Carbonic anhydrase inhibitors. Selective inhibition of human tumor-associated isozymes IX and XII and cytosolic isozymes I and II with some substituted-2-mercapto-benzenesulfonamides

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Abstract
A series of 2-mercapto-substituted-benzenesulfonamides has been prepared by a unique two-step procedure starting from the corresponding 2-chloro-substituted benzenesulfonamides. Compounds bearing an unsubstituted mercapto group and the corresponding *S*-benzoyl derivatives were investigated as inhibitors of four isoforms of the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1), i.e., the cytosolic, ubiquitous isozymes CA I and II, as well as the transmembrane, tumor associated isozymes CA IX and XII. These derivatives were medium potency hCA I inhibitors (K_Is in the range of $1.5-5.7\,\mu M$), two derivatives were strong hCA II inhibitors (K_Is in the range of $15-16\,nM$), whereas the others showed weak activity. These compounds inhibited hCA IX with inhibition constants in the range $160-1950\,nM$ and hCA XII with inhibition constants in the range $1.2-413\,nM$. Some of these derivatives showed a certain degree of selectivity for inhibition of the tumor-associated over the cytosolic isoforms, being thus interesting leads for the development of potentially novel applications in the management of hypoxic tumors which overexpress CA IX and XII.

Keywords: *Carbonic anhydrase, isozymes, inhibition, CA I, CA II, CA IX*

Introduction

The α-carbonic anhydrases (CAs, EC 4.2.1.1) are a family of metalloenzymes involved in the catalysis of an important physiological reaction: the hydration of CO_2 to bicarbonate and a proton ($CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$). At least 13 enzymatically active isoforms have been discovered in higher vertebrates [1–4]. CAs are involved in pH regulation, secretion of electrolytes, respiration [5–7], biosynthetic reactions which require CO_2/bicarbonate as substrate such as gluconeogenesis, lipogenesis, ureagenesis and pyrimidines synthesis among others [8].

Other roles for these enzymes have been highlighted, such as calcification and bone resorption [9]. The discovery that CA IX, a transmembrane tumor-associated protein [10], was prevalently expressed in several human cancer cells and not in their normal counterparts [11] suggests a role for some CA isoforms in oncogenesis [8]. Several studies showed a clearcut relationship between high CA IX levels in tumors and a poor prognosis [12,13]. CA IX also acts on cellular adhesion and differentiation by its N-terminal proteoglycan related-region which is absent in other transmembrane CA isozymes,

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such as CA XII (which is present in some tumors [8]) and CA XIV (which is not associated with tumors) [14].

Tumor cells have a lower extracellular pH (pH_e) than normal cells due to lactic acid produced by glycolysis [15]. An acidic pH_e contributes to increase tumor progression by promoting the action of growth factors [16,17], proteases [18] and an increased rate of mutation [19–22]. Recently CO_2 in addition to lactic acid were demonstrated to be significant sources of acidity in tumors [23], pointing out the implication of CAs (such as CA IX and XII) in tumor progression [8]. The expression of CA IX is both regulated by the von Hippel-Lindau (VHL) tumor suppressor protein and by hypoxia present in many tumor types [8,22,23]. Thus, an inactivation of the VHL factor gene enhances the expression of CA IX [21], whereas hypoxia induces the expression of CA IX via a direct transcriptional activation of *CA9* gene by the hypoxia-inducible factor-1 (HIF-1) [22]. Moreover, hypoxia stimulates CA IX to acidify the pH_e (by an as yet unknown mechanism), proving that the expression levels and the catalytic activity of CA IX are dependent on the availability of oxygen within the tumor [23].

CA IX was clearly demonstrated to be involved in the acidification of the pH_e by Svastova et al. [23]. Teicher and collaborators showed earlier that acetazolamide (**AAZ**) decreased tumor growth *in vivo* and enhanced the action of some chemotherapeutic agents, such as cisplatin, melphalan, $PtCl_4$, when used in combination therapy [24]. Several CA IX-selective sulfonamide inhibitors were able to reduce the extracellular acidification of Madin-Darby canine kidney (MDCK)-CA IX cells in hypoxia but not in normoxia [23]. Furthermore, a decrease of the extracellular pH reduces the cytotoxicity of weakly basic chemotherapeutics drugs such as paclitaxel, mitoxantrone and topotecan [25]. Taken together, these data suggest the growing interest for specific CA IX/XII inhibitors in cancer therapy. Such compounds may prevent the decrease of pH_e and may be used in combinations with other antitumor drugs to increase the efficacy or the uptake of weakly basic drugs [15,24]. Thus, the aim of the present study is the design, synthesis and *in vitro* pharmacological evaluation of novel sulfonamides as CA IX and XII inhibitors.

