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Glycomimetic Based Approach toward Selective Carbonic Anhydrase Inhibitors

Debora Pratesi, Camilla Matassini, Andrea Goti, Andrea Angeli, Fabrizio Carta, Claudiu T. Supuran,* Rolando Spanevello, and Francesca Cardona*

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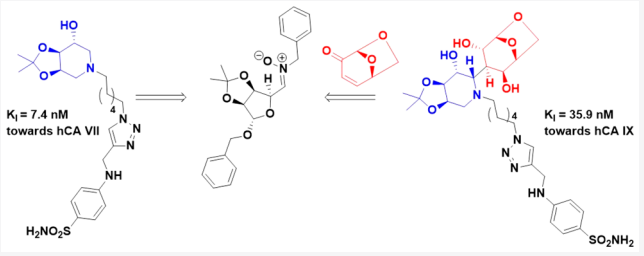
ABSTRACT: The synthesis of selective inhibitors of human carbonic anhydrases (hCAs) is of paramount importance to avoid side effects derived from undesired interactions with isoforms not involved in the targeted pathology, and this was partially addressed with the introduction of a sugar moiety (the so-called "sugar approach"). Since glycomimetics are considered more selective than the parent sugars in inhibiting carbohydrate-processing enzyme, we explored the possibility of further tuning the selectivity of hCAs inhibitors by combining the sulfonamide moiety with a sugar analogue residue. In particular, we report the synthesis of two novel hCAs inhibitors **2** and **3** which feature the presence of a piperidine iminosugar and an additional carbohydrate moiety derived from levoglucosenone (**1**), a key intermediate derived from cellulose pyrolysis. Biological assays revealed that iminosugar **2** is a very strong inhibitor of the central nervous system (CNS) abundantly expressed hCA VII (K_I of 7.4 nM) and showed a remarkable selectivity profile toward this isoform. Interestingly, the presence of levoglucosenone in glycomimetic **3** imparted a strong inhibitory activity toward the tumor associated hCA IX (K_I of 35.9 nM).



KEYWORDS: *Carbonic anhydrase inhibitors, Sulfonamide, Iminosugars, Levoglucosenone*

The human (h) expressed carbonic anhydrases (CAs, EC 4.2.1.1) are zinc(II) metalloenzymes that catalyze the reversible hydration of carbon dioxide (CO_2) to hydrogen carbonate (HCO_3^-) and protons (H^+).[1] Although such a transformation also occurs spontaneously, it is not able to fulfill the biological needs and for that reason CAs have the primary function to accelerate the whole process. This is a fundamental physiological reaction that underpins a multitude of essential cellular processes, such as respiration, acid−base regulation, electrolyte secretion, bone resorption, calcification, and biosynthetic processes.[2,3] Fifteen different isozymes are present in humans. At the cellular level, they are distributed as cytosolic (hCA I−III, VII, and XIII), four are membrane bound or transmembrane proteins (hCA IV, IX, XII, and XIV), two are mitochondrial (hCA VA and VB), and one is secreted (hCA VI). Since hCAs have important roles in physiological processes, it is not surprising that any disruption of their expressions or activities may result in pathological events. The use of inhibitors of different hCA isoforms is well established for the management of hypertension, elevated intraocular pressure, arteriosclerosis, memory impairments, depression, obesity, epilepsy, and hypoxic cancers.[4] In this context, hCA IX and XII have been recently validated as pharmacological targets for the management of hypoxic tumors such as carcinoma of the cervix, colon, lungs, esophagus, and breast.[5] Therefore, CA isoenzymes have become an important target for the design of inhibitors with biomedical applications. The primary sulfonamide group ($R-SO_2NH_2$) is the most important and largely used zinc binding moiety, which, in its deprotonated form, coordinates the catalytic Zn^{2+} ion and Thr199 by H-bonds.[6] Due to the large number of different CA isoforms, the main requirement for new compounds, besides their inhibition potency, is to improve their selectivity profile, in order to avoid side effects derived from undue interaction with isoforms not involved in the targeted pathology.[7] This is not an easy task due to the high degree of preservation between isoenzymes. One promising strategy that has emerged in recent years to differentiate transmembrane (*i.e.*, hCA IX) from the physiologically dominant cytosolic isozymes hCA I and II is to design inhibitors with polar or charged tails, thus impairing their ability to diffuse through lipid membranes.[8] Carbohydrates are among the best candidates for this function, and their use to impart selectivity to modulators toward the different CA isoforms was defined by Winum et al. as the "sugar approach."[9] This concept is revolutionary since

