 (C-14), 18.8 (C-8 Me), 18.6 (C-5" Me), 16.3 (C-12 Me), 16.2 (C-2 Me), 14.8/14.1 (C-10 Me), 10.9/10.6 (C-15), 9.5/9.2 (C-4 Me), 97.5, 71.9, 68.1, 59.0 ($OCH_2OCH_2CH_2OCH_3$), 167.8 (CONMe); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (H-13), 4.85 (H-1"), 4.39 (H-1'), 3.29 (3"-OMe), 2.93 (NMe), 5.19, 3.75, 3.58, 3.43 ($OCH_2OCH_2CH_2OCH_3$), 3.84 ($NCOCH_2$); MS (ESI, *m/z*): 1687.7 [$M+H^+$], 1531.9 [$M+HCOO^-$]. Anal. Calcd. for $C_{82}H_{148}N_4O_{31}$: C, 58.41; H, 8.85; N, 3.32. Found: C, 58.40; H, 8.87; N, 3.28.



2a

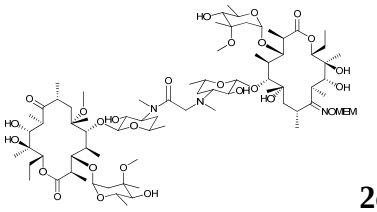
To a solution of compound **5a** (0.10 g, 0.14 mmol) in anhydrous dichloromethane (5.0 mL), was

added dropwise *N*,*N*-diisopropylethylamine (0.12 mL, 0.70 mmol) and chloroacetyl chloride (10.5 μL, 0.14 mmol). The reaction mixture was stirred at room temperature for 12 h, then compound **5b** (0.10 g, 0.14 mmol) was added. After being stirred at room temperature for 48 h, the solution was diluted with water and extracted with dichloromethane. The organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the resulting crude product was purified by column chromatography on silica gel eluting with chloroform-methanol-ammonium hydroxide solution (10:0.5:0.01 to 10:1:0.05) to give **2a** (0.15 g, 71%) as a white solid. M.p. 147-151°C. ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.8/221.0 (C-9), 175.7 (C-1), 104.1/103.7 (C-1'), 96.9/96.5 (C-1"), 83.0 (C-5), 80.4/78.8 (C-3), 78.4/74.6 (C-6), 77.8 (C-4"), 75.1 (C-13), 74.6/74.3 (C-12), 72.9 (C-3"), 71.3/71.0 (C-2'), 69.1/69.0 (C-11), 68.4 (C-5'), 65.7 (C-5"), 65.8 (C-3'), 57.0 (NCH_2), 50.7 (6-OMe), 49.4 (3"-OMe), 45.2 (C-2), 45.1 (C-8), 39.4 (C-4), 38.9/38.0 (C-7), 37.3 (C-10), 37.2/37.1 (NMe), 35.0 (C-2"), 30.2 (C-4'), 26.9/19.7 (C-6 Me), 22.7 (C-5' Me), 21.5/21.4 (C-3" Me), 21.1/21.0 (C-14), 18.7/18.6 (C-5" Me), 18.3/18.0 (C-8 Me), 16.2 (C-2 Me), 16.0 (C-12 Me), 12.3/11.9 (C-10 Me), 10.7/10.6 (C-15), 9.5 (C-4 Me), 167.7 (CONMe); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (H-13), 4.89 (H-1"), 4.40 (H-1'), 3.30 (3"-OMe), 3.03 (6-OMe), 2.92 (NMe), 3.76 ($NCOCH_2$); MS (ESI, *m/z*): 1494.6 [$M+H^+$], 1529.4 [$M+Cl^-$]. Anal. Calcd. for $C_{75}H_{132}N_2O_{27}$: C, 60.30; H, 8.91; N, 1.88. Found: C, 60.24; H, 8.94; N, 1.85.



2b

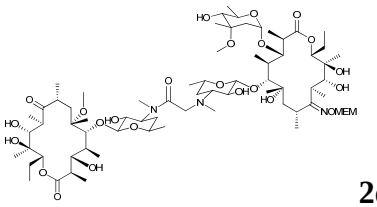
White solid, yield 77%, mp 146–148°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 222.5/220.7 (C-9), 175.8/175.7 (C-1), 104.5/103.2 (C-1'), 96.6/96.5 (C-1"), 81.5 (C-5), 80.7/78.8 (C-3), 78.4/74.3 (C-6), 78.3/77.7 (C-4"), 77.2/77.0 (C-13), 75.1/74.7 (C-12), 72.9/72.6 (C-3"), 71.6/71.2 (C-2'), 69.1/68.9 (C-11), 68.8/68.2 (C-5'), 66.3 (C-3'), 65.2/64.3 (C-5"), 56.5 (NCH_2), 50.7 (6-OMe), 49.4 (3"-OMe), 45.2 (C-2), 45.1/44.9 (C-8), 39.4/39.1 (C-4), 38.6 (C-7), 37.8/37.4 (C-10), 37.0 (NMe), 35.1/35.0 (C-2"), 29.7 (C-4'), 26.9/19.7 (C-6 Me), 21.5 (C-5' Me), 21.5/21.3 (C-3" Me), 21.1 (C-14), 18.8/18.7 (C-5" Me), 18.3/18.0 (C-8 Me), 16.2/15.9 (C-2 Me), 16.0 (C-12 Me), 12.3/11.9 (C-10 Me), 10.6 (C-15), 9.4/9.1 (C-4 Me), 172.0 (CONMe); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (H-13), 4.89 (H-1"), 4.48/4.30 (H-1'), 3.32/3.30 (3"-OMe), 3.04 (6-OMe), 2.87/2.83 (NMe), 3.75 ($NCOCH_2$); MS (ESI, *m/z*): 1493.8 [$M+H^+$],1516.7 [$M+Na^+$], 1528.7 [$M+Cl^-$]. Anal. Calcd. for $C_{75}H_{132}N_2O_{27}$: C, 60.30; H, 8.91; N, 1.88. Found: C, 60.27; H, 8.88; N, 1.83.



2c

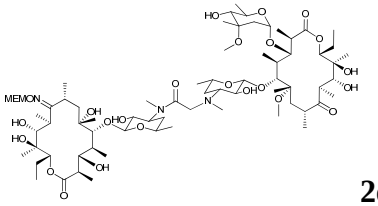
White solid, yield 63%, mp 133–135°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.9/172.8 (C-9), 175.1 (C-1), 102.4 (C-1'), 96.5 (C-1"), 86.2/82.5 (C-5), 81.0 (C-3), 78.6/74.3 (C-6), 78.3/77.6 (C-4"), 77.1 (C-13), 74.9/74.3 (C-12), 72.9 (C-3"), 71.3 (C-2'), 69.1 (C-11), 68.3 (C-5'), 66.0/65.3 (C-3'), 65.4

(C-5"), 57.2 (NCH_2), 53.5 (6-OMe), 49.4 (3"-OMe), 45.1 (C-2), 44.8/26.7 (C-8), 39.3/37.5 (C-7), 39.1/39.0 (C-4), 37.3/33.0 (C-10), 37.0 (NMe), 35.7/35.0 (C-2"), 32.0/31.6 (C-4'), 27.7/19.7 (C-6 Me), 22.7 (C-5' Me), 21.6/21.1 (C-3" Me), 21.0/20.5 (C-14), 18.6/18.5 (C-5" Me), 18.8/18.0 (C-8 Me), 16.3/16.0 (C-12 Me), 16.0 (C-2 Me), 14.1/12.3 (C-10 Me), 11.5/10.6 (C-15), 9.4 (C-4 Me), 97.5, 71.9, 68.1, 59.1 ($OCH_2OCH_2CH_2OCH_3$), 167.1 (CONMe); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (H-13), 4.90/4.85 (H-1"), 4.36 (H-1'), 3.30 (3"-OMe), 3.04 (6-OMe), 2.92 (NMe), 5.19, 3.75, 3.58, 3.42 ($OCH_2OCH_2CH_2OCH_3$), 3.85 ($NCOCH_2$); MS (ESI, *m/z*): 1596.8 [$M+H^+$], 1618.7 [$M+Na^+$], 1630.8 [$M+Cl^-$]. Anal. Calcd. for $C_{79}H_{141}N_3O_{29}$: C, 59.42; H, 8.90; N, 2.63. Found: C, 59.47; H, 8.92; N, 2.58.



