European Journal of Medicinal Chemistry 130 (2017) 308–319

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Design, synthesis and biological evaluation of gentiopicroside derivatives as potential antiviral inhibitors

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ARTICLE INFO

Article history:
Received 27 December 2016
Received in revised form
10 February 2017
Accepted 11 February 2017
Available online 21 February 2017

Keywords:
Natural product
Secoiridoid
Gentiopicroside derivatives
Antiviral agents
Anti-influenza virus

ABSTRACT

Based on classical drug design theory, a novel series of gentiopicroside derivatives was designed and synthesized. All synthesized compounds were then biologically evaluated for their inhibition of influenza virus and anti-HCV activity *in vitro*. Some of the gentiopicroside derivatives, such as **11a**, **13d** and **16** showed interesting anti-influenza virus activity with IC_{50} at 39.5 μM, 45.2 μM and 44.0 μM, respectively. However, no significant anti-HCV activity was found for all of gentiopicroside derivatives. The preliminary results indicate that modification of the sugar moiety on gentiopicroside was helpful for enhancing the anti-influenza activities. Our works demonstrate the importance of secoiridoid natural products as new leads in the development of potential antiviral inhibitors.

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1. Introduction

Viral infections pose a threat to virtually every organism in every domain of life. Some are of great public health importance worldwide, such as influenza virus and Hepatitis C virus (HCV). Influenza virus is a major human pathogen that can cause annual epidemics and occasional pandemics. It was estimated that influenza epidemics cause 250,000–500,000 deaths every year worldwide [1]. Currently, two classes of anti-influenza drugs, M2 ion channel inhibitors and neuraminidase inhibitors, are approved by the FDA for the treatment of influenza virus infection. However, resistance to individual antiviral drugs is probably to appear [2]. On the other hand, HCV is a major cause of chronic liver diseases which can lead to permanent liver damage, hepatocellular carcinoma and death [3]. The World Health Organization estimates that 130–170 million individuals have detectable antibodies to HCV worldwide, corresponding to 3% of the world's population. Prior to 2011, HCV infections were treated with a combination of pegylated interferon A and ribavirin [4]. In 2011 the protease inhibitors boceprevir and telaprevir became available to treat HCV infection with genotype 1 in combination with ribavirin and pegylated interferon [5,6]. However, the SVR (Sustained Virologic Response) with current treatment is not optimal, and significant side effects (depression, fatigue, irritability, worsening of mania, insomnia) exist for these drugs. Therefore, there is still a grand challenge for the development of new antiviral inhibitors with unique scaffolds for higher efficacy and improved tolerability.

Natural products play a crucial role in the development of drugs for the treatment of human diseases [7], and to this very day numerous marketed drugs are of natural origin, either as original compounds or after modification [8]. It was found that 10% of the drugs on the market are unaltered natural products, 29% are their derivatives (semi-synthetics) and the rest (61%) have a synthetic origin [9]. The modification of natural products in an effort to alter their biochemical capacity is a common technique utilized by synthetic and medicinal chemists. Moreover, the structural

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http://dx.doi.org/10.1016/j.ejmech.2017.02.028
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modification of biologically active natural products aims at increasing potency and selectivity, improving physico-chemical, biochemical and pharmacokinetic properties, and eliminating or reducing side effects. More recently, the analogues of natural products are increasingly reported as antiviral inhibitors [10].

Gentiopicroside (GPS), a secoiridoid compound isolated from *Gentiana lutea* which is called *Qin Jiao* in Chinese (Fig. 1), is one of the most common herbal medicines used in China. Animal experiments have revealed choleretic, anti-hepatotoxic, adaptogenic, and anti-inflammatory activities [11]. It has been investigated for its possible effects on the central nervous system, such as antidepressant, anticonvulsant, and analgesic activities in mice [12]. Recently, Khuraman Mustafayeva et al. evaluated the possible genotoxic, mutagenic, and clastogenic effects of gentiopicroside [13]. Very recently, L. Yang et al. reported the hepatoprotective effect of gentiopicroside on anit-induced cholestatic liver injury in mice [14]. However, the main drawback of the gentiopicroside currently being evaluated in clinical trials is its relatively poor lipophilicity and suboptimal pharmacokinetic properties.

As part of our ongoing program in the study of gentiopicroside [15,16], in the current work, we describe the design, synthesis and pharmacological evaluation of a series of gentiopicroside derivatives as potential antiviral inhibitors.

