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# Discovery of a Potent, Selective Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor (HSK0935) for the Treatment of Type 2 Diabetes

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ABSTRACT: A new class of potent and highly selective SGLT2 inhibitors is disclosed. Compound **31** (HSK0935) demonstrated excellent hSGLT2 inhibition of 1.3 nM and a high hSGLT1/hSGLT2 selectivity of 843 fold. It showed robust urinary glucose excretion in Sprague-Dawley (SD) rats and affected more urinary glucose excretion in Rhesus monkeys. Finally, an efficient synthetic route has been developed featuring a ring closing cascade reaction to incorporate a double ketal 1-methoxy-6, 8- dioxabicyclo[3.2.1]octane ring system.

## INTRODUCTION

The incidence of diabetes has been increasing at an alarming rate worldwide.[1-3] About 90% of diabetes is type 2 diabetes, which is characterized by chronically increased glycemic levels, insulin resistance (IR) and $\beta$-cell dysfunction.[4, 5] Currently, a wide range of antidiabetic agents are prescribed for tight glycemic control, but many of them can't achieve and maintain satisfactory target glycemic levels. Thus, additional therapies with novel molecular mechanisms are still in great demand. It is well-known that the kidneys play an important role in glucose homeostasis via gluconeogenesis, glucose uptake from the circulation and glucose recovery from the urine. Sodium-dependent glucose cotransporters (SGLT) are a family of glucose transporters and contribute to glucose reabsorption. The two most well-known members of SGLT family are SGLT1 and SGLT2, which are members of the SLC5A gene family. In the kidney of rats, approximately 90% of glucose reabsorption has been shown to occur in the site expressing the low-affinity, high-capacity SGLT2.[5, 6] The remaining 10% of glucose is thought to be recovered during passage of the filtrate through the site expressing the high-affinity, low-capacity SGLT1. Some recent studies indicate that SGLT2 is responsible for 97% of renal glucose recovery.[7, 8] The case for selective inhibition of SGLT2 is bolstered by the fact that SGLT2 appears to be expressed only in the kidney, while SGLT1 is mainly present in the small intestine (the transporter responsible for absorption of both glucose and galactose) and in the heart (function unknown). Moreover, individuals with a defective SGLT2 are marked only with significant glycosuria (as much as 140 g daily) with no other ill effects,[9, 10] while individuals expressing a defective SGLT1 are unable to transport glucose or galactose normally across the intestinal wall, resulting in the potentially life-threatening condition known as glucose-galactose malabsorption.[11, 12] Therefore, selective SGLT2 inhibitors provide an attractive strategy for the treatment of type 2 diabetes. Since 2013, leading SGLT2 inhibitors, such as dapagliflozin[13] (**1**),

empagliflozin[14] (**2**) and canagliflozin[15] (**3**), have been approved by the FDA. Ipragliflozin[16], luseoglifozin[17] and tofogliflozin[18] were approved in Japan in 2014. The glucose-lowering effect of SGLT2 inhibitors is independent of insulin secretion or insulin action. These marketed SGLT2 inhibitors exhibit a modest reduction in body weight as well as blood pressure, and they are generally well tolerated and have low risk of hypoglycemia. It is noteworthy that empagliflozin was reported to show a significant reduction in both cardiovascular risk and cardiovascular death in a dedicated outcome trial which has rarely been reported with other antidiabetic agents.[19] Thus, in recent years, although there are some concerns on the risks of ketoacidosis,[20] SGLT2 inhibitors are considered to have more benefits than risks for diabetic patients, and have become more and more commonly prescribed.

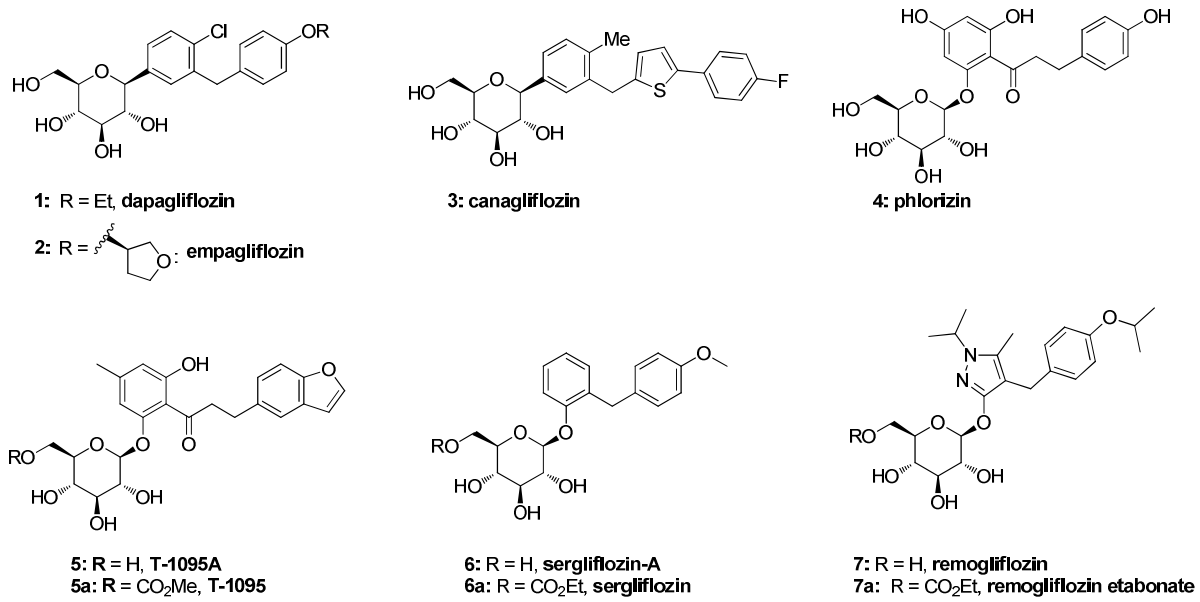



**Figure 1.** Selected examples of SGLT2 inhibitors

Over the last decade, many compounds have been reported as SGLT inhibitors. They are generally divided into two classes, *O*-glucosides and *C*-glucosides.[17, 21-22] The natural product, phlorizin[23] (**4**), is the first nonselective SGLT1/2 dual inhibitor. It was not clinically developed as

a drug candidate due to its poor metabolic stability to *β*-glucosidases. Optimization of phlorizin led to the identification of several selective *O*-aryl glucoside SGLT2 inhibitors such as T-1095A[24] (**5**), sergliflozin-A[25] (**6**), remogliflozin[26] (**7**) and remogliflozin etabonate[27a, b] (**7a**). However, these *O*-glucosides are usually associated with degradation by *β*-glucosidases found in the gut as well. **5a**, **6a** and **7a** were all discontinued after phase II trials for treating type 2 diabetes (**7a** is still active in phase II trials for the treatment of non-alcoholic steatohepatitis (NASH)).[27c] In contrast, *C*-glucosides are generally more metabolically stable, and exhibit better oral bioavailability and plasma exposure.[28] The leading *C*-glucosides, dapagliflozin and canagliflozin, show good *in vitro* and *in vivo* potencies against SGLT2. Herein we report the discovery of compound **31** (HSK0935), a potent and selective SGLT2 inhibitor.

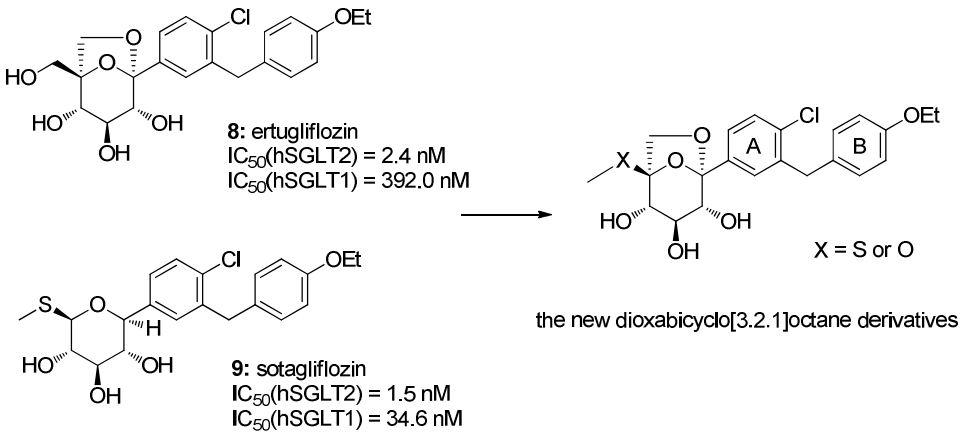



**Figure 2.** The hybrid design of the new dioxabicyclo[3.2.1]octane derivatives

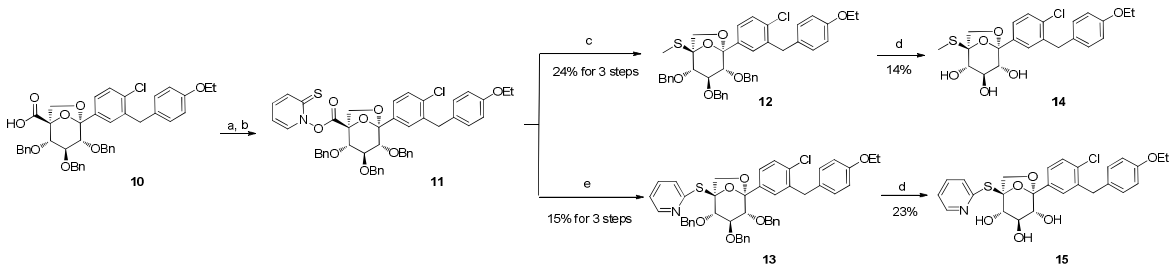
## RESULTS AND DISCUSSION

**Chemistry.** The design of SGLT inhibitors began with combination of the rigid and SGLT2 selective dioxabicyclo[3.2.1]octane motif of ertugliflozin[29] (**8**) and the thiomethyl xyloside core

of sotagliflozin[30] (**9**). To our knowledge when this project was initiated, ertugliflozin and sotagliflozin were in phase II clinical trials for type 2 diabetes (now both are in phase III clinical trials). Both compounds showed good results and possessed novel structures. Based on the skeleton of the dual SGLT1/2 inhibitor sotagliflozin, a new class of highly selective SGLT2 inhibitors incorporating a structurally new 1-methoxy-6,8-dioxabicyclo[3.2.1]octane ring system featured by a cascade ring closing reaction to form the double ketal *O*-glycoside were designed by introducing the dioxabicyclo[3.2.1]octane motif of ertugliflozin (Figure 2). The synthetic methods are described as follows.

The known carboxylic acid **10**[31] was first converted to the corresponding acid chloride (Scheme 1) and then directly reacted with sodium 2-thioxopyridin-1(2H)-olate to furnish the Barton ester **11**. Compound **11** then underwent photochemical decarboxylation with a 500 W halogen lamp and the radical intermediate was either trapped with MeSSMe to give methylthioether **12** or trapped with its pyridyl-2-thio radical intermediate to provide pyridylthioether **13**.[32] Finally debenzylation reactions of compounds **12**-**13** were carried out in the presence of $BCl_3$ to furnish the thioether compounds **14**-**15**, respectively.