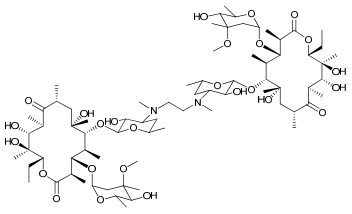
2d

White solid, yield 66%, mp 140–144°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.6/172.5 (C-9), 175.1 (C-1), 105.9/102.8 (C-1'), 96.9/96.4 (C-1"), 87.6/82.5 (C-5), 80.2 (C-3), 78.7/74.6 (C-6), 77.9 (C-4"), 77.6/76.6 (C-13), 74.2 (C-12), 73.1 (C-3"), 70.8 (C-2'), 70.5/69.9 (C-11), 68.7 (C-5'), 64.9/64.6 (C-3'), 66.5 (C-5"), 58.5 (NCH_2), 51.2 (6-OMe), 49.5 (3"-OMe), 45.8/44.7 (C-2), 44.5/26.6 (C-8), 39.1/37.5 (C-7), 39.1/35.9 (C-4), 37.6/33.1 (C-10), 37.4 (NMe), 35.2 (C-2"), 29.7 (C-4'), 26.9/18.9 (C-6 Me), 21.5/21.2 (C-5' Me), 21.6 (C-3" Me), 21.1/21.0 (C-14), 18.7 (C-5" Me), 18.4/17.8 (C-8 Me), 16.4/16.2 (C-12 Me), 16.1/15.3 (C-2 Me), 14.8/12.7 (C-10 Me), 10.6/10.5 (C-15), 9.6/8.6 (C-4 Me), 97.5, 71.9, 68.3, 59.1 ($OCH_2OCH_2CH_2OCH_3$), 167.0 (CONMe); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (H-13), 4.85 (H-1"), 4.50/4.33 (H-1'), 3.41 (3"-OMe), 3.29 (6-OMe), 2.97/2.91 (NMe), 5.18, 3.75, 3.56, 3.42 ($OCH_2OCH_2CH_2OCH_3$), 3.83 ($NCOCH_2$); MS (ESI, *m/z*): 1438.9 [$M+H^+$], 1461.3 [$M+Na^+$]. Anal. Calcd. for $C_{71}H_{127}N_3O_{26}$: C, 59.27; H, 8.90; N, 2.92. Found: C, 59.24; H, 8.86; N, 2.79.



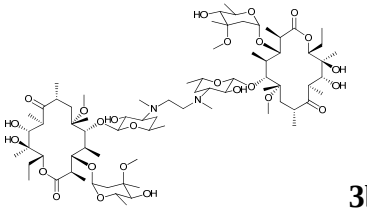
2e

White solid, yield 75%, mp 114–117°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.5/172.3 (C-9), 175.7/175.2 (C-1), 108.6/102.5 (C-1'), 96.9 (C-1"), 83.2 (C-5), 81.6/78.5 (C-3), 78.3/73.9 (C-6), 77.9 (C-4"), 76.9 (C-13), 74.1 (C-12), 71.8 (C-3"), 71.1/70.8 (C-2'), 70.5/69.1 (C-11), 68.6 (C-5'), 65.5 (C-3'), 65.2 (C-5"), 55.9 (NCH_2), 50.3 (6-OMe), 49.2 (3"-OMe), 44.8/43.8 (C-2), 44.7/26.6 (C-8), 39.2/36.3 (C-4), 39.1/36.8 (C-7), 37.1 (NMe), 37.0/33.1 (C-10), 35.0 (C-2"), 31.4/30.5 (C-4'), 25.2/19.4 (C-6 Me), 22.2/21.1 (C-5' Me), 21.3 (C-3" Me), 20.9/20.5 (C-14), 18.3 (C-5" Me), 17.9/17.7 (C-8 Me), 16.1/15.6 (C-12 Me), 15.7/14.9 (C-2 Me), 14.3/13.7 (C-10 Me), 10.2/10.1 (C-15), 8.8/7.9 (C-4 Me), 97.3, 71.4, 68.2, 58.8 ($OCH_2OCH_2CH_2OCH_3$), 170.4 (CONMe); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (H-13), 4.88 (H-1"), 4.43 (H-1'), 3.35 (3"-OMe), 3.30 (6-OMe), 3.02 (NMe), 5.18, 3.77, 3.54, 3.39 ($OCH_2OCH_2CH_2OCH_3$), 3.85 ($NCOCH_2$); MS (ESI, *m/z*): 1439.2 [$M+H^+$], 1461.2 [$M+Na^+$], 1437.1 [$M-H^+$], 1473.2 [$M+Cl^-$]. Anal. Calcd. for $C_{71}H_{127}N_3O_{26}$: C, 59.27; H, 8.90; N, 2.92. Found: C, 59.24; H, 8.94; N, 2.85.



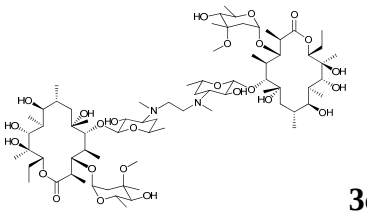
3a

To a solution of compound **5a** (0.10 g, 0.14 mmol) in anhydrous DMF (5.0 mL) was added *N*,*N*-diisopropylethylamine (0.46 mL, 2.78 mmol) and 1-bromo-2-chloroethane (0.23 mL, 2.78 mmol) at room temperature. The reaction mixture was stirred at room temperature for 120 h. The solution was diluted with water and extracted with dichloromethane. The organic phase was washed with Brine and dried over Na_2SO_4. After the evaporation of the solvent, the residue was purified by preparative thin layer chromatography with chloroform-methanol-ammonium hydroxide solution (20:1:0.1) to yield **3a** (0.06 g, 64%) as a white solid. M.p. 162-165°C. ^{13}C NMR (75 MHz, $CDCl_3$): δ 222.0 (C-9), 175.7 (C-1), 103.1 (C-1'), 96.2 (C-1"), 83.3 (C-5), 79.8 (C-3), 77.9 (C-4"), 76.8 (C-13), 75.0 (C-6/C-12), 72.6 (C-3"), 70.9 (C-2'), 68.8 (C-5'/C-11), 65.5 (C-5"), 65.3 (C-3'), 51.1 (NCH_2), 49.5 (3"-OMe), 45.1 (C-8), 44.8 (C-2), 39.4 (C-4), 38.4 (C-7), 37.8 (C-10), 37.5 (NMe), 34.9 (C-2"), 30.1 (C-4'), 27.0 (C-6 Me), 21.5 (C-5' Me), 21.3 (C-3" Me), 21.0 (C-14), 18.7 (C-5" Me/C-8 Me), 16.2 (C-2 Me/C-12 Me), 12.0 (C-10 Me), 10.6 (C-15), 9.1 (C-4 Me); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (H-13), 4.96 (H-1"), 4.48 (H-1'), 3.41 (3"-OMe), 2.38 (NMe); MS (ESI, *m/z*): 1465.9 [M+H$^+$]. Anal. Calcd. for $C_{74}H_{132}N_2O_{26}$: C, 60.63; H, 9.08; N, 1.91. Found: C, 60.65; H, 8.99; N, 1.90.



