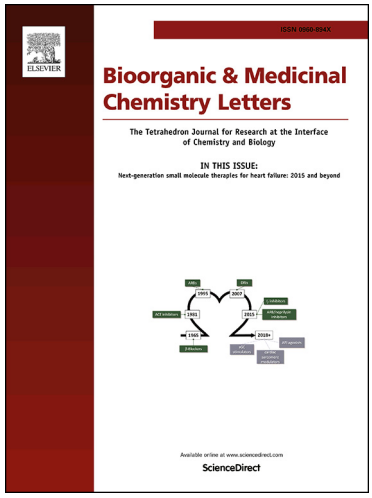
Accepted Manuscript



Discovery of a Potent, Low-Absorbable Sodium-Dependent Glucose Cotransporter 1 (SGLT1) Inhibitor (TP0438836) for the Treatment of Type 2 Diabetes

Shoichi Kuroda, Yohei Kobashi, Takahiro Oi, Hideaki Amada, Lisa Okumura-Kitajima, Fusayo Io, Koji Yamamto, Hiroyuki Kakinuma

PII: S0960-894X(18)30777-7
DOI: https://doi.org/10.1016/j.bmcl.2018.09.035
Reference: BMCL 26056

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 22 June 2018
Revised Date: 10 September 2018
Accepted Date: 27 September 2018

Please cite this article as: Kuroda, S., Kobashi, Y., Oi, T., Amada, H., Okumura-Kitajima, L., Io, F., Yamamto, K., Kakinuma, H., Discovery of a Potent, Low-Absorbable Sodium-Dependent Glucose Cotransporter 1 (SGLT1) Inhibitor (TP0438836) for the Treatment of Type 2 Diabetes, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.09.035

Discovery of a Potent, Low-Absorbable Sodium-Dependent Glucose Cotransporter 1 (SGLT1) Inhibitor (TP0438836) for the Treatment of Type 2 Diabetes

Shoichi Kuroda[a,*], Yohei Kobashi[a], Takahiro Oi[b], Hideaki Amada[c], Lisa Okumura-Kitajima[d], Fusayo Io[e], Koji Yamamto[d], Hiroyuki Kakinuma [a,*]

[a] *Chemistry Laboratories, Taisho Pharmaceutical Co., Ltd. ; 1-403 Yoshino-cho, Kita-ku, Saitama 331-9530, Japan.*

[b] *Pharmaceutical Science Laboratories, Taisho Pharmaceutical Co., Ltd. ; 1-403 Yoshino-cho, Kita-ku, Saitama 331-9530, Japan.*

[c] *Development Management, Taisho Pharmaceutical Co., Ltd, 3-24-1, Takada, Toshima-ku, Tokyo 170-8633, Japan.*

[d] *Pharmacology Laboratories, Taisho Pharmaceutical Co., Ltd. ; 1-403 Yoshino-cho, Kita-ku, Saitama 331-9530, Japan.*

[e] *Medical Affairs Group, Taisho Toyama Pharmaceutical Co., 3-25-1, Takada, Toshima-ku, Tokyo 170-8635, Japan.*

Abstract

The design and synthesis of a novel class of low-absorbable SGLT1 inhibitors are described. To achieve low absorption in the new series, we performed an optimization study based on a strategy to increase TPSA. Fortunately, the optimization of an aglycon moiety and a side chain of the distal aglycon moiety led to the identification of compound **30b** as a potent and low-absorbable SGLT1 inhibitor. Compound **30b** showed a desirable PK profile in Sprague-Dawley (SD) rats and a favorable glucose-lowering effect in diabetic rats.

The number of people with type 2 diabetes mellitus (T2DM) is increasing. The International Diabetes Federation estimates that approximately 415 million adults have diabetes, and this total is expected to rise to 642 million by 2040. T2DM can cause serious health problems such as cardiovascular disease, blindness, kidney failure and lower limb amputation. Recently, the association between sugar intake, particularly from sugar-sweetened beverages, and the risk of T2DM has been discussed.[1] In 2014, the World Health Organization (WHO) issued new recommendations to limit sugar intake. Maintaining blood glucose levels is important for the prevention of T2DM.

Sodium-dependent glucose cotransporters (SGLTs) have attracted considerable attention as a new target for T2DM. SGLT2 is expressed mostly in early renal proximal tubules and is responsible

for >90% of the renal reabsorption of filtered glucose (160-180 g/day).[2,3,4] In fact, several SGLT2 inhibitors including dapagliflozin,[5] canagliflozin,[6] empagliflozin,[7] ipragliflozin,[8] luseogliflozin[9] and tofogliflozin[10] have been approved. On the other hand, SGLT1 plays an important role in glucose absorption from the intestinal lumen into the epithelial cells of the small intestine. In fact, small intestinal SGLT1 mRNA expression and intestinal glucose uptake were increased in patients with T2DM. Therefore, creating an SGLT1 inhibitor is an attractive option for the treatment of T2DM.[11] Some glucose derivatives have been reported as SGLT1 inhibitors.[12,13,14]

