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SUPPLEMENTARY MATERIAL TO

Synthesis and antiproliferative activity of simplified goniofufurone analogues

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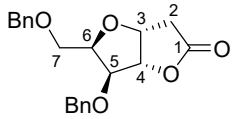
PHYSICAL AND SPECTRAL DATA OF SYNTHESIZED COMPOUNDS

*3,6-Anhydro-5,7-di-*O*-benzyl-2-deoxy-D-ido-heptono-1,4-lactone (**10**).*



10

Colourless needles, m.p.: 90 °C (MeOH), $[\alpha]_D$ = +8.6° (*c* 1.2, $CHCl_3$), R_f = 0.62 (4:1 hexane/Et_2O). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.71 (*m*, 2 H, $J_{2a,3}$ = 4.4, $J_{2b,3}$ = 2.9 Hz, H-2), 3.73 (*d*, 2 H, $J_{6,7}$ = 5.5 Hz, 2×H-7), 4.22 (*dd*, 1 H, $J_{4,5}$ = 0.6, $J_{5,6}$ = 4.1 Hz, H-5), 4.31 (*m*, 1 H, H-6), 4.59 and 4.64 (4×*d*, partially overlapped, 4 H, J_{gem} = 11.9 Hz, 2×CH_2Ph), 4.93 (*dd*, 1 H, $J_{3,4}$ = 4.8, $J_{4,5}$ = 0.6 Hz, H-4), 4.96 (*m*, 1 H, H-3), 7.26-7.42 ppm (*m*, 10 H, 2×Ph). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 36.0 (C-2), 68.2 (C-7), 72.8 and 73.6 (2×*C*H_2Ph), 77.0 (C-3), 79.7 (C-6), 81.6 (C-5), 85.6 (C-4), 127.8, 127.9, 128.2, 128.5, 128.7, 137.3, 138.0 (2×Ph), 175.5 ppm (C-1). LRMS (CI): *m*/*z* 355 (M^++H), 263 (M^+−Bn). Anal.: Found: C, 70.89; H, 6.39. Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26.

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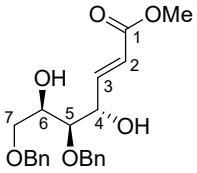
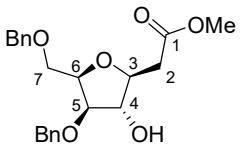
*Methyl (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-D-xylo-hept-2-enonate (**11**).*



11

Colourless syrup, $[\alpha]_D$ = −188.9° (*c* 1.1, $CHCl_3$), R_f = 0.50 (4:1 Et_2O/ /hexane). IR (film): ν_{max} 3430 (OH), 1730 (C=O), 1670 (C=C), 1610 cm^{-1} (Ph). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.81 and 3.22 (2×d, 1 H each, exchangeable with D_2O, J = 6.1 Hz, 2×OH), 3.52 (*dd*, 1 H, $J_{6,7a}$ = 5.6, $J_{7a,7b}$ = 9.7 Hz, H-7a), 3.60 (*dd*, 1 H, $J_{7a,7b}$ = 9.7, $J_{6,7b}$ = 5.7 Hz, H-7b), 3.62 (*t*, 1 H, $J_{4,5} = J_{5,6} =$ = 4.1 Hz, H-5), 3.76 (*s*, 3 H, OMe), 3.97 (*m*, 1 H, H-6), 4.50 (*m*, 1 H, $J_{3,4}$ = 4.3, $J_{2,4}$ = 2.0 Hz, H-4), 4.51 (*s*, 2 H, CH_2Ph), 4.61 (2×*d*, 2 H, J_{gem}=11.3 Hz, CH_2Ph), 6.16 (*dd*, 1 H, $J_{2,3}$ = 15.6 Hz, H-2), 7.03 (*dd*, 1 H, $J_{3,4}$ = 4.3, $J_{2,3}$ = 15.6 Hz, H-3), 7.25–7.42 ppm (*m*, 10 H, 2×Ph). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 51.5 (OMe), 70.7 (C-4), 70.8 (C-6), 71.1 (C-7), 73.4 and 74.7 (2×CH_2Ph), 80.6 (C-5), 121.1 (C-2), 127.9, 128.1, 128.2, 128.4, 128.45, 137.3, 137.4 (2×Ph), 147.5 (C-3), 166.7 ppm (C-1). LRMS (FAB): *m/z* 409 (M^++Na), 387 (M^++H). Anal.: Found: C, 68.10; H, 6.83. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78.

