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Design and synthesis of sinomenine isoxazole derivatives *via* 1,3-dipolar cycloaddition reaction

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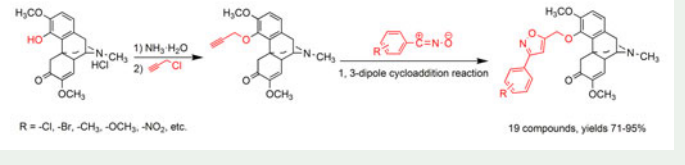
ABSTRACT

A novel structure of sinomenine isoxazole derivatives is synthesised from sinomenine hydrochloride and aromatic aldehydes and requires six steps. 19 target compounds have been obtained in good yields. The sinomenine hydrochloride transforms to 4-alkynyl sinomenine, which is a key intermediate product to synthesise the target sinomenine isoxazole compounds, after a neutralisation reaction with ammonia and substitution reaction with 3-chloropropyne. Another key intermediate product is 1,3-dipole, which can be obtained from aromatic aldehyde. After treatment with hydroxylamine hydrochloride and then sodium carbonate solution, aromatic aldehyde is converted to aldehyde oxime, which reacts with N-chlorosuccinimide (NCS) to afford aryl hydroximino chloride. 1,3-Dipole is eventually formed *in situ* while triethylamine (TEA) in DMF is added dropwise. Then 4-alkynyl sinomenine is added to provide the sinomenine isoxazole derivative *via* 1,3-dipolar cycloaddition reaction as the key step. All the target compounds are characterised by melting point, ^{1}H NMR, ^{13}C NMR, HRMS and FT-IR spectroscopy.



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Sinomenine; isoxazole; synthesis; derivative; 1,3-dipolar cycloaddition reaction

1. Introduction

Sinomenine is a natural product mainly used for the treatment of rheumatoid arthritis (Tang et al. 2006), joint swelling and pain (Teng et al. 2011), and has a curative effect with an effective rate of over 90% (Huang and Cheng 2002). However, there are some disadvantages when treating diseases, for example, hypersusceptibility and large dose

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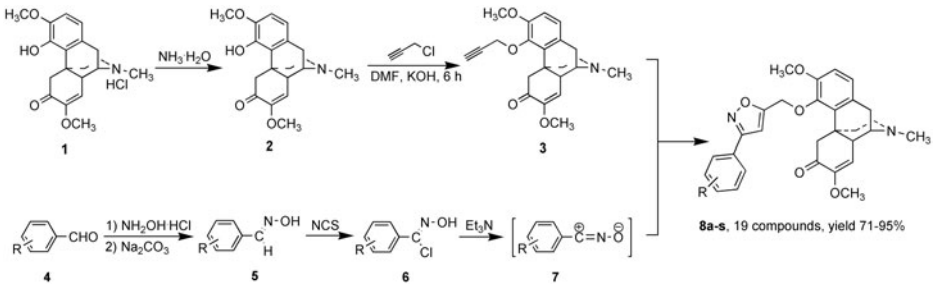

Scheme 1. Synthesis of sinomenine isoxazole derivatives.

(Tang et al. 2006). In order to obtain derivatives with less side effects and better biological activities, many structural modification researches of sinomenine have been reported to reduce these side effects and improve its further applications, some compounds show good biological activities (Zhou et al. 2014; Zhao et al. 2016; Wei et al. 2017).

Sinomenine is isolated from the stems and roots of the plant *Sinomenium acutum* (Cheong et al. 2007), native to China and Japan (Yamasaki 1976; Garcia et al. 2016). Structurally, sinomenine is similar to morphinane skeleton, and possesses four fused rings and a number of chemically active groups (Tang et al. 2018), such as 1-aromatic hydrogen, 3-anisole, 4-phenol, 6-carbonyl group, 7-enol ether, and 17-tertiary amine, this determines that sinomenine is suitable for structural modification. Heterocycles are often considered to be key active structures of drug molecules, therefore, modifying the heterocyclic structure on sinomenine is an effective way to increase biological activities (Zheng et al. 2011; Chai et al. 2012; Wang et al. 2012; Zhou et al. 2015). Our group has previously reported isoxazoline derivatives of sinomenine with moderate to good activities (Jin et al. 2013). Consequently, as an in-depth research work, here we report a novel sinomenine heterocyclic derivative, sinomenine isoxazole derivatives, as far as we know, this is also the first report of this type of structure.

