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Synthesis and biological evaluation of *N*-glucosyl indole derivatives as sodium-dependent glucose co-transporter 2 inhibitors

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A B S T R A C T

Sodium-dependent glucose co-transporter 2 (SGLT2) inhibition has been demonstrated to efficiently control hyperglycemia via an insulin secretion-independent pathway. The unique mode of action eliminates the risk of hypoglycemia and makes SGLT2 inhibitors an attractive option for the treatment of type 2 diabetes. In a continuation of our previous studies on SGLT2 inhibitors bearing different sugar moieties, sixteen new *N*-glucosyl indole derivatives were designed, synthesized, and evaluated for their inhibitory activity against hSGLT2. Of these sixteen, acethydrazide-containing *N*-glucosyl indole **9d** was found to be the most potent SGLT2 inhibitor, and caused a significant elevation in urine glucose excretion in rats at 50 mg/kg, relative to the vehicle control.

1. Introduction

Sodium-dependent glucose co-transporter 2 (SGLT2) regulates glucose homeostasis by reabsorbing glucose from the glomerular filtrate, and is therefore an attractive target for the treatment of type 2 diabetes. SGLT2, a member of the solute carrier 5A (SLC5A) gene family, is a high-capacity and low-affinity glucose transporter located on the S1 segment of the proximal tubule in the kidney, which mediates the reabsorption of the majority (> 90%) of renal glucose [1–4]. Inhibition of SGLT2 has been demonstrated to control hyperglycemia via an insulin secretion-independent pathway by suppressing the reabsorption of glucose in the kidney and inducing urinary glucose excretion [5]; and SGLT2 inhibitors such as dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, empagliflozin, and ertugliflozin have been successfully used in the treatment of type 2 diabetes [6–12]. In addition to lowering blood sugar, SGLT2 inhibitors have also been found to show pleiotropic effects on other disorders, including cardiovascular protection, hepatoprotective potential, renoprotection, and so on [13,14]. Their unique mode of action eliminates the risk of hypoglycemia and makes SGLT2 inhibitors more attractive than conventional therapeutic agents currently used in the treatment of type 2 diabetes.

SGLT1, which belongs to the same solute carrier family as SGLT2, is responsible for the reuptake of the remaining renal glucose that is not reabsorbed by SGLT2. SGLT1 is mainly distributed in the small intestine as well as the kidney; and its inhibition gives rise to gastrointestinal side effects [15,16]. Accordingly, most studies recommend the use of selective SGLT2 inhibitors; but SGLT2 inhibitors with the ability to partially inhibit SGLT1 have been proposed based on the results of clinical efficacy evaluations [17,18]. Additionally, a promising dual SGLT1/SGLT2 inhibitor sotagliflozin (LX4211) has also been developed (phase III) [19]. Whether or not good selectivity for SGLT2 over SGLT1 is an essential prerequisite for the development of a practical drug remains to be seen.

Numerous effective and structurally diverse SGLT2 inhibitors, including selective and dual SGLT1/SGLT2 inhibitors, have been identified [20,21]. When our discovery program was initiated, we found that most SGLT2 inhibitor development focused on the modification of the aglycone moieties. Instead, we sought to explore the role of the sugar moiety in SGLT inhibition; to help researchers better understand the associated structure-activity relationships (SARs); and to discover novel and potent SGLT2 inhibitors [22–25]. As shown in Fig. 1, we have identified several potential SGLT2 inhibitors with hSGLT1/hSGLT2 selectivities of 1.3- to 78-fold, and bearing a variety of *C*- and *N*-sugar moieties. Comparisons between our results and those reported in the literature [26–28] revealed that the C6 position of the sugar moiety plays a critical role in SGLT2 inhibitory potency and selectivity. For *N*-glycosyl indoles, the SGLT2 inhibitory potency of a selection of compounds with a glucose moiety was better than those bearing xylose (**1**) or 6-amido-6-deoxyglucose (**3**) units when the same aglycone moiety was installed at the C1 position; however, the latter imparted better hSGLT1/hSGLT2 selectivity [24]. In the series of *C*-glycosyl compounds, 6-oxime-containing *C*-glucosylarene (**4**) was found to exhibit inferior SGLT2 inhibition and selectivity than glucose-based dapagliflozin, but comparable *in vivo* efficacy in glucosuria and anti-hyperglycemic studies [25]. Accordingly, whether *N*-glucosyl indoles bearing oxime, hydrazone, hydroxylamine, or hydrazide at the C6-

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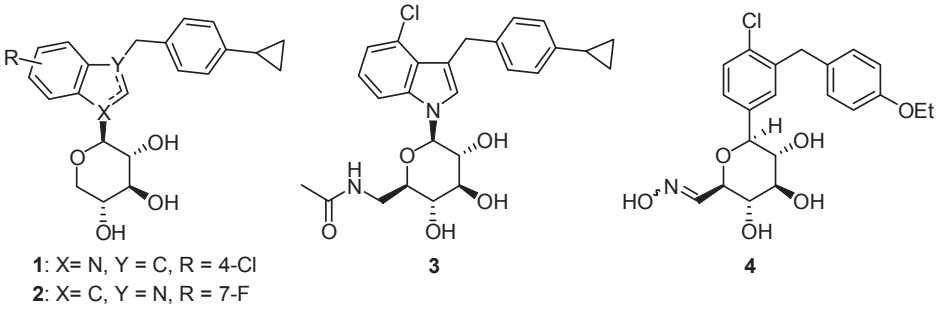


Fig. 1. Our previously-reported SGLT2 inhibitors, bearing differing sugar moieties.

position of glucose show the same trend is of interest to us, too.

