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Substituted benzene sulfonamides incorporating 1,3,5-triazinyl moieties potently inhibit human carbonic anhydrases II, IX and XII

Amrita K. Saluja [a], Meena Tiwari [a,*], Daniela Vullo [b,c], Claudiu T. Supuran [b,c,*]

[a] Shri G.S. Institute of Technology and Science, Department of Pharmacy, 23, Park Road, Indore 452003, Madhya Pradesh, India
[b] Università degli Studi di Firenze, Dipartimento di Chimica, Lab. Chimica Bioinorganica, Via della Lastruccia 3, 50019 Sesto Fiorentino (Florence), Italy
[c] Università degli Studi di Firenze, NEUROFARBA Dept., Sezione di Scienze Farmaceutiche e Nutraceutiche, Via Ugo Schiff 6, I-50019 Sesto Fiorentino (Florence), Italy

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ABSTRACT

A series of benzene sulfonamides incorporating 1,3,5-triazinyl moieties were synthesized using cyanuric chloride as starting material. Inhibition studies against human carbonic anhydrase (hCA, EC 4.2.1.1) isoforms I, II (cytosolic) and IX, XII (transmembrane, tumor-associated) isoforms were performed with the new compounds. hCA I was modestly inhibited (K_Is in the range of 87 nM–4.35 μM), hCA II was moderately inhibited by most of the new compounds (K_Is in the range of 12.5–130 nM), whereas the tumor associated isoforms were potently inhibited, with K_Is in the range of 1.2–34.1 nM against hCA IX and of 2.1–33.9 against hCA XII, respectively. Docking studies of some of the new compounds showed an effective binding mode within the enzyme active site, as demonstrated earlier by X-ray crystallography for structurally-related sulfonamides incorporating 1,3,5-triazinyl functionalities.

Carbonic anhydrases (CA, E.C.4.2.1.1) are ubiquitous metalloenzymes that catalyze a simple reaction, the conversion of CO_2 to bicarbonate ion and a proton.[1] They are involved in various physiological and pathological processes, such as gluconeogenesis, lipogenesis, ureagenesis and tumorigenicity, serving as an important target for designing drugs useful in diseases like glaucoma, obesity, epilepsy and cancer.[1–4] CA inhibitors (CAIs) are well established drugs as diuretics and antiglaucoma agents, but recent research has shown that several CA isozymes are drug targets for epilepsy, cancer and infective diseases.[2] CA II is responsible for increasing sodium bicarbonate secretion in the anterior uvea of the eye leading to visual dysfunctioning and glaucoma.[5] Tumour hypoxia, through hypoxia inducible factor 1 (HIF-1), is involved in the regulation of expression of several genes involved in pH regulation, glucose metabolism and angiogenesis, among which the tumor-associated isoform CA IX. Overexpression of CA IX contributes to acidification of the extracellular tumor pH, enhancing tumorigenesis and metastatic spread.[6]

Sulfonamide and sulfamate CAIs were reported to show substantial anti-glaucoma as well as anti-tumour activity in vitro and in vivo, thus constituting interesting leads or new therapeutic approaches, when targeting either CA II (for the antiglaucoma action) or CA IX/XII (for the antitumor activity).[6,7] We reported earlier that incorporation of a 1,3,5-triazine moiety in 4-aminobenzene sulfonamide scaffold leads to compounds with enhanced efficacy and specificity against the transmembrane isoforms hCA IX and XII, over the cytosolic forms hCA I and II.[10]

Considering sulfonamides, which have high binding affinity for most CA isozymes, we have designed novel compounds to achieve selectivity and specificity against the transmembranous CA IX isozyme over the cytosolic, ubiquitous one CA II.[3,4] The rationale for designing the new compounds reported here is based on the earlier findings (kinetic and X-ray crystallography) that 1,3,5-triazinyl-containing sulfonamides show potent and selective inhibition of CA IX/XII over CA I and II.[8–10]

