A novel class of carbonic anhydrase inhibitors: glycoconjugate benzene sulfonamides prepared by "click-tailing"

Author
Wilkinson, Brendan, Bornaghi, Laurent, Houston, Todd, Innocenti, Alessio, T. Supuran, Claudiu, Poulsen, Sally-Ann

Published
2006

Journal Title
Journal of Medicinal Chemistry

DOI
https://doi.org/10.1021/jm060967z

Copyright Statement
Copyright 2006 American Chemical Society. Self-archiving of the author-manuscript version is not yet supported by this publisher. Please use the hypertext link to access the journal's website or contact the author for more information. Please refer to the journal for the definitive published version.

Downloaded from
http://hdl.handle.net/10072/11308

Link to published version
http://pubs.acs.org/journal/jmcmar?cookieSet=1
A novel class of carbonic anhydrase inhibitors: glycoconjugate benzene sulfonamides
prepared by “click-tailing”

Brendan L. Wilkinson,† Laurent F. Bornaghi,† Todd A. Houston,‡ Alessio Innocenti,§ Claudiu T. Supuran*§ and Sally-Ann Poulsen*†

Eskitis Institute for Cell and Molecular Therapies, Griffith University, 170 Kessels Road,
Nathan, Queensland 4111, Australia, Institute for Glycomics, Griffith University, PMB 50
Gold Coast Mail Centre, Gold Coast, Queensland 9726, Australia, and Polo Scientifico,
Laboratorio di Chimica Bioinorganica, Rm. 188, Università degli Studi di Firenze, Via della
Lastruccia 3, 50019 Sesto Fiorentino, Florence, Italy

*Corresponding authors. S.-A.P. Telephone: +61 7 3735 7825; Fax: +61 7 3735 7656; e-mail:
s.poulsen@griffith.edu.au. C.T.S. Telephone: +39 055 457 3005; Fax: +39 055 457 3385; e-
mail: claudiu.supuran@unifi.it.
†,‡ Griffith University
§ Università degli Studi di Firenze
¥Nonstandard abbreviations: CA, carbonic anhydrase; 1,3-DCR, 1,3-dipolar cycloaddition
reaction; HBTU, O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate;
AZA, acetazolamide; MZA, methazolamide; EZA, ethoxzolamide; DCP, dichlorphenamide;
BRZ, brinzolamide; IND, Indisulam
Abstract

Aryl and heteroaryl sulfonamides (ArSO₂NH₂) are therapeutically used to inhibit the catalytic activity of carbonic anhydrases (CAs). Using a ‘click-tail’ approach a novel class of glycoconjugate benzene sulfonamides have been synthesized that contain diverse carbohydrate-triazole tails. These compounds were assessed for their ability to inhibit three human CA isozymes in vitro: cytosolic hCA I and hCA II, and transmembrane, tumour-associated hCA IX. This isozyme has a minimal expression in normal tissue but is overexpressed in hypoxic tumours and its inhibition is a current approach towards new cancer therapies. The qualitative structure-activity for all derivatives demonstrated that the stereochemical diversity present within the carbohydrate tails effectively interrogated the CA active site topology, to generate several inhibitors that were potent and selective towards hCA IX – an important outcome in the quest for potential cancer therapy applications based on CA inhibition.
Introduction

The carbonic anhydrase (CA, EC 4.2.1.1) family of Zn(II) metalloenzymes is ubiquitous to all eukaryotic and most prokaryotic cells.\textsuperscript{1} This enzyme efficiently catalyses the hydration of carbon dioxide (CO\textsubscript{2}) to give bicarbonate anion (HCO\textsubscript{3}\textsuperscript{-}) and a proton (H\textsuperscript{+}), a regulatory reaction that underpins fundamental physiological processes associated with pH control, ion transport and fluid secretion.\textsuperscript{2-4} For decades, inhibitors of CA have been a mainstay of human clinical intervention for a range of diseases, however more recently a role for CA inhibition as an anticancer therapy has been identified owing to the overexpression of some CA isoforms (CA IX and CA XII) in cancer cells and a minimal expression in normal tissue. The latter has further increased interest in this enzyme family as a therapeutic target.\textsuperscript{5-7}

The classical recognition fragment for small molecules to bind the active site of CA is an aromatic sulfonamide moiety - ArSO\textsubscript{2}NH\textsubscript{2}.\textsuperscript{1-3,8} The sulfonamide anion (ArSO\textsubscript{2}NH\textsuperscript{-}) coordinates to the CA active site Zn(II) and so inhibits the catalytic ability of the enzyme. This aromatic sulfonamide group has served as a very reliable anchor upon which medicinal chemists have appended ‘tails’ to deliver inhibitors with improved potency and desirable selectivity profiles - known in this field as ‘the tail approach’ (there are 16 known human CA isozymes).\textsuperscript{1} Clinically used CA inhibitors include acetazolamide, methazolamide, ethoxazolamide, brinzolamide and dichlorophenamide while Indisulam is in Phase II clinical trials as an anticancer agent to treat solid tumours.\textsuperscript{6,7}

Insert Chemical Structures: group A

For drug development the physiochemical properties (for example aqueous solubility, lipophilicity, stability, bioavailability) that make a compound a good drug must be considered alongside the goal to prepare compounds with desirable potency and selectivity profiles.\textsuperscript{9} For
poorly soluble chemotherapeutic drugs that are administered by intravenous injection (such as the taxanes) this balance has been achieved indirectly through solubilizing vehicle formulations. Unfortunately the solubilizing additives themselves exhibit adverse effects outside those of the drug, leading to a requirement for co-treatment with other medications, long drug infusion times and sometimes even preventing the most relevant drug dose to be administered.\textsuperscript{10} The development of drug solubilizing strategies that are free from side effects caused by the formulation vehicle is thus of immense interest, particularly for chemotherapy applications - the recent development of ABRAXANE\textsuperscript{®} (human albumin bound paclitaxel) is evidence for the success of this strategy.\textsuperscript{11}

**Insert Chemical Structure Group B**

An alternative approach to equip drug molecules with improved solubility and tolerability is to attach carbohydrate moieties to generate glycoconjugates.\textsuperscript{12-15} This carbohydrate-based strategy has however not often received significant attention by the pharmaceutical industry, with sugars ‘sidelined’ owing to the stigma of both weak binding and a poor ability to cross cell membranes – leaving more traditional small organic molecules to be pursued for drug discovery.\textsuperscript{16} The cancer relevant hCA isozymes, unlike the physiologically dominant cytosolic hCA I and hCA II, are transmembrane proteins with extracellular enzyme active sites. Owing to the success of the ‘tail approach’ to generate potent CA inhibitors and the extracellular location of the hCA IX active site (circumventing the need for targeting drugs to cross cell membranes) we decided to explore tethering carbohydrate tails to the high-affinity ArSO\textsubscript{2}NH\textsubscript{2} pharmacophore to synthesize sulfonamide glycoconjugates. We anticipated that the immense stereochemical diversity inherent to carbohydrate scaffolds might facilitate added opportunities to survey regions of biological space removed from the CA active-site
core to exploit for improved CA affinity and isozyme selectivity. Despite the synthesis of a vast multitude of CA inhibitors utilising the tail strategy and the potential benefits of appending carbohydrate moieties to drug molecules, the combination of these two strategies to generate CA inhibitors is essentially unexplored - there is just a single literature example\textsuperscript{17} (nine compounds - which were not evaluated against cancer relevant CA isozymes). This relatively untouched medicinal chemistry landscape has served as the primary inspiration for the compounds synthesized and presented in the current study.

We have recently demonstrated the versatility of the 1,3-dipolar cycloaddition reaction (1,3-DCR; ‘click chemistry’) to readily generate 1,4-disubstituted-1,2,3-triazole glycoconjugates from azido sugars and varied alkyne substrates (Scheme 1).\textsuperscript{18} This high degree of versatility has encouraged us to now explore 1,3-DCR as a novel ‘click-tailing’ strategy to append carbohydrate tails onto the CA ArSO\textsubscript{2}NH\textsubscript{2} recognition motif to generate glycoconjugate CA inhibitors. Specifically we report the synthesis of 28 benzene sulfonamides containing carbohydrate triazole tails. All compounds were investigated for their in vitro inhibition of hCA I, hCA II, and hCA IX. A number of derivatives were found to be selective for the cancer associated isozyme hCA IX.

Insert Scheme 1

Results and Discussion

Chemistry

To facilitate our synthetic strategy it was necessary to synthesize CA recognition scaffolds that possessed dual functionality, both (i) an anchor for reliable CA affinity (i.e. an aryl
sulfonamide), and (ii) either a terminal alkyne or azide moiety to act as the complementary partner for the 1,3-DCR with our panel of sugar building blocks. Many ester and amide derivatives of 4-carboxy benzene sulfonamide (1) are potent (low nM) inhibitors of hCA II. The amide derivatives have also shown good in vivo activity and prolonged duration as anti-glaucoma agents.\textsuperscript{19} The N-propynyl amide derivative 2 and O-propynyl ester derivative 3 were thus designed as the scaffolds for 1,3-DCR with a panel of azido sugars. Scaffold 2 was synthesized by HBTU mediated amide coupling of 1 with propargyl amine, while scaffold 3 was synthesized by carbodiimide mediated esterification of 1 with propargyl alcohol.

**Insert Chemical Structures Group C**

A panel of seven peracetylated azido sugars a-g were also prepared, the carbohydrate derived from: a glucose, b galactose, c arabinose, d N-acetyl glucosamine, e glucuronic acid and f methyl-\(\alpha\)-D-glucopyranoside, respectively (Figure 1). Glycosyl azides a-f were synthesized by the stereoselective bimolecular displacement of the halide substituent of glycosyl halides precursors with an azide nucleophile,\textsuperscript{20} while the methyl 2,3,4-tri-\(O\)-acetyl-6-azido-6-deoxy-\(\alpha\)-D-glucopyranoside g was prepared from methyl-\(\alpha\)-D-glucopyranoside as previously described.\textsuperscript{21} The glycosyl halide precursors were prepared from the corresponding peracetates or purchased from commercial sources.

**Insert Figure 1**

Scaffolds 2 and 3 were each reacted with the azido sugar panel a-g to generate the amide and ester series of peracetylated glycoconjugates, 2a-2g and 3a-3g, respectively (Scheme 2, Figure 2). When using catalyst loading as described by Sharpless,\textsuperscript{22} the triazole forming
reaction was found to be sluggish, even at elevated temperatures. However, when using 10 mol% of the Cu(I) source and 20 mol% of ascorbate, triazole formation proceeded smoothly in all cases and under very mild conditions. Reactions were generally complete following 30 min of vigorous stirring (as evidenced by TLC). The O-acetate groups of the amide series 2a-2g were subsequently removed using methanolic sodium methoxide to liberate the fully deprotected sugar analogues 2a’-2g’ in quantitative or near quantitative yields. These basic reaction conditions proved unsuitable for the synthesis of the ester series 3a’-3g’, owing to the methoxide anion participating also in transesterification, whereby cleaving the CA anchor from the sugar triazole tail. More conveniently, the azido sugar panel were first de-O-acetylated to give the deprotected azido sugars a’-g’ (R = Ac -> R = H) which were then reacted with scaffold 3 to give the deprotected sugar ester series 3a’-3g’. All new compounds were characterized using 1D $^1$H and $^{13}$C NMR spectroscopy, 2D NMR spectroscopy (gCOSY, gHSQC, gHMBC as required), elemental analysis and HRMS.

Insert Scheme 2

Insert Figure 2

**Carbonic Anhydrase Inhibition**

hCA I, II, and IX enzyme inhibition data (determined by assaying the CA catalyzed hydration of CO$_2$) for 2, 3 and the 28 new glycoconjugate sulfonamides are presented in Table 1. The selectivity ratios for inhibition of isozyme IX cf. I and II are also given in Table 1. Data for clinically used CA inhibitors acetazolamide (AZA), methazolamide (MZA), ethoxzolamide
(EZA), dichlorophenamide (DCP), brinzolamide (BRZ) and Indisulam (IND) are included for comparison.

