Inhibition of Carbonic Anhydrases with Glycosyltriazole Benzene Sulfonamides

Brendan L. Wilkinson,[†] Alessio Innocenti,[‡] Daniela Vullo,[‡] Claudiu T. Supuran,*[,‡] and Sally-Ann Poulsen*[,†]

Eskitis Institute for Cell and Molecular Therapies, Griffith University, 170 Kessels Road, Nathan, Queensland 4111, Australia, and Polo Scientifico, Laboratorio di Chimica Bioinorganica, Rm. 188, Università degli Studi di Firenze, Via della Lastruccia 3, 50019 Sesto Fiorentino, Florence, Italy

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A library of glycoconjugate benzene sulfonamides have been synthesized and investigated for their ability to inhibit the enzymatic activity of physiologically relevant human carbonic anhydrase (hCA) isozymes: hCA I, II, and tumor-associated IX. Our synthetic strategy directly links the known CA pharmacophore ($ArSO_2NH_2$) to a sugar "tail" moiety through a rigid 1,2,3-triazole linker unit using the Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction or "click chemistry". Many of the glycoconjugates were potent CA inhibitors and exhibited some isozyme selectivity. In particular, the methyl-D-glucuronate triazoles **6** and **14** were potent inhibitors of hCA IX (K_is 9.9 and 8.4 nM, respectively) with selectivity also favoring this isozyme. Other exceptional compounds included the deprotected β-D-ribofuranosyl triazole **15** and α-D-mannosyl triazole **17**, which were potent and selective hCA II inhibitors (K_i 7.5 nM and K_i 2.3 nM, respectively). Collectively, the results confirm that modification of ring size, stereochemical configuration, and chain length in the sugar tail moiety of glycoconjugate CA inhibitors permits tunable potency and selectivity that may constitute an important avenue for the future development of efficacious and selective CA-based therapeutics.

Introduction

The carbonic anhydrases (CA,[a] EC 4.2.1.1) are ubiquitous zinc(II) metalloenzymes that are found in higher vertebrates, green plants, algae, bacteria, and archaea.[1] CA catalyzes the reversible hydration of carbon dioxide (CO_2) to give bicarbonate (HCO_3^-) and a proton (H^+), a fundamental physiological reaction that underpins a multitude of essential cellular processes associated with respiration and transport of CO_2/HCO_3^- between metabolizing tissues and the lungs, photosynthesis in higher plants, provision of HCO_3^- for biosynthetic pathways (gluconeogenesis, lipogenesis and ureagenesis), pH regulation and CO_2 homeostasis, electrolyte and fluid secretion, as well as bone resorption and calcification.[1,2] In mammals, 16 different α-CA isozymes and CA related proteins (CARP) have been identified and characterized to date, 15 of these are present in humans (designated hCA; CA XV is absent in humans and primates but is present in rodents and other higher mammals). hCA isozymes exhibit variable enzyme kinetics, tissue distribution, expression levels, and subcellular locations.[1,2] Several hCA isozymes are cytosolic (hCA I-III, hCA VII, hCA 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 into the saliva and milk (hCA VI). Many hCA isozymes are quite recent discoveries compared with the physiologically abundant and widely distributed isozymes hCA I and hCA II (known since the 1930s, with isozymes acknowledged in the 1960s). The dysregulation of hCA expression is now implicated in a host of pathophysiological processes such as oncogenesis,[3] elevated intraocular pressure,[4] obesity,[5] memory loss, depression,[6] arteriosclerosis, and renal pathology.[7] The modulation of CA activity through inhibition (or activation) is therefore a promising avenue for the treatment of a wide range of acquired and inherited diseases.[2]

Since the original report by Mann and Keilin concerning the inhibition of CA with sulfanilamide (SA),[8] followed some time later with the pioneering work of Krebs,[9] primary aryl and heteroaryl sulfonamide CA inhibitors have become a clinical mainstay as antihypertensive, antiglaucoma, antithyroid and hypoglycemic drugs. The aryl- and heteroaryl sulfonamides acetazolamide (AZA), methazolamide (MZA), ethoxazolamide (EZA), and the bis-sulfonamide, dichlorophenamide (DCP) have been used clinically for over 40 years as systemic CA inhibitors (Figure 1). Acetazolamide AZA is the first nonmercurial diuretic used clinically.[1a] In addition to orally available CA inhibitor-based drugs, the topically acting sulfonamides dorzolamide (DRZ) and the structurally related brinzolamide (BRZ) are potent inhibitors of hCA II and hCA XII within the ciliary processes of the eye and are used for the treatment of open-angle glaucoma.[10] Furthermore, the fructopyranose sulfamate ester, topiramate (TPZ) has been assessed as a powerful inhibitor of hCA II and hCA VII in vitro and, apart from its well established anticonvulsant activity, its inhibition of brain CA isozymes also makes it a promising candidate for the treatment of memory disorders and depression.[11]

Furthermore, several important developments within the CA-based disciplines have also provided new and viable targets for molecular medicine. Of particular relevance to cancer chemotherapy is the overexpression of transmembrane isozyme hCA IX on certain tumor cells (primarily carcinomas) within tissues not normally known to express hCA IX, including carcinomas of the lung, breast, colon, esophagus, and cervix. This hCA IX is found ectopically expressed in many hypoxic tissues through the transcriptional activation of hypoxia-induced factor 1 (HIF-1).[12] Also, hCA IX is a high activity CA isozyme responsible for the extracellular acidification of the tumor microenvironment, leading to multiple downstream effects, including tumor progression and poor prognosis.[13] The differential expression

* To whom correspondence should be addressed. Tel.: +61 7 3735 7825 (S.-A.P.); +39 055 457 3005(C.T.S.). Fax: +61 7 3735 7656 (S.-A.P.); +39 055 457 3385 (C.T.S.). E-mail: s.poulsen@griffith.edu.au (S.-A.P.); claudiu.supuran@unifi.it. (C.T.S.).

[†] Griffith University.

[‡] Università degli Studi di Firenze.

[a] Abbreviations: CA, carbonic anhydrase; 1,3-DCR, 1,3-dipolar cycloaddition reaction; AZA, acetazolamide; MZA, methazolamide; EZA, ethoxzolamide; DCP, dichlorophenamide; DRZ, dorzolamide; BRZ, brinzolamide; IND, indisulamm; TPZ, topiramate.

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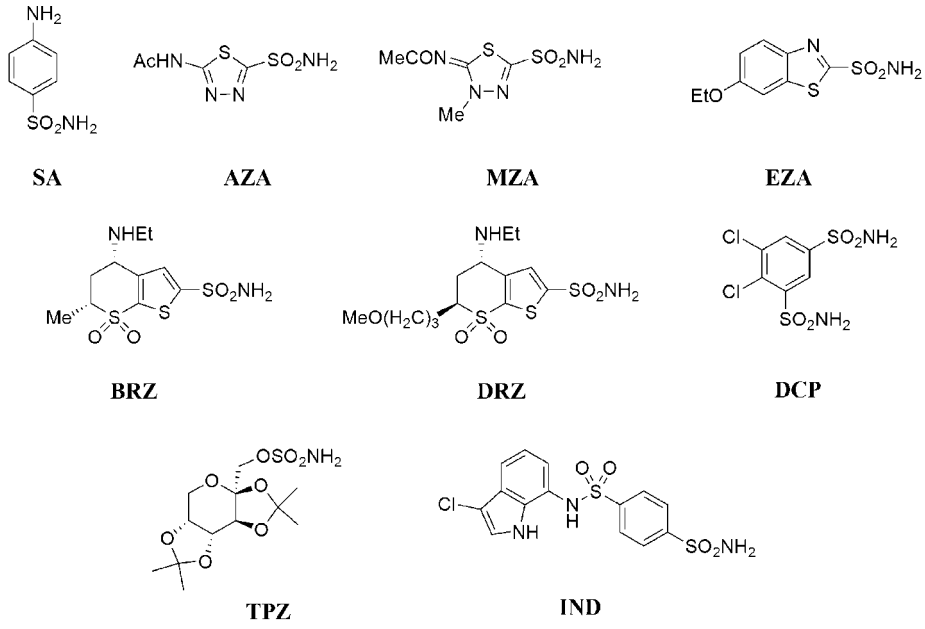


Figure 1. Known human CA inhibitors including some clinically used drugs.

patterns of hCA IX has the potential to function as a cancer biomarker for the early detection of gastric cancer and certain other carcinomas. It is known that hCA IX displays high affinity for primary aryl and heteroaryl sulfonamides and thus its inhibition can reverse the acidification of the tumor microenvironment, thus retarding tumor growth and reducing the chemoresistance to weakly basic frontline drugs such as paclitaxel, topotecan, and mitoxantrone.[3,9] The bis-sulfonamide indisulam (IND) is in phase II clinical trials for the treatment of solid tumors and is a potent inhibitor of hCA IX in vitro (K_i 24 nM).[14]