The nucleophilic aromatic substitution reaction has been widely used for the synthesis of sulfonamides incorporating 1,3,5-triazine (Scheme 1), pyridine or diazine moieties (Scheme 2), as reported earlier.[11] Here we explored new substitution patterns at the triazine ring, as by means of X-ray crystallography it has been shown that the tails present in the scaffold significantly contribute to the potency and isoform-selectivity of the benzenesulfonamides incorporating disubstituted-1,3,5-triazinyl moieties. Reaction of cyanuric chloride (**1**) with 4-amino benzene sulfonamide (**2**) in presence of base afforded the key intermediate, the dichlorotriazine-benzenesulfonamide derivative reported earlier (compound **3**, Scheme 1). Reaction of (**3**) with different nucleophiles in the molar ratio of 1:1 produced monosubstituted products **4** (**a**–**e**) whereas working at the ratio of 1:2, the

* Corresponding authors. Tel.: +91 731 2454095x537 (M.T.); tel.: +39 055 4573005; fax: +39 055 4573385 (C.T.S.).
E-mail addresses: mtiwari@sgsits.ac.in (M. Tiwari), claudiu.supuran@unifi.it (C.T. Supuran).

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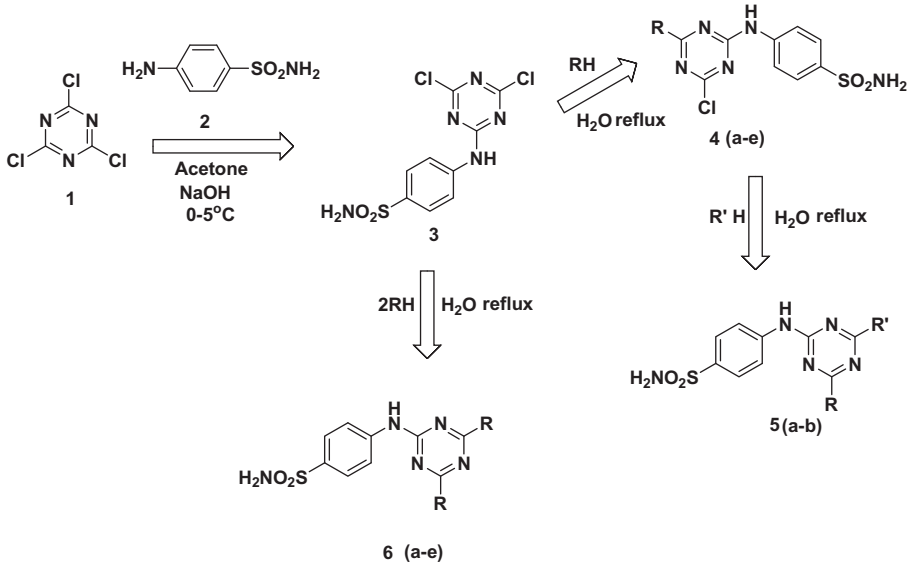
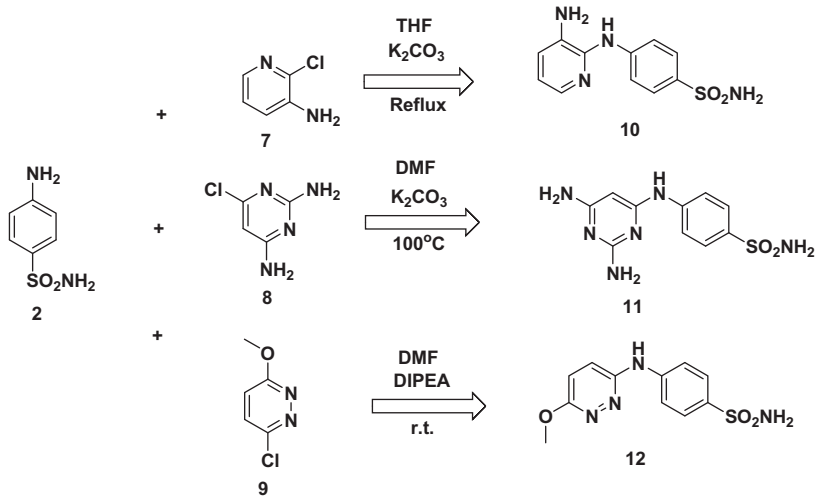


Scheme 1. Synthesis of sulfonamides **4** (**a**–**e**), **5** (**a**–**b**), **6** (**a**–**e**) incorporating triazine moieties by reaction of dichlorotriazine (**3**) with nucleophiles.