3b

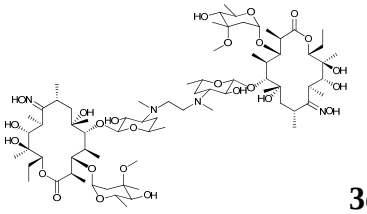
White solid, yield 55%, mp 186–188°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.0 (C-9), 175.8 (C-1), 102.7 (C-1'), 96.0 (C-1"), 80.6 (C-5), 78.3 (C-3/C-6), 77.9 (C-4"), 76.8 (C-13), 74.2 (C-12), 72.6 (C-3"), 71.0 (C-2'), 69.0 (C-11), 68.6 (C-5'), 65.6 (C-5"), 65.4 (C-3'), 51.0 (NCH_2), 50.6 (6-OMe), 49.5 (3"-OMe), 45.2 (C-2), 45.0 (C-8), 39.3 (C-7), 39.2 (C-4), 37.6 (C-10), 37.1 (NMe), 34.8 (C-2"), 30.0 (C-4'), 21.4 (C-5' Me/C-3" Me), 20.9 (C-14), 19.7 (C-6 Me), 18.7 (C-5" Me), 18.0 (C-8 Me), 15.9 (C-2 Me/C-12 Me), 12.3 (C-10 Me), 10.5 (C-15), 9.0 (C-4 Me); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (H-13), 4.94 (H-1"), 4.42 (H-1'), 3.37 (3"-OMe), 3.06 (6-OMe), 2.30 (NMe); MS (ESI, *m/z*): 1494.0 [M+H$^+$]. Anal. Calcd. for $C_{76}H_{136}N_2O_{26}$: C, 61.10; H, 9.18; N, 1.88. Found: C, 61.05; H, 9.13; N, 1.88.



3c

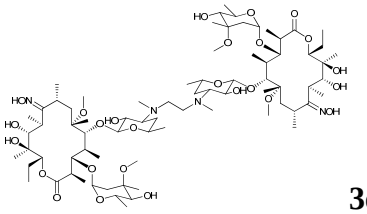
White solid, yield 76%, mp 168–172°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8 (C-1), 102.7 (C-1'), 96.2 (C-1"), 82.8 (C-5), 79.6 (C-3), 77.2 (C-4"), 76.7 (C-9), 76.3 (C-13), 74.7 (C-12), 74.2 (C-6), 72.5 (C-3"), 70.4 (C-2'), 68.8 (C-11), 68.7 (C-5'), 66.4 (C-5"), 65.3 (C-3'), 50.5 (NCH_2), 49.1 (3"-OMe), 45.5 (C-2), 41.7 (C-4), 36.9 (NMe), 36.8 (C-7), 34.7 (C-2"), 34.0 (C-8), 31.7 (C-10),

29.1/29.4 (C-4'), 25.1 (C-6 Me), 21.4 (C-5' Me), 21.2 (C-3" Me), 20.7 (C-14), 18.3 (C-8 Me), 18.2 (C-5" Me), 16.3 (C-12 Me), 14.8 (C-2 Me), 11.7 (C-10 Me), 10.9 (C-15), 9.2 (C-4 Me); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (H-13), 4.91 (H-1"), 4.56 (H-1'), 3.33 (3"-OMe), 2.36 (NMe); MS (ESI, *m/z*): 1470.1 [M+H$^+$]. Anal. Calcd. for $C_{74}H_{136}N_2O_{26}$: C, 60.47; H, 9.33; N, 1.91. Found: C, 60.38; H, 9.26; N, 1.85.



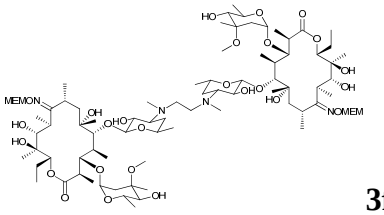
3d

White solid, yield 62%, mp 179–182^{o}C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (C-1), 169.3 (C-9), 101.9 (C-1'), 95.7 (C-1"), 82.5 (C-5), 79.3 (C-3), 78.5 (C-4"), 77.4 (C-13), 76.1 (C-6), 74.4 (C-12), 72.7 (C-3"), 70.4 (C-2'), 70.2 (C-11), 69.9 (C-5'), 66.9 (C-3'), 65.0/64.2 (C-5"), 52.2 (NCH_2), 49.0 (3"-OMe), 44.3 (C-2), 41.4 (C-4), 37.6 (C-7), 37.3 (NMe), 34.9 (C-2"), 31.2 (C-10), 29.1 (C-4'), 26.7 (C-6 Me), 25.2 (C-8), 21.4 (C-5' Me), 20.9 (C-3" Me), 21.0 (C-14), 18.8 (C-8 Me), 18.7 (C-5" Me), 17.2 (C-12 Me), 16.1 (C-2 Me), 14.7 (C-10 Me), 11.1/10.6 (C-15), 9.3/8.8 (C-4 Me); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.18/5.06 (H-13), 4.88/4.79 (H-1"), 4.27/4.24 (H-1'), 2.10 (NMe); MS (ESI, *m/z*): 1496.3 [M+H$^+$]. Anal. Calcd. for $C_{74}H_{134}N_4O_{26}$: C, 60.47; H, 9.33; N, 1.91. Found: C, 60.38; H, 9.26; N, 1.85.



3e

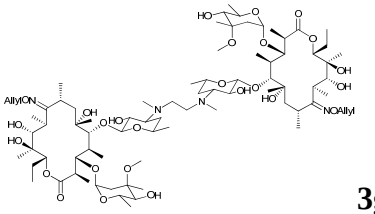
White solid, yield 70%, mp 188–190^{o}C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6 (C-1), 169.7 (C-9), 102.6 (C-1'), 95.9 (C-1"), 81.0 (C-5), 78.6 (C-3), 78.2 (C-4"), 77.4 (C-13), 76.6 (C-6), 74.0 (C-12), 72.6 (C-3"), 71.1 (C-2'), 70.1 (C-11), 68.3 (C-5'), 65.5 (C-3'), 65.2 (C-5"), 51.1 (NCH_2), 51.0 (6-OMe), 49.4 (3"-OMe), 45.0 (C-2), 40.6 (C-4), 37.6 (C-7), 37.5 (NMe), 33.4 (C-2"), 31.3 (C-10), 28.9 (C-4'), 25.7 (C-8), 21.4 (C-5' Me), 21.3 (C-3" Me), 21.1 (C-14), 19.9 (C-6 Me), 18.6 (C-5" Me), 18.5 (C-8 Me), 16.0 (C-2 Me), 15.9 (C-12 Me), 14.9 (C-10 Me), 10.5 (C-15), 9.1/8.6 (C-4 Me); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (H-13), 4.95 (H-1"), 4.44 (H-1'), 3.34 (3"-OMe), 3.12 (6-OMe), 2.35 (NMe); MS (ESI, *m/z*): 1524.2 [M+H$^+$]. Anal. Calcd. for $C_{76}H_{138}N_4O_{26}$: C, 59.90; H, 9.13; N, 3.68. Found: C, 59.81; H, 9.16; N, 3.73.



3f

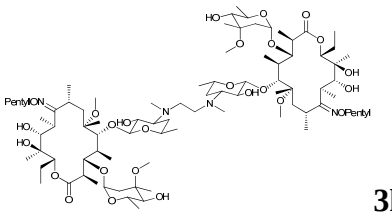
White solid, yield 77%, mp 132–134^{o}C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2 (C-1), 172.7 (C-9), 103.0 (C-1'), 96.1 (C-1"), 83.6 (C-5), 80.0 (C-3), 78.0 (C-4"), 76.8 (C-13), 74.8 (C-6), 74.2 (C-12), 72.7 (C-3"), 71.1 (C-2'), 70.3 (C-11), 68.7 (C-5'), 65.4 (C-3'), 65.2 (C-5"), 51.2 (NCH_2), 49.5 (3"-OMe), 44.7 (C-2), 39.0 (C-4), 37.5 (C-7/NMe), 35.0 (C-2"), 33.0 (C-10), 30.3 (C-4'), 26.9 (C-6 Me), 26.8 (C-8), 21.5 (C-5' Me), 21.4 (C-14), 21.0 (C-3" Me), 18.7 (C-8 Me), 18.6 (C-5" Me), 16.3

(C-12 Me), 16.1 (C-2 Me), 14.7 (C-10 Me), 10.6 (C-15), 9.2 (C-4 Me), 97.4, 71.8, 68.3, 59.0 ($OCH_2OCH_2CH_2OCH_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (H-13), 4.88 (H-1"), 4.40/4.38 (H-1'), 3.32 (3"-OMe), 2.30 (NMe), 5.18, 3.74, 3.56, 3.42 ($OCH_2OCH_2CH_2OCH_3$); MS (ESI, *m/z*): 1672.0 [M+H$^+$]. Anal. Calcd. for $C_{82}H_{150}N_4O_{30}$: C, 58.90; H, 9.04; N, 3.35. Found: C, 58.88; H, 9.01; N, 3.32.



