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Synthesis and evaluation of benzylisoquinoline derivatives for their inhibition on pancreatic lipase and preadipocyte proliferation

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[ABSTRACT] The present study was designed to synthesize and evaluate a series of benzylisoquinoline derivatives. These compounds were synthesized by Bischler-Napieralski cyclization to yield 1-benzyl-3,4-dihydroisoquinolines, and the products were obtained by reductions. All these compounds were identified by MS, ^{1}H NMR and ^{13}C NMR. The inhibitory activities on pancreatic lipase and preadipocyte proliferation for the synthesized compounds and alkaloids from *Nulembo nucifera* were assessed *in vitro*. Most of the compounds showed inhibitory activities on both pancreatic lipase and preadipocyte proliferation. Particularly, compounds **7p**−**7u** and **9d**−**9f** exhibited significant inhibitory activity on pancreatic lipase while compounds **7c**, **7d**, **7f**, **7g**, **7i**, and **7j** potently inhibited the proliferation of 3T3-L1 preadipocytes. Our results provided a basis for future evaluation and development of these compounds as leads for therapeutics for human diseases.

[KEY WORDS] *Nelumbo nucifera*; Benzylisoquinoline alkaloid; Anti-obesity; Pancreatic lipase inhibitor; Adipocyte proliferation

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Introduction

Nowadays, obesity has become a global epidemic and is increasing at an alarming rate. Although it is widely accepted that obesity results from a prolonged imbalance between energy intake and expenditure [1], the etiology of obesity is regarded as complex, consisting of the interactions of a variety of behavioral, environmental, metabolic, and genetic factors [2]. Obesity not only affects the appearance, but also is associated with a greater risk of mortality and development of lifestyle diseases, including hypertension, dyslipidemia [3], coronary artery disease, and type 2 diabetes mellitus [4-5]. Due to the increasing risks of hazardous side effects of the anti-obesity drugs on the market, there is an urgent need for developing new and efficacious substituents to control and prevent obesity.

Nelumbo nucifera Gaertn., commonly known as lotus, has been consumed as an edible plant and traditional Chinese medicine since ancient times. Previous researches have uncovered that lotus has abundant pharmacological activities, including antioxidant [6-7], anti-pyretic [8], hepatoprotective, and anti-obesity effects [9]. A lot of health products associated with lotus leaves have been widely used to treat obesity in China at present [10-11]. However, the pharmacological mechanisms of the components that mainly cause this effect remain to be resolved.

Some studies have been concluded that alkaloids are responsible for their anti-obesity actions [12-13]. An extract of lotus leaves improves obesity by reducing fat storing or by inducing lipolysis in adipocytes and in high-fat diet animal models [14-15]. However, little is known about the anti-