Scheme 2. Synthesis of sulfonamides (**10**–**12**) incorporating pyridine, pyrimidine, and pyridazine moieties.

disubstituted products **6** (**a**–**e**) were obtained.[8–10] The monosubstituted derivatives (**4a** and **4b**) were treated with different nucleophiles to replace the second chlorine atom, leading to the disubstituted derivatives **5** (**a**–**b**).

Isostructural rings to the 1,3,5-triazine ones, such as pyridine, pyrimidine and pyridazine incorporating a chlorine in position 2-, 4-, or 6-, also possess a high reactivity towards various nucleophiles, and were less investigated for the synthesis of CA inhibitors until now. The new monosubstituted products (**10**–**12**) were thus obtained when 3-amino-2-chloropyridine (**7**), 6-chloropyrimidine-2,4-diamine (**8**) or 3-chloro-6-methoxypyridazine (**9**) were reacted with an equivalent of 4-amino benzene sulfonamide (**2**) in the presence of anhydrous potassium carbonate or diisopropylethylamine under an inert nitrogen atmosphere (Scheme 2).[12–14]

It was observed that replacement of chlorine atoms from the triazine nucleus requires harsher conditions after the first chlorine has been replaced, since the accumulation of electron donating amine substituents gradually decreases the reactivity of the triazine ring. Then, the subsequent replacements occured slower than the first one. The nucleophiles used for the synthesis included 4-amino benzene sulfonamide, ammonia, anilines, morpholine, *tert*-butylamine, *N*-methyl-2-amino ethanol and 1, 3-diaminopropane, in order to explore a chemical space which has not been investigated in the previous communications.[8–10]

The synthesized compounds were evaluated[15] using a stopped flow assay against CA isoforms I, II, IX, XII and the inhibition data are shown in Table 1.

The following structure activity relationship can be drawn from the inhibition data of Table 1:

(i) All the 15 synthesized compounds modestly inhibited hCA I with K_Is in the range of 87 nM–4.35 μM. The best activity in the series of the synthesized compounds was shown by (2,6-diaminopyrmidin-4-ylamino) benzene sulfonamide (compound **11**) and **4a** which incorporated a chloro and an anilino moiety, both of them possessing a K_I value of 87 nM. The diamino derivative **6a** (repored earlier)[9] was also an effective hCA I inhibitor with a much better K_I (90 nM) compared to that of the standard drug acetazolamide (**AAZ**). The weakest activity was observed for (4,6-bis

Table 1
Inhibition data of human carbonic anhydrase isozyme I, II, IX and XII with synthesized compounds by a stopped-flow, CO_2 hydration assay method[15]

No	R	R′	K_I[a] (nM)			
			hCA I	hCA II	hCA IX	hCA XII
4a	Cl	NHPh	87	18.0	5.9	4.2
4b	Cl	3-NHC_6H_4Me	354	18.3	5.1	4.3
4c	Cl	$HOC_2H_4N(Me)$	1070	40.7	1.2	2.1
4d	Cl	$H_2N(CH_2)_3NH$	1375	67.1	21.4	8.6
4e	Cl	4-F-3-ClC_6H_3NH	2540	130	21.2	25.4
5a	$O(CH_2CH_2)_2N$	NHPh	430	34.1	20.1	16.4
5b	$O(CH_2CH_2)_2N$	3-NHC_6H_4Me	447	21.9	10.2	15.1
6a	NH_2	NH_2	90	21.2	2.4	3.9
6b	$O(CH_2CH_2)_2N$	$O(CH_2CH_2)_2N$	583	12.5	34.1	33.9
6c	*t*-BuNH	*t*-BuNH	410	54.3	19.3	18.5
6d	$HOC_2H_4N(Me)$	$HOC_2H_4N(Me)$	2365	72.6	5.9	12.3
6e	$H_2N(CH_2)_3NH$	$H_2N(CH_2)_3NH$	4350	75.9	18.3	4.1
10	—		421	24.2	10.7	11.5
11	—		87	15.6	3.9	5.4
12	—		110	21.4	8.5	6.7
AAZ	—		250	12.1	25.0	5.7
EZA	—		25.2	8.0	34.3	22.1

[a] Mean from three different assay, by a stopped flow technique (errors were in the range of 5–10% of the reported values).

