European Journal of Medicinal Chemistry 46 (2011) 2662–2675

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Thiazolylmethyl *ortho*-substituted phenyl glucoside library as novel C-aryl glucoside SGLT2 inhibitors

Suk Ho Lee [a,b], Min Ju Kim [a], Sung-Han Lee [a], Jeongmin Kim [a], Hyun-Ju Park [b], Jinhwa Lee [a,*]

[a] Green Cross Corporation Research Center, 303 Bojeong-Dong, Giheung-Gu, Yongin, Gyeonggi-Do 446-770, Republic of Korea
[b] College of Pharmacy, Sungkyunkwan University, Cheoncheon-Dong, Jangan-Gu, Suwon, Gyeonggi-Do 440-746, Republic of Korea

ARTICLE INFO

Article history:
Received 1 November 2010
Received in revised form
21 March 2011
Accepted 24 March 2011
Available online 2 April 2011

Keywords:
SGLT
Dapagliflozin
Thiazole
Glucoside
Diabetes

ABSTRACT

In order to investigate SAR regarding proximal phenyl ring in novel C-aryl glucoside SGLT2 inhibitors containing a thiazole motif, a series of chemical modifications on proximal phenyl ring was conducted. During a series of lead optimization efforts, *ortho*-allyloxyphenyl **10p** or *ortho*-hydroxyphenyl **11a** showed subnanomolar inhibitory activity against *h*SGLT2.

© 2011 Elsevier Masson SAS. All rights reserved.

1. Introduction

Diabetes has become an increasing concern to the world's population. In 2010, approximately 285 million people around the world will have diabetes, corresponding to 6.4% of the world's adult population, with a prediction that the number of people with diabetes will have grown to 438 million by 2030 [1]. Type 2 diabetes is the most common disorder of glucose homeostasis, accounting for approximately 90–95% of all cases of diabetes [2].

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 essential 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 a merely 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, while the remaining 10% is 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], SGLT2 has become a target of therapeutic interest.

Bristol-Myers Squibb has identified dapagliflozin (**1**), a potent, selective SGLT2 inhibitor for the treatment of type 2 diabetes [9–11]. At present, **1** is the most advanced SGLT2 inhibitor in clinical trials [12]. On the other hand, **2**, **3**, **4** from Johnson & Johnson, Lexicon, and Pfizer are being tested in various phase of clinical trials (Fig. 1) [13].

In the previous study, C-glucosides bearing a heterocyclic ring were exploited in order to develop novel SGLT2 targeting antidiabetic agents, since we envisioned that replacement of the distal or proximal phenyl ring of **1** with a heterocyclic ring might improve the overall physicochemical properties of SGLT2 inhibitors [14]. Based on the structure of dapagliflozin, the distal phenyl ring was surrogated by the corresponding thiazole ring. A series of lead optimization efforts led to the discovery of thiazole **5** bearing a furanyl moiety as shown in Fig. 2 [15]. In the present study, diverse modifications on the C-2 position of the proximal phenyl ring (as shown in **6**) were conducted to establish SAR on the phenyl ring, while keeping the structure of potent thiazole **5** [16]. Along this line, we report the synthesis and biological evaluation of thiazolylmethyl *ortho*-substituted phenyl glucoside analogs as novel C-aryl glucoside SGLT2 inhibitors.

2. Chemistry

Preparation of the requisite bromides **15a**, **15b**, **15c**, **17a** and **17b** is described in Scheme 1. Thus, commercially available 2-chloro-4-

* Corresponding author. Tel.: +82 31 260 9892; fax: +82 31 260 9020.
E-mail address: jinhwalee@greencross.com (J. Lee).

0223-5234/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2011.03.052

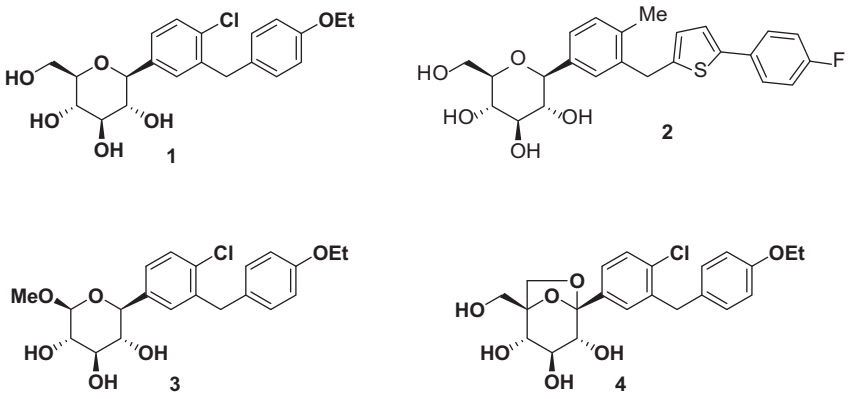


Fig. 1. Structures of *C*-aryl glucoside SGLT2 inhibitors.

hydroxybenzonitrile (**7**) was converted to the corresponding bromo-acids **14a**–**14c** by way of triflic acid-mediated bromination at C-5 [17], alkylation on C-1 hydroxyl, and subsequent hydrolysis of cyanides. The reduction of acids **14a**–**14c** with a borane–dimethyl sulfide complex, and subsequent silylation of the corresponding alcohol with triisopropylsilyl chloride (TIPSCl) in the presence of imidazole and 4-(dimethylamino)pyridine (DMAP) generated bromides **15a**–**15c** in reasonable yields. Similarly, 4-halogenated benzyloxytriisopropylsilanes **17a**, **17b** were prepared as shown in Scheme 1. Bromination using bromine and sulfur was conducted on 2,4-dichlorobenzoic acid (**8**) or 2-chloro-4-fluorobenzoic acid (**9**) in the presence of chlorosulfonic acid [18]. The resulting bromo-acids were transformed into the corresponding bromides **17a**, **17b** following the same procedure previously described.

Preparation of key intermediates **20a**–**20e** is described in Scheme 2. Thus, lithium-halogen exchange, followed by the addition of the nascent lithiated aromatic compound to perbenzylated gluconolactone **10**, produced a mixture of the corresponding lactols. The lactols were reduced using triethylsilane and BF_3 etherate [19], desilylated and afforded alcohols **18a**–**18e**, respectively. Then alcohols **18a**–**18e** were converted to bromides using PBr_3 in the presence of catalytic pyridine. The resulting bromides were treated with KCN in refluxing aqueous EtOH to generate cyanides. A mixture of the two isomers in each case was separated through recrystallization from ethanol to produce the required beta-isomers **19a**–**19e**. Hydrolysis of cyanides **19a**–**19e** with sodium hydroxide in aqueous ethanol generated the carboxylic acids **20a**–**20e** in quantitative yields, respectively.

Preparation of the thiazole compound is described in Scheme 3. Thus, the carboxylic acid **20** prepared previously was coupled with 2-amino-1-(furan-2-yl)ethanone hydrochloride in the presence of EDCI, HOBt, and NMM to provide the corresponding amide **21** in 96% yield. Amide **21** smoothly underwent thionation and subsequent cyclization by the action of Lawesson reagent in refluxing THF to lead to thiazole **22**. Finally, total removal of benzyl protection was affected with TMSI at mild heating overnight to produce the target compound **10a** in 50% yield.

Alternative approach toward derivatization on *ortho*-position of proximal phenyl ring is described in Scheme 4. Thus, treatment of allyl ether **23** with sodium borohydride in the presence of a catalytic amount of $Pd(PPh_3)_4$ [20], followed by total deprotection of the remaining benzyl groups by use of BCl_3 [21] smoothly provided the phenol **11a**. This pentaol was used for direct alkylation to provide *n*-propyl-ether **11b** or two-step conversion to 1,2,4-triazolylethoxyphenyl **11g**.

The C–C bond substituents on *ortho*-position of proximal phenyl ring were also attempted. Preparation of the requisite key intermediate **27** is described in Scheme 5. First, 3-amino-4-methylbenzoic acid (**24**) which is commercially available was converted to bromide **25** via three steps (bromination, esterification, and chlorination) in 53% yields overall. Next, methyl 2-bromo-5-chloro-4-methylbenzoate (**25**) was transformed into 4-(hydroxymethyl)benzoic acid **26** by benzylic bromination reaction as illustrated in Scheme 5. The alcohol functionality of **26** was then introduced by treating the resulting bromide with sodium acetate, followed by basic hydrolysis of the corresponding acetate with concomitant conversion from methyl ester to acid as shown in structure **26**. Finally, silyl protection of alcohol **26** with TIPSCl in the presence of imidazole, and subsequent borane–dimethylsulfide-mediated reduction of benzoic acid to the corresponding benzyl alcohol, followed by alkylated with allyl bromide in the presence of sodium hydride furnished the requisite bromide **27** in 53% yields for three steps.

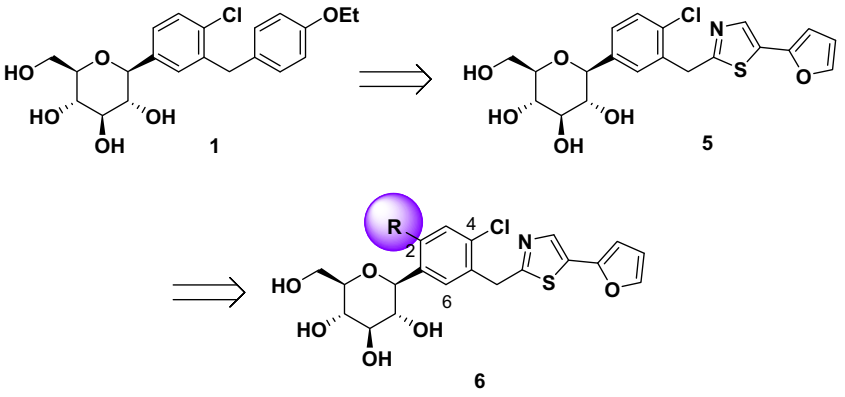
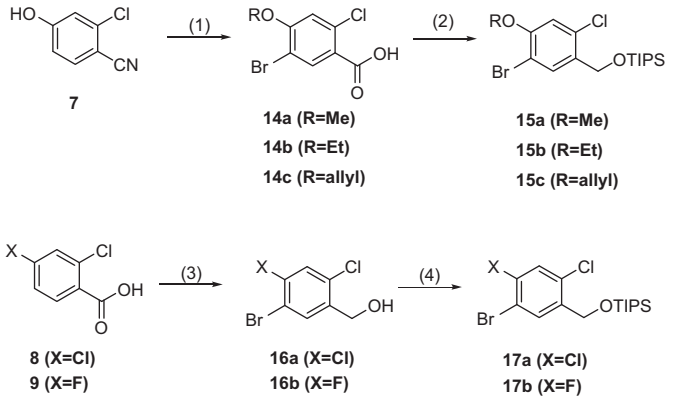


Fig. 2. Explorations of C-2 position of proximal ring in novel *C*-glucoside bearing thiazole **5**.



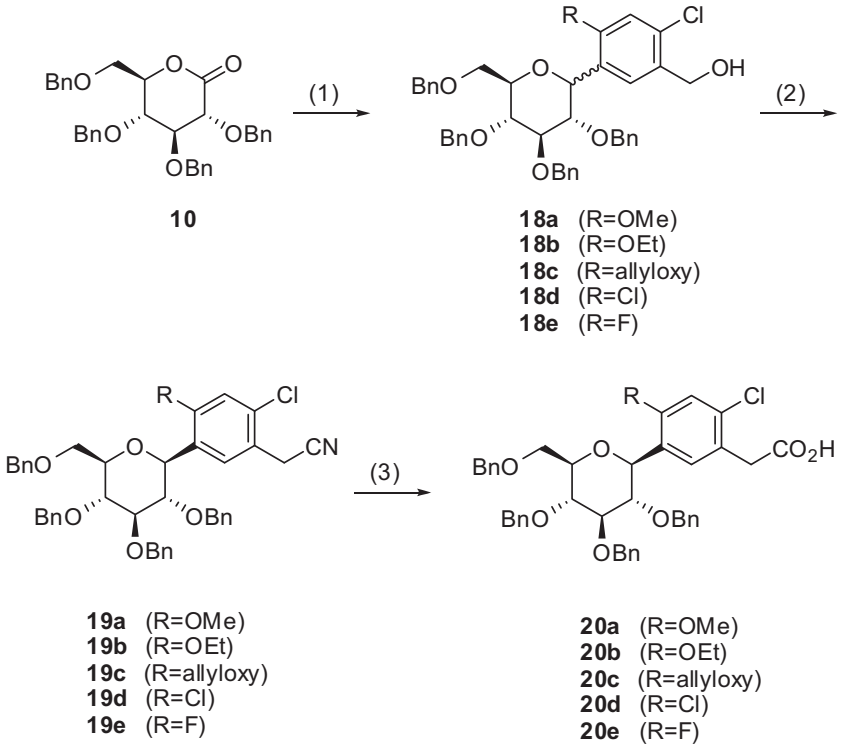
Scheme 1. Preparation of bromides (**15a**, **15b**, **15c**, **17a** and **17b**). (1) (a) triflic acid, NBS, CH_3CN, 57% (b) LiOH monohydrate, dimethyl sulfate, THF, 65 °C, 80% (R = Me) or alkyl bromide, Cs_2CO_3, acetone, 65 °C, 79%–85% (R = Et or allyl) (c) NaOH, EtOH/H_2O, 100 °C, 95%–100% (2) (a) borane–dimethylsulfide complex, THF, 65 °C, 95%–97% (b) TIPSCl, imidazole, cat. DMAP, DMF, rt, 89%–93% (3) (a) Br_2, sulfur, chlorosulfonic acid, 70 °C, 89%–95% (b) borane–dimethylsulfide complex, THF, 65 °C, 92%–95% (4) TIPSCl, imidazole, cat. DMAP, DMF, rt, 91%–95%.

