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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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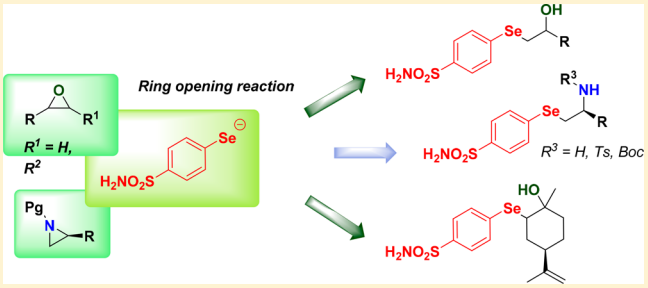
Supporting Information

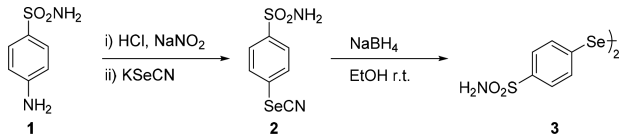
ABSTRACT: A series of novel selenides bearing benzenesulfonamide moieties was synthesized and investigated for the inhibition of five human (h) isoforms of zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1), hCA I, II, IV, VII, and IX. These enzymes are involved in a variety of diseases, including glaucoma, 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.



KEYWORDS: *Carbonic anhydrase, inhibitor, metalloenzymes, selenium, selenides, organoselenium compounds*

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 catalyze 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 in 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 synthesizing a new series of hydroxy- and amino-functionalized selenium containing CAI, we sought to exploit the reactivity of the 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 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 the 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



Having obtained 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-

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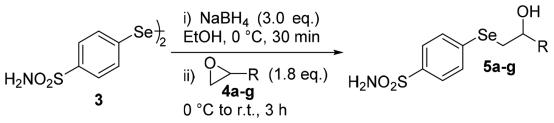
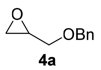
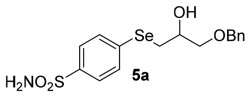
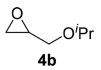
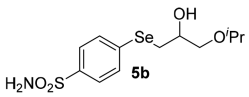
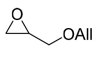
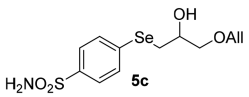
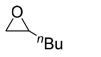
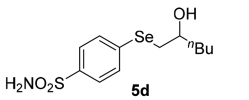
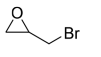
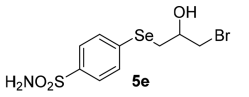
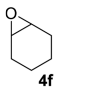
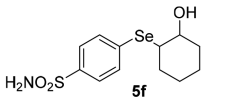
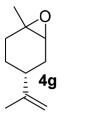
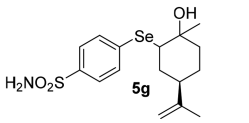
hydroxyselenide **5a** in good yield (Table 1, entry 1). The process proved to be highly regioselective, as only the isomer

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

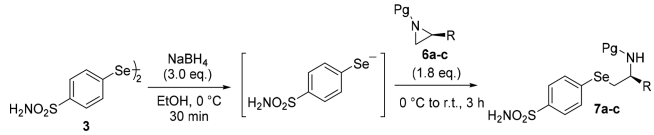
[a]Yields refer to isolated products.

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 occurred exclusively on the epoxide, and the halide was 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).

In order to access benzenesulfonamide-substituted selenides bearing the amino group, the procedure was extended to differently N-protected aziridines **6**,[29,30] synthesized from natural amino acids. As reported in t he Scheme 2, enantioenriched *N*-tosyl and *N*-Boc selenides **7a−c** were obtained in good yields from **6a−c** through a regio- and stereoselective reaction.

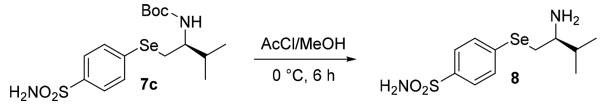
Finally, the free selenoamine **8** was obtained from the *N*-Boc derivative **7c** by the acetyl chloride promoted cleavage of the protecting group (Scheme 3).[31]

Scheme 2. Synthesis of N-Protected β-Amino Selenides Bearing Benzenesulfonamide Moiety



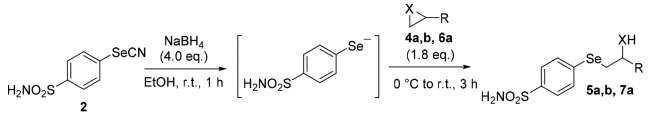
a: R=^{i}Pr, *Pg*=Ts
b: R=Bn, *Pg*=Ts
c: R=^{i}Pr, *Pg*=Boc

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 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=^{i}Pr, *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).

