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Construction of turmerone motif-fused spiropyrrolidine oxindoles and their biological evaluation for anticancer activities

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ABSTRACT

Developed herein is a facile and efficient methodology toward the synthesis of novel turmerone motif-fused spiropyrrolidine oxindoles via a multicomponent 1,3-dipolar cycloaddition event of dienones **2** with azomethine ylides (thermally generated in situ from isatin derivatives and sarcosine). Products bearing adjacent quaternary–tertiary centers were smoothly obtained in high yields (up to 93% yield) with good diastereoselectivity (up to >20:1). In addition, their biological activity has been preliminarily demonstrated by in vitro evaluation against human lung cancer cells A549 and human leukemia cells K562 by the MTT-based assays, using the commercially available standard drug of Cisplatin as a positive control. The results also demonstrated that most of the compounds showed considerable cytotoxicities to these two cell lines of K562 and A549, showed comparably potent or even more potent than the positive control of Cisplatin (up to 5.1 times), and indicated that novel turmerone motif-fused spiropyrrolidine oxindoles may be potential leads for further biological screenings and may generate drug-like molecules.

Introduction

The molecular hybridization has been well employed as an effective strategy for designing new drugs based on the recognition of pharmacophoric sub-units in the molecular structure of two or more known bioactive derivatives which, through the adequate fusion of these sub-units, lead to the design of new hybrid architectures that maintain pre-selected characteristics of the original templates and promising results with different classes of compounds have been elegantly described.[1] Spiropyrrolidine oxindole ring systems possessing interesting structural characteristics and strong bioactivity profiles, such as antibacterial,[2] antiviral,[3] and local anesthetic activities,[4] have particularly emerged as promising synthetic targets, because they serve as useful molecular scaffolds for the exploration and exploitation of pharmacophore space via diversity-oriented synthesis (DOS), which has led to the findings of new drug leads.[5] For example, naturally occurring spirooxindoles horsfiline[6] and elacomine[7] exhibit significant biological activities.[8] Importantly, even non-natural spirooxindoles (compounds **A** and **B**) inhibit the cell-cycle and are non-peptidic inhibitors of the p53–MDM2 protein–protein interaction, which is critical for the tumor-suppressing activity of the p53 protein. The inhibition of MDM2–p53 interactions is an appealing therapeutic strategy for the treatment of cancer. On the other hand, the sesquiterpenes Turmerone **I**,[9a] (*S*)-*ar*-Turmerone **II**[9a] and turmerone derivatives **III**–**V**[9a] isolated from rhizomes of *Curcuma longa*[9b–e] are reported to exhibit cytotoxic, anti-inflammatory, anti-cancer, and anti-venom activity.[9b–e] However, a close look into the literature data revealed that this biologically important turmerone scaffold has not yet been widely studied, particularly those turmerone motifs fused with other biological scaffolds. On account of the good biological activities of spiropyrrolidine oxindoles and the natural turmerone compounds, we wondered if turmerone motif-fused spiropyrrolidine oxindoles with a general formula of **3** might generate novel anticancer drug-like molecules (Scheme 1).

Stereoselective construction of spiropyrrolidine oxindoles is one of the most challenging works in catalytic organic reactions.[10,11] Generally, isatin and its derivatives have been employed as starting materials in 1,3-dipolar cycloaddition reactions yielding the spirooxindole core[12–16] due to the facile preparation of the corresponding azomethine ylides in the presence of *a*-amino acids.[17] Although some progress has been made, demand for other practical processes to construct the spiropyrrolidine oxindole motif-fused biological scaffolds, which might generate novel potential

