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Sulfonamide Linked Neoglycoconjugates−A New Class of Inhibitors for Cancer-Associated Carbonic Anhydrases

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The contribution of membrane-bound carbonic anhydrases (CAs) to hypoxic tumor growth and progression in cancer implicates cancer-associated CAs as a promising drug target for oncology. In this paper, we present a new class of sulfonamide-linked neoglycoconjugate that was designed to selectively target and inhibit the extracellular domains of the cancer-relevant CA isozymes. We describe the application of novel, yet straightforward, chemistry toward the synthesis of inhibitors that comprise both *S*-glycosyl sulfenamides and *S*-glycosyl sulfonamides. We also present the CA inhibition profile of our new neoglycoconjugates, more specifically a library of 30 compounds (**3**−**32**) that were designed to optimize both SAR (structure−activity relationship) and SPR (structure−property relationship) characteristics. We show that our approach produces neutral, water-soluble, and potent inhibitors (K_is in the low nanomolar range) that target cancer-associated CAs.

Introduction

In solid tumors, vasculature is poor; this limits blood supply to the tumor mass and in turn reduces delivery of O_2 to the tumor cells. At a molecular level, low O_2, known as hypoxia ($\equiv$ 0.1−5% O_2), induces the activation of a transcription factor, appropriately named hypoxia-inducible factor (HIF[a]).[1] High levels of HIF regulate a signaling cascade, involving ∼hundred genes, that adapt cellular functions to allow solid tumor cells to not only survive hypoxia but to proliferate and metastasize.[1] Carbonic anhydrase IX (CA IX) is one of the most highly induced HIF responsive genes and is overexpressed and sustained in a number of solid tumors including breast, brain (glioblastoma), clear cell renal, colorectal, head and neck, bladder, and nonsmall cell lung carcinomas.[2−4] CA IX is a multidomain protein consisting of an N-terminal proteoglycan like domain, a transmembrane domain, a short intracellular domain and an *extracellular* catalytic domain.[5] The catalytic domain of CAs contains an active site Zn^{2+}. This metal cation is a strong Lewis acid that binds to and activates a substrate H_2O molecule to catalyze the reversible reaction: $CO_2 + H_2O \rightleftarrows HCO_3^- + H^+$.[6] The hydration of CO_2 does not proceed at an appreciable rate under physiological conditions in the absence of CA enzymes.[6]

Tumor cells also experience elevated metabolism and acid production compared to normal cells.[7,8] If this acid-load is allowed to accumulate, then intracellular pH (pH_i) would fall to dangerously low levels and disrupt critical biological functions.[7,8] To counter this, tumor cells have evolved mechanisms to extrude acid into the extracellular environment. Recent evidence has demonstrated that it is cell-generated CO_2 that is primarily responsible for the rapid removal of acid equivalents from tumor cells and not lactic acid, which has been the popular belief until now.[7,8] Cell-derived CO_2 is freely membrane permeable, so provided there is sufficient outward gradient this CO_2 diffuses to the extracellular space, where in poorly vascularized hypoxic tumor regions, it is hydrated to bicarbonate (HCO_3^-) and a proton (H^+): $CO_2 + H_2O \rightleftarrows HCO_3^- + H^+$. The net effect is to trap acid extracellularly to lower extracellular pH (pH_e ∼6.9−7.0) and maintain pH_i (∼7.2) with HCO_3^- recycled back into the cell, where it combines with a proton to give CO_2 (catalyzed by intracellular CA II) to continue this cycle, Figure 1.[8] The contribution of CA IX (and CA XII, which is also HIF activated) to hypoxic tumor growth and progression has long been debated, however the intensity of recent research has provided convergent evidence that affirms that these transmembrane CAs, with their extracellular oriented active sites, are the key molecules for regulating cancer cell pH_i during hypoxia and thus are major tumor prosurvival enzymes.[7,8] Very recently, it was reported that "knockout" of CA IX and CA XII using gene silencing technology led to a remarkable 85% tumor growth retardation in colorectal cancer xenograft models—this research has advanced our understanding of the pivotal role of CAs in cancer and implicates cancer-associated CAs as a new and promising drug target for oncology therapies.[7] Of the 12

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[a] Abbreviations: CA, carbonic anhydrase; AZA, acetazolamide; TPM, topiramate; SAR, structure−activity relationship; SPR, structure−property relationship; HIF, hypoxia-inducible factor; PAMPA, parallel artificial membrane permeability assay; P_e, apparent in vitro effective permeability.

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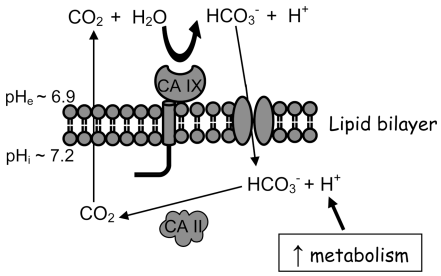


Figure 1. Schematic of CA IX mediated pH_i regulation of a hypoxic tumor cell microenvironment. CA IX is a transmembrane enzyme with an extracellular oriented active site domain.

catalytically active CAs known, only the membrane bound CA IX and CA XII isozymes are associated with cancer.[6]

The CA-mediated pH_i regulation of hypoxic tumor cells underpins a compelling case for the development of small-molecule CA inhibitors as chemical probes and as lead molecules to appraise the potential of cancer-associated CA IX and XII for therapeutic intervention. In the past few years, our group has established a novel approach to targeting CA IX and XII with small molecule inhibitors.[9−15] Our inhibitors comprise a carbohydrate "tail" moiety tethered to the well characterized, high-affinity aromatic sulfonamide CA pharmacophore [aromatic-SO_2NH_2], leading to glycoconjugates with the triple motif [carbohydrate-aromatic-SO_2NH_2]. The $-SO_2NH_2$ group is a Zn^{2+} binding function that anchors the small molecule inhibitor molecule within the CA enzyme active site.[6] We and others have shown that the CA active site is tolerant to diverse structural characteristics within the tail moiety of inhibitors such as size, shape and charge, polar and hydrophobic groups, etc.[6,9−15] This structural tolerance permits a flexible ligand design approach to allow finetuning of biopharmaceutical and toxicological properties of the inhibitor through structural manipulation. In our experience, and consistent with this premise, the tail group of the CA inhibitor can impact the compound's physicochemical properties, i.e. structure−property relationships (SPR), more so than structure−activity relationships (SAR). Recently, we demonstrated that a selection of our glycoconjugates was unable to passively diffuse through an artificial lipid membrane barrier (a mimic of the cell membrane); this observation was consistent with calculated Log *P* values.[10] The results confirmed that selectively targeting extracellular CA active sites over intracellular CAs is possible by altering membrane permeability properties through deliberate structural changes of the inhibitor compounds. This combined SAR−SPR characteristics of our general inhibitor motif thus offers excellent potential for the development of isozyme selective inhibitors of cancer-associated CAs in vivo.

Results and Discussion

Artificial glycoconjugates already constitute a diverse family of clinically used therapeutics, including small molecule antibacterial glycoconjugates.[16] The continuing need for new therapeutic neoglycoconjugates requires the development of straightforward synthetic methodology toward stable, novel glycoconjugate linkers in place of native, enzyme labile covalent linkages.[17] Here we outline the targeting of transmembrane CAs over cytosolic CAs by incorporation of a carbohydrate tail group into the CA inhibitor structure in accord with our combined SPR−SAR strategy. We describe the application of novel chemistry toward this new class of sulfonamide-linked glycoconjugate. We also present the CA inhibition profile of our library, comprising 30 new compounds **3**−**32**, against the cancer-associated (hCA IX and XII) and physiologically dominant (hCA I and II) CA isozymes (h = human). We show that our approach to targeting cancer-associated CAs is achieved with minimal SAR penalties.

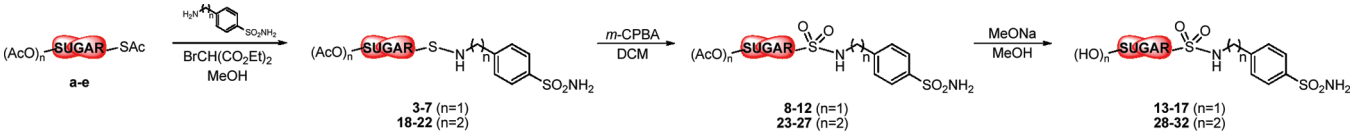
In principle, anomeric sulfonyl chlorides through reaction with myriad primary amines could serve as precursors to a multitude of carbohydrate-based *S*-glycosyl sulfonamides. However, it has been shown that anomeric sulfonyl chlorides are unstable and rapidly convert to the corresponding anomeric chlorides by loss of SO_2.[18] This lack of stability eliminates these compounds as precursors to sulfonamides, and as a result, *S*-glycosyl primary sulfonamides have remained an unknown class of compounds, quite remarkable given the broad utility of the sulfonamide functional group across medicinal chemistry.[19] We recently developed a simple and efficient synthesis for *S*-glycosyl primary sulfonamides, based on oxidation of *S*-glycosyl sulfenamides and subsequent removal of the acetate protecting group.[20] The primary sulfonamide functional group $-SO_2NH_2$ of these compounds is attached directly to the anomeric position of the carbohydrate. In this study, we discovered that anomeric *S*-glycosyl sulfenamides could be synthesized by reaction of sugar thioacetates with either primary (RNH_2) or secondary amines (R_2NH) to give sulfenamides [sugar-S-NHR] and [sugar-SNR_2], respectively; this reaction had previously been reported as being only suited with secondary amines.[21] Herein we postulate that our synthetic strategy could be readily adapted for the synthesis of hitherto unknown *S*-glycosyl secondary sulfonamides [sugar-SO_2NH-R] to give a non-native glycoconjugate covalent linkage with potential for enzymatic resistance. Interestingly, we have found reported only a small number of monosaccharide tertiary *S*-glycosyl sulfonamides [sugar-SO_2NR_2][18,22,23] in addition to our own reported compounds.[20] Herein we explore this novel synthetic opportunity as an avenue to append carbohydrate "tail" moieties to the well established aromatic sulfonamide CA inhibitor pharmacophore to generate robust, sulfonamide-linked, neoglycoconjugate CA inhibitors of the type [sugar-SO_2NH-aromatic-SO_2NH_2].

Per-*O*-acetylated sugar precursors derived from monosaccharides D-glucose, D-galactose, and D-glucuronic acid methyl ester, and disaccharides lactose and maltose, were reacted with boron trifluoride diethyl etherate and thiourea to synthesize the corresponding glycosyl thioacetates **a**−**e**.[24] The *para*-substituted aminobenzyl and aminophenethyl sulfonamides **1** and **2** have a primary aliphatic amino functional group in their structure and are known CA inhibitors. These primary amines were each reacted with the sugar thioacetate panel **a**−**e** to give 10 per-*O*-acetylated sulfenamide glycoconjugates, **3**−**7** and **18**−**22** (Scheme 1).[25] Oxidation of the sulfenamides with excess *m*CPBA in CH_2Cl_2 gave per-*O*-acetylated glycosylsulfonamidyl benzenesulfonamides **8**−**12** and **23**−**27** (Scheme 1). Oxidation was typically complete following 1 h of stirring at room temperature as evidenced by TLC. The *O*-acetate groups of the carbohydrate moiety were next removed using Zemplen's conditions[26] to liberate the fully deprotected sugar analogues **13**−**17** and **28**−**32** in a quantitative or nearly quantitative yield (Scheme 1).

Carbonic Anhydrase Inhibition

The enzyme inhibition characteristics for the 30 new glycoconjugates **3**−**32** were determined by assaying the CA catalyzed

Scheme 1. Synthesis of *S*-Glycosyl Sulfenamides (**3**−**7**, **18**−**22**) and *S*-Glycosyl Sulfonamides (**8**−**17**, **23**−**32**) from Glycosyl Thioacetates (**a**−**e**) and Amino Sulfonamide Scaffolds (**1** and **2**)[a]



Glycosyl thioacetate \ Amino sulfonamide	**1**	**2**
a	**3** X = S; R = Ac **8** X = SO_2; R = Ac **13** X = SO_2; R = H	**18** X = S, R = Ac; **23** X = SO_2, R = Ac; **28** X = SO_2; R = H
b	**4** X = S; R = Ac **9** X = SO_2; R = Ac **14** X = SO_2; R = H	**19** X = S, R = Ac; **24** X = SO_2, R = Ac; **29** X = SO_2; R = H
c	**5** X = S; R = Ac; R' = Me **10** X = SO_2; R = Ac; R' = Me **15** X = SO_2; R = H; R' = H	**20** X = S, R = Ac; R' = Me **25** X = SO_2, R = Ac; R' = Me **30** X = SO_2; R = H; R' = H
d	**6** X = S, R = Ac; **11** X = SO_2, R = Ac; **16** X = SO_2; R = H	**21** X = S, R = Ac; **26** X = SO_2, R = Ac; **31** X = SO_2; R = H
e	**7** X = S; R = Ac **12** X = SO_2; R = Ac **17** X = SO_2; R = H	**22** X = S, R = Ac; **27** X = SO_2, R = Ac; **32** X = SO_2; R = H

[a] Glycosyl thioacetates **a**−**e** are employed to incorporate a carbohydrate "tail" moiety to give novel sulfonamide-linked neoglycoconjugate CA inhibitors.

hydration of CO_2, Table 1.[27] Isozyme selectivity ratios for **3**−**32** are in Table 2. Reference data for clinically used CA inhibitors acetazolamide (AZA) and topiramate (TPM) as well as for aminosulfonamide precursors **1** and **2** are included for comparison with the new glycoconjugates reported in this study.

