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Novel C-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents: 1,3,4-Thiadiazolylmethylphenyl glucoside congeners

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ABSTRACT

Novel C-aryl glucoside SGLT2 inhibitors containing 1,3,4-thiadiazole moieties were designed and synthesized. Among the compounds tested, biaryl-type compounds containing pyrazine **59**, 2-furan **61**, and 3-thiophene **71** showed the best in vitro inhibitory activities to date (IC_{50} = 3.51–7.03 nM) against SGLT2. A selected compound **61**, demonstrated reasonable blood glucose-lowering effects, indicating that the information obtained from the SAR studies in this 1,3,4-thiadiazolylmethylphenyl glucoside series might help to design more active SGLT2 inhibitors that are structurally related.

1. Introduction

Diabetes has become an increasing concern to the world's population. In 2007, approximately 246 million people were considered diabetic, with an additional 7 million people diagnosed with the disease every year.[1] Diabetes is a chronic metabolic disorder that is defined by the body's inability to generate insulin or to respond adequately to circulating insulin. There are two identified forms of diabetes: type 1 diabetes is distinguished as an autoimmune disease involving pancreatic β-cells, while type 2 diabetes is defined by β-cell dysfunction and insulin resistance.[2] Type 2 diabetes is the most common disorder of glucose homeostasis, accounting for nearly 90–95% of all cases of diabetes.

Sodium-dependent glucose cotransporters (SGLTs) couple the transport of glucose against a concentration gradient with the simultaneous transport of Na^+ down a concentration gradient.[3] Two important SGLT isoforms have been cloned and identified as SGLT1 and SGLT2.[4] SGLT1 is located in the gut, kidney, and heart where its expression regulates cardiac glucose transport.[5] SGLT1 is a high-affinity, low-capacity transporter and therefore accounts for only a small fraction of renal glucose reabsorption.[6] In contrast, SGLT2 is a low-affinity, high-capacity transporter located exclusively at the apical domain of the epithelial cells in the early proximal convoluted tubule. It is estimated that 90% of renal glucose reabsorption is facilitated by SGLT2; the remaining 10% is likely mediated by SGLT1 in the late proximal straight tubule.[7] Since SGLT2 appears to be responsible for the majority of renal glucose reabsorption based on human mutation studies,[8] it has become a target of therapeutic interest. Phlorizin **1**, which was isolated form the root bark of the apple tree, demonstrated antidiabetic activity, lowering plasma glucose and improving insulin resistance by increasing renal glucose excretion. However, phlorizin was not developed as a drug for the treatment of diabetes because the compound was found to be metabolically unstable. This instability is due to β-glucosidase cleavage in the intestinal tract and prevented oral administration (Fig. 1). In addition, enzymatic release of the aglycone phloretin **2**, a micromolar inhibitor of sodium-independent facilitative glucose transporters (GLUTs), could potentially inhibit GLUT-mediated cellular uptake of glucose.[9,15]

Subsequently, T-1095 **3**, by Tanabe Seiyaku, was reported as the first orally absorbable SGLT2 inhibitor, overcoming the disadvantage of phlorizin **1** (Fig. 2).[10] **3** was absorbed in the intestine and converted to an active form, T-1095A **4**. Following the discovery of **3**, O-glucosides such as sergliflozin **5** and remogliflozin **7** advanced furthest in clinical trials. Compound **5** was disclosed by Kissei in 2003 as a potential treatment for diabetes and obesity.[11] In 2007, Kissei, in collaboration with GlaxoSmithKline, initiated the development of **7**, a pyrazole-based O-glucoside.[12] Again, concern regarding gut β-glucosidase-mediated degradation, resulted in

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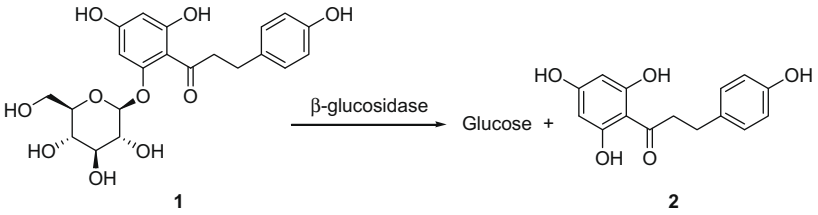


Figure 1. Structure and β-glucosidase-mediated cleavage of phlorizin (**1**).

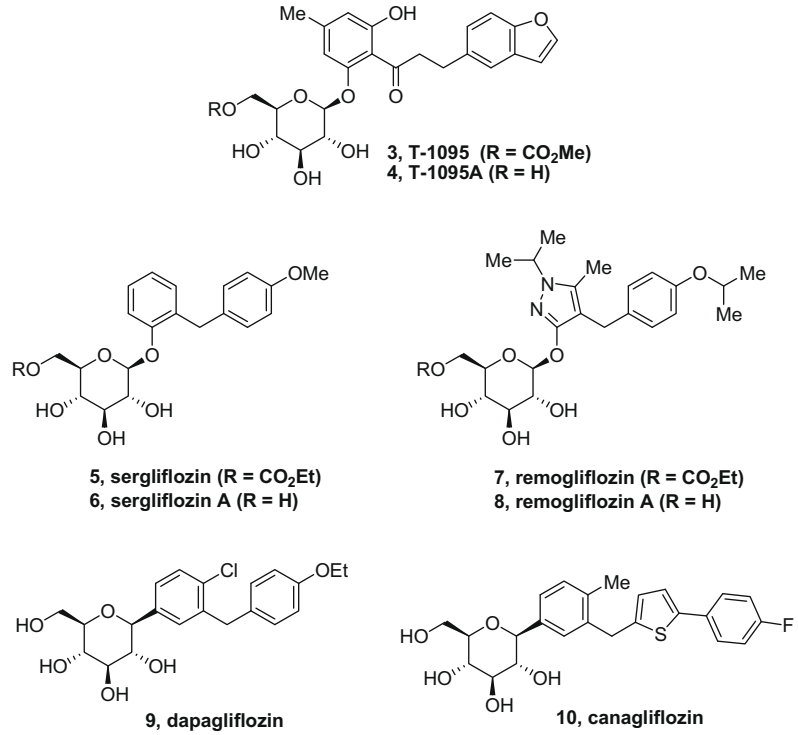


Figure 2. Structures of SGLT2 inhibitors.

developing sergliflozin A **6** and remogliflozin A **8** being administered as the ethyl carbonate prodrugs **5** and **7**, respectively.

Subsequent endeavors to identify SGLT2 inhibitors suitable for oral administration without the need for a prodrug led to the discovery of *C*-glucoside-derived SGLT2 inhibitors. C-glucosides appear to have drug-like properties with enhanced chemical stability of the glucosidic bond. Extensive SAR studies by Bristol–Myers Squibb identified dapagliflozin **9**, a potent, selective SGLT2 inhibitor for the treatment of type 2 diabetes.[13–15] At present, dapagliflozin is the most advanced SGLT2 inhibitor in clinical trials and is believed to be the first SGLT2 inhibitor to go to market.[18] On the other hand, Mitsubishi Tanabe Pharma, in collaboration with Johnson & Johnson, is developing canagliflozin **10**, another novel *C*-glucoside-derived SGLT2 inhibitor.[16] In August 2009, a phase 3 study was reportedly initiated to evaluate the safety and efficacy of **10** in patients with type 2 diabetes.[17]

In the present study, metabolically more stable C-glucosides bearing a heteroaromatic ring were exploited in order to develop novel SGLT2 targeting antidiabetic agents. We envisioned that replacement of the distal ring of dapagliflozin **9** with a heterocyclic ring would be a worthy approach for the improvement of the partition coefficient (log P) value, to potentially decrease plasma protein binding. For this purpose, the structure of dapagliflozin **9** was modified into **11**, bearing a heterocyclic ring as shown in Figure 3. Among a variety of heterocycles, we decided to screen thiadiazole **13** as our initial efforts. Herein, we report the design, synthesis and biological evaluation of 1,3,4-thiadiazolylmethylphenyl glucoside congeners.

2. Results and discussion

2.1. Chemistry

Synthesis of the target compounds commenced with the preparation of the lactone **15**. Commercially available perbenzylated gluconolactol **14**[20] was treated with TPAP (tetrapropylammonium perruthenate) in the presence of NMO (4-methylmorpholine N-oxide) to provide the requisite perbenzylated gluconolactone **15** in high yield as shown in Scheme 1.

As shown in Scheme 2, the reduction of commercially available 5-bromo-2-chlorobenzoic acid (**16**) with a borane-dimethyl sulfide complex, and subsequent silylation of the corresponding alcohol with TIPSCl (triisopropylsilyl chloride) in the presence of imidazole and DMAP (4-(dimethylamino)pyridine) generated bromide **17** in 95% yield over two steps. Lithium–halogen exchange, followed by the addition of the nascent lithiated aromatic compound to perbenzylated gluconolactone **15**, produced a mixture of the corresponding lactols. The lactols were reduced using triethylsilane and BF_3 etherate,[19] desilylated and afforded alcohol **18** in 98% yield over the three steps.

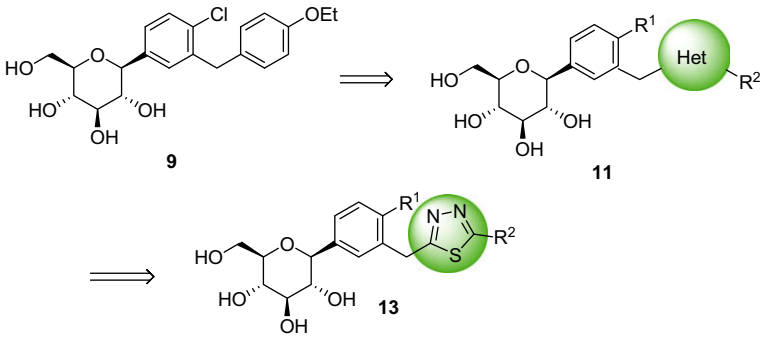
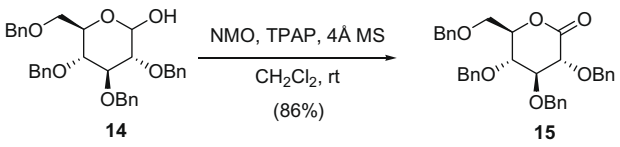


Figure 3. Exploration of C-glucoside bearing heteroaryl group at the distal ring.



Scheme 1. Oxidation of lactol **14** to lactone **15**.

The preparation of a key intermediate **21** is described in Scheme 3. Thus, alcohol **18** was converted to bromide using PBr_3 in the presence of pyridine. The bromide was then treated with KCN in refluxing aqueous EtOH to generate cyanide **19** in 80% yield over two steps. A mixture of the two isomers **19** was separated through recrystallization from ethanol to produce the required beta-isomer **20** in about 40% yield. Hydrolysis of **20** with sodium hydroxide in aqueous ethanol generated the carboxylic acid **21** in quantitative yield. Treatment of **21** with thionyl chloride in refluxing methanol produced the corresponding methyl ester **22** in 89% yield.

A thiazole-containing C-glucoside **61** was synthesized as shown in Scheme 4. Coupling of acid **21** and a hydrazide, such as furan-2-carbohydrazide (**23**), using EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide), HOBt (1-hydroxybenzotriazole), and NMM (4-methylmorpholine) in the presence of DMF (*N*,*N*-dimethylformamide) yielded the corresponding acylhydrazide **24**, which was cyclized using Lawesson's reagent to generate thiadiazole **25** in 81% over two steps. Deprotection of the four benzyl groups using TMSI (trimethyliodosilane)[21] followed by peracetylation using acetic anhydride and purification by either column chromatography or recrystallization generated the corresponding tetraacetate. The tetraacetate was hydrolyzed with NaOMe in methanol to yield the target compound **61** in 31% yield over three steps.

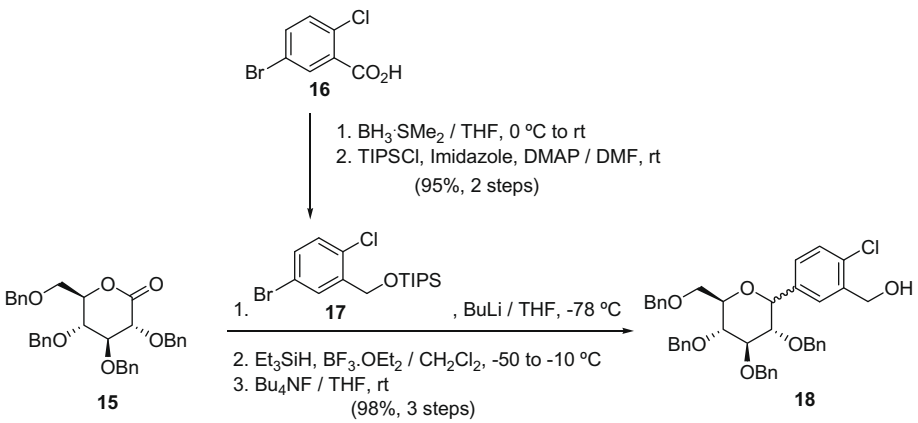
Alternatively, another target compound was prepared as shown in Scheme 5. Thus, the acid **21** was converted to the hydrazide **26** using hydrazine in the presence of EDCI, HOBt, and DMF in 95% yield. This hydrazide **26** was coupled with commercially available 5-phenylfuran-2-carboxylic acid (**27**) in the presence of EDCI, HOBt, and DMF to produce the corresponding acylhydrazide. Subsequent cyclization using Lawesson's reagent followed by deprotection of the benzyl groups using TMSI yielded the target compound **65** in 36% yield over three steps as shown in Scheme 6.

