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Synthesis of pyridazine and thiazole analogs as SGLT2 inhibitors

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ABSTRACT

With anticipation of the improvement in biological aspects in our SGLT2 program, novel pyridazinyl and thiazolyl analogs were designed and efficiently synthesized. The installation of the pyridazine ring at the anomeric carbon of D-glucopyranose was carried out in a stereoselective fashion. On the other hand, a series of thiazolyl analogs was also synthesized through a coupling reaction between perbenzyl gluconolactone **9** and 2-lithiothiazole. Biological activities of the compounds thus prepared were evaluated by the in vitro SGLT2 inhibition assay. Considering assay results, the novel benzylpyridazinyl and benzylthiazolyl analogs, disclosed in this article, could be a quick reference to prospective SGLT2 inhibitors useful for pharmacotherapy.

1. Introduction

It has been known for a long time that substances such as the natural product phlorizin **1** cause the renal excretion of glucose, thereby potentially being able to improve control of diabetes (Fig. 1). But this inhibitor was not suitable as a candidate of clinical development due to its nonselectivity against SGLT1. More recent studies of the physiology of renal glucose transport have allowed the drugs that selectively target the sodium glucose co-transporter 2 (SGLT2) as potentially effective treatments for Type 2 diabetes and other diseases.[1]

Dapagliflozin **2** discovered by BMS, currently the most advanced SGLT2 inhibitor in this field, is being co-developed by BMS and AstraZeneca with 1200-fold selectivity over SGLT1 (Fig. 1).[2] Its structure consists of glucoside and benzylphenyl group, in which the bond between the glucose and the aglycone is a carbon–carbon bond. Because of its unique molecular structure in **2**, it is rather difficult to modify its basic framework. However, we envisioned that addition of heteroatoms to phenyl ring could provide a valuable approach for the improvement in *c* log *P* value, in turn possibly leading to decrease plasma protein binding of **2**, while maintaining its biological activity. Thus, replacement of phenyl ring with the corresponding heterocyclic ring was anticipated to provide a promising platform for the improvement in developability characteristics of SGLT2 inhibitor if successful. As the first step, we considered pyridazine and thiazole group as potential surrogates of phenyl group. Herein, we report the chemical synthesis and biological evaluation of a few of novel SGLT2 inhibitors including pyridazine **3** and thiazole **4**.

2. Results and discussion

2.1. Synthesis of pyridazine analog

As shown in Figure 2, the target compound **3** consists of glucoside part and benzyl pyridazine part as an aglycone, in which two units are connected with β-configuration from the glucose ring. Pyridazinyl group is substituted with chlorine at 3-position therein. Thus, it would be reasonable to install pyridazinyl group onto glucose stereoselectively, and subsequent transformation from pyridazinone **15** by two steps ((i) treatment with $POCl_3$, (ii) deprotection of benzyl groups) would then provide the target 3-chloropyridazine **3**. From a retrosynthetic point of view, we envisioned that pyridazine ring would be prepared from pyridazinone **15**, which could be provided by cyclization of γ-ketoester **6** with hydrazine followed by requisite oxidation. 4-Methoxybenzylation would then take place by alkylation of 2-carboxylated butyrolactone **6**, which would be generated in turn from protected vinyl glucose derivative **7**.

Per-benzylated D-glucose **8** was selected as a starting material.[3,4] Lactol **8** was oxidized to lactone **9** in the presence of TPAP and NMO at room temperature in CH_2Cl_2 in 95% yield (Scheme 1). Lactone **9** was then treated with vinyl magnesium bromide in THF at −78 °C to give rise to the corresponding hemiketal. Without further purification, β-*C*-vinyl glucoside **7** was obtained by reduction of the resulting hemiketal with triethylsilane and TMSOTf in CH_2Cl_2 at −30 °C in 53% overall yield. Epoxidation of double bond

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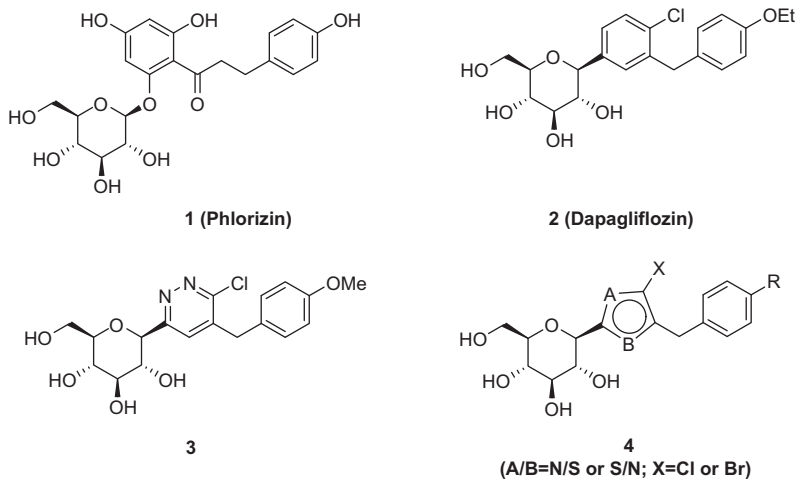


Figure 1. Representative SGLT2 inhibitors (**1** and **2**) and newly designed SGLT2 inhibitors (**3** and **4**).

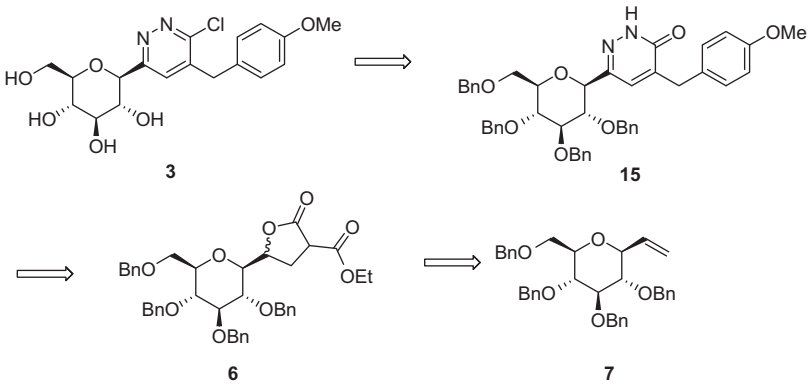
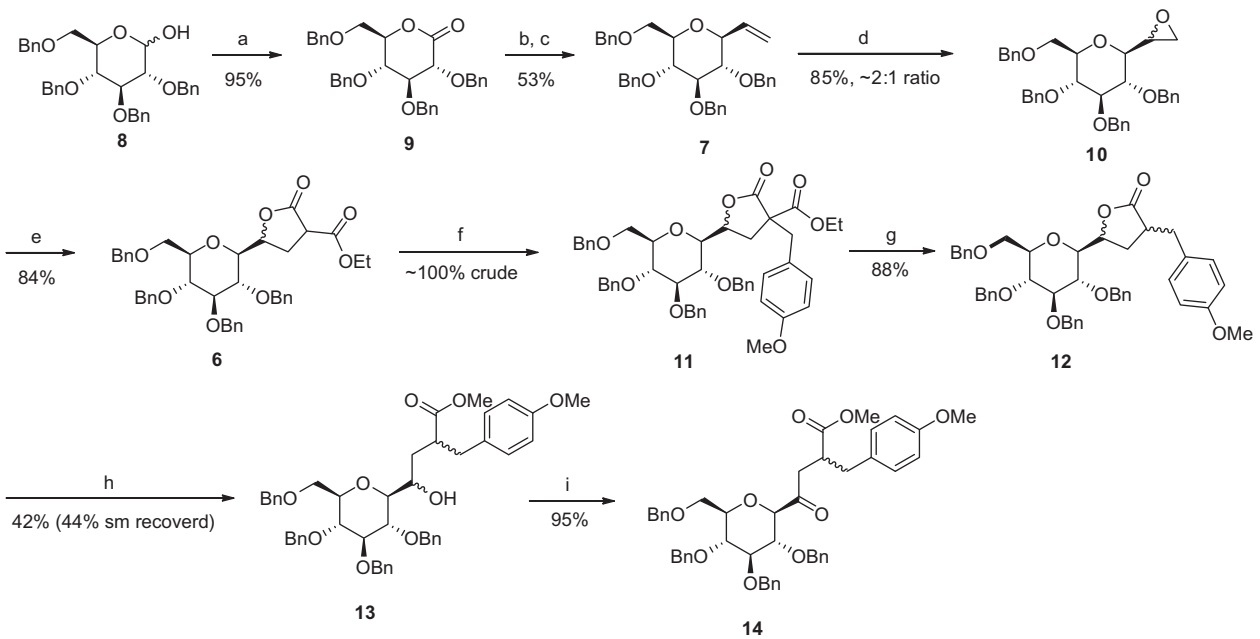


Figure 2. Retrosynthetic analysis for the synthesis of compound **3**.



