Supplementary Material

for

Bipiperidine conjugates as soluble sugar surrogates in DNA-intercalating antiproliferative polyketides


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Instrumentation
All 1D ($^1$H, $^{13}$C, DEPT) and 2D NMR ($^1$H-$^1$H COSY, $^1$H-$^{13}$C HSQC, $^1$H-$^{13}$C HMBC) were recorded in deuterated solvents on a Bruker AVANCE II 300, a AVANCE III 500 or 600 MHz instrument equipped with a Bruker Cryo Platform. The chemical shifts are reported in ppm relative to the solvent residual peak ($\delta$ $^1$H (DMSO-$D_6$) = 2.50 ppm, $\delta$ $^{13}$C (DMSO-$D_6$) = 39.52 ppm, $\delta$ $^1$H (CD$_3$OD) = 3.31 ppm, $\delta$ $^{13}$C (CD$_3$OD) = 49.15 ppm, $\delta$ $^1$H (CD$_2$Cl$_2$) = 5.32 ppm, $\delta$ $^{13}$C (CD$_2$Cl$_2$) = 54.00 ppm, $\delta$ $^1$H (D$_3$CCN) = 1.94 ppm, $\delta$ $^{13}$C (D$_3$CCN) = 118.69 ppm). Following abbreviations are used for multiplicities of resonance signals: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, qt = quintet, m = multiplet. br broad. HR-ESI-MS measurements were conducted on either a Thermo Exactive or a Q-Exactive apparatus. Semi-preparative HPLC purification was achieved by using a Agilent 1260 device equipped with a quaternary Pump, a UV/Vis detector and a fraction collector (Column: Zorbax Eclipse XDB-C8, 5 µm, 250 x 9.4 mm, eluent: H$_2$O/0.1% HCOOH, MeOH). Preparative HPLC for the chartreusin derivatives was performed on a Gilson 321 Pump with a UV/VIS 156 detector system using a Phenomenex Kinetix C18 column 5 µm, Ø 21.2 mm x 250 mm at 21 mL/min with a gradienten from 10 to 83% acetonitrile in water containing 0.1% formic acid.

General methods
All reactions were carried out in standard glassware with magnetic stirrer. Syntheses requiring an inert reaction atmosphere were carried out under a positive stream of Argon applying the Schlenk technique. All solvents were dried and distilled under an inert atmosphere before being used. Anhydrous pyridine was purchased from Sigma-Aldrich. All other reagents were purchased from commercial available suppliers and used without further purification. Reaction progresses were monitored by thin layer chromatography (TLC) GC-MS or HPLC-MS. Analytical thin-layer chromatography for reaction monitoring was performed on pre-coated aluminum-backed silica gel plates (silica gel 60 F254, Merck KGaA, Darmstadt), visualized with an UV lamp (254 nm) or with a 4-anisaldehyde-solution (1 mL 4-anisaldehyde-solution in a mixture of 100 mL of methanol, acetic acid, sulfuric acid in a ratio of 85:10:5).

UV-Titration
A 1 mg/mL solution of chartreusin or its analogues in DMSO were diluted to 1 mL with PBS-buffer (pH 7.5) to a final concentration of 50 μmol/L in a fused quartz cuvette. Then a 10 mg/mL herring sperm DNA solution (GC content ≈43%, $M_{mid.}$ = 649.66 g/mol) in PBS buffer were added to give the ratios substrate :
DNA as 1:0, 1:0.5, 1:1, 1:2, 1:5, 1:10, 1:20, 1:30, 1:50 and 1:100. After each dilution step a UV-VIS spectrum between 300 and 500 nm was recorded.¹

**Determination of growth inhibition and cytotoxicity of HUVEC, K-562 and HeLa**

Compounds were assayed using human umbilical vein endothelial cells HUVEC (ATCC CRL-1730) and human chronic myeloid leukemia cells K-562 (DSM ACC 10) for their antiproliferative effects (GI₅₀) and using human cervix carcinoma cells HeLa (DSM ACC 57) for their cytotoxic effects (CC₅₀) as previously described.²

**Metabolomics analysis on K-562 cells**

A culture of K-562 (5 mL) was treated with 21 (10 mg / L in 10% aq. NH₄Cl solution) to a final concentration of 3.125 µg / mL. After 48 h of cultivation (conditions see above) 5 mL ethanol were added and the suspension was shaken for 1 h followed by evaporation to dryness. Then 200 µL of a 1:1 mixture of 10% aq. NH₄Cl solution and methanol were added followed by filtration through a 0.2 µm filter. The samples were analyzed using HPLC/HRMS.
Preparation and analytical data

