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Structure–activity relationship studies of 4-benzyl-1*H*-pyrazol-3-yl β-D-glucopyranoside derivatives as potent and selective sodium glucose co-transporter 1 (SGLT1) inhibitors with therapeutic activity on postprandial hyperglycemia

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ABSTRACT

Sodium glucose co-transporter 1 (SGLT1) plays a dominant role in the absorption of glucose in the gut and is considered a promising target in the development of treatments for postprandial hyperglycemia. A series of 4-benzyl-1*H*-pyrazol-3-yl β-D-glucopyranoside derivatives have been synthesized, and its inhibitory activity toward SGLTs has been evaluated. By altering the substitution groups at the 5-position of the pyrazole ring, and every position of the phenyl ring, we studied the structure–activity relationship (SAR) profiles and identified a series of potent and selective SGLT1 inhibitors. Representative derivatives showed a dose-dependent suppressing effect on the escalation of blood glucose levels in oral mixed carbohydrate tolerance tests (OCTT) in streptozotocin–nicotinamide-induced diabetic rats (NA-STZ rats).

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion and/or insulin action.[1] The global prevalence of DM is increasing; in 2011, there were 366 million people with DM, and this number is expected to rise to 552 million by 2030.[2] DM is a risk factor for microvascular diseases including retinopathy, neuropathy, and nephropathy and is also known to be associated with increases in cardiovascular (CV) disease and mortality. Increased postprandial glucose excursion is a frequently observed abnormality in DM that is associated with endothelial dysfunction as well as oxidative and nitrosative stress. A large number of epidemiological studies have consistently shown that postprandial hyperglycemia is a powerful predictor of CV disease. Hence, there is now greater awareness of the importance of controlling postprandial hyperglycemia.[3] α-Glucosidase inhibitors that delay the digestion of carbohydrates have been used clinically for the treatment of postprandial hyperglycemia. In a clinical trial to prevent non-insulin-dependent DM (NIDDM) in impaired glucose tolerance (IGT) patients (STOP-NIDDM), the α-glucosidase inhibitor, acarbose, not only decreased the progression to DM but also protected them against CV disease.[4]

Carbohydrates in the diet, mainly in the form of poly- or disaccharides, are digested into monosaccharides by hydrolytic enzymes (α-amylase, α-glucosidases, and β-galactosidases) before absorption.[5] The resulting monosaccharides are absorbed via several types of transporters in the small intestine.[6] Sodium glucose co-transporter 1 (SGLT1), expressed in the brush border membrane of the enterocytes, plays a central role in the absorption of glucose and galactose.[7] Mutations in the SGLT1 gene cause malabsorption of these sugars.[8] Furthermore, SGLT1 protein levels were found to be higher in duodenum biopsy samples obtained from diabetic patients relative to the control subjects.[9] Increased expression of SGLT1 in the small intestine was also observed in streptozotocin-induced diabetic rats.[10] These findings suggest that the inhibition of SGLT1 can be an efficacious approach to improve postprandial hyperglycemia in DM and IGT patients.

To date, multiple classes of compounds have been reported to show inhibitory activities on SGLTs.[11] However, most of these compounds intend to inhibit renal SGLT2, and little is known about the structure–activity relationship (SAR) and the in vivo efficacy of

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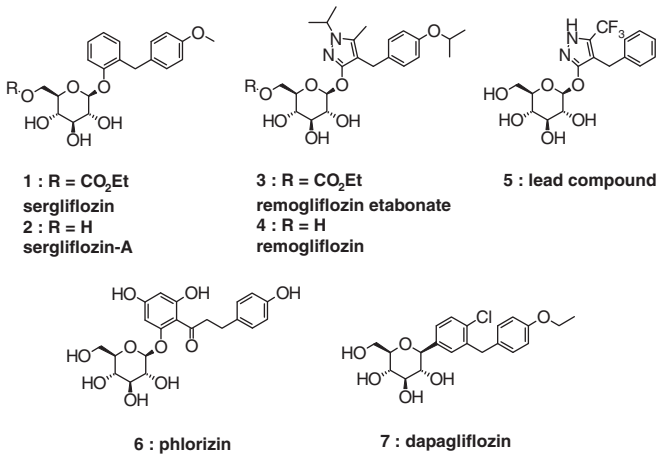


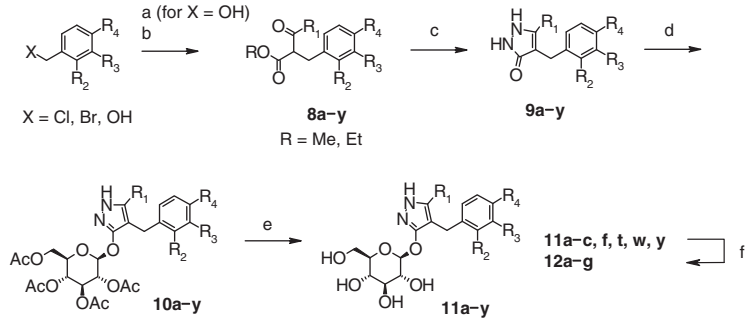
Figure 1. Structure of known SGLT inhibitors and the lead compound in this study.

SGLT1-targeted inhibitors.[12] SGLT2, the isoform of SGLT1, is distributed predominantly in the proximal tubules of the kidney, and plays a dominant role in the reabsorption of glomerular-filtered glucose.[13] Since SGLT2 inhibitors can normalize blood glucose levels by excreting excess glucose into the urine, large numbers of compounds developed by pharmaceutical companies are undergoing clinical trials to evaluate their efficacy as antidiabetic agents.[14] We previously discovered two prodrugs of selective SGLT2 inhibitors, sergliflozin (**1**)[15] and remogliflozin etabonate (**3**)[16] (Fig. 1). In the course of this research, 4-benzyl-5-trifluoromethyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (**5**), an analog of remogliflozin (**4**), was found to have strong inhibitory activity on both SGLTs, and its potency toward SGLT1 was comparable with that of naturally occurring phlorizin (**6**), a nonselective inhibitor of these SGLTs.[17] With this novel lead compound in hand, we embarked on a research program to improve the potential of SGLT1 inhibitors on postprandial hyperglycemia and performed a series of SAR studies focusing on SGLT1 activity to develop improved profile compounds. Since compounds that inhibit both SGLTs could induce urinary glucose excretion and normalize blood glucose levels by inhibiting renal SGLT2 if they were absorbed, our exploratory effort was directed to achieve an SGLT1-selective molecule to investigate efficacy based on the inhibition of SGLT1 alone. Ultimately, this selectivity for SGLT1 activity on intestinal transporters might facilitate the combined use with SGLT2 inhibitors targeting renal glucose excretion.

In the present paper, we report the synthesis and SAR of 4-benzyl-1*H*-pyrazol-3-yl β-D-glucopyranoside derivatives to find potent and selective SGLT1 inhibitors. We also describe the in vivo pharmacological profiles of several derivatives in association with their in vitro intestinal metabolic stability and aqueous solubility.

2. Chemistry

4-Benzyl-1*H*-pyrazol-3-yl β-D-glucopyranoside derivatives were prepared as illustrated in Scheme 1. Benzyl halides or benzyl alcohols, in which hydroxyl groups of benzyl alcohols were methanesulfonylated using methanesulfonyl chloride (MsCl) with Et_3N before condensation, were allowed to react with ketoesters in the presence of NaH to afford 2-substituted ketoesters (**8a–y**). Subsequent cyclization with hydrazine monohydrate gave aglycones (**9a–y**). Reaction of aglycones (**9a–y**) with acetobromoglucose was carried out in two-phase solvents consisting of CH_2Cl_2 and aqueous NaOH solution in the presence of the phase-transfer catalyst, $BnN(n\text{-}Bu)_3Cl$.[18] The glucosidated structure of the product was confirmed by X-ray crystal structure analysis of the intermediate (**10a**),



Cpd 8–11	R_1	R_2	R_3	R_4
a	CF_3	H	H	OBn
b	CF_3	H	OBn	H
c	CF_3	OBn	H	H
d	Me	OBn	H	H
e	Et	OBn	H	H
f	iPr	OBn	H	H
g	tBu	OBn	H	H
h	cPr	OBn	H	H
i	iPr	H	H	H
j	iPr	F	H	H
k	iPr	Me	H	H
l	iPr	CF_3	H	H
m	iPr	Et	H	H

Cpd 8–11	R_1	R_2	R_3	R_4
n	iPr	OMe	H	H
o	iPr	CN	H	H
p	iPr	H	H	F
q	iPr	H	H	Me
r	iPr	H	H	Et
s	iPr	H	H	OMe
t	iPr	H	H	OBn
u	iPr	H	H	CN
v	iPr	H	Me	H
w	iPr	H	OBn	H
x	iPr	Me	H	Me
y	iPr	Me	H	OBn

Cpd 12	R_1	R_2	R_3	R_4
a	CF_3	H	H	OH
b	CF_3	H	OH	H
c	CF_3	OH	H	H
d	iPr	OH	H	H
e	iPr	H	H	OH
f	iPr	H	OH	H
g	iPr	Me	H	OH

Scheme 1. Reagents and conditions: (a) MsCl, Et_3N, DME or THF, 0 °C; (b) NaH, $R_1COCH_2CO_2R$, DME or THF, 0 °C to reflux; (c) $N_2H_4{\cdot}H_2O$, toluene or EtOH, reflux or rt; (d) 5 M NaOH aq, $BnN(n\text{-}Bu)_3Cl$, acetobromoglucose, CH_2Cl_2, rt; (e) NaOMe, MeOH, rt; (f) H_2, Pd–C, MeOH, rt.

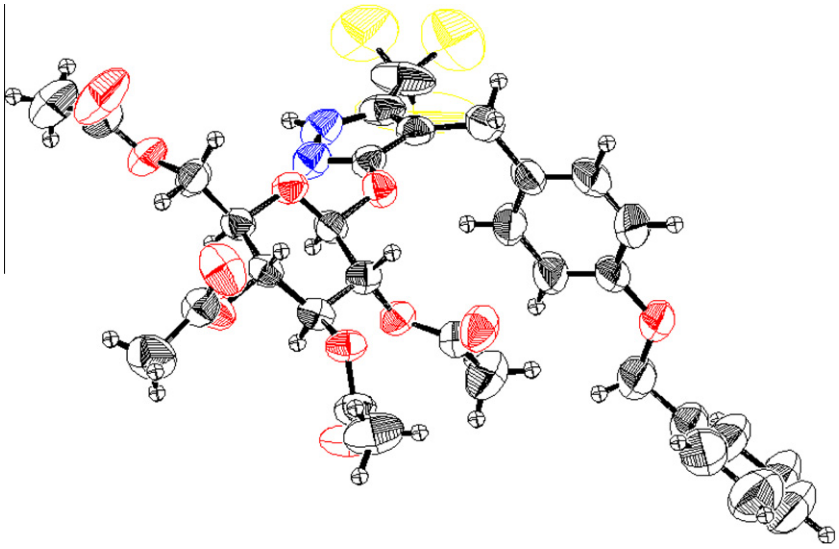


Figure 2. ORTEP representation of the X-ray crystal structure of **10a**.

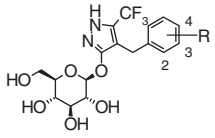
as shown in Figure 2. Finally, the acetyl groups protecting the hydroxyl groups on the sugars were removed by hydrolysis using NaOMe in MeOH to give 4-benzyl-1*H*-pyrazol-3-yl β-D-glucopyranoside derivatives **11a–y**. For the synthesis of compounds possessing hydroxyl groups on the aglycones (**12a–g**), benzyl protective groups were removed by Pd–C-catalyzed hydrogenation.

3. Results and discussion

All compounds were screened for their inhibitory effects on the uptake of radiolabeled α-methyl-D-glucopyranoside ([^{14}C]-AMG) into COS-7 cells transiently expressing human SGLT1 (hSGLT1) or SGLT2 (hSGLT2).

In phrolizin (**6**), one of the hydroxyl groups exists in the 4-position of the distal phenyl ring. SAR studies of 4′-dehydroxyphlorizin derivatives demonstrated that a hydroxyl group at this position helps to retain the inhibitory effects on glucose uptake in the small intestine.[19] It has also been reported that the replacement of the ethoxy group at the 4-position of the distal phenyl ring of dapagliflozin (**7**), the most advanced selective SGLT2 inhibitor in the clinic,[20] with a hydroxyl group enhanced the inhibitory activity of SGLT1 and reduced the selectivity for SGLT2.[21] These findings led us to assume that the introduction of hydroxyl groups into the distal phenyl ring might also improve SGLT1 inhibitory activity in our scaffold. Hence, we examined the effects of introducing hydroxyl groups into the phenyl ring of our lead compound (**5**). Since the substitution point might slide between each scaffold, we examined every position of the phenyl ring of compound **5** to confirm suitability, and the results are shown in Table 1. Contrary to our expectation, none of the hydoxylated derivatives (**12a–c**) showed improved inhibitory activity for SGLT1. Indeed, of these compounds, only the 4-hydroxylated compound (**12a**) showed a maintained, but not enhanced, activity with slightly diminished selectivity for SGLT1 compared with the unsubstituted compound **5**. Introduction of hydroxyl groups into other positions decreased the activity for both SGLTs (**12b, c**). Although no improvements were observed in these initial attempts, the 4-position was relatively favored for hydroxyl-group substitution, indicating that this position on a benzyl pyrazole derivative might be similar to that in the other scaffolds described above. During these explorations, synthetic precursors possessing benzyl protective groups (**11a–c**) were also evaluated for their activities. Substitution at the 3-and

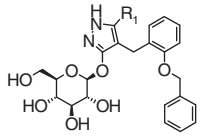
Table 1
The hSGLT1 and hSGLT2 inhibitory activities and selectivity of 5-trifluoromethyl pyrazole derivatives substituted with hydroxyl and benzyloxy groups on the phenyl ring



Compound	R	SGLT IC_{50}[a] (nM)		Selectivity[b]
		hSGLT1	hSGLT2	
6	—	536 ± 19[c]	38 ± 2[c]	0.071
5	H	442	342	0.77
12a	4-OH	500	154	0.31
12b	3-OH	1940	2790	1.4
12c	2-OH	4310	14,900	3.5
11a	4-OBn	1720	7	0.0041
11b	3-OBn	8930	5680	0.64
11c	2-OBn	37	14,000	380

[a] IC_{50} values for SGLT inhibition were determined in duplicate or triplicate.
[b] Selectivity values were calculated by IC_{50} hSGLT2/IC_{50} hSGLT1.
[c] Mean ± S.E. of 19 experiments.

