4(5)-Aryl-2-C-glucopyranosyl-imidazoles as New Nanomolar Glucose Analogue Inhibitors of Glycogen Phosphorylase

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S Supporting Information

ABSTRACT: Inhibition of glycogen phosphorylases may lead to pharmacological treatments of diseases in which glycogen metabolism plays an important role: first of all in diabetes, but also in cardiovascular and tumorous disorders. C-(β-D-Glucopyranosyl) isoxazole, pyrazole, thiazole, and imidazole type compounds were synthesized, and the latter showed the strongest inhibition against rabbit muscle glycogen phosphorylase b. Most efficient was 2-(β-D-glucopyranosyl)-4(5)-(2-naphthyl)-imidazole (**11b**, K_i = 31 nM) representing the best nanomolar glucose derived inhibitor of the enzyme.

KEYWORDS: C-Glucopyranosyl derivative, isoxazole, pyrazole, thiazole, imidazole, glycogen phosphorylase, inhibitor

Glycogen phosphorylase inhibitors (GPIs) have potential for multifaceted biomedical applications. By far the most intensively studied field is the use of GPIs in antidiabetic research due to the fact that glycogen phosphorylase (GP) in the liver is directly responsible for the regulation of blood sugar levels.¹ Since hepatic glucose output was shown to be elevated especially in type 2 diabetes mellitus, GP became a validated target in combating this disease.^{2–4} In addition, GPIs were shown to have potential against cerebral^{5,6} and cardiac⁷ ischemias, cardiovascular disorders,^{7,8} and tumors.^{9,10}

GPIs comprise a very broad array of compounds with high structural diversity due to the peculiarities of several binding clefts (the catalytic, allosteric and new allosteric, inhibitor, glycogen storage, benzimidazole, and quercetin sites) discovered so far.^{11,12} Several nanomolar inhibitors with various heterocyclic scaffolds, amply discussed in review articles,^{11,12} bind to the allosteric or the new allosteric sites of GP. The most populated class of GPIs is represented by glucose derivatives, which bind primarily to the catalytic site of the enzyme showing competitive inhibition.^{13,14} From the variety of the investigated glucose analogue GPIs glucopyranosylidene-spiro-heterocycles, N-acyl-N'-β-D-glucopyranosyl ureas, and C-glucopyranosyl heterocycles^{13,14} (cf **1** in Chart 1), especially 1,2,4-triazoles,^{15,16} emerged as submicromolar inhibitors against rabbit muscle glycogen phosphorylase b (RMGPb) the prototype of glycogen phosphorylases.¹⁷

Some of the glucose derived GPIs were also studied in hepatic cellular systems and *in vivo*. Thus, glucopyranosylidene-spiro-thiohydantoin (TH, K_i = 29.8 μM against rat liver GP)

was demonstrated to exert considerable blood sugar diminishing activity in streptozotocin-induced diabetic rats¹⁸ and, in addition, restored whole body insulin sensitivity.¹⁹ Besides these effects TH and N-(3,5-dimethyl-benzoyl)-N'-(β-D-glucopyranosyl) urea were also shown to elicit unexpected metabolic changes, such as enhanced mitochondrial oxidation and mTORC2 (mammalian target of rapamycin complex 2) signaling, which need further explorations to be understood and exploited.²⁰

Among the first C-(β-D-glucopyranosyl) heterocycles studied as GPIs^{21,22} were benzothiazole **2** and benzimidazole **3** (Chart 1). The significant difference in the binding strength of these compounds was ascribed to the H-bond forming capacity of the NH moiety in **3** to the main chain C=O of His377 next to the catalytic site of the protein as revealed by X-ray crystallography of the RMGPb-**3** complex.²² Further studies with each isomer of C-glucosyl oxadiazoles^{21,23,24} **4–6** indicated that the constitution of the heterocycle significantly influenced the inhibition. The 1,2,4-triazoles **7**, with the heteroatoms in the same relative position as in the oxadiazoles, proved even stronger inhibitors. Although no X-ray structure of the corresponding enzyme–inhibitor complex has yet been available, it may be assumed that formation of a H-bridge from the triazole NH, similar to that of **3**, contributes to the binding. In each series of compounds **5–7** also the aromatic

Received: September 10, 2015

Accepted: October 19, 2015

Published: October 19, 2015

Chart 1. Selected C-Glucosyl Heterocycles as Inhibitors of Glycogen Phosphorylase and Their Efficiency^{a,b} ^aK_i [μM] against RMGPb.^bA K_i value of 2.4 μM was measured independently by N. G. Oikonomakos and co-workers cited as an unpublished result in ref 23.

