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Synthesis of 1-oxa-9-azaspiro[5.5]undecane-9-sulfonamides bearing a diverse molecular periphery and a rare zinc-binding group for carbonic anhydrase interrogation

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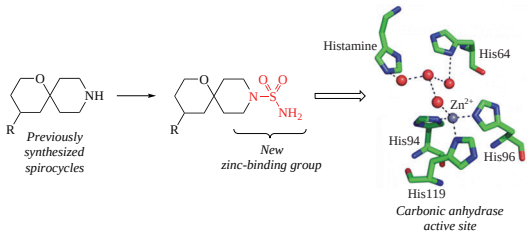
A fundamentally novel type of molecular probes for the recognition by carbonic anhydrase zinc enzymes which constitute promising target family in diverse therapeutic areas has been designed and synthesized. To the best of our knowledge, these molecular tools of 1-oxa-9-azaspiro[5.5]-undecane-9-sulfonamide chemotype for the first time combine in their structure diversely substituted spirocyclic piperidines and an aminosulfamoyl moiety.



Keywords: 1-oxa-9-azaspiro[5.5]undecanes, spiro compounds, sulfamide zinc binding group, carbonic anhydrases, chemical diversity, druglikeness.

We dedicate this article to the anniversary of the brilliant organic scientist Irina Petrovna Beletskaya.

Carbonic anhydrases (CAs) are Zn^{II} metalloenzymes (EC 4.2.1.1) which catalyze the fundamental reaction of reversible hydration of carbon dioxide to bicarbonate anion, the process which is central to the pH control, ion transport and fluid secretion.[1] Hyperactivity of certain CA isoforms[2] under pathological conditions makes these proteins targets for small-molecule carbonic anhydrase inhibitors (CAIs).[3] Currently, CAIs find applications in the clinic for the treatment of glaucoma,[4] idiopathic intracranial hypertension,[5] high-altitude sickness,[6] congestive heart failure,[7] peptic ulcers[7] and epilepsy.[9] An emerging investigational application of inhibitors of human (*h*) CA IX and XII isoforms[10] is in therapy of cancer.[11,12] The most advanced therapeutic agents of this class are the *h*CA IX-selective drug SLC-0111[13] currently undergoing phase Ib clinical trials for neoplasms overexpressing *h*CA IX[14] and non-selective inhibitor E7070 (indisulam) developed by Eisai Co., Ltd. which has successfully completed phase II clinical trials.[15]

Therefore, the discovery of new chemotypes capable of inhibiting various CAs continues being a significant goal. Since CAs contain a Zn^{2+} ion in its active site, this determines the zinc-binding nature of the pharmacophoric groups for its targeting. Indeed, most of the CAIs in clinical investigation (SLC-0111 and E7070) and clinical use (*e.g.*, acetazolamide, methazolamide, dorzolamide, brinzolamide and zonisamide) are primary sulfonamides in which the sulfonamide group coordinates to the prosthetic zinc ion while the molecular periphery is the critical determinant of the inhibitor's potency and isoform selectivity (Figure 1).

The sulfamide group (sulfone moiety connected to two nitrogen atoms) as opposed to sulfonamides (sulfone group is connected to carbon and nitrogen atoms) are by far less explored as zinc-binding groups for CA interrogation.[16,17] At the same time, introduction of a nitrogen atom in lieu of a carbon atom is likely to have not only a bearing on the coordinating ability of the sulfamide group but will also reflect positively on the compounds' physicochemical profile, in particular, its aqueous solubility. Additional significant void in the chemical space of

