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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

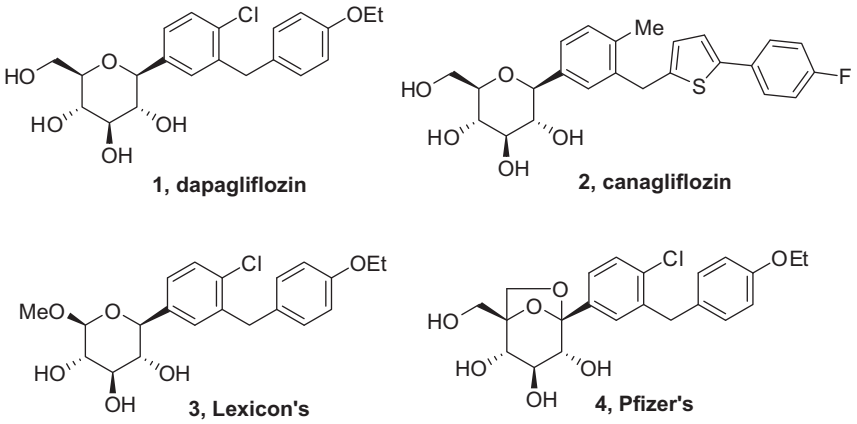

Figure 1. Structures of *C*-aryl glucoside SGLT2 inhibitors.

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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

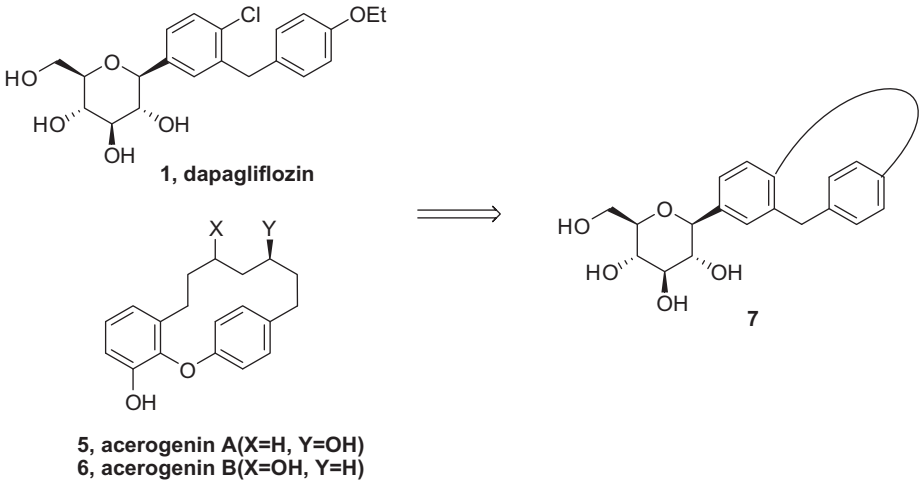
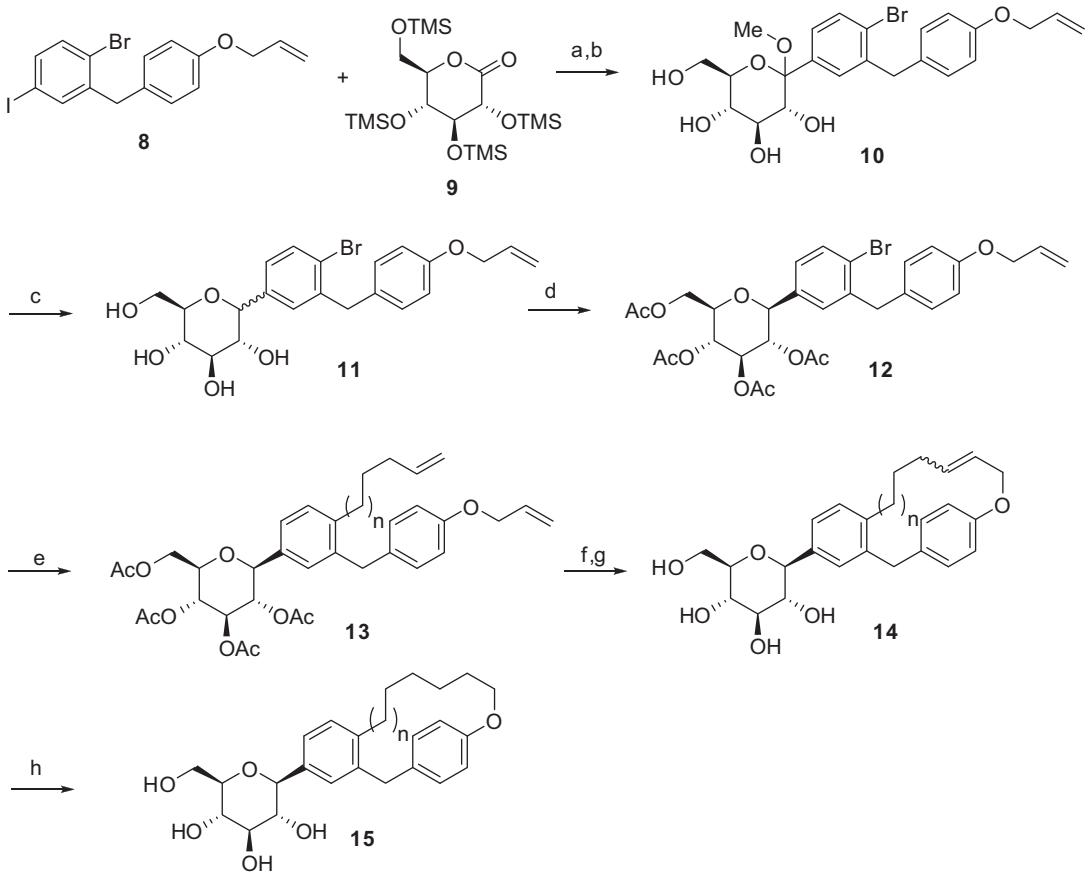


Figure 2. Design of novel C-glucosides bearing cyclic diarylpolynoid



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%.