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Design, Synthesis, and Biological Evaluation of Novel Carbohydrate-Based Sulfamates as Carbonic Anhydrase Inhibitors

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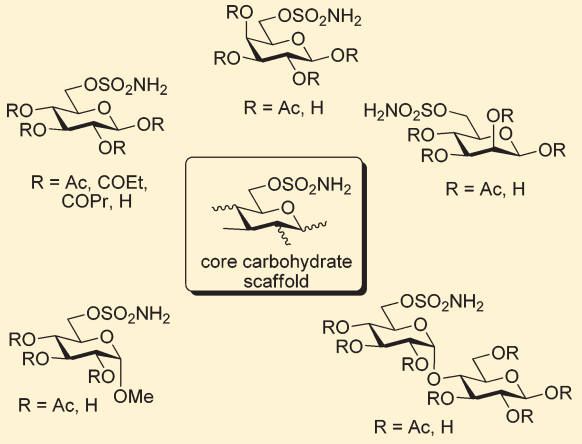
Supporting Information

ABSTRACT: Carbonic anhydrases (CAs) IX and XII are enzymes with newly validated potential for the development of personalized, first-in-class cancer chemotherapies. Here we present the design and synthesis of novel carbohydrate-based CA inhibitors, several of which were very efficient inhibitors (K_i<10 nM) with good selectivity for cancer-associated CA isozymes over off-target CA isozymes. All inhibitors comprised a carbohydrate core with one hydroxyl group derivatized as a sulfamate. Five different carbohydrates were chosen to present a selection of molecular shapes with subtle stereochemical differences to the CA enzymes active site. Variable modifications of the remaining sugar hydroxyl groups were incorporated to provide an incremental coverage of chemical property parameters that are associated with biopharmaceutical performance. All sulfamate inhibitors displayed ligand efficiencies that are consistent with those reported for good drug lead candidates.



INTRODUCTION

Carbonic anhydrases (CAs, EC 4.2.1.1) are zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide (CO_2) to generate bicarbonate anion (HCO_3^-) and a proton (H^+) (Scheme 1).[1,2] This equilibrium contributes to a range of physiological functions that involve the production, transport, or consumption of CO_2, H^+, and HCO_3^-.[1] CA isozymes IX and XII are transmembrane enzymes with an extracellularly oriented active site. They are predominantly expressed in poorly vascularized hypoxic tumors and have minimal expression in healthy cells.[3] Tumor cells experience elevated metabolism, and thus increased acid production, compared to healthy cells.[3−6] If this acid load is allowed to accumulate, then intracellular pH (pH_i) would fall and disrupt critical biological functions. Recent evidence has demonstrated that cell-generated CO_2, in addition to lactic acid, is predominantly responsible for the removal of excess acid from tumor cells.[4] CO_2 is freely membrane permeable and rapidly exits metabolically active tumor cells via passive diffusion.[5] The role of CAs IX and XII is to catalyze the hydration of tumor generated CO_2 to form HCO_3^- and H^+ (Scheme 1). The net effect is to trap H^+ extracellularly, lowering extracellular pH (pH_e) while maintaining normal pH_i.[3−5] This process favors tumor growth and invasion, allowing hypoxic tumor cells to survive and proliferate.[4,7]

Scheme 1. Endogenous Reaction Catalyzed by Carbonic Anhydrases

$$CO_2 + H_2O \leftrightarrows HCO_3^- + H^+$$

The importance of modulating pH in the hypoxic tumor microenvironment underpins a strong case to develop well designed small-molecule inhibitors of CAs IX and XII for application as chemical probes. These compounds are needed to appraise the potential of cancer-associated CAs as a possible mode for therapeutic intervention in cancer.[1,8] The extracellular active site location of CAs IX and XII together with their expression in hypoxic cancer cells (overexpression) compared to healthy cells (minimal expression) improves the odds for the development of tumor selective CA inhibitors.

The implied target for small molecule drug design of CA inhibitors is the CA active site Zn^{2+} cation, and both sulfonamide ($-SO_2NH_2$) and, less frequently, sulfamate ($-OSO_2NH_2$) zinc binding groups feature in the structures of many small molecule CA inhibitors.[1,9] In the past few years our group has established a

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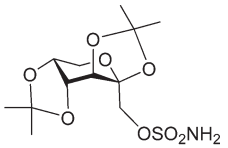
novel approach to targeting the inhibition of CAs IX and XII using carbohydrate-based small molecules.[10−15] Druglike carbohydrate-based molecules are now viewed as a vast but relatively untapped source of potential new therapeutics.[16,17] We have demonstrated that through appending sugar moieties to the Ar-SO_2NH_2 zinc binding pharmacophore of classical CA inhibitors we were able to deliver potent inhibitors for CAs IX and XII in vitro.[18] More recently we reported a new class of compound that incorporates a sulfonamide moiety directly attached to the anomeric center of a mono- or disaccharide, i.e., [sugar]-SO_2NH_2.[19] The value of these anomeric sulfonamides was 3-fold. First, they were novel chemical entities. Second, they lacked the classical aromatic component of classical CA inhibitors, and third, they allowed us to tune the physicochemical properties of the inhibitor toward selective inhibition of CAs IX and XII owing to the glycoconjugates compromised ability to diffuse across cell membranes. The CA inhibition activity of these compounds was, however, only moderate with K_is in the micromolar range. In the present contribution we extend our focus on modulating structure−property relationships (SPRs) of CA inhibitors while delivering novel compounds with good CA inhibition activity and isozyme selectivity. Specifically we present the design, synthesis, and biological evaluation of carbohydrate-based sulfamates of the motif [sugar]-OSO_2NH_2.

RESULTS AND DISCUSSION

Compound Design. Topiramate (2,3:4,5-bis-*O*-(1-methylethy1idene)-6-D-fructopyranosyl sulfamate, TPM) is a billion dollar drug that is marketed worldwide for the treatment of epilepsy and migraine.[20] TPM is a fructose sulfamate and is an excellent inhibitor of CAs in vitro.[21] The chemical structure of TPM has two isopropylidene groups masking four secondary hydroxyl groups, with the primary hydroxyl group sulfamoylated (Figure 1).



Topiramate (TPM)

Figure 1. Structure of topiramate, a fructose sulfamate CA inhibitor.

The sulfamate compounds **7**−**18** of this study were derived from the monosaccharides D-glucose, D-galactose, D-mannose, and methyl α-glucopyranoside and the disaccharide maltose (Figure 2a). The sulfamate group is on the C-6 (or C-6′ for maltose) primary hydroxyl group. Compounds **13** and **18** are methyl glycosides, while the remaining hydroxyls of compounds are either acylated (**7**−**13**) or fully deprotected to provide free sugars (**14**−**18**).

