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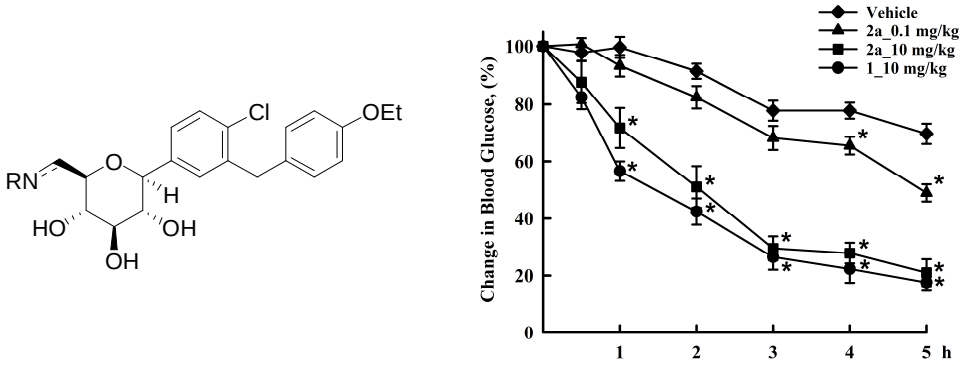
Graphical Abstract



Twenty-seven aryl *C*-glycosides, whose glycone is a 6-amino-/6-imino-6-deoxy-β-D-glucosyl group, were synthesized. Biological, pharmacokinetic and efficacy studies culminated in the identification of oxime **2a** as a potential SGLT2 inhibitor.

Identification of an oxime-containing *C*-glucosylarene as a potential inhibitor of sodium-dependent glucose co-transporter 2

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Abstract: Treatment of hyperglycemia with drugs that block renal glucose reabsorption via inhibition of sodium-dependent glucose cotransporter 2 (SGLT2) is a novel approach to diabetes management. In this study, twenty-seven aryl *C*-glycosides bearing a C=N/C−N linkage at the glucosyl C6 position were designed, synthesized and evaluated for their inhibitory activity against human SGLT2 (hSGLT2). Compounds with good hSGLT2 inhibition were further investigated to determine their selectivity over hSGLT1. Of these, five representative aryl *C*-glycosides were chosen for pharmacokinetic analysis. Oxime **2a** was determined to have the most promising pharmacokinetic properties and was selected for *in vivo* glucosuria and plasma glucose level studies, which found it to exhibit comparable efficacy to dapagliflozin (**1**). Furthermore, **2a** was not found to exhibit either significant cytotoxicity (CC_{50} >50 μM) or human ether-a-go-go related gene (hERG) inhibition (2% inhibition at 10 μM). Taken together, these efforts culminated in the discovery of oxime **2a** as a potential SGLT2 inhibitor.

Keywords: oxime, sodium-dependent glucose co-transporter, aryl *C*-glycosides, diabetes management

Abbreviations used

Ac_2O, acetic anhydride; AMG, α-methyl-D-glucopyranoside; $BF_3 \cdot OEt_2$, boron trifluoride etherate; CHO, Chinese hamster ovary; DMAP, 4-*N*,*N*-dimethylaminopyridine; hERG, low human ether-a-go-go related gene; *$NaBH_3CN$, sodium cyanoborohydride;* SAR, structure-activity relationship; SD, Sprague-Dawley; SGLT2, sodium-dependent glucose co-transporter 2; STZ, streptozotocin; TBSCl, *tert*-butylchlorodimethylsilane; T2DM, type 2 diabetes mellitus; TBAF, tetra-*n*-butylammonium fluoride; TLC, thin layer chromatography.

1. Introduction

Due to the increasing prevalence of type 2 diabetes mellitus (T2DM) and the adverse effects associated with traditional anti-diabetic drugs, novel treatments for this disease are urgently required. *Since the kidneys of diabetic patients are known to reabsorb* greater amounts of glucose back into the bloodstream compared to healthy individuals [1], one possible approach entails the use of *sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors,* which inhibit reabsorption of glucose in the kidney and induce urinary glucose excretion, thereby lowering blood sugar without a significant risk of hypoglycemia (because of their insulin-independent mechanism of action) [2]. *SGLT2 inhibitors are also associated with a reduced risk of* cardiovascular disease, lower blood pressure, and modest weight loss [3]; and *can be administered in combination with other oral, anti-diabetic drugs as well as insulin [4,5].* Although adverse effects of SGLT2 inhibitors include ketoacidosis [6], currently the benefits of SGLT2 inhibitors are considered to outweigh the risks.

SGLT2 is a high-capacity and low-affinity glucose transporter located on the S1 segment of the proximal tubule in the kidney, and mediates the reabsorption of the majority (>90%) of renal glucose filtered by the kidney glomeruli; the remainder is performed by SGLT1, *a low-capacity and high-affinity glucose transporter mainly expressed in the small intestine, but also presented in the S2/S3 segment of the proximal tubule [7-10].* Some studies recommend the use of selective SGLT2 inhibitors, in order to avoid the gastrointestinal side effects involved in SGLT1 inhibition [11,12]. On the contrary, dual SGLT1/SGLT2 or selective SGLT1 inhibitors have also been proposed; of these, sotagliflozin (LX4211) is the most highly developed (Phase III) [13,14]. The trial data acquired so far indicates that sotagliflozin is well tolerated: adverse events were mild, and equally distributed across treatment and placebo groups; and no dose-limiting toxicities have been reported. Additionally, and based on the results of clinical trials [15,16], SGLT2 inhibitors with the ability to partially inhibit SGLT1 have also been proposed. Taken together, these findings cast doubt on the notion that good selectivity over SGLT1 is an essential prerequisite for the development of a practical drug.

The first known SGLT inhibitor, phlorizin, was isolated from the bark of the apple tree in 1835

[17], but found to be metabolically unstable due to the presence of an *O*-glycosidic bond in its structure. Structural modifications of phlorizin have given rise to several, selective, SGLT2 inhibitors; including prodrugs and *N*-/*C*-linked glycosides [18]. Of these, the β-*C*-glycosides were found to exhibit particularly high metabolic stability, oral bioavailability, and plasma exposure; and six have been approved for the treatment of type 2 diabetes: dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, and empagliflozin [19-24]. Also, phlorizin *C*-glucoside and analogues were recently reported as potent and selective SGLT2 inhibitors [25]. Regarding the role of the sugar, we have shown that *N*-xylosylindole is less well tolerated than *N*-glucosylindole within the family of *N*-glycosylindoles reported as SGLT2 inhibitors [26]. We also found that inhibitors bearing 6-amido-6-deoxyglucosyl groups imparted good bioactivities and better selectivity than unmodified *N*-glucosides. Herein, we build on these results and explore *C*-glycosides bearing modifications at the glucosyl C6 position, whose C1 is C-C-linked to position 4 of 1-chloro-2-(4-ethoxybenzyl)benzene (Fig. 1). Dapagliflozin (**1**) was used as a template; and all compounds were designed to be structural modifications of it. Synthesis and structure-activity relationship (SAR) studies of the newly developed aryl *C*-glycosides, incorporating the C=N/C−N linkage at the glucosyl C6 position, are presented. Further pharmacokinetic and animal studies of selected compounds are also discussed.

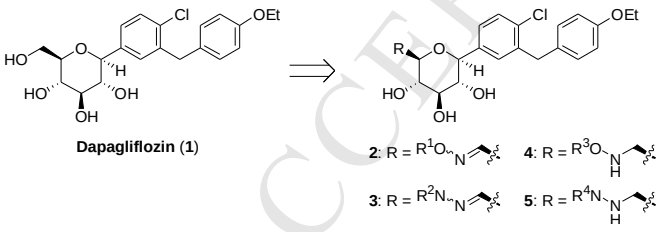
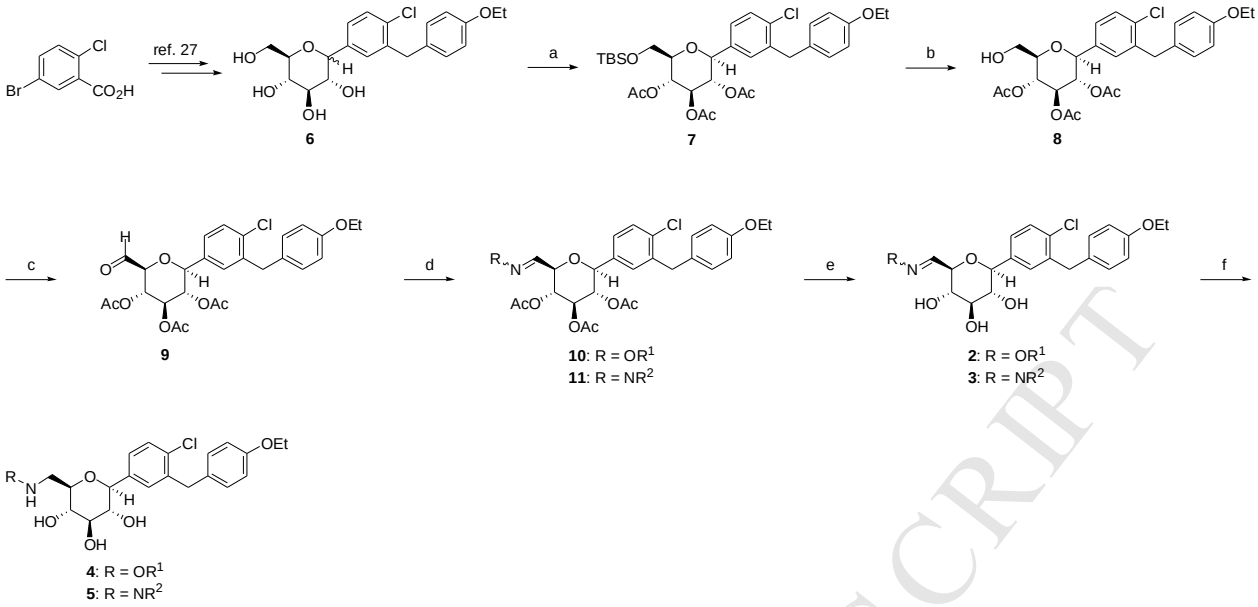


Fig. 1. Design and general structures of desired molecules.