Daunorubicin-10-1,4'-bipiperidine-1'-carboxylate (3)

A solution of daunorubicin aglycone (12 mg, 30 µmol, 1 eq. 4), 4-piperidinopiperidine-1-carbonyl chloride (15.6 mg, 68 µmol, 2.25 eq.) and DMAP (12.4 mg, 102 µmol, 3.38 eq.) in pyridine (2 mL) was stirred for 72 h at 45 °C under argon. Subsequently the pyridine was removed under reduced pressure and the remaining solid was dissolved in a mixture of MeOH/HCl (1 M in water, 200/1) and purified by preparative HPLC yielding compound 3 (9.5 mg, 16 µmol, 53%) as a red solid.

**1H NMR** (500 MHz, CD3OD): δ = 7.94 (d, 1H, J = 7.8 Hz, CH-aryl), 7.83 (t, 1H, J = 8.1 Hz, CH-aryl), 7.57 (d, 1H, J = 8.3 Hz, CH-aryl), 6.17 (m, 1H, CHOCON), 4.36 and 4.16 (m, 2H, CONC2H2), 4.02 (s, 3H, OC3H3), 3.47 and 3.00 (m, 4H, NC2H2), 3.37 (m, 1H, NC), 3.09 and 2.71 (m, 2H, CCH2C), 2.85 (m, 2H, CONCH2), 2.35 (s, 3H, COCH3), 2.31 and 2.22 (m, 2H, CCH2CH), 2.05, 1.76 and 1.50 (m, 4H, NCH2CH2), 2.00 and 1.76 (m, 4H, NCH2CH2), 1.85 and 1.51 (m, 2H, NCH2CH2) ppm. Spectrum: see Figure S1 on page S16.

**13C NMR** (150 MHz, CD3OD): δ = 214.3 (CH3CO), 188.5 (CO), 188.1 (CO), 162.6 (C-OH-aryl), 157.1 (NCO), 156.6 (C-OH-aryl), 156.2 (C-OH-aryl), 137.3 (CH-aryl), 136.5 (C-aryl), 136.5 (C-aryl), 134.0 (C-aryl), 121.6 (C-aryl), 120.6 (CH-aryl), 120.4 (CH-aryl), 112.6 (C-aryl), 112.6 (C-aryl), 76.6 (CCOCH3), 65.9 (CHOCON), 65.1 (NCH), 57.1 (OCH3), 51.3 and 51.1 (NCH2), 43.9 and 43.7 (CONCH2), 36.0 (CCH2CH), 32.8 (CCH2C), 27.4 and 27.3 (NCH2CH2), 24.6 (CH3CO), 24.5 (NCH2CH2), 22.9 (NCH2CH2CH2) ppm. Spectrum: see Figure S2 on page S17.

**HRMS** (ESI+) calc. for C32H37N2O9 [M+H]+: 593.2476, found 593.2480.
Daunorubicin aglycone (4)

A solution of daunorubicin (75 mg, 142 µmol, 1) in 1 M aqueous HCl was stirred at 80 °C for 2 h. The precipitated solid was filtered off, washed with water and dried under reduced pressure. 4 was obtained as a red solid quantitatively.

\[^{1}H\] NMR (500 MHz, CDCl\(_{3}\)): \(\delta = 13.90\) (s, 1H, OH), 13.21 (s, 1H, OH), 7.98 (dd, 1H, \(J_1 = 7.7\) Hz, \(J_2 = 0.9\) Hz, CH-aryl), 7.76 (dd, 1H, \(J_1 = 7.8\) Hz, \(J_2 = 7.8\) Hz, CH-aryl), 7.37 (m, 1H, CH-aryl), 5.29 (m, 1H, CH), 4.07 (s, 3H, OCH\(_3\)), 3.14 (dd, 1H, \(J_1 = 18.5\) Hz, \(J_2 = 2.1\) Hz, CH\(_2\)), 2.89 (d, 1H, \(J = 18.5\) Hz, CH\(_2\)), 2.41 (s, 3H, CH\(_3\)), 2.32 (m, 1H, CH\(_2\)), 2.13 (dd, 1H, \(J_1 = 14.5\) Hz, \(J_2 = 4.9\) Hz, CH\(_2\)) ppm.

\[^{13}C\] NMR (125 MHz, CDCl\(_{3}\)): \(\delta = 211.9\) (CH\(_3\)CO), 187.0 (CO), 186.6 (CO), 161.0 (C-aryl), 156.0 (C-aryl), 155.8 (C-aryl), 136.0 (C-aryl), 135.8 (CH-aryl), 135.5 (C-aryl), 133.6 (C-aryl), 120.8 (C-aryl), 119.8 (CH-aryl), 118.4 (CH-aryl), 111.5 (C-aryl), 111.1 (C-aryl), 76.8 (CCOCH\(_3\)), 61.9 (CHOH), 56.7 (OCH\(_3\)), 35.3 (CH\(_2\)), 33.2 (CH\(_2\)), 24.6 (CH\(_3\)).

