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Original article

Synthesis and evaluation of (−)-Massoialactone and analogues as potential anticancer and anti-inflammatory agents

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ABSTRACT

(−)-Massoialactone, an α,β-unsaturated δ-lactone isolated from *Cryptocarya massoia*, and five analogues were synthesized and their antiproliferative and anti-inflammatory activities were evaluated. The lactones were able to mimic the "core" functional group required for the biological activity of their parent natural compounds suggesting that substantially altered analogues may retain their properties.

1. Introduction

The α,β-unsaturated δ-lactone unit is present in several compounds isolated from plants and marine organisms. These compounds exhibit different structural complexities and a broad range of biological activities. Examples are fostriecin, cytostatin, leptomicin B, goniothalamin, and massoialactone (Fig. 1).

Fostriecin and cytostatin are structurally related compounds produced by *Streptomyces pulveraceus* [1] and *Streptomyces* sp. *MJ654-Nf4* [2], respectively. These compounds are described as potent inhibitors of a subset of PPP-family serine/threonine protein phosphatases, being fostriecin a potent inhibitor of PP2/PP4, and cytostatin a potent and selective inhibitor of PP2A [3].

Leptomycin B (LMB) is produced by *Streptomyces* sp. strain ATS 1287 [4], and attracted attention due to its antitumor [5] and antifungal [6] activities. It is a potent inhibitor of the nuclear export of proteins [7] and its mode of action involves the binding to the chromosome maintenance region I (CRM1) exporting through its α,β-unsaturated δ-lactone moiety [8] which leads to selective inhibition of the protein–protein interaction in the ternary CRM1-RAN-cargo protein complex.

Goniothalamin is a styryl lactone isolated from various species of the genus *Goniothalamus* [9], and displays significant cytotoxic and anti-proliferative activities against a variety of cancer cell lines [10]. This lactone also displays other biological activities such as insecticidal [11], larvicidal [12], antifungal [13], antimicrobial [14], and trypanocidal [15].

(−)-Massoailactone, **1** was first isolated from the bark of *Cryptocarya massoia*, and later from other sources [16]. The structural simplicity of (−)-Massoialactone, **1** compared to its α,β-unsaturated δ-lactone analogues shown of Fig. 1 makes this compound a particularly attractive target and many approaches to **1** have been reported [17]. In addition, (−)-Massoialactone is a powerful skin irritant and produces systolic standstill in frog heart muscles [18]. Moreover, it showed good antimicrobial activity against *Staphylococcus aureus*, *B. subtilis* and *E. coli* [19].

The synthesis of relatively simple molecules which could be able to effectively mimic the key elements for the biological activity of a complex natural product such as those depicted in Fig. 1 is a subject of the great interest. As the "*core*" functional group required for the

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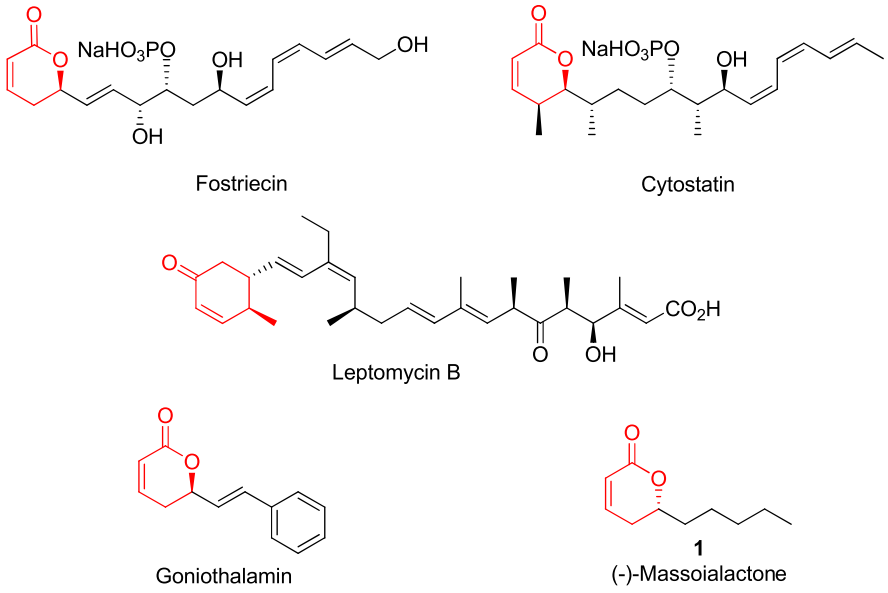


Fig. 1. Examples of natural products containing a α,β-unsaturated δ-lactone unit.

in vitro antiproliferative activity of cytostatin, fostriecin, leptomycin and goniothalamin is the α,β-unsaturated δ-lactone, substantially altered analogues of these natural products may retain their properties.

In this work, we performed molecular docking simulations on (−)-Massoialactone and some analogues in order to gain a better understanding of how these compounds would interact with CRM1, one of the most important molecular targets for the design of new inhibitors that could mimic natural toxins such as LMB. The results of this study provided a new insight for the synthesis of these compounds and the *in vitro* evaluation of their antiproliferative and anti-inflammatory properties.

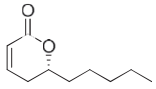
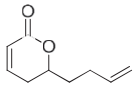
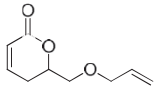
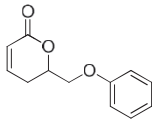
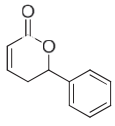
2. Results and discussion

2.1. Docking analysis

Leptomycin B (LMB) efficiently suppresses the nuclear export by inhibiting CRM1, a nuclear export receptor responsible for shuttling a large number of proteins and chemotherapeutic targets [19], playing an essential role in canonical nuclear export signal (NES)-dependent nuclear export, including major tumor suppressor proteins (TSPs).

The crystallographic structure of CRM1-RAN in complex with inhibitors were taken from the Research Collaboratory of Structural Bioinformatics Protein Data Bank (PDB 4HAT) [20]. The ligands and water molecules were extracted from the PDB file. All of the calculations were performed with the package docking program Autodock Tools 4.2 [21]. Initially, the structure was built using the Gauss View 4.1 [22] and optimized using the semi-empiric model AM1 [23] using the atomic charge units (Gasteiger model) [24] were marked and the flexibility of both receptor and ligand were determined using the standard program parameters, in which it was permitted to twist the lactone side chain. The electrostatic energy maps, atom-specific affinity and desolvation were calculated using Autogrid 4.2 with the centre grid at −39.174, 72.955, 29.907; with 19.5 × 15.75 × 15.75 Å dimensions, and 0.375 Å spacing. Fifty populations each with 2.500.000 fits were evaluated using the Generic Algorithm of energy minimization with the Autodock 4.2 program. The predicted binding energies of the envisioned compounds into the CRM1 active site are listed in Table 1.

Table 1
Docking interaction energy of α,β-unsaturated δ-lactones, **1** and **10a**–**e** against CRM1.

	Compound	ΔG (Kcal mol^{-1})
1	 **1**	−6.42
2	 **10a**	−5.61
3	 **10b**	−5.61
4	 **10c**	−7.25
5	 **10d**	−7.72
6	 **10e**	−7.21