(3-amino propyl amino)-1,3,5-triazin-2-ylamino)benzene sulfonamide (compound **6e**), which had a K_I value of 4.35 μM against this isoform and possesses the rather bulky, long 1,3-propylene diamine arms. The bulkiness present in this or structurally related compounds (e.g., **6d**, **4d** and **4e**) probably interferes with the effective binding within the restricted space of the hCA I active site, leading to a lower activity of these compounds, with inhibition constants in the micromolar range (Table 1).

(ii) The synthesized compounds showed effective hCA II inhibitory activity with K_Is ranging between 12.5 and 130 nM, having thus a better inhibition profile against this isoform compared to hCA I (Table 1). Some of the new compounds, such as **6a**, **4a**, **4b**, **5b**, **6b**, **10**, **11 and 12** showed quite potent hCA II inhibition, with K_Is in the range of 12.5–24.2 nM, comparable to the standard drugs **AAZ** and **EZA**. They incorporate both the 1,3,5-triazine or the isostructural rings (pyridine, pyrimidine or diazine) in their molecules, as well as amino, methoxy, chloro, anilino and morpholino groups. Derivatives **5a**, **6c**, **4c**, **6d**, **4d**, **6e** and **4e** showed a weaker hCA II inhibitory activity, with inhibition constants ranging between 34.1 and 130 nM (Table 1). They seem to incorporate bulkier moieties compared to the previous ones, of the *tert*-butylamino, hydroxyethylamino-methyl or 3-chloro-4-fluoroanilino. Probably the most important structural feature interfering with the effective binding is again the bulkiness of the moieties substituting the 1,3,5-triazine ring, as the derivatives with compact or less bulky such moieties showed a better activity compared to those incorporating one or two bulky functionalities.

(iii) The transmembrane tumor associated isoform hCA IX was effectively inhibited by the synthesized compounds with K_Is in the range of 1.2–34.1 nM. Compounds **6a**, **4a–c**, **6d** and **11** showed inhibition constants K_I ranging from 1.2 to 5.9 nM, which is better than standard drugs **AZM** and **EZM**. The active compounds incorporated –Cl or $–NH_2$ substituents at position 2 of the triazine nucleus whereas compounds **5a–b** and **6b**, having morpholine substitution at position 2 of triazine ring showed less potent hCA IX inhibitory activity. Compound **6b**, with the worst activity was equipotent with **EZM** and incorporated two morpholine moieties with the 1,3,5-triazine nucleus. It was observed that compounds with small, compact substituents possessing lower molecular weights, and an increased number of hydrogen acceptor atoms were more effective against hCA IX isoforms over hCA II (e.g., **6a**, **4a–c**, **6d**, and **10–12**). Again the 1,3,5-triazine ring could be substituted by the isostructural pyridine, pyrimidine or diazine rings without loss of hCA IX inhibitory activity or selectivity for inhibiting the tumor-associated over the cytosolic isoforms (Table 1).

(iv) hCAXII was also potently inhibited by the new compounds reported here, with inhibition constants ranging from 2.1 to 33.9 nM. Most of the compounds, such as **6a**, **4a–c**, **6e**, and **11** showed a very good activity with K_Is in the low nanomolar range, of 2.1–4.1 nM, comparable with **AZM** (K_I of 5.7 nM). It was observed that the disubstituted compounds with bulkier moieties, such as aniline-morpholine, 3-methyl aniline- and morpholine, or dimorpholino, were less active against hCA XII, a situation already encountered at the inhibition of the other CA isozymes discussed here, and probably due to their too bulky nature and difficulties to effectively bind within the restricted space of the enzyme active site cavity. The monosubstituted compounds showed better hCA IX/hCA XII inhibition activity compared to the disubstituted derivatives incorporating similar scaffolds.