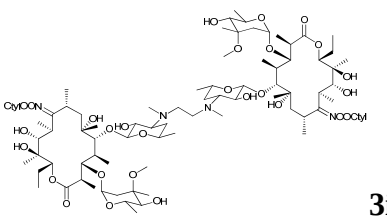
3g

White solid, yield 59%, mp 136–139°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1 (C-1), 171.7 (C-9), 102.8 (C-1'), 96.4 (C-1"), 83.5 (C-5), 80.2 (C-3), 77.9 (C-4"), 75.4 (C-13), 74.8 (C-6), 74.3 (C-12), 72.8 (C-3"), 71.0 (C-2'), 70.6 (C-11), 68.3 (C-5'), 65.7 (C-3'), 65.4 (C-5"), 51.1 (NCH_2), 49.6 (3"-OMe), 44.7 (C-2), 39.0 (C-4), 37.8 (C-7), 37.3 (NMe), 35.2 (C-2"), 33.0 (C-10), 29.4 (C-4'), 27.0 (C-6 Me), 26.5 (C-8), 22.7 (C-3" Me), 21.5 (C-5' Me), 21.2 (C-14), 18.7 (C-8 Me/C-5" Me), 16.3 (C-12 Me), 16.1 (C-2 Me), 14.5/14.1 (C-10 Me), 10.7 (C-15), 9.5 (C-4 Me), 77.2, 133.8, 118.1 ($OCH_2CH{=}CH_2$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (H-13), 4.90 (H-1"), 4.51 (H-1'), 3.33 (3"-OMe), 2.52 (NMe), 5.93, 5.25, 4.52 ($OCH_2CH{=}CH_2$); MS (ESI, *m/z*): 1576.1 [M+H$^+$], 1610.5 [M+Cl$^-$]. Anal. Calcd. for $C_{80}H_{142}N_4O_{26}$: C, 60.97; H, 9.08; N, 3.56. Found: C, 60.91; H, 9.10; N, 3.53.



3h

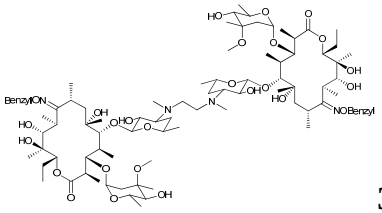
White solid, yield 69%, mp 205–208°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6 (C-1), 169.2 (C-9), 102.7 (C-1'), 96.0 (C-1"), 80.4 (C-5), 78.6 (C-3), 78.4 (C-4"), 77.2 (C-13), 76.8 (C-6), 73.9 (C-12), 72.7 (C-3"), 71.1 (C-2'), 70.0 (C-11), 68.4 (C-5'), 65.6 (C-3'), 65.4 (C-5"), 51.1 (NCH_2), 50.8 (6-OMe), 49.5 (3"-OMe), 45.1 (C-2), 39.1 (C-4), 37.6 (C-7), 37.4 (NMe), 34.9 (C-2"), 32.7 (C-10), 28.6 (C-4'), 26.2 (C-8), 22.5 (C-3" Me), 21.5 (C-5' Me), 21.2 (C-14), 19.9 (C-6 Me), 18.8 (C-5" Me), 18.6 (C-8 Me), 16.0 (C-2 Me), 15.9 (C-12 Me), 14.0 (C-10 Me), 10.6 (C-15), 9.2 (C-4 Me), 78.0, 30.3, 29.7, 28.2, 15.2 (OPentyl); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (H-13), 4.93 (H-1"), 4.22 (H-1'), 3.33 (3"-OMe), 3.07 (6-OMe), 2.34 (NMe); MS (ESI, *m/z*): 1664.3 [M+H$^+$], 1697.9 [M+Cl$^-$]. Anal. Calcd. for $C_{86}H_{158}N_4O_{26}$: C, 62.07; H, 9.57; N, 3.37. Found: C, 62.01; H, 9.49; N, 3.34.



3i

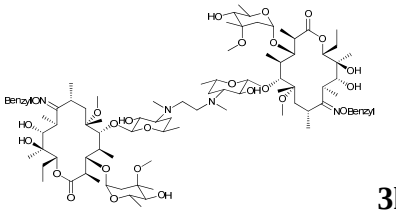
White solid, yield 56%, mp 192–196°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0 (C-1), 169.4 (C-9), 101.7 (C-1'), 95.4 (C-1"), 83.1 (C-5), 80.0 (C-3), 77.3 (C-4"), 76.0 (C-13), 74.2 (C-6), 74.0 (C-12), 72.9 (C-3"), 72.7 (C-2'), 69.8 (C-11), 69.7 (C-5'), 65.0 (C-3'), 64.6 (C-5"), 51.2 (NCH_2), 49.0 (3"-OMe), 44.5 (C-2), 39.3 (C-4), 37.3 (C-7), 37.1 (NMe), 34.9 (C-2"), 31.3 (C-10), 29.0 (C-4'),

26.2 (C-6 Me), 25.7 (C-8), 22.2 (C-3" Me), 21.2 (C-5' Me), 21.0 (C-14), 18.9 (C-8 Me), 18.6 (C-5" Me), 17.1 (C-12 Me), 15.9 (C-2 Me), 14.9 (C-10 Me), 10.7 (C-15), 9.3 (C-4 Me), 78.2, 29.0, 28.8, 28.6, 26.0, 14.0 (OOctyl); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (H-13), 4.75 (H-1"), 4.33 (H-1'), 3.22 (3"-OMe), 2.48 (NMe), 3.42 (OOctyl); MS (ESI, *m/z*): 1742.4 [M+Na^+]. Anal. Calcd. for $C_{90}H_{166}N_4O_{26}$: C, 62.84; H, 9.73; N, 3.26. Found: C, 62.83; H, 9.71; N, 3.22.



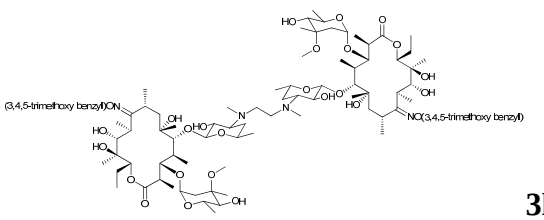
3j

White solid, yield 72%, mp 128–131°C; ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.2 (C-1), 172.5 (C-9), 102.9 (C-1'), 96.2 (C-1"), 83.1 (C-5), 80.0 (C-3), 78.0 (C-4"), 76.0 (C-13), 74.7 (C-6), 74.2 (C-12), 72.7 (C-3"), 71.0 (C-2'), 70.4 (C-11), 68.7 (C-5'), 65.4 (C-3'), 65.3 (C-5"), 51.1 (NCH_2), 49.5 (3"-OMe), 44.7 (C-2), 39.1 (C-4), 37.7 (C-7), 37.5 (NMe), 35.0 (C-2"), 33.0 (C-10), 29.7 (C-4'), 26.9 (C-8), 26.6 (C-6 Me), 21.5 (C-3" Me), 21.4 (C-5' Me), 21.1 (C-14), 18.6 (C-8 Me), 18.5 (C-5" Me), 16.3 (C-12 Me), 16.1 (C-2 Me), 14.5 (C-10 Me), 10.6 (C-15), 9.2 (C-4 Me), 137.3, 128.5, 128.2, 128.0, 75.2 (OBenzyl); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.14 (H-13), 4.91 (H-1"), 4.39 (H-1'), 3.32 (3"-OMe), 2.31 (NMe), 7.32-7.37, 5.06 (OBenzyl); MS (ESI, *m/z*): 1675.8 [M+H^+]. Anal. Calcd. for $C_{88}H_{146}N_4O_{26}$: C, 63.06; H, 8.78; N, 3.34. Found: C, 63.09; H, 8.75; N, 3.30.