In this study, we further explored the role of the sugar moiety of the synthesized *N*-glucosyl indoles on inhibitory potency, wherein the aglycone unit is fixed as 4-chloro-3-(4-cyclopropylbenzyl)-1*H*-indole. Detailed descriptions of syntheses, SAR, pharmacokinetics, and animal studies are all presented.

2. Results and discussion

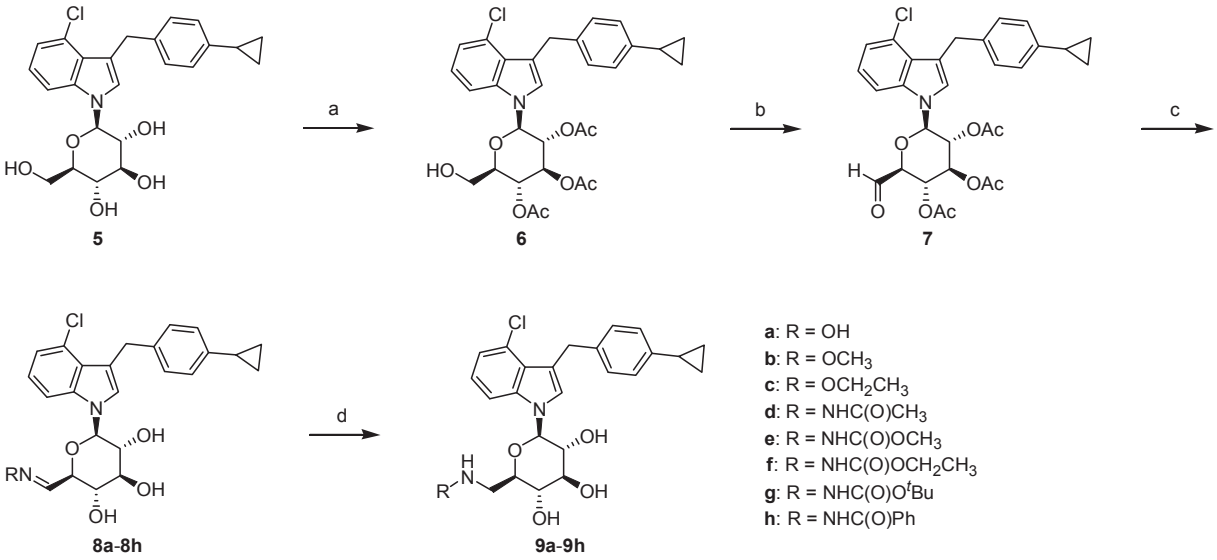
2.1. Synthesis

The synthesis of test compounds is depicted in Scheme 1, starting from *N*-glucosyl indole **5**. As reported previously [25], the key intermediate 6-aldehyde **7** could be obtained via a straightforward reaction sequence: (1) selective protection of the primary alcohol with *tert*-butylchlorodimethylsilane (TBDMSCl) in pyridine at 70 °C, followed by immediate peracetylation by addition of acetic anhydride to give the fully protected *N*-glucoside (83%); (2) desilylation under acidic conditions to avoid the exchange with the O4-acetyl group with boron trifluoride etherate ($BF_3{\cdot}OEt_2$) yielded the free primary alcohol at the 6-position (91%); (3) Dess-Martin Periodinane (DMP) oxidation of the generated 6-OH **6** to give the desired aldehyde **7**, which was used without further purification. Condensation of **7** with a small library of hydroxylamines and hydrazides followed by deacetylation gave oxime ethers **8a-8c** and *N*-acylhydrazones **8d-8h**, respectively. Their corresponding reduction product hydroxylamine *N*-glucosyl indoles **9a-9c** and hydrazide *N*-glucosyl indoles **9d-9h** were also successfully synthesized, using sodium cyanoborohydride ($NaBH_3CN$) under acidic conditions.

2.2. Inhibitory activity against hSGLT2

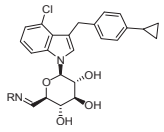
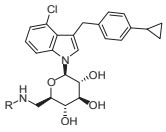
The inhibitory activities (EC_{50}) of all synthesized *N*-glucosyl indole derivatives **8a-8h** and **9a-9h** were determined by measuring the inhibition of the uptake of [^{14}C]-labeled α-methyl-D-glucopyranoside into Chinese hamster ovary (CHO) cells stably expressing human SGLT2 (hSGLT2) or hSGLT1 [29,30]; using phlorizin (hSGLT2: EC_{50} = 96 ± 21 nM; hSGLT1: EC_{50} = 179 ± 42 nM) and dapagliflozin (hSGLT2: EC_{50} = 2.8 ± 0.7 nM; hSGLT1: EC_{50} = 501 ± 147 nM) as positive controls. The effect of oxime and *N*-acylhydrazone moieties on activity was tested first, using eight *N*-glucosyl indoles, as shown in Table 1. In the case of oxime ethers **8a-8c**, those bearing small substituents (**8a**: EC_{50} = 212 nM; **8b**: EC_{50} = 286 nM) possessed better inhibitory activity against hSGLT2, as discovered for *C*-glycosyl compounds [25]. Replacing the oxime ether functionality with *N*-acylhydrazone moiety gave **8d-8h**, which were of similar potency to compounds **8a** and **8b**, except **8f** (EC_{50} = 1162 nM) and **8g** (EC_{50} = 867 nM). Of these, compound **8h** (EC_{50} = 258 nM) bearing a phenyl group was a more potent inhibitor of SGLT2.

