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Letter

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4(5)-Aryl-2-*C*-glucopyranosyl-imidazoles As New Nanomolar Glucose Analog Inhibitors of Glycogen Phosphorylase

Éva Bokor,[a] Sándor Kun,[a] Tibor Docsa,[b] Pál Gergely,[b] and László Somsák[a*]

[a]Department of Organic Chemistry, University of Debrecen, POB 20, H-4010 Debrecen, Hungary

[b]Department of Medical Chemistry, Medical and Health Science Centre, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary

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

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.

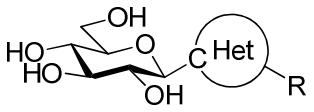
Glycogen phosphorylase inhibitors (GPIs) have potential for multifaceted biomedical applications. By far the most intensively studied field is the use of GPIs in antidiabetic research due to the fact that glycogen phosphorylase (GP) in the liver is directly responsible for the regulation of blood sugar 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 cardiac[7] 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 analog 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 rats[18] 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]

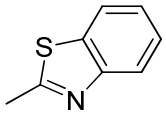
Among the first *C*-(β-D-glucopyranosyl) heterocycles studied as GPIs[21, 22] were benzothiazole **2** and benzimidazole **3** (Chart 1). The significant difference in the binding strength of these compounds was ascribed to the H-bond forming capacity of the NH moiety in **3** to the main chain C=O of 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 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]

Chart 1. Selected *C*-Glucosyl Heterocycles as Inhibitors of Glycogen Phosphorylase and Their Efficiency[a]

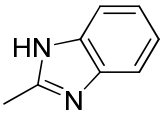


1

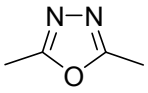
Het



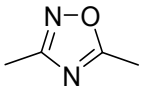
2
229[21]
76[22]



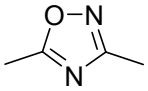
3
11[21]
9[22]



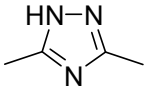
4a R = Ph
10 % at 625 μM[23]
4b R = 2-naphthyl
10 % at 625 μM[23]



5a R = Ph
10 % at 625 μM[24]
5b R = 2-naphthyl
38[24]

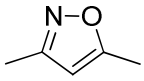


6a R = Ph
64[23]
6b R = 2-naphthyl
12[23,b]

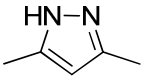


7a R = Ph
7[15, 16]
7b R = 2-naphthyl
0.41[15, 16]

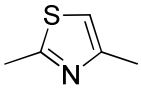
target compounds of this work



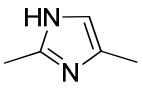
8



9



10



11

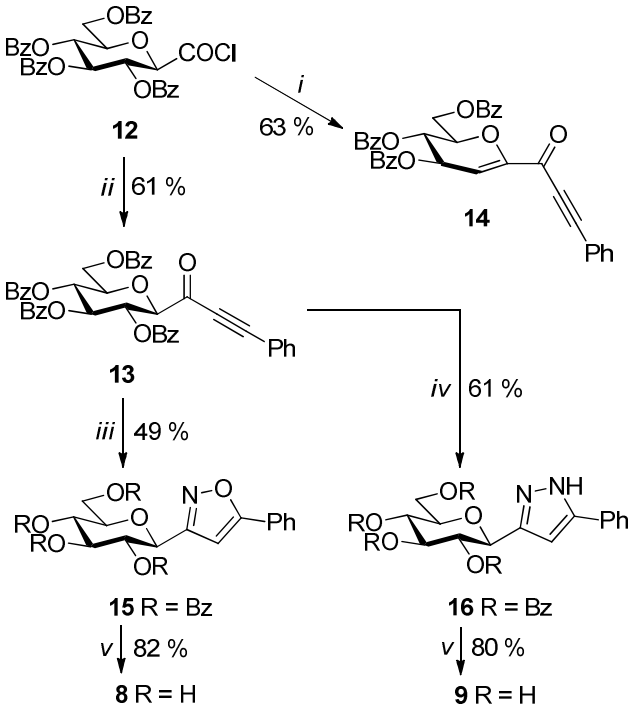
[a] K_i [μM] against RMGPb.

