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Conformationally Constrained Spiro *C*-Arylglucosides as Potent and Selective Renal Sodium-Dependent Glucose Co-transporter 2 (SGLT2) Inhibitors

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Diabetes is a highly prevalent modern disease with over 246 million people afflicted worldwide in 2007.[1] A failure of glycemic homeostasis secondary to nutritional imbalance is considered to be the principle explanation for the alarming and increasing incidence of type 2 diabetes mellitus (DM2) in both developed and developing countries.[2] Although a large number of antihyperglycemic agents have been developed to treat the disease, 63% of DM2 patients fail to achieve the target levels of glycosylated hemoglobin (HbA1C $<$ 7%) recommended by the American Diabetes Association,[3,4] and consequently these individuals are at risk of developing complications, such as accelerated cardiovascular disease, diabetic nephropathy, retinopathy and ulceration.[1] Recently, renewed emphasis on the development of safe oral antidiabetic agents with a favorable cardiovascular profile has highlighted the attractions of inhibition of renal glucose resorption as a therapeutic mechanism.

Sodium glucose co-transporter 2 (SGLT2) is a 672-amino acid, high-capacity, low-affinity transporter expressed nearly exclusively in the S1 and S2 segments of the renal proximal tubule and believed to mediate the majority of renal glucose resorption from the glomerular filtrate.[5] Because the etiology of type 2 diabetes mellitus (DM2) depends on a hypertrophic adipose reservoir, mechanisms that promote glucose disposal by urinary output are therapeutically attractive compared to mechanisms that promote increased glucose assimilation by adipocytes. Selective inhibitors of SGLT2 are expected to be safe because individuals homozygous or compound heterozygous for mutations in *SLC5A2*, the gene encoding SGLT2, exhibit no significant morbidities.[6] In contrast, penetrant alleles leading to SGLT1 deficiency are the genetic cause of glucose–galactose malabsorption syndrome, which is associated with severe neonatal diarrhea and failure to thrive.[7] In particular, the high selectivity could potentially reduce the gastrointestinal side effect.[8] Hence inhibitors selective for SGLT2 over SGLT1 are attractive candidates for development.

Following the initial disclosure of T-1095A, a selective and potent SGLT2 inhibitor designed based on the naturally occurring inhibitor phlorizin, by Tanabe Seiyaku Co., Ltd. (Osaka, Japan),[9–11] multiple classes of SGLT2 inhibitors have been reported, including *O*- and *C*-glucosides.[12–14] The most advanced inhibitors currently undergoing clinical development in phase III trials, dapagliflozin (**1**)[15,16] and canagliflozin,[17] are *C*-arylglucosides.

The studies described here were directed at identifying metabolically robust agents with high selectivity towards SGLT2. Information gained from modeling studies and analysis of the crystal structure of dapagliflozin (**1**)[18] suggested the possibility of creating novel and conformationally constrained chemotypes with improved potency for SGLT2 by cyclizing the 1- and 6′-positions of the glucose moiety and glucose-proximal phenyl ring (Figure 1). Preliminary studies showed that retention of a chlorine substituent at the 4′-position on the proximal phenyl ring is critical for activity.[19] The synthesis and evaluation of three series of novel analogues, which have a different scaffold than previously reported inhibitors, are described here.

The synthesis of spiro[isobenzofuran-1,2′-pyran] analogues **12a–e** was addressed first (Scheme 1). Persilylated gluconolactone **3** was prepared in 89% yield by the slow addition of trimethylsilyl chloride (TMSCl) to commercially available gluconolactone **2** in the presence of *N*-methylmorpholine.[20,21] Benzoic acid **4** was subjected to bromination with *N*-bromosuccinimide (NBS) followed by esterification to yield aniline **6**. Sandmeyer reaction and subsequent oxidation of **7** provided the key electron-deficient tetra-substituted benzene **8**. Friedel–Crafts acylation of R^1 substituted benzenes generated the benzophenone **9**. Selective reduction of the resulting ketone with triethylsilane and further reduction of the methyl ester gave the corresponding benzyl alcohol **10**. Protection of the primary hydroxy group with chloromethyl methyl ether produced bromide **11**. Lithium–halogen exchange and subsequent coupling with lactone **3** gave a mixture of lactols,[22] which were converted in situ to the desired spiro[isobenzofuran-1,2′-pyran] derivatives **12a–e** in 40 to 63% yield after purification by preparative thin layer chromatography (TLC).[23]