2. Results and discussion

The free phenolic hydroxyl on ring A is readily oxidised by air and may be the main cause of hypersusceptibility (Zheng et al. 2012, 2014), therefore, we choose 4-OH as our modification site to reduce this side effect. Isoxazole is a five-membered nitrogen heterocycle, which is present in a variety of molecules with excellent biological activities. Isoxazole can be synthesised by 1,3-dipolar cycloaddition reaction from an alkyne and a 1,3-dipole. There are two ways to construct sinomenine isoxazole derivatives. One is to construct an alkyne on sinomenine and then react it with a 1,3-dipole, and the other is to construct 1,3-dipole on sinomenine and then react it with an alkyne, however, this method may cause the 6-carbonyl group to participate simultaneously in the formation of 1,3-dipole reaction, resulting in unwanted by-products. So, we choose the first method to synthesise our target sinomenine isoxazole moleculars. The synthetic route toward the target compounds is outlined in Scheme 1 and requires 6 steps (Scheme 1).

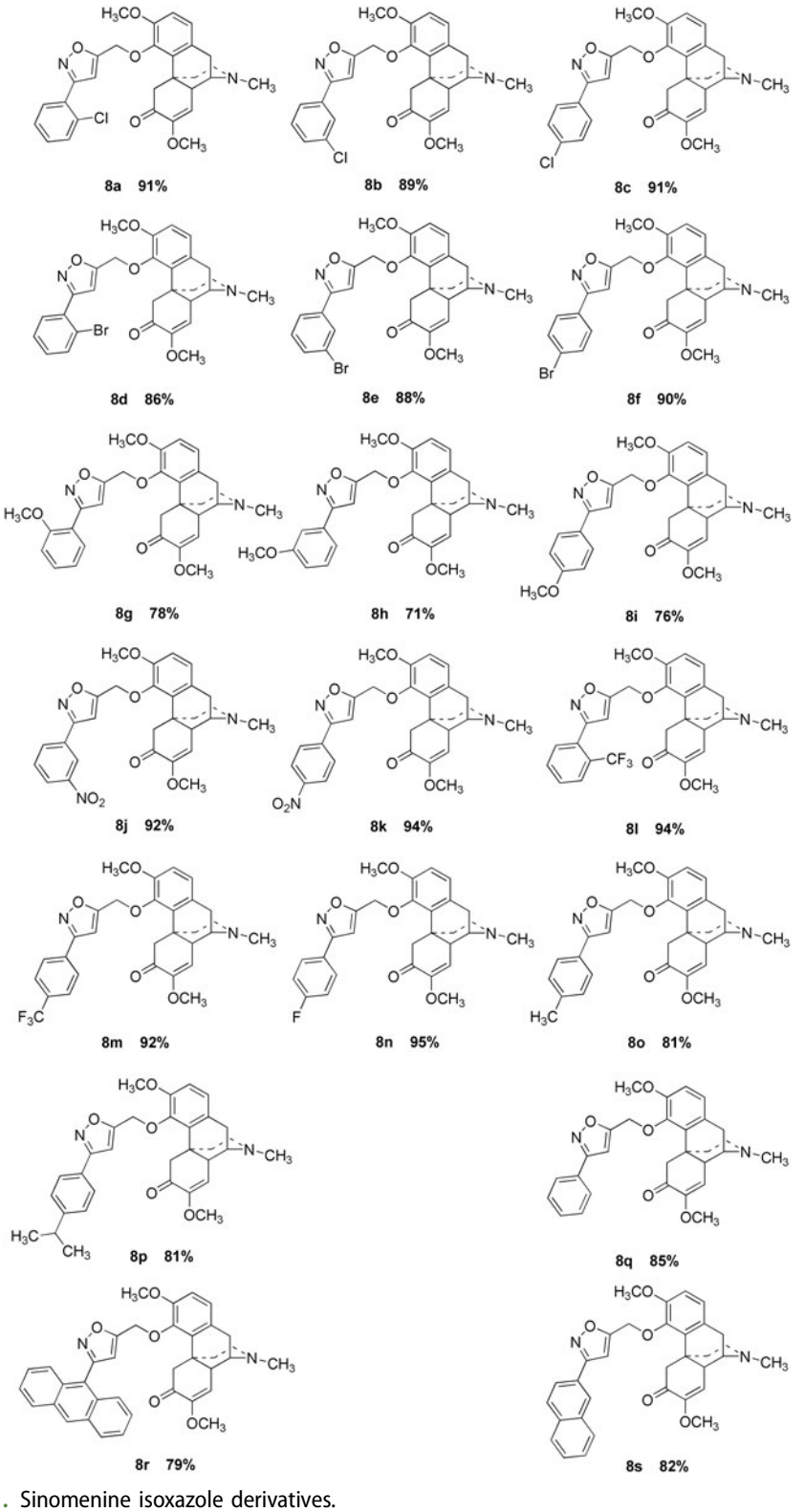

Figure 1. Sinomenine isoxazole derivatives.

The sinomenine hydrochloride **one** is neutralised with ammonia to form sinomenine **2**, which reacts with 3-chloropropyne under the action of KOH in DMF to form 4-alkynyl sinomenine **3**, this is a key intermediate product to synthesise the target sinomenine isoxazole compounds. Another key intermediate product to synthesise the isoxazole is 1,3-dipole, which can be obtained from aromatic aldehyde **4**. After treatment with hydroxylamine hydrochloride and then sodium carbonate solution, aromatic aldehyde **four** is converted to aldehyde oxime **5**, which reacts with N-chlorosuccinimide (NCS) to afford aryl hydroximino chloride **6**, 1,3-dipole **seven** is eventually formed *in situ* from **six** while triethylamine (TEA) in DMF is added dropwise. Then 4-alkynyl sinomenine **three** is added to provide the sinomenine isoxazole derivative **8**.