Table 2
The hSGLT1 and hSGLT2 inhibitory activities and selectivity of 4-(2-benzyloxy phenylmethyl)pyrazole derivatives substituted with various groups on the 5-position of the pyrazole ring



Compound	R_1	SGLT IC50[a] (nM)		Selectivity[b]
		hSGLT1	hSGLT2	
11c	CF_3	37	14,000	380
11d	Me	871	5010	5.8
11e	Et	306	13,900	45
11f	*i*Pr	60	74,000	1200
11g	*t*Bu	203	64,700	320
11h	cPr	278	156,000	560

[a] IC_{50} values for SGLT inhibition were determined in duplicate or triplicate.
[b] Selectivity values were calculated by IC_{50} hSGLT2/IC_{50} hSGLT1.

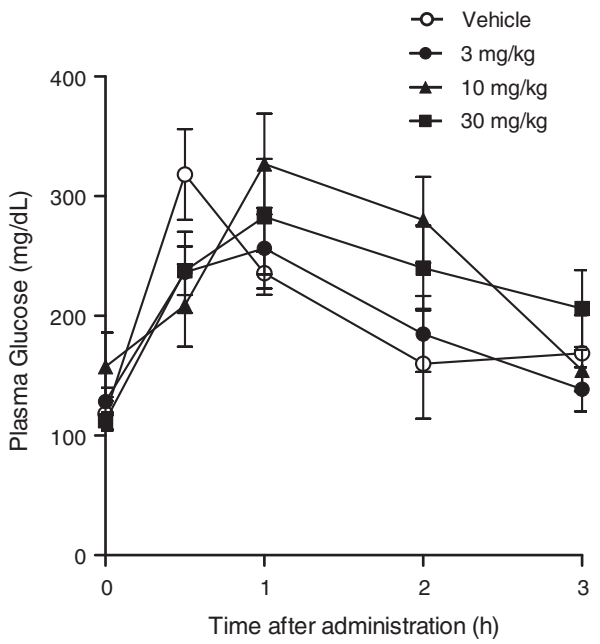
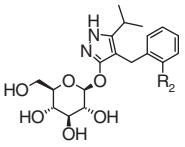


Figure 3. Effects of compound **11f** on OCTT in NA-STZ rats. Points and bars represent the mean and S.E. values, respectively ($n = 7$).

Table 3
The hSGLT1 and hSGLT2 inhibitory activities and selectivity of 5-isopropylpyrazole derivatives substituted with various groups on the 2-position of the phenyl ring



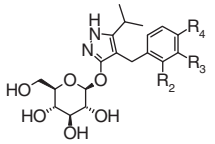
Compound	R_2	SGLT IC50[a] (nM)		Selectivity[b]
		hSGLT1	hSGLT2	
11f	OBn	60	74,000	1200
11i	H	738	2020	2.7
11j	F	298	1390	4.7
11k	Me	725	18,500	26
11l	CF_3	2430	60,500	25
11m	Et	675	14,100	21
11n	OMe	7280	204,000	28
12d	OH	9520	75,900	8.0
11o	CN	7170	65,700	9.2

[a] IC_{50} values for SGLT inhibition were determined in duplicate or triplicate.
[b] Selectivity values were calculated by IC_{50} hSGLT2/IC_{50} hSGLT1.

4-positions resulted in loss of activity (**11a, b**); however the 2-benzyloxy-substituted derivative (**11c**) showed greater selectivity against SGLT2 with dramatically improved the inhibitory activity on SGLT1 compared with the unsubstituted compound **5**.

In general, to find selective SGLT2 inhibitors, the exploratory efforts on the substituents of the distal phenyl rings were mainly directed to the 4-position. Hence, we found that this remarkable substituent effect of the 2-benzyloxy group was unique, and this encouraged us to explore derivatives of this scaffold further. Before another investigation, we assessed the intestinal metabolic stability of the compound **11c**. It is known that phlorizin (**6**) is easily hydrolyzed into its aglycone form, phloretin, by β-glucosidase in the intestine.[17] As shown in Table 5, incubation with rat intestinal microsomes immediately decreased compound **11c**, as well as phlorizin (**6**), and the corresponding aglycone of **11c** was detected. Since, the aglycone of **11c** (**9c**) has no inhibitory activity on SGLT1

Table 4
The hSGLT1 and hSGLT2 inhibitory activities and selectivity of 5-isopropylpyrazole derivatives substituted with various groups on the phenyl ring



Compound	R_2	R_3	R_4	SGLT IC50[a] (nM)		Selectivity[b]
				hSGLT1	hSGLT2	
11i	H	H	H	738	2020	2.7
11k	Me	H	H	725	18,500	26
11p	H	H	F	1190	4140	3.5
11q	H	H	Me	94	231	2.5
11r	H	H	Et	223	68	0.30
11s	H	H	OMe	689	377	0.55
12e	H	H	OH	207	285	1.4
11u	H	H	CN	4310	3580	0.83
11v	H	Me	H	1330	5980	4.5
12f	H	OH	H	1230	13,300	11
11x	Me	H	Me	246	6010	24
12g	Me	H	OH	320	6890	22

[a] IC_{50} values for SGLT inhibition were determined in triplicate.
[b] Selectivity values were calculated by IC_{50} hSGLT2/IC_{50} hSGLT1.

(IC_{50} >100 μM), it was expected that **11c** would show weak efficacy in vivo. To achieve efficacious compounds in vivo, the metabolic stability of the glucosidic linkages should be improved. As common structural features between phlorizin (**6**) and compound **11c**, electron-withdrawing groups on the ring connecting to glucose were suggested. We anticipated that the trifluoromethyl group may have a deleterious effect on the stability of the glucosidic linkages, and turned our attention to find other non-electron-withdrawing groups at the 5-position of the pyrazole ring of compound **11c**.

Table 2 shows the results of investigation of substituents at the 5-position of the pyrazole ring. Replacement with a methyl group markedly decreased the inhibitory activity and selectivity for SGLT1 (**11d**), while introducing longer alkyl groups (**11e–h**) enhanced activity and selectivity compared with compound **11d**. Of these, the isopropyl derivative **11f** showed comparable potency and further improved the selectivity for SGLT1 relative to compound **11c**. The bulkier *tert*-butyl group (**11g**) and cyclized propyl group (**11h**) showed diminished activity on SGLT1 compared with the isopropyl group (**11f**), indicating that SGLT1 would recognize subtle difference in the shape of the groups incorporated onto the 5-position of the pyrazole ring. On the basis of these results, the isopropyl group was considered to be optimal as a substitution group of this position, and an intestinal metabolic stability test of compound **11f** was performed (Table 5). Fortunately, **11f** clearly improved stability compared with the 5-trifluoromethyl pyrazole derivative (**11c**), and 51% of **11f** was found in the unchanged form, even at 60 min. These findings demonstrate that substituents at the 5-position of the pyrazole ring would affect not only the activity and selectivity for SGLT1 but also the metabolic stability of the glucosidic linkage connecting to the 3-position. Prior to in vivo examinations, the inhibitory activity on rat SGLTs (rSGLT1,2) was also evaluated (Table 5). Compound **11f** showed decreased activity, especially in rSGLT1 relative to hSGLT1, but was still effective compared with phlorizin (**6**), and high selectivity remained.

Despite the strong inhibitory activity on SGLT1 and the relatively stable profile in the intestine, compound **11f** showed insufficient efficacy in an oral mixed carbohydrate tolerance test (OCTT) in streptozotocin–nicotinamide-induced diabetic rats (NA-STZ rats).[22] As shown in Figure 3, suppressing effects of com-

Table 5
Aqueous solubility and parameters in rats: inhibitory activity and selectivity of SGLT1 and SGLT2, intestinal metabolic stability, and urinary glucose excretion of key compounds

Compound	SGLT IC_{50}[a] (nM)		Selectivity[b]	Metabolic stability at 30/60 min[c]	Solubility[d] (mg/mL)	Urinary excreted glucose[e] (mg)		
	rSGLT1	rSGLT2				Test compound	Sergliflozin (**1**)	Control
6	350 ± 34[f]	96 ± 11[f]	0.27	ND/ND[g]	NT[h]	NT[h]	—	—
11c	227	40,800	180	ND/ND[g]	NT[h]	NT[h]	—	—
11f	308	100,000	320	71/51	0.24	0.4 ± 0.1	64.1 ± 5.0***	0.4 ± 0.1
11i	NT[h]	NT[h]	—	NT[h]	19	NT[h]	—	—
11x	67	4650	69	91/67	3.7	0.8 ± 0.1	53.3 ± 8.2**	0.5 ± 0.1
12g	183	4370	24	96/83	>18	0.7 ± 0.2	53.3 ± 8.2**	0.5 ± 0.1

[a] IC_{50} values for SGLT inhibition were determined in duplicate or triplicate.
[b] Selectivity values were calculated by IC_{50} rSGLT2/IC_{50} rSGLT1.
[c] Incubated with rat intestinal microsomes. Data are shown as % remaining.
[d] Determined in distilled water.
[e] Each value represents the mean ± S.E. (n = 5).
** p < 0.01 versus control.
*** p <0.001 versus control.
[f] Mean ± S.E. of three experiments.
[g] ND = not detected.
[h] NT = not tested.

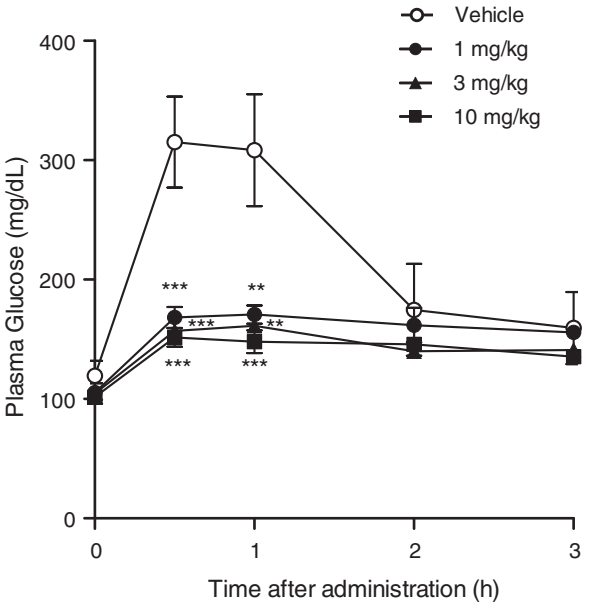


Figure 4. Effects of compound **11x** on OCTT in NA-STZ rats. Points and bars represent the mean and S.E. values, respectively (n = 7). Asterisks indicate significant differences from the control (**p <0.01, ***p <0.001).

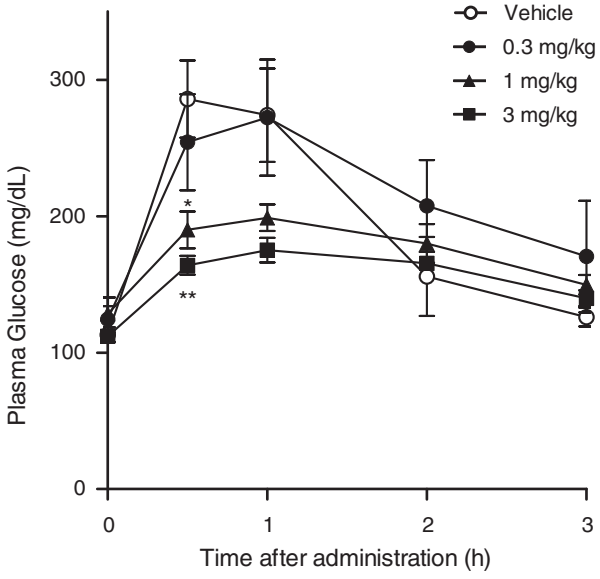


Figure 5. Effects of compound **12g** on OCTT in NA-STZ rats. Points and bars represent the mean and S.E. values, respectively (n = 7). Asterisks indicate significant differences from the control (*p <0.05, **p <0.01).

pound **11f** on the escalation of blood glucose was actually observed at 30 min, although the effect was moderate and could not be observed after 60 min. Moreover, no dose-dependent efficacy was observed. Subsequent assessment of the aqueous solubility of compound **11f** (Table 5) suggested that low solubility to water might explain this unsatisfactory result. Since an SGLT1 inhibitor might compete against highly water-soluble glucose in the intestine, higher water solubility might be advantageous in order to facilitate rapid diffusion into the gut and efficient inhibition of SGLT1. To confirm this idea, we next directed our attention to find highly soluble compounds.

The aromatic ring count of a molecule must be reduced to improve its aqueous solubility.[23] Removal of the 2-benzyloxy group on the phenyl ring of compound **11f** dramatically increased aqueous solubility (**11i**), as expected (Table 5). However, the unsubstituted compound **11i** showed markedly decreased inhibitory activity and selectivity for SGLT1. To recover these parameters, other less hydrophobic groups were next introduced into the 2-position of the phenyl ring, and the results are illustrated in Table 3.

Introduction of a fluorine atom enhanced activity compared with the unsubstituted compound **11i**, but the improvement in selectivity was slight (**11j**). Although the inhibitory activity for SGLT1 was not improved, a moderate recovery of the selectivity for SGLT1 was observed after a methyl group was introduced (**11k**). Replacement of this methyl group with a trifluoromethyl group resulted in marked loss of activity (**11l**). Elongation into an ethyl group led to almost no improvement in activity, but slightly reduction in selectivity versus SGLT2 (**11m**). Compounds containing a methoxy group (**11n**) demonstrated weaker activity compared with compounds containing a benzyloxy group (**11f**), suggesting that the phenyl ring on the methoxy group plays a critical role in improving SGLT1 inhibitory activity in compound **11f**. In addition, the introduction of either OH (**12d**) or CN (**11o**) reduced potency, indicating that these small polar groups were not preferred at this position. In these explorations of less hydrophobic substitution groups at the 2-position of phenyl ring, we could not

find groups that were fully comparable to the benzyloxy group. However, it was found that the selectivity toward SGLT1 could at least be recovered moderately by the introduction of a methyl group (**11k**).

