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Synthesis and biological evaluation of 6-hydroxyl *C*-aryl glucoside derivatives as novel sodium glucose co-transporter 2 (SGLT2) inhibitors

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ABSTRACT

The sodium glucose co-transporter 2 (SGLT2) was considered as an important target for the treatment of type 2 diabetes mellitus in recent years. This report describes the design and synthesis of a series of novel SGLT2 inhibitors (**11a**–**17a**) as well as their dehydrate dihydrofuran derivatives (**11b**–**17b**), which were prepared by Mitsunobu reaction. Their SGLT2 inhibitory activity was also evaluated, and **16a** and **17a** were found to be the most potent compounds with IC_{50} values of 0.63 and 0.81 nM, respectively. However, all the dehydrate derivatives lose the SGLT2 inhibitory activity, with inhibition percentage no more than 66.5% at the concentration of 0.5 μM, which might because of the configuration inversion at C-2 of glucose. In conclusion, the present study improves understanding of the SAR of SGLT2 inhibitors, and provided more information that could be applied to design new molecules.

Diabetes mellitus is becoming a common and frequently occurring disease, trending to be a serious threat to human health.[1] It is predicted that the number of diabetes patients will grown to 438 million by 2030.[2] Type 2 diabetes mellitus (T2DM), a chronic metabolic disorder of glucose homeostasis characterized by hyperglycemia,[3] accounts for nearly 90% of all cases of diabetes.[4,5] Several therapeutic agents, which enhance insulin secretion and/or improve insulin sensitivity, are available for monotherapy or combination therapy to treat diabetics, such as metformin, rosiglitazone, sitagliptin, acarbose, and glimepiride.[6] Although there are many anti-diabetic drugs, the hyperglycemia still cannot be controlled in many cases.[7] In addition, these agents described above are known to cause undesirable side effects such as hypoglycemia, body weight gain, gastric symptoms, etc.[8] Thus, there is a strong medical need for novel potent hypoglycemic agents with novel mechanisms of action and a good safety and efficacy to treat patients with uncontrolled T2DM. In recent years, the renal sodium glucose co-transporter 2 (SGLT2), has emerged as an attractive target for the treatment of T2DM in the context of metabolic syndrome.[9]

Sodium-dependent glucose co-transporters (SGLTs) are membrane proteins and mediators of reabsorption of filtered glucose in the kidney. Suppressing glucose reabsorption through inhibition of human SGLTs would promote urinary glucose excretion, thereby reducing plasma glucose levels.[10] There are two major types of glucose co-transporters in SGLTs, namely SGLT1 and SGLT2. SGLT2, a high-capacity, low-affinity transporter, is located mainly on the luminal surface of the epithelial cells lining S1 segment of the proximal convoluted tubule in the kidney,[11] which is responsible for approximately 90% of renal glucose reabsorption against a concentration gradient.[12,13] Therefore, SGLT2 is a very important target for the T2DM treatment, and the inhibitors of SGLT2 have received considerable attention due to their distinct mechanism of action that reduces blood glucose levels independently of insulin secretion.[3]

It was well known that the *C*-aryl glucoside class of SGLT2 inhibitors were more potent and stable in vivo than the *O*-glucosides,[14] and to date, some *C*-glucoside SGLT2 inhibitors, such as dapagliflozin (**1**), canagliflozin (**2**), ipragliflozin (**3**), empagliflozin (**4**), luseogliflozin (**5**) have been approved for the treatment of type 2 diabetes (Fig. 1).[15]

The discovery of structurally distinct SGLT2 inhibitors has been mostly focused on the modification of the aglycones.[16] However, the investigation on the glucose residue is rarely reported. Recently, some novel *C*-aryl glucoside derivatives with the dioxabicycle or spiroketal moiety have been disclosed as potent SGLT2 inhibitors, such as ertugliflozin (**7**), compound **8**, tofogliflozin (**9**), and compound **10** (Fig. 2). Moreover, tofogliflozin were approved