Off-Target CA Isozymes. Fourteen of the 20 glycoconjugates with *O*-acetate protected carbohydrate tail moieties are low micromolar inhibitors of hCA I; the exceptions are compounds **4**, **5**, **8**, **9**, **20**, and **23**, which displayed slightly stronger inhibition with K_is of 90−120 nM. The SAR of the acetylated compounds were independent of the linker type (sulfenamide compared to sulfonamide) or the parent compound (**1** or **2**). The 10 deprotected sugar analogues (**13**−**17** and **28**−**32**) all had closely grouped hCA I inhibition constants that ranged from 81 to 107 nM, which is similar to the stronger inhibitors of the acetylated series. The incorporation of the five different sugar tails onto the benzene sulfonamide scaffolds **1** and **2** via a sulfenamide or a sulfonamide revealed some notable SAR trends at hCA II. All 10 deprotected compounds (**13**−**17** and **28**−**32**) exhibited potent hCA II inhibition (K_is < 10 nM). All acetylated compounds were slightly less potent (with K_is > 10 nM). The acetylated sulfenamides (**3**−**7** and **18**−**22**) exhibited a narrow range of K_is, from 12.0 to 18.1 nM, while the acetylated sulfonamides had K_is in two distinct groupings: 14.8−16.3 nM for **8**, **9**, **23**, and **27**, and 56.2−73.8 nM for compounds **10**−**12**, **24**−**26**. These two groupings are again spread across both scaffolds (**1** and **2**) and across sugar types (**a**−**e**).

Table 1. Inhibition Data for New Sulfonamide-Linked Glycoconjugates **3**−**32**, Precursors **1** and **2**, and the Established Drugs and CA Inhibitors AZA and TPM against Human Isozymes hCA I, II, IX, and XII[a]

			K_i (nM)[c]			
compd	Log P[b]	P_e (10^{-6} cm s^{-1})	hCA I[d]	hCA II[e]	hCA IX[e]	hCA XII[e]
AZA	−1.0	< 0.15[g]	250	12	25	5.7
TPM	+0.04	nd	250	5	58	3.8
1	−0.73[f]	nd	25000	170	103	0.3
2	−0.47[f]	nd	21000	160	33	3.2
3	−0.09	nd	4160	14.8	105	11.5
4	−0.09	nd	120	13.4	91	15.5
5	−0.07	nd	110	18.1	102	15.6
6	−0.54	nd	6830	15.5	100	9.8
7	−0.54	nd	3460	13.1	84	8.5
8	−1.40	< 0.05[g]	120	14.8	79	9.3
9	−1.40	nd	110	16.3	89	9.9
10	−1.38	nd	2400	65.8	89	9.8
11	−1.85	nd	4930	58.8	102	10.4
12	−1.85	nd	2040	62.5	88	9.1
13	−3.17	< 0.05[g]	102	9.1	95	8.3
14	−3.17	nd	87	7.8	99	8.7
15	−2.85	nd	81	7.1	97	8.9
16	−4.94	nd	107	5.0	106	8.9
17	−4.94	nd	101	4.8	98	8.2
18	+0.20	nd	3890	14.5	97	13.6
19	+0.20	nd	4100	13.3	107	16.7
20	+0.22	nd	110	16.2	90	9.5
21	−0.25	nd	8040	12.0	97	8.7
22	−0.25	nd	6750	15.1	94	8.8
23	−1.11	nd	90	15.4	95	9.5
24	−1.11	nd	4710	73.8	96	9.4
25	−1.15	nd	3210	62.7	95	9.7
26	−1.56	nd	3460	56.2	97	9.5
27	−1.56	nd	5570	15.2	93	8.8
28	−2.88	nd	88	7.8	84	7.6
29	−2.88	nd	82	7.6	100	7.8
30	−2.56	nd	97	4.7	96	9.5
31	−4.65	nd	78	4.6	100	9.1
32	−4.65	nd	102	5.2	81	7.3

[a] The calculated value for compound Log P is also included as well as P_e for compounds AZA, **8** and **13**. [b] Log P data calculated using InstantJChem 3.0.4 from ChemAxon.[28] [c] Errors in the range of ±5−10% of the reported value, from three determinations. [d] Human (cloned) isozymes. [e] Catalytic domain of human (cloned) isozymes. [f] Calculated for neutral compound. [g] The concentration of test compound in the acceptor chamber was lower than the LLQ. Upper limits for the P_e values were estimated using the respective analytical LLQ values as the maximum concentration in the acceptor chamber. nd not determined.

Cancer-Associated CA Isozymes. The 30 glycoconjugates were good hCA IX inhibitors and exhibited a clustered inhibition profile at hCA IX (K_is 79−106 nM). This inhibition is however ∼10-fold weaker inhibition than for hCA II (or XII; see below) and was either similar to, or selective over, inhibition compared to the hCA I isozyme. All glycoconjugates were very good inhibitors of hCA XII; the 20 sulfonamide-linked glycoconjugates had K_is ≤ 10 nM, while the 10 sulfenamide compounds had K_is that ranged from 8.5 to 16.7 nM. Many compounds (**3**, **6**, **7**, **10**−**12**, **18**, **19**, **21**, **22**, **24**−**27**) had quite notable (several hundred-fold) selectivity compared to the physiologically abundant hCA I isozyme, with compound **21** 3 orders of magnitude (924-fold) hCA XII selective. Although not as striking in magnitude, several of the compounds also had some selectivity compared for hCA II (compounds **10**−**12**, **24**−**26**).

Comparison with Other Glycoconjugate CA Inhibitors. We have previously observed that the CA active sites are tolerant to diverse structural characteristics within the tail moiety of inhibitors.[9−15] Table 3 presents data for a selection of glucoconjugate CA inhibitors wherein the glucosyl moiety is either a free sugar (**33a**−**37a**) or a peracetylated sugar (**33b**−**37b**) (Figure 2). These inhibitors differ by the nature of the linkage between the sugar and the sulfonamide zinc binding function and have been selected for comparison to glucosides **8** and **13** of the present study. The inhibitor structures encompass 1,2,3-triazoles with *O*-glucoside (**33a**, **33b**), sulfonyl glucoside (**34a**, **34b**), amide (**35a**, **35b**), and ester (**36a**, **36b**) covalent linkages, as well as anomeric *S*-glucosyl sulfonamides (**37a**, **37b**) in which the sulfonamide and sugar are directly linked. With the exception of the *S*-glucosyl sulfonamides (**37a**, **37b**) that are micromolar inhibitors for CA I, II, IX, and XII, the glucoconjugates exhibit similarities in their isozyme inhibition profiles. The glucoconjugates are typically weak CA I inhibitors (micromolar K_is) and good CA II and XII inhibitors (low nanomolar K_is). We do however observe variation at CA IX, with the K_is for this selection of inhibitors ranging from low nM to micromolar. The observed trends demonstrate that the compounds of this study are consistent with our premise regarding the active site tolerance of CAs to variable inhibitor structures, although interestingly have allowed us to identify that the cancer-associated CA IX isozyme is the least tolerant to structural changes. This observation should prove a useful aid in defining the opportunities for future medicinal chemistry efforts to selectively target this

Table 2. Cancer-Associated CA Isozyme Selectivity Ratio Data for New Sulfonamide-Linked Glycoconjugates **3**−**32**, Precursors **1** and **2**, and the Established Drugs and CA Inhibitors Acetazolamide (AZA) and Topiramate (TPM)

	selectivity ratios[a]			
compd	hCA I/ hCA IX	hCA I/ hCA XII	hCA II/ hCA IX	hCA II/ hCA XII
AZA	10	43.9	0.48	2.1
TPM	4.3	65.8	0.09	1.3
1	243	83330	1.7	566.7
2	636	6563	4.9	50.0
3	39.6	361.7	0.14	1.3
4	1.3	7.7	0.15	0.86
5	1.1	7.1	0.18	1.2
6	68.3	696.9	0.16	1.6
7	41.2	407.1	0.16	1.5
8	1.5	12.9	0.19	1.6
9	1.2	11.1	0.18	1.7
10	27.0	244.9	0.74	6.7
11	48.3	474.0	0.58	5.7
12	23.2	224.2	0.71	6.9
13	1.1	12.3	0.10	1.1
14	0.9	10.0	0.08	0.90
15	0.8	9.1	0.07	0.80
16	1.0	12.0	0.05	0.56
17	1.0	12.3	0.05	0.59
18	40.1	286.0	0.15	1.1
19	38.3	245.5	0.12	0.80
20	1.2	11.6	0.18	1.7
21	82.9	924.1	0.12	1.4
22	71.8	767.1	0.16	1.7
23	0.95	9.5	0.16	1.6
24	49.1	501.1	0.77	7.9
25	33.8	330.9	0.66	6.5
26	35.7	364.2	0.58	5.9
27	59.9	633.0	0.16	1.7
28	1.1	11.6	0.09	1.0
29	0.8	10.5	0.08	0.97
30	1.0	10.2	0.05	0.49
31	0.8	8.6	0.05	0.51
32	1.3	14.0	0.06	0.71

[a] The K_i ratios are indicative of isozyme selectivity in vitro and are calculated using the K_i values in Table 1.

Table 3. Inhibition Data for hCA Isozymes I, II, IX and XII with Compounds **8** and **13** of the Present Study and with a Selection of Previously Reported Glucoconjugate CA Inhibitors (**33a**−**37a**, **33b**−**37b**)

	K_i (nM)[a]			
compd	hCA I[b]	hCA II[b]	hCA IX[c]	hCA XII[c]
8	120	14.8	79	9.3
13	102	9.1	95	8.3
33a	7.0	8.7	101	nd
33b	1500	46	107	nd
34a	101	7.6	9.5	10.3
34b	97	6.9	9.3	9.1
35a	2000	8.2	442	11.4
35b	5600	384	430	4.3
36a	4400	7.0	183	7.1
36b	2300	119	1238	7.7
37a	3900	4910	4050	4690
37b	4530	4500	3910	4660

[a] Errors in the range of ±5−10% of the reported value, from three determinations. [b] Human (cloned) isozymes. [c] Catalytic domain of human (cloned) isozymes. nd not determined.

important tumor-associated CA isozyme with drug-like small molecule inhibitors.

Passive Membrane Permeability. The physical barrier of the cell membrane is not a contributing factor in CA inhibition studies that utilize pure recombinant enzymes, however, in the development of compounds that target hCA IX and XII in vivo, the passive diffusion across biological membrane barriers is likely to be central. In general, passive diffusion across a biological membrane correlates very well with the lipophilicity of the small molecule, with membrane permeability generally decreasing with increasing small molecule polarity or with capacity for hydrogen bonding. Our strategy to target the extracellular catalytic domain of cancer-associated CAs is to deliberately manipulate physicochemical properties of the inhibitor so as to impart membrane impermeability. Log *P* represents intrinsic lipophilicity, and compounds with Log $P < 0$ typically have good solubility but poor lipid bilayer permeability (although paracellular permeability may be a contributor for very small hydrophilic molecules).[29,30a] Table 1 includes calculated Log *P* values for the glycoconjugates of this study. These calculated values are a very useful guide in the prediction of passive membrane permeability, with Log *P* prediction software one of the most reliable in silico tools for property profiling.[30b] Calculated Log *P* values of compounds generated from **1** and **2** differ in magnitude by 0.29, with scaffold **2** more hydrophobic (higher Log *P*) than **1** owing to one additional methylene group. The Log *P* trend is acetylated sulfenamides > acetylated sulfonamides > free sugar sulfonamides. This is consistent with (i) the incorporated acetate groups increasing the lipophilicity and (ii) the sulfonamide oxygens increasing

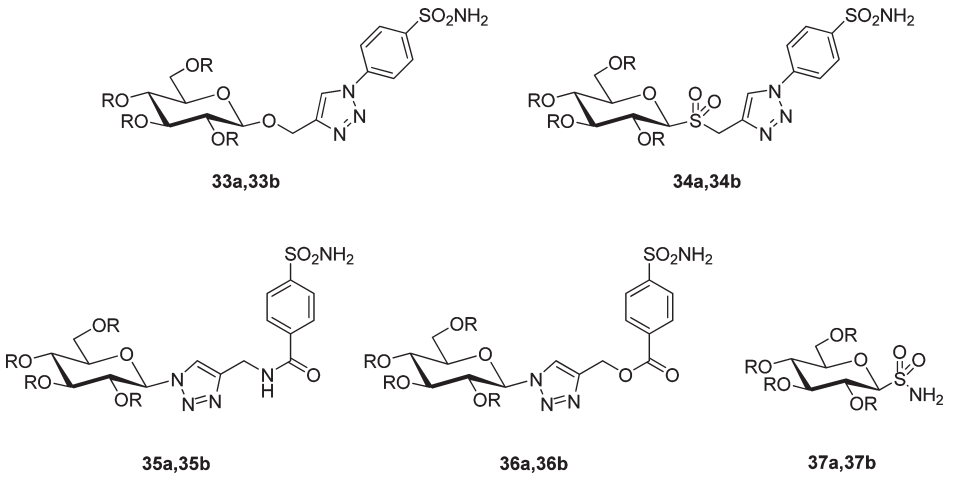


Figure 2. Structures of previously reported glucoconjugate CA inhibitors (**33a**−**37a** R = H, **33b**−**37b** R = Ac).

the polarity of the glycoconjugates. The calculated Log *P* values for the acetylated sulfonamides range from −1.11 to −1.85, while the more hydrophilic free sugar sulfonamides have log *P* values that range from −2.56 to −4.94. All sulfonamides have Log *P* values that fall within the range indicative of molecules with poor membrane permeability, i.e., Log $P < 0$.

