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Design, synthesis, and structure–activity relationships of a series of 4-benzyl-5-isopropyl-1*H*-pyrazol-3-yl β-D-glycopyranosides substituted with novel hydrophilic groups as highly potent inhibitors of sodium glucose co-transporter 1 (SGLT1)

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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 therapeutic options for postprandial hyperglycemia. Previously, we reported potent and selective SGLT1 inhibitors **1** and **2** showing efficacy in oral carbohydrate tolerance tests in diabetic rat models. In a pharmacokinetic (PK) study of **2**, excessive systemic exposure to metabolites of **2** was observed, presumably due to the high permeability of its aglycone (**2a**). To further improve SGLT1 inhibitory activity and reduce aglycone permeability, a series of 4-benzyl-5-isopropyl-1*H*-pyrazol-3-yl β-D-glycopyranoside derivatives bearing novel hydrophilic substitution groups on the phenyl ring were synthesized and their inhibitory activity toward SGLTs was evaluated. Optimized compound **14c** showed an improved profile satisfying both higher activity and lower permeability of its aglycone (**22f**) compared with initial leads **1** and **2**. Moreover, the superior efficacy of **14c** in various carbohydrate tolerance tests in diabetic rat models was confirmed compared with acarbose, an α-glucosidase inhibitor (α-GI) widely used in the clinic.

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1. Introduction

In individuals with prediabetes, the metabolic abnormalities are frequently found as elevations in postprandial plasma glucose. Epidemiological studies have shown that postprandial glycemia has a strong association with cardiovascular (CV) risks, and addressing postprandial hyperglycemia is now recommended by International Diabetes Federation (IDF).[1] In a clinical trial to prevent progression to non-insulin-dependent diabetes mellitus (NIDDM) in patients with impaired glucose tolerance (IGT) (STOP-NIDDM), an α-glucosidase inhibitor (α-GI), acarbose, that delays the digestion of carbohydrates, not only reduced progression to diabetes mellitus (DM) but also protected patients against CV disease.[2]

Digested monosaccharides derived from carbohydrates in the diet are absorbed via several types of transporters in the small intestine.[3] 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.[4] Therefore, inhibition of SGLT1 can be an efficacious approach to improve postprandial hyperglycemia in DM and IGT patients.[5]

Currently, high-fructose corn syrup (typically comprising 45% glucose and 55% fructose) and other forms of sugar that are rich in glucose are routinely added to processed food and many types of beverages.[6] Thus, patients are frequently exposed to carbohydrates in the form of glucose. Therefore, the ability to suppress postprandial hyperglycemia after the intake of glucose may be an advantage of SGLT1 inhibitors over α-GI as an antidiabetic medication. We have been exploring SGLT1 inhibitors as novel agents for the treatment of postprandial hyperglycemia.

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.[7] Because compounds that inhibit both SGLTs could induce urinary glucose excretion and normalize blood glucose levels by inhibiting renal SGLT2 if they were absorbed, we targeted synthesis of an SGLT1-selective molecule to investigate efficacy based on the inhibition of SGLT1 alone.

In a previous paper,[8] we reported a structure–activity relationship (SAR) study of 4-benzyl-1*H*-pyrazol-3-yl β-D-glucopyranoside derivatives having inhibitory activity on SGLT1. Among the analogs

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explored, compounds **1** and **2** (Fig. 1) were potent and selective SGLT1 inhibitors in vitro and demonstrated robust efficacy in oral mixed carbohydrate tolerance tests[9] in streptozotocin-nicotinamide-induced diabetic rats (NA-STZ rats).[10] In a pharmacokinetic (PK) study of compound **2** (10 mg/kg, p.o.) in rats, very low levels of **2** were detected in the plasma and were eliminated immediately, indicating that systemic exposure to **2** was low (C_{max}: 8.2 ng/mL, $AUC_{(0-6\,h)}$: 67 min ng/mL). However, in the same plasma, relatively high levels of the aglycone of **2** (**2a**) were also observed (C_{max}: 201 ng/mL, $AUC_{(0-6\,h)}$: 8600 min ng/mL). Furthermore, levels of **2a** were further increased by enzymatic hydrolysis with β-glucuronidase (an enzyme with hydrolytic activity for conjugates including glycosides, glucuronides, and sulfates) before quantification analysis (C_{max}: 1087 ng/mL, $AUC_{(0-6\,h)}$: 81,227 min ng/mL), suggesting that systemic exposure to metabolites derived from **2** was high. The Caco-2 cell permeability of **2** and **2a** indicated that the higher permeability of the aglycone, formed by hydrolysis of **2** in the gut, meant that **2a** would be easily absorbed (Table 5).[11] Because these metabolites would have no impact on efficacy, we considered that the permeability of the aglycone should be reduced to avoid unnecessary systemic exposure and ensure the safety of the administered compounds. Accordingly, the additional objective of reducing the permeability of the aglycones as well as further enhancement of the inhibitory activity of SGLT1 was included in this study.

It is known that some physicochemical parameters of compounds show correlation with membrane permeability,[12] and hydrophilic compounds having a larger polar surface area (PSA) are preferable to reduce absorption. In our previous study, we focused on investigations into relatively simple substitution groups.[8] Therefore, in this study, we instead explored analogs bearing higher functionalized hydrophilic groups in order to concurrently achieve improvement of both pharmacological and physicochemical parameters.

In the present paper, we report the design, synthesis, and SAR of a series of 4-benzyl-5-isopropyl-1*H*-pyrazol-3-yl β-D-glycopyranoside derivatives bearing novel hydrophilic functional groups on the phenyl ring. These compounds were investigated in order to identify further improved SGLT1 inhibitors. We also describe the Caco-2 cell permeability of the aglycones of several derivatives as well as in vivo pharmacological profiles of selected compounds.

2. Chemistry

4-Benzyl-5-isopropyl-1*H*-pyrazol-3-yl β-D-glycopyranoside derivatives bearing various functional groups on the phenyl ring were prepared as illustrated in Schemes 1–4. As shown in Scheme 1, 4-benzyl-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one derivatives (**5a–g**) were synthesized by the cyclization of substituted 2-benzyl ketoesters (**4a–g**), prepared by either Knoevenagel condensation of 4-nitrobenzaldehyde (**3a**) and methyl 4-methyl-3-oxopentanoate followed by Pd–C-catalyzed hydrogenation of both the double bond and nitro group of the benzylidene intermediate or by alkylation of the same ketoester with substituted benzyl mesylates prepared by methanesulfonylation of the hydroxyl groups of the corresponding benzyl alcohols (**3b–g**). The pyrazolone derivatives obtained (**5a–g**) were glycosidated to react with tetra-*O*-acetyl-β-D-glycopyranosyl bromides in two-phase solvents consisting of CH_2Cl_2 and aqueous NaOH solution in the presence of the phase transfer catalyst $BnN(n\text{-}Bu)_3Cl$.[13] The yields of these glycosylation reactions were low to moderate (11–38%, see Section 5) due to decomposition of the sugar donors and remaining of the unreacted aglycones. Subsequent removal of the benzyl (Bn) protective groups of the ester derivatives, except for aniline (**6a**), was performed by Pd–C-catalyzed hydrogenation, in which the double bonds of the alkene-containing derivatives were simultaneously reduced to afford carboxylates (**6b–h**). Within these intermediates, the acetyl (Ac) groups on the sugar of the aniline (**6a**) were removed by solvolysis using NaOMe in MeOH to give deprotected glucopyranoside (**7**).

Substituted aniline derivatives (**8a–f**) were synthesized via reaction of aniline (**6a**) with acid anhydrides or acid chlorides in the presence of pyridine (method A) or by reaction of carboxylic acids with condensing agents, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBt) (method B), following removal of the Ac groups as described above. In the synthesis of amines (**9a**, **b**), benzyloxycarbonyl (Cbz) groups of **8e** and **8f** were removed by Pd–C-catalyzed hydrogenation (Scheme 2).

Various amide derivatives (**10a–e**, **11a–f**) were prepared via similar reaction sequences of condensation and deprotection as described for the synthesis of **8e** and **8f**, but using carboxylic acids (**6b–e**, **h**) as precursors (Scheme 3).

For the synthesis of 2-acylamino-2-methylpropanamide derivatives (**14a–i**), 2-acylamino-2-methylpropanoic acids (**12a–c**) were prepared initially via condensation of butanoic acids (**6e–g**) and benzyl 2-amino-2-methylpropanoate followed by removal of Bn groups by Pd–C-catalyzed hydrogenation. Subsequent conversion of **12a–c** into amides (**14a–i**) was performed using similar reaction sequences as described above. In **14a–c**, Cbz groups were removed by Pd–C-catalyzed hydrogenation before removal of the Ac groups (Scheme 4).

Starting materials (**3b–g**) were synthesized by either benzylation of carboxylic acids (**20a**, **b**) using BnBr and K_2CO_3 or by reduction of benzaldehydes (**17a**, **b**, **19**, **21**) by $NaBH_4$, as illustrated in Scheme 5. Benzyl butanoates (**17a**, **b**) were prepared by conversion of ethyl esters (**16a**, **b**), which were obtained by the PEPPSI™–IPr-catalyzed[14] Negishi cross-coupling reaction of aryl bromides (**15a**, **b**) with an alkylzinc bromide reagent, into benzyl esters via hydrolysis. Pent-4-enoate (**19**) was synthesized by benzylation of pent-4-enoic acid, prepared by Wittig olefination of mono-protected terephthalaldehyde (**18**), in which the diethyl acetal group was deprotected under acidic work-up of the Wittig reaction.

In the above PK study of compound **2**, hydrolysis of the glucosidic linkage of **2** was observed by treatment with β-glucuronidase. Therefore, synthesis of the aglycones of the key compounds was carried out by enzymatic hydrolysis of the parent glycosides using β-glucuronidase in a 0.2 M acetate buffer (pH 5.0). For the amine (**22c**), the Cbz group was removed by following Pd–C-catalyzed hydrogenation of the *N*-protected aglycone (**22b**) (Scheme 6).

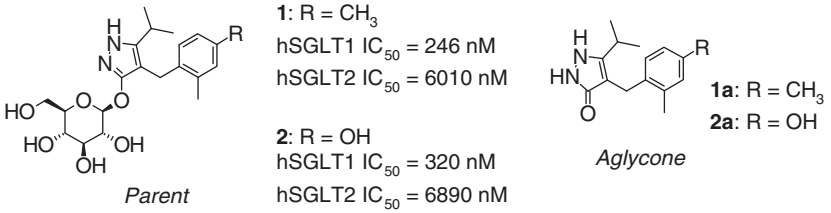
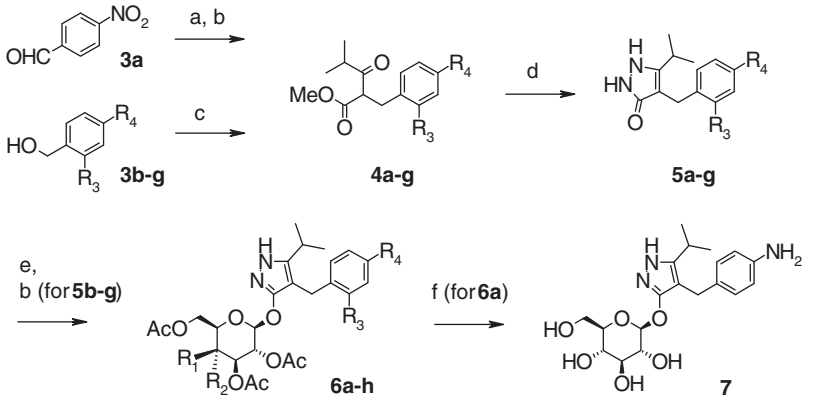


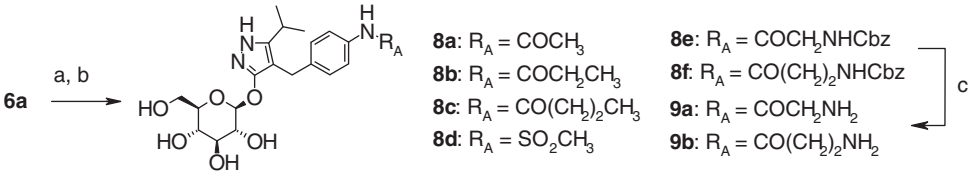
Figure 1. Structure of SGLT1 selective inhibitors and each aglycone of our previous work.



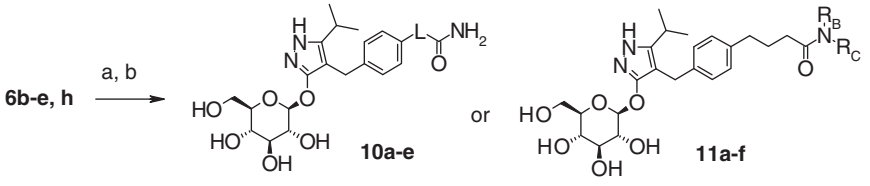
Cpd	R_3	R_4
4a, 5a	H	NH_2
3-5b	H	CO_2Bn
3-5c	H	CH_2CO_2Bn
3-5d	H	(*E*)-CH=$CHCO_2Bn$
3-5e	H	$(CH_2)_3CO_2Bn$
3-5f	CH_3	$(CH_2)_3CO_2Bn$
3-5g	H	(*E*)-CH=$CH(CH_2)_2CO_2Bn$

Cpd	R_1	R_2	R_3	R_4
6a	H	OAc	H	NH_2
6b	H	OAc	H	CO_2H
6c	H	OAc	H	CH_2CO_2H
6d	H	OAc	H	$(CH_2)_2CO_2H$
6e	H	OAc	H	$(CH_2)_3CO_2H$
6f	H	OAc	CH_3	$(CH_2)_3CO_2H$
6g	OAc	H	H	$(CH_2)_3CO_2H$
6h	H	OAc	H	$(CH_2)_4CO_2H$

Scheme 1. Reagents and conditions: (a) *i*PrCOCH$_2$CO$_2$CH$_3$, piperidine, AcOH, *i*PrOH, rt; (b) H$_2$, Pd-C, MeOH, rt; (c) (i) MsCl, Et$_3$N, THF, 0 °C; (ii) NaH, *i*PrCOCH$_2$CO$_2$CH$_3$, THF, 0 °C to reflux; (d) N$_2$H$_4$·H$_2$O, toluene or *i*PrOH, reflux or rt; (e) 5 N NaOHaq, BnN(*n*-Bu)$_3$Cl, acetobromoglucose or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide, CH$_2$Cl$_2$, rt; (f) NaOMe, MeOH, rt.



Scheme 2. Reagents and conditions: (a) method A: $(R_A)_2O$ or R_ACl, pyridine, CH_2Cl_2, 0 °C to rt; method B: $CbzNH(CH_2)_{1-2}CO_2H$, EDCI·HCl, HOBt·H$_2$O, DMF, rt; (b) NaOMe, MeOH, rt; (c) H$_2$, Pd-C, MeOH, rt.



Cpd	L
10a	bond
10b	CH_2
10c	$(CH_2)_2$

Cpd	L
10d	$(CH_2)_3$
10e	$(CH_2)_4$

Cpd	R_B	R_C
11a	$(CH_2)_2OH$	H
11b	$(CH_2)_2OH$	CH_3
11c	$(CH_2)_3OH$	H

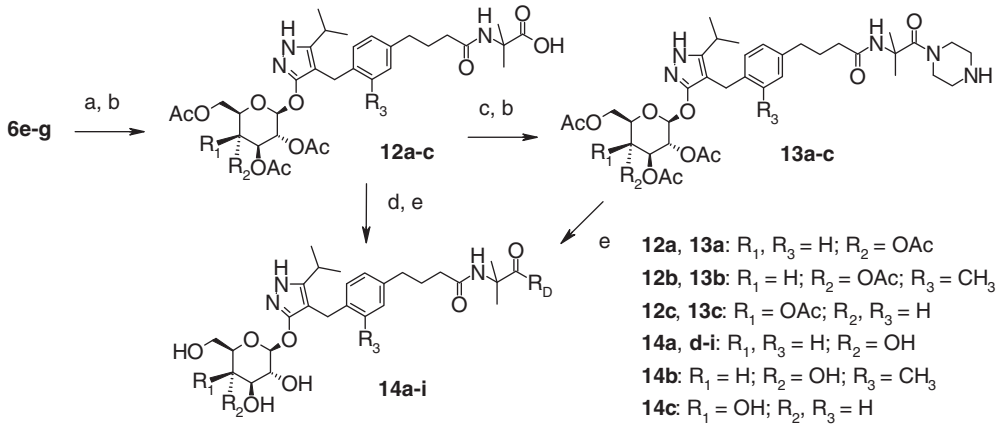
Cpd	R_B	R_C
11d	$C(CH_3)_2CH_2OH$	H
11e	CH_2CONH_2	H
11f	$C(CH_3)_2CONH_2$	H

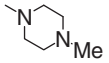
Scheme 3. Reagents and conditions: (a) 28% NH_3 aq or HNR_BR_C (HCl), EDCI·HCl, HOBt·H$_2$O, (Et$_3$N,) DMF, rt; (b) NaOMe, MeOH, rt.