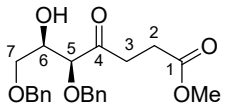
*Methyl 3,6-anhydro-5,7-di-*O*-benzyl-2-deoxy-D-gulo-heptonoate (**12**).*



12

Colourless oil, $[\alpha]_D$ = −18.7° (*c* 1.0, $CHCl_3$), R_f = 0.50 (4:1 Et_2O/hexane). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.68 (*dd*, 1 H, $J_{2a,3}$ = 9.6, $J_{2a,2b}$ = 17 Hz, H-2a), 2.97 (*dd*, 1 H, $J_{2b,3}$ = 5.0, $J_{2a,2b}$ = 17 Hz, H-2b), 3.12 (*bs*, 1 H, OH), 3.60–3.80 (*m*, 5 H, 2×H-7 and OMe), 3.93 (*m*, 1 H, H-3), 3.99 (*dd*, 1 H, $J_{4,5}$ = 2.3, $J_{5,6} =$ = 5.1 Hz, H-5), 4.08 (dd, 1 H, $J_{3,4}$ = 4.9, $J_{4,5}$ = 2.3 Hz, H-4), 4.23 (*m*, 1 H, H-6), 4.48–4.72 (4×*d*, 1 H each, J_{gem} = 12.0 Hz, 2×CH_2Ph), 7.24–7.39 ppm (*m*, 10 H, 2×Ph). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 38.3 (C-2), 52.0 (OMe), 68.7 (C-7), 71.6 and 73.4 (2×CH_2Ph), 79.7 (C-6), 80.8 (C-3), 81.1 (C-4), 85.3 (C-5), 127.5, 127.6, 127.8, 128.3, 128.4, 137.9, 138.1 (Ph), 172.9 ppm (C-1).

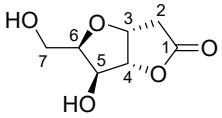
*Methyl 5,7-di-*O*-benzyl-2,3-dideoxy-4-oxo-D-threo-heptonate (**13**).*



13

Bright yellow oil, $[\alpha]_D$ = −69.9° (*c* 1.4, $CHCl_3$), R_f = 0.71 (4:1 Et_2O/ /hexane). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.59 (*t*, 2 H, *J* = 6.4 Hz, H-2a and H-2b), 2.84 (*bs*, 1 H, exchangeable with D_2O, OH), 2.87 and 2.88 (2×*t*, 1 H each, *J* = 6.4 Hz, H-3a and H-3b), 3.52 (*dd*, 1 H, $J_{7a,7b}$ = 9.5, $J_{6,7a}$ = 6.1 Hz, H-7a), 3.60 (*dd*, 1 H, $J_{6,7b}$ = 5.6 Hz, H-7b), 3.68 (*s*, 3 H, OMe), 4.04 (*d*, 1 H, $J_{5,6}$ = 3.3 Hz, H-5), 4.11 (*m*, 1 H, H-6), 4.42–4.55 (*m*, 3 H, 2×PhCH_2), 4.74 (*d*, 1 H, J_{gem} = = 11.5 Hz, PhCH_2), 7.25–7.42 ppm (*m*, 10 H, 2×*Ph*CH_2). ^{13}C-NMR ($CDCl_3$): δ 27.2 (C-2), 34.4 (C-3), 51.8 (OMe), 70.1 (C-7), 71.1 (C-6), 73.2 and 73.3 (2×PhCH_2), 83.9 (C-5), 127.6, 127.65, 128.0, 128.1, 128.2, 128.4, 136.9 and 137.6 (2×*Ph*CH_2), 173.3 (C-1), 210.4 ppm (C-4). LRMS (FAB): *m/z* 409 (M^++Na), 387 (M^++H).