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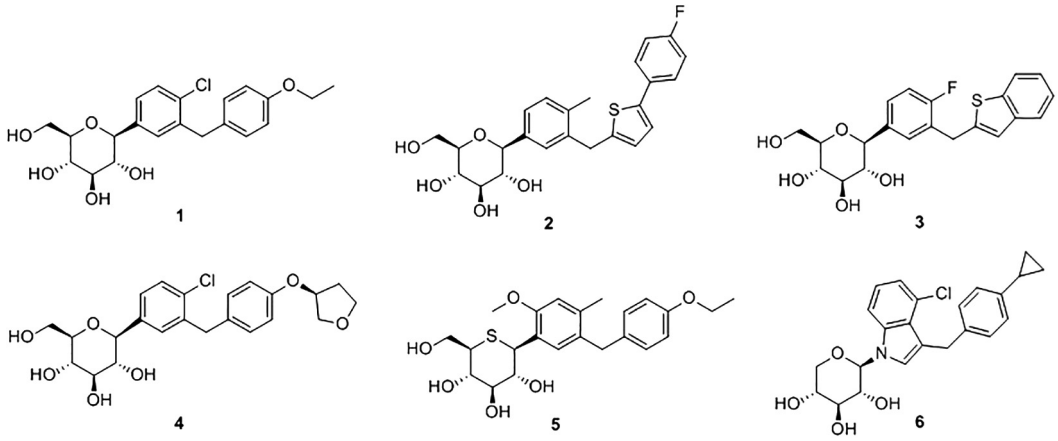

Fig. 1. Structures of SGLT2 inhibitors.

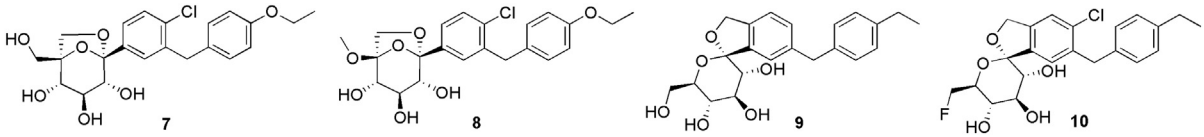

Fig. 2. Structures of *C*-glucoside SGLT2 inhibitors with the dioxa-bicycle or spiroketal moiety.

in Japan in 2014,[5] and ertugliflozin is currently under phase-III clinical trial.[15] All these motivated us to synthesize the novel SGLT2 inhibitors by modifying the glucoside moiety, and a number of 6-hydroxyl *C*-aryl glucosides (**11a**[3]–**17a**) and their intramolecular dehydrate derivatives (**11b**–**17b**) were then prepared (Fig. 3).

The preparation of *C*-glucoside derivatives **11a**, **11b**, **12a** and **12b** is outlined in Scheme 1. Lithiation of benzothiophene (**20**) and 1-bromo-4-ethoxybenzene (**25**) followed by the addition of a lithiated aromatic to MOM-protected 3-bromo-4-hydroxybenzaldehyde (**19**) yielded alcohols, which were then reduced by treatment with Et_3SiH and $BF_3{\cdot}OEt_2$ to give aglycones **21** and **26**. Lithium halogen exchange of **21** and **26** followed by the addition of a lithiated aromatic to 2,3,4,6-tetra-*O*-benzylgluconolactone (**22**), respectively, yielded lactols, which were reduced by treatment with Et_3SiH and $BF_3{\cdot}OEt_2$ to give compounds **23** and **27**. Successive removal of the methoxymethyl group and benzyl groups with HCl and BCl_3 generated compounds **11a** and **12a**. The dihydrofuran ring of compounds **11b** and **12b** were formed by the intramolecular Mitsunobu reaction upon treatment of **11a** and **12a** with PPh_3 and diethyl azodicarboxylate (DEAD).

