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Original article

Thiazolylmethyl *ortho*-substituted phenyl glucoside library as novel C-aryl glucoside SGLT2 inhibitors

Suk Ho Lee [a,b], Min Ju Kim [a], Sung-Han Lee [a], Jeongmin Kim [a], Hyun-Ju Park [b], Jinhwa Lee [a,*]

[a] Green Cross Corporation Research Center, 303 Bojeong-Dong, Giheung-Gu, Yongin, Gyeonggi-Do 446-770, Republic of Korea
[b] College of Pharmacy, Sungkyunkwan University, Cheoncheon-Dong, Jangan-Gu, Suwon, Gyeonggi-Do 440-746, Republic of Korea

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ABSTRACT

In order to investigate SAR regarding proximal phenyl ring in novel C-aryl glucoside SGLT2 inhibitors containing a thiazole motif, a series of chemical modifications on proximal phenyl ring was conducted. During a series of lead optimization efforts, *ortho*-allyloxyphenyl **10p** or *ortho*-hydroxyphenyl **11a** showed subnanomolar inhibitory activity against *h*SGLT2.

1. Introduction

Diabetes has become an increasing concern to the world's population. In 2010, approximately 285 million people around the world will have diabetes, corresponding to 6.4% of the world's adult population, with a prediction that the number of people with diabetes will have grown to 438 million by 2030 [1]. Type 2 diabetes is the most common disorder of glucose homeostasis, accounting for approximately 90–95% of all cases of diabetes [2].

Sodium-dependent glucose cotransporters (SGLTs) couple the transport of glucose against a concentration gradient with the simultaneous transport of Na^+ down a concentration gradient [3]. Two essential SGLT isoforms have been cloned and identified as SGLT1 and SGLT2 [4]. SGLT1 is located in the gut, kidney, and heart where its expression regulates cardiac glucose transport [5]. SGLT1 is a high-affinity, low-capacity transporter and therefore accounts for a merely small fraction of renal glucose reabsorption [6]. In contrast, SGLT2 is a low affinity, high-capacity transporter located exclusively at the apical domain of the epithelial cells in the early proximal convoluted tubule. It is estimated that 90% of renal glucose reabsorption is facilitated by SGLT2, while the remaining 10% is mediated by SGLT1 in the late proximal straight tubule [7]. Since SGLT2 appears to be responsible for the majority of renal glucose reabsorption based on human mutation studies [8], SGLT2 has become a target of therapeutic interest.

Bristol-Myers Squibb has identified dapagliflozin (**1**), a potent, selective SGLT2 inhibitor for the treatment of type 2 diabetes [9–11]. At present, **1** is the most advanced SGLT2 inhibitor in clinical trials [12]. On the other hand, **2**, **3**, **4** from Johnson & Johnson, Lexicon, and Pfizer are being tested in various phase of clinical trials (Fig. 1) [13].

In the previous study, C-glucosides bearing a heterocyclic ring were exploited in order to develop novel SGLT2 targeting antidiabetic agents, since we envisioned that replacement of the distal or proximal phenyl ring of **1** with a heterocyclic ring might improve the overall physicochemical properties of SGLT2 inhibitors [14]. Based on the structure of dapagliflozin, the distal phenyl ring was surrogated by the corresponding thiazole ring. A series of lead optimization efforts led to the discovery of thiazole **5** bearing a furanyl moiety as shown in Fig. 2 [15]. In the present study, diverse modifications on the C-2 position of the proximal phenyl ring (as shown in **6**) were conducted to establish SAR on the phenyl ring, while keeping the structure of potent thiazole **5** [16]. Along this line, we report the synthesis and biological evaluation of thiazolylmethyl *ortho*-substituted phenyl glucoside analogs as novel C-aryl glucoside SGLT2 inhibitors.

2. Chemistry

Preparation of the requisite bromides **15a**, **15b**, **15c**, **17a** and **17b** is described in Scheme 1. Thus, commercially available 2-chloro-4-

* Corresponding author. Tel.: +82 31 260 9892; fax: +82 31 260 9020.
E-mail address: jinhwalee@greencross.com (J. Lee).

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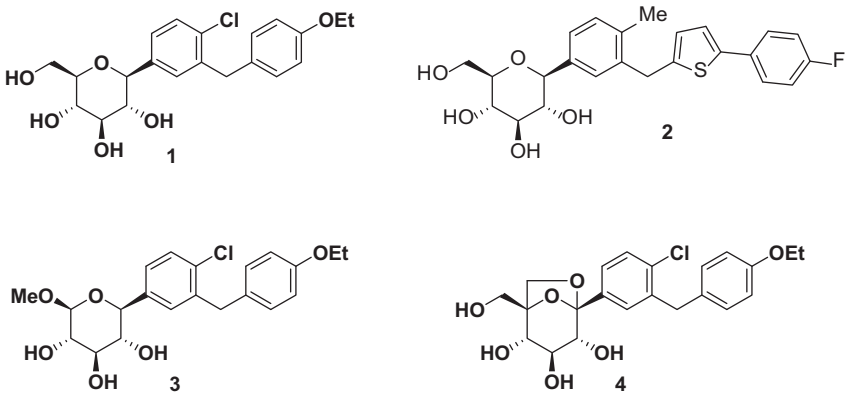

Fig. 1. Structures of *C*-aryl glucoside SGLT2 inhibitors.

