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Research paper

Discovery of dehydroabietic acid sulfonamide based derivatives as selective matrix metalloproteinases inactivators that inhibit cell migration and proliferation

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ABSTRACT

A series of dehydroabietic acid (DHAA) dipeptide derivatives containing the sulfonamide moiety were designed, synthesized and evaluated for inhibition of MMPs as well as the effects of *in vitro* cell migration. These compounds exhibited relatively good inhibition activity against MMPs with IC_{50} values in low micromolar range. A docking study of the most active compound **8k** revealed key interactions between **8k** and MMP-3 in which the sulfonamide moiety and the dipeptide group were important for improving activity. It is noteworthy that further antitumor activity screening revealed that some compounds exhibited better inhibitory activity than the commercial anticancer drug 5-FU. In particular, compound **8k** appeared to be the most potent compound against the HepG2 cell line, at least partly, by inhibition of the activity of MMP-3 and apoptosis induction. The treatment of HepG2 cells with compound **8k** resulted in inhibition of *in vitro* cell migration through wound healing assay and G1 phase of cell cycle arrested. In addition, **8k**-induced apoptosis was significantly facilitated in HepG2 cells. Thus, we conclude that DHAA dipeptide derivatives containing the sulfonamide moiety may be the potential MMPs inhibitors with the ability to suppress cells migration.

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1. Introduction

Cancer metastasis, the essential hallmarks of cancer, is initiated by migration and invasion of cancer cells [1]. Metastasis has been a major impediment to effective cancer treatment with conventional chemotherapeutic drugs and has been the leading cause of cancer-associated death in several cancers including liver, breast and lung cancers. Notably, several proteins play important role to initiate or repress cancer metastasis such as matrix metalloproteinases (MMPs) [2]. Therefore, targeting pivotal inhibition of metastasis-associated proteins or signaling pathways are the critical point for efficient cancer treatment.

The MMPs, which play a crucial role in many normal physiological functions, are a group of structurally related zinc-dependent endopeptidases involved in the degradation of extracellular matrix (ECM) components and a diverse array of non-ECM proteins [3]. Recent studies revealed that MMPs frequently up-regulated in cancer cells, facilitated migration and have a significant effect on the ability of cancer cells to grow in a secondary site [4–6]. It is also well-known that MMPs participate in several steps of cancer progression, including cancer cell growth, apoptosis, migration, invasion, and angiogenesis, thereby playing a key role in the development of human breast, colon, thyroid, lung, and prostate cancers [7,8]. In particular, stromelysin-1 (MMP-3) has been the subject of intense research due to its presence in the vicinity of melanomas and metastatic tumors associated with breast cancer; it also functions as an active precursor to the action of other endopeptidases [9–11]. Therefore, MMPs could serve as promising targets for the development of new therapeutics to suppress cancer

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metastasis and down-regulation the expressions of MMPs may have benefits in enhancing the efficacy of anticancer drugs. Some MMPs inhibitors have been employed as sensitizers in the established cancer therapy over recent years. Despite evident and convincing data, indicating that MMP inhibitors have a high potential in clinical trial for cancer [12], their use in the clinic has been stalled due to their limited proof of efficacy and their adverse side effects, which might be related to insufficient target validation [13–15]. In this reason, gaining selectivity between the metalloproteases without decreasing inhibitory potency is a primary goal in the development of MMP inhibitors, which would help to improve their efficacy and avoid undesirable side effects.

Dehydroabietic acid (DHAA) is a naturally occurring diterpenic resin acid and has been found to exhibit a broad spectrum of biological activities, especially anticancer activities [16–19]. Moreover, previous research has shown that DHAA derivatives could act at various stages of tumor development to inhibit tumor initiation and promotion, as well as to induce tumor cell differentiation and apoptosis [20–22]. These findings suggest that DHAA may be a promising starting tool for the discovery of new anticancer agents. On the other hand, sulfonamides are currently an important group of organic compounds and have been reported for potent antitumor activity against numerous types of cancers [23,24]. Derivatives containing sulfonamides moiety have been widely used as MMPs or carbonic anhydrase inhibitors, some of which are already in clinical trial [25–28] (Fig. 1). Also, from the literature survey it was found that aryl sulfonamides might act as antitumor agents through several mechanisms [29]. Furthermore, peptides, which are among the most versatile bioactive molecules, have been reported to act as the inhibitors of some proteins and to exert their action by binding to membrane receptors [30–32]. In the present work, we designed and synthesized a series of DHAA dipeptide sulfonamides derivatives as selective MMPs inhibitors which suppress the migration of liver cancer cells. A docking analysis using the crystal structure of the MMP-3 was performed to clarify the binding mode of the designed inhibitors. Moreover, growth inhibitory effects of these compounds were evaluated against four human tumor cell lines. The migration inhibition, apoptosis inducing effects and cell cycle arrest in HepG2 cells by the representative target compound **8k** was also investigated.

