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Sulfur, selenium and tellurium containing amines act as effective carbonic anhydrase activators

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ABSTRACT

A new series of β-aminochalcogenides were designed and synthesized to identify new carbonic anhydrase activator (CAA) agents as novel tools for the management of several neurodegenerative and metabolic disorders which represent a clinical challenge without effective therapies available. Some β-aminoselenides and β-aminotellurides showed effective CA activating effects and a potent antioxidant activity. CAAs may have applications for memory therapy and CA deficiency syndromes.

1. Introduction

Carbonic anhydrases (CAs; EC 4.2.1.1) are ubiquitous metalloenzymes known for decades to be involved in the reversible hydration of CO_2 to bicarbonate and H^+ ions [1,2]. This simple reaction plays a key role in many crucial physiologic functions connected to metabolic pathways in which CO_2 is implicated [3–6]. For this reason, their modulation is used for a long time in the treatment of different diseases such as glaucoma, [7] edema, [8] epilepsy [9] and, more recently, inhibitors of CAs are used as a new approach for treatment of neuropathic pain, [10,11] cerebral ischemia [12] and different forms of tumor [13]. The activation of CA, to date, does not yet have a clinical application and has been a subject of debate for a long time. Only recently their pharmacological exploration started [2,14]. Histamine (Fig. 1) was one of the first CA activators (CAAs) discovered [15] and also one of the most investigated scaffolds [16,17]. X-ray crystal structure of CA-Histamine has been reported in the 90's showing the mechanism of activation, where the molecule participates to the rate-determining step of the catalytic cycle, facilitating the formation of the nucleophilic species of the enzyme [15]. In the last years, our group focused on new molecules with activating propriety against CAs, most of which amines of the general formula Ar–CH_2CH(R)NHR' [18–20]. In a recent study from our group, [21] psychoactive drugs such as amphetamine and related compounds (Fig. 1) showed strong activating proprieties against different CA isoforms.

In order to continue our studies in this less investigated field, we synthetized, for the first time, organic chalcogenides structurally related to the psychoactive drug Amphetamine. We sought to use N—H unactivated aziridines in reactions with suitable nucleophiles for preparing these derivatives. Indeed, ring opening reactions of strained heterocycles with chalcogen nucleophiles, including silyl chalcogenides [22–27] represents a versatile way to obtain a large variety of biologically and synthetically valuable organosulfur, [28] organoselenium, [29] and organotellurium [30] compounds.

2. Results and discussion

2.1. Compounds design and synthesis

We began our investigations by establishing the conditions required to obtain aminosulfide **2a** through the ring opening reaction of 2-methylaziridine **2a** with thiophenol **1a**. Among several organic or inorganic bases (Et_3N, DMAP, Cs_2CO_3/TBAI) and solvents (THF, CH_2Cl_2) evaluated, the use of KOH in DMF proved to be the most effective conditions in promoting the desired transformation, allowing to access **3a** in acceptable yield. Evaluation of different temperatures (−15 °C, r.t.) gave no yield improvement. Having found suitable conditions for the synthesis of β-aminosulfides bearing a free amino function, we next explored the scope of this procedure. Thus, *o*-, *m*-, and *p*-bromothiophenol (**1b-d**) were smoothly converted into the corresponding β-aminosulfides **3b-d** upon reaction with **2a** under the same conditions. Interestingly, the yield proved to be strongly influenced by the position of the bromine on the aromatic ring, increasing from 44% (for the more hindered *o*-Br-C_6H_4 substituent) to 63% (for the less hindered *p*-Br-C_6H_4). Furthermore, the reaction of 2-mercaptopyrimidine **1e** with 2-methylaziridine resulted in the formation of the heteroaromatic

