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Synthesis of 8-hydroxyquinoline glycoconjugates and preliminary assay of their β1,4-GalT inhibitory and anti-cancer properties

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ABSTRACT

8-Hydroxyquinoline scaffold is a privileged structure used in designing a new active agents with therapeutic potential. Its connections with the sugar unit is formed to improve the pharmacokinetic properties. The broad spectrum of activity of quinoline derivatives, especially glycoconjugates, is often associated with the ability to chelate metal ions or with the ability to intercalate into DNA. Simple and effective methods of synthesis glycoconjugates of 8-hydroxyquinoline and 8-hydroxyquinaldine derivatives, containing an *O*-glycosidic bond or a 1,2,3-triazole linker in their structure, have been developed. The obtained glycoconjugates were tested for their ability to inhibit β-1,4-Galactosyltransferase, as well as inhibit cancer cell proliferation. It was found that used glycoconjugation strategy influenced both improvement of activity and improvement of the bioavailability of 8-HQ derivatives. Their activity depends on type of attached sugar, presence of protecting groups in sugar moiety and presence of a linker between sugar and quinolone aglycone.

1. Introduction

The starting point in the search for new drugs of synthetic origin is the discovery of a privileged structure [1,2] such as 8-hydroxyquinoline **I** (8-HQ), which is a fragment of particular importance in the design of new active derivatives [3–6].

The 8-HQ scaffold can be found in many compounds having a therapeutic activity such as clioquinol **II**, intestopan **III**, nitroxoline **IV**, cloxiquine **V**, iodoquinol **VI**, chloroxine **VII** or chlorquinaldol **VIII** [7–12] (Scheme 1). In addition, some derivatives have been comprehensively tested for their anticancer activity, because of their abilities to chelate the metal ions that are necessary for cancer growth [13–16]. 8-HQ has at least two potential protonation sites: a nitrogen atom of the pyridine ring and an oxygen atom of phenol. Therefore, they form complexes with most of divalent transition metal ions, such as: Mn^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+} which has been widely described in the literature. The ability of chelating metals through 8-HQ derivatives has become a promising therapeutic strategy in clinical practice [17–23].

On the other hand, design and synthesis of new molecules containing a sugar fragment is an increasingly active area of current chemical research [24–30]. The presence of a sugar unit improves the pharmacokinetic properties of potential drugs, including improved solubility, reduced toxicity and facilitated intermembrane transport and selectivity in targeting drugs for a specific purpose.

In 2012–2015 G. Vecchio and his co-workers, conducted a series of studies on the synthesis and anticancer properties of quinoline glycosides [31–33]. The whole range of glycosides of 8-HQ derivatives, containing the D-glucose and D-galactose units, were synthesized and evaluated. In these studies, the glycosidic bond was obtained by reaction a per-*O*-acetylated glucopyranosyl or galactopyranosyl bromides with 8-HQ derivatives, formed through an S_N2 type mechanism, in the two-phase system used TBABr as a phase transfer catalyst and K_2CO_3 as a base. Under the described conditions, mainly glycosides with a deprotected sugar part were obtained. These compounds were evaluated for their antiproliferative activity against cells of various types of cancer (A-2780, A-549, MDA-MB-231, Hep-G2), as well as the effect of

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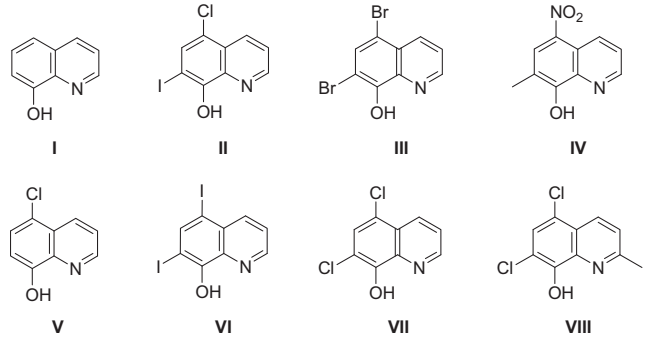


Scheme 1. 8-Hydroxyquinoline derivatives having a biological activity.

addition of Cu^{2+} ions on their biological activity. The results showed that the average antiproliferative activity of glycosides without the addition of copper ions were lower compared to their parent compounds. However, after the addition of Cu^{2+} ions, similar activity to the starting derivatives was obtained. The authors suggest that the test compounds must be subject to hydrolysis by specific β-glycosidases, to release the active aglycone only in target cells, where aglycone was able to complex copper(II) ions.