Resistomycin-10-1,4'-bipiperidine-1'-carboxylate (8)

A solution of resistomycin (3.0 mg, 8.0 µmol, 1 eq. 5), 4-piperidinopiperidine-1-carbonyl chloride (2.1 mg, 9.2 µmol, 1.15 eq.) and DMAP (1.7 mg, 13.8 µmol, 1.75 eq.) in pyridine (1 mL) was stirred for 24 h at room temperature under argon. Subsequently the pyridine was removed under reduced pressure and the
remaining solid was dissolved in a mixture of THF/MeOH/HCl (1 M in water, 100/100/1) and purified by preparative HPLC yielding compound 8 (3.4 mg, 6.0 µmol, 75%) as a yellow solid.

\(^1H\) NMR \((600 \text{ MHz, CD}_2\text{Cl}_2)\): \(\delta = 14.67 \text{ (s, 1H, OH)}, 14.27 \text{ (s, 1H, OH)}, 13.90 \text{ (s, 1H, OH)}, 7.41 \text{ (s, 1H, CH-aryl)}, 7.16 \text{ (s, 1H, CH-aryl)}, 6.52 \text{ (s, 1H, CH-aryl)}, 4.64 \text{ and 4.50 (m, 2H, CONCH)}, 3.60 \text{ (m, 2H, NCH)}, 3.45 \text{ (m, 1H, NCH)}, 3.22 \text{ and 3.01 (m, 2H, CONCH)}, 2.85 \text{ (s, 3H, CH)}, 2.83 \text{ (m, 2H, NCH)}, 2.30 \text{ and 2.21 (m, 2H, NCH)}, 1.98 \text{ (m, 4H, NCHCH)}, 1.94 \text{ and 1.88 (m, 2H, NCHCH)}, 1.92 \text{ and 1.44 (m, 2H, NCHCH)}, 1.68 \text{ (s, 6H, CH)} \text{ ppm. Spectrum: see Figure S3 on page S18.}

\(^{13}C\) NMR \((150 \text{ MHz, CD}_2\text{Cl}_2)\): \(\delta = 205.9 \text{ (C=O)}, 187.7 \text{ (CO)}, 171.8 \text{ (C-OH-aryl)}, 171.1 \text{ (C-OH-aryl)}, 169.4 \text{ (C-OH-aryl)}, 153.2 \text{ (C-aryl)}, 153.0 \text{ (NCOO)}, 151.3 \text{ (C-aryl)}, 148.7 \text{ (C-aryl)}, 141.0 \text{ (C-aryl)}, 130.0 \text{ (C-aryl)}, 123.6 \text{ (CH-aryl)}, 119.5 \text{ (C-aryl)}, 119.1 \text{ (CH-aryl)}, 115.5 \text{ (C-aryl)}, 108.2 \text{ (C-aryl)}, 108.2 \text{ (C-aryl)}, 105.3 \text{ (C-aryl)}, 103.5 \text{ (CH-aryl)}, 64.0 \text{ (NCH)}, 51.3 \text{ and 50.3 (NCH)}, 47.3 \text{ (CHCH)}, 44.0 \text{ and 43.6 (CONCH)}, 29.1 \text{ (CHCH)}, 27.3 \text{ and 26.3 (NCHCH)}, 25.3 \text{ (CH)}, 23.6 \text{ and 23.5 (NCHCH)}, 22.8 \text{ (NCHCHCH)} \text{ ppm. Spectrum: see Figure S4 on page S19.}

HRMS \((\text{ESI}+)\) calc. for C\(_{33}\)H\(_{35}\)N\(_2\)O\(_7\) [M+H]\(^+\): 571.2439, found 571.2442.

