


## AUTHOR QUERY FORM

 ELSEVIER	<b>Journal:</b> CRAS2C  <b>Article Number:</b> 3372	<b>Please e-mail or fax your responses and any corrections to:</b>  <b>E-mail:</b> <a href="mailto:corrections.esme@elsevier.thomsondigital.com">corrections.esme@elsevier.thomsondigital.com</a>  <b>Fax:</b> +33 (0) 1 71 16 51 88
---	---	--

Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list.

For correction or revision of any artwork, please consult <http://www.elsevier.com/artworkinstructions>.

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof. Click on the 'Q' link to go to the location in the proof.

Location in article	Query / Remark: <a href="#">click on the Q link to go</a> Please insert your reply or correction at the corresponding line in the proof
	Reference(s) given here were noted in the reference list but are missing from the text – please position each reference in the text or delete it from the list.
<a href="#">Q1</a>	To maintain sequential order, citation of fig. [3] has been placed after citation of fig. [2]. Please check, and correct if necessary.
<a href="#">Q2</a>	Please note that tables 1 to 11 have been treated as figures. Hence, tables 1–11 become figures 3–13. Please check, and correct if necessary.
<a href="#">Q3</a>	Uncited references: This section comprises references that occur in the reference list but not in the body of the text. Please position each reference in the text or, alternatively, delete it. Any reference not dealt with will be retained in this section.
<a href="#">Q4</a>	Please provide the volume number for the bibliography in References [44, 63 and 67].

Thank you for your assistance.



ELSEVIER

Contents lists available at ScienceDirect

## Comptes Rendus Chimie

www.sciencedirect.com



1 Account/Revue

3 Glucose derived inhibitors of glycogen phosphorylase<sup>☆</sup>

4 László Somsák

6 Department of Organic Chemistry, University of Debrecen, POB 20, 4010 Debrecen, Hungary

## ARTICLE INFO

## Article history:

Received 24 January 2010

Accepted after revision 8 September 2010

## Keywords:

Type 2 diabetes mellitus

Glycogen phosphorylase

Inhibitor

Glucose derivatives

## ABSTRACT

Design, synthesis, and structure–activity relationships of glucose analogue inhibitors of glycogen phosphorylase are surveyed.

© 2010 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

7  
8 1. Introduction

9 One of the major aims of chemical biology [1], the  
10 young and developing scientific field between chemistry  
11 and biology, is to find matches between the biological and  
12 chemical space [2]. The chemical space comprises (small)  
13 molecules, some of which show complementary features  
14 to certain points of the biological space constituted by the  
15 structure of binding sites of biomacromolecules (mainly  
16 but not only proteins). Good matches may result in  
17 efficient agonists/antagonists of receptors or activators/  
18 inhibitors of enzymes. Such interactions contribute to the  
19 basic understanding of the way of biological action of the  
20 macromolecule, and may ultimately be utilised in drug  
21 design and discovery.

22 In the context of this survey, the biological space is  
23 represented by glycogen phosphorylase (GP), the main  
24 regulatory enzyme of glycogen metabolism. GP, catalysing  
25 the rate-determining step of glycogen degradation in the  
26 liver by phosphorylase, is directly responsible for the  
27 regulation of blood glucose levels. Thus, the enzyme has  
28 become a validated target in combatting non-insulin-  
29 dependent or type 2 diabetes mellitus (NIDDM or T2DM),  
30 and its inhibitors are considered as potential antidiabetic

agents. The biochemical and pharmacological background  
of this research has been amply summarized in several  
reviews of the past decade, therefore, the reader is kindly  
referred to those papers [3–8].

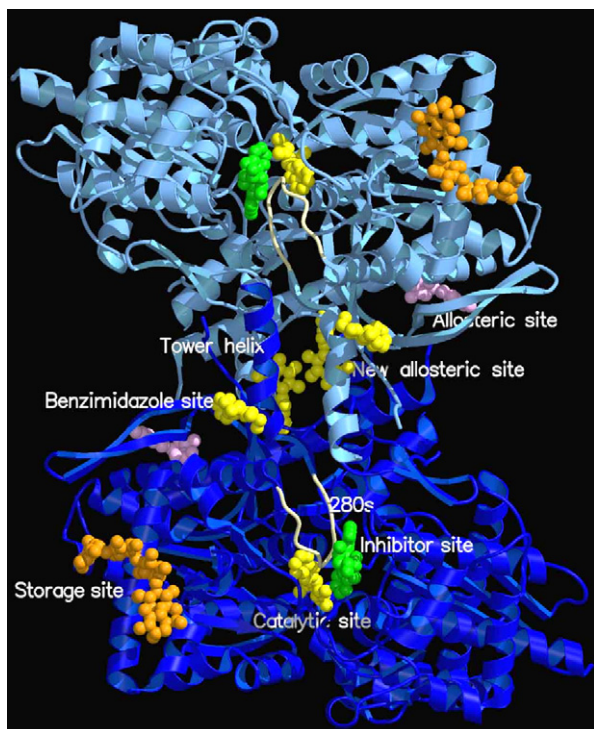
Diverse classes of compounds [4,9–12] can be found  
among inhibitors of GP binding to one (or in specific cases  
more) of the so far discovered binding sites of the enzyme  
(Fig. 1). The most populated class of compounds is that of  
glucose derivatives, first proposed and investigated  
[4,13,14] by Fleet, Johnson, and Oikonomakos,<sup>1</sup> which  
bind primarily to the active site of GP. This paper highlights  
the most important “historical” moments of GP inhibitor  
design among glucose analogues, and the main emphasis is  
put on developments of the past couple of years, not or not  
fully included in the last comprehensive reviews [11,12].  
Although the design of compounds was heavily based on  
and supported by results of crystallographic investigations  
of enzyme–inhibitor complexes and molecular dockings,  
the syntheses and structure–activity relationships of the  
inhibitors are pointed out in this overview.

2. Early glucose analogue inhibitors of glycogen  
phosphorylase

The weak binding of D-glucose anomers **1** and **2** to the  
catalytic site of GP to act as the physiological regulator of

<sup>☆</sup> Dedicated to Professor András Lipták on the occasion of his 75th birthday.

Adresse e-mail : [somsak@tigris.unideb.hu](mailto:somsak@tigris.unideb.hu).<sup>1</sup> Passed away on Aug 31, 2008.



**Fig. 1.** A schematic diagram of the muscle GPb dimeric molecule viewed down the molecular dyad. The positions are shown for the catalytic, allosteric, glycogen storage, the caffeine, the indole site, and the novel binding site for benzimidazole. The catalytic site, marked by 2- $\beta$ -D-glucopyranosyl benzimidazole, is buried at the centre of the subunit and is accessible to the bulk solvent through a 15 Å-long channel. Binding of the competitive inhibitor benzimidazole promotes the less active T state through stabilization of the closed position of the 280 s loop (shown in white). The allosteric site, which binds the activator AMP (indicated in the figure), is situated at the subunit–subunit interface some 30 Å from the catalytic site. The inhibitor site or caffeine binding site, which binds purine compounds, such as caffeine and flavopiridol (indicated), is located on the surface of the enzyme some 12 Å from the catalytic site and, in the T state, obstructs the entrance to the catalytic site tunnel. The glycogen storage site (with bound maltopentaose) is on the surface of the molecule some 30 Å from the catalytic site, 40 Å from the allosteric site and 50 Å from the new allosteric inhibitor site. The new allosteric or indole binding site, located inside the central cavity, formed an association of the two subunits, bound indole-2 carboxamide analogues, *N*-benzoyl-*N'*- $\beta$ -D-glucopyranosyl urea, and benzimidazole (indicated). The novel binding site with bound benzimidazole, also located on the surface of the molecule, is some 31 Å from the catalytic site, 32 Å from the allosteric site, and 32 Å from the indole site (figure by courtesy of N.-G. Oikonomakos and E.-D. Chrysina).

55 the enzyme [15] raised the possibility to design glucose  
56 derivatives with much higher affinity to the active site.  
57 Enzymatic tests of a large series of  $\alpha$ - and  $\beta$ -D-glucopyr-  
58 anosides, 1-thio-D-glucopyranosides, *N*-acyl- $\beta$ -D-gluco-  
59 pyranosylamines and related compounds [13] revealed  
60 1-deoxy-D-gluco-heptulopyranose 2-phosphate (**3**) and *N*-  
61 acetyl- $\beta$ -D-glucopyranosylamine (**4**) as the first glucose  
62 derivatives with an inhibitor constant ( $K_i$ ) in the low  
63 micromolar range. Anhydro-heptonamides **5** and **6** were  
64 less effective, however, a formal combination of **6** with an  
65 anomeric substituent similar to that of **4** gave again a low  
66 micromolar inhibitor **7**. Ring closure of **7** to glucopyr-  
67 anosylidene-spiro-hydantoin **8** strengthened the binding

by a factor of  $\sim 5$ . The spiro-epimeric hydantoin **9** proved 68  
much less efficient, indicating that the presence of a  $\beta$ -D- 69  
anomeric NH was very important to make a good inhibitor. 70  
This was rationalized by crystallographic investigation of 71  
the enzyme–inhibitor complex [16] to show the presence 72  
of a specific H-bridge between NH and His377 next to the 73  
catalytic site also present in *N*-acyl- $\beta$ -D-glucopyranosyl- 74  
amine type inhibitors (Fig. 2a for an illustration). The 75  
synthetic problems with the stereoselective preparation of 76  
the properly configured spiro-hydantoin **8** [17–19] were 77  
essentially overcome by the highly stereoselective synthe- 78  
sis of spiro-thiohydantoin **10** [20] which proved equipo- 79  
tent with **8** (Fig. 3). 80