We then examined hydroxylamines **9a-9c** and hydrazides **9d-9h**,



Scheme 1. The synthetic route to compounds **8a-8h** and **9a-9h**. Reagents and conditions: (a) (i) TBDMSCl, DMAP, pyridine, 70 °C, 18 h; then Ac_2O, rt, 2 h, 83%; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 20 min, 91%; (b) Dess-Martin periodinane, CH_2Cl_2, rt, 2 h; (c) For **8a-8c**: (i) hydroxylamines, pyridine, rt, 2 h; (ii) NaOMe, MeOH/CH_2Cl_2 = 2/1, 0 °C to rt, 2 h, 44% (3 steps) (**8a**), 33% (3 steps) (**8b**), 66% (3 steps) (**8c**); For **8d-8 h**: (i) hydrazides, EtOH, rt, 2 h; (ii) 1 N $LiOH_{(aq)}$, THF/MeOH/CH_2Cl_2 = 2/3/1, 0 °C, 2 h, 53% (3 steps) (**8d**), 78% (3 steps) (**8e**), 43% (3 steps) (**8f**), 45% (3 steps) (**8g**), 55% (3 steps) (**8h**); (d) $NaBH_3CN$, 6 N HCl in MeOH, MeOH, 0 °C to rt, 1 h, 31% (**9a**), 27% (**9b**), 62% (**9c**), 80% (**9d**), 84% (**9e**), 76% (**9f**), 79% (**9g**), 87% (**9h**).

Table 1
In vitro inhibitory activity of *N*-glucosyl indole derivatives **8a**-**8h** and **9a**-**9h** on hSGLT2.

Compd	R =		hSGLT2 EC_{50} (nM)[a]	Compd	R =		hSGLT2 EC_{50} (nM)[a]
8a	HO		212 ± 17	**9a**	HO		160 ± 14
8b	CH_3O		286 ± 36	**9b**	CH_3O		45 ± 1
8c	CH_3CH_2O		1222 ± 212	**9c**	CH_3CH_2O		294 ± 45
8d	$CH_3C(O)HN$		355 ± 56	**9d**	$CH_3C(O)HN$		33 ± 6
8e	$CH_3OC(O)HN$		316 ± 69	**9e**	$CH_3OC(O)HN$		63 ± 1
8f	$CH_3CH_2OC(O)HN$		1162 ± 129	**9f**	$CH_3CH_2OC(O)HN$		134 ± 11
8g	^{t}BuOC(O)HN		867 ± 258	**9g**	^{t}BuOC(O)HN		1761 ± 228
8h	PhC(O)HN		258 ± 72	**9h**	PhC(O)HN		156 ± 3
PZN[b]			96 ± 21	**Dapa**[c]			2.8 ± 0.7

[a] Data obtained by at least two independent experiments, each experiment performed in triplicate.
[b] PZN: phlorizin.
[c] Dapa: dapagliflozin.

the reduction products of oximes **8a**-**8c** and *N*-acylhydrazones **8d**-**8h**, respectively. Reduction products **9a**-**9c** showed improved inhibitory activity against hSGLT2 compared to oximes **8a**-**8c**, with EC_{50} values ranging from of 45 to 294 nM. Among them, compound **9b** (EC_{50} = 45 nM) bearing a methoxyamine group was found to be the most potent SGLT2 inhibitor; in contrast, substitution with a simple hydroxylamine (**9a**, EC_{50} = 160 nM) and ethoxyamine group (**9c**, EC_{50} = 294 nM) weakened the hSGLT2 inhibition 3.5- and 6.5-fold, respectively. Among the series of hydrazides **9d**-**9h**, acethydrazide **9d** was found to exhibit the greatest hSGLT2 inhibition with an EC_{50} value of 33 nM. Similar potency was observed when the carbomethoxyhydrazino group (**9e**, EC_{50} = 63 nM) occupied the glucosyl C6 position. Replacement of the methoxy unit with ethoxy or *tert*-butoxy gave **9f** (EC_{50} = 134 nM) and **9g** (EC_{50} = 1761 nM), both of which were less potent than **9e**, suggesting that larger alkoxy groups may not be tolerated. Decreased potency was also observed when the methyl moiety (**9d**) was substituted with a phenyl group (**9h**, EC_{50} = 156 nM).