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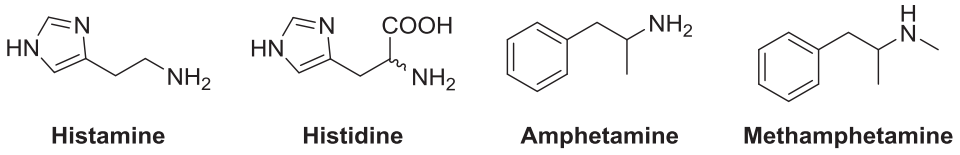
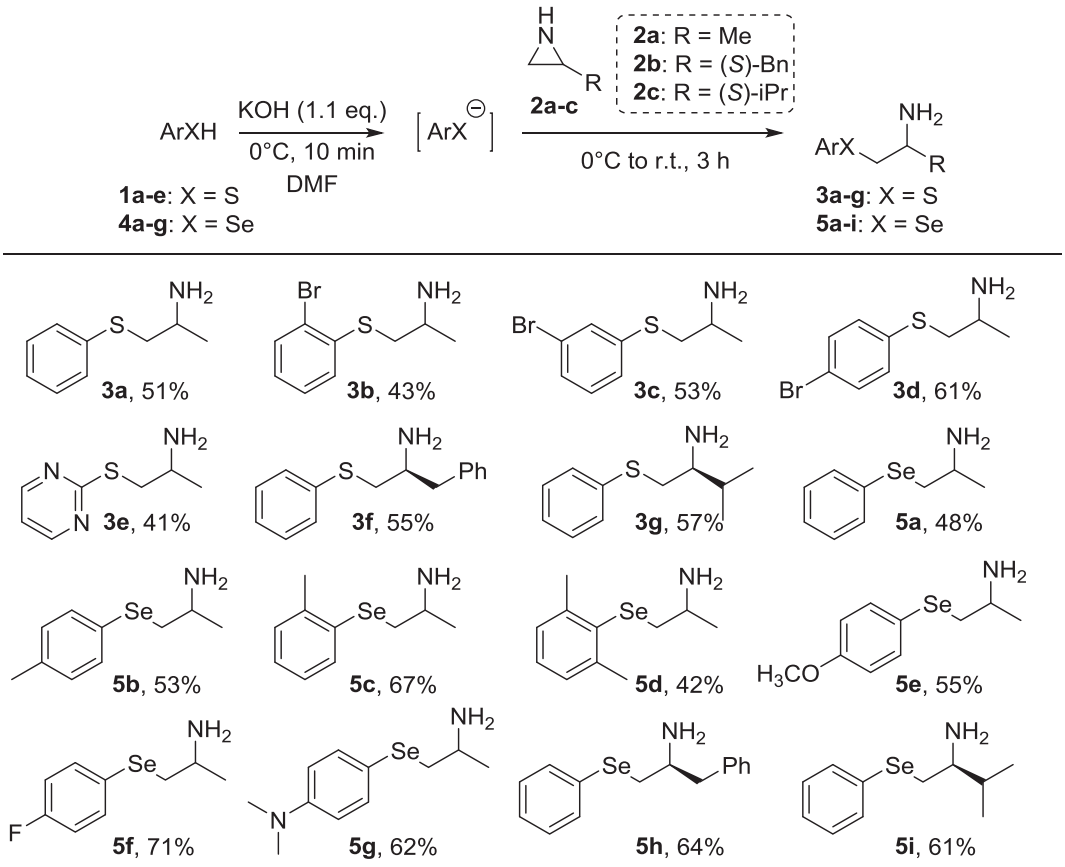


Fig. 1. Examples of CAAs: Histamine, Histidine, Amphetamine and Methamphetamine.



Scheme 1. Synthesis of β-amino sulfides **3a-g** and β-amino selenides **5a-i** from *N*—H aziridines, Yields refer to isolated products.

aminosulfide **3e**. In order to evaluate the effect of the substituent on the stereogenic centre and to further enlarge the scope of the reaction, we also synthesized enantioenriched aminosulfides **3f,g** from thiophenol and (*S*)—*N*—H aziridines **2b,c**. Having obtained different novel sulfur-containing hCA activator candidates, we next evaluated the reactivity of selenols [31,32] with 2-methylaziridine, in order to access new β-aminoselenides with potential activity as hCA activators. Therefore, a series of differently substituted aryl selenols (**4a-g**) were treated with aziridines **2a** in the presence of KOH to afford the corresponding β-aminoselenides **5a-g**. Furthermore, chiral enantioenriched β-phenylseleno amines **5h,i** were successfully achieved from the corresponding (*S*)-aziridines **2b,c** and benzeneselenol **4a**. These findings describe the first example of ring opening reaction of *N*-unactivated aziridines with stable aryl selenols (See Scheme 1).

Having synthesised a wide variety of arylthio- and arylseleno-amines, we also investigated the reactivity of unprotected aziridines with tellurium-containing nucleophiles. Owing to the instability of tellurols, we sought to exploit the reactivity of *in situ* generated aryltellurolate anions. Thus, differently substituted diaryl ditellurides **6a-e** were treated with $NaBH_4$ and, then, reacted with *N*—H aziridine **2a**, affording the corresponding β-amino aryltellurides **7a-e**, bearing different substituted phenyl rings (**7a-d**) or the naphthyl group (**7e**). Furthermore, enantioenriched β-phenyltelluro amines **7e,f** were achieved from ditelluride **6a** and (*S*)-2-benzyl- or (*S*)-2-isopropyl-aziridine, respectively (See Scheme 2).

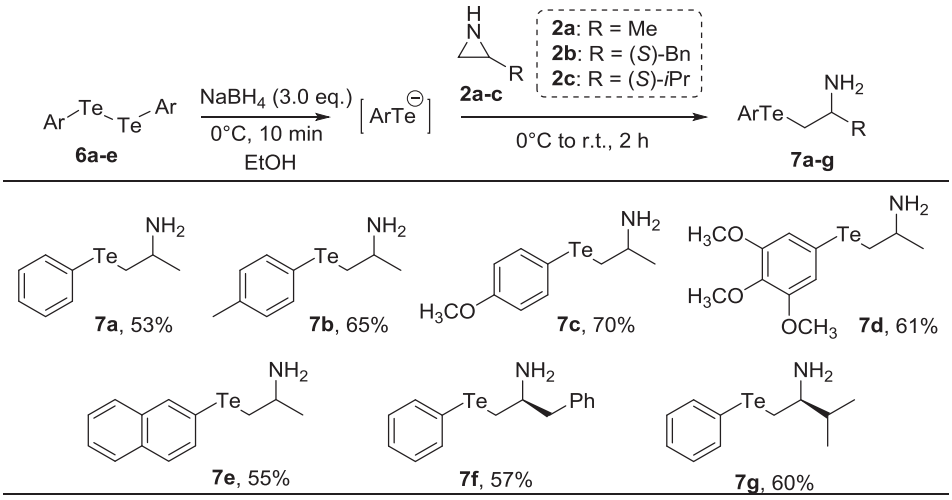
2.2. Carbonic anhydrase activation

To the best of our knowledge, this is the first study which evaluates the activation profile of different β-aminochalcogenides. For this reason, we investigated the CA activating properties of amines **3a-g**, **5a-I** and **7a-g** against 4 catalytically active and physiologically relevant hCA isoforms, the hCA I, II, VA and VII. Amphetamine (**AMP**) and histamine (**HIST**) were used as standard activators and shown in Table 1.