The third thiadiazole-containing compound was synthesized as in Scheme 6. Thus, acid **21** was coupled and concomitantly cyclized with thiosemicarbazide using phosphorus (III) oxychloride to provide the corresponding aminothiadiazole. The aminothiadiazole was converted to chlorothiadiazole **29** using sodium nitrite and a catalytic amount of copper in the presence of concentrated HCl and acetic acid in 22% overall yield.[22] Treatment of chlorothiadiazole **29** with NaSMe and subsequent deprotection of the benzyl groups yielded the target methylthio-thiadiazole **47** in 25% yield over two steps.

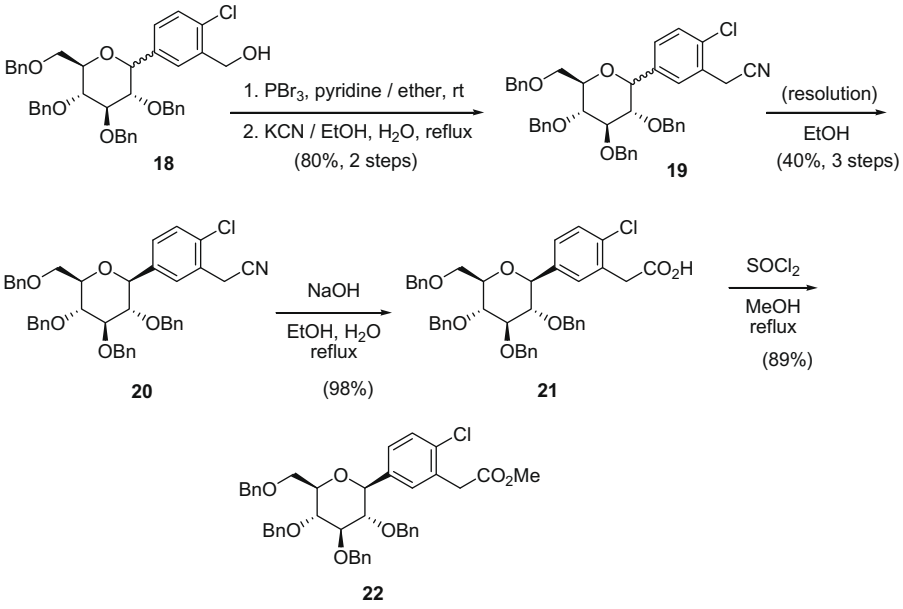
The fourth target compound was prepared as in Scheme 7. Typical coupling of **21** with the hydrazide **30** and the following cyclization produced the corresponding acylhydrazide, which was treated with TMSOTf (trimethylsilyl trifluoromethanesulfonate) and acetic anhydride to provide the corresponding tetraacetate.[23] The peracetylated compound was hydrolyzed to yield the target compound **59** in 10% yield over four steps. This alternative deprotection method was frequently employed, especially in the case of unsatisfactory reactions with TMSI.

2.2. SAR (Structure–activity relationship) studies

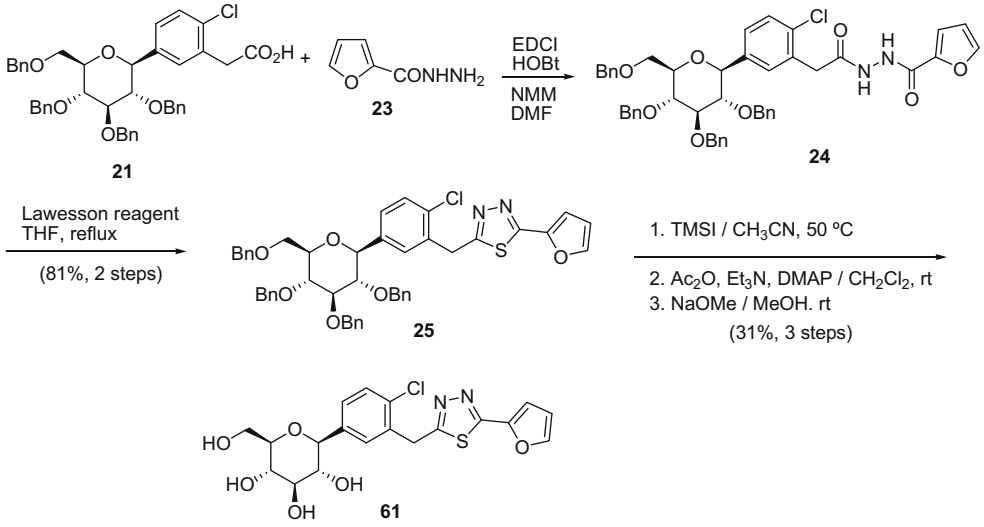
The cell-based SGLT2 AMG (Methyl-α-D-glucopyranoside) inhibition assay was performed to evaluate the inhibitory effects of all prepared compounds on *h*SGLT2 activities.[24,25] Exploration of the SAR began by replacing the phenyl moiety at the distal ring posi-



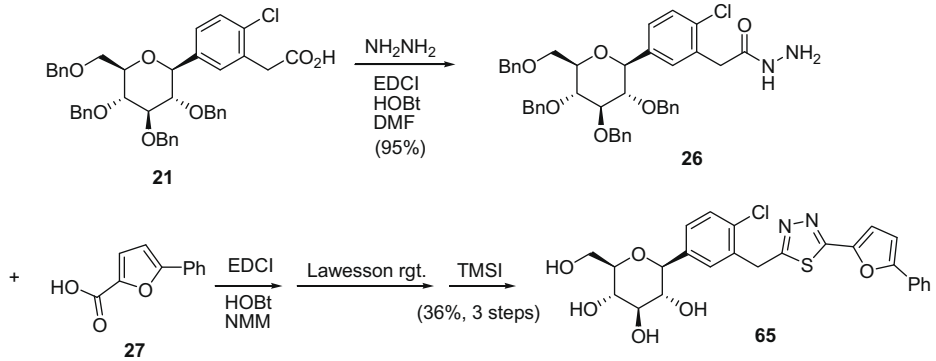
Scheme 2. Synthesis of C-glucoside alcohol intermediate **18**.



Scheme 3. Preparation of key C-glucoside intermediates **21**, **22**.

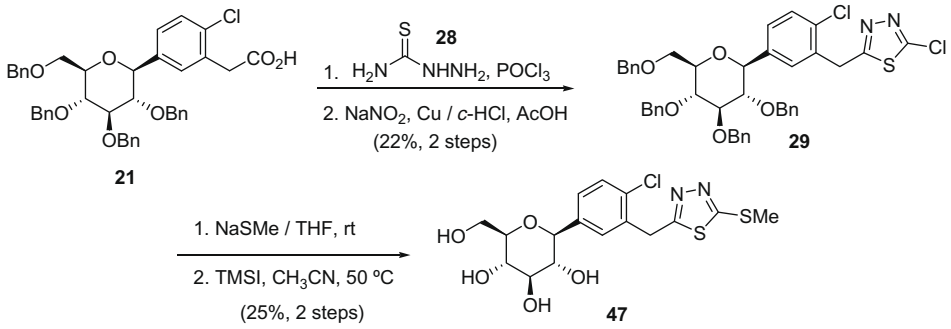


Scheme 4. Synthesis of target compound **61**.

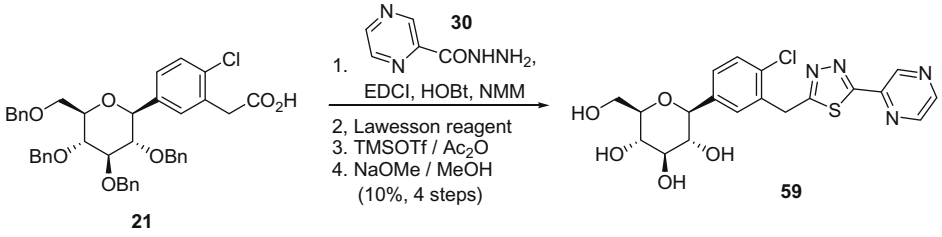


Scheme 5. Synthesis of target compound **65**.

tion of dapagliflozin **9** with a 1,3,4-oxadiazole or a 1,3,4-thiadiazole moiety. After it was discovered that the 1,3,4-oxadiazole series demonstrated significantly lower activity than the corresponding 1,3,4-thiadiazole series, SAR studies focused mostly



Scheme 6. Synthesis of target compound **47**.

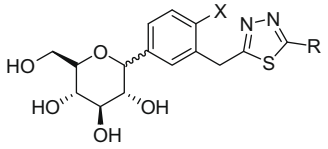


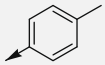
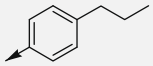
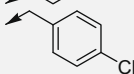
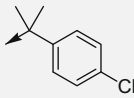
Scheme 7. Synthesis of target compound **59**.

on thiadiazoles at the distal ring. The initial results of the mixture of anomers are shown in Table 1. Straight aliphatic chains on the thiadiazole ring showed weak activity (**31**, IC_{50} = 6.9 μM), while bulky groups such as *t*-butyl provided a complete loss of activity (**32**, IC_{50} >10 μM), suggesting that branched aliphatic chains are not tolerated at this position. Replacement of this moiety with either phenyl **33** or pyridinyl **34** groups improved the inhibitory activity against *h*SGLT2 approximately fivefold (**33**, IC_{50} = 1.4 μM; **34**, IC_{50} = 1.2 μM). The introduction of a small lipophilic substituent, chlorine, at the C4' position of the C-glucoside proximal phenyl ring improved the inhibitory activity by an order of magnitude. Among these compounds, diaryl-types exhibited more favorable activity (**36–39**, IC_{50} = 25–103 nM) than carbocycle (**35**, IC_{50} = 542 nM) or benzyl-type moiety (**40**, IC_{50} = 2.4 μM). Among substituted phenyls on the thiadiazole ring, 4-propyl (**37**, IC_{50} = 24.9 nM) turned out to be more active than the corresponding 4-methyl group (**36**, IC_{50} = 103 nM), implying the importance of lipophilicity in this region.

Table 2 shows the structure–activity relationship upon alteration of the substituent at the distal 1,3,4-thiadiazole ring employing only the β-anomer. Compounds bearing aliphatic chains at the distal 1,3,4-thiadiazole ring were prepared and tested. These compounds showed only moderate *h*SGLT2 inhibitory activities (**42–45**, IC_{50} = 122–379 nM). Both trifluoromethyl substituted **48** and trifluoroethyl substituted **49** did not improve in vitro activity against *h*SGLT2. Substitution with a carbocycle, such as cyclopentyl **50**, demonstrated suboptimal activity (IC_{50} = 445 nM). However, as described in the initial SAR studies (Table 1), the diaryl-type compound containing a phenyl group, **51**, showed good in vitro inhibitory activity against *h*SGLT2 (IC_{50} = 16.6 nM). At this juncture, a variety of different aromatic rings were explored. Five-membered heterocycles, including 2-furan **61**, 3-furan **62**, 2-thiophene **70**, and 3-thiophene **71**, were shown to be highly active, demonstrating low nanomolar inhibitory activity against *h*SGLT2. Compared to phenyl **51** (IC_{50} = 16.6 nM), the incorporation of 3-furan **62** or 2-thiophene **70** resulted in similar levels of inhibitory activity (**62**, IC_{50} = 17.7 nM; **70**, IC_{50} = 14.4 nM). Surprisingly, varying the bonding position, for example, 3-furan **62** to 2-furan **61** or 2-thiophene

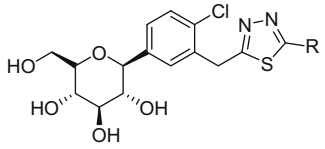
Table 1
In vitro screening data for *h*SGLT inhibitory activity[a,b]

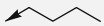
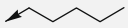
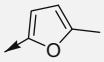
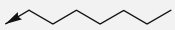
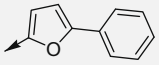
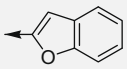
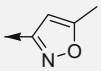
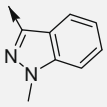
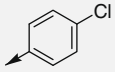
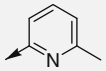
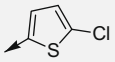
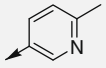
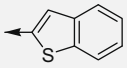


Compound	X	R	IC_{50} (nM)
6			6.25 ± 0.62
9			0.49 ± 0.04
31	H		6910
32	H		>10,000
33	H		1420
34	H		1230
35	Cl		542
36	Cl		103
37	Cl		24.9
38	Cl		45.3
39	Cl		53.0
40	Cl		2390
41	Cl		>10,000

[a] The IC_{50} values of **6** and **9** were obtained by in-house assay.
[b] These data were obtained by single determinations.