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).

It is known that some aniline derivatives can mimic the phenol structure and function as biologically equivalent groups.[15]

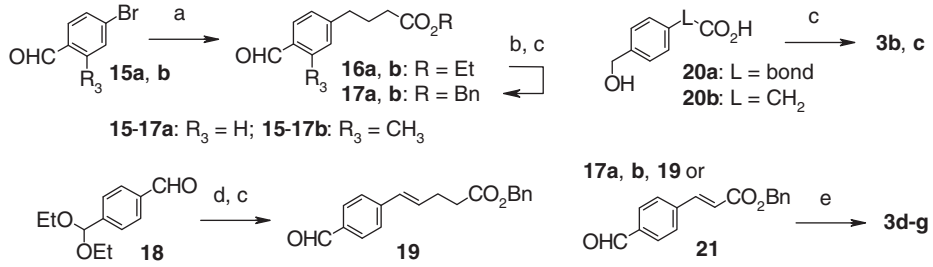


Cpd	R_D
14a-c	
14d	

Cpd	R_D
14e	
14f	

Cpd	R_D
14g	$NH(CH_2)_2OH$
14h	$NHCH_2CONH_2$
14i	$NH(CH_2)_2N(CH_3)_2$

Scheme 4. Reagents and conditions: (a) $Cl^-H_3N^+C(CH_3)_2CO_2Bn$, EDCI·HCl, HOBt·$H_2O$, Et_3N, DMF, rt; (b) H_2, Pd–C, MeOH, rt; (c) 1-benzyloxycarbonylpiperazine, EDCI·HCl, HOBt·H_2O, DMF, rt; (d) HR_D(·HCl), EDCI·HCl, HOBt·H_2O, (Et_3N,) DMF, rt; (e) NaOMe, MeOH, rt.

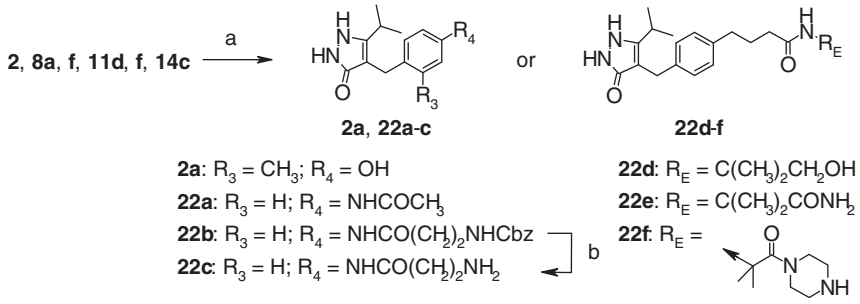


Scheme 5. Reagents and conditions: (a) $BrZn(CH_2)_3CO_2Et$, PEPPSI™-IPr catalyst, THF, rt; (b) 5 N NaOHaq, MeOH–THF, rt; (c) BnBr, K_2CO_3, DMF, rt; (d) $Br^-Ph_3P^+(CH_2)_3CO_2H$, NaOMe, THF, rt; (e) $NaBH_4$, THF, rt.

Focusing on the para-hydroxyl group of the phenyl ring of our lead compound **2**, we first examined the effects of the replacement with phenol bioisoster groups. For synthetic ease, novel designed groups were assessed in the absence of the methyl group at the ortho-position to the pyrazolylmethyl group, and the results are summarized in Table 1.

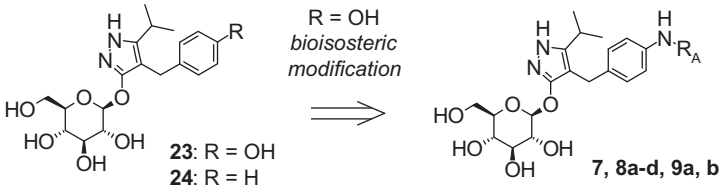
Compared with phenol (**23**), aniline (**7**) showed reduced SGLT1 inhibitory activity. However, it was slightly more potent than unsubstituted compound **24**, suggesting that the amino group had some enhancing effect on activity. Conversion of aniline (**7**) into acetoanilide (**8a**) was well tolerated and its inhibitory activity was maintained, with a slight improvement in selectivity versus SGLT2 also observed. In contrast, elongation of the acyl group was found to be an unfavorable conversion, and the resulting propanamide (**8b**) and butanamide (**8c**) showed diminished activity according to chain length. In addition, methanesulfonamide (**8d**) showed decreased activity and reduced selectivity for SGLT1 compared with every aniline derivative described above, except for compound **8c**. To reduce the lipophilic parameter, introduction of an amino group onto the acyl groups was next examined. Although, glycinamide (**9a**) showed weaker activity than acetoanilide (**8a**), recovery of activity with improved selectivity for SGLT1 was observed in β-alaninamide (**9b**) compared with glycinamide (**9a**) or propanamide (**8b**). Butanamide (**8c**), possessing a methyl group instead of the terminal amino group of **9b**, showed weaker activity than **9b**, indicating that the hydrogen-bond donor character and/or basic functionality of the amino group at this position might contribute to the interaction with SGLT1. By the introduction of these phenol bioisosteric groups, a reduction in calculated Log*D* values and/or larger topological PSA (TPSA) values were observed and reduced permeability of their aglycones was expected. Indeed, in the Caco-2 cell permeability test, the aglycones (**22a**, **c**) of selected compounds (**8a**, **9b**) were found to be less permeable than the aglycones of lead compounds **1** and **2** (**1a**, **2a**) (Table 5).

Because these amide derivatives incorporate an aniline structure, the formation of aniline metabolites was of concern owing to the known mutagenicity of anilines.[16] Therefore, a PK study of a representative amide (**8a**) was performed in rats (10 mg/kg, p.o.) before further optimization of this series of compounds. The plasma concentration of the aglycone of compound **8a** (**22a**) was found to be lower, even after hydrolysis by β-glucuronidase (C_{max}: 78 ng/mL, $AUC_{(0-6\,h)}$: 16,107 min ng/mL), than that of the aglycone



Scheme 6. Reagents and conditions: (a) β-glucuronidase, 0.2 M acetate buffer (pH 5.0), 37 °C; (b) H_2, Pd–C, MeOH, rt.

Table 1
hSGLT1 and hSGLT2 inhibitory activities and selectivity of derivatives having phenol bioisoster groups on the phenyl ring



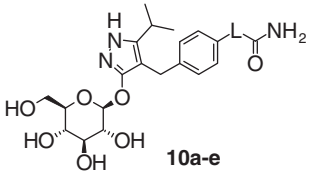
Compd	R_A	*c*Log *D*[a]	TPSA[a](Å^2)	SGLT IC_{50}[b] (nM)		Selectivity[c]
				hSGLT1	hSGLT2	
23	–	0.43	148	207	285	1.4
24	–	0.89	128	738	2020	2.7
7	H	−0.03	154	422	1590	3.8
8a	$COCH_3$	0.22	157	392	3090	7.9
8b	$COCH_2CH_3$	0.54	157	724	5100	7.0
8c	$CO(CH_2)_2CH_3$	0.86	157	1500	3980	2.7
8d	SO_2CH_3	−0.07	183	931	936	1.0
9a	$COCH_2NH_2$	−2.66	183	831	4700	5.7
9b	$CO(CH_2)_2NH_2$	−3.39	183	446	5620	13

[a] Calculated Log *D* at pH 6.5, and TPSA values were calculated using Percepta/ADME Suite 2012 (ACD labs, Toronto, Canada).
[b] IC_{50} values for SGLT inhibition were determined in triplicate.
[c] Selectivity values were calculated by IC_{50} hSGLT2/IC_{50} hSGLT1.

of compound **2** (**2a**), as described above. However, a trace amount of the particular aniline metabolite (**7**) and its aglycone (**5a**) was detected in the same plasma, and the level of **5a** increased after treatment with β-glucuronidase (C_{max}: 38 ng/mL, $AUC_{(0-6\,h)}$: 7458 min ng/mL), indicating that the amide bond of **8a** is not stable in vivo and that aniline metabolites could be formed easily. Moreover, one of the aniline metabolites (**5a**) was unfortunately found to be positive in the Ames test (**7**: not tested). Based on these disappointing results, we discontinued further optimization of this series of compounds and turned our attention instead to nonaniline derivatives to ensure greater safety.

As we wished to incorporate some characteristics of the above aniline amide derivatives in order to improve physicochemical parameters and the potential to introduce further substitution groups, we next investigated the effects of introducing inverse amide-containing groups.[17] The results are summarized in Table 2. Initial use of benzamide (**10a**) or derivatives having relatively short linking alkylene groups (**10b**, **c**) afforded a disappointing reduction in SGLT1 inhibitory activity compared with phenol (**23**). However, a marked recovery of activity was observed by elongation of the linking group to propyrene (**10d**). Good consistency observed in the number of tethering atoms between the phenyl group and the terminal $–NH_2$ group with a previous β-alaninamide derivative (**9b**) suggested that at least the hydrogen-bond donor character at this position might be efficacious to interact with SGLT1. Because further elongation into pentanamide (**10e**) led to a decrease in activity, we selected butanamide (**10d**) as a lead compound for further optimization investigations.

Table 2
hSGLT1 and hSGLT2 inhibitory activities and selectivity of carboxamide derivatives having various linkers



Compd	L	*c*Log *D*[a]	TPSA[a](Å^2)	SGLT IC_{50}[b] (nM)		Selectivity[c]
				hSGLT1	hSGLT2	
10a	bond	−0.31	171	1470	2470	1.7
10b	$–CH_2–$	−0.19	171	6170	9950	1.6
10c	$–(CH_2)_2–$	0.15	171	1990	2540	1.3
10d	$–(CH_2)_3–$	0.45	171	351	1070	3.0
10e	$–(CH_2)_4–$	0.83	171	1030	457	0.44

[a] Calculated Log *D* at pH 6.5, and TPSA values were calculated using Percepta/ADME Suite 2012 (ACD Labs, Toronto, Canada).
[b] IC_{50} values for SGLT inhibition were determined in triplicate.
[c] Selectivity values were calculated by IC_{50} hSGLT2/IC_{50} hSGLT1.

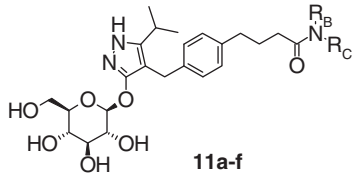
With a nonaniline lead compound in hand, we next examined the effects of introducing functional groups on the amide-nitrogen atom of butanamide (**10d**). Because the presence of substitution groups should improve not only SGLT1 inhibitory activity but also physicochemical parameters, alkyl groups possessing polar groups such as an alcohol or amide were used for investigation and the

results are illustrated in Table 3. Substitution with a 2-hydroxylethyl group on the amide-nitrogen atom was well tolerated and resulting compound **11a** showed a slightly increased inhibitory activity on both SGLTs compared with the *N*-unsubstituted amide (**10d**). In contrast, further substitution with a methyl group on the nitrogen atom of 2-hydroxyethyl amide (**11a**) resulted in a decrease in activity, indicating that at least one of the hydrogen atoms on the nitrogen of the amide group should be left for hydrogen-bond donation (**11b**). In addition, 3-hydroxypropyl amide (**11c**) showed comparable inhibitory activity on SGLT1 with 2-hydroxyethyl amide (**11a**), but a slight decrease in selectivity for SGLT1 was observed. Although lipophilicity was increased and not limited to SGLT1, a notable enhancement of inhibitory activity was achieved by disubstitution with methyl groups on the methylene bonded to the amide-nitrogen atom of compound **11a**, suggesting that a degree of bulkiness at this position might be critical for the expression of higher activities (**11d**). These enhancement effects on the inhibitory activities on both SGLTs of the dimethyl groups were also observed in subsequent glycinamide derivatives investigated. Glycinamide (**11e**) was less potent than basal *N*-unsubstituted amide (**10d**), but substitution with dimethyl groups at the corresponding position to **11d** led to a marked increase of inhibitory activities on both SGLTs (**11f**). In addition to the strong potency, the permeability of the aglycone of compound **11f** (**22e**) was distinctly lowered relative to that of the aglycones of initial lead compounds **1** and **2** (**1a**, **2a**) and was further reduced even compared with those of the aglycones of the above aniline derivatives (**22a**, **c**), possibly owing to changes in physicochemical properties (Table 5). On the other hand, the aglycone of the most potent compound **11d** (**22d**) showed higher permeability than that of **22e**. Of these two types of potent compounds, **11d** and **11f**, we focused on the terminal carbamoyl group of **11f**. The effects of further modification of this group were finally investigated (Table 4).

Based on the same objective to explore substituents on the butanamide nitrogen atom, 2-hydroxyethyl amide (**14g**) and glycinamide (**14h**) were designed but no improvement in activity or selectivity was observed compared with the *N*-unsubstituted amide (**11f**). In contrast, a further increase of inhibitory activity could be achieved by conversion of the carbamoyl group into amine-containing amide groups such as 2-(dimethylamino)ethylamide (**14i**) and 4-methylpiperazin-1-ylamide (**14d**). Because cyclized amine (**14d**) was more potent than alkylamine (**14i**), fixation of the amine position might be advantageous to the interaction with SGLTs. To reduce the lipophilic parameter, a methyl group on the piperazine ring of compound **14d** was eliminated and the resulting unsubstituted piperazine (**14a**) showed a slightly decreased but still potent inhibitory activity on SGLT1 along with potent inhibition of SGLT2. Conversion of this piperazine group into either piperidine (**14e**) or morpholine (**14f**) caused a decrease of activity, suggesting that basic functionality at this position might be efficacious in achieving strong inhibitory activities on both SGLTs. The above conversion of the *N*-unsubstituted amide into piperazinamide was also found to be efficacious in maintaining the low permeability of the aglycone. The aglycone of **14a** (**22f**) showed a corresponding low permeability compared with that of the aglycone of **11f** (**22e**) (Table 5).