2.3. Selectivity and in vivo studies

The selectivity of the most active acethydrazide-containing *N*-glucosyl indole **9d** for hSGLT2 over hSGLT1 was evaluated. The obtained data indicated that **9d** lacked selectivity for hSGLT1, with an EC_{50} value of 37 nM for hSGLT1. In the course of our discovery program, compounds with good hSGLT2 inhibition were evaluated for their *in vivo* ability to induce urinary glucose excretion, to assess their potential for further development. Thus, **9d** was administered orally in single doses of 1, 10 and 50 mg/kg to normal Sprague-Dawley (SD) rats; the results are presented in Fig. 2. Unfortunately, increased urinary glucose excretion could only be observed at a relatively high dose of 50 mg/kg (825 mg glucose per 200 g body weight (BW) over 24 h); which indicated **9d** exhibited inferior efficacy compared to dapagliflozin (2762 mg glucose/200 g BW at a single dose of 1 mg/kg). The pharmacokinetic data suggests **9d** to be a metabolically stable compound with low total body clearance (15.4 mL/min/kg) after intravenous administration of a single dose of 1.1 mg/kg to rats; however, the very low plasma concentration (below the limit of quantification) observed after oral administration (1.1 mg/kg) to rats indicated the absorption of **9d** to be very poor – this is believed to be the cause of the unfavorable *in vivo* results.

3. Conclusion

Sixteen new glucose-modified *N*-glucosyl indoles have been synthesized and evaluated for their hSGLT2 inhibitory activity. Of these, hydrazide **9d** with an EC_{50} value of 33 nM for hSGLT2 was identified and advanced into selectivity, pharmacokinetic, and *in vivo* glucosuria studies; unfortunately, it was found to have poor pharmacokinetic properties and increased glucosuria in rats only at high doses.

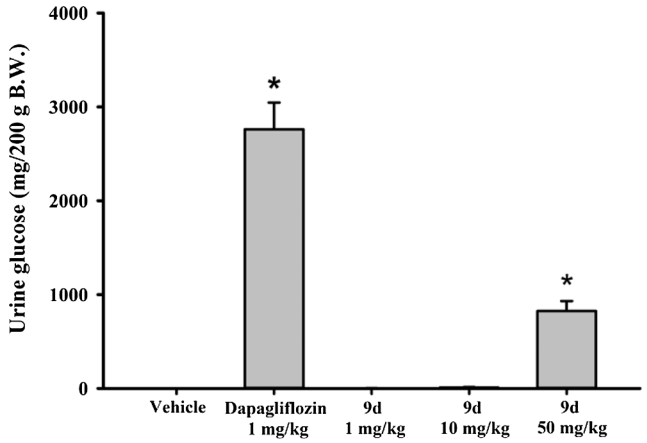


Fig. 2. Effect of acethydrazide-containing *N*-glucosyl indole **9d** and dapagliflozin on urine glucose excretion over 24 h in normal Sprague–Dawley rats. Data are expressed as the mean ± SEM (n = 5/group): $^*p < 0.05$ vs vehicle.

Compared to our earlier reports, regardless of the amide or hydrazide moiety at the C6-position of glucose, the resulting sugar-modified *N*-glucosyl indole SGLT2 inhibitors showed unsatisfactory *in vivo* profiles. Although prospects for their further development are limited, the *in vitro*/*in vivo* outcomes obtained indeed improve our understanding of *N*-glucosyl indoles.

4. Experimental

4.1. General

All chemicals and solvents were used as received without further purification (unless stated otherwise). Chemical reactions were monitored by analytical thin layer chromatography (TLC) on glass-backed plates pre-coated with SiO_2 60 F254. Column chromatography was performed using SiliaFlash P60 SiO_2 of 230–400 mesh size. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mrcury-300 or Mercury-400 spectrometers; chemical shifts are reported in δ (ppm) relative to the internal standard signal of CD_3OD (^{1}H, δ = 3.31 ppm; ^{13}C, δ = 49.15 ppm). High resolution mass spectra were measured with an electrospray ionization (ESI) source, and spectral data were recorded as *m/z* values.

4.2. Test compounds *8a-8h* and *9a-9h*

All test compounds were synthesized using our previously reported procedures for sugar-modified *C*-glycosyl compounds [25].

*4.2.1. (2R,3R,4S,5S,6R)-2-[4-Chloro-3-(4-cyclopropylbenzyl)-1H-indol-1-yl]-6-[(hydroxyimino)methyl]-tetrahydro-2H-pyran-3,4,5-triol (**8a**)*

According to the literature, the proton signals of CH=N and Glc H5 revealed the configuration of the major isomer was (*E*) [31]. The NMR data of **8a** specified is for the major isomer only. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, J = 8.4 Hz, 1H, ArH), 7.31 (d, J = 7.2 Hz, 1H, CH=N), 7.10–7.05 (m, 3H, ArH), 7.01–6.95 (m, 4H, ArH), 5.46 (d, J = 8.8 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 4.09 (dd, J = 9.2, 7.2 Hz, 1H, Glc H5), 3.83 (t, J = 8.8 Hz, 1H, Glc H2), 3.58 (dd, J = 9.2, 8.8 Hz, 1H, Glc H3), 3.53 (dd, J = 9.2, 8.8 Hz, 1H, Glc H4), 1.88–1.81 (m, 1H, cyclopropyl CH), 0.92–0.86 (m, 2H, cyclopropyl CH_2), 0.64–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 148.81, 142.75, 140.28, 139.91, 129.88, 127.48, 126.64, 126.61, 123.67, 121.91, 117.64, 110.53, 86.52, 78.60, 77.54, 73.40, 73.26, 33.23, 15.95, 9.55; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{26}ClN_2O_5$ 457.152476, found 457.152044.

