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Synthesis and antiproliferative activity of (5*R*)-cleistenolide and analogues

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Abstract: (5*R*)-Cleistenolide and a few related analogues have been synthesized starting from d-glucose. The key steps of the synthesis included a *Z*-selective Wittig olefination and an intramolecular Mitsunobu reaction with an inversion of configuration at the C-5 position. *In vitro* antiproliferative activity of synthesized compounds was tested on a panel of eight human tumour cells and against a single normal cell line (MRC-5). The majority of tested compounds showed strong antiproliferative effects on certain human tumour cells and all of them showed negligible toxicity to normal foetal lung fibroblasts (MRC-5). The most active compound obtained in this work is lactone **5**, which in MDA-MB 231 cell culture showed the same activity as doxorubicin (IC_{50} 0.09 μM). Strong antiproliferative activities of analogues **2**, **5** and **6** were recorded in the K562 cell line (IC_{50} 0.21, 0.34 and 0.33 μM, respectively), in which they showed very similar activities to doxorubicin (IC_{50} 0.25 μM). A performed SAR study revealed that a change in the stereochemistry at the C-5 position may increase the activity of resulting stereoisomers.

Keywords: antitumour agents; sugar *δ*-lactones; (5*R*)-cleistenolide; *Z*-selective Wittig olefination; intramolecular Mitsunobu reaction; SAR analysis.

INTRODUCTION

(−)-Cleistenolide (**1**, Fig. 1) is a naturally occurring *α*,*β*-unsaturated *δ*-lactone isolated from *Cleistochlamis kirkii* Oliver, a plant species that grows in southeast Africa.[1] The extract of this plant has been used in Tanzania and Mozambique in traditional medicine for the treatment of infected wounds, rheumat-

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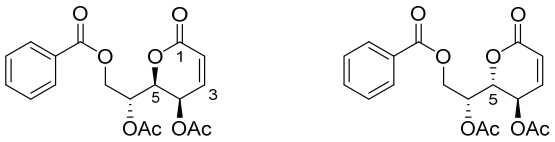
ism and tuberculosis.[2] Recently, Pereira *et al.*[3] isolated from the ethanolic extract of *C. kirkii* a new natural product (−)-cleistenolide, and eight other compounds of different structures: chamanetin, isochamanetin, dichamanetin, echunuline, *cis*--solamine, acetylmelodorinol, polycarpol and benzophenone. Noteworthy are recent findings that isolated fractions, dominated by pyranone (−)-cleistenolide, showed antibacterial activity against *Bacillus anthracis* and *Staphilococcus aureus* as well as antifungal activity against *Candida albicans*.[1,2,4] We have also confirmed that (−)-cleistenolide and some of its analogues demonstrated antimicrobial activity against a panel of nine microbial strains.[5] Finally, we were among the first to discover that (−)-cleistenolide and some new analogues of it may inhibit the growth of certain tumour cell lines.[6–8] After our first report dealing with this issue,[6] only one paper has been published on the cytotoxicity of natural product **1** towards a single malignant cell line.[9] Herein we describe a new total synthesis of the (5*R*)-cleistenolide (**2**), which is a C-5 epimer of natural product **1**. Our new synthesis of compound **2** is based on the chiral pool strategy, which involves the chirality transfer from D-glucose, which ensures obtaining the target in an optically pure form. The sequence contains only one step in which three benzyl-protecting groups are introduced, while their deprotection was carried out simultaneously with the introduction of acyl groups. Only one synthesis of **2** has been achieved so far;[10] however, no studies addressing its biological activity have been published yet. To elucidate the effects of stereochemistry at the C-5 position on the activity of lactones **1** and **2**, a study of their *in vitro* cytotoxicity on a panel of malignant cell lines was performed.



(–)-Cleistenolide (**1**) (5*R*)-cleistenolide (**2**)

Fig. 1. Structures of (−)-cleistenolide (**1**) and (5*R*)-cleistenolide (**2**).