part had an important impact on the efficiency: the 2-naphthyl derivatives **5b–7b** were better inhibitors than the phenyl substituted counterparts **5a–7a**. This trend was also observed and discussed in other types of glucose derived GPIs.^{13,14}

Since the constitution of the heterorings had a strong bearing on the inhibition of the oxadiazoles, we set out to investigate C-glucopyranosyl heterocycles with two heteroatoms in 1,2- and 1,3-positions with and without H-bond forming capabilities. Thus, the syntheses and enzyme kinetic tests of C-glucosyl isoxazole **8**, pyrazole **9**, thiazole **10**, and imidazole **11** type compounds have been carried out and are disclosed here.

Some 3-C-glucopyranosyl isoxazoles were reported in the literature prepared by cycloadditions of C-glycosyl nitrile-oxides with alkynes;^{25,26} however, the required aryl substituted ones remained unknown. No literature precedents could be located for 3-C-glucopyranosyl pyrazoles, although, a furanoid derivative was obtained from the corresponding glycosyl alkynyl

ketone and hydrazine.²⁷ In order to have a common intermediate for both planned heterocycles the use of glucopyranosyl phenylethynyl ketone **13** (Scheme 1) was envisaged.

Scheme 1. Synthesis of 3-(β-D-Glucopyranosyl)-5-phenyl-isoxazole (**8**) and -Pyrazole (**9**)^a

^aReagents and conditions: (i) 1. One equiv of PhC≡CSnBu₃, 0.05 equiv of Pd(PPh₃)₄, dry toluene, Ar atm., 50 °C; 2. One equiv of Et₃N, rt; (ii) 1 equiv of PhC≡CSnBu₃, 0.05 equiv of Pd(PPh₃)₄, dry toluene, Ar atm., 50 °C; (iii) 1 equiv of NH₂OH·HCl, dry EtOH, reflux; (iv) 1 equiv of NH₂NH₂·AcOH, dry pyridine, rt; (v) ~1 M NaOMe in MeOH, rt.

Literature syntheses of glucopyranosyl alkynyl ketones comprise In catalyzed reactions of C-glycosyl aldehydes with alkynyl iodides followed by oxidation,²⁸ or methylation of 2-C-glycosyl benzothiazoles followed by alkylation with the corresponding Grignard-reagent and subsequent hydrolysis.²⁹ For the preparation of ynones in general, several methods were proposed from acid chlorides as starting materials. Under a variety of these conditions the glucose derived acid chloride **12**³⁰ and metalated phenylethyne derivatives gave no reaction (see Supporting Information for details). In a Pd-catalyzed transformation³¹ of **12** with PhC≡CSnBu₃, the expected ynone was formed; however, during usual silica gel column chromatography only the elimination product **14** could be isolated in 31% yield. By using flash chromatography **13** could be obtained in 61% yield. Reaction of **12** with PhC≡CSnBu₃ and subsequent treatment by Et₃N in a one-pot manner yielded **14** in higher yield (63%). Reactions of **13** with H₂NOH and H₂NNH₂ gave the expected isoxazole **15** and pyrazole **16**, from which the protecting groups were removed by Zemplén transesterification to give the test compounds **8** and **9**, respectively. The constitution of **8** was proven by mass spectrometry:^{32,33} the appearance of a *m/z* = 105 peak for [PhCO]⁺ indicated the depicted structure for this compound (see Supporting Information for the mass spectrum and fragmentation patterns).

For the synthesis of 2-C-glucopyranosyl thiazoles, the addition of 2-metalated-thiazoles to glyconolactones,³⁴ cyclocondensation of anhydro-aldononitriles with cysteine derivatives followed by oxidation,³⁵ and the reaction of anhydro-

aldonothioamides with α -haloketones³⁶ are the most frequently used procedures. According to the latter method, C-glucopyranosyl thioformamide **17** (Scheme 2) was reacted

Scheme 2. Synthesis of 4-Aryl-2-(β -D-glucopyranosyl)-thiazoles (10**)^a**

^aReagents and conditions: (i) 1 equiv of ArCOCH₂Br, dry DMF, 100 °C; (ii) ~1 M NaOMe in MeOH, rt.

with phenacyl bromide or 2-bromo-acetonaphthone to give high yields of the protected 2- β -D-glucopyranosyl thiazoles **18a** and **18b**, whose deprotection by the Zemplén method furnished the test compounds **10a** and **10b**, respectively.