2. Results and Discussion

2.1.Chemistry

Scheme 1 depicts our synthesis of the novel compounds described herein. Starting from *5-bromo-2-chloro-benzoic acid,* a mixture of α- and β-*C*-glucosides **6** was obtained *[27]*. A sequential one-pot process, involving regioselective 6-*O*-silylation and per-*O*-acetylation of **6**, was carried out to synthesize the fully protected β-*C*-glucoside **7**. S*elective O-silylation at 6-OH* of the glucose *moiety was performed with tert*-butylchlorodimethylsilane (TBSCl) / pyridine in the presence of a catalytic amount of 4-*N,N*-dimethylaminopyridine (DMAP), to provide the 6-OTBS glucoside. Per-*O*-acetylation was then accomplished by immediate addition of acetic anhydride (Ac_2O), and the fully protected **7** could be purified by column chromatography on silica gel and isolated in 62% yield. The next step was to introduce the aldehyde at C6 position, for further coupling with various hydrazines or hydroxylamines. In order to avoid the exchange with the O4-acetyl group, the TBS group was removed under acidic condition by treatment of **7** with boron trifluoride etherate ($BF_3 \cdot OEt_2$) in CH_2Cl_2, instead of the more widely used desilylation reagent tetra-*n*-butylammonium fluoride (TBAF). Subsequent oxidation of the resulting primary alcohol **8** using *Dess-Martin periodinane* gave the key intermediate aldehyde **9**. Without further purification, condensation of **9** with a diverse range of hydroxylamines in pyridine followed by deacetylation under Zemplén conditions afforded the desired oxime ether derivatives **2**. *In a similar fashion, the corresponding hydrazones* **3** *were also successfully synthesized by the sequential coupling of* **9** *with various hydrazines in EtOH, and* LiOH/MeOH-mediated deacetylation. Further reduction of **2** and **3** with *sodium cyanoborohydride (*$NaBH_3CN$*) under acidic condition provided the hydroxylamines* **4** *and hydrazines/*hydrazides **5**, *respectively.*



Scheme 1. *Reagents and conditions: (a) TBSCl, DMAP, pyridine, 0 °C to rt, 18 h; then Ac_2O, rt, 3 h; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 1 h; (c) Dess-Martin periodinane, CH_2Cl_2, rt, 3 h; (d) For* **10***: H_2NOR^1, pyridine, rt, 2 h; For* **11***: H_2NNHR^2, EtOH, rt, 2 h; (e) For* **2***: NaOMe, MeOH/CH_2Cl_2, 0 °C, 1-2 h; For* **3***: 1 N $LiOH_{(aq)}$, MeOH/THF/CH_2Cl_2, 0 °C, 2 h; (f) $NaBH_3CN$, 6 N HCl in MeOH, 0 °C, 2 h.*

2.2.Biological evaluations

The *inhibitory activities* of all synthesized oximes **2**, hydrazones **3**, *and their reduction products* **4** *and* **5** *against human SGLT2 (hSGLT2)* or hSGLT1 *were ascertained* by measuring the inhibition of the sodium-dependent uptake of [^{14}C]-labeled α-methyl-D-glucopyranoside (AMG) into Chinese hamster ovary (CHO) cells stably expressing hSGLT [28,29]; the data are presented as EC_{50} values. Phlorizin and dapagliflozin (**1**) were used as standards in this *in vitro* activity evaluation system. *The results are* compiled *in Table 1*, and the results of related SAR studies are discussed below.

In this study, SAR exploration was initiated by investigating the effect of oxime/oxime ether-containing *C*-glycosides (**2a**-**2j**), as shown in Table 1. Of these, compound **2a** bearing an oxime group at the C6 position of the sugar was found to be the most potent SGLT2 inhibitor, with an EC_{50} value of 46 nM. Replacing the hydrogen with a methyl group (**2b**, EC_{50} = 92 nM) or an ethyl group (**2c**, EC_{50} = 335 nM) led to a 2-fold and 7-fold loss in hSGLT2 inhibitory activity, respectively. Decreased

potency was also observed when the ethyl moiety was modified to a 2-hydroxyethyl (**2d**, EC_{50} = 194 nM), 2-methoxyethyl (**2e**, EC_{50} = 678 nM), or 3,3-dimethylbutyl (**2f**, EC_{50} = 8541 nM) group, compared to **2a**. Furthermore, potency was not recovered by substitution with an alkynyl linker (**2g**, EC_{50} = 431 nM; **2h**, EC_{50} = 396 nM), a cyclopropylmethyl group (**2i**, EC_{50} = 1953 nM), or a benzyl group (**2j**, EC_{50} = 2251 nM). Accordingly, the *O*-substituent on the oxime ethers was restricted to hydrogen and methyl only.

In an effort to improve the potency of the glucose-C6-substituted *C*-glycosides, we built functionality into hydrazone derivatives **3a**-**3m**. In contrast, compound **3a** with a 2-hydroxyethyl group was found to exhibit greater potency (EC_{50} = 88 nM) than **2d**, with an oxime ether (EC_{50} = 194 nM). The same trend was observed when the benzyl group was incorporated (**3b**, EC_{50} = 38 nM; **2j**, EC_{50} = 2251 nM); suggesting that hydrazone functionality is a potential liability when seeking to enhance inhibitory activity against hSGLT2.

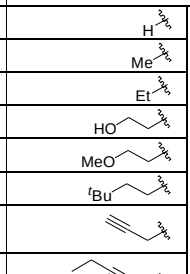
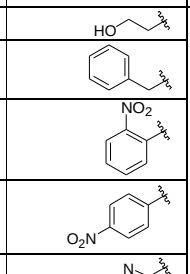
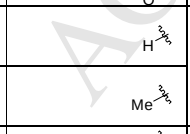
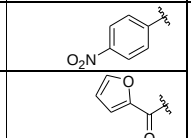
More analogues were synthesized and explored. When those bearing a nitro substituent on the *ortho*- (**3c**) or *para*-position (**3d**) of the phenyl group were constructed, decreased potency was noted with EC_{50} values of 457 nM and 370 nM, respectively. In addition, there was no improvement in hSGLT2 inhibition using imidazoline (**3e**, EC_{50} = 429 nM) or benzothiazole (**3f**, EC_{50} = 204 nM) substitution, indicating that aryl or heteroaryl rings bound to nitrogen without a spacer are not well tolerated at this site. As the project progressed, the *N*-acylhydrazone moiety was also included to study the corresponding hSGLT2 inhibition, being a privileged structure associated with diverse pharmacological activities [30,31]. In general, this subset (**3g**-**3m**) of compounds exhibited moderate to good hSGLT2 inhibitory activity, with EC_{50} values ranging from 65 to 395 nM. Among them, compound **3i** bearing a 4-chlorophenyl group was found to be the most potent inhibitor of hSGLT2 (EC_{50} = 65 nM); in contrast, the unsubstituted phenyl group made the resulting **3h** (EC_{50} = 130 nM) two times less potent than **3i**. Decreased potency was also observed when a small methyl group was introduced (**3g**, EC_{50} = 395 nM), which weakened the hSGLT2 inhibition 6-fold. In addition, replacement of the phenyl group with heteroaryl rings, pyridine, thiophene or furan, gave rise to

compounds **3j**-**3m**; no improvements in inhibitory potency compared to **3h** resulted (EC_{50} = 173 – 301 nM).

We next investigated the contribution of the hydroxylamine **4a** and methoxyamine **4b**, the reduction products of **2a** and **2b**, respectively. Interestingly, the reverse trend in potency was observed: the hydroxylamine **4a** (EC_{50} = 95 nM) was an inferior inhibitor of hSGLT2 compared with **4b** (EC_{50} = 63 nM). The methoxyamine **4b** possessed slightly improved potency compared to oxime ether **2b**, whereas the reduction product of **2a**, the hydroxylamine **4a**, exhibited a 2-fold loss in hSGLT2 inhibitory activity. In the case of reduction of hydrazone **3d** and *N*-acylhydrazone **3m**, the resulting *p*-nitrophenyl hydrazine **5a** and 2-furoic hydrazide **5b** were found to show somewhat improved inhibitory activity against hSGLT2, with EC_{50} values of 211 nM and 151 nM, respectively.