The antiproliferative activity of 2-methyl-7-carboxy-8-hydroxyquinoline derivatives of glycoconjugates has recently been reported [34]. The obtained compounds were tested for anticancer activity in terms of colon cancer cells (HCT 116). Some of the combinations showed over 100 times higher activity than their parent compounds. It was observed that the glycoconjugates with unprotected sugar part lose their activity relative to their protected analogues. It has also been observed that the improvement of the activity occurs in the presence of an aromatic or heteroaromatic linkage between sugar and quinoline fragment.

As reported in the literature, 8-HQ derivatives containing in their structure a tetrazolium linker [35] or a triazole linker [36] and glucose units, show high antiproliferative activity against various cancer cell lines, comparable to the activity of anti-cancer drugs. It was also confirmed, that the presence of lone electron pairs on the nitrogen atoms in the triazole ring, improves the chelating properties of 8-HQ [37]. In addition, derivatives based on 1,2,3-triazoles play an important role in the preparation of inhibitors of various enzymes [38–42]. It is probably related to the ability to complex metal cations present in the active centers of many enzymes and thus to inhibit their activity.

Due to the more and more frequent relationships between tumor progression and the increase in the level of glycosyltransferases expression, a large number of quinoline derivatives have been tested for the ability to inhibit representatives of this class of enzymes. Glycosyltransferases (GTs) are characterized by a large variety of substrates and the prevalence of cells of eukaryotic organisms. Due to a number of important functions they perform, among others: post-translational protein modifications and the synthesis of oligosaccharide chains, they are an important object of research on potential anticancer drugs [43–45]. However, in spite of this, so far there are no effective inhibitors capable of hampering their activity selectively.

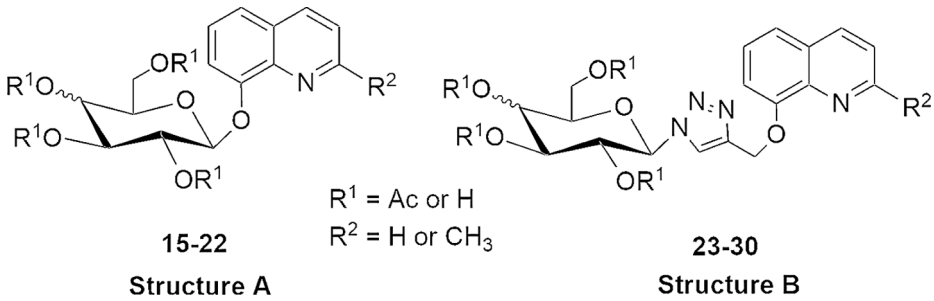
One of the best-known GTs in biochemical terms is β-(1,4)-Galactosyltransferase (β-(1,4)-GalT). It catalyses the synthesis of glycosidic bonds by transferring the D-galactose fragment from UDP-Gal, which is the sugar donor, to specific acceptor molecules. Their classification is based mainly on the specificity of the donor and acceptor and the structure of the product being created [46]. The β-(1,4)-GalT inhibitors are very often designed based on the introduction, instead of the diphosphate group, of another, preferably non-charged, linker capable of coordinating the divalent metal ion bound at the active site of the enzyme. The presence of a metal ion binding moiety, seems to be necessary to inhibit GTs activity [43,46–48]. GT inhibitors have a large therapeutic potential due to the ability to regulate the biosynthesis of oligosaccharides that are involved in many disease processes. An effective inhibitor, in addition to demonstrating sufficient affinity and selectivity for the enzyme, should have the ability to penetrate into the organism and cross biological barriers to achieve its goal inside the cell [47].