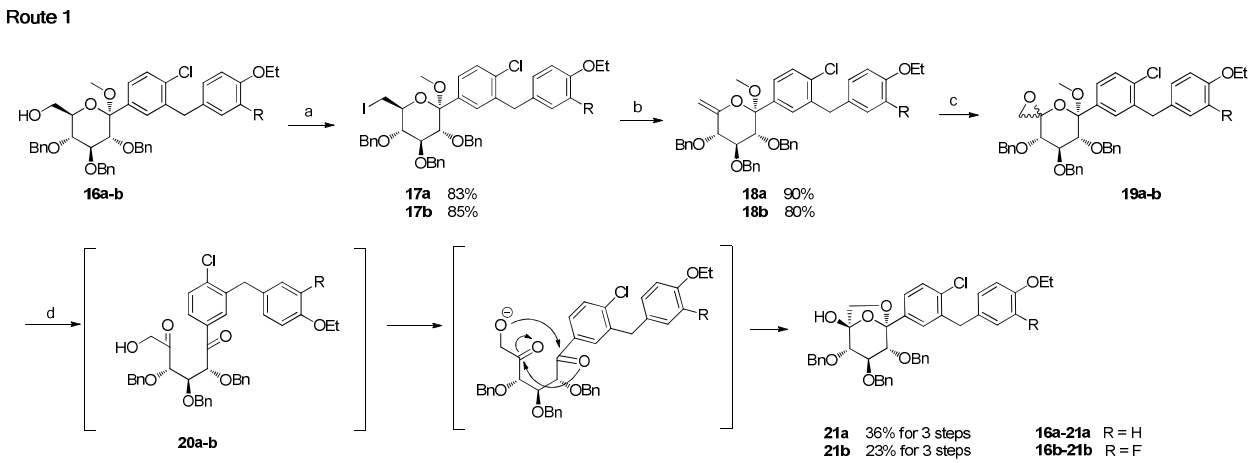
**Scheme 1.** Synthesis of derivatives of 6, 8-dioxabicyclo[3.2.1]octane with a thioether moiety



Reagents and conditions: (a) $(COCl)_2$, DMF, rt to reflux, 2 h; (b) sodium 2-thioxopyridin-1(2H)-olate, DCM, 0 ℃, 2 h; (c) 500 W halogen lamp, MeSSMe, 0 ℃, 1.5 h; (d) $BCl_3$, DCM, -78 ℃, 1.5–2 h; (e) 500 W halogen lamp, DCM, 0 ℃, 1.5 h.

Target compounds **31-42** were synthesized from key intermediates **21a-d** by one of three strategies. As shown in Route 1 (Scheme 2), the known C-glycosides[33] **16a-b** were first iodinated with triphenylphosphine and iodine to give the iodo intermediates **17a-b** which underwent dehydroiodination to provide alkenes **18a-b**.[34] Epoxidation of compounds **18a-b** with *m*CPBA led to epoxides **19a-b**[35] which underwent epoxide opening in the presence of trifluoroacetic acid to provide the hydroxyl diketone intermediates **20a-b**. The crude hydroxyl diketone intermediates underwent a ring closure cascade in 2 M NaOH to produce the key 1-hydroxy-6,8-dioxabicyclo[3.2.1]octane skeleton of intermediates **21a-b**.[36]

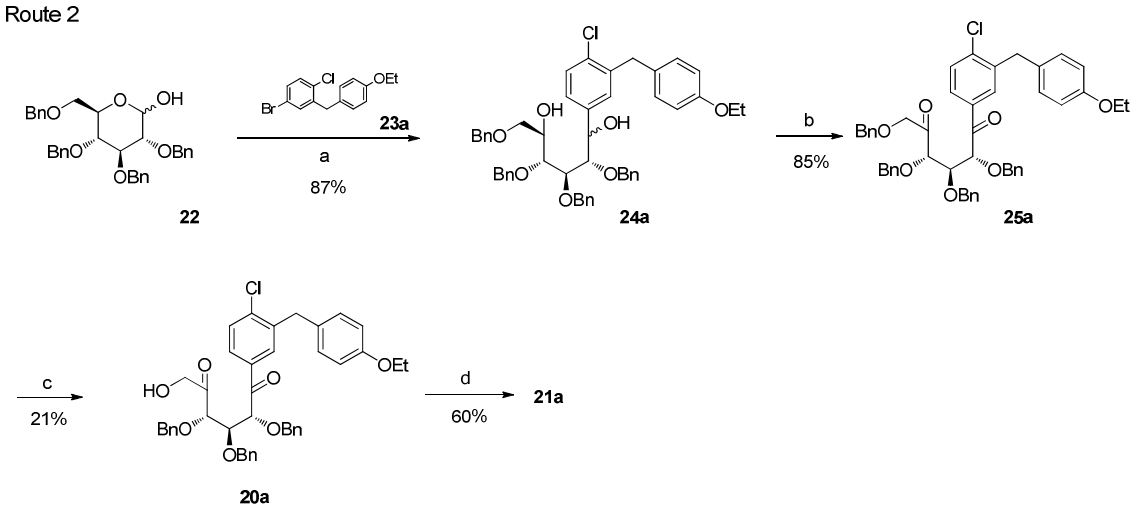
**Scheme 2.** Route 1 synthesis of intermediate **21**



Reagents and conditions: (a) $PPh_3$, imidazole, $I_2$, toluene, 70 ℃, 3–5 h; (b) NaH, DMF, rt, 3 h; (c) $NaHCO_3$, *m*CPBA, DCM, rt, 2.5–4 h; (d) TFA, THF/$H_2O$, rt, overnight; then 2 M NaOH, rt, 2 h.

Alternatively as shown in Route 2 (Scheme 3), hydroxyl diketone **20a** was also prepared in three simple steps. The dihydroxyl compound **24a** was prepared by reacting the freshly prepared Grignard reagent of bromide **23a** with 3,4,5,6-tetra-*O*-benzyl-D-glucopyranose **22**. The resulting dihydroxy compound **24a** was oxidized using trifluoroacetic anhydride in DMSO to provide diketone **25a**. Since benzyl-protected primary alcohols are more susceptible to deprotection under acidic conditions, selective debenzylation of **25a** with $BCl_3$ produced alcohol **20a** in acceptable yield.

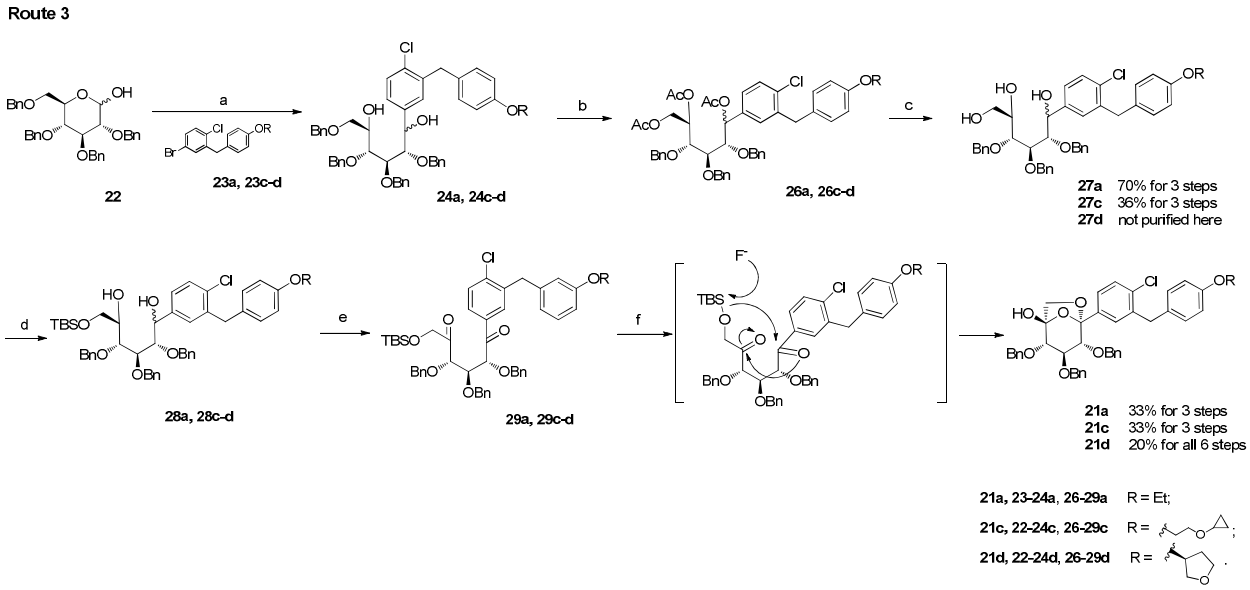
**Scheme 3.** Route 2 synthesis of intermediate **21**




Reagents and conditions: (a) Mg, $I_2$, THF, 60 ℃, 3 h; (b) TFAA, DMSO, $Et_3N$, DCM, -78 ℃, 2 h; (c) $BCl_3$, DCM, -78 ℃, 3 h; (d) MeONa, MeOH, rt, 2 h.

Furthermore, as shown in Route 3 (Scheme 4), selective debenzylation and acetylation of the dihydroxy intermediates **24a**,**c-d** led to the triacetoxy intermediates **26a**,**c-d**. These were hydrolyzed, selectively silylated and oxidized to diketone compounds **29a**,**c-d**. Treatment of **29a**,**c-d** with TBAF produced the desired intermediates **21a**,**c-d**. The chemistry as described in Route 3 allowed a more scalable synthesis for kilogram production.[37]

