Novel Indole-N-glucoside, TA-1887 As a Sodium Glucose Cotransporter 2 Inhibitor for Treatment of Type 2 Diabetes

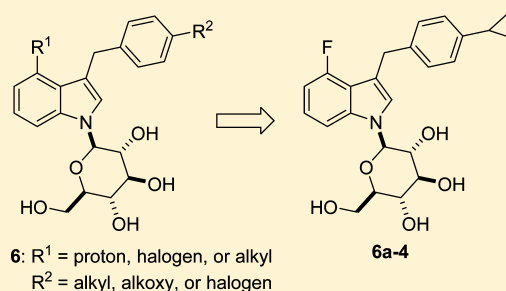Sumihiro Nomura,*,[†] Yasuo Yamamoto,[†] Yosuke Matsumura,[†] Kiyomi Ohba,[†] Shigeki Sakamaki,[†] Hirotaka Kimata,[‡] Keiko Nakayama,[‡] Chiaki Kuriyama,[‡] Yasuaki Matsushita,[‡] Kiichiro Ueta,[‡] and Minoru Tsuda-Tsukimoto[§]

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Ⓢ *Supporting Information*

ABSTRACT: Inhibition of the renal sodium glucose cotransporter (SGLT) increases urinary glucose excretion (UGE) and thus reduces blood glucose levels during hyperglycemia. To explore the potential of new antihyperglycemic agents, we synthesized and determined the human SGLT2 (hSGLT2) inhibitory potential of novel substituted 3-benzylindole-N-glucosides **6**. Optimization of **6** resulted in the discovery of 3-(4-cyclopropylbenzyl)-4-fluoroindole-N-glucoside **6a-4** (TA-1887), a highly potent and selective hSGLT2 inhibitor, with pronounced antihyperglycemic effects in high-fat diet-fed KK (HF-KK) mice. Our results suggest the potential of indole-N-glucosides as novel antihyperglycemic agents through inhibition of renal SGLT2.

6: R[1] = proton, halogen, or alkyl
R[2] = alkyl, alkoxy, or halogen

6a-4

In patients with type 2 diabetes, the goal of therapy is to strictly control blood glucose levels within the normal range. Many agents for the treatment of type 2 diabetes improve insulin secretion or insulin sensitivity; i.e., those are insulin-dependent agents. Treatment with these agents is often accompanied by the adverse events of hypoglycemia and weight gain, and the therapeutic effect was found to be attenuated along with a loss of pancreatic beta cell function in some years.[1]

Recently, the inhibition of renal glucose reabsorption has been studied as a novel method for controlling blood glucose levels in patients with type 2 diabetes. Plasma glucose filtered in the glomerulus is mainly reabsorbed by the sodium glucose cotransporter 2 (SGLT2), which is located in the early proximal tubules in the kidney.[2−4] Under hyperglycemic conditions, the reabsorption process is saturated and urinary glucose excretion (UGE) increases linearly.[5] The inhibition of renal glucose reabsorption by an SGLT2 inhibitor **1** (T-1095, Figure 1) enhances UGE and consequently lowers blood glucose levels in diabetic animal models independently of insulin-action.[6,7] Although SGLT1, which also functions to reabsorb glucose in the distal segment of the proximal tubules, is expressed in the intestine, heart, and trachea, SGLT2 is expressed exclusively in the kidney.[8] Extensive inhibition of SGLT1 could be accompanied by undesired gastrointestinal effects. Therefore, selective inhibition of SGLT2, rather than nonselective inhibition of both SGLT1 and SGLT2, would be desirable for antidiabetic agents.