The following SAR can be observed regarding the activation data of Table 1:

(i) The cytosolic, widespread isoform hCA II was not activated by these amines except for compound **5g** which showed an activation constant of 45.1 μM.

(ii) The widely abundant cytosolic isozyme hCA I was moderately activated by most of the compounds here studied. β-Aminosulfides **3a-g** showed K_As spanning between 7.7 and 13.5 μM. The presence of the bromine atom on aromatic ring plays a crucial role in modulation of activity. Indeed, bromine in position 3 decreased the potency almost 2 times for compound **3d** and 1.5 time when Br is placed in position 4 (**3d**). The replacement of the sulfur with



Scheme 2. Synthesis of β-amino tellurides **7a-g** from *N*—H aziridines. Yields refer to isolated products.

selenium or tellurium in compounds **3a**, **5a** and **7a** did not influence significantly the activity (K_As of 11.8–9.9 μM). On the other hand, this replacement from sulfur to tellurium influenced the potency for the analogous compounds **3f**, **5h** and **7f**. Indeed, such structures showed an increased activity moving within the chalcogen series, from sulfur to tellurium (K_As 8.8 to 5.1 μM). A different trend was observed for β-aminochalcogenides with isopropyl moiety (**3g**, **5i** and **7g**). Compound **3g** showed a K_A of 7.9 μM and the activity increased with the passage of selenium analog **5i** (K_A 5.9 μM), but this time, organo-tellurium compound **7g** showed less activating effects near two time than **3g** (K_A 13.3 μM).

(iii) The mitochondrial isoform hCA VA, involved in different metabolic pathway such as ureagenesis, lipogenesis and neoglucogenesis, [34] was also activated by β-aminochalcogenides **3a-g**, **5a-I** and **7a-g** with K_As ranging between 3.3 and 43.7 μM (Table 1). The best activators against this isoform were compounds with para substitution **7b** and **7c** with K_As of 4.0 and 3.3 μM, respectively. Additional substitution (**7d**) or replacement with a more bulky scaffold (**7e**) decreases the activity. Additional substitution (**7d**) or replacement with a more bulky scaffold (**7e**) decrease the activity (K_A 9.4 and 20.2 μM respectively). On the other hand, β-aminosulfides **3a-g** showed a flat SAR against hCA VA with K_As ranging in a narrow interval of 10.2 to 13.3 μM except for compound **3e** with K_A of 43.7 μM. It should be noted that, also for this isoform, replacing the chalcogen atom within the homologous series of compounds **3f**, **5h** and **7f** results in increased potency moving from sulfur- to tellurium-containing derivatives (K_As 10.2–4.7 μM). These compounds remained, in any case, less effective on mitochondrial hCA compared to the psychotropic amine **AMP**.

(iv) The brain-associated cytosolic CA isoform, hCA VII, [35] is moderately activated by compounds here reported, with activation constants in the range of 8.9–44.9 μM. The less active compounds (**7a**, **7c** and **7e**) contain a tellurium atom. Contrarily, all other analog compounds such as **3a**, **5a** and **5e** showed near two time more efficacy than them (K_As 20.4–23.4 versus 41.2–44.9 μM). It is interesting to note there were not differences between the activating effects of β-aminosulfides **3a-g** and β-aminoselenides **5a-i**.

Table 1
Activation data of human CA isoforms I, II, VA and VII with compounds **3a-g, 5a-i, 7a-g, AMP** and **HIST** by a stopped flow CO_2 hydrase assay [33].

K_A (μM)*				
Cmp	hCA I	hCA II	hCA VA	hCA VII
3a	11.8	> 100	12.4	23.4
3b	9.5	> 100	13.3	23.2
3c	13.5	> 100	12.9	11.4
3d	7.7	> 100	12.4	14.8
3e	9.7	> 100	43.7	21.8
3f	8.8	> 100	10.2	14.8
3g	7.9	> 100	11.6	14.3
5a	9.9	> 100	14.7	20.6
5b	5.2	> 100	9.1	10.4
5c	12.1	> 100	20.0	14.2
5d	6.0	> 100	20.9	21.4
5e	21.4	> 100	20.3	23.3
5f	19.6	> 100	13.1	13.4
5g	22.1	45.1	14.0	12.1
5h	6.3	> 100	6.6	10.1
5i	5.9	> 100	8.3	11.4
7a	9.9	> 100	14.2	41.2
7b	8.2	> 100	4.0	21.9
7c	4.6	> 100	3.3	44.9
7d	9.5	> 100	9.4	14.3
7e	12.6	> 100	20.2	44.7
7f	5.1	> 100	4.7	8.9
7g	13.3	> 100	13.7	11.0
AMP[a]	> 100	> 100	0.81	0.91
HIST[a]	2.1	> 100	0.01	37.5

* Mean from 3 different assays, by a stopped flow technique (errors were in the range of ± 5–10% of the reported values).
[a] Data from Ref. [21].