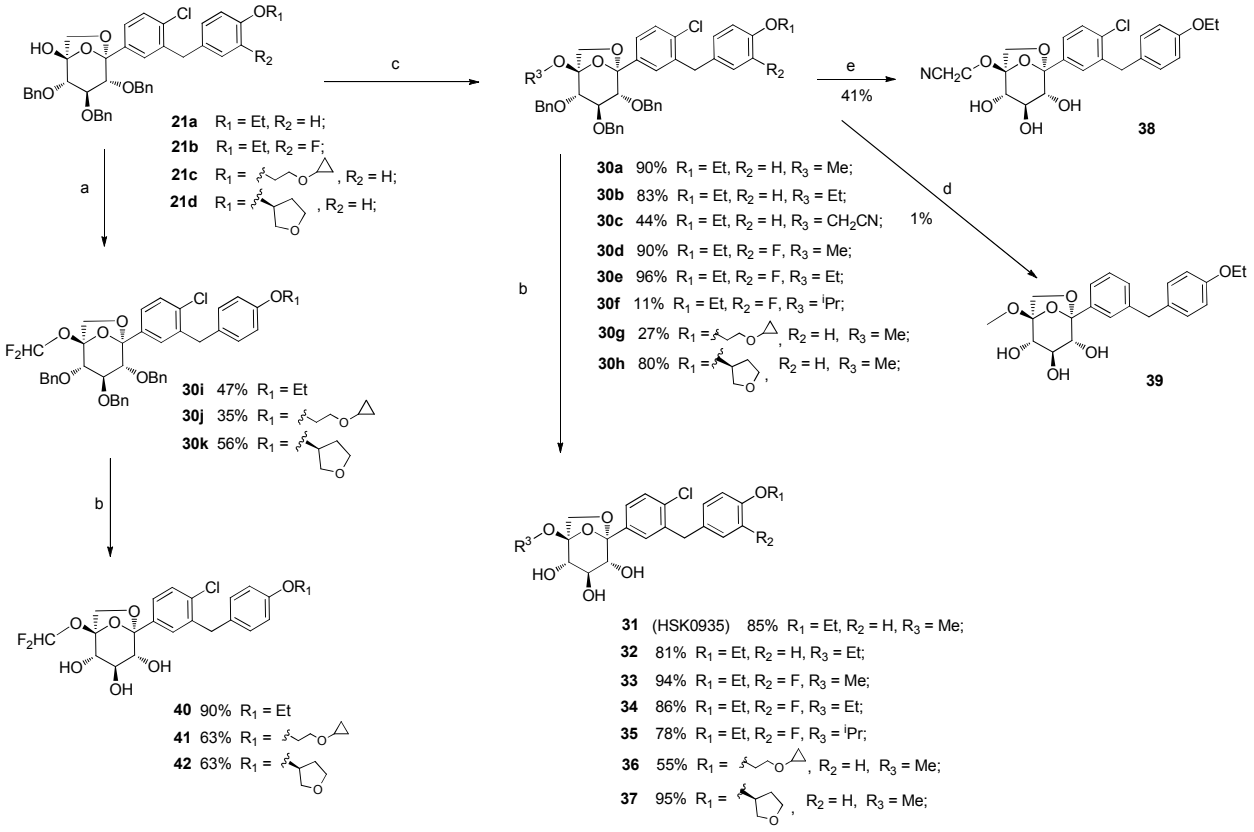
**Scheme 4.** Route 3 synthesis of intermediate **21**




Reagents and conditions: (a) Mg, $I_2$, THF, 60 ℃ to 70 ℃, 3 h; (b) $Ac_2O$, *p*-TsOH, 70 ℃, 2–3 h; (c) $K_2CO_3$, MeOH, rt, 2 h; (d) TBSCl, imidazole, DCM, rt, monitored by TLC; (e) DMSO, TFAA, $Et_3N$, DCM, -78 ℃, 2 h; (f) $Bu_4NF$, THF, -10 ℃ to -5 ℃, 1 h.

With key intermediates **21a-d** ready in hand, compounds **31-42** were synthesized (Scheme 5) from compounds **30a-k** respectively by debenzylation. Compounds **30a-k** could be obtained by alkylation of intermediates **21a-d**.

**Scheme 5.** Synthesis of compounds **31**-**42**

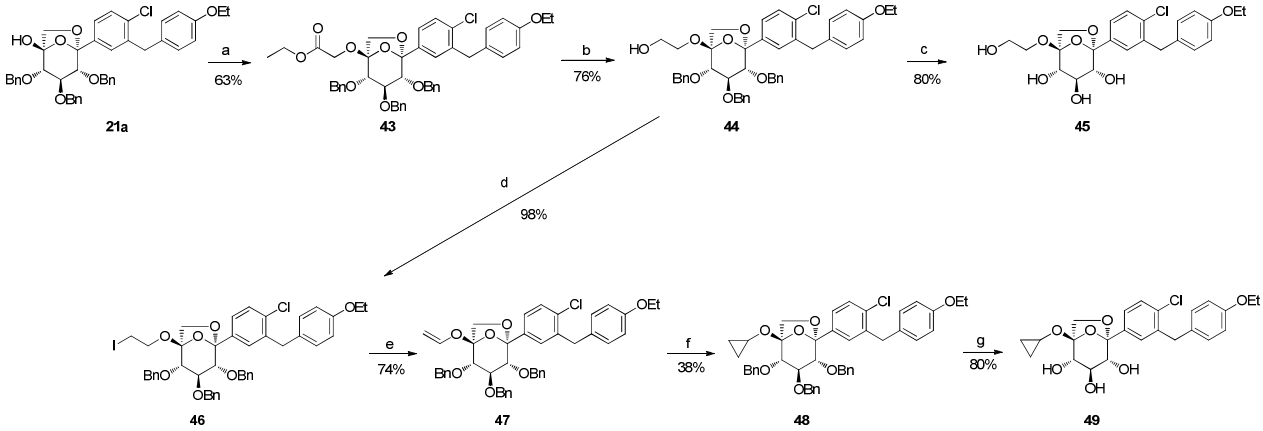



Reagents and conditions: (a) $BrF_2CPO_3(Et)_2$, KOH, $MeCN/H_2O$, -5 ℃ to rt, 1–3 h; (b) $H_2$, 10% Pd/C, 1,2-dichlorobenzene, THF/MeOH, rt, 1–5 h; (c) alkylation reagents, NaH, DMF, rt, 1–3 h; (d) $H_2$, 10% Pd/C, THF/MeOH, rt, 5 h; (e) $BCl_3$, DCM, -78 ℃, 4 h.

As shown in Scheme 6, compounds **45** and **49** were prepared from the common intermediate ethyl ester **43** which was prepared by reacting the key intermediate **21a** with ethyl 2-bromoacetate. Reduction of compound **43** with $LiBH_4$ gave hydroxyethyl compound **44** which

was debenzylated to produce compound **45**. The cyclopropyl compound **49** was prepared from alcohol **44** in four standard steps: iodination, elimination, cyclopropanation and debenzylation.

**Scheme 6.** Synthesis of compounds **45** and **49**

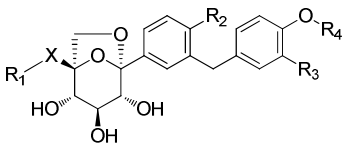



Reagents and conditions: (a) $BrCH_2COOEt$, NaH, DMF, rt, 3 h; (b) $LiBH_4$, THF, rt, 5 h; (c) $H_2$, 10% Pd/C, 1,2-dichlorobenzene, $THF/H_2O$, rt, 2 h; (d) $PPh_3$, imidazole, $I_2$, toluene, 70 ℃, 1 h; (e) NaH, DMF, rt, 1 h; (f) $Et_2Zn$, $CH_2I_2$, DCM, 0 ℃ to rt, 24 h; (g) $H_2$, 10% Pd/C, 1,2-dichlorobenzene, THF/MeOH, rt, 1 h.

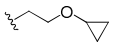
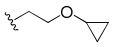
**Biological Evaluation.** As shown in Table 1, compounds **14** and **15** where X = S and $R_1$ = methyl or 2-pyridyl were found to have only moderate inhibitory activity (IC50 = 13.9 and 28.4 nM, respectively). However, when the sulfur atom of compound **14** was replaced by an oxygen atom, compound **31** exhibited 10-fold stronger inhibitory activity ($IC_{50}$ = 1.3 nM) than compound **14**. Based on this observation, the X group was kept as an oxygen atom and the $R_1$

group was varied to explore the SAR. Initially, the small $R_1$ groups such as ethyl, cyanomethyl, difluoromethyl and cyclopropyl (compounds **32**, **38**, **40** and **49**) were all well tolerated ($IC_{50}$ = 2.5, 1.1, 1.0, and 4.4 nM, respectively). However, when $R_1$ was elongated one more atom than ethyl, such as hydroxyethyl (compound **45**), the inhibitory potency was found to decrease to 31.0 nM. After exploration of $R_1$, the $R_2$, $R_3$ and $R_4$ substitutions on the bisaryl aglycon were further investigated. The replacement of the chlorine atom with a hydrogen atom at the $R_2$ position decreased the SGLT2 inhibitory potency from 1.3 nM (compound **31**) to 5.0 nM (compound **39**). Introduction of a fluorine atom at the $R_3$ position was found to decrease the potencies as well (compounds **33**-**35**). Finally, when $R_4$ group was modified from the smaller ethyl group (compound **31**) to larger groups, such as tetrahyrofuran-3-yl (compound **37**) and 2-cyclopropoxyethyl group (compound **36**), the inhibitory potencies decreased to 5.9 nM and 10.8 nM, respectively. A similar trend was observed for compounds **40**-**42** as well.

**Table 1.** *In Vitro* Inhibitory Activity of hSGLT2[a]




| Compound | X | $R_1$ | $R_2$ | $R_3$ | $R_4$ | hSGLT2 $IC_{50}$ (nM) |
|---|---|---|---|---|---|---|
| **14** | S | $CH_3$ | Cl | H | Et | 13.9 |
| **15** | S |  | Cl | H | Et | 28.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **31** | O | $CH_3$ | Cl | H | Et | 1.3 |
| **32** | O | $CH_2CH_3$ | Cl | H | Et | 2.5 |
| **38** | O | $CH_2CN$ | Cl | H | Et | 1.1 |
| **40** | O | $CHF_2$ | Cl | H | Et | 1.0 |
| **49** | O | Cyclopropyl | Cl | H | Et | 4.4 |
| **45** | O | $CH_2CH_2OH$ | Cl | H | Et | 31.0 |
| **39** | O | $CH_3$ | H | H | Et | 5.0 |
| **33** | O | $CH_3$ | Cl | F | Et | 5.9 |
| **34** | O | $CH_2CH_3$ | Cl | F | Et | 22.3 |
| **35** | O | *i*-Pr | Cl | F | Et | 6.8 |
| **37** | O | $CH_3$ | Cl | H |  | 5.9 |
| **36** | O | $CH_3$ | Cl | H |  | 10.8 |
| **41** | O | $CHF_2$ | Cl | H |  | 5.9 |
| **42** | O | $CHF_2$ | Cl | H |  | 3.4 |
| **1** | | | | | | 1.5–2.6 |
| **3** | | | | | | 2.2 |

| | |
|---|---|
| **8** | 2.4 |
| **9** | 1.5 |

[a]In vitro human SGLT2 inhibition activities of compounds were determined at the same laboratory by evaluating the sodium-dependent uptake of methyl-$\alpha$-D-[U-14C]glucopyranoside in Chinese hamster ovary (CHO) cells stably expressing human SGLT2.

Compounds **14**, **15**, **31** and **40** were further evaluated for selectivity against hSGLT1 by measuring their *in vitro* hSGLT1 inhibitory activities (Table 2). Compounds **31** and **40** showed better selectivity profiles. It is noteworthy that the selectivity of compound **31** was even better than that of compound **1** (dapagliflozin). However, compounds **14** and **15** showed moderate selectivities (32 and 39 fold respectively). This observation indicated that the replacement of the sulfur atom at the X position with an oxygen atom could improve not only the inhibitory potency of hSGLT2 but also the selectivity of hSGLT2 over hSGLT1.

**Table 2.** *In vitro* inhibitory activity and selectivity[a]

| Compound | hSGLT2 $IC_{50}$ (nM) | hSGLT1 $IC_{50}$ (nM) | selectivity hSGLT1/ hSGLT2 |
|---|---|---|---|
| **14** | 13.9 | 453 | 32 |
| **15** | 28.4 | 1082 | 39 |

| | | | |
|---|---|---|---|
| **31** | 1.3 | 1096 | 843 |
| **40** | 1.0 | 235 | 235 |
| **1** | 1.5–2.6 | 629 | 242–419 |
| **3** | 2.2 | 265 | 120 |
| **8** | 2.4 | 392 | 163 |
| **9** | 1.5 | 34.6 | 23 |

[a]In vitro human SGLT1 and SGLT2 inhibition activities of compounds were determined at the same laboratory by evaluating the sodium-dependent uptake of methyl-*α*-D-[U-14C]glucopyranoside in Chinese hamster ovary (CHO) cells stably expressing human SGLT1 or SGLT2.