Preparation of the target thiazole compounds is described in Scheme 6. Thus, the carboxylic acid **28** which was prepared following the procedure similar to Scheme 2, was coupled with 2-amino-1-(furan-2-yl)ethanone hydrochloride in the presence of EDCI, HOBT, and NMM in a suitable solvent such as DMF at rt. The resulting amide underwent thionation and subsequent cyclization by Lawesson reagent in refluxing THF to result in thiazole **29** in 72% yields for the two steps. Attempts to deprotect benzyl groups using boron trichloride in methylene dichloride provided **12e** in 20% yield along with pentaol **12a** in 9% yield.

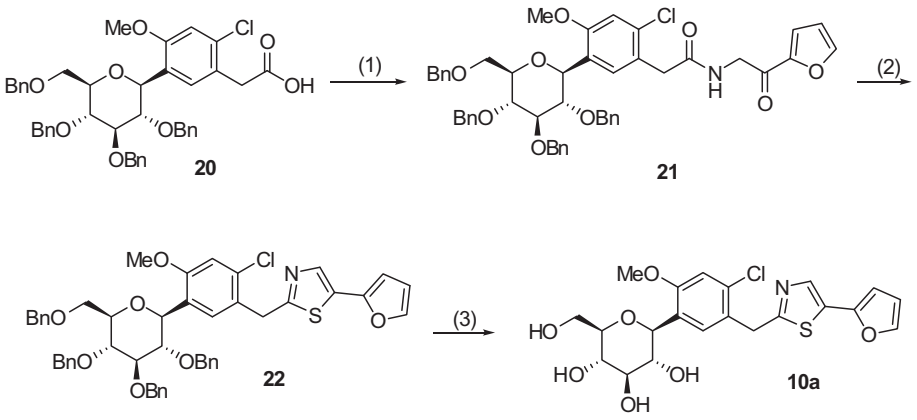
3. Results and discussion

The cell-based SGLT2 AMG (Methyl-α-D-glucopyranoside) inhibition assay was performed to evaluate the inhibitory effects of all prepared compounds on hSGLT2 activities [22,23]. Table 1 shows the structure-activity relationship upon alteration of the C-2 substituent at the glucose employing only the (beta-anomer. We focused on 2-furyl, 3-furyl, 2-thiophenyl, 3-thiophenyl, phenyl, or 4-F-phenyl ring connected to the distal thiazole ring, since our previous findings [15] indicate that these small 5-membered aryl rings favorably affected the biological activity of the examined thiazolylmethylphenyl glucosides. Initially, 2-furyl **10a**, 2-thiophenyl **10c**, 3-thiophenyl **10d**, or phenyl **10e** at the proximal methoxyphenyl ring demonstrated good inhibitory activity against *h*SGLT2 (IC_{50} = 1.29 nM–2.15 nM). When the proximal methoxyphenyl ring is replaced with the corresponding ethoxyphenyl ring, there appears to be a tendency that its inhibitory activity against *h*SGLT2 drops in approximately twofold as exemplified by **10g** (IC_{50} = 3.98 nM) or **10h** (IC_{50} = 4.35 nM). However, the *in vitro* activity is recovered or even more improved than before as the ethoxyphenyl ring as a proximal ring is replaced with the corresponding allyloxyphenyl ring. For example, furyls **10m**, **10n** or thiophenyls **10o**, **10p** connected to the distal thiazole ring showed very promising activity against *h*SGLT2 (IC_{50} = 0.934 nM–1.69 nM, **10m**–**10p**). Interestingly, 3-thiophenyl connected to the distal thiazole ring demonstrates improved *in vitro* inhibitory activity against *h*SGLT2 as the number of carbons increases from methyl **10d** or ethyl **10j** to allyl **10p** on *ortho*-position ether linkage of the proximal phenyl ring, albeit to a small amount (**10d**:IC_{50} = 1.29 nM; **10d**:IC_{50} = 1.18 nM; **10d**:IC_{50} = 0.934 nM).

At this juncture, several representative compounds anchored on (4-chloro-5-(furan-2-yl)thiazol-2-yl)methylphenyl moiety have been prepared in order to test the effect of the *ortho*-O-substituents



Scheme 2. Preparation of key intermediates (**20a**–**20e**). (1) (a) bromides (**15a**, **15b**, **15c**, **17a** and **17b**), n-BuLi, THF, −78 °C (b) Et_3SiH, BF_3OEt_2, CH_2Cl_2, −55 °C to −20 °C (c) TBAF, THF, 0 °C to rt, 51%–85% (3-steps) (2) (a) PBr_3, cat. pyridine, ether, 0 °C to rt (b) KCN, EtOH/H_2O, 80 °C (c) selective crystallization, 31%–55% (3-steps) (3) NaOH, EtOH/H_2O, 100 °C, 97%–100%.



Scheme 3. Representative scheme for preparation of derivatives (**10a**–**10r** and **13a**–**13j**). (1) 2-amino-1-(furan-2-yl)ethanone hydrochloride, EDC, HOBT, NMM, DMF, rt, 96% (2) Lawesson reagent, THF, 75 °C, 88% (3) TMSI, CH_3CN, 50 °C, 50%.

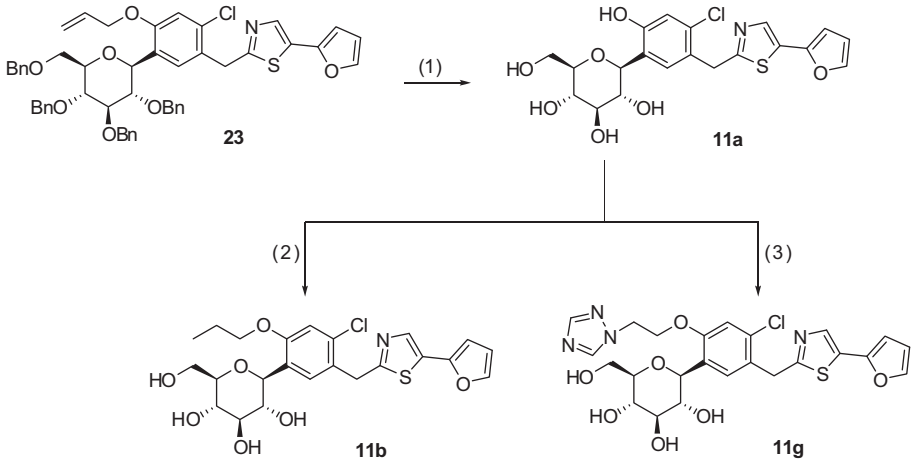
on the proximal phenyl ring against *in vitro* *h*SGLT2. The results are shown in Table 2. 2-Hydroxyphenyl **11a** shows outstanding *in vitro* inhibitory activity against *h*SGLT2, suggesting that hydrogen donor might be beneficial at this position. Allyloxy **10m** or propargyloxy **11c** which has terminal sp^2 or sp^3 character shows favorable inhibitory activity against *h*SGLT2 (IC_{50} = 1.24 nM for **10m**; IC_{50} = 2.23 nM for **11c**). But this effect disappears as it is homologated as exemplified in butenyloxy **11d** (IC_{50} = 32.8 nM). Hydroxyethoxyphenyl **11e** regains *in vitro* inhibitory activity against *h*SGLT2 (IC_{50} = 1.51 nM), showing that the terminal hydroxyl group is advantageous like hydroxyl group in hydroxyphenyl **11a**. As the hydroxyl group in **11e** (IC_{50} = 1.51 nM) is replaced with the corresponding methoxy as exemplified in **11f**, its inhibitory activity against *h*SGLT2 shows fourfold decrease (IC_{50} = 5.55 nM). Nitrogen-containing groups such as 1,2,4-triazolylethoxyphenyl **11g** or *N*,*N*-dimethylphenoxyethanamine **11h** are observed to drop *in vitro* inhibitory activity in approximately two-orders of magnitude, demonstrating that amine or amine-characters is intolerant at this region.

Next, in order to test the *in vitro* inhibitory effect of *ortho*-C-substituents against *h*SGLT2, *ortho*-alkoxy moiety was replaced with hydroxymethylphenyl (**12a**–**12d**) or allyloxymethylphenyl (**12e**–**12h**). The inhibitory activity data of key compounds for *h*SGLT2 are shown in Table 3. Although 3-thiophenyl **12d** appears to maintain similar level of inhibitory activity against *h*SGLT2 (IC_{50} = 2.23 nM), 3-furyl **12b** demonstrated only moderate activity (IC_{50} = 20.5 nM). When allyl moiety is introduced on oxygen at this position, its inhibitory activity is observed to drop in approximately three to fourfold (IC_{50} = 10.0 nM–38.7 nM for **12e**–**12h**), compared with hydroxymethylphenyl counterparts, implying that the extra carbon linker on the *ortho*-phenyl makes the molecules a bit too lengthy and suboptimal.

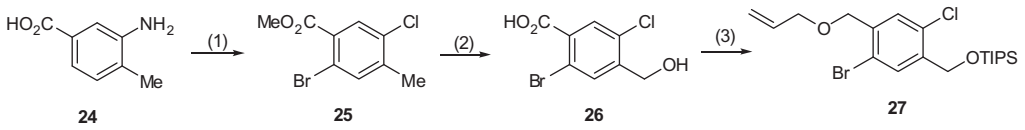
Finally, we installed *ortho*-halogen instead of alkoxy or carbon linker on the proximal phenyl ring to explore the halogen effect for *h*SGLT2. The results are shown in Table 4. It is noted that a series of exercise provides comparable *in vitro* inhibitory activity against *h*SGLT2 as exemplified by 2-fluorophenyl **13d** (IC_{50} = 2.12 nM) and **13g** (IC_{50} = 2.24 nM), but none of them are better than hydroxyphenyl **11a** (IC_{50} = 0.797 nM). Also these types of compounds appear to have relatively poor solubility.

4. Conclusion

In summary, a diverse series of structural modifications regarding thiazolylmethyl *ortho*-substituted phenyl glucoside library were conducted in the present study to establish SAR based on structure of potent thiazole **5**. Among the compounds tested,



Scheme 4. Representative scheme for preparation of derivatives (**11a**–**11h**). (1) (a) $NaBH_4$, cat. $Pd(PPh_3)_4$, THF, 0 °C to rt, 83% (b) BCl_3, CH_2Cl_2, 0 °C, 47% (2) n-PrBr, K_2CO_3, acetone, 50 °C, 43% (3) (a) 1,2-dibromoethane, Cs_2CO_3, DMF, rt (b) sodium 1,2,4-triazole derivatives, DMF, rt, 33%(2-steps).



Scheme 5. Preparation of bromide **27** for preparation of compounds (**12a**–**12h**). (1) (a) NBS, DMF, 0 °C, 89% (b) $SOCl_2$, MeOH, 65 °C, 92% (c) aq. HCl, $NaNO_2$, 1,4-dioxane, 0 °C then CuCl, c-HCl, 0 °C, 65% (2) (a) (i) NBS, AIBN, CCl_4, 90 °C (ii) NaOAc, DMF, rt, 51%(2-steps) (b) LiOH monohydrate, THF/MeOH/H_2O, rt, 96% (3) (a) TIPSCl, imidazole, cat. DMAP, DMF, rt, 66% (b) borane–dimethylsulfide complex, THF, 65 °C, 85% (c) allyl bromide, NaH, rt, 95%.

2-hydroxyphenyl **11a** appears to be tolerated at this position, showing the best potency in this series against *h*SGLT2 up to date.

