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Letter

Inhibition Profiles of Some Novel Sulfonamide-Incorporated α-Aminophosphonates on Human Carbonic Anhydrases

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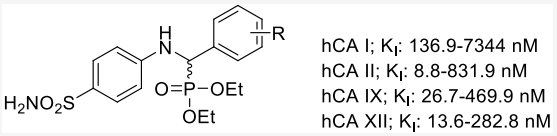
ABSTRACT: A series of hitherto unknown sulfonamide-incorporated α-aminophosphonate derivatives were synthesized through the one-pot, two-step $FeCl_3$-catalyzed coupling of 4-aminobenzenesulfonamide with the appropriate benzaldehydes and diethyl phosphite. The new sulfonamides inhibition studies were performed on four carbonic anhydrase isoforms, i.e., the cytosolic human (h) hCA I and II (off-targets) as well as transmembrane cancer-related hCA IX and XII (targets). Among the synthesized compounds, derivative **23** resulted in the most selective compound against both cancer-associated isoforms over the off-target hCA I (hCA I/IX = 78; hCA I/XII = 458) and hCA II (hCA II/IX = 10; hCA II/XII = 56) and the binding mode of both enantiomers *R* and *S* was investigated *in silico*.



KEYWORDS: *Carbonic anhydrases, Tumor-related isoforms, Sulfonamides, α-Aminophosphonates, Tail approach, Docking, In silico*

The carbonic anhydrases (CAs, EC 4.2.1.1) belonging to a superfamily of metalloenzymes that play a vital role in various pathological processes such as respiration, pH balance, and secretion of electrolytes among a host of other functions;[1] however, abnormal levels and/or activities of these enzymes have often been associated with many human disease states such as glaucoma, obesity, osteoporosis, neurological disorders, cancer, *etc.*[2] Therefore, targeting of CAs can be and is exploited as one of the important therapeutic approaches to reduce its hyperactivity in relevant disorders.[3] However, a general problem in the field of drug design of CA inhibitors (CAIs) is selectivity.[4] So far, 15 human CA isoforms have been identified,[5] which despite their different catalytic activity, localization in tissues, and subcellular localization, their active site and overall fold are very similar. Therefore, it is the greatest challenge to selectively inhibit a specific isoform over the others.

Needless to say, primary sulfonamides are the oldest and still the main class of CAIs (Figure 1).[6,7] In this family of CAIs, benzenesulfonamide derivatives are the most explored scaffolds, and in general, they behave as very good CAIs but are not selective, limiting their potential. In order to bypass this limitation, the "tail approach" has emerged as a powerful strategy to obtain selective CAIs.[8] This approach consists in appending one or more "tails" to the aromatic ring, leading to an elongated molecule that will be able to interact with the amino acid residues located at the middle and outer rims of the enzymatic cavity, which are the regions with the lowest homology sequences among the different isoforms.[9] Amino acids are among the most popular groups, which were widely used as tail moieties that besides improving the selectivity of action of inhibitors also increase their water solubility.[10]

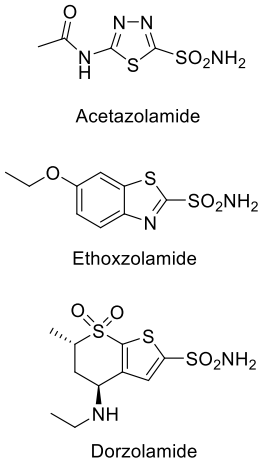


Figure 1. Selected examples of commercialized sulfonamide-based CAIs.

The α-aminophosphonates are important analogues of α-amino acids, known to have high cell permeability[11] and important roles in medicinal chemistry due to diverse biological activities such as antifungal[12] antibacterial,[13] antiviral,[14] antioxidant,[15] anticancer,[16] and anti-Alzheimer[17] activities. Therefore, appending this unique organophosphorus

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structural motif at the aromatic ring periphery of benzenesulfonamide derivatives may afford opportunities for the development of selective CAIs.

