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Selenides bearing benzenesulfonamide show potent inhibition activity against carbonic anhydrases from pathogenic bacteria *Vibrio cholerae* and *Burkholderia pseudomallei*

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ABSTRACT

A series of selenides bearing benzenesulfonamide moieties was evaluated as carbonic anhydrase (CA, EC 4.2.1.1) inhibitors against the pathogenic bacteria *Vibrio cholerae* (VchCAα and VchCAβ) and *Burkholderia pseudomallei* (BpsCAβ) enzymes. The molecules represent an interesting lead for antibacterial agents with a possibly new mechanism of action showing excellent inhibitory action and selectivity for inhibiting VchCAα and BpsCAβ over the human (h) off-target isoforms hCA I and II. Identification of potent and possibly selective inhibitors of bacteria CAs over the human counterparts may lead to pharmacological tools useful for understanding the physiological role(s) of these under-investigated proteins.

1. Introduction

The carbonic anhydrases (CAs, EC 4.2.1.1) are a superfamily of metalloenzymes which catalyse the interconversion reaction of CO_2 and H_2O with HCO_3^- and H^+ to perform a pivotal role in pH regulation [1]. It is an essential enzyme in all life kingdoms, from Archaea to Bacteria and Eukaryotes [2]. To date, was discovered seven genetically distinct families, named α – (present in vertebrates, protozoa, algae, cytoplasm of green plants, and in many gram-negative Bacteria), β – (in both gram-negative and -positive Bacteria, mono and dicotyledons plants, fungi and Archaea), γ – (Bacteria, cyanobacteria and Archaea), δ-, ζ-, θ – (in marine diatoms) and η – CAs (protozoa belonging to the *Plasmodium* spp) [1–3]. Recently, the inhibition of bacterial CAs was demonstrated to influence both growth and pathogenicity of microorganisms [4–6], thus, could be a new approach for obtaining anti-infective agents with a new mechanism of action compared to classical antibiotics [7]. Discover and develop new anti-infective agents, at present, is inevitable because infectious diseases are the second-leading cause of death in the world. In this particular contest, *Burkholderia pseudomallei* and *Vibrio cholerae* are Gram-negative bacteria that cause different endemic diseases. The first is a saprophytic bacterium responsible for melioidosis, an endemic disease present in tropical and sub-tropical areas of the world [8,9]. *B. pseudomallei* is highly virulent by inhalation and also acquired resistance to penicillin, ampicillin, first-generation and second-generation cephalosporins, macrolides, quinolones and most aminoglycoside antibiotics [8,9]. The second Gram-negative bacterium, *Vibrio cholerae,* is causative of cholera, a human disease that is characterized by massive loss of water and electrolytes, which leads to severe dehydration and hypovolemic shock if the condition is not treated [10]. This study may be of interest for designing new organoselenium inhibitors of VchCAα, VchCAβ and BpsCAβ that may have clinical applications [11].

2. Results and discussion

2.1. Chemistry

Commercially available sulfanilamide **1**, has been used for preparing the corresponding selenocyanate derivative **2** and diselenide **3**, as reported earlier [12] (Scheme 1).

Thereafter, **3** was reduced with $NaBH_4$ to the corresponding selenolate, which in turn was treated *in situ* with the appropriate halo-alkyl moieties **4a-j**, affording the selenides **5a-j** in good yield (Table 1) [13].

Finaly, the selenide **6** was obtained from reduction of diphenyldiselenide with $NaBH_4$ and *in situ* was added 4-(bromomethyl)benzenesulfonamide to afford in good yield as outlined in Scheme 2[13].

Our main interest was to investigate structure-activity relationship related to the inhibition of the two pathogenic bacteria from *Vibrio*

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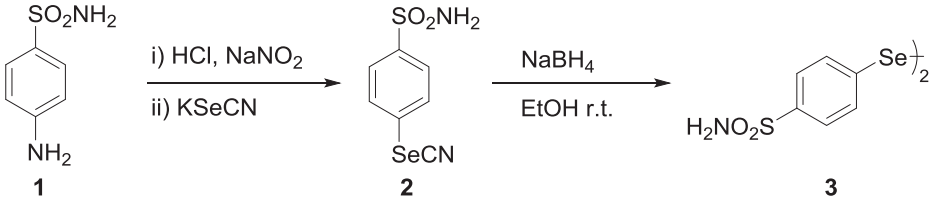
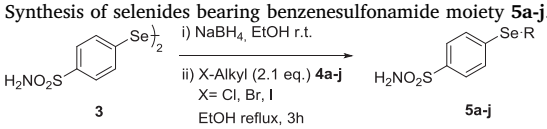
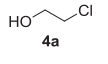
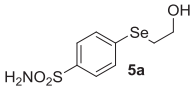
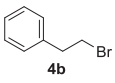
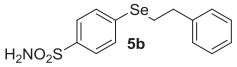
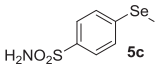
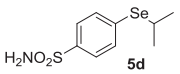
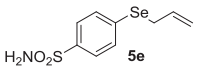
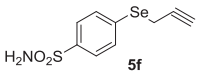
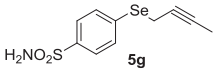
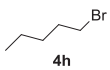
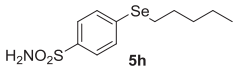
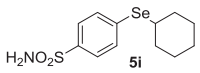
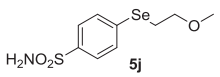