5. Experimental

All reactions are conducted under an inert atmosphere at room temperature, unless otherwise noted. *n*-Butyllithium (Aldrich) was titrated with *N*-benzylbenzamide as indicator. All reagents were purchased at the highest commercial quality and used without further purification, unless otherwise indicated. All experiment involving moisture- and/or air-sensitive compounds were performed in oven- and/or flame-dried glassware with rubber septa under a positive pressure of nitrogen using standard Schlenk technique. 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 DMSO-d_6 (δ = 39.7). Mass spectra were obtained with an Agilent 6110 quadruple LC-MSD (ESI+). 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 30 × 100 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.

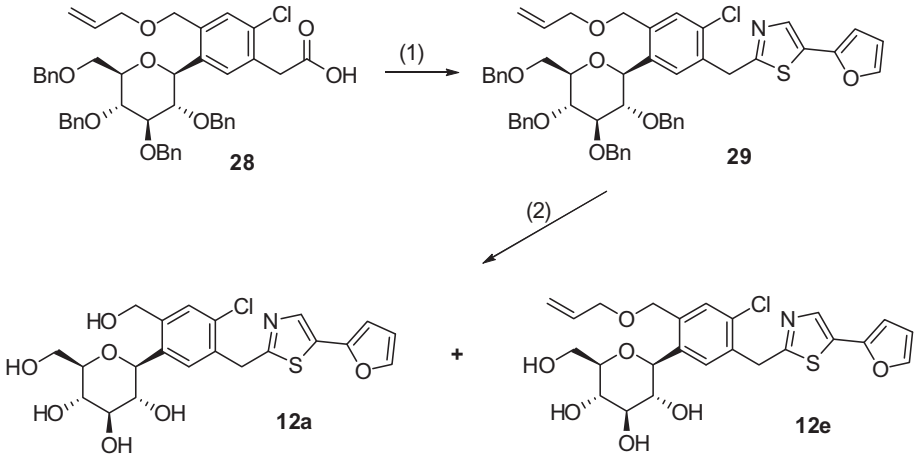
5.1. Chemistry

5.1.1. Preparation of 5-bromo-2-chloro-4-methoxybenzoic acid (*14a*)

To a solution of 2-chloro-4-hydroxybenzonitrile (**7**) (10.0 g, 65.1 mmol) in CH_3CN (200 mL) were added triflic acid (10 mL, 71.6 mmol), NBS (16.2 g, 91.2 mmol) at −30 °C. The mixture was warmed up to room temperature and stirred at room temperature for 15 h. The reaction was quenched by addition of aq. saturated $NaHSO_3$ solution. The mixture was extracted with EtOAc. The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using silica column chromatography to provide 5-bromo-2-chloro-4-hydroxybenzonitrile (9.8 g, 65%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 7.03 (s, 1H), 4.85 (s, 1H); MH+ 232.

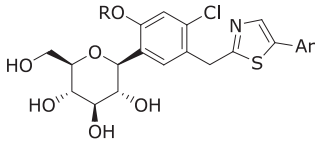
To a solution of 5-bromo-2-chloro-4-hydroxybenzonitrile (35.2 g, 151 mmol) in THF (500 mL) were added lithium hydroxide monohydrate (9.0 g, 197 mmol) and dimethyl sulfate (20 mL, 197 mmol). The reaction mixture was stirred at 75 °C for 15 h. The mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with aq. 50% NaCl solution and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using silica column chromatography to provide the intermediate (30.7 g).

To a solution of intermediate (30.7 g) in EtOH (500 mL)/H_2O (250 mL) was added NaOH (127 g, 3.11 mol). The mixture was stirred at 100 °C for 9 h. The mixture was cooled to room temperature and evaporated *in vacuo* to remove EtOH. The residue was diluted with H_2O, cooled to 0 °C and acidified with aq. 6N HCl solution. The titled compound **14a** was precipitated as a solid, filtered off and washed



Scheme 6. Representative scheme for preparation of derivatives (**12a**–**12h**). (1) (a) 2-amino-1-(furan-2-yl)ethanone hydrochloride, EDC, HOBT, NMM, DMF, rt (ii) Lawesson reagent, THF, 75 °C, 72%(2-steps) (2) BCl_3, CH_2Cl_2, 0 °C, 20% (for **12e**), and 9% (for **12a**).

Table 1
In vitro screening data of compound **10a**–**10r** for *h*SGLT2 inhibitory activities.



Ar	Compound	R	*h*SGLT2 IC_{50} (nM)[a]	Compound	R	*h*SGLT2 IC_{50} (nM)[a]	Compound	R	*h*SGLT2 IC_{50} (nM)[a]
	1		0.49 ± 0.04[b]						
	**10a**	Me	2.15	**10g**	Et	3.98	**10m**	allyl	1.24
	**10b**	Me	7.37	**10h**	Et	4.35	**10n**	allyl	1.54
	**10c**	Me	1.59	**10i**	Et	4.29	**10o**	allyl	1.69
	**10d**	Me	1.29	**10j**	Et	1.18	**10p**	allyl	0.934
	**10e**	Me	2.01	**10k**	Et	2.87	**10q**	allyl	3.38
	**10f**	Me	6.08	**10l**	Et	7.55	**10r**	allyl	4.22

[a] These data were obtained by single determinations.
[b] The IC_{50} value was obtained by in-house multiple determinations.

with H_2O. The solid was dried under vacuum at 50 °C for 16 h to obtain the product (33.7 g, 76%, 2 steps). MH+ 265.

5.1.2. Preparation of (5-bromo-2-chloro-4-methoxybenzyloxy) triisopropylsilane (**15a**)

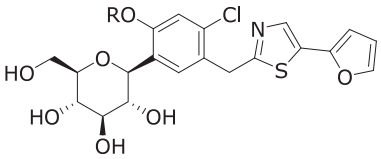
To a solution of acid **14a** (2.73 g, 11.0 mmol) in THF (300 mL) was added borane–dimethylsulfide complex (1 M in THF, 13 mL) at 0 °C. The mixture was stirred 0 °C for 15 min, at room temperature at 30 min, and at 75 °C for 15 h. The mixture was cooled to 0 °C. MeOH and H_2O were added to the cooled mixture to quench the reaction. After dilution with water, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using silica column chromatography to provide alcohol (22.9 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.90 (s, 1H), 4.70 (d, J = 6.4 Hz, 2H), 3.89 (s, 3H).

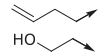
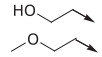
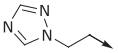
To a solution of alcohol (23.2 g, 87.5 mmol) in DMF (250 mL) were added TIPSCl (77 mL, 358.5 mmol), imidazole (33 g, 481.3 mmol) and DMAP (4.1 g, 33.6 mmol). The mixture was stirred at room temperature for 15 h. After dilution with water, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using silica column chromatography to provide the titled compound **15a** (38 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 6.85 (s, 1H), 4.78 (s, 2H), 3.88 (s, 3H), 1.23–1.15 (m, 3H), 1.10 (d, J = 6.4 Hz, 18H).

5.1.3. Preparation of (5-bromo-2-chloro-4-ethoxybenzyloxy) triisopropylsilane (**15b**)

Yield: 40%(5-steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.84 (s, 1H), 4.86 (s, 2H), 4.07 (quartet, J = 6.8 Hz, 2H), 1.47 (t, J = 6.8 Hz, 3H), 1.25–1.17 (m, 3H), 1.11 (d, J = 6.8 Hz, 18H).

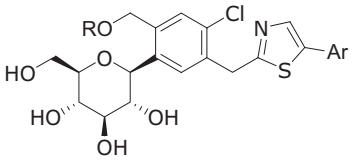
Table 2
In vitro screening data of various *ortho*-substituted thiazoles for *h*SGLT2 inhibitory activities.



Compound	R	*h*SGLT2 IC_{50} (nM)[a]	Compound	R	*h*SGLT2 IC_{50} (nM)[a]
11a	H	0.797	**11d**		32.8
10a	Me	2.15	**11e**		1.51
10g		3.98	**11f**		5.55
10m		1.24	**11g**		131
11b		21.6	**11h**		713
11c		2.23			

[a] These data were obtained by single determinations.

Table 3
In vitro screening data of compound **12a**–**12h** for *h*SGLT2 inhibitory activities.



Compound	R	Ar	*h*SGLT2 IC_{50} (nM)[a]	Compound	R	Ar	*h*SGLT2 IC_{50} (nM)[a]
12a	H		5.81	**12e**	allyl		17.5
12b	H		20.5	**12f**	allyl		38.7
12c	H		5.88	**12g**	allyl		16.2
12d	H		2.23	**12h**	allyl		10.0

[a] These data were obtained by single determinations.

*5.1.4. Preparation of (4-(allyloxy)-5-bromo-2-chlorobenzyloxy) triisopropylsilane (**15c**)*

Yield: 61%(5-steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 6.85 (s, 1H), 6.11–6.01 (m, 1H), 5.49 (doublet and quartet, J = 17.2 Hz, 1.6 Hz, 1H), 5.33 (doublet and doublet, J = 10.8 Hz, 1.6 Hz, 1H), 4.78 (s, 2H), 4.58 (d, J = 1.6 Hz, 2H), 1.27–1.15 (m, 3H), 1.12 (d, J = 6.8 Hz, 18H)

*5.1.5. Preparation of (5-bromo-2,4-dichlorobenzyloxy) triisopropylsilane (**17a**)*

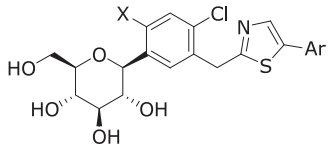
To a solution of benzoic acid **8** (15.0 g, 78.5 mmol) in chlorosulfonic acid (60 mL) was added bromine (2.0 mL, 39.3 mmol) and sulfur (0.15 g). The reaction mixture was stirred at 70 °C overnight and then cooled to ambient temperature. The reaction mixture was poured into iced water. The resulting solid was isolated by filtration and dried *in vacuo* to obtain 5-bromo-2,4-dichlorobenzoic acid (20 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.63 (s, 1H); MH+ 269

The titled compound (23.5 g, 57.1 mmol, 83%(2-steps) from 5-bromo-2,4-dichlorobenzoic acid) was obtained in the same manner as the synthesis of **15a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.29 (s, 1H), 5.01 (s, 2H), 1.27–1.14 (m, 3H), 1.11 (d, J = 6.8 Hz, 18H).

*5.1.6. Preparation of (5-bromo-2-chloro-4-fluorobenzyloxy) triisopropylsilane (**17b**)*

5-Bromo-2-chloro-4-fluorobenzoic acid was prepared in the same manner as the synthesis of **2,4-dichlorobenzoic acid** and the titled compound (Yield: 86% (3-steps)) from 5-bromo-2-chloro-4-fluorobenzoic acid was obtained in the same manner as the synthesis of **17a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 1H),

Table 4
In vitro screening data of compound **13a**–**13j** for *h*SGLT2 inhibitory activities.



Compound	X	Ar	*h*SGLT2 IC_{50} (nM)[a]	Compound	X	Ar	*h*SGLT2 IC_{50} (nM)[a]
13a	F		3.49	**13g**	Cl		2.24
13b	F		5.35	**13h**	Cl		13.3
13c	F		3.88	**13i**	Cl		4.77
13d	F		2.12	**13j**	Cl		2.31
13e	F		4.57				
13f	F		27.4				

[a] These data were obtained by single determinations.

7.12 (d, J = 8.4 Hz, 1H), 4.78 (s, 2H), 1.25–1.18 (m, 3H), 1.10 (d, J = 6.8 Hz, 18H).

*5.1.7. Preparation of (2-chloro-4-methoxy-5-((3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl) phenyl)methanol (**18a**)*

To a solution of (5-Bromo-2-chloro-4-methoxybenzyloxy)triisopropylsilane (**15a**, 9.7 g, 25.7 mmol) in tetrahydrofuran (100 mL) at −78 °C under an atmosphere of nitrogen was added dropwise *n*-butyllithium (2.5 M in hexanes, 10.3 mL, 25.7 mmol), and the mixture was stirred for 1.5 h at the same temperature. Then a solution of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranone (**10**, 10.6 g, 19.8 mmol) in tetrahydrofuran (50 mL) was added dropwise, and the mixture was stirred for 1.5 h at the same temperature. The reaction mixture was quenched by addition of saturated ammonium chloride solution. After complete addition, the solution was gradually raised to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield the title compound as a yellow solid which was used without further purification.

To a stirred −50 °C solution of (2-chloro-4-methoxy-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)phenyl)methanol (19.8 mmol) in dichloromethane (50 mL) was added triethylsilane (6.3 mL, 39.6 mmol) followed by boron trifluoride diethyl etherate (5.0 mL, 39.6 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 solution. After removal of organic volatiles under reduced pressure, the residue was partitioned between ethyl acetate and water. Following extraction of the aqueous layer with ethyl acetate, the combined organic layers were washed with water prior to drying over magnesium sulfate. Filtration and concentration under reduced pressure yield the titled compound as a yellow oil which was used without further purification.