Of all derivatives investigated in this study, we selected **14a** as the most promising compound and examined whether its inhibitory activity toward SGLT2 could be reduced. In the previous study, we discovered that the introduction of a methyl group at the ortho-position of the pyrazolylmethyl group on the phenyl ring could improve selectivity toward SGLT1;[8] therefore, an analog of **14a** bearing the methyl group at the corresponding position was synthesized. Obtained compound **14b** actually exhibited weaker inhibitory activity on SGLT2 compared with **14a** (Table 4). Moreover, unlike lead compounds **1** and **2**, the potency on SGLT1 of **14b** was not diminished even by the introduction of this methyl group. This conversion was not so efficient to maintain the potency on SGLT1 in the lead compound analogs (for example, **2** vs. **23**).[8] As another approach to improve selectivity for SGLT1, conversion of the sugar portion into galactoside was also investigated. Unlike glucose, which is a substrate of both SGLT1 and SGLT2, galactose is a substrate of SGLT1 only.[7] As expected, the inhibitory activity of galactoside (**14c**) on SGLT2 was notably reduced compared with glucoside (**14a**), and this conversion of sugar was more effective than the introduction of the methyl group on the phenyl ring with respect to decreasing activity on SGLT2 (**14c**: 87-fold reduction vs. **14b**: 19-fold reduction). Galactoside (**14c**) also showed reduced inhibitory activity on SGLT1 compared with glucoside (**14a**), but the superior activity of **14a** ensured that **14c** was a still potent compound. A slight difference in the recognition of the natural substrates, glucose and galactose, might be a possible explanation of this reduction of the inhibitory activity on SGLT1.[18] Selectivity toward SGLT1 might not be important for the compounds that would be poorly absorbed such as **14b** and **14c**. However, simplicity of the structure modifications, installation of methyl group or conversion

Table 3
hSGLT1 and hSGLT2 inhibitory activities and selectivity of butanamide derivatives substituted with various groups on the nitrogen atom of the carboxamide group

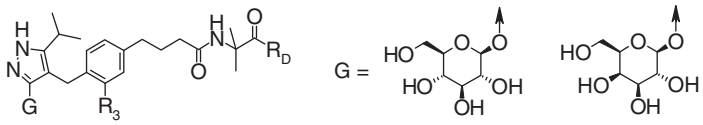


11a-f

Compd	R_B	R_C	*c*Log *D*[a]	TPSA[a] (Å^2)	SGLT IC_{50}[b] (nM)		Selectivity[c]
					hSGLT1	hSGLT2	
10d	H	H	0.45	171	351	1070	3.0
11a	$(CH_2)_2OH$	H	0.27	177	217	608	2.8
11b	$(CH_2)_2OH$	CH_3	0.54	169	517	358	0.69
11c	$(CH_2)_3OH$	H	0.42	177	170	319	1.9
11d	$C(CH_3)_2CH_2OH$	H	1.05	177	12	8	0.67
11e	CH_2CONH_2	H	−0.34	200	772	1050	1.4
11f	$C(CH_3)_2CONH_2$	H	0.47	200	45	80	1.8

[a] Calculated Log *D* at pH 6.5 and TPSA values were calculated using Percepta/ADME Suite 2012 (ACD Labs, Toronto, Canada).
[b] IC_{50} values for SGLT inhibition were determined in triplicate.
[c] Selectivity values were calculated by IC_{50} hSGLT2/IC_{50} hSGLT1.

Table 4
hSGLT1 and hSGLT2 inhibitory activities and selectivity of *N*-(propan-2-yl)butanamide derivatives substituted with various carboxamides at the 2-position of the propyl group



14a, b, d-i **14c**

Compd	R_3	R_D	*c*Log*D*[a]	TPSA[a](Å^2)	SGLT IC_{50}[b] (nM)		Selectivity[c]
					hSGLT1	hSGLT2	
11f	H	NH_2	0.47	200	45	80	1.8
14g	H	$NH(CH_2)_2OH$	0.15	206	70	151	2.2
14h	H	$NHCH_2CONH_2$	−0.37	229	103	209	2.0
14i	H	$NH(CH_2)_2N(CH_3)_2$	−0.97	190	23	46	2.0
14d	H	4-Methylpiperazin-1-yl	0.42	181	10	18	1.8
14a	H	Piperazin-1-yl	−1.18	190	15	20	1.3
14e	H	Piperidin-1-yl	1.84	177	25	42	1.7
14f	H	Morpholin-4-yl	0.96	187	124	98	0.79
14b	CH_3	Piperazin-1-yl	−0.84	190	11	371	34
14c	H	Piperazin-1-yl	−1.18	190	50	1730	35

[a] Calculated Log *D* at pH 6.5 and TPSA values were calculated using Percepta/ADME Suite 2012 (ACD Labs, Toronto, Canada).
[b] IC_{50} values for SGLT inhibition were determined in triplicate.
[c] Selectivity values were calculated by IC_{50} hSGLT2/IC_{50} hSGLT1.

Table 5
Calculated Log*D* at pH 6.5, TPSA values and Caco-2 cell permeability of key compounds

Parent				Aglycone			
Compd	*c* Log *D*[a]	TPSA[a](Å^2)	Caco-2 ratio[b]	Compd	*c* Log *D*[a]	TPSA[a](Å^2)	Caco-2 ratio[b]
1	1.58	128	0.092	**1a**	3.44	41	23
2	0.73	148	0.067	**2a**	2.06	61	9.6
8a	0.22	157	NT[c]	**22a**	1.61	70	2.8
9b	−3.39	183	NT[c]	**22c**	−1.53	96	1.5
11d	1.05	177	NT[c]	**22d**	2.40	90	1.5
11f	0.47	200	NT[c]	**22e**	1.94	113	0.22
14a/14c	−1.18	190	0.11[d]	**22f**	1.01	103	0.41

[a] Calculated Log*D* at pH 6.5, and TPSA values were calculated using Percepta/ADME Suite 2012 (ACD labs, Toronto, Canada).
[b] Caco-2 cell permeability ratio: atenolol = 1. Mean of 2 experiments. Papp value of atenolol was $0.43 \pm 0.10 \times 10^{-6}$ cm/s (mean ± S.E. of 6 experiments).
[c] NT = not tested.
[d] Value of compound **14c**.

Table 6
Inhibitory activities and selectivity of rat SGLT1 (rSGLT1) and SGLT2 (rSGLT2), intestinal metabolic stability, and suppressing effects on the plasma glucose escalation in OMTT in NA-STZ rats of key compounds

Compd	SGLT IC_{50}[a] (nM)		Selectivity[b]	Metabolic Stability at 30/60 min[c]	OMTT in NA-STZ rats	
	rSGLT1	rSGLT2			mg/kg	$\Delta AUC_{(0-1\ h)}$ (% of control)[d]
2	183	4370	24	96/83	1	62.0 ± 5.8[e], 74.6 ± 15.8[f]
					3	41.1 ± 9.2[e], 49.0 ± 21.0[f]
14b	22	1160	53	79/76	0.3	64.2 ± 7.7
					1	46.8 ± 6.8
14c	104	4280	41	92/91	0.3	44.7 ± 9.2
					1	23.5 ± 5.1

[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] Each value represents the mean ± S.E. (n = 5).
[e] Values in the same examination of **14b**.
[f] Values in the same examination of **14c**.

of glucoside into galactoside, led us to pursue the selectivity to exclude possibility of increasing urinary glucose excretion, if they were absorbed unexpectedly.

As shown in Table 6, these potent and selective SGLT1 inhibitors (**14b**, **c**) showed greater efficacy than initial lead compound **2** in oral liquid meal tolerance tests (OMTT)[19] in NA-STZ rats. The higher metabolic stability of compound **14c** might contribute to the higher efficacy compared with compound **14b**, despite the relatively weaker inhibitory activity on rat SGLT1 of compound **14c**. On the basis of these in vivo efficacies of the two compounds, we selected **14c** and a comparison of its efficacy with acarbose, an α-GI that is widely used in the clinic, was conducted.

In tolerance tests in streptzotocin-induced-diabetic rats (STZ rats), **14c** suppressed the escalation of plasma glucose levels

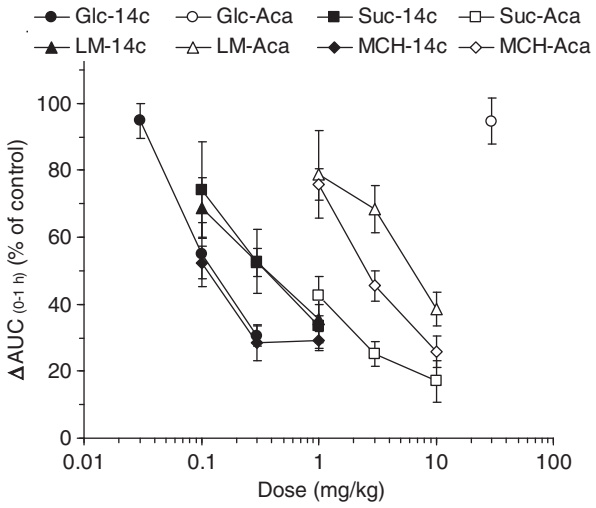


Figure 2. Suppressing effects of compound **14c** and acarbose on escalation of plasma glucose levels by oral loading of various glucose sources in STZ rats. Points and bars represent the mean and S.E. values, respectively. (n = 5–6). All abbreviations are defined as follows. Glc = glucose; Suc = sucrose; LM = liquid meal; MCH = mixed carbohydrate; Aca = acarbose.

induced by oral loading of various carbohydrates and carbohydrate-containing meals in a dose-dependent manner, as shown in Figure 2. Furthermore, its efficacy was greater than that of acarbose. An ability to respond with glucose would be an advantage of SGLT1 inhibitors over α-GI, because they have no effects on monosaccharide absorption. While acarbose showed no efficacy, even at a high dose (30 mg/kg), distinct suppressing effects on glucose absorption were observed with **14c** in this study.

In in vivo experiments, the abdominal symptoms such as soft feces or diarrhea, which were common adverse effects with α-GI,[2] were not observed in every treatment groups, except for the higher dose (1.0 mg/kg) of **14c** in the comparative study among SGLT1 inhibitors (Table 6). Continuous administration for 2 days with liquid meal (t.i.d., see Section 5) before OMTT and the greater efficacy of **14c** (Table 6), might be possible factors that induced those symptoms of **14c**.

4. Conclusions

To improve potency of SGLT1 inhibition and reduce the permeability of the aglycones of initial lead compounds **1** and **2**, novel hydrophilic substitution groups on the phenyl ring were investigated. SAR studies identified that *N*-substituted butanamide derivatives exhibited strong inhibitory activities on both SGLTs, whereas the introduction of a methyl group into the meta-position of the butanamide group on the phenyl ring or conversion of glucoside into galactoside was found to improve selectivity toward SGLT1. Finally, reduction of lipophilic parameters and/or enlargement of PSA were effective to lower the Caco-2 cell permeability of the aglycones.

We achieved both enhancement of inhibitory activity on SGLT1 and a marked reduction in the permeability of its aglycone in **14c** compared with initial lead compounds **1** and **2**. The improved profile of **14c** might contribute to a lower required dose and reduced risks of unnecessary systemic exposure to compounds, including metabolites. Compound **14c** showed superior efficacy over acarbose in various carbohydrate tolerance tests in STZ rats and could suppress absorption of glucose itself. These findings indicate the potential of this compound instead of α-GI as a novel therapeutic option for the treatment of postprandial hyperglycemia in DM or IGT patients.

5. Experimental

5.1. Chemistry

^{1}H nuclear magnetic resonance (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 (ppm) (δ), downfield from tetramethylsilane as the internal standard. In experiments using D_2O as the solvent, chemical shifts were referenced to dioxane as the internal standard (δ_c = 66.5 ppm). Peak patterns are 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 (electrospray ionization; ESI) or Shimadzu LCMS-2010EV (ESI) spectrometer. 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 or aminopropyl silica gel (APS)-precoated NH plates from Fuji Silysia Chemical Ltd. were used for thin-layer chromatography (TLC). Flash or medium-pressure liquid chromatography was performed on silica gel BW-350 from Fuji Silysia Chemical Ltd. or APS Daisogel IR-60 (particle size, 25–40 μM) from Daiso Co., Ltd. or SNAP cartridge KP-Sil or KP-NH from Biotage®. All reagents and solvents were commercially available unless otherwise indicated.

5.1.1. 4-(4-Aminophenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (5a)

A mixture of **3a** (5.00 g, 33.1 mmol), methyl 4-methyl-3-oxopentanoate (4.77 g, 33.1 mmol), piperidine (196 μL, 1.98 mmol), and AcOH (133 μL, 2.32 mmol) in *i*PrOH (15 mL) was stirred at room temperature for 4 days. After dilution with water, the resulting mixture was extracted with Et_2O. The extract was washed with water and brine, dried over anhydrous $MgSO_4$, and then, concentrated under reduced pressure to give crude methyl 4-methyl-2-(4-nitrobenzylidene)-3-oxopentanoate. This intermediate was dissolved in MeOH (90 mL), and 10% Pd–C (50% wet with water, 3.00 g) was added to the solution. The mixture was stirred under a hydrogen atmosphere at room temperature overnight. The insoluble material was removed by filtration and washed with MeOH. The filtrate and washing were concentrated under reduced pressure to give crude **4a**. This intermediate was dissolved in toluene (50 mL) and $N_2H_4{\cdot}H_2O$ (3.21 mL, 66.2 mmol) was added to the solution. After refluxing for 2 h, the reaction mixture was cooled to room temperature. The precipitates were collected by filtration, washed with hexane and water, and then, dried under reduced pressure to give **5a** (5.28 g, 69%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 7.0 Hz), 2.80 (1H, heptet, J = 7.0 Hz), 3.39 (2H, s), 4.73 (2H, s), 6.40–6.45 (2H, m), 6.79 (2H, d, J = 8.3 Hz), 8.40–12.20 (2H, br); MS m/z: 232 $(M+H)^+$.

5.1.2. Benzyl 4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)benzoate (5b)

Methanesulfonyl chloride (MsCl) (1.74 mL, 22.4 mmol) was added to a solution of **3b** (5.18 g, 21.4 mmol) and Et_3N (3.28 mL, 23.5 mmol) in tetrahydrofuran (THF) (20 mL) under ice cooling, and the mixture was stirred for 20 min. The insoluble material was removed by filtration and washed with THF (4 mL). The filtrate and washing were added to a mixture prepared by the addition of NaH (855 mg, 21.4 mmol, 60% oil dispersion) into a solution of methyl 4-methyl-3-oxopentanoate (3.08 g, 21.4 mmol) in THF (40 mL) under ice cooling and stirring for 5 min. The mixture was then refluxed for 10 h. After the mixture was cooled to room temperature, 1 N HCl (30 mL) was added and then the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and then, concentrated under

reduced pressure to give crude **4b**. This intermediate was dissolved in *i*PrOH (15 mL), and $N_2H_4{\cdot}H_2O$ (1.56 mL, 32.0 mmol) was added to the solution. After the mixture was stirred at room temperature overnight, it was diluted with water and then the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 1:0–19:1–9:1) to give **5b** (4.14 g, 55%) as an oil with a slight yellow color.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 7.0 Hz), 2.83 (1H, heptet, J = 7.0 Hz), 3.66 (2H, s), 5.33 (2H, s), 7.27–7.48 (7H, m), 7.85–7.91 (2H, m), 8.60–12.20 (2H, br); MS m/z: 351 $(M+H)^+$.

5.1.3. Benzyl 2-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]acetate (5c)

The title compound was prepared from **3c**, as described for the synthesis of **5b**, in 23% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.83 (1H, heptet, J = 7.0 Hz), 3.55 (2H, s), 3.65 (2H, s), 5.09 (2H, s), 7.09 (2H, d, J = 8.2 Hz), 7.13 (2H, d, J = 8.2 Hz), 7.27–7.38 (5H, m), 8.80–9.80 (1H, br), 10.70–11.50 (1H, br); MS m/z: 365 $(M+H)^+$.

5.1.4. Benzyl (*E*)-3-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]acrylate (5d)

The title compound was prepared from **3d**, as described for the synthesis of **5b**, in 47% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.60 (2H, s), 5.21 (2H, s), 6.62 (1H, d, J = 15.9 Hz), 7.19 (2H, d, J = 8.3 Hz), 7.30–7.45 (5H, m), 7.61 (2H, d, J = 8.3 Hz), 7.64 (1H, d, J = 15.9 Hz), 9.00–10.00 (1H, br), 10.70–11.60 (1H, br); MS m/z: 377 $(M+H)^+$.

5.1.5. Benzyl 4-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]butanoate (5e)

The title compound was prepared from **3e**, as described for the synthesis of **5b**, in 62% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 7.0 Hz), 1.74–1.84 (2H, m), 2.32 (2H, t, J = 7.4 Hz), 2.48–2.54 (2H, m), 2.82 (1H, heptet, J = 7.0 Hz), 3.53 (2H, s), 5.07 (2H, s), 7.01 (2H, d, J = 8.4 Hz), 7.05 (2H, d, J = 8.4 Hz), 7.28–7.40 (5H, m), 8.90–10.00 (1H, br), 10.60–11.50 (1H, br); MS m/z: 393 $(M+H)^+$.

5.1.6. Benzyl 4-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)-3-methylphenyl]butanoate (5f)

The title compound was prepared from **3f**, as described for the synthesis of **5b**, in 64% yield.

