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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[1]

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We discovered that *C*-glucosides **4** bearing a heteroaromatic ring formed metabolically more stable inhibitors for sodium-dependent glucose cotransporter 2 (SGLT2) than the *O*-glucoside, **2** (T-1095). A novel thiophene derivative **4b-3** (canagliflozin) was a highly potent and selective SGLT2 inhibitor and showed pronounced anti-hyperglycemic effects in high-fat diet fed KK (HF-KK) mice.

Introduction

The incidence of type 2 diabetes mellitus (T2DM[a]) is markedly increasing in Westernized societies and some developing countries.[2−4] However, at present, no single agent is capable of achieving acceptable, long-lasting blood glucose control in the majority of patients.[5] Accordingly, there is a strong incentive to develop novel drugs with improved efficacy and safety.

Plasma glucose is filtered in the glomerulus and then reabsorbed in the proximal tubules in the kidney. Renal glucose reabsorption is mediated predominantly by SGLT2 and to a lesser extent by SGLT1.[6−8] In the normoglycemic state, all filtered glucose is transported from the tubular lumen to the blood. However, under hyperglycemic conditions, the reabsorption process is saturated and urinary glucose excretion (UGE) increases linearly.[9] An SGLT2 inhibitor, **2** (T-1095, Figure 1), enhanced UGE and consequently lowered blood glucose levels in diabetic animal models independent of insulin action.[10,11] SGLT1 is distributed in the intestine, heart and trachea besides the kidney, while SGLT2 is located solely in the kidney.[12] Therefore, selective SGLT2 inhibitors would be desirable for anti-diabetic agents. Given that SGLT2 inhibition lowers plasma glucose levels in an insulin-independent fashion, SGLT2 inhibitors are not predicted to be associated with hypoglycemia, which is a major concern for the current therapies with insulin and sulfonylureas. In addition, increases in urinary caloric loss due to UGE predict that SGLT2 inhibitors will not be associated with weight gain that is often seen with other classes of currently approved antihyperglycemic agents. As a consequence of these anticipated properties, identification of novel SGLT2 inhibitors became a goal for medicinal chemistry.[13−16]

Orally active **2** is an ester prodrug of active metabolite **1** (T-1095A), which enhances the resistance against hydrolysis by β-glucosidase in the intestine.[10] Nevertheless, the *O*-glucoside part of **2** is at least hydrolyzed to its aglycon in vivo (data not shown). The *C*-glucoside **3** was disclosed as SGLT2 inhibitor by Bristol-Myers Squibb Co.[17,18] Accordingly, to explore novel *C*-glucosides metabolically more stable than *O*-glucosides, we evaluated a series of *C*-glucosides **4** bearing a heteroaromatic ring.

Chemistry

We describe herein the syntheses of *C*-glucosides **4a**−**4e** bearing a heteroaromatic ring. The synthetic route is outlined in Scheme 1. We took advantage of the synthetic strategy outlined by Deshpande et al.[19−21] Aglycons **5a**−**5d** were dissolved in tetrahydrofuran and toluene, and treated with *n*-butyllithium at −78 °C to generate aryllithium, followed by addition of 2,3,4,6-tetra-*O*-trimethylsilyl-β-D-gluconolactone.[22] Aglycon **5e** underwent deprotonation with 1 equiv of *n*-butyllithium at the benzylic position rather than lithium−bromine exchange. Additional amounts of *n*-butyllithium did not induce lithiation at all. The aryllithium of **5e** was generated by *tert*-butyllithium as the second equivalent. The resulting anomeric mixture of lactols was immediately converted into desilylated methyl ethers **6a**−**6e** by addition of methanesulfonic acid in methanol. Finally, *C*-glucoside derivatives **4a**−**4e** were obtained by stereoselective reduction of **6a**−**6e** using a combination of triethylsilane and boron trifluoride etherate in methylene chloride.[23,24] The stereochemistry of **4a**−**4e** was determined as β-configuration by the coupling constant between anomeric C−H and adjacent C−H ($J \approx 9.5$ Hz) in the ^{1}H NMR spectrum.