To a solution of (2-chloro-4-methoxy-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl) benzyloxy)triisopropylsilane (19.8 mmol) in tetrahydrofuran (50 mL) was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 59.4 mL, 59.4 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 ethyl acetate and saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified using silica column chromatography to yield the titled compound (13.0 g, 19.5 mmol, 98%) as a white solid. MNa+ 717.

*5.1.8. Preparation of 2-(2-chloro-4-methoxy-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)phenyl)acetonitrile (**19a**)*

To a solution of (2-chloro-4-methoxy-5-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl) phenyl)methanol (**18a**, 6.5 g, 9.35 mmol) in ether (200 mL) at 0 °C was added pyridine (2 drops) and phosphorus tribromide (0.44 mL, 4.67 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 ethyl acetate and washed with water then brine. The organic extract was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield the bromide compound as a yellow oil, which was used without further purification. MNa+ 779.

To a solution of crude bromide in CH_3CN (100 mL) were added potassium cyanide (913 mg, 14 mmol) and 18-crown-6 (3.7 g, 14 mmol) at room temperature. The mixture was stirred at 85 °C for 1 h. The mixture was cooled to room temperature and concentrated *in vacuo*. After dilution with water, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using normal phase column chromatography to provide beta and alpha anomeric mixture (4.59 g, 70%). The preceding Intermediate (mixture of α:β-anomer in about 1:2 ratio) was slurried in ethanol (100 mL) and heated to reflux with stirring. The reaction mixture was held at reflux for 1 h to ensure that all of solution had homogenized; it was then cooled slowly to ambient temperature and stirred overnight at this temperature. The resulting solid was isolated by filtration and dried *in vacuo* to yield the titled compound (3.24 g, 4.6 mmol, 49%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: δ 7.40–7.27 (m, 14H), 7.20–7.13 (m, 5H), 6.88–6.74 (m, 3H), 4.93 (d, J = 4.8 Hz, 2H), 4.86 (d, J = 10.8 Hz, 1H), 4.74 (d, J = 9.6 Hz, 1H), 4.64–4.59 (m, 2H), 4.57–4.52 (m, 2H), 4.06 (d, J = 11.2 Hz, 1H), 3.85–3.81 (m, 1H), 3.77 (s, 3H), 3.75–3.70 (m, 3H), 3.68 (s, 2H), 3.62–3.58 (m, 2H); MNa+ 726.

*5.1.9. Preparation of 2-(2-chloro-4-methoxy-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)phenyl)acetic acid (**20a**)*

To a solution of cyanide **19a** (3.24 g, 4.6 mmol) in EtOH/H_2O (60 mL/30 mL) was added NaOH (11.04 g, 276 mmol). The mixture was stirred at 100 °C for 15 h. The mixture was cooled to room temperature and evaporated *in vacuo* to remove EtOH. The residue was diluted with H_2O, cooled to 0 °C and acidified with *c*-HCl solution. The titled compound **20a** was precipitated as a solid, dissolved with EtOAc and extracted. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to provide the titled compound **20a** (3.22 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 14H), 7.17–7.08 (m, 5H), 6.86 (dd, J = 7.2 Hz, 1.2 Hz, 2H), 6.79 (s, 1H), 4.96–4.81 (m, 3H), 4.75–4.64 (m, 1H), 4.56–4.51 (m, 2H), 4.48–4.39 (m, 2H), 3.97 (d, J = 11.2 Hz, 1H), 3.81–3.58 (m, 10H), 3.55–3.49 (m, 1H); MNa+ 745.

*5.1.10. 2-(2-Chloro-4-ethoxy-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl) phenyl)acetic acid (**20b**)*

Yield: 47% (7-steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (m, 14H), 7.16–7.06 (m, 5H), 6.94–6.83 (m, 2H), 6.74 (s, 1H), 4.96–4.74 (m, 4H), 4.57–4.41 (m, 3H), 4.39–4.28 (m, 1H), 3.99 (d, J = 11.2 Hz, 1H), 3.82–3.47 (m, 10H), 1.26 (t, J = 6.8 Hz, 3H); MNa+ 759.

*5.1.11. 2-(4-(allyloxy)-2-chloro-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl) phenyl)acetic acid (**20c**)*

Yield: 35% (7-steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 14H), 7.21–7.18 (m, 2H), 7.17–7.10 (m, 3H), 6.93–6.87 (m, 2H), 6.82 (s, 1H), 5.98–5.84 (m, 1H), 5.34 (dd, J = 17.6 Hz, 1.6 Hz, 1H), 5.19 (dd, J = 10.8 Hz, 1.2 Hz, 1H), 4.96–4.83 (m, 3H), 4.77–4.64 (m, 1H), 4.63–4.57 (m, 2H), 4.54–4.45 (m, 2H), 4.40 (d, J = 4.0 Hz, 2H), 4.01 (d, J = 11.2 Hz, 1H), 3.75–3.64 (m, 7H), 3.60–3.54 (m, 1H); MNa+ 771.

*5.1.12. 2-(2,4-Dichloro-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)phenyl)acetic acid (**20d**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.37 (s, 1H), 7.33–7.25 (m, 13H), 7.19–7.12 (m, 5H), 6.95–6.93 (m, 2H), 4.94 (d, J = 10.8 Hz, 1H), 4.89 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 10.8 Hz, 1H), 4.74 (d, J = 9.6 Hz, 1H), 4.62 (d, J = 10.8 Hz, 1H), 4.60 (d, J = 12.0 z, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 10.8 Hz, 1H), 4.04 (d, J = 10.8 Hz, 1H), 3.84 (t, J = 8.8 Hz, 1H), 3.78–3.69 (m, 5H), 3.61–3.54 (m, 2H); MNa+ 749.

*5.1.13. 2-(2-Chloro-4-fluoro-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl) phenyl)acetic acid (**20e**)*

MNa+ 733.

*5.1.14. Preparation of 2-(2-chloro-4-methoxy-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)phenyl)-N-(2-(furan-2-yl)-2-oxoethyl)acetamide (**21**)*

To a mixture of the carboxylic acid **20** (700 mg, 0.97 mmol), 2-amino-1-(furan-2-yl)ethanone hydrochloride (203 mg, 1.26 mmol), EDCI (278 mg, 1.45 mmol), and HOBt (262 mg, 1.94 mmol) in DMF (5 mL) was added NMM (0.33 mL, 2.9 mmol). The resulting mixture was stirred at room temperature for 15 h. The reaction mixture was poured into aq. HCl solution (1.0 M, 25 mL), and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified using normal phase column chromatography to provide the titled amide compound (775 mg, 0.93 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.32–7.23 (m, 14H), 7.20–7.11 (m, 5H), 6.91–6.89 (m, 3H), 6.53 (dd, J = 3.6, 1.6 Hz, 2H), 6.34–6.32 (m, 1H), 4.92 (d, J = 12 Hz, 2H), 4.86 (d, J = 10.8 Hz, 1H), 4.76 (d, J = 9.2 Hz, 1H), 4.64–4.60 (m, 2H), 4.54–4.51 (m, 2H), 4.47 (d, J = 4.4 Hz, 1H), 4.05 (d, J = 10.8 Hz, 1H), 3.84–3.80 (m, 1H), 3.74 (s, 6H), 3.69 (s, 2H), 3.65–3.59 (m, 2H); MH+ 830.

*5.1.15. Preparation of 2-(2-chloro-4-methoxy-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)benzyl)-5-(furan-2-yl)thiazole (**22**)*

To a solution of the amide (775 mg, 0.93 mmol) in anhydrous THF (25 mL) was added Lawesson reagent (755 mg, 1.87 mmol). The reaction mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was poured into a saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified using normal phase column chromatography to provide the titled compound **22** (678 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.35–7.23 (m, 14H), 7.20–7.13 (m, 5H), 6.90–6.89 (m, 3H), 6.37 (dd, J = 3.2, 1.6 Hz, 2H), 6.31 (d, J = 2.8 Hz, 1H), 4.90 (d, J = 9.2 Hz, 2H), 4.86 (d, J = 10.8 Hz, 1H), 4.75 (d, J = 8.4 Hz, 1H), 4.64–4.59 (m, 2H), 4.53–4.48 (m, 2H), 4.36 (d, J = 5.2 Hz, 1H), 4.01 (d, J = 10.8 Hz, 1H), 3.84–3.79 (m, 1H), 3.77–3.69 (m, 3H), 3.75 (s, 3H), 3.64–3.58 (m, 2H); MH+ 828.

*5.1.16. Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)-2-methoxyphenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**10a**)*

2-(2-chloro-4-methoxy-5-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)benzyl)-5-(furan-2-yl)thiazole (678 mg, 0.82 mmol) in acetonitrile (3 mL) reacted with TMSI (5 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 1 day. After quenching the reaction with methanol, solvent was evaporated under reduced pressure. Purification by RP preparative provided the titled compound (192 mg, 50%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.69 (m, 1H), 7.44 (s, 1H), 7.07 (s, 1H), 6.74 (d, J = 3.6 Hz, 1H), 6.55–6.54 (m, 1H), 4.90 (t, J = 4.8 Hz, 2H), 4.65 (d, J = 5.6 Hz, 1H), 4.43–4.37 (m, 3H), 4.34 (s, 2H), 3.76 (s, 3H), 3.62 (m, 1H), 3.38–3.30 (m, 1H), 3.28–3.22 (m, 1H), 3.15–3.12 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.4, 158.0, 146.1, 143.8, 140.0, 138.0, 133.4, 131.7, 128.5, 127.3, 112.8, 112.7, 107.9, 82.1, 79.0, 74.6, 74.4, 71.0, 61.8, 56.6, 36.50; MH+ 468.

*5.1.17. (2S,3R,4R,5S,6R)-2-(4-Chloro-5-((5-(furan-3-yl)thiazol-2-yl) methyl)-2-methoxyphenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10b**)*

Yield: 15%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.83(s, 1H), 7.70 (t, J = 1.6 Hz, 1H), 7.42 (s, 1H), 7.06 (s, 1H), 6.88–6.83 (m, 1H), 4.42 (d, J = 9.2 Hz, 1H), 4.31 (s, 2H), 4.09 (br s, 4H), 3.76 (s, 1H), 3.66 (d, J = 10.4 Hz, 1H), 3.36 (dd, J = 12.0, 5.2 Hz, 1H), 3.32–3.07 (m, 4H); MH+ 468.

*5.1.18. (2S,3R,4R,5S,6R)-2-(4-Chloro-3-((4-phenylthiazol-2-yl) methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10c**)*

Yield: 51%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.52 (dd, J = 4.8, 1.2 Hz, 1H), 7.44 (m, 1H), 7.26 (dd, J = 3.6, 1.2 Hz, 1H), 7.07–7.04 (m, 2H), 4.88 (t, J = 4.0 Hz, 2H), 4.64 (d, J = 5.2 Hz, 1H), 4.41 (d, J = 9.2 Hz, 1H), 4.37 (t, J = 6.0 Hz, 1H), 4.33 (s, 2H), 3.76 (s, 3H), 3.65 (dd, J = 10.8, 5.6 Hz, 1H), 3.40–3.29 (m, 1H), 3.28–3.21 (m, 2H), 3.18–3.11 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 158.0, 138.5, 133.4, 132.9, 132.2, 131.7, 128.8, 128.5, 127.3, 126.8, 126.3, 112.8, 82.1, 79.0, 74.6, 74.3, 71.0, 61.9, 56.6, 36.70; MH+ 484.

*5.1.19. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-methoxy-5-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10d**)*

Yield: 52%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.67 (dd, J = 2.8, 1.2 Hz, 1H), 7.60 (dd, J = 4.8, 2.8 Hz, 1H), 7.43 (s, 1H), 7.39 (dd, J = 5.2, 1.2 Hz, 1H), 7.07 (s, 1H), 4.41 (d, J = 9.6 Hz, 1H), 4.32 (s, 2H), 4.05 (br s, 4H), 3.76 (s, 3H), 3.64 (d, J = 10.4 Hz, 1H), 3.39–3.35 (m, 1H), 3.32–3.18 (m, 2H), 3.15–3.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9, 157.9, 138.7, 133.9, 133.4, 132.0, 131.7, 128.5, 128.2, 127.4, 126.6, 122.4, 112.8, 82.1, 79.0, 74.6, 74.4, 71.0, 61.9, 56.7, 36.70; MH+ 484.

*5.1.20. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-methoxy-5-((5-phenylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10e**)*

Yield: 41%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.58–7.52 (m, 2H), 7.44 (s, 1H), 7.39–7.34 (m, 2H), 7.31–7.25 (m, 1H), 7.07 (s, 1H), 4.52 (br s, 4H), 4.43 (d, J = 9.6 Hz, 1H), 4.34 (2H), 3.77 (s, 3H), 3.62 (d, J = 10.4 Hz, 1H), 3.37 (dd, J = 12.0, 5.6 Hz, 1H), 3.32–3.07 (m, 4H); MH+ 478.