**Insert Table 1**

The parent amide scaffold **2** and ester scaffold **3** exhibited inhibition and isozyme selectivity similar to each other against the three hCA isozymes investigated. Compounds **2** and **3** had greatest efficacy at hCA II ($K_i$s of 47 and 45 nM, respectively), approximately 2-fold weaker inhibition at hCA IX (113 and 104 nM, respectively) and an order of magnitude again weaker inhibition at hCA I (6100 and 4000 nM, respectively).

**Isozyme hCA I.** At hCA I the triazole linked carbohydrate moiety had minimal effect on inhibition, with 26 of the 28 compounds exhibiting affinity similarly ($\mu$M range) to the parent compounds **2** and **3**. The two notable exceptions were compounds **3c’** and **3e’**, both contained an ester linkage and a deprotected (free hydroxy) sugar. Compounds **3c’** and **3e’** were 400 to 500-fold more potent than their parent ester scaffold **3** ($K_i$s of 7.7 nM and 9.6 nM, respectively) and more potent than any of the standard sulfonamide inhibitors tested. This result was extremely encouraging as it provided confirmation that the subtle structural differences in the sugar tail could indeed discriminate CA isozyme active site topology to substantially influence enzyme inhibition characteristics.

**Isozyme hCA II.** At hCA II the sugar triazole tail had a variable effect on CA inhibition - with some derivatives improved inhibition was observed while with others weaker inhibition was observed - when compared to the parent compounds **2** and **3**. The ester linked deprotected sugars (**3a’-3g’**) had tightly grouped $K_i$s, ranging from 5.8 - 8.6 nM, that were ~5
to 6-fold more potent than the parent 3. In striking contrast the amide linked deprotected sugars (2a'-2g') did not exhibit the same tight grouping of $K_i$s and only the glucose and galactose derivatives (2a' and 2b') paralleled the improved inhibition of their ester counterparts with $K_i$s of 7.0 and 8.1 nM, respectively. The remaining amide linked deprotected sugars (compounds 2c'-2g') had weaker inhibition than the parent 2, with $K_i$ values ranging from 90 - 378 nM. For the ester linked series with the sugar acetates in place derivatives 3b, 3c and 3e had $K_i$s similar to the ester linked deprotected sugar derivatives, again ~5 to 6-fold more potent than the parent 3 ($K_i$s ranging from 6.8 – 7.3 nM), while 3g had a similar $K_i$ to the parent 3 (50 nM vs. 45 nM) and 3a, 3d and 3f all exhibited weaker $K_i$s than the parent 3 or deprotected sugar counterparts ($K_i$s ranging from 119-423 nM). For the acetylated sugars of the amide series (2a-2g) the derivative 2g had 2-fold higher inhibition than the deprotected sugar derivatives 2g' and similar inhibition to parent amide 2. Derivatives 2d, 2e and 2f exhibited 6-, 50- and 36-fold higher inhibition, respectively, than their deprotected sugar counterparts, while derivatives 2a, 2b and 2c were each weaker hCA II inhibitors than their deprotected sugar counterparts. In summary, for the seven different glycosyl triazole tails studied, the four groupings of amide, ester, sugar-OAc or sugar-OH, did not behave in a consistent direction with respect to hCA II inhibition. This in vitro data will be important for understanding future in vivo data, as it is clear that the acetates could serves as prodrugs in the in vivo environment. 29 Similarly to the results for hCA I, these results again demonstrate that the sugar tails interrogate the enzyme active site with an intricacy of interactions that permit marked discrimination of enzyme inhibition.

**Isozyme hCA IX.** At hCA IX the parent compounds 2 and 3 had $K_i$s of 113 and 104 nM, respectively, approximately 2-fold weaker than hCA II inhibition and 40 to 50-fold more potent than hCA I inhibition. With five of the sugar tails (b, c, e, f, g) there was at least one
compound of the grouping (amide, ester, sugar-OAc or sugar-OH) that exhibited improved hCA IX inhibition over the parent scaffolds. The exceptions were the glucose tail a and the N-acetyl glucosamine tail d in which the sugar triazole tail lead always to reduced inhibition when compared to the non-glycoconjugate parent scaffolds. For each sugar tail the amide sugar-OAc derivatives (2x) were more potent than sugar-OH derivatives (2x’) except for the glucuronic acid derivatives (2e’ more potent than 2e), while in the ester series this trend was completely reversed, with sugar-OH derivatives (3x’) more potent than sugar-OAc derivatives (3x), again with the exception of the glucuronic acid derivatives (3e more potent than 3e’). Compounds 2b, 3b’, 3e’, 2e’, 3f’, 3g and 3g’ were all stronger inhibitors of hCA IX than the parents 2 and 3, with $K_i$s ranging from 23 – 96 nM. The strongest hCA IX inhibitor was the amide linked deprotected glucuronic acid derivative 2e’ ($K_i = 23$ nM). Importantly this compound was also 16.4-fold selective for hCA IX over hCA II and 100-fold selective over hCA I. Glucuronate 2e’ has a similar $K_i$ to the sulfonamide indisulam (24 nM) that is in phase II clinical trials as an anticancer agent, however indisulam is not selective for hCA IX whereas 2e’ is. There were several other compounds with mild hCA IX selectivity cf. hCA II, of note is the amide linked acetylated galactose derivative 2b with 6.2-fold selectivity (76 nM versus 470 nM). These results demonstrate that by tethering a sugar triazole tail onto the CA anchor pharmacophore it is possible to reverse the CA isozyme selectivity trends observed in the non-glycoconjugate parent compounds 2 and 3 and also all standard inhibitors - none of which are hCA IX selective.

**Conclusions**

Selective inhibition among isozymes is often a challenging hurdle in the drug discovery process, however to maximise the benefits of any future therapies involving CA inhibition, it is essential to develop isozyme-specific compounds. Conservation of active site structure and
topology within the CA enzyme family has made it difficult to target subtle isozyme differences by rational drug design. Here we have explored ‘click-tailing’ carbohydrates onto the ArSO2NH2 CA pharmacophore as a drug solubilizing and isozyme differentiating strategy. This work presents a new class of CA inhibitors comprising triazole-tethered carbohydrate tails, the first of which to have been generated through ‘click chemistry’. The qualitative structure-activity demonstrated that the stereochemical diversity within the carbohydrate tails effectively interrogated the CA active site topology, generating in some instances inhibitors with hCA IX selectivity – an important outcome in the quest for potential cancer therapy applications. Sugar tails may therefore prove a valuable approach to generate CA isozyme selective compounds. A powerful example is glucose (2a, 2a’, 3a, 3a’) and galactose (2b, 2b’, 3b, 3b’) epimer derivatives that have drastically different inhibition and selectivity profiles yet the sole stereochemical difference is over 14 atoms removed from the sulfonamide moiety. The relative ease of synthetic access to azido sugars coupled with the venerability of the cycloaddition reaction has provided an efficient route to the carbohydrate-based CA inhibitors. We intend to more fully explore this “click tailing” strategy for the development of CA inhibitors for therapeutic investigation.
Experimental section

Chemistry. Reagents were purchased from Sigma Aldrich and Fluka chemical companies and were used without further purification. Solvents were dried and distilled where necessary prior to use, or purchased as such from Sigma Aldrich. Reactions were monitored by TLC using Merck F60$_{254}$ silica plates with visualization of product bands by UV fluorescence ($\lambda = 254$ nm) and charring by 10% v/v ethanolic H$_2$SO$_4$. Flash chromatography was performed on Merck flash silica gel (0.04 mm – 0.06 mm). Melting points were acquired on a Gallenkamp melting point apparatus and are reported as uncorrected. NMR ($^1$H and $^{13}$C ($^1$H)) spectra were recorded on a Varian Unity 400 MHz spectrometer at room temperature using DMSO-$d_6$ solvent unless otherwise stated. Chemical shifts are reported in $\delta$ (ppm) from a TMS internal standard (0.0 ppm). Coupling constants ($J$) are reported in hertz. High resolution electrospray ionisation mass spectra were performed in negative ion mode on an Apex III Bruker Daltonics 4.7T Fourier Transform mass spectrometer (FTMS) fitted with an Apollo ESI source.

$N$-(Prop-2-ynyl)-4-sulfamoylbenzamide (2). To a stirring solution of 1 (2.0 g, 9.9 mmol) and propargyl amine (0.64 mL, 9.9 mmol, 1.0 equiv) in dry DMF (40 mL) was successively added $N$-hydroxybenzotriazole monohydrate (0.94 g, 6.6 mmol, 0.6 equiv), diisopropylethylamine (1.7 mL, 9.9 mmol, 1.0 equiv) and HBTU (3.8 g, 9.9 mmol, 1.0 equiv). The deep yellow solution was stirred at room temperature under nitrogen for 1 hour when found complete by TLC. The mixture was concentrated under reduced pressure and ethyl acetate (40 mL) was added. The organic extract was washed with water (40 mL) and back extracted with ethyl acetate (3 x 40 mL). The organic extracts were combined, and washed with brine (50 mL). The organic layer was dried (MgSO$_4$), filtered and evaporated to a crude white solid. Recrystallization from hot methanol:water (9:1) afforded the title compound 2 as
white crystalline solid (1.9 g, 8.2 mmol, 82 %). $R_f$ 0.58 (100% EtOAc); mp 216 - 217 °C (decomp). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.12 (t, $^4$J$_{\text{CH-CH}}$ = 2.4 Hz, 1H, propynyl CH), 4.05 (dd, $^2$J$_{\text{NH-CH}}$ = 5.6 Hz, $^4$J$_{\text{CH-CH}}$ = 2.8 Hz, 2H, propynyl CH$_2$), 7.45 (br s, 2H, SO$_2$NH$_2$), 7.86 – 7.98 (m, 4H, Ph), 9.09 (t, $^3$J$_{\text{NH-CH}}$ = 5.6 Hz, 1H, CONH); $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 29.03 (propynyl CH$_2$), 73.81 (propynyl CH), 81.67 (propynyl C), 126.37 (Ph CH), 128.64 (Ph CH), 137.34 (Ph C), 147.14 (Ph C), 165.62 (C=O). HRMS (ESI) calcd for C$_{10}$H$_9$N$_2$O$_3$S$: 237.033936; found: 237.034388. Anal. (C$_{10}$H$_{10}$N$_2$O$_3$S) C, H, N, S.

**Prop-2-ynyl 4-sulfamoylbenzoate (3).** To a stirring solution of 1 (2.0 g, 9.9 mmol) in dry DMF (40 mL) was successively added propargyl alcohol (1.17 mL, 19.8 mmol, 2.0 equiv), Et$_3$N (2.8 mL, 19.9 mmol, 2.0 equiv) and EDC (1.9 g, 9.9 mmol, 1.0 equiv). The solution was stirred at room temperature under N$_2$ for an additional 4 hours. The mixture was then concentrated under reduced pressure and ethyl acetate (40 mL) was added. The organic extract was washed with saturated aqueous NaHCO$_3$ (40 mL) and back extracted with ethyl acetate (40 mL). The organic layers were combined and washed with brine (40 mL), dried (MgSO$_4$), filtered and evaporated. The crude oil was purified by flash silica chromatography (1:1 EtOAc:hexanes) to afford the title compound 3 as white crystalline solid (0.91 g, 3.8 mmol, 38 %). $R_f$ 0.38 (6:4 EtOAc:hexanes); mp 110 - 111 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.63 (t, $^4$J$_{\text{CH-CH}}$ = 2.4 Hz, 1H, propynyl CH), 4.97 (d, $^4$J$_{\text{CH-CH}}$ = 2.8 Hz, 2H, propynyl CH$_2$), 7.55 (br s, 2H, SO$_2$NH$_2$), 7.93 – 8.13 (m, 4H, Ph); $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 53.00 (propynyl CH$_2$), 78.12 (propynyl CH), 78.28 (propynyl C), 126.16 (Ph CH), 130.03 (Ph CH), 131.68 (Ph C), 148.32 (Ph C), 164.05 (C=O). HRMS (ESI) calcd for C$_{10}$H$_8$NO$_3$S$: 238.017952. Found: 238.017952. Anal. (C$_{10}$H$_9$NO$_3$S) C, H, N, S.