Permeability measurements through artificial lipid membrane biolayers have been extensively used to classify small molecules for their passive membrane permeability characteristics.[31−33] We have previously used this technique to measure the apparent in vitro effective permeability (P_e) of anomeric sulfonamides.[10] Typical P_e values for high permeability compounds are $> 3 \times 10^{-6}$ cm s^{-1}, while for low permeability compounds are $< 3 \times 10^{-6}$ cm s^{-1}.[34,35] The P_e of per-*O*-acetylated glucoconjugate (**8**), fully deprotected glucoconjugate (**13**), AZA, and control compounds were determined using a parallel artificial membrane permeability assay (PAMPA)[31−33] as previously described.[10] The experimental values of P_e at pH 7.4 using the PAMPA assay are included in Table 1. For the compounds tested (AZA, **8** and **13**), the concentrations in the acceptor chamber were below the analytical lower limits of quantitation (LLQ), suggesting that these compounds have very low permeability in this assay. A theoretical estimate of the maximum P_e value for each compound was calculated using the respective LLQ values, Table 1. The PAMPA results for these representative neoglycoconjugates (that include an example of a sugar−OAc and sugar−OH moiety) confirm that this class of compound would be expected to have poor passive membrane permeability and thus may preferentially inhibit the transmembrane CAs IX and XII over cytosolic CAs in the in vivo environment.

To ensure that the intrinsically low permeability characteristics of the CA inhibitors is unlikely to limit bioavailability for compounds that may progress to animal studies we envisage either intravenous administration (the free sugars have good aqueous solubility) or for oral delivery a prodrug strategy that utilizes ester groups on the sugar hydroxyls to improve intestinal absorption, with ester hydrolysis to follow absorption.

Experimental Section

Chemistry. All starting materials and reagents, including per-*O*-acetylated sugars, were purchased from commercial suppliers with the exception of methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate, which was synthesized as described in the literature.[36] Solvents were dried prior to use, or purchased anhydrous from Sigma-Aldrich. All reactions were monitored by TLC using Merck $F60_{254}$ silica plates with visualization of product bands by UV fluorescence (λ = 254 nm) and charring by sulphuric acid stain (5% H_2SO_4 in ethanol) and/or orcinol stain (1 g of orcinol monohydrate in a mixture of EtOH:H_2O:H_2SO_4 72.5:22.5:5). Silica gel flash chromatography was performed using silica gel 60 Å (230−400 mesh). NMR (^{1}H, ^{13}C {^{1}H}, gCOSY, and HSQC) spectra were recorded on a Varian 500 MHz spectrometer at room temperature using DMSO-d_6 solvent unless otherwise stated. Chemical shifts are reported in δ (ppm). Chemical shifts for ^{1}H and ^{13}C NMR run in DMSO are reported in ppm relative to residual solvent proton (δ = 2.50 ppm) and carbon (δ = 39.5 ppm) signals, respectively. For ^{1}H NMR run in D_2O chemical shifts are reported in ppm relative to the solvent residual peak: proton (δ = 4.80 ppm). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), br s (broad singlet). Coupling constants are reported in hertz (Hz). Melting points were acquired on a Gallenkamp melting point apparatus and are reported as uncorrected. Low resolution mass spectra were acquired in positive ion mode on an Applied Biosystems Pty Ltd. Mariner ESI-TOF mass spectrometer. High resolution mass spectra were performed in positive ion mode on an Apex III Bruker Daltonics 4.7T Fourier transform mass spectrometer (FTMS) fitted with an Apollo electrospray ionization source. All MS analysis samples were prepared as solutions in methanol. Optical rotation were measured at 25 °C and reported as an average of 10 measurements. The purities of isolated products were determined by HPLC obtained on an LCMS instrument (MS-ZQ Waters; HPLC-Alliance Waters) using a HPLC column (Ascentis, C18 3 μm, 5 cm × 4.6 mm). Elution was performed with a gradient of water:methanol (containing 1% formic acid) from 95:5 to 0:100 for 10 min at a flow rate of 1 mL/min. UV (200−400 nm) and evaporative light scattering detection (ELSD-Alltech) detection were used. Purity of all compounds proved to be ≥95%.

General Procedure 1. To a solution of per-*O*-acetylated derivative (1.0 equiv) in acetonitrile was added thiourea (1.3 equiv) and boron trifluoride diethyl etherate (2.1 equiv). The reaction mixture was refluxed until starting material was consumed (~30 min) then cooled to room temperature (rt). Acetic anhydride (2.5 equiv) and triethylamine (4.5 equiv) were added and the solution stirred at rt overnight in the absence of light. The reaction mixture was concentrated and the residue diluted in dichloromethane (CH_2Cl_2) before washing with

aqueous 5% HCl (×1) and brine (×2). The aqueous extracts were combined and back extracted with CH_2Cl_2 (×2). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated.

2,3,4,6-Tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (a). Thioacetate **a** was prepared from per-*O*-acetylated D-glucose using General Procedure 1. Recrystallization from ethanol afforded off-white crystals (77% yield); R_f = 0.67 (1:1 EtOAc/hexane); mp = 105−108 °C; $[\alpha]^{25}_D$ = +9 (*c* = 1.0, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.28 (t, *J* = 9.5 Hz, 1H, H-3), 5.26 (d, *J* = 10.0 Hz, 1H, H-1), 5.13 (t, *J* = 9.5 Hz, 1H, H-2), 5.11 (t, *J* = 9.5 Hz, 1H, H-4), 4.27 (dd, *J* = 12.5, 4.5 Hz, 1H, H-6a), 4.11 (dd, *J* = 12.5, 2.0 Hz, 1H, H-6b), 3.84 (ddd, *J* = 10.0, 4.5, 2.0 Hz, 1H, H-5), 2.39 (s, 3H, SCOCH_3), 2.08, 2.04, 2.03, 2.01 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. LRMS (ESI$^+$): *m*/*z* = 429 [M + Na]$^+$.

2,3,4,6-Tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-galactopyranose (b). Thioacetate **b** was prepared from per-*O*-acetylated D-galactose using General Procedure 1. Recrystallization from ethanol afforded off-white crystals (75% yield); R_f = 0.67 (1:1 EtOAc/hexane); mp = 99−103 °C; $[\alpha]^{25}_D$ = +29 (*c* = 1.0, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.46 (d, *J* = 3.5 Hz, 1H, H-4), 5.32 (t, *J* = 10.0 Hz, 1H, H-2), 5.25 (d, *J* = 10.5 Hz, 1H, H-1), 5.12 (dd, *J* = 3.5, 10.0 Hz, 1H, H-3), 4.15−4.05 (m, 3H, H-5, H-6a, H-6b), 2.40 (s, 3H, SCOCH_3), 2.16, 2.04, 2.03, 1.99 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. LRMS (ESI$^+$): *m*/*z* = 429 [M + Na]$^+$.

Methyl 2,3,4-Tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranuronate (c). Thioacetate **c** was prepared from methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate using General Procedure 1. Recrystallization from methanol afforded off-white crystals (47% yield); R_f = 0.57 (1:1 EtOAc/hexane); mp = 149−150 °C; $[\alpha]^{25}_D$ = +19 (*c* = 1.1, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.34 (t, *J* = 9.5 Hz, 1H, H-3), 5.30 (t, *J* = 10.0 Hz, 1H, H-1), 5.20 (d, *J* = 9.5 Hz, 1H, H-4), 5.15 (t, *J* = 10.0 Hz, 1H, H-2), 4.17 (d, *J* = 10.0 Hz, 1H, H-5), 3.74 (s, 3H, OCH_3), 2.39 (s, 3H, SCOCH_3), 2.04, 2.03 (2 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. LRMS (ESI$^+$): *m*/*z* = 415 [M + Na]$^+$.

2,2′,3,3′,4′,6,6′-Hepta-*O*-acetyl-1-*S*-acetyl-1-thio-β-lactose (d). Thioacetate **d** was prepared from per-*O*-acetylated lactose using General Procedure 1. Purification by flash chromatography (1:1 EtOAc/hexane) afforded a colorless oil (79% yield); R_f = 0.25 (1:1 EtOAc/hexane); $[\alpha]^{25}_D$ = −3 (*c* = 1.3, chloroform). ^{1}H NMR (500 Mz, $CDCl_3$): δ = 5.36 (d, *J* = 3.0 Hz, 1H, H-4′), 5.26 (t, *J* = 9.0 Hz, 1H, H-3), 5.22 (d, *J* = 10.5 Hz, 1H, H-1), 5.12 (dd, *J* = 8.0, 10.5 Hz, 1H, H-2′), 5.05 (t, *J* = 10.5 Hz, 1H, H-2), 4.95 (dd, *J* = 3.0, 10.5 Hz, 1H, H-3′), 4.46 (d, *J* = 8.0 Hz, 1H, H-1′), 4.45 (dd, *J* = 2.0, 10.0 Hz, 1H, H-6a′), 4.15−4.07 (m, 3H, H-6a, H-6b′, H-5′), 3.87 (m, 1H, H-6b), 3.83 (t, *J* = 9.0 Hz, 1H, H-4), 3.76 (m, 1H, H-5), 2.38 (s, 3H, SCOCH_3), 2.16, 2.12, 2.08, 2.05, 2.05, 2.03, 1.97 (7 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H COSY. LRMS (ESI$^+$): *m*/*z* = 713 [M + NH_4]$^+$, 717 [M + Na]$^+$.

2,2′,3,3′,4′,6,6′-Hepta-*O*-acetyl-1-*S*-acetyl-1-thio-β-maltose (e). The title compound was prepared from per-*O*-acetylated maltose using General Procedure 1. Recrystallization from methanol afforded off-white crystals (68% yield); R_f = 0.48 (1:1 EtOAc/hexane); mp = 139−141 °C; $[\alpha]^{25}_D$ = +57 (*c* = 1.0, chloroform). ^{1}H NMR (500 Mz, $CDCl_3$): δ = 5.40 (d, *J* = 3.5 Hz, 1H, H-1′), 5.36 (t, *J* = 10.0 Hz, 1H, H-3′), 5.33 (t, *J* = 9.0 Hz, 1H, H-3), 5.29 (d, *J* = 10.5 Hz, 1H, H-1), 5.06 (t, *J* = 10.0 Hz, 1H, H-4′), 4.99 (t, *J* = 9.5 Hz, 1H, H-2), 4.87 (dd, *J* = 4.0, 10.5 Hz, 1H, H-2′), 4.45 (dd, *J* = 2.0, 12.5 Hz, 1H, H-6a), 4.24 (dd, *J* = 4.5, 12.5 Hz, 1H, H-6b), 4.21 (dd, *J* = 4.5, 12.5 Hz, 1H, H-6a′), 4.04 (dd, *J* = 2.0, 12.5 Hz, 1H, H-6b′), 4.00 (t, *J* = 9.5 Hz, 1H, H-4), 3.95(m, 1H, H-5′), 3.83 (m, 1H, H-5), 2.38 (s, 3H, SCOCH_3), 2.13, 2.10, 2.06, 2.03, 2.01, 2.00 (6 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H COSY. LRMS (ESI$^+$): *m*/*z* = 713 [M + NH_4]$^+$, 717 [M + Na]$^+$.

Synthesis of Sulfenamides 3−7 and 18−22: General Procedure 2. A solution of thioacetate (**a**−**e**, 1.0 equiv) under nitrogen was prepared in anhydrous methanol. Diethylbromomalonate (2.5 equiv) was added and the reaction was maintained under stirring for 20 min at rt, after which the benzene sulfonamide derivative was added (3.0 equiv), either with no other reactant in the case of 4-aminoethylbenzenesulfonamide **2** or with diisopropylethylamine (3.0 equiv) when 4-aminomethylbenzenesulfonamide hydrochloride (hydrochloride salt of **1**) is used. The mixture was stirred at rt under nitrogen until completion, typically 1.5 h. The methanol was evaporated and the residue solubilized in CH_2Cl_2 and washed with brine (×3). Each aqueous phase was back extracted with CH_2Cl_2 (×2), the organic phases were combined, dried over $MgSO_4$, filtered, concentrated, and purified.