[b] A 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]

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*-glycopyranosyl 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*-glycopyranosyl 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)

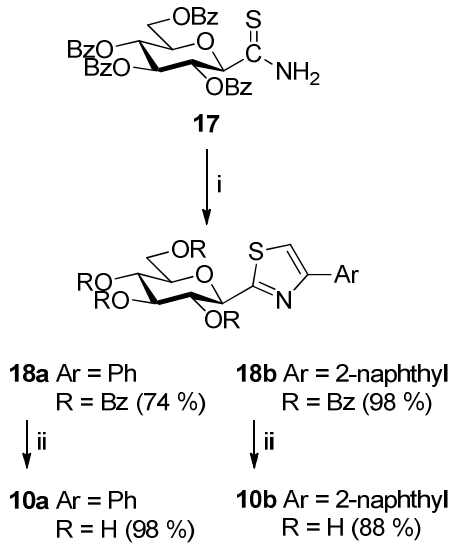


i) 1. 1 equiv PhC≡CSnBu$_3$, 0.05 equiv Pd(PPh$_3$)$_4$ dry toluene, Ar atm., 50 °C, 2. 1 equiv Et3N, rt; *ii*) 1 equiv PhC≡CSnBu$_3$, 0.05 equiv Pd(PPh$_3$)$_4$, dry toluene, Ar atm., 50 °C; *iii*) 1 equiv $NH_2OH{\cdot}HCl$, dry EtOH, reflux; *iv)* 1 equiv $NH_2NH_2{\cdot}AcOH$, dry pyridine, rt; *v*) ~1M NaOMe in MeOH, rt.

Literature syntheses of glycopyranosyl alkynyl ketones comprise In catalysed reactions of *C*-glycosyl aldehydes with alkynyl iodides followed by oxidation,[28] or methylation of 2-*C*-glycosyl benzothiazoles followed by alkynylation 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 transformation[31] of **12** with PhC≡CSnBu$_3$ 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 $PhC{\equiv}CSnBu_3$ and subsequent treatment by Et3N in a one-pot manner yielded **14** in higher yield (63 %). Reactions of **13** with H_2NOH and H_2NNH_2 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).

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

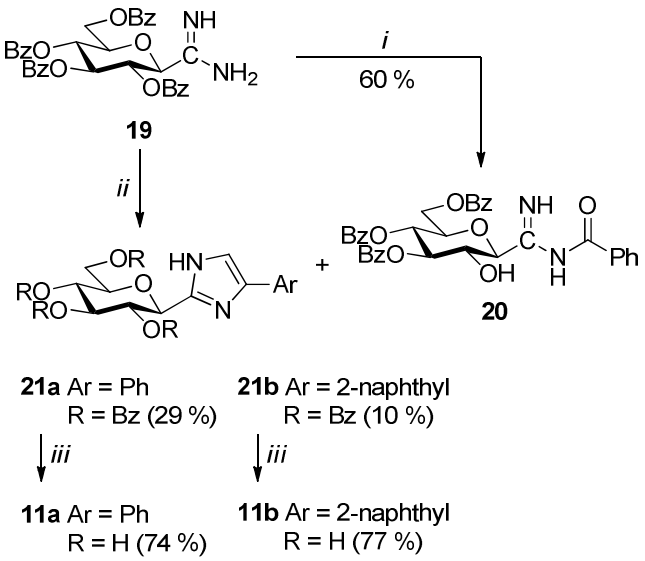


i) 1 equiv ArCOCH2Br, dry DMF, 100 °C; *ii*) ~1M NaOMe in MeOH, rt.