Scheme 1. Reagents and conditions: (a) TPAP, 4 Å MS, NMO, CH_2Cl_2, rt; (b) vinyl magnesium bromide, THF, −78 °C; (c) triethylsilane, trimethylsilyl trifluoromethylsulfonate, CH_2Cl_2, −30 °C; (d) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt; (e) diethylmalonate, NaOEt, EtOH, rt; (f) 4-methoxybenzyl bromide, sodium hydride, THF, rt; (g) NaCl, DMSO, reflux; (h) *p*-toluenesulfonic acid, MeOH; (i) TPAP, NMO, CH_3CN.

underwent smoothly with *m*CPBA and $NaHCO_3$ in CH_2Cl_2 to produce approximately 2:1 mixture of epoxides **10** in 84% combined yields. The coupling reaction between epoxide **10** and diethylmalonate was accomplished using sodium ethoxide at room temperature, which was concurrently cyclized to 2-carboxylated butyrolactone **6** in 84% yield. In order to afford 2-(*p*-methoxybenzyl)-2-carboxylated lactone **11**, 2-carboxylated butyrolactone **6** was treated with sodium hydride and *p*-methoxybenzyl bromide in THF at room temperature. Subsequently, heating a mixture of NaCl and **11** in DMSO and water, 2-carboxylated lactone **11** underwent facile decarboxylation to provide *p*-methoxybenzyl lactone **12** in 88% yield. At this stage, composition of the whole carbon framework was accomplished. The unspecified asymmetric centers in **12** are insignificant because both of them will be incorporated into pyridazine ring at the later stage. For the oxidation of γ-hydroxy group, butyrolactone **12** was opened under the conditions of a catalytic amount of *p*-toluenesulfonic acid in methanol. The desired alcohol **13** was produced in 42% yield along with the recovered starting material **12** (44% yield). γ-Keto methyl ester **14** was then generated from alcohol **13** using TPAP and NMO in acetonitrile at room temperature in 95% yield.

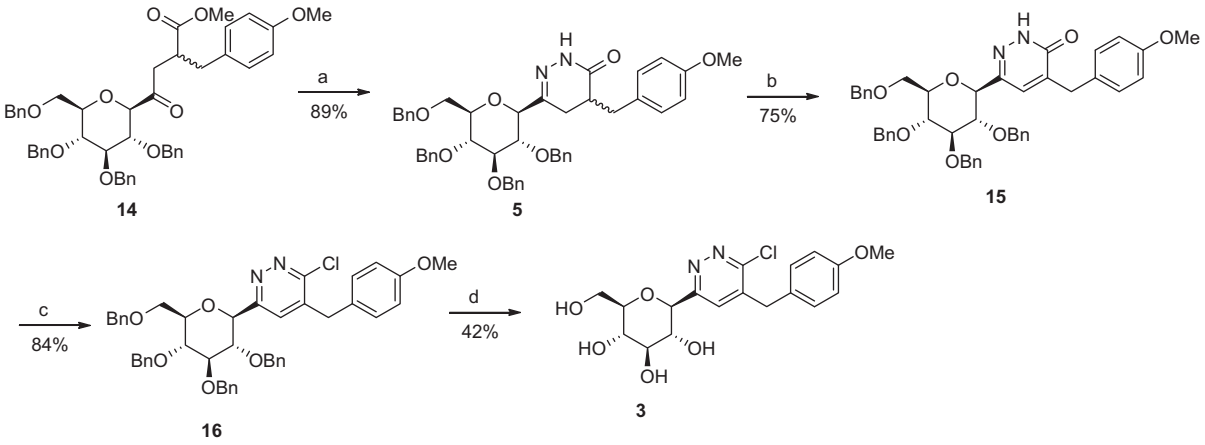
Cyclization from γ-keto ester **14** to dihydropyridazinone **5** was accomplished with hydrazine monohydrate under the conditions of refluxing methanol (Scheme 2). Using bromine under acetic acid at 80 °C, dihydropyridazinone **5** was oxidized to pyridazinone **15** uneventfully and two diastereoisomers became a single compound **15** in 75% yield.[5] Pyridazinone **15** was then converted to 6-chloro-5-benzylpyridazine **16** by treatment of **15** with $POCl_3$ in refluxed toluene in 84% yield. Final removal of the four benzyl groups to produce the target compound **3** was accomplished when TMSI was used in acetonitrile at room temperature.[6]

By NMR studies, the *trans*-stereochemistry was evident by either analysis of the coupling constants of H_a and H_b ($J_{Ha,Hb}$ = 9.6 Hz) at compound **3** or NOE enhancement data between hydrogens in glucoside of acetylated compound **17** (H_a and H_c = 2.1%; H_a and H_d = 3.7%) as shown in Figure 3.

2.2. Synthesis of thiazole analogs

We next extended a method developed by Dondoni and Scherrmann[7] for preparation of novel thiazolyl analogs **4** as shown in Scheme 4. The coupling reaction of D-gluconolactone **9** with 2-lithiothiazole prepared in situ from *n*-BuLi and 2-bromothiazole afforded thiazolyl ketose **18** in 83% yield. The activation of the anomeric position by O-acetylation, and subsequent removal of the acetoxy group by reduction with excess triethylsilane in the presence of BF_3 etherate converted ketal **19** to a mixture of glucosides **20** in good yields (73%).[8] Thiazolyl *C*-glucosides **20** were purified by flash column chromatography (Biotage, hexane–ethyl acetate gradient elution) and analyzed by ^{1}H NMR spectroscopy to confirm the anomeric configurations. Thus, a doublet peak, observed at 5.29 ppm (J = 6.0 Hz), indicated an existence of the α-anomeric form of **20**. The α-anomeric proton peak intensity was estimated as a half of the proton peak intensity in 4-thiazolyl position at 7.78 ppm. According to this ^{1}H NMR spectral data, the thiazolyl *C*-glucosides **20** turned out to be a 1:1 isomeric mixture.[7]

Lithiation of the thiazole moiety in the 5-position was achieved by the treatment of thiazolyl *C*-glucosides **20** with *n*-BuLi at low



Scheme 2. Reagents and conditions: (a) hydrazine monohydrate, MeOH, reflux; (b) bromine, acetic acid, 80 °C; (c) $POCl_3$, toluene, reflux; (d) trimethylsilyl iodide, acetonitrile, rt.

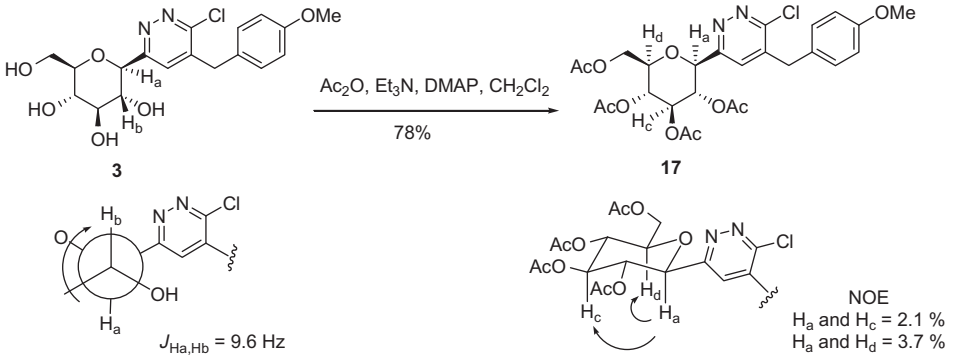


Figure 3. NMR experiments for determination of stereochemistry (analysis of coupling constants and NOE)

temperature (−78 °C). The subsequent reaction involved the addition of the lithiated thiazole group to the requisite benzaldehyde, providing a mixture of diastereomers **21** in 50–60% yields.[9] To our delight, it was observed that thiazolyl α-*C*-glucoside was transformed into the desired β-anomer **21** during the addition reaction. The characteristic doublet signal for α-anomeric proton was not detected on ^{1}H NMR spectral data of alkylated products **21**. The basic conditions derived from *n*-BuLi in the addition reaction are presumed to transform the α-anomer (axial) into the thermodynamically more stable β-anomer (equatorial). This base-promoted transformation through the sugar carbanion was previously observed and reported by Dondoni and Marra.[10] The reduction followed by concomitant debenzylation of alcohol **21** was accomplished by warming **21** in neat TMSI at 50 °C for 12–24 h.[11a] At this stage, the hydroxyl group in 5-methyl position of thiazole was also completely reduced to the corresponding methylene at this final step[11b] (Scheme 3).

