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Original article

Design, synthesis and biological activity of cyclohexane-bearing *C*-glucoside derivatives as SGLT2 inhibitors

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ABSTRACT

Seven cyclohexane-bearing *C*-glucoside derivatives (**7**, **9**, **12**, **13** and **17–19**) were designed and synthesized as SGLT2 inhibitors starting from a potent SGLT2 inhibitor we discovered in earlier work, (1*S*)-1-deoxy-1-[4-methoxy-3-(*trans*-*n*-propylcyclohexyl)methylphenyl]-D-glucose (**1**). The *in vitro* and *in vivo* biological activities were evaluated by hSGLT2/hSGLT1 inhibition and urinary glucose excretion (UGE), respectively. Among the synthesized compounds **12**, the 6-deoxy derivative of **1** was the most active and selective SGLT2 inhibitor (IC_{50} = 1.4 nmol/L against hSGLT2; selectivity = 1576). Compound **12** was a potent SGLT2 inhibitor, which could induce more urinary glucose than **1** and dapagliflozin in UGE.

1. Introduction

Diabetes is a kind of chronic metabolic disease that is characterized by hyperglycemia, either because the pancreas does not produce enough insulin and/or because the tissue cells poorly respond to the insulin that is produced. Diabetes without adequate treatment can cause a number of severe complications. Although there are many anti-diabetic drugs currently available, the hyperglycemia still can not be controlled in many cases, indicating that new anti-diabetic drugs with novel action mechanisms are urgently needed.

Most 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 [1,2]. Therefore, inhibition of SGLT2 is able to suppress the reabsorption of glucose from the glomerular filtrate into blood, which will lower the blood glucose levels. SGLT2 inhibitors have become a promising class of hypoglycemic agents for the treatment of type-2 diabetes, and many SGLT2 inhibitors are now in clinical trials. One of the SGLT2 inhibitors, dapagliflozin, has been approved recently in EU (Fig. 1).

In an earlier work, we discovered a class of novel SGLT2 inhibitors which incorporated a cyclohexane moiety in the molecules, among which a potent SGLT2 inhibitor, (1*S*)-1-deoxy-1-[4-methoxy-3-(*trans*-*n*-propylcyclohexyl)methylphenyl]-D-glucose (**1**), was discovered (Fig. 2) [3,4]. Encouraged by these promising results, we moved on to further study this class of novel SGLT2 inhibitors in anticipation of discovering more potent SGLT2 inhibitors, and herein would like to report the study on the compounds resulting from the derivatizations of the 6-OH of the sugar ring in **1** (Schemes 1–3).

2. Experimental

^{1}H NMR spectra were recorded on a Bruker AV400 spectrometer with DMSO-d_6 as solvent and TMS as internal standard. The HR-MS data were obtained on an Agilent Q-TOF 6510 mass spectrometer using electrospray ionization (ESI) technique. The synthetic routes of target compounds, **7**, **9**, **12**, **13**, **17–19**, are depicted in Schemes 1–3 and the steps involved are described in "Results and discussion".

A 50-mL dried flask was charged with 5 mL of dried MeOH and 0.10 g (4 mmol) of sodium, and the mixture was stirred at room temperature until all the sodium disappeared. Compounds **6**, **10**, **11** and **14–16** (1 mmol) were added to the solution, individually. The stirring was continued at room temperature until all the starting compounds were consumed completely (typical within

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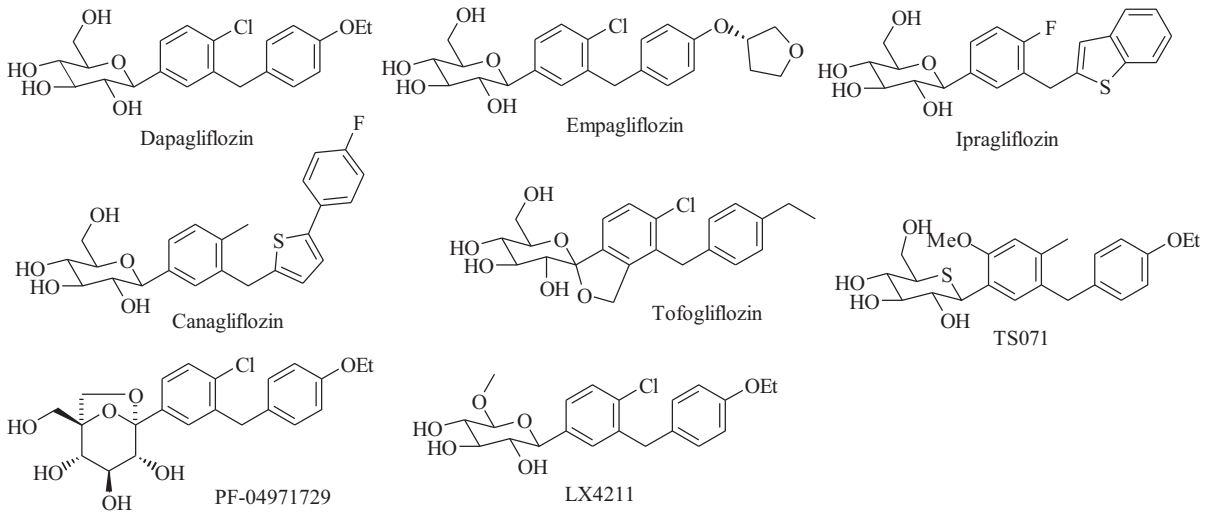


Fig. 1. Molecular structures of some SGLT2 inhibitors that are now in clinical trials or launched.

