Bioorganic & Medicinal Chemistry Letters 22 (2012) 642–644

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Facile synthesis of 1,2,3-triazole analogs of SGLT2 inhibitors by 'click chemistry'

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ARTICLE INFO

Article history:
Received 2 September 2011
Revised 14 October 2011
Accepted 19 October 2011
Available online 24 October 2011

Keywords:
Metabolic diseases
SGLT2
Click chemistry
Triazole
Diabetes

ABSTRACT

Novel analogs of SGLT2 inhibitors containing the 1,2,3-triazole motif were designed and synthesized for urinary glucose excretion evaluation. The C-glucosides with triazole aglycone can be easily constructed by click chemistry. Most of the synthesized compounds increased urinary glucose excretion and demonstrated inhibition of glucose transport.

Diabetes prevalence throughout the world has rapidly increased over the past decades and has become a major health issue. It is predicted that in 2030, 439 million people worldwide will live with diabetes.[1] Type 2 diabetes is a very costly disease because of its chronic, progressive nature, the severity of related complications, and the medical treatment required to treat advanced stages. Despite lifestyle intervention and the availability of several classes of oral antidiabetic agents and insulin, most diabetic patients are still failing to achieve adequate glycaemic control.[2] Recently, sodium–glucose cotransporter 2 (SGLT2) inhibitors with novel mechanism have received considerable attentions for the treatment of type 2 diabetes. Inhibitors of SGLT2 can prevent reabsorption of glucose in the proximal tubule and will result in urinary glucose loss.[3] To date, dapagliflozin (Bristol-Myers Squibb), canagliflozin (Johnson & Johnson/Mitsubishi Tanabe), ASP1941 (Astellas/Kotobuki), and BI-10773 (Boehringer Ingelheim) with C-aryl glucosides are undergoing phase III clinical trials (Fig. 1).

It has been reported that many heterocyclic C-aryl glucosides are potent inhibitors with indole,[2a] benzisothiazole, and indolizine[4] aglycones. Substituted 1,2,3-triazole is a very important building block for more complex bioactive compounds, such as Tazobactam,[5] antiviral,[6] anti-HIV,[7] antibacterial,[8] and antiallergic agents.[9] Recently, N-glucosides with tetrazole[10] or triazole[11] aglycones have been investigated for inhibition of SGLT2. In our program to discover novel SGLT2 inhibitors, we focused on the C-glucosides with triazole aglycon, which can be constructed easily by copper catalyzed azide–alkyne cycloadditions (CuAACs).[12] Herein, we report the synthesis and glucosuria assessment of triazolylmethylaryl glucoside congeners.

The synthesis of the key alkyne intermediate is outlined in Scheme 1. Alkyne **6** can be obtained from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1** in five steps.[13] 2,3,4,6-Tetra-*O*-benzyl-D-(+)-glucono-1,5-lactone **2** was prepared by Swern oxidation of benzyl protected D-glucopyranose **1** in good yield (93%). Trimethylsilylacetylene was deprotonated with *n*-BuLi and treated with lactone **2** to provide ketose **3**. The anomeric isomers **3** can be confirmed by the ^{1}H NMR spectrum of crude product. The free hydroxyl group was reduced and the trimethylsilyl group can be removed easily by stirring in a mixture of NaOH, methanol, and dichloromethane, yielding the benzyl protected alkyne **5**. In our initial work, alkyne **5** and azides were used directly to construct triazole aglycon by click chemistry. However,

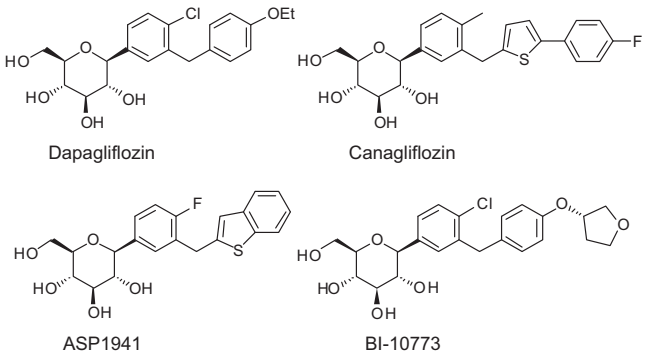

Figure 1. Representative SGLT2 inhibitors.

