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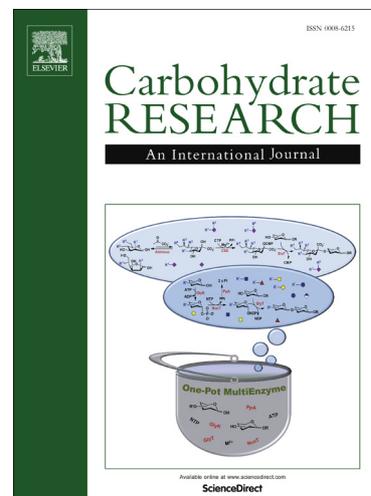
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Synthesis of *C*-xylopyranosyl- and xylopyranosylidene-spiro-heterocycles as potential inhibitors of glycogen phosphorylase

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Abstract

New derivatives of D-xylose with aglycons of the most efficient glucose derived inhibitors of glycogen phosphorylase were synthesized to explore the specificity of the enzyme towards the structure of the sugar part of the molecules. Thus, 2-(β -D-xylopyranosyl)benzimidazole and 3-substituted-5-(β -D-xylopyranosyl)-1,2,4-triazoles were obtained in multistep procedures from *O*-perbenzoylated β -D-xylopyranosyl cyanide. Cycloadditions of nitrile-oxides and *O*-peracetylated *exo*-xylal obtained from the corresponding β -D-xylopyranosyl cyanide furnished xylopyranosylidene-spiro-isoxazoline derivatives. Oxidative ring closure of *O*-peracetylated β -D-xylopyranosyl-thiohydroximates prepared from 1-thio- β -D-xylopyranose and nitrile-oxides gave xylopyranosylidene-spiro-oxathiazoles. The fully deprotected test compounds were assayed against rabbit muscle glycogen phosphorylase *b* to show moderate inhibition for 3-(2-naphthyl)-5-(β -D-xylopyranosyl)-1,2,4-triazole (IC₅₀ = 0.9 mM) only.

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Keywords

C-Glycosyl heterocycle; Glycosylidene-spiro-heterocycle; *exo*-Glycal; Xylose derivative;
Benzimidazole; 1,2,4-Triazole; Spiro-isoxazoline; Spiro-1,4,2-oxathiazole; Glycogen
phosphorylase; Inhibitor.

1. Introduction

1 The quest for inhibitors of glycogen phosphorylases (GPs) has been based on and fuelled
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3 by the potential application of such compounds as medication in type II *diabetes mellitus*¹⁻³
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5 and also as possible therapeutic means in other diseased states like myocardial^{4,5} and
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7 cerebral^{6,7} ischemias and tumors.⁸⁻¹¹
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11 A large variety of compounds targeting one of the six binding sites of GP (catalytic,
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13 inhibitor, allosteric, new allosteric, storage, and benzimidazole sites) have been developed to
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15 reach the nanomolar range in their inhibitory efficiency.^{3,12} Catalytic site inhibitors are almost
16
17 exclusively glucose derivatives¹³ which have been designed and studied following the
18
19 observation that both anomeric forms of D-glucose (**A** and **B** in Chart 1) are modest inhibitors
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21 of GP.¹⁴ Early inhibitor design resulted in glucopyranosylidene-spiro-hydantoin **C** and **D**
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23 with low micromolar inhibition constants.^{15,16} Most efficient representatives of *N*-
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25 glucopyranosyl-1,2,3-triazoles^{17,18} **E** and *C*-glucopyranosyl-benzimidazoles¹⁹⁻²¹ **F** proved
26
27 similarly or somewhat less effective than the hydantoin. Among the recently designed and
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29 synthesized 5- β -D-glucopyranosyl-3-substituted-1,2,4-triazoles submicromolar inhibitors of
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31 GP (e. g. **G**) were found.^{22,23} Best compounds in series of other types of anomeric spirocycles
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33 like isoxazolines²⁴ (e. g. **H**) and oxathiazoles^{25,26} (e. g. **I**) showed inhibition approaching the
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35 low nanomolar range. To explain the strong binding of these compounds extensive
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37 interactions with the so-called β -channel* of the enzyme were invoked besides the ideal fit of
38
39 the sugar moiety in the catalytic site.^{12,13} Thus, the increasing binding strength must largely be
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41 attributed to the aglycon part of the molecules.
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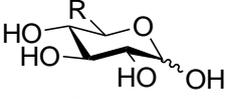
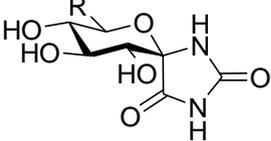
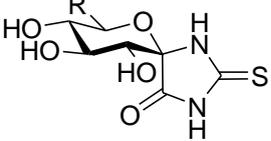
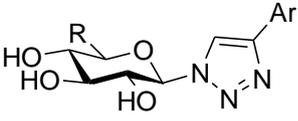
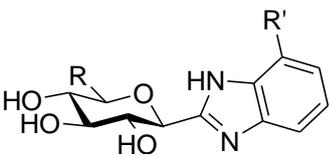
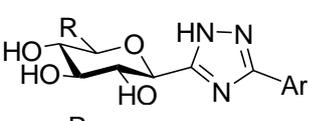
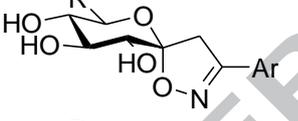
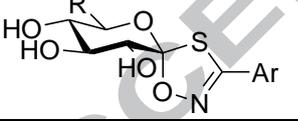
51 Investigations into the specificity of GP towards various monosaccharides revealed that
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53 changes in the sugar configuration or constitution resulted in a significant decrease of the
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58 * The β -channel of GPs is an empty space next to the active site in the direction of the β -substituent of the bound
59 D-glucose surrounded by amino acid side chains of both polar and apolar character.
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1 inhibition: e. g. D-xylose (**J**) proved a ~13-60-fold weaker inhibitor in comparison to the D-
2 glucose anomers **A** and **B**.²⁷ Since the efficiency of the glucose derived inhibitors depended to
3 a large extent on the fit of the aglycon in the β -channel, the D-*xylo* configured analogues of
4 the best inhibitors were time to time synthesized and tested against GP to check if the
5 interactions of the aglycon might overbalance the worse binding of the 'truncated' glycon. Up
6 to now xylopyranosylidene-spiro-hydantoin¹⁶ **K** and **L** as well as *N*-(β -D-xylopyranosyl)-
7 1,2,3-triazoles (e. g. **M**) together with similar derivatives of 5-thio-xylose and the related
8 cyclic sulfoxides and sulfones²⁸ were studied, however, showed no significant effect against
9 RMGP*b*.
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21 In this paper we report on the synthesis and enzymatic evaluation of xylose derived
22 analogues **N-Q** of the best glucose based inhibitors of rabbit muscle glycogen phosphorylase
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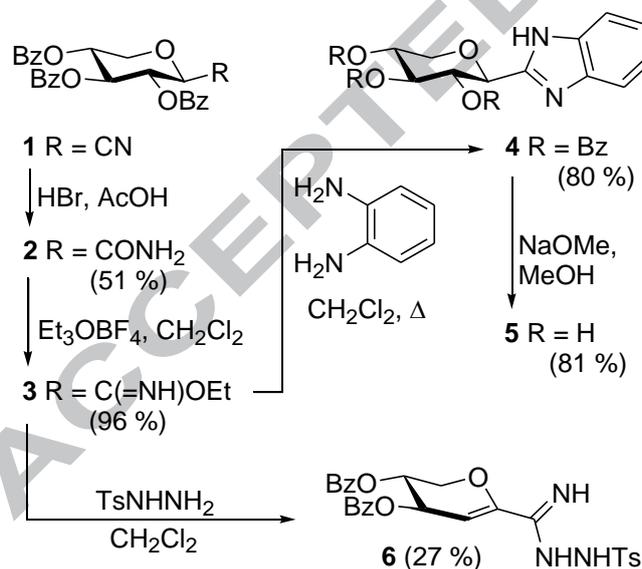
Chart 1. Selected inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGP*b*, K_i [μ M])

	R = CH ₂ OH		R = H	
	A α	1700 ¹⁴		
	B β	7400 ¹⁴	J	>100 000 ²⁷
	C	3.1 ¹⁵ 4.2 ¹⁶	K	11 500 ¹⁶
	D	5.1 ¹⁶	L	>10 000 ¹⁶
	E	Ar = 2-naphthyl 16 ¹⁷ 36 ¹⁸	M	Ar = 2-naphthyl No inhibition at 625 μ M ²⁸
	F	R' = H 9 ²⁰ 11 ¹⁹ R' = Me 2.8 ²¹	N	
	G	Ar = 2-naphthyl 0.41 ^{22,23}	O	target compounds of this work with various Ar groups
	H	Ar = 2-naphthyl 0.63 ²⁴	P	
	I	Ar = 2-naphthyl 0.16 ^{25,26}	Q	

2. Results and Discussion

For the preparation of the desired *C*-xylosyl benzimidazole **N**, our recently published reaction sequence was applied.²¹ Thus, 2,3,4-tri-*O*-benzoyl- β -D-xylopyranosyl cyanide²⁹ (**1**, Scheme 1) was hydrated to anhydro-aldonamide **2** which, on treatment by Et₃O·BF₄ gave ethyl imidate **3**. Reaction of **3** with 1,2-diamino-benzene furnished the protected benzimidazole **4** which was *O*-debenzoylated under Zemplén conditions³⁰ to give the test compound **5**. Structure elucidation of the compounds was straightforward by NMR methods, and it is to be noted that line broadening of some resonances in the ¹³C spectra, due to fast proton exchange of the two nitrogens, was observed similarly to earlier experiences.²¹

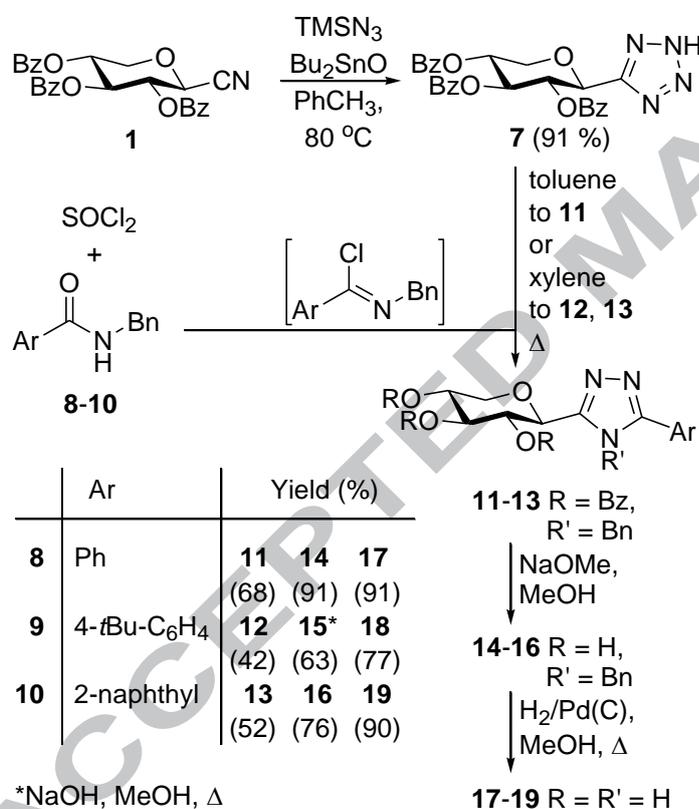
Next, to get an intermediate for the preparation of *C*-xylosyl-1,2,4-triazoles **O**, imidate **3** was reacted with tosylhydrazine,^{22,31} however, instead of the expected *N*^l-tosyl-(*C*-xylopyranosyl)formamidrazone only its benzoic acid elimination product **6** could be isolated.



Scheme 1. Some transformations starting from

O-perbenzoylated β -D-xylopyranosyl cyanide **1**.

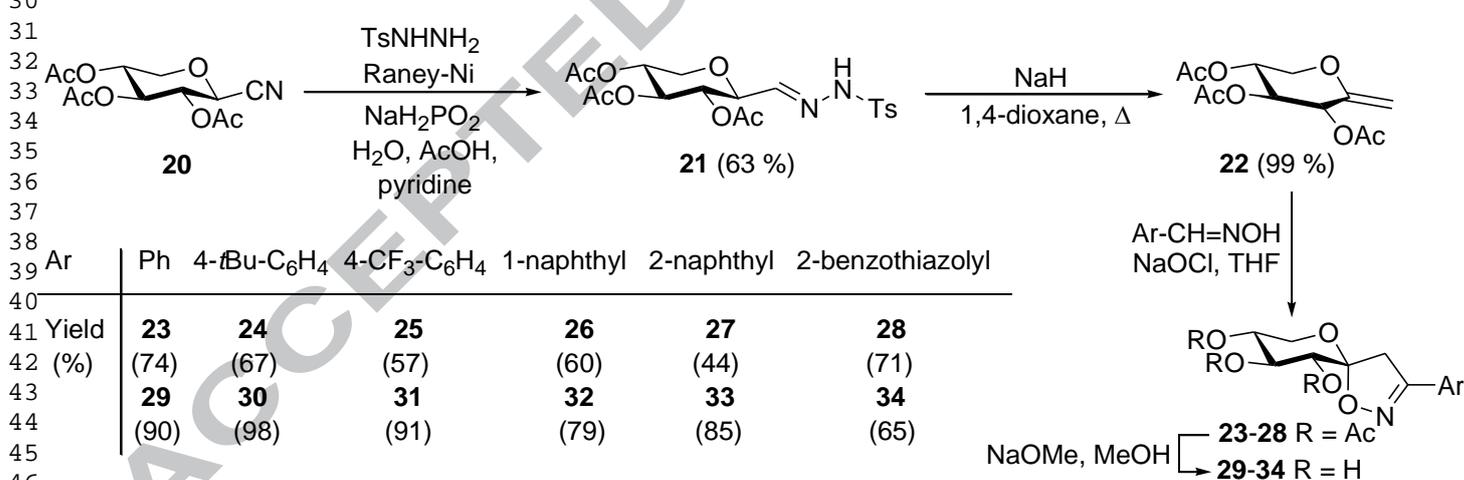
Therefore, we turned to an alternative route²³ (Scheme 2) and, to this end, **1** was transformed to tetrazole* **7** by $\text{TMSN}_3\text{-Bu}_2\text{SnO}$.³³ Reactions of **7** with non-purified *N*-benzyl-arenecarboximidoyl chlorides obtained from the corresponding carboxamides **8-10** gave the *O*-perbenzoylated *N*-benzyl-1,2,4-triazoles **11-13**. These compounds were first *O*-deprotected by the Zemplén protocol³⁰ or NaOH in MeOH to give **14** and **16**, as well as **15**, respectively, followed by catalytic hydrogenation to remove the *N*-benzyl protection to yield the test compounds **17-19**.