### 3. Glucose derivatives tested recently as inhibitors of glycogen phosphorylase

#### 3.1. *N*-Acyl- $\beta$ -D-glucopyranosylamines and related compounds

Following the success of the first *N*-acyl- $\beta$ -D-glucopyr- 86  
anosylamine type inhibitors like **4**, several modifications of 87  
the acyl group were carried out. A widely applied general 88  
method for the preparation of such compounds starts with 89  
the reaction of per-*O*-acetylated  $\beta$ -D-glucopyranosyl azide 90  
**11** with triaryl- or trialkyl phosphanes (PMe<sub>3</sub> proved the 91  
most advantageous [27]) and the intermediate phosphini- 92  
mine is then reacted with a carboxylic acid or acid chloride 93  
or anhydride to get protected amides **14** (Scheme 1, for an 94  
exhaustive review see [28]). Reduction of **11** to **15** followed 95  
by acylation can be an alternative synthetic route. Subse- 96  
quent deprotection yields test compounds of type **14** (R = H), 97  
and several recent examples as inhibitors of rabbit muscle 98  
GP *b* (RMGP*b*) are shown in Fig. 4. 99

Substitution in the methyl group of *N*-acetyl- $\beta$ -D- 100  
glucopyranosylamine makes the inhibition weaker (Fig. 101  
**4**, compare **4** and **14a,b**). The  $\alpha$ -anomeric trifluoroaceta- 102  
mide **17** proved configurationally stable (for a discussion on 103  
the stability of *N*-acyl-glycosylamine anomers see ref. 104  
[27]) but showed no inhibition. From a larger collection of 105  
monoamides of dicarboxylic acids, **14c** showed similar 106  
inhibition to that of **4**, while its methylester **14d** proved 107  
significantly weaker. In the series of oxamic acid deriva- 108  
tives, the efficiencies of acid **14e** and ester **14f** were 109  
reversed, both being much less effective than **4**. Introduc- 110  
tion of a large side chain as in **14g** made a weak inhibitor. 111  
Among aromatic amides, the 2-naphthoyl derivative **14h** 112  
proved the most efficient, and in this series, the position 113  
occupied by the aromatic moiety becomes also important 114  
(Fig. 5 also). Necessity of the intact homoaromatic system 115  
is indicated by 1,4-benzodioxane carboxamide **14i**. Chang- 116  
ing the acyl part to a dimethoxyphosphoryl residue (**18**) 117  
resulted in a practical loss of inhibition. 118

Syntheses of analogues **19** of spiro-hydantoin **8–10** 119  
were envisaged by photocyclization of acyl urea deriva- 120  
tives **20** outlined in Scheme 2a. To this end, reported 121  
cyclizations of 3-oxoalkyl glycosides [38,39] **23** resulting 122  
in stereoselective formation of spiro-acetals **24** (Scheme 123  
2b) served as analogies. Thus, a photoexcitation of **20** 124  
might have resulted in intermediate **22** which, upon

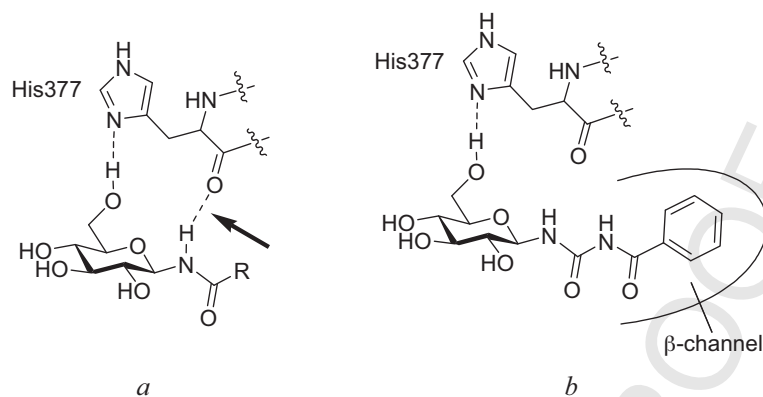


Fig. 2. Outline of binding of glucose analogues at the active site of glycogen phosphorylase (GP) highlighting (a) important H-bonds between *N*-acyl- $\beta$ -*D*-glucopyranosylamine type inhibitors and His377 and (b) binding modes of *N*-acyl-*N'*- $\beta$ -*D*-glucopyranosyl ureas as observed by X-ray crystallography.

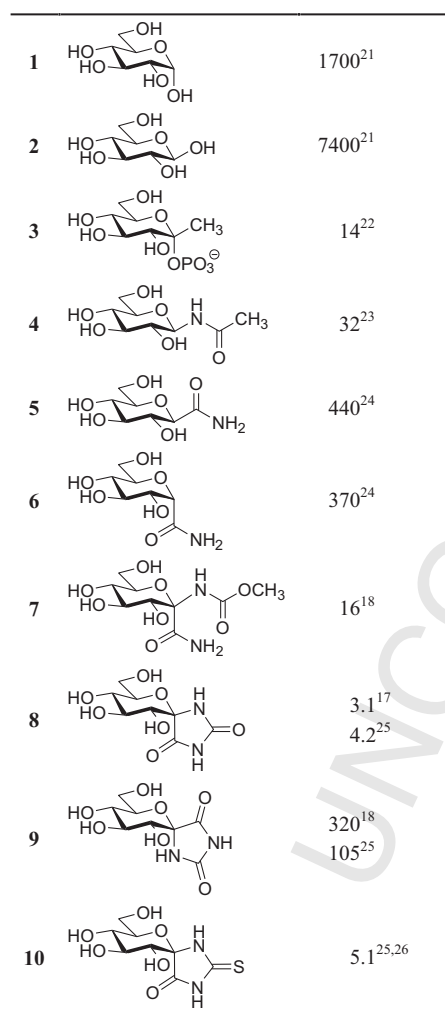
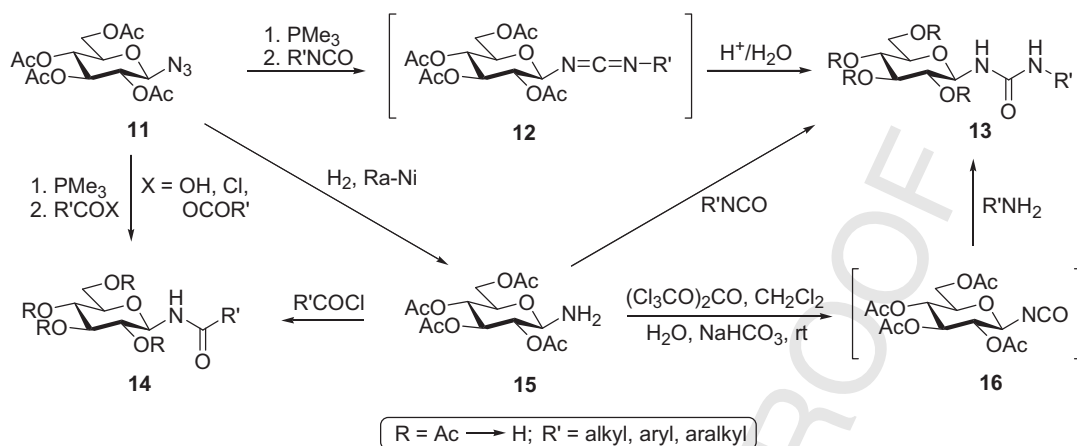


Fig. 3. Inhibition of glycogen phosphorylase (GP) by *D*-glucose and the most efficient inhibitors of early glucose analogue derivatives ( $K_i$  [ $\mu$ M] against RMGPb).

intramolecular hydrogen abstraction to give **21** and subsequent radical combination could have given the target compounds **19**.

To test this hypothesis, *N*-acyl-*N'*- $\beta$ -*D*-glucopyranosyl ureas of type **27** (Scheme 3) were needed. Only two examples of this class of compounds were known in the literature [40] which were obtained by a modification of the original synthesis. Azide **11** was transformed to urea **26** by Pintér et al.'s method [41] and then acylation was carried out to give **27** ( $R = \text{Ac}$ ,  $R' = \text{Me}$  or  $\text{Ph}$ ). Irradiation of **27** under various conditions brought about a Norrish I type cleavage of the  $R'\text{CO}$  moieties leading back to **26** instead of the expected Norrish II type cyclization [42]. Quite unexpectedly, the deprotected compounds **27** ( $R = \text{H}$ ,  $R' = \text{Me}$   $K_i = 305 \mu\text{M}$ ;  $R' = \text{Ph}$   $K_i = 4.6 \mu\text{M}$ ) proved efficient inhibitors of GP [43] and the benzoyl derivative had similar potency to those of spiro-hydantoin **8** and **10**. Initiated by this serendipitous finding, synthetic and enzymatic studies were started to get insight in structure-activity relationships of  $\beta$ -*D*-glucopyranosyl derivatives attached to aromatic rings by linkers of 3-6 atoms analogous to amide groups.

*N*-Aryl-*N'*- $\beta$ -*D*-glucopyranosyl ureas **13** were obtained (Scheme 1) either via acid catalysed hydration of carbodiimide **12** obtained from azide **11** by a Staudinger type transformation, or by reacting glucosylamine **15** with isocyanates, or by *in situ* conversion of **15** into glucosylisocyanate **16** [44] followed by amine addition. Removal of the protecting groups was straightforward under Zemplén conditions. Further compounds of the protected *N*-acyl-*N'*- $\beta$ -*D*-glucopyranosyl urea series **27** (Scheme 3) were obtained in reactions of glucosylamine **15** with acylisocyanates or from glucosylisocyanate **16** upon treatment with arenecarboxamides. During these syntheses, anomerization was observed in almost every cases thereby diminishing the yield of the target compounds [45]. Furthermore, deprotection of acyl ureas **27** was always accompanied by the cleavage of the  $R'\text{CO}$  group, both under base or acid catalysed transesterification conditions. These side reactions could be circumvented by the addition of unprotected  $\beta$ -*D*-glucopyranosylamine obtained *in situ* from  $\beta$ -*D*-glucopyranosylammonium carbamate [46] (**25**) to various acyl-isocyanates to give directly the unprotected



Scheme 1.

