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Synthesis, enzyme kinetics and computational evaluation of *N*-(β-D-glucopyranosyl) oxadiazolecarboxamides as glycogen phosphorylase inhibitors

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ABSTRACT

All possible isomers of *N*-β-D-glucopyranosyl aryl-substituted oxadiazolecarboxamides were synthesised. *O*-Peracetylated *N*-cyanocarbonyl-β-D-glucopyranosylamine was transformed into the corresponding *N*-glucosyl tetrazole-5-carboxamide, which upon acylation gave *N*-glucosyl 5-aryl-1,3,4-oxadiazole-2-carboxamides. The nitrile group of the *N*-cyanocarbonyl derivative was converted to amidoxime which was ring closed by acylation to *N*-glucosyl 5-aryl-1,2,4-oxadiazole-3-carboxamides. A one-pot reaction of protected β-D-glucopyranosylamine with oxalyl chloride and then with arenecarboxamidoximes furnished *N*-glucosyl 3-aryl-1,2,4-oxadiazole-5-carboxamides. Removal of the *O*-acetyl protecting groups by the Zemplén method produced test compounds which were evaluated as inhibitors of glycogen phosphorylase. Best inhibitors of these series were *N*-(β-D-glucopyranosyl) 5-(naphth-1-yl)-1,2,4-oxadiazol-3-carboxamide (K_i = 30 μM), *N*-(β-D-glucopyranosyl) 5-(naphth-2-yl)-1,3,4-oxadiazol-2-carboxamide (K_i = 33 μM), and *N*-(β-D-glucopyranosyl) 3-phenyl-1,2,4-oxadiazol-5-carboxamide (K_i = 104 μM). ADMET property predictions revealed these compounds to have promising oral drug-like properties without any toxicity.

1. Introduction

Glycogen phosphorylase (GP), the main regulatory enzyme of the glycogen metabolism pathway, is a validated target to control hepatic glucose output in non-insulin dependent or type 2 diabetes mellitus (T2DM).[1–3] T2DM is a major concern to public health[4,5] with several long term complications[6] such as cardiovascular disease, neuropathy, retinopathy and nephropathy. Biochemical and pharmacological aspects of T2DM have been amply reviewed and for a detailed rationalization of the possible use of GP inhibitors (GPIs) as antidiabetics, the reader is kindly referred to those articles.[1–3] Besides T2DM, inhibition of GP has also been studied in connection with diseases caused by abnormalities in glycogen metabolism,[7,8] such as myocardial ischemia[9], cerebral ischemia[10] and tumors.[11,12]

Several types of compounds have been shown to inhibit this enzyme under in vitro conditions.[13] Among them the glucose based inhibitors targeting the catalytic site are the most extensively investigated derivatives[14–17] and a glucopyranosylidene-spiro-thiohydantoin has been shown to have appreciable in vivo hypoglycaemic effects.[18]

N-Acyl-β-D-glucopyranosylamines[19–21] (Chart 1, **I**), *N*-aryl-[13] and *N*-acyl-*N*′-β-D-glucopyranosyl ureas (**II**)[13,22,23] are among the best glucose analogue inhibitors of GP discovered to date, which are efficient in or below the low micromolar range.

Bioisosteric replacement is widely used in medicinal chemistry to design new drug molecules by systematic modification of lead compounds.[29] Nonclassical bioisosteric replacements of the NHCO moiety in **I** by heterocyclic linkers **A**–**D** (Chart 1) resulted in inhibitors of varying efficiency.[24–27] While 1,2,3-triazoles **IA** proved equipotent with the amides **I**, among oxadiazoles **IB**–**D** the constitution of the ring was decisive for the effect, and only **ID** was of similar efficiency as **I**. In these compounds the presence of a large hydrophobic aromatic ring was very advantageous for the inhibition, and derivatives with a 2-naphthyl group were the best inhibitors in each series. Replacements of the 'second' amide moiety in **II** (highlighted in Chart 1) with heterocycles **E** and **F** were detrimental for the binding, but revealed that compounds with a phenyl

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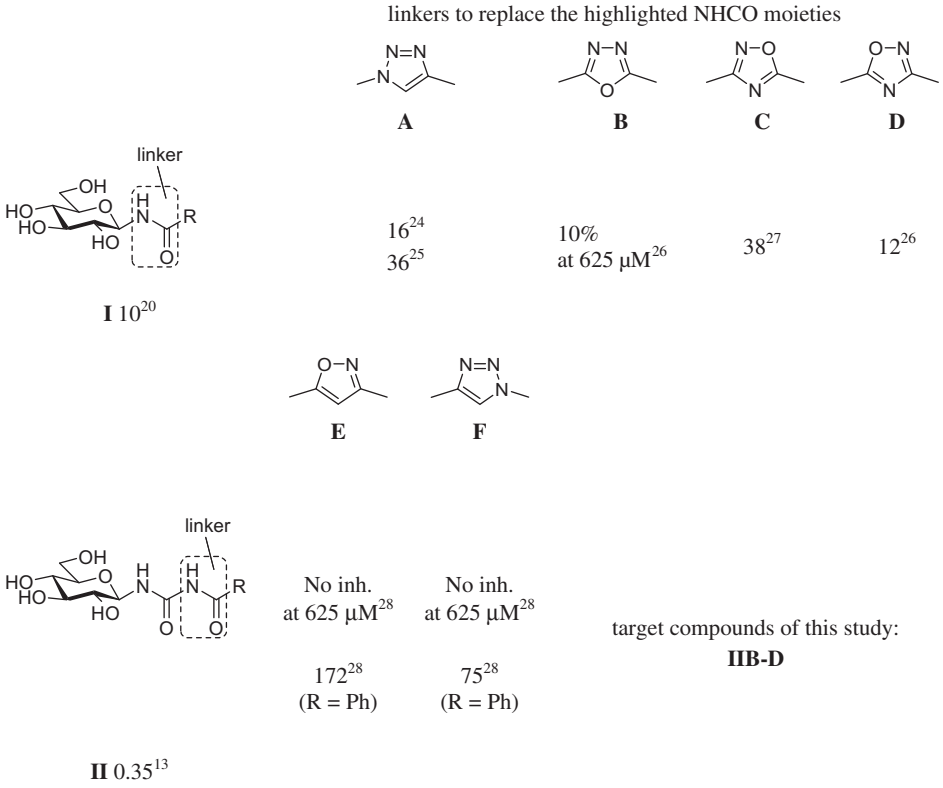
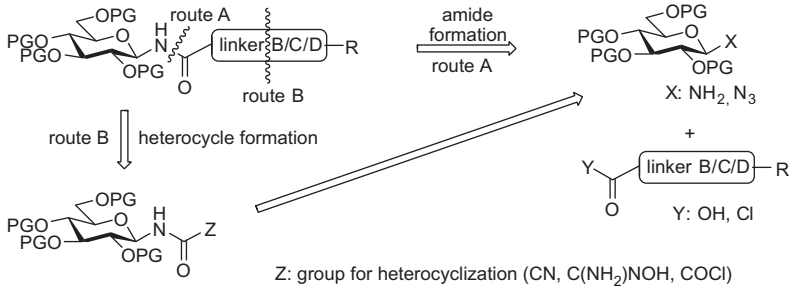


Chart 1. Selected inhibitors of GP and their efficiency against rabbit muscle GPb (K_i [μM] for R = 2-naphthyl).



Scheme 1. Retrosynthetic analysis of the target compounds.

group could bind stronger than those with a 2-naphthyl substituent.[28]

As a continuation of our systematic structure–activity relationship studies[25,26,28,30] on bioisosteric replacements of NHCO moieties in inhibitors **I** and **II**, we have now synthesised new oxadiazolecarboxamide derivatives **IIB**–**D** and evaluated through kinetic experiments their potential for GP inhibition. In addition, prediction of absorption, distribution, metabolism, excretion and toxicity (ADMET) properties was also performed to evaluate the drug-like potential of these derivatives.

2. Results and discussion

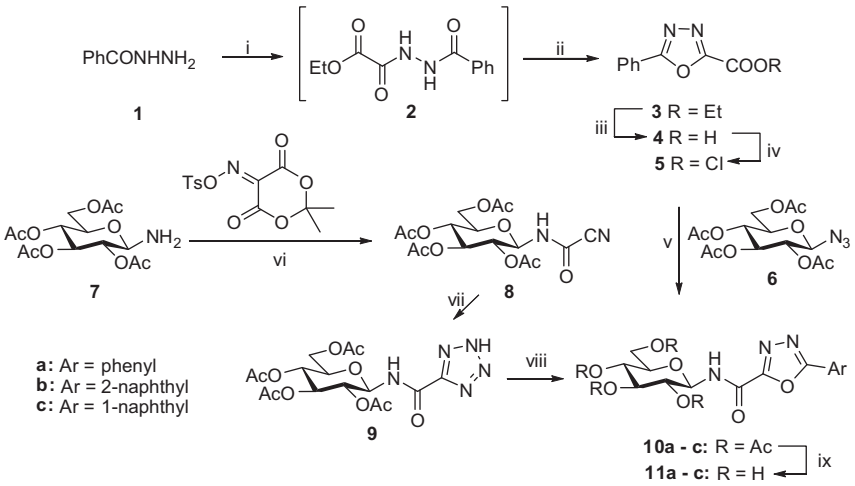
2.1. Syntheses

Preparation of the target compounds was envisaged and investigated by two possible routes (Scheme 1): formation of the amide C–N bond in a direct transformation of protected glucopyranosyl azide via acylation of the in situ generated iminophosphorane with an oxadiazolecarboxylic acid or acid chloride, or equivalently, by acylation of glucopyranosylamine (route A), or heterocyclisation of suitable functional groups of the corresponding *N*-acylated glucopyranosylamine derivatives (route B).

