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Research paper

Spirooxindole-derived morpholine-fused-1,2,3-triazoles: Design, synthesis, cytotoxicity and apoptosis inducing studies

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ABSTRACT

A series of new spirooxindole-derived morpholine-fused-1,2,3-triazole derivatives has been synthesized from isatin *spiro*-epoxides. The protocol involves regiospecific isatin-epoxide ring opening with azide nucleophile followed by sequential *O*-propargylation, and intramolecular 1,3-dipolar cycloaddition reaction. These compounds have been evaluated for their antiproliferative activity against selected human tumor cell lines of lung (A549), breast (MCF–7), cervical (HeLa), and prostate (DU–145). Among the tested compounds, **6i**, **6n** and **6p** showed potent growth inhibition against A549 cell line with IC_{50} values in the range of 1.87–4.36 μM, which are comparable to reference standards doxorubicin and 5-flourouracil. The compounds **6i** and **6p** treated A549 cells displayed typical apoptotic morphological features such as cell shrinkage, nuclear condensation, fragmentation, and decreased migration potential. Flow-cytometry analysis revealed that the compounds arrested the cells in G2/M phase of cell cycle. Hoechst and acridine orange/ethidium bromide staining studies also showed that the cell proliferation was inhibited through induction of apoptosis. Moreover, the compounds treatment led to collapse of the mitochondrial membrane potential (DΨm) and increased levels of reactive oxygen species (ROS) were noted in A549 cells.

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1. Introduction

Cancer remains a challenging problem and treatment usually involves a combination of chemotherapy, surgery and radiotherapy. Chemotherapy is considered to be one of the effective approaches in suppressing tumor growth and eradication of tumors [1,2]. The development of resistance to chemotherapeutic agents and associated side effects are major obstacle to the effective treatment of cancer [3]. In spite of recent advances in understanding the etiology of cancer and a greater emphasis placed on early detection of disease, the overall mortality rate has not been changed and is not expected to diminish. Therefore, it is necessary to identify and develop new anti-cancer agents with improved efficacy and reduced side effects to complement the present chemotherapeutic strategies. Hence, further research regarding the development of new therapeutic drugs that more effectively combat cancer is needed.

The spirooxindole core is a kinase-privileged scaffold which has emerged as an attractive synthetic target because of occurrence in numerous natural products and biologically active molecules [4,5]. In particular, the spirooxindole alkaloids are inspiration for the development of potential therapeutic agents [6,7]. Among these motifs, the synthesized spirooxindoles such as MI-888 have been in preclinical research for the treatment of human cancers [8]. Specifically, the spiro ring systems have been successfully incorporated into some of kinase (*e.g.* c-Met/ALK, PLK4) inhibitors [9–11]. The key structural characteristic of these compounds is the spiro ring fused at the C3-position of the oxindole core with varied heterocyclic motifs. The prevalence of these structures has resulted in the production of diverse libraries of small molecules for *in vitro* biological evaluation. As such, these spirooxindoles seem to be promising candidates for drug discovery due to their inherent three-dimensionality and structural novelty [12]. Furthermore, the spiro ring fusion tends to impose the conformational restriction on the oxindole scaffold [13]. Additionally, these spirocyclic compounds have reduced conformational entropies upon binding to a

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protein targets. As an outcome, there is a huge interest in both industry and academia to develop novel spirooxindoles with interesting biological activities, particularly anticancer potential.

On the other hand, the morpholine moiety has been found to be an excellent pharmacophore in medicinal chemistry and a number of molecules possessing morpholine skeleton are the clinically approved drugs [14]. It does form critical hydrogen bond with the target proteins. For instance, the chemical inhibitors of most of the kinases usually carry analogous structural heterocyclic motifs. The most common feature of these inhibitors is a critical hydrogen bond of heterocyclic motifs to target receptors [15]. These phenomena served as a valuable chemical tool for the development of new chemotherapeutic agents for cancer treatment. Likewise, the 1,2,3-triazole moiety is also an attractive pharmacophoric unit because it is stable to metabolic degradation and readily associate with several biological targets, through hydrogen-bonding and dipole interactions [16–20]. Moreover, it does not protonate at physiological pH because of its poor basicity, while thus, improves the solubility. The 1,2,3-triazole moiety is the part of well-known drugs including β-lactum antibiotic (*i.e.*, tazobactum) and the cephalosporine (*i.e.*, cefatrizine).