Subsequently, the selectivity profile of the most active glucose-C6-substituted *C*-glycosides from each series was evaluated. The ratios of these eight selected compounds ranged from 63 for **3i** to 143 for **3a**. Taken together, from the SAR studies of the SGLT2 inhibitors, we have shown (1) good tolerance for small substituents on the oxime ether moiety; and (2) the moderate to good hSGLT2 inhibitory activity of hydrazone-based glycosides.

Table 1
Effect of aryl *C*-glycosides with the C=N/C−N linkage at glucose C6-position on hSGLT inhibitory activity and selectivity.

Compound	Structures	hSGLT2 EC_{50} (nM)[a]	hSGLT1 EC_{50} (nM)[a]	Sel.[b]
2a		46 ± 7	3576 ± 1206	78
2b		92 ± 14	5933 ± 527	64
2c		335 ± 111	—	—
2d		194 ± 7	—	—
2e		678 ± 85	—	—
2f		8541 ± 3245	—	—
2g		431 ± 67	—	—
2h		396 ± 78	—	—
2i		1953 ± 376	—	—
2j		2251 ± 1159	—	—
3a		88 ± 36	12572 ± 4095	143
3b		38 ± 4	4931 ± 420	130
3c		457 ± 111	—	—
3d		370 ± 133	—	—
3e		429 ± 71	—	—
3f		204 ± 64	—	—
3g		395 ± 79	—	—
3h		130 ± 42	18080 ± 6739	139
3i		65 ± 5	4091 ± 30	63
3j		173 ± 58	—	—
3k		175 ± 31	—	—
3l		208 ± 45	—	—
3m		301 ± 111	—	—
4a		95 ± 15	8167 ± 1822	86
4b		63 ± 17	5390 ± 772	86
5a		211 ± 98	—	—
5b		151 ± 25	—	—
1		2 ± 1	860 ± 162	430
phlorizin		79 ± 10	240 ± 10	3

[a] Data obtained by at least two independent experiments, each experiment performed in triplicate. [b] Sel: Selectivity values were calculated by EC_{50} hSGLT1/EC_{50} hSGLT2.

2.3.Pharmacokinetic and animal studies

To assess the potential of the designed molecules as SGLT2 inhibitors, representative aryl *C*-glycosides from each series, **2a**, **2b**, **3a**, **3h**, and **4b**, were chosen for pharmacokinetic analysis using an established model [32]; the results are presented in Table 2. Among them, oxime **2a** has the most favorable pharmacokinetic properties, with the low clearance (5.0 mL/min/kg) and good oral bioavailability (64%) in Sprague-Dawley (SD) rats. The elimination half-life was 9.0 hr. Methyloxime **2b** and its reduction product **4b** possessed similar pharmacokinetic profiles with moderate bioavailability (F% = 40.5 and 32.8%, respectively). On the contrary, neither hydrazone **3a** nor *N*-acylhydrazone **3h** showed druggable properties in rats. Even though the *N*-acylhydrazone scaffold is a privileged structure in medicinal chemistry, its vulnerability to hydrolysis is a major consideration for drug discovery. *N*-Acylhydrazone **3h** was found to convert into dapagliflozin (**1**) after administration to rats.

Table 2
Pharmacokinetic properties of selected compounds after oral and intravenous administration to rats

Compound / Parameter	2a		2b		3a		3h		4b	
	IV	PO	IV	PO	IV	PO	IV	PO	IV	PO
N	3	3	3	3	3	3	3	3	3	3
Dose (mg/kg)	1.0	1.1	1.0	1.0	1.1	1.1	0.9	0.9	1.0	1.0
$T_{1/2}$ (hr)	4.7	9.0	3.0	2.5	0.7	1.2	0.36	–	1.9	3.0
Clearance (mL/min/kg)	5.0		12.6		17.6		75.7		16.5	
Vss (L/kg)	1.8		2.9		0.8		1.4		1.8	
Cmax (ng/mL)		238.7		115.9		34.5		–		67.2
Tmax (hr)		1.0		1.0		0.7		–		1.3
$AUC_{(0\text{-inf.})}$ (ng/mL*hr)	3267	2273	1316	540	1026	73	206	–	1067	352
F (%)		64.0		40.5		7.1		–		32.8

To advance the development of oxime **2a** for hyperglycemia management via inhibition of SGLT2, animal studies including glucosuria evaluation and an anti-hyperglycemic assessment were carried out [32]. As shown in Figure 2A, single oral administrations of **2a** of 0.1, 1, 10, and 50 mg/kg to SD rats induced urine glucose excretions of 275, 2215, 1935, and 2732 mg of glucose per 200 g of body weight

over 24 h, respectively; resulting in a 476- to 4730-fold elevation in glucosuria relative to the vehicle control. The efficacy profile of oxime **2a** at various doses in this experiment was similar to that of **1**. Compound **2a** was further evaluated for anti-hyperglycemic effects in streptozotocin (STZ)-induced diabetic SD rats (blood glucose of >450 mg/dL). After a single oral administration of **2a** (0.1 mg/kg or 10 mg/kg), dapagliflozin (**1**) (10 mg/kg), or vehicle, blood samples were collected from the tail vein at 0 (predose), 0.5, 1, 2, 3, 4, and 5 h for blood glucose analysis. As shown in Figure 2B, a gradual decrease in blood glucose level was observed during the period of 5 h; it was found that **2a** caused a 44% reduction in blood glucose level compared with the control, and showed comparable efficacy with **1** at an oral dose of 10 mg/kg. Additional results of low inhibitory activity in the human ether-a-go-go related gene (hERG) binding assay (2% inhibition at 10 μM), and a lack of significant cytotoxicity (CC_{50} >50 μM), emphasize the potential of **2a** as a promising SGLT2 inhibitor.

(A) (B)

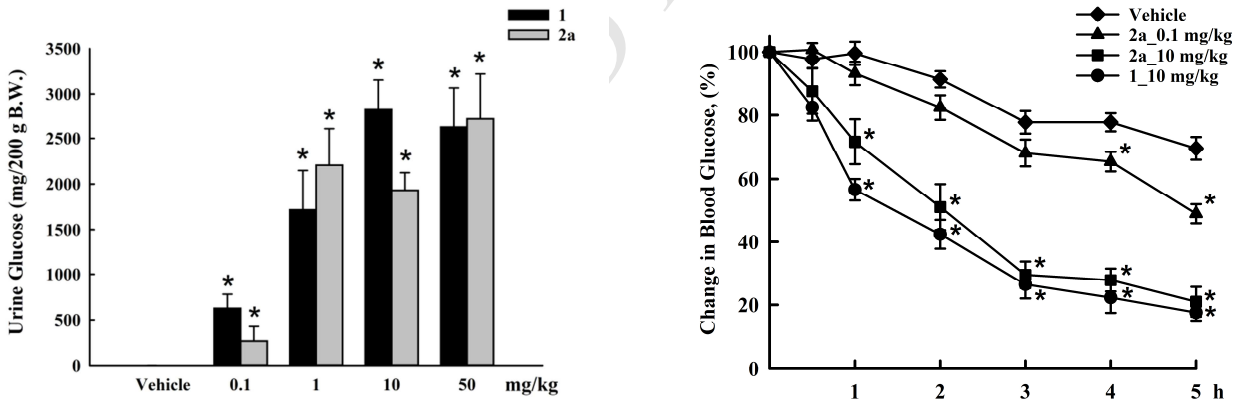


Fig. 2. (A) Effect of oral administration of oxime **2a** and dapagliflozin (**1**) on urine glucose excretion over 24 h in normal Sprague-Dawley rats. Data are expressed as the mean ± SEM (n = 4/group; vehicle: n = 8): *p < 0.05 vs vehicle. (B) Antihyperglycemic effect of oxime **2a** (0.1 mg/kg or 10 mg/kg) and dapagliflozin (**1**) (10 mg/kg) in STZ-induced diabetic Sprague-Dawley rats. Data are expressed as the mean ± SEM (n = 6/group): *p < 0.05 vs vehicle.

3. Conclusion

The rational design of aryl *C*-glycoside SGLT2 inhibitors with the C=N/C−N linkage at the glucosyl C6 position led to the identification of oxime **2a** as a potential lead compound. Oxime **2a** showed good *in vitro* inhibitory activity against hSGLT2, 78-fold selectivity over SGLT1, no significant cytotoxicity, and low hERG inhibition. Further *in vivo* studies indicated that dapagliflozin (**1**) and **2a** could induce glucosuria in normal SD rats and lower plasma glucose levels in STZ-induced diabetic rats to a comparable extent. The favorable pharmacokinetic profile exhibited by **2a** establishes it as a promising SGLT2 inhibitor for further development. Finally, since **2a** is a SGLT2 inhibitor that also partially inhibits SGLT1, it may inform discussions regarding the importance of selectivity towards SGLT1 and should be of utility for investigative studies.