**Synthesis of glycosyl triazole aryl sulfonamides (2a -g, 3a’ – g’): General Procedure 1.** A mixture of the azide (1.0 equiv) and acetylene (1.0 equiv) was suspended in a tert-butyl
alcohol and water (1:1, 0.2 – 0.5 M final concentration). A solution of sodium ascorbate (0.2 equiv) in water, followed by a solution CuSO₄·5H₂O (0.1 equiv) in water was successively added. The bright yellow suspension was stirred vigorously at 40 °C until TLC indicated reaction completion (generally within 2 hours). The mixture was evaporated under reduced pressure and the resulting residue was purified by flash chromatography to yield pure material.

**Preparation of deprotected glycosyl triazole aryl sulfonamides (2a’ – g’ and 3a’-g’):**

**General Procedure 2.** Compounds 2a’ – g’ were prepared by the treating the acetylated precursors 2a – g (final concentration of ~0.1 – 0.2 M) with dry methanolic sodium methoxide (final pH 9 – 12). Reactions were found to be complete within 30 minutes by TLC. Neutralization of the solution by Amberlite IR-120 ion exchange resin, followed by filtration and evaporation of the filtrate to dryness afforded pure material by NMR. Likewise, the analogous esters 3a’ – g’ were prepared by deprotecting the peracetylated glycosyl azides a – f or the 6-deoxy-6-azido glucoside g in the same way as described above, prior to the cycloaddition reaction with 3 (see scheme 2).

**4-({[4-(Aminosulfonyl)benzoyl]amino}methyl-1-(2’,3’,4’,6’-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazole (2a).** The title compound was prepared according to the General Procedure 1 and isolated as white solid (172 mg, 0.28 mmol, 86 %). Rf 0.15 (100% EtOAc); mp 198 – 199 °C. 1H NMR (400 MHz, DMSO-d₆): δ 1.75 (s, 3H, OAc CH₃), 1.92 (s, 3H, OAc CH₃), 1.95 (s, 3H OAc CH₃), 1.99 (s, 3H OAc CH₃), 4.01 – 4.10 (m, 2H, H₆’, H₆’’), 4.27 – 4.33 (m, 1H, H₅’), 4.50 (d, 3Jᵦ(CH-NH) = 6.0 Hz, 2H, CH₂NH), 5.11 – 5.16 (m, 1H, H₄’), 5.47 – 5.52 (m, 1H, H₃’), 5.61 – 5.66 (m, 1H, H₂’), 6.28 (d, 3J₁-₁²’ = 9.2 Hz, 1H, H₁’), 7.44 (s, 2H, SO₂NH₂), 7.86 – 7.99 (m, 4H, Ph H), 8.26 (s, 1H, triazole H), 9.22 (t, 3Jᵦ(NH-CH) = 5.2 Hz,
4-({[4-(Aminosulfonyl)benzoyl]amino}methyl-1-(β-D-glucopyranosyl)-1-\(H\)-1,2,3-triazole (2a'). Title compound was prepared according to General Procedure 2 and isolated as white solid (71 mg, 0.16 mmol, ~ 100 \%); mp 205 - 210 \degree C (decomp). \(R_f\) 0.15 (1:9 H\(_2\)O:CH\(_3\)CN). \(^1\)H NMR (400 MHz, D\(_2\)O): \(\delta\) 3.46 – 3.51 (m, 1H, H\(_4\)'), 3.55 – 3.60 (m, 1H, H\(_3\)'), 3.58 – 3.66 (m, 2H, H\(_5\), H\(_6\)'), 3.74 – 3.79 (m, 1H, H\(_6''\)'), 3.84 – 3.88 (m, 1H, H\(_2\)'), 4.59 (s, 2H, CH\(_2\)NH), 5.61 (d, \(^3\)J\(_{1'\cdot2'}\) = 8.8 Hz, 1H, H\(_1'\)), 7.80 – 7.88 (m, 4H, Ph), 8.07 (s, 1H, triazole CH); \(^{13}\)C {\(^1\)H} NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 35.19 (CH\(_2\)NH), 60.53 (C\(_6'\)), 69.07 (C\(_6\)'), 72.41 (C\(_2\)'), 76.02 (C\(_3\)'), 79.04 (C\(_5\)'), 87.59 (C\(_1\)'), 123.36 (triazole CH), 126.44 (Ph CH), 128.44 (Ph CH), 137.71 (Ph C), 144.35 (triazole C or Ph C), 144.94 (triazole C or Ph C), 169.54 (C=O). HRMS (ESI) caleld for C\(_{16}\)H\(_{20}\)N\(_5\)O\(_8\)S: 442.10387. Found: 442.103042.

4-({[4-(Aminosulfonyl)benzoyl]amino}methyl-1-(2',3',4',6'-tetra-O-acetyl-β-D-galactopyranosyl)-1-\(H\)-1,2,3-triazole (2b). The title compound was prepared according to the General Procedure 1 and isolated as white solid (174 mg, 0.28 mmol, 87 \%). \(R_f\) 0.11 (8:2 EtOAc:hexanes); mp 161 – 162 \degree C (decomp). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 1.78 (s, 3H, OAc CH\(_3\)), 1.91 (s, 3H, OAc CH\(_3\)), 1.95 (s, 3H, OAc CH\(_3\)), 2.15 (s, 3H, OAc CH\(_3\)), 3.98 (dd, \(^2\)J\(_{6'\cdot6''}\) = 11.6 Hz, \(^3\)J\(_{6'\cdot5}\) = 7.6 Hz, 1H, H\(_6''\)'), 4.10 (dd, \(^2\)J\(_{6''\cdot6'}\) = 11.6 Hz, \(^3\)J\(_{6''\cdot5'}\) = 5.2 Hz, 1H, H\(_6''\)'), 4.51 (d, \(^3\)J\(_{\text{CH-NH}}\) = 5.5 Hz, 2H, CH\(_2\)NH), 4.52 – 4.55 (m, 1H, H\(_5\)'), 5.38 – 5.43 (m, 2H,
H_3', H_4'), 5.55 – 5.60 (m, 2H, H_2'), 6.21 (d, \(^3J\_1'-2' = 9.2\) Hz, 1H, H_1'), 7.45 (s, 2H, SO_2NH_2), 7.86 – 7.99 (m, 4H, Ph), 8.16 (s, 1H, triazole H), 9.19 (t, \(^3J_{\text{NH-CH}} = 5.1\) Hz, 1H, CH_2NH); \(^{13}\)C \(^1\)H NMR (100 MHz, DMSO-d_6): \(\delta\) 20.69 (OAc CH_3), 20.98 (OAc CH_3), 21.10 (OAc CH_3), 21.17 (OAc CH_3), 35.46 (CH_2NH), 62.25 (C_6'), 68.01 (C_4'), 68.30 (C_3'), 71.14 (C_2'), 73.63 (C_5'), 84.85 (C_1'), 123.13 (triazole CH), 126.29 (Ph CH), 128.66 (Ph CH), 137.63 (Ph C), 145.97 (triazole C or Ph C), 147.05 (triazole C or Ph C), 165.89 (C=O), 169.18 (C=O), 170.12 (C=O), 170.66 (C=O). HRMS (ESI) calcd for C_{24}H_{28}N_5O_{12}S: 610.146066. Found: 610.147458. Anal. (C_{24}H_{29}N_5O_{12}S•0.5H_2O) C, H, N.

4-(4-Sulfamoylbenzamido)methyl-1-(\(\beta\)-D-galactopyranosyl)-1-H-1,2,3-triazole (2b'). The title compound was prepared according to General Procedure 2 and isolated as white foam (72 mg, 0.16 mmol, ~ 100 %). \(R_f\) 0.13 (1:9 H_2O:CH_3CN). \(^1\)H NMR (400 MHz, D_2O): \(\delta\) 3.64 – 3.65 (m, 2H, H_{6'}, H_{6''}), 3.74 (dd, \(^3J\_3'-2' = 9.6\) Hz, \(^3J\_3'-4' = 3.2\) Hz, 1H, H_3'), 3.87 (m, 1H, H_5'), 3.95 – 3.96 (dd, \(^3J\_4'-3' = 3.4\) Hz, \(^3J\_4'-5' = 0.8\) Hz, 1H, H_4'), 4.05 – 4.10 (m, 1H, H_2'), 4.59 (s, 2H, CH_2NH), 5.55 (d, 1H, \(^3J\_1'-2' = 8.8\) Hz, 1H, H_1'), 7.80 – 7.88 (m, 4H, Ph), 8.11 (s, 1H, triazole CH); \(^{13}\)C \(^1\)H NMR (100 MHz, D_2O): \(\delta\) 35.24 (CH_2NH), 60.99 (C_6'), 68.71 (C_4'), 69.91 (C_2'), 73.06 (C_3'), 78.45 (C_5'), 88.20 (C_1'), 123.05 (triazole CH), 126.44 (Ph H), 128.44 (Ph H), 137.72 (Ph C), 144.32 (Ph C or triazole C), 145.63 (triazole C or Ph C), 169.53 (C=O). HRMS (ESI) calcd for C_{16}H_{20}N_5O_8S: 442.103807. Found: 442.103051.

4-({[4-(Aminosulfonyl)benzoyl]amino}methyl-1-(2',3',4'-tri-O-acetyl-\(\beta\)-D-arabinopyranosyl)-1-H-1,2,3-triazole (2c). The title compound was prepared according to the General Procedure 1 and isolated as off-white solid (147 mg, 0.27 mmol, 82 %). \(R_f\) 0.10 (8:2 EtOAc:hexanes); mp 125 – 126 °C. \(^1\)H NMR (400 MHz, DMSO-d_6): \(\delta\) 1.78 (s, 3H, OAc CH_3), 1.92 (s, 3H, OAc CH_3), 2.12 (s, 3H, OAc CH_3), 3.99 (dd, \(^2J_{5'-5''} = 13.2\) Hz, \(^3J_{5'-4'} = 2.0\) Hz, 3H, OAc CH_3), 5.15 (d, \(^3J_{1'-2'} = 8.8\) Hz, 1H, H_1'), 5.60 (d, \(^3J_{1'-2'} = 7.0\) Hz, 1H, H_1'), 6.10 (s, 1H, triazole H), 7.45 – 7.55 (m, 2H, H_3'), 7.60 (d, \(^3J_{1'-2'} = 8.8\) Hz, 1H, H_1'), 7.80 – 7.90 (m, 4H, Ph), 8.11 (s, 1H, triazole CH); \(^{13}\)C \(^1\)H NMR (100 MHz, DMSO-d_6): \(\delta\) 20.69 (OAc CH_3), 20.98 (OAc CH_3), 21.10 (OAc CH_3), 21.17 (OAc CH_3), 35.46 (CH_2NH), 62.25 (C_6'), 68.01 (C_4'), 68.30 (C_3'), 71.14 (C_2'), 73.63 (C_5'), 84.85 (C_1'), 123.13 (triazole CH), 126.29 (Ph CH), 128.66 (Ph CH), 137.63 (Ph C), 145.97 (triazole C or Ph C), 147.05 (triazole C or Ph C), 165.89 (C=O), 169.18 (C=O), 170.12 (C=O), 170.66 (C=O). HRMS (ESI) calcd for C_{24}H_{28}N_5O_{12}S: 610.146066. Found: 610.147458. Anal. (C_{24}H_{29}N_5O_{12}S•0.5H_2O) C, H, N.
4-({4-(Aminosulfonyl)benzoyl]amino}methyl-1-((β-D-garabinopyranosyl)-1-H-1,2,3-triazole (2c'). The title compound was prepared according to General Procedure 2 and isolated as pale yellow solid (77 mg, 0.19 mmol, ~ 100 %). Rf 0.26 (1:9 EtOAc:MeOH); mp 210 - 212 °C (decomp). 1H NMR (400 MHz, 1:9 DMSO-d₆ : D₂O): δ 3.74 (dd, 3J₃'-2' = 10 Hz, 3J₃'-₄' = 3.6 Hz, 1H, H₃'), 3.80 - 3.83 (m, 1H, H₅'), 3.93 – 3.96 (m, 2H, H₄', H₅''), 4.06 – 4.11 (m, 1H, H₂'), 4.59 (s, 2H, CH₂NH), 5.48 (d, 1H, 3J₁'-₂' = 9.2 Hz, 1H, H₁'), 7.83 – 7.91 (m, 4H, Ph H), 8.12 (s, 1H, triazole H); 13C 1H NMR (100 MHz, 2% D₂O in DMSO-d₆): δ 35.20 (CH₂NH), 68.55 (C₄'), 69.68 (C₅'), 69.84 (C₂'), 72.77 (C₃'), 88.55 (C₁'), 123.02 (triazole CH), 125.51 (Ph CH), 128.53 (Ph CH), 137.67 (Ph C), 144.64 (triazole C or Ph C), 145.83 (triazole C or Ph C), 169.18 (C=O). HRMS (ESI) calcd for C₁₅H₁₈N₅O₇S: 412.093242. Found: 412.092448.

