Electronic Supplementary Material (ESI) for Chemical Communications.

Supplementary Material

for

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

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Content

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 (δ ^{1}H (DMSO-D_6) = 2.50 ppm, δ ^{13}C (DMSO-D_6) = 39.52 ppm, δ ^{1}H (C**D**$_3$OD) = 3.31 ppm, δ ^{13}C (**C**D_3OD) = 49.15 ppm, δ ^{1}H (CD_2Cl_2) = 5.32 ppm, δ ^{13}C (CD_2Cl_2) = 54.00 ppm, δ ^{1}H (**D**$_3$CCN) = 1.94 ppm, δ ^{13}C (D_3C**C**N) = 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_2O/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 Phenomenx Kinetix C18 column 5 µm, Ø 21.2 mm × 250 mm at 21 mL/min with a gradientent 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 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

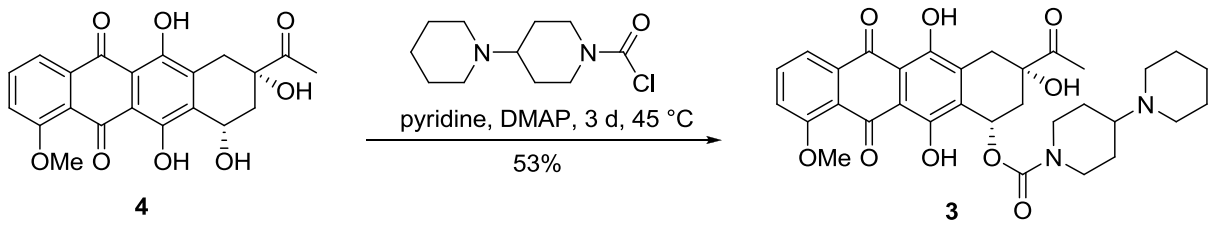
Compounds were assayed using human umbilical vein endothelial cells HUVEC (ATCC CRL-1730) and human chronic myeloid leukemia cells K-562 (DSM ACC 10) for their antiproliferative effects (GI_{50}) and using human cervix carcinoma cells HeLa (DSM ACC 57) for their cytotoxic effects (CC_{50}) as previously 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. NH_4Cl 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. NH_4Cl 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)



4 3

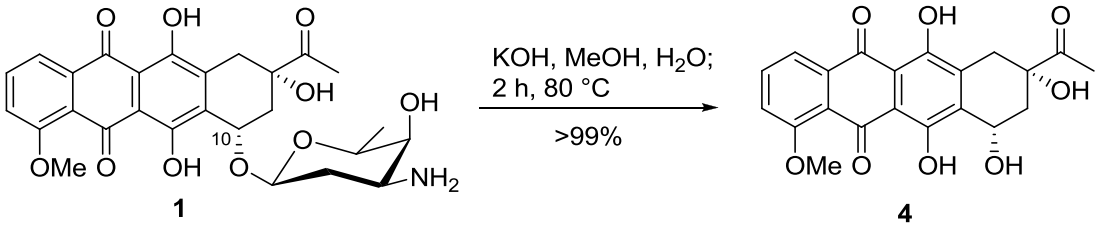
A solution of daunorubicin aglycone (12 mg, 30 µmol, 1 eq. **4**), 4-piperidinopiperidine-1-carbonyl chloride (15.6 mg, 68 µmol, 2.25 eq.) and DMAP (12.4 mg, 102 µmol, 3.38 eq.) in pyridine (2 mL) was stirred for 72 h at 45 °C under argon. Subsequently the pyridine was removed under reduced pressure 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.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.94 (d, 1H, *J* = 7.8 Hz, C**H**-aryl), 7.83 (t, 1H, *J* = 8.1 Hz, C**H**-aryl), 7.57 (d, 1H, *J* = 8.3 Hz, C**H**-aryl), 6.17 (m, 1H, C**H**OCON), 4.36 and 4.16 (m, 2H, CONC**H**$_2$), 4.02 (s, 3H, OC**H**$_3$), 3.47 and 3.00 (m, 4H, NC**H**$_2$), 3.37 (m, 1H, NC**H**), 3.09 and 2.71 (m, 2H, CC**H**$_2$C), 2.85 (m, 2H, CONC**H**$_2$), 2.35 (s, 3H, COC**H**$_3$), 2.31 and 2.22 (m, 2H, CC**H**$_2$CH), 2.05, 1.76 and 1.50 (m, 4H, NCHC**H**$_2$), 2.00 and 1.76 (m, 4H, NCH$_2$C**H**$_2$), 1.85 and 1.51 (m, 2H, NCH$_2$CH$_2$C**H**$_2$) ppm. Spectrum: see **Figure S1** on page S16.

^{13}C NMR (150 MHz, CD_3OD): δ = 214.3 (CH_3**C**O), 188.5 (**C**O), 188.1 (**C**O), 162.6 (**C**-OH-aryl), 157.1 (N**C**O), 156.6 (**C**-OH-aryl), 156.2 (**C**-OH-aryl), 137.3 (**C**H-aryl), 136.5 (**C**-aryl), 136.5 (**C**-aryl), 134.0 (**C**-aryl), 121.6 (**C**-aryl), 120.6 (**C**H-aryl), 120.4 (**C**H-aryl), 112.6 (**C**-aryl), 112.6 (**C**-aryl), 76.6 (**C**COCH$_3$), 65.9 (**C**HOCON), 65.1 (N**C**H), 57.1 (O**C**H$_3$), 51.3 and 51.1 (N**C**H$_2$), 43.9 and 43.7 (CON**C**H$_2$), 36.0 (C**C**H$_2$CH), 32.8 (C**C**H$_2$C), 27.4 and 27.3 (NCH**C**H$_2$), 24.6 (**C**H$_3$CO), 24.5 (NCH$_2$**C**H$_2$), 22.9 (NCH$_2$CH$_2$**C**H$_2$) ppm. Spectrum: see **Figure S2** on page S17.

HRMS (ESI+) calc. for $C_{32}H_{37}N_2O_9$ $[M+H]^+$: 593.2476, found 593.2480.

Daunorubicin aglycone (**4**)



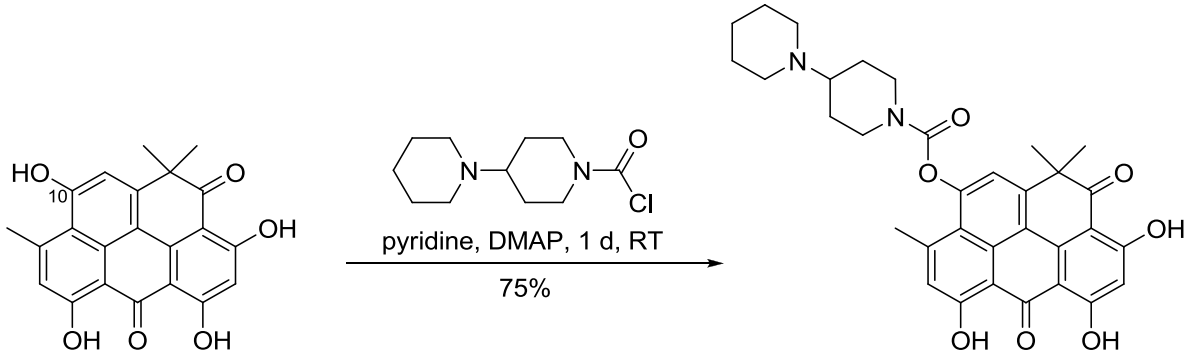
1 **4**

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, $CDCl_3$): δ = 13.90 (s, 1H, O**H**), 13.21 (s, 1H, O**H**), 7.98 (dd, 1H, J_1 = 7.7 Hz, J_2 = 0.9 Hz, C**H**-aryl), 7.76 (dd, 1H, J_1 = 7.8 Hz, J_2 = 7.8 Hz, C**H**-aryl), 7.37 (m, 1H, C**H**-aryl), 5.29 (m, 1H, C**H**), 4.07 (s, 3H, OC**H**$_3$), 3.14 (dd, 1H, J_1 = 18.5 Hz, J_2 = 2.1 Hz, C**H**$_2$), 2.89 (d, 1H, J = 18.5 Hz, C**H**$_2$), 2.41 (s, 3H, C**H**$_3$), 2.32 (m, 1H, C**H**$_2$), 2.13 (dd, 1H, J_1 = 14.5 Hz, J_2 = 4.9 Hz, C**H**$_2$) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.9 (CH_3**C**O), 187.0 (**C**O), 186.6 (**C**O), 161.0 (**C**-aryl), 156.0 (**C**-aryl), 155.8 (**C**-aryl), 136.0 (**C**-aryl), 135.8 (**C**H-aryl), 135.5 (**C**-aryl), 133.6 (**C**-aryl), 120.8 (**C**-aryl), 119.8 (**C**H-aryl), 118.4 (**C**H-aryl), 111.5 (**C**-aryl), 111.1 (**C**-aryl), 76.8 (**C**COCH_3), 61.9 (**C**HOH), 56.7 (O**C**H_3), 35.3 (**C**H_2), 33.2 (**C**H_2), 24.6 (**C**H_3).

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



5 **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

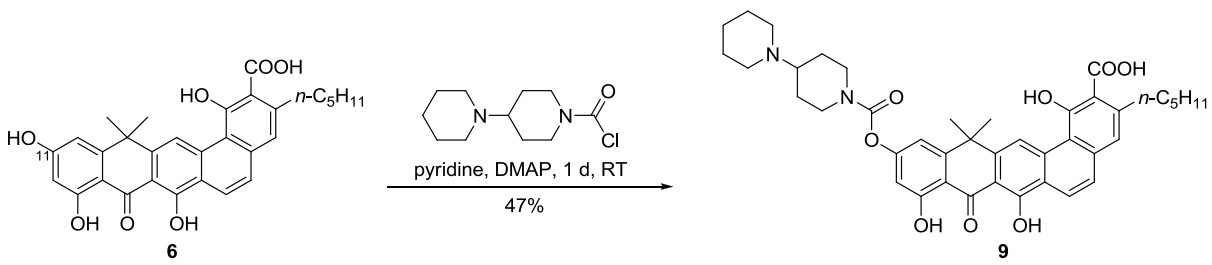
remaining solid was dissolved in a mixture of THF/MeOH/HCl (1 M in water, 100/100/1) and purified by preparative HPLC yielding compound **8** (3.4 mg, 6.0 µmol, 75%) as a yellow solid.

^{1}H NMR (600 MHz, CD_2Cl_2): δ = 14.67 (s, 1H, O**H**), 14.27 (s, 1H, O**H**), 13.90 (s, 1H, O**H**), 7.41 (s, 1H, C**H**-aryl), 7.16 (s, 1H, C**H**-aryl), 6.52 (s, 1H, C**H**-aryl), 4.64 and 4.50 (m, 2H, CONC**H**$_2$), 3.60 (m, 2H, NC**H**$_2$), 3.45 (m, 1H, NC**H**), 3.22 and 3.01 (m, 2H, CONC**H**$_2$), 2.85 (s, 3H, C**H**$_3$), 2.83 (m, 2H, NC**H**$_2$), 2.30 and 2.21 (m, 2H, NCHC**H**$_2$), 1.98 (m, 4H, NCH$_2$C**H**$_2$), 1.94 and 1.88 (m, 2H, NCHC**H**$_2$), 1.92 and 1.44 (m, 2H, NCH$_2$CH$_2$C**H**$_2$), 1.68 (s, 6H, C**H**$_3$) ppm. Spectrum: see **Figure S3** on page S18.

^{13}C NMR (150 MHz, CD_2Cl_2): δ = 205.9 (**C**O), 187.7 (**C**O), 171.8 (**C**-OH-aryl), 171.1 (**C**-OH-aryl), 169.4 (**C**-OH-aryl), 153.2 (**C**-aryl), 153.0 (N**C**OO), 151.3 (**C**-aryl), 148.7 (**C**-aryl), 141.0 (**C**-aryl), 130.0 (**C**-aryl), 123.6 (**C**H-aryl), 119.5 (**C**-aryl), 119.1 (**C**H-aryl), 115.5 (**C**-aryl), 108.2 (**C**-aryl), 108.2 (**C**-aryl), 105.3 (**C**-aryl), 103.5 (**C**H-aryl), 64.0 (N**C**H), 51.3 and 50.3 (N**C**H$_2$), 47.3 [**C**(CH$_3$)$_2$], 44.0 and 43.6 (CON**C**H$_2$), 29.1 [C(**C**H$_3$)$_2$], 27.3 and 26.3 (NCH**C**H$_2$), 25.3 (**C**H$_3$), 23.6 and 23.5 (NCH$_2$**C**H$_2$), 22.8 (NCH$_2$CH$_2$**C**H$_2$) ppm. Spectrum: see **Figure S4** on page S19.

HRMS (ESI+) calc. for $C_{33}H_{35}N_2O_7$ $[M+H]^+$: 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.

^{1}H NMR (600 MHz, DMSO-D_6): δ = 13.59 (s, 1H, O**H**), 12.83 (s, 1H, O**H**), 10.20 (s, 1H, C**H**-aryl), 8.12 (d, 1H, *J* = 9.1 Hz, C**H**-aryl), 7.57 (d, 1H, *J* = 9.1 Hz, C**H**-aryl), 7.19 (d, 1H, *J* = 2.2 Hz, C**H**-aryl), 6.86

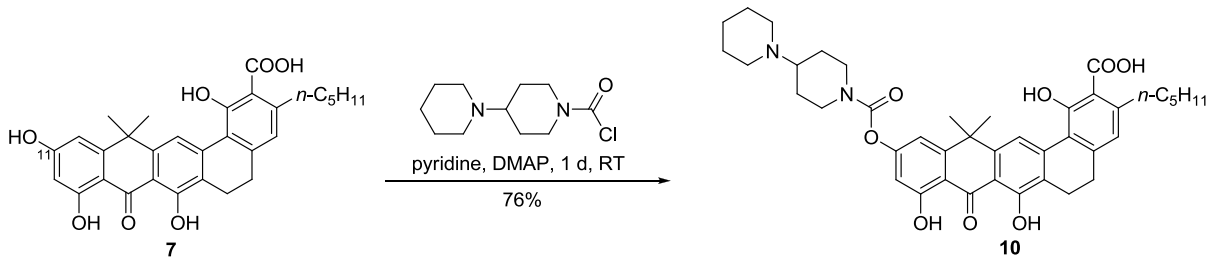
(s, 1H, C**H**-aryl), 6.77 (d, 1H, *J* = 2.2 Hz, C**H**-aryl), 4.29 and 4.14 (m, 2H, CONC**H**$_2$), 3.20 (t, 2H, *J* = 2.2 Hz, C**H**$_2$), 3.06 and 2.92 (m, 2H, CONC**H**$_2$), 2.92 (m, 4H, NC**H**$_2$), 1.76 (s, 6H, C**H**$_3$), 2.51 (m, 1H, NC**H**), 2.00-1.20 (m, 10H, C**H**$_2$), 1.58 (m, 2H, C**H**$_2$), 1.31 (m, 4H, C**H**$_2$), 0.86 (t, *J* = 6.9 Hz, C**H**$_3$) ppm. Spectrum: see **Figure S5** on page S20.

^{1}H NMR (600 MHz, CD_3OD): δ = 9.64 (s, 1H, C**H**-aryl), 8.35 (d, 1H, *J* = 9.1 Hz, C**H**-aryl), 7.57 (d, 1H, *J* = 9.1 Hz, C**H**-aryl), 7.21 (s, 1H, C**H**-aryl), 7.11 (d, 1H, *J* = 2.0 Hz, C**H**-aryl), 6.72 (d, 1H, *J* = 2.0 Hz, C**H**-aryl), 4.50 and 4.39 (m, 2H, CONC**H**$_2$), 3.56 and 3.09 (m, 4H, NC**H**$_2$), 3.48 (m, 1H, NC**H**), 3.16 and 3.01 (m, 2H, CONC**H**$_2$), 3.10 (t, 2H, *J* = 2.2 Hz, C**H**$_2$), 2.20 and 1.82 (m, 4H, NCHC**H**$_2$), 2.02 and 1.84 (m, 4H, NCH_2C**H**$_2$), 1.87 and 1.55 (m, 2H, NCH_2CH_2C**H**$_2$), 1.80 (s, 6H, C**H**$_3$), 1.67 (m, 2H, C**H**$_2$), 1.40 (m, 4H, C**H**$_2$), 0.93 (t, *J* = 7.0 Hz, C**H**$_3$) ppm. Spectrum: see **Figure S6** on page S21.

^{13}C NMR (150 MHz, CD_3OD): δ = 193.1 (**C**O), 176.3 (**C**OOH), 166.7 (**C**-OH-aryl), 165.7 (**C**-OH-aryl), 162.0 (**C**-OH-aryl), 159.1 (**C**-aryl), 156.0 (**C**-aryl), 153.8 (N**C**O), 148.2 (**C**-aryl), 146.3 (**C**-aryl), 140.4 (**C**-aryl), 138.0 (**C**-aryl), 127.0 (**C**H-aryl), 125.2 (**C**H-aryl), 122.9 (**C**H-aryl), 121.9 (**C**-aryl), 118.3 (**C**H-aryl), 118.2 (**C**-aryl), 113.0 (**C**-aryl), 112.7 (**C**H-aryl), 110.1 (**C**-aryl), 109.8 (**C**-aryl), 109.3 (**C**H-aryl), 64.9 (N**C**H), 51.4 (N**C**H_2), 44.3 and 43.9 (CON**C**H_2), 40.8 [**C**$(CH_3)_2$], 38.0 (**C**H_2), 34.9 [C$(\mathbf{C}H_3)_2$], 33.3 (**C**H_2), 32.9 (**C**H_2), 27.6 and 27.2 (NCH**C**H_2), 24.6 (NCH_2**C**H_2), 23.6 (**C**H_2), 22.9 (NCH_2CH_2**C**H_2), 14.4 (**C**H_3) ppm. Spectrum: see **Figure S7** on page S22.

HRMS (ESI+) calc. for $C_{41}H_{47}N_2O_8$ $[M+H]^+$: 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.**7**;), 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.

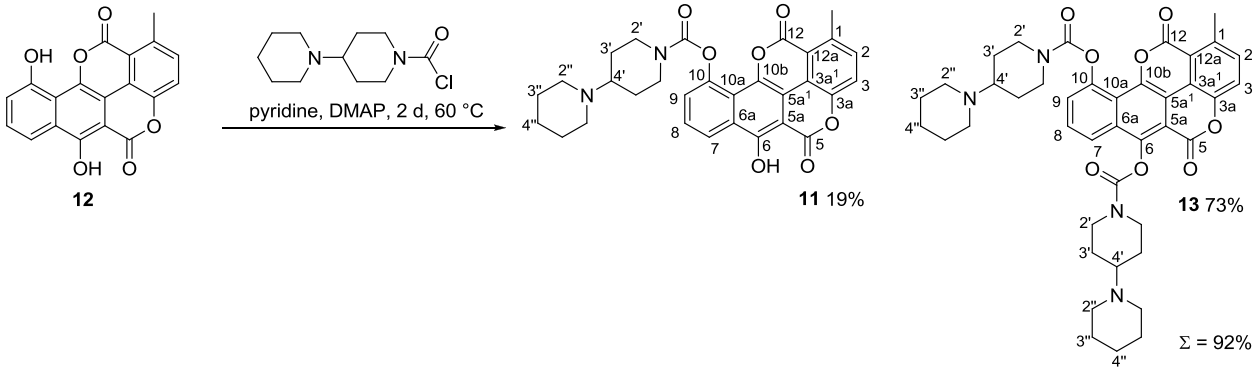
^{1}H NMR (600 MHz, CD_2Cl_2): δ = 16.30 (s, b, 1H, O**H**), 12.99 (s, 1H, O**H**), 12.81 (s, 1H, O**H**), 8.58 (s, 1H, C**H**-aryl), 6.95 (d, 1H, *J* = 2.2 Hz, C**H**-aryl), 6.80 (m, 1H, C**H**-aryl), 6.57 (s, 1H, C**H**-aryl), 4.48 (m, 2H, CONC**H**$_2$), 3.54 and 2.85 (m, 4H, NC**H**$_2$), 3.47 (m, 1H, NC**H**), 3.13 (m, 2H, C**H**$_2$), 3.13 and 2.99 (m, 2H, CONC**H**$_2$), 2.60-1.20 (various m, 10H, C**H**$_2$), 1.76 (s, 6H, C**H**$_3$), 1.64 (m, 2H, C**H**$_2$), 1.37 (m, 4H, C**H**$_2$), 0.92 (t, 3H, *J* = 7.0 Hz, C**H**$_3$) ppm. Spectrum: see **Figure S8** on page S23.

^{1}H NMR (600 MHz, CD_3OD): δ = 8.40 (s, 1H, C**H**-aryl), 7.07 (d, 1H, *J* = 2.2 Hz, C**H**-aryl), 6.74 (s, 1H, C**H**-aryl), 6.69 (d, 1H, *J* = 2.2 Hz, C**H**-aryl), 4.49 and 4.36 (m, 2H, CONC**H**$_2$), 3.56 and 3.06 (m, 4H, NC**H**$_2$), 3.50 (m, 1H, NC**H**), 3.16 and 3.02 (m, 2H, CONC**H**$_2$), 2.97 (m, 2H, C**H**$_2$), 2.81 (m, 2H, C**H**$_2$), 2.74 (m, 2H, C**H**$_2$), 2.24 and 1.85 (m, 4H, NCHC**H$_2$**), 1.99 and 1.88 (m, 4H, NCH_2C**H**$_2$), 1.86 and 1.54 (m, 2H, NCH_2CH_2C**H**$_2$), 1.70 (s, 6H, C**H**$_3$), 1.61 (m, 2H, C**H**$_2$), 1.37 (m, 4H, C**H**$_2$), 0.91 (t, 3H, *J* = 7.1 Hz, C**H**$_3$) ppm. Spectrum: see **Figure S9**on page S24.

^{13}C NMR (150 MHz, CD_3OD): δ = 192.9 (**C**O), 175.5 (**C**OOH), 165.5 (**C-**OH-aryl), 162.8 (**C-**OH-aryl), 159.9 (**C-**OH-aryl), 158.3 (**C**-aryl), 156.0 (**C**-aryl), 153.9 (N**C**O), 150.1 (**C**-aryl), 149.3 (**C**-aryl), 148.0 (**C**-aryl), 142.2 (**C**-aryl), 124.3 (**C**-aryl), 123.5 (**C**H-aryl), 120.7 (**C**-aryl), 119.3 (**C**H-aryl), 112.9 (**C**-aryl), 112.8 (**C**-aryl), 112.8 (**C**-aryl), 112.2 (**C**-aryl), 109.3 (**C**H-aryl), 64.7 (N**C**H), 51.3 (N**C**H$_2$), 44.3 and 43.9 (CON**C**H$_2$), 40.2 [**C**(CH$_3$)$_2$], 37.7 (**C**H$_2$), 34.3 [C(**C**H$_3$)$_2$], 33.3 (**C**H$_2$), 32.9 (**C**H$_2$), 30.7 (**C**H$_2$), 27.5 and 27.2 (NCH**C**H$_2$), 24.5 (NCH$_2$**C**H$_2$), 23.4 (**C**H$_2$), 22.9 (NCH$_2$CH$_2$**C**H$_2$), 20.7 (**C**H$_2$), 14.4 (**C**H$_3$) ppm. Spectrum: see **Figure S10** on page S25.