The synthesis of spiro[indane-1,2′-pyran] glucosides **19a–e** was more challenging than that of *O*-spiroketal *C*-arylglucosides analogues (Scheme 2). Benzyl alcohol **13** was oxidized with Dess–Martin reagent and subsequently subjected to

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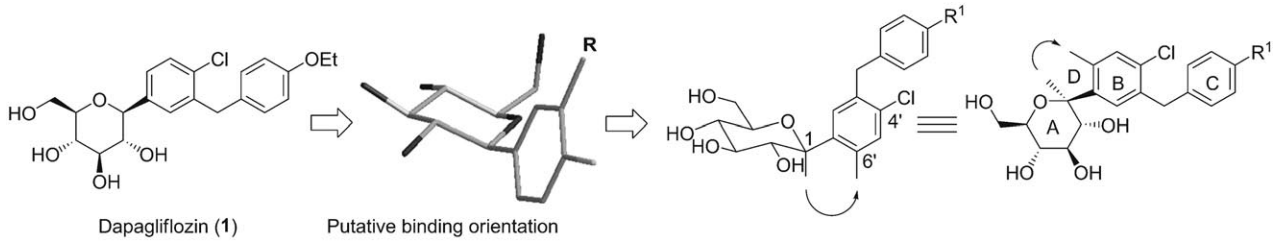
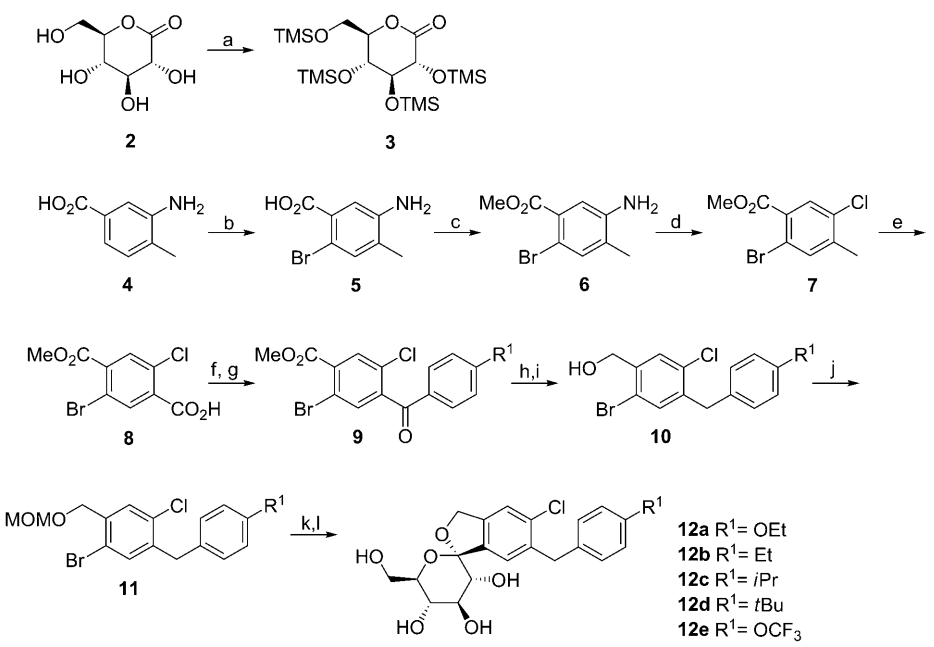


Figure 1. Origin and design of spiro *C*-arylglucosides as SGLT2 inhibitors.



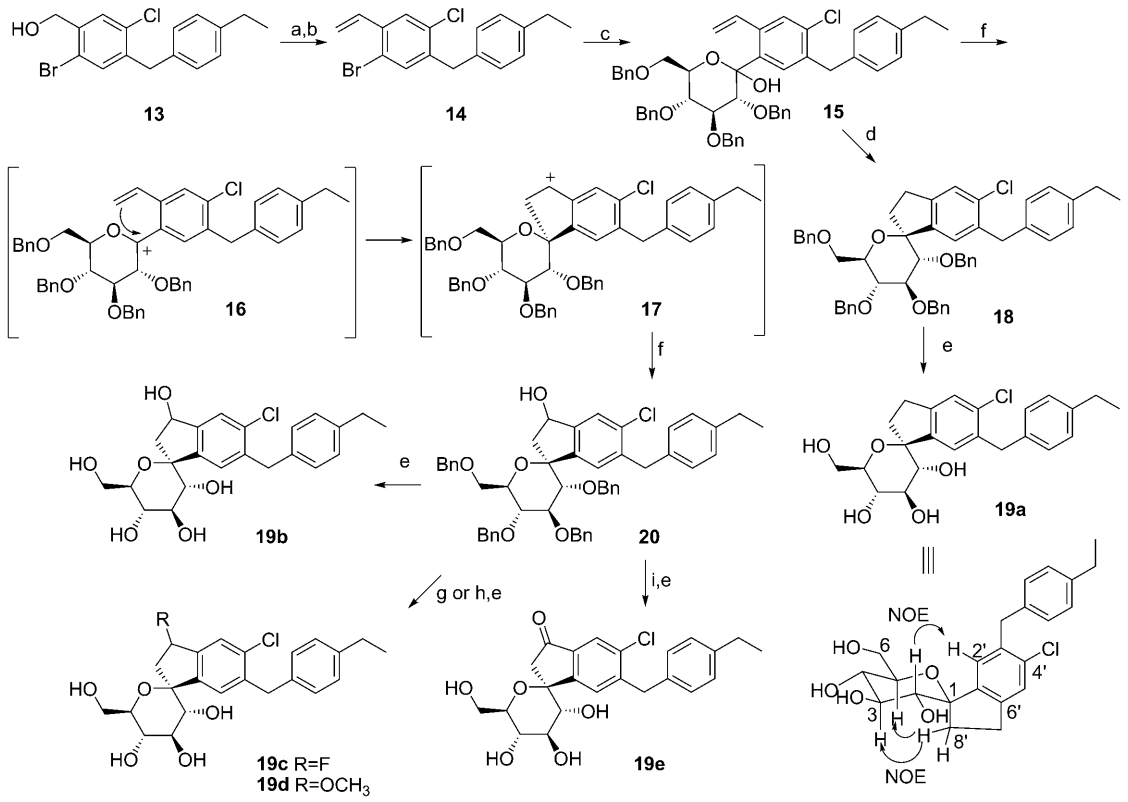
Scheme 1. Synthesis of spiro[isobenzofuran-1,2′-pyran] analogues **12a**–**e**. *Reagents and conditions*: a) TMSCl, *N*-methylmorpholine, THF, 20 °C, overnight, 89%; b) NBS, DMF, 5 °C, 1 h, 87%; c) $SOCl_2$, MeOH, reflux, 6 h, 99%; d) $NaNO_2$, concd HCl, CuCl, 1,4-dioxane, H_2O, 0 °C, 40 min, 93%; e) $KMnO_4$, *t*BuOH, 18-crown-6, H_2O, reflux, overnight, 73%; f) $(COCl)_2$, DMF, CH_2Cl_2; g) $AlCl_3$, R^1 substituted phenyl, CH_2Cl_2; h) Et_3SiH, CF_3SO_3H, TFA; i) $NaBH_4$, MeOH, THF; j) MOMCl, DIPEA, CH_2Cl_2, 0 °C→RT; k) *n*BuLi, THF, toluene, −78 °C, lactone **3**; l) CH_3SO_3H, MeOH, −78 °C→RT, 40–63% (two steps).

Wittig olefination to give styrene **14** in 72% overall yield. Lithiation of **14** via lithium–halogen exchange, followed by addition of the aryl-lithium salt to the known 2,3,4,6-tetra-*O*-benzyl-β-D-glucolactone, gave a mixture of lactols **15** ($\beta/\alpha =$ 10:1).

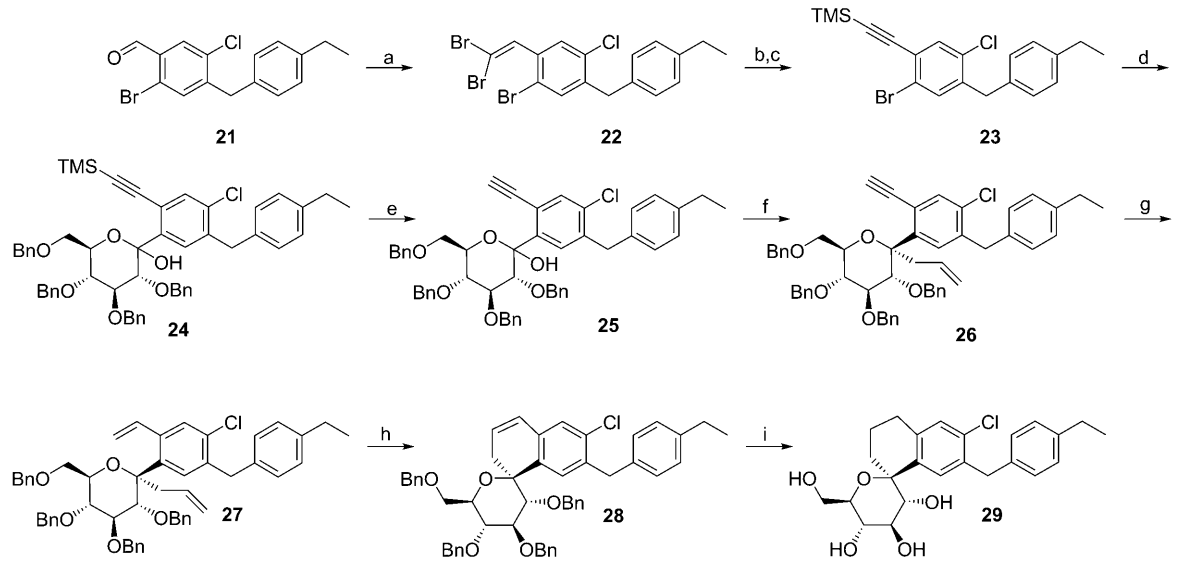
Two routes to the the spiro[indane-1,2′-pyran] scaffold from precursor **15** were explored. In the initial test, lactols **15** were exposed to a mixture of triethylsilane and boron trifluoride etherate at −30 °C and subsequent deprotection by hydrogenolysis. These reaction conditions predominantly generated spiro[indane-1,2′-pyran] **19a** in 40% yield after purification by preparative LC–MS. The configuration of **19a** was assigned using nuclear Overhauser effects (NOEs) in which correlations were observed between the chemical shifts assigned to 8′-H and 3-H, 8′-H and 5-H, 2′-H and 2-H of the chair conformation of **19a** (see Supporting Information for characterization).

Compound **19f** was obtained through a similar synthetic sequence to that of **19a** starting from (2-bromo-5-chloro-4-(4-ethoxybenzyl)phenyl)methanol.[23] Treatment with an excess amount of a proton source to yield cation **16** followed by a regio- and stereoselective cyclization should generate carbocycle **17**, a compound which is favored, in principle, by neighboring group steric hindrance and energy minimization. Lactols **15** were exposed to trifluoroacetic acid (TFA) in dichloromethane at −20 °C for 6 h, followed by hydrolysis with lithium hydroxide to give alcohol **20** in 37% yield. This intermediate was smoothly converted into hexahydroxy spiro[indane-1,2′-pyran] **19b** by reductive debenzylation. The indane hydroxy group in compound **20** was modified using diethylaminosulfur trifluoride (DAST) fluorination, iodomethane alkylation or Dess–Martin periodinane-mediated oxidation, followed by deprotection to give **19c**–**e**, respectively, in 75 to 81% overall yield.

Our initial attempts to synthesize spiro[tetrahydronaphthalene-1,2′-pyran] glucosides **29** by allylation of lactols **15** followed by cyclization did not construct the carbocyclic skeleton since the allyl anion acted as a carbon nucleophile and directly attacked the cation **17** rather than the anomeric oxonium ion.[23] Thus, spiro[tetrahydronaphthalene-1,2′-pyran] was prepared from trimethylsilyl ethyne **23**, which was generated from aldehyde **21** through Corey–Fuchs alkyne synthesis and subsequent protection with trimethylsilyl chloride (Scheme 3). Lithium–halogen exchange with **23** followed by its addition to the known 2,3,4,6-tetra-*O*-benzyl-β-D-glucolactone gave a mixture of **24**. Subsequent deprotection using tetra-*n*-butylammonium fluoride (TBAF) provided lactol **25** ($\beta/\alpha = 1{:}1$) in 71% overall yield. Allylation in the presence of boron trifluoride etherate favored axial nucleophilic attack at the oxocarbenium in the



Scheme 2. Synthesis of spiro[indane-1,2′-pyran] glucosides **19a**–**e**. *Reagents and conditions*: a) Dess–Martin reagent, CH_2Cl_2, −5 °C→RT, 2 h, 96%; b) Ph_3PCH_3I, $KN(TMS)_2$, toluene, RT, 4 h, 75%; c) *n*BuLi, 2,3,4,6-tetra-*O*-benzyl-β-D-gluconolactone, dry THF, toluene, −78 °C, 3.5 h, 59%; d) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C, 40%; e) 10% Pd/C, H_2, THF, MeOH, RT; f) 1. TFA, CH_2Cl_2, −20 °C, 6 h; 2. $LiOH{\cdot}H_2O$, THF/MeOH/H_2O (4:1), RT, 5 h, 37% (two steps); g) DAST (Et_2NSF_3), CH_2Cl_2, −78 °C, 3 h, 87%; h) CH_3I, NaH (60% in mineral oil), dry THF, RT, 1 h, 85%; i) Dess–Martin reagent, CH_2Cl_2, 0 °C→RT, 2 h, 90%.



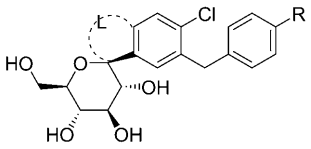
Scheme 3. Synthesis of spiro[naphthalene-1,2′-pyran] glucosides **29**. *Reagents and conditions*: a) CBr_4, PPh_3, CH_2Cl_2, RT, overnight, 60%; b) LDA, THF, −78 °C, 1.5 h; c) TMSCl, RT, 4 h, quantitative; d) *n*BuLi, 2,3,4,6-tetra-*O*-benzyl-β-D-gluconolactone, dry THF, toluene, −78 °C, 2.5 h; e) TBAF, THF, 0 °C, 1 h, 71% (two steps); f) $BF_3{\cdot}OEt_2$, allyl TMS, −5 °C, overnight, 50%; g) Lindlar catalyst, H_2, EtOAc, RT, 3 h, 69%; h) Second generation Grubbs' catalyst, CH_2Cl_2, reflux, overnight, 78%; i) 10% Pd/C, H_2, THF, MeOH, RT, 1 h,73%.

gluco configuration to form only one isomer of bis-*C*,*C*-glucoside **26**.[24] Reduction of the resulting alkyne using Lindlar catalyst followed by ring-closing metathesis using second generation Grubbs' catalyst formed carbocyclic compound **28**, which was finally converted to spiro[tetrahydronaphthalene-1,2′-pyran] **29** by hydrogenolysis in 73% yield.

All derivatives were screened for their inhibitory activity in cell-based SGLT functional assays (Table 1). As indicated by the IC_{50} value for compound **12a**, the first generation spiro[isobenzofuran-1,2′-pyran] exhibited comparable potency against human SGLT2 (hSGLT2) and 1.5-fold improvement of selectivity over human SGLT1 (hSGLT1) compared with dapagliflozin (**1**).[25,26] With respect to the alkyl substituent at the *para*-position of the distal aryl ring (compounds **12b–d**), the ethyl-substituted derivative (**12b**) showed an IC_{50} value of 6.6 nM for hSGLT2 and only 91-fold selectivity over hSGLT1, whereas the *iso*-propyl and *tert*-butyl derivatives (**12c** and **12d**, respectively) exhibited increased selectivity and slightly reduced inhibitory activity against hSGLT2 indicating a trend towards greater selectivity for hSGLT2 over hSGLT1 with increasing substituent size. Replacement of the ethoxy group with a trifluoromethoxy moiety in this position (compound **12e**) led to a pronounced increase in inhibition and selectivity towards hSGLT2 compared with dapagliflozin (**1**). Overall, all analogues **12a–e** with small, lipophilic *para*-substituents on the distal aryl ring in this series had equivalent or increased potency and selectivity for SGLT2 inhibition relative to dapagliflozin (**1**), possibly because of the greater conformational constraints imposed by the spiro[isobenzofuran-1,2′-pyran] scaffold.

Since the ketal structure in the spiro[isobenzofuran-1,2′-pyran] analogues might be metabolically labile, the spiro[indane-1,2′-pyran] analogues **19a–f** were investigated. Substitution of a methylene group for an oxygen atom in the isobenzofuran analogue **12b** gave a more potent inhibitor **19a**, which exhibited an IC_{50} value of 0.3 nM and greater than 18600-fold selectivity for SGLT2 over SGLT1. Introduction of a hydroxy group at the indane 7′-position led to compound **19b** and subsequent oxidation generated ketone **19e**, both of which showed diminished SGLT2 inhibition compared with the parent compound. However, good activity was observed when the 7′-position was substituted with a fluorine atom or a methoxy group (compounds **19c** and **19d**, respectively). To the best of our knowledge, compounds **19c** and **19d** are among the most selective SGLT2 inhibitors, with potency ratios in the order of 5×10^4. Interestingly, compound **19f**, derived from the replacement of the ethyl substituent with an ethoxy group on the distal ring of **19a**, exhibited reduced inhibitory activity against SGLT2 but retained the high selectivity for SGLT2 over SGLT1. To further understand the influence of the size of the spiro ring between the carbohydrate moiety and the proximal aryl ring of the aglycon moiety on selectivity, spiro[tetrahydronaphthalene-1,2′-pyran] analogue **29** (shown in Scheme 3) was synthesized. Although compound **29** exhibited a fivefold decrease in potency towards SGLT2 compared to dapagliflozin (**1**), the selectivity over SGLT1 was still greater than 6060-fold. A detailed explanation for the observed selectivity is not possible without definitive determination of the active-site geometry, however, we speculate that the binding pocket of SGLT2 may accomodate the rigid conformation of the spiro[indane-1,2′-pyran] and spiro[naphthalene-1,2′-pyran] better.

Table 1. Structures, binding affinities (IC_{50}) of spiro *C*-arylglucosides on human SGLT2 and SGLT1.



Compound	L[a]	R	IC_{50}[b] hSGLT2 [nM]	IC_{50}[b] hSGLT1 [μM]	Selectivity hSGLT1/hSGLT2
12a	$-OCH_2-$	OEt	6.5	1.3	200
12b	$-OCH_2-$	Et	6.6	0.6	91
12c	$-OCH_2-$	*i*Pr	7.1	2.5	352
12d	$-OCH_2-$	*t*Bu	13	9.7	746
12e	$-OCH_2-$	OCF_3	0.3	3.1	10333
19a	$-CH_2CH_2-$	Et	0.3	5.6	18667
19b	$-CH_2CH(OH)-$	Et	40	138	3450
19c	$-CH_2CHF-$	Et	0.9	51	56667
19d	$-CH_2CH(OCH_3)-$	Et	1.8	99	55000
19e	$-CH_2CO-$	Et	>100	ND	ND
19f	$-CH_2CH_2-$	OEt	11	10-100	909–9090
29	$-CH_2CH_2CH_2-$	Et	33	>200	>6060
Dapagliflozin (**1**)[c]			6.7	0.89	132

[a] Linker (L) connecting the anomeric carbon to the proximal phenyl ring. [b] Values given are the mean of two independent experiments conducted in duplicate; a reference standard was always included in the assays. [c] The IC_{50} value of dapagliflozin (CAS: 461432-26-8) was determined by in vitro assay (see Supporting Information for more details on the binding assay used in this report).

As compound **19a** showed the highest potency against hSGLT2, it was evaluated for its ability to induce urinary glucose excretion in healthy Sprague–Dawley rats. Oral administration of **19a** to rats in a single dose of 0.33, 1, 3, 9, 27 mg kg^{-1} induced urinary glucose excretions of 110, 370, 650, 1470 and 1450 mg, respective, per 200 g of body weight over 24 h, resulting in a 10- to 100-fold elevation relative to the vehicle control. Figure 2 compares the dose-dependent glucosuric response with previously reported data for oral dosing (1.0 mg kg^{-1}) of dapagliflozin (**1**).[27] As glucosuria excretion induced by **19a** was less than that observed with dapagliflozin (**1**) at the same dose in rats (1 mg kg^{-1}), we speculated that **19a** may be liable to metabolic degradation. In a separated experiment, the predicted elimination half-life for **19a** was 1.2, 10.5, 1.5 and 6.4 h following incubation with liver microsomes and hepatocytes from rat, dog, monkey and human, respectively. The calculated hepatic clearance rate in rats was 33 mL/min kg^{-1} compared to low in vitro metabolic rate (<2.2 mL/min kg^{-1}) of dapagliflozin.[27,28] The SGLT2 inhibition,

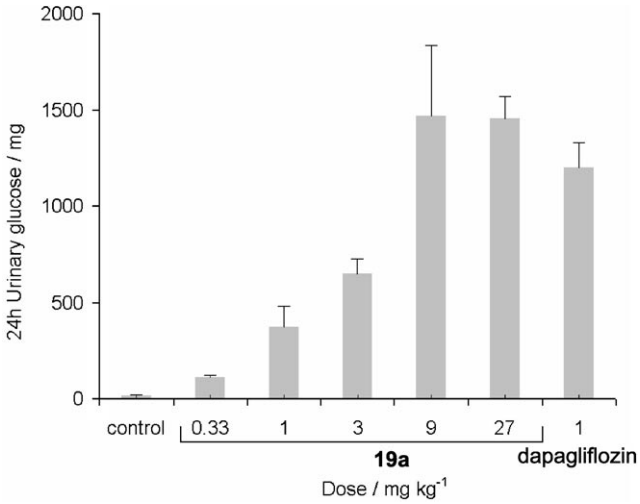


Figure 2. Dose-dependent glucosuric response to treatment with **19a** over 24 h (per 200 g body weight) following a single oral dose (Sprague–Dawley rats). Data shown are the mean ±SD ($n=5$).

glucosuria and in vitro metabolic rate of compound **19a** suggest the spiro[indane-1,2′-pyran] series may be merit further exploration.

In conclusion, we have identified a rigid spiro *C*-arylglucoside scaffold that gave rise to a viable series of potent, selective SGLT2 inhibitors that are conformationally constrained compared to previously reported *C*- and *O*-glucosides. The structure–activity relationship exploration of this series established the higher binding affinity and greater selectivity for SGLT2 of the spiro chemotype compared with previously reported agents.

Experimental Section

For experimental details on the synthesis and biological assays see the Supporting Information.

All biological experiments involving animals were performed in accordance with the PR China law and the local ethical committee guidelines for animal research.

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Keywords: *C*-glycosides · diabetes mellitus · inhibitors · SGLT2 · spiro compounds

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