EXPERIMENTAL

General procedures

Melting points were determined on a hot stage microscope Nagema PHMK 05 apparatus, and were not corrected. Optical rotations were measured on a Rudolph Research Analytical automatic polarimeter, Autopol IV. IR spectra were recorded on a FTIR Nexus 670 (Thermo--Nicolet) spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC 250 E (at 250 and 62.5 MHz, respectively) or a Bruker Avance III spectrometer (at 400 and 100 MHz, respectively) using TMS as the internal standard. Chemical shifts were expressed in ppm (δ values) and coupling constants (J) in Hz. High-resolution mass spectra were taken on a Micromass LCT KA111 spectrometer or LTQ Orbitrap XL (Thermo Fisher Scientific Inc.) mass spectrometer. TLC was performed on DC Alufolien Kieselgel 60 F254 (E. Merck). Flash

column chromatography was performed using Kieselgel 60 (0.040–0.063, E. Merck). All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated in a rotary evaporator under reduced pressure at a bath temperature below 35 °C. The purity of the synthesized compounds was determined by HRMS or elemental microanalysis and was greater than 95 % (errors were less than 5 ppm).

Synthetic procedures

Methyl (2Z)-4,6,7-tri-O-*benzyl-2,3-dideoxy-D*-arabino-*hept-2-enoate (**4**)*. To a cooled (0 °C) and stirred solution of compound **3** in anhydrous DMF (75 mL) was added NaH (1.66 g, 69.16 mmol) and after the vigorous evolution of H_2 had stopped, BnBr (4.8 mL, 40.3 mmol) was slowly added over 10 min. After 0.5 h, the cooling vessel was removed and the stirring was continued for an additional 2 h at room temperature. Anhydrous MeOH (12 mL) was slowly added to the reaction solution. And after the intense release of hydrogen had stopped, the mixture was evaporated. The resulting residue was dissolved in small volume of CH_2Cl_2/ /H_2O, poured into H_2O (250 mL) and extracted with CH_2Cl_2 (3×40 mL). The organic phases were combined, washed with 10 % NaCl (3×150 mL), then dried and evaporated. The remaining crude compound **3a** was dissolved in 50 % aq. TFA (60 mL) and vigorously stirred at room temperature for 18 h. The reaction solution was evaporated by co-distillation with toluene to remove the acid and water, and the resulting residue was dried under high vacuum overnight. To a stirred solution of remaining crude lactol **3b** in anhydrous MeOH (500 mL) was added $NaIO_4$ (3.68 g, 17.29 mmol) and the stirring at room temperature was continued for 2 h, whereby crude intermediate **3c** was obtained. The reaction solution was then cooled to 0 °C and methyl 2-(triphenylphosphoranylidene)acetate (7.50 g, 22.46 mmol) was added. After 1 h, the cooling vessel was removed and the reaction was continued at room temperature for another 3 h. A new portion of reagent (4.05 g, 12.12 mmol) was added and stirring was continued for additional 20 h. The reaction solution was evaporated and the residue was dissolved in CH_2Cl_2 and evaporated with silica gel. The residue was purified twice by flash chromatography (1:1 light petroleum/Et_2O) to give pure **4** (4.10 g, 75 % from four steps) as a colourless syrup, $[\alpha]_D = -19.1$ (*c* 1.0, $CHCl_3$); $R_f = 0.32$ (3:2 light petroleum/Et_2O). Spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS) were in good agreement with our previously reported values.[6]

4,6,7-Tri-O-*benzyl-2,3-dideoxy-D*-arabino-*hept-2-eno-1,5-lactone (**5**)*. To a solution of compound **4** (2.05 g, 4.19 mmol) in CH_2Cl_2 (85 mL) was added TsOH×H_2O (0.021 g, 0.105 mmol). The mixture was stirred at room temperature for 96 h, then evaporated and the residue was purified by flash chromatography (1:1 light petroleum/Et_2O). Pure product **5** (1.782 g, 96 %) was obtained as a colourless syrup. Crystallization from a mixture of light petroleum/Et_2O gave analytical sample **5** as a white powder, mp 64 °C, $[\alpha]_D = -194.6$ (*c* 0.5, $CHCl_3$), R_f = 0.30 (1:1 light petroleum/Et_2O). Spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS) were in good agreement with the values we reported previously.[6]