Taking into account the above premises, it was decided to obtain heterocyclic sugar conjugates of rather low metabolic stability, i.e. 8-HQ derivatives glycoconjugates (acetals and hemiaminals), in which the sugar part will be connected to the quinoline fragment both by *O*-glycosidic linkage or via the linker containing the 1,2,3-triazole moiety (Scheme 2). The acylation of the sugar fragment, leading to increased hydrophobicity of the compounds, can be used to improve the bioavailability of the glycoconjugates. It seems that this modification may not only reduce the hydrophilicity of the compound, but also significantly affect the bioavailability and transport of the quinoline structures across the cell membrane in the biological environment compared to derivatives containing analogous sugar units with unprotected OH groups. In this work we present new, simple and effective methods of synthesis of designed connections and the results of the preliminary assessment of their biological activity. Considering the possibility of metal ions chelation by glycoconjugates derivatives of 8-HQ, the ability of obtained glycoconjugates to inhibition of commercially available, manganese ions dependent β-(1,4)-GalT and to inhibition of a cancer cell proliferation (in which overexpression of this enzyme was observed) was investigated. The addition of both the D-glucose and the D-galactose fragment to the 8-HQ derivatives was dictated by the overexpression of glucose transporters observed in the case of cancers, and in the case of the HCT 116 line by the additional overexpression of galactose transporters [49–52].

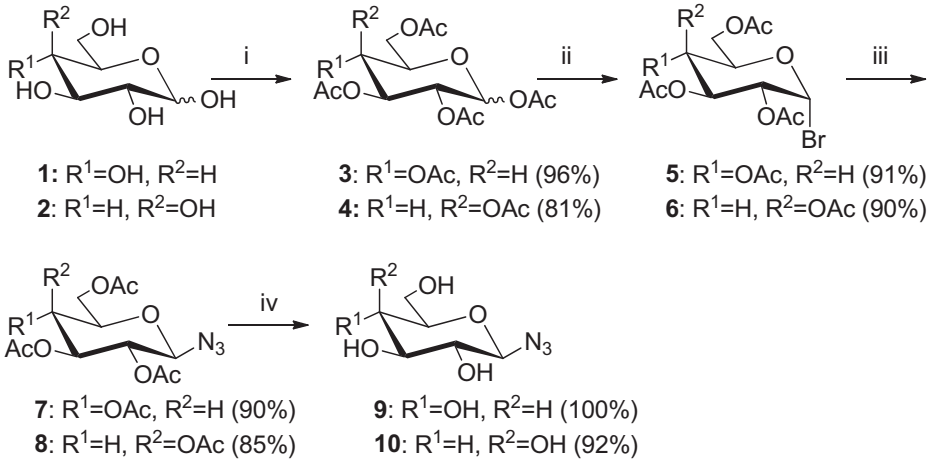
2. Results and discussion

2.1. Synthesis

8-Hydroxyquinoline or 8-hydroxyquinaldine fragment were connected with the sugar derivatives (D-glucose or D-galactose unit) by *O*-glycosidic linkage or via *O*-methylene 1,2,3-triazole linker. This treatment was aimed to improving the solubility and bioavailability of potential drugs. Based on this assumption, we obtained a whole range of



Scheme 2. General structure of the glycoconjugates **15–30**.



Scheme 3. Synthesis of sugar derivatives. *Reagents and Conditions:* (i) CH_3COONa, Ac_2O, b.p., 1 h; (ii) CH_3COOH, 33% HBr/AcOH, r.t. 1 h; (iii) NaN_3, TBASH, $CHCl_3$/$NaHCO_3$, r.t. 2 h; (iv) 1. NaOMe, MeOH, r.t. 20 min; 2. Amberlyst-15.

quinoline glycoconjugates (Scheme 2).

In the first step of the synthesis, sugar derivatives **5–10** were prepared according to known procedures (Scheme 3) involving the acetylation of free sugars **1** or **2** and conversion of per-*O*-acetylated derivatives **3** or **4** into the corresponding glycosyl bromides **5** or **6** [53,54] The glycosyl bromides were used immediately for further reactions leading to obtain 2,3,4,6-tetra-*O*-acetyl-β-glycosyl azides **7** and **8** [54]. The last step was the removal of the acetyl groups under Zemplén conditions which allowed to get deprotected β-glycosyl azides **9** or **10**, which was sufficiently pure for a further reaction [55].