4-({4-(Aminosulfonyl)benzoyl]amino}methyl-1-(2'-acetamido-2'-deoxy-3',4',6'-tri-O-acetyl-β-D-glucopyranosyl)-1-H-1,2,3-triazole (2d). The title compound was prepared
according to General Procedure 1 and isolated as white solid (149 mg, 0.24 mmol, 91%). \( R_f \) 0.32 (1:9 CH\(_3\)OH:EtOAc); mp 231 - 232 °C (decomp). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \)

- 1.55 (s, 3H, NHAc CH\(_3\)), 1.91 (s, 3H, OAc CH\(_3\)), 1.95 (s, 3H, OAc, CH\(_3\)), 1.97 (s, 3H, OAc CH\(_3\)), 4.00 (dd, \( ^2J_{6',6''} = 12.4 \) Hz, \( ^3J_{6',5'} = 2 \) Hz, 1H, H\(_6\)), 4.10 (dd, \( ^2J_{6',6''} = 12\) Hz, \( ^3J_{6',5'} = 4.8 \) Hz, 1H, H\(_6\)), 1.91 (s, 3H, OAc CH\(_3\)), 1.94 (s, 3H, OAc, CH\(_3\)), 1.97 (s, 3H, OAc CH\(_3\)), 4.18 (ddd, \( ^3J_{5',4'} = 7.2 \) Hz, \( ^3J_{5',6''} = 4.8 \) Hz, \( ^3J_{5',6'} = 2 \) Hz, 1H, H\(_5'\)), 4.50 (d, \( ^3J_{CH-NH} = 6.0 \) Hz, 2H, C\(_2\)NH), 7.44 (s, 2H, SO\(_2\)NH\(_2\)), 7.85 – 8.00 (m, Ph H), 8.03 (d, \( ^3J_{NH-2'} = 9.2 \) Hz, 1H, NHAc CONH), 8.13 (t, \( ^3J_{NH-CH} = 6.0 \) Hz, 1H, CH\(_2\)NH); \(^{13}\)C \( \{^1\} \) H NMR (100 MHz, DMSO-\(d_6\)): \( \delta \)

- 20.96 (OAc CH\(_3\)), 21.09 (OAc CH\(_3\)), 21.20 (OAc CH\(_3\)), 23.02 (OAc CH\(_3\)), 35.49 (CH\(_2\)NH), 52.69 (C\(_{2'}\)), 62.50 (C\(_{6'}\)), 68.67 (C\(_{3'}\)), 73.07 (C\(_{4'}\)), 74.05 (C\(_{5'}\)), 85.29 (C\(_{1'}\)), 122.45 (triazole CH), 126.70 (Ph CH), 128.67 (Ph CH), 137.70 (Ph C), 145.80 (triazole C or Ph C) 147.02 (triazole C or Ph C), 165.87 (C=O), 170.01 (C=O), 170.11 (C=O), 170.72 (C=O). HRMS (ESI) calcd. for C\(_{24}\)H\(_{29}\)N\(_6\)O\(_{11}\)S: 609.16205. Found: 609.162988. Anal. (C\(_{24}\)H\(_{30}\)N\(_6\)O\(_{11}\)S) C, H; N: calcd, 13.76; found, 12.87.

The title compound was prepared to General Procedure 2 and isolated as white solid (79 mg, 0.16 mmol, ~ 100 %). \( R_f \) 0.09 (1:9 H\(_2\)O:CH\(_3\)CN); mp 214 – 215 °C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \)

- 1.62 (s, 3H, NHAc CH\(_3\)), 3.47 – 3.52 (m, 1H, H\(_3'\)), 3.64 – 3.68 (m, 1H, H\(_4'\)), 3.97 – 4.05 (m, 1H, H\(_2'\)), 4.48 (d, \( ^3J_{CH-NH} = 5.8 \) Hz, 2H, CH\(_2\)NH), 4.58 – 4.61 (m, 1H, H\(_6\)), 5.21 – 5.24 (m, 2H, H\(_3'\), H\(_4'\)), 5.66 (d, 1H, \( ^3J_{1' - 2'} = 9.6 \) Hz, 1H, H\(_1'\)), 7.44 (br s, 2H, SO\(_2\)NH\(_2\)), 7.82 (d, \( ^3J_{NH-2'} = 8.8 \) Hz, 1H, NHAc NH), 7.85 – 8.00 (m, 4H, Ph), 7.97 (s, 1H, triazole 1H), 9.19 (t, \( ^3J_{NH-CH} = 6.0 \) Hz, 1H, CH\(_2\)NH); \(^{13}\)C \( \{^1\} \) H NMR (100 MHz, 2% D\(_2\)O in DMSO-\(d_6\)): \( \delta \)

- 23.30 (NHAc CH\(_3\)), 35.40 (CH\(_2\)NH), 55.00 (C\(_2'\)), 61.81 (C\(_6\)), 70.44 (C\(_4'\)), 74.46 (C\(_3'\)), 80.63 (C\(_5'\)), 86.59 (C\(_{1'}\)), 122.22 (triazole CH),
126.32 (Ph CH), 128.66 (Ph CH), 137.68 (Ph C), 145.26 (triazole C or Ph C), 146.87 (triazole C or Ph C), 166.10 (O=C), 169.982 (C =O). HRMS (ESI) calcd for C_{18}H_{23}N_{6}O_{8}S:\ 483.130356. Found: 483.129389.

4-({4-(Aminosulfonyl)benzoyl}amino)methyl-1-(2',3',4'-tri-O-acetyl-β-D-glucuronic acid methyl ester)-1-H-1,2,3-triazole (2e). The title compound was prepared according to General Procedure 1 and isolated as white solid (153 mg, 0.26 mmol, 92 %). R_f 0.12 (1:9 Hexanes:EtOAc); mp 221 – 222 °C (decomp). \(^1\)H NMR (400 MHz, DMSO-d_6): \(\delta\) 1.76 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.98 (s, 3H, OAc), 3.59 (s, 3H, OCH_3), 4.51 (d, \(^3\)J_{CH-NH} = 5.2 Hz, 2H, CH_2NH), 4.76 (d, \(^3\)J_{5'-4'} = 10.0 Hz, 1H, H_5'), 5.19 – 5.24 (m, 1H, H_4'), 5.44 – 5.59 (m, 1H, H_3'), 5.72 – 5.76 (m, 1H, H_2'), 6.34 (d, \(^3\)J_{1'-2'} = 9.6 Hz, 1H, H_1'), 7.45 (br s, 2H, SO_2NH_2), 7.86 – 8.01 (m, 4H, Ph H), 8.35 (s, 1H, triazole H), 9.23 (t, \(^3\)J_{NH-CH} = 5.6 Hz, 1H, NH/CH_2); \(^13\)C {\(^1\)H} NMR (100 MHz, DMSO-d_6): \(\delta\) 20.6 (OAc CH_3), 20.9 (OAc CH_3), 21.0 (OAc CH_3), 35.5 (CH_2NH), 53.3 (CO_2CH_3), 69.0 (C_4'), 70.4 (C_2'), 72.3 (C_3'), 73.5 (C_5'), 84.4 (C_1'), 122.9 (triazole CH), 126.3 (Ph CH), 128.7 (Ph CH), 137.6 (Ph C), 146.4 (triazole C or Ph C), 147.1 (triazole C or Ph C), 165.9 (C=O), 167.3 (C=O), 169.1 (C=O), 170.0 (C=O), 170.2 (C=O). HRMS (ESI) calcd for C_{23}H_{26}N_{5}O_{12}S:\ 596.130416. Found: 596.132499. Anal. (C_{23}H_{27}N_{3}O_{12}S) C, H, N.

4-({4-(Aminosulfonyl)benzoyl}amino)methyl-1-(β-D-glucuronic acid methyl ester)-1-H-1,2,3-triazole (2e'). The title compound was prepared according to General Procedure 2 and isolated as clear gum (79 mg, 0.17 mmol, ~ 100 %). R_f 0.13 (1:9 MeOH:EtOAc). \(^1\)H NMR (400 MHz, 2% D_2O in DMSO-d_6): \(\delta\) 3.40 – 3.49 (m, 2H, H_3', H_4'), 3.61 (s, 3H, COCH_3), 3.82 – 3.86 (m, 1H, H_2'), 4.08 (d, \(^3\)J_{5'-4'} = 9.6 Hz, 1H, H_5'), 4.51 (s, 2H, CH_2NH), 5.66 (d, \(^3\)J_{1'-2'} = 9.6 Hz, 1H, H_1'), 7.85 – 8.00 (m, 4H, Ph), 8.16 (s, 1H, triazole CH); \(^13\)C {\(^1\)H} NMR (100
MHz, 2% D$_2$O in DMSO-$d_6$): δ 35.43 (CH$_2$NH), 52.74 (COCH$_3$), 71.63 (C$_3$), 71.94 (C$_4$), 76.63 (C$_2$), 78.02 (C$_5$), 87.66 (C$_1$), 123.08 (triazole CH), 126.31 (Ph CH), 128.69 (Ph CH), 137.64 (Ph C), 145.52 (triazole C or Ph C), 146.89 (triazole C or Ph C), 165.85 (C=O), 169.37 (C=O). HRMS (ESI) calcd for C$_{17}$H$_{20}$N$_5$O$_9$S$: 470.098722. Found: 470.097959.