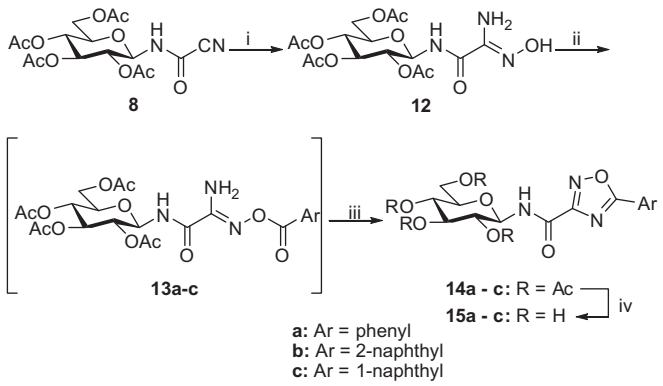
To study synthetic routes A, preparation of the necessary oxadiazolecarboxylic acids was first attempted. Following a literature protocol, commercially available benzhydrazide (**1**) was ethoxalylated to give **2** (Scheme 2) which was closed to ethyl 5-phenyl-1,3,4-oxadiazole-2-carboxylate (**3**) in 47% yield.[31] Hydrolysis of **3** gave carboxylic acid **4** in 70% yield.[32] Synthesis of 1,2,4-oxadiazole-carboxylic acids was also tried from the corresponding ethyl esters,[33] however, we were unable to reproduce the reported hydrolytic step[34] because of opening of the heterocycle.

Acylation of the glycosylimino-trimethylphosphorane obtained from 2,3,4,6-penta-*O*-acetyl-β-D-glucopyranosyl azide (**6**) with carboxylic acid **4** failed, however, oxadiazolecarboxamide derivative **10a** could be prepared in 10% yield by using acid chloride **5**.

In view of the low yield of this transformation and the failure of getting other oxadiazolecarboxylic acids, we turned to the



Scheme 2. (i) EtOCOCOCl, 3 equiv Et_3N, CH_2Cl_2, 0 °C to rt and in the same pot (ii) TsCl, rt, overnight; (iii) LiOH in THF/H_2O = 1:1; (iv) $SOCl_2$, reflux; (v) PMe_3; CH_2Cl_2; (vi) dry toluene, 50 °C; (vii) Me_3SiN_3, Bu_2SnO; dry toluene 80 °C; (viii) ArCOCl, dry toluene, reflux; (ix) NaOMe (cat.), MeOH, rt.

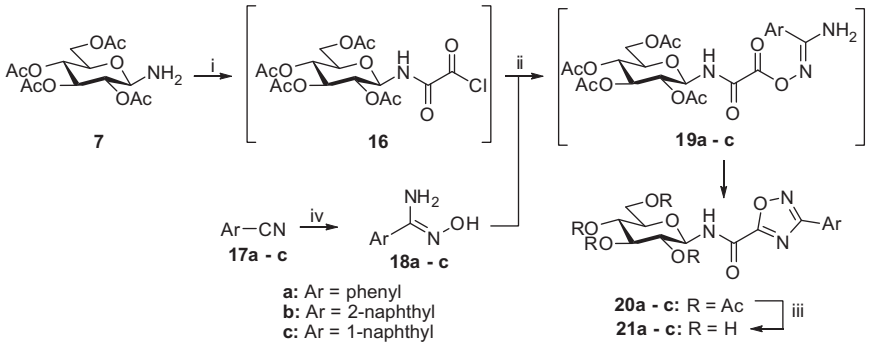


Scheme 3. (i) $NH_2OH{\cdot}HCl$; dry pyridine; 50 °C; (ii) 1. ArCOCl, dry pyridine–toluene, 110 °C; (iii) TBAF in THF-dry toluene, 110 °C; (iv) NaOMe (cat.), dry MeOH.

preparation of our target compounds by route B (Scheme 1). *N*-Cyanocarbonyl-2,3,4,6-penta-*O*-acetyl-β-D-glucopyranosylamine (**8**, Scheme 2) was the key intermediate of this pathway, which was prepared from glucosylamine **7** in 57% yield by using Renslo's method.[35] Transformation of **8** into *N*-glucopyranosyl tetrazol-5-carboxamide **9** was achieved with Me_3SiN_3–Bu_2SnO[36] in 88% yield. The necessary 5-aryl-1,3,4-oxadiazole derivatives **10a**–**c** were obtained from **9** by the corresponding aroyl chloride in dry toluene at elevated temperature[37] in moderate to good yields (**10a**: 80%; **10b**: 74%, **10c**: 30%). *O*-Deacetylations were performed by the Zemplén protocol to give excellent yields (up to 87%) of unprotected 1,3,4-oxadiazole derivatives **11a**–**c**.

Next, we turned to the synthesis of *N*-glucopyranosyl 5-aryl-1,2,4-oxadiazole-3-carboxamides **15a**–**c** (Scheme 3). In a continuous operation, *N*-cyanocarbonyl derivative **8** was transformed into amidoxime **12** by NH_2OH, followed by acylation with aroyl chlorides and ring closure in the presence TBAF to the desired 1,2,4-oxadiazole derivatives **14a**–**c** in moderate overall yields (22–24%). Synthesis of **14a** was also carried out via the isolated but unpurified **12** and fully characterized **13a** in a two steps procedure, but the overall yield was similar (28% as compared to 24% by the one-pot reaction). *O*-Deacetylations by the Zemplén protocol gave the unprotected 5-aryl-1,2,4-oxadiazole derivatives **15a**–**c** in acceptable yields (49–64%).

Synthesis of *N*-glucopyranosyl 3-aryl-1,2,4-oxadiazole-5-carboxamides **20** was attempted by cycloaddition of nitrile-oxides to the CN group of **8**, however, this resulted in an unseparable multicomponent product mixture. To get **20** in a less direct but one-pot procedure, acylation of glucopyranosylamine **7** was achieved with $(COCl)_2$ in dry THF (Scheme 4) to give the *N*-substituted oxamidoyl chloride **16**. Next, freshly prepared arenecarboxamidoximes **18a**–**c**,[38–40] obtained from the corresponding nitriles **17a**–**c**, were acylated by **16** to furnish **19a**–**c** which underwent immediate ring closure to the desired 3-aryl-1,2,4-oxadiazole-5-carboxamides **20a**–**c** in low to acceptable yields (15–55%). *O*-Deacetylations were



Scheme 4. (i) $(COCl)_2$ in dry THF at 0 °C; (ii) amidoximes **18a**–**c**, THF, rt; (iii) NaOMe in dry MeOH; (iv) $NH_2OH{\cdot}HCl$, dry pyridine, 50 °C.

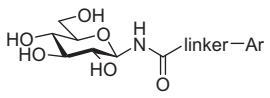
performed by the Zemplén protocol to give good (62–79%) yields of unprotected 3-aryl-1,2,4-oxadiazole derivatives **21a–c**.

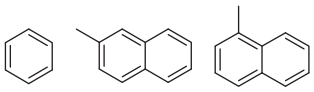
2.2. Enzyme inhibition studies

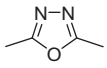
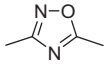
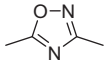
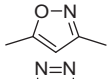
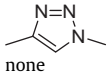
The kinetic parameters of the deprotected compounds (inhibition constants (K_i) against rabbit muscle glycogen phosphorylase *b* (RMGP*b*)) were determined according to the protocol described earlier.[41] The results are summarized in Table 1, together with the K_i-s of relevant reference compounds.

The new *N*-glucopyranosyl oxadiazole-carboxamides showed inhibitory properties in a very broad range from inactive compounds to low micromolar inhibitors. The most remarkable observation was that the best compounds in the different series did not have the same aromatic moiety as it could have been expected from previous experiences. Thus, from 1,3,4-oxadiazoles **11**, from 5-aryl-1,2,4-oxadiazoles **15**, and from 3-aryl-1,2,4-oxadiazoles **21**, the 2-naphthyl **11b**, the 1-naphthyl **15c**, and the phenyl **21a** derivatives, respectively, were the best inhibitors. Since the size of the heterocycles must be very similar, this phenomenon might be due to variations of interactions between the oxadiazole rings and the enzyme as well as to the probably different orientations of the aromatic substituents. It is also worth noting that in two series the 2-naphthyl derivatives **15b** and **21b** were inactive, although this was similar to the cases of isoxazoles **22** and 1,2,3-triazoles **23**. In comparison to the homoaromatic *N*-glucopyranosyl arenecarboxamides **24** the inhibition of the oxadiazolecarboxamides was generally weaker for the phenyl (**a**) and the 2-naphthyl (**b**) derivatives, while stronger for the 1-naphthyl (**c**) compounds. This may be attributed to the different size of the molecules and the orientation of the aromatic rings. Finally, a comparison to the 'parent' molecules **25** used as lead for the bioisosteric replacement showed a significant loss of the activity with each of the aromatic substituents. Molecular dockings to get a better insight in the structural details of the binding peculiarities of these and other heterocyclic *N*-glucopyranosyl carboxamides as well as to predict more efficient structures are in progress.

