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N-Indolylglycosides Bearing Modifications at the Glucose C6-Position as Sodium-Dependent Glucose Co-transporter 2 Inhibitors

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Abstract:

Suppression of glucose reabsorption through the inhibition of sodium-dependent glucose co-transporter 2 (SGLT2) is a promising therapeutic approach for the treatment of type 2 diabetes. To investigate the effect of C6-substitution on inhibition of SGLT2 by *N*-indolylglucosides, a small library of 6-triazole, 6-amide, 6-urea, and 6-thiourea *N*-indolylglycosides were synthesized and tested. A detailed structure-activity relationship (SAR) study culminated in the identification of 6-amide derivatives **6a** and **6o** as potent SGLT2 inhibitors, which were further tested for inhibitory activity against SGLT1. The data obtained indicated that **6a** and **6o** are mildly to moderately selective for SGLT2 over SGLT1. Both compounds were also evaluated in a urinary glucose excretion test and pharmacokinetic study; **6a** was found capable of inducing urinary glucose excretion in normal SD rats.

Keywords

N-indolylglycosides, sodium-dependent glucose co-transporter, structure-activity relationship, type 2 diabetes mellitus

1. Introduction

Inhibitors of sodium-dependent glucose co-transporter 2 (SGLT2) are a uniquely attractive method of type 2 diabetes treatment because of their distinct mechanism of action, in which blood glucose levels are reduced independently of insulin secretion.[1] SGLT2, one of twelve constituents of the solute carrier family 5A (SLC5A), is located on the S1 segment of the proximal tubule in the kidney and mediates the reabsorption of the majority (>90%) of renal glucose filtered by the kidney glomeruli.[2-5] Reabsorption of the remainder is accomplished by SGLT1, another member of the SLC5A gene family, which is mainly expressed in the small intestine but also presented in the S2/S3 segment of the proximal tubule. The reabsorbed glucose is then delivered into bloodstream, which is hazardous to people with diabetes. Accordingly, SGLT2 inhibition is a promising new therapeutic approach for the control of blood glucose levels by suppressing the reuptake of glucose, which leads to glucose excretion in urine and hence reduces blood glucose levels. SGLT2 inhibitors could also increase the caloric output in urine due to the urinary glucose excretion, suggesting that their use would not result in the weight gain often seen with other anti-hyperglycemic agents currently prescribed.[6] A modest reduction in blood pressure has also been observed in patients following treatment with SGLT2 inhibitors, another potential benefit.

To avoid the gastrointestinal side effects associated with SGLT1 inhibition,[7-9] inhibitors selective for SGLT2 are sought. Several selective SGLT2 inhibitors have been developed by structural modification of phlorizin,[10] the first known SGLT inhibitor, and *C*-linked β-glycosides are at advanced stages of development because of their metabolic stability, high oral bioavailability, and plasma exposure. Of these, dapagliflozin,[11] canagliflozin,[12] ipragliflozin,[13] tofogliflozin,[14] luseogliflozin[15] and empagliflozin[16] have been approved for the treatment of type 2 diabetes mellitus (T2DM) recently (Figure 1); however, long-term follow-up of patients was recommended due to various unexpected side-effects, including cancers, liver injury, cardiovascular diseases and ketoacidosis.[6,17,18] Also, clinical efficacy studies revealed that current agents can only induce <50%

of filtered glucose load in humans into the urine, perhaps because inhibition of SGLT2 forces SGLT1 to reabsorb glucose as its maximum capacity.[19,20] Accordingly, novel, safer SGLT2 inhibitors also able to partially inhibit SGLT1 without gastrointestinal side effects are sought. Also, the optimal degree of selectivity for SGLT2 over SGLT1 needs to be determined.

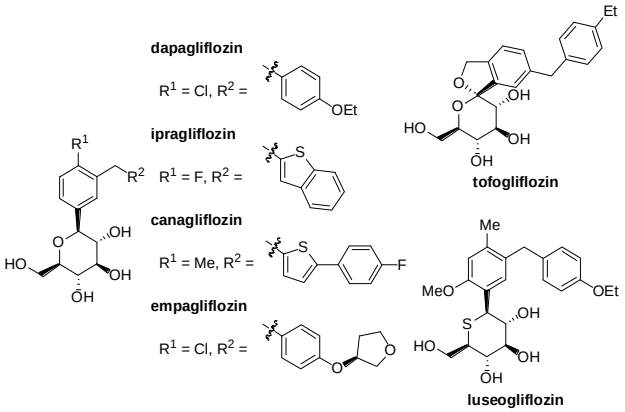


Figure 1. SGLT2 inhibitors in clinical use.

In our previous study, a series of *N*-indolylxyloside derivatives were synthesized and their inhibitory potency against hSGLT2 demonstrated. This work culminated in the identification of a potent SGLT2 inhibitor 4-chloro-3-(4-cyclopropylbenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole **1**.[21] Pharmacokinetic studies of **1** found it to be metabolically stable with low clearance and good oral bioavailability (56.3%) in Sprague-Dawley (SD) rats. In further efficacy studies, **1** was found to significantly increase urine glucose excretion and lower blood glucose levels in streptozotocin (STZ)-induced diabetic rats. Comparison of *N*-indolylglucoside 4-chloro-3-(4-cyclopropylbenzyl)-1-(β-D-glucopyranosyl)-1*H*-indole **2**[22-24] with *N*-indolylxyloside **1** showed that **2** possessed better SGLT2 inhibition when the same aglycone moiety was installed at the C1 position (**1**: EC_{50} = 203 nM; **2**: EC_{50} = 14 nM). This result suggested that the C6 position of the sugar moiety may play a critical role in the suppression of SGLT2. Therefore, in this article, lead optimization of *N*-glycosides proceeded via modification at the C6 position only, the aglycone unit 4-chloro-3-(4-cyclopropylbenzyl)-1*H*-indole being fixed (Figure 2). A detailed description of the design, synthesis, and structure-activity relationship (SAR) studies of these newly developed

C6-substituted *N*-glycosides is presented.

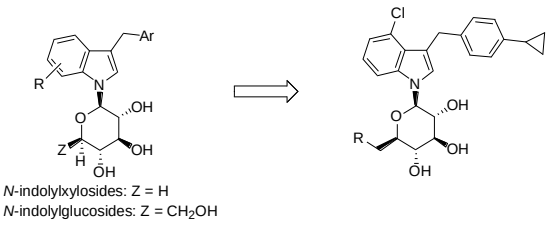
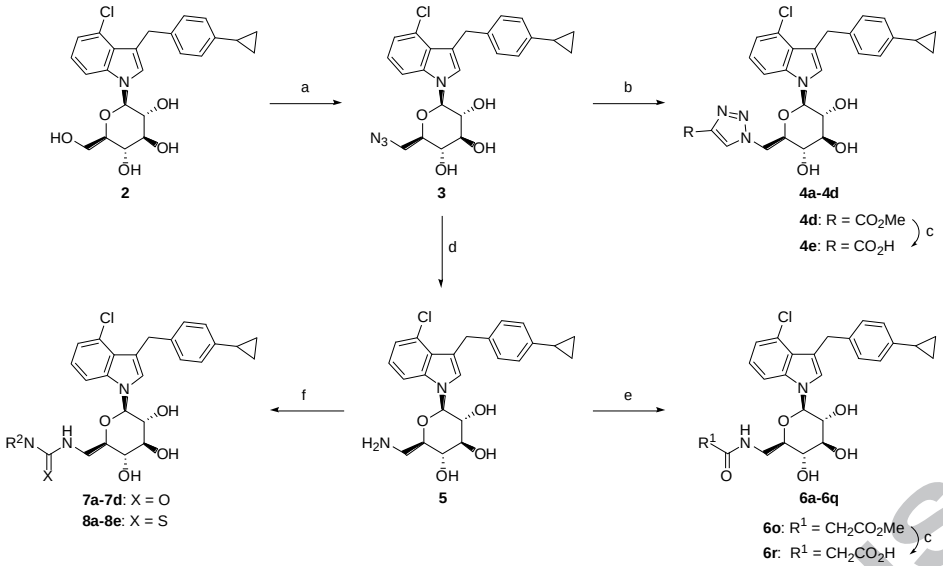


Figure 2. Design of *N*-indolylglycoside SGLT2 inhibitors with C6-modification on the glucose moiety.

2. Results and discussion

2.1 Chemistry

The test compounds of Table 1 were prepared according to a general synthetic method depicted in Scheme 1, using *N*-indolylglucoside **2** as the starting material. Treatment of **2** with methanesulfonyl chloride (MsCl) in pyridine gave the corresponding 6-OMs *N*-glycoside, which was sequentially reacted with sodium azide (NaN_3) to afford the 6-azido compound **3** in 77% yield over 2 steps. Copper-catalyzed azide-alkyne click chemistry was used to prepare the 1,2,3-triazole derivatives **4a**–**4d** in yields of 76-87%.[25,26] Hydrolysis of **4d** gave the carboxylic acid **4e** in 69% yield. Next, the synthesis of amide, urea, or thiourea derivatives was carried out via the intermediate amine **5**, generated by the reduction of azido group in **3** with Zn/HOAc in THF (91%). Amine **5** underwent direct amide bond formation with a variety of acyl chlorides to furnish 6-amide derivatives **6a**–**6q** in fair to good yields (29–82%). The carboxylic acid **6r** was then obtained successfully in 86% yield via the hydrolysis of methyl ester **6o**. In addition, reaction of **5** with isocyanate or isothiocyanate afforded the desired ureas **7a**–**7d** (48–59%) and thioureas **8a**–**8e** (50–71%), respectively.