3k

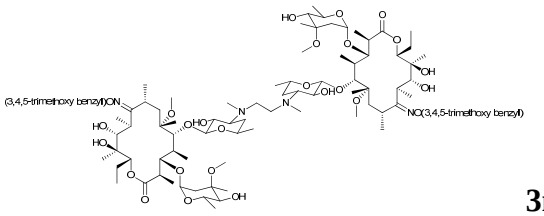
White solid, yield 77%, mp 145–149°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7 (C-1), 162.6 (C-9), 102.6 (C-1'), 96.1 (C-1"), 81.0 (C-5), 78.8 (C-3), 78.6 (C-4"), 77.9 (C-13), 76.1 (C-6), 74.5 (C-12), 72.8 (C-3"), 71.1 (C-2'), 70.0 (C-11), 68.4 (C-5'), 65.8 (C-3'), 65.3 (C-5"), 51.4 (NCH_2), 50.8 (6-OMe), 49.9/49.6 (3"-OMe), 45.1 (C-2), 39.2 (C-4), 37.6 (C-7), 37.3 (NMe), 35.0 (C-2"), 31.9 (C-10), 29.7 (C-4'), 29.4 (C-8), 21.5 (C-3" Me), 21.3 (C-5' Me), 20.8 (C-14), 19.8 (C-6 Me), 18.9 (C-5" Me), 18.7 (C-8 Me), 16.1 (C-2 Me), 15.9 (C-12 Me), 14.2/14.1 (C-10 Me), 10.6 (C-15), 9.4 (C-4 Me), 129.0, 128.5, 128.4, 128.2, 128.1, 127.8, 77.5 (OBenzyl); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.09 (H-13), 4.92 (H-1"), 4.47 (H-1'), 3.33 (3"-OMe), 3.05 (6-OMe), 2.47 (NMe), 7.31-7.38, 5.02 (OBenzyl); MS (ESI, *m/z*): 1703.8 [M+H^+]. Anal. Calcd. for $C_{90}H_{150}N_4O_{26}$: C, 63.43; H, 8.87; N, 3.29. Found: C, 63.37; H, 8.80; N, 3.25.



3l

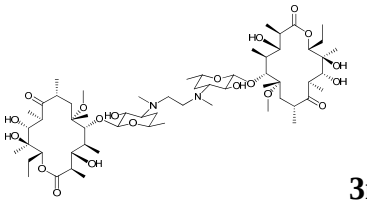
White solid, yield 63%, mp 127–130°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (C-1), 171.7 (C-9), 102.5 (C-1'), 95.8 (C-1"), 82.6 (C-5), 79.3 (C-3), 77.8 (C-4"), 77.6 (C-13), 75.0 (C-6), 73.8 (C-12), 72.3 (C-3"), 70.6 (C-2'), 70.0 (C-11), 68.2 (C-5'), 65.0 (C-3'), 64.8 (C-5"), 50.6 (NCH_2), 49.1 (3"-OMe), 44.3 (C-2), 38.7 (C-4), 37.2 (C-7), 37.1 (NMe), 36.1 (C-2"), 32.6 (C-10), 29.3 (C-4'),

26.7 (C-8), 26.2 (C-6 Me), 21.1 (C-3" Me), 21.0 (C-5' Me), 20.7 (C-14), 18.3 (C-8 Me), 18.2 (C-5" Me), 15.9 (C-12 Me), 15.7 (C-2 Me), 14.2 (C-10 Me), 10.2 (C-15), 8.8 (C-4 Me), 152.9, 137.3, 132.5, 104.7, 75.8, 60.5, 55.7 [O(3,4,5- trimethoxy benzyl)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (H-13), 4.94 (H-1"), 4.31 (H-1'), 3.28 (3"-OMe), 2.34 (NMe), 6.51, 5.04, 3.82, 3.81 [O(3,4,5-trimethoxy benzyl)]; MS (ESI, *m/z*): 1856.0 [M+H$^+$]. Anal. Calcd. for $C_{94}H_{158}N_4O_{32}$: C, 60.82; H, 8.58; N, 3.02. Found: C, 60.73; H, 8.55; N, 3.06.



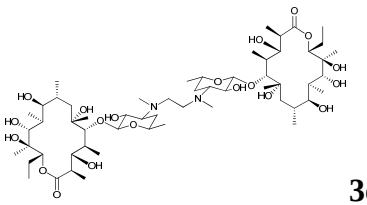
3m

White solid, yield 74%, mp 149–151^{o}C; ^{13}C NMR (75 MHz, $CDCl_3$): ^{13}C NMR (75 MHz, CDCl3): δ 175.6 (C-1), 170.5 (C-9), 102.9 (C-1'), 96.1 (C-1"), 81.1 (C-5), 78.7 (C-3), 78.5 (C-4"), 77.4 (C-13), 76.8 (C-6), 74.0 (C-12), 72.8 (C-3"), 71.0 (C-2'), 70.0 (C-11), 68.4 (C-5'), 65.4 (C-3'/C-5"), 50.8 (6-OMe), 49.5 (3"-OMe), 45.1 (C-2), 39.1 (C-4), 37.5 (C-7/NMe), 34.9 (C-2"), 33.0 (C-10), 29.7 (C-4'), 26.6 (C-8), 20.1 (C-6 Me), 21.5 (C-3" Me), 21.3 (C-5' Me), 21.2 (C-14), 18.7 (C-8 Me), 18.6 (C-5" Me), 16.0 (C-2 Me), 15.3 (C-12 Me), 14.2 (C-10 Me), 10.7 (C-15), 9.3 (C-4 Me), 153.2, 137.5, 133.5, 105.0, 76.0, 60.9, 56.0 [O(3,4,5- trimethoxy benzyl)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (H-13), 4.93 (H-1"), 4.49 (H-1'), 3.35 (3"-OMe), 3.09 (6-OMe), 2.34 (NMe), 6.59, 4.98, 3.86, 3.77 [O(3,4,5-trimethoxy benzyl)]; MS (ESI, *m/z*): 1884.8 [M+H$^+$]. Anal. Calcd. for $C_{96}H_{162}N_4O_{32}$: C, 61.19; H, 8.67; N, 2.97. Found: C, 61.08; H, 8.72; N, 2.95.



3n

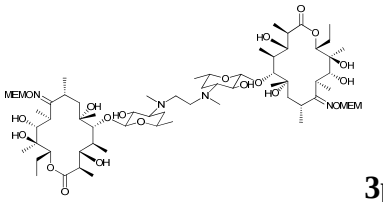
White solid, yield 80%, mp 174–177^{o}C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.6 (C-9), 174.9 (C-1), 106.1 (C-1'), 88.3 (C-5), 78.8 (C-3), 77.9 (C-6), 76.6 (C-13), 74.1 (C-12), 71.2 (C-2'), 69.7 (C-11), 69.4 (C-5'), 64.8 (C-3'), 50.6 (NCH_2), 49.5 (6-OMe), 45.5 (C-2), 44.5 (C-8), 38.7 (C-7), 37.5 (C-10/NMe), 35.7, (C-4), 30.9 (C-4'), 21.4 (C-5' Me), 21.1 (C-14), 18.8 (C-6 Me), 17.7 (C-8 Me), 16.1 (C-12 Me), 15.3 (C-2 Me), 12.6 (C-10 Me), 10.4 (C-15), 8.3 (C-4 Me); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.15 (H-13), 4.40 (H-1'), 2.95 (6-OMe), 2.30 (NMe); MS (ESI, *m/z*): 1177.7 [M+H$^+$], 1212.2 [M+Cl$^-$]. Anal. Calcd. for $C_{60}H_{108}N_2O_{20}$: C, 61.20; H, 9.24; N, 2.38. Found: C, 61.13; H, 9.18; N, 2.37.



