Tetrahedron 72 (2016) 8523–8536

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Diversity-oriented one-pot multicomponent synthesis of spirooxindole derivatives and their biological evaluation for anticancer activities

Jun Yang [a, 1], Xiong-Wei Liu [a, 1], Dan-Dan Wang [a], Min-Yi Tian [a], Shuo-Nan Han [a], Ting-Ting Feng [a], Xiong-Li Liu [a, *], Ren-Qiang Mei [b], Ying Zhou [a, **]

[a] Guizhou Engineering Center for Innovative Traditional Chinese Medicine and Ethnic Medicine, Guizhou University, Guiyang, 550025, China
[b] State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, 650201, Yunnan, China

ARTICLE INFO

Article history:
Received 31 August 2016
Received in revised form
8 October 2016
Accepted 14 October 2016
Available online 2 November 2016

Keywords:
Five-membered carbocyclic spirooxindoles
One-pot multicomponent synthesis
Knoevenagel condensation/Michael/cyclization
Aminomethylation
Antitumor activity

ABSTRACT

Described herein is a facile and efficient methodology for diversity-oriented one-pot multicomponent synthesis of 3-aminomethyl quaternary carbon oxindole fused five-membered carbocyclic spirooxindoles **5** *via* knoevenagel condensation/Michael/cyclization and then aminomethylation reaction. A wide variety of products with varying degrees of substitution around it, were obtained smoothly with high efficiency (up to overall yield 73% and >20:1 diastereoselectivity). In particular, their biological activities against these three cell lines K562, A549 and PC-3 have been evaluated. These results suggested that most of 3-aminomethyl quaternary carbon oxindole fused five-membered carbocyclic spirooxindoles **5** showed equipotent or more potent than the positive control of Cisplatin (up to 3.4 times).

1. Introduction

Multifunctional spiropyrrolidine oxindoles possessing interesting structural characteristics and strong bioactivity profiles, such as antibacterial,[1] antiviral[2] and local anaesthetic activities,[3] have particularly emerged as attractive synthetic targets, since 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.[4] Especially, five-membered carbocyclic spirooxindoles possess interesting structural properties found in a number of biologically active synthetic[5] and natural products[6] with activities in a variety of disease areas (Fig. 1). On the other hand, many natural products and pharmaceuticals ((S)-(−)-spirobrassinin, horsfiline,[7] (+)-Dioxibrassinin and coerulescine,[8] etc.), share a common 3-aminomethyl quaternary carbon oxindole unit and exhibit significant biological activities.[9] In this context, on account of the good biological activities of five-membered carbocyclic spirooxindole scaffolds and 3-aminomethyl quaternary carbon oxindole scaffolds, which are considered “privileged structures”, we wondered if a hybrid of these two motifs for the construction of 3-aminomethyl quaternary carbon oxindole fused five-membered carbocyclic spirooxindoles **5** might generate novel drug-like molecules for biological screenings (Scheme 1).

Stereoselective construction of spiropyrrolidine oxindoles is one of the most challenging work 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] and a variety of 1,3-dipolarophiles such as *α*, *β*-unsaturated ketones,[18–20] arylidenemalono-dinitriles,[21] *α*, *β*-unsaturated lactones,[22] nitrostyrenes,[23] acrylamides[24] and various other electron deficient alkenes[25–27] have been documented. Although many synthetic methods have been developed for the selective synthesis of spiropyrrolidine oxindoles, but existing stereoselective catalytic

* Corresponding author.
** Corresponding author.
E-mail addresses: xlliu1@gzu.edu.cn (X.-L. Liu), yingzhou71@yeah.net (Y. Zhou).
[1] These two authors contributed equally to this work.

