Carbohydrate Research 412 (2015) 71–79

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

C-(2-Deoxy-D-*arabino*-hex-1-enopyranosyl)-oxadiazoles: synthesis of possible isomers and their evaluation as glycogen phosphorylase inhibitors

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ARTICLE INFO

Article history:
Received 6 March 2015
Received in revised form
8 April 2015
Accepted 22 April 2015
Available online 2 May 2015

Keywords:
C-Glycosyl compounds
D-Glucal
Oxadiazoles
Glycogen phosphorylase
Inhibitor

ABSTRACT

Synthetic methods were elaborated for D-glucals attached to oxadiazoles by a C–C bond. Introduction of the double bond was effected by either DBU induced elimination of PhCOOH from the *O*-perbenzoylated glucopyranosyl precursors or Zn/*N*-methylimidazole mediated reductive elimination from the 1-bromoglucopyranosyl starting compounds. Alternatively, heterocyclizations of 2-deoxy-D-*arabino*-hex-1-enopyranosyl cyanide were also carried out. Test compounds were obtained by Zemplén debenzoylation, however, none of them showed significant inhibition of rabbit muscle glycogen phosphorylase *b*.

1. Introduction

The continuous interest in glycogen phosphorylase inhibitors (GPIs) is primarily derived from the antihyperglycemic potential of such molecules involving their possible application in the medication of patients with type II diabetes.[1] On the other hand, inhibition of glycogen phosphorylase (GP) enzymes has also become an investigational approach in the context of other diseases such as ischemic lesions[2–5] and tumors.[6–10]

The inhibitors targeting the seven binding sites of GP (catalytic, inhibitor, allosteric, new allosteric, glycogen storage, benzimidazole[11] and the recently discovered quercetin binding site[12]) show a large molecular diversity.[13–17] Among them various glucose derivatives bind mostly to the catalytic site of the enzyme.[18,19] At present, *N*-acyl-β-D-glucopyranosylamines, *N*-acyl-*N*′-β-D-glucopyranosyl ureas, glucopyranosylidene-spiro-heterocycles as well as *N*- and *C*-glucosylated heterocycles (see Chart 1 for some important representatives of the latter e.g., **1**–**7**, **13**–**20**) belong to the most potent classes of this inhibitor family displaying their activity in or below the low micromolar range against rabbit muscle GP*b* (RMGP*b*).[17–19] X-Ray crystallographic studies on the binding modes of several of these molecules elucidated their increased binding strengths in comparison to that of D-glucose (K_i=1.7 and 7.4 mM for the α and β anomers,[20] respectively). Besides the ideal fit of the glucose part of these inhibitors in the active site, the strong binding must be ascribed to the H-bonding capacities of the aglycons as well as van der Waals interactions of an aromatic appendage (if present) in the so-called β-channel of the enzyme.[13] These findings highlight the decisive contribution of the aglycon to the good inhibition and account for the fact that the structure-based inhibitor design of glucose analog GPIs has mainly been focused on the anomeric substitution patterns. Nevertheless, to get a thorough insight into the structure-activity relationships, the exploration of the specificity of the sugar unit is also necessary. Early investigations on the inhibitory and binding properties of different monosaccharides indicated the superior effectiveness of D-glucose.[21,22] Changes in the sugar configuration (e.g., for D-mannose[21] K_i>100 mM against RMGP*b*) as well as removal or replacement of substituents of the glucose moiety (e.g., for 2-deoxy-D-glucose[21] K_i=27 mM, for D-xylose[21] K_i>100 mM, for 3-deoxy-3-fluoro-D-glucose[22] K_i=200 mM against RMGP*b*) proved detrimental for the inhibition. Taking into account the crucial role