*5.1.21. (2S,3R,4R,5S,6R)-2-(4-Chloro-5-((5-(4-fluorophenyl)thiazol-2-yl)methyl)-2-methoxyphenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10f**)*

Yield: 43%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.65–7.57 (m, 2H), 7.44 (s, 1H), 7.25–7.18 (m, 2H), 7.06 (s, 1H), 4.57 (br s, 4H), 4.42 (d, J = 9.2 Hz, 1H), 4.34 (s, 2H), 3.76 (s, 3H), 3.64 (d, J = 10.4 Hz, 1H), 3.36 (dd, J = 12.0, 5.6 Hz, 1H), 3.32–3.08 (m, 4H); MH+ 496.

*5.1.22. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-ethoxy-5-((5-(furan-2-yl) thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10g**)*

Yield: 33%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (s, 1H), 7.55–7.46 (m, 2H), 7.03 (s, 3H), 6.60(d, J = 3.2 Hz, 1H), 7.03 (s, 1H), 6.50–6.44 (m, 1H), 4.84 (s, 4H), 4.64 (d, J = 9.2 Hz, 1H), 4.43–4.32 (m, 2H), 4.10–4.01 (m, 2H), 3.82 (dd, J = 12.0, 1.6 Hz, 1H), 3.66 (dd, J = 12.0, 5.6 Hz, 1H), 3.57–3.32 (m, 4H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.91, 156.88, 145.61, 143.28, 137.45, 132.81, 131.28, 128.16, 127.98, 126.71, 113.33, 112.14, 107.38, 81.64, 78.53, 74.22, 73.79, 70.43, 64.33, 61.33, 36.05, 14.53; MH+ 482.

*5.1.23. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-ethoxy-5-((5-(furan-3-yl) thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**10h**)*

Yield: 29%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.83 (s, 1H), 7.71 (t, J = 1.6 Hz, 1H), 7.41 (s, 1H), 7.04 (s, 1H), 6.84–6.78 (m, 1H), 4.82 (s, 4H), 4.39 (d, J = 9.6 Hz, 1H), 4.31 (s, 2H), 4.00 (q, J = 1.2 Hz, 1H), 3.63 (d, J = 1.04 Hz, 1H), 3.41–3.29 (m, 2H), 3.23 (t, J = 8.4 Hz, 1H), 3.18–3.04 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.41, 156.87, 144.50, 139.72, 138.49, 132.81,

131.29, 128.14, 126.80, 116.77, 113.32, 109.13, 81.64, 78.54, 74.24, 73.76, 70.44, 64.33, 61.34, 36.14, 14.54; MH+ 482.

*5.1.24. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-ethoxy-5-((5-(thiophen-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10i**)*

Yield: 43%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.53 (s, 1H), 7.43 (dd, J = 5.6, 0.8 Hz, 1H), 7.25 (dd, J = 5.6, 0.8 Hz, 1H), 7.09–7.04 (m, 2H), 4.84 (s, 4H), 4.64 (d, J = 9.2 Hz, 1H), 4.47–3.76 (m, 2H), 4.11–4.02 (m, 2H), 3.83 (dd, J = 12.0, 1.6 Hz, 1H), 3.65 (dd, J = 12.0, 1.2 Hz, 1H), 3.57–3.33 (m, 4H), 1.40 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.97, 156.86, 137.98, 132.79, 132.33, 131.64, 131.28, 128.30, 128.12, 126.62, 126.31, 125.76, 113.28, 81.61, 78.50, 74.20, 73.74, 70.40, 64.29, 61.31, 36.13, 14.51; MH+ 498.

*5.1.25. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-ethoxy-5-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10j**)*

Yield: 39%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.55–7.46 (m, 1H), 7.03 (s, 1H), 6.60(d, J = 3.2 Hz, 1H), 7.03 (s, 1H), 6.51–6.45 (m, 1H), 4.84 (s, 4H), 4.64 (d, J = 9.2 Hz, 1H), 4.43–4.32 (m, 2H), 4.10–4.01 (m, 2H), 3.82 (dd, J = 12.0, 1.6 Hz, 1H), 3.66 (dd, J = 12.0, 5.6 Hz, 1H), 3.57–3.32 (m, 4H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.45, 156.88, 138.16, 133.41, 132.81, 131.53, 131.31, 128.15, 127.71, 126.81, 126.09, 121.86, 113.34, 81.66, 78.57, 74.26, 73.79, 70.46, 64.35, 61.36, 54.91, 36.19, 14.56; MH+ 482.

*5.1.26. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-ethoxy-5-((5-phenylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10k**)*

Yield: 31%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (s, 1H), 7.56–7.51 (m, 3H), 7.39–7.34 (m, 2H), 7.32–7.26 (m, 1H), 7.03 (s, 1H), 4.84 (s, 4H), 4.64 (d, J = 9.2 Hz, 1H), 4.43–4.33 (m, 2H), 4.09–4.01 (m, 2H), 3.82 (dd, J = 12.0, 1.6 Hz, 1H), 3.64 (dd, J = 12.0, 5.6 Hz, 1H), 3.56–3.37 (m, 4H), 1.40 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.35, 156.86, 138.31, 138.22, 132.81, 131.30, 130.92, 129.18, 128.17, 128.14, 126.84, 126.22, 113.33, 81.66, 78.56, 74.25, 73.81, 70.46, 64.34, 61.36, 36.05, 14.55; MH+ 492.

*5.1.27. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-ethoxy-5–((5-(4-fluorophenyl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol (**10l**)*

Yield: 41%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.58–7.52 (m, 2H), 7.51 (s, 3H), 7.15–7.08 (m, 2H), 7.03 (s, 1H), 4.84 (s, 4H), 4.64 (d, J = 9.2 Hz, 1H), 4.43–4.32 (m, 2H), 4.10–4.02 (m, 2H), 3.83 (dd, J = 12.0, 1.6 Hz, 1H), 3.65 (dd, J = 12.0, 5.6 Hz, 1H), 3.57–3.34 (m, 4H), 1.40 (t, J = 7.2 Hz, 3H); MH+ 510.

*5.1.28. (2S,3R,4R,5S,6R)-2-(2-(Allyloxy)-4-chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10m**)*

Yield: 17%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.71–7.62 (m, 1H), 7.44 (s, 1H), 7.06 (s, 1H), 6.74 (d, J = 3.6 Hz, 1H), 6.69–6.63 (m, 1H), 6.06–5.93 (m, 1H), 5.41 (dd, J = 17.2, 1.6 Hz, 1H), 5.22 (dd, J = 10.4, 1.6 Hz, 1H), 4.91 (dd, J = 18.8, 3.6 Hz, 2H), 4.68 (d, J = 4.8 Hz, 1H), 4.59–4.52 (m, 2H), 4.47–4.29 (m, 4H), 3.69–3.59 (m, 1H), 3.41–3.06 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.84, 156.42, 145.64, 143.32, 137.48, 133.41, 132.81, 131.46, 128.21, 128.02, 126.99, 116.84, 113.59, 112.18, 107.42, 81.73, 78.58, 74.50, 73.72, 70.42, 68.86, 61.33, 36.06; MH+ 494.

*5.1.29. (2S,3R,4R,5S,6R)-2-(2-(Allyloxy)-4-chloro-5-((5-(furan-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10n**)*

Yield: 23%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.83 (s, 1H), 7.71 (t, J = 1.6 Hz, 1H), 7.43 (s, 1H), 7.05 (s, 1H), 6.85–6.79 (m, 1H), 6.06–5.95 (m, 1H), 5.40 (quartet and doublet, J = 17.2, 1.6 Hz, 1H), 5.22 (qd, J = 10.4, 1.6 Hz, 1H), 4.90 (dd, J = 18.8, 4.8 Hz, 2H), 4.66 (d, J = 5.2 Hz, 1H), 4.59–4.53 (m, 2H), 4.42 (d, J = 9.6 Hz, 1H), 4.38 (t, J = 5.6 Hz, 1H), 4.31 (s, 2H), 3.64 (dd, J = 12.0, 5.6 Hz, 1H), 3.43–3.31 (m, 2H), 3.27–3.20 (m, 1H), 3.19–3.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.24, 156.39, 144.52, 139.73, 138.56, 133.40, 132.80, 131.45, 129.06, 128.17, 127.09, 116.83, 116.81, 113.57, 109.15, 81.72, 78.57, 74.48, 73.67, 70.41, 68.85, 61.32, 36.14; MH+ 494.

*5.1.30. (2S,3R,4R,5S,6R)-2-(2-(Allyloxy)-4-chloro-5-((5-(thiophen-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10o**)*

Yield: 30%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.52 (dd, J = 5.2, 1.2 Hz, 1H), 7.44 (s, 1H), 7.27 (dd, J = 3.6, 1.2 Hz, 1H), 7.08–7.02 (m, 2H), 6.06–5.95 (m, 1H), 5.41 (dd, J = 17.6, 1.6 Hz, 1H), 5.22 (dd, J = 11.2, 1.6 Hz, 1H), 4.90 (dd, J = 18.8, 4.8 Hz, 2H), 4.68 (d, J = 5.2 Hz, 1H), 4.59–4.53 (m, 2H), 4.42 (d, J = 9.6 Hz, 1H), 4.38 (t, J = 5.6 Hz, 1H), 4.32 (s, 2H), 3.64 (dd, J = 12.0, 5.6 Hz, 1H), 3.42–3.31 (m, 2H), 3.29–3.20 (m, 1H), 3.19–3.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.91, 156.42, 138.09, 133.40, 132.81, 132.40, 131.69, 131.48, 128.36, 128.19, 126.94, 126.36, 125.81, 116.84, 113.59, 81.72, 78.58, 74.35, 73.69, 70.42, 68.86, 61.33, 36.17; MH+ 510.

*5.1.31. (2S,3R,4R,5S,6R)-2-(2-(Allyloxy)-4-chloro-5-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10p**)*

Yield: 17%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.71–7.65 (m, 1H), 7.67–7.58 (m, 1H), 7.42 (s, 1H), 7.39 (dd, J = 1.6 Hz, 1H), 7.05 (s, 1H), 6.06–5.95 (m, 1H), 5.41 (dd, J = 17.2, 1.6 Hz, 1H), 5.22 (dd, J = 11.8, 1.6 Hz, 1H), 4.93 (dd, J = 18.8, 4.4 Hz, 2H), 4.70 (d, J = 5.2 Hz, 1H), 4.60–4.53 (m, 2H), 4.48–4.39 (m, 2H), 4.32 (s, 2H), 3.59–3.51 (m, 1H), 3.41–3.05 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.29, 156.37, 138.24, 133.40, 132.79, 131.55, 131.44, 128.16, 127.69, 127.09, 126.09, 121.83, 116.82, 113.57, 81.71, 78.58, 74.48, 73.68, 70.41, 68.85, 61.33, 38.87; MH+ 510.

*5.1.32. (2S,3R,4R,5S,6R)-2-(2-(Allyloxy)-4-chloro-5-((5-phenylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**10q**)*

Yield: 31%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.58–7.53 (m, 2H), 7.45 (s, 1H), 7.40–7.32 (m, 2H), 7.31–7.26 (m, 1H), 7.06 (s, 1H), 6.07–5.95 (m, 1H), 5.42 (dd, J = 17.6, 1.6 Hz, 1H), 5.22 (dd, J = 11.2, 1.6 Hz, 1H), 4.90 (dd, J = 19.2, 4.8 Hz, 2H), 4.68 (d, J = 5.2 Hz, 1H), 4.62–4.51 (m, 2H), 4.40 (d, J = 11.2 Hz, 1H), 4.38 (t, J = 5.6 Hz, 1H), 4.34 (s, 2H), 3.64 (d, J = 10.4 Hz, 1H), 3.41–3.32 (m, 2H), 3.24 (t, J = 8.0 Hz, 1H), 3.28–3.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.23, 156.34, 138.31, 138.21, 133.39, 132.78, 131.43, 130.89, 129.17, 128.16, 128.13, 127.07, 126.20, 116.81, 113.56, 81.69, 78.56, 74.90, 73.68, 70.40, 68.85, 61.31, 36.26; MH+ 504.