In addition to inspiration from the impressive pharmaceutical pedigree of the carbohydrate−sulfamate drug TPM, the design principle toward the target molecules **7**−**18** was to develop a family of compounds that provided incremental coverage of chemical property space. The application of esters as a prodrug strategy to mask polar hydroxyl groups is prevalent across medicinal chemistry and chemical biology.[22] Such prodrugs take advantage of hydrolysis by nonspecific esterases to unmask the hydroxyl groups in vivo, the prodrugs often survive the GI tract and may be absorbed into the bloodstream where they are hydrolyzed by plasma enzymes.[23] Esterification of the hydroxyl groups of carbohydrates has been used to modulate the membrane permeability and downstream activity of carbohydrate-based molecules.[24,25] In this study we explore the acetyl, propionyl, and butryl acyl groups; each is expected to be substrates of esterases. The five different sugar types of this study were chosen to present a selection of molecular shapes with subtle stereochemical differences to the CA enzyme active site and contribute to building valuable SAR. This is demonstrated by an overlay of stick models of sulfamates **7**, **10**, **12**, and **13** (Figure 2b). All compounds **7**−**18** preserve the sulfamate zinc binding group that is critical for good CA inhibition.

Chemical Synthesis. The carbohydrate sulfamate compounds **7**−**18** of this study were derived from commercially available monosaccharides D-glucose, D-galactose, D-mannose, and methyl α-glucopyranoside and the disaccharide maltose. The synthetic route to the monosaccharide sulfamates is presented in Scheme 2. The regioselective protection of the 6-position of the monosaccharides was achieved by reaction with trityl chloride in pyridine to introduce a trityl group, shown for D-glucose in Scheme 2.[26] The remaining secondary hydroxyl groups were then acylated with acetic anhydride, propionic anhydride, or butyric anhydride to give **1**, **2**, or **3**, respectively. A mixture of α- and β-anomers was obtained with D-glucose, D-galactose, and D-mannose, from which the β-anomer was either separated or carried through the detritylation step as a mixture of anomers, then separated. The α/β ratio was dependent both on the glycosyl residue and on the nature of the protecting group. The trityl ether protecting groups were removed with NaI/TMSCl to unmask the C-6 primary hydroxyl groups, providing precursor compounds **4**−**6**. The yield for detritylation using this method is low compared to more traditional conditions; however, these reagents avoid acyl group migration and the associated mixture of products.[27,28] Selective sulfamoylation of the now free C-6 hydroxyl groups of **4**−**6** with sulfamoyl chloride (generated in situ from formic acid and chlorosulfonylisocyanate) gave target sulfamates **7**−**9**.[29] Lastly, the *O*-acetate groups of the carbohydrate moiety of the sulfamates were removed using Zemplen's conditions[30] to liberate the fully deprotected sugar analogue **14** as a mixture of anomers. Sulfamates **10**, **11**, **13**, **15**, **16**, and **18** were prepared similarly to Scheme 2.

The synthesis of the target maltose sulfamates **12** and **17** followed an analogous strategy to the monosaccharides; however, several additional steps were needed to accommodate selectivity in the presence of the two primary alcohols of the disaccharide (Scheme 3). First the 4′,6′-*O*-benzylidene acetal of maltose is prepared, and the remaining six hydroxyl groups were acetylated. Removal of the benzylidene acetal with aqueous acetic acid provides a diol precursor that is manipulated similarly to the procedure outlined for the monosaccharides. All target sulfamates **7**−**18** were spectroscopically characterized using 1D and 2D NMR (^1H, ^{13}C, gCOSY, gHSQC). The characterization data were consistent with the target structures, with a characteristic broad singlet for the sulfamate protons (O-SO_2NH_2) for all compounds observed at δ 7.40−7.60 ppm in DMSO-d_6.

Carbonic Anhydrase Inhibition. The enzyme inhibition data for sulfamates **7**−**18** as well as the sulfamate drug TPM were determined by assaying the CA catalyzed hydration of CO_2 (Table 1).[31] Enzyme inhibition data for the physiologically dominant CAs I and II and tumor-associated CAs IX and XII

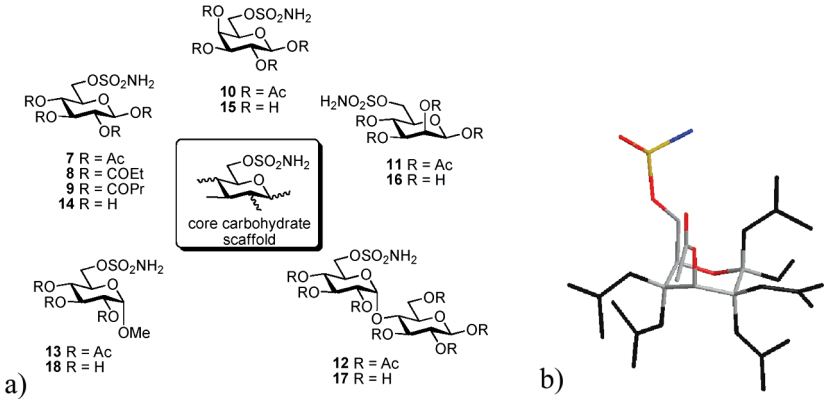
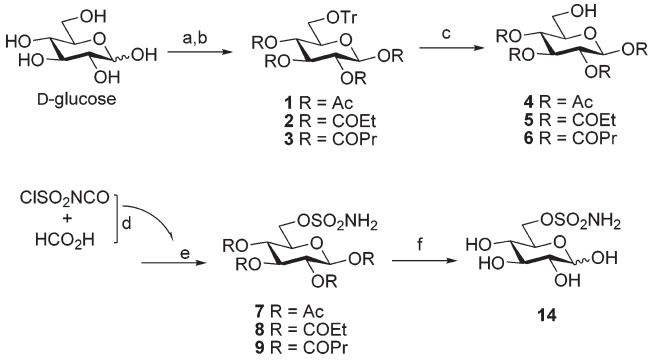


Figure 2. (a) Target carbohydrate sulfamates. (b) Overlay of stick models of sulfamates **7**, **10**, **12**, and **13**. Common scaffold is colored by atom type (red, gray, blue and yellow). Variable acetate groups are colored black.

Scheme 2. Synthetic Route to Target Monosaccharide Sulfamates, Shown for D-Glucose Derivatives 7−9 and 14[a]



[a] Reagents and conditions: (a) Ph_3CCl, pyridine, 80 °C, 1.5 h; (b) R_2O, H_2O, 0 °C, 1 h, yield over two steps 37−59%; (c) TMSCl, NaI, MeCN, 0 °C, then $Na_2S_2O_3$, 19−57%; (d) HCO_2H, $ClSO_2NCO$, 0 °C to room temp, 30 min; (e) $ClSO_2NH_2$ from (d), DMA, 0 °C to room temp, 1 h, yield over two steps 26−70%; (f) compound **7**, MeONa, MeOH, room temp, 1 h, 71%.

were obtained. Isozyme selectivity ratios for **7**−**18** and TPM are also provided (Table 1).

Off-Target CA Isozyme I. The sulfamate compounds were micromolar inhibitors of the off-target CA I isozyme, with K_is ranging from 0.86 to 12.6 μM. Inhibition at CA I is weaker than for the other CA isozymes. The TPM inhibition profile behaves similarly, also showing poorer inhibition of CA I (K_i = 250 nM) than for the other CA isozymes. The structural variability provided by the three different acyl groups had no remarkable impact on structure−activity relationships (SAR) at CA I with the K_i values for acetyl **7** (K_i = 4.6 μM), propionyl **8** (K_i = 3.4 μM), and butryl **9** (K_i = 5.6 μM) glucose sulfamates being similar. Notable, however, was that the free sugar glucose analogue **14** was a better CA I inhibitor (K_i = 1.2 μM) than the acylated analogues **7**−**9**. The disaccharide maltose derivatives **12** (K_i = 12.6 μM) and **17** (K_i = 8.75 μM) were weaker inhibitors than the monosaccharides.

