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Research paper

Synthesis and biological evaluation of novel bavachinin analogs as anticancer agents

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ABSTRACT

A library of 28 analogs of bavachinin including aliphatic and aromatic ethers, epoxide, chalcone, oxime, semicarbazide, oxime ether and triazole derivatives have been synthesized and evaluated for cytotoxicity against four different human cancer cell lines. Bio-evaluation studies exhibited better cytotoxic profile for many analogs compare to bavachinin. Best results were observed for a 1,2,3-triazole analog (**17i**) with IC_{50} values 7.72, 16.08, 7.13 and 11.67 μM against lung (A549), prostate (PC-3), colon (HCT-116) and breast (MCF-7) cancer cell lines respectively. This analog showed three and four fold improvement in cytotoxicity against HCT-116 and A549 cell lines than parent molecule (**1**). Structure activity relationship (SAR) study for all synthesized analogs was carried out. Further, mechanistic study of the lead molecule (**17i**) revealed that it inhibits colony formation and *in vitro* migration of human colon cancer cells (HCT-116). Also, it induced the morphological changes and mediated the apoptotic cell death of HCT-116 cells with perturbance in mitochondrial membrane potential (MMP) and PARP cleavage.

1. Introduction

Flavanoids are one of largest classes of polyphenolic compounds that occur naturally in plants which possess broad spectrum of biological activities and are considered as suitable therapeutic agents against cancer. They generally possess a phenylbenzopyrone structure (C6-C3-C6) consisting of two aromatic rings, A and B connected by a central pyran ring C. The saturation level and opening of central pyran ring categorize various classes of flavonoids namely flavones, flavonols, isoflavones, flavanols, flavanones and flavanonols [1,2]. Unlike other flavonoids, flavanones like bavachinin **1**, hesperetin **2** and naringenin **3** (Fig. 1) have been potential sources to search for new leads in the area of cancer therapy [3,4].

The seeds of *Psoralea corylifolia* are major source of bavachinin [5] and exhibit diverse pharmacological activities including anticancer [3], PPAR agonist [6], anti-inflammatory [7], anti-alzheimer [8] and immunomodulatory [9]. Cytotoxic effects of bavachinin have also been studied on various cancer cell lines [3,10] and possess 20 S proteasome inhibitory activity that inhibits the signaling action of NFκB leading to cell death *via* apoptosis [11]. Beside this bavachinin also inhibited *in vitro* migration of human KB cells and during *in vivo* studies in nude mice with KB xenografts, it significantly reduced tumor volume and CD31 expression [12]. Bavachinin **1** nucleus is capable of undergoing suitable chemical transformation studies at various key positions available on molecule (Fig. 1). Several bavachinin derivatives have synthesized and reported for their different biological activities. Chen et al. prepared bavachinin derivatives **4** and **5** *via* biotransformation to study their T cell differentiation effects [13]. Dai et al. reported anticancer activity of bavachinin and its enzymatically synthesized glucoside **6** [14] while Du et al. reported PPAR-γ agonist activity of several bavachinin analogs among which compounds **7** and **8** were found as most potent derivatives [15] (Fig. 2). However, further investigation is desired to develop the potent anticancer agents based on bavachinin.

Therefore, the natural product bavachinin was isolated in bulk quantity from the seeds of *Psoralea corylifolia* for synthesis of its

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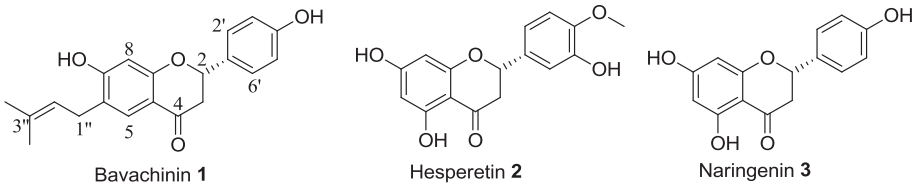

Fig. 1. Structures of some flavanones exhibiting anticancer activity.