Scheme 1. The General Synthetic Route towards C6-Modified *N*-Indolylglycosides. Reagents and conditions: (a) (i) MsCl, pyridine, 0 °C to rt; (ii) NaN_3, DMF, 80 °C, 77% over 2 steps; (b) RC≡CH, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, saturated $NaHCO_{3(aq)}$, ^{t}BuOH, 50 °C, 76-87%; (c) NaOMe, MeOH, H_2O, rt, **4e**: 69%, **6r**: 86%; (d) Zn, HOAc, THF, rt, 91%; (e) R^1COCl, K_2CO_3, THF, rt, 29-82%; (f) for **7a**-**7d**, R_2NCO, K_2CO_3, THF, or R_2NCO, pyridine, 48-59%; for **8a**-**8e**, R_2NCS, K_2CO_3, THF, or R_2NCS, pyridine, 50-71%.

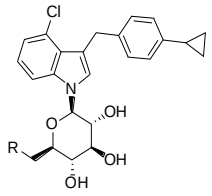
2.2 Biological evaluation

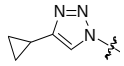
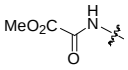
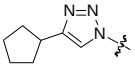
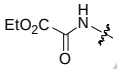
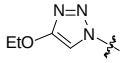
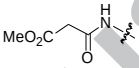
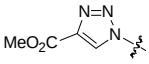
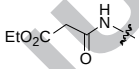
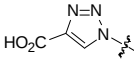
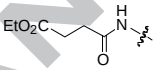
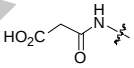
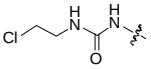
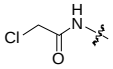
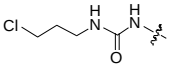
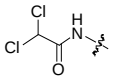
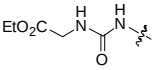
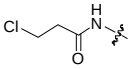
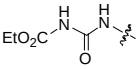
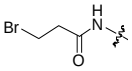
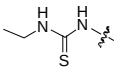
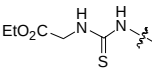
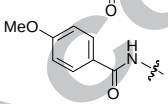
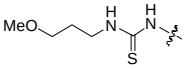
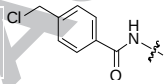
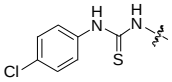
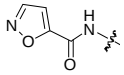
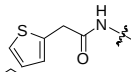
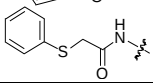
All the *N*-glycosides synthesized were evaluated for their inhibitory activity against hSGLT2. The EC_{50} values were calculated by measuring inhibition of the sodium-dependent uptake of [^{14}C]-labeled α-methyl-D-glucopyranoside (AMG) into Chinese hamster ovary (CHO) cells stably expressing human SGLT2 (hSGLT2).[27] Phlorizin, the first known SGLT inhibitor, was used as reference compound in this in vitro activity evaluation system.

Table 1 shows the structure-activity relationships elucidated upon the alteration of only the C6-substituent of glucose. First, the SAR was explored by introducing a 4-substituted triazolyl group (**4a**–**4e**) at the C6-position of the glucose moiety of *N*-indolylglucoside **2**. Of these, compound **4d** bearing a 4-carboxylic acid methyl ester-triazolyl group was found to be the most potent SGLT2 inhibitor, with an EC_{50} value of 119 nM. Its hydrolyzed acid product **4e** showed a 23-fold decrease in hSGLT2 inhibitory activity (EC_{50} = 2723 nM). This result suggests that a

Table 1

Effect of C6-modified *N*-indolylglycosides on hSGLT inhibitory activity and selectivity



Cpd	R	EC_{50} (nM)[a,b] hSGLT2	EC_{50} [nM][a,c] hSGLT1	Sel.[d]	Cpd	R	EC_{50} (nM)[a,b] hSGLT2	EC_{50} [nM][a,c] hSGLT1	Sel.[d]
4a		359 ± 83	—	—	**6m**		284 ± 36	5758 ± 498	20
4b		1585 ± 320	—	—	**6n**		249 ± 76	4692 ± 663	19
4c		655 ± 90	—	—	**6o**		39 ± 7	5424 ± 1357	139
4d		119 ± 32	1859 ± 221	16	**6p**		118 ± 15	3813 ± 602	32
4e		2723 ± 918	—	—	**6q**		588 ± 96	—	—
5		237 ± 216	2027 ± 218	9	**6r**		3441 ± 1185	—	—
6a		42 ± 23	1412 ± 241	34	**7a**		598 ± 125	—	—
6b		113 ± 10	3049 ± 708	27	**7b**		151 ± 33	874 ± 154	6
6c		184 ± 17	—	—	**7c**		515 ± 55	—	—
6d		160 ± 44	—	—	**7d**		1004 ± 24	—	—
6e		151 ± 10	—	—	**8a**		315 ± 28	—	—
6f		649 ± 209	—	—	**8b**		716 ± 99	—	—
6g		552 ± 155	—	—	**8c**		286 ± 22	845 ± 188	3
6h		2367 ± 373	—	—	**8d**		586 ± 118	—	—
6i		2591 ± 1371	—	—	**8e**		485 ± 17	—	—
6j		387 ± 73	—	—	**1**		203 ± 29	488 ± 182	2
6k		499 ± 14	—	—	**2**		14 ± 1	27 ± 19	2
6l		2091 ± 547	—	—	**PZN**[d]		123 ± 11	153 ± 44	1

[a]Data obtained by at least two independent experiments, each experiment performed in triplicate.

[b]Inhibition of uptake of [^{14}C]-AMG in CHO-K1 cells stably transfected with human SGLT2.

[c]Inhibition of uptake of [^{14}C]-AMG in CHO-K1 cells stably transfected with human SGLT1.

[d]Sel: Selectivity values were calculated by EC_{50} hSGLT1/EC_{50} hSGLT2.

[e]PZN: phlorizin.

4-substituted triazolyl group with relatively high hydrophilicity is less well tolerated for hSGLT2 inhibition; although, when an ethoxy group was attached in place of the methyl ester group, the inhibitory activity decreased (**4c**, EC_{50} = 655 nM). On the other hand, when the rigid and compact cyclopropyl substituent was attached at the 4-position of the triazole unit, the EC_{50} value of the resulting glycoside 4a was just 359 nM, making it 3 times less potent than **4d**; and indicating that increased steric bulk in this region is disfavored. This effect was even more evident when a cyclopentyl group was introduced at this position; the resulting product, **4b**, was found to have an even higher EC_{50} of 1585 nM.

A series of 6-amide derivatives (**6a**–**6r**) were also synthesized and their inhibitory activity against hSGLT2 evaluated. Initially, compound **5** bearing a free amino group was examined for its ability to suppress the reuptake of hSGLT2, and found to be moderately active (EC_{50} = 237 nM). With this promising data, we then evaluated the inhibitory effect of 6-amide *N*-indolylglycosides on hSGLT2. Encouragingly, it was found that when the amino group was acylated with acetyl chloride, the resulting compound **6a** was a more potent inhibitor of SGLT2, with an EC_{50} value of 42 nM. We then attempted to replace the side chain with other functional groups without changing the amido bond. When the methyl group was modified to a monochloromethyl (**6b**) or dichloromethyl (**6c**) group, a loss in inhibitory potency resulted (EC_{50} = 113 nM for **6b** and 184 nM for **6c**). Extension of the spacer to two methylene units gave rise to **6d** (EC_{50} = 160 nM) and **6e** (EC_{50} = 151 nM), both with similar potencies to **6b**. In addition, there was no improvement in hSCLT2 inhibition using isopropyl (**6f**, EC_{50} = 649 nM) or cyclopropyl (**6g**, EC_{50} = 552 nM) substitution, indicating that a hydrocarbon moiety bulkier than methyl group is not tolerated at this site. The decreased inhibitory activity was also noted when substituted phenyl groups (**6h**, EC_{50} = 2367 nM; **6i**, EC_{50} = 2591 nM) or isoxazolyl (**6j**, EC_{50} = 387 nM) were introduced at this position. Also, the potency was not recovered as indicated by 2-methylthiophene **6k** (EC_{50} = 499 nM) and methylsulfanylbenzene **6l** (EC_{50} = 2091 nM). Accordingly, the amido substituent was restricted to sterically small groups for

further exploration of potential inhibitors. As expected, replacement of the bulky group with a methyl or ethyl ester to give compounds **6m** and **6n** improved the potency (EC_{50} = 284 nM and 249 nM, respectively). Even more encouragingly, it was found that when a methyl acetyl group was introduced in place of the methyl ester group, the corresponding *N*-glycoside **6o** exhibited a substantial improvement in inhibitory activity with an EC_{50} of 39 nM. A similar structural modification was also extended to **6n**, leading to the identification of **6p** (EC_{50} = 118 nM) with modestly enhanced on hSGLT2 inhibition. The hydrolyzed acid product **6r** was found to be a greatly inferior inhibitor (EC_{50} = 3441 nM). Moreover, decreased potency was also observed when the spacer was lengthened to two methylenes (**6q**, EC_{50} = 588 nM), compared to **6p**.