Benastatin A-11-1,4'-bipiperidine-1'-carboxylate (9)

A solution of benastatin A (8.0 mg, 16 µmol, 1 eq. 6), 4-piperidinopiperidine-1-carbonyl chloride (4.2 mg, 18.4 µmol, 1.2 eq.) and DMAP (3.4 mg, 27.6 µmol, 1.7 eq.) in pyridine (3.0 mL) was stirred for 24 h at room temperature under argon. Subsequently the pyridine was removed under reduced pressure and the remaining solid was dissolved in a mixture of MeOH/HCl (1 M in water, 200/1) and purified by preparative HPLC yielding compound 9 (5.2 mg, 7.5 µmol, 47%) as a yellow solid.

\(^1H\) NMR \((600 \text{ MHz, DMSO-D}_6)\): \(\delta = 13.59 \text{ (s, 1H, OH)}, 12.83 \text{ (s, 1H, OH)}, 10.20 \text{ (s, 1H, CH-aryl)}, 8.12 \text{ (d, 1H, J = 9.1 Hz, CH-aryl)}, 7.57 \text{ (d, 1H, J = 9.1 Hz, CH-aryl)}, 7.19 \text{ (d, 1H, J = 2.2 Hz, CH-aryl)}, 6.86
(s, 1H, CH-aryl), 6.77 (d, 1H, J = 2.2 Hz, CH-aryl), 4.29 and 4.14 (m, 2H, CONCH₂), 3.20 (t, 2H, J = 2.2 Hz, CH₂), 3.06 and 2.92 (m, 2H, CONCH₂), 2.92 (m, 4H, NCH₂), 1.76 (s, 6H, CH₃), 2.51 (m, 1H, NCH), 2.00-1.20 (m, 10H, CH₂), 1.58 (m, 2H, CH₂), 1.31 (m, 4H, CH₂), 0.86 (t, J = 6.9 Hz, CH₃) ppm. Spectrum: see Figure S5 on page S20.

\[^1\text{H} \text{NMR}\] (600 MHz, CD₂OD): δ = 9.64 (s, 1H, CH-aryl), 8.35 (d, 1H, J = 9.1 Hz, CH-aryl), 7.57 (d, 1H, J = 9.1 Hz, CH-aryl), 7.21 (s, 1H, CH-aryl), 7.11 (d, 1H, J = 2.0 Hz, CH-aryl), 4.50 and 4.39 (m, 2H, CONCH₂), 3.56 and 3.09 (m, 4H, NCCH₂), 3.48 (m, 1H, NC), 3.16 and 3.01 (m, 2H, CONCH₂), 3.10 (t, 2H, J = 2.2 Hz, CH₂), 2.20 and 1.82 (m, 4H, NCHCH₂), 2.02 and 1.84 (m, 4H, NCH₂CH₂), 1.87 and 1.55 (m, 2H, NCH₂CH₂CH₂), 1.80 (s, 6H, CH₃), 1.67 (m, 2H, CH₂), 1.40 (m, 4H, CH₂), 0.93 (t, J = 7.0 Hz, CH₃) ppm. Spectrum: see Figure S6 on page S21.

\[^{13}\text{C} \text{NMR}\] (150 MHz, CD₂OD): δ = 193.1 (CO), 176.3 (COOH), 166.7 (C-OH-aryl), 165.7 (C-OH-aryl), 159.1 (C-aryl), 156.0 (C-aryl), 153.8 (NCO), 148.2 (C-aryl), 146.3 (C-aryl), 140.4 (C-aryl), 138.0 (C-aryl), 127.0 (CH-aryl), 125.2 (CH-aryl), 122.9 (CH-aryl), 121.9 (C-aryl), 118.3 (CH-aryl), 118.2 (C-aryl), 113.0 (C-aryl), 112.7 (CH-aryl), 110.1 (C-aryl), 109.8 (C-aryl), 109.3 (CH-aryl), 64.9 (NCH), 51.4 (NCH₂), 44.3 and 43.9 (CONCH₂), 40.8 [C(CH₃)₂], 38.0 (CH₂), 34.9 [C(CH₃)₂], 33.3 (CH₂), 32.9 (CH₂), 27.6 and 27.2 (NCHCH₂), 24.6 (NCH₂CH₂), 23.6 (CH₂), 22.9 (NCH₂CH₂CH₂), 14.4 (CH₃) ppm. Spectrum: see Figure S7 on page S22.

HRMS (ESI+) calc. for C₄₁H₄₇N₇O₈ [M+H]⁺: 695.3327, found 697.3333.

