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ARTICLE

Synthesis and anti-proliferative evaluation of novel 3,4-dihydro-2H-1,3-oxazine derivatives of bakuchiol†

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A new series of 3,4-dihydro-2H-1,3-oxazine derivatives of bakuchiol **1** was synthesized through Mannich type condensation-cyclization reaction of 1 with formaldehyde and appropriate primary amines. On cytotoxicity evaluation against a panel of four human cancer cell lines, most of the derivatives have shown higher cytotoxic profile than the parent molecule. The best results were observed for compound **15** with IC_{50} values 2, 2, 2.4 and 3 µM against MIA-Pa-Ca-2, HCT-116, MCF-7 and HL-60 cells, respectively. Mechanistic study of compound **15** revealed that it caused mitochondrial membrane potential loss in a concentration dependent manner accompanied by activation of caspase-9 and -3, which cleave the PARP-1. It also activates caspase-8, which is involved in extrinsic apoptotic pathway. Therefore, it induces apoptosis via both intrinsic and extrinsic pathways in human pancreatic cancer MIA-Pa-Ca-2 cells.

Introduction

Natural Products (NPs) are an indispensable source of lead structures for drug discovery and development for the treatment of wide spectrum of diseases.[1] Within the sphere of cancer, out of 175 U.S. FDA approved drug entities in the time frame from 1940s to the end of 2014, 75% are other than synthetic and 49% are either NPs or NPs derived.[2] Further, NPs derived from plant as such or their derivatives has played a vital role in the therapeutic area of cancer, hence a large number of new chemical entities (NCEs) are in different stages of clinical development.[3]

Bakuchiol **1**, a meroterpene isolated from *Psoralea corylifolia* (Leguminosae) known for its various pharmacological activities.[4-6] However, cytotoxicity of bakuchiol has got considerable interest as it inhibits proliferation of various human cancer cells such as breast (MCF-7), prostate (PC-3), cervical (HeLa), gastric (AGS), lung (A-549), CNS (IMR-32), ovarian (OVCAR-5) and leukemia (THP-1).[7,8,10] The anticancer mechanism of action involves mitochondrial membrane potential loss, S phase arrest, caspase 9/3 activation, DNA fragmentation as well as inhibition of hypoxia-inducible factor-1 (HIF-1) and nuclear factor kappa B (NFκB) in a number of human cancer cell lines.[8-10] The natural product **1** has also been found to facilitate tumor necrosis factor related apoptosis inducing ligand (TRAIL) induced apoptosis in human colon cancer cells (HCT-116 and HT-29).[11] The key functionalities such as phenolic-OH, aryl, vinyl and isopropylidene groups embodied in bakuchiol makes it amenable for a variety of chemical transformations. To date several reports are available wherein considerable structural modification has been done on bakuchiol for the improvement of anticancer activity.[7,10,12-14] Literature survey revealed that 3,4-dihydro-2H-benzo[e][1,3]oxazine moieties exhibited broad range of pharmacological activities including anticancer, anti-inflammatory and antiinfective[15-18] which showed their large development value and wide potential as therapeutic agents. Therefore, in continuation to our interest in structural modification of natural products for development of anticancer leads,[7,19-20] herein, we report synthesis of new 3,4-dihydro-2H-1,3-oxazine derivatives of bakuchiol by Mannich type condensation-cyclization reaction and their *in vitro* cytotoxicity evaluation against four human cancer cell lines (MIA-Pa-Ca-2, HCT-116, MCF-7 and HL-60). The mechanistic study was also carried out for the most potent analog.

Results and discussion

Chemistry

Bakuchiol **1** was isolated in preparative scale from seeds of *Psoralea corylifolia* and taken for structural modification. The 3,4-dihydro-2H-benzo[e][1,3]oxazines analogs (**2**-**26**) were prepared by treatment of **1** with 37% formaldehyde (w/v) and respective primary amines in tetrahydrofuran (THF) *via* Mannich type condensation-cyclization reaction (scheme 1) in good to excellent yields. Structures of all the derivatives were

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