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carbohydrates have good solubility in water, their presence in natural products is often a prerequisite for biological activity, and they can influence the pharmacokinetics and the mechanism of action. Once the importance of the sugar portion had been realized, several anomeric sulfonamides (Figure 1) were studied, where the sulfonamide moiety is directly connected to the anomeric carbon.[9]

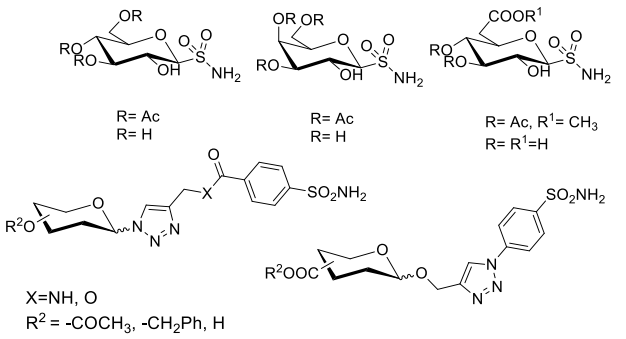


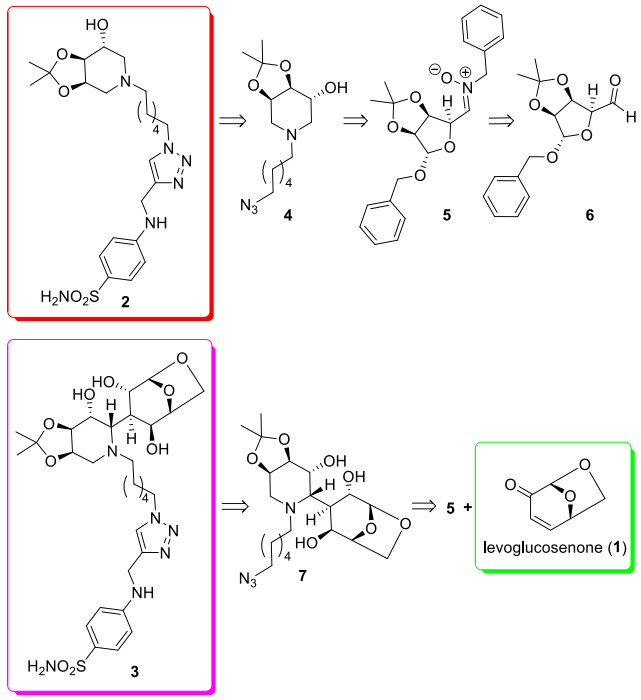
Figure 1. Examples of anomeric sulfonamide and benzenesulfonamide glycoconjugates.

Another relevant example concerns the synthesis of a class of glycosides where the sulfonamide moiety is anchored to sugar by means of a triazole ring assembled in a CuAAC reaction ("copper(I)-catalyzed azide-alkyne cycloaddition").[10,11] In particular, Wilkinson and co-workers[12] reported the synthesis of a class of benzenesulfonamide glycoconjugates (Figure 1) by reaction of a benzenesulfonamide bearing a terminal alkyne with a glycosyl azide.

Carbohydrates often do not receive adequate attention from the pharmaceutical industry due to their weak binding strength toward receptors. However, the introduction of a carbohydrate moiety may confer a higher selectivity to the final drug. In this context, introduction of a heavily hydroxylated fragment in the backbone bearing the sulfonamide pharmacophore may increase the selectivity toward different CA isoforms, besides imparting the desired hydrophilicity. In this regard, the search for new glycomimetics that can increase the affinity toward the biological target is important. We aimed at synthesizing new CAs inhibitors focusing on iminosugars. These are nitrogenated glycomimetics with a nitrogen atom replacing the endocyclic oxygen of carbohydrates, widely known for their inhibitory properties toward glycosidases and glycosyltransferases.[13] Whereas it has been recently demonstrated that CA inhibitors may take advantage by the presence of a sugar in their structure, there is no precedent addressing the connection with an iminosugar. The presence of a basic nitrogen which can be protonated under physiological conditions may result in significant alterations in the interaction with enzymes compared to the corresponding carbohydrate.