Because SGLT2 inhibition lowers plasma glucose levels in an insulin-independent manner, SGLT2 inhibitors would be effective for various diabetic patients, including those with a progressive loss of beta cell function. In addition, we may not expect the occurrence of hypoglycemia, which is a major concern for current therapies with insulin and sulfonylureas and weight gain that is often observed with other classes of currently approved antihyperglycemic agents. Therefore, the identification of novel SGLT2 inhibitors has become a goal for medicinal chemistry.[9−13]

SGLT2 inhibitors, including *O*-glucosides such as **1** (T-1095)[6] and **2** (sergliflozin)[14] and *C*-glucosides such as **3** (dapagliflozin)[15] and **4** (canagliflozin)[16] have been studied in clinical trials for the treatment of type 2 diabetes (Figure 1). *C*-Glucosides appear to be metabolically more stable than *O*-glucosides. During the search for the SGLT inhibitory activity of various *N*-glucosides, we found that a novel indole-*N*-glucoside **5** (Figure 1) inhibits human SGLT2 (hSGLT2).[17] Accordingly, we report the optimization and antihyperglycemic effects of the substituted 3-benzylindole-N-glucosides **6** (Figure 1).

We describe herein the syntheses of 3-benzylindole-N-glucosides **6** according to the route outlined in Scheme 1. Indolines **7** were *N*-glucosylated with D-glucose, followed by
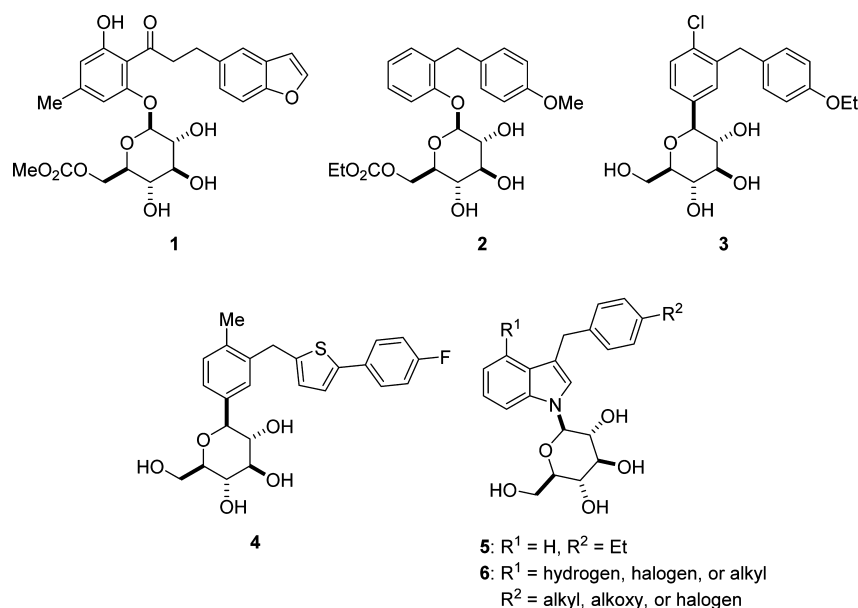
Figure 1. Structures of some *O*-, *C*-, and *N*-glucosides.

acetylation of the hydroxyl groups of the glucose moiety with acetic anhydride and pyridine to provide indoline-tetra-*O*-acetyl-*N*-glucosides **8**. The stereochemistry of **8** was determined as the *β*-configuration by the coupling constant between anomeric C−H and adjacent C−H ($J = 9.3$ Hz) in the ^{1}H NMR spectrum. Indolines **8** were oxidized by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 1,4-dioxane and water to indoles **9**.[18] Following this, Friedel−Crafts acylation of **9** with *para*-substituted benzoyl chlorides[19] and aluminum trichloride formed the corresponding 3-benzoylindole-*N*-glucosides **10**. The ketone group was sequentially reduced with sodium borohydride in the presence of cerium(III) chloride[20] and with triethylsilane and boron trifluoride diethyl etherate to convert **10** to 3-benzylindole-tetra-*O*-acetyl-*N*-glucosides **11**. Partially deacetylated **11a-1** was then acetylated with a small amount of acetic anhydride. Compounds **11** were also prepared by an alternative route. Vilsmeier formylation of **9** with *N,N*-dimethylformamide and phosphorus(III) oxychloride afforded 3-formylindoles **12**. To generate **11**, 3-formylindoles **12** were coupled with 2 equivalents of aryl magnesium bromide[21] in tetrahydrofuran at 0 °C, followed by the reduction of the resulting carbinols with triethylsilane. Finally, 3-benzylindole-*N*-glucosides **6** were obtained by the deacetylation of **11** using catalytic sodium methoxide in methanol and tetrahydrofuran.