We have focused on low-absorbable SGLT1 inhibitors that suppress glucose absorption in the small intestine to control blood glucose with minimal side effects. However, a systemic and orally available SGLT1 inhibitor might have an overly strong blood glucose lowering effect because of the suppression of glucose absorption from the intestine and the excretion of urinary glucose via the inhibition of SGLT1 on the distal proximal tubules in the kidney, thereby inducing hypoglycemia. Furthermore, SGLT1 is also expressed in the heart, where its function is unclear.[15,16]

We previously reported the structure-activity relationship (SAR) of *C*-phenyl 1-thio-D-glucitol derivatives with selective SGLT2 inhibitory activities.[9] We found that the SGLT2 selectivity to SGLT1 was lowered while the SGLT2 inhibition potency was maintained when R^1 of compound **1** was a hydroxyl group. Thus, we selected compound **2** as a starting core structure for a moderate SGLT1 inhibitor.

Next, low absorbability was imparted by introducing a side chain with a highly water-soluble polar functional group into R^4 of the distal aglycon moiety. Furthermore, conversion from thioglucose to glucose was performed from the viewpoint of reducing both lipophilicity and cost (Figure 1).

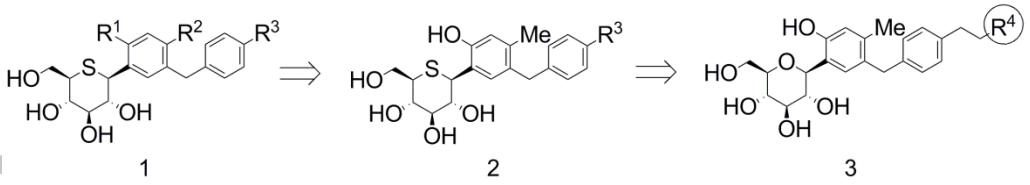


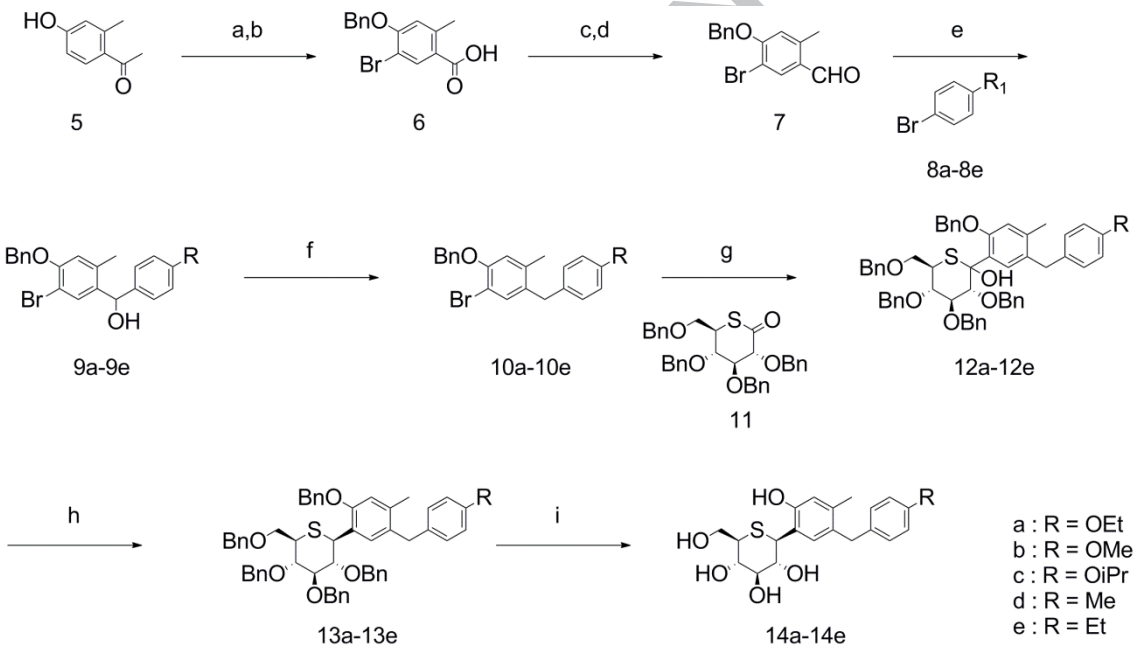
Figure 1. Strategy for creating a low-absorbable SGLT1 inhibitor.

Herein, we optimized the substituents on the aglycon moiety of **2** to improve the SGLT1 inhibition activity (Figure 1). We describe the synthesis and structure-activity relationships (SARs) of this new series of *C*-phenyl 1-thio-D-glucitol derivatives and *C*-phenyl D-glucitol derivatives, focusing on improving the SGLT1 inhibition potency and decreasing absorbability, to create a low-absorbable functional SGLT1 inhibitor.

