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Stereoselective Synthesis of N-Glycosyl Oxazolines and Evaluation of Their Antiproliferative Activity

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Abstract

A stereoselective synthesis of protected N-glycosyl oxazolines has been developed from available acylated sugar 1,2-O-acetonides using intramolecular Ritter-like reactions. New N-α- and β-D-pentofuranosyl, α-D-hexofuranosyl oxazolines as valuable intermediates for preparation of diverse N-glycosides were obtained by $BF_3{\cdot}OEt_2$-KHF_2 or $BF_3{\cdot}OEt_2$-promoted reactions of pentofuranose and hexafuranose acetonide derivatives with nitriles. When selectively acylated D-xylo - or ribofuranoses were employed in the reactions, N-α-pentofuranosyl oxazolines were prepared in good yields. A mechanism for the formation of glycosyl oxazolines was proposed. A series of oxazoline derivatives were evaluated for their antiproliferative activity on three human cancer cell lines (MCF-7, Hela and K562).

Keywords

Ketal and acyl-protected carbohydrate derivatives, Ritter-like reactions, N-glycosyl oxazolines, antiproliferative activity

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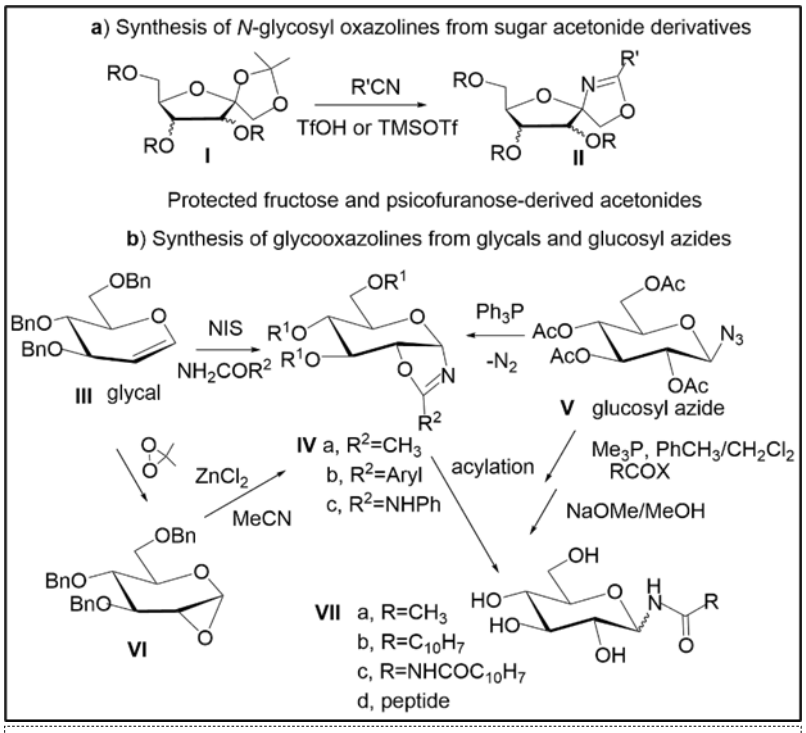
Introduction

2-Oxazolines belong to an interesting class of heterocyclic compounds with versatile synthetic applications [1-2]. Carbohydrate-fused oxazolines with a C1-O-linkage have found significant use for the chemical and enzymatic synthesis of oligosaccharides [3] and glycoconjugates [4], the preparation of modified carbohydrates, and the design of synthetic oligoamidosaccharides through cationic ring-opening polymerization [5]. It is worth noting that isomeric *C*1-N linked N-glycosyl oxazolines are of special interest in carbohydrate chemistry and these molecules have been used as valuable intermediates in constructing different N-glycoproteins [6]. However, only a few synthetic routes have been reported to produce isomeric N-glycosyl oxazolines (Scheme 1). Garcia Fernandez and co-workers explored conversions of β-D-fructopyranose and D-fructofuranose 1,2-O-acetonide derivatives (**I**) with various nitriles in the presence of triflic acid to obtain spiro glycosyl oxazolines (**II**) [7] by Ritter-like transformations (Scheme 1a). Vangala and Shinde synthesized spiro 2-substituted 2-oxazolines ribosides (**II**) in good yields from 1,2;3,4-di-O-acetonide β-D-psicofuranose derivatives, using stereoselective TMSOTf-mediated Ritter-like reactions with nitriles [8]. One-pot syntheses of different protected N-glycooxazolines (**IV a,b**) and - glycoaminooxa-

zolines (**IV c**) of interest as potential inhibitors of glycosidases and chitinases have been developed by De Castra *et al*. via reactions of benzyl- and TBDMS-protected D-glucals with various amides in the presence of N-iodosuccinimide (Scheme 1b) [9]. In addition, syntheses of the protected glucopyranosyl oxazoline (**IVa**) were also investigated from glucopyranosyl azides (e.g., **V**) [6,10], 1,2-anhydroglucopyranose derivative (**VI**) prepared by oxidation of glucal (**III**) [11], but there is still need for development of practical and efficient routes to various furanosyl or pyranosyl oxazolines containing the C1-nitrogen linkage.



Scheme 1. Stereoselective synthetic routes to N-glycosyl oxazolines from different carbohydrate precursors

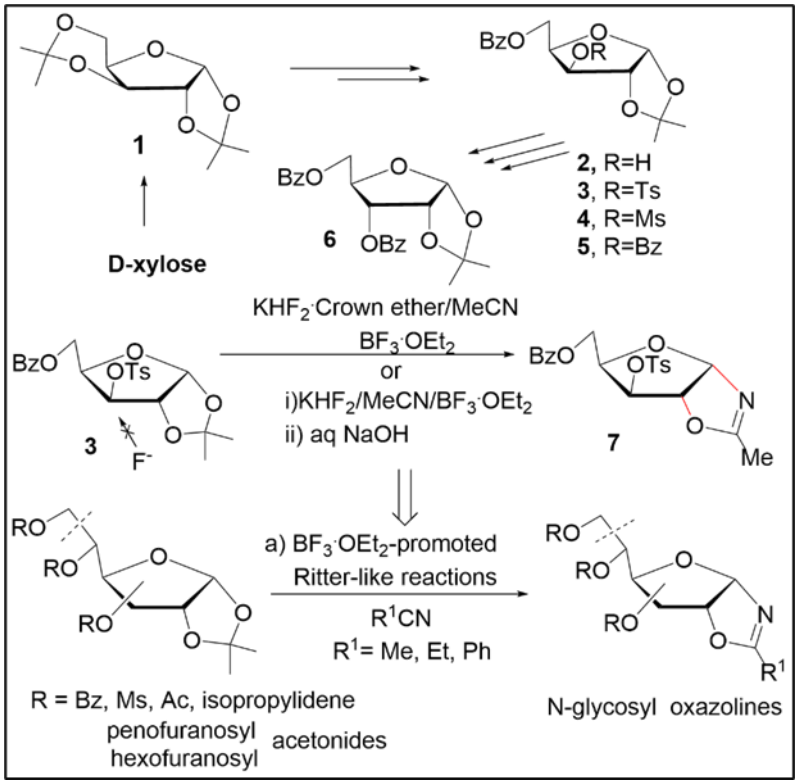
Carbohydrate-based N-glycosyl oxazolines have been employed as precursors in stereoselective syntheses of glycosyl isothiocyanates and amides. Acylated α-glycopyranosyl isothiocyanate was synthesized from N-glycooxazoline using copper (II) chloride as additive, and the similar ring-opening reaction of the glycooxazoline precursor with thiophosgene afforded β-glycopyranosyl isothiocyanate in the absence of any additive [12]. N-α-Glycosyl amides and N-α- or β-glycopeptides were obtained from azide **V** through the formation of the intermediate glucopyranosyl oxazoline (**IVa**) followed by α- or β-acylation [6,13]. The stereoselective approach to diverse N-β-glycosyl amides (**VII**) was developed via a PMe_3 mediated Staudinger reaction of glycopyranosyl azides (e.g. **V**) with carboxylic acid derivatives [13,14] (Scheme 1b). This paper reports a convenient and efficient method towards various N-furanosyl oxazolines based upon $BF_3{\cdot}OEt_2$-promoted Ritter-like reactions of protected sugar derivatives and evaluation of the antiproliferative activity of acylated N-glycosyl oxazolines.

Results and Discussion

Synthesis of N-glycosyl oxazoliones from sugar 1,2-O-acetonides and selectively protected D-pentofuranose deivatives

During investigation of different approaches towards fluorodeoxy D-pentofuranoses we have found that reaction of the 3-O-*p*-toluenesulfonyl xylofuranose derivative **3**, prepared via diacetonide **1** [15] from D-xylose, with a 3.5-fold access of the complex of KHF_2 with dibenzo-18-crown-6 in acetonitrile in the

presence of $BF_3{\cdot}Et_2O$ resulted in the formation of N-xylofuranosyl oxazoline **7** after the basic aqueous work-up of the reaction mixture and chromatography on silica gel. A selective transformation of the xylofuaranose acetonide derivative **3** with the solvent was observed at the 1,2-O-isopropylidene group in the presence of the Lewis acid (6-7.0 equiv) without formation of fluorinated products by a nucleophilic substitution reaction of the 3-O-*p*-toluenesulfonyloxy group with inorganic fluoride (Scheme 2). However, application of crown ether gave rise to tedious purification of the product by column chromatography. No reaction was observed under treatment of the tosylate **3** with a 3.5-fold access of KHF_2 in CH_3CN at rt and only the starting acetonide was recovered unchanged. Further, it was shown that the oxazoline **7** can be prepared from the acetonide derivative **3** in a high 98% yield using $BF_3{\cdot}Et_2O$/ KHF_2 in CH_3CN without column chromatography on silica gel (Scheme 2) as compared to the previous findings reported earlier [16].

