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Discovery of Novel *N*-β-D-Xylosylindole Derivatives as Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitors for the Management of Hyperglycemia in Diabetes

Chun-Hsu Yao, Jen-Shin Song, Chiung-Tong Chen, Teng-Kuang Yeh, Ming-Shiu Hung, Chih-Chun Chang, Yu-Wei Liu, Mao-Chia Yuan, Chieh-Jui Hsieh, Chung-Yu Huang, Min-Hsien Wang, Ching-Hui Chiu, Tsung-Chih Hsieh, Szu-Huei Wu, Wen-Chi Hsiao, Kuang-Feng Chu, Chi-Hui Tsai, Yu-Sheng Chao, and Jinq-Chyi Lee*

Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes, No. 35, Keyan Road, Zhunan Town, Miaoli County 35053, Taiwan, R.O.C.

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A novel series of *N*-linked β-D-xylosides were synthesized and evaluated for inhibitory activity against sodium-dependent glucose cotransporter 2 (SGLT2) in a cell-based assay. Of these, the 4-chloro-3-(4-cyclopropylbenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole **19m** was found to be the most potent inhibitor, with an EC_{50} value similar to that of the natural SGLT2 inhibitor phlorizin. Further studies in Sprague−Dawley (SD) rats indicated that **19m** significantly increased urine glucose excretion in a dose-dependent manner with oral administration. The antihyperglycemic effect of **19m** was also observed in streptozotocin (STZ) induced diabetic SD rats. These results described here are a good starting point for further investigations into *N*-glycoside SGLT2 inhibitors.

Introduction

Type 2 or non-insulin dependent diabetes mellitus (NIDDM[a]) is a metabolic disorder characterized by both fasting and postprandial hyperglycemia. Almost all type 2 diabetes patients display with varying degrees both insulin resistance and relative insulin deficiency.[1] Untreated hyperglycemics are at risk of micro- and macrovascular complications including retinopathy, nephropathy, neuropathy, stroke, amputation, and myocardial infarction.[2] Although a wide range of medications are prescribed for type 2 diabetes, recent studies suggest that only about one-third of patients treated for type 2 diabetes achieved the glycemic target, glycosylated hemoglobin (HbA1c) of $<7\%$.[3,4] Thus, development of novel molecules with new modes of action to supplement the older therapies for treating patients with uncontrolled type 2 diabetes is required.

Under normal circumstances, and in healthy individuals, approximately 180 g of glucose is filtered daily in the kidney glomerulus and nearly all the filtered plasma glucose (>99%) is reabsorbed by two sodium-dependent glucose cotransporters (SGLTs), SGLT1 and SGLT2, in the renal proximal tubules.[5,6] The SGLTs are members of the solute carrier family 5A (SLC5A), which is involved in the transport of sugars, amino acids, vitamins, iodide, ions, neurotransmitters, and osmolytes across the renal and intestinal membranes.[7] The SLC5A gene family contains 12 constituents, of which only some transport glucose and the most important and well studied being SGLT1 and SGLT2. It is estimated that 90% of glomerular filtrate reabsorption is mediated by high-capacity, low-affinity SGLT2 located on the S1 segment of the proximal tubule; the remaining 10% is accomplished by low-capacity, high-affinity SGLT1 mainly expressed in the small intestine but also presented in the S3 segment of the proximal tubule. Inhibition of SGLT1 and SGLT2 is thus expected to suppress the renal glucose reabsorption and increase the excretion of urinary sugar and consequentially reduce glycemic levels. However, reports of the studies on genetic mutations in the SGLT1 gene indicated that glucose−galactose malabsorption syndrome is a serious consequence for afflicted individuals, and no apparent glucosuria is observed.[8−10] In contrast, persistent renal glucose excretion is the sole phenotype for those who have SGLT2 mutations with no other adverse effects known to be associated with the variants.[11,12] The observation suggests that SGLT2 is responsible for the majority of renal glucose reabsorption and that selective SGLT2 inhibitors would be desired for avoiding gastrointestinal side effects involved in SGLT1 inhibition.

The natural product β-*O*-glucoside phlorizin **1** was isolated from the root bark of the apple tree in 1835 and subsequently identified as the first SGLT inhibitor (Figure 1).[13] There is evidence that phlorizin can induce renal glucose excretion by suppressing the reabsorption and therefore reduce plasma glucose levels, but owing to its lack of selectivity toward SGLT1 and poor metabolic stability in the presence of *O*-glucosidase, it was not considered to be an antidiabetic drug candidate. By use of structure−activity relationships (SARs), several new compounds have been developed as SGLT2 inhibitors and studied in clinical trials, including the *O*-glucosides T-1095 **2b**, sergliflozin **3b**, and remogliflozin etabonate **4b**.[14−16] Designed as prodrugs to avoid degradation by glucosidase within the gastrointestinal tract, they required relatively high dosage in the clinic, and all clinical studies have been discontinued because of poor selectivity, poor efficacy, and lack of competitive

*To whom correspondence should be addressed. Phone: +886-37-246166, extension 35781. Fax: +886-37-586456. E-mail: jinqchyi@nhri.org.tw.

[a]Abbreviations: AMG, [^{14}C]-labeled α-methyl-D-glucopyranoside; CHO, Chinese hamster ovary; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; HbA1c, glycosylated hemoglobin; NIDDM, non-insulin dependent diabetes mellitus; SAR, structure−activity relationship; SD, Sprague−Dawley; SGLT, sodium-dependent glucose cotransporter; SLC5A, solute carrier family 5A; STZ, streptozotocin.

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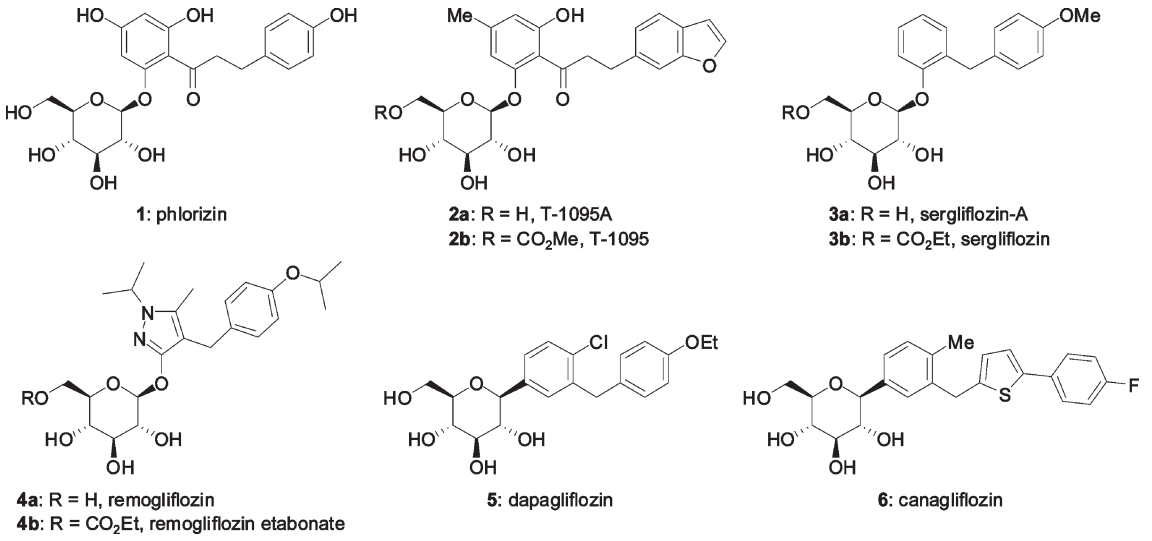


Figure 1. Structures of known SGLT2 inhibitors.

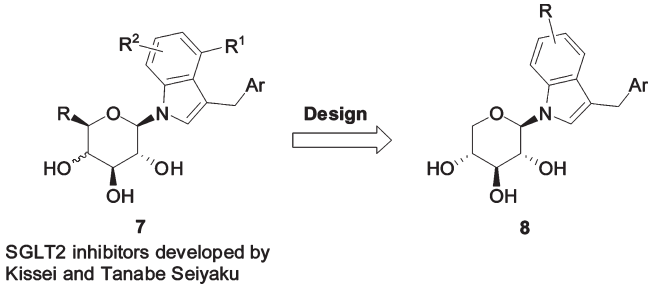


Figure 2. Design of *N*-indolylxyloside SGLT2 inhibitors.

advantage.[17−19] In contrast, *C*-glucosides are more metabolically stable and combine higher oral bioavailability and plasma exposure. Dapagliflozin **5** and canagliflozin **6** are the corresponding *C*-aryl glucosides, which present good in vitro and in vivo potencies against SGLT2 and are currently in phase III clinical trials.[20−22] *N*-Glucosides are another series of SGLT2 inhibitors expected with greater metabolic stability compared to *O*-glucosides, but evaluation of their therapeutic potentials is difficult because no pharmacokinetic data or clinical results have been presented.[23] The absence of advanced studies left us curious about the role of the *N*-glycoside SGLT2 inhibitors in the treatment of type 2 diabetes.

Building on the encouraging disclosures of Tanabe Seiyaku and Kissei,[24−26] we initiated our program to explore the *N*-glycoside SGLT2 inhibitors **8**, in which the aglycone is a 3-substituted indole and the sugar unit is D-xylose instead of the original D-glucose (Figure 2). D-Xylose is a natural pentose, obtained from plants cell walls and fiber, which has the same configuration at C-1, -2, -3, and -4 as D-glucose. Recently, Lexicon Pharmaceuticals reported a series of SGLT2 inhibitors wherein the glucose was replaced with L-xylose and the resulting *O*-xylosides found to be potent in vitro and in vivo.[27] The structural similarity of D-xylose versus D-glucose and the positive results of *O*-xylosides suggested to us that the use of *N*-linked β-D-xylosides to inhibit SGLT2 would be feasible. Herein, we describe the design, synthesis, and SAR of the newly developed *N*-linked β-D-xylosides, as well as the pharmacokinetic and animal studies for selected compound.

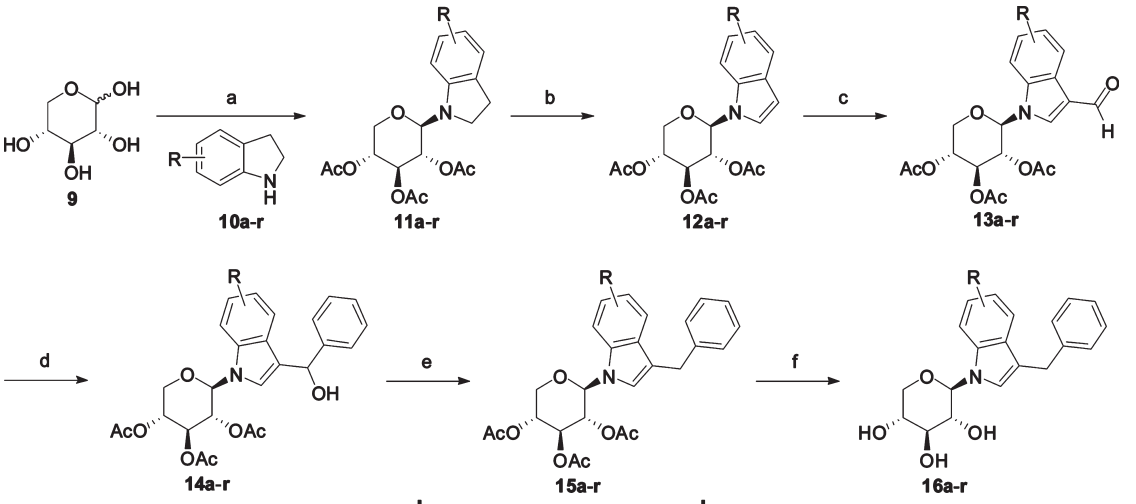
Chemistry

The novel *N*-xylosides detailed in this account were synthesized according to the well-established chemistry of Kissei and Tanabe Seiyaku, with appropriate modifications.[24−26] As shown in Scheme 1, condensation of D-xylose **9** with freshly prepared or commercially available indolines **10a**−**r** at 50 °C gave the β-linked D-xylosylindoline, which in turn, without purification, underwent per-*O*-acetylation with acetic anhydride in pyridine to furnish the fully protected β-xylosylindoline **11a**−**r**. Initially, we took advantage of the strategy described by Tanade Seiyaku, namely, treatment of D-xylose **9** with indoline **10a** in mixed solvent under reflux conditions. Although this method worked well for *N*-glucosides, it failed to introduce the indoline into xylose, giving instead an intractable mixture of products. Compounds **11a**−**r** were then subjected to oxidation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford the indole derivatives **12a**−**r**, from which the indole-3-carboxaldehydes **13a**−**r** were obtained through a Vilsmeier−Haack formylation with $POCl_3$ in DMF.[28] Grignard reaction of compounds **13a**−**r** with phenylmagnesium bromide to introduce the distal aryl ring followed by reduction of the resulting alcohols **14a**−**r** with triethylsilane (Et_3SiH) and boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) gave the corresponding diarylmethanes **15a**−**r**. Finally, the acetyl groups were removed under Zemplén conditions to provide the desired β-linked *N*-xylosides **16a**−**r**.

