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Synthesis of novel selenides bearing benzenesulfonamide moieties as carbonic anhydrase I, II, IV, VII and IX inhibitors

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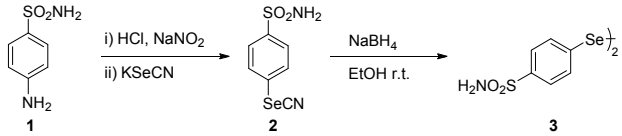
KEYWORDS carbonic anhydrase; inhibitor, metalloenzymes, selenium, selenides, organoselenium compounds

ABSTRACT: A series of novel selenides bearing benzenesulfonamide moieties was synthesized and investigated for the inhibition of five human (h) isoforms of zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1), hCA I, II, IV, VII and IX. These enzymes are involved in a variety of diseases among which glaucoma, retinitis pigmentosa, epilepsy, arthritis and tumors. The investigated compounds showed potent inhibitory action against hCA II, VII and IX, in the low nanomolar range, thus making them of interest for the development of isoform-selective inhibitors and as candidates for biomedical applications**.**

Selenium has a long history of association with human health and disease.[1,2] Interest in the potential biological, pharmacological and therapeutic exploitation of synthetic organoselenium compounds started several decades ago. Organochalcogen derivatives played a crucial role in identifying free radical scavengers or antioxidants that can inhibit or retard oxidative damage.[3,4] Oxidative stress, induced by the generation of reactive oxygen species (ROS), is considered a major causative factor of many serious conditions, including diabetes, cardiovascular diseases, cancer and several neurodegenerative diseases.[5,6] Furthermore, organoselenium derivatives showed inhibitory effects on a variety of enzymes such as nitric oxide synthase (NOS)[7-10], lipoxygenases (LOX)[11] and, carbonic anhydrases[12-14] (CAs, EC 4.2.1.1). CAs are metalloenzymes that catalyse a very simple reaction: the hydration of carbon dioxide to bicarbonate and protons[15]. This reaction plays an important role in many physiological and pathological processes associated with pH control, ion transport, fluid secretion, biosynthetic reactions, etc.[16-17] For this reason, we continued to investigate a new type of organoselenium derivatives as human (h) CA inhibitors (CAIs). Our long standing interest on the reactivity of strained heterocycles with chalcogen-containing nucleophiles led us to disclose novel procedures for the synthesis of a wide variety of functionalized selenium- and tellurium-containing organic small molecules.[18-21] Some of these structures exhibited interesting catalytic antioxidant activity.[22-24] With the aim of synthesising a new series of hydroxy- and amino- functionalized selenium containing CAI, we sought to exploit the reactivity of three-membered ring, such as epoxides and aziridines, with a suitable selenolate, bearing the benzenesulfonamide moiety (as CA inhibiting chemotype),[25] generated from the corresponding diselenide **3**.

In the present study, we investigated different selenides incorporating a benzenesulfonamide moiety as CAI. We began our investigation with the synthesis of diselenide **3**, as shown in the **Scheme 1**. The diazonium salt of sulfanilamide was prepared by reaction of **1** with sodium nitrite in the presence of acid (Sandmeyer reaction) and used as key intermediate for the synthesis of compound **2**. Successively, the selenocyanate derivative **2** was converted easily into the diselenide **3** by reaction with $NaBH_4$ in ethanol, as outlined in **Scheme 1**.

Scheme 1: Synthesis of selenocyanate and diselenide bearing benzenesulfonamide moiety

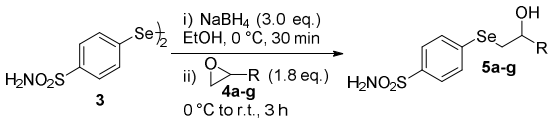


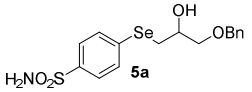
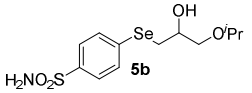
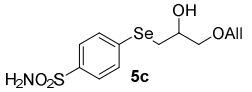
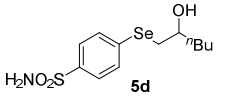
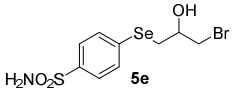
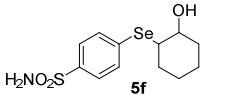
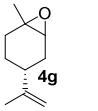
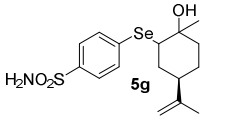
1 2 3