^{1}H NMR (DMSO-d_6) δ: 1.03 (6H, d, J = 7.0 Hz), 1.74–1.84 (2H, m), 2.24 (3H, s), 2.32 (2H, t, J = 7.3 Hz), 2.48 (2H, t, J = 7.8 Hz), 2.72 (1H, heptet, J = 7.0 Hz), 3.47 (2H, s), 5.07 (2H, s), 6.79 (1H, d, J = 7.9 Hz), 6.83 (1H, d, J = 7.9 Hz), 6.90 (1H, s), 7.29–7.41 (5H, m), 8.80–9.80 (1H, br), 10.60–11.60 (1H, br); MS m/z: 407 $(M+H)^+$.

5.1.7. Benzyl (*E*)-5-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]pent-4-enoate (5g)

The title compound was prepared from **3g**, as described for the synthesis of **5b**, in 29% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 6.9 Hz), 2.39–2.56 (4H, m), 2.82 (1H, heptet, J = 6.9 Hz), 3.55 (2H, s), 5.10 (2H, s), 6.17 (1H, dt, J = 16.1, 6.7 Hz), 6.36 (1H, d, J = 16.1 Hz), 7.08 (2H, d, J = 8.3 Hz), 7.21 (2H, d, J = 8.3 Hz), 7.28–7.37 (5H, m), 9.00–9.80 (1H, br), 10.70–11.45 (1H, br); MS m/z: 405 $(M+H)^+$.

5.1.8. 4-(4-Aminophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (6a)

To a mixture of **5a** (5.50 g, 23.8 mmol), acetobromoglucose (9.79 g, 23.8 mmol), and BnN(n-Bu)$_3$Cl (7.42 g, 23.8 mmol) in CH_2Cl_2 (100 mL) was added 5 N NaOH (19.0 mL, 95.0 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc, and the extract was washed with brine and concentrated under reduced pressure. The residue was purified by column chromatography on aminopropyl silica gel (eluent: hexane/EtOAc = 3:2–2:3–3:7–1:4) to give **6a** (1.41 g, 11%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.92 (3H, s), 1.95 (3H, s), 1.989 (3H, s), 1.992 (3H, s), 2.86 (1H, heptet, J = 7.0 Hz), 3.33 (1H, d, J = 15.6 Hz), 3.38 (1H, d, J = 15.6 Hz), 3.97 (1H, dd, J = 12.3, 2.0 Hz), 4.09–4.16 (1H, m), 4.20 (1H, dd, J = 12.3, 4.5 Hz), 4.80 (2H, br s), 4.95–5.03 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.72 (1H, d, J = 8.3 Hz), 6.39–6.44 (2H, m), 6.74 (2H, d, J = 8.3 Hz), 11.63 (1H, s); MS m/z: 562 $(M+H)^+$.

5.1.9. 4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]benzoic acid (6b)

To a mixture of **5b** (2.00 g, 5.71 mmol), acetobromoglucose (2.35 g, 5.71 mmol), and BnN(n-Bu)$_3$Cl (1.78 g, 5.71 mmol) in CH_2Cl_2 (25 mL) was added 5 N NaOH (4.57 mL, 22.9 mmol), and the mixture was stirred at room temperature overnight. After the addition of 1 N HCl (40 mL), the resulting mixture was extracted with EtOAc. The extract was washed with brine and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 7:3–2:3–3:7–1:4) to give benzyl 4-[3-(tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]benzoate (1.46 g, 38%). This intermediate (1.39 g, 2.04 mmol) was dissolved in MeOH (14 mL), and 10% Pd–C (50% wet with water, 278 mg) was added to the solution. The mixture was stirred under a hydrogen atmosphere at room temperature overnight. The insoluble material was 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: hexane/EtOAc = 1:4–0:1) to give **6b** (1.07 g, 88%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.076 (3H, d, J = 7.0 Hz), 1.077 (3H, d, J = 7.0 Hz), 1.88 (3H, s), 1.95 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.89 (1H, heptet, J = 7.0 Hz), 3.63 (2H, s), 3.97 (1H, dd, J = 12.1, 2.0 Hz), 4.10–4.16 (1H, m), 4.18 (1H, dd, J = 12.1, 4.5 Hz), 4.94–5.01 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.75 (1H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.3 Hz), 7.80 (2H, d, J = 8.3 Hz), 11.78 (1H, br s), 12.76 (1H, br s); MS m/z: 591 $(M+H)^+$.

5.1.10. 2-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}acetic acid (6c)

The title compound was prepared from **5c**, as described for the synthesis of **6b**, in 34% yield.

^{1}H NMR (DMSO-d_6) δ: 1.08 (3H, d, J = 6.9 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.88 (3H, s), 1.95 (3H, s), 1.985 (3H, s), 1.987 (3H, s), 2.90 (1H, heptet, J = 6.9 Hz), 3.47 (2H, s), 3.50 (1H, d, J = 15.8 Hz), 3.55 (1H, d, J = 15.8 Hz), 3.97 (1H, dd, J = 12.2, 2.0 Hz), 4.09–4.15 (1H, m), 4.19 (1H, dd, J = 12.2, 4.5 Hz), 4.95–5.04 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.74 (1H, d, J = 8.3 Hz), 7.03 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 11.71 (1H, br s), 12.22 (1H, br s); MS m/z: 605 $(M+H)^+$.

5.1.11. 3-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}propanoic acid (6d)

The title compound was prepared from **5d**, as described for the synthesis of **6b**, in 32% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.88 (3H, s), 1.95 (3H, s), 1.99 (6H, s), 2.45 (2H, t, J = 7.7 Hz), 2.73 (2H, t, J = 7.7 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, 2.0 Hz), 4.09–4.15 (1H, m), 4.19 (1H, dd, J = 12.2, 4.6 Hz), 4.94–5.03 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.72 (1H, d, J = 8.0 Hz),

6.99 (2H, d, J = 8.0 Hz), 7.06 (2H, d, J = 8.0 Hz), 11.71 (1H, br s), 11.73–12.50 (1H, br); MS m/z: 619 $(M+H)^+$.

5.1.12. 4-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanoic acid (6e)

The title compound was prepared from **5e**, as described for the synthesis of **6b**, in 31% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.69–1.79 (2H, m), 1.88 (3H, s), 1.95 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.17 (2H, t, J = 7.3 Hz), 2.48–2.54 (2H, m), 2.88 (1H, heptet, J = 7.0 Hz), 3.49 (1H, d, J = 15.8 Hz), 3.54 (1H, d, J = 15.8 Hz), 3.97 (1H, dd, J = 12.2, 2.1 Hz), 4.09–4.15 (1H, m), 4.19 (1H, dd, J = 12.2, 4.5 Hz), 4.95–5.03 (2H, m), 5.42 (1H, t, J = 9.7 Hz), 5.73 (1H, d, J = 8.3 Hz), 6.98–7.05 (4H, m), 11.71 (1H, br s), 12.02 (1H, br s); MS m/z: 633 $(M+H)^+$.

5.1.13. 4-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]-3-methylphenyl}butanoic acid (6f)

The title compound was prepared from **5f**, as described for the synthesis of **6b**, in 26% yield.

^{1}H NMR (DMSO-d_6) δ: 1.03 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 1.68–1.78 (2H, m), 1.81 (3H, s), 1.93 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.17 (2H, t, J = 7.4 Hz), 2.22 (3H, s), 2.48 (2H, t, J = 7.8 Hz), 2.76 (1H, heptet, J = 7.0 Hz), 3.44 (1H, d, J = 16.6 Hz), 3.50 (1H, d, J = 16.6 Hz), 3.94 (1H, dd, J = 12.2, 2.1 Hz), 4.05–4.11 (1H, m), 4.16 (1H, dd, J = 12.2, 4.5 Hz), 4.90–4.99 (2H, m), 5.39 (1H, t, J = 9.5 Hz), 5.67 (1H, d, J = 8.3 Hz), 6.74 (1H, d, J = 7.9 Hz), 6.84 (1H, dd, J = 7.9, 1.5 Hz), 6.93 (1H, d, J = 1.5 Hz), 11.76 (1H, br s), 12.01 (1H, br s); MS m/z: 647 $(M+H)^+$.

5.1.14. 4-{4-[3-(Tetra-*O*-acetyl-β-D-galactopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanoic acid (6g)

The title compound was prepared from **5e**, as described for the synthesis of **6b** using 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide instead of acetobromoglucose, in 30% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.68–1.79 (2H, m), 1.91 (3H, s), 1.93 (3H, s), 1.97 (3H, s), 2.14 (3H, s), 2.17 (2H, t, J = 7.3 Hz), 2.48–2.54 (2H, m), 2.87 (1H, heptet, J = 6.9 Hz), 3.49 (1H, d, J = 15.8 Hz), 3.55 (1H, d, J = 15.8 Hz), 3.97–4.08 (2H, m), 4.34 (1H, dd, J = 7.3, 6.5 Hz), 5.16 (1H, dd, J = 10.3, 8.0 Hz), 5.27–5.35 (2H, m), 5.67 (1H, d, J = 8.0 Hz), 6.98–7.06 (4H, m), 11.70 (1H, br s), 12.01 (1H, br s); MS m/z: 633 $(M+H)^+$.

5.1.15. 5-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}pentanoic acid (6h)

The title compound was prepared from **5g**, as described for the synthesis of **6b**, in 38% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.41–1.57 (4H, m), 1.88 (3H, s), 1.95 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.20 (2H, t, J = 7.0 Hz), 2.47–2.52 (2H, m), 2.87 (1H, heptet, J = 7.0 Hz), 3.48 (1H, d, J = 15.7 Hz), 3.53 (1H, d, J = 15.7 Hz), 3.97 (1H, dd, J = 12.2, 2.1 Hz), 4.09–4.15 (1H, m), 4.19 (1H, dd, J = 12.2, 4.5 Hz), 4.95–5.03 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.72 (1H, d, J = 8.3 Hz), 6.97–7.05 (4H, m), 11.71 (1H, br s), 11.94 (1H, br s); MS m/z: 647 $(M+H)^+$.

5.1.16. 4-(4-Aminophenylmethyl)-5-isopropyl-1*H*-pyrazol-3-yl β-D-glucopyranoside (7)

NaOMe (28% MeOH solution, 83 mg, 0.43 mmol) was added to a solution of **6a** (120 mg, 0.214 mmol) in MeOH (2 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by solid-phase extraction on Bond Elut–C18® (VARIAN Inc.) (charged as an aqueous solution, washed with water and then eluted with MeOH). The product was further purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 1:0–4:1) to give **7** (56 mg, 67%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.81 (1H, heptet, J = 6.9 Hz), 3.09–3.26 (4H, m), 3.40–3.52 (3H, m), 3.60–3.68 (1H, m), 4.46 (1H, t, J = 5.6 Hz), 4.74 (2H, s), 4.93 (1H, d, J = 4.3 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.12 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.5 Hz), 6.43 (2H, d, J = 8.3 Hz), 6.83 (2H, d, J = 8.3 Hz), 11.45 (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, 100.0, 100.5, 113.8, 128.5, 128.7, 146.1, 146.3, 159.5; MS m/z: 394 $(M+H)^+$; HRMS (FAB+) calcd for $C_{19}H_{28}N_3O_6$ 394.1973; found 394.1970 $(M+H)^+$.

5.1.17. *N*-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}acetoamide (8a)

Ac_2O (26 μL, 0.28 mmol) was added to a solution of **6a** (150 mg, 0.267 mmol) and pyridine (32 μL, 0.40 mmol) in CH_2Cl_2 (3 mL) under ice cooling, and the mixture was stirred at ambient temperature overnight. After dilution with EtOAc, the mixture was washed with 1 N HCl and water and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1:1–3:7–1:4–1:9) to give *N*-{4-[3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}acetoamide (140 mg, 87%) as a white solid. This intermediate (125 mg, 0.207 mmol) was dissolved in MeOH (2.5 mL) and NaOMe (28% MeOH solution, 79 mg, 0.41 mmol) was added. After the mixture was stirred at room temperature overnight, AcOH (47 μL, 0.83 mmol) was added and then concentrated under reduced pressure. The residue was purified by solid-phase extraction on Bond Elut–C18® (VARIAN Inc.) (charged as an aqueous solution, washed successively with water, saturated aqueous $NaHCO_3$ solution and water and then eluted with MeOH). The product was further purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 1:0–7:3) to give **8a** (80 mg, 89%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.00 (3H, s), 2.83 (1H, heptet, J = 6.9 Hz), 3.10–3.27 (4H, m), 3.43–3.68 (4H, m), 4.47 (1H, t, J = 5.8 Hz), 4.94 (1H, d, J = 4.5 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.17 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.3 Hz), 7.11 (2H, d, J = 8.4 Hz), 7.42 (2H, d, J = 8.4 Hz), 9.79 (1H, s), 11.52 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 21.7, 23.9, 24.6, 26.4, 60.7, 69.6, 73.3, 76.7, 77.3, 99.8, 100.1, 118.9, 128.2, 136.3, 136.9, 146.5, 159.5, 167.9; MS m/z: 436 $(M+H)^+$; HRMS (FAB+) calcd for $C_{21}H_{30}N_3O_7$ 436.2078; found 436.2078 $(M+H)^+$.

5.1.18. *N*-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}propionamide (8b)

The title compound was prepared, as described for the synthesis of **8a** using propionic anhydride instead of acetic anhydride, in 80% yield.

^{1}H NMR (DMSO-d_6) δ: 1.02–1.09 (9H, m), 2.27 (2H, q, J = 7.5 Hz), 2.83 (1H, heptet, J = 7.0 Hz), 3.10–3.27 (4H, m), 3.43–3.68 (4H, m), 4.47 (1H, t, J = 5.9 Hz), 4.94 (1H, d, J = 4.5 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.17 (1H, d, J = 5.0 Hz), 5.23 (1H, d, J = 7.5 Hz), 7.10 (2H, d, J = 8.3 Hz), 7.44 (2H, d, J = 8.3 Hz), 9.72 (1H, s), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.7, 21.6, 21.7, 24.6, 26.4, 29.4, 60.7, 69.6, 73.3, 76.7, 77.3, 99.8, 100.1, 118.9, 128.2, 136.2, 136.9, 146.5, 159.5, 171.6; MS m/z: 448 $(M-H)^-$; HRMS (FAB+) calcd for $C_{22}H_{32}N_3O_7$ 450.2235; found 450.2232 $(M+H)^+$.

5.1.19. *N*-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butyramide (8c)

The title compound was prepared, as described for the synthesis of **8a** using butyryl chloride instead of acetic anhydride, in 77% yield.

^{1}H NMR (DMSO-d_6) δ: 0.89 (3H, t, J = 7.4 Hz), 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.53–1.64 (2H, m), 2.24 (2H, t, J = 7.4 Hz), 2.83 (1H, heptet, J = 6.9 Hz), 3.10–3.25 (4H, m), 3.42–3.50 (1H, m), 3.51–3.67 (3H, m), 4.47 (1H, t, J = 5.8 Hz), 4.94 (1H, d, J = 4.8 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.17 (1H, d, J = 5.3 Hz), 5.23 (1H, d, J = 7.8 Hz), 7.10 (2H, d, J = 8.4 Hz), 7.44 (2H, d, J = 8.4 Hz), 9.73 (1H, s), 11.52 (1H, s); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 13.6, 18.5, 21.6, 21.7, 24.6, 26.4, 38.2, 60.7, 69.7, 73.3, 76.8, 77.3, 99.8, 100.1, 118.9, 128.2, 136.3, 136.9, 146.5, 159.6, 170.8; MS m/z: 462 $(M-H)^-$; HRMS (FAB+) calcd for $C_{23}H_{34}N_3O_7$ 464.2391; found 464.2394 $(M+H)^+$.

5.1.20. *N*-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}methanesulfonamide (8d)

The title compound was prepared, as described for the synthesis of **8a** using MsCl instead of acetic anhydride, in 82% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.2 Hz), 1.07 (3H, d, J = 7.2 Hz), 2.79–2.94 (4H, m), 3.10–3.27 (4H, m), 3.42–3.51 (1H, m), 3.58 (2H, s), 3.60–3.68 (1H, m), 4.47 (1H, t, J = 5.6 Hz), 4.94 (1H, d, J = 3.8 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.17 (1H, d, J = 4.8 Hz), 5.22 (1H, d, J = 7.5 Hz), 7.08 (2H, d, J = 8.4 Hz), 7.17 (2H, d, J = 8.4 Hz), 9.52 (1H, br s), 11.53 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.65, 21.74, 24.6, 26.3, 38.9, 60.6, 69.6, 73.3, 76.7, 77.2, 99.7, 100.1, 120.3, 128.9, 135.8, 137.6, 146.5, 159.5; MS m/z: 470 $(M-H)^-$; HRMS (FAB+) calcd for $C_{20}H_{30}N_3O_8S$ 472.1748; found 472.1749 $(M+H)^+$.