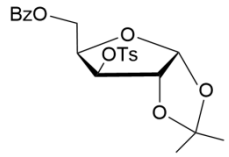
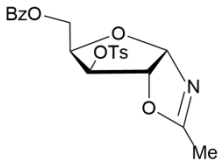
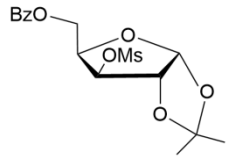
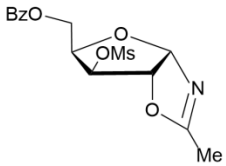
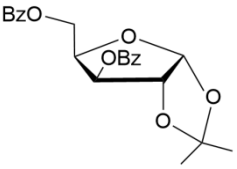
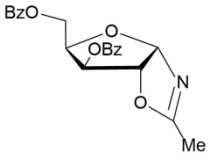
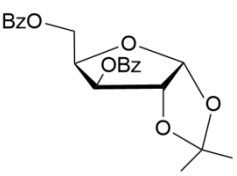
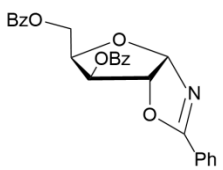


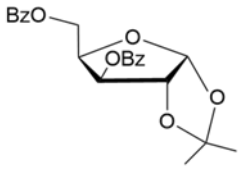
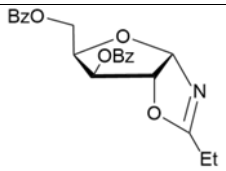
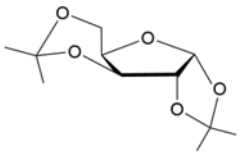
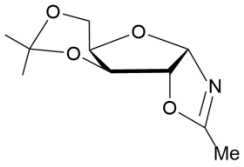
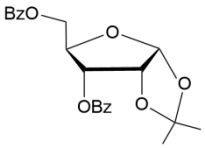
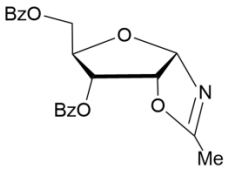
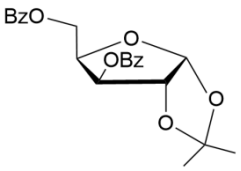
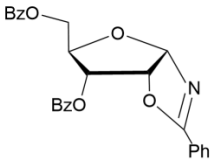
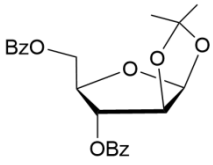
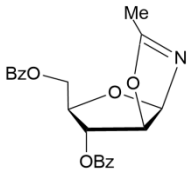
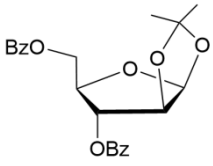
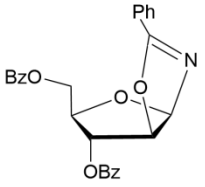
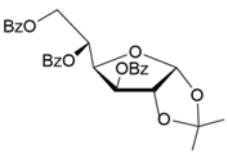
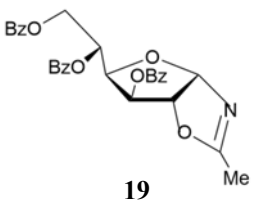
Scheme 2. Synthetic study of N-glycosyl oxazolines from sugar acetonides

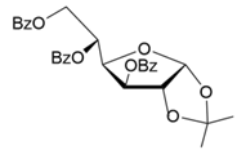
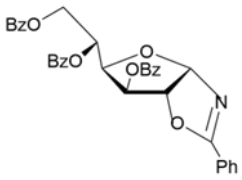
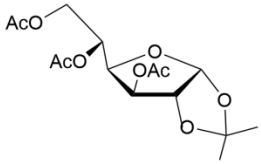
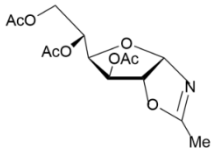
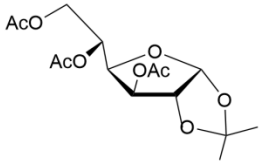
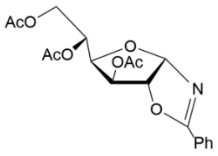
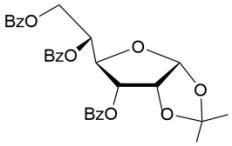
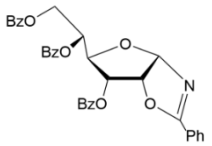
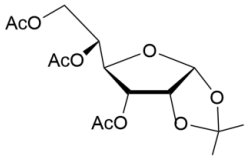
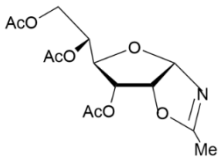
In the course of present comprehensive study, conversions of various protected D-pentofuranose and -hexofuranose acetonides with nitriles to glycosyl oxazoline derivatives were explored under $BF_3{\cdot}Et_2O/KHF_2$ reaction conditions at room temperature (Scheme 2 and Table 1). The reaction of the 3-O-mesyl xylofuranose derivative **4** gave the oxazoline **8** in 93% yield without formation of nucleophilic substitution products as with the tosylate **3**. N-Pentofuranosyl oxazolines **9**, **13** and **16** were synthesized in high 96-99% yields in acetonitrile (Table 1, entries 3,7 and 9) from isomeric benzoylated 1,2-O-isopropylidene-D-pentofuranose derivatives **5-6**, and **15**, prepared by the known methods decribed earlier from D-xylose and arabinose [17-21]. 1,2;3,5-Di-O-isopropylidene-D-xylofuranose (**1**) also afforded the protected xylofuranosyl oxazoline **12** in 76% yield as the result of regioselective transformations in the 1,2-O-isopropylidene group (table 1, entry 6). The reactions of benzoyl-protected D-xylofuranose, ribofuranose and arabinofuranose 1,2-O-acetonides studied in acetonitrile at room temperature gave rise to the stereoselective formation of *cis*-fused bicyclic N-α- and β- D-pentofuranosyl

oxazolines after the work-up of the reaction mixture without using column chromatography on silica gel (Table 1, entries 1-3, 6,7 and 9). Further, we explored scope of the $BF_3{\cdot}Et_2O$-KHF_2-mediated reaction of benzoylated 1,2-O-isopropylidene-D-pentofuranose derivatives with other nitriles such as propionitrile and benzonitrile. The reaction **6** with benzonitrile or propionitrile gave oxazolines **10** and **11** in 97% and 86% yields, respectively (entries 4 and 5). The protected α-ribofuranosyl and β-arabinofuranosyl oxazolines **14** and **17** were smoothly prepared from the Ritter-like reactions of acylated 1,2-O-acetonides of **6** and **15** in benzonitrile in 97% yield (Table 1, entries 8 and 10). Next, the above stereoselective reactions were investigated for acyl-protected hexofuranose 1,2-O-acetonide derivatives under the similar conditions. 3,5,6-Tri-*O*-benzoyl-1,2-O-isopropylidene-α-D-glucofuranose (**18**) as well as isomeric allofuranose derivative **24**, prepared according to the known methods [22], gave protected N-glycofuranosyl oxazolines **19** and **20** in acetonitrile and benzonitrile, oxazoline **25** in benzonitrile, respectively, in the high yields (Table 1, entries 11, 12 and 15). The Ritter reaction of fully O-acetylated 1,2-O-acetonide-α-D-glucofuranose **21** [23] or α-D-allofuranose **26** [24] in acetonitrile or benzonitrile furnished oxazolines **22** (entry 13), **23** (entry 14) and **27** (entry 16) in 95-98% yields. The structures of synthesized oxazolines were supported by ^1H, ^{13}C NMR, IR spectral data and mass spectra (Experimental part). Resonance signals of CH_3 groups of oxazoline rings for all synthesized glycosyl oxazolines were observed as singlets in the range of ~ 1.97-2.18 ppm and 13.2-14.2 ppm [7] in ^1H and ^{13}C NMR spectra,

Table 1. Synthesis of *N*-pentofuranosyl and *N*-hexofuranosyl oxazolines from protected D-sugar acetonides using BF_3 OEt_2-KHF_2-promoted reactions with nitriles

Entry	Protected acetonide	Nitrile	Time (h)	KHF_2/ $BF_3{\cdot}Et_2O$ (Mol equiv)	Product	Yield[a] (%)
1	 **3**	CH_3CN	18	3.0/7.2	 **7**	98%
2	 **4**	CH_3CN	18	3.1/7.2	 **8**	93%
3	 **5**	CH_3CN	18	3.5/6.3	 **9**	96%
4	 **5**	C_6H_5CN	18	3.5/6.2	 **10**	97%[b]

5	 **5**	C_2H_5CN	18	2.7/4.9	 **11**	86%[c]
6	 **1**	CH_3CN	4	2.1/6.2	 **12**	76%
7	 **6**	CH_3CN	18	3.5/6.3	 **13**	99%
8	 **6**	C_6H_5CN	18	2.7/6.2	 **14**	97%[b]
9	 **15**	CH_3CN	18	3.5/6.3	 **16**	99%
10	 **15**	C_6H_5CN	18	4.8/6.3	 **17**	97%[b]
11	 **18**	CH_3CN	18	3.4/8.4	 **19**	93%

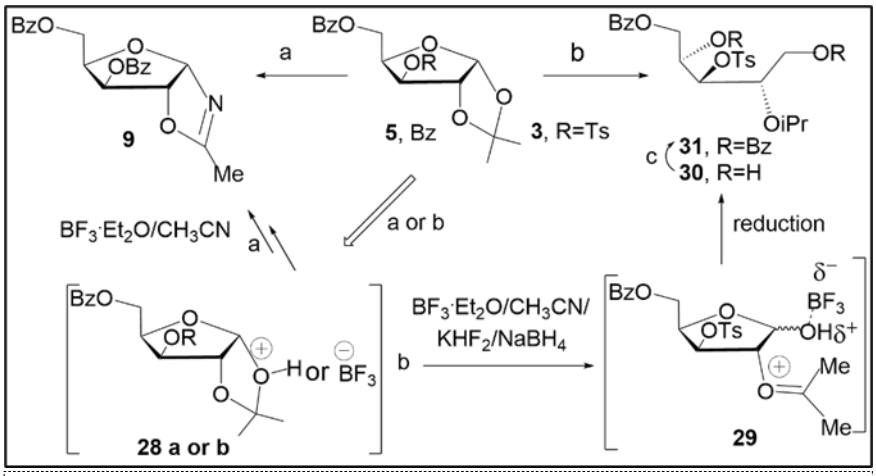
12	 **18**	C_6H_5CN	18	4.9/8.3	 **20**	92%[b]
13	 **21**	CH_3CN	18	2.5/8.1	 **22**	95%
14	 **21**	C_6H_5CN	18	4.9/8.3	 **23**	92%[b]
15	 **24**	C_6H_5CN	18	4.3/8.3	 **25**	86%[b]
16	 **26**	CH_3CN	18	2.4/8.0	 **27**	98%

[a] Isolated yield after basic treatment of reaction mixture without CC on silica gel
[b] Isolated yield after column chromatography on silica gel
[c] Yield was determined from ^{1}H NMR spectral data of the reaction mixture

respectively, measured in $CDCl_3$. Signals of the tertiary carbon atoms of the sugar oxazolines with 2-Me, Et or Ph substituents displayed at 167-173 ppm in ^{13}C NMR spectra. Absorption bands of the -*C*=N-bonds were revealed at 1642-1675 cm^{-1} in IR-spectra of *N*-glycosyl oxazolines.

Thus, we have found that the Ritter-like reactions [25-26] of the protected pentofuranose and hexofuranose 1,2-O-acetonides with nitriles in the presence of $BF_3{\cdot}Et_2O$ and KHF_2 resulted in stereoselective transformations in the 1,3-dioxolane ring to give the only reaction products containing the five-membered 2-oxazoline derivatives. Next, to understand the assumed role of KHF_2 as a promoter with acidic properties in the studied conversions of acetonides **1**, **3** and **5** into glycosyl α-D-oxazolines in the presence of $BF_3{\cdot}Et_2O$, the Ritter-like reaction of benzoylated D-xylofuranose 1,2-O-acetonide **5** was tested with acetonitrile in the presence of 7.2 equiv of $BF_3{\cdot}Et_2O$ and 3.4 equiv of *p*-toluenesulfonic acid instead of KHF_2 at room temperature (Scheme 3, conditions a).