Synthetic routes to aglycons **5a**−**5e** are shown in Scheme 2. Aglycon **5a-1** having furan was prepared by a coupling reaction of bromophenyllithium and furaldehyde in diethyl ether followed by reduction of hydroxyl group with iodotrimethylsilane, in situ generated by chlorotrimethylsilane and sodium iodide in acetonitrile.[25] Thiophene aglycons **5b-1**, **2** and **3** were synthesized by Friedel−Crafts acylation of corresponding

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[a]Abbreviations: SGLT, sodium-dependent glucose cotransporter; HF-KK, high-fat diet fed KK; T2DM, type 2 diabetes mellitus; UGE, urinary glucose excretion; SD, Sprague−Dawley; SAR, structure−activity relationship; GLUT, facilitated glucose transporter; AMG, α-methyl-D-glucopyranoside; CHOK, Chinese hamster ovary-K; 2-DG, 2-deoxy-D-glucose.

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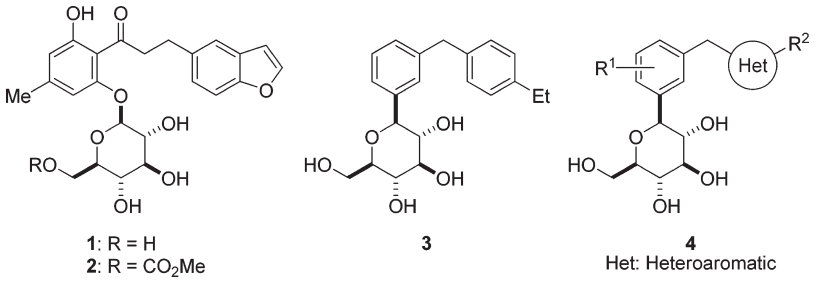
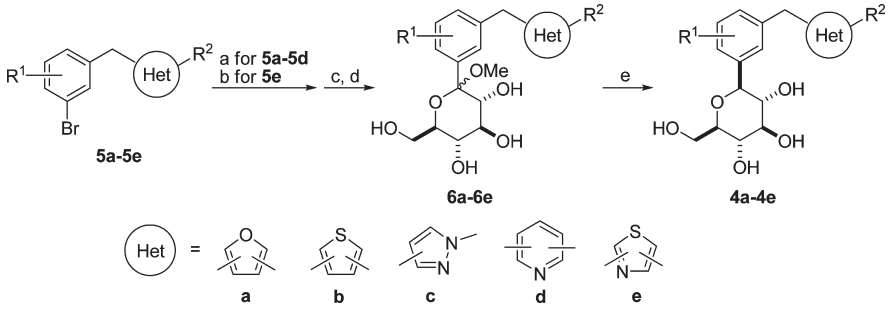


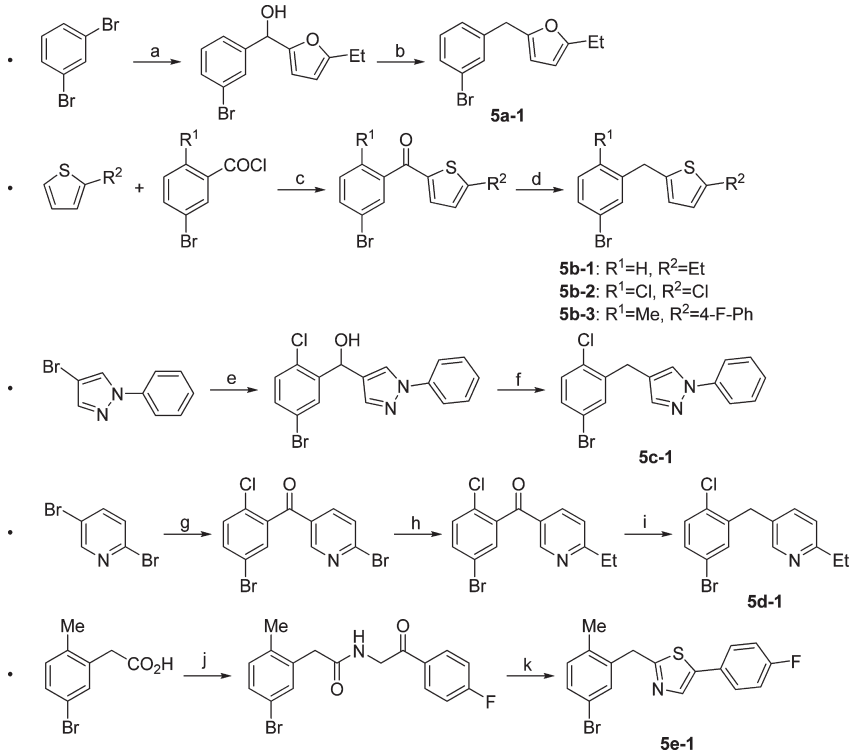
Figure 1. Structures of some *O*- and *C*-glucosides.