Scheme 1. Synthesis of selenocyanate **2** and diselenide **3** derivative.

Table 1
Synthesis of selenides bearing benzenesulfonamide moiety **5a-j**.



Entry	X-Alkyl	Product	Yield (%)[a]
1	 **4a**	 **5a**	68
2	 **4b**	 **5b**	69
3	 **4c**	 **5c**	60
4	 **4d**	 **5d**	68
5	 **4e**	 **5e**	54
6	 **4f**	 **5f**	50
7	 **4g**	 **5g**	53
8	 **4h**	 **5h**	60
9	 **4i**	 **5i**	72
10	 **4j**	 **5j**	87

[a] Yields are referred to isolated products

Table 2
Inhibition data against human (h) isoforms hCA I, II and bacterial enzymes VchCAα, VchCAβ and BpsCAβ of derivates **2, 3, 5a-j, 6** and acetazolamide (**AAZ**) by a stopped flow CO_2 hydrase assay [14].

Cmp	K_I (nM)[a]				
	VhCAα	VhCAβ	BpsCAβ	hCAI	hCAII
2	4.6	2172.5	75.3	95.6	53.1
3	5.7	6804.3	83.6	1522.7	7.9
5a	5.9	7597.7	754.2	338.3	355.3
5b	4.1	5941.7	845.6	256.8	9.3
5c	6.1	8726.9	529.8	352.2	73.2
5d	6.5	5264.4	51.9	9.7	69.9
5e	28.6	7853.1	9.1	5.2	36.5
5f	6.7	2589.9	21.4	7.3	9.3
5g	6.0	6900.8	5.4	293.5	7.6
5h	4.4	5068.3	823.9	297.1	70.8
5i	4.3	5897.1	876.9	21.9	6.3
5j	7.5	1852.8	866.6	261.7	41.2
6	5.4	7697.1	650.4	226.1	53.0
AAZ	6.8	451	745	250	12.1

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

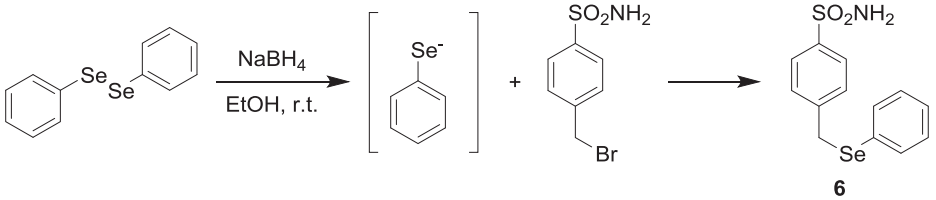
cholerae (VchCAα, VchCAβ) and, *Burkholderia pseudomallei* (BpsCAβ).

2.2. Carbonic anhydrase inhibition

The inhibition studies of VchCAα, VchCAβ and BpsCAβ with compounds **2, 3, 5a-j** and **6** were performed in order to detect possible candidates for anti-infective studies. We tested *in vitro* these compounds for their inhibitory activity against the two off-targets physiologically relevant hCA isoforms I, II and the bacterial enzymes VchCAα, VchCAβ and BpsCAβ by means of the stopped-flow carbon dioxide hydration assay [14]. These activities were compared to those of the standard, clinically used CAI acetazolamide (**AAZ**) (Table 2).

The following structure–activity relationship (SAR) can be drawn from the data of this table:

(i) Selenides **2, 5a-j, 6** and diselenide **3** exhibited potent inhibitory activity towards VchCAα with inhibition constants in the low-nanomolar range, except for compound **5c**, which was active in the medium nanomolar range (overall, the K_Is ranged between 4.3 and 28.6 nM). However, small structural differences in the tail moiety, such as the replacement of methyl moiety (**5c**) with different methylene chains (**5a-b**, **5d-j**, **6**), did not lead to particular effects on



Scheme 2. Synthesis of 4-((phenylselanyl)methyl) benzenesulfonamide **6**.