We aimed at a preliminary investigation of putative inhibitors of hCAs possessing only an iminosugar or both an iminosugar and a carbohydrate moieties and we report herein the results of this study, to evaluate the possible influence on selectivity given by these glycomimetics. The carbohydrate moiety was derived from levoglucosenone, a highly functionalized compound that can be obtained from renewable feedstocks. Levoglucosenone (**1**) (Scheme 1) is a small highly functionalized compound produced by pyrolysis of cellulose-containing urban and industrial residual materials such as waste paper.[14] The highly functionalized structure of levoglucosenone makes it an attractive chiral synthon for the synthesis of a wide variety of natural and unnatural compounds.[15,16] Based on our previous experience, we envisaged levoglucosenone as a convenient starting material for accessing an iminosugar/carbohydrate conjugate in a straightforward and selective fashion.[17]

Scheme 1. Retrosynthetic Strategy for the Synthesis of Iminosugar Sulfonamide Derivatives 2 and 3



In order to achieve these targets, we designed a new synthetic strategy to obtain two different iminosugars **2** and **3** containing the sulfonamide moiety (Scheme 1).

The retrosynthetic strategy for the iminosugar **2** containing the piperidine ring and the sulfonamide moiety relies on a CuAAC reaction of a suitable benzenesulfonamide bearing an alkyne moiety with piperidine **4** possessing an azido-ending alkyl chain. Compound **4**, in turn, may originate by reductive amination of the carbohydrate-derived nitrone **5** obtained from aldehyde **6**. The same carbohydrate-derived nitrone **5** should allow to introduce the levoglucosenone fragment in the backbone through 1,3-dipolar cycloaddition with the synthesis of piperidine **7** possessing an alkyl chain terminating with an azido group. This strategy would access iminosugar **3** containing the levoglucosenone scaffold besides the piperidine and sulfonamide moieties through an analogous CuAAC approach.

The aldehyde **6** was synthesized in four steps from D-mannose at the gram scale as reported,[18,19] and the nitrone **5** was readily accessed from **6** in 88% yield (Scheme 2).[20] We recently synthesized compound **8**[21] via a double reductive amination (DRA) strategy from **6**.[18,22,23] In this case, having nitrone **5** in hand, we managed to obtain **8** in quantitative yield through the reductive amination of nitrone **5** followed by subsequent alkylation to yield compound **4** in 55% yield. Finally, the target iminosugar-sulfonamide **2** was obtained in 86% yield through a CuAAC reaction with the sulfonamide **9**. (See the Supporting Information for further details.)

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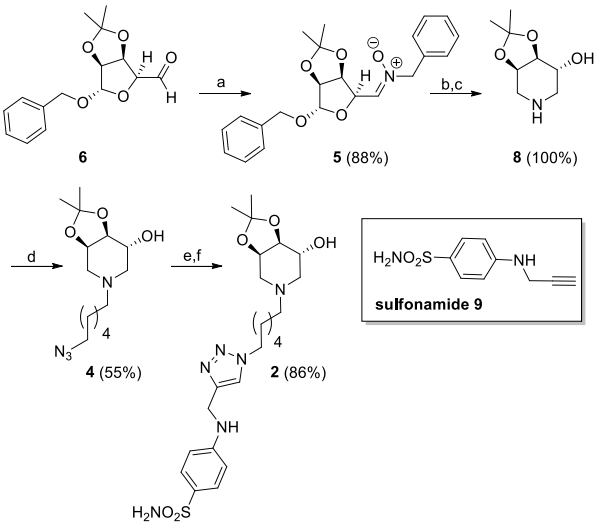
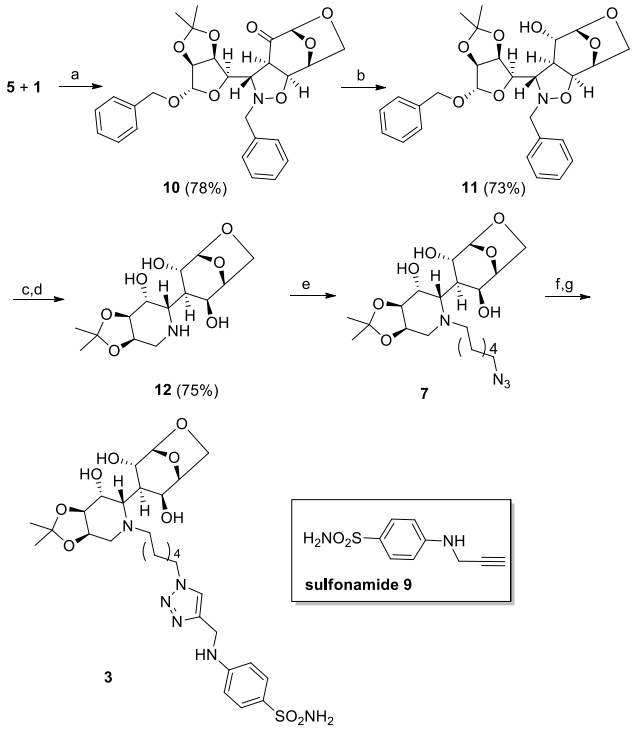
Scheme 2. Synthesis of Compound 2[a]