2.3. Antioxidant assays

In order to develop novel hCA activators with antioxidant properties, we also evaluated the thiol peroxidase-like properties of selected β-arylchalcogeno amines. Therefore, the activity of sulfides **3a**,**c**, selenides **5a**,**e**,**l** and tellurides **7a-c**,**f** as mimics of Glutathione peroxidase (GPx) was assessed by using the dithiothreitol (DTT) oxidation test [36–39] and the GSH/GR coupled assay [39,40]. Results of this investigation are reported in Table 2.

Whilst aminosulfides did not show significant catalytic properties ($T_{50} \gg 24$ h for DTT assay), according both tests, all tested organoselenides and organo-tellurides exhibited remarkable catalytic antioxidant activity. Particularly, as expected, β-aryltelluro amines **7a-c**,**f** proved to behave as excellent catalysts, being able to promote DTT and GSH oxidation in 2 min and in 15 s, respectively [39]. As previously reported, aminoselenides and aminotellurides bearing a free amino function behave as better catalysts with respect to their *N*-Ts protected analogues (Table 2, entries 3, 7 *vs* entries 8, 9); [39] this suggests important criteria in order to maintain both the hCA activator and the

Table 2
Thiol peroxidase-like activity of β -arylchalcogeno amines according to different methods.

Entry	Compound	DTT(T_{50})[a,b,c]	GSH(T_{50})[a,d]
1	5a	442(± 42)	24(± 7)
2	5e	434(± 38)	21(± 6)
3	5i	398(± 54)	28(± 6)
4	5h	402(± 48)	32(± 9)
5	7a	< 60	< 5
6	7b	< 60	< 5
7	7c	< 60	< 5
8	7f	< 60	< 5
9	*N*-T_s-5i	3186(± 198)	129(± 16)
10	*N*-T_s-7f	600(± 61)	14(± 3)

[a] T_{50} is the time required, in seconds, to reduce the initial thiol concentration with 50% after the addition of H_2O_2; data in parenthesis are the experimental error.

[b] DTT oxidation was monitored by the mean of ^{1}H NMR spectroscopy; 10 mol % of organoselenide and 1 mol % of organotelluride with respect to the thiol were used.

[c] T_{50} for PhSeSePh (commonly used reference compound) was found to be 796 (± 84) seconds, according to DTT oxidation test.

[d] NADPH consumption was monitored by UV spectroscopy (340 nm); 10 mol % of organoselenide and 1 mol % of organotelluride with respect to GSH were used.

GPx-like properties.

3. Conclusions

We have used a fast and easy synthetic strategy to obtain ring opening reactions of strained heterocycles with chalcogen-containing nucleophiles to afford novel CA activators. Many of them showed an interesting pattern of activation against four of the most important physiologic carbonic anhydrase isoforms such as the cytosolic enzymes hCA I, II and VII, but also, against the mitochondrial isoform hCA VA. Compounds with selenium and in particular tellurium atoms are also able to prevent the generation of ROS metabolites that cause oxidative stress and cellular damage. In this context, CAAs may be used in the memory therapy and cognitive neurodegenerative disorders where the levels of ROS are particular high, but also in the metabolic pathologies where is present a decreased function of hCA VA without increased ROS levels.

4. Experimental part

4.1. General

Anhydrous solvents and all reagents were purchased from Sigma-Aldrich, Alfa Aesar and TCI. All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere using dried glassware and syringes techniques to transfer solutions. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ^{77}Se-NMR and ^{125}Te-NMR) spectra were recorded using a Bruker Advance III 400 MHz spectrometer in DMSO-d_6. $(PhSe)_2$ was used as an external reference for ^{77}Se NMR (δ = 461 ppm). Diphenyl ditelluride $(PhTe)_2$ was used as an external reference for ^{125}Te NMR (δ = 420 ppm). Chemical shifts are reported in parts per million (ppm) and the coupling constants (*J*) are expressed in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; brs, broad singlet; dd, double of doublets. The assignment of exchangeable protons (O*H* and N*H*) was confirmed by the addition of D_2O. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel F-254 plates. Flash chromatography purifications were performed on Merck Silica gel 60 (230–400 mesh ASTM) as the stationary phase and ethyl acetate/*n*-hexane were used as eluents. Melting points (mp) were measured in open capillary tubes with a Gallenkamp MPD350.BM3.5 apparatus and are uncorrected. The solvents used in MS measures were acetone, acetonitrile (Chromasolv grade), purchased from Sigma-Aldrich (Milan - Italy), and mQ water 18 MΩ, obtained from Millipore's Simplicity system (Milan-Italy). The mass spectra were obtained using a Varian 1200L triple quadrupole system (Palo Alto, CA, USA) equipped by Electrospray Source (ESI) operating in both positive and negative ions. Stock solutions of analytes were prepared in acetone at 1.0 mg mL^{-1} and stored at 4 °C. Working solutions of each analyte were freshly prepared by diluting stock solutions in a mixture of mQ H_2O/ACN 1/1 (*v/v*) up to a concentration of 1.0 μg mL^{-1} The mass spectra of each analyte were acquired by introducing, via syringe pump at 10 μL min^{-1}, of the its working solution. Raw-data were collected and processed by Varian Workstation Vers. 6.8 software. The HPLC was performed by using a Waters 2690 separation module coupled with a photodiode array detector (PDA Waters 996) using a Nova-Pak C18 4 μm 3.9 mm × 150 mm (Waters) silica-based reverse phase column. The sample was dissolved in 10% acetonitrile/H_2O and an injection volume of 45 μL. The mobile phase (flow rate 1.0 mL/min) was a gradient of H_2O + trifluoroacetic acid (TFA) 0.1% (A) and acetonitrile + TFA 0.1% (B), with steps as follows: (A%/B%), 0–10 min 90:10, 10–25 min gradient to 60:40, 26:28 min isocratic 20:80, 29–35 min isocratic 90:10. TFA 0.1% in water as well in acetonitrile was used as counterion. All compounds reported here were ≥ 95% HPLC pure.

