

Review on the Structure Modification of Lycorine

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Abstract. Lycorine has attracted considerable attention because of its promising biological activities. These promising biological results have led to some exploration of structure–activity relationships (SAR) through synthesis of its derivatives. The recent progresses in structure modification of Lycorine are summarized in this review.

1. Introduction

Lycorine belongs to isoquinoline alkaloid, which is pyrrolo[de]phenanthridine ring-type alkaloid, and the structure is shown in **Figure 1**. In 1877, for the first time, lycorine was isolated from *Narcissus* plants, but its structure was not elucidated until 1935^[1]. In 1956, scientists determined the three-dimensional structure of lycorine by single crystal. Modern pharmacological research shows that lycorine has anti-inflammatory, inhibiting acetylcholinesterase, alkali resistant malaria, cardiovascular protection and a variety of tumor cell apoptosis induced by alkali, lycorine also has broad antiviral activity, such as SARS virus, herpes simplex virus, vaccinia virus, Punta Toro virus and Rift Valley fever virus^[2-4]. On the other hand, the study of lycorine and its derivatives have also greatly promoted the progress in the treatment of diseases such as cancer, Alzheimer's disease, viral infection and other serious harm to human health^[5-7]. Therefore, It is of great significance to study the structure modification of lycorine for drug research.

In recent years, pharmacologists and organic chemists have done a lot of work in the modification and transformation of the lycorine. The modification of lycorine mainly concentrated in the following aspects: (1) Modifications hydroxyl at C1 and C2 positions; (2) Modification of A ring; (3) E ring opening and aromaticity of D ring; (3) Oxidation of C2 position; (4) C7 position oxidation and reduction of the D ring; (5) Oxidation of C7 position and the reduction of the double bond of D ring. Therefore, through the transformation of the structure of lycorine compounds to find more active lycorine derivatives, this work has attracted much attention. In this paper, the research on the modification of lycorine was reviewed.



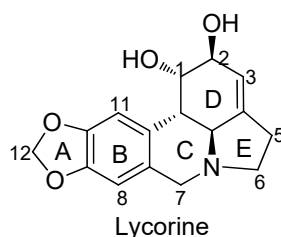
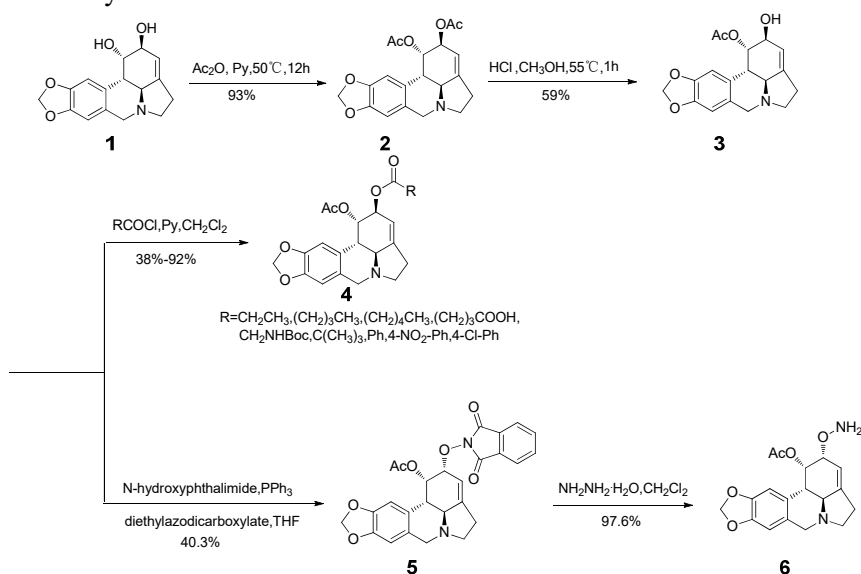


Figure 1 The structure of Lycorine

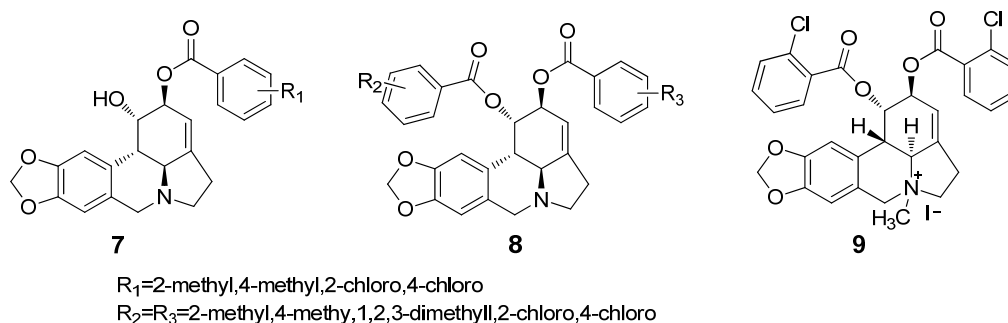
1.1. Modifications hydroxyl at C1 and C2 positions