The same synthetic strategy was applied to prepare 4-chloroindolyl-*N*-xylosides **19a**−**q** over three steps using **13j** as starting material (Scheme 2). Addition of various Grignard reagents to **13j** introduced the substituted or nonsubstituted aryl, heteroaryl, and benzofused rings at the distal ring position. The resulting alcohols **17a**−**q** were then reduced under standard conditions (Et_3SiH and $BF_3 \cdot OEt_2$) to generate **18a**−**q**, which were hydrolyzed with sodium methoxide to yield the desired products **19a**−**q**.

Scheme 3 depicts the synthetic strategy for the installation of various alkoxy substitutes at the para-position of the distal phenyl ring. A Lewis acid mediated brominolysis of **18c** with boron tribromide (BBr_3) to convert the methoxy group into the corresponding phenol, followed by Zemplén deacetylation with sodium methoxide, provided the intermediate **20**. Further alkylation of **20** was performed in the presence of either

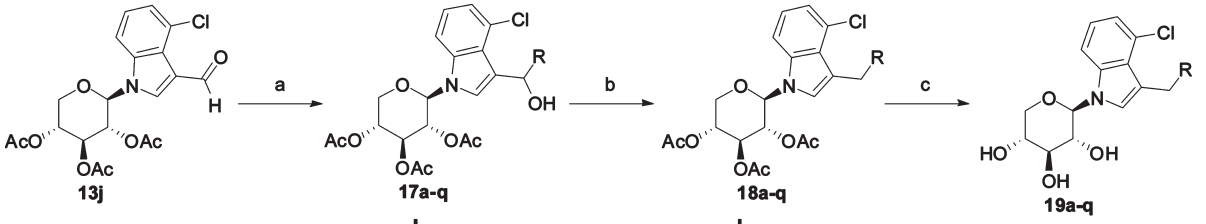
Scheme 1. Synthesis of *N*-Xylosides **16a**−**r**[a]

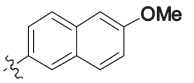
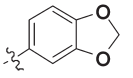
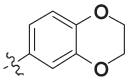


compd	R	compd	R	compd	R
16a	H	**16g**	5-F	**16m**	7-Cl
16b	4-Me	**16h**	6-F	**16n**	4-Br
16c	5-Me	**16i**	7-F	**16o**	4-NO_2
16d	6-Me	**16j**	4-Cl	**16p**	4-OMe
16e	7-Me	**16k**	5-Cl	**16q**	4-OH
16f	4-F	**16l**	6-Cl	**16r**	5-F, 6-Cl

[a] Reagents and conditions: (a) (i) indolines **10a**−**r**, EtOH, H_2O, 50 °C, 24 h; (ii) Ac_2O, pyridine, 0 °C to room temp, 16 h; (b) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 1,4-dioxane, room temp, 18 h; (c) $POCl_3$, DMF, 75 °C, 1 h; (d) phenylmagnesium bromide, THF, −78 °C, 1−3 h; (e) $BF_3 \cdot OEt_2$, Et_3SiH, CH_2Cl_2, CH_3CN, 0 °C, 1−3 h; (f) NaOMe, MeOH, CH_2Cl_2, 0 °C to room temp, 2 h.

Scheme 2. Synthesis of *N*-Xylosides **19a**−**q**[a]

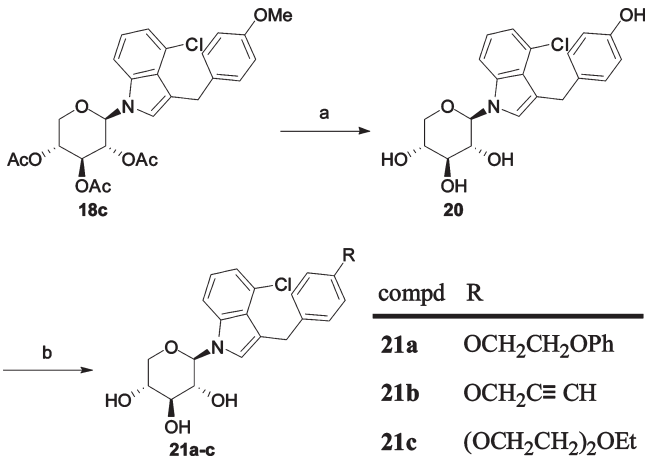


compd	R	compd	R	compd	R
19a	2-OMe-Ph	**19h**	4-^{i}Pr-Ph	**19o**	
19b	3-OMe-Ph	**19i**	4-^{n}Pr-Ph		
19c	4-OMe-Ph	**19j**	4-Ph-Ph	**19p**	
19d	3-F-Ph	**19k**	4-SMe-Ph		
19e	4-F-Ph	**19l**	4-[$N(CH_3)_2$]-Ph	**19q**	
19f	2,4-diOMe-Ph	**19m**	4-cyclopropyl-Ph		
19g	3-F, 4-OMe-Ph	**19n**	2-thienyl		

[a] Reagents and conditions: (a) Grignard reagents, THF, −78 °C, 1−3 h; (b) $BF_3 \cdot OEt_2$, Et_3SiH, CH_2Cl_2, CH_3CN, 0 °C, 1−3 h; (c) NaOMe, MeOH, CH_2Cl_2, 0 °C to room temp, 2 h.

cesium or potassium carbonate and alkyl bromides to afford the corresponding *N*-xylosides **21a** and **21b**. In addition, **21c** was prepared by alkylation of **20** with 2-(2-ethoxyethoxy)-ethyl mesylate. Purity of all the final compounds was found

Scheme 3. Synthesis of *N*-Xylosides **20** and **21a−c**[a]



[a] Reagents and conditions: (a) (i) 1 M solution of BBr_3 in CH_2Cl_2, CH_2Cl_2, −78 to 0 °C, 4 h; (ii) NaOMe, MeOH, CH_2Cl_2, 0 °C to room temp, 2 h; (b) for **21a**, Cs_2CO_3, 2-phenoxyethyl bromide, DMF, room temp, 17 h; for **21b**, K_2CO_3, propargyl bromide, DMF, room temp, 21 h; for **21c**, Cs_2CO_3, $CH_3CH_2(OCH_2CH_2)_2OMs$, DMF, room temp, 2 days.

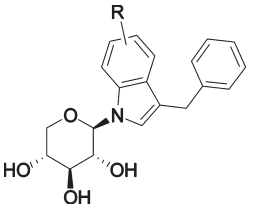
to be more than 95% unless otherwise stated, as measured by reverse phase HPLC on a C_{18} column (see Supporting Information).

Results and Discussion

All the synthesized *N*-xylosides **16a−r**, **19a−q**, **20**, and **21a−c** were evaluated for their in vitro inhibitory activity against human SGLT2 (hSGLT2); the results are presented in Tables 1−3. EC_{50} values were calaulated 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 hSGLT2.[29] Because the difference of protein expression levels of cells will result in the difference of EC_{50} values, phlorizin **1** and dapagliflozin **5** were used as reference compounds in the in vitro activity evaluation system.

We began with the SAR studies on the effect of the indole moiety by fixing the phenyl ring in the distal position; the results are presented in Table 1. The unsubstituted indolyl analogue **16a** (EC_{50} = 7129 nM) was used as a template, to which all structural modifications were compared. First, we attempted to introduce an electron donating methyl group (**16b−e**) at various positions of the indole moiety. The 4-methyl substitution (**16b**) was found to exhibit 6.5 times the potency against hSGLT2 (EC_{50} = 1307 nM) compared to **16a**, whereas substitution at the 5-position (**16c**) resulted in drastic loss of potency (EC_{50} = 40589 nM). When the methyl group was replaced with an electron-withdrawing fluoro (**16f−i**) or chloro (**16j−m**) group, the same trend was observed: the 4-substituted indole moiety exhibited enhanced activity toward hSGLT2 compared with the 5, 6, or 7-substituted moiety. Of the aforementioned xylosides, the 4-chloro analogue **16j** was the most potent hSGLT2 inhibitor, with an EC_{50} value of 865 nM. On the basis of the above results, more functional groups were incorporated at the 4- position and the potency of these molecules evaluated. The inhibition exhibited by 4-bromoindolylxyloside **16n** (EC_{50} = 923 nM) was found to be the same as that exhibited by 4-chloro analogue **16j**. Substitution at the 4-position with the strongly electron-withdrawing nitro group (**16o**) resulted in 2-fold less potency compared to **16j**. Regarding strongly electron-donating substituents, the 4-methoxy analogue **16p** showed similar activity compared to the unsubstituted indolyl analogue **16a**, and the xyloside with a 4-hydroxy group (**16q**) was significantly less potent (EC_{50} > 50 000 nM). The disubstituted compound **16r** was also prepared but proved to be an ineffective inhibitor (EC_{50} = 8600 nM).

Table 1. In Vitro Inhibitory Activity of *N*-Xylosides **16a−r** on hSGLT2

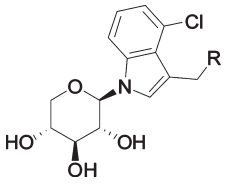


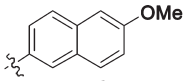
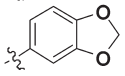
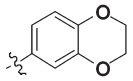
compd	R	hSGLT2 EC_{50} (nM)[a]
16a	H	7129 ± 1033
16b	4-Me	1094 ± 153
16c	5-Me	40589 ± 10644
16d	6-Me	3033 ± 911
16e	7-Me	12956 ± 4319
16f	4-F	2237 ± 353
16g	5-F	12415 ± 1612
16h	6-F	23627 ± 1412
16i	7-F	9821 ± 2407
16j	4-Cl	865 ± 266
16k	5-Cl	28217 ± 8178
16l	6-Cl	10279 ± 976
16m	7-Cl	10680 ± 3675
16n	4-Br	923 ± 92
16o	4-NO_2	1819 ± 590
16p	4-OMe	5487 ± 1865
16q	4-OH	> 50000
16r	5-F, 6-Cl	8600 ± 2723
1		108 ± 21[b]
5		3 ± 0.7[b]

[a] The data were obtained from at least two independent experiments. [b] The data were obtained from multiple independent experiments.