Finally, urea (**7a**–**7d**) and thiourea (**8a**–**8e**) functionality was installed at the C6-position of the sugar moiety. In the urea analogue series, **7b** bearing a 3-chloropropyl group was found to be the most potent inhibitor of hSGLT2, with an EC_{50} value of 151 nM. Changing the length of the methylene spacer of **7b** from three to two (**7a**, EC_{50} = 598 nM), or substitution of the side chain with the ethyl acetyl (**7c**, EC_{50} = 515 nM) or ethyl ester (**7d**, EC_{50} = 1004 nM) resulted in a 4-, 3-, and 7-fold loss in potency, respectively. The decreased inhibitory activity against hSGLT2 was also found in the series *N*-glycosides bearing 6-thiourea (**8a**-**8e**), with EC_{50} values ranging from 286 to 716 nM.

N-indolylglycosides with good hSGLT2 inhibition in each series were selected for further evaluation of their selectivity for hSGLT2 over hSGLT1. Of these, compound **6m** was the least potent inhibitor, suppressing the reuptake of hSGLT1 with an EC_{50} = 5758 nM, and exhibiting a 20-fold selectivity over hSGLT1. In contrast, the hSGLT1 inhibitory activity of the most potent SGLT2 inhibitors **6a** and **6o** were 1412 nM and 5424 nM, respectively; these were also the most selective inhibitors, with the ratio of hSGLT1/2 = 34 and 139, respectively. Compounds **6a** and **6o** were found to be more potent and more selective SGLT2 inhibitors than our previously reported *N*-indolylxyloside **1** (EC_{50} = 203 nM; hSGLT1/2 = 2), and yet less potent but more selective

inhibitors compared to *N*-indolylglucoside **2** (EC_{50} = 14 nM; hSGLT1/2 = 2). Although the synthesized 6-amide *N*-indolylglycosides **6a** and **6o** are less potent than **2**, their mild and moderate selectivity with regard to SGLT1 has come to our attention for new-generation SGLT2 inhibitors evaluation.

*2.3 In Vivo Evaluation of compounds **6a** and **6o***

Potent *N*-indolylglycoside SGLT2 inhibitors **6a** and **6o** with mild and moderate selectivity over hSGLT1were further studied to evaluate their ability to induce urinary glucose excretion in normal SD rats. After oral administration of **6a** in single doses of 10 and 50 mg/kg to SD rats, only increased glucosuria was observed at 50 mg/kg of 101 mg glucose per 200 g body weight (BW) over 24 h compared with that of the control (0.23 mg glucose/200 g BW) (Figure 3). Blood glucose levels were also evaluated over a 5 h period after the oral glucose challenge. Although marginal reduction in glucose levels at 0.5 h and 1 h compared with the control, no statistically significant reduction in the areas under the blood glucose levels versus time curve (AUC) was observed at 50 mg/kg (data not shown). These results could be attributed to the fact that **6a** has unfavorable pharmacokinetic properties (Table 2). Administration of a single 1.1 mg/kg intravenous dose to the rats revealed that **6a** has a low total body clearance (18.8 mL/min/kg), suggesting it to be a metabolically stable compound; however, the low plasma concentration ($AUC_{0–inf.}$ = 99 ng/mL*h) of **6a** observed after oral administration indicated poor absorption, reflected in low oral bioavailability (F = 10%). In the case of **6o**, no increased urinary glucose excretion was observed at oral doses up to 50 mg/kg (data not shown). The pharmacokinetic evaluation of **6o** showed the only signal corresponded to the hydrolyzed acid product **6r**; **6o** could not be detected regardless of the mode of administration (intravenous or oral administration) proving it to be a metabolically unstable compound. Compound **6r** has already been proven to be a poor SGLT2 inhibitor (EC_{50} = 3441 nM) in vitro.

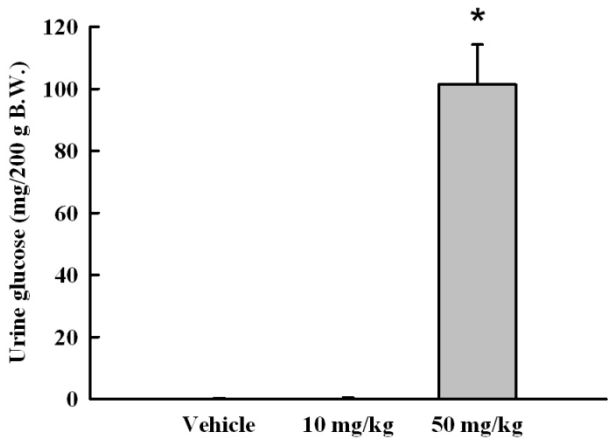


Figure 3. Urine glucose excretion of *N*-indolylglycoside **6a** over 24 h in normal Sprague-Dawley rats. *$P < 0.05$ vs vehicle.

Table 2

Pharmacokinetic Properties of *N*-indolylglycoside **6a** after Oral and Intravenous Administration to Rats

	iv	po
dose **(**mg/kg**)**	1.1	1.1
$t_{1/2}$ (h)	3.2	2.5
Cl (mL/min/kg)	18.8	
Vss (L/kg)	2.7	
C_{max} (ng/mL)		25.2
t_{max} (h)		1.2
$AUC_{(0\text{-inf.})}$ (ng/mL*h)	996	99
F (%)		10

3. Conclusion

Structural modifications of 6-triazole, 6-amide, 6-urea, and 6-thiourea *N*-indolylglycosides have been conducted to identify potential SGLT2 inhibitors. Among the compounds assayed, 6-amide *N*-indolylglycosides **6a** and **6o** were found to show the best inhibitory activity against hSGLT2 with EC_{50} values of 42 nM and 39 nM, respectively. Moreover, the mild and moderate selectivity over SGLT1 made their SGLT2 inhibition particularly interesting. Although their poor pharmacokinetic

properties resulted in an unfavorable outcome in a glucosuria study in rats, the in vivo efficacy of **6a** was proven, as shown by the increased glucose excretion in the urine. Further structural modifications and in vivo efficacy studies on the series will be reported in due course.

4. Experimental methods

4.1. Chemistry

The general information of test compounds used in this study are published as supplementary material.

4.1.1. 1-(6-Azido-6-deoxy-β-D-glucopyranosyl)-4-chloro-3-(4-cyclopropylbenzyl)-1*H*-indole (3). MsCl (56 μL, 0.72 mmol) was added to a stirred solution of **2** (267 mg, 0.60 mmol) in pyridine (5.0 mL) at 0 °C under nitrogen. The reaction was warmed to room temperature and stirred for 3 h. The reaction was quenched by the addition of H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 1/30) to provide 6-OMs *N*-glucoside (263 mg, 84%).

Sodium azide (328 mg, 5.04 mmol) was added to a stirred solution of 6-OMs *N*-glucoside (263 mg, 0.50 mmol) in DMF (5.0 mL) at room temperature. The reaction was warmed to 80 °C and heated overnight. The reaction was quenched by the addition of H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 1/10) to provide **3** (217 mg, 92%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.45 (d, J = 8.0 Hz, 1H), 7.10-6.93 (m, 7H), 5.41 (d, J = 9.2 Hz, 1H), 4.27 (s, 2H), 3.79 (t, J = 9.2 Hz, 1H), 3.72-3.67 (m, 1H), 3.62-3.46 (m, 3H), 3.40 (dd, J = 13.2, 5.2 Hz, 1H), 1.88-1.81 (m, 1H), 0.92-0.85 (m, 2H), 0.63-0.59 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 142.7, 140.2, 139.9, 129.9, 127.4, 126.7, 126.6, 123.6, 121.8, 117.5, 110.7, 86.7, 79.1, 78.8, 73.7, 71.9, 52.5, 33.2, 15.9, 9.5; ESI-MS *m/z*: 469 (MH^+), 491 (MNa^+); HPLC purity 95.6%.

4.1.2. General Procedure for the Synthesis of Compound 4a-4d

A solution of $CuSO_4 \cdot 5H_2O$ (0.4 equiv) and sodium ascorbate (1.0 equiv) in H_2O was added to a stirred solution of **3** (1.0 equiv) and 1-alkyne (2.5 equiv) in *t*-BuOH (a mixed solvent system comprising equal volumes of *t*-BuOH and saturated $NaHCO_3$(aq) was used for alkynes bearing an ester group) at 50 °C. After 2 h, the reaction was diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired products **4a**–**4d**.

