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Glucosides with cyclic diarylpolynoid as novel *C*-aryl glucoside SGLT2 inhibitors

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ABSTRACT

Novel *C*-aryl glucoside SGLT2 inhibitors containing cyclic diarylpolynoid motif were designed and synthesized for biological evaluation. Alkylzinc bromides have been efficiently prepared by the direct insertion of zinc metal into alkyl bromides. The organozinc reagents underwent smooth Pd-catalyzed cross-coupling reactions. Subsequent ring closing metathesis using 2nd generation Grubbs catalyst successfully generated novel class of ansa-compounds. These glucosides with cyclic diarylpolynoids demonstrated moderate in vitro inhibitory activity against SGLT2 in this series to date (IC_{50} = 59.5–103 nM).

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 by 2030 the number of people with diabetes will have grown to 438 million.[1] Type 2 diabetes is the most common disorder of glucose homeostasis, accounting for nearly 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] It is estimated that 90% of renal glucose reabsorption is facilitated by SGLT2.[4]

Bristol-Myers Squibb has identified dapagliflozin **1** (Fig. 1), a potent, selective SGLT2 inhibitor for the treatment of type 2 diabetes.[5–7] At present, dapagliflozin is the most advanced SGLT2 inhibitor in clinical trials and is expected to be the first SGLT2 inhibitor to market.[8] On the other hand, Mitsubishi Tanabe, in collaboration with Johnson & Johnson, is developing canagliflozin **2**, another

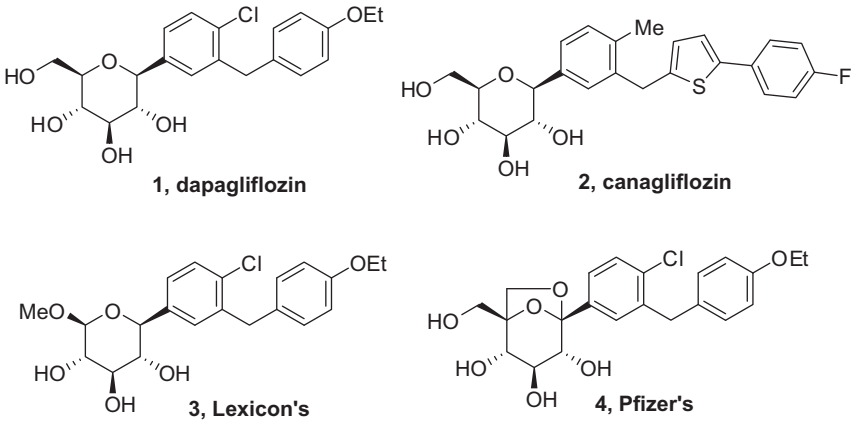

Figure 1. Structures of *C*-aryl glucoside SGLT2 inhibitors.

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novel C-glucoside-derived SGLT2 inhibitor.[9] In addition, Boehringer Ingelheim (BI 10773), Lexicon (LX4211), Astellas (ASP1941), and Pfizer (code unknown) are reported to be in various phase of clinical trials.[10] Our efforts on identifying inhibitors that target SGLT2 have been previously described.[11]

In the middle of exploring of SGLT2 inhibitors, two cyclic diarylheptanoids, acerogenin A (**5**) and B (**6**) have been reportedly isolated from the bark of Acer nikoense as inhibitors of SGLT.[12] Although effects of acerogenins on SGLT inhibitory activity was only moderate, these unique diarylheptanoid structure was very similar with diaryl or heteroaryl part of reported SGLT2 inhibitors. Thus, we expected that combination of cyclic diaryl formation and structure of dapagliflozin could lead to novel potent SGLT2 inhibitor analogs. These interests directed us to design ansa-structure **7** of *C*-aryl glucoside SGLT2 inhibitors as shown in Figure 2. Herein, we report the synthesis and biological evaluation of glucosides