The *C*-phenyl 1-thio-D-glucitol derivatives **4a-4c**, shown in Table 1, were synthesized as described in our previous paper.[9]

The synthesis of the *C*-phenyl 1-thio-D-glucitol derivatives **14a-14e**, also shown in Table 1, is

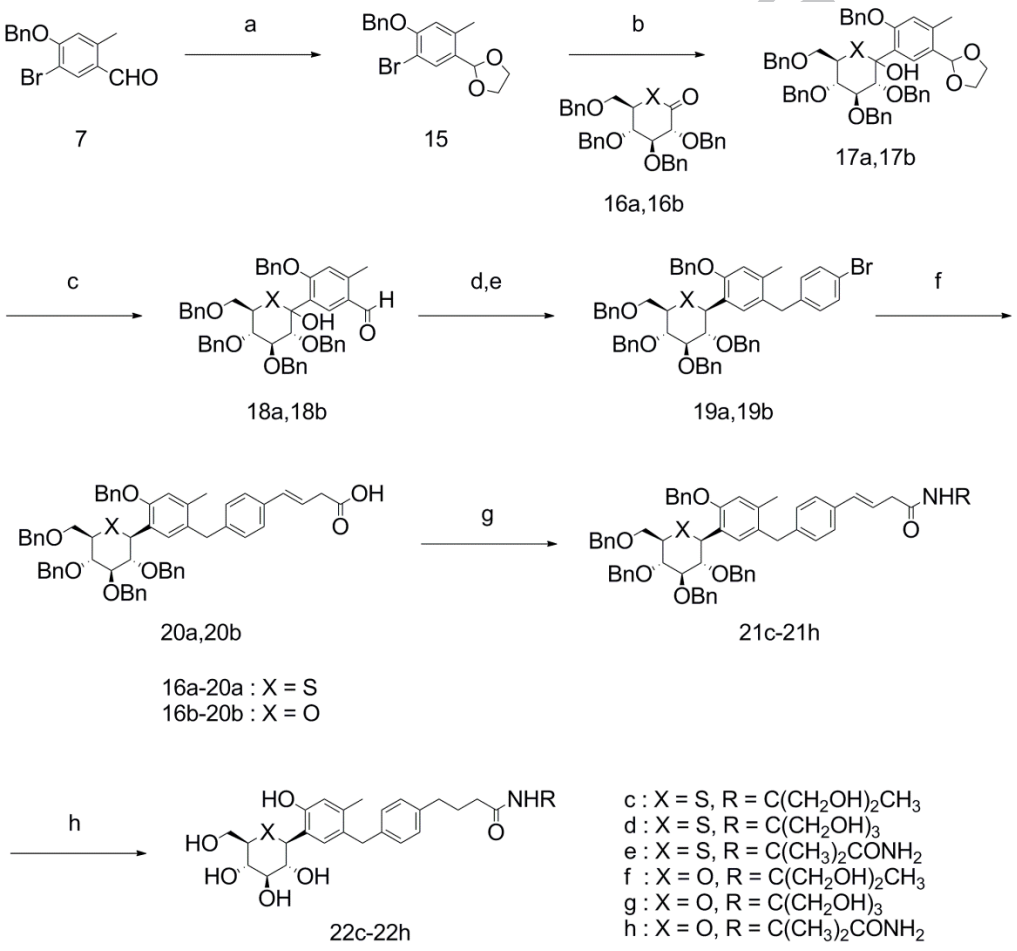
shown in Scheme 1. For the synthesis of compounds **14a-14e**, commercially available 4-hydroxy-2-methyl-acetophenone (**5**) was protected by a benzyl group using benzyl bromide and then oxidatively brominated using NaBr in the presence of OXONE® to generate **6**. The carboxyl group of **6** was converted to aldehyde via a Winreb amide reduction to yield **7**. After the halogen lithium exchange of compounds **8a-8e,** these compounds were coupled with **7**, leading to **9a-9e**. Reduction of the hydroxyl group of **9a-9e** using triethylsilane and boron trifluoride diethyletherate produced aglycon **10a-10e**. **12a-12e** were obtained by adding thiolactone **11**, synthesized as described in our previous paper, to the THF solution of Grignard reagents prepared from compounds **10a-10e** and magnesium powder. The resulting hydroxyl group of **12a-12e** was reduced *β*-stereoselectively to yield compounds **13a-13e**. Finally, the benzyl group of **13a-13e** was removed by catalytic hydrogenation with palladium hydroxide under a hydrogen atmosphere to yield **14a-14e**.



Scheme 1. (a) BnBr, K_2CO_3, TBAI, DMF, rt; (b) NaBr, OXONE®, acetone-H_2O, rt; (c) $(COCl)_2$, DMF(cat.), $CHCl_3$, rt, then *N*-methoxy-*N*-methylamine hydrochloride, Et_3N, rt ; (d) $LiAlH_4$, THF, 0˚C; (e) **8a-8e**, *n*-BuLi, THF, -78˚C, then **7**; (f) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, 0˚C; (g) Mg, THF; (h) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, -15˚C; (i) $Pd(OH)_2/H_2$, EtOH, rt.

