Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *84* (12) 1345–1353 (2019)
JSCS–5268
UDC 547.724+547.455.623:547.466.1:576+615.9
Original scientific paper

Novel (–)-goniofufurone mimics: Synthesis, antiproliferative activity and SAR analysis

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(Received 12 September, accepted 23 September 2019)

Abstract: Divergent syntheses of novel (–)-goniofufurone mimics with an alkoxymethyl group as the side chain have been accomplished from D-glucose in nine synthetic steps and in overall yields 6.7–8.7 %. Their *in vitro* antiproliferative activity was evaluated against eight human tumour cell lines as well as a single normal cell line. All analogues demonstrated powerful to good antiproliferative effects toward all malignant cell lines under evaluation. Against the HL-60 cell line, all mimics showed increased activities being 27- to 1604-fold more potent than the lead compound, (–)-goniofufurone. Remarkably, the majority of synthesized analogues displayed higher or similar activity to the commercial antitumour agent doxorubicin (DOX) against A549 cell line. The most potent compound exhibited 196-fold stronger cytotoxicity than DOX in the culture of this cell line.

Keywords: D-glucose; antitumour agents; goniofufurone mimics; cytotoxic lactones, structure–activity relationships.

INTRODUCTION

(–)-Goniofufurone (**1**) is a synthetic styryl lactone, which represents the opposite enantiomer of naturally occurring (+)-goniofufurone (*ent*-**1**, Fig. 1). After isolation of (+)-goniofufurone from the stem bark of *Gonithalamus giganteus* (Annonaceae)[1] in 1990, and the confirmation of the absolute stereochemistry of both **1** and *ent*-**1**,[2,3] many syntheses of these compounds with unique and intriguing structures have been published.[4–18]

Both, **1** and *ent*-**1**, demonstrated a remarkable antiproliferative activity toward several human tumour cell lines.[19,20] Synthetic molecule **1** and some of

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https://doi.org/10.2298/JSC190912104S

its analogues showed more powerful cytotoxicity than the natural product *ent*-**1** and the corresponding analogues from the (+)-series.[21]

Previous studies in our laboratory showed that dephenylated (–)-goniofufurone derivatives bearing an ether group with C_9- and C_{10}-hydrocarbon chains (compounds **6** and **7**) exhibited *in vitro* antitumour activity against several human cancer cell lines.[22]

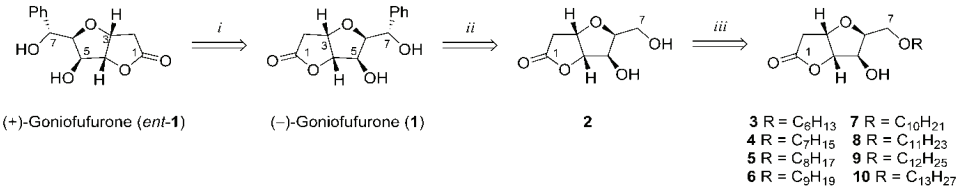


Fig. 1. Design of (+)-goniofufurone analogues **2**–**10**: *i*) enantiomerization of *ent*-**1**; *ii*) dephenylation of **1**; *iii*) *O*-alkylation of HO-7 in **2**.

As an extension of this work, herein the synthesis and *in vitro* antitumour activity of six novel (–)-goniofufurone mimics (**3**–**5** and **8**–**10**) and full experimental details for the preparation of **6** and **7** are reported. The preparation and cytotoxicity of known[23,24] dephenylated (–)-goniofufurone analogue **2** is also disclosed.

EXPERIMENTAL

General procedures

Melting points were determined on a Büchi 510, or on a hot stage microscope Nagema PHMK 05 apparatus and are not corrected. Optical rotations were measured on an Autopol IV (Rudolph Research) automatic polarimeter. The IR spectra were recorded with a FTIR Nexus 670 (Thermo-Nicolet) spectrophotometer. The NMR spectra were recorded on a Bruker AC 250 E or a Bruker Avance III 400 MHz instrument and the chemical shifts are expressed in ppm downfield from tetramethylsilane. Low resolution mass spectra were recorded on a 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., USA) mass spectrometer. TLC was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). Flash column chromatography was performed using Kieselgel 60 (0.040–0.063 mm, E. Merck). All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated on a rotary evaporator under diminished pressure at a bath temperature below 35 °C.

Synthetic procedures

*General procedure for the synthesis of the intermediates **12**–**19**.* To a solution of compound **11** (1 eq) in dry Et_2O (2 mL) were added Ag_2O (2.6 eq), AgOTf (0.3 eq) and the corresponding alkyl bromide (3 eq). The mixture was stirred under reflux for 8–32 h (Table I). After completion of the reaction, which was detected by TLC, the mixture was purified by flash column chromatography (eluents in Table I). The characterization data for **12**–**19** are given in the Supplementary material to this paper.

