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Divergent synthesis and antitumour activity of novel conformationally constrained (–)-muricatacin analogues

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Abstract: Four novel conformationally restricted (–)-muricatacin analogues, bearing a methoxy group at the C-5 position and with an alkoxymethyl group as the C-7 side chain, have been synthesised and their *in vitro* antiproliferative activity was evaluated against a panel of seven human tumour cell lines, as well as a single normal cell line. All analogues (**9**–**12**) showed diverse antiproliferative effects against all tested human malignant cell lines, but were devoid of any significant cytotoxicity towards the normal foetal lung fibroblasts (MRC-5). A structure–activity relationship study reveals that the introduction of tetrahydrofuran ring, the replacement of C-8 methylene group in the side chain of muricatacin analogues with the O-8 ether functionality, as well as the length of side chain may be beneficial for the antiproliferative effects of these lactones. All novel analogues were more potent than lead compound, (–)-muricatacin, against HL-60 cell line.

Keywords: D-glucose; antitumour agents; muricatacin mimics; furanolactones; cytotoxicity; SAR analysis.

INTRODUCTION

(–)-Muricatacin (**1**) is a naturally occurring acetogenin derivative, which has been isolated by McLaughlin and co-workers[1] from the seeds of *Annona muricata L.* together with its enantiomer (+)-muricatacin (*ent*-**1**). Both natural products (**1** and *ent*-**1**) have received a great deal of attention due to their similar biological profiles: remarkable antiproliferative activities towards various human tumour cells,[2,3] antimalarial as well as pesticidal activities.[1]

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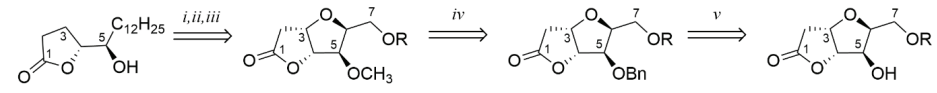
Many syntheses of **1** from various precursors have been reported.[4–16] Also, several muricatacin analogues have been synthesised[3,7,17–20] and some of them were evaluated for their antitumour activity.[7,19,20]

As a part of our ongoing program in the synthesis of oxygenated lactones as potential antitumour agents from abundant monosaccharides, the synthesis of four novel 8-oxa analogues of (–)-muricatacin (**9**–**12**, Fig. 1) with furano-furanone ring system and methoxy group at the C-5 position was achieved from D--glucose. These molecules represent conformationally constrained oxa-analogues of lactone **1**, with methoxy group at the C-5 position. Analogue **9** is a heteroannelated mimic of **1** with the restricted geometry of the C_4–C_6 segment, due to the presence of the tetrahydrofuran (THF) ring. The molecule **10** represents a one-carbon lower homologue of **9**, while the molecules **11** and **12** are two- and three-carbon lower homologues of lactone **9**.



(–)-Muricatacin (**1**)

9 R = C_9H_{19}
10 R = C_8H_{17}
11 R = C_7H_{15}
12 R = C_6H_{13}

13 R = C_9H_{19}
14 R = C_8H_{17}
15 R = C_7H_{15}
16 R = C_6H_{13}

17 R = C_9H_{19}
18 R = C_8H_{17}
19 R = C_7H_{15}
20 R = C_6H_{13}

Fig. 1. Design of (–)-muricatacin analogues with a methoxy group (**9**–**12**), a benzyl group (**13**–**16**) and with a hydroxyl group at C-5 position (**17**–**20**): *i*) THF-ring closure; *ii*) 5-*O*-methylation; *iii*) exchange of C_8 methylene group with O_8 ether function; *iv*) substitution of methyl with benzyl group at C-5; *v*) debenzylation at C-5.

Our recent results on the antiproliferative activity of analogues **17**–**20** showed that they exhibit moderate to submicromolar cytotoxicity.[21] That led us to prepare C-5 methoxy derivatives **9**–**12**, and to examine their cytotoxic activity, as well as the cytotoxicity of previously synthesised analogues **13**–**16**,[21] for a detailed structure–activity relationship (SAR) analysis.

EXPERIMENTAL

General procedures

Melting points were determined on Büchi 510, or on hot stage microscope Nagema PHMK 05 apparatus and were not corrected. Optical rotations were measured on Autopol IV (Rudolph Research) automatic polarimeter. IR spectra were recorded with a FTIR Nexus 670 (Thermo-Nicolet) spectrophotometer. NMR spectra were recorded on a Bruker AC 250 E or a Bruker Avance III 400 MHz instrument and chemical shifts are expressed in ppm downfield from tetramethylsilane. Low resolution mass spectra were recorded on Finnigan-MAT 8230 (CI) mass spectrometer. High-resolution mass spectra were taken on a Micromass LCT KA111 spectrometer or on LTQ OrbitrapXL (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 ext-

racts 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.