With the identification of potent compound **16j**, we next turned our attention to the optimization of the distal phenyl ring by evaluation of substituents at various positions and the use of benzofused and heteroaryl rings. Encouragingly, it was found that when the methoxy group was placed in the para-position, the resulting compound **19c** showed significantly more potency with an EC_{50} value of 275 nM (Table 2). In contrast, shifting the methoxy group to the ortho- (**19a**) and meta-position (**19b**) led to a 47-fold and 3-fold loss in hSGLT2 inhibitory activity, respectively, compared to **19c**. Incorporation of the electron-withdrawing fluoro group onto the phenyl ring gave compounds **19d** and **19e**, which are inferior inhibitors of hSGLT2 compared with **19c**. Retaining the essential *p*-methoxy group, and adding an *o*-methoxy group gave compound **19f** which showed a drastic loss of activity (EC_{50} = 30931 nM). Replacing the *o*-methoxy group with a *m*-fluoro group (**19g**) led to a slight decrease in activity, indicating that monosubstitution at para-position of the phenyl ring is optimal. We also replaced the *p*-methoxyphenyl group with different benzofused rings such as 6-methoxynaphthalene (**19o**), benzodioxole (**19p**), and benzodioxane (**19q**). It was observed that compounds **19o** and **19p** showed 2- to 3-fold loss of activity compared to **19c**, but the benzodioxane analogue **19q** exhibited similar inhibitory activity to **19c**, with an EC_{50} value of 233 nM. Moreover, decreased activity was observed when the heteroaromatic group, thiophene (**19n**), was attached in place of the *p*-methoxyphenyl ring. This result clearly reveals

Table 2. In Vitro Inhibitory Activity of *N*-Xylosides **19a−g** and **19n−q** on hSGLT2



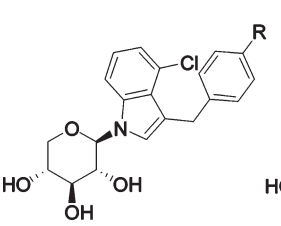
compd	R	hSGLT2 EC_{50} (nM)[a]
16j	Ph	865 ± 266
19a	2-OMe-Ph	12915 ± 3616
19b	3-OMe-Ph	893 ± 79
19c	4-OMe-Ph	275 ± 41
19d	3-F-Ph	1161 ± 227
19e	4-F-Ph	1376 ± 100
19f	2,4-diOMe-Ph	30931 ± 9458
19g	3-F, 4-OMe-Ph	473 ± 36
19n	2-thienyl	1682 ± 19
19o		633 ± 156
19p		863 ± 149
19q		233 ± 29
1		108 ± 21[b]
5		3 ± 0.7[b]

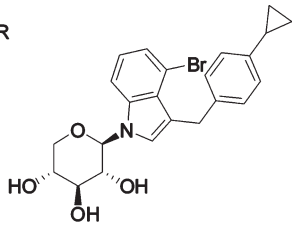
[a] The data were obtained from at least two independent experiments. [b] The data were obtained from multiple independent experiments.

the importance of the para-substituted nature of the phenyl ring of *N*-xylosides for good inhibitory activity. The effect of substituents on the distal phenyl ring was further explored in order to identify the optimal substituent at the para-position.

As illustrated in Table 3, replacing the *p*-methoxy group with an isopropyl (**19h**) or *n*-propyl (**19i**) group weakened hSGLT2 inhibition 5-fold. Substitution with the more bulky 4-phenyl group (**19j**) resulted in drastic loss of potency. When the methylthio group was substituted for the methoxy group, the resulting xyloside **19k** was a slightly less potent hSGLT2 inhibitor, with an EC_{50} value of 426 nM. Introduction of strongly electron-donating groups such as *N*,*N*-dimethylamino or hydroxyl groups at the para-position led to xylosides **19l** and **20**, the potency of which was similar to **19c**. Furthermore, capping of the hydroxyl group with various alkyl chains (**21a−c**) led to a decrease in activity, suggesting that a longer alkyl chain may not be tolerated at the para-position. It is noteworthy that when the *p*-cyclopropyl substituent was introduced (**19m**), the activity improved slightly and the potency was similar to that of phlorizin **1** with an EC_{50} value of 161 nM. On the other hand, **16n** (EC_{50} = 923 nM) and **16j** (EC_{50} = 865 nM) were identified with the same inhibitory potency

Table 3. In Vitro Inhibitory Activity of *N*-Xylosides **19h−m** and **20−22** on hSGLT2





22

compd	R	hSGLT2 EC_{50} (nM)[a]
19c	OMe	275 ± 41
19h	^{i}Pr	1288 ± 135
19i	^{n}Pr	1410 ± 177
19j	Ph	11137 ± 2277
19k	SMe	426 ± 46
19l	$N(CH_3)_2$	297 ± 4
19m	cyclopropyl	161 ± 7
20	OH	255 ± 71
21a	OCH_2CH_2OPh	1334 ± 154
21b	$OCH_2C{\equiv}CH$	530 ± 77
21c	$(OCH_2CH_2)_2OEt$	577 ± 49
22		241 ± 45
1		108 ± 21[b]
5		3 ± 0.7[b]

[a] The data were obtained from at least two independent experiments. [b] The data were obtained from multiple independent experiments.

toward hSGLT2. The 4-bromoindolyl-*p*-cyclopropyl derivative **22** was hence prepared to evaluate the corresponding biological activity for comparison purposes. Little difference in potency was observed between xyloside **19m** (EC_{50} = 161 nM) and **22** (EC_{50} = 241 nM).

Compounds with good hSGLT2 inhibition were selected for further study of their selectivity for hSGLT1 over hSGLT2. The results are presented in Table 4. By use of the same protocol for the hSGLT2 inhibition measurement, the EC_{50} values of hSGLT1 were obtained by measuring inhibition of the sodium-dependent uptake of [^{14}C]AMG into CHO cells stably expressing hSGLT1.[29,30] Unfortunately, all the SGLT2 inhibitors tested showed no significant selectivity for hSGLT2 versus hSGLT1 (hSGLT1/hSGLT2 = 0.8−2.1). Among them, compound **19l** with a *p*-*N*,*N*-dimethylamino substituent was found to be the least potent inhibitor in suppressing the reuptake of hSGLT1 with an EC_{50} = 628.8 nM. The selectivity for hSGLT2 over hSGLT1 was 2.1.

Among the aforementioned *N*-xylosides, the most potent SGLT2 inhibitor **19m** was chosen for further pharmacokinetic and animal studies.[20] Administration of a single 1 mg/kg intravenously to rats revealed that **19m** has the low clearance and good oral bioavailability in rats, indicating that **19m** is stable (Table 5). Our in vitro metabolic stability study also suggested that **19m** was resistant upon metabolic incubation with about 100% remaining after 30 min of rat microsomal incubation (data not shown). After oral administration of a 1 mg/kg dose of **19m** to rats, a C_{max} of 1631 ng/mL was attained at 2 h. The elimination half-life of **19m** was 4.1 h in rats.

As shown in Figure 3A, statistically significant dose-dependent efficacy on increasing urine glucose excretion of doses ranging from 3 to 50 mg/kg of **19m** was measured, resulting in a 12- to 783-fold elevation in glucosuria relative to the vehicle control. Oral administration of compound **19m** in a single dose of 3, 10, 30, and 50 mg/kg to SD rats induced urine

Table 4. In Vitro hSGLT Inhibition and Selectivity Data for *N*-Xylosides **19c**, **19k**−**m**, **19q**, **20**, and **22**

compd	hSGLT2 EC_{50} (nM)	hSGLT1 EC_{50} (nM)[a]	selectivity hSGLT1/hSGLT2
19c	275 ± 41	229.5 ± 28.8	0.8
19k	426 ± 46	461.6 ± 53.9	1.1
19l	297 ± 4	628.8 ± 111.7	2.1
19m	161 ± 7	208.6 ± 17.2	1.3
19q	233 ± 29	305.9 ± 87.7	1.3
20	255 ± 71	233.9 ± 41.5	0.9
22	241 ± 45	327.3 ± 74.5	1.4
1	108 ± 21	197.4 ± 69.7[b]	1.8
5	3 ± 0.7	482.5 ± 116.8[b]	161

[a] The data were obtained from a single experiment. [b] The data were obtained from three independent experiments.

Table 5. Pharmacokinetic Properties of *N*-Xyloside **19m** after Oral and Intravenous Administration to Rats

parameter	unit	iv	po
dose	mg/kg	1.0	1.0
$T_{1/2}$	h	3.6	4.1
clearance	mL/min/kg	1.2	
V_{ss}	L/kg	0.32	
C_{max}	ng/mL		1631.3
T_{max}	h		2.0
$AUC_{(0-inf)}$	ng·h/mL	14787	8370
F	%		56.3

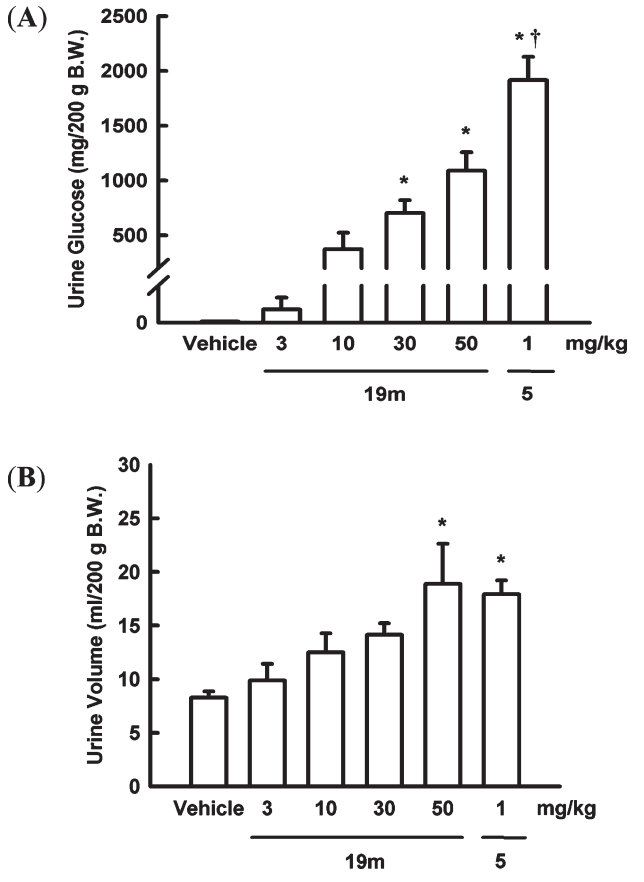


Figure 3. Dose-dependent response of *N*-xyloside **19m** over 24 h in normal Sprague−Dawley rats: (A) urine glucose excretion; (B) urine volume. Data are expressed as the mean ± SEM (n = 4/group): ∗, $P < 0.05$ vs vehicle.

glucose excretions of 2, 19, 372, and 701 mg of glucose per 200 g of body weight over 24 h, respectively. Urine volumes were also

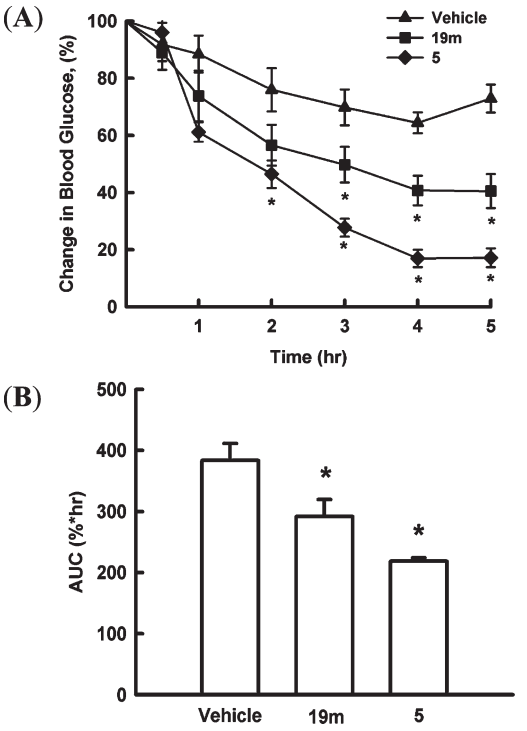


Figure 4. Antihyperglycemic effect of single oral dosing (10 mg/kg) of **19m** and dapagliflozin **5** in STZ-induced diabetic Sprague−Dawley rats: (A) change in blood glucose levels; (B) suppression of glucose AUC. Data are expressed as the mean ± SEM (n = 3/group): ∗, $P < 0.05$ vs vehicle.

measured in the glucosuria experiment, and the results are shown in Figure 3B. Compound **19m** was found to increase urine volume in a dose-dependent manner. For assessment of the antihyperglycemic effect, streptozotocin (STZ) induced (STZ at 65 mg/kg, ip) diabetic SD rats (blood glucose of >450 mg/dL) were used to evaluate the capacity of **19m** to lower blood glucose. Blood samples were obtained from the tail vein at 0, 0.5, 1, 2, 3, 4, and 5 h after a single oral administration of **19m** (10 mg/kg), **5** (10 mg/kg), or vehicle for blood glucose analysis. Figure 4A illustrates the gradual decrease in blood glucose level during the observation period of 5 h. The areas under the glucose levels versus time curve (AUC) were calculated (Figure 4B); **19m** at 10 mg/kg was found to cause a 24% reduction in blood glucose level compared with the control.

It was found that **19m** significantly increased urine glucose excretion and urine volume. Although **19m** increased urine glucose excretion less than **5**, **19m** was equally effective at increasing urine volume excretion. Furthermore, the antihyperglycemic effects of **19m** and **5** at the same dose of 10 mg/kg were not significantly different. The diarrheogenic activity test for **19m** was also carried out to explore the possible adverse effects involved in the lack of selectivity for hSGLT2 versus hSGLT1. Herein no diarrhea was observed in the **19m**-treated mice within 8 h after the oral administration with a single dose at a range of 10, 50, and 200 mg/kg.