*General procedure for the synthesis of the analogues **2**–**10**.* A solution of starting compound **11**–**19** (0.1 mmol) in dry EtOH (2 mL) was hydrogenated over 10 % Pd/C (≈10 % of Pd) at room temperature for 18–24 h (Table II). After completion of the reaction (TLC), the mixture was purified by flash column chromatography (eluents in Table II). The characterization data for **2**–**10** are presented in the Supplementary material.

Cytotoxic activity

Cell cultures. Human myelogenous leukaemia (K562), promyelocytic leukaemia (HL-60), T cell leukaemia (Jurkat), Burkitt's lymphoma (Raji) and ER^+ breast adenocarcinoma (MCF-7) malignant cells were grown in a suspension in RPMI 1640 nutrient medium, while ER^- breast adenocarcinoma (MDA-MB 231), cervix carcinoma (HeLa), lung adenocarcinoma epithelial cells (A549), and normal foetal lung fibroblasts (MRC-5) were cultured as a monolayer in DMEM medium. Both media were supplemented with 10 % of foetal calf serum (FTS, NIVNS) and antibiotics (100 IU mL^{-1} of penicillin and 100 mg mg^{-1} of streptomycin). The cell lines were cultured in flasks (Costar, 25 mL) at 37 °C in an atmosphere of 100 % humidity and 5 % of CO_2 (Heraeus). Exponentially growing viable cells were used throughout the assays.

MTT test.[25] 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 the substances. The tested substances, at 10-fold the required final concentration, were added (10 μL $well^{-1}$) to all wells, 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 all wells 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 all wells and mixed thoroughly to dissolve the dark blue crystals of formazan. After a few minutes at room temperature, to ensure that all crystals were dissolved, 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

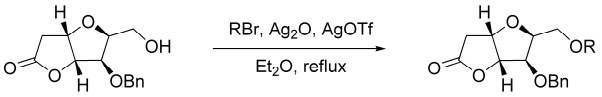
The syntheses of intermediates **12**–**19** is presented in Table I. Starting compound **11** was prepared from D-glucose in seven synthetic steps as previously reported.[22]

O-Alkylation of alcohol **11** with an excess of hexyl bromide in ether, in the presence of silver(I) oxide and silver(I) triflate as catalysts, gave the expected 7-*O*-hexyl derivative **12** in 69 % yield (Table I, entry 1). Compound **11** under the similar experimental conditions reacted with different alkyl bromides (C_7–C_{13}) to afford the corresponding ether derivatives **13**–**19** in good yields (Table I, entries 2–8).

Hydrogenolytic removal of the benzyl ether protective group in **12**–**19**, under standard reaction conditions furnished the target (–)-goniofufurone mimics **3**–**10**

in good to excellent yields (Table II, entries 2–9). Finally, under similar reaction conditions, alcohol **11** gave the known[23,24] diol **2** in 97 % yield (entry 1).

TABLE I. Preparation of intermediates **12**–**19**

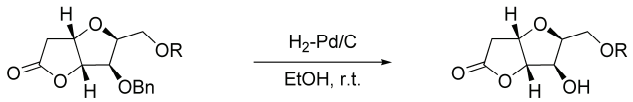


11 **12**–**19**

Entry	R	Reaction time, h	Eluent for FCC[a]	Product (yield, %)
1	C_6H_{13}	18	3:2 light petroleum/Et_2O	**12** (69)
2	C_7H_{15}	15	1:1 light petroleum/Et_2O	**13** (71)
3	C_8H_{17}	8	1:1 light petroleum/Et_2O	**14** (77)
4	C_9H_{19}	28	3:2 light petroleum/Et_2O	**15** (33)
5	$C_{10}H_{21}$	32	3:2 light petroleum/Et_2O	**16** (54)
6	$C_{11}H_{23}$	22.5	1:1 light petroleum/Et_2O	**17** (78)
7	$C_{12}H_{25}$	12	3:2 light petroleum/Et_2O	**18** (73)
8	$C_{13}H_{27}$	17.5	7:3 light petroleum/Et_2O	**19** (69)