4-([4-(Aminosulfonyl)benzoyl]amino)methyl-1-(hepta-O-acetyl-$\beta$-D-maltosyl)-1H-1,2,3-triazole (2f). The title compound was prepared according to General Procedure 1 and isolated as pale yellow foam (424 mg, 0.47 mmol, 78%). $R_f$ 0.23 (2:8 Hexanes:EtOAc). 1H NMR (400 MHz, DMSO-$d_6$): δ 1.72 (s, 3H, OAc CH$_3$), 1.92 (s, 3H, OAc CH$_3$), 1.93 (s, 3H, OAc CH$_3$), 1.96 (s, 3H, OAc CH$_3$), 1.97 (s, 3H, OAc CH$_3$), 1.99 (s, 3H, OAc CH$_3$), 2.00 (s, 3H, OAc CH$_3$), 3.98 – 4.01 (m, 2H, Glc$_\alpha$H$_5'$, Glc$_\beta$H$_6'$), 4.05 – 4.16 (m, 3H, Glc$_\alpha$H$_6''$, Glc$_\beta$H$_4'$, Glc$_\beta$H$_6'$), 4.29 (ddd, $^3J_{5',4'} = 9.6$ Hz, $^3J_{5',6'} = 5.6$ Hz, $^3J_{5',6''} = 2.4$ Hz, 1H, Glc$_\beta$H$_5'$), 4.40 (dd, $^2J_{6',6''} = 12.4$ Hz, $^3J_{6'-5'} = 2.4$ Hz, 1H, Glc$_\beta$H$_6'$), 4.50 (d, $^3J_{\text{CH-NH}} = 5.6$ Hz, 2H, CH$_2$NH), 4.88 (dd, $^3J_{2',3'} = 10.8$ Hz, $^3J_{2',1'} = 4.0$ Hz, 1H, Glc$_\beta$H$_2'$), 4.95 – 5.00 (m, 1H, Glc$_\alpha$H$_4'$), 5.18 – 5.23 (m, 1H, Glc$_\alpha$H$_3'$), 5.32 (d, $^3J_{1',2'} = 4.0$ Hz, 1H, Glc$_\alpha$H$_1'$), 5.47 – 5.57 (m, 2H, Glc$_\beta$H$_2'$, Glc$_\beta$H$_3'$), 6.25 (d, $^3J_{1',2'} = 9.2$ Hz, 1H, Glc$_\beta$H$_1'$), 7.45 (br s, 2H, SO$_2$NH$_2$), 7.86 – 7.99 (m, 4H, Ph), 8.16 (s, 1H, triazole CH), 9.21 (t, $^3J_{\text{NH-CH}} = 5.6$ Hz, 1H, CH$_2$NH$\_2$); $^{13}$C $^1$H NMR (100 MHz, DMSO-$d_6$): δ 20.63 (OAc CH$_3$), 20.94 (OAc CH$_3$), 21.00 (OAc CH$_3$), 21.10 (OAc CH$_3$), 21.20 (OAc CH$_3$), 21.24 (OAc CH$_3$), 35.51 (CH$_2$NH), 62.06 (Glc$_\alpha$ C$_6'$), 63.52 (Glc$_\alpha$ C$_6'$), 68.34 (Glc$_\alpha$ C$_4'$), 68.83 (Glc$_\alpha$ C$_5'$), 69.59 (Glc$_\alpha$ C$_3'$), 70.09 (Glc$_\alpha$ C$_2'$), 71.30 (Glc$_\beta$ C$_3'$), 73.98 (Glc$_\beta$ C$_4'$), 74.50 (Glc$_\beta$ C$_5'$), 75.13 (Glc$_\beta$ C$_2'$), 84.07 (Glc$_\beta$ C$_1'$), 96.40 (Glc$_\alpha$ C$_1'$), 122.74 (triazole CH), 126.29 (Ph CH), 128.64 (Ph CH), 137.64 (Ph C), 146.19 (triazole C or Ph C), 147.05 (triazole C or Ph C), 165.87 (C=O). HRMS (ESI) calcd for C$_{36}$H$_{44}$N$_5$O$_{20}$S$: 898.230583. Found: 898.228045. Anal (C$_{36}$H$_{45}$N$_5$O$_{20}$S$\_3$H$_2$O) C, H, N, S.
4-({4-(Aminosulfonyl)benzoyl}amino)methyl-1-(β-d-maltosyl)-1H-1,2,3-triazole (2f').

The title compound was prepared according to General Procedure 2 and isolated as pale yellow foam (134 mg, 0.22 mmol ~ 100 %). Rf 0.10 (1:9 H2O:CH3CN). 1H NMR (400 MHz, D2O): δ 3.27 – 3.32 (m, 1H, Glcα H4' or Glcβ H4'), 3.46 (dd, 3J2'-3' = 10.0 Hz, 3J2'-1' = 4.0 Hz, Glcα H2'), 3.55 – 3.79 (m, 8 H, Glcα H3', Glcα H5', Glcα H6/H6', and Glcβ H3', Glcβ H5', Glcβ H6'/H6'), 3.83 – 3.87 (m, 1H, Glcβ H3'), 3.88 – 3.92 (m, 1H, Glcβ H2') 4.58 (s, 2H, CH2NH), 5.33 (d, 3J1'-2' = 4.0 Hz, 1H, Glcα H1'), 5.62 (d, 3J1'-2' = 9.2 Hz 1H, Glcβ H1'), 7.77 – 7.86 (m, 4H, Ph), 8.07 (s, 1H, triazole CH); 13C {1H} NMR (100 MHz, D2O): δ 35.18 (CH2NH), 60.58 (Glcα C6' or Glcβ C6'), 60.59 (Glcα C6' or Glcβ C6'), 69.47, 71.84, 72.27, 72.91, 72.99, 75.97, 76.50, 77.63 (Glcα C2', Glcα C3', Glcα C4', Glcα C5' and Glcβ C2', Glcβ C3', Glcβ C4', Glcβ C5'), 87.42 (Glcβ C1'), 99.83 (Glcα C1'), 123.32 (triazole CH), 126.33 (Ph CH), 128.36 (Ph CH), 137.39 (Ph C), 144.70 (triazole C or Ph C), 144.97 (triazole C or Ph C), 169.32 (C=O). HRMS (ESI) calcd for C22H30N5O13S-: 604.15663. Found: 604.155698.

Methyl 2',3',4'-tri-O-acetyl-6-{4-({aminosulfonyl)benzoyl}amino)methyl}-1H-1,2,3-triazol-1-yl]-6-deoxy-β-D-glucopyranoside (2g). The title compound was prepared according to General Procedure 1 and isolated as white foam (278 mg, 0.48 mmol, 82 %). Rf 0.1 (100% EtOAc). 1H NMR (400 MHz, DMSO-d6): δ 1.92 (s, 3H, OAc CH3), 1.96 (s, 3H, OAc CH3), 1.98 (s, 3H, OAc CH3), 3.03 (s, 3H, OCH3), 4.11 (m, 1H, H5), 4.44 – 4.49 (m, 2H, C=O CH2NH), 4.55 (dd, 2J6'-6'' = 14.4 Hz, 3J6'-5' = 2.8 Hz, 1H, H6'), 4.78 – 4.82 (m, 2H, H1', H2'), 4.83 – 4.88 (m, 1H, H6), 5.21 – 5.26 (m, 1H, H3'), 7.44 (br s, 2H, SO2NH2), 7.85 – 7.98 (m, 4H, Ph), 7.97 (s, 1H, triazole CH), 9.19 (t, 3JNH-CH = 5.6 Hz, 1H, CH2NH); 13C NMR {1H} (100 MHz, DMSO-d6): δ 20.96 (OAc CH3), 21.03 (OAc CH3), 21.13 (OAc CH3), 35.55 (CH2NH), 50.40 (C6'), 55.28 (OCH3), 68.00 (C5'), 70.12 (C1' or C2'), 70.17 (C1' or C2'), 70.33 (C3'), 96.57 (C1'), 124.54 (triazole CH), 126.31 (Ph CH), 128.58 (Ph CH), 137.68 (Ph C),
Methyl 6-[4-({aminosulfonyl)benzoyl]amino)methyl]-1H-1,2,3-triazol-1-yl]-6-deoxy-β-D-glucopyranoside (2g'). The title compound was prepared according to General Procedure 1 and isolated as pale yellow foam (76 mg, 0.17 mmol, 97 %). \( R_f 0.21 \) (1:9 CH\(_3\)OH:EtOAc).

\( ^1\)H NMR (400 MHz, 2% D\(_2\)O in DMSO-\(d_6\)): \( \delta 2.87 \) (s, 3H, OCH\(_3\)), 2.96 (dd, \( ^3J_{4'-5'} = 10.4 \) Hz, \( ^3J_{4'-3'} = 8.8 \) Hz, 1H, H\(_4'\)), 3.14 (dd, \( ^3J_{2'-3'} = 9.6 \) Hz, \( ^3J_{2'-1'} = 3.6 \) Hz, 1H, H\(_2'\)), 3.31 - 3.36 (m, 1H, H\(_3'\)), 3.59 – 3.65 (m, 1H, H\(_5'\)), 4.33 (dd, \( ^3J_{6'-5'} = 14.0 \) Hz, \( ^3J_{6'-6''} = 9.2 \) Hz, 1H, H\(_6'\)), 4.42 (d, 1H, \( ^3J_{1'-2'} = 3.6 \) Hz, 1H, H\(_1'\)), 4.47 – 4.48 (m, 2H, CH\(_2\)NH), 4.65 (dd, \( ^3J_{6''-6'} = 14.0 \) Hz, 1H, H\(_6''\)), 7.85 (s, 1H, triazole CH), 7.86 – 7.97 (m, 4H, Ph), 9.18 (t, \( ^3J_{NH-CH} = 5.2 \) Hz, 1H CH\(_2\)NH); \( ^13\)C NMR \( \{^1\}H \) (100 MHz, 2% D\(_2\)O in DMSO-\(d_6\)): \( \delta 35.45 \) (CH\(_2\)NH), 51.50 (C\(_6'\)), 54.87 (OCH\(_3\)), 71.07 (C\(_5\)), 72.12 (C\(_4'\) or C\(_2'\)), 72.21 (C\(_4'\) or C\(_2'\)), 73.53 (C\(_3\)), 100.31 (C\(_1\)), 124.50 (triazole CH), 126.33 (Ph CH), 128.57 (Ph CH), 137.67 (Ph C), 145.33 (triazole C or Ph C), 146.87 (triazole C or Ph C), 165.74 (C=O). HRMS (ESI) calcd for C\(_{23}H_{27}N_4O_{12}S^-\): 582.151151. Found: 582.150947. Anal (C\(_{23}H_{29}N_5O_{11}S\)•H\(_2\)O) C, H, N.

4-({4-(Aminosulfonyl)benzoyl]oxy)methyl-1-(2’-3’-4’-6’-tetra-O-acetyl-β-D-glucopyranosyl)-1-H-1,2,3-triazole (3a). The title compound was prepared according to General Procedure 1 and isolated as white solid (142 mg, 0.23 mmol, 86 %). \( R_f 0.43 \) (2:8 Hexanes:EtOAc); mp 196 – 197 °C. \( ^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta 1.75 \) (s, 3H, OAc CH\(_3\)), 1.93 (s, 3H, OAc CH\(_3\)), 1.97 (s, 3H, OAc CH\(_3\)), 2.00 (s, 3H, OAc CH\(_3\)), 4.05 (dd, \( ^2J_{6'-6''} = 12.8 \) Hz, \( ^3J_{6'-5'} = 2.4 \) Hz, 1H, H\(_6'\)), 4.10 (dd, \( ^2J_{6''-6'} = 12.8 \) Hz, \( ^3J_{6''-5'} = 5.2 \) Hz, 1H, H\(_6''\)), 4.35 (ddd, \( ^3J_{5’-4'} = 10 \) Hz, \( ^3J_{5’-6'} = 5.2 \) Hz, \( ^3J_{5’-6''} = 2.4 \) Hz, 1H, H\(_5'\)), 5.13 – 5.18 (m, 1H, H\(_4'\)).
5.40 – 5.46 (m, 2H, CH$_2$O), 5.51 – 5.55 (m, 1H, H$_3$), 5.63 – 5.67 (m, 1H, H$_2$), 6.35 (d, $^3J_{1'-2'}$ = 9.2 Hz, 1H, H$_1'$), 7.54 (s, 2H, SO$_2$NH$_2$), 7.92 – 8.11 (m, 4H, Ph H), 8.57 (s, 1H, triazole H);

$^{13}$C {$^1$H} NMR (100 MHz, DMSO-$_d_6$): δ 20.56 (OAc CH$_3$), 20.92 (OAc CH$_3$), 21.06 (OAc CH$_3$), 21.19 (OAc CH$_3$), 58.91 (CH$_2$O), 62.46 (C$_6'$), 68.19 (C$_4'$), 70.84 (C$_3'$), 72.76 (C$_2'$), 73.97 (C$_5'$), 84.56 (C$_1'$), 124.70 (triazole CH), 126.76 (Ph CH) 130.68 (Ph CH) 132.69 (Ph C) 143.16 (triazole C or Ph C) 148.92 (triazole C or Ph C), 165.09 (C=O), 169.16 (C=O), 170.04 (C=O), 170.22 (C=O), 170.70 (C=O). HRMS (ESI) calcd for C$_{24}$H$_{27}$N$_4$O$_{13}$S: 611.130081. Found: 611.127932. Anal (C$_{24}$H$_{28}$N$_4$O$_{13}$S) C, H, N, S.