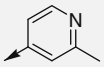
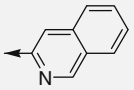
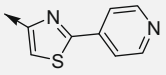
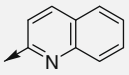
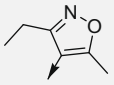
Table 2
In vitro screening data for *h*SGLT inhibitory activity[a,b]



Compound	R	IC_{50} (nM)	Compound	R	IC_{50} (nM)
6		6.25 ± 0.62	**60**		190
9		0.49 ± 0.04	**61**		7.03
42		214	**62**		17.7
43		379	**63**		106
44		353	**64**		58.3
45		122	**65**		10.6
46		146	**66**		249
47		10.9	**67**		257
48		155	**68**		119
49		758	**69**		3280
50		445	**70**		14.4
51		16.6	**71**		3.51
52		126	**72**		762
53		30.3	**73**		712
54		638	**74**		18.2
55		97.4	**75**		44.5

(*continued on next page*)

Table 2 (*continued*)

Compound	R	IC_{50} (nM)	Compound	R	IC_{50} (nM)
56		36.4	**76**		21.8
57		81.6	**77**		72.6
58		562	**78**		>10,000
59		4.06	**79**		>10,000

[a] The IC_{50} values of **6** and **9** were obtained by in-house assay.
[b] These data were obtained by single determinations.

70 to 3-thiophene **71**, improved the inhibitory activity by approximately 2.5-fold or fourfold, respectively (**61**, IC_{50} = 7.03 nM; **71**, IC_{50} = 3.51 nM). Substitution at the C5 position of 2-furan **61** or 2-thiophene **70** with methyl **64**, phenyl **65**, or chloride **74** resulted in a decreased potency. Moreover, addition of substituents at C3 of 2-furan **61** or 2-thiophene **70** resulted in significantly lower *h*SGLT2 inhibitory activities (**63**, **72**, and **73**), likely suggesting that even slightly increased steric hindrance is not tolerated in the region. Other heteroaryl groups such as pyrrole (**68**, IC_{50} = 119 nM), benzofuran (**66**, IC_{50} = 249 nM), quinoline (**58**, IC_{50} = 562 nM), and pyridazine (**60**, IC_{50} = 190 nM) were not tolerated. Meanwhile, pyridine **53**, isoquinoline **57**, benzothiophene **75**, and thiazoles **76** and **77** were found to be somewhat tolerable replacements (IC_{50} = 21.8–81.6 nM), but none appeared to be more potent than the simple phenyl group. Interestingly, six-membered heteroaryl compounds with two *para* heteroatoms, such as pyrazine **59**, proved to have highly potent inhibitory activity against *h*SGLT2 (**I**C_{50} = 4.06 nM). Thus, the results indicate that the addition of small heteroaryl rings with a favorable orientation of the heteroatom at the distal ring might be able to further increase *h*SGLT2 inhibitory activity. It is noteworthy that any substitution at the aryl or heteroaryl ring connected with the distal thiadiazole ring resulted in products with significantly lower *h*SGLT2 inhibitory activities, except furanophenyl **65** (IC_{50} = 10.6 nM). Di-substitution at the heteroaryl ring on the distal thiadiazole moiety further deteriorated *h*SGLT2 inhibitory activities, as shown for compounds **78** and **79**, indicating very limited tolerance in the specific area. Among the tested compounds, as shown in Table 2, biaryl-type compounds containing 3-thiophene **71**, pyrazine **59**, or 2-furan **61** showed the best in vitro inhibitory activities (IC_{50} = 3.51 nM, 4.06 nM, 7.03 nM, respectively). This implies that the 1,3,4-thiadiazole heterocycle at the distal ring could become a reasonable surrogate for the phenyl group of dapagliflozin **9**, and a properly oriented small heteroaryl substituent at the distal ring might be capable of augmenting in vitro *h*SGLT2 inhibitory activity.

A selected promising compound **61** was tested on animal models for in vivo efficacy. Urinary glucose excretion was evaluated in normal Sprague-Dawley (SD) rats.[24–26] Male SD rats weighing 250–300 g (7–8 weeks old) were purchased from Orient-Bio Laboratory Animal Research Center Co. (Gyeonggi-do, Korea). They were housed in a temperature (25 ± 2 °C) and moisture (55 ± 10%) controlled room, exposed to a controlled 12 h cycle of light and darkness, and allowed free access to food and water. All animals were acclimated for one week prior to the experiment. For glucosuria assessment, overnight-fasted SD rats were placed into metabolism cages for baseline urine collection over 24 h. Rats were weighed, randomized into three groups (n = 3), dosed orally with single doses of vehicle or drug (**9**@1 mg/kg, **61**@10 mg/kg), and subsequently dosed orally with 50% aqueous glucose solution (2 g/kg). Immediately after dosing, rats were returned to the metabolism cages for 24 h urine collection and re-fed at 1 h after the glucose challenge. The urine glucose and urine volume data were normalized per 200 g of body weight. As shown in Figure 4, a single oral dose of thiadiazole **61** increased urinary glucose excretion in normal SD rats, resulting in a 100-fold elevation in glucose disposal relative to vehicle controls. Urinary glucose excretion of compounds **9** and **61** were 1648 ± 228 mg/200 g body weight and 195 ± 84 mg/200 g body weight, respectively. Urine volume excreted in normal SD rats are also shown in Figure 5. Dapagliflozin **9** caused increased urine volume over vehicle by 5.7-fold, while thiadiazole **61** increased urine volume merely 1.4-fold (vehicle: 3.9 ± 0.23, **9**: 22.36 ± 4.18, **61**: 5.33 ± 0.67 ml/200 mg body weight, respectively).

For assessment of acute blood glucose effects in diabetic db/db mice, the animals were weighed and randomized into two groups (n = 4). Mice were dosed with vehicle or drug (**9**@1 mg/kg, **61**@10 mg/kg), and blood glucose levels were measured immediately before dosing and at 1, 2, 4, 5, 6, and 24 h post-dose. The animals were allowed to re-feed after the 6-h time point. In this experiment, a 72.8% reduction in blood glucose levels versus controls were observed at 4 h after a single 10 mg/kg oral dose of **61** was administered to db/db mice with an initial blood glucose level of 430 mg/dL. By comparison, a 61.3% reduction in blood glucose

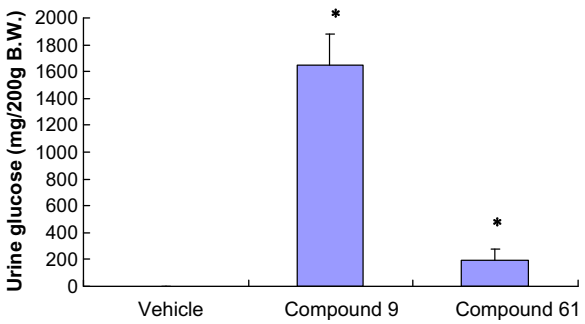


Figure 4. Urinary glucose excretion test of vehicle, compound **9** (1 mg/kg) and **61** (10 mg/kg) in normal SD rats. All results are expressed as means ± S.E.M. The statistical analysis was performed by one-way ANOVA followed by the Dunnett's post hoc test. *P <0.05 versus vehicle.

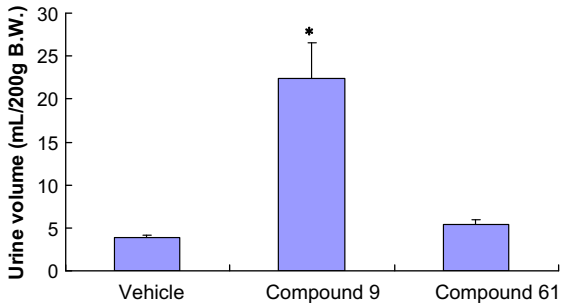


Figure 5. Urine volume of excreted of vehicle, compound **9** (1 mg/kg) and **61** (10 mg/kg) in normal SD rats. All results are expressed as means ± S.E.M. The statistical analysis was performed by one-way ANOVA followed by the Dunnett's post hoc test. $^{*}P$ <0.05 versus vehicle.

levels versus controls was observed at 4 h after a single 1 mg/kg oral dose of **9** was administered to db/db mice having the same initial blood glucose levels (Fig. 6).

In order to further evaluate this series, the pharmacokinetic properties of **61** were measured in male SD rats. After oral administration of 5 mg/kg of **61** to rats, a C_{max} of 0.05 μg/mL was obtained at 0.33 h. The elimination half-life of **61** following oral administration was 0.86 h in rats. Compound **61** showed relatively low oral bioavailability (F = 7.7%) in rats, suggesting its likely solubility-limited absorption. It is concluded that the decreased in vivo efficacy of the current SGLT2 inhibitor **61**, compared with dapagliflozin, could be attributed to the difference in inherent in vitro potencies (**61**: IC_{50} = 7.03 nM vs **9**: IC_{50} = 0.49 nM) as well as its pharmacokinetic properties. Thus, replacement of the distal ring of dapagliflozin **9** with a 1,3,4-thiadiazole ring, as in compound **61**, appeared to diminish the in vitro activity and oral absorption as well as the in vivo efficacy in animal models. However, the information obtained from the SAR studies in this thiadiazole series should help to design more active SGLT2 inhibitors that are structurally related.

3. Conclusion

In the present study, metabolically more stable C-glucosides bearing heteroaromatic rings were exploited in order to develop novel SGLT2 targeting antidiabetic agents. We envisioned that replacement of the distal ring of dapagliflozin **9** with a heterocyclic ring was a worthy approach for the improvement of the partition coefficient (log P) value and to improve characteristics for development, including non-specific plasma protein binding. For this purpose, the structure of dapagliflozin **9** was modified into a general structure bearing a heterocycle ring at the distal ring position. Along these lines, novel C-aryl glucoside SGLT2 inhibitors containing 1,3,4-thiadiazole moieties were designed and synthesized. Among the compounds tested, biaryl-type compounds containing pyrazine **59**, 2-furan **61**, or 3-thiophene **71** exhibited the best in vitro inhibitory activities against SGLT2 to date in this series (IC_{50} = 3.51–7.03 nM). A selected compound **61** demonstrated reasonable urinary glucose excretion and glucosuria in normal SD rats along with favorable blood glucose-lowering effects in db/db mice, thereby demonstrating that this 1,3,4-thiadiazolylmethylphenyl glucoside series possesses both in vitro SGLT2 inhibition and in vivo efficacy, albeit to a lower degree. Consequently, the information acquired from this series of compounds can be utilized as a quick reference to achieve more advanced series in this field.

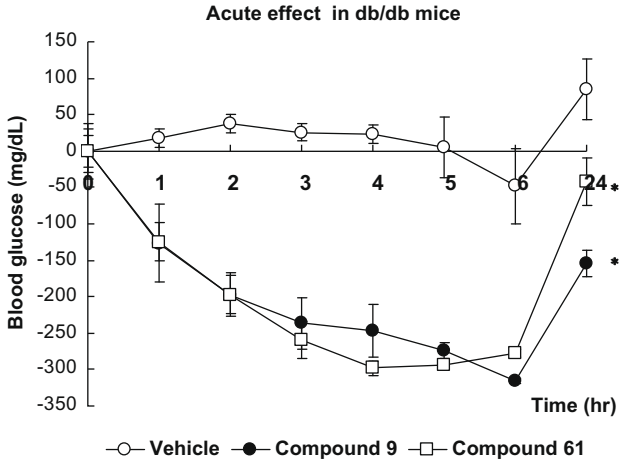


Figure 6. Blood glucose level in db/db mice following a single oral dose of vehicle compound **9** (1 mg/kg) or compound **61** (10 mg/kg). All results are expressed as means ± S.E.M. The statistical analysis was performed by one-way ANOVA followed by the Dunnett's post hoc test. $^{*}P$ <0.05 versus vehicle.