Off-Target CA Isozyme II. CA II is a much more efficient enzyme than CA I, and inhibition of this isozyme is largely responsible for side effects associated with clinically used CA inhibitors.[1] TPM is a very potent CA II inhibitor with a K_i of 5.0 nM. Compound **11**, the acetylated mannose derivative, was the only potent CA II inhibitor of the novel sulfamates (K_i = 11.3 nM). The remaining monosaccharide sulfamates were moderately active at this off-target enzyme, with K_i ranging from 66 to 307 nM. Given that the sole structural difference between compound **11** and compounds **7** and **10** is the stereochemistry of one position on the monosaccharide moiety, this is intriguing SAR that may assist to identify further opportunities in CA inhibitor design. As for CA I, the maltose derivatives **12** (K_i = 754 nM) and **17** (K_i = 513 nM) were the weakest inhibitors at CA II, while the three different acyl groups of **7**−**9** also had little impact on SAR at CA II.

Cancer-Associated CA Isozymes IX and XII. Sulfamates **11**, **13**, **14**, and **18** were good CA IX inhibitors with inhibition constants clustered below 10 nM (K_i = 7.9−9.0 nM) with very good selectivity over the off-target CA I (124- to 674-fold) and up to 14-fold selectivity against CA II. The latter is very good and contrasts with the behavior of TPM, which is nonselective for CA II. At hCA IX compounds **7**−**10**, **15**, and **16** had K_is ranging from 53 to 86 nM similar to TPM (K_i of 58 nM). These compounds generally had good selectivity over CA I (up to 112-fold) but were nonselective over CA II. At CA XII sulfamates were generally more effective inhibitors than for other isozymes, with K_is for compounds **13**−**16** ranging from 7.3 to 9.5 nM, compared to TPM with a K_i of 3.8 nM. Compounds **10** and **14**−**16** had >10-fold selectivity over CA II and >70-fold selectivity over CA I. With the exception of **14**, these compounds were also selective over CA IX (5.6- to 8.2-fold), a property that is likely to prove valuable for applications as chemical probes. Compounds **7**−**9** and **18** were moderate CA XII inhibitors with K_is ranging from 85 to 96 nM. These compounds had good selectivity over CA I but were nonselective compared to CA II inhibition.

Comparison with Anomeric Sulfonamides. Recently we reported the CA inhibition properties of *S*-glycosyl primary sulfonamides.[19,32] These were a new class of compound wherein a primary sulfonamide moiety was directly bonded to a stereochemically rich carbohydrate scaffold, notably without an intervening aromatic moiety. The enzyme inhibition data and isozyme selectivity ratios for glucose, galactose, and maltose anomeric sulfonamides **19**−**24** at CAs I, II, IX, and XII are provided in Table 2. When the anomeric sulfonamides **19**−**24** are compared with their corresponding sulfamates **7**, **14**, **10**, **15**, **12**, and **17**, it is readily apparent that the sulfamates are far superior CA inhibitors at CAs II, IX, and XII while both groups of compounds are weak CA I inhibitors. As well, the anomeric

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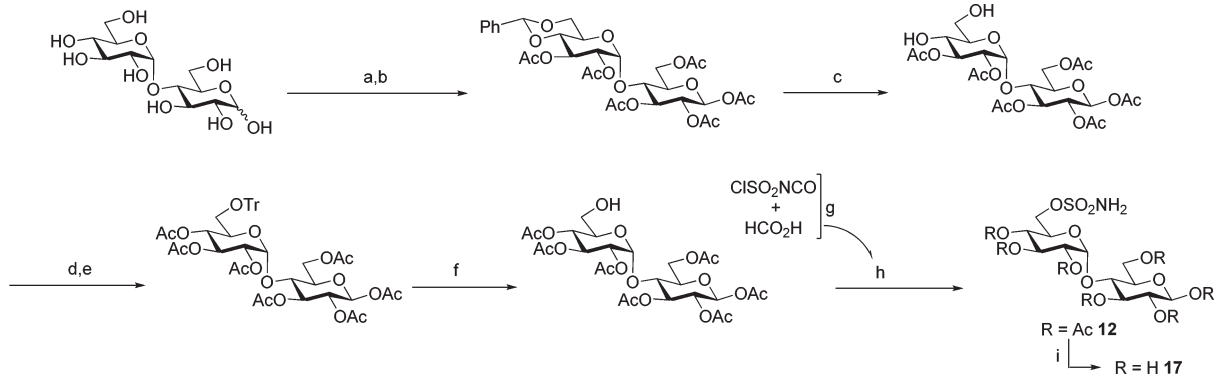
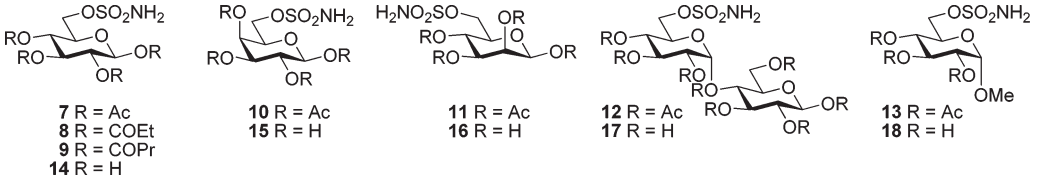
Scheme 3. Synthetic Route To Target Disaccharide Sulfamates 12 and 17 Starting from Commercially Available Maltose[a]



[a] Reagents and conditions: (a) α,α′-dimethoxytoluene, *p*-TSA, DMF, 40 °C, 40 mbar; (b) Ac_2O, NaOAc, reflux, 0.5 h, yield over two steps 72% (β-anomer); (c) 80% $AcOH_{aq}$, room temp, 30 min, 46%; (d) Ph_3CCl, pyridine, 80 °C, 1.5 h; (e) Ac_2O, H_2O, 0 °C, 1 h, yield over two steps 81%; (f) TMSCl, NaI, MeCN, 0 °C, then $Na_2S_2O_3$, 60%; (g) HCO_2H, $ClSO_2NCO$, 0 °C to room temp, 30 min; (h) $ClSO_2NH_2$ from (g), DMA, 0 °C to room temp, 1 h, yield over two steps 50%; (i) MeONa, MeOH, room temp, 1 h, 37%.