We evaluated the effects of 3-benzylindole-*N*-glucosides **5** and **6** (Figure 1) on hSGLT2 activity and on UGE in male Sprague−Dawley (SD) rats. The structure−activity relationships (SARs) of the representative compounds are shown in Table 1. Initially, we determined the effects of R^1 substitution in R^2-ethyl derivatives **5**. The substitution of R^1 with a lower alkyl (methyl) group (**6b-1**) resulted in potent hSGLT2 inhibition, whereas substitution with a halogeno (fluoro) group (**6a-1**) increased UGE. Thus, the effect of R^2-substitution in R^1-fluoro derivatives was determined. The introduction of an alkyl (ethyl, **6a-1**) or alkoxy (ethoxy, **6a-2**) group as R^2-substituents provided higher in vitro potency than that of a halogeno (chloro, **6a-3**) group. Because the R^2-cyclopropyl derivative **6b-4** showed high potency both in vitro and in vivo, further optimization of cycloalkyl derivatives **6** was performed (Table 2). We found that the cyclopropyl derivatives **6a-4** and **6c-4**
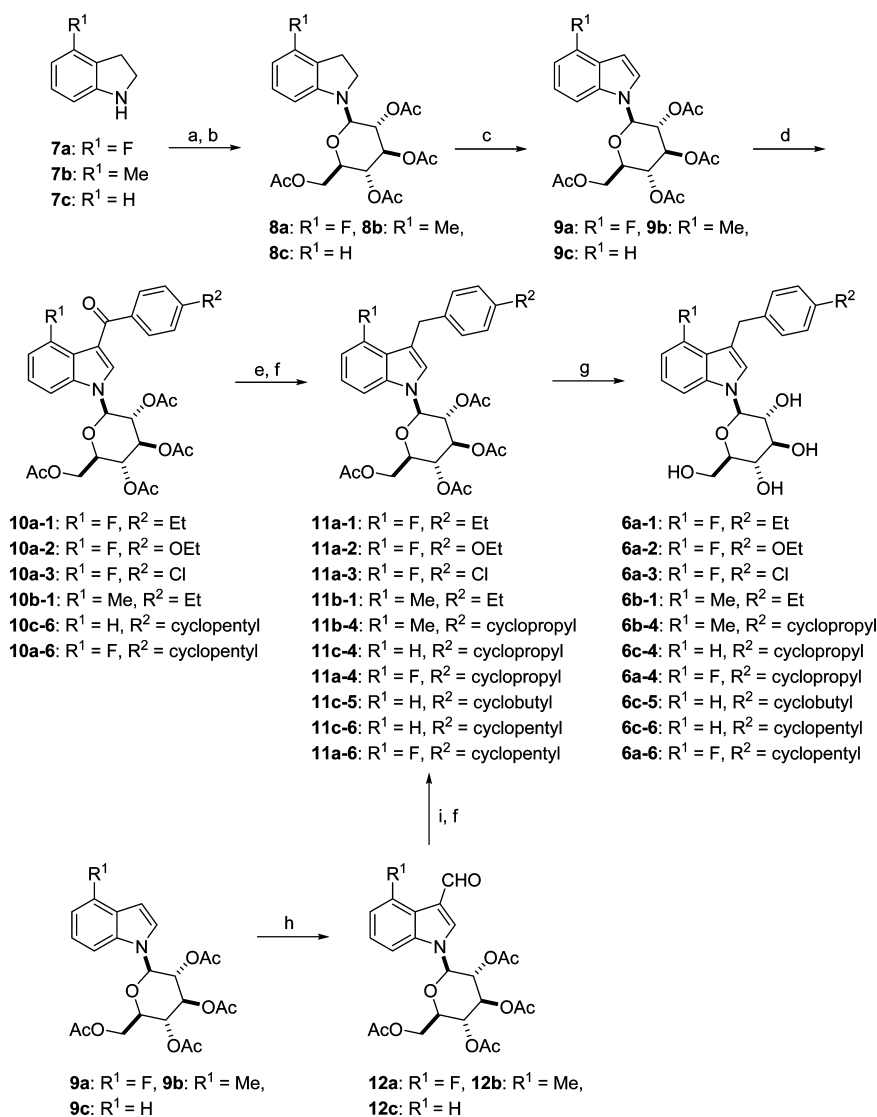
Table 1. SAR of Representative Substituted 3-Benzylindole-*N*-glucosides