4. Experimental section

4.1. Chemistry

Unless otherwise stated, all reagents and solvents were used as received without further purification. Reaction progress was monitored by analytical thin layer chromatography (TLC), carried out on glass-backed plates pre-coated with SiO_2 60 F254. Column chromatography was carried out using SiliaFlash P60 SiO_2 of 230−400 mesh size. Chromatograms were visualized with UV irradiation at 254 nm, followed by staining with an aqueous solution of $Ce(NH_4)_2(NO_3)_6$, $(NH4)_6Mo_7O_{24}$, and H_2SO_4, and heating on a hot plate. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury-300 or Mercury-400 spectrometers. Chemical shifts are reported relative to the internal standard signal of CD_3OD (^1H, δ = 3.31 ppm; ^{13}C, δ = 49.00 ppm), DMSO-d6 (^1H, δ = 2.50 ppm; ^{13}C, δ = 39.50 ppm) or $CDCl_3$ (^1H, δ = 7.26 ppm; ^{13}C, δ = 77.00 ppm), and splitting patterns are recorded as s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. LC/MS data are recorded as *m/z* values obtained with an Agilent MSD-1100 mass spectrometer using electrospray ionization (ESI) source. High-resolution mass spectra were obtained on MAT-95XL or JEOL JMS-700 high resolution mass spectrometers in electron impact (EI) or fast atom bombardment (FAB) ionization modes. The analysis of test compounds was

performed by a Hitachi 2000 series HPLC system with an Agilent ZORBAX Eclipse XDB-C18 reverse-phase column (5 μm, 4.6 mm × 150 mm) in gradient conditions starting from mobile phase A (MeCN) / mobile phase B (10 mM NH_4OAc aqueous solution containing 0.1% formic acid) = 10/90% to A/B = 90/10% in 45 min at a flow rate of 0.5 mL/min.

*4.1.1. (1S)-2,3,4-Tri-O-acetyl-1,5-anhydro-6-O-[tert-butyl(dimethyl)silyl]-1-[4-chloro-3-(4-ethoxy-benzyl)phenyl]-D-glucitol (**7**)*

A solution of TBSCl (724 mg, 4.8 mmol) in pyridine (3.7 mL) was added to a mixture of **6** (1.51 g, 3.7 mmol) and DMAP (207 mg, 1.8 mmol) in pyridine (3.7 mL) at 0 ^oC under $N_{2(g)}$. The reaction mixture was allowed to warm to room temperature and left overnight, with stirring. After the reaction was complete, Ac_2O (3.5 mL, 36.9 mmol) was added and the solution stirred at room temperature for another 3 h. The reaction was quenched with H_2O at 0 °C, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was sequentially washed with 1 N $HCl_{(aq)}$, H_2O, and saturated $NaHCO_{3(aq)}$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/n-Hexane = 1/3) to provide **7** (1.48 g, 62%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 1H, ArH), 7.16 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.10 (d, *J* = 2.0 Hz, 1H, ArH), 7.07−7.03 (m, 2H, ArH), 6.82−6.79 (m, 2H, ArH), 5.28 (t, *J* = 9.6 Hz, 1H, Glc H3), 5.20 (t, *J* = 9.6 Hz, 1H, Glc H4), 4.99 (t, *J* = 9.6 Hz, 1H, Glc H2), 4.28 (d, *J* = 10.0 Hz, 1H, Glc H1), 4.08−3.93 (m, 4H, 2 x CH_2), 3.78−3.68 (m, 2H, Glc H6a, H6b), 3.63 (ddd, *J* = 9.6, 4.8, 2.4 Hz, 1H, Glc H5), 2.04 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.39 (t, *J* = 7.2 Hz, 3H, CH_3), 0.86 (s, 9H, 3 x CH_3), 0.01 (s, 3H, CH_3), -0.03 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.51, 169.33, 168.80, 157.39, 138.90, 135.58, 134.30, 131.08, 129.73, 129.56, 126.03, 114.41, 79.31, 78.92, 74.46, 72.85, 68.81, 63.30, 62.44, 38.25, 25.74, 20.69, 20.68, 20.31, 18.26, 14.83, -5.37; MS (ESI) m/z: 671 (MNa^+).

*4.1.2 General procedure for the synthesis of compound **2***

$BF_3 \cdot OEt_2$ (2.7 equiv) was added to a stirred solution of **7** (1.0 equiv) in CH_2Cl_2 at 0 °C under $Ar_{(g)}$. After stirring at 0 °C for 30 min, the reaction was quenched by the addition of saturated $NaHCO_{3(aq)}$,

and the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a crude extract of **8**, which was used for oxidation directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.08−7.03 (m, 3H), 6.83−6.80 (m, 2H), 5.33 (dd, *J* = 9.6, 9.2 Hz, 1H), 5.13 (t, *J* = 9.6 Hz, 1H), 5.04 (dd, *J* = 10.0, 9.6 Hz, 1H), 4.28 (d, *J* = 9.6 Hz, 1H), 4.07−3.95 (m, 4H), 3.77−3.70 (m, 1H), 3.65-3.58 (m, 2H), 2.25 (dd, *J* = 8.8, 5.2 Hz, 1H), 2.04 (s, 3H), 2.00 (s, 3H), 1.71 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); MS (ESI) m/z: 557 (MNa^+).

Dess-Martin periodinane (1.5 equiv) was added to a stirred solution of crude **8** (1.0 equiv) in CH_2Cl_2 *at room temperature under* $Ar_{(g)}$*. After stirring for 3 h, the solution was diluted with* CH_2Cl_2*, saturated* $NaHCO_{3(aq)}$ *and saturated* $Na_2S_2O_{3(aq)}$ *were then added* to the reaction sequentially. T*he resulting mixture was stirred for another 30 min at room temperature.* The organic layer was separated, and the aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a crude extract of the aldehyde **9**, which was used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.21 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.10−7.04 (m, 3H), 6.84−6.80 (m, 2H), 5.34 (t, *J* = 9.2 Hz, 1H), 5.27 (dd, *J* = 10.0, 9.6 Hz, 1H), 5.08 (dd, *J* = 9.6, 9.2 Hz, 1H), 4.39 (d, *J* = 9.6 Hz, 1H), 4.09−3.91 (m, 5H), 2.07 (s, 3H), 2.01 (s, 3H), 1.71 (s, 3H), 1.40 (t, *J* = 6.8 Hz, 3H); MS (ESI) m/z: 555 (MNa^+).

Hydroxylamine *(1.5 equiv)* was added to a stirred solution of aldehyde **9** *(1.0 equiv)* in pyridine at room temperature. After *stirring* at the same temperature for 2 h, the solvent was removed under reduced pressure. Water was added to the residue, and the mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/ n-Hexane) to provide compound **10** as a mixture of *E*/*Z*-isomers.

A 30% solution of NaOMe in MeOH (1.1 equiv) was added to a stirred solution of compound **10** *(1.0 equiv)* in mixed solvents (MeOH/CH_2Cl_2, v/v: 1/1) in an ice bath. The reaction was warmed up to room temperature and stirred for 1~2 h. The reaction was neutralized with Amberlite-120 acidic resin,

and the mixture was filtered to remove the resin followed by washing with MeOH. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography ($MeOH/CH_2Cl_2$) to give compound **2** as a mixture of *E*/*Z* isomers. The major isomer was determined to be present in at least 80% for all samples by HPLC analysis. The NMR data specified is for the major isomer only.

*4.1.2.1 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-[(hydroxyimino)methyl]tetrahydro-2H-pyran-3,4,5-triol (**2a**)*

The title compound was obtained from **7** according to the general procedure in 40% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.34 (d, *J* = 8.0 Hz, 1H, ArH), 7.33 (d, *J* = 7.2 Hz, 1H, C<u>H</u>=N), 7.26−7.21 (m, 2H, ArH), 7.10−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.13 (d, *J* = 9.2 Hz, 1H, Glc H1), 4.05−3.87 (m, 5H, 2 x CH_2, Glc H5), 3.50−3.46 (m, 2H, Glc H3, H4), 3.34−3.30 (m, 1H, Glc H2), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.85, 149.31, 140.04, 139.56, 134.60, 132.78, 131.76, 130.86, 130.19, 128.06, 115.43, 82.93, 79.12, 79.08, 76.19, 73.51, 64.41, 39.23, 15.20; MS (ESI) *m/z*: 422 (MH^+), 444 (MNa^+); HRMS (FAB) for $C_{21}H_{25}ClNO_6$: calcd, 422.1370; found, 422.1375.

*4.1.2.2 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-[(methoxyimino)methyl]tetrahydro-2H-pyran-3,4,5-triol (**2b**)*

The title compound was obtained from **7** according to the general procedure in 35% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.34 (d, *J* = 8.0 Hz, 1H, ArH), 7.33 (d, *J* = 7.2 Hz, 1H, C<u>H</u>=N), 7.26−7.21 (m, 2H, ArH), 7.09−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.13 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.05−3.86 (m, 5H, 2 x CH_2, Glc H5), 3.82 (s, 3H, OCH_3), 3.49−3.44 (m, 2H, Glc H3, H4), 3.33−3.28 (m, 1H, Glc H2), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.86, 149.13, 140.07, 139.49, 134.63, 132.77, 131.75, 130.86, 130.20, 128.07, 115.43, 82.96, 79.12, 78.83, 76.14, 73.40, 64.41, 62.08, 39.22, 15.20; MS (ESI) *m/z*: 436 (MH^+), 458 (MNa^+); HRMS (EI) for $C_{22}H_{26}ClNO_6$: calcd, 435.1449; found, 435.1456.