2. Results and discussion

2.1. Chemistry

The general procedures for the synthesis of DHAA dipeptide sulfonamides derivatives are shown in Scheme 1. As shown in Scheme 1, compound **3** was synthesized by the treatment of phenylalanine **1** with phthalic anhydride (**2**) in the presence of acetic acid according to the literature [33]. Compound **4** was then obtained by the condensation of compound **3** and oxalyl chloride, followed by treatment with series of aromatic primary amines. Compounds **5** were synthesized by the treatment of compounds **4** with hydrazine hydrate in the presence of ethanol at room temperature. Compound **6** was synthesized by the treatment of dehydroabietic acid with vitriol at room temperature [34]. Compound **6** was treated with oxalyl chloride to offer compound **7**. Compounds **8** were finally acquired by the condensation of compound **7** and compounds **5** (1:2) for 18 h in the presence of triethylamine at room temperature. Compounds **9** were finally acquired by the condensation of compound **7** and compounds **5** (1:1) for 6 h in the presence of triethylamine at room temperature. The structures of target compounds **8** and **9** were then confirmed by ^{1}H NMR, ^{13}C NMR and high resolution mass spectrometry (HRMS).

2.2. Biological evaluation

2.2.1. In vitro MMPs assays

The synthesized DHAA derivatives containing sulfonamide dipeptide moiety were assayed *in vitro* against human recombinant MMP-3, MMP-8 and MMP-9 using synthetic fluorogenic substrates according to a previously reported procedure [35]. The broad spectrum inhibitor CGS-27023A was taken as positive control. The IC_{50} values obtained in the performed *in vitro* inhibition assays of DHAA derivatives are summarized in Table 1.

As shown in Table 1, the newly synthesized DHAA derivatives are potent MMPs inhibitors, with IC_{50} values mostly in micromolar or submicromolar levels. As can be seen from Table 1, the sulfonic acid group in compounds **9** formed a sulfonamide to give compounds **8**, substantially increased MMPs inhibitory activities, which may be due to sulfonamides derivatives were more active than

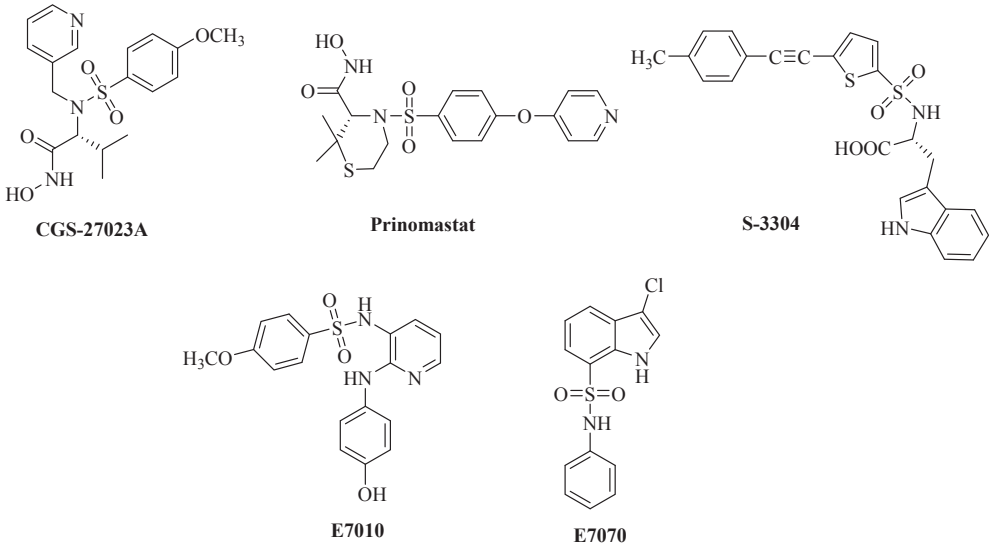

Fig. 1. Chemical structures of sulfonamide-based MMP and CA inhibitors.

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