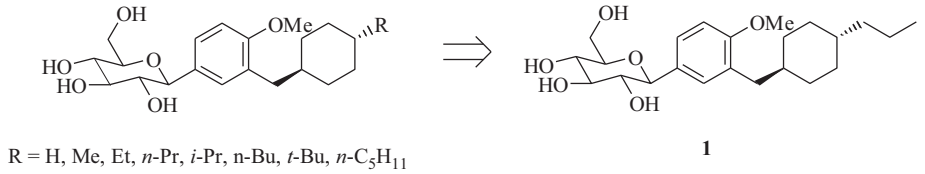
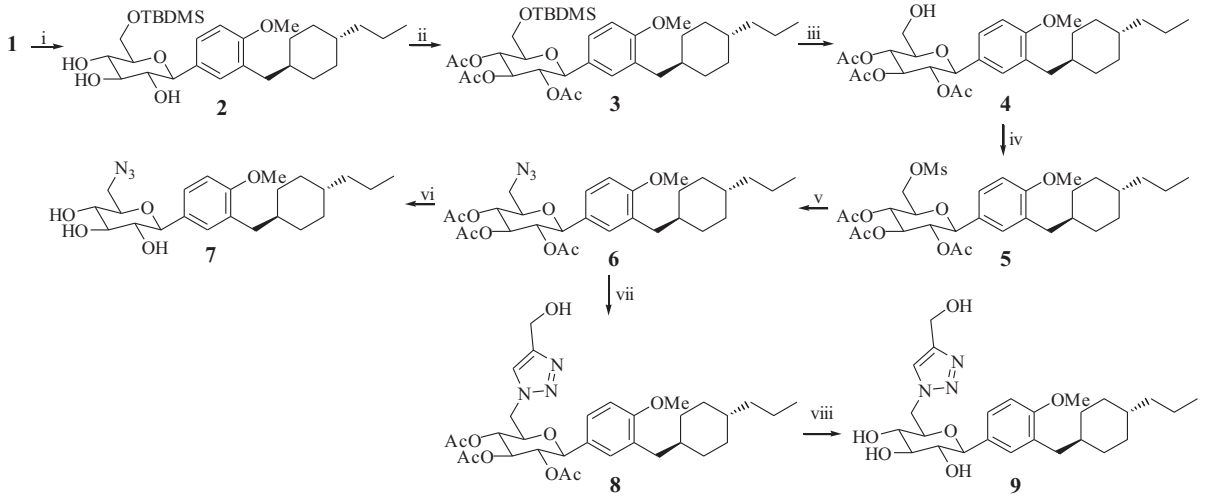


Fig. 2. The cyclohexane-bearing SGLT2 inhibitors discovered previously in our laboratories.

1 h) as demonstrated by TLC. On completion, 2 g of dried acidic resin was added to the reaction mixture and the stirring was continued at room temperature until the pH 7. The reaction mixture was filtered, and the filtrate was evaporated on a rotary evaporator to afford a white residue as crude products, which were further dried by vacuum oil pump to yield the pure products **7**, **13**, **12** and **17**–**19**, respectively.

A 50-mL flask was charged with **8** (1 mmol) and 10 mL of EtOH. The mixture was stirred at room temperature, followed by addition of 2 mL of 30% aqueous NaOH. The mixture thus obtained was refluxed for 10 min, cooled to room temperature and poured to 100 mL of water. The aqueous mixture was adjusted to pH 7 with concentrated hydrochloric acid and extracted with CH_2Cl_2 (15 mL × 3). The combined extracts were washed with saturated brine, dried over Na_2SO_4 and evaporated on a rotary evaporator to afford a residue, which was further dried *in vacuo* to yield the pure product **9**.

7: White foam, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.10 (dd, 1 H, J = 2.0 Hz and 8.4 Hz), 7.02 (d, 1H, J = 2.0 Hz), 6.85 (d, 1H, J = 8.4 Hz), 5.15 (d, 1H, J = 4.8 Hz), 4.97 (d, 1H, J = 4.8 Hz), 4.76 (d, 1H, J = 5.6 Hz), 4.01 (d, 1H, J = 9.6 Hz), 3.73 (s, 3H), 3.52 (dd, 1H, J = 2.0 Hz and 13.2 Hz), 3.42–3.44 (m, 1H), 3.21–3.37



Scheme 1. Synthetic route of target molecule **7** and **9**. Reaction conditions: i) TBDMSC l (1.1 eq), imidazole, dried DMF, 0-r.t.; ii) Ac_2O, DMAP, pyridine, 0-r.t.; iii) 90% AcOH, 45 °C; iv) MsCl, EtN, CH_2Cl_2, 0-r.t.; v) NaN_3, DMF, 100 °C; vi) MeONa, MeOH, r.t., then strongly acidic ion exchange resin (H^+ form); vii) propargyl alcohol, Cu(I), DMF, r.t.; viii) 30% NaOH, EtOH, reflux.