3o

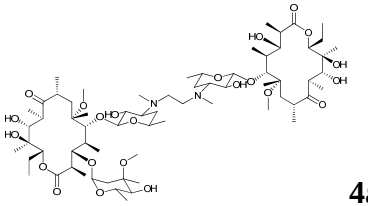
White solid, yield 75%, mp 167–169^{o}C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6 (C-1), 104.8 (C-1'), 83.4 (C-5), 79.1 (C-3), 78.5 (C-13), 77.2 (C-9), 74.9 (C-12), 74.6 (C-6), 70.4 (C-2'), 69.9 (C-11), 69.8 (C-5'), 64.7 (C-3'), 53.6 (NCH_2), 44.3 (C-2), 41.9/40.9 (C-4), 37.7 (NMe), 36.5 (C-7), 34.3 (C-8), 32.0 (C-10), 29.6 (C-4'), 28.1 (C-6 Me), 20.8 (C-5' Me/C-14), 17.1 (C-8 Me), 15.7 (C-12 Me), 15.5 (C-2 Me), 12.6/12.0 (C-10 Me), 11.0 (C-15), 6.6 (C-4 Me); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.68 (H-13), 4.50 (H-1'), 2.46 (NMe); MS (ESI, *m/z*): 1154.0 [M+H$^+$], 1175.9 [M+Na$^+$]. Anal.

Calcd. for $C_{58}H_{108}N_2O_{20}$: C, 60.39; H, 9.44; N, 2.43. Found: C, 60.32; H, 9.39; N, 2.46.



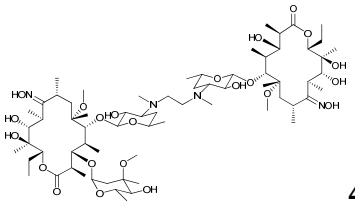
3p

White solid, yield 70%, mp 113–115°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (C-1), 171.9 (C-9), 105.5 (C-1'), 92.1 (C-5), 78.7 (C-3), 76.9 (C-13), 73.9 (C-6), 74.0 (C-12), 70.7 (C-2'), 70.5 (C-11), 69.1 (C-5'), 64.1 (C-3'), 50.2 (NCH_2), 44.1 (C-2), 36.6 (C-7), 36.2 (C-4), 37.2 (NMe), 33.1 (C-10), 31.1 (C-4'), 26.7 (C-8), 25.4 (C-6 Me), 21.2 (C-5' Me), 20.7 (C-14), 17.9 (C-8 Me), 16.1 (C-12 Me), 15.1 (C-2 Me), 14.5 (C-10 Me), 10.2 (C-15), 7.8 (C-4 Me), 97.2, 71.4, 68.1, 58.7 ($OCH_2OCH_2CH_2OCH_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (H-13), 4.20 (H-1'), 2.30 (NMe), 5.10, 3.67, 3.47, 3.31 ($OCH_2OCH_2CH_2OCH_3$); MS (ESI, *m/z*): 1356.2 [M+H$^+$], 1378.1 [M+Na$^+$]. Anal. Calcd. for $C_{66}H_{122}N_4O_{24}$: C, 58.47; H, 9.07; N, 4.13. Found: C, 58.43; H, 9.12; N, 4.10.



4a

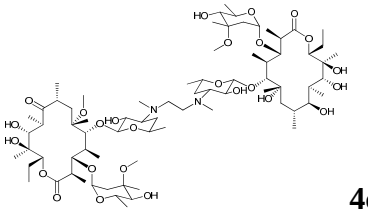
1-bromo-2-chloroethane (0.25 mL, 3.0 mmol) was added to a solution of compound **5b** (0.11 g, 0.15 mmol), compound **5d** (0.09 g, 0.15 mmol) and *N*,*N*-diisopropylethylamine (0.50 mL, 3.0 mmol) in anhydrous DMF (10.0 mL). The reaction mixture was stirred at room temperature for 120 h. The mixture was poured into water and extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography with chloroform-methanol-ammonium hydroxide solution (20:1:0.1) to yield **4a** (0.05 g, 24%) as a white solid. M.p. 176-178°C. ^{13}C NMR (150 MHz, $CDCl_3$): δ 220.6/220.5 (C-9), 175.5/174.9 (C-1), 101.8 (C-1'), 96.4 (C-1"), 82.3 (C-5), 79.0/78.7 (C-3), 78.2/77.8 (C-6), 77.6 (C-4"), 76.6 (C-13), 74.2 (C-12), 73.0 (C-3"), 71.4/70.5 (C-2'), 69.9 (C-11), 69.1 (C-5'), 67.3 (C-3'), 66.5 (C-5"), 50.6 (NCH_2), 49.4 (6-OMe), 49.3 (3"-OMe), 45.7/45.1 (C-2), 45.0/44.7 (C-8), 39.2/38.8 (C-7), 39.1/35.4 (C-4), 37.6 (C-10), 37.4 (NMe), 35.2 (C-2"), 31.9/30.9 (C-4'), 21.6 (C-3" Me), 21.5 (C-5' Me), 21.0/20.9 (C-14), 19.9/18.9 (C-6 Me), 18.4 (C-5" Me), 18.0/17.7 (C-8 Me), 16.2/16.0 (C-12 Me), 15.3/14.1 (C-2 Me), 12.7/12.3 (C-10 Me), 10.6/10.4 (C-15), 9.7/8.4 (C-4 Me); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.18/5.06 (H-13), 4.91 (H-1"), 4.53 (H-1'), 3.32 (3"-OMe), 3.03/2.96 (6-OMe), 2.35 (NMe); MS (ESI, *m/z*): 1336.0 [M+H$^+$], 1369.7 [M+Cl$^-$]. Anal. Calcd. for $C_{68}H_{122}N_2O_{23}$: C, 61.15; H, 9.21; N, 2.10. Found: C, 61.15; H, 9.24; N, 2.03.



4b

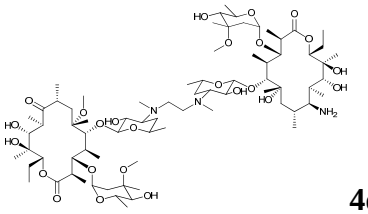
White solid, yield 22%, mp 166–168°C; ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.7/175.2 (C-1), 170.4 (C-9), 106.5/103.2 (C-1'), 96.3 (C-1"), 87.9/81.3 (C-5), 78.8/78.6 (C-3), 78.5 (C-4"), 78.2 (C-13), 76.8 (C-6), 74.1 (C-12), 72.8 (C-3"), 71.7/71.5 (C-2'), 70.2/70.0 (C-11), 68.6 (C-5'), 65.4/65.3 (C-3'), 65.2 (C-5"), 51.2 (NCH_2), 50.7/49.9 (6-OMe), 49.7/49.5 (3"-OMe), 45.2/44.4 (C-2), 39.1/36.1 (C-4), 37.8/37.3 (C-7), 37.4 (NMe), 35.0 (C-2"), 31.9/31.1 (C-10), 29.8/29.3 (C-4'), 25.3 (C-8), 22.0/21.5 (C-5' Me), 21.3 (C-3" Me), 21.2/21.1 (C-14), 19.9/18.6 (C-6 Me), 18.7 (C-5" Me), 18.6/18.3 (C-8

Me), 16.3/16.0 (C-12 Me), 15.3/15.1 (C-2 Me), 14.9/14.1 (C-10 Me), 10.6/10.5 (C-15), 9.3/8.3 (C-4 Me); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.22/5.10 (H-13), 4.92 (H-1"), 4.39 (H-1'), 3.32 (3"-OMe), 3.10/2.99 (6-OMe), 2.32/2.30 (NMe); MS (ESI, *m/z*): 1365.8 [$M+H^+$], 1363.0 [$M-H^+$], 1399.5 [$M+Cl^-$]. Anal. Calcd. for $C_{68}H_{124}N_4O_{23}$: C, 59.80; H, 9.15; N, 4.10. Found: C, 59.84; H, 9.13; N, 4.05.



