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5,5-Difluoro- and 5-Fluoro-5-methyl-hexose-based C-Glucosides as Potent and Orally Bioavailable SGLT1 and SGLT2 Dual Inhibitors

Guozhang Xu[1]*, Fuyong Du[2], Gee-Hong Kuo[1], June Zhi Xu[2], Yin Liang[2], Keith Demarest[2], Michael D. Gaul[1]

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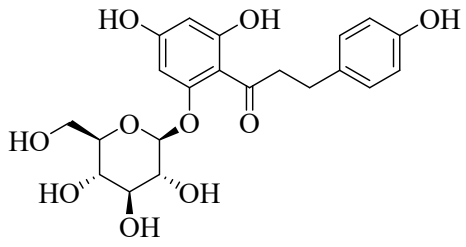
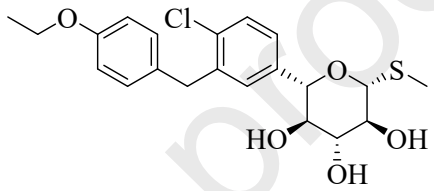
Type 2 diabetes mellitus (T2DM) is characterized by a reduction in insulin function in peripheral tissues and an increase in gluconeogenesis in the liver that together result in hyperglycemia.[1-2] Uncontrolled hyperglycemia is associated with an increased risk for cardiovascular and end-stage kidney disease.[3] Currently approved antihyperglycemic agents act by increasing insulin secretion, enhancing insulin sensitivity, reducing hepatic glucose production or glucose absorption.[4] However, therapeutic efficacy is also offset by side effects such as weight gain and hypoglycemia.[5] In recent years, much attention has been on excretion of excessive glucose directly into urine, which involves sodium-glucose co-transporters (SGLTs), for the treatment of hyperglycemia.[6]

SGLTs are a family of glucose transporter proteins, which rely on the electrochemical potential for sodium ion to actively transport extracellular glucose into the cytoplasm.[7] The physiological and pathophysiological roles of the two major isoforms, SGLT1 and SGLT2, are well-documented.[8] Since 2013, the FDA has approved multiple SGLT2 selective inhibitors (known as gliflozins) for the treatment of type 2 diabetes mellitus (T2DM).[9-11] Interestingly, SGLT2 knockout or treatment with an SGLT2 selective inhibitor only causes a fractional glucose excretion (~60%), an effect attenuated by up-regulation of renal SGLT1.[12] Adding SGLT1 inhibition on top of SGLT2 inhibition (e.g. SGLT1 and SGLT2 dual inhibition) is expected to reduce glucose burden by inhibiting the uptake of dietary glucose (mediated by SGLT1) in the intestine and excreting filtered glucose (mediated by SGLT2 and SGLT1) via the kidney. Therefore, an orally bioavailable SGLT1/2 dual inhibitor could not only achieve even better glycemic control and weight loss, but also help reduce glycemic variability through the day via a *non-insulin*-dependent mechanism.

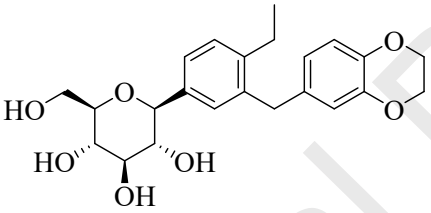
Besides phlorizin, a natural product with modest inhibitory activities against both SGLT1 and SGLT2,[13] several synthetic SGLT1/2 dual inhibitors have been reported (Figure 1). Sotagliflozin (**1**, Figure 1) is the first SGLT1/2 dual inhibitor that has received approval in the European Union for certain patients with T1D.[14] Licogliflozin (**2**, Figure 1) helped obese patients lose more than 5% of their body weight in 12 weeks and improve key health measures in those with T2D.[15] HM41322 (**3**, Figure 1) showed a favorable preclinical profile of postprandial glucose control.[16]



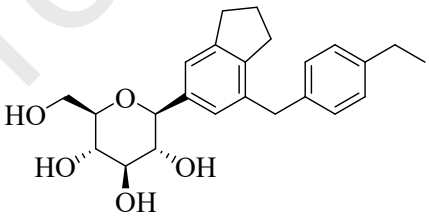
Phlorizin SGLT1 IC_{50} = 210 nM
SGLT2 IC_{50} = 34.6 nM



1 SGLT1 IC_{50} = 36 nM
SGLT2 IC_{50} = 1.8 nM



2 SGLT1 IC_{50} = 22 nM
SGLT2 IC_{50} = 0.5 nM



3 SGLT1 IC_{50} = 54.6 nM
SGLT2 IC_{50} = 5.6 nM

Figure 1. Representative examples of SGLT1/2 dual inhibitors

These inhibitors exhibit very potent half-maximal inhibitory concentrations (IC_{50}) in the range of 0.5~5.6 nM against human SGLT2 and IC_{50} values in the range of 22~54.6 nM against human SGLT1 *in vitro*.