Synthesis procedures

*Methyl (Z)- (**4**) and (E)-3-O-methyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hept-5--enofuranuronate (**5**)*. To a solution of compound **2** (1.923 g, 7.01 mmol), in dry EtOAc (193 mL), H_5IO_6 (2.008 g, 8.76 mmol) was added. The mixture was stirred at room temperature for 3 h, then filtered and evaporated to afford crude aldehyde **3**. To a stirred and cooled (0 °C) solution of **3** (1.530 g, 7.56 mmol) in dry MeOH (35 mL) MCMP (2.558 g, 7.56 mmol) was added and the mixture was stirred for 0.5 h at 0 °C and then for 2.5 h at room temperature. The reaction mixture was evaporated and the residue was purified by flash chromatography (3:2 light petroleum/Et_2O). The pure product **4** (1.240 g, 69 %) was first eluted, isolated as a colourless oil. Further elution gave compound **5** which was additionally purified (1:1 $^iPr_2O$/ /light petroleum) to give the pure *E*-olefin **5** (0.133 g, 7 %).

*Dimethylacetal 2,5-Anhydro-6-deoxy-3-O-methyl-L-ido-hepturono-4,7-lactone (**6**)*. A solution of **4** (0.245 g, 0.95 mmol) in dry MeOH (7 mL) which contains 2.5 % H_2SO_4, was refluxed for 2 h. The mixture was cooled to 35 °C and alkalized (pH 9) by adding solid $NaHCO_3$ (0.917 g, 10.92 mmol, 11.5 eq) in three portions every 5 min. After adding the entire amount of base, the suspension was stirred at 35 °C for 1 h, then filtered and evaporated. The residue was purified by flash column chromatography (3:2 cyclohexane/EtOAc) to give pure **6** (0.174 g, 79 %).

*3,6-Anhydro-2-deoxy-5-O-methyl-L-ido-heptono-1,4-lactone (**8**)*. Dimethylacetal **6** (0.769 g, 3.31 mmol) was dissolved in 9:1 TFA/H_2O (15.5 mL) and stirred at room temperature for 1 h. After completion of the reaction, the solution was evaporated by co-distillation with toluene. The crude aldehyde **7** was dissolved in dry MeOH (39 mL) and treated with a first portion of $NaBH_4$ (0.094 g, 2.49 mmol, 3 eq). After stirring the mixture at room temperature for 0.5 h, an additional amount of $NaBH_4$ (0.063 g, 1.67 mmol, 2 eq) was added. The mixture was stirred at room temperature for additional hour. The reaction mixture was neutralized with AcOH and evaporated. The residue was purified by flash chromatography (4:1 CH_2Cl_2/EtOAc) to give pure alcohol **8** (0.399 g, 64 %).

*General procedure for the synthesis of analogues **9**–**12***

To a solution of compound **8** (1 equiv.) in dry Et_2O (2 mL) Ag_2O (2.5 equiv.), AgOTf (0.3 eq) and the corresponding alkyl bromide RBr (2.5 equiv.) were added. The mixture was stirred under reflux for 16–27 h (Table I). After completion of the reaction, which was detected by thin layer chromatography (TLC), the mixture was purified by flash column chromatography (7:3 light petroleum/Et_2O).

The characterization data for all synthesised compounds (**4**–**6** and **8**–**12**) are given in the Supplementary material to this paper.

TABLE I. Preparation of final products **9**–**12**

Entry	R	Reaction time, h	Product	Yield, %
1	C_9H_{19}	22.5	9	72
2	C_8H_{17}	16	10	86
3	C_7H_{15}	23	11	80
4	C_6H_{13}	27	12	73