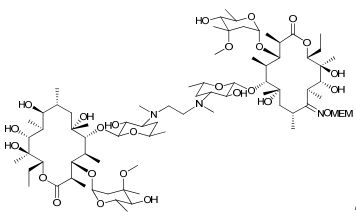
4c

White solid, yield 18%, mp 111–114°C; ^{13}C NMR (150 MHz, $CDCl_3$): δ 220.9/76.6 (C-9), 177.0/175.9 (C-1), 103.1/102.7 (C-1'), 96.3/96.0 (C-1"), 83.1/80.7 (C-5), 79.2/78.4 (C-3), 77.9/74.2 (C-6), 77.7 (C-4"), 75.0 (C-13), 74.5 (C-12), 72.7 (C-3"), 70.8/70.7 (C-2'), 69.0 (C-11), 68.4 (C-5'), 66.2/ 65.6 (C-5"), 65.1/65.0 (C-3'), 51.1 (NCH_2), 50.6 (6-OMe), 49.5/49.3 (3"-OMe), 45.4/45.2 (C-2), 45.0/34.3 (C-8), 41.7/39.2 (C-4), 39.3/37.2 (C-7), 37.5/37.4 (NMe), 37.2/31.9 (C-10), 34.9 (C-2"), 30.9/29.6 (C-4'), 25.3/19.7 (C-6 Me), 21.5/21.4 (C-5' Me), 21.3/21.1 (C-3" Me), 21.0/20.0 (C-14), 18.7 (C-5" Me), 18.2/18.0 (C-8 Me), 16.5/15.9 (C-12 Me), 15.0/14.7 (C-2 Me), 12.3 (C-10 Me), 11.1/10.6 (C-15), 9.4/9.0 (C-4 Me); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.05/4.98 (H-13), 4.92 (H-1"), 4.53/4.43 (H-1'), 3.34/3.33 (3"-OMe), 3.04 (6-OMe), 2.37/2.36 (NMe); MS (ESI, *m/z*): 1482.0 [$M+H^+$]. Anal. Calcd. for $C_{75}H_{136}N_2O_{26}$: C, 60.79; H, 9.25; N, 1.89. Found: C, 60.68; H, 9.16; N, 1.84.



4d

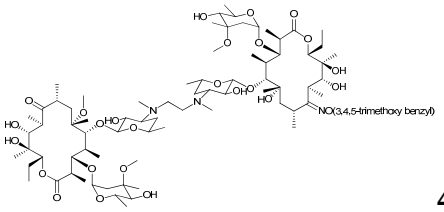
White solid, yield 26%, mp 137–139°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.9/62.7 (C-9), 177.0/175.8 (C-1), 102.7 (C-1'), 96.1 (C-1"), 83.3/80.7 (C-5), 78.3/77.9 (C-3), 77.9/75.6 (C-6), 77.7 (C-4"), 77.2/76.3 (C-13), 75.8/74.2 (C-12), 72.7/72.5 (C-3"), 70.9 (C-2'), 70.8/68.6 (C-11), 69.1/68.5 (C-5'), 65.7 (C-5"), 65.1 (C-3'), 51.1 (NCH_2), 50.6 (6-OMe), 49.5 (3"-OMe), 45.7/45.2 (C-2), 45.0/31.9 (C-8), 39.3/37.5 (C-7), 39.2 (C-4), 37.5/30.3 (C-10), 37.2 (NMe), 34.9 (C-2"), 29.3 (C-4'), 24.5/18.7 (C-6 Me), 21.7/21.0 (C-14), 21.5 (C-3" Me), 21.4/21.2 (C-5' Me), 19.7/17.1 (C-8 Me), 18.6/18.0 (C-5" Me), 16.2/12.3 (C-10 Me), 16.0/14.1 (C-2 Me), 15.7 (C-12 Me), 10.8/10.6 (C-15), 9.4/9.1 (C-4 Me); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.97 (H-13), 4.89 (H-1"), 4.36 (H-1'), 3.26 (3"-OMe), 2.96 (6-OMe), 2.32 (NMe); MS (ESI, *m/z*): 741.0 [$M/2+H^+$], 1480.7 [$M+H^+$], 1515.5 [$M+Cl^-$]. Anal. Calcd. for $C_{75}H_{137}N_3O_{25}$: C, 60.83; H, 9.32; N, 2.84. Found: C, 60.77; H, 9.31; N, 2.85.



4e

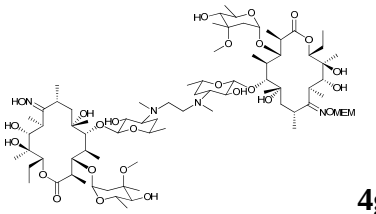
White solid, yield 24%, mp 142–146°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0/175.2 (C-1),

172.7/76.8 (C-9), 102.9 (C-1'), 96.0 (C-1"), 83.7/83.1 (C-5), 79.9/79.0 (C-3), 78.0/77.7 (C-4"), 77.2 (C-13), 75.0/74.7 (C-6), 74.6/74.2 (C-12), 72.6 (C-3"), 71.1/70.8 (C-2'), 70.3/69.1 (C-11), 68.6 (C-5'), 66.0/65.1 (C-5"), 65.3 (C-3'), 51.3/51.0 (NCH_2), 49.5/49.3 (3"-OMe), 45.3/44.7 (C-2), 41.8/38.9 (C-4), 37.5/36.8 (C-7), 37.4 (NMe), 34.8 (C-2"), 34.2/26.8 (C-8), 33.0/31.9 (C-10), 30.5/30.3 (C-4'), 26.9/25.3 (C-6 Me), 21.7/21.5 (C-5' Me), 21.3 (C-14), 21.1 (C-3" Me), 18.7 (C-8 Me), 18.6/18.2 (C-5" Me), 16.5 (C-12 Me), 16.0/14.7 (C-2 Me), 14.6/11.1 (C-10 Me), 10.6 (C-15), 9.4/9.1 (C-4 Me), 97.4, 71.8, 68.3, 59.0 ($OCH_2OCH_2CH_2OCH_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10/5.00 (H-13), 4.91/4.89 (H-1"), 4.52/4.39 (H-1'), 3.33 (3"-OMe), 2.30 (NMe), 5.18, 3.74, 3.56, 3.42 ($OCH_2OCH_2CH_2OCH_3$); MS (ESI, *m/z*): 1571.1 [$M+H^+$], 1569.1 [$M-H^+$]. Anal. Calcd. for $C_{78}H_{143}N_3O_{28}$: C, 59.63; H, 9.17; N, 2.67. Found: C, 59.55; H, 9.07; N, 2.64.



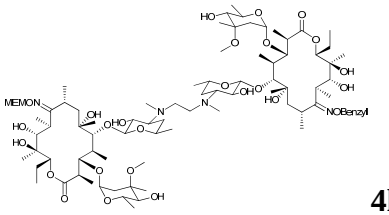
4f

White solid, yield 21%, mp 151–154°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.9/172.1 (C-9), 175.8/175.0 (C-1), 102.7 (C-1'), 96.1 (C-1"), 82.6/80.1 (C-5), 79.4/78.5 (C-3), 78.3/74.2 (C-6), 77.8 (C-4"), 77.2/76.8 (C-13), 74.2 (C-12), 72.7 (C-3"), 70.8 (C-2'), 70.5 (C-11), 69.0 (C-5'), 65.4 (C-3'), 65.2 (C-5"), 50.9 (NCH_2), 50.6 (6-OMe), 49.5 (3"-OMe), 45.2/44.6 (C-2), 45.0/27.1 (C-8), 39.2/37.3 (C-7), 39.1/38.9 (C-4), 37.6/33.0 (C-10), 37.2 (NMe), 35.0/34.8 (C-2"), 30.9/29.6 (C-4'), 26.5/19.8 (C-6 Me), 21.4/21.1 (C-3" Me), 21.3/21.0 (C-5' Me), 20.9 (C-14), 18.6 (C-5" Me), 18.5/18.0 (C-8 Me), 16.2/16.1 (C-12 Me), 15.9 (C-2 Me), 14.5/12.3 (C-10 Me), 10.6 (C-15), 9.7 (C-4 Me), 153.2, 137.6, 132.8, 105.0, 75.3, 60.8, 56.0 [O(3,4,5- trimethoxy benzyl)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10/5.06 (H-13), 4.91/4.86 (H-1"), 4.43/4.32 (H-1'), 3.34/3.32 (3"-OMe), 3.03 (6-OMe), 2.37/2.32 (NMe), 6.55, 4.98, 3.87, 3.86 [O(3,4,5-trimethoxy benzyl)]; MS (ESI, *m/z*): 1675.0 [$M+H^+$], 1709.2 [$M+Cl^-$]. Anal. Calcd. for $C_{85}H_{147}N_3O_{29}$: C, 60.95; H, 8.85; N, 2.51. Found: C, 60.92; H,8.87; N, 2.48.