4,6,7-Tri-O-*benzyl-2,3-dideoxy-D*-lyxo-*hept-2-eno-1,5-lactone (**6**)*. To a stirred mixture of lactone **5** (0.200 g, 0.45 mmol) and LiBr (0.391 g, 4.5 mmol) in CH_3CN (5 mL) was added anhydrous Et_3N (0.19 mL, 1.35 mmol). The mixture was stirred at room temperature for 24 h, then acidified with glacial AcOH (2.0 mL) while stirring at room temperature for additional 3 min. The reaction mixture was poured into H_2O (80 mL) and extracted with EtOAc (3×20 mL). The organic solutions were combined, dried and evaporated, and the residue was dried under a vacuum for 4 h. To the stirred solution of the residue in anhydrous EtOAc (25 mL) was added Ph_3P (0.295 g, 1.12 mmol) and 40 % DEAD (0.47 mL, 1.08 mmol) over 3 min. The reaction solution was stirred at room temperature for 20 h, then evaporated, and the residue was purified on two columns of flash silica (first with 1:1 light petroleum/Et_2O, then with

99:1 CH_2Cl_2/Me_2CO). Pure **6** (0.125 g, 62 %) was obtained as a glassy solid, $[\alpha]_D = -86.4$ (*c* 0.5, $CHCl_3$), $R_f = 0.33$ (1:1 Et_2O/light petroleum).

*(5*R*)-Cleistenolide (**2**)*. To a stirred solution of compound **6** (0.100 g, 0.22 mmol), Bz_2O (0.124 g, 0.55 mmol) and BzOH (0.134 g, 1.1 mmol) in anhydrous CH_2Cl_2 (15 mL) was added anhydrous $FeCl_3$ (0.007 g, 0.04 mmol). After stirring at room temperature for 2 h, $FeCl_3$ (0.004 g, 0.02 mmol) and AcBr (0.16 mL, 2.2 mmol) were successively added and the reaction at room temperature continued for an additional 20 h. The reaction solution was diluted with CH_2Cl_2 (10 mL), poured into 10 % $NaHCO_3$ (60 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with 10 % NaCl (30 mL), dried and evaporated. The residue was purified by flash chromatography (2:1 Et_2O/light petroleum) to give pure product **2** (0.061 g, 76 %) as a colourless solid, which after recrystallization from a mixture of CH_2Cl_2/hexane, gave colourless needles, mp 152 °C (phase transition at 140−143 °C), lit.[10] mp 140 °C (the sample not recrystallized), $[\alpha]_D = -30.0$ (*c* 0.5, $CHCl_3$), lit.[10] $[\alpha]_D = -22.0$ (*c* 1.0, $CHCl_3$), $R_f = 0.33$ (2:1 Et_2O/light petroleum).

Analytical and spectral data of the compounds are given in the Supplementary material to this paper.

Antiproliferative activity

Tested cells. Eight human cancer cell lines were used to evaluate *in vitro* antiproliferative activity of tested compounds: myelogenous leukaemia, K562 (ATCC CCL-243), promyelocytic leukaemia, HL-60 (ATCC CCL-240), T cell leukaemia, Jurkat (ATCC CCL-1435), Burkitt's lymphoma, Raji (ATCC CCL-86), ER^+ breast adenocarcinoma, MCF-7 (ATCC HTB-22), ER^- breast adenocarcinoma, MDA-MB 231 (ATCC HTB-26), cervix carcinoma, HeLa (ATCC CCL2), and epithelial lung carcinoma, A549 (ATCC HTB-38). The toxicity of each compound was also recorded in the culture of normal foetal lung fibroblasts, MRC-5 (ATCC CCL-185).