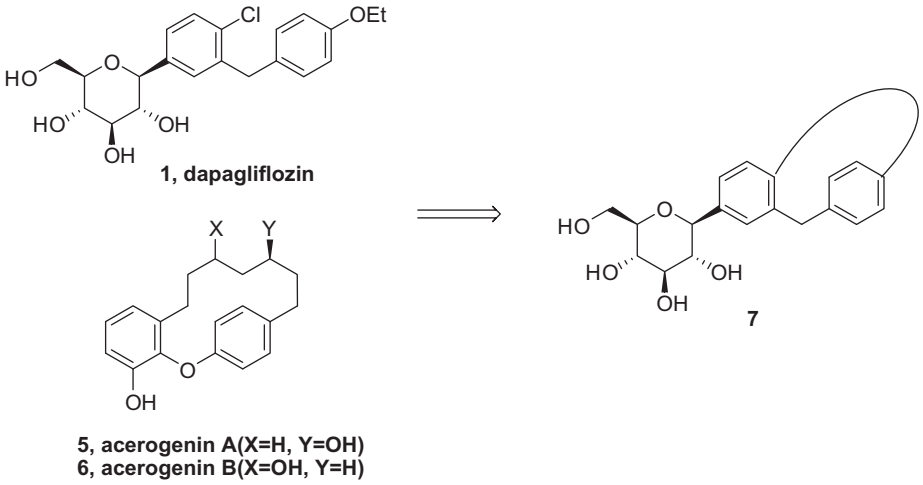
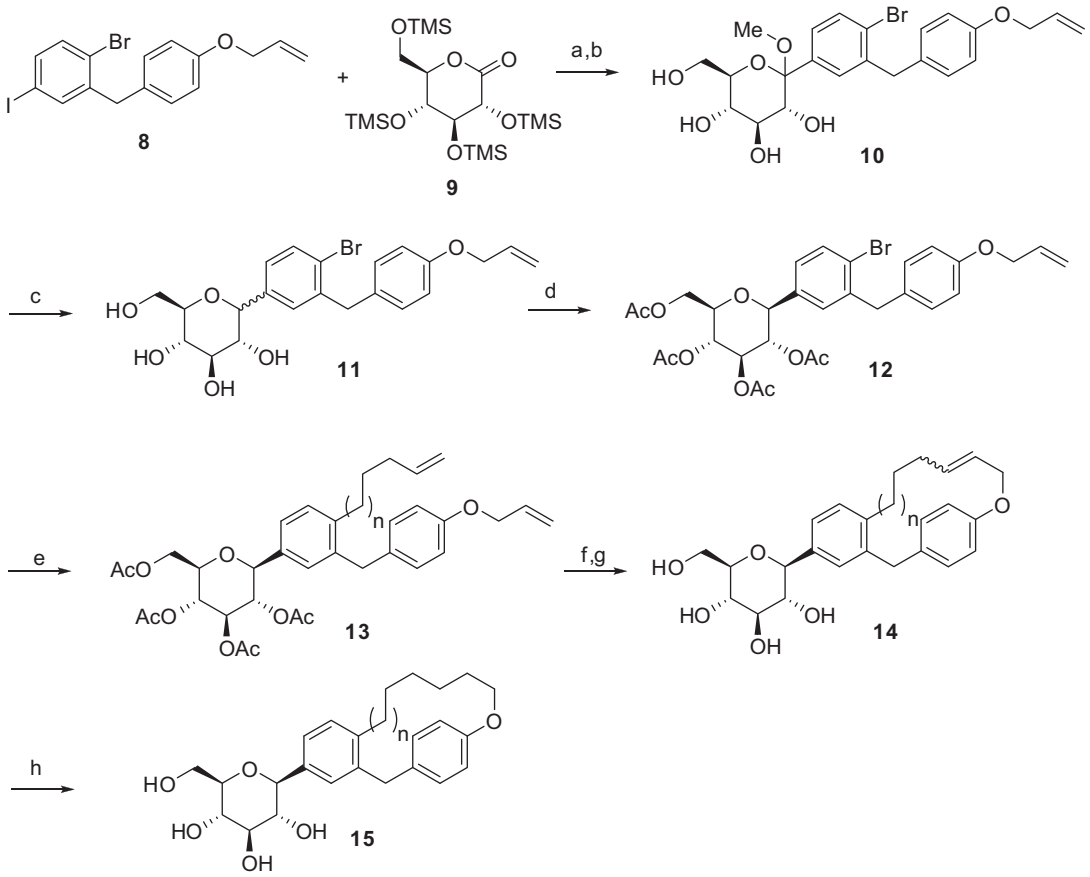


Figure 2. Design of novel C-glucosides bearing cyclic diarylpolynoid



Scheme 1. Reagents and conditions: (a) *i*-PrMgCl.LiCl, THF, −78 °C; (b) $MeSO_3H$, MeOH, rt; (c) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_3CN–CH_2Cl_2, −10 °C; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 47% (four steps); (e) (i) $Br(CH_2)_{2+n}CH{=}CH_2$, Zn, I_2, DMA, 80 °C, (ii) $Pd(PPh_3)_4$, rt, 34–72%; (f) 2nd generation Grubbs cat., $(ClCH_2)_2$, 80 °C, 21–46%; (g) NaOMe, MeOH, 67–81%; (h) 10% Pd/C, H_2, MeOH, 36–56%.