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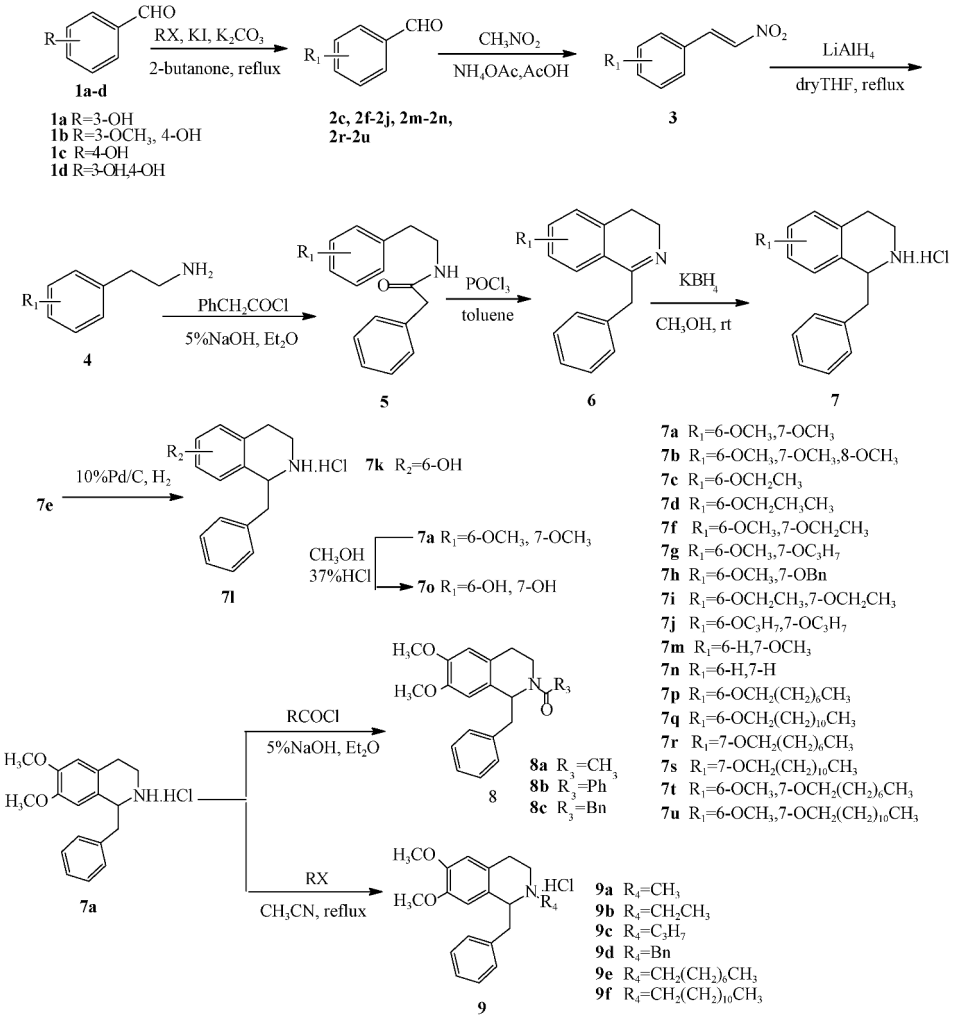
obesity effect of lotus alkaloid monomers, except for a few aporphine alkaloids which have a lower activity [16-17]. Benzylisoquinoline is another kind of alkaloid existing in lotus leaves [18]. Although benzylisoquinoline alkaloids have attracted widespread attention as they possess an extensive pharmacological properties including anti-HIV effect [19], cytotoxicity [20] and as multifunctional agents against Alzheimer's disease [21], few studies have focused on their anti-obesity effects. In addition, the contents of benzylisoquinoline alkaloids are quite different and even extremely low in the lotus. In order to evaluate the potential of benzylisoquinoline derivatives for their anti-obesity activities, a series of targeted compounds were synthesized in the present study. Their inhibitory activities on pancreatic lipase and preadipocyte proliferation were assessed *in vitro*. Preliminary structure-activity relationships were also discussed in this report.

Results and Discussion

Chemistry

The synthetic strategy adopted to obtain various potential molecules, and the sequence of reactions and the resulting products are displayed in Scheme 1. Thus, the classic Williamson procedure was based [22], the substituted hydroxy-benzaldehydes **1a−1d** used as starting substrates were reacted with bromoalkane to yield benzaldehyde derivatives **2**. The intermediate **2** were converted to corresponding nitroalkenes **3** via Henry reaction under reported conditions [23]. The intermediate **3** were then reduced to phenylethylamine analogues **4** in the presence of $LiAlH_4$. Then the intermediate **4** was reacted with phenylacetyl chloride and obtained phenylacetamide derivatives **5** [24]. Bischler-Napieralski cyclization of the intermediate **5** in the presence of phosphorous oxychloride was followed immediately by reduction of the dihydroisoquinoline **6**, thus forming the secondary amines, and then ether-hydrogen chloride solution was added to obtain **7a−7d**, **7f−7j**, **7m−7n**, and **7p−7u**. Furthermore, **7k** was prepared from **7h** via debenzylation; similarly **7a** was converted to **7o** by demethylation [25]. Finally, **8a−8c** and **9a−9f** were prepared from **7a** through acylation [26] and alkylation at nitrogen-atoms of benzyliso-quinoline alkaloid, respectively.



Scheme 1 Synthetic routes for benzylisoquinoline derivatives

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