With the aim to enrich the knowladge on carbonic anhydrase inhibitors and in continuation of our works on this field,[18] in this paper we report the design and synthesis of a panel of novel sulfonamide-incorporated α-aminophosphonates by Kabachnik–Fields reaction. Inhibitory activity of prepared compounds on the cytosolic isoforms hCA I and II, and the transmembrane, cancer-associated isoforms hCA IX and XII were studied (Figure 2).

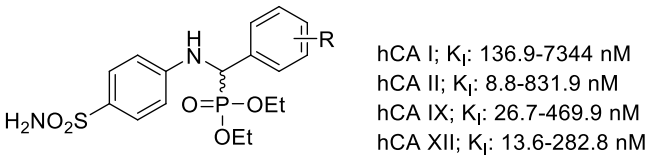


Figure 2. General structure of sulfonamides discussed in the paper.

The preparation of sulfonamide-incorporated α-aminophosphonates **20–34** was performed by following the synthetic scheme illustrated in Table 1 and described in detail in the Experimental Protocols section in Supporting Information (SI). The protected benzenesulfonamide **2** has been synthesized by following literature procedures.[19] Reaction of this intermediate **2** with the appropriate benzaldehyde derivative **3** in the presence of a catalytic amount of $FeCl_3$ afforded the corresponding imines **4**, which by treatment with overstoichiometric amounts of diethyl phosphite led to the *N*-protected sulfonamide incorporating α-aminophosphonates **5–19**. Removal of the protecting group in the presence of hydrazine hydrate afforded the desired α-aminophosphonate derivatives **20–34**.

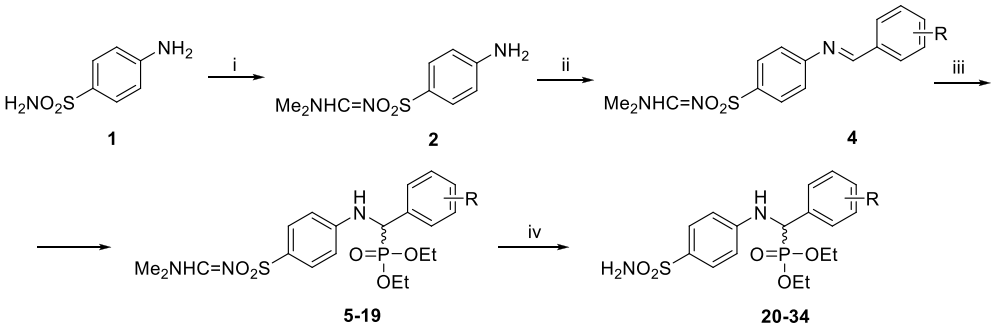
The inhibitory ability of prepared sulfonamide-incorporated α-aminophosphonates was screened on hCA I and II (off-targets) and the transmembrane, cancer-related hCA IX and XII (anticancer drug targets) using stopped-flow assay method.[20] The K_i data are summarized in Table 2 in comparison to those of the well-known carbonic anhydrase inhibitor acetazolamide (**AAZ**) as the reference drug.

Based on the inhibition data (Table 2), the following structure–activity relationship (SAR) can be drawn:

(i) The cytosolic off-target isoform hCA I was moderately to poorly inhibited by the tested compounds with K_i values in the range of 136.9–7344 nM. Indeed, all of the synthesized compounds were less active than **AAZ** (K_i of 250 nM), except compounds **27**, **29**, and **30**, with K_i values 136.9, 162.9, and 234.0 nM, respectively. The results clearly indicated that the inhibitory activity of the newly developed sulfonamides against this isoform was strongly dependent on the electronic effects of the substituent on the phenyl ring. Generally, electron-withdrawing groups (e.g., NO_2, F, Cl, Br) at any position of the phenyl ring induced higher inhibitory activities compared to electron-donating groups (e.g., Me, OMe, SMe).