4. Experimental

4.1. General methods

All reactions are conducted under an inert atmosphere at room temperature, unless otherwise noted. All reagents were purchased at the highest commercial quality and used without further purification, unless otherwise indicated. Microwave reaction was conducted with a Biotage Initiator microwave reactor. NMR spectra were obtained on a Varian 400-MR (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer. NMR spectra were recorded in ppm (δ) relative to tetramethylsilane (δ = 0.00) as an internal standard unless stated otherwise and are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, and br = broad), coupling constant, and integration. ^{13}C NMR spectra were referenced to the residual chloroform-d_1 (δ = 77.0) or DMSO-d_6 (δ = 39.7). Mass spectra were obtained with an Agilent 6110 quadruple LC-MSD (ESI+). High resolution mass spectra were obtained on a Jeol JMS-700 Mstation (10 kV, HFAB). Optical rotations were obtained on a Rudolph Autopol III digital polarimeter. Preparative HPLC purifications were performed on a Gilson purification system. For preparative HPLC, ca. 100 mg of a product was injected in 1 mL of methanol onto a SunFire Prep C18 OBD 5 μm 30x100 mm Column with a 30 min gradient from 5% to 90% acetonitrile in water and a 45 mL/min flow rate. Biotage SP1 and Isolera purification systems were used for normal phase column chromatography with ethyl acetate and hexane. Flash chromatography was performed using E. Merck 230–400 mesh silica gel according to the procedure of Still et al. Reactions were monitored by either thin-layer chromatography (TLC) on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and *p*-anisaldehyde solution as visualizing agents or HPLC analysis on an Agilent 1200 series system.

4.2. Chemistry

4.2.1. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranone (15)

To a solution of lactol **14** (125 g, 231 mmol) in dichloromethane (1 L) was added 4 Å molecular sieve (40 g) and 4-methylmorpholine N-oxide (40.7 g, 347 mmol). The solution is stirred for 20 min at room temperature, before adding of tetrapropylammonium perruthenate (2.0 g, 5.6 mmol). After 3 h stirring at ambient temperature, the solution was filtered through a plug of Celite. The filtrate was washed with saturated sodium thiosulfate, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting crude residue was purified by column chromatography

(5–40% EtOAc/hexanes) to yield the title compound (106 g, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.16 (m, 20H), 4.98 (d, J = 11.2 Hz, 1H), 4.74–4.44 (m, 8H), 4.12 (d, J = 6.4 Hz, 1H), 3.97–3.89 (m, 2H), 3.72 (dd, J = 10.8, 2.4 Hz, 1H), 3.67 (dd, J = 10.8, 3.2 Hz, 1H).

4.2.2. (5-Bromo-2-chlorobenzyloxy)triisopropylsilane (17)

To a solution 5-bromo-2-chlorobenzoic acid **16** (100 g, 425 mmol) in THF (500 mL) at 0 °C was added borane-dimethyl sulfide complex (170 mL, 1,700 mmol). The resulting mixture was stirred with gradual warming to ambient temperature over 12 h, re-cooled to 0 °C, and quenched with MeOH and then water. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to yield a white solid, which was carried on to the next step without further purification.

To a solution of the benzyl alcohol in DMF (400 mL) was added imidazle (57.9 g, 850 mmol), 4-(dimethylamino)pyridine (2.6 g, 21 mmol), and triisopropylsilyl chloride (136 mL, 683 mmol). The resulting solution was stirred at ambient temperature for 12 h, diluted with a saturated ammonium chloride and extracted with EtOAc. The organic layer was washed with water then brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (3–10% EtOAc/hexanes) to yield the title compound (152 g, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 8.4, 2.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 4.83 (s, 2H), 1.25–1.17 (m, 3H), 1.11 (d, J = 6.8 Hz, 18H).

4.2.3. (2-Chloro-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)methanol (18)

To a solution of bromide **17** (97 g, 257 mmol) in THF (1 L) at −78 °C under an atmosphere of nitrogen was added dropwise *n*-butyllithium (2.5 M in hexanes, 103 mL, 257 mmol), and the mixture was stirred for 1.5 h at the same temperature. Then a solution of lactone **15** (106 g, 198 mmol) in THF (500 mL) was added dropwise, and the mixture was stirred for 3 h at the same temperature. The reaction mixture was quenched by addition of saturated ammonium chloride. After complete addition, the solution was gradually raised to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil, which was carried on to the next step without further purification.

To a stirred −50 °C solution of the lactols in dichloromethane (500 mL) was added triethylsilane (63 mL, 396 mmol) followed by boron trifluoride diethyl etherate (50 mL, 396 mmol) at a rate such that the reaction temperature was maintained between −40 and −50 °C. The solution was allowed to warm to −10 °C over 2 h prior to quenching with saturated potassium carbonate. After removal of organic volatiles under reduced pressure, the residue was partitioned between EtOAc and water. Following extraction of the aqueous layer with ethyl acetate, the combined organic layers were washed with water prior to drying over anhydrous $MgSO_4$. Filtration and concentration under reduced pressure yielded a yellow oil, which was carried on to the next step without further purification.

To a solution of the silyl ether in THF (500 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 594 mL, 594 mmol) and the reaction mixture stirred at ambient temperature for 2 h. After removal of organic volatiles under reduced pressure, the residue was partitioned between EtOAc and saturated ammonium chloride. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified on column chromatography (10–60% EtOAc/hexanes) to yield the title compound (130 g, 98%, ca. 2:1 β:α) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ 7.50 (s, 1H), 7.38–7.17 (m, 20H), 6.94–6.92 (m, 2H), 4.96–4.46 (m, 9H), 4.23 (d, J = 9.2 Hz, 1H), 3.86 (d, J = 10.4 Hz, 1H), 3.81–3.67(m, 4H), 3.61–3.59 (m, 1H), 3.44 (t, J = 9.2 Hz, 1H); α-anomer: δ 7.78 (s, 1H), 7.63 (dd, J = 8.4, 1.6 Hz, 1H), 7.38–7.17 (m, 19H), 7.13–7.10 (m, 2H), 5.15 (d, J = 3.6 Hz, 1H), 4.96–4.46 (m, 8H), 4.01–3.95 (m, 2H), 3.83–3.64 (m, 5H), 3.55–3.51 (m, 1H); MS (ESI) m/z 682 $(M+NH_4)^+$, 687 $(M+Na)^+$.

4.2.4. 2-(2-Chloro-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)acetonitrile (19)

To a solution of 2-chlorobenzyl alcohol **18** (130 g, 195 mmol) in ether (600 mL) at 0 °C was added pyridine (0.79 mL, 9.8 mmol) and phosphorus tribromide (6.4 mL, 68 mmol). The reaction was allowed to slowly warm to room temperature over 15 h and refluxed for 1 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with water then brine. The organic extract was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to yield a yellow solid, which was carried on to the next step without further purification.

To a solution of the 2-chlorobenzyl bromide in ethanol (260 mL) and water (130 mL) was added potassium cyanide (31.8 g, 488 mmol). The reaction mixture was refluxed overnight. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification was accomplished by chromatography to give the title compound (105 g, 80%, ca. 2:1 β:α) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ 7.48 (s, 1H), 7.37–7.17 (m, 20H), 6.93–6.91 (m, 2H), 4.93 (s, 2H), 4.86 (d, J = 10.8 Hz, 1H), 4.63 (d, J = 10.8 Hz, 1H), 4.62 (d, J = 12.4 Hz, 1H), 4.56 (d, J = 12.4 Hz, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.22 (d, J = 9.6 Hz, 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.84–3.68 (m, 6H), 3.62–3.58 (m, 1H), 3.43 (t, J = 8.8 Hz, 1H); α-anomer: δ 7.83 (d, J = 1.6 Hz, 1H), 7.64 (dd, J = 8.4, 1.6 Hz, 1H), 7.37–7.19 (m, 19H), 7.13–7.10 (m, 2H), 5.11 (d, J = 2.8 Hz, 1H), 4.93–4.46 (m, 8H), 3.96–3.92 (m, 2H), 3.79–3.71 (m, 3H), 3.70–3.62 (m, 2H), 3.55–3.51 (m, 1H); MS (ESI) m/z 696 $(M+Na)^+$.

4.2.5. 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)acetonitrile (20)

The mixture of cyanides **19** (105 g, 156 mmol, ca. 2:1 β:α) was slurried in ethanol (1 L) and heated to reflux with stirring. The reaction mixture was held at reflux for 1 h to insure that all of solution had homogenized. It was then cooled evenly at 15 °C/h to ambient temperature and stirred overnight at this temperature. The resulting solid was isolated by filtration and dried in vacuo to yield the title compound (53 g, 51%, ca. 75% separation yield) as a white solid. $[\alpha]_D^{21}$ −10.6 (c 1.01, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.37–7.17 (m, 20H), 6.93–6.91 (m, 2H), 4.93 (s, 2H), 4.86 (d, J = 10.8 Hz, 1H), 4.63 (d, J = 10.8 Hz, 1H), 4.62 (d, J = 12.4 Hz, 1H), 4.56 (d, J = 12.4 Hz, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.22 (d, J = 9.6 Hz, 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.84–3.68 (m, 6H), 3.62–3.58 (m, 1H), 3.43 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.49, 128.86, 128.45, 128.38, 128.26, 128.08, 128.01, 127.87, 127.82, 127.70, 127.68, 127.67, 127.64, 127.61, 139.09, 138.52, 138.23, 138.07, 137.41, 132.97, 129.49, 128.86, 128.45, 128.38, 128.26, 128.08, 128.01, 127.87, 127.82, 127.70, 127.68, 127.67, 127.64, 127.61, 116.57, 86.87, 83.59, 80.47, 79.41, 78.28, 75.67, 75.16, 74.96, 73.47, 69.07, 22.12; MS

(ESI) m/z 696 $(M+Na)^+$; HRMS (FAB) m/z 674.2672 [calcd for $C_{42}H_{41}ClNO_5$ $(M+H)^+$ 674.2673].

4.2.6. 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)acetic acid (21)

To a solution of cyanide **20** (53 g, 79 mmol) in EtOH (300 mL) was added aq NaOH solution (8.0 N, 300 mL, 2.4 mol). The reaction mixture was refluxed overnight. After cooling to room temperature, hydrochloric acid (3.0 N) was added to neutralize the reaction mixture. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine prior to drying over anhydrous $MgSO_4$. Filtration and concentration under reduced pressure yielded the title compound, which was used in the next step without further purification. $[\alpha]_D^{21}$ −4.7 (c 1.10, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.14 (m, 21H), 6.93–6.90 (m, 2H), 4.94 (d, J = 10.8 Hz, 1H), 4.90 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.63 (d, J = 10.8 Hz, 1H), 4.62 (d, J = 14.0 Hz, 1H), 4.55 (d, J = 12.4 Hz, 1H), 4.43 (d, J = 10.4 Hz, 1H), 4.20 (d, J = 9.6 Hz, 1H), 3.88 (d, J = 10.8 Hz, 1H). 3.81–3.70 (m, 6H), 3.59–3.56 (m, 1H), 3.43 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.84, 139.10, 138.69, 138.66, 138.17, 133.72, 133.49, 131.99, 129.18, 128.68, 128.66, 128.45, 128.26, 128.19, 128.10, 128.00, 127.92, 127.87, 127.84, 86.25, 83.53, 80.14, 78.77, 78.55, 74.97, 74.51, 74.30, 72.75, 69.39, 39.19; MS (ESI) m/z 710 $(M+NH_4)^+$, 715 $(M+Na)^+$.

4.2.7. 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris-(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)-acetate (22)

To a solution of acid **21** (10 g, 14 mmol) in MeOH (140 mL) was added thionyl chloride (2.1 mL, 29 mmol). The reaction mixture was refluxed overnight and cooled to room temperature. After removal of organic volatiles under reduced pressure, the residue was partitioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated sodium bicarbonate and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (5–40% EtOAc/hexanes) to yield the title compound (9.1 g, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 21H), 6.94–6.92 (m, 2H), 4.96 (d, J = 11.2 Hz, 1H), 4.90 (d, J = 11.2 Hz, 1H), 4.86 (d, J = 10.8 Hz, 1H), 4.63 (d, J = 11.6 Hz, 2H), 4.55 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 10.8 Hz, 1H), 4.20 (d, J = 9.2 Hz, 1H), 3.90 (d, J = 10.8 Hz, 1H), 3.82–3.67 (m, 6H), 3.67 (s, 3H), 3.60–3.57 (m, 1H), 3.47 (t, J = 8.8 Hz, 1H); MS (ESI) m/z 729 $(M+Na)^+$.

4.2.8. 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzyl)-5-(furan-2-yl)-1,3,4-thiadiazole (25)

To a mixture of acid **21** (500 mg, 0.72 mmol), 2-furoic hydrazide **23** (119 mg, 0.94 mmol), EDCI (207 mg, 1.08 mmol), and HOBt hydrate (224 mg, 1.44 mmol) in DMF (10 mL) was added NMM (0.24 mL, 2.16 mmol). The resulting mixture was stirred at ambient temperature overnight. After dilution with EtOAc, the organic layer was subsequently washed with water, hydrochloric acid (1.0 N), saturated sodium bicarbonate, and brine prior to drying over anhydrous $MgSO_4$. Filtration and removal of the volatiles under reduced pressure yielded a glassy off-white amorphous solid, which was carried on to the next step without further purification.