***N*-4-(Aminosulfonyl)benzyl-*S*-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)sulfenamide (3).** Sulfenamide **3** was prepared from 4-aminomethylbenzenesulfonamide hydrochloride and thioacetate derivative **a** according to General Procedure 2. The expected compound was obtained after flash chromatography (1:1 EtOAc/hexane) as a slightly yellow solid (94% yield); R_f = 0.27 (1:1 EtOAc/hexane); mp = 122−129 °C; $[\alpha]^{25}_D$ = −117 (*c* = 1.2, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.77 (d, *J* = 8.0 Hz, 2H, H_{arom}), 7.45 (d, *J* = 8.0 Hz, 2H, H_{arom}), 7.28 (s, 2H, NH_2), 5.34 (d, *J* = 9.5 Hz, 1H, H-3), 4.97 (t, *J* = 10.0 Hz, 1H, H-2), 4.93 (t, *J* = 9.5 Hz, 1H, H-4), 4.76 (d, *J* = 10.0 Hz, 1H, H-1), 4.44 (t, *J* = 10.5 Hz, 1H, N*H*), 4.16 (m, 1H, H-6a), 4.11 (m, 1H, H-6b), 4.07 (m, 2H, CH_2), 4.02 (m, 1H, H-5), 2.01, 2.00, 1.99, 1.95 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.0, 169.5, 169.3, 169.2 (O*C*OCH$_3$), 144.3, 142.6 (C_{arom}), 128.3, 125.4 (*C*H$_{arom}$), 87.4 (C-1), 74.3 (C-5), 73.2 (C-3), 68.1 (C-4), 67.5 (C-2), 62.0 (C-6), 55.8 (*C*H$_2$), 20.5, 20.4, 20.3, 20.2 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): *m*/*z* = 549 [M + H]$^+$; 571 [M + Na]$^+$. LRMS (ESI$^-$): *m*/*z* = 547 [M − H]$^-$, 583 [M + Cl]$^-$. HRMS: calcd for $C_{21}H_{28}N_2O_{11}S_2Na$, 571.1027; found, 571.1039.

***N*-4-(Aminosulfonyl)benzyl-*S*-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranosyl)sulfenamide (4).** Sulfenamide **4** was prepared from 4-aminomethylbenzenesulfonamide hydrochloride and thioacetate derivative **b** according to the General Procedure 2. The expected compound was obtained after flash chromatography (1:1 EtOAc/hexane) as a white, highly hygroscopic solid (58% yield); R_f = 0.22 (1:1 EtOAc/hexane); $[\alpha]^{25}_D$ = −82 (*c* = 1.2, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.77 (d, *J* = 8.0 Hz, 2H, H_{arom}), 7.60 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.29 (s, 2H, NH_2), 5.32 (d, *J* = 3.5 Hz, 1H, H-4), 5.26 (dd, *J* = 3.5, 10.0 Hz, 1H, H-3), 5.07 (t, *J* = 10.0 Hz, 1H, H-2), 4.75 (d, *J* = 9.5 Hz, 1H, H-1), 4.45 (t, *J* = 6.0 Hz, 1H, N*H*), 4.24 (m, 1H, H-5), 4.11 (m, 2H, CH_2), 4.06−4.04 (m, 2H, H-6a, H-6b), 2.13, 2.01, 2.00, 1.93 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.9 (2C), 169.6, 169.4 (O*C*OCH$_3$), 144.2, 142.7 (C_{arom}), 128.3, 125.5 (*C*H$_{arom}$), 88.2 (C-1), 73.3 (C-5), 71.1 (C-3), 67.6 (C-4), 65.1 (C-2), 61.7 (C-6), 55.8 (*C*H$_2$), 20.5 (2C), 20.4, 20.3 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): *m*/*z* = 571 [M + Na]$^+$. LRMS (ESI$^-$): *m*/*z* = 547 [M − H]$^-$, 583 [M + Cl]$^-$. HRMS: calcd for $C_{21}H_{29}N_2O_{11}S_2$, 549.1207; found, 549.1234.

Methyl *N*-4-(Aminosulfonyl)benzyl-*S*-(2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranuronoyl)sulfenamide (5). Sulfenamide **5** was prepared from 4-aminomethylbenzenesulfonamide hydrochloride and thioacetate derivative **c** according to the General Procedure 2. The expected compound was obtained after flash chromatography (3:2 EtOAc/hexane) as a white solid (88% yield); R_f = 0.40 (2:1 EtOAc/hexane); mp = 152−156 °C; $[\alpha]^{25}_D$ = −109 (*c* = 1.1, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.75 (d, *J* = 8.0 Hz, 2H, H_{arom}), 7.45 (d, *J* = 8.0 Hz, 2H, H_{arom}), 7.28 (s, 2H, NH_2), 5.40 (t, *J* = 9.5 Hz, 1H, H-3), 4.98 (t, *J* = 9.5 Hz, 1H, H-2), 4.96 (t, *J* = 9.5 Hz, 1H, H-4), 4.83 (d, *J* = 10.0 Hz, 1H, H-1), 4.50 (t, *J* = 5.0 Hz, 1H, N*H*), 4.45 (d,

J = 10.0 Hz, 1H, H-5), 4.08 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 1.98, 1.97, 1.96 (3 × s, 9H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.7, 169.5, 169.5 (O*C*OCH$_3$), 144.3, 142.7 (C$_{arom}$), 128.6, 125.7 (*C*H$_{arom}$), 87.5 (C-1), 74.5 (C-5), 72.5 (C-3), 69.3 (C-4), 67.4 (C-2), 55.8 (*C*H$_2$), 52.7 (O*C*H$_3$), 20.5, 20.4, 20.3 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 535 [M + H]$^+$. LRMS (ESI$^-$): m/z = 533 [M − H]$^-$. HRMS: calcd for $C_{20}H_{27}N_2O_{11}S_2$, 535.1051; found, 535.1061.

***N*-4-(Aminosulfonyl)benzyl-*S*-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-1-thio-β-maltosyl)sulfenamide (6).** Sulfenamide **6** was prepared from 4-aminomethylbenzenesulfonamide hydrochloride and thioacetate derivative **d** according to the General Procedure 2. The expected compound was obtained after flash chromatography (2:1 EtOAc/hexane) as a white solid (93% yield); R_f = 0.32 (2:1 EtOAc/hexane); mp = 99−102 °C; $[\alpha]^{25}_D$ = −80 (c = 1.0, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.75 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.42 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.29 (s, 2H, NH_2), 5.22 (d, J = 3.5 Hz, 1H, H-4′), 5.19 (t, J = 9.0 Hz, 1H, H-3), 5.13 (dd, J = 3.5, 9.5 Hz, 1H, H-3′), 4.85 (t, J = 10.0, 1H, H-2′), 4.83 (t, J = 9.0 Hz, 1H, H-2), 4.74 (d, J = 8.0 Hz, 1H, H-1′), 4.68 (d, J = 10.0 Hz, 1H, H-1), 4.37 (t, J = 5.5 Hz, 1H, N*H*), 4.36 (m, 1H, H-6a), 4.20 (br t, J = 7.0 Hz, 1H, H-5′), 4.05−4.00 (m, 5H, H-6b, H-6a′, H-6b′, CH_2), 3.80 (m, 1H, H-5), 3.77 (t, J = 10.0 Hz, 1H, H-4), 2.08, 2.05, 1.99, 1.97, 1.96, 1.89 (6 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.7, 170.4, 170.3, 169.9 (2C), 169.8, 169.6, (O*C*OCH$_3$), 144.6, 142.8 (C$_{arom}$), 128.7, 125.8 (*C*H$_{arom}$), 100.2 (C-1′), 87.5 (C-1), 76.3 (C-4), 75.9 (C-5), 73.7 (C-3), 70.6 (C-3′), 70.0 (C-5′), 69.2 (C-2), 68.1 (C-2′), 67.3 (C-4′), 62.7 (C-6), 61.1 (C-6′), 55.9 (*C*H$_2$), 20.9, 20.7 (3C), 20.6, 20.5 (2C) (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 837 [M + H]$^+$, 859 [M + Na]$^+$. LRMS (ESI$^-$): m/z = 835 [M − H]$^-$. HRMS: calcd for $C_{33}H_{44}N_2O_{19}S_2Na$, 859.1872; found, 859.1872.

***N*-4-(Aminosulfonyl)benzyl-*S*-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-1-thio-β-lactosyl)sulfenamide (7).** Sulfenamide **7** was prepared from 4-aminomethylbenzenesulfonamide hydrochloride and thioacetate derivative **e** according to the General Procedure 2. The expected compound was obtained after flash chromatography (2:1 EtOAc/hexane) as a white solid (48% yield); R_f = 0.12 (1:1 EtOAc/hexane); mp = 92−94 °C; $[\alpha]^{25}_D$ = −16 (c = 1.1, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.75 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.42 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.29 (s, 2H, NH_2), 5.36 (t, J = 8.5 Hz, H-3), 5.29 (d, J = 3.5 Hz, 1H, H-1′), 5.22 (t, J = 10.0 Hz, 1H, H-3′), 4.98 (t, J = 10.0 Hz, 1H, H-4′), 4.86 (dd, J = 3.0, 10.5 Hz, 1H, H-2′), 4.86 (t, J = 10.0, 1H, H-2), 4.72 (d, J = 10.0 Hz, 1H, H-1), 4.45 (m, 1H, H6a), 4.37 (t, J = 6.0 Hz, 1H, N*H*), 4.18−4.14 (m, 2H, H-6a′, H-6b), 4.07 (dd, J = 6.0, 14.0 Hz, 1H, H-6b′), 4.02−3.96 (m, 4H, H-5, H-5′, CH_2) 3.93 (t, J = 8.5 Hz, 1H, H-4), 2.04, 2.01, 1.98, 1.97, 1.94 (5 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.4, 170.3, 170.1, 169.9, 169.8 (2C), 169.4, (O*C*OCH$_3$), 144.5, 142.7 (C$_{arom}$), 128.5, 125.6 (*C*H$_{arom}$), 95.6 (C-1′), 87.2 (C-1), 75.5 (C-3), 75.2 (C-5), 73.8 (C-4), 69.6 (C-2′), 69.0 (C-3′), 68.3 (C-2), 68.2 (C-5′), 67.9 (C-4′), 63.1 (C-6′), 61.6 (C-6), 56.0 (*C*H$_2$), 20.7 (2C), 20.6 (2C), 20.5, 20.4, 20.3 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. HRMS: calcd for $C_{33}H_{44}N_2O_{19}S_2Na$, 859.1872; found, 859.1873.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)sulfenamide (18).** Sulfenamide **18** was prepared from 4-aminoethylbenzenesulfonamide and thioacetate derivative **a** according to the General Procedure 2. Expected compound was obtained after flash chromatography (1:1 EtOAc/hexane) as a white solid (66% yield); R_f = 0.23 (1:1 EtOAc/hexane); mp = 124−125 °C; $[\alpha]^{25}_D$ = −102 (c = 1.2, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.72 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.37 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.25 (s, 2H, NH_2), 5.34 (d, J = 9.5 Hz, 1H, H-3), 4.92 (t, J = 9.5 Hz, 1H, H-2), 4.89 (t, J = 9.5 Hz, 1H, H-4), 4.71 (d, J = 10.0 Hz, 1H, H-1), 4.12 (dd, J = 5.0, 12.0 Hz, 1H, H-6a), 4.05 (m, 1H, H-6b), 4.01(m, 1H, H-5), 3.92 (t, J = 10.0 Hz, 1H, N*H*), 3.09 (m, 2H, NHCH_2), 2.82 (t, J = 7.0 Hz, NHCH$_2$CH_2), 2.01, 1.99, 1.95, 1.89 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.9, 169.5, 169.3, 169.2 (O*C*OCH$_3$), 144.0, 141.8 (C$_{arom}$), 129.0, 125.6 (*C*H$_{arom}$), 87.4 (C-1), 74.2 (C-5), 73.2 (C-3), 68.0 (C-4), 67.5 (C-2), 61.9 (C-6), 54.0 (NH*C*H$_2$), 35.7 (NHCH$_2$*C*H$_2$), 20.4, 20.3 (2C), 20.2, (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 563 [M + H]$^+$, 585 [M + Na]$^+$. LRMS (ESI$^-$): m/z = 561 [M − H]$^-$. HRMS: calcd for $C_{22}H_{31}N_2O_{11}S_2$, 563.1364; found, 563.1392.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranosyl)sulfenamide (19).** Sulfenamide **19** was prepared from 4-aminoethylbenzenesulfonamide and thioacetate derivative **b** according to the General Procedure 2. The expected compound was obtained after flash chromatography (1:1 EtOAc/hexane) as a yellow gum (46% yield); R_f = 0.33 (1:1 EtOAc/hexane); $[\alpha]^{25}_D$ = −82 (c = 1.1, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.72 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.38 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.25 (s, 2H, NH_2), 5.30 (d, J = 3.0 Hz, 1H, H-4), 5.26 (dd, J = 3.5, 10.0 Hz, 1H, H-3), 5.03 (t, J = 10.0 Hz, 1H, H-2), 4.69 (d, J = 10.0 Hz, 1H, H-1), 4.23 (m, 1H, H-5), 4.02 (m, 2H, H-6a, H-6b), 3.96 (t, J = 5.0 Hz, 1H, N*H*), 3.12 (m, 2H, NHCH_2), 2.86 (t, J = 7.0 Hz, NHCH$_2$CH_2), 2.07, 2.04, 1.99, 1.92 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.9 (2C), 169.6, 169.4 (O*C*OCH$_3$), 144.0, 141.9 (C$_{arom}$), 129.0, 125.6 (*C*H$_{arom}$), 88.4 (C-1), 73.3 (C-5), 71.1 (C-3), 67.7 (C-4), 65.1 (C-2), 61.7 (C-6), 54.0 (NH*C*H$_2$), 35.7 (NHCH$_2$*C*H$_2$), 20.5, 20.4, 20.3 (2C) (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 563 [M + H]$^+$, 585 [M + Na]$^+$. LRMS (ESI$^-$): m/z = 561 [M − H]$^-$. HRMS: calcd for $C_{22}H_{31}N_2O_{11}S_2$, 563.1364; found, 563.1364.