HRMS (ESI+) calc. for $C_{41}H_{49}N_2O_8$ $[M+H]^+$: 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. NH_4Cl 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}H NMR (600 MHz; D_3CCN): see **Table S1** on page S14; spectrum: see **Figure S11** on page S26.

^{13}C NMR (150 MHz; D_3CCN): 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) λ_{max} = 234, 264, 327, 371, 394, 414 nm.

HRMS (ESI+) calc. for $C_{31}H_{31}O_7N_4$ $[M+H]^+$: 543.2126, found. 543.2138.

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

^{1}H NMR (600 MHz; D_3CCN): see **Table S1** on page S14; spectrum: see **Figure S14** on page s29.

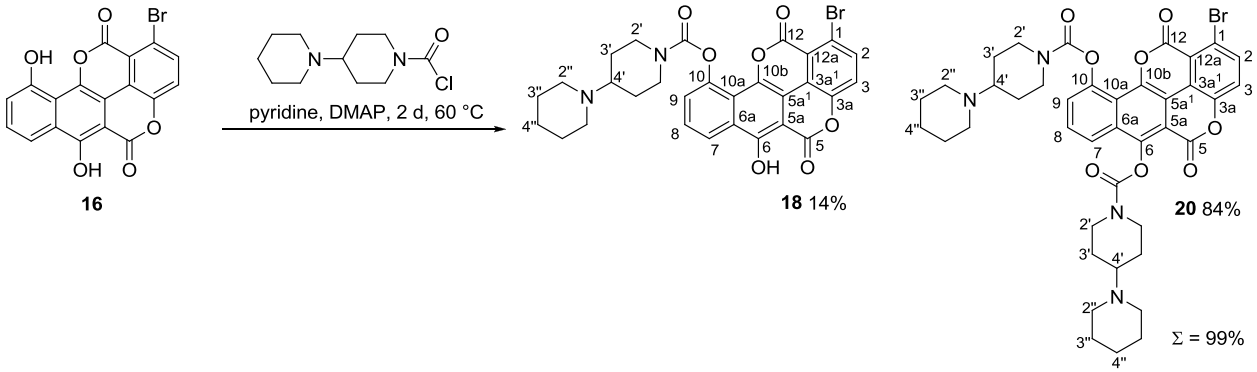
^{13}C NMR (150 MHz; D_3CCN): see **Table S2** on page S15; spectrum: see **Figure S15** on page S30.

UV-Vis (from LC/MS run using acetonitrile/water with 0.1% formic acid) λ_{max} = 233, 267, 318, 356, 383, 401 nm.

HRMS (ESI+) calc. for $C_{41}H_{48}O_8N_4$ $[M+H]^+$: 723.3388, found. 723.3395.

(ESI+) calc. for $C_{41}H_{48}O_8N_4$ $[M+2H]^{2+}$: 362.1731, found. 362.1738.

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_3CCN): see **Table S1** on page s14; spectrum: see **Figure S16** on page S31.

^{13}C NMR (125 MHz; D_3CCN): 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) λ_{max} = 234, 267, 276, 332, 376, 394, 416 nm.

HRMS (ESI+) calc. for $C_{29}H_{26}{}^{79}BrO_7N_2$ $[M+H]^+$: 593.0918, found 593.0918.

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

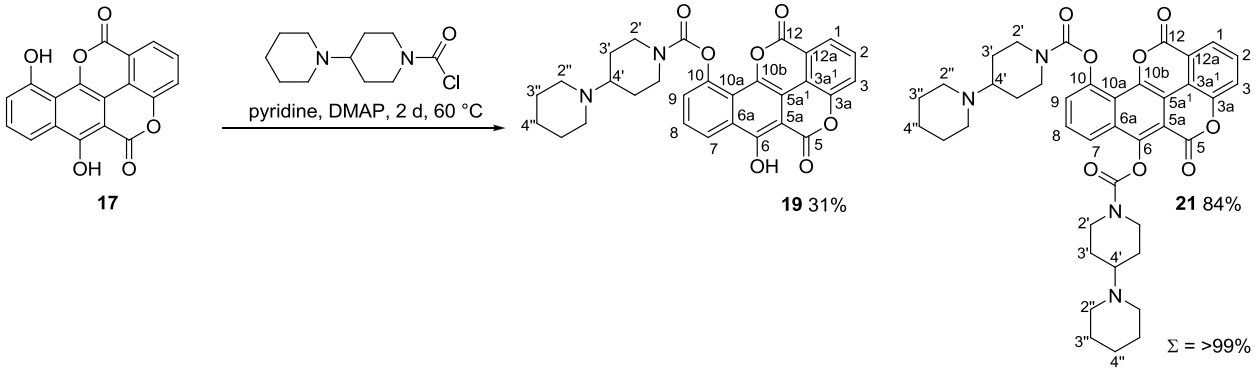
^{1}H NMR (600 MHz; D_3CCN): see **Table S1** on page S14; spectrum: see **Figure S20** on page S35.

^{13}C NMR (150 MHz; D_3CCN): see **Table S2** on page S15; spectrum: see **Figure S21** on page S36.

UV-Vis (from LC/MS run using acetonitrile/water with 0.1% formic acid) λ_{max} = 233, 266, 323, 362, 383, 403 nm.

HRMS (ESI+) calc. for $C_{40}H_{44}{}^{79}BrO_8N_4$ $[M+H]^+$: 787.2337, found 787.2325.
(ESI+) calc. for $C_{40}H_{44}{}^{79}BrO_8N_4$ $[M+2H]^{2+}$: 394.1205, found 394.1202.

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)

^{1}H NMR (600 MHz; D_3CCN): see **Table S1** on page S14; spectrum: see **Figure S18** on page S33.

^{13}C NMR (150 MHz; D_3CCN): 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) λ_{max} = 234, 265, 275, 327, 369, 388, 409 nm.

HRMS (ESI+) calc. for $C_{29}H_{27}O_7N_2$ $[M+H]^+$: 515.1813; found: 515.1807.

data for norchartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (21)

^{1}H NMR (600 MHz; D_3CCN): see **Table S1** on page S14; spectrum: see **Figure S22** on page S37.

^{13}C NMR (150 MHz; D_3CCN): see **Table S2** on page S15; spectrum: see **Figure S23** on page S38.

UV-Vis (from LC/MS run using acetonitrile/water with 0.1% formic acid) λ_{max} = 234, 256, 265, 274, 303, 317, 337, 351, 380, 397 nm.

HRMS (ESI+) calc. for $C_{40}H_{46}O_8N_4$ $[M+H]^+$: 709.3232; found: 709.3221.
(ESI+) calc for $C_{40}H_{46}O_8N_4$ $[M+2H]^{2+}$: 355.1652; found: 355.1649.

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.

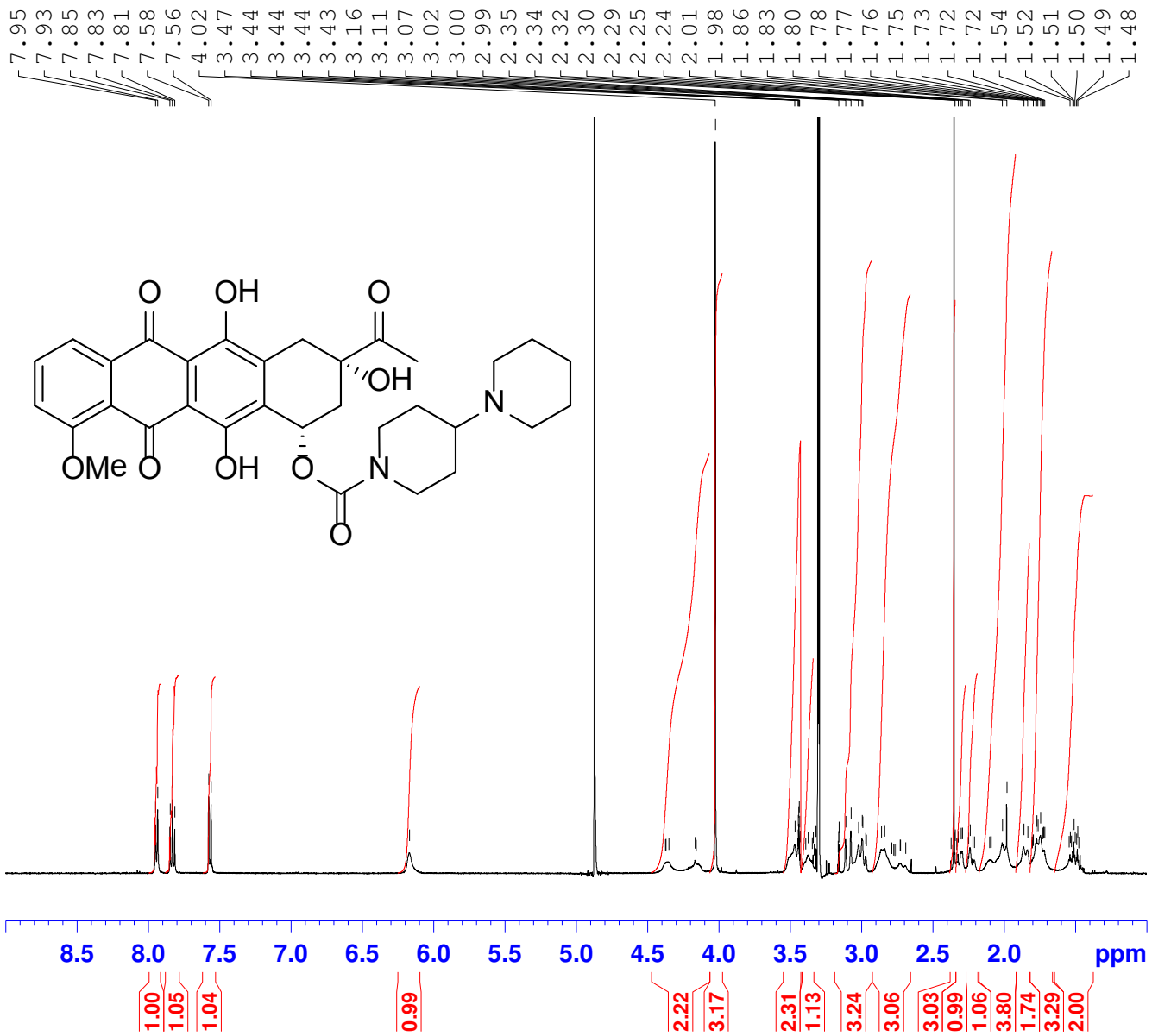
Table S1: ^{13}C NMR shifts of chartreusin (**2**) and the derivatives **11**, **13**, **18-21** a: pyridine-D_5, b: D_3CCN, c: CD_3OD. (δ [ppm], J [Hz], *: signals are overlapping)

	2[a]					**13**[b]			**11**[b]					**20**[c]					**18**[b]					**21**[b]			**18**[b]				
pos.	δ	∫	m	J_1	J_2	δ	∫	m	δ	∫	m	J_1	J_2	δ	∫	m	J_1	J_2	δ	∫	m	J_1	J_2	δ	∫	m	δ	∫	m	J_1	J_2
1	-					-			-					-					-					8.1-7.9		m	8.13	1	dd	7.7	0.9
1a	2.73	3	s			2.65	3	s	2.66	3	s			-					-					-					-		
2	7.32	1	d	8.8		7.53	1	br m	7.48	1	d	8.3		8.08	1	d	9.5		7.97	1	d	8.8		7.75		m	7.75	1	m		
3	7.47	1	d	8.3		7.53	1	br m	7.52	1	d	8.2		7.65	1	d	9.5		7.57	1	d	8.8		7.65		m	7.56	1	dd	7.6	0.9
7	8.36	1	dd	8.3	0.6	8.1-7.9	1	br m	8.29	1	d	8.3		8.2-8.1	1	m			8.38	1	dd	8.2	1.2	8.1-7.9		m	8.42	1	dd	8.6	0.8
8	7.66	1	t	8.1		7.68	1	br m	7.66	1	dd	8.3	7.5	7.8-7.9	1	m			7.74	1	dd	8.3	7.7	7.75		m	7.81	1	dd	8.0	7.8
9	7.77	1	d	7.8		7.45	1	br m	7.44	1	d	7.5		7.6-7.7	1	m			7.51	1	dd	7.6	1.2	7.44		m	7.77	1	dd	8.2	0.9
1'	5.83	1	d	4.1		-			-					-					-					-			-				
2'	5.08	1	dd	9.5	7.7	4.62; 4.23; 3.28; 2.97	8	m	4.58; 4.23; 3.27; 2.94	4	m			4.66 4.56 4.29 4.23		m			4.61; 4.26; 3.24; 3.00	4	m			4.63; 4.28; 3.36; 3.01	8	m	4.63; 4.28; 3.36; 3.01	4	m		
3'	4.34	1	dd	9.6	3.5	2.21; 1.86	8	m	2.07; 1.86	4	m			2.40; 2.26		m			2.18; 2.09	4	m			2.20; 1.90	8	m	2.18; 1.92	4	m		
4'	4.22	1	d	3.4		3.48	2	m	3.46	1	m			3.64*		m			3.46	1	m			3.46	2	m	3.46	1	m		
5'	4.12	1	q	6.5		-			-					-					-					-			-				
6'	1.58	3	d	6.5		-			-					-					-					-			-				
1''	6.56	1	d	4.1		-			-					-					-					-			-				
2''	4.57	1	dd	10.0	4.1	3.53; 2.90	8	m	3.58; 3.51; 3.02	4	m			3.65*; 3.17		m			3.55; 3.51, 3.02	4	m			3.54; 3.00	8	m	3.54; 2.99	4	m		
3''	3.87	1	dd	10.1	3.1	1.94	8	m	1.91	4	m			2.09; 1.92		m			1.94	4	m			1.92	8	m	1.94	4	m		
3''OMe	3.34	3	s			-			-					-					-					-			-				
4''	4.16	1	d	1.7		1.84; 1.51	4	m	1.86; 1.56	2	m			1.59; 1.61		m			1.82; 1.49	1	m			1.84; 1.50	4	m	1.83; 1.50	1	m		
5''	5.03	1	dq	6.3	0.9	-			-					-					-					-			-				
6''	1.59	3	d	6.5		-			-					-					-					-			-				

Table S2: ^{13}C NMR shifts of chartreusin (**2**) and the derivatives **11**, **13**, **18-21** a: pyridine-D_5, b: D_3CCN, c: CD_3OD. (δ [ppm], J [Hz], *: signal under solvent residual signal)

	2[a]	**11**[b]	**13**[b]	**18**[b]	**19**[b]	**820**[c]	**21**[b]
1	139.8	141.3	140.8	119.8	126.8	120.5	126.9
1a	22.5	22.6	22.6	-	-	-	-
2	133.2	135.0	135.3	138.3	132.6	138.9	132.8
3	121.1	122.7	122.8	123.9	122.9	124.2	122.9
3a	147.2	148.1	148.4	149.4	148.3	149.0	148.4
3a[1]	120.5	120.6	119.5	120.7	120.3	120.7	120.6
5	165.1	165.9	161.7	165.3	166.0	157.6	161.6
5a	97.8	98.4	109.8	98.0	98.8	109.0	109.8
5a[1]	109.5	111.0	112.4	110.3	111.0	111.4	112.4
6	159.5	158.46	153.3	158.7	158.6	153.7	152.3
6a	127.7	127.52	131.7	127.8	127.8	131.7	126.9
7	119.9	123.33	122.8	123.4	123.4	123.4	122.9
8	128.8	129.45	130.8	130.0	129.4	131.6	130.6
9	115.5	127.43	126.8	127.7	127.6	127.6	126.8
10	155.5	148.3	148.1	148.3	148.3	148.9	148.0
10a	119.7	122.9	121.8	122.8	123.5	121.3	121.9
10b	139.9	138.4	143.4	138.6	138.5	142.9	143.2
12	157.4	159.9	159.2	161.1	160.5	156.8	159.7
12a	118.5	118.8*	118.0	119.2	121.5	117.6	119.2
carbamate	-	154.5	153.3; 154.4	154.4	154.7	155.0; 155.4	154.7; 154.4
1'	101.6	-	-	-	-	-	-
2'	80.7	44.5; 44.0	45.1; 44.6; 44.5; 44.0	44.5; 44.0	44.6; 44.0	44.9; 44.5; 44.1; 43.9	45.1; 44.5; 44.0
3'	74.6	26.7; 26.5	27.1; 27.0; 26.6; 26.1	26.7; 26.5	26.8; 26.7	27.0; 26.6; 26.4; 26.2	26.4; 27.0; 27.7
4'	73.1	65.1	65.1; 64.7	65.1	65.0; 64.9	64.8; 64.4	65.0; 64.8; 64.7; 64.4
5'	72.3	-	-	-	-	-	-
6'	17.5	-	-	-	-	-	-
1''	102.3	-	-	-	-	-	-
2''	67.8	51.4; 50.8	51.8; 51.7; 50.8; 50.7; 50.5	51.5; 51.0	51.4; 51.3; 51.1; 51.0	51.6; 51.4; 51.2	50.7; 51.7
3''	82.0	24.4	22.4; 22.3	24.4	24.4	24.5; 24.4	24.3
3''OMe	57.2	-	-	-	-	-	-
4''	69.4	23.2	23.1	23.2	23.2	22.9; 22.8	23.1
5''	67.2	-	-	-	-	-	-
6''	17.5	-	-	-	-	-	-

Figure S1 ^{1}H NMR (CD_3OD) of daunorubicin-10-1,4‘-bipiperidine-1‘-carboxylate (**3**)

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PROCNO                 1
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PULPROG             zg30
TD                 65536
SOLVENT             MeOD
NS                   128
DS                     2
SWH          10000.000 Hz
FIDRES           0.152588 Hz
AQ            3.2768500 sec
RG                   645
DW              50.000 usec
DE               6.50 usec
TE               295.9 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1              14.00 usec
PL1              5.50 dB
PL1W         7.71660900 W
SFO1        500.3045027 MHz
SI               131072
SF          500.3000157 MHz
WDW                 GM
SSB                  0
LB              -0.30 Hz
GB                 0.3
PC                1.00
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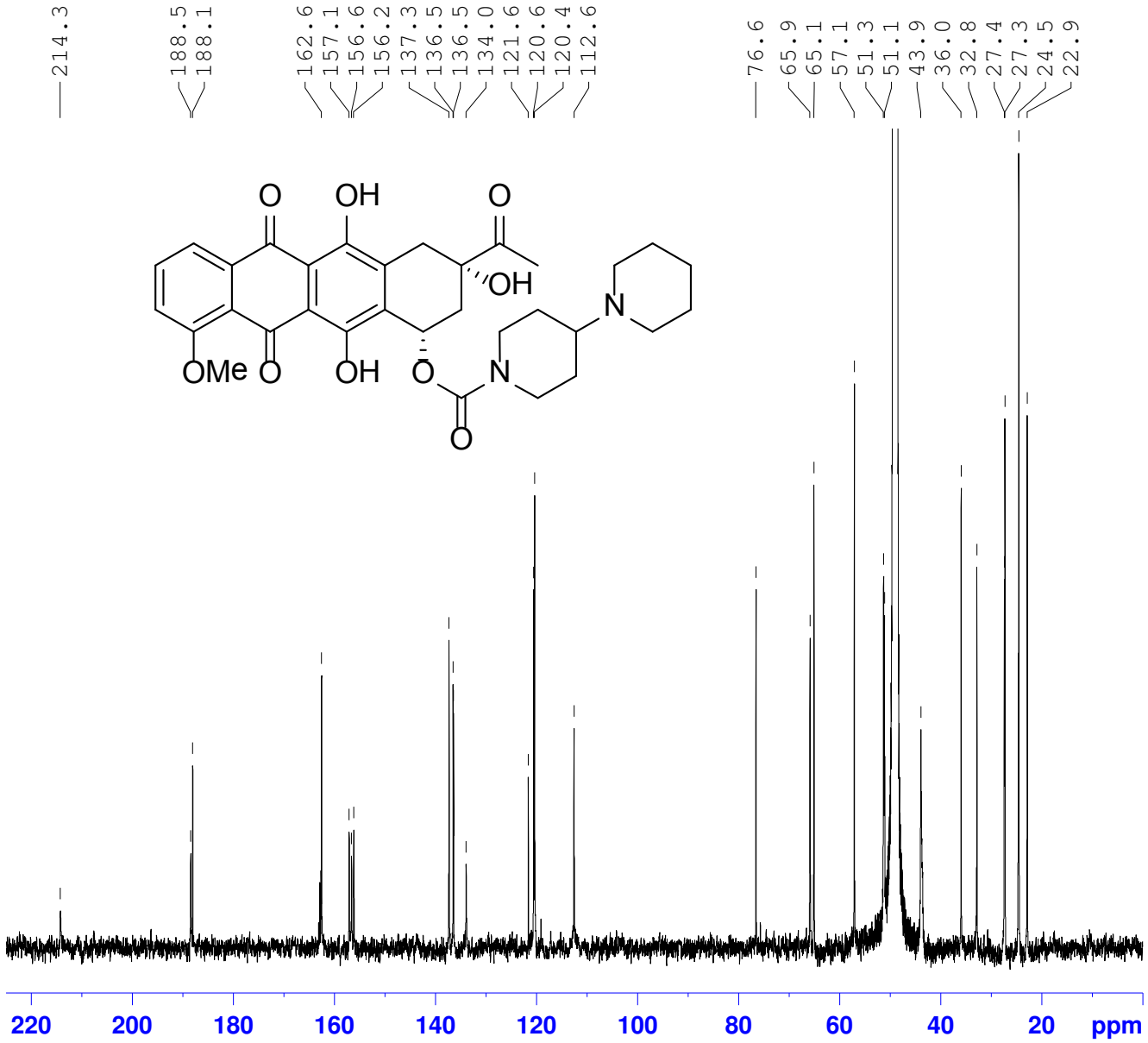
Figure S2 ^{13}C NMR (CD_3OD) of daunorubicin-10-1,4'-bipiperidine-1'-carboxylate (**3**)



