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Unprotected primary sulfonamide group facilitates ring-forming cascade en route to polycyclic [1,4]oxazepine-based carbonic anhydrase inhibitors

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ABSTRACT

4-Chloro-3-nitrobenzenesulfonamide reacted cleanly at room-temperature with a range of bis-electrophilic phenols bearing an NH-acidic functionality (secondary carboxamide or pyrazole) in the *ortho*-position. This produced a novel class of [1,4]oxazepine-based primary sulfonamides which exhibited strong inhibition of therapeutically relevant human carbonic anhydrases. 2-Chloronitrobenzene did not enter a similar cyclocondensation process, even under prolonged heating. Thus, the primary sulfonamide functionality plays a dual role by enabling the [1,4]oxazepine ring construction and acting as a enzyme prosthetic zinc-binding group when the resulting [1,4]oxazepine sulfonamides are employed as carbonic anhydrase inhibitors.

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1. Introduction

Carbonic anhydrases (CAs) catalyze the reversible hydration of carbon dioxide to produce bicarbonate anion and a proton. Thus, members of this enzyme superfamily (comprising 15 isoforms in humans) are primary regulators of pH within and outside the cell [1]. Differing in catalytic activity and subsellular localizaiton, CA isoforms represent important range of biological targets with diverse therapeutic potential. In particlular, inhibitors of cytosolic CA I and II isoforms in human are used as agents to treat edema and glaucoma [2,3]. Membrane-bound brain-associated human CA IV isoform is involved in extracellular pH regulation in neurons and glial cells [4] analogously to the tumor-associated CA IX which has an important role in tumor progression, acidification and metastasis in several cancer types [5]. Inhibition of specific isoforms of CA is also being investigated as a novel approach to treat epilepsy [6] and obesity [7]. Moreover, selective inhibition of CAs in pathogenic microorganisms which are vital for survival of the latter is gaining increasing attention as a novel way to treat infectious disease [8]. This raises the importance of being able to inhibit one specific CA isoform selectively, which is a formidable task considering the similarity in structure and function of these enzymes [9].

One of the most important classes of CA inhibitors contain a primary sulfonamide functionality which acts as a zinc-binding group (ZBG) and is responsible for anchoring a small molecule inhibitor within the enzyme's active site [10]. Due to this pharmacophoric feature, even simplest primary sulfonamides (such as alkyl or benzenesulfonamides) display a weak CA inhibition. However, in order to achieve a higher affinity to a specific enzyme in the CA family, additional specific interations between the sulfonamide-tagged inhibitor scaffold and the enzyme's aminoacid residues in proximity to the prosthetic zinc ion are required [11]. Thus, variations of the inhibitor's 'tail' constitute an actively pursued approach to isoform-selective CA inhibitor disovery [12]. Both polar and lipophilic groups are acceptable motifs for the design of CA inhibitor periphery [13] as potential contacts with lipophilic and hydrophilic portions of the active site surroundings are possible [14] (see Fig. 1).

Recently, we developed a unfied approach to constructing polycyclic [1,4]oxazepines **1** (as well as their thia-isosteres) that is

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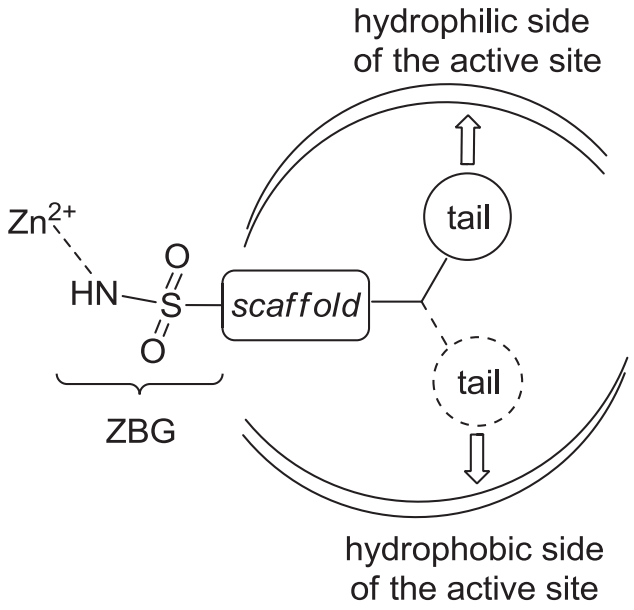

Fig. 1. Schematic representation of a primary sulfonamide CA inhibitor within CA active site.

based on a simple, K_2CO_3-promoted cyclocondensation of a phenol bearing an N—H acidic functionality in the *ortho*-position (**2**) and a bis-electrophilic aromatic partner (**3**) vicinally substituted with two leaving groups (Hal/Hal or Hal/NO_2) and, often, additionally activated by an electron-withdrawing substituent (e. g., NO_2, CO_2R). The reaction was shown to involve two acts of aromatic nucleophilic substitution (S_NAr) intermitted by a Smiles rearrangement (Fig. 2) [15–22].