Scheme 1. Syntheses of **4a**−**4e**[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF−toluene, −78 °C; (b) *n*-BuLi, then *tert*-BuLi, THF−toluene, −78 °C; (c) 2,3,4,6-tetra-*O*-trimethylsilyl-β-D-gluconolactone, toluene, −78 °C; (d) $MeSO_3H$, MeOH; (e) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 to 0 °C.

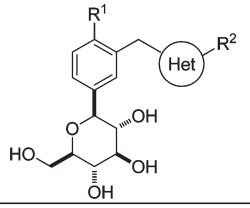
Scheme 2. Syntheses of Aglycons **5a**−**5e**[a]

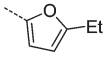
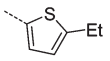
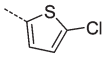
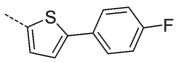
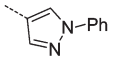
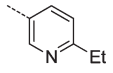
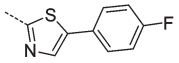


[a] Reagents and conditions: (a) *n*-BuLi, Et_2O, −78 °C, then 5-ethyl-2-furaldehyde, −78 °C; (b) TMSCl, NaI, CH_3CN, 0 °C; (c) $AlCl_3$, CH_2Cl_2, 0 °C; (d) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C; (e) *n*-BuLi, Et_2O, −78 °C, then 5-bromo-2-chlorobenzaldehyde, −78 °C; (f) $NaBH(OAc)_3$, TFA, 0 °C; (g) *n*-BuLi, Et_2O, −78 °C, then 5-bromo-2-chloro-*N*-methoxy-*N*-methylbenzamide, −78 °C; (h) Et_3Al, $Pd(PPh_3)_4$, $CeCl_3$, THF, 30 °C; (i) $NH_2NH_2 \cdot H_2O$, KOH, ethylene glycol, 190 °C; (j) 2-amino-4′-fluoroacetophenone hydrochloride, EDC, HOBt, Et_3N, CH_2Cl_2; (k) Lawesson's reagent, 1,4-dioxane, 100 °C.

benzoyl chloride and thiophene in methylene chloride, followed by reduction of ketone with triethylsilane and boron trifluoride etherate in methylene chloride. Bromine-substituted phenylpyrazole[26] was lithiated with *n*-butyllithium and reacted with bromobenzaldehyde in diethyl ether, and the resulting alcohol was reduced using sodium triacetoxyborohydride in trifluoroacetic acid[27] to give pyrazole derivative **5c-1**. Pyridinyl aglycon **5d-1** was synthesized by a coupling reaction of Weinreb amide and pyridyllithium[28] in diethyl ether, followed by a cross-coupling of triethylaluminum with bromopyridine in

Table 1. SAR of the Representative *C*-Glucosides with Heteroaromatic Ring[a]



compd	R^1	Het-R^2	hSGLT2 IC_{50} (nM)	UGE[a] (mg/day)
4a-1	H		920	N.D.[b]
4b-1	H		17	373
4b-2	Cl		2.4	2495
4b-3	Me		2.2	3696
4c-1	Cl		32	N.D.[b]
4d-1	Cl		28	N.D.[b]
4e-1	Me		8.1	1277

[a] Each compound was orally administered at a dose of 30 mg/kg to male Sprague−Dawley (SD) rats. Urinary glucose excretion (UGE) data over 24 h were normalized per 200 g body weight. [b] N.D.: not determined.