168 **27** ureas [45]. Biurets **28** [47] and **29** [42] were prepared in  
169 reactions of urea **26** with phenyl and 2-naphthoyl  
170 isocyanates, respectively.

171 Most important results of the enzyme kinetic studies are  
172 collected in Fig. 5. Comparison of entries 1, 2, 4, 13, and 8  
173 shows that the inhibition is strongest for the acyl urea type  
174 compounds (entry 4). Introduction of a tetrahedral element  
175 into the linker makes weaker inhibitors (compare entries 2–  
176 3, 4–6). Replacement of one NHCO by a more rigid bond  
177 (entries 4, 7, 9) seems less detrimental, although the

178 inhibition is weakened, showing the necessity of a polar part  
179 capable for participation in H-bonds as well. Entries 7 and 8  
180 indicate again that higher flexibility due to a rotatable  
181 element of the linker is not advantageous (of course, the  
182 absence of the H-bond donor amide moiety from the  
183 anomeric carbon must also contribute to the weaker  
184 binding). Constitutional isomers of the NHCONHCO moiety  
185 (entries 10–12) also make significantly less efficient  
186 inhibitors. Comparison of columns A–C demonstrate the  
187 importance of the size and orientation of the aromatic  
188 appendage the 2-naphthyl derivatives exhibiting the  
189 strongest binding. Accordingly, *N*-2-naphthoyl-*N'*-β-D-  
190 glucopyranosyl urea (entry 4C) was the first nanomolar glucose  
191 analogue inhibitor of GP. Protein crystallography showed  
192 acyl ureas of entries 4A and 4C to bind also to the new  
193 allosteric site of the enzyme [43].

194 X-Ray crystallographic studies of GP-*N*-acyl-*N'*-β-D-  
195 glucopyranosyl urea complexes revealed that, contrary to  
196 the *N*-acyl-β-D-glucopyranosylamines, there is no H-bond  
197 between the β-anomeric NH and His377 (Fig. 2b) [43]. As  
198 the acyl ureas are much more inhibitory than the  
199 corresponding glucosylamines (Fig. 5, entries 1 and 4),  
200 the stronger binding must be due to extended interactions  
201 of the urea and especially the aromatic parts of the  
202 molecules in the β-channel<sup>2</sup> of the enzyme. This observa-  
203 tion was utilized in further inhibitor design discussed in  
204 Section 3.4.

205 Very recently, a new series of aldehyde 4-(β-D-  
206 glucopyranosyl)-thiosemicarbazones [52,53] was pre-  
207 pared from per-*O*-acetylated β-D-glucopyranosylisothio-  
208 cyanate (Fig. 6) and several of them showed micromolar  
209 inhibition.

### 3.2. *N*-β-D-glucopyranosyl heterocycles

210  
211 The problems encountered in the synthesis of *N*-acyl-β-  
212 D-glucopyranosyl ureas necessitated a quest for more  
213 stable compounds. To this end, bioisosteric replacement of

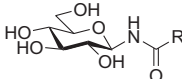
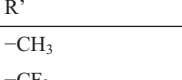
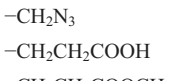
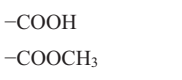
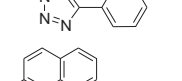
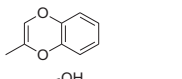
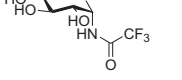
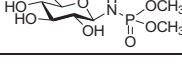
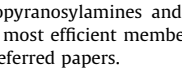
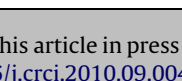

R'	$K_i$ [ $\mu\text{M}$ ]
<b>4</b> 	32 <sup>23</sup>
<b>14a</b> 	75 <sup>29</sup>
<b>14b</b> 	49 <sup>30</sup>
<b>14c</b> 	20 <sup>31</sup>
<b>14d</b> 	170 <sup>31</sup>
<b>14e</b> 	710 <sup>32</sup>
<b>14f</b> 	210 <sup>32</sup>
<b>14g</b> 	180 <sup>33</sup>
<b>14h</b> 	10 <sup>34</sup> 13 <sup>35</sup>
<b>14i</b> 	85 <sup>36</sup>
<b>17</b> 	No inh. <sup>26</sup>
<b>18</b>	5900 <sup>37</sup>

Fig. 4. Inhibition of rabbit muscle glycogen phosphorylase *b* (RMGPb) by *N*-acyl-β-D-glucopyranosylamines and related compounds. Illustrative examples of the most efficient members of larger series of compounds detailed in the referred papers.

<sup>2</sup> The β-channel or β-pocket is an empty space next to the catalytic site of GP in the direction of the β-anomeric substituent of bound D-glucose surrounded by amino acid side chains of mixed character.

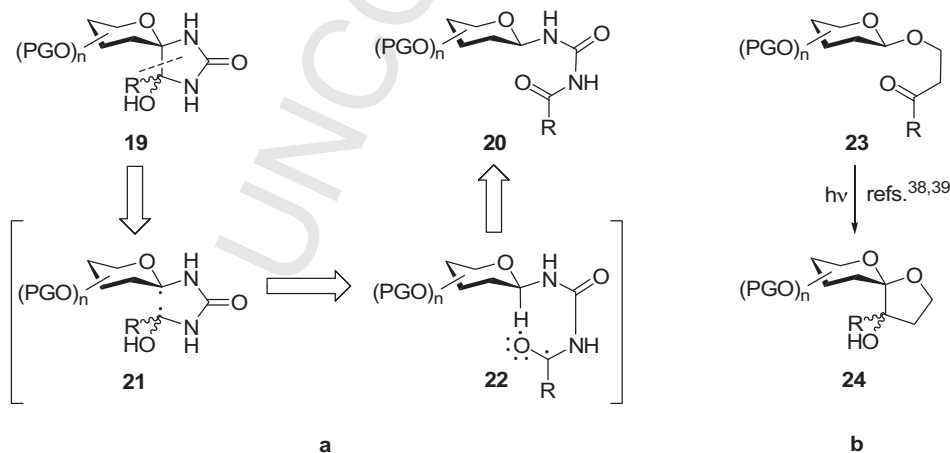


Entry	linker	Ar		
		A	B	C
1.	NHCO	81 <sup>23</sup> 144 <sup>26</sup>	191 <sup>35</sup> 444 <sup>34</sup>	10 <sup>34</sup> 13 <sup>35</sup>
2.	NHCONH	18 <sup>48</sup>	350 <sup>48</sup> (IC <sub>50</sub> )	5.2 <sup>48</sup>
3.	NHCOCH <sub>2</sub>	1100 (IC <sub>50</sub> ) <sup>34</sup>	-	-
4.	NHCONHCO	4.6 <sup>43</sup>	10 <sup>42</sup>	0.35 <sup>42</sup>
5.	NHCONHCH <sub>2</sub>	42 % (1 mM) <sup>48</sup>	-	-
6.	NHCOCH <sub>2</sub> CH <sub>2</sub>	85 <sup>34</sup>	-	-
7.	NHCOCH=CH	18 <sup>34</sup>	-	3.5 <sup>34</sup>
8.	CH <sub>2</sub> COCH=CH	-	-	52 % (100 μM) <sup>49*</sup>
9.	NHCOC≡C	62 <sup>34</sup>	-	-
10.	NHCOCONH	100 <sup>50</sup>	144 <sup>50</sup>	56 <sup>50</sup>
11.	CONHCONH	No inh. <sup>48</sup>	-	-
12.	CONHNHCO	22 % (3.75 mM) <sup>50</sup>	-	-
13.	NHCONHCONH	21 <sup>47</sup>	-	-
14.	NHCONHCONHCO	-	-	45 % (625 μM) <sup>42</sup>
15.		151 <sup>35</sup>	136 <sup>35</sup>	16 <sup>35</sup>
		162 <sup>51</sup>	625 <sup>51</sup> (IC <sub>50</sub> )	36 <sup>51</sup>

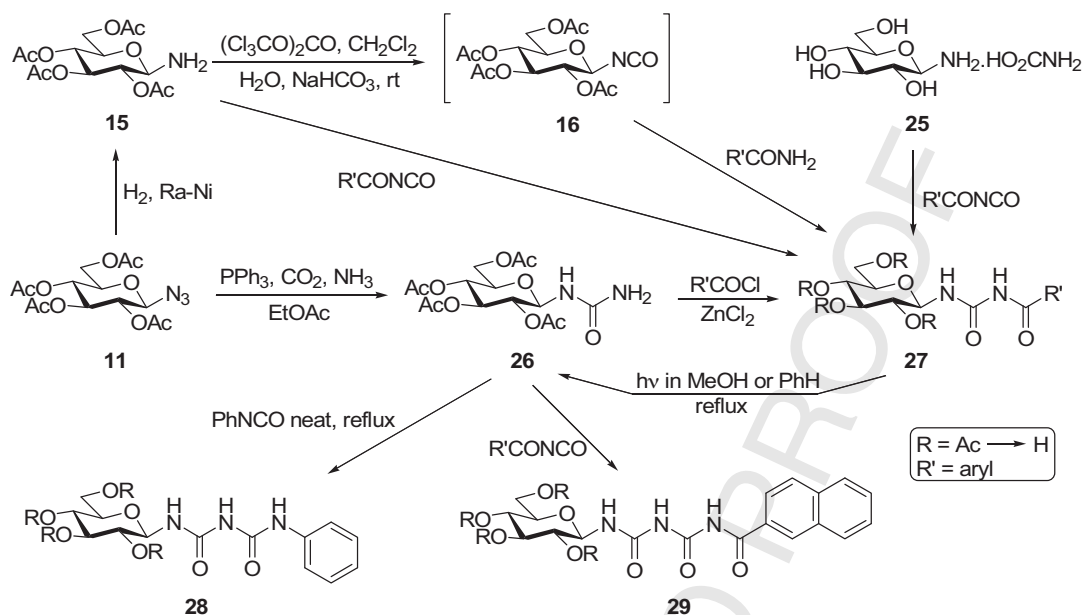
Fig. 5. Comparison of inhibition of rabbit muscle glycogen phosphorylase *b* (RMGPb) ( $K_i$  [ $\mu$ M]) by *N*-acyl- $\beta$ -D-glucopyranosylamines, *N*-substituted-*N'*- $\beta$ -D-glucopyranosyl ureas and related compounds. Against rat liver glycogen phosphorylase (GP).