Table 1. Inhibition and Isozyme Selectivity Ratio Data of hCA Isozymes I, II, IX, and XII with Sulfamates 7−18, and the Carbohydrate Sulfamate Drug TPM



	K_i (nM)[a]				selectivity ratio[d]			
compd	CA I[b]	CA II[b]	CA IX[c]	CA XII[c]	I/IX	I/XII	II/IX	II/XII
TPM[e]	250	5.0	58	3.8	4.3	65.8	0.1	1.3
7	4610	307	73	85	63.2	54.2	4.2	3.6
8	3360	105	77	96	43.6	35.0	1.4	1.1
9	5640	114	86	87	65.6	64.8	1.3	1.3
10	860	106	75	9.5	11.5	90.5	1.4	11.2
11	970	11.3	7.8	8.4	124.4	115.5	1.5	1.4
12	12600	754	631	145	20.0	96.9	1.2	5.2
13	5660	66	8.4	7.6	673.8	744.7	7.9	8.7
14	1180	82	8.6	7.3	137.2	161.6	9.5	11.2
15	4500	93	62	7.6	72.6	592.1	1.5	12.2
16	5960	104	53	9.5	112.5	627.4	1.97	10.9
17	8750	513	497	138	17.6	63.4	1.0	3.7
18	1190	129	9.0	93	132.2	12.8	14.3	1.4

[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. [d] These are K_i ratios and are indicative of isozyme selectivity in vitro. [e] The values for TPM are consistent with those of previous reports.[18]

sulfonamides showed no isozyme selectivity, while the reverse is true for the C-6 sulfamates, some of which display excellent selectivity for the cancer-associated CAs. Using protein X-ray crystallography, we demonstrated that the shape of the anomeric sulfonamide ligands resulted in less than optimal CA active site interactions.[19] The design of the new compounds of this study addresses this limitation and has provided better performing compounds.

Structure−Property Relationships (SPR). The incorporation of variable acyl protecting groups onto the carbohydrate core of glucose derivatives **7**−**9**, **13**, **14**, and **18** has encapsulated a range of log *P* and topological polar surface area (TPSA) values (Table 3). Manipulating these physicochemical parameters is a useful way to refine druggability, and notably this coverage of chemical property space was achieved with retention of the underlying glucose sulfamate core.[33,34] Values for TPSA, calculated log *P* (cLogP), molecular weight (MW), and ligand efficiency (LE) for TPM and all glucose sulfamates are provided in Table 3. TPSA is a descriptor for characterizing lipid membrane

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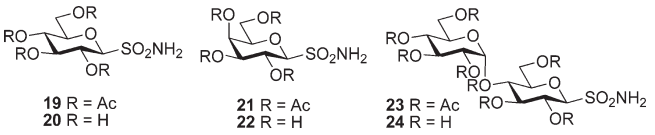
Table 2. Inhibition and Isozyme Selectivity Ratio Data of hCA Isozymes I, II, IX, and XII with Anomeric Sulfonamides 19−24[19]



	K_i (nM)[a]				selectivity ratio[d]			
compd	CA I[b]	CA II[b]	CA IX[c]	CA XII[c]	I/IX	I/XII	II/IX	II/XII
19	4530	4500	3910	4660	1.15	0.97	1.15	0.97
20	3900	4910	4050	4690	0.96	0.83	1.21	1.05
21	4340	4350	4150	4710	1.05	0.92	1.05	0.92
22	3710	4550	4190	4800	0.89	0.77	1.09	0.95
23	4120	4980	4080	4610	1.01	0.89	1.22	1.08
24	4150	4100	4220	4840	0.98	0.86	0.97	0.85

[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. [d] These are K_i ratios and are indicative of isozyme selectivity in vitro.

Table 3. Calculated Properties for TPM and Glucose Sulfamate Derivatives 7−9, 13, 14, and 18

compd	cLogP[a]	TPSA (Å^2)[b]	MW (Da)	$LE_{(CA\ IX)}$[c]	$LE_{(CA\ XII)}$[c]
TPM	+0.04	116	339.4	21.3	24.8
7	−0.72	184	427.4	16.7	16.6
8	+1.40	184	483.5	14.7	14.5
9	+3.52	184	539.6	13.1	13.1
13	−0.79	167	399.4	17.9	20.4
14	−3.30	160	259.2	31.1	31.4
18	−2.67	149	273.3	20.2	20.3

[a] cLogP data calculated using InstantJChem, version 3.0.4, from ChemAxon. [b] TPSA calculated using ChemBioDraw Ultra, version 11.0. [c] LE calculated using equation LE = pK_i/MW (MW in kDa).[38]

barrier diffusion. Molecules with a TPSA > 140 Å^2 are likely to have a low capacity for penetrating cell membranes, while those with TPSA ≤ 60 Å^2 typically have good passive permeability properties.[35,36] For the glucose sulfamates the calculated TPSA values ranged from 160 to 184 Å^2, which is above the upper limit (140 Å^2) for good passive permeability properties. cLogP values of <0 are indicative of molecules with poor membrane permeability. The cLogP values are consistent with the compound design and provide a broad range that extends from −3.3 for compound **14** (four free hydroxyl groups) to +3.52 for compound **9** (four butyryl protected hydroxyl groups). This again is noteworthy given that the underlying active core structure is retained. The per-*O*-acetylated compounds **7** and **13**, despite no free hydroxyl groups, still have cLogP values of <0 (values of −0.72 and −0.79, respectively), while the propionyl and butyryl protected compounds **8** and **9** have cLogP values of +1.40 and +3.52, respectively. The implications of these values may prove useful for the provision of compounds suited for oral administration. Compounds **8** and **9** are predicted to be orally bioavailable, yet once absorbed, their physicochemical properties altered by esterase activity to give a more polar molecule (compound **14**) that as a consequence selectively targets the extracellular active site of cancer-associated CAs.

LE represents the relationship between a compound's potency and its MW and is now emerging as an important metric to guide drug discovery campaigns. The LE value is indicative of the prospects for druggability properties such as bioavailability, stability, and solubility and permits the comparison of the relative quality of different leads.[37] Perola recently reported an analysis of 60 lead/drug pairs.[38] The findings from this analysis revealed a number of useful threshold values to guide medicinal chemists, notably that 90% of drug leads had LE > 12.4 while 90% of drugs had LE > 14.7. All sulfamates of this study have LE similar to or far exceeding these thresholds at the cancer-associated CAs (Table 3). Compound **14**, a free sugar, represents the core scaffold of all the novel sulfamates of this study and has the highest LE (>30) at both CA IX and CA XII. The other free sugar of this study, compound **18**, was also a very efficient ligand, with LE > 20 at both CA IX and CA XII. The precursors to **14**, compounds **8** and **9**, have LE values of >14 and >13, respectively, indicative of good drug leads and supporting our strategy with masking of the hydroxyl groups.

CONCLUSIONS

Our study has delivered novel, potent, and selective carbohydrate-based sulfamates that inhibit cancer-associated CAs. Compounds comprised a sulfamate zinc binding group appended to the C-6 hydroxyl of a panel of monosaccharides or the C-6′ hydroxyl of maltose. The SAR and SPR properties for these compounds, with variable acyl protecting groups, have provided a new approach to CA inhibitor development. Parent sulfamates are predicted to have good oral bioavailability, yet target selectively the active site of extracellular CAs IX and XII over intracellular CAs once processed by esterases. Collectively this library of carbohydrate-based sulfamates exhibits biopharmaceutical properties that render these compounds potentially valuable for applications as chemical probes in medicinal chemistry.