Per-*O*-acetylated glucopyranosyl or galactopyranosyl bromides **5** or **6** respectively were used as glycosyl donors in a *O*-glycosidic bond formation, while 8-hydroxyquinoline **11** and 8-hydroxyquinaldine **12** were used as glycosyl acceptors. Synthetic approach described earlier in the literature for glycosylation of 8-HQ in the phase transfer catalytic system, was compared to the several other known glycosylation methods for containing hydroxyl groups aromatic compounds. There are some problems in the case of phenols *O*-glycosylation. The first is associated with electron withdrawing character of phenol ring causes less nucleophilicity of phenols compared to alcohols, so phenols are difficult to glycosylate. Second, the glycosylation of phenols under acidic conditions can lead to obtaining significant amounts of *C*-glycosides, due to the electron-donating properties of the hydroxyl group [56]. Among methods of aromatic *O*-glycosylation can be mention those using donors such as glycosyl acetates [57,58], glycosyl halides-especially bromides [56,59] or fluorides [60], trichloroacetimidates [61,62], thioglycosides [63,64] under different catalytic systems. Other methods for aromatic *O*-glycosylation are the use of unprotected sugars in Mitsonobu reaction [65], nucleophilic aromatic substitution [66,67] as well as use of glycals [68], 2-nitroglycals [69], glycosyl phosphates [70] or glycosylidene carbenes [71].

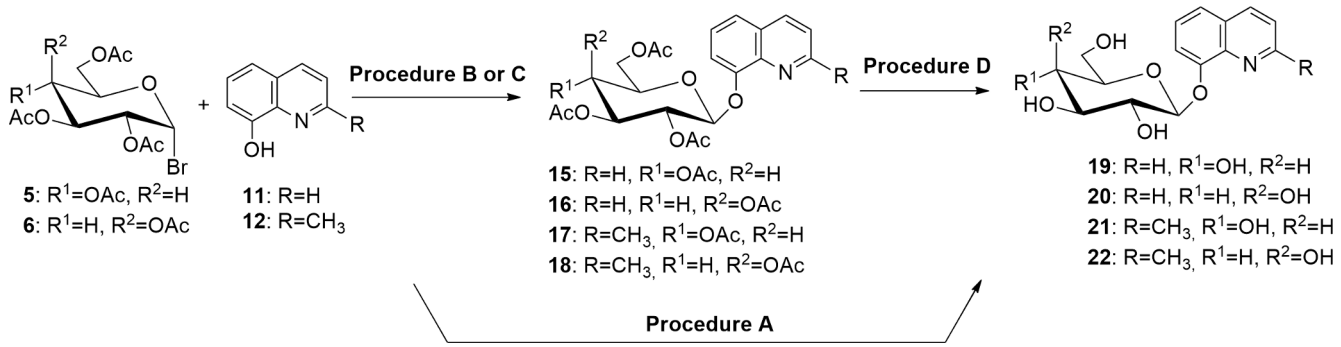
The overview of the reactions used to obtaining of glycoconjugates **15–22** provides in Scheme 4.

The procedure A previously described in the literature [31], taking place according to S_N2 mechanism at anomeric carbon, performed in the classical two-phase system. The reaction conditions were selected for compounds **5** and **11** used as substrates. Synthesis with various molar ratio of sugar derivative **5** to quinoline **11** were performed (3:1, 2:1 and 1:1, Table 1). The obtained results indicated that gycosylation product could be isolated in the best yield, when three times the molar excess of the glycosyl donor relative to the quinoline acceptor was used. However, it is associated with significant amounts of by-products, difficult to separate from the post-reaction mixture. During the reaction carried out in a basic condition, acetyl protecting groups were removed and as a result, mainly glycoconjugate **19** with the deprotected sugar part was obtained. The same regularity was observed during glycoconjugation using the acceptor **12**, as well as in case of using of donor **6**. Taking into account earlier mentioned requirements for improving the bioavailability of drugs, it was necessary to obtain glycoconjugates with a protected sugar part, in order to carry out biological tests on cancer cell lines. Therefore, other phenols glycosylation methods were tested to obtain desired quinoline glycosides.