Table 2. hSGLT1, hSGLT2, Facilitated Glucose Transporter **1** (GLUT1) Inhibitory Activity, and Rat Urinary Glucose Excretion (UGE) Data for **1**, **2**, and **4b-3**

	IC_{50} (nM)			
compd	hSGLT1	hSGLT2	GLUT1	UGE[a] (mg/day)
1	240	5.2	> 10000	
2[b]				422
4b-3	910	2.2	> 10000	3696

[a] Compound **2** or **4b-3** was orally administered at a dose of 30 mg/kg to male SD rats. UGE data over 24 h were normalized per 200 g body weight. [b] An ester prodrug **2** is rapidly converted to active metabolite **1** in vivo, thus in vitro hSGLT inhibitory activities of **2** are not shown.

tetrahydrofuran and reduction of the carbonyl group with hydrazine hydrate and potassium hydroxide in ethylene glycol.[29] To provide thiazole derivative **5e-1**, ketoamide was cyclized using Lawesson's reagent in 1,4-dioxane.

Results and Discussion

Effects of furan, thiophene, pyrazole, pyridine and thiazole derivatives **4** (Figure 1) were evaluated on human SGLT2 (hSGLT2) activity and on urinary glucose excretion (UGE) in male Sprague−Dawley (SD) rats per 200 g of body weight over 24 h. The structure−activity relationship (SAR) of the representative compounds are shown in Table 1. Ethylthiophene derivative **4b-1** possessed good hSGLT2 inhibitory potency compared with the corresponding furan **4a-1** or pyridine **4d-1** derivative. Also, phenylthiophene derivative **4b-3** showed higher hSGLT2 inhibitory activity and UGE effect than the corresponding pyrazole **4c-1** or thiazole **4e-1** derivative. Therefore, we selected the novel thiophene derivatives for further optimization. For R^1 substituents, halogeno (chloro of **4b-2**) or lower alkyl (methyl of **4b-3**) group provided better in vitro potency than proton (**4b-1**). Substituted aryl (4-fluorophenyl of **4b-3**) group was preferred to alkyl (ethyl of **4b-1**) or halogeno (chloro of **4b-2**) group as R^2 substituents for in vivo potency and chemical stability (data not shown). From these thiophene derivatives, compound **4b-3** (canagliflozin, TA-7284/JNJ-28431754) was selected as a clinical candidate.

Table 3. Pharmacokinetic (PK) Parameters of **1** and **4b-3** in Male Sprague−Dawley (SD) Rats Following Intravenous and Oral Administrations

compd	**1**	**2**[a]	**4b-3**	**4b-3**
dose (mg/kg)	1	10	3	10
route	iv	po	iv	po
C_{max} (ng/mL)		80		2513
t_{max} (h)		1.3		5.0
AUC_{0-inf} (ng·h/mL)	153	304	12703	35980
$t_{1/2}$ (h)	1.3	2.2	5.0	5.2
CL_{tot} (mL/h/kg)	7506		236	
Vd_{ss} (mL/kg)	11390		1357	
F (%)		20		85

[a] Because a prodrug **2** is very rapidly converted to **1** in vivo, PK parameters of **1** are shown.

Table 2 displays effects of **1**, **2**, and **4b-3** on hSGLT1, hSGLT2, facilitated glucose transporter 1 (GLUT1) activity and UGE in rats. The inhibitory effects of **1** and **4b-3** on the uptake of [^{14}C]α-methyl-D-glucopyranoside (AMG) were investigated in Chinese hamster ovary-K (CHOK) cells stably expressing either hSGLT1 or hSGLT2. IC_{50} values of **1** and **4b-3** were 240 and 910 nM for hSGLT1, and 5.2 and 2.2 nM for hSGLT2, respectively. Since GLUT1 mediates the uptake of glucose in almost all tissues, selectivity of versus GLUT1 was determined using L6 myoblast cells. Neither compound inhibited the incorporation of [^{3}H]2-deoxy-D-glucose (2-DG) mediated by GLUT1 predominantly expressed in L6 myoblast cells.[30] Namely, compound **4b-3** was identified as a potent and selective inhibitor of hSGLT2.