To a solution of the acylhydrazide **24** in THF (15 mL) was added Lawesson reagent (874 mg, 2.16 mmol). The reaction mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with saturated sodium bicarbonate. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting crude residue was purified by column chromatography (10–60% EtOAc/hexanes) to yield the title compound (468 mg, 81%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.35–7.13 (m, 19H), 7.08 (d, J = 3.6 Hz, 1H), 6.90–6.88 (m, 2H), 6.53–6.52 (m, 1H), 4.90 (s, 2H), 4.85(d, J = 10.8 Hz, 1H), 4.63–4.51 (m, 4H), 4.45 (d, J = 10.8 Hz, 1H), 4.20 (d, J = 9.6 Hz, 1H), 3.88 (d, J = 10.8 Hz, 1H), 3.81–3.72 (m, 5H), 3.60–3.57 (m, 1H), 3.43 (t, J = 8.8 Hz, 1H); MS (ESI) m/z 799 $(M+H)^+$, 821 $(M+Na)^+$.

4.2.9. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(furan-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (61)

To a solution of perbenzylated **25** (468 mg, 0.58 mmol) in acetonitrile (5 mL) was added iodotrimethylsilane (5 mL). The resulting reaction mixture was heated to 50 °C overnight. After cooling to 0 °C, the reaction was quenched with methanol and concentrated in vacuo. Peracetylation was achieved by addition of acetic anhydride (3 mL) and DMAP (10 mg, 0.08 mmol) to a solution of this residue in dichloromethane (10 mL) and triethylamine (3 mL). After 2 h stirring at ambient temperature, the reaction was quenched by addition of water, whereupon the resulting mixture was extracted with dichloromethane. The organic layer was washed with hydrochloric acid (1.0 N) and brine prior to drying over anhydrous $MgSO_4$. After filtration through a plug of silica gel and concentration under reduced pressure, the residue was carried on to the next step without further purification.

To a solution of the tetraacetate in MeOH (10 mL) was added sodium methoxide (25 wt.% in MeOH, 0.5 mL). The reaction mixture was stirred at ambient temperature for 2 h. Amberlite IR120 hydrogen form was then added to neutralize the reaction mixture. The resin was filtered off and the filtrate was concentrated in vacuo. The resulting crude residue was purified by reverse phase preparative HPLC to provide the title compound (78 mg, 31%) as a white solid. $[\alpha]_D^{21}$ +21.4 (c 0.21, methanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 1.6 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 8.0, 2.0 Hz, 1H), 7.23 (d, J = 3.6 Hz, 1H), 6.70 (dd, J = 3.6, 1.6 Hz, 1H), 5.00 (br, 2H), 4.88 (d, J = 5.6 Hz, 1H), 4.59 (d, J = 16.0 Hz, 1H), 4.53 (d, J = 16.0 Hz, 1H), 4.43 (t, J = 5.6 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.68–3.65 (m, 1H), 3.46–3.40 (m, 1H), 3.26–3.06 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.62, 158.77, 146.61, 144.94, 140.68, 134.60, 132.39, 131.23, 129.35, 129.26, 113.23, 112.67, 81.67, 80.89, 78.71, 75.19, 70.68, 61.75, 33.77, MS (ESI) m/z 439 $(M+H)^+$; HRMS (FAB) m/z 439.0730 [calcd for $C_{19}H_{20}ClN_2O_6S$ $(M+H)^+$ 439.0731]

4.2.10. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(furan-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (31)

Compound **31** was synthesized from de-chlorinated analogue of **21** (ca. 2:1 (β:α) mixture of anomers) and butyrohydrazide according to the procedure used to prepare **61**. A white solid. Yield 17%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (s, 1H), 7.35–7.28 (m, 2H), 7.24–7.22 (m, 1H), 4.39 (s, 2H), 4.11 (d, J = 9.2 Hz, 1H), 3.87 (d, J = 11.2 Hz, 1H), 3.71–3.66 (m, 1H), 3.48–3.30 (m, 4H), 3.00 (t, J = 7.6 Hz, 2H), 1.75 (sext, J = 7.6 Hz, 2H), 0.97 (t, J = 7.6 Hz, 3H); MS (ESI) m/z 381 $(M+H)^+$.

4.2.11. (3*R*,4*R*,5*S*,6*R*)-2-(3-((5-*tert*-Butyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (32)

Compound **32** was synthesized from de-chlorinated analogue of **21** (ca. 2:1 (β:α) mixture of anomers) and pivalohydrazide according to the procedure used to prepare **61**. A white solid. Yield 20%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (s, 1H), 7.37–7.31 (m, 2H),

7.27–7.25 (m, 1H), 4.40 (s, 2H), 4.13 (d, J = 9.6 Hz, 1H), 3.88 (d, J = 11.6 Hz, 1H), 3.72–3.64 (m, 1H), 3.47–3.32 (m, 4H), 1.43 (s, 9H); MS (ESI) m/z 395 $(M+H)^+$, 417 $(M+Na)^+$.

4.2.12. (2*R*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)-6-(3-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-tetrahydro-2*H*-pyran-3,4,5-triol (33)

Compound **33** was synthesized from de-chlorinated analogue of **21** (ca. 2:1 (β:α) mixture of anomers) and benzoic hydrazide according to the procedure used to prepare **61**. A white solid. Yield 30%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (d, J = 7.6 Hz, 2H), 7.01–7.45 (m, 4H), 7.37–7.29 (m, 3H), 4.47 (br, 1H), 4.13 (d, J = 9.6 Hz, 1H), 3.88–3.85 (m 1H), 3.68 (dd, J = 12.0, 5.2 Hz, 1H), 3.48–3.38 (m, 3H), 3.35–3.30 (m, 2H); MS (ESI) m/z 415 $(M+H)^+$, 437 $(M+Na)^+$.

4.2.13. (2*R*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)-6-(3-((5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-tetrahydro-2*H*-pyran-3,4,5-triol (34)

Compound **34** was synthesized from de-chlorinated analogue of **21** (ca. 2:1 (β:α) mixture of anomers) and nicotinohydrazide according to the procedure used to prepare **61**. A white solid. Yield 6.5%. ^{1}H NMR (400 MHz, CD_3OD) δ 9.05 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 8.34–8.31 (m, 1H), 7.56 (dd, J = 8.0, 5.2 Hz, 1H), 7.46 (s, 1H), 7.37–7.31 (m, 3H), 4.51 (s, 2H), 4.13 (d, J = 9.6 Hz, 1H), 3.86 (d, J = 11.6 Hz, 1H), 3.68 (dd, J = 11.6, 5.2 Hz, 1H), 3.48–3.32 (m, 4H); MS (ESI) m/z 416 $(M+H)^+$, 438 $(M+Na)^+$.

4.2.14. (3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-cyclohexyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (35)

Compound **35** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and cyclohexanecarbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 25%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.4, 2.0 Hz, 1H), 5.07–4.89 (br, 3H), 4.48 (d, J = 15.6 Hz, 1H), 4.43 (d, J = 15.6 Hz, 1H), 4.42 (br, 1H), 3.99 (d, J = 9.6 Hz, 1H), 3.69–3.65 (m, 1H), 3.46–3.40 (m, 1H), 3.24–3.00 (m, 5H), 1.99–1.94 (m, 2H), 1.73–1.67 (m, 2H), 1.64–1.59 (m, 1H), 1.46–1.28 (m, 3H), 1.24–1.14 (m, 1H); MS (ESI) m/z 455 $(M+H)^+$, 477 $(M+Na)^+$.

4.2.15. (3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-*p*-tolyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (36)

Compound **36** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and 4-methylbenzohydrazide according to the procedure used to prepare **61**. A white solid. Yield 34%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 2.0 Hz, 1H), 7.43–7.37 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.58 (s, 2H), 4.14 (d, J = 9.6 Hz, 1H), 3.87 (dd, J = 12.0, 2.0 Hz, 1H), 3.70 (dd, J = 12.0, 5.2 Hz, 1H), 3.48–3.38 (m, 3H), 3.26 (d, J = 9.2 Hz, 1H), 2.37 (s, 3H); MS (ESI) m/z 463 $(M+H)^+$, 485 $(M+Na)^+$.

4.2.16. (3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(4-propylphenyl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (37)

Compound **37** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and 4-propylbenzohydrazide according to the procedure used to prepare **61**. A white solid. Yield 12%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 1.6 Hz, 1H), 7.43–7.37 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.14 (d, J = 9.6 Hz, 1H), 3.87 (dd, J = 12.0, 2.0 Hz, 1H), 3.70 (dd, J = 12.0, 5.2 Hz, 1H), 3.48–3.38 (m, 3H), 3.33 (s, 1H), 3.26 (d, J = 9.2 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 1.65 (sext, J = 7.6 Hz, 2H), 0.93 (t, J = 7.6 Hz, 3H); MS (ESI) m/z 491 $(M+H)^+$, 513 $(M+Na)^+$.

4.2.17. (3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (38)

Compound **38** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and nicotinohydrazide according to the procedure used to prepare **61**. A white solid. Yield 21%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, J = 1.6 Hz, 1H), 8.80 (dd, J = 4.8, 1.6 Hz, 1H), 8.30–8.27 (m, 1H), 7.55–7.51 (m, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H), 5.02–4.84 (br, 3H), 4.63 (d, J = 16.0 Hz, 1H), 4.58 (d, J = 16.0 Hz, 1H), 4.41 (br, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.69–3.66 (m, 1H), 3.46–3.41 (m, 1H), 3.23–3.06 (m, 4H);MS (ESI) m/z 450 $(M+H)^+$, 472 $(M+Na)^+$.

4.2.18. (3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (39)

Compound **39** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and isonicotinohydrazide according to the procedure used to prepare **61**. A white solid. Yield 22%. ^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (d, J = 6.4 Hz, 2H), 8.12 (d, J = 6.4 Hz, 2H), 7.59 (d, J = 1.2 Hz, 1H), 7.44–7.39 (m, 2H). 4.68 (s, 2H), 4.14 (d, J = 9.6 Hz, 1H), 3.87 (dd, J = 12.0, 2.0 Hz, 1H), 3.70 (dd, J = 12.0, 5.2 Hz, 1H), 3.48–3.38 (m, 3H), 3.34 (s, 1H), 3.26 (d, J = 8.8 Hz, 1H); MS (ESI) m/z 450 $(M+H)^+$, 472 $(M+Na)^+$.

4.2.19. (3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(4-chlorobenzyl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (40)

Compound **40** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and 2-(4-chlorophenyl)acetohydrazide according to the procedure used to prepare **61**. A white solid. Yield 14%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (s, 1H), 7.37–7.25 (m, 6H), 4.47 (s, 2H), 4.35 (s, 2H), 4.10 (d, J = 9.6 Hz, 1H), 3.85 (dd, J = 12.0, 1.6 Hz, 1H), 3.68 (dd, J = 12.0, 5.2 Hz, 1H), 3.44–3.29 (m, 3H), 3.24 (t, J = 9.2 Hz, 1H); MS (ESI) m/z 497 $(M+H)^+$, 519 $(M+Na)^+$.

4.2.20. (3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(2-(4-chlorophenyl) propan-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (41)

Compound **41** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and 2-(4-chlorophenyl)-2-methylpropanehydrazide according to the procedure used to prepare **61**. A white solid. Yield 58%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (s, 1H), 7.38–7.34 (m, 2H), 7.29 (s, 4H), 4.49 (s, 2H), 4.11 (d, J = 9.2 Hz, 1H), 3.85 (dd, J = 12.4, 2.0 Hz, 1H), 3.68 (dd, J = 12.4, 5.6 Hz, 1H), 3.47–3.31 (m, 3H), 3.24 (t, J = 8.8 Hz, 1H), 1.80 (s, 6H); MS (ESI) m/z 525 $(M+H)^+$, 547 $(M+Na)^+$.

4.2.21. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-propyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (42)

Compound **42** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and butyrohydrazide according to the procedure used to prepare **61**. The small amount of the α-anomer was removed by reverse phase preparative HPLC. A white solid. Yield 12%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, J = 1.6 Hz, 1H), 7.41–7.36 (m, 2H), 4.52 (s, 2H), 4.12 (d, J = 9.2 Hz, 1H), 3.86 (dd, J = 12.0, 1.6 Hz, 1H), 3.69 (dd, J = 12.0, 5.2 Hz, 1H), 3.47–3.37 (m, 3H), 3.25 (d, J = 8.8 Hz, 1H), 3.01 (t, J = 7.6 Hz, 2H), 1.76 (sext, J = 7.6 Hz, 2H), 0.97 (t, J = 7.6 Hz, 3H); MS (ESI) m/z 415 $(M+H)^+$.