The oxazoline **9** was prepared in 78% yield after column chromatography on silica gel. Besides, the $BF_3{\cdot}Et_2O$-KHF_2-assisted reaction of the tosylate **3** in acetonitrile was studied in the presence of $NaBH_4$ at room temperature (Scheme 3, conditions b). Such treatment of compound **3** did not result in the reduction of the C3-O-*p*-toluenesulfonyloxy group and acyclic product **30** was obtained in 40% yield after chromatography on silica gel. The structure of the xylitol derivative **30** was confirmed by the preparation of fully O-benzoylated derivative **31** (70%) and analysis of their ^1H and ^{13}C NMR, HRMS spectral data. Proposed synthetic pathway to compound **30** via the possible reductive cleavage of the ketal-protected xylofuranose derivative **3** is outlined in Scheme 3. Activation of the 1,3-dioxolane ring in **3** may proceecd in the presence of the Lewis acid BF_3 or an acidic promoter with generation of intermediate **29** in the first step. Then, the formation of an intermediate oxocarbenium ion **29** occurs from **28**. A selective reduction of aldofuranose counterpart of **29** with diborane forming in situ from $NaBH_4$ and BF_3 yields the selectively protected xylitol derivative **30** in the next steps (Scheme 3).The



Scheme 3. Study of $BF_3{\cdot}OEt_2$-assisted transformations of protected xylofuranose acetonides **3** and **5** on the 1,3-dioxolane ring in acetonitrile. Reagents and conditions: (a) **5**, CH_3CN, *p*-TsOH, $BF_3{\cdot}Et_2O$, rt, 18 h; 1N aq NaOH, **9**, 78%; (b) **3**, $KHF_2/BF_3{\cdot}Et_2O$, $NaBH_4$, CH_3CN, rt, 5% aq $NaHCO_3$, 40%, **30**; (c) BzCl, Py, rt, **31**, 65%.

above findings indicate that the $BF_3{\cdot}Et_2O$-mediated reactions of benzoylated D-pentofuranose 1,2-acetonides imply a regioselective activation of the 1,2-O-isopropylidene group with involvement of the Lewis acid and acid promoters such as $KF{\cdot}HF$ or *p*-TsOH, as with the Ritter-like reactions described for the fructofuranose acetonides in the presence of triflic acid [7] or natural monosaccharides in liquid HF [27].

To further explore Ritter reactions, syntheses of the protected N-glycosyl oxazolines were investigated from the D-pentofuranose **1**, **3**, **5** and hexofuranose **18**, **21**, **24** acetonide derivatives under various Lewis acid-assisted conditions (Table 2).

The control Ritter reaction of xylofuranose acetonides **3** or **5** was tested in acetonitrile in the presence of catalytic amounts of $BF_3{\cdot}Et_2O$ (0.5-0.8 equiv) and the excess of KHF_2 (3.5 equiv). No formation of oxazolines **7** and **9** was observed under these conditions (Table 2, entries 1 and 2). The reactions of acetonides **3** and **5** did not proceed in MeCN containing the excess of KHF_2 or a complex of KHF_2 with 18 crown 6 prepared previously in anhydrous methanol (entries 3 and 4). It was found that treatment of acetonides **3** and **5**, unlike diacetonide **1** (entry 9), with 7.2 and 6.3 equiv of $BF_3{\cdot}Et_2O$ in dry acetonitrile without KHF_2 led to oxazolines **7** and **9** in high 93% and 92% yields, respectively (entries 7 and 8). Ritter

Table 2. Screening in Ritter-like reactions of protected xylofuranosyl, glucofuranosyl and allofuranosyl acetonides with nitriles under the Lewis acid activated conditions

Entry	Protected acetonide	Reaction conditions	Oxazoline (yield,%)[a]
1	**3**	$BF_3{\cdot}Et_2O$ (0.5 equiv)/CH_3CN/KHF_2 (3.5 equiv), rt, 18 h	-
2	**5**	$BF_3{\cdot}Et_2O$ (0.8 equiv)/CH_3CN/KHF_2 (3.5 equiv), rt, 18 h	-
3	**3**	CH_3CN/ KHF_2 (5.6 equiv)·18 crown 6, rt, 18 h	-
4	**5**	CH_3CN/KHF_2 (3.5 equiv), rt, 18 h	-
5	**5**	$BF_3{\cdot}Et_2O$ (2.0 equiv)/CH_3CN/KHF_2 (3.5 equiv), rt, 18 h	**9** (20%)
6	**5**	$BF_3{\cdot}Et_2O$ (3.0 equiv)/CH_3CN/KHF_2 (3.5 equiv), rt, 18 h	**9** (87%)
7	**3**	$BF_3{\cdot}Et_2O$ (7.2 equiv)/CH_3CN, rt, 18 h	**7** (93%)
8	**5**	$BF_3{\cdot}Et_2O$ (6.3 equiv)/CH_3CN, rt, 18 h	**9** (92%)
9	**1**	$BF_3{\cdot}Et_2O$ (6.2 equiv)/CH_3CN, rt, 3 h	**12** (54%)[b]
10	**5**	$BF_3{\cdot}Et_2O$ (6.3 equiv)/PhCN, rt, 18 h	**10** (91%)[b]
11	**5**	$BF_3{\cdot}Et_2O$ (4.9 equiv)/EtCN, $0^0 \rightarrow$ rt, 18 h	**11** (72%)
12	**18**	$BF_3{\cdot}Et_2O$ (7.5 equiv)/PhCN, rt, 18 h	**20** (44%)[b]
13	**21**	$BF_3{\cdot}Et_2O$ (7.6 equiv)/PhCN, rt, 18 h	**23** (40%)[b]
14	**24**	$BF_3{\cdot}Et_2O$ (7.8 equiv)/PhCN, rt, 18 h	**25** (50%)[b]
15	**3**	TMSOTf (7.2 equiv)/CH_3CN/KHF_2 (3.5 equiv), rt, 18 h	**7** (98%)
16	**3**	TMSOTf (7.2 equiv)/CH_3CN, rt, 18 h	**7** (95%)

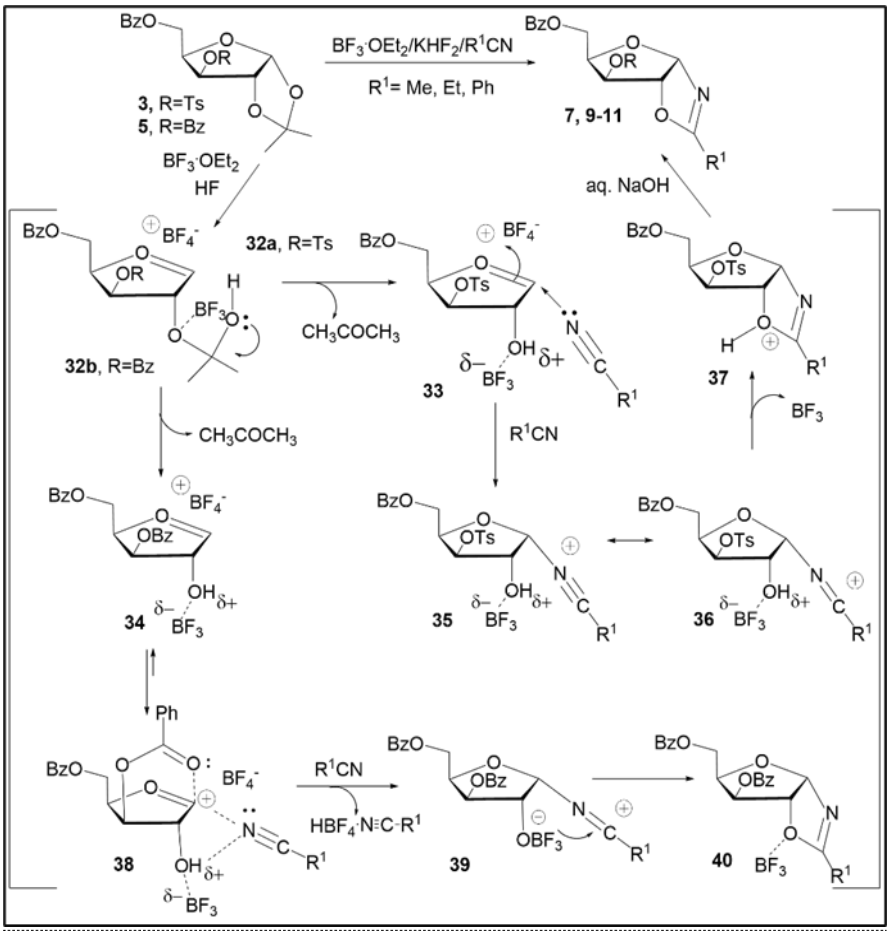
[a] Yield was determined from ^1H NMR spectral data of the reaction mixture

[b] Isolated yield after column chromatography on silica gel

reactions of benzoylated xylofuranosyl acetonide **5** with benzonitrile or propionitrile in the presence of 6.0 or 4.9 of equiv $BF_3{\cdot}Et_2O$ resulted in oxazolines **10** and **11** in 91% and 72% yields (entries 8 and 9). The Ritter reaction of *O*-benzoylated or acetylated 1,2-O-acetonide-D-glucofuranose derivatives **18** and **21** with benzonitrile in the presence of $BF_3{\cdot}Et_2O$ (7.5 equiv) gave the oxazolines **20** and **23** in 44% and 40% yields (entries 12 and 13) compared to the same reactions under the $BF_3{\cdot}Et_2O$-KHF_2-promoted conditions (92% and 95%) (Table 1, entries 12 and 13). The allofuranosyl oxazoline derivative **25** was prepared in high yields using the $BF_3{\cdot}Et_2O$-KHF_2- or $BF_3{\cdot}Et_2O$ conditions for Ritter reactions of the D-allofuranose acetonide **24** with benzonitrile in the presence of 7.5 equiv of the Lewis acid (Table 2, entry 14 and Table 1, entry 15). Ritter reactions of the acetonide **3** with acetonitrile have been tested using the TMSOTf-KHF_2 or TMSOTf-mediated conditions (entries 15 and 16) and the oxazoline **7** was prepared in 98% and 95% yields, respectively.

After screening of various $BF_3{\cdot}Et_2O$-promoted reactions of xylofuranose acetonides **1**, **3**, and **5** with different protecting groups we have found that benzoyl-protected N-glycosyl oxazolines can be prepared in good yields under the $BF_3{\cdot}Et_2O$-KHF_2 (Tables 1) or $BF_3{\cdot}Et_2O$ (table 2) conditions in the presence of the excess of the Lewis acid. In the case of a series of acylated hexofuranose 1,2-O-acetonide derivatives **18**, **21**, **24** and **26**, the excess of the Lewis acid (about 8 equiv) along with KHF_2 (2.5-4.0 equiv), that may generate HF or HBF_4 and KBF_4 after interaction with the strong Lewis acid in polar solvent, needs for conversions of acetonides into oxazolines under the $BF_3{\cdot}Et_2O$-KHF_2 (Table 1, entries 11-16) with good yields compared to the $BF_3{\cdot}Et_2O$-promoted reactions for glucofuranose acetonides **18, 21** and

allofuranose acetonide **24** (table 2, entries 12-14). It is important to note that selection of optimal conditions (the use of the acidic promoter, ratio of reagents, excess of LW) for achieving high yields of glycosyl oxazolines in the Ritter reactions under consideration depends on the structure of the starting sugar, a character of protecting groups and nitrile used as solvent/reagent. Based on analysis of different conditions explored for a series of the Ritter-like reactions of sugar acetonides, mechanistic pathways leading to the formation of N-α-glycosyl oxazolines from protected xylofuranose acetonides **1**, **3** and **5** were proposed (Schemes 4 and 5). Proposed mechanism for stereoselective $BF_3{\cdot}Et_2O$-KHF_2-assisted reactions of xylofuranose acetonide derivatives **3** and **5** with nitriles is illustrated in Scheme 4.



