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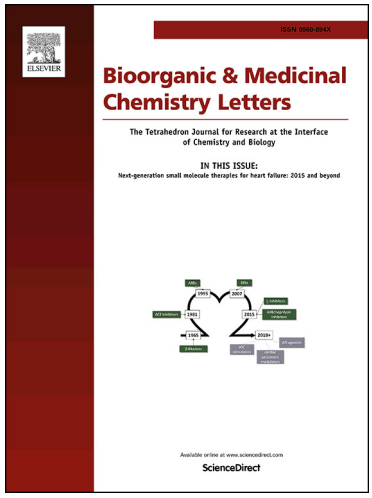

Design, Synthesis and Biological Evaluation of (2S,3R,4R,5S,6R)-5-Fluoro-6-(hydroxymethyl)-2-aryltetrahydro-2H-pyran-3,4-diols as Potent and Orally Active SGLT Dual Inhibitors

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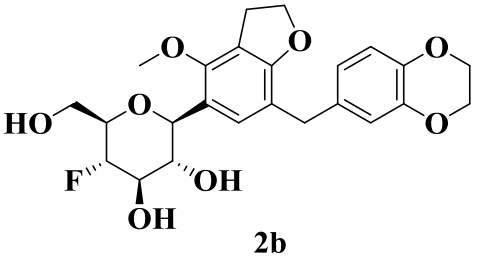
ABSTRACT: A new series of (2S,3R,4R,5S,6R)-5-fluoro-6-(hydroxymethyl)-2-aryltetrahydro-2H-pyran-3,4-diols as dual inhibitors of sodium glucose co-transporter proteins (SGLTs) were disclosed. Two methods were developed to efficiently synthesize C_5-fluoro-lactones **3** and **4**, which are key intermediates to the C_5-fluoro-hexose based C-aryl glucosides. Compound **2b** demonstrated potent hSGLT1 and hSGLT2 inhibition (IC_{50} = 43 nM for SGLT1 and IC_{50} = 9 nM for SGLT2). It showed robust inhibition of blood glucose excursion in oral glucose tolerance test (OGTT) in Sprague Dawley (SD) rats and exerted pronounced antihyperglycemic effects in *db/db* mice and high-fat diet-fed ZDF rats when dosed orally at 10 mg/kg.



2b

IC_{50} (hSGLT2) = 9 nM
IC_{50} (hSGLT1) = 43 nM

Keywords
Diabetes
Glucose transporter
SGLT1 inhibitor
SGLT2 inhibitor
Bioisostere
C-Aryl Glucoside

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