EXPERIMENTAL SECTION

Chemistry. All starting materials and reagents were purchased from commercial suppliers. 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 with 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 (Davisil) 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 30 °C. For ^{1}H and ^{13}C NMR acquired in $CDCl_3$ chemical shifts (δ) are reported in ppm relative to the solvent residual peak: proton (δ = 7.27 ppm) and carbon (δ = 77.2 ppm), respectively. Chemical shifts for ^{1}H and ^{13}C NMR acquired in DMSO-d_6 are reported in ppm relative to residual solvent proton (δ = 2.50 ppm) and carbon (δ = 39.5 ppm) signals, respectively. 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 measured on a Cole Parmer instrument are reported uncorrected. Low resolution mass spectra were acquired on an Applied Biosystems Pty Ltd. Mariner ESI-TOF mass spectrometer using electrospray as the ionization technique in positive

ion and/or negative ion modes as stated. High resolution mass spectra were performed in positive ion mode on an Apex III Bruker Daltonics 4.7 T Fourier transform mass spectrometer fitted with an Apollo electrospray ionization source. All MS analysis samples were prepared as solutions in methanol. Optical rotations were measured on a Jasco P-1020 polarimeter at 25 °C with Na 589 nm wavelength and a 100 mm cell 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 ELSD (evaporative light scattering detection, Alltech) detection were used. Purity of all compounds proved to be ≥95%. The synthesis of all intermediates was adapted from literature methods and is described in Supporting Information.

General Procedure 1. Synthesis of Sulfamates 7−13.[29,39] The carbohydrate precursor (1.0 equiv) was dried under vacuum and solubilized in anhydrous *N*,*N*-dimethylacetamide (15 equiv) under argon. Sulfamoyl chloride (3.8 equiv) was prepared from formic acid and chlorosufonyl isocyanate at 0 °C in a dry two-neck flask connected to a bubbler and under an anhydrous atmosphere of argon. The alcohol solution was added slowly to the flask containing sulfamoyl chloride. Then the mixture was allowed to warm to room temperature and stirred under argon for 1 h. The crude reaction mixture was diluted in EtOAc, washed with H_2O (×1) and brine (×2). The aqueous fractions were back-extracted with EtOAc (×2), then the organic fractions combined, dried over $MgSO_4$, filtered, and concentrated.

1,2,3,4-Tetra-*O*-acetyl-6-sulfamoyl-*β*-D-glucopyranose (7). The title compound **7** was prepared from 1,2,3,4-tetra-*O*-acetyl-*β*-D-glucopyranose according to general procedure 1. Recrystallization of the crude product from EtOH afforded **7** (67% yield) as white crystals. Mp = 126 °C. $[\alpha]^{25}_D$ +8 (*c* 1.0, chloroform). R_f = 0.58 (3:1 EtOAc/hexane). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.56 (s, 2H, NH_2); 5.98 (d, *J* = 8.5 Hz, 1H, H-1); 5.44 (t, *J* = 9.5 Hz, 1H, H-3); 4.95 (t, *J* = 10.0 Hz, 1H, H-2); 4.94 (t, *J* = 9.5 Hz, 1H, H-4); 4.28 (ddd, *J* = 8.5, 5.5, 2.5 Hz, 1H, H-5); 4.04 (dd, *J* = 11.5, 2.5 Hz, 1H, H-6a); 4.00 (dd, *J* = 11.5, 5.5 Hz, 1H, H-6b); 2.07, 2.01, 2.00, 1.94 (4 × s, 12H, OCOCH_3); assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.5, 169.2, 169.1, 168.7 (4 × $OCOCH_3$); 90.8 (C-1); 71.8 (C-3); 71.4 (C-5); 70.7 (C-4); 67.8 (C-2); 66.6 (C-6); 20.5, 20.4, 20.3, 20.3 (4 × OCOCH_3); assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI^+): *m*/*z* = 450 $[M + Na]^+$. HRMS: calcd for $C_{14}H_{21}NO_{12}SNa^+$ 450.0677; found 450.0657.

1,2,3,4-Tetra-*O*-propionyl-6-sulfamoyl-*β*-D-glucopyranose (8). The title compound **8** was prepared from 1,2,3,4-tetra-*O*-propionyl-*β*-D-glucopyranose according to general procedure 1. Purification of the crude product by flash chromatography (2:3 EtOAc/hexane) afforded **8** (70% yield) as a white solid. Mp =119 °C. $[\alpha]^{25}_D$ = +11 (*c* = 1.0, chloroform). R_f = 0.21 (1:2 EtOAc/hexane). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.55 (s, 2H, NH_2); 6.02 (d, *J* = 8.5 Hz, 1H, H-1); 5.48 (t, *J* = 9.5 Hz, 1H, H-3); 4.98 (t, *J* = 10.0 Hz, 1H, H-2); 4.97 (t, *J* = 9.5 Hz, 1H, H-4); 4.31 (ddd, *J* = 9.5, 5.0, 2.5 Hz, 1H, H-5); 4.03 (dd, *J* = 11.0, 2.5 Hz, 1H, H-6a); 4.00 (dd, *J* = 11.0, 5.5 Hz, 1H, H-6b); 2.36, 2.29, 2.25, 2.19 (4 × m, 8H, $OCOCH_2CH_3$); 1.01, 1.00, 0.98, 0.96 (4 × br t, *J* = 7.5 Hz, 12H, $OCOCH_2CH_3$); assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.5, 169.2, 169.1, 168.7 (4 × OCOEt); 91.2 (C-1); 72.1 (C-3); 71.9 (C-5); 70.4 (C-4); 68.2 (C-2); 67.1 (C-6); 27.2, 27.2, 27.1, 27.1 (4 × $OCOCH_2CH_3$); 9.5, 9.4, 9.3, 9.0 (4 × $OCOCH_2CH_3$); assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI^+): *m*/*z* = 506 $[M + Na]^+$. HRMS: calcd for $C_{18}H_{29}N_1O_{12}SNa^+$ 506.1303; found 506.1290.

1,2,3,4-Tetra-*O*-butyryl-6-sulfamoyl-*β*-D-glucopyranose (9). The title compound **9** was prepared from 1,2,3,4-tetra-*O*-butyryl-*β*-D-glucopyranose according to general procedure 1. Purification of the crude product (1:9 acetone/toluene) afforded the title compound as a mixture of α- and *β*-anomers. A further recrystallization from EtOH afforded the *β*-anomer **9** (26% yield) as white crystals. Mp = 109 °C. $[\alpha]^{25}_D$ +9 (*c* 1.0, chloroform). R_f = 0.25 (1:9 acetone/toluene). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.55 (s, 2H, NH_2); 6.02 (d, *J* = 8.5 Hz, 1H, H-1); 5.50 (t, *J* = 9.5 Hz, 1H, H-3); 4.99 (t, *J* = 9.5 Hz, 2H, H-2, H-4); 4.30 (m, 1H, H-5); 4.03−3.99 (m, 2H, H-6a, H-6b); 2.31, 2.28, 2.22, 2.16 (4 × m, 8H, $OCOCH_2$); 1.54−1.44 (m, 8H, CH_2CH_3); 0.86, 0.84, 0.83, 0.82 (4 × t, *J* = 7.5 Hz, 12H, CH_2CH_3); assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.7, 171.5, 171.3, 171.0 (4 × OCOPr); 90.6 (C-1); 71.5, 71.4 (C-3, C-5); 69.8 (C-4); 67.7 (C-2); 66.6 (C-6); 35.1, 35.1, 35.0, 35.0 (4 × $OCOCH_2$); 17.8, 17.7, 17.6, 17.5 (4 × CH_2CH_3); 13.3, 13.2, 13.1, 13.1 (4 × CH_2CH_3); assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI^+): *m*/*z* = 562 $[M + Na]^+$. HRMS: calcd for $C_{22}H_{37}N_1O_{12}SNa^+$ 562.1929; found 562.1941.