We previously reported a series of potent and orally active SGLT1/2 dual inhibitors based on a mono-fluorine-substituted C-aryl glucoside skeleton (**5**, Figure 2).[17] The isosteric replacement of the equatorial hydroxy group at the C5 position (**4**, Figure 2) with a fluorine atom is well tolerated. We report here further modification of the glucose ring as well as the aglycone moiety (*vide infra*). The remaining axial hydrogen at the C5 position of **5** was replaced with either a fluorine atom or a methyl group, which resulted in a new series of (2S,3R,4R,5S,6R)-2-aryl-5,5-difluoro-6-(hydroxymethyl)tetrahydro-2H-pyran-

3,4-diols (**6**) and (2S,3R,4R,5S,6R)-2-aryl-5-fluoro-5-methyl-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diols (**7**) in which Ar represents a generic aglycone moiety. Interestingly, there are few reports of *orally active* SGLT dual inhibitors based on template **6** or template **7**.[18]

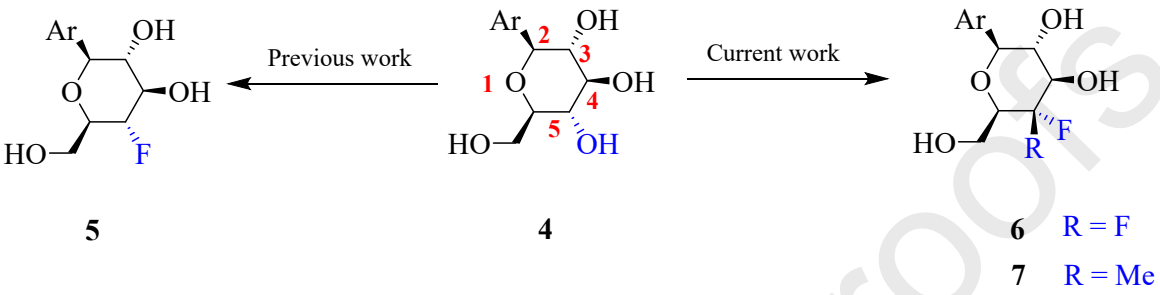
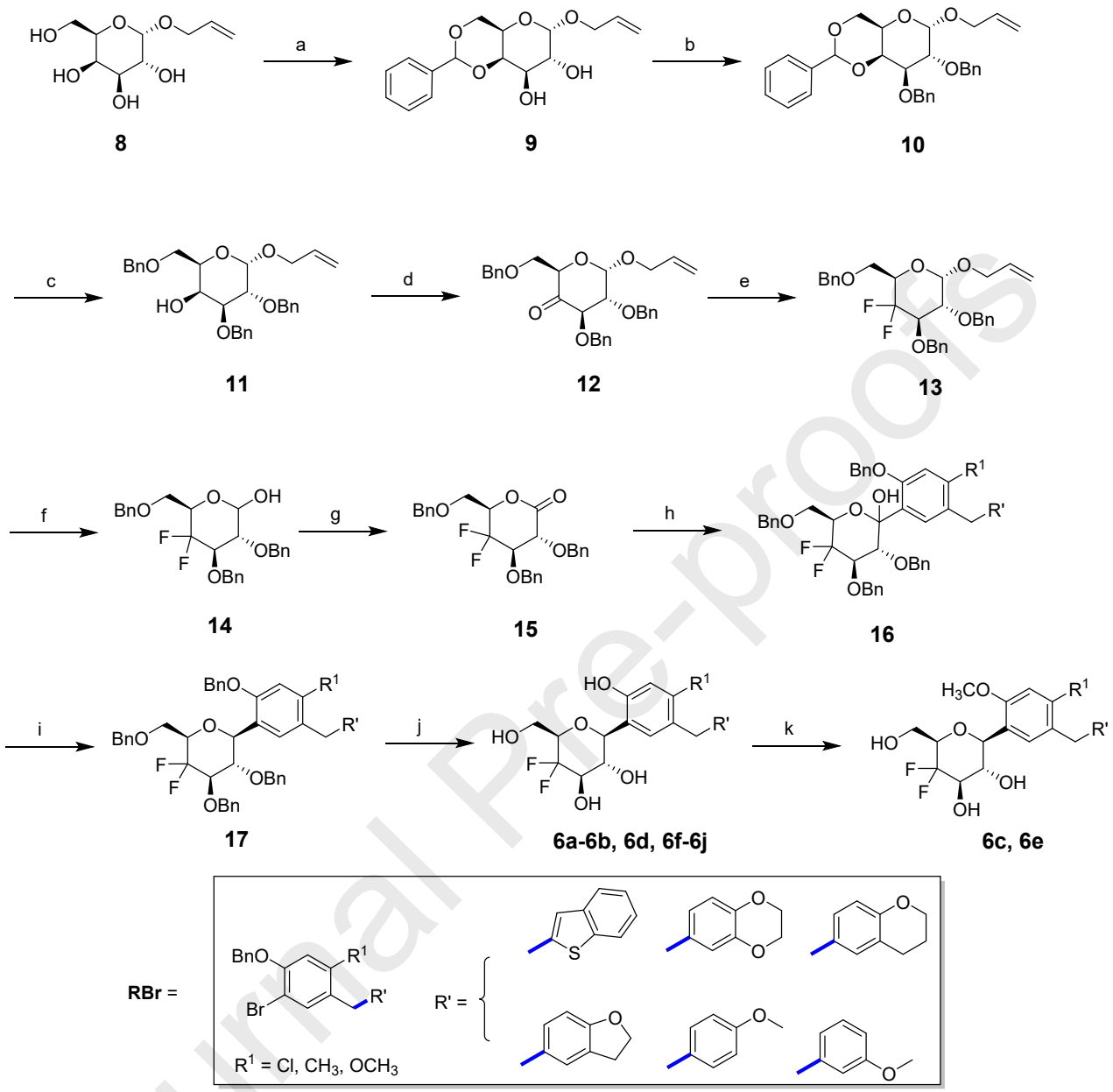