For the synthesis of 2-*C*-glycopyranosyl 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-haloketones[36] are the most frequently used procedures. According to the latter method, *C*-glucopyranosyl thioformamide[37] **17** (Scheme 2) was reacted 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 K_2CO_3 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 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 non-aqueous solvents (THF, 1,4-dioxane, MeCN, $CHCl_3$, DMF, acetone, MeOH) or different bases ($KHCO_3$, $NaHCO_3$, NaOAc, Et3N, pyridine) failed. Deprotection was effected by the Zemplén protocol to give the test compounds **11a** and **11b** in very good yields.

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

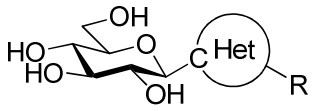


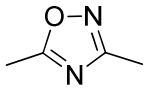
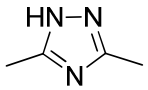
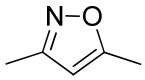
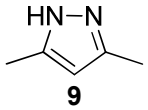
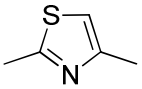
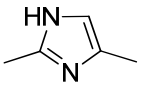
i) 1 equiv K2CO3, THF-H2O 8 : 1, rt; *ii*) 1 equiv ArCOCH2Br, 1 equiv K2CO3, THF-H2O 8 : 1, rt;; *iii*) ~1M NaOMe in MeOH, rt.

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-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.

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



Het	R = a	R = b
 **6**	64[23]	12[23,b]
 **7**	7[15, 16]	0.41[15, 16]
 **8**	no inh. at 625 μM	--
 **9**	400[a]	--
 **10**	310	158
 **11**	0.28	0.031

[a]Calculated from the IC_{50} value by using a web-based tool.[40]

[b]A 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]

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.

Supporting Information. Synthetic procedures, compound characterization, and enzyme kinetic measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

Corresponding Author

* L. Somsák – Tel.: +3652512900 ext. 22348, fax: +3652512744, e-mail: somsak@tigris.unideb.hu.

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REFERENCES

1. Henke, B. R. Inhibition of glycogen phosphorylase as a strategy for the treatment of type 2 diabetes. *RSC Drug Discovery Ser.* **2012,** 27, 324-365.
2. Kurukulasuriya, R.; Link, J. T.; Madar, D. J.; Pei, Z.; Richards, S. J.; Rohde, J. J.; Souers, A. J.; Szczepankiewicz, B. G. Potential drug targets and progress towards pharmacologic inhibition of hepatic glucose production. *Curr. Med. Chem.* **2003,** 10, 123-153.
3. Ross, S. A.; Gulve, E. A.; Wang, M. H. Chemistry and biochemistry of type 2 diabetes. *Chem. Rev.* **2004,** 104, 1255-1282.
4. Agius, L. New hepatic targets for glycaemic control in diabetes. *Best Pract. Res. Clin. Endocrin. Metab.* **2007,** 21, 587-605.
5. Sun, H.; Xu, L. Pharmacological manipulation of brain glycogenolysis as a therapeutic approach to cerebral ischemia *Mini-Rev. Med. Chem.* **2010,** 10, 1188-1193.
6. Guan, T.; Qian, Y. S.; Tang, X. Z.; Huang, M. H.; Huang, L. F.; Li, Y. M.; Sun, H. Maslinic acid, a natural inhibitor of glycogen phosphorylase, reduces cerebral ischemic injury in hyperglycemic rats by GLT-1 up-regulation. *J. Neurosci. Res.* **2011,** 89, 1829-1839.
7. Tracey, W. R.; Treadway, J. L.; Magee, W. P.; Sutt, J. C.; McPherson, R. K.; Levy, C. B.; Wilder, D. E.; Yu, L. J.; Chen, Y.; Shanker, R. M.; Mutchler, A. K.; Smith, A. H.; Flynn, D. M.; Knight, D. R. Cardioprotective effects of ingliforib, a novel glycogen phosphorylase inhibitor. *Am. J. Physiol.-Heart Circul. Physiol.* **2004,** 286, H1177-H1184.
8. Treadway, J. L.; Magee, W. P.; Hoover, D. J.; McPherson, R. K.; Martin, W. H.; Zavadoski, W. J.; Gibbs, E. M.; Tracey, W. R. Cardioprotective effect of the glycogen phosphorylase inhibitor CP-380867. *Diabetes* **2000,** 49, A127-A127.
9. Favaro, E.; Bensaad, K.; Chong, M. G.; Tennant, D. A.; Ferguson, D. J. P.; Snell, C.; Steers, G.; Turley, H.; Li, J.-L.; Günther, U. L.; Buffa, F. M.; McIntyre, A.; Harris, A. L. Glucose utilization via glycogen phosphorylase sustains proliferation and

