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Conformationally restricted goniofufurone mimics with halogen, azido or benzoyloxy groups at the C-7 position: Design, synthesis and antiproliferative activity

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ABSTRACT

A series of new conformationally restricted goniofufurone mimics, bearing an additional 1,3-dioxan ring and a halogen, azido or benzoyloxy functionality at the C-7 position has been designed and synthesized. The Appel reaction was used for replacement of 7-OH group with Cl or Br functions in tricyclic lactone (**3**). 7-Iodo derivative (**3d**) was prepared by using the Ph_3P/I_2/2,6-lutidine reagent system. 7-Fluoro group was introduced by treatment of **3** with DAST, while the corresponding 7-azido and 7-benzoyloxy derivatives have been prepared by multistep sequences. Synthesized products were evaluated for their ability to inhibit growth of selected human malignant cell lines. Structure-activity relationships demonstrated that the nature of a substituent at the C-7 position could enhance the antiproliferative activity of the analogues. The preliminary study on the mechanisms indicated that all synthesized compounds induced apoptosis in 61–77% of K562 cells.

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1. Introduction

(+)-Goniofufurone (**1**, Scheme 1), is a bioactive styryl lactone that was isolated from the stem bark of Thailand plant *Goniothalamus giganteus* Hook. f., Thomas (Annonaceae) in 1990 [1]. Due to its unique structural features and promising antitumour activity [2–5], natural product **1**, along with a number of its analogues and derivatives have been the targets of many syntheses [6–8]. The development of practical and efficient routes for the synthesis of analogues or derivatives of natural products is of considerable interest for drug design and discovery [9]. Among other, more potent compounds can be designed by using the manipulation of functional groups (isosterism), or by introduction of conformational constrains.

We have recently demonstrated that the insertion of a 1,3-dioxan ring between the C-5 and C-7 position increases the antitumour potency originally displayed by lead **1** [10]. On the other hand, a study carried out earlier in our laboratory showed that the dephenylated goniofufurone mimics **2a**–**e**, strongly inhibit the growth of certain human neoplastic cell lines [11]. Based on the above mentioned observations, we have planned the synthesis of tricyclic lactones of type **3a**–**f**, which represent conformationally constrained analogues of **2a**–**e**, annelated with a 1,3-dioxan acetal ring. Analogues **3a**–**f** are designed by combining the isosterism and the ring insertion methods (Scheme 1).

2. Results and discussion

2.1. Chemistry

Conversion of compound **3** [10] to conformationally constrained goniofufurone mimics **3a**–**d** and **3f** is summarized in Table 1.

Treatment of compound **3** with diethylaminosulfur trifluoride (DAST) in a mixture of acetonitrile and dichloromethane (entry 1)

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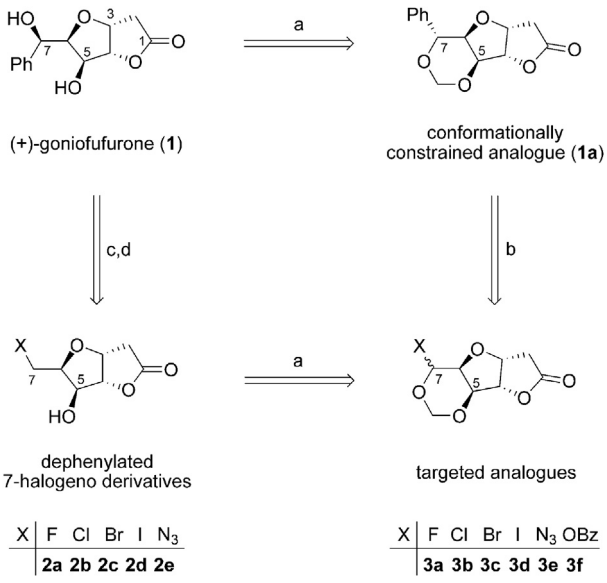


Scheme 1. Design of targets **3a**–**f**: (a) 1,3-dioxan ring insertion; (b) Ph → X replacement; (c) dephenylation; (d) OH → X replacement.

gave the expected 7-deoxy-7-fluoro derivative **3a** in 36% yield. Two different methods have been used for the preparation of 7-chloro derivative **3b**. First, we have examined the reaction previously developed in our laboratory for the conversion of sugar lactols into the corresponding glycosyl chlorides [12]. Accordingly, compound **3** was treated with mesyl chloride and triethylamine in dry dichloromethane to give a low yield of 7- chloro derivative **3b** (entry 2). In order to develop alternative and more efficient routes to 7-chloro- (**3b)** and 7-bromo-7-deoxy (**3c)** derivatives we have evaluated the potential of the reagent combinations such as Ph_3P/CCl_4/2,6-lutidine and Ph_3P/CBr_4/2,6-lutidine known as Appel agents [13]. 7-Iodo derivative (**3d**) was prepared by using the Holton's protocol [14] based on the Ph_3P/I_2/2,6-lutidine reagent system. Thus, treatment of lactol **3** with Ph_3P/CCl_4/2,6-lutidine reagent system provided the desired 7-chloro derivative **3b** in 79% yield (entry 3). The required 7-bromo derivative **3c** was prepared in 86% yield using the reagent combination of Ph_3P/CBr_4/2,6-lutidine under the similar reaction conditions (entry 4). The reaction of **3** with Ph_3P/I_2/2,6-lutidine reagent system provided the desired 7-iodo derivative **3d** in 79% yield (entry 5).