214 NHCO moieties in acyl ureas and related compounds was  
 215 envisaged. As the first example of such studies, the NHCO  
 216 unit of *N*-acyl- $\beta$ -D-glucopyranosylamines was changed to  
 217 1,2,3-triazole because some literature examples indicated  
 218 similarities [56] of these two moieties. Three series of 1-D-  
 219 glucopyranosyl-4-substituted-1,2,3-triazoles [51] were

220 prepared by copper(I) catalysed azide-alkyne cycloaddi-  
 221 tion (CuAAC) [57] outlined in Scheme 4. From  $\beta$ -D-  
 222 glucopyranosyl azide **11** conditions 1a, frequently applied  
 223 in the literature, proved to be a straightforward way to the  
 224 per-*O*-acetylated 1- $\beta$ -D-glucopyranosyl-4-substituted-  
 225 1,2,3-triazoles in 58–96% yields. Transformations of the



Scheme 2.



Scheme 3.

226  $\alpha$ -azide **30** required higher catalyst loads (conditions 1b) and the yields for the corresponding per-*O*-acetylated 1- $\alpha$ -*D*-glucopyranosyl-4-substituted-1,2,3-triazoles were lower (36–72%). The aqueous conditions were unsatisfactory for the reactions of (hept-2-ulyopyranosylazide)onamide **31** for which conditions 1c were found the best to give 75–87% of the corresponding *O*-protected glucosyl triazoles with 51–73% conversion of the starting **31** in one day. Removal of the protecting groups was effected by the Zemplén protocol to give triazoles **32–34** in generally very good yields.

237 From these 1,2,3-triazoles, only compounds **32** showed significant inhibition (e.g. R = CH<sub>2</sub>OH  $K_i$  = 26  $\mu$ M [51] or 14  $\mu$ M; [35]). Inhibitor constants for other members of this series can be found in Fig. 5, entry 15 to show acceptable similarity with those of glucosyl amides in entry 1. Comparative crystallographic studies of the amide and triazole series revealed that pairs of the compounds with the same aglycon bound to the enzyme in essentially the same way in most cases [35]. Thereby, the bioisosteric

246 relationship for NHCO-1,2,3-triazole was proven for the GP 246 case as well. 247

248 Investigations of some *N*- $\beta$ -*D*-glucopyranosyl deriva- 248 tives of pyrimidine and purine heterocycles (“glucosyl 249 nucleosides”) showed these compounds to have inhibitory 250 effect towards GP, and the best inhibitors are collected in 251 Fig. 7. 252

### 253 3.3. *C*- $\beta$ -*D*-glucopyranosyl derivatives 253

254 The first *C*- $\beta$ -*D*-glucopyranosyl heterocycles tested as 254 inhibitors of GP were methyl-1,3,4-oxadiazole **38**, tetra- 255 zole **39**, benzothiazole **40**, and benzimidazole **41** (Scheme 256 5, R = H in each) [59]. Common starting material for the 257 syntheses of these compounds was the per-*O*-acetylated or 258 -benzoylated 2,6-anhydro-aldononitrile ( $\beta$ -*D*-glucopyra- 259 nosyl cyanide) **36**. 1,3-dipolar cycloaddition of protected 260 **36** with azide ion gave 5- $\beta$ -*D*-glucopyranosyl tetrazole **39** 261 which was transformed into 2- $\beta$ -*D*-glucopyranosyl-5- 262 substituted-1,3,4-oxadiazoles **38** via an *N*-acyl-nitrilimine 263

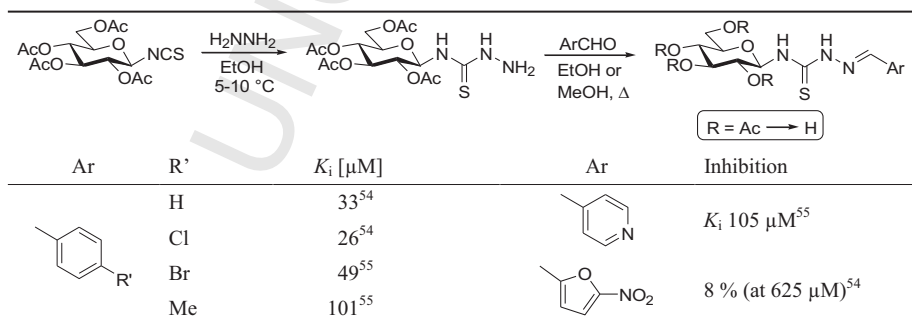
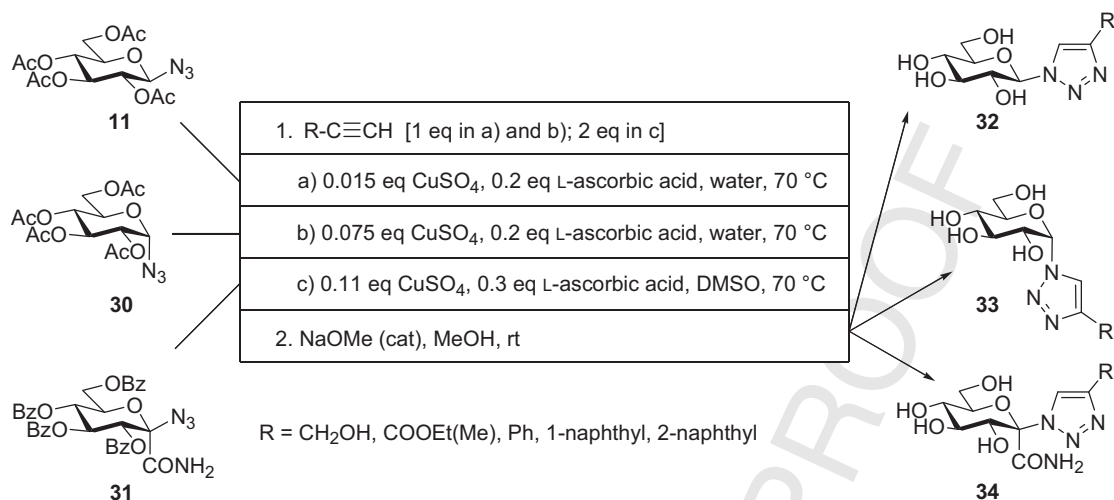


Fig. 6. Synthesis of aldehyde 4-( $\beta$ -*D*-glucopyranosyl)thiosemicarbazones and their enzymatic evaluation against rabbit muscle glycogen phosphorylase *b* (RMGPb).



Scheme 4.

264 intermediate obtained by acylation of **39** [59,60]. Oxadia-  
 265 zoles **38** could also be prepared by oxidation [60] of 2,6-  
 266 anhydro-aldose acylhydrazones [61] **35**, and the two  
 267 pathways proved comparable with respect of yields and  
 268 operational difficulties. Nitrile **36** was ring-closed to  
 269 benzothiazole **40** with 2-aminothiophenol. The analogous  
 270 reaction with 1,2-diaminobenzene was unsuccessful,  
 271 therefore, benzimidazole **41** was obtained via thioimide  
 272 **37**. Deprotection was carried out by the Zemplén method.

Per-*O*-benzoylated or -benzylated nitriles **36** were also  
 transformed into two other series of 1,2,4-oxadiazoles  
 (Scheme 6). 1,3-dipolar cycloaddition with nitrile-oxides  
 generated *in situ* furnished 5-β-D-glucopyranosyl-3-  
 substituted-1,2,4-oxadiazoles **43** [60,62]. Addition of  
 hydroxylamine to **36** produced amidoxime **42** which upon  
*O*-acylation with either carboxylic acids or acid chlorides  
 followed by cyclodehydration gave 3-β-D-glucopyranosyl-  
 5-substituted-1,2,4-oxadiazoles **44** [63]. The protecting  
 groups were removed by standard methods.

Results of enzyme kinetic studies are presented in Fig. 8.  
 β-D-glucopyranosyl cyanide **36** is a somewhat better  
 inhibitor than anhydro-aldonamide **5**, while tetrazole **39**  
 and amidoxime **42** are inactive. Benzimidazole **41** binds  
 stronger than benzothiazole **40**, and this can be attributed to  
 the H-bond between the NH of the heterocycle and His377  
 which is necessarily absent for **40**. X-ray crystallography has  
 shown **41** also to be present at the new allosteric site and the  
 new "benzimidazole site" has been discovered by investi-  
 gating this compound (Fig. 1) [64]. From the three  
 oxadiazole series (**38**, **43**, **44**), compounds **43** are the most  
 active. The tendency of strengthening the inhibition by a

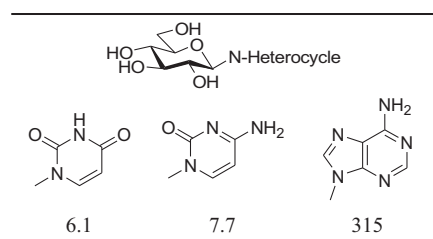
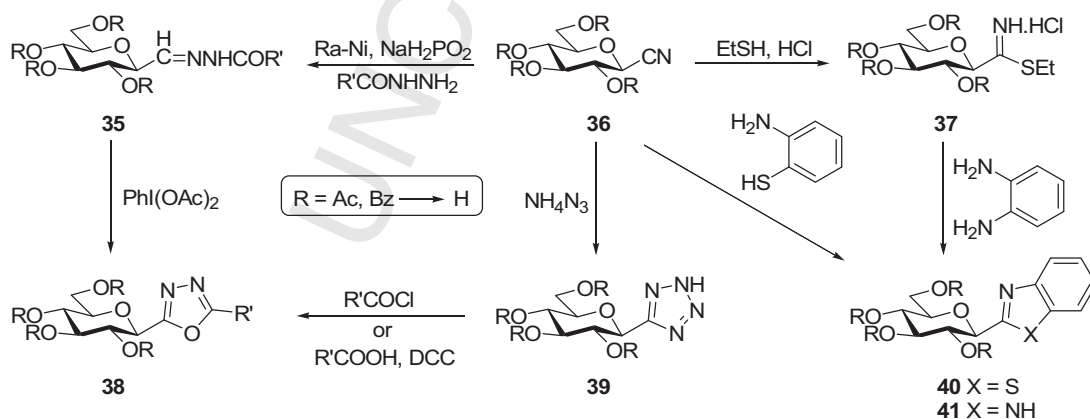


Fig. 7. Inhibitory effect of β-D-glucopyranosyl nucleosides against rabbit muscle glycogen phosphorylase *b* (RMGPb) [58] (*K<sub>i</sub>* [μM]).



