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One-pot four-component domino strategy for the synthesis of novel spirooxindole–pyrrolidine/pyrrolizidine-linked 1,2,3-triazole conjugates *via* stereo- and regioselective [3+2] cycloaddition reactions: *In vitro* antibacterial and antifungal studies

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ABSTRACT

In this study, a series of highly diversified novel functionalized spirooxindolopyrrolidine and spirooxindolopyrrolizidine-linked 1,2,3-triazole conjugates have been synthesized by a *one-pot*, four-component condensation of *(E)*-2-(1-propargyl-2-oxoindoline-3-ylidene) acetophenones as bifunctional dipolarophiles, acenaphthenequinone, α-amino acids with substituted aryl azides using coinage metal catalysts. It was found that $CuSO_4$/Na ascorbate as a catalyst was more performant than Ag_2CO_3 or CuI. The single-crystal X-ray analysis of one of the cycloadducts proves the structure and the regiochemistry of this reaction. The compounds have been screened for their *in vitro* antibacterial and antifungal activities using the agar dilution method and display good activities.

1. Introduction

The multicomponent reaction (MCR) has become an important area of research in organic, medicinal, and combinatorial chemistry [1–4]. Its simplicity and atomic economy of the process offer rapid and easy access to complex *N*-heterocyclic systems in a single eco-friendly synthetic operation [5].

Spirooxindole–pyrrolidines are an important subset of the oxindole-based molecules [6], which represent attractive targets in the organic synthesis because of their highly marked biological activities such as antimicrobial [7], antitumoral [8], anti-inflammatory [9], anti-HIV [10], and anticancer properties [11]. On the other hand, triazole and their derivatives display a wide range of biological activities incorporating anticancer [12], antitubercular [13], antimicrobial [14], antifungal [15], and antibacterial [16,17] activities that are also found in drugs like fluconazole [18] (Fig. 1).

In view of the biological importance of the oxindole scaffold and to increase the breadth of accessible library members of this family, it was of considerable interest to develop novel structures including both the oxindole structure and the five-membered ring hoping that such a combination could be more biologically effective.

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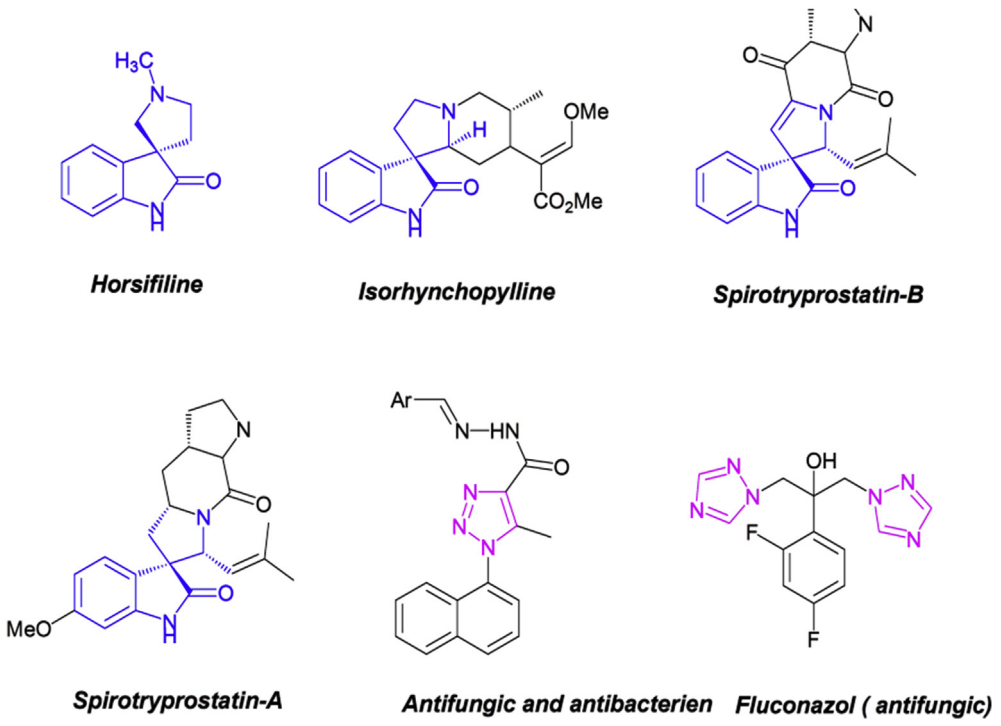

Fig. 1. Representative examples of biologically active molecules containing a spirooxindole and triazole core.

