Bioorganic & Medicinal Chemistry Letters 26 (2016) 2170–2173

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Modification on the *O*-glucoside of Sergliflozin-A: A new strategy for SGLT2 inhibitor design

Xuefeng Cao [a,†], Wenpeng Zhang [b,†], Xu Yan [a], Zhi Huang [a], Zhenqing Zhang [b], Peng Wang [a,*], Jie Shen [a,*]

[a] *State Key Laboratory of Medicinal Chemical Biology, College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin 300071, PR China*
[b] *State Key Laboratory of Toxicology and Medical Countermeasures, Beijing Institute of Pharmacology and Toxicology, Beijing 100850, PR China*

ARTICLE INFO

Article history:
Received 18 February 2016
Revised 14 March 2016
Accepted 16 March 2016
Available online 16 March 2016

Keywords:
SGLT2 inhibitor
Sergliflozin-A
O-Glucoside
Pharmacokinetic stability

ABSTRACT

Poor pharmacokinetic stability is one of the issues of *O*-glucoside SGLT2 inhibitors in clinical trials, hence *C*-glucoside inhibitors have been developed and extensively applied. Herein, we provided an alternative approach to improve the pharmacokinetic stability of such inhibitors. Nine derivatives of Sergliflozin-A with modifications on the *O*-glucoside fragment were prepared, among which the 4-*O*-methyl derivative exhibited similar pharmacodynamics potency in excreted glucose urine test. Most attractively, significantly increased pharmacokinetic stability was observed for 4-*O*-methyl derivative of *O*-glucosides. This work proved that modification on the *O*-glucoside fragment could be a promising approach to the future SGLT2 inhibitor design.

© 2016 Elsevier Ltd. All rights reserved.

During the past few years, great efforts have been devoted to develop sodium glucose co-transporter 2 (SGLT2) inhibitors as a new class of drugs for the treatment of diabetes.[1–8] These compounds (Fig. 1) could effectively relieve diabetic hyperglycemia via lowering the renal glucose reabsorption.[9–11] Phlorizin, isolated from the bark of apple roots, was the first *O*-glucoside compound which can inhibit both SGLT1 and SGLT2.[12,13] Other *O*-glucoside inhibitors with high selectivity towards SGLT2 were also developed. However, most of *O*-glucoside inhibitors, for example, T-1095[14] and Sergliflozin,[15,16] were suspended. Currently, majority of the launched SGLT2 inhibitors, e.g., Dapagliflozin,[4] Empagliflozin[6,17] and Canagliflozin,[7,18] are *C*-glucosides. This could at least partially be attributed to the poor metabolic stability of *O*-glucosides, arising from the glucosidase mediated hydrolysis.

Alternatively, it is understandable that modification on the *O*-glucoside fragment may affect the substrate-glucosidase binding, thus could also help to improve in vivo stability. In this work, taking Sergliflozin-A (active form of Sergliflozin) as a parent structure, a series of derivatives with modification on hydroxyl groups (e.g., methylated, fluorine-substituted, deoxidized) of its *O*-glycoside were synthesized (Fig. 2) and evaluated.