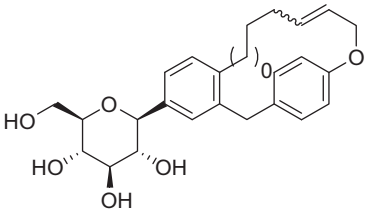
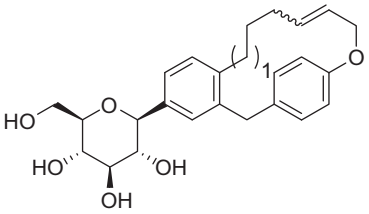
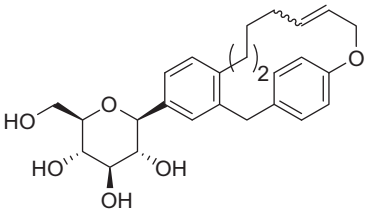
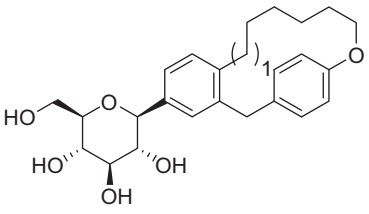
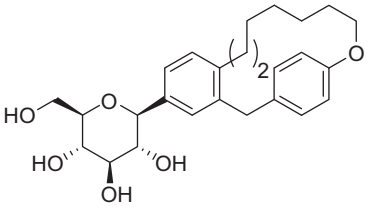
with cyclic diarylpolynoid as novel *C*-aryl glucoside SGLT2 inhibitors.

Preparation of *C*-glucosides bearing the cyclic diarylpolynoid is described in Scheme 1. Thus, treatment of 2-(4-(allyloxy)benzyl)-1-bromo-4-iodobenzene (**8**)[13] with isopropylmagnesium chloride lithium chloride complex solution effected magnesium-halogen exchange.[14] Subsequently, the addition of the nascent magnesiated aromatic compound to persilylated gluconolactone **9** produced a mixture of the corresponding lactols. The lactols were then treated with methanol in the presence of methanesulfonic acid to produce the corresponding methyl acetal **10**, concurrently desilylated. The methyl acetals were reduced with triethylsilane and BF_3 etherate to afford **11**.[15] A mixture of alcohols **11** was then peracetylated using acetic anhydride and triethylamine in the presence of DMAP (4-(dimethylamino)pyridine), and subsequently was separated through column chromatography to produce the requisite beta-isomer **12** in 47% yield over four steps.

With the key bromide **12** in hand, focus shifted to the efficient preparation of the divinyl compounds **13**, precursors for ring closing metathesis. The initial approach toward **13** involves Suzuki coupling of **12** using alkenylboronic acid in the presence of a suitable Pd(0) catalyst.[16] However, despite rather extensive experimentation, we were unable to effect the required coupling reaction in a satisfactory manner. Some typical coupling conditions invariably provided the desired products in merely low yields. At this stage, we were intrigued by the possibility of using alkylzinc reagents for Pd-catalyzed cross-coupling reactions.[17] Thus, treatment of alkenyl bromide with zinc dust (1.5 equiv), activated with I_2 (5 mol %) in DMA (*N*,*N*-dimethylacetamide) provides the corresponding alkenylzinc bromide. Its subsequent cross-coupling with phenylbromide **12** using a catalytic amount of $Pd(PPh_3)_4$ proceeded smoothly to completion within 4 h at room temperature. Under these conditions, divinyl compounds **13** were routinely obtained in 34–72% yields.

The stage was set for the key ring-closing metathesis to form macrocycle. After rather extensive experimentation, we were delighted to find out that treatment of divinyl **13** with 2nd generation Grubbs catalyst (0.1 equiv) in 1,2-dichloroethane (0.01 M) at 80 °C

Table 1
In vitro inhibitory activity against *h*SGLT2

Compound		*h*SGLT2 IC_{50}[a] (nM)
Dapagliflozin (**1**)		1.35 ± 0.15[b]
14a		59.5
14b		89.6
14c		103
15a		81.9
15b		99.7

[a] These data were obtained by single determinations.
[b] The IC_{50} value was obtained by in-house multiple determinations.

for 72 h provided the desired macrocycles in moderate yields (21–46%).[18] The geometric isomers were inseparable (*E*/*Z* = 2.5–3.0/1 based on ^{1}H NMR analysis). Subsequently, hydrolysis of **13** using NaOMe in methanol produced the corresponding deacetylated compounds **14** in good yields (67–81%). Finally, hydrogenation of **14** on 10% Pd/C in methanol generated the corresponding macrocycles **15** uneventfully.