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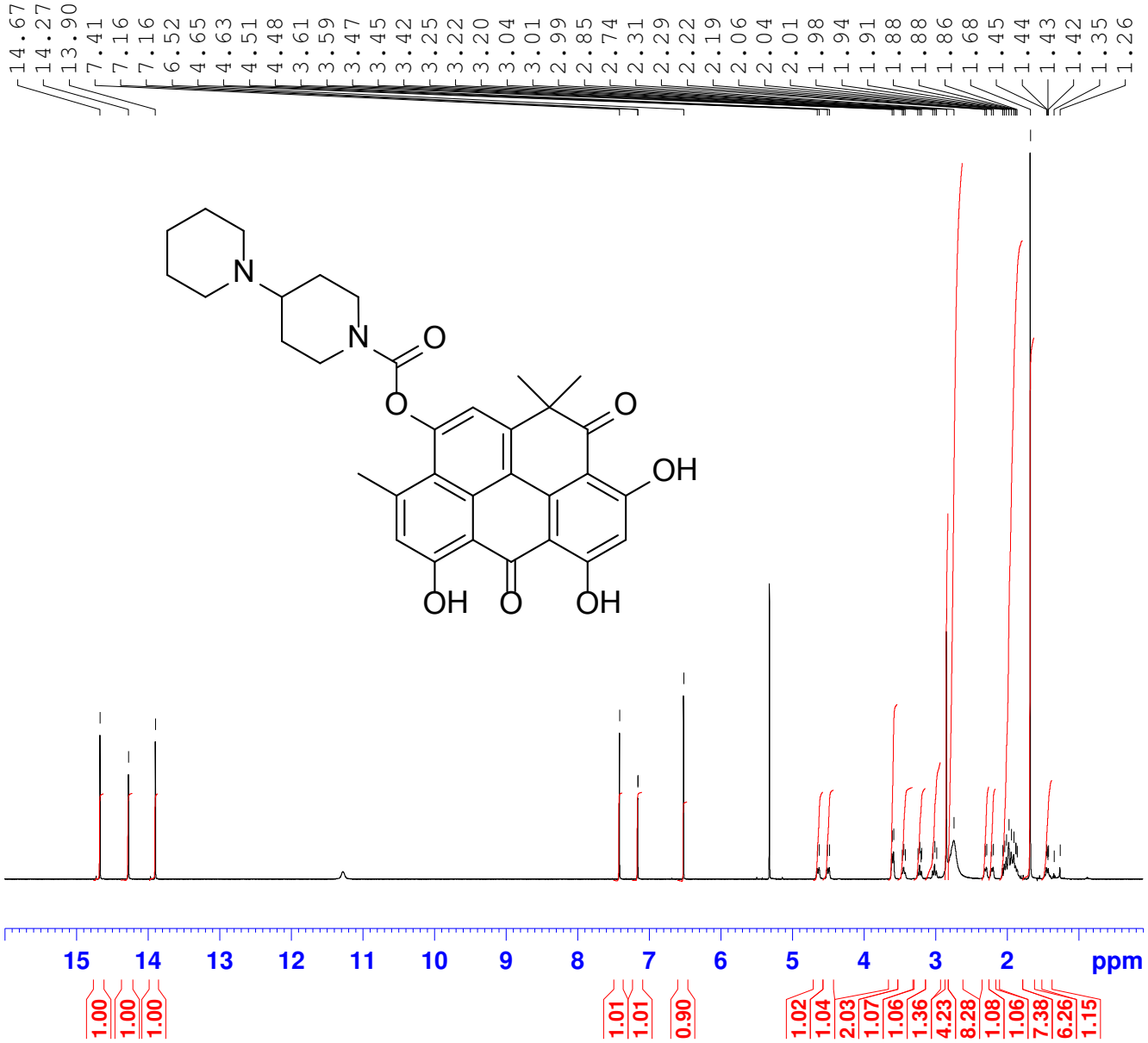
PULPROG	udeft
TD	23860
SOLVENT	MeOD
NS	4711
DS	4
SWH	36231.883 Hz
FIDRES	1.518520 Hz
AQ	0.3293180 sec
RG	2050
DW	13.800 usec
DE	20.00 usec
TE	298.8 K
D1	3.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
D20	10.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	14.00 usec
P12	2000.00 usec
P26	500.00 usec
PL1	0.00 dB
PL1W	75.60778046 W
SFO1	150.9553699 MHz
SP2	5.24 dB
SP8	5.24 dB
SPNAM2	Crp60comp.4
SPNAM8	Crp60,0.5,20.1
SPOAL2	0.500
SPOAL8	0.500
SPOFFS2	0.00 Hz
SPOFFS8	0.00 Hz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	4.00 dB
PL12	26.00 dB
PL2W	5.00000000 W
PL12W	0.03154787 W
SFO2	600.2724011 MHz
SI	262144
SF	150.9378005 MHz
WDW	EM
SSB	0
LB	5.00 Hz
GB	0
PC	1.40

Figure S3 ^{1}H NMR (CD_2Cl_2) of resistomycin-10-1,4‘-bipiperidine-1‘-carboxylate (**8**)

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PROCNO                 1
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Time               12.26
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PULPROG             zg30
TD                 65536
SOLVENT           CD2Cl2
NS                    36
DS                     2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2768500 sec
RG                   912
DW                50.000 usec
DE                 6.50 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 14.00 usec
PL1                5.50 dB
PL1W          7.71660900 W
SFO1        500.3045027 MHz
SI                131072
SF          500.3000204 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
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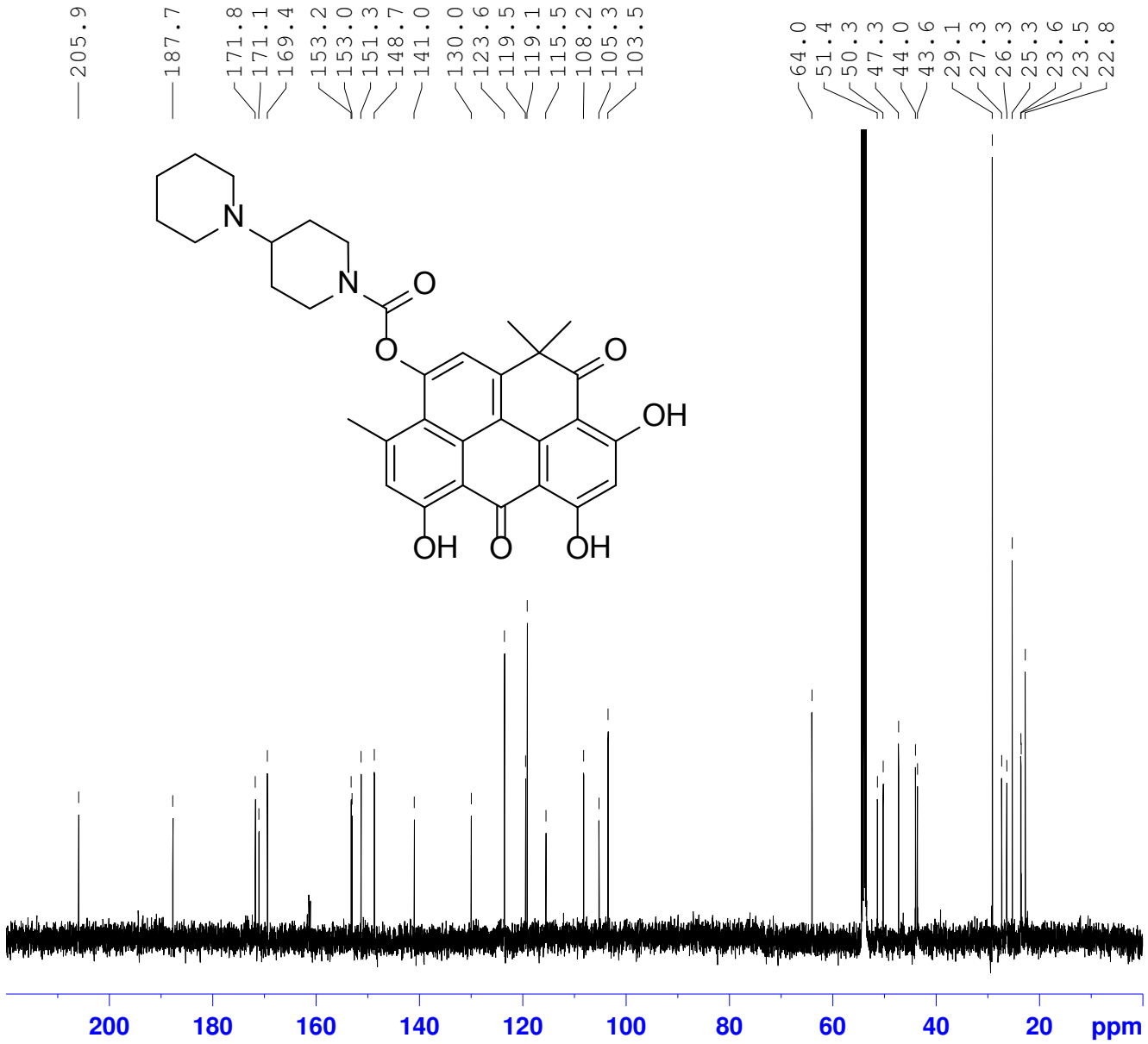
Figure S4 ^{13}C NMR (CD_2Cl_2) of resistomycin-10-1,4‘-bipiperidine-1‘-carboxylate (**8**)



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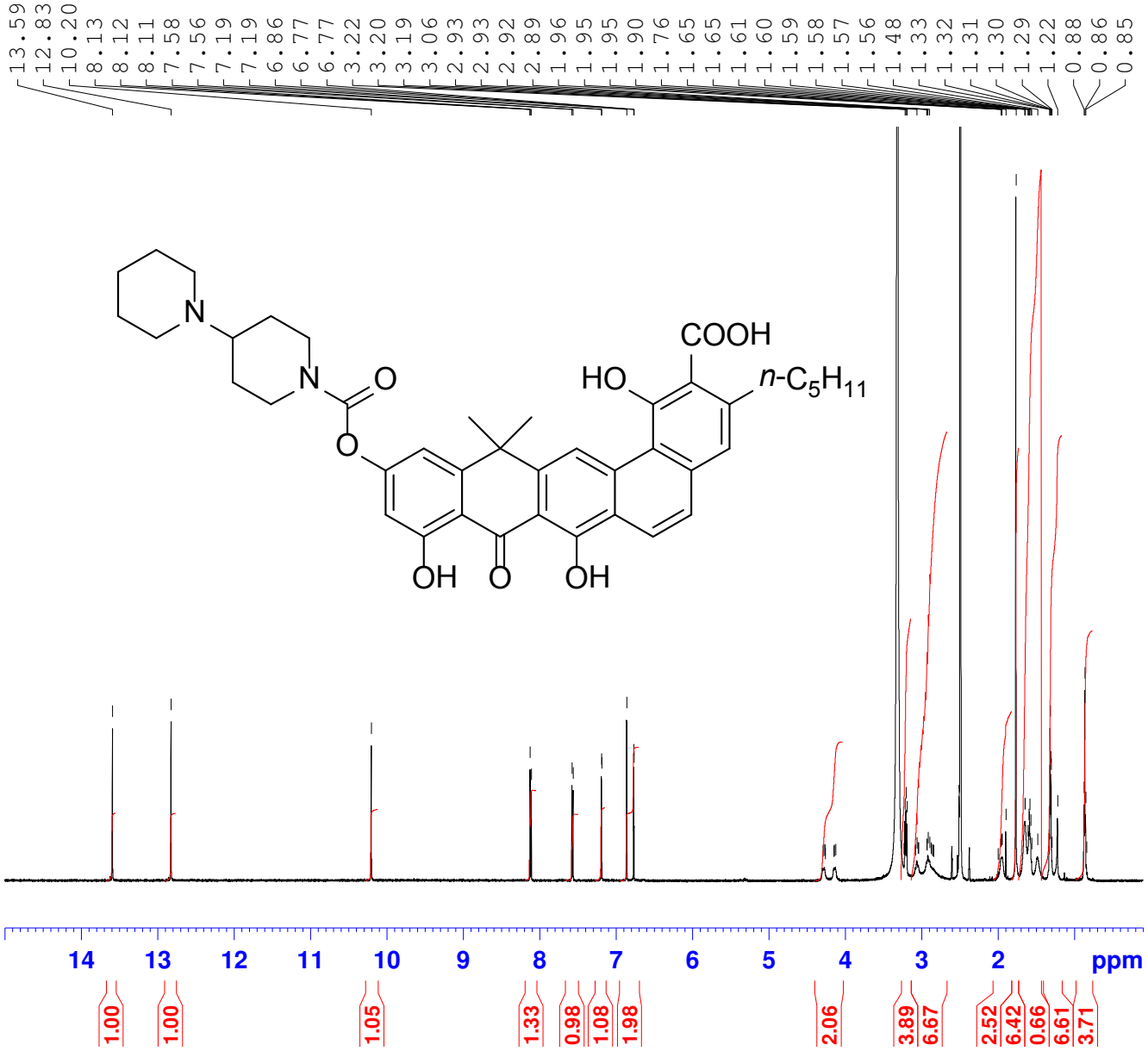
PROCNO	1
Date_	20140606
Time	14.32
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	udeft
TD	19996
SOLVENT	CD2C12
NS	12288
DS	4
SWH	29761.904 Hz
FIDRES	1.488393 Hz
AQ	0.3359828 sec
RG	2050
DW	16.800 usec
DE	6.50 usec
TE	298.0 K
D1	3.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
D20	10.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	13.00 usec
P12	2000.00 usec
P26	500.00 usec
PL1	3.30 dB
PL1W	44.17614746 W
SFO1	125.8150021 MHz
SP2	9.18 dB
SP8	9.18 dB
SPNAM2	Crp60comp.4
SPNAM8	Crp60,0.5,20.1
SPOAL2	0.500
SPOAL8	0.500
SPOFFS2	0.00 Hz
SPOFFS8	0.00 Hz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	5.50 dB
PL12	22.58 dB
PL2W	7.71660900 W
PL12W	0.15115638 W
SFO2	500.3020012 MHz
SI	262144
SF	125.8004641 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Figure S5 ^{1}H NMR (DMSO-D_6) of benastatin A-11-1,4‘-bipiperidine-1‘-carboxylate (**9**)

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PROCNO                  1
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Time                13.14
INSTRUM             spect
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PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ              2.7263477 sec
RG                     8
DW                41.600 usec
DE                 6.50 usec
TE                298.0 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  8.00 usec
PL1                 4.00 dB
PL1W          5.00000000 W
SFO1         600.2754024 MHz
SI                262144
SF           600.2700076 MHz
WDW                   GM
SSB                    0
LB                -0.30 Hz
GB                   0.3
PC                  1.00
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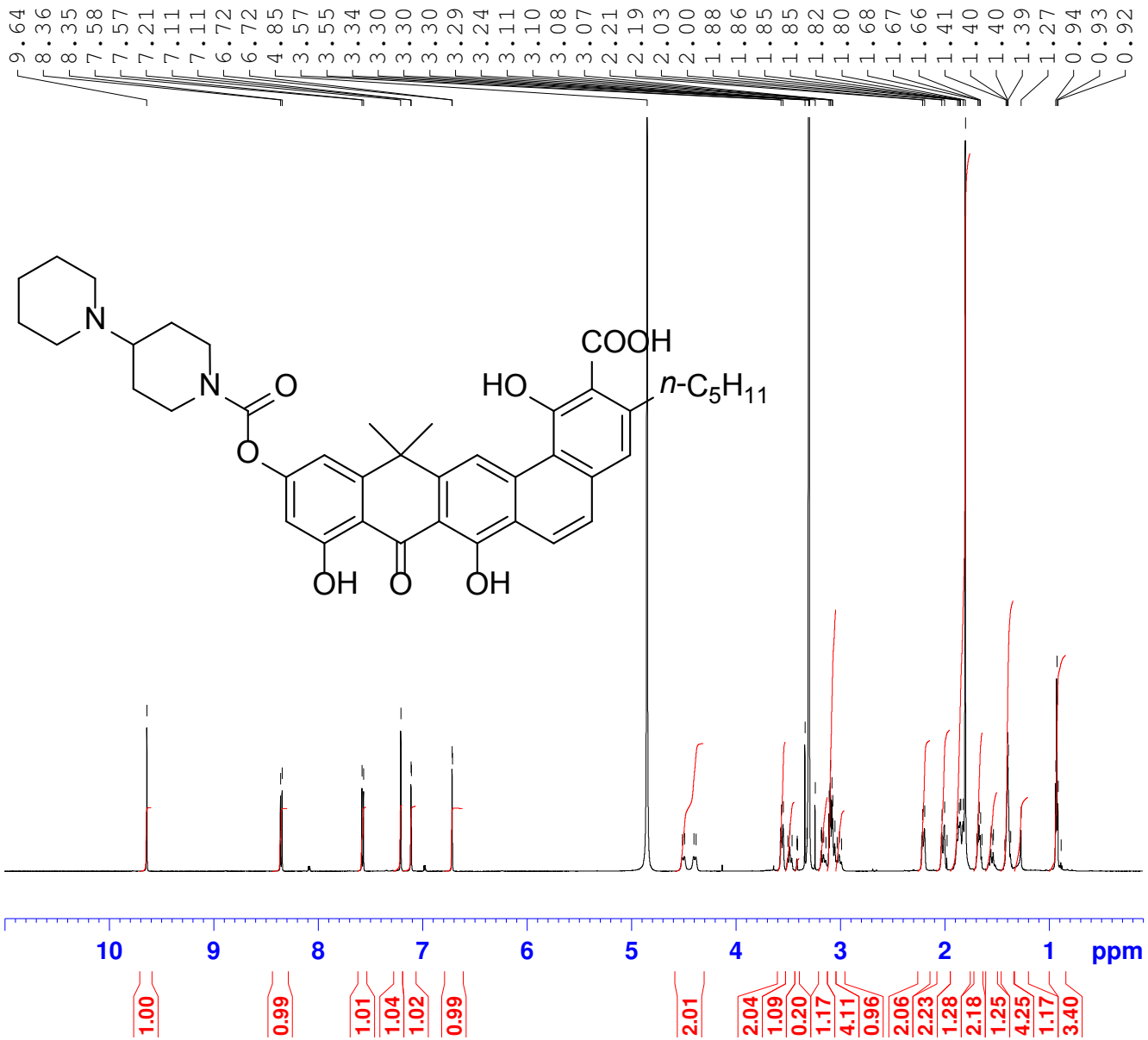
Figure S6 ^{1}H NMR (CD_3OD) of benastatin A-11-1,4‘-bipiperidine-1‘-carboxylate (**9**)

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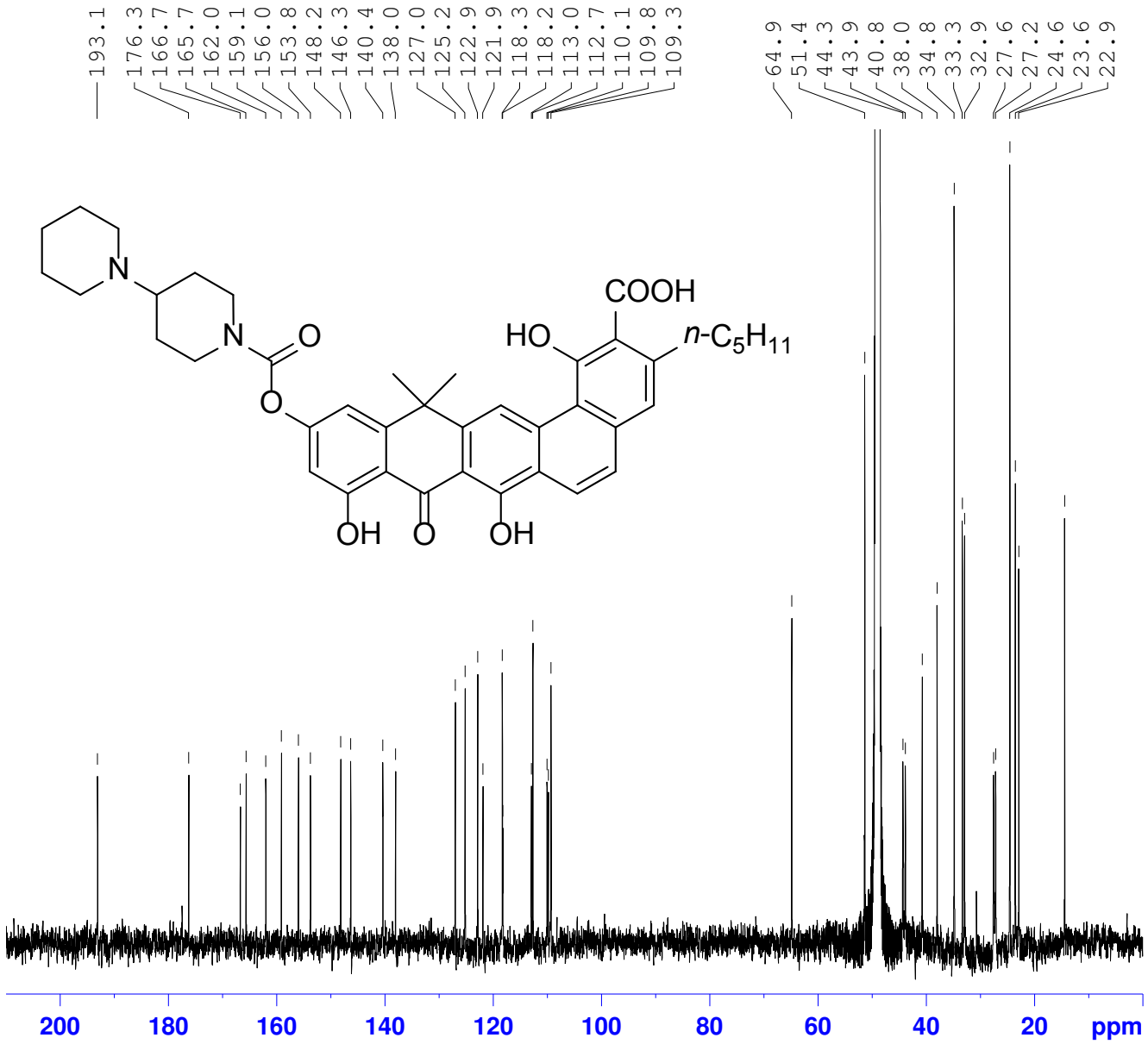
EXPNO                  1
PROCNO                 1
Date_           20150123
Time               11.38
INSTRUM            spect
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT             MeOD
NS                   128
DS                     2
SWH          12019.230 Hz
FIDRES        0.183399 Hz
AQ            2.7263477 sec
RG                  11.3
DW                41.600 usec
DE                 6.50 usec
TE                298.8 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.00 dB
PL1W         5.00000000 W
SFO1        600.2754024 MHz
SI               262144
SF          600.2700197 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

Figure S7 ^{13}C NMR (CD_3OD) of benastatin A-11-1,4‘-bipiperidine-1‘-carboxylate (**9**)