The synthesis of Sergliflozin-A and its nine derivatives were illustrated in Scheme 1. Briefly, the peracetylated α-glucosyl bromide donor **A0** was coupled with the aglycon acceptor **S2**[19] to afford the intermediate **A1** which was deacetylated to give the compound **A**, Sergliflozin-A. Promoted by boron trifluoride etherate, the glycosyl donor **B0**[19] was coupled with **S2** to provide the intermediate **B1**, which was sequentially deacetylated and methylated at its *O*2 position to afford the 2-*O*-methyl 3,4,6-tri-*O*-benzyl derivative **B3**. Pd-catalyzed debenzylation of **B3** gave the compound **B**. The 2-fluorinated glucosyl Schimidt donor **C0**[19] was coupled with **S2** to provide the intermediate **C1** as an unseparable α/β mixture.[19] After the sequential debenzylation, acetylation and flash chromatography separation, **C1** was converted to the intermediate **C3** as a pure β isomer, which was converted to the compound **C** by the global deacetylation. The compounds **D**, **E**, **I** were prepared from the 1-acetylated donors **D0**,[19] **E0**[19] and **I0**[19] respectively via a similar two-step procedure, including a glycosylation reaction followed by a global deacetylation. The compound **F** was prepared from compound **A** in 5 steps. Specifically, after the 4,6-benzylidenation and 2,3-benzylation reactions, **A** was converted to the intermediate **F2**. Regioselective and reductive ring opening of the 4,6-benzylidene of **F2** gave the intermediate **F3** whose 4-hydroxyl group was then methylated with MeI. Then the obtained intermediate was converted to the product **F** via global debenzylation. Regioselective benzoylation of the thioglycoside **G0**[19] gave the intermediate **G1** whose 4-hydroxyl group was thiocarbonylated to give the intermediate **G2**. Barton–McCombie radical reduction was then performed to convert **G2** to the 4-deoxy intermediate, which was converted to 1-acetylated donor compound **G3**. Then **G3** was coupled with **S2** to afford the glycosylation product **G4**,

---

* Corresponding authors.
E-mail addresses: pwang@nankai.edu.cn (P. Wang), jieshen@nankai.edu.cn (J. Shen).
† Authors contributed equally to this work.

http://dx.doi.org/10.1016/j.bmcl.2016.03.065
0960-894X/© 2016 Elsevier Ltd. All rights reserved.

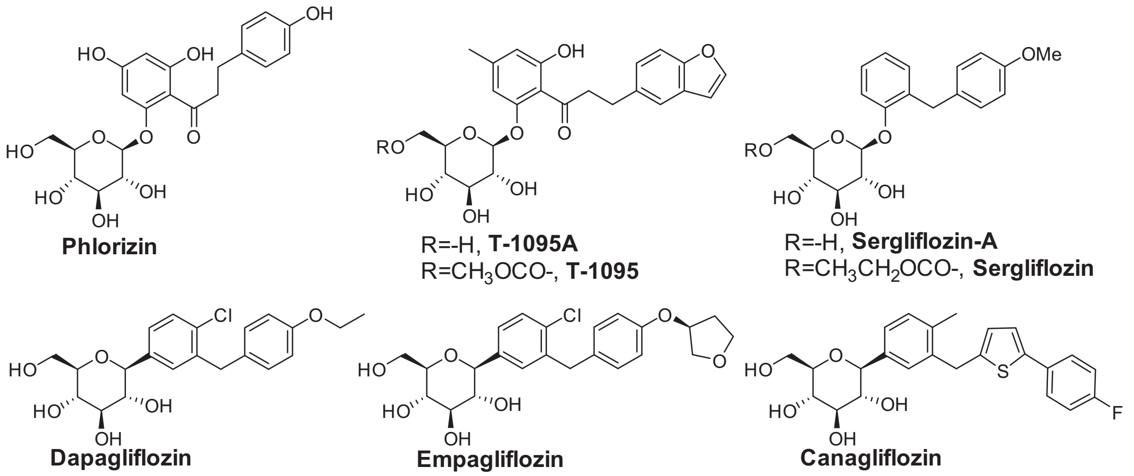

Figure 1. Important SGLT2 inhibitors.