Scheme 2. Synthesis of 3-(β-D-xylopyranosyl)-5-substituted-1,2,4-triazoles **17-19**.

* The analogous *O*-peracetylated 5-(β-D-xylopyranosyl)tetrazole is known in the literature.³²

For the preparation of xylopyranosylidene-spiro-isoxazolines **P**, *O*-peracetylated β -D-xylopyranosyl cyanide³⁴ **20** was transformed to the corresponding anhydro-aldose tosylhydrazone **21** by applying our published method.^{35,36} Bamford-Stevens reaction³⁷ of **21** was performed by thermal decomposition of the intermediate salt^{35,38} to give *exo*-xylal **22** in excellent yield. 1,3-Dipolar cycloaddition of **22** and nitrile-oxides,³⁹ generated *in situ* by bleach oxidation of the corresponding aromatic aldoximes,⁴⁰ gave stereoselectively the protected spiro-isoxazolines **23-28**, which were *O*-deacetylated under Zemplén conditions³⁰ to obtain the test compounds **29-34**. The configuration of the spiro-carbon was proven by Nuclear Overhauser Effect (NOE) difference spectra showing spatial vicinity of the isoxazoline methylene protons with H-2' (but not with H-3' and H-5') of the sugar ring. Similar exclusive stereoselectivity was observed in the formation of the glucose-derived isoxazolines²⁴ (Chart 1, **H**).



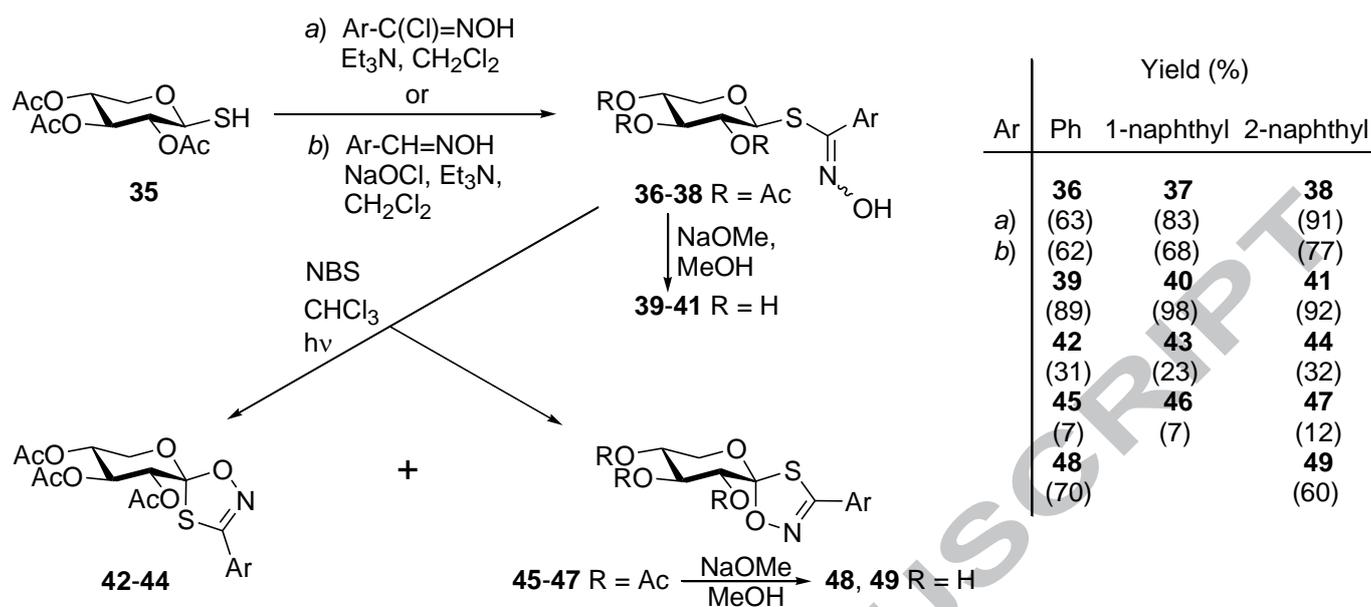
Scheme 3. Synthesis of D-xylopyranosylidene-spiro-isoxazolines **29-34**.

Synthesis of the xylopyranosylidene-spiro-oxathiazoles **Q** was started by the conversion of *O*-peracetylated 1-thio- β -D-xylopyranose⁴¹ **35** to *S*- β -D-xylopyranosyl thiohydroximates **36-38** (Scheme 4). One of the generally applied methods to get *S*-glycosyl thiohydroximates⁴²

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is the reaction of the corresponding 1-thio-sugars with nitrile-oxides. In addition to the above mentioned oxidative processes, a frequently used way to obtain nitrile-oxides *in situ* is the base-induced dehydrohalogenation of hydroximoyl halides which are isolable after halogenation (by e. g. Cl₂, NCS, or NBS) of aldoximes.³⁹ Because of the sensitivity of thiols to oxidation, nitrile oxides were generated from hydroximoyl chlorides by Et₃N (method *a* in Scheme 4) in the presence of **35**. A recently reported procedure to perform the chlorination and HCl elimination in one continuous operation (method *b*), suggested to be superior especially for the preparation of glycosyl thiohydroximates,⁴³ was also studied. Although both methods gave good yields of the expected products **36-38**, in our hands the conventional dehydrochlorination of the isolated hydroximoyl chlorides gave better results (compare yields for methods *a* and *b* in Scheme 4). Thiohydroximates **36-38** were deacetylated by the Zemplén method³⁰ to give the test compounds **39-41**.

Ring closure of the thiohydroximates was effected by NBS under irradiation as reported for the preparation of several glycoenzyme inhibitors of this spiro-oxathiazole type.^{26,44,45} Expectedly, the formation of two spiro epimers was observed, however, in contrast to earlier findings with hexopyranose derived compounds where the anomeric configuration of the thiohydroximate was retained in the major cyclised product, in these reactions compounds of the inverted configuration **42-44** were isolated as the main products. The minor products **45** and **47** having the same spiro configuration (1'*S*) as the glucose-derived inhibitors **I** in Chart 1 were deacetylated under Zemplén conditions³⁰ to obtain the test compounds **48** and **49**.



Scheme 4. Synthesis of D-xylopyranosylidene-spiro-oxathiazoles **42-49**.

Structural elucidation of the xylopyranosylidene-spiro-oxathiazoles **42-47** was based on comparisons of their NMR spectral and optical rotation data to those of the *D-gluco* counterparts where at least for one compound (**I** Ar = Ph in Chart 1) the structure was determined by X-ray crystallography.⁴⁴ For **42-47** the presence of a xylopyranose ring in the ⁴C₁ conformation was deduced from the vicinal coupling constants in the ¹H NMR spectra. To establish the configuration of the spiro centre, characteristic differences observed for the 1'*R* and 1'*S* epimers of the *D-gluco* derivatives (Table 1, **50, 51**, and **52, 53**, respectively) were sought for in the data of the *D-xylo* compounds. Thus, for the *D-gluco* configured epimeric pairs **50, 51**, and **52, 53** the change of the spiro configuration had practically no influence on the chemical shifts of the H-2' and H-4' protons, but H-3' and H-5' showed ~0.5 and ~0.3 ppm difference, respectively, depending on the presence of an axial S vs. O atom in the spiro-heterocycle. The same tendency was also present in the chemical shift values of the respective protons of the *D-xylo* derivatives **42-44** vs. **45-47**. The chemical shifts for the spiro carbons were consistently higher for the 1'*R* than for the 1'*S* compounds in both series. Finally, the

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1'*R* derivatives were significantly more dextrorotatory than the 1'*S* compounds. The spiro configurations were assigned by utilizing these coincidences.

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Table 1. Selected spectral data for spiro-oxathiazoles of D-glucose and D-xylose


Ar (Compound)	R = H			R = CH ₂ OAc*		R = H			R = CH ₂ OAc*	
	(42)	(43)	(44)	(50)	(51)	(45)	(46)	(47)	(52)	(53)
H-2'	5.52	5.58	5.56	5.60	5.66	5.56	5.59	5.60	5.63	5.67
H-3'	5.13	5.15	5.17	5.10	5.13	5.62	5.68	5.66	5.63	5.67
H-4'	5.07	5.10	5.11	5.27	5.29	5.12	5.14	5.15	5.27	5.29
H-5' _{ax}	3.79	3.85	3.83	4.10	4.18	4.04	4.11	4.07	4.42	4.51
H-5' _{eq}	4.19	4.28	4.22	-	-	4.00	4.06	4.02	-	-
C-1'	126.6	125.8	126.7	127.3	126.3	122.6	121.9	122.6	122.4	121.8
[α] _D	+178	+151	+182	+179	+99	+78	+73	+61	+53	+44

*Data taken from ref.⁴⁴

Enzymatic evaluation of the deprotected compounds against rabbit muscle glycogen phosphorylase *b* (RMGP*b*) was carried out as described before.¹⁶ All but one of the deprotected xylose derivatives had no inhibition at 625 μ M concentration. The only compound of the series having a moderate effect was 3-(2-naphthyl)-5-(β -D-xylopyranosyl)-1,2,4-triazole (**19**) with an IC₅₀ value of 900 μ M (calculated⁴⁶ K_i = 491 μ M). This inhibition is more than three orders of magnitude weaker than that of the *D*-gluco counterpart (**G** in Chart 1, K_i = 0.41 μ M). However, a comparison of the ratio of inhibitor constants for the *xylo*/*gluco* hydantoins (Chart 1, compounds **K/C** ~2800-3800), thiohydantoins (Chart 1, compounds **L/D** ~2300), and 3-(2-naphthyl)-1,2,4-triazoles (Chart 1, compounds **O**(= **19**)/**G** ~1200) shows a clear tendency in making the binding stronger by the aglycons which fit better in the β -channel. Although the findings reveal that the aglycons in these xylose derived compounds (provided that they indeed bind to the catalytic site of GP) still have no strong enough interactions to fully overcompensate the loss of the CH₂OH side chain of the sugar moiety, the above tendency may foreshadow much more efficient xylose-derived inhibitors of GP.

In conclusion, new *C*-xylopyranosyl benzimidazole and 1,2,4-triazoles as well as xylopyranosylidene-spiro-isoxazolines and -oxathiazoles were prepared by adapting procedures used for the syntheses of analogous glucose-derived inhibitors of glycogen phosphorylase. Evaluation of the compounds as inhibitors of rabbit muscle glycogen phosphorylase *b* showed very weak inhibition for 3-(2-naphthyl)-5-(β -D-xylopyranosyl)-1,2,4-triazole only, while all other compounds proved ineffective in a concentration of 625 μ M. These observations show that the aglycons rendering their glucose derivatives to nanomolar inhibitors, are not yet capable to completely override the effect of losing the side chain of the glucose moiety. Nevertheless, the increase in the binding strength of the xylose derivatives with the more efficient aglycons may predict strongly binding inhibitors derived from sugars other than glucose.

3. Experimental

3.1. General methods

Melting points were measured on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at rt. NMR spectra were recorded with a Bruker 360 (360/90 MHz for $^1\text{H}/^{13}\text{C}$) spectrometer. Chemical shifts are referenced to Me_4Si (^1H), or to the residual solvent signals (^{13}C). Microanalyses were performed on an Elementar Vario Micro cube instrument. ESI-MS spectra were measured with a Thermo Scientific LTQ XL spectrometer. TLC was performed on DC-Alurolle Kieselgel 60 F₂₅₄ (Merck) plates, visualized under UV light and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063-0.200 mm) was used. CH_2Cl_2 , CHCl_3 , toluene and *m*-xylene were distilled from P_4O_{10} and stored over 4 Å molecular sieves or sodium wires. MeOH was purified by distillation after refluxing for a couple of hours with magnesium turnings and iodine. 1,4-Dioxane was distilled from sodium benzophenone ketyl and stored over sodium wires. 2,3,4-Tri-*O*-benzoyl- β -D-xylopyranosyl cyanide²⁹ (**1**), *N*-benzyl-arenecarboxamides²³ (**8-10**), 2,3,4-tri-*O*-acetyl- β -D-xylopyranosyl-cyanide³⁴ (**20**), 2,3,4-tri-*O*-acetyl-1-thio- β -D-xylopyranose⁴¹ (**35**), arenecarbaldoximes,⁴⁷ and *N*-hydroxy-arenecarboximidoyl chlorides⁴⁷ were synthesized according to published procedures.