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PROCNO                  1
Date_            20150123
Time                12.53
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PULPROG             udeft
TD                  23860
SOLVENT              MeOD
NS                   1316
DS                      4
SWH            36231.883 Hz
FIDRES          1.518520 Hz
AQ             0.3293180 sec
RG                   2050
DW                13.800 usec
DE                20.00 usec
TE                298.8 K
D1           3.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D20         10.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                 14.00 usec
P12              2000.00 usec
P26               500.00 usec
PL1                 0.00 dB
PL1W         75.60778046 W
SFO1         150.9553699 MHz
SP2                 5.24 dB
SP8                 5.24 dB
SPNAM2       Crp60comp.4
SPNAM8    Crp60,0.5,20.1
SPOAL2              0.500
SPOAL8              0.500
SPOFFS2             0.00 Hz
SPOFFS8             0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                 4.00 dB
PL12               25.94 dB
PL2W          5.00000000 W
PL12W         0.03198674 W
SFO2         600.2724011 MHz
SI                262144
SF           150.9378012 MHz
WDW                  EM
SSB                   0
LB                 4.00 Hz
GB                    0
PC                 1.40
```
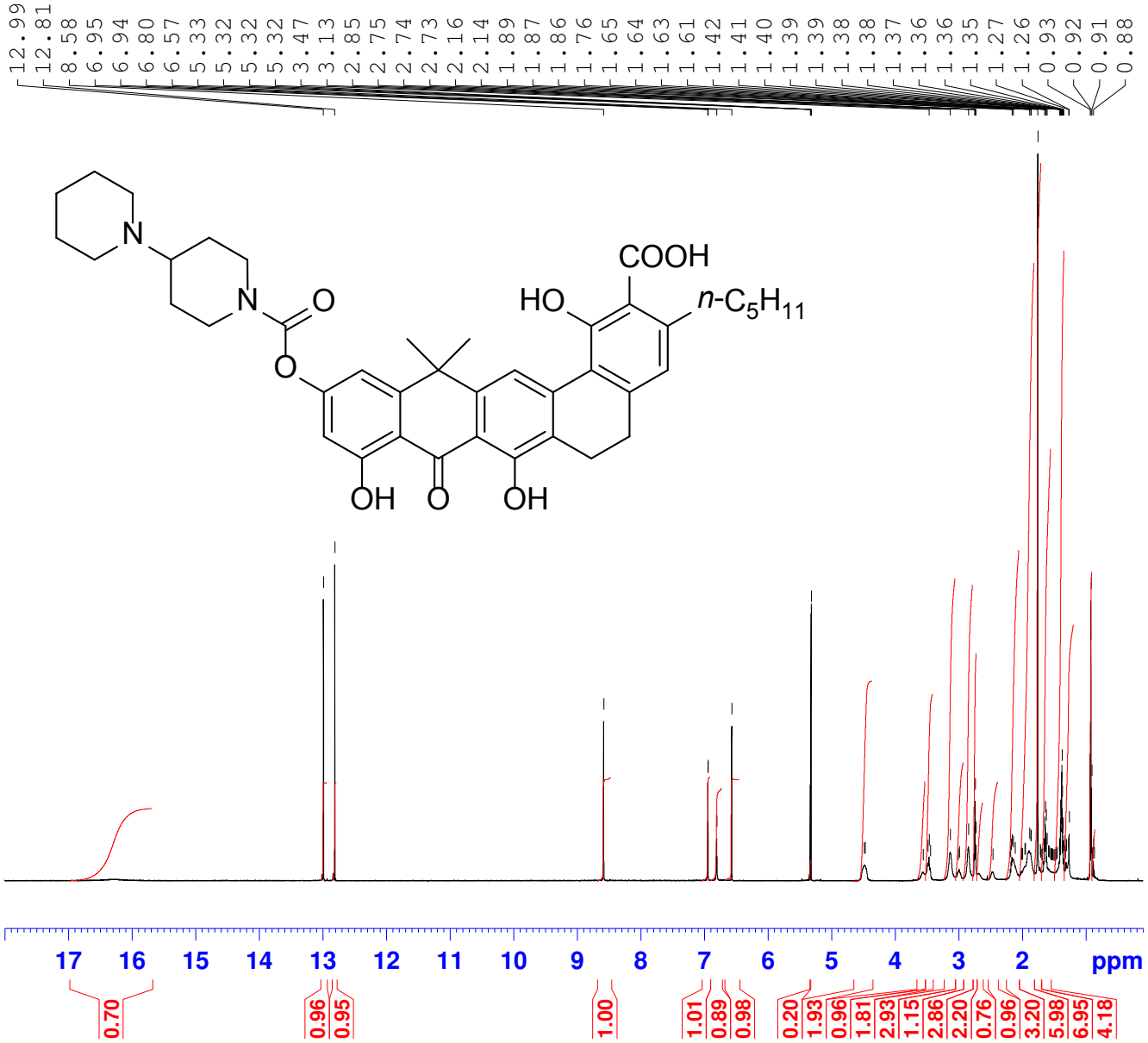
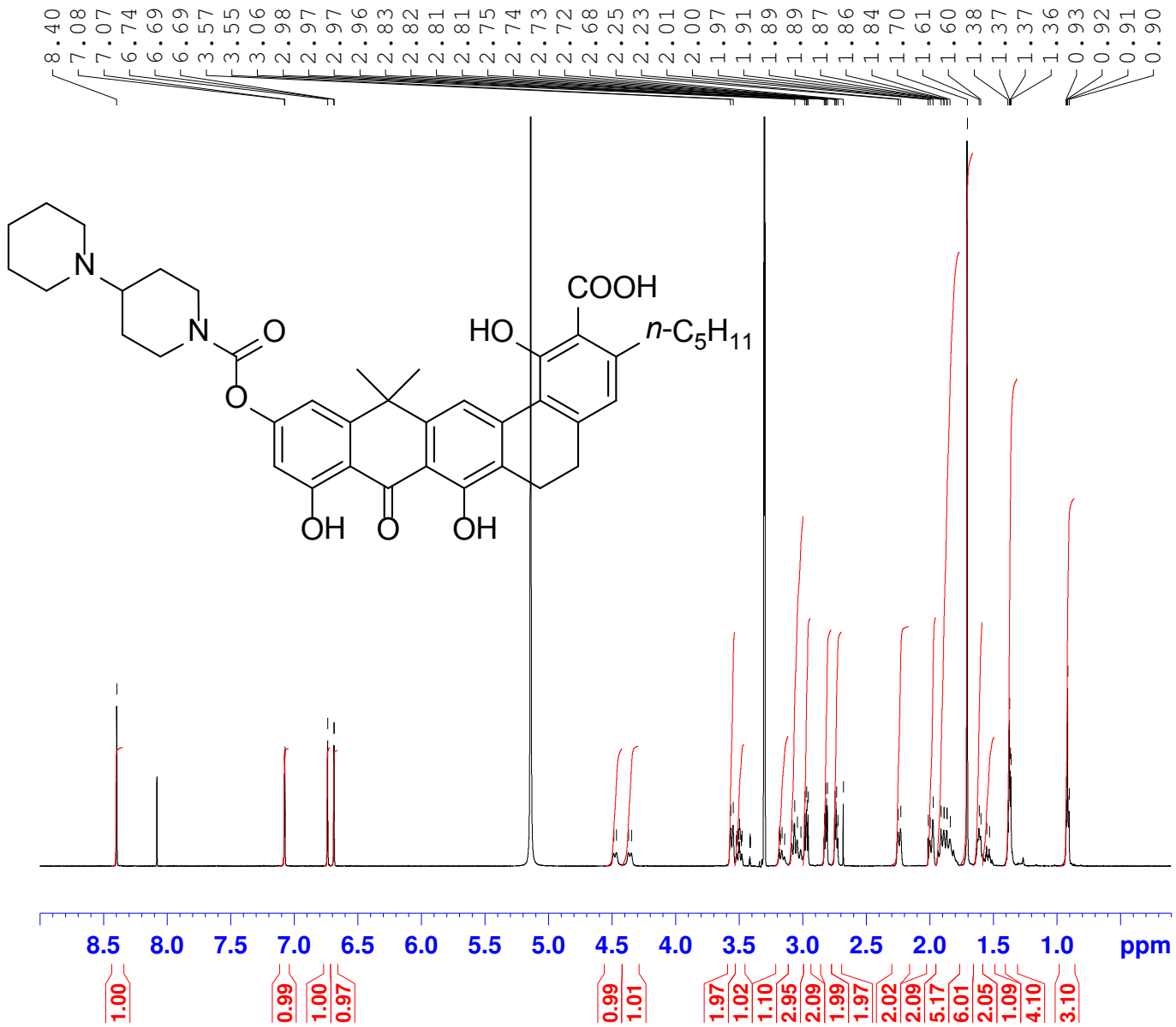

Figure S8 ^{1}H NMR (CD_2Cl_2) of benastatin B-11-1,4‘-bipiperidine-1‘-carboxylate (**10**)



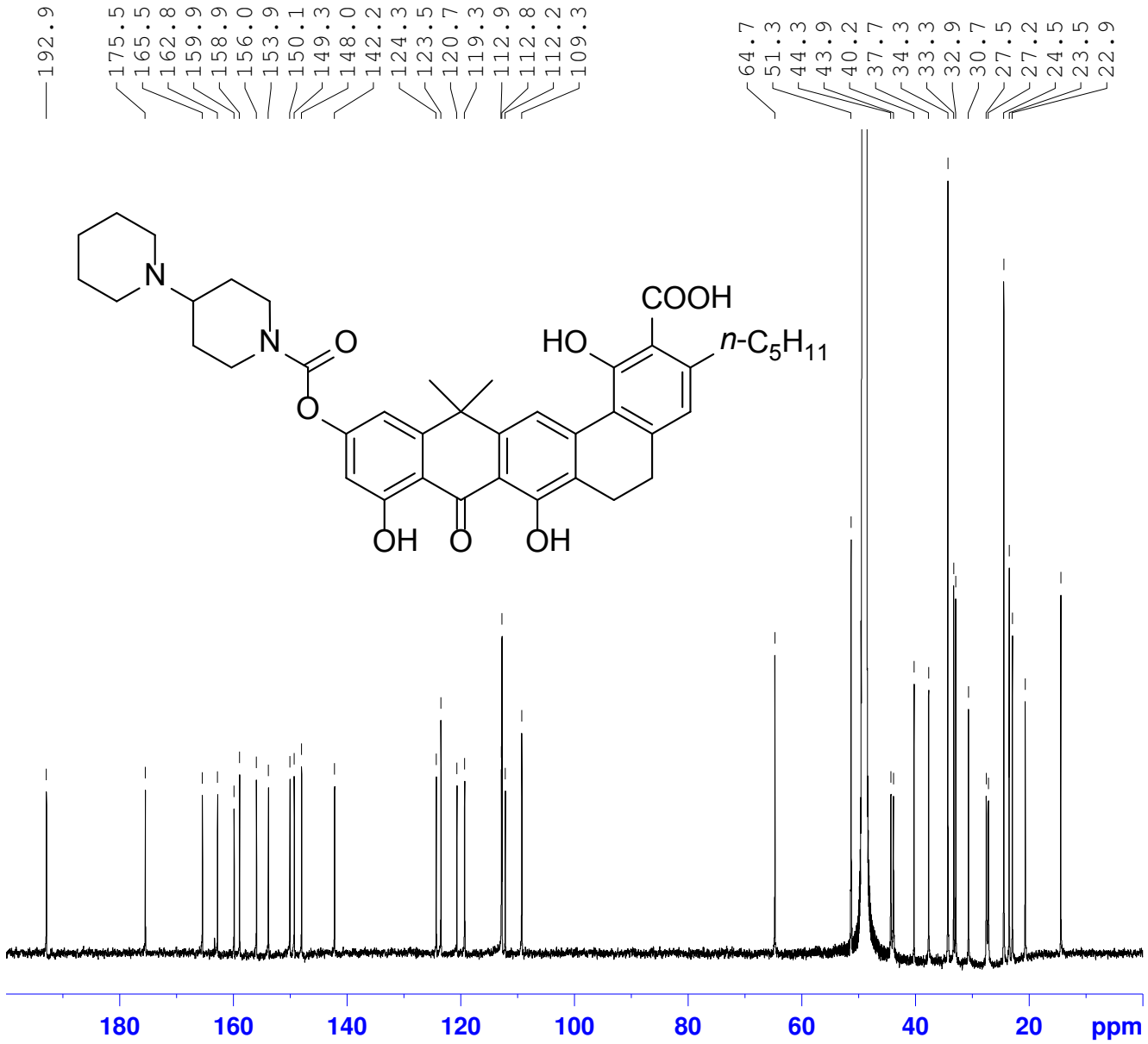

```
EXPNO                  1
PROCNO                 1
Date_           20140804
Time               11.12
INSTRUM            spect
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT           CD2Cl2
NS                   128
DS                     2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ             2.7263477 sec
RG                     8
DW                41.600 usec
DE                 6.50 usec
TE                298.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.00 dB
PL1W         5.00000000 W
SFO1        600.2754024 MHz
SI               262144
SF          600.2700202 MHz
WDW                  GM
SSB                   0
LB                -0.30 Hz
GB                  0.2
PC                 1.00
```

Figure S9 ^{1}H NMR (CD_3OD) of benastatin B-11-1,4‘-bipiperidine-1‘-carboxylate (**10**)



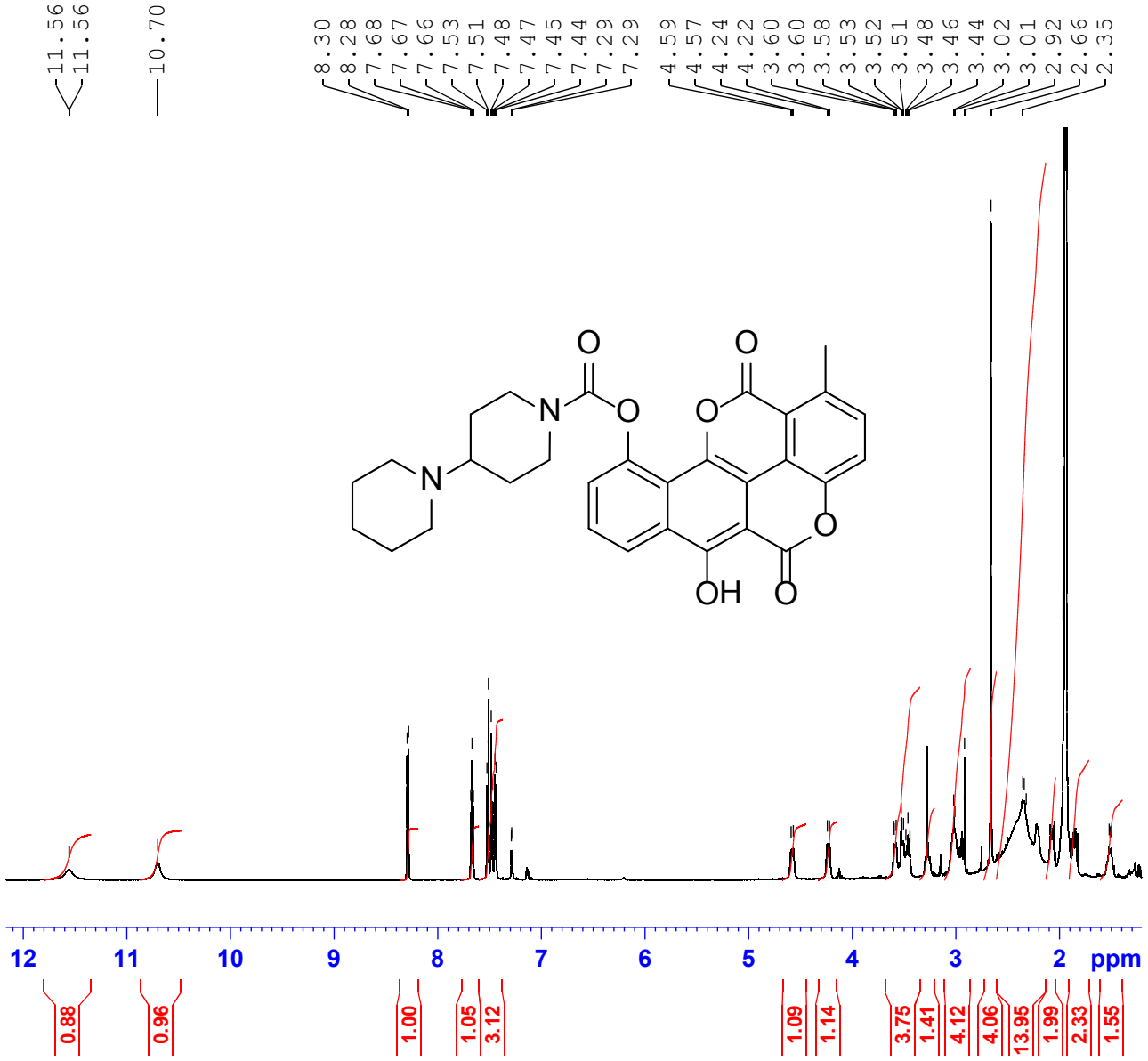

```
EXPNO                 10
PROCNO                 1
Date_           20150205
Time                6.08
INSTRUM            spect
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT             MeOD
NS                    64
DS                     2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                  25.4
DW                41.600 usec
DE                 6.50 usec
TE                298.8 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.00 dB
PL1W         5.00000000 W
SFO1        600.2754024 MHz
SI               262144
SF          600.2700212 MHz
WDW                  GM
SSB                   0
LB                -0.30 Hz
GB                  0.3
PC                 1.00
```

Figure S10 ^{13}C NMR (CD_3OD) of benastatin B-11-1,4'-bipiperidine-1'-carboxylate (**10**)



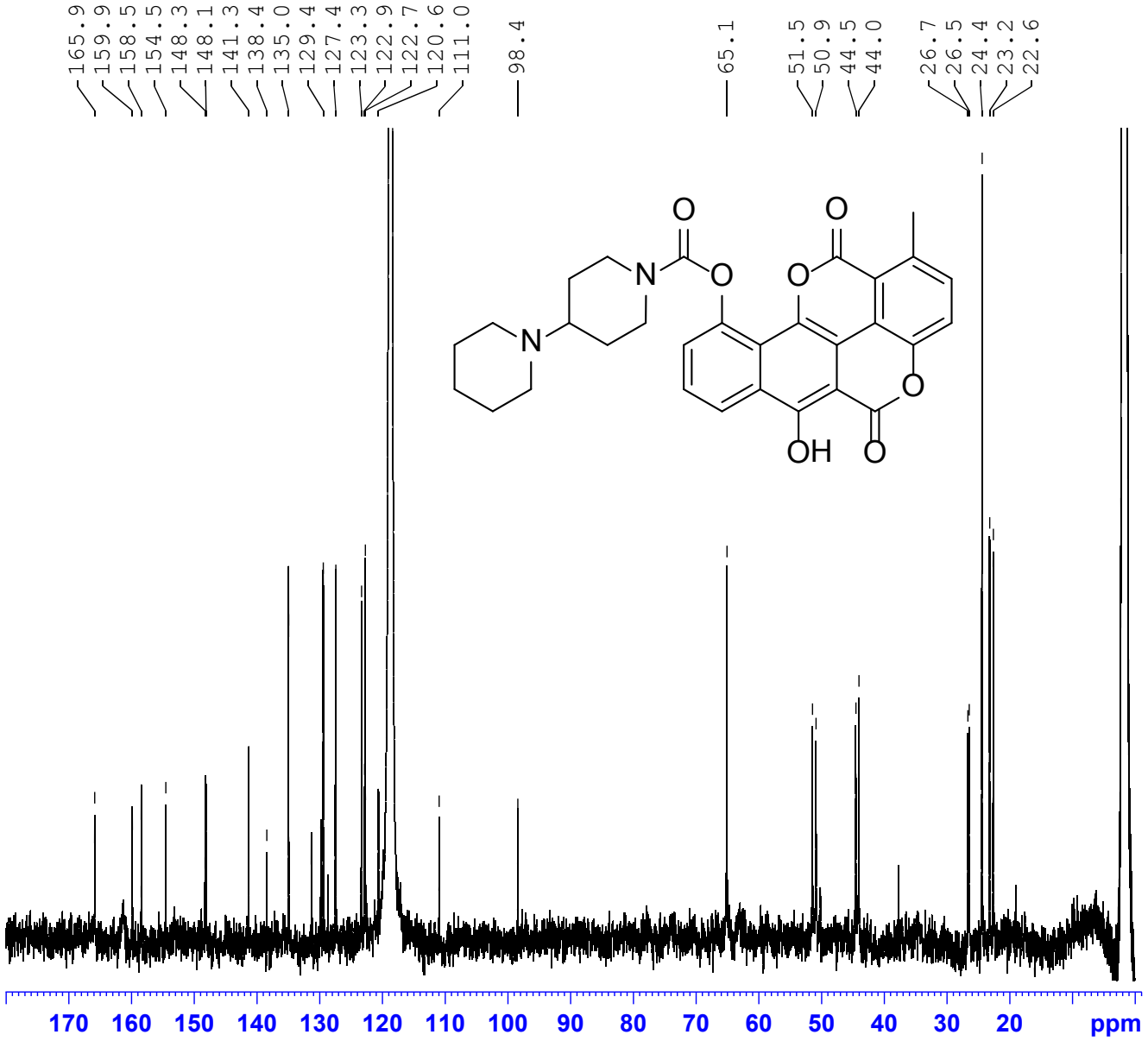
EXPNO	50
PROCNO	1
Date_	20150205
Time	4.04
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	udeft
TD	23860
SOLVENT	MeOD
NS	8192
DS	4
SWH	36231.883 Hz
FIDRES	1.518520 Hz
AQ	0.3293180 sec
RG	2050
DW	13.800 usec
DE	20.00 usec
TE	298.8 K
D1	3.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
D20	10.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	14.00 usec
P12	2000.00 usec
P26	500.00 usec
PL1	0.00 dB
PL1W	75.60778046 W
SFO1	150.9553699 MHz
SP2	5.24 dB
SP8	5.24 dB
SPNAM2	Crp60comp.4
SPNAM8	Crp60,0.5,20.1
SPOAL2	0.500
SPOAL8	0.500
SPOFFS2	0.00 Hz
SPOFFS8	0.00 Hz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	4.00 dB
PL12	26.00 dB
PL2W	5.00000000 W
PL12W	0.03154787 W
SFO2	600.2724011 MHz
SI	262144
SF	150.9378037 MHz
WDW	EM
SSB	0
LB	4.00 Hz
GB	0
PC	1.40

Figure S11 ^{1}H NMR (CD_3CN) of chartarin-10-1,4‘-bipiperidine-1‘-carboxylate (**11**)



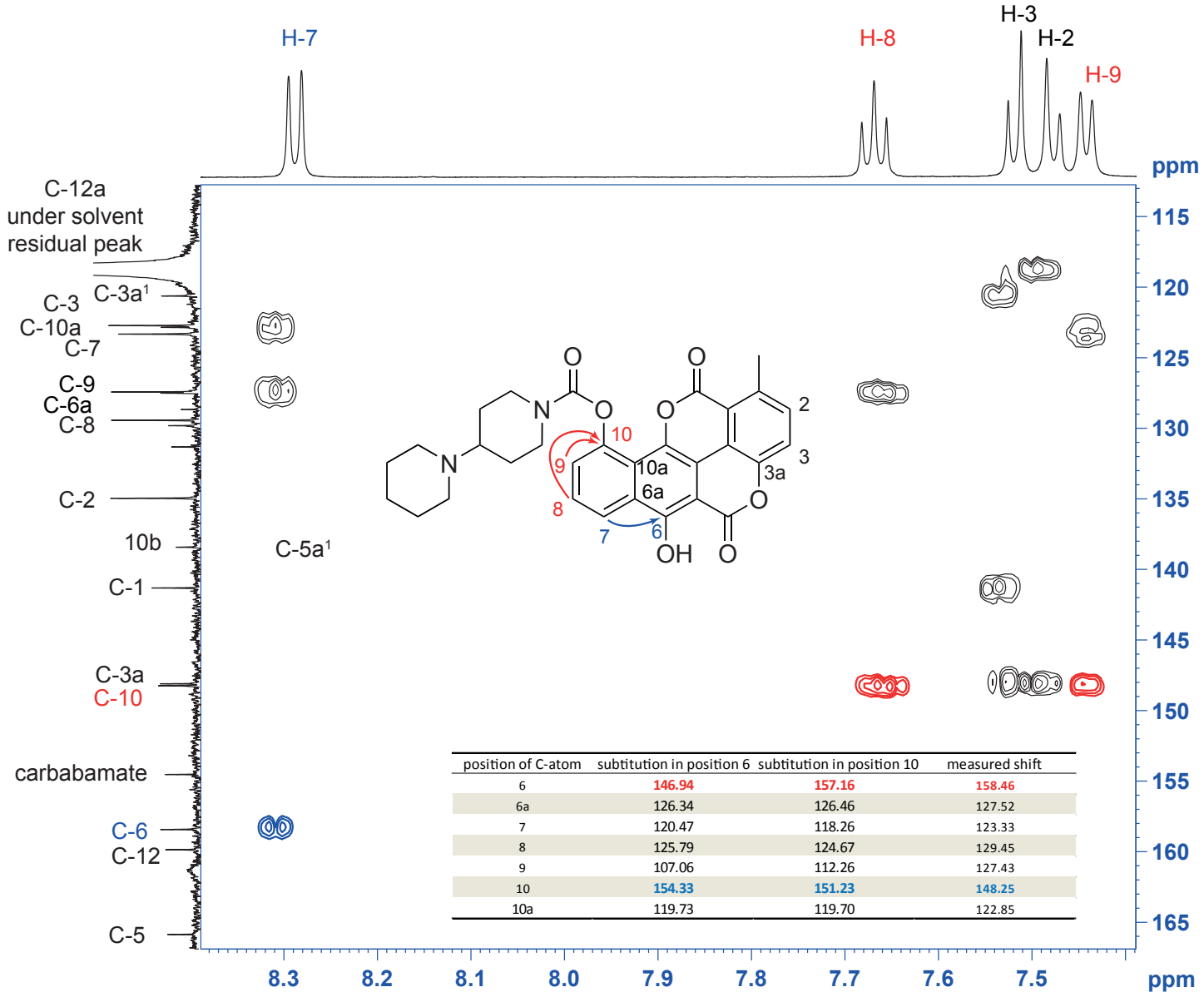