Oral administration at 30 mg/kg of **2** and **4b-3** to male SD rats induced glucose excretion over 24 h by 422 and 3,696 mg, respectively, per 200 g body weight. Pharmacokinetic studies revealed a much higher exposure of **4b-3** following oral administration (Table 3). Following intravenous and oral doses of 3 and 10 mg/kg, respectively, to male SD rats, $AUC_{0-inf,po}$, $t_{1/2,po}$, and oral bioavailability were determined to be 35,980 ng·h/mL, 5.2 h, and 85%, respectively. Thus, inhibition of SGLT2 in renal tubules after oral dosing of **4b-3** is likely to continuously suppress reabsorption of glucose. The extensive UGE would reflect excellent pharmacokinetic properties of **4b-3** in vivo as well as high potency of SGLT2 inhibition. Since most of the filtered glucose is reabsorbed by SGLT2 in the renal tubules, the novel compound would be useful for an anti-diabetic agent.

Single oral administration of **4b-3** at 3 mg/kg remarkably reduced blood glucose levels without influencing food intake in hyperglycemic high-fat diet fed KK (HF-KK) mice (Figure 2A). There was a 48% reduction in blood glucose level versus vehicle at 6 h. In contrast, compound **4b-3** only slightly affected blood glucose levels in normoglycemic mice (Figure 2B). Therefore, this compound would control hyperglycemia in the therapy of T2DM with low risk of hypoglycemia.

In brief, compound **4b-3** is a highly potent and selective inhibitor for hSGLT2 with favorable pharmacokinetic profiles, and remarkably increases urinary glucose excretion. In addition, oral administration of **4b-3** induced anti-hyperglycemic