In 2014, professor Yin Zheng's team modified the lycorine and assayed to study the structure–activity relationships with respect to their anti-DENV activity. Lycorine is commercially available, as reactant, selective acetylation at the C1 position obtain Compound **3** (Scheme 1), the biological analysis revealed that the potency of **3** is two times that of lycorine **1**, **3** was selected as a chemical starting point, and esterification modifications at the 2-hydroxy group were generated to study their effect on the anti-DENV activity. A series of lycorine derivatives **4** were prepared through acyl chlorides in the presence of pyridine. The result of esterification modification resulted in a reduction in the antiviral activity, the potencies of the esters decreased with an increasing length of the carbon chain. In order to investigate the effects of chirality against anti-DENV activity, Yin Zheng et al. use the Mitsunobu reaction to change C2 position from *S* to *R*, get the product of **5** and **6**, but the results are not satisfactory, the antiviral activity still greatly reduced, but this does not eliminate interference on modification at the C2 hydroxy group. Therefore, the influence of the chirality at the C2 position remains to be addressed in a future study^[8].

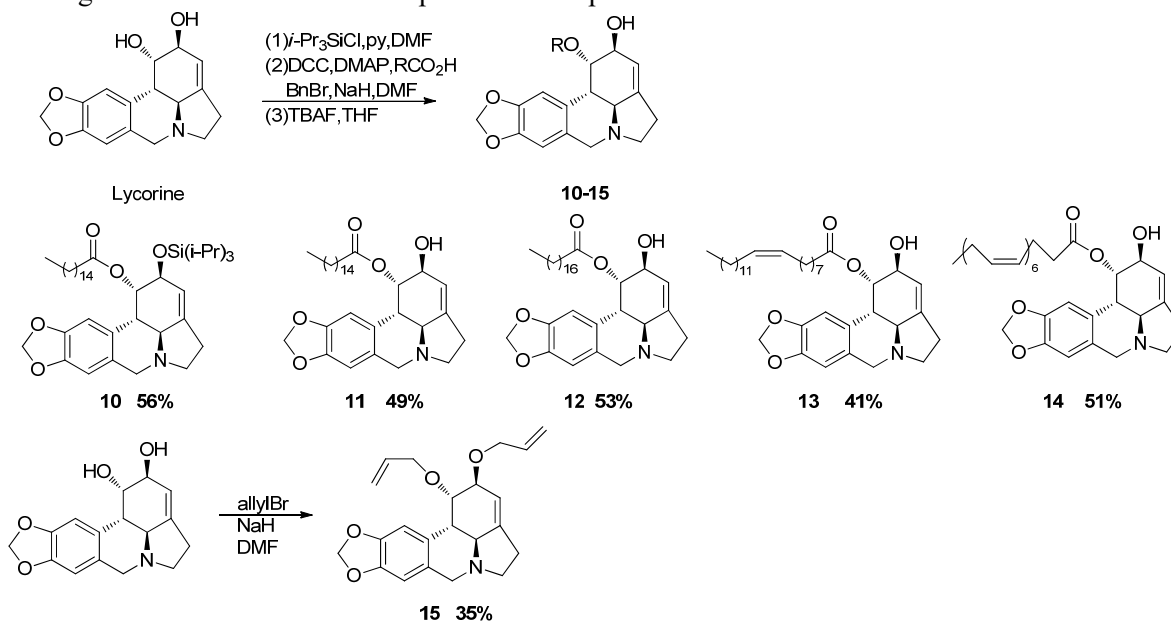


Scheme 1

In 2011, the Rimando team were interested in improving the activity of lycorine and discovering promising compounds with the potential to control columnaris disease (Scheme 2). The research shows that the lycorine analogues synthesized having substitution at both the C1-O- and C2-O-positions **8** have better antibacterial activity compared to having only one substitution **7** at either carbon. To improve water solubility, an iodo-salt was prepared, yielding **9**. However, improved solubility did not correspond to improved antibacterial activity^[9].