Despite the widespread use of sulfonamides in the clinic, their systemic administration often causes side effects due to the indiscriminate inhibition of CA isozymes in other tissues. This is prompting the development of tissue specific delivery systems and isozyme specific inhibitors with the aim of producing therapeutics with improved tolerability and efficacy. In the latter respect, it has become imperative to target subtle differences in active site topology and structure, a challenging process given the high degree of conservation among the CA isozymes. One promising strategy that has emerged in recent years to differentiate transmembrane hCA IX from the physiologically dominant cytosolic isozymes hCA I and II, is to develop inhibitors with polar or charged tails, thus impairing their ability to diffuse through lipid membranes.[15,16] In this respect, carbohydrates offer unique advantages to this fragment-based approach, whereby a high degree of polyfuntionality and hydrophilicity can be imparted onto the sulfonamide pharmacophore. The fine-tuning of the stereochemical arrangement of the carbohydrate tail and physicochemical properties of CA inhibitor can potentially allow for the differentiation of subtle differences in CA active site topology, as well as impairing membrane diffusion for the selective targeting of transmembrane hCA isozymes of clinical interest. Carbohydrates are powerful structural motifs for attenuating the magnitude and selectivity of binding to native and non-native protein receptors,[17] and their presence within many natural products is often a prerequisite for biological activity and can thus heavily influence the pharmacokinetics, drug targeting, and mechanism of action. Indeed, the literature is replete with examples of carbohydrate-containing natural products possessing antimicrobial and anticancer properties, such as the aminoglycosides, saponins, and anthracyclines.[18] Furthermore, carbohydrate prodrugs of cytoxic agents are a promising avenue for the selective targeting of anticancer drugs to the desired site of action.[19]

The Cu(I)-catalyzed ligation of a terminal acetylene to an organic azide to form regiospecifically a 1,4-disubstituted-1,2,3-triazole has emerged as a venerable synthetic tool in the drug discovery/medicinal chemistry and biotechnology sectors.[20] The transformation, now known as "click chemistry" occurs under ambient conditions, has a high degree of biocompatibility, and has been shown to be orthogonal to pre-existing synthetic methodologies.[21] Furthemore, the methodology has also applied to the synthesis and screening potent CA II inhibitors in situ.[22]

We have recently demonstrated the versatility of the click chemistry methodology as an expedient method of generating 1,4-disubstituted-1,2,3-triazole sulfonamide glycoconjugates.[23–25] These compounds contain a benzene sulfonamide moiety linked via a 1,2,3-triazole to a sugar tail. In our first and second generation glycoconjugates the triazole linker was in combination with either an ester, amide or *O*-glycoside functionality (Figure 2). These compounds have so far been evaluated for their inhibition in vitro of hCA I, II, and IX and, in some cases, also for transmembrane CAs XII and XIV. The impressive potency and selectivity of several inhibitors within these libraries reflects not only the significance of the carbohydrate tail at differentiating isozyme selectivity, but also for the fact that the high affinity aryl sulfonamide "anchor" moiety more than compensates for the potential loss of energy on binding to the carbohydrate moiety.

Encouraged by these earlier results, we have recently undertaken the expedient synthesis of sulfonamide glycoconjugates using click chemistry, differing in this new generation of compounds is that the carbohydrate tail is linked directly to the benzene sulfonamide fragment through a rigid 1,2,3-triazole unit. The removal of the carboxy ester, amide or *O*-glycoside linker functionality endows these third generation inhibitors with potentially enhanced stability toward esterase, protease or glycosidase hydrolysis in the in vivo environment.[26] In addition to the glycoconjugate sulfonamides previously reported by our

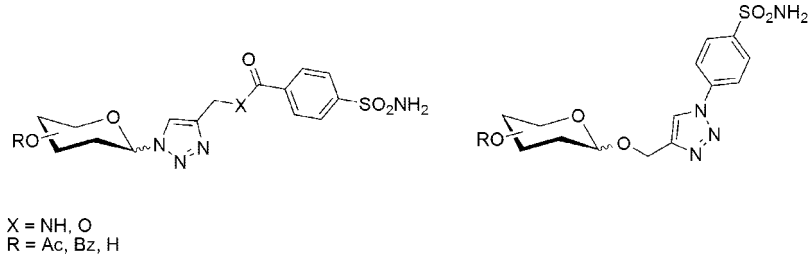
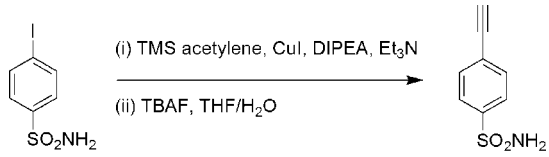


Figure 2. Generation I and II benzene sulfonamide glycoconjugates.[23–25]

Scheme 1. Synthesis of 4-Ethynyl Benzene Sulfonamide (**1**) CA Anchor Fragment



group, the inclusion now of a conformationally rigid library provides a useful comparative surveillance of the active sites of clinically relevant CA isozymes, a necessary step toward the discovery of novel CA-based therapeutics and diagnostics displaying improved potency and selectivity.

Results and Discussion

To facilitate our synthetic strategy, it was necessary to design and synthesize an aryl sulfonamide anchor fragment with reliable hCA recognition and with the complementary reactive functionality (i.e., an acetylene moiety) for the expedient 1,3-DCR ligation to a panel of acyl-protected glycosyl azide fragments (**a**−**h**). Sharpless and colleagues have previously employed 4-ethynyl benzenesulfonamide (**1**) as the reactive fragment for developing bovine CA inhibitors in situ.[22] This fragment was selected by ourselves as it represents a minimal fragment for the facile parallel synthesis of the proposed glycoconjugate hCA inhibitor library. Compound **1** was prepared via a Sonagashira coupling of 4-iodobenzene sulfonamide with trimethylsilyl acetylene, followed by fluoride mediated silyl deprotection (Scheme 1).[27]

The azide panel employed for ligation to **1** was comprised of carbohydrates with varying ring size, chain length and relative stereochemistry so as to access variable physicochemical properties across the downstream inhibitor library to allow for efficient interrogation of CA active site architecture. In this respect, a panel of eight peracylated glycosyl azides **a**−**h** derived from (**a**) glucose, (**b**) galactose, (**c**) *N*-acetyl glucosamine, (**d**) maltose, (**e**) glucuronic acid, (**f**) ribose, (**g**) mannose, and (**h**) arabinose were synthesized (Figure 3). Glycosyl azides (**a**−**e**, **h**) were synthesized by the stereoselective nucleophilic displacement of the respective glycosyl halides with azide.[28] The glycosyl halide precursors were themselves prepared from the corresponding per-*O*-acetates or purchased from commercial sources. The β-D-ribosyl azide (**f**) and α-D-mannosyl azide (**g**) were prepared by the Lewis acid ($SnCl_4$)-promoted azidolysis of the respective 1-*O*-acetate precursors.[29]

By employing a modified click chemistry methodology,[30] fragment **1** was reacted with the azido sugar panel **a**−**h** to generate a series of acyl-protected 1,4-disubsituted glycosyltriazole benzene sulfonamides **2**–**9** in moderate to good yields (69–88%) following flash chromatography or normal phase solid phase extraction (Scheme 2). The Cu(I) catalyst loading was achieved by employing 10 mol% of $CuSO_4$ and 20 mol% of sodium ascorbate reductant. The *O*-acetate and *O*-benzoate groups of **2**−**9** were subsequently removed using methanolic sodium methoxide (Zemplen conditions) to liberate the fully deprotected sugar analogues **10**−**17** in near quantitative yields (Scheme 2).

Carbonic Anhydrase Inhibition. hCA I, II, and IX enzyme inhibition data for the new glycoconjugate sulfonamides were determined by assaying the impact of these compounds on the CA-catalyzed hydration of CO_2[31] (Table 1). The selectivity ratios for inhibition of isozyme IX compared to I and II are also given in Table 1. Data for clinically used CA inhibitors are included for comparison.