Having obtained the diselenide **3**, we evaluated the possibility to access β-hydroxy selenides by using the ring opening reaction of this compound with epoxides.[26-28] Thus, **3** was reduced with $NaBH_4$ to the corresponding selenolate which was treated in situ with benzyl glycidyl ether **4a**, affording the β-hydroxyselenide **5a** in good yield (**Table 1**, entry 1). The process proved to be highly regioselective, as only the isomer arising from the nucleophilic attack at the less hindered carbon of the oxirane was observed. On the basis of these results, and in order to study the generality of such a procedure, a series of epoxides was reacted with **3** under the same conditions, as reported in **Table 1**. Thus, differently substituted hydroxyl selenides **5b-g** were obtained from the corresponding epoxides **4b-g** through a regioselective ring opening route (**Table 1**, entries 2-4). Interestingly, epibromohydrin **4e** was smoothly

converted into **5e** in excellent yields; the nucleophilic attack occured exclusively on the epoxide, the halide being preserved on the side chain (**Table 1**, entry 5). Disubstituted hydroxy selenides **5f, g** were obtained by reacting **3** with cyclohexene oxide **4f** and limonene oxide **4g** (**Table 1**, entries 6,7).

Table 1: Synthesis of β-hydroxy selenides bearing benzenesulfonamide moiety

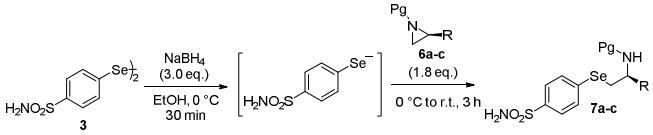


Entry	Epoxide	Product	Yield (%)[a]
1	 **4a**	 **5a**	89
2	 **4b**	 **5b**	93
3	 **4c**	 **5c**	74
4	 **4d**	 **5d**	68
5	 **4e**	 **5e**	91
6	 **4f**	 **5f**	41
7	 **4g**	 **5g**	57

[a] Yields are referred to isolated products

In order to access benzenesulfonamide-substituted selenides bearing the amino group, the procedure was extended to differently N-protected aziridines 6,[29,30] synthesised from natural aminoacids. As reported in the Scheme 2, enantioenriched N-Tosyl and N-Boc selenides 7a-c were obtained in good yields from 6a-c through a regio- and stereo-selective reaction.

Scheme 2: Synthesis of N-protected β-amino selenides bearing benzenesulfonamide moiety

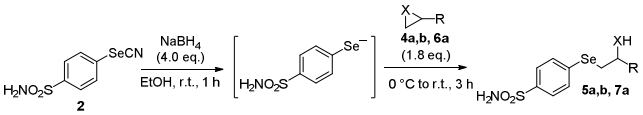


Finally, the free selenoamine **8** was obtained from the N-Boc derivative 7c by the acetyl chloride promoted cleavage of the protecting group (Scheme 3).[31]

Scheme 3: Synthesis of β-amino selenide bearing benzenesulfonamide moiety

As a further investigation, in order to propose an alternative way to access the target compounds, we sought to achieve β-hydroxy- and β-amino- selenides from the selenocyanate 2, thus avoiding the synthesis of the diselenide 3. After having optimized the reaction conditions, we were pleased to observe that selenides 5a,b and 7a were obtained by ring opening of epoxides 4a,b and aziridine 6a with the selenolate, in situ generated by reducing 2, as reported in the Scheme 4.

Scheme 4: Synthesis of selenides bearing benzenesulfonamide moiety



5a: R=CH_2OBn, *X=O* (76% yield)
5b: R=CH_2Br, *X=O* (85% yield)
7a: R=iPr, *X=N-Ts* (68% yield)

We investigated the CA inhibitory proprieties of compounds **2**, **3**, **5a-g**, **7a-c** and **8** against the physiologically relevant hCA isoforms I, II, IV, VII and IX by means of the stopped-flow carbon dioxide hydration assay[32] after a period of 15 min of incubation of the enzyme and inhibitor solutions.[33–38] Their activities were compared to the standard CAI acetazolamide (**AAZ**) (**Table 2**).

Table 2. Inhibition data of human CA isoforms I, II, IV, VII and IX with compounds **2**, **3**, **5a-g**, **7a-c** and **8** and **AAZ** by a stopped flow CO_2 hydrase assay.[32]

Compounds	Ki* (nM)				
	hCA I	hCA II	hCA IV	hCA VII	hCA IX
2	95.6	53.1	30.6	7.1	9.3
3	1522.7	7.9	298.4	40.5	2.7
5a	193.8	1.4	377.7	1.9	10.1
5b	73.2	4.4	403.1	0.71	15.9
5c	8084.3	920.8	8133.0	74.2	11.9
5d	228.8	8.8	429.2	0.85	5.6
5e	127.2	4.9	319.3	7.4	6.5
5f	148.6	7.4	458.2	0.77	8.3
5g	8.4	0.18	34.8	0.68	2.4
7a	881.1	14.0	435.2	0.35	10.1
7b	4365.5	90.2	5601.0	3.4	2.4
7c	1471.2	15.9	2825.0	3.5	2.3
8	93.0	0.51	2321.0	36.2	2.4
AAZ	250	12.1	74	6	25.8