Structures of halogen derivatives **3a**–**d** have been elucidated by the IR, ^1H and ^{13}C NMR spectra, as well as on the basis of the corresponding elemental microanalysis. Their stereochemistry was definitely confirmed by X-ray crystallography (see the Supplementary data for details). However, we did not manage to obtain the HRMS of synthesized compounds, because none of them could be ionized in the positive or in the negative ionization mode. Nevertheless, we obtained the satisfactory analytical data that confirmed the purity of synthesized products.

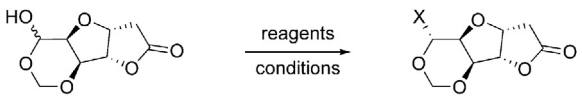
In order to prepare 7-*O*-benzoyl derivative **3f** we first examined the standard *O*-benzoylation procedure (BzCl/Py). Quite unexpectedly, treatment of compound **3** with benzoyl chloride in pyridine gave a poor yield of the desired 7-*O*-benzoyl derivative **3f** (Table 1, entry 6). However, when compound **3** was treated with benzoyl cyanide, using an adapted procedure developed by Prasad and co-workers [15], the desired 7-*O*-benzoyl derivative **3f** was obtained in 45% yield (Table 1, entry 7). Stereochemistry of **3f** was confirmed by X-ray crystallography (see the Supplementary data for details).

The preparation of azido derivative **3e** is summarized in Scheme 2.

This five-step sequence started with the conversion of commercially available monoacetone D-glucose (**4**) to lactol **5** by slightly modified literature procedure [16,17]. The expected lactol **5** was obtained as a mixture of stereoisomers. The mixture was not separated but was rather further treated with CCl_4, Ph_3P and 2,6-lutidine in dichloromethane, whereby the chloro derivative **6** was obtained as a single stereoisomer in 42% overall yield (two steps). Stereochemistry of **6** was confirmed by single crystal X-ray crystallography (see the Supplementary data for details). Treatment of **6** with sodium azide in DMSO afforded the corresponding 7-azido derivative **7** as the only reaction product in 57% yield. Hydrolytic removal of the isopropylidene protective group in **7** gave the expected lactol **8**, which upon treatment with Meldrum's acid in the presence of triethylamine gave target **3e**, in 22% overall yield. Structure and stereochemistry of **3e** was unequivocally confirmed by X-ray crystallography (see the Supplementary data for details).

An alternative four-step synthesis of 7-*O*-benzoyl derivative **3f** is presented in Scheme 3. The commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**9**) was used as a convenient starting material for this part of the work. The terminal isopropylidene domain in **9** was directly converted to a mixture of stereoisomers **5** in a single step using periodic acid in dry ethyl acetate [10,16]. Again, the mixture was not separated but was further treated with benzoyl cyanide in DMSO, in the presence of 4 Å molecular sieves, to give the expected 5-*O*-benzoyl derivatives **10** and **11** as a 4:1 mixture of stereoisomers, as determined by integration of the H-5 proton signals in the crude reaction mixture

Table 1
Preparation of compounds **3a**–**d** and **3f** from **3**.



3 **3a-d, 3f**

Entry	Reagents	Conditions	Product (% yield)[a]
1	DAST, CH_2Cl_2, MeCN	0 °C (0.5 h), rt (3 h)	**3a** X = F (36)
2	MsCl, Et_3N, CH_2Cl_2	0 °C (48 h)	**3b** X = Cl (20)
3	CCl_4, Ph_3P, 2,6-lutidine, CH_2Cl_2	rt (24 h)	**3b** X = Cl (79)
4	CBr_4, Ph_3P, 2,6-lutidine, CH_2Cl_2	rt (4 h)	**3c** X = Br (86)
5	I_2, Ph_3P, 2,6-lutidine, CH_2Cl_2	rt (26 h)	**3d** X = I (79)
6	BzCl, Py	0 °C → rt (48 h)	**3f** X = OBz (14)
7	BzCN, 4 Å mol. sieves, DMSO	0 °C → rt (60 h)	**3f** X = OBz (45)

[a] Isolated yields.

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