Isozyme hCA I. At hCA I the glycoconjugates with acyl-protected sugar tails (**2**–**9**) were generally weaker inhibitors than the parent alkyne **1** (K_i 1.1 μM) with two notable exceptions, the α-D-mannosyl triazole **8** and α-D-arabinopyranosyl triazole **9**, which showed potent inhibition (K_i 1.6 nM and 10.5 nM, respectively). In addition, the α-D-configured deprotected analogues **16** (K_i 2.8 nM) and **17** (K_i 2.5 nM) were also excellent hCA I inhibitors, similarly to their per-*O*-acetylated counterparts **8** and **9**. In this respect, the α-configuration at the anomeric center may be a significant stereochemical feature toward inhibitory potency at hCA I, with these compounds up to 3 orders of magnitude more potent than the parent alkyne **1**. Of the remaining deprotected sugar analogues **10**–**15**, compounds **12**–**15** were micromolar inhibitors similar to the corresponding per-*O*-acylated analogues **3**–**7**, while potent inhibition was detected for the D-*gluco*- and D-*galacto*-configured triazoles **10** (K_i 9.4 nM) and **11** (K_i 9.3 nM), being ∼500-fold stronger inhibitors than their per-*O*-acetylated counterparts **2** and **3**, respectively. Interestingly, inhibition data for the *N*-acetyl glucosamine derivative **13** (K_i 4.4 μM) when compared with data observed for the corresponding D-*gluco*-configured analogue **10** (K_i 9.4 nM) showed a significant loss in hCA I inhibitory potency due the presence of the 2-acetamido group. Collectively, these results demonstrate that subtle structural differences in the sugar tail can indeed discriminate the hCA I isozyme active site topology to substantially influence enzyme inhibition characteristics.

Isozyme hCA II. The parent alkyne **1** had a K_i of 5.1 nM at hCA II, ∼200-fold more potent than at hCA I. The incorporation of the eight different sugar tails onto the benzene sulfonamide scaffold **1** had a variable effect on the inhibition of hCA II in vitro with K_i values in the range of 2.1–440 nM for the protected sugar series **2**–**9** and 2.3–460 nM for the deprotected sugar series **10**–**17**. As for hCA I, the α-configuration at the anomeric center gave the most potent hCA II inhibitors: the per-*O*-acetylated α-D-mannosyl triazole **8** (K_i 2.1 nM) and the deprotected α-D-arabinopyranosyl triazole **17** (K_i 2.3 nM). There were several library members with hCA II inhibition less than 10 nM (**2**, **3**, **8**, **9**, **11**, **15**, **16**, **17**), many of these were comparable with

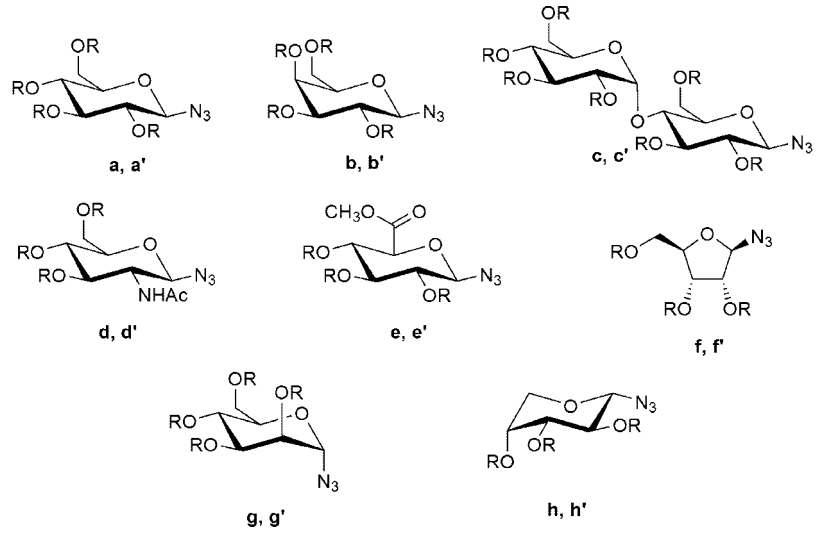
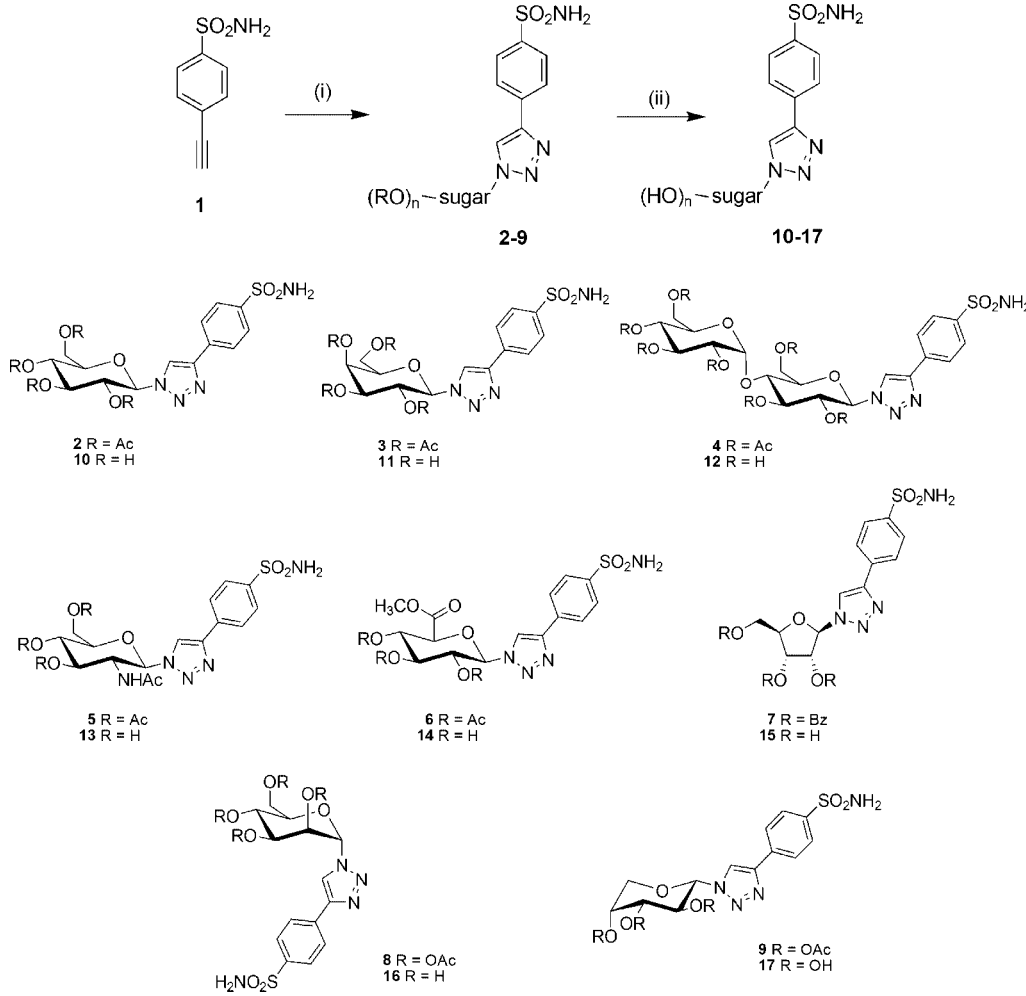


Figure 3. Azido sugar "tail" fragment panel: **a**−**e**, **g**, **h** (R = Ac); **f** (R = Bz); and **a′**−**h′** (R = H).

Scheme 2. Synthesis of Glycoconjugate Benzene Sulfonamide Library (**2**–**17**) from **1** and Sugar Panel **a**−**h**[a]



[a] Reagents and conditions: (i) **a**−**h** (1.0 equiv), $CuSO_4$ (0.1 equiv), sodium ascorbate (0.2 equiv), 1:1 *tert*-butanol–water, 40 °C, 30 min–1 h, 69–88%; (ii) $NaOCH_3$, CH_3OH, rt, 15 min–2 h, quantitative.

corresponding hCA I activity, while a few were quite selective for hCA II over hCA I (**2**, **3**, and **15**). Noteworthy, the deprotected ribose analogue **15** displayed high selectivity for the hCA II isozyme compared with both hCA I (573-fold) and IX (16-fold). Interestingly, the removal of the acetate groups from the disaccharide motif of **4** (K_i 235 nM) to afford **12** (K_i 432 nM) and the *O*-acetates from the GlcNAc derivative **5** (K_i 440 nM) to afford **13** (K_i 460 nM) did not result in enhanced inhibitory potency at hCA II, a pattern not mirrored by the other glycoconjugates within the series. This observation is in contrast with the removal of the bulky benzoate groups from the D-ribofuranosyl triazole **7** (K_i 427 nM) to afford **15** (K_i 7.5 nM),

Table 1. Inhibition and Isozyme Selectivity Ratio Data for Clinically Used CA Inhibitors, 4-Ethynyl Benzenesulfonamide **1**, and the 16 New Glycoconjugates **2–17** against Human Isozymes hCA I, II, and IX