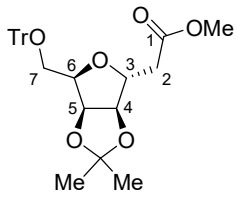
*3,6-Anhydro-2-deoxy-D-ido-heptono-1,4-lactone (**2**).*



2

Transparent needles, m.p.: 71–73 °C (EtOAc/MeOH), $[\alpha]_D$ = +26.8° (*c* 1.8, H_2O), lit[1] m.p.: 72–74 °C, $[\alpha]_D$ = +28.4° (*c* 1.9, H_2O), R_f = 0.72 (9:1 CH_2Cl_2/MeOH). ^{1}H-NMR (250 MHz, acetone-d_6): δ 2.47 (*d*, 1 H, $J_{2a,2b}$ = 18.8 Hz, H-2a), 2.85 (*dd*, 1 H, $J_{2b,3}$ = 6.1, $J_{2a,2b}$ = 18.8 Hz, H-2b), 3.66 (*dd*, 1 H, $J_{7a,7b}$ = 11.6, $J_{6,7a}$ = 5.2 Hz, H-7a), 3.75 (*dd*, 1 H, $J_{6,7b}$ = 5.1, $J_{7a,7b}$ = 11.6 Hz, H-7b), 3.96 (*m*, 1 H, $J_{5,6}$ = 1.8 Hz, $J_{6,7a}$ = 5.2, $J_{6,7b}$ = 5.1 Hz, H-6), 4.25 and 5.01 (*bs*, 2 H, exchangeable with D_2O, 2×OH), 4.34 (*d*, 1 H, $J_{5,6}$ = 1.8 Hz, H-5), 4.88 (*d*, 1 H, $J_{3,4}$ = 4.4 Hz, H-4), 4.94 ppm (*dd*, 1 H, $J_{2b,3}$ = 6.1, $J_{3,4}$ = 4.4 Hz, H-3). ^{13}C-NMR (62.9 MHz, acetone-d_6): δ 36.2 (C-2), 60.0 (C-7), 73.9 (C-5), 77.2 (C-3), 81.9 (C-6), 88.9 (C-4), 177.7 ppm (C-1). LRMS (FAB): *m/z* 371 ($2M^+$+Na), 349 ($2M^+$+H), 197 (M^++Na), 175 (M^++H), 157 (M^+−OH).

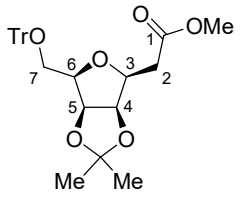
Methyl 3,6-anhydro-2-deoxy-4,5-O-*isopropylidene-D-talo-heptanoate* (***18***).



18

White needles, m.p.: 138 °C (MeOH), $[\alpha]_D$ = −21.7° (*c* 0.8, $CHCl_3$), R_f = = 0.30 (19:1 toluene/EtOAc). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.31 and 1.35 (2×*s*, 3 H each, CMe_2), 2.47 (*dd*, 1 H, $J_{2a,2b}$ = 15.3, $J_{2a,3}$ = 7.9 Hz, H-2a), 2.57 (*dd*, 1 H, $J_{2a,2b}$ = 15.3, $J_{2b,3}$ = 7.4 Hz, H-2b), 3.37 (*dd*, 1 H, $J_{7a,7b}$ = 9.5, $J_{6.7a}$ = 6.3 Hz, H-7a), 3.45 (*dd*, 1 H, $J_{7a,7b}$ = 9.5, $J_{6,7b}$ = 5.7 Hz, H-7b), 3.73 (*s*, 3 H, OMe), 3.97 (*m*, 1 H, $J_{5,6}$ = 3.9 Hz, H-6), 4.47 (*td*, 1 H, $J_{3,4}$ = 1.1 Hz, H-3), 4.61 (*dd*, 1 H, $J_{3,4}$ = 1.1, $J_{4,5}$ = 6.1 Hz, H-4), 4.78 (*dd*, 1 H, $J_{4,5}$ = 6.1, $J_{5,6}$ = 3.9 Hz, H-5), 7.19–7.54 ppm (*m*, 15 H, 3×Ph). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 25.3 and 26.2 (C*Me*$_2$), 36.3 (C-2), 51.9 (OMe), 61.7 (C-7), 79.3 (C-6), 80.3 (C-3), 81.0 (C-5), 84.8 (C-4), 86.8 (Ph$_3$*C*), 112.7 (*C*Me$_2$) 126.9, 127.7, 128.82, 144.0 (3×Ph), 170.8 ppm (C-1). LRMS (FAB): *m*/*z* 511 (M^++Na), 411 (M^+−Ph), 243 (Ph_3C^+). Anal.: Found: C, 73.48; H, 6.53. Calcd. for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60.

