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Synthesis, characterization and biological activity of Rhein-cyclodextrin conjugate

Manshuo Liu [a, 1], Pin Lv [a, 1], Rongqiang Liao [a], Yulin Zhao [b, **], Bo Yang [a, *]

[a] Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, PR China
[b] Faculty of Chemical Engineering, Kunming University of Science and Technology, Kunming 650500, PR China

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ABSTRACT

Cyclodextrin conjugate complexation is a useful method to enhance the solubility and absorption of poorly soluble drugs. A series of new Rhein-β-cyclodextrin conjugates (Rh-CD conjugates) have been synthesized and examined. Rhein is covalently linked with the β-CD by amido linkage in a 1:1 molar ratio. The conjugates were characterized by ^{1}H NMR, ^{13}C NMR, HRMS, powder X-ray diffraction (powder XRD) as well as thermogravimetric analysis (TGA). The results reveal that incorporation of β-CD could improve the aqueous solubility of Rhein and the cytotoxicity against hepatocellular carcinoma (HepG2) cell line as well as antibacterial activity against three organisms. The improved biological activity and the satisfactory water solubility of the conjugates will be potentially useful for developing novel drug-cyclodextrin conjugates, such as herbal medicine.

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1. Introduction

Rhein (4,5-dihydroxy-9,10-dioxoanthracene-2-carboxylate) is a natural anthraquinone derivative (Scheme 1), that exists as the free form glucoside in different species of plant such as Polygonaceae and Leguminosae [1,2]. The biological study of Rhein has been reported, including anti-angiogenic, anti-microbial, anti-inflammatory, anti-cancer activities and it also acts as an effective material in experimental treatment of diabetic nephropathy [3–7]. It is reported that Rhein has the better antibacterial activity towards *P. gingivalis*. Furthermore, it was also found to inhibit the proteolytic activity of the bacterium [8]. However, the clinical application of Rhein in chemotherapy is limited by the low water solubility, poor oral bioavailability and photo-sensitivity [9]. Therefore, it is urging to develop an efficient and nontoxic method to tackle those limitations for clinical applications.

β-cyclodextrin (β-CD) is a cyclic oligosaccharide which consists of glucose units interconnected by α-1,4 linkages. Due to its unique chemical structure, β-CD can form inclusion complexes with small molecule that its size allows it fit into the cavities of β-CD. It has been applied to modify the properties of guest molecules in many fields, such as food, chemical, textile industrial, agricultural and pharmaceutical area. β-CD is also widely used in advanced drug delivery systems because of the versatility of biodegradability, low toxicity, biocompatibility, and facile chemical modification [10]. Therefore, β-CD-tagged drugs are extensively studied as the drug delivering strategy [11].

Based on the promising properties of Rhein, a simple procedure for the structure of the compound modification was designed. In the present study, we developed a series of new active Rhein-β-CD conjugates (Rhein-1*N*-β-CD conjugate, Rhein-2*N*-β-CD conjugate and Rhein-3*N*-β-CD conjugate, Scheme 2) as prodrug to improve water solubility and enhance anticancer activity comparing with free Rhein. The structures of Rhein and their conjugates were characterized by NMR and mass spectrometry. The compounds were also studied by powder XRD and TGA. Then the solubility, stabilization effects and their anti-cancer activities on hepatocellular carcinoma (HepG2) cell lines were investigated. The results demonstrate the potential application of β-CD-tagged drugs as the drug delivery system. Furthermore, the antibacterial activity of Rhein-β-CD conjugates was also studied. The results show Rhein-β-CD conjugates have improved antibacterial activity.

* Corresponding author.
** Corresponding author.
E-mail addresses: zhaoyulin919@sina.com (Y. Zhao), yangbo6910@sina.com (B. Yang).
[1] These authors contributed equally to this work.

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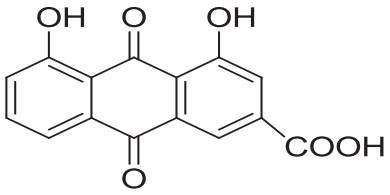


Scheme 1. The structures of Rhein.

2. Results and discussion

2.1. Chemistry

The mono (6-deoxy-6-amino)-β-CD (1*N*-β-CD) was synthesized through the method reported in our previous work [12]. Mono (6-deoxy-6-ethyleneamino)-β-CD (2*N*-β-CD) and mono (6-deoxy-6-diethyleneamino)-β-CD (3*N*-β-CD) were obtained according to the reported procedure [13]. The three types of CDs (1*N*-β-CD, 2*N*-β-CD and 3*N*-β-CD) was respectively coupled to the carboxyl group of Rhein which was achieved by EDCI and HOBt in ice bath for 3 h. And the Rhein-CD conjugates were obtained by purification with acetone. Their structures were characterized by NMR spectra (Figs. 1 and 2). Seen from the high resolution mass spectrum, there are 1422.7087 $[M+Na]^+$ (Fig. S1), 1465.7570 $[M+Na]^+$ (Fig. S2) and 1486.8189 $[M+H]^+$ (Fig. S3), respectively. The results show that the Rhein is incorporated to one of the primary hydroxyl groups of β-CD through a 1:1 molar ratio.