As shown in Scheme 4, 2-bromo-4-((triisopropylsilyloxy)-methyl)thiazole **23** was lithiated with *n*-BuLi and subsequently coupled with D-gluconolactone **9** to produce 4-((triisopropylsilyl-oxy)methyl)thiazolyl *C*-glucoside **24** in 63% yield. The hydroxyl group at the anomeric position of **24** was reduced by acetylation and subsequent treatment of triethylsilane in the presence of BF_3 etherate in good yield (>90%). The triisopropylsilyl protecting group of glucoside **26** was efficiently removed using TBAF.[12] The resulting alcohol of compound **27** was converted to aldehyde **28** by oxidation with Dess–Martin periodinane (DMP).[13] Grignard reactions of *p*-substituted phenylmagnesium bromide with the aldehyde **28** provided the corresponding phenyl(thiazol-4-yl) methanols **29**.[14] The final products were obtained by warming **29** in neat TMSI at 50 °C. The β-anomers of final products **30** were purified by preparative HPLC equipped with a reverse phase column.

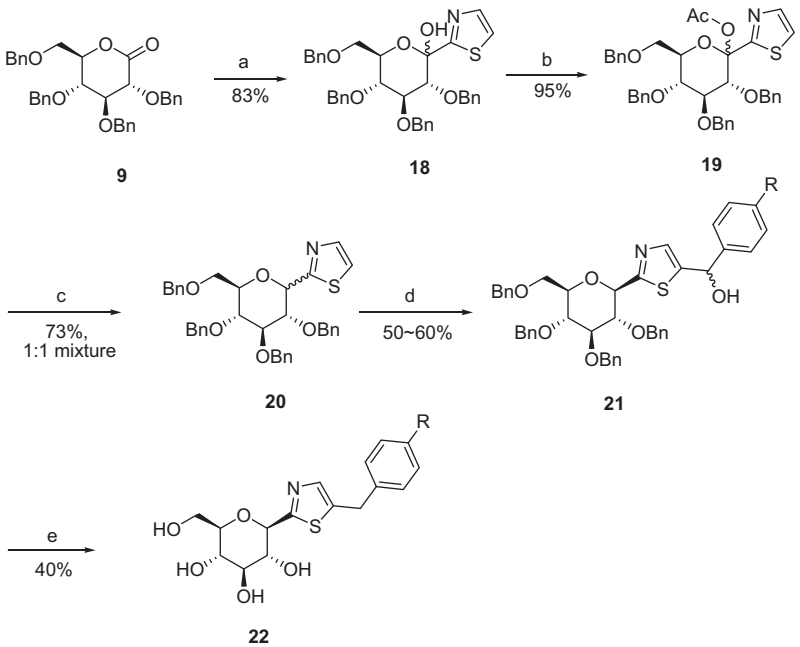
As shown in Scheme 5, the lithiated thiazolylglucoside **20** was converted to 5-chlorothiazolylglucoside **31** and 5-bromothiazolylglucoside **32** by electrophilic halogenation using CCl_4 and CBr_4, respectively.[15] The intermediate **31** or **32** was carefully separated by silica gel column chromatography in order to proceed to the next reaction. As mentioned above, the base-promoted transformation of α-anomer produced the thermodynamically more stable β-anomers **31** and **32**, respectively.

Lithiation of 5-bromothiazole intermediate **32** was performed by treatment of LDA, and the resulting anion underwent metal–halogen exchange reaction so that a bromine atom moved to a new position (4-position) on the thiazole ring.[16,17] The newly formed lithiated intermediate **33** was subjected to subsequent coupling with requisite aldehydes at low temperature (−78 °C) to produce the desired alcoholic products **34**. The same conditions were applied to 5-chlorothiazole intermediate **31** with the expectation for the halogen dance rearrangement. However, in the 5-chlorothiazole case, the chlorine atom did not move to 4-position but maintain the original position. Thus, the coupling reactions of 5-chlorothiazole intermediate **31** with requisite aldehydes produced 4-benzyl type **36**. Both debenzylation and reduction of **34** and **36** were concurrently performed to prepare final products **35** and **37** in an analogous fashion as described previously.

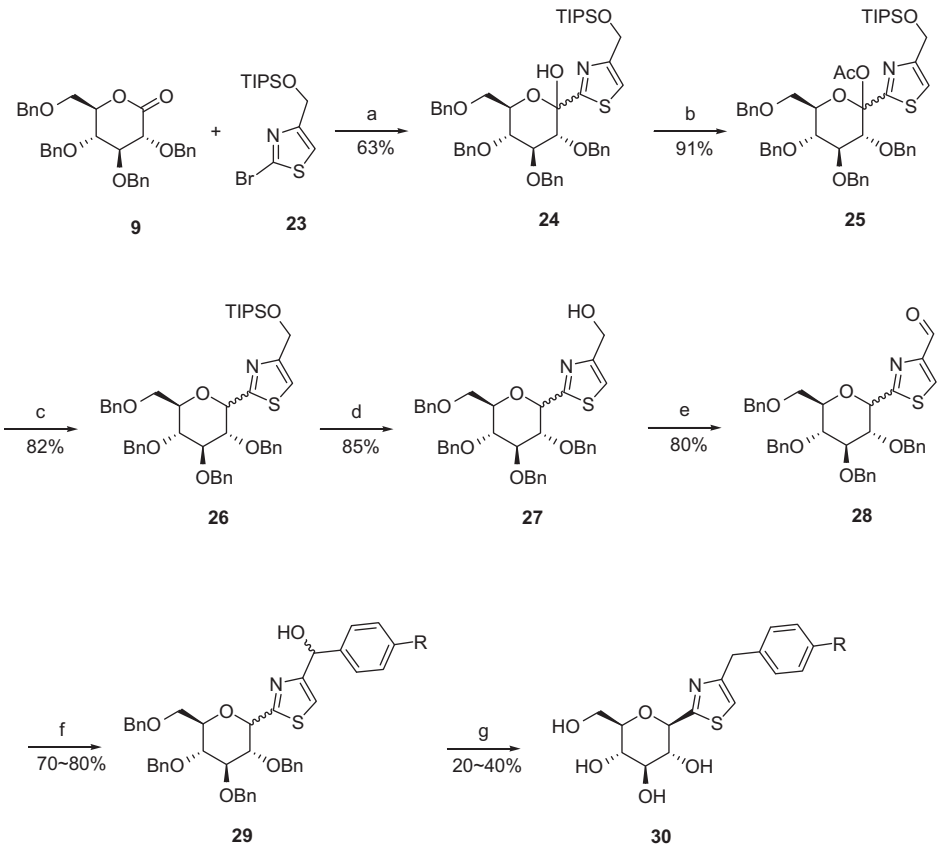
Reductive dehalogenation was performed in order to confirm the halogen atom positions. Two representative analogs **35a** and **37a** were hydrogenated in the presence of Pd/C and the chemical structures of resulting products were analyzed by their ^{1}H NMR spectra. While ^{1}H NMR spectrum of the hydrogenated product from **35a** was exactly matched to one of **22a** in Scheme 4, one of the hydrogenated products of **37a** was not identical to one of **22b** but one of **30a**. These results support that bromine atom is placed on 4-position of thiazole as in **35a** and chlorine atom remains on 5-position as in **37a**.

2.3. Structure–activity relationship

The inhibitory effects of all synthesized compounds against *h*SGLT2 were evaluated using the cell-based SGLT2 AMG (methyl-α-D-glucopyranoside) assay.[18,19] The results of biological activities are summarized in Table 1. The replacement of 4-chlorophenyl moiety in **2** with 6-chloropyridazinyl group in **3** resulted in significant loss of *h*SGLT2 inhibitory activity. Even though the pyridazinyl analog **3** (IC_{50} = 610 nM) has a similar structure to **2**, it demonstrated only moderate inhibitory activity against *h*SGLT2.