prevents premature senescence in cancer cells. *Cell Metab.* **2012,** 16, 751-764.

10. Zois, C. E.; Favaro, E.; Harris, A. L. Glycogen metabolism in cancer. *Biochem. Pharmacol.* **2014,** 92, 3-11.

11. Somsák, L.; Czifrák, K.; Tóth, M.; Bokor, É.; Chrysina, E. D.; Alexacou, K. M.; Hayes, J. M.; Tiraidis, C.; Lazoura, E.; Leonidas, D. D.; Zographos, S. E.; Oikonomakos, N. G. New inhibitors of glycogen phosphorylase as potential antidiabetic agents. *Curr. Med. Chem.* **2008,** 15, 2933-2983.

12. Hayes, J.; Kantsadi, A.; Leonidas, D. Natural products and their derivatives as inhibitors of glycogen phosphorylase: potential treatment for type 2 diabetes. *Phytochem. Rev.* **2014,** 13, 471-498.

13. Praly, J. P.; Vidal, S. Inhibition of glycogen phosphorylase in the context of type 2 diabetes, with focus on recent inhibitors bound at the active site *Mini-Rev. Med. Chem.* **2010,** 10, 1102-1126.

14. Somsák, L. Glucose derived inhibitors of glycogen phosphorylase. *Compt. Rend. Chimie* **2011,** 14, 211-223.

15. Bokor, É.; Docsa, T.; Gergely, P.; Somsák, L. *C*-Glucopyranosyl-1,2,4-triazoles as new potent inhibitors of glycogen phosphorylase. *ACS Med. Chem. Lett.* **2013,** 4, 612-615.

16. Kun, S.; Bokor, É.; Varga, G.; Szőcs, B.; Páhi, A.; Czifrák, K.; Tóth, M.; Juhász, L.; Docsa, T.; Gergely, P.; Somsák, L. New synthesis of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles, nanomolar inhibitors of glycogen phosphorylase. *Eur. J. Med. Chem.* **2014,** 76, 567-579.

17. Chrysina, E. D. The prototype of glycogen phosphorylase *Mini-Rev. Med. Chem.* **2010,** 10, 1093-1101.

18. Docsa, T.; Czifrák, K.; Hüse, C.; Somsák, L.; Gergely, P. The effect of glucopyranosylidene-spiro-thiohydantoin on the glycogen metabolism in liver tissues of streptozotocin-induced and obese diabetic rats. *Mol. Med. Rep.* **2011,** 4, 477-481.

19. Docsa, T.; Marics, B.; Németh, J.; Hüse, C.; Somsák, L.; Gergely, P.; Peitl, B. Insulin sensitivity is modified by a glycogen phosphorylase inhibitor: glucopyranosylidene-spiro-thiohydantoin in streptozotocin-induced diabetic rats. *Curr. Top. Med. Chem.* **2015**, *15*, 1-5.