This sequence of events is thought to ensure that the phenoxide anion is the acting nucleophile in the both S_NAr, which is crucial for the successful formation of [1,4]oxazepine ring. In the context of our recent involvement in the development of heterocycle-substituted primary aromatic sulfonamides as isoform-selective CA inhibitors [23–26], we thought it of interest to incoprorate an unprotected primary sulfonamide functionality into the structure of **3** where it would activate the latter toward the S_NAr steps due to its strongly electron-widrawing character. Potentially, such an approach carried the risk of the resulting bis-electorphilic aromatic partner **3a** being capable of *N*-arylating the SO_2NH_2 functionality under basic conditions, which would lead to a homocoupling of **3a** [27]. Additionally, this *NH*-acidic functionality cleates an additional site for intramolecular proton transfer, which may interfere with the intricate reactive species interplay shown in Fig. 2. In this Communication, we report on the successful realization of this strategy despite the foreseeable obstacles.

2. Results and discussion

In order to explore the viability of the strategy outlined above, we selected a set of secondary carboxamide- and *NH*-pyrazole-substituted bis-nucleophilic substrates **2a–h**. Carboxamides **2a–d** were prepared by a direct, CDI-promoted amidation of salycilyc acid [15]. Pyrazolyl phenols **2e–h** were synthesized via the Claisen condensation of *o*-hydroxyacetophenone with the corresponding ethyl acetates followed by treatment with hydrazine hydrate, as described previously (Scheme 1) [15,17].

To our delight, cyclocondensation of compounds **2a–h** with 4-chloro-3-nitrobenzenesulfonamide (**3a**) proceeded smoothly in anhydrous DMF in presence of anhydrous (freshly calcinated) K_2CO_3 at room temperature overnight (Scheme 2). Examination of the reaction mixtures by TLC revealed the presence of a major product (**1a–h**) along with a small amount of lower polarity products. The latter were easily separated from **1a–h** in the course of chromatographic purification of the latter and were confirmed by ^{1}H NMR to be a mixture of **3a** self-condensation products as they displayed no signals attributable to **2a–h**. The isolated yields of **1a–h** were generally good to excellent. Somewhat lower yields were most likely caused by the minor self-condensation of **3a** and were not optimized further. The regiochemistry of products **1a–h** is determined by the Smiles rearrangement occurring, without exception, in all cases studied previously [14–21], in the interim of the two of the S_NAr events leading to the [1,4]oxazepine cycle formation (*vide supra*). In this case, the initial S_NAr involves the displacement of the more labile chlorine and the closing S_NAr event is what is often termed 'denitrocyclization' [28]. What is particularly interesting in the context of present study, the primary sulfonamide group is not only an important pharmacophoric element that endows the resulting [1,4]oxazepines with CA inhibitory activity. It is also required for the base-promoted cyclocondensation of **3a** with bis-nucleophilic partners **2a–h** to occur. Indeed, even prolonged (48 h) heating (120 °C) of the latter in combination with 2-chloronitrobenzene (lacking the electron-withdrawing SO_2NH_2 group) in the presence of anhydrous K_2CO_3 produced no cyclocondensation product.

Compounds **1a–h** were tested for their CA inhibitory activity using a stopped-flow CO_2 hydration assay [29], against a panel of human carbonic anhydrases *h*CA I, II, IV and IX. The first two isoforms are cytosolic enzymes, a valid drug targets for glaucoma

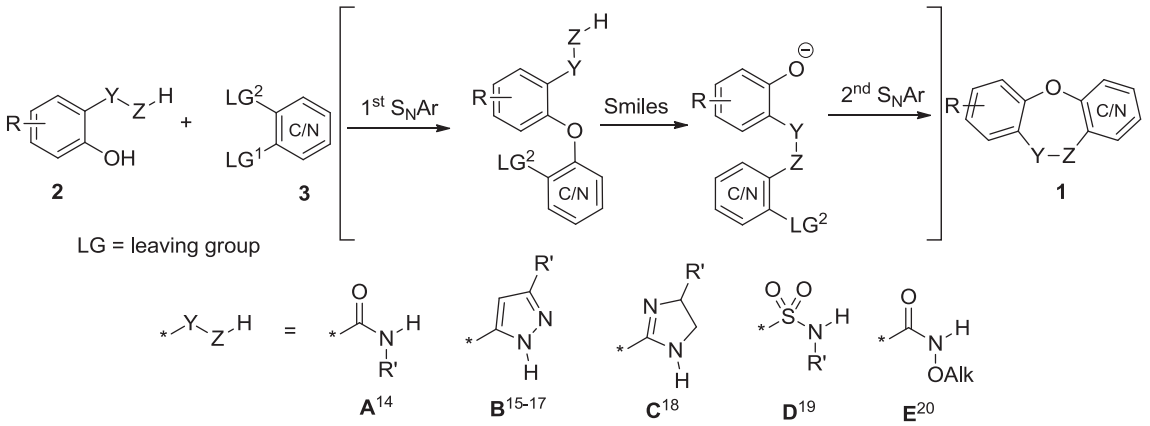

Fig. 2. General approach to polycyclic [1,4]oxazepines **1** [14–21].

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