*4.2.2. (2R,3R,4S,5S,6R)-2-[4-Chloro-3-(4-cyclopropylbenzyl)-1H-indol-1-yl]-6-[(methoxyimino)methyl]tetrahydro-2H-pyran-3,4,5-triol (**8b**)*

According to the literature, the proton signals of CH=N and Glc H5 revealed the configuration of the major isomer was (*E*) [31]. The NMR data of **8b** specified is for the major isomer only. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (d, J = 8.0 Hz, 1H, ArH), 7.31 (d, J = 6.8 Hz, 1H, CH=N), 7.10–7.05 (m, 3H, ArH), 7.01–6.93 (m, 4H, ArH), 5.46 (d, J = 9.2 Hz, 1H, Glc H1), 4.27 (s, 2H, CH_2), 4.08 (dd, J = 9.2, 6.8 Hz, 1H, Glc H5), 3.84 (t, J = 8.8 Hz, 1H, Glc H2), 3.80 (s, 3H, OCH_3), 3.58 (dd, J = 9.2, 8.8 Hz, 1H, Glc H3), 3.52 (t, J = 9.2 Hz, 1H, Glc H4), 1.87–1.80 (m, 1H, cyclopropyl CH), 0.91–0.85 (m, 2H, cyclopropyl CH_2), 0.63–0.59 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 148.66, 142.75, 140.29, 139.88, 129.88, 127.49, 126.61, 123.70, 121.94, 117.70, 110.50, 86.49, 78.58, 77.25, 73.33, 73.15, 62.28, 33.23, 15.94, 9.55; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{28}ClN_2O_5$ 471.168126, found 471.166869.

*4.2.3. (2R,3R,4S,5S,6R)-2-[4-Chloro-3-(4-cyclopropylbenzyl)-1H-indol-1-yl]-6-[(ethoxyimino)methyl]tetrahydro-2H-pyran-3,4,5-triol (**8c**)*

According to the literature, the proton signals of CH=N and Glc H5 revealed the configuration of the major isomer was (*E*) [31]. The NMR data of **8c** specified is for the major isomer only. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (dd, J = 8.4, 0.8 Hz, 1H, ArH), 7.32 (d, J = 7.2 Hz, 1H, CH=N), 7.11–7.06 (m, 3H, ArH), 7.02–6.95 (m, 4H, ArH), 5.47 (d, J = 9.2 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 4.12–4.05 (m, 3H, CH_2, Glc H5), 3.85 (dd, J = 9.2, 8.8 Hz, 1H, Glc H2), 3.60 (t, J = 8.8 Hz, 1H, Glc H3), 3.54 (dd, J = 9.6, 8.8 Hz, 1H, Glc H4), 1.87–1.81 (m, 1H, cyclopropyl CH), 1.20 (t, J = 6.8 Hz, 3H, CH_3), 0.92–0.88 (m, 2H, cyclopropyl CH_2), 0.64–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 148.41, 142.74, 140.27, 139.88, 129.88, 127.49, 126.61, 123.69, 121.93, 117.69, 110.51, 86.51, 78.59, 77.38, 73.36, 73.16, 70.70, 33.24, 15.95, 14.87, 9.55; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{30}ClN_2O_5$ 485.183776, found 485.183010.

*4.2.4. N′-({(2R,3S,4S,5R,6R)-6-[4-Chloro-3-(4-cyclopropylbenzyl)-1H-indol-1-yl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene) acetohydrazide (**8d**)*

The ratio of the obtained isomers was ~1.4:1. The proton chemical shifts of CH=N groups of the isomers are at 7.33 (d, J = 5.2 Hz, 1H) and 7.18 (d, J = 6.4 Hz, 1H) ppm, respectively; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{29}ClN_3O_5$ 498.179025, found 498.178590.

*4.2.5. Methyl 2-({(2R,3S,4S,5R,6R)-6-[4-chloro-3-(4-cyclopropylbenzyl)-1H-indol-1-yl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene) hydrazinecarboxylate (**8e**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (dd, J = 8.4, 0.8 Hz, 1H, ArH), 7.20 (d, J = 6.0 Hz, 1H, CH=N), 7.11–7.06 (m, 3H, ArH), 7.01–6.95 (m, 4H, ArH), 5.49 (d, J = 9.2 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 4.13 (dd, J = 9.2, 6.0 Hz, 1H, Glc H5), 3.85 (t, J = 9.2 Hz, 1H, Glc H2), 3.74 (s, 3H, OCH_3), 3.64–3.57 (m, 2H, Glc H3, H4), 1.89–1.82 (m, 1H, cyclopropyl CH), 0.93–0.88 (m, 2H, cyclopropyl CH_2), 0.65–0.61 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 156.99, 145.46, 142.76, 140.32, 139.89, 129.88, 127.49, 126.59, 123.70, 121.95, 117.72, 110.53, 86.45, 78.86, 78.61, 73.34, 73.02, 53.21, 33.23, 15.95, 9.55; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{29}ClN_3O_6$ 514.173940, found 514.173493.