Benastatin B-11-1,4'-bipiperidine-1'-carboxylate (10)

A solution of benastatin B (5 mg, 9.9 µmol, 1 eq.), 4-piperidinopiperidine-1-carbonyl chloride (2.8 mg, 11.9 µmol, 1.2 eq.) and DMAP (2.2 mg, 17.9 µmol, 1.8 eq.) in pyridine (2.5 mL) was stirred for 24 h at room temperature under argon. Subsequently the pyridine was removed under reduced pressure and the
remaining solid was dissolved in a mixture of MeOH/HCl (1 M in water, 200/1) and purified by preparative HPLC yielding compound 10 (5.3 mg, 7.6 µmol, 76%) as a yellow solid.

\(^1H\) NMR (600 MHz, CD\(_2\)Cl\(_2\)): \(\delta = 16.30 (s, b, 1\ H, \text{OH}), 12.99 (s, 1\ H, \text{OH}), 12.81 (s, 1\ H, \text{OH}), 8.58 (s, 1\ H, \text{CH-aryl}), 6.95 (d, 1\ H, J = 2.2\ Hz, \text{CH-aryl}), 6.80 (m, 1\ H, \text{CH-aryl}), 6.57 (s, 1\ H, \text{CH-aryl}), 4.48 (m, 2\ H, CONCH\(_2\)), 3.54 and 2.85 (m, 4\ H, NCH\(_2\)), 3.47 (m, 1\ H, NCH), 3.13 (m, 2\ H, CH\(_2\)), 3.13 and 2.99 (m, 2\ H, CONCH\(_2\)), 2.60-1.20 (various m, 10\ H, C\(_2\)H\(_2\)), 1.76 (s, 6\ H, CH\(_3\)), 1.64 (m, 2\ H, CH\(_2\)), 1.37 (m, 4\ H, CH\(_2\)), 0.92 (t, 3\ H, J = 7.0\ Hz, CH\(_3\)) ppm. Spectrum: see Figure S8 on page S23.

\(^1H\) NMR (600 MHz, CD\(_3\)OD): \(\delta = 8.40 (s, 1\ H, \text{CH-aryl}), 7.07 (d, 1\ H, J = 2.2\ Hz, \text{CH-aryl}), 6.74 (s, 1\ H, \text{CH-aryl}), 6.69 (d, 1\ H, J = 2.2\ Hz, \text{CH-aryl}), 4.49 and 4.36 (m, 2\ H, CONCH\(_2\)), 3.56 and 3.06 (m, 4\ H, NCH\(_2\)), 3.50 (m, 1\ H, NCH), 3.16 and 3.02 (m, 2\ H, CONCH\(_2\)), 2.97 (m, 2\ H, CH\(_2\)), 2.81 (m, 2\ H, CH\(_2\)), 2.74 (m, 2\ H, CH\(_3\)), 2.24 and 1.85 (m, 4\ H, NCHCH\(_2\)), 1.99 and 1.88 (m, 4\ H, NCH\(_2\)CH\(_2\)), 1.86 and 1.54 (m, 2\ H, NCH\(_2\)CH\(_2\)CH\(_2\)), 1.70 (s, 6\ H, CH\(_3\)), 1.61 (m, 2\ H, CH\(_3\)), 1.37 (m, 4\ H, CH\(_3\)), 0.91 (t, 3\ H, J = 7.1\ Hz, CH\(_3\)) ppm. Spectrum: see Figure S9 on page S24.

\(^{13}C\) NMR (150 MHz, CD\(_3\)OD): \(\delta = 192.9 (C\text{O}), 175.5 (\text{COOH}, 165.5 (\text{C-OH-aryl}), 162.8 (\text{C-OH-aryl}), 159.9 (\text{C-OH-aryl}), 158.3 (C-aryl), 156.0 (C-aryl), 153.9 (NCO), 150.1 (C-aryl), 149.3 (C-aryl), 148.0 (C-aryl), 142.2 (C-aryl), 124.3 (C-aryl), 123.5 (CH-aryl), 120.7 (C-aryl), 119.3 (C-aryl), 112.9 (C-aryl), 112.8 (C-aryl), 112.8 (C-aryl), 112.2 (C-aryl), 109.3 (CH-aryl), 64.7 (NCH), 51.3 (NCH\(_2\)), 44.3 and 43.9 (CONCH\(_2\)), 40.2 [C(CH\(_3\))\(_2\)], 37.7 (CH\(_2\)), 34.3 [C(CH\(_3\))\(_2\)], 33.3 (CH\(_2\)), 32.9 (CH\(_2\)), 30.7 (CH\(_2\)), 27.5 and 27.2 (NCHCH\(_2\)), 24.5 (NCH\(_2\)CH\(_2\)), 23.4 (CH\(_2\)), 22.9 (NCH\(_2\)CH\(_2\)CH\(_2\)), 20.7 (CH\(_2\)), 14.4 (CH\(_3\)) ppm. Spectrum: see Figure S10 on page S25.