1,2,3,4-Tetra-*O*-acetyl-6-sulfamoyl-*β*-D-galactopyranose (10). The title compound **10** was prepared from 1,2,3,4-tetra-*O*-acetyl-*β*-D-galactopyranose according to general procedure 1. Purification of the crude product by flash chromatography (1:1 EtOAc/hexane) afforded **10** (48% yield) as a white solid. Mp = 154 °C. $[\alpha]^{25}_D$ +14 (*c* 1.0, chloroform). R_f = 0.64 (3:1 EtOAc/hexane). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.60 (s, 2H, NH_2); 5.91 (d, *J* = 8.5 Hz, 1H, H-1); 5.35 (dd, *J* = 10.0, 3.5 Hz, 1H, H-3); 5.33 (br d, *J* = 3.5 Hz, 1H, H-4); 5.09 (dd, *J* = 9.5, 8.5 Hz, 1H, H-2); 4.47 (br t, *J* = 6.0 Hz, 1H, H-5); 4.04−3.99 (m, 2H, H-6a, H-6b); 2.13, 2.07, 2.02, 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 = 169.8, 169.5, 169.3, 168.8 (4 × $OCOCH_3$); 91.3 (C-1); 71.0 (C-5); 69.9 (C-3); 67.6 (C-2); 67.2 (C-4); 66.2 (C-6); 20.5, 20.4, 20.4, 20.3 (4 × $OCOCH_3$); assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI^+): *m*/*z* = 445 $[M + NH_4]^+$, 450 $[M + Na]^+$. HRMS: calcd for $C_{14}H_{21}NO_{12}SNa^+$ 450.0677; found 450.0678.

1,2,3,4-Tetra-*O*-acetyl-6-sulfamoyl-*β*-D-mannopyranose (11). The title compound **11** was prepared from 1,2,3,4-tetra-*O*-acetyl-*β*-D-mannopyranose according to general procedure 1. Purification by flash chromatography (1:1 EtOAc/hexane) afforded **5** (15% yield) as a colorless oil. $[\alpha]^{25}_D$ −15 (*c* 1.0, chloroform). R_f = 0.58 (3:1 EtOAc/hexane). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.57 (s, 2H, NH_2); 6.12 (br s, 1H, H-1); 5.38 (dd, *J* = 10.0, 3.5 Hz, 1H, H-3); 5.37 (br d, *J* = 3.5 Hz, 1H, H-2); 5.02 (t, *J* = 10.0 Hz, 1H, H-4); 4.15 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H, H-5); 4.05−4.00 (m, 2H, H-6a, H-6b); 2.15 (s, 3H, OCOCH_3); 2.04 (s, 6H, 2 × $OCOCH_3$); 1.94 (s, 3H, OCOCH_3); assignments were confirmed by ^{1}H−^{1}H gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.8, 169.4, 169.4, 168.1 (4 × $OCOCH_3$); 90.1 (C-1); 71.6 (C-5); 69.8 (C-3); 67.9 (C-2); 66.8 (C-6); 65.2 (C-4); 20.7, 20.4, 20.4, 20.3 (4 × $OCOCH_3$); assignments were confirmed by ^{1}H−^{13}C HSQC. LRMS (ESI^+): *m*/*z* = 445 $[M + NH_4]^+$, 450 $[M + Na]^+$. HRMS: calcd for $C_{14}H_{21}NO_{12}SNa^+$ 450.0677; found 450.0660.

1,2,2′,3,3′,4′,6-Hepta-*O*-acetyl-6′-sulfamoyl-*β*-maltose (12). The title compound **12** was prepared from 1,2,2′,3,3′,4′,6-hepta-*O*-acetyl-*β*-maltose according to general procedure 1. The crude material was purified by flash chromatography (2:1 EtOAc/hexane) to give pure *β*-anomer **12** as a white solid (50% yield). R_f = 0.52 (2:1 EtOAc/hexane). Mp = 98−99 °C. $[\alpha]^{25}_D$ +40 (*c* 1.0, chloroform). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.51 (s, 2H, NH_2); 5.89 (d, *J* = 8.5 Hz, 1H, H-1); 5.43 (t, *J* = 9.5 Hz, 1H, H-3); 5.31 (d, *J* = 4.0 Hz, 1H, H-1′); 5.20 (t, *J* = 10.0 Hz, 1H, H-3′); 4.95 (t, *J* = 9.5 Hz, 1H, H-4′); 4.85 (dd, *J* = 10.5, 3.5 Hz, 1H, H-2′); 4.80 (dd, *J* = 9.5, 8.5 Hz, 1H, H-2); 4.37 (dd, *J* = 13.0, 3.5 Hz, 1H, H-6a); 4.12 (m, 2H, H-6b, H-5); 4.06−4.01 (m, 3H, H-5′, H-6a′, H-6b′); 3.99 (t, *J* = 9.5 Hz, 1H, H-4); 2.06, 2.04, 1.98, 1.97, 1.95, 1.94, 1.93 (7 × 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, 169.8, 169.8, 169.5, 169.3, 168.9 (7 × $OCOCH_3$); 95.4 (C-1′); 90.8 (C-1); 73.9, (C-3); 73.2 (C-5′); 72.3 (C-5); 70.9 (C-2); 69.5 (C-2′); 69.1

(C-3′); 68.1 (C-4); 67.8 (C-4′); 66.6 (C-6′); 62.6 (C-6); 20.9, 20.7, 20.7, 20.6, 20.5, 20.4, 20.4 (7 × $OCOCH_3$); assignments were confirmed by $^1H-^{13}C$ HSQC and $^1H-^{13}C$ HMBC. LRMS (ESI^+): m/z = 738 $[M + Na]^+$. HRMS: calcd for $C_{26}H_{37}N_1O_{20}SNa^+$ 738.1522; found 738.1548.