Table 1
Inhibition of rabbit muscle glycogen phosphorylase *b* (RMGP*b*) by the new compounds and selected glucose derivatives K_i (μM)



Ar 

Linker		a	b	c
	**11**	545[a]	30	172[a]
	**15**	136[a]	No inhibition[b]	33
	**21**	104	No inhibition[b]	145[a]
	**22**	172[28]	No inhibition[b28]	—
	**23**	75[28]	No inhibition[b28]	—
none	**24**	81[20]	10[20]	444[20]
	**25**	4.6[13]	0.35[13]	15[13]

[a] Calculated from the IC_{50} values by the Cheng–Prusoff equation: $K_i = IC_{50}/(1 + [S]/K_m)$.[42]
[b] No inhibition at 625 μM.

2.3. ADMET properties calculations

Unfavourable pharmacokinetic properties can in many cases lead to the clinical trials failure of otherwise potentially successful drug candidates. Their evaluation, therefore, at an earlier stage is desired.[43,44] Accordingly, we have predicted ADMET properties of our inhibitors using the QikProp 3.5 program (Schrodinger, LLC) which estimates both physically significant descriptors and pharmaceutically relevant properties. Considering the reported accuracy of ALOGPS[45] in comparison with other programs,[46] log *S* (aqueous solubilities) and log *P*(*o*/*w*) (partition of ligands in an octanol/water mixture) values from ALOGPS 2.1 are also reported. Meanwhile, toxicity is the leading cause of drug attrition in clinical trials, together with lack of efficacy.[47] Therefore, toxicity structural warnings for our inhibitors were also probed using the FAF-Drugs2 server.[48]

The results of our calculations are given in Table 2. Property predictions that are outside the range observed for 95% of known drugs (QikProp, version 3.5, User Manual) are flagged with an asterisk (*), while violations of Lipinski's 'rule of five'[49] and Jorgensen's 'rule of three'[50,51] (QikProp 3.5 User Manual) for oral bioavailability are highlighted in italics. The property values should be treated as approximate but serve as a useful guideline for future ligand studies, of particular relevance here.

As a first test of the drug-likeness of the ligands, we applied Lipinski's 'rule of five' requiring candidates to have no more than 5 and 10 hydrogen bond donors (HBDs) and acceptors (HBAs), respectively, molecular weights (MW) less than 500 amu, and log *P*(*o*/*w*) values less than 5. An orally active compound/drug should have no more than one violation of these rules. No violations of these rules was observed for any of our inhibitors. Furthermore, the properties were within the range of values for 95% of known drugs. Satisfactory agreement between QikProp and 'consensus' ALOGPS[45] log *P*(*o*/*w*) values was obtained, with a root-mean-square deviation (RMSD; Eq. (1)) of 1.1 and a maximum absolute difference of 1.3 units.

Jorgensen's 'rule of three' considers a Caco-2 cell permeability value >22 nm s^{-1} (used as a model for gut–blood barrier), [53] a log *S* value >−5.7 and number of primary metabolites (NPM) <7 to be characteristic of potential drugs with better oral bioavailability, more 'drug-like' molecules having fewer violations. The log *S* and NPM criteria are satisfied for all ligands. The RMSD (Eq. (1)) between QikProp and ALOGPS log *S* values was 0.6, with a maximum absolute difference of 0.7 units. The Caco-2 cell permeabilities (18–22 nm s^{-1}), however, are generally borderline the Jorgensen limit and outside the desirable range of 95% of known drugs (>25 nm s^{-1}). This is consistent with inhibitor polar surface areas (PSAs; ~170 $Å^2$) exceeding Veber et al.,[52] suggested limit (PSA <140 $Å^2$), but contrary to the PSAs lying within the range for 95% of known drugs (7–200 $Å^2$). It is clear, however, that the sensitive balance between adequate lipophilicity and solubility properties will need attention in 'lead optimization' of any heterocylic derivative conjugated to glucose found to have attractive GP inhibitory potential (low μM activity or better).

The degree of plasma protein binding also affects the amount of bioavailable drug. Log K_{hsa} is the prediction of the degree of binding to human serum albumin (hsa) and is satisfactory for all ligands (~1), within the range for 95% of known drugs (−1.5–1.5). Likewise, the predicted blood–brain barrier co-efficients (log *BB* values: −3.0 to −2.7) are within the desirable limits (−3.0–1.2). Finally, a complete lack of toxicity structural warnings from FAF-Drugs2 is encouraging with respect to the toxicity profiles for conjugates of glucose and substituted heterocycles.[48]

Table 2
Results of ADMET property predictions for the inhibitors studied in this work[a]

Inhibitor	Lipinskis's rule of five and violations (V)[b]				V	Jorgensen's rule of three and violations (V)[b]			V	PSA[c] (Å^2)	LogK_{hsa}[d]	LogBB[e]	TSW[f]
	M_r (Da)	HBD[g]	HBA[h]	Log$P$ (o/w)[i]		Caco-2[j] (nm s^{-1})	Log$S$[i]	NMP[k]					
	(<500)	(⩽5)	(⩽10)	(<5)		(>22)	(>−5.7)	(<7)		(<140 Å^2)			
11a	351.3	5	10	−1.4 (−0.8 ± 0.7)	0	22.3*	−2.6 (−2.0)	6	0	*170.7*	−1.04	−2.7	—
11b	401.4	5	10	−0.6 (0.3 ± 0.7)	0	22.3*	−3.4 (−2.7)	6	0	*170.7*	−0.85	−2.8	—
11c	401.4	5	10	−0.7 (0.3 ± 0.7)	0	*21.8**	−3.3 (−2.7)	6	1	*171.2*	−0.85	−2.8	—
15a	351.3	5	10	−1.6 (−0.7 ± 0.5)	0	*18.5**	−2.6 (−2.0)	5	1	*171.9*	−1.10	−2.8	—
15b	401.4	5	10	−0.8 (0.4 ± 0.5)	0	*21.1**	−3.3 (−2.7)	5	1	*170.4*	−0.91	−2.9	—
15c	401.4	5	10	−0.9 (0.4 ± 0.5)	0	*21.9**	−3.3 (−2.7)	5	1	*170.5*	−0.92	−2.8	—
21a	351.3	5	10	−1.6 (−0.7 ± 0.5)	0	*19.4**	−2.6 (−2.0)	5	1	*171.3*	−1.10	−2.8	—
21b	401.4	5	10	−0.9 (0.4 ± 0.5)	0	*18.1**	−3.4 (−2.7)	5	1	*172.4*	−0.91	−3.0	—
21c	401.4	5	10	−0.9 (0.4 ± 0.5)	0	*20.0**	−3.3 (−2.6)	5	1	*171.4*	−0.92	−2.9	—
Range[l]	130–725	0–6	2–20	−2.0–6.5	—	<25 poor; >500 great	−6.5–0.5	1–8	—	7–200	−1.5–1.5	−3.0–1.2	—

[a] ADMET data were calculated as described in the text using Qikprop 3.5; predicted properties outside the range for 95% of known drugs are indicated with an asterisk (*).
[b] Rules as listed in the columns, with any violations of the rules highlighted in italics.
[c] PSA represents the van der Waals (polar) surface areas of N and O atoms with a recommended PSA <140 Å^2 [52].
[d] LogK_{hsa}: predicted binding to human serum albumin.
[e] LogBB: the predicted blood–brain barrier co-efficient.
[f] Toxicity structural warnings from FAF-Drugs2.
[g] Number of hydrogen bond donors.
[h] Number of hydrogen bond acceptors.
[i] Values calculated with ALOGPS are given in parentheses (a 'consensus' value ± standard deviation in the case of log$P_{(o/w)}$).
[j] Caco-2 cell permeability.
[k] Number of primary metabolites.
[l] Range for 95% of known drugs; reference: QikProp version 3.5 User's Manual.

3. Conclusions

Synthetic procedures were elaborated for all possible isomers of *N*-β-D-glucopyranosyl aryl-substituted-oxadiazolecarboxamides. The compounds with phenyl, 1- and 2-naphthyl substituents were assayed against rabbit muscle GPb to show low micromolar efficiency for the best inhibitors. Both the constitution of the oxadiazole ring and the type of the aryl substituent had a strong bearing on the inhibition, and the best compounds of the different series were **11b** (K_i = 30 μM), **15c** (K_i = 33 μM), and **21a** (K_i = 104 - μM). ADMET property predictions revealed all ligands to have oral 'drug-like' properties based on Lipinski's 'rule of 5'. Apart from potential permeability issues which would require 'optimization' based on Jorgensens 'rule of three', the inhibitors had satisfactory pharmacokinetic profiles and were devoid of any toxicity structural warnings. The consideration of heterocyclic substitutions in *N*-β-D-glucopyranosyl carboxamides is thus justified and further syntheses and computational evaluation of such compounds will be reported in due course.

4. Experimental

4.1. General synthetic methods

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with Bruker 360 (360/90 MHz for ^{1}H/^{13}C) spectrometer. Chemical shifts are referenced to TMS as the internal reference (^{1}H), or to the residual solvent signals. Microanalyses were performed on an Elementar vario Micro cube. TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck). TLC plates were visualized under UV light, and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size (0.063–0.200 mm) was applied.