Scheme 4. Proposed mechanism for the formation of oxazolines from D-xylofuranose acetonide derivatives **3** and **5**

The synthetic route to protected N-α-xylofuranosyl oxazolines likely to include the formation of intermediate ions **32a** and **32b** with assistance of a mild acidic promoter (gradual generation from KHF_2 in the presence of excess of $BF_3{\cdot}Et_2O$ in polar solvent) and the Lewis acid, and the subsequent occurrence of oxocarbenium ions **33** and **34**, respectively [12, 27]. We suggest that mechanistic pathway towards the nitrilium intermediate **35** from tosylate **3** may occur through a direct nitrile addition to the furanosyl oxocarbenium ion **33** from α or β-face and without remote participation of the protecting groups. The formation of the thermodynamically more stable the α-nitrilium ion **35** as compared with an intermediate β-nitrilium ion is probably favored by activated with the Lewis acid the 2-hydroxyl group, which is capable of stabilizing the adjacent cation via interaction with the α-nitrilium group in the presence of BF_3. Notice that the preferential generation of an intermediate stable α-nitrilium ion under the conversion of the protected xylofuranose derivative in CD_3CN in the presence of the Lewis acid (Me_3OBF_4) has been supported by Turnbull and co-workers using ^1H NMR experimental data and DFT

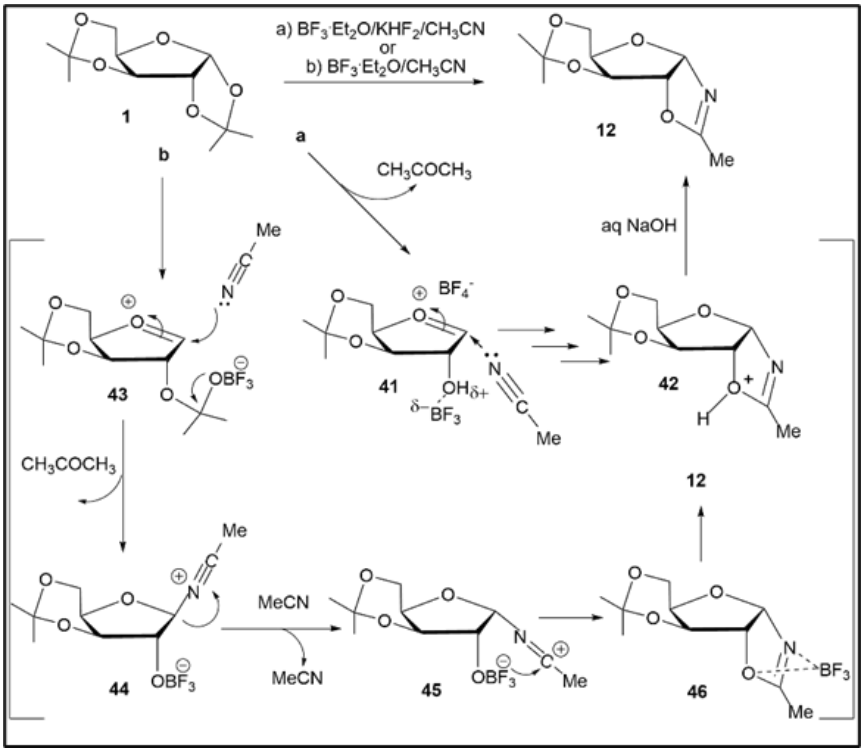
calculations [28]. The kinetically controlled formation of the α-xylofuranosyl nitrilium ion **35** can result from the oxocarbenium ion **33** or contact tetrafluoroborate ion pairs via solvation of the intermediate oxonium cation under S_N1-reaction and a fast attack with nitrile from the α-face due to an anomeric effect, as has been reported for the glycosylation reactions of pyranose derivatives through pyranosyl nitrilium ions [29-32]. The generation of oxazolinium intermediate **37** [29] proceeds from the cation **36** via intramolecular trapping of the 2-O-hydroxyl group with the electrophilic nitrilium carbon.

Another possible pathway for formation of acylated N-α-xylofuranosyl oxazolines via generation of intermediate cyclic benzoxonium ions with participation of acyl protecting groups should be considered in the case of $BF_3{\cdot}Et_2O$-KHF_2-assisted reactions of benzoylated D-xylofuranose 1,2-O-acetonide **5**. α-Xylofuranosyl nitrilium intermediates may arise by nitrile addition to the intermediate cyclic 1,3(1,5)-dioxacarbenium ions, which would be produced via assistance of the O-benzoyl groups in the oxocarbenium ion **34** in the presence of the Lewis acid. The influence of vicinal and remote O-acyl groups has been invoked on many glycosylation reactions of monosaccharide derivatives in the presence of Lewis acids [32-34]. The remote stereodirecting participation of 3-O- or 4-O-acyl (benzoyl, 4-methylbenzoyl or acetyl) protecting groups and their distinct stereochemical effects for promoted glycosylation reactions of protected pyranoses and furanoses as glycosyl donors have earlier been examined [34,35]. An interesting concept of catalysis for the glycosylation reactions was reported which was introduced by the Schmidt group [36-38]. It includes activation of acceptor and glycosyl donor in the presence of Lewis acids as catalysts followed by generation of a cyclic intermediate to give rise to O-glycoside(s) as a result of the stereoselective glycosidation. From those mechanistic considerations, pathway for the $BF_3{\cdot}Et_2O$-KHF_2-promoted reaction of acetonide **5** was proposed (Scheme 4). One may pass through an intermediate transition state or complex **38** that originates from coordination of a transient glycosyl cation, stabilized by the remote participation of 3-O-benzoyl group in the oxocarbenium ion, with acetonitrile under assistance of the 2-OH group activated in the presence of $BF_3{\cdot}Et_2O$ as a strong Lewis acid [32, 37].

The further stereoselective course of the Ritter reaction of acetonide **5** would result in α-xylofuranosyl nitrilium ions **39** and generation of an adduct **40** as a complex of the oxazoline with BF_3. The basic work-up of intermediate oxazolinium derivatives **37** and **40** with aqueous sodium hydroxide gave protected *N*-α-xylofuranosyl oxazolines **7**, **9**-**11** (Scheme 4).

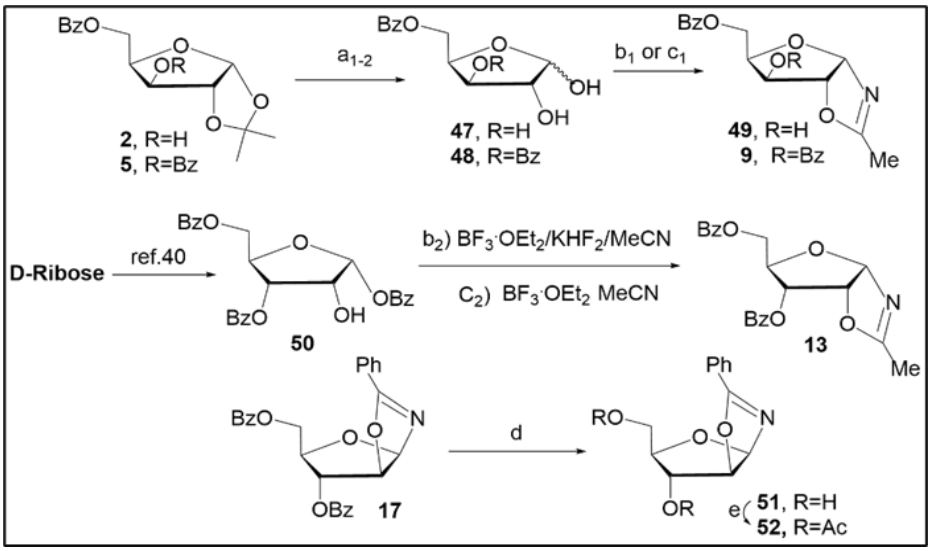
Two different pathways for $BF_3{\cdot}Et_2O$-promoted Ritter-like reactions of D-xylofuranose diacetonide **1**, bearing non-participating isopropylidene groups, are shown in Scheme 5.

The formation of the oxazoline **12** from diacetonide **1** in acetonitrile under the $BF_3{\cdot}Et_2O$-KHF_2-assisted conditions (a) may proceed via the oxocarbenium ion **41** after a regioselective activation of the 1,2-O-isopropylidene group with an acidic promoter and the Lewis acid followed by generation of the oxazolinium intermediate **42** similar to conversions of the 3-O-tosyl xylofuranose derivative **3** (Scheme 4) into the oxazoline **7** through the cation **36** and key oxazolinium derivative **37**. Under the $BF_3{\cdot}Et_2O$-mediated conditions (b), the Ritter-like reaction of **1** with acetonitrile would occur in a different pathway through activation of the 1,3-dioxolane ring with $BF_3{\cdot}Et_2O$ in the first step, generation of the oxocarbenium ion **43** and a subsequent bottom attack of solvent to give the β-nitrilium intermediate **44**, as has been reported for the preparation of oxazolines by reacting epoxides with nitriles in the presence of Lewis acids [11, 39]. The further inversion of **44** at C1 with acetonitrile would result in an intermediate α-nitrilium ion, and subsequently the electrophilic α-nitrilium cation **45**, a complex of the oxazoline with the Lewis acid **46**, giving the target oxazoline **16** after the basic work-up.



Scheme 5. Proposed intermediates during $BF_3{\cdot}Et_2O$-promoted reactions of diacetonide **1** with acetonitrile

In order to explore the scope of the $BF_3{\cdot}Et_2O$-mediated approach for other protected D-pentofuranose derivatives with free hydroxyl groups we have undertaken synthesis of *N*-xylofuranosyl oxazolines from selectively benzoylated xylofuranoses **47-48** readily prepared by the acidic removal of 1,2-O-isopropylidene groups from xylofuranose acetonide derivatives **2** and **5** with aqueous trifluoroacetic acid (Scheme 6, conditions $a_{1\text{-}2}$). 5-O-Benzoyl-α,β-D-xylofuranose (**47**) gave the benzoyl-protected oxazoline **49** (75%) under the the KHF_2-$BF_3{\cdot}Et_2O$ conditions (conditions b_1). Interestingly, the reaction of 3,5-di-O-



Scheme 6. Synthesis of acylated D-xylo-, ribo- and arabinofuranosyl oxazolines. Reagents and conditions: (a_1) **2**, 93% aq TFA, rt, 2 h, **47**, 80%; (a_2) **5**, 93% aq TFA, rt, 2 h, **48**, 80%; (b_1) benzoylated D-xylofuranoses **47-48**, CH_3CN, KHF_2,$BF_3{\cdot}Et_2O$, rt; 3-4 h, 5 % aq $NaHCO_3$, **49**, 75%; **9**, 99%; (c_1) **48**, CH_3CN/ $BF_3{\cdot}Et_2O$, rt, 3 h, 5 % aq $NaHCO_3$, **9**, 65%; (b_2) **50**, CH_3CN, KHF_2, $BF_3{\cdot}Et_2O$, rt; 3 h, 1N aq NaOH, **13**, 99%; (c_2) **50**, CH_3CN, $BF_3{\cdot}Et_2O$, rt, 3 h, 1N aq NaOH, **13**, 65%; d) **17**, NH_3/MeOH, rt, 18 h, **51**, 93%; e) **51**, Ac_2O, Py, rt, **52**, 80%.

benzoyl-α,β-D-xylofuranose (**48**) in acetonitrile furnished the oxazoline **9** (99%), as in the case of the Ritter reaction of 3,5-di-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose (**5**) (Table 1, entry 3).