	K_i[a] (nM)			selectivity ratios[b]	
cmpd	hCA I[c]	hCA II[c]	hCA IX[d]	hCA I/hCA IX	hCA II/hCA IX
AZA	250	12	25	10	0.48
MZA	50	14	27	18.5	0.52
EZA	25	8	34	0.74	0.24
BRZ	450	3	47	9.6	0.06
DRZ	500	9	52	9.6	0.17
DCP	1200	38	50	24	0.76
1	1080	5.1	8.1	133.3	0.63
2	4400	9.1	120	36.7	0.08
3	4300	8.7	110	39.1	0.08
4	2500	235	120	20.8	1.96
5	5000	440	101	49.5	4.36
6	48	13	9.9	4.84	1.3
7	5300	427	100	53.0	4.27
8	1.6	2.1	5.0	0.32	0.42
9	10.5	8.2	134	0.09	0.06
10	9.4	380	89	0.11	4.3
11	9.3	8.8	120	0.08	0.07
12	5000	432	130	38.5	3.32
13	4400	460	85	51.8	5.41
14	560	13	8.4	50.8	1.6
15	4300	7.5	121	35.5	0.06
16	2.8	7.6	5.4	0.52	1.41
17	2.5	2.3	28	0.09	0.08

[a] Errors in the range of ±5–10% of the reported value, from three determinations. [b] The K_i ratios are indicative of isozyme selectivity. [c] Human (cloned) isozymes, by the CO_2 hydration method.[31] [d] Catalytic domain of human (cloned) isozyme, by the CO_2 hydration method.[31]

resulting in a 57-fold increase in inhibitory potency, the steric demands of the hCA II active site may account for this observation.

Isozyme hCA IX. The parent alkyne **1** had a K_i of 8.1 nM at hCA IX. Many of the glycoconjugates (**2**−**5**, **7**, **9**−**13**, **15**, and **17**) exhibited clustered inhibition of hCA IX but were ∼10-fold weaker inhibitors than the parent acetylene **1**. The methyl D-glucuronates (**6** and **14**) were exceptional, however, and exhibited potent inhibition of hCA IX (K_i values 9.9 nM and 8.4 nM, respectively) as were the α-D-mannosyl triazole **8** and **16** (K_i values 5.0 nM and 5.4 nM, respectively), these are among the most potent inhibitors of hCA IX reported to date. In addition to their potent hCA IX inhibition, triazoles **6** and **14** also exhibited mild selectivity for hCA IX with respect to both hCA I and II. Noteworthy, these compounds exhibit up to 56-fold stronger inhibition potencies at hCA IX than the hitherto described carboxy ester and amide-linked glucuronate triazoles.[23,25] The parent fragment **1** displays no selectivity for hCA IX with respect to hCA II, while a number of our moderate hCA IX inhibitors (**4**, **5**, **7**, **12**, and **13**) were selective for hCA IX with respect to isozymes I and II, representing an important result for future therapeutic applications. Collectively, these results confirm our earlier observations that by tethering a sugar triazole tail onto the CA anchor pharmacophore it is possible to generate hCA IX selective inhibitors over the physiologically abundant hCA I and II isozymes.

Conclusions

To maximize the benefits and safety of future CA-based therapies, it has become a matter of acute importance to develop isozyme selective CA inhibitors and/or drug delivery systems so as to avoid side effects associated with indiscriminate inhibition of CAs present in multiple tissue sites. The polypharmacology and strong conservation of amino acid sequence and three-dimensional architecture of the catalytic site among the human isozymes does however make this a challenging process. Within this study, we have prepared of a library of hydrolytically stable benzene sulfonamides with triazole-tethered carbohydrate tails as a dual isozyme differentiating and solubilizing strategy. The evaluation of in vitro inhibition at cytosolic isozymes hCA I, II, and the cancer-related and membrane-associated extracellular hCA IX has demonstrated the successful interrogation of CA active site topology via the carbohydrate tail moiety. The facile conjugation of carbohydrate tails to a primary aryl sulfonamide fragment using click chemistry has provided an expedient and powerful means to generate these glycoconjugate CA inhibitors. The stereochemical and structural variability of the carbohydrate "tail" region allows for exploration of active site architecture and the potential development of neutral, water soluble CA inhibitors for drug delivery applications, and as a means of specifically targeting extracellular and clinically relevant CA isozymes due to impaired permeation of the plasma membrane. This strategy has successfully led to the identification of several potent and selective inhibitors of the pharmacologically relevant isozymes hCA II and hCA IX. In particular, the methyl-D-glucuronate triazoles **6** and **14** were shown to be potent inhibitors of hCA IX (K_i values 9.9 and 8.4 nM, respectively), and the β-D-ribofuranosyl triazole **15** and α-D-mannosyl triazole **17** exhibited potent and selective inhibition of hCA II (K_i 7.5 nM and K_i 2.3 nM, respectively). Such compounds may constitute important leads for the development of safe and efficacious CA inhibitor-based therapeutics, thus further highlighting the significance of glycoconjugates in CA-based inhibitor research.

Experimental Section

General. Glycosyl azide precursors were prepared by phase transfer nucleophilic displacement of corresponding peracetylated α-glycosylbromide.[28] All reagents were purchased from commercial sources and were used without further purification. All solvents were available commercially dried or freshly dried and distilled prior to use. Reaction progress was monitored by TLC using silica gel-60 F_{254} plates with detection by short wave UV fluorescence ($\lambda = 254$ nm) and staining with 10% (v/v) H_2SO_4 in ethanol char. Flash chromatography was conducted using Merk flash silica gel 60 (60–240 mesh). Solid phase extraction was performed using Phenomenex Strata cartridges prepacked with silica (SI-1). ^{1}H NMR (400 or 300 MHz), ^{13}C{^{1}H} NMR (100 or 75 MHz), 2D gCOSY, gHSQC, and gHMBC spectra were recorded on a Varian NMR spectrometers with chemical shift values given in ppm (δ) using deuterated solvent as specified. ^{13}C NMR spectra were referenced to either δ 77 ppm ($CDCl_3$) or δ 39.5 ppm (DMSO-d_6). Melting points were recorded on a GallenKamp Variable Temperature Apparatus by capillary method and are reported as uncorrected. Mass spectra were recorded on a Fisons VG platform II and a Waters Micromass ZQ4000 spectrometer employing a single quad dual source and using electrospray as the ionization technique in positive and negative ion modes. High resolution electrospray ionization mass spectra were recorded on a Bruker Daltonix 4.7T Fourier transform ion cyclotron resonance mass spectrometer (FTICR MS) fitted with an Apollo ESI source in positive ion or negative ion as stated. All MS analysis samples were prepared as solutions in methanol.

General Procedure 1: Synthesis of Glycoconjugate Benzene Sulfonamides (2–9). A mixture of azide (1.0 equiv.) and acetylene (1.0 equiv.) was suspended in a *tert*-butyl alcohol and distilled water (1:1, 0.2–0.5 M final concentration). A solution of sodium ascorbate (0.2 equiv) in water, followed by a solution of $CuSO_4 \cdot 5H_2O$ (0.1 equiv) in water was successively added. The bright yellow heterogeneous mixture was stirred vigorously at 40 °C until TLC indicated reaction completion (generally within 2 h). The mixture was evaporated under reduced pressure and the resulting residue was purified by flash chromatography to yield

analytically pure material. The 1,4-regioselectivity of the reaction was verified by ^{1}H and ^{13}C NMR chemical shifts of the triazole moiety in products obtained using DMSO-d_6 and D_2O and are in agreement with literature values.[30,32]

General Procedure 2: Deprotection of Glycoconjugate Benzene Sulfonamides (2–9 → 10–17). Deprotected triazoles **10–17** were prepared by treating the corresponding per-*O*-acylated precursor **2–9** with anhydrous methanolic sodium methoxide (final concentration of ∼0.1–0.2 M, pH 9–12) at room temperature. Reactions were found to be complete within 30 min by TLC. Neutralization of the methoxide by Amberlite IR-120 acidic ion-exchange resin, followed by filtration and evaporation of the filtrate afforded pure material by ^{1}H NMR and ^{13}C NMR spectroscopy. Special precaution was required for the deprotection of methyl D-glucuronate **6** to prevent saponification of the methyl ester using sodium methoxide in methanol. In this case, the pH was kept as near as possible to 8–9 with a lengthened reaction time (∼1 h).