Scheme 5.



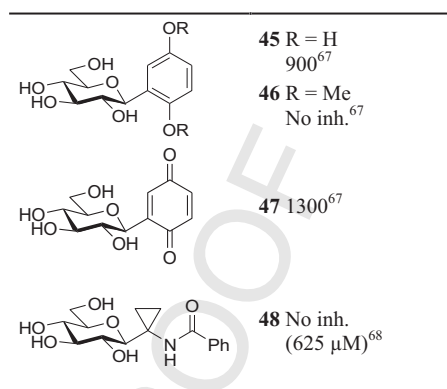
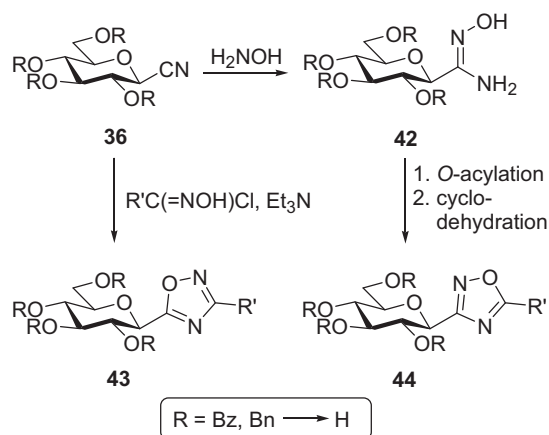


Fig. 9.  $\beta$ -D-Glucopyranosyl carbocycles as inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGPb) ( $K_i$  [ $\mu$ M]).

295 large and properly oriented aromatic substituent can be  
296 observed in the oxadiazoles, too: compounds with a 2-  
297 naphthyl appendage (**43d**, **44d**) are the best inhibitors.  
298 Although all three oxadiazoles could be considered as  
299 bioisosteric replacements [65,66] of NHCO, these results  
300 suggest that in the case of GP, 5- $\beta$ -D-glucopyranosyl-3-  
301 substituted-1,2,4-oxadiazoles **43** are the best choice.

302  $\beta$ -D-glucopyranosyl hydroquinone derivative **46** in its  
303 *O*-acetyl protected form was prepared by aromatic  
304 electrophilic substitution in 1,4-dimethoxybenzene using  
305 penta-*O*-acetyl- $\beta$ -D-glucopyranose as a source of glucosy-  
306 lium ion. Subsequent oxidation gave protected benzoqui-  
307 none **47** which was reduced to **45** [67]. The deprotected  
308 compounds were moderately inhibitory against GP (Fig.

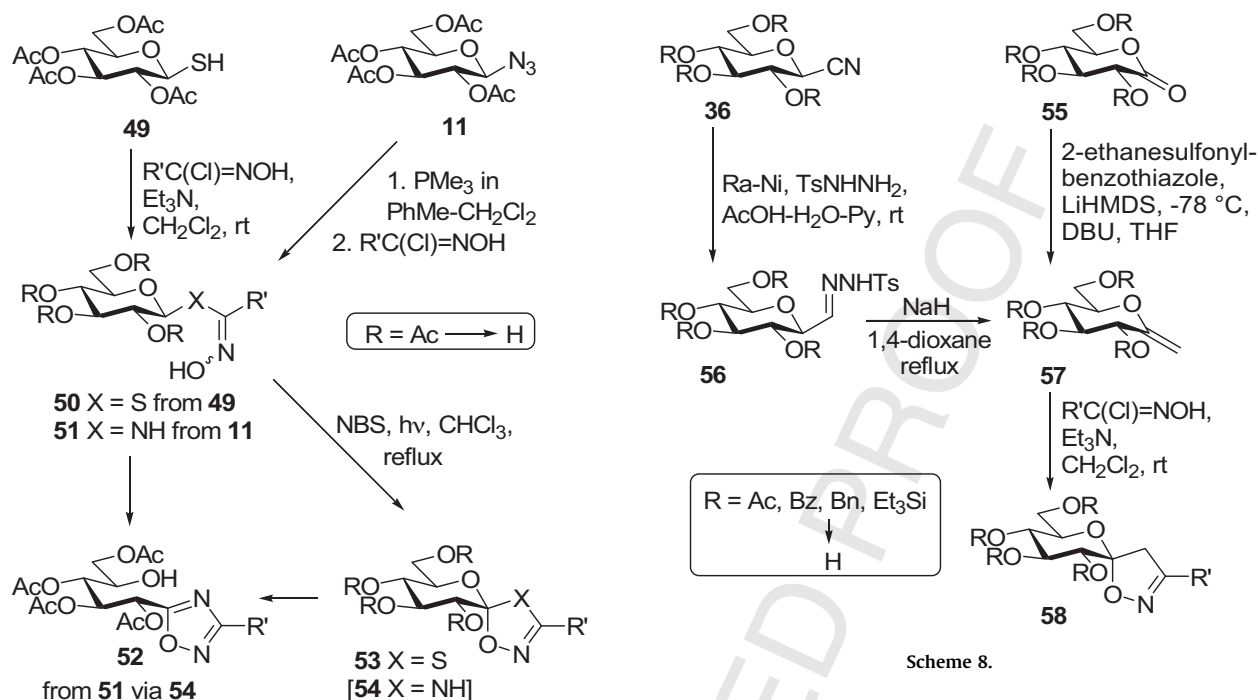
9). Cyclopropane **48** was obtained from per-*O*-benzoylated  
nitrile **36** by EtMgBr-Ti(OiPr)<sub>4</sub> followed by Zemplén  
deprotection [68]. This compound had no inhibition of GP.

### 3.4. Glucopyranosylidene-spiro-heterocycles

312  
313 Studies on *N*-acyl- $\beta$ -D-glucopyranosylamines and *N*-  
314 acyl-*N'*- $\beta$ -D-glucopyranosyl ureas allowed to conclude that  
315 it is possible to make very efficient inhibitors even in the  
316 absence of a H-bond to His377, provided that interactions  
317 in the  $\beta$ -channel are strong enough. Combining these facts  
318 with the spirobicyclic structure of hydantoin, a novel  
319 design principle for efficient glucose-based inhibitors of GP  
320 could be set up [69,70]:

	<b>5</b> R = CONH <sub>2</sub>	<b>36</b> R = CN	<b>42</b> R = C(=NOH)NH <sub>2</sub>	<b>39</b> No inh. <sup>59</sup>	<b>40</b> X = S	<b>41</b> X = NH
	440 <sup>24</sup>	130 <sup>59</sup>	No inh. <sup>63</sup>		229 <sup>59</sup>	11 <sup>59</sup>
					76 <sup>64</sup>	9 <sup>64</sup>
R'						
CH <sub>3</sub>	<b>38a</b> 212 <sup>59</sup>	<b>38b</b> 10 %	<b>38c</b> 10 %	<b>38d</b> 10 %	<b>43a</b> --	<b>43b</b> 27 <sup>62</sup>
		(625 $\mu$ M) <sup>60</sup>	(625 $\mu$ M) <sup>60</sup>	(625 $\mu$ M) <sup>60</sup>		64 <sup>60</sup>
					<b>44a</b> No inh. <sup>63</sup>	<b>44b</b> 10 %
						(625 ?M) <sup>63</sup>
						<b>44c</b> No inh. <sup>63</sup>
						<b>44d</b> 38 <sup>63</sup>

Fig. 8. C- $\beta$ -D-glucopyranosyl heterocycles and their precursors as inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGPb) ( $K_i$  [ $\mu$ M]).



Scheme 7.

Scheme 8.

- 321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335
- such molecules should have a rigid spirobicyclic scaffold in which a (preferably five-membered hetero) cycle is attached to the anomeric carbon of  $D$ -glucopyranose;
  - this cycle, although it may, should not necessarily be a H-bond donor towards His 377;
  - a suitably oriented, large aromatic appendage must be present on this cycle to fit into the  $\beta$ -channel.

This principle was first verified by spiro-oxathiazolines **53**, the synthesis of which followed well elaborated pathways [71] (Scheme 7): per- $O$ -acetylated 1-thio- $\beta$ - $D$ -glucopyranose **49** was reacted with *in situ* generated nitrile-oxides to give hydroximidates **50** which underwent a ring-closure upon oxidation by NBS to yield the target compounds **53** after Zemplén deprotection. Synthe-

sis of the analogous spiro-oxadiazoline **54** was also attempted. To this end, glucosyl azide **11** was transformed in a Staudinger type reaction into  $N$ - $\beta$ - $D$ -glucopyranosyl amidoxime **51**. Oxidative treatment of **51** gave oxadiazole **52** probably via **54**. The driving force for the tautomeric ring opening must be the aromatization of the heterocycle.

