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Heteroaryl-*O*-glucosides as novel sodium glucose co-transporter 2 inhibitors. Part 1

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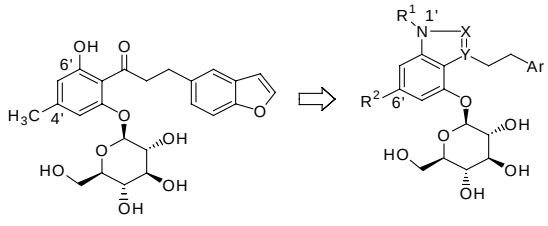
Abstract—A series of benzo-fused heteroaryl-*O*-glucosides was synthesized and evaluated in SGLT1 and 2 cell-based functional assays. Indole-*O*-glucoside **10a** and benzimidazole-*O*-glucoside **18** exhibited potent in vitro SGLT2 inhibitory activity.

Controlling levels of fasting and postprandial plasma glucose is the first goal of therapy for non-insulin dependent diabetes mellitus (NIDDM). Since plasma glucose is continuously filtered in the kidney glomerulus and is subsequently transepithelially reabsorbed by the sodium-glucose co-transporters (SGLTs) in the proximal tubules, a therapeutic agent which blocks glucose reabsorption in the kidney should provide a novel treatment for NIDDM.[1–3] There is evidence that at least three isoforms of SGLT are present in the human body, referred to as SGLT1 through SGLT3.[4] SGLT1 is present primarily in the intestinal cells, whereas SGLT2 is found predominantly in the epithelium of the kidney. Glucose absorption in the intestine is mediated by SGLT1, a high-affinity low-capacity transporter. Renal reabsorption of glucose is mediated by both SGLT1 and SGLT2 on the luminal side of the proximal tubule of the kidney. SGLT2 is a low-affinity high-capacity transporter and is likely responsible for the bulk of glucose reabsorption in the renal proximal tubule. SGLT3, formerly known as SAAT1, may serve as a glucose sensor in cholinergic neurons, skeletal muscle, and other tissues. SGLT4 is a low-affinity transporter that may act as a mannose/fructose transporter in the intestine and kidney.[4b] Inhibition of SGLTs in diabetic patients would be expected to normalize plasma glucose by reducing glucose uptake at the intestine (SGLT1) and promoting glucose excretion into the urine (SGLT2).[5] Phlorizin is a natural SGLT inhibitor. Compound **1**, (T1095A), a phlorizin analogue, inhibited both SGLT1 and SGLT2, and demonstrated efficacy in numerous animal models as an antidiabetic agent.[5] Recently, we reported structure–activity relationship (SAR) studies of compound **1** and found potent and selective SGLT2 inhibitors.[6] As part of our ongoing SAR studies, we designed and synthesized a series of novel compounds different from both the core structure of compound **1** and other reported structures.[7] The key modification was to replace the ketone/phenol portion of **1** with a heteroaryl ring, wherein the 1′ NH group of the heteroaryl ring mimics the 6′ OH group in compound **1**. Since there is no clinical evidence to show whether a selective SGLT2 inhibitor or a mixed SGLT1/SGLT2 inhibitor is better for treatment of diabetes, we were interested in developing both types of inhibitors to better understand the mechanism of action. Herein, we describe the initial SAR surrounding a novel series of heteroaryl-*O*-glucosides with potent in vitro SGLT2 inhibitory activity.