4.1.2.1. 4-Chloro-3-(4-cyclopropylbenzyl)-1-[6-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)-6-deoxy-β-D-glucopyranosyl]-1*H*-indole (4a). The title compound was obtained from **3** with cyclopropyl acethylene according to the general procedure in 76% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.30 (s, 1H), 7.13 (dd, J = 7.6, 1.6 Hz, 1H), 7.10–6.94 (m, 7H), 5.36 (d, J = 9.2 Hz, 1H), 4.74 (dd, J = 14.4, 2.4 Hz, 1H), 4.45 (dd, J = 14.4, 7.2 Hz, 1H), 4.27 (s, 2H), 3.86 (ddd, J = 9.6, 7.2, 2.4 Hz, 1H), 3.79 (t, J = 9.2 Hz, 1H), 3.57 (dd, J = 9.2, 8.8 Hz, 1H), 3.25 (dd, J = 9.6, 8.8 Hz, 1H), 1.87–1.79 (m, 2H), 0.92–0.85 (m, 4H), 0.64–0.58 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD): δ 142.8, 140.1, 139.9, 129.9, 127.5, 126.8, 126.6, 123.8, 122.0, 117.5, 110.6, 86.5, 78.9, 78.0, 72.9, 72.3, 52.1, 33.2, 16.0, 9.6, 8.4, 8.3, 7.4; ESI-MS *m/z*: 535 (MH^+), 557 (MNa^+); HPLC purity 100%.

4.1.2.2. 4-Chloro-1-[6-(4-cyclopentyl-1*H*-1,2,3-triazol-1-yl)-6-deoxy-β-D-glucopyranosyl]-3-(4-cyclo-propylbenzyl)-1*H*-indole (4b). The title compound was obtained from **3** with cyclopentyl acethylene according to the general procedure in 83% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.34 (s, 1H), 7.18–7.14 (m, 1H), 7.08–6.93 (m, 7H), 5.38 (d, J = 9.2 Hz, 1H), 4.77 (dd, J = 14.4, 2.4 Hz, 1H), 4.44 (dd, J = 14.4, 7.2 Hz, 1H), 4.28, 4.26 (ABq, J = 15.6 Hz, 2H), 3.86 (ddd, J = 9.6, 7.2, 2.4 Hz, 1H), 3.81 (dd, J = 9.2, 8.8 Hz, 1H), 3.58 (dd, J = 9.2, 8.8 Hz, 1H), 3.27 (dd, J = 9.6, 9.2 Hz, 1H), 3.01 (quint, J = 8.0 Hz, 1H), 1.96–1.91 (m, 2H), 1.87–1.80 (m, 1H), 1.65–1.56 (m, 4H), 1.49–1.40 (m, 2H), 0.92–0.87 (m, 2H), 0.63–0.59 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 142.8, 140.3,

139.9, 129.8, 127.6, 126.8, 126.7, 126.6, 123.8, 122.0, 117.6, 110.4, 86.3, 78.9, 77.9, 72.8, 72.4, 52.2, 37.9, 34.3, 34.2, 33.1, 26.1, 16.0, 9.6; ESI-MS *m/z*: 563 (MH^+), 585 (MNa^+); HPLC purity 100%.

4.1.2.3. 4-Chloro-3-(4-cyclopropylbenzyl)-1-[6-deoxy-6-(4-ethoxy-1H-1,2,3-triazol-1-yl)-β-D-gluco-pyranosyl]-1H-indole (4c). The title compound was obtained from **3** with 1-ethoxyacetylene according to the general procedure in 87% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.17 (dd, J = 6.8, 2.4 Hz, 1H), 7.09–6.94 (m, 8H), 5.39 (d, J = 9.2 Hz, 1H), 4.71 (dd, J = 14.4, 2.4 Hz, 1H), 4.42 (dd, J = 14.4, 7.2 Hz, 1H), 4.27 (s, 2H), 3.93–3.79 (m, 4H), 3.58 (dd, J = 9.2, 8.8 Hz, 1H), 3.28 (dd, J = 9.6, 8.8 Hz, 1H), 1.86–1.82 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.93–0.88 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 162.2, 142.8, 140.2, 139.9, 129.8, 127.6, 126.8, 126.6, 123.7, 122.0, 117.6, 110.6, 109.4, 86.4, 78.9, 78.0, 72.9, 72.3, 67.9, 53.0, 33.2, 16.0, 15.1, 9.6; ESI-MS *m/z*: 539 (MH^+), 561 (MNa^+); HPLC purity 97.3%.

4.1.2.4. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[4-(methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]-β-D-glucopyranosyl}-1*H*-indole (4d). The title compound was obtained from **3** with methyl propiolate according to the general procedure in 79% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 8.04 (s, 1H), 7.07–7.03 (m, 3H), 7.02–6.92 (m, 5H), 5.35 (d, J = 9.2 Hz, 1H), 4.83 (dd, J = 14.4, 2.8 Hz, 1H), 4.49 (dd, J = 14.4, 7.2 Hz, 1H), 4.24 (s, 2H), 3.90 (ddd, J = 9.6, 7.2, 2.8 Hz, 1H), 3.82–3.76 (m, 1H), 3.80 (s, 3H), 3.58 (t, J = 8.8 Hz, 1H), 3.28 (dd, J = 9.6, 8.8 Hz, 1H), 1.85–1.79 (m, 1H), 0.91–0.87 (m, 2H), 0.63–0.59 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 162.4, 142.8, 140.3, 140.0, 139.7, 131.2, 129.9, 127.5, 126.8, 126.7, 126.6, 123.8, 122.0, 117.6, 110.6, 86.6, 78.9, 77.5, 72.8, 72.3, 52.6, 52.4, 33.2, 15.9, 9.6; ESI-MS *m/z*: 553 (MH^+), 575 (MNa^+); HPLC purity 97.8%.

4.1.3. 1-[6-(4-Carboxy-1*H*-1,2,3-triazol-1-yl)-6-deoxy-β-D-glucopyranosyl]-4-chloro-3-(4-cyclopropylbenzyl)-1*H*-indole (4e).

A 30% solution of NaOMe in MeOH (10 μL), and water were sequentially added to a solution of **4d** (20 mg) in MeOH (1.0 mL) at room temperature. After being stirred overnight, the reaction was diluted with MeOH and neutralized with acidic resin Dowex 50 W2-200. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography ($MeOH/CH_2Cl_2$ = 1/5) to provide **4e** (13.5 mg, 69%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.12 (s, 1H), 7.09–7.05 (m, 3H), 7.01–6.93 (m, 5H), 5.37 (d, J = 9.2 Hz, 1H), 4.84 (dd, J = 14.4, 2.8 Hz, 1H), 4.59 (dd, J = 14.4, 7.2 Hz, 1H), 4.25 (s, 2H), 3.93 (ddd, J = 9.6, 7.2, 2.8 Hz, 1H), 3.78 (dd, J = 9.2, 8.8 Hz, 1H), 3.58 (dd, J = 9.2, 8.8 Hz, 1H), 3.30–3.25 (m, 1H), 1.87–1.81 (m, 1H), 0.92–0.83 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 141.5, 138.7, 138.5, 129.8, 128.6, 126.2, 125.42, 125.37, 125.3, 122.5, 120.7, 116.3, 109.2, 85.3, 77.6, 76.3, 71.6, 70.9, 51.0, 31.9, 14.6, 8.3; ESI-MS *m/z*: 539 (MH^+), 561 (MNa^+); HPLC purity 91.8%.

4.1.4. 1-(6-Amino-6-deoxy-β-D-glucopyranosyl)-4-chloro-3-(4-cyclopropylbenzyl)-1*H*-indole (5).

A mixture of **3** (447 mg, 1.01 mmol), Zn (1.06 g, 16.14 mmol), and acetic acid (1.1 mL) in THF (10 mL) was stirred at room temperature under nitrogen overnight. The reaction was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography ($MeOH/CH_2Cl_2$ = 1/5 to 1/1) to provide the desired product **5** (406 mg, 91%) as a yellowish solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.47 (dd, J = 8.1, 0.9 Hz, 1H), 7.13–7.07 (m, 3H), 7.05–7.01 (m, 2H), 6.98–6.95 (m, 2H), 5.44 (d, J = 9.0 Hz, 1H), 4.29 (s, 2H), 3.85 (t, J = 9.0 Hz, 1H), 3.66 (ddd, J = 10.5, 8.4, 3.0 Hz, 1H), 3.57 (t, J = 9.0 Hz, 1H), 3.38–3.34 (m, 1H), 3.26 (dd, J = 13.5, 3.0 Hz, 1H), 2.91 (dd, J = 13.5, 8.4 Hz, 1H), 1.89–1.83 (m, 1H), 0.95–0.88 (m, 2H), 0.66–0.60 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 142.8, 140.2, 139.9, 129.9, 127.5, 126.8, 126.6, 123.7, 121.9, 117.6, 110.6, 86.8, 80.0, 79.0, 73.6, 73.2, 43.7, 33.2, 15.9, 9.6; ESI-MS *m/z*: 443 (MH^+), 465 (MNa^+); HPLC purity 95.8%.