Conclusions

The synthesis and structure−activity relationships of *N*-linked β-D-xylosides as SGLT2 inhibitors have been explored. *N*-linked glycosides were expected to have greater metabolic stability compared to *O*-glucosides, and because the configuration at C-1, -2, -3, and -4 of D-xylose and D-glucose is the same, the use of *N*-linked β-D-xylosides was considered to be a

worthy approach for further study on SGLT2 inhibition. Current SAR studies show that of the compounds tested, compound **19m**, 4-chloroindolyl-*N*-xyloside with the 4-cyclopropylbenzyl at the distal position, exhibited the best in vitro inhibitory activity against SGLT2. The pharmacokinetic data demonstrated that **19m** was metabolically stable with a low clearance and good oral bioavailability in SD rats. In further efficacy studies, **19m** was found to significantly increase 12- to 783-fold urine glucose excretion in normal SD rats and lower blood glucose levels of STZ-induced diabetic rats. Although the synthesized *N*-linked β-D-xylosides are less potent than dapagliflozin and exhibit almost no selectivity for SGLT2 over SGLT1, these results are a good starting point for further study in the absence of other information about *N*-glycoside SGLT2 inhibitors. Our research is ongoing, and the results of further investigations will be reported in due course.

Experimental Section

General Methods. All chemicals were purchased as reagent grade and used without further purification unless otherwise stated. Column chromatography was performed with silica gel (Merck Kieselgel 60, 230−400 mesh). Reactions were monitored with thin-layer chromatography (TLC) using Merck 60 F254 silica gel glass-backed plates (5N10 cm2) and visualized under UV (254 nm) and/or by staining with acidic ceric ammonium molybdate. ^{1}H NMR spectra were recorded on a Varian Mercury-300 (300 MHz) or Mercury-400 (400 MHz) spectrometer. Chemical shifts (in ppm) are reported relative to the internal standard signal of CD_3OD ($\delta = 3.30$ ppm). ^{13}C NMR spectra were obtained with Varian Mercury-300 (75 MHz) or Mercury-400 (100 MHz) spectrometer and reported relative to CD_3OD ($\delta = 49.00$ ppm). Coupling constants (*J*) are reported in hertz (Hz). Splitting patterns are described by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sext, sextet; sept, septet; m, multiplet. LC/MS data were obtained on an Agilent MSD-1100 ESI-MS/MS system. High-resolution mass spectra were obtained on a MAT-95XL or JEOL JMS-700 high resolution mass spectrometer in electron impact (EI) or fast atom bombardment (FAB) ionization modes. Purity of the final compounds was determined on a Hitachi 2000 series HPLC system with a reverse phase C_{18} column (Agilent ZORBAX Eclipse XDB-C18 5 μm, 4.6 mm × 150 mm, 0.5 mL/min flow rate). Mobile phase A was acetonitrile. Mobile phase B was 10 mM NH_4OAc aqueous solution containing 0.1% formic acid. The gradient system started from A/B (10%:90%) at 0 min to A/B (90%:10%) at 45 min. All tested compounds were found to be >95% pure at 254 nm unless otherwise stated.

General Precedure for the Synthesis of Indolines 10b−e, 10i−l, and 10p,q. Acetic acid (10 mL/1 mmol indole) was added to a mixture of indole (1.0 equiv) and $NaBH_3CN$ (3.0 equiv) at 0 °C under nitrogen. The mixture was warmed to room temperature and stirred for 2−5 h. The reaction mixture was concentrated under reduced pressure and the residue redissolved in CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired indoline derivatives.

General Precedure for the Synthesis of Indolines 10f−h, 10m−o, and 10r. A solution of indole (1.0 equiv), Et_3SiH (2.6 equiv), and TFA (1.5 mL/1 mmol indole) was heated at 50 °C under nitrogen, with stirring. After 0.5−3 h, the mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and neutralized by the addition of saturated aqueous sodium bicarbonate. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to provide the desired indoline derivatives.

General Procedure for the Synthesis of Compounds 11a−r. D-Xylose **9** (1.5 equiv) was added to a solution of indolines **10a−r** (1.0 equiv) in $EtOH/H_2O$ (7/1) at room temperature. The mixture was heated to 50 °C and maintained at this temperature for 24 h. The solvent was removed under reduced pressure and the crude product used for per-acetylation without further purification. This crude product was dissolved in pyridine, cooled to 0 °C, and stirred under nitrogen. Acetic anhydride was added. The mixture was warmed to room temperature gradually and stirred overnight (~16 h). The mixture was cooled to 0 °C and neutralized with 1 N HCl (aq). The mixture was extracted with dichloromethane and the organic layer dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired products **11a−r**.

General Procedure for the Synthesis of Compounds 12a−r. DDQ (2.0 equiv) was added to a solution of **11a−11r** (1.0 equiv) in 1,4-dioxane at room temperature. After stirring for 18 h, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate. The mixture was concentrated under reduced pressure and then extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired products **12a−r**.

General Procedure for the Synthesis of Compounds 13a−r. $POCl_3$ (8.0 equiv) was added to a stirred solution of **12a−r** (1.0 equiv) in anhydrous DMF at room temperature under nitrogen. The mixture was warmed to 75 °C and heated for 1 h. The reaction was quenched with water at 0 °C and then extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to provide **13a−r**.

General Procedure for the Synthesis of Compounds 14a−r and 17a−q. A 1 M solution of aryl- or heteroarylmagnesium bromide in THF (4.0 equiv) was added to a solution of **13a−r** (1.0 equiv) in THF at −78 °C under argon. After being stirred at −78 °C for 3 h, the mixture was poured into saturated aqueous ammonium chloride. The mixture was extracted with dichloromethane and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude **14a−r** or **17a−q**. The residue was used for the next step without further purification.

General Procedure for the Synthesis of Compounds 15a−r and 18a−q. Et_3SiH (5.0 equiv) and then $BF_3 \cdot OEt_2$ (0.5 equiv) were added to a stirred solution of crude **14a−r** or **17a−q** in CH_3CN/CH_2Cl_2 (2/1) at 0 °C under argon. After 1 h, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give **15a−r** or **18a−q** as a white solid.

General Procedure for the Synthesis of Compounds 16a−r and 19a−q. A 30% solution of NaOMe in MeOH (3.6 equiv) was added to a solution of **15a−r** or **18a−q** (1.0 equiv) in $MeOH/CH_2Cl_2$ (2/1) at 0 °C under nitrogen. The mixture was slowly warmed to room temperature and then neutralized with acidic resin after 2 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography to give the desired products **16a−r** or **19a−q** as a white solid.

3-Benzyl-1-(β-D-xylopyranosyl)-1*H*-indole (16a). The title compound was obtained from D-xylose **9** and 2,3-dihydro-1*H*-indole **10a** according to the general procedure in 9% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (d, $J = 8.1$ Hz, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.29−7.20 (m, 4H), 7.15−7.10 (m, 3H), 7.01−6.96 (m, 1H), 5.32 (d, $J = 9.0$ Hz, 1H), 4.06 (s, 2H), 3.95 (dd, $J = 10.8$, 5.4 Hz, 1H), 3.86 (t, $J = 9.0$ Hz, 1H), 3.70−3.62 (m, 1H), 3.50 (t, $J = 9.0$ Hz, 1H), 3.46 (t, $J = 10.8$ Hz, 1H). ^{13}C

NMR (100 MHz, CD_3OD) δ 142.6, 138.7, 130.1, 129.8, 129.3, 126.9, 124.5, 123.0, 120.7, 120.2, 117.1, 111.4, 87.4, 79.3, 73.5, 71.2, 69.5, 32.6. ESMS m/z: 340 (MH^+), 362 (MNa^+). HRMS (EI) for $C_{20}H_{21}NO_4$: calcd, 339.1471; found, 339.1468.

3-Benzyl-4-methyl-1-(β-D-xylopyranosyl)-1*H*-indole (16b). The title compound was obtained from D-xylose **9** and 2,3-dihydro-4-methyl-1*H*-indole **10b** according to the general procedure in 7% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.31−7.11 (m, 6H), 7.02−6.97 (m, 2H), 6.73−6.70 (m, 1H), 5.31 (d, J = 9.0 Hz, 1H), 4.25 (s, 2H), 3.95 (dd, J = 11.1, 5.4 Hz, 1H), 3.85 (t, J = 9.0 Hz, 1H), 3.69−3.61 (m, 1H), 3.50 (t, J = 9.0 Hz, 1H), 3.46 (t, J = 11.1 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ 143.5, 139.4, 132.0, 129.6, 129.4, 128.6, 126.9, 125.6, 123.1, 122.5, 116.9, 109.3, 87.2, 79.3, 73.4, 71.6, 71.2, 69.5, 34.2, 20.4. ESMS m/z: 354 (MH^+), 376 (MNa^+). HRMS (EI) for $C_{21}H_{23}NO_4$: calcd, 353.1627; found, 353.1622.

3-Benzyl-5-methyl-1-(β-D-xylopyranosyl)-1*H*-indole (16c). The title compound was obtained from D-xylose **9** and 2,3-dihydro-5-methyl-1*H*-indole **10c** according to the general procedure in 10% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.35−7.11 (m, 7H), 7.05 (s, 1H), 6.97 (dd, J = 8.4, 0.9 Hz, 1H), 5.27 (d, J = 9.0 Hz, 1H), 4.02 (s, 2H), 3.94 (dd, J = 10.8, 5.1 Hz, 1H), 3.85 (t, J = 9.0 Hz, 1H), 3.69−3.61 (m, 1H), 3.50 (t, J = 9.0 Hz, 1H), 3.44 (t, J = 10.8 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 142.7, 137.1, 130.3, 130.0, 129.8, 129.3, 129.3, 124.7, 124.5, 119.9, 116.6, 111.1, 87.5, 79.3, 73.5, 71.2, 69.5, 32.5, 21.6. ESMS m/z: 354 (MH^+), 376 (MNa^+). HRMS (EI) for $C_{21}H_{23}NO_4$: calcd, 353.1627; found, 353.1625.

3-Benzyl-6-methyl-1-(β-D-xylopyranosyl)-1*H*-indole (16d). The title compound was obtained from D-xylose **9** and 2,3-dihydro-6-methyl-1*H*-indole **10d** according to the general procedure in 13% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.28−7.10 (m, 7H), 7.02 (s, 1H), 6.83 (d, J = 8.7 Hz, 1H), 5.29 (d, J = 9.0 Hz, 1H), 4.03 (s, 2H), 3.94 (dd, J = 11.1, 5.1 Hz, 1H), 3.88 (t, J = 9.0 Hz, 1H), 3.69−3.61 (m, 1H), 3.50 (t, J = 9.0 Hz, 1H), 3.45 (t, J = 11.1 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 142.7, 139.2, 132.8, 129.8, 129.3, 128.0, 126.9, 123.9, 122.4, 120.0, 117.1, 111.3, 87.3, 79.3, 73.5, 71.2, 69.5, 32.6, 22.0. ESMS m/z: 354 (MH^+), 376 (MNa^+). HRMS (EI) for $C_{21}H_{23}NO_4$: calcd, 353.1627; found, 353.1624.

3-Benzyl-7-methyl-1-(β-D-xylopyranosyl)-1*H*-indole (16e). The title compound was obtained from D-xylose **9** and 2,3-dihydro-7-methyl-1*H*-indole **10e** according to the general procedure in 3% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.28−7.10 (m, 7H), 6.90−6.85 (m, 2H), 5.69 (d, J = 8.7 Hz, 1H), 4.04 (s, 2H), 3.91 (dd, J = 11.0, 5.1 Hz, 1H), 3.85 (t, J = 8.7 Hz, 1H), 3.66−3.58 (m, 1H), 3.48 (t, J = 8.7 Hz, 1H), 3.42 (t, J = 11.0 Hz, 1H), 2.68 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 142.5, 137.8, 130.7, 129.8, 129.3, 126.9, 126.6, 124.1, 122.1, 120.8, 118.3, 117.4, 87.4, 79.5, 73.6, 71.1, 68.7, 32.5, 20.4. ESMS m/z: (MH^+), 376 (MNa^+). HRMS (EI) for $C_{21}H_{23}NO_4$: calcd, 353.1627; found, 353.1619.