Methyl *N*-4-(Aminosulfonyl)phenethyl-*S*-(2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranuronoyl)sulfenamide (20). Sulfenamide **20** was prepared from 4-aminoethylbenzenesulfonamide and thioacetate derivative **c** according to the General Procedure 2. The expected compound was obtained after flash chromatography (3:2 EtOAc/hexane) as a slightly yellow solid (88% yield); R_f = 0.16 (1:1 EtOAc/hexane); mp = 124−128 °C; $[\alpha]^{25}_D$ = −88 (c = 1.2, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.72 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.37 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.25 (s, 2H, NH_2), 5.40 (t, J = 9.5 Hz, 1H, H-3), 4.94 (t, J = 10.0 Hz, 1H, H-4), 4.93 (t, J = 10.0 Hz, 1H, H-2), 4.79 (d, J = 10.0 Hz, 1H, H-1), 4.45 (d, J = 10.0 Hz, 1H, H-5), 3.95 (t, J = 5.0 Hz, 1H, N*H*), 3.62 (s, 3H, OCH_3), 3.08 (m, 2H, NHCH_2), 2.82 (t, J = 7.0 Hz, NHCH$_2$CH_2), 2.00, 1.97, 1.96 (3 × s, 9H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.7, 169.5, 169.4, 167.5 (*C*OCH$_3$), 144.2, 141.9 (C$_{arom}$), 129.2, 125.7 (*C*H$_{arom}$), 87.4 (C-1), 74.5 (C-5), 72.5 (C-3), 69.2 (C-4), 67.4 (C-2), 55.8 (NH*C*H$_2$), 52.6 (O*C*H$_3$), 35.7 (NHCH$_2$*C*H$_2$), 20.6, 20.4, 20.3 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 549 [M + H]$^+$. LRMS (ESI$^-$): m/z = 547 [M − H]$^-$. HRMS: calcd for $C_{21}H_{29}N_2O_{11}S_2$, 549.1207; found, 549.1224.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-1-thio-β-lactosyl)sulfenamide (21).** Sulfenamide **21** was prepared from 4-aminoethylbenzenesulfonamide and thioacetate derivative **d** according to the General Procedure 2. The expected compound was obtained after flash chromatography (2:1 EtOAc/hexane) as a white solid (88% yield); R_f = 0.44 (2:1 EtOAc/hexane); mp = 91−93 °C; $[\alpha]^{25}_D$ = −70 (c = 1.0, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.70 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.35 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.26 (s, 2H, NH_2), 5.21 (d, J = 3.5 Hz, 1H, H-4′), 5.18 (t, J = 9.5 Hz, 1H, H-3), 5.12 (dd, J = 3.5, 10.5 Hz, 1H, H-3′), 4.83 (dd, J = 8.0,

10.0 Hz, 1H, H-2′), 4.80 (t, J = 9.5 Hz, 1H, H-2), 4.73 (d, J = 8.0 Hz, 1H, H-1), 4.63 (d, J = 10.5 Hz, 1H, H-1′), 4.32 (br d, J = 11.0 Hz, 1H, H6a′), 4.19 (br t, J = 6.5 Hz, 1H, H-5′), 4.01−3.98 (m, 3H, H-6a, H-6b, H-6b′), 3.86 (br t, J = 5.0 Hz, 1H, N*H*), 3.81 (m, 1H, H-5), 3.73 (t, J = 9.5 Hz, 1H, H-4), 3.05 (m, 2H, NHCH_2), 2.79 (t, J = 7.0 Hz, NHCH$_2$CH_2), 2.08, 1.99, 1.98, 1.97, 1.91, 1.88 (6 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR 125 MHz, DMSO-d_6): δ = 170.4, 170.1 (2C), 169.8, 169.7, 169.6, 169.3 (O*C*OCH$_3$), 144.3, 141.9 (C$_{arom}$), 129.3, 125.8 (*C*H$_{arom}$), 100.1 (C-1′), 87.5 (C-1), 76.2 (C-4), 75.7 (C-5), 73.6 (C-3), 70.5 (C-3′), 69.9 (C-5′), 69.1 (C-2′), 68.0 (C-2), 67.2 (C-4′), 62.6 (C-6′), 61.0 (C-6), 54.1 (NH*C*H$_2$), 35.8 (NHCH$_2$*C*H$_2$), 20.7, 20.6 (3C), 20.5 (2C), 20.4 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 873 [M + Na]$^+$. HRMS: calcd for $C_{34}H_{46}N_2O_{19}S_2Na$, 873.2028; found, 873.2063.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-1-thio-β-maltosyl)sulfenamide (22).** Sulfenamide **22** was prepared from 4-aminoethylbenzenesulfonamide and thioacetate derivative **e** according to the General Procedure 2. The expected compound was obtained after flash chromatography (1:1 EtOAc/hexane) as a slightly yellow gum (49% yield); R_f = 0.18 (1:1 EtOAc/hexane); $[\alpha]^{25}_D$ = −2 (c = 1.3, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.72 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.36 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.24 (s, 2H, NH_2), 5.38 (t, J = 9.0 Hz, H-3), 5.29 (d, J = 4.0 Hz, 1H, H-1′), 5.22 (t, J = 10.0 Hz, 1H, H-3′), 4.98 (t, J = 9.5 Hz, 1H, H-4′), 4.87 (dd, J = 3.5, 10.5 Hz, 1H, H-2′), 4.80 (t, J = 9.5, 1H, H-2), 4.70 (d, J = 10.0 Hz, 1H, H-1), 4.41 (dd, J = 3.0, 12.0 Hz, 1H, H6a′), 4.16 (dd, J = 4.5, 12.5 Hz, 1H, H-6a), 4.13 (dd, J = 4.5, 12.5 Hz, 1H, H-6b′), 4.02 (m, 1H, H-6b), 4.00−3.97 (m, 2H, H-5, H-5′), 3.89 (t, J = 9.5 Hz, 1H, H-4), 3.88 (m, 1H, N*H*), 3.06 (m, 2H, NHCH_2), 2.80 (t, J = 6.5 Hz, NHCH$_2$CH_2), 2.00, 1.99, 1.98, 1.97, 1.95, 1.94 (6 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR 125 MHz, DMSO-d_6): δ = 170.0, 169.9, 169.8, 169.6, 169.4 (2C), 169.1 (O*C*OCH$_3$), 144.5, 141.8 (C$_{arom}$), 129.0, 125.5 (*C*H$_{arom}$), 95.4 (C-1′), 87.0 (C-1), 75.3 (C-3), 74.8 (C-5′), 73.6 (C-4), 69.4 (C-2′), 68.8 (C-3′), 68.2 (C-2), 68.0 (C-5), 67.8 (C-4′), 63.0 (C-6′), 61.4 (C-6), 53.9 (NH*C*H$_2$), 35.7 (NHCH$_2$*C*H$_2$), 20.5, 20.4 (2C), 20.3 (3C), 20.2 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 873 [M + Na]$^+$. HRMS: calcd for $C_{34}H_{46}N_2O_{19}S_2Na$, 873.2028; found, 873.2043.

Oxidation of Sulfenamide Derivatives: General Procedure 3. The sulfenamide derivative (1.0 equiv) was solubilized in CH_2Cl_2. *meta*-Chloroperoxybenzoic acid (7.0 equiv) was added dropwise as a solution in CH_2Cl_2 over ∼20 min. The reaction was maintained under stirring at rt until the full disappearance of the starting material, as evidenced by TLC, typically 1 h. The reaction mixture was then diluted in CH_2Cl_2 and quenched with $NaHCO_{3\ satd}$. The resulting mixture was next filtered through celite. After extraction with CH_2Cl_2, the organic layer was washed with $NaHCO_{3\ satd}$ (×1) and brine (×1). The aqueous phases were back extracted with CH_2Cl_2 (×2), organic phases were combined, dried with $MgSO_4$, filtered, and concentrated. Expected sulfonamides were purified as described for each compound, **8**−**12** and **23**−**27**.

***N*-4-(Aminosulfonyl)benzyl-*S*-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)sulfonamide (8).** Sulfonamide **8** was prepared from sulfenamide **3** according to the General Procedure 3. Expected derivative was obtained as white crystals following recrystallization from ethanol (63% yield); R_f = 0.13 (1:1 EtOAc/hexane); mp = 182−185 °C; $[\alpha]^{25}_D$ = −32 (c = 1.1, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.29 (t, J = 6.0 Hz, 1H, N*H*), 7.79 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.49 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.31 (s, 2H, NH_2), 5.39 (t, J = 9.5 Hz, 1H, H-3), 5.23 (t, J = 9.5 Hz, 1H, H-2), 4.95 (d, J = 9.0 Hz, 1H, H-1), 4.94 (t, J = 9.0 Hz, 1H, H-4), 4.29 (d, J = 5.5 Hz, 2H, CH_2), 4.20 (dd, J = 5.5, 12.5 Hz, 1H, H-6a), 4.13 (ddd, J = 2.0, 5.5, 10.0 Hz, 1H, H-5), 4.02 (dd, J = 1.5, 12.0 Hz, 1H, H-6b), 2.01, 2.00, 1.96, 1.95 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.1, 169.6, 169.3, 168.7 (O*C*OCH$_3$), 143.0, 142.6 (C$_{arom}$), 127.6, 125.7 (*C*H$_{arom}$), 86.3 (C-1), 74.6 (C-5), 72.8 (C-3), 67.6, 67.5 (C-4, C-2), 61.6 (C-6), 46.1 (*C*H$_2$), 20.5, 20.4, 20.3, 20.2 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 603 [M + Na]$^+$. LRMS (ESI$^-$): m/z = 579 [M − H]$^-$. HRMS: calcd for $C_{21}H_{28}N_2O_{13}S_2Na$, 603.0925; found, 603.0942.

***N*-4-(Aminosulfonyl)benzyl-*S*-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranosyl)sulfonamide (9).** Sulfonamide **9** was prepared from sulfenamide **4** according to the General Procedure 3. Following flash chromatography using solid addition (2:1 EtOAc/hexane), the expected derivative was obtained as a slightly yellow oil (46% yield); R_f = 0.31 (2:1 EtOAc/hexane); $[\alpha]^{25}_D$ = −28 (c = 1.3, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.26 (t, J = 6.0 Hz, 1H, N*H*), 7.80 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.50 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.31 (s, 2H, NH_2), 5.41 (t, J = 9.5 Hz, 1H, H-3), 5.34 (br d, J = 3.5 Hz, 1H, H-4), 5.30 (dd, J = 3.5, 9.5 Hz, 1H, H-3), 4.85 (d, J = 9.5 Hz, 1H, H-1), 4.37 (br t, J = 6.0 Hz, 1H, H-5), 4.30 (br d, J = 4.5 Hz, 2H, CH_2), 4.06 (br d, J = 6.0 Hz, 2H, H-6a, H-6b), 2.13, 2.00, 1.98, 1.93 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.9, 169.8, 169.4, 168.6 (O*C*OCH$_3$), 142.9, 142.5 (C$_{arom}$), 127.5, 125.7 (*C*H$_{arom}$), 86.8 (C-1), 74.9 (C-5), 70.7 (C-3), 67.3 (C-4), 64.7 (C-2), 61.4 (C-6), 46.0 (*C*H$_2$), 20.5 (2C), 20.4, 20.3 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 603 [M + Na]$^+$. HRMS: calcd for $C_{21}H_{28}N_2O_{13}S_2Na$, 603.0925; found, 603.0944.

Methyl *N*-4-(Aminosulfonyl)benzyl-*S*-(2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranuronoyl)sulfonamide (10). Sulfonamide **10** was prepared from sulfenamide **5** according to the General Procedure 3. The expected derivative was obtained after flash chromatography (2:1 EtOAc/hexane) as a white solid (40% yield); R_f = 0.29 (2:1 EtOAc/hexane); mp = 235−236 °C; $[\alpha]^{25}_D$ = −25 (c = 1.0, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.36 (t, J = 6.0 Hz, 1H, N*H*), 7.78 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.48 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.31 (s, 2H, NH_2), 5.47 (t, J = 9.5 Hz, 1H, H-3), 5.26 (t, J = 9.5 Hz, 1H, H-2), 5.03 (d, J = 9.5 Hz, 1H, H-1), 4.97 (t, J = 9.5 Hz, 1H, H-4), 4.56 (d, J = 10.0 Hz, 1H, H-5), 4.32 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 2.00, 1.97, 1.96 (3 × s, 9H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.4, 169.2, 168.6, 166.6 (O*C*OCH$_3$), 142.9, 142.5 (C$_{arom}$), 127.5, 125.6 (*C*H$_{arom}$), 86.1 (C-1), 73.9 (C-5), 71.9 (C-3), 68.5 (C-4), 67.4 (C-2), 52.7 (O*C*H$_3$), 46.1 (*C*H$_2$), 20.3, 20.2, 20.1 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^-$): m/z = 565 [M − H]$^-$. HRMS: calcd for $C_{20}H_{26}N_2O_{13}S_2Na$, 589.0769; found, 589.0769.