4.1.5. General Procedure for the Synthesis of Compounds 6a–6q

Acyl chloride (1.1 equiv) was added to a suspension of **5** (1.0 equiv) and potassium carbonate (10 equiv) in THF at room temperature under nitrogen. After 2 h, the reaction was quenched by the addition of H_2O and the resulting mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to provide the desired products **6a**–**6q**.

4.1.5.1. 1-[6-(Acetylamino)-6-deoxy-β-D-glucopyranosyl]-4-chloro-3-(4-cyclopropylbenzyl)-1*H*-indole (6a). The title compound was obtained from **5** with acetyl chloride according to the general procedure in 55% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.43 (d, J = 8.4 Hz, 1H), 7.10–7.06 (m, 3H), 7.01–6.95 (m, 4H), 5.38 (d, J = 8.8 Hz, 1H), 4.28 (s, 2H), 3.80 (t, J = 8.8 Hz, 1H), 3.67 (dd, J = 14.4, 2.8 Hz, 1H), 3.59–3.55 (m, 1H), 3.55 (t, J = 8.8 Hz, 1H), 3.33–3.25 (m, 2H), 1.88 (s, 3H), 1.88–1.81 (m, 1H), 0.92–0.88 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 174.1, 142.8, 140.2, 140.0, 129.9, 127.5, 126.8, 126.61, 126.58, 123.6, 121.9, 117.4, 110.7, 86.7, 78.7, 78.6, 73.6, 72.8, 41.9, 33.2, 22.5, 15.9, 9.5; ESI-MS *m/z*: 485 (MH^+), 507 (MNa^+); HPLC purity 95.1%.

4.1.5.2. 4-Chloro-1-{6-[(chloroacetyl)amino]-6-deoxy-β-D-glucopyranosyl}-3-(4-cyclopropyl-benzyl)-1*H*-indole (6b). The title compound was obtained from **5** with chloroacetyl chloride according to the general procedure in 50% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.43 (d, J = 8.0 Hz, 1H), 7.10–6.94 (m, 7H), 5.39 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 3.98 (s, 2H), 3.82 (t, J = 9.2 Hz, 1H), 3.75 (dd, J = 14.0, 2.8 Hz, 1H), 3.62 (ddd, J = 9.6, 6.8, 2.8 Hz, 1H), 3.56 (t, J = 9.2 Hz, 1H), 3.37-3.28 (m, 2H), 1.88–1.81 (m, 1H), 0.93–0.88 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 169.8, 142.8, 140.2, 139.9, 129.9, 127.5, 126.7, 126.6, 123.7, 121.9, 117.5, 110.7, 86.7, 78.7, 78.3, 73.5, 72.9, 43.2, 42.1, 33.2, 15.9, 9.6; ESI-MS *m/z*: 519 (MH^+), 541 (MNa^+); HPLC purity 93.9%.

4.1.5.3. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(dichloroacetyl)amino]-β-D-gluco-pyranosyl}-1*H*-indole (6c). The title compound was obtained from **5** with dichloroacetyl chloride according to the general procedure in 52% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.42 (dd, J = 8.0, 0.8 Hz, 1H), 7.10–6.95 (m, 7H), 6.19 (s, 1H), 5.40 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 3.85–3.80 (m, 2H), 3.64 (ddd, J = 9.6, 7.2, 2.4 Hz, 1H), 3.56 (t, J = 9.2 Hz, 1H), 3.35–3.26 (m, 2H), 1.89–1.82 (m, 1H), 0.93–0.88 (m, 2H), 0.67–0.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 167.1, 142.8, 140.3, 140.0, 129.9, 127.5, 126.7, 126.62, 126.58, 123.7, 121.9, 117.5, 110.7, 86.6, 78.8, 78.2, 73.4, 73.1, 67.6, 42.5, 33.2, 15.9, 9.5; ESI-MS *m/z*: 575 (MNa^+); HPLC purity 99.0%.

4.1.5.4. 4-Chloro-1-{6-[(3-chloropropanoyl)amino]-6-deoxy-β-D-glucopyranosyl}-3-(4-cyclo-propylbenzyl)-1*H*-indole (6d). The title compound was obtained from **5** with 3-chloropropanoyl chloride according to the general procedure in 75% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.44 (dd, J = 8.0, 0.8 Hz, 1H), 7.11–7.06 (m, 3H), 7.02–6.96 (m, 4H), 5.38 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 3.81 (t, J = 9.2 Hz, 1H), 3.76–3.69 (m, 3H), 3.61–3.54 (m, 2H), 3.37–3.29 (m, 2H), 2.60 (t, J = 6.4 Hz, 2H), 1.89–1.83 (m, 1H), 0.94–0.89 (m, 2H), 0.65–0.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 173.3, 142.8, 140.2, 140.0, 129.9, 127.5, 126.8, 126.62, 126.58, 123.6, 121.9, 117.4, 110.7, 86.7, 78.7, 78.6, 73.6, 72.8, 41.8, 41.3, 39.9, 33.2, 15.9, 9.5; ESI-MS *m/z*: 533 (MH^+), 555 (MNa^+); HPLC purity 92.7%.

4.1.5.5. 1-{6-[(3-bromopropanoyl)amino]-6-deoxy-β-D-glucopyranosyl}-4-chloro-3-(4-cyclo-propylbenzyl)-1*H*-indole (6e). The title compound was obtained from **5** with 3-bromopropanoyl chloride according to the general procedure in 43% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.44 (dd, J = 8.0, 0.8 Hz, 1H), 7.11–6.95 (m, 7H), 5.38 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 3.81 (t, J = 9.2 Hz, 1H), 3.70 (dd, J = 14.0, 2.8 Hz, 1H), 3.62–3.54 (m, 4H), 3.37–3.30 (m, 2H), 2.72 (t, J = 6.4 Hz, 2H), 1.89–1.82 (m, 1H), 0.93–0.88 (m, 2H), 0.65–0.61 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 173.5, 142.8, 140.2, 139.9, 129.9, 127.5, 126.8, 126.63, 126.57, 123.6, 121.9, 117.5, 110.7, 86.7,

78.7, 78.6, 73.6, 72.8, 41.8, 40.0, 33.2, 28.6, 16.0, 9.6; ESI-MS *m/z*: 599 (MNa^+); HPLC purity 83.8%.

4.1.5.6. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(2-methylpropanoyl)amino]-β-D-glucopyranosyl}-1*H*-indole (6f). The title compound was obtained from **5** with 2-methylpropanoyl chloride according to the general procedure in 66% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 7.43 (dd, J = 8.1, 0.9 Hz, 1H), 7.11–6.95 (m, 7H), 5.39 (d, J = 9.0 Hz, 1H), 4.28 (s, 2H), 3.81 (t, J = 9.0 Hz, 1H), 3.67–3.54 (m, 3H), 3.36–3.23 (m, 2H), 2.39 (sept, J = 6.6 Hz, 1H), 1.90–1.81 (m, 1H), 1.054 (d, J = 6.6 Hz, 3H), 1.046 (d, J = 6.6 Hz, 3H), 0.94–0.88 (m, 2H), 0.65–0.60 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 181.0, 142.8, 140.3, 140.0, 129.9, 127.5, 126.7, 126.6, 123.6, 121.9, 117.5, 110.6, 86.6, 78.65, 78.58, 73.5, 72.9, 41.6, 36.2, 33.2, 20.1, 20.0, 15.9, 9.6; ESI-MS *m/z*: 513 (MH^+), 535 (MNa^+), HPLC purity 98.8%.

4.1.5.7. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-[(cyclopropylcarbonyl)amino]-6-deoxy-β-D-glucopyranosyl}-1*H*-indole (6g). The title compound was obtained from **5** with cyclopropanecarbonyl chloride according to the general procedure in 56% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.45 (dd, J = 8.0, 0.8 Hz, 1H), 7.11–6.94 (m, 7H), 5.39 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 3.82 (t, J = 9.2 Hz, 1H), 3.68 (dd, J = 14.4, 2.4 Hz, 1H), 3.59–3.54 (m, 2H), 3.38–3.25 (m, 2H), 1.87–1.81 (m, 1H), 1.55–1.49 (m, 1H), 0.93–0.88 (m, 2H), 0.84–0.80 (m, 2H), 0.73–0.68 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 177.4, 142.7, 140.2, 140.0, 129.8, 127.5, 126.8, 126.60, 126.57, 86.7, 78.8, 78.5, 73.6, 72.7, 41.9, 33.1, 15.9, 14.8, 9.6, 9.5, 7.6, 7.5; ESI-MS *m/z*: 511 (MH^+); HPLC purity 98.1%.