4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(β-D-glucopyranosyl)-1-H-1,2,3-triazole (3a'). The title compound was prepared according to General Procedure 1 and isolated as white foam (82 mg, 0.19 mmol, 72 %). $R_f$ 0.10 (3:7 EtOH:CHCl$_3$).$^1$H NMR (400 MHz, D$_2$O): δ 3.47 – 3.53 (m, 2H, H$_4'$, H$_5'$), 3.56 – 3.66 (m, 2H, H$_3'$, H$_6'$), 3.74 – 3.79 (m, 1H, H$_6''$), 3.86 – 3.90 (m, 1H, H$_2''$), 5.65 (d, $^3J_{1'-2'}$ = 8 Hz, 1H, H$_1'$), 7.81 – 8.00 (Ph H), 8.25 (s, triazole CH);

$^{13}$C {$^1$H} NMR (100 MHz, D$_2$O): δ 58.33 (CH$_2$O), 60.55 (C$_6'$), 69.09 (C$_4'$), 72.44 (C$_2'$), 76.04 (C$_3'$), 79.04 (C$_5'$), 87.66 (C$_1'$), 125.21 (triazole CH), 126.24 (Ph CH), 130.62 (Ph CH), 133.21 (Ph C), 142.80 (triazole C or Ph C), 145.67 (triazole Ph C), 166.64 (C=O). HRMS (ESI) calcd for C$_{16}$H$_{19}$N$_4$O$_9$S$: 443.087822. Found: 443.087455.

4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(2'-3'-4'-6'-tetra-O-acetyl-β-D-galactopyranosyl)-1-H-1,2,3-triazole (3b). The title compound was prepared according to General Procedure 1 and isolated as white foam (184 mg, 0.30 mmol, 92 %). $R_f$ 0.41 (8:2 EtOAc:Hexanes).$^1$H NMR (400 MHz, DMSO-$_d_6$): δ 1.78 (s, 3H, OAc CH$_3$), 1.92 (s, 3H, OAc CH$_3$), 1.96 (s, OAc CH$_3$), 2.16 (s, OAc CH$_3$), 4.00 (dd, $^2J_{6'-6''}$ = 11.6 Hz, $^3J_{6'-5'}$ = 1.2 Hz, 1H, H$_6$'), 4.11 (dd, $^2J_{6''-6'}$ = 11.6 Hz, $^3J_{6''-5'}$ = 4.8 Hz, 1H, H$_6''$), 4.55 – 4.58 (m, 1H, H$_5$'), 5.40
(dd, $^3J_{4',3'} = 3.6$ Hz, $^3J_{4',5'} = 1.2$ Hz, H$_4'$), 5.42 (s, 2H, CH$_2$O), 5.44 – 5.45 (m, 1H, H$_3$), 5.56 – 5.61 (m, 1H, H$_2$), 6.27 (d, $^3J_{1',2'} = 9.2$ Hz, 1H, H$_1'$), 7.53 (s, 2H, SO$_2$NH$_2$), 7.91 – 8.11 (m, 4H, Ph H), 8.50 (s, 1H, triazole H); $^{13}$C {$_1^1$H} NMR (100 MHz, DMSO-d$_6$): δ 20.65 (OAc CH$_3$), 20.99 (OAc CH$_3$), 21.09 (OAc CH$_3$), 21.17 (OAc CH$_3$), 58.78 (CH$_2$O), 62.25 (C$_6'$), 67.98 (C$_4'$), 68.43 (C$_3'$), 71.04 (C$_2'$), 73.70 (C$_5'$), 84.96 (C$_1'$), 125.23 (triazole CH), 126.77 (Ph CH), 130.68 (Ph CH), 132.70 (Ph C), 142.92 (Ph C), 148.91 (triazole C), 165.13 (C=O), 169.20 (C=O), 170.13 (C=O), 170.60 (C=O), 170.66 (C=O). HRMS (ESI) calculated for C$_{24}$H$_{27}$N$_4$O$_{13}$S: 611.130081. Found: 611.129142.

4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(β-D-galactopyranosyl)-1-H-1,2,3-triazole (3b'). The title compound was prepared according to General Procedure 1 and isolated as white foam (136 mg, 0.31 mmol, 63 %). $R_f$ 0.12 (3:7 EtOH:CHCl$_3$). $^1$H NMR (400 MHz, 2% D$_2$O in DMSO-d$_6$): δ 3.41 – 3.48 (m, 3H, H$_5$, H$_6'$, H$_6''$), 3.51 (dd, $^3J_{3',2'} = 9.2$ Hz, $^3J_{3',4'} = 3.2$ Hz, 1H, H$_3'$), 3.67 – 3.73 (m, 1H, H$_4'$), 3.98 – 4.03 (m, 1H, H$_2'$), 5.43 (s, 2H, CH$_2$O), 5.48 (d, $^3J_{1',2'} = 8.8$ Hz, 1H, H$_1'$), 7.91 – 8.12 (m, 4H, Ph), 8.37 (s, 1H, triazole CH); $^{13}$C {$_1^1$H} NMR (100 MHz, 2% D$_2$O in DMSO-d$_6$): δ 58.42 (CH$_2$O), 60.38 (C$_6'$), 68.39 (C$_4'$), 69.24 (C$_2'$), 73.52 (C$_3'$), 78.46 (C$_5'$), 88.19 (C$_1'$), 124.01 (triazole CH), 126.21 (Ph CH), 130.10 (Ph CH), 132.16 (Ph C), 141.69 (Ph C), 148.13 (triazole C), 164.62 (C=O). HRMS (ESI) calcd for C$_{16}$H$_{19}$N$_4$O$_9$S$: 443.087822. Found: 443.087859.

4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(2'-3'-4’tri-O-acetyl-β-D-arabinopyranosyl)-1-H-1,2,3-triazole (3c). The title compound was prepared according to General Procedure 1 and isolated as white foam (228 mg, 0.42 mmol, 88 %). $R_f$ 0.55 (8:2 EtOAc:Hexanes). $^1$H NMR (400 MHz, DMSO-d$_6$): 1.78 (s, 3H, OAc CH$_3$), 1.93 (s, 3H, OAc CH$_3$), 2.13 (s, 3H, OAc CH$_3$), 4.02 (dd, $^2J_{5',5''} = 13.2$ Hz, $^3J_{5',4'} = 1.6$ Hz, 1H, H$_5'$), 4.14 – 4.18
(m, 1H, H₅), 5.28 – 5.30 (m, 1H, H₄), 5.38 (dd, 3J₃'·₂' = 10.0 Hz, 3J₃'·₄' = 3.6 Hz, 1H, H₃' ), 5.42 (s, 2H, CH₂O), 5.55 – 5.60 (m, 1H, H₂'), 6.13 (d, 3J₁'·₂' = 9.2 Hz, 1H, H₁'), 7.53 (br s, 2H, SO₂NH₂), 7.91 – 8.10 (m, 4H, Ph CH), 8.46 (s, 1H, triazole H); ¹³C {¹H} NMR (100 MHz, DMSO-d₆): δ 20.66 (OAc CH₃), 21.07 (OAc CH₃), 21.40 (OAc CH₃), 58.81 (CH₂O), 67.18 (C₅'), 68.57 (C₄'), 68.69 (C₂'), 70.95 (C₃'), 85.52 (C₁'), 125.11 (triazole CH), 126.76 (Ph CH), 130.67 (Ph CH), 132.71 (Ph C), 142.86 (Ph C), 148.91 (triazole CH), 165.11 (C=O), 169.24 (C=O), 170.20 (C=O), 170.55 (C=O). HRMS (ESI) calculated for C₂₁H₂₃N₄O₁₁S: 539.108952. Found: 539.107401. Anal (C₂₁H₂₄N₄O₁₁S•1.5H₂O) C, H, N, S.

4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(β-D-arabinopyranosyl)-1-H-1,2,3-triazole (3c'). The title compound was prepared according to procedure 1 and isolated as white solid (105 mg, 0.25 mmol, 84 %). Rf 0.26 (3:7 EtOH:CHCl₃); mp 184 - 189 °C. ¹H NMR (400 MHz, 2% D₂O in DMSO-d₆): δ 3.53 (dd, 3J₃'·₂' = 9.6 Hz, 3J₃'·₄' = 3.6 Hz, 1H, H₃' ), 3.72 – 3.74 (m, 2H, H₄', H₅'), 3.78 (dd, 2J₅''·₅' = 12.4 Hz, 3J₅''·₄' = 2.0 Hz, 1H, H₅'' ), 3.98 – 4.03 (m, 1H, H₂'), 5.41 (d, 3J₁'·₂' = 10.0 Hz, 1H, H₁'), 5.43 (s, 2H, CH₂O), 8.36 (s, 1H, triazole CH), 7.91 – 8.12 (m, 4H, Ph); ¹³C {¹H} NMR (100 MHz, 2% D₂O in DMSO-d₆): δ 59.06 (CH₂O), 69.03 (C₅'), 69.96 (C₄'), 73.86 (C₃'), 89.10 (C₁'), 124.59 (triazole CH), 126.79 (Ph CH), 130.70 (Ph CH), 132.74 (Ph C), 142.25 (triazole C or Ph C), 148.81 (triazole C or Ph C), 165.21 (C=O). HRMS (ESI) calcd for C₁₅H₁₇N₄O₆S¹: 413.077258. Found: 413.076552.

4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(2'-acetamido-2'-deoxy-3',4',6'-tri-O-acetyl-β-D-glucopyranosyl)-1-H-1,2,3-triazole (3d). The title compound was prepared according to the General Procedure 1 and isolated as white solid (292 mg, 0.60 mmol, 89 %). Rf 0.45 (100 % EtOAc); mp 217 - 218 °C. ¹H NMR (400 MHz, DMSO-d₆): δ 1.55 (s, 3H, NHaC CH₃), 1.92 (s, 3H, OAc CH₃), 1.97 (s, 3H, OAc CH₃), 1.98 (s, OAc CH₃), 4.03 (dd,
$J_6''-6'' = 12.4$ Hz, $J_5''-5'' = 5.6$ Hz, $J_6'-6' = 2$ Hz, 1H, H$_6'$), 4.12 (dd, $J_6''-5'', J_6'-6' = 12.8$ Hz, 1H, H$_6'$), 4.56 – 4.64 (m, 1H, H$_2$), 6.11 (d, $J_{1'-2'} = 9.6$ Hz, 1H, H$_{1'}$), 7.54 (s, 2H, SO$_2$NH$_2$), 7.91 – 8.12 (m, 4H, Ph H), 8.05 (d, $J_{NH-2} = 9.6$ Hz, 1H, NHAc CONH), 8.44 (s, triazole H); $^{13}$C $^1$H NMR (100 MHz, DMSO-$d_6$): $\delta$ 20.96 (OAc CH$_3$), 21.10 (OAc CH$_3$), 21.20 (OAc CH$_3$), 22.97 (NHAc CH$_3$), 52.74 (C$_2$), 58.96 (CH$_2$O), 62.45 (C$_6$), 68.66 (C$_3$), 72.99 (C$_4$), 74.10 (C$_5$), 85.45 (C$_1'$), 124.49 (triazole CH), 126.75 (Ph CH), 130.70 (Ph CH), 132.71 (Ph CH), 142.64 (Ph C), 148.91 (triazole C), 165.10 (C=O), 170.02 (C=O), 170.10 (C=O), 170.27 (C=O), 170.71 (C=O). HRMS (ESI) calcd for C$_{24}$H$_{28}$N$_5$O$_{12}$S: 610.14606. Found: 610.14535.