Materials and methods

Chemistry

The clinically used sulfonamide CA inhibitors (CAIs) acetazolamide **AAZ**, methazolamide **MZA**, ethoxzolamide **EZA**, dichlorophenamide **DCP** and indisulam **IND**, employed as standard inhibitors in the enzyme assays were commercially available from Sigma-Aldrich or have been prepared as previously described [26]. Recombinant human CA isoforms I, II, IX and XII have been prepared as reported earlier by our group [27–30], and their activity assayed by the stopped flow method of Khalifah [31].
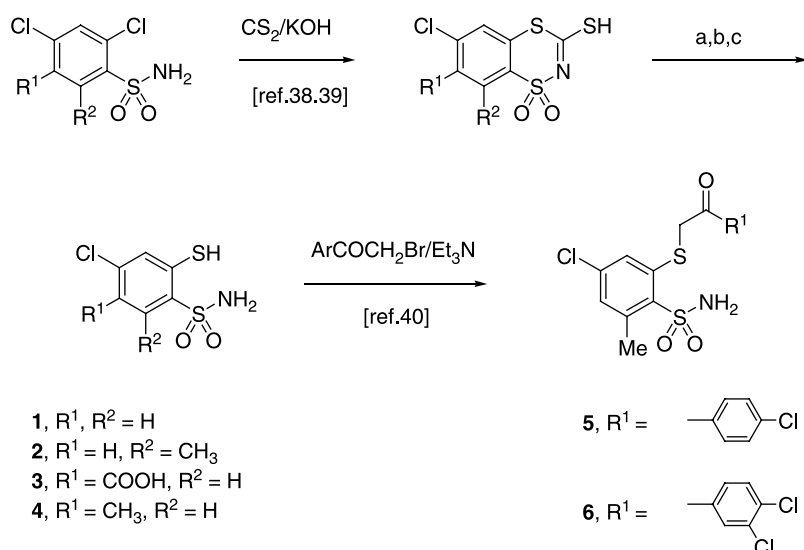
Compounds **1**–**6** investigated in the present study belong to the substituted-2-mercapto-benzenesulfonamide class with proven anti-HIV [32–34] and anticancer activities [35–37]. Synthesis and spectral data for the compounds **3,4** [38,39] and **5,6** [40] have been reported earlier, and according to a procedure depicted in Scheme 1, the synthesis of sulfonamides **1** and **2** was achieved:

Compound 1. mp. 247–249°C; IR (KBr) 3360, 3245 (NH_2), 2565 (SH), 1330, 1155 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-*d6*) δ = 3.70 (br s, 1H, SH), 7.35 (dd, J_{ortho} = 8.5 Hz, J_{meta} = 2.1 Hz, 1H, H-5), 7.56 (s, 2H, NH_2), 772 (d, J = 2.1 Hz, 1H, H-3), 7,81 (d, J = 8.5 Hz, 1H, H-6) ppm.

Compound 2. mp. 176–178°C; IR (KBr) 3335, 3235 (NH_2); 2550 (SH), 1330, 1165 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-*d6*) δ = 2.57 (s, 3H, CH_3), 3,60 (br s, 1H, SH), 7.21 (d, J = 1.9 Hz, 1H, H-5), 7.55 (s, 2H, NH_2), 7.63 (d, J = 1.9 Hz, 1H, H-3) ppm Figure 1.

CA inhibition assay

An Applied Photophysics (Oxford, UK) stopped-flow instrument was used for assaying the CA-atalysed CO_2 hydration activity [31]. Phenol red (at a concentration of 0.2 mM) was used as indicator, working at the absorbance maximum of 557 nm, with 10 mM Hepes (pH 7.5) as buffer, 0.1 M Na_2SO_4 (for maintaining the ionic strength constant), and the CA-catalyzed CO_2 hydration reaction was followed for a period of 10–100 s. The CO_2 concentrations ranged from 1.7–17 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 was 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 (1 mM) were prepared in distilled-deionized water with 10–20% (v/v) DMSO (which is not inhibitory at these concentrations) and dilutions up to 0.1 nM were done thereafter with distilled-deionized water. 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. The inhibition constants were obtained by non-linear least-squares methods using PRISM 3, from Lineweaver-Burk plots, as reported earlier, and represent the

Scheme 1.   Preparation of sulfonamides **1**–**6**.