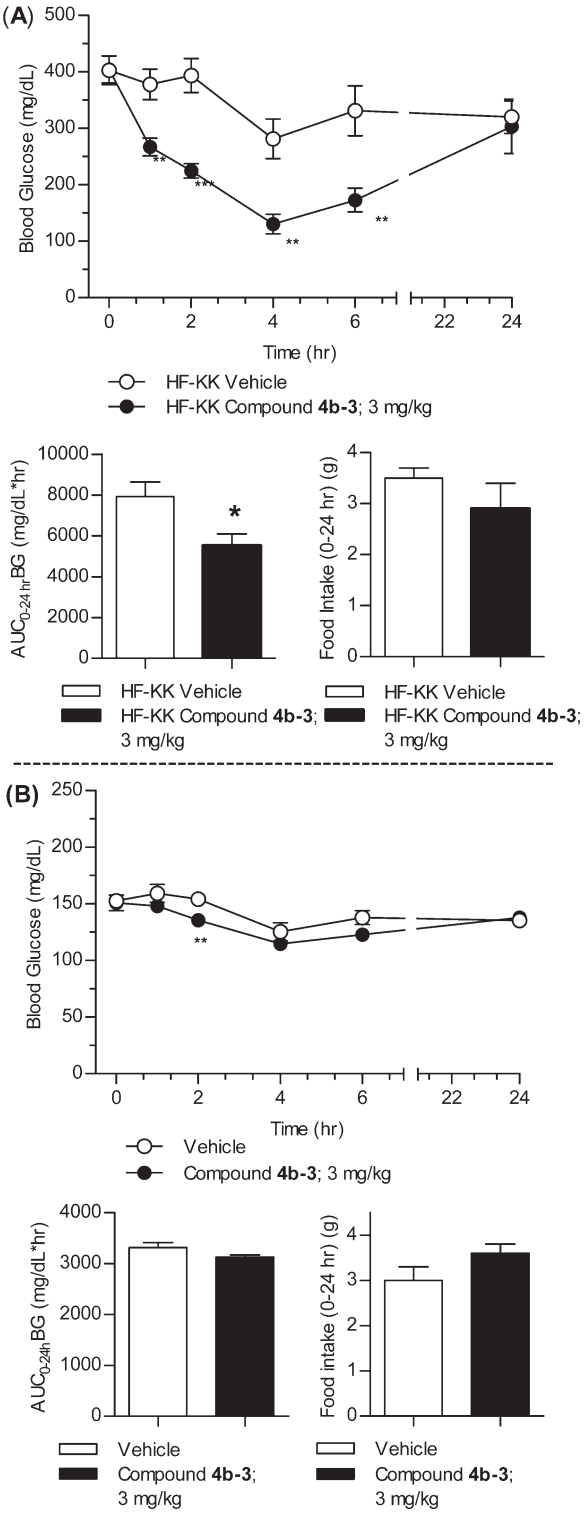


Figure 2. Effects of single oral dosing of **4b-3** on blood glucose levels and food intake in high-fat diet fed KK (HF-KK) (A) and normal (B) mice. Data are expressed as the mean ± SEM ($n = 5$): * $P < 0.05$, ** $P < 0.01$ vs vehicle.

effects in HF-KK mice. Currently, the thiophene derivative **4b-3** (canagliflozin) is being developed for the treatment of type 2 diabetes mellitus.

Experimental Section

All reactions were carried out under inert gas or with $CaCl_2$ tube, and reaction mixtures were stirred magnetically. All reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise noted. Reaction products were monitored by TLC using 0.25 mm E. Merck silica gel plates (60 F254) and were visualized using UV light or 5% phosphomolybdic acid in 95% EtOH. NMR spectra were collected on JEOL JNM-ECX400P and Varian UNITY INOVA500 spectrometers. Chemical shifts are given in parts per million (ppm) downfield from internal reference tetramethylsilane standard; coupling constants (J value) are given in hertz (Hz). Elemental analyses were conducted by Medicinal Chemistry Research Laboratories, Mitsubishi Tanabe Pharma. Melting points were measured by a Büchi model B-545 instrument and were uncorrected. Infrared spectra were measured on Perkin-Elmer PARAGON1000. APCI-MS spectra were obtained on Finnigan MAT SSQ7000C or ThermoQuest LCQ Advantage, eluting with 10 mM $AcONH_4$/MeOH. GC-MS spectra were measured on Shimadzu GCMS-QP2010. Analytical HPLC spectra were reported using Agilent 1100 with a UV detector measuring absorbance at 210 nm. All compounds were found to be >95% pure by HPLC analysis unless otherwise noted.

1-(β-D-Glucopyranosyl)-4-methyl-3-(5-(4-fluorophenyl)-2-thienylmethyl)benzene (4b-3). 5-Bromo-2-methylbenzoic acid[17,18] (44.43 g, 206.6 mmol) was suspended in dichloromethane (600 mL), and to the mixture were added oxalyl chloride (20.0 mL, 229 mmol) and *N*, *N*-dimethylformamide (0.74 mL, 9.55 mmol). The mixture was stirred at room temperature for 6 h (clear solution). The solvent was evaporated under reduced pressure to give 5-bromo-2-methylbenzoyl chloride as an oil. This compound and 2-(4-fluorophenyl)thiophene[31] (36.83 g, 206.6 mmol) were dissolved in dichloromethane (1,200 mL), and to the mixture was added aluminum chloride (30.3 g, 227.2 mmol) at 0 °C (internal temperature). After being stirred at the same temperature for 30 min, the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into ice−water (1,200 mL). The organic layer was separated, and the aqueous layer was extracted with chloroform (500 mL) three times. The organic layers were combined and dried over potassium carbonate. The solvent was concentrated under reduced pressure, and to the mixture was added *n*-hexane to produce a precipitate. The precipitate was collected by filtration, washed with *n*-hexane, and dried to give (5-bromo-2-methylphenyl)(5-(4-fluorophenyl)-2-thienyl)methanone (66.44 g, 85.7%) as yellow crystals: mp 121−122 °C. IR (Nujol) 1668, 1627, 1597, 1585, 1556, 1532, 1505 cm^{-1}. APCI-MS m/z 375/377 (M + H). ^1H NMR (DMSO-d_6) δ 2.24 (3H, s), 7.31−7.37 (3H, m), 7.46 (1H, d, $J = 4.0$ Hz, thio), 7.63−7.68 (3H, m), 7.87 (2H, m). Anal. Calcd for $C_{18}H_{12}BrFOS$: C, 57.61; H, 3.22; Br, 21.29; F, 5.06; S, 8.54. Found: C, 57.61; H, 3.14; Br, 21.07; F, 4.96; S, 8.58.