Compounds **31** and **40** with their better *in vitro* activities and greater selectivity for SGLT2 were further investigated for pharmacokinetic (PK) studies in Sprague-Dawley (SD) rats. After single oral or intravenous doses of compounds **31** and **40**, blood samples were taken at planned time points and the unchanged drugs in plasma were quantified using a LC-MS/MS method. Major PK parameters were calculated using Winnolin software, version 6.3. As shown in Table 3, compounds **31** and **40** presented acceptable oral PK profiles. Compound **31** showed better systemic exposure and oral bioavailability than compound **40** (76% and 46%, respectively). And the low CL demonstrated that the test compounds were metabolized and excreted very slowly.

**Table 3.** Pharmacokinetic parameters of compounds **31** and **40** in SD rats

| | Compound **31** | | Compound **40** | |
|---|---|---|---|---|
| | p.o. | i.v. | p.o. | i.v. |
| Dose (mg/kg) | 10 | 1 | 10 | 1 |
| $C_{max}$ (ng/mL) | 1826 | | 758 | |
| AUC $_{0\rightarrow\infty}$ (ng·h/mL) | 15284 | 2007 | 5824 | 1274 |
| $t_{1/2}$ (h) | 3.6 | 3.4 | 2.8 | 3.1 |
| CL (mL/min/kg) | | 8.82 | | 13.2 |
| F (%) | 76 | | 46 | |

As shown in Figure 3A, single oral administrations of compounds **31** and **40** of 1, 3, and 10 mg/kg to SD rats induced dose-dependent urinary glucose excretion, resulting in a more than 1000-fold elevation in glucosuria relative to the vehicle control. The ability of compound **31** to increase urinary glucose excretion was similar to that of canagliflozin. Compound **40** was found to be more efficacious than compound **31** and canagliflozin in this experiment. Afterwards, a single dose of compounds **31** or **40** of 25 mg/kg was orally administrated to Rhesus monkeys. As indicated in Figure 3B, compounds **31** and **40** could increase urinary glucose excretion robustly, which was superior to that of canagliflozin. In addition, both compounds **31** and **40** could maintain a comparatively high urinary glucose excretion level for 4 to 5 days similar to dapagliflozin, while canagliflozin could maintain a high level of excretion for less than 3 days.

These results indicated that both compounds **31** and **40** are potent SGLT2 inhibitors and exhibit a long duration of action.

**Figure 3A**

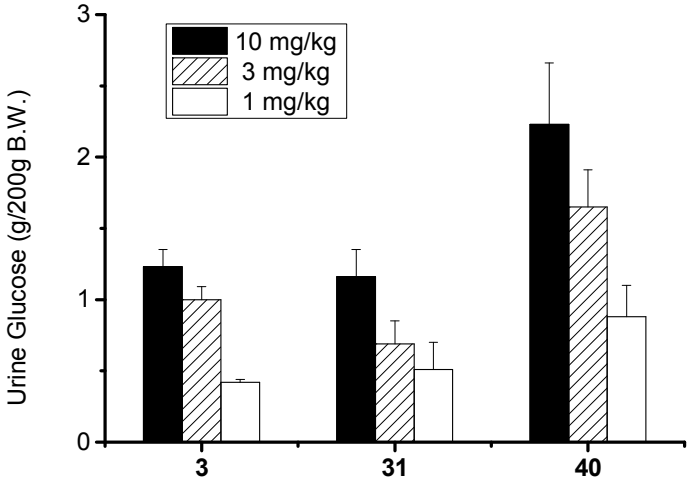



**Figure 3B**

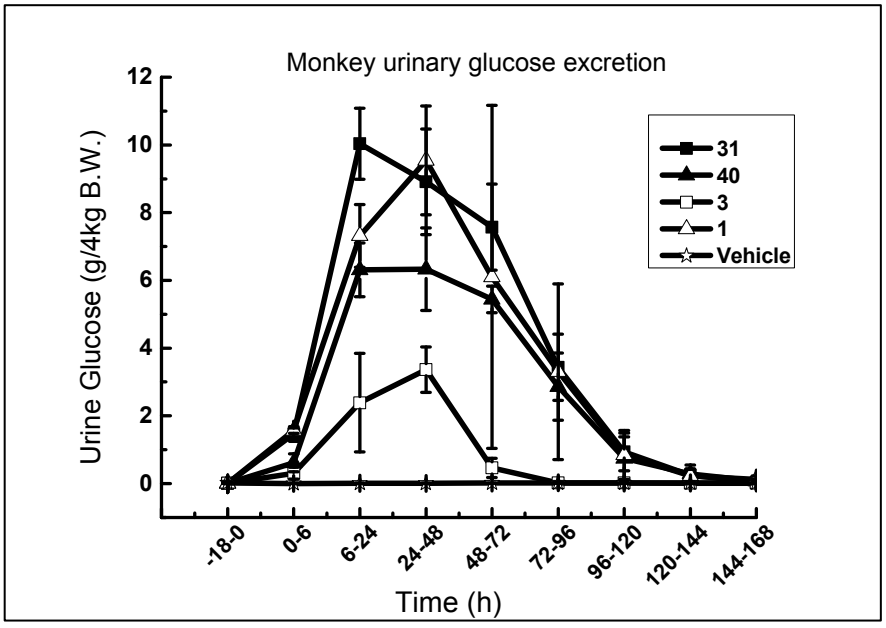


**Figure 3:** Effects of oral administration of selected compounds on urinary glucose excretion in SD rats and Rhesus monkeys. Animals were fasted overnight and orally administrated vehicle or selected compounds at 1, 3, 10 mg/kg for SD rats (n = 3) and 25 mg/kg for Rhesus monkeys (n = 2).

Furthermore, streptozotocin (STZ) and high-fat diet (HFD) induced Institute of Cancer Research (ICR) mice were used to assess the antihyperglycemic effect in an oral glucose tolerance test (OGTT). A single oral dose of compounds **31** or **40** (10 mg/kg) reduced the blood glucose excursion when the compounds were administrated half an hour before an oral glucose challenge. The area under the curve of blood glucose-time ($AUC_{0\text{-}120min}$) showed that compounds **31** and **40** had statistically significant antihyperglycemic efficacies (Figure 4) compared with vehicle treatment ($P$<0.001).

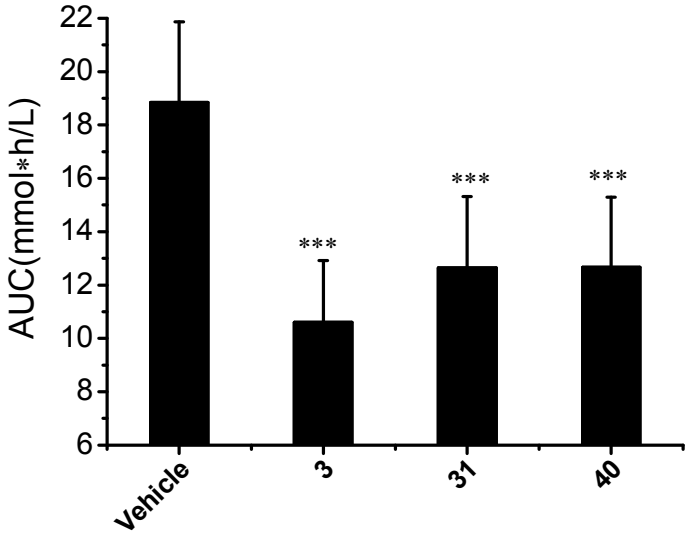



**Figure 4:** Effects of SGLT2 inhibitors during an OGTT in STZ and HFD induced ICR mice.

Animals were fasted overnight and orally given vehicle or SGLT2 inhibitors (10 mg/kg). All animals received an oral glucose load (1 g/kg) half an hour later; areas under the curve of blood glucose-time (0-120 min) are shown. Values are means ± SDs (n = 10). ***, $P < 0.001$.

Due to the good *in vivo* profiles, compounds **31** and **40** were selected for preclinical development. They were tested for their ability to inhibit the hERG channel as part of the evaluation of these compounds. Compounds **31** and **40** were not found to block the hERG channel at concentrations up to 30 μM in the manual whole-cell patch-clamp assay. In a single oral dose toxicology study in SD rats, the Maximum Tolerated Doses (MTDs) of the two compounds were over 1000 mg/kg. Compound **31** was also evaluated in a 28-day repeat-dose toxicology study in Beagle dogs.[38] It was found that compound **31** was well tolerated up to 300 mg/kg without any mortality or severe untoward effects being noted.

## CONCLUSION

We have disclosed a new class of potent and highly selective SGLT2 inhibitors that feature a novel double ketal dioxabicyclo[3.2.1]octane scaffold. Compound **31**, which is currently undergoing further pre-clinical development for the treatment of type 2 diabetes, increased urinary glucose excretion efficaciously and exhibited a long duration of action in Rhesus monkeys.

## EXPERIMENTAL SECTION

**In Vitro hSGLTs Uptake Assays.** The CHO cells stably expressing human SGLT2 or SGLT1 were seeded into 96-well plates (Corning, NY) at a density of 30,000 cells/well and

incubated for 48 h in a 5% $CO_2$ atmosphere at 37 ℃ in growth medium (1 : 1 F-12/DMEM media and 10% FBS). The culture medium was removed and the cells were washed three times with 200 μL of KRH solution (120 mM NaCl, 4.7 mM KCl, 1.2 mM $MgCl_2$, 2.2 mM $CaCl_2$, and 10 mM HEPES, pH 7.4). Then incubated in KRH solution containing 3 μM methyl-α-D-[U-$^{14}$C]-glucopyranoside ([$^{14}$C]AMG) in the absence or presence of inhibitors for up to 120 min at 37 ℃. After that, the KRH solution was removed and the wells were rinsed three times with 200 μL of ice-cold KRH solution. The cells were lysed in 0.1% sodium dodecyl sulfate (Sigma). After 24 h, plates were quantitated in a TopCount (Perkin-Elmer) for counting of radioactive [$^{14}$C]AMG. The percent effect of compounds to inhibit AMG uptake was calculated by comparing counts per minute (CPM) in inhibitor-containing wells with in DMSO wells. The $IC_{50}$ values were fitted to a sigmoidal dose-response model using Origin 8.0 software.