(v) All the synthesized compounds showed better inhibition of the transmembrane tumor associated isoforms hCA IX and hCA XII over cytosolic isoforms hCA I and hCA II with good selectivity profile and specificity. For example, **4c** showed a selectivity ratio of 891 for inhibiting hCA IX over hCA I, and of 33.9 for inhibiting hCA IX over hCA II. The selctivity ratios for inhibiting hCA XII over hCA I and II were in the same range like that of hCA IX (selectivity ratio of 509 for inhibiting hCA XII over hCA I and of 19 over hCAII), making this compound highly selective for the inhibition of the tumor-associated over the cytosolic CA isoforms.

In order to have a hint on the binding orientation of these inhibitors within the active site of the enzyme, docking of some of the new compounds was performed using the GOLD suite program.[9] The PDB ID 3IAI, of a triazinyl-substituted benzenesulfonamide bound to hCA II reported earlier by our and McKenna's group[10] was downloaded from RCSB protein data bank and used for the docking experiments. Protein and ligand files were prepared using DockPrep tool in CHIMERA software, which included addition of charges, addition or removal of hydrogens, repairing of residues by adding missing chains, etc. Binding site was defined at $X = 70.5457$, $Y = 51.4075$, $Z = 11.8884$ by selecting all atoms within 12 Å, considering the co-crystallized bound ligand. Docking was carried out using Genetic algorithm and validated using the co-crystallized bound ligand, acetazolamide. After validation, all the compounds were docked into the binding pocket keeping the same value of coordinates and positioned all the ligands in the same orientation as acetazolamide (Fig. 1).

As for all other hCA II–sulfonamide adducts investigated so far, it was observed that the nitrogen atom of the sulfonamide **6b** (a potent hCA II inhibitor, K_I of 12.5 nM) coordinates to Zn(II) ion and participates in a network of hydrogen bonds involving residues Thr199 and Glu106. An oxygen function of sulfonamide group also hydrogen bonds to the –NH moiety of Thr199. Additionally, the polar amino acids Gln67, Asn62, Ser65 were found to be in close contact with the inhibitor **6b** (Fig. 1a), thus stabilizing the enzyme–inhibitor adduct. In the docking analysis of compound **4e** (the least potent against hCA II in the series reported here, K_I of 130 nM, Fig. 1b), it was observed that due to presence of bulky, fluorophenyl functionality at the 1,3,5-triazine ring, the orientation and alignment of the inhibitor was not perfectly fitted within the hCA II active site. The scaffold of the inhibitor was found