Results and discussion

The sulfonamides **1**–**6** investigated in this study as CA inhibitors belong to the substituted-2-mercapto-benzenesulfonamide class, it having being proven earlier that they possess anti-HIV [32–34] and anticancer activities [35–37]. The synthesis and spectral data for the compounds **3**, **4** [38,39] and **5**, **6** [40] have been reported earlier, whereas derivatives **1** and **2** are novel and described here for the first time. All these compouonds have been prepared according to the procedure depicted in Scheme 1. Thus, treatment of the 2,4-dichloro-5,6-disubstituted benzenesulfon-amide with carbon disulfide in alkaline medium lead to

the formation of a bicyclic intermediate which was not isolated, which on treatment with hydrazine followed by neutralization with hydrochloric acid gave the 2-mercapto-benzenesulfonamides **1**–**4** (Scheme 1). Treatment of some of these derivatives with bromo-methyl-aryl-ketones [40] in the presence of base lead to the corresponding *S*-benzoyl derivatives **5** and **6**.

Compounds **1**–**6** and standard, clinically used CAIs, such as acetazolamide **AAZ**, methazolamide **MZA**, ethoxzolamide **EZA**, dichlorophenamide **DCP** and indisulam **IND**, were tested for the inhibition of two cytosolic, ubiquitous isozymes of human origin, i.e., hCA I and hCA II [1–6], as well as the two human, tumor-associated isoforms hCA IX and XII (Table I).

The data of Table I shows the following: (i) against the slow isozyme hCA I, the sulfonamides **1**–**6**
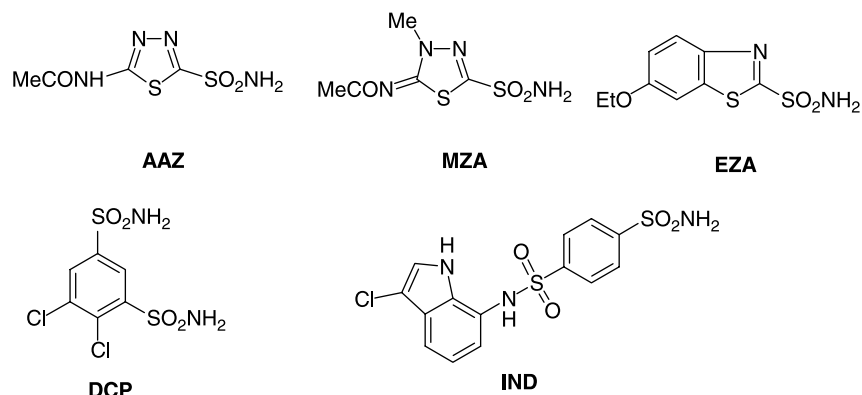
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mean from at least three different determinations [27–30].

Figure 1.   Structures **AAZ** – **IND**.

Table I. Inhibition data for sulfonamides **1–6** reported in the present paper and standard CA inhibitors, against isozymes I, II, IX and XII, by a stopped-flow, CO_2 hydration assay [31].

Inhibitor	hCA I[a] (μM)	hCA II[a] (nM)	hCA IX[b] (nM)	hCA XII[b] (nM)
AAZ	0.31	12	25	5.7
MZA	0.78	14	27	3.4
EZA	0.025	8	34	22
DCP	1.20	38	50	50
IND	0.031	15	24	3.4
1	3.1	445	165	7.9
2	5.7	15	160	1.2
3	3.7	428	1950	413
4	3.7	16	483	41
5	2.5	26000	211	78
6	1.5	17000	683	35

*Errors in the range of 5–10% of the reported value (from 3 different assays).
[a] Human (cloned) isozymes, by the CO_2 hydration method.
[b] Catalytic domain of human, cloned isozymes [29,30], by the CO_2 hydration method [31].

investigated here show moderate inhibitory activity, with inhibition constants in the range 1.5–5.7 μM. It may be observed that all these derivatives show a rather similar activity, being much less effective as the clinically used sulfonamides **AAZ, MZA, EZA** or **IND**, but having an activity comparable to that of **DCP**; (ii) against the physiologically most relevant isoform hCA II, two of the investigated compounds, **2** and **4**, showed a good inhibitory activity (comparable to that of the clinically used drugs mentioned above), with K_I-s in the range of 15–16 nM, two others, (compounds **1** and **3**, were moderate inhibitors with K_I-s in the range of 428–445 nM), whereas the remaining two derivatives (**5** and **6**) were very weak hCA II inhibitors (K_I-s in the range of 17–26 μM). Several SAR features are immediately obvious: the bulky chloro/dichloro-benzoylmethylsulfide moieties present in **5** and **6** are detrimental to hCA II inhibitory activity, probably because they are too bulky and interfere with the favourable binding of the sulfona-mide moiety (in ionised form, as sulfonamidate anion [1–6,26]) to the Zn(II) ion within the enzyme active site (however, it should be noted that these compounds still do inhibit hCA I well, but it has previously been observed that many *ortho*-substituted benzenesulfonamides incorporating rather bulky moieties do inhibit hCA I but only slightly do the same with hCA II [26]). Among the compounds incorporating the more compact 2-mercapto moiety (derivatives **1–4**), the nature of the R^1 and R^2 moieties substituting the benzene ring strongly influenced hCA II inhibitory activity. Thus, unexpectedly, the *ortho*-disubstituted compound **2** was the most active one, and its potency was very high as compared to its desmethyl derivative **1**, which is roughly 30-fold less