Cytotoxic activity

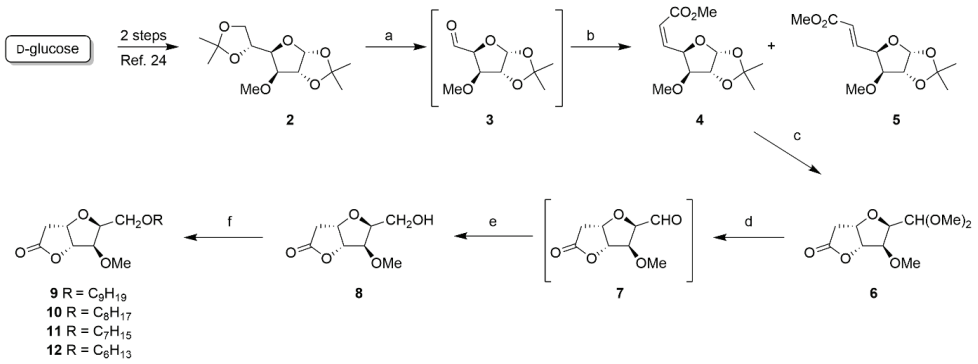
Test cells. The *in vitro* cytotoxicity of test compounds was evaluated against seven human malignant cell lines: myelogenous leukaemia (K562), promyelocytic leukaemia (HL-60), T cell leukaemia (Jurkat), Burkitt's lymphoma (Raji), ER^+ breast adenocarcinoma (MCF-7), ER^- breast adenocarcinoma (MDA-MB 231) and cervix carcinoma (HeLa). Cytotoxic activity against normal foetal lung fibroblasts (MRC-5) was also estimated.

MTT test. Cytotoxic activity was evaluated by using standard MTT assay,[22] after exposure of cells to the tested compounds for 72 h.

RESULTS AND DISCUSSION

Chemistry

The syntheses of (–)-muricatacin analogues **9**–**12** are presented in Scheme 1. Starting compound **2** was prepared from D-glucose in two synthetic steps as previously reported by us.[23] Methyl derivative **2** was treated with periodic acid in dry ethyl acetate and the crude aldehyde **3** was obtained. Compound **3** reacted with stabilized ylide, $Ph_3P{=}CHCO_2Me$, in anhydrous MeOH and gave the expected *Z*-olefin **4** (69 %) as the major product of the Wittig olefination. A minor amount of corresponding *E*-olefin **5** (7 %) was also obtained in this reaction.



Scheme 1. Reagents and conditions: a) H_5IO_6, EtOAc, rt, 3 h; b) $Ph_3P{=}CHCO_2Me$, MeOH, 0 °C, 0.5 h, then rt 1.5 h, 69 % for **4**, 7 % for **5** (from **2**); c) 2.5 % H_2SO_4/MeOH, reflux, 2 h, $NaHCO_3$, rt, 1 h, 79 %; d) 9:1 TFA/H_2O, rt, 1 h; e) $NaBH_4$, MeOH, rt, 1.5 h, 64 % (from **6**); f) $C_9H_{19}Br$ for **9**, $C_8H_{17}Br$ for **10**, $C_7H_{15}Br$ for **11**, $C_6H_{13}Br$ for **12**, Ag_2O, AgOTf, CH_2Cl_2, reflux, 22.5 h (for **9**), 16 h (for **10**), 23 h (for **11**), 27 h (for **12**), 72 % (for **9**), 86 % (for **10**), 80 % (for **11**), 73 % (for **12**).

An acid-catalyzed methanolysis of **4**, in the presence of a catalytic amount of sulphuric acid gave furano-lactone **6** in 79 % yield. Hydrolytic removal of the dimethyl acetal protective group in **6** followed by a subsequent $NaBH_4$ reduction of the resulting aldehyde **7** gave the corresponding primary alcohol **8** in 64 % yield.

The stereochemistry of compound **8** was confirmed by single crystal X-ray diffraction analysis (for selected crystallographic and refinement details see the

Table S-II of the Supplementary material). The molecular structure of **8** is depicted in Fig. 2. All structural parameters of the molecule are within limits found in structures with similar fragments. The furano-lactone ring core is fused in *cis* manner and both five-membered rings are puckered, details of which are analysed by Cremer–Pople formalism.[24] The furanose ring (counting clockwise O3→C3→C4→C5→C6) is moderately puckered (q_2 = 36.05(17) pm), and its conformation is close to twisted at C5–C6 bond. The pseudorotational phase angle φ_2 = 130.5(3)° indicates its deformation towards the envelope form, as the ring formally traversed 25 % along ${}^6T_5 \rightarrow {}^6E$ pseudorotational pathway. Ring substituents C2 (δ = 29.58(13)°), O4 (δ = 16.44(11)°), and O5 (δ = 9.82(11)°) can be classified as axial, while C7 (δ = 65.96(13)°) is equatorial; δ is the angle subtended between Cremer–Pople ring mean plane normal and substituent bond vector.[25] The lactone ring (counting clockwise O4→C1→C2→C3→C4) is less puckered (q_2 = 14.0(2) pm) and its conformation is closer to the envelope form, with C3 as the flap. Its exact conformation is determined by φ_2 = 130.5(3)°, which means that the ring formally traversed 37 % along $E_4 \rightarrow {}^3T_4$ pseudorotational pathway.