```
Current Data Parameters
NAME           6NNU350PR
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20131129
Time               11.13
INSTRUM            spect
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT            CD3CN
NS                    64
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7262976 sec
RG                    16
DW                41.600 usec
DE                 6.50 usec
TE                300.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.00 dB
PL1W          5.00000000 W
SFO1         600.2754024 MHz

F2 - Processing parameters
SI                262144
SF           600.2700202 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

Figure S12 ^{13}C NMR (CD_3CN) of chartarin-10-1,4‘-bipiperidine-1‘-carboxylate (**11**)




```
Current Data Parameters
NAME          6NNU350CA
EXPNO                50
PROCNO                1

F2 - Acquisition Parameters
Date_          20131130
Time              15.01
INSTRUM           spect
PROBHD   5 mm CPTCI 1H-
PULPROG           udeft
TD                23860
SOLVENT           CD3CN
NS                 8192
DS                    4
SWH           36231.883 Hz
FIDRES         1.518520 Hz
AQ            0.3292680 sec
RG                 2050
DW               13.800 usec
DE               20.00 usec
TE               300.1 K
D1            3.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D20          10.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                14.00 usec
P12             2000.00 usec
P26              500.00 usec
PL1       0 dB
PL1W         75.60778046 W
SFO1        150.9553699 MHz
SP2               5.24 dB
SP8               5.24 dB
SPNAM[2]    Crp60comp.4
SPNAM[8] Crp60,0.5,20.1
SPOAL2            0.500
SPOAL8            0.500
SPOFFS2  0 Hz
SPOFFS8  0 Hz

======== CHANNEL f2 ========
CPDPRG[2         waltz16
NUC2                1H
PCPD2            100.00 usec
PL2                4.00 dB
PL12              26.00 dB
PL2W          5.00000000 W
PL12W         0.03154787 W
SFO2        600.2724011 MHz

F2 - Processing parameters
SI                262144
SF          150.9378021 MHz
WDW                 EM
SSB       0
LB                4.00 Hz
GB        0
PC                1.40
```

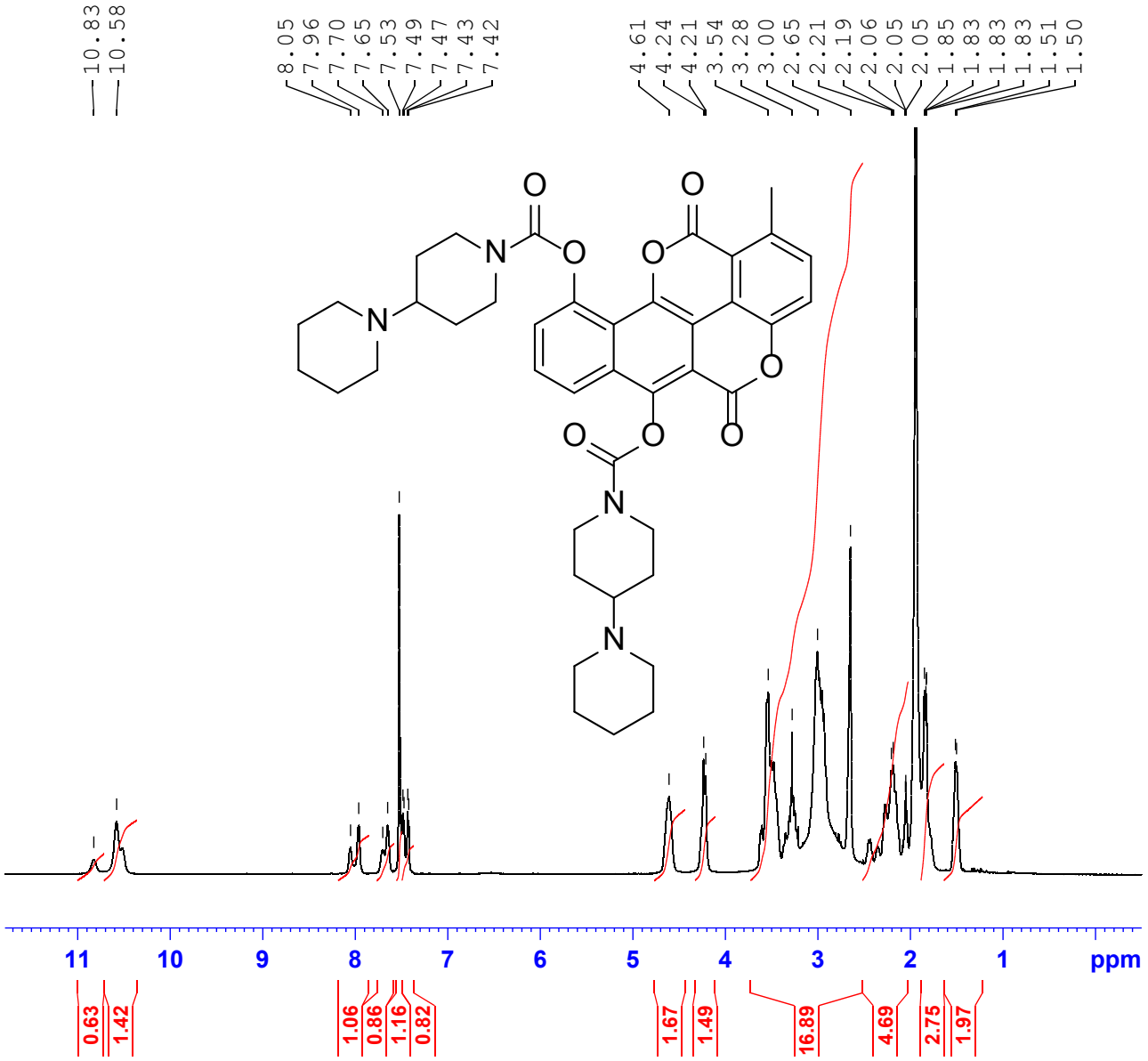
Figure S13 ^{1}H-^{13}C HMBC NMR (CD_3CN) of chartarin-10-1,4‘-bipiperidine-1‘-carboxylate (**11**)



position of C-atom	subtitution in position 6	subtitution in position 10	measured shift
6	146.94	157.16	158.46
6a	126.34	126.46	127.52
7	120.47	118.26	123.33
8	125.79	124.67	129.45
9	107.06	112.26	127.43
10	154.33	151.23	148.25
10a	119.73	119.70	122.85

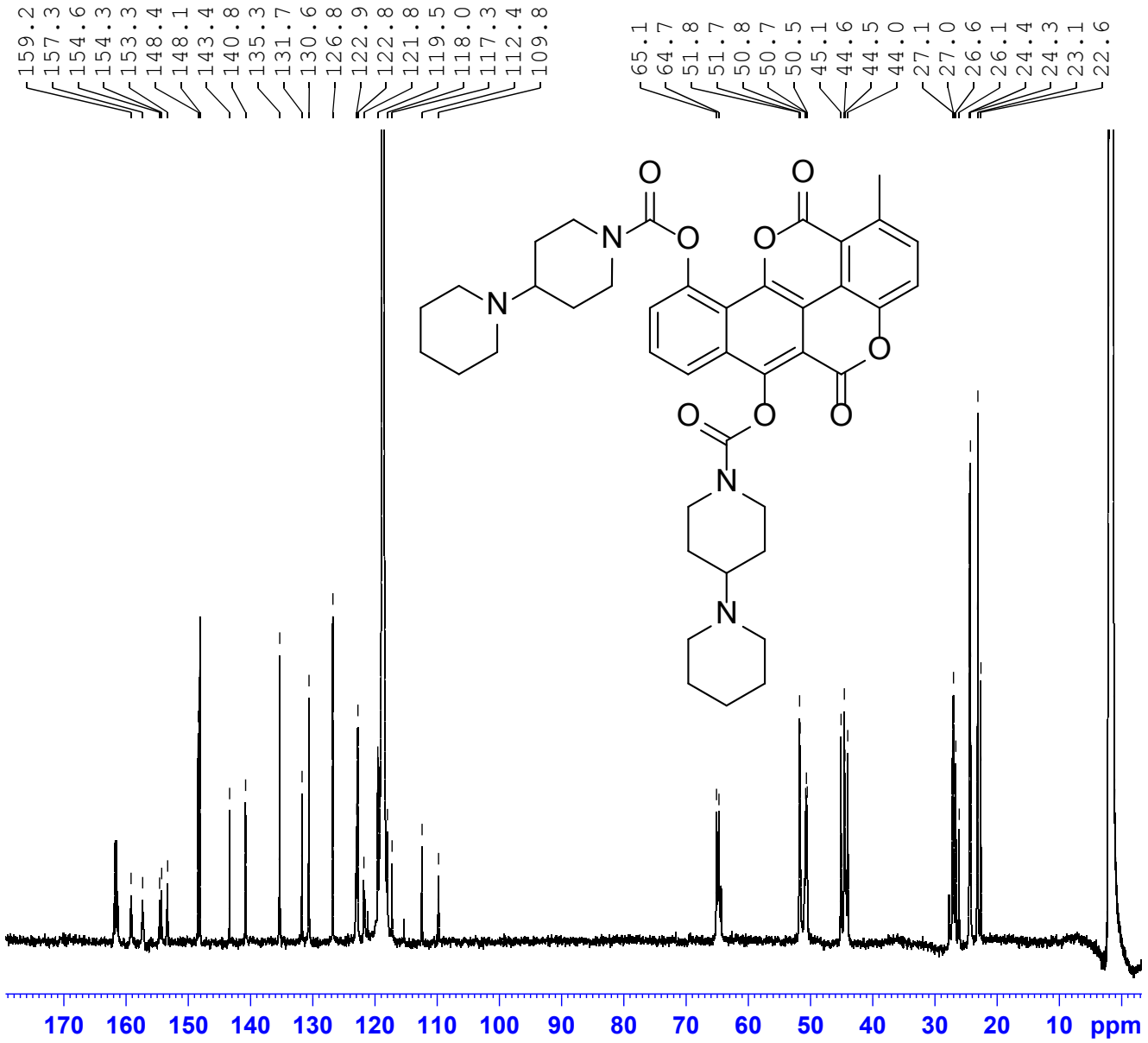
```
NAME            6NNU350HM
EXPNO                  10
PROCNO                  1
Date_            20131130
Time                16.26
INSTRUM             spect
PROBHD    5 mm CPTCI 1H-
PULPROG     hmbcgplpndqf
TD                   4096
SOLVENT             CD3CN
NS                     64
DS                      0
SWH              8417.509 Hz
FIDRES           2.055056 Hz
AQ             0.2433524 sec
RG                   2050
DW                59.400 usec
DE                 6.50 usec
TE                300.1 K
CNST2        145.0000000
CNST13        10.0000000
D0             0.00000300 sec
D1             1.50000000 sec
D2             0.00344828 sec
D6             0.05000000 sec
D16            0.00010000 sec
IN0            0.00001505 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.00 usec
P2                  16.00 usec
PL1                  4.00 dB
PL1W          5.00000000 W
SFO1         600.2742019 MHz

======== CHANNEL f2 ========
NUC2                  13C
P3                  14.00 usec
PL2                  0.00 dB
PL2W         75.60778046 W
SFO2         150.9546152 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPNAM3           SINE.100
GPZ1                50.00 %
GPZ2                30.00 %
GPZ3                40.10 %
P16               1000.00 usec
ND0                    2
TD                   192
SFO1           150.9546 MHz
FIDRES         172.968826 Hz
SW               220.000 ppm
FnMODE                 QF
SI                   2048
SF           600.2700426 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.40
SI                  1024
MC2                    QF
SF           150.9377842 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
```

Figure S14 ^{1}H NMR (CD_3CN) of chartarin-6,10 di-1,4‘-bipiperidine-1‘-carboxylate (**13**)



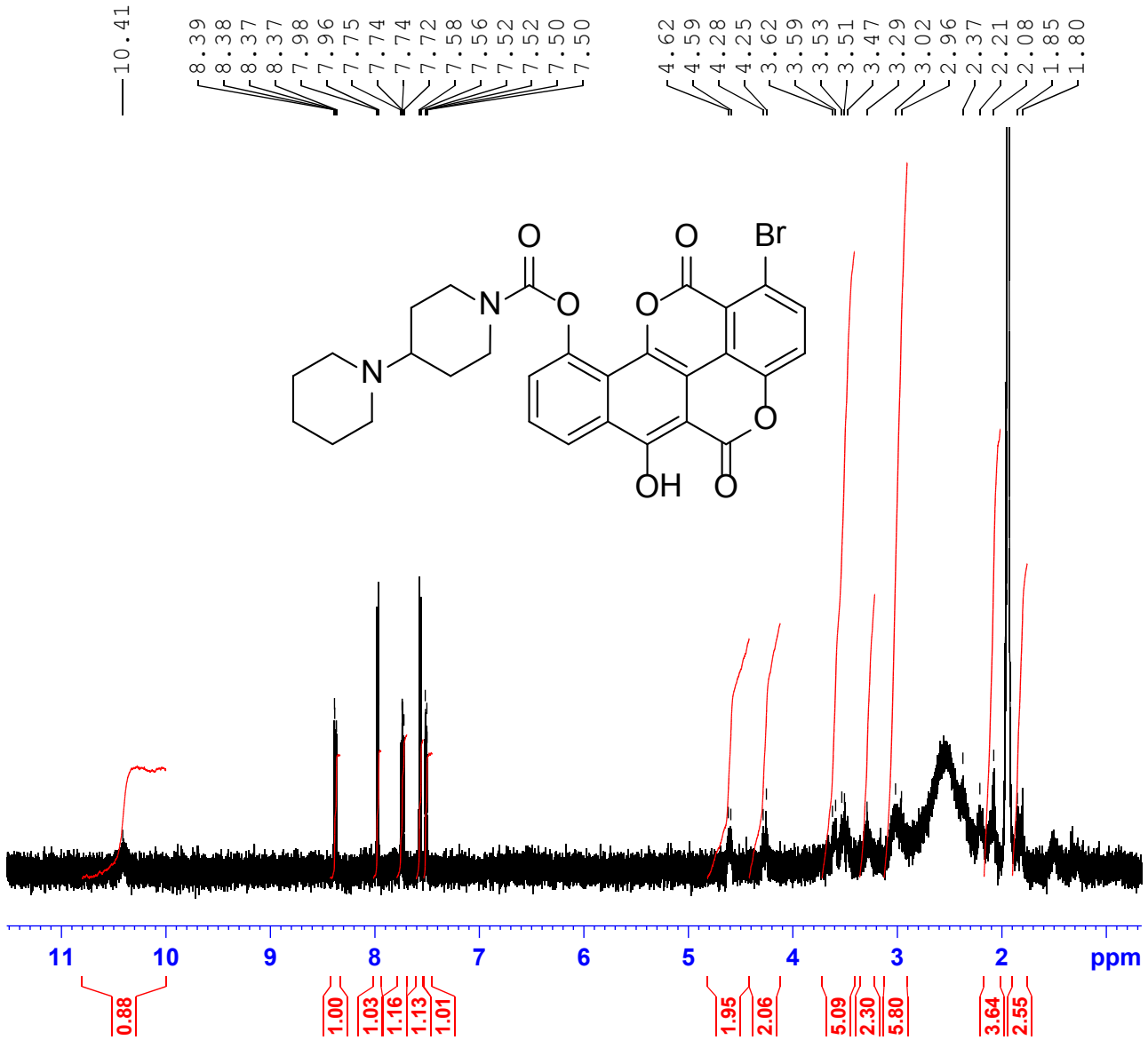

```
Current Data Parameters
NAME            6NNU349PR
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20131129
Time                11.07
INSTRUM             spect
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT            CD3CN
NS                    46
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7262976 sec
RG                    18
DW                41.600 usec
DE                 6.50 usec
TE                300.0 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                4.00 dB
PL1W         5.00000000 W
SFO1        600.2754024 MHz

F2 - Processing parameters
SI                262144
SF          600.2700201 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

Figure S15 ^{13}C NMR (CD_3CN) of chartarin-6,10 di-1,4‘-bipiperidine-1‘-carboxylate (**13**)



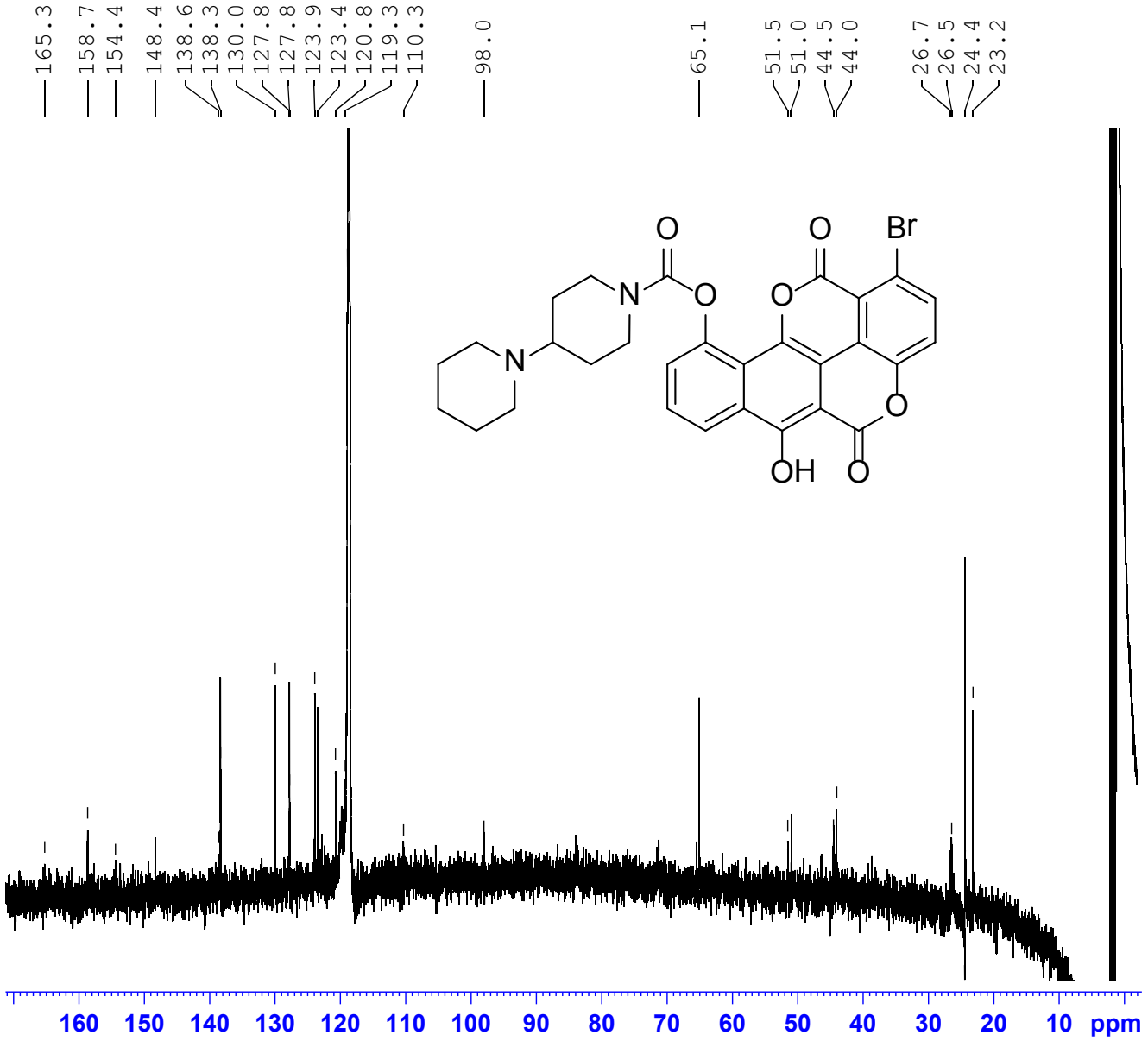

```
Current Data Parameters
NAME          6NNU349CA
EXPNO                50
PROCNO                1

F2 - Acquisition Parameters
Date_          20131201
Time               9.10
INSTRUM           spect
PROBHD   5 mm CPTCI 1H-
PULPROG           udeft
TD                23860
SOLVENT           CD3CN
NS                10240
DS                    4
SWH           36231.883 Hz
FIDRES         1.518520 Hz
AQ            0.3292680 sec
RG                 2050
DW               13.800 usec
DE               20.00 usec
TE               300.0 K
D1            3.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D20          10.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 14.00 usec
P12              2000.00 usec
P26               500.00 usec
PL1       0 dB
PL1W         75.60778046 W
SFO1        150.9553699 MHz
SP2                5.24 dB
SP8                5.24 dB
SPNAM[2]     Crp60comp.4
SPNAM[8] Crp60,0.5,20.1
SPOAL2             0.500
SPOAL8             0.500
SPOFFS2  0 Hz
SPOFFS8  0 Hz

======== CHANNEL f2 ========
CPDPRG[2         waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                4.00 dB
PL12              26.00 dB
PL2W          5.00000000 W
PL12W         0.03154787 W
SFO2         600.2724011 MHz