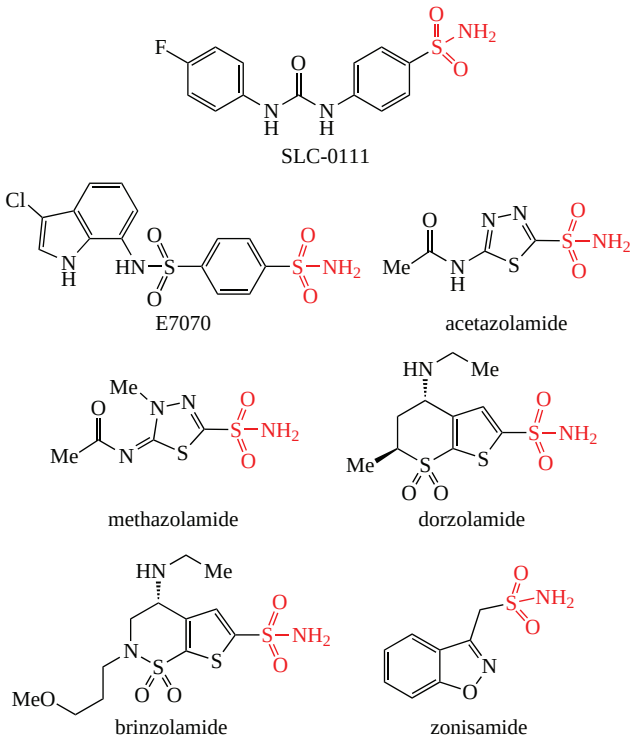


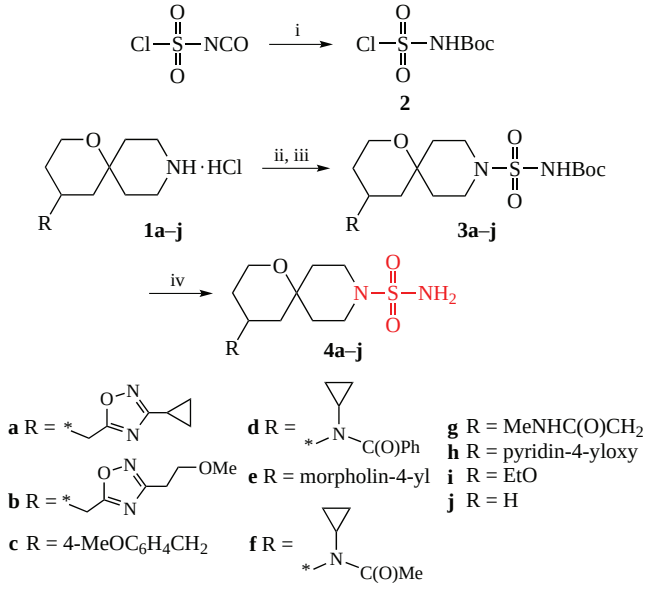
Figure 1 CAIs currently in clinical development and clinical use.

known CAIs are spirocycles.[18] While the majority of known CAIs are flat aromatic carba- and heterocycles (benzenesulfonamides and their heterocyclic analogues), the high-F_{sp3}, three-dimensional character of spirocyclic moieties is largely overlooked in the CAI design. This is unfortunate considering the widely accepted privileged character of spirocycles in the contemporary drug design.[19] Furthermore, incorporating spirocycles into investigational drugs makes the latter more 'natural-like' considering the omnipresence of such frameworks in natural products.[20]

In this work, we aimed to fill that void by combining both of the 'unjustly underutilized' motifs, *i.e.*, a spirocycle and the sulfamide linkage within the same molecule and thus create a novel set of compounds for carbonic anhydrase interrogation. To this end, we turned to our arsenal of 1-oxa-9-azaspiro[5.5]-undecanes **1a**–**j** (Scheme 1) which we previously successfully employed in the synthesis of free fatty acid receptor 1 agonists (**1a**–**c**,**i**,**j** in ref. 20; **1e**,**g**,**h** in ref. 21; **1d**,**f** in ref. 22) as well as, more recently, in the design of efficacious antibacterial derivatives of ciprofloxacin.[23] We considered these shelf-stable spirocyclic amine hydrochloride salts a diverse enough set of spirocyclic piperidines to be converted into the target sulfamides.

With the arsenal of building blocks **1a**–**j** at hand, we proceeded converting them into the target sulfamides (see Scheme 1). Commercially available chlorosulfonyl isocyanate was reacted with *tert*-butyl alcohol in dichloromethane at 0 °C. The resulting *tert*-butyl *N*-(chlorosulfonyl)carbamate **2** was reacted with building blocks **1a**–**j** in the presence of excess triethylamine to scavenge two equivalents of liberated HCl. Finally, after brief fractionation on the pad of silica, the intermediate Boc-protected derivatives **3a**–**j** were treated with 4 M HCl in 1,4-dioxane to remove the Boc group. Thus, target spirocyclic sulfamides **4a**–**j** were obtained in modest to good yields over three steps (see Scheme 1).

Analysis of key molecular characteristics defining druglikeness, solubility and prospects of compound's absorption through the gastrointestinal tract was performed from compounds **4a**–**j** using swissadme.ch online tool (Table 1). All ten compounds strictly conform to the rules of druglikeness, show optimum lipophilicity, zero violations of the Lipinski rule of five[24] and are predicted to be soluble in aqueous medium which is likely



Scheme 1 *Reagents and conditions*: i, Bu^{t}OH, CH_2Cl_2, 0 °C, 1 h; ii, $ClSO_2NHBoc$ **2**, Et_3N (3 equiv.), CH_2Cl_2, room temperature, 18 h; iii, aqueous workup, flash chromatography; iv, 4 M HCl in 1,4-dioxane, 0→20 °C, 18 h. Compounds **4e**,**h** were isolated as hydrochlorides.

Table 1 Molecular characteristics of compounds **4a**–**j**.[a]

Compound	M_w	log*P*	Solubility
4a	336.4	–2.75	Yes
4b	373.5	1.39	Yes
4c	354.5	1.89	Yes
4d	393.5	1.47	Yes
4e	319.4	0.02	Very soluble
4f	331.4	0.34	Very soluble
4g	305.4	–0.04	Very soluble
4h	327.4	0.66	Yes
4i	278.4	0.47	Very soluble
4j	234.3	0.40	Very soluble

[a] For all compounds, gastrointestinal absorption is high, and the Lipinski violations are 0.

connected to their being predicted to absorb well in the gastrointestinal tract.

In summary, we have designed and synthesized a fundamentally novel type of molecular probes for the recognition by carbonic anhydrase zinc enzymes which constitute promising target family in diverse therapeutic areas. To the best of our knowledge, these molecular tools for the first time combine in their structure diversely substituted spirocyclic piperidines and an aminosulfamoyl moiety which diversifies them from the so far published potential carbonic anhydrase inhibitors. Biological profiling of these compounds against a panel of carbonic anhydrases is scheduled for the near future. The results of this investigation will be reported in due course.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.013.

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