3-Benzyl-4-fluoro-1-(β-D-xylopyranosyl)-1*H*-indole (16f). The title compound was obtained from D-xylose **9** and 2,3-dihydro-4-fluoro-1*H*-indole **10f** according to the general procedure in 4% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.29−7.02 (m, 8H), 6.71−6.64 (m, 1H), 5.30 (d, J = 9.0 Hz, 1H), 4.14 (s, 2H), 3.95 (dd, J = 10.8, 5.4 Hz, 1H), 3.80 (t, J = 9.0 Hz, 1H), 3.69−3.61 (m, 1H), 3.49 (t, J = 9.0 Hz, 1H), 3.46 (t, J = 10.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.8, 157.4, 142.9, 141.5, 141.4, 129.8, 129.3, 126.9, 125.0, 123.6, 123.5, 118.2, 115.8, 107.9, 107.8, 105.9, 105.7, 87.6, 79.2, 73.6, 71.1, 69.6, 33.5. ESMS m/z: 358 (MH^+), 380 (MNa^+). HRMS (EI) for $C_{20}H_{20}FNO_4$: calcd, 357.1376; found, 357.1372.

3-Benzyl-5-fluoro-1-(β-D-xylopyranosyl)-1*H*-indole (16g). The title compound was obtained from D-xylose **9** and 2,3-dihydro-5-fluoro-1*H*-indole **10g** according to the general procedure in 30% overall yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (dd, J = 8.8, 4.4 Hz, 1H), 7.28−7.13 (m, 6H), 7.00 (dd, J = 9.6, 2.4 Hz, 1H), 6.88 (td, J = 9.2, 2.4 Hz, 1H), 5.28 (d, J = 9.0 Hz, 1H), 4.02 (s, 2H), 3.94 (dd, J = 11.2, 5.6 Hz, 1H), 3.82 (t, J = 9.0 Hz, 1H), 3.69−3.63 (m, 1H), 3.50 (t, J = 9.0 Hz, 1H), 3.45 (t, J = 11.2 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 160.9, 157.8, 142.3, 135.2, 130.5, 130.4, 129.8, 129.4, 127.1, 126.5, 117.1, 117.0, 112.4, 112.3, 111.0, 110.7, 105.1, 104.8, 87.7, 79.2, 73.6, 71.2, 69.6, 32.5. ESMS m/z: 358 (MH^+), 380 (MNa^+). HRMS (EI) for $C_{20}H_{20}FNO_4$: calcd, 357.1376; found, 357.1371. HPLC purity 83.6%.

3-Benzyl-6-fluoro-1-(β-D-xylopyranosyl)-1*H*-indole (16h). The title compound was obtained from D-xylose **9** and 2,3-dihydro-6-fluoro-1*H*-indole **10h** according to the general procedure in 34% overall yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (dd, J = 8.6, 5.2 Hz, 1H), 7.27−7.11 (m, 6H), 7.11 (s, 1H), 6.79−6.74 (m, 1H), 5.25 (d, J = 9.2 Hz, 1H), 4.04 (s, 2H), 3.96 (dd, J = 11.1, 5.2 Hz, 1H), 3.81 (t, J = 9.2 Hz, 1H), 3.69−3.63 (m, 1H), 3.50 (t, J = 9.2 Hz, 1H), 3.46 (t, J = 11.1 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 162.6, 160.2, 142.4, 138.9, 138.7, 129.8, 129.4, 127.0, 126.6, 125.1, 125.0, 121.2, 121.1, 117.3, 109.1, 108.8, 98.1, 97.8, 87.5, 79.2, 73.6, 71.1, 69.5, 32.5. ESMS m/z: 358 (MH^+), 380 (MNa^+). HRMS (EI) for $C_{20}H_{20}FNO_4$: calcd, 357.1376; found, 357.1375.

3-Benzyl-7-fluoro-1-(β-D-xylopyranosyl)-1*H*-indole (16i). The title compound was obtained from D-xylose **9** and 2,3-dihydro-7-fluoro-1*H*-indole **10i** according to the general procedure in 14% overall yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.27−7.12 (m, 7H), 6.95−6.83 (m, 2H), 5.56 (d, J = 9.2 Hz, 1H), 4.05 (s, 2H), 3.94 (dd, J = 11.2, 5.6 Hz, 1H), 3.81 (td, J = 9.2, 2.0 Hz, 1H), 3.66−3.60 (m, 1H), 3.47 (t, J = 9.2 Hz, 1H), 3.40 (t, J = 11.2 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 152.9, 149.7, 142.3, 133.9, 129.8, 129.4, 127.1, 125.5, 121.0, 120.9, 118.4, 116.4, 116.3, 109.3, 109.0, 88.7, 79.4, 73.9, 71.1, 69.5, 32.5. ESMS m/z: 358 (MH^+), 380 (MNa^+). HRMS (EI) for $C_{20}H_{20}FNO_4$: calcd, 357.1376; found, 357.1374.

3-Benzyl-4-chloro-1-(β-D-xylopyranosyl)-1*H*-indole (16j). The title compound was obtained from D-xylose **9** and 4-chloro-2,3-dihydro-1*H*-indole **10j** according to the general procedure in 41% overall yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (d, J = 8.0 Hz, 1H), 7.25−7.19 (m, 4H), 7.16−7.11 (m, 2H), 7.07 (t, J = 7.6 Hz, 1H), 7.02−6.98 (m, 2H), 5.31 (d, J = 9.0 Hz, 1H), 4.33 (s, 2H), 3.95 (dd, J = 11.2, 5.6 Hz, 1H), 3.78 (t, J = 9.0 Hz, 1H), 3.67−3.61(m, 1H), 3.49 (t, J = 9.0 Hz, 1H), 3.45 (t, J = 11.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 143.0, 140.2, 129.9, 129.3, 127.4, 126.9, 126.8, 126.5, 123.6, 121.8, 117.1, 110.5, 87.4, 79.2, 73.6, 71.1, 69.6, 33.5. ESMS m/z: 374 (MH^+), 396 (MNa^+). HRMS (EI) for $C_{20}H_{20}ClNO_4$: calcd, 373.1081; found, 373.1074.

3-Benzyl-5-chloro-1-(β-D-xylopyranosyl)-1*H*-indole (16k). The title compound was obtained from D-xylose **9** and 2,3-dihydro-5-chloro-1*H*-indole **10k** according to the general procedure in 24% overall yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, J =8.8 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.26−7.22 (m, 4H), 7.17−7.14 (m, 2H), 7.09 (dd, J = 8.8, 2.0 Hz, 1H), 5.29 (d, J = 8.8 Hz, 1H), 4.02 (s, 2H), 3.95 (dd, J = 11.0, 5.2 Hz, 1H), 3.82 (t, J = 8.8 Hz, 1H), 3.69−3.63 (m, 1H), 3.50 (t, J = 8.8 Hz, 1H), 3.45 (t, J =11.0 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 142.6, 137.0, 131.0, 129.7, 129.4, 127.0, 126.4, 126.2, 123.0, 119.6, 116.7, 112.7, 87.5, 79.1, 73.5, 71.0, 69.5, 32.3. ESMS m/z: 374 (MH^+), 396 (MNa^+). HRMS (EI) for $C_{20}H_{20}ClNO_4$: calcd, 373.1081; found, 373.1082.

3-Benzyl-6-chloro-1-(β-D-xylopyranosyl)-1*H*-indole (16l). The title compound was obtained from D-xylose **9** and 2,3-dihydro-6-chloro-1*H*-indole **10j** according to the general procedure in 31% overall yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (d, J = 1.6 Hz, 1H), 7.33 (dd, J = 8.6, 0.8 Hz, 1H), 7.28−7.22 (m, 4H), 7.17−7.15 (m, 2H), 6.99−6.97 (m, 1H), 5.29 (d, J = 8.8 Hz, 1H), 4.05 (s, 2H), 3.97 (dd, J = 11.1, 5.6 Hz, 1H), 3.81 (t, J = 8.8 Hz, 1H), 3.70−3.64 (m, 1H), 3.51 (t, J = 8.8 Hz, 1H), 3.48 (t, J = 11.1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 142.1, 138.9, 129.7, 129.3, 128.9, 128.6, 127.0, 125.5, 121.3, 121.2, 117.2, 111.5, 87.3, 79.0, 73.5, 71.0, 69.4, 32.3. ESMS m/z: 374 (MH^+), 396 (MNa^+). HRMS (EI) for $C_{20}H_{20}ClNO_4$: calcd, 373.1081; found, 373.1076.

3-Benzyl-7-chloro-1-(β-D-xylopyranosyl)-1*H*-indole (16m). The title compound was obtained from D-xylose **9** and 2,3-dihydro-7-chloro-1*H*-indole **10m** according to the general procedure in 12%

overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.34 (dd, J = 8.0, 1.2 Hz, 1H), 7.28−7.12 (m, 7H), 6.95 (t, J = 7.8 Hz, 1H), 6.28 (d, J = 9.6 Hz, 1H), 4.06 (s, 2H), 3.91 (dd, J = 10.9, 5.4 Hz, 1H), 3.85 (dd, J = 9.6, 8.7 Hz, 1H), 3.65−3.57 (m, 1H), 3.48 (t, J = 8.7 Hz, 1H), 3.44 (t, J = 10.9 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 142.0, 134.1, 133.2, 129.8, 129.4, 127.1, 125.5, 121.5, 119.3, 117.9, 117.7, 79.6, 73.3, 71.2, 68.9, 32.3. ESMS m/z: 374 (MH^+), 396 (MNa^+). HRMS (FAB) for $C_{20}H_{20}ClNO_4$: calcd, 373.1081; found, 373.1087.

3-Benzyl-4-bromo-1-(β-D-xylopyranosyl)-1*H*-indole (16n). The title compound was obtained from D-xylose **9** and 4-bromo-2,3-dihydro-1*H*-indole **10n** according to the general procedure in 32% overall yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (dd, J = 8.2, 0.8 Hz, 1H), 7.25−7.19 (m, 5H), 7.16−7.11 (m, 1H), 7.01 (s, 1H), 6.99 (t, J = 8.0 Hz, 1H), 5.30 (d, J = 9.2 Hz, 1H), 4.37, 4.34 (ABq, J = 16.4 Hz, 2H), 3.94 (dd, J = 11.2, 5.6 Hz, 1H), 3.78 (t, J = 9.2 Hz, 1H), 3.67−3.61 (m, 1H), 3.50 (t, J = 9.2 Hz, 1H), 3.44 (t, J = 11.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 141.6, 138.7, 128.7, 128.0, 126.6, 125.9, 125.6, 124.1, 122.6, 116.2, 113.9, 109.8, 86.0, 77.9, 72.2, 69.8, 68.3, 32.2. ESMS m/z: 418 (MH^+), 440 (MNa^+). HRMS (EI) for $C_{20}H_{20}BrNO_4$: calcd, 417.0576; found, 417.0581.

3-Benzyl-4-nitro-1-(β-D-xylopyranosyl)-1*H*-indole (16o). The title compound was obtained from D-xylose **9** and 2,3-dihydro-4-nitro-1*H*-indole **10o** according to the general procedure in 12% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.89 (dd, J = 8.1, 0.9 Hz, 1H), 7.65 (dd, J = 8.1, 0.9 Hz, 1H), 7.39 (s, 1H), 7.25 (t, J = 8.1 Hz, 1H), 7.20−7.06 (m, 5H), 5.44 (d, J = 9.0 Hz, 1H), 4.16 (s, 2H), 3.99 (dd, J = 10.8, 5.1 Hz, 1H), 3.81 (t, J = 9.0 Hz, 1H), 3.73−3.64 (m, 1H), 3.53 (t, J = 9.0 Hz, 1H), 3.50 (t, J = 10.8 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 144.8, 142.5, 141.2, 130.4, 129.7, 129.4, 126.9, 121.9, 121.2, 118.3, 117.5, 116.0, 87.4, 79.1, 73.8, 71.0, 69.7, 34.2. ESMS m/z: 385 (MH^+), 407 (MNa^+). HRMS (EI) for $C_{20}H_{20}N_2O_6$: calcd, 384.3826; found, 384.1326. HPLC purity 94.1%.