4.2. General procedure for the synthesis of β-arylthio- and β -arylseleno-amines

Potassium hydroxide (1.1 eq.) was added to a solution of thiol 1a-e or selenol **4a-g** (1.0 eq.) in DMF (2 mL) under inert atmosphere (N_2) at 0 °C. Then *N*—H aziridine **2a-c** (1.2 eq.) was slowly added and the mixture was stirred at 0 °C for 3 h. Afterwards the reaction was diluted with EtOAc (5 mL) and saturated *aq.* NH_4Cl (2 mL) was added. The organic phase was collected and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography to yield the desired β -arylthioamine **3** or β-arylselenoamine **5**.

1-(Phenylthio)propan-2-amine (3a):

Following the general procedure, thiophenol **1a** (22 mg, 0.2 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-(phenylthio)propan-2-amine **3a** (17 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.23 (3H, d, *J* = 6.3 Hz), 2.49 (2H, bs, NH_2), 2.84 (1H, dd, *J* = 7.9,13.1 Hz, CH_aH_bS), 3.07 (1H, dd, *J* = 4.7, 13.1 Hz, CH_aH_bS), 3.09–3.17 (1H, m, $CHNH_2$), 7.19–7.23 (1H, m), 7.28–7.32 (2H, m), 7.38–7.41 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.4, 43.6, 46.2, 126.3, 129.0, 129.8, 135.9. All recorded spectroscopic data matched those reported in the literature [41].

1-((2-Bromophenyl)thio)propan-2-amine (3b)

Following the general procedure, 2-bromobenzenethiol **1b** (38 mg, 0.2 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-((2-bromophenyl)thio)propan-2-amine **3b** (21 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.23 (3H, d, *J* = 6.3 Hz), 2.23 (2H, bs, NH_2), 2.83 (1H, dd, *J* = 7.9,12.9 Hz, CH_aH_bS), 3.05 (1H, dd, *J* = 4.7, 12.9 Hz, CH_aH_bS), 3.11–3.19 (1H, m, $CHNH_2$), 7.04 (1H, td, *J* = 1.6, 7.9 Hz), 7.23–7.28 (1H, m), 7.28, 7.33 (1H, m), 7.55 (1H, dd, *J* = 1.0, 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.8, 43.0, 45.9, 124.1, 126.9, 127.7, 128.9, 133.0, 137.4. MS (ESI, positive): 246.2 $[M + H]^+$.

1-((3-Bromophenyl)thio)propan-2-amine (3c)

Following the general procedure, 3-bromobenzenethiol **1c** (47 mg, 0.25 mmol) and 2-methylaziridine **2a** (17 mg, 0.30 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-((3-bromophenyl)thio)propan-2-amine **3c** (33 mg, 54%).

^{1}HMR (400 MHz, $CDCl_3$): δ (ppm) 1.18 (3H, d, J = 6.3 Hz), 1.86 (2H, bs, NH_2), 2.78 (1H, dd, J = 7.9, 13.0 Hz, CH_aH_bS), 3.02 (1H, dd, J = 4.7, 13.0, CH_aH_bS), 3.06–3.14 (1H, m, $CHNH_2$), 7.13 (1H, t, J = 7.9 Hz), 7.25–7.31 (2H, m), 7.48 (1H, apt, J = 1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.8, 43.6, 46.0, 122.7, 127.5, 128.9, 130.1, 131.4, 138.7. MS (ESI, positive): 246.6 $[M + H]^+$.

1-((4-Bromophenyl)thio)propan-2-amine (3d)

Following the general procedure, 4-bromobenzenethiol **1d** (38 mg, 0.2 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-((4-bromophenyl)thio)propan-2-amine **3d** (30 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.13 (3H, d, J = 6.3 Hz), 1.78 (2H, bs, NH_2), 2.72 (1H, dd, J = 8.0, 13.1, CH_aH_bS), 2.96 (1H, dd, J = 4.6, 13.1, CH_aH_bS), 2.99–3.08 (1H, m, $CHNH_2$), 7.18 (2H, apd, J = 8.5 Hz), 7.35 (2H, apd, J = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.8, 43.9, 45.9, 119.8, 130.89, 131.84, 135.7. MS (ESI, positive): 246.3 $[M + H]^+$.

1-(Pyrimidin-2-ylthio)propan-2-amine (3e)

Following the general procedure, pyrimidine-2-thiol **1e** (23 mg, 0.2 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-(pyrimidin-2-ylthio)propan-2-amine **3e** (14 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.25 (3H, d, J = 6.3 Hz), 2.09 (2H, bs, NH_2), 3.09 (1H, dd, J = 6.7, 12.9 Hz, CH_aH_bS), 3.33 (1H, dd, J = 4.9, 12.9 Hz, CH_aH_bS), 3.25–3.32 (1H, m, $CHNH_2$), 6.96 (1H, t, J = 4.8 Hz), 8.50 (2H, d, J = 4.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.5, 40.1, 46.8, 116.6, 157.2, 127.2. MS (ESI, positive): 169.9 $[M + H]^+$.