4.2.22. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-Butyl-1,3,4-thiadiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (43)

Compound **43** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and pentanehydrazide according to the procedure used to prepare **61**. The small amount of the α-anomer was re-

moved by reverse phase preparative HPLC. A white solid. Yield 19%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.4, 2.0 Hz, 1H), 5.04 (br, 2H), 4.87 (d, J = 5.6 Hz, 1H), 4.48 (d, J = 16.0 Hz, 1H), 4.43 (d, J = 16.0 Hz, 1H), 4.43 (br, 1H), 3.99 (d, J = 9.2 Hz, 1H), 3.68–3.65 (m, 1H), 3.46–3.40 (m, 1H), 3.26–3.04 (m, 4H), 2.97 (t, J = 7.6 Hz, 2H), 1.61 (quint, J = 7.6 Hz, 2H), 1.29 (sext, J = 7.6 Hz, 2H), 0.85 (t, J = 7.6 Hz, 3H); MS (ESI) m/z 429 (M+H)$^+$, 451 (M+Na)$^+$.

4.2.23. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-pentyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (44)

Compound **44** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and hexanehydrazide according to the procedure used to prepare **61**. The small amount of the α-anomer was removed by reverse phase preparative HPLC. A white solid. Yield 20%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 2.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.28 (dd, J = 8.0, 2.0 Hz, 1H), 4.90 (br, 2H), 4.80 (d, 1H), 4.49 (d, J = 15.6 Hz, 1H), 4.43 (d, J = 15.6 Hz, 1H), 4.39 (t, J = 6.0 Hz, 1H), 4.00 (d, J = 9.2 Hz, 1H), 3.69–3.65 (m, 1H), 3.45–3.40 (m, 1H), 3.24–3.04 (m, 4H), 2.96 (t, J = 7.6 Hz, 2H), 1.67–1.60 (m, 2H), 1.30–1.22 (m, 4H), 0.82 (t, J = 7.6 Hz, 3H); MS (ESI) m/z 443 (M+H)$^+$, 465 (M+Na)$^+$.

4.2.24. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-heptyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (45)

Compound **45** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and octanehydrazide according to the procedure used to prepare **61**. The small amount of the α-anomer was removed by reverse phase preparative HPLC. A white solid. Yield 38%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, J = 1.6 Hz, 1H), 7.40–7.36 (m, 2H), 4.12 (d, J = 9.2 Hz, 1H), 3.86 (dd, J = 12.0, 2.0 Hz, 1H), 3.69 (dd, J = 12.0, 5.2 Hz, 1H), 3.47–3.38 (m, 3H), 3.25 (d, J = 8.8 Hz, 1H), 3.03 (t, J = 7.6 Hz, 2H), 1.72 (quint, J = 7.6 Hz, 2H), 1.38–1.24 (m, 8H), 0.87 (t, J = 7.6 Hz, 3H); MS (ESI) m/z 471 (M+H)$^+$, 493 (M+Na)$^+$.

4.2.25. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-cyclopentyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (50)

Compound **50** was synthesized from **21** and cyclopentanecarbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 46%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 1.6 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.29 (dd, J = 8.4, 2.0 Hz, 1H), 4.96–4.93 (m, 2H), 4.85 (d, J = 5.6 Hz, 1H), 4.50–4.41 (m, 3H), 4.00 (d, J = 9.2 Hz, 1H), 3.69–3.65 (m, 1H), 3.47–3.40 (m, 2H), 3.26–3.03 (m, 4H), 2.09–2.04 (m, 2H), 1.69–1.57 (m, 6H); MS (ESI) m/z 441 (M+H)$^+$, 463 (M+Na)$^+$.

4.2.26. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-phenyl-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (51)

Compound **51** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and benzoic hydrazide according to the procedure used to prepare **61**. The small amount of the α-anomer was removed by reverse phase preparative HPLC. A white solid. Yield 27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (dd, J = 7.2, 2.0 Hz, 2H), 7.53–7.42 (m, 5H), 7.32 (dd, J = 8.0, 2.0 Hz, 1H), 5.03 (br, 2H), 4.94 (br, 1H), 4.59 (d, J = 16.0 Hz, 1H), 4.54 (d, J = 16.0 Hz, 1H), 4.50 (br, 1H), 4.03 (d, J = 9.6 Hz, 1H), 3.69 (d, J = 11.2 Hz, 1H), 3.46–3.42 (m, 1H), 3.28–3.13 (m, 3H), 3.09 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.75, 140.69, 134.65, 132.43, 131.72, 131.31, 129.94, 129.87, 129.38, 129.26, 127.99, 81.70, 80.89, 78.68, 75.18, 70.62, 61.71, 34.08; MS (ESI) m/z 449 (M+H)$^+$, 471 (M+Na)$^+$.

4.2.27. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (52)

Compound **52** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and 4-chlorobenzohydrazide according to the procedure used to prepare **61**. The small amount of the α-anomer was removed by reverse phase preparative HPLC. A white solid. Yield 50%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.0, 2.0 Hz, 1H), 4.96–4.93 (m, 2H), 4.86 (d, J = 5.6 Hz, 1H), 4.60 (d, J = 16.0 Hz, 1H), 4.55 (d, J = 16.0 Hz, 1H), 4.43 (t, J = 5.6 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.68–3.65 (m, 1H), 3.26–3.07 (m, 4H); MS (ESI) m/z 483 (M+H)$^+$, 505 (M+Na)$^+$.

4.2.28. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (53)

Compound **53** was synthesized from **21** and picolinohydrazide according to the procedure used to prepare **61**. A white solid. Yield 18%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (dd, J = 3.6, 0.8 Hz, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.98 (td, J = 7.6, 1.6 Hz, 1H), 7.54–7.50 (m, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.0, 1.6 Hz, 1H), 4.94–4.91 (m, 2H), 4.84 (d, J = 5.6 Hz, 1H), 4.59 (d, J = 16.0 Hz, 1H), 4.54 (d, J = 16.0 Hz, 1H), 4.42 (t, J = 5.6 Hz, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.69–3.65 (m, 1H), 3.44–3.41 (m, 1H), 3.27–3.07 (m, 4H); MS (ESI) m/z 450 (M+H)$^+$, 472 (M+Na)$^+$.

4.2.29. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(6-methylpyridin-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (55)

Compound **55** was synthesized from **21** and 6-methylnicotinohydrazide according to the procedure used to prepare **61**. A white solid. Yield 17%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J = 2.0 Hz, 1H), 8.16 (dd, J = 8.0 Hz, 2.4 Hz, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.48–7.37 (m, 2H), 7.32 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 4.99–4.90 (m, 2H), 4.86 (d, J = 5.6 Hz, 1H), 4.65–4.53 (m, 2H), 4.43 (t, J = 6.0 Hz, 1H), 4.01 (d, J = 9.2 Hz, 1H), 3.71–3.63 (m, 1H), 3.47–3.05 (m, 5H), 2.50 (s, 3H); MS (ESI) m/z 464 (M+H)$^+$.

4.2.30. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(isoquinolin-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (57)

Compound **57** was synthesized from **21** and isoquinoline-3-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.72 (s, 1H), 8.18 (d, J = 8.8 Hz, 2H), 7.86 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.76 (td, J = 8.0 Hz, 1.2 H, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.32 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.66–4.52 (m, 3H), 4.03 (d, J = 9.2 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 3.44 (dd, J = 11.6 Hz, 5.6 Hz, 2H), 3.33–3.05 (m, 6H); MS (ESI) m/z 500 (M+H)$^+$.

4.2.31. ((2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(quinolin-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (58)

Compound **58** was synthesized from **21** and quinoline-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 25%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.04 (t, J = 9.4 Hz, 2H), 7.81 (td, J = 8.0, 1.6 Hz, 1H), 7.67 (td, J = 7.2, 1.2 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.33 (dd, J = 6.4, 2.0 Hz, 1H), 4.99–4.90 (m, 2H), 4.86 (d, J = 5.6 Hz, 1H), 4.67–4.55 (m, 2H), 4.43 (t, J = 5.6 Hz, 1H), 4.04 (d, J = 9.6 Hz, 1H), 3.67 (dd, J = 7.6, 3.6 Hz, 1H), 3.49–3.38 (m, 1H), 3.29–3.07 (m, 4H); MS (ESI) m/z 500 (M+H)$^+$.

4.2.32. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(furan-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (62)

Compound **62** was synthesized from **21** and 3-furoic hydrazide according to the procedure used to prepare **61**. A white solid. Yield 32%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (dd, J = 1.2, 0.4 Hz, 1H), 7.83 (t, J = 2.0 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.4, 2.0 Hz, 1H), 6.96 (dd, J = 2.0, 0.8 Hz, 1H), 4.96–4.93 (m, 2H), 4.85 (d, J = 6.0 Hz, 1H), 4.56 (d, J = 16.0 Hz, 1H), 4.51 (d, J = 16.0 Hz, 1H), 4.44 (t, J = 6.0 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.70–3.65 (m, 1H), 3.45–3.39 (m, 1H), 3.27–3.04 (m, 4H); MS (ESI) m/z 439 $(M+H)^+$, 461 $(M+Na)^+$.

4.2.33. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(3-methylfuran-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (63)

Compound **63** was synthesized from **21** and 3-methylfuran-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 28%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 1.2 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.0, 2.0 Hz, 1H), 6.61 (d, J = 1.2 Hz, 1H), 4.97–4.80 (m, 2H), 4.83 (d, J = 5.2 Hz, 1H), 4.60–4.50 (m, 1H), 4.47–4.39 (m, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.71–3.62 (m, 1H), 3.48–3.37 (m, 1H), 3.33–3.03 (m, 4H), 2.32 (s, 3H); MS (ESI) m/z 453 $(M+H)^+$.

4.2.34. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(5-methylfuran-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (64)

Compound **64** was synthesized from **21** and 5-methylfuran-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 30%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 6.32 (d, J = 3.6 Hz, 1H), 4.94–4.91 (m, 2H), 4.83 (d, J = 5.6 Hz, 1H), 4.56 (d, J = 16.0 Hz, 1H), 4.51 (d, J = 16.0 Hz, 1H), 4.42 (t, J = 5.6 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.70–3.65 (m, 1H), 3.45–3.40 (m, 1H), 3.27–3.04 (m, 4H), 2.32 (s, 3H); MS (ESI) m/z 453 $(M+H)^+$.

4.2.35. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(Benzofuran-2-yl)-1,3,4-thiadiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (66)

Compound **52** was synthesized from an anomeric mixture of **21** (ca. 2:1 β:α) and benzofuran-2-carbohydrazide according to the procedure used to prepare **61**. The small amount of the α-anomer was removed by reverse phase preparative HPLC. A white solid. Yield 50%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, J = 8.0 Hz, 1H), 7.60–7.52 (m, 3H), 7.44–7.39 (m, 3H), 7.31 (t, J = 7.6 Hz, 2H), 4.15 (d, J = 9.2 Hz, 1H), 3.87 (dd, J = 12.0, 1.6 Hz, 1H), 3.70 (dd, J = 12.0, 5.2 Hz, 3.48–3.38 (m, 3H), 3.33 (s, 2H); MS (ESI) m/z 489 $(M+H)^+$.

4.2.36. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(5-methylisoxazol-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (67)

Compound **67** was synthesized from **21** and 5-methylfuran-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 16%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.0, 1.6 Hz, 1H), 6.87 (s, 1H), 4.93 (t, J = 4.8 Hz, 2H), 4.85 (d, J = 5.6 Hz, 1H), 4.64 (d, J = 16.0 Hz, 1H), 4.59 (d, J = 16.0 Hz, 1H), 4.42 (t, J = 6.0 Hz, 1H), 4.02 (d, J = 9.2 Hz, 1H), 3.69–3.65 (m, 1H), 3.46–3.39 (m, 1H), 3.29–3.05 (m, 4H), 2.48 (s, 3H); MS (ESI) m/z 454 $(M+H)^+$, 476 $(M+Na)^+$.

4.2.37. ((2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(1-methyl-1*H*-pyrrol-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (68)

Compound **68** was synthesized from **21** and 1-methyl-1*H*-pyrrole-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 18%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.0, 2.0 Hz, 1H), 7.02 (t, J = 2.0 Hz, 1H), 6.65–6.60 (m, 1H), 6.13–6.07 (m, 1H), 4.57–4.42 (m, 4H), 4.01 (d, J = 9.6 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, J = 11.6, 1.6 Hz, 1H), 3.47–3.38 (m, 1H), 3.27–3.05 (m, 6H); MS (ESI) m/z 452 $(M+H)^+$.

4.2.38. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(1-methyl-1*H*-indazol-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (69)

Compound **69** was synthesized from **21** and 1-methyl-1*H*-indazole-3-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 26%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.54–7.49 (m, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.36–7.30 (m, 2H), 4.94–4.91 (m, 2H), 4.85 (d, J = 5.6 Hz, 1H), 4.61 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 15.6 Hz, 1H), 4.43 (t, J = 5.6 Hz, 1H), 4.10 (s, 3H), 4.03 (d, J = 9.2 Hz, 1H), 3.70–3.66 (m, 1H), 3.43 (quint, J = 5.6 Hz, 1H), 3.27–3.06 (m, 4H); MS (ESI) m/z 503 $(M+H)^+$.