The cell-based SGLT2 AMG (Methyl-α-D-glucopyranoside) inhibition assay was performed to evaluate the inhibitory effects of all prepared compounds on *h*SGLT2 activities.[19,20] Table 1 shows the structure–activity relationship upon alteration on the ring size of ansa-macrocycles. The smallest ring **14a** showed the moderate inhibitory activity against *h*SGLT2 (IC_{50} = 59.5 nM). As the ring size increases, the in vitro inhibitory activity gradually decreases as exemplified by compounds **14b** and **14c** (IC_{50} = 89.6 nM for **14b**, IC_{50} = 103 nM for **14c**), suggesting that bulky macrocyclic diarylpolynoid is not so favorable for overall in vitro inhibitory activity against *h*SGLT2. Also saturated macrocycles **15a** and **15b** proved to maintain the similar level of inhibitory activity against *h*SGLT2 to that of the corresponding parent molecules.[23,24]

In summary, although effects of acerogenins on SGLT inhibitory activity were reported to be only moderate, our interest of SGLT inhibition for cyclic diaryl compound combined with structure of potent dapagliflozin led to design ansa-structure **7** of *C*-aryl glucoside SGLT2 inhibitors. We successfully performed the synthesis of C-glucosides associated with cyclic diarylpolynoid utilizing versatile organozinc chemistry and subsequent ring-closing olefin metathesis using 2nd generation Grubbs catalyst. The synthesized ansa-analogs were subsecutively subjected to biological evaluation as novel *C*-aryl glucoside SGLT2 inhibitors. All of the analogs tested showed the modest in vitro inhibitory activity against *h*SGLT2 (**14a**, IC_{50} = 59.5 nM).

Acknowledgments

This letter is dedicated to Dr. Yoshito Kishi, a Harvard University chemistry professor on the occasion of recent U.S. approval of Eisai Co.'s Halaven. We appreciate Dr. Eun Chul Huh for his leadership as Head of R&D, Green Cross Corporation (GCC). We are also thankful to Dr. Jeongmin Kim and Mr. Sung-Han Lee for their helpful discussions.

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13. *Preparation of 2-(4-(allyloxy)benzyl)-1-bromo-4-iodobenzene* (**8**): To a mixture of 2-bromo-5-iodo-benzoic acid (25 g, 76.5 mmol) in CH_2Cl_2 (80 ml) were added $(COCl)_2$ (9 ml) and DMF (0.5 ml). The reaction mixture was stirred for 14 h at rt, and all volatile constituents were removed on rotary evaporator in vacuo. The residue was dissolved in CH_2Cl_2 (50 ml), and the resultant solution was cooled to 0 °C. After addition of anisole (23 ml) to the mixture, $AlCl_3$ (12.5 g) was added portionwise not to exceed 10 °C. The solution was stirred at rt for overnight and then poured into ice. The organic phase was separated off, and aqueous phase was extracted with CH_2Cl_2 twice. After drying organic phases with $MgSO_4$, the volatile compound was evaporated *in vacuo*. The crude product was purified with Biotage® to afford (2-bromo-5-iodophenyl)(4-methoxyphenyl)methanone (25.8 g, 81%) as a light yellow solid. A solution of (2-bromo-5-iodophenyl)(4-methoxyphenyl)methanone (10 g, 24 mmol) and triethylsilane (TESH, 15.3 ml, 96 mmol) in a mixture of CH_2Cl_2 (30 ml) and CH_3CN (60 ml) is cooled to 0 °C. Then with stirring, BF_3 etherate (5.0 ml, 36 mmol) was added slowly. The solution was stirred for 14 hr at rt. The solution was stirred for additional 3 hr at 50~60 °C and then cooled to rt. The resulting solution was quenched with aqueous KOH solution (50 ml) and the aqueous layer was extracted with ethyl acetate. After solvent was evaporated, the residue was purified with column chromatography to produce 1-bromo-4-iodo-2-(4-methoxybenzyl)benzene (6.96 g, 72%) as colorless oil. To a solution of 1-bromo-4-iodo-2-(4-methoxybenzyl)benzene (7.5 g, 18.6 mmol) in CH_2Cl_2 (50 ml) at 0 °C was added BBr_3 in CH_2Cl_2 (1.0 M, 37.5 ml) dropwise, and the reaction solution was then stirred for 3 h at rt. The resulting solution was quenched with MeOH and the volatile constituents were removed on rotary evaporator. The residue was purified with Biotage® to afford 4-(2-bromo-5-iodobenzyl)phenol (6.7 g, 92%) as a white solid. To a mixture of 4-(2-bromo-5-iodobenzyl)phenol (6.7 g, 17.2 mmol) and K_2CO_3 (9.5 g, 68.8 mmol) in CH_3CN (50 ml) was added allylbromide (3.2 ml, 37 mmol). The reaction mixture was stirred for 24 hr at rt. After filteration of insoluble compounds, the filtrate was evaporated, and the residue was purified with Biotage® to produce 2-(4-(allyloxy)benzyl)-1-bromo-4-iodobenzene (6.9 g, 95%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 2.4 Hz, 1H), 7.41 (dd, J = 8.4, 2.0 Hz, 1H), 7.29 (s, 1H), 7.13–7.11 (m, 2H), 6.91–6.89 (m, 2H), 6.13–6.06 (m, 1H), 5.47–5.43 (m, 1H), 5.34–5.31 (m, 1H), 5.55 (dt, J = 5.2, 2.0 Hz, 2H). MH^+ 429.
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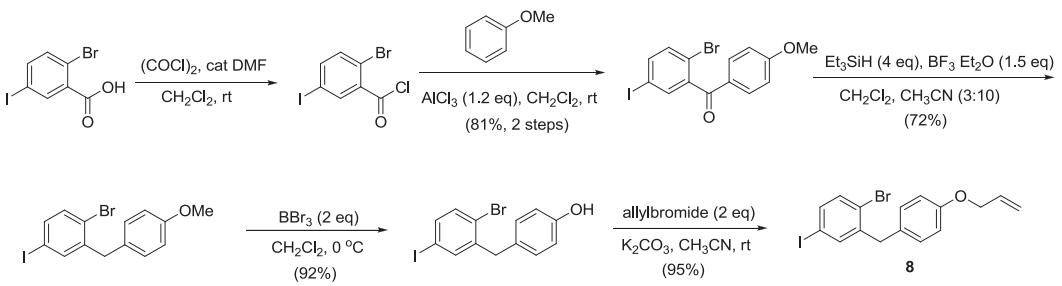