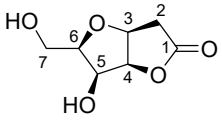
Methyl 3,6-anhhydro-2-deoxy-4,5-O-*isopropylidene-D-galacto-heptanoate* (***19***).



19

Colourless oil $[\alpha]_D$ = −26.3° (*c* 1.0, $CHCl_3$), R_f = 0.35 (19:1 toluene/EtOAc). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.43 and 1.36 (2×*s*, 3 H each, CMe_2), 2.78 (*dd*, 1 H, $J_{2a,3}$ = 6.6, $J_{2a,2b}$ = 16.7 Hz, H-2a), 2.83 (*dd*, 1 H, $J_{2a,2b}$ = 16.7, $J_{2b,3}$ = = 7.0 Hz, H-2b), 3.42 (*dd*, 1 H, $J_{6,7a}$ = 6.4, $J_{7a,7b}$ = 9.5 Hz, H-7a), 3.49 (*dd*, 1 H, $J_{7a,7b}$ = 9.5, $J_{6,7b}$ = 6.0 Hz, H-7b), 3.70 (*td*, 1 H, $J_{5,6}$ = 2.9 Hz, H-6), 3.72 (*s*, 3 H, OMe), 3.94 (*td*, 1 H, $J_{3,4}$ = 2.9 Hz, H-3), 4.78 (*m*, 2 H, H-4 and H-5), 7.17–7.58 ppm (*m*, 15 H, 3×Ph). ^{13}C-NMR (62.5 MHz, $CDCl_3$): δ 25.2 and 25.8 (C*Me*$_2$), 33.4 (C-2), 51.7 (OMe), 61.3 (C-7), 77.4 (C-3), 80.6 (C-6), 81.0 and 81.1 (C-4 and C-5), 86.8 (Ph$_3$*C*), 112.2 (*C*Me$_2$), 126.8, 127.6, 128.8, 144.0 (3×Ph), 171.5 ppm (C-1).

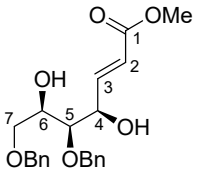
*3,6-Anhydro-2-deoxy-D-galacto-heptono-1,4-lactone (**3**).*



3

White crystals, m.p.: 126–127 °C ($CHCl_3$), $[\alpha]_D$ = −98.0° (*c* 0.9, MeOH), R_f = 0.20 (EtOAc). ^{1}H-NMR (250 MHz, acetone-d_6): δ 3.92 and 4.46 (*bs*, 2 H, exchangeable with D_2O, 2×OH), 2.50 (*dd*, 1 H, $J_{2a,2b}$ = 18.4, $J_{2a,3}$ = 2.6 Hz, H-2a), 2.80 (*dd*, 1 H, $J_{2a,2b}$ = 18.4, $J_{2b,3}$ = 7.3 Hz, H-2b), 3.63 (*dd*, 1 H, $J_{7a,7b}$ = = 11.6, $J_{6,7a}$ = 4.6 Hz, H-7a), 3.78 (*dd*, 1 H, $J_{7a,7b}$ = 11.6, $J_{7b,6}$ = 5.8 Hz, H-7b), 3.93 (*m*, 1 H, $J_{5,6}$ = 5.0 Hz, H-6), 4.45 (*t*, 1 H, $J_{4,5}$ = 5.0 Hz, H-5), 4.69 (*ddd*, 1 H, $J_{2a,3}$ = 2.6, $J_{2b,3}$ = 7.3, $J_{3,4}$ = 6.0 Hz, H-3), 5.03 ppm (*t*, 1 H, H-4). ^{13}C-NMR (62.9 MHz, acetone-d_6): δ 36.9 (C-2), 61.4 (C-7), 72.1 (C-5), 76.6 (C-3), 83.4 (C-6), 83.9 (C-4), 176.5 ppm (C-1). LRMS (FAB): *m*/*z* 371 ($2M^+$+Na), 349 ($2M^+$+H), 197 (M^++Na), 175 (M^++H). Anal.: Found: C, 48.56; H, 5.48. Calcd. for $C_7H_{10}O_5$: C, 48.28; H, 5.79.