3.2. General procedure I for the Zemplén-deacylation³⁰

An *O*-acylated compound was dissolved in anhydrous MeOH (5 mL/100 mg, a few drops of CHCl_3 were added in case of incomplete dissolution) and a catalytic amount of a NaOMe solution (~1 M in MeOH) was added. The mixture was kept at rt and monitored by TLC (7:3 CHCl_3 -MeOH). After disappearance of the starting material the mixture was neutralized with a cation exchange resin Amberlyst 15 (H^+ form), then the resin was filtered off and the

1 solvent removed. The residue was purified either by column chromatography or by
2 crystallization.
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7 **3.3. General procedure II for the synthesis of 4-benzyl-3-(2',3',4'-tri-*O*-benzoyl- β -D-
8 xylopyranosyl)-5-substituted-1,2,4-triazoles (11-13)**
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10 An *N*-benzyl-arenecarboxamide²³ (**8-10**, 4.63 mmol, 3 equiv.) was dissolved in SOCl₂ (20
11 mL), and refluxed for 2 hours. After distilling off the excess of SOCl₂ under reduced pressure,
12 anhydrous toluene (20 mL) was evaporated from the residue. 5-(2,3,4-Tri-*O*-benzoyl- β -D-
13 xylopyranosyl)tetrazole (**7**, 1.54 mmol, 1 equiv.) and anhydrous toluene or *m*-xylene (20 mL)
14 were added, the mixture was heated to reflux temperature, and the reaction was monitored by
15 TLC (1:1 EtOAc-hexane). After total consumption of the tetrazole the solvent was removed
16 and the residue was purified by column chromatography.
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31 **3.4. General procedure III for the removal of benzyl protecting groups**
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33 A benzylated compound (0.5 mmol) was dissolved in anhydrous MeOH (25 mL), 10% Pd(C)
34 (20 mg) was added, and H₂ gas was bubbled through the reaction mixture at 50 °C. After
35 disappearance of the starting material (monitored by TLC, 7:3 CHCl₃-MeOH) the reaction
36 mixture was filtered through a pad of celite, the solvent was evaporated, and the residue was
37 purified by column chromatography.
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51 **3.5. General procedure IV for the synthesis of (1'*R*)-2',3',4'-tri-*O*-acetyl-1',5'-anhydro-
52 D-xylitol-spiro[1',5]-3-aryl-4,5-dihydro-isoxazoles (23-28)**

53 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-D-xylo-hex-1-enitol (**22**, 100 mg, 0.37 mmol) and an
54 arenecarbaldoxime (1.85 mmol, 5 equiv.) was dissolved in THF (4.8 mL) under N₂
55 atmosphere. To this stirred solution domestic bleach (5 % available chlorine, 3.86 mL) was
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1 added with a syringe pump in 5 hours at rt. The reaction was stirred for additional 24 h. After
2 complete disappearance of the starting *exo*-xylal (TLC, 1:1 EtOAc-hexane) the reaction was
3
4 diluted with EtOAc (20 mL), the phases were separated, and the organic layer was washed
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6 with water (3 × 15 mL), dried over MgSO₄, and the solvent was evaporated under reduced
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8 pressure. The residue was purified by column chromatography (1:3 EtOAc-hexane).
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14 **3.6. General procedure V (method *a*) for the synthesis of 2,3,4-tri-*O*-acetyl-1-*S*-(*Z*)-**
15 **arylhydroximoyl-1-thio-β-D-xylopyranoses (36-38)**
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18 2,3,4-Tri-*O*-acetyl-1-thio-β-D-xylopyranose⁴¹ (**35**, 0.29 g, 1 mmol) and the corresponding *N*-
19
20 hydroxy-arenecarboximidoyl chloride (1.5 mmol) were dissolved in anhydrous CH₂Cl₂ (10
21
22 mL), Et₃N was added (3 mmol) and the reaction mixture was stirred at rt under Ar. After
23
24 completion of the reaction (1.5 h, monitored by TLC, 1:2 EtOAc-hexane) the mixture was
25
26 treated with 2 M HCl solution (20 mL), then the separated organic phase was washed with
27
28 water (2 × 20 mL). The organic layer was dried over MgSO₄, filtered and evaporated. The
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30 residue was purified by column chromatography (1:2 EtOAc-hexane) to give an oil that was
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32 crystallized from hexane.
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41 **3.7. General procedure VI (method *b*)⁴³ for the synthesis of 2,3,4-tri-*O*-acetyl-1-*S*-(*Z*)-**
42 **arylhydroximoyl-1-thio-β-D-xylopyranoses (36-38)**
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46 An arenecarbaldoxime (1.5 mmol) was dissolved in CH₂Cl₂ (10 mL) and the solution was
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48 extracted with domestic bleach (5 % available chlorine, 5 mL). After drying over MgSO₄ the
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50 organic phase was added dropwise to a solution of 2,3,4-tri-*O*-acetyl-1-thio-β-D-
51
52 xylopyranose⁴¹ (**35**, 0.29 g, 1 mmol) in CH₂Cl₂ (10 mL). After addition of Et₃N (3 mmol) the
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54 reaction mixture was stirred at rt under Ar, and monitored by TLC (1:2 EtOAc-hexane).
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58 When the starting material was consumed (1.5 h) the mixture was treated with 2 M HCl
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1 solution (20 mL), then the separated organic phase was washed with water (2 × 20 mL). The
2 organic layer was dried over MgSO₄, filtered and evaporated. The residue was purified by
3 column chromatography (1:2 EtOAc-hexane) to give an oil that was crystallized from hexane.
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6 7 8 9 10 **3.8. General procedure VII for the synthesis of (1'S/1'R)-2',3',4'-tri-O-acetyl-1',5'-** 11 **anhydro-D-xylitol-spiro[1',5]-3-aryl-1,4,2-oxathiazoles (42-47)**

12 A 2,3,4-tri-O-acetyl-1-S-(Z)-arylhydroximoyl-1-thio-β-D-xylopyranose (**36-38**, 1 mmol) and
13 NBS (1.2 mmol) were dissolved in anhydrous CHCl₃ (20 mL) and the mixture was boiled and
14 illuminated by a 250 W heat lamp. When TLC (1:2 EtOAc-hexane) showed total consumption
15 of the starting material (1 h) the reaction mixture was diluted with CHCl₃ (30 mL), extracted
16 with satd aq Na₂S₂O₄ solution (40 mL), satd aq NaHCO₃ solution (40 mL) and water (40 mL).
17 The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure. The
18 residue was purified by column chromatography.
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31 32 33 **3.9. Synthesis and characterization of the compounds**

34 **3.9.1. C-(2,3,4-Tri-O-benzoyl-β-D-xylopyranosyl)formamide (2)**

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39 2,3,4-Tri-O-benzoyl-β-D-xylopyranosyl cyanide²⁹ (**1**, 3.0 g, 6.4 mmol) was suspended in a
40 solution of HBr in AcOH (8 ml, 33% m/m) and the mixture was stirred at rt. After
41 disappearance of the starting material (3 h, monitored by TLC, 1:1 EtOAc-hexane) the
42 reaction mixture was poured into ice-water (40 mL) and extracted with CHCl₃ (2 × 30 mL).
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The combined organic phases were washed with satd aq NaHCO₃ solution (2 × 30 mL), then
with water (30 mL), dried over MgSO₄, filtered and the solvent was removed. The remaining
oil was crystallized from Et₂O to give 1.58 g (51 %) of **2** as a white solid. Mp: 173-175 °C;
[α]_D = -15 (c 0.5, DMSO); ¹H NMR (DMSO-d₆) δ (ppm): 7.88-7.38 (17H, m, Ar, CONH₂),

5.89, 5.63 (2 × 1H, 2 pseudo t, $J = 9.2, 9.2$ Hz in each, H-2, H-3), 5.40 (1H, ddd, $J = 10.5, 9.2,$
5.5 Hz, H-4), 4.35-4.32 (2H, m, H-1, H-5eq), 3.90 (1H, pseudo t, $J = 11.2, 10.5$ Hz, H-5ax);
 ^{13}C NMR (DMSO- d_6) δ (ppm): 168.7 (CONH $_2$), 165.1, 164.8, 164.4 (C=O), 133.7-128.6 (Ar),
76.7, 73.2, 70.0, 69.3 (C-1 – C-4), 65.3 (C-5). Anal. Calcd for C $_{27}$ H $_{23}$ NO $_8$ (489.47): C, 66.25;
H, 4.74; N, 2.86. Found: C, 66.11; H, 4.83; N, 2.73.

3.9.2. Ethyl *C*-(2,3,4-tri-*O*-benzoyl- β -D-xylopyranosyl)formimidate (**3**)

C-(2,3,4-Tri-*O*-benzoyl- β -D-xylopyranosyl)formamide (**2**, 1.0 g, 2.04 mmol) and Et $_3$ O·BF $_4$
(1.16 g, 6.13 mmol, 3 equiv.) were stirred in anhydrous CH $_2$ Cl $_2$ (15 mL) at rt under Ar, and
monitored by TLC (1:1 EtOAc-hexane). After completion of the reaction (24 h), the mixture
was diluted with CH $_2$ Cl $_2$ (50 mL), extracted with satd aq NaHCO $_3$ solution (40 mL) and then
with water (40 mL). The organic phase was dried over MgSO $_4$, filtered and the solvent was
removed under diminished pressure. The pale yellow amorphous crude product (1.02 g, 96 %)
was used without further purification. R $_f$: 0.59 (1:1 EtOAc-hexane); ^1H NMR (CDCl $_3$) δ
(ppm): 8.00-7.23 (16H, m, Ar, NH), 6.00, 5.59 (2 × 1H, 2 pseudo t, $J = 9.2, 9.2$ Hz in each, H-
2, H-3), 5.46 (1H, ddd, $J = 10.6, 9.2, 5.3$ Hz, H-4), 4.53 (1H, dd, $J = 11.2, 5.3$ Hz, H-5eq),
4.14 (1H, d, $J = 9.2$ Hz, H-1), 4.12-3.92 (2H, m, CH $_2$), 3.71 (1H, pseudo t, $J = 11.2, 10.6$ Hz,
H-5ax), 0.86 (3H, t, 7.3 Hz, CH $_3$); ^{13}C NMR (CDCl $_3$) δ (ppm): 167.5, 165.4, 165.1, 164.9
(C=O, C=NH), 133.2-128.0 (Ar), 75.1, 72.6, 70.3, 69.4 (C-1 – C-4), 66.0 (C-5), 61.8 (CH $_2$),
13.2 (CH $_3$).

3.9.3. 2-(2',3',4'-Tri-*O*-benzoyl- β -D-xylopyranosyl)-benzimidazole (**4**)

Ethyl *C*-(2,3,4-tri-*O*-benzoyl- β -D-xylopyranosyl)formimidate (**3**, 0.15 g, 0.29 mmol) and *o*-
phenylenediamine (63 mg, 0.58 mmol) were heated in anhydrous CH $_2$ Cl $_2$ (3 mL) at reflux
temperature, and the reaction was monitored by TLC (1:1 EtOAc-hexane). After completion

of the reaction (5 h) the solvent was evaporated, and the residue was purified by column chromatography (2:3 EtOAc-hexane) to give 0.13 g (80 %) pale yellow solid. Mp: 123-125 °C; $[\alpha]_D = -96$ (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 11.17 (1H, br s, NH), 7.97-7.17 (19H, m, Ar), 6.06, 5.85 (2 \times 1H, 2 pseudo t, $J = 9.4, 9.4$ Hz in each, H-2', H-3'), 5.42 (1H, ddd, $J = 9.8, 9.4, 5.4$ Hz, H-4'), 5.17 (1H, d, $J = 9.4$ Hz, H-1'), 4.42 (1H, dd, $J = 11.3, 5.4$ Hz, H-5'eq), 3.76 (1H, pseudo t, $J = 11.3, 9.8$ Hz, H-5'ax); ¹³C NMR (CDCl₃) δ (ppm): 165.6, 165.4, 165.3 (C=O), 149.1 (C-2), 138.3 (C-3a, C-7a), 133.3-128.1 (Ar), 122.7 (C-5, C-6), 115.5 (C-4, C-7), 75.4, 73.2, 71.4, 69.7 (C-1' - C-4'), 67.0 (C-5'). Anal. Calcd for C₃₃H₂₆N₂O₇ (562.57): C, 70.45; H, 4.66; N, 4.98. Found: C, 70.51; H, 4.80; N, 4.76.

3.9.4. 2-(β -D-Xylopyranosyl)-benzimidazole (5)

From compound 4 (0.22 g, 0.39 mmol) according to General procedure I (section 3.2.).

Reaction time: 1.5 h. Purified by column chromatography (85:15 CHCl₃-MeOH) to yield 79 mg (81 %) white amorphous solid. R_f : 0.45 (7:3 CHCl₃-MeOH); $[\alpha]_D = -18$ (c 0.5, DMSO); ¹H NMR (DMSO-d₆) δ (ppm): 12.53 (1H, s, NH), 7.56-7.48 (2H, m, benzimidazole), 7.17-7.16 (2H, m, benzimidazole), 5.21-5.14 (3H, m, 3 \times OH), 4.31 (1H, d, $J = 9.2$ Hz, H-1'), 3.87 (1H, dd, $J = 11.2, 5.3$ Hz, H-5'eq), 3.64 (1H, pseudo t, $J = 9.2, 9.2$ Hz, H-2' or H-3'), 3.47 (1H, ddd, $J = 10.6, 9.2, 5.3$ Hz, H-4'), 3.31 (1H, pseudo t, $J = 9.2, 9.2$ Hz, H-2' or H-3'), 3.26 (1H, pseudo t, $J = 11.2, 10.6$ Hz, H-5'ax); ¹³C NMR (DMSO-d₆) δ (ppm): 152.4 (C-2), 142.5, 134.1 (C-3a, C-7a), 122.1, 121.1, 118.7, 111.3 (C-4 - C-7), 78.0, 76.9, 72.8, 70.2 (C-1' - C-4'), 69.6 (C-5'). Anal. Calcd for C₁₂H₁₄N₂O₄ (250.25): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.51; H, 5.79; N, 11.13.

3.9.5. *N*^l-Tosyl-*C*-(3,4-di-*O*-benzoyl-2-deoxy-*D*-*threo*-pent-1-enopyranosyl)formamidrazone (6)

Ethyl *C*-(2,3,4-tri-*O*-benzoyl-β-*D*-xylopyranosyl)formimidate (**3**, 0.39 g, 0.76 mmol) and *p*-toluenesulfonylhydrazide (0.21 g, 1.13 mmol, 1.5 equiv) were dissolved in anhydrous CH₂Cl₂ (12 mL), stirred at rt, and monitored by TLC (1:1 EtOAc-hexane). After completion of the reaction (3 days) the solvent was evaporated, and the residue was purified by column chromatography (4:7 EtOAc-hexane). The resulting pale yellow oil was crystallized from Et₂O to give 0.11 g (27 %) white solid. Mp: 120-121 °C; [α]_D = -120 (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 8.01-7.28 (14H, m, Ar), 5.97, 5.58-5.35 (5H, 3 br signals, H-2, H-3, H-4, NH₂), 4.54, 4.26 (2 × 1H, 2 br signals, H-5eq, H-5ax), 2.37 (3H, s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 165.3, 165.0 (C=O), 154.5, 148.2, 144.1 (C-1, C=N, Ts-C-1) 134.5-128.3 (Ar), 97.9 (C-2), 67.2 (C-3 or C-4), 65.0 (C-5), 63.9 (C-3 or C-4), 21.5 (CH₃). MS-ESI (*m/z*): calcd for C₂₇H₂₆N₃O₇S⁺ [M+H]⁺: 536.15. Found: 536.42.