3-Benzyl-4-methoxy-1-(β-D-xylopyranosyl)-1*H*-indole (16p). The title compound was obtained from D-xylose **9** and 2,3-dihydro-4-methoxy-1*H*-indole **10p** according to the general procedure in 6% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.26−7.18 (m, 4H), 7.13−7.07 (m, 3H), 6.85 (s, 1H), 6.52−6.46 (m, 1H), 5.25 (d, J = 9.0 Hz, 1H), 4.19 (s, 2H), 3.93 (dd, J = 10.8, 5.4 Hz, 1H), 3.80 (t, J = 9.0 Hz, 1H), 3.78 (s, 3H), 3.67−3.59 (m, 1H), 3.48 (t, J = 9.0 Hz, 1H), 3.39 (t, J = 10.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 156.3, 143.9, 140.4, 129.9, 129.1, 126.6, 123.9, 123.2, 119.7, 117.7, 104.7, 101.3, 87.4, 79.2, 73.5, 71.1, 69.5, 55.5, 34.1. ESMS m/z: 370 (MH^+), 392 (MNa^+). HRMS (EI) for $C_{21}H_{23}NO_5$: calcd, 369.1576; found, 369.1579.

3-Benzyl-4-hydroxy-1-(β-D-xylopyranosyl)-1*H*-indole (16q). The title compound was obtained from D-xylose **9** and 4-acetyl-2,3-dihydro-1*H*-indole **10q** according to the general procedure in 18% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.32−7.29 (m, 2H), 7.23−7.19 (m, 2H), 7.13−7.08 (m, 1H), 6.94−6.88 (m, 2H), 6.76 (s, 1H), 6.40−6.36 (m, 1H), 5.22 (d, J = 9.0 Hz, 1H), 4.24 (s, 2H), 3.92 (dd, J = 10.8, 5.1 Hz, 1H), 3.78 (t, J = 9.0 Hz, 1H), 3.66−3.57 (m, 1H), 3.46 (t, J = 9.0 Hz, 1H), 3.43 (t, J = 10.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 153.6, 143.9, 140.9, 130.1, 130.0, 129.1, 126.6, 123.9, 122.8, 119.2, 118.0, 105.5, 103.2, 87.4, 79.2, 73.4, 71.2, 69.5, 33.9. ESMS m/z: 356 (MH^+), 378 (MNa^+). HRMS (EI) for $C_{20}H_{21}NO_5$: calcd, 355.1420; found, 355.1423.

3-Benzyl-6-chloro-5-fluoro-1-(β-D-xylopyranosyl)-1*H*-indole (16r). The title compound was obtained from D-xylose **9** and 2,3-dihydro-6-chloro-5-fluoro-1*H*-indole **10r** according to the general procedure in 22% overall yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.58 (d, J = 6.3 Hz, 1H), 7.26−7.13 (m, 7H), 5.28 (d, J = 9.0 Hz, 1H), 4.02 (s, 2H), 3.97 (dd, J = 10.8, 5.1 Hz, 1H), 3.78 (t, J = 9.0 Hz, 1H), 3.71−3.63 (m, 1H), 3.51 (t, J = 9.0 Hz, 1H), 3.44 (t, J = 10.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 155.4, 153.0, 142.0, 134.9, 129.8, 129.5, 129.0, 128.9, 127.2, 127.1, 117.3, 116.5, 113.0, 106.4, 106.1, 87.7, 79.1, 73.7, 71.1, 69.6, 32.3. ESMS m/z: 392 (MH^+), 414 (MNa^+). HRMS (EI) for $C_{20}H_{19}ClFNO_4$: calcd, 391.0987; found, 391.0984. HPLC purity 91.7%.

4-Chloro-3-(2-methoxybenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19a). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 2-methoxyphenylmagnesium bromide according to the general procedure in 88% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.44 (d, J = 7.5 Hz, 1H), 7.20−7.14 (m, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.01−6.94 (m, 4H), 6.83−6.77 (m, 1H), 5.30 (d, J = 9.0 Hz, 1H), 4.30, 4.26 (ABq, J = 22.4 Hz, 2H), 3.84 (s, 3H), 3.95 (dd, J = 11.0, 5.3 Hz, 1H), 3.77 (t, J = 9.0 Hz, 1H), 3.68−3.60 (m, 1H), 3.52−3.42 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 158.7, 140.2, 131.3, 131.0, 128.2, 127.5, 126.8, 126.6, 123.4, 121.7, 121.5, 116.5, 111.4, 110.5, 87.4, 79.2, 73.6, 71.1, 69.6, 56.0, 27.5. ESMS m/z: 404 (MH^+), 426 (MNa^+). HRMS (EI) for $C_{21}H_{22}ClNO_5$: calcd, 403.1187; found, 403.1187. HPLC purity 91.6%.

4-Chloro-3-(3-methoxybenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19b). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 3-methoxyphenylmagnesium bromide according to the general procedure in 64% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.45 (dd, J = 8.1, 0.9 Hz, 1H), 7.19−6.99 (m, 4H), 6.83−6.71 (m, 3H), 5.32 (d, J = 9.0 Hz, 1H), 4.32 (s, 2H), 3.96 (dd, J = 11.0, 5.4 Hz, 1H), 3.79 (t, J = 9.0 Hz, 1H), 3.73 (s, 3H), 3.70−3.61 (m, 1H), 3.50 (t, J = 9.0 Hz, 1H), 3.46 (t, J = 11.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.9, 143.3, 138.8, 128.9, 126.1, 125.5, 125.2, 122.2, 121.0, 120.5, 115.6, 114.3, 110.9, 109.2, 86.1, 77.9, 72.2, 69.8, 68.3, 54.3, 32.2. ESMS m/z: 404 (MH^+), 426 (MNa^+). HRMS (EI) for $C_{21}H_{22}ClNO_5$: calcd, 403.1187; found, 403.1193.

4-Chloro-3-(4-methoxybenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19c). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 4-methoxyphenylmagnesium bromide according to the general procedure in 67% yield over three steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (dd, J = 8.4, 0.8 Hz, 1H), 7.14−7.12 (m, 2H), 7.07 (t, J = 7.6 Hz, 1H), 7.00−6.98 (m, 2H), 6.82−6.80 (m, 2H), 5.30 (d, J = 9.0 Hz, 1H), 4.26 (s, 2H), 3.94 (dd, J = 11.2, 5.6 Hz, 1H), 3.77 (t, J = 9.0 Hz, 1H), 3.75 (s, 3H), 3.67−3.57 (m, 1H), 3.48 (t, J = 9.0 Hz, 1H), 3.45 (t, J = 11.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.4, 140.2, 135.0, 130.8, 127.4, 126.6, 126.5, 123.5, 121.8, 117.7, 114.7, 110.5, 87.4, 79.2, 73.6, 71.1, 69.6, 55.7, 32.7. ESMS m/z: 404 (MH^+). HRMS (EI) for $C_{21}H_{22}ClNO_5$: calcd, 403.1187; found, 403.1181.

4-Chloro-3-(3-fluorobenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19d). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 3-fluorophenylmagnesium bromide according to the general procedure in 65% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.45 (d, J = 7.2 Hz, 1H), 7.27−7.20 (m, 1H), 7.14 (s, 1H), 7.11−6.98 (m, 3H), 6.92−6.83 (m, 2H), 5.34 (d, J = 9.0 Hz, 1H), 4.34 (s, 2H), 3.97 (dd, J = 10.9, 5.1 Hz, 1H), 3.82 (t, J = 9.0 Hz, 1H), 3.70−3.62 (m, 1H), 3.50 (t, J = 9.0 Hz, 1H), 3.47 (t, J = 10.9 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 165.7, 163.3, 146.4, 146.3, 140.2, 130.9, 130.8, 127.3, 127.1, 126.4, 125.7, 125.6, 123.7, 121.9, 116.4, 116.2, 115.9, 113.5, 113.3, 110.6, 87.4, 79.2, 73.6, 71.1, 69.6, 33.1. ESMS m/z: 392 (MH^+), 414 (MNa^+). HRMS (FAB) for $C_{20}H_{19}ClFNO_4$: calcd, 391.0987; found, 391.0983.

4-Chloro-3-(4-fluorobenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19e). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 4-fluorophenylmagnesium bromide according to the general procedure in 66% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.44 (dd, J = 8.2, 0.6 Hz, 1H), 7.23−7.18 (m, 2H), 7.10−7.05 (m, 2H), 7.00−6.92 (m, 3H), 5.32 (d, J = 9.3 Hz, 1H), 4.31 (s, 2H), 3.95 (dd, J = 11.1, 5.1 Hz, 1H), 3.79 (t, J = 9.3 Hz, 1H), 3.69−3.61 (m, 1H), 3.49 (t, J = 9.3, 1H), 3.46 (t, J = 11.1, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 163.0, 159.8, 138.9, 137.8, 137.7, 130.1, 130.0, 126.0, 125.6, 125.1, 122.3, 120.5, 115.4, 114.6,

114.3, 109.3, 86.1, 77.9, 72.2, 69.8, 68.3, 31.3. ESMS *m*/*z*: 392 (MH^+), 414 (MNa^+). HRMS (EI) for $C_{20}H_{19}ClFNO_4$: calcd, 391.0987; found, 391.0983.

4-Chloro-3-(2,4-dimethoxybenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19f). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 2,4-dimethoxyphenylmagnesium bromide according to the general procedure in 78% yield over three steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.88 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 5.27 (d, *J* = 9.0 Hz, 1H), 4.21, 4.18 (ABq, *J* = 16.8 Hz, 2H), 3.93 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.78 (s, 3H), 3.78−3.73 (m, 1H), 3.73 (s, 3H), 3.66−3.59 (m, 1H), 3.48 (t, *J* = 9.0 Hz, 1H), 3.43 (t, *J* = 11.0 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 160.8, 159.4, 140.1, 131.4, 127.5, 126.7, 126.4, 123.5, 123.4, 121.7, 117.0, 110.5, 105.2, 99.3, 87.4, 79.1, 73.5, 71.0, 69.5, 55.9, 55.8, 27.0. HRMS (EI) for $C_{22}H_{24}ClNO_6$: calcd, 433.1292; found, 433.1289.

4-Chloro-3-(3-fluoro-4-methoxybenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19g). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 3-fluoro-4-methoxyphenylmagnesium bromide according to the general procedure in 65% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.45 (d, *J* = 8.1 Hz, 1H), 7.12−6.91 (m, 6H), 5.33 (d, *J* = 9.0 Hz, 1H), 4.27 (s, 2H), 3.97 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.83 (s, 3H), 3.81 (t, *J* = 9.0 Hz, 1H), 3.71−3.62 (m, 1H), 3.51 (t, *J* = 9.0 Hz, 1H), 3.47 (t, *J* = 11.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 154.9, 152.5, 147.2, 147.1, 140.2, 136.6, 136.5, 127.3, 126.9, 126.4, 125.5, 125.4, 123.7, 121.9, 117.3, 117.1, 116.6, 114.7, 110.6, 87.4, 79.2, 73.6, 71.1, 69.6, 56.9, 32.5. ESMS *m*/*z*: 422 (MH^+), 444 (MNa^+). HRMS (EI) for $C_{21}H_{21}ClNO_5$: calcd, 421.1092; found, 421.1083.

4-Chloro-3-(4-isopropylbenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19h). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 4-isopropylphenylmagnesium bromide according to the general procedure in 78% yield over three steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.16−6.99 (m, 7H), 5.30 (d, *J* = 9.2 Hz, 1H), 4.30 (s, 2H), 3.95 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.78 (t, *J* = 9.2 Hz, 1H), 3.68−3.62 (m, 1H), 3.49 (t, *J* = 9.2 Hz, 1H), 3.46 (t, *J* = 11.2 Hz, 1H), 2.86 (sept, *J* = 7.2 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 147.5, 140.3, 140.2, 129.9, 127.4, 127.3, 126.7, 126.6, 123.5, 121.8, 117.4, 110.5, 87.4, 79.2, 73.5, 71.1, 69.6, 35.1, 33.2, 24.7. ESMS *m*/*z*: 416 (MH^+), 438 (MNa^+). HRMS (EI) for $C_{23}H_{26}ClNO_4$: calcd, 415.1550; found, 415.1546.

