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Synthesis and carbonic anhydrase inhibitory effects of new *N*-glycosylsulfonamides incorporating the phenol moiety

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ABSTRACT

A small series of *N*-glycosylsulfonamides incorporating the phenol moiety has been prepared by Ferrier sulfonamidoglycosylation of D-glycals. *N*-Glycosides were tested for the inhibition of four isoforms of carbonic anhydrase. In this study, all compounds showed good inhibitory activity against hCA I and II, with selectivity against the cytosolic hCA II versus the tumor associated isozymes. These results confirm that attaching carbohydrate moieties to CA phenol pharmacophore improves and enhances its inhibitory activity.

Carbonic anhydrases (CAs, EC 4.2.1.1) are the most studied members of a great family of metalloenzymes. CAs catalyze the reversible hydration of carbon dioxide and they are found in multiple organisms such as vertebrates, bacteria, algae.[1] Five genetically distinct CA families are known to date, the α-, β-, γ-, δ- and ζ-CAs. α-CAs are involved in several physiological processes and have been exploited for the treatment or prevention of various pathologies such as glaucoma, neurological disorders, osteoporosis, obesity and cancer.[2–7] During the last years, the interest in the therapeutic use of carbonic anhydrase inhibitors (CAIs), has improved remarkably due to the validation of several CA isozymes as drug targets.

Phenols inhibit CAs by anchoring to the Zn(II)-bound solvent molecule, that is, a water or hydroxide ion, as initially reported by Christianson's group.[8] Although phenol-based natural and synthetic compounds are largely known to exhibit biological activity (mainly as antioxidants), they have been only recently studied as carbonic anhydrase inhibitors.[9,10]

The use of glycomimetics in the design of CAIs has proven to be a successful approach and now constitutes one of the most attractive ways to develop new generations of effective and selective inhibitors.[11,12] In many cases, use of carbohydrates as drugs has an important drawback: they are sensitive to the presence of enzymes and acidic or basic media. Thus, design of mimetics that bind to enzymes but are not processed to product in the usual way is an active area of research.[13] Usual enzyme-resistant replacement for the glycosidic linkage are the thio, methylene or sulfonamidoglycosides. Recently our group has applied the 'sugar approach' to the preparation of *C*-cinnamoyl phenols, where the carbohydrate moiety is tethered to a phenol CA pharmacophore through a carbon chain.[14] These compounds have been tested as inhibitors of the *Mycobacterium tuberculosis* β-CAs and have shown better inhibitory activity against mtCAs than phenol. Also the antitubercular activity of the *C*-glycosyl phenols was investigated, allowing us to identify the first mtCAs inhibitor with antimycobacterial activity.[15] These glycosides also showed to be very good inhibitors of *Brucella suis* CAs.[16]

In 2007 our group described the Ferrier sulfonamidoglycosylation of peracetylated D-glycals in the presence boron trifluoride etherate.[17] The D-hex-2-enopyranosylsulfonamides were obtained in high yield with very good α-stereoselectivity. Then this methodology was applied to the synthesis of *N*-glycosyl sulfamides, which showed to be potent carbonic anhydrase inhibitors.[18] Recently Winum's group reported on the synthesis and biological activities of carbonic anhydrase glycoinhibitors developed by Ferrier sulfonamidoglycosylation of peracetylated glycals by reaction with hydroxysulfamide[19] or aminoxysulfamide[20] using nitrosyl tetrafluoroborate as catalyst.

Thus, in the search of non-sulfonamide CAIs belonging to different classes of compounds, we report here the synthesis of a series of new *N*-glycosylsulfonamides incorporating phenol moiety