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

The following structure activity relationship (SAR) may be noted regarding the inhibition data of **Table 2**:

i) The ubiquitous cytosolic hCA I was inhibited by all compounds with Ki spanning between low nanomolar (8.4 nM) to the high micromolar range (K_i 8084.3 nM). Selenocyanate derivative **2** inhibited hCA I in the medium nanomolar range (K_i 95 nM) but the diselenide **3** showed a decreased potency of inhibition by almost 15-fold. The β-hydroxy selenide **5g** showed the best inhibition potency, with a K_i of 8.4 nM. Moreover, a less bulky tail moiety such as in the cyclohexane derivative (**5f**) decreased the activity 16 folds. Compound **8** inhibited this isoform in medium nanomolar range with a K_i of 93 nM. Compound with different *N*- protecting groups, such as **7a** and **7c** led to a decrease of the inhibitory activity of nearly 9 times (with the tosyl group in **7a**) and 18 times (for the Boc derivative **7c**) compared to **8**.

ii) The dominant cytosolic human isoform hCA II, was inhibited in the low-medium nanomolar range by all compounds investigated here, except for derivative **5c** which acted in the high nanomolar range (K_i 920.8 nM). Selenocyanate derivate **2** showed a 6 folds loss of activity compared to the diselenide **3**. β-Hydroxy selenides **5a-g** proved to be potent inhibitors of this isoform, with K_is ranging between 0.18 and 8.8 nM, except for **5c** mentioned earlier. In addition, the β-amino selenide **8** showed a very potent inhibition profile of hCA II (K_i of 0.51 nM). The introduction of N-protecting groups as in **7a** and **7c** led to a decrease of the inhibition potency of nearly 29 times compared to **8**.

iii) The last cytosolic human isoform studied, hCA VII, was inhibited by all compounds in the subnanomolar – nanomolar range (K_is of 0.35 – 74.2 nM, Table 2). Many of the new selenium-containing derivatives, such as **5b, 5d, 5f, 5g** and **7a** were subnanomolar hCA VII inhibitors,m making them of great interest for further studies, considering that this isoform was shown to be involved in oxidative stress.[39,40] The presence of N-protecting groups for compounds **7a** and **7c**, increased the efficacy 10 times for the Boc moiety and, 100 times for tosyl moiety. with respect to the compound without such moieties (**8**).

iv) Almost all compounds investigated here possessed low inhibitory activity for the membrane-bound hCA IV with K_is spanning between the high nanomolar range to the micromolar range. Compound **2** showed the best activity against this isoform with a K_i of 30.6 nM but, the efficacy decreased for the diselenide derivative **4** (K_i 298.4 nM). Different substituents on the β-hydroxy selenides **5a-g** did not influenced significantly the inhibition activity. except for **5c** which had a decrease of the efficacy (K_i 8133 nM). Compound **7a**, with a tosyl moiety as protecting group, proved to have a better inhibition profile compared to the other β-amino selenides investigated here.

v) The transmembrane, tumor-associated hCA IX, was effectively inhibited by all compounds investigated here, in the low nanomolar range (K_is of 2.3 – 154.9 nM), all of them being more effective inhibitors compared to the clibnically used standard acetazolamide (**AAZ**) – Table 1. As for the other membrane isoform, hCA IV, the substituents on the β-hydroxy selenides **5a-g** did not influenced significantly the inhibitory efficacy in this small series of derivatives. N-protection for compounds **7a** and **7c** did not change significantly the inhibition profile compared to the β-amino selenide **8**. A special mention regading the important differences of inhibitory activity of 5b and 5c against all isoforms except CA IX. In fact, the two compounds only differ by the presence of an allyl instead of an iso-propyl moiety. Although these structural differences are minor, in many similar cases when the X-ray structures were reported in complex with various CA isoforms,[41,42] important differences in the orientation within the active site were observed, which may explain the difference of inhibitory power of these quite similar derivatives.

In conclusion, we have developed methods for the synthesis of novel series of selenoethers as inhibitors on five α-carbonic anhydrases (CAs, EC 4.2.1.1) of pharmacologic relevance, i.e., hCA I, II, IV, VII and IX. These isoform are drug targets for antiglaucoma (hCA I, II and IV), antiepileptic (hCA VII) or antitumor (hCA IX) agents. β-Hydroxy **5a-g** and N-protected β-amino selenides prove to be potent inhibitor for hCA VII. Indeed, β-amino selenide **8** showed a potent inhibition against hCA II. In this contest, the investigated selenoether compounds showed potent inhibitory action, thus making them interesting leads for the development of more potent and more isoform-selective inhibitors.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic procedures, characterization of compounds and in vitro kinetic procedure (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

CAI(s), carbonic anhydrase inhibitor(s); AAZ, acetazolamide; (h)CA, (human) carbonic anhydrase; KI, inhibition constant

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