*4.1.2.3 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-[(ethoxyimino)methyl]tetrahydro-2H-pyran-3,4,5-triol (**2c**)*

The title compound was obtained from **7** according to the general procedure in 17% yield over four steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.34 (d, *J* = 8.1 Hz, 1H, ArH), 7.33 (d, *J* = 6.9 Hz, 1H, C<u>H</u>=N), 7.26−7.20 (m, 2H, ArH), 7.10−7.05 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.13 (d, *J* = 9.3 Hz, 1H, Glc H1), 4.08 (q, *J* = 7.2 Hz, 2H, CH_2), 4.01−3.86 (m, 5H, 2 x CH_2, Glc H5), 3.50−3.43 (m, 2H, Glc H3, H4), 3.42−3.28 (m, 1H, Glc H2), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3), 1.21 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.86, 148.89, 140.07, 139.51, 134.62, 132.77, 131.75, 130.86, 130.20, 128.07, 115.43, 82.95, 79.13, 78.96, 76.16, 73.42, 70.49, 64.40, 39.23, 15.20, 14.77; MS (ESI) *m/z*: 450 (MH^+), 472 (MNa^+); HRMS (EI) for $C_{23}H_{28}ClNO_6$: calcd, 449.1605; found, 449.1603.

*4.1.2.4 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-{[(2-hydroxyethoxy)imino]methyl}-tetrahydro-2H-pyran-3,4,5-triol (**2d**)*

The title compound was obtained from **7** according to the general procedure in 23% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, *J* = 6.8 Hz, 1H, C<u>H</u>=N), 7.34 (d, *J* = 8.4 Hz, 1H, ArH), 7.26−7.21 (m, 2H, ArH), 7.09−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.15−4.09 (m, 3H, CH_2, Glc H1), 4.05−3.88 (m, 5H, 2 x CH_2, Glc H5), 3.74−3.71 (m, 2H, CH_2), 3.51−3.44 (m, 2H, Glc H3, H4), 3.34−3.28 (m, 1H, Glc H2), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.83, 149.56, 140.06, 139.45, 134.63, 132.75, 131.73, 130.84, 130.20, 128.07, 115.43, 82.93, 79.06, 78.90, 76.31, 76.11, 73.38, 64.41, 61.40, 39.21, 15.20; MS (ESI) *m/z*: 466 (MH^+), 488 (MNa^+); HRMS (EI) for $C_{23}H_{28}ClNO_7$: calcd, 465.1554; found, 465.1552.

*4.1.2.5 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-{ [(2-methoxyethoxy)imino]methyl}-tetrahydro-2H-pyran-3,4,5-triol (**2e**)*

The title compound was obtained from **7** according to the general procedure in 20% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (d, *J* = 6.8 Hz, 1H, C<u>H</u>=N), 7.34 (d, *J* = 8.4 Hz, 1H, ArH), 7.26−7.21 (m, 2H, ArH), 7.09−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.19−4.12 (m, 3H, CH_2, Glc H1), 4.05−3.88 (m, 5H, 2 x CH_2, Glc H5), 3.62−3.59 (m, 2H, CH_2), 3.48−3.46 (m, 2H, Glc H3, H4), 3.33−3.29 (m, 4H, OCH_3, Glc H2), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.85, 149.58, 140.06, 139.50, 134.62, 132.75, 131.74, 130.86, 130.19, 128.07, 115.42, 82.95, 79.08,

78.90, 76.15, 74.10, 73.37, 71.92, 64.39, 59.11, 39.21, 15.20; MS (ESI) *m/z*: 480 (MH^+), 502 (MNa^+); HRMS (EI) for $C_{24}H_{30}ClNO_7$: calcd, 479.1711; found, 479.1713.

*4.1.2.6 (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-{[(3,3-dimethylbutoxy)imino]-methyl}tetrahydro-2 H-pyran-3,4,5-triol (**2f**)*

The title compound was obtained from **7** according to the general procedure in 74% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (d, *J* = 8.4 Hz, 1H, ArH), 7.32 (d, *J* = 7.2 Hz, 1H, C<u>H</u>=N), 7.26−7.21 (m, 2H, ArH), 7.09−7.05 (m, 2H, ArH), 6.80−6.76 (m, 2H, ArH), 4.15−4.08 (m, 3H, CH_2, Glc H1), 4.05−3.87 (m , 5H, 2 x CH_2, Glc H5), 3.50−3.44 (m, 2H, Glc H3, H4), 3.34−3.28 (m, 1H, Glc H2), 1.55 (t, *J* = 7.2 Hz, 2H, CH_2), 1.34 (t, *J* = 7.2 Hz, 3H, CH_3), 0.92 (s ,9H, 3 x CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.82, 148.83, 140.05, 139.47, 134.62, 132.76, 131.75, 130.85, 130.20, 128.06, 115.44, 82.92, 79.13, 78.91, 76.13, 73.42, 72.57, 64.40, 43.10, 39.22, 30.43, 30.17, 15.21; MS (ESI) *m/z*: 506 (MH^+), 528 (MNa^+); HRMS (EI) for $C_{27}H_{36}ClNO_6$: calcd, 505.2231; found, 505.2224.

*4.1.2.7 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-{[(prop-2-yn-1-yloxy)imino]-methyl}tetrahydro-2H-pyran-3,4,5-triol (**2g**)*

The title compound was obtained from **7** according to the general procedure in 39% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, *J* = 7.2 Hz, 1H, C<u>H</u>=N), 7.34 (d, *J* = 8.0 Hz, 1H, ArH), 7.26−7.21 (m, 2H, ArH), 7.10−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.63 (d, *J* = 2.4 Hz, 2H, CH_2), 4.14 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.06−3.90 (m, 5H, 2 x CH_2, Glc H5), 3.49−3.46 (m, 2H, Glc H3, H4), 3.34−3.29 (m, 1H, Glc H2), 2.84 (t, *J* = 2.4 Hz, 1H, CH), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.85, 150.44, 140.07, 139.45, 134.64, 132.77, 131.75, 130.87, 130.20, 128.07, 115.43, 82.97, 80.27, 79.09, 78.75, 76.13, 76.06, 73.35, 64.41, 62.38, 39.22, 15.20; MS (ESI) *m/z*: 460 (MH^+), 482 (MNa^+); HRMS (EI) for $C_{24}H_{26}ClNO_6$: calcd, 459.1449; found, 459.1440.

*4.1.2.8 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-{[(pent-2-yn-1-yloxy)imino]-methyl}tetrahydro-2H-pyran-3,4,5-triol (**2h**)*

The title compound was obtained from **7** according to the general procedure in 20% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (d, *J* = 6.8 Hz, 1H, C<u>H</u>=N), 7.34 (d, *J* = 8.4 Hz, 1H, ArH),

7.26−7.21 (m, 2H, ArH), 7.09−7.07 (m, 2H, ArH), 6.80−6.78 (m, 2H, ArH), 4.59 (t, *J* = 2.4 Hz, 2H, CH_2), 4.14 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.05−3.89 (m, 5H, 2 x CH_2, Glc H5), 3.50−3.44 (m, 2H, Glc H3, H4), 3.34−3.27 (m, 1H, Glc H2), 2.17 (qt, *J* = 7.6, 2.4 Hz, 2H, CH_2), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3), 1.09 (t, *J* = 7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.85, 150.03, 140.06, 139.46, 134.63, 132.77, 131.76, 130.86, 130.20, 128.07, 115.43, 89.29, 82.96, 79.08, 78.80, 76.13, 75.92, 73.37, 64.40, 62.97, 39.22, 15.20, 14.15, 13.04; MS (ESI) *m/z*: 510 (MNa^+); HRMS (EI) for $C_{26}H_{30}ClNO_6$: calcd, 487.1762; found, 487.1765.

4.1.2.9 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-{[(cyclopropylmethoxy)imino]-methyl}tetrahydro-2H-pyran-3,4,5-triol ***(2i)***

The title compound was obtained from **7** according to the general procedure in 49 % yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (d, *J* = 7.2 Hz, 1H, C<u>H</u>=N), 7.34 (d, *J* = 8.0 Hz, 1H, ArH), 7.26−7.21 (m, 2H, ArH), 7.10−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.13 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.05−3.95 (m, 4H, 2 x CH_2), 3.91−3.83 (m, 3H, CH_2, Glc H5), 3.50−3.44 (m, 2H, Glc H3, H4), 3.34−3.28 (m, 1H, Glc H2), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3), 1.15−1.06 (m, 1H, CH), 0.53−0.48 (m, 2H, CH_2), 0.26−0.22 (m, 2H, CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 158.85, 148.83, 140.06, 139.50, 134.63, 132.80, 131.74, 130.86, 130.19, 128.06, 115.47, 82.94, 79.83, 79.14, 78.93, 76.16, 73.46, 64.44, 39.23, 15.20, 10.98, 3.43, 3.37; MS (ESI) *m/z*: 476 (MH^+), 498 (MNa^+); HRMS (EI) for $C_{25}H_{30}ClNO_6$: calcd, 475.1762; found, 475.1763.