In addition, the Ritter-like reaction of **48** with acetonitrile in the presence of $BF_3{\cdot}Et_2O$ (6.0 equiv) without KHF_2 (conditions c_1) also afforded the protected N-α-xylofuranosyl oxazoline **9** (65%). Furthermore, we have found that the Lewis acid promoted reactions of 1,3,5-tri-O-benzoyl-α-D-ribofuranose (**50**) [40] with CH_3CN in the presence of KHF_2 or without the inorganic salt gave the α-oxazoline **13** in 99% and 65% yields, respectively, after the basic work-up of reaction mixtures (Scheme 6, conditions b_2 and c_2). Removing benzoyl protecting groups in the oxazoline **17** with NH_3/MeOH (conditions d) resulted in the β-arabinofuranosyl oxazoline **51** (93%). Acetylation of the latter with acetic anhydride in pyridine at room temperature afforded fully O-acetylated oxazoline **52** in 80% yield.

From the above-considered synthetic routes to oxazolines from protected D-pentofuranose derivatives it should be noted that the $BF_3{\cdot}Et_2O$-promoted reactions of selectively acylated D-xylofuranose and -ribofuranose derivatives (Scheme 6), diacetonide **1** (Scheme 5) and acylated 1,2-O-isopropylidene-α-D-pentofuranoses **3**, **5**, **6** and **15** (Schemes 4 and 3) differ in producing intermediate oxocarbenium ions in the presence of the Lewis acid in the first steps and, probably, different oxazolinium intermediates in the next steps. The formation of α-nitrilium ions is the general peculiarity for the Ritter-like transformations of D-xylofuranose and -ribofuranose derivatives studied with nitriles. Prepared sugar oxazolines can be used for obtaining various N-glycosyl amides via hydrolysis reactions and novel N-glycoside derivatives.

In vitro antiproliferative activity of N-glycosyl oxazoline derivatives with 2-phenyl substituent

A series of newly synthesized N-glycosyl oxazoline derivatives with 2-phenyl substituent were tested for their *in vitro* inhibitory effects on proliferation of myelogenous leukemia (K562), cervical carcinoma (Hela) and breast carcinoma (MCF-7) using the resazurin assay [41]] that, together with other high-throughput screening methods, had been developed previously to measure viability or cytotoxicity [42]. 5-Fluorouracil (5-FU) was used as the reference compound. The findings are listed in Table 3.

Table 3. Antiproliferative activities of a series of *N*-glycosyl oxazoline derivatives with 2-phenyl substituent on human cancer cell lines

Compound	IC_{50}[a] (μM)		
	MCF-7	K-562	Hela
10	99.76±0.45	> 100	> 100
14	> 100	23.01±0.31	63.92±0.21
17	79.4±0.34	> 100	> 100
20	> 100	> 100	21.92±0.25
51	NI	NI	NI
52	> 100	> 100	> 100
5-FU	26.32±0.32	11.02±0.26	32.43±0.17

[a] IC_{50} is concentration of compound required to inhibit cancer cell proliferation by 50%. IC_{50} values were calculated from the cell growth inhibition curves obtained from the treatments done with increasing concentrations. NI: no inhibition.

Among N-pentofuranosyl oxazolines with *xylo*-, *ribo*- and *arabino*-configurations tested (compounds **10**, **14**, **17**, **51** and **52**), only benzoylated xylo- and arabinofuranosyl oxazolines **10** and **17** displayed weak inhibitory effects against MCF cell line with IC_{50} values of 99.76 and 79.4 μM, respectively. Unlike to isomeric *xylo*- and *arabino*-furanosyl oxazolines **10** and **17**, 3,5-di-*O*-benzoyl α-ribofuranosyl oxazoline **14** showed moderate activity with IC_{50} value of 63.92 μM in Hela cells and good antiproliferative activity against K562 cell line (IC_{50} 23.01 μM). Deprotected N-β-D-arabinofuranosyl oxazoline **51** did not show activity on all cell lines at the highest concentration of tested compound. The benzoylated N-α-glycofuranosyl oxazoline derivative **20**, bearing 2-phenyl substituent in the oxazoline ring, displayed significant antiproliferative activity with IC_{50} value (21.92 μM) comparable to those of the known nucleobase analog 5-FU on Hela cells. Comparative biological assessment of the oxazoline **20** and its close structural analogs the N-glycosyl oxazoline derivatives **23** and **25** is underway in cancer cell lines. To gain insight into the mode action/mechanism for the inhibitory effects of the oxazolines with 2-phenyl substituent, the apoptosis assays for compound **20** as well as its two analogs are currently under investigation in Hela cancer cell line, applying DAPI and Annexin V-FITC/PI staining methods, and the results will be published elsewhere.

Conclusion

In summary, a convenient and stereoselective approach to prepare various N-glycosyl oxazolines has been developed from sugar 1,2-O-acetonides using mild reaction conditions for the $BF_3{\cdot}OEt_2$-mediated Ritter-like reactions. Scope of a novel method based upon the reactions of selectively protected D-pentofuranose derivatives with nitriles as solvents in the presence of the excess of the Lewis acid and potassium hydrogen difluoride, or $BF_3{\cdot}OEt_2$-assisted conditions, was examined for the preparation of blocked carbohydrate-based oxazolines. A series of new oxazolines as valuable intermediates to prepare N-glycosyl amides, modified sugars and N-glycopeptides were synthesized in high yields, and screened for their inhibitory effects on proliferation of three human cancer cell lines. Of various 2-phenyl substituted N-furanosyl oxazolines evaluated, only the benzoyl-protected glucofuranosyl and ribofuranosyl oxazoline derivatives were found to exhibit good growth inhibition activities against two different cancer cell lines.

Experimental section

General information. Column chromatography was performed on silica gel 60 H (70-230 mesh; Merck, Darmstadt, Germany), and thin-layer chromatography (TLC) on Merck silica gel aluminum 60 F_{254} precoated plates. All commercially available reagents were used without further purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and CD_3OD with a Bruker Avance-500-DRX spectrometer at 500.13 and 126.76MHz, respectively. ^1H and ^{13}C NMR chemical shifts (δ, ppm) are relative to internal chloroform peak (7.26 ppm for ^1H and 77.0 for ^{13}C NMR). Splitting patterns were reported as following: s: singlet, d: doublet, t: triplet, m: multiplet. *J* values are reported in Hz. Optical rotations were measured with Autopol III automatic polarimeter. IR spectra were measured with on PerkinElmer Spectrum 100FT -IR spectrometer. Melting points were determined on a Boetius apparatus and were uncorrected. High resolution mass spectra (HRMS) were recorded on an Agilent Q-TOF 6550 Instrument (USA) using ESI (electrospray ionization).

Synthesis of N-glycosyl oxazolines from protected pentofuranose 1,2-O-acetonides

a_1. Synthesis 2-alkyl-α-D-pentofurano-[1,2-d]-2-oxazoline derivatives under the $BF_3{\cdot}Et_2O$-KHF_2-promoted conditions. To a stirred solution of pentofuranose acetonide derivative (1.4 mmol) in anhy-

drous acetonitrile (8.6 ml) or benzonitrile (3.8 ml) KHF_2 (4.8 mmol) and boron trifluoride diethyl etherate (1.42 ml,10.3 mmol) were added successively. The resulting solution was stirred at room temperature for 18 h, and then the reaction mixture was poured into cooled 22.6 ml 1N aq NaOH. The aqueous phase was extracted with $CHCl_3$ (3x100 ml). The combined organic extracts were washed with water, dried over anh. Na_2SO_4, and evaporated to dryness. Oxazolines **7-8**, **11-13** were prepared in 76-99% yields, and oxazolines **10**, **14**, **17** with 2-phenyl substituent were isolated in 97% yield after column chromatography on silica gel using for elution mixtures of hexane-ethylacetate and ethylacetate-methanol 6:1.

a_2. Synthesis 2-methyl-α-D-pentofurano-[1,2-d]-2-oxazoline derivatives under the $BF_3{\cdot}Et_2O$-promoted conditions. To a stirred solution of xylofuranose acetonide derivative (0.2 mmol) in anhydrous acetonitrile (1.5 ml) boron trifluoride diethyl etherate (0.2 ml, 1.44 mmol) was added successively. The resulting solution was stirred at room temperature for 18 h, and then the reaction mixture was poured into cooled 5% aq. $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$ (3x50 ml). The combined organic extracts were washed with water, dried over anh. Na_2SO_4, and evaporated to dryness. Oxazolines **7**, **9** and **12** were prepared in 54-93% yields.

Synthesis of N-glycosyl oxazolines from protected hexofuranose 1,2-O-acetonides

a_1. To a stirred solution of acylated glucofuranose or allofuranose acetonide (0.4 mmol) in anhydrous benzonitrile (3.8 ml) or acetonitrile (3.1 ml) KHF_2 (1.95 mmol) and boron trifluoride diethyl etherate (0.45 ml, 3.3 mmol) were added successively. The reaction mixture was stirred at room temperature for 18 h, and then poured into cooled 7.3 ml 1N aq NaOH. The aqueous phase was extracted with $CHCl_3$ (3x30 ml). The combined organic extracts were washed with water, dried over anh. Na_2SO_4, and evaporated. Oxazolines with 2-phenyl substituent were isolated by column chromatography on silica gel using for elution mixtures of hexane-ethylacetate 6:1, 4:1, 2:1, and ethylacetate or ethylacetate-methanol 6:1. Oxazolines **19-20**, **22-23** and **25**, **27** were prepared in 86-98% yields.

2-Methyl-(5-O-benzoyl-3-O-p-toluenesulfonyl-α-D-xylofurano)-[1,2-d]-2-oxazoline (**7**).

Yield (98%), a colorless oil (method a_1). $[\alpha]_D^{20}$ –44.4 (c 0.5, $CHCl_3$). IR (film, CCl_4): ν 1725, 1670, 1615, 1375, 1272 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.85 (m, 9H, COC_6H_5 and $OSO_2C_6H_4CH_3$), 6.09 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 5.02 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 4.86 (d, 1H, H-2), 4.33 (dd, 1H, $J_{5,4}$ = 6.2, $J_{5,5'}$ = 11.3 Hz, H-5), 4.22 (dd, 1H, $J_{5',4}$ = 5.7 Hz, H-5′), 3.98-4.01 (m, 1H, H-4), 2.31 (s, 3H, $OSO_2C_6H_4CH_3$), 1.96 (s, 3H, NCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.4 (CN), 164.9 (C=O, COC_6H_5), 145.6, 133.4, 130.3, 129.2, 128.5, 127.6 (COC_6H_5 and $OSO_2C_6H_4CH_3$), 100.2 (C-1), 88.4 (C-4), 81.1, 74.2 (C-2, C-3), 60.3 (C-5), 21.0 ($OSO_2C_6H_4CH_3$), 13.2 (NMe). HRMS (ESI^+): m/z calcd for $C_{21}H_{21}NO_7S$ $[M+H]^+$: 432.1117, found 432.1120; and $C_{21}H_{21}NO_7SNa$ $[M+Na]^+$: 454.0936, found 454.0935.