4-Ethynyl Benzene Sulfonamide (1). Prepared by Sonagashira coupling according to a literature procedure.[27] R_f 0.37 (1:1 EtOAc−hexanes); mp 174–175 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.41 (s, 1H, C≡CH), 7.41 (br s, 2H, SO_2NH_2), 7.63–7.79 (m, 4H, *Ar* H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 82.98 (*C*≡CH), 84.05 (C≡*C*H), 125.72 (*Ar* C), 126.63 (*Ar* CH), 132.92 (*Ar* CH), 144.78 (*Ar* C).

4-[4-(Aminosulfonyl)phenyl]-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (2). The title compound was prepared according to the general procedure 1 and isolated as white solid (102 mg, 0.18 mmol, 69%). R_f 0.29 (3:7 hexanes−EtOAc); mp 218–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.78 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.98 (s, 3H, OAc), 2.01 (s, 3H, OAc), 4.07 (dd, 1H, $^2J_{6'-6''}$ = 12.8 Hz, $^3J_{6'-5'}$ = 2.4 Hz, 1H, H$_{6'}$), 4.14 (dd, $^2J_{6''-6'}$ = 12.8 Hz, $^3J_{6''-5'}$ = 5.6 Hz, 1H, H$_{6''}$), 4.41 (ddd, $^3J_{5'-4'}$ = 10 Hz, $^3J_{5'-6''}$ = 5.6 Hz, $^3J_{5'-6'}$ = 2.4 Hz, 1H, H$_{5'}$), 5.10–5.16 (m, 1H, H$_{4'}$), 5.56–5.61 (m, 1H, H$_{3'}$), 5.62–5.67 (m, 1H, H$_{2'}$), 6.41 (d, $^3J_{1'-2'}$ = 8.8 Hz, 1H, H$_{1'}$), 7.37 (br s, 2H, SO_2NH_2), 7.87–8.01 (m, *Ar*), 8.68 (s, 1H, triazole CH); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 20.56 (OAc), 20.92 (OAc), 21.07 (OAc), 21.20 (OAc), 62.43 (C$_{6'}$), 68.21 (C$_{4'}$), 70.99 (C$_{3'}$), 72.68 (C$_{2'}$), 73.88 (C$_{5'}$), 84.69 (C$_{1'}$), 122.34 (triazole CH), 126.21 (*Ar* CH), 127.18 (*Ar* CH), 133.81 (*Ar* C), 144.27 (triazole C or *Ar* C), 146.40 (triazole C or *Ar* C), 169.30 (OAc), 170.07 (OAc), 170.24 (OAc), 170.70 (OAc). HRMS (ESI) calcd for $C_{22}H_{25}N_4O_{11}S_1^-$, 553.12460; found, 553.12368. Anal. ($C_{22}H_{26}N_4O_{11}S.2H_2O$) C, N, S. H: calcd, 5.12; found, 4.64.

4-[4-(Aminosulfonyl)phenyl]-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (10). The title compound was prepared from **2** according to general procedure 2 and isolated as white crystalline solid (32 mg, 0.08 mmol, ∼100%); mp 243–244 °C (decomp). ^{1}H NMR (400 MHz, 2% D_2O in DMSO-d_6) δ 3.20–3.25 (m, 1H, H$_{4'}$), 3.38–3.49 (m, 3H, H$_{3'}$, H$_{5'}$ H$_{6'}$), 3.67–3.69 (m, 1H, H$_{6''}$), 3.74–3.78 (m, 1H, H$_{2'}$), 5.57 (d, $^3J_{1'-2'}$ = 9.2 Hz, 1H, H$_{1'}$), 7.86–8.05 (m, 4H, *Ar* CH), 8.94 (s, 1H, triazole CH); ^{13}C{^{1}H} NMR (100 MHz, 1% D_2O in DMSO-d_6) δ 61.28 (C$_{6'}$), 70.10 (C$_{4'}$), 72.81 (C$_{2'}$), 77.23 (C$_{3'}$), 80.53 (C$_{5'}$), 88.37 (C$_{1'}$), 122.38 (triazole CH), 126.11 (*Ar* CH), 127.15 (*Ar* CH), 134.41 (*Ar* C), 143.76 (triazole C or *Ar* C), 145.83 (triazole C or *Ar* C). HRMS (ESI) calcd for $C_{14}H_{17}N_4O_7S^-$, 387.09689; found, 387.09752.

4-[4-(Aminosulfonyl)phenyl]-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazole (3). The title compound was prepared according to general procedure 1 and isolated as white solid (255 mg, 0.46 mmol, 86%). R_f 0.21 (1:4 hexanes−EtOAc); mp 219–220 °C (decomp). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (s, 3H, OAc), 1.93 (s, 3H, OAc), 1.97 (s, 3H, OAc), 2.19 (s, 3H, OAc), 4.03 (dd, $^2J_{6'-6''}$ = 11.6 Hz, $^3J_{6'-5'}$ = 7.2 Hz, 1H, H$_{6'}$), 4.13 (dd, $^2J_{6''-6'}$ = 11.2 Hz, $^3J_{6'-5}$ = 4.8 Hz, 1H, H$_{6'}$), 4.61–4.64 (m, 1H, H$_{5'}$), 5.42–4.53 (m, 1H, H$_{4'}$), 5.49 (dd, $^3J_{3'-2'}$ = 10.4 Hz, $^3J_{3'-4'}$ = 3.6 Hz, 1H, H$_{3'}$), 5.58–5.63 (m, 1H, H$_{2'}$), 6.32 (d, $^3J_{1'-2'}$ = 9.2 Hz, 1H, H$_{1'}$), 7.37 (br s, 2H, SO_2NH_2), 7.87–8.10 (m, 4H, *Ar*), 8.75 (s, 1H, triazole CH); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 20.67 (OAc), 20.99 (OAc), 21.11 (OAc), 21.15 (OAc), 62.27 (C$_{6'}$), 67.95 (C$_{4'}$), 68.59 (C$_{3'}$), 71.00 (C$_{2'}$), 73.72 (C$_{5'}$), 85.23 (C$_{1'}$), 122.51 (triazole CH), 126.33 (*Ar* CH), 127.05 (*Ar* CH), 133.85 (*Ar* C), 144.23 (*Ar* C), 146.39 (triazole C), 169.36 (OAc), 170.16 (OAc), 170.62 (OAc), 170.68 (OAc). HRMS (ESI) calcd for $C_{22}H_{26}N_4O_{11}SNa^+$, 577.12110; found, 577.12222. Anal. ($C_{22}H_{26}N_4O_{11}S$) C, H, S. N: calcd, 10.10; found, 9.67.

4-[4-(Aminosulfonyl)phenyl]-1-(β-D-galactopyranosyl)-1*H*-1,2,3-triazole (11). The title compound was prepared from **3** according to general procedure 2 and isolated as pale yellow crystalline solid (140 mg, 0.36 mmol, ∼100%). R_f 0.12 (1:9 H_2O-CH_3CN); mp 171–172 °C (decomp). ^{1}H NMR (400 MHz, ∼1% D_2O in DMSO-d_6) δ 3.45–3.52 (m, 2H, H$_{6'}$, H$_{6''}$), 3.56 (dd, $^3J_{3'-2'}$ = 9.2 Hz, $^3J_{3'-4'}$ = 3.2 Hz, 1H, H$_{3'}$), 3.72–3.75 (m, 1H, H$_{5'}$), 3.76–3.77 (m, 1H, H$_{4'}$), 4.04−4.09 (m, 1H, H$_{2'}$), 5.52 (d, $^3J_{1'-2'}$ = 9.2 Hz, 1H, H$_{1'}$), 7.36 (br s, 2H, SO_2NH_2), 7.86–8.08 (m, 4H, *Ar* H), 8.90 (s, 1H, triazole CH); ^{13}C{^{1}H} NMR (100 MHz, 1% D_2O in DMSO-d_6) δ 61.04 (C$_{6'}$), 68.97 (C$_{5'}$), 69.97 (C$_{2'}$), 74.11 (C$_{3'}$), 79.14 (C$_{4'}$), 88.03 (C$_{1'}$), 122.17 (triazole CH), 126.13 (*Ar* CH), 127.10 (*Ar* CH), 143.76 (triazole C or *Ar* C), 145.84 (triazole C or *Ar* C). HRMS (ESI) calcd for $C_{14}H_{18}N_4O_7S^+$, 409.07902; found, 409.07817.