4.1.5.8. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(4-methoxybenzoyl)amino]-β-D-gluco-pyranosyl}-1*H*-indole (6h). The title compound was obtained from **5** with methyl 4-methoxybenzoyl chloride according to the general procedure in 44% yield. ^{1}H NMR (400 MHz,

CD_3OD): δ 7.73–7.69 (m, 2H), 7.42–7.37 (m, 1H), 7.09–6.91 (m, 9H), 5.42 (d, J = 9.2 Hz, 1H), 4.28, 4.25 (ABq, J = 16 Hz, 2H), 3.87–3.81 (m, 2H), 3.82 (s, 3H), 3.70 (ddd, J = 9.6, 6.8, 2.8 Hz, 1H), 3.60 (t, J = 9.2 Hz, 1H), 3.54 (dd, J = 14.4, 6.8 Hz, 1H), 3.35–3.30 (m, 1H), 1.87–1.80 (m, 1H), 0.92–0.87 (m, 2H), 0.63–0.58 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 170.5, 164.1, 142.7, 140.3, 140.0, 130.4, 129.8, 127.5, 127.4, 126.7, 126.61, 126.57, 123.6, 121.9, 86.6, 78.7, 78.6, 73.4, 73.0, 56.1, 42.2, 33.1, 15.9, 9.6; ESI-MS *m/z*: 577 (MH^+), 599 (MNa^+); HPLC purity 95.0%.

4.1.5.9. 4-Chloro-1-(6-{[4-(chloromethyl)benzoyl]amino}-6-deoxy-β-D-glucopyranosyl)-3-(4-cyclopropylbenzyl)-1*H*-indole (6i). The title compound was obtained from **5** with 4-(chloromethyl)benzoyl chloride according to the general procedure in 60% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.73–7.70 (m, 2H), 7.45–7.42 (m, 2H), 7.38 (dd, J = 7.6, 1.6 Hz, 1H), 7.09–7.04 (m, 3H), 7.00–6.92 (m, 4H), 5.42 (d, J = 9.2 Hz, 1H), 4.66 (s, 2H), 4.28, 4.25 (ABq, J = 16.4 Hz, 2H), 3.88 (dd, J = 14.0, 2.8 Hz, 1H), 3.85 (dd, J = 9.2, 8.8 Hz, 1H), 3.72 (ddd, J = 9.6, 6.8, 2.8 Hz, 1H), 3.60 (t, J = 8.8 Hz, 1H), 3.51 (dd, J = 14.0, 6.8 Hz, 1H), 3.36–3.30 (m, 1H), 1.87–1.80 (m, 1H), 0.92–0.87 (m, 2H), 0.63–0.58 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 170.3, 143.1, 142.7, 140.3, 140.0, 135.3, 129.9, 129.8, 128.9, 127.5, 126.7, 126.62, 126.58, 123.6, 121.9, 117.4, 110.6, 86.6, 78.7, 78.5, 73.4, 73.1, 46.2, 42.4, 33.1, 15.9, 9.6; ESI-MS *m/z*: 595 (MH^+), 617 (MNa^+); HPLC purity 89.0%.

4.1.5.10. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(1,2-oxazol-5-ylcarbonyl)amino]-β-D-glucopyranosyl}-1*H*-indole (6j). The title compound was obtained from **5** with isoxazole-5-carbonyl chloride according to the general procedure in 74% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 8.45 (d, J = 1.6 Hz, 1H), 7.40–7.37 (m, 1H), 7.09–6.93 (m, 7H), 6.86 (d, J = 1.6 Hz, 1H), 5.40 (d, J = 9.2 Hz, 1H), 4.27 (s, 2H), 3.89 (dd, J = 14.0, 2.8 Hz, 1H), 3.85 (dd, J = 9.2, 8.8 Hz, 1H), 3.73 (ddd, J = 10.0, 7.2, 2.8 Hz, 1H), 3.58 (dd, J = 9.2, 8.8 Hz, 1H), 3.48 (dd, J = 14.0, 7.2 Hz, 1H), 3.34 (t, J = 9.2 Hz, 1H), 1.87–1.80 (m, 1H), 0.92–0.87 (m, 2H), 0.64–0.59 (m, 2H); ^{13}C

NMR (100 MHz, CD_3OD): δ 164.0, 158.6, 152.4, 142.7, 140.2, 139.9, 129.9, 127.5, 126.8, 126.6, 123.6, 121.9, 117.4, 110.7, 107.3, 86.7, 78.8, 78.2, 73.4, 73.2, 42.0, 33.2, 15.9, 9.6; ESI-MS *m/z*: 538 (MH^+), 560 (MNa^+); HPLC purity 98.0%.

4.1.5.11. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(thiophen-2-ylacetyl)amino]-β-D-glucopyranosyl}-1*H*-indole (6k). The title compound was obtained from **5** with 2-thiopheneacetyl chloride according to the general procedure in 62% yield. ^{1}H NMR(400 MHz, CD_3OD): δ 7.41 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.13–7.07 (m, 4H), 7.02 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.99–6.95 (m, 3H), 6.83–6.78 (m, 2H), 5.36 (d, *J* = 9.2 Hz, 1H), 4.29 (s, 2H), 3.77 (dd, *J* = 9.2, 8.8 Hz, 1H), 3.69 (dd, *J* = 14.0, 2.8 Hz, 1H), 3.65 (d, *J* = 0.8 Hz, 2H), 3.59–3.52 (m, 2H), 3.36–3.30 (m, 1H), 3.25 (dd, *J* = 9.6, 8.8 Hz, 1H), 1.89–1.82 (m, 1H), 0.93–0.88 (m, 2H), 0.65–0.60 (m, 2H); ^{13}C NMR(75 MHz, CD_3OD): δ 173.6, 142.8, 140.3, 140.0, 138.1, 129.9, 128.0, 127.8, 127.5, 126.7, 126.64, 126.56, 125.9, 123.7, 121.9, 117.5, 110.7, 86.6, 78.6, 78.5, 73.6, 72.9, 41.8, 37.9, 33.2, 16.0, 9.6; ESI-MS *m/z*: 589 (MNa^+); HPLC purity 95.7%.

4.1.5.12. 4-Chloro-3-(4-cyclopropylbenzyl)-1-(6-deoxy-6-{[(phenylsulfanyl)acetyl]amino}-β-D-glucopyranosyl)-1*H*-indole (6l). The title compound was obtained from **5** with (phenylthio)acetyl chloride according to the general procedure in 65% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.40 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.25–7.22 (m, 2H), 7.16–7.05 (m, 6H), 7.01 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.99–6.97 (m, 2H), 6.90 (s, 1H), 5.31 (d, *J* = 9.2 Hz, 1H), 4.30 (s, 2H), 3.65 (dd, *J* = 9.2, 8.8 Hz, 1H), 3.62–3.58 (m, 1H), 3.58 (s, 2H), 3.53–3.48 (m, 2H), 3.39 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.13 (dd, *J* = 9.6, 9.2 Hz, 1H), 1.90–1.82 (m, 1H), 0.92–0.88 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 172.1, 142.8, 140.2, 139.9, 136.4, 130.6, 130.4, 129.9, 128.0, 127.5, 126.7, 126.6, 126.5, 123.7, 121.9, 117.6, 110.7, 86.6, 78.43, 78.40, 73.5, 72.4, 41.8, 38.5, 33.3, 16.0, 9.6; ESI-MS *m/z*: 593 (MH+), 615 (MNa+); HPLC purity 100%.

4.1.5.13. 4-Chloro-3-(4-cyclopropylbenzyl)-1-(6-deoxy-6-{[methoxy(oxo)acetyl]amino}-β-D-

glucopyranosyl)-1*H*-indole (6m). The title compound was obtained from **5** with methyl oxalyl chloride according to the general procedure in 57% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.41 (dd, J = 8.4, 1.2 Hz, 1H), 7.11–7.05 (m, 3H), 7.02–6.95 (m, 4H), 5.39 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 3.82 (t, J = 9.2 Hz, 1H), 3.80 (s, 3H), 3.79 (dd, J = 14.0, 2.8 Hz, 1H), 3.68 (ddd, J = 10.0, 7.6, 2.8 Hz, 1H), 3.55 (t, J = 9.2 Hz, 1H), 3.36 (dd, J = 14.0, 7.6 Hz, 1H), 3.35–3.28 (m, 1H), 1.89–1.82 (m, 1H), 0.93–0.87 (m, 2H), 0.65–0.61 (m, 2H); ^{13}C NMR(100 MHz, CD_3OD): δ 161.9, 159.4, 142.8, 140.2, 139.9, 129.9, 127.5, 126.8, 126.6, 123.7, 121.9, 117.5, 110.7, 86.7, 78.7, 78.0, 73.4, 73.2, 42.3, 33.2, 16.0, 9.6; ESI-MS *m/z*: 529 (MH^+), 551 (MNa^+); HPLC purity 95.4%.

4.1.5.14. 4-Chloro-3-(4-cyclopropylbenzyl)-1-(6-deoxy-6-{[ethoxy(oxo)acetyl]amino}-β-D-glucopyranosyl)-1*H*-indole (6n). The title compound was obtained from **5** with ethyl oxalyl chloride according to the general procedure in 29% yield. ^{1}H NMR(400 MHz, CD_3OD): δ 7.41 (dd, J = 8.4, 1.2 Hz, 1H), 7.11–6.95 (m, 7H), 5.39 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.85–3.76 (m, 2H), 3.68 (ddd, J = 10.0, 7.6, 2.8 Hz, 1H), 3.56 (t, J = 9.2 Hz, 1H), 3.38–3.28 (m, 2H), 1.88–1.82 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.93–0.88 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 161.9, 159.4, 142.8, 140.2, 139.9, 129.9, 127.5, 126.8, 126.6, 123.7, 121.9, 117.5, 110.7, 86.7, 78.7, 78.0, 73.4, 73.2, 58.5, 42.3, 33.2, 18.5, 16.0, 9.6; ESI-MS *m/z*: 565 (MNa^+); HPLC purity 92.6%.