To investigate whether further improvement of the profile could be achieved, we next studied the effects of substituents at the 4-position of the phenyl ring, and the results are shown in Table 4. Unlike at the 2-position, introduction of a fluorine atom at the 4-position resulted in almost no improvement of inhibitory activity and selectivity for SGLT1 (**11p**) compared with unsubstituted compound **11i**. While, SGLT2 inhibition was also enhanced and selectivity was not improved, introduction of a methyl group was effective in improving inhibitory activity on SGLT1 (**11q**). Extension of this methyl group into an ethyl group (**11r**) or replacement with methoxy group (**11s**) both reduced SGLT1 inhibitory activity with loss of selectivity versus SGLT2, suggesting that these groups were relatively SGLT2-targeted. Compared with the 4-methyl derivative **11q**, the 4-hydroxylated compound **12e** was not potent and was slightly less selective toward SGLT1, but showed an enhancement of the inhibition of SGLT1 from the unsubstituted compound **11i**. This finding was not seen in the 5-trifluoromethyl pyrazole derivative (**5** vs **12a**), indicating that substitution of groups at the 5-position of the pyrazole ring might influence the alignment of the distal phenyl ring and groups substituted onto this phenyl ring. A cyano group was also examined as another hydrophilic group, resulting in marked decrease in activity (**11u**). The relatively preferred methyl and hydroxyl groups were also introduced into the 3-position of the phenyl ring. A slight-to-moderate improvement in selectivity was observed, but the inhibitory activity on SGLT1 was reduced compared with that of the unsubstituted compound **11i** (**11v, 12f**), indicating that the 3-position was not favored for the incorporation of these groups compared with other positions of the phenyl ring.

On the basis of these SAR studies, the effects of combining the relatively preferred substitution groups of the phenyl ring were finally investigated. A 2-methyl group was introduced as a selectivity-improving group into compounds bearing a 4-methyl or 4-hydroxyl group. Although the inhibition of SGLT1 was slightly reduced, the resulting disubstituted compounds **11x** and **12g** showed better selectivity profiles compared with basal monosubstituted compounds **11q** and **12e**. Furthermore, since these non-aromatic functional groups would have less effect on the hydrophobicity of molecules, the aqueous solubility of compounds **11x** and **12g** was higher than that of the compound possessing a 2-benzyloxy group (**11f**) (Table 5).

As shown in Figures 4 and 5, in contrast to the results of the less water-soluble compound **11f**, the lowering of blood glucose levels by compounds **11x** and **12g**, respectively, in OCTT in NA-STZ rats was markedly improved in a dose-dependent manner. In this model, metabolically-unstable phlorizin (**6,** 1 mg/kg) showed almost no efficacy (data not shown). These findings suggest that both improved metabolic stability in intestinal content and higher aqueous solubility would contribute to the impressive in vivo efficacy of compounds **11x** and **12g**. As common adverse effects with α-glucosidase inhibitors,[4] these compounds also may cause gastrointestinal disturbances. However, the obvious symptoms such as soft feces or diarrhea were not observed in this study.

In a pharmacokinetic study of compound **12g** (10 mg/kg) in Sprague–Dawley rats, very low levels (8.2 ng/mL) of **12g** were detected in the plasma and were eliminated immediately, causing no detection at 40 min after administration (data not shown). Furthermore, urinary glucose excretion was not observed in normal rats when **11x** and **12g** were administered orally at a dose of 10 mg/kg, and urine was collected overnight (Table 5). In contrast, the orally available SGLT2 inhibitor sergliflozin significantly increased the excretion of glucose into the urine. These findings strongly suggest that the effects of **11x** and **12g** in suppressing the escalation of blood glucose levels in OCTT in NA-STZ rats were based not on the enhancement of urinary glucose excretion by the inhibition of SGLTs in the renal proximal tubule of the kidney but on slowing or preventing digestive glucose absorption by SGLT1 inhibition in the small intestine.

4. Conclusions

A series of 4-benzyl-1*H*-pyrazole-3-yl β-D-glucopyranoside derivatives was explored to develop a compound with potent and selective SGLT1 inhibitory activity. These investigations identified that substituents at the 5- and 2-positions of the pyrazole and phenyl rings, respectively, could improve both inhibitory activity and selectivity toward SGLT1, while substitution at the 4-position on the phenyl ring could enhance only inhibitory activity. In vitro intestinal metabolic stability and aqueous solubility of several compounds were also evaluated, and groups at the 5-position of the pyrazole ring was found to affect the hydrolytic stability of the glucosidic linkage, and compounds possessing non-aromatic functional groups on the phenyl ring showed higher solubility. These SAR studies identified compounds **11x** and **12g** as potent and selective SGLT1 inhibitors, both of which showed improved in vitro intestinal stability over phlorizin (**6**), high solubility to water, and robust efficacy in OCTT in NA-STZ rats. To the best of our knowledge, this is the first report of SAR studies of SGLT1-selective inhibitors. We continue the optimization and evaluation of these derivatives and will report further developments in due course.

5. Experimental

5.1. Chemistry

^{1}H NMR spectra were recorded using Bruker Avance II$^+$ 400 instruments. ^{13}C NMR spectra were recorded using Bruker Avance II$^+$ 400 or Avance III 600 instruments, and chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane as the internal standard. Peak patterns were shown using the following abbreviations: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra (MS) were measured using an Agilent Technologies 6140 (ESI) or Shimadzu LCMS-2010EV (ESI). High resolution mass spectra (HRMS) were recorded using an Agilent Technologies 6520 Accurate-Mass Q-TOF instrument. Silica gel 60F_{254}-precoated glass plates from Merck KgaA were used for thin layer chromatography (TLC). Flash or medium pressure liquid chromatography (MPLC) was performed on silica gel BW-350 from Fuji Silysia Chemical Ltd or SNAP cartridge KP-Sil from Biotage®. All reagents and solvents were commercially available unless otherwise indicated.

5.1.1. 4-(4-Benzyloxyphenylmethyl)-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one (9a)

MsCl (0.88 mL, 11.4 mmol), under ice cooling, was added to a solution of 4-benzyloxyphenylmethanol (2.33 g, 10.9 mmol) and Et_3N (1.67 mL, 11.9 mmol) in 1,2-dimethoxyethane (DME: 10 mL), and the mixture was stirred for 5 min. The insoluble material was removed by filtration and washed with DME (2 mL). The filtrate and washing were added to the mixture prepared by the addition of NaH (478 mg, 12.0 mmol, 60% oil dispersion) into a solution of ethyl 4,4,4-trifluoroacetoacetate (2.00 g, 10.9 mmol) in DME (15 mL) under ice cooling and stirring for 5 min, then the mixture was refluxed for 11 h. After cooling to room temperature, 1 M HCl (20 mL) was added, and the resulting mixture was

extracted with EtOAc. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give crude ethyl 2-(4-benzyloxyphenylmethyl)-4,4,4-trifluoroacetoacetate (**8a**). This material was dissolved in toluene (30 mL), and $N_2H_4 \cdot H_2O$ (1.05 mL, 21.7 mmol) was added to the solution. After refluxing for 7 h, water was added, and the mixture was extracted with EtOAc. The extract was washed with brine and dried over anhydrous $MgSO_4$. Next, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 10:1) to give **9a** (2.46 g, 65%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 3.66 (2H, s), 5.04 (2H, s), 6.87–6.92 (2H, m), 6.98–7.07 (2H, m), 7.28–7.46 (5H, m), 10.20 (0.17H, br s), 10.74 (0.83H, br s), 12.81 (1H, s); MS m/z: 347 $(M-H)^-$.

5.1.2. 4-(3-Benzyloxyphenylmethyl)-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one (9b)

The title compound was prepared from 3-benzyloxyphenylmethanol, as described for the synthesis of **9a**, in 31% yield.

^{1}H NMR (DMSO-d_6) δ: 3.70 (2H, s), 5.03 (2H, s), 6.66–6.77 (2H, m), 6.80 (1H, dd, J = 8.1, 2.3 Hz), 7.16 (1H, t, J = 8.1 Hz), 7.29–7.47 (5H, m), 10.22 (0.15H, br s), 10.78 (0.85H, br s), 12.83 (1H, s); MS m/z: 347 $(M-H)^-$.

5.1.3. 4-(2-Benzyloxyphenylmethyl)-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one (9c)

The title compound was prepared from 2-benzyloxyphenylmethanol, as described for the synthesis of **9a**, in 36% yield.

^{1}H NMR (DMSO-d_6) δ: 3.76 (2H, s), 5.17 (2H, s), 6.71 (1H, d, J = 7.1 Hz), 6.82 (1H, t, J = 7.1 Hz), 7.02 (1H, d, J = 7.8 Hz), 7.10–7.16 (1H, m), 7.29–7.50 (5H, m), 10.11 (0.15H, br s), 10.67 (0.85H, br s), 12.87 (1H, s); MS m/z: 347 $(M-H)^-$.

For the synthesis of following aglycones (**9d–h**, **m**, **n**, **r**, **t**, **v–y**), tetrahydrofuran (THF) was used as the solvent instead of DME.

5.1.4. 4-(2-Benzyloxyphenylmethyl)-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one (9d)

The title compound was prepared from 2-benzyloxyphenylmethanol and methyl acetoacetate, as described for the synthesis of **9a**, in 61% yield.

^{1}H NMR (DMSO-d_6) δ: 1.90 (3H, s), 3.55 (2H, s), 5.14 (2H, s), 6.81 (1H, td, J = 7.4, 1.0 Hz), 6.93–7.02 (2H, m), 7.07–7.14 (1H, m), 7.29–7.36 (1H, m), 7.37–7.43 (2H, m), 7.45–7.50 (2H, m), 8.60–11.80 (2H, br); MS m/z: 295 $(M+H)^+$.

5.1.5. 4-(2-Benzyloxyphenylmethyl)-5-ethyl-1,2-dihydro-3*H*-pyrazol-3-one (9e)

The title compound was prepared from 2-benzyloxyphenylmethanol and methyl 3-oxopentanoate, as described for the synthesis of **9a**, in 74% yield.

^{1}H NMR (DMSO-d_6) δ: 0.94 (3H, t, J = 7.6 Hz), 2.31 (2H, q, J = 7.6 Hz), 3.56 (2H, s), 5.14 (2H, s), 6.81 (1H, td, J = 7.5, 0.9 Hz), 6.95 (1H, dd, J = 7.5, 1.5 Hz), 7.00 (1H, dd, J = 8.2, 0.9 Hz), 7.07–7.14 (1H, m), 7.29–7.50 (5H, m), 8.60–11.90 (2H, br); MS m/z: 309 $(M+H)^+$.

5.1.6. 4-(2-Benzyloxyphenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9f)

The title compound was prepared from 2-benzyloxyphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 67% yield.

^{1}H NMR (DMSO-d_6) δ: 1.11 (6H, d, J = 7.0 Hz), 2.77 (1H, heptet, J = 7.0 Hz), 3.58 (2H, s), 5.14 (2H, s), 6.81 (1H, td, J = 7.4, 1.0 Hz), 6.94 (1H, dd, J = 7.4, 1.5 Hz), 7.00 (1H, dd, J = 8.2, 1.0 Hz), 7.07–7.14 (1H, m), 7.30–7.51 (5H, m), 8.50–12.00 (2H, br); MS m/z: 323 $(M+H)^+$.

5.1.7. 4-(2-Benzyloxyphenylmethyl)-5-*tert*-butyl-1,2-dihydro-3*H*-pyrazol-3-one (9g)

The title compound was prepared from 2-benzyloxyphenylmethanol and methyl 4,4-dimethyl-3-oxopentanoate, as described for the synthesis of **9a**, in 3% yield.

^{1}H NMR (DMSO-d_6) δ: 1.13 (9H, s), 3.71 (2H, s), 5.17 (2H, s), 6.74–6.83 (2H, m), 7.01 (1H, d, J = 7.5 Hz), 7.06–7.13 (1H, m), 7.29–7.52 (5H, m), 8.75–9.75 (1H, br), 10.60–11.50 (1H, br); MS m/z: 337 $(M+H)^+$.

5.1.8. 4-(2-Benzyloxyphenylmethyl)-1,2-dihydro-5-cyclopropyl-3*H*-pyrazol-3-one (9h)

The title compound was prepared from 2-benzyloxyphenylmethanol and methyl 3-cyclopropyl-3-oxopropanoate, as described for the synthesis of **9a**, in 56% yield.

^{1}H NMR (DMSO-d_6) δ: 0.55–0.64 (4H, m), 1.56–1.65 (1H, m), 3.63 (2H, s), 5.14 (2H, s), 6.82 (1H, td, J = 7.4, 1.0 Hz), 6.95–7.03 (2H, m), 7.08–7.14 (1H, m), 7.29–7.51 (5H, m), 8.50–11.60 (2H, br); MS m/z: 321 $(M+H)^+$.

5.1.9. 4-(2-Ethylphenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9m)

The title compound was prepared from 2-ethylphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 63% yield.

^{1}H NMR (DMSO-d_6) δ: 1.03 (6H, d, J = 7.0 Hz), 1.14 (3H, t, J = 7.5 Hz), 2.67 (2H, q, J = 7.5 Hz), 2.72 (1H, heptet, J = 7.0 Hz), 3.58 (2H, s), 6.92 (1H, dd, J = 7.3, 1.3 Hz), 7.00–7.15 (3H, m), 8.40–12.00 (2H, br); MS m/z: 245 $(M+H)^+$.

5.1.10. 1,2-Dihydro-4-(2-methoxyphenylmethyl)-5-isopropyl-3*H*-pyrazol-3-one (9n)

The title compound was prepared from 2-methoxyphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 65% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.81 (1H, heptet, J = 7.0 Hz), 3.50 (2H, s), 3.80 (3H, s), 6.76–6.82 (1H, m), 6.87–6.93 (2H, m), 7.09–7.15 (1H, m), 8.40–12.20 (2H, br); MS m/z: 247 $(M+H)^+$.

5.1.11. 4-(4-Ethylphenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9r)

The title compound was prepared from 4-ethylphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 71% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 1.13 (3H, t, J = 7.5 Hz), 2.53 (2H, q, J = 7.5 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.53 (2H, s), 7.06 (4H, s), 8.40–12.00 (2H, br); MS m/z: 245 $(M+H)^+$.

5.1.12. 4-(4-Benzyloxyphenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9t)

The title compound was prepared from 4-benzyloxyphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 70% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.83 (1H, heptet, J = 7.0 Hz), 3.51 (2H, s), 5.03 (2H, s), 6.85–6.90 (2H, m), 7.03–7.08 (2H, m), 7.28–7.45 (5H, m), 8.40–12.20 (2H, br); MS m/z: 323 $(M+H)^+$.