In the drug discovery process, incorporation of medicinally active moieties into a core bioactive natural product provides the means for accessing wider range of pharmacological profiles. Despite the tremendous biological significance of spirooxindole (Fig. 1), morpholine and 1,2,3-triazole derivatives, their fused-derivatives are not explored. Inspired by the synthetic feasibility and biological profiles of spirooxindoles, it would thus be considering worthwhile to fuse these moieties as a single molecular entity to evaluate their anticancer properties. The incorporation of a morpholine and 1,2,3-triazole moiety in oxindole scaffold might unleash the potential to access a new dimension of structural diversity to the molecules *via* intramolecular 1,3-dipolar cycloaddition reaction. We herein report the study of morpholine-spirooxindoles containing an additional five-membered morpholine-fused 1,2,3-traizole ring. To the best of our knowledge, this is the first report for the synthesis of spirooxindole-derived morpholine-fused-1,2,3-triazole derivatives. Hence, we have synthesized a library of novel spirooxindole-derived morpholine-fused-1,2,3-triazoles containing different substituent's around the oxindole moiety and evaluated for their *in vitro* anticancer activity on selected human cancer cell lines.

2. Results and discussion

2.1. Chemistry

The tetracyclic spirooxindole-derived morpholine-fused-1,2,3-triazoles (4,7-dihydrospiro[[1,2,3]triazolo[5,1-*c*][1,4]oxazine-6,3′-indolin]-2′-one derivatives) were synthesized from isatin-epoxides *via* epoxide-ring opening with azide nucleophile followed by sequential *O*-propargylation, and intramolecular 1,3-dipolar cycloaddition reaction. The isatin-epoxides **4a**–**t** were synthesized from the corresponding *N*-alkylated-isatins by treatment with trimethylsulphoxonium ylide as illustrated in Scheme 1. Isatins were directly synthesized from anilines by the Sandmeyer reaction with chloral hydrate under acidic conditions in a polar medium [21–23]. Further, they were *N*-alkylated with alkyl iodide in the presence of NaH.

In particular, our strategy involved the regiospecific ring-opening of isatin-epoxides **4a**–**t** with sodium azide in water as reaction media, to furnish the corresponding oxindole-azido alcohols **5a**–**t**. The epoxide ring was opened from the less hindered side, affording the oxindole-azido alcohols regiospecifically. The azido alcohols **5a**–**t** were then further utilized for the synthesis of diverse range of spirooxindole-derived morpholine-fused-1,2,3-triazoles. Specifically, when these oxindole-azido alcohols were subjected to *O*-propargylation with propargyl bromide followed by

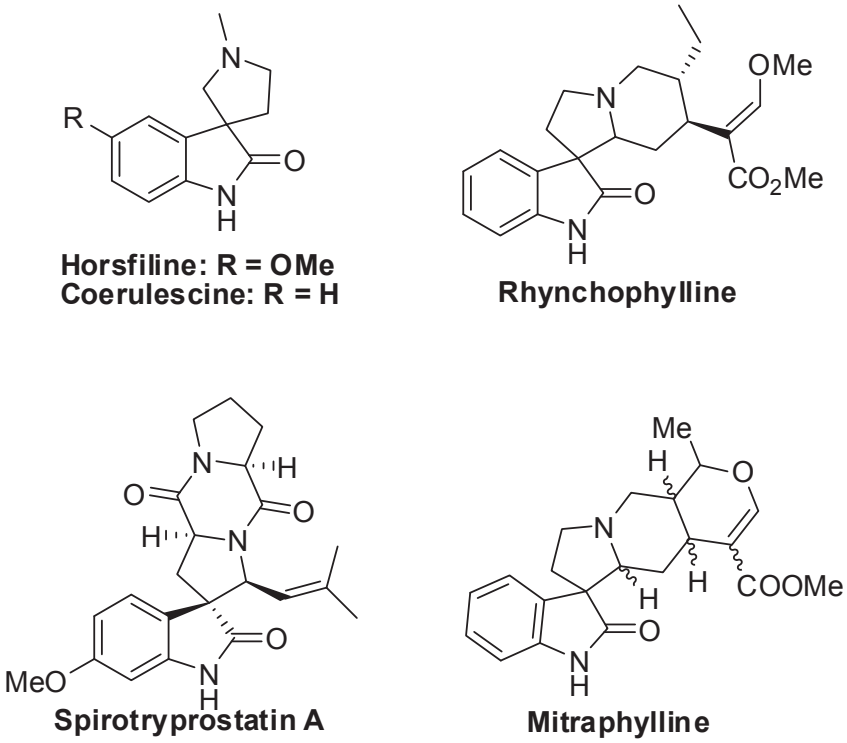

Fig. 1. Representative structures of spirooxindole natural products.

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