A solution of the above obtained (5-bromo-2-methylphenyl)-(5-(4-fluorophenyl)-2-thienyl)methanone (62.23 g, 165.8 mmol) and triethylsilane (76.8 mL, 481 mmol) in dichloromethane (620 mL)−acetonitrile (620 mL) was cooled to 0 °C (internal temperature), and to the mixture was added dropwise boron trifluoride−ethyl ether complex (58.8 mL, 464 mmol) over 15 min under nitrogen atmosphere. Subsequently, the mixture was stirred at room temperature for 4 h and was cooled again under ice−water. To the mixture was added slowly a saturated aqueous sodium hydrogen carbonate solution (1,200 mL) under stirring. The organic layer was separated, and the aqueous layer was extracted with chloroform (500 mL) three times. The combined organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (1,200 mL)−methanol (600 mL), and the mixture was treated with activated carbon (3.0 g). The insoluble was filtered off, and the filtrate was concentrated under reduced pressure. To the mixture was added methanol to produce a precipitate. The precipitate was collected by filtration, washed with ethyl acetate−methanol (1:3), and dried to give 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene **5b-3** (46.83 g, 78.2%) as pale-yellow crystals: mp 101−103 °C. IR (Nujol) 1879, 1746, 1592, 1511

cm^{-1}. GC-MS m/z 362 (M^+). ^{1}H NMR (DMSO-d_6) δ 2.25 (3H, s), 4.15 (2H, s, Ph-CH_2-thio), 6.85 (1H, d, J = 3.5 Hz, thio), 7.17 (1H, d, J = 8.0 Hz), 7.21 (2H, quasi-t), 7.31 (1H, d, J = 3.5 Hz, thio), 7.36 (1H, dd, J = 8.0, 1.9 Hz), 7.44 (1H, d, J = 1.9 Hz), 7.60 (2H, m). Anal. Calcd for $C_{18}H_{14}BrFS$: C, 59.84; H, 3.91; Br, 22.12; F, 5.26; S, 8.87. Found: C, 59.89; H, 3.86; Br, 21.93; F, 5.17; S, 8.85.