5.1.21. 2-Benzyloxycarbonylamino-*N*-{4-[3-(β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}acetoamide (8e)

To a mixture of **6a** (200 mg, 0.356 mmol), *N*-benzyloxycarbonylglycine (112 mg, 0.534 mmol) and HOBt·H_2O (82 mg, 0.53 mmol) in *N*,*N*-dimethylformamide (DMF) (3 mL) was added EDCI·HCl (205 mg, 1.07 mmol), and the mixture was stirred at room temperature overnight. After dilution with water, the resulting mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and water and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 3:7–1:4–1:9–0:1) to give *N*-{4-[3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-2-benzyloxycarbonylaminoacetoamide (193 mg, 72%) as a white solid. This intermediate was dissolved in MeOH (3 mL) and NaOMe (28% MeOH solution, 98 mg, 0.51 mmol) was added. After the mixture was stirred at room temperature for 1 h, AcOH (43 μL, 0.76 mmol) was added and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 9:1–4:1) to give **8e** (114 mg, 76%) as a white solid.

^{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), 3.42–3.68 (4H, m), 3.77 (2H, d, J = 6.1 Hz), 4.43–4.52 (1H, m), 4.80–5.28 (6H, m), 7.13 (2H, d, J = 8.4 Hz), 7.20–7.40 (5H, m), 7.44 (2H, d, J = 8.4 Hz), 7.52 (1H, t, J = 6.1 Hz), 9.85 (1H, s), 11.52 (1H, br s); MS m/z: 585 $(M+H)^+$.

5.1.22. 3-Benzyloxycarbonylamino-*N*-{4-[3-(β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl} propanamide (8f)

The title compound was prepared, as described for the synthesis of **8e** using 3-benzyloxycarbonylaminopropanoic acid instead of *N*-benzyloxycarbonylglycine, in 75% yield.

^{1}H NMR (DMSO-d_6) δ: 1.04 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.47 (2H, t, J = 7.0 Hz), 2.82 (1H, heptet, J = 6.9 Hz), 3.10–3.32 (6H, m), 3.47 (1H, dd, J = 11.4, 4.5 Hz), 3.54 (1H, d, J = 16.7 Hz), 3.58 (1H, d, J = 16.7 Hz), 3.64 (1H, d, J = 11.4 Hz), 4.20–4.70 (1H, br), 4.70–5.50 (6H, m), 7.11 (2H, d, J = 8.5 Hz), 7.25–7.38 (6H, m), 7.44 (2H, d, J = 8.5 Hz), 9.83 (1H, s), 11.00–12.00 (1H, br); MS m/z: 621 $(M+Na)^+$.

5.1.23. 2-Amino-*N*-{4-[3-(β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}acetoamide (9a)

A mixture of **8e** (99 mg, 0.17 mmol) and 10% Pd–C (50% wet with water, 30 mg) in MeOH (4 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The insoluble material was removed by filtration and washed with MeOH. The filtrate and washing were concentrated under reduced pressure, and the residue was purified by preparative high performance liquid chromatography (HPLC) on a CAPCELL PAK C18 UG120 column (Shiseido Co., Ltd.) (5 μm, 20 × 50 mm, eluent: H_2O/CH_3CN = 9:1–3:2–2:3, flow rate: 30 mL/min) to give **9a** (65 mg, 85%) as a white solid.

^{1}H NMR (CD_3OD) δ: 1.12 (3H, d, J = 7.0 Hz), 1.13 (3H, d, J = 7.0 Hz), 2.90 (1H, heptet, J = 7.0 Hz), 3.30–3.42 (6H, m), 3.67 (1H, dd, J = 12.0, 5.0 Hz), 3.71 (1H, d, J = 15.9 Hz), 3.77 (1H, d, J = 15.9 Hz), 3.84 (1H, dd, J = 12.0, 1.4 Hz), 5.05–5.12 (1H, m), 7.16 (2H, d, J = 8.4 Hz), 7.43 (2H, d, J = 8.4 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 21.6, 21.7, 24.7, 26.4, 45.3, 60.7, 69.7, 73.3, 76.8, 77.3, 99.9, 100.2, 118.9, 128.4, 136.4, 136.5, 146.6, 159.5, 171.6; MS m/z: 451 $(M+H)^+$; HRMS (FAB+) calcd for $C_{21}H_{31}N_4O_7$ 451.2187; found 451.2180 $(M+H)^+$.

5.1.24. 3-Amino-*N*-{4-[3-(β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}propanamide (9b)

The title compound was prepared from **8f**, as described for the synthesis of **9a**, in 71% yield.

^{1}H NMR (CD_3OD) δ: 1.125 (3H, d, J = 7.1 Hz), 1.130 (3H, d, J = 7.1 Hz), 2.53 (2H, t, J = 6.5 Hz), 2.90 (1H, heptet, J = 7.1 Hz), 2.98 (2H, t, J = 6.5 Hz), 3.28–3.42 (4H, m), 3.67 (1H, dd, J = 12.0, 5.1 Hz), 3.70 (1H, d, J = 16.1 Hz), 3.77 (1H, d, J = 16.1 Hz), 3.84 (1H, dd, J = 12.0, 1.5 Hz), 5.04–5.11 (1H, m), 7.15 (2H, d, J = 8.8 Hz), 7.41 (2H, d, J = 8.8 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 21.6, 21.7, 24.7, 26.4, 38.1, 40.1, 60.7, 69.7, 73.3, 76.8, 77.3, 99.9, 100.2, 118.9, 128.2, 136.3, 136.9, 146.6, 159.6, 170.3; MS m/z: 465 $(M+H)^+$; HRMS (FAB+) calcd for $C_{22}H_{33}N_4O_7$ 465.2344; found 465.2347 $(M+H)^+$.

5.1.25. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanamide (10d)

To a mixture of **6e** (173 mg, 0.273 mmol), NH_3 (28% aqueous solution, 166 mg, 2.73 mmol), and HOBt·H_2O (63 mg, 0.41 mmol) in DMF (4 mL) was added EDCI·HCl (157 mg, 0.819 mmol), and the mixture was stirred at room temperature overnight. After dilution with water, the resulting mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and water and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1:4–0:1 then EtOAc/MeOH = 19:1–9:1 then CH_2Cl_2/MeOH = 9:1) to give 4-{4-[3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanamide (168 mg, 98%) as a white solid. This intermediate (152 mg, 0.241 mmol) was dissolved in MeOH (3 mL), and NaOMe (28% MeOH solution, 93 mg, 0.48 mmol) was added. After the mixture was stirred at room temperature for 3 h, AcOH (55 μL, 0.96 mmol) was added and then concentrated under reduced pressure. The residue was purified by solid-phase extraction, as described for the synthesis of **8a**. The product was further purified by preparative HPLC, as described for the synthesis of **9a**, to give **10d** (105 mg, 94%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.68–1.78 (2H, m), 2.03 (2H, t, J = 7.5 Hz), 2.45–2.52 (2H, m), 2.84 (1H, heptet, J = 6.9 Hz), 3.10–3.26 (4H, m), 3.43–3.52 (1H, m), 3.53–3.68 (3H, m), 4.47 (1H, t, J = 5.8 Hz), 4.94 (1H, d, J = 4.3 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.15 (1H, d, J = 4.8 Hz), 5.22

(1H, d, J = 7.5 Hz), 6.69 (1H, br s), 7.04 (2H, d, J = 8.0 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.23 (1H, br s), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.66, 21.72, 24.6, 26.5, 26.9, 34.2, 34.5, 60.6, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 127.99, 128.02, 138.8, 139.0, 146.5, 159.5, 172.9, 174.0; MS m/z: 464 $(M+H)^+$; HRMS (FAB+) calcd for $C_{23}H_{34}N_3O_7$ 464.2391; found 464.2391 $(M+H)^+$.

5.1.26. 4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]benzamide (10a)

The title compound was prepared from **6b**, as described for the synthesis of **10d**, in 85% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 2.85 (1H, heptet, J = 6.9 Hz), 3.10–3.28 (4H, m), 3.43–3.53 (1H, m), 3.60–3.74 (3H, m), 4.48 (1H, t, J = 5.7 Hz), 4.95 (1H, d, J = 4.0 Hz), 5.02 (1H, d, J = 4.5 Hz), 5.18 (1H, d, J = 5.0 Hz), 5.23 (1H, d, J = 7.8 Hz), 7.24 (1H, br s), 7.27 (2H, d, J = 8.2 Hz), 7.75 (2H, d, J = 8.2 Hz), 7.86 (1H, br s), 11.58 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 21.7, 24.6, 26.8, 60.7, 69.6, 73.3, 76.7, 77.3, 99.3, 100.2, 127.4, 127.9, 131.6, 145.2, 146.6, 159.6, 167.8; MS m/z: 420 $(M-H)^-$; HRMS (FAB+) calcd for $C_{20}H_{28}N_3O_7$ 422.1922; found 422.1927 $(M+H)^+$.

5.1.27. 2-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}acetoamide (10b)

The title compound was prepared from **6c**, as described for the synthesis of **10d**, in 82% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.9 Hz), 2.84 (1H, heptet, J = 6.9 Hz), 3.09–3.26 (4H, m), 3.29 (2H, s), 3.42–3.52 (1H, m), 3.54–3.68 (3H, m), 4.47 (1H, t, J = 5.8 Hz), 4.93 (1H, d, J = 4.5 Hz), 4.99 (1H, d, J = 4.5 Hz), 5.16 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.5 Hz), 6.81 (1H, br s), 7.11 (4H, s), 7.38 (1H, br s), 11.52 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.68, 21.74, 24.6, 26.5, 41.8, 60.6, 69.6, 73.3, 76.8, 77.3, 99.6, 100.1, 127.8, 128.7, 133.5, 139.6, 146.5, 159.6, 172.3; MS m/z: 434 $(M-H)^-$; HRMS (FAB+) calcd for $C_{21}H_{30}N_3O_7$ 436.2078; found 436.2080 $(M+H)^+$.

5.1.28. 3-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}propanamide (10c)

The title compound was prepared from **6d**, as described for the synthesis of **10d**, in 88% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 2.30 (2H, t, J = 7.7 Hz), 2.73 (2H, t, J = 7.7 Hz), 2.84 (1H, heptet, J = 6.9 Hz), 3.09–3.27 (4H, m), 3.42–3.68 (4H, m), 4.48 (1H, t, J = 5.7 Hz), 4.94 (1H, d, J = 4.0 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.16 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.5 Hz), 6.73 (1H, br s), 7.06 (2H, d, J = 8.2 Hz), 7.10 (2H, d, J = 8.2 Hz), 7.26 (1H, br s), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.67, 21.73, 24.6, 26.5, 30.5, 36.8, 60.6, 69.6, 73.3, 76.8, 77.2, 99.7, 100.1, 127.9, 128.0, 138.4, 139.1, 146.5, 159.5, 173.5; MS m/z: 450 $(M+H)^+$; HRMS (FAB+) calcd for $C_{22}H_{32}N_3O_7$ 450.2235; found 450.2229 $(M+H)^+$.

5.1.29. 5-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}pentanamide (10e)

The title compound was prepared from **6h**, as described for the synthesis of **10d**, in 84% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.9 Hz), 1.06 (3H, d, J = 6.9 Hz), 1.41–1.55 (4H, m), 2.00–2.07 (2H, m), 2.46–2.53 (2H, m), 2.83 (1H, heptet, J = 6.9 Hz), 3.10–3.26 (4H, m), 3.43–3.51 (1H, m), 3.53–3.68 (3H, m), 4.47 (1H, t, J = 5.6 Hz), 4.94 (1H, d, J = 4.3 Hz), 5.00 (1H, d, J = 4.3 Hz), 5.15 (1H, d, J = 4.8 Hz), 5.22 (1H, d, J = 7.5 Hz), 6.67 (1H, br s), 7.03 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 7.22 (1H, br s), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.65, 21.71, 24.6, 24.7, 26.5, 30.7, 34.5, 34.9, 60.6, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 127.9, 128.0, 138.9, 139.1, 146.5, 159.5, 174.2; MS m/z: 478 $(M+H)^+$; HRMS (FAB+) calcd for $C_{24}H_{36}N_3O_7$ 478.2548; found 478.2550 $(M+H)^+$.

5.1.30. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-(2-hydroxyethyl)butanamide (11a)

The title compound was prepared, as described for the synthesis of **10d** using 2-aminoethanol instead of NH_3, in 60% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.68–1.79 (2H, m), 2.05 (2H, t, J = 7.4 Hz), 2.48 (2H, t, J = 7.8 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.05–3.26 (6H, m), 3.32–3.40 (2H, m), 3.43–3.51 (1H, m), 3.52–3.68 (3H, m), 4.46 (1H, t, J = 5.6 Hz), 4.61 (1H, t, J = 5.4 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), 5.22 (1H, d, J = 7.5 Hz), 7.04 (2H, d, J = 8.0 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.75 (1H, t, J = 5.4 Hz), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.66, 21.72, 24.6, 26.5, 27.1, 34.2, 34.8, 41.4, 59.9, 60.6, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 127.99, 128.01, 138.8, 139.0, 146.5, 159.5, 171.9; MS m/z: 508 $(M+H)^+$; HRMS (FAB+) calcd for $C_{25}H_{38}N_3O_8$ 508.2653; found 508.2655 $(M+H)^+$.

5.1.31. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-(2-hydroxyethyl)-*N*-methylbutanamide (11b)

The title compound was prepared, as described for the synthesis of **10d** using 2-(methylamino)ethanol instead of NH_3, in 81% yield.

^{1}H NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.8 Hz), 1.06 (3H, d, J = 6.8 Hz), 1.68–1.80 (2H, m), 2.20–2.35 (2H, m), 2.47–2.55 (2H, m), 2.80 (1.5H, s), 2.83 (1H, heptet, J = 6.8 Hz), 2.92 (1.5H, s), 3.09–3.26 (4H, m), 3.27–3.34 (2H, m), 3.40–3.52 (3H, m), 3.53–3.68 (3H, m), 4.47 (1H, t, J = 5.7 Hz), 4.61 (0.5H, t, J = 5.4 Hz), 4.77 (0.5H, t, J = 5.4 Hz), 4.93 (1H, d, J = 4.5 Hz), 5.00 (1H, d, J = 4.3 Hz), 5.15 (1H, d, J = 4.8 Hz), 5.23 (1H, d, J = 7.5 Hz), 7.04 (2H, d, J = 6.7 Hz), 7.11 (2H, d, J = 6.7 Hz), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 21.7, 24.6, 26.45, 26.54, 26.8, 31.5, 31.9, 33.1, 34.2, 34.3, 36.1, 49.7, 51.2, 58.5, 58.7, 60.6, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 127.9, 127.99, 128.02, 128.1, 138.9, 139.0, 139.17, 139.21, 146.5, 159.5, 171.7, 171.9; MS m/z: 522 $(M+H)^+$; HRMS (FAB+) calcd for $C_{26}H_{40}N_3O_8$ 522.2810; found 522.2814 $(M+H)^+$.

5.1.32. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-(3-hydroxypropyl)butanamide (11c)

The title compound was prepared, as described for the synthesis of **10d** using 3-aminopropanol instead of NH_3, in 88% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.48–1.57 (2H, m), 1.69–1.79 (2H, m), 2.04 (2H, t, J = 7.4 Hz), 2.48 (2H, t, J = 7.5 Hz), 2.84 (1H, heptet, J = 7.0 Hz), 3.03–3.27 (6H, m), 3.34–3.42 (2H, m), 3.43–3.52 (1H, m), 3.53–3.69 (3H, m), 4.41 (1H, t, J = 5.3 Hz), 4.47 (1H, t, J = 5.6 Hz), 4.94 (1H, d, J = 4.3 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.15 (1H, d, J = 5.0 Hz), 5.23 (1H, d, J = 7.5 Hz), 7.04 (2H, d, J = 7.9 Hz), 7.11 (2H, d, J = 7.9 Hz), 7.74 (1H, t, J = 5.5 Hz), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.66, 21.72, 24.6, 26.5, 27.1, 32.4, 34.2, 34.8, 35.6, 58.4, 60.6, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 127.99, 128.03, 138.8, 139.0, 146.5, 159.5, 171.8; MS m/z: 522 $(M+H)^+$; HRMS (FAB+) calcd for $C_{26}H_{40}N_3O_8$ 522.2810; found 522.2808 $(M+H)^+$.