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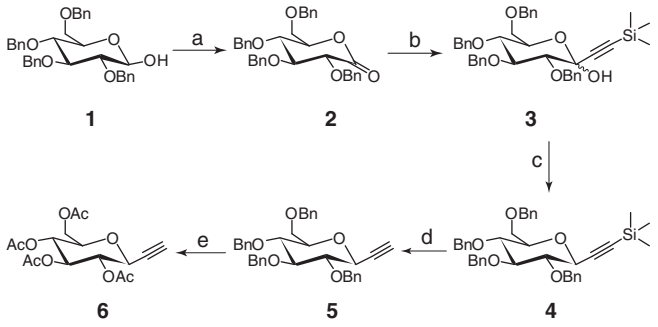
doi:10.1016/j.bmcl.2011.10.062



Scheme 1. Synthesis of key alkyne **6** (a) DMSO, Ac_2O, rt; (b) trimethylsilylacetylene, *n*-BuLi, THF, −78 °C; (c) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_3CN/CH_2Cl_2, −15 °C; (d) NaOH, CH_3OH/CH_2Cl_2, rt; (e) Ac_2O, $BF_3{\cdot}Et_2O$, rt.

complete removal of benzyl protecting groups was very difficult in the Pd/C H_2 system. As a result, compound **5** was transformed into the acetyl protected form **6** by the reported procedure.[14] The azide intermediates can be obtained from corresponding benzyl bromide according to Miller′ procedure[15] or prepared by the substitution reactions of DPPA and alcohols catalyzed by DBU, a method used by Melander.[16]

With the key alkyne **6** in hand, triazoles **7a–m** were then synthesized through CuAAC with the corresponding azides (Table 1).[12] Finally, the acetyl protecting groups were removed to give the triazole-linked C-glycosides compounds **7a–m**. A representative procedure is shown in Table 1. Substituted phenyl, naphthyl groups and heterocycles were easily introduced by click chemistry in good yields (55–88%).

Compound **7a–m** was tested in normal SD rats to assess inhibition of glucose transport via urinary glucose excretion.[1a,17] As shown in Figure 2, compared to the vehicle control, most of the compounds (30 mg/kg) increased urinary glucose excretion (**7a–c**, **7i**, and **7k–m**). However, we observed that all the compounds were less potent than dapagliflozin. Exploring the triazole analogs of known inhibitors ASP1941 and canagliflozin, we found that the benzothiophene analog **7k** and 4-fluorophenyl thiophene analog **7m** displayed less inhibition potential than dapagliflozin.

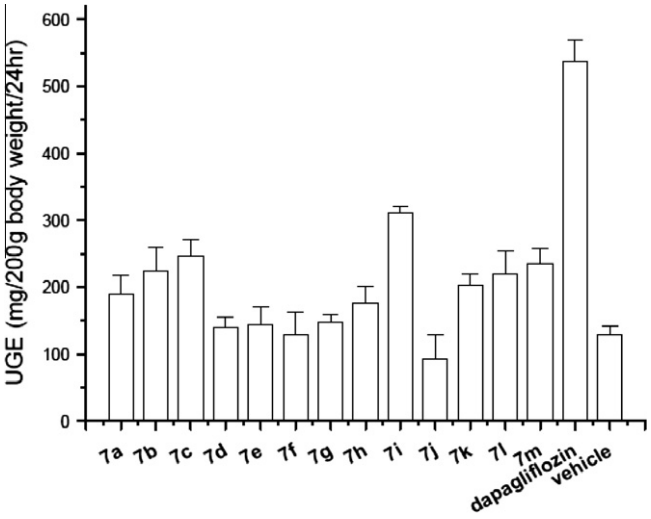
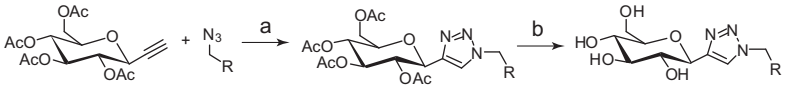
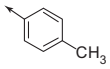
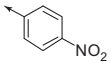
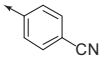
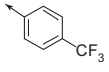
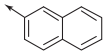
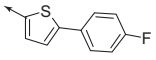
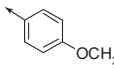


Figure 2. Rat 24 h UGE following treatment with compounds **7a–m**.

In summary, we have taken advantage of 'click chemistry' to synthesize a series of triazole C-glucosides, and evaluated their urinary glucose excretion. Most of the compounds demonstrated increased urinary glucose excretion in SD rats, but they increased urine volume to a lesser degree than that of dapagliflozin.

Table 1
Representative procedure of target compounds **7a–m**



R		Yield (%)	R		Yield (%)
7a		81	**7h**		55
7b		75	**7i**		79
7c		77	**7j**		88
7d		75	**7k**		74
7e		82	**7l**		78
7f		77	**7m**		80
7g		87			

Reagents and conditions: (a) sodium ascorbate, $CuSO_4$, H_2O/CH_2Cl_2, rt; (b) CH_3ONa, CH_3OH, rt.

Acknowledgments

We gratefully acknowledge financial support by the National Science Foundation of China (No. 21172120 and 20902050) and Tianjin Municipal Science and Technology Commission (No. 09JCYBJC09200).

Supplementary data

Supplementary data (Experimental section and general procedures.) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.10.062.

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