http://dx.doi.org/10.1016/j.tet.2016.10.050
0040-4020/

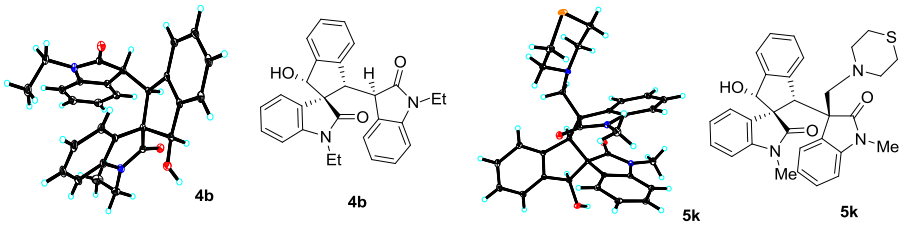
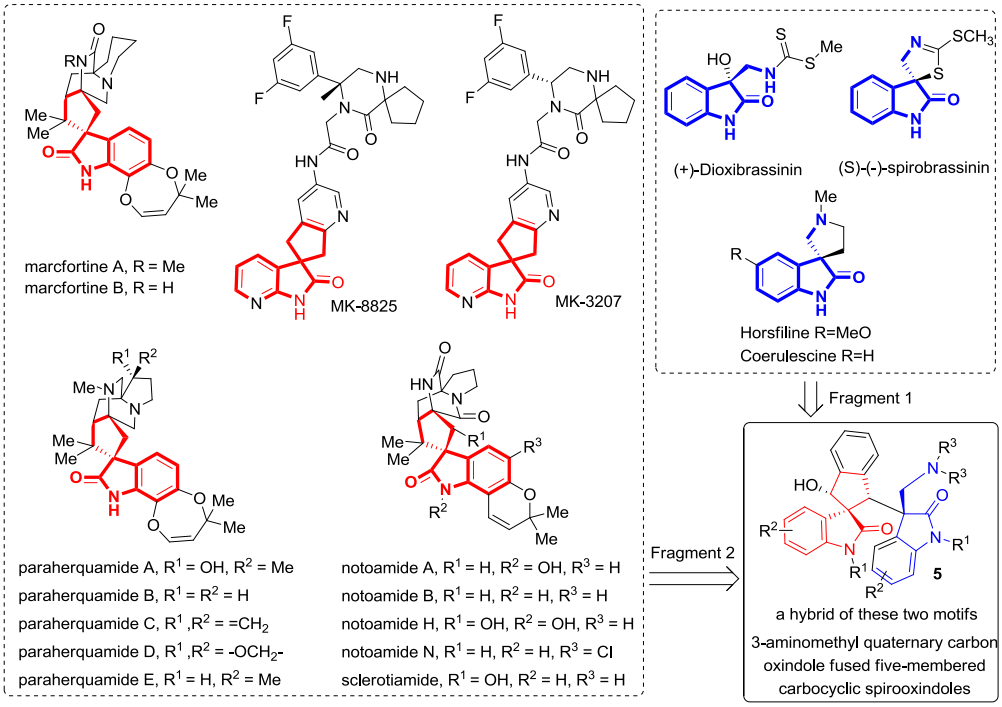


Fig. 1. X-ray crystallographic structures of **4b** and **5k.**



Scheme 1. Design of diversity-oriented spirooxindole derivatives for drup discovery.

syntheses of substituted five-membered carbocyclic spirooxindoles from simple substrates and catalysts are very few.[28,29] In particular, their high-yielding synthesis with multiple stereocenters and a spiro-quaternary carbon is a still demanding task.[30] Therefore, the development of a catalytic stereoselective protocol for the diversity-oriented synthesis of functionalized five-membered carbocyclic spirooxindoles is a significant challenge. On the other hand, oxindoles containing a aminomethyl group at the C3 position are very attractive and valuable synthetic targets. Due to the ease of transforming aminomethyl group to other functionalities, aminomethylation oxindoles can act as potential intermediates for further elaboration. In this context, as a continuing effort to develop new methodology for the construction of complex oxindole-containing drug-like molecules,[31] we report herein a facile diversity-oriented one-pot multicomponent synthesis of 3-aminomethyl quaternary carbon oxindole fused five-membered carbocyclic spirooxindoles **5** *via* knoevenagel condensation/michael/cyclization and then aminomethylation reaction (Scheme 2). In particular, their biological activity against human prostate cancer cells PC-3, human lung cancer cells A549 and human leukemia cells K562 have been evaluated.

2. Results and discussion

In our initial endeavor, we screened different tertiary amines and secondary amines (*e.g.*, DABCO, Et_3N, Et_2NH, pyrrolidine and piperidine, entries 1–5, Table 1) as organocatalysts in the reaction of *N*-CH_3-oxindole **1a** with phthalaldehyde **2a** to substantiate the feasibility of the strategy, as shown in Table 1. We were pleased to discover that the commonly used secondary amine catalyst of piperidine, was shown to catalyze the reaction more successfully, delivering the desired product **4a** with 67% yield (Table 1, entry 5). Further solvent screening demonstrated that the reaction could deliver the product **4a** (71% yield) preferentially with MeOH as the solvent (Table 1, entry 9). However, when the reaction was performed in toluene and CH_3CN, only along with intractable product mixtures from which no main product could be identified by the HRMS spectra analysis (Table 1, entries 7 and 8). Extending the reaction time from 10 h to 16 h had a little positive effect on the yield of **4a** with high diastereoselectivity (Table 1, entry 10). With this promising result in hand, the temperature effect of the reaction was further examined (Table 1, entries 11 and 12). The reaction also occurs at 40 °C but extended reaction time (24 h) is required, albeit, much lower yield (25%) of product **4a** was obtained (Table 1, entry 11). Thus, the optimal reaction conditions for synthetic intermediate oxindole **4a** we established were, *N*-CH_3-oxindole **1a** (0.9 mmol), phthalaldehyde **2a** (0.3 mmol), piperidine (10 mol%) in 6.0 mL of MeOH at reflux for 16 h.

With this promising result in hand and considering the fact that oxindoles containing a aminomethyl group at the C3 position may