Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 1215–1218
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Design, synthesis and *in vivo* anti-hyperglycemic activity of *gem*-dimethyl-bearing *C*-glucosides as SGLT2 inhibitors

Wen Jing Zhao [a], Yong Heng Shi [b,c], Gui Long Zhao [b,*], Yu Li Wang [b], Hua Shao [b], Li Da Tang [b], Jian Wu Wang [a,*]

[a] *School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, China*
[b] *Tianjin Key Laboratory of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, China*
[c] *School of Pharmacy, Tianjin Medical University, Tianjin 300070, China*

Available online 18 July 2011

Abstract

A series of *gem*-dimethyl-bearing *C*-glucosides were designed and synthesized as SGLT2 inhibitors, with anhydrous aluminum chloride-mediated Friedel-Crafts alkylation to construct the *gem*-dimethyl functionality being the key step. The *in vivo* anti-hyperglycemic activity was evaluated with mice oral glucose tolerance test (OGTT), and all the synthesized compounds showed significant but less potent anti-hyperglycemic activity than the positive control dapagliflozin.

Keywords: Synthesis; *C*-Glucoside; SGLT2 inhibitor; Anti-hyperglycemic activity; *gem*-Dimethyl

Diabetes is a chronic metabolic disease which is characterized by hyperglycemia. If not being controlled appropriately, hyperglycemia would lead to a variety of severe diabetic complications.

Over 99% of the plasma glucose that is filtered in the renal glomerulus is reabsorbed into the blood mainly by sodium-glucose co-transporter 2 (SGLT2) in the renal proximal tubule [1]. Therefore, inhibition of SGLT2 would suppress the reabsorption of glucose from glomerular filtrate, thus lowering the blood glucose levels. SGLT2 inhibitors have become a promising class of hypoglycemic agents for the treatment of type 2 diabetes.

The origin of the discovery of SGLT2 inhibitors was the natural product phlorizin (Fig. 1), which has been discovered as a glycosuric agent more than several decades ago. More recently, phlorizin was found to be a SGLT2 inhibitor, but it was non-selective against SGLT2/SGLT1 and was liable to the degradation by β-glycosidase in the small intestine [2]. Encouraged by these observations, a number of *O*-glucosides were discovered as SGLT2 inhibitors based on the molecular structure of phlorizin in the earlier stage (Fig. 1). However, like phlorizin, they were later found to be still liable to the degradation by β-glycosidase [3], whose pre-clinical or clinical trials were all discontinued.

The *C*-glucosides were subsequently designed, and they were found to be robust to the degradation by β-glycosidase (Fig. 2). Among the *C*-glucosides discovered as SGLT2 inhibitors so far, dapagliflozin was the most advanced one, which is now in phase III clinical trials [1].

The benzylic methylene group between the two benzene rings of dapagliflozin was liable to be hydroxylated in *in vivo* metabolism, and the metabolite thus formed was not a SGLT2 inhibitor [4]. Inspired by these observations, a

* Corresponding author.
E-mail addresses: zhao_guilong@126.com (G.L. Zhao), jwwang@sdu.edu.cn (J.W. Wang).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2011.05.022

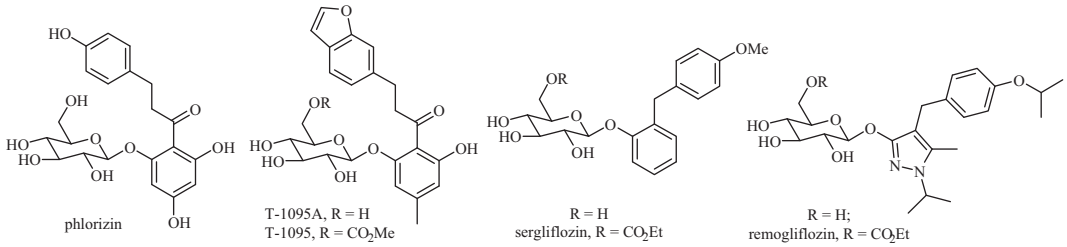


Fig. 1. Molecular structures of some well-established *O*-glucosides as SGLT2 inhibitors in the earlier stage.

variety of *gem*-dimethyl-bearing *C*-glucosides have been designed and evaluated *in vivo* in our laboratories, which were found to be potent SGLT2 inhibitors (Fig. 3) [5]. In order to further investigate the structure-activity relationship of this novel class of *gem*-dimethyl-bearing SGLT2 inhibitors, a new series of *C*-glucosides were further designed here to explore the effect of the substituents at the different positions of benzene ring adjacent to the glucose moiety on the anti-hyperglycemic activity (Scheme 1).