Figure 2. Design of new SGLT1/2 dual inhibitors

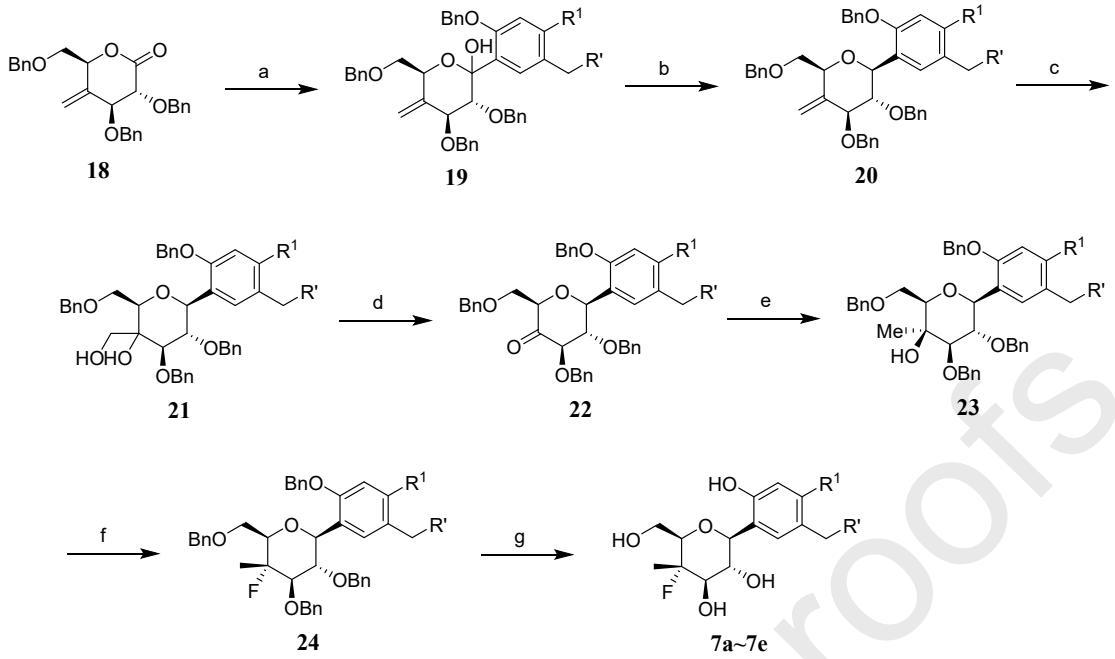
The synthesis of the (2S,3R,4R,5S,6R)-2-aryl-5,5-difluoro-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diols (**6a-6j**) is described in Scheme 1. Treatment of commercially available (2S,3R,4S,5R,6R)-2-(allyloxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol with dimethoxymethylbenzene in the presence of a catalytic amount of D-camphorsulfonic acid afforded (4aR,6S,7R,8R,8aR)-6-(allyloxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (**9**) in 89% yield. Benzylation of the resulting diol **9** followed by selective reduction of **10** provided alcohol **11** in 57% yield over two steps.



Scheme 1. Reagents and conditions: (a) (Dimethoxymethyl)benzene, cat. D-camphorsulfonic acid, $CHCl_3$, reflux, 89%; (b) BnBr, NaH, DMF, room temperature 75.7% yield; (c) Et_3SiH, TfOH, 4A MS, DCM, -78 °C 74.7% yield or $NaBH_3CN$, THF, HCl(g) in diethyl ether 41.7% yield; (d) Ac_2O, DMSO, 65 °C or PCC, DCM 95.4%; (e) BAST, DCM 73.5%: (f) $PdCl_2$, NaOAc 95% HOAc or n-Bu_3SnH, $Pd(PPh_3)_4$, $ZnCl_2$, THF, room temperature 77.3 %; (g) Ac_2O, DMSO, room temperature 87%; (h) n-BuLi, RBr (shown in the box), THF/toluene, -78 °C; (i) Triethylsilane/$BF_3.Et_2O$ or TFA, DCM, at 0 °C for 1 h, 65%; (j) BCl_3, 1,2,3,4,5-pentamethylbenzene, DCM, at -78 °C for 30 min, 42%; (k) MeI, K_2CO_3, acetone 90%.

Pyridinium chlorochromate (PCC) oxidation or Albright-Goldman oxidation of **11** and fluorination of the resulting ketone **12** using BAST (Deoxy-Fluoro®) gave (2R,4R,5R,6S)-6-(allyloxy)-4,5-bis(benzyloxy)-2-((benzyloxy)methyl)-3,3-difluorotetrahydro-2H-pyran **13** in 69% yield. Selective removal of the allyl protecting group followed by Albright-Goldman oxidation of **14** provided the $C_{5,5}$-difluoro-lactone **15** as a key intermediate. The addition of the aryl lithium species generated by lithium/bromide exchange of the RBr species shown in Scheme 1 to lactone **15** generates the corresponding lactol (**16**). Triethylsilane/$BF_3.Et_2O$ or triethylsilane/TFA reduction in dichloromethane (DCM) at 0 ^oC gave the corresponding β-C-aryl glucoside **17**, which was confirmed by the coupling constant (J = 9.0 ~ 9.6 Hz) between the anomeric hydrogen and the adjacent hydrogen in the ^1H NMR spectra. Mild debenzylation of **17** proceeded at low temperature with a combination of BCl_3 and pentamethylbenzene as a non-Lewis-basic cation scavenger to afford the corresponding target compound (**6a-b, 6d, 6f-6j**).[19] Methylation of **6b** or **6d** with MeI/K_2CO_3 in acetone provided **6c** or **6e**, respectively.

The preparation of 5-fluoro-5-methyl C-aryl glucoside derivatives **7a-7e** is outlined in Scheme 2. Addition of an aryl lithium reagent, generated by lithium/bromide exchange of the RBr species shown in Scheme 1 to (3R,4S,6S)-3,4-bis(benzyloxy)-6-((benzyloxy)methyl)-5-methylenetetrahydro-2H-pyran-2-one (**18**),[20] followed by triethylsilane/trimethylsilyl trifluoromethanesulfonate (TMSOTf)-mediated reduction generates 5-methylene derivative **20**. Upjohn dihydroxylation (N-methylmorpholine N-oxide and a catalytic amount of OsO_4) of the methylene group at the C5 position provides the diol **21**, which is then oxidatively cleaved by $PhI(OAc)_2$ to give the corresponding ketone **22**. Addition of methyl lithium to **22** and subsequent DAST-mediated fluorination of the *axial* hydroxyl group in **23** affords the precursor **24**. Global debenzylation of **24** either by hydrogenolysis catalyzed by $Pd(OH)_2$ on carbon or treatment with BCl_3/pentamethylbenzene affords the target compounds **7a-7e**.