4.2.39. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(thiophen-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (70)

Compound **70** was synthesized from **21** and thiophene-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 47%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (dd, J = 4.8, 1.2 Hz, 1H), 7.69 (dd, J = 3.6, 1.2 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.0, 2.0 Hz, 1H), 7.16 (dd, J = 8.0, 4.0 Hz, 1H), 4.97–4.93 (m, 2H), 4.86 (d, J = 6.0 Hz, 1H), 4.57 (d, J = 16.0 Hz, 1H), 4.52 (d, J = 15.6 Hz, 1H), 4.45 (t, J = 5.6 Hz, 1H), 4.02 (d, J = 9.2 Hz, 1H), 3.70–3.65 (m, 1H), 3.46–3.39 (m, 1H), 3.27–3.05 (m, 4H); MS (ESI) m/z 455 $(M+H)^+$, 477 $(M+Na)^+$.

4.2.40. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(thiophen-3-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (71)

Compound **71** was synthesized from **21** and thiophene-3-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 66%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (dd, J = 2.8, 1.2 Hz, 1H), 7.72–7.69 (m, 1H), 7.58 (dd, J = 4.8, 1.2 Hz, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.0, 1.6 Hz, 1H), 4.94–4.91 (m, 2H), 4.84 (d, J = 6.0 Hz, 1H), 4.57 (d, J = 16.0 Hz, 1H), 4.52 (d, J = 16.0 Hz, 1H), 4.42 (t, J = 6.0 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.70–3.65 (m, 1H), 3.46–3.40 (m, 1H), 3.25–3.05 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.40, 162.06, 139.16, 133.14, 130.89, 129.85, 129.74, 127.85, 127.68, 127.36, 126.69, 125.08, 80.14, 79.35, 77.19, 73.65, 69.18, 60.24, 32.47; MS (ESI) m/z 455 $(M+H)^+$, 477 $(M+Na)^+$; HRMS (FAB) m/z 455.0501 [calcd for $C_{19}H_{20}ClN_2O_5S_2$ $(M+H)^+$ 455.0502].

4.2.41. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(3-methylthiophen-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (72)

Compound **72** was synthesized from **21** and 3-methylthiophene-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J = 5.2 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.4, 1.6 Hz, 1H), 7.06 (d, J = 5.2 Hz, 1H), 4.96(m, 2H), 4.85 (d, J = 5.6 Hz, 1H), 4.59 (d, J = 16.0 Hz, 1H), 4.55 (d, J = 16.0 Hz, 1H), 4.44 (t, J = 5.6 Hz, 1H), 4.01 (d, J = 9.2 Hz, 1H),

3.69–3.65 (m, 1H), 3.45–3.39 (m, 1H), 3.27–3.04 (m, 4H), 2.37 (s, 3H); MS (ESI) *m*/*z* 489 $(M+H)^+$.

4.2.42. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(3-chlorothiophen-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (73)

Compound **73** was synthesized from **21** and 3-chlorothiophene-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 5.2 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.0, 2.0 Hz, 1H), 7.27 (d, J = 5.6 Hz, 1H), 4.92–4.90 (m, 2H), 4.82 (d, J = 5.6 Hz, 1H), 4.62 (d, J = 16.0 Hz, 1H), 4.58 (d, J = 16.0 Hz, 1H), 4.40 (t, J = 6.0 Hz, 1H), 4.02 (d, J = 9.2 Hz, 1H), 3.70–3.65 (m, 1H), 3.46–3.40 (m, 1H), 3.25–3.05 (m, 4H); MS (ESI) *m*/*z* 489 $(M+H)^+$.

4.2.43. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(3-chlorothiophen-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (74)

Compound **74** was synthesized from **21** and 5-chlorothiophene-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 36%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, J = 4.0 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.27 (dd, J = 8.4, 2.0 Hz, 1H), 7.19 (d, J = 4.0 Hz, 1H), 4.64–4.38 (m, 5H), 3.97 (d, J = 9.6 Hz, 1H), 3.64 (d, J = 8.0 Hz, 1H), 3.42–3.36 (m, 1H), 3.25–3.10 (m, 5H); MS (ESI) *m*/*z* 489 $(M+H)^+$.

4.2.44. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-((5-(Benzo[*b*]thiophen-2-yl)-1,3,4-thiadiazol-2-yl)methyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (75)

Compound **75** was synthesized from **21** and benzo[*b*]thiophene-2-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 36%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 8.02 (d, J = 7.2 Hz, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.47–7.39 (m, 3H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H), 4.95 (br, 2H), 4.87 (d, J = 5.6 Hz, 1H), 4.62 (d, J = 16.0 Hz, 1H), 4.57 (d, J = 16.0 Hz), 4.45 (t, J = 5.6 Hz, 1H), 4.02 (d, J = 9.2 Hz, 1H), 3.70–3.66 (m, 1H), 3.46–3.40 (m, 1H), 3.26–3.06 (m, 4H); MS (ESI) *m*/*z* 505 $(M+H)^+$.

4.2.45. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(thiazol-4-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (76)

Compound **76** was synthesized from **21** and thiazole-4-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 2.0 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.0, 2.0 Hz, 1H), 4.93–4.91 (m, 2H), 4.83 (d, J = 5.6 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.54 (d, J = 15.6 Hz, 1H), 4.42 (t, J = 5.6 Hz, 1H), 4.01 (d, J = 9.2 Hz, 1H), 3.69–3.64 (m, 1H), 3.45–3.39 (m, 1H), 3.26–3.05 (m, 4H); MS (ESI) *m*/*z* 456 $(M+H)^+$, 478 $(M+Na)^+$.

4.2.46. ((2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(2-(pyridin-4-yl)thiazol-5-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxylmethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (77)

Compound **77** was synthesized from **21** and 2-(pyridin-4-yl)thiazole-4-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 19%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 6.0 Hz, 2H), 8.68 (s, 1H), 7.96 (d, J = 4.4 Hz, 2H), 7.54 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.0, 1.6 Hz, 1H), 4.67–4.51 (m, 5H), 4.02 (d, J = 9.2 Hz, 1H), 3.67 (d, J = 10.4 Hz, 1H), 3.49–3.39 (m, 1H), 3.27–3.07 (m, 5H); MS (ESI) *m*/*z* 533 $(M+H)^+$.

4.2.47. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(3,5-dimethylisoxazol-4-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (78)

Compound **78** was synthesized from **21** and 3,5-dimethylisoxazole-4-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 9.5%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 4.74 (br, 4H), 4.61 (d, J = 16.0 Hz, 1H), 4.56 (d, J = 16.0 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.67 (dd, J = 11.6, 1.6 Hz, 1H), 3.44–3.40 (m, 1H), 3.26–3.19 (m, 2H), 3.16–3.11 (m, 1H), 3.07 (t, J = 9.2 Hz, 1H), 2.60 (s, 3H), 2.39 (s, 3H); MS (ESI) *m*/*z* 468 $(M+H)^+$.

4.2.48. ((2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(3-ethyl-5-methylisoxazol-4-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (79)

Compound **79** was synthesized from **21** and 3-ethyl-5-methylisoxazole-4-carbohydrazide according to the procedure used to prepare **61**. A white solid. Yield 12%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 4.75 (br, 4H), 4.61 (d, J = 16.0 Hz, 1H), 4.57 (d, J = 16.0 Hz, 1H), 4.01 (d, J = 9.2 Hz, 1H), 3.67 (d, J = 10.0 Hz, 1H), 3.44–3.40 (m, 1H), 3.26–3.19 (m, 2H), 3.16–3.11 (m, 1H), 3.07 (t, J = 9.2 Hz, 1H), 2.85 (q, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.75 (t, J = 7.2 Hz, 3H); MS (ESI) *m*/*z* 468 $(M+H)^+$.

4.2.49. 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)phenyl)acetohydrazide (26)

To a mixture of acid **21** (693 mg, 1.0 mmol), EDCI (249 mg, 1.3 mmol), and HOBt hydrate (233 mg, 1.5 mmol) in DMF (10 mL) was added hydrazine monohydrate (2 mL). The resulting mixture was stirred at ambient temperature for 12 h and then poured into water. The resulting solid was isolated by filtration and dried in vacuo to yield (674 mg, 95%) a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 7.39–7.14 (m, 21H), 6.88–6.86 (m, 2H), 4.80 (d, J = 11.2 Hz, 1H). 4.77 (d, J = 11.2 Hz, 1H), 4.70 (d, J = 13.6 Hz, 1H), 4.54 (d, J = 10.8 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 4.44 (d, J = 12.4 Hz, 1H), 4.32 (d, J = 10.8 Hz, 1H), 4.26 (d, J = 9.6 Hz, 1H), 3.83 (d, J = 10.8 Hz, 1H), 3.73 (t, J = 8.8 Hz, 1H), 3.66–3.45 (m, 7H); MS (ESI) *m*/*z* 707 ($[M+H]^+$), 729 $(M+Na)^+$.

4.2.50. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(5-phenylfuran-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (65)

To a mixture of hydrazide **32** (674 mg, 0.95 mmol), 5-phenyl-2-furoic acid (233 mg, 1.24 mmol), EDCI (273 mg, 1.43 mmol), and HOBt hydrate (295 mg, 1.90 mmol) in DMF (10 mL) was added NMM (0.31 mL, 2.85 mmol). The resulting mixture was stirred at ambient temperature overnight. After dilution with EtOAc, the organic layer was subsequently washed with water, hydrochloric acid (1.0 N), saturated sodium bicarbonate, and brine prior to drying over anhydrous $MgSO_4$. Filtration and removal of the volatiles under reduced pressure yielded a glassy yellow amorphous solid, which was carried on to the next step without further purification.

To a solution of the acylhydrazide in THF (20 mL) was added Lawesson reagent (1.2 g, 2.9 mmol). The reaction mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with saturated sodium bicarbonate. The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica gel and concentrated in vacuo. The resulting crude residue was carried on to the next step without further purification.

To a solution of the perbenzylated thiadiazole in acetonitrile (5 mL) was added TMSI (5 mL). The resulting reaction mixture was heated to 50 °C overnight. After cooling to 0 °C, the

reaction quenched with methanol and concentrated in vacuo. The resulting crude residue was purified by reverse phase preparative HPLC to provide the title compound (176 mg, 36%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79–7.77 (m, 2H), 7.52 (d, J = 2.0 Hz, 1H), 7.46–7.31 (m, 6H), 7.20 (d, J = 3.6 Hz, 1H), 4.95 (dd, J = 6.8, 4.8 Hz, 2H), 4.87 (d, J = 5.6 Hz, 1H), 4.61 (d, J = 16.0 Hz, 1H), 4.56 (d, J = 16.0 Hz, 1H), 4.50 (t, J = 6.0 Hz, 1H). 4.02 (d, J = 9.6 Hz, 1H), 3.68–3.62 (m, 1H), 3.43–3.40 (m, 1H), 3.27–3.06 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.63, 158.60, 155.97, 144.51, 143.71, 140.72, 134.63, 132.43, 131.30, 129.52, 129.41, 129.29, 129.14, 124.34, 114.87, 109.08, 81.68, 80.90, 78.73, 75.19, 70.71, 61.78, 33.88; MS (ESI) m/z 515 (M+H)$^+$.

4.2.51. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (48)

Compound **48** was synthesized from **26** and trifluoroacetic acid according to the procedure used to prepare **65**. A white solid. Yield 56%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.33 (dd, J = 8.4, 2.4 Hz, 1H), 4.95–4.91 (m, 2H), 4.85 (d, J = 5.6 Hz, 1H), 4.71 (d, J = 16.4 Hz, 1H), 4.67 (d, J = 16.4 Hz, 1H), 4.41 (t, J = 6.0 Hz, 1H), 4.01 (d, J = 9.2 Hz, 1H), 3.69–3.65 (m, 1H), 3.46–3.40 (m, 1H), 3.25–3.04 (m, 4H); MS (ESI) m/z 441 (M+H)$^+$, 463 (M+Na)$^+$.

4.2.52. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(2,2,2-trifluoroethyl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (49)

Compound **49** was synthesized from **26** and 3,3,3-trifluoropropanoic acid according to the procedure used to prepare **65**. A white solid. Yield 61%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.29 (dd, J = 8.4, 1.6 Hz, 1H), 4.97–4.94 (m, 2H), 4.85 (d, J = 6.0 Hz, 1H), 4.56 (d, J = 16.0 Hz, 1H), 4.51 (d, J = 16.0 Hz, 1H), 4.44 (t, J = 6.0 Hz, 1H), 4.33 (q, J = 10.8 Hz, 2H), 4.00 (d, J = 9.2 Hz, 1H), 3.69–3.63 (m, 1H), 3.45–3.41 (m, 1H), 3.27–3.03 (m, 4H); MS (ESI) m/z 455 (M+H)$^+$, 477 (M+Na)$^+$.

