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The discovery of oxazolones-grafted spirooxindoles via three-component diversity oriented synthesis and their preliminary biological evaluation

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ABSTRACT

A facile method via 1,3-dipolar cycloaddition of substituted benzylidene-2-phenyloxazolone under mild conditions with azomethine ylides, which were generated in situ by a decarboxylative route from a common set of diverse isatins and amino acid derivatives was developed for a 15-membered library of regio- and stereoselective oxazolones-grafted spirooxindole-pyrrolidine, pyrrolizidines and pyrrolothiazoles. After screening their cytotoxic activities against a spectrum of cell-lines, compound **4h** was identified as potent antitumor agent and inducing apoptosis. The present study has provided an effective entry to rapidly construct a chemical library of oxazolones-grafted spirooxindoles and developed a good lead compound for subsequent optimization.

Natural products have been considered as invaluable sources of leading compounds in developing first-in-class drugs since the past 50 years.[1] It is estimated that 50–70% of launched drugs in clinical are natural products or natural product-derived molecules.[2] For example, the spirooxindole core is a privileged heterocyclic ring system, which constitutes the core structural element of pharmaceutically relevant natural products.[3,4] The natural spirotryprostatin A and its related alkaloids which have been identified as novel inhibitors of microtubule assembly, have encouraged the design and synthesis of novel spirocyclic oxindoles exhibiting a wide spectrum of important bioactivities such as antitumor,[5] antimycobacterial,[6] anti-inflammatory[7] and antitubercular[8] properties (Fig. 1A). Though these biologically active heterocycles have already been synthesized by total synthesis, the targeted drug discovery process toward natural products is always tedious. In addition, the total synthesis is time-consuming and impractical, and it may lack structural variability. Therefore, the design of an efficient protocol to access this novel target with structural diversity is highly desirable and valuable for medicinal chemistry and drug discovery.

A more quick and effective solution should be provided by diversity-oriented synthesis (DOS) of natural product-like molecules.[9] Diversity oriented synthesis (DOS) is a strategy for quick access to molecule libraries with an emphasis on skeletal diversity.[10] One of the most important starting points for DOS is multicomponent reactions (MCRs): MCRs fill an important niche in library synthesis by providing direct access to library compounds.[11,12]

1,3-Dipolar cycloadditions of azomethine ylides with electron-deficient olefins have offered a robust method to construct pyrrolizidine alkaloids,[13] which are the common constituents of hundreds of vegetable species. It has been reported that they present in about 3% of flowering plants in the world. This multi-component reaction featured wide structural diversity, high atom economy, excellent bond-forming efficiency and high regio- and stereo-selectivity in one pot process.[14,15] Furthermore, the designed three-component 1,3-dipolar reactions of isatins, amino acid and olefins will facilitate the diversity-oriented synthesis, which provides an important role in offering a source of 'natural-like' spirocyclic oxindoles compounds for bioactivity screening to discover novel biologically active entities.[16]

Prompted by these considerations and as a part of our own interest in cycloaddition reactions,[17–20] we report here in the preliminary studies about the efficient synthesis of novel regioselective spiropyrrolidine pyrrolidines, pyrrolizidines, and pyrrolothiazole frameworks containing an oxazolone moiety via the one-pot, multicomponent condensation of azomethine ylides (generated in situ from amino acids and isatin) with the 4-ethylidene-2-phenyloxazolone (preformed from the reaction of hippuric acid with substituted benzaldehydes). The oxazolone moiety