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http://dx.doi.org/10.1016/j.carres.2015.04.016
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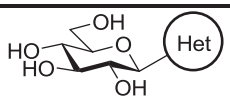
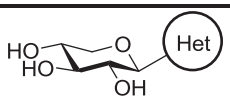
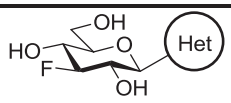
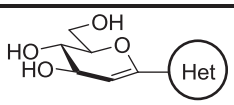
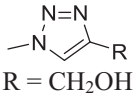
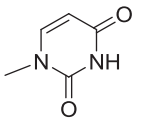
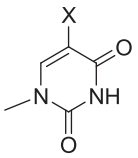
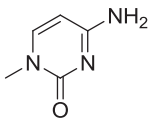
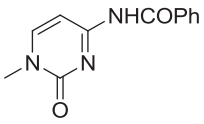
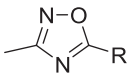
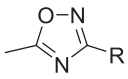
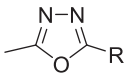
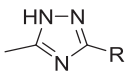
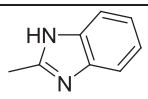
	 Glc	 Xyl	 3-F-Glc	 Glucal
Sugar part	*N*-Glycosyl heterocycles			
	 R = CH_2OH				
Glc	**1** 26[36] 14[37]	**2** 6.1[15] 12[38]	**3** X = F 5.5[15] 7.9[38] **4** X = Cl 1.0[38] **5** X = Br 3.3[38] **6** X = I 1.9[38]	**7** 7.7[15]	-
Xyl	**8** No inh. at 625 μM[28]	-	-	-	-
3-F-Glc	-	**9** 3460[29]	**10** X = F 3670[29]	**11** 4010[29]	**12** 46[29]
	C-Glycosyl heterocycles				
					
Glc	R = Me				
	13 No inh. at 625 μM[39]	-	**16** 212[40] 145[41]	**18** 499[42]	**20** 11 [40] 8.6 [41]
	R = 2-Naphthyl				
	14 38[43]	**15** 12 (2.4)[39]	**17** 10 % inh. at 625 μM[39]	**19** 0.41[42,44]	
Xyl	-	-	-	**21** 491[24]	**22** No inh. at 625 μM[24]
Glucal	**Target compounds of this study**			-	-

Chart 1. Inhibitory potency (K_i [μM]) of selected *N*- and *C*-glycosyl heterocycles against rabbit muscle glycogen phosphorylase *b* (RMGP*b*).[15, 24, 28, 29, 36–44] The superscript numbers represent the reference citations.

of the aglycon in the efficiency of the glucose based inhibitors alterations of the sugar moiety in cases of some potent heterocyclic glucose derivatives were also examined to test whether the interactions of the anomeric substituent could compensate the impaired binding affinity of the glycon.

As part of this program D-xylose derived analogs of the best glucose based inhibitors were most often studied. Xylopyranosylidene-spiro-hydantoins, the first compounds investigated in this series, proved practically inactive.[23] Xylopyranosylidene-spiro-isoxazolines and oxathiazoles,[24] having the most potent aglycones of the glucopyranosyl series,[25–27] remained also ineffective.[24] Xylopyranosyl counterparts of *N*-(β-D-glucopyranosyl)-1,2,3-triazoles (e.g., **8** in Chart 1) as well as analogous derivatives of 5-thio-xylose and their oxidized variants (sulfoxides and sulfones) showed also negligible or no inhibition against RMGP*b*.[28] Very recently, *C*-β-D-xylopyranosyl-heterocycles were synthesized (e.g., **21** and **22**), and among them only the 2-naphthyl substituted 1,2,4-triazole derivative **21** had modest activity towards RMGP*b*.[24]

Other studies with *N*-β-D-glucopyranosyl-pyrimidines[15,17] **2**–**7** and **9**–**12** showed that replacement of the 3-OH group of the glucose moiety by fluorine caused very significant weakening of the inhibitions (see Chart 1 for the directly comparable pairs **2** and **9**, **3** and **10**, and **7** and **11**, respectively).[29] Nevertheless, elongation of the aglycon by a hydrophobic group proved advantageous (compare **11** and **12**) rendering compound **12** to be the first micromolar inhibitor of this class.[29] Furthermore, insertion of an axially oriented hydroxymethyl group into the C-3 position of the glucose part of **2** induced a slightly decreased inhibition (K_i=27.1 μM against RMGP*b*) in spite of additional molecular interactions of the $-CH_2OH$ group that was evidenced by X-ray crystallography.[30]

Additionally, in the frame of a study of conformationally restricted pseudonucleosides, an *N*-substituted spiro-thiohydantoin ring was constructed at the C-3 position of