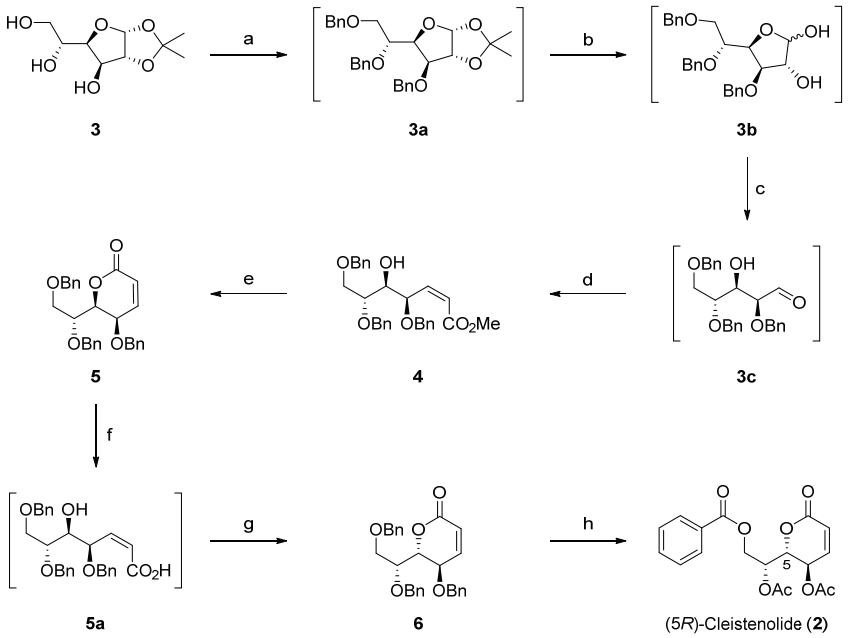
MTT test. After cells were exposed to the test compounds for 72 h, antiproliferative activities were assessed using the standard MTT assay.[11] Briefly, cells were harvested, counted using trypan blue and plated into 96-well microtiter plates (Costar) at the optimal seeding density of 5×10^3 cells per well to assure a logarithmic growth rate throughout the assay period. Viable cells were placed in a volume of 90 μL per well, and preincubated in complete medium at 37 °C for 24 h to allow cell stabilization prior to the addition of test substances. The substances, at 10-fold the required final concentration, were added (10 μL $well^{-1}$) to each well, except for the control ones, and the microplates were incubated for 72 h. The wells containing cells without tested substances were used as controls. MTT solution (10 μL) was added to each well 3 h before the end of incubation period. MTT was dissolved in medium at 5 mg mL^{-1} and filtered to sterilize and remove the small amount of insoluble residue present in some batches of MTT. Acidified 2-propanol (100 μL of 0.04 M·HCl in 2-propanol) was added to each well and mixed thoroughly to dissolve the dark blue crystals of formazan. After a few minutes at room temperature, the plates were read on a spectrophotometer plate reader (Multiscan MCC340, Labsystems) at 540 and 690 nm. The wells without cells containing complete medium and MTT acted as blanks.

RESULTS AND DISCUSSION

Chemistry

The eight-step synthesis of (5*R*)-cleistenolide (**2**) was presented in Scheme 1. The synthesis commenced from a commercially available D-glucose derivative **3**. The first four steps of the synthesis, the preparation of enoate **4**, involve optimiz-

ation of the corresponding synthetic sequence that we recently published.[6] In contrast to the previous procedure, intermediates **3a**, **3b** and **3c** were not purified or characterized but were used in the following synthetic steps in their crude form. This provided the key intermediate **4** with an overall yield of 75 % (from four steps). Closure of the lactone ring was achieved as previously reported (TsOH, CH_2Cl_2, rt),[6] giving the desired *δ*-lactone **5** in 96 % yield. For the configurational inversion at the C-5 position of **5**, a modified two-step procedure was applied, which involves the sequential hydrolysis of the lactone ring under the basic conditions (Et_3N, LiBr, 98 % aq MeCN, rt), and intramolecular Mitsunobu reaction (Ph_3P, DEAD, anhydrous EtOAc, rt).[12] The key intermediate **6** was thus obtained in a yield of 62 % (from **5**). The final step in the synthesis involved replacing the benzyl protecting groups with ester functions. It was achieved by successive treatment of **6** with Bz_2O, BzOH and AcBr in the presence of catalytic amounts of $FeCl_3$. These transformations gave (5*R*)-cleistenolide (**2**) in 76 % yield.



Scheme 1. a) BnBr, NaH, DMF, 0 °C, 0.5 h, rt, 2 h; b) 50 % aq. TFA, rt, 18 h; c) $NaIO_4$, MeOH, rt, 2 h; d) $Ph_3P{=}CHCO_2Me$, MeOH, 0 °C, 1 h, rt, 3 h, 75 % from **3**; e) TsOH, CH_2Cl_2, rt, 96 h, 96 %; f) Et_3N, LiBr, 98 % aq MeCN, rt, 24 h; g) Ph_3P, DEAD, anhydrous EtOAc, rt, 20 h; 62 %; h) Bz_2O, BzOH, $FeCl_3$, AcBr, anhydrous CH_2Cl_2, rt, 22 h, 76 %.