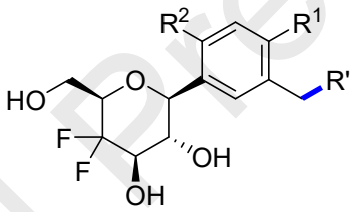
Scheme 2. Reagents and conditions: (a) RBr (shown in Scheme **1**), BuLi, THF, -78 °C, 90%; (b) Et_3SiH, TMSOTf, DCM, 60-70% yield; (c) NMO, cat. OsO_4, acetone/water, 88% yield; (d) $PhI(OAc)_2$ 61%; (e) MeLi, THF, -78 °C 79.1%: (f) DAST, DCM, 63.7%; (g) $Pd(OH)_2$, H_2, EtOAc or BCl_3, 1,2,3,4,5-pentamethylbenzene, DCM, at -78 °C for 30 min, 40-50%.

The *in vitro* inhibitory activities of newly synthesized compounds for SGLT1 and SGLT2 were evaluated by monitoring the inhibition of [^{14}C]methyl D-glucopyranoside (AMG) accumulation in Chinese hamster ovary (CHO) cells expressing human SGLT1 or SGLT2. The IC_{50} values against SGLT1 and SGLT2 were summarized in Table 1.

Within the (2S,3R,4R,5S,6R)-2-aryl-5,5-difluoro-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diol series, compound **6b** (R^1 = Cl) with an *ortho*-hydroxy group exhibited potent SGLT2 (IC_{50} = 4.2 nM) and SGLT1 inhibitory activity (IC_{50} = 93 nM). Methylation of the phenol (**6c**) resulted in a greater than 2-fold loss of potency for SGLT1 (IC_{50} = 221 nM) although SGLT2 inhibitory activity was maintained (IC_{50} = 4.3 nM). The introduction of a methoxy group at C4 on the central ring (**6a**) produced an analog with only modest SGLT1 (IC_{50} = 165 nM) and SGLT2 (IC_{50} = 24.1 nM) potencies. An analogous trend was observed when the distal benzothiophene was replaced with 2,3-dihydrobenzo[b][1,4]dioxine. Compound **6d** (R^1 = Cl) was more potent than **6f** (R^1 = MeO) in both SGLT1 and SGLT2

assays. Interestingly, compound **6e** with the hydroxyl group replaced by methoxy was much less active against both SGLT1 and SGLT2. Other distal aryl groups such as chromane (**6g**) and *p*-methoxyphenyl (**6i**) were well tolerated and displayed potent SGLT1 and SGLT2 inhibitory activities although 2,3-dihydrobenzofuran (**6h**) showed only modest SGLT dual activity. The *meta*-methoxyphenyl **6j** was less potent than the *para*-methoxyphenyl analog **6i** against SGLT1 and SGLT2. All compounds except **6e** and **6j** were also evaluated in liver microsome stability assays (Table 1). Compounds **6a**, **6b**, **6g**, **6h**, and **6i** showed good *in vitro* stability across species (human, mouse, rat) as exemplified by more than 50% of test compound remaining after 10 minutes incubation. However, **6c**, **6d**, and **6f** were less stable in either mouse or rat liver microsomes.

Table 1. *In vitro* potency at SGLT1 and SGLT2 assays and liver microsomal stability



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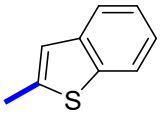
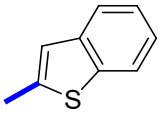
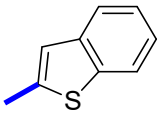
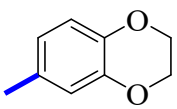
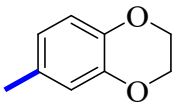
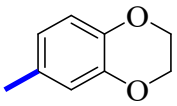
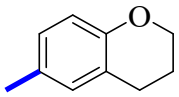
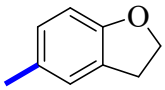
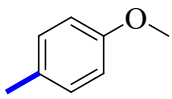
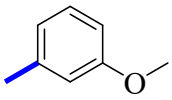
Cpd	R^1	R^2	R'	SGLT1 IC_{50} (nM)	SGLT2 IC_{50} (nM)	Microsomal stability[a] Human/mouse/rat
6a	CH_3O	OH		165	24.1	103/111/98
6b	Cl	OH		93 (+/- 38)[b]	4.2 (+/- 2.6)	120[c]/106/94
6c	Cl	OCH_3		221	4.3	65/37/123
6d	Cl	OH		49 (+/- 12)	1.4 (+/- 1.4)	96/74/18

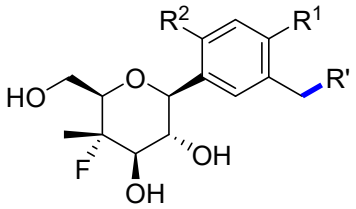
6e	Cl	OCH_3		37% inh. at 0.3 µM	78% inh. at 0.3 µM	ND[d]
6f	OCH_3	OH		895	26.3	99/97/26
6g	OCH_3	OH		96	1.3	95/85/57
6h	OCH_3	OH		708	17.3	100/91/70
6i	Cl	OH		34 (+/- 6.7)	1.1 (+/- 0.28)	90/97/58
6j	Cl	OH		112	2.6	ND

[a]Liver microsomal stability assay conditions: 1 µM compound concentration; liver microsomal protein content: 0.5 mg/ml, cofactor NADPH was added, percentage of compound remaining at 10-minute time point; solvents: 0.01% DMSO, 0.05% acetonitrile; positive control: verapamil, cerivastatin, and warfarin. [b]Standard derivation (+/- SD) was added when multiple batches were tested; [c] $T_{1/2}$ (human) > 180 mins; [d]ND, not determined.