Scheme 3. Reagents and conditions: (a) *n*-BuLi, 2-bromothiazole, Et_2O/THF, −78 °C to rt; (b) Ac_2O, TEA, DCM, rt; (c) Et_3SiH, BF_3 etherate, 4 Å MS, DCM, 0 °C to rt; (d) *n*-BuLi, *p*-substituted benzaldehyde, THF, −78 °C to rt; (e) TMSI (neat), at 50 °C.



Scheme 4. Reagents and conditions: (a) *n*-BuLi, ether/THF, −40 °C to rt; (b) Ac_2O, TEA, DCM, rt; (c) Et_3SiH, BF_3 etherate, 4 Å MS, DCM, 0 °C to rt; (d) TBAF, THF, 0 °C to rt; (e) DMP, DCM, rt; (f) R-C_6H_4MgBr, THF, 0 °C to rt; (g) TMSI (neat), 50 °C/prep. HPLC.

A series of thiazolyl analogs also represented only moderate inhibitory activities against *h*SGLT2 as shown in Table 1. Nonsubstituted thiazolyl analogs **22**, **30** with benzyl-type moiety linked at either 4- or 5-position of the thiazole group lacked any obvious SGLT2 inhibitory activity. Most of the analogs exhibit IC_{50} values greater than 10 μM, and only one analog **22b** displayed merely marginal potency (IC_{50} = 4630 nM). In order to perform further SAR study on thiazole moiety, 4-bromothiazole and 5-chlorothiazole analogs were prepared. On the whole, the incorporation of a halogen atom into either 4- or 5-position of thiazole group exhibited considerable improvement in inhibitory activity. Even though a 4-bromothiazole analog **35a** with nonsubstituted benzyl moiety demonstrated no inhibitory activity (IC_{50} > 10,000 nM), increased potencies were observed when *p*-substituted benzyl moiety (**35b–e**) was incorporated into 5-position of thiazole. Especially compound **35c** with *p*-ethylbenzyl moiety was found to have somewhat potent inhibitory activity (IC_{50} = 786 nM). However, other *p*-substituted benzyl moieties in the 4-bromothiazole series turned out to be less favorable (IC_{50} > 1000 nM) than 4-ethylbenzyl moiety. Another series containing 5-chlorothiazole moiety demonstrated more significant inhibitory activities than 4-bromothiazole series. All tested compounds (**37a–d**) in this series demonstrated less than 500 nM of IC_{50} values at *h*SGLT2. Compound **37b**, containing 4-ethylbenzyl moiety at 5-position of thiazole, exhibited the most potent inhibition (IC_{50} = 121 nM) in the thiazole series to date. However, introduction of other moieties, such as 4-methylbenzyl **37a**, 4-*n*-butylbenzyl **37c**, biphenyl-4-ylmethyl **37d**, only slightly decreased the inhibitory activities. Nonetheless, none of them proved to improve inhibitory activity against *h*SGLT2 over dapagliflozin **2**, indicating that replacement of the proximal ring in **2** with pyridazine or thiazole is intolerant most likely due to its unfavorable electronic environments.

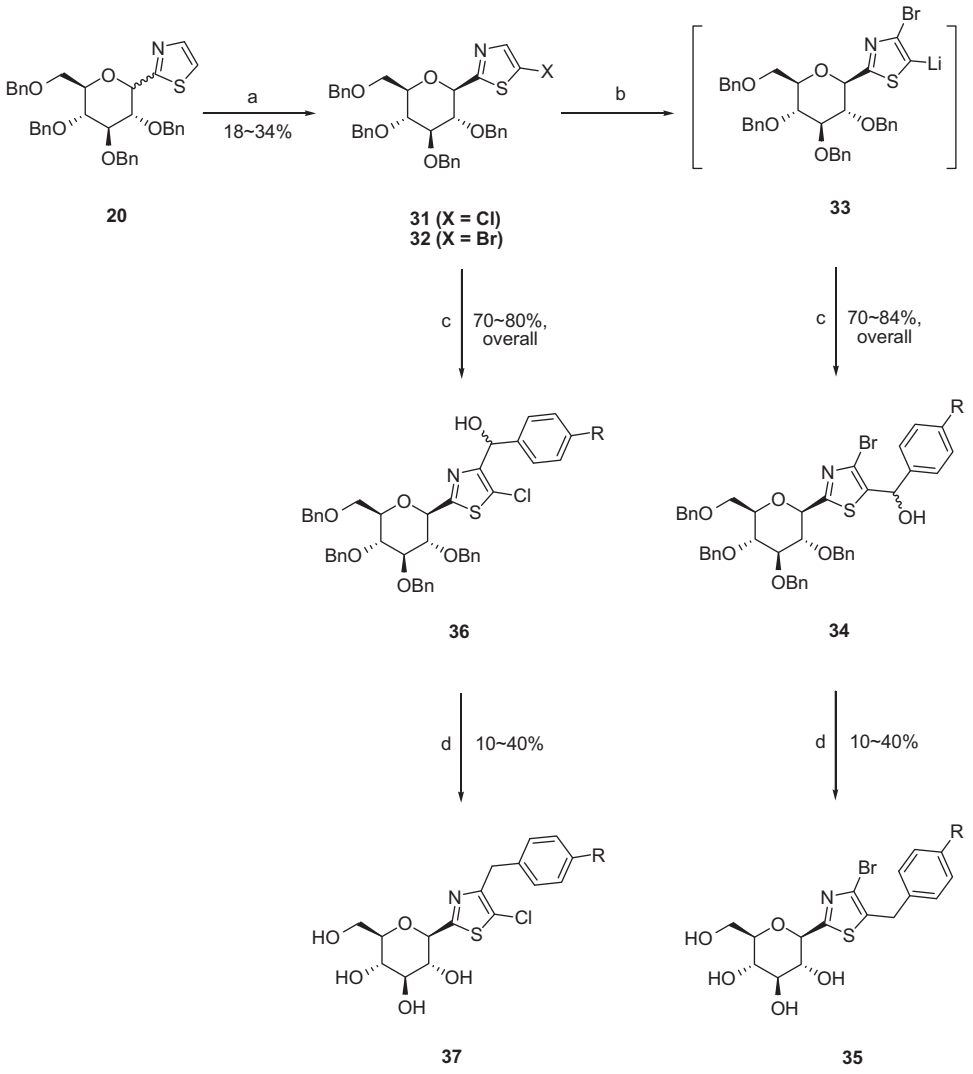
3. Conclusion

In conclusion, we prepared novel SGLT2 inhibitors containing benzylpyridazine and benzylthiazole moieties at the proximal ring. Pyridazinyl functional group was installed smoothly from γ-ketoester **14**, which was prepared from β-*C*-vinyl glucoside **7**. Thiazole group was linked to *C*-glucoside using 2-lithiated thiazole, and halogen atoms were introduced at either 4-position or 5-position of thiazole ring. The analogs thus prepared were subjected to biological evaluation involving *h*SGLT2 inhibition assay. While dapagliflozin (**2**) shows highly potent inhibitory activity against *h*SGLT2, it was discovered that neither pyridazinyl nor thiazolyl analogs improved *h*SGLT2 inhibition probably due to unfavorable electronic environments around proximal ring of the current compounds.

4. Experimental

4.1. General

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centrigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are of the highest available purity unless otherwise indicated. ^{1}H NMR spectra were recorded on either a Jeol ECX-400, or a Jeol JNM-LA300 spectrometer. Chemical shifts were expressed in parts per million (ppm, units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Mass spectra were obtained with either a Micromass, Quattro LC Triple Quadruple Tandem Mass



Scheme 5. Reagents and conditions: (a) *n*-BuLi, CCl_4 or CBr_4, THF, −78 °C to −10 °C; (b) LDA, THF, −78 °C; (c) *p*-substituted benzaldehyde, THF, −78 °C to rt; (d) TMSI (neat), 50 °C.

Spectometer, ESI or Agilent, 1100LC/MSD, ESI. For preparative HPLC, ca. 100 mg of a product was injected in 1 mL of DMSO onto a SunFire™ Prep C18 OBD 5 μm 19 × 100 mm column with a gradient from 10% acetonitrile to 90% acetonitrile in water. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh) or Biotage system equipped with a silica pre-packed cartridge. Most of the reactions were monitored by thin-layer chromatography on 0.25 mm Merck silica gel plates (60F-254), visualized with UV light using a 5% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution.