Procedure B is based on the *O*-glycosidation reaction of per-*O*-acetyl-α-glycosyl bromides **5** or **6** and quinoline derivatives **11** or **12** using an ionic liquid (BMIm·BF_4) [72]. In this case, the ionic liquid acted as a solvent and substrate in the generation of an activating agent in the glycosylation reaction. Silver *N*-heterocyclic carbene complexes (Ag-NHC) are formed *in situ* in ionic liquids. Reaction were performed in the presence of silver carbonate and various tetraalkylammonium salts. Treatment of imidazolium halide salts with silver carbonate generated Ag–NHC complexes that subsequently promoted *O*-glycosidation reactions. The reaction mechanism involved the dual role of Ag–NHC complexes as heavy metal ion sources and as bases, that were more effective in promoting the glycosidation reaction than silver carbonate. Four tetraalkylammonium salts (TBABr, Me_4NCl, Me_4NBF_4 and Et_4NClO_4) were tested for preparation of the compound **15**, to see which one is the best anion donor in the formation of the active Ag-NHC complex. The best salt turned out to be Me_4NCl, at which the product yield was 44%. Whereas, the worst catalyst for the reaction turned out to be Et_4NClO_4, where the product yield was only 24%. However, in the absence of tetraalkylammonium salts, the desired product was not found (Table 1).

Another effective way of forming the *O*-glycosidic linkage with phenol as glycosyl acceptor was published by Kur'yanov and co-workers [73]. In the next variant of the research (Procedure C) the glycosylation of quinoline catalyzed by polyethylene glycol (PEG 4000) was tested. The reaction was carried out in the phase transfer catalytic system, using anhydrous acetonitrile as a solvent at room temperature. We checked if it was necessary to conduct the reaction for 48 h. It turned out that shortening of the reaction time to 24 h does not significantly affect the yield of the obtained product. On the other hand, a further shortening of the reaction time to 2 h resulted in a decreased yield of product **15** from 22% to 16% (Table 1). After optimizing the conditions of individual glycosylation procedures, synthesis of the remaining quinoline glycosides was performed. The yields of the respective glycoconjugates are presented in Table 2.

During the glycosylation reaction performed according to procedures B and C, the formation of small amount of a product of 1,2-elimination of hydrogen bromide to give tetra-*O*-acetyl glycal was observed.



Scheme 4. Synthesis of glycoconjugates **15–22**. *Reagents and Conditions:* (Procedure A) K_2CO_3, Bu_4NBr, $H_2O/CH_3OH/CH_2Cl_2$, r.t., 72 h; (Procedure B) Ag_2CO_3, Me_4NCl, $BMIm{\cdot}BF_4$, r.t., 24 h; (Procedure C) K_2CO_3, PEG 4000, CH_3CN, r.t., 48 h; (Procedure D) 1. NaOMe, MeOH, r.t. 0.5 h; 2. Amberlyst-15.

Part of the per-*O*-acetylated glycoconjugates **15–18** were deprotected under mild conditions using 1 M methanolic solution of sodium methoxide in methanol. The reaction was carried out at room temperature for only 25–30 min. The final step was to neutralize the reaction mixture with the use of Amberlyst-15 ion exchange resin, after which the mixture was filtered to give glycoconjugates **19–22** (Procedure D). This approach was slightly more efficient compared to Procedure A.

On the basis of literature reports and previously obtained results, it can be concluded that the presence in the glycoconjugate structure aromatic or heteroaromatic ring is important for their biological activity. Therefore, in subsequent syntheses quinoline derivatives were also combined with sugar units using copper(I)-catalyzed 1,3-dipolar azide-alkyne cycloaddition (CuAAC) [74]. The 1,2,3-triazole unit was introduced to investigate if such heteroaromatic system will affect the activity of the glycoconjugates.

