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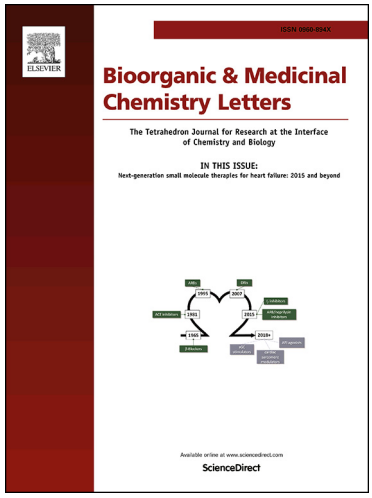

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Synthesis and anticancer activity studies of indolylisoxazoline analogues

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ABSTRACT

A new library of thirteen indolylisoxazolines **6a-m** has been synthesized by the treatment of indolylchalcones with hydroxylamine hydrochloride. Evaluation of anticancer activity of indolylisoxazolines **6a-m** led to the identification of potent compounds **6c-d**, **6i** and **6l**, with IC_{50} ranging 2.5-5.0 μM against the tested cancer cell lines. Using a number of complementary techniques such as acridine orange/ethidium bromide staining, PARP1 cleavage and DNA strand breaks assay, we show that the compounds **6c** and **6i** induce apoptosis in highly aggressive C4-2 cells. Our data further revealed that **6c** and **6i** inhibited C4-2 cells proliferation without inducing ROS. Finally, we show that compounds **6c** and **6i** also potently inhibit cell migration, indicating these compounds have the potential to serve as effective anti-cancer agents.

Indole scaffold is frequently present in many important synthetic and natural drug molecules including anticancer, anti-oxidants, anti-inflammatory, analgesics and anti-pyretic drugs.[1,2] Greater versatility and biodiversity of indole nucleus makes it highly privileged motif for the target-based drug design and development of anticancer agents. In the last decade, importance of indole motif in the anticancer drug development is reflected by the identification of many indole-based natural and synthetic anticancer agents with distinct mechanism of actions.[3-5] Among the indole-based compounds, indolylazoles containing five- and six-membered heterocycles linked indole have received greater attention due to their unique properties such as stability and hydrophilic nature, which improves aqueous solubility and thus simplify the formulation and *in vivo* uses (Fig 1).[6] 5-(3'- Indolyl) oxazoles isolated from different micro-organisms are reported to display interesting biological activities. For example, Labradorins **1** and **2** were found to be potential inhibitors (GI_{50} = 9.6-9.8 μg/mL) of lung cancer cell line.[7,8] Inspired by naturally occurring indolylazoles, we identified 5-(3-indolyl)-1,3,4-oxadiazoles **2** and indolyl-1,2,4-triazoles **3** as potent anticancer agents.[9] Some of the indolylazoles **3** are reported to show selective cytotoxicity against prostate cancer cell line (IC_{50} = 0.8 μM) and found to inhibits tubulin polymerization.[5] Compound A–289099 **(4)** with oxazoline ring was recognized as an orally active antimitotic agent with most promising anticancer property (IC_{50} = 6.2 nM) against NCI-H460 cells.[10]

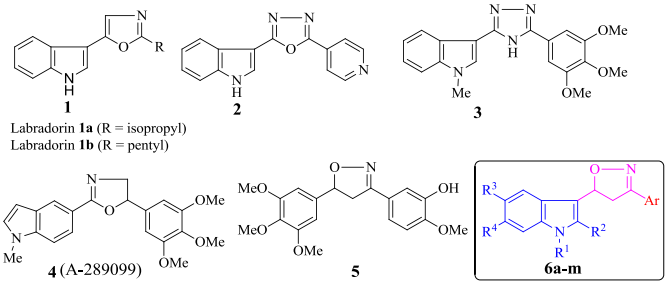

Fig. 1. Representative examples of cytotoxic indolyl(aryl)azoles

In recent years, accumulating evidences have revealed that isoxazolines possess important biological properties such as anticancer, antimicrobial, fungicidal, anticonvulsant, anti-inflammatory.[11] Some of the isoxazolines containing molecules have been found to elicit interesting anticancer activities with improved pharmacokinetics profile. For example, diaryl analogues **5** demonstrated potent cytotoxic activity by blocking most of the cancer cells in G2 phase.[12] Isoxazoline linked dihydro-quinazolinones significantly reduced the growth of cancer cell lines, and disrupted tubulin polymerization.[13]

As a part of our search for novel anticancer agents, in the present study, we designed indole-based heterocycles by linking indole and (hetero) aryl moieties through stable isoxazoline scaffold found in many biologically active molecules and drugs.[14-17] Many anticancer agents with substantial cytotoxicity have been

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