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Syntheses and structure–activity relationship studies of N-substituted-β-D-glucosaminides as selective cytotoxic agents

Bo Wang, Yang Liu, Yanshi Wang, Xin Liu, Mao-Sheng Cheng *

Key Laboratory of Structure-Based Drugs Design & Discovery of Ministry of Education, School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, PR China

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ABSTRACT

Twenty-four diosgenyl saponins bearing cinnamoyl, carbamido and thiosemicarbazone groups were synthesized concisely. The cytotoxicities of the synthetic compounds on six human caner cell lines were evaluated employing MTT method. Structure–activity relationship could be observed, and two of the synthesized compounds (**5c** and **5f**) exhibited selective inhibition on HeLa and MCF-7 cells, while three of them (**5d**, **5f** and **5h**) showed strong inhibition against HT1080.

Saponins which are composed of a saccharide moiety and the aglycone have attracted much attention due to their cytotoxic activity. Among the saponins isolated from nature, either steroidal or triterpenoidal, the presenting saccharides attached on the aglycon are usually β-D-glucopyranose, α-L-rhamnopyranose, and β-D-galactopyranose. Though it is quite common as a constituent of many natural poly- or oligosaccharides, glucosamine rarely emerged in natural saponin, however they are presenting strong in vitro cytotoxicity towards different tumor cell lines.[1,2] The potent cytotoxic property indicates that the sugar chains of glucosamine dramatically enhance the bioactivity of their aglycons. Therefore, it is a quite rational design that some modifications are performed on the glucosamine. Up to date, most researches are focused on the isolation of glucosaminides, fewer works are done with the structural modification of those saponins.[3,4] The earliest reference could date back to the year of 2003 in which 2-amino-2-deoxy-β-D-glucopyranoside hydrochloride was synthesized, and in combination with cladribine it can increase the number of apoptotic B cells isolated from B-CLL patients.[5,6] Later in 2008 and 2009, modifications on the amino group of diosgenyl 2-amino-2-deoxy-β-D-glucopyranoside were initially reported, which showed that the substitutents on amino groups had great influences on their cytotoxicity against several tumor cell lines.[7,8]

Inspired by the previous results, we assumed that the introduction of some cytotoxic pharmaphores onto glucosamine saponin might be a rational method to produce more potent lead structures. Since *trans*-Cinnamic acid has been demonstrated to possess a variety of biological activities including anti-cancer and used to induce a reversal of malignant properties of several human tumor cells in vitro.[9–12] While both carbamido and thiosemicarbazone groups are quite common substructures in the anti-cancer compounds. Especially for thiosemicarbazone, it has been researched for decades, and believed that the antitumor activity seems to be due to an inhibition of DNA synthesis.[13–15] Based on these researches, three series of diosgenyl glucosaminide with substituents of cinnamoyl, carbamido and thiosemicarbazone on their amino groups were designed and synthesized to test their in vitro cytotoxicities against different cancer cell lines and find the SARs of these compounds (Fig. 1).

As parts of our research on saponins, the representative aglycons of steroidal saponins diosgenin was selected as scaffolds to prepare the N-substituted-β-D-glucosaminide derivatives (Scheme 1). 2,2,2-Trichloroethoxycarbonyl group (Troc) was used to protect amino group in glycosyl imidate, considering the toleration and deprotection conditions of the protecting group.[16] The synthetic route began with the glycosylation between diosgenin and glycosyl imidate catalyzed by TMSOTf as showing in Scheme 1. The configuration of newly formed glucosidic bond was β (demonstrated by the 8.2 Hz coupling constant of $J_{1\text{-}2}$ in ^{1}H NMR), due to Troc group's neighboring group participating capacity. Intermediate **2** was prepared by following known procedures.[7,8] After deprotection of the Troc group, the amine **3** was condensed with substituted cinnamoyl chloride, which were prepared via Knoevenagel reaction from commercially available substituted benzaldehydes and malonic acid in the presence of pyridine to afford intermediates **4a–4n**,[17]

* Corresponding author. Tel.: +86 24 23986413; fax: +86 24 23995043.
E-mail address: mscheng@syphu.edu.cn (M.-S. Cheng).