4.1.2.10 (2R,3S,4R,5R,6S)-2-{[(Benzyloxy)imino]methyl}-6-[4-chloro-3-(4-ethoxybenzyl)phenyl]tetra-hydro-2H-pyran-3,4,5-triol ***(2j)***

The title compound was obtained from **7** according to the general procedure in 79% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, *J* = 7.2 Hz, 1H, C<u>H</u>=N), 7.35−7.20 (m, 8H, ArH), 7.09−7.06 (m, 2H, ArH), 6.80−6.75 (m, 2H, ArH), 5.06 (s, 2H, CH_2), 4.13 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.04−3.88 (m, 5H, 2 x CH_2, Glc H5), 3.48−3.46 (m, 2H, Glc H3, H4), 3.34−3.31 (m, 1H, Glc H2), 1.34 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.83, 149.65, 140.06, 139.45, 138.87, 134.62, 132.75, 131.75, 130.86, 130.19, 129.35, 129.28, 128.87, 128.07, 115.42, 82.92, 79.07, 78.85,

77.07, 76.12, 73.40, 64.39, 39.21, 15.20; MS (ESI) *m/z*: 534 (MNa^+); HRMS (EI) for $C_{28}H_{30}ClNO_6$: calcd, 511.1762; found, 511.1755.

*4.1.3 General procedure for the synthesis of compound **3***

As described above, key intermediate aldehyde **9** for the synthesis of hydrazone/*N*-acylhydrazone **3** could be obtained from **7** via a 2-step procedure. Without purification, **9** *(1.0 equiv.) was reacted with various hydrazines (1.0 equiv.) in EtOH at room temperature for 2 h. Water was added to the reaction, and the resulting mixture was extracted with CH_2Cl_2 or EtOAc. The organic layer was dried* over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/ n-Hexane) to provide compound **11**.

A 1 M solution of LiOH in H_2O (1.17 equiv) was added to a stirred solution of compound **11** *(1.0 equiv)* in mixed solvents (MeOH/THF/CH_2Cl_2, v/v: 2/2/1) in an ice bath. After stirring at 0 ^oC for 2 h, the reaction was neutralized with CH_3COOH. The reaction mixture was *extracted with EtOAc, and the organic layer was dried* over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (MeOH/CH_2Cl_2) to provide compound **3** as see above *E*/*Z* isomers. The major isomer was determined to be present in at least 90% for all samples by HPLC analysis except compound **3g** (The ratio of the isomers was ~1.4:1 presented in ^1H-NMR spectrum). The NMR data specified is for the major isomer only.

*4.1.3.1 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-{[2-(2-hydroxyethyl)hydrazinyl-idene]methyl}tetrahydro-2H-pyran-3,4,5-triol (**3a**)*

The title compound was obtained from **7** according to the general procedure in 51% yield over four steps. ^1H NMR (400 MHz, CD_3OD) δ 7.33 (d, *J* = 8.0 Hz, 1H, ArH), 7.26−7.20 (m, 2H, ArH), 7.09−7.05 (m, 2H, ArH), 6.94 (d, *J* = 6.0 Hz, 1H, C<u>H</u>=N), 6.80−6.77 (m, 2H, ArH), 4.12 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.05−3.95 (m, 4H, 2 x CH_2), 3.83 (dd, *J* = 9.2, 6.0 Hz, 1H, Glc H5), 3.65 (t, *J* = 5.6 Hz, 2H, CH_2), 3.52−3.45 (m, 2H, Glc H3, H4), 3.34−3.27 (m, 1H, Glc H2), 3.17 (t, *J* = 5.6 Hz, 2H, CH_2), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.86, 140.06, 139.71, 138.84, 134.58, 132.78, 131.81, 130.85, 130.18, 128.14, 115.43, 82.89, 81.07, 79.17, 76.25, 73.84, 64.41, 60.91, 51.68,

39.21, 15.20; MS (ESI) *m/z*: 465 (MH^+), 487 (MNa^+); HRMS (EI) for $C_{23}H_{29}ClN_2O_6$: calcd, 464.1714; found, 464.1707.

*4.1.3.2 (2R,3S,4R,5R,6S)-2-[(2-Benzylhydrazinylidene)methyl]-6-[4-chloro-3-(4-ethoxybenzyl)phenyl]-tetrahydro-2H-pyran-3,4,5-triol (**3b**)*

The title compound was obtained from **7** according to the general procedure in 11% yield over four steps. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.35 (d, *J* = 8.0 Hz, 1H, ArH), 7.29−7.15 (m, 8H, ArH, NH), 7.09−7.05 (m, 2H, ArH), 6.82−6.79 (m, 2H, ArH), 6.75 (d, *J* = 6.8 Hz, 1H, CH=N), 5.03 (d, *J* = 4.0 Hz, 1H, OH), 4.89−4.86 (m, 2H, 2 x OH), 4.12 (d, *J* = 5.2 Hz, 2H, CH_2), 4.03 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.00−3.92 (m, 4H, 2 x CH_2), 3.67 (dd, *J* = 9.2, 6.8 Hz, 1H, Glc H5), 3.39−3.12 (m, 3H, Glc H2, H3, H4), 1.28 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.37, 139.13, 136.96, 136.87, 136.37, 134.26, 131.15, 130.35, 129.78, 129.69, 128.73, 128.23, 127.73, 126.48, 114.43, 81.13, 77.98, 77.20, 74.50, 72.80, 63.34, 52.44, 38.37, 14.84; MS (ESI) *m/z*: 511 (MH^+), 533 (MNa^+); HRMS (FAB) for $C_{28}H_{31}ClN_2O_5$: calcd, 510.1921; found, 510.1922.

*4.1.3.3 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-{[2-(2-nitrophenyl)hydrazinyl-idene] methyl}tetrahydro-2H-pyran-3,4,5-triol (**3c**)*

The title compound was obtained from **7** according to the general procedure in 43% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (dd, *J* = 8.8, 1.6 Hz, 1H, ArH), 7.81 (dd, *J* = 8.8, 1.6 Hz, 1H, ArH), 7.49 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H, ArH), 7.44 (d, *J* = 6.0 Hz, 1H, CH=N), 7.33 (d, *J* = 8.4 Hz, 1H, ArH), 7.29−7.23 (m, 2H, ArH), 7.07−7.03 (m, 2H, ArH), 6.82 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H, ArH), 6.77−6.73 (m, 2H, ArH), 4.20 (d, *J* = 9.2 Hz, 1H, Glc H1), 4.06−3.90 (m, 5H, 2 x CH_2, Glc H5), 3.61 (dd, *J* = 9.6, 8.8 Hz, 1H, Glc H4), 3.53 (dd, *J* = 9.2, 8.8 Hz, 1H, Glc H3), 3.37 (dd, *J* = 9.6, 8.8 Hz, 1H, Glc H2), 1.32 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.82, 145.03, 142.95, 140.11, 139.59, 136.99, 134.63, 132.74, 132.45, 131.74, 130.84, 130.20, 128.14, 126.61, 119.30, 117.20, 115.42, 82.94, 81.03, 79.22, 76.21, 73.48, 64.38, 39.21, 15.19; MS (ESI) *m/z*: 564 (MNa^+); HRMS (FAB) for $C_{27}H_{28}ClN_3O_7$: calcd, 541.1616; found, 541.1619.

4.1.3.4 (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-{[2-(4-nitrophenyl)hydrazinyl-

*idene]methyl}tetrahydro-2H-pyran-3,4,5-triol (**3d**)*

The title compound was obtained from **7** according to the general procedure in 26% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (d, *J* = 9.2 Hz, 2H, ArH), 7.33 (d, *J* = 8.4 Hz, 1H, ArH), 7.28−7.20 (m, 3H, ArH, C<u>H</u>=N), 7.07−7.02 (m, 4H, ArH), 6.78−6.75 (m, 2H, ArH), 4.19 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.04−3.92 (m, 5H, 2 x CH_2, Glc H5), 3.58 (t, *J* = 8.8 Hz, 1H, Glc H4), 3.53 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.37 (t, *J* = 8.8 Hz, 1H, Glc H2), 1.32 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.82, 152.15, 142.09, 140.72, 140.09, 139.57, 134.64, 132.74, 131.77, 130.84, 130.21, 128.13, 126.90, 115.43, 112.28, 82.94, 81.02, 79.28, 76.20, 73.59, 64.40, 39.22, 15.19; MS (ESI) *m/z*: 542 (MH^+), 564 (MNa^+); HRMS (FAB) for $C_{27}H_{29}ClN_3O_7$: calcd, 542.1694; found, 542.1687.

*4.1.3.5 (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-{[2-(4,5-dihydro-1H-imidazol-2-yl)-hydrazinylidene]methyl}tetrahydro-2H-pyran-3,4,5-triol (**3e**)*

The title compound was obtained from **7** according to the general procedure in 17% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, *J* = 5.6 Hz, 1H, C<u>H</u>=N), 7.35 (d, *J* = 8.4 Hz, 1H, ArH), 7.25−7.21 (m, 2H, ArH), 7.09−7.05 (m, 2H, ArH), 6.80−6.76 (m, 2H, ArH), 4.16 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.05−3.94 (m, 5H, 2 x CH_2, Glc H5), 3.69 (s, 4H, 2 x CH_2), 3.56 (t, *J* = 9.2 Hz, 1H, Glc H4), 3.50 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.36 (dd, *J* = 9.6, 8.8 Hz, 1H, Glc H2), 1.34 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.85 149.71, 140.14, 139.37, 134.72, 132.74, 131.82, 130.85, 130.26, 128.13, 115.44, 83.07, 80.43, 79.18, 76.01, 73.25, 64.42, 44.02, 39.18, 15.20; MS (ESI) *m/z*: 489 (MH^+), 511 (MNa^+); HRMS (FAB) for $C_{24}H_{29}ClN_4O_5$: calcd, 488.1826; found, 488.1833.