compd	R^1	R^2	hSGLT2[a] IC$_{50}$ (nM)	UGE[b] (mg/200 g BW/day)
5	H	Et	7.1	1830 ± 75
6a-1	F	Et	5.2	2937 ± 106
6a-2	F	OEt	4.8	2683 ± 83
6a-3	F	Cl	18	N.D.[c]
6b-1	Me	Et	1.1	1664 ± 63
6b-4	Me	⊲	1.6	2830 ± 150

[a]Values are means of duplicate determinations ($N = 1$) unless indicated otherwise. [b]Each compound was orally administered at a dose of 30 mg/kg to male Sprague−Dawley (SD) rats. Urinary glucose excretion (UGE) data over a 24 h period were normalized per 200 g of body weight (BW). Values represent the mean ± SEM ($N = 3$). [c]N.D.: not determined.

were more potent inhibitors of hSGLT2 than the 4- and 5-membered ring derivatives **6c-5**, **6c-6**, and **6a-6**. Extensive UGE was induced by **6a-4** and **6c-4**, similar to **6b-4**. While these cycloalkyl derivatives were potent SGLT2 inhibitors, R^1-unsubstituted **6c-4** seemed to be chemically unstable, similar to R^1-unsubstituted **5** (data not shown).

Subsequently, we determined the selectivity of the highly active compounds among glucose transporters. hSGLT1 or hSGLT2 was stably expressed in Chinese hamster ovary-K (CHOK) cells, and the inhibitory effects of **6a-1**, **6a-4**, and **6b-4** were investigated on the uptake of [^{14}C]α-methyl-D-glucopyranoside (AMG).[22] The IC$_{50}$ values of **6a-1**, **6a-4**, and

Scheme 1. Synthesis of 6[a]

7a: R[1] = F
7b: R[1] = Me
7c: R[1] = H

8a: R[1] = F, **8b**: R[1] = Me,
8c: R[1] = H

9a: R[1] = F, **9b**: R[1] = Me,
9c: R[1] = H

10a-1: R[1] = F, R[2] = Et
10a-2: R[1] = F, R[2] = OEt
10a-3: R[1] = F, R[2] = Cl
10b-1: R[1] = Me, R[2] = Et
10c-6: R[1] = H, R[2] = cyclopentyl
10a-6: R[1] = F, R[2] = cyclopentyl

11a-1: R[1] = F, R[2] = Et
11a-2: R[1] = F, R[2] = OEt
11a-3: R[1] = F, R[2] = Cl
11b-1: R[1] = Me, R[2] = Et
11b-4: R[1] = Me, R[2] = cyclopropyl
11c-4: R[1] = H, R[2] = cyclopropyl
11a-4: R[1] = F, R[2] = cyclopropyl
11c-5: R[1] = H, R[2] = cyclobutyl
11c-6: R[1] = H, R[2] = cyclopentyl
11a-6: R[1] = F, R[2] = cyclopentyl

6a-1: R[1] = F, R[2] = Et
6a-2: R[1] = F, R[2] = OEt
6a-3: R[1] = F, R[2] = Cl
6b-1: R[1] = Me, R[2] = Et
6b-4: R[1] = Me, R[2] = cyclopropyl
6c-4: R[1] = H, R[2] = cyclopropyl
6a-4: R[1] = F, R[2] = cyclopropyl
6c-5: R[1] = H, R[2] = cyclobutyl
6c-6: R[1] = H, R[2] = cyclopentyl
6a-6: R[1] = F, R[2] = cyclopentyl

9a: R[1] = F, **9b**: R[1] = Me,
9c: R[1] = H

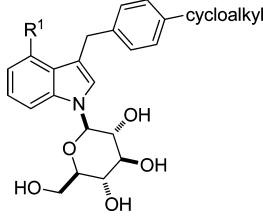**12a**: R[1] = F, **12b**: R[1] = Me,
12c: R[1] = H