[a]Reagents and conditions: (a) *N*-benzyl hydroxylamine, dry CH_2Cl_2, rt, 18 h; (b) Pd/C, H_2, CH_3COOH, MeOH, rt, 2 days; (c) Ambersep 900-OH, rt, MeOH, 40 min; (d) $Br(CH_2)_6N_3$, K_2CO_3, CH_3CN/H_2O, MW 120 °C, 2.5 h; (e) sulfonamide **9**, $CuSO_4$, sodium ascorbate, THF/H_2O, rt, 16 h; (f) Quadrasil MP, MeOH, rt, 1 h.

Scheme 3. Synthesis of Compound 3[a]



[a]Reagents and conditions: (a) dry toluene, 60 °C, 24 h; (b) L-selectride, dry toluene, −78 °C, 4 h; (c) Pd/C, H_2, CH_3COOH, EtOH, rt, 4 days; (d) Ambersep 900-OH, rt, EtOH, 40 min; (e) $Br(CH_2)_6N_3$, CH_3CN/H_2O, MW 120 °C, 7 h; (f) sulfonamide **9**, $CuSO_4$, sodium ascorbate, THF/H_2O, rt, 23 h at rt, 17 h at 50 °C; (g) Quadrasil MP, MeOH, rt, 1 h (12% yield over three steps).

The synthesis of the iminosugar derivative **3** containing the levoglucosenone scaffold was then undertaken. The 1,3-dipolar cycloaddition of nitrone **5** with levoglucosenone (**1**), prepared following the previously reported procedure,[14] afforded the adduct **10** in 78% yield with complete regioselectivity and high stereoselectivity (Scheme 3), with only traces of a minor isomer being detected.

The regioselectivity of the cycloaddition placed the nitrone oxygen atom at the *β*-carbon of the unsaturated ketone, as expected on the basis of FMO considerations and in agreement with previous findings on cycloadditions of levoglucosenone with both acyclic[24] and cyclic nitrones.[17]

Assignment of the configuration to the isolated cycloadduct was less straightforward. In principle, the 1,3-dipolar cycloaddition may afford four diastereoisomers depending on the type of approach between the nitrone and levoglucosenone, both chiral enantiopure reagents. Based on extensive investigation through 1D-NOESY spectra recorded in different deuterated solvents and logical considerations, we assigned the obtained cycloadduct the structure **10** (see the Supporting Information for further discussion).

The cycloadduct **10** was subjected to hydrogenation in order to obtain the piperidine ring. However, none of the conditions attempted led to isolation of the desired compound. We speculated that the simultaneous presence of a carbonyl and the amine resulting from N−O bond cleavage may lead to undesired reactions. In such case, reduction of the C═O bond prior to hydrogenation should circumvent this drawback. L-selectride was chosen as the reducing agent for its superior stereoselectivity demonstrated on levoglucosenone derivatives.[25] Indeed, reduction of **10** with L-selectride gave the single stereoisomer **11** in 73% yield (Scheme 3). The steric hindrance of the reducing agent accounts for the observed stereoselectivity, with nucleophilic attack occurring exclusively from the less encumbered face of C═O.