The synthesis of the *C*-phenyl 1-thio-D-glucitol derivatives **22c-22h** is shown in Scheme 2. Compound **7** was protected by an acetal group using ethylene glycol under acidic conditions, yielding **15**. **17a** and **17b** were obtained by adding thiolactone **16a** or commercially available lactone **16b** to lithium reagents prepared from **15** and *n*-BuLi. The removal of the acetal group of **17a** and

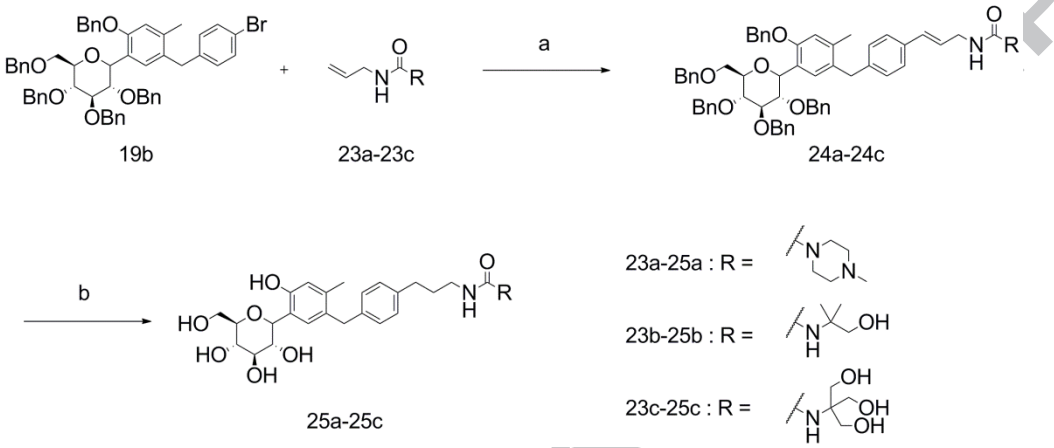
17b yielded **18a** and **18b,** respectively. 1,4-Dibromobenzene was mono-lithiated using *n*-BuLi and coupled with **18a** and **18b**, followed by the reduction of the hydroxyl group at the anomeric position to yield **19a** and **19b**, respectively. A subsequent Mizoroki-Heck reaction of **19a**, **19b** with vinylacetate under microwave irradiation yielded **20a** and **20b**, respectively. **21c-21h** were obtained by condensing **20a**, **20b** and the corresponding amines using water soluble carbodiimide hydrochloride. Finally, the benzyl group removal and double bond reduction of **21c-21h** were performed under conditions similar to those used for **13a-13e** in Scheme 1 to yield the desired products **22c-22h**.



Scheme 2. (a) *p*-TsOH, ethylene glycol, PhMe, reflux; (b) *n*-BuLi, THF, -78˚C, then **16a**,**16b**; (c) 6NHCl, THF; (d) 1,4-dibromobenzene, *n*-BuLi, THF, -78˚C, (e) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, 0˚C; (f) vinyl acetate, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, MeCN, 120˚C; (g) amine, WSCI-HCl, HOBt, $CHCl_3$, rt; (h) $Pd(OH)_2/H_2$, EtOH, rt.

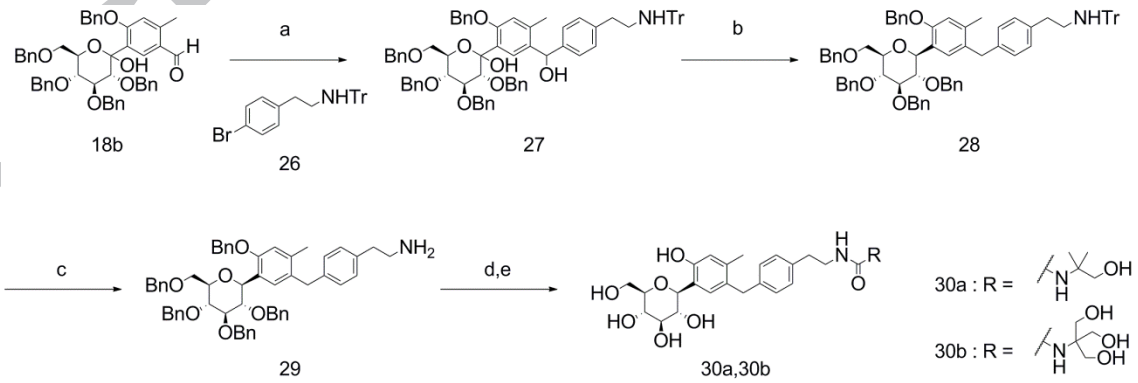
Scheme 3 shows the synthesis of compounds **25a-25c**. Mizoroki-Heck coupling of **19b** with

allyl urea derivatives **23a-23c** under heating yielded **24a-24c**. The benzyl group removal and double bond reduction of **24a-24c** were performed under conditions similar to those used for **13a-13e** in Scheme 1 to yield the desired products **25a-25c**.