In the last decade, multicomponent 1,3-dipolar cycloaddition reactions of azomethine ylides derived from isatin and α-amino acids with dipolarophiles have been emerged as a fascinating and powerful tool for the synthesis of spirooxindolopyrrolidine [7,11] and spirooxindolopyrrozilidine [19] derivatives in a highly regio- and stereoselectivity fashion. For example, P.T. Perumal et al. have demonstrated that spirooxindole–pyrrolidine compounds, which exhibit an anticancer activity, are accessible by the reaction of azomethine ylides generated from isatin and sarcosine or thioproline with the dipolarophile 3-(1H-imidazol-2-yl)-2-(1H-indole-3-carbonyl) acrylonitrile [11]. The group of V.V. Lipson has developed a regioselective synthesis of spirooxindolopyrrolidines and pyrrolizidines via three-component reactions of acrylamides and aroylacrylic acids with isatin and α-amino acids [19].

Also, it is well-known that the conventional route to triazole relies on [3+2] cycloaddition between alkynes and organic azides [20]. We describe in this article an efficient synthesis of a series of novel spirooxindolopyrrolidine- and spirooxindolopyrrolizidine-linked 1,2,3-triazole conjugates via a *one-pot*, four-component condensation of *(E)*-2-(1-propargyl-2-oxoindoline-3-ylidene)acetophenones **1a**–**b**, acenaphthenequinone **2**, sarcosine **3a** or proline **3b**, and substituted aryl azides **4a**–**e** using Cu(I) as the catalyst (Scheme 1).

Exocyclic enones and terminal triple bonds have been occasionally served as dipolarophiles for the synthesis of spiropyrrolidine, spiropyrrolizidine, and triazole derivatives. However, a survey of the literature reveals that there is no example describing the synthesis of spirooxindoles incorporating triazole and pyrrolidine or pyrrolizidine units at the same time by the *one-pot*, four-component synthesis. We therefore prompted to investigate the chemical activity of exocyclic enones and terminal triple bonds for [3+2] cycloaddition reactions that were not reported to date. Thus, it appeared to be highly desirable to explore this kind of a reaction that could constitute a promising strategy for the synthesis of diverse spirooxindole–pyrrolidine/pyrrolizidine-linked 1,2,3-triazole conjugates. In continuation of our interest in the synthesis of novel heterocycles employing MCRs [21–24], we therefore explored a new protocol for the synthesis of highly diversified novel functionalized spirooxindolopyrrolidine- and spirooxindolopyrrolizidine-linked 1,2,3-triazole conjugates via the *one-pot*, four-component condensation of *(E)*-2-(1-propargyl-2-oxoindoline-3-ylidene)acetophenones, acenaphthenequinone, proline or sarcosine, and substituted aryl azides.

2. Results and discussion

The *N*-propargylated dipolarophiles **1** possess two dipolar functional groups (C]C and CC), making them versatile synthons for the synthesis of triazoles and pyrrolidines/pyrrolizidines. The condensation involves two sequential [3+2] cycloaddition reactions, namely, azomethine ylide–alkene and azide–alkyne coupling. First of all, we studied these reactions step by step. The first step is the cycloaddition of aryl azides **4a**–**e** with the propargylic function of *(E)*-2-(1-propargyl-2-oxoindoline-3-ylidene) acetophenone **1a** using $CuSO_4.5H_2O$/Na ascorbate as the catalyst. Then, the second step is the cycloaddition of azomethine generated in situ from acenaphthenequinone **2**

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