4.2. Synthesis of lactone 9

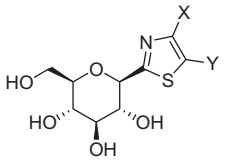
To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**8**) (1.01 g, 1.86 mmol) in dry CH_2Cl_2 (30 mL) under nitrogen atmosphere, were added 3 Å molecular sieves (1 g) and 4-methylmorpholine-*N*-oxide (0.5 g, 4.26 mmol). After stirring at room temperature for 10 min, tetra-*n*-propylammonium perruthenate (TPAP) (64 mg, 0.18 mmol) was added. After stirring for over night, the suspension was filtered through Celite and concentrated in vacuo. The residue was purified with silica gel column chromatography (EtOAc/Hx = 1:5) to give lactone **9** as an oil (954 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.16 (m, 20H), 4.98 (d, J = 11.2 Hz, 1H), 4.74–4.44 (m, 8H), 4.12 (d, J = 6.4 Hz, 1H), 3.97–3.89 (m, 2H), 3.72 (dd, J = 10.8, 2.4 Hz, 1H), 3.67 (dd, J = 10.8, 3.2 Hz, 1H).

4.3. Pyridazine analog synthesis

4.3.1. Vinyl compound 7

To a solution of lactone **9** (4.8 g, 8.9 mmol) in THF (50 mL) at −78 °C under nitrogen atmosphere was added dropwise the vinylmagnesium bromide (1.0 M in ether, 11.5 mL, 11.5 mmol). After 2.5 h of stirring at −78 °C, the reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated to give the hemiketal. To a solution of the hemiketal in anhydrous CH_2Cl_2 (50 mL) at −30 °C were added triethylsilane (4.2 mL, 26.7 mmol) and TMSOTf (1.8 mL, 8.9 mmol). The solution was stirred −30 °C for 1 h, then quenched with MeOH (5 mL) then evaporated. The residue was purified with silica gel column chromatography (EtOAc/Hx = 1:5) to afford the desired product (2.6 g, 53% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.11 (m, 20H), 6.01–5.92 (m, 1H), 5.46 (d, J = 17.2 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 4.89 (dd, J = 11.2, 19.2 Hz, 2H), 4.82 (d,

Table 1
*h*SGLT2 inhibition data for a pyridazinyl analog **3** and thiazolyl analogs **22**, **30**, **35**, and **37**



Code	X	Y	SGLT2 IC_{50}[a] (nM)
2 (dapagliflozin)	—	—	0.49[b]
3	—	—	610
22a	H	Benzyl	>10,000
22b	H	4-Methylbenzyl	4630
22c	H	4-Chlorobenzyl	>10,000
22d	H	4-*tert*-Butylbenzyl	>10,000
30a	4-Methylbenzyl	H	>10,000
30b	4-Ethylbenzyl	H	>10,000
30c	4-*n*-Propylbenzyl	H	>10,000
35a	Br	Benzyl	>10,000
35b	Br	4-Methylbenzyl	1050
35c	Br	4-Ethylbenzyl	786
35d	Br	4-*tert*-Butylbenzyl	2360
35e	Br	4-Chlorobenzyl	8640
37a	4-Methylbenzyl	Cl	257
37b	4-Ethylbenzyl	Cl	121
37c	4-*n*-Butylbenzyl	Cl	251
37d	Biphenyl-4-ylmethyl	Cl	411

[a] These data were obtained by single determinations.
[b] The IC_{50} value of **2** was obtained by in-house assay.

J = 10.8 Hz, 1H), 4.74 (d, *J* = 10.4 Hz, 1H), 4.68–4.51 (m, 4H), 3.80–3.63 (m, 5H), 3.50–3.46 (m, 1H), 3.34 (t, *J* = 8.8 Hz, 1H).

4.3.2. Epoxide 10

*m*CPBA (1.8 g, 6.1 mmol) was added to vinyl compound **7** (2.25 g, 4 mmol) dissolved in CH_2Cl_2 (40 mL) at 0 °C and then stirred at room temperature for 1 day. After reaction complete, the mixture was quenched with 1 N NaOH (20 mL), work-up with Et_2O, and evaporated in vacuo. The residue was purified with silica gel column (EtOAc/Hx = 1:5) to give desired product (2.05 g, 88% yield) with about 2:1 ratio inseparable diastereoisomer mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 18H), 7.17–7.15 (m, 1H), 4.91–4.86 (m, 3H), 4.84–4.79 (m, 1H), 4.76–4.69 (m, 1H), 4.63–4.50 (m, 4H), 3.75–3.33 (m, 8H), 3.17–3.14 (m, 3H), 2.88–2.66 (m, 3H). M+Na 589.2.

4.3.3. 2-Carboxylated butyrolactone 6

To a solution of epoxide **10** (500 mg, 0.88 mmol) in ethanol (20 mL) was added diethyl malonate (212 mg, 1.32 mmol) and sodium ethoxide (21% wt in EtOH, 430 mg,, 1.32 mmol). The reaction mixture was stirred for overnight, and then it was quenched with saturated aqueous NH_4Cl solution. The organic layer was extracted with ether, dried with $MgSO_4$, and evaporated. The residue was purified with silica gel column chromatography (EtOA/Hx = 1:4) to afford desired product (505 mg, 84%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.19 (m, 20H), 4.96–4.84 (m, 4H), 4.80–4.59 (m, 3H), 4.52–4.48 (m, 4H), 4.30–4.22 (m, 2H), 3.85–3.50 (m, 10), 1.34–1.16 (m, 4H). MH^+ 681.31.

4.3.4. 2-(*p*-Methoxybenzyl)-2-carboylated lactone 12

To a solution of 2-carboxylated butyrolactone **6** (1 g, 1.47 mmol) in THF (25 mL) was added NaH (88 mg, 60% in mineral oil, 2.2 mmol) and *p*-methoxybenzyl bromide (0.5 mL, 2.2 mmol). After stirring 3 h at room temperature, the resulting solution was quenched with satd aqueous NH_4Cl. Organic layer was extracted with ether, dried with $MgSO_4$, evaporated the volatile solvent under reduced pressure. The residue was purified shortly to give crude benzylated lactone **11** which was used for the next step without further purification.

NaCl (5 g, 30 mmol) was added to lactone **11** dissolved in DMSO (10 mL) at room temperature and then it was refluxed for 1 day. After reaction completes, the resulting solution was cooled down to room temperature. Water and ether were added and organic layer was extracted with ether. After evaporated the volatile solvent, the residue was purified with silica gel column chromatography (EtOAc/Hx = 1:3) to afford desire product (960 mg, 88% from compound **12**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.18 (m, 22H), 7.11–7.04 (m, 2H), 4.95–4.74 (m, 5H), 4.70–4.01 (m, 4H), 3.83 (s, 3H), 3.75–3.33 (m, 8H), 3.17–3.14 (m, 3H), 2.88–2.66 (m, 3H), 1.93–1.84 (m, 2H). MH^+ 729.

4.3.5. Pyridazinone 15

To a solution of dihydropyridazinone **5** (420 mg, 0.57 mmol) in acetic acid (10 mL) was added bromine (0.5 mL) dropwise. The reaction mixture was stirred at 80 °C overnight. After reaction completes, water (10 mL) was added and then the organic layer was extracted with CH_2Cl_2, dried with $MgSO_4$. The volatile solvent was evaporated under reduced pressure, and the residue was purified with silica gel column (EtOAc/Hx = 1:1) to give the desired product (314 mg, 75% yield) as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.22 (m, 17H), 7.22–7.18 (m, 4H), 7.05 (d, *J* = 9.1 Hz, 1H), 6.92 (dd, *J* = 1.4, 7.1 Hz, 2H), 6.78 (d, *J* = 9.1 Hz, 1H), 6.42 (br s, 1H), 4.87 (s, 2H), 4.85 (d, *J* = 10.2 Hz, 1H), 4.66 (d, *J* = 10.2 Hz, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 10.2 Hz, 2H), 4.28 (d, *J* = 12.3 Hz, 2H), 4.18 (d, *J* = 9.3 Hz, 1H), 4.11 (s, 3H), 3.86 (d, *J* = 10.4 Hz, 1H), 3.82–3.74 (m, 4H), 3.57–3.53 (m, 1H), 3.42 (dt, *J* = 1.2, 9.2 Hz, 1H).