The synthetic route to the title compounds was outlined in Scheme 1. D-Glucolactone **2** was pertrimethylsilylated according to a known procedure [1,6]. Benzoic acids **4a–d** were converted to their ethyl esters **5a–d** following a standard procedure. Esters **5a–d** were treated with excess MeMgCl in THF to smoothly furnish the tertiary alcohols **6a–d**, which were coupled with phenetol to give rise to **7a–d** by $AlCl_3$-mediated Friedel-Crafts alkylation. Bromides **7a–d** were treated with *n*-BuLi at −78 °C to give the corresponding aryl lithiums, which were trapped *in situ* with **3** to afford **8a–d**. The intermediates **8a–d** formed were treated *in situ* with methanol in the presence of MsOH to yield **9a–d**. The anomeric methoxy group in **9a–d** was reductively removed with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ to furnish *C*-glucosides **10a–d** as anomeric mixtures. Peracetylation of **10a–d** to **11a–d** with Ac_2O was achieved in refluxing acetic acid in the presence of anhydrous NaOAc. Tetraacetates **11a–d**, which were still in the form of anomeric mixtures, were subjected to column chromatography to separate the desired *β*-anomers **12a–d**. Treatment of tetraacetates **12a–d** with MeONa in methanol at room temperature smoothly cleavaged all the acetyl groups to afford the desired products **1a–d** [8] after neutralizing the MeONa in the reaction mixture with strongly acidic resin in H^+ form.

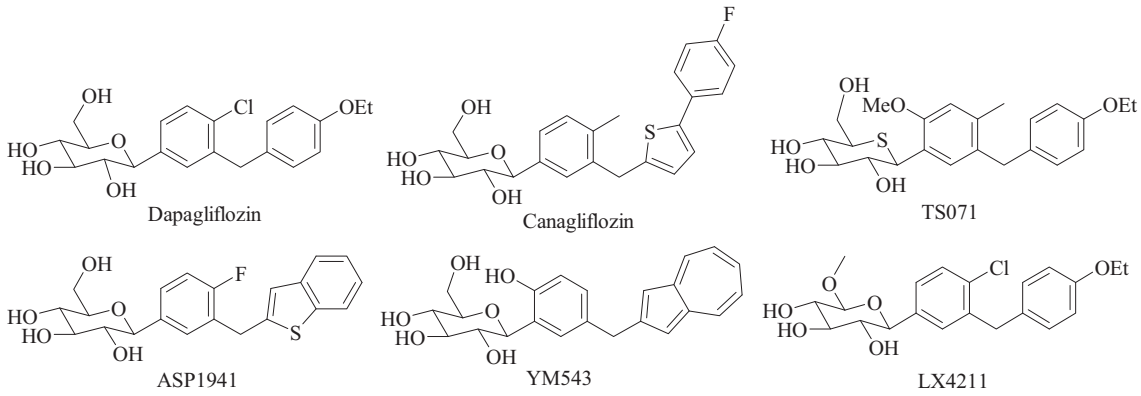


Fig. 2. Molecular structures of some SGLT2 inhibitors that are now in clinical trials.