3.9.6. 5-(2',3',4'-Tri-*O*-Benzoyl-β-*D*-xylopyranosyl)tetrazole (7)

2,3,4-Tri-*O*-benzoyl-β-*D*-xylopyranosyl cyanide²⁹ (**1**, 2.00 g, 4.24 mmol), TMSN₃ (2.23 mL, 16.96 mmol) and Bu₂SnO (0.10 g, 0.42 mmol) was dissolved in anhydrous toluene (60 mL) and heated at 80 °C overnight. Toluene was then removed under reduced pressure, and the residue was crystallized from MeOH to yield 1.98 g (91 %) white solid. Mp: 176-177 °C; [α]_D = -29 (c 1.02, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 14.73 (1H, br s, NH), 7.99-7.19 (15H, m, Ar), 6.08, 5.87 (2 × 1H, 2 pseudo t, *J* = 9.5, 9.4 Hz in each, H-2', H-3'), 5.61 (1H, ddd, *J* = 10.8, 9.7, 5.7 Hz, H-4'), 5.26 (1H, d, *J* = 9.6 Hz, H-1'), 4.56 (1H, dd, *J* = 11.3, 5.3 Hz, H-5'eq), 3.80 (1H, pseudo t, *J* = 11.3, 10.8 Hz, H-5'ax); ¹³C NMR (CDCl₃) δ (ppm): 165.9, 165.8, 165.5 (C=O), 152.3 (tetrazole C-5), 133.7-128.3 (Ar), 72.9, 72.2, 71.1, 69.7 (C-1' - C-

4'), 67.4 (C-5'). Anal: Calcd for C₂₇H₂₂N₄O₇ (514.49): C, 63.03; H, 4.31; N, 10.89. Found: C, 62.99; H, 4.29; N, 10.90.

3.9.7. 4-Benzyl-3-phenyl-5-(2',3',4'-tri-*O*-benzoyl-β-D-xylopyranosyl)-1,2,4-triazole (11)

From tetrazole **7** (0.70 g, 1.36 mmol) and *N*-benzyl-benzamide (**8**, 0.86 g, 4.08 mmol) in toluene according to General procedure **II** (section 3.3.). Reaction time: 16 h. Purified by column chromatography (1:1 EtOAc-hexane) to yield 0.65 g (68 %) white crystals. Mp: 230-231 °C; [α]_D = -33 (c 0.50, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 7.96-7.05 (25H, m, Ar), 6.02, 5.92 (2 × 1H, 2 pseudo t, *J* = 9.4, 9.5 Hz in each, H-2', H-3'), 5.49 (1H, d, *J* = 16.3 Hz, PhCH₂), 5.41 (1H, ddd, *J* = 9.8, 9.4, 5.3 Hz, H-4'), 5.33 (1H, d, *J* = 16.3 Hz, PhCH₂), 4.94 (1H, d, *J* = 9.6 Hz, H-1'), 4.46 (1H, dd, *J* = 11.1, 5.3 Hz, H-5'eq), 3.60 (1H, pseudo t, *J* = 11.1, 10.7 Hz, H-5'ax); ¹³C NMR (CDCl₃) δ (ppm): 165.7, 165.4, 164.6 (C=O), 156.4, 150.2 (triazole C-3, C-5), 135.3-126.3 (Ar), 73.3, 73.3, 69.8, 69.7 (C-1' - C-4'), 67.2 (C-5'), 48.0 (PhCH₂). Anal: Calcd for C₄₁H₃₃N₃O₇ (679.72): C, 72.45; H, 4.89; N, 6.18. Found: C, 72.56; H, 4.94; N, 6.12.

3.9.8. 4-Benzyl-3-(4-*tert*-butylphenyl)-5-(2',3',4'-tri-*O*-benzoyl-β-D-xylopyranosyl)-1,2,4-triazole (12)

From tetrazole **7** (1.00 g, 1.94 mmol) and *N*-benzyl-4-*tert*-butylbenzamide (**9**, 1.56 g, 5.83 mmol) in *m*-xylene according to General procedure **II** (section 3.3.). Reaction time: 4 h. Purified by column chromatography (2:3 EtOAc-hexane) to yield 0.60 g (42 %) white crystals. Mp: 234-236 °C; [α]_D = -18 (c 0.52, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 7.96-7.07 (24H, m, Ar), 6.00, 5.90 (2 × 1H, 2 pseudo t, *J* = 9.4 Hz in each, H-2', H-3'), 5.47 (1H, d, *J* = 16.5 Hz, PhCH₂), 5.41-5.33 (2H, m, H-4', PhCH₂), 4.89 (1H, d, *J* = 9.7 Hz, H-1'), 4.44 (1H, dd, *J* = 11.2, 5.1 Hz, H-5'eq), 3.57 (1H, pseudo t, *J* = 11.2, 10.7 Hz, H-5'ax), 1.30 (9H, s,

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$C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8, 165.4, 164.5 (C=O), 156.5, 153.4 (triazole C-3, C-5), 150.0, 135.5-123.7 (Ar), 73.4, 73.2, 69.8, 69.7 (C-1' – C-4'), 67.2 (C-5'), 48.0 (PhCH₂), 34.8 ($C(CH_3)_3$), 31.1 ($C(CH_3)_3$). Anal: Calcd for $C_{45}H_{41}N_3O_7$ (735.82): C, 73.45; H, 5.62; N, 5.71. Found: C, 73.50; H, 5.59; N, 5.67.

3.9.9. 4-Benzyl-3-(2-naphthyl)-5-(2',3',4'-tri-*O*-benzoyl- β -D-xylopyranosyl)-1,2,4-triazole (13)

From tetrazole **7** (1.00 g, 1.94 mmol) and *N*-benzyl-naphthalene-2-carboxamide (**10**, 1.52 g, 5.82 mmol) in *m*-xylene according to General procedure **II** (section 3.3.). Reaction time: 3 h. Purified by column chromatography (1:1 EtOAc-hexane) to yield 0.73 g (52 %) white crystals. Mp: 226-227 °C; $[\alpha]_D = -39$ (c 0.47, $CHCl_3$); 1H NMR ($CDCl_3$) δ (ppm): 7.97-7.08 (27H, m, Ar), 6.04, 5.95 (2 \times 1H, 2 pseudo t, $J = 9.5, 9.4$ Hz in each, H-2', H-3'), 5.55 (1H, d, $J = 16.4$ Hz, PhCH₂), 5.45-5.38 (2H, m, H-4', PhCH₂), 5.00 (1H, d, $J = 9.6$ Hz, H-1'), 4.47 (1H, dd, $J = 11.2, 5.3$ Hz, H-5'eq), 3.62 (1H, pseudo t, $J = 11.2, 10.7$ Hz, H-5'ax); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.7, 165.4, 164.7 (C=O), 156.5, 150.3 (triazole C-3, C-5), 135.3-123.8 (Ar), 73.3, 73.2, 69.9, 69.7 (C-1' – C-4'), 67.2 (C-5'), 48.2 (PhCH₂). Anal: Calcd for $C_{45}H_{35}N_3O_7$ (729.78): C, 74.06; H, 4.83; N, 5.76. Found: C, 74.11; H, 4.85; N, 5.72.

3.9.10. 4-Benzyl-3-phenyl-5-(β -D-xylopyranosyl)-1,2,4-triazole (14)

From compound **11** (0.44 g, 0.63 mmol) according to General procedure **I** (section 3.2.). Reaction time: 4 h. Purified by column chromatography (9:1 $CHCl_3$ -MeOH) to yield 0.21 g (91 %) white amorphous solid. R_f : 0.46 (4:1 $CHCl_3$ -MeOH); $[\alpha]_D = -15$ (c 0.50, DMSO); 1H NMR ($DMSO-d_6$) δ (ppm): 7.49-7.41 (5H, m, Ar), 7.23-7.22 (3H, m, Ar), 6.94 (2H, d, $J = 6.3$ Hz, Ar), 5.38 (1H, d, $J = 19.2$ Hz, PhCH₂), 5.32 (1H, d, $J = 18.2$ Hz, PhCH₂), 4.31 (1H, d, $J = 9.6$ Hz, H-1'), 3.86 (1H, pseudo t, $J = 9.1, 8.9$ Hz, H-2' or H-3'), 3.73 (1H, dd, $J = 10.7, 5.8$

Hz, H-5'eq), 3.43 (1H, ddd, $J = 10.6, 9.4, 5.8$ Hz, H-4'), 3.26 (1H, pseudo t, $J = 9.1, 8.7$ Hz, H-2' or H-3'), 3.16 (1H, pseudo t, $J = 10.7, 10.6$ Hz, H-5'ax); ^{13}C NMR (DMSO- d_6) δ (ppm): 154.8, 153.5 (triazole C-3, C-5), 136.2, 130.2, 129.0, 128.8, 128.7, 127.9, 127.3, 126.5 (Ar), 78.1, 73.3, 71.8, 69.5 (C-1' – C-4'), 70.2 (C-5'), 47.0 (PhCH₂). Anal: Calcd for C₂₀H₂₁N₃O₄ (367.40): C, 65.38; H, 5.76; N, 11.44. Found: C, 65.30; H, 5.78; N, 11.45.

3.9.11. 4-Benzyl-3-(4-*tert*-butylphenyl)-5-(β -D-xylopyranosyl)-1,2,4-triazole (15)

Triazole **12** (0.53 g, 0.63 mmol) was dissolved in anhydrous MeOH (4 mL), 1M NaOH/MeOH (3 mL) was added and the mixture was refluxed for 1 hour. The excess of NaOH was neutralized by AcOH. After evaporation the crude product was purified by column chromatography (9:1 CHCl₃-MeOH) to yield 0.19 g (63 %) white amorphous solid. R_f : 0.56 (4:1 CHCl₃-MeOH); $[\alpha]_D = -15.0$ (c 0.50, DMSO); ^1H NMR (DMSO- d_6) δ (ppm): 7.42 (4H, m, Ar), 7.26-7.24 (3H, m, Ar), 6.96 (2H, d, $J = 6.5$ Hz, Ar), 5.37 (1H, d, $J = 18.1$ Hz, PhCH₂), 5.32 (1H, d, $J = 17.8$ Hz, PhCH₂), 4.23 (1H, d, $J = 9.6$ Hz, H-1'), 3.83 (1H, pseudo t, $J = 9.1, 9.0$ Hz, H-2' or H-3'), 3.72 (1H, dd, $J = 10.6, 4.7$ Hz, H-5'eq), 3.40 (1H, ddd, $J = 10.6, 9.1, 4.7$ Hz, H-4'), 3.21 (1H, pseudo t, $J = 8.7, 8.7$ Hz, H-2' or H-3'), 3.12 (1H, pseudo t, $J = 10.7, 10.6$ Hz, H-5'ax), 1.25 (9H, s, C(CH₃)₃); ^{13}C NMR (DMSO- d_6) δ (ppm): 154.6, 153.3 (triazole C-3, C-5), 152.8, 136.2, 128.8, 128.4, 127.8, 126.3, 125.8, 124.4 (Ar), 78.0, 73.3, 71.7, 69.4 (C-1' – C-4'), 70.1 (C-5'), 46.8 (PhCH₂), 34.7 (C(CH₃)₃), 31.0 (C(CH₃)₃). Anal: Calcd for C₂₄H₂₉N₃O₄ (423.50): C, 68.06; H, 6.90; N, 9.92. Found: 68.19; H, 6.92; N, 9.91.

3.9.12. 4-Benzyl-3-(2-naphthyl)-5-(β -D-xylopyranosyl)-1,2,4-triazole (16)

From compound **13** (0.34 g, 0.47 mmol) according to General procedure **I** (section 3.2.). Reaction time: 3 h. Purified by column chromatography (9:1 CHCl₃-MeOH) to yield 0.15 g (76 %) white amorphous solid. R_f : 0.40 (4:1 CHCl₃-MeOH); $[\alpha]_D = -14$ (c 0.50, DMSO); ^1H

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NMR (DMSO- d_6) δ (ppm): 8.04-6.97 (12H, m Ar), 5.49 (1H, d, $J = 18.3$ Hz, PhCH₂), 5.44 (1H, d, $J = 18.3$ Hz, PhCH₂), 4.39 (1H, d, $J = 9.6$ Hz, H-1'), 3.91 (1H, pseudo t, $J = 9.1, 9.0$ Hz, H-2' or H-3'), 3.78 (1H, dd, $J = 10.7, 4.8$ Hz, H-5'eq), 3.45 (1H, ddd, $J = 9.6, 9.0, 5.1$ Hz, H-4'), 3.29 (1H, pseudo t, $J = 8.8, 8.7$ Hz, H-2' or H-3'), 3.13 (1H, pseudo t, $J = 10.8, 10.8$ Hz, H-5'ax); ¹³C NMR (DMSO- d_6) δ (ppm): 154.7, 153.8 (triazole C-3, C-5), 136.3-124.7 (Ar), 78.1, 73.4, 71.8, 69.5 (C-1' – C-4'), 70.2 (C-5'), 47.2 (PhCH₂). Anal: Calcd for C₂₄H₂₃N₃O₄ (417.46): C, 69.05; H, 5.55; N, 10.07. Found: C, 68.99; H, 5.49; N, 10.12.

3.9.13. 3-Phenyl-5-(β -D-xylopyranosyl)-1,2,4-triazole (17)

From compound **14** (0.20 g, 0.54 mmol) according to General procedure **III** (section 3.4.).

Reaction time: 2 h. Purified by column chromatography (9:1 CHCl₃-MeOH) to yield 0.14 g

(91 %) white amorphous solid. R_f: 0.30 (4:1 CHCl₃-MeOH); $[\alpha]_D = -24$ (c 0.48, MeOH); ¹H

NMR (CD₃OD) δ (ppm): 7.90 (2H, br s, Ar), 7.40 (3H, m, Ar), 4.37 (1H, d, $J = 9.6$ Hz, H-1'),

4.00 (1H, dd, $J = 11.1, 5.3$ Hz, H-5'eq), 3.80 (1H, br s, H-2' or H-3'), 3.68 (1H, ddd, $J = 10.1,$

9.0, 5.3 Hz, H-4'), 3.49 (1H, pseudo t, $J = 9.0, 9.0$ Hz, H-2' or H-3'), 3.36 (1H, pseudo t, $J =$

11.1, 10.8 Hz, H-5'ax); ¹³C NMR (CD₃OD) δ (ppm): 163.0, 156.9 (triazole C-3, C-5), 131.1,

129.9, 127.5 (Ar), 79.5, 77.2, 74.2, 71.1 (C-1' – C-4'), 71.5 (C-5'). Anal: Calcd for

C₁₃H₁₅N₃O₄ (277.28): C, 56.31; H, 5.45; N, 15.15. Found: C, 56.43; H, 5.49; N, 15.07.

3.9.14. 3-(4-*tert*-Butylphenyl)-5-(β -D-xylopyranosyl)-1,2,4-triazole (18)

From compound **15** (0.18 g, 0.43 mmol) according to General procedure **III** (section 3.4.).