4-Chloro-3-(4-*n*-propylbenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19i). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 4-*n*-propylphenylmagnesium bromide according to the general procedure in 66% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.43 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.13−6.98 (m, 7H), 5.30 (d, *J* = 9.0 Hz, 1H), 4.29 (s, 2H), 3.94 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.77 (t, *J* = 9.0 Hz, 1H), 3.68−3.59 (m, 1H), 3.48 (t, *J* = 9.0 Hz, 1H), 3.45 (t, *J* = 11.0 Hz, 1H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.61 (sext, *J* = 7.5 Hz, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 141.2, 140.3, 140.2, 129.8, 129.4, 127.4, 126.7, 126.6, 123.5, 121.8, 117.4, 110.5, 87.4, 79.2, 73.6, 71.1, 69.6, 38.8, 33.2, 25.9, 14.2. ESMS *m*/*z*: 416 (MH^+), 438 (MNa^+). HRMS (EI) for $C_{23}H_{26}ClNO_4$: calcd, 415.1550; found, 415.1555.

4-Chloro-3-(4-phenylbenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19j). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 4-biphenylmagnesium bromide according to the general procedure in 78% yield over three steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58−7.28 (m, 10H), 7.10−6.99 (m, 3H), 5.32 (d, *J* = 9.2 Hz, 1H), 4.37 (s, 2H), 3.95 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.80 (t, *J* = 9.2 Hz, 1H), 3.67−3.61 (m, 1H), 3.49 (t, *J* = 9.2 Hz, 1H), 3.45 (t, *J* = 11.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 142.5, 142.3, 140.2,140.1, 130.4, 130.0, 129.9, 128.1, 128.0, 127.9, 127.4, 126.9, 126.5, 123.6, 121.8, 116.9, 110.6, 87.4, 79.2, 73.6, 71.1, 69.6, 33.2. ESMS *m*/*z*: 450 (MH^+), 472 (MNa^+). HRMS (EI) for $C_{26}H_{24}ClNO_4$: calcd, 449.1394; found, 449.1397.

4-Chloro-3-[4-(methylsulfanyl)benzyl]-1-(β-D-xylopyranosyl)-1*H*-indole (19k). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 4-thioanisolemagnesium bromide according to the general procedure in 65% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.43 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.15 (s, 1H,), 7.18−6.98 (m, 6H), 5.31 (d, *J* = 9.0 Hz, 1H), 4.29 (s, 2H), 3.95 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.78 (t, *J* = 9.0 Hz, 1H), 3.69−3.60 (m, 1H), 3.49 (t, *J* = 9.0 Hz, 1H), 3.45 (t, *J* = 11.2, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 140.3, 140.2, 136.9, 130.6, 130.5, 130.4, 128.0, 127.4, 126.8, 126.5, 123.6, 121.8, 116.9, 110.6, 87.4, 79.2, 73.5, 71.1, 69.6, 33.0, 16.2. ESMS *m*/*z*: 420 (MH^+), 442 (MNa^+). HRMS (EI) for $C_{21}H_{22}ClNO_4S$: calcd, 419.0958; found, 419.0960.

4-Chloro-3-[4-(*N*,*N*-dimethylamino)benzyl]-1-(β-D-xylopyranosyl)-1*H*-indole (19l). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 4-(*N*,*N*-dimethylamino)phenylmagnesium bromide according to the general procedure in 32% yield over three steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.10−7.04 (m, 3H), 6.99 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.93 (s, 1H), 6.76−6.72 (m, 2H), 5.29 (d, *J* = 9.0 Hz, 1H), 4.23 (s, 2H), 3.94 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.75 (t, *J* = 9.0 Hz, 1H), 3.66−3.60 (m, 1H), 3.48 (t, *J* = 9.0 Hz, 1H), 3.44 (t, *J* = 11.2 Hz, 1H), 2,86 (s, 6H). ^{13}C NMR (75 MHz, CD_3OD) δ 150.8, 140.2, 131.9, 130.5, 127.5, 126.6, 126.5, 123.5, 121.7, 118.2, 115.0, 110.5, 87.4, 79.2, 73.6, 71.1, 69.6, 41.7, 32.8. ESMS *m*/*z*: 417 (MH^+), 439 (MNa^+). HRMS (EI) for $C_{22}H_{25}ClN_2O_4$: calcd, 416.1503; found, 416.1499.

4-Chloro-3-(4-cyclopropylbenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19m). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 4-cyclopropylphenylmagnesium bromide according to the general procedure in 79% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.10−6.94 (m, 7H), 5.30 (d, *J* = 9.0 Hz, 1H), 4.27 (s, 2H), 3.94 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.76 (t, *J* = 9.0 Hz, 1H), 3.68−3.59 (m, 1H), 3.48 (t, *J* = 9.0 Hz, 1H), 3.44 (t, *J* = 10.8 Hz, 1H), 1.88−1.79 (m, 1H), 0.93−0.86 (m, 2H), 0.64−0.59 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 142.7, 140.2, 139.9, 129.8, 127.4, 126.7, 126.6, 123.5, 121.8, 117.5, 110.5, 87.4, 79.2, 73.5, 71.1, 69.6, 33.2, 15.9, 9.5. ESMS *m*/*z*: 414 (MH^+), 436 (MNa^+). HRMS (EI) for $C_{23}H_{24}ClNO_4$: calcd, 413.1394; found, 413.1390.

4-Chloro-3-(2-thienylmethyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19n). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 2-thienylmagnesium bromide according to the general procedure in 35% yield over three steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.20 (s, 1H), 7.15 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.88 (dd, *J* = 5.0, 3.2 Hz, 1H), 6.80−6.78 (m, 1H), 5.33 (d, *J* = 8.8 Hz, 1H), 4.52, 4.49 (ABq, *J* = 16.8 Hz, 2H), 3.96 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.80 (t, *J* = 8.8 Hz, 1H), 3.69−3.62 (m, 2H), 3.50 (t, *J* = 8.8 Hz, 1H), 3.46 (t, *J* = 11.1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 146.5, 140.1, 127.7, 127.3, 126.8, 126.1, 125.8, 124.3, 123.6, 121.9, 116.7, 110.6, 87.4, 79.2, 73.6, 71.1, 69.6, 27.8. ESMS *m*/*z*: 380 (MH^+), 402 (MNa^+). HRMS (EI) for $C_{18}H_{18}ClNO_4S$: calcd, 379.0645; found, 379.0642.

4-Chloro-3-(6-methoxy-2-naphthylmethyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19o). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 6-methoxy-2-naphthylmagnesium bromide according to the general procedure in 83% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.67 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.54 (s, 1H), 7.45 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.37 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.11−6.98 (m, 4H), 5.32 (d, *J* = 9.0 Hz, 1H), 4.46 (s, 2H), 3.94 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.88 (s, 3H), 3.77 (t, *J* = 9.0 Hz, 1H), 3.66−3.58 (m, 1H), 3.48 (t, *J* = 9.0 Hz, 1H), 3.45 (t, *J* = 11.0 Hz,

1H). ^{13}C NMR (100 MHz, CD_3OD) δ 158.8, 140.2, 138.2, 134.7, 130.7, 130.1, 129.3, 127.9, 127.8, 127.5, 126.9, 126.6, 123.9, 123.6, 123.6, 121.8, 119.5, 117.2, 110.6, 106.7, 87.4, 79.2, 73.5, 71.1, 69.6, 55.8, 33.6. ESMS m/z: 454 (MH^+), 476 (MNa^+). HRMS (EI) for $C_{25}H_{24}ClNO_5$: calcd, 453.1343; found, 453.1342.

3-(1,3-Benzodioxol-5-ylmethyl)-4-chloro-1-(β-D-xylopyranosyl)-1*H*-indole (19p). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 3,4-(methylenedioxy)phenylmagnesium bromide according to the general procedure in 47% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.43 (dd, J = 8.2, 0.6 Hz, 1H), 7.10−6.98 (m, 3H), 6.71−6.65 (m, 3H), 5.87 (s, 2H), 5.31 (d, J = 9.0 Hz, 1H), 4.24 (s, 2H), 3.95 (dd, J = 11.1, 5.4 Hz, 1H), 3.79 (t, J = 9.0 Hz, 1H), 3.69−3.61 (m, 1H), 3.49 (t, J = 9.0 Hz, 1H), 3.45 (t, J = 11.1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 149.1, 147.1, 140.2, 137.0, 127.4, 126.7, 126.4, 123.6, 122.7, 121.8, 117.3, 110.5, 110.3, 108.9, 102.1, 87.4, 79.2, 73.6, 71.1, 69.6, 33.2. ESMS m/z: 418 (MH^+), 440 (MNa^+). HRMS (FAB) for $C_{21}H_{20}ClNO_6$: calcd, 417.0979; found, 417.0985.

4-Chloro-3-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-1-(β-D-xylopyranosyl)-1*H*-indole (19q). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-chloro-3-formyl-1*H*-indole **13j** and 3,4-(ethylenedioxy)phenylmagnesium bromide according to the general procedure in 68% yield over three steps. ^{1}H NMR (300 MHz, CD_3OD) δ 7.42 (dd, J = 8.1, 0.6 Hz, 1H), 7.09−6.98 (m, 3H), 6.72−6.66 (m, 3H), 5.31 (d, J = 9.0 Hz, 1H), 4.64 (s, 2H), 4.20−4.17 (m, 4H), 3.95 (dd, J = 10.8, 5.4 Hz, 1H), 3.79 (t, J = 9.0 Hz, 1H), 3.69−3.61 (m, 1H), 3.49 (t, J = 9.0 Hz, 1H), 3.45 (t, J = 10.8 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 144.8, 143.2, 140.2, 136.2, 127.4, 126.7, 126.5, 123.5, 122.7, 121.8, 118.5, 117.9, 117.3, 110.5, 87.4, 79.2, 73.5, 71.1, 69.6, 65.7, 65.6, 32.8. ESMS m/z: 432 (MH^+), 454 (MNa^+). HRMS (FAB) for $C_{22}H_{22}ClNO_6$: calcd, 431.1136; found, 431.1139.

4-Chloro-3-(4-hydroxybenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (20). A 1 M BBr_3 solution in CH_2Cl_2 (5 mL) was added to a stirred solution of **18c** (267 mg, 0.50 mmol) in CH_2Cl_2 (16 mL) at −78 °C under nitrogen. The mixture was warmed to 0 °C gradually. After 4 h, the reaction was quenched by the addition of saturated $NaHCO_3$ (aq) and the solvent was removed under reduced pressure. The residue was redissolved in ethyl acetate and H_2O. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate twice. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/Hex = 1/3 to 1/2) to give 4-chloro-3-(4-hydroxybenzyl)-1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1*H*-indole (68 mg, 26%).

A 30% solution of NaOMe in MeOH (95 μL) was added to a solution of 4-chloro-3-(4-hydroxybenzyl)-1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1*H*-indole (68 mg, 0.13 mmol) in MeOH/CH_2Cl_2 (2/1, 1.5 mL) at 0 °C under nitrogen. The mixture was warmed to room temperature gradually and then neutralized with acidic resin after 2 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 1/15 → 1/10) to give the desired product **20** (29 mg, 56%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.42 (dd, J = 8.1, 0.9 Hz, 1H), 7.09−6.95 (m, 5H), 6.71−6.67 (m, 2H), 5.30 (d, J = 9.0 Hz, 1H), 4.23 (s, 2H), 3.94 (dd, J = 11.0, 5.4 Hz, 1H), 3.76 (t, J = 9.0 Hz, 1H), 3.68−3.59 (m, 1H), 3.48 (t, J = 9.0 Hz, 1H), 3.45 (t, J = 11.0 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 156.1, 139.9, 133.7, 130.8, 127.3, 126.5, 126.4, 123.5, 121.7, 117.9, 116.0, 110.4, 87.1, 78.9, 73.3, 70.9, 69.3, 32.7. ESMS m/z: 390 (MH^+), 412 (MNa^+). HRMS (EI) for $C_{20}H_{20}ClNO_5$: calcd, 389.1030; found, 389.1038.