Scheme 3. (a) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, MeCN, 120˚C; (b) $Pd(OH)_2/H_2$, EtOH, rt.

Scheme 4 shows the synthesis of compounds **30a** and **30b**. Compound **27** was obtained by adding **18b** to aryl lithium prepared from **26**. The hydroxyl groups of **27** were reduced at the same time to yield **28** as a *β-C*-glucoside. The trityl group removal of **28** was removed under acidic conditions to yield **29**. The preparations of **30a** and **30b** were performed by the condensation of **29** with the corresponding amines followed by the removal of the benzyl group under the same conditions as those used for **13a-13e** in Scheme 1.



Scheme 4. (a) **26**, *n*-BuLi, THF, then **18b**, -78˚C, (b) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, 0˚C; (c) TFA, r.t.; (d) *p*-nitrophenyl chloroformate, pyridine, rt; (e) $Pd(OH)_2/H_2$, MeOH, rt.

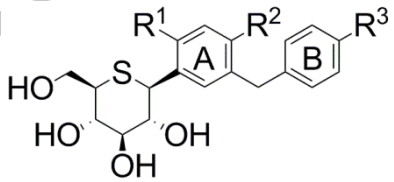
To assess the in vitro potency of SGLT1 and SGLT2 inhibition, the inhibitory activities of the compounds on SGLTs were determined using a cell-based assay in which the inhibition of the rate of glucose uptake was monitored using CHO-K1 cells expressing human SGLT1 and SGLT2.
The inhibitory activities of SGLT1 and SGLT2 together with the topological PSA (TPSA)[17] are listed in Table 1.

A number of physicochemical property-based rules for oral bioavailability were evaluated. Veber et al. proposed that a polar surface area (PSA) equal to or less than 140 Å^2 (or 12 or fewer H-bond donors and acceptors) is likely to have a high probability of good oral bioavailability in rats.[18] Tian et al. proposed that two simple parameters (PSA < 160 Å^2 and log P > -2.2) were well correlated with intestinal absorption, but not bioavailability.[19] Therefore, we designed compounds with polar functional groups focusing on TPSA and the number of H-bond donors and acceptors.

The inhibitory activities of SGLT1 and SGLT2 were significantly improved by incorporating the methyl group on R^2 **4b**, compared with our previously reported **4a**. The substitution of R^1 by hydroxyl group **4c** enhanced the SGLT1 and SGLT2 inhibition activities by several-fold, compared with **4a**. Then, we evaluated the SAR of the para position on the B ring (R^3) by preparing compounds **14a**-**14e** with substitutions of low alky and alkoxy groups on R^3. Compounds **14d** and **14e** had slightly more potent SGLT1 inhibitory activities than those of **14a** and **14b**, suggesting that a linear alkyl group had some enhancing effect on the activity. The derivative **14d** created by introducing a methyl group had an SGLT1 inhibitory activity of 25 nM and an SGLT2 inhibitory activity of 2 nM, with a TPSA value of 126 and 11 H-bond donors and acceptors. Since the physicochemical properties of **14d** were similar to those of the selective SGLT2 inhibitor luseogliflozin, **14d** was expected to exhibit good intestinal absorption. To acquire a low-absorbable compound, we performed further optimization synthesis with the aim of increasing the TPSA and the number of H-bond donors and acceptors.

Table 1

Structure-activity/TPSA relationships of *C*-phenyl 1-thio-D-glucitol derivatives



Cpd.	R^1	R^2	R^3	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	TPSA[b]
4a	H	H	OEt	26100[c]	73.6	115
4b	H	Me	OEt	671[c]	2.29	115
4c	OH	H	OEt	4040[c]	17.4	136

14a	OH	Me	OEt	162	3	136
14b	OH	Me	OMe	65	NT[d]	136
14c	OH	Me	OiPr	414	3	136
14d	OH	Me	Me	25	2	126
14e	OH	Me	Et	32[c]	2	126

[a] IC_{50} values for hSGLT1 and hSGLT2 activities represent the mean values of at least two experiments.

[b] The TPSA value was calculated using software from ACD/ Percepta, version 2015, Advanced Chemistry Development, Inc.

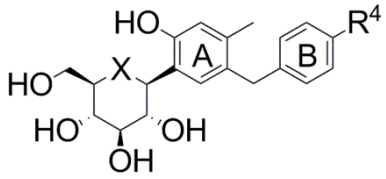
[c] 0.1 mM methyl-α-D-glucopyranoside containing [^{14}C] methyl-α-D-glucopyranoside.

[d] Not tested.