4.3.6. Pyridazine 16

To a solution of pyridazinone **15** (314 mg, 0.42 mmol) in toluene (20 mL) was added $POCl_3$ (5 mL) slowly at 0 °C. The reaction temperature was raised up to 100 °C and stirred for 3 h. The reaction mixture was cooled down to room temperature. After quenching with water carefully, the resulting solution was extracted with CH_2Cl_2. The residue after evaporation was purified with silica gel column chromatography (EtOAc/Hx = 1:3) to afford the title product **16** (270 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 17H), 7.20–7.17 (m, 4H), 7.04 (d, *J* = 9.2 Hz, 1H), 6.89 (dd, *J* = 1.6, 7.2 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 1H), 4.89 (s, 2H), 4.85 (d, *J* = 10.4 Hz, 1H), 4.62 (d, *J* = 10.8 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 10.4 Hz, 2H), 4.32 (d, *J* = 15.6 Hz, 2H), 4.17 (d, *J* = 9.6 Hz, 1H), 4.08 (s, 3H), 3.84 (d, *J* = 10.8 Hz, 1H), 3.79–3.71 (m, 4H), 3.58–3.55 (m, 1H), 3.43 (t, *J* = 9.2 Hz, 1H).

4.3.7. Deprotection of benzyl group of pyridazine 16

TMSI (5 mL) wad added to protected pyridazine (270 mg, 0.36 mmol) in CH_3CN (20 mL) at 0 °C, and reaction temperature was raised to room temperature. The reaction mixture was stirred for 20 h at room temperature. The resulting solution was quenched with MeOH (5 mL) and the volatile solvent was evaporated under reduced pressure. The residue was purified with silica gel column (5% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to produce the desired compound **3** (59 mg, 42%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.31 (m, 4H), 7.05 (d, *J* = 8.8 Hz, 1H), 4.33 (s, 2H), 4.10 (d, *J* = 9.6 Hz, 1H), 4.03 (s, 3H), 3.85 (dd, *J* = 2.4, 12.4 Hz, 1H), 3.64 (dd, *J* = 4.8, 12.0 Hz, 1H), 3.48–3.26 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.48, 157.0, 139.1, 135.2, 133.1, 130.8, 130.4, 128.9, 127.8, 118.3, 81.3, 80.7, 78.2, 75.1, 70.4, 51.6, 53.8, 34.0.

4.3.8. Acetylated compound 17

To a solution of **3** (20 mg, 0.05 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (2 mL) and Ac_2O (1 mL) with a catalytic amount of

DMAP. The reaction mixture was stirred for 1 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The organic layer was collected with EtOAc, dried with $MgSO_4$, and evaporated under reduced pressure. The residue was purified with silica gel (EtOAc/Hx = 2:1) to afford the acetylated compound **17** (22 mg, 78%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 2.0, 8.4 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 9.2 Hz, 1H), 5.30 (t, J = 9.2 Hz, 1H), 5.19 (t, J = 9.6 Hz, 1H), 5.05 (t, J = 9.6 Hz, 1H), 4.42–4.32 (m, 3H), 4.26 (dd, J = 4.8, 12.4 Hz, 1H), 4.14 (dd, J = 2.4, 12.4 Hz, 1H), 4.11 (s, 3H), 3.83–3.78 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.77 (s, 3H).

4.4. Thiazole analog synthesis

4.4.1. (3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(thiazol-2-yl)tetrahydro-2H-pyran-2-ol (18)

To a solution of *n*-BuLi (14.5 mL, 2.5 M in hexane) in anhydrous ether (51 mL) was added dropwise (over a 30-min period) a solution of 2-bromothiazole (5.4 g, 32.9 mmol) in THF (15 mL) at −78 °C. After stirring at −78 °C for 20 min, a solution of lactone **9** (15 g, 27.8 mmol) in THF (51 mL) was added slowly (over a 25-min period) to the mixture. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was poured into a 1 M phosphate buffer solution (300 mL, pH 7.4) and extracted with DCM (300 mL). The DCM extract was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage™) to provide the title compound **18** (14.4 g, 23.0 mmol, 83%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 3.6 Hz, 1H), 7.34–7.24 (m, 14H), 7.21–7.18 (m, 4H), 7.00–6.98 (m, 2H), 4.90–4.85 (m, 3H), 4.64–4.51 (m, 4H), 4.18 (d, J = 10.4 Hz, 2H), 4.10–3.80 (m, 2H), 3.89–3.80 (m, 2H), 3.2 (d, J = 12.0 Hz, 1H).

4.4.2. (3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(thiazol-2-yl)tetrahydro-2H-pyran-2-yl acetate (19)

To a solution of **18** (14.4 g, 23.0 mmol) in DCM (43 mL) was added TEA (27.5 mL) and Ac_2O (27.5 mL) at room temperature. After an additional stirring for 16 h, the mixture was evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage™) to provide the title compound **19** (14.6 g, 21.9 mmol, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 3.6 Hz, 1H), 7.41–7.18 (m, 21H), 4.95–4.85 (m, 3H), 4.74–4.59 (m, 3H), 4.41 (d, J = 10.4 Hz, 1H), 4.15–4.09 (m, 2H), 3.96–3.80 (m, 4H), 3.59 (d, J = 9.6 Hz, 1H), 2.21 (s, 3H). MH^+ 666.

4.4.3. 2-((3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)thiazole (20)

To a stirred mixture of **19** (14.6 g, 21.9 mmol) and activated 4 Å powdered molecular sieve (14.6 g) in anhydrous DCM (68 mL) was added dropwise (over a 20-min period) triethylsilane (36.4 mL, 43.0 mmol) at 0 °C. After stirring at room temperature for additional 30 min, a BF_3 etherate solution (7.7 mL) was added dropwise to the mixture. The reaction mixture was stirred at room temperature for 4 h and then neutralized with TEA (6–7 mL). The resulting mixture was filtered through Celite, and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage™) to provide the title compound **20** (9.72 g, 16.0 mmol, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, J = 3.2 Hz, 1H), 7.39–7.17 (m, 19H), 7.13–7.11 (m, 1H), 7.02–7.01 (m, 1H), 5.30–4.45 (m, 7H; doublet signal of α-anomeric proton was detected at 5.29 with J = 6.0 Hz, 0.5H), 4.32–3.94 (m, 2H), 3.83–3.64 (m, 6H). MH^+ 608.

4.4.4. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-(5-(4-methylbenzyl)thiazol-2-yl)tetrahydro-2H-pyran-3,4,5-triol (22b)

To a solution of **20** (608 mg, 1 mmol) in anhydrous THF (5–6 mL) under nitrogen atmosphere was added dropwise *n*-BuLi (0.72 mL of a 2.5 M solution in hexane, 1.8 mmol) at −78 °C. After an additional stirring 15 min at −78 °C, a solution of *p*-tolualdehyde (192 mg, 1.6 mmol) in THF (1 mL) was added dropwise. After an additional 1 h stirring at −78 °C, the reaction mixture was allowed to warm to room temperature for 3 h, and then poured into the saturated aqueous NH_4Cl solution (50 mL). The resulting mixture was extracted with ethyl acetate (50 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage) to provide the intermediate **21b**, (434 mg, 0.60 mmol, 60%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–5.56 (m, 1H), 7.36–7.24 (m, 16H), 7.20–7.15 (m, 6H), 7.02–6.99 (2H), 6.06–6.02 (m, 1H), 4.94–4.81 (m, 2H), 4.75–4.66 (m, 1H), 4.61–4.50 (m, 5H), 4.36–3.95 (m, 3H), 3.87–3.60 (m, 4H), 2.36 (s, 3H). MH^+ 728.

The mixture of **21b** (268 mg, 0.37 mmol) and TMSI (4 mL) was heated at 50 °C for 15 h. The reaction mixture was quenched by a slow addition of MeOH, and evaporated under vacuum. The residue was dissolved in MeOH (3–4 mL) and further purified by prep HPLC (C18 column) to provide the title compound **22** (30 mg, 0.085 mmol, 14%). ^1H NMR (400 MHz, CD_3OD_3) δ 7.47 (s, 1H), 7.10 (d, J = 1.2 Hz, 4H), 4.41 (d, J = 8.8 Hz, 1H), 4.10 (s, 2H), 3.84 (d, J = 14.8 Hz, 1H), 3.66–3.63 (m, 1H), 3.45–3.32 (m, 4H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD_3) δ 168.14, 140.73, 138.27, 136.55, 136.13, 128.92, 128.03, 81.03,78.50, 77.84, 74.44, 69.95, 61.50, 31.95, 19.64. MH^+ 352.

4.4.5. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Benzylthiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (22a)

The procedure described for the synthesis of **22b** was applied to **20** and benzaldehyde instead of *p*-tolualdehyde providing the title compound **22a**. ^1H NMR (400 MHz, CD_3OD_3) δ 7.49 (s, 1H), 7.30–7.18 (m, 5H), 4.42 (d, J = 9.2 Hz, 1H), 4.16 (s, 2H), 3.84 (dd, J = 12.0, 2.0 Hz, 1H), 3.64 (dd, J = 12.0, 5.2 Hz, 1H), 3.47–3.32 (m, 4H). MH^+ 338.