1

X = CH, or N or C=O
Y = C, or N
R^1 or R^2 = H or alkyl groups

Keywords: SGLT; Heteroaryl-*O*-glucosides.
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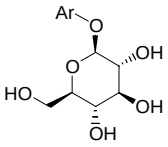
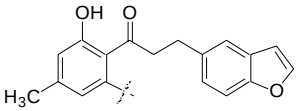
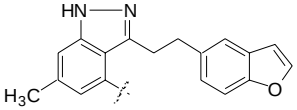
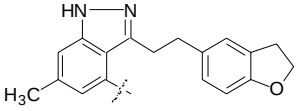
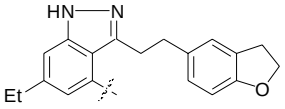
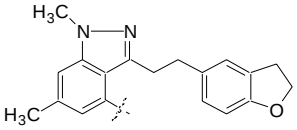
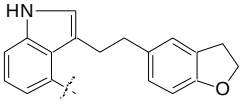
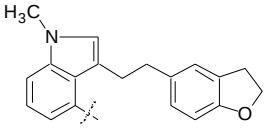
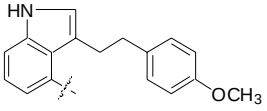
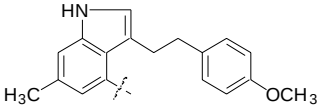
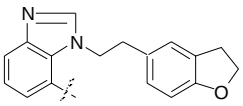
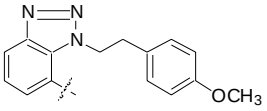
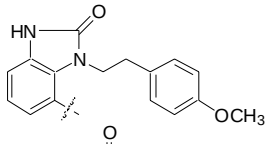
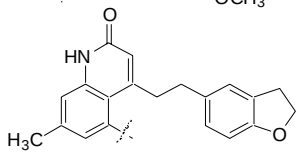
Table 1. In vitro activity to inhibit SGLT2



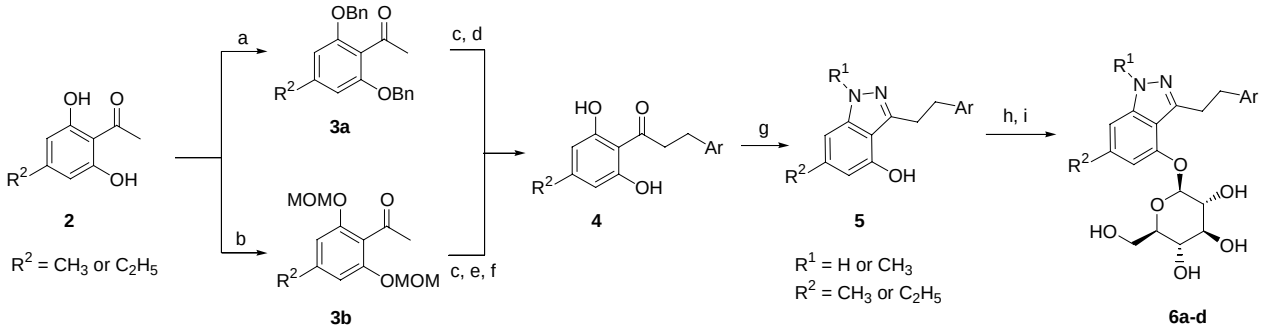
Compound	Ar	IC_{50} ± SEM (μM)	
		SGLT1	SGLT2
1		0.139 ± 0.013	0.011 ± 0.002
6a		52%[a]	0.491 ± 0.056
6b		48%[a]	0.458 ± 0.061
6c		0%[a]	0.532 ± 0.047
6d		47%[a]	0.754 ± 0.069
10a		0.145 ± 0.011	0.024 ± 0.004
10b		0.198 ± 0.002	0.067 ± 0.003
10c		0.611 ± 0.091	0.163 ± 0.019
10d		3.05 ± 0.23	0.394 ± 0.013
18		0.718 ± 0.126	0.039 ± 0.001
19		40%[a]	0.380 ± 0.022

(*continued on next page*)

Table 1 (*continued*)

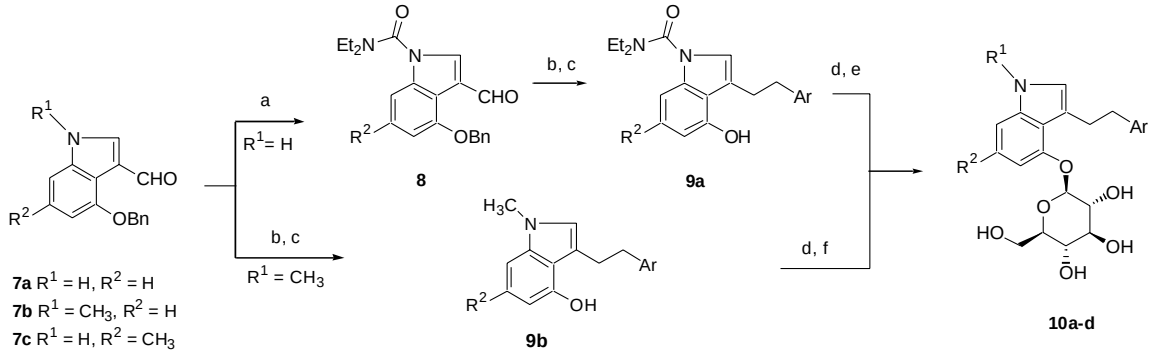
Compound	Ar	$IC_{50} \pm SEM$ (μM)	
		SGLT1	SGLT2
20		0%[a]	18%[a]
25		0%[a]	22%[a]