F2 - Processing parameters
SI                 262144
SF          150.9378025 MHz
WDW                   EM
SSB       0
LB                 4.00 Hz
GB        0
PC                 1.40
```

Figure S16 ^{1}H NMR (CD_3CN) of bromochartarin-10-1,4‘-bipiperidine-1‘-carboxylate (**18**)



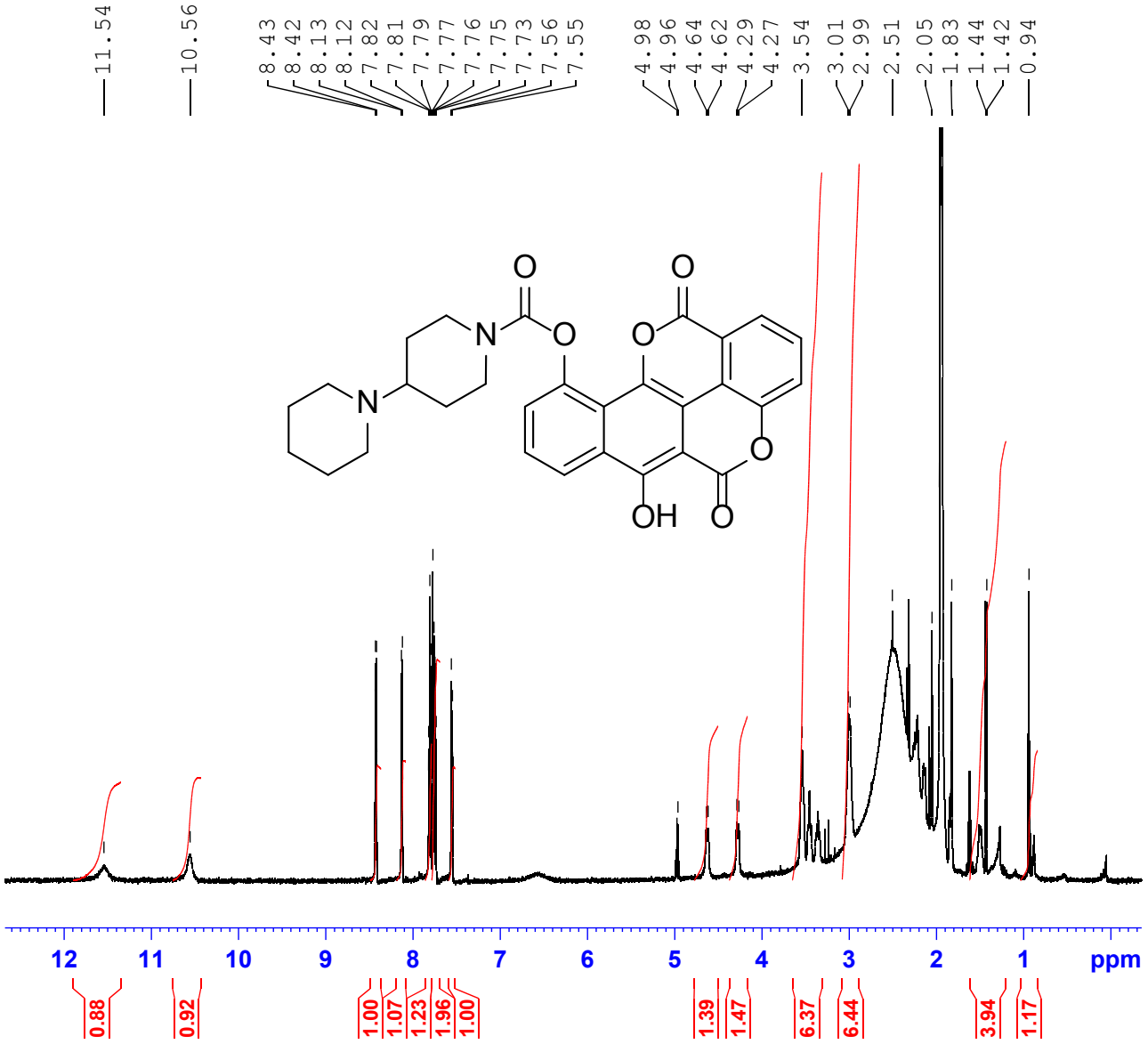

```
Current Data Parameters
NAME                  5NNU352
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20131207
Time                  14.34
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CD3CN
NS                       32
DS                        2
SWH               10000.000 Hz
FIDRES                0.152588 Hz
AQ                3.2767999 sec
RG                     1030
DW                   50.000 usec
DE                    6.50 usec
TE                   299.9 K
D1              1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                    14.00 usec
PL1                    5.50 dB
PL1W            7.71660900 W
SFO1           500.3045027 MHz

F2 - Processing parameters
SI                    131072
SF             500.3000151 MHz
WDW                       no
SSB       0
LB        0 Hz
GB        0
PC                     1.00
```

Figure S17 ^{13}C NMR (CD_3CN) of bromochartarin-10-1,4‘-bipiperidine-1‘-carboxylate (**18**)



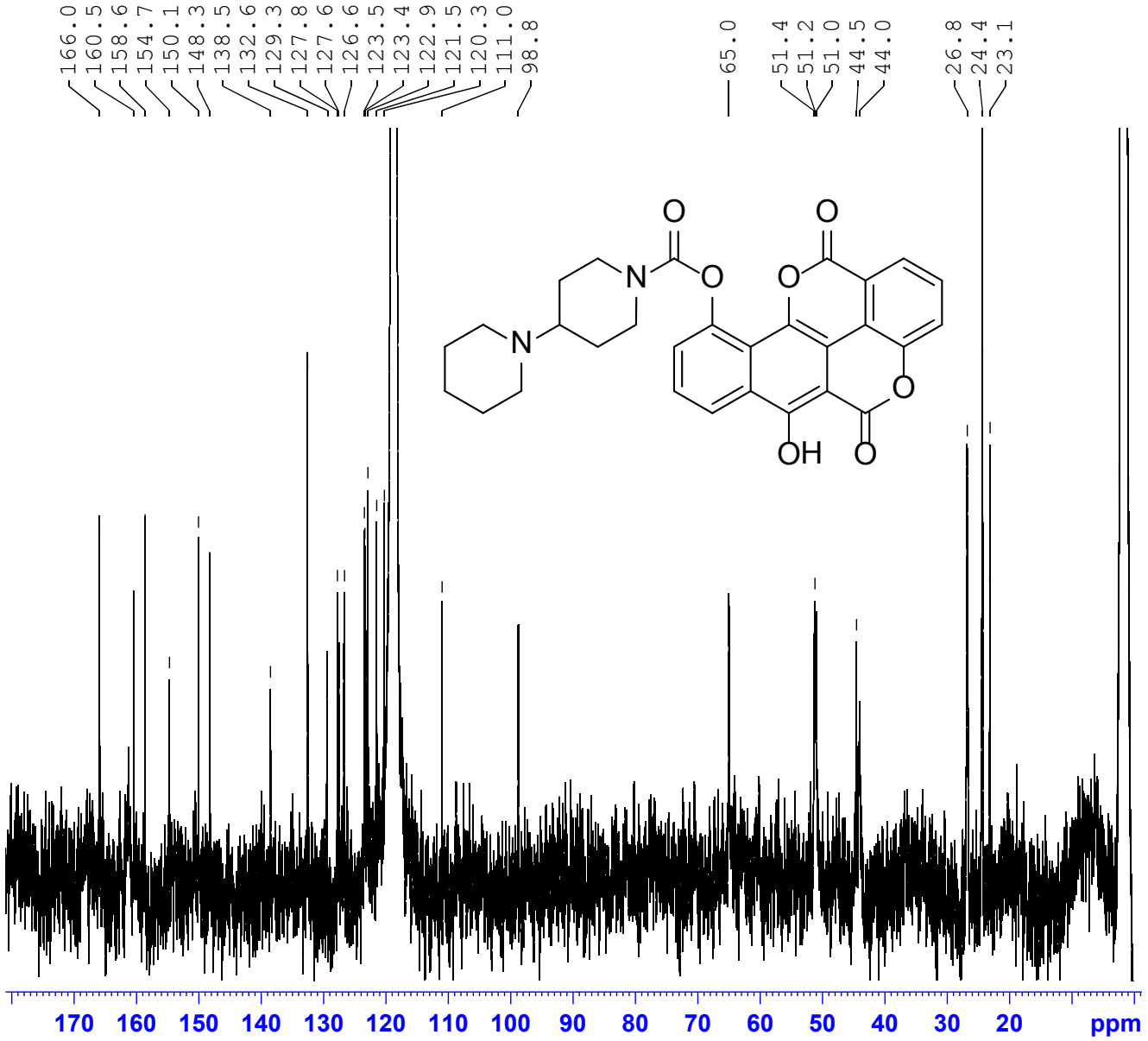

```
Current Data Parameters
NAME             5NNU352
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20131208
Time                0.50
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG            udeft
TD                 19996
SOLVENT            CD3CN
NS                 24000
DS                     4
SWH            29761.904 Hz
FIDRES          1.488393 Hz
AQ             0.3359328 sec
RG                  2050
DW                16.800 usec
DE                 6.50 usec
TE                300.0 K
D1           3.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D20         10.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 13.00 usec
P12              2000.00 usec
P26               500.00 usec
PL1                 3.30 dB
PL1W         44.17614746 W
SFO1         125.8150021 MHz
SP2                9.18 dB
SP8                9.18 dB
SPNAM[2]     Crp60comp.4
SPNAM[8] Crp60,0.5,20.1
SPOAL2             0.500
SPOAL8             0.500
SPOFFS2  0 Hz
SPOFFS8  0 Hz

======== CHANNEL f2 ========
CPDPRG[2         waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                5.50 dB
PL12              22.58 dB
PL2W          7.71660900 W
PL12W         0.15115638 W
SFO2         500.3020012 MHz

F2 - Processing parameters
SI                262144
SF         125.8003612 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

Figure S18 ^{1}H NMR (CD_3CN) of norchartarin-10-1,4‘-bipiperidine-1‘-carboxylate (**19**)



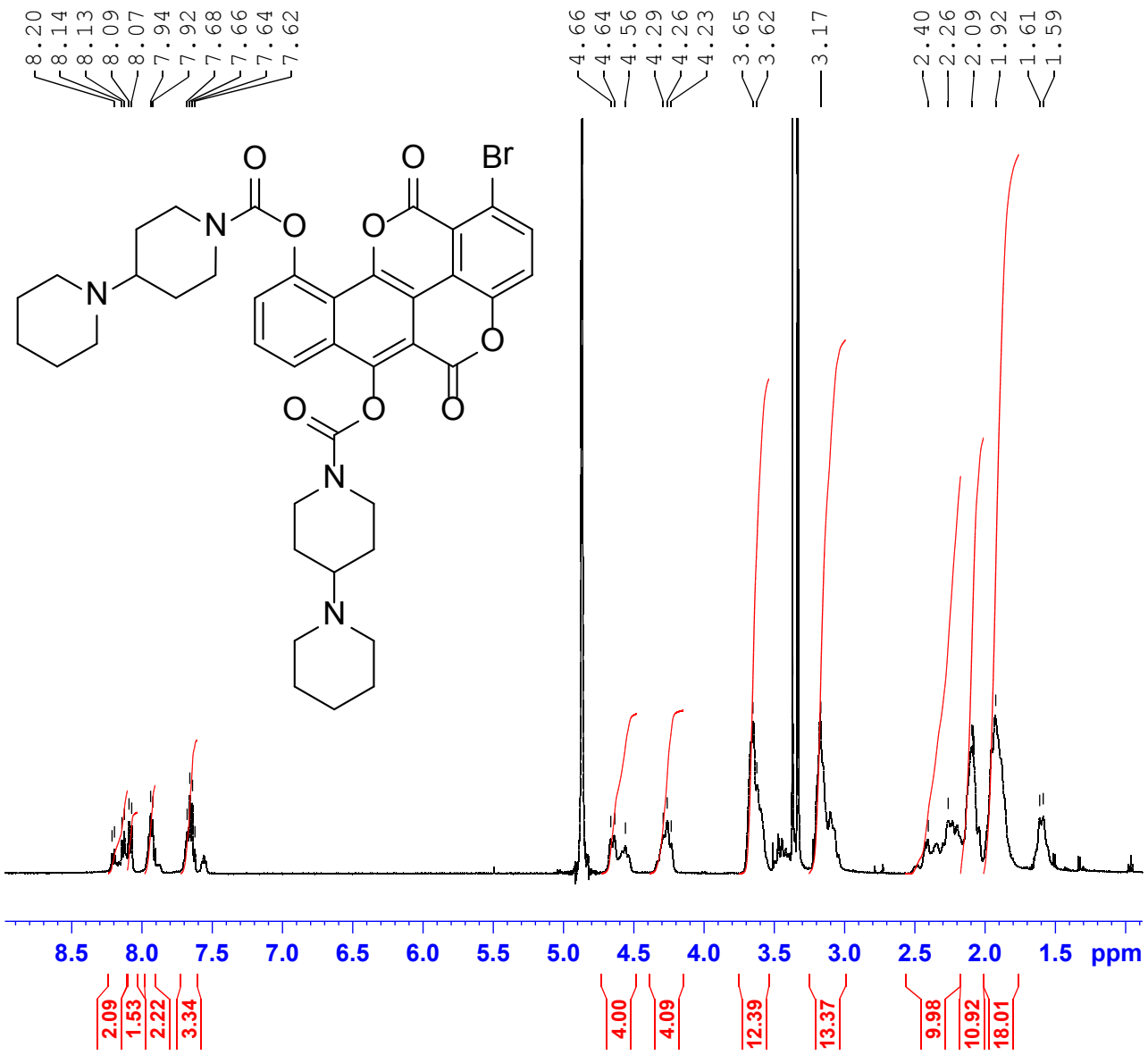

```
Current Data Parameters
NAME                  6NNU354MU
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20131205
Time                       8.07
INSTRUM                   spect
PROBHD    5 mm CPTCI 1H-
PULPROG                   zg30
TD                       65536
SOLVENT                  CD3CN
NS                          32
DS                           2
SWH                  12019.230 Hz
FIDRES                0.183399 Hz
AQ                   2.7262976 sec
RG                        11.3
DW                      41.600 usec
DE                       6.50 usec
TE                      300.1 K
D1                   1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                        8.00 usec
PL1                       4.00 dB
PL1W                 5.00000000 W
SFO1                600.2754024 MHz

F2 - Processing parameters
SI                       262144
SF                  600.2700203 MHz
WDW                          EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
```

Figure S19 ^{13}C NMR (CD_3CN) of norchartarin-10-1,4‘-bipiperidine-1‘-carboxylate (**19**)



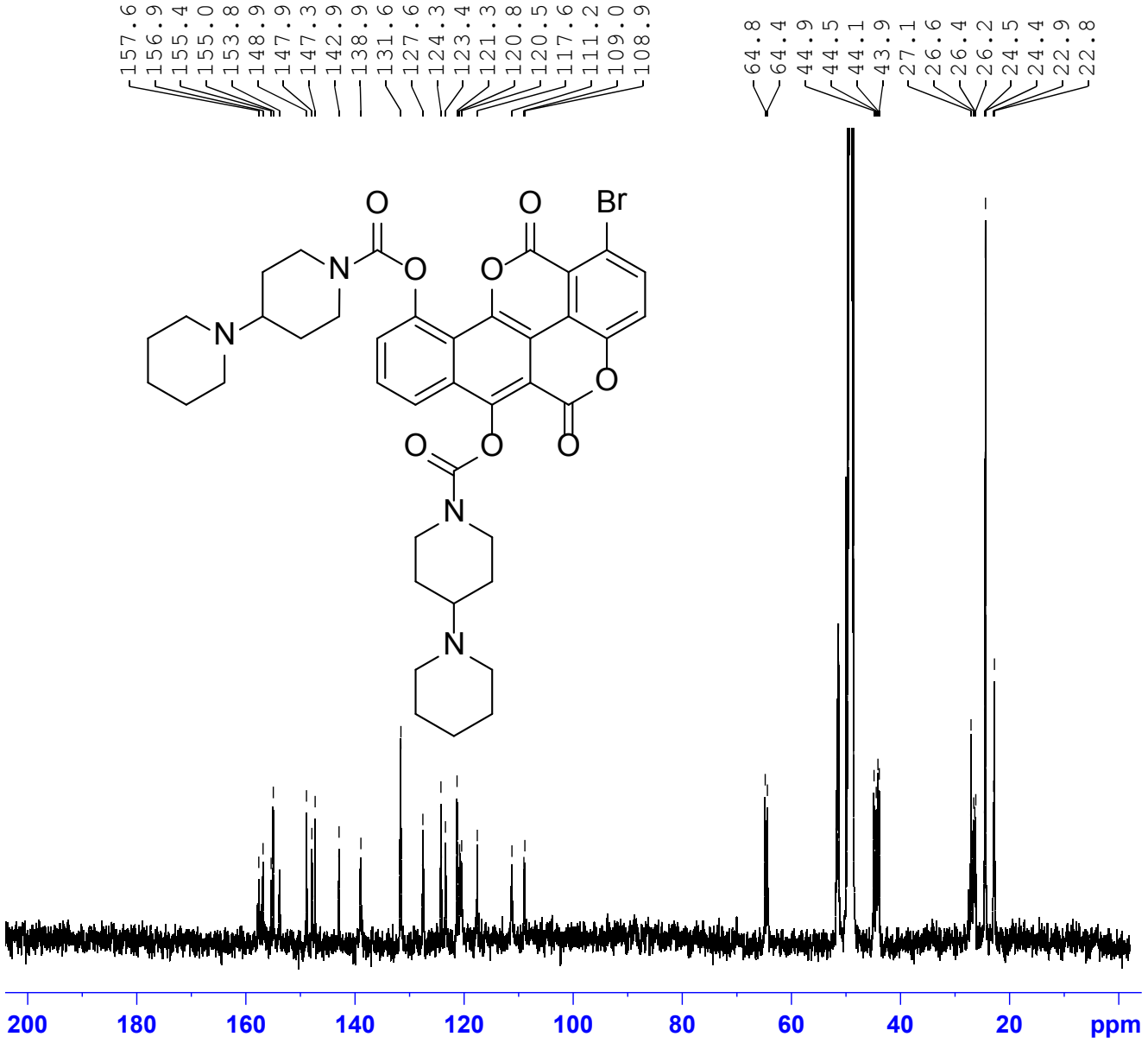

```
Current Data Parameters
NAME          6NNU354MU
EXPNO                50
PROCNO                1

F2 - Acquisition Parameters
Date_          20131205
Time               8.35
INSTRUM           spect
PROBHD   5 mm CPTCI 1H-
PULPROG           udeft
TD                23860
SOLVENT           CD3CN
NS                 6000
DS                    4
SWH           36231.883 Hz
FIDRES         1.518520 Hz
AQ            0.3292680 sec
RG                 2050
DW               13.800 usec
DE               20.00 usec
TE               300.1 K
D1            3.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D20          10.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 14.00 usec
P12              2000.00 usec
P26               500.00 usec
PL1       0 dB
PL1W         75.60778046 W
SFO1        150.9553699 MHz
SP2                5.24 dB
SP8                5.24 dB
SPNAM[2]     Crp60comp.4
SPNAM[8] Crp60,0.5,20.1
SPOAL2             0.500
SPOAL8             0.500
SPOFFS2   0 Hz
SPOFFS8   0 Hz

======== CHANNEL f2 ========
CPDPRG[2         waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                4.00 dB
PL12              25.94 dB
PL2W          5.00000000 W
PL12W         0.03198674 W
SFO2         600.2724011 MHz

F2 - Processing parameters
SI                262144
SF          150.9378028 MHz
WDW                 EM
SSB       0
LB                 4.00 Hz
GB        0
PC                 1.40
```

Figure S20 ^{1}H NMR (CD_3OD+DCl) of bromochartarin-6,10 di-1,4‘-bipiperidine-1‘-carboxylate (**20**)




```
F2 - Acquisition Parameters
Date_            20150312
Time                8.00
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT              MeOD
NS                     64
DS                      2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                    228
DW                 50.000 usec
DE                  6.50 usec
TE                295.9 K
D1            1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  14.00 usec
PL1                  5.50 dB
PL1W          7.71660900 W
SFO1         500.3045027 MHz

F2 - Processing parameters
SI                  131072
SF           500.2999990 MHz
WDW                    no
SSB       0
LB        0 Hz
GB        0
PC                  1.00
```