**Oral Glucose-Tolerance Test in STZ and HFD Induced Mice.** Male ICR mice of 4 weeks of age were obtained from Vital River (Beijing, China), fed with high fat diet (15% fat by weight). All mice were given access to food and water ad libitum. At 7 weeks of age, all mice were injected with a single dose of 50 mg/kg of streptozotocin (STZ). The diet induced obesity (DIO) mice at 8 weeks of age (n = 10/group) were randomly assigned to treatment groups and fasted overnight. Mice were then treated orally with vehicle (0.5% methylcellulose) or 10 mg/kg of **3**, **31**, and **40** respectively. Half an hour after treatment (t = 0 min), blood was taken via tail nick and glucose concentration was measured with a glucometer. Also at 30 minutes after treatment, the mice were orally challenged with glucose (1 g/kg, 10 mL/kg). Blood samples for glucose measurement were obtained at 15, 30, 60, and 120 min after the glucose load. The blood glucose excursion profile from t = 0 to t = 120 min was used to integrate an area under the curve (AUC) for each treatment.

**In Vivo Pharmacokinetics Evaluation in SD Rats.** Male Sprague-Dawley rats of 8 weeks of age were obtained from Vital River (Beijing, China). Compounds were administered intravenously to three male rats at 1 mg/kg or orally at 10 mg/kg dose. Blood samples (~200 μL) were collected from each animal via the jugular-vein cannula at 0, 5 (iv only), 15, and 30 min and at 1, 2, 4, 8, 12 and 24 h after dosing. Plasma was separated from the blood by centrifugation at 5000 g for 15 min at 4 ℃ and stored in a freezer (-80 ℃). All samples were analyzed for the test compounds by LC-MS/MS (ABI 4000Q Trap). The concentration data were analyzed with a standard noncompartmental method with Kinetica (version 4.1.1, InnaPhase Corporation, PA).

**Urinary Glucose Excretion in Normal SD Rats and Rhesus Monkeys.** Normal male Sprague-Dawley rats of 8 weeks of age were obtained from Vital River (Beijing, China). Male SD rats were overnight-fasted and divided into 3 rats per group. The rats were treated orally with a single dose of compounds in different doses (1, 3, and 10 mg/kg) or vehicle respectively. Half an hour later, the rats were orally challenged with a 50% glucose solution at a dose of 2 g/kg. The animals were refed at 1 h after glucose challenge, and urine was collected at 24 h. After the urine volumes were measured, the urine samples were measured for glucose levels by using a DRI-CHEM 3500s (FUJI, Tokyo, Japan).

Male Rhesus monkeys of 2 years age were obtained from Sichuan Primed Bio-Tech Group Co., Ltd (Chengdu, China). The animals were overnight-fasted and divided into 2 monkeys per group. The monkeys were treated orally with a single dose of the compounds in 25 mg/kg or vehicle respectively. Half an hour later, the monkeys were orally challenged with a 50% glucose solution at a dose of 2 g/kg. The monkeys were refed at 1 h after glucose challenge, and urine over 24 h was collected. After the urine volumes were measured, the urine samples were measured for glucose levels by using a DRI-CHEM 3500s (FUJI, Tokyo, Japan).

**Ethics Statement** All the animal experimental studies were performed in accordance with the Guide for the Care and Use of Laboratory Animals, formulated by the State Council of the People's Republic of China. And it was approved by the Office of the Experimental Animal Management Committee of Sichuan Province.

**General Procedures** All purchased starting materials were used without further purification. $^{1}$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra were acquired on a Bruker Avance-400 spectrometer (400 MHz) or a Bruker Avance-300 spectrometer (300 MHz), with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed in parts per million (ppm, $\delta$ units). Mass spectra were obtained on a Finnigan LCQAd instrument (ESI) and Agilent 6120 (APCI). Most masses were reported as those of the protonated parent ions. Preparative column chromatography was performed using Yantai Huanghai 200–300 mesh silica. High-resolution mass spectra (HRMS) were recorded on an Apex III 7.0 T FTMS from Bruker Daltonics, Inc. (U.S.). High Performance Liquid Chromatography (HPLC) was performed on an Agilent1260 (chromatographic column (Agilent Zorbax SB-C18 4.6×100mm, 3.5μm)). Rotation was performed on Automatic Polarimeter SGW-3. Melting point was obtained on an OptiMelt MPA100. All compounds submitted for in vitro testing were >95% purity (HPLC) and those for in vivo testing were >98% purity (HPLC).

**General Procedure A**: for the preparation of compounds **14**, **15** and **38**, taking the preparation for compound **14** as an example.

**(1R,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-(methylthio)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (14).** To a solution of **12** (640.0 mg, 0.89 mmol) in DCM (5 mL), was added boron trichloride (17.7 mL, 1 M in DCM, 17.70 mmol) at -78 ℃. Upon completion of the addition, the mixture was stirred for 2 h. The resulting mixture was quenched

by the dropwise addition of a solution of DCM and MeOH (20 mL, v / v = 1 : 1). Water (20 mL) was then added. The water layer was extracted with DCM (20 mL × 2). The combined organic extracts were dried ($Na_2SO_4$), filtered and concentrated. The crude product was purified by column chromatography (DCM / MeOH (v / v) = 40 : 1 ~ 30 : 1, Rf = 0.1) to afford compound **14** as a white solid (55.0 mg, yield 14%, HPLC: 95.72% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.90–7.84 (m, 2 H, ArH), 7.54 (d, $J$ = 8.3 Hz, 1 H, ArH), 7.12 (d, $J$ = 8.5 Hz, 2 H, ArH), 6.85 (d, $J$ = 8.3 Hz, 2 H, ArH), 5.63 (d, $J$ = 6.6 Hz, 1 H, CH), 4.67 (dd, $J$ = 6.6, 4.5 Hz, 1 H, CH), 4.41 (d, $J$ = 4.5 Hz, 1 H, CH), 4.10 (s, 2 H, $CH_2$), 4.04–3.95 (m, 3 H, $CH_2$, CH), 3.74 (d, $J$ = 12.2 Hz, 1 H, CH), 2.02 (s, 3 H, $CH_3$), 1.37 (t, $J$ = 7.0 Hz, 3 H, $CH_3$); $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 196.4, 157.7, 139.9, 139.4, 134.6, 130.7, 130.7, 129.6, 129.5, 127.5, 114.3, 95.1, 80.9, 79.1, 78.7, 63.1, 37.7, 13.8, 8.3. LC-MS *m/z* (ESI): 475.0 $[M + Na]^+$, HRMS: calc. $C_{22}H_{29}ClNO_6S$ $(M + NH_4)^+$ 470.1404, found 470.1394.

**(1R,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-(pyridin-2-ylthio)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (15).** Compound **13** was treated following general procedure A to afford compound **15** as a white solid (20.0 mg, yield 23%, HPLC: 96.31% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 8.38 (dt, $J$ = 4.9, 1.4 Hz, 1 H, pyridine ArH), 7.57 (dd, $J$ = 5.0, 1.5 Hz, 2 H, ArH), 7.34–7.15 (m, 4 H, ArH), 7.00 (d, $J$ = 8.7 Hz, 2 H, ArH), 6.73 (d, $J$ = 8.7 Hz, 2 H, ArH), 4.32 (d, $J$ = 7.9 Hz, 1 H, CH), 3.94 (d, $J$ = 2.6 Hz, 2 H, $CH_2$), 3.90 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 3.61 (d, $J$ = 8.1 Hz, 2 H, CH, CH), 3.56 (t, $J$ = 7.9 Hz, 1 H, CH), 3.47 (d, $J$ = 7.6 Hz, 1 H, CH), 1.27 (t, $J$ = 7.0 Hz, 3 H, $CH_3$); $^{13}$C NMR (101 MHz, DMSO-$d_6$): $\delta$ 157.4, 154.7, 150.3, 138.4, 137.6, 137.3, 133.5, 131.5, 130.1, 129.5, 129.1, 127.6, 126.7, 122.8, 114.8, 108.8, 92.6, 77.2, 76.3, 74.6, 69.0, 63.4, 38.1, 15.1. LC-MS *m/z* (ESI): 516.0 $[M + H]^+$, HRMS: calc. $C_{26}H_{30}ClN_2O_6S$ $(M + NH_4)^+$ 533.1513, found 533.1525.

**(1S,2S,3S,4R,5S)-2,3,4-Tris(benzyloxy)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6,8-ioxabicyclo[3.2.1]octan-1-ol (21a).** A solution of tetra-*n*-butylammonium fluoride (1.2 kg) in THF (3 L) was added dropwise to a solution of **29a** in THF (6 L) at -10 ℃. After the addition was complete the temperature was allowed to reach -5 ℃. The mixture was stirred for 1 h, poured into water (3 L) and extracted with EA (3 L × 3). The combined organic extracts were washed with brine (5 L), dried ($Na_2SO_4$) and concentrated. The crude product was purified by column chromatography (PE / EA (v / v) = 10 : 1, Rf = 0.2) to give compound **21a** as a light yellow solid (480.0 g, yield 33% for 3 steps, HPLC: 96.15% (210 nm)). M.P.: 135.9 ℃, $[\alpha]_D^{25}$ = -44 (c = 0.1, MeOH). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.14–7.37 (m, 16 H, ArH), 7.08 (d, $J$ = 6 Hz, 2 H, ArH), 6.88 (d, $J$ = 6 Hz, 2 H, ArH), 6.77 (d, $J$ = 9 Hz, 2 H, ArH), 4.80–5.01 (m, 4 H, $CH_2$), 4.43 (d, $J$ = 6 Hz, 1 H, CH), 4.30 (d, $J$ = 9 Hz, 1 H, CH), 3.89–4.03 (m, 8 H, CH, $CH_2$), 3.68 (d, $J$ = 6 Hz, 1 H, $CH_2$), 3.54 (d, $J$ = 9 Hz, 1 H, CH), 1.41 (t, $J$ = 6 Hz, 3 H, $CH_3$). LC-MS *m/z* (APCI): 715.0 $[M + Na]^+$.

**(1S,2S,3R,4R)-2,3,4,6-Tetrakis(benzyloxy)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)hexane-1,5-diol (24a).** To a suspension of Mg powder (88.0 g, 3.66 mol) and iodine (a catalytic amount) in anhydrous THF (200 mL) was slowly added **23a** (1.1 kg, 3.36 mol) in anhydrous THF (1 L). The reaction mixture was kept at 60 ℃ for 1 h. In the meantime isopropylmagnesiumbromide (1 M in THF, 2.77 mol) was added dropwise to the solution of **22** (1.5 kg, 2.77 mol) in anhydrous THF (2 L) at 0 ℃. The freshly prepared Grignard reagent was then added dropwise to the solution of **22** at 0 ℃. The reaction mixture was kept at 60 ℃ for 2 h and was quenched by the addition of 2 M hydrochloric acid at 0 ℃. The mixture was extracted with EA (1.2 L × 3). The combined organic extracts were washed with brine (3 L), dried ($Na_2SO_4$) and concentrated to give crude product **24a** as a light yellow syrup. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.40–7.23 (m, 24

H), 7.19 (dd, *J* = 7.2, 2.1 Hz, 3 H), 4.90 (ddd, *J* = 32.4, 16.3, 7.0 Hz, 4 H), 4.73–4.51 (m, 5 H), 4.07–3.91 (m, 4 H), 3.82–3.64 (m, 4 H), 3.58 (d, *J* = 11.3 Hz, 1 H), 3.46 (d, *J* = 11.3 Hz, 1 H), 1.27 (d, *J* = 12.5 Hz, 3 H). LC-MS *m/z* (APCI): 787.3 $[M + H]^+$.