[a] Inhibition at a screening concentration of 10 μM.



Scheme 1. Reagents and conditions: (a) BnBr (4 equiv), K_2CO_3 (10 equiv), DMF; (b) MOM Br (2 equiv), K_2CO_3 (5 equiv), CH_3CN; (c) ArCHO, KOH, EtOH; (d) H_2 (45 psi), 10% Pd/C, EtOH/EtOAc (1:1); (e) H_2 (15 psi), 10% Pd/C, EtOAc; (f) concn HCl, *i*-PrOH/dioxane; (g) NH_2-NHR_1, $HOCH_2CH_2OH$, 160 °C; (h) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2 equiv), K_2CO_3 (5 equiv), acetone; (i) K_2CO_3, MeOH.

Our initial attempt to synthesize indazole **6a** (Table 1) by cyclization of compound **1** with hydrazine[8] did not yield the desired product. Thus, conjugated indazoles **6a**–**d** were prepared from resorcinol derivatives **2**[6] (Scheme 1). Aldol condensation of **3a** with 2,3-dihydrobenzofuran-5-carbaldehyde provided an α,β-unsaturated ketone. Hydrogenation at 45 psi produced dihydrochalcone **4** (Ar = 2,3-dihydrobenzofuran). Alternatively, aldol condensation of **3b** with benzofuran-5-carbaldehyde, selective hydrogenation of the α,β-unsaturated ketone at 15 psi, and deprotection with HCl gave dihydrochalcone **4** (Ar = benzofuran). Dihydrochalcone **4** cyclized with hydrazine or methyl hydrazine to form 1*H*-indazole **5** in moderate yield.[8] Glycosylation of **5** using the biphasic conditions previously described to prepare analogues of compound **1** was not successful, probably due to the poor solubility of aglycone **5** in either phase.[6] Glycosylation could be achieved with 2 equiv of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide and 5 equiv of K_2CO_3 in acetone for 24 h. Subsequent saponification of the acetyl groups provided compounds **6a**–**d** in 20–30% yield for the two steps.[9a] No *N*-glucoside of **5** was isolated from the reaction under the conditions investigated. The last two steps have