2. Results and discussion

2.1. Chemistry

Structurally, gentiopicroside possesses a complex skeleton featuring fused dipyran glycoside. The compact structure of **1** containing two stereocenters, conjugation system and hemiketal, is further exacerbated by its extreme acid and base sensitivity. So we need a mild and efficient protocol for the regioselective preparation of gentiopicroside derivatives. The expeditious and straightforward synthetic route is depicted in Scheme 1. Our synthetic studies commenced with the gentiopicroside that was isolated from the *Gentiana lutea*. Regioselective protection of the primary hydroxyl group was accomplished by the reaction of **1** with triphenylmethyl chloride. Subsequent acetylation of the remaining hydroxyl groups with acetic anhydride gave the triacetyl derivative **3**. Detriphenylmethylation by treatment with $FeCl_3$ produced the desired intermediates with a free hydroxyl group at primary position [17]. With the alcohol **4** in hands, some common atom or functional group in drug design, such as halogen [18], sulfur [19], and amino group [20] and so on, could be introduced at primary position. The alcohol **4** was smoothly converted to the corresponding iodide **5f** and bromide **5e** in good yield using Br_2/Ph_3P [21] and I_2/Ph_3P [22] system. Furthermore, the introduction of a triflate at C-6′ in alcohol **4** afforded an unstable intermediate which was followed by displacement with thioacetate [23], thiomethoxide, azide [24], fluor [25] to yield the desired compounds **5a-5d** in good yield at two steps. In addition, the azide compound **5c** was reduced into amino compound by Staudinger reaction [26] as shown in Scheme 2. Unfortunately, two compounds, which could not be separated by silica gel chromatography, were obtained on account of acetyl migration [27]. After acetylation, one pure compound **7** was obtained in excellent yield. Final deacetylation could afford the target compound **8**. However, attempt to deprotection of the acetyl groups of **5** using various reagents such as (i) NaOMe/MeOH [28], (ii) K_2CO_3/MeOH [29], (iii) Et_3N/MeOH/H_2O [30], (iv) NH_4OH/MeOH [31] failed to give the desired compounds; all of compounds underwent decomposition or no reaction under such conditions. Nevertheless, the deprotections were achieved *via* treating the compounds in methanol with dibutyltin oxide [32] under reflux condition, furnishing the target compounds **6a-6f** in excellent yield.

On the other hand, the sugar moiety of gentiopicroside was selectively and quantitatively converted into the corresponding 6′-TIPS derivative **9** by treatment with TIPSCl in DMF at room temperature for overnight in the presence of imidazole. Subsequent benzoylation reaction generated the compound **10** in high yields. Treatment of **10** with TBAF cleaved the TIPS protecting group to give rise an intramolecular migration of the benzoyl group at C-4′ to the less crowded C-6′ position [33]. The structures of **11** was confirmed by its conversion into the corresponding mesyl derivatives **11a** as its ^{1}H NMR for H-4′ of the glucose moiety displayed deshielded signals at δ 5.18 (dd, $J_{4,5}$ = 12.2 Hz, $J_{3,4}$ = 9.7 Hz), indicating the position of the formed free hydroxyl in the derivative **11** to be at 4′ position in sugar moiety. The alcohol **11** was then converted into the corresponding triflate derivative, followed by nucleophilic substitution with KNO_2, KSAc, NaN_3, and TBAF to provide the derivatives **12a**–**12d** in excellent yields. Finally the desired compounds were obtained in moderate yields after debenzoylation under the aforementioned conditions. At the same time, the alcohol **12a** was converted into the corresponding equatorial SH, N_3, F substituents by the same two-step process. The final deprotection of **12b**–**12d** using dibutyltin oxide proceeded successfully to afford the target molecules **13b**–**13d** in moderate yields (Scheme 3.). It is worth to note that the C-4′ triflate was reacted with TBAF starting from the suitably protected **12a** to unsuccessfully give the desired 4′-fluoro compound **14c**, the elimination product **16** (see Supporting information) was observed as described in the literature [34]. DAST reagent was used to introduce an equatorial fluorine at C-4′ of sugar moiety in gentiopicroside. Final deprotection of **14a**–**14c** by using dibutyltin oxide proceeded to afford the target molecules **15a**–**15c** in moderate yields (Scheme 4.). Unfortunately, **15b** and **15c** were obtained as mixture of compounds.

The synthesized compounds were fully characterized by physicochemical and spectral means. The MS and ^{1}H NMR, ^{13}C NMR spectral data were found in agreement with the assigned molecular structures.

2.2. Biological evaluations

2.2.1. Inhibition of influenza virus infectivity

To explore the novel gentiopicroside derivatives as anti-influenza agents, we first determined their cytotoxicity in MDCK

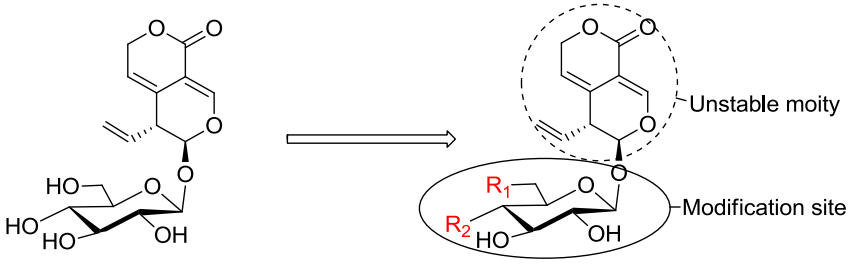

Fig. 1. Structure of gentiopicroside and the designed derivatives.

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