*5.1.33. (2S,3R,4R,5S,6R)-2-(2-(Allyloxy)-4-chloro-5-((5-(4-fluorophenyl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol (**10r**)*

Yield: 24%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.65–7.57 (m, 2H), 7.45 (s, 1H), 7.21 (t, J = 1.2 Hz, 2H), 7.05 (s, 1H), 6.07–5.95 (m, 1H), 5.42 (dd, J = 17.6, 1.6 Hz, 1H), 5.22 (dd, J = 11.2, 1.6 Hz, 1H), 4.90 (dd, J = 19.2, 4.8 Hz, 2H), 4.69 (d, J = 5.2 Hz, 1H), 4.62–4.51 (m, 2H), 4.43 (d, J = 9.6 Hz, 1H), 4.38 (t, J = 5.6 Hz, 1H), 4.33 (s, 2H), 3.64 (dd, J = 11.2, 5.2 Hz, 1H), 3.42–3.31 (m, 2H), 3.29–3.21 (m, 1H), 3.20–3.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.81, 163.54, 161.10, 156.87, 138.82, 137.72, 133.89, 133.29, 131.94, 128.88, 128.02, 127.56, 117.32, 116.72, 116.50, 114.06, 82.21, 79.07, 74.20, 70.91, 69.35, 61.83, 36.75; MH+ 522.

*5.1.34. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-fluoro-5-((5-(furan-2-yl) thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13a**)*

Yield: 35%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.70 (m, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 9.6 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 6.56–6.55 (m, 1H), 4.95 (triplet and doublet, J = 10.8, 4.0 Hz, 3H), 4.43 (t, J = 6.0 Hz, 1H), 4.41 (s, 2H), 4.28 (d, J = 9.2 Hz, 1H), 3.67 (dd, J = 10.4, 5.2 Hz, 1H), 3.43–3.37 (m, 1H), 3.27–3.20 (m, 3H), 3.17–3.13 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 159.9 (d, J = 248.1), 146.0, 143.9, 138.0, 133.5 (d, J = 10.7), 132.5 (d, J = 5.1), 132.0, 128.6, 127.4 (d, J = 13.9), 117.0 (d, J = 26.3), 112.7, 108.0, 82.1, 78.7, 75.1, 74.6, 70.7, 61.7, 36.50; MH+ 456.

*5.1.35. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-fluoro-5-((5-(furan-3-yl) thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13b**)*

Yield: 23%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.84 (m, 1H), 7.72–7.71 (m, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.40 (d, J = 9.6 Hz, 1H), 6.83 (m, 1H), 4.96 (br s, 4H), 4.38 (s, 2H), 4.28 (d, J = 9.2 Hz, 1H), 3.66 (d, J = 10.4 Hz, 1H), 3.39 (dd, J = 11.6, 5.6 Hz, 1H), 3.28–3.21 (m, 3H), 3.16–3.11 (m, 1H); MH+ 456.

*5.1.36. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-fluoro-5-((5-(thiophen-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13c**)*

Yield: 29%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.53 (dd, J = 5.2, 1.2 Hz, 1H), 7.41 (d, J = 9.6 Hz, 1H), 7.28 (dd, J = 3.6, 1.2 Hz, 1H), 7.06 (dd, J = 5.2, 4.0 Hz, 1H), 5.01–4.95 (m, 3H), 4.46–4.44 (m, 1H), 4.40 (s, 2H), 4.28 (d, J = 9.2 Hz, 1H), 3.66 (dd, J = 11.6, 3.6 Hz, 1H), 3.43–3.38 (m, 1H), 3.25–3.21 (m, 3H), 3.17–3.13 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 159.9 (d, J = 248 Hz), 138.6, 133.5 (d, J = 10.8), 132.8, 132.6 (d, J = 5.1), 132.3, 131.9 (d, J = 3.5), 128.9, 127.5 (d, J = 13.9), 126.9, 126.4, 116.9 (d, J = 26.5), 82.1, 78.7, 75.1, 74.6, 70.7, 61.7, 36.6; MH+ 472.

*5.1.37. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-fluoro-5–((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13d**)*

Yield: 25%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.70 (dd, J = 3.2, 1.2 Hz, 1H), 7.62–7.60 (m, 2H), 7.42–7.39 (m, 2H), 5.01–4.93 (m, 3H), 4.45 (t, J = 5.6 Hz, 1H), 4.39 (s, 2H), 4.28 (d, J = 8.8 Hz, 1H), 3.69–3.65 (m, 1H), 3.43–3.37 (m, 1H), 3.27–3.21 (m, 3H), 3.17–3.13 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 159.8 (d, J = 247.7 Hz), 138.8, 134.0, 133.5 (d, J = 10.7 Hz), 132.5 (d, J = 5.1 Hz), 132.0 (d, J = 3.5 Hz), 131.9, 128.2, 127.4 (d, J = 13.9 Hz), 126.6, 122.5, 116.9 (d, J = 26.4 Hz), 82.1, 78.7, 75.1, 74.6, 70.7, 61.7, 36.6; MH+ 472.

*5.1.38. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-fluoro-5-((5-phenylthiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13e**)*

Yield: 24%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.58–7.56 (m, 2H), 7.42–7.36 (m, 3H), 7.32–7.28 (m, 1H), 4.94 (br s, 4H), 4.41 (d, J = 10.0 Hz, 1H), 3.67 (d, J = 10.4 Hz, 1H), 3.40 (dd, J = 12.0, 6.0 Hz, 1H), 3.28–3.21 (m, 3H), 3.16–3.12 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 159.8 (d, J = 247.9 Hz), 139.0, 138.8, 133.5 (d, J = 10.8 Hz), 132.5 (d, J = 5.1 Hz), 132.0 (d, J = 3.5 Hz), 131.3, 129.7, 128.7, 127.4 (d, J = 13.9 Hz), 126.8, 116.9 (d, J = 26.5 Hz), 82.1, 78.7, 75.1, 74.6, 70.7, 61.7, 36.7; MH+ 466.

*5.1.39. (2S,3R,4R,5S,6R)-2-(4-Chloro-2-fluoro-5-((5-(4-fluorophenyl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol (**13f**)*

Yield: 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.63–7.60 (m, 3H), 7.40 (d, J = 9.2 Hz, 1H), 7.22 (t, J = 8.4 Hz, 2H), 7.40 (d, J = 9.6 Hz, 1H), 4.98–4.92 (m, 3H), 4.45–4.41 (m, 1H), 4.41 (s, 2H), 4.28 (d, J = 8.8 Hz, 1H), 3.68–3.66 (m, 1H), 3.42–3.38 (m, 1H), 3.25–3.21 (m, 3H), 3.16–3.14 (m, 1H); MH+ 484.

*5.1.40. (2S,3R,4R,5S,6R)-2-(2,4-Dichloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13g**)*

Yield: 29%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.69 (d, J = 1.2 Hz, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 6.76 (d, J = 3.6 Hz, 1H), 6.59–6.51 (m, 1H), 4.91 (br s, 4H), 4.49–4.39 (m, 3H), 3.66 (d, J = 10.4 Hz, 1H), 3.37–3.14 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.94, 146.02, 143.88, 138.01, 137.65, 134.89, 133.95, 133.59, 132.60, 129.70, 128.69, 112.69, 108.05, 82.22, 78.74, 77.39, 74.82, 70.68, 61.68, 37.37; MH+ 472.

*5.1.41. (2S,3R,4R,5S,6R)-2-(2,4-Dichloro-5-((5-(furan-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13h**)*

Yield: 31%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.84(s, 1H), 7.71 (t, J = 1.6 Hz, 1H), 7.65 (s, 1H), 7.59 (s, 1H), 6.89–6.83 (m, 1H), 5.03 (br s, 4H), 4.43 (d, J = 9.2 Hz, 1H), 4.40 (s, 2H), 3.66 (dd, J = 12.0, 1.6 Hz, 1H), 3.39 (dd, J = 12.0, 5.6 Hz, 1H), 3.35–3.15 (m, 5H); MH+ 472.

*5.1.42. (2S,3R,4R,5S,6R)-2-(2,4-Dichloro-5-((5-(thiophen-2-yl) thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13i**)*

Yield: 25%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.67 (s, 1H), 7.61 (s, 1H), 7.54 (dd, J = 5.2, 1.2 Hz, 1H), 7.29 (dd, J = 3.6, 0.8 Hz, 1H), 7.09–7.04 (m, 1H), 4.71–4.49 (m, 5H), 3.67 (d, J = 10.4 Hz, 1H), 3.41 (dd, J = 12.0, 5.4 Hz, 1H), 3.38–3.17 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.01, 138.62, 137.65, 134.84, 133.95, 133.60, 132.74, 132.63, 132.37, 129.71, 128.86, 126.96, 126.45, 82.23, 78.73, 77.39, 74.80, 70.67, 61.68, 36.82; MH+ 488.

*5.1.43. (2S,3R,4R,5S,6R)-2-(2,4-Dichloro-5-((5-(thiophen-3-yl) thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**13j**)*

Yield: 32%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.77–7.68 (m, 1H), 7.66 (s, 1H), 7.64–7.58 (m, 2H), 7.40 (dd, J = 4.8, 1.6 Hz, 1H), 6.76 (d, J = 3.6 Hz, 1H), 6.59–6.51 (m, 1H), 4.49–4.35 (m, 4H), 3.67 (dd, J = 11.6, 1.6 Hz, 1H), 3.40 (dd, J = 12.0, 5.6 Hz, 1H), 3.37–3.11 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.47, 138.79, 137.62, 135.00, 134.08, 133.90, 133.60, 132.61, 131.93, 129.70, 128.23, 126.61, 122.48, 82.23, 78.74, 77.39, 74.79, 70.70, 61.68, 36.85; MH+ 488.

*5.1.44. Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)-2-hydroxyphenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol (**11a**)*

5.1.44.1. Step 1: 5-Chloro-4-((5-(furan-2-yl)thiazol-2-yl)methyl)-2-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)phenol. To a solution of allyl ether **23** (3.76 g, 4.40 mmol) in THF (50 mL) were added sodium borohydride (1.0 g, 26.4 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.25 g, 0.22 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and at room temperature for 15 h. Saturated $NaHCO_3$ solution was added slowly to the mixture to quench the reaction. The mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using normal phase column chromatography to provide the titled compound (3.2 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.75 (s, 1H), 7.43–7.37 (m, 2H), 7.35–7.24 (m, 3H), 7.21–7.13 (m, 11H), 7.15–6.94 (m, 5H), 6.46–6.36 (m, 3H), 4.92–4.82 (m, 6H), 4.59–4.22 (m, 8H), 3.85–3.55 (m, 4H); MH+ 814.

*5.1.44.2. Step 2: (2S,3R,4R,5S,6R)-2-(4-Chloro-5-((5-(furan-2-yl) thiazol-2-yl)methyl)-2-hydroxyphenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**11a**).* To a solution of perbenzylated thiazole which was prepared in step 1 (261 mg, 0.314 mmol) in CH_2Cl_2 (15 mL) was added BCl_3 (1.0 M in CH_2Cl_2, 2.5 mL, 2.51 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. MeOH was added to the mixture to quench the reaction. The mixture was concentrated *in vacuo*. After dilution with water, the residue was extracted with EtOAc/H_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using RP preparative HPLC to provide the titled compound **11a** (68 mg, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.48 (s, 1H), 7.11 (s, 1H), 6.78 (d, J = 3.2 Hz, 1H), 6.65–6.57 (m, 1H), 5.10–4.92 (m, 2H), 4.55–4.46 (m, 3H), 4.15–4.09 (m, 2H), 3.78–3.60 (m, 2H), 3.51–3.12 (m, 11H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.87, 156.30, 146.16, 143.76, 137.94, 132.65, 131.86, 128.45, 126.87, 125.72, 116.37, 112.64, 107.86, 81.95, 79.02, 74.94, 74.62, 70.85, 61.76, 36.56; MH+ 512.

*5.1.45. Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)-2-propoxyphenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**11b**)*

To a solution of phenol **11a** (150 mg, 0.330 mmol) in acetone (10 mL) were added 1-iodopropane (1.2 mL, 11.6 mmol) and K_2CO_3 (1.6 g, 11.6 mmol) at r.t. The mixture was stirred at 50 °C for 40 h. The mixture was cooled to r.t. and filtered off. The filtrate was concentrated *in vacuo*. The residue was purified using RP preparative to provide the titled compound **11b** (70 mg, 43%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.45 (s, 1H), 7.07 (s, 1H), 6.78 (d, J = 3.2 Hz, 1H), 6.58 (q, J = 1.6 Hz, 1H), 4.52 (br s, 4H), 4.43 (d, J = 9.6 Hz, 1H), 4.36 (s, 1H), 3.95 (triplet and doublet, J = 6.4, 1.6 Hz, 2H), 4.48–4.75 (m, 4H), 3.67 (d, J = 10.8 Hz, 1H), 3.47–3.37 (m, 2H), 3.26 (t, J = 8.0 Hz, 1H), 3.23–3.11 (m, 2H), 1.73 (sext, J = 6.4 Hz, 2H), 0.99 (d, J = 7.2 Hz, 3H); MH+ 496.