4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(2'-acetamido-2'-deoxy-β-D-glucopyranosyl)-1H-1,2,3-triazole (3d'). The title compound was prepared according to the General Procedure 1 and isolated as off-white solid (180 mg, 0.38 mmol, 68 %) $R_f$ 0.09 (3:7 EtOH:CHCl$_3$); mp 205 – 208 °C (decomp). $^1$H NMR (400 MHz, 2% D$_2$O in DMSO-$d_6$): $\delta$ 1.57 (s, 3H, NHAc CH$_3$), 3.22 – 3.27 (m, 1H, H$_4$-), 3.68 – 3.46 (m, 2H, H$_5'$, H$_6'$), 3.49 – 3.54 (m, 1H, H$_3$-), 3.65 – 3.69 (m, 1H, H$_6''$), 4.01 – 4.08 (m, 1H, H$_2''$), 5.39 (s, 2H, CH$_2$O), 5.71 (d, $J_{1'-2'} = 9.6$ Hz, 1H, H$_{1'}$), 7.85 (d, $J_{NH-2} = 9.2$ Hz, 1H, NHAc CONH), 7.91 – 8.10 (m, 4H, Ph), 8.27 (s, 1H, triazole CH); $^{13}$C $^1$H NMR (100 MHz, DMSO-$d_6$): $\delta$ 23.36 (NHAc CH$_3$), 55.20 (C$_2$), 58.99 (CH$_2$O), 61.35 (C$_6$), 70.61 (C$_4$), 74.57 (C$_5$), 80.81 (C$_1'$), 86.74 (C$_1'$), 124.34 (triazole CH), 126.76 (Ph CH), 130.69 (Ph CH), 132.76 (Ph C), 142.10 (triazole C or Ph C), 148.87 (triazole C), 165.13 (C=O), 169.82 (C=O). HRMS (ESI) calcd for C$_{13}$H$_{22}$N$_2$O$_2$S$: 484.114372. Found: 484.113226.
4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(2',3',4'-tri-O-acetyl-β-D-glucuronic acid methyl ester)-1H-1,2,3-triazole (3e). The title compound was prepared according to General Procedure 1 and isolated as white foam (307 mg, 92 %). \( R_f \) 0.58 (2:8 Hexanes:EtOAc). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 1.76 (s, 3H, OAc CH\(_3\)), 1.96 (s, 3H, OAc CH\(_3\)), 1.99 (s, 3H, OAc CH\(_3\)), 3.60 (s, 3H, COCH\(_3\)), 4.79 (d, \( ^3J_{5'-4'} = 10.0 \) Hz, 1H, H\(_{5'}\)), 5.21 – 5.26 (m, 1H, H\(_{4'}\)), 5.43 (s, 2H, CH\(_2\)O), 5.57 – 5.62 (m, 1H, H\(_3\)), 5.73 – 5.78 (m, 1H, H\(_2\)), 6.40 (d, \( ^3J_{1'-2'} = 9.2 \) Hz, 1H, H\(_1\)), 7.54 (br s, 2H, SO\(_2\)NH\(_2\)), 7.91 – 8.12 (m, 4H, Ph H), 8.65 (s, 1H, triazole H); \(^13\)C \(^1\)H NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) 20.56 (OAc CH\(_3\)), 20.90 (OAc CH\(_3\)), 20.95 (OAc CH\(_3\)), 53.30 (COCH\(_3\)), 58.90 (CH\(_2\)O), 69.05 (C\(_4'\)), 70.48 (C\(_3'\)), 72.13 (C\(_2'\)), 73.56 (C\(_5'\)), 84.48 (C\(_1'\)), 124.90 (triazole CH), 126.77 (Ph CH), 130.69 (Ph CH), 132.67 (Ph C), 143.28 (triazole C or Ph C), 148.92 (triazole C or Ph C), 165.09 (C=O), 167.24 (C=O), 169.10 (C=O), 169.98 (C=O), 170.19 (C=O). HRMS (ESI) calculated for C\(_{23}\)H\(_{25}\)N\(_4\)O\(_{13}\)SCl: 633.091109. Found: 633.094227. Anal (C\(_{23}\)H\(_{26}\)N\(_4\)O\(_{13}\)S•1.5H\(_2\)O) C, H, N, S.

4-({[4-(Aminosulfonyl)benzoyl]oxy}methyl-1-(β-D-glucuronic acid methyl ester)-1H-1,2,3-triazole (3e'). The title compound was prepared according to General Procedure 1 and isolated as hygroscopic white foam (42 mg, 0.08 mmol, 72 %). \( R_f \) 0.32 (1:9 MeOH:EtoAc). \(^1\)H NMR (400 MHz, 2% D\(_2\)O in DMSO-\(d_6\)): \( \delta \) 3.27 – 3.32 (m, 1H, H\(_3\)), 3.96 – 3.01 (m, 1H, H\(_4\)), 3.65 (s, 3H, COCH\(_3\)), 3.84 – 3.88 (m, 1H, H\(_2\)), 4.63 (d, \( ^3J_{5'-4'} = 9.6 \) Hz, 1H, H\(_5\)), 5.42 (s, 2H, CH\(_2\)O), 5.72 (d, \( ^3J_{1'-2'} = 9.6 \) Hz, 1H, H\(_1\)), 7.91 – 8.12 (m, 4H, Ph H), 8.46 (s, 1H, triazole CH); \(^13\)C \(^1\)H NMR (100 MHz, 2% D\(_2\)O in DMSO-\(d_6\)): \( \delta \) 52.81 (COCH\(_3\)), 58.92 (CH\(_2\)O), 71.56 (C\(_3'\)), 71.89 (C\(_4'\)), 76.68 (C\(_2'\)), 78.00 (C\(_5'\)), 87.79 (C\(_1'\)), 125.09 (triazole CH), 126.80 (Ph CH), 130.73 (Ph CH), 136.85 (Ph C), 142.40 (triazole C or Ph C), 148.49 (triazole C or Ph C), 165.20 (C=O), 169.35 (C=O). HRMS (ESI) calcd for C\(_{17}\)H\(_{19}\)N\(_4\)O\(_{10}\)S: 471.082737. Found: 471.082075.
4-([(4-(Aminosulfonyl)benzoyl)oxy]methyl-1-(hepta-O-acetyl-β-D-maltosyl)-1H-1,2,3-triazole (3f). The title compound was prepared according to General Procedure 1 and isolated as white foam (185 mg, 0.21 mmol, 91 %). $R_f$ 0.46 (8:2 EtOAc:Hexanes). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.71 (s, 3H, OAc CH$_3$), 1.93 (s, 6H, 2 x OAc CH$_3$), 1.96 (s, 3H, OAc CH$_3$), 1.97 (s, 3H, OAc CH$_3$), 1.99 (s, 3H, OAc CH$_3$), 2.02 (s, 3H, OAc CH$_3$), 3.97 – 4.02 (m, 2H, Glc$\alpha$H$_5'$, Glc$\beta$H$_6'$), 4.07 – 4.17 (m, 3H, Glc$\alpha$H$_6''$, Glc$\beta$H$_4'$, Glc$\beta$H$_6''$), 4.32 (ddd, $^3$J$_{5'-4'}$ = 10 Hz, $^3$J$_{5'-6'}$ = 5.6 Hz, $^3$J$_{5'-6''}$ = 2.4 Hz, 1H, Glc$\beta$H$_5'$), 4.42 (dd, $^2$J$_{6''-6'}$ = 12.4 Hz, $^3$J$_{6''-5'}$ = 2 Hz, 1H, Glc$\beta$H$_6''$), 4.50 – 4.54 (m, 2H, Glc$\alpha$H$_1'$), 4.67 (s, 2H, SO$_2$NH$_2$), 7.91 – 8.10 (m, 4H, Ph CH), 8.47 (s, 1H, triazole H); $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 20.57 (OAc CH$_3$), 20.95 (OAc CH$_3$), 21.01 (OAc CH$_3$), 21.02 (OAc CH$_3$), 21.12 (OAc CH$_3$), 21.19 (OAc CH$_3$), 21.25 (OAc CH$_3$), 58.91 (CH$_2$O), 62.06 (Glc$\alpha$C$_6$), 63.45 (Glc$\beta$C$_6$), 68.37 (Glc$\alpha$C$_4$), 68.85 (Glc$\beta$C$_4$), 69.58 (Glc$\alpha$C$_3'$), 70.11 (Glc$\alpha$C$_2'$), 71.38 (Glc$\beta$C$_3'$), 73.94 (Glc$\alpha$C$_5'$), 74.58 (Glc$\beta$C$_5'$), 74.96 (Glc$\beta$C$_5'$), 79.85 (Glc$\beta$C$_2'$), 84.16 (Glc$\beta$C$_1'$), 96.41 (Glc$\alpha$C$_1'$), 124.74 (triazole CH), 126.76 (Ph CH), 130.67 (Ph CH), 132.68 (Ph C), 143.06 (Ph C), 148.91 (triazole C), 165.09 (C=O), 169.36 (OAc C=O), 169.84 (OAc C=O), 170.19 (OAc C=O), 170.35 (C=O), 170.53 (C=O), 170.78 (C=O). HRMS (ESI) calcd for C$_{36}$H$_{43}$N$_4$O$_{21}$S: 899.214599. Found: 899.211425. Anal. (C$_{36}$H$_{44}$N$_4$O$_{21}$S•1.5H$_2$O) C, H, N, S.

4-([(4-(Aminosulfonyl)benzoyl)oxy]methyl-1-(β-D-maltosyl)-1H-1,2,3-triazole (3f'). The title compound was prepared according to General Procedure 1 and isolated as white foam (161 mg, 0.26 mmol, 58 %). $R_f$ 0.39 (2:8 MeOH:EtOAc). $^1$H NMR (400 MHz, D$_2$O): δ 3.27 –
3.32 (m, 1H, Glcα H4' or Glcβ H4'), 3.55 – 3.79 (m, 8 H, Glcα H3', Glcα H5', Glcα H6/H6', and Glcβ H3', Glcβ H5', Glcβ H6/H6'), 3.46 (dd, \(^3J_{2'-3'} = 10.0\) Hz, \(^3J_{2'-1'} = 3.6\) Hz, 1H, Glcα H2'), 3.84 – 3.94 (m, 8 H, Glcα H3', Glcα H5', Glcα H6/H6', and Glcβ H3', Glcβ H5', Glcβ H6/H6'), 3.46 (dd, \(^3J_{2'-3'} = 10.0\) Hz, \(^3J_{2'-1'} = 3.6\) Hz, 1H, Glcα H2'), 3.84 – 3.94 (m, 2H, CH₂O), 5.34 (d, \(^3J_{1'-2'} = 3.6\) Hz, 1H, Glcα H1'), 5.39 (s, 2H, CH₂O), 5.66 (d, \(^3J_{1'-2'} = 8.8\) Hz, 1H, Glcβ H1'), 7.78 – 7.97 (m, 4H, Ph H), 8.25 (s, 1H, triazole CH); \(^13C\) \(^{1H}\) NMR (100 MHz, D₂O): δ 58.33 (CH₂O), 60.54 (Glcα C₆' or Glcβ C₆'), 69.47, 71.84, 72.31, 72.92, 72.99, 75.93, 76.52, 77.66 (Glcα C₂', Glcα C₃', Glcα C₄', Glcα C₅' and Glcβ C₂', Glcβ C₃', Glcβ C₄', Glcβ C₅'), 87.49 (Glcβ C₁'), 99.81 (Glcα C₂'), 125.16 (triazole CH), 126.23 (Ph CH), 130.69 (Ph CH), 133.57 (Ph CH), 142.82 (triazole C or Ph C), 145.68 (triazole C or Ph C), 166.59 (C=O). HRMS (ESI) calcd for C₂₂H₂₉N₄O₁₄S⁻: 605.14064. Found: 605.138433.