2-Methyl-(5-O-benzoyl-3-O-methanesulfonyl-α-D-xylofurano)-[1,2-d]-2-oxazoline (**8**).

Yield (93%), a colorless oil (method a_1). $[\alpha]_D^{20}$ –35.1 (c 0.8, $CHCl_3$). IR (film): ν 1722, 1675, 1357, 1275 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ =7.47-8.09 (m, 5H, COC_6H_5), 6.22 (d, 1H, $J_{1,2}$=5.6 Hz, H-1), 5.23 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 5.09 (d, 1H, H-2), 4.66 (dd, 1H, $J_{5,4}$ = 6.3, $J_{5,5'}$ = 11.8 Hz, H-5), 4.62 (dd, 1H, $J_{5',4}$ = 3.4 Hz, H-5′), 4.13-4.16 (m, 1H, H-4), 3.16 (s, 3H, OSO_2CH_3), 2.12 (s, 3H, NCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 168.8 (CN), 166.1 (C=O, COC_6H_5), 133.5, 129.8, 129.3, 128.5, (COC_6H_5), 100.8 (C-

1), 84.2 (C-4), 77.3, 75.1 (C-2, C-3), 60.8 (C-5), 38.5 (OSO_2CH_3), 13.9 (NMe). HRMS (ESI^+): m/z calcd for $C_{15}H_{17}NO_7S$ $[M+H]^+$: 356.0798, found 356.0791; and $C_{21}H_{21}NO_7SNa$ $[M+Na]^+$: 378.0610, found 378.0511.

2-Methyl-(3,5-di-O-benzoyl-α-D-xylofurano)-[1,2-d]-2-oxazoline (**9**).

Yield (96%), foam (method a_1). $[\alpha]_D^{20}$ –73.2 (c 1.0, $CHCl_3$). IR (KBr): ν 1722, 1672, 1364, 1275, 1180 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.39-8.04 (m, 10H, 2 x COC_6H_5), 6.21 (d, 1H, $J_{1,2}$ =5.7 Hz, H-1), 5.59 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-3), 4.86 (d, 1H, $J_{2,1}$ = 5.7 Hz, H-2), 4.64 (d, 2H, H-5, H-5′), 4.19-4.25 (m, 1H, H-4), 2.1 (s, 3H, NCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.7 (CN), 166.1 and 165.2 (C=O, 2xCOC_6H_5), 140.2, 140.0, 131.3, 131.2, 128.9, 128.8, 128.7, 128.2 (2xCOC_6H_5), 100.8 (C-1), 84.6 (C-4), 76.3, 75.5 (C-2, C-3), 61.6 (C-5), 13.8 (NMe). HRMS (ESI^+): m/z calcd for $C_{21}H_{19}NO_6$ $[M+H]^+$: 382.1285, found 382.1287.

2-Phenyl-(3,5-di-O-benzoyl-α-D-xylofurano)-[1,2-d]-2-oxazoline (**10**).

Yield(97%), a colorless oil (method a_1). $[\alpha]_D^{20}$ -27.5 (c 1.0, $CHCl_3$). IR (KBr): ν 1725, 1665, 1268, 1112 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$) δ = 7.42-8.13 (m, 15H, 2 x COC_6H_5, -N=C-C_6H_5), 6.52 (d, 1H, $J_{1,2}$ =4.0 Hz, H-1), 5.79 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 5.15 (d, 1H, $J_{2,1}$ = 4.0 Hz, H-2), 4.74 (d, 2H, H-5, H-5′), 4.33-4.36 (m, 1H, H-4). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.0 (CN), 166.1 and 165.4 (C=O, 2xCOC_6H_5), 133.9, 133.2, 132.8, 129.9, 129.8, 129.2, 128.7, 128.6, 128.4 (2xCOC_6H_5, -N=C-C_6H_5), 100.8 (C-1), 84.8 (C-4), 76.4, 75.6 (C-2, C-3), 61.5 (C-5). HRMS (ESI^+): m/z calcd for $C_{26}H_{21}NO_6$ $[M+Na]^+$: 466.1261, found 466.1263.

2-Ethyl-(3,5-di-O-benzoyl-α-D-xylofurano)-[1,2-d]-2-oxazoline (**11**).

Yield (86%), foam, (method a_1). $[\alpha]_D^{20}$ - 36.3 (c 1.0, $CHCl_3$). IR (KBr): ν 1724, 1670, 1363, 1275, 1182 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.44-8.09 (m, 10H, 2 x COC_6H_5), 6.29 (d, 1H, $J_{1,2}$ = 5.7 Hz, H-1), 5.65 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-3), 4.92 (d, 1H, $J_{2,1}$ = 5.7 Hz, H-2), 4.70 (d, 2H, H-5, H-5′), 4.21-4.28 (m, 1H, H-4), 2.45-2.49 (m, 2H, -N=C-CH_2CH_3), 1.29 (t, 3H, -N=C-CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.1 (CN), 166.2 and 165.3 (C=O, 2xCOC_6H_5), 133.8, 133.3, 129.9, 129.8, 129.5, 128.9, 128.7, 128.4 (2xCOC_6H_5), 100.6 (C-1), 84.5 (C-4), 76.3, 75.4 (C-2, C-3), 61.6 (C-5), 21.5 (N=C-CH_2CH_3), 10.2 (N=C-CH_2CH_3). HRMS (ESI^+)**:** m/z calcd for $C_{21}H_{21}NO_6$ $[M+H]^+$: 396.1442, found 396.1446.

2-Methyl-(3,5-O-isopropylidene-α-D-xylofurano)-[1,2-d]-2-oxazoline (**12**).

Yield (76%), oil (method a_1). $[\alpha]_D^{20}$ +6.9 (c 1.0, $CHCl_3$). IR (film): ν 2993, 2940, 1669, 1384, 1228, 1043 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.10 (d, 1H, $J_{1,2}$ = 5.5 Hz, H-1), 4.65 (d, 1H, $J_{2,1}$ = 5,5 Hz, H-2), 4.30 (d, 1H, $J_{3,4}$= 2.4 Hz, H-3), 4.09 (dd, 1H, $J_{5,4}$= 2.5, $J_{5,5'}$= 13.6 Hz, H-5), 4,07 (d, 1H, H-5′), 3.47-3.3.49 (m, 1H, H-4), 2.00 (s, 3H, NCH_3), 1.42 and 1.36 [2 s, 3H, $(CH_3)_2C$-)]. ^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.3 (CN), 101.3 (C-1), 97.7 [C-$CH_3)_2$], 85.9 (C-4), 72.9, 69.6 (C-2, C-3), 59.5 (C-5), 28.8 and 18.6 [$(CH_3)_2$C-], 13.7 (NMe). HRMS (ESI^+): m/z calcd for $C_{10}H_{15}NO_4$ $[M+H]^+$: 214.1074, found 214.1084.

2-Methyl-(3,5-di-O-benzoyl-α-D-ribofurano)-[1,2-d]-2-oxazoline (**13**).

Yield (99%), a colorless oil (method a_1). $[\alpha]_D^{20}$ +74.5 (c 1.0, $CHCl_3$). IR (film): ν 1729, 1665, 1272, 1119 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.40-8.08 (m, 10H, 2 x COC_6H_5), 6.17 (d, 1H, $J_{1,2}$ =5.5 Hz, H-1), 5.22 (t, 1H, $J_{2,1}$ =5.5, $J_{2,3}$ =5.7 Hz, H-2), 5.16 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.75 (dd, 1H, $J_{5,4}$=3.6, $J_{5,5'}$=12.0 Hz, H-5), 4.57 (dd, 1H, $J_{5',4}$ =5.2 Hz, H-5′), 4.19-4.23 (m, 1H, H-4), 2.1 (s, 3H, NCH_3). ^{13}C NMR ($CDCl_3$) δ = 169.7 (CN), 166.1 and 165.5 (C=O, 2xCOC_6H_5), 133.6, 133.2, 129.8, 129.7, 129.4,

128.8, 128.5, 128.3 (2xCOC_6H_5), 100.6 (C-1), 78.5 (C-4), 74.1, 74.0 (C-2, C-3), 63.0 (C-5), 13.8 (NMe). HRMS (ESI$^+$): m/z calcd for $C_{21}H_{19}NO_6$ [M+H]$^+$: 382.1285, found 382.1287.

2-Phenyl-(3,5-di-O-benzoyl-α-D-ribofurano)-[1,2-d]-2-oxazoline (**14**).

Yield (97%), a white solid (method a_1). M.p. 128-129 °C. $[\alpha]_D^{20}$ +113.8 (c 1.0, $CHCl_3$). IR (KBr): ν 1739, 1716, 1646, 1277, 1101 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35-8.04 (m, 15H, 2 x COC_6H_5, -N=C-C_6H_5), 6.37 (d, 1H, $J_{1,2}$ =5.6 Hz, H-1), 5.38 (t, 1H, $J_{3,2}$ = 5.7 Hz, H-2), 5.24 (d, 1H, $J_{3,4}$ =$J_{3,2}$ = 5.9 Hz, H-3), 4.72 (dd, 1H, $J_{5,4}$ = 4.7, $J_{5,5'}$ = 12.1 Hz, H-5), 4.55 (dd, 1H, $J_{5',4}$ = 4.7 Hz, H-5′), 4.20-4.24 (m, 1H, H-4). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.5 (CN), 166.1 and 165.7 (C=O, 2xCOC_6H_5), 133.6, 133.1, 132.5, 129.8, 129.7, 129.4, 128.9, 128.8, 128.5 (2xCOC_6H_5, -N=C-C_6H_5), 100.8 (C-1), 78.4 (C-4), 74.1, 74.09 (C-2, C-3), 63.0 (C-5). HRMS (ESI$^+$): m/z calcd for $C_{26}H_{21}NO_6$ [M+Na]$^+$: 466.1261, found 466.1264.

2-Methyl-(3,5-di-O-benzoyl-β-D-arabinofurano)-[1,2-d]-2-oxazoline(**16**).

Yield (99%), a colorless oil (method a_1). $[\alpha]_D^{20}$ -36.1 (c 1.0, $CHCl_3$). IR (KBr): ν 1725, 1669, 1321, 1269, 1108 см$^{-1}$.^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.41-8.06 (m, 10H, 2 x COC_6H_5), 6.14 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 5.51 (br.d, 1H, $J_{3,4}$ = 2.5, $J_{3,2}$ = 1.2 Hz, H-3), 4.98 (br. d, 1H, $J_{2,1}$ = 5.5 Hz, H-2), 4,54-4,57 (m, 1H, H-4), 4,39 (dd, 1H, $J_{5,4}$= 6.2, $J_{5,5'}$=11.7 Hz, H-5), 4.36 (dd, 1H, $J_{5',4}$=3.9 Hz, H-5′), 2.07 (s, 3H, NCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 168.7 (CN), 166.1 and 165.4 (C=O, 2xCOC_6H_5), 133.7, 133.1, 129.8, 129.8, 129.6, 128.8, 128.5, 128.3 (2xCOC_6H_5), 101.8 (C-1), 86.4 (C-4), 80.7, 79.0 (C-2, C-3), 63.7 (C-5), 14.3 (NMe). HRMS (ESI$^+$): m/z calcd for $C_{21}H_{19}NO_6$ [M+H]$^+$: 382.1285, found 382.1287.