4.2. 5-Phenyl-1,3,4-oxadiazole-2-carboxylic acid (4)

To the solution of ethyl 5-phenyl-1,3,4-oxadiazole-2-carboxylate (**3**) (1.5 g, 6.91 mmol) in the 1:1 mixture of THF/water (78 mL) LiOH (248 mg; 10 mmol) was added and stirred at room temperature for 30 min. Then the mixture was acidified with *c* H_2SO_4 and the precipitated product was filtered off, washed with water and dried on air. The product is light yellow crystals (900 mg, 68%, mp: decomposed over 230 °C). ^{1}H NMR (DMSO-d_6): δ (ppm) = 7.5–7.7 (m, 3H, aromatic), 8.0–8.1 (m, 2H, aromatic), 9.1 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ (ppm): 124.5, 128.23, 130.5, 133.5, 166.15 (aromatic carbons), 178.5 (*C*OOH). Anal. Calcd for $C_9H_6N_2O_3$ (190.04): C, 56.85; H, 3.18; N, 14.73; Found: C, 56.94; H, 14.85.

4.3. 5-Phenyl-1,3,4-oxadiazole-2-carbonyl chloride (5)

5-Phenyl-1,3,4-oxadiazole-2-carboxylic acid (**4**) (400 mg, 2.11 mmol) was dissolved in thionyl chloride (4 mL) and refluxed for four hours. Then the mixture was concentrated in vacuum and used without any purification.

4.4. *N*-Cyanocarbonyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (8)

To a stirred solution of 2,2-dimethyl-5-(*p*-tosyloxyimino)-1,3-dioxane-4,6-dione[35] (2.19 g, 6.7 mmol) in dry toluene (50 mL) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (**7**) (2.35 g,

6.8 mmol) was added and the mixture was stirred for 2 days at 50 °C. Subsequently the mixture was concentrated in vacuum, and the residue purified by column chromatography (eluent: hexane/ethyl-acetate = 1:1) to give **8** as white crystals. (1.54 g, 57%; $[\alpha]_D$ = 9.33 in $CHCl_3$; *c* = 0.51); mp.: 125–145 °C). ^{1}H NMR ($CDCl_3$): δ (ppm): 2.02 (3H, s, $COCH_3$), 2.04 (3H, s, $COCH_3$), 2.08 (3H, s, $COCH_3$), 2.10 (3H, s, $COCH_3$), 3.79–3.88 (1H, m, H-5), 4.10 (1H, dd; *J* = 1.8 and 12.3 Hz; H-6$_A$), 4.29, (1H, dd, *J* = 4.8 and 12.6 Hz; H-6$_B$), 5.00, 5.08, 5.29 (3 × 1H; *pseudo* t; *J* = 9.5–9,8; H-2; H-3; H-4), 5.22 (1H, t, *J* = 9,2; H-1), 7.86 (1H, d, *J* = 9.2 Hz, NH). ^{13}C NMR ($CDCl_3$): δ (ppm): 20.66, 20.78 (4 × $COCH_3$), 61.66 (C-6), 67.85; 70.25; 72.58; 74.20; 77.92 (C-1, C-2; C-3; C-4; C-5), 110.86 (CN), 143.48 (NH*C*O), 169.71; 170.05; 170.80; 171.18 ($COCH_3$) Anal. Calcd for $C_{16}H_{20}N_2O_{10}$ (400.11): C, 48.00; H, 5.04; N, 7.00; Found: C: 48.05; H: 5.09; N: 7.03

4.5. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*2H*-tetrazole-5-carboxamide (9)

A solution of *N*-cyanocarbonyl derivative (**8**) (2.00 g, 5.0 mmol), trimethylsilyl azide (2.23 mL, 16.96 mmol) and Bu_2SnO (0.10 g, 0.42 mmol) in anhydrous toluene (90 mL) was stirred overnight at 80 °C. Subsequently the mixture was concentrated in vacuum, and the residue was crystallized from methanol to give **9** as white crystals (1.95 g; 88%); mp: 110–113 °C; $[\alpha]_D$ = −1.61 in $CHCl_3$; *c* = 0.335, mp: 174–177 °C) white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.93 (3H, s, $COCH_3$), 1.99 (9H, s, $COCH_3$), 3.99 (1H, m, H-5), 4.10 (1H, dd, *J* = 12.3, <1, H-6$_A$), 4.24 (1H, dd, *J* = 12.3, 2.8, H-6$_B$), 5.22, 5.32, 5.47, 5.66 (4 × 1H, *pseudo* t, *J* = 9.6, 9.1 Hz in each, H-1, H-2, H-3, H-4,), 7.26-7.01 (1H, brs, NH), 8.74 (1H, brs, CONH), ^{13}C NMR ($CDCl_3$) δ (ppm): 20.54 and 20.61 (*C*O*C*H$_3$), 61.78 (C-6), 68.01, 70.42, 73.07, 73.74 (C-2, C-3, C-4, C-5), 77.96 (C-1), 152.59 (tetrazole C-5), 156.97 (amide CO), 169.69, 170.23, 170.47, 170.83 (*C*OCH$_3$). Anal. Calcd for $C_{16}H_{21}N_5O_{10}$ (443.13): C, 43.34; H, 4.77; N, 15.80. Found: C: 43.39; H: 4.89; N: 15.94.

4.6. General procedures for the preparation of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-aryl-1,3,4-oxadiazole-2-carboxamides

Method A: To a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**6**, 2.3 mmol) in dry dichloromethane (14 mL) a solution of PMe_3 in toluene (2.3 mL) was added and the mixture was stirred at room temperature. When the starting material was transformed (TLC, eluent: hexane/ethyl-acetate = 1:1) an acid chloride (2.3 mmol) was added to the mixture and stirred at room temperature for one day. Subsequently the mixture was concentrated in vacuum and the residue was purified by column chromatography (eluent hexane/ethyl-acetate = 2:1).

Method B: A solution of an aroyl-chloride (3.37 mmol) and tetrazole **9** (2.25 mmol) in dry toluene (15 mL) was stirred at 80 °C for 2 h. Then the mixture was cooled and concentrated in vacuum and the residue was purified by column chromatography (eluent hexane/ethyl-acetate = 2:1).

4.7. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-phenyl-1,3,4-oxadiazole-2-carboxamide (10a)

By method A, starting from **6** (858 mg, 2.3 mmol) and 5-phenyl-1,3,4-oxadiazole-2-carbonyl chloride (**5**) (436 mg, 2.3 mmol) to give **10a** as white crystals (110 mg, 10%).

By method B, starting from benzoyl chloride (196 μl, 1.68 mmol) and tetrazole **9** (500 mg, 1.12 mmol) in dry toluene (6 mL) to give **10a** as white crystals (470 mg, 80%, mp: 169–171 °C; $[\alpha]_D$ = −4.672 in DMSO, *c* = 0.6). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.02 (6H, s, 2 × CH_3), 2.04, 2.05 (6H, s, 2 × CH_3), 3.95 (1H, ddd, *J* = 9.8, 4.6 and 2.1 Hz, H-5), 4.16 (1H, dd, *J* = 12.6 and 4.6 Hz, H-6$_A$), 4.28 (1H, dd, *J* = 12.6 and 2.1 Hz, H-6$_B$), 5.13, 5.18, 5.36 (3 × 1H, *pseudo* t, *J* = 9.8, 9.4 and 9.4 Hz, H-2, H-3, H-4), 5.44 (1H, d, *J* = 9.4 Hz, H-1), 7.50 (2H, t, *J* = 7.3 Hz, aromatic), 7.56 (1H, m, aromatic), 8.15 (2H, d, *J* = 7.3 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.68 (CO*C*H$_3$), 20.79 (3 × CO*C*H$_3$), 61.74 (C-6), 68.09, 70.38, 72.90, 73.95 (C-2, C-3, C-4, C-5), 78.12 (C-1), 122.69, 127.68, 129.35, 132.95 (phenyl), 153.68, 157.67 (1,3,4-oxadiazole), 166.89 (NH*C*O), 169.64, 170.11, 170.63, 170.76, (*C*OCH$_3$). Anal. Calcd for $C_{23}H_{25}N_3O_{11}$ (519.15): C, 53.18; H, 4.85; N, 8.09. Found: C, 53.25; H, 4.96; N, 8.18.

4.8. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-(naphth-2-yl)-1,3,4-oxadiazole-2-carboxamide (10b)

By method B, starting from 2-naphthoyl chloride (640 mg, 3.37 mmol) and tetrazole **9** (1 g, 2.25 mmol) in dry toluene (15 mL) to give **10b** as white crystals (943 mg, 74%, mp: 186–188 °C; $[\alpha]_D$ = −12.843 in DMSO, *c* = 0.61). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.04 (3H, s, $COCH_3$), 2.06 (6H, s, 2 × $COCH_3$), 2.07 (3H, s, $COCH_3$), 3.95 (ddd, *J* = 10.0, 4.3 and 2.0 Hz, H-5), 5.16, 5.23, 5.40, 5.49 (4 × 1H, *pseudo* t; *J* = 11.6, 11.3, 9.5, and 9.4 Hz; H-1, H-2, H-3, H-4), 4.15 (1H, dd, *J* = 12.3 and 4.3, H-6$_A$), 4.30 (1H, dd, *J* = 12.6 and 2.0 Hz, H-6$_B$), 7.54 (2H, m, aromatic), 7.81 (1H, d J = 7.6 Hz; NH), 7.88 (2H, t, *J* = 7.2 Hz; aromatic), 8.09 (2H, m, aromatic), 8.57 (1H, s, H-1 naphthalene). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.67 (4 × CO*C*H$_3$), 61.83 (C-6), 68.24, 70.54, 72.96, 74.05, (C-2; C-3; C-4; C-5), 78.29 (C-1), 123.23, 127.39, 128.03, 128.68, 129.12, 129.30, 132.75, 135.19 (aromatic), 153.76, 157.75 (1,3,4-oxadiazole), 167.09 (NHCO), 169.59, 170.06, 170.68, 170.98 (*C*OCH$_3$). Anal. Calcd for $C_{27}H_{27}N_3O_{11}$ (569.16): C, 56.94; H, 4.78; N, 7.38. Found: C, 57.02; H, 4.86; N, 7.45.