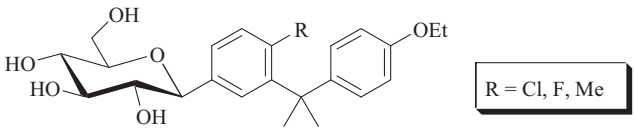
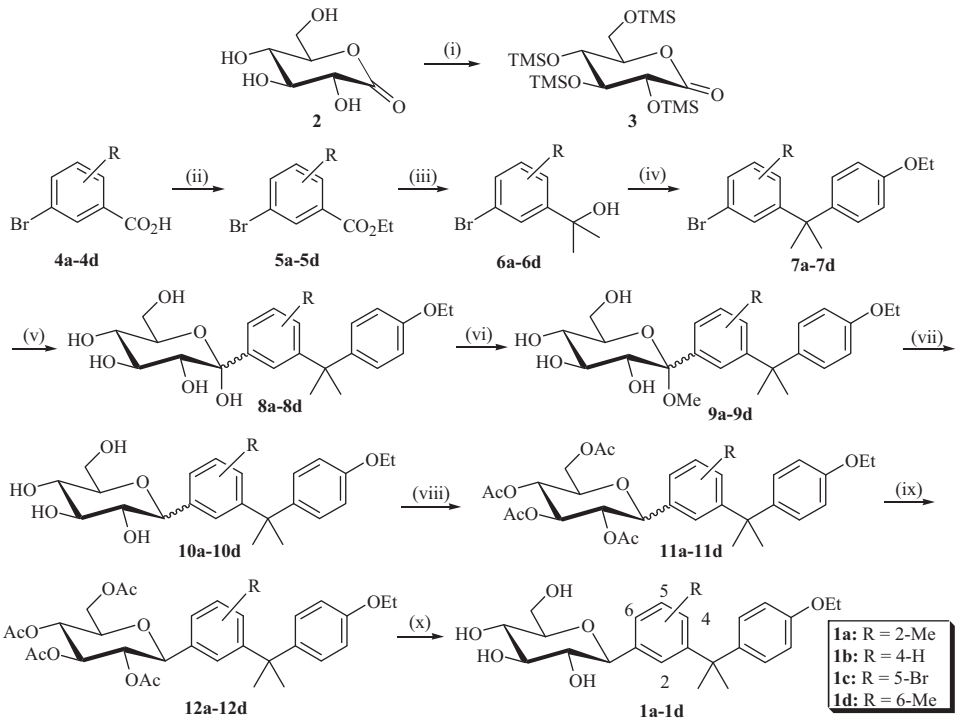


Fig. 3. The SGLT2 inhibitors designed previously in our laboratories.



Scheme 1. Reagents and conditions: (i) TMSCl (6 eq), NMM (8 eq), THF, 0–35 °C; (ii) CH_2SO_4, EtOH, PhH, reflux; (iii) 2MeMgCl, THF, −5 °C to 0 °C; (iv) $AlCl_3$, PhOEt, CH_2Cl_2, 0 °C – rt; (v) *n*-BuLi, THF, −78 °C; then, 3 in PhMe, −78 °C; (vi) MsOH, MeOH, rt; (vii) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0–5 °C and then rt; (viii) NaOAc, Ac_2O, AcOH, reflux; (ix) column chromatography; (x) NaOMe, MeOH, rt; then strongly acidic resin (H^+ form), rt.

The anti-hyperglycemic activities of **1a–d** were evaluated *in vivo* using mice oral glucose tolerance test (OGTT) according to a known procedure [5,7], and the results were summarized in Fig. 4 and Table 1. As shown in Table 1, the anti-hyperglycemic activities of **1a–d** were all significant but less potent than the positive control dapagliflozin, and the inhibition rates were in the following order, **1b** > **1d** > **1c** > **1a**, demonstrating that substituents at the 4-postion of the benzene ring adjacent to the glucose moiety were the most preferred and the order of preference for positions on this benzene ring is 4-position > 6-position > 5-position > 2-position, which is consistent with the SAR obtained from analogous structures [1].

In conclusion, a series of *gem*-dimethyl *C*-glucosides were designed and synthesized as SGLT2 inhibitors, and the *in vivo* anti-hyperglycemic activities were evaluated with mice oral glucose tolerance test, which revealed that substituents at the 4-position of the benzene adjacent to the glucose moiety were most preferred.

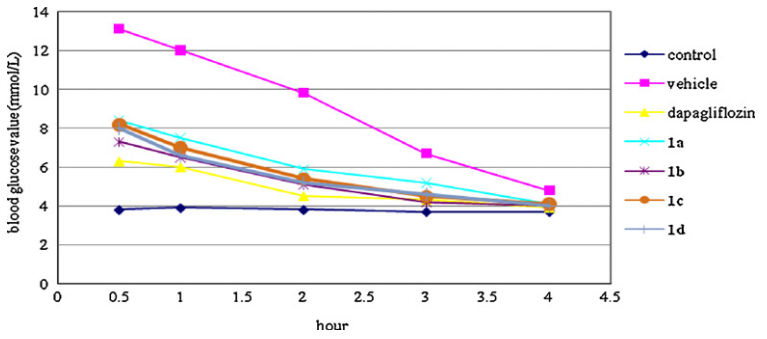


Fig. 4. Changes of mean blood glucose levels following administration of compounds **1a-c**.