Reaction time: 2 h. Purified by column chromatography (9:1 CHCl₃-MeOH) to yield 0.11 g

(77 %) white amorphous solid. R_f: 0.43 (4:1 CHCl₃-MeOH); $[\alpha]_D = -24$ (c 0.49, MeOH); ¹H

NMR (CD₃OD) δ (ppm): 7.88 (2H, d, $J = 8.2$ Hz, Ar), 7.47 (2H, d, $J = 8.2$ Hz, Ar), 4.38 (1H,

d, $J = 9.7$ Hz, H-1'), 4.01 (1H, dd, $J = 11.1, 5.3$ Hz, H-5'eq), 3.83 (1H, pseudo t, $J = 8.6, 8.3$

1 Hz, H-2' or H-3'), 3.68 (1H, ddd, $J = 10.0, 9.2, 5.3$ Hz, H-4'), 3.50 (1H, pseudo t, $J = 9.0, 9.0$
2 Hz, H-2' or H-3'), 3.37 (1H, pseudo t, $J = 11.1, 10.0$ Hz, H-5'ax), 1.29 (9H, s, C(CH₃)₃); ¹³C
3 NMR (CD₃OD) δ (ppm): 162.1, 158.4 (triazole C-3, C-5), 154.6, 127.4, 126.9 (Ar), 79.5,
4 77.3, 74.2, 71.1 (C-1' – C-4'), 71.5 (C-5'), 35.6 (C(CH₃)₃), 31.6 (C(CH₃)₃). Anal: Calcd for
5 C₁₇H₂₃N₃O₄ (333.38): C, 61.25; H, 6.95; N, 12.60. Found: C, 61.20; H, 6.96; N, 12.54.
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14 3.9.15. 3-(2-Naphthyl)-5-(β -D-xylopyranosyl)-1,2,4-triazole (19)

15 From compound **16** (0.14 g, 0.33 mmol) according to General procedure **III** (section 3.4.).

16 Reaction time: 16 h. Purified by column chromatography (9:1 CHCl₃-MeOH) to yield 0.10 g
17 (90 %) white amorphous solid. R_f: 0.44 (4:1 CHCl₃-MeOH); $[\alpha]_D = -22$ (c 0.47, MeOH); ¹H
18 NMR (CD₃OD) δ (ppm): 8.36 (1H, s, Ar), 7.93 (1H, d, $J = 8.2$ Hz, Ar), 7.78-7.69 (3H, m,
19 Ar), 7.38-7.35 (2H, m, Ar), 4.40 (1H, d, $J = 9.7$ Hz, H-1'), 4.00 (1H, dd, $J = 11.0, 5.3$ Hz, H-
20 5'eq), 3.84 (1H, pseudo t, $J = 8.9, 8.7$ Hz, H-2' or H-3'), 3.71 (1H, ddd, $J = 9.9, 9.5, 5.3$ Hz,
21 H-4'), 3.51 (1H, pseudo t, $J = 8.9, 8.9$ Hz, H-2' or H-3'), 3.37 (1H, pseudo t, $J = 11.0, 9.9$ Hz,
22 H-5'ax); ¹³C NMR (CD₃OD) δ (ppm): 160.7, 159.0 (triazole C-3, C-5), 138.8, 135.3, 134.4,
23 129.7, 129.5, 128.7, 128.1, 127.7, 127.2, 124.5 (Ar), 79.5, 77.2, 74.3, 71.1 (C-1' – C-4'), 71.5
24 (C-5'). Anal: Calcd for C₁₇H₁₇N₃O₄ (327.33): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.40;
25 H, 5.19; N, 12.80.
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46 3.9.16. C-(2,3,4-Tri-*O*-acetyl- β -D-xylopyranosyl)formaldehyde-tosylhydrazone (21)

47 To a vigorously stirred solution of pyridine (10 mL), AcOH (6 mL), and water (6 mL) an
48 aqueous suspension of Raney-Ni (2.60 g) was added at rt. 2,3,4-Tri-*O*-acetyl- β -D-
49 xylopyranosyl-cyanide³⁴ (**20**, 0.50 g, 1.75 mmol), *p*-toluenesulfonylhydrazide (0.39 g, 4.43
50 mmol) and NaH₂PO₂ (1.30 g, 15 mmol) were then added to the mixture. When the reaction
51 was complete (TLC, 1:1 EtOAc-hexane) the insoluble materials were filtered off, and washed
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with EtOAc (40 mL). The organic layer of the filtrate was separated, washed with 10% aq HCl solution (3 × 10 mL), satd aq NaHCO₃ solution (3 × 10 mL), water (10 mL), and then dried over MgSO₄. The solution was concentrated under reduced pressure, the residue was purified by column chromatography (1:1 EtOAc-hexane) to give 0.50 g (63 %) white crystals. Mp: 143-147 °C; [α]_D = -14 (c 0.98, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 9.20 (1H, s, NH), 7.79 (2H, d, *J* = 8.1 Hz, Ph), 7.32 (2H, d, *J* = 8.0 Hz, Ph), 7.00 (1H, d, *J* = 6.4 Hz, CH), 5.25 (1H, pseudo t, *J* = 9.5, 9.5 Hz, H-2 or H-3), 4.98 (1H, ddd, *J* = 11.1, 9.6, 5.5 Hz, H-4), 4.92 (1H, pseudo t, *J* = 9.6, 9.6 Hz, H-2 or H-3), 4.10 (1H, dd, *J* = 11.1, 5.5 Hz, H-5eq), 3.90 (1H, dd, *J* = 9.7, 6.4 Hz, H-1), 3.32 (1H, pseudo t, *J* = 11.0, 10.9 Hz, H-5ax), 2.41 (3H, s, CH₃), 2.04 (6H, s, 2 × CH₃) 1.75, (3H, s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 170.5, 170.1, 169.9 (C=O), 143.9 (CH=N), 135.1, 127.7, 129.5 (Ar), 77.9, 72.4, 69.5, 68.7 (C-1 – C-4), 66.3 (C-5), 21.3, 20.5 (2 × CH₃), 20.1 (CH₃). Anal: Calcd for C₁₉H₂₄N₂O₉S (456.47): C, 49.99; H, 5.30; N, 6.14. Found: C, 50.06; H, 5.38; N, 6.19.

3.9.17. 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-D-xylo-hex-1-enitol (22)

In a flame-dried three-necked flask NaH (95 %, 44 mg, 1.75 mmol) was added to anhydrous 1,4-dioxane. This stirred suspension was heated to reflux and a solution of **21** (200 mg, 0.44 mmol) in anhydrous 1,4-dioxane (13 mL) was added dropwise during 1.5 h. The reaction was refluxed until the complete disappearance of the starting material (TLC, 1:1 EtOAc-hexane).

After cooling to rt the insoluble material was filtered off and washed with anhydrous 1,4-dioxane (10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (1:1 EtOAc-hexane) to yield 118 mg (99 %) white amorphous solid. R_f: 0.59 (1:1 EtOAc-hexane); [α]_D = +8 (c 0.51, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 5.38 (1H, ddd, *J* = 8.0, < 1 Hz, H-3), 5.11 (1H, pseudo t, *J* = 7.9, 7.8 Hz, H-4), 5.03 (1H, ddd, *J* = 8.4, 7.9, 4.8 Hz, H-5), 4.73 (1H, pseudo t, *J* = 1.5, 1.5 Hz, H-1a), 4.47 (1H,

pseudo t, $J = 1.5, 1.5$ Hz, H-1b), 4.18 (1H, dd, $J = 11.1, 4.8$ Hz, H-6eq), 3.55 (1H, dd, $J = 11.1, 8.4$ Hz, H-6ax), 2.04 (3H, s, CH₃), 2.09 (6H, s, 2 × CH₃); ¹³C NMR (CDCl₃) δ (ppm): 169.7 (2), 169.2 (C=O), 153.5 (C-2), 95.9 (C-1), 72.1, 68.7 (2) (C-3 – C-5), 66.9 (C-6), 20.7 (3 × CH₃). Anal: Calcd for C₁₂H₁₆O₇ (272.25): C, 52.94; H, 5.92. Found: C, 53.07; H, 5.99.

3.9.18. (1'*R*)-2',3',4'-Tri-*O*-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-phenyl-4,5-dihydro-isoxazole (23)

From compound **22** (100 mg, 0.37 mmol) and benzaldoxime (222 mg, 1.85 mmol) according to General procedure **IV** (section 3.5.) to yield 105 mg (74 %) white amorphous solid. R_f: 0.38 (1:2 EtOAc-hexane); [α]_D = +34 (c 0.79, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 7.59-7.19 (5H, m, Ar), 5.49 (1H, pseudo t, $J = 10.6, 9.2$ Hz, H-3'), 5.29 (1H, d, $J = 10.6$ Hz, H-2'), 5.00 (1H, ddd, $J = 10.6, 9.2, 6.6$ Hz, H-4'), 3.92-3.78 (2H, m, H-5'ax, H-5'eq), 3.25 (2H, br s, CH₂), 1.98 (9H, m, 3 × CH₃); ¹³C NMR (CDCl₃) δ (ppm): 170.3, 169.9, 169.7 (C=O), 157.7 (C=N), 130.8, 128.8, 128.3, 126.8 (Ar), 107.0 (C-1'), 71.1, 69.4, 68.9 (C-2' – C-4'), 60.2 (C-5'), 43.2 (CH₂), 20.6 (3 × CH₃). Anal: Calcd for C₁₉H₂₁NO₈ (391.38): C, 58.31; H, 5.41; N, 3.58. Found: C, 58.42; H, 5.54; N, 3.62.

3.9.19. (1'*R*)-2',3',4'-Tri-*O*-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(4-*tert*-butylphenyl)-4,5-dihydro-isoxazole (24)

From compound **22** (100 mg, 0.37 mmol) and 4-*tert*-butylbenzaldoxime (327 mg, 1.85 mmol) according to General procedure **IV** (section 3.5.) to yield 110 mg (67 %) white amorphous solid. R_f: 0.54 (1:2 EtOAc-hexane); [α]_D = +29 (c 1.95, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 7.59 (2H, d, $J = 8.5$ Hz, Ar), 7.44 (2H, d, $J = 8.5$ Hz, Ar), 5.56 (1H, pseudo t, $J = 9.9, 9.8$ Hz, H-3'), 5.36 (1H, d, $J = 10.1$ Hz, H-2'), 5.08 (1H, ddd, $J = 10.5, 9.8, 6.2$ Hz, H-4'), 3.96 (1H, pseudo t, $J = 11.0, 10.9$ Hz, H-5'ax), 3.73 (1H, dd, $J = 11.2, 6.2$ Hz, H-5'eq), 3.31 (2H, s,

CH₂), 2.06-2.04 (9H, m, 3 × CH₃), 1.33 (9H, s, C(CH₃)₃); ¹³C NMR (CDCl₃) δ (ppm): 170.3, 170.0, 169.7 (C=O), 157.5 (C=N), 125.5, 125.8, 126.6, 154.3 (Ar), 106.9 (C-1'), 71.1, 69.4, 68.9 (C-2' – C-4'), 60.2 (C-5'), 43.4 (CH₂), 34.9 (C(CH₃)₃), 31.1 (C(CH₃)₃), 20.6 (3 × CH₃). Anal: Calcd for C₂₃H₂₉NO₈ (447.48): C, 61.73; H, 6.53; N, 3.13. Found: C, 61.80; H, 6.61; N, 3.24.

3.9.20. (1'R)-2',3',4'-Tri-O-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(4-trifluoromethylphenyl)-4,5-dihydro-isoxazole (25)

From compound **22** (100 mg, 0.37 mmol) and 4-(trifluoromethyl)benzaloxime (327 mg, 1.85 mmol) according to General procedure **IV** (section 3.5.) to yield 96 mg (57 %) white amorphous solid. R_f: 0.49 (1:2 EtOAc-hexane); [α]_D = +29 (c 2.07, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 7.79-7.67 (4H, m, Ar) 5.58 (1H, pseudo t, *J* = 9.8, 9.8 Hz, H-3'), 5.38 (1H, d, *J* = 10.1 Hz, H-2'), 5.09 (1H, ddd, *J* = 10.0, 9.8, 6.5 Hz, H-4'), 3.96 (1H, pseudo t, *J* = 11.1, 11.0 Hz, H-5'ax), 3.91 (1H, dd, *J* = 11.2, 6.5 Hz, H-5'eq), 3.34 (2H, s, CH₂), 2.07-2.05 (9H, m, 3 × CH₃); ¹³C NMR (CDCl₃) δ (ppm): 170.3, 170.0, 169.7 (C=O), 156.7 (C=N), 131.8, 127.1, 125.8 (Ar), 123.5 (q, ¹*J*_(C,F) = 271.3, CF₃), 107.5 (C-1'), 70.9, 69.4, 68.8 (C-2' – C-4'), 60.3 (C-5'), 42.6 (CH₂), 20.6 (3 × CH₃). Anal: Calcd for C₂₀H₂₀F₃NO₈ (459.37): C, 52.29; H, 4.39; N, 3.05. Found: C, 52.21; H, 4.52; N, 2.96.

3.9.21. (1'R)-2',3',4'-Tri-O-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(1-naphthyl)-4,5-dihydro-isoxazole (26)

From compound **22** (100 mg, 0.37 mmol) and 1-naphthaldoxime (316 mg, 1.85 mmol) according to General procedure **IV** (section 3.5.) to yield 100 mg (60 %) white amorphous solid. R_f: 0.40 (1:2 EtOAc-hexane); [α]_D = +46 (c 0.81, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 8.98-7.45 (7H, m, Ar), 5.63 (1H, pseudo t, *J* = 9.9, 9.8 Hz, H-3'), 5.42 (1H, d, *J* = 10.1 Hz, H-

2'), 5.12 (1H, ddd, $J = 10.2, 9.8, 6.2$ Hz, H-4'), 4.04 (1H, pseudo t, $J = 11.0, 10.9$ Hz, H-5'ax), 3.93 (1H, dd, 1H, $J = 11.0, 6.1$ Hz, H-5'eq), 3.53 (2H, s, CH₂), 2.07-2.06 (9H, m, 3 × CH₃); ¹³C NMR (CDCl₃) δ (ppm): 170.3, 170.0, 169.8 (C=O), 158.5 (C=N), 133.9-124.7 (Ar), 106.0 (C-1'), 71.2, 69.4, 69.0 (C-2' - C-4'), 60.3 (C-5'), 46.1 (CH₂), 20.7 (3 × CH₃). Anal: Calcd for C₂₃H₂₃NO₈ (441.44): C, 62.58; H, 5.25; N, 3.17. Found: C, 62.66; H, 5.31; N, 3.23.

