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Carbonic anhydrase inhibitory properties of novel benzylsulfamides using molecular modeling and experimental studies

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ABSTRACT

In this study, a series of sulfamoyl carbamates and sulfamide derivatives were synthesized. Six commercially available benzyl amines and BnOH were reacted with chlorosulfonyl isocyanate (CSI) to give sulfamoyl carbamates. Pd–C catalyzed hydrogenolysis reactions of carbamates afforded sulfamides. The inhibition effects of novel benzylsulfamides on the carbonic anhydrase I, and II isoenzymes (CA I, and CA II) purified from fresh human blood red cells were determined by Sepharose-4B-L-Tyrosine-sulfanilamide affinity chromatography. In vitro studies were shown that all of novel synthesized benzylsulfamide analogs inhibited, concentration dependently, both hCA isoenzyme activities. The novel benzylsulfamide compounds investigated here exhibited nanomolar inhibition constants against the two isoenzymes. K_i values were in the range of 28.48 ± 0.01–837.09 ± 0.19 nM and 112.01 ± 0.01–268.01 ± 0.22 nM for hCAI and hCA II isoenzymes, respectively. Molecular modeling approaches were also applied for studied compounds.

1. Introduction

Sulfamides are beneficial organic compounds in medicinal chemistry [1]. They show a wide biological activity spectrum. For example, an injectable antibiotic doripenem (**1**) [2], anti-hyperprolactinemic agent quinagolide (**2**) [3] and anticonvulsant **3** (JNJ-26990990) [4] are small molecule drugs containing sulfamide moiety. In addition, anti-trypanosomal [5], anticonvulsant [6], smooth muscle relaxant [7], carbonic anhydrase inhibitory [8] activities of sulfamide **4** has been reported (Fig 1).

The sulfonamide group (–SO_2NH–) is present in many organic compounds that are known as potent inhibitors of the carbonic anhydrases (CA) [9,10]. They bind as anions to the Zn^{2+} ion in the enzyme active site with high affinities for CA isozymes [11]. Zn^{2+} is an essential metal and necessary for more than 300 enzymes functions. The discovery of presence of Zn^{2+} as the catalytic center of CA enzymes was found in 1939 [12]. This exploration was followed by Zn^{2+} characterization in carboxypeptidase in 1950 [13,14]. Then, a study related to analysis on coordination spheres around Zn^{2+} in existing protein crystal structures was published [15]. In this analysis, authors defined the spacer rule for native Zn^{2+} containing proteins. Recently, the general principles for the coordination of Zn^{2+} in proteins have been demonstrated in a number of scientific reports [16,17]. In most cases, Zn^{2+} is arranged by a combination of His, Glu or Asp, and Cys residues. More rarely, Zn^{2+} ion interacts with phenolic group of Tyr residue [18], and the carboxamide oxygen of Glu or Asp residues [19].

The carbonic anhydrase (CA, E.C. 4.2.1.1) is a superfamily of metalloenzymes family. CA catalyzes the interconversion of CO_2 and H_2O to bicarbonate (HCO_3^-) and protons (H^+) using a metal hydroxide nucleophilic mechanism [20]. The sixteen human CA isozymes differ in their subcellular localization and distribution, catalytic activity. They are included in regulation of important physiological and pathological processes such as acid-base balance, respiration, CO_2 and ion transport, gluconeogenesis, bone resorption, lipogenesis, ureagenesis, and body fluid generation [21]. So far, this enzyme has been purified from a large scale of tissues, involving human erythrocytes [22].

Many chemical substances and drugs changed activities of enzyme and affect some metabolic processes. Chemicals usually activate or inhibit activities of several enzymes in vivo and effect

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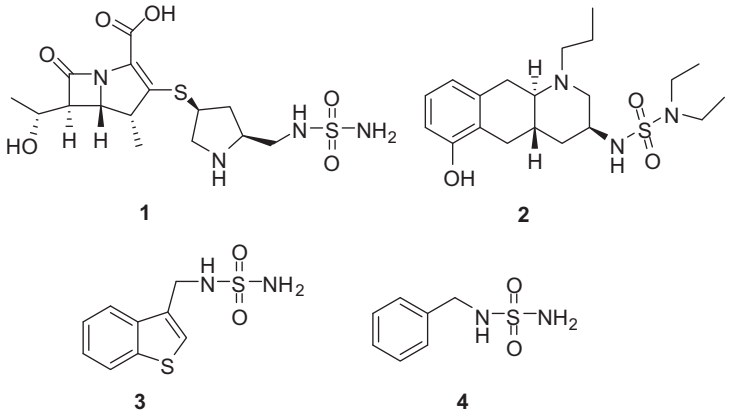

Fig. 1. Sulfamide drugs **1–3**, and biologically active sulfamide **4**.

metabolic pathways [23]. It is well known that some chemicals inhibit CA isoenzymes in different tissues [20,24,25]. So far, inhibition profiles of different chemicals, anions, cations, metal ions, phenolics, sulfamides and sulfonamides have been investigated against many CA isoenzymes. The human CA isoenzymes belong to the α-class. So far, 16 CA isozymes have been found and identified. CA plays an important role in water and ion transport and pH regulation in the kidney, eye, central nervous system, inner ear, and other systems [20–26]. Especially, CA isoenzyme inhibitors are utilized for different purposes particularly for the remedy of glaucoma, epilepsy, diuretics, antitumor agents and diagnostic tools. Hence, finding of novel CA inhibitors targeting various isoenzymes has considerably gained attention nowadays [27]. Recently it was reported that phenols, aryl or alkyl carboxylic acids, sulfonamides, sulfamoylcarbamates and sulfamides may act as CA inhibitors [28].