The following structure−activity relationships (SARs) may be noted regarding the inhibition data of Table 2:

(i) The ubiquitous cytosolic hCA I was inhibited by all compounds with K_i spanning between low nanomolar (K_i 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-fold. Compound **8** inhibited this isoform in medium nanomolar range with a K_i of 93 nM. Compounds with different N-protecting groups, such as **7a** and **7c**, led to a decrease of the inhibitory activity of nearly nine times (with the tosyl group in **7a**) and 18 times (for the Boc derivative **7c**) compared to **8**.

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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]

	K_i[a] (nM)				
Compound	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

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

(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 six-fold 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,d,f,g** and **7a** were subnanomolar hCA VII inhibitors, 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 influence significantly the inhibition activity, except for **5c**, which had a decrease of efficacy (K_i 8133 nM). Compound **7a**, with a tosyl moiety as a 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 clinically 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 influence 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 regarding the important difference 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 a 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 isoforms 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 inhibitors 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 at DOI: 10.1021/acsmedchemlett.7b00387.

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

■ REFERENCES

(1) Olcott, H. S.; Brown, W. D.; Van Derveen, J. Selenomethionine as an Antioxidant. *Nature* **1961**, *191*, 1201.

DOI: 10.1021/acsmedchemlett.7b00387
ACS Med. Chem. Lett. 2017, 8, 1213−1217

(2) Walter, R.; Schwartz, I. L.; Roy, J. Can selenoamino acids act as reversible biological antioxidants? *Ann. N. Y. Acad. Sci.* **1972**, *192*, 175−180.
(3) Halliwel, B.; Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*, 4th ed.; Oxford University Press: Oxford, 2007.
(4) Halliwell, B. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiol.* **2006**, *141*, 312.
(5) Andersen, J. K. Oxidative stress in neurodegeneration: cause or consequence? *Nat. Rev. Neurosci.* **2004**, *5*, S18−25.
(6) Seet, R. C. S.; Lee, C.-Y. J.; Lim, E. C. H.; Tan, J. J. H.; Quek, A. M. L.; Chong, W.-L.; Looi, W.-F.; Huang, S.-H.; Wang, H.; Chan, Y.-H.; Halliwell, B. Oxidative damage in Parkinson disease: Measurement using accurate biomarkers. *Free Radical Biol. Med.* **2010**, *48*, 560.
(7) Wang, J.-F.; Komarov, P.; Sies, H.; de Groot, H. Inhibition of superoxide and nitric oxide release and protection from reoxygenation injury. *Hepatology* **1992**, *15*, 1112.
(8) Wang, J.-F.; Komarov, P.; Sies, H.; de Groot, H. Contribution of nitric oxide synthase to luminol-dependent chemiluminescence generated by phorbol-ester-activated Kupffer cells. *Biochem. J.* **1991**, *279*, 311.
(9) Zembowicz, A.; Hatchett, R. J.; Radziszewski, W.; Gryglewski, R. J. Inhibition of endothelial nitric oxide synthase by ebselen. Prevention by thiols suggests the inactivation by ebselen of a critical thiol essential for the catalytic activity of nitric oxide synthase. *J. Pharmacol. Exp. Therap.* **1993**, *267*, 1112.
(10) Southan, G. J.; Salzman, A. L.; Szabó, C. Potent inhibition of the inducible isoform of nitric oxide synthase by aminoethylisoselenourea and related compounds. *Life Sci.* **1996**, *58*, 1139.
(11) Schewe, C.; Schewe, T.; Wendel, A. Strong inhibition of mammalian lipoxygenases by the antiinflammatory seleno-organic compound ebselen in the absence of glutathione. *Biochem. Pharmacol.* **1994**, *48*, 65.
(12) Angeli, A.; Carta, F.; Bartolucci, G.; Supuran, C. T. Synthesis of novel acyl selenoureido benzensulfonamides as carbonic anhydrase I, II, VII and IX inhibitors. *Bioorg. Med. Chem.* **2017**, *25*, 3567.
(13) Angeli, A.; Tanini, D.; Viglianisi, C.; Panzella, L.; Capperucci, A.; Menichetti, S.; Supuran, C. T. Evaluation of selenide, diselenide and selenoheterocycle derivatives as carbonic anhydrase I, II, IV, VII and IX inhibitors. *Bioorg. Med. Chem.* **2017**, *25*, 2518.
(14) Angeli, A.; Peat, T. S.; Bartolucci, G.; Nocentini, A.; Supuran, C. T.; Carta, F. Intramolecular oxidative deselenization of acylselenoureas: a facile synthesis of benzoxazole amides and carbonic anhydrase inhibitors. *Org. Biomol. Chem.* **2016**, *14*, 11353−11356.
(15) Supuran, C. T. Carbonic anhydrases: novel therapeutic applications for inhibitors and activators. *Nat. Rev. Drug Discovery* **2008**, *2*, 168−181.
(16) Supuran, C. T. How many carbonic anhydrase inhibition mechanisms exist? *J. Enzyme Inhib. Med. Chem.* **2016**, *31*, 345−360.
(17) Supuran, C. T. Structure and function of carbonic anhydrases. *Biochem. J.* **2016**, *473*, 2023−2032.
(18) Tanini, D.; Grechi, A.; Dei, S.; Teodori, E.; Capperucci, A. An easy one-step procedure for the synthesis of novel β-functionalised tellurides. *Tetrahedron* **2017**, *73*, 5646−5653.