5.1.13. 1,2-Dihydro-4-(3-methylphenylmethyl)-5-isopropyl-3*H*-pyrazol-3-one (9v)

The title compound was prepared from 3-methylphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 22% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.23 (3H, s), 2.82 (1H, heptet, J = 7.0 Hz), 3.53 (2H, s), 6.90–6.97 (3H, m), 7.11 (1H, t,

J = 7.4 Hz), 8.90–10.00 (1H, br), 10.55–11.50 (1H, br); MS m/z: 231 $(M+H)^+$.

5.1.14. 4-(3-Benzyloxyphenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9w)

The title compound was prepared from 3-benzyloxyphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 75% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 7.0 Hz), 2.82 (1H, heptet, J = 7.0 Hz), 3.54 (2H, s), 5.03 (2H, s), 6.71–6.81 (3H, m), 7.14 (1H, t, J = 7.8 Hz), 7.28–7.44 (5H, m), 8.80–10.20 (1H, br), 10.30–11.70 (1H, br); MS m/z: 323 $(M+H)^+$.

5.1.15. 1,2-Dihydro-4-(2,4-dimethylphenylmethyl)-5-isopropyl-3*H*-pyrazol-3-one (9x)

The title compound was prepared from 2,4-dimethylphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 74% yield.

^{1}H NMR (DMSO-d_6) δ: 1.04 (6H, d, J = 7.0 Hz), 2.20 (3H, s), 2.24 (3H, s), 2.72 (1H, heptet, J = 7.0 Hz), 3.46 (2H, s), 6.77 (1H, d, J = 7.8 Hz), 6.84 (1H, d, J = 7.8 Hz), 6.91 (1H, s), 8.60–10.10 (1H, br), 10.40–11.90 (1H, br); MS m/z: 245 $(M+H)^+$.

5.1.16. 4-(4-Benzyloxy-2-methylphenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9y)

The title compound was prepared from 4-benzyloxy-2-methylphenylmethanol and methyl 4-methyl-3-oxopentanoate, as described for the synthesis of **9a**, in 80% yield.

^{1}H NMR (DMSO-d_6) δ: 1.04 (6H, d, J = 7.0 Hz), 2.24 (3H, s), 2.73 (1H, heptet, J = 7.0 Hz), 3.44 (2H, s), 5.02 (2H, s), 6.70 (1H, dd, J = 8.4, 2.6 Hz), 6.76–6.81 (2H, m), 7.27–7.45 (5H, m), 8.70–9.90 (1H, br), 10.70–11.60 (1H, br); MS m/z: 337 $(M+H)^+$.

5.1.17. 4-Benzyl-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9i)

NaH (916 mg, 22.9 mmol, 60% oil dispersion), under ice cooling, was added to a solution of methyl 4-methyl-3-oxopentanoate (3.00 g, 20.8 mmol) in THF (25 mL), and the mixture was stirred for 5 min. Benzyl bromide (2.48 mL, 20.8 mmol) was added, and the mixture was refluxed for 5 h. After cooling to room temperature, 1 M HCl (25 mL) was added, and the resulting mixture was extracted with EtOAc. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give crude methyl 2-benzyl-4-methyl-3-oxopentanoate (**8i**). This material was dissolved in toluene (20 mL), and $N_2H_4{\cdot}H_2O$ (2.02 mL, 41.6 mmol) was added. After refluxing for 10 h, water was added, and the mixture was extracted with EtOAc. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 10:1) to give **9i** (3.43 g, 76%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.58 (2H, s), 7.08–7.18 (3H, m), 7.19–7.26 (2H, m), 8.40–12.00 (2H, br); MS m/z: 217 $(M+H)^+$.

5.1.18. 4-(2-Fluorophenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9j)

The title compound was prepared from 2-fluorophenylmethyl bromide, as described for the synthesis of **9i**, in 71% yield.

^{1}H NMR (DMSO-d_6) δ: 1.08 (6H, d, J = 7.0 Hz), 2.83 (1H, heptet, J = 7.0 Hz), 3.58 (2H, s), 7.04–7.23 (4H, m), 8.90–10.10 (1H, br), 10.50–11.70 (1H, br); MS m/z: 235 $(M+H)^+$.

5.1.19. 1,2-Dihydro-4-(2-methylphenylmethyl)-5-isopropyl-3*H*-pyrazol-3-one (9k)

The title compound was prepared from 2-methylphenylmethyl bromide, as described for the synthesis of **9i**, in 45% yield.

^{1}H NMR (DMSO-d_6) δ: 1.04 (6H, d, J = 7.0 Hz), 2.28 (3H, s), 2.74 (1H, heptet, J = 7.0 Hz), 3.52 (2H, s), 6.87–6.93 (1H, m), 7.00–7.13 (3H, m), 8.40–12.00 (2H, br); MS m/z: 231 $(M+H)^+$.

5.1.20. 4-(2-Trifluoromethylphenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9l)

The title compound was prepared from 2-trifluoromethylphenylmethyl bromide, as described for the synthesis of **9i**, in 28% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (6H, d, J = 7.0 Hz), 2.71 (1H, heptet, J = 7.0 Hz), 3.78 (2H, s), 7.13 (1H, d, J = 7.8 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.54 (1H, t, J = 7.8 Hz), 7.68 (1H, d, J = 7.8 Hz), 8.90–12.10 (2H, br); MS m/z: 285 $(M+H)^+$.

5.1.21. 4-(2-Cyanophenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9o)

The title compound was prepared from 2-cyanophenylmethyl bromide, as described for the synthesis of **9i**, in 43% yield. In the cyclization step, EtOH was used as the solvent, and the reaction was carried out at room temperature.

^{1}H NMR (DMSO-d_6) δ: 1.09 (6H, d, J = 7.0 Hz), 2.87 (1H, heptet, J = 7.0 Hz), 3.79 (2H, s), 7.24 (1H, d, J = 7.7 Hz), 7.33–7.39 (1H, m), 7.59 (1H, td, J = 7.7, 1.3 Hz), 7.76 (1H, dd, J = 7.7, 1.3 Hz), 8.40–12.20 (2H, br); MS m/z: 242 $(M+H)^+$.

5.1.22. 4-(4-Fluorophenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9p)

The title compound was prepared from 4-fluorophenylmethyl bromide, as described for the synthesis of **9i**, in 58% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.83 (1H, heptet, J = 7.0 Hz), 3.56 (2H, s), 7.01–7.09 (2H, m), 7.13–7.20 (2H, m), 8.40–12.20 (2H, br); MS m/z: 235 $(M+H)^+$.

5.1.23. 1,2-Dihydro-4-(4-methylphenylmethyl)-5-isopropyl-3*H*-pyrazol-3-one (9q)

The title compound was prepared from 4-methylphenylmethyl bromide, as described for the synthesis of **9i**, in 33% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 7.0 Hz), 2.23 (3H, s), 2.82 (1H, heptet, J = 7.0 Hz), 3.52 (2H, s), 7.03 (4H, s), 8.40–12.20 (2H, br); MS m/z: 231 $(M+H)^+$.

5.1.24. 1,2-Dihydro-4-(4-methoxyphenylmethyl)-5-isopropyl-3*H*-pyrazol-3-one (9s)

The title compound was prepared from 4-methoxyphenylmethyl chloride, as described for the synthesis of **9i**, in 61% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.83 (1H, heptet, J = 7.0 Hz), 3.51 (2H, s), 3.69 (3H, s), 6.77–6.82 (2H, m), 7.03–7.08 (2H, m), 8.40–12.20 (2H, br); MS m/z: 247 $(M+H)^+$.

5.1.25. 4-(4-Cyanophenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (9u)

The title compound was prepared from 4-cyanophenylmethyl bromide, as described for the synthesis of **9i**, in 33% yield. In the cyclization step, EtOH was used as the solvent, and the reaction was carried out at room temperature.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.67 (2H, s), 7.31–7.37 (2H, m), 7.69–7.74 (2H, m), 8.80–10.30 (1H, br), 10.40–11.90 (1H, br); MS m/z: 242 $(M+H)^+$.

5.1.26. 4-(4-Benzyloxyphenylmethyl)-5-trifluoromethyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10a)

Aqueous 5 M NaOH (3.80 mL, 18.8 mmol) was added to a mixture of **9a** (1.64 g, 4.71 mmol), acetobromoglucose (1.94 g, 4.71 mmol), and $BnN(n\text{-}Bu)_3Cl$ (1.47 g, 4.71 mmol) in CH_2Cl_2 (30 mL), and the mixture was stirred at room temperature overnight. 1 M HCl (25 mL) was added, and the resulting mixture was

extracted with EtOAc. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 2:1–1:1) to give **10a** (266 mg, 8%) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 3.78 (2H, s), 3.79–3.85 (1H, m), 4.20 (1H, dd, J = 12.5, 2.0 Hz), 4.26 (1H, dd, J = 12.5, 4.3 Hz), 5.02 (2H, s), 5.16–5.30 (3H, m), 5.38 (1H, br s), 6.83–6.89 (2H, m), 7.04–7.10 (2H, m), 7.27–7.44 (5H, m), 9.00–11.00 (1H, br); MS m/z: 677 $(M-H)^-$.

5.1.27. 4-(3-Benzyloxyphenylmethyl)-5-trifluoromethyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10b)

The title compound was prepared from **9b**, as described for the synthesis of **10a**, in 9% yield.

^{1}H NMR ($CDCl_3$) δ: 1.87 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 3.75 (2H, s), 3.77–3.84 (1H, m), 4.15–4.28 (2H, m), 5.02 (2H, s), 5.12–5.48 (4H, m), 6.73–6.82 (3H, m), 7.16 (1H, t, J = 8.0 Hz), 7.27–7.44 (5H, m), 9.30–11.00 (1H, br); MS m/z: 677 $(M-H)^-$.

5.1.28. 4-(2-Benzyloxyphenylmethyl)-5-trifluoromethyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10c)

The title compound was prepared from **9c**, as described for the synthesis of **10a**, in 7% yield.

^{1}H NMR ($CDCl_3$) δ: 1.76 (3H, s), 1.99 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 3.69–3.77 (1H, m), 3.82 (1H, d, J = 16.8 Hz), 3.90 (1H, d, J = 16.8 Hz), 4.16 (1H, dd, J = 12.4, 1.9 Hz), 4.23 (1H, dd, J = 12.4, 4.4 Hz), 5.08–5.33 (6H, m), 6.80–6.90 (3H, m), 7.11–7.17 (1H, m), 7.29–7.41 (5H, m), 9.40–10.70 (1H, br); MS m/z: 677 $(M-H)^-$.

5.1.29. 4-(2-Benzyloxyphenylmethyl)-5-methyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10d)

The title compound was prepared from **9d**, as described for the synthesis of **10a**, in 23% yield.

^{1}H NMR (DMSO-d_6) δ: 1.80 (3H, s), 1.92 (3H, s), 1.94 (3H, s), 1.97 (3H, s), 1.98 (3H, s), 3.52 (2H, s), 3.93 (1H, dd, J = 12.2, 2.1 Hz), 4.05–4.12 (1H, m), 4.17 (1H, dd, J = 12.2, 4.5 Hz), 4.92–4.99 (2H, m), 5.13 (2H, s), 5.39 (1H, t, J = 9.5 Hz), 5.67 (1H, d, J = 8.3 Hz), 6.76–6.82 (1H, m), 6.89 (1H, dd, J = 7.4, 1.6 Hz), 6.99 (1H, d, J = 7.3 Hz), 7.08–7.14 (1H, m), 7.29–7.48 (5H, m), 11.66 (1H, s); MS m/z: 625 $(M+H)^+$.

5.1.30. 4-(2-Benzyloxyphenylmethyl)-5-ethyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10e)

The title compound was prepared from **9e**, as described for the synthesis of **10a**, in 27% yield.

^{1}H NMR (DMSO-d_6) δ: 0.92 (3H, t, J = 7.5 Hz), 1.81 (3H, s), 1.94 (3H, s), 1.97 (3H, s), 1.98 (3H, s), 2.32 (2H, q, J = 7.5 Hz), 3.53 (2H, s), 3.94 (1H, dd, J = 12.3, 2.1 Hz), 4.05–4.12 (1H, m), 4.17 (1H, dd, J = 12.3, 4.6 Hz), 4.92–5.00 (2H, m), 5.13 (2H, s), 5.39 (1H, t, J = 9.5 Hz), 5.69 (1H, d, J = 8.0 Hz), 6.78 (1H, t, J = 7.2 Hz), 6.89 (1H, dd, J = 7.2, 1.6 Hz), 6.99 (1H, d, J = 7.8 Hz), 7.08–7.14 (1H, m), 7.30–7.49 (5H, m), 11.70 (1H, s); MS m/z: 639 $(M+H)^+$.

5.1.31. 4-(2-Benzyloxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10f)

The title compound was prepared from **9f**, as described for the synthesis of **10a**, in 32% yield.

^{1}H NMR (DMSO-d_6) δ: 0.988 (3H, d, J = 7.0 Hz), 0.992 (3H, d, J = 7.0 Hz), 1.81 (3H, s), 1.94 (3H, s), 1.97 (3H, s), 1.98 (3H, s), 2.80 (1H, heptet, J = 7.0 Hz), 3.55 (2H, s), 3.94 (1H, dd, J = 12.3, 2.1 Hz), 4.06–4.13 (1H, m), 4.17 (1H, dd, J = 12.3, 4.6 Hz), 4.92–4.99 (2H, m), 5.13 (2H, s), 5.40 (1H, t, J = 9.7 Hz), 5.70 (1H, d, J = 8.3 Hz), 6.75–6.81 (1H, m), 6.86 (1H, dd, J = 7.5, 1.5 Hz), 7.00 (1H, d, J = 7.5 Hz), 7.07–7.14 (1H, m), 7.30–7.50 (5H, m), 11.70 (1H, s); MS m/z: 653 $(M+H)^+$.

5.1.32. 4-(2-Benzyloxyphenylmethyl)-5-*tert*-butyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10g)

The title compound was prepared from **9g**, as described for the synthesis of **10a**, in 28% yield.