4-[4-(Aminosulfonyl)phenyl]-1-(hepta-*O*-acetyl-β-D-maltopyranosyl)-1*H*-1,2,3-triazole (4). The title compound was prepared according to the general procedure 1 and isolated as white solid (210 mg, 0.25 mmol, 83%). R_f 0.26 (3:7 hexanes−EtOAc); mp 241–242 °C (decomp). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75 (s, 3H, OAc), 1.94 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.97 (s, 3H, OAc), 1.99 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.03 (s, 3H, OAc), 3.89–4.03 (m, 2H, Glcα H$_{5'}$, Glcα H$_{6'}$), 4.09–4.18 (m, 3H, Glcβ H$_{4'}$, Glcβ H$_{6'}$, Glcα H$_{6''}$), 4.38 (ddd, $^3J_{5'-4'}$ = 9.6 Hz, $^3J_{5'-6'}$ = 5.6 Hz, $^3J_{5'-6''}$ = 2.0 Hz, 1H, Glcβ H$_{5'}$), 4.44 (dd, $^2J_{6''-6'}$ = 12.4 Hz, $^3J_{6''-5'}$ = 2.4 Hz, 1H, Glcβ H$_{6''}$), 4.90 (dd, $^3J_{2'-3'}$ = 10 Hz Hz, $^3J_{2'-1'}$ = 4.0 Hz, 1H, Glcα H$_{2'}$), 4.97–5.02 (m, 1H, Glcα H$_{4'}$), 5.23 (dd, $^3J_{3'-2'}$ = 10 Hz, $^3J_{3'-4'}$ = 9.6 Hz, 1H, Glcα H$_{3'}$), 5.36 (d, $^3J_{1'-2'}$ = 4.0 Hz, 1H, Glcα H$_{1'}$), 5.50–5.54 (m, 1H, Glcβ H$_{2'}$), 5.61–5.66 (m, 1H, Glcβ H$_{3'}$), 6.37 (d, $^3J_{1'-2'}$ = 9.2 Hz, 1H, Glcβ H$_{1'}$), 7.37 (br s, 2H, SO_2NH_2), 7.87–8.02 (m, 4H, *Ar*), 9.87 (s, 1H, triazole CH); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 20.61 (OAc), 20.95 (OAc), 21.03 (2 × OAc), 21.12 (OAc), 21.20 (OAc), 21.25 (OAc), 62.08 (Glcα C$_{6'}$), 63.48 (Glcβ C$_{6'}$), 68.38 (Glcα C$_{4'}$), 68.87 (Glcβ C$_{4'}$), 69.59 (Glcα C$_{3'}$), 70.12 (Glcα C$_{2'}$), 71.47 (Glcβ C$_{2'}$), 74.13 (Glcα C$_{5'}$), 74.59 (Glcβ C$_{5'}$), 74.92 (Glcβ C$_{3'}$), 84.27 (Glcβ C$_{1'}$), 96.44 (Glcα C$_{1'}$), 122.42 (triazole CH), 126.23 (*Ar* CH), 127.15 (*Ar* CH), 133.79 (*Ar* C), 144.26 (triazole C or *Ar* C), 146.31 (triazole C or *Ar* C), 169.48 (OAc), 169.85 (OAc), 170.20 (OAc), 170.37 (OAc), 170.55 (OAc), 170.68 (OAc), 170.80 (OAc). HRMS (ESI) calcd for $C_{34}H_{42}N_4O_{19}S_1Na^+$, 865.20562; found, 865.20611. Anal. ($C_{34}H_{42}N_4O_{19}S$) C, H, N, S.

4-[4-(Aminosulfonyl)phenyl]-1-(β-D-maltopyranosyl)-1*H*-1,2,3-triazole (12). The title compound was prepared from **4** according to general procedure 2 and isolated as white solid (45 mg, 0.08 mmol, 92%). R_f 0.14 (1:9 H_2O−CH_3CN); mp 228–230 °C (decomp). ^{1}H NMR (400 MHz, D_2O) δ 3.28–3.33 (m, 1H, Glcα H$_{3'}$/H$_{4'}$ or Glcβ H$_{3'}$/H$_{4'}$), 3.48 (dd, $^3J_{2'-3'}$ = 10.0 Hz, $^3J_{2'-1'}$ = 3.6 Hz, 1H, Glcα H$_{2'}$), 3.57–3.85 (m, 8H, Glcα H$_3$/H$_{4'}$, Glcα H$_5$′, Glcα H$_6$, Glcα H$_{6''}$, Glcβ H$_{3'}$/H$_{4'}$, Glcβ H$_5$′, Glcβ H$_{6'}$ and Glcβ H$_{6''}$), 3.87–3.86 (m, 2H, Glcβ H$_{2'}$, Glcβ H$_{3'}$), 3.35 (d, 1H, Glcα H$_{1'}$), 5.68 (d, $^3J_{1'-2'}$ = 8.0 Hz, 1H, Glcβ H$_{1'}$), 7.72–7.79 (m, 4H, *Ar*), 8.46 (s, 1H, triazole CH); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 60.65 (Glcα C$_{6'}$ and Glcβ C$_{6'}$), 69.49, 71.86, 72.40, 72.95, 73.06, 76.01, 76.54, 77.72 (Glcα C$_{2'}$, Glcα C$_{3'}$, Glcα C$_{4'}$, Glcα C$_{5'}$ and Glcβ C$_{2'}$, Glcβ C$_{3'}$, Glcβ C$_{4'}$ Glcβ C$_{5'}$), 87.59 (Glcβ C$_{1'}$), 99.85 (Glcα C$_1$), 122.51 (triazole CH), 126.49 (*Ar* CH), 126.77 (*Ar* CH), 133.74 (*Ar* C), 141.07 (triazole C or *Ar* C), 146.25 (triazole C or *Ar* C). HRMS (ESI) calcd for $C_{20}H_{28}N_4O_{12}S_1Na^+$, 571.13166; found, 571.13127.

4-[4-(Aminosulfonyl)phenyl]-1-(2′-acetamido-2′-deoxy′-3′,4′,6′-tri-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (5). The title compound was prepared according to general procedure 1 and isolated as white solid (195 mg, 3.52 mmol, 88%). R_f 0.42 (1:9 CH_3OH−EtOAc); mp 249.6 °C (decomp). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.57 (s, 3H, NHAc), 1.93 (s, 3H, OAc), 1.98 (s, 3H, OAc), 2.00 (s, 3H, OAc), 4.06 (dd, $^2J_{6'-6''}$ = 12.4 Hz, $^3J_{6'-5'}$ = 2.0 Hz, 1H, H$_{6'}$), 4.15 (dd, $^2J_{6''-6'}$ = 12.5 Hz, $^3J_{6''-5'}$ = 5.2 Hz, 1H,

$H_{6''}$), 4.28 (ddd, $^3J_{5'-4'} = 10.4$ Hz, $^3J_{5'-6''} = 5.2$ Hz, $^3J_{5'-6'} = 2.4$ Hz, 1H, $H_{5'}$), 4.58–4.67 (m, 1H, $H_{2'}$), 5.06–5.11 (m, 1H, $H_{4'}$), 5.34–5.39 (m, 1H, $H_{3'}$), 6.14 (d, 1H, $^3J_{1'-2'} = 10.0$ Hz, 1H, $H_{1'}$), 7.37 (br s, 2H, SO_2NH_2), 7.87–8.00 (m, 4H, *Ar*), 8.10 (d, $^3J_{NH\text{-}2} =$ 9.2 Hz, 1H, NHAc NH), 8.98 (s, 1H, triazole H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 20.96 (OAc), 21.10 (OAc), 21.20 (OAc), 22.98 (NHAc), 53.05 ($C_{2'}$), 62.43 ($C_{6'}$), 68.70 ($C_{4'}$), 72.91 ($C_{3'}$), 74.10 ($C_{5'}$), 85.68 ($C_{1'}$), 122.81 (triazole CH), 126.14 (*Ar* CH), 127.17 (*Ar* CH), 134.01 (*Ar* C), 144.16 (triazole CH or *Ar* C), 145.98 (triazole CH or *Ar* C), 170.06 (*C*═O), 170.21 (*C*═O), 170.27 (*C*═O), 170.71 (*C*═O). HRMS (ESI) calcd for $C_{22}H_{26}N_5O_{10}S^-$, 577.12110; found, 577.12222. Anal. ($C_{22}H_{27}N_5O_{10}S$) C, H, S. N: calcd, 12.65; found, 12.18.