*4.2.6. Ethyl 2-({(2R,3S,4S,5R,6R)-6-[4-chloro-3-(4-cyclopropylbenzyl)-1H-indol-1-yl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene) hydrazinecarboxylate (**8f**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (dd, J = 8.4, 0.8 Hz, 1H, ArH), 7.19 (d, J = 6.0 Hz, 1H, CH=N), 7.09–7.05 (m, 3H, ArH), 7.01–6.94 (m, 4H, ArH), 5.49 (d, J = 9.2 Hz, 1H, Glc H1), 4.27 (s, 2H, CH_2), 4.17 (q, J = 7.2 Hz, 2H, CH_2), 4.13 (dd, J = 9.2, 6.0 Hz, 1H, Glc H5), 3.86 (t, J = 9.2 Hz, 1H, Glc H2), 3.65–3.58 (m, 2H, Glc H3, H4), 1.87–1.80 (m, 1H, cyclopropyl CH), 1.25 (t, J = 7.2 Hz, 3H, CH_3), 0.92–0.87 (m, 2H, cyclopropyl CH_2), 0.63–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 156.54, 145.35, 142.74, 140.30, 139.88, 129.88, 127.48, 126.60, 123.70, 121.94, 117.71, 110.53, 86.45, 78.85, 78.59, 73.33, 73.00, 62.80, 33.23, 15.95, 14.95, 9.56; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{31}ClN_3O_6$ 528.189590, found 528.188070.

*4.2.7. tert-Butyl 2-({(2R,3S,4S,5R,6R)-6-[4-chloro-3-(4-cyclopropylbenzyl)-1H-indol-1-yl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene) hydrazinecarboxylate (**8g**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (dd, J = 8.4, 0.8 Hz, 1H, ArH), 7.15 (d, J = 5.6 Hz, 1H, CH=N), 7.10–7.05 (m, 3H, ArH), 7.01–6.93 (m, 4H, ArH), 5.48 (d, J = 9.2 Hz, 1H, Glc H1), 4.27 (s, 2H, CH_2), 4.12 (dd, J = 9.2, 5.6 Hz, 1H, Glc H5), 3.86 (t, J = 9.2 Hz, 1H, Glc H2), 3.65–3.58 (m, 2H, Glc H3, H4), 1.87–1.81 (m, 1H, cyclopropyl CH), 1.47 (s, 9H, $3CH_3$), 0.92–0.87 (m, 2H, cyclopropyl CH_2), 0.64–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 155.59, 144.51, 142.74, 140.29, 139.87, 129.87, 127.47, 126.60, 123.69, 121.93, 117.68, 110.54, 86.45, 82.20, 78.86, 78.59, 73.33, 72.98, 33.23, 28.68, 15.95, 9.56; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{35}ClN_3O_6$ 556.220890, found 556.219917.

*4.2.8. N′-({(2R,3S,4S,5R,6R)-6-[4-Chloro-3-(4-cyclopropylbenzyl)-1H-indol-1-yl]-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl}methylidene) benzohydrazide (**8h**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.86–7.84 (m, 2H, ArH), 7.61–7.55 (m, 2H, ArH, CH=N), 7.49–7.45 (m, 3H, ArH), 7.10–7.06 (m, 3H, ArH), 7.01–6.94 (m, 4H, ArH), 5.54 (d, J = 9.2 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 4.26 (dd, J = 9.2, 5.6 Hz, 1H, Glc H5), 3.89 (t, J = 9.2 Hz, 1H, Glc H2), 3.72–3.64 (m, 2H, Glc H3, H4), 1.88–1.81 (m, 1H, cyclopropyl CH), 0.92–0.87 (m, 2H, cyclopropyl CH_2), 0.64–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 167.39, 149.84, 142.76, 140.34, 139.88, 133.89, 133.61, 129.87, 128.93, 127.49, 126.61, 123.73, 121.97, 117.77, 110.55, 86.52, 78.83, 78.64, 73.33, 72.93, 33.23, 15.95, 9.55; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{31}ClN_3O_5$ 560.194675, found 560.193241.

*4.2.9. 4-Chloro-3-(4-cyclopropylbenzyl)-1-[6-deoxy-6-(hydroxyamino)-β-D-glucopyranosyl]-1H-indole (**9a**)*

^{1}H NMR(400 MHz, CD_3OD) δ 7.46 (dd, J = 8.4, 0.8 Hz, 1H, ArH), 7.11–7.06 (m, 3H, ArH), 7.02–6.95 (m, 4H, ArH), 5.39 (d, J = 9.2 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 3.85–3.79 (m, 2H, Glc H2, H5), 3.55 (dd, J = 9.2, 8.8 Hz, 1H, Glc H3), 3.36–3.30 (m, 2H, Glc H4, H6a), 2.91 (dd, J = 13.6, 8.4 Hz, 1H, Glc H6b), 1.89–1.82 (m, 1H, cyclopropyl CH), 0.93–0.89 (m, 2H, cyclopropyl CH_2), 0.65–0.61 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 142.76, 140.19, 139.97, 129.88, 127.49, 126.82, 126.61, 123.65, 121.87, 117.46, 110.69, 86.78, 79.12, 75.73, 73.93, 73.63, 56.57, 33.21, 15.95, 9.55; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{28}ClN_2O_5$ 459.168126, found 459.171187.