3.9.22. (1'R)-2,3,4-Tri-O-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(2-naphthyl)-4,5-dihydro-isoxazole (27)

From compound **22** (100 mg, 0.37 mmol) and 2-naphthaldoxime (316 mg, 1.85 mmol) according to General procedure **IV** (section 3.5.) to yield 71 mg (44 %) white amorphous solid. R_f: 0.42 (1:2 EtOAc-hexane); [α]_D = +12 (c 0.86, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 7.98-7.46 (7H, m, Ar), 5.61 (1H, pseudo t, $J = 9.9, 9.8$ Hz, H-3'), 5.41 (1H, d, $J = 10.1$ Hz, H-2'), 5.12 (1H, ddd, $J = 10.3, 6.2$ Hz, H-4'), 4.00 (1H, pseudo t, $J = 11.0, 10.9$ Hz, H-5'ax), 3.90 (1H, dd, $J = 11.1, 6.1$ Hz, H-5'eq), 3.45 (2H, br s, CH₂), 2.06-2.05 (9H, m, 3 × CH₃); ¹³C NMR (CDCl₃) δ (ppm): 170.3, 169.9, 169.7 (C=O), 157.8 (C=N), 134.2-123.0 (Ar), 107.1 (C-1'), 71.1, 69.4, 68.9 (C-2' - C-4'), 60.2 (C-5'), 43.2 (CH₂), 20.6 (3 × CH₃). Anal: Calcd for C₂₃H₂₃NO₈ (441.44): C, 62.58; H, 5.25; N, 3.17. Found: C, 62.51; H, 5.19; N, 3.26.

3.9.23. (1'R)-2',3',4'-Tri-O-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(2-benzothiazolyl)-4,5-dihydro-isoxazole (28)

From compound **22** (100 mg, 0.37 mmol) and benzothiazole-2-carbaldoxime (329 mg, 1.85 mmol) according to General procedure **IV** (section 3.5.) to yield 117 mg (71 %) yellow amorphous solid. R_f: 0.40 (1:2 EtOAc-hexane); [α]_D = +1 (c 1.83, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 8.05-7.45 (4H, m, Ar), 5.59 (1H, pseudo t, $J = 9.8, 9.8$ Hz, H-3'), 5.43 (1H, d, $J = 10.1$ Hz, H-2'), 5.17-5.09 (1H, m, H-4'), 3.98-3.95 (2H, m, H-5'ax, H-5'eq), 3.63 (1H, d, $J =$

18.4 Hz, CH_{2a}), 3.56 (1H, d, *J* = 18.5 Hz, CH_{2b}), 2.07-2.06, (9H, m, 3 × CH₃); ¹³C NMR (CDCl₃) δ (ppm): 169.8, 169.7, 169.6 (C=O), 156.4, 155.5, 152.7 (C=N, C–N), 126.7, 126.5, 123.7, 121.7 (Ar), 108.3, (C-1'), 68.5, 69.1, 70.8 (C-2' – C-4'), 60.4 (C-5'), 42.6 (CH₂), 20.4 (3 × CH₃). Anal: Calcd for C₂₀H₂₀N₂O₈S (448.45): C, 53.57; H, 4.50; N, 6.25. Found: C, 53.63; H, 4.57; N, 6.31.

3.9.24. (1'*R*)-1',5'-Anhydro-D-xylitol-spiro[1',5]-3-phenyl-4,5-dihydro-isoxazole (29)

From compound **23** (100 mg, 0.26 mmol) according to General procedure **I** (section 3.2.). The crude product was crystallized from EtOH to yield 61 mg (90 %) white crystals. Mp: 180-183 °C; [α]_D = +70 (c 0.90, MeOH); ¹H NMR (CD₃OD) δ (ppm): 7.69-7.67 (2H, m, Ph), 7.44-7.43 (3H, m, Ph), 3.76-3.56 (6H, m, H-2', H-3', H-4', H-5'ax, H-5'eq, CH_{2a}), 3.25 (1H, d, *J* = 17.7 Hz, CH_{2b}); ¹³C NMR (CD₃OD) δ (ppm): 159.8 (C=N), 131.7, 130.3, 130.0, 127.8 (Ar), 110.9 (C-1'), 76.4, 73.0, 71.2 (C-2' – C-4'), 64.9 (C-5'), 44.2 (CH₂). Anal: Calcd for C₁₃H₁₅NO₅ (265.26): C, 58.86; H, 5.70; N, 5.28. Found: C, 58.92; H, 5.59; N, 5.21.

3.9.25. (1'*R*)-1',5'-Anhydro-D-xylitol-spiro[1',5]-3-(4-*tert*-butylphenyl)-4,5-dihydro-isoxazole (30)

From compound **24** (100 mg, 0.23 mmol) according to General procedure **I** (section 3.2.). The crude product was crystallized from EtOH to yield 69 mg (98 %) white crystals. Mp: 238-242 °C; [α]_D = +63 (c 2.50, DMSO); ¹H NMR (DMSO-*d*₆) δ (ppm): 7.59 (2H, d, *J* = 7.9 Hz, Ar), 7.46 (2H, d, *J* = 8.0 Hz, Ar), 5.33 (1H, br s, OH), 5.08 (2H, m, 2 × OH), 3.58 (1H, d, *J* = 17.8 Hz, CH_{2a}), 3.53-3.36 (5H, m, H-2', H-3', H-4', H-5'ax, H-5'eq), 3.18 (1H, d, *J* = 17.7 Hz, CH_{2b}), 1.28 (9H, s, C(CH₃)₃); ¹³C NMR (DMSO-*d*₆) δ (ppm): 157.0 (C=N), 153.0, 126.3, 125.6 (Ar), 109.6 (C-1'), 74.4, 71.4, 69.6 (C-2' – C-4'), 63.7 (C-5'), 42.7 (CH₂), 34.5

(C(CH₃)₃), 30.8 (C(CH₃)₃). Anal: Calcd for C₁₇H₂₃NO₅ (321.37): C, 63.54; H, 7.21; N, 4.36.

Found: C, 63.61; H, 7.10; N, 4.42.

3.9.26. (1'R)-1',5'-Anhydro-D-xylitol-spiro[1',5]-3-(4-trifluoromethylphenyl)-4,5-dihydro-isoxazole (31)

From compound **25** (100 mg, 0.23 mmol) according to General procedure **I** (section 3.2.). The crude product was crystallized from EtOH to yield 66 mg (91 %) white crystals. Mp: 197-198 °C; [α]_D = +47 (c 0.36, MeOH); ¹H NMR (CD₃OD) δ (ppm): 7.79-7.62 (4H, m, Ar), 3.71-3.49 (7H, m, H-2', H-3', H-4', H-5'ax, H-5'eq, CH₂); ¹³C NMR (CD₃OD) δ (ppm): 158.4 (C=N), 134.2, 128.3, 126.7 (Ar), 111.5 (C-1'), 76.3, 73.1, 71.1 (C-2' – C-4'), 65.0 (C-5'), 43.8 (CH₂). Anal: Calcd for C₁₄H₁₄F₃NO₅ (333.26): C, 50.46; H, 4.23; N, 4.20. Found: C, 50.39; H, 4.33; N, 4.26.

3.9.27. (1'R)-1',5'-Anhydro-D-xylitol-spiro[1',5]-3-(1-naphthyl)-4,5-dihydro-isoxazole (32)

From compound **26** (100 mg, 0.23 mmol) according to General procedure **I** (section 3.2.). The crude product was crystallized from EtOH to yield 57 mg (79 %) white crystals. Mp: 179-180 °C; [α]_D = +66 (c 0.95, MeOH); ¹H NMR (CD₃OD) δ (ppm): 8.73-8.71 (1H, m, Ar), 7.81-7.79 (2H, m, Ar), 7.48-7.36 (4H, m, Ar), 3.82 (1H, d, *J* = 17.6 Hz, CH₂a), 3.76-3.56 (6H, m, H-2', H-3', H-4', H-5'ax, H-5'eq, CH₂b); ¹³C NMR (CD₃OD) δ (ppm): 160.3 (C=N), 135.4-126.1 (Ar), 109.9 (C-1'), 76.5, 73.0, 71.3 (C-2' – C-4'), 65.0 (C-5'), 47.2 (CH₂). Anal: Calcd for C₁₇H₁₇NO₅ (315.32): C, 64.75; H, 5.43; N, 4.44. Found: C, 64.89; H, 5.37; N, 4.39.

3.9.28. (1'R)-1',5'-Anhydro-D-xylitol-spiro[1',5]-3-(2-naphthyl)-4,5-dihydro-isoxazole (33)

From compound **27** (100 mg, 0.23 mmol) according to General procedure **I** (section 3.2.). The crude product was crystallised from EtOH to yield 61 mg (85 %) white crystals. Mp: 191-194 °C; $[\alpha]_D = +44$ (c 1.07, DMSO); $^1\text{H NMR}$ (DMSO- d_6) δ (ppm): 8.14-7.58 (7H, m, Ar), 5.41 (1H, br s, OH), 5.14-5.11 (2H, m, 2 \times OH), 3.73 (1H, d, $J = 17.6$ Hz, CH_{2a}), 3.56-3.38 (6H, m, H-2', H-3', H-4', H-5'ax, H-5'eq, CH_{2b}); $^{13}\text{C NMR}$ (DMSO- d_6) δ (ppm): 157.4 (C=N), 133.5-122.8 (Ar), 109.9 (C-1'), 74.4, 71.5, 69.5 (C-2' - C-4'), 63.8 (C-5'), 42.6 (CH₂). Anal: Calcd for C₁₇H₁₇NO₅ (315.32): C, 64.75; H, 5.43; N, 4.44. Found: C, 64.89; H, 5.42; N, 4.36.

3.9.29. (1'R)-1',5'-Anhydro-D-xylitol-spiro[1',5]-3-(2-benzothiazolyl)-4,5-dihydro-isoxazole (34)

From compound **28** (100 mg, 0.23 mmol) according to General procedure **I** (section 3.2.). The crude product was crystallized from EtOH to yield 47 mg (65 %) white crystals. Mp: 225-230 °C; $[\alpha]_D = +47$ (c 1.15, MeOH); $^1\text{H NMR}$ (CD₃OD) δ (ppm): 7.88-7.73 (2H, m, Ar), 7.46-7.33 (2H, m, Ar), 3.79-3.67 (7H, m, H-2', H-3', H-4', H-5'ax, H-5'eq, CH₂); $^{13}\text{C NMR}$ (CD₃OD) δ (ppm): 158.5, 156.7, 153.0 (C=N, C-N), 135.3, 128.3, 128.0, 124.0, 123.0 (Ar), 112.5 (C-1'), 75.7, 72.5, 70.4 (C-2' - C-4'), 64.9 (C-5'), 43.3 (CH₂). Anal: Calcd for C₁₄H₁₄N₂O₅S (322.33): C, 52.17; H, 4.38; N, 8.69. Found: C, 52.25; H, 4.45; N, 8.75.

3.9.30. 2,3,4-Tri-O-acetyl-1-S-(Z)-benzhydroximoyl-1-thio- β -D-xylopyranose (36)

A: From compound **35** (1.61 g, 5.51 mmol) and *N*-hydroxy-benzenecarboximidoyl chloride (1.29 g, 8.27 mmol) according to General procedure **V** (section 3.6.). Yield: 1.43 g (63 %).

B: From compound **35** (1.00 g, 3.42 mmol) and benzaldoxime (0.62 g, 5.14 mmol) according to General procedure **VI** (section 3.7.). Yield: 0.88 g (62 %), white crystals. Mp: 165-168 °C; $[\alpha]_D = +14$ (c 0.46, CHCl₃); $^1\text{H NMR}$ (CDCl₃) δ (ppm): 9.10 (1H, s, OH), 7.52-7.40 (5H, m, Ar), 5.02-4.97 (2H, m, H-2, H-3), 4.86 (1H, ddd, $J = 8.7, 8.3, 4.9$ Hz, H-4), 4.60 (1H, strongly

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coupled m, H-1), 4.06 (1H, dd, $J = 11.8, 4.9$ Hz, H-5eq), 2.88 (1H, dd, $J = 11.8, 8.7$ Hz, H-5ax), 2.04, 2.03, 1.98 ($3 \times 3\text{H}$, 3 s, CH_3); ^{13}C NMR (CDCl_3) δ (ppm): 169.9, 169.7, 169.3 (C=O), 152.5 (C=N), 132.3, 130.0, 128.9, 128.5 (Ar), 81.8 (C-1), 71.7, 69.8, 68.1 (C-2 – C-4), 64.9 (C-5), 20.6 ($3 \times \text{CH}_3$). Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_8\text{S}$ (411.43): C, 52.55; H, 5.14; N, 3.40. Found: C, 52.39; H, 5.17; N, 3.49.

3.9.31. 2,3,4-Tri-*O*-acetyl-1-*S*-(*Z*)-1-naphthhydroximoyl-1-thio- β -D-xylopyranose (37)

A: From compound **35** (0.93 g, 3.17 mmol) and *N*-hydroxy-1-naphthalenecarboximidoyl chloride (0.98 g, 4.75 mmol) according to General procedure **V** (section 3.6.). Yield: 1.22 g (83 %).

B: From compound **35** (1.50 g, 5.14 mmol) and 1-naphthaldoxime (1.32 g, 7.71 mmol) according to General procedure **VI** (section 3.7.). Yield: 1.62 g (68 %), white amorphous solid. R_f : 0.57 (1:1 EtOAc-hexane); $[\alpha]_D = +22$ (c 0.52, CHCl_3); ^1H NMR (CDCl_3) δ (ppm): 9.24 (1H, br s, OH), 7.98-7.51 (7H, m, Ar), 4.91 (1H, pseudo t, $J = 8.6, 8.4$ Hz, H-2 or H-3), 4.78-4.69 (2H, m, H-2 or H-3, H-4), 4.03 (1H, d, $J = 8.6$ Hz, H-1), 3.66 (1H, dd, $J = 11.9, 4.6$ Hz, H-5eq), 2.23 (1H, dd, $J = 11.9, 8.7$ Hz, H-5ax), 1.97, 1.94, 1.89 ($3 \times 3\text{H}$, 3 s, CH_3); ^{13}C NMR (CDCl_3) δ (ppm): 169.9, 169.6, 169.1 (C=O), 152.5 (C=N), 133.2, 131.8, 130.3, 128.7, 128.2, 126.9, 126.6, 125.1, 124.7 (Ar), 81.4 (C-1), 71.9, 69.2, 68.1 (C-2 – C-4), 64.7 (C-5), 20.6 ($3 \times \text{CH}_3$). Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_8\text{S}$ (461.48): C, 57.26; H, 5.02; N, 3.04. Found: C, 57.32; H, 5.14; N, 2.93.