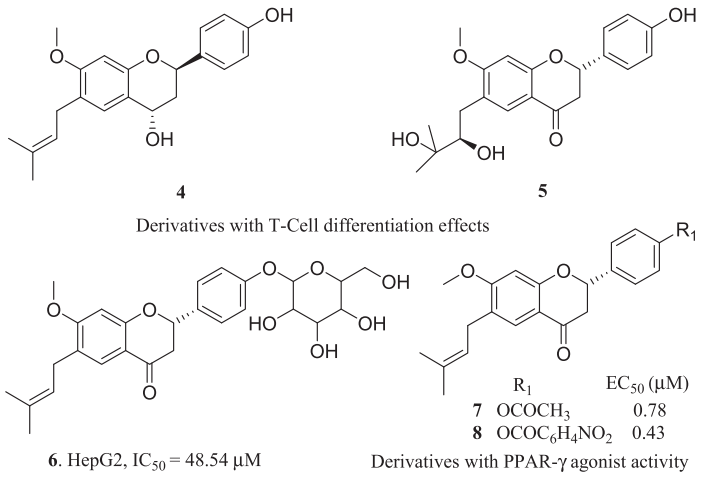

Fig. 2. Structures of various bavachinin derivatives.

analogs being our interest in isolation and structural modification of natural products for drug discovery of potent analogs in the area of anticancer [16–19]. Further the synthesized analogs were screened for cytotoxicity against four different human cancer cell lines (A549, PC3, HCT-116 and MCF-7). The most active compound was taken further to study its cytotoxic mode of action.

2. Results and discussion

2.1. Chemistry

Bavachinin **1** was isolated in gram quantities from the seeds of *P. corylifolia* and was used for structural modification studies. The configuration at C-2 an asymmetric center in the molecule was observed (*S*) based on NOESY (Fig. S1) which was also confirmed by comparing the observed specific rotation value $[\alpha]_D = -20$ (c = 1.0, $CHCl_3$) with literature [5,20]. Different analogs of bavachinin **1** were synthesized with modifications at ring A, B, C and prenyl chain of the molecule (Fig. 3) as shown in Schemes 1 and 2. Aliphatic ether

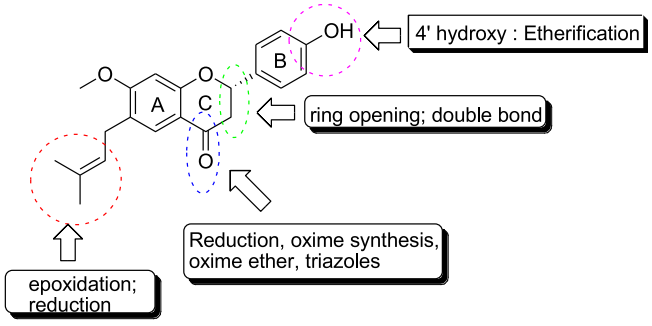

Fig. 3. Design rationale of target anticancer compounds.

analogs of bavachinin (**9a-e**) were synthesized by reacting **1** with appropriate alkyl halides in acetone in the presence of potassium carbonate as base [21]. Analogs **9f-i**, aromatic ethers of bavachinin were synthesized through Chan-Lam coupling by reacting **1** with various aryl boronic acids in DCM in the presence of copper acetate and pyridine [22]. Epoxide analog of bavachinin (**10**) was synthesized by reacting **1** with *m*-chloroperbenzoic acid (*m*-CPBA) in DCM as per earlier report [23]. NOESY spectra (Fig S2) is provided in supporting information. Compound **11**, chalcone analog of **1** was obtained by treating it with sodium hydride in ethanol. Compound **12**, carbonyl reduction analog was synthesized by reacting **1** with sodium borohydride ($NaBH_4$) in methanol as per our earlier report [17] and its configuration was found 2*S*, 4*R* at C-2 and C-4 position on the basis of 2D NMR (COSY, HSQC and HMBC) experiments including NOESY (Fig S3-8). Further the configuration was also confirmed through observed specific rotation $[\alpha]_D = +19$ (c = 1.0, $CHCl_3$) which was found in comparison with literature [24]. Compound **12a**, double bond reduced product was prepared by hydrogenation of bavachinin in presence of 10% Pd/C [23]. Compounds **13** and **14**, oxime and semicarbazide analogs of bavachinin were synthesized by treating **1** with hydroxylamine hydrochloride and semicarbazide hydrochloride respectively in ethanol as solvent [25].

Bavachinin triazoles were synthesized at oxime moiety to prepare anticancer analogs in the light of literature [19,26]. For this, methyl ether of bavachinin **9a** was reacted with hydroxylamine hydrochloride to prepare its oxime analog **15**. Compound **15** was reacted with propargyl bromide in acetone in presence of potassium carbonate to furnish compound **16** which was further subjected to Cu (I) catalyzed 1,3-dipolar cycloaddition reaction (click chemistry) using various substituted aromatic azides to provide 1,2,3-triazole derivatives **17a-k** in excellent yields [27] (Scheme 2). To confirm the configuration of C=N double bond in triazole analogs **17a-k**, NOESY experiment of one compound i.e. **17i** was