^{1}H NMR ($CDCl_3$) δ: 1.22 (9H, s), 1.70 (3H, s), 1.97 (3H, s), 2.01 (3H, s), 2.04 (3H, s), 3.77–3.92 (3H, m), 4.12 (1H, dd, J = 12.5, 2.1 Hz), 4.29 (1H, dd, J = 12.5, 3.8 Hz), 5.11–5.26 (5H, m), 5.51 (1H, d, J = 8.0 Hz), 6.75–6.82 (2H, m), 6.88 (1H, d, J = 8.0 Hz), 7.06–7.13 (1H, m), 7.29–7.50 (5H, m), 8.30–9.90 (1H, br); MS m/z: 667 $(M+H)^+$.

5.1.33. 4-(2-Benzyloxyphenylmethyl)-5-cyclopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10h)

The title compound was prepared from **9h**, as described for the synthesis of **10a**, in 29% yield.

^{1}H NMR (DMSO-d_6) δ: 0.53–0.65 (4H, m), 1.57–1.68 (1H, m), 1.80 (3H, s), 1.93 (3H, s), 1.97 (3H, s), 1.98 (3H, s), 3.60 (2H, s), 3.93 (1H, dd, J = 12.3, 2.3 Hz), 4.04–4.11 (1H, m), 4.16 (1H, dd, J = 12.3, 4.5 Hz), 4.91–4.99 (2H, m), 5.13 (2H, s), 5.39 (1H, t, J = 9.7 Hz), 5.67 (1H, d, J = 8.0 Hz), 6.76–6.83 (1H, m), 6.90 (1H, dd, J = 7.5, 1.8 Hz), 7.00 (1H, d, J = 7.3 Hz), 7.08–7.15 (1H, m), 7.29–7.49 (5H, m), 11.49 (1H, s); MS m/z: 651 $(M+H)^+$.

5.1.34. 4-Benzyl-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10i)

The title compound was prepared from **9i**, as described for the synthesis of **10a**, in 26% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.89 (3H, s), 1.95 (3H, s), 1.985 (3H, s), 1.988 (3H, s), 2.89 (1H, heptet, J = 6.9 Hz), 3.53 (1H, d, J = 15.8 Hz), 3.58 (1H, d, J = 15.8 Hz), 3.97 (1H, dd, J = 12.2, 2.1 Hz), 4.09–4.16 (1H, m), 4.19 (1H, dd, J = 12.2, 4.6 Hz), 4.95–5.03 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.73 (1H, d, J = 8.0 Hz), 7.07–7.25 (5H, m), 11.72 (1H, s); MS m/z: 547 $(M+H)^+$.

5.1.35. 4-(2-Fluorophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10j)

The title compound was prepared from **9j**, as described for the synthesis of **10a**, in 20% yield.

^{1}H NMR (DMSO-d_6) δ: 1.08 (3H, d, J = 7.3 Hz), 1.10 (3H, d, J = 7.3 Hz), 1.87 (3H, s), 1.94 (3H, s), 1.98 (6H, s), 2.88 (1H, heptet, J = 7.3 Hz), 3.54 (1H, d, J = 16.1 Hz), 3.59 (1H, d, J = 16.1 Hz), 3.96 (1H, dd, J = 12.1, 2.0 Hz), 4.08–4.15 (1H, m), 4.18 (1H, dd, J = 12.1, 4.6 Hz), 4.93–5.01 (2H, m), 5.41 (1H, t, J = 9.5 Hz), 5.72 (1H, d, J = 8.3 Hz), 7.00–7.14 (3H, m), 7.15–7.24 (1H, m), 11.78 (1H, s); MS m/z: 565 $(M+H)^+$.

5.1.36. 4-(2-Methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10k)

The title compound was prepared from **9k**, as described for the synthesis of **10a**, in 30% yield.

^{1}H NMR (DMSO-d_6) δ: 1.03 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.81 (3H, s), 1.93 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.24 (3H, s), 2.77 (1H, heptet, J = 7.0 Hz), 3.48 (1H, d, J = 16.8 Hz), 3.54 (1H, d, J = 16.8 Hz), 3.94 (1H, dd, J = 12.3, 2.1 Hz), 4.06–4.13 (1H, m), 4.16 (1H, dd, J = 12.3, 4.6 Hz), 4.89–4.98 (2H, m), 5.39 (1H, t, J = 9.7 Hz), 5.69 (1H, d, J = 8.3 Hz), 6.80–6.87 (1H, m), 6.99–7.13 (3H, m), 11.76 (1H, s); MS m/z: 561 $(M+H)^+$.

5.1.37. 4-(2-Trifluoromethylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10l)

The title compound was prepared from **9l**, as described for the synthesis of **10a**, in 28% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 1.79 (3H, s), 1.92 (3H, s), 1.98 (6H, s), 2.73 (1H, heptet, J = 7.0 Hz), 3.73 (1H, d, J = 17.1 Hz), 3.79 (1H, d, J = 17.1 Hz), 3.92 (1H, dd, J = 11.8, 1.5 Hz), 4.07–4.18 (2H, m), 4.86–4.97 (2H, m), 5.39 (1H, t, J = 9.5 Hz), 5.69 (1H, d, J = 8.0 Hz), 7.02 (1H, d, J = 7.7 Hz), 7.38 (1H, t, J = 7.7 Hz), 7.51 (1H, t, J = 7.7 Hz), 7.68 (1H, d, J = 7.7 Hz), 11.91 (1H, s); MS m/z: 615 $(M+H)^+$.

5.1.38. 4-(2-Ethylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10m)

The title compound was prepared from **9m**, as described for the synthesis of **10a**, in 29% yield.

^{1}H NMR (DMSO-d_6) δ: 1.03 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 1.12 (3H, t, J = 7.5 Hz), 1.80 (3H, s), 1.93 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.63 (2H, q, J = 7.5 Hz), 2.75 (1H, heptet, J = 7.0 Hz), 3.53 (1H, d, J = 16.6 Hz), 3.60 (1H, d, J = 16.6 Hz), 3.93 (1H, dd, J = 12.1, 2.0 Hz), 4.06–4.13 (1H, m), 4.17 (1H, dd, J = 12.1, 4.6 Hz), 4.89–4.99 (2H, m), 5.40 (1H, t, J = 9.7 Hz), 5.69 (1H, d, J = 8.3 Hz), 6.83 (1H, d, J = 7.3 Hz), 7.02 (1H, td, J = 7.3, 1.7 Hz), 7.05–7.15 (2H, m), 11.77 (1H, s); MS m/z: 575 $(M+H)^+$.

5.1.39. 4-(2-Methoxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10n)

The title compound was prepared from **9n**, as described for the synthesis of **10a**, in 30% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.09 (3H, d, J = 7.0 Hz), 1.83 (3H, s), 1.94 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.87 (1H, heptet, J = 7.0 Hz), 3.48 (2H, s), 3.79 (3H, s), 3.94 (1H, dd, J = 12.3, 2.1 Hz), 4.05–4.13 (1H, m), 4.17 (1H, dd, J = 12.3, 4.6 Hz), 4.92–4.99 (2H, m), 5.39 (1H, t, J = 9.7 Hz), 5.69 (1H, d, J = 8.3 Hz), 6.74–6.85 (2H, m), 6.91 (1H, d, J = 8.3 Hz), 7.09–7.16 (1H, m), 11.72 (1H, s); MS m/z: 577 $(M+H)^+$.

5.1.40. 4-(2-Cyanophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10o)

The title compound was prepared from **9o**, as described for the synthesis of **10a**, in 30% yield.

^{1}H NMR (DMSO-d_6) δ: 1.09 (3H, d, J = 7.0 Hz), 1.10 (3H, d, J = 7.0 Hz), 1.85 (3H, s), 1.94 (3H, s), 1.98 (6H, s), 2.91 (1H, heptet, J = 7.0 Hz), 3.75 (1H, d, J = 16.3 Hz), 3.80 (1H, d, J = 16.3 Hz), 3.94 (1H, dd, J = 12.1, 1.8 Hz), 4.08–4.15 (1H, m), 4.16 (1H, dd, J = 12.1, 4.6 Hz), 4.91–4.99 (2H, m), 5.40 (1H, t, J = 9.7 Hz), 5.72 (1H, d, J = 8.0 Hz), 7.16 (1H, d, J = 7.7 Hz), 7.34–7.40 (1H, m), 7.53–7.59 (1H, m), 7.76 (1H, dd, J = 7.7, 1.3 Hz), 11.88 (1H, s); MS m/z: 572 $(M+H)^+$.

5.1.41. 4-(4-Fluorophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10p)

The title compound was prepared from **9p**, as described for the synthesis of **10a**, in 39% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.90 (3H, s), 1.95 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.89 (1H, heptet, J = 7.0 Hz), 3.52 (1H, d, J = 16.6 Hz), 3.56 (1H, d, J = 16.6 Hz), 3.97 (1H, dd, J = 12.1, 2.0 Hz), 4.09–4.16 (1H, m), 4.19 (1H, dd, J = 12.1, 4.5 Hz), 4.94–5.02 (2H, m), 5.42 (1H, t, J = 9.7 Hz), 5.73 (1H, d, J = 8.3 Hz), 6.99–7.15 (4H, m), 11.74 (1H, s); MS m/z: 565 $(M+H)^+$.

5.1.42. 4-(4-Methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10q)

The title compound was prepared from **9q**, as described for the synthesis of **10a**, in 28% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.89 (3H, s), 1.95 (3H, s), 1.987 (3H, s), 1.988 (3H, s), 2.22 (3H, s), 2.87 (1H, heptet, J = 6.9 Hz), 3.47 (1H, d, J = 15.9 Hz), 3.52 (1H, d, J = 15.9 Hz), 3.97 (1H, dd, J = 12.2, 2.1 Hz), 4.09–4.16 (1H, m), 4.19 (1H, dd, J = 12.2, 4.6 Hz), 4.94–5.02 (2H, m), 5.42 (1H, t, J = 9.7 Hz), 5.73 (1H, d, J = 8.3 Hz), 6.97 (2H, d, J = 7.9 Hz), 7.06 (2H, d, J = 7.9 Hz), 11.71 (1H, s); MS m/z: 561 $(M+H)^+$.

5.1.43. 4-(4-Ethylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10r)

The title compound was prepared from **9r**, as described for the synthesis of **10a**, in 14% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 6.9 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.12 (3H, t, J = 7.5 Hz), 1.88 (3H, s), 1.95 (3H, s), 1.985 (3H, s), 1.987 (3H, s), 2.52 (2H, q, J = 7.5 Hz), 2.89 (1H, heptet, J = 6.9 Hz), 3.48 (1H, d, J = 15.8 Hz), 3.53 (1H, d, J = 15.8 Hz), 3.97 (1H, dd, J = 12.2, 2.3 Hz), 4.08–4.15 (1H, m), 4.19 (1H, dd, J = 12.2, 4.6 Hz), 4.94–5.03 (2H, m), 5.42 (1H, t, J = 9.7 Hz), 5.72 (1H, d, J = 8.3 Hz), 7.00 (2H, d, J = 7.5 Hz), 7.04 (2H, d, J = 7.5 Hz), 11.70 (1H, s); MS m/z: 575 $(M+H)^+$.

5.1.44. 4-(4-Methoxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10s)

The title compound was prepared from **9s**, as described for the synthesis of **10a**, in 27% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.90 (3H, s), 1.95 (3H, s), 1.986 (3H, s), 1.988 (3H, s), 2.88 (1H, heptet, J = 7.0 Hz), 3.46 (1H, d, J = 15.8 Hz), 3.50 (1H, d, J = 15.8 Hz), 3.69 (3H, s), 3.97 (1H, dd, J = 12.3, 2.0 Hz), 4.08–4.16 (1H, m), 4.19 (1H, dd, J = 12.3, 4.6 Hz), 4.94–5.03 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.72 (1H, d, J = 8.3 Hz), 6.77 (2H, d, J = 8.7 Hz), 7.01 (2H, d, J = 8.7 Hz), 11.69 (1H, s); MS m/z: 577 $(M+H)^+$.

5.1.45. 4-(4-Benzyloxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10t)

The title compound was prepared from **9t**, as described for the synthesis of **10a**, in 36% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.88 (3H, s), 1.95 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.88 (1H, heptet, J = 7.0 Hz), 3.46 (1H, d, J = 15.9 Hz), 3.50 (1H, d, J = 15.9 Hz), 3.97 (1H, dd, J = 12.2, 1.9 Hz), 4.09–4.16 (1H, m), 4.19 (1H, dd, J = 12.2, 4.5 Hz), 4.94–5.02 (2H, m), 5.03 (2H, s), 5.42 (1H, t, J = 9.7 Hz), 5.72 (1H, d, J = 8.0 Hz), 6.82–6.88 (2H, m), 6.98–7.03 (2H, m), 7.27–7.44 (5H, m), 11.70 (1H, s); MS m/z: 653 $(M+H)^+$.

5.1.46. 4-(4-Cyanophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10u)

The title compound was prepared from **9u**, as described for the synthesis of **10a**, in 32% yield.

^{1}H NMR (DMSO-d_6) δ: 1.079 (3H, d, J = 7.0 Hz), 1.082 (3H, d, J = 7.0 Hz), 1.89 (3H, s), 1.94 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.90 (1H, heptet, J = 7.0 Hz), 3.64 (1H, d, J = 16.9 Hz), 3.68 (1H, d, J = 16.9 Hz), 3.96 (1H, dd, J = 12.0, 1.9 Hz), 4.09–4.16 (1H, m), 4.18 (1H, dd, J = 12.0, 4.7 Hz), 4.93–5.00 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.73 (1H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.69 (2H, d, J = 8.3 Hz), 11.82 (1H, s); MS m/z: 572 $(M+H)^+$.

5.1.47. 4-(3-Methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10v)

The title compound was prepared from **9v**, as described for the synthesis of **10a**, in 34% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.88 (3H, s), 1.95 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.23 (3H, s), 2.88 (1H, heptet, J = 7.0 Hz), 3.49 (1H, d, J = 15.8 Hz), 3.53 (1H, d, J = 15.8 Hz), 3.96 (1H, dd, J = 12.2, 2.1 Hz), 4.09–4.16 (1H, m), 4.19 (1H, dd, J = 12.2, 4.5 Hz), 4.94–5.03 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.72 (1H, d, J = 8.3 Hz), 6.87 (1H, d, J = 7.8 Hz), 6.91 (1H, s), 6.93 (1H, d, J = 7.8 Hz), 7.09 (1H, t, J = 7.8 Hz), 11.71 (1H, s); MS m/z: 561 $(M+H)^+$.