A series of glucopyranosylidene-spiro-isoxazolines **58** was prepared by 1,3-dipolar cycloaddition of nitrile-oxides to *exo*-glycals **57** (Scheme 8) [62]. The exomethylene sugars were made by Julia olefination of per- $O$ -benzylated or -silylated lactone **55**. Protecting group exchange to get the per- $O$ -acetylated **57** was necessary because upon hydrogenolytic debenzoylation of **58**, the isoxazoline ring also opened up due to a cleavage of the N-O bond.  $O$ -deacetylation of **58** could be achieved by the Zemplén protocol. Another way to **57** was reported by transforming per- $O$ -acylated nitriles **36** to 2,6-anhydro-aldose tosylhy-

340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356

$R'$		$K_i$ [ $\mu M$ ]		$K_i$ [ $\mu M$ ]
	<b>53a</b>	26	<b>58a</b>	19.6
	<b>53b</b>	-	<b>58b</b>	7.9
	<b>53c</b>	8.2	<b>58c</b>	6.6
	<b>53d</b>	0.16	<b>58d</b>	0.63

Fig. 10. Inhibition of rabbit muscle glycogen phosphorylase *b* (RMGPb) ( $K_i$  [ $\mu M$ ]) by glucopyranosylidene-spiro-heterocycles.

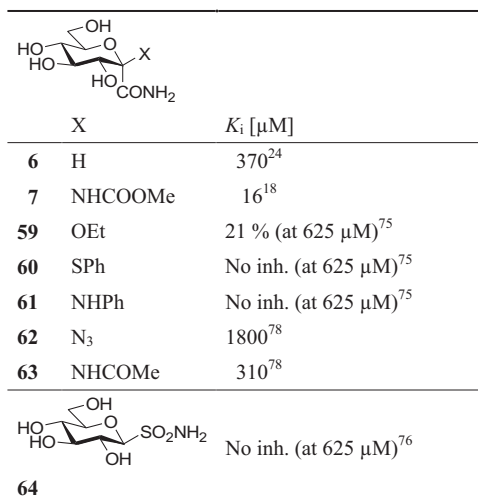


Fig. 11. Inhibition of rabbit muscle glycogen phosphorylase *b* (RMGPb) by various monosaccharide derivatives.

357 drazones followed by a Bamford-Stevens type carbene  
358 generation to yield the target *exo*-glycals [72,73].  
359 Enzyme kinetic investigation of these spirocycles (Fig.  
360 10) indicated low micromolar inhibition of GP by the

phenyl substituted derivatives **53a** and **58a**. Substitution 361  
in the para-position of the aromatic ring gave somewhat 362  
better inhibitors (**53c**, **58b,c**). The 2-naphthyl derivatives 363  
(**53d**, **58d**) were nanomolar inhibitors, thereby fully 364  
validating the design principles. 365

### 3.5. Miscellaneous compounds 366

Several *O*-, *S*-, and *N*-glucosides (Fig. 11, **59-63**) of  $\beta$ -D- 367  
*gluco*-hept-2-uloopyranosonamide were prepared by nu- 368  
cleophilic substitutions of the corresponding glycosyl 369  
bromide [75]. These compounds can be regarded as 370  
anomerically extended variants of amide **6** for which a 371  
 $\beta$ -anomeric carbamate moiety (**7**) significantly improved 372  
the inhibitory efficiency. On the other hand, the new 373  
substitution patterns of **59-63** weakened the inhibition. 374

Sulfonamide **64** prepared recently by two different 375  
methods [76,77] had no inhibition against RMGPb. 376

Very recently, multivalent molecules have been designed 377  
and proposed for inhibition of GP [79]. Compound **65** (Fig. 378  
12) was prepared by acylation of amidoxime **42** with 379  
trimesic acid chloride. To get compound **67** containing a 380  
spacer, **42** was acylated with 4-pentynoic acid followed by 381  
CuAAC with 1,3,5-tris(azidomethyl)benzene. These com- 382  
pounds have three glucose units, each potentially capable to 383

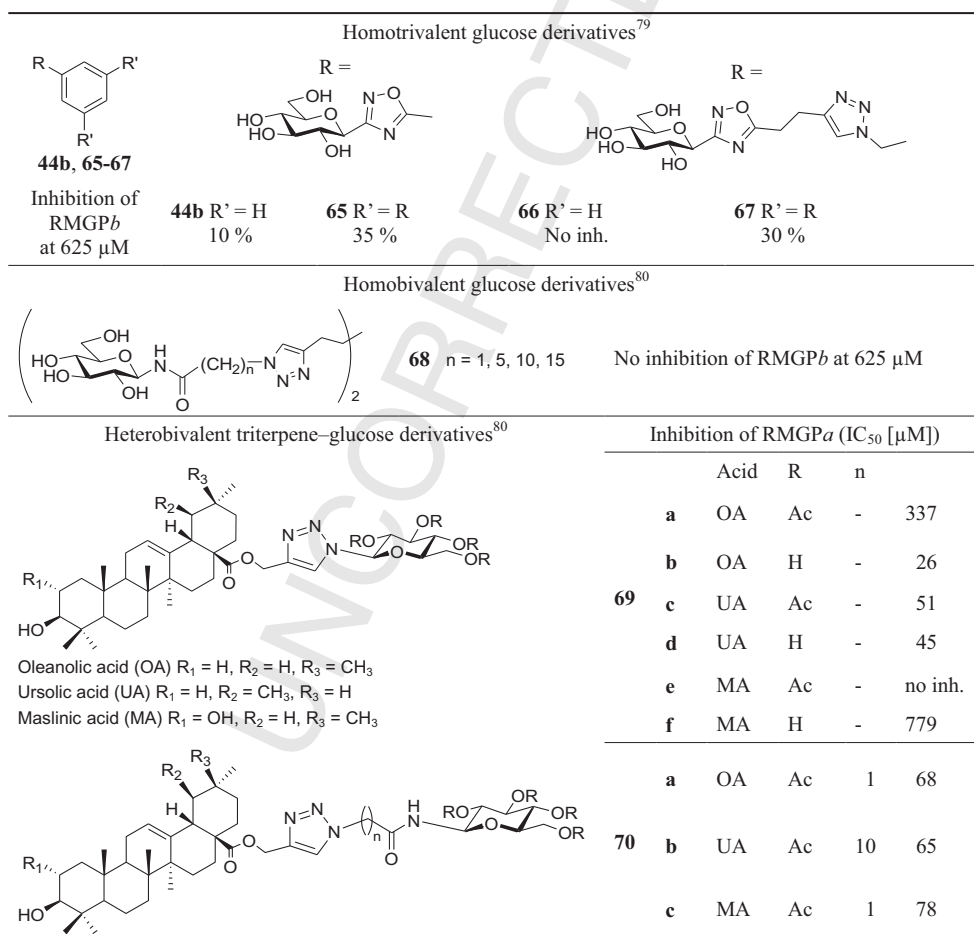


Fig. 12. Probing multivalency for the inhibition of rabbit muscle glycogen phosphorylase (RMGP).

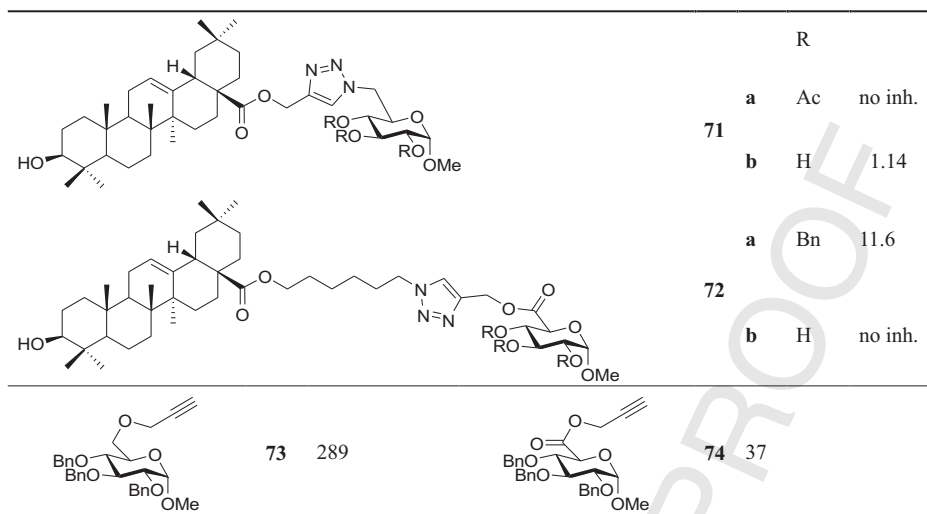


Fig. 13. Triterpene–glucose conjugates and protected monosaccharide derivatives [81] as inhibitors of rabbit muscle glycogen phosphorylase  $\alpha$  (RMGP $\alpha$ ) (IC<sub>50</sub> [ $\mu$ M]).

bind to an active site of GP. It was found that the homotrivalent derivatives **65** and **67** had slightly better inhibitory activity than the corresponding monovalent compounds **44b** and **66**, respectively. Homobivalent compounds **68** were made by CuAAC from *N*- $\omega$ -azidoalkanoyl- $\beta$ -D-glucopyranosylamines and 1,7-octadiyne, but had no effect on the enzyme [80].

Potentially heterobivalent compounds were designed by tethering pentacyclic triterpenes and D-glucose derivatives [80]: C-28 propargyl esters of oleanolic, ursolic, or maslinic acids were coupled by CuAAC with  $\beta$ -D-glucopyranosyl azide and *N*- $\omega$ -azidoalkanoyl- $\beta$ -D-glucopyranosylamines to give compounds **69** and **70**, respectively. Derivatives with both per-*O*-acetylated and unprotected sugar parts were tested against GP and the best inhibitors are shown in Fig. 12. Micromolar inhibitors could be identified among both protected and unprotected glucose derivatives, and also the triterpene part and, in some cases, the linker length had a bearing on the efficiency of the compounds.