*4.1.3.6 (2R,3S,4R,5R,6S)-2-{[2-(1,3-benzothiazol-2-yl)hydrazinylidene]methyl}-6-[4-chloro-3-(4-ethoxybenzyl)phenyl]tetrahydro-2H-pyran-3,4,5-triol (**3f**)*

The title compound was obtained from **7** according to the general procedure in 28% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (d, *J* = 7.6 Hz, 1H, ArH), 7.42 (d, *J* = 8.0 Hz, 1H, ArH), 7.35 (d, *J* = 6.4 Hz, 1H, C<u>H</u>=N), 7.32 (d, *J* = 8.4 Hz, 1H, ArH), 7.29−7.22 (m, 3H, ArH), 7.11−7.03 (m, 3H, ArH), 6.77−6.73 (m, 2H, ArH), 4.19 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.02−3.98 (m, 3H, CH_2, Glc H5), 3.92 (q, *J* = 7.2 Hz, 2H, CH_2), 3.59 (dd, *J* = 9.2, 8.8 Hz, 1H, Glc H4), 3.54 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.37

(dd, *J* = 9.2, 8.8 Hz, 1H, Glc H2), 1.31 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 169.86, 158.83, 140.09, 139.56, 134.65, 132.75, 131.75, 130.86, 130.20, 128.14, 127.09, 123.28, 122.25, 115.42, 82.92, 80.79, 79.19, 76.20, 73.55, 64.39, 39.24, 15.19; MS (ESI) *m/z*: 554 (MH^+), 576 (MNa^+); HRMS (FAB) for $C_{28}H_{29}ClN_3O_5S$: calcd, 554.1516; found, 554.1509.

*4.1.3.7 N'-[{(2R,3S,4R,5R,6S)-6-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene]acetohydrazide (**3g**)*

The title compound was obtained from **7** according to the general procedure in 23% yield over four steps. The ratio of the isomers was ~1.4:1. The proton chemical shifts of CH_3 groups of the isomers are at 2.19 (s) and 2.00 (s) ppm, respectively; MS (ESI) *m/z*: 463 (MH^+); HRMS (EI) for $C_{23}H_{27}ClN_2O_6$: calcd, 462.1558; found, 462.1557.

*4.1.3.8 N'-[{(2R,3S,4R,5R,6S)-6-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene]benzohydrazide (**3h**)*

The title compound was obtained from **7** according to the general procedure in 34% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (dd, *J* = 7.2, 1.6 Hz, 2H, ArH), 7.63 (d, *J* = 6.0 Hz, 1H, C<u>H</u>=N), 7.63−7.56 (m, 1H, ArH), 7.51−7.47 (m, 2H, ArH), 7.34 (d, *J* = 8.4 Hz, 1H, ArH), 7.27−7.23 (m, 2H, ArH), 7.09−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.20 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.07−3.94 (m, 5H, 2 x CH_2, Glc H5), 3.62 (t, *J* = 9.2 Hz, 1H, Glc H4), 3.53 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.36 (t, *J* = 9.2 Hz, 1H, Glc H2), 1.34 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6) δ 163.18, 156.91, 148.55, 139.08, 138.06, 133.23, 132.20, 131.81, 131.14, 130.80, 129.59, 128.84, 128.50, 127.58, 127.36, 114.29, 80.96, 79.45, 77.83, 74.33, 72.02, 62.87, 37.64, 14.70; MS (ESI) *m/z*: 525 (MH^+), 547 (MNa^+); HRMS (FAB) for $C_{28}H_{29}ClN_2O_6$: calcd, 524.1714; found, 524.1711.

*4.1.3.9 4-Chloro-N'-[{(2R,3S,4R,5R,6S)-6-[4-chloro-3-(4-ethoxybenzyl)phenyl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene]benzohydrazide (**3i**)*

The title compound was obtained from **7** according to the general procedure in 34% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (d, *J* = 8.4 Hz, 2H, ArH), 7.62 (d, *J* = 5.6 Hz, 1H, C<u>H</u>=N), 7.51 (d, *J* = 8.8 Hz, 2H, ArH), 7.35 (d, *J* = 8.0 Hz, 1H, ArH), 7.26−7.23 (m, 2H, ArH), 7.07 (d, *J* = 8.8

Hz, 2H, ArH), 6.80−6.78 (m, 2H, ArH), 4.20 (d, *J* = 10.0 Hz, 1H, Glc H1), 4.07−3.95 (m, 5H, 2 x CH_2, Glc H5), 3.62 (dd, *J* = 9.6, 9.2 Hz, 1H, Glc H4), 3.53 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.36 (t, *J* = 9.2 Hz, 1H, Glc H2), 1.27 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6) δ 162.09, 156.90, 148.96, 139.08, 138.05, 136.65, 132.20, 131.90, 131.14, 130.78, 129.58, 129.53, 128.84, 128.61, 127.35, 114.29, 80.95, 79.38, 77.82, 74.33, 71.99, 62.87, 37.64, 14.70; MS (ESI) *m/z*: 559 (MH^+), 581 (MNa^+); HRMS (FAB) for $C_{28}H_{28}Cl_2N_2O_6$: calcd, 558.1324; found, 558.1325.

*4.1.3.10 N'-[{(2R,3S,4R,5R,6S)-6-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene]pyridine-4-carbohydrazide (**3j**)*

The title compound was obtained from **7** according to the general procedure in 8% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 8.73−8.70 (m, 2H, ArH), 7.84−7.80 (m, 2H, ArH), 7.67 (d, *J* = 5.6 Hz, 1H, C<u>H</u>=N), 7.35 (d, *J* = 8.0 Hz, 1H, ArH), 7.27−7.23 (m, 2H, ArH), 7.10−7.06 (m, 2H, ArH), 6.81−6.78 (m, 2H, ArH), 4.20 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.08−3.94 (m, 5H, 2 x CH_2, Glc H5), 3.62 (dd, *J* = 9.6, 9.2 Hz, 1H, Glc H4), 3.53 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.67 (t, *J* = 9.2 Hz, 1H, Glc H2), 1.34 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6) δ 161.66, 156.88, 150.32, 149.92, 140.27, 139.04, 138.02, 132.18, 131.12, 130.75, 129.55, 128.81, 127.32, 121.47, 114.28, 80.92, 79.26, 77.80, 74.29, 71.95, 62.85, 37.61, 14.67; MS (ESI) *m/z*: 548 (MNa^+); HRMS (FAB) for $C_{27}H_{28}ClN_3O_6$: calcd, 525.1667; found, 525.1664.

*4.1.3.11 N'-[{(2R,3S,4R,5R,6S)-6-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene]thiophene-2-carbohydrazide (**3k**)*

The title compound was obtained from **7** according to the general procedure in 51% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, *J* = 2.8 Hz, 1H, ArH), 7.74 (d, *J* = 4.4 Hz, 1H, ArH), 7.61 (d, *J* = 5.6 Hz, 1H, C<u>H</u>=N), 7.36−7.15 (m, 4H, ArH), 7.07 (d, *J* = 8.8 Hz, 2H, ArH), 6.78 (d, *J* = 8.4 Hz, 2H, ArH), 4.19 (d, *J* = 9.2 Hz, 1H, Glc H1), 4.06−3.93 (m, 5H, 2 x CH_2, Glc H5), 3.61 (dd, *J* = 9.6, 8.8 Hz, 1H, Glc H4), 3.53 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.36 (dd, *J* = 9.2, 8.8 Hz, 1H, Glc H2), 1.34 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$) δ 160.81, 157.88, 148.90, 139.37, 138.13, 137.06, 134.38, 132.35, 132.04, 131.08, 130.29, 130.13, 129.85, 128.41, 127.25, 114.95, 82.23, 79.35,

78.34, 75.12, 72.11, 63.98, 38.80, 15.02; MS (ESI) *m/z*: 531 (MH^+), 553 (MNa^+); HRMS (FAB) for $C_{26}H_{27}ClN_2O_6S$: calcd, 530.1278; found, 530.1282.

*4.1.3.12 N'-[{(2R,3S,4R,5R,6S)-6-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene]thiophene-3-carbohydrazide (**3l**)*

The title compound was obtained from **7** according to the general procedure in 41% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, *J* = 1.6 Hz, 1H, ArH), 7.61 (d, *J* = 5.6 Hz, 1H, CH=N), 7.57−7.50 (m, 2H, ArH), 7.34 (d, *J* = 8.0 Hz, 1H, ArH), 7.27−7.23 (m, 2H, ArH), 7.08-7.05 (m, 2H, ArH), 6.80-6.77 (m, 2H, ArH), 4.19 (d, *J* = 9.2 Hz, 1H, Glc H1), 4.06−3.94 (m, 5H, 2 x CH_2, Glc H5), 3.62 (dd, *J* = 9.6, 9.2 Hz, 1H, Glc H4), 3.53 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.36 (t, *J* = 9.2 Hz, 1H, Glc H2), 1.34 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6) δ 158.67, 156.94, 148.13, 139.14, 138.08, 135.89, 132.24, 131.16, 130.79, 129.93, 129.62, 128.87, 127.37, 127.20, 126.97, 114.31, 80.98, 79.44, 77.86, 74.42, 72.07, 62.90, 37.69, 14.73; MS (ESI) *m/z*: 531 (MH^+), 553 (MNa^+); HRMS (FAB) for $C_{26}H_{27}ClN_2O_6S$: calcd, 530.1278; found, 530.1274.