5.1.33. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-(2-hydroxy-1,1-dimethylethyl)butanamide (11d)

The title compound was prepared, as described for the synthesis of **10d** using 2-amino-2-methylpropanol instead of NH_3, in 89% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.6 Hz), 1.07 (3H, d, J = 6.6 Hz), 1.15 (6H, s), 1.65–1.76 (2H, m), 2.03 (2H, t, J = 7.3 Hz), 2.47 (2H, t, J = 7.5 Hz), 2.84 (1H, heptet, J = 6.6 Hz), 3.09–3.26 (4H, m), 3.36 (2H, d, J = 5.8 Hz), 3.43–3.52 (1H, m), 3.53–3.68 (3H, m), 4.46 (1H, t, J = 5.4 Hz), 4.85 (1H, t, J = 5.8 Hz), 4.93 (1H, d, J = 3.5 Hz), 5.00 (1H, d, J = 4.3 Hz), 5.14 (1H, d, J = 4.5 Hz), 5.22 (1H, d, J = 7.5 Hz), 7.03 (2H, d, J = 7.7 Hz), 7.11 (2H, d, J = 7.7 Hz), 7.21 (1H, s), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.66, 21.73, 23.7, 24.6, 26.5, 27.2, 34.2, 35.5, 54.1, 60.6, 67.5, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 127.99, 128.01, 138.9, 139.0, 146.5, 159.5, 172.0; MS m/z: 536 (M+H)$^+$; HRMS (FAB+) calcd for $C_{27}H_{42}N_3O_8$ 536.2966; found 536.2965 (M+H)$^+$.

5.1.34. *N*-Carbamoylmethyl-4-{4-[3-(β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanamide (11e)

The title compound was prepared, as described for the synthesis of **10d** using glycinamide hydrochloride and Et_3N (a slight excess of glycinamide salt) instead of NH_3, in 82% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.69–1.80 (2H, m), 2.12 (2H, t, J = 7.4 Hz), 2.46–2.53 (2H, m), 2.84 (1H, heptet, J = 6.9 Hz), 3.09–3.27 (4H, m), 3.43–3.52 (1H, m), 3.53–3.68 (5H, m), 4.47 (1H, t, J = 5.7 Hz), 4.94 (1H, d, J = 4.0 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.15 (1H, d, J = 4.8 Hz), 5.22 (1H, d, J = 7.5 Hz), 6.97 (1H, s), 7.05 (2H, d, J = 7.9 Hz), 7.11 (2H, d, J = 7.9 Hz), 7.24 (1H, s), 7.94 (1H, t, J = 5.6 Hz), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.66, 21.72, 24.6, 26.5, 26.9, 34.2, 34.6, 41.7, 60.6, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 128.0, 138.8, 139.0, 146.5, 159.6, 171.1, 172.2; MS m/z: 521 (M+H)$^+$; HRMS (FAB+) calcd for $C_{25}H_{37}N_4O_8$ 521.2606; found 521.2605 (M+H)$^+$.

5.1.35. *N*-(1-Carbamoyl-1-methylethyl)-4-{4-[3-(β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanamide (11f)

The title compound was prepared, as described for the synthesis of **10d** using 2-amino-2-methylpropanamide instead of NH_3, in 90% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.30 (6H, s), 1.67–1.78 (2H, m), 2.07 (2H, t, J = 7.4 Hz), 2.49 (2H, t, J = 8.0 Hz), 2.85 (1H, heptet, J = 6.9 Hz), 3.10–3.26 (4H, m), 3.43–3.51 (1H, m), 3.53–3.68 (3H, m), 4.47 (1H, t, J = 5.7 Hz), 4.93 (1H, d, J = 4.3 Hz), 5.00 (1H, d, J = 4.5 Hz), 5.14 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.8 Hz), 6.75 (1H, br s), 6.96 (1H, br s), 7.04 (2H, d, J = 8.0 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.68 (1H, s), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.66, 21.73, 24.6, 25.1, 26.5, 26.9, 34.2, 35.0, 55.5, 60.6, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 128.0, 138.9, 139.0, 146.5, 159.5, 171.4, 176.4; MS m/z: 549 (M+H)$^+$; HRMS (FAB+) calcd for $C_{27}H_{41}N_4O_8$ 549.2919; found 549.2915 (M+H)$^+$.

5.1.36. 2-(4-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanoylamino)-2-methylpropanoic acid (12a)

To a mixture of **6e** (1.75 g, 2.77 mmol), benzyl 2-amino-2-methylpropanoate hydrochloride (1.27 g, 5.55 mmol), HOBt·H_2O (636 mg, 4.15 mmol), and Et_3N (1.55 mL, 11.1 mmol) in DMF (30 mL) was added EDCI·HCl (1.59 g, 8.32 mmol), and the mixture was stirred at room temperature overnight. After dilution with water, the resulting mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and water and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 3:7–1:4–0:1) to give benzyl 2-(4-{4-[3-(tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanoylamino)-2-methylpropanoate (2.22 g, 99%) as a white solid. This intermediate (2.20 g, 2.72 mmol) was dissolved in MeOH (30 mL), and 10% Pd–C (50% wet with water, 400 mg) was added to the solution. The mixture was stirred under a hydrogen atmosphere at room temperature for 2 h. The insoluble material was removed by filtration and washed with MeOH. The filtrate and washing were concentrated under reduced pressure to give **12a** (1.85 g, 95%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.30 (6H, s), 1.65–1.76 (2H, m), 1.89 (3H, s), 1.95 (3H, s), 1.986 (3H, s), 1.988 (3H, s), 2.04 (2H, t, J = 7.0 Hz), 2.44–2.51 (2H, m), 2.89 (1H, heptet, J = 7.0 Hz), 3.48 (1H, d, J = 15.8 Hz), 3.53 (1H, d, J = 15.8 Hz), 3.97 (1H, dd, J = 12.2, 2.1 Hz), 4.03–4.16 (1H, m), 4.19 (1H, dd, J = 12.2, 4.5 Hz), 4.95–5.03 (2H, m), 5.42 (1H, t, J = 9.5 Hz), 5.73 (1H, d, J = 8.0 Hz), 6.98–7.05 (4H, m), 7.95 (1H, s), 11.70 (1H, br s), 12.04 (1H, br s); MS m/z: 718 (M+H)$^+$.

5.1.37. 2-(4-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]-3-methylphenyl}butanoylamino)-2-methylpropanoic acid (12b)

The title compound was prepared from **6f**, as described for the synthesis of **12a**, in 91% yield.

^{1}H NMR (DMSO-d_6) δ: 1.04 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.31 (6H, s), 1.64–1.75 (2H, m), 1.81 (3H, s), 1.93 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.04 (2H, t, J = 7.3 Hz), 2.22 (3H, s), 2.45 (2H, t, J = 7.5 Hz), 2.77 (1H, heptet, J = 7.0 Hz), 3.43 (1H, d, J = 16.6 Hz), 3.49 (1H, d, J = 16.6 Hz), 3.95 (1H, dd, J = 12.2, 2.1 Hz), 4.06–4.13 (1H, m), 4.17 (1H, dd, J = 12.2, 4.5 Hz), 4.90–4.99 (2H, m), 5.39 (1H, t, J = 9.5 Hz), 5.68 (1H, d, J = 8.3 Hz), 6.73 (1H, d, J = 7.8 Hz), 6.84 (1H, dd, J = 7.8, 1.1 Hz), 6.91 (1H, d, J = 1.1 Hz), 7.95 (1H, s), 11.75 (1H, br s), 12.02 (1H, br s); MS m/z: 732 (M+H)$^+$.

5.1.38. 2-(4-{4-[3-(Tetra-*O*-acetyl-β-D-galactopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanoylamino)-2-methylpropanoic acid (12c)

The title compound was prepared from **6g**, as described for the synthesis of **12a**, in 92% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.30 (6H, s), 1.65–1.76 (2H, m), 1.91 (3H, s), 1.93 (3H, s), 1.97 (3H, s), 2.04 (2H, t, J = 7.3 Hz), 2.14 (3H, s), 2.45–2.52 (2H, m), 2.88 (1H, heptet, J = 7.0 Hz), 3.49 (1H, d, J = 15.8 Hz), 3.54 (1H, d, J = 15.8 Hz), 4.01 (1H, dd, J = 11.2, 6.7 Hz), 4.05 (1H, dd, J = 11.2, 6.2 Hz), 4.31–4.37 (1H, m), 5.16 (1H, dd, J = 10.3, 8.3 Hz), 5.27–5.35 (2H, m), 5.67 (1H, d, J = 8.3 Hz), 7.00 (2H, d, J = 7.0 Hz), 7.03 (2H, d, J = 7.0 Hz), 7.95 (1H, s), 11.70 (1H, br s), 11.80–12.20 (1H, br); MS m/z: 718 (M+H)$^+$.

5.1.39. 4-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-[1,1-dimethyl-2-oxo-2-(piperazin-1-yl)ethyl]butanamide (13a)

The title compound was prepared from **12a**, as described for the synthesis of **12a** using 1-benzyloxycarbonylpiperazine without Et_3N, instead of benzyl 2-amino-2-methylpropanoate hydrochloride, in 69% yield. The product was purified by column chromatography on aminopropyl silica gel (eluent: EtOAc/MeOH = 1:0–19:1–9:1–4:1).

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.29 (6H, s), 1.67–1.77 (2H, m), 1.89 (3H, s), 1.95 (3H, s), 1.986 (3H, s), 1.988 (3H, s), 2.04 (2H, t, J = 7.5 Hz), 2.17–2.35 (1H, br), 2.44–2.59 (6H, m), 2.89 (1H, heptet, J = 7.0 Hz), 3.27–3.47 (4H, br), 3.48 (1H, d, J = 15.7 Hz), 3.53 (1H, d, J = 15.7 Hz), 3.97 (1H, dd, J = 12.3, 2.0 Hz), 4.09–4.16 (1H, m), 4.19 (1H, dd, J = 12.3, 4.5 Hz), 4.95–5.03 (2H, m), 5.42 (1H, t, J = 9.7 Hz), 5.73 (1H, d, J = 8.3 Hz), 7.01 (2H, d, J = 9.0 Hz), 7.03 (2H, d, J = 9.0 Hz), 8.02 (1H, s), 11.70 (1H, s); MS m/z: 786 (M+H)$^+$.

5.1.40. 4-{4-[3-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]-3-methylphenyl}-*N*-[1,1-dimethyl-2-oxo-2-(piperazin-1-yl)ethyl]butanamide (13b)

The title compound was prepared from **12b**, as described for the synthesis of **13a**, in 78% yield.

^{1}H NMR (DMSO-d_6) δ: 1.04 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.29 (6H, s), 1.65–1.76 (2H, m), 1.82 (3H, s), 1.93 (3H, s), 1.98 (3H, s), 1.99 (3H, s), 2.04 (2H, t, J = 7.5 Hz), 2.22 (3H, s), 2.28 (1H, br s), 2.45 (2H, t, J = 7.7 Hz), 2.51–2.59 (4H, m), 2.77 (1H, heptet, J = 7.0 Hz), 3.29–3.47 (5H, m), 3.49 (1H, d, J = 16.6 Hz), 3.95 (1H, dd, J = 12.2, 2.1 Hz), 4.06–4.13 (1H, m), 4.17 (1H, dd, J = 12.2, 4.5 Hz), 4.90–4.98 (2H, m), 5.39 (1H, t, J = 9.7 Hz), 5.69 (1H, d, J = 8.3 Hz), 6.74 (1H, d, J = 7.8 Hz), 6.84 (1H, dd, J = 7.8, 1.5 Hz), 6.92 (1H, d, J = 1.5 Hz), 8.02 (1H, s), 11.75 (1H, s); MS m/z: 800 (M+H)$^+$.

5.1.41. 4-{4-[3-(Tetra-*O*-acetyl-β-D-galactopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-[1,1-dimethyl-2-oxo-2-(piperazin-1-yl)ethyl]butanamide (13c)

The title compound was prepared from **12c**, as described for the synthesis of **13a**, in 50% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.29 (6H, s), 1.67–1.77 (2H, m), 1.91 (3H, s), 1.93 (3H, s), 1.97 (3H, s), 2.04 (2H, t, J = 7.5 Hz), 2.14 (3H, s), 2.18–2.38 (1H, br), 2.45–2.58 (6H, m), 2.88 (1H, heptet, J = 6.9 Hz), 3.30–3.47 (4H, br), 3.49 (1H, d, J = 15.7 Hz), 3.55 (1H, d, J = 15.7 Hz), 3.98–4.08 (2H, m), 4.31–4.37 (1H, m), 5.16 (1H, dd, J = 10.3, 8.2 Hz), 5.29 (1H, dd, J = 3.5, 1.0 Hz), 5.33 (1H, dd, J = 10.3, 3.5 Hz), 5.68 (1H, d, J = 8.2 Hz), 7.01 (2H, d, J = 8.7 Hz), 7.04 (2H, d, J = 8.7 Hz), 8.03 (1H, s), 11.70 (1H, s); MS m/z: 786 (M+H)$^+$.

5.1.42. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-[1,1-dimethyl-2-oxo-2-(piperazin-1-yl)ethyl]butanamide (14a)

NaOMe (28% MeOH solution, 65 mg, 0.34 mmol) was added to a solution of **13a** (133 mg, 0.169 mmol) in MeOH (4 mL), and the mixture was stirred at room temperature for 2 h. After addition of AcOH (39 μL, 0.68 mmol), the resulting mixture was concentrated under reduced pressure. The residue was purified by solid-phase extraction, as described for the synthesis of **8a**. The product was further purified by preparative HPLC, as described for the synthesis of **9a**, to give **14a** (73 mg, 70%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.29 (6H, s), 1.68–1.78 (2H, m), 2.04 (2H, t, J = 7.0 Hz), 2.14–2.40 (1H, br), 2.46–2.58 (6H, m), 2.85 (1H, heptet, J = 7.0 Hz), 3.09–3.26 (4H, m), 3.30–3.52 (5H, m), 3.53–3.68 (3H, m), 4.50 (1H, br s), 4.95 (1H, d, J = 3.5 Hz), 5.03 (1H, d, J = 3.3 Hz), 5.17 (1H, d, J = 4.0 Hz), 5.22 (1H, d, J = 7.8 Hz), 7.04 (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz), 8.03 (1H, s), 11.52 (1H, s); ^{13}C NMR (150 MHz, D_2O) δ: 20.8, 24.9, 25.0, 26.0, 26.6, 33.9, 34.6, 43.5, 44.3, 46.8, 56.2, 60.6, 69.2, 72.9, 75.4, 76.2, 100.4, 101.2, 128.2, 128.6, 138.8, 139.4, 149.8, 159.6, 173.4, 175.0; MS m/z: 618 (M+H)$^+$; HRMS (FAB+) calcd for $C_{31}H_{48}N_5O_8$ 618.3497; found 618.3499 (M+H)$^+$.