**Methyl 2',3',4'-tri-O-acetyl-6-[[4-(aminosulfonyl)benzoyl]oxy]methyl]-1H-triazol-1-yl]-6-deoxy-β-D-glucopyranoside (3g).** The title compound was prepared according to General Procedure 1 and isolated as white foam (123 mg, 0.21 mmol, 89 %). \(R_f\) 0.42 (8:2 EtOAc:Hexanes). \(^1H\) NMR (400 MHz, DMSO-\(d_6\)): δ 1.92 (OAc CH₃), 1.96 (OAc CH₃), 1.99 (OAc CH₃), 2.99 (OAc CH₃), 4.13 (ddd, \(^3J_{5'-4'} = 10.8\) Hz, \(^3J_{5'-6'} = 8.4\) Hz, \(^3J_{5'-6''} = 2.8\) Hz, 1H, H₅'), 4.52 (dd, \(^2J_{6,6'} = 14.4\) Hz, \(^3J_{6,5'} = 8.4\) Hz, 1H, H₆'), 4.62 (dd, \(^2J_{6''6'} = 14.4\) Hz, \(^3J_{6''5'} = 3.0\) Hz, 1H, H₆''), 4.80 – 4.84 (m, 2H, H₁', H₂'), 4.87 – 4.91 (m, 1H, H₄'), 5.22 – 5.23 (m, 1H, H₃'), 5.41 (s, 2H, CH₂O), 7.53 (br s, 2H, SO₂NH₂), 7.91 – 8.08 (m, 4H, Ph CH), 8.27 (s, triazole H); \(^13C\) \(^{1H}\) NMR (100 MHz, DMSO-\(d_6\)): δ 20.99 (OAc CH₃), 21.05 (OAc CH₃), 21.17 (OAc CH₃), 50.59 (C₆'), 55.17 (OCH₃), 59.06 (CH₂O), 68.03 (C₅'), 70.08 (C₁' or C₂'), 70.20 (C₁' or C₂'), 70.35 (C₃'), 96.57 (C₁'), 126.55 (triazole CH), 126.77 (Ph CH), 130.58 (Ph CH), 132.75 (Ph C), 142.34 (triazole C or Ph C), 148.87 (triazole C or Ph C), 165.11 (C=O), 170.03 (C=O), 170.27 (C=O), 170.34 (C=O). HRMS (ESI) calcd for C₂₃H₂₉N₄O₁₄S⁻:
Methyl 6-deoxy-6-(4-{4-Sulfamoylbenzoyloxy}methyl-1H-1,2,3-triazol-1-yl)-α-D-glucopyranoside (3g’). The title compound was prepared according to procedure 1 and isolated as white solid (75 mg, 0.16 mmol, 72 %). Rf 0.52 (3:7 EtOH:CHCl3); mp 121 – 122 °C. 1H NMR (400 MHz, 2% D2O in DMSO-d6): δ 2.85 (s, 3H, OCH3), 2.98 (dd, 3J4’-5’ = 10.0 Hz, 3J2’-3’ = 9.6 Hz, 3J2’-1’ = 3.6 Hz, 1H, H2’), 3.16 – 3.37 (m, 1H, H3’), 3.61 – 3.66 (m, 1H, H5’), 4.38 (dd, 2J2’-6’ = 14.0, 3J6’-5’ = 9.2 Hz, 1H, H6’), 4.43 (d, 3J1’-2’ = 4.0 Hz, 1H, H1’), 4.70 (dd, 2J6’-6’ = 14.0 Hz, 3J6’-5’ = 2.4 Hz, 1H, H6’), 5.40 (s, 2H, CH2O), 7.90 – 8.07 (m, 4H, Ph), 8.16 (s, 1H, triazole CH); 13C {1H} NMR (100 MHz, 2% D2O in DMSO-d6): δ 51.01 (C6’), 54.04 (OCH3), 58.39 (CH2O), 70.41 (C5’), 71.66 (C4’), 73.06 (C3’), 99.67 (C1’), 125.89 (triazole CH), 126.08 (Ph CH), 129.89 (Ph CH), 132.08 (Ph C), 141.41 (triazole C or Ph C), 148.75 (triazole C or Ph C), 164.43 (C=O). HRMS (ESI) calcd for C17H21N4O9S•0.5H2O: 457.10347. Found: 457.103411.

CA inhibition assay. An Applied Photophysics stopped-flow instrument has been used for assaying the CA catalysed CO2 hydration activity. Phenol red (at a concentration of 0.2 mM) has been used as indicator, working at the absorbance maximum of 557 nm, with 10 mM Hepes (pH 7.5) as buffer, 0.1 M Na2SO4 (for maintaining constant the ionic strength), at 25 °C, following the CA-catalyzed CO2 hydration reaction for a period of 10-100 s (the uncatalyzed reaction needs around 60-100 s in the assay conditions, whereas the catalyzed ones are of around 6-10 s). The CO2 concentrations ranged from 1.7 to 17 mM for the determination of kinetic parameters. For each inhibitor, tested in the concentration range between 0.01 nM to 100 μM, at least six traces of the initial 5-10% of the reaction have been
used for determining the initial velocity. The uncatalyzed rates were determined in the same manner and subtracted from the total observed rates. Stock solutions of inhibitor (1 mM) were prepared in distilled-deionized water with 10-20% (v/v) DMSO (which is not inhibitory at these concentrations) and dilutions up to 0.01 nM were done thereafter with distilled-deionized water. 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 non-linear 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.\textsuperscript{24-28} The catalytic activity (in the absence of inhibitors) of these enzymes was calculated from Lineweaver-Burk plots, as reported earlier, and represent the mean from at least three different determinations.\textsuperscript{24-28} Enzyme concentrations in the assay system were: 9.2 nM for hCA I, 7.3 nM for hCA II and 8.5 nM for hCA IX. Enzymes used here were recombinant ones, prepared and purified as described earlier.\textsuperscript{24-28,30}

**Acknowledgement**

This work was financed in part by the Australian Research Council (DP0343419); the Eskitis Institute for Cell and Molecular Therapies and the School of Science (Griffith University) and an EU grant of the 6\textsuperscript{th} framework programme (EUROXY project) (University of Florence).

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


Table 1. Inhibition and selectivity ratio data for sulfonamides 2, 3, the 28 new glycoconjugates and standard inhibitors against human isozymes hCA I, II, and IX.

<table>
<thead>
<tr>
<th>Compound</th>
<th>(K_i) (nM)(^a)</th>
<th>(K_i) (hCA I)/ (hCA IX)(^b)</th>
<th>(K_i) (hCA II)/ (hCA IX)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hCA I(^c)</td>
<td>hCA II(^c)</td>
<td>hCA IX(^d)</td>
</tr>
<tr>
<td>AZA</td>
<td>900</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>MZA</td>
<td>780</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>EZA</td>
<td>25</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>BRZ</td>
<td>15</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>DCP</td>
<td>1200</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>IND</td>
<td>31</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>6100</td>
<td>47</td>
<td>113</td>
</tr>
<tr>
<td>3</td>
<td>4000</td>
<td>45</td>
<td>104</td>
</tr>
<tr>
<td>2a</td>
<td>5600</td>
<td>384</td>
<td>430</td>
</tr>
<tr>
<td>2a'</td>
<td>2000</td>
<td>8.2</td>
<td>442</td>
</tr>
<tr>
<td>3a</td>
<td>2300</td>
<td>119</td>
<td>1238</td>
</tr>
<tr>
<td>3a'</td>
<td>4400</td>
<td>7.0</td>
<td>183</td>
</tr>
<tr>
<td>2b</td>
<td>8700</td>
<td>470</td>
<td>76</td>
</tr>
<tr>
<td>2b'</td>
<td>6600</td>
<td>7.4</td>
<td>360</td>
</tr>
<tr>
<td>3b</td>
<td>3600</td>
<td>6.8</td>
<td>132</td>
</tr>
<tr>
<td>3b'</td>
<td>5800</td>
<td>8.1</td>
<td>65</td>
</tr>
<tr>
<td>2c</td>
<td>2400</td>
<td>279</td>
<td>103</td>
</tr>
<tr>
<td>2c'</td>
<td>2700</td>
<td>128</td>
<td>420</td>
</tr>
<tr>
<td>3c</td>
<td>4900</td>
<td>7.3</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>3e'</td>
<td>7.7</td>
<td>5.8</td>
<td>96</td>
</tr>
<tr>
<td>2d</td>
<td>1200</td>
<td>45</td>
<td>124</td>
</tr>
<tr>
<td>2d'</td>
<td>9100</td>
<td>265</td>
<td>238</td>
</tr>
<tr>
<td>3d</td>
<td>5100</td>
<td>218</td>
<td>1200</td>
</tr>
<tr>
<td>3d'</td>
<td>4800</td>
<td>7.3</td>
<td>108</td>
</tr>
<tr>
<td>2e</td>
<td>5800</td>
<td>7.6</td>
<td>471</td>
</tr>
<tr>
<td>2e'</td>
<td>2400</td>
<td>378</td>
<td>23</td>
</tr>
<tr>
<td>3e</td>
<td>5400</td>
<td>7.0</td>
<td>125</td>
</tr>
<tr>
<td>3e'</td>
<td>9.6</td>
<td>7.2</td>
<td>241</td>
</tr>
<tr>
<td>2f</td>
<td>9200</td>
<td>7.5</td>
<td>221</td>
</tr>
<tr>
<td>2f'</td>
<td>9500</td>
<td>267</td>
<td>1100</td>
</tr>
<tr>
<td>3f</td>
<td>3900</td>
<td>423</td>
<td>130</td>
</tr>
<tr>
<td>3f'</td>
<td>3500</td>
<td>7.3</td>
<td>39</td>
</tr>
<tr>
<td>2g</td>
<td>10400</td>
<td>44</td>
<td>135</td>
</tr>
<tr>
<td>2g'</td>
<td>9300</td>
<td>90</td>
<td>204</td>
</tr>
<tr>
<td>3g</td>
<td>3400</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>3g'</td>
<td>3100</td>
<td>8.6</td>
<td>67</td>
</tr>
</tbody>
</table>

*Errors in the range of ± 5-10 % of the reported value, from three determinations. The $K_i$ ratios are indicative of isozyme selectivity. Human (cloned) isozymes, by the CO$_2$ hydration method. 23-28*

* Catalytic domain of human (cloned) isozyme, by the CO$_2$ hydration method. 23-28
Figure Legends

**Figure 1.** Azido sugar building block panel: a-g (R = Ac) and a’-g’ (R = H).

**Figure 2.** Glycoconjugate benzene sulfonamides.
Scheme Titles and Footnotes

**Scheme 1.** Cu(I) catalyzed 1,3-dipolar cycloaddition reaction (1,3-DCR) of azido sugars and terminal alkynes.\(^{18}\)

**Scheme 2.**\(^a\)

\(^a\)Reagents and conditions: (i) azide (0.2 - 0.5 M), acetylene (1 equiv), CuSO\(_4\).5H\(_2\)O (0.1 - 0.2 equiv), sodium ascorbate (0.2 - 0.4 equiv), 1:1 t-BuOH/H\(_2\)O, 40 °C, 30 min – 1 h, 58-96%; (ii) NaOCH\(_3\), CH\(_3\)OH, rt, 2 h, quantitative.
Figure 1.
Figure 2.
Scheme 1.
Scheme 2.

\[ \text{SO}_2\text{NH}_2 \]

\[ \text{X} = \text{NH} \quad 2 \]
\[ \text{X} = \text{O} \quad 3 \]

\[ \text{(AcO)}_n \]

\[ \text{N}_3 \]

\[ \text{(i), a-g} \]

\[ \text{X} = \text{NH} \quad 2a-2g \]
\[ \text{X} = \text{O} \quad 3a-3g \]

\[ \text{(ii), 2a-2g} \]
\[ \text{(HO)}_n \]

\[ \text{H}_3\text{CO}^+ \]

\[ \text{SO}_2\text{NH}_2 \]

\[ \text{X} = \text{NH} \quad 2a'-2g' \]
\[ \text{X} = \text{O} \quad 3a'-3g' \]

\[ \text{(HO)}_n \]

\[ \text{(i), 3} \]

\[ \text{a'-g'} \]

\[ \text{SO}_2\text{NH}_2 \]

\[ \text{H}_2\text{CO} \]
Chemical Structures Group A

acetazolamide

methazolamide

ethoxazolamide

brinzolamide
dichlorphenamide

indisulam
Chemical Structure Group B

paclitaxel
Chemical Structures Group C

1. \[
\text{SO}_2\text{NH}_2 \quad \text{HO}\quad \text{CO}
\]

2. \[
\text{SO}_2\text{NH}_2 \quad \text{N} \quad \text{CN}
\]

3. \[
\text{SO}_2\text{NH}_2 \quad \text{CHO}
\]
A novel class of carbonic anhydrase inhibitors: glycoconjugate benzene sulfonamides prepared by “click-tailing”

Brendan L. Wilkinson,† Laurent F. Bornaghi,† Todd A. Houston,‡ Alessio Innocenti,§ Claudiu T. Supuran*§ and Sally-Ann Poulsen*†