HRMS (ESI+) calc. for C\(_{41}\)H\(_{49}\)N\(_2\)O\(_8\) [M+H]\(^+\): 697.3483, found 697.3500.
Chartarin-10-1,4'-bipiperidine-1'-carboxylate (11) and chartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (13)

Chartarin (10 mg; 30 μM; 1.0 eq. 12), 1,4'-bipiperidin-1'-carbonylchloride (27.6 mg; 120 μM; 4.0 eq.) and \( N,N \)-dimethyl4-aminopyridin (22 mg; 180 μM; 6 eq.) were placed in a Schlenk tube and flushed with argon. Pyridin (2.4 mL) was added and the solution was stirred for 24 h at 60 °C. After cooling the solution was evaporated under reduced pressure to yield the crude product which was taken up in a mixture of methanol, THF and 10% aq. \( \text{NH}_4 \text{Cl} \) solution (1:1:1; v/v/v). The mixture was suspended to preparative column chromatography monitoring the wavelength of 254 and 400 nm.

**data for chartarin-10-1,4'-bipiperidine-1'-carboxylate (11)**

\(^1\text{H NMR} \) (600 MHz; \( \text{D}_3\text{CCN} \)): see Table S1 on page S14; spectrum: see Figure S11 on page S26.

\(^{13}\text{C NMR} \) (150 MHz; \( \text{D}_3\text{CCN} \)): see Table S2 on page S15; spectrum: see Figure S12 on page S27.

**UV-Vis** (from LC/MS run using acetonitrile/water with 0.1% formic acid) \( \lambda_{\text{max}} \) = 234, 264, 327, 371, 394, 414 nm.

**HRMS** (ESI+) calc. for \( \text{C}_{31}\text{H}_{31}\text{O}_7\text{N}_4 \) [M+H]^+: 543.2126, found. 543.2138.

**data for chartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (13)**

\(^1\text{H NMR} \) (600 MHz; \( \text{D}_3\text{CCN} \)): see Table S1 on page S14; spectrum: see Figure S14 on page S29.

\(^{13}\text{C NMR} \) (150 MHz; \( \text{D}_3\text{CCN} \)): see Table S2 on page S15; spectrum: see Figure S15 on page S30.

**UV-Vis** (from LC/MS run using acetonitrile/water with 0.1% formic acid) \( \lambda_{\text{max}} \) = 233, 267, 318, 356, 383, 401 nm.
Bromochartarin-10-1,4'-bipiperidine-1'-carboxylate (18) and bromochartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (20)

The preparation of (18 and 20) follows the procedure of Chartarin-10-1,4'-bipiperidine-1'-carboxylate (11) and chartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (13) (page S10) using 15 mg starting material (using the same molar equivalents).

data for bromochartarin-10-1,4'-bipiperidine-1'-carboxylate (18)

$^1$H NMR (500 MHz; D$_3$CCN): see Table S1 on page S14; spectrum: see Figure S16 on page S31.

$^{13}$C NMR (125 MHz; D$_3$CCN): see Table S2 on page S15; spectrum: see Figure S17 on page S32.

UV-Vis (from LC/MS run using acetonitrile/water with 0.1% formic acid) $\lambda_{\text{max}}$ = 234, 267, 276, 332, 376, 394, 416 nm.

HRMS (ESI+) calc. for C$_{29}$H$_{26}$^{79}BrO$_7$N$_2$ [M+H]$^+$: 593.0918, found 593.0918.

data for bromochartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (20)

$^1$H NMR (600 MHz; D$_3$CCN): see Table S1 on page S14; spectrum: see Figure S20 on page S35.

$^{13}$C NMR (150 MHz; D$_3$CCN): see Table S2 on page S15; spectrum: see Figure S21 on page S36.
Norchartarin-10-1,4'-bipiperidine-1'-carboxylate (19) and norchartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (21)

The preparation of (19 and 21) follows the procedure of Chartarin-10-1,4'-bipiperidine-1'-carboxylate (11) and chartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (13) (page S10) using 10 mg starting material (using the same molar equivalents).