4.9. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-(naphth-1-yl)-1,3,4-oxadiazole-2-carboxamide (10c)

By method B, starting from 1-naphthoyl chloride (178 μl, 1.17 mmol) and tetrazole **9** (345 mg, 0.78 mmol) in dry toluene (15 mL) to give **10c** as white crystals (133 mg, 30%, mp: 124–126 °C; $[\alpha]_D$ = −19.64 in $CHCl_3$, *c* = 0.52). ^{1}H NMR ($CDCl_3$): δ (ppm) 2.06 (3H, s, $COCH_3$), 2.07 (3H, s, $COCH_3$), 2.08 (3H, s, $COCH_3$), 2.09 (3H, s, $COCH_3$), 3.98 (1H, ddd, *J* = 10.2, 4.6 and 2.2 Hz, H-5), 4.18 (1H, dd, *J* = 12.6 and 2.2 Hz, H-6$_A$), 4.33 (1H, dd, *J* = 12.6 and 4,5 Hz, H-6$_B$), 5,19; 5,28; 5,43, 5,55 (4 × 1H, *pseudo* t, *J* = 9.7, 9.4, 9.5 and 9.3, H-1; H-2; H-3; H-4) 7.46 (1H, m, aromatic), 7.53 (1H, m, aromatic), 7.66 (1H, m, aromatic), 7.84 (1H, t, *J* = 8.6 Hz, aromatic), 7.97 (1H, d, *J* = 8.1 Hz, aromatic), 8.19 (1H, d, *J* = 7.3 Hz, aromatic), 8.51 (1H, d, *J* = 9.2 Hz, CON*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) 20.60, 20.70, 20.71 (CO*C*H$_3$), 61.79 (C-6), 68.09, 70.41, 72.97, 73.87, (C-2, C-3, C-4, C-5), 78.16 (C-1), 118.99, 124.84, 125.80, 136.88, 128.58, 128.81, 129.52, 129.90, 133.70 (aromatic), 153.85, 157.19 (1,3,4-oxadiazole), 166.77 (NH*C*O), 169.61, 170.08, 170.62, 170.70 (*C*OCH$_3$). Anal. Calcd for $C_{27}H_{27}N_3O_{11}$ (569.16): C, 56.94; H, 4.78; N, 7.38. Found: C, 57.04; H, 4.89; N, 7.46.

4.10. *N*-[2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl]-1-(*N'*-hydroxycarbamimidoyl) formamide (12)

To the solution of *N*-cyanocarbonyl derivative (**9**) (100 mg, 0.25 mmol) in anhydrous pyridine (0.5 mL) hydroxylamine hydrochloride (43.6 mg, 0.63 mmol) was added, and the reaction was stirred for one hour at 50 °C. Subsequently it was acidified with 5% aqueous solution of HCl (10 mL) and extracted with ethyl acetate (3 × 10 mL) and washed with water (2 × 10 mL) The organic

layer was dried over $MgSO_4$ and concentrated in vacuum. The residue was used without any purification. (77 mg, 71%).

4.11. *N*-[2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl]-1-(*N*′-benzoyloxycarbamimidoyl) formamide (13a)

A solution of **12** (77 mg, 0.178 mmol), benzoyl-chloride (23 μl, 0.196 mmol) and anhydrous pyridine (16 μl, 0.196 mmol) in anhydrous toluene (5 mL) was stirred for 24 h at 40 °C. for a day. Subsequently it was acidified with 5% aqueous solution of HCl (10 ml) and extracted with ethyl acetate (3 × 10 ml) and washed with water (2 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuum. Purification of the residue by column chromatography (hexane/ethyl acetate = 1:1) gave **13a** as white a crystal (50 mg, 52%, mp: 240–246 °C; $[\alpha]_D = -18.415$ in $CHCl_3$; $c = 0.5$). ^{1}H NMR ($CDCl_3$): δ (ppm): 2.03 (3H, s, $COCH_3$,), 2.04 (2 × 3H, s, $COCH_3$), 2.10 (3H, s; $COCH_3$), 3.84 (1H, ddd, $J = 10.1$, 3.8 and 2.2 Hz, H-5), 4.12 (1H, dd, $J = 12.4$ and 2.2 Hz, H-6_A), 4.26 (1H, dd, $J = 12.4$ and 4.0 Hz, H-6_B), 5.08, 5.11, 5.32, 5.33(4× 1H, *pseudo* t; H-1, H-2, H-3; H-4), 5.65 (2H, brs; NH_2), 7.47 (2H, t, $J = 7.2$ Hz; aromatic), 7.61 (1H, t, $J = 7.2$ Hz, aromatic), 7.98 (1H, d, $J = 9.5$ Hz, NH)8.04 (2H, d, $J = 7.2$ Hz, aromatic). ^{13}H NMR ($CDCl_3$): δ (ppm): 20.07, 20.85 ($COCH_3$); 61.64 (C-6); 68.02, 70.40, 73.03, 73.83, 78.34 (C-1, C-2, C-3, C-4, C-5), 128.76, 129.72, 133.63, 147.77 (aromatic), 160.08, 163.26, 169.54, 170.15, 170.25, 170.86 (C=N, COPh, $COCH_3$). Anal. Calcd for $C_{23}H_{27}N_3O_{12}$ (537.16): C, 51.40; H, 5.06; N, 7.82. Found: C, 51.49; H, 5.15; N, 7.91.

4.12. General procedure for the synthesis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-aryl-1,2,4-oxadiazole-3-carboxamides

Method C: To a solution of *N*-cyanocarbonyl derivative **8** (300 mg, 0.75 mmol) in dry pyridine (1.5 mL) hydroxylamine hydrochloride (131 mg, 1.87 mmol) was added and stirred at 50°C for 45 min. Dry toluene (10 mL) and 0.76 mmol acid chloride was then added and the mixture was refluxed for 1.5 h. Subsequently a solution of TBAF (0.37 mL of a 1 M solution in THF) was added to the mixture and refluxed for seven days (the progress of the reaction was monitored by TLC using hexane/ethyl-acetate = 1:1 as eluent). The mixture was diluted with 5% aq HCl (30 mL) and extracted with ethyl acetate (3 × 30 mL), washed with water (2 × 20 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuum and the residue was purified by column chromatography (eluent hexane/ethyl-acetate = 1: 1).

4.13. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-phenyl-1,2,4-oxadiazol-3-carboxamide (14a)

To the solution of **13a** (80 mg 0.15 mmol) in dry toluene (2 mL) a solution of TBAF (0.37 mL of a 1 M solution in THF) was added and the mixture was refluxed for four days. Then the mixture was diluted with 5% aq HCl (30 mL) and extracted with ethyl acetate (3 × 30 mL), washed with water (2 × 20 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuum and the residue was purified by column chromatography (eluent: hexane/ethyl-acetate = 1:1) to give **14a** as white crystals (60 mg, 76%, mp: 152–156 °C)

By method C, starting from **8** (300 mg, 0.75 mmol), hydroxylamine hydrochloride (130.8 mg, 1.88 mmol) and benzoyl-chloride (0.09 mL, 0.76 mmol) to give **14a** as white crystals (96 mg, 24%, mp: 150–157 °C; $[\alpha]_D = -27.07$ in $CHCl_3$; $c = 0.25$). ^{1}H NMR ($CDCl_3$): δ (ppm): 2.05 (6H, s; 2 × $COCH_3$), 2.07 (3H, s; $COCH_3$), 2.10 (3H, s; $COCH_3$), 3.94 (1H, m, C-5), 4.13 (1H, m, H-6_A), 4.34 (1H, dd, $J = 12.4$ and 3.8 Hz, H-6_B), 5.14 (2H, *pseudo* t, $J = 9.4$ Hz, H-3, H-4), 5.39; 5.50 (2 × 1H, *pseudo* t, $J = 9.4$ Hz, H-1, H-2), 7.57 (2H, t, $J = 7.2$ Hz, aromatic), 7.66 (1H, t, $J = 7.4$ Hz, aromatic), 7.85 (1H, d, $J = 9.4$ Hz; CONH), 8.19 (2H, d, $J = 7.2$ Hz, aromatic). ^{13}C NMR: δ (ppm): 20.67, 20.79 (4× $COCH_3$), 61.71 (C-6), 68.10, 70.51, 72.75, 73.97 (C-1, C-2, C-3, C-4), 78.10 (C-5), 123.14, 128.53, 129.40, 133.77 (phenyl), 156.78 (NHC=O), 162.27 (C-3 in 1,2,4-oxadiazole), 169.66, 170.00, 170.71, 170.88 (4 × $COCH_3$), 177.34 (C-5 in oxadiazole). Anal. Calcd for $C_{23}H_{25}N_3O_{11}$ (519.15): C, 53.18; H, 4.85; N, 8.09. Found: C, 53.27; H, 4.95; N, 8.19.