The *in vitro* cell-based SGLT inhibitory activities and liver microsomal stability data for (2S,3R,4R,5S,6R)-2-aryl-5-fluoro-5-methyl-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diols (**7a-7e**) are summarized in Table 2. Compound **7a** displayed potent SGLT2 activity (IC_{50} = 2.1 nM), however was less potent against SGLT1 (IC_{50} = 269 nM). Unlike the 5,5-difluoro-C-aryl glucoside **6f** which showed modest SGLT1 (IC_{50} = 895 nM) and SGLT2 (IC_{50} = 26 nM) activities, **7b** exhibited potent SGLT2 (IC_{50} = 4.3 nM) and SGLT1 (IC_{50} = 37 nM) inhibitory activity. Surprisingly, **7d** and **7e** were less potent than the corresponding 5,5-difluoro-C-aryl glucoside counterpart **6b** and **6g** in both SGLT assays. In the liver microsomal stability assays, compounds **7a** and **7b** were stable across species (human, mouse, and rat).

We selected compounds (**6b**, **6g**, **6i** and **7b**) with a balanced SGLT1 and SGLT2 inhibitory profile (10 nM < IC_{50} < 100 nM for SGLT1 and IC_{50} < 10 nM for SGLT2) as well as good liver microsomal stability (more than 50% remaining after 10 minutes incubation) for pharmacokinetic (PK) studies in Sprague Dawley (SD) rats.

Table 2. *In vitro* potency at SGLT1 and SGLT2 assays and liver microsomal stability



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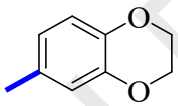
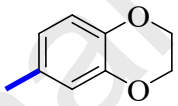
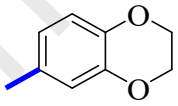
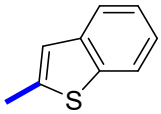
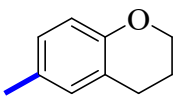
Cpd	R^1	R^2	R'	SGLT1 IC_{50} (nM)	SGLT2 IC_{50} (nM)	Microsomal stability[a] Human/mouse/rat
7a	Cl	OH		269 (+/- 43)[b]	2.1 (+/- 0.49)	74/96/56
7b	OCH_3	OH		37	4.3	103/98/101
7c	OCH_3	OCH_3		25% inh. at 0.3 µM	59% inh. at 0.3 µM	ND[c]
7d	Cl	OH		287	10.2	89/105/15
7e	OCH_3	OH		31% inh. at 0.3 µM	67% inh. at 0.3 µM	ND

[a]Liver microsomal stability assay conditions: 1 µM compound concentration; liver microsomal protein content: 0.5 mg/ml, cofactor NADPH was added, percentage of compound remaining at 10 minute time point; solvents: 0.01% DMSO, 0.05% acetonitrile; positive control: verapamil, cerivastatin, and warfarin. [b]Standard derivation (+/- SD) was added when multiple batches were tested; [c]ND, not determined.

The PK data are summarized in Table 3. Administration of a 2.0 mg/kg dose intravenously or a 10 mg/kg dose orally to rat revealed that **6g** and **7b** had very high clearance (Cl = 75.6 ml/min/kg for **6g** and 72.0 ml/min/kg for **7b**, respectively) while **6b** exhibited low *in vivo* clearance, a higher C_{max}, and good oral bioavailability (F = 46.8%). Compound **6i** had low clearance, but also low oral bioavailability (F = 17.4%). The high clearance seen for **6g** could be due to metabolism as only 57% remained upon 10 minutes incubation in rat liver microsomes. Compound **6g** was more stable in mouse liver microsomes, thus it was further examined in a mouse PK study (Table 3). Compound **6g** had relatively low clearance, a high C_{max} of 4680 ng/ml, and oral bioavailability of 52.2% in C57BL mice.

Table 3. Pharmacokinetic profiles of selected SGLT1/2 dual inhibitors[a]

Compound	Species	CL (ml/min/Kg)	Vss (L/Kg)	$t_{1/2}$ (iv) (h)	$AUC_{0\text{-}inf}$ (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	F%
6b	rat	3.92	0.91	3.71	18601	5245	0.31	46.8
6g	rat	75.6	3.85	2.28	524	258	0.25	22.3
6g	mouse	19.0	0.96	0.83	9158	4680	1.0	52.2
6i	rat	10.9	1.89	4.85	2701	549	0.42	17.4
7b	rat	72.0	2.41	1.52	ND	274	0.25	21.8

[a]Compounds were dosed in male C57 black mice at 5 mg/kg IV and 20 mg/kg PO and male Sprague Dawley rats at 2 mg/kg IV and 10 mg/kg PO. 20% HPbCD was vehicle for iv dosing and 0.5% Methocel was the vehicle for po dosing. Compounds were formulated with 20% HPbCD for iv dosing and 0.5% Methocel for po dosing, respectively.