Methyl 2,3,4-Tri-*O*-acetyl-6-sulfamoyl-α-D-glucopyranose (13). The title compound **13** was prepared from methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranose according to general procedure 1. Purification of the crude product by flash chromatography (1:2 acetone/hexane) afforded the **11** (61% yield) as a colorless gum. R_f = 0.29 (1:1 EtOAc/hexane). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.47 (s, 2H, NH_2); 5.30 (t, J = 10.0 Hz, 1H, H-3); 4.94 (d, J = 3.5 Hz, 1H, H-1); 4.94 (t, J = 10.0 Hz, 1H, H-4); 4.84 (dd, J = 10.0, 3.5 Hz, 1H, H-2); 4.07−4.04 (m, 2H, H-6a, H-6b); 3.98 (m, 1H, H-5); 3.35 (s, 3H, OCH_3); 2.02, 1.99, 1.96 (3 × s, 9H, $OCOCH_3$); assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.6, 169.2, 169.1 (3 × $OCOCH_3$); 96.0 (C-1); 69.8 (C-2); 69.4 (C-3); 68.2 (C-5); 66.9 (C-4); 66.8 (C-6); 54.9 (OCH_3); 20.2, 20.3, 20.3 (3 × $OCOCH_3$); assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 422 $[M + Na]^+$. HRMS: calcd for $C_{13}H_{21}N_1O_{11}SNa^+$ 422.0728; found 422.0726.

General Procedure 2. Synthesis of Sulfamates 14−18. Fully deprotected sulfamates were prepared by treating a solution of the per-*O*-acetylated parent compound (1.0 equiv) in anhydrous MeOH at 0 °C with methanolic sodium methoxide (0.05 M final concentration), final pH 12. The mixture was warmed to room temperature and left to stir until full deprotection was evident by TLC (30 min to 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 the product lyophilized to dryness.

6-Sulfamoyl-α,β-D-glucopyranose (14). The title compound **14** was prepared from the **7** according to general procedure 2 and obtained as a hygroscopic white solid (91% yield, α/β 4/6). R_f = 0.53 (9:1 CH_3CN/H_2O). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.43 (s, 1.2H, $NH_{2\beta}$); 7.40 (s, 0.8H, $NH_{2\alpha}$); 6.72 (d, J = 6.5 Hz, 0.6H, OH-1$_\beta$); 6.41 (d, J = 4.5 Hz, 0.4H, OH-1$_\alpha$); 5.13 (d, J = 5.5 Hz, 0.6H, OH-4$_\beta$); 5.08 (d, J = 5.5 Hz, 0.4H, OH-4$_\alpha$); 4.95 (br s, 0.6H, OH-3$_\beta$); 4.92 (t, J = 3.5 Hz, 0.4H, H-1$_\alpha$); 4.92 (br s, 0.6H, OH-2$_\beta$); 4.76 (br s, 0.4H, OH-3$_\alpha$); 4.54 (d, J = 5.0 Hz, 0.4H, OH-3$_\alpha$); 4.32 (br d, J = 7.0 Hz, 0.6H, H-1$_\beta$); 4.28 (dd, J = 10.5, 1.5 Hz, 0.6H, H-6a$_\beta$); 4.22 (dd, J = 10.0, 1.5 Hz, 0.4H, H-6a$_\alpha$); 4.02 (dd, J = 10.5, 6.5 Hz, 0.4H, H-6b$_\alpha$); 3.99 (dd, J = 10.5, 7.0 Hz, 0.6H, H-6b$_\beta$); 3.82 (m, 0.4H, H-5$_\alpha$); 3.44 (br t, J = 9.0 Hz, 0.4H, H-3$_\alpha$); 3.40 (m, 0.6H, H-5$_\beta$); 3.16 (m, 0.6H, H-3$_\beta$); 3.13 (m, 0.4H, H-2$_\alpha$); 3.04−3.02 (m, 1H, H-4$_\alpha$, H-4$_\beta$); 2.91 (m, 0.4H, H-2$_\beta$); assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 96.9 (C-1$_\beta$); 92.3 (C-1$_\alpha$); 76.5 (C-3$_\beta$); 74.7 (C-2$_\beta$); 73.5 (C-5$_\beta$); 73.0 (C-3$_\alpha$); 72.1 (C-2$_\alpha$); 70.4 (C-4$_\alpha$); 70.0 (C-4$_\beta$); 69.2 (C-6$_\alpha$); 69.0 (C-5$_\alpha$); 68.9 (C-6$_\beta$); assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 282 $[M + Na]^+$. HRMS: calcd for $C_6H_{13}NO_8SNa^+$ 282.0254; found 282.0251.

6-Sulfamoyl-α,β-D-galactopyranose (15). The title compound **15** was prepared from **10** according to general procedure 2. Purification of the crude product by flash chromatography (95:5 CH_3CN/H_2O) afforded **4** (71% yield, α/β 4/6) as a colorless oil. R_f = 0.28 (95:5 CH_3CN/H_2O). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.45 (s, 1.2H, $NH_{2\beta}$); 7.43 (s, 0.8H, $NH_{2\alpha}$); 6.64 (d, J = 6.5 Hz, 0.6H, OH-1$_\beta$); 6.29 (d, J = 4.5 Hz, 0.4H, OH-1$_\alpha$); 4.96 (t, J = 4.0 Hz, 0.4H, H-1$_\alpha$); 4.74 (d, J = 4.5 Hz, 1H), 4.72 (d, J = 5.5 Hz, 0.4H), 4.62 (d, J = 4.5 Hz, 0.6H), 4.56 (m, 0.6H), 4.32 (d, J = 5.5 Hz, 0.4H) (OH-2, OH-3, OH-4); 4.27 (t, J = 7.0 Hz, 0.6H, H-1$_\beta$); 4.12−4.06 (m, 2H, H-6a$_\alpha$, H-6a$_\beta$, H-6b$_\alpha$, H-6b$_\beta$); 3.70 (br t, J = 3.5 Hz, 0.4H, H-5$_\alpha$); 3.66 (br t, J = 6.0 Hz, 0.6H, H-3$_\beta$); 3.62 (br t, J = 3.5 Hz, 0.6H, H-5$_\beta$); 3.59 (m, 0.4H, H-3$_\alpha$); 3.52 (m, 0.4H, H-2$_\alpha$); 3.31 (dd, J = 5.0, 3.5 Hz, 0.4H, H-4$_\alpha$); 3.29 (dd, J = 5.0, 3.5 Hz, 0.6H, H-4$_\beta$); 3.24 (m, 0.4H, H-2$_\beta$); assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 97.4 (C-1$_\beta$); 92.7 (C-1$_\alpha$); 75.8 (C-4$_\alpha$); 73.1 (C-4$_\beta$); 72.1 (C-5$_\beta$); 71.8 (C-3$_\beta$); 69.4 (C-5$_\alpha$); 69.2 (C-2$_\alpha$); 69.0 (C-3$_\alpha$); 68.8 (C-2$_\beta$); 67.9 (C-6$_\beta$) 67.3 (C-6$_\alpha$); assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 282 $[M + Na]^+$. HRMS: calcd for $C_6H_{13}NO_8SNa^+$ 282.0254; found 282.0268.