*4.1.3.13 N'-[{(2R,3S,4R,5R,6S)-6-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene]furan-2-carbohydrazide (**3m**)*

The title compound was obtained from **7** according to the general procedure in 39% yield over four steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 1.2 Hz, 1H, ArH), 7.63 (d, *J* = 5.6 Hz, 1H, CH=N), 7.34 (d, *J* = 8.4 Hz, 1H, ArH), 7.26−7.22 (m, 3H, ArH), 7.08−7.05 (m, 2H, ArH), 6.79−6.76 (m, 2H, ArH), 6.62 (dd, *J* = 3.6, 1.6 Hz, 1H, ArH), 4.19 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.06−3.93 (m, 5H, 2 x CH_2, Glc H5), 3.61 (t, *J* = 9.2 Hz, 1H, Glc H4), 3.52 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.36 (t, *J* = 9.2 Hz, 1H, Glc H2), 1.33 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.84, 157.62, 150.68, 147.40, 147.23, 140.09, 139.48, 134.65, 132.74, 131.79, 130.85, 130.21, 128.10, 117.36, 115.43, 113.27, 83.05, 80.42, 79.14, 76.12, 73.19, 64.40, 39.20, 15.20; MS (ESI) *m/z*: 515 (MH^+), 537 (MNa^+); HRMS (EI) for $C_{26}H_{27}ClN_2O_7$: calcd, 514.1507; found, 514.1504.

*4.1.4 General procedure for the synthesis of compounds **4** and **5***

A 6 N solution of HCl in MeOH was added dropwise to a solution of oxime / hydrazone (1.0 equiv)

and sodium cyanoborohydride ($NaBH_3CN$, 2.0 equiv.) in MeOH at 0 ^oC until pH 1~3. After stirring at 0 °C for 2 h, the reaction was quenched by the addition of saturated $NaHCO_{3(aq)}$, and the resulting mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography ($MeOH/CH_2Cl_2$) to provide **4** or **5**.

*4.1.4.1 (1S)-1,5-Anhydro-1-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-deoxy-6-(hydroxyamino)-D-glucitol (**4a**)*. Yield 41%; ^1H NMR (400 MHz, CD_3OD) δ 7.34 (d, *J* = 8.4 Hz, 1H, ArH), 7.26−7.22 (m, 2H, ArH), 7.10−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.08 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.06−3.95 (m, 4H, 2 x CH_2), 3.62 (ddd, *J* = 9.6, 8.4, 2.8 Hz, 1H, Glc H5), 3.44 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.41−3.24 (m, 3H, Glc H2, H4, H6a), 2.91 (dd, *J* = 13.2, 8.4 Hz, 1H, Glc H6b), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.86, 140.02, 139.91, 134.47, 132.82, 131.78, 130.86, 130.17, 128.06, 115.42, 82.83, 79.58, 77.24, 76.50, 74.27, 64.41, 56.80, 39.19, 15.20; MS (ESI) *m/z*: 424 (MH^+), 446 (MNa^+); HRMS (FAB) for $C_{21}H_{27}ClNO_6$: calcd, 424.1527; found, 424.1523.

*4.1.4.2 (1S)-1,5-Anhydro-1-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-deoxy-6-(methoxyamino)-D-glucitol (**4b**)*. Yield 68%; ^1H NMR(400 MHz, CD_3OD) δ 7.34 (d, *J* = 8.0 Hz, 1H, ArH), 7.25−7.21 (m, 2H, ArH), 7.10−7.06 (m, 2H, ArH), 6.81−6.77 (m, 2H, ArH), 4.06 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.05−3.95 (m, 4H, 2 x CH_2), 3.55 (ddd, *J* = 9.6, 8.4, 2.4 Hz, 1H, Glc H5), 3.45 (s, 3H, OCH_3), 3.42 (t, *J* = 9.2 Hz, 1H, Glc H3), 3.38 (dd, *J* = 13.6, 2.4 Hz, 1H, Glc H6a), 3.29-3.23 (m, 2H, Glc H2, H4), 2.87 (dd, *J* = 13.6, 8.4 Hz, 1H, Glc H6b), 1.35 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 158.86, 140.04, 139.87, 134.47, 132.80, 131.75, 130.87, 130.16, 128.06, 115.42, 82.82, 79.56, 77.49, 76.46, 74.17, 64.39, 61.21, 53.93, 39.18, 15.20; MS (ESI) *m/z*: 438 (MH^+), 460 (MNa^+); HRMS (EI) for $C_{22}H_{28}ClNO_6$: calcd, 437.1605; found, 437.1601.

*4.1.4.3 (1S)-1,5-Anhydro-1-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-deoxy-6-[2-(4-nitrophenyl)-hydrazinyl]-D-glucitol (**5a**)*. Yield 12%; ^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, *J* = 9.6 Hz, 2H, ArH), 7.31 (d, *J* = 8.0 Hz, 1H, ArH), 7.19−7.14 (m, 2H, ArH), 7.09−7.06 (m, 2H, ArH), 6.80−6.74 (m, 4H, ArH), 4.00−3.92 (m, 5H, 2 x CH_2, Glc H1), 3.50 (ddd, *J* = 9.2, 8.0, 2.4 Hz, 1H, Glc H5), 3.43−3.23 (m, 4H, Glc H2, H3, H4, H6a), 2.95 (dd, *J* = 13.2, 8.0 Hz, 1H, Glc H6b), 1.33 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C

NMR (100 MHz, CD_3OD) δ 158.87, 157.34, 139.99, 139.91, 138.61, 134.47, 132.79, 131.62, 130.85, 130.08, 128.03, 127.02, 115.44, 111.19, 82.88, 79.89, 79.68, 76.45, 73.48, 64.40, 53.56, 39.18, 15.19; MS (ESI) *m/z*: 544 (MH^+), 566 (MNa^+); HRMS (FAB) for $C_{27}H_{31}ClN_3O_7$: calcd, 544.1851; found, 544.1844.

*4.1.4.4 (1S)-1,5-Anhydro-1-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-deoxy-6-[2-(furan-2-ylcarbonyl)-hydrazinyl]-D-glucitol (**5b**).* Yield 67%; ^1H NMR (400 MHz, CD_3OD) δ 7.50 (dd, *J* = 2.0, 0.8 Hz, 1H, ArH), 7.31 (d, *J* = 8.4 Hz, 1H, ArH), 7.27−7.22 (m, 2H, ArH), 7.10−7.06 (m, 2H, ArH), 6.99 (dd, *J* = 3.6, 0.8 Hz, 1H, ArH), 6.80−6.76 (m, 2H, ArH), 6.50 (dd, *J* = 3.6, 2.0 Hz, 1H, ArH), 4.09 (d, *J* = 9.6 Hz, 1H, Glc H1), 4.05−3.93 (m, 4H, 2 x CH_2), 3.54 (ddd, *J* = 10.0, 7.6, 2.4 Hz, 1H, Glc H5), 3.43 (t, *J* = 8.8 Hz, 1H, Glc H3), 3.37−3.27 (m, 3H, Glc H2, H4, H6a), 3.02 (dd, *J* = 12.8, 7.6 Hz, 1H, Glc H6b), 1.33 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 159.37, 158.85, 147.85, 146.22, 139.96, 139.91, 134.40, 132.79, 131.82, 130.89, 130.15, 128.03, 115.42, 115.33, 112.77, 82.79, 80.19, 79.56, 76.35, 73.34, 64.40, 53.92, 39.24, 15.19; MS (ESI) *m/z*: 517 (MH^+), 539 (MNa^+); HRMS (EI) for $C_{26}H_{29}ClN_2O_7$: calcd, 516.1663; found, 516.1659.

4.2. In vitro human SGLT inhibition assays

In vitro transporter assays were carried out according to the methods of Castaneda and Kinne, with necessary modification [28,29,32].

4.3. hERG potassium channel assay

The radioligand binding assay was performed by Ricerca Biosciences, LLC.

4.4. Pharmacokinetics, glucosuria, and anti-hyperglycemia evaluations

Studies of pharmacokinetics, glucosuria, and the anti-hyperglycemic effect of selected aryl *C*-glycoside(s) were performed as previously reported [27,32].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Highlights

- A target-focused library of twenty-seven aryl *C*-glycosides, whose glycone is a 6-amino-/6-imino-6-deoxy-β-D-glucosyl group, was designed and synthesized.
- All the synthesized derivatives were evaluated for their inhibitory activities against hSGLT2.
- Potent aryl C-glycoside SGLT2 inhibitors were studied for selectivity over hSGLT1.
- Five representative aryl C-glycosides were subjected to pharmacokinetic analysis.
- Oxime **2a** was identified as a potential SGLT2 inhibitor with promising pharmacokinetic properties and good *in vivo* performance.