***N*-4-(Aminosulfonyl)benzyl-*S*-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-1-thio-β-maltosyl)sulfonamide (11).** Sulfonamide **11** was prepared from sulfenamide **6** according to the General Procedure 3. Expected derivative was obtained after flash chromatography (2:1 EtOAc/hexane) as a white solid (64% yield); R_f = 0.23 (2:1 EtOAc/hexane); mp = 151−152 °C; $[\alpha]^{25}_D$ = −19 (c = 1.4, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.23 (t, J = 6.0 Hz, 1H, N*H*), 7.79 (d, J = 8.0 Hz, 2H, H$_{arom}$), 7.47 (d, J = 8.5 Hz, 2H, H$_{arom}$), 7.31 (s, 2H, NH_2), 5.27 (t, J = 9.5, 1H, H-3), 5.23 (d, J = 3.5 Hz, 1H, H-4′), 5.16 (d, J = 9.5 Hz, 1H, H-2), 5.16 (dd, J = 3.5, 10.0 Hz, 1H, H-3′), 4.90 (d, J = 9.5 Hz, 1H, H-1), 4.85 (dd, J = 8.0, 10.0 Hz, 1H, H-2′), 4.77 (d, J = 8.0 Hz, 1H, H-1′), 4.32 (br d, J = 10.5 Hz, 1H, H-6a′), 4.26 (d, J = 6.0 Hz, 2H, CH_2), 4.22 (t, J = 7.0 Hz, 1H, H-6a), 4.09 (dd, J = 7.0, 12.0 Hz, 1H, H-6b′), 4.01 (m, 3H, H-5, H-5′, H-6b), 3.84 (t, J = 9.5 Hz, 1H, H-4), 2.10, 2.06, 2.01, 1.98, 1.94, 1.90 (7 × s, 24H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.3, 170.0 (2C), 169.5, 169.4, 169.2, 168.8 (O*C*OCH$_3$), 143.0, 142.6 (C$_{arom}$), 127.6, 125.8 (*C*H$_{arom}$), 100.0 (C-1′), 86.2 (C-1), 75.8 (C-4), 75.7

(C-5′), 73.0 (C-3), 70.4 (C-3′), 69.8 (C-5), 68.9 (C-2′), 67.8 (C-2), 67.1 (C-4′), 62.2 (C-6′), 60.9 (C-6), 46.1 (CH_2), 20.6, 20.5 (2C), 20.4 (3C), 20.3 (OCOCH_3), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 891 [M + Na]$^+$. LRMS (ESI$^-$): m/z = 867 [M − H]$^-$. HRMS: calcd for $C_{33}H_{44}N_2O_{21}S_2$Na, 891.1770; found, 891.1786.

***N*-4-(Aminosulfonyl)benzyl-*S*-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-1-thio-β-lactosyl)sulfonamide (12).** Sulfonamide **12** was prepared from sulfenamide **7** according to the General Procedure 3. The expected derivative was obtained after flash chromatography (2:1 EtOAc/hexane) as a white solid (37% yield); R_f = 0.24 (2:1 EtOAc/hexane); mp = 112−115 °C; $[\alpha]^{25}_D$ = +37 (c = 1.3, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.23 (t, J = 6.0 Hz, 1H, NH), 7.80 (d, J = 8.5 Hz, 2H, H_{arom}), 7.48 (d, J = 8.0 Hz, 2H, H_{arom}), 7.31 (s, 2H, NH_2), 5.44 (t, J = 9.0 Hz, 1H, H-3), 5.30 (d, J = 4.0 Hz, 1H, H-1′), 5.23 (t, J = 10.0 Hz, 1H, H-3′), 5.13 (t, J = 9.5 Hz, 1H, H-2), 5.00 (t, J = 10.0 Hz, 1H, H-4′), 4.95 (d, J = 10.0 Hz, 1H, H-1), 4.89 (dd, J = 4.0, 10.0 Hz, 1H, H-2′), 4.43 (br d, J = 10.0 Hz, 1H, H-6a), 4.27 (d, J = 6.0 Hz, 2H, CH_2), 4.21 (dd, J = 6.0, 12.5 Hz, 1H, H-6b), 4.17 (dd, J = 4.0, 12.0 Hz, 1H, H-6a′), 4.14 (m, 1H, H-5) 4.02 (br d, J = 12.0 Hz, 1H, H-6b′), 4.00 (m, 1H, H-5′) 3.98 (t, J = 9.0 Hz, 1H, H-4), 2.06, 2.02, 1.99, 1.98, 1.95, 1.93 (6 × s, 24H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.3, 170.1, 170.0, 169.8, 169.6, 169.3, 169.0 (OCOCH$_3$), 143.0, 142.7 (C_{arom}), 127.6, 125.8 (CH_{arom}), 95.8 (C-1′), 86.4 (C-1), 75.3 (C-5), 74.8 (C-3), 73.6 (C-4), 69.5 (C-2′), 69.0 (C-3′), 68.3 (C-2), 68.2 (C-5′), 67.8 (C-4′), 62.8 (C-6), 61.5 (C-6′), 46.2 (CH_2), 20.7, 20.6, 20.5 (2C), 20.4 (2C), 20.3 (OCOCH_3), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 891 [M + Na]$^+$. LRMS (ESI$^-$): m/z = 867 [M − H]$^-$. HRMS: calcd for $C_{33}H_{44}N_2O_{21}S_2$Na, 891.1770; found, 891.1770.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)sulfonamide (23).** Sulfonamide **23** was prepared from sulfenamide **18** according to the General Procedure 3. Expected derivative was obtained after recrystallization from ethanol as white crystals (57% yield); R_f = 0.29 (2:1 EtOAc/hexane); mp = 112−115 °C; $[\alpha]^{25}_D$ = −32 (c = 1.1, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.74 (d, J = 8.0 Hz, 2H, H_{arom}), 7.73 (t, J = 6.0 Hz, 1H, NH), 7.40 (d, J = 8.0 Hz, 2H, H_{arom}), 7.28 (s, 2H, NH_2), 5.39 (t, J = 9.5 Hz, 1H, H-3), 5.20 (t, J = 9.5 Hz, 1H, H-2), 4.97 (d, J = 9.5 Hz, 1H, H-1), 4.92 (t, J = 9.5 Hz, 1H, H-4), 4.18 (m, 2H, H-5, H-6a), 4.04 (m, 1H, H-6b), 3.26 (m, 2H, NHCH_2), 2.84 (t, J = 7.5 Hz, 2H, NHCH$_2$CH_2), 1.99, 1.95, 1.94, 1.93 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.9, 169.5, 169.2, 168.6 (OCOCH$_3$), 142.8, 142.2 (C_{arom}), 129.1, 125.6 (CH_{arom}), 85.7 (C-1), 74.5 (C-5), 72.7 (C-3), 67.5 (2C) (C-4, C-2), 61.8 (C-6), 44.0 (NHCH_2), 35.6 (NHCH$_2$$CH_2$), 20.4, 20.3 (2C), 20.2 (OCOCH_3), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 612 [M + NH$_4$]$^+$, 617 [M + Na]$^+$. HRMS: calcd for $C_{22}H_{30}N_2O_{13}S_2$Na, 617.1082; found, 617.1084.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranosyl)sulfonamide (24).** Sulfonamide **24** was prepared from sulfenamide **19** according to the General Procedure 3. Expected derivative was obtained after flash chromatography (2:1 EtOAc/hexane) as a white solid (52% yield); R_f = 0.21 (2:1 EtOAc/hexane); mp = 88−92 °C; $[\alpha]^{25}_D$ = −17 (c = 1.3, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.75 (d, J = 8.5 Hz, 2H, H_{arom}), 7.72 (t, J = 6.0 Hz, 1H, NH), 7.41 (d, J = 8.0 Hz, 2H, H_{arom}), 7.28 (s, 2H, NH_2), 5.39 (t, J = 9.5 Hz, 1H, H-2), 5.34 (d, J = 2.5 Hz, 1H, H-4), 5.28 (dd, J = 3.5, 10.0 Hz, 1H, H-3), 4.89 (d, J = 9.5 Hz, 1H, H-1), 4.40 (br t, J = 6.0 Hz, 1H, H-5), 4.06 (m, 2H, H-6a, H-6b), 3.26 (m, 2H, NHCH_2), 2.86 (t, J = 7.5 Hz, 2H, NHCH$_2$CH_2), 2.11, 1.97, 1.93 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.9, 169.8, 169.4, 168.6 (OCOCH$_3$), 142.8, 142.2 (C_{arom}), 129.1, 125.7 (CH_{arom}), 86.3 (C-1), 73.9 (C-5), 70.8 (C-3), 67.4 (C-4), 64.7 (C-2), 61.7 (C-6), 44.0 (NHCH_2), 35.8 (NHCH$_2$$CH_2$), 20.5, 20.4, 20.3 (2C) (OCOCH_3), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 617 [M + Na]$^+$. HRMS: calcd for $C_{22}H_{30}N_2O_{13}S_2$Na, 617.1082; found, 617.1097.

Methyl *N*-4-(Aminosulfonyl)phenethyl-*S*-(2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranuronoyl)sulfonamide (25). Sulfonamide **25** was prepared from sulfenamide **20** according to the General Procedure 3. The expected derivative was obtained after flash chromatography (3:2 EtOAc/hexane) as a white solid (61% yield); R_f = 0.26 (3:2 EtOAc/hexane); mp = 203−204 °C; $[\alpha]^{25}_D$ = −18 (c = 1.0, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.78 (t, J = 6.0 Hz, 1H, NH), 7.75 (d, J = 8.0 Hz, 2H, H_{arom}), 7.39 (d, J = 8.0 Hz, 2H, H_{arom}), 7.27 (s, 2H, NH_2), 5.45 (t, J = 9.5 Hz, 1H, H-3), 5.23 (t, J = 9.5 Hz, 1H, H-2), 5.00 (d, J = 9.5 Hz, 1H, H-1), 4.97 (t, J = 9.5 Hz, 1H, H-4), 4.62 (d, J = 10.0 Hz, 1H, H-5), 3.63 (s, 3H, OCH_3), 3.28 (m, 2H, NHCH_2), 2.83 (t, J = 7.5 Hz, 2H, NHCH$_2$CH_2), 2.00, 1.97, 1.96 (3 × s, 9H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.5, 169.2, 168.6, 166.7 (OCOCH$_3$), 142.8, 142.2 (C_{arom}), 129.1, 125.6 (CH_{arom}), 86.0 (C-1), 73.9 (C-5), 71.9 (C-3), 68.5 (C-4), 67.4 (C-2), 52.7 (OCH_3), 44.1 (NHCH_2), 35.8 (NHCH$_2$$CH_2$), 20.4, 20.2, 20.1 (OCO$CH_3$), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^-$): m/z = 579 [M − H]$^-$. HRMS: calcd for $C_{21}H_{28}N_2O_{13}S_2$Na, 603.0925; found, 603.0895.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-1-thio-β-lactosyl)sulfonamide (26).** Sulfonamide **26** was prepared from sulfenamide **21** according to the General Procedure 3. The expected derivative was obtained after flash chromatography (2:1 EtOAc/hexane) as a off-white solid (37% yield);. R_f = 0.24 (2:1 EtOAc/hexane); mp = 105−107 °C; $[\alpha]^{25}_D$ = −22 (c = 1.3, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.75 (d, J = 8.5 Hz, 2H, H_{arom}), 7.70 (t, J = 5.5 Hz, 1H, NH), 7.39 (d, J = 8.5 Hz, 2H, H_{arom}), 7.28 (s, 2H, NH_2), 5.27 (t, J = 9.5 Hz, 1H, H-3), 5.23 (d, J = 3.5 Hz, 1H, H-4′), 5.16 (d, J = 9.5 Hz, 1H, H-2), 5.16 (dd, J = 3.5, 10.0 Hz, 1H, H-3′), 4.90 (d, J = 9.5 Hz, 1H, H-1), 4.85 (dd, J = 8.0, 10.0 Hz, 1H, H-2′), 4.77 (d, J = 8.0 Hz, 1H, H-1′), 4.31 (br d, J = 10.5 Hz, 1H, H-6a), 4.21 (t, J = 6.5 Hz, 1H, H-5′), 4.08 (m, 1H, H-6b), 4.06 (m, 1H, H-5), 4.02 (m, 2H, H-6a′, H-6b′), 3.83 (t, J = 9.5 Hz, 1H, H-4), 3.23 (m, 2H, NHCH_2), 2.84 (t, J = 7.5 Hz, 2H, NHCH$_2$CH_2), 2.10, 2.00, 1.99, 1.97, 1.96, 1.94, 1.89 (7 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.2, 169.9 (2C), 169.5, 169.4, 169.0, 168.7 (OCOCH$_3$), 142.9, 142.2 (C_{arom}), 129.1, 125.7 (CH_{arom}), 99.9 (C-1′), 85.6 (C-1), 75.8 (C-4), 75.6 (C-5), 73.0 (C-3), 70.3 (C-3′), 69.8 (C-5′), 68.9 (C-2′), 67.8 (C-2), 67.1 (C-4′), 62.4 (C-6), 60.9 (C-6′), 44.0 (NHCH_2), 35.8 (NHCH$_2$$CH_2$), 20.5, 20.4 (3C), 20.3 (2C), 20.2 (OCOCH_3), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 891 [M + Na]$^+$. LRMS (ESI$^-$): m/z = 867 [M − H]$^-$. HRMS: calcd for $C_{34}H_{46}N_2O_{21}S_2$Na, 905.1927; found, 905.1944.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-1-thio-β-maltosyl)sulfonamide (27).** Sulfonamide **27** was prepared from sulfenamide **22** according to the General Procedure 3. The expected derivative was obtained after flash chromatography (2:1 EtOAc/hexane) as a white solid (37% yield); R_f = 0.19 (2:1 EtOAc/hexane); mp = 100−103 °C; $[\alpha]^{25}_D$ = +32 (c = 1.1, chloroform). ^{1}H NMR bad spectra (500 MHz, DMSO-d_6): δ = 7.75 (d, J = 8.0 Hz, 2H, H_{arom}), 7.70 (t, J = 6.0 Hz, 1H, NH), 7.40 (d, J = 8.0 Hz, 2H, H_{arom}), 7.28 (s, 2H, NH_2), 5.43 (t, J = 9.0 Hz, 1H, H-3), 5.28 (d, J = 4.0 Hz, 1H, H-1′), 5.21 (t, J = 10.0 Hz, 1H, H-3′), 5.09 (t, J = 9.5 Hz, 1H, H-2), 4.99 (t, J = 9.5 Hz, 1H, H-4′), 4.95 (d, J = 9.5 Hz, 1H, H-1), 4.88 (dd, J = 4.0, 10.0 Hz, 1H, H-2′), 4.40 (m, 1H, H-6a), 4.19 (m, 1H, H-6b), 4.17 (m, 1H, H-5), 4.15 (m, 1H, H6a′), 4.02 (m, 1H, H-6b′), 3.97 (m, 1H, H-5′), 3.95 (t, J = 9.0 Hz, H-4), 3.24 (br q, J = 8.0 Hz, 2H, NHCH_2), 2.84 (t, J = 7.5 Hz, 2H, NHCH$_2$CH_2), 2.01, 1.99, 1.98, 1.96, 1.95, 1.92 (6 × s, 21H, OCOCH_3), assignments were

confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.0, 169.9, 169.8, 169.6, 169.4, 169.1, 168.8 ($OCOCH_3$), 142.8, 142.2 (C_{arom}), 129.1, 125.6 (CH_{arom}), 95.6 (C-1′), 85.6 (C-1), 75.0 (C-5), 74.7 (C-3), 73.6 (C-5′), 69.4 (C-2′), 68.8 (C-3′), 68.8 (C-2), 68.0 (C-4), 67.7 (C-4′), 62.9 (C-6), 61.4 (C-6′), 44.0 ($NHCH_2$), 35.8 ($NHCH_2CH_2$), 20.5, 20.4 (2C), 20.3 (3C), 20.2 ($OCOCH_3$), assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 883 $[M + H]^+$, 906 $[M + Na]^+$. LRMS (ESI^-): m/z = 881 $[M - H]^-$. HRMS: calcd for $C_{34}H_{46}N_2O_{21}S_2Na$, 905.1927; found, 905.1921.

Deacetylation of Peracetylated Compounds: General Procedure 4. Fully deprotected compounds were prepared by treating a solution of the per-*O*-acetylated compound (1.0 equiv) in anhydrous MeOH at 0 °C with methanolic sodium methoxide (0.05 M final concentration), final pH = 12. The reaction was warmed to rt and left to stir until full deprotection was evident by TLC (~2 h). The solution was neutralized with Amberlite IR-120 [H^+], filtered and the resin washed several times with methanol. The solvent was evaporated under reduced pressure and lyophilized to dryness to afford fully deprotected compounds **13**−**17** and **28**−**32**.

***N*-(4-Aminosulfonyl)benzyl-*S*-(1-thio-β-D-glucopyranosyl)sulfonamide (13).** Sulfonamide **13** was prepared from sulfonamide **8** according to the General Procedure 4. The expected derivative was obtained after freeze-drying as a white solid (100% yield); R_f = 0.31 (95:5 CH_3CN/H_2O); mp = 185 °C; $[\alpha]^{25}_D = -9$ (c = 1.1, methanol). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.78 (d, J = 8.5 Hz, 2H, H_{arom}), 7.52 (d, J = 8.0 Hz, 2H, H_{arom}), 7.30 (br s, 2H, NH_2), 5.17 (br s, 1H, O*H*), 5.09 (br s, 1H, O*H*), 4.55 (br s, 1H, O*H*), 4.29 (t, J = 6.0 Hz, 1H, $NHCH_2$), 4.27 (t, J = 6.0 Hz, 1H, $NHCH_2$), 4.14 (d, J = 9.5 Hz, 1H, H-1), 3.70 (br d, J = 12.0 Hz, 1H, H-6a), 3.48 (m, 1H, H-6b), 3.46 (t, J = 9.0 Hz, 1H, H-2), 3.23 (m, 2H, H-3, H-5), 3.07 (t, J = 9.0 Hz, 1H, H-4), assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 142.9, 142.8 (C_{arom}), 127.8, 125.6 (CH_{arom}), 89.8 (C-1), 81.2 (C-5), 77.5 (C-3), 70.5 (C-2), 69.6 (C-4), 61.1 (C-6), 46.0 (CH_2), assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 413 $[M + Na]^+$, 435 $[M + Na]^+$. HRMS: calcd for $C_{13}H_{20}N_2O_9S_2Na$, 435.0502; found, 435.0524.

***N*-(4-Aminosulfonyl)benzyl-*S*-(1-thio-β-D-galactopyranosyl)-sulfonamide (14).** Sulfonamide **14** was prepared from sulfonamide **9** according to the General Procedure 4. Expected derivative was obtained after freeze-drying as a white solid (78% yield);. R_f = 0.50 (9:1 CH_3CN/H_2O); mp = 181−183 °C; $[\alpha]^{25}_D = -3$ (c = 1.1, methanol). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.79 (d, J = 8.0 Hz, 2H, H_{arom}), 7.63 (br t, J = 6.0 Hz, 1H, N*H*), 7.52 (d, J = 8.0 Hz, 2H, H_{arom}), 7.30 (s, 2H, NH_2), 4.95 (d, J = 5.5 Hz, 1H, O*H*-2), 4.92 (d, J = 5.5 Hz, 1H, O*H*-3), 4.60 (t, J = 5.5 Hz, 1H, O*H*-6), 4.57 (d, J = 3.5 Hz, 1H, O*H*-4), 4.27 (m, 2H, CH_2), 4.10 (d, J = 9.0 Hz, 1H, H-1), 3.81 (dt, J = 5.5, 9.0 Hz, 1H, H-2), 3.71 (br t, J = 3.5 Hz, 1H, H-4), 3.55 (m, 2H, H-6a, H-6b), 3.49 (t, J = 6.0 Hz, 1H, H-5), 3.38 (m, 1H, H-3), 3.05 (td, J = 5.5, 9.5 Hz, 1H, H-4), 3.25 (br t, J = 7.0 Hz, 1H, $NHCH_2CH_2$), 2.84 (t, J = 7.0 Hz, 2H, $NHCH_2CH_2$), assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 142.9, 142.8 (C_{arom}), 127.8, 125.6 (CH_{arom}), 90.8 (C-1), 79.8 (C-5), 74.0 (C-3), 68.0 (C-4), 67.2 (C-2), 60.4 (C-6), 46.0 (CH_2), assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 411 $[M - H]^-$. HRMS: calcd for $C_{13}H_{20}N_2O_9S_2Na$, 435.0502; found, 435.0510.

***N*-(4-Aminosulfonyl)benzyl-*S*-(1-thio-β-D-glucopyranuronoyl)-sulfonamide (15).** Sulfonamide **15** was prepared from sulfonamide **10** according to the General Procedure 4. Expected derivative was obtained after freeze-drying as a slightly yellow gum (40% yield); R_f = 0.15 (9:1 CH_3CN/H_2O); $[\alpha]^{25}_D = -13$ (c = 1.1, methanol). ^1H NMR (500 MHz, D_2O): δ = 7.98 (d, J = 8.0 Hz, 2H, H_{arom}), 7.68 (d, J = 8.0 Hz, 2H, H_{arom}), 4.57 (d, J = 16.0 Hz, 1H, CH*H*), 4.49 (d, J = 16.0 Hz, 1H, C*H*H), 4.23 (d, J = 9.5 Hz, 1H, H-1), 3.84 (m, 1H, H-5), 3.55 (m, 3H, H-2, H-3, H-4), assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.7 (CO_2H), 142.8 (C_{arom}), 127.7, 125.6 (CH_{arom}), 90.2 (C-1), 78.9 (C-5), 76.9 (C-3), 71.0 (C-4), 70.4 (C-2), 46.0 (CH_2), assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^-): m/z = 425 $[M - H]^-$. HRMS: calcd for $C_{13}H_{18}N_2O_{10}S_2Na$, 449.0295; found, 449.0305.

***N*-4-(Aminosulfonyl)benzyl-*S*-(1-thio-β-maltosyl)sulfonamide (16).** Sulfonamide **16** was prepared from sulfonamide **11** according to the General Procedure 4. The expected derivative was obtained after freeze-drying as a white solid (85% yield); R_f = 0.24 (95:5 CH_3CN/H_2O); mp = 162−164 °C; $[\alpha]^{25}_D = -5$ (c = 1.1, methanol). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.79 (d, J = 8.5 Hz, 2H, H_{arom}), 7.67 (br s, 1H, N*H*), 7.52 (d, J = 8.0 Hz, 2H, H_{arom}), 7.31 (s, 2H, NH_2), 5.38 (d, J = 4.5 Hz, 1H, O*H*-2), 5.08 (d, J = 4.0 Hz, 1H, O*H*-2′), 4.83 (d, J = 1.5 Hz, 1H, O*H*-3), 4.77 (d, J = 4.0 Hz, 1H, O*H*-3′), 4.64 (t, J = 5.0 Hz, 1H, O*H*-6′), 4.58 (t, J = 6.0 Hz, 1H, O*H*-6), 4.50 (d, J = 4.5 Hz, 1H, O*H*-4′), 4.29 (m, 2H, CH_2), 4.26 (d, J = 9.5 Hz, 1H, H-1), 4.22 (d, J = 7.0 Hz, 1H, H-1′), 3.80 (dd, J = 6.0, 10.5 Hz, 1H, H-6a), 3.62 (m, 2H, H-6b, H-4′), 3.52 (m, 3H, H-2, H-6a′, H-6b′), 3.43 (m, 3H, H-3, H-4, H-5′), 3.32 (m, 3H, H-2′, H-3′, H-5), assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 142.9 (2C) (C_{arom}), 127.8, 125.6 (CH_{arom}), 103.7 (C-1′), 89.4 (C-1), 79.8 (C-5), 79.1 (C-5′), 75.7 (C-4′), 75.5 (C-3), 73.2 (C-3′), 70.5 (C-2′), 70.4 (C-2), 68.1 (C-4), 60.4 (C-6, C-6′), 46.0 (CH_2), assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 573 $[M - H]^-$. HRMS: calcd for $C_{19}H_{30}N_2O_{14}S_2Na$, 597.1031; found, 597.1059.

***N*-4-(Aminosulfonyl)benzyl-*S*-(1-thio-β-lactosyl)sulfonamide (17).** Sulfonamide **17** was prepared from sulfonamide **12** according to the General Procedure 4. The expected derivative was obtained after freeze-drying as a white highly hygroscopic solid (84% yield); R_f = 0.52 (9:1 CH_3CN/H_2O); $[\alpha]^{25}_D = +53$ (c = 1.0, methanol). ^1H NMR (500 MHz, DM SO-d_6): δ = 7.79 (d, J = 8.5 Hz, 2H, H_{arom}), 7.68 (t, J = 6.0 Hz, 1H, N*H*), 7.52 (d, J = 8.0 Hz, 2H, H_{arom}), 7.31 (s, 2H, NH_2), 5.65 (br s, 1H, O*H*-4′), 5.40 (d, J = 6.0 Hz, 1H, O*H*-2′), 5.32 (d, J = 5.0 Hz, 1H, O*H*-2), 5.05 (d, J = 3.5 Hz, 1H, H-1′), 4.90 (d, J = 5.5 Hz, 1H, O*H*-3), 4.87 (d, J = 4.5 Hz, 1H, O*H*-3′), 4.53 (t, J = 6.0 Hz, 1H, O*H*-6), 4.52 (t, J = 6.0 Hz, 1H, O*H*-6′), 4.29 (m, 2H, CH_2), 4.26 (d, J = 9.5 Hz, 1H, H-1), 3.76 (dd, J = 6.5, 11.0 Hz, 1H, H-6a), 3.64 (m, 1H, H-6a′), 3.59 (m, 1H, H-6b), 3.55 (m, 1H, H-2), 3.53 (m, 1H, H-4′), 3.48 (m, 1H, H-4), 3.45 (m, 1H, H-6b′), 3.40 (m, 1H, H-5), 3.38 (m, 1H, H-3′), 3.35 (m, 1H, H-5′), 3.24 (m, 1H, H-2′), 3.07 (m, 1H, H-3), assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 142.9, 142.8 (C_{arom}), 127.8, 125.6 (CH_{arom}), 100.7 (C-1′), 89.6 (C-1), 79.3 (C-5), 78.8 (C-5′), 77.1 (C-4′), 73.5 (C-4), 73.2 (C-3′), 72.4 (C-2′), 70.2 (C-2), 69.9 (C-3), 60.8(C-6′), 60.6 (C-6), 46.0 (CH_2), assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 573 $[M - H]^-$. HRMS: calcd for $C_{19}H_{30}N_2O_{14}S_2Na$, 597.1031; found, 597.1043.