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19. For cloning and cell line construction for human SGLT2, human SGLT2 (*h*SGLT2) gene was amplified by PCR from cDNA-Human Adult Normal Tissue Kidney (Invitrogen, Carlsbad, CA). The *h*SGLT2 sequence was cloned into pcDNA3.1(+) for mammalian expression and were stably transfected into chinese hamster ovary (CHO) cells. SGLT2-expressing clones were selected based on resistance to G418 antibiotic (Geneticin®, Invitrogen, Carlsbad, CA) and activity in the ^{14}C-α-methyl-D-glucopyranoside (^{14}C-AMG) uptake assay.
20. For sodium-dependent glucose transport assay, cells expressing *h*SGLT2 were seeded into a 96-well culture plate at a density of 5×10^4 cells/well in RPMI medium 1640 containing 10% fetal bovine serum. The cells were used 1 day after plating. They were incubated in pretreatment buffer (10 mM HEPES, 5 mM Tris, 140 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, and 1 mM $MgCl_2$, pH 7.4) at 37 °C for 10 min. They were then incubated in uptake buffer (10 mM HEPES, 5 mM Tris, 140 mM NaCl, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 1 mM ^{14}C-nonlabeled AMG pH 7.4) containing ^{14}C-labeled (8 μM) and inhibitor or dimethyl sulfoxide (DMSO) vehicle at 37 °C for 2 h. Cells were washed twice with washing buffer (pretreatment buffer containing 10 mM AMG at room temperature) and then the radioactivity was measured using a liquid scintillation counter. IC_{50} was determined by nonlinear regression analysis using GraphPad PRISM.[21,22]
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23. Initially, we expected that the novel series of designed compounds would be able to provide potent inhibition against hSGLT2, showing synergistic effect by macrocyclization. Although these current compounds appear to show only moderate inhibition activity, the authors think that this series hinted valuable possibilities about combination of two different structures. As a matter of fact, we have identified much more potent series of macrocycles as SGLT2 inhibitors in house by extending conceptually from this series.
24. In this communication, SGLT2 inhibiton data were obtained by single determinations. Whenever we evaluate our new compounds against *h*SGLT2, dapagliflozin was also included as a reference compound. The SGLT2 inhibition for dapagliflozin has shown a certain number in the close range in each different assay. Thus, we believe that all SAR discussions in the manuscript are scientifically valid.