5.1.48. 4-(3-Benzyloxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10w)

The title compound was prepared from **9w**, as described for the synthesis of **10a**, in 31% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.86 (3H, s), 1.94 (3H, s), 1.96 (3H, s), 1.99 (3H, s), 2.86 (1H, heptet, J = 7.0 Hz), 3.49 (1H, d, J = 15.9 Hz), 3.54 (1H, d, J = 15.9 Hz), 3.96 (1H, dd, J = 12.2, 2.1 Hz), 4.09–4.16 (1H, m), 4.19 (1H, dd, J = 12.2, 4.5 Hz), 4.94–5.03 (2H, m), 5.03 (2H, s), 5.42 (1H, t, J = 9.7 Hz), 5.73 (1H, d, J = 8.0 Hz), 6.68 (1H, d, J = 7.8 Hz), 6.73 (1H, d, J = 2.1 Hz), 6.78 (1H, dd, J = 7.8, 2.1 Hz), 7.13 (1H, t, J = 7.8 Hz), 7.28–7.44 (5H, m), 11.73 (1H, s); MS m/z: 653 $(M+H)^+$.

5.1.49. 4-(2,4-Dimethylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10x)

The title compound was prepared from **9x**, as described for the synthesis of **10a**, in 24% yield.

^{1}H NMR (DMSO-d_6) δ: 1.04 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 1.82 (3H, s), 1.93 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.193 (3H, s), 2.199 (3H, s), 2.76 (1H, heptet, J = 7.0 Hz), 3.42 (1H, d, J = 16.6 Hz), 3.48 (1H, d, J = 16.6 Hz), 3.94 (1H, dd, J = 12.3, 2.3 Hz), 4.06–4.12 (1H, m), 4.16 (1H, dd, J = 12.3, 4.5 Hz), 4.89–4.98 (2H, m), 5.39 (1H, t, J = 9.7 Hz), 5.68 (1H, d, J = 8.0 Hz), 6.71 (1H, d, J = 7.0 Hz), 6.83 (1H, d, J = 7.0 Hz), 6.92 (1H, s), 11.74 (1H, s); MS m/z: 575 $(M+H)^+$.

5.1.50. 4-(4-Benzyloxy-2-methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10y)

The title compound was prepared from **9y**, as described for the synthesis of **10a**, in 22% yield.

^{1}H NMR (DMSO-d_6) δ: 1.03 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 1.81 (3H, s), 1.93 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.21 (3H, s), 2.77 (1H, heptet, J = 7.0 Hz), 3.40 (1H, d, J = 16.4 Hz), 3.46 (1H, d, J = 16.4 Hz), 3.95 (1H, dd, J = 12.2, 2.1 Hz), 4.06–4.13 (1H, m), 4.17 (1H, dd, J = 12.2, 4.4 Hz), 4.90–4.99 (2H, m), 5.02 (2H, s), 5.39 (1H, t, J = 9.5 Hz), 5.68 (1H, d, J = 8.0 Hz), 6.67 (1H, dd, J = 8.4, 2.5 Hz), 6.74 (1H, d, J = 8.4 Hz), 6.79 (1H, d, J = 2.5 Hz), 7.27–7.44 (5H, m), 11.73 (1H, s); MS m/z: 667 $(M+H)^+$.

5.1.51. 4-(4-Benzyloxyphenylmethyl)-5-trifluoromethyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11a)

NaOMe (28% MeOH solution, 563 mg, 2.92 mmol) was added to a solution of **10a** (0.99 g, 1.46 mmol) in MeOH (6 mL), and the mixture was stirred at room temperature for 21 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 19:1–9:1–4:1) to give **11a** (356 mg, 48%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 3.08–3.27 (4H, m), 3.42–3.53 (1H, m), 3.60–3.76 (3H, m), 4.55 (1H, br s), 4.64–4.88 (1H, br), 4.92–5.17 (4H, m), 5.20–5.62 (1H, br), 6.89 (2H, d, J = 8.4 Hz), 7.09 (2H, d, J = 8.4 Hz), 7.27–7.45 (5H, m), 13.27 (1H, br s); MS m/z: 509 $(M-H)^-$. HRMS (FAB+) calcd for $C_{24}H_{26}F_3N_2O_7$ 511.1687; found 511.1688 $(M+H)^+$.

5.1.52. 4-(3-Benzyloxyphenylmethyl)-5-trifluoromethyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11b)

The title compound was prepared from **10b**, as described for the synthesis of **11a**, in 42% yield.

^{1}H NMR (DMSO-d_6) δ: 3.06–3.26 (4H, m), 3.40–3.53 (1H, m), 3.60–3.72 (1H, m), 3.76 (2H, s), 4.55 (1H, br s), 4.66–4.90 (1H, br), 4.94–5.17 (4H, m), 5.18–5.62 (1H, br), 6.71–6.85 (3H, m), 7.16 (1H, t, J = 8.0 Hz), 7.28–7.45 (5H, m), 13.31 (1H, s); MS m/z: 509 $(M-H)^-$. HRMS (FAB+) calcd for $C_{24}H_{26}F_3N_2O_7$ 511.1687; found 511.1686 $(M+H)^+$.

5.1.53. 4-(2-Benzyloxyphenylmethyl)-5-trifluoromethyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11c)

The title compound was prepared from **10c**, as described for the synthesis of **11a**, in 55% yield.

^{1}H NMR (DMSO-d_6) δ: 3.06–3.20 (4H, m), 3.46 (1H, d, J = 11.2 Hz), 3.64 (1H, d, J = 11.2 Hz), 3.82 (2H, s), 4.50 (1H, br s), 4.60–4.86 (1H, br), 5.00 (1H, br s), 5.07 (1H, br s), 5.12–5.54 (3H, m), 6.75–6.85 (2H, m), 7.01 (1H, d, J = 8.0 Hz), 7.09–7.16 (1H, m), 7.29–7.35 (1H, m), 7.36–7.49 (4H, m), 13.34 (1H, br s); MS m/z: 511 $(M+H)^+$. HRMS (FAB+) calcd for $C_{24}H_{26}F_3N_2O_7$ 511.1687; found 511.1686 $(M+H)^+$.

5.1.54. 4-(2-Benzyloxyphenylmethyl)-5-methyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11d)

The title compound was prepared from **10d**, as described for the synthesis of **11a**, in 64% yield.

^{1}H NMR (DMSO-d_6) δ: 1.92 (3H, s), 3.05–3.23 (4H, m), 3.40–3.49 (1H, m), 3.54–3.66 (3H, m), 4.42 (1H, t, J = 5.8 Hz), 4.91 (1H, d, J = 4.8 Hz), 4.98 (1H, d, J = 4.5 Hz), 5.10 (1H, d, J = 5.0 Hz), 5.15 (2H, s), 5.19 (1H, d, J = 7.5 Hz), 6.82 (1H, td, J = 7.5, 0.8 Hz), 6.97–7.03 (2H, m), 7.07–7.14 (1H, m), 7.29–7.36 (1H, m), 7.37–7.43 (2H, m), 7.45–7.50 (2H, m), 11.50 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 10.1, 22.6, 62.7, 71.1, 71.3, 75.0, 78.0, 78.4, 102.5, 103.3, 112.8, 121.7, 128.1, 128.6, 128.9, 129.6, 130.6, 130.8, 139.0, 140.0, 157.7, 162.0; MS m/z: 457 $(M+H)^+$; HRMS (FAB+) calcd for $C_{24}H_{29}N_2O_7$ 457.1969; found 457.1969 $(M+H)^+$.

5.1.55. 4-(2-Benzyloxyphenylmethyl)-5-ethyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11e)

The title compound was prepared from **10e**, as described for the synthesis of **11a**, in 52% yield.

^{1}H NMR (DMSO-d_6) δ: 0.93 (3H, t, J = 7.6 Hz), 2.32 (2H, q, J = 7.6 Hz), 3.05–3.24 (4H, m), 3.40–3.49 (1H, m), 3.55–3.67 (3H, m), 4.43 (1H, t, J = 5.8 Hz), 4.91 (1H, d, J = 4.8 Hz), 4.98 (1H, d, J = 4.5 Hz), 5.10 (1H, d, J = 5.0 Hz), 5.15 (2H, s), 5.21 (1H, d, J = 7.8 Hz), 6.78–6.84 (1H, m), 6.98–7.04 (2H, m), 7.07–7.14 (1H, m), 7.30–7.36 (1H, m), 7.37–7.44 (2H, m), 7.45–7.51 (2H, m), 11.53 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 13.7, 19.2, 22.3, 62.7, 71.1, 71.3, 75.0, 78.0, 78.4, 102.5, 102.6, 112.8, 121.7, 128.1, 128.6, 128.9, 129.6, 130.8, 130.9, 139.0, 145.8, 157.6, 162.0; MS m/z: 471 $(M+H)^+$; HRMS (FAB+) calcd for $C_{25}H_{31}N_2O_7$ 471.2126; found 471.2124 $(M+H)^+$.

5.1.56. 4-(2-Benzyloxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11f)

The title compound was prepared from **10f**, as described for the synthesis of **11a**, in 67% yield.

^{1}H NMR (DMSO-d_6) δ: 1.00 (6H, d, J = 7.0 Hz), 2.77 (1H, heptet, J = 7.0 Hz), 3.06–3.24 (4H, m), 3.40–3.49 (1H, m), 3.56–3.68 (3H, m), 4.45 (1H, t, J = 5.9 Hz), 4.82–5.21 (5H, m), 5.22 (1H, d, J = 7.5 Hz), 6.81 (1H, td, J = 7.5, 0.9 Hz), 6.98–7.03 (2H, m), 7.07–7.14 (1H, m), 7.30–7.36 (1H, m), 7.38–7.44 (2H, m), 7.46–7.51 (2H, m), 11.53 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ: 22.0, 22.1, 26.5, 62.8, 71.1, 71.3, 75.0, 78.0, 78.4, 101.9, 102.5, 112.8, 121.7, 128.0, 128.6, 128.9, 129.6, 130.7, 131.1, 139.0, 149.7, 157.5, 161.9; MS m/z: 485 $(M+H)^+$; HRMS (FAB+) calcd for $C_{26}H_{33}N_2O_7$ 485.2282; found 485.2276 $(M+H)^+$.

5.1.57. 4-(2-Benzyloxyphenylmethyl)-5-*tert*-butyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11g)

The title compound was prepared from **10g**, as described for the synthesis of **11a**, in 68% yield.

^{1}H NMR (DMSO-d_6) δ: 1.13 (9H, s), 3.04–3.23 (4H, m), 3.39–3.52 (1H, m), 3.59–3.66 (1H, m), 3.76 (2H, s), 4.43 (1H, t, J = 5.7 Hz), 4.92 (1H, d, J = 4.8 Hz), 4.97 (1H, d, J = 4.8 Hz), 5.08 (1H, d, J = 5.5 Hz),

5.17 (2H, s), 5.25 (1H, d, J = 8.0 Hz), 6.77–6.87 (2H, m), 7.01 (1H, d, J = 7.5 Hz), 7.07–7.14 (1H, m), 7.29–7.36 (1H, m), 7.38–7.44 (2H, m), 7.47–7.52 (2H, m), 11.49 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 22.7, 29.9, 33.4, 62.7, 71.1, 71.2, 74.9, 78.0, 78.3, 101.2, 102.4, 112.6, 121.6, 127.8, 128.5, 128.8, 129.5, 130.1, 131.5, 139.0, 150.9, 157.3, 163.1; MS m/z: 499 $(M+H)^+$; HRMS (FAB+) calcd for $C_{27}H_{35}N_2O_7$ 499.2439; found 499.2438 $(M+H)^+$.

5.1.58. 4-(2-Benzyloxyphenylmethyl)-5-cyclopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11h)

The title compound was prepared from **10h**, as described for the synthesis of **11a**, in 58% yield.

^{1}H NMR (DMSO-d_6) δ: 0.55–0.67 (4H, m), 1.55–1.66 (1H, m), 3.05–3.23 (4H, m), 3.39–3.48 (1H, m), 3.57–3.73 (3H, m), 4.42 (1H, t, J = 5.8 Hz), 4.91 (1H, d, J = 4.8 Hz), 4.98 (1H, d, J = 4.8 Hz), 5.10 (1H, d, J = 5.0 Hz), 5.15 (2H, s), 5.20 (1H, d, J = 7.8 Hz), 6.82 (1H, td, J = 7.4, 1.0 Hz), 6.98–7.06 (2H, m), 7.08–7.15 (1H, m), 7.29–7.36 (1H, m), 7.37–7.43 (2H, m), 7.45–7.51 (2H, m), 11.33 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ: 6.4, 6.5, 7.1, 22.4, 62.7, 71.1, 71.2, 75.0, 78.0, 78.3, 102.5, 104.1, 112.7, 121.6, 128.0, 128.6, 128.8, 129.5, 130.7, 130.9, 139.0, 145.4, 157.6, 162.0; MS m/z: 483 $(M+H)^+$; HRMS (FAB+) calcd for $C_{26}H_{31}N_2O_7$ 483.2126; found 483.2130 $(M+H)^+$.

5.1.59. 4-Benzyl-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11i)

The title compound was prepared from **10i**, as described for the synthesis of **11a**, in 43% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.10–3.25 (4H, m), 3.41–3.51 (1H, m), 3.55–3.68 (3H, m), 4.46 (1H, t, J = 5.7 Hz), 4.93 (1H, d, J = 4.8 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.15 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.5 Hz), 7.08–7.26 (5H, m), 11.53 (1H, s); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 21.57, 21.63, 24.6, 26.9, 60.6, 69.6, 73.3, 76.7, 77.2, 99.6, 100.1, 125.4, 128.0, 128.1, 141.7, 146.5, 159.5; MS m/z: 379 $(M+H)^+$; HRMS (FAB+) calcd for $C_{19}H_{27}N_2O_6$ 379.1864; found 379.1869 $(M+H)^+$.

5.1.60. 4-(2-Fluorophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11j)

The title compound was prepared from **10j**, as described for the synthesis of **11a**, in 78% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.09–3.25 (4H, m), 3.40–3.51 (1H, m), 3.57–3.70 (3H, m), 4.47 (1H, t, J = 5.9 Hz), 4.86–5.28 (4H, m), 7.04–7.14 (2H, m), 7.15–7.23 (2H, m), 11.60 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ: 20.7 (d, J = 4 Hz), 22.0, 26.6, 62.8, 71.3, 75.0, 78.1, 78.4, 101.0, 102.6, 115.7 (d, J = 22 Hz), 125.1 (d, J = 4 Hz), 128.7 (d, J = 8 Hz), 129.4 (d, J = 15 Hz), 131.8 (d, J = 4 Hz), 149.7, 161.8, 162.1 (d, J = 242 Hz); MS m/z: 397 $(M+H)^+$; HRMS (FAB+) calcd for $C_{19}H_{26}FN_2O_6$ 397.1769; found 397.1777 $(M+H)^+$.