(*S*)-1-Phenyl-3-(phenylthio)propan-2-amine (3f)

Following the general procedure, thiophenol **1a** (22 mg, 0.2 mmol) and (*S*)-2-benzylaziridine **2b** (32 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:1), (*S*)-1-phenyl-3-(phenylthio)propan-2-amine **3f** (27 mg, 55%). All recorded spectroscopic data matched those reported in the literature [42].

(*S*)-3-Methyl-1-(phenylthio)butan-2-amine (3 g)

Following the general procedure, thiophenol **1a** (28 mg, 0.25 mmol) and (*S*)-2-isopropylaziridine **2c** (26 mg, 0.30 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:1), (*S*)-3-methyl-1-(phenylthio)butan-2-amine **3 g** (28 mg, 57%). All recorded spectroscopic data matched those reported in the literature [41].

1-(Phenylselanyl)propan-2-amine (5a)

Following the general procedure, benzeneselenol **4a** (31 mg, 0.2 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-(phenylselanyl)propan-2-amine **5a** (21 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.19 (3H, dd, J = 6.3, 12.4 Hz), 2.45 (2H, bs, NH_2), 2.84 (1H, dd, J = 7.7, 12.2 Hz, CH_aH_bSe), 3.05 (1H, dd, J = 4.8, 12.2 Hz, CH_aH_bSe), 3.08–3.16 (1H, m, $CHNH_2$), 2.24–2.30 (3H, m), 7.52–7.56 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 23.1, 38.7, 46.7, 127.0, 129.1, 130.0, 132.8. ^{77}Se NMR(76 MHz, $CDCl_3$): δ (ppm) 254.1. MS (ESI, positive): 216.5 $[M + H]^+$.

1-(*p*-Tolylselanyl)propan-2-amine (5b)

Following the general procedure, 4-methylbenzeneselenol **4b** (43 mg, 0.25 mmol) and 2-methylaziridine **2a** (17 mg, 0.30 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-(*p*-tolylselanyl)propan-2-amine **5b** (30 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.18 (3H, d, J = 6.3 Hz), 2.31 (3H, s), 2.48 (2H, bs, NH_2), 2.79 (1H, dd, J = 7.9, 12.4 Hz, CH_aH_bSe), 2.99 (1H, dd, J = 4.8, 12.4 Hz, CH_aH_bSe), 3.04–3.12 (1H, m, $CHNH_2$), 7.07 (2H, apd, J = 8.0 Hz), 7.42 (2H, apd, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 23.0, 38.8, 46.7, 125.9, 133.4, 137.2. ^{77}Se NMR (76 MHz, $CDCl_3$): δ (ppm) 246.7. MS (ESI, positive): 230.2 $[M + H]^+$.

1-(*o*-Tolylselanyl)propan-2-amine (5c)

Following the general procedure, 2-methylbenzeneselenol **4c** (34 mg, 0.20 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-(*o*-tolylselanyl)propan-2-amine **5c** (31 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.20 (3H, d, J = 6.3 Hz), 2.08 (2H, bs, NH_2), 2.42 (3H, s), 2.80 (1H, dd, J = 7.9, 12.2 Hz, CH_aH_bSe), 3.01 (1H, dd, J = 4.8, 12.2 Hz, CH_aH_bSe), 3.07–3.15 (1H, m, $CHNH_2$), 7.09 (1H, td, J = 1.7, 7.4 Hz), 7.14 (1H, td, J = 1.3, 7.4 Hz), 7.14–7.19 (1H, m), 7.44 (1H, apd, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.4, 23.3, 37.6, 46.7, 126.5, 126.8, 130.0, 131.0, 131.8, 139.5. ^{77}Se NMR (76 MHz, $CDCl_3$): δ (ppm) 206.7. MS (ESI, positive): 229.8 $[M + H]^+$.

1-((2,6-Dimethylphenyl)selanyl)propan-2-amine (5d)

Following the general procedure, 2,6-dimethylbenzeneselenol **4d** (37 mg, 0.20 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-((2,6-dimethylphenyl)selanyl)propan-2-amine **5d** (20 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.21 (3H, d, J = 6.4 Hz), 2.58 (6H, s), 2.70 (1H, dd, J = 7.3, 12.0 Hz, CH_aH_bSe), 2.79 (1H, dd, J = 5.5, 12.0 Hz, CH_aH_bSe) 2.92–3.08 (3H, m, $CHNH_2$ partially overlapped con NH_2), 7.07–7.14 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.4, 24.7, 47.6, 127.7, 128. 4, 136.5, 143.0. MS (ESI, positive): 244.1 $[M + H]^+$.

1-((4-Methoxyphenyl)selanyl)propan-2-amine (5e)

Following the general procedure, 4-methoxybenzeneselenol **4e** (56 mg, 0.30 mmol) and 2-methylaziridine **2a** (21 mg, 0.36 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-((4-methoxyphenyl)selanyl)propan-2-amine **5e** (40 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.17 (3H, d, J = 6.3 Hz), 2.40 (2H, bs, NH_2), 2.73 (1H, dd, J = 8.0, 12.3 Hz, CH_aH_bSe), 2.93 (1H, dd, J = 4.7,12.3 Hz, CH_aH_bSe), 3.0–3.08 (1H, m, $CHNH_2$), 3.78 (3H, s, CH_3O), 6.80 (2H, apd, J = 8.6 Hz), 7.48 (2H, apd, J = 8.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.9, 39.6, 46.6, 55.3, 114.8, 119.6, 135.7, 159.3. MS (ESI, positive): 245.8 $[M + H]^+$.