This new synthesis of (5*R*)-cleistenolide (**2**) was achieved in eight synthetic steps and in a yield of 34 %. The first synthesis[10] of **2** was achieved in seven steps and in a total yield of 25 %.

In vitro *antiproliferative activities and SAR analysis*

The biological activities of synthesized compounds **1**, **2**, **5** and **6** were evaluated by an *in vitro* cytotoxicity test against a panel of eight human malignant cell lines, including human myelogenous leukaemia (K562), human promyelocytic leukaemia (HL-60), T cell leukaemia (Jurkat), Burkitt's lymphoma (Raji), ER^+ breast adenocarcinoma (MCF-7), ER^- breast adenocarcinoma (MDA-MB 231), cervix carcinoma (HeLa) and lung adenocarcinoma epithelial cells (A549) and against single normal cell line, foetal lung fibroblasts (MRC-5). Cell growth inhibition was evaluated using the standard MTT colorimetric assay after exposure of cells to the test compounds for 72 h.[11] (–)-Cleistenolide (**1**), and the commercial antitumour agent doxorubicin (DOX) were used as positive controls. The results are shown in Table I. According to the resulting IC_{50} values, all of cell lines tested were sensitive to the natural product **1**, as well as to the synthesized analogues **2**, **5** and **6**.

TABLE I. *In vitro* cytotoxicity (IC_{50} / μM)[a]* of (−)-cleistenolide (**1**), (5*R*)-cleistenolide (**2**), DOX and analogues (**5** and **6**)

Compound	Cell line								
	K562	HL-60	Jurkat	Raji	MCF-7	MDA-MB 231	HeLa	A549	MRC-5
1[a]	7.65	1.21	14.22	36.94	26.07	2.25	7.32	16.34	>100
2	0.21	7.31	19.41	2.47	21.28	7.66	6.45	9.38	>100
5	0.34	12.55	9.24	29.66	1.39	0.09	3.58	1.85	64.39
6	0.33	8.27	17.03	1.05	20.06	7.04	5.90	17.21	>100
DOX	0.25	0.92	0.03	2.98	0.20	0.09	0.07	4.91	0.10

[a]Data taken from reference 6

All analogues (**2**, **5** and **6**) showed strong antiproliferative effects against K562 cells (IC_{50} values in the range 0.21–0.33 μM). In contrast, lead **1** showed significantly lower activity against this cell line (IC_{50} 7.65 μM). The most active compound in the K562 cell culture was target **2**, which showed more than 36 times stronger activity than lead **1**. At the same time, analogue **2** showed almost the same activity as doxorubicin against the mentioned malignant cell line. The most potent compounds against Raji cells are analogues **2** and **6**. Compound **2** was about fifteen times more active than lead **1** while showing similar activity to doxorubicin. Analogue **6** was the most active molecule against Raji cells. This compound showed even stronger potency than lead **1** (over 35 times), and about 3 times over doxorubicin. The most active compound in the MCF-7 cell culture is lactone **5**, which showed over 18 time greater potency than lead **1**. Also, lactone **5** is the most active compound obtained in this work, given that it showed an

* 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 %.

IC_{50} 0.09 μM in the MDA-MB 231 cell culture. Compared to lead **1**, lactone **5** is 25 times more potent, and shows the same activity as the commercial drug doxorubicin against the mentioned malignant cell line. In HeLa and A549 cells, lactone **5** is consistently the most potent antiproliferative agent, being twice (HeLa) and 9 times (A549) more active than lead **1**. In the A549 cell culture, compound **5** showed, again, almost three times stronger antiproliferative activity than doxorubicin.