With balanced SGLT 1/2 potencies and reasonable rat PK profiles, compounds **6b**, **6g**, and **6i** were next studied in an oral glucose tolerance test (OGTT) in SD-rats. In this experiment, overnight fasted rats were orally dosed with either vehicle or compound (at 1 and 10 mg/kg) 60 minutes prior to OGTT. The percentage (%) of blood glucose

area under the curve (AUC) versus vehicle control, the percent reduction of blood glucose AUC, and urinary glucose excretion (UGE) over a 4-hr period post OGTT for **6b**, **6g**, and **6i** are summarized in Table 4.

Table 4. Effect of SGLT1/2 inhibitors on glucose control and UGE in SD-rats

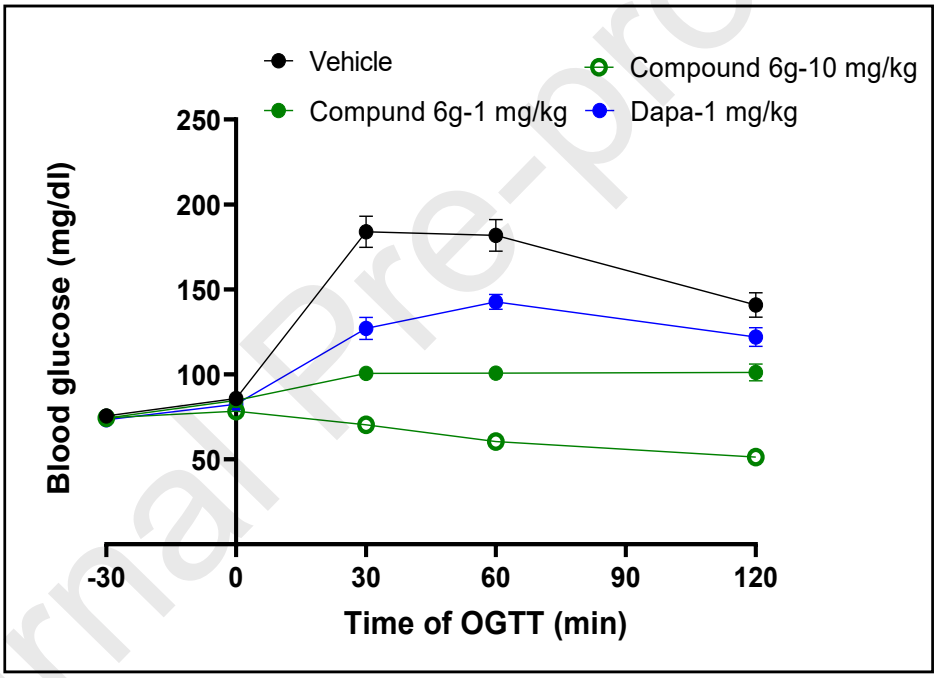
Compound	Dose (mg/kg)	Reduction of blood glucose AUC (%)[a]	UGE (grams/4-hrs)
6b	1	16.0 ± 2.0	0.001 ± 0.00
6b	10	41.4 ± 3.0	0.005 ± 0.002
6g	1	38.3 ± 2.1	0.002 ± 0.001
6g	10	60.7 ± 1.7	0.2 ± 0.02
6i	1	38.4 ± 2.4	0.099 ± 0.037
6i	10	62.8 ± 1.4	0.276 ± 0.032

[a]Vehicle was 0.5% Methocel from Sigma. All compounds were formulated in 0.5% Methocel. Data was expressed as mean ± standard error of mean. N=8 in each group. The data was statistically analyzed using one-way ANOVA-Dunnett's analysis.

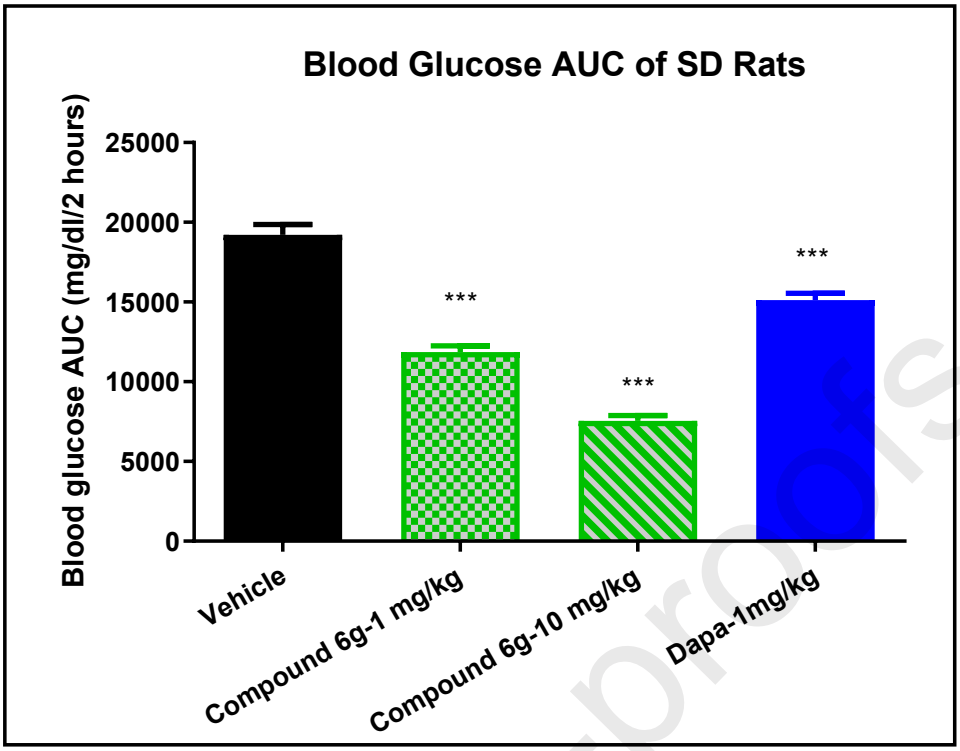
As shown in Table 4, compound **6b** was least potent in reducing blood glucose excursion in rats compared to compounds **6g** and **6i**. Moreover, UGE for compound **6b** was modest suggesting that the blood glucose reduction was almost completely mediated through SGLT1 inhibition in this model. In contrast, compounds **6g** and **6i** showed robust dose-dependent efficacy in lowering blood glucose excursion during OGTT, indicating that both compounds worked through dual inhibition of SGLT1/2 *in vivo*. Given that compound **6g** had a good *in vitro* safety profile (*data are shown in the supporting material*) and oral bioavailability in mice as shown in Table 3, it was further evaluated in a separate OGTT study relative to the marketed SGLT2 inhibitor dapagliflozin (Dapa). After an overnight fast, rats were administered a single oral dose of Dapa (1 mg/kg corresponding to the clinical dose) or **6g** (1 mg/kg or 10 mg/kg) and 2g/kg glucose (60 mins after compound dosing). The effect of **6g** or Dapa on blood glucose excursion and urinary glucose excretion are illustrated in Figure 3. Compared to vehicle-treated animals, treatment with **6g** significantly reduced blood glucose levels during OGTT in a dose-dependent manner. The reduction of blood glucose was superior to Dapa at a dose of 1 mg/kg (Figure 3, panel **A**). Blood glucose excursion AUC was