*5.1.46. (2S,3R,4R,5S,6R)-2-(4-Chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)-2-(prop-2-ynyloxy)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**11c**)*

Yield: 33%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.51 (s, 1H), 7.17 (s, 1H), 6.79–6.74 (m, 1H), 6.57 (q, J = 1.6 Hz, 1H), 4.92 (dd, J = 11.2, 4.8 Hz, 2H), 4.85 (d, J = 2.4 Hz, 2H), 4.71 (d, J = 5.2 Hz, 1H), 4.48–4.75 (m, 4H), 3.68 (dd, J = 10.4, 5.2 Hz, 1H), 3.62 (t, J = 2.4 Hz, 1H), 3.45–3.11 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.91, 156.42, 138.09, 133.40, 132.81, 132.40, 131.69, 131.48, 128.36, 128.19, 126.94, 126.36, 125.81, 116.84, 113.59, 81.72, 78.58, 74.35, 73.69, 70.42, 68.86, 61.33, 36.17; MH+ 492.

*5.1.47. (2S,3R,4R,5S,6R)-2-(2-(But-3-enyloxy)-4-chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol (**11d**)*

Yield: 19%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.912 (s, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.46 (s, 1H), 7.10 (s, 1H), 6.77 (d, J = 3.2 Hz, 1H), 6.58 (q, J = 2.0 Hz, 1H), 5.99–5.87 (m, 1H), 5.18 (dd, J = 17.2, 1.6 Hz, 1H), 5.09 (d, J = 9.2 Hz, 1H), 5.00 (br s, 2H), 4.52 (br s, 2H), 4.42 (d, J = 9.6 Hz, 2H), 4.36 (s, 2H), 4.04 (td, J = 6.4, 1.2 Hz, 2H), 4.48–4.75 (m, 4H), 3.67 (d, J = 11.2 Hz, 1H), 3.40 (t, J = 8.8 Hz, 2H), 3.28–3.11 (m, 4H); MH+ 508.

*5.1.48. (2S,3R,4R,5S,6R)-2-(4-Chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)-2-(2-hydroxyethoxy)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol (**11e**)*

Yield: 29%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.74–7.71 (m, 1H), 7.47 (s, 1H), 7.12 (s, 1H), 6.77 (d, J = 3.2 Hz, 1H), 6.59–6.53 (m, 1H), 4.97–4.91 (m, 2H), 4.81 (t, J = 6.0 Hz, 1H), 4.70 (d, J = 5.2 Hz, 1H), 4.51 (d, J = 9.2 Hz, 1H), 4.44 (t, J = 5.6 Hz, 1H), 4.37 (s, 2H), 4.03 (t, J = 4.8 Hz, 2H), 3.76–3.63 (m, 3H), 3.48–3.39 (m, 1H), 3.31–3.13 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.42, 157.39, 146.12, 143.79, 137.96, 133.23, 131.56, 129.12, 128.50, 127.50, 114.22, 112.66, 107.91, 81.99, 78.99, 74.85, 74.51, 71.42, 70.92, 61.81, 60.05, 39.37; MH+ 498.

*5.1.49. (2S,3R,4R,5S,6R)-2-(4-Chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)-2-(2-methoxyethoxy)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**11f**)*

Yield: 18%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.40 (s, 1H), 6.90 (s, 1H), 6.78 (d, J = 3.2 Hz, 1H), 6.62–6.55 (m, 1H), 4.94 (t, J = 5.2 Hz, 2H), 4.49–4.39 (m, 2H), 4.33 (s, 2H), 3.75–3.66 (m, 1H), 3.47–3.15 (m, 7H); MH+ 512.

*5.1.50. Preparation of (2S,3R,4R,5S,6R)-2-(2-(2-(1H-1,2,4-triazol-1-yl)ethoxy)-4-chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**11g**)*

To a solution of phenol **11a** (200 mg, 0.441 mmol) and cesium carbonate (158 mg, 0.485 mmol) in DMF (10 mL) was added 1,2-dibromoethane (96 μL, 1.11 mmol). The resulting mixture was stirred at room temperature for 60 h. After dilution with water, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was carried on to the next step without further purification.

To a solution of the crude bromide in DMF (10 mL) was added 1,2,4-triazole sodium derivative (122 mg, 1.34 mmol). The mixture was stirred at room temperature for 15 h. After dilution with water, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using RP preparative HPLC to provide the titled compound **11g** (78 mg, 33%, 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.02 (s, 1H), 7.95 (s, 1H), 7.77–7.71 (m, 1H), 7.47 (s, 1H), 7.13 (s, 1H), 6.78 (d, J = 3.2 Hz, 1H), 6.62–6.58 (m, 1H), 5.02–4.92 (m, 2H), 4.71–4.35 (m, 8H), 3.71–3.61 (m, 1H), 3.49–3.41 (m, 1H), 3.38–3.15 (m, 5H); MH+ 549.

*5.1.51. (2S,3R,4R,5S,6R)-2-(4-chloro-2-(2-(dimethylamino)ethoxy)-5-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol trifluoroacetic acid salt(**11h**)*

Yield: 21%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 7.95 (s, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.56 (s, 1H), 7.25 (s, 1H), 6.84–6.77 (m, 1H), 6.64–6.58 (m, 1H), 4.58–4.53 (m, 1H), 4.48–4.33 (m, 5H), 3.71 (*d*, J = 10.4 Hz, 1H), 3.61–3.52 (m, 3H), 3.48–3.41 (m, 1H), 3.35–3.24 (m, 4H), 3.21–3.16 (m, 1H), 2.98–2.86 (m, H); MH+ 525.

*5.1.52. Preparation of 2-bromo-5-chloro-4-(hydroxymethyl)benzoic acid (**26**)*

To a solution of acid **24** (81 g, 535.8 mmol) in DMF (500 mL) was added NBS portionwise at 0 °C. The mixture was stirred at 0 °C for 70 min. The mixture was poured into H_2O (1 L) with stirring. The product was precipitated and filtered. The solid was washed with H_2O and the solid was dried under vacuum at 50 °C for 24 h to obtain the bromide (109 g, 89%)

To a solution of bromide (109 g, 473.8 mmol) in MeOH (900 mL) was added thionyl chloride (70 mL, 947.6 mmol) dropwise at 0 °C. The mixture was warmed up to r.t. and stirred at 65 °C for 18 h. The mixture was evaporated *in vacuo*. The residue was diluted with EtOAc (500 mL) and washed with aq. sat'd $NaHCO_3$ solution (700 mL×3). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to obtain the ester **25** (107 g, 92%).

To a solution of ester **25** (60.4 g, 229 mmol) in CCl_4 (900 mL) were added NBS (49.0 g, 275 mmol) and AIBN (3.80 g, 22.9 mmol). The mixture was stirred at 85 °C for 15 h. The mixture was cooled to room temperature and filtered off through celite to remove

insoluble solids. The filtrate was evaporated *in vacuo* to obtain the crude benzyl bromide.

To a solution of benzyl bromide (93.6 g, 273 mmol) in DMF (500 mL) was added NaOAc (56 g, 683 mmol). The mixture was stirred at room temperature for 20 h and diluted with EtOAc. The organic layer was washed with aq. 50% NaCl solution and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was tritulated with MeOH and the titled compound was precipitated as a solid. The solid was filtered off, washed with MeOH, and dried under vacuum to obtain the product (36 g, 51%, 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.71 (s, 2H), 5.19 (s, 2H), 3.94 (s, 3H), 2.19 (s, 3H); MH+ 321.

To a solution of acetate (33.5 g, 104.1 mmol) in THF/MeOH/H_2O (250 mL/250 mL/90 mL) was added lithium hydroxide monohydrate (13.1 g, 312 mmol). The mixture was stirred at room temperature for 15 h. The mixture was evaporated *in vacuo* to remove organic solvents. The residue was diluted with H_2O, cooled to 0 °C and acidified with aq. 1 N HCl solution. The titled compound **26** was precipitated as a solid, filtered off and washed with H_2O. The solid was dried under vacuum at 50 °C for 15 h to obtain the product (27.2 g, 96%). MH+ 265.

*5.1.53. Preparation of (4-(allyloxymethyl)-5-bromo-2-chlorobenzyloxy)triisopropylsilane (**27**)*

To a solution of alcohol **26** (23.2 g, 87.5 mmol) in DMF (250 mL) were added TIPSCl (77 mL, 358.5 mmol), imidazole (33 g, 481.3 mmol) and DMAP (4.1 g, 33.6 mmol). The mixture was stirred at room temperature for 15 h. After dilution with water, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using normal phase chromatography to provide silyl ester (38 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.50 (s, 1H), 4.81 (s, 2H), 2.01 (m, 1H), 1.26–1.15 (m, 6H), 1.15 (d, J = 6.8 Hz, 36H).

To a solution of silyl ester (38.0 g, 65.8 mmol) in THF (300 mL) was added borane–dimethylsulfide complex (1M in THF, 13 mL) at 0 °C. The mixture was stirred 0 °C for 15 min, at room temperature at 30 min, and at 75 °C for 15 h. The mixture was cooled to 0 °C. MeOH and H_2O were added to the cooled mixture to quench the reaction. After dilution with water, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using normal phase column chromatography to provide the alcohol (22.9 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.44 (s, 1H), 4.78 (s, 2H), 4.71 (d, J = 5.2 Hz, 2H), 2.01 (m, 1H), 1.26–1.16 (m, 3H), 1.12 (d, J = 6.8 Hz, 18H).

To a solution of alcohol (31 g, 75.5 mmol) in DMF (300 mL) were added NaH (60% dispersion in mineral oil, 4.0 g, 98.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and allyl bromide (23 mL, 264 mmol) was added to the mixture at 0 °C. The mixture was warmed up to room temperature and stirred at room temperature for 2 h. After dilution with water, the mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified using normal phase column chromatography to provide the titled compound **27** (32.1 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.45 (s, 1H), 6.05–5.91 (m, 1H), 5.35 (quartet and doublet, J = 17.2,S 1.6 Hz, 1H), 5.24 (quartet and doublet, J = 10.4, 1.2 Hz, 1H), 4.82 (s, 2H), 4.53 (s, 2H), 4.11 (triplet and doublet, J = 5.6, 1.2 Hz, 2H), 1.25–1.16 (m, 1H), 1.10 (d, J = 7.2 Hz, 18H).

*5.1.54. Preparation of 2-(4-(allyloxymethyl)-2-chloro-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl) tetrahydro-2H-pyran-2-yl)phenyl)acetic acid (**28**)*

The titled compound (Yield: 25% (7-steps) using bromide **27**) was obtained in the same manner as the synthesis of Scheme 2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.37 (s, 1H), 7.35–7.22 (m, 13H), 7.20–7.08 (m, 5H), 6.85 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 5.96–5.81 (m, 1H), 5.25 (doublet and quartet, J = 17.2 Hz, 1.6 Hz, 1H), 5.15 (doublet and quartet, J = 10.4 Hz, 1.2 Hz, 1H), 4.95–4.83 (m, 3H), 4.78–4.49 (m, 4H), 4.43–4.37 (m, 3H), 3.95–3.89 (m, 2H), 3.86 (d, J = 10.8 Hz, 1H), 3.81–3.71 (m, 6H), 3.55 (t, J = 9.2 Hz, 2H); MH+ 785.

*5.1.55. Preparation of 2-(4-(allyloxymethyl)-2-chloro-5-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)benzyl)-5-(furan-2-yl)thiazole (**29**)*

The titled compound was prepared in the same manner as the synthesis of Scheme 3.

Yield: 72%(2-steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.44 (m, 2H), 7.38–7.16 (m, 21H), 6.91–6.82 (m, 2H), 6.43–6.33 (m, 1H), 5.97–5.83 (m, 1H), 5.27 (doublet and quartet, J = 17.2 Hz, 2.0 Hz, 1H), 5.17 (doublet and quartet, J = 10.8 Hz, 1.6 Hz, 1H), 4.93–4.82 (m, 3H), 4.77–4.56 (m, 3H), 4.54–4.36 (m, 6H), 3.97–3.85 (m, 3H), 3.81–3.68 (m, 4H), 3.62–3.51 (m, 2H); MH+ 868.

*5.1.56. Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)-2-(hydroxymethyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**12a**)*

The titled compound was prepared in the same manner as the synthesis of Scheme 4.

Yield: 20%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.55 (s, 1H), 7.49 (s, 1H), 6.77 (d, J = 3.2 Hz, 1H), 6.60–6.54 (m, 1H), 4.95 (br s, 1H), 4.63 (s, 4H), 4.42 (s, 3H), 4.27 (d, J = 9.2 Hz, 2H), 3.69 (d, J = 10.0 Hz, 1H), 3.43 (dd, J = 11.6, 1.6 Hz, 1H), 3.32–3.14 (m, 4H); MH+ 468.