Oleanolic acid and D-glucose were also conjugated via C-6 ethers and glucuronic esters in several ways [81]. Most efficient compounds are **71b** and **72a** (Fig. 13) interestingly with an unprotected and a protected sugar unit, respectively. Based on molecular docking, **71b** was proposed to bind at the allosteric site of GP. Per-*O*-benzylated precursor sugars **73** and **74** containing a propargyl group also exhibited inhibition of GP, the latter in the low micromolar range.

#### 4. Conclusion

Extensive synthetic efforts supported by crystallographic studies on enzyme–inhibitor complexes have resulted in several new types of glucose analogue inhibitors of GP. Among them, *N*-acyl-*N'*- $\beta$ -D-glucopyranosyl ureas, glucopyranosylidene-spiro-oxathiazolines and -isoxazolines represent novel scaffolds which, in the

presence of suitable substituents, exhibit nanomolar efficiency. Further increase in the binding strength of glucose analogues may be expected from a better exploitation of interactions of the molecules in the  $\beta$ -channel of the enzyme. This will need a strong collaboration between synthetic and computational chemists, as well as crystallographers and biochemists. Nevertheless, due to the extremely high flexibility of the catalytic site of GP, synthesis and enzyme kinetic study of a large number of compounds will be inevitable.

#### 5. Note added in proof

While this manuscript was under review, an interesting paper appeared on enzyme kinetic and crystallographic investigations of a series of 3-deoxy-3-fluoro- $\beta$ -D-glucopyranosyl pyrimidine derivatives [82].

#### Uncited references

[21–26,] [29–37], [48–51], [54,55,58], [74,78].

#### Acknowledgement

This work was supported by the Hungarian Scientific Research Fund (OTKA CK 77712) and an ongoing bilateral project of the Hungarian Academy of Sciences and Centre national de la recherche scientifique (PICS 4576). Sincere thanks are due to coworkers in the author's laboratory (V. Nagy, M. Tóth, K. Czifrák, Zs. Hadady, N. Felföldi, E. Berzsényi, É. Bokor, B. Kónya, S. Kun, L. Kóder, C. Hüse, K. Telepó) participating in the syntheses of the compounds, as well as P. Gergely and T. Docsa (Debrecen) for the kinetic studies. Cooperations with J.-P. Praly and S. Vidal (Lyon), H.-B. Sun (Nanjing), D. Postel (Amiens) in the field of organic synthesis, N.-G. Oikonomakos and E.-D. Chrysinia (Athens, protein crystallography, enzyme kinetics), I. Tvaroška

451 (Bratislava, computational chemistry) continuously gave  
452 new impetus and ideas for the work. These collaborations  
453 were supported by the Hungarian Academy of Sciences, the  
454 National Office for Research and Technology and the  
455 relevant funding organizations of the partner countries.

456

## References

457 [1] S.L. Schreiber, T.M. Kapoor, G. Wess, *Chemical biology – from small*  
458 *molecules to systems biology and drug design*, Wiley-VCH, Weinheim,  
459 2007.  
460 [2] H.P. Nestler, in : S.L. Schreiber, T.M. Kapoor, G. Wess (Eds.), *Chemical*  
461 *biology – from small molecules to systems biology and drug design*,  
462 Wiley-VCH, Weinheim, 2007, p. 825.  
463 [3] J.L. Treadway, P. Mendys, D.J. Hoover, *Expert Opin. Investig. Drugs* 10  
464 (2001) 439.  
465 [4] N.G. Oikonomakos, *Curr. Protein Pept. Sci.* 3 (2002) 561.  
466 [5] R. Kurukulasuriya, J.T. Link, D.J. Madar, Z. Pei, J.J. Rohde, S.J. Richards, A.J.  
467 Souers, B.G. Szczepankiewicz, *Curr. Med. Chem.* 10 (2003) 99.  
468 [6] R. Kurukulasuriya, J.T. Link, D.J. Madar, Z. Pei, S.J. Richards, J.J. Rohde, A.J.  
469 Souers, B.G. Szczepankiewicz, *Curr. Med. Chem.* 10 (2003) 123.  
470 [7] S.A. Ross, E.A. Gulve, M.H. Wang, *Chem. Rev.* 104 (2004) 1255.  
471 [8] L. Agius, *Best Pract. Res. Clin. Endocrinol. Metab.* 21 (2007) 587.  
472 [9] T. Barf, *Mini Rev. Med. Chem.* 4 (2004) 897.  
473 [10] B.R. Henke, S.M. Sparks, *Chem. Rev. Med. Chem.* 6 (2006) 845.  
474 [11] N.G. Oikonomakos, L. Somsák, *Curr. Opin. Investig. Drugs* 9 (2008) 379.  
475 [12] L. Somsák, K. Czifrák, M. Tóth, É. Bokor, E.D. Chrysiná, K.M. Alexacou,  
476 J.M. Hayes, C. Tiraidis, E. Lazoura, D.D. Leonidas, S.E. Zographos, N.G.  
477 Oikonomakos, *Curr. Med. Chem.* 15 (2008) 2933.  
478 [13] L. Somsák, V. Nagy, Z. Hadady, T. Docsa, P. Gergely, *Curr. Pharm. Des.* 9  
479 (2003) 1177.  
480 [14] L. Somsák, V. Nagy, Z. Hadady, N. Felföldi, T. Docsa, P. Gergely, in : A.B.  
481 Reitz, C.P. Kordik, M.I. Choudhary, A.U. Rahman (Eds.), *Frontiers in*  
482 *medicinal chemistry*, Bentham, 2005, p. 253.  
483 [15] M. Board, M. Hadwen, L.N. Johnson, *Eur. J. Biochem.* 228 (1995) 753.  
484 [16] M. Gregoriou, M.E.M. Noble, K.A. Watson, E.F. Garman, T.M. Krülle, C.  
485 Fuente, G.W.J. Fleet, N.G. Oikonomakos, L.N. Johnson, *Protein Sci.* 7  
486 (1998) 915.  
487 [17] C.J.F. Bichard, E.P. Mitchell, M.R. Wormald, K.A. Watson, L.N. Johnson,  
488 S.E. Zographos, D.D. Koutra, N.G. Oikonomakos, G.W.J. Fleet, *Tetrahedron*  
489 *Lett.* 36 (1995) 2145.  
490 [18] T.M. Krülle, C. Fuente, K.A. Watson, M. Gregoriou, L.N. Johnson, K.E.  
491 Tsitsanou, S.E. Zographos, N.G. Oikonomakos, G.W.J. Fleet, *Synlett*  
492 (1997) 211.  
493 [19] C. Fuente, T.M. Krülle, K.A. Watson, M. Gregoriou, L.N. Johnson, K.E.  
494 Tsitsanou, S.E. Zographos, N.G. Oikonomakos, G.W.J. Fleet, *Synlett*  
495 (1997) 485.  
496 [20] L. Somsák, V. Nagy, *Tetrahedron: Asymmetry* 11 (2000) 1719 [Corri-  
497 gendum 2247].  
498 [21] N.G. Oikonomakos, M. Kontou, S.E. Zographos, H.S. Tsitoura, L.N. John-  
499 son, K.A. Watson, E.P. Mitchell, G.W.J. Fleet, J.C. Son, C.J.F. Bichard, D.D.  
500 Leonidas, K.R. Acharya, Eur. J. Drug Metab. Pharmacokinet. (1994) 185.  
501 [22] L.N. Johnson, K.R. Acharya, M.D. Jordan, P.J.J. McLaughlin, *Mol. Biol.* 211  
502 (1990) 645.  
503 [23] K.A. Watson, E.P. Mitchell, L.N. Johnson, G. Cruciani, J.C. Son, C.J.F.  
504 Bichard, G.W.J. Fleet, N.G. Oikonomakos, M. Kontou, S.E. Zographos,  
505 *Acta Crystallogr. D51* (1995) 458.  
506 [24] K.A. Watson, E.P. Mitchell, L.N. Johnson, J.C. Son, C.J.F. Bichard, M.G.  
507 Orchard, G.W.J. Fleet, N.G. Oikonomakos, D.D. Leonidas, M. Kontou, A.  
508 Papageorgiou, *Biochemistry* 33 (1994) 5745.  
509 [25] E. Ósz, L. Somsák, L. Szilágyi, L. Kovács, T. Docsa, B. Tóth, P. Gergely,  
510 *Bioorg. Med. Chem. Lett.* 9 (1999) 1385.  
511 [26] L. Somsák, L. Kovács, M. Tóth, E. Ósz, L. Szilágyi, Z. Györgydeák, Z. Dinya,  
512 T. Docsa, B. Tóth, P.J. Gergely, *Med. Chem.* 44 (2001) 2843.  
513 [27] L. Kovács, E. Ósz, V. Domokos, W. Holzer, Z. Györgydeák, *Tetrahedron*  
514 57 (2001) 4609.  
515 [28] Z. Györgydeák, J. Thiem, *Adv. Carbohydr. Chem. Biochem.* 60 (2006)  
516 103.  
517 [29] E. Anagnostou, M.N. Kosmopoulou, E.D. Chrysiná, D.D. Leonidas, T.  
518 Hadjiloi, C. Tiraidis, S.E. Zographos, Z. Györgydeák, L. Somsák, T. Docsa,  
519 P. Gergely, F.N. Kolisis, N.G. Oikonomakos, *Bioorg. Med. Chem.* 14  
520 (2006) 181.  
521 [30] E.I. Petsalakis, E.D. Chrysiná, C. Tiraidis, T. Hadjiloi, D.D. Leonidas, N.G.  
522 Oikonomakos, U. Aich, B. Varghese, D. Loganathan, *Bioorg. Med. Chem.*  
523 14 (2006) 5316.  
524 [31] K. Czifrák, Z. Hadady, T. Docsa, P. Gergely, J. Schmidt, L.A. Wessjohann,  
525 L. Somsák, *Carbohydr. Res.* 341 (2006) 947.