(19) Tanini, D.; Capperucci, A.; Degl'Innocenti, A. Bis-(trimethylsilyl)selenide in the Selective Synthesis of β-Hydroxy, β-Mercapto, and β-Amino Diorganyl Diselenides and Selenides Through Ring Opening of Strained Heterocycles. *Eur. J. Org. Chem.* **2015**, *2015*, 357−369.
(20) Capperucci, A.; Tanini, D.; Borgogni, C.; Degl'Innocenti, A. Thiosilane- and Organoselenosilane-Mediated Novel Access to 3,7-Disubstituted-1,2,5- trithiepanes and −1,2,5-dithiaselenepanes. *Heteroat. Chem.* **2014**, *25*, 678−683.
(21) Capperucci, A.; Tiberi, C.; Pollicino, S.; Degl'Innocenti, A. Fluoride Ion Induced Thiophilic Reactivity of Organosilanes with Sulfines: Regiospecific Access to Allyl and Benzyl Sulfoxides. *Tetrahedron Lett.* **2009**, *50*, 2808−2810.
(22) Tanini, D.; D'Esopo, V.; Chen, D.; Barchielli, G.; Capperucci, A. Novel sulfur and selenium-containing antioxidants: Synthesis and evaluation of their GPx-like activity. *Phosphorus, Sulfur Silicon Relat. Elem.* **2017**, *192*, 166−168.
(23) Menichetti, S.; Capperucci, A.; Tanini, D.; Braga, A. L.; Botteselle, G. V.; Viglianisi, C. A One-Pot Access to Benzo[b][1,4]-selenazines from 2-Aminoaryl Diselenides. *Eur. J. Org. Chem.* **2016**, *2016*, 3097−3102.
(24) Tanini, D.; Panzella, L.; Amorati, R.; Capperucci, A.; Pizzo, E.; Napolitano, A.; Menichetti, S.; D'Ischia, M. Resveratrol-based benzoselenophenes with an enhanced antioxidant and chain breaking capacity. *Org. Biomol. Chem.* **2015**, *13*, 5757−5764.
(25) Capperucci, A.; Tanini, D. Silicon-assisted synthesis and functionalization of sulfurated and selenated compounds. *Phosphorus, Sulfur Silicon Relat. Elem.* **2015**, *190*, 1320−1338.
(26) Silva, P. C.; Borges, E. L.; Lima, D. B.; Jacob, R. G.; Lenardão, E. J.; Perin, G.; Silva, M. S. A simple and non-conventional method for the synthesis of selected β-arylalkylchalcogeno substituted alcohols, amines and carboxylic acids. *Arkivoc* **2016**, *5*, 376−389.
(27) Ganesh, V.; Chandrasekaran, S. One-Pot Synthesis of β-Amino/β-Hydroxy Selenides and Sulfides from Aziridines and Epoxides. *Synthesis* **2009**, *19*, 3267−3278.
(28) Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. intramolecular addition of carbon radicals to aldehydes: synthesis of enantiopure tetrahydrofuran-3-ols. *Tetrahedron* **2007**, *63*, 5482−5489.
(29) Tanini, D.; Barchielli, G.; Benelli, F.; Degl'Innocenti, A.; Capperucci, A. Aziridines Ring Opening by Silyl Chalcogenides: a Stereoselective Access to Polyfunctionalized Molecules as Precursor of Sulfurated and Selenated Heterocycles. *Phosphorus, Sulfur Silicon Relat. Elem.* **2015**, *190*, 1265−1270.
(30) Braga, A. L.; Schneider, P. H.; Paixao, M. W.; Deobald, A. M.; Peppe, C.; Bottega, D. P. Chiral Seleno-Amines from Indium Selenolates. A Straightforward Synthesis of Selenocysteine Derivatives. *J. Org. Chem.* **2006**, *71*, 4305−4307.
(31) Charrat, C.; Biscotti, A.; Godeau, G.; Greiner, J.; Vierling, P.; Guigonis, J. M.; Di Giorgio, C. Formulation of highly functionalizable DNA nanoparticles based on 1,2-dithiolane derivatives. *ChemBioChem* **2015**, *16*, 792−804.
(32) Khalifah, R. G. The carbon dioxide hydration activity of carbonic anhydrase. I. Stop flow kinetic studies on the native human isoenzymes B and C. *J. Biol. Chem.* **1971**, *246*, 2561.
(33) Mollica, A.; Locatelli, M.; Macedonio, G.; Carradori, S.; Sobolev, A. P.; De Salvador, R. F.; Monti, S. M.; Buonanno, M.; Zengin, G.; Angeli, A.; Supuran, C.T. Microwave-assisted extraction, HPLC analysis, and inhibitory effects on carbonic anhydrase I, II, VA, and VII isoforms of 14 blueberry Italian cultivars. *J. Enzyme Inhib. Med. Chem.* **2016**, *31*, 1−6.
(34) De Vita, D.; Angeli, A.; Pandolfi, F.; Bortolami, M.; Costi, R.; Di Santo, R.; Suffredini, E.; Ceruso, M.; Del Prete, S.; Capasso, C.; Scipione, L.; Supuran, C. T. Inhibition of the α-carbonic anhydrase from Vibrio cholerae with amides and sulfonamide incorporating imidazole moieties. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 798.
(35) Bruno, E.; Buemi, M. R.; Di Fiore, A.; De Luca, L.; Ferro, S.; Angeli, A.; Cirilli, R.; Sadutto, D.; Alterio, V.; Monti, S. M.; Supuran, C. T.; De Simone, G.; Gitto, R. Probing Molecular Interactions between Human Carbonic Anhydrases (hCAs) and a Novel Class of Benzenesulfonamides. *J. Med. Chem.* **2017**, *60*, 4316.
(36) Abdoli, M.; Angeli, A.; Bozdag, M.; Carta, F.; Kakanejadifard, A.; Saeidian, H.; Supuran, C. T. Synthesis and carbonic anhydrase I, II, VII, and IX inhibition studies with a series of benzo[d]thiazole-5- and 6-sulfonamides. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 1071−1078.
(37) Mishra, C. B.; Kumari, S.; Angeli, A.; Monti, S. M.; Buonanno, M.; Tiwari, M.; Supuran, C. T. Discovery of Benzenesulfonamides with Potent Human Carbonic Anhydrase Inhibitory and Effective Anticonvulsant Action: Design, Synthesis, and Pharmacological Assessment. *J. Med. Chem.* **2017**, *60*, 2456−2469.
(38) Abdel-Aziz, A. A.; Angeli, A.; El-Azab, A. S.; Abu El-Enin, M. A.; Supuran, C. T. Synthesis and biological evaluation of cyclic imides incorporating benzenesulfonamide moieties as carbonic anhydrase I, II, IV and IX inhibitors. *Bioorg. Med. Chem.* **2017**, *25*, 1666−1671.