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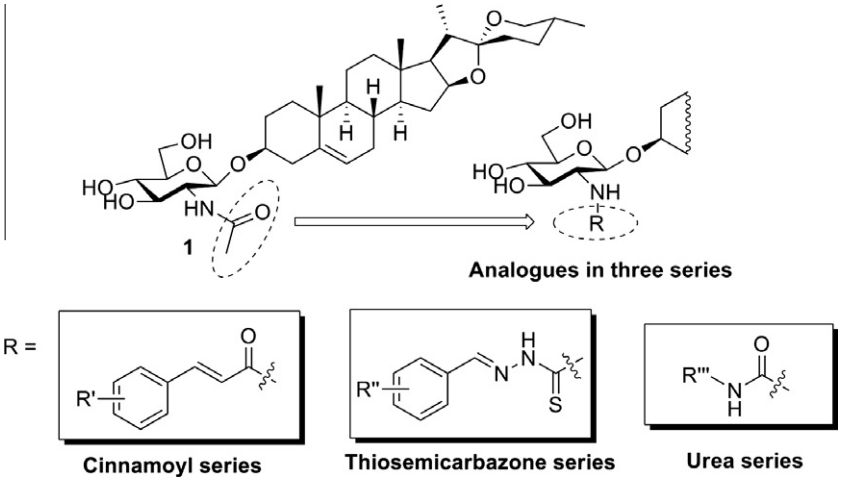
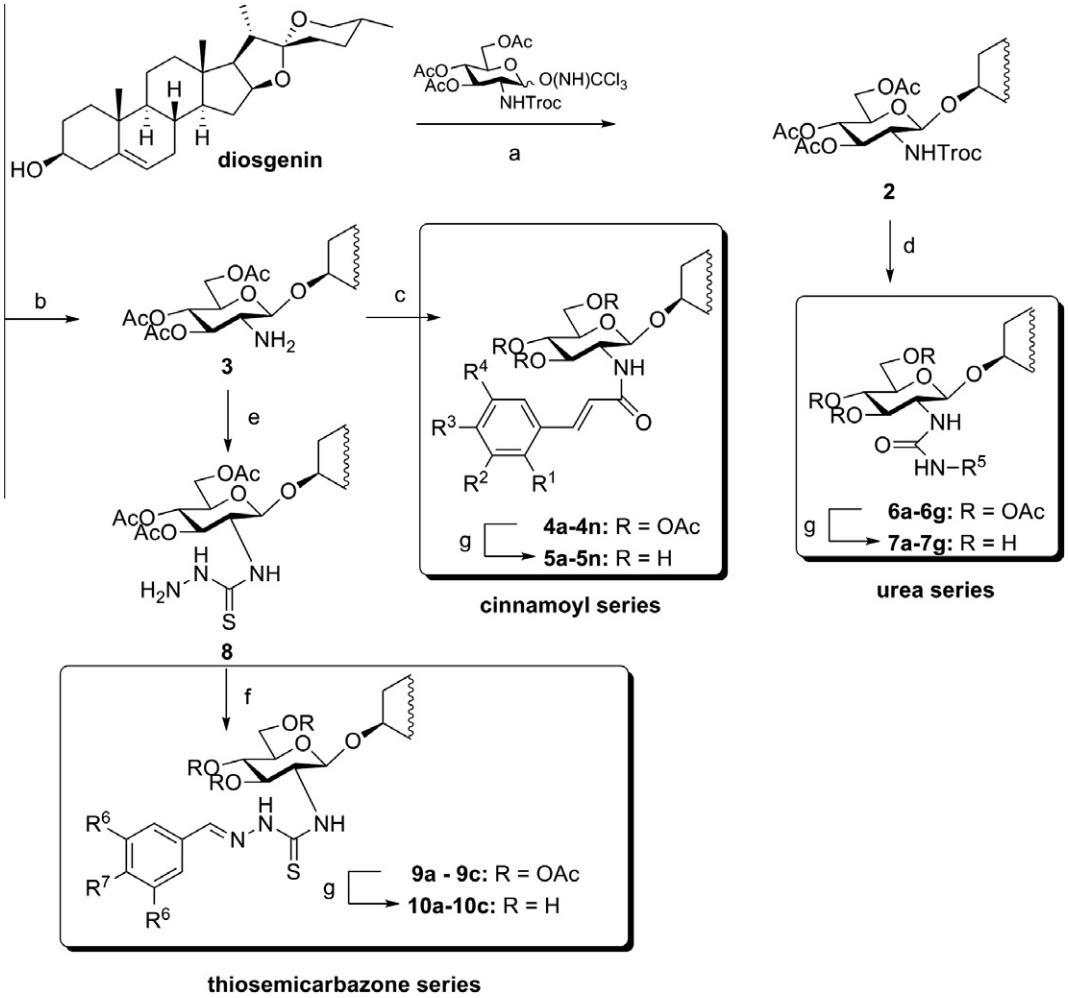


Figure 1. Structures of N-substituted-β-D-glucosaminide.



Scheme 1. Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 0 °C, 84%; (b) Zinc dust, AcOH, overnight; (c) substituted cinnamoyl chloride, pyridine, CH_2Cl_2, 5 h; (d) R-NH_2, DIEA, DMSO, 70 °C; (e) thiocarbonyl chloride, $CaCO_3$, CH_2Cl_2, H_2O, rt, then 80% hydrazine hydrate, ethanol, rt, 52.4% in two steps; (f) substituted benzaldehydes, THF, reflux, 1 h; (g) NH_3, MeOH, overnight, yields and compound details of cinnamoyl series see Table 1; **7a**: R_5 = benzyl, 62.7%; **7b**: R_5 = 4-flurobenzyl, 55.4%; **7c**: R_5 = 4-methoxybenzyl, 68.3%; **7d**: R_5 = cyclopropyl, 71.2%; **7e**: R_5 = *t*-butyl, 69.4%; **7f**: R_5 = heptyl, 54.6%; **7g**: R_5 = piperidyl, 75.1%; **10a**: R_6 = R_7 = H, 48.4%; **10b**: R_6 = H, R_7 = OMe, 52.5%; **10c**: R_6 = CF_3, R_7 = H, 53.0%.

followed by a fully deprotection in NH_3-MeOH to provide the *N*-cinnamoyl-β-D-glucosaminide **5a–5n**. All the synthetic compounds' structural details and yields were summerized in Table 1. For the synthesis of urea series, the key intermediate **2** was directly condensed with commercially available amines in the presence of DIEA in DMSO at 70 °C as shown in Scheme 1, then