2-Phenyl-(3,5-di-O-benzoyl-β-D-arabinofurano)-[1,2-d]-2-oxazoline (**17**).

Yield (97%), a colorless oil (method a_1). $[\alpha]_D^{20}$ -8.5 (c 1.0, $CHCl_3$). IR (film): ν 1721, 1642, 1269, 1109 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.30-8.14 (m, 15H, 2 x COC_6H_5, -N=C-C_6H_5), 6.46 (d, 1H, $J_{1,2}$ =5.7 Hz, H-1), 5.76 (d, 1H, $J_{3,4}$ = 2.6 Hz, H-3), 5.29 (d, 1H, $J_{2,1}$ = 5.7 Hz, H-2), 4.65-4.68 (m, 1H, H-4), 4.48 (dd, 1H, $J_{5,4}$ 5.8, $J_{5,5'}$= 11.6 Hz, H-5), 4.38 (dd, 1H, $J_{5',4}$ = 6.4 Hz, H-5′). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.9 (CN), 166.1 and 165.5 (C=O, 2xCOC_6H_5), 133.8, 133.1, 132.8, 129.9, 129.8, 129.2, 128.7, 128.6, 128.3 (2xCOC_6H_5, -N=C-C_6H_5), 100.9 (C-1), 86.7 (C-4), 81.4, 79.3 (C-2, C-3), 63.8 (C-5). HRMS (ESI$^+$): m/z calcd for $C_{26}H_{21}NO_6$ [M+Na]$^+$: 466.1261, found 466.1265.

2-Methyl-(3,5,6-tri-O-benzoyl-α-D-glucofurano)-[1,2-d]-2-oxazoline (**19**).

Yield (93%), a colorless oil (method a_1). $[\alpha]_D^{20}$-173.0 (c 1.0, $CHCl_3$). IR (film): ν 1725, 1667, 1375, 1266 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40-8.04 (m, 15H, 3 x COC_6H_5), 6.26 (d, 1H, $J_{1,2}$= 5.6 Hz, H-1), 5.90-5.93 (m, 1H, H-5), 5.62 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 5.02 (dd, 1H, H-6), 4.90 (d, 1H, H-2), 4.63 (dd, 1H, H-6′), 4.27 (dd, 1H, H-4), 2.18 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.04 (CN), 166.11, 165.3 and 165.1 (C=O, 3xCOC_6H_5), 133.69, 133.27, 133.06, 131.18, 129.9, 129.73, 129.68, 128.56 128.37 (3xCOC_6H_5), 100.88 (C-1), 84.56, 75.71, 75.64, 75.51 (C-4, C-5, C-2, C-3), 64.25 (C-6), 13.9 (NMe). HRMS (ESI$^+$): m/z calcd for $C_{29}H_{25}NO_8$ [M+Na]$^+$: 538.1478, found 538.1453.

2-Phenyl-(3,5,6-tri-O-benzoyl-α-D-glucofurano)-[1,2-d]-2-oxazoline (**20**).

Yield (92%), a colorless oil (method a_1). $[\alpha]_D^{20}$-34.6 (c 1.0, $CHCl_3$). IR (KBr): ν 1728, 1646, 1268, 1102 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-8.15 (m, 20H, 2 x COC_6H_5, -N=C-C_6H_5), 6.52 (d, 1H, $J_{1,2}$ = 5.5 Hz, H-1), 5.95-5.99 (m, 1H, H-5), 5.75 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 5.13 (d, 1H, $J_{2,1}$ = 5.5 Hz, H-2), 5.06 (dd, 1H, $J_{6,5}$= 5.8, $J_{6,6'}$ = 11.6 Hz, H-6), 4.65 (dd, 1H, $J_{6,5}$= 5.4 Hz, H-6′), 4.36 (dd, 1H, H-4). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.9 (CN), 166.0, 165.3 and 165.0 (C=O, 3xCOC_6H_5), 133.6, 133.1,

132.9, 132.7, 129.8, 129.6, 128.6, 128.5, 128.2 (3xCOC_6H_5, -N=C-C_6H_5), 100.9 (C-1), 84.8, 75.6, 75.6, 68.4 (C-5, C-4, C-2, C-3), 64.2 (C-6). HRMS (ESI^+): m/z calcd for $C_{34}H_{27}NO_8$ $[M+Na]^+$: 600.1634, found 600.1630.

2-Methyl-(3,5,6-tri-O-acetyl-α-D-glucofurano)-[1,2-d]-2-oxazoline (**22**).

Yield (95%), a colorless oil (method a_1). $[\alpha]_D^{20}$ +7.2 (c 1.0, $CHCl_3$). IR (film): ν 1743, 1662, 1375, 1243 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.07 (d, 1H, $J_{1,2}$=5.6 Hz, H-1), 5.34 (br.s, 1H, H-3), 5.23-5.26 (m, 1H, H-5), 4.63 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-2), 4.54(dm, 1H, H-4), 4.04 (dd, 1H, H-6), 3.82 (dd, 1H, H-6'), 2.06, 2.05, 2.02, and 1.97 (4s, 3H, 3x $COCH_3$, NCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ= 170.6 (CN), 169.6, 169.6 and 168.8 (C=O, 3x$COCH_3$), 100.9 (C-1), 84.5, 75.2, 74.3, 67.5 (C-4, C-5, C-2, C-3), 63.4 (C-6), 20.8 and 20.7 (3x$CO\mathit{CH}_3$), 13.9 (NMe). HRMS (ESI^+): m/z calcd for $C_{14}H_{19}NO_8$ $[M+Na]^+$: 352.1003, found 352.1006.

2-Phenyl-(3,5,6-tri-O-acetyl-α-D-glucofurano)-[1,2-d]-2-oxazoline (**23**).

Yield (92%), a white solid (method a_1). M.p. 169-172 ^0C. $[\alpha]_D^{20}$ +25.0 (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ = 7.43-8.02 (m, 5H, Ph), 6.33 (d, 1H, $J_{1,2}$=5.5 Hz, H-1), 5.49 (d, 1H, $J_{3,2}$ = 3.0 Hz, H-3), 5.31 (ddd, 1H, H-5), 4.86 (d, 1H, $J_{2,1}$ = 5.5 Hz, H-2), 4.60 (dd, 1H, $J_{6,5}$ = 2.1, $J_{6,6'}$ = 12.3 Hz, H-6), 4.08 (dd, 1H, $J_{6,5}$ = 5.8, H-6'), 3.91 (dd, 1H, H-4), 2.11, 2.01 and 1.99 (3s, 3H, 3x$COCH_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.7 (-C=N), 169.75, 169.71 and 166.6 (C=O, 3x$COCH_3$), 113.3, 129.1, 128.6, 115.9 (Ph-C=N-), 101.1 (C-1), 84.5, 75.4, 74.5, 67.5 (C-4, C-5, C-2, C-3), 63.4 (C-6), 20.81 and 20.76 (3x$CO\mathit{CH}_3$). HRMS (ESI^+): m/z calcd for $C_{18}H_{21}NO_8$ $[M+Na]^+$: 402.1003, found 402.1008.

2-Phenyl-(3,5,6-tri-O-benzoyl-α-D-allofurano)-[1,2-d]-2-oxazoline (**25**).

Yield (86%), a colorless oil (method a_1). $[\alpha]_D^{20}$ +58.5 (c 1.0, $CHCl_3$). IR (film): ν 1728, 1649, 1265, 1118 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.29-8.00 (m, 15H, 3 x COC_6H_5), 6.40 (d, 1H, $J_{1,2}$ = 5.6 Hz, H-1), 5.87-5.90 (m, 1H, H-5), 5.43-5.47 (m, 2H, H-2 and H-3), 4.88 (dd, 1H, $J_{6,5}$ = 3.3, $J_{6,6'}$ = 12.1 Hz, H -6), 4.68 (dd, 1H, $J_{6,5}$ = 6.8 Hz, H-6'), 4.27 (dd, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.8 (-C=N), 166.1, 165.54 and 165.5 (C=O, 3xCOC_6H_5, C_6H_5), 133.4, 133.2, 133.1, 132.6, 129.8, 129.7, 129.0, 128.5, 128.4, 128.3,128.2 (3xCOC_6H_5, Ph-C=N-), 100.8 (C-1), 78.6, 75.1, 74.7, 71.2 (C-4, C-5, C-2, C-3), 63.4 (C-6). HRMS (ESI^+): m/z calcd for $C_{34}H_{27}NO_8$ $[M+H]^+$: 578.1810, found 578.1816; $[M+Na]^+$: 600.1634, found 600.1637.

2-Methyl-(3,5,6-tri-O-acetyl-α-D-allofurano)-[1,2-d]-2-oxazoline (**27**).

Yield (98%), a colorless oil (method a_1). $[\alpha]_D^{20}$ +107.2 (c 1.0, $CHCl_3$). IR (film): ν 17440, 1667, 1375, 1247 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.01 (d, 1H, $J_{1,2}$=5.6 Hz, H-1), 5.34 (dm, 1H, H-5), 5.02 (t, 1H, $J_{2,3}$ = 5.8 Hz, H-2), 4.94 (dd, 1H, H-3), 4.41(dd, 1H, H-4), 4.14 (dd, 1H, H-6), 3.80 (dd, 1H, H-6'), 2.16, 2.11, 2.10, and 2.08 (4s, 3H, 3x $COCH_3$, NCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.5 (CN), 169.8, 169.7 and 169.6 (C=O, 3x$COCH_3$), 100.4 (C-1), 78.2, 74.5, 73.9, 70.0 (C-4, C-5, C-2, C-3), 62.3 (C-6), 20.8, 20.7 and 20.4 (3x$CO\mathit{CH}_3$), 13.9 (NMe). HRMS (ESI^+): m/z calcd for $C_{14}H_{19}NO_8$ $[M+Na]^+$: 352.1003, found 352.1004.

Synthesis of 2-O-isopropyl-3-O-p-toluenesulfonyl-5-O-benzoylxylitol (**30**).

To a stirred solution of acetonide **3** (147 mg, 0.33 mmol) in anhydrous acetonitrile (1.9 ml) KHF_2 (103 mg, 1.32 mmol), $NaBH_4$ (59 mg, 1.5 mmol) and then boron trifluoride diethyl etherate (1.42 ml, 11.38 mmol) were added successively. The reaction mixture was stirred at room temperature for 18 h, and then was gradually poured into cooled 5% $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$ (3x30 ml).