[a]FCC – Flash column chromatography

TABLE II. Preparation of final products **2**–**10**



11–**19** **2**–**10**

Entry	Starting compound	R	Reaction time, h	Eluent for FCC[a]	Product (yield, %)
1	11	H	20	7:3 CH_2Cl_2/EtOAc	**2** (97)
2	12	C_6H_{13}	24	7:3 light petroleum/Et_2O	**3** (96)
3	13	C_7H_{15}	20	7:3 light petroleum/Et_2O	**4** (91)
4	14	C_8H_{17}	18	7:3 light petroleum/Et_2O	**5** (84)
5	15	C_9H_{19}	18	Et_2O	**6** (82)
6	16	$C_{10}H_{21}$	21	9:1 CH_2Cl_2/EtOAc	**7** (80)
7	17	$C_{11}H_{23}$	20	7:3 light petroleum/Et_2O	**8** (86)
8	18	$C_{12}H_{25}$	20	3:2 light petroleum/Et_2O	**9** (72)
9	19	$C_{13}H_{27}$	21	7:3 light petroleum/Et_2O	**10** (88)

[a]FCC – Flash column chromatography

In vitro *antiproliferative activity*

The biological activities of synthesized compounds **2**–**10** 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.[25] (–)-Goniofufurone (**1**), analogue **2** and the commercial antitumour agent doxorubicin (DOX) were used as positive controls.

According to the resulting IC_{50} values (Table III), of all cell lines tested, four were sensitive to all of the synthesized analogues **2**–**10** (K562, HL-60, HeLa and A549). Of the remaining four cell lines, Jurkat and Raji cells were sensitive to eight, while MCF-7 and MDA-MB 231 cell lines were sensitive to seven of nine synthesized analogues.

The most active compound in A549 cell culture is analogue **10** (IC_{50} = 0.025 μM) that exhibited 94- and 196-fold higher potency when compared to lead **1** and DOX, respectively. Simultaneously, analogue **10** represents the most active compound described in this paper.

TABLE III. *In vitro* cytotoxicity of (–)-goniofufurone (**1**), DOX and the analogues **2**–**10** after 72 h

Compound	IC_{50} / μM[a]								
	K562	HL-60	Jurkat	Raji	MCF-7	MDA-MB 231	HeLa	A549	MRC-5
1	2.96	>100	2.49	23.42	51.27	>100	>100	2.36	>100
2	2.69	9.97	9.51	7.40	9.64	0.24	5.22	31.45	59.88
3	0.70	4.91	8.87	1.11	12.34	15.62	3.54	2.43	>100
4	1.02	1.10	11.53	5.98	2.38	9.76	0.56	4.43	>100
5	0.74	0.68	19.78	4.25	0.34	28.70	3.41	4.19	>100
6	8.61[b]	1.53[b]	6.64[b]	7.25	>100	>100	9.59[b]	0.92	>100[b]
7	1.25[b]	0.14[b]	>100[b]	76.36	89.36	>100	0.30[b]	29.05	>100[b]
8	0.18	1.83	16.26	2.79	2.28	26.57	4.11	7.72	>100
9	3.46	8.25	8.02	3.52	5.31	7.63	2.25	3.96	>100
10	4.87	3.96	4.29	4.88	15.36	36.47	10.32	0.025	>100
DOX	0.25	0.92	0.03	2.98	0.20	0.09	0.07	4.91	0.10

[a]IC_{50} is the concentration of compound required to inhibit the cell growth by 50 % compared to an untreated control. The values are means of three independent experiments. The coefficients of variation were less than 10 %; [b]taken from the literature[22]

All the synthesized analogues exhibited strong antiproliferative effects on K562 cells with IC_{50} values in the range of 0.18–8.61 μM. The highest potency against this cell line was recorded after treatment with analogue **8** (IC_{50} = 0.18 μM), which is approximately as active as DOX (IC_{50} = 0.25 μM), but 16-fold more active than lead **1**.

All analogues (**2**–**10**) demonstrated powerful to good antiproliferative effects towards HL-60 cells (IC_{50} values in the range 0.14–9.97 μM), in contrast to lead **1**, which was completely inactive against this cell line. Moreover, all analogues with an alkoxymethyl grou(**3**–**10**) showed better antiproliferative effects against the HL-60 cell line than diol **2** (IC_{50} = 9.97 μM).

The most active molecule against HL-60 cell line was analogue **5** (IC_{50} = = 0.68 μM), which exhibited similar activity as DOX, but was 330-fold more potent than lead **1**.

Analogue **3** was the most active compound in the culture of Raji cells that exhibited over 2.5-, 6.5- and 21-fold higher potency than control compounds, DOX, **2** and **1**, respectively. All novel ether analogues (**3**–**5** and **8**–**10**) demonstrated 4- (**4**, IC_{50} = 5.98 μM) to 21-fold (**3**, IC_{50} = 1.11 μM) higher activity than lead **1**, against Raji cells.