(ii) The other off-target hCA II was potently inhibited by the compounds (**25–31**) substituted with electron-

Table 1. Preparation of Sulfonamide-Incorporated α-Aminophosphonates 20–34[a]



1 2 4 5-19 20-34

compd	R	yield (%)[b]	compd	R	yield (%)[b]
5	4-Me	71	**20**	4-Me	56
6	4-Ph	24	**21**	4-Ph	41
7	4-OMe	66	**22**	4-OMe	51
8	4-SMe	43	**23**	4-SMe	60
9	4-F	84	**24**	4-F	67
10	4-Cl	69	**25**	4-Cl	66
11	4-Br	58	**26**	4-Br	45
12	3-F	75	**27**	3-F	37
13	3-Br	87	**28**	3-Br	31
14	2-F	65	**29**	2-F	57
15	2-NO_2	41	**30**	2-NO_2	42
16	2-OMe-6-Br	93	**31**	2-OMe-6-Br	56
17	2,5-$(OMe)_2$	57	**32**	2,5-$(OMe)_2$	69
18	3,4-$(OMe)_2$	80	**33**	3,4-$(OMe)_2$	59
19	2,4,5-$(OMe)_3$	56	**34**	2,4,5-$(OMe)_3$	63

[a]Reagents and conditions: (i) DMF-DMA (1.2 equiv), DMF, 0 °C, 1 h, 25 °C, 2 h; (ii) aldehyde (**3**, 1 equiv), $FeCl_3$ (20 mol %), dry DMF, 100 °C, 2 h; (iii) $HP(O)(OEt)_2$ (1.2 equiv), dry DMF, 100 °C, 2 h; (iv) $NH_2NH_2{\cdot}xH_2O$ (24–26%), DMF (or NMP), r.t., 1.5 h. [b]Isolated yields.

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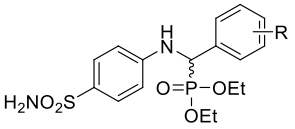
Table 2. Inhibition Data of Human CA I, II, IX, and XII with Sulfonamide-Incorporated α-Aminophosphonates 20−34 and the Standard Sulfonamide Inhibitor Acetazolamide (AAZ) by a Stopped-Flow CO_2 Hydrase Assay[20]



		K_i (nM)[a]			
compd	R	hCA I	hCA II	hCA IX	hCA XII
20	4-Me	5603	231.8	146.6	30.7
21	4-Ph	7344	561.1	224.7	27.6
22	4-OMe	4815	831.9	140.2	14.8
23	4-SMe	6231	759.7	80.2	13.6
24	4-F	424.3	616.2	91.6	45.4
25	4-Cl	528.6	33.8	141.7	71.9
26	4-Br	289.2	27.2	153.5	240.5
27	3-F	136.9	44.8	39.1	86.4
28	3-Br	436.9	72.9	61.3	282.8
29	2-F	162.9	8.8	26.7	72.0
30	2-NO_2	234.0	15.7	293.2	49.3
31	2-Br,5-OMe	312.8	26.9	346.3	197.6
32	2,5-$(OMe)_2$	516.3	55.8	469.9	58.3
33	3,4-$(OMe)_2$	707.3	65.5	117.8	38.2
34	2,4,5-$(OMe)_3$	4623	51.8	249.3	142.5
AAZ		250	12.5	25.0	5.7

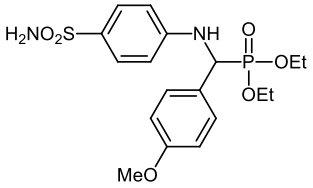
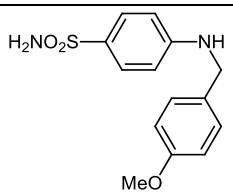
[a]Mean from 3 different assays, by a stopped-flow technique (errors were in the range of ±5−10% of the reported values).

withdrawing groups, with inhibition constants ranging between 8.8 and 72.9 nM, in a similar range as **AAZ** (K_i of 12.5 nM). However, exceptionally, compound **24**, possessing a 4-fluoro substituent displayed weak inhibitory action (K_i = 616.2 nM). The results indicated that the replacement of electron-withdrawing groups with electron-donating groups led to a decrease in the hCA II inhibition potency. As shown in Table 2, the molecules **20**−**23** bearing an electron-donating group poorly inhibited this isoform (K_i in the range of 231.8−831.9 nM). Interestingly, the installation of one more electron-donating functional group capable of forming hydrogen bonds to the electron-poor compounds, as in compounds **32** (K_i = 55.8 nM), **33** (K_i = 65.5 nM), and **34** (K_i = 51.8 nM) with respect to **22** (K_i = 831.9 nM), causes a considerable increase of the inhibitory activity against the target isoform.