***N*-(4-Aminosulfonyl)phenethyl-*S*-(1-thio-β-D-glucopyranosyl-sulfonamide (28).** Sulfonamide **28** was prepared from sulfonamide **23** according to the General Procedure 4. The expected derivative was obtained after freeze-drying as a white highly hygroscopic solid (96% yield); R_f = 0.38 (95:5 CH_3CN/H_2O); $[\alpha]^{25}_D = -16$ (c = 1.0, methanol). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.74 (d, J = 8.5 Hz, 2H, H_{arom}), 7.41 (d, J = 8.0 Hz, 2H, H_{arom}), 7.27 (s, 2H, NH_2), 7.05 (t, J = 6.0 Hz, 1H, N*H*), 5.12 (d, J = 4.5 Hz, 1H, O*H*), 5.11 (d, J = 1.0 Hz, 1H, O*H*), 5.04 (d, J = 6.5 Hz, 1H, O*H*), 4.49 (t, J = 6.0 Hz, 1H, O*H*-6), 4.24 (d, J = 9.5 Hz, 1H, H-1), 3.69 (dd, J = 1.5, 12.0 Hz, 1H, H-6a), 3.46 (m, 1H, H-6b), 3.42 (m, 1H, H-2), 3.28−3.23 (m, 4H, H-3, H-5, $NHCH_2CH_2$), 3.05 (dt, J = 5.5, 9.5 Hz, 1H, H-4), 2.84 (t, J = 7.0 Hz, 2H, $NHCH_2CH_2$), assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 142.2, 142.1 (C_{arom}), 129.2, 125.6 (CH_{arom}), 89.2 (C-1), 81.1 (C-5), 77.4 (C-3), 70.5 (C-2), 69.7 (C-4), 61.1 (C-6), 43.8 ($NHCH_2CH_2$), 35.7 ($NHCH_2CH_2$), assignments were confirmed by $^1H-^{13}C$ HSQC.

LRMS (ESI$^+$): m/z = 449 [M + Na]$^+$. HRMS: calcd for $C_{14}H_{28}N_2O_9S_2Na$, 449.0659; found, 449.0680.

***N*-(4-Aminosulfonyl)phenethyl-*S*-(1-thio-β-D-galactopyranosyl)-sulfonamide (29).** Sulfonamide **29** was prepared from sulfonamide **24** according to the General Procedure 4. The expected derivative was obtained after freeze-drying as a white solid (75% yield); R_f = 0.53 (9:1 CH_3CN/H_2O); mp = 185 °C; $[\alpha]^{25}_D$ = −2 (c = 1.0, methanol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.74 (d, J = 8.0 Hz, 2H, H_{arom}), 7.41 (d, J = 8.0 Hz, 2H, H_{arom}), 7.27 (s, 2H, NH_2), 7.06 (br s, 1H, NH), 4.90 (d, J = 5.5 Hz, 1H, OH-3), 4.87 (d, J = 4.5 Hz, 1H, OH-2), 4.57 (m, 1H, OH-6), 4.56 (m, 1H, OH-4), 4.17 (d, J = 9.5 Hz, 1H, H-1), 3.69 (dt, J = 4.5, 9.0 Hz, 1H, H-2), 3.69 (t, J = 3.5 Hz, 1H, H-4), 3.53 (m, 3H, H-5, H-6a, H-6b), 3.40 (m, 1H, H-3), 3.25 (br t, J = 7.0 Hz, 1H, NHCH_2CH$_2$), 2.84 (t, J = 7.0 Hz, 2H, NHCH$_2$CH_2), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 142.2, 142.1 (C_{arom}), 129.2, 125.6 (CH_{arom}), 90.2 (C-1), 79.7 (C-5), 74.0 (C-3), 68.0 (C-4), 67.3 (C-2), 60.4 (C-6), 43.9 (NHCH_2CH$_2$), 35.7 (NHCH$_2$-CH_2), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 425 [M − H]$^-$. HRMS: calcd for $C_{14}H_{22}N_2O_9S_2Na$, 449.0659; found, 449.0668.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(1-thio-β-maltosyl)sulfonamide (30).** Sulfonamide **30** was prepared from sulfonamide **25** according to the General Procedure 4. The expected derivative was obtained after freeze-drying as a yellow gum (60% yield); R_f = 0.12 (9:1 CH_3CN/H_2O); $[\alpha]^{25}_D$ = −23 (c = 1.1, methanol). ^{1}H NMR (500 MHz, D_2O): δ = 7.94 (d, J = 8.0 Hz, 2H, H_{arom}), 7.57 (d, J = 8.5 Hz, 2H, H_{arom}), 4.46 (d, J = 9.5 Hz, 1H, H-1), 3.98 (d, J = 9.5 Hz, 1H, H-5), 3.78 (br t, J = 9.0 Hz, 1H, H-2), 3.62 (m, 1H, H-4), 3.59 (m, 1H, H-3), 3.57 (m, 2H, NHCH_2-CH$_2$), 3.02 (t, J = 8.5 Hz, 2H, NHCH$_2$CH_2), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.7 (CO_2H), 143.1, 142.1 (C_{arom}), 129.1, 125.6 (CH_{arom}), 89.9 (C-1), 78.9 (C-5), 76.8 (C-3), 71.0 (C-4), 70.4 (C-2), 43.9 (NHCH_2CH$_2$), 35.8 (NHCH$_2$CH_2), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^-$): m/z = 439 [M − H]$^-$. HRMS: calcd for $C_{14}H_{20}N_2O_{10}S_2Na$, 463.0452; found, 463.0460.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(1-thio-β-maltosyl)sulfonamide (31).** Sulfonamide **31** was prepared from sulfonamide **26** according to the General Procedure 4. The expected derivative was obtained after freeze-drying as a slightly yellow gum (77% yield); R_f = 0.15 (9:1 CH_3CN/H_2O); $[\alpha]^{25}_D$ = 0 (c = 1.0, methanol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.74 (d, J = 8.0 Hz, 2H, H_{arom}), 7.41 (d, J = 8.0 Hz, 2H, H_{arom}), 7.27 (s, 2H, NH_2), 7.08 (t, J = 6.0 Hz, 1H, NH), 5.33 (d, J = 6.0 Hz, 1H, OH-2), 5.08 (d, J = 4.0 Hz, 1H, OH-2′), 4.83 (d, J = 1.5 Hz, 1H, OH-3), 4.76 (d, J = 4.0 Hz, 1H, OH-3′), 4.68 (t, J = 5.0 Hz, 1H, OH-6′), 4.58 (t, J = 6.0 Hz, 1H, OH-6), 4.50 (d, J = 4.0 Hz, 1H, OH-4′), 4.32 (d, J = 9.5 Hz, 1H, H-1), 4.20 (d, J = 7.0 Hz, 1H, H-1), 3.80 (dd, J = 6.0, 10.0 Hz, 1H, H-6a), 3.62 (m, 2H, H-6b, H-4′), 3.52−3.45 (m, 6H, H-2, H-3, H-4, H-5′, H-6a′, H-6b′), 3.32−3.28 (m, 3H, H-2′, H-3′, H-5), 3.25 (m, 2H, NHCH_2CH$_2$), 2.84 (t, J = 8.0 Hz, 2H, NHCH$_2$CH_2), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 143.2, 142.1 (C_{arom}), 129.3, 125.7 (CH_{arom}), 103.8 (C-1′), 88.7 (C-1), 80.0 (C-5), 79.1 (C-5′), 75.7 (C-4′), 75.6 (C-3), 73.3 (C-3′), 70.6 (C-2′), 70.4 (C-2), 68.2 (C-4), 60.5 (2C) (C-6, C-6′), 43.9 (NHCH_2CH$_2$), 35.8 (NHCH$_2$CH_2), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 587 [M − H]$^-$. HRMS: calcd for $C_{20}H_{32}N_2O_{14}S_2Na$, 611.1187; found, 611.1201.

***N*-4-(Aminosulfonyl)phenethyl-*S*-(1-thio-β-lactosyl)sulfonamide (32).** Sulfonamide **32** was prepared from sulfonamide **27** according to the General Procedure 4. The expected derivative was obtained after freeze-drying as a slightly yellow gum (84% yield); R_f = 0.17 (9:1 CH_3CN/H_2O); $[\alpha]^{25}_D$ = +46 (c = 1.1, methanol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.75 (d, J = 8.5 Hz, 2H, H_{arom}), 7.41 (d, J = 8.5 Hz, 2H, H_{arom}), 7.27 (s, 2H, NH_2), 7.11 (t, J = 6.0 Hz, 1H, NH), 5.62 (d, J = 3.5 Hz, 1H, OH-4′), 5.39 (d, J = 6.0 Hz, 1H, OH-2′), 5.26 (d, J = 6.0 Hz, 1H, OH-2), 5.04 (d, J = 3.5 Hz, 1H, H-1′), 4.89 (d, J = 6.0 Hz, 1H, OH-3), 4.86 (d, J = 5.0 Hz, 1H, OH-3′), 4.52 (t, J = 5.0 Hz, 1H, OH-6′), 4.48 (t, J = 6.0 Hz, 1H, OH-6), 4.32 (d, J = 8.5 Hz, 1H, H-1), 3.75 (dd, J = 7.0, 10.5 Hz, 1H, H-6a), 3.63 (dd, J = 5.5, 9.5 Hz, 1H, H-6a′), 3.57 (m, 1H, H-6b), 3.52−3.47 (m, 2H, H-2, H-4′), 3.48−3.44 (m, 3H, H-4, H-5′, H-6b′), 3.38−3.34 (m, 2H, H-5, H-3′), 3.27−3.22 (m, 3H, H-2′, NHCH_2CH$_2$), 3.06 (m, 1H, H-3), 2.84 (t, J = 7.5 Hz, 2H, NHCH$_2$CH_2), assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 143.1, 142.1 (C_{arom}), 129.2, 125.6 (CH_{arom}), 100.7 (C-1′), 88.8 (C-1), 79.2 (C-5′), 79.0 (C-5), 77.0 (C-4′), 73.5 (C-4), 73.2 (C-3′), 72.4 (C-2′), 70.2 (C-2), 69.9 (C-3), 60.8 (C-6′), 60.7 (C-6), 43.8 (NHCH_2CH$_2$), 35.7 (NHCH$_2$CH_2), assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI$^+$): m/z = 587 [M − H]$^-$. HRMS: calcd for $C_{20}H_{32}N_2O_{14}S_2Na$, 611.1187; found, 611.1188.

Carbonic Anhydrase Inhibition Assay. An SX.18MV-R Applied Photophysics stopped-flow instrument was used for assaying the CA I, II, and IX CO_2 hydration activity.[27] 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 $NaClO_4$ (for maintaining constant the 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 performed with the assay buffer mentioned above. Inhibitor and enzyme solutions were preincubated together for 15 min at room temperature prior to assay in order 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 and represent the mean from at least three different determinations. Enzyme concentrations were 10 nM for CA I and CA II, 14 nM for CA IX, and 0.11 μM for hCA XII. Kinetic parameters and inhibition constants were calculated as described previously.[37,38] Enzymes used here were recombinant ones, prepared and purified as described earlier.[37,38]

Conclusions

Recent experimental evidence has implicated CAs as a drug target with promising potential for the development of much needed personalized cancer therapies targeting hard-to-treat hypoxic tumors. Here we have developed a novel and straightforward method for the stereoselective synthesis of small molecule sulfonamide-linked neoglycoconjugates. In these compounds, the carbohydrate fragment is linked to the classical aromatic sulfonamide CA pharmacophore to target inhibition of cancer-associated CAs. The synthesis has been achieved by reaction of *S*-glycosyl acetates with either an aminobenzyl or aminophenethyl sulfonamide scaffold to form *S*-glycosylsulfenamide glycoconjugates, which are then oxidized to give robust *S*-glycosyl sulfonamide linked glycoconjugates.

The CA inhibitors of this study are designed in accord with a combined SAR−SPR strategy and compounds were very good CA IX inhibitors and potent CA XII inhibitors. The role of the carbohydrate fragment is of most relevance in the context of *selectively* targeting the *extracellular* active sites of CA IX and XII. The sugar group takes advantage of the cell membranes lipophilic properties as a physical barrier to

minimize passive membrane permeability of the polar small molecule inhibitors, this in turn can promote the preferential inhibition of extracellular CAs. Our approach has delivered neutral, water-soluble CA inhibitors that have excellent potential as isozyme selective inhibitors of cancer-associated CAs in vivo and represents an important outcome for investigating future therapeutic applications of CA inhibitors.

Finally, our results also showcase new chemistry toward *S*-glycosyl secondary sulfonamides. This chemistry is straightforward and synthetically tractable, needing only a primary amine functional group in the molecule of interest and a *S*-glycosyl acetate partner. We believe this chemistry may readily be applied toward the synthesis of diverse range of therapeutically relevant neoglycoconjugates and thus will have significant impact across broad areas of medicinal chemistry and chemistry.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for new compounds **3**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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