**data for norchartarin-10-1,4'-bipiperidine-1'-carboxylate (19)**

**1H NMR** (600 MHz; D$_3$CCN): see Table S1 on page S14; spectrum: see Figure S18 on page S33.

**13C NMR** (150 MHz; D$_3$CCN): see Table S2 on page S15; spectrum: see Figure S19 on page S34.

**UV-Vis** (from LC/MS run using acetonitrile/water with 0.1% formic acid) $\lambda_{max} = 234, 265, 275, 327, 369, 388, 409 \text{ nm}$.

**HRMS** (ESI+) calc. for C$_{29}$H$_{27}$O$_7$N$_2$ [M+H]$^+$: 515.1813; found: 515.1807.

**data for norchartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (21)**
Assigning the regiochemistry of chartreusin derivatives

Because of the possibility that two phenol groups may be converted into the carbamate we tried to use HBMC NMR experiments to visualize couplings from the core aglycon to the carbamate residue and vice versa to elucidate the position of the modified phenol group. Unfortunately, this approach enables us not to elucidate the structure. Next, we tried to incorporate a methyl group into the remaining phenol but during synthesis, decomposition of the starting material hampers this approach. So we used $^{13}$C-NMR shift prediction for the structure elucidation. Comparing the $^{13}$C shift of the phenol carbon atom of both possible isomers ($R_2 = pip$ in position 6 and $R_3 = pip$ in position 10) with the measured values it becomes clear, that compound 11 is modified in position 10 which is equal position to the glycoside residue of chartreusin (5) [ref: ACD CNMR predictor version 8.15]. Due to overlapping NMR signals we are not able to assign the $^{13}$C carbon atom shifts unambiguously for the other derivatives. Due to the almost same structure and similar behavior during analysis we assume the same substitution for the compounds 18 and 19.

For detailed table of the calculated and measured values including the corresponding HMBC-NMR spectrum and a structure with the basic couplings see Figure S13 on page S28.
Table S1: $^{13}$C NMR shifts of chartreusin (2) and the derivatives 11, 13, 18-21: a: pyridine-D$_5$, b: D$_2$CCN, c: CD$_3$OD. ($\delta$ [ppm], J [Hz], *: signals are overlapping)

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Table S2: $^{13}$C NMR shifts of chartreusin (2) and the derivatives 11, 13, 18-21 a: pyridine-$D_5$, b: $D_3$CCN, c: CD$_3$OD. (δ [ppm], J [Hz], *: signal under solvent residual signal)

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Figure S1 $^1$H NMR (CD$_3$OD) of daunorubicin-10-1,4′-bipiperidine-1′-carboxylate (3)
Figure S2 13C NMR (CD$_3$OD) of daunorubicin-10-1,4’-bipiperidine-1’-carboxylate (3)

![NMR Spectrum](image)

**Figure Legend**

The Figure S2 shows the 13C NMR spectrum of daunorubicin-10-1,4’-bipiperidine-1’-carboxylate (3) in CD$_3$OD. The spectrum displays the chemical shifts (ppm) corresponding to various carbon atoms in the molecule. The structural formula is also provided, highlighting the positions of the different functional groups such as oxygen, methoxy, hydroxyl, and nitrogen. The spectrum reveals the presence of multiple peaks at different chemical shifts, indicating the complexity of the molecule's structure and the presence of various functional groups. The spectrum is a crucial tool for understanding the molecular composition and the interactions of the compound in its solvent environment.
Figure S3 $^1$H NMR (CD$_2$Cl$_2$) of resistomycin-10-1,4'-bipiperidine-1'-carboxylate (8)
Figure S4 ¹³C NMR (CD₂Cl₂) of resistomycin-10-1,4'-bipiperidine-1'-carboxylate (8)

Figure S4 ¹³C NMR (CD₂Cl₂) of resistomycin-10-1,4'-bipiperidine-1'-carboxylate (8)
Figure S5 ¹H NMR (DMSO-D₆) of benastatin A-11-1,4'-bipiperidine-1'-carboxylate (9)
Figure S6 ¹H NMR (CD₃OD) of benastatin A-11-1,4'-bipiperidine-1'-carboxylate (9)
Figure S7 $^{13}$C NMR (CD$_3$OD) of benastatin A-11-1,4'-bipiperidine-1'-carboxylate (9)
Figure S8 $^1$H NMR (CD$_2$Cl$_2$) of benastatin B-11-1,4'-bipiperidine-1'-carboxylate (10)

== CHANNEL f1 ==

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PL1         4.00 usec
PL1W       5.00000000 W
SF01       600.2754024 MHz
SI        262144
SF       600.2700202 MHz
WDW         GM
SBB          0
LB         0.30 Hz
GH         0.2
PC          1.00
Figure S9 $^1$H NMR (CD$_3$OD) of benastatin B-11-1,4'-bipiperidine-1'-carboxylate (10)