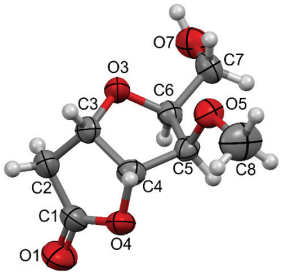


Fig. 2. Molecular structure of **8** determined by single crystal X-ray diffraction. Ellipsoids are drawn at 50 % probability level. Hydrogen atoms are shown as spheres of arbitrary radii.

The key intermediate, alcohol **8**, readily reacted with an excess of nonyl bromide in ether, in the presence of silver(I)-oxide and a catalytic amount of silver(I)-triflate, to give the expected 7-*O*-nonyl derivative **9** in 72 % yield. Under similar experimental conditions, the primary alcohol **8** reacted with different alkyl bromides (C_8–C_6) to afford the corresponding ether derivatives **10**––**12** in good yields (Scheme 1).

In vitro *antiproliferative activity*

After completion of the synthesis, analogues **9**–**12** were evaluated for their *in vitro* cytotoxicity against a panel of seven human tumour cell lines (human myelogenous leukaemia, K562, promyelocytic leukaemia, HL-60, T cell leukaemia, Jurkat, Burkitt's lymphoma, Raji, ER^+ breast adenocarcinoma, MCF-7, ER^- breast adenocarcinoma, MDA-MB 231, and cervix carcinoma, HeLa) and one normal cell line (foetal lung fibroblasts, MRC-5). Cell growth inhibition was evaluated after 72 h of cells treatment by using the MTT test.[22] (–)-Muricatacin (**1**)

and the commercial antitumour agent doxorubicin (DOX) were used as positive controls in this assay.

According to the recorded IC_{50} (Table II), all tumour cell lines were sensitive to all of the synthesised analogues (**9**–**12**). All four (–)-muricatacin mimics (**9**–**12**) demonstrated diverse antiproliferative effects toward MDA-MB 231 and Jurkat cells, in contrast to the lead **1**, which was completely inactive against these cell lines.

TABLE II. *In vitro* cytotoxicity (IC_{50}* / μM) of (–)-muricatacin (**1**), DOX and analogues **9**–**20** after 72 h

Compound	Cell line							
	K562	HL-60	Jurkat	Raji	MCF-7	MDA-MB 231	HeLa	MRC-5
1	0.04	25.85	>100	0.1	21.35	>100	0.17	>100
9	10.25	17.70	15.40	21.75	4.85	11.32	13.50	>100
10	18.12	13.68	7.36	35.84	1.11	28.33	9.12	>100
11	5.60	24.54	22.97	28.49	12.31	25.33	11.51	>100
12	7.69	21.18	25.34	27.03	18.33	15.81	15.22	>100
13	8.76	6.12	9.71	15.95	22.18	39.48	68.32	>100
14	9.09	13.92	5.47	16.85	18.77	28.26	18.02	>100
15	8.87	5.67	8.86	17.33	22.87	34.59	10.90	>100
16	5.65	7.42	5.25	11.82	25.31	8.50	33.79	>100
17[a]	5.66	4.75	6.97	7.25	>100	>100	6.39	>100
18[a]	0.74	0.68	19.78	4.25	0.34	28.70	3.41	>100
19[a]	1.02	1.10	11.53	5.98	2.38	9.76	0.56	>100
20[a]	0.70	4.91	8.87	1.11	12.34	15.62	3.54	>100
DOX	0.25	0.92	0.03	2.98	0.20	0.09	0.07	0.10

[a]Taken from reference[21]

Also, all novel analogues (**9**–**12**) were more potent than lead **1** against HL-60 cell line.

The most active compound against the MCF-7 cells was analogue **10**. This molecule exhibited strong cytotoxicity (IC_{50} = 1.11 μM) although its potency was 5.5 times lower than the activity of DOX (IC_{50} = 0.20 μM), but 19 times higher than that of the control compound **1** (IC_{50} = 21.35 μM). The analogue **9** also showed very good activity (IC_{50} = 4.85 μM) against this cell line, which was 4 times higher than that of lead **1**.