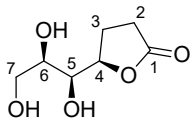
*Methyl (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-D-lyxo-hept-2-enoate (**22**).*



22

Colourless needles, m.p.: 95–96 °C (toluene/hexane), $[\alpha]_D$ = +14.0° (*c* 1.1, $CHCl_3$), R_f = 0.45 (4:1 Et_2O/hexane). IR ($CHCl_3$): ν_{max} 3368 (OH), 1724 (C=O), 1660 cm^{-1} (C=C). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.85 and 3.60 (2×*bs*, 1 H each, 2×OH), 3.47 (*dd*, $J_{7a,7b}$ = 9.4, $J_{6,7a}$ = 5.8 Hz, H-7a), 3.51 (*dd*, 1 H, $J_{4,5}$ = = 7.0, $J_{5,6}$ = 2.4 Hz, H-5), 3.58 (*dd*, 1 H, $J_{7a,7b}$ = 9.4, $J_{6,7b}$ = 6.4 Hz, H-7b), 3.73 (*s*, 3 H, OMe), 4.01 (*td*, 1 H, H-6), 4.48–4.50 (4×*d*, 1 H each, J_{gem} = 11.4 and 11.7 Hz, 2×PhCH_2), 4.60 (*m*, 1 H, $J_{2,4}$ = 2.0, $J_{3,4}$ = 4.0 Hz, H-4), 6.20 (*dd*, 1 H, $J_{2,4}$ = 2.0, $J_{2,3}$ = 15.6 Hz, H-2), 7.00 (*dd*, 1 H, $J_{3,4}$ = 4.0, $J_{2,3}$ = 15.6 Hz, H-3), 7.24–7.38 ppm (*m*, 10 H, 2×Ph). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 51.6 (OMe), 70.4 (C-6), 70.7 (C-4), 71.1 (C-7), 73.0 and 73.5 (2×PhCH_2), 78.9 (C-5), 121.4 (C-2), 127.9, 128.1, 128.2, 128.5, 128.53, 137.2, 137.5 (Ph), 147.0 (C-3), 166.7 ppm (C-1). LRMS (FAB): *m*/*z* 387 (M^++H), 409 (M^++Na). Anal.: Found: C, 68.10; H, 6.83. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78.

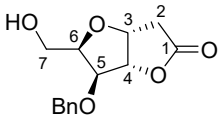
*2,3-Dideoxy-D-lyxo-heptono-1,4-lactone (**6**).*



6

Pale yellow syrup, $[\alpha]_D$ = −1.2° (*c* 0.4, $CHCl_3$), R_f = 0.21 (47:3 EtOAc/ /MeOH). IR (KBr): ν_{max} 3377 (OH), 1755 cm^{-1} (C=O). ^{1}H-NMR (250 MHz, acetone-d_6): δ 2.28 (*m*, 2 H, $J_{2,3}$ = 8.3, $J_{3,4}$ = 7.3 Hz, 2×H-3), 2.48 (*t*, $J_{2,3}$ = 8.3 Hz, 2 H, H-2), 3.54–3.68 (*m*, 3 H, $J_{5,6}$ = 2.5 Hz, H-6 and 2×H-7), 3.74 (*dd*, 1 H, $J_{4,5}$ = 5.8, $J_{5,6}$ = 2.5 Hz, H-5), 4.61 ppm (*m*, 1 H, H-4). ^{13}C-NMR (62.9 MHz, acetone-d_6): δ 24.0 (C-3), 28.7 (C-2), 64.0 (C-7), 71.9 (C-6), 72.7 (C-5), 80.7 (C-4), 177.7 ppm (C-1). HRMS (ESI): *m*/*z* 177.0764 (M^++H). Calcd. for $C_7H_{13}O_5$: 177.0758.