The alcohol **11** was then subjected to catalytic hydrogenation which afforded the desired compound **12** in 4 days with a good yield (75%). The subsequent alkylation step of piperidine nitrogen was troublesome. Despite several attempts, compound **7** was always obtained with low yields and affected by the presence of minor impurities. The best procedure involved the use of 4 equiv of potassium carbonate and 4 equiv of $Br(CH_2)_6N_3$ (Scheme 3). The crude material was directly employed in the following CuAAC reaction with sulfonamide **9** to afford the target iminosugar **3** with a 12% yield over three steps (see the Supporting Information for further details).

The final compounds **2** and **3** were assayed *in vitro* for their inhibition properties against the most relevant hCA isoforms (*i.e.*, I, II, IV, VA, VB, VI, VII, IX, XII and XIII) and compared to the sulfonamide reference compound AAZ (Table 1).

The *in vitro* kinetic profile of the iminosugar derivative **2** showed such compound to be a low micromolar inhibitor of the ubiquitous hCA I isoform (K_I of 2880.0 nM). Interestingly, the second widely distributed isoform (*i.e.*, the hCA II) was inhibited in the medium nanomolar range with an almost superimposable inhibition value reported for the membrane bound hCA IV (K_I's of 80.3 and 80.9 nM, respectively). A good discrimination between the mitochondrial expressed hCAs VA and VB was also obtained as the latter resulted in being 11.6-fold less liable to inhibition from compound **2**. Again, medium inhibition potencies were obtained for the secreted hCA VI and for the cytosolic expressed XIII (K_I's of 68.7 and 65.3 nM respectively). It is noteworthy that compound **2** resulted in being a very potent inhibitor of the hCA VII with a K_I value of 7.4 nM and thus just 3.0-fold less active when compared to the reference AAZ (K_I of 2.5 nM).

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Table 1. Inhibition Data of 2 and 3 on hCAs I, II, IV, VA. VB, VI, VII, IX, XII, and XIII by a Stopped Flow CO_2 Hydrase Assay[26a]

	K_I (nM)[b]		
	2	3	AAZ
hCA I	2880.0	955.5	250.0
hCA II	80.3	800.8	12.1
hCA IV	80.9	658.8	74.0
hCA VA	70.3	34.1	63.0
hCA VB	812.7	4353.0	54.0
hCA VI	68.7	542.9	11.0
hCA VII	7.4	31.2	2.5
hCA IX	2980.0	35.9	25.8
hCA XII	541.0	770.3	5.7
hCA XIII	65.3	429.1	17.0

[a]Acetazolamide (AAZ) was used as reference inhibitor. [b]Mean from three different assays, by a stopped flow technique (errors were in the range of ±5−10% of the reported values).

Such a low inhibition value for the central nervous system (CNS) abundantly expressed hCA VII makes compound **2** highly valuable for further explorations within the Medicinal Chemistry field such as for neuropathic pain.[27,28] Although the iminosugar derivative **2** resulted in being a very high nanomolar inhibitor of the tumor associated hCAs IX and XII, it is worth noting that a good isoform selectivity was obtained. As reported in Table 1, the K_I for the IX resulted in being 5-fold higher when compared to the experimental value of XII.

The introduction of the levoglucosenone moiety, as in compound **3**, deeply influenced the kinetic profile (Table 1). Overall, the hCA isoforms tested were inhibited with much less potency when compared to **2**, as the K_I values spanned between the medium and high nanomolar range. An almost flat profile was reported for the hCAs I, II, and IV (K_I's of 955.5, 800.8, and 658.8 nM, respectively). Quite interestingly, the preferential inhibition of compound **3** against the mitochondrial hCA VA over the VB was maintained, in analogy to the iminosugar **2**. Even better, the inhibition potency of **3** against the hCA VA was shown to be up to 127.7-fold higher than that against VB. Again, the hCAs VI and XIII were fairly inhibited from compound **3** (K_I's of 542.9 and 429.1 nM, respectively). Among the isoforms tested, the hCA VII resulted in being the most potently inhibited from compound **3**, although its K_I value was slightly lower than those of hCAs VA and IX (see Table 1). Quite interestingly, the kinetic inhibition profile of compound **3** for the tumor associated hCAs IX and XII was shown to be inverted when compared to **2**. Data in Table 1 account for the IX isoform to be preferentially inhibited over the XII isoform with a selectivity index (SI; K_I hCAXII/K_I hCA IX) of 21.5.