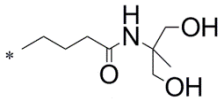
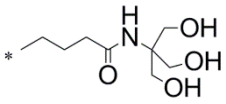
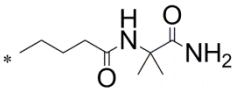
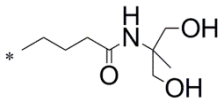
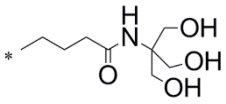
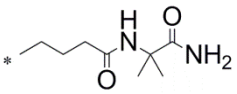
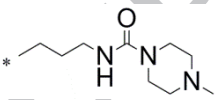
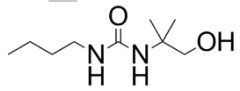
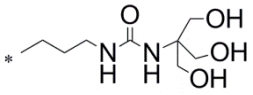
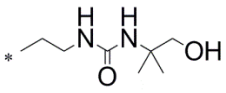
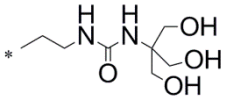
We anticipated obtaining a low absorbable compound by introducing an alkyl chain with a water-soluble functional group on R^3. Compounds **22c**, **22d** and **22e**, in which a highly water-soluble amide were introduced into a linear alkyl linker, achieved an increase in TPSA and the number of H-bond donors and acceptors while maintaining the activity (Table 2). For future mass production, we next confirmed the tolerability of a glucose structure instead of a 5-thio-glucose structure, for which intermediate **11** has a 14-step synthesis from D-glucurono-3,6-lactone. As a result, the SGLT1 inhibitory activities of amide derivatives **22f**, **22g** and **22h** were equivalent to those of **22c**, **22d** and **22e**, respectively. In addition, the urea derivatives **25b** and **25c** showed slightly weaker SGLT1 inhibitory activities. Also, **25a** with basic methylpiperazine exhibited a significantly weakened SGLT1 inhibitory activity. Next, urea derivatives **30a** and **30b**, in which one carbon chain was shortened, were obtained; these compounds had the same inhibitory activities as the amide derivatives. Compound **30b** showed strong inhibitory activities, with an SGLT1 inhibitory activity of 28 nM and an SGLT2 inhibitory activity of 7 nM, a TPSA value of 212, and 22 H-bond donors and acceptors.

Table 2

Structure-activity/TPSA relationships of R^4 on B ring



Cpd.	X	R^4	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	TPSA[b]

22c	S		22	5	196
22d	S		35	9	216
22e	S		47	4	199
22f	O		32	NT[c]	180
22g	O		35	NT[c]	200
22h	O		51	7	183
25a	O		764	5	146
25b	O		65	5	172
25c	O		175	7	212
30a	O		51	4	172
30b	O		28	7	212

[a] IC_{50} values for hSGLT1 and hSGLT2 activities represent the mean values of at least two experiments.

[b] The TPSA value was calculated using software from ACD/ Percepta, version 2015, Advanced Chemistry Development, Inc.

[c] Not tested.

Given the promising good potency and low absorbability, we evaluated the pharmacokinetic (PK) profile of compound **30b** (TP0438836) in SD rats and the membrane permeability of compound **30b** using parallel artificial membrane permeability assays (PAMPA). The resulting PK parameters and permeability of **30b** are shown in Table 3. The total clearance (CL_{total}), volume of distribution at steady state (Vd_{ss}), and elimination half-life ($t_{1/2}$) after the single intravenous administration of compound **30b** (2 mg/kg) were 1080 mL/h/kg, 439 mL/kg, and 0.362 hours, respectively. As expected, compound **30b** exhibited a low membrane permeability (0.3×10^{-6} cm/s). Also, the bioavailability of compound **30b** was very low in vivo. The maximum concentration (C_{max}) after the oral administration of compound **30b** (1 mg/kg) was 1.46 ng/mL, and the bioavailability (F) was 0.05%. These data indicated that compound **30b** had a low absorbability.

Table 3

Pharmacokinetic parameters in SD rats and permeability of **30b**

Compound	Pharmacokinetic parameters						Permeability
	IV (2 mg/kg)[a]			PO (1 mg/kg)[b]			PAMPA
	CL_{total} (mL/h/kg)	Vd_{ss} (mL/kg)	$t_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)	F (%)	at pH7.4 ($\times 10^{-6}$ cm/s)
30b	1080	439	0.362	1.46	0.25	0.05	0.3

[a] Dosing vehicle: saline

[b] Dosing vehicle: 0.5% CMC Na

The PK parameters were calculated using the mean value of the plasma concentration in three animals at each point.

Next, the glucose-lowering effect of **30b** was evaluated using an oral glucose tolerance test (oGTT) in SD rats. Compound **30b** was orally administered just prior to glucose loading, and the plasma glucose concentration was then measured over 2 h. The reductions in glucose excursion compared with vehicle administration (ΔAUC from 0 to 2 h) were 31.5%, 58.5% and 62.2% at 0.1, 0.3 and 1 mg/kg, respectively (Figure 2). Thus, the glucose-lowering effect increased in a dose-dependent manner.

Moreover, we confirmed the absence of urinary glucose excretion after repeated dosing of **30b** for 4 days at doses of 0.1 or 0.3 mg/kg twice a day, followed by subcutaneous glucose administration on day 5. However, slightly urinary glucose excretions were observed at a dose of 1

mg/kg twice a day, but the value was not significant compared with the vehicle control.