4.4.6. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-(4-Chlorobenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (22c)

The procedure described for the synthesis of **22b** was applied to **20** and *p*-chlorobenzaldehyde instead of *p*-tolualdehyde providing the title compound **22c**. ^1H NMR (400 MHz, CD_3OD_3) δ 7.51 (s, 1H), 7.30–7.22 (m, 4H), 4.42 (d, J = 8.8 Hz, 1H), 4.16 (s, 2H), 3.84 (dd, J = 12.0, 2.0 Hz, 1H), 3.64 (dd, J = 12.0, 5.6 Hz, 1H), 3.47–3.32 (m, 4H). MH^+ 372.

4.4.7. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-(4-*tert*-Butylbenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (22d)

The procedure described for the synthesis of **22b** was applied to **20** and *p*-*tert*-butylbenzaldehyde instead of *p*-tolualdehyde providing the title compound **22d**. ^1H NMR (400 MHz, CD_3OD_3) δ 7.49 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 4.41 (d, J = 9.2 Hz, 1H), 4.11 (s, 2H), 3.84 (dd, J = 12.0, 2.0 Hz, 1H), 3.64 (dd, J = 12.0, 5.6 Hz, 1H), 3.44–3.34 (m, 4H), 1.28 (s, 9H). MH^+ 394.

4.4.8. (3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(4-((triisopropylsilyloxy)methyl)thiazol-2-yl)tetrahydro-2H-pyran-2-ol (24)

To a solution of *n*-BuLi (3.39 mL, 2.5 M in hexane) in anhydrous ether (11.9 mL) was added dropwise (over a 30-min period) a solution of 2-bromo-4-((triisopropylsilyloxy)methyl)thiazole **23** (2.7 g, 7.7 mmol) in THF (7.0 mL) at −40 °C. After stirring at −40 °C for 20 min, a solution of lactone **9** (3.5 g, 6.5 mmol) in THF (11.9 mL) was added slowly (over a 25-min period) to the mixture. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The mixture was poured into a 1 M phosphate buffer solution (100 mL, pH 7.4) and extracted with DCM (150 mL). The DCM extract was dried over $MgSO_4$ and evaporated under vacuum.

The residue was further purified by silica column chromatography (Biotage) to provide the title compound **24** (3.95 g, 4.88 mmol, 75%). MH^+ 810.

4.4.9. (3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(4-((triisopropylsilyloxy)methyl)thiazol-2-yl)tetrahydro-2H-pyran-2-yl acetate (25)

To a solution of **24** (3.95 g, 4.88 mmol) in DCM (4.9 mL) was added TEA (5.8 mL) and Ac_2O (5.8 mL) at room temperature. After an additional stirring for 16 h, the mixture was evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage) to provide the title compound **25** (3.80 g, 4.45 mmol, 91%). MNa^+ 874.

4.4.10. 4-((Triisopropylsilyloxy)methyl)-2-((3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl) tetrahydro-2H-pyran-2-yl)thiazole (26)

To a stirred mixture of **25** (3.80 g, 4.45 mmol) and activated 4 Å powdered molecular sieve (3.8 g) in anhydrous DCM (17 mL) was added dropwise (over a 20-min period) triethylsilane (7.32 mL, 8.65 mmol) at 0 °C. After stirring at room temperature for additional 30 min, a BF_3 etherate solution (1.55 mL) was added dropwise to the mixture. The reaction mixture was stirred at room temperature for 4 h and then neutralized with TEA (2–3 mL). The resulting mixture was filtered through Celite, and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage) to provide the title compound **26** (2.88 g, 3.63 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 17H), 7.21–7.13 (m, 3H), 7.03–7.01 (m, 1H), 5.28–4.45 (m, 9H; doublet signal of α-anomeric proton was detected at 5.28 with J = 5.6 Hz, 0.5H), 4.25–3.99 (m, 2H), 3.84–3.63 (m, 6H), 1.23–1.13 (m, 3H), 1.10–1.08 (m, 18H). MH^+ 794.

4.4.11. (2-((3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)thiazol-4-yl)methanol (27)

To a solution of **26** (2.88 g, 3.63 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere was added dropwise TBAF (9.1 mL of a 1 solution in THF, 9.1 mmol) at 0 °C. After an additional stirring 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature for 2 h, and then poured into water (100 mL). The resulting mixture was extracted with ethyl acetate (150 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage) to provide the intermediate **27** (1.97 g, 3.08 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (m, 17H), 7.22–7.11 (m, 3H), 7.04–7.02 (m, 1H), 5.29–4.47 (m, 9H; doublet signal of α-anomeric proton was detected at 5.28 with J = 5.6 Hz, 0.5H), 4.21–4.00 (m, 2H), 3.84–3.63 (m, 6H). MH^+ 638.

4.4.12. 2-((3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)thiazole-4-carbaldehyde (28)

To a solution of **27** (1.96 g, 3.07 mmol) in DCM (45 mL) was added DMP (1.56 g, 3.7 mmol) at RT for 16 h. The reaction mixture was quenched with 1 M $Na_2S_2O_3$ solution (100 mL). The resulting mixture was extracted with DCM (2× 100 mL), and successively washed with saturated aqueous $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage) to provide the title compound **28** (1.57 g, 2.47 mmol, 80%). MH^+ 636.

4.4.13. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-(4-(4-methylbenzyl)thiazol-2-yl)tetrahydro-2H-pyran-3,4,5-triol (30a)

To a solution of **28** (380 mg, 0.60 mmol) in anhydrous THF (2 mL) under nitrogen atmosphere was added dropwise a solution of *p*-toluylmagnesium bromide (2.38 mL, 1.19 mmol, 0.5 M in THF) at 0 °C. After an additional stirring 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature for 5 h, and then quenched with a saturated aqueous NH_4Cl solution (15 mL). The resulting mixture was extracted with ethyl acetate (30 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage) to provide the intermediate **29a** (324 mg, 0.45 mmol, 74%). MH^+ 728.

The mixture of **29a** (324 mg, 0.45 mmol) and TMSI (4.5 mL) was heated at 50 °C for 24 h. The reaction mixture was quenched by a slow addition of MeOH, and evaporated under vacuum. The residue was dissolved in MeOH (4–5 mL) and further purified by prep HPLC (C18 column) to provide the title compound **30a** (59 mg, 0.17 mmol, 37%). ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.11–7.06 (m, 4H), 7.03 (s, 1H), 4.50–4.45 (m, 1H), 4.04 (s, 2H), 3.86 (d, J = 12.4 Hz, 1H), 3.69–3.65 (m, 1H), 3.50–3.35 (m, 4H), 2.27 (s, 3H). MH^+ 352.

4.4.14. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-(4-Ethylbenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (30b)

The procedure described for the synthesis of **30a** was applied to **28** and 4-ethylphenylmagnesium bromide instead of *p*-toluylmagnesium bromide providing the title compound **30b**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.14–7.09 (m, 4H), 7.04 (s, 1H), 4.49–4.46 (m, 1H), 4.05 (s, 2H), 3.86 (d, J = 12.4 Hz, 1H), 3.69–3.65 (m, 1H), 3.50–3.37 (m, 4H), 2.58 (q, J = 7.6 Hz, 2H), 1.18 (t, J = 7.6 Hz, 3H). MH^+ 366.

4.4.15. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-(4-(4-propylbenzyl)thiazol-2-yl)tetrahydro-2H-pyran-3,4,5-triol (30c)

The procedure described for the synthesis of **30a** was applied to **28** and 4-propylphenylmagnesium bromide instead of *p*-toluylmagnesium bromide providing the title compound **30c**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.14–7.07 (m, 4H), 7.04 (s, 1H), 4.49–4.46 (m, 1H), 4.05 (s, 2H), 3.86 (d, J = 10.0 Hz, 1H), 3.69–3.65 (m, 1H), 3.49–3.36 (m, 4H), 2.53 (t, J = 7.6 Hz, 2H), 1.64–1.55 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H). MH^+ 380.