[a]Reagents and conditions: (a) D-glucose, EtOH–H₂O, reflux; (b) Ac₂O, pyridine, cat DMAP, CHCl₃, rt; (c) DDQ, 1,4-dioxane–H₂O, rt; (d) ArCOCl, AlCl₃, CH₂Cl₂, 0 °C; (e) NaBH₄, CeCl₃·5H₂O, EtOH–THF, 0 °C; (f) Et₃SiH, BF₃·OEt₂, CH₃CN–CH₂Cl₂, −10 °C; (g) cat NaOMe, MeOH–THF, rt; (h) DMF, POCl₃, DCE, 70 °C; (i) ArMgBr, THF, 0 °C.

6b-4 were 210, 230, and 22 nM for hSGLT1, respectively, and 5.2, 1.4, and 1.6 nM for hSGLT2, respectively. Therefore, the ratios of IC_{50} (SGLT1)/IC_{50} (SGLT2) for **6a-1**, **6a-4**, and **6b-4** were 40.4, 164.3, and 13.8, respectively. The effect of these compounds on the facilitated glucose transporter 1 (GLUT1) was determined using the incorporation of [³H]2-deoxy-D-glucose (2-DG) in L6 myoblast cells.[23] These compounds did not inhibit GLUT1 activity at 10 μM in L6 myoblast cells. Because selective inhibition of SGLT2, rather than nonselective inhibition of both SGLT1 and SGLT2, would be desirable as described above, compound **6a-4** (TA-1887/JNJ-39933673) was selected as a clinical candidate.

Oral administration of **6a-4** at 30 mg/kg to male SD rats induced glucose excretion over a 24 h period of 2502 mg per 200 g body weight, which is comparable to UGE induced by C-glucosides.[16] Pharmacokinetic studies showed elevated plasma levels of **6a-4** following oral administration (Table 3). In male SD rats, $AUC_{0-inf,po}$, $t_{1/2}$, and oral bioavailability were 28 169 ng·h/mL, 3.9 h, and 78%, respectively. Thus, pharmacokinetic

studies demonstrated that oral dosing resulted in plasma levels of **6a-4** that were sufficient to inhibit SGLT2. C-Glucosides are metabolically more stable than O-glucosides.[16] The N-glucoside part of **6a-4** was not hydrolyzed to its aglycon in human and animal intestinal microsomes in vitro.[24] This indicates that the C–N bond of indole-N-glucosides is metabolically stable in the presence of intestinal β-glucosidase, similar to the corresponding C–C bond of C-glucosides. We suggest that **6a-4** induces extensive UGE through continuous suppression of renal glucose reuptake that is supported by excellent pharmacokinetic properties as well as high potency of SGLT2 inhibition.

Single oral administration of **6a-4** at 3 mg/kg continuously reduced blood glucose levels without influencing food intake in hyperglycemic high-fat diet-fed KK (HF-KK) mice (Figure 2). Analysis of $AUC_{0-24\,h}$ of blood glucose levels revealed a 50% reduction in **6a-4**-treated animals compared with the vehicle-treated group. Moreover, we observed a 50% reduction in blood glucose level versus vehicle at 24 h. These data indicate

Table 2. SAR of 3-(4-Cycloalkylbenzyl)indole-N-glucosides

compd	R[1]	cycloalkyl	hSGLT2[a] IC$_{50}$ (nM)	UGE[c] (mg/200 g BW/day)
6c-4	H	▷	2.2	2435 ± 150
6a-4	F	▷	1.4[b]	2502 ± 75
6c-5	H	□	11	N.D.[d]
6c-6	H	⬠	93	N.D.[d]
6a-6	F	⬠	24	N.D.[d]

