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Synthesis of nature product kinsenoside analogues with anti-inflammatory activity

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ABSTRACT

Kinsenoside is the major bioactive component from herbal medicine with a broad range of pharmacological functions. Goodyeroside A, an epimer of kinsenoside, remains less explored. In this report we chemically synthesized kinsenoside, goodyeroside A and their analogues with glycan variation, chirality inversion at chiral center(s), and bioisosteric replacement of lactone with lactam. Among these compounds, goodyeroside A and its mannosyl counterpart demonstrated superior anti-inflammatory efficacy. Furthermore, goodyeroside A was found to suppresses inflammatory through inhibiting NF-κB signal pathway, effectively. Structure-activity relationship is also explored for further development of more promising kinsenoside analogues as drug candidates.

1. Introduction

Kinsenoside (**1**, Fig. 1) is the major bioactive compound isolated from the whole plants of genus *Anoectochilus*.[1] These plants are commonly distributed among tropical and subtropical areas; their herbs are popular as folk medicines. In Taiwan area, the herbs are renown as "the Medicine of Kings" for treatment of a variety of diseases, and the vegetative extract from the herb is used as a health supplement.[2]

Consistent with the widespread popularity of the herbs, kinsenoside was found to possess a broad range of pharmacological functions, including hepatoprotective,[3] vascular protective,[4] anti-hyperglycemic,[5] anti-hyperliposis,[6,7] and anti-inflammatory effects.[8] On the other hand, goodyeroside A (**2**, Fig. 1), an epimer of kinsenoside (**1**) which was isolated as major constituent from genus *Goodyera*,[9] displayed different pharmacological profile.[9,10] The minute change in structure and correspondingly distinct effects on health call for thorough investigation of the underlying structure-activity relationship (SAR), which would lead to better understanding of their bioactivity and eventually contribute to expanded medicinal applications.

Unfortunately, the further research is largely impeded by the scarcity of materials. Current approach towards kinsenoside and goodyeroside A mainly relies on isolation of chemical components from plant materials, which is a long-termed process and generally requires sophisticated expertise of extraction and fractionation. In particular, the presence of acid-labile lactone moiety brings more challenge, that the original bioactive components may be destroyed into its butanoic acid and butanoic methylate counterparts where aqueous methanol solvent system is extensively utilized.[7]

As an alternative, chemical synthesis is a powerful tool for the construction of natural products and their analogues, in large quantities and with high purity. Moreover, the establishment of efficient chemical approach enables researchers to gain greater structural diversity and to expand the study towards broader medicinal application. Although the synthetic routes were reported for kinsenoside and goodyeroside A by chemical or chemoenzymatic approaches,[11–13] no structural variation was obtained, and the structure-activity relationship is not yet established. Hence, we aim to establish the chemical synthesis strategy of kinsenoside, goodyeroside A and their analogues (Fig. 2), towards the search for better drug candidates.

Based on the structural feature of kinsenoside, i.e. the butanoic acid glucoside, we aimed to investigate the functional role of each moiety. Hence, a series of kinsenoside analogues were designed based on the following considerations. First of all, we aim to study the role of the glycan by replacing D-glucose with other hexose glycans, such as D-

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