*3,6-Anhydro-5-*O*-benzyl-2-deoxy-D-ido-heptono-1,4-lactone (**8**).*



8

Colourless syrup, $[\alpha]_D$ = +4.3° (*c* 1.0, $CHCl_3$), R_f = 0.31 (Et_2O). IR ($CHCl_3$): ν_{max} 3467 (OH), 1789 cm^{-1} (C=O). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.52 (*bs*, 1 H, OH), 2.58–2.78 (*m*, 2 H, 2×H-2), 3.76 (*dd*, 1 H, $J_{6,7a}$ = 4.3, $J_{7a,7b}$ = = 12.0 Hz, H-7a), 3.84 (*dd*, 1 H, $J_{6,7b}$ = 5.1, $J_{7a,7b}$ = 12.0 Hz, H-7b), 4.17 (*m*, 1 H, $J_{5,6}$ = 4.9 Hz, H-6), 4.25 (*d*, 1 H, $J_{5,6}$ = 4.9 Hz, H 5), 4.56 and 4.71 (2×*d*, J_{gem} = 11.9 Hz, CH_2Ph), 4.91–5.01 (*m*, 2 H, H-3 and H-4), 7.26–7.42 ppm (*m*, 5 H, Ph). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 35.8 (C-2), 61.1 (C-7), 72.7 (*C*H_2Ph), 76.7 (C 3), 80.7 (C-6), 82.1 (C-5), 85.7 (C-4), 127.6, 128.2, 128.6, 136.7 (Ph), 175.2 ppm (C-1). HRMS (ESI): *m*/*z* 265.1066 (M^++H), Calcd. for $C_{14}H_{17}O_5$: 265.1070.

SAR ANALYSIS

The structure–activity relationships were accessed as follows: the IC_{50} values of two compounds were compared, and the Δlog IC_{50} was calculated (Δlog IC_{50} is the difference between the log IC_{50} values of an analogue and the corresponding control compound). Positive Δlog IC_{50} values show a decrease of antiproliferative activity, whereas negative values indicate an increase in the activity upon the structural modification being considered. The results are presented in Fig. S-1.

TABLE S-1. Cytotoxicity data for SAR analysis

Compound	IC_{50} / μM[a], 72 h						
	K562	HL-60	Jurkat	Raji	HT-29	MDA-MB 231	HeLa
1	0.41	201.32	32.45	18.45	0.59	75.34	8.32
2	0.003	5.56	3.73	115.78	564.31	75.31	0.01
3	0.0051	221.32	321.52	0.0093	0.056	0.11	312.46
4	0.54 [b]	0.09 [b]	2.23 [b]	2.21[b]	2001.21	5031.23	2.34 [b]
5	4.21	0.02	102.89	364.25	94.35	0.011	486.25
6	3.54	112.89	11.84	89.64	0.12	489.16	4.10
7	0.12	20.62	9.45	56.37	12.45	67.50	0.03
8	0.065	0.09	1.02	11.39	669.48	664.25	5.92

[a]IC_{50} is the concentration of compound required to inhibit the cell growth by 50 % compared to an untreated control. Values are means of three independent experiments. Coefficients of variation were less than 10 %; [b]taken from reference[2]

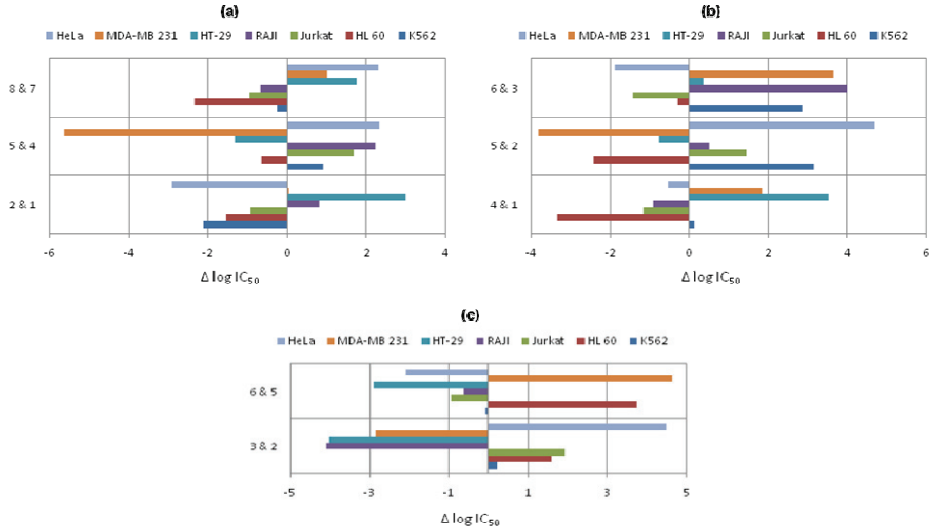


Fig. S-1. SAR analysis of goniofufurone (**1**) and analogues (**2**–**8**): (a) influence of the phenyl group; (b) influence of the tetrahydrofuran ring; (c) influence of stereochemistry at C-3 and/or C-4.

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