[a]Values are means of duplicate determinations ($N = 1$) unless indicated otherwise. [b]$N = 3$. [c]Each compound was orally administered at a dose of 30 mg/kg to male Sprague−Dawley (SD) rats. Urinary glucose excretion (UGE) data over a 24 h period were normalized per 200 g of body weight (BW). Values represent the mean ± SEM ($N = 3$). [d]N.D.: not determined.
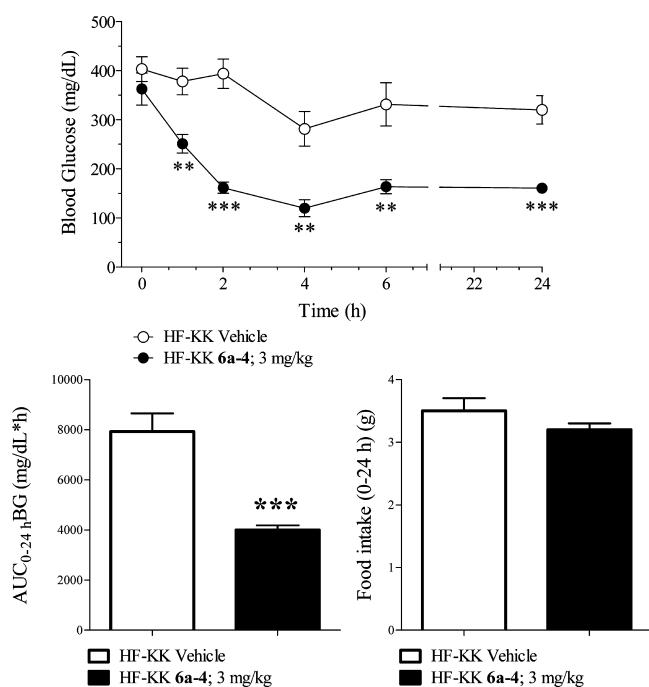

Figure 2. Effects of single oral dosing of **6a-4** on blood glucose (BG) levels and food intake in high-fat diet-fed KK (HF-KK) mice. Data are expressed as the mean ± SEM ($N = 6$): **$P < 0.01$, ***$P < 0.001$ vs vehicle.

that **6a-4** is as effective as previously reported O- and C-glucoside SGLT2 inhibitors in controlling hyperglycemia.

In summary, we have demonstrated that the SGLT2 inhibitory activity of indole-N-glucosides is comparable to

Table 3. Pharmacokinetic (PK) Parameters of 6a-4 in Male Sprague−Dawley (SD) Rats Following Intravenous and Oral Administrations

compd	6a-4	6a-4
dose (mg/kg)	3	10
route	iv	po
C_{max} (ng/mL)		2723
t_{max} (h)		1.5
AUC$_{0-inf}$ (ng·h/mL)	10893	28169
$t_{1/2}$ (h)	3.9	3.9
CL$_{tot}$ (mL/h/kg)	278	
Vd$_{ss}$ (mL/kg)	1147	
F (%)		78

those of O- and C-glucoside SGLT2 inhibitors. The optimized compound **6a-4** (TA-1887), a highly potent and selective inhibitor of hSGLT2 with favorable pharmacokinetic profiles, remarkably increases UGE. In addition, oral administration of **6a-4** induced antihyperglycemic effects in HF-KK mice. We conclude that these indole-N-glucosides have potential as a novel chemical class of SGLT2-selective inhibitors for the treatment of type 2 diabetes. Together with the recent disclosure of indole-N-xylosides,[25] N-glucosides would provide a structural diversity of new SGLT inhibitors.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Description of in vitro hSGLT1, hSGLT2, and GLUT1 assays and in vivo urinary glucose excretion and blood glucose-lowering studies; detailed synthetic procedure for **6a-1**, **6a-2**, **6a-3**, **6b-1**, **6b-4**, **6c-4**, **6a-4**, **6c-5**, **6c-6**, and **6a-6**; HPLC analysis of **6a-4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

SGLT, sodium glucose cotransporter; UGE, urinary glucose excretion; SD rat, Sprague−Dawley rat; SAR, structure−activity relationship; CHOK, Chinese hamster ovary-K; AMG, α-methyl-D-glucopyranoside; GLUT, facilitated glucose transporter; 2-DG, 2-deoxy-D-glucose; HF-KK, high-fat diet-fed KK

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