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Original Article

Synthesis and *in-vitro* cytotoxic evaluation of novel chromano-piperidine fused isoxazolidines: Discovery of a potent lead

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ABSTRACT

Background/Aim: Chromone derivatives are naturally occurring compounds possessing a wide spectrum of biological activities such as anti-inflammatory, antifungal, antimicrobial, antiviral, antitumor and anticancer. The *N* and *O* containing five-membered heterocycles, isoxazolidines, and isoxazoline derivatives have been shown to display useful anticancer and antiviral properties. In continuation in search of chemical moieties possessing anticancer/cytotoxic potential, it was considered worthwhile to screen synthesized chromano-piperidine fused isoxazolidines (**3a**–**j**) for *in-vitro* cytotoxic potential against different human cancer cell lines.

Methods: Compounds 2-(*N*-allyl/cinnamyl-anilino)-3-formylchromones were synthesized and on reaction with *N*-methylhydroxylamine in dichloromethane at ice cold temperature underwent intramolecular 1,3-dipolar cycloadditions of *in-situ* generated nitrones (**2**) to yield chromano-piperidine fused isoxazolidines (**3a-j**). All the synthesized compounds were characterized and evaluated for their cytotoxic potential against various human cancer cell lines.

Results: The compound (**3a**–**j**) under investigation for cytotoxic potential responded differently to human cancer cell lines. Compound **3e** was found be most active against neuroblastoma revealed by IC_{50} of 10.07 μM where as compounds **3b** and **3f** were found to potent against colon cancer cells having IC_{50} of 12.6 and 29.7 μM respectively.

Conclusion: The present investigations have provided an easy access to novel chromone derivatives bearing fused isoxazolidine moiety possessing significant cytotoxic potential.

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1. Introduction

Chromone nucleus has been recognized as a versatile molecular framework, which is part of the pharmacophore of a wide variety of biologically active molecules and has affinity for a variety of macromolecular targets.[1] Recently, we have reported the synthesis and evaluation of chromone derivatives as topoisomerase inhibitors.[2] Among the other cytotoxic/anticancer/antitumor chromone derivatives developed includes phosphoric ester derivatives[3] Flavone acetic acid derivatives.[4] Replacement of the furanose ring of nucleoside with isoxazolidine and isoxazoline to obtain modified nucleoside with anticancer and antiviral applications has recently drawn considerable attention[5] as chemical moieties bearing above nucleus were reported to possess important biological activities anticancer, antiviral, anti-inflammatory, antibacterial or antifungal activity.[6] The DNA intercalative and cytotoxic properties of different isoxazolidinyl polycyclic aromatic hydrocarbons have been reported.[7,8] Recently, we have reported synthesis and cytotoxic studies of isoxazolidines against selected human cancer cell lines.[9]

Keeping in view the anticancer/cytotoxic activities of chromone derivatives and isoxazolidine bearing chemical moiety, it was considered worthwhile to evaluate our previously designed and synthesized chromano-piperidine fused isoxazolidines (**3a–b**) along with new derivatives (**3c–j**) for *in-vitro* cytotoxic potential against different human cancer cell lines.

2. Methods

2.1. Synthetic chemistry

The compounds (**3a–j**) were obtained by adopting synthetic protocol reported by us.[10] which involve reaction of compounds (**1a–j**) with *N*-methylhydroxylamine in dichloromethane at ice cold temperature and the stirred solution is slowly brought to the room temperature, where the intramolecular 1,3-dipolar cycloadditions of the *in-situ* generated nitrones (**2**) lead to novel chromano-piperidine-fused isoxazolidines (**3a–j**, Scheme 1). The products were isolated by column chromatography and have been characterized by detailed spectroscopic analysis.

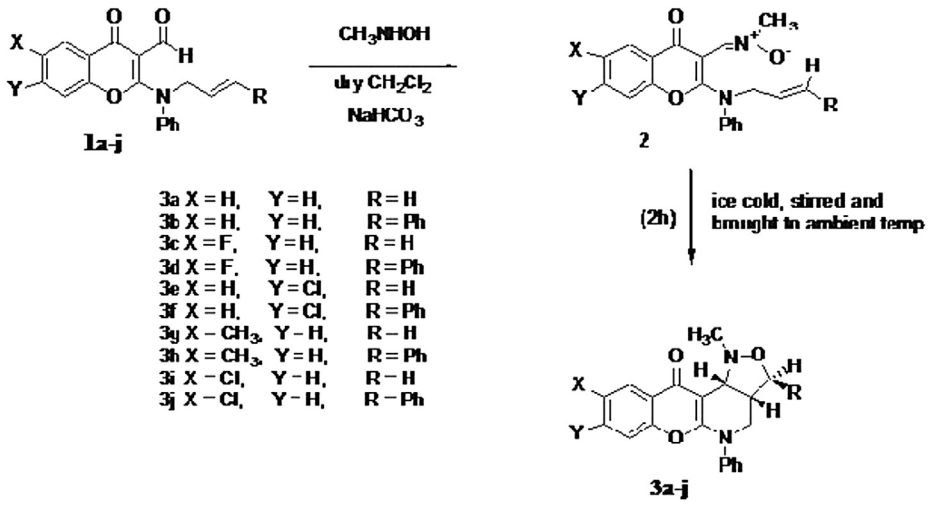
2.2. Cytotoxic evaluation

In-vitro cytotoxic evaluation of the investigational compounds (**3a–j**) were carried out on Colon (COLO-205), Prostate (PC-3), Ovary (OVCAR-5), Lung (A-549) and Neuroblastoma (IMR-32) cancer cell lines following the protocol reported by Skehan et al[11] The cytotoxicity of compounds is determined in terms of IC_{50}. 5-flourouracil was used as positive control against Colon (COLO-205) and for Prostate (PC-3) cancer cells mitomycin was used. Paclitaxel was used as standard against Ovary (OVCAR-5) and Lung (A-549) cancer cell lines where as Adriamycin was used as positive controls for Neuroblastoma (IMR-32) cancer cell line respectively.

3. Results and discussion

The results of *in-vitro* cytotoxic studies were found to be significant and presented in Table 1. Among the compounds (**3a–j**) under investigation for cytotoxic potential, compounds **3b** was found to be more active than standard 5-flourouracil (IC_{50} 21 μM) against colon (COLO-05) cancer cells as evident by the IC_{50} 12.6 μM and **3f** was found to be comparable (IC_{50} 27.7 μM). The compounds **3h** (IC_{50} 46.9 μM) and **3i** (IC_{50}59.4 μM) were moderately potent, where as compounds **3e** (IC_{50} 87.1 μM) and **3d** (IC_{50} 95.2 μM) were less active and for compounds **3a**, **c**, **g** and **j** colon cancer cells were found to be resistant.

The results for prostate (PC-3) cancer cells revealed that compounds **3b**, **e**, **f** and **h** were able to inhibit the growth of cancer but found to be less active than positive control mitomycin as observed from the value of IC_{50} (Table 1) where as the rest of tested compounds were not active toward prostate cancer cells. Similar were the results for ovary (OVCAR-5) cancer cells where only compounds **3b** (IC_{50} 76.5 μM) and **3e** (IC_{50} 85.5 μM) were shown to possess moderate cytotoxic



Scheme 1 – Synthesis of different Chromano-piperidine fused Isoxazolidines.