Figure S21 ^{13}C NMR (CD_3OD+DCl) of bromochartarin-6,10 di-1,4‘-bipiperidine-1‘-carboxylate (**20**)




```
F2 - Acquisition Parameters
Date_            20150312
Time                14.24
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG             udeft
TD                  19996
SOLVENT              MeOD
NS                  10000
DS                      4
SWH             29761.904 Hz
FIDRES          1.488393 Hz
AQ              0.3359328 sec
RG                   2050
DW                 16.800 usec
DE                  6.50 usec
TE                 297.8 K
D1            3.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D20          10.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  13.00 usec
P12               2000.00 usec
P26                500.00 usec
PL1                  3.30 dB
PL1W         44.17614746 W
SFO1         125.8150021 MHz
SP2                  9.18 dB
SP8                  9.18 dB
SPNAM[2]     Crp60comp.4
SPNAM[8] Crp60,0.5,20.1
SPOAL2              0.500
SPOAL8              0.500
SPOFFS2   0 Hz
SPOFFS8   0 Hz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                  5.50 dB
PL12                22.58 dB
PL2W          7.71660900 W
PL12W         0.15115638 W
SFO2          500.3020012 MHz

F2 - Processing parameters
SI                  262144
SF           125.8003832 MHz
WDW                    EM
SSB       0
LB                  4.00 Hz
GB        0
PC                  1.40
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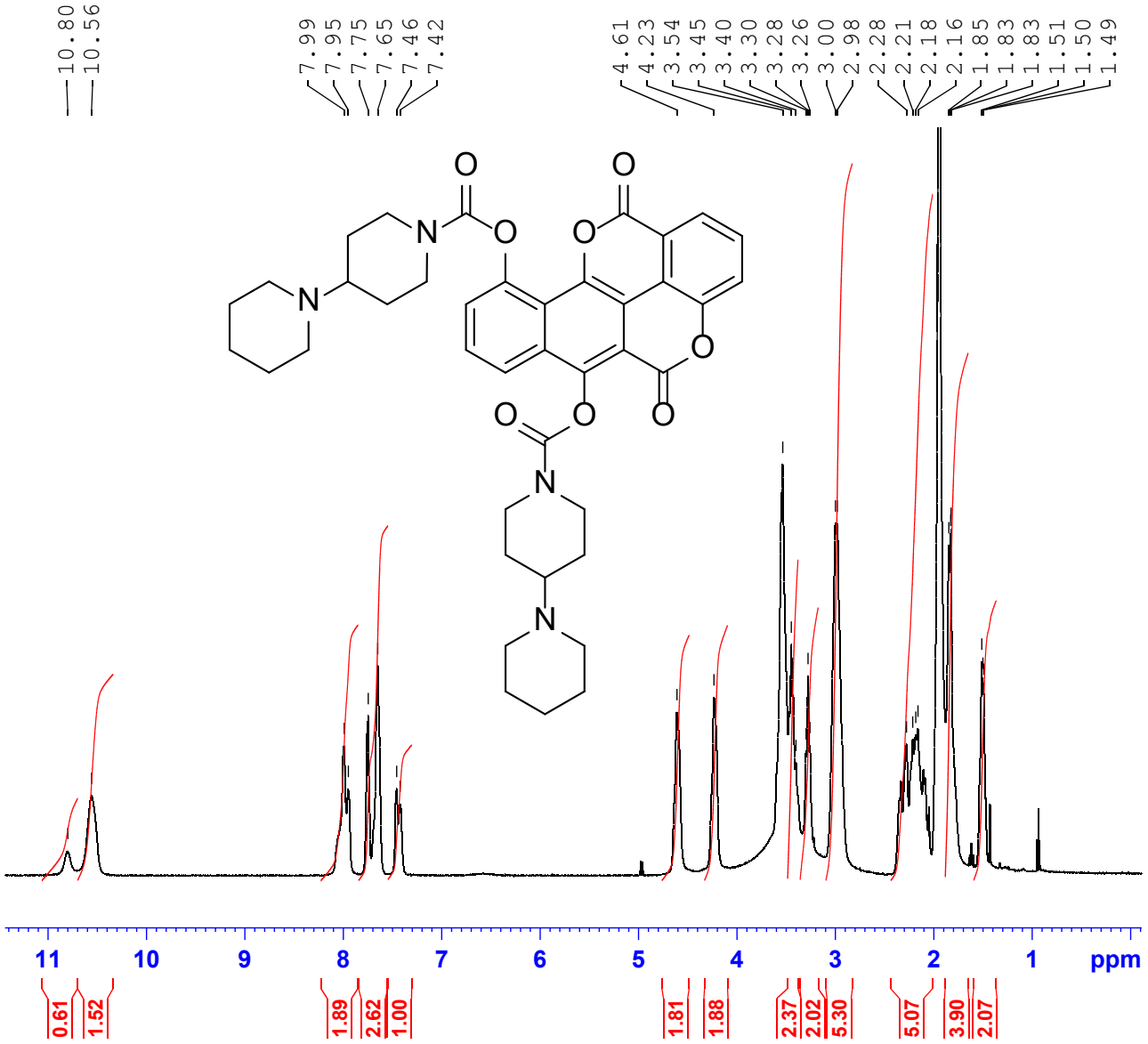
Figure S22 ^{1}H NMR (CD_3CN) of norchartarin-6,10 di-1,4‘-bipiperidine-1‘-carboxylate (**21**)

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Current Data Parameters
NAME                  6NNU353MU
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20131204
Time                      12.47
INSTRUM                   spect
PROBHD    5 mm CPTCI 1H-
PULPROG                   zg30
TD                       65536
SOLVENT                  CD3CN
NS                          20
DS                           2
SWH                  12019.230 Hz
FIDRES                0.183399 Hz
AQ                    2.7262976 sec
RG                           10
DW                      41.600 usec
DE                       6.50 usec
TE                       300.1 K
D1                  1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                        8.00 usec
PL1                       4.00 dB
PL1W                5.00000000 W
SFO1               600.2754024 MHz

F2 - Processing parameters
SI                       262144
SF                 600.2700202 MHz
WDW                          EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
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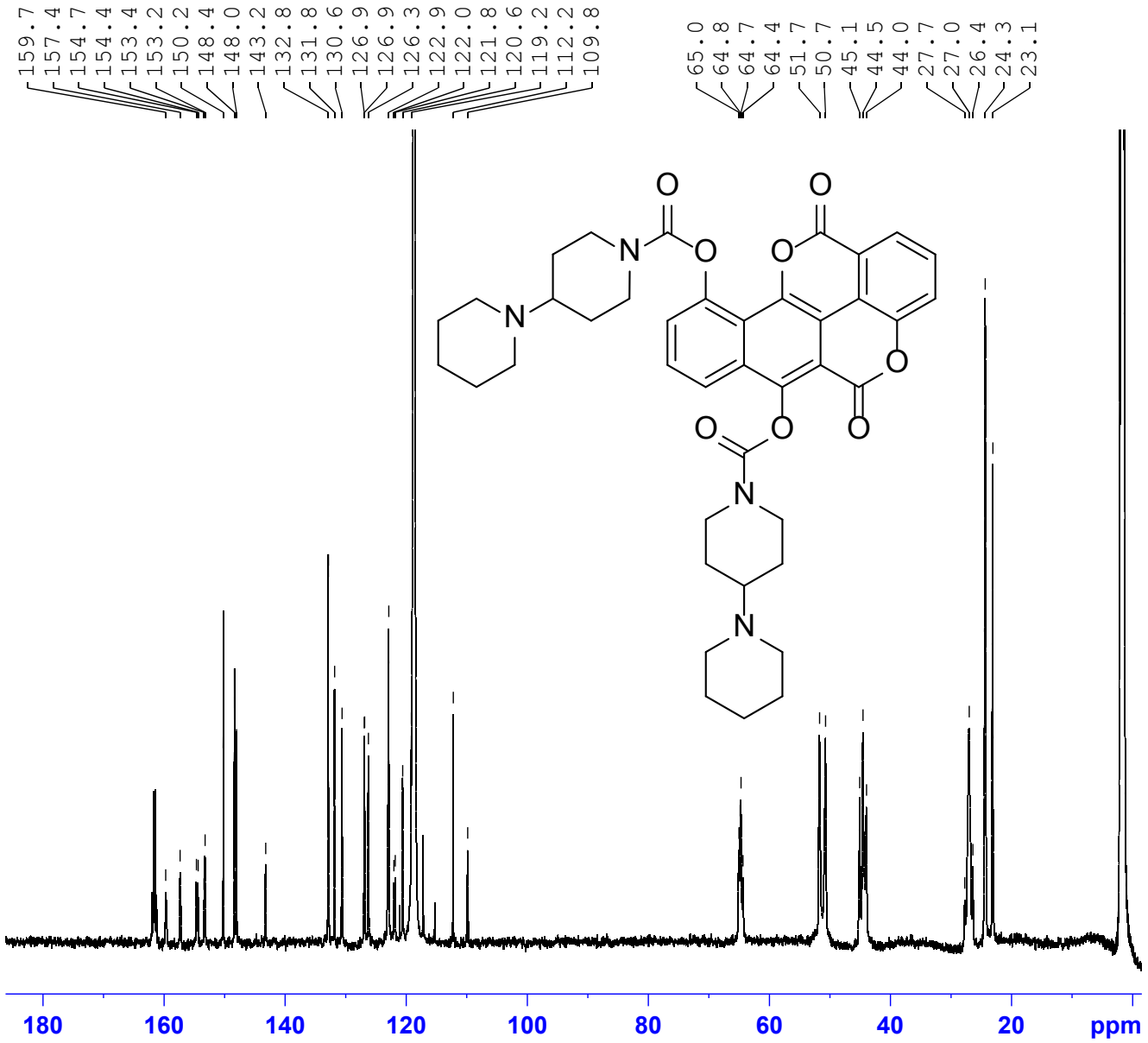
Figure S23 ^{13}C NMR (CD_3CN) of norchartarin-6,10 di-1,4‘-bipiperidine-1‘-carboxylate (**21**)

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Current Data Parameters
NAME           6NNU353MU
EXPNO                 50
PROCNO                 1

F2 - Acquisition Parameters
Date_           20131204
Time              13.46
INSTRUM           spect
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PULPROG           udeft
TD                23860
SOLVENT           CD3CN
NS                 6000
DS                    4
SWH           36231.883 Hz
FIDRES         1.518520 Hz
AQ            0.3292680 sec
RG                 2050
DW               13.800 usec
DE               20.00 usec
TE               300.0 K
D1            3.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D20          10.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                14.00 usec
P12             2000.00 usec
P26              500.00 usec
PL1       0 dB
PL1W         75.60778046 W
SFO1        150.9553699 MHz
SP2               5.24 dB
SP8               5.24 dB
SPNAM[2]     Crp60comp.4
SPNAM[8] Crp60,0.5,20.1
SPOAL2             0.500
SPOAL8             0.500
SPOFFS2   0 Hz
SPOFFS8   0 Hz

======== CHANNEL f2 ========
CPDPRG[2         waltz16
NUC2                1H
PCPD2             100.00 usec
PL2                 4.00 dB
PL12               25.94 dB
PL2W          5.00000000 W
PL12W         0.03198674 W
SFO2         600.2724011 MHz

F2 - Processing parameters
SI                262144
SF           150.9378043 MHz
WDW                 EM
SSB       0
LB                4.00 Hz
GB        0
PC                1.40
```
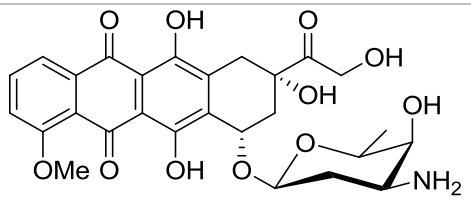
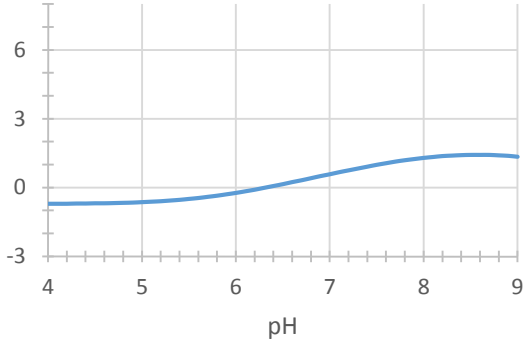
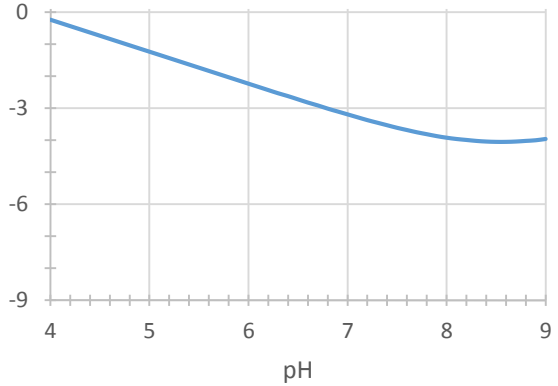
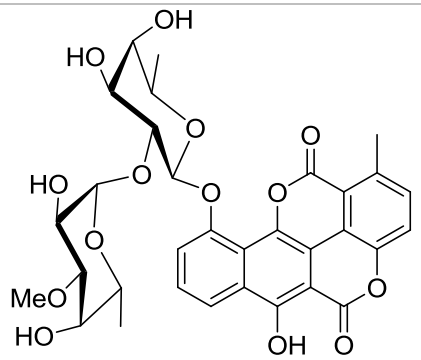
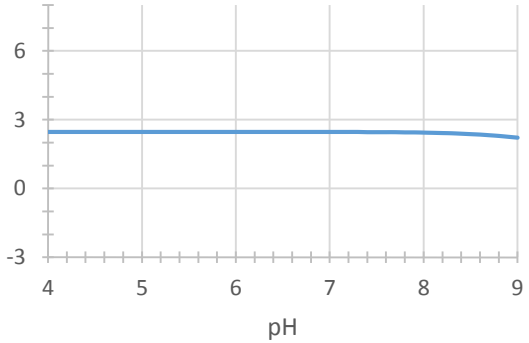
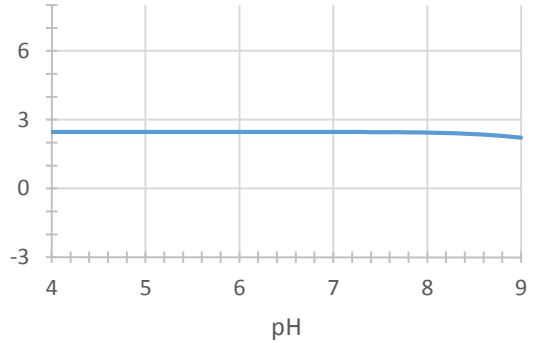
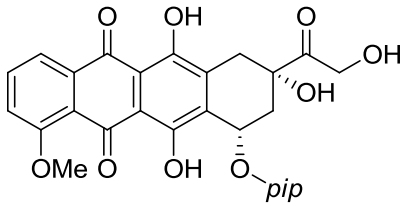
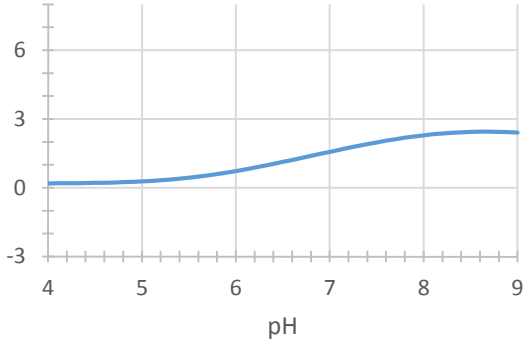
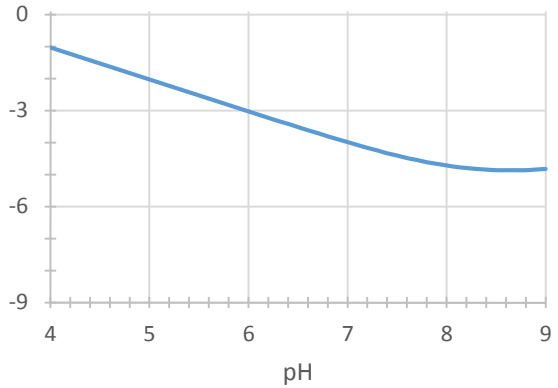
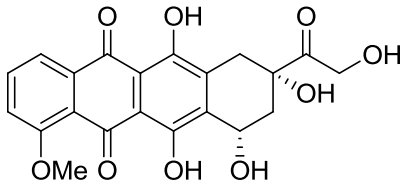
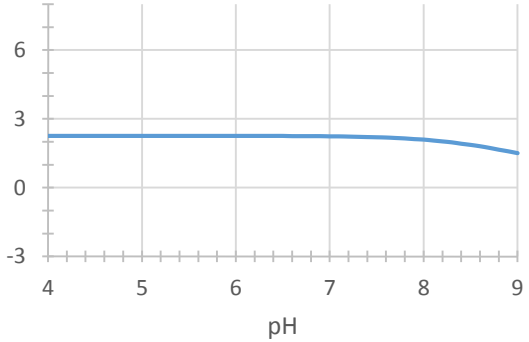
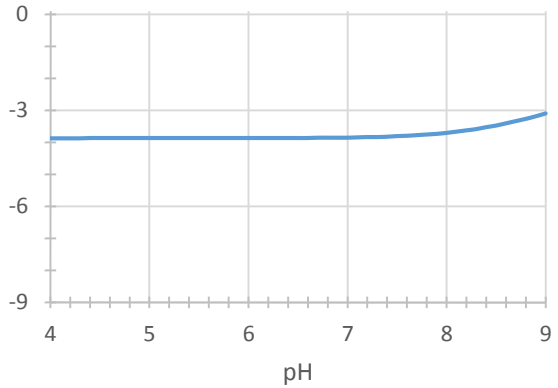
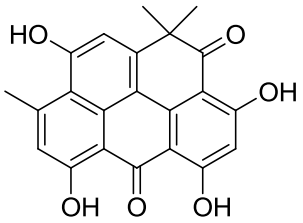
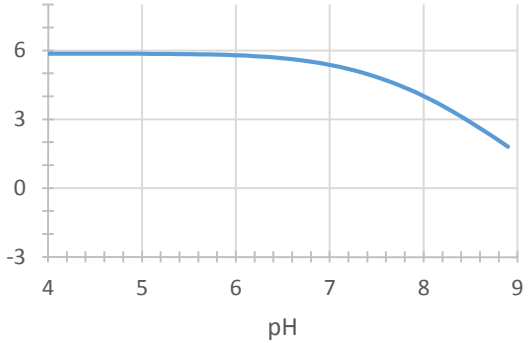
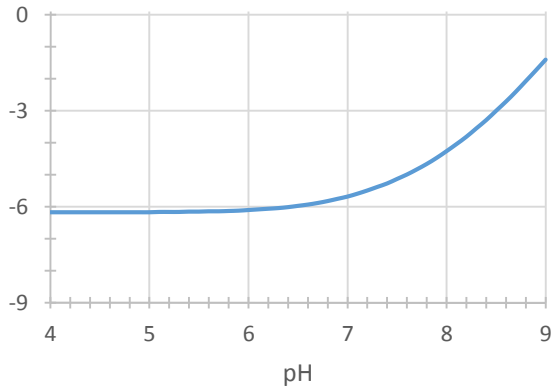
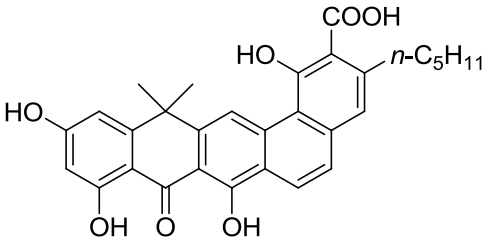
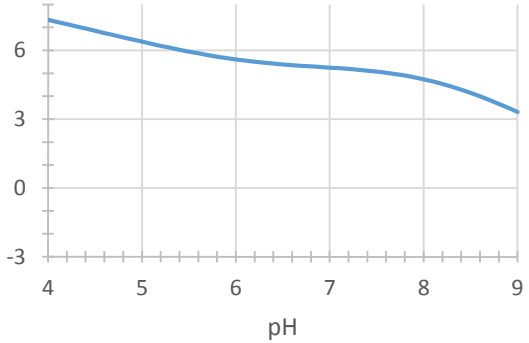
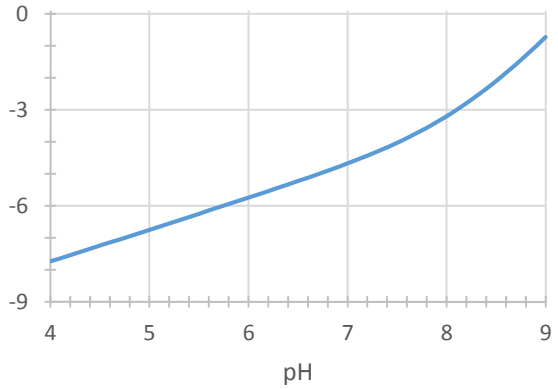
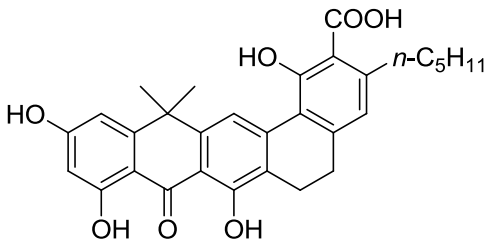
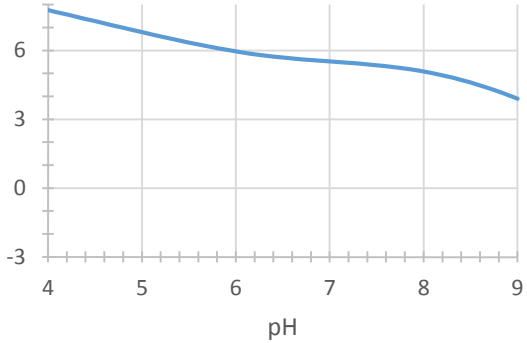
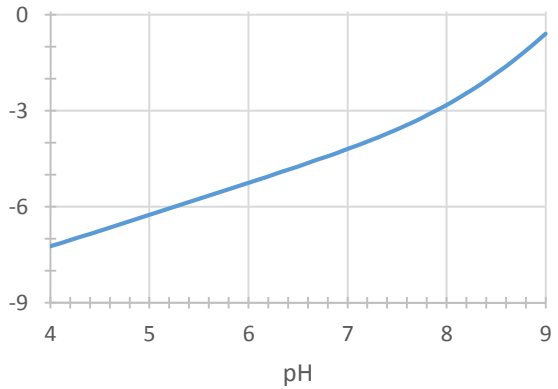
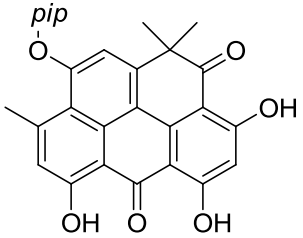
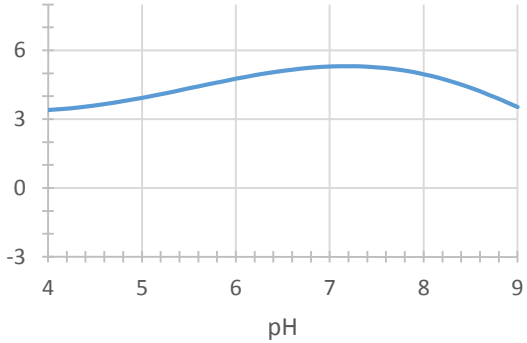
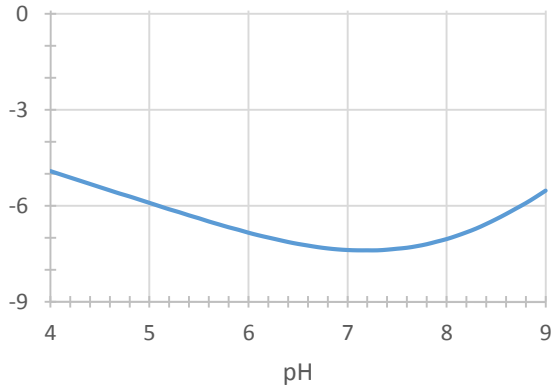

LogD and Log S values

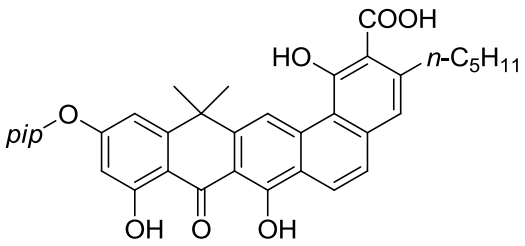
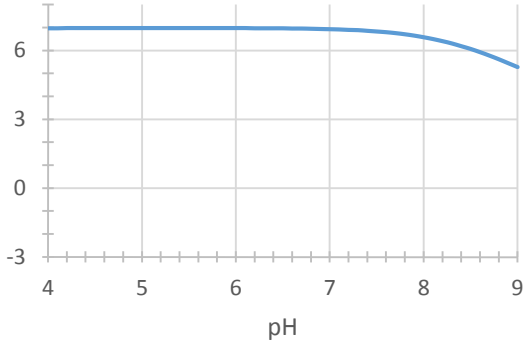
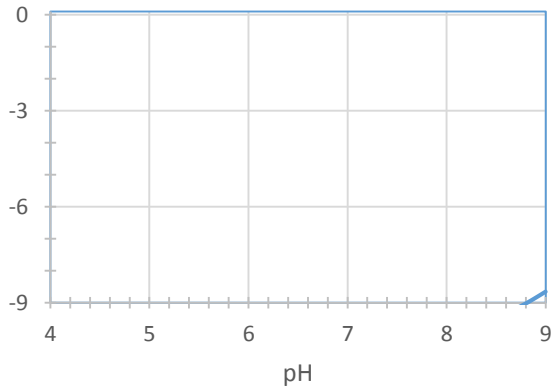
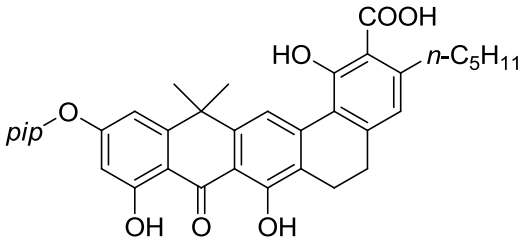
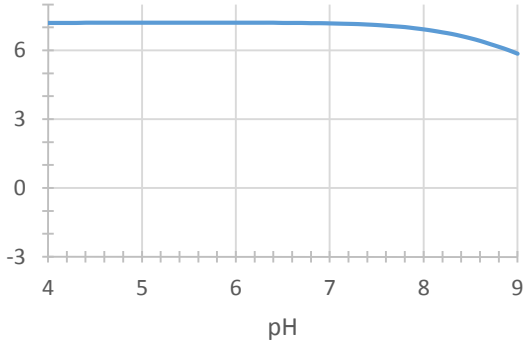
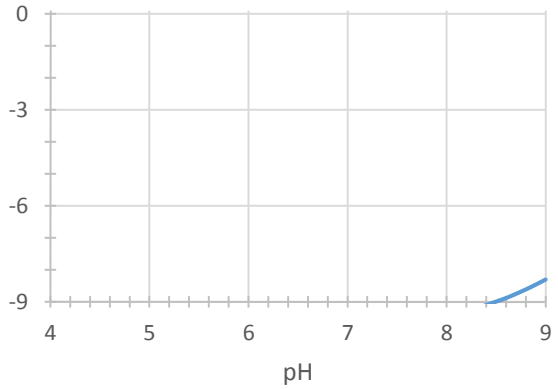
All logD and logS values were calculated using the ChemAxon calculation PlugIn.[3] LogD options: lopP method: Consensus; Electrolyte concentration: 0.1 mol/L Cl^-; 0.1 mol/L Na^+, K^+.