1-((4-Fluorophenyl)selanyl)propan-2-amine (5f)

Following the general procedure, 4-fluorobenzeneselenol **4f** (35 mg, 0.20 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-((4-fluorophenyl)selanyl)propan-2-amine **5f** (33 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.17 (3H, d, J = 6.3 Hz), 2.24 (2H, bs, NH_2), 2.78 (1H, dd, J = 7.9, 12.3 Hz, CH_aH_bSe), 2.97 (1H, dd, J = 4.8, 12.3 Hz, CH_aH_bSe), 3.01–3.1 (1H, m, $CHNH_2$), 6.95 (2H, apt, J = 8.7 Hz), 7.50 (2H, apdd, J = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 23.1, 39.5, 46.6, 116.3 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 124.2 ($^4J_{C\text{-}F}$ = 3.4 Hz), 135.4 ($^3J_{C\text{-}F}$ = 7.9 Hz), 162.4 ($^1J_{C\text{-}F}$ = 247.1 Hz). ^{77}Se NMR (76 MHz, $CDCl_3$): δ (ppm) 251.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) −114.6 (tt, J = 5.4, 8.7 Hz). MS (ESI, positive): 234.4 $[M + H]^+$.

4-((2-Aminopropyl)selanyl)-*N*,*N*-dimethylaniline (5g)

Following the general procedure, 4-(dimethylamino)benzeneselenol **4g** (40 mg, 0.20 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 4-((2-aminopropyl)selanyl)-N,*N*-dimethylaniline **5g** (32 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.18 (3H, d, J = 6.4 Hz), 2.64 (2H, bs, NH_2), 2.69 (1H, dd, J = 8.2, 12.4 Hz, CH_aH_bSe), 2.90 (1H, dd, J = 4.7, 12.4 Hz, CH_aH_bSe), 2.94 (6H, s, $(CH_3)_2N$), 3.01–3.09 (1H, m, $CHNH_2$), 6.61 (2H, apd, J = 8.8 Hz), 7.43 (2H, apd, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.6, 39.4, 40.3, 46.7, 133.1, 113.9, 136.0, 150.2. MS (ESI, positive): 258.8 $[M + H]^+$.

(*S*)-1-Phenyl-3-(phenylselanyl)propan-2-amine (5h)

Following the general procedure, benzeneselenol **4a** (31 mg, 0.2 mmol) and (*S*)-2-benzylaziridine **2b** (32 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:1), (*S*)-1-phenyl-3-(phenylselanyl)propan-2-amine **5h** (37 mg, 64%). All recorded spectroscopic data matched those reported in the literature

[42].

(*S*)-3-Methyl-1-(phenylselanyl)butan-2-amine (5i)

Following the general procedure, benzeneselenol **4a** (39 mg, 0.25 mmol) and (*S*)-2-isopropylaziridine **2c** (26 mg, 0.30 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:1), (*S*)-3-methyl-1-(phenylselanyl)butan-2-amine **5i** (37 mg, 61%). All recorded spectroscopic data matched those reported in the literature [43].

4.3. General procedure for the synthesis of β-aryltelluro amines

Sodium borohydride (3.0 eq.) was added to a suspension of diaryl ditelluride **6a-e** (1.0 eq.) in dry EtOH (2 mL) under inert atmosphere (N_2) at 0 °C. Then *N*—H aziridine **2a-c** (2.4 eq.) was slowly added and the mixture was allowed to warm to room temperature and then stirred 2 h. Afterwards the reaction was diluted with EtOAc (5 mL) and saturated *aq.* NH_4Cl (2 mL) was added. The organic phase was collected and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography to yield the desired β -aryltelluroamine **7**.

1-(Phenyltellanyl)propan-2-amine (7a)

Following the general procedure, 1,2-diphenylditellane **6a** (41 mg, 0.1 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-(phenyltellanyl)propan-2-amine **7a** (28 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.23 (3H, d, J = 6.2 Hz), 2.31 (2H, bs, NH_2), 2.95 (1H, dd, J = 7.0, 11.8 Hz, CH_aHbTe), 3.11 (1H, dd, J = 5.2, 11.8 Hz, CH_aH_bTe), 3.14–3.21 (1H, m, $CHNH_2$), 7.2–7.24 (2H, m), 7.28–7.32 (1H, m), 7.75–7.78 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 24.3, 47.8, 111.6, 127.7, 129.2, 138.4. ^{125}Te NMR (126 MHz, $CDCl_3$): δ (ppm) 390.5. MS (ESI, positive): 266.1 $[M + H]^+$.

1-(*p*-Tolyltellanyl)propan-2-amine (7b)

Following the general procedure, 1,2-di-*p*-tolylditellane **6b** (44 mg, 0.1 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-(*p*-tolyltellanyl)propan-2-amine **7b** (36 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.19 (3H, d, J = 6.2 Hz), 2.15 (2H, bs, NH_2), 2.33 (3H, s), 2.87 (1H, dd, J = 7.1, 11.9 Hz, CH_aH_bTe), 3.04 (1H, dd, J = 5.1, 11.9 Hz, CH_aH_bTe), 3.08–3.15 (1H, m, $CHNH_2$), 7.01 (2H, apd, J = 7.9 Hz), 7.64 (2H, apd, J = 7.09 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 21.2, 22.0, 24.4, 47.7, 107.3, 130.2, 137.7, 138.8. ^{125}Te NMR (126 MHz, $CDCl_3$): δ (ppm) 377.1. MS (ESI, positive): 280.4 $[M + H]^+$.