4.4.16. 5-Chloro-2-((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)thiazole (31)

To a solution of **20** (4 g, 6.58 mmol) in anhydrous THF (45 mL) was added dropwise *n*-BuLi (5.8 mL, 14.5 mmol, 2.5 M in hexane) at −78 °C. After stirring for 20 min at −78 °C, a solution of carbon tetrachloride (1.90 mL, 19.7 mmol) in anhydrous THF (5 mL) was added dropwise over 5 min. The reaction mixture was allowed to warm to −10 °C over a 4-h period, and then quenched with a saturated aqueous NH_4Cl solution (100 mL). The resulting mixture was extracted with ethyl acetate (150 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by silica column chromatography (Biotage) to provide the title compound **31** (0.78 g, 1.21 mmol, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.37–7.23 (m, 16H), 7.20–7.16 (m, 2H), 7.09–7.06 (m, 2H), 4.94–4.83 (m, 3H), 4.64–4.52 (m, 5H), 4.31 (d, J = 10.8 Hz, 1H), 3.83–3.60 (m, 6H). MH^+ 642.

4.4.17. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-Chloro-5-(4-methylbenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (37a)

To a solution of **31** (385 mg, 0.60 mmol) in anhydrous THF (4 mL) under nitrogen atmosphere was added dropwise a solution of LDA (1.43 mL, 2.57 mmol, 1.8 M in heptane/THF/ethylbenzene, Aldrich 494585) at −78 °C. After an additional stirring 30 min at −78 °C, *p*-tolualdehyde (0.43 mL, 3.6 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature for 3 h, and then quenched with 1 M HCl (15 mL). The resulting mixture was extracted with ethyl acetate (30 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The

residue was further purified by silica column chromatography (Biotage) to provide the title compound **36a** (382 mg, 0.50 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 18H), 7.19–7.16 (m, 3H), 7.10–7.00 (m, 3H), 5.87 (br, 1H), 4.94–4.82 (m, 4H), 4.70–4.45 (m, 6H), 4.27–4.01 (m, 1H), 3.80–3.56 (m, 4H), 2.33 (s, 3H). MH^+ 762.

The mixture of **36a** (382 mg, 0.50 mmol) and TMSI (5 mL) was heated at 50 °C for 12 h. The reaction mixture was quenched by a slow addition of MeOH, and evaporated under vacuum. The residue was dissolved in MeOH (3–4 mL) and further purified by prep HPLC (C18 column) to provide the title compound **37a** (41 mg, 0.22 mmol, 11%). ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.07 (q, J = 6.8 Hz, 4H), 4.39 (d, J = 9.2 Hz, 1H), 4.01 (s, 2H), 3.85 (dd, J = 12.0, 2.0 Hz, 1H), 3.65 (dd, J = 12.4, 5.6 Hz, 1H), 3.44–3.32 (m, 4H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD_3) δ 166.15, 150.77, 135.68, 134.96, 128.68, 128.04, 121.83, 81.19, 78.63, 77.73, 74.38, 69.85, 61.43, 33.28, 19.61. MH^+ 386.

4.4.18. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Chloro-4-(4-ethylbenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (37b)

The procedure described for the synthesis of **37a** was applied to **31** and *p*-ethylbenzaldehyde instead of *p*-tolualdehyde providing the title compound **37b**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.09 (q, J = 8.4 Hz, 4H), 4.40 (d, J = 9.2 Hz, 1H), 4.02 (s, 2H), 3.85 (dd, J = 12.0, 2.0 Hz, 1H), 3.65 (dd, J = 12.4, 6.0 Hz, 1H), 3.47–3.32 (m, 4H), 2.56 (q, J = 7.6 Hz, 2H), 1.17 (t, J = 7.6 Hz, 3H). MH^+ 400.

4.4.19. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-(4-Butylbenzyl)-5-chlorothiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (37c)

The procedure described for the synthesis of **37a** was applied to **31** and *p*-butylbenzaldehyde instead of *p*-tolualdehyde providing the title compound **37c**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11–7.06 (m, 4H), 4.27 (d, J = 9.2 Hz, 1H), 3.94 (s, 2H), 3.85 (dd, J = 12.0, 2.0 Hz, 1H), 3.64 (d, J = 10.8 Hz, 1H), 3.37 (dd, J = 12.0, 6.0 Hz, 1H), 3.32–3.21 (m, 3H), 3.14–3.09 (m, 1H), 2.48 (t, J = 7.6 Hz, 2H), 1.51–1.43 (m, 2H), 1.29–1.20 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H). MH^+ 428.

4.4.20. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-(Biphenyl-4-ylmethyl)-5-chlorothiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (37d)

The procedure described for the synthesis of **37a** was applied to **31** and biphenyl-4-carbaldehyde instead of *p*-tolualdehyde providing the title compound **37d**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.56–7.49 (m, 4H), 7.38 (t, J = 8.0 Hz, 2H), 7.33–7.26 (m, 3H), 4.42 (d, J = 8.8 Hz, 1H), 4.11 (s, 2H), 3.86 (dd, J = 12.0, 2.0 Hz, 1H), 3.66 (dd, J = 12.0, 5.6 Hz, 1H), 3.47–3.32 (m, 4H). MH^+ 448.

4.4.21. 5-Bromo-2-((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)thiazole (32)

The procedure described for the synthesis of **31** was applied to **20** and carbon tetrabromide instead of carbon tetrachloride providing the title compound **32**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.34–7.22 (m, 16H), 7.19–7.17 (m, 2H), 7.08–7.05 (m, 2H), 4.94–4.83 (m, 3H), 4.62–4.53 (m, 5H), 4.30 (d, J = 10.8 Hz, 1H), 3.84–3.60 (m, 6H). MH^+ 688.

4.4.22. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(5-Benzyl-4-bromothiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (35a)

The procedure described for the synthesis of **37a** was applied to **32** and benzaldehyde providing the title compound **35a**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.31–7.19 (m, 5H), 4.40 (d, J = 9.2 Hz, 1H), 4.11 (s, 2H), 3.84 (dd, J = 12.0, 2.0 Hz, 1H), 3.64 (dd, J = 12.0, 5.6 Hz, 1H), 3.46–3.35 (m, 4H). MH^+ 416.

4.4.23. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-Bromo-5-(4-methylbenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (35b)

The procedure described for the synthesis of **37a** was applied to **32** and *p*-tolualdehyde providing the title compound **35b**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.11 (d, J = 6.0 Hz, 4H), 4.39 (d, J = 9.2 Hz, 1H), 4.05 (s, 2H), 3.84 (dd, J = 12.4, 2.0 Hz, 1H), 3.64 (dd, J = 12.4, 5.6 Hz, 1H), 3.45–3.32 (m, 4H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD_3) δ 167.55, 136.42, 135.54, 135.45, 129.01, 128.01, 121.95, 81.09, 78.34, 77.76, 74.27, 69.81, 61.42, 34.89, 19.64. MH^+ 432.

4.4.24. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-Bromo-5-(4-ethylbenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (35c)

The procedure described for the synthesis of **37a** was applied to **32** and *p*-ethylbenzaldehyde providing the title compound **35c**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.13 (d, J = 4.8 Hz, 4H), 4.39 (d, J = 9.2 Hz, 1H), 4.06 (s, 2H), 3.84 (dd, J = 12.4, 2.0 Hz, 1H), 3.64 (dd, J = 12.4, 5.2 Hz, 1H), 3.43–3.31 (m, 4H), 2.59 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H). MH^+ 446.

4.4.25. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-Bromo-5-(4-*tert*-butylbenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (35d)

The procedure described for the synthesis of **37a** was applied to **32** and *p*-*tert*-butylbenzaldehyde providing the title compound **35d**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.33 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 4.39 (d, J = 8.8 Hz, 1H), 4.06 (s, 2H), 3.82 (dd, J = 12.0, 2.0 Hz, 1H), 3.64 (dd, J = 12.0, 5.6 Hz, 1H), 3.43–3.34 (m, 4H), 1.28 (s, 9H). MH^+ 474.

4.4.26. (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(4-Bromo-5-(4-chlorobenzyl)thiazol-2-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (35e)

The procedure described for the synthesis of **37a** was applied to **32** and *p*-chlorobenzaldehyde providing the title compound **35e**. ^{1}H NMR (400 MHz, CD_3OD_3) δ 7.30 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.41 (d, J = 9.2 Hz, 1H), 4.11 (s, 2H), 3.84 (dd, J = 12.4, 2.0 Hz, 1H), 3.64 (dd, J = 12.4, 5.6 Hz, 1H), 3.46–3.31 (m, 4H), 2.28 (s, 3H). MH^+ 452.

4.5. Inhibitory effect on human SGLT2 activities

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

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