On our target isoxazole heterocycle, sinomenine is linked to the 5-site of isoxazole, and the 3-site substituent is an aromatic ring derived from the aromatic aldehyde reactant. In this report, a variety of different substituted aromatic aldehydes are used as reactants to obtain a total of 19 sinomenine isoxazole derivatives (Figure 1). From the experimental results, we can see that aromatic aldehydes with electron withdrawing groups provide higher yields of sinomenine isoxazole derivatives, while slightly lower yields with electron-donating aromatic aldehydes, this indicates that electron withdrawing groups can enhance the cyclisation activity of the 1,3-dipole.

3. Experimental

For all experimental procedures and compound characterisation information, please see the supplementary material relating to this article.

4. Conclusion

In conclusion, we have described an effective method to synthesise a novel structure of sinomenine isoxazole derivatives. The key intermediate product of 4-alkynyl sinomenine **three** is obtained with almost quantitative yield, which can be used directly in the next step by simply washing off the base with water and drying with anhydrous sodium sulfate, and does not require column chromatography. The key step of 1,3-dipolar cycloaddition reaction is suitable for all different substituent groups, and 19 target compounds have been synthesised in good to excellent yields. Sinomenine is clinically available for the treatment of rheumatoid arthritis (RA), so these compounds might serve as valuable candidates for anti-inflammatory drug discovery. Further applications of 4-alkynyl sinomenine **three** for the synthesis of other sinomenine heterocyclic derivatives are in progress.

Disclosure statement

No potential conflict of interest is reported by the authors.

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