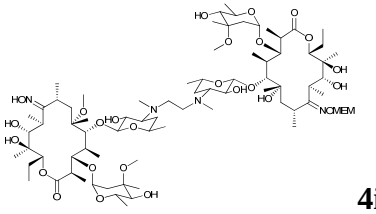
4g

White solid, yield 22%, mp 147–150°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6/175.2 (C-1), 172.7/171.2 (C-9), 103.0 (C-1'), 96.2 (C-1"), 83.8/83.2 (C-5), 80.1 (C-3), 78.0 (C-4"), 77.2/76.8 (C-13), 75.3/74.8 (C-6), 74.4/74.2 (C-12), 72.7 (C-3"), 71.1 (C-2'), 70.3 (C-11), 68.5 (C-5'), 65.3 (C-3'/C-5"), 50.9 (NCH_2), 49.5 (3"-OMe), 44.7 (C-2), 38.9 (C-4), 37.6 (C-7), 37.4 (NMe), 35.0 (C-2"), 33.0/32.6 (C-10), 30.5/29.3 (C-4'), 27.0 (C-6 Me), 26.8/25.4 (C-8), 21.5 (C-5' Me), 21.3/21.1 (C-14), 21.0 (C-3" Me), 18.6 (C-5" Me), 18.5 (C-8 Me), 16.4/16.3 (C-12 Me), 16.1 (C-2 Me), 14.7/14.3 (C-10 Me), 10.6 (C-15), 9.2 (C-4 Me), 97.4, 71.8, 68.3, 59.1 ($OCH_2OCH_2CH_2OCH_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10/5.06 (H-13), 4.88 (H-1"), 4.40 (H-1'), 3.32 (3"-OMe), 2.36 (NMe), 5.18, 3.77, 3.57, 3.42 ($OCH_2OCH_2CH_2OCH_3$); MS (ESI, *m/z*): 1584.1 [$M+H^+$], 1606.1 [$M+Na^+$]. Anal. Calcd. for $C_{78}H_{142}N_4O_{28}$: C, 59.14; H, 9.04; N, 3.54. Found: C, 59.10; H, 9.06; N, 3.49.



4h

White solid, yield 19%, mp 126–129°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2 (C-1), 172.7/172.2 (C-9), 102.9 (C-1'), 96.1 (C-1"), 83.3 (C-5), 80.0 (C-3), 78.0 (C-4"), 76.8/76.1 (C-13), 74.8 (C-12), 74.2 (C-6), 72.7 (C-3"), 71.0 (C-2'), 70.4 (C-11), 68.5 (C-5'), 65.4 (C-3'), 65.3 (C-5"), 51.0 (NCH_2), 49.5 (3"-OMe), 44.7 (C-2), 39.0 (C-4), 37.7 (C-7), 37.4 (NMe), 35.0 (C-2"), 33.0 (C-10), 31.9/29.3 (C-4'), 27.0/26.8 (C-8), 26.6 (C-6 Me), 21.5 (C-5' Me), 21.3 (C-3" Me), 21.1 (C-14), 18.6 (C-8 Me/C-5" Me), 16.3 (C-12 Me), 16.2 (C-2 Me), 14.7/14.5 (C-10 Me), 10.6 (C-15), 9.2 (C-4 Me), 137.3, 128.5, 128.2, 128.0, 75.2 (OBenzyl), 97.5, 71.8, 68.3, 59.1 ($OCH_2OCH_2CH_2OCH_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (H-13), 4.91/4.88 (H-1"), 4.38 (H-1'), 3.32 (3"-OMe), 2.34 (NMe), 7.31-7.37, 5.05 (OBenzyl), 5.18, 3.74, 3.56, 3.42 ($OCH_2OCH_2CH_2OCH_3$); MS (ESI, *m/z*): 837.1 [M/2+H$^+$]. Anal. Calcd. for $C_{85}H_{148}N_4O_{28}$: C, 60.98; H, 8.91; N, 3.35. Found: C, 60.94; H, 8.83; N, 3.29.



4i

White solid, yield 25%, mp 146–148°C; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7/175.1 (C-1), 172.7/170.5 (C-9), 103.0 (C-1'), 96.1 (C-1"), 83.8 (C-5), 80.1/78.7 (C-3), 78.4/78.0 (C-4"), 77.4/76.8 (C-13), 77.2/74.8 (C-6), 74.2/74.1 (C-12), 72.7 (C-3"), 71.1 (C-2'), 70.1 (C-11), 68.5 (C-5'), 65.6 (C-3'), 65.3 (C-5"), 51.2 (NCH_2), 51.0 (6-OMe), 49.5 (3"-OMe), 45.1/44.7 (C-2), 39.0 (C-4), 37.6 (C-7), 37.4 (NMe), 35.0/33.0 (C-2"), 32.8/31.9 (C-10), 30.6/29.3 (C-4'), 27.0/20.0 (C-6 Me), 26.8/25.4 (C-8), 21.5 (C-5' Me), 21.3 (C-3" Me), 21.1 (C-14), 18.7 (C-8 Me/C-5" Me), 16.3 (C-2 Me), 16.1 (C-12 Me), 14.9/14.7 (C-10 Me), 10.6 (C-15), 9.2 (C-4 Me), 97.5, 71.8, 68.3, 59.1 ($OCH_2OCH_2CH_2OCH_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (H-13), 4.93/4.87 (H-1"), 4.40 (H-1'), 3.32 (3"-OMe), 3.10 (6-OMe), 2.34 (NMe), 5.18, 3.74, 3.57, 3.42 ($OCH_2OCH_2CH_2OCH_3$); MS (ESI, *m/z*): 1598.2 [M+H$^+$], 1632.5 [M+Cl$^-$]. Anal. Calcd. for $C_{79}H_{144}N_4O_{28}$: C, 59.38; H, 9.08; N, 3.51. Found: C, 59.35; H, 9.01; N, 3.46.

Growth inhibition assay

The antiproliferative activity of the synthetic compounds was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Tumor cell lines were seeded in 96-well flat bottom plates (Corning, NY, USA) at a density of 8×10^3 per well. After 24 h of incubation in the RPIM-1640 (Sigma, St. Louis, MO) with 10% FBS (TBD, Tianjin, China), cells were treated with different concentrations (10, 3, 1, 0.3, 0.lμg/ml) of the new compounds for another 48h. Afterwards, MTT (Sigma, St. Louis, MO) solution (5.0 mg/ml in PBS) was added (20μl/well) and then plates were incubated for another 4 h at 37°C. The purple formazan crystals were dissolved in 100μl dimethyl sulfoxide (DMSO). After 5 min, the plates were read on a plate microreader (TECANSPECTRA, Wetzlar, Germanay) at 490 nm. The IC_{50} values were obtained

using the software of Dose–Effect Analysis with Microcomputers and were defined as concentration of drug causing 50% inhibition in absorbance compared with control cells. Assays were performed in triplicate in three independent experiments.

Cell-cycle analysis

HT-1080 cancer cells were dispensed in 25 ml culture bottle at a density of 5×10^5 per bottle. After 24 h incubation, they were treated with compound **3d** or compound **3e** at given concentrations for indicated time (24h or 48 h). The cells were harvested by 0.05% trypsin (Sigma, St. Louis, MO), then collected by centrifugation, washed with phosphate-buffered saline (PBS), and fixed with 10 ml ice-cold 70% ethanol at 20°C for 24 h, then after wash with PBS, the cells were suspended with 1ml propidium iodide PI solution including 50 mg/L PI (Sigma, St. Louis, MO) and 1g/L RNase A (Sigma, St. Louis, MO). Then the samples were analyzed by FACScan flowcytometer (Becton Dickinson, Franklin, NJ, USA).