effective as a hCA II inhibitor. It is difficult to interpret these data without an X-ray structure of the enzyme-inhibitor complex but we hypothesize that the additional methyl group present in **2** leads to some additional favourable van der Waals contacts which further stabilize the enzyme-inhibitor adduct, as compared to the desmethyl derivative **1**. The same is true for the pair **3** and **4**, with the last compound being approximately 26-fold more inhibitory than **3**, and again the two derivatives differ only by the moiety substituting the benzene ring in *meta* to the sulfonamide functionality. Thus, a methyl group which is *meta* to the sulfonamide moiety leads to a good inhibition of hCA II; whereas its substitution by a carboxy moiety decreases inhibitory properties 26-fold. These data are quite interesting, since although many benzenesulfonamide derivatives have been investigated as CAIs [26], most of them were sulfanilamide, homosulfanilamide or 4-aminoethyl-benzenesulfonamide derivatives, with very few compounds incorporating moieties other than H in the ortho- and/or meta positions to the sulfamoyl group investigated up to now; (iii) against the tumor-associated isoform hCA IX, compounds **1**, **2** and **5** showed moderate inhibitory activity, with K_Is in the range of 160–211 nM. The other investigated compounds were much weaker inhibitors, with K_Is in the range of 483–1950 nM. All these compounds are much less effective hCA IX inhibitors as compared to the clinically used sulfonamides **AAZ – IND**, which showed K_Is in the range of 24–50 nM. SAR is not so obvious in this case, since both compounds incorporating the compact mercapto group ortho to the sulfonamide (such as **1** and **2**) as well as a sterically hindered derivative such as **5**, showed comparable activity; (iv) a very interesting activity was observed for the inhibition of hCA XII, the second tumor-associated isoform, with compounds **1–6** investigated here. Thus, compounds **1** and **2** behaved as very potent hCA XII inhibitors (K_Is in the range 1.2–7.9 nM), being more effective (or as effective) than the clinically used derivatives **AAZ, MZA** and **IND** (**EZA** and **DCP** are weaker hCA XII inhibitors, with K_Is in the range of 22–50 nM [28]). Derivatives **4–6** on the other hand showed K_Is in the range of 35–41 nM, just in the same range as **EZA** and **DCP**, whereas **3** was a moderate hCA XII inhibitor, with a K_I of 413 nM.

What is most notable with all these compounds, is the rather varied inhibition profile for such a small series of derivatives. Thus, compound **2** is a potent hCA II/hCA XII inhibitor, being a medium potency hCA IX and an ineffective hCA I inhibitor. Compound **6** on the other hand is a more effective hCA I inhibitor and a rather strong hCA XII inhibitor, at the same time being very ineffective as a hCA II/hCA IX inhibitor, a situation never encountered up to now with the thousands of sulfonamides tested by this group for the inhibition of various CAs. Such

compounds which are to a certain degree isozyme-selective may bring novel insights regarding the physiological functions of some CA isoforms, which are not well understood at this time [1].

Conclusions

A series of 2-mercapto-substituted-benzenesulfona-mides and the corresponding *S*-benzoyl derivatives, were investigated as inhibitors of four CAs, i.e., the cytosolic, ubiquitous isozymes CA I and II, as well as the transmembrane, tumor associated isozymes CA IX and XII. These derivatives were medium potency hCA I inhibitors (K_Is in the range $1.5-5.7\,\mu M$), two derivatives were strong hCA II inhibitors (K_Is in the range $15-16\,nM$), whereas the others showed weak activity. These compounds inhibited hCA IX with inhibition constants in the range $160-1950\,nM$; and hCA XII with inhibition constants in the range $1.2-413\,nM$. Some of these derivatives showed a certain degree of selectivity for inhibition of the tumor-associated over the cytosolic isoforms, being thus interesting leads for the development of potentially novel applications in the managment of hypoxic tumors which overexpress CA IX and XII.

Acknowledgement

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