*5.1.57. (2S,3R,4R,5S,6R)-2-(4-chloro-5-((5-(furan-3-yl)thiazol-2-yl) methyl)-2-(hydroxymethyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**12b**)*

Yield: 25%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.74 (t, J = 1.6 Hz, 1H), 7.55 (s, 1H), 7.49 (s, 1H), 6.88–6.83 (m, 1H), 5.05 (br s, 1H), 4.63 (s, 4H), 4.42 (s, 3H), 4.27 (d, J = 9.2 Hz, 2H), 3.69 (d, J = 10.0 Hz, 1H), 3.43 (dd, J = 11.6, 1.6 Hz, 1H), 3.31–3.12 (m, 4H); MH+ 468.

*5.1.58. (2S,3R,4R,5S,6R)-2-(4-chloro-2-(hydroxymethyl)-5-((5-(thiophen-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**12c**)*

Yield: 31%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.56 (s, 1H), 7.54 (d, J = 0.8 Hz, 1H), 7.31 (dd, J = 4.0, 0.8 Hz, 1H), 7.11–7.05 (m, 1H), 4.90 (br s, 1H), 4.63 (s, 4H), 4.41 (s, 3H), 4.27 (d, J = 9.2 Hz, 2H), 3.69 (d, J = 10.0 Hz, 1H), 3.43 (dd, J = 11.6, 1.6 Hz, 1H), 3.33–3.13 (m, 4H); MH+ 484.

*5.1.59. (2S,3R,4R,5S,6R)-2-(4-chloro-2-(hydroxymethyl)-5-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**12d**)*

Yield: 26%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.75–7.70 (m, 1H), 7.66–7.61 (m, 1H), 7.55 (s, 1H), 7.49 (s, 1H), 7.42 (dd, J = 5.2, 1.2 Hz, 1H), 4.96 (br s, 1H), 4.63 (s, 4H), 4.40 (s, 3H), 4.28 (d, J = 9.2 Hz, 2H), 3.69 (d, J = 10.4 Hz, 1H), 3.44 (dd, J = 11.6, 1.6 Hz, 1H), 3.33–3.13 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.38, 143.07, 138.74, 137.33, 133.96, 133.57, 132.58, 132.02, 130.82, 128.18, 127.61, 126.60, 122.37, 81.80, 78.91, 76.77, 75.14, 70.76, 61.79, 60.02, 37.35; MH+ 484

*5.1.60. Preparation of (2S,3R,4R,5S,6R)-2-(2-(allyloxymethyl)-4-chloro-5-((5-(furan-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**12e**)*

Yield: 9%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.59 (s, 1H), 7.45 (s, 1H), 6.78 (d, J = 3.2 Hz, 1H),

6.59–6.54 (m, 1H), 6.03–5.91 (m, 1H), 5.31 (quartet and doublet, $J = 17.2$, 1.6 Hz, 1H), 5.19 (quartet and doublet, $J = 10.4$, 2.0 Hz, 1H), 4.70 (d, $J = 12.8$ Hz, 2H), 4.55 (d, $J = 12.8$ Hz, 2H), 4.43 (s, 3H), 4.28 (d, $J = 8.8$ Hz, 2H), 4.05 (triplet and doublet, $J = 5.6$, 1.6 Hz, 2H), 3.69 (d, $J = 10.0$ Hz, 1H), 3.45 (dd, $J = 11.6$, 5.2 Hz, 1H), 3.32–3.16 (m, 4H); MH+ 508.

*5.1.61. (2S,3R,4R,5S,6R)-2-(2-(Allyloxymethyl)-4-chloro-5-((5-(furan-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**12f**)*

Yield: 10%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.87 (s, 1H), 7.74 (t, $J = 1.6$ Hz, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 6.86–6.82 (m, 1H), 6.03–5.91 (m, 1H), 5.32 (quartet and doublet, $J = 18.0$, 1.6 Hz, 1H), 5.19 (quartet and doublet, $J = 10.4$, 2.0 Hz, 1H), 4.70 (d, $J = 12.8$ Hz, 2H), 4.55 (d, $J = 12.8$ Hz, 2H), 4.41 (s, 3H), 4.28 (d, $J = 9.2$ Hz, 2H), 4.05 (triplet and doublet, $J = 5.6$, 1.6 Hz, 2H), 3.69 (d, $J = 10.4$ Hz, 1H), 3.44 (dd, $J = 12.0$, 5.6 Hz, 1H), 3.31–3.17 (m, 4H); MH+ 508.

*5.1.62. (2S,3R,4R,5S,6R)-2-(2-(Allyloxymethyl)-4-chloro-5-((5-(thiophen-2-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**12g**)*

Yield: 15%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.59 (s, 1H), 7.56 (dd, $J = 5.2$, 1.2 Hz, 1H), 7.45 (s, 1H), 7.31 (dd, $J = 2.4$, 1.2 Hz, 1H), 7.12–7.07 (m, 1H), 6.04–5.91 (m, 1H), 5.30 (quartet and doublet, $J = 17.2$, 1.6 Hz, 1H), 5.18 (quartet and doublet, $J = 10.4$, 2.0 Hz, 1H), 4.70 (d, $J = 12.8$ Hz, 2H), 4.61 (d, $J = 12.8$ Hz, 2H), 4.42 (s, 3H), 4.29 (d, $J = 9.2$ Hz, 2H), 4.04 (triplet and doublet, $J = 5.6$, 1.6 Hz, 2H), 3.70 (d, $J = 10.0$ Hz, 1H), 3.45 (dd, $J = 12.0$, 5.6 Hz, 1H), 3.32–3.15 (m, 4H); MH+ 524.

*5.1.63. (2S,3R,4R,5S,6R)-2-(2-(Allyloxymethyl)-4-chloro-5-((5-(thiophen-3-yl)thiazol-2-yl)methyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (**12h**)*

Yield: 14%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.74–7.70 (m, 1H), 7.15–7.11 (m, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 7.43 (dd, $J = 5.2$, 1.2 Hz, 1H), 6.04–5.91 (m, 1H), 5.32 (qd, $J = 18.0$, 1.6 Hz, 1H), 5.18 (quartet and doublet, $J = 10.4$, 2.0 Hz, 1H), 4.70 (d, $J = 13.4$ Hz, 2H), 4.55 (d, $J = 13.4$ Hz, 2H), 4.46 (s, 3H), 4.28 (d, $J = 8.8$ Hz, 2H), 4.05 (triplet and doublet, $J = 5.6$, 1.6 Hz, 2H), 3.69 (d, $J = 10.0$ Hz, 1H), 3.44 (dd, $J = 12.0$, 5.6 Hz, 1H), 3.31–3.16 (m, 4H); MH+ 524.

5.2. In vitro assay

5.2.1. 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.

5.2.2. 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 uM) 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 [22,23].

Acknowledgments

Dr. Kwang-Seop Song is appreciated for his previous contribution to the thiazole series. We also appreciate Dr. Eun Chul Huh for his leadership and valuable advice as CTO at Green Cross Corporation.

References

[1] International Diabetes Federation, Diabetes Atlas, fourth ed. International Diabetes Federation, Montreal, Canada, 2009.
[2] A. Dwarakanathan, J. Insur. Med. 38 (2006) 20–30.
[3] B. Mackenzie, D.D.F. Loo, P.-H. Mariana, E.M. Wright, J. Biol. Chem. 271 (1996) 32678–32683.
[4] E.M. Wright, Am. J. Physiol. 208 (2001) F10–F18.
[5] L. Zhou, E.V. Cryan, M.R. D'Andrea, S. Belkowski, B.R. Conway, K.T. Demarest, J. Cell. Biochem. 90 (2003) 339–346.
[6] S. Evans, E. Grasset, M. Heyman, A.M. Dumonitier, J.P. Beau, J.-F. Desjeux, J. Pediatr. Gastroenterol. Nutr. 4 (1985) 878–886.
[7] O.W. Moe, C.A. Berry, F.C. Rector, in: B.M. Brenner, F.C. Rector (Eds.), The Kidney, W.B. Saunders Co., Philadelphia, 1996 pp. 375–415.
[8] L.P. van den Heuvel, K. Assink, M. Willemsen, L. Monnens, Hum. Genet. 111 (2002) 544–547.
[9] B.A. Ellsworth, W. Meng, M. Patel, R.N. Girotra, G. Wu, P.M. Sher, D.L. Hagan, M.T. Obermeier, W.G. Humphreys, J.G. Robertson, A. Wang, S. Han, T.L. Waldron, N.N. Morgan, J.M. Whaley, W.N. Washburn, Bioorg. Med. Chem. Lett. 18 (2008) 4770–4773.
[10] W. Meng, B.A. Ellsworth, A.A. Nirschl, P.J. McCann, M. Patel, R.N. Girotra, G. Wu, P.M. Sher, E.P. Morrison, S.A. Biller, R. Zahler, P.P. Deshpande, A. Pullockaran, D.L. Hagan, N. Morgan, J.R. Taylor, M.T. Obermeier, W.G. Humphreys, A. Khanna, L. Discenza, J.G. Robertson, A. Wang, S. Han, J.R. Wetterau, E.B. Janovitz, O.P. Flint, J.M. Whaley, W.N. Washburn, J. Med. Chem. 51 (2008) 1145–1149.
[11] W.N. Washburn, J. Med. Chem. 52 (2009) 1785–1794.
[12] According to a report from Business Wire on June 26, 2010, dapagliflozin as add on therapy to insulin demonstrated improved glycemic control in patients with type 2 diabetes inadequately controlled with insulin.
[13] (a) S. Nomura, S. Sakamaki, M. Hongu, E. Kawanishi, Y. Koga, T. Sakamoto, Y. Yamamoto, K. Ueta, H. Kimata, K. Nakayama, M. Tsuda-Tsukimoto, J. Med. Chem. 53 (2010) 6355–6360;
(b) Lexicon Pharmaceuticals (2009).www.clinicaltrials.gov NCT00962065. 12;
(c) V. Mascitti, Presented at the 240th American Chemical Society National Meeting and Exposition, Boston, MA, August 22–26, 2010; Medi-151.
[14] (a) J. Lee, S.-H. Lee, H.J. Seo, E.-J. Son, S.H. Lee, M.E. Jung, M. Lee, H.-K. Han, J. Kim, J. Kang, J. Lee, Bioorg. Med. Chem. 18 (2010) 2178–2194;
(b) M.J. Kim, J. Lee, S.Y. Kang, H. S,-Lee, E.-J. Son, M.E. Jung, S.H. Lee, K.-S. Song, M. Lee, H.-K. Han, J. Kim, J. Lee, Bioorg. Med. Chem. Lett. 20 (2010) 3420–3425;
(c) S.Y. Kang, K.-S. Song, J. Lee, S.-H. Lee, J. Lee, Bioorg. Med. Chem. 18 (2010) 6069–6079;
(d) J. Lee, J.Y. Kim, J. Choi, S.-H. Lee, J. Kim, J. Lee, Bioorg. Med. Chem. Lett. 20 (2010) 7046–7049.
[15] K.-S. Song, S.H. Lee, M.J. Kim, H.J. Seo, J. Lee, S.-H. Lee, M.E. Jung, E.-J. Son, M. Lee, J. Kim, J. Lee, ACS Med. Chem. Lett. 2 (2011) 182–187.
[16] According to Dr. Washburn (BMS)'s article (see Ref. [11]) regarding discovery of dapagliflozin, exploration of the proximal ring appears to provide SAR information that small lipophilic substituents at the C-4 position of the proximal ring increase SGLT2 affinity, while substitution at C-2 or C-3 modestly improves affinity and C-6 substitution is detrimental.
[17] T. Oberhauser, J. Org. Chem. 62 (1997) 4504–4506.
[18] J.C. Rodriguez-Dominguez, A. Balbuzano-Deus, M.A. Lopez-Lopez, G. Kirsch, J. Heterocycl. Chem. 44 (2007) 273–275.
[19] B.A. Ellsworth, A.G. Doyle, M. Patel, J. Caceres-Cortes, W. Meng, P.P. Deshpande, A. Pullockaran, W.N. Washburn, Tetrahedron Asymmetry 14 (2003) 3243–3247.
[20] R. Beugelmans, S. Bourdet, A. Bigot, J. Zhu, Tetrahedron Lett. 35 (1994) 4349–4350.
[21] D.R. Williams, D.L. Brown, J.W. Benbow, J. Am. Chem. Soc. 111 (1989) 1923–1925.
[22] S. Han, D.L. Hagan, J.R. Taylor, L. Xin, W. Meng, S.A. Biller, J.R. Wetterau, W.N. Washburn, J.M. Whaley, Diabetes 57 (2008) 1723–1729 GraphPad PRISM.
[23] K. Katsuno, Y. Fujimori, Y. Takemura, M. Hiratochi, F. Itoh, Y. Komatsu, H. Fujikura, M. Isaji, J. Pharmacol. Exp. Ther. 320 (2007) 323–330 GraphPad PRISM.