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C-Glucosides with heteroaryl thiophene as novel sodium-dependent glucose cotransporter 2 inhibitors

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ABSTRACT

Canagliflozin (**1**), a novel inhibitor for sodium-dependent glucose cotransporter 2 (SGLT2), has been developed for the treatment of type 2 diabetes. To investigate the effect of replacement of the phenyl ring in **1** with heteroaromatics, *C*-glucosides **2** were designed, synthesized, and evaluated for their inhibitory activities against SGLT2. Of these, 3-pyridyl, 2-pyrimidyl or 5-membered heteroaryl substituted derivatives showed highly potent inhibitory activity against SGLT2, while 5-pyrimidyl substitution was associated with slightly reduced activity. In particular, **2g** (TA-3404) had remarkable anti-hyperglycemic effects in high-fat diet fed KK (HF-KK) mice.

1. Introduction

The achievement and maintenance of near-normal glycemia reduces the risk of diabetes complications.[1,2] Despite lifestyle and pharmacological interventions, glucose levels increase over time in type 2 diabetes, probably as a consequence of declining pancreatic β-cell function.[3] The progressive nature of type 2 diabetes makes it difficult to maintain good glycemic control with several glucose-lowering agents,[4] and as a result, it requires the gradual dose escalation, the use of combination therapies or insulin.[5] Therefore, there is a need for agents with a newer and complementary mechanism of action which can be used throughout the life of patients with type 2 diabetes. Inhibitors of sodium-glucose cotransporters (SGLTs) is an attractive approach to such need, as their action of reducing blood glucose is independent from insulin.[6] The kidney contributes to glucose homeostasis by reabsorbing approximately 180 g of glucose from the glomerular filtrate each day, and SGLT2 expressed in the early convoluted segment (S1) of the proximal tubule mediates 80–90% of renal glucose reabsorption.[7–9] The remaining 10–20% of renal glucose reabsorption occurs through SGLT1, which is expressed in the more distal, straight section of the proximal tubule (S3).[9] Besides the kidney, SGLT1 is distributed in the intestine, heart, and trachea, while SGLT2 is expressed solely in the kidney.[10] By enhancing glucose excretion into urine, SGLT2 inhibitors should lead to a significant loss of calories. Their potential advantage would be reducing blood glucose and leading to weight loss; thus, they could be used at any stage of type 2 diabetes.[11] In fact, several specific and potent SGLT2 inhibitors have been developed.[12–15]

Canagliflozin (**1**), one of potent SGLT2 inhibitors, is being studied in clinical trials, and a more thorough understanding of its derivatives is required. To explore the structure–activity relationship (SAR) of the aryl substituent at thiophene ring on **1**, we developed synthetic strategies for *C*-glucosides with heteroaryl thiophene **2** and evaluated these compounds on SGLT2 activity and urinary glucose excretion (UGE). Herein, we report the synthesis and the biological result of **2**.

2. Chemistry

We initially planned to synthesize *C*-glucosides **2** bearing a heteroaromatic ring using a previously reported strategy,[12,13] and compound **2a** was prepared as shown in Scheme 1. 2-(3-Pyridyl) thiophene (**3**) was treated with *n*-butyllithium, followed by addition of 5-bromo-2-methylbenzaldehyde to give diarylcarbinol **4**. One of the reducing agents of diarylcarbinols is a combination of sodium tetrahydroborate and trifluoroacetic acid along with

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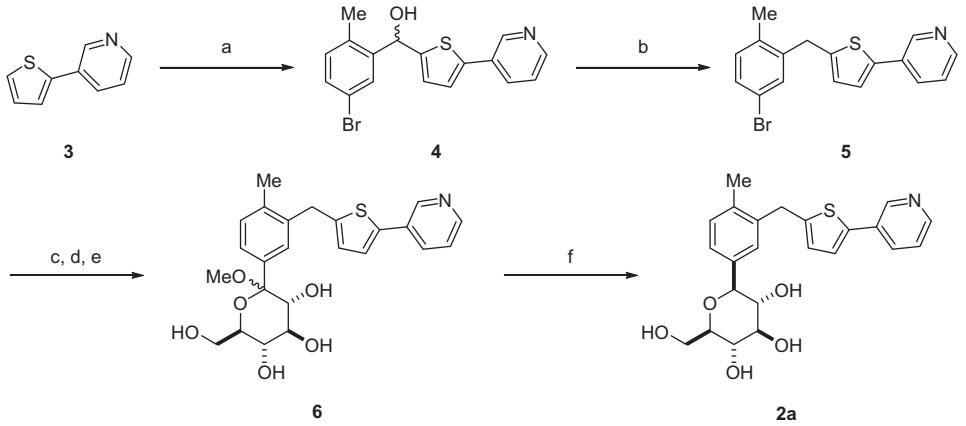
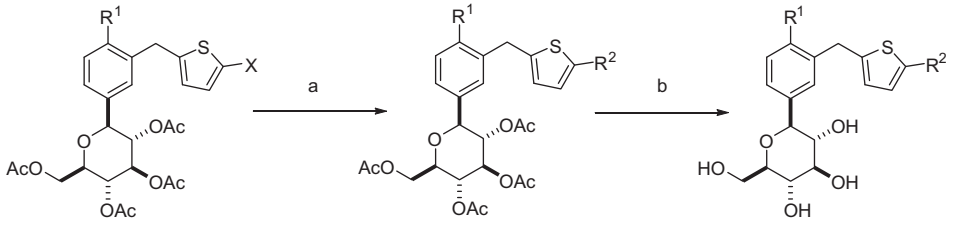


Scheme 1. Synthesis of **2a**. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, then 5-bromo-2-methyl-benzaldehyde, −78 °C, 67%; (b) $NaBH(OAc)_3$, TFA, 0 °C to rt, quant.; (c) *n*-BuLi, THF–toluene, −78 °C; (d) 2,3,4,6-tetrakis-*O*-trimethylsilyl-D-gluconolactone, −78 °C; (e) $MeSO_3H$, MeOH, −78 °C to rt, 2.3%; (f) Et_3SiH, $BF_3{\cdot}Et_2O$, $CHCl_3$, 0 °C, 30%.