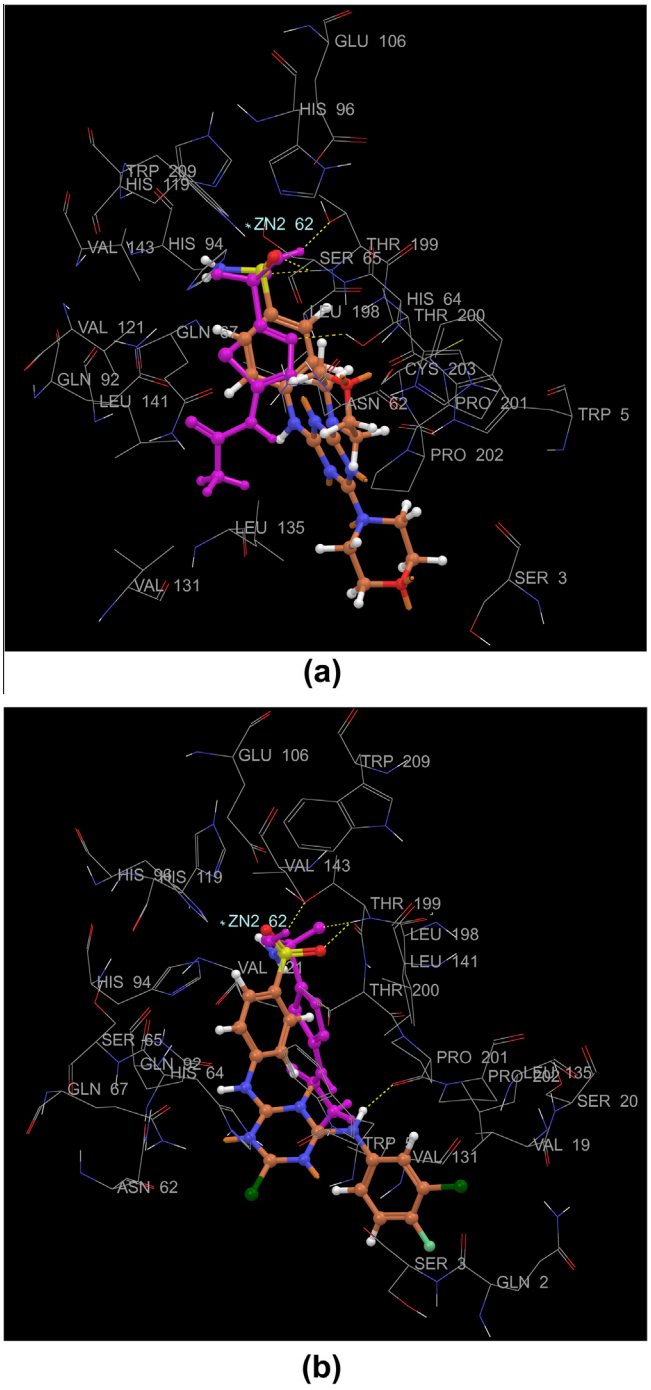


Figure 1. Orientation and interaction with the metal ion and amino acid residues from the hCA II active site of some of the synthesized compounds: (a) **6b** (brown) superposed on the acetazolamide (AAZ)—purple adduct, and (b) compound **4e** (brown) superposed to the acetazolamide adduct (purple), obtained by docking **6b** and **4e** in the 3IAI PDB file.[10]

surrounded by hydrophobic amino acid residues, such as Val121, Val131, Trp5, Pro201, and Pro202 (Fig. 1b). Thus, the two sulfonamides 6b (strong hCA II inhibitor) and 4e (much weaker hCA II inhibitor), bind with different orienations and make diverse contacts with amino acid residues from the hCA II active site (Fig. 1a and b), which explains their different inhibition profile against the enzyme.

In conclusion, we report here a new series of 15 benzenesulfonamides incorporating triazinyl- pyridinyl, pyrimidinyl or diazinyl-substituted moieties. The new derivatives selectively and specifically inhibited the transmembrane, tumor associated isoforms hCA IX and hCA XII in low nanomolar range over cytosolic isoforms hCA I and II, which were moderately inhibited. Docking studies of the synthesized compounds within the hCA II active site revealed similar orientation and interaction at the active site as acetazolamide and other triazinyl-substituted sulfonamides investigated earlier by means of X-ray crystallography.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.01.048.

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15. Khalifah, R. G. *J. Biol. Chem.* **1971**, *246*, 2561. An Applied Photophysics stopped-flow instrument has been used for assaying the CA catalyzed CO_2 hydration activity. Phenol red (at a concentration of 0.2 mM) has been used as indicator, working at the absorbance maximum of 557 nm, with 20 mM Hepes, pH 7.5, as buffer, and 20 mM $NaClO_4$ (for maintaining constant the ionic strength), following the initial rates of the CA-catalyzed CO_2 hydration reaction for a period of 10–100 s. The CO_2 concentrations ranged from 1.7 to 17 mM for the determination of the kinetic parameters and inhibition constants. For each inhibitor at least six traces of the initial 5–10% of the reaction have been used

for determining the initial velocity. The uncatalyzed rates were determined in the same manner and subtracted from the total observed rates. Stock solutions of inhibitor (10–50 mM) were prepared in distilled-deionized water and dilutions up to 0.1 nM were done thereafter with the assay buffer. Inhibitor and enzyme solutions were preincubated together for 15 min at room temperature prior to assay, in order to allow for the formation of the E–I complex or for the eventual active site mediated hydrolysis of the inhibitor. The inhibition constants were obtained by non-linear least-squares methods using PRISM 3 and the Cheng–Prusoff equation, as reported earlier,[16] and represent the mean from at least three different determinations. All CA isoforms were recombinant ones obtained in-house as reported earlier.[16–18] hCA I, II, IX and XII were recombinant proteins obtained in-house as described earlier.[16–18]

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