2.2. Powder X-ray diffraction (powder XRD)

The Powder XRD analysis allows examination of the medium and long range ordering of materials [14]. It could provide insightful characterization of the conjugates and drug molecules, such as powder XRD pattern of Rhein, 1*N*-βCD, Rhein−1*N*-βCD physical mixture and Rhein-1*N*-βCD. As shown in Fig. 3, Rhein showed a high degree of crystallinity and exhibited characteristic peaks between 5° and 60° (2θ = 9.8°, 9.9°, 17.5°, 23.0°, 27.4°, 31.5°, 41.7°)(A). In contrast, 1*N*-βCD (B) and Rhein-1*N*-βCD (D) were of amorphous form. Their physical mixture (C) showed a superposition of the above and displayed the characteristic peaks of Rhein (2θ = 27.4°), indicating the formation of the conjugate. We also performed different powder XRD experiments (scan with mixed solvent) in order to evaluate the crystallinity of their samples under different environments (Fig. S5). The results showed that the conjugates in solvent mixtures were all amorphous.

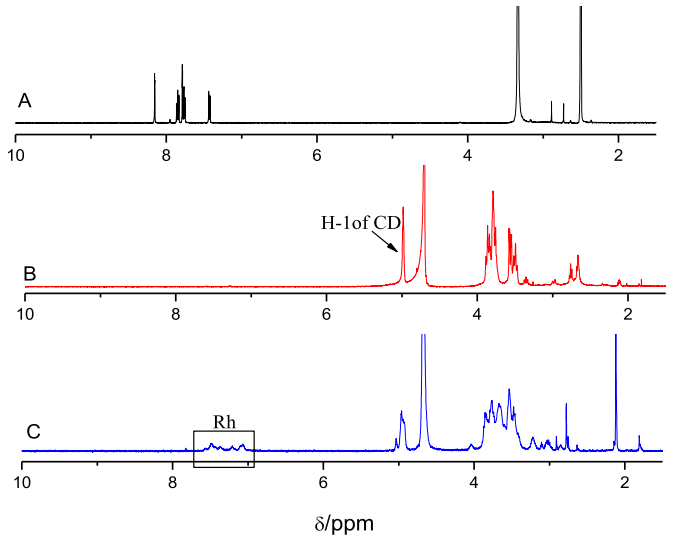
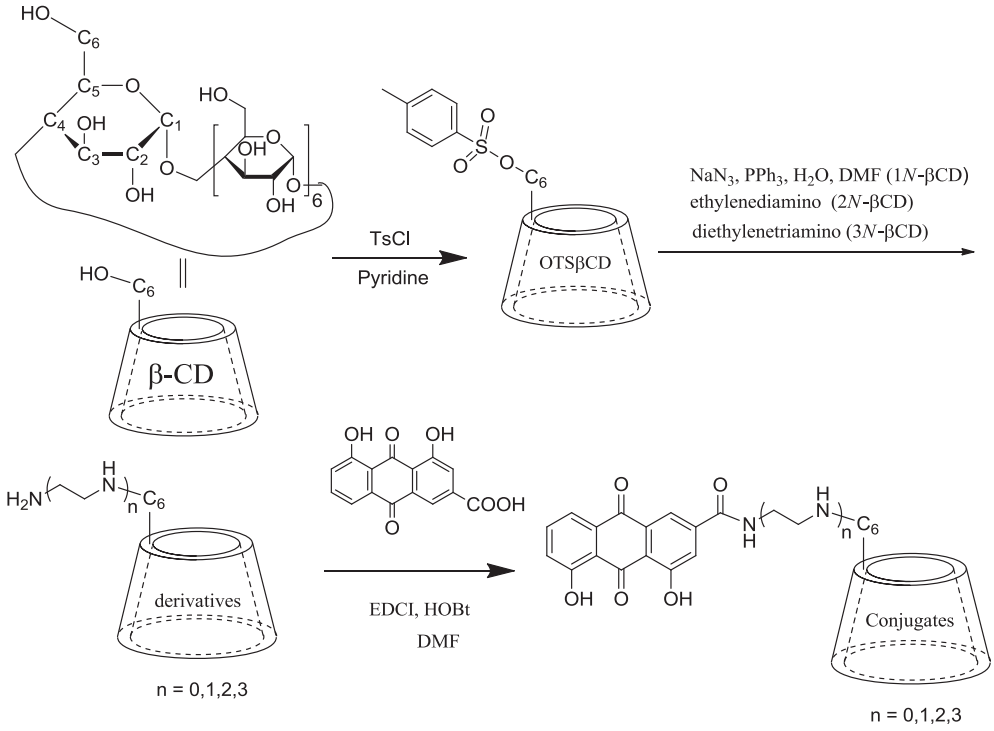


Fig. 1. ^{1}H NMR spectra of Rhein (A, DMSO-d_6), 2*N*-βCD (B, D_2O) and Rhein-2*N*-βCD (C, D_2O).



Scheme 2. The synthesis of Rhein-β-cyclodextrin conjugates.

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