As can be further seen from Table I, all synthesized analogues (**2**, **5** and **6**), as well as lead compound **1**, were almost completely inactive toward normal MRC-5 cells. Compound **5** alone showed weak growth inhibition of this cell line (IC_{50} 64.39 μM), with selectivity indices (SI)[13] as follows: 189.38 (K562 cells), 5.13 (HL-60), 6.97 (Jurkat), 2.17 (Raji), 46.32 (MCF-7), 715.44 (MDA-MB 231), 17.99 (HeLa) and 34.8 (A549). On the contrary, the commercial antitumour agent DOX exhibited a potent cytotoxicity against this cell line. This indicates the selectivity of synthesized compounds toward tumour cells, which is a desirable feature and represents a good basis for the further development of potent and selective antitumour agents.

In order to correlate the stereochemistry of synthesized compounds with their cytotoxic activities, we wanted to explore the effects of changing absolute stereochemistry at C-5 to antiproliferative activity of resulting analogues. The natural product **1**, and lactone **5** have been used as controls in this SAR analysis. The data in Table I reveal that target *δ*-lactone **2**, which has (5*R*)-stereochemistry, represents a more potent cytotoxic agent compared to the natural product **1** of (5*S*)-stereochemistry, given that analogue **2** shows stronger activity against 5 of 8 tested malignant cells. Unfortunately, changing the absolute stereochemistry at the C-5 position (5*S* → 5*R*) in lactones of type **5** and **6** is not as effective, as an increase in activity was detected in only 3 out of 8 cancer cell lines tested (for more details see Supplementary material). However, these results still indicate that a change in stereochemistry at C-5 in cleistenolide-type lactones may increase the antiproliferative activity of the analogues.

CONCLUSION

In this work, a new total synthesis of (5*R*)-cleistenolide (**2**) was achieved in eight synthetic steps and in a total yield of 34 %. In terms of the economy of atoms and synthetic steps, this new synthesis of **2** utilizes 3 of 4 chiral centres of D-glucose. Although it was carried out in a sequence that is one step longer than the synthesis described in the literature,[10] our synthesis is more efficient, at least in terms of overall yield. The target compound **2** and the corresponding intermediates **5** and **6** were tested for their *in vitro* antiproliferative activity against a panel of eight human malignant cell lines as well as one normal cell line. All tested compounds had different antiproliferative effects on human malignant cell

lines but had no significant toxicity on normal foetal lung fibroblasts (MRC-5). The most active compound obtained in this work is lactone **5**, given that it showed an IC_{50} value of 0.09 μM in the MDA-MB 231 cell culture. Compared to lead **1**, lactone **5** is 25 times more potent and shows the same activity as the commercial drug doxorubicin against the mentioned malignant cell line. The obtained results indicate that changing the stereochemistry at the C-5 position may improve antiproliferative activity toward some of evaluated cell lines. The obtained biological results further indicated that the change of stereochemistry at C-5 (from 5*S* in natural product **1** to 5*R* in analogue **2**) increases the cytotoxicity of the analogue toward majority of tested malignant cells.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12250, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА И АНТИПРОЛИФЕРАТИВНА АКТИВНОСТ (5*R*)-КЛЕИСТЕНОЛИДА И АНАЛОГА

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(5*R*)-Клеистенолид и неколико сродних аналога су синтетизовани полазећи од d-глукозе. Кључни кораци синтезе укључивали су *Z*-селективну Витигову (Wittig) олефинацију и интрамолекулску Мицунобуову (Mitsunobu) реакцију уз инверзију конфигурације на C-5. *In vitro* антипролиферативна активност синтетизованих једињења је тестирана на панелу од осам хуманих туморских ћелија и према једној нормалној ћелијској линији (MRC-5). Већина тестираних једињења показала је снажне антипролиферативне ефекте према одређеним хуманим туморским ћелијама, а сва су показала занемарљиву токсичност према нормалним ћелијама феталних фибробласта плућа (MRC-5). Најактивније једињење добијено у овом раду био је лактон **5**, који је у ћелијској култури MDA-MB 231 показао исту активност као доксорубицин (IC_{50} 0,09 μM). Јаке антипролиферативне активности аналога **2**, **5** и **6** су забележене у ћелијској култури K562 (IC_{50} 0,21, 0,34 и 0,33 μM, редом), показујући при томе веома сличне активности доксорубицину (IC_{50} 0,25 μM). Прелиминарна САР анализа указује да промена стереохемије на C-5 може повећати антипролиферативну активност резултујућих стереоизомера.

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