4-Chloro-3-[4-(2-phenoxyethoxy)benzyl]-1-(β-D-xylopyranosyl)-1*H*-indole (21a). Cs_2CO_3 (23 mg, 71 μmol) and 2-phenoxyethyl bromide (22 mg, 107 μmol) were added to a stirred solution of **20** (14 mg, 35 μmol) in DMF (0.4 mL) at room temperature under nitrogen. After 17 h, the reaction was quenched by the addition of H_2O and the resulting solution extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 1/20) to afford the desired product **21a** (13.3 mg, 73%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (dd, J = 8.0, 0.8 Hz, 1H), 7.28−7.24 (m, 2H), 7.16−7.13 (m, 2H,), 7.07 (t, J = 8.0 Hz, 1H), 7.00−6.87 (m, 7H), 5.31 (d, J = 9.2 Hz, 1H), 4.27 (s, 6H), 3.94 (dd, J = 10.8, 5.2 Hz, 1H), 3.77 (t, J = 9.2 Hz, 1H), 3.67−3.61 (m, 1H), 3.49 (t, J = 9.2 Hz, 1H), 3.45 (t, J = 10.8 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 160.3, 158.5, 140.2, 135.5, 130.9, 130.6, 127.4, 126.7, 126.5, 123.6, 122.1, 117.6, 115.7, 115.6, 110.5, 87.4, 79.2, 73.6, 71.1, 69.6, 68.0, 67.9, 32.8. ESMS m/z: 510 (MH^+), 532 (MNa^+). HRMS (FAB) for $C_{28}H_{28}ClNO_6$: calcd, 509.1605; found, 509.1603.

4-Chloro-3-[4-(prop-2-yn-1-yloxy)benzyl]-1-(β-D-xylopyranosyl)-1*H*-indole (21b). K_2CO_3 (124 mg, 897 μmol) and propargyl bromide (30 μL, 569 μmol) were added to a stirred solution of **20** (35 mg, 89 μmol) in DMF (0.9 mL) at room temperature under nitrogen. The mixture was heated to 50 °C and stirred for 21 h. The reaction was quenched by the addition of H_2O, and the resulting solution was extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 1/20) to give the desired product **21b** (26.8 mg, 70%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.43 (dd, J = 8.1, 0.9 Hz, 1H), 7.17−7.12 (m, 2H), 7.07 (t, J = 8.1 Hz, 1H), 7.01−6.98 (m, 2H), 6.90−6.85 (m, 2H), 5.30 (d, J = 9.0 Hz, 1H), 4.66 (d, J = 2.1 Hz, 2H), 4.72 (s, 2H), 3.99 (dd, J = 11.1, 5.4 Hz, 1H), 3.78 (t, J = 9.0 Hz, 1H), 3.68−3.60 (m, 1H), 3.49 (t, J = 9.0 Hz, 1H), 3.45 (t, J = 11.1 Hz, 1H), 2.89 (t, J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 157.4, 140.2, 135.9, 130.8, 127.4, 126.7, 126.5, 123.6, 121.8, 117.5, 115.8, 110.5, 87.4, 80.2, 79.2, 76.6, 73.5, 71.1, 69.6, 56.8, 32.7. ESMS m/z: 428 (MH^+). HPLC purity 85.6%.

4-Chloro-3-{4-[2-(2-ethoxyethoxy)ethoxy]benzyl}-1-(β-D-xylopyranosyl)-1*H*-indole (21c). MsCl (0.86 mL, 10.96 mmol) and triethylamine (3.0 mL, 21.91 mmol) were added to a stirred solution of diethylene glycol monoethyl ether (0.98 g, 7.30 mmol) in CH_2Cl_2 (30 mL) at 0 °C under nitrogen. The mixture was slowly warmed to room temperature. After 3 days, the mixture was diluted with CH_2Cl_2 and concentrated under reduced pressure. The residue was redissolved in Et_2O and washed with 1 N HCl (aq). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue (885 mg, 57%) was used for alkylation directly without further purification.

To a stirred solution of the aforementioned mesylate residue (70 mg, 329 μmol) and **20** (17 mg, 43 μmol) in DMF (0.4 mL) at room temperature under nitrogen was added Cs_2CO_3 (42 mg, 130 μmol). After 2 days, the reaction was quenched by the addition of H_2O, and the resulting solution was extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 1/20 to 1/10) to provide the desired product **21a** (15.1 mg, 68%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.42 (dd, J = 8.2, 0.9 Hz, 1H), 7.14−7.04 (m, 3H), 7.00−6.97 (m, 2H), 6.84−6.81 (m, 2H), 5.30 (d, J = 9.0 Hz, 1H), 4.26 (s, 2H), 4.09−4.05 (m, 2H), 3.94 (dd, J = 11.0, 5.1 Hz, 1H), 3.81−3.77 (m, 3H), 3.68−3.55 (m, 5H), 3.52−3.41 (m, 4H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 158.5, 140.2, 135.3, 130.9, 127.4, 126.7, 126.5, 123.5, 121.8, 117.6, 115.5, 110.5, 87.4, 79.2, 73.6, 71.8, 71.2, 71.1, 71.0, 69.6, 68.6, 67.7, 32.7, 15.5. ESMS m/z: 528 (MNa^+). HRMS (EI) for $C_{26}H_{32}ClNO_7$: calcd, 505.1867; found, 505.1187. HPLC purity 89.5%.

4-Bromo-3-(4-cyclopropylbenzyl)-1-(β-D-xylopyranosyl)-1*H*-indole (22). The title compound was obtained from 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-4-bromo-3-formyl-1*H*-indole **13n** and 4-cyclopropylphenylmagnesium bromide according to the general procedure for the preparation of **19m** in 58% yield over three steps. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, J = 8.0 Hz, 1H), 7.19 (dd, J = 8.0, 0.4 Hz, 1H), 7.09−7.02 (m, 2H), 7.02−6.95 (m, 4H), 5.30 (d, J = 8.8 Hz, 1H), 4.32, 4.29 (ABq, J = 16.4 Hz, 2H), 3.94 (dd, J = 11.2, 5.2 Hz, 1H), 3.75 (t, J = 8.8 Hz, 1H),

3.66−3.60 (m, 1H), 3.48 (t, J = 8.8 Hz, 1H), 3.44 (t, J = 11.2 Hz, 1H), 1.88−1.82 (m, 1H), 0.93−0.88 (m, 2H), 0.64−0.60 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 142.7, 139.9, 139.7, 129.9, 127.8, 127.0, 126.5, 125.3, 123.8, 117.9, 115.2, 111.0, 87.3, 79.1, 73.5, 71.0, 69.5, 33.1, 15.9, 9.59. ESMS m/z: 458 (MH^+). HRMS (EI) for $C_{23}H_{24}BrNO_4$: calcd, 457.0889; found, 457.0898.

In Vitro Human SGLT Uptake Assays. Stably transfected CHO-K1 cells were used for transporter studies. SGLT was determined by uptake of [^{14}C]α-methyl-D-glucopyranoside ([^{14}C]AMG, specific radioactivity of 310 mCi/mmol) purchased from Perkin-Elmer (Boston, MA). For the purpose of this study, Krebs−Ringer−Henseleit (KRH) solution containing 120 mM NaCl, 4.7 mM KCl, 1.2 mM $MgCl_2$, 2.2 mM $CaCl_2$, and 10 mM Hepes (pH 7.4 with Tris) was used for SGLT uptake assays. All chemicals were purchased from Sigma (Deisenhofen, Germany). Briefly, hSGLT2/CHO-K1 cells or hSGLT1/CHO-K1 cells were seeded into a white-walled 96-well culture plate (Corning, NY) at a density of 30 000 cells/well (hSGLT2) or 20 000 cells/well (hSGLT1) and incubated for 48 h at 37 °C in a 5% CO_2 atmosphere in growth medium. After 48 h, the culture medium in the wells was removed and wells were washed three times with 280 μL of KRH solution and then incubated in KRH solution containing 3 μM [^{14}C]AMG in the absence or presence of inhibitors for up to 120 min at 37 °C. At the end of the uptake period, the KRH solution was removed and the uptake of [^{14}C]AMG was stopped by adding ice-cold KRH solution (stop solution). The wells were rinsed three times with 150 μL of stop buffer using the microplate washer (TEcan, Männedorf, Switzerland). After the third rinse, the stop solution was completely removed from the wells and the cells were solubilized by adding 0.1% sodium dodecyl sulfate (Sigma). After 24 h, the microtiter plate was taken for scintillation counting of radioactive [^{14}C]AMG using a TopCount (Perkin-Elmer). The percent of inhibition of inhibitors was calculated by comparing counts per minute (CPM) in inhibitor-containing well with CPM in wells containing only DMSO vehicle. Phlorizin and dapagliflozin were evaluated in parallel in every assay. A dose-response curve was fitted to a sigmoidal dose-response model using GraphPad software to determine the inhibitor concentration at half-maximal response (EC_{50}).

In Vivo Pharmacokinetics Evaluation of 19m in Rats. The animal study was approved by Institutional Animal Care and Use Committee of National Health Research Institutes. A solution of test compound (1 mg/mL) was prepared by dissolving the appropriate amount of compound in a mixture of PEG 400/DMA (20:80, v/v). Male Sprague−Dawley rats, weighing 250−350 g each (8−10 weeks old), were obtained from BioLASCO, Ilan, Taiwan. **19m** was administered to three male rats each intravenously by a bolus injection to the jugular vein or orally at 1 mg/kg dose. At 0 (prior to dosing), 2, 5 (iv only), 15, and 30 min and at 1, 2, 4, 6, 8, and 24 h after dosing, a blood sample (∼150 μL) was collected from each animal via the jugular-vein cannula and stored in ice (0−4 °C). Plasma was separated from the blood by centrifugation (14000g for 15 min at 4 °C in a Beckman model AllegraTM 6R centrifuge) and stored in a freezer (−60 °C). All samples were analyzed for the test compound by LC−MS/MS (ABI 4000Q Trap). Data were acquired via multiple reactions monitoring. Plasma concentration data were analyzed with standard noncompartmental method with Kinetica (version 4.1.1, InnaPhase Corporation, PA).

Urine Glucose Excretion in Normal Sprague−Dawley Rats.[20] Male Sprague−Dawley rats of 8−10 weeks old were purchased from BioLasco, Ilan, Taiwan. Male Sprague−Dawley rats were overnight-fasted and divided into several groups in which no body weight difference between groups was significant (n = 4). The rats were mildly anesthetized with 30% O_2 and 70% CO_2 mixed gas inhalation and orally gavaged with a single dose of **19m** in different doses (3, 10, and 50 mg/kg) and vehicle (dapagliflozin **5**, 1 mg/kg), respectively, and subsequently dosed orally with 50% glucose solution at dose of 2 g/kg. The rats were returned to metabolism cages (ISHIHALA, Tokyo, Japan) for a 24 h urine collection, and the experimental animals were refed at 1 h after glucose challenge. After the urine volumes were measured and recorded, the urine samples were measured for glucose levels by using a DRI-CHEM 3500s (FUJI, Tokyo, Japan). A P value of less than 0.05 was considered statistically significant.

Blood Glucose Lowering Effects in the Streptozotocin-Induced Diabetes Rats.[20] Adult male Sprague−Dawley rats (BioLasco, Ilan, Taiwan) received three intraperitoneal injections of streptozotocin from Sigma (catalog no. S0130, St. Louis, MO) at 65 mg/kg freshly prepared in 0.01 M citrate buffer at one injection every other day. The animals were then monitored by using blood glucometer (ACCU-CHEK from Roche, Basel, Switzerland), for the glucose levels in blood collected via stabbing the tail vein with 25G needle once a week. A streptozotocin-induced diabetes was confirmed when the blood glucose levels were up more than 450 mg/dL. The diabetic rats were divided into experimental groups at three rats each and orally administered a single dose of **19m**, **5**, or vehicle as control. Blood samples were obtained from the tail vein at 0 (predose), 0.5, 1, 2, 3, 4, and 5 h after the oral administration and measured for blood glucose levels with the glucometer. A P value of less than 0.05 was considered statistically significant.

Diarrheogenic Activity Test.[31] Male CD-1 (ICR) mice at the age of 5−6 weeks purchased from BioLASCO (Ilan, Taiwan) were used in this study. The mice were administrated orally with **19m** at doses of 200, 50, 10 mg/kg and vehicle (5% DMSO, 20% Cremophor EL, and 75% ddH_2O). After dosing, all animals were housed in the metabolism cages (SHINANO, SN-783, Tokyo, Japan) individually and given diet and water ad libitum during the experiment. The mice were monitored once hourly within 8 h after dosing. The bottom of each cage was covered with white paper for convenient observation of fecal state.

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Supporting Information Available: Details of synthetic procedures for compound **19m** and HPLC purity determination conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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