5.1.43. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]-3-methylphenyl}-*N*-[1,1-dimethyl-2-oxo-2-(piperazin-1-yl)ethyl]butanamide (14b)

The title compound was prepared from **13b**, as described for the synthesis of **14a**, in 44% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 1.29 (6H, s), 1.67–1.78 (2H, m), 2.04 (2H, t, J = 7.5 Hz), 2.15–2.38 (1H, br), 2.28 (3H, s), 2.46 (2H, t, J = 7.5 Hz), 2.51–2.59 (4H, m), 2.75 (1H, heptet, J = 6.9 Hz), 3.05–3.23 (4H, m), 3.30–3.66 (8H, m), 4.47 (1H, br s), 4.93 (1H, d, J = 3.3 Hz), 5.00 (1H, d, J = 2.8 Hz), 5.10 (1H, d, J = 4.0 Hz), 5.20 (1H, d, J = 8.0 Hz), 6.81–6.88 (2H, m), 6.93 (1H, s), 8.03 (1H, s), 11.57 (1H, s); ^{13}C NMR (150 MHz, D_2O) δ: 18.6, 20.7, 23.8, 24.9, 25.0, 26.6, 33.8, 34.7, 43.6, 44.3, 46.8, 56.2, 60.5, 69.2, 72.8, 75.3, 76.2, 100.1, 100.4, 125.8, 127.9, 130.1, 136.4, 136.6, 139.6, 150.0, 159.8, 173.4, 174.9; MS m/z: 632 (M+H)$^+$; HRMS (FAB+) calcd for $C_{32}H_{50}N_5O_8$ 632.3654; found 632.3654 (M+H)$^+$.

5.1.44. 4-{4-[3-(β-D-Galactopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-[1,1-dimethyl-2-oxo-2-(piperazin-1-yl)ethyl]butanamide (14c)

The title compound was prepared from **13c**, as described for the synthesis of **14a**, in 86% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 7.0 Hz), 1.29 (6H, s), 1.68–1.78 (2H, m), 2.04 (2H, t, J = 7.5 Hz), 2.20–2.62 (7H, m), 2.84 (1H, heptet, J = 7.0 Hz), 3.28–3.64 (11H, m), 3.69 (1H, br s), 4.47 (1H, br s), 4.59 (1H, br s), 4.79 (1H, br s), 5.00 (1H, br s), 5.18 (1H, d, J = 7.8 Hz), 7.03 (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz), 8.04 (1H, s), 11.50 (1H, s); ^{13}C NMR (150 MHz, D_2O) δ: 20.8, 24.9, 25.1, 26.1, 26.7, 33.9, 34.6, 43.6, 44.3, 46.8, 56.2, 60.8, 68.4, 70.4, 72.4, 75.4, 101.0, 101.1, 128.1, 128.6, 138.8, 139.4, 149.6, 159.8, 173.3, 174.8; MS m/z: 618 (M+H)$^+$; HRMS (FAB+) calcd for $C_{31}H_{48}N_5O_8$ 618.3497; found 618.3495 (M+H)$^+$.

5.1.45. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-[1,1-dimethyl-2-(4-methylpiperazin-1-yl)-2-oxoethyl]butanamide (14d)

The title compound was prepared from **12a**, as described for the synthesis of **10d** using 1-methylpiperazine instead of NH_3, in 59% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.29 (6H, s), 1.68–1.78 (2H, m), 2.05 (2H, t, J = 7.5 Hz), 2.12 (3H, s), 2.14–2.23 (4H, m), 2.46–2.52 (2H, m), 2.84 (1H, heptet, J = 7.0 Hz), 3.10–3.26 (4H, m), 3.37–3.53 (5H, m), 3.53–3.68 (3H, m), 4.47 (1H, t, J = 5.7 Hz), 4.94 (1H, d, J = 4.3 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.15 (1H, d, J = 5.0 Hz), 5.22 (1H, d, J = 7.5 Hz), 7.04 (2H, d, J = 8.2 Hz), 7.11 (2H, d, J = 8.2 Hz), 8.05 (1H, s), 11.52 (1H, s); ^{13}C NMR (150 MHz, D_2O) δ: 20.8, 24.9, 25.0, 26.0, 26.5, 33.8, 34.5, 42.7, 44.3, 45.6, 53.5, 56.2, 60.6, 69.2, 72.9, 75.4, 76.2, 100.4, 101.2, 128.2, 128.6, 138.9, 139.4, 149.8, 159.6, 173.4, 175.0; MS m/z: 632 (M+H)$^+$; HRMS (FAB+) calcd for $C_{32}H_{50}N_5O_8$ 632.3654; found 632.3651 (M+H)$^+$.

5.1.46. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-[1,1-dimethyl-2-oxo-2-(piperidin-1-yl)ethyl]butanamide (14e)

The title compound was prepared from **12a**, as described for the synthesis of **10d** using piperidine instead of NH_3, in 48% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.29 (6H, s), 1.31–1.41 (4H, m), 1.46–1.56 (2H, m), 1.68–1.78 (2H, m), 2.05 (2H, t, J = 7.5 Hz), 2.46–2.52 (2H, m), 2.84 (1H, heptet, J = 7.0 Hz), 3.10–3.26 (4H, m), 3.37–3.52 (5H, m), 3.53–3.68 (3H, m), 4.46 (1H, t, J = 5.5 Hz), 4.94 (1H, br s), 5.01 (1H, d, J = 2.8 Hz), 5.14 (1H, d, J = 4.5 Hz), 5.23 (1H, d, J = 7.5 Hz), 7.03 (2H, d, J = 8.2 Hz), 7.11 (2H, d, J = 8.2 Hz), 8.04 (1H, s), 11.52 (1H, s); ^{13}C NMR (150 MHz, pyridine-d_5) δ: 22.6, 22.7, 25.4, 26.3, 26.8, 27.1, 28.2, 28.3, 35.7, 36.3, 46.4, 57.3, 62.8, 71.8, 75.7, 79.1, 79.2, 101.6, 102.7, 129.2, 129.3, 139.9, 140.5, 148.3, 162.1, 171.9, 172.1; MS m/z: 639 (M+Na)$^+$; HRMS (FAB+) calcd for $C_{32}H_{49}N_4O_8$ 617.3545; found 617.3545 (M+H)$^+$.

5.1.47. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-[1,1-dimethyl-2-(morpholin-4-yl)-2-oxoethyl]butanamide (14f)

The title compound was prepared from **12a**, as described for the synthesis of **10d** using morpholine instead of NH_3, in 87% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.30 (6H, s), 1.68–1.78 (2H, m), 2.05 (2H, t, J = 7.5 Hz), 2.46–2.52 (2H, m), 2.84 (1H, heptet, J = 7.0 Hz), 3.10–3.26 (4H, m), 3.40–3.52 (9H, m), 3.53–3.68 (3H, m), 4.46 (1H, t, J = 5.8 Hz), 4.94 (1H, d, J = 4.5 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.14 (1H, d, J = 5.0 Hz), 5.23 (1H, d, J = 7.8 Hz), 7.04 (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz), 8.07 (1H, s), 11.52 (1H, s); ^{13}C NMR (150 MHz, D_2O) δ: 20.8, 24.9, 25.0, 26.0, 26.6, 33.9, 34.5, 43.3, 46.8, 56.2, 60.6, 65.9, 66.5, 69.2, 72.8, 75.4, 76.2, 100.4, 101.2, 128.2, 128.6, 138.9, 139.4, 149.7, 159.7, 173.6, 175.0; MS m/z: 641 $(M+Na)^+$; HRMS (FAB+) calcd for $C_{31}H_{47}N_4O_9$ 619.3338; found 619.3331 $(M+H)^+$.

5.1.48. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-[2-(2-hydroxyethylamino)-1,1-dimethyl-2-oxoethyl]butanamide (14g)

The title compound was prepared from **12a**, as described for the synthesis of **10d** using 2-aminoethanol instead of NH_3, in 87% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 6.8 Hz), 1.07 (3H, d, J = 6.8 Hz), 1.29 (6H, s), 1.67–1.78 (2H, m), 2.08 (2H, t, J = 7.3 Hz), 2.44–2.52 (2H, m), 2.85 (1H, heptet, J = 6.8 Hz), 3.03–3.26 (6H, m), 3.29–3.37 (2H, m), 3.43–3.52 (1H, m), 3.53–3.68 (3H, m), 4.40–4.49 (2H, m), 4.93 (1H, d, J = 3.8 Hz), 5.00 (1H, d, J = 4.3 Hz), 5.14 (1H, d, J = 4.8 Hz), 5.23 (1H, d, J = 7.5 Hz), 7.04 (2H, d, J = 7.9 Hz), 7.11 (2H, d, J = 7.9 Hz), 7.35 (1H, t, J = 5.5 Hz), 7.82 (1H, s), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 21.7, 24.6, 25.1, 26.5, 26.8, 34.2, 34.9, 41.5, 55.6, 59.7, 60.6, 69.6, 73.2, 76.7, 77.2, 99.7, 100.0, 128.0, 138.8, 138.9, 146.4, 159.5, 171.7, 174.1; MS m/z: 593 $(M+H)^+$; HRMS (FAB+) calcd for $C_{29}H_{45}N_4O_9$ 593.3181; found 593.3182 $(M+H)^+$.

5.1.49. *N*-(2-Carbamoylmethylamino-1,1-dimethyl-2-oxoethyl)-4-{4-[3-(β-D-glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}butanamide (14h)

The title compound was prepared from **12a**, as described for the synthesis of **10d** using glycinamide hydrochloride and Et_3N (a slight excess of glycinamide salt) instead of NH_3, in 69% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.28 (6H, s), 1.68–1.79 (2H, m), 2.13 (2H, t, J = 7.5 Hz), 2.46–2.52 (2H, m), 2.85 (1H, heptet, J = 7.0 Hz), 3.10–3.26 (4H, m), 3.43–3.52 (3H, m), 3.53–3.68 (3H, m), 4.47 (1H, t, J = 5.7 Hz), 4.94 (1H, d, J = 4.3 Hz), 5.01 (1H, d, J = 4.8 Hz), 5.14 (1H, d, J = 5.3 Hz), 5.22 (1H, d, J = 7.5 Hz), 7.02–7.07 (3H, m), 7.09–7.14 (3H, m), 7.98 (1H, t, J = 6.0 Hz), 8.25 (1H, s), 11.52 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.7, 21.8, 24.6, 25.1, 26.5, 26.9, 34.3, 34.9, 42.7, 55.5, 60.6, 69.6, 73.3, 76.8, 77.2, 99.7, 100.1, 128.0, 128.1, 138.8, 139.0, 146.5, 159.5, 171.7, 172.9, 174.1; MS m/z: 604 $(M-H)^-$; HRMS (FAB+) calcd for $C_{29}H_{44}N_5O_9$ 606.3134; found 606.3136 $(M+H)^+$.

5.1.50. 4-{4-[3-(β-D-Glucopyranosyloxy)-5-isopropyl-1*H*-pyrazol-4-ylmethyl]phenyl}-*N*-{1,1-dimethyl-2-[2-(dimethylamino)ethylamino]-2-oxoethyl}butanamide (14i)

The title compound was prepared from **12a**, as described for the synthesis of **10d** using *N*,*N*-dimethylethylenediamine instead of NH_3, in 44% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.28 (6H, s), 1.68–1.78 (2H, m), 2.04–2.11 (8H, m), 2.23 (2H, t, J = 6.8 Hz), 2.46–2.52 (2H, m), 2.84 (1H, heptet, J = 7.0 Hz), 3.04–3.26 (6H, m), 3.43–3.52 (1H, m), 3.53–3.68 (3H, m), 4.47 (1H, br s), 4.94 (1H, br s), 5.01 (1H, br s), 5.15 (1H, br s), 5.22 (1H, d, J = 7.5 Hz), 7.04 (2H, d, J = 8.0 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.21 (1H, t, J = 5.4 Hz), 7.81 (1H, s), 11.52 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.66, 21.72, 24.6, 25.2, 26.5, 27.0, 34.3, 35.0, 36.8, 45.0, 55.7, 57.8, 60.6, 69.6, 73.3, 76.8, 77.2, 99.8, 100.1, 128.0, 138.8, 139.0, 146.5, 159.5, 171.5, 174.0; MS m/z: 620 $(M+H)^+$; HRMS (FAB+) calcd for $C_{31}H_{50}N_5O_8$ 620.3654; found 620.3655 $(M+H)^+$.

5.1.51. Ethyl 4-(4-formylphenyl)butanoate (16a)

To a solution of **15a** (4.43 g, 23.9 mmol) in THF (100 mL) were added 4-ethoxy-4-oxobutylzinc bromide (0.5 M THF solution, 48 mL, 24 mmol) and [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI™-IPr catalyst) (163 mg, 0.239 mmol) under an argon atmosphere, and the mixture was stirred at room temperature overnight. After dilution with EtOAc, the resulting mixture was washed with 1 N HCl and water and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 97:3–9:1–4:1) to give **16a** (4.60 g, 87%) as an oil with a slight yellow color.

^{1}H NMR ($CDCl_3$) δ: 1.26 (3H, t, J = 7.2 Hz), 1.94–2.04 (2H, m), 2.33 (2H, t, J = 7.4 Hz), 2.74 (2H, t, J = 7.7 Hz), 4.13 (2H, q, J = 7.2 Hz), 7.35 (2H, d, J = 8.0 Hz), 7.79–7.83 (2H, m), 9.98 (1H, s).

5.1.52. Ethyl 4-(4-formyl-3-methylphenyl)butanoate (16b)

The title compound was prepared from **15b**, as described for the synthesis of **16a**, in 82% yield.

^{1}H NMR ($CDCl_3$) δ: 1.26 (3H, t, J = 7.2 Hz), 1.92–2.02 (2H, m), 2.33 (2H, t, J = 7.4 Hz), 2.65 (3H, s), 2.68 (2H, t, J = 7.7 Hz), 4.13 (2H, q, J = 7.2 Hz), 7.08 (1H, s), 7.18 (1H, d, J = 7.9 Hz), 7.72 (1H, d, J = 7.9 Hz), 10.22 (1H, s).

5.1.53. Benzyl 4-(4-formylphenyl)butanoate (17a)

To a solution of **16a** (4.75 g, 21.6 mmol) in MeOH (20 mL) and THF (20 mL) was added 5 N NaOH (13 mL, 65 mmol), and the mixture was stirred at room temperature for 5 h. After dilution with 1 N HCl (80 mL), the resulting mixture was extracted with EtOAc. The extract was washed with water and dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure to give 4-(4-formylphenyl)butanoic acid (3.96 g, 96%) as a white solid. This intermediate was dissolved in DMF (30 mL). To the solution were added K_2CO_3 (3.99 g, 28.9 mmol) and BnBr (3.2 mL, 27 mmol), and the mixture was stirred at room temperature overnight. After dilution with water, the resulting mixture was extracted with EtOAc. The extract was washed with water and then concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1:0–9:1) to give **17a** (5.71 g, 98%) as an oil with a slight yellow color.

^{1}H NMR ($CDCl_3$) δ: 1.95–2.05 (2H, m), 2.39 (2H, t, J = 7.4 Hz), 2.73 (2H, t, J = 7.7 Hz), 5.12 (2H, s), 7.29–7.39 (7H, m), 7.77–7.82 (2H, m), 9.97 (1H, s).

5.1.54. Benzyl 4-(4-formyl-3-methylphenyl)butanoate (17b)

The title compound was prepared from **16b**, as described for the synthesis of **17a**, in 94% yield.

^{1}H NMR ($CDCl_3$) δ: 1.94–2.04 (2H, m), 2.39 (2H, t, J = 7.3 Hz), 2.63 (3H, s), 2.67 (2H, t, J = 7.7 Hz), 5.12 (2H, s), 7.04 (1H, s), 7.14 (1H, d, J = 7.7 Hz), 7.30–7.40 (5H, m), 7.71 (1H, d, J = 7.7 Hz), 10.21 (1H, s).

5.1.55. Benzyl (*E*)-5-(4-formylphenyl)pent-4-enoate (19)

NaOMe (28% MeOH solution, 8.34 g, 43.2 mmol) was added to a suspension of (3-carboxypropyl)triphenylphosphonium bromide (9.28 g, 21.6 mmol) in THF (93 mL) at 60 °C, and the mixture was stirred at the same temperature for 30 min. After addition of a solution of **18** (4.20 g, 20.2 mmol) in THF (42 mL), the mixture was stirred at the same temperature for 1.5 h and then cooled to room temperature. A solution of NaOH (1.73 g, 43.2 mmol) in water (80 mL) and iPr$_2$O (37 mL) were added to the mixture. The organic layer was separated and washed with a solution of NaOH (1.87 g, 46.8 mmol) in water (50 mL). The aqueous layers were combined and acidified with 1 N HCl (133 mL), and the resulting

mixture was extracted with EtOAc. The extract was washed with water and concentrated under reduced pressure to give crude (*E*)-5-(4-formylphenyl)pent-4-enoic acid. This intermediate was dissolved in DMF (50 mL). K_2CO_3 (6.76 g, 48.9 mmol) and BnBr (4.4 mL, 37 mmol) were added to the solution, and the mixture was stirred at room temperature overnight. After dilution with water, the resulting mixture was extracted with EtOAc. The extract was washed with water and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1:0–19:1–9:1–4:1) to give **19** (4.99 g, 84%) as an oil with a slight yellow color.