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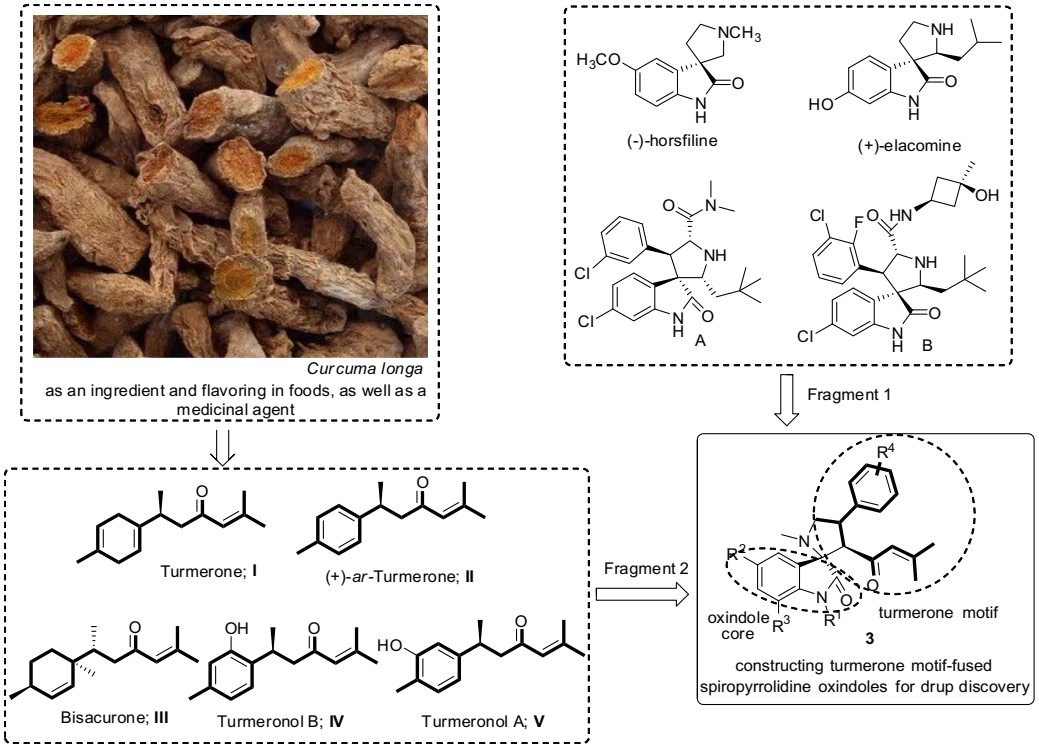
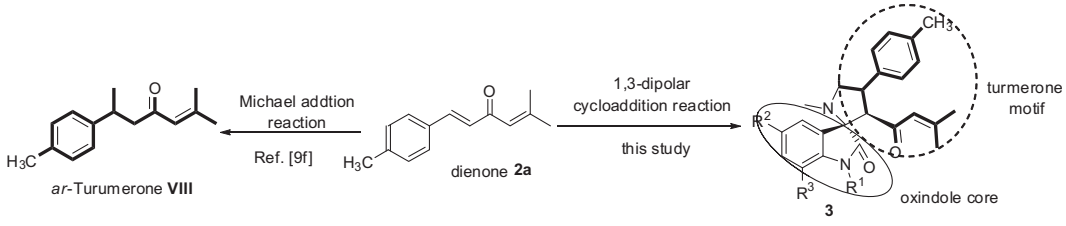


Scheme 1. Design of turmerone motif-fused spiropyrrolidine oxindoles by a hybrid of these two motifs.



Scheme 2. The synthesis of turmerone motif-fused spiropyrrolidine oxindoles via a 1,3-dipolar cycloaddition reaction.

leads for biological screenings, still remains in this area. In this context, we have been recently attracted by these spirooxindole family due to their potential pharmaceutical applications, as a continuing effort to develop new methodology for the construction of complex oxindole-containing drug-like molecules,[18] we report herein a facile construction of novel turmerone motif-fused spiropyrrolidine oxindoles **3** via a multicomponent 1,3-dipolar cycloaddition reaction of dienones **2** with azomethine ylides (thermally generated in situ from isatin derivatives and sarcosine) (Scheme 2). In particular, their biological activities against human lung cancer cells A549 and human leukemia cells K562 have been evaluated.

Results and discussion

In our initial endeavor, the dienone **2a** was prepared by reaction of mesityl oxide with 4-methylbenzaldehyde. The three-component 1,3-dipolar cycloaddition reaction of sarcosine, isatin and dienone **2a** was investigated to substantiate the feasibility of the strategy under various reaction conditions, as shown in Table 1. We were pleased to find that the reaction led to the desired product **3aa** in moderate to good yields and dr values in different solvents (e.g., CH_3CN, DCE, EtOAc, EtOH, THF, H_2O, and toluene). Finally, CH_3CN was found to be the best choice among all the solvents with respect to the stereoselectivity and yield (Table 1, entries 1–7). With this promising result in hand, the temperature effect of the reaction was further examined (Table 1, entries 8–10). The reaction also occurs at room temperature but extended reaction time (48 h) is required, albeit, a much lower yield (41%) of isolated product **3aa** was obtained (Table 1, entry 9). Further improvement of the dr value of **3aa** has been achieved by increasing the reaction temperature from 60 °C to 80 °C, while high level of conversion was retained (Table 2, entry 10). By decreasing the amount of CH_3CN to 5.0 mL, however, we found that the reaction delivered the desired product **3aa** in the lower yield (72%) with some starting materials remaining (Table 1, entry 11), mainly because the lower amount of CH_3CN decreased the solubility of the starting material of isatin **1a**. Thus, the optimal reaction conditions we established were, isatin **1a** (0.4 mmol), dienone **2a** (0.6 mmol), sarcosine (0.8 mmol) in 10.0 mL of CH_3CN at 80 °C for 24 h.

With the optimized reaction conditions in hands, we next turned our interest to the reaction scope, and the results are summarized in Table 2. The dienone **2a** was first used as a model substrate to probe the reactivity of different isatin derivatives **1** in this reaction. It clearly indicated that all of the reactions pro-