Together, these results suggest that compound **30b** exerted its hypoglycemic effect through the inhibition of SGLT1 only in the gastrointestinal tract when administered at doses of 0.1 and 0.3 mg/kg. On the other hand, administration at a dose of 1 mg/kg twice a day in the high-dose group might have resulted in some absorption of **30b**, which most likely inhibited the activity of SGLT2 in the renal tubules.

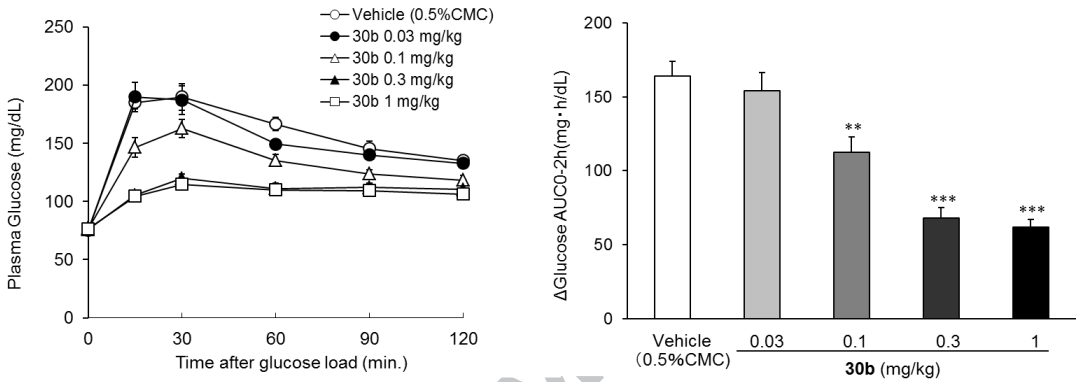


Figure 2. Effects of oral administration of **30b** (0.03, 0.1, 0.3, or 1 mg/kg) on plasma glucose during an oGTT in SD rats. Each point represents the mean ± SE. $^{**}P < 0.01$, $^{***}P < 0.001$ vs. Vehicle group, Dunnett's test.(n=8)

In summary, a new series of *C*-phenyl D-glucitol derivatives was designed, synthesized and evaluated for their SGLT1 inhibitory potency and low absorption. To achieve low absorption in this new series, we performed an optimization study based on a strategy to increase the TPSA. The optimization study led to the identification of compound **30b**, which possessed the targeted PK properties (low bioavailability) in SD rats and exhibited a glucose-lowering effect at a dose of 0.1 mg/kg (p.o.) in SD rats, suggesting its potential for the treatment of T2DM. Further optimization of **30b** aimed at improving its safety is ongoing and will be reported in due course.

Acknowledgements

The authors thank Yoshiki Fukasawa for helpful suggestions and the collection of the ADME data.

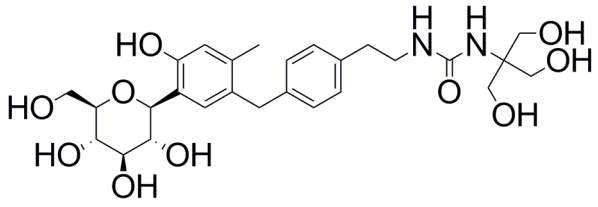
References

1. International Diabetes Federation, *IDF diabetes atlas 8th edition*, http://www.diabetesatlas.org/.
2. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. *Physiol Rev*. 2011;91:733–94.

3. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med.* 2015;66:255–70.
4. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. *Diab Vasc Dis Res.* 2015;12:78–89.
5. Meng W, Ellsworth BA, Nirschl AA, McCann PJ, Patel M, Girotra RN, Wu G, Sher PM, Morrison EP, Biller SA, Zahler R, Deshpande PP, Pullockaran A, Hagan DL, Morgan N, Taylor JR, Obermeier MT, Humphreys WG, Khanna A, Discenza L, Robertson JG, Wang A, Han S, Wetterau JR, Janovitz EB, Flint OP, Whaley JM, Washburn WN. Diabetes. Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. *J. Med. Chem.* 2008;51:1145−1149.
6. Nomura S, Sakamaki S, Hongu M, Kawanishi E, Koga Y, Sakamoto T, Yamamoto Y, Ueta K, Kimata H, Nakayama K, Tsuda-Tsukimoto M. Discovery of Canagliflozin, a Novel *C*-Glucoside with Thiophene Ring, as Sodium-Dependent Glucose Cotransporter 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus. *J. Med. Chem.* 2010;53:6355−6360.
7. Eckhardt M, Himmelsbach F, Wang X-J, Sun X, Zhang L, Tang W, Krishnamurthy D, Senanayake CH, Han Z. Processes for preparing of glucopyranosyl-substituted benzyl-benzene derivatives and intermediates therein. PCT Int. Appl. WO 2006120208, 2006.
8. Imamura M, Nakanishi K, Suzuki T, Ikegai K, Shiraki R, Ogiyama T, Murakami T, Kurosaki E, Noda A, Kobayashi Y, Yokota M, Koide T, Kosakai K, Ohkura Y, Takeuchi M, Tomiyama H, Ohta M. Discovery of ipragliflozin (ASP1941): A novel *C*-glucoside with benzothiophene structure as a potent and selective sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes mellitus. *Bioorg. Med. Chem.* 2012;20:3263−3279.
9. Kakinuma H, Oi T, Hashimoto-Tsuchiya Y, Arai M, Kawakita Y, Fukusawa Y, Iida I, Hagima N, Takeuchi H, Chino Y, Asami J, Okumura-Kitajima L, Io F, Yamamoto D, Miyata N, Takahashi T, Uchida S, Yamamoto K.
(1S)-1,5-Anhydro-1-[5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl]-1-thio-D-glucitol (TS-071) is a Potent, Selective Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for Type 2 Diabetes Treatment. *J. Med. Chem.* 2010;53:3247–3261.
10. Ohtake Y, Sato T, Kobayashi T, Nishimoto M, Taka N, Takano K, Yamamoto K, Ohmori M, Yamaguchi M, Takami K, Yeu SY, Ahn KH, Matsuoka H, Morikawa K, Suzuki M, Hagita H, Ozawa K, Yamaguchi K, Kato M, Ikeda S. Discovery of Tofogliflozin, a Novel C-Arylglucoside with an *O*-Spiroketal Ring System, as a Highly Selective Sodium Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes. *J. Med.Chem.* 2012;55:7828−7840.
11. Panai S, Onishi A, Koepsell H, Vallon V. Sodium glucose cotransporter SGLT1 as a therapeutic target in diabetes mellitus. *Expert Opin. Ther. Targets* 2016;20:1109–1125.