^{1}H NMR ($CDCl_3$) δ: 2.55–2.63 (4H, m), 5.14 (2H, s), 6.33–6.42 (1H, m), 6.47 (1H, d, J = 16.1 Hz), 7.28–7.46 (7H, m), 7.78–7.82 (2H, m), 9.97 (1H, s).

5.1.56. Benzyl 4-hydroxymethylbenzoate (3b)

A mixture of **20a** (4.00 g, 26.3 mmol), K_2CO_3 (4.00 g, 28.9 mmol), and BnBr (3.1 mL, 26 mmol) in DMF (30 mL) was stirred at room temperature overnight. After dilution with water, the resulting mixture was extracted with EtOAc. The extract was washed with water and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 4:1–7:3–3:2) to give **3b** (5.18 g, 81%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.79 (1H, t, J = 5.9 Hz), 4.77 (2H, d, J = 5.9 Hz), 5.37 (2H, s), 7.31–7.48 (7H, m), 8.07 (2H, d, J = 8.0 Hz).

5.1.57. Benzyl 2-(4-hydroxymethylphenyl)acetate (3c)

The title compound was prepared from **20b**, as described for the synthesis of **3b**, in 95% yield.

^{1}H NMR ($CDCl_3$) δ: 1.62 (1H, t, J = 6.0 Hz), 3.67 (2H, s), 4.69 (2H, d, J = 6.0 Hz), 5.13 (2H, s), 7.25–7.39 (9H, m).

5.1.58. Benzyl 4-(4-hydroxymethylphenyl)butanoate (3e)

$NaBH_4$ (765 mg, 20.2 mmol) was added to a solution of **17a** (5.71 g, 20.2 mmol) in THF (50 mL), and the mixture was stirred at room temperature for 4 h. After dilution with water, the resulting mixture was extracted with EtOAc. The extract was washed with brine and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 4:1–7:3–3:2) to give **3e** (4.29 g, 75%).

^{1}H NMR ($CDCl_3$) δ: 1.57 (1H, t, J = 5.9 Hz), 1.92–2.01 (2H, m), 2.37 (2H, t, J = 7.5 Hz), 2.64 (2H, t, J = 7.5 Hz), 4.66 (2H, d, J = 5.9 Hz), 5.11 (2H, s), 7.15 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.2 Hz), 7.30–7.40 (5H, m).

5.1.59. Benzyl (*E*)-3-(4-hydroxymethylphenyl)acrylate (3d)

The title compound was prepared from **21**,[20] as described for the synthesis of **3e**, in 48% yield.

^{1}H NMR ($CDCl_3$) δ: 1.74 (1H, t, J = 5.9 Hz), 4.72 (2H, d, J = 5.9 Hz), 5.25 (2H, s), 6.48 (1H, d, J = 16.1 Hz), 7.31–7.44 (7H, m), 7.52 (2H, d, J = 8.0 Hz), 7.72 (1H, d, J = 16.1 Hz).

5.1.60. Benzyl 4-(4-hydroxymethyl-3-methylphenyl)butanoate (3f)

The title compound was prepared from **17b**, as described for the synthesis of **3e**, in 83% yield.

^{1}H NMR ($CDCl_3$) δ: 1.44 (1H, t, J = 5.9 Hz), 1.90–2.01 (2H, m), 2.33 (3H, s), 2.37 (2H, t, J = 7.4 Hz), 2.60 (2H, t, J = 7.7 Hz), 4.66 (2H, d, J = 5.9 Hz), 5.11 (2H, s), 6.96–7.01 (2H, m), 7.24 (1H, d, J = 6.8 Hz), 7.29–7.40 (5H, m).

5.1.61. Benzyl (*E*)-5-(4-hydroxymethylphenyl)pent-4-enoate (3g)

The title compound was prepared from **19**, as described for the synthesis of **3e**, in 50% yield.

^{1}H NMR ($CDCl_3$) δ: 1.59 (1H, t, J = 6.1 Hz), 2.50–2.60 (4H, m), 4.67 (2H, d, J = 6.1 Hz), 5.13 (2H, s), 6.14–6.25 (1H, m), 6.41 (1H, d, J = 15.8 Hz), 7.24–7.36 (9H, m).

5.1.62. *N*-(2-Hydroxy-1,1-dimethylethyl)-4-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]butanamide (22d)

A mixture of **11d** (459 mg, 0.857 mmol) and β-glucuronidase (from *Helix pomatia*, Type H-1, Sigma-Aldrich Co., Ltd., 40 mg) in a 0.2 M acetate buffer (pH 5.0, 40 mL) was stirred at 37 °C overnight. The reaction mixture was extracted with EtOAc, and the extract was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 1:0–9:1–4:1–7:3) to give **22d** (236 mg, 74%) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.1 Hz), 1.15 (6H, s), 1.65–1.76 (2H, m), 2.03 (2H, t, J = 7.4 Hz), 2.47 (2H, t, J = 7.8 Hz), 2.83 (1H, heptet, J = 7.1 Hz), 3.36 (2H, d, J = 5.9 Hz), 3.53 (2H, s), 4.85 (1H, t, J = 5.9 Hz), 7.00–7.08 (4H, m), 7.22 (1H, br s), 8.90–9.90 (1H, br), 10.70–11.45 (1H, br); MS m/z: 374 $(M+H)^+$.

5.1.63. 4-(4-Hydroxy-2-methylphenylmethyl)-1,2-dihydro-5-isopropyl-3*H*-pyrazol-3-one (2a)

The title compound was prepared from **2**, as described for the synthesis of **22d**, in 70% yield.

^{1}H NMR (DMSO-d_6) δ: 1.03 (6H, d, J = 7.0 Hz), 2.18 (3H, s), 2.71 (1H, heptet, J = 7.0 Hz), 3.39 (2H, s), 6.43 (1H, dd, J = 8.2, 2.4 Hz), 6.52 (1H, d, J = 2.4 Hz), 6.68 (1H, d, J = 8.2 Hz), 8.91 (1H, s), 9.00–9.42 (1H, br), 10.92–11.32 (1H, br); MS m/z: 247 $(M+H)^+$.

5.1.64. *N*-[4-(1,2-Dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]acetoamide (22a)

The title compound was prepared from **8a**, as described for the synthesis of **22d**, in 72% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 7.0 Hz), 2.00 (3H, s), 2.81 (1H, heptet, J = 7.0 Hz), 3.51 (2H, s), 7.04 (2H, d, J = 8.5 Hz), 7.41 (2H, d, J = 8.5 Hz), 9.12–9.46 (1H, br), 9.79 (1H, s), 10.98–11.25 (1H, br); MS m/z: 274 $(M+H)^+$.

5.1.65. 3-Benzyloxycarbonylamino-*N*-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]propanamide (22b)

The title compound was prepared from **8f**, as described for the synthesis of **22d**, in 34% yield.

^{1}H NMR (DMSO-d_6) δ: 1.06 (6H, d, J = 7.0 Hz), 2.47 (2H, t, J = 6.7 Hz), 2.81 (1H, heptet, J = 7.0 Hz), 3.28 (2H, q, J = 6.7 Hz), 3.52 (2H, s), 5.01 (2H, s), 7.05 (2H, d, J = 8.5 Hz), 7.26–7.37 (6H, m), 7.44 (2H, d, J = 8.5 Hz), 9.82 (1H, s), 9.90–11.60 (2H, br); MS m/z: 437 $(M+H)^+$.

5.1.66. 3-Amino-*N*-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]propanamide (22c)

The title compound was prepared from **22b**, as described for the synthesis of **9a**, in 90% yield.

^{1}H NMR (CD_3OD) δ: 1.11 (6H, d, J = 7.0 Hz), 2.54 (2H, t, J = 6.5 Hz), 2.87 (1H, heptet, J = 7.0 Hz), 2.99 (2H, t, J = 6.5 Hz), 3.64 (2H, s), 7.13 (2H, d, J = 8.5 Hz), 7.41 (2H, d, J = 8.5 Hz); MS m/z: 303 $(M+H)^+$.

5.1.67. *N*-(1-Carbamoyl-1-methylethyl)-4-[4-(1,2-dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]butanamide (22e)

The title compound was prepared from **11f**, as described for the synthesis of **22d**, in 63% yield.

^{1}H NMR (DMSO-d_6) δ: 1.07 (6H, d, J = 7.0 Hz), 1.30 (6H, s), 1.67–1.77 (2H, m), 2.07 (2H, t, J = 7.5 Hz), 2.44–2.52 (2H, m), 2.84 (1H, heptet, J = 7.0 Hz), 3.53 (2H, s), 6.75 (1H, br s), 6.96 (1H, br s),

7.01–7.08 (4H, m), 7.69 (1H, s), 8.90–9.80 (1H, br), 10.70–11.50 (1H, br); MS *m*/*z*: 387 $(M+H)^+$.

5.1.68. 4-[4-(1,2-Dihydro-3-oxo-5-isopropyl-3*H*-pyrazol-4-ylmethyl)phenyl]-*N*-[1,1-dimethyl-2-oxo-2-(piperazin-1-yl)ethyl]butanamide (22f)

A mixture of **14c** (185 mg, 0.299 mmol) and β-glucuronidase (from *Helix pomatia*, Type H-1, Sigma-Aldrich Co., Ltd., 15 mg) in a 0.2 M acetate buffer (pH 5.0, 15 mL) was stirred at 37 °C overnight. The reaction mixture was purified directly by solid-phase extraction, as described for the synthesis of **8a**. The product was further purified by preparative HPLC, as described for the synthesis of **9a**, to give **22f** (103 mg, 75%) as a white solid.

^{1}H NMR (CD_3OD) δ: 1.11 (6H, d, J = 7.1 Hz), 1.42 (6H, s), 1.81–1.91 (2H, m), 2.13–2.20 (2H, m), 2.58 (2H, t, J = 7.5 Hz), 2.69–2.78 (4H, m), 2.89 (1H, heptet, J = 7.1 Hz), 3.54–3.62 (4H, m), 3.63 (2H, s), 7.06 (2H, d, J = 8.2 Hz), 7.10 (2H, d, J = 8.2 Hz); MS *m*/*z*: 456 $(M+H)^+$.

5.2. Biology

5.2.1. SGLT1 and SGLT2 inhibition assay

Human and rat SGLT expression plasmids were constructed as reported previously.[21,22] Cell culture, transfection procedure, and [^{14}C]-AMG uptake experiments were performed as reported previously.[22] 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 a logit plot. Phlorizin[23] was always included in the experiments as a reference standard.

5.2.2. Pharmacokinetic studies

Compound **2** or **8a** was orally administered to fasted Sprague–Dawley rats (male, 6 weeks old, n = 3) at a dose of 10 mg/kg. Blood samples were collected at 5, 10, 20, and 40 min and 1, 2, 4, and 6 h after administration of **2** or at 5, 15, and 30 min and 1, 2, 4, and 6 h after administration of **8a**. After centrifugation, the plasma samples were deproteinized with CH_3CN. To detect conjugates of aglycones as aglycone itself, the same plasma samples were acidified to pH 5.0 with AcOH and incubated at 37 °C for 2 h with β-glucuronidase (from *Helix pomatia*, Type H-1, 400,000 units/g, Sigma-Aldrich Co., Ltd.) (100 units/μL) and then deproteinized with CH_3CN. After centrifugation of each deproteinized sample, concentrations of the compounds administered and their aglycones, in which aniline metabolites (**7** and **5a**) were also detected in the administration of compound **8a**, were determined by LC–MS/MS using API 365 (Applied Biosystems Inc.) coupled with the Alliance 2690 HPLC system (Waters Inc.). The analytical conditions using HPLC were as follows: column, SYNERGI MAX-RP 80 A (4 μm, 50 × 4.6 mm, Phenomenex Inc.); mobile phase, (A) CH_3CN: (B) 0.1% AcOH = 50:50; flow rate, 0.4 mL/min; column temperature, 50 °C. $AUC_{(0-6\,h)}$ values of respective compounds were calculated using Analyst® software, version 1.4.2 (Applied Biosystems Inc.).

5.2.3. Permeability of test compounds across Caco-2 cell monolayers

Caco-2 cell culture and transport experiments were performed according to the literature.[24] Caco-2 cells were plated at a density of 1.0×10^5 cells/well on polycarbonate membranes (0.3 cm^2 growth area, 1 μm pores). Cell confluence was monitored by trans-epithelial electrical resistance measurements. Transport experiments were performed on monolayers, 21 days post-seeding.

The apical-to-basal permeability of the compounds was measured using Caco-2 cell monolayers. The transport buffer used for the transport study was Hank's buffered salt solution, adjusting the pH to 6.5 (apical side) or 7.4 (basal side) with 10 mM 2-(morpholin-4-yl)ethanesulfonic acid (MES) or 10 mM 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES), respectively. After 20 min of incubation of both sides of the monolayers with the compound-free transport buffer, the apical side of the buffer was replaced with a compound-containing transport buffer. Caco-2 monolayers were incubated at 37 °C, and aliquots were sampled from the receiver compartment at 2 h for LC–MS/MS analysis. The permeability of each drug was calculated using the following formula.

$$\mathrm{Papp} = (dQ/dt)/A \cdot C_0,$$

where Papp is apparent permeability; dQ/dt is the rate of drug transport; A is the surface area of the membrane; and C_0 is the initial donor concentration. Atenolol was always included in the experiments as a reference standard.

5.2.4. 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, a 50 mM ammonium acetate buffer (pH 5.0), and 10 mM $MgCl_2$ 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 min and 60 min incubation.

5.2.5. OMTT in NA-STZ rats

5.2.5.1. Preparation of NA-STZ diabetic rat model. Male Wistar rats, aged 8 weeks, were injected intraperitoneally with NA (230 mg/kg). Fifteen minutes after injection, these rats were injected intravenously with STZ (85 mg/kg) from the tail vein under anesthesia with ether. One week after NA-STZ administration, the rats were starved overnight, and a glucose tolerance test (2 g/kg) was performed. The rats that showed a plasma glucose level of approximately 400 mg/dL 1 h after glucose load were selected for use in subsequent experiments.

5.2.5.2. Liquid meal tolerance test. Diabetic rats were starved overnight prior to the start of the experiment. On the first and second day of the experiment, the rats were administered a liquid meal (3 mL/body) orally three times a day (9:00, 13:00, and 17:00). Immediately before liquid meal administration, the rats were administered test compounds or vehicle (distilled water) orally. On the third morning, the rats were administered test compounds and a liquid meal orally. 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. The change in area under the curve of the plasma glucose concentration of 0–1 h ($AUC_{(0-1\,h)}$) from the pretreatment value ($\Delta AUC_{(0-1\,h)}$) was calculated using the trapezoidal rule.

5.2.6. Effects of compounds on plasma glucose escalation after carbohydrate loading

5.2.6.1. Preparation of STZ rats. Male Wistar rats, aged 8 weeks, were injected intravenously with STZ (45 mg/kg) from the tail vein under anesthesia with ether. One week after STZ administration, the rats were starved overnight, and a glucose tolerance test (2 g/kg) was performed. The rats that showed a plasma glucose level of approximately 400 mg/dL 1 h after glucose load were selected for use in subsequent experiments.

5.2.6.2. Carbohydrate tolerance tests. After being starved overnight, diabetic rats were orally administered test compounds or vehicle (distilled water). Immediately after test compound

administration, 2 g/kg of glucose, sucrose, mixed carbohydrate (starch/sucrose/lactose = 6:3:1),[9] or liquid meal (carbohydrates conversion) was loaded orally. 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. The change in $AUC_{(0-1\ h)}$ from the pretreatment value ($\Delta AUC_{(0-1\ h)}$) was calculated using the trapezoidal rule.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.11.041.

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