3.9.32. 2,3,4-Tri-*O*-acetyl-1-*S*-(*Z*)-2-naphthhydroximoyl-1-thio- β -D-xylopyranose (38)

A: From compound **35** (0.86 g, 2.96 mmol) and *N*-hydroxy-2-naphthalenecarboximidoyl chloride (0.91 g, 4.43 mmol) according to General procedure **V** (section 3.6.). Yield: 1.23 g (91 %).

B: From compound **35** (1.71 g, 5.84 mmol) 2-naphthaldoxime (1.50 g, 8.76 mmol) according to General procedure **VI** (section 3.7.). Yield: 2.10 g (77 %), white crystals. Mp: 169-172 °C; $[\alpha]_D = +17$ (c 0.50, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 9.09 (1H, s, OH), 8.06-7.52 (7H, m, Ar), 5.04, 4.97 (2 \times 1H, 2 pseudo t, $J = 8.0, 8.0$ Hz in each, H-2, H-3), 4.87 (1H, ddd, $J = 8.6, 8.0, 4.9$ Hz, H-4), 4.70 (1H, d, $J = 8.0$ Hz, H-1), 4.08 (1H, dd, $J = 11.7, 4.9$ Hz, H-5eq), 2.88 (1H, dd, $J = 11.7, 8.6$ Hz, H-5ax), 2.05, 2.03, 1.95 (3 \times 3H, 3 s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 169.8, 169.7, 169.3 (C=O), 152.4 (C=N), 133.8, 132.7, 129.8, 129.0, 128.5, 128.2, 127.7, 127.3, 126.7, 125.5 (Ar), 81.8 (C-1), 71.5, 69.8, 68.1 (C-2 – C-4), 64.8 (C-5), 20.7 (3 \times CH₃). Anal. Calcd for C₂₂H₂₃NO₈S (461.48): C, 57.26; H, 5.02; N, 3.04. Found: C, 57.34; H, 4.89; N, 3.10.

3.9.33. 1-S-(Z)-Benzhydroximoyl-1-thio- β -D-xylopyranose (39)

From compound **36** (0.20 g, 0.49 mmol) according to General procedure **I** (section 3.2.).

Purified by column chromatography (9:1 CHCl₃-MeOH) to yield 0.12 g (89 %) white solid.

Mp: 174-178 °C; $[\alpha]_D = -5$ (c 0.50, DMSO); ¹H NMR (DMSO-d₆) δ (ppm): 7.44-7.43 (5H, m, Ar), 5.41, 5.12, 4.90 (3 \times 1H, 3 d, OH), 4.12 (1H, d, $J = 9.2$ Hz, H-1), 3.57 (1H, dd, $J = 11.2, 4.9$ Hz, H-5eq), 3.23 (1H, m, H-4), 3.07, 2.91 (2 \times 1H, 2 m, H-2, H-3), 2.38 (1H, pseudo t, $J = 11.2, 9.9$ Hz, H-5ax); ¹³C NMR (DMSO-d₆) δ (ppm): 151.1 (C=N), 133.6, 129.0, 128.5, 128.0 (Ar), 84.2 (C-1), 77.6, 72.5, 69.1 (C-2 – C-4), 68.9 (C-5). Anal. Calcd for C₁₂H₁₅NO₅S (285.32): C, 50.52; H, 5.30; N, 4.91. Found: 50.46; H, 5.52; N, 4.87.

3.9.34. 1-S-(Z)-1-Naphthhydroximoyl-1-thio- β -D-xylopyranose (40)

From compound **37** (0.20 g, 0.43 mmol) according to General procedure **I** (section 3.2.).

Purified by column chromatography (9:1 CHCl₃-MeOH) to yield 0.14 g (98 %) brownish

solid. Mp: 198-202 °C; $[\alpha]_D = +16$ (c 0.53, DMSO); ¹H NMR (CD₃OD) δ (ppm): 8.04-7.51

(7H, m, Ar), 3.72 (1H, d, $J = 9.7$ Hz, H-1), 3.31-3.25 (2H, m, H-4, H-5eq), 3.20 (1H, pseudo t, $J = 9.7, 8.7$ Hz, H-2 or H-3), 2.83 (1H, pseudo t, $J = 8.7, 8.3$ Hz, H-2 or H-3), 1.91 (1H, strongly coupled m, H-5ax); ^{13}C NMR (CD_3OD) δ (ppm): 154.1 (C=N), 134.7, 133.5, 131.3, 130.9, 129.5, 129.1, 127.7, 127.4, 126.8, 125.8 (Ar), 85.6 (C-1), 79.2, 73.5, 70.6 (C-2 – C-4), 69.9 (C-5). Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_5\text{S}$ (335.37): C, 57.30; H, 5.11; N, 4.18. Found: C, 57.34; H, 5.26; N, 4.09.

3.9.35. 1-*S*-(*Z*)-2-Naphthhydroximoyl-1-thio- β -D-xylopyranose (41)

From compound **38** (0.20 g, 0.43 mmol) according to General procedure **I** (section 3.2.).

Purified by column chromatography (9:1 CHCl_3 -MeOH) to yield 0.13 g (92 %) pale yellow solid. Mp: 185-188 °C; $[\alpha]_{\text{D}} = +1$ (c 0.46, DMSO); ^1H NMR (CD_3OD) δ (ppm): 8.05-7.51 (7H, m, Ar), 4.26 (1H, d, $J = 9.7$ Hz, H-1), 3.68 (1H, dd, $J = 11.7, 5.3$ Hz, H-5eq), 3.41 (1H, ddd, $J = 10.2, 8.7, 5.3$ Hz, H-4), 3.29 (1H, pseudo t, $J = 9.7, 8.7$ Hz, H-2 or H-3), 3.04 (1H, t, $J = 8.7$ Hz, H-2 or H-3), 2.43 (1H, pseudo t, $J = 11.2, 10.2$ Hz, H-5ax); ^{13}C NMR (CD_3OD) δ (ppm): 154.1 (C=N), 135.0, 134.1, 132.3, 130.0, 129.4, 128.8, 128.1, 127.7, 127.3 (Ar), 85.9 (C-1), 79.2, 74.1, 70.6 (C-2 – C-4), 70.3 (C-5). Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_5\text{S}$ (335.37): C, 57.30; H, 5.11; N, 4.18. Found: C, 57.40; H, 5.03; N, 4.27.

3.9.36. (1'*R*)-2',3',4'-Tri-*O*-acetyl-1',5'-anhydro-D-xylylitol-spiro[1',5]-3-phenyl-1,4,2-oxathiazole (42) and (1'*S*)-2',3',4'-tri-*O*-acetyl-1',5'-anhydro-D-xylylitol-spiro[1',5]-3-phenyl-1,4,2-oxathiazole (45)

From compound **36** (1.00 g, 2.43 mmol) according to General procedure **VII** (section 3.8.).

Purified by column chromatography (1:4 EtOAc-hexane) to give **45** as the first and **42** as the second fraction.

Compound **42**: Yield: 310 mg (31 %), white solid. Mp: 158-161°C; $[\alpha]_D = +178$ (c 1.68, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 7.70-7.41 (7H, m, Ar), 5.52 (1H, d, $J = 8.7$ Hz, H-2'), 5.13 (1H, pseudo t, $J = 8.7, 8.3$ Hz, H-3'), 5.07 (1H, ddd, $J = 8.7, 8.3, 4.9$ Hz, H-4'), 4.19 (1H, dd, $J = 12.1, 4.9$ Hz, H-5'eq), 3.79 (1H, dd, $J = 12.1, 8.7$ Hz, H-5'ax), 2.08 (2), 2.07 (9H, 2 s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 169.4 (2), 168.4 (C=O), 155.5 (C=N), 131.4, 128.8, 127.7, 127.1 (Ar), 126.6 (C-1'), 71.7, 68.3, 67.3 (C-2' - C-4'), 61.1 (C-5'), 20.4 (3 \times CH₃). Anal. Calcd for C₁₈H₁₉NO₈S (409.41): C, 52.81; H, 4.68; N, 3.42. Found: C, 52.96; H, 4.64; N, 3.33.

Compound **45**: Yield: 71 mg (7 %), pale yellow solid. Mp: 122-124°C; $[\alpha]_D = +78$ (c 0.26, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 7.67-7.41 (5H, m, Ar), 5.62 (1H, pseudo t, $J = 9.8, 9.2$ Hz, H-3'), 5.56 (1H, d, $J = 9.8$ Hz, H-2'), 5.12 (1H, ddd, $J = 9.7, 9.2, 6.8$ Hz, H-4'), 4.04 (1H, pseudo t, $J = 11.2, 9.7$ Hz, H-5'ax), 4.00 (1H, dd, $J = 11.2, 6.8$ Hz, H-5'eq), 2.08, 2.07, 2.06 (3 \times 3H, 3 s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 169.7, 169.4 (2) (C=O), 156.2 (C=N), 131.5, 128.9, 127.9, 127.0 (Ar), 122.6 (C-1'), 70.4, 68.4, 68.1 (C-2' - C-4'), 61.2 (C-5'), 20.5 (3 \times CH₃). Anal. Calcd for C₁₈H₁₉NO₈S (409.41): C, 52.81; H, 4.68; N, 3.45. Found: C, 52.63; H, 4.75; N, 3.57.

3.9.37. (1'R)-2',3',4'-Tri-O-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(1-naphthyl)-1,4,2-oxathiazole (43) and (1'S)-2',3',4'-tri-O-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(1-naphthyl)-1,4,2-oxathiazole (46)

From compound **37** (1.00 g, 2.17 mmol) according to General procedure **VII** (section 3.8.).

Purified by column chromatography (1:4 EtOAc-hexane) to give **46** as the first and **43** as the second fraction.

Compound **43**: Yield: 233 mg (23 %), pale yellow solid. Mp: 153-156 °C; $[\alpha]_D = +151$ (c 1.18, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 8.61-7.47 (7H, m, Ar), 5.58 (1H, d, $J = 8.3$ Hz, H-

2'), 5.15 (1H, pseudo t, $J = 8.3, 7.8$ Hz, H-3'), 5.10 (1H, ddd, $J = 8.7, 7.8, 3.9$ Hz, H-4'), 4.28 (1H, dd, $J = 11.2, 3.9$ Hz, H-5'eq), 3.85 (1H, dd, $J = 11.2, 8.7$ Hz, H-5'ax), 2.13, 2.10, 2.08 (3 \times 3H, 3 s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 169.5 (2), 168.5 (C=O), 154.9 (C=N), 133.6, 131.9, 130.2, 129.5, 128.4, 127.6, 126.6 (Ar), 125.8 (C-1'), 125.5, 124.7, 123.7 (Ar), 71.6, 68.5, 67.3 (C-2' - C-4'), 61.2 (C-5'), 20.5 (3 \times CH₃). Anal. Calcd for C₂₂H₂₁NO₈S (459.47): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.68; H, 4.56; N, 3.13.

Compound **46**: Yield: 66 mg (7 %), pale yellow solid. Mp: 145-148 °C; $[\alpha]_D = +73$ (c 0.23, CHCl₃); ¹H NMR (CDCl₃) δ ppm: 8.65-7.46 (7H, m, Ar), 5.68 (1H, pseudo t, $J = 9.7, 9.2$ Hz, H-3'), 5.59 (1H, d, $J = 9.7$ Hz, H-2'), 5.14 (1H, ddd, $J = 10.2, 9.2, 6.3$ Hz, H-4'), 4.11 (1H, dd, $J = 11.2, 10.2$ Hz, H-5'ax), 4.06 (1H, dd, $J = 11.2, 6.3$ Hz, H-5'eq), 2.13, 2.08, 2.07 (3 \times 3H, 3 s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 169.8, 169.5, 169.4 (C=O), 155.6 (C=N), 133.7, 132.0, 130.3, 129.8, 128.5, 127.8, 126.7, 125.6, 124.8, 123.6 (Ar), 121.9 (C-1'), 70.5, 68.4, 68.2 (C-2' - C-4'), 61.3 (C-5'), 20.6 (3 \times CH₃). Anal. Calcd for C₂₂H₂₁NO₈S (459.47): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.62; H, 4.70; N, 2.94.

3.9.38. (1'R)-2',3',4'-Tri-O-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(2-naphthyl)-1,4,2-oxathiazole (44) and (1'S)-2',3',4'-tri-O-acetyl-1',5'-anhydro-D-xylitol-spiro[1',5]-3-(2-naphthyl)-1,4,2-oxathiazole (47)

From compound **38** (1.00 g, 2.17 mmol) according to General procedure **VII** (section 3.8.). Purified by column chromatography (1:4 EtOAc-hexane) to give **47** as the first and **44** as the second fraction.

Compound **44**: Yield: 315 mg (32 %), white powder. Mp: 181-184 °C, $[\alpha]_D = +182$ (c 0.85, CHCl₃); ¹H NMR (360 MHz, CDCl₃) δ (ppm): 8.04-7.53 (7H, m, Ar), 5.56 (1H, d, $J = 8.7$ Hz, H-2'), 5.17 (1H, pseudo t, $J = 8.7, 8.3$ Hz, H-3'), 5.11 (1H, ddd, $J = 8.7, 8.3, 4.9$ Hz, H-4'), 4.22 (1H, dd, $J = 12.1, 4.9$ Hz, H-5'eq), 3.83 (1H, dd, $J = 12.1, 8.7$ Hz, H-5'ax), 2.09,

2.08 (9H, 2 s, CH₃); ¹³C NMR (CDCl₃) δ ppm: 169.5 (2), 168.4 (C=O), 155.7 (C=N), 134.4, 132.6, 129.0, 128.6, 128.4, 127.7, 126.9 (Ar), 126.7 (C-1'), 124.6, 123.5 (Ar), 71.8, 68.4, 67.3 (C-2' – C-4'), 61.2 (C-5'), 20.5 (3 × CH₃). Anal. Calcd for C₂₂H₂₁NO₈S (459.47): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.57; H, 4.49; N, 3.01.