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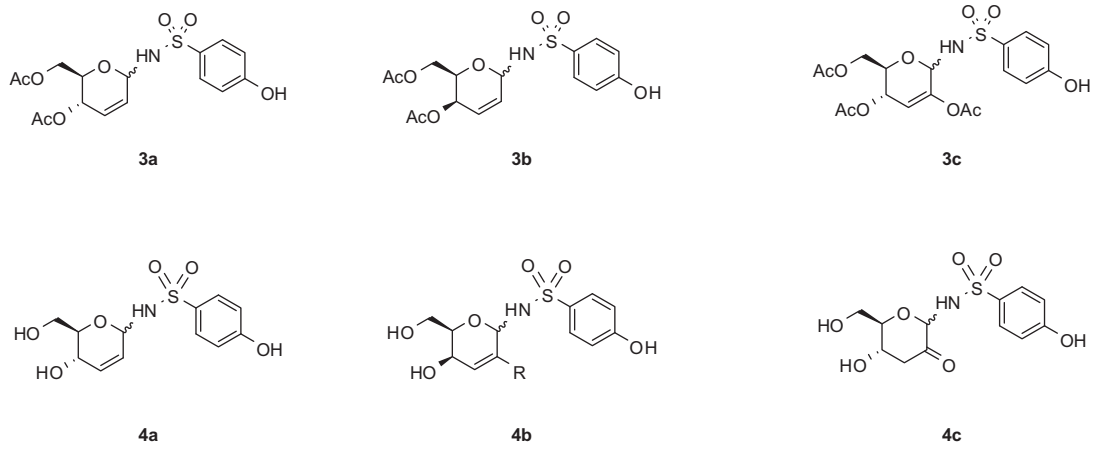
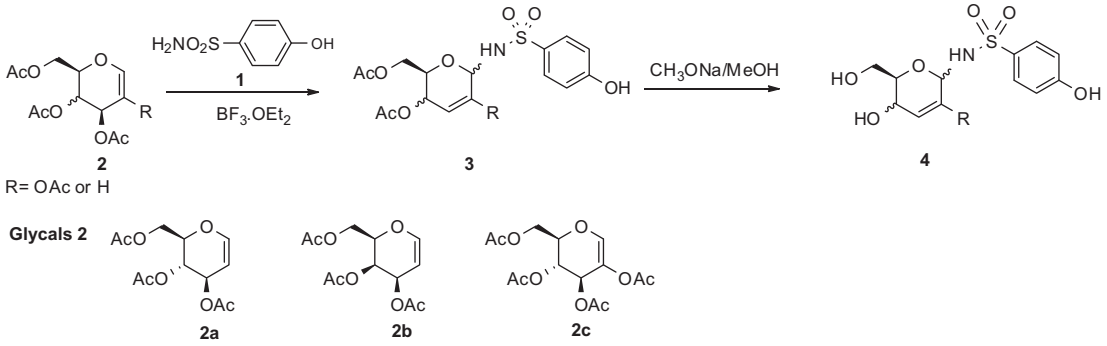


Figure 1. Peracetylated *N*-glycosylsulfonamides (**3a**–**3c**) and fully deprotected derivatives (**4a**–**4c**).



Scheme 1.

(Fig. 1) vía Ferrier sulfonamidoglycosylation of D-glycals and their inhibitory activity against the cytosolic hCA I and II, and tumor-associated hCA IX and XII.

N-Glycosylsulfonamides **3** were synthesized as depicted in Scheme 1. Starting from peracetylated glycals **2**, and using the same methodology previously reported by us on Ferrier sulfonamidoglycosylation, we were able to obtain compounds **3** by reacting **2** with *p*-hydroxybenzenesulfonamide (**1**) in the presence of 1% mol of boron trifluoride etherate in dichloromethane (Scheme 1).[21]

Sulfonamidoglycosides **3** were obtained as a mixture of α and β anomers with a slight selectivity for the α-anomer (see Table 1). Similar selectivities were reported in other sulfonamidoglycosylations. Our group showed that the α-selectivity could be explained in terms of the *endo* and *exo*-anomeric effects, suggesting a thermodynamical control of the reaction.[22]

The α and β anomers of the *threo*-hex-2-enopyranosyl sulfonamide **3b** could be easily separated by flash column chromatography. Although compounds **3a** and **3c** were obtained analytically pure by chromatography, the anomers could not be separated. The anomeric configuration was supported by NOESY experiments (in $CDCl_3$), for example, the configuration of α-anomer of **3a** is consistent with NOEs between NH and H-5, and between H-4 and H-5.

Final deprotection of acetate groups of glycosides **3** with methanolic solution of sodium methoxide led to compounds **4** in very good yields.[23]

Compounds **1**, **3a**–**3c** and **4a**–**4c** as well as clinically used acetazolamide (standard compound) were tested for their inhibitory activity against the two cytosolic CA isoforms hCA I and II and the two membrane tumor-associated isoforms hCA IX and XII using a Stopped-Flow, CO_2 Hydration Assay Method.[24] Results are reported in Table 2.

A number of structure–activity relationships (SARs) were identified in this study and are summarized as follows:

(i) hCA I: *erythro* sulfonamides **3a** and **4a** are nanomolar inhibitors of the hCA I; the other *N*-glycosylsulfonamides are very poor hCA I inhibitors. It should be noted that the β-anomers

Table 1
Synthesis of *N*-glycosylsulfonamides

Glycal	Sulfonamidoglycosylation			Deprotection		
	Reaction time (h)	α:β	Yield (%)	Reaction time (h)	α:β	Yield (%)
2a	1.5	61:39	71	1.5	61:39	80[a]
2b	2	65:45	70	2	—[b]	83α + 85β
2c	5	78:22	72	2	78:22	82[a]

[a] Deprotection of the mixture of anomers.
[b] Anomers of compound **3b** could be separated and thus the pure anomers were deprotected.