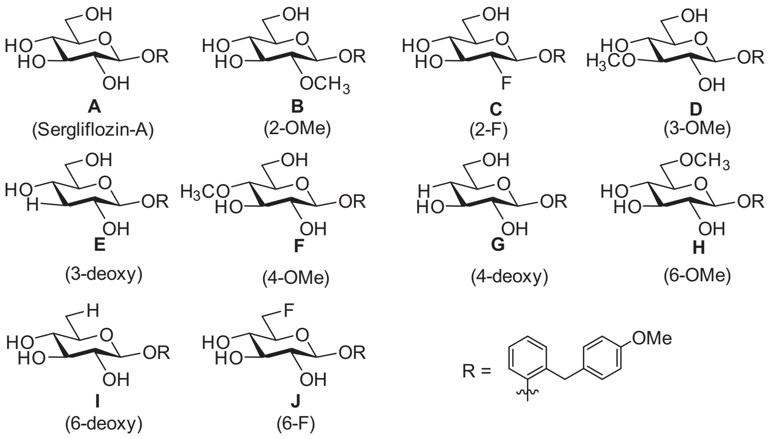

Figure 2. Sergliflozin-A and its 9 derivatives.

which was converted to the compound **G** via the global de-esterification. Syntheses of the last two compounds **H** and **J** shared the same intermediated **H1**, which was prepared from **A** via regioselective protection of 6-hydrxoyl group with trityl chloride. For the synthesis of **H**, **H1** was per-benzylated to afford the intermediate **H2**, whose trityl group at *O*6 was replaced with a methyl group in two steps. The therefore obtained intermediated **H4** was converted to the compound **H** via global debenzylation. For the synthesis of **J**, **H1** was per-acetylated to afford the intermediate **J2**. After the trityl group of **J2** was removed, DAST reagent was utilized to accomplish the fluorine substitution reaction at *C*6, so as to convert **J3** to **J4**, whose global deacetylation led to the product **J**.

As for the glycosylation reactions that promoted by boron trifluoride etherate to give products **B1**, **D1**, **E1**, **I1** and **G4**, product isomerization at 0 °C was observed for **B1** which is an armed glycoside. As the kinetically favored β-isomer, **B1** was formed as the major product initially with little amount of α-isomer. However, it was gradually converted to its more stable α-isomer. Therefore whereas the glycosylation of the disarmed **D1** was performed at 0 °C, the other the other four reactions were performed at −20 °C.

Rat urinary glucose excretion experiments were then performed to evaluate the in vivo hypoglycemic effects of the ten compounds **A**–**J** (Fig. 3). The results clearly indicated that the 2-hydroxyl group and 3-hydroxyl group were essential to the inhibition potency of the compound **A** against SGLT2, since any modification at these two hydroxyl groups (compounds **B**, **C**, **D**, **E**) almost completely abolished the hypoglycemic effect. In contrast, 4-methylated derivative **F** and the 6-deoxy derivative **H** are the two most potent derivatives, which maintained 73% and 31% in vivo potency compare with the parent compound **A**. These observations were in good consistence with structural data, where both 2- and 3-hydroxyl groups formed at least two hydrogen bonds with the bacterial vSGLT (PDB# 3DH4)[20,21] or human SGLT2[22] in their substrate recognition pocket. On the contrary, the 4- and 6-hydroxyl groups bound much loosely to the pocket and each of them formed only one hydrogen bond in both structures.

We also envisioned that pharmacokinetic factors might also benefit the in vivo potency of the compound **F**. To compare the metabolic stability of glucoside and its 4-methylated derivative, two fluorescent compounds **K** and **L** were prepared and treated in rat liver homogenate for 8 h. Whereas over 80% glucoside **K** was hydrolyzed, neglected amount of hydrolysis product could be detected for the corresponding 4-methylated compound **L** (Fig. 4). It should be addressed that the poor metabolic stability was one of the reasons for the failure of *O*-glucoside SGLT2 inhibitors in clinical trials.

It is now well accepted that the topological polar surface area (tPSA) of an orally administrated drug should be less than 140 Å^2. Considering the tPSA value of a glucoside fragment is around 100 Å^2, it is of no wonder that the glycons of all SGLT2 inhi-

Download English Version:

https://daneshyari.com/en/article/1368586

Download Persian Version:

https://daneshyari.com/article/1368586

Daneshyari.com