The configuration at C-1 of glucose in compounds **11a** and **12a** was determined as β-linkage by the coupling constant (J = 9.3 Hz, J = 9.4 Hz, respectively) between anomeric hydrogen and adjacent hydrogen in the ^1H NMR spectra.[12] The configuration at C-2 of glucose in dihydrofuran derivatives, which were formed by Mitsunobu reaction, was determined by single-crystal X-ray diffraction analysis, and the crystal structure of representative compound **11b** was shown in Fig. 4.

In order to construct the derivatives with structural diversity more efficiently and conveniently, the synthetic route was then modified as follows: the key intermediate **36** was synthesized as shown in Scheme 2. Firstly, 2-chloro-4-hydroxybenzaldehyde (**29**) was treated with pyridinium tribromide to give compound **30**, and the phenolic hydroxyl group was then protected with benzyl bromide to give compound **31**. Subsequently, the aldehyde group of compound **31** was reduced with $NaBH_4$ and was protected with a *tert*-butyldiphenylsilyl (TBDPS) group to give compound **33**. Lithium halogen exchange of **33** followed by the addition of a lithiated aromatic to 2,3,4,6-tetra-*O*-benzylgluconolactone (**22**) yielded lactols, which was reduced by treatment with Et_3SiH and $BF_3{\cdot}OEt_2$ to give compounds **34**. The removal of the TBDPS group by tetrabutylammonium fluoride (TBAF) followed by the oxidation of benzylalcohol to benzaldehyde with MnO_2 afforded the key intermediate **36**.

The synthesis of C-glucoside derivative **13a**[17]–**17a** and **13b**–**17b** was shown in Scheme 3. The lithiation of thianaphthene (**20**), 1-bromo-4-ethoxybenzene (**25**), 1-bromo-4-methoxybenzene (**37**), 1-bromo-4-ethylbenzene (**38**) and 1-bromo-4-methylbenzene (**39**) followed by the addition of a lithiated aromatic to **36** yielded lactols, which were reduced by treatment with Et_3SiH and $BF_3{\cdot}OEt_2$ to give compounds **13**–**17**. The removal of benzyl groups with BCl_3 generated compounds **13a**–**17a**. The dihydrofuran rings of compounds **13b**–**17b** were formed by the intramolecular Mitsunobu reaction upon treatment of **13a**–**17a** with PPh_3 and DEAD.

The cell-based SGLT2 inhibition assay was then performed to evaluate the inhibitory effects of all synthesized compounds on *h*SGLT2 activities, and used dapagliflozin as positive reference. As shown in Table 1, compounds **12a**, **14a**–**17a** exhibited excellent SGLT2 inhibitory activity, with IC_{50} values ranging from 0.63 nM to 12.17 nM. In addition, compounds **16a** and **17a** were the most potent compounds with IC_{50} values of 0.63 and 0.81 nM, respectively, and comparable with the reference drug dapagliflozin (IC_{50} = 1.05 nM). Compound **12a** displayed moderate SGLT2 inhibitory potency (IC_{50} = 12.17 nM), and the introduction of chlorine atom at C-4 of arene *B* led to potent compound **14a**, with IC_{50} value of 1.03 nM, which was comparable to that of dapagliflozin. This suggests the addition of chlorine atom at the 4-position of arene *B* is critical for the improved SGLT2 inhibitory activity. When the ethoxyl group of compound **14a** was changed to methoxyl group, the resulting compound **15a** displayed a comparable SGLT2 inhibitory activity to that of **14a**. Surprisingly, introduction of the ethyl or methyl group at C-4 of arene *C* result in the most potent compounds **16a** and **17a**, respectively. Unexpectedly, all the dehydrate derivatives lose the SGLT2 inhibitory activity, with inhibition percentage no more than 66.5% at the concentration of 0.5 μM, which might because of the configuration inversion at C-2 of glucose.