*4.2.10. 4-Chloro-3-(4-cyclopropylbenzyl)-1-[6-deoxy-6-(methoxyamino)-β-D-glucopyranosyl]-1H-indole (**9b**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, J = 8.4 Hz, 1H, ArH), 7.10–7.05 (m, 3H, ArH), 7.02–6.94 (m, 4H, ArH), 5.38 (d, J = 8.8 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 3.81 (dd, J = 9.2, 8.8 Hz, 1H, Glc H2), 3.76 (ddd, J = 9.6, 8.4, 2.8 Hz, 1H, Glc H5), 3.54 (dd, J = 9.2, 8.8 Hz, 1H, Glc H3), 3.45 (s, 3H, OCH_3), 3.41 (dd, J = 13.6, 2.8 Hz, 1H, Glc H6a), 3.34–3.27 (m, 1H, Glc H4), 2.86 (dd, J = 13.6, 8.4 Hz, 1H, Glc H6b), 1.88–1.81 (m, 1H, cyclopropyl CH), 0.92–0.87 (m, 2H, cyclopropyl CH_2), 0.64–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 142.74, 140.21, 139.93, 129.88, 127.51, 126.75, 126.60, 123.65, 121.89, 117.50, 110.58, 86.67, 79.11, 75.93, 73.86, 73.54, 61.41, 53.73, 33.20, 15.94, 9.56; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{30}ClN_2O_5$ 473.183776, found 473.182591.

*4.2.11. 4-Chloro-3-(4-cyclopropylbenzyl)-1-[6-deoxy-6-(ethoxyamino)-β-D-glucopyranosyl]-1H-indole (**9c**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, J = 8.0 Hz, 1H, ArH), 7.10–7.06 (m, 3H, ArH), 7.01 (d, J = 8.0 Hz, 2H, ArH), 6.95 (d, J = 8.0 Hz, 2H, ArH), 5.38 (d, J = 9.2 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 3.81 (t, J = 9.2 Hz, 1H, Glc H2), 3.80–3.75 (m, 1H, Glc H5), 3.68–3.62 (m, 2H, CH_2), 3.55 (t, J = 9.2 Hz, 1H, Glc H3), 3.39 (dd, J = 14.0, 2.8 Hz, 1H, Glc H6a), 3.34–3.30 (m, 1H, Glc H4), 2.87 (dd, J = 14.0, 8.8 Hz, 1H, Glc H6b), 1.88–1.81 (m, 1H, cyclopropyl CH), 1.09 (t, J = 7.2 Hz, 3H, CH_3), 0.92–0.88 (m, 2H, cyclopropyl CH_2), 0.64–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 142.74, 140.22, 139.94, 129.88, 127.52, 126.75, 126.60, 123.62, 121.89, 117.50, 110.59, 86.67, 79.13, 76.04, 73.91, 73.54, 69.76, 54.24, 33.20, 15.94, 14.59, 9.55; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{32}ClN_2O_5$ 487.199426, found 487.199100.

*4.2.12. 1-[6-(2-Acetylhydrazinyl)-6-deoxy-β-D-glucopyranosyl]-4-chloro-3-(4-cyclopropylbenzyl)-1H-indole (**9d**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (dd, J = 8.4, 0.8 Hz, 1H, ArH), 7.12–7.07 (m, 3H, ArH), 7.04–6.95 (m, 4H, ArH), 5.36 (d, J = 8.8 Hz, 1H, Glc H1), 4.29 (s, 2H, CH_2), 3.81 (dd, J = 9.2, 8.8 Hz, 1H, Glc H2), 3.65 (ddd, J = 10.0, 7.6, 2.4 Hz, 1H, Glc H5), 3.53 (dd, J = 9.2, 8.8 Hz, 1H, Glc H3), 3.36 (dd, J = 9.6, 9.2 Hz, 1H, Glc H4), 3.18 (dd, J = 12.8, 2.4 Hz, 1H, Glc H6a), 2.94 (dd, J = 12.8, 7.6 Hz, 1H, Glc H6b), 1.89–1.82 (m, 1H, cyclopropyl CH), 1.74 (s, 3H, CH_3), 0.93–0.88 (m, 2H, cyclopropyl CH_2), 0.65–0.61 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 171.70, 142.75, 140.20, 140.01, 129.88, 127.47, 126.85, 126.63, 123.66, 121.86, 117.43, 110.79, 86.81, 79.06, 78.40, 73.59, 73.06, 53.85, 33.20, 20.74, 15.95, 9.54; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{31}ClN_3O_5$ 500.194675, found 500.193341.

*4.2.13. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[2-(methoxycarbonyl)hydrazinyl]-β-D-glucopyranosyl}-1H-indole (**9e**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, J = 7.6 Hz, 1H, ArH), 7.11–7.06 (m, 3H, ArH), 7.01–6.95 (m, 4H, ArH), 5.37 (d, J = 9.2 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 3.80 (t, J = 9.2 Hz, 1H, Glc H2), 3.67 (ddd, J = 10.0, 8.0, 2.4 Hz, 1H, Glc H5), 3.55–3.51 (m, 4H, Glc H3, OCH_3), 3.36 (dd, J = 9.6, 9.2 Hz, 1H, Glc H4), 3.18 (dd, J = 12.8, 2.4 Hz, 1H, Glc H6a), 2.94 (dd, J = 12.8, 8.0 Hz, 1H, Glc H6b), 1.89–1.82 (m, 1H, cyclopropyl CH), 0.93–0.89 (m, 2H, cyclopropyl CH_2), 0.65–0.61 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 160.14, 142.74, 140.17, 139.99, 129.88, 127.43, 126.86, 126.60, 123.61, 121.81, 117.38, 110.78, 86.78, 79.02, 78.16, 73.67, 73.22, 54.18, 52.73, 33.20, 15.94, 9.55; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{31}ClN_3O_6$ 516.189590, found 516.188604.