**(2S,3R,4R,5S,6R)-3,4,5-Tris(benzyloxy)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)hexane 1,2,6-triyl triacetate (26a).** Crude **24a** (2.18 kg) was dissolved in acetic anhydride (5 L) and *p*-TsOH (590.0 g) was added at 0 ℃. The mixture was stirred for 3 h at 70 ℃. The reaction mixture was cooled to room temperature and poured into ice water (3 L). The aqueous layer was extracted with EA (2 L × 3). The combined organic extracts were washed with sodium bicarbonate solution (2 L × 2) and water (2 L × 1), dried ($Na_2SO_4$) and concentrated. The residue (2.28 kg) was directly used for the next step without purification. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.37–7.15 (m, 15 H), 7.09–6.93 (m, 5 H), 6.77–6.67 (m, 2 H), 4.77–4.42 (m, 6 H), 4.34–4.15 (m, 2 H), 4.13–3.74 (m, 8 H), 3.61 (m, 1 H), 2.04–1.87 (m, 9 H), 1.36 (t, *J* = 7.0 Hz, 3 H). LC-MS *m/z* (APCI): 823.3 $[M + H]^+$.

**(3R,4R,5S)-3,4,5-Tris(benzyloxy)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)hexane-1,2,6-triol (27a).** Potassium carbonate (1.5 kg) was added in batches to a solution of **26a** (2.28 kg) in MeOH (4.7 L) and water (0.2 L) at 0 ℃. The mixture was allowed to reach room temperature and stirred for 2 h. The resulting mixture was filtered and the filtrate was poured into saturated $NH_4Cl$ solution (5 L) and concentrated. The residue was extracted with EA (2 L × 3). The combined organic extracts were washed with brine (2 L), dried ($Na_2SO_4$) and concentrated. The crude product was purified by column chromatography (PE / EA (v / v) = 4 : 1, Rf = 0.1) to give compound **27a** as a light yellow syrup (1.5 kg, yield 70% for 3 steps). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.39–7.17 (m, 15 H), 7.12–6.96 (m, 5 H), 6.81–6.66 (m, 2 H), 4.60–4.43 (m, 5 H), 4.22 (d, *J* = 10.8 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 1 H), 3.92 (ddd, *J* = 12.5, 12.0, 7.4 Hz, 6 H), 3.73

(td, $J$ = 6.3, 3.3 Hz, 2 H), 3.64 (dd, $J$ = 11.5, 4.4 Hz, 1 H), 3.42 (dd, $J$ = 9.1, 5.0 Hz, 1 H), 1.28–1.21 (m, 3 H). LC-MS *m/z* (ESI): 697.0 $[M + H]^+$.

**(2S,3R,4R)-2,3,4-Tris(benzyloxy)-6-((tert-butyldimethylsilyl)oxy)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)hexane-1,5-diol (28a). 27a** (1.5 kg, 2.10 mol) was treated under a nitrogen atmosphere with TBSCl (366.0 g, 2.31 mol), imidazole (266.0 g, 3.15 mol) and DCM (4 L) at room temperature. After completion of reaction, the mixture was poured into ice water (4 L). The mixture was extracted with DCM (2 L × 2). The organic layer was dried ($Na_2SO_4$), concentrated, and the residue was directly used for the next step without purification.

**(2R,3R,4S)-2,3,4-Tris(benzyloxy)-6-((tert-butyldimethylsilyl)oxy)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)hexane-1,5-dione (29a).** A solution of dimethylsulfoxide (971 mL) in DCM (2.8 L) was added dropwise to a solution of trifluoroacetic anhydride (1424 mL) in DCM (1.4 L) at -78 ℃. **28a** in DCM (2.3 L) was then added. After stirring for 1 h at -78 ℃, triethylamine (2530 mL, 18.20 mol) in DCM (1.4 L) was added, the temperature was allowed to reach room temperature and the mixture was poured into water (3 L). The mixture was extracted with DCM (4 L × 2). The organic layer was dried ($Na_2SO_4$), concentrated, and the residue was directly used for the next step without purification.

**(1S,2S,3R,4R,5S)-2,3,4-Tris(benzyloxy)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-methoxy-6,8-dioxabicyclo[3.2.1]octane (30a).** To a solution of **21a** (330.0 g, 0.48 mol) in DMF (1.5 L) was added iodomethane (101.0 g, 0.72 mol) under nitrogen atmosphere at 0 ℃. Then NaH (14.0 g, 0.61 mol) was added in batches and the mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was adjusted to pH = 7 with saturated $NH_4Cl$ solution. The water phase was extracted with EA (2 L × 3). The combined organic extracts were washed with brine (5 L × 1) and water (5 L × 1), dried ($Na_2SO_4$) and

concentrated. The crude product was purified by column chromatography (PE / EA (v / v) = 15 : 1, Rf = 0.2) to give compound **30a** as a light yellow oil (303.0 g, yield 90%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.13–7.35 (m, 16 H, ArH), 7.06 (d, $J$ = 6 Hz, 2 H, ArH), 6.85 (d, $J$ = 6 Hz, 2 H, ArH), 6.75 (d, $J$ = 9 Hz, 2 H, ArH), 4.74–4.95 (m, 4 H, $CH_2$), 4.27 (d, $J$ = 9 Hz, 1 H, $CH_2$), 4.20 (d, $J$ = 9 Hz, 1 H, $CH_2$), 3.80–4.01 (m, 8 H, CH, $CH_2$), 3.62 (m, 1 H, CH), 3.43 (s, 3 H, $OCH_3$), 1.38 (t, $J$ = 6 Hz, 3 H, $CH_3$). LC-MS *m/z* (APCI): 707.2 $[M + H]^+$.

**(1R,2S,3R,4R,5S)-2,3,4-Tris(benzyloxy)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(difluoromethoxy)-6,8-dioxabicyclo[3.2.1]octane (30i).** To a solution of **21a** (12.5 g, 18.06 mmol) in acetonitrile (150 mL) and water (25 mL) was added potassium hydroxide (12.1 g, 216.07 mmol) at -5 ℃ in an ice-water bath. Bromodifluoromethane diethyl phosphate (14.3 g, 53.56 mmol) was added and the reaction mixture was stirred for 3 h at room temperature. The resulting mixture was quenched with water (100 mL) and extracted with EA (200 mL × 3). The combined organic extracts were washed with saturated $NH_4Cl$ solution (150 mL × 3) and water (100 mL × 2), dried ($Na_2SO_4$), filtered and concentrated. The crude product was purified by column chromatography (PE / EA (v / v) = 30 : 1, Rf = 0.2) to afford compound **30i** as a light yellow oil (6.3 g, yield 47%, HPLC: 96.30% (210 nm)). $[\alpha]_D^{25}$ = -37.5 (c = 0.1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.39–7.27 (m, 11 H, ArH), 7.25–7.10 (m, 5 H, ArH), 7.05 (t, $J$ = 8.6 Hz, 2 H, ArH), 6.83 (m, 2 H, ArH), 6.78–6.71 (m, 2 H, ArH), 6.71–6.37 (t, $J$ = 67.6 Hz, 1 H, $CF_2H$), 4.95 (d, $J$ = 11.1 Hz, 1 H, CH), 4.80 (dd, $J$ = 33.1, 11.0 Hz, 3 H, CH,$CH_2$), 4.45 (d, $J$ = 8.7 Hz, 1 H, CH), 4.26 (d, $J$ = 10.9 Hz, 1 H, CH), 4.09–3.82 (m, 7 H, CH, $CH_2$), 3.78 (d, $J$ = 8.6 Hz, 1 H, CH), 3.66 (d, $J$ = 7.8 Hz, 1 H, CH), 1.38 (t, $J$ = 7.0 Hz, 3 H, $CH_3$). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ -79.51, -79.97, -84.03, -84.49. LC-MS *m/z* (APCI): 743.2 $[M + H]^+$.

**General Procedure B**: The preparation of compounds **31-37**, **40-42**, **45**, **49**, followed the method for compound **31**.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-methoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (31).** Compound **30a** (275.0 g, 0.39 mol) was dissolved in MeOH / THF (1.3 L, v / v = 1 : 1), 1,2-dichlorobenzene (573.0 g, 3.91 mol) and 10% Pd/C (220.0 g) were added and the mixture was stirred for 16 h under hydrogen atmosphere at room temperature. The reaction mixture was filtered and washed with MeOH/DCM (1 L, v / v = 1 : 1). The organic filtrate was concentrated. The crude product was purified by column chromatography (DCM / MeOH (v / v) = 20 : 1, Rf = 0.1) to give compound **31** as a white solid (144.0 g, yield 85%, HPLC: 98.50% (210 nm)). M.P.: 47.6 ℃. $[\alpha]_D^{25}$ = -23 (c = 0.1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.38 (d, $J$ = 1.7 Hz, 1 H), 7.28 (d, $J$ = 8.3 Hz, 1 H), 7.23 (d, $J$ = 1.9 Hz, 1 H), 7.03 (d, $J$ = 8.6 Hz, 2 H), 6.73 (d, $J$ = 8.6 Hz, 2 H), 4.04 (s, 3 H, OH), 4.01 – 3.95 (m, 3 H), 3.90 (q, $J$ = 7.0 Hz, 2 H), 3.85 (d, $J$ = 8.0 Hz, 1 H), 3.74 (t, $J$ = 8.0 Hz, 1 H), 3.66 (d, $J$ = 7.8 Hz, 1 H), 3.61 (d, $J$ = 7.9 Hz, 1 H), 3.32 (s, 3 H), 1.32 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 157.5, 138.5, 136.8, 133.8, 131.3, 129.5, 128.8, 128.5, 125.4, 114.1, 106.3, 106.1, 78.1, 75.9, 72.6, 65.3, 63.1, 50.0, 37.9, 13.8. LC-MS *m/z* (ESI): 459.0 $[M + Na]^+$, HRMS: calc. $C_{22}H_{29}ClNO_7$ $(M + NH_4)^+$ 454.1633, found 454.1623.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-ethoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (32).** Prepared from compound **30b** following general procedure B to afford compound **32** as a white solid (0.2 g, yield 83%, HPLC: 95.17% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.40 (s, 1 H, ArH), 7.38–7.33 (m, 2 H, ArH), 7.08 (d, $J$ = 8.7 Hz, 2 H, ArH), 6.79 (d, $J$ = 8.7 Hz, 2 H, ArH), 4.10 (d, $J$ = 7.9 Hz, 1 H, CH), 4.02 (s, 2 H, $CH_2$), 3.97 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 3.85–3.78 (m, 2 H, CH), 3.69 (m, 1 H, CH), 3.63–3.57 (m, 2 H, $CH_2$),