In our ongoing projects, we have already addressed the synthesis and CA inhibition properties of sulfamides incorporating dopamine [29], indane [20], and tetralin [24] scaffolds. Results concluded from these investigations showed that the synthetic sulfamides are good candidates for CA inhibitors. In the present study, we aimed to synthesize more simple sulfamides, and investigate their CA I, and CA II isoenzymes inhibition properties. In this context, five novel and a known sulfamides were synthesized from methoxylated benzyl amines and they were evaluated for their human hCA I, and hCA II inhibitory properties. In addition, molecular modeling approaches were used to investigate drug–receptor interactions as well as predictions of pharmacokinetic profiles of these compounds.

2. Results and discussion

2.1. Chemistry

The synthesis of sulfamide carbamates and sulfamides were started with commercially available benzylamines **5–10**. The reactions of amines in the presence of alcohols with chlorosulfonyl isocyanate (CSI) are giving sulfamoylcarbamates [20,24,29]. By the similar approach, the reactions of benzylamines **5–10** and benzylalcohol with CSI in the presence of Et_3N at 0–25 °C for 4 h yielded novel sulfamoyl carbamates **11–16** in good yields. Pd–C catalyzed hydrogenolysis reaction of carbamates is one of the most convenient procedures for the synthesis of amine related compounds [30–32]. Hence, hydrogenolysis reactions of carbamates with H_2 in the presence of Pd–C catalysis afforded a known sulfamide **18** [33], new benzyl sulfamides **17** and **19–22** with yields 68–77% respectively (Scheme 1). The structures of synthesized compounds **11–22** were characterized by ^{1}H-, ^{13}C-NMR, IR and elemental analysis techniques.

2.2. Biochemistry

Carbonic anhydrase inhibitors (CAIs) are important class of chemical or pharmaceutical agents that suppress and prevent the CA activity. The clinical usage of CAIs has been determined as antiepileptics, antiglaucoma agents, diuretics, in the management of gastric and duodenal ulcers, mountain sickness, osteoporosis, and neurological disorders [9]. Both isoenzymes (hCA I, and hCA II) inhibition profiles were extensively studied. Recently, our groups examined the interaction of both isoenzymes with melatonin [34], morphine [35], caffeic acid phenethyl ester (CAPE) [36], a series of antioxidant phenols [37], a series of phenolic acids [38], a series of natural product polyphenols and phenolic acids [39], some bromophenol derivatives [40], naturally occurring bromophenols and their synthetic derivatives [23,41], dopaminergic compounds [42], a series of sulfamides [20,24,29] and sulfonamides [22,25].

The main goal of this study was to investigate the effect of novel sulfamide carbamates **11–16** and sulfamides **17–22** at hCA I, and hCA II isoenzymes. The inhibition data related to novel sulfamide carbamates **11–16** and sulfamides **17–22** are given in Table 1. As it can be seen from the data presented in Table 1, these novel sulfamide carbamates **11–16** and sulfamides **17–22** showed effective inhibitory activity against both tested isoforms. It is well known that sulfamides have high affinity for all CA isozymes, which leads to a lack of specificity. Two sulfamide NH and NH_2 groups are slightly acidic and provide hydrogen bond donors. Considering the data in Table 1, the following results were obtained. For cytosolic hCA I isoenzyme, novel benzylsulfamides were inhibited with inhibition constants in the low nanomolar level. All of the newly synthesized sulfamide carbamates **11–16** and sulfamides **17–22** (**11–22**), which demonstrated IC_{50} values range of 212.58–577.02 nM. Also, K_i values of these novel benzylamine derivatives are around 28.48 ± 0.01–837.09 ± 0.19 nM (Table 1). Especially, Compound **13**, possessing methoxy group (-OMe) with *para*-position, was the best hCA I inhibitor (K_i: 28.48 ± 0.01 nM). On the other hand, CA II isoenzyme has very important physiological effects in cytosol and increases intraocular pressure, in the anterior uvea of the eye, leading to visual dysfunction. Conversely, the best hCA II inhibitor in benzylsulfamide series was compound **22.** This compound showed the highest inhibition activity on physiologically dominant CA II with K_i values of 112.01 ± 0.01 nM. Many studies performed on sulfamides revealed that inhibition of CA II is brought about by their ability to mimic the tetrahedral transition state when binding to catalytic Zn^{2+} settled at the CA active site [43]. K_i values of novel sulfamide carbamates **11–16** and sulfamides **17–22** were much more effective when compared to clinically used drug aceta-