Compound **47**: Yield: 120 mg (12 %), pale yellow solid, Mp: 140-143 °C, [α]_D = +61 (c 0.28, CHCl₃); ¹H NMR (360 MHz, CDCl₃) δ ppm: 7.98-7.50 (7H, m, Ar), 5.66 (1H, pseudo t, *J* = 9.7, 8.7 Hz, H-3'), 5.60 (1H, d, *J* = 9.7 Hz, H-2'), 5.15 (1H, ddd, *J* = 9.7, 8.7, 6.8 Hz, H-4'), 4.07 (1H, dd, *J* = 11.2, 9.7 Hz, H-5'ax), 4.02 (1H, dd, *J* = 11.2, 6.8 Hz, H-5'eq), 2.09, 2.07 (2) (9H, 2 s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 169.7, 169.4 (2) (C=O), 156.2 (C=N), 134.5, 132.6, 129.2, 128.7, 128.5, 127.8, 127.0, 124.5, 123.4 (Ar), 122.6 (C-1'), 70.4, 68.3, 68.1 (C-2' – C-4'), 61.2 (C-5'), 20.5 (3 × CH₃). Anal. Calcd for C₂₂H₂₁NO₈S (459.47): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.37; H, 4.65; N, 3.21.

3.9.39. (1'S)-1',5'-Anhydro-D-xylitol-spiro[1',5]-3-phenyl-1,4,2-oxathiazole (**48**)

From compound **45** (50 mg, 0.12 mmol) according to General procedure **I** (section 3.2.).

Reaction time: 10 min. Purified by column chromatography (4:1 CHCl₃-MeOH) to yield 24 mg (70 %) white crystals. Mp: 123-126 °C; [α]_D = +64 (c 0.25, CHCl₃); ¹H NMR (DMSO-d₆) δ (ppm): 7.66-7.49 (5H, m, Ar), 5.76, 5.42, 5.24 (3 × 1H, 3 d, OH), 3.78-3.68 (2H, m, H-2', H-5'a), 3.59 (1H, m, H-5'b), 3.52-3.40 (2H, m, H-3', H-4'); ¹³C NMR (DMSO-d₆) δ (ppm): 155.3 (C=N), 131.4, 129.2, 127.3, 126.6 (Ar), 125.1 (C-1'), 73.9, 71.2, 68.6 (C-2' – C-4'), 64.7 (C-5'). Anal. Calcd for C₁₂H₁₃NO₅S (283.30): C, 50.87; H, 4.63; N, 4.94. Found: C, 50.96; H, 4.74; N, 4.88.

3.9.40. (1'S)-1',5'-Anhydro-D-xylitol-spiro[1',5]-3-(2-naphthyl)-1,4,2-oxathiazole (**49**)

From compound **47** (80 mg, 0.17 mmol) according to General procedure **I** (section 3.2.).

Reaction time: 10 min. Purified by column chromatography (4:1 CHCl₃-MeOH) to yield 35 mg (60 %) white solid. Mp: 175-178 °C, [α]_D = +25 (c 0.25, CHCl₃); ¹H NMR (DMSO-d₆) δ (ppm): 8.14-7.57 (7H, m, Ar), 5.80, 5.47, 5.28 (3 \times 1H, 3 d, OH), 3.81 (1H, m, H-2'), 3.74 (1H, m, H-5'a), 3.64 (1H, m, H-5'b), 3.58-3.46 (2H, m, H-3', H-4'); ¹³C NMR (DMSO-d₆) δ (ppm): 155.7 (C=N), 134.2, 132.8, 129.0, 128.7, 128.1, 127.9, 127.4, 126.8, 125.2, 123.3 (Ar), 123.5 (C-1'), 73.9, 71.4, 68.8 (C-2' – C-4'), 64.9 (C-5'). Anal. Calcd for C₁₆H₁₅NO₅S (333.07): C, 57.65; H, 4.54; N, 4.20. Found: C, 57.73; H, 4.61; N, 4.06.

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References

1. Henke, B. R.; Sparks, S. M. *Mini-Rev. Med. Chem.* **2006**, *6*, 845-857.
2. Praly, J. P.; Vidal, S. *Mini-Rev. Med. Chem.* **2010**, *10*, 1102-1126.
3. Gaboriaud-Kolar, N.; Skaltsounis, A.-L. *Expert Opin. Ther. Pat.* **2013**, *23*, 1017-1032.
4. Tracey, W.; Treadway, J.; Magee, W.; McPherson, R.; Levy, C.; Wilder, D.; Li, Y.; Yue, C.; Zavadoski, W.; Gibbs, E.; Smith, A.; Flynn, D.; Knight, D. *Diabetes* **2003**, *52*, A135-A135.
5. 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. *Am. J. Physiol.-Heart Circul. Physiol.* **2004**, *286*, H1177-H1184.
6. Sun, H.; Xu, L. *Mini-Rev. Med. Chem.* **2010**, *10*, 1188-1193.
7. Guan, T.; Qian, Y. S.; Tang, X. Z.; Huang, M. H.; Huang, L. F.; Li, Y. M.; Sun, H. B. *J. Neurosci. Res.* **2011**, *89*, 1829-1839.
8. Schnier, J. B.; Nishi, K.; Monks, A.; Gorin, F. A.; Bradbury, E. M. *Biochem. Biophys. Res. Commun.* **2003**, *309*, 126-134.
9. Geschwind, J.-F.; Georgiades, C. S.; Ko, Y. H.; Pedersen, P. L. *Expert Rev. Anticanc. Ther.* **2004**, *4*, 449-457.
10. Laszlo, G. B. *Pancreas* **2003**, *27*, 368-420.
11. 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. *Cell Metab.* **2012**, *16*, 751-764.

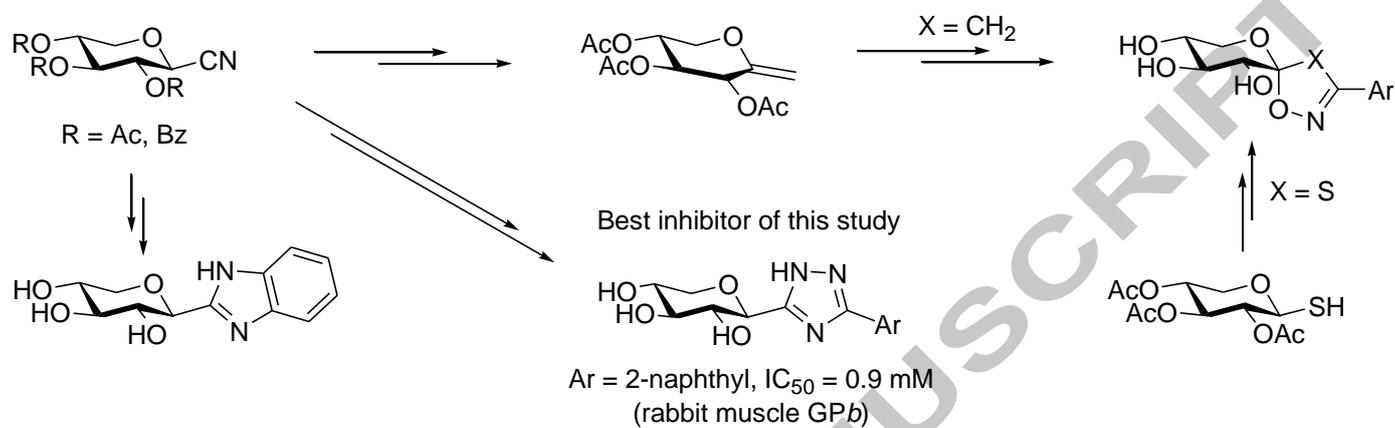
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12. Somsák, L.; Czifrák, K.; Tóth, M.; Bokor, É.; Chrysina, E. D.; Alexacou, K. M.;
Hayes, J. M.; Tiraidis, C.; Lazoura, E.; Leonidas, D. D.; Zographos, S. E.;
Oikonomakos, N. G. *Curr. Med. Chem.* **2008**, *15*, 2933-2983.
 13. Somsák, L. *Compt. Rend. Chimie* **2011**, *14*, 211-223.
 14. Oikonomakos, N. G.; Kontou, M.; Zographos, S. E.; Tsitoura, H. S.; Johnson, L. N.;
Watson, K. A.; Mitchell, E. P.; Fleet, G. W. J.; Son, J. C.; Bichard, C. J. F.; Leonidas,
D. D.; Acharya, K. R. *Eur. J. Drug Metabol. Pharmacokin.* **1994**, 185-192.
 15. Bichard, C. J. F.; Mitchell, E. P.; Wormald, M. R.; Watson, K. A.; Johnson, L. N.;
Zographos, S. E.; Koutra, D. D.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron
Lett.* **1995**, *36*, 2145-2148.
 16. Somsák, L.; Kovács, L.; Tóth, M.; Ósz, E.; Szilágyi, L.; Györgydeák, Z.; Dinya, Z.;
Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 2843-2848.
 17. Chrysina, E. D.; Bokor, É.; Alexacou, K.-M.; Charavgi, M.-D.; Oikonomakos, G. N.;
Zographos, S. E.; Leonidas, D. D.; Oikonomakos, N. G.; Somsák, L. *Tetrahedron:
Asymm.* **2009**, *20*, 733-740.
 18. Bokor, É.; Docsa, T.; Gergely, P.; Somsák, L. *Bioorg. Med. Chem.* **2010**, *18*, 1171-
1180.
 19. Hadady, Z.; Tóth, M.; Somsák, L. *Arkivoc* **2004**, (vii), 140-149.
 20. 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.
Protein Sci. **2005**, *14*, 873-888.
 21. Bokor, É.; Szilágyi, E.; Docsa, T.; Gergely, P.; Somsák, L. *Carbohydr. Res.* **2013**,
381, 179-186.
 22. Bokor, É.; Docsa, T.; Gergely, P.; Somsák, L. *ACS Med. Chem. Lett.* **2013**, *4*, 612-
615.

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65
23. Kun, S.; Bokor, É.; Varga, G.; Szőcs, B.; Páhi, A.; Czifrák, K.; Tóth, M.; Juhász, L.;
Docsa, T.; Gergely, P.; Somsák, L. *Eur. J. Med. Chem.* **2014**, *76*, 567-579.
24. Benlifa, M.; Hayes, J. M.; Vidal, S.; Gueyrard, D.; Goekjian, P. G.; Praly, J.-P.;
Kizilis, G.; Tiraidis, C.; Alexacou, K.-M.; Chrysina, E. D.; Zographos, S. E.;
Leonidas, D. D.; Archontis, G.; Oikonomakos, N. G. *Bioorg. Med. Chem.* **2009**, *17*,
7368-7380.
25. Somsák, L.; Nagy, V.; Vidal, S.; Czifrák, K.; Berzsényi, E.; Praly, J.-P. *Bioorg. Med.*
Chem. Lett. **2008**, *18*, 5680-5683.
26. Nagy, V.; Vidal, S.; Benlifa, M.; Berzsényi, E.; Teilhet, C.; Czifrák, K.; Batta, G.;
Docsa, T.; Gergely, P.; Somsák, L.; Praly, J.-P. *Bioorg. Med. Chem.* **2009**, *17*, 5696-
5707.
27. Sprang, S. R.; Goldsmith, E. J.; Fletterick, R. J.; Withers, S. G.; Madsen, N. B.
Biochem. **1982**, *21*, 5364-5371.
28. Goyard, D.; Baron, M.; Skourti, P. V.; Chajistamatiou, A. S.; Docsa, T.; Gergely, P.;
Chrysina, E. D.; Praly, J. P.; Vidal, S. *Carbohydr. Res.* **2012**, *364*, 28-40.
29. Dong, L.; Li, L.; Ma, L.; Zhang, L. *Chin. Chem. Lett.* **1992**, *3*, 597-600.
30. Zemplén, G.; Pacsu, E. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 1613-1614.
31. Bokor, É.; Fekete, A.; Varga, G.; Szőcs, B.; Czifrák, K.; Komáromi, I.; Somsák, L.
Tetrahedron **2013**, *69*, 10391-10404.
32. Farkas, I.; Szabó, I. F.; Bognár, R. *Carbohydr. Res.* **1977**, *56*, 404-406.
33. Kun, S.; Nagy, G. Z.; Tóth, M.; Czece, L.; Nguyen van Nhien, A.; Docsa, T.;
Gergely, P.; Charavgi, M.-D.; Skourti, P. V.; Chrysina, E. D.; Patonay, T.; Somsák, L.
Carbohydr. Res. **2011**, *346*, 1427-1438.
34. Helferich, B.; Ost, W. *Chem. Ber.* **1962**, *95*, 2612-2615.

- 1
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63
64
65
35. Tóth, M.; Kövér, K. E.; Bényei, A.; Somsák, L. *Org. Biomol. Chem.* **2003**, *1*, 4039-4046.
36. Tóth, M.; Somsák, L.; Goyard, D. In *Carbohydrate Chemistry: Proven Synthetic Methods*; Kováč, P. Ed.; CRC Press: Boca Raton, 2012; pp. 355-365.
37. Zeller, K.-P.; Gugel, H. In *Methoden der organischen Chemie (Houben-Weyl)*; Regitz, M. Ed.; Thieme: Stuttgart, 1989; pp. 225-243.
38. Tóth, M.; Kun, S.; Somsák, L.; Goyard, D. In *Carbohydrate Chemistry: Proven Synthetic Methods*; Kováč, P. Ed.; CRC Press: Boca Raton, 2012; pp. 367-375.
39. Jäger, V.; Colinas, P. A. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry*; Padwa, A.; Pearson, W. H. Eds.; John Wiley & Sons, 2002; pp. 361-472.
40. van Mersbergen, D.; Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8801-8805.
41. Cerný, M.; Vrkoč, J.; Staněk, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 64-9.
42. Rollin, P.; Tatibouët, A. *Compt. Rend. Chimie* **2011**, *14*, 194-210.
43. Cobb, S. E.; Morgan, K. F.; Botting, N. P. *Tetrahedron Lett.* **2011**, *52*, 1605-1607.
44. Praly, J.-P.; Faure, R.; Joseph, B.; Kiss, L.; Rollin, P. *Tetrahedron* **1994**, *50*, 6559-6568.
45. Elek, R.; Kiss, L.; Praly, J. P.; Somsák, L. *Carbohydr. Res.* **2005**, *340*, 1397-1402.
46. Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108.
47. Tóth, M.; Kun, S.; Bokor, É.; Benlifa, M.; Tallec, G.; Vidal, S.; Docsa, T.; Gergely, P.; Somsák, L.; Praly, J.-P. *Bioorg. Med. Chem.* **2009**, *17*, 4773-4785.

Synthesis of C-xylopyranosyl- and xylopyranosylidene-spiro-heterocycles as potential inhibitors of glycogen phosphorylase

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- Synthesis of *C*-xylopyranosyl benzimidazole and 1,2,4-triazoles
- Synthesis of xylopyranosylidene-spiro-isoxazolines and -1,4,2-oxathiazoles
- Weak inhibition of rabbit muscle glycogen phosphorylase *b* by a *C*-xylopyranosyl 1,2,4-triazole

ACCEPTED MANUSCRIPT