4-[4-(Aminosulfonyl)phenyl]-1-(2′-acetamido-2′-deoxy-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (13). The title compound was prepared from **5** according to general procedure 2 and isolated as white solid (116 mg, 0.27 mmol, ∼100%); mp 215–217 °C. ^1H NMR (400 MHz, 1% D_2O in DMSO-d_6) δ 1.59 (s, 3H, NHAc), 3.24–3.23 (m, 1H, $H_{4'}$), 3.43–3.49 (m, 2H, $H_{6'}$, $H_{6''}$), 3.55–3.59 (m, 1H, $H_{3'}$), 3.68–3.73 (m, 1H, $H_{5'}$), 4.04–4.09 (m, 1H, $H_{2'}$), 5.73 (d, $^3J_{1'-2'} = 10.0$ Hz, 1H, $H_{1'}$), 7.85–8.02 (m, 4H, *Ar* H), 8.81 (s, 1H, triazole CH); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 23.28 (NHAc CH_3), 55.46 ($C_{2'}$), 61.32 ($C_{6'}$), 70.55 ($C_{4'}$), 74.25 ($C_{5'}$), 80.74 ($C_{3'}$), 86.99 ($C_{1'}$), 122.02 (triazole CH), 126.10 (*Ar* CH), 127.10 (*Ar* CH), 134.35 (*Ar* C), 143.86 (triazole C or *Ar* C), 145.59 (triazole C or *Ar* C), 169.92 (NHAc *C*═O). HRMS (ESI) calcd for $C_{16}H_{20}N_5O_7S^-$, 426.10889; found, 426.10768.

4-[4-(Aminosulfonyl)phenyl]-1-(2′,3′,4′-tri-*O*-acetyl-β-D-glucuronic acid methyl ester)-1*H*-1,2,3-triazole (6). The title compound was prepared according to general procedure 1 and isolated as white solid (145 mg, 0.27 mmol, 87%). R_f 0.63 (1:9 $CH_3OH-CH_2Cl_2$); mp 249–251 °C (decomp). ^1H NMR (400 MHz, DMSO-d_6) δ 1.79 (s, 3H, OAc), 1.98 (s, 3H, OAc), 2.01 (s, 3H, OAc), 3.61 (s, 3H, $COCH_3$), 4.84 (d, $^3J_{5'-4'} = 10.4$ Hz, 1H, $H_{5'}$), 5.19–5.24 (m, 1H, $H_{4'}$), 5.63–5.74 (m, $H_{2'}$ and $H_{3'}$), 6.46 (d, $^3J_{1'-2'} = 8.8$ Hz, 1H, $H_{1'}$), 7.37 (br s, 2H, SO_2NH_2), 7.88–8.01 (m, 4H, *Ar* CH), 9.15 (s, 1H, triazole CH); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 20.57 (OAc), 20.90 (OAc), 20.95 (OAc), 53.39 (OCH_3), 69.13 ($C_{4'}$), 70.65 ($C_{2'}$), 72.03 ($C_{3'}$), 73.59 ($C_{5'}$), 84.58 ($C_{1'}$), 122.52 (triazole CH), 126.22 (*Ar* CH), 127.21 (*Ar* CH), 133.73 (*Ar* C), 144.32 (*Ar* C), 156.52 (triazole C), 167.22 (*C*═O), 164.24 (OAc), 170.02 (OAc), 170.20 (OAc). HRMS (ESI) calcd for $C_{21}H_{24}N_4O_{11}SNa^+$, 563.10545; found, 563.10376.

4-[4-(Aminosulfonyl)phenyl]-1-(β-D-glucuronic acid methyl ester)-1*H*-1,2,3-triazole (14). The title compound was prepared from **6** according to general procedure 2 and isolated as pale yellow foam (22 mg, 0.05 mmol, ∼100%). ^1H NMR (400 MHz, 2% D_2O in DMSO-d_6) δ 3.45−3.54 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.63 (s, 3H, OCH_3), 3.85–3.89 (m, 1H, $H_{2'}$), 4.19 (d, $^3J_{5'-4'} = 8.8$ Hz, 1H, $H_{5'}$), 5.79 (d, $^3J_{1'-2'}$.06 (m, 4H, *Ar* CH), 8.98 (s, 1H, triazole CH); $^{13}C\{^1H\}$ NMR (100 MHz, 2% D_2O in DMSO-d_6) δ 52.78 (OCH_3), 71.80 ($C_{3'}$), 72.31 ($C_{4'}$), 76.39 ($C_{2'}$), 78.02 ($C_{5'}$), 87.95 ($C_{1'}$), 122.51 (triazole CH), 126.16 (*Ar* CH), 127.14 (*Ar* CH), 134.28 (*Ar* C), 143.86 (*Ar* C), 145.97 (triazole C), 169.39 (*C*═O). HRMS (ESI) calcd for $C_{15}H_{18}N_4O_8S^+$, 437.07376; found, 437.07397.

4-[4-(Aminosulfonyl)phenyl]-1-(2′,3′,4′-tri-*O*-benzoyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazole (7). The title compound was prepared according to general procedure 1 and isolated as white solid (343 mg, 0.51 mmol, 88%). R_f 0.52 (2:3 hexanes−EtOAc); mp 168–169 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 4.58 (dd, $^2J_{5'-5''} = 12.0$ Hz, $^3J_{5'-4'} = 4.4$ Hz, 1H, $H_{5'}$), 4.70 (dd, $^2J_{5''-5'} = 12.4$ Hz, $^3J_{5''-4'} = 3.6$ Hz, 1H, $H_{5''}$), 4.96–5.00 (m, 1H, $H_{4'}$), 6.13 (dd, $^3J_{3'-4'} = 6.0$ Hz, $^3J_{3'-2'} = 5.2$ Hz, 1H, $H_{3'}$), 6.33 (dd, $^3J_{2'-3'} = 5.2$ Hz, $^3J_{2'-1'} = 2.8$ Hz, 1H, $H_{2'}$), 6.78 (d, $^3J_{1'-2'} = 2.8$ Hz, 1H, $H_{1'}$), 7.39 (br s, 2H, SO_2NH_2), 7.40–7.50 (m, 6H, *Ar*), 7.56–7.68 (m, 3H, *Ar*), 7.87–8.01 (m, 10H, *Ar*), 8.97 (s, 1H, triazole CH); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 63.86 ($C_{5'}$), 71.69 ($C_{3'}$), 75.19 ($C_{2'}$), 80.61 ($C_{4'}$), 90.25 ($C_{1'}$), 123.24 (triazole CH), 126.29, 127.09, 129.31, 129.43, 129.55, 129.78, 129.93, 130.07, 130.15, 133.88, 134.18, 134.61, 134.77 (*Ar* CH and *Ar* C), 144.20 (triazole C or *Ar* C), 146.33 (triazole C or *Ar* C), 165.15 (*C*═O), 165.37 (*C*═O), 166.08 (*C*═O). HRMS (ESI) calcd for $C_{34}H_{28}N_4O_9SNa^+$, 691.14692; found, 691.14614. Anal. ($C_{34}H_{28}N_4O$) H, N, S. C: calcd, 61.07; found, 60.61.

4-[4-(Aminosulfonyl)phenyl]-1-(β-D-ribofuranosyl)-1*H*-1,2,3-triazole (15). The title compound prepared from **7** according to general procedure 2 and isolated as white solid (84 mg, 0.24 mmol, ∼100%). R_f 0.16 (1:9 $CH_3OH-EtOAc$); mp 219–220 °C. ^1H NMR (400 MHz, 1% D_2O in DMSO-d_6) δ 3.51 (dd, $^2J_{5'-5''} = 12.0$ Hz, $^3J_{5'-4'} = 4.4$ Hz, 1H, $H_{5'}$), 3.62 (dd, $^2J_{5''-5'} = 12.4$ Hz, $^3J_{5''-4'} =$ 4.0 Hz, 1H, $H_{5''}$), 3.87–4.00 (m, 1H, $H_{4'}$), 4.12–4.15 (m, 1H, $H_{3'}$), 4.40–4.43 (m, 1H, $H_{2'}$), 5.96 (d, $^3J_{1'-2'} = 4.4$ Hz, 1H, $H_{1'}$), 3.73 (br s, 2H, SO_2NH_2), 7.87–8.03 (m, 4H, *Ar*), 8.88 (s, 1H, triazole CH); ^{13}C NMR (100 MHz, 1% D_2O in DMSO-d_6) δ 61.88 ($C_{5'}$), 70.86 ($C_{3'}$), 75.63 ($C_{2'}$), 86.57 ($C_{4'}$), 92.90 ($C_{1'}$), 121.72 (triazole CH), 126.15 (*Ar* CH), 127.14 (*Ar* CH), 134.34 (*Ar* C), 143.89 (triazole C), 146.06 (*Ar* C). HRMS (ESI) calcd for $C_{13}H_{17}N_4O_6S^+$, 357.08650; found, 357.08299.