[32] T. Hadjiloi, C. Tiraidis, E.D. Chrysiná, D.D. Leonidas, N.G. Oikonomakos,  
P. Tsipos, T. Gimisis, *Bioorg. Med. Chem.* 14 (2006) 3872.  
[33] K.M. Alexacou, J.M. Hayes, C. Tiraidis, S.E. Zographos, D.D. Leonidas, E.D.  
Chrysiná, G. Archontis, N.G. Oikonomakos, J.V. Paul, B. Varghese, D.  
Loganathan, *Proteins: Struct. Funct. Bioinf.* 71 (2008) 1307.  
[34] Z. Györgydeák, Z. Hadady, N. Felföldi, A. Krakomperger, V. Nagy, M.  
Tóth, A. Brunyánszky, T. Docsa, P. Gergely, L. Somsák, *Bioorg. Med.  
Chem.* 12 (2004) 4861.  
[35] E.D. Chrysiná, É. Bokor, K.M. Alexacou, M.D. Charavgi, G.N. Oikonomako-  
s, S.E. Zographos, D.D. Leonidas, N.G. Oikonomakos, L. Somsák,  
*Tetrahedron: Asymmetry* 20 (2009) 733.  
[36] Z. Czákó, L. Juhász, Á. Kenéz, K. Czifrák, L. Somsák, T. Docsa, P. Gergely, S.  
Antus, *Bioorg. Med. Chem.* 17 (2009) 6738.  
[37] E.D. Chrysiná, M.N. Kosmopoulou, R. Kardakaris, N. Bischler, D.D.  
Leonidas, T. Kannan, D. Loganathan, N.G. Oikonomakos, *Bioorg. Med.  
Chem.* 13 (2005) 765.  
[38] G. Remy, L. Cottier, G. Descotes, *Can. J. Chem. Rev. Can. Chim.* 58 (1980)  
2660.  
[39] G. Descotes, *Bull. Soc. Chim. Belg.* 91 (1982) 973.  
[40] B. Helferich, W. Kosche, *Chem. Ber.* 59 (1926) 69.  
[41] I. Pintér, J. Kovács, G. Tóth, *Carbohydr. Res.* 273 (1995) 99.  
[42] Nagy, V. PhD Thesis, University of Debrecen–University of Lyon,  
2003.  
[43] N.G. Oikonomakos, M. Kosmopolou, S.E. Zographos, D.D. Leonidas, L.  
Somsák, V. Nagy, J.P. Praly, T. Docsa, B. Tóth, P. Gergely, *Eur. J. Biochem.*  
269 (2002) 1684.  
[44] Y. Ichikawa, Y. Matsukawa, T. Nishiyama, M. Isobe, *Eur. J. Org. Chem.* Q4  
552 (2004) 586.  
[45] L. Somsák, N. Felföldi, B. Kónya, C. Hüse, K. Telepó, É. Bokor, K. Czifrák,  
*Carbohydr. Res.* 343 (2008) 2083.  
[46] L.M. Likhoshherstov, O.S. Novikova, V.N. Shibaev, *Dokl. Chem.* 383  
556 (2002) 89.  
[47] N. Felföldi, M. Tóth, E.D. Chrysiná, M.D. Charavgi, K.M. Alexacou, L.  
Somsák, *Carbohydr. Res.* 345 (2010) 208.  
[48] N. Felföldi, PhD Thesis, University of Debrecen, 2009.  
[49] S.S. Bishr, S. Fatima, A.K. Tamrakar, N. Rahuja, N. Jaiswal, A.K. Srivastava,  
R.P. Tripathi, *Bioorg. Med. Chem. Lett.* 19 (2009) 2699.  
[50] Czifrák, K., Somsák, L. Unpublished results.  
[51] É. Bokor, T. Docsa, P. Gergely, L. Somsák, *Bioorg. Med. Chem.* 18 (2010)  
1171.  
[52] R. Bognár, L. Somogyi, L. Szilágyi, Z. Györgydeák, *Carbohydr. Res.* 5  
567 (1967) 320.  
[53] A.C. Tenchiu (Deleanu), I.D. Kostas, D. Kovala-Demertzi, A. Terzis,  
*Carbohydr. Res.* 344 (2009) 1352.  
[54] Szilágyi, L., Somsák, L., Docsa, T., Gergely, P. unpublished results.  
[55] A.C. Deleanu, I.D. Kostas, I. Liratzis, K.M. Alexacou, D.D. Leonidas, S.E.  
Zographos, N.G. Oikonomakos, 4th Central European Conference  
Chemistry towards Biology, Dobogókő, Hungary, September 8–11,  
(2008), p. 80 [Book of Abstracts].  
[56] Y.L. Angell, K. Burgess, *Chem. Soc. Rev.* 36 (2007) 1674.  
[57] M. Meldal, C.W. Tornøe, *Chem. Rev.* 108 (2008) 2952.  
[58] C. Cismaş, T. Hadjiloi, A. Pantzou, T. Gimisis, N.G. Oikonomakos, 13th  
European Carbohydrate Symposium, Bratislava, Slovakia, (2005), p. 141  
[Book of Abstracts].  
[59] Z. Hadady, M. Tóth, L. Somsák, *Arkivoc* (2004) 140.  
[60] M. Tóth, S. Kun, É. Bokor, M. Benlifa, G. Tallec, S. Vidal, T. Docsa, P.  
Gergely, L. Somsák, J.P. Praly, *Bioorg. Med. Chem.* 17 (2009) 4773.  
[61] M. Tóth, L. Somsák, *Carbohydr. Res.* 338 (2003) 1319.  
[62] M. Benlifa, S. Vidal, D. Gueyraud, P.G. Goekjian, M. Msaddek, J.P. Praly,  
*Tetrahedron Lett.* 47 (2006) 6143.  
[63] M. Benlifa, S. Vidal, B. Fenet, M. Msaddek, P.G. Goekjian, J.P. Praly,  
A. Brunyánszky, T. Docsa, P. Gergely, *Eur. J. Org. Chem.* (2006)  
4242.  
[64] E.D. Chrysiná, M.N. Kosmopolou, C. Tiraidis, R. Kardarakis, N. Bischler,  
D.D. Leonidas, Z. Hadady, L. Somsák, T. Docsa, P. Gergely, N.G.  
Oikonomakos, *Protein Sci.* 14 (2005) 873.  
[65] G.A. Patani, E.J. LaVoie, *Chem. Rev.* 96 (1996) 3147.  
[66] L.M.A. Lima, E.J. Barreiro, *Curr. Med. Chem.* 12 (2005) 23.  
[67] L. He, Y.Z. Zhang, M. Tanoh, G.R. Chen, J.P. Praly, E.D. Chrysiná, C.  
Tiraidis, M. Kosmopoulou, D.D. Leonidas, N.G. Oikonomakos, *Eur. J.  
Org. Chem.* (2007) 596.  
[68] P. Bertus, J. Szymoniak, E. Jeanneau, T. Docsa, P. Gergely, J.P. Praly, S.  
Vidal, *Bioorg. Med. Chem. Lett.* 18 (2008) 4774.  
[69] L. Somsák, V. Nagy, S. Vidal, K. Czifrák, E. Berzsényi, J.P. Praly, *Bioorg.  
Med. Chem. Lett.* 18 (2008) 5680.  
[70] V. Nagy, S. Vidal, M. Benlifa, E. Berzsényi, C. Teilhet, K. Czifrák, G. Batta,  
T. Docsa, P. Gergely, L. Somsák, J.P. Praly, *Bioorg. Med. Chem.* 17 (2009)  
5696.  
[71] J.P. Praly, R. Faure, B. Joseph, L. Kiss, P. Rollin, *Tetrahedron* 50 (1994)  
6559.

526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605



- 606 [72] M. Tóth, L. Somsák, J. Chem. Soc., Perkin Trans. 1 1 (2001) 942. 617  
607 [73] M. Tóth, K.E. Kövér, A. Bényei, L. Somsák, Org. Biomol. Chem. 1 (2003) 618  
608 4039. 619  
609 [74] M. Benltifa, J.M. Hayes, S. Vidal, D. Gueyrard, P.G. Goekjian, J.P. Praly, G. 620  
610 Kizilis, C. Tiraidis, K.M. Alexacou, E.D. Chrysina, S.E. Zographos, D.D. 621  
611 Leonidas, G. Archontis, N.G. Oikonomakos, Bioorg. Med. Chem. 17 622  
612 (2009) 7368. 623  
613 [75] V. Nagy, K. Czifrák, A. Bényei, L. Somsák, Carbohydr. Res. 344 (2009) 921. 624  
614 [76] K. Czifrák, L. Somsák, Carbohydr. Res. 344 (2009) 269. 625  
615 [77] M. Lopez, N. Drillaud, L.F. Bornaghi, S.A.J. Poulsen, Org. Chem. 74 (2009) 626  
616 2811. 627  
[78] E.D. Chrysina, N.G. Oikonomakos, S.E. Zographos, M.N. Kosmopoulou, 617  
N. Bischler, D.D. Leonidas, L. Kovács, T. Docsa, P. Gergely, L. Somsák, 618  
Biocatal. Biotransform. 21 (2003) 233. 619  
[79] S. Cecioni, O.A. Argintaru, T. Docsa, P. Gergely, J.P. Praly, S. Vidal, New J. 620  
Chem. 33 (2009) 148. 621  
[80] K. Cheng, J. Liu, X. Liu, H. Li, H. Sun, J. Xie, Carbohydr. Res. 344 (2009) 841. 622  
[81] K. Cheng, J. Liu, H. Sun, É. Bokor, K. Czifrák, B. Kónya, M. Tóth, T. Docsa, P. 623  
Gergely, L. Somsák, New J. Chem. 34 (2010) 1450. 624  
[82] V.G. Tsirkone, E. Tsoukala, C. Lamprakis, S. Manta, J.M. Hayes, V.T. 625  
Skamnaki, C. Drakou, S.E. Zographos, D. Komiotis, D.D. Leonidas, Bioorg. 626  
Med. Chem. 18 (2010) 3413. 627  
628

UNCORRECTED PROOF