2-C-Glycopyranosyl imidazoles appear in a sole publication in the literature: reaction of lithiated imidazole with O-perbenzylated D-glucono-1,5-lactone followed by removal of the hemiacetalic OH and the protecting groups gave 2- β -D-glucopyranosyl imidazole.³⁸ To get 4(5)-aryl-2-C-glucopyranosyl imidazoles, amidine **19**³⁰ was reacted with phenacyl bromide or 2-bromo-acetonaphthone in aqueous THF in the presence of K₂CO₃ as an acid scavenger (Scheme 3). The respective imidazoles **21a** and **21b** were obtained in moderate yields due to the formation of *N*-benzoyl-amidine **20** as a result of benzoyl group migration under the alkaline conditions. This compound

Scheme 3. Synthesis of 4(5)-Aryl-2-(β -D-glucopyranosyl)-imidazoles (11**)^a**

^aReagents and conditions: (i) 1 equiv of K₂CO₃, THF–H₂O 8:1, rt; (ii) 1 equiv of ArCOCH₂Br, 1 equiv of K₂CO₃, THF–H₂O 8:1, rt; (iii) ~1 M NaOMe in MeOH, rt.

was obtained in good yield under the same conditions in the absence of an α -haloketone. Any attempt to increase the yield of the imidazoles by using nonaqueous solvents (THF, 1,4-dioxane, MeCN, CHCl₃, DMF, acetone, MeOH) or different bases (KHCO₃, NaHCO₃, NaOAc, Et₃N, pyridine) failed. Deprotection was effected by the Zemplén protocol to give the test compounds **11a** and **11b** in very good yields.

The C-glucopyranosyl heterocycles were assayed against RMGPb as described earlier,³⁹ and the kinetic results, indicating that the compounds are competitive inhibitors, are summarized in Table 1 together with data for the best 1,2,4-

Table 1. Inhibition (*K_i* [μ M]) of RMGPb by C-Glucopyranosyl Heterocycles

Het	R	
	a	b
	64 ²³	12 ^{23,b}
	7 ^{15,16}	0.41 ^{15,16}
	no inh. at 625 μ M	--
	400 ^a	--
	310	158
	0.28	0.031

^aCalculated from the IC₅₀ value by using a web-based tool.⁴⁰ ^bA *K_i* value of 2.4 μ M was measured independently by N. G. Oikonomakos and co-workers cited as an unpublished result in ref 23.

oxadiazoles **6** and 1,2,4-triazoles **7**. Phenyl isoxazole **8** showed no significant binding, but the pyrazole counterpart **9** had weak inhibition. This might indicate that the H-bond donor nature of the latter heterocycle contributed to the binding. The inhibition by phenyl thiazole **10a** was stronger than that of the pyrazole **9** suggesting that the 1,3-position of the heteroatoms was more favorable than the 1,2-arrangement. Phenyl imidazole **11a** bound considerably stronger (by a factor of ~1100) than thiazole **10a**, and this again might be attributed to the H-bond forming capacity of the former. The 2-naphthyl substituted compounds **10b** and **11b** proved better inhibitors than the phenyl substituted ones **10a** and **11a**, respectively, in accordance with previous observations^{13,14} regarding the nature of the aromatic substituent of the heterocycles (cf. the pairs **6a** and **6b**, **7a** and **7b**). The 2-(β -D-glucopyranosyl)-4(5)-(2-

naphthyl)-imidazole (**11b**), being ~5000-fold more efficient than its thiazole counterpart **10b**, is the presently known most efficient glucose derived inhibitor of RMGPb. Further investigations to clear up the binding modes and detailed molecular interactions of the new inhibitors and especially the comparison of imidazoles to 1,2,4-triazoles by X-ray crystallography and computational methods are in progress and will be published in due course.

In conclusion, four types of scarcely known C-glucopyranosyl heterocycles, namely, isoxazole, pyrazole, thiazole, and imidazole were synthesized. The compounds were tested for their inhibition of rabbit muscle glycogen phosphorylase b, and the 4(5)-(2-naphthyl)-imidazole derivative proved the best glucose derived inhibitor known to date,⁴¹ regarding the very low nanomolar K_i value.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acsmedchemlett.5b00361](https://doi.org/10.1021/acsmedchemlett.5b00361).

Synthetic procedures, compound characterization, enzyme kinetic measurements, and copies of NMR spectra (PDF)

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Funding

This work was supported by the Hungarian Scientific Research Fund (OTKA CK77712, PD105808). T.D. thanks the Hungarian Academy of Sciences for a János Bolyai research fellowship.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A. Kiss and L. Nagy are thanked for running the mass spectrometric measurements.

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