4.1.5.15. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(3-methoxy-3-oxopropanoyl)amino]-β-D-glucopyranosyl}-1*H*-indole (6o). The title compound was obtained from **5** with methyl 3-chloro-3-oxopropanoate according to the general procedure in 46% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.46 (dd, J = 8.4, 0.8 Hz, 1H), 7.11–6.96 (m, 7H), 5.40 (d, J = 9.2 Hz, 1H), 4.29 (s, 2H), 3.81 (t, J = 9.2 Hz, 1H), 3.73 (dd, J = 14.0, 2.4 Hz, 1H), 3.65 (s, 3H), 3.63–3.54 (m, 2H), 3.38–3.25 (m, 4H), 1.90–1.84 (m, 1H), 0.94–0.89 (m, 2H), 0.65–0.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 170.2, 169.1, 142.8, 140.2, 140.0, 129.9, 127.4, 126.8, 126.60, 126.57, 123.6, 121.9, 117.4, 110.8,

86.7, 78.59, 78.57, 73.6, 72.7, 52.9, 41.9, 33.2, 15.9, 9.6; ESI-MS *m/z*: 543 (MH^+), 565 (MNa^+); HPLC purity 100%.

4.1.5.16. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(3-ethoxy-3-oxopropanoyl)amino]-β-D-glucopyranosyl}-1*H*-indole (6p). The title compound was obtained from **5** with ethyl 3-chloro-3-oxopropanoate according to the general procedure in 38% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.46 (dd, J = 8.4, 0.8 Hz, 1H), 7.11–6.95 (m, 7H), 5.39 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 4.13–4.08 (q, J = 7.2 Hz, 2H), 3.82 (t, J = 9.2 Hz, 1H), 3.72 (dd, J = 14.4, 2.8 Hz, 1H), 3.60 (ddd, J = 9.6, 6.8, 2.8 Hz, 1H), 3.56 (t, J = 9.2 Hz, 1H), 3.39–3.24 (m, 4H), 1.88–1.82 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H), 0.93–0.89 (m, 2H), 0.64–0.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 169.8, 169.2, 142.8, 140.2, 140.0, 129.9, 127.4, 126.8, 126.6, 123.6, 121.9, 117.4, 110.8, 86.7, 78.6, 73.6, 72.7, 62.5, 41.9, 33.2, 16.0, 14.6, 9.6; ESI-MS *m/z*: 557 (MH^+), 579 (MNa^+); HPLC purity 96.9%.

4.1.5.17. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(4-ethoxy-4-oxobutanoyl)amino]-β-D-glucopyranosyl}-1*H*-indole (6q). The title compound was obtained from **5** with ethyl succinyl chloride according to the general procedure in 56% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.47 (dd, J = 8.0, 0.8 Hz, 1H), 7.11–6.94 (m, 7H), 5.38 (d, J = 9.2 Hz, 1H), 4.28 (s, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.82 (t, J = 9.2 Hz, 1H), 3.65 (dd, J = 14.0, 2.4 Hz, 1H), 3.58–3.53 (m, 2H), 3.36–3.26 (m, 2H), 2.56–2.53 (m, 2H), 2.43–2.39 (m, 2H), 1.88–1.82 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H), 0.93–0.88 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 175.2, 174.5, 142.7, 140.2, 140.0, 129.9, 127.4, 126.8, 126.6, 126.5, 123.6, 121.9, 117.4, 110.8, 86.7, 78.7, 78.5, 73.6, 72.7, 61.8, 41.7, 33.2, 31.4, 30.6, 15.9, 14.7, 9.6; ESI-MS *m/z*: 593 (MNa^+); HPLC purity 89.8%.

4.1.6. 1-{6-[(carboxyacetyl)amino]-6-deoxy-β-D-glucopyranosyl}-4-chloro-3-(4-cyclopropyl-benzyl)-1*H*-indole (6r). A 30% solution of NaOMe in MeOH (5 μL) and water were sequentially added to a solution of **6o** (30 mg, 0.055 mmol) in MeOH (1.0 mL) at room temperature. After being stirred 1 h, the reaction was diluted with MeOH and neutralized with acidic resin Dowex 50

W2-200. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 1/3) to provide **6r** (25 mg, 86%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.46 (dd, J = 8.4, 0.8 Hz, 1H), 7.12–6.95 (m, 7H), 5.39 (d, J = 8.8 Hz, 1H), 4.28 (s, 2H), 3.82 (dd, J = 9.2, 8.8 Hz, 1H), 3.74 (dd, J = 14.4, 2.8 Hz, 1H), 3.61 (ddd, J = 9.6, 6.8, 2.8 Hz, 1H), 3.56 (t, J = 9.2 Hz, 1H), 3.37 (dd, J = 14.4, 6.8 Hz, 1H), 3.35 (t, J = 9.6, 9.2 Hz, 1H), 3.23 (s, 2H), 1.89–1.82 (m, 1H), 0.93–0.88 (m, 2H), 0.64–0.61 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 171.6, 169.8, 142.7, 140.2, 140.0, 129.8, 127.4, 126.9, 126.6, 123.7, 121.9, 117.3, 110.8, 86.8, 78.6, 73.6, 72.7, 41.8, 33.1, 15.9, 9.5; ESI-MS *m/z*: 529 (MH^+), 551 (MNa^+); HPLC purity 96.0%.

4.1.7. General Procedure for the Synthesis of Compounds 7a–7d

7a and **7d**: Isocyanate (1.2 equiv) was added to a suspension solution of **5** (1.0 equiv) and potassium carbonate (5 equiv) in THF at room temperature. After 3 h, the reaction was quenched by the addition of H_2O and the resulting mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to provide the desired products **7a** and **7d**.

7b and **7c**: Isocyanate (1.2 equiv) was added to a suspension solution of **5** (1.0 equiv) in pyridine at room temperature. After 3~4 h, the reaction was concentrated under reduced pressure and the residue was purified by column chromatography to provide the desired products **7b** and **7c**.

4.1.7.1. 4-Chloro-1-(6-{[(2-chloroethyl)carbamoyl]amino}-6-deoxy- β-D-glucopyranosyl)-3-(4-cyclopropylbenzyl)-1*H*-indole (7a). The title compound was obtained from **5** with 2-chloroethyl isocyanate according to the general procedure in 53% yield. ^{1}H NMR (300 MHz, CD_3OD) : δ 7.45 (dd, J = 8.4, 0.9 Hz, 1H), 7.11–6.95 (m, 7H), 5.40 (d, J = 9.0 Hz, 1H), 4.29 (s, 2H), 3.81 (t, J = 9.0 Hz, 1H), 3.64–3.46 (m, 5H), 3.37–3.26 (m, 4H), 1.88–1.81 (m, 1H), 0.94–0.88 (m, 2H), 0.65–0.60 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 161.3, 142.8, 140.2, 140.0, 129.9, 127.5, 126.8, 126.63,

126.59, 123.7, 121.9, 117.4, 110.6, 86.7, 79.4, 78.6, 73.7, 72.6, 44.9, 43.2, 42.3, 33.2, 16.0, 9.5; ESI-MS *m/z*: 548 (MH^+), 570 (MNa^+); HPLC purity 92.7%.

4.1.7.2. 4-Chloro-1-(6-{[(3-chloropropyl)carbamoyl]amino}-6-deoxy- β-D-glucopyranosyl)-3-(4-cyclopropylbenzyl)-1*H*-indole (7b). The title compound was obtained from **5** with 3-chloropropyl isocyanate according to the general procedure in 59% yield. ^{1}H NMR (300 MHz, CD_3OD) : δ 7.44 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.11–6.95 (m, 7H), 5.40 (d, *J* = 9.0 Hz, 1H), 4.29 (s, 2H), 3.81 (t, *J* = 9.0 Hz, 1H), 3.63–3.46 (m, 5H), 3.32–3.26 (m, 2H), 3.17 (t, *J* = 6.6 Hz, 2H), 1.95–1.75 (m, 3H), 0.94–0.88 (m, 2H), 0.65–0.60 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 161.6, 142.8, 140.2, 140.0, 129.9, 127.5, 126.8, 126.62, 126.59, 123.7, 121.9, 117.5, 110.6, 86.7, 79.5, 78.6, 73.6, 72.6, 43.3, 42.4, 38.4, 34.2, 33.2, 15.9, 9.6; ESI-MS *m/z*: 562 (MH^+), 584 (MNa^+); HPLC purity 94.3%.