To a solution of the above obtained 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene **5b-3** (28.9 g, 80.0 mmol) in tetrahydrofuran (480 mL) and toluene (480 mL) was added *n*-butyllithium (1.6 M *n*-hexane solution, 50.0 mL, 80.0 mmol) dropwise over 10 min at −67 to −70 °C (internal temperature) under argon atmosphere, and the mixture was stirred for 20 min at the same temperature (dark-blue solution). To the mixture was added a solution of 2,3,4,6-tetra-*O*-trimethylsilyl-β-D-gluconolactone[22] (34.0 g, 72.8 mmol) in toluene (240 mL) dropwise over 30 min at −67 to −70 °C (internal temperature), and the mixture was further stirred for 1 h at the same temperature (slightly brown solution). Subsequently, to the mixture was added a solution of methanesulfonic acid (21.0 g, 219 mmol) in methanol (480 mL) dropwise over 15 min, and the resulting mixture was allowed to warm to room temperature and stirred for 17 h. The mixture was again cooled in ice−water, and to it was added a saturated aqueous sodium hydrogen carbonate solution (1,000 mL). The mixture was extracted with ethyl acetate (1,000 mL) twice, and the combined organic layer was washed with brine (1,000 mL) and dried over magnesium sulfate. The insoluble was filtered off, and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 mL)−*n*-hexane (400 mL) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-(5-(4-fluorophenyl)-2-thienylmethyl)benzene **6b-3** (31.6 g, 91.3%) as a pale-yellow powder: HPLC 88.5% (t_R = 8.1 min, L-column ODS (5 μm particle size, 4.6 × 150 mm), CH_3CN/20 mM phosphate buffer (pH 6.5) (45/55)). APCI-MS m/z 492 (M + NH_4), 460 (M + NH_4 − MeOH), 443 (M + H − MeOH). ^{1}H NMR (DMSO-d_6) δ 2.26 (3H, s, Me), 2.91 (1H, m, sugar), 2.95 (3H, s, OMe), 3.21 (1H, m, sugar), 3.37 (1H, m, sugar), 3.51−3.61 (2H, m, sugar), 3.75 (1H, m, sugar), 4.09, 4.18 (each 1H, d, J = 15.9 Hz, Ph-CH_2-thio), 4.51 (1H, t, J = 6.0 Hz, OH), 4.65 (1H, d, J = 7.2 Hz, OH), 4.69 (1H, d, J = 5.1 Hz, OH), 4.94 (1H, d, J = 5.5 Hz, OH), 6.77 (1H, d, J = 3.5 Hz, Thio), 7.14 (1H, d, J = 8.0 Hz, Ph), 7.20 (2H, quasi-t, J = 8.8 Hz, Ph), 7.26 (1H, d, J = 3.5 Hz, thio), 7.32 (1H, dd, J = 8.0, 1.5 Hz, Ph), 7.42 (1H, d, J = 1.5 Hz, Ph), 7.57 (2H, m, Ph).

A solution of the above obtained 1-(1-methoxyglucopyranosyl)-4-methyl-3-(5-(4-fluorophenyl)-2-thienylmethyl)benzene **6b-3** (63.1 g, 132 mmol) and triethylsilane (46.4 g, 399 mmol) in dichloromethane (660 mL) was cooled in a dry ice−acetone bath under argon atmosphere, and to the mixture was added dropwise boron trifluoride−ethyl ether complex (50.0 mL, 395 mmol) over 5 min. The mixture was stirred at the same temperature. The mixture was allowed to warm to 0 °C and stirred under ice−water for 2 h. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 mL) was added, and the mixture was stirred for 30 min. The organic solvent was evaporated under reduced pressure, and the residue was poured into water (1,500 mL) and extracted with ethyl acetate (1,000 mL) twice. The combined organic layer was washed with water (500 mL) twice, dried over magnesium sulfate, and treated with activated carbon. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate (300 mL)−diethyl ether (600 mL)−water (6 mL) to give desired 1-(β-D-glucopyranosyl)-4-methyl-3-(5-(4-fluorophenyl)-2-thienylmethyl)benzene **4b-3** (33.5 g, 56.7%) as colorless crystals: mp 98−100 °C. IR (Nujol) 1626, 1600, 1549, 1507 cm^{-1}. HPLC 99.5% (t_R = 11.6 min, L-column ODS (5 μm particle size, 4.6 × 150 mm), CH_3CN/20 mM phosphate buffer (pH 6.5) (40/60)). APCI-MS m/z 462 (M + NH_4). ^{1}H NMR (DMSO-d_6) δ 2.26 (3H, s, Me), 3.13−3.28 (4H, m, sugar), 3.44 (1H, m, sugar), 3.69 (1H, m, sugar), 3.96 (1H, d, J = 9.3 Hz, sugar), 4.10, 4.15 (each 1H, d, J = 16.0 Hz, Ph-CH_2-thio), 4.43 (1H, t, J = 5.8 Hz, OH), 4.72 (1H, d, J = 5.6 Hz, OH), 4.92 (2H, d, J = 4.8 Hz, OH), 6.80 (1H, d, J = 3.5 Hz, thio), 7.11−7.15 (2H, m, Ph), 7.18−7.25 (3H, m, Ph), 7.28 (1H, d, J = 3.5 Hz, thio), 7.59 (2H, dd, J = 8.8, 5.4 Hz, Ph). Anal. Calcd for $C_{24}H_{25}FO_5S \cdot 0.5H_2O$: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

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

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