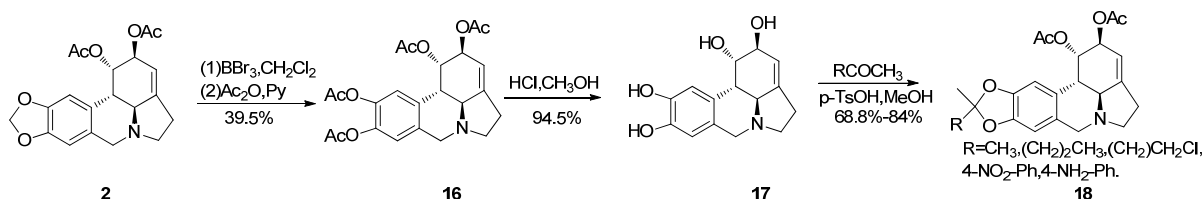
**Scheme 2**

In 2011, the Kornienko group selected lycorine from Amaryllidaceae plant family, mainly to modify the hydroxy group at the C1 position of lycorine, under etherification modification, 32 lycorine C1-derivatives were synthesized, all synthesized compounds were evaluated for antiproliferative activities in vitro in a panel of tumor cell lines, the results can enhanced antitumor activity (Scheme 3). Diallyllycorine **15** was identified as lycorine analogue, which is 100 times more potent against a U373 human glioblastoma model than the parent natural product^[10].

**Scheme 3**

1.2. Modification of A ring

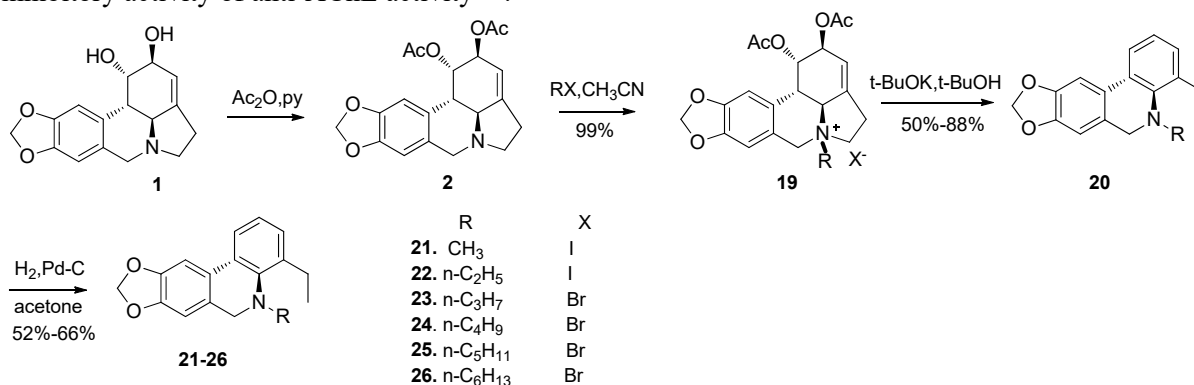
In 2014, Professor Yin Zheng's research group modified Lycoris alkaloids to study its inhibitory effect on dengue virus activity (Scheme 4), the modification of A-ring was studied. It was found that A-ring (1,3- dioxolane) was opened under the catalysis of boron tribromide, and compounds **16** and **17** were obtained, greatly reduces the dengue virus activity, to modified methylene of 1,3- dioxolane, after reduction and cyclization to form a series of derivatives containing various functionalized A ring **18**. This series of products basically lost the inhibitory activity against dengue virus. The above results show that 1,3- dioxolane ring is essential condition for dengue virus activity^[8].



Scheme 4

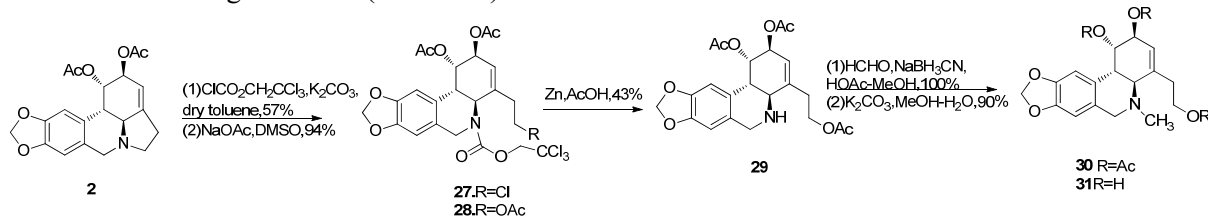
1.3. E ring opening and aromaticity of D ring

Before 2007, researchers found that the D ring played a key role in the biological activity of Lycoris alkaloids, but scientists did not show how the E-ring had any effect on the activity (Scheme 5). In 2007, Lin group study various functionalized D-ring derivatives, and evaluate their anti-AChE activity. Lin group get lycorine extracted from *Crinum asiaticum* var *sinicum* as reactant, the 3,6-diacetyl. Then, With various alkyl halides under refluxing CH_3CN gave the corresponding quaternary ammonium salts. First under the condition of potassium- t -butoxide as base and refluxing t -butanol, elimination of diacetyl then aromatic ring D, then run Hoffman degradation E ring, not only the E ring opened but also elimination of two acetoxyl groups. Afford compound **21-26**, compound obtained by in vitro tests found that the open-loop E ring did not affect its activity, but may be due to the changes of solubility and increased its activity. The results of this study indicate that the aromaticity of D rings enhances the inhibitory activity of anti-AChE activity^[11].