(iii) The cancer-associated target hCA IX was moderately inhibited by the newly developed sulfonamides showing K_i values in the range of 26.7−469.9 nM. Among the tested compounds, **29** exhibited the best activity against this isoform. Although this compound showed almost 6- and 3-fold more selectivity toward hCA IX over hCA I and hCA XII, it was 3-fold less selective toward this isoform versus hCA II. Compound **23** was the most selective inhibitor of the hCA IX K_i value of 80.2 nM, being 78- and 9.5-fold more selective toward this isoform versus the off-targeth CA I and II, respectively. It is interesting to note that comparison studies showed that the newly developed compounds displayed considerably better inhibition and selectivity against the titled isoform compared to their phosphonate-free analogues. For instance, compound **22** inhibits hCA IX up to 6-fold compared to its phosphonate-free analogue **35**, while they exhibit almost same inhibitory activities toward the other tumor-associated isoform, hCA XII (Table 3),[21] indicating that the presence of $P(O)(OEt)_2$ fragment significantly improve the inhibitory activity and selectivity against hCA IX.

(iv) The second cancer-associated hCA XII was the most inhibited isoform among the studied ones, with K_i in the range between 13.6 and 282.8 nM. Quite different behavior is found in the inhibition profile of the hCA XII compared to the off-target hCA I and II. The SAR

Table 3. Inhibition Data of Human CA I, II, IX, and XII with Compound 22 and Its Phosphonate-Free Analogue 35

cmpd	Structure	K_I (nM)[a]			
		hCA I	hCA II	hCA IX	hCA XII
22		4815	831.9	140.2	14.8
35		>50,000	464	883	11.2

[a]Mean from 3 different assays, by a stopped-flow technique (errors were in the range of ±5−10% of the reported values).

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showed that compounds bearing an electron-donating group exhibited better activity on CA XII compared to the corresponding electron-withdrawing substituted derivatives. 4-OMe-substituted derivative **22** and the 4-SMe-substituted derivative **23** were the most promising inhibitors of the series against hCA XII, which showed considerably high selectivity toward this isoform over hCA I (**22**, hCAI/XII = 325, **23**, hCA I/XII = 458), hCA II (**22**, hCAII/XII = 56, **23**, hCA II/hCA XII = 56), and hCA IX (**22**, hCAIX/XII = 10, and **23**, hCA IX/XII = 6). Notably, **AAZ** displayed the following selectivity for hCA XII over the other isoforms considered in this study: hCAI/XII = 44, hCA II/XII = 2, and hCAIX/XII = 4. Therefore, of course, these compounds can be considered an interesting starting point for the discovery and development of novel anticancer agents.

Because three-tailed compound **23** displayed effective and selective inhibitory actions toward the target isoforms over the off-target isoforms CA I and II, both enantiomer *R* and *S* of this compound have been chosen to be submitted to docking studies to unveil the relationship between structural features and inhibition profile and to investigate their binding mode within the tumor-associated hCA IX and XII active site. The studies were extended to off-target hCA I and II for comparison. According to the literature,[22−25] the benzenesulfonamide group binds the zinc ion through the deprotonated nitrogen of the $-SO_2NH^-$ moiety (Figures 3 and 4), while the