3.52 (d, $J$ = 7.9 Hz, 1 H, CH), 1.34 (t, $J$ = 7.9 Hz, 3 H, $CH_3$), 1.19 (t, $J$ = 7.0 Hz, 3 H, $CH_3$); $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 157.5, 138.5, 136.8, 133.8, 131.3, 129.5, 128.8, 128.5, 125.4, 114.1, 106.3, 106.0, 78.1, 75.9, 72.6, 65.3, 63.1, 49.9, 37.9, 14.5, 13.8. LC-MS *m/z* (ESI): 405.0 [M - EtO]$^+$, HRMS: calc. $C_{23}H_{31}ClNO_7$ $(M + NH_4)^+$ 468.1789, found 468.1778.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-1-methoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (33).** Prepared from compound **30d** following general procedure method B to afford compound **33** as a white solid (0.2 g, yield 94%, HPLC: 97.81% (210 nm)). M.P.: 47.9 ℃. $[\alpha]_D^{25}$ = -22.5 (c = 0.1, MeOH). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.43 (s, 1 H, ArH), 7.42–7.36 (m, 2 H, ArH), 6.99–6.87 (m, 3 H, ArH), 4.11–4.02 (m, 5 H, CH,$CH_2$), 3.84 (m, 1 H, CH), 3.68–3.56 (m, 2 H, $CH_2$), 3.53 (d, $J$ = 7.9 Hz, 1 H), 3.46 (s, 3 H, $OCH_3$), 1.38 (t, $J$ = 7.0 Hz, 3 H, $CH_3$); $^{19}$F NMR (376 MHz, $CD_3OD$): $\delta$ -136.78, $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 153.7–151.2 (ArCF), 145.2, 137.8, 136.9, 132.7, 128.9, 128.7, 125.8, 124.3, 116.1, 115.9, 114.9, 106.3, 106.1, 78.0, 75.9, 72.6, 65.3, 64.7, 50.1, 37.8, 13.8. LC-MS *m/z* (ESI): 423.0 [M - MeO]$^+$, HRMS: calc. $C_{22}H_{28}ClFNO_7$ $(M + NH_4)^+$ 472.1538, found 472.1527.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-1-ethoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (34).** Prepared from compound **30e** following general procedure B to afford compound **34** as a white solid (0.2 g, yield 86%, HPLC: 98.81% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.42 (s, 1 H, ArH), 7.41–7.35 (m, 2 H, ArH), 6.96 (t, $J$ = 8.3 Hz, 1 H, ArH), 6.90 (d, $J$ = 10.4 Hz, 2 H, ArH), 4.12–4.08 (m, 1 H, CH), 4.07 (m, 4 H, $CH_2$), 3.85–3.80 (m, 2 H, $CH_2$), 3.75–3.66 (m, 1 H, CH), 3.64–3.57 (m, 2 H, $CH_2$), 3.52 (d, $J$ = 7.9 Hz, 1 H, CH), 1.38 (t, $J$ = 7.0 Hz, 3 H, $CH_3$), 1.20 (t, $J$ = 7.1 Hz, 3 H, $CH_3$); $^{19}$F NMR (376 MHz, $CD_3OD$): $\delta$ -136.78; $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 153.7–151.3 (ArCF), 145.2, 137.7, 137.0, 133.8, 132.8, 128.9, 128.6, 125.8, 124.3, 116.0, 114.8, 106.2, 106.0, 78.0, 75.9, 73.0, 65.9, 64.7,

58.9, 37.8, 14.5, 13.8. LC-MS *m/z* (ESI): 423.0 [M - EtO]$^+$, HRMS: calc. $C_{23}H_{30}ClFNO_7$ (M + $NH_4$)$^+$ 486.1695, found 486.1683.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxy-3-fluorobenzyl)phenyl)-1-isopropoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (35).** Compound **30f** was treated following general procedure B to afford compound **35** as a colorless syrup. (25.0 mg, yield 78%, HPLC: 97.94% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.38 (d, $J$ = 7.6 Hz, 3 H, ArH), 7.02–6.79 (m, 3 H, ArH), 4.21 (dt, $J$ = 12.3, 6.1 Hz, 1 H, CH), 4.13–3.97 (m, 5 H, $CH_2$, $CH_2$, CH), 3.75 (dd, $J$ = 8.2, 1.7 Hz, 1 H, CH), 3.65–3.54 (m, 2 H, CH, CH), 3.49 (d, $J$ = 7.9 Hz, 1 H, CH), 1.38 (t, $J$ = 7.0 Hz, 3 H, $CH_3$), 1.19 (d, $J$ = 6.1 Hz, 3H, $CH_3$), 1.16 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 153.8–151.3 (ArCF), 145.3, 138.1, 135.8, 134.7, 132.3, 129.4, 128.7, 125.7, 124.4, 116.6, 116.5, 114.9, 106.0, 105.4, 78.2, 75.6, 74.6, 67.1, 65.0, 38.4, 24.1, 23.8, 14.8. LC-MS *m/z* (ESI): 423.1 [M - $OCH(CH_3)_2$]$^+$, HRMS: calc. $C_{24}H_{32}ClFNO_7$ (M + $NH_4$)$^+$ 500.1851, found 500.1838.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-1-methoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (36).** Compound **30g** was treated following general procedure B to compound **36** as a white solid (30.0 mg, yield 55%, HPLC: 95.40% (210 nm)). M.P.: 48.5 ℃. $[\alpha]_D^{25}$ = -25 (c = 0.1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.33–7.41 (m, 3 H, ArH), 7.09 (d, $J$ = 8.7 Hz, 2 H, ArH), 6.83–6.72 (m, 2 H, ArH), 4.11–4.05 (m, 5 H, CH, $CH_2$), 3.95 (dd, $J$ = 8.2, 1.8 Hz, 1 H, CH), 3.85–3.83 (m, 2 H, $CH_2$), 3.79–3.71 (m, 3 H, $CH_2$), 3.47 (s, 3 H, $OCH_3$), 3.39 (m, 1 H, CH), 0.63–0.60 (m, 2 H, $CH_2$), 0.50–0.47 (m, 2 H, $CH_2$); $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 157.3, 138.4, 136.8, 133.8, 131.7, 129.5, 128.8, 128.5, 125.5, 114.2, 106.3, 106.05, 78.1, 75.9, 72.6, 68.8, 66.9, 65.3, 53.0,49.9, 37.9, 4.5. LC-MS *m/z* (ESI): 515.0 [M + Na]$^+$, HRMS: calc. $C_{25}H_{33}ClNO_8$ (M + $NH_4$)$^+$ 510.1895, found 510.1880.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-(((S)-THF-3-yl)oxy)benzyl)phenyl)-1-methoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (37).** Compound **30h** was treated following following general procedure B to afford compound **37** as a white solid (0.7 g, yield 95%, HPLC: 97.70% (210 nm)). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.39–7.29(m, 3 H, ArH), 7.09–7.07 (d, $J$ = 7.3 Hz, 2 H, ArH), 6.76–6.73 (m, 2 H, ArH), 4.84 (m, 1 H, CH), 4.06–4.02 (m, 3 H, CH, $CH_2$), 3.95–3.92 (m, 4 H, $CH_2$), 3.88–3.82 (m, 1 H, CH), 3.79–3.75 (m, 1 H, CH), 3.72–3.68 (m, 1 H, CH), 3.42 (s, 3 H, $CH_3$), 2.15–2.10 (m, 1 H, CH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 155.8, 138.8, 135.4, 134.9, 131.7, 129.9, 129.4, 128.8, 125.6, 115.4, 105.9, 105.8, 77.9, 77.3, 75.6, 73.0, 67.2, 64.5, 53.4, 51.0, 38.5, 32.9. LC-MS *m/z* (ESI): 501.0 $[M + Na]^+$, HRMS: calc. $C_{24}H_{31}ClNO_8$ $(M + NH_4)^+$ 496.1724, found 496.1733.

**2-(((1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4-trihydroxy-6,8- dioxabicyclo[3.2.1]octan-1-yl)oxy)acetonitrile (38).** Compound **30c** was treated following general procedure A to afford compound **38** as a white solid (0.1 g, yield 39%, HPLC: 98.47% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.44 (s, 1 H, ArH), 7.37 (s, 2 H, ArH), 7.09 (d, $J$ = 8.0 Hz, 2 H, ArH), 6.79 (dd, $J$ = 8.0, 4.0 Hz, 2 H, ArH), 4.57 (s, 2 H, $CH_2$), 4.17 (d, $J$ = 8.0 Hz, 1 H, CH), 4.03 (s, 2 H, $CH_2$), 3.98 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 3.81 (d, $J$ = 8.0 Hz, 1 H, CH), 3.69 (d, $J$ = 8.0 Hz, 1 H, $CH_2$), 3.60 (t, $J$ = 8.1 Hz, 1 H, CH), 3.54 (d, $J$ = 8.0 Hz, 1 H, $CH_2$), 1.35 (t, $J$ = 7.0 Hz, 3 H, $CH_3$); $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 157.5, 138.6, 136.7, 136.0, 134.0, 131.3, 129.6, 128.7, 125.4, 114.2, 107.0, 106.6, 106.0, 77.9, 65.2, 65.1, 63.1, 61.9, 48.8, 37.9, 13.8. LC-MS *m/z* (ESI: 462.1 $[M + H]^+$, HRMS: calc. $C_{23}H_{28}ClN_2O_7$ $(M + NH_4)^+$ 479.1575, found 479.1575.

**(1S,2S,3R,4R,5S)-5-(3-(4-Ethoxybenzyl)phenyl)-1-methoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (39).** Compound **30a** (1.6 g, 2.27 mmol), and 10% Pd/C (1.6 g, 10%) were added to MeOH/THF (120 mL, v / v = 1 : 1). The reaction mixture was stirred

for 5 h at room temperature under hydrogen atmosphere. The mixture was diluted with MeOH (100 mL), filtered and washed with MeOH/DCM (50 mL, v / v = 1 : 1). The organic phase was concentrated under reduced pressure. The crude residue was purified by column chromatography (DCM / MeOH (v / v) = 20 : 1, Rf = 0.1) to afford the compound **39** as a white solid (8.0 mg, yield 1%, HPLC: 96.85% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.42–7.32 (m, 2 H, ArH), 7.26 (dd, $J$ = 13.1, 5.5 Hz, 1 H, ArH), 7.14 (d, $J$ = 7.6 Hz, 1 H, ArH), 7.11–7.06 (m, 2 H, ArH), 6.81–6.77 (m, 2 H, ArH), 4.12–4.01 (m, 2 H, $CH_2$), 3.97 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 3.90 (s, 2 H, $CH_2$), 3.66–3.53 (m, 3 H, CH), 3.45 (d, 3 H, $CH_3$), 1.34 (t, $J$ = 7.0 Hz, 3 H, $CH_3$); $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 156.5, 137.5, 135.8, 133.5, 130.3, 129.7, 128.5, 127.5, 125.9, 114.0, 106.1, 105.1, 77.1, 75.4, 72.3, 65.2, 62.1, 50.3, 37.7, 13.6. LC-MS *m/z* (ESI): 371.0 $[M - MeO]^+$, HRMS: calc. $C_{22}H_{30}NO_7$ $(M + NH_4)^+$ 420.2022, found 420.2014.