calculated using blood glucose levels at multiple time points (0-120 mins) during OGTT. Compared to vehicle-treated rats, compound **6g** significantly lowered blood glucose AUC in a dose-dependent manner (Figure 3, panel **B**; one-way ANOVA analysis, P<0.001). As shown in panel **C** (Figure 3) the urinary glucose excretion was measured 0-4 hours after glucose challenge. Compound **6g** did not increase UGE at the 1 mg/kg dose, but it substantially increased UGE at 10 mg/kg (one-way ANOVA analysis, P<0.001 vs. vehicle). This *in vivo* result suggests that compound **6g** may only inhibit SGLT1 at 1 mg/kg but inhibit both SGLT1 and SGLT2 at the 10 mg/kg dose.

(**A**)



(**B**)



(**C**)

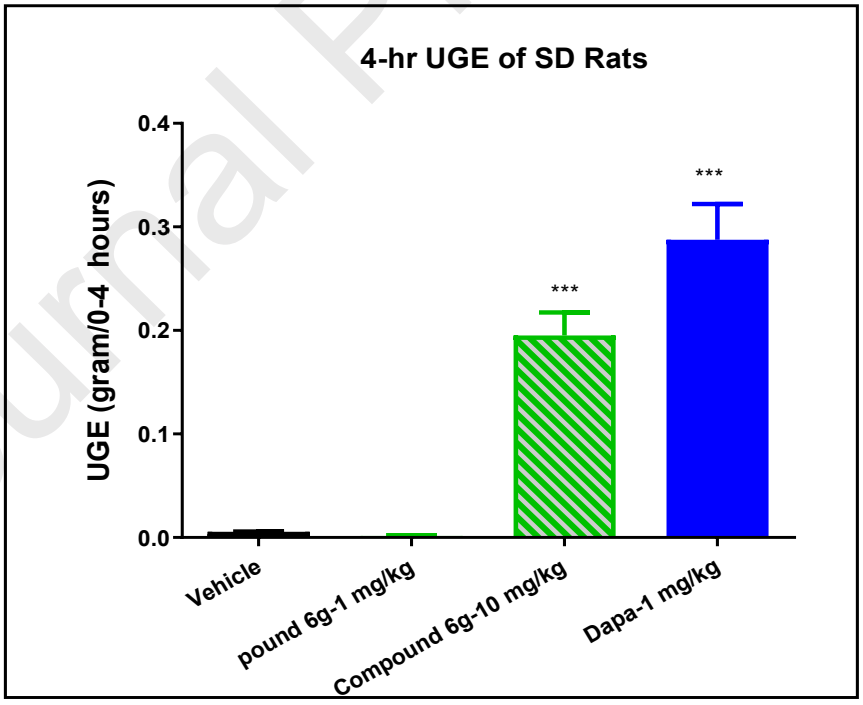
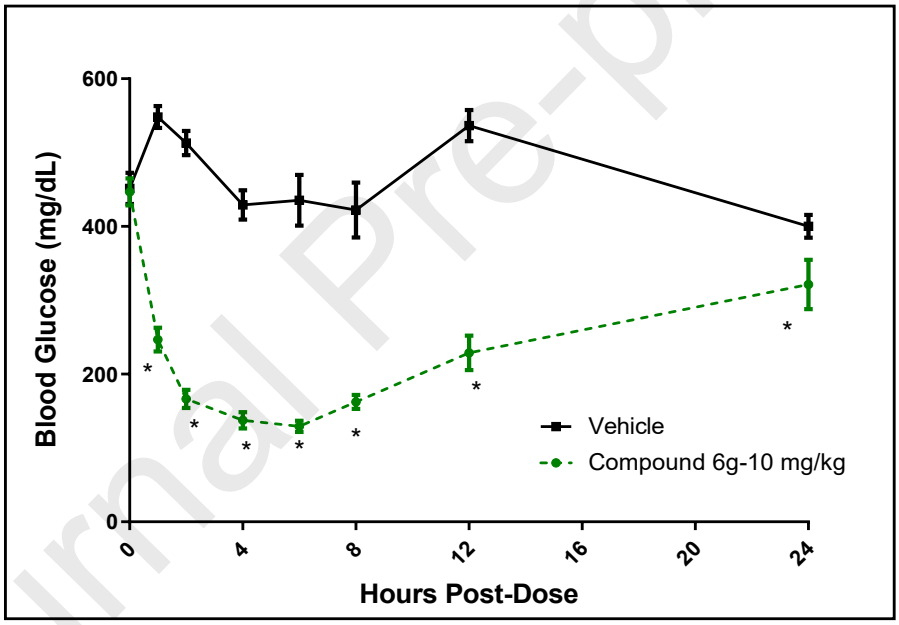


Figure 3. Effect of compound **6g** or Dapa on post-prandial glucose control in SD rats (n=8) at 0, 30, 60, and 120 min after glucose administration (panel **A**), blood glucose excursion AUC (panel **B**), and urinary glucose excretion measured during 0-4 hrs period after glucose challenge (panel **C**). (***: P<0.001, one-way ANOVA followed by Dunnett's multiple comparison

test).