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PROCNO 1
Date_ 20150205
Time 6.08
INSTRUM spect
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PULPROG zg30
TD 65536
SOLVENT MeOD
NS 64
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 25.4
DW 41.600 usec
DE 6.50 usec
TE 298.8 K
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======== CHANNEL f1 ========
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S1 262144
SF 600.2700212 MHz
WDW 0M
SSB 0
LB 0.3 Hz
GB 0.3
PC 1.00
Figure S10 $^{13}$C NMR (CD$_3$OD) of benastatin B-11-1,4'-bipiperidine-1'-carboxylate (10)
Figure S11 $^1$H NMR (CD$_3$CN) of chartarin-10-1,4'-bipiperidine-1'-carboxylate (11)
Figure S12 $^{13}$C NMR (CD$_3$CN) of chartarin-10-1,4′-bipiperidine-1′-carboxylate (11)
Figure S13 $^1$H-$^{13}$C HMBC NMR (CD$_3$CN) of chartarin-10-1,4'-bipiperidine-1'-carboxylate (11)

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Figure S14 ¹H NMR (CD₃CN) of chartarin-6,10 di-1,4′-bipiperidine-1′-carboxylate (13)
Figure S15 $^{13}$C NMR (CD$_3$CN) of chartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (13)
Figure S16 $^1$H NMR (CD$_3$CN) of bromochartarin-10-1,4'-bipiperidine-1'-carboxylate (18)
Figure S17 $^{13}$C NMR (CD$_3$CN) of bromochartarin-10-1,4'-bipiperidine-1'-carboxylate (18)
Figure S18 $^1$H NMR (CD$_3$CN) of norchartarin-10-1,4'-bipiperidine-1'-carboxylate (19)
Figure S19 $^{13}$C NMR (CD$_3$CN) of norchartarin-10-1,4'-bipiperidine-1'-carboxylate (19)
Figure S20 $^1$H NMR (CD$_3$OD+DCl) of bromochartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (20)
Figure S21 $^{13}$C NMR (CD$_3$OD+DCI) of bromochartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (20)
Figure S22 $^1$H NMR (CD$_3$CN) of norchartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (21)
Figure S23 $^{13}$C NMR (CD$_3$CN) of norchartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (21)
LogD and Log S values

All logD and logS values were calculated using the ChemAxon calculation PlugIn. LogD options: lopP method: Consensus; Electrolyte concentration: 0.1 mol/L Cl⁻; 0.1 mol/L Na⁺, K⁺.

<table>
<thead>
<tr>
<th>compound</th>
<th>logD</th>
<th>logS</th>
</tr>
</thead>
<tbody>
<tr>
<td>daunorubicin (1)</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

![Graph](image1.png)

![Graph](image2.png)
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>chartreusin (2)</strong></td>
<td><img src="image" alt="Chartreusin" /></td>
<td><img src="image" alt="Chartreusin pH" /></td>
</tr>
<tr>
<td><strong>Daunorubicin-10-1,4''-bipiperidine-1''-carboxylate (3)</strong></td>
<td><img src="image" alt="Daunorubicin-10-1,4''-bipiperidine-1''-carboxylate" /></td>
<td><img src="image" alt="Daunorubicin-10-1,4''-bipiperidine-1''-carboxylate pH" /></td>
</tr>
<tr>
<td><strong>daunorubicin aglycon (4)</strong></td>
<td><img src="image" alt="daunorubicin aglycon" /></td>
<td><img src="image" alt="daunorubicin aglycon pH" /></td>
</tr>
</tbody>
</table>
resistomycin (5)

benastatin A (6)
benastatin B (7)

resistomycin-10-1,4'-bipiperidine-1'-carboxylate (8)
Benastatin A-11-1,4'-bipiperidine-1'-carboxylate (9)

Benastatin B-11-1,4'-bipiperidine-1'-carboxylate (10)
**chartarin-10-1,4'-bipiperidine-1'-carboxylate (11)**

**chartarin (12)**
chartarín-6,10 di-1,4'-bipiperidina-1'-carboxylato (13)

bromochartreusina (14)
norchartreusin (15)

bromochartarin (16)
norchartarin (17)

bromchartarin-10-1,4'-bipiperidine-1'-carboxylate (18)
norchartarin-10-1,4'-bipiperidine-1'-carboxylate (19)

bromochartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (20)
norchartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (21)

irinotecan
ciprofloxacin
References: