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Indole-glucosides as novel sodium glucose co-transporter 2 (SGLT2) inhibitors. Part 2

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Abstract—A series of indole-*O*-glucosides and *C*-glucosides was synthesized and evaluated in SGLT1 and SGLT2 cell-based functional assays. Compounds **2a** and **2o** were identified as potent SGLT2 inhibitors and screened in ZDF rats.

Non-insulin-dependent diabetes mellitus (NIDDM) is a metabolic disorder characterized by hyperglycemia as well as insulin resistance and/or impaired insulin secretion. Normalization of plasma glucose in NIDDM patients would be predicted to improve insulin action and to offset the development of diabetic complications. An inhibitor of the sodium-glucose co-transporters (SGLTs) in the kidney would be expected to aid in the normalization of plasma glucose levels by enhancing glucose excretion.[1] Multiple classes of glucose conjugates and *C*-glucosides have been reported as SGLT inhibitors.[2] Compound **1** has been reported to lower blood glucose levels by inhibiting both SGLT1 and SGLT2, the two major isoforms of SGLT in the human body.[3] In our earlier studies, we demonstrated that modification of the benzofuran moiety of compound **1** resulted in compounds with potent SGLT2 inhibitory activity similar to that of compound **1**, but highly selective for SGLT2 over SGLT1.[4] Further modification of the ketone/phenol moiety of compound **1** to benzo-fused heteroaromatic rings led to the identification of a series of novel heteroaryl-*O*-glucosides as potent SGLT2 inhibitors.[5] A good example from this series is indole analog **2a** (Fig. 1), which showed in vitro SGLT2 inhibitory activity and selectivity similar to that of compound **1**. We have continued SAR studies of compound **2a** by

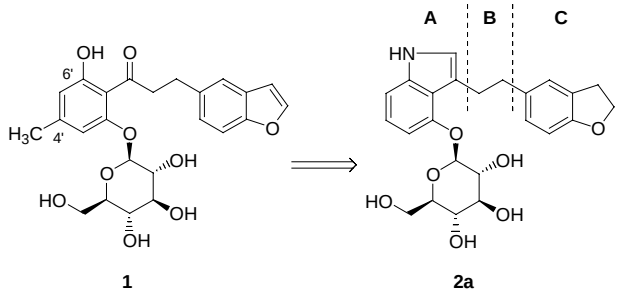

Figure 1.

varying the carbon chain length (region B) and replacing the dihydrobenzofuran moiety with other aromatic rings (region C). We report herein a series of novel indole-*O*-glucosides that are selective inhibitors of SGLT2. Indole-*C*-glucosides are a logical extension of the *O*-glucosides, and we report our progress in this area as well (Fig. 2, compounds **3** and **4**).

All of the indole-*O*-glucosides **2a**–**2v** were synthesized from the corresponding indole aglycones **5**. The two-carbon linker indoles **5** ($n = 2$) were prepared following the synthetic route previously described.[5] Preparation of indoles **5a**–**d** is outlined in Schemes 1 and 2.

As illustrated in Scheme 1, the aglycones **5a**–**b** were constructed by addition of a commercially available Grignard reagent to indole-3-carbaldehyde **7** or by

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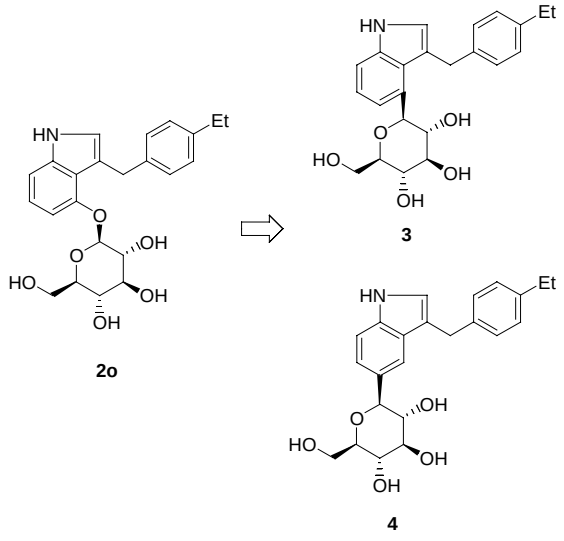
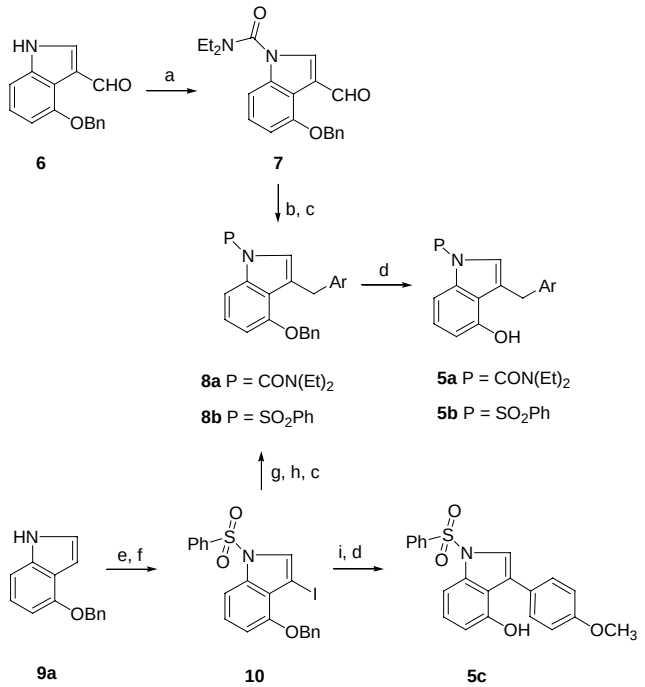


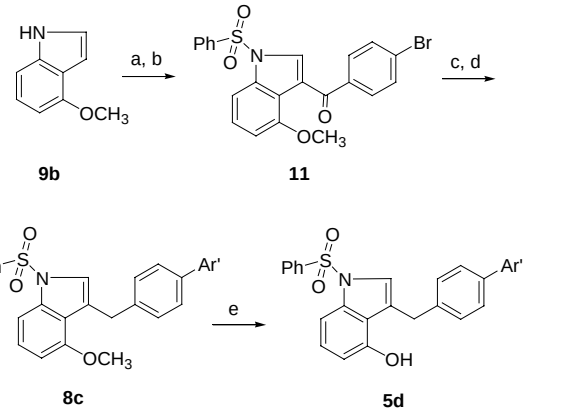
Figure 2.

generation of indolemagnesium bromide from compound **10** followed by addition to an aryl aldehyde. The indolecarbinols generated by either pathway were deoxygenated with triethylsilane and tin (IV) chloride to give 3-alkylindoles **8a**–**b** in excellent yield.[6] Deprotection of the phenol yielded **5a**–**b**. Indole **5c** was accessed by Suzuki coupling of iodoindole **10** followed by deprotection of the phenol group.[7]

Scheme 2 describes the synthesis of indole aglycones **5d** containing a biaryl moiety. Friedel–Crafts acylation of



Scheme 1. Reagents and conditions: (a) *N*,*N*-diethylcarbamoyl chloride, NaH, THF; (b) ArMgBr, THF, 0 °C; (c) Et_3SiH, $SnCl_4$, CH_2Cl_2, −78 °C, 20 min; (d) H_2 (14 psi), 10% Pd/C, EtOAc/EtOH; (e) ICl, Py, CH_2Cl_2; (f) $PhSO_2Cl$, Bu_4NBr (cat.), PhH, 25% aq NaOH; (g) EtMgBr, THF; (h) ArCHO, THF, rt; (i) 4-MeOPhB$(OH)_2$, $PdCl_2(dppf)_2$, CsF, $CH_3OCH_2CH_2OCH_3$, 72 °C.



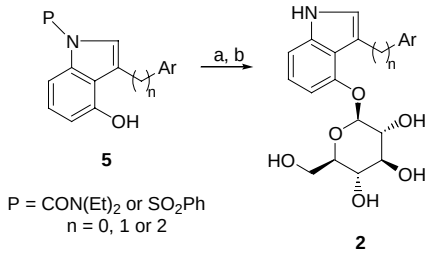
Scheme 2. Reagents and conditions: (a) 4-BrPhCOCl, CH_2Cl_2, $AlCl_3$; (b) $PhSO_2Cl$, Bu_4NBr (cat.), PhH, 25% aq NaOH; (c) $NaBH_4$, TFA, CH_2Cl_2; (d) Ar′B$(OH)_2$, $PdCl_2(dppf)_2$, CsF, $CH_3OCH_2CH_2OCH_3$, 72 °C; (e) BBr_3, CH_2Cl_2, −78 °C to rt.

indole **9b** introduced a 4-bromophenyl group, which was further coupled with an arylboronic acid under standard Suzuki coupling conditions to provide biaryl intermediate **8c**. Deprotection of the phenol gave **5d**.

Finally, glucosides **2a**–**2v** were synthesized by conjugating indoles **5** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide using the conditions as previously described (Scheme 3).[5]

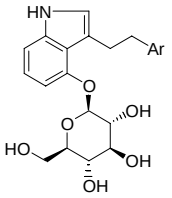
Target compounds were screened in the cell-based SGLT functional assays.[8] Exploration of the SAR began by replacing the dihydrobenzofuran moiety of compound **2a** with other aromatic groups (Fig. 1, region C). Previous SAR studies of compound **1** showed that benzofuran can be replaced with aromatics such as benzodioxanyl, naphthyl or 4-ethoxyphenyl with retention of good SGLT2 inhibitory activity.[4] However, as shown in Table 1, replacement of 2,3-dihydrobenzofuran moiety of **2a** resulted in compounds **2b**–**2f** which were at least 5-fold less potent against SGLT2. Thus, this line of SAR was abandoned.

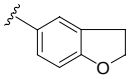
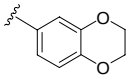
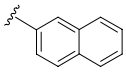
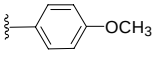
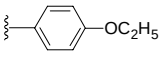
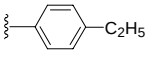
We next studied the carbon-chain linker (Fig. 1, region B) and the data are presented in Table 2. Truncation of the linker in **2a** by one carbon provided analog **2g** with significant loss of SGLT2 inhibitory activity. However, modification of 2,3-dihydrobenzofuran in compound **2g** with other aromatic groups provided several



Scheme 3. Reagents and conditions: (a) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, K_2CO_3, acetone; (b) 25% aq KOH, EtOH, reflux.

Table 1. In vitro SGLT inhibition



Compound	Ar	SGLT1 IC_{50} ± SEM (μM)	SGLT2 IC_{50} ± SEM (μM)
1	—	0.139 ± 0.013	0.011 ± 0.002
2a[a]		0.145 ± 0.011	0.024 ± 0.004
2b		3.61 ± 0.16	0.121 ± 0.021
2c		1.1 ± 0.028	0.201 ± 0.037
2d[a]		0.611 ± 0.091	0.163 ± 0.019
2e		1.19 ± 0.103	0.202 ± 0.013
2f		46%[b]	50%[b]

[a] See Ref. 5.
[b] Inhibition at a screening concentration of 10 μM.

potent SGLT2 inhibitors. The most interesting compound among this series is compound **2o**, which has the same SGLT2 inhibitory activity as compound **2a**. By comparison, the two-carbon linker analog **2f** exhibited much weaker SGLT2 inhibitory activity. In some cases, shortening the linker did not result in significant changes in SGLT2 inhibitory activity, such as **2c** versus **2h**, **2d** versus **2i**, and **2e** versus **2k**. However, the one-carbon linker analogs showed higher selectivity for SGLT2 versus SGLT1. Further truncation of the carbon-chain linker of compound **2i** provided compound **2v** with a much weaker SGLT2 inhibitory activity.

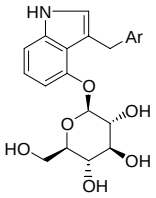
The SGLT2 selective inhibitor **2o** and SGLT1/SGLT2 mixed inhibitor **2a** were evaluated by iv administration in male Zucker Diabetic Fatty (ZDF) rats. The effects on urinary glucose excretion and the pharmacokinetic properties were measured and the results are summarized in Table 3.[9] When a 3 mg/kg dose was administered iv, both compounds showed pharmacokinetic profiles similar to that of compound **1**. Compounds **2a** and **2o** had similar efficacy toward urinary glucose excretion in spite of their different in vitro selectivity profiles. Unfortunately, the efficacy of neither compound exceeded that of compound **1**. Finally, compounds **2a** and **2o** suffered from short half-life and rapid clearance, which precluded further development of this series.

One drawback of compound **1** as an oral anti-diabetic agent is inactivation via conversion to its aglycone by intestinal β-glucosidase.[3a] Instability toward β-glucosidase is also a potential problem for the indole-*O*-glucosides. One solution to this problem is the construction of *C*-glucosides, **3** and **4** (Fig. 2), based on compound **2o**. This strategy has been reported in the literature.[2e]

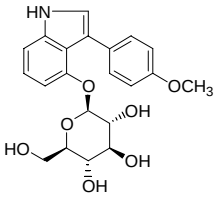
Scheme 4 depicts the synthesis of *C*-glucosides **3** and **4**.[10] Bromoindoles **12** and **15** were elaborated to compounds **14a** and **14b**, respectively.[11] Stereoselective *C*-glucosylation was accomplished in two steps. First, conversion of the bromoindoles **14a**–**b** to the organolithium derivatives and addition to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranolactone provided the corresponding lactols. Second, reduction of the lactols with triethylsilane and boron trifluoride etherate set the new stereocenter in **17a**–**b**.[12] Debenzylation provided the desired products **3** and **4**.

In vitro examination of *C*-glucosides **3** and **4** in the cell-based SGLT functional assay indicated that both compounds were inactive at SGLT1. Compound **3** showed only 12% inhibition of SGLT2 at a screening concentration of 10 μM. Compound **4** had a functional IC_{50} value of 0.132 μM at SGLT2. These data suggests the importance of the glycosidic oxygen in this series of SGLT inhibitors.

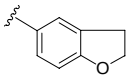
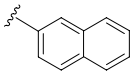
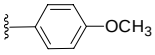
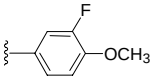
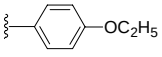
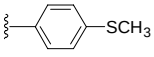
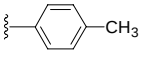
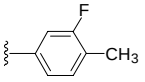
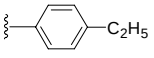
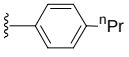
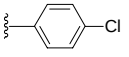
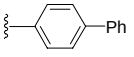
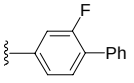
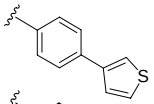
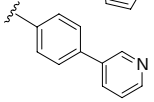
Table 2. In vitro SGLT inhibition



2g – 2u



2v

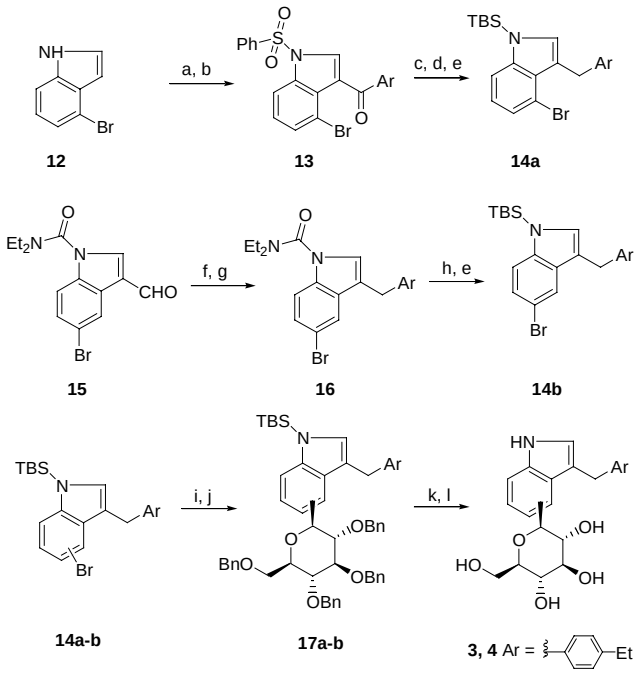
Compound	Ar	SGLT1 IC_{50} ± SEM (μM)	SGLT2 IC_{50} ± SEM (μM)
2g		30%[a]	1.87[b]
2h		68%[a]	0.293 ± 0.045
2i		1.51 ± 0.174	0.121 ± 0.014
2j		79%[a]	0.143 ± 0.029
2k		49%[a]	0.094 ± 0.022
2l		2.89 ± 0.473	0.052 ± 0.011
2m		4.39 ± 0.358	0.066 ± 0.009
2n		42%[a]	0.099 ± 0.022
2o		2.14 ± 0.016	0.028 ± 0.004
2p		3.2[b]	0.119 ± 0.042
2q		58%[a]	0.296 ± 0.042
2r		63%[a]	0.089 ± 0.021
2s		35%[a]	0.182 ± 0.048
2t		2.24 ± 0.245	0.050 ± 0.011
2u		1.97 ± 0.599	0.143 ± 0.007
2v	Structure at the top of the table	0%[a]	37%[a]

[a] Inhibition at a screening concentration of 10 μM.
[b] The compound had one IC_{50} determination.

Table 3. In vivo urinary glucose excretion and pharmacokinetic profiles of SGLT2 inhibitors in ZDF rats[a]

Compound	Glucosuria (mg/4 h)	AUC (nM h)	$T_{1/2}$ (h)	Clp (mL/min/kg)
1	244 ± 114	2087 ± 335	0.97	53.1 ± 7.9
2a	148 ± 63	2460 ± 326	0.67	46.6 ± 4.8
2o	155 ± 87	1992±154	0.86	61.0 ± 4.8

[a] Dose, iv 3.0 mpk.



Scheme 4. Reagents and conditions: (a) ArCOCl, $AlCl_3$, CH_2Cl_2; (b) $PhSO_2Cl$, Bu_4NBr (cat.), PhH, 25% aq NaOH; (c) *t*-$BuNH_2$–BH_3, $AlCl_3$, CH_2Cl_2, 0 °C; (d) 50% aq NaOH, THF, reflux; (e) NaH, TBSCl, THF, 0 °C to rt; (f) ArMgBr, THF, 0 °C; (g) Et_3SiH, $SnCl_4$, CH_2Cl_2, −78 °C, 20 min; (h) 25% aq NaOH, EtOH, reflux; (i) *t*-BuLi (2 equiv), 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone, THF, −78 °C; (j) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_3CN, −30 °C; (k) 25% aq NaOH, THF, reflux; (l) H_2 (14 psi), Pearlman's cat., EtOAc, EtOH.

In summary, the SAR study of indole-*O*-glucosides extends our previous work. Several potent SGLT2 inhibitors were identified with a range of SGLT1/SGLT2 selectivity. The reduced biological activity of the *C*-glucosides suggests the importance of the anomeric oxygen to SGLT inhibitory activity. The important questions as to the functional significance of SGLT1 in the kidney and the consequence of SGLT subtype selectivity are the subject of ongoing studies.

References and notes

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7. All compounds provided satisfactory spectral data (^{1}H NMR, LCMS) and were homogeneous by TLC. Full experimental details on individual compounds can be found in Beavers, M.P.; Patel, M.; Urbanski, M.; Zhang, X. WO05/012243A2; *Chem. Abstr.* **2005**, *142*, 219489.
8. CHO-K1 cells overexpressing human SGLT2 or SGLT1 were used for the cell-based functional screens. Cells were treated with compound in the absence or presence of NaCl for 15 min. Cells were then labeled with ^{14}C α-methylglucopyranoside (AMG)—a non-metabolizable glucose analog specific for sodium-dependent glucose transporters. After 2 h the labeled cells were washed three times with ice-cold PBS. Cells were then solubilized and Na-dependent ^{14}C AMG uptake was quantified by measuring radioactivity.
9. Male Zucker Diabetic Fatty (ZDF) rats (7–8 weeks) were obtained from Charles River. Animals were maintained on a 12 h light/dark cycle in a temperature-controlled room. Animals were given ad libitum access to food (standard rodent diet Purina 5008) and water. Animals were fasted for 12 h prior to initiation of the experiment. On the morning of the experiment, animals were administered (10% Solutol) or compound (2 mL/kg) by intravenous injection. After 1 h, animals received an oral glucose challenge (4 mL/kg of 50% solution) and were immediately placed in metabolism cages. Animals were given free access to water and urine was collected for 4 h. Urinary glucose was quantified using the Trinder Reagent (Sigma).
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