5.1.61. 4-(2-Methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11k)

The title compound was prepared from **10k**, as described for the synthesis of **11a**, in 62% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 2.30 (3H, s), 2.74 (1H, heptet, J = 7.0 Hz), 3.05–3.23 (4H, m), 3.40–3.48 (1H, m), 3.52–3.65 (3H, m), 4.44 (1H, t, J = 5.7 Hz), 4.92 (1H, d, J = 4.5 Hz), 4.98 (1H, d, J = 4.5 Hz), 5.08 (1H, d, J = 5.3 Hz), 5.18 (1H, d, J = 7.5 Hz), 6.90–6.96 (1H, m), 7.01–7.13 (3H, m), 11.58 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ: 19.8, 21.9, 22.0, 25.9, 26.6, 62.7, 71.3, 74.9, 78.0, 78.4, 101.5, 102,7, 126.7, 127.0, 129.2, 130.9, 137.3, 140.3, 149.8, 161.7; MS m/z: 393 $(M+H)^+$; HRMS (FAB+) calcd for $C_{20}H_{29}N_2O_6$ 393.2020; found 393.2022 $(M+H)^+$.

5.1.62. 4-(2-Trifluoromethylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11l)

The title compound was prepared from **10l**, as described for the synthesis of **11a**, in 65% yield.

^{1}H NMR (DMSO-d_6) δ: 1.035 (3H, d, J = 7.0 Hz), 1.040 (3H, d, J = 7.0 Hz), 2.69 (1H, heptet, J = 7.0 Hz), 3.07–3.25 (4H, m), 3.45 (1H, d, J = 11.4 Hz), 3.65 (1H, d, J = 11.4 Hz), 3.80 (1H, d, J = 17.4 Hz), 3.85 (1H, d, J = 17.4 Hz), 4.47 (1H, br s), 4.72–5.36 (4H, m), 7.23 (1H, d, J = 7.6 Hz), 7.37 (1H, t, J = 7.6 Hz), 7.54 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.6 Hz), 11.73 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.4, 21.5, 22.9, 24.7, 60.7, 69.6, 73.2, 76.7, 77.3, 97.5, 100.3, 124.7 (q, J = 273 Hz), 125.3 (q, J = 6 Hz), 126.2, 126.4 (q, J = 29 Hz), 130.2, 132.4, 139.6, 147.0, 160.0; MS m/z: 447 $(M+H)^+$; HRMS (FAB+) calcd for $C_{20}H_{26}F_3N_2O_6$ 447.1738; found 447.1737 $(M+H)^+$.

5.1.63. 4-(2-Ethylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11m)

The title compound was prepared from **10m**, as described for the synthesis of **11a**, in 73% yield.

^{1}H NMR (DMSO-d_6) δ: 1.03 (3H, d, J = 6.8 Hz), 1.05 (3H, d, J = 6.8 Hz), 1.15 (3H, t, J = 7.5 Hz), 2.64–2.77 (3H, m), 3.06–3.23 (4H, m), 3.40–3.49 (1H, m), 3.57–3.69 (3H, m), 4.44 (1H, t, J = 5.8 Hz), 4.92 (1H, br s), 4.99 (1H, br s), 5.07 (1H, d, J = 5.0 Hz), 5.19 (1H, d, J = 7.8 Hz), 6.95 (1H, d, J = 7.3 Hz), 7.01–7.15 (3H, m), 11.57 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ: 15.3, 21.9, 22.0, 25.2, 26.7, 26.8, 62.8, 71.3, 75.0, 78.0, 78.4, 101.9, 102.6, 126.7, 127.2, 129.2, 129.7, 139.6, 143.2, 149.8, 161.7; MS m/z: 407 $(M+H)^+$; HRMS (FAB+) calcd for $C_{21}H_{31}N_2O_6$ 407.2177; found 407.2175 $(M+H)^+$.

5.1.64. 4-(2-Methoxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11n)

The title compound was prepared from **10n**, as described for the synthesis of **11a**, in 55% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 2.82 (1H, heptet, J = 7.0 Hz), 3.06–3.24 (4H, m), 3.39–3.67 (4H, m), 3.80 (3H, s), 4.45 (1H, br s), 4.78–5.19 (3H, m), 5.21 (1H, d, J = 7.8 Hz), 6.77–6.83 (1H, m), 6.91 (1H, d, J = 7.8 Hz), 6.97 (1H, dd, J = 7.4, 1.4 Hz), 7.09–7.16 (1H, m), 11.54 (1H, br s); ^{13}C NMR (150 MHz, CD_3OD) δ: 21.9, 22.0, 26.5, 55.8, 62.8, 71.3, 75.0, 78.0, 78.4, 101.8, 102.5, 111.1, 121.3, 128.1, 130.4, 130.6, 149.8, 158.5, 161.9; MS m/z: 409 $(M+H)^+$; HRMS (FAB+) calcd for $C_{20}H_{29}N_2O_7$ 409.1969; found 409.1977 $(M+H)^+$.

5.1.65. 4-(2-Cyanophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11o)

The title compound was prepared from **10o**, as described for the synthesis of **11a**, in 58% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.9 Hz), 2.87 (1H, heptet, J = 6.9 Hz), 3.09–3.25 (4H, m), 3.41–3.50 (1H, m), 3.60–3.68 (1H, m), 3.81 (1H, d, J = 16.6 Hz), 3.86 (1H, d, J = 16.6 Hz), 4.46 (1H, t, J = 5.8 Hz), 4.94 (1H, d, J = 4.8 Hz), 5.01 (1H, d, J = 4.8 Hz), 5.13 (1H, d, J = 5.3 Hz), 5.22 (1H, d, J = 7.8 Hz), 7.33–7.41 (2H, m), 7.59 (1H, td, J = 7.7, 1.2 Hz), 7.76 (1H, dd, J = 7.5, 1.2 Hz), 11.68 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 22.0, 22.1, 26.7, 26.8, 62.8, 71.3, 74.9, 78.0, 78.4, 100.6, 102.4, 112.8, 119.1, 127.9, 131.0, 133.6, 134.2, 146.6, 149.7, 161.7; MS m/z: 404 $(M+H)^+$; HRMS (FAB+) calcd for $C_{20}H_{26}N_3O_6$ 404.1816; found 404.1820 $(M+H)^+$.

5.1.66. 4-(4-Fluorophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11p)

The title compound was prepared from **10p**, as described for the synthesis of **11a**, in 60% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 2.85 (1H, heptet, J = 7.0 Hz), 3.10–3.26 (4H, m), 3.42–3.52 (1H, m), 3.54–3.69 (3H, m), 4.48 (1H, t, J = 5.5 Hz), 4.94 (1H,

br s), 5.02 (1H, br s), 5.14–5.24 (2H, m), 7.00–7.08 (2H, m), 7.21–7.28 (2H, m), 11.56 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 21.7, 24.6, 26.1, 60.7, 69.6, 73.3, 76.7, 77.3, 99.8, 100.3, 114.6 (d, J = 21 Hz), 129.9 (d, J = 7 Hz), 137.9 (d, J = 3 Hz), 146.6, 159.4, 160.4 (d, J = 239 Hz); MS m/z: 397 (M+H)$^+$; HRMS (FAB+) calcd for $C_{19}H_{26}FN_2O_6$ 397.1769; found 397.1770 (M+H)$^+$.

5.1.67. 4-(4-Methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11q)

The title compound was prepared from **10q**, as described for the synthesis of **11a**, in 53% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.23 (3H, s), 2.83 (1H, heptet, J = 6.9 Hz), 3.09–3.26 (4H, m), 3.41–3.69 (4H, m), 4.46 (1H, t, J = 5.6 Hz), 4.93 (1H, d, J = 4.5 Hz), 5.00 (1H, d, J = 4.8 Hz), 5.14 (1H, d, J = 5.3 Hz), 5.22 (1H, d, J = 7.5 Hz), 7.03 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 11.51 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.5, 21.57, 21.63, 24.6, 26.4, 60.6, 69.6, 73.2, 76.7, 77.2, 99.7, 100.1, 127.9, 128.5, 134.1, 138.5, 146.4, 159.5; MS m/z: 393 (M+H)$^+$; HRMS (FAB+) calcd for $C_{20}H_{29}N_2O_6$ 393.2020; found 393.2030 (M+H)$^+$.

5.1.68. 4-(4-Ethylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11r)

The title compound was prepared from **10r**, as described for the synthesis of **11a**, in 54% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.13 (3H, t, J = 7.5 Hz), 2.53 (2H, q, J = 7.5 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.08–3.26 (4H, m), 3.40–3.68 (4H, m), 4.46 (1H, t, J = 5.8 Hz), 4.92 (1H, d, J = 4.5 Hz), 4.99 (1H, d, J = 4.5 Hz), 5.14 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.5 Hz), 7.03–7.13 (4H, m), 11.51 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 16.3, 21.99, 22.0, 26.6, 27.8, 29.5, 62.8, 71.3, 75.0, 78.0, 78.4, 102.6, 102.8, 128.7, 129.3, 140.1, 142.9, 149.6, 161.7; MS m/z: 407 (M+H)$^+$; HRMS (FAB+) calcd for $C_{21}H_{31}N_2O_6$ 407.2177; found 407.2172 (M+H)$^+$.

5.1.69. 4-(4-Methoxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11s)

The title compound was prepared from **10s**, as described for the synthesis of **11a**, in 53% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.84 (1H, heptet, J = 6.9 Hz), 3.10–3.26 (4H, m), 3.42–3.68 (4H, m), 3.69 (3H, s), 4.46 (1H, t, J = 5.8 Hz), 4.93 (1H, d, J = 4.5 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.15 (1H, d, J = 5.3 Hz), 5.22 (1H, d, J = 7.8 Hz), 6.76–6.81 (2H, m), 7.08–7.14 (2H, m), 11.50 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ: 22.00, 22.01, 26.6, 27.3, 55.7, 62.8, 71.3, 75.0, 78.0, 78.4, 102.6, 103.0, 114.7, 130.2, 134.9, 149.4, 159.3, 161.7; MS m/z: 409 (M+H)$^+$; HRMS (FAB+) calcd for $C_{20}H_{29}N_2O_7$ 409.1969; found 409.1972 (M+H)$^+$.

5.1.70. 4-(4-Benzyloxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11t)

The title compound was prepared from **10t**, as described for the synthesis of **11a**, in 68% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.83 (1H, heptet, J = 6.9 Hz), 3.09–3.27 (4H, m), 3.42–3.68 (4H, m), 4.47 (1H, t, J = 5.6 Hz), 4.93 (1H, d, J = 4.8 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.03 (2H, s), 5.15 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.3 Hz), 6.87 (2H, d, J = 8.5 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.28–7.45 (5H, m), 11.51 (1H, s); MS m/z: 485 (M+H)$^+$.

5.1.71. 4-(4-Cyanophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11u)

The title compound was prepared from **10u**, as described for the synthesis of **11a**, in 38% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.86 (1H, heptet, J = 6.9 Hz), 3.10–3.27 (4H, m), 3.41–3.52 (1H, m), 3.60–3.78 (3H, m), 4.49 (1H, t, J = 5.7 Hz), 4.94 (1H, d, J = 4.8 Hz), 5.02 (1H, d, J = 4.8 Hz), 5.17–5.29 (2H, m), 7.43 (2H, d, J = 8.3 Hz), 7.70 (2H, d, J = 8.3 Hz), 11.63 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.66, 21.71, 24.6, 27.1, 60.7, 69.6, 73.3, 76.7, 77.3, 98.8, 100.4, 108.3, 119.1, 129.3, 132.0, 146.8, 147.8, 159.5; MS m/z: 402 (M−H)$^-$; HRMS (FAB+) calcd for $C_{20}H_{26}N_3O_6$ 404.1816; found 404.1817 (M+H)$^+$.

5.1.72. 4-(3-Methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11v)

The title compound was prepared from **10v**, as described for the synthesis of **11a**, in 62% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 2.24 (3H, s), 2.83 (1H, heptet, J = 7.0 Hz), 3.10–3.26 (4H, m), 3.42–3.51 (1H, m), 3.53–3.68 (3H, m), 4.46 (1H, t, J = 5.8 Hz), 4.93 (1H, d, J = 4.8 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.13 (1H, d, J = 5.3 Hz), 5.23 (1H, d, J = 7.5 Hz), 6.93 (1H, d, J = 7.5 Hz), 6.98 (1H, d, J = 7.5 Hz), 7.02 (1H, s), 7.11 (1H, t, J = 7.5 Hz), 11.52 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0, 21.6, 21.7, 24.6, 26.8, 60.6, 69.6, 73.3, 76.8, 77.2, 99.6, 100.0, 125.2, 126.1, 127.9, 128.8, 137.0, 141.6, 146.5, 159.5; MS m/z: 393 (M+H)$^+$; HRMS (FAB+) calcd for $C_{20}H_{29}N_2O_6$ 393.2020; found 393.2022 (M+H)$^+$.

5.1.73. 4-(3-Benzyloxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11w)

The title compound was prepared from **10w**, as described for the synthesis of **11a**, in 74% yield.

^{1}H NMR (DMSO-d_6) δ: 1.04 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.83 (1H, heptet, J = 6.9 Hz), 3.10–3.26 (4H, m), 3.40–3.50 (1H, m), 3.53–3.68 (3H, m), 4.46 (1H, t, J = 5.7 Hz), 4.87–5.10 (4H, m), 5.16 (1H, d, J = 3.5 Hz), 5.24 (1H, d, J = 7.5 Hz), 6.74–6.81 (2H, m), 6.82–6.87 (1H, m), 7.14 (1H, t, J = 7.9 Hz), 7.28–7.45 (5H, m), 11.53 (1H, br s); MS m/z: 485 (M+H)$^+$.