hydroxybenzonitrile (**7**) was converted to the corresponding bromo-acids **14a**–**14c** by way of triflic acid-mediated bromination at C-5 [17], alkylation on C-1 hydroxyl, and subsequent hydrolysis of cyanides. The reduction of acids **14a**–**14c** with a borane–dimethyl sulfide complex, and subsequent silylation of the corresponding alcohol with triisopropylsilyl chloride (TIPSCl) in the presence of imidazole and 4-(dimethylamino)pyridine (DMAP) generated bromides **15a**–**15c** in reasonable yields. Similarly, 4-halogenated benzyloxytriisopropylsilanes **17a**, **17b** were prepared as shown in Scheme 1. Bromination using bromine and sulfur was conducted on 2,4-dichlorobenzoic acid (**8**) or 2-chloro-4-fluorobenzoic acid (**9**) in the presence of chlorosulfonic acid [18]. The resulting bromo-acids were transformed into the corresponding bromides **17a**, **17b** following the same procedure previously described.

Preparation of key intermediates **20a**–**20e** is described in Scheme 2. Thus, lithium-halogen exchange, followed by the addition of the nascent lithiated aromatic compound to perbenzylated gluconolactone **10**, produced a mixture of the corresponding lactols. The lactols were reduced using triethylsilane and BF_3 etherate [19], desilylated and afforded alcohols **18a**–**18e**, respectively. Then alcohols **18a**–**18e** were converted to bromides using PBr_3 in the presence of catalytic pyridine. The resulting bromides were treated with KCN in refluxing aqueous EtOH to generate cyanides. A mixture of the two isomers in each case was separated through recrystallization from ethanol to produce the required beta-isomers **19a**–**19e**. Hydrolysis of cyanides **19a**–**19e** with sodium hydroxide in aqueous ethanol generated the carboxylic acids **20a**–**20e** in quantitative yields, respectively.

Preparation of the thiazole compound is described in Scheme 3. Thus, the carboxylic acid **20** prepared previously was coupled with 2-amino-1-(furan-2-yl)ethanone hydrochloride in the presence of EDCI, HOBt, and NMM to provide the corresponding amide **21** in 96% yield. Amide **21** smoothly underwent thionation and subsequent cyclization by the action of Lawesson reagent in refluxing THF to lead to thiazole **22**. Finally, total removal of benzyl protection was affected with TMSI at mild heating overnight to produce the target compound **10a** in 50% yield.

Alternative approach toward derivatization on *ortho*-position of proximal phenyl ring is described in Scheme 4. Thus, treatment of allyl ether **23** with sodium borohydride in the presence of a catalytic amount of $Pd(PPh_3)_4$ [20], followed by total deprotection of the remaining benzyl groups by use of BCl_3 [21] smoothly provided the phenol **11a**. This pentaol was used for direct alkylation to provide *n*-propyl-ether **11b** or two-step conversion to 1,2,4-triazolylethoxyphenyl **11g**.

The C–C bond substituents on *ortho*-position of proximal phenyl ring were also attempted. Preparation of the requisite key intermediate **27** is described in Scheme 5. First, 3-amino-4-methylbenzoic acid (**24**) which is commercially available was converted to bromide **25** via three steps (bromination, esterification, and chlorination) in 53% yields overall. Next, methyl 2-bromo-5-chloro-4-methylbenzoate (**25**) was transformed into 4-(hydroxymethyl)benzoic acid **26** by benzylic bromination reaction as illustrated in Scheme 5. The alcohol functionality of **26** was then introduced by treating the resulting bromide with sodium acetate, followed by basic hydrolysis of the corresponding acetate with concomitant conversion from methyl ester to acid as shown in structure **26**. Finally, silyl protection of alcohol **26** with TIPSCl in the presence of imidazole, and subsequent borane–dimethylsulfide-mediated reduction of benzoic acid to the corresponding benzyl alcohol, followed by alkylated with allyl bromide in the presence of sodium hydride furnished the requisite bromide **27** in 53% yields for three steps.

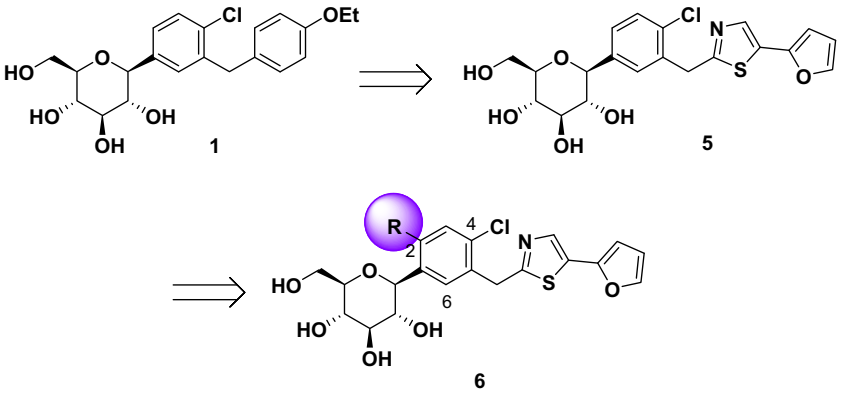

Fig. 2. Explorations of C-2 position of proximal ring in novel *C*-glucoside bearing thiazole **5**.