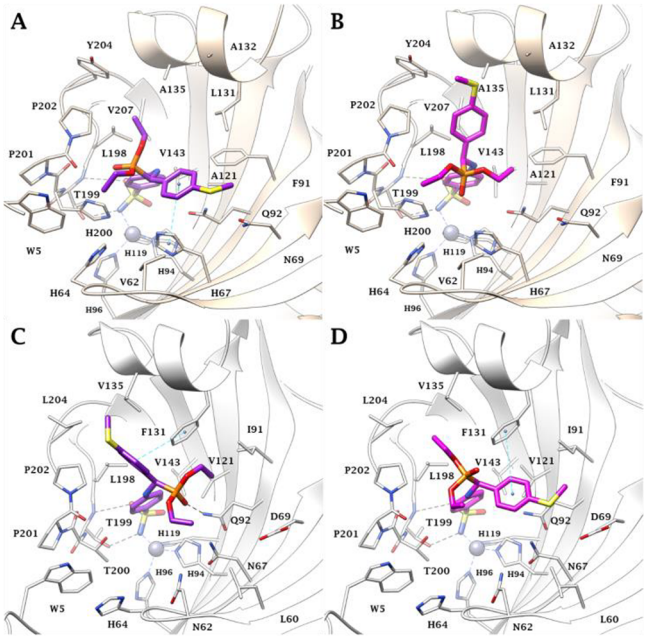

Figure 3. Predicted binding mode of ligands (*R*)-**23** (purple) and (*S*)-**23** (magenta) within hCA I (orange: A,B) and hCA II (white; C,D) active site. H-Bonds are depicted as black; $\pi-\pi$ stacking interactions are depicted cyan dashed lines.

interactions involving T199 and the sulfonamide NH^- and S═O, in H-bond distance with the hydroxyl side chain OH (O−H···N) and backbone NH (N−H···O═S) of T199, respectively, stabilize the metal coordination by the ligand. van der Waals (vdW) interactions between the aromatic ring and residues A121/V121 (hCA I/hCA II, IX, and XII,), V143,

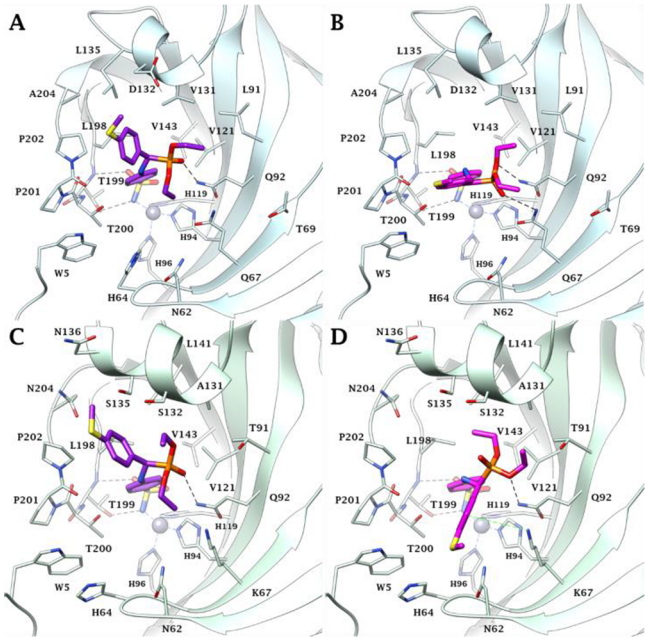

Figure 4. Predicted binding mode of ligands (*R*)-**23** (purple) and (*S*)-**23** (magenta) within the hCA IX (blue: A,B) and hCA XII (green; C,D) active site. H-bonds are depicted as black; $\pi-$cation interactions are depicted in green dashed lines.

L198, and W205 further contribute to the stabilization of the compound within the binding site (Figures 3 and 4).

Generally, the position of the 4-methylthiophenyl pendant characterizes the binding of both ligands (*R*)-**23** and (*S*)-**23** within isoforms I−II−IX and XII of the carbonic anhydrase. In hCA I, the pendant of (*R*)-**23** orients toward the hydrophilic half of the active site engaging $\pi-\pi$ stacking interaction with the peculiar H67 and vdW contacts between the ethyl tails and residues W5, H64, A135, H200, P201, P202, and V207 (Figure 3A).

The aromatic tail of the enantiomer (*S*)-**23** is turned toward the hydrophobic cleft lined by L131, A132, A135, Y204, and P202, while the two aliphatic tails lodge into a hydrophobic area defined by residues W5, H200, and P201 and F91, L131, Q92, and H67 (Figure 3B).