The conformationally restricted benzyl analogues of **1**, compounds **13**–**16**, exhibited cytotoxic activity against all seven malignant cell lines. Against the HL-60 cell line the previously synthesised analogues **13**–**16** showed from 1.85

* 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 %.

times (analogue **14**, IC_{50} = 13.92 μM) to 4.5 times (analogue **15**, IC_{50} = 4.85 μM) better cytotoxicity than natural product **1** (IC_{50} = 25.85 μM).

Against Jurkat cell line benzyl derivatives **13**–**16** exhibited strong antiproliferative effects (IC_{50} values in the range of 5.25−9.71 μM). However, the parent compound **1** was completely inactive against this cell line.

Against the MCF-7 cell line analogues **13**–**16** demonstrated similar cytotoxicity (IC_{50}: 18.77−25.31 μM) as parent compound **1** (IC_{50} = 21.35 μM).

All synthesised compounds showed diverse growth inhibitory effects against the tested malignant cells, but were devoid of any significant cytotoxicity toward the normal foetal lung fibroblasts (MRC-5), as well as the natural product **1**, in contrast to the commercial antitumour agent doxorubicin (DOX) that exhibited potent cytotoxic activity (IC_{50} = 0.10 μM) against this cell line.

SAR analysis

Our previous findings showed that the introduction of an oxygen atom in the side chain of (–)-muricatacin analogues increases the antiproliferative activity.[21] In this work we compared (–)-muricatacin analogues with this structural feature and the changes were based on the position C-5, so we compared three series of analogues: with OMe-group (**9**–**12**), with OBn-group (**13**–**16**) and with OH-group (**17**–**20**) at that position.

Analogues **9**–**12** demonstrated better cytotoxicity than the parent compound **1** against most of the cell lines tested in this study (Fig. S-17A of the Supplementary material). The corresponding benzyl derivatives (**13**–**16**) performed better antiproliferative effects in comparison to the analogues **9**–**12** (Fig. S-17B). Finally, the analogues with OH-group at C-5 position (**17**–**20**) were more potent than benzyl analogues (**13**–**16**, Fig. S-17C). So, our further work will be focused on the preparation of a larger number of similar analogues and then we will be able to make a reliable conclusion that the free OH-group at position C-5 increases the cytotoxic activity of conformationally restricted (–)-muricatacin analogues.

CONCLUSION

In conclusion, four novel (−)-muricatacin analogues (**9**–**12**) were designed and synthesised from D-glucose as a starting compound. The newly synthesised molecules, as well as the previously synthesised benzyl analogues (**13**–**16**), were evaluated for their *in vitro* cytotoxic activity against seven human malignant cell lines. A SAR study showed that the presence of additional tetrahydrofuran ring, O-8 ether functionality, as well as the length of alkyl chain, may improve the cytotoxicity of analogues toward the majority of cell lines under evaluation.

All synthesised compounds demonstrated diverse antiproliferative effects against the human malignant cell lines but were devoid of any significant cytotoxicity towards the normal foetal lung fibroblasts (MRC-5). Hence, we believe

that this approach may be of use in the search for novel, more potent and selective anticancer agents, derived from the natural product **1**.

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/11924, or from the corresponding author on request.

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И З В О Д

ДИВЕРГЕНТНА СИНТЕЗА И АНТИТУМОРСКА АКТИВНОСТ НОВИХ КОНФОРМАЦИОНО КРУТИХ АНАЛОГА (−)-МУРИКАТАЦИНА

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Синтетизована су четири нова конформационо крута аналога (−)-мурикатацина са метокси-групом у положају C-5 и са алкоксиметил-групом у бочном низу и испитана је њихова *in vitro* антипролиферативна активност према седам хуманих туморских и једној здравој ћелијској линији. Сви аналози (**9–12**) су показали различите антипролиферативне ефекте према свим испитиваним малигним ћелијским линијама, а изостала је цитотоксична активност према ћелијској линији нормалних феталних фибробласта плућа (MRC-5). SAR анализа показује да увођење тетрахидрофуранског прстена, замена C-8 метиленске групе са етарском функцијом у бочном низу, као и дужина бочног ланца, могу бити од значаја за цитотоксичне ефекте ових лактона. Сви новодобијени аналози су били потентнији од водећег једињења (−)-мурикатацина према HL-60 ћелијској линији..

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