4.14. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-(naphth-2-yl)-1,2,4-oxadiazol-3-carboxamide (14b)

By method C, starting from **8** (300 mg, 0.75 mmol), hydroxylamine hydrochloride (130.8 mg, 1.88 mmol) and 2-naphthoyl chloride (157 mg, 0.83 mmol) to give **14b** as white crystals (95 mg; 22%; mp: 175–180 °C; $[\alpha]_D = -27.102$ in $CHCl_3$; $c = 0.5$). ^{1}H NMR ($CDCl_3$): δ (ppm): 2.03 (6H, s, 2 × $COCH_3$), 2.04 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 3.96 (1H, ddd, $J = 10.01$, 4.5 and 2.0 Hz H-5), 4.15 (1H; dd; $J = 12.6$ and 4.5 Hz H-6_A), 4.35 (1H, dd, $J = 12.6$, 4.6 Hz, H-6_B), 5.13, 5.14; 5,38; 5,51 (4 × ^{1}H *pseudo* t, $J = 9.8$, 9.5, 9.5, 9.4 Hz, C-1; C-2; C-3; C-4), 7.54–7.68 (2H, m, aromatic), 7.90 (2H, d, $J = 9.6$ Hz), 7.97 (2H, d, $J = 8.3$ Hz, aromatic and N*H*CO), 8.14 (1H, dd, $J = 8.6$; 1.6 Hz, aromatic), 8.72 (1H, s, aromatic). ^{13}C NMR ($CDCl_3$): δ (ppm): 20.65; 20.76 ($COCH_3$), 61.74 (C-6), 68.12, 70.54, 72.79, 73.96 (C-2; C-3; C-4; C-5), 78.80 (C-1), 120.22, 123.64, 127.50, 128.06, 129.07, 129.35, 130.02 132.62, 135.57 (aromatic), 156.82 (NH*C*O), 163.33 (C-3 in 1,2,4-oxadiazole), 169.64, 169.98, 170.68, 170.78 (*C*OCH_3), 177.46 (C-5 in 1,2,4-oxadiazole). Anal. Calcd for $C_{27}H_{27}N_3O_{11}$ (569.16): C, 56.94; H, 4.78; N, 7.38. Found: C, 57.02; H, 4.91; N, 7.47.

4.15. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-(naphth-1-yl)-1,2,4-oxadiazol-3-carboxamide (14c)

By method C, starting from **8** (300 mg, 0.75 mmol), hydroxylamine hydrochloride (1308 mg, 1.88 mmol) and 1-naphthoyl chloride (124 μl, 0.83 mmol) to give **14c** as white crystals (145 mg, 22%, mp: 175–180 °C; $[\alpha]_D = -27.47$ in $CHCl_3$; $c = 0.5$). ^{1}H NMR ($CDCl_3$): δ (ppm): 2.04 (3H, s, $COCH_3$), 2.08 (9H, s, $COCH_3$), 3.94 (1H, m, H-5), 4.12 (1H, d, $J = 12.4$ Hz, H-6_A), 4.34 (1H, dd, $J = 12.5$ and 3.7 Hz, H-6_B), 5.14, 5.16, 5.40, 5.50 (4 × 1H, *pseudo* t; $J = 9.7$ Hz; 1H, t, $J = 9.7$, 9.4 and 9.3 Hz, H-1; H-2; H-3; H-4), 7.55–7.65 (2H, m, aromatic), 7.72 (1H, t, $J = 7.2$ Hz, aromatic), 7.93 (1H, d, $J = 8.1$ Hz, aromatic), 8.10 (1H, d, $J = 9.1$ Hz, N*H*CO), 8.10 (1H, d, $J = 8.1$ Hz, aromatic), 8.39 (1H, d, $J = 7.3$ Hz, aromatic), 9.10 (1H, d, $J = 8.6$ Hz, aromatic). ^{13}C NMR ($CDCl_3$): δ (ppm): 20.67; 20.72; 20.80 (*C*OCH_3), 61.73 (C-6), 68.81, 70.58, 72.72, 73.99 (C-2; C-3; C-4; C-5) 78.30 (C-1), 119.51, 130.08, 133.90, 124.95, 125.54, 127.10, 128.90, 129.02, 130.77, 134.76 (aromatic), 156.89 (NH*C*O), 163.14 (C-3 in 1,2,4-oxadiazole), 169.66, 169.99, 170.72, 170.96 ($COCH_3$), 177.47 (C-5 in 1,2,4-oxadiazole). Anal. Calcd for $C_{27}H_{27}N_3O_{11}$ (569.16): C, 56.94; H, 4.78; N, 7.38. Found: C, 57.03; H, 4.90; N, 7.46.

4.16. General procedure for the synthesis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-aryl-1,2,4-oxadiazole-5-carboxamides

Method D: A solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (**7**, 275 mg, 0.79 mmol) in dry THF (15 mL) was added dropwise to the cooled solution of oxalyl chloride (0.79 mmol) in dry THF (10 mL) in one hour. Subsequently an arene-carboxamidoxime (**18a–c**, 0.79 mmol) was added to the reaction mixture and stirring was continued at room temperature for seven days. The progress of the reaction was monitored by TLC (eluent: hexane/ethyl-acetate = 1: 1). When the reaction was completed, the solvent was removed in vacuum and the residue was purified by column chromatography (eluent hexane/ethyl-acetate = 1: 1).

4.17. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-phenyl-1,2,4-oxadiazole-5-carboxamide (20a)

By method D, starting from benzamidoxime (**18a**) (389 mg; 2.87 mmol) to give **14** as white crystals (845 mg, 55%, mp: 154–162 °C; $[\alpha]_D = -23.55$ in $CHCl_3$; $c = 0.5$). ^1H NMR ($CDCl_3$): δ (ppm): 2.01 (6H, s, $COCH_3$), 2.02 (3H, s, $COCH_3$), 2.05 (3H, s, $COCH_3$), 3.92 (1H, ddd, $J = 10.1$, 4.1 and 2.0 Hz, C-5), 4.13 (1H, dd, $J = 12.5$, 2.0 Hz, H-6_A), 4.42 (1H, dd, $J = 12.6$, 4.6 Hz, H-6_B), 5.10, 5.11, 5.36, 5.41 (4 × 1H, *pseudo* t $J = 9.3$, 9.7, 9.5 and 9.4 Hz, H-1 H-2; H-3; H-4), 7.40–7.61 (3H, m, aromatic), 7.9 (1H, d, $J = 9.4$ Hz; NHCO), 8.0–8.1 (2H, m, aromatic). ^{13}C NMR ($CDCl_3$): δ (ppm): 20.79, 20.68 ($COCH_3$), 61.71 (C-6), 68.14, 70.55, 72.72, 74.19 (C-2; C-3; C-4; C-5), 78.42 (C-1), 125.59, 127.78, 129.18, 132.09 (aromatic), 153.31 (C-3 in 1,2,4-oxadiazole), 167.66 (NH*C*O), 169.10, 169.61, 169.96, 170.64 (*C*$COCH_3$), 170.85 (C-5 in 1,2,4-oxadiazole). Anal. Calcd for $C_{23}H_{25}N_3O_{11}$ (519.15): C, 53.18; H, 4.85; N, 8.09. Found: C, 53.29; H, 4.97; N, 8.18.

4.18. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(naphth-2-yl)-1,2,4-oxadiazole-5-carboxamide (20b)

By method D, starting from naphth-2-amidoxime (**18b**) (233 mg, 1.25 mmol) to give **20b** as white crystals (109 mg; 15%, mp: 70–83 °C; $[\alpha]_D = -21.85$ in $CHCl_3$; $c = 0.5$). ^1H NMR ($CDCl_3$): δ (ppm): 2.06 (3H, s, $COCH_3$), 2.07 (6H, s; 2 × $COCH_3$), 2.09 (3H, s, $COCH_3$), 3.92 (1H, ddd, $J = 9.7$, 4.6 and 1.8 Hz, H-5), 4.14 (1H; dd; $J = 12.6$ and 1.8 Hz; H-6_A), 4.34 (1H, dd, $J = 12$,6 and 4.6 Hz; H-6_B), 5.14, 5.15 5.39, 5.46 (4 × 1H, *pseudo* t; $J = 9.7$, 9.7, 9.5 and 9.4 Hz, H-1, H-2, H-3, H-4), 7.51–7.69 (2H, m, aromatic), 7.90 (1H, d, $J = 8.8$ Hz, aromatic), 7.96 (3H, m, aromatic), 8.14 (1H, d, $J = 8$,53 Hz, NHCO), 8.66 (1H, s, aromatic). ^{13}C NMR: δ (ppm): 20.71, 29.82 (*C*OCH_3), 61.72 (C-6), 68.12, 70.58, 72.76, 74.21 (C-2; C-3; C-4; C-5), 78.41 (C-1), 122.85, 123.74, 127.16, 128.08, 128.72, 129.16, 130.02, 133.07, 135,08 (aromatic), 153,37 (C-3 in 1,2,4-oxadiazole), 167.68 (NHCO), 169.26, 169.66, 170.01, 170.71 (*C*OCH_3), 170,91 (C-5 in 1,2,4-oxadiazole). Anal. Calcd for $C_{27}H_{27}N_3O_{11}$ (569.16): C, 56.94; H, 4.78; N, 7.38. Found: C, 56.99; H, 4.83; N, 7.41.