1-((4-Methoxyphenyl)tellanyl)propan-2-amine (7c)

Following the general procedure, 1,2-bis(4-methoxyphenyl)ditellane **6c** (47 mg, 0.1 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-((4-methoxyphenyl)tellanyl)propan-2-amine **7c** (41 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.21 (3H, d, J = 6.3 Hz), 2.86 (1H, dd, J = 7.1, 12.0 Hz, CH_aH_bTe), 2.92 (2H, bs, NH_2), 2.99 (1H, dd, J = 5.5, 12.0 Hz, CH_aH_bTe), 3.08–3.16 (1H, m, $CHNH_2$), 3.78 (3H, s, CH_3O), 6.75 (2H, apd, J = 8.7 Hz), 7.69 (2H, apd, J = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 23.9, 47.9, 55.1, 100.3, 115.2, 141.0, 159.8. ^{125}Te NMR (126 MHz, $CDCl_3$): δ (ppm) 379.8. MS (ESI, positive): 295.9 $[M + H]^+$.

1-((3,4,5-Trimethoxyphenyl)tellanyl)propan-2-amine (7d)

Following the general procedure, 1,2-bis(3,4,5-trimethoxyphenyl) ditellane **6d** (59 mg, 0.1 mmol) and 2-methylaziridine **2a** (14 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:2), 1-((3,4,5-trimethoxyphenyl)tellanyl) propan-2-amine **7d** (43 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.22 (3H, t, J = 6.2 Hz), 2.19 (2H, bs, NH_2), 2.93 (1H, dd, J = 7.1, 11.8 Hz, CH_aH_bTe), 3.09 (1H, dd, J = 5.2, 11.8 Hz, CH_aH_bTe), 3.13–3.21 (1H, m, $CHNH_2$), 3.83 (3H, s), 3.85 (6H, s) 6.97 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.5, 24.5, 47.8, 56.3, 60.9, 104.2, 116.4, 138.4, 153.4. ^{125}Te NMR (126 MHz, $CDCl_3$) δ (ppm): 434.6. MS (ESI, positive): 356.4 $[M + H]^+$.

(*S*)-1-Phenyl-3-(phenyltellanyl)propan-2-amine (7f)

Following the general procedure, 1,2-diphenylditellane **6a** (41 mg, 0.1 mmol) and (*S*)-2-benzylaziridine **2b** (32 mg, 0.24 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:1), (*S*)-1-phenyl-3-(phenyltellanyl)propan-2-amine **7f** (39 mg, 57%). All recorded spectroscopic data matched those reported in the literature [26].

(*S*)-3-Methyl-1-(phenyltellanyl)butan-2-amine (7g)

Following the general procedure, benzeneselenol **4a** (41 mg, 0.1 mmol) and (*S*)-2-isopropylaziridine **2c** (26 mg, 0.30 mmol) gave, after purification by flash column chromatography (petroleum ether:EtOAc 1:1), (*S*)-3-methyl-1-(phenyltellanyl)butan-2-amine **7g** (35 mg, 60%). All recorded spectroscopic data matched those reported in the literature [39].

4.4. Carbonic anhydrase enzyme activation assay

An Sx.18Mv-R Applied Photophysics (Oxford, UK) stopped-flow instrument has been used to assay the catalytic activity of various CA isozymes for CO_2 hydration reaction [33]. 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 constant ionic strength), following the CA-catalyzed CO_2 hydration reaction for a period of 10 s at 25 °C. The CO_2 concentrations ranged from 1.7 to 17 mM for the determination of the kinetic parameters and activation constants. For each activator 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 activators (10 mM) were prepared in distilled-deionized water and dilutions up to 1 nM were done thereafter with the assay buffer. Activator and enzyme solutions were pre-incubated together for 15 min (standard assay at room temperature) prior to assay, in order to allow for the formation of the E–A complex. The activation constant (K_A), defined similarly with the inhibition constant K_I, can be obtained by considering the classical Michaelis–Menten equation (Eq. (1)), which has been fitted by non-linear least squares by using

PRISM 3:

$$V = \frac{V_{max}}{\{1 + K_M/[S](1 + [A]_f/K_A)\}} \quad (1)$$

where $[A]_f$ is the free concentration of activator. Working at substrate concentrations considerably lower than K_M ($[S] \ll K_M$), and considering that $[A]_f$ can be represented in the form of the total concentration of the enzyme ($[E]_t$) and activator ($[A]_t$), the obtained competitive steady-state equation for determining the activation constant is given by Eq. (2):

$$V = \frac{V_0 K_A}{\{K_A + ([A]_t - 0.5\{([A]_t + [E]_t + K_A) - ([A]_t + [E]_t + K_A)^2 - 4[A]_t[E]_t\})^{1/2}\}} \quad (2)$$

where V_0 represents the initial velocity of the enzyme-catalyzed reaction in the absence of activator. The enzymes were recombinant ones, prepared in-house as reported earlier [28–31].

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