*4.2.14. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[2-(ethoxycarbonyl)hydrazinyl]-β-D-glucopyranosyl}-1H-indole (**9f**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, J = 8.0 Hz, 1H, ArH), 7.11–7.05 (m, 3H, ArH), 7.02–6.94 (m, 4H, ArH), 5.36 (d, J = 9.2 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 3.97–3.95 (m, 2H, CH_2), 3.81 (dd, J = 9.2, 8.8 Hz, 1H, Glc H2), 3.67 (ddd, J = 10.0, 8.0, 2.8 Hz, 1H, Glc H5), 3.54 (dd, J = 9.2, 8.8 Hz, 1H, Glc H3), 3.37 (dd, J = 9.6, 9.2 Hz, 1H, Glc H4), 3.19 (dd, J = 12.8, 2.8 Hz, 1H, Glc H6a), 2.95 (dd, J = 12.8, 8.0 Hz, 1H, Glc H6b), 1.88–1.81 (m, 1H, cyclopropyl CH), 1.12 (t, J = 7.2 Hz, 3H, CH_3), 0.92–0.88 (m, 2H, cyclopropyl CH_2), 0.64–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 159.69, 142.73, 140.15, 139.96, 129.89, 127.44, 126.87, 126.59, 123.60, 121.81, 117.38, 110.79, 86.80, 79.00, 78.22, 73.65, 73.22, 62.17, 54.17, 33.21, 15.94, 14.99, 9.56; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{33}ClN_3O_6$ 530.205240, found 530.203954.

*4.2.15. 1-{6-[2-(tert-Butoxycarbonyl)hydrazinyl]-6-deoxy-β-D-glucopyranosyl}-4-chloro-3-(4-cyclopropylbenzyl)-1H-indole (**9g**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (d, J = 8.0 Hz, 1H, ArH), 7.11–7.06 (m, 3H, ArH), 7.02–6.94 (m, 4H, ArH), 5.37 (d, J = 9.2 Hz, 1H, Glc H1), 4.28 (s, 2H, CH_2), 3.82 (t, J = 9.2 Hz, 1H, Glc H2), 3.65 (ddd, J = 10.0, 8.0, 2.8 Hz, 1H, Glc H5), 3.54 (t, J = 8.8 Hz, 1H, Glc H3), 3.37 (dd, J = 9.6, 9.2 Hz, 1H, Glc H4), 3.16 (dd, J = 12.8, 2.8 Hz, 1H, Glc H6a), 2.93 (dd, J = 12.8, 8.0 Hz, 1H, Glc H6b), 1.88–1.81 (m, 1H, cyclopropyl CH), 1.37 (s, 9H, $3CH_3$), 0.92–0.88 (m, 2H, cyclopropyl CH_2), 0.64–0.60 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 158.83, 142.72, 140.20, 139.96, 129.88, 127.45, 126.84, 126.61, 123.62, 121.85, 117.41, 110.77, 86.75, 81.07, 79.03, 78.02, 73.58, 73.21, 54.20, 33.21, 28.80, 15.95, 9.53; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{37}ClN_3O_6$ 558.236540, found 558.234633.

*4.2.16. 1-[6-(2-Benzoylhydrazinyl)-6-deoxy-β-D-glucopyranosyl]-4-chloro-3-(4-cyclopropyl-benzyl)-1H-indole (**9h**)*

^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, J = 8.0 Hz, 1H, ArH), 7.42–7.38 (m, 3H, ArH), 7.21 (t, J = 7.6 Hz, 2H, ArH), 7.07–6.98 (m, 5H, ArH), 6.93 (d, J = 8.0 Hz, 2H, ArH), 5.42 (d, J = 9.2 Hz, 1H, Glc H1), 4.26 (s, 2H, CH_2), 3.85 (t, J = 9.2 Hz, 1H, Glc H2), 3.79–3.74 (m, 1H, Glc H5), 3.56 (t, J = 9.2 Hz, 1H, Glc H3), 3.41 (dd, J = 9.6, 9.2 Hz, 1H, Glc H4), 3.36–3.31 (m, 1H, Glc H6a), 3.05 (dd, J = 13.6, 8.0 Hz, 1H, Glc H6b), 1.88–1.81 (m, 1H, cyclopropyl CH), 0.92–0.87 (m, 2H, cyclopropyl CH_2), 0.63–0.59 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 168.57, 142.73, 140.12, 139.90, 134.15, 132.70, 129.90, 129.61, 128.01, 127.54, 126.89, 126.69, 126.61, 123.75, 121.93, 117.46, 110.74, 86.81, 79.67, 79.05, 73.47, 72.98, 53.58, 33.23, 15.94, 9.54; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{33}ClN_3O_5$ 562.210325, found 562.208968.

4.3. In vitro human SGLT inhibition assays

The transporter assays were performed according to the protocols of Castaneda and Kinne [29,30], with necessary modification [22].

4.4. Pharmacokinetics and urine glucose excretion studies

Pharmacokinetics and urine glucose excretion effect of acethydrazide-containing *N*-glucosyl indole **9d** were studied using our previously reported protocols [22].

Conflicts of interest

The authors declare no competing interests.

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