4.19. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-(naphth-1-yl)-1,2,4-oxadiazole-5-carboxamide (20c)

By method D, starting from naphth-1-amidoxime (**18c**) (168 mg, 0.90 mmol) to give **20c** as a yellow oil (85 mg; 16%, $[\alpha]_D = -31.53$ in $CHCl_3$; $c = 0.5$). ^1H NMR: δ (ppm): 2.06, 2.07, 2.08 (12H, s, 3 × $COCH_3$), 3.92–3.97 (1H, ddd, $J = 10.1$, 4.36 and 1.90 Hz, H-5), 4.11–4.16 (1H, m, H-6_A), 4.34 (1H, dd, $J = 9.8$ and 4.64, H-6_B), 5.16, 5.41, 5.48 (2H, m; 1H, t,$J = 9$,5 Hz; 1H, t, $J = 9$,3 Hz; H-1; H-2; H-3; H-4), 7.57 (2H, t, $J = 3.4$ Hz, aromatic), 7.65 (1H, m, aromatic), 7.92 (1H, d, $J = 7.9$ Hz, aromatic), 8.02 (1H, d, $J = 8.2$ Hz, aromatic), 8.17 (1H, d, $J = 9.3$ Hz, NHCO), 8.27 (1H, dd, $J = 0.5$, 7.2 Hz, aromatic), 8.88 (1H, d, $J = 8.5$ Hz, aromatic). ^{13}C NMR: δ (ppm): 20.61, 20.66, 20.74 ($COCH_3$), 61.68 (C-6), 68.04, 70.49, 72.68, 74.03, 78.32 (C-1, C-2, C-3, C-4, C-5), 122.34, 130.32, 133.88, 125.07, 126.01, 126.62, 128.04, 128.84, 30.03, 132.74 (aromatic), 153.39 (NHCO), 166.73 (oxadiazole), 169.32, 169.59, 169.93, 170.62 (*C*OCH_3), 170.79 (oxadiazole). Anal. Calcd for $C_{27}H_{27}N_3O_{11}$ (569.16): C, 56.94; H, 4.78; N, 7.38. Found: C, 57.16; H, 4.88; N, 7.48.

4.20. General procedure for the removal of *O*-acetyl protecting groups

Method E: To the solution of a protected sugar derivative in dry methanol (or in dry methanol and dry chloroform) a catalytic amount of NaOMe (1 M solution in methanol) was added and stirred at room temperature. The progress of the reaction was monitored by TLC (chloroform/methanol = 9:1). When the starting material was consumed the mixture was neutralised with a cation exchange resin Amberlyst 15 (H^+ form) or with acetic acid, then the resin was filtered off and the solvent removed. The precipitated product was filtered off, washed with ether and dried.

4.21. *N*-(β-D-Glucopyranosyl)-5-phenyl-1,3,4-oxadiazole-2-carboxamide (11a)

By method E, starting from **10a** (90 mg, mmol) in a mixture of dry methanol (3 mL) and dry chloroform (1.5 mL) to give **11a** as white crystals (56 mg, 50%, mp: 229–232 °C, $[\alpha]_D = 7.82$ in DMSO; $c = 0.45$). ^1H NMR (D_2O): δ (ppm): 4.90 (1H, d, $J = 8.7$ Hz, H-1), 7,57–7,78 (m; 3H), 8.04–8.18 (m, 2H), ^{13}C NMR (D_2O): δ (ppm): 60.59 (C-6), 69.43, 71.34, 76.75, 78.62, 79.61 (C-1; C-2; C-3; C-4; C-5), 122.34, 127.01, 129.41, 132.71 (aromatic), 153.40, 157.99 (1,3,4-oxadiazole), 165.02 (NHCO). Anal. Calcd for $C_{15}H_{17}N_3O_7$ (351.11): C, 51.28; H, 4.88; N, 11.96. Found: C, 51.38, H, 4.96, N, 12.01.

4.22. *N*-(β-D-Glucopyranosyl)-5-(naphth-2-yl)-1,3,4-oxadiazole-2-carboxamide (11b)

By method E, starting from **10b** (411 mg, 0.72 mmol) in dry methanol (2 mL) to give **11b** as white crystals (244 mg, 85%, mp: 219–221 °C; $[\alpha]_D = 8.776$ in DMSO; $c = 0.69$). ^1H NMR (DMSO-d_6) δ (ppm): 3.12 (1H, *pseudo* t, $J = 9.2$, Hz, H-3), 3.21–3.31 (4H, m, H-2, H-4, H-5, H-6_A), 3.69 (1H, d, $J = 11.2$ Hz H-6_B), 4.61 (1H, brs OH), 4.96 (1H, d, $J = 9.2$ Hz, H-1), 5.11 (2H, brs 2 × OH), 7.52–7.79 (2H, m, aromatic), 8.05 (1H, d, $J = 7.8$ Hz, aromatic), 8.18 (3H, s, aromatic), 8.75 (1H, s, aromatic), 9.86 (1H, brs, NHCO). ^{13}C NMR (DMSO-d_6) δ (ppm): 60.9 (C-6), 70.00, 71. 93, 77.44, 79.18, 80.17 (C-1, C-2, C-3, C-4, C-5), 120.18, 123.23, 127.75, 128.15, 129.20, 129.57, 123.57, 134.74 (aromatic) 158.4, 153.6 (1,3,4-oxadiazole), 165.47 (NHCO). Anal. Calcd for $C_{19}H_{19}N_3O_7$ (401.12): C, 56.86; H, 4.77; N, 10.47. Found: C: 56.94; H, 4.87; N, 10.58.

4.23. *N*-(β-D-Glucopyranosyl)-5-(napht-1-yl)-1,3,4-oxadiazole-2-carboxamide (11c)

By method E, starting from **10c** (300 mg, 0.53 mmol) in a mixture of dry methanol (7 mL) and dry chloroform (7 mL) to give **11c** as white crystals (185 mg, 87%, mp: 230–234 °C; $[\alpha]_D = 3.84$ in DMSO; $c = 0.62$). ^1H NMR (DMSO-d_6) δ (ppm):3.07–3.17 (1H, m, H-5), 3.32–3.20 (2H, m, H-2, H-3), 3.41–3.51 (2H, m, H-4, H-6_B), 3.70 (1H, dd, $J = 10.5$ and 5.4 Hz, H-6_A), 4.55–4.65 (1H, m, OH), 4.95–5.05 (2H, m, H-1, OH) 5.10–5.17 (2H, m, OH), 7.59–7.90 (3H, m, aromatic), 8.13 (1H, d, $J = 8.0$ Hz, aromatic), 8.28 (1H, d, $J = 8.2$ Hz, aromatic), 8.40 (1H, d, $J = 7.3$ Hz, aromatic), 9.13 (1H, d, $J = 8.5$ Hz, aromatic), 9.92 (1H, d, $J = 8.7$ Hz, NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 62.56 (C-6), 71.27, 73.44, 78.75, 80.25, 81.41 (C-1; C-2; C-3; C-4; C-5), 120.61, 126.44, 126.75, 128.16, 129.60, 132.20, 130.69, 131.04, 134.69, 135.16 (aromatic), 155.51, 159.42 (oxadiazole), 167.08 (NHCO). Anal. Calcd for $C_{19}H_{19}N_3O_7$ (401.12): C, 56.86; H, 4.77; N, 10.47; O, 27.90. Found: C: 56.91; H, 4.86; N, 10.56.

4.24. *N*-(β-D-Glucopyranosyl)-5-phenyl-1,2,4-oxadiazol-3-carboxamide (15a)

By method E, starting from **14a (**132 mg, mmol) in dry methanol (2 mL) to give **15a** as white crystals (56 mg, 64%, mp: 245–250 °C; $[\alpha]_D = 8.83$ in DMSO; $c = 0.5$). ^1H NMR (DMSO-d_6): δ (ppm): 3.07-3.71 (5H, m, H-2, H-3, H-4, H-5, H-6_A), 3.79 (1H, d,

J = 10.8, H-6$_B$), 4.58 (1H, brs; OH), 4.93 (1H, d, J = 8.6 Hz, H-1), 5.07 (^{1}H brs; OH), 7.6–7.8 (3H, m, aromatic), 8.10–8.25 (2H, m, aromatic), 9.49 (1H, brs; NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 60.98 (C-6), 69.89, 71.70, 77.45, 79.06, 79.84 (C-1, C-2, C-3, C-4, C-5), 122.96, 128.14, 129.74, 133.85 (aromatic), 156.88 (NHCO), 164.24, 176.03 (oxadiazole). Anal. Calcd for $C_{15}H_{17}N_3O_7$ (351.11): C, 51.28; H, 4.88; N, 11.96. Found: C, 51.40, H, 4.99, N, 12.05.

4.25. *N*-(β-D-Glucopyranosyl)-5-(naphth-2-yl)-1,2,4-oxadiazol-3-carboxamide (15b)

By method E, starting from **14b** (95 mg, 0.17 mmol) in a mixture of dry methanol (3 mL) and dry chloroform (1.5 mL) to give **15b** as white crystals (33 mg, 49%, mp: 254–258 °C; $[\alpha]_D$ = 11.73 in DMSO; c = 0.5). ^{1}H NMR (DMSO-d_6): δ (ppm): 2.97-3.88 (6H, m, H-2, H-3, H-4, H-5,H-6), 4.58 (1H, m), 4.99 (1H, m, H-1), 5.04 (brm, OH), 7.7 (2H, m, aromatic), 8.05 (1H, m, aromatic), 8.20 (3H, m, aromatic), 8.89 (1H, s, aromatic), 9.48 (1H, brs, NHCO). ^{13}C NMR (DMSO-d_6): δ (ppm): 60.99 (C-6), 69.92, 71.73, 77.44, 79.05, 79.85 (C-1, C-2, C-3, C-4, C-5), 120.20, 123.52, 127.65, 128.01, 129.16, 129.34, 129.50, 132.33, 135.50 (aromatic), 156.89 (NHCO), 164.30, 176.16 (oxadiazole). Anal. Calcd for $C_{19}H_{19}N_3O_7$ (401.12): C, 56.86; H, 4.77; N, 10.47. Found: C: 56.99; H, 4.91; N, 10.62.