The parent compound **1** showed poor activity (IC_{50} = 51.27 μM) against MCF-7 cells, as did the previously synthesized compounds **6** and **7**, which were practically inactive to these cells (IC_{50} >100 μM and IC_{50} = 89.36 μM, respectively). However, all new analogues (**3–5** and **8–10**) and compound **2** exhibited good cytotoxic effects toward this cell line with IC_{50} values in the range 0.34–15.36 μM, being essentially 3–150-fold more active than **1**.

The most active compound against the MCF-7 cell line was the ether analogue **5**. This molecule exhibited submicromolar cytotoxicity (IC_{50} = 0.34 μM) although its potency was slightly lower than the activity of DOX (IC_{50} = 0.20 μM).

Lead compound **1** was inactive against HeLa and MDA-MB 231 cells, but all novel analogues and dephenylated analogue **2** showed good (0.56–10.32 μM) to moderate inhibitory activity (7.63–36.47 μM), respectively, against these cell lines.

All the synthesized ether analogues (**3**–**10**) as well as lead compound **1**, were completely inactive toward normal MRC-5 cells. Only molecule **2** showed low cytotoxicity (IC_{50} = 59.88 μM) against this cell line. On the contrary, the commercial antitumour agent DOX exhibited a potent cytotoxicity against this cell line.

SAR analysis

As shown in Table III, replacement of the α-hydroxylbenzyl group in **1** with an alkoxymethyl chain significantly increased the activities of the resulting analogues **3**–**10**. (For a graphical presentation see, Fig. S-35A of the Supplementary material).

As is further evident from Table III, the introduction of a hydrophobic group, by *O*-alkylation of OH-7 in **2**, resulted in analogues **3**–**10** of improved cytotoxicity toward the majority of cell lines under evaluation (Fig. S-35B of the Supplementary material).

Finally, it was found that the length of the side chain of the analogues is not crucial for antiproliferative activity of the analogues **3**–**10** (Table III and Fig. S--35C of the Supplementary material). This is in contrast with previous findings,[22] which suggested that one- or two-carbon homologation of the side chain increases the activity of the resulting homologues against most of the cells tested. However, the results of SAR analysis presented in this work are more reliable

because they were conducted on seven pairs of analogues, unlike the previous SAR study that was realized with a lower number of compounds.

CONCLUSIONS

To summarize, nine novel (–)-goniofufurone analogues were designed and synthesized from D-glucose as the starting compound. The newly synthesized molecules were evaluated for their antiproliferative activity against eight human malignant cell lines. Eight of the nine synthesized analogues showed submicromolar anticancer activity against at least one of the tested cell lines and five of them were more potent than DOX (**10**, IC_{50} = 0.025 μM, and **6**, IC_{50} = 0.92 μM against A549; **7**, IC_{50} = 0.14 μM, and **5**, IC_{50} = 0.68 μM against HL-60 and **8**, IC_{50} = 0.18 μM against K562).

SAR analysis showed that the replacement of *α*-hydroxylbenzyl group in **1** with an alkoxymethyl chain, as well as *O*-alkylation of OH-7 in **2**, may improve the cytotoxicity of the analogues towards the majority of the cell lines under evaluation.

All analogues were devoid of any toxicity against a normal human cell line (MRC-5). It is believed that this approach could be used in the search for novel, more potent and selective antitumour agents derived from lead **1**.

SUPPLEMENTARY MATERIAL

Analytical and spectral data, as well as additional experimental data, are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgements. This work was supported by research grants from the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. OI 172006). This work also received funding from the Serbian Academy of Sciences and Arts under the strategic projects programme (Grant agreement No 01-2019-F65).

ИЗВОД

НОВИ МИМЕТИЦИ (–)-ГОНИОФУФУРОНА: СИНТЕЗА, АНТИПРОЛИФЕРАТИВНА АКТИВНОСТ И SAR АНАЛИЗА

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Дивергентна синтеза нових миметика (–)-гониофуфурона, са алкоксиметил групом у бочном низу, остварена је полазећи из D-глукозе у девет синтетских фаза са укупним приносима од 6,7 до 8,7 %. Њихова *in vitro* антипролиферативна активност је испитана према осам хуманих туморских и једној нормалној ћелијској линији. Сви аналози су испољили снажне или добре антипролиферативне ефекте према већини испитиваних ћелијских линија. Према ћелијској линији HL-60, сви миметици су испољили повећану активност и били су 27–1604 пута потентнији од водећег једињења (–)-гониофуфурона. Такође, већина синтетизованих аналога је показала бољу или сличну активност као комерцијални антитуморски агенс доксорубицин (DOX) према A549 ћелијама. Најак-

тивније једињење је испољило чак 196 пута снажнију цитотоксичност од DOX, према овој ћелијској линији.

(Примљено 12. септембра, прихваћено 23. септембра 2019)

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