5.1.74. 4-(2,4-Dimethylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11x)

The title compound was prepared from **10x**, as described for the synthesis of **11a**, in 57% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 2.20 (3H, s), 2.25 (3H, s), 2.73 (1H, heptet, J = 7.0 Hz), 3.06–3.23 (4H, m), 3.40–3.66 (4H, m), 4.45 (1H, t, J = 5.8 Hz), 4.92 (1H, d, J = 4.5 Hz), 4.98 (1H, d, J = 4.5 Hz), 5.08 (1H, d, J = 5.3 Hz), 5.18 (1H, d, J = 7.8 Hz), 6.80 (1H, d, J = 8.0 Hz), 6.90 (1H, d, J = 8.0 Hz), 6.92 (1H, s), 11.56 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.2, 20.4, 21.6, 21.7, 23.9, 24.6, 60.6, 69.6, 73.2, 76.7, 77.2, 98.4, 100.1, 126.0, 127.8, 130.3, 134.2, 135.2, 136.1, 146.8, 159.7; MS m/z: 407 (M+H)$^+$; HRMS (FAB+) calcd for $C_{21}H_{31}N_2O_6$ 407.2177; found 407.2179 (M+H)$^+$.

5.1.75. 4-(4-Benzyloxy-2-methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (11y)

The title compound was prepared from **10y**, as described for the synthesis of **11a**, in 73% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 2.26 (3H, s), 2.73 (1H, heptet, J = 7.0 Hz), 3.06–3.23 (4H, m), 3.40–3.56 (3H, m), 3.58–3.66 (1H, m), 4.44 (1H, t, J = 5.8 Hz), 4.91 (1H, d, J = 4.5 Hz), 4.98 (1H, d, J = 4.5 Hz), 5.02 (2H, s), 5.08 (1H, d, J = 5.3 Hz), 5.19 (1H, d, J = 7.8 Hz), 6.70 (1H, dd, J = 8.3, 2.8 Hz), 6.79 (1H, d, J = 2.8 Hz), 6.84 (1H, d, J = 8.3 Hz), 7.28–7.44 (5H, m), 11.55 (1H, s); MS m/z: 499 (M+H)$^+$.

5.1.76. 4-Benzyl-5-trifluoromethyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (5)

The title compound was prepared from 4-benzyl-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one[24] via 4-benzyl-5-trifluoromethyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside,

as described for the synthesis of **10a** and **11a**, in 8% and 48% yield, respectively.

^{1}H NMR (DMSO-d_6) δ: 3.08–3.25 (4H, m), 3.48 (1H, d, J = 10.2 Hz), 3.67 (1H, d, J = 10.2 Hz), 3.79 (2H, s), 4.54 (1H, br s), 4.62–5.00 (1H, br), 5.03 (1H, br s), 5.12 (1H, br s), 5.25–5.62 (1H, br), 7.08–7.28 (5H, m), 13.31 (1H, br s); MS m/z: 403 $(M-H)^-$; HRMS (FAB+) calcd for $C_{17}H_{20}F_3N_2O_6$ 405.1268; found 405.1270 $(M+H)^+$.

5.1.77. 5-Trifluoromethyl-4-(4-hydroxyphenylmethyl)-1*H*-pyrazol-3-yl β-D-glucopyranoside (12a)

To a solution of **11a** (100 mg, 0.196 mmol) in MeOH (6 mL), 10% Pd–C (50% wet with water, 30 mg) was added. The mixture was stirred under a hydrogen atmosphere at room temperature overnight. Insoluble materials were removed by filtration and washed with MeOH. The filtrate and washing were concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 9:1–3:1) to give **12a** (70 mg, 85%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 3.10–3.25 (4H, m), 3.48 (1H, dd, J = 11.9, 5.1 Hz), 3.62–3.70 (3H, m), 4.35–5.20 (4H, m), 5.20–5.70 (1H, br), 6.60–6.65 (2H, m), 6.96 (2H, d, J = 8.5 Hz), 9.15 (1H, s), 12.80–13.70 (1H, br); MS m/z: 419 $(M-H)^-$; HRMS (FAB+) calcd for $C_{17}H_{20}F_3N_2O_7$ 421.1217; found 421.1222 $(M+H)^+$.

5.1.78. 5-Trifluoromethyl-4-(3-hydroxyphenylmethyl)-1*H*-pyrazol-3-yl β-D-glucopyranoside (12b)

The title compound was prepared from **11b**, as described for the synthesis of **12a**, in 80% yield.

^{1}H NMR (DMSO-d_6) δ: 3.10–3.24 (4H, m), 3.49 (1H, dd, J = 11.8, 5.0 Hz), 3.63–3.75 (3H, m), 4.40–5.20 (4H, m), 5.20–5.75 (1H, br), 6.51–6.57 (2H, m), 6.60 (1H, d, J = 7.7 Hz), 7.03 (1H, dd, J = 8.7, 7.7 Hz), 9.22 (1H, br s), 12.80–13.80 (1H, br); MS m/z: 419 $(M-H)^-$; HRMS (FAB+) calcd for $C_{17}H_{20}F_3N_2O_7$ 421.1217; found 421.1215 $(M+H)^+$.

5.1.79. 5-Trifluoromethyl-4-(2-hydroxyphenylmethyl)-1*H*-pyrazol-3-yl β-D-glucopyranoside (12c)

The title compound was prepared from **11c**, as described for the synthesis of **12a**, in 77% yield.

^{1}H NMR (DMSO-d_6) δ: 3.09–3.20 (4H, m), 3.42–3.52 (1H, m), 3.65 (1H, d, J = 11.8 Hz), 3.71 (2H, s), 4.30–5.70 (5H, m), 6.61–6.73 (2H, m), 6.77 (1H, d, J = 7.8 Hz), 6.94–7.00 (1H, m), 9.42 (1H, br s), 12.80–13.70 (1H, br); MS m/z: 419 $(M-H)^-$; HRMS (FAB+) calcd for $C_{17}H_{20}F_3N_2O_7$ 421.1217; found 421.1222 $(M+H)^+$.

5.1.80. 4-(2-Hydroxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (12d)

The title compound was prepared from **11f**, as described for the synthesis of **12a**, in 86% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 2.83 (1H, heptet, J = 7.0 Hz), 3.08–3.24 (4H, m), 3.41–3.67 (4H, m), 4.45 (1H, br s), 4.82–5.18 (3H, m), 5.22 (1H, d, J = 7.8 Hz), 6.64 (1H, td, J = 7.6, 1.2 Hz), 6.75 (1H, dd, J = 7.6, 1.2 Hz), 6.87 (1H, dd, J = 7.6, 1.5 Hz), 6.94 (1H, td, J = 7.6, 1.5 Hz), 9.34 (1H, br s), 11.52 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ: 21.8, 22.1, 26.5, 62.8, 71.3, 75.0, 78.0, 78.4, 102.0, 102.7, 115.6, 120.5, 127.8, 128.8, 130.6, 149.8, 155.9, 161.8; MS m/z: 395 $(M+H)^+$; HRMS (FAB+) calcd for $C_{19}H_{27}N_2O_7$ 395.1813; found 395.1816 $(M+H)^+$.

5.1.81. 4-(4-Hydroxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (12e)

The title compound was prepared from **11t**, as described for the synthesis of **12a**, in 87% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 2.82 (1H, heptet, J = 7.0 Hz), 3.09–3.26 (4H, m), 3.42–3.56 (3H, m), 3.59–3.68 (1H, m), 4.46 (1H, t, J = 5.8 Hz), 4.93 (1H, d, J = 4.5 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.14 (1H, d, J = 5.0 Hz), 5.21 (1H, d, J = 7.3 Hz), 6.61 (2H, d, J = 8.5 Hz), 6.98 (2H, d, J = 8.5 Hz), 9.04 (1H, s), 11.48 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 21.7, 24.6, 26.1, 60.6, 69.6, 73.3, 76.8, 77.2, 100.1, 100.3, 114.8, 128.9, 131.8, 146.4, 155.0, 159.5; MS m/z: 395 $(M+H)^+$; HRMS (FAB+) calcd for $C_{19}H_{27}N_2O_7$ 395.1813; found 395.1816 $(M+H)^+$.

5.1.82. 4-(3-Hydroxyphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (12f)

The title compound was prepared from **11w**, as described for the synthesis of **12a**, in 86% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.82 (1H, heptet, J = 7.0 Hz), 3.10–3.26 (4H, m), 3.43–3.61 (3H, m), 3.65 (1H, d, J = 11.3 Hz), 4.55 (1H, br s), 4.75–5.20 (3H, m), 5.21 (1H, d, J = 7.5 Hz), 6.51 (1H, dd, J = 7.9, 1.8 Hz), 6.57–6.60 (1H, m), 6.63 (1H, d, J = 7.9 Hz), 7.01 (1H, t, J = 7.9 Hz), 9.16 (1H, br s), 11.54 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 21.7, 24.7, 26.8, 60.6, 69.6, 73.3, 76.7, 77.2, 99.6, 100.3, 112.5, 115.0, 118.8, 128.9, 143.1, 146.7, 157.1, 159.5; MS m/z: 395 $(M+H)^+$; HRMS (FAB+) calcd for $C_{19}H_{27}N_2O_7$ 395.1813; found 395.1816 $(M+H)^+$.

5.1.83. 4-(4-Hydroxy-2-methylphenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (12g)

The title compound was prepared from **11y**, as described for the synthesis of **12a**, in 85% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 2.20 (3H, s), 2.73 (1H, heptet, J = 7.0 Hz), 3.06–3.25 (4H, m), 3.39–3.53 (3H, m), 3.58–3.67 (1H, m), 4.46 (1H, t, J = 5.8 Hz), 4.93 (1H, d, J = 4.5 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.09 (1H, d, J = 5.0 Hz), 5.19 (1H, d, J = 7.8 Hz), 6.44 (1H, dd, J = 8.3, 2.4 Hz), 6.53 (1H, d, J = 2.4 Hz), 6.72 (1H, d, J = 8.3 Hz), 8.95 (1H, s), 11.53 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.4, 21.6, 21.7, 23.5, 24.6, 60.6, 69.6, 73.3, 76.7, 77.2, 98.9, 100.0, 112.1, 116.5, 128.9, 129.3, 136.4, 146.7, 155.0, 159.7; MS m/z: 409 $(M+H)^+$; HRMS (FAB+) calcd for $C_{20}H_{29}N_2O_7$ 409.1969; found 409.1970 $(M+H)^+$.

5.1.84. X-ray crystallographic analysis of compound 10a

A single crystal (1.0 × 0.20 × 0.16 mm) of **10a** was obtained by recrystallization from EtOAc/hexane. Reflection data were collected using a Rigaku AFC7R diffractometer with graphite monochromated Mo Kα radiation. The structure was determined by direct methods ($_{SIR}$92) and refined using the full-matrix least-squares technique (CrystalStructure: Rigaku) with anisotropic temperature factors for the non-hydrogen atoms. Hydrogen atoms were included using a riding model. The crystal contained four molecules in the asymmetric unit. Crystal data: $C_{32}H_{33}F_3N_2O_{11}$; M = 678.61; monoclinic; space group $P2_12_12_1$ (#19); cell constants α = 19.705(4) Å, b = 29.043(7) Å, c = 5.911(3) Å, $\alpha = \beta = \gamma$ = 90.000(7)°, V = 3382.86(19) Å^3; Z = 4; Dc = 1.332 g/cm^3; unique reflections, 4431; observed reflections [$I > 3\sigma(I)$], 3682; R_1 = 0.049, wR_2 = 0.148; GOF = 0.932.

5.1.85. Solubility determination

Compounds were incubated in distilled water, and precipitates were separated by filtration. The solubility was determined by high-performance liquid chromatography (HPLC) analysis of each filtrate.

5.2. Biology

5.2.1. SGLT1 and SGLT2 inhibition assay

Human and rat SGLT expression plasmids were constructed as reported previously.[15,16] Cell culture, transfection procedure, and [^{14}C]-AMG uptake experiments were performed as reported previously.[16] In the experiments, 1 mM [^{14}C]-AMG concentration in the

uptake buffer was used. The concentration of the test compounds required to inhibit 50% uptake of [^{14}C]-AMG (IC_{50}) was calculated using logit plot. Phlorizin (**6**) was always included in the experiments as a reference standard.

5.2.2. Oral mixed carbohydrate tolerance tests in NA-STZ rats

5.2.2.1. Preparation of diabetic rat model. Male Wistar rats, aged 8 weeks, were injected intraperitoneally with nicotinamide (230 mg/kg). Fifteen minutes after injection, these rats were injected intravenously with streptozotocin (85 mg/kg) from the tail vein under anesthesia with ether. After 1 week, the rats were starved overnight, and a glucose tolerance test (2 g/kg) was performed. Rats, which displayed greater than 250 mg/dL plasma glucose concentration at 1 h after glucose load, were selected for use in subsequent tests.

5.2.2.2. Mixed carbohydrate tolerance test. After being starved overnight, the diabetic rats were orally administered test compounds suspended in 0.5% carboxymethyl cellulose (CMC), or 0.5% CMC alone (vehicle group). Immediately after test compound administration, 2 g/kg of mixed carbohydrate (starch/sucrose/lactose = 6:3:1)[25] was loaded orally. The blood was collected from the tail artery immediately before and after administration and treated instantly with heparin. The blood was centrifuged, and the plasma was collected to quantify the plasma glucose concentration using the glucose oxidase method. Dunnett's multiple comparison (two-sided) was used to estimate the degree of statistical significance of the difference between the vehicle and individual groups.

5.2.3. Metabolic stability

Test compounds (final concentration, 50 μM) were incubated in the assay buffer containing 0.8 mg/mL rat intestinal microsomes, 1 mg/mL β-nicotinamide-adenine-dinucleotide phosphate, 50 mM ammonium acetate buffer (pH 5.0) and 10 mM magnesium chloride at 37 °C. Concentrations of the test compounds were determined by LC–MS. Metabolic stability was calculated from the ratio of the test compound concentration at 0 min to its concentration after 30 and 60 min incubation.

5.2.4. Urinary glucose excretion in rats

Male Wistar rats, aged 8 weeks, were housed in metabolic cages. Rats were fasted from morning (08:00 hours) to the next morning. In the afternoon (16:00 hours), rats were administered test compounds (10 mg/kg) suspended in 0.5% CMC or vehicle orally. Urine was then collected until the following morning (08:00 hours). After measuring urine volume, an aliquot of each urine sample was stored at −20 °C until use. The glucose concentration in urine was measured using the glucose oxidase method. An *F*-test followed by Student's *t*-test or Welch's test was used to estimate the degree of statistical significance of the difference between the vehicle group and the test compound group.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.09.037.

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