DOI: 10.1021/acsmedchemlett.7b00387
ACS Med. Chem. Lett. 2017, 8, 1213−1217

(39) Monti, D. M.; De Simone, G.; Langella, E.; Supuran, C. T.; Di Fiore, A.; Monti, S. M. Insights into the role of reactive sulfhydryl groups of Carbonic Anhydrase III and VII during oxidative damage. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 5−12.
(40) Del Giudice, R.; Monti, D. M.; Truppo, E.; Arciello, A.; Supuran, C. T.; De Simone, G.; Monti, S. M. Human carbonic anhydrase VII protects cells from oxidative damage. *Biol. Chem.* **2013**, *394*, 1343−8.
(41) De Simone, G.; Langella, E.; Esposito, D.; Supuran, C. T.; Monti, S. M.; Winum, J. Y.; Alterio, V. Insights into the binding mode of sulphamates and sulphamides to hCA II: crystallographic studies and binding free energy calculations. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 1002−1011.
(42) Kalinin, S.; Kopylov, S.; Tuccinardi, T.; Sapegin, A.; Dar'in, D.; Angeli, A.; Supuran, C. T.; Krasavin, M. Lucky Switcheroo: Dramatic Potency and Selectivity Improvement of Imidazoline Inhibitors of Human Carbonic Anhydrase VII. *ACS Med. Chem. Lett.* **2017**, *8*, 1105−1109.

DOI: 10.1021/acsmedchemlett.7b00387
ACS Med. Chem. Lett. 2017, 8, 1213−1217