**(1R,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-(difluoromethoxy)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (40).** Compound **30i** was treated following general procedure B to afford compound **40** as a white solid (3.4 g, yield 90%, HPLC: 98.60% (210 nm)). M.P.: 48.2 ℃. $[\alpha]_D^{25}$ = 29.8 (c = 0.1, MeOH), $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.48–7.33 (m, 3 H, ArH), 7.11 (dd, $J$ = 6.7, 4.8 Hz, 2 H, ArH), 6.87–6.80 (m, 2 H, ArH), 6.95–6.59 (t, $J$ = 67.6 Hz, 1 H, $CF_2H$), 4.35 (d, $J$ = 8.3 Hz, 1 H,CH), 4.06 (s, 2 H, $CH_2$), 4.01 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 3.83 (d, $J$ = 7.0 Hz, 1 H, CH), 3.73 (dd, $J$ = 8.3, 1.9 Hz, 1 H, CH), 3.62 (q, $J$ = 8.1 Hz, 2 H, $CH_2$), 1.38 (t, $J$ = 7.0 Hz, 3 H, $CH_3$); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ -78.07, -78.53, -80.73, -81.19; $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 157.5, 138.7, 135.8, 134.2, 131.2, 129.5, 128.7, 125.4, 117.1-112.1($CHF_2$), 114.1, 107.2, 104.8, 77.6, 75.5, 74.0, 66.7, 63.1, 37.9, 13.8. LC-MS *m/z* (ESI): 473.0 $[M + H]^+$, 495.0 $[M + Na]^+$, HRMS: calc. $C_{22}H_{27}ClNF_2O_7$ $(M + NH_4)^+$ 490.1444, found 490.1431.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-1-difluoromethoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (41).** Compound **30j** was treated following general procedure B to afford compound **41** as a white solid (120.0 mg, yield 63%, HPLC: 95.57% (210 nm)). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.38 (d, $J$ = 8.2 Hz, 1 H, ArH), 7.34–7.27 (m, 2 H, ArH), 7.08 (d, $J$ = 8.7 Hz, 2 H, ArH), 6.85–6.80 (m, 2 H, ArH), 6.72–6.36 (t, $J$ = 67.6 Hz, 1 H, $CF_2H$), 4.32 (d, $J$ = 8.6 Hz, 1 H, CH), 4.08–4.02 (m, 4 H, $CH_2$), 3.94 (d, $J$ = 6.8 Hz, 1 H, CH), 3.85–3.79 (m, 2 H, $CH_2$), 3.76 (d, $J$ = 7.9 Hz, 1 H, CH), 3.71 (ddd, $J$ = 7.7, 4.7, 2.9 Hz, 2 H, $CH_2$), 3.37 (dq, $J$ = 9.1, 3.0 Hz, 1 H, CH), 0.64–0.57 (m, 2 H, $CH_2$), 0.50–0.44 (m, 2 H, $CH_2$); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ -81.31, -81.77, -82.50, -82.96; $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 157.4, 138.6, 135.9, 134.1, 131.6, 129.5, 128.8, 128.6, 125.4, 117.1-112.1 ($CHF_2$), 114.3, 107.2, 104.8, 77.6, 75.5, 74.0, 68.8, 66.9, 66.6, 53.0, 37.8, 4.5. LC-MS *m/z* (ESI): 529.0 $[M + H]^+$, 551.0 $[M + Na]^+$, HRMS: calc. $C_{25}H_{31}ClF_2NO_8$ $(M + NH_4)^+$ 546.1706, found 546.1693.

**(1R,2S,3R,4R,5S)-5-(4-Chloro-3-(4-(((S)-THF-3-yl)oxy)benzyl)phenyl)-1-(difluoromethoxy)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (42).** Compound **30k** was treated following general procedure B to afford compound **42** as a white solid (0.4 g, 63%, HPLC: 98.85% (210 nm)). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.35–7.32 (m, 1 H, ArH), 7.25–7.23 (m, 1 H, ArH), 7.07–7.05 (d, $J$ = 8.6 Hz, 2 H, ArH), 6.74–6.70 (m, 2 H, ArH), 6.70–6.33 (t, $J$ = 67.6 Hz, 1 H, $CF_2H$), 4.84–4.80 (m, 1 H, CH), 4.01 (s, 2 H, $CH_2$), 3.96–3.88 (m, 4 H, CH), 3.85–3.80 (m, 1 H, $CH_2$), 3.75–3.71 (t, $J$ = 16 Hz, 1 H, CH), 3.67–3.64 (m, 2 H, $CH_2$), 2.14–2.18 (m, 2 H, $CH_2$); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ -79.19, -79.66, -80.89, -81.35; $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 155.9, 138.5, 135.2, 134.1, 131.8, 128.7, 127.9, 127.4, 125.4, 117.1–112.1 ($CHF_2$), 115.5, 107.2,

104.8, 77.6, 77.2, 75.5, 74.0, 72.6, 66.7, 66.6, 37.8, 32.5. LC-MS *m/z* (ESI): 537.0 $[M + Na]^+$, HRMS: calc. $C_{24}H_{29}ClF_2NO_8$ $(M + NH_4)^+$ 532.1538, found 532.1544.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-(2-hydroxyethoxy)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (45).** Compound **44** was treated following general procedure B to afford compound **45** as a white solid (0.3 g, yield 80%, HPLC: 95.89% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.40 (s, 1 H, ArH), 7.36 (dd, $J$ = 17.7 Hz, $J$ = 9.5 Hz, 2 H, ArH), 7.08 (d, $J$ = 8.6 Hz, 2 H, ArH), 6.79 (d, $J$ = 8.6 Hz, 2 H, ArH), 4.11 (d, $J$ = 7.9 Hz, 1 H, CH), 4.02 (s, 2 H, $CH_2$), 3.98 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 3.80–3.86 (m, 2 H, CH), 3.65–3.73 (m, 4 H, CH, $CH_2$), 3.61 (t, $J$ = 8.0 Hz, 1 H, $CH_2$), 3.53 (d, $J$ = 7.9 Hz, 1 H, $CH_2$), 1.35 (t, $J$ = 7.0 Hz, 3 H, $CH_3$), $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 157.5, 138.5, 136.8, 133.8, 131.3, 129.5, 128.8, 128.5, 125.4, 114.1, 106.3, 105.9, 78.0, 75.6, 73.1, 65.6, 64.5, 63.0, 60.8, 37.9, 13.8. LC-MS *m/z* (ESI): 448.2 $[M - H_2O]^+$, HRMS: calc. $C_{23}H_{31}ClNO_8$ $(M + NH_4)^+$ 484.1726, found 484.1738.

**(1S,2S,3R,4R,5S)-5-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-1-cyclopropoxy-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (49).** Compound **48** was treated following general procedure B to afford compound **49** as a white solid (0.2 g, yield 80%, HPLC: 98.55% (210 nm)). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.37 (d, $J$ = 7.9 Hz, 3 H, ArH), 7.11–7.06 (m, 2 H, ArH), 6.83–6.78 (m, 2 H, ArH), 4.10 (d, $J$ = 7.8 Hz, 1 H, CH), 4.03 (s, 2 H, $CH_2$), 3.98 (q, $J$ = 7.0 Hz, 2 H, $CH_2$), 3.90 (dd, $J$ = 8.1, 1.8 Hz, 1 H, $CH_2$), 3.81 (dd, $J$ = 7.9, 1.9 Hz, 1 H, CH), 3.66–3.56 (m, 2 H, CH, $CH_2$), 3.51 (d, $J$ = 7.9 Hz, 1 H, CH), 1.35 (t, $J$ = 7.0 Hz, 3 H, $CH_3$), 0.73 (ddd, $J$ = 6.3, 5.2, 2.7 Hz, 1 H, $CH_2$), 0.59 (ddd, $J$ = 10.1, 5.4, 3.4 Hz, 1 H, $CH_2$), 0.55–0.48 (m, 2 H, $CH_2$); $^{13}$C NMR (101 MHz, $CD_3OD$): $\delta$ 157.5, 138.5, 136.9, 133.8, 131.3, 129.6, 128.8, 128.5, 125.5, 114.2, 107.0, 106.1, 78.0, 76.0, 73.4, 65.6, 63.1, 37.9, 13.8, 5.2, 4.2. LC-MS *m/z* (ESI): 485.0 $[M + Na]^+$, HRMS: calc. $C_{24}H_{31}ClNO_7$ $(M + NH_4)^+$ 480.1789, found 480.1779.

ASSOCIATED CONTENT

**Supporting Information**

The supporting information is available free of charge on the ACS publications website. The supporting information includes experimental, analytical details and spectra data for compounds **10**–**49**.

AUTHOR INFORMATION

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ABBREVIATIONS USED

AMG, methyl-$\alpha$-D-glucopyranoside; AUC, area under the plasma concentration time curve; $BCl_3$, boron trichloride; $Bu_4NF$, $BrCH_2CO_2Et$, ethyl 2-bromoacetate; tetrabutylammonium fluoride; $BrF_2CPO_3(Et)_2$, diethyl (bromodifluoromethyl)phosphonate; $CH_3ONa$, sodium methoxide; $CH_2I_2$, diiodomethane; CL, clearance; $(COCl)_2$, oxalyl chloride; DCM, dichloromethane; DIO, diet induced obesity; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; EA, ethyl acetate; $Et_3N$, triethylamine; $Et_2Zn$, diethyl zinc; *F*, oral bioavailability; FDA, U.S. Food and Drug Administration; $H_2$, hydrogen; HFD, high-fat diet; $I_2$, iodine; $IC_{50}$,

half-maximal inhibitory concentration; $K_2CO_3$, potassium carbonate; KOH, potassium hydrate; KRH, Krebs-Ringer HEPES buffer; $LiBH_4$, lithium borohydride; mCPBA, 3-chlorobenzoperoxoic acid; MeCN, methyl cyanide; Mg, magnesium; MeOH, methanol; MeSSMe, 1, 2-dimethyldisulfane; MTD, maximum tolerated doses; NaH, sodium hydride; $NaHCO_3$, sodium hydrogen carbonate; $Na_2SO_4$, sodium sulfate; OGTT, oral glucose tolerance test; PE, petroleum ether; $PPh_3$, triphenylphosphine; PK, pharmacokinetics; *p*-TsOH, *p*-toluenesulfonic acid; Rf, retention factor value; rt, room temperature; SGLT, sodium-dependent glucose cotransporter; SD, Sprague-Dawley; SAR, structure activity relationship; STZ, streptozotocin; t-$BuMe_2SiCl$, tert-butyl dimethylsilylchloride; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; Toluene, methylbenzene; T2DM, type 2 diabetes mellitus; UGE, urinary glucose excretion; WHO, world health organization.

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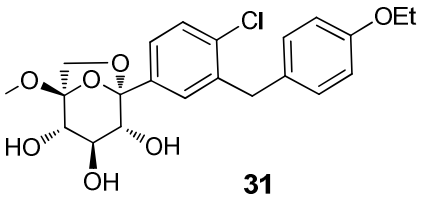
(37) The cost for compound **22** is no more than $250 per kilogram, and the cost for compound **23a** is less than $1400 per kilogram in P. R. China.

(38) This study was designed according to the NDA data of canagliflozin.




**31**

$IC_{50}$(hSGLT2) = 1.3 nM
$IC_{50}$(hSGLT1) = 1096.0 nM

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