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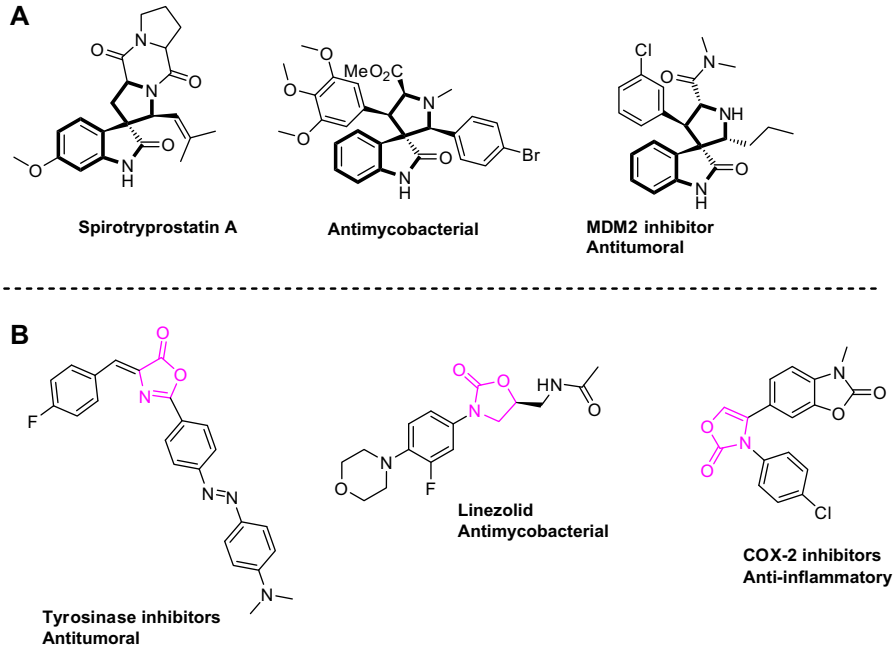
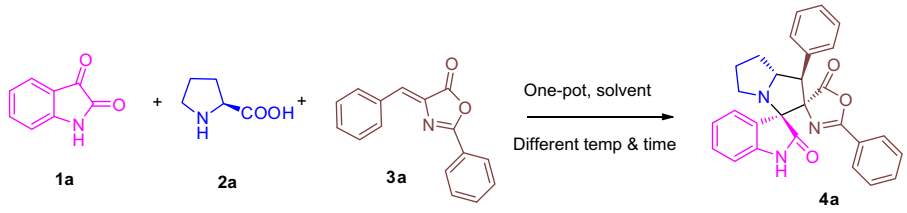


Figure 1. (A) Representative bioactive small-molecule natural products that have a spirooxindolo-pyrrolidine building block. (B) Representative bioactive small-molecules that have a oxazolone moiety.

Table 1
Optimization of reaction conditions[a]



Entry	Solvent	Temp (°C)	Yield[b,e] (%)
1	DMSO	80	36
2	THF	80	41
3	CH_3CN	80	33
4	Toluene	80	19
5	Methanol	Reflux	53
6	Ethanol	80	65
7	Ethanol	rt	—[d]
8	Ethanol/H_2O	100	51
9	Ethanol	50	75
10[c]	Ethanol	50	93

[a] Unless indicated otherwise, the reaction was performed with **3a** (0.5 mmol), **1a** isatin (0.5 mmol), and **2a**, L-proline (0.5 mmol) in different solvents (10.0 mL) and under different temperatures for 5 h.
[b] Isolated yield based on isatin.
[c] 10 h.
[d] No reaction.
[e] The dr>20:1, referred to the diastereoselectivity and was calculated from ^{1}HNMR.

presents in some of the synthesized compounds illustrated in Figure 1B, and it is one of the main structural fragments on which this study is based.[21] The best-known derivatives possessing this moiety are tyrosine kinase inhibitors, antibiotic or COX-2 inhibitors.

Our research was focused on: (i) Establishing the optimal conditions for the reaction of isatin, L-proline and 4-ethylidene-2-phenyloxazolones, according to the variables: solvent, reaction time, temperature, yield and regio- and stereoselectivities in which the desired product is obtained. (ii) On the established conditions, preparing a 15-membered library of new spiropyrrolidine pyrrolidines, pyrrolizidines, and pyrrolothiazole frameworks through the 1,3-dipolar cycloaddition of azomethine ylide. (iii) Identifying their safety and toxicity profiles (ADME-Tox properties) through in silico methods based on Lipinski's rule (drug-likeness) and drug-score criteria. (iv) Determining the cytotoxicity of the prepared spirooxindoles through the MTT assay with a variety of cancer cells. (v) Predicting and analyzing their protein targets through docking studies. All these works are performed in order to contribute to future SAR studies of this interesting class of molecules.