4.26. *N*-(β-D-Glucopyranosyl)-5-(naphth-1-yl)-1,2,4-oxadiazol-3-carboxamide (15c)

By method E, starting from **14c** (170 mg, 0.3 mmol) in a mixture of dry methanol (3 mL) and dry chloroform (2 mL) to give **15c** as white crystals (64 mg, 54%, mp: 235–237 °C; $[\alpha]_D$ = 7.68 in DMSO; c = 0.5). ^{1}H NMR (DMSO-d_6): δ (ppm): 2.99–3.91; (6H, m, H-2, H-3, H-4, H-5, H-6), 4.58 (1H, brs, H-1), 5.06 (2H, br m, OH), 7.74 (3H, m, aromatic), 8.09 (1H, m, aromatic), 8.41 (2H, m, aromatic), 9.14 (1H, s, aromatic), 9.61 (1H, brs; NHCO). ^{13}C NMR (DMSO-d_6): δ (ppm): 60.90 (C-6), 69.85, 71.65, 77.40, 79.02, 79.82 (C-1, C-2, C-3, C-4, C-5), 119.09, 125.18, 125.33, 127.33, 128.68, 128.97, 130.44, 134.40, 129.22, 133.39 (aromatic), 156.83 (NHCO), 164.03, 175.79 (oxadiazole). Anal. Calcd for $C_{19}H_{19}N_3O_7$ (401.12): C, 56.86; H, 4.77; N, 10.47. Found: C: 56.93; H, 4.91; N, 10.61.

4.27. *N*-(β-D-glucopyranosyl)-3-phenyl-1,2,4-oxadiazol-5-carboxamide (21a)

By method E, starting from **20a** (467 mg, 0.9 mmol) in a mixture of dry methanol (4 mL) and dry chloroform (4 mL) to give **21a** as white crystals (251 mg, 79%, mp: 250–256 °C; $[\alpha]_D$ = 7.74 in DMSO; c = 0.5).^{1}H NMR (DMSO-d_6): δ (ppm): 3.15–3.51 (5H, m, H-2, H-3, H-4, H-5, H-6$_A$), 3.69 (1H, dd, J = 11.5 and 2.0 Hz, H-6$_B$), 4.53 (1H, brs, OH),4.92 (1H, brs, OH), 4.93 (1H, d, J = 9.0 Hz, H-1), 5.08 (^{1}H bs, OH), 7.66 (3H, m, aromatic), 8.13 (2H, m, aromatic), 9.96 (1H, brs, NH). ^{13}C NMR (DMSO-d_6): δ (ppm): 60.98 (C-6), 69.88, 71.70, 77.30, 79.14, 80.11 (C-1, C-2, C-3, C-4, C-5), 125.48, 127.25, 129.44, 132.12 (aromatic), 153.57 (NHCO), 168.15, 169.15 (oxadiazole). Anal. Calcd for $C_{15}H_{17}N_3O_7$ (351.11): C, 51.28; H, 4.88; N, 11.96. Found: C, 51.34, H, 4.98, N, 12.03.

4.28. *N*-(β-D-glucopyranosyl)-3-(napht-2-yl)-1,2,4-oxadiazol-5-carboxamide (21b)

By method E, starting from **20b** (90 mg, 0.16 mmol) in a mixture of dry methanol (2 mL) and dry chloroform (1 mL) to give **21b** as white crystals (39 mg, 62%, mp: 256–259 °C; $[\alpha]_D$ = −2.25 in DMSO; c = 0.5).^{1}H NMR (DMSO-d_6): δ (ppm): 3.08–3.19 (1H, m, H-5), 3.21–3.32 (2H, m, H-2, H-3); 4.41–3.52 (2H, m, H-4, H-6$_A$), 3.71 (1H, dd, J = 10.9 and 3.3 Hz, H-6$_B$), 4.59 (1H, brs, OH), 4.96 (1H, d, J = 9.1 Hz, H-1), 4.98; 4.99; 5.12 (3× 1H, brs, OH), 7.58–7.75 (2H, m aromatic), 8.04 (1H; d, J = 7.3 Hz, aromatic), 8.14 (3H, s, aromatic), 8.72 (1H, s, aromatic), 10.01 (1H, brs; NHCO). ^{13}C NMR (DMSO-d_6): δ (ppm): 60.99 (C-6), 69.89, 71.74, 77.30, 79.15, 80.12 (C-1, C-2, C-3, C-4, C-5), 122.85, 123.33, 127.34, 127.94, 128.21, 128.88, 129.26, 132.56, 133.40 (aromatic), 153.59 (NHCO), 168.24, 169.19 (oxadiazole). Anal. Calcd for $C_{19}H_{19}N_3O_7$ (401.12): C, 56.86; H, 4.77; N, 10.47. Found: C: 56.97; H, 4.88; N, 10.55.

4.29. *N*-(β-D-glucopyranosyl)-3-(napht-1-yl)-1,2,4-oxadiazol-5-carboxamide (21c)

By method E, starting from **20c** (127 mg, 0.22 mmol) in a mixture of dry methanol (2 mL) and dry chloroform (1 mL) to give **21c** as white crystals (64 mg, 72%, mp: 245–250 °C; $[\alpha]_D$ = −6.17 in DMSO; c = 0.5). ^{1}H NMR (DMSO-d_6): δ (ppm): 3.08–3.17 (1H, m, H-5), 3.20–3.32 (2H, m, H-2, H-3); 3.40–3.55 (2H, m, H-4, H-6$_A$),, 4.60 (1H, brs, OH), 4.98 (1H, d, J = 9.3 Hz, H-1), 4.99 (1H, brs, OH), 5.05–5.20 (2H, brs; 2 × OH), 7.69–7.73 (3H, m, aromatic), 8.10 (1H, d, J = 7.1 Hz, aromatic), 8.23 (1H, d, J = 7.5, aromatic), 8.3 (1H, d, J = 7.5, aromatic), 8.81 (1H, d, J = 7.7 Hz, aromatic), 10.05 (1H, brs. NHCO). ^{13}C NMR (DMSO-d_6): δ (ppm): 60.99 (C-6), 69.89. 71.78. 77.32. 79.18. 80.19 (C-1; C-2; C-3; C-4; C-5), 119.56, 122.34, 125.44, 126.79, 128.08, 128.94, 129.70, 132.54, 129.76, 133.52 (aromatic), 153.71 (NHCO), 164.03, 175.79 (oxadiazole). Anal. Calcd for $C_{19}H_{19}N_3O_7$ (401.12): C, 56.86; H, 4.77; N, 10.47. Found: C: 56.99; H, 4.90; N, 10.60.

4.30. General procedure for GP inhibition assay

Glycogen phosphorylase b was prepared from rabbit skeletal muscle according to the method of Fischer and Krebs[54] using 2-mercaptoethanol instead of L-cysteine, and recrystallized at least three times before use. The kinetic studies with glycogen phosphorylase were performed as described previously.[41] Kinetic data for the inhibition of rabbit skeletal muscle glycogen phosphorylase by monosaccharide compounds were collected using different concentrations of α-D-glucose-1-phosphate (4, 6, 8, 10, 12 and 14 mM) and constant concentrations of glycogen (1% w/v) and AMP (1 mM). The enzymatic activities were presented in the form of double-reciprocal plots (Lineweaver–Burk) applying a nonlinear data-analysis programme. The inhibitor constants (K_i) were determined by Dixon plots, by replotting the slopes from the Lineweaver–Burk plots against the inhibitor concentrations. The means of standard errors for all calculated kinetic parameters averaged to less than 10%. IC_{50} values were determined in the presence of 4 mM glucose 1-phosphate, 1 mM AMP, 1% glycogen, and varying concentrations of an inhibitor.

4.31. ADMET property predictions

ADMET properties of the inhibitor analogues were predicted using the QikProp 3.5 program (Schrodinger, LLC) in normal mode. ALOGPS 2.1[45] was used to calculate supplementary log$S$ and 'consensus' log$P$(o/w) values for comparison with the QikProp values. The RMSD between QikProp and ALOGPS values was calculated as:

$$RMSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(P_{QP} - P_{ALOGPS})^2} \quad (1)$$

where P_{QP} and P_{ALOGPS} represent the QikProp and ALOGPS values, respectively, of a property P. The FAF-Drugs2 server[48] was used to extract any toxicity structural warnings for the ligands.

Inhibitors were initially prepared for the QikProp calculations using Maestro and LigPrep (Schrodinger, LLC). Use of more extended conformations of ligands as input to QikProp can lead to ADMET property predictions closer to their experimental equivalents (QikProp version 3.5, User Manual). Confgen 2.3 (Schrodinger, LLC), therefore, employing the OPLS-AA (2005) forcefield and the Generalised Born/Surface Area (GB/SA) continuum model for bulk solvation effects was used to generate low energy conformations for each ligand (energy window of 5 kcal/mol). The most extended conformation was then selected based on the calculated solvent accessible surface areas (SASAs) using the Schrodinger python script 'conformer_geom_extent.py' and used as input for the ADMET property predictions.

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