Scheme 5

With the above method, the E ring opened, but it changed the D ring, made it aromatic, if the following methods are used, the original appearance of the D ring can be retained and the E ring open. However, in vitro activity studies showed that the activity of the compounds obtained by this method was greatly reduced. Treatment of **2** with TCECF, followed by NaOAc-DMSO and reductive cleavage of the N-protected group **27-28**, and under Zn/HOAc yield **29**, respectively, O-Deacetylation under alkaline conditions gave **30-31** (Scheme 6).

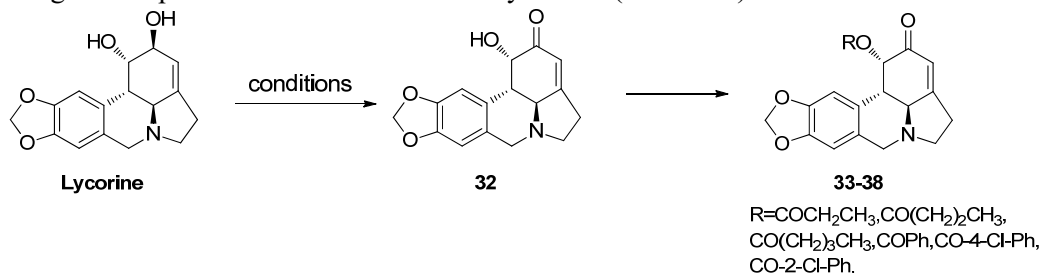


Scheme 6

1.4. Oxidation of C2 position

For the oxidation of lycorine C2 position, Evian et al. was prepared in 1983 by Evidente et al.^[12] Using phosphoric acid and DCC in dry DMSO solution. Jones reagents have recently been used as oxidants, but the yield of both methods is low. In 2011, Kornienko et al.^[10] chose to use the Day-Martin reagent

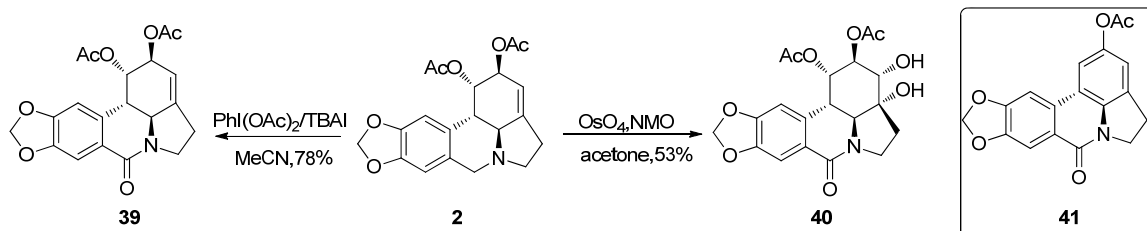
as an oxidant to yield an oxidation product in 66% yield. In 2014, the Yinzheng task group^[8] obtained the yield of 86% with the conditions of the oxidation. Oxidation of C2 hydroxyl groups into carbonyl groups can increase anti-West Nile virus as well as dengue virus activity and reduce cytotoxic activity. Oxidation of C2 hydroxyl groups into carbonyl groups can increase anti-West Nile virus as well as dengue virus activity and reduce cytotoxic activity. C1 was modified with this compound as the initial reactant to give compounds **33-38** with satisfactory results (Scheme 7).



Scheme 7

1.5. Oxidation of C7 position and the reduction of the double bond of D ring

In 2002, the Lee group^[13] obtained the C7 position oxidized catalyzed by $\text{PhI}(\text{OAc})_2$ **39** in 78%, the Yield of by-product **41** was 5%. In 2011, the Kornienko task group^[10] used OsO_4 / NMO to oxidize to obtain 53% C7 position of oxidized product **40**, the yield of by-product **41** was 13%. Studies on the structural modification of the above structures have been conducted, and oxidation at position C7 is not conducive to the improvement of antitumor activity (Scheme 8).



Scheme 8

2. Results and Prospects

The research of lycorine is getting more and more attention, as in recent years about lycorine and derivatives in anti-tumor, anti-viral and research for Alzheimer's disease. It is an important subject of pharmaceutical chemists to modify lycorine by changing the substitution of changing the core structure and to develop a group that is more reactive derivative lycorine. It is far from over on developing more easily and found a new type of lycorine derivatives. Obviously through the scientists in-depth research and unremitting efforts, lycorine base compounds will be developed into new drugs and bring significant economic benefits and great academic value.

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