12. Fushimi N, Fujikura H, Shiohara H, Teranishi H, Shimizu K, Yonekubo S, Ohno K, Miyagi T, Itoh F, Shibazaki K, Tomoe M, Ishikawa-Takemura Y, Nakabayashi T, Kamada N, Ozawa T, Kobayashi S, isaji M. Structure–activity relationship studies of 4-benzyl-1H-pyrazol-3-yl *β*-D-glucopyranoside derivatives as potent and selective sodium glucose co-transporter 1 (SGLT1) inhibitors with therapeutic activity on postprandial hyperglycemia. *Bioorg. Med. Chem.* 2012;20:6598–6612.
13. Fushimi N, Teranishi H, Shimizu K, Yonekubo S, Ohno K, Miyagi T, Itoh F, Shibazaki K, Tomoe M, Ishikawa-Takemura Y, Nakabayashi T, Kamada N, Yamauchi Y, Kobayashi S, isaji M. Design, synthesis, and structure–activity relationships of a series of 4-benzyl-5-isopropyl-1H-pyrazol-3-yl *β*-D-glycopyranosides substituted with novel hydrophilic groups as highly potent inhibitors of sodium glucose co-transporter 1 (SGLT1). *Bioorg. Med. Chem.* 2013;21:748–765.
14. Goodwin NC, Ding Z, Harrison BA, Stobel ED, Harris AL, Smith M, Thompson AY, Xiong W, Mseeh F, Bruce DJ, Diaz D, Gopinathan S, Li L, O'Neill E, Thiel M, Wilson AGE, Carson KG, Powell DR, Rawlins DB. Discovery of LX2761, a Sodium-Dependent Glucose Cotransporter 1 (SGLT1) Inhibitor Restricted to the Intestinal Lumen, for the Treatment of Diabetes. *J. Med. Chem.* 2017;60:710−721.
15. Zhou L, Cryan EV, D'Andrea MR, belkowski S, Conway BR, Demarest KT. Human cardiomyocytes express high level of Na+/glucose cotransporter 1 (SGLT1). *J. Cell. Biochem.* 2003;90:339–46.
16. Banerjee SK, Mcgaffin KR, Pator-Soler NM, Ahmad F. SGLT1 is a novel cardiac glucose transporter that is perturbed in disease states. *Cardiovasc Res.* 2009;84:111–118.
17. Ertl P, Rohde B, Selzer P. Fast Calculation of Molecular Polar Surface Area as a Sum of Fragment-Based Contributions and Its Application to the Prediction of Drug Transport Properties. *J. Med. Chem*. 2000;43:3714-3717.
18. Veber DF, Johnson SR, Cheng H, Smith BR, Ward KW, Kopple KD. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem*. 2002;45:2615-2623.
19. Tian S, Li Y, Wang J, Zhang J, Hou T. ADME Evaluation in Drug Discovery. 9. Prediction of Oral Bioavailability in Humans Based on Molecular Properties and Structural Fingerprints. *Mol. Pharmaceutics*. 2011;8:841–851.

- Novel *C*-phenyl D-glucitol derivatives were evaluated as SGLT1 inhibitor.
- The low absorption compounds were chosen based on TPSA.
- Compound **30b** (TP0438836) exhibited a potential for the treatment of T2DM.



30b (TP0438836)

hSGLT1 IC_{50} = 28nM
hSGLT2 IC_{50} = 7nM
TPSA = 212