We further examined the antihyperglycemic effect of **6g** in diabetic mice. As shown in Figure 4, a single oral dose (10 mg/kg) of compound **6g** in db/db mice significantly lowered the fed blood glucose levels up to 24 h (panel **A**). Compared to the vehicle-treated group, compound **6g** had a strong trend of increasing 24-hour UGE in db/db mice (panel **B**, unpaired T test. P = 0.0621). The pronounced antihyperglycemic effect of **6g** reflected a combination of decreased glucose absorption by SGLT1 inhibition at the intestinal lumen and increased urinary glucose excretion mediated by SGLT2 inhibition.

A:



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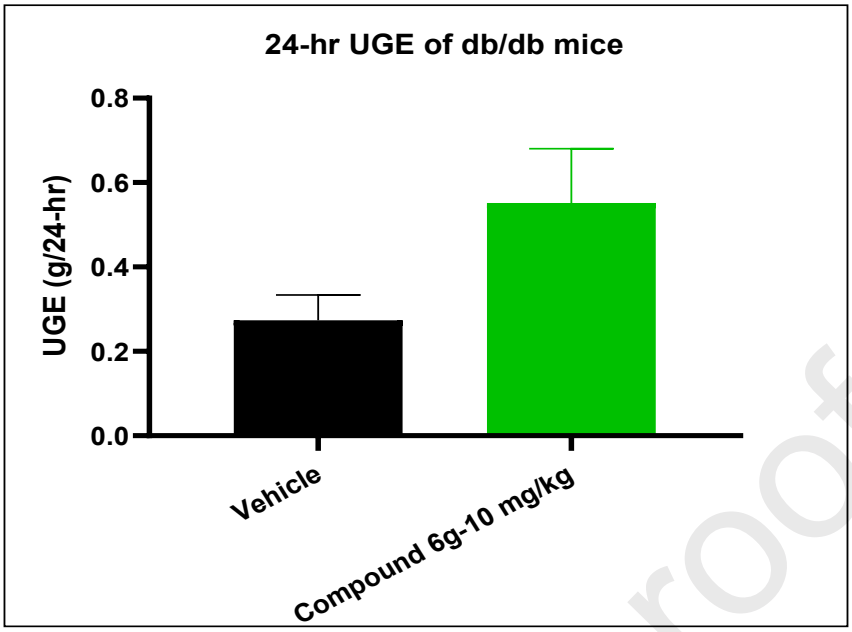

Figure 4. Anti-hyperglycemic effect of compound **6g** in db/db mice. Male db/db mice were treated with either vehicle or compound at 10 mg/kg. Fed blood glucose levels (panel **A**) and 24-hr UGE (panel **B**) (mean ± SE, one-way ANOVA analysis: $p<0.05$ vs vehicle control).

We previously reported that a C5-fluoro-aryl glucoside derivative (compound **2b**[17]**)** was a potent SGLT1/2 dual inhibitor. Our present results showed that compound **6g** had the comparable anti-diabetic efficacy to our early lead **2b** in both OGTT model of rats and diabetic model of db/db mice. The discovery of compound **6g** has provided us with more selections in the candidates' pool of anti-diabetic molecules to be further evaluated and developed.

In conclusion, we successfully designed and synthesized a new series of (2S,3R,4R,5S,6R)-2-aryl-5,5-difluoro-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diols and (2S,3R,4R,5S,6R)-2-aryl-5-fluoro-5-methyl-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diols as potent SGLT dual inhibitors. Several compounds (**6b**, **6g**, and **6i**) in the C5,5-difluoro-aryl glucoside series demonstrated excellent postprandial glucose control in an OGTT test in SD-rats. Furthermore, compound **6g** was orally active in a db/db mouse model of diabetes.

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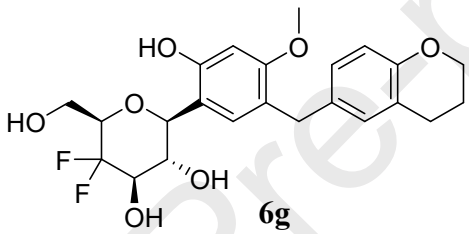
ABSTRACT: (2S,3R,4R,5S,6R)-2-Aryl-5,5-difluoro-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diols and (2S,3R,4R,5S,6R)-2-aryl-5-fluoro-5-methyl-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diols were discovered as dual inhibitors of sodium glucose co-transporter proteins (e.g. SGLT1 and SGLT2) through rational drug design, efficient synthesis, and *in vitro* and *in vivo* evaluation. Compound **6g** demonstrated potent dual inhibitory activities (IC_{50} = 96 nM for SGLT1 and IC_{50} = 1.3 nM for SGLT2). It showed robust inhibition of blood glucose excursion in an oral glucose tolerance test (OGTT) in Sprague Dawley (SD) rats when dosed at both 1 mg/kg and 10 mg/kg orally. It also demonstrated postprandial glucose control in db/db mice when dosed orally at 10 mg/kg.



6g

SGLT1 IC_{50} = 96 nM
SGLT2 IC_{50} = 1.3 nM