In conclusion, we reported the synthesis of two novel hCAs ligands **2** and **3** featuring the presence of a piperidine iminosugar and an additional carbohydrate moiety derived from levoglucosenone (**1**). While the synthesis of **2** takes advantage of a ring-closing reductive amination (RA) strategy of the carbohydrate-derived nitrone **5** to access the piperidine skeleton, the synthesis of **3** relies on a highly regio- and stereoselective 1,3-dipolar cycloaddition of **5** to levoglucosenone (**1**), followed by an unprecedented RA on the isoxazolidine derivative **11**, in turn obtained through a stereoselective C═O reduction of adduct **10**. *N*-Alkylation with an azido-ended linker and CuAAC reaction with a benzensulfonamide bearing a terminal alkyne moiety completed the synthesis of both **2** and **3**. We reported for the first time a complete kinetic profile of both compounds on the hCAs which accounted for both as hCA inhibitors. Structure−activity relationship (SAR) analyses clearly showed the iminosugar **2** being a very strong inhibitor of the CNS abundantly expressed hCA VII (K_I of 7.4 nM), whereas the levoglucosenone derivative **3** showed a mitigated activity against such an isoform (K_I of 31.2 nM) in favor of both the mitochondrial hCA VA and the tumor associated hCA IX (K_I's of 34.1 and 35.9 nM respectively).

The kinetic results here reported pave the way for deeper drug design strategies intended to better develop such compounds for biomedical applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.9b00590.

General synthetic procedures and characterization data of key compounds; general procedure for biochemical characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Francesca Cardona − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Firenze, Italy; Consorzio Interuniversitario Nazionale di ricerca in Metodologie e Processi Innovativi di Sintesi (CINMPIS), 70100 Bari, Italy;* orcid.org/0000-0002-6766-4624; Phone: (+39) 0554573504; Email: francesca.cardona@unifi.it

Claudiu T. Supuran − *Dipartimento Neurofarba, Sezione di Scienze Farmaceutiche e Nutraceutiche, Università degli Studi di Firenze, 50019 Florence, Italy;* orcid.org/0000-0003-4262-0323; Email: claudiu.supuran@unifi.it

Authors

Debora Pratesi − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Firenze, Italy*

Camilla Matassini − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Firenze, Italy;* orcid.org/0000-0002-8336-383X

Andrea Goti − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Firenze, Italy; Consorzio Interuniversitario Nazionale di ricerca in Metodologie e Processi Innovativi di Sintesi (CINMPIS), 70100 Bari, Italy;* orcid.org/0000-0002-1081-533X

Andrea Angeli − *Dipartimento Neurofarba, Sezione di Scienze Farmaceutiche e Nutraceutiche, Università degli Studi di Firenze, 50019 Florence, Italy;* orcid.org/0000-0002-1470-7192

Fabrizio Carta − *Dipartimento Neurofarba, Sezione di Scienze Farmaceutiche e Nutraceutiche, Università degli Studi di Firenze, 50019 Florence, Italy;* orcid.org/0000-0002-1141-6146

Rolando Spanevello − *Instituto de Química Rosario, Facultad de Ciencias Bioquímica y Farmacéuticas, Universidad Nacional de Rosario, CONICET, S2002LRK Rosario, Argentina;* orcid.org/0000-0003-3701-5807

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.9b00590

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Author Contributions

D.P. carried out the syntheses. Fr.C., C.M., and A.G. designed the syntheses. C.T.S., A.A. and Fa.C. planned and carried out the biological tests. R.S. prepared levoglucosenone. All authors contributed to writing of the manuscript. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CA, carbonic anhydrase; hCA, human carbonic anhydrase; AAZ, acetazolamide

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