20. Nagy, L.; Docsa, T.; Brunyánszki, A.; Szántó, M.; Hegedős, C.; Marton, J.; Kónya, B.; Virág, L.; Somsák, L.; Gergely, P.; Bai, P. Glycogen phosphorylase inhibitor *N*-(3,5-dimethyl-benzoyl)-*N*'-(β-D-glucopyranosyl) urea improves glucose tolerance under normoglycemic and diabetic conditions through rearranging hepatic metabolism. *PLoS ONE* **2013,** 8, e69420.

21. Hadady, Z.; Tóth, M.; Somsák, L. *C*-(β-D-glucopyranosyl) heterocycles as potential glycogen phosphorylase inhibitors. *Arkivoc* **2004,** (vii), 140-149.

22. Chrysina, E. D.; Kosmopolou, M. N.; Tiraidis, C.; Kardarakis, R.; Bischler, N.; Leonidas, D. D.; Hadady, Z.; Somsák, L.; Docsa, T.; Gergely, P.; Oikonomakos, N. G. Kinetic and crystallographic studies on 2-(β-D-glucopyranosyl)-5-methyl-1,3,4-oxadiazole, -benzothiazole, and -benzimidazole, inhibitors of muscle glycogen phosphorylase *b*. Evidence for a new binding site. *Protein Sci.* **2005,** 14, 873-888.

23. Tóth, M.; Kun, S.; Bokor, É.; Benltifa, M.; Tallec, G.; Vidal, S.; Docsa, T.; Gergely, P.; Somsák, L.; Praly, J.-P. Synthesis and structure-activity relationships of *C*-glycosylated oxadiazoles as inhibitors of glycogen phosphorylase. *Bioorg. Med. Chem.* **2009,** 17, 4773-4785.

24. Benltifa, M.; Vidal, S.; Fenet, B.; Msaddek, M.; Goekjian, P. G.; Praly, J.-P.; Brunyánszki, A.; Docsa, T.; Gergely, P. In the search of glycogen phosphorylase inhibitors: 5-substituted 3-*C*-glucopyranosyl-1,2,4-oxadiazoles from β-D-glucopyranosyl cyanides upon cyclization of *O*-acyl-amidoxime intermediates. *Eur. J. Org. Chem.* **2006**, 4242-4256.

25. Baker, K. W. J.; Gibb, A.; March, A. R.; Paton, R. M. Generation and cycloaddition reactions of pyranose-1-carbonitrile oxides. *Tetrahedron Lett.* **2001,** 42, 4065-4068.

26. Dondoni, A.; Giovannini, P. P.; Massi, A. Assembling heterocycle-tethered *C*-glycosyl and α-amino acid residues via 1,3-dipolar cycloaddition reactions. *Org. Lett.* **2004,** 6, 2929-2932.

27. Logue, M. W.; Sarangan, S. *C*-Nucleosides via glycosyl alkynyl ketones - synthesis of 5(3)-phenyl-3(5)-(β-D-ribofuranosyl)pyrazole. *Nucl. Nucl.* **1982,** 1, 89-98.

28. Picard, J.; Lubin-Germain, N.; Uziel, J.; Auge, J. Indium-mediated alkynylation in *C*-glycoside synthesis. *Synthesis* **2006**, 979-982.

29. Dondoni, A.; Catozzi, N.; Marra, A. Concise and practical synthesis of *C*-glycosyl ketones from sugar benzothiazoles and their transformation into chiral tertiary alcohols. *J. Org. Chem.* **2005,** 70, 9257-9268.

30. Bokor, É.; Fekete, A.; Varga, G.; Szőcs, B.; Czifrák, K.; Komáromi, I.; Somsák, L. *C*-(β-D-Glucopyranosyl)formamidrazones, formic acid hydrazides and their transformations into 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles: a synthetic and computational study. *Tetrahedron* **2013,** 69, 10391-10404.

31. Kuhn, H.; Neumann, W. P. Investigations on the Stille reaction carried out with polymer-supported organotin reagents. *Synlett* **1994**, 123-124.