Due to the F91/I91, L131/F131, H200/T200, and H67/N67 hCA I/II mutations, in hCA II the 4-methylthiophenyl pendant of **23** is positioned in a different area than hCA I, orienting toward the hydrophilic or hydrophobic half of the enzyme depending on the *R* (hydrophobic) or *S* (hydrophilic) enantiomer. In both cases, the compound can engage in a $\pi-\pi$ stacking interaction with the peculiar F131 (Figure 3C,D). However, only the phosphate P═O group of enantiomer *R* is in H-bond distance with the side chain NH_2 of Q92, while the ethyl tails of (*R*)-**23** and (*S*)-**23** are in vdW contacts with N62, N67, I91, V121, and Q92 and F131, V135, P201, P202, and L204, respectively.

In the wider hCA IX active site, the hydrophobic pocket lined by L135, P201, P202, and A204 accommodates the aromatic tail of both enantiomers of ligand **23**, the phosphonate P═O moiety of (*R*)-**23** is in H-bond distance with the side chains NH_2 of Q92, while the P−O and P═O groups of (*S*)-**23** form hydrogen bonds with the side chains NH_2 of Q92 and Q67 (Figure 4A,B). In both *R* and *S* enantiomers, the two aliphatic tails undertake vdW interactions with N62, Q67, L91, Q92, V121, and V131.

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In hCA XII active site, while (*R*)-**23** allocates the 4-methylthiophenyl tails within the pocket defined by S135 P201, P202, and A204, engaging an H-bond with the phosphonate P=O and the side chain NH_2 of Q92 (Figure 4C), the aromatic pendant of enantiomer *S* is involved in a π−cation interaction with the charged NH_3^+ of the peculiar residue K67 (Figure 4D). Furthermore, the P−O group of (*S*)-**23** is in H-bond distance with side chain NH_2 of Q92, and the ethyl tails of both enantiomers are in vdW contacts with K67, T91, Q92, A131, and S132.

The analysis of the binding modes resulting from docking points out the best complementarity of the investigated compound **23** within the tumor-associated isoform active clefts. It is likely that this is related to the best inhibition profile of compound **23** against hCA IX and XII.

In summary, a series of novel α-aminophosphonates bearing the biologically active benzenesulfonamide moiety were synthesized through the condensation of 4-aminobenzenesulfonamide with an appropriate benzaldehyde, followed by hydrophosphonylation of *in situ* generated imine with diethyl phosphite. The carbonic anhydrase inhibitory capability of these compounds was evaluated against the ubiquitous hCA I and hCA II and the transmembrane hCA IX and hCA XII being overexpressed in solid hypoxic tumors and being valid targets for anticancer agents. Among all isoforms considered in this study, hCA XII was more effectively inhibited by the newly developed compounds. Compound **22** was the most promising inhibitor of the series against hCA XII, which displayed high selectivity toward this isoform over hCA I (hCAI/XII = 325), hCA II (hCAII/XII = 56), and hCA IX (hCAIX/XII = 10). Instead, derivative **23** resulted in the most selective inhibitor against both tumor-associated isoforms over the off-target hCA I (hCA I/IX = 78; hCA I/XII = 458) and hCA II (hCA II/IX = 10; hCA II/XII = 56), and the binding mode of its enantiomers *R* and *S* was investigated *in silico* within the hCA I, II, IX, and XII active site.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.3c00200.

Chemical synthesis procedures, biological assay protocols, supporting figures, docking study protocol, compound characterization, and ^1H and ^{13}C NMR spectra of all final compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors./All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

AAZ, acetazolamide; CA, carbonic anhydrase; CAIs, carbonic anhydrase inhibitors; DMF, *N*,*N*-dimethylformamide; DMF-DMA, *N*,*N*-dimethylformamide dimethyl acetal; K_i, inhibitor constant; Me, methyl; NMP, *N*-methyl-2-pyrrolidone; Ph, phenyl; SAR, structure−activity relationship; vdW, van der Waals

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