Scheme 2. Syntheses of **2b**–**2d**, **2f**, **2g**. Reagents and conditions: (a) **7**, $Pd_2(dba)_3$, P(*tert*-Bu)$_3{\cdot}HBF_4$, CsF, 5-tri(*n*-butyl)stannylpyrimidine, dioxane, 100 °C, 41% (for **10b**) or **8**, $PdCl_2(PPh_3)_2$, CuI, 2-tri(*n*-butyl)stannylpyrimidine, NMP, 100 °C, 66% (for **10c**) or **8**, $Pd(PPh_3)_4$, CuI, 5-tri(*n*-butyl)stannylthiazole, dioxane, reflux, 23% (for **10d**) or **9**, $Pd(PPh_3)_4$, CsF, pyridine-3-boronic acid or 6-fluoropyridine-3-boronic acid pinacol ester, DME, reflux, 53–81% (for **10f**, **10g**); (b) NaOMe, MeOH–THF, rt, 55–100%.

hydrogen gas evolution.[16] To avoid gas evolution, sodium triacetoxyborohydride was used instead of sodium tetrahydroborate. With this combination, compound **4** was rapidly reduced to yield aglycon **5**. Lithium halogen exchange of **5** with *n*-butyllithium followed by addition of 2,3,4,6-tetrakis-*O*-trimethylsilyl-D-gluconolactone[12] generated an anomeric mixture of lactols, which were converted in situ to the desilylated methyl ether **6** by treatment with methanesulfonic acid in methanol. Unfortunately, the lithiation of 3-pyridylthiophene derivative **5** was problematic and this reaction resulted in a low yield (2.3%). Finally, the *C*-glucoside derivative **2a** was obtained by stereoselective reduction of **6** using a combination of triethylsilane and boron trifluoride etherate. The stereochemistry of **2a** was determined as the β-configuration based on the coupling constant between anomeric C–H and adjacent C–H (J = 9.5 Hz) in the ^{1}H NMR spectrum.

To avoid the problematic lithium halogen exchange reaction, we designed new approaches to compounds **2** using palladium catalyzed coupling reactions of *C*-glucosides having halogenothiophene. The coupling reactions of halogenothiophene derivatives **7**, **8** or **9** with the heteroaryl stannanes, boronic acid, or boronate ester proceeded smoothly to give *O*-acetyl protected *C*-glucosides **10** in moderate to good yields as shown in Scheme 2. *C*-glycosides **2b**–**2d**, **2f**, and **2g** were obtained by methanolysis of the corresponding **10b**–**10d**, **10f**, and **10g**.

The synthetic route to intermediates **7** and **8** is outlined in Scheme 3. Benzoic acid **11** was treated with oxalyl chloride, followed by addition of 2-chlorothiophene and aluminum trichloride to give ketone **12**. Reduction of **12** with triethylsilane and boron trifluoride etherate in acetonitrile–chloroform afforded thiophene aglycon **13**. The aglycon **13** was converted into β-*C*-glucoside **14** in a manner similar to **2e**. The chlorothiophene derivative **7** was obtained by protection of the hydroxyl groups with acetic anhydride. The bromothiophene derivative **8** was synthesized by hydrogenolysis of **7** with palladium on carbon and triethylamine in methanol–tetrahydrofuran, followed by bromination with bromine.

The synthetic route to **9** is outlined in Scheme 4. While the *tert*-butyl ester group of **16** did not tolerate conditions of lithium halogen exchange with *n*-butyllithium or *tert*-butyllithium, we found that aryllithium was generated from **16** successfully using 2,4,6-trimethylphenyllihium (mesityllithium), which has a less nucleophilic character.[17] In addition, Barbier-type conditions had a good result. In particular, a mixture of **16** and 2,3,4,6-tetrakis-*O*-trimethylsilyl-D-gluconolactone was added dropwise to mesityllithium in tetrahydrofuran, followed by addition of methanesulfonic acid in methanol to generate desilylated methyl ether **17** as an amorphous powder (89.9% pure by HPLC). Acetylation of **17** with acetic anhydride and recrystallization from toluene–*n*-hexane gave **18** with a purity of 98.7% by HPLC. The *tert*-butyl ester **18** was converted into carboxylic acid using formic acid, and treated with oxalyl chloride, then 2-bromothiophene and aluminum trichloride to afford **19**. Finally, intermediate **9** was obtained by reduction of the carbonyl group of **19** to the benzyl alcohol using sodium tetrahydroborate, followed by simultaneous reduction of the resultant hydroxyl group and the anomeric methoxy group with triethylsilane and boron trifluoride etherate in acetonitrile–water.

C-Glucoside **2e** was synthesized according to the method described previously by our group using palladium-catalyzed coupling of aglycon **24** with glucal boronate **25**[18] as shown in Scheme 5. The coupling of 2-bromothiophene (**20**) with pyrazole