4-[4-(Aminosulfonyl)phenyl]-1-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-mannopyranosyl)-1*H*-1,2,3-triazole (8). The title compound was prepared according to general procedure 1 and isolated as white glassy foam (189 mg, 0.34 mmol, 51%). R_f 0.37 (3:7 hexanes−EtOAc). ^1H NMR (400 MHz, DMSO-d_6) δ 1.98 (s, 3H OAc), 2.00 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.04 (s, 3H, OAc), 3.88 (ddd, $^3J_{5'-4'} =$ 9.2 Hz, $^3J_{5'-6'} = 5.6$ Hz, $^3J_{5'-6''} = 3.2$ Hz, 1H, $H_{5'}$), 4.06 (dd, $^2J_{6''-6'} =$ 17.2 Hz, $^3J_{6''-5} = 3.6$ Hz, 1H, $H_{6''}$), 4.24 (dd, $^2J_{6'-6''} =$16.8 Hz, $^3J_{6'-5'} = 6.4$ Hz, 1H, $H_{6'}$), 5.25–5.31 (m, 1H, $H_{4'}$), 5.23 (dd, $^3J_{3'-4'} = 12.8$ Hz, $^3J_{3'-2'} = 5.2$ Hz, 1H, $H_{4'}$), 5.88 (dd, $^3J_{2'-3'} = 5.2$ Hz, $^3J_{2'-1'} = 3.2$ Hz, 1H, $H_{2'}$), 6.47 (d, $^3J_{1'-2'} = 3.0$ Hz, 1H, $H_{1'}$), 7.41 (br s, 2H, SO_2NH_2), 7.91–8.12 (m, 4H, *Ar*), 8.94 (s, 1H, triazole CH). HRMS (ESI) calcd for $C_{22}H_{26}N_4O_{11}SNa^+$, 577.12109; found, 577.11897.

4-[4-(Aminosulfonyl)phenyl]-1-(α-D-mannopyranosyl)-1*H*-1,2,3-triazole (16). The title compound prepared from **8** according to general procedure 2 and isolated as white solid (110 mg, 0.28 mmol, ∼100%). R_f 0.12 (1:9 $CH_3OH-EtOAc$); mp 239–240 °C. ^1H NMR (400 MHz, 1% D_2O in DMSO-d_6) δ 3.40–3.45 (m, 2H, $H_{6''}$, $H_{5'}$), 3.57–3.63 (m, 2H, $H_{6'}$, $H_{4'}$), 3.85 (dd, $^3J_{3'-4'} = 9.9$ Hz, $^3J_{3'-2'} = 3.3$ Hz, 1H, $H_{3'}$), 4.43–4.46 (m, 1H, $H_{2'}$), 5.95 (d, $^3J_{1'-2'} = 4.8$ Hz, 1H, $H_{1'}$), 7.87–8.07 (m, 4H, *Ar*), 8.85 (s, 1H, triazole CH). $^{13}C\{^1H\}$ NMR (75 MHz, 1% D_2O in DMSO-d_6) δ 61.19 ($C_{6'}$), 68.29 ($C_{4'}$), 68.59 ($C_{2'}$), 71.82 ($C_{3'}$), 79.18 ($C_{5'}$), 86.55 ($C_{1'}$), 122.98 (triazole CH), 126.18 (*Ar* CH), 127.13 (*Ar* CH), 134.35 (*Ar* C), 143.93 (*Ar* C), 145.81 (triazole C). HRMS (ESI) calcd for $C_{14}H_{18}N_4O_7SNa^+$, 409.07884; found, 409.07856.

4-[4-(Aminosulfonyl)phenyl]-1-(2′,3′,4′-tri-*O*-acetyl-α-D-arabinopyranosyl)-1*H*-1,2,3-triazole (9). The title compound was prepared according to general procedure 1 and isolated as white solid (154 mg, 0.32 mmol, 60%). R_f 0.52 (1:1 $CH_2Cl_2-EtOAc$); mp 229–230 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 1.84 (s, 3H, OAc), 1.97 (s, 3H, OAc), 2.20 (s, 3H, OAc), 4.09 (dd, $^2J_{5'-5''} =$ 13.2 Hz, $^3J_{5'-4'} = 1.8$ Hz, 1H, $H_{5'}$), 4.24 (dd, 1H, $^2J_{5'-5''} = 12.3$ Hz, $^3J_{5''-4'} = 1.3$ Hz, 1H, $H_{5''}$), 5.34–5.35 (m, 1H, $H_{4'}$), 5.46 (dd, $^3J_{3'-2'} = 10.2$ Hz, $^3J_{3'-4'} = 3.6$ Hz, 1H, $H_{3'}$), 5.58–5.65 (m, 1H, $H_{2'}$), 6.22 (d, $^3J_{1'-2'} = 9.0$ Hz, 1H, $H_{1'}$), 7.40 (br s, 2H, SO_2NH_2), 7.88–8.13 (m, 4H, *Ar* H), 9.03 (s, 1H, triazole H); ^{13}C $\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 20.02 (OAc), 20.41 (OAc), 20.75 (OAc), 66.54 ($C_{5'}$), 67.86 ($C_{4'}$), 68.21 ($C_{3'}$), 70.22 ($C_{2'}$), 85.11 ($C_{1'}$), 121.71 (triazole CH), 125.63 (*Ar* CH), 126.38 (*Ar* CH), 133.26 (*Ar* C), 143.51 (triazole C or *Ar* C), 145.62 (triazole C or *Ar* C), 168.72 (*C*═O), 168.73 (*C*═O), 169.57 (*C*═O). HRMS (ESI) calcd for $C_{19}H_{22}N_4O_9SNa^+$, 505.09998; found, 505.09996.

4-[4-(Aminosulfonyl)phenyl]-1-(α-D-arabinopyranosyl)-1*H*-1,2,3-triazole (17). The title compound prepared from **9** according to general procedure 2 and isolated as clear oil (76 mg, 0.21 mmol, ∼100%). ^1H NMR (300 MHz, 2% D_2O in DMSO-d_6) δ 3.59 (dd, $^3J_{3'-2'} = 9.6$ Hz, $^3J_{3'-4'} = 3.3$ Hz, 1H, $H_{3'}$), 3.78–3.84 (m, 2H, $H_{4'}$, $H_{5''}$), 4.06–4.12 (m, 1H, $H_{2'}$), 5.48 (d, 1H, $^3J_{1'-2'} = 9.0$ Hz, 1H, $H_{1'}$), 7.88–8.10 (m, 4H, *Ar* H), 8.90 (s, 1H, triazole H); ^{13}C $\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 68.28 ($C_{4'}$ or $C_{5'}$), 69.43 ($C_{4'}$ or $C_{5'}$), 69.44 ($C_{2'}$), 73.04 ($C_{3'}$), 88.72 ($C_{1'}$), 121.57 (triazole CH), 125.57 (*Ar* CH), 126.54 (*Ar* CH), 132.37 (*Ar* C), 133.90 (*Ar* C), 145.22

(triazole C). HRMS (ESI) calcd for $C_{13}H_{16}N_4O_6SNa^+$, 379.0683; found, 379.06931.

Carbonic Anhydrase Catalytic/Inhibition Assay. An SX.18MV-R Applied Photophysics stopped-flow instrument has been used for assaying the CA I, II, and IX CO_2 hydration activity.[31] Phenol red (at a concentration of 0.2 mM) has been used as indicator, working at the absorbance maximum of 557 nm, with 10 mM Hepes (pH 7.5) as buffer, 0.1 M $NaClO_4$ (for maintaining constant ionic strength, this anion is not inhibitory), following the CA-catalyzed CO_2 hydration reaction for a period of 10–100 s. Saturated CO_2 solutions in water at 20 °C were used as substrate. Stock solutions of inhibitors were prepared at a concentration of 10–50 mM (in the assay buffer) and dilutions up to 1 nM done with the assay buffer mentioned above. Inhibitor and enzyme solutions were preincubated together for 15 min at room temperature prior to assay, to allow for the formation of the E-I complex. The inhibition constants were obtained by nonlinear least-squares methods using PRISM 3. The curve-fitting algorithm allowed us to obtain the IC_{50} values (working at the lowest concentration of substrate of 1.7 mM) from which K_i values were calculated by using the Cheng−Prusoff equation. The catalytic activity (in the absence of inhibitors) of these enzymes was calculated from Lineweaver–Burk plots, as reported earlier, and represent the mean from at least three different determinations.[33–35] Enzyme concentrations were 10 nM for CA I and CA II and 14 nM for CA IX. Kinetic parameters and inhibition constants were calculated as described previously.[33–35] Enzymes used here were recombinant ones, prepared and purified as described earlier.

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Supporting Information Available: Elemental analysis data and ^1H and ^{13}C NMR spectra for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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