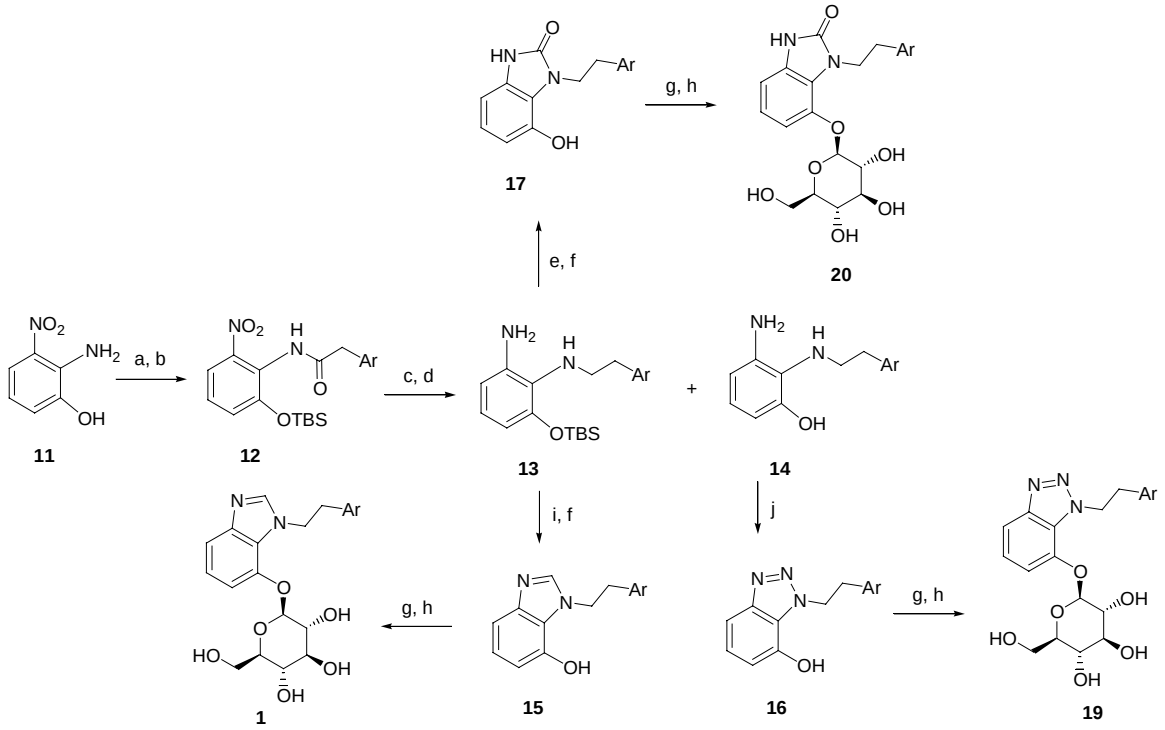
Scheme 2. Reagents and conditions: (a) *N*,*N*-diethylcarbamoyl chloride, NaH, THF; (b) ArCH = PPh_3, THF, −78 °C to rt; (c) H_2 (15 psi), 10% Pd/C, EtOH/EtOAc; (d) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, K_2CO_3, acetone; (e) KOH (25%), EtOH, reflux; (f) K_2CO_3, MeOH.

application to other heteroaromatic systems in this study.

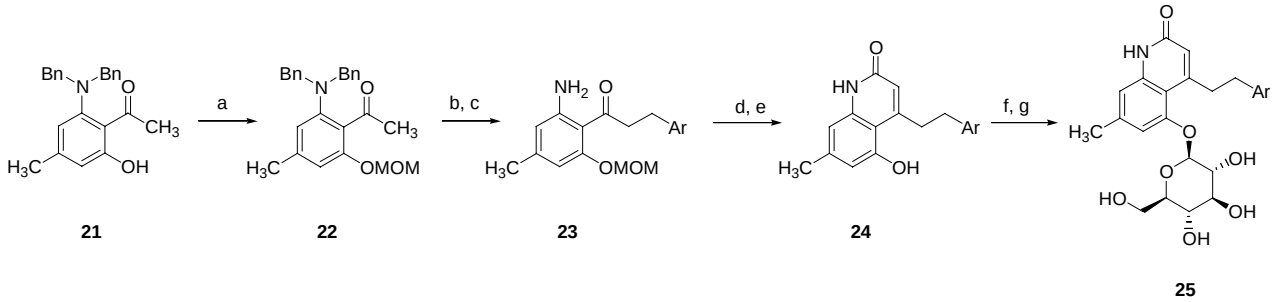
Scheme 2 depicts the synthesis of indole analogues **10a–d**. Aglycones **9a** and **b** were obtained from indolecarbaldehydes **7a–c**[10] by the Wittig reaction and hydrogenation at 15 psi. Glycosylation of aglycone **9** was carried out under the conditions described above to provide tetra-acetylglucosides in yields of 40–75%. Lithium hydroxide-promoted glycosylation of indoles has been reported,[11] but did not afford higher yields. Saponification of the acetyl groups provided compounds **10a–d** in 20–30% yield for the two steps.[9b]