32. Grünanger, P.; Vita-Finzi, P. Isoxazoles. In *The chemistry of heterocyclic compounds*, Taylor, E. C., Ed. John Wiley & Sons: New York, 1991; Vol. 49, Part 1.

33. Stephens, C. E.; Arafa, R. K. 3,5-Diarylisoxazoles: individualized three-step synthesis and isomer determination using C-13 NMR or mass spectroscopy. *J. Chem. Ed.* **2006,** 83, 1336-1340.

34. Dondoni, A.; Marra, A. Thiazole-mediated synthetic methodology. *Chem. Rev.* **2004,** 104, 2557-2599.

35. Merino, P.; Ghirardello, M.; Tejero, T.; Delso, I.; Matute, R. Recent advances on the enantioselective synthesis of *C*-nucleosides inhibitors of inosine monophosphate dehydrogenase (IMPDH). *Curr. Top. Med. Chem.* **2014,** 14, 1212-1224.

36. Kovács, L.; Herczegh, P.; Batta, G.; Farkas, I. Thiazole *C*-nucleosides III. Synthesis of pyranose analogues of tiazofurin. *Tetrahedron* **1991,** 47, 5539-5548.

37. Ösz, E.; Czifrák, K.; Deim, T.; Szilágyi, L.; Bényei, A.; Somsák, L. Preparation of 3,5-bis-(β-D-glycopyranosyl)-1,2,4-thiadiazoles from *C*-(β-D-glycopyranosyl)thioformamides. *Tetrahedron* **2001,** 57, 5429-5434.

38. Granier, T.; Vasella, A. Synthesis and evaluation as glycosidase inhibitors of 1*H*-imidazol-2-yl *C*-glycopyranosides. *Helv. Chim. Acta* **1995,** 78, 1738-1746.

39. Ösz, E.; Somsák, L.; Szilágyi, L.; Kovács, L.; Docsa, T.; Tóth, B.; Gergely, P. Efficient inhibition of muscle and liver glycogen phosphorylases by a new glucopyranosylidene-spiro-thiohydantoin. *Bioorg. Med. Chem. Lett.* **1999,** 9, 1385-1390.

40. Cer, R. Z.; Mudunuri, U.; Stephens, R.; Lebeda, F. J. IC_{50}-to-K_i: a web-based tool for converting IC_{50} to K_i values for inhibitors of enzyme activity and ligand binding. *Nucl. Acids Res.* **2009,** 37, W441-W445.

41. Somsák, L.; Bokor, É.; Vágvölgyiné Tóth, M.; Juhász, L.; Czifrák, K.; Kónya, B.; Kun, S.; Páhi, A.; Szőcs, B.; Varga, G.; Gergely, P.; Docsa, T.; Kóder, L.; Nagy, K. Preparation of imidazolyl and triazolyl glycosides as glycogen phosphorylase inhibitors and antitumor agents. WO2013061105A2, 2013.

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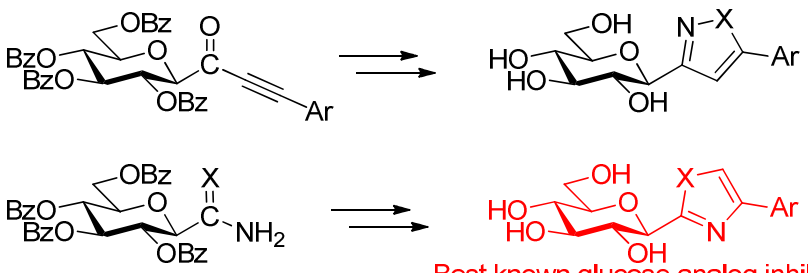

X	Ar	K_i [μM]
O	Ph	no inh.
NH	Ph	400
S	Ph	310
	2-naphthyl	158
NH	Ph	0.28
	2-naphthyl	0.031

Best known glucose analog inhibitor of rabbit muscle glycogen phosphorylase b