4.1.7.3. 4-Chloro-3-(4-cyclopropylbenzyl)-1-(6-deoxy-6-{[(ethoxycarbonylmethyl)carbamoyl]-amino}-β-D-glucopyranosyl)-1*H*-indole (7c). The title compound was obtained from **5** with ethyl isocyanatoacetate according to the general procedure in 56% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.46 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.11–7.03 (m, 4H), 7.01 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.97–6.94 (m, 2H), 5.39 (d, *J* = 9.2 Hz, 1H), 4.29 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.82 (dd, *J* = 9.2, 8.8 Hz, 1H), 3.79 (s, 2H), 3.61 (dd, *J* = 14.0, 2.8 Hz, 1H), 3.57 (t, *J* = 8.8 Hz, 1H), 3.56–3.52 (m, 1H), 3.37–3.28 (m, 2H), 1.88–1.82 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.93–0.88 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 172.8, 161.4, 142.7, 140.2, 140.0, 129.8, 127.4, 126.8, 126.6, 126.5, 123.7, 121.8, 117.4, 110.7, 86.8, 79.4, 78.5, 73.7, 72.5, 62.3, 42.9, 42.3, 33.1, 15.9, 14.6, 9.6; ESI-MS *m/z*: 594 (MNa^+); HPLC purity 90.5%.

4.1.7.4. 4-Chloro-3-(4-cyclopropylbenzyl)-1-(6-deoxy-6-{[(ethoxycarbonyl)carbamoyl]amino}-β-D-glucopyranosyl)-1*H*-indole (7d). The title compound was obtained from **5** with ethyl isocyanatoformate according to the general procedure in 48% yield. ^{1}H NMR (400 MHz, CD_3OD):

δ 7.42 (dd, J = 8.0, 0.8 Hz, 1H), 7.10–6.94 (m, 7H), 5.36 (d, J = 9.2 Hz, 1H), 4.27 (s, 2H), 4.01 (q, J = 7.2 Hz, 2H), 3.80 (dd, J = 9.2, 8.8 Hz, 1H), 3.59–3.51 (m, 3H), 3.33–3.21 (m, 2H), 1.87–1.81 (m, 1H), 1.16 (t, J = 7.2 Hz, 3H), 0.92–0.83 (m, 2H), 0.63–0.59 (m, 2H); APCI-MS m/z: 556 $(M-H)^-$; HPLC purity 100%.

4.1.8. General Procedure for the Synthesis of Compounds 8a–8e

8a: Isothiocyanate (1.2 equiv) was added to a suspension solution of **5** (1.0 equiv) and potassium carbonate (5 equiv) in THF at room temperature. After 3 h, the reaction was quenched by the addition of H_2O and the resulting mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to provide the desired product **8a**.

8b–**8e**: Isocyanate (1.2 equiv) was added to a suspension solution of **5** (1.0 equiv) in pyridine at room temperature. After 3~6 h, the reaction was concentrated under reduced pressure and the residue was purified by column chromatography to provide the desired products **8b**–**8e**.

4.1.8.1. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(methylcarbamothioyl)amino]-β-D-glucopyranosyl}-1*H*-indole (8a). The title compound was obtained from **5** with methyl isothiocyanate according to the general procedure in 69% yield. ^{1}H NMR(400 MHz, CD_3OD): δ 7.44 (dd, J = 8.4, 0.8, Hz, 1H), 7.11–7.00 (m, 5H), 6.97–6.94 (m, 2H), 5.41 (d, J = 9.2 Hz, 1H), 4.29 (s, 2H), 4.00–3.56 (m, 3H), 3.82 (t, J = 9.2 Hz, 1H), 3.58 (t, J = 9.2 Hz, 1H), 3.36 (t, J = 9.2 Hz, 1H), 2.81 (brs, 3H), 1.89–1.82 (m, 1H), 0.93–0.88 (m, 2H), 0.64–0.60 (m, 2H); ESI-MS *m/z*: 516 (MH^+), 538 (MNa^+); HPLC purity 100%.

4.1.8.2. 4-Chloro-3-(4-cyclopropylbenzyl)-1-{6-deoxy-6-[(ethylcarbamothioyl)amino]-β-D-glucopyranosyl}-1*H*-indole (8b). The title compound was obtained from **5** with ethyl isothiocyanate according to the general procedure in 71% yield. ^{1}H NMR (400 MHz, CD_3OD) : δ

7.44 (dd, *J* = 8.0, 0.8, Hz, 1H), 7.11–7.04 (m, 4H), 7.02 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.98–6.94 (m, 2H), 5.42 (d, *J* = 9.2 Hz, 1H), 4.29 (s, 2H), 4.00–3.57 (m, 3H), 3.83 (t, *J* = 9.2 Hz, 1H), 3.59 (t, *J* = 9.2 Hz, 1H), 3.40–3.30 (m, 2H), 3.36 (t, *J* = 9.2 Hz, 1H), 1.88–1.82 (m, 1H), 0.99 (brs, 3H), 0.93–0.88 (m, 2H), 0.64–0.60 (m, 2H); ESI-MS *m/z*: 530 (MH^+), 552 (MNa^+); HPLC purity 99.2%.

4.1.8.3. 4-Chloro-3-(4-cyclopropylbenzyl)-1-(6-deoxy-6-{[(ethoxycarbonylmethyl)carbamothioyl]amino}-β-D-glucopyranosyl)-1*H*-indole (8c). The title compound was obtained from **5** with ethyl isothiocyanatoacetate according to the general procedure in 58% yield. ^{1}H NMR (400 MHz, CD_3OD): *δ* 7.45 (d, *J* = 8.4 Hz, 1H), 7.11–7.05 (m, 4H), 7.01 (dd, *J* = 7.6, 0.8, Hz, 1H), 6.97–6.95 (m, 2H), 5.42 (d, *J* = 9.2 Hz, 1H), 4.28 (s, 2H), 4.26–4.00 (m, 5H), 3.83 (t, *J* = 9.2 Hz, 1H), 3.80–3.71 (m, 1H), 3.69–3.65 (m, 1H), 3.58 (t, *J* = 9.2 Hz, 1H), 3.38 (t, *J* = 9.2 Hz, 1H), 1.88–1.82 (m, 1H), 1.22 (t, *J* = 6.8 Hz, 3H), 0.93–0.88 (m, 2H), 0.64–0.61 (m, 2H); ESI-MS *m/z*: 588 (MH^+), 610 (MNa^+); HPLC purity 95.8%.

4.1.8.4. 4-Chloro-3-(4-cyclopropylbenzyl)-1-(6-deoxy-6-{[(3-methoxypropyl)carbamothioyl]amino}-β-D-glucopyranosyl)-1*H*-indole (8d). The title compound was obtained from **5** with 3-methoxypropyl isothiocyanate according to the general procedure in 50% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.43 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.11–6.94 (m, 7H), 5.42 (d, *J* = 9.0 Hz, 1H), 4.28 (s, 2H), 4.00–3.54 (m, 3H), 3.82 (t, *J* = 9.0 Hz, 1H), 3.57 (t, *J* = 9.0 Hz, 1H), 3.37–3.30 (m, 1H), 3.33 (s, 3H), 3.20 (brs, 4H), 1.90–1.84 (m, 1H), 1.59 (brs, 2H), 0.93–0.86 (m, 2H), 0.67–0.61 (m, 2H); ESI-MS *m/z*: 596 (MNa^+); HPLC purity 98.1%.

4.1.8.5. 4-Chloro-3-(4-cyclopropylbenzyl)-1-(6-deoxy-6-{[(4-methoxyphenyl)carbamothioyl]amino}-β-D-glucopyranosyl)-1*H*-indole (8e). The title compound was obtained from **5** with 4-chlorophenyl isothiocyanate according to the general procedure in 61% yield. ^{1}H NMR (400 MHz, CD_3OD): *δ* 7.47 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.12–7.01 (m, 7H), 6.97–6.92 (m, 4H), 5.46 (d, *J* = 9.2 Hz, 1H), 4.30 (s, 2H), 4.40-4.20 (m, 1H), 3.87 (t, *J* = 8.0 Hz, 1H), 3.78 (ddd, *J* = 10.0, 7.2, 2.8 Hz,

1H), 3.61 (t, *J* = 9.2 Hz, 1H), 3.64–3.57 (m, 1H), 3.37 (t, *J* = 9.2 Hz, 1H), 1.86–1.80 (m, 1H), 0.91–0.86 (m, 2H), 0.62–0.58 (m, 2H); ESI-MS *m/z*: 612 (MH^+), 634 (MNa^+); HPLC purity 100%.

4.2. In Vitro Human SGLT Inhibition Assays[21,27,28]

The transporter assays were performed according to the method from Castaneda and Kinne with some modification, which are published as supplementary material.

4.3. In Vivo Efficacy and Pharmacokinetics Evaluations of 6a and 6o in Rats[21,29]

The assessments of urinary glucose excretion and pharmacokinetics were performed using previously reported procedures. For the Oral Glucose Tolerance Test of **6a**, blood glucose levels of rats were monitored at 0, 0.5, 1, 1.5, 2, 3, 4 and 5 h after the oral glucose challenge. The detailed description of these experiments is published as supplementary material.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Graphical abstract

N-Indolylglycosides Bearing Modifications at the Glucose C6-Position as Sodium-Dependent Glucose Co-transporter 2 Inhibitors

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