4.2.53. (2-Chloro-5-(2-chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)-benzyl)-1,3,4-thiadiazole (29)

To a solution of acid **21** (2.8 g, 4.0 mmol) in 1,4-dioxane (30 mL) was added thiosemicarbazide **28** (0.40 g, 4.4 mmol). The solution is stirred for 1 h at 90 °C, before adding of phosphorus oxychloride (0.41 mL, 4.4 mmol). After overnight stirring at 110 °C, the reaction was concentrated in vacuo to yield a glassy off-white amorphous solid, which was carried on to the next step without further purification.

To a mixture of the thiadiazole amine and copper (0.04 g, 0.62 mmol) in *c*-hydrochloric acid (6 mL) and acetic acid (30 mL) at 0 °C was slowly added sodium nitrite (2.8 g, 40 mmol) while maintaining an internal reaction temperature below 10 °C. After 1 h stirring at 0 °C, the resulting mixture was stirred with gradual warming to ambient temperature over 2 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification was accomplished by column chromatography (10–60% EtOAc/hexanes) to yield the title compound (0.66 g, 022%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.37–7.17 (m, 20H), 6.93–6.91 (m, 2H), 4.90 (s, 2H), 4.85(d, J = 10.8 Hz, 1H), 4.63–4.51 (m, 4H), 4.45 (d, J = 10.8 Hz, 1H), 4.20 (d, J = 9.6 Hz, 1H), 3.88 (d, J = 10.8 Hz, 1H), 3.81–3.72 (m, 5H), 3.60–3.57 (m, 1H), 3.43 (t, J = 8.8 Hz, 1H); MS (ESI) m/z 767 (M+H)$^+$, 789 (M+Na)$^+$.

4.2.54. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(methylthio)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (47)

To a solution of chlorothiadiazole **29** (419 mg, 0.55 mmol in THF (10 mL) was added sodium methanethiolate (77 mg, 1.1 mmol). The resulting mixture was stirred at ambient temperature overnight. After cooling to 0 °C, the reaction was quenched with hydrochloric acid (1.0 N) and diluted with EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was carried on to the next step without further purification.

To a solution of the perbenzylated thiadiazole in acetonitrile (5 mL) was added TMSI (5 mL). The resulting reaction mixture was heated to 50 °C overnight. After cooling to 0 °C, the reaction quenched with methanol and concentrated in vacuo. The resulting crude residue was purified by reverse phase preparative HPLC to yield the title compound (58 mg, 25%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 2.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.29 (dd, J = 8.0, 2.0 Hz, 1H), 4.49 (d, J = 15.6 Hz, 1H), 4.44 (d, J = 15.6 z, 1H), 3.99 (d, J = 9.6 Hz, 1H), 3.67 (dd, J = 12.0, 2.0 Hz, 1H), 3.42 (dd, J = 11.6, 5.6 Hz, 1H), 3.25–3.11 (m, 3H), 3.06 (t, J = 9.2 Hz, 1H), 2.67 (s, 3H); MS (ESI) m/z 419 (M+H)$^+$, 441 (M+Na)$^+$.

4.2.55. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-methoxy-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (46)

Compound **46** was synthesized from **29** and sodium methoxide according to the procedure used to prepare **47**. A white solid. Yield 57%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42–7.39 (m, 2H), 7.29 (dd, J = 8.4, 2.0 Hz, 1H), 4.97–4.94 (m, 2H), 4.85 (d, J = 5.6 Hz, 1H), 4.44 (t, J = 5.6 Hz, 1H), 4.37 (d, J = 15.6 Hz, 1H), 4.32 (d, J = 15.6 Hz, 1H), 4.01 (d, J = 9.2 Hz, 1H), 3.69–3.65 (m, 1H), 3.45–3.40 (m, 1H), 3.27–3.03 (m, 4H), 3.39(s, 3H); MS (ESI) m/z 403 (M+H)$^+$, 425 (M+Na)$^+$.

4.2.56. 2-(2-Chloro-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)benzyl)-5-(pyrazin-2-yl)-1,3,4-thiadiazole (59)

To a mixture of acid **21** (1.00 g, 1.44 mmol), pyrazine-2-carbohydrazide **30** (259 mg, 1.88 mmol), EDCI (415 mg, 2.16 mmol), and HOBt hydrate (448 mg, 2.89 mmol) in DMF (10 mL) was added NMM (0.476 mL, 4.33 mmol). The resulting mixture was stirred at ambient temperature overnight. After dilution with EtOAc, the organic layer was subsequently washed with water, hydrochloric acid (1.0 N), saturated sodium bicarbonate, and brine prior to drying over anhydrous $MgSO_4$. Filtration and removal of the volatiles under reduced pressure yielded a glassy off-white amorphous solid, which was carried on to the next step without further purification.

To a solution of the acylhydrazide in THF (20 mL) was added Lawesson reagent (874 mg, 2.16 mmol). The reaction mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with saturated sodium bicarbonate. The organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica gel and concentrated in vacuo. The resulting crude residue was carried on to the next step without any purification.

To a solution of perbenzylated pyrazine at −50 °C in Ac_2O (10 mL) was slowly added a solution of trimethylsilyl trifluoromethanesulfonate (1.5 mL, 8.4 mmol) in Ac_2O (5 mL). The resulting mixture was stirred with gradual warming to ambient temperature over 12 h, cooled to 0 °C, and quenched with saturated sodium bicarbonate. After dilution with EtOAc, the organic layer was washed with sodium bicarbonate and brine prior to drying over

anhydrous $MgSO_4$. Filtration and removal of volatiles under reduced pressure yielded peracetylated compound as a yellow amorphous solid. Deacetylation was achieved by addition of sodium methoxide (25 wt.% in methanol, 0.5 mL) to a solution of this residue in methanol (5 mL). The reaction mixture was stirred at ambient temperature for 2 h. Amberlite IR120 hydrogen form was then added to neutralize the reaction mixture. The resin was filtered off and the filtrate was concentrated in vacuo. The resulting crude residue was purified by reverse phase preparative HPLC to yield the title compound (47 mg, 10%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (d, J = 1.6 Hz, 1H), 8.78 (d, J = 2.4 Hz, 1H), 8.73 (dd, J = 2.4, 1.6 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.4, 1.6 Hz, 1H), 4.50 (br, 2H), 4.87 (d, J = 5.6 Hz, 1H), 4.64 (d, J = 16.4 Hz, 1H), 4.59 (d, J = 16.4 Hz, 1H), 4.43 (t, J = 5.6 Hz, 1H), 4.02 (d, J = 9.2 Hz, 1H), 3.69–3.65 (m, 1H), 3.44–3.41 (m, 1H), 3.26–3.07 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.09, 168.42, 147.00, 145.34, 144.40, 141.88, 140.72, 134.59, 132.40, 131.24, 129.35, 129.32, 81.67, 80.92, 78.71, 75.21, 70.70, 61.76, 34.10, MS (ESI) m/z 451 $(M+H)^+$; HRMS (FAB) m/z 451.0842 [calcd for $C_{19}H_{20}ClN_4O_5S$ $(M+H)^+$ 451.0843]

4.2.57. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(6-methylpyridin-2-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (54)

Compound **54** was synthesized from **21** and 6-methylpicolinohydrazide according to the procedure used to prepare **59**. A white solid. Yield 31%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 7.6 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.31 (dd, J = 8.4, 1.6 Hz, 1H), 4.96–4.93 (m, 2H), 4.86 (d, J = 5.6 Hz, 1H), 4.58 (d, J = 15.6 Hz, 1H), 4.53 (d, J = 15.6 Hz, 1H), 4.44 (t, J = 5.6 Hz, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.69–3.65 (m, 1H), 3.45–3.40 (m, 1H), 3.27–3.05 (m, 4H), 2.47 (s, 3H); MS (ESI) m/z 464 $(M+H)^+$, 486 $(M+Na)^+$.

4.2.58. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(2-methylpyridin-4-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (56)

Compound **56** was synthesized from **21** and 2-methylisonicotinohydrazide according to the procedure used to prepare **59**. A white solid. Yield 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, J = 4.8 Hz, 1H), 7.74 (s, 1H), 7.67 (d, J = 4.8 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.32 (dd, J = 8.0, 1.6 Hz, 1H), 4.98–4.94 (m, 2H), 4.87 (d, J = 6.0 Hz, 1H), 4.64 (d, J = 16.0 Hz, 1H), 4.53 (d, J = 16.0 Hz, 1H), 4.44 (t, J = 5.6 Hz, 1H), 4.01 (d, J = 9.2 Hz, 1H), 3.68–3.66 (m, 1H), 3.45–3.39 (m, 1H), 3.27–3.05 (m, 4H), 2.56 (s, 3H); MS (ESI) m/z 464 $(M+H)^+$, 486 $(M+Na)^+$.

4.2.59. (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-Chloro-3-((5-(pyridazin-4-yl)-1,3,4-thiadiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (60)

Compound **60** was synthesized from **21** and pyridazine-4-carbohydrazide according to the procedure used to prepare **59**. A white solid. Yield 21%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (d, J = 2.4 Hz, 1H), 9.51 (d, J = 5.6 Hz, 1H), 8.15 (dd, J = 5.6, 2.4 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 1.6 Hz, 1H), 5.03–4.98 (m, 2H), 4.91 (d, J = 5.6 Hz, 1H), 4.68 (d, J = 16.0 Hz, 1H), 4.63 (d, J = 16.0 Hz, 1H), 4.45 (t, J = 5.6 Hz, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.69–3.65 (m, 1H), 3.44–3.41 (m, 1H), 3.26–3.06 (m, 4H); MS (ESI) m/z 451 $(M+H)^+$, 473 $(M+Na)^+$.

4.3. In vitro assay

4.3.1. Cloning and cell line construction for human SGLT2

Human SGLT2 (*h*SGLT2) gene was amplified by PCR from cDNA-Human Adult Normal Tissue Kidney (Invitrogen, Carlsbad, CA). The hSGLT2 sequence was cloned into pcDNA3.1(+) for mammalian expression and were stably transfected into chinese hamster ovary (CHO) cells. SGLT2-expressing clones were selected based on resistance to G418 antibiotic (Geneticin®, Invitrogen, Carlsbad, CA) and activity in the ^{14}C-α-methyl-D-glucopyranoside (^{14}C-AMG) uptake assay.

4.3.2. Inhibitory effects on human SGLT2 activities

For sodium-dependent glucose transport assay, cells expressing *h*SGLT2 were seeded into a 96-well culture plate at a density of 5×10^4 cells/well in RPMI medium 1640 containing 10% fetal bovine serum. The cells were used 1 day after plating. They were incubated in pretreatment buffer (10 mM HEPES, 5 mM Tris, 140 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, and 1 mM $MgCl_2$, pH 7.4) at 37 °C for 10 min. They were then incubated in uptake buffer (10 mM HEPES, 5 mM Tris, 140 mM NaCl, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 1 mM ^{14}C-nonlabeled AMG pH 7.4) containing ^{14}C-labeled (8 μM) and inhibitor or dimethyl sulfoxide (DMSO) vehicle at 37 °C for 2 h. Cells were washed twice with washing buffer (pretreatment buffer containing 10 mM AMG at room temperature) and then the radioactivity was measured using a liquid scintillation counter. IC_{50} was determined by nonlinear regression analysis using GraphPad PRISM.[24,25]

4.4. Normal and diabetic animal studies

4.4.1. Animals

Male SD rats and diabetic db/db mice were purchased by Charles River Laboratory. All animals were housed at 23 ± 2 °C under a 12-h light/dark cycle (light on 7:00) and were fed a standard chow and water ad libitum.

4.4.2. Urinary glucose excretion in normal animal[24–26]

For glucosuria assessment, overnight-fasted SD rats (5 weeks of ages) were placed into metabolism cages for baseline urine collection over 24 h. Rats were weighted, randomized into experimental groups (n = 4) and orally administered with 50% aqueous glucose solution (2 g/kg) and drugs. Rats were returned to metabolism cages for 24 h urine collection. After the urine volume had been measured, the glucose concentration in the urine was determined using a LabAssay™ (Wako Pure Chemicals). These data were normalized per 200 g body weight.

4.4.3. Blood glucose effects in diabetic db/db mice[24–26]

For assessment of acute blood glucose effects in db/db mice, the animals were weighed and randomized into two groups (n = 4). Mice were dosed with vehicle or drug (9@1 mg/kg, 61@10 mg/kg) and blood glucose level were measured immediately before dosing and at 1, 2, 4, 5, 6, and 24 h post-dose using blood glucose meter (Lifescan, a Johnson & Johnson). The animals were allowed to refeed after the 6-h time point.

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