6-Sulfamoyl-α,β-D-mannopyranose (16). The title compound **16** was prepared from **11** according to general procedure 1. Purification of the crude product by flash chromatography (95:5 CH_3CN/H_2O) afforded **16** (36% yield, α/β 4/6) as a colorless oil. R_f = 0.32 (95:5 CH_3CN/H_2O). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.42 (s, 0.8H, $NH_{2\alpha}$); 7.40 (s, 1.2H, $NH_{2\beta}$); 6.44 (d, J = 4.5 Hz, 0.6H, OH-1$_\beta$); 6.32 (d, J = 8.0 Hz, 0.4H, OH-1$_\alpha$); 4.96 (d, J = 3.0 Hz, 0.4H, OH-4$_\alpha$); 4.92 (d, J = 4.5 Hz, 0.6H, OH-4$_\beta$); 4.88 (d, J = 4.0 Hz, 0.6H, H-1$_\beta$); 4.67 (d, J = 4.0 Hz, 0.6H, OH-2$_\beta$); 4.65 (br s, 0.4H, OH-2$_\alpha$); 4.60 (d, J = 8.0 Hz, 0.4H, H-1$_\alpha$); 4.57 (d, J = 6.0 Hz, 0.6H, OH-3$_\beta$); 4.54 (d, J = 4.5 Hz, 0.4H, OH-3$_\alpha$); 4.29 (br d, J = 10.5 Hz, 0.4H, H-6a$_\alpha$); 4.26 (dd, J = 10.0, 1.5 Hz, 0.6H, H-6a$_\beta$); 4.03 (dd, J = 10.0, 7.0 Hz, 0.6H, H-6b$_\beta$); 4.00 (m, 0.4H, H-6b$_\alpha$); 3.76 (m, 0.6H, H-5$_\beta$); 3.57−3.53 (m, 1.6H, H-2$_\beta$, H-3$_\alpha$, H-3$_\beta$); 3.36 (m, 0.4H, H-4$_\beta$); 3.31−3.30 (m, 1.2H, H-2$_\alpha$, H-4$_\alpha$, H-5$_\alpha$); assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 94.2 (C-1$_\alpha$); 94.1 (C-1$_\beta$); 74.0 (C-5$_\alpha$); 73.5 (C-3$_\alpha$); 71.5 (C-2$_\alpha$); 71.3 (C-3$_\beta$); 70.5 (C-2$_\beta$); 70.4 (C-5$_\beta$); 69.3 (C-6$_\beta$); 69.1 (C-6$_\alpha$); 67.0 (C-4$_\beta$); 66.6 (C-4$_\alpha$); assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 282 $[M + Na]^+$. HRMS: calcd for $C_6H_{13}NO_8SNa^+$ 282.0254; found 282.0258.

6′-Sulfamoyl-α,β-maltose (17). The title compound **17** was prepared from **12** according to general procedure 2. Purification of the crude product by flash chromatography (95:5 CH_3CN/H_2O) afforded **17** (37% yield, α/β 4/6) as a hygroscopic white solid. R_f = 0.32 (95:5 CH_3CN/H_2O). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.40 (s, 2H, NH_2); 6.68, 6.34, 5.43, 5.15 (4 × br s, 4H, OH); 5.08, 5.04 (2 × d, J = 3.5 Hz, 1H, H-1′$_\alpha$, H-1′$_\beta$); 4.97 (br s, 1H, OH); 4.91 (br s, 0.4H, H-1$_\alpha$); 4.54, 4.44 (2 × br s, 2H, OH); 4.31 (d, J = 7.5 Hz, 0.6H, H-1$_\beta$); 4.19 (br d, J = 10.5 Hz, 1H, H-6a′); 4.10 (dd, J = 10.5, 5.5 Hz, 1H, H-6b′); 3.73 (m, 1H, H-5′); 3.69−3.64 (m, 2H, H-6a, H-4); 3.62−3.58 (m, 1H, H-6b); 3.50 (m, 0.4H, H-3$_\alpha$); 3.40−3.37 (m, 2.2H, H-3$_\beta$, H-3′, H-5$_\beta$); 3.32 (m, 0.4 H, H-5$_\alpha$); 3.25−3.18 (m, 1.4H, H-2$_\alpha$, H-2′); 3.09 (t, J = 9.5 Hz, 1H, H-4′); 2.95 (t, J = 0.6H, H-2$_\beta$); assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 100.8, 100.6 (C-1′$_\alpha$, C-1′$_\beta$); 96.8 (C-1$_\beta$); 92.2 (C-1$_\alpha$); 80.2 (C-5$_\alpha$); 79.5 (C-5$_\beta$); 76.6 (C-3$_\beta$); 75.2 (C-2$_\alpha$); 74.5 (C-2$_\beta$); 73.3, 73.2 (C-3′$_\alpha$, C-3′$_\beta$); 73.0 (C-4$_\alpha$ or C-4$_\beta$); 72.5, 72.4 (C-2′$_\alpha$, C-2′$_\beta$); 72.0 (C-3$_\alpha$); 70.5 (C-5′$_\alpha$, C-5′$_\beta$); 70.4 (C-4$_\beta$ or C-4$_\alpha$); 69.6, 69.5 (C-4′$_\alpha$, C-4′$_\beta$); 68.4, 68.4 (C-6′$_\alpha$ C-6′$_\beta$); 60.7, 60.6 (C-6$_\alpha$, C-6$_\beta$); assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 444 $[M + Na]^+$, LRMS (ESI^-): m/z = 420 $[M - H]^-$, 455 $[M + Cl]^-$. HRMS: calcd for $C_{12}H_{23}N_1O_{13}SNa^+$ 444.0782; found 444.0797.

Methyl-6-sulfamoyl-α-D-glucopyranose (18). The title compound **18** was prepared from compound **13** according to general procedure 2. The crude product was purified by flash chromatography (9:1 CH_3CN/H_2O) affording **18** (94% yield) as a hygroscopic white solid. $[\alpha]^{25}_D$ +30 (c 1.0, methanol). R_f = 0.50 (9:1 CH_3CN/H_2O). ^1H NMR (500 MHz, DMSO-d_6): δ = 7.43 (NH_2); 5.14 (d, J = 6.0 Hz, 1H, OH-4); 4.86 (d, J = 5.0 Hz, 1H, OH-3); 4.78 (d, J = 6.0 Hz, 1H, OH-2); 4.56 (d, J = 4.0 Hz, 1H, H-1); 4.26 (m, 1H, H-6a); 4.05 (m, 1H, H-6b); 3.58 (m, 1H, H-5); 3.39 (m, 1H, H-3); 3.27 (s, 3H, OCH_3); 3.23 (m, 1H, H-2), 3.04 (m, 1H, H-4); assignments were confirmed by $^1H-^1H$ gCOSY. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 99.7 (C-1); 73.2 (C-3); 71.7 (C-5); 70.1 (C-4); 69.5 (C-5); 68.6 (C-6); 54.5 (OCH_3); assignments were confirmed by $^1H-^{13}C$ HSQC. LRMS (ESI^+): m/z = 296 $[M + Na]^+$; HRMS: calcd for $C_7H_{15}N_1O_8SNa^+$ 296.0411; found 296.0424.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for sulfamates **7**−**18** and novel intermediates and the synthesis of all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

CA, carbonic anhydrase; TPM, topiramate; pH_e, extracellular pH; pH_i, intracellular pH; cLogP, calculated log *P*; TPSA, total polar surface area; LE, ligand efficiency; SAR, structure−activity relationship; SPR, structure−property relationship

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