Benzimidazole **18**, benztriazole **19**, and benzimidazolone **20** were constructed from **12**, which was prepared by acylation and silylation of commercially available 2-amino-3-nitrophenol (Scheme 3). Hydrogenation of the nitro group and borane reduction of the amide fortuitously provided a 3:2 ratio of **13** and **14**, separable by flash chromatography. The benzimidazole system was formed by treatment of compound **13** with triethylorthoformate. Subsequent deprotection of the phenol group provided the benzimidazole aglycone **15**. Treatment of compound **14** with sodium nitrite provided the benztriazole aglycone **16**. Cyclization of **13** with triphosgene, followed by deprotection of the phenol group, led to the benzimidazolone aglycone **17**. Glycosylation of aglycones **15–17** under the conditions described above provided analogues **18–20** in low to moderate yields.[9c]

In Scheme 4, the intermediate **23** was prepared from compound **21** using a synthetic approach that was similar to that outlined for the formation of the dihydrochalcone **4** described in Scheme 1. Cyclization of **23** with



Scheme 3. Reagents: (a) $ArCH_2COCl$, Et_3N, CH_2Cl_2; or $ArCH_2CO_2H$, EDCI, HOBt, DMF; (b) TBSCl, imidazole; (c) H_2 (15 psi), 10% Pd/C, EtOH; (d) BH_3·THF; (e) CDI or triphosgene, THF; (f) TBAF, THF; (g) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2 equiv), K_2CO_3 (5 equiv), acetone; (h) K_2CO_3, MeOH; (i) $HC(OEt)_3$, p-TSA; (j) $NaNO_2$, HCl (3 N).



Scheme 4. Reagents: (a) MOMBr, K_2CO_3, acetone; (b) ArCHO, KOH, EtOH; (c) H_2 (45 psi), 10% Pd/C, DMAP, EtOH; (d) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (e) concn HCl, *i*-PrOH, dioxane; (f) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2 equiv), K_2CO_3 (5 equiv) acetone, DMF; (g) K_2CO_3, MeOH.

the ylide derived from triethylphosphonoacetate afforded a 1*H*-quinolin-2-one in 31% yield.[12] Subsequent deprotection of the phenol group provided aglycone **24**. Glycosylation and deprotection as described above gave analogue **25** in low yield.[9d]

All compounds were screened in a cell-based SGLT functional assay,[13] and IC_{50} values are presented in Table 1. The indazole analogues **6a–d** showed only moderate inhibitory activity toward SGTL2, but were selective for SGLT2 compared to the parent compound **1**. Replacement of the benzofuran in analogue **6a** with 2,3-dihydrobenzofuran in compound **6b** did not change the SGLT2 inhibitory activity. However, the benzofuran moiety could cause unwanted P450 inhibition of **1**.

The SAR of compound **1** suggested that the phenol group at the 6′-position participates in a hydrogen bonding interaction,[5b,6] which supported the computational hypotheses by Weilert-Badt et al.[14] However, this trend was not observed with the heterocyclic analogues. Good activity was preserved when the N-1 position of the indole was alkylated as in compound **10b**. Likewise, the lack of hydrogen bonding ability at the N-1 position of the benzimidazoles **18** did not diminish SGLT2 inhibitory activity. In addition, urea **20** and lactam **25** showed much weaker SGLT2 inhibitory activity than the other scaffolds, though this may be due to steric effects.

In summary, we have demonstrated that the ketone/phenol portion of compound **1** can be replaced with a benzo-fused heterocycle while retaining the desired in vitro SGLT2 inhibitory activity. Further modification of this series will be reported in due course.

References and notes

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10. Compound **7a** is commercially available. Compound **7b** was prepared by methylation of the sodium salt of **7a** with methyl iodide in DMF. Compound **7c** was prepared using literature procedures: (a) Blair, J. B.; Kurrasch-Orbaugh, D.; Marona-Lewicka, D.; Cumbay, M. G.; Watts, V. J.; Barker, E. L.; Nichols, D. E. *J. Med. Chem.* **2000**, *43*, 4710; (b) Fresneda, P. M.; Molina, P.; Bleda, J. A. *Tetrahedron* **2001**, *57*, 2355.
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13. CHO-K1 cells overexpressing human SGLT2 or SGLT1 were used in 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-methyl-glucopyranoside (AMG)—a non-metabolizable glucose analogue 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.
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