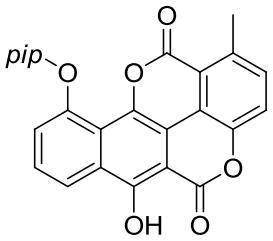
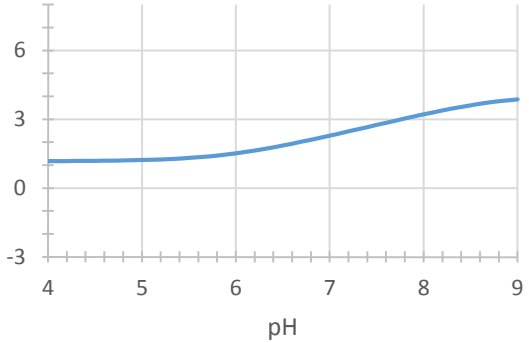
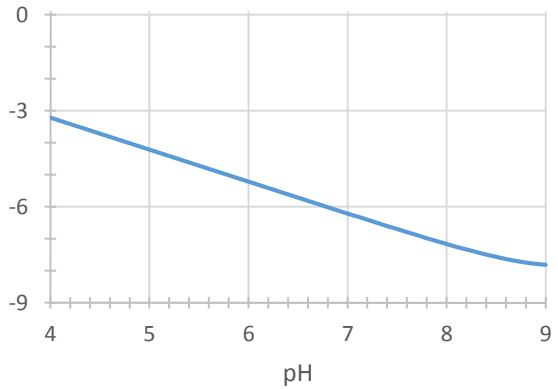
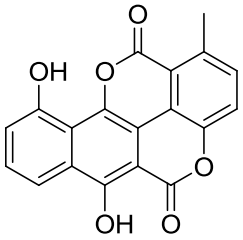
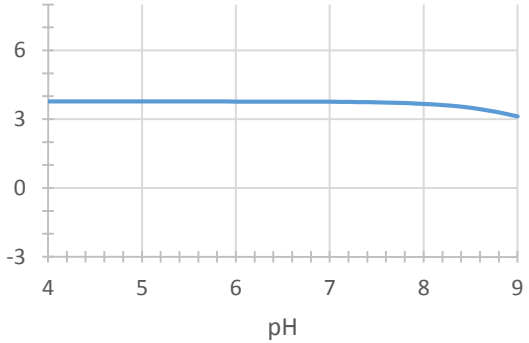
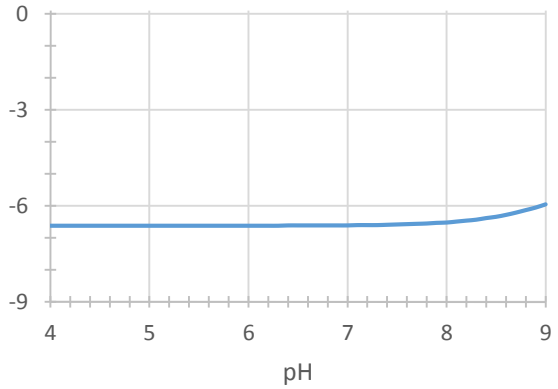
compound	logD	logS
 daunorubicin (**1**)		
		

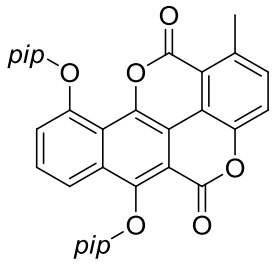
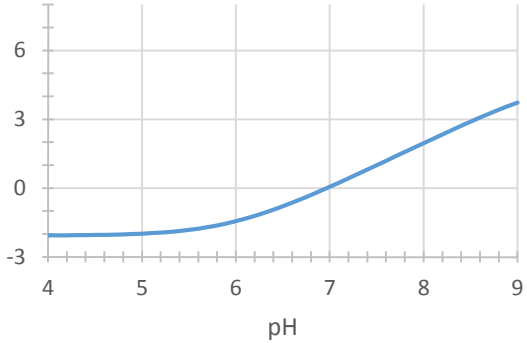
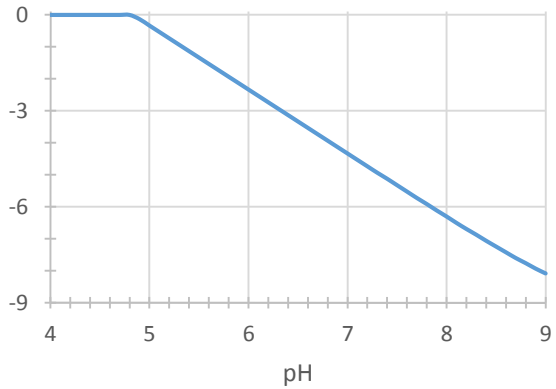
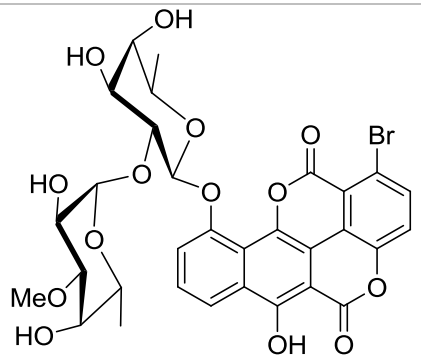
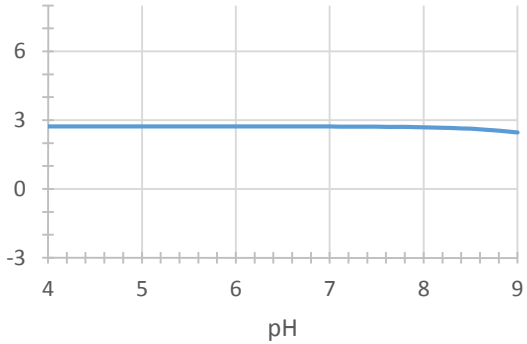
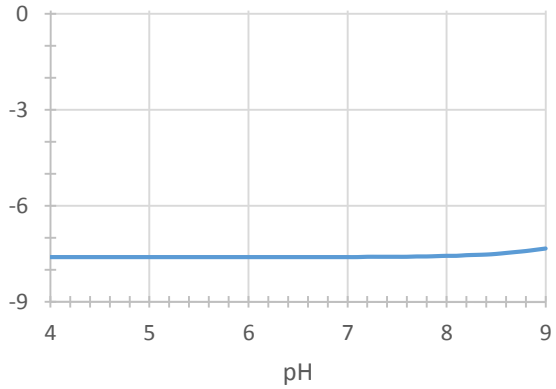
chartreusin (**2**)		
 Daunorubicin-10-1,4'-bipiperidine-1'-carboxylate (**3**)		
 daunorubicin aglycon (**4**)		

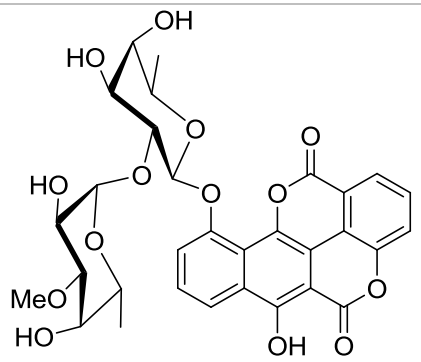
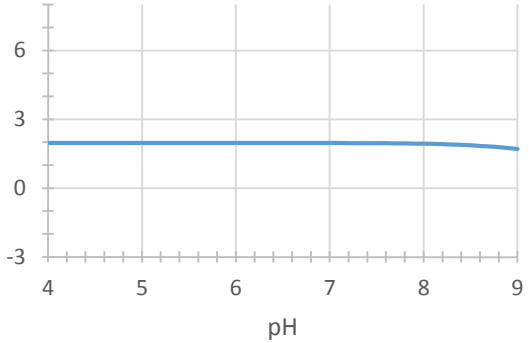
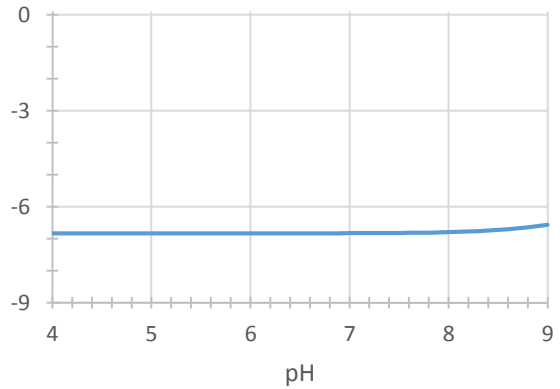
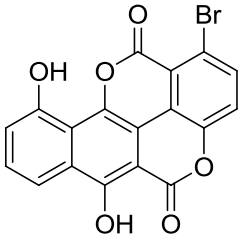
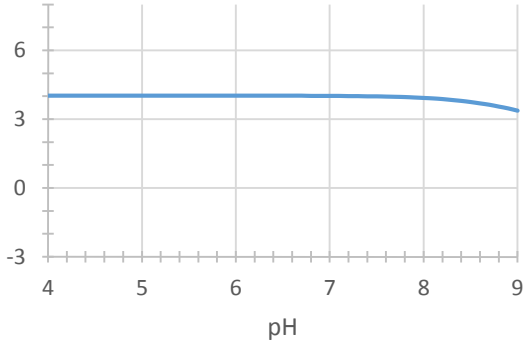
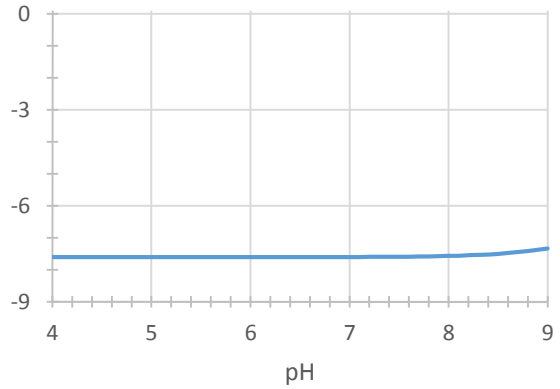
 resistomycin (**5**)		
 benastatin A (**6**)		

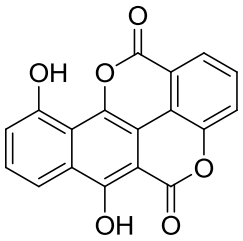
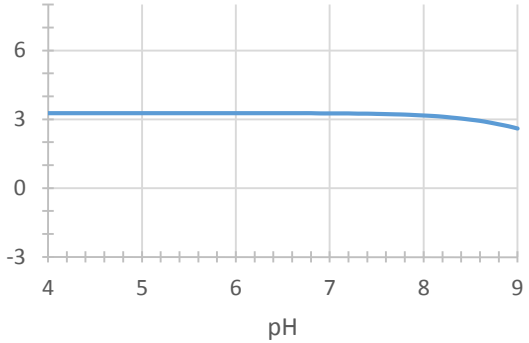
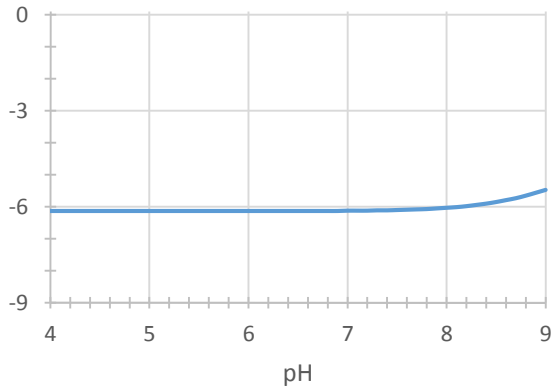
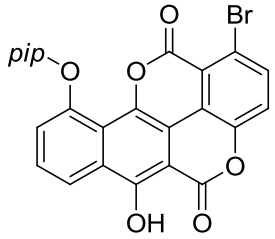
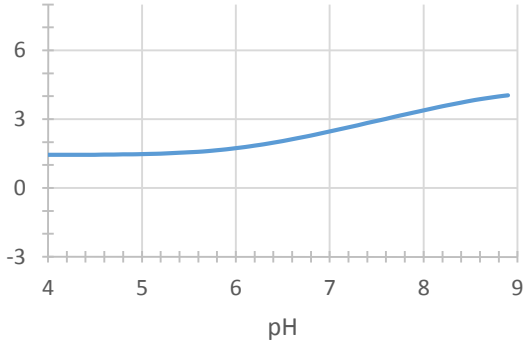
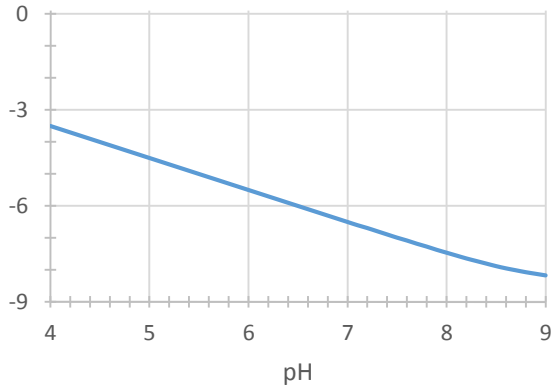
 benastatin B (**7**)		
 resistomycin-10-1,4'-bipiperidine-1'-carboxylate (**8**)		

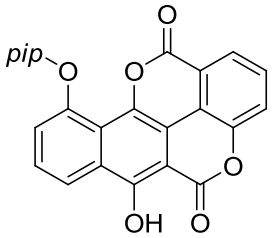
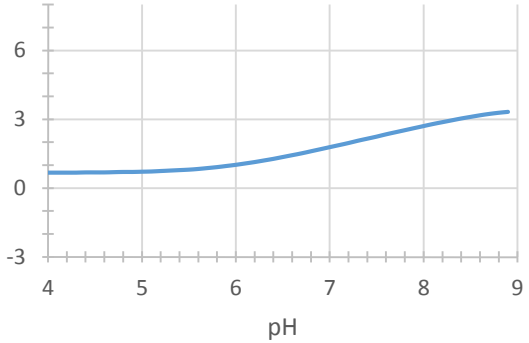
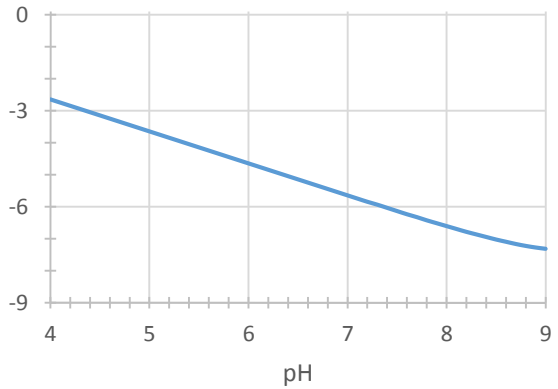
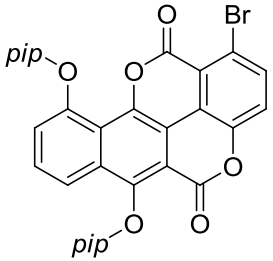
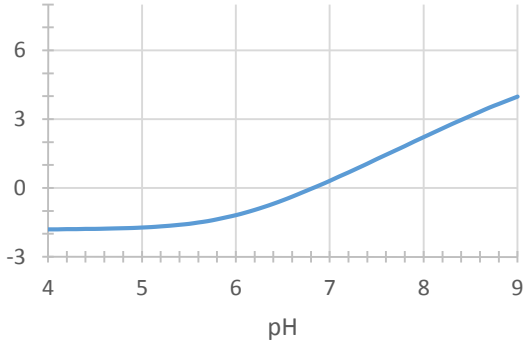
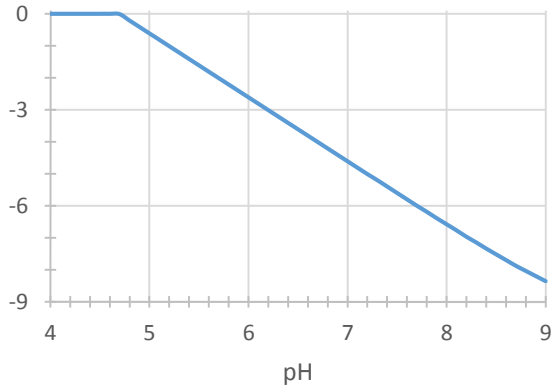
 Benastatin A-11-1,4'-bipiperidine-1'-carboxylate (**9**)		
 Benastatin B-11-1,4'-bipiperidine-1'-carboxylate (**10**)		

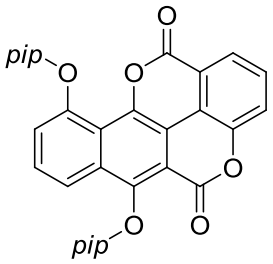
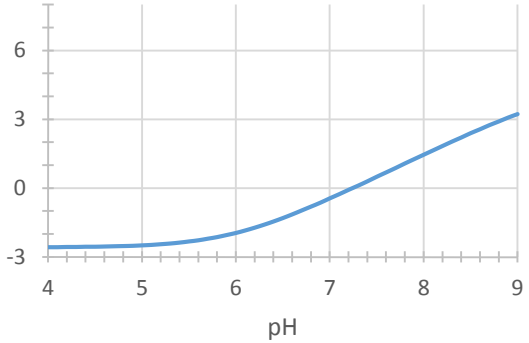
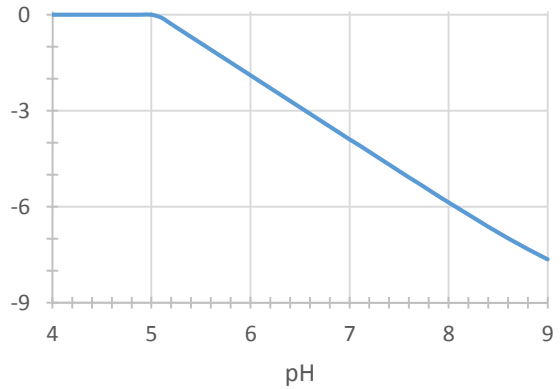
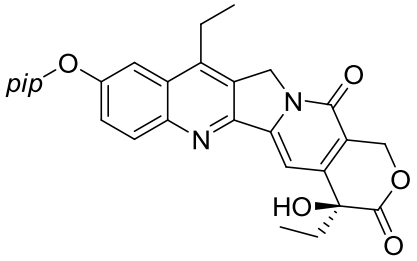
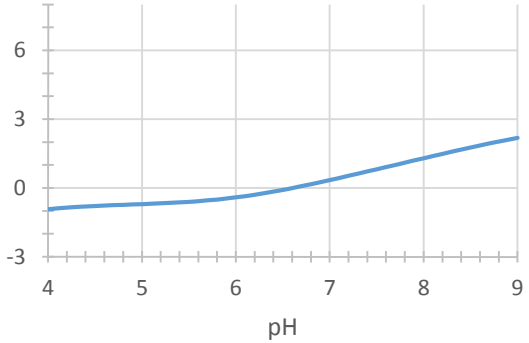
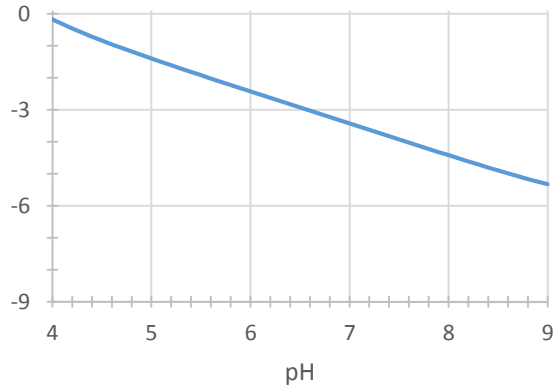
 chartarin-10-1,4'-bipiperidine-1'-carboxylate (**11**)		
 chartarin (**12**)		

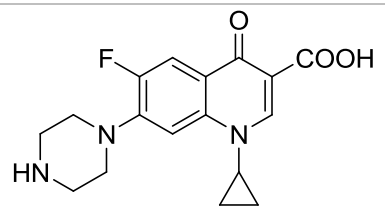
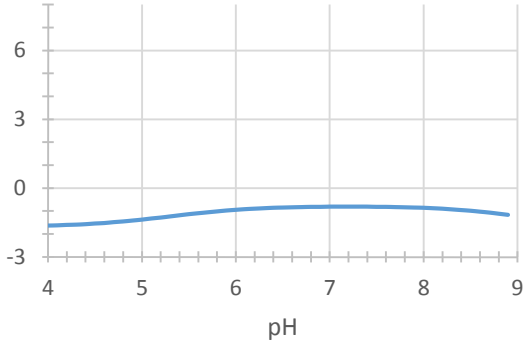
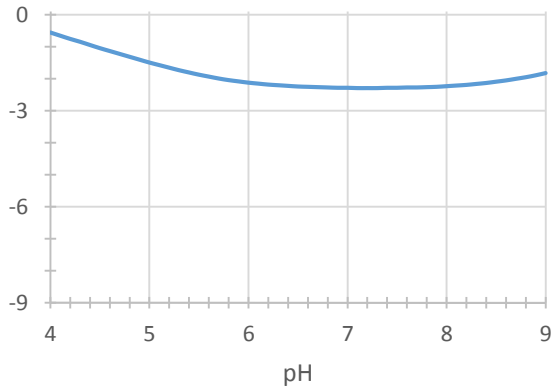
 chartarin-6,10 di-1,4'-bipiperidine-1'-carboxylate (**13**)		
 bromochartreusin (**14**)		

 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:

1. N. Ueberschaar, Z. Xu, K. Scherlach, M. Metsä-Ketelä, T. Bretschneider, H.-M. Dahse, H. Goerls and C. Hertweck, *J. Am. Chem. Soc.*, 2013, **135**, 17408-17416.
2. K. Scherlach, L. P. Partida-Martinez, H. M. Dahse and C. Hertweck, *J. Am. Chem. Soc.*, 2006, **128**, 11529-11536.
3. ChemAxon, *MarvinSketch*, (2015) ChemAxon Ltd.