Table 1
In vivo inhibition of blood glucose levels of **1a–c**.

Compounds	Dapagliflozin	**1a**	**1b**	**1c**	**1d**
Inhibition rates/%	79	57	72[a]	65	68[b]

[a] $p < 0.05$ (vs dapagliflozin).
[b] $p < 0.05$ (vs dapagliflozin).

Acknowledgment

The authors are very grateful to Key Projects of Tianjin Science and Technology Support Plan (No. 10ZCKFSH01300) for financial support.

References

[1] M. Meng, B.A. Ellsworth, A.A. Nirschl, et al. J. Med. Chem. 51 (2008) 1145.
[2] J.T. Link, B.K. Sorensen, Tetrahedron Lett. 41 (2000) 9213.
[3] W.N. Washburn, J. Med. Chem. 52 (2009) 1785.
[4] M. Obermeier, M. Yao, A. Khanna, et al. Drug Metab. Disp. 38 (2010) 405.
[5] Y.H. Shi, G.L. Zhao, Y.Y. Lou, et al. Chin. J. Chem. 29 (6) (2011) 1192.
[6] H. Shao, G.L. Zhao, W. Liu, et al. Chin. J. Synth. Chem 18 (2010) 389.
[7] Y.L. Gao, G.L. Zhao, W. Liu, et al. Indian J. Chem 49B (2010) 1499.
[8] ^{1}H NMR data for **1a–d**. **1a**, white foam, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.45 (d, 1H, J = 8.0 Hz), 7.28 (d, 1H, J = 7.6 Hz), 7.19 (t, 1H, J = 7.8 Hz), 7.00 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J = 8.4 Hz), 4.88 (d, 1H, J = 4.4 Hz), 4.85 (d, 1H, J = 4.8 Hz), 4.68 (d, 1H, J = 5.6 Hz), 4.38 (t, 1H, J = 5.8 Hz), 4.21 (d, 1H, J = 9.2 Hz), 3.96 (q, 2H, J = 6.9 Hz), 3.64 (dd, 1H, J = 5.4 Hz and 11.4 Hz), 3.31–3.40 (m, 2H), 3.22–3.27 (m, 1H), 3.13–3.17 (m, 2H), 1.80 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.17 (t, 3H, J = 7.0 Hz); **1b**, white foam, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.04–7.22 (m, 6H), 6.80 (d, 2H, J = 8.8 Hz), 4.89 (t, 2H, J = 4.8 Hz), 4.70 (d, 1H, J = 5.6 Hz), 4.41 (t, 1H, J = 5.8 Hz), 3.94–3.99 (m, 3H), 3.67–3.72 (m, 1H), 3.40–3.46 (m, 1H), 3.23–3.29 (m, 1H), 3.12–3.21 (m, 3H), 1.60 (s, 6H), 1.30 (t, 3H, J = 7.0 Hz); **1c**, white foam, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.33 (s, 1H), 7.21 (s, 1H), 7.16 (t, 1H, J = 1.6 Hz), 7.11 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.8 Hz), 4.91 (bs, 2H), 4.82 (bs, 1H), 4.44 (bs, 1H), 3.94–4.00 (m, 3H), 3.68 (d, 1H, J = 11.6 Hz), 3.42–3.46 (m, 1H), 3.14–3.26 (m, 3H), 3.08 (t, 1H, J = 5.6 Hz), 1.58 (s, 6H), 1.30 (t, 3H, J = 6.8 Hz); **1d**, white foam, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.27 (s, 1H), 7.09 (d, 2H, J = 8.8 Hz), 7.00 (d, 1H, J = 8.0 Hz), 6.90 (d, 1H, J = 8.0 Hz), 6.79 (d, 2H, J = 8.4 Hz), 4.88–4.91 (m, 2H), 4.74 (d, 1H, J = 5.6 Hz), 4.41 (t, 1H, J = 5.6 Hz), 4.21 (d, 1H, J = 9.6 Hz), 3.97 (q, 2H, J = 6.9 Hz), 3.69 (dd,1H, J = 5.6 Hz and 11.2 Hz), 3.35–3.43 (m, 2H), 3.27–3.30 (m, 1H), 3.20–3.23 (m, 1H), 3.10–3.16 (m, 1H), 2.28 (s, 3H), 1.58 (s, 6H), 1.30 (t, 3H, J = 6.8 Hz).