The combined organic extracts were washed water, dried over anh. Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel, using for elution a mixture of hexane-ethylacetate 6:1 and 3:1, and 1:2 as the eluent to give the starting acetonide **3** (38 mg, 26%) and the xylitol derivative **30** (59 mg, 40%) as a colorless oil. $[\alpha]_D^{20}$ +1.4 (c 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.30-8.03 (m, 9H, COC_6H_5 and $OSO_2C_6H_4CH_3$), 4.84 (dd, 1H), 4.31-4.38 (m, 2H), 3.90-3.97 (m, 3H), 3.82-3.91 (m, 2H), 2.41 (s, 3H, $OSO_2C_6H_4CH_3$), 1.22 [d, 3H, (CH_3)CH-], 1.21 [d, 3H, (CH_3)CH-]. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 165.9 (C=O, COC_6H_5), 145.4, 133.3, 130.0, 129.8, 129.7, 128.5 (COC_6H_5 and $OSO_2C_6H_4CH_3$), 78.3, 75.5, 72.2, 65.5, 64.5 (-CH_2OBz), 59.9 (-CH_2OH), 22.8 [(CH_3)$_2$CH-], 22.7 [(CH_3)$_2$CH-], 21.7 ($OSO_2C_6H_4CH_3$). HRMS (ESI$^+$): m/z calcd for $C_{22}H_{22}O_8SNa$ $[M+Na]^+$: 475.1403, found 475.1391.

Synthesis of 2-O-isopropyl-3-O-p-toluenesulfonyl-1,4,5-tri-O-benzoylxylitol (**31**).

To a stirred solution of xylitol derivative **30** (45 mg, 0.099 mmol) in anhydrous pyridine (2 ml) BzCl (0.068 ml, 0.57 mmol) was added at 0 °C and then the reaction mixture was stirred for 48 h at room temperature, diluted with CH_2Cl_2 and poured into cold 5% aq $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3x50 ml), the combined organic extracts were washed with water, dried and evaporated. The residue was chromatographed on a silica gel, using for elution a mixture of hexane-ethylacetate 6:1, 5:1, and chloroform to give (42.7 mg, 65%) of protected xylitol derivative **31** as a colorless oil. $[\alpha]_D^{20}$ -17.8 (c 0.79, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40-8.18 (m, 15H, 3xCOC_6H_5), 7.77 and 7.11 (2d, 4H, $OSO_2C_6H_4CH_3$), 5.91 (q, 1H, H-4), 5.26 (dd, 1H, H-3), 4.64 (dd,1H, H-5), 4.60 (dd,1H, H-5′), 4.54 (dd, 1H, H-1), 4.47 (dd, 1H, H-1′), 4.19-4.22 (m, 1H, H-2), 3.89-3.94 [m, 1H, (CH_3)$_2$*CH*-], 2.30 (s, 3H, $OSO_2C_6H_4CH_3$), 1.25 [d, 3H, (CH_3)CH-], 1.21 [d, 3H, (CH_3)CH-]. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.1, 165.8, and 165.3 (C=O, 3xCOC_6H_5), 145.0, 133.8, 133.4, 133.2, 133.16, 130.2, 130.0, 129.8 (COC_6H_5 and $OSO_2C_6H_4CH_3$), 77.9, 73.5, 72.4, 69.6, 62.7, 62.6, 22.9 [(CH_3)$_2$CH-], 22.2 [(CH_3)$_2$CH-], 21.6 ($OSO_2C_6H_4CH_3$). HRMS (ESI$^+$): m/z calcd for $C_{36}H_{36}O_{10}SNa$ $[M+Na]^+$: 683.1927, found 683.1929.

Synthesis of 2-methyl-(5-O-benzoyl-α-D-xylofurano)-[1,2-d]-2-oxazoline (**49**) *from 5-O-benzoyl-D-xylofuranose* (**47**).

b$_1$. To a stirred solution of 5-O-benzoyl xylofuranose **47** (49 mg, 0.19 mmol) in anhydrous acetonitrile (2.5 ml) KHF_2 (57 mg, 0.89 mol) and boron trifluoride diethyl etherate (0.14 ml, 1.10 mmol) were added successively. The reaction mixture was stirred at room temperature for 3 h, and then poured into cooled 5% aq $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$ (3x50 ml). The combined organic extracts were washed with water, dried over anh. Na_2SO_4, and evaporated to dryness. The oxazoline **49** (40 mg, 75%) was prepared as a colorless oil. $[\alpha]_D^{20}$ -15.9 (c 0.56, $CHCl_3$). M.p. 63-65 °C (crystallized under storing). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.49-8.09 (m, 5H, COC_6H_5), 6.14 (d, 1H, $J_{1,2}$ = 5.5 Hz, H-1), 4.86 (dd, 1H, $J_{5,4}$ = 7.4 Hz, $J_{5,5'}$ = 11.6 Hz, H-5), 4.82 (d, 1H, $J_{2,1}$ = 5.6 Hz, H-2), 4.47 (dd, 1H, $J_{5',4}$ = 5.1 Hz, H-5′), 4.27 (d, 1H, $J_{3,4}$ = 2.3 Hz, H-3), 3.86-3.89 (m, 1H, H-4), 2.09 (s, 3H, NCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 168.9 (CN), 167.3 (C=O, COC_6H_5), 100.0 (C-1), 86.6 (C-4), 76.7, 74.1 (C-2, C-3), 61.3 (C-5), 13.9 (NMe). HRMS (ESI$^+$): m/z calcd for $C_{14}H_{15}NO_5$ $[M+H]^+$: 278.1028, found 278.1025.

Synthesis of 2-methyl-(3,5-di-O-benzoyl-α-D-ribofurano)-[1,2-d]-2-oxazoline (**13**) *from 1,3,5-tri-O-benzoyl-α-D-ribofuranose* (**50**).

b$_2$. To a stirred solution of 1,3,5-tri-O-benzoyl-α-D-ribofuranose (**50**) (250 mg, 0.54 mmol) in anhydrous acetonitrile (10.0 ml) KHF_2 (156 mg, 1.99 mmol) and boron trifluoride diethyl etherate (0.39 ml, 3.08 mmol) were added successively. The reaction mixture solution was stirred at room temperature for 3.5 h,

and then poured into cooled 1N aq NaOH. The oxazoline **13** (204 mg, 99%) was prepared as a colorless oil after the work-up.

$c_{2.}$ To a stirred solution of ribofuranose derivative **50** (100 mg, 0.22 mmol) in anhydrous acetonitrile (4.0 ml) boron trifluoride diethyl etherate (0.16 ml, 1.26 mmol) was added. The reaction mixture solution was stirred at room temperature for 3.5 h, and then poured into cooled 2.7 ml 1N aq NaOH. The oxazoline **13** (90 mg) as yellowish oil was prepared in 65% yield estimated by ^{1}H NMR in $CDCl_3$.

2-Phenyl-(β-D-arabinofurano)-[1,2-d]-2-oxazoline (**51**).

3,5-Di-O-benzoyl oxazoline derivative **17** (95 mg, 0.21 mmol) was dissolved in 7 ml methanol saturated at 0 °C with ammonia, then reaction mixture was left for 14 h at room temperature and evaporated to dryness. The residue was chromatographed on a silica gel, using for elution chloroform, chloroform-methanol 15:1, 10:1 and 6:1 to give (47 mg, 93%) of the oxazoline **51** as oil. $[\alpha]_D^{20}$ -18.7 (c 0.56, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ = 7.99-7.49 (m, 5H, -N=C-C_6H_5), 6.18 (d, 1H, $J_{1,2}$ = 6.2 Hz, H-1), 5.03 (dd, 1H, $J_{2,3}$ = 1.3 Hz, H-2), 4.36 (br.d, 1H, H-3), 3.98-4.01 (m, 1H, H-4), 3.49 (dd, 1H, $J_{5,4}$ = 6.0, $J_{5,5'}$ = 11.8 Hz, H-5), 3.44 (dd, 1H, $J_{5',4}$ = 6.1 Hz, H-5′). ^{13}C NMR (126 MHz, CD_3OD) δ = 168.74 (CN), 134.08, 130.01 and 128.04 (N-C_6H_5), 101.98 (C-1), 90.85 (C-4), 87.31, 77.86 (C-2, C-3), 62.93 (C-5). HRMS (ESI^+): m/z calcd for $C_{12}H_{13}NO_4$ $[M+H]^+$: 236.0923, found 236.0927.

2-Phenyl-(3,5-di-O-acetyl β-D-arabinofurano)-[1,2-d]-2-oxazoline (**52**).

The oxazoline **51** (20 mg, 0.085 mmol) was dissolved in 1.7 ml anhydrous pyridine, acetic anhydride (0.04 ml, 0.42 mmol) was added, then reaction mixture was stirred for 48 h at room temperature and then poured into a mixture of ice and water. The aqueous phase was extracted with CH_2Cl_2 (3x20 ml). The combined organic extracts were washed with water, dried over anh. Na_2SO_4, and evaporated to dryness. The residue was chromatographed on a silica gel, using for elution elution mixtures of ethylacetate-petroleum ether to give (22 mg, 80%) of the oxazoline **52** as oil. $[\alpha]_D^{20}$ -4.6 (c 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42-8.03 (m, 5H, -N=C-C_6H_5), 6.30 (d, 1H, $J_{1,2}$ = 6.2 Hz, H-1), 5.32 (br.d, 1H, H-3), 5.04 (br.d, 1H, $J_{2,3}$ = 1.3, $J_{2,1}$ = 6.2 Hz, H-2), 4.26-4.33 (m, 1H, H-4), 4.06 (dd, 1H, $J_{5,4}$ = 5.9, $J_{5,5'}$ = 11.8 Hz, H-5), 4.02 (dd, 1H, $J_{5',4}$ = 6.1 Hz, H-5′), 2.15 and 1.89 (2s, 3H, -$COCH_3$). ^{13}C NMR (126 MHz, CD_3OD) δ= 170.6, 169.9 and 166.5 (2-$COCH_3$ and CN), 132.7, 129.1, 128.8, 128.6 (N-C_6H_5), 102.2 (C-1), 86.1 (C-4), 81.2, 78.8 (C-2, C-3), 62.5 (C-5), 20.9 and 20.6 (2x$COCH_3$). HRMS (ESI^+): m/z calcd for $C_{16}H_{17}NO_6$ $[M+Na]^+$: 3430940, found 343.0945.

Biological assays of antiproliferative activity

Cell culturing

Anti-proliferative activities of newly synthesized compounds were tested against myelogenous leukemia (K562), cervical carcinoma (Hela), breast carcinoma (MCF-7) in comparison with 5-fluorouracil as the positive control. Human cell lines were obtained from the Institute of Cytology, Russian Academy of Sciences. Human cell lines were cultured as monolayers and maintained in Eagle's medium (DMEM) supplemented with 10% foetal bovine serum (FBS), 2 mM L-glutamine, 100 U/ml amoxicillin, 100 μg/ml streptomysin in a humidified atmosphere of 5% CO_2 at 37 ^{0} C. Stock solutions of compounds were prepared in DMSO and kept at – 20^{0}C. Controls were added with the final concentration of DMSO (0.01%).

Proliferation assays

The cytotoxic effects on human cancer cells were assessed after 72 h incubation of sugar oxazoline derivative in concentrations 0.1 - 50 μM with the cell culture in a 96-well flat-bottomed plate at 37 ^{0}C

under conditions of 5% CO_2 and 95% air humidity using resazurin assay with triplicate experiments. Aliquots of resazurin solution (10 μL) was added to each well and incubated for 3 h at 37 ^{0}C. In all experiments, DMSO controls were included. Fluorescene resorufin measurements were performed on a multimodal absorbance fluorimeter Infinite® 200 PRO (Tecan, Switzerland) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm. IC_{50} values for each compound were calculated from the cell growth inhibition curves obtained from the treatments done with increasing concentrations.

Conflict of interest

There are no conflicts to declare.

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