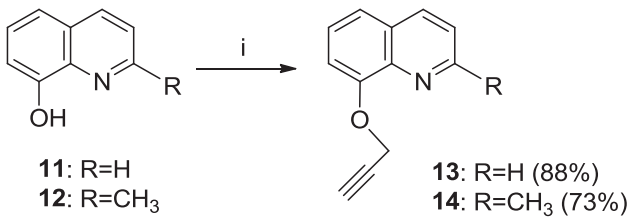
The first essential structural element of the glycoconjugate are propargyl quinoline derivatives **13** or **14** which were obtained by reaction of quinoline derivatives **11** or **12** with propargyl bromide (Scheme 5) according to the previously published procedure [75].

New glycoconjugates were synthesized by the connection of 1-azido sugars, protected or unprotected derivatives of D-glucose **7, 9** or D-galactose **8, 10** with 8-(2-propyn-1-yloxy)quinoline **13** or 2-methyl-8-(2-propyn-1-yloxy)quinoline **14** (Scheme 6). For the above mentioned conjugation CuACC was applied. The reaction in an aqueous-alcoholic medium was carried out, using $CuSO_4{\cdot}5H_2O$ as a catalyst and sodium ascorbate (NaAsc) as a reducing agent, which was designed to reduce Cu(II) to Cu(I). The reaction was carried out for 24 h at room temperature. The crude products of these reactions were purified by column chromatography.

The main advantage of this approach is the capability of employing both protected or unprotected sugar derivatives. This solves the problem of the final deprotection of glycoconjugates by the action of 1 M

Table 2
Yields of glycoconjugates **15–22**.

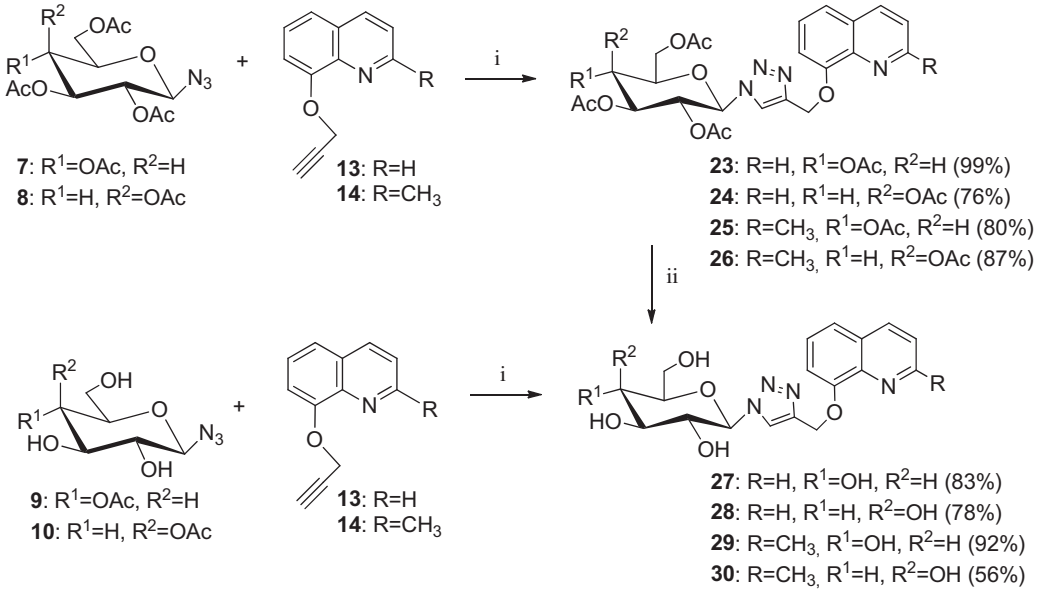
Product	Procedure	Yield [%]
15	**B**	44
	C	22
16	**B**	37
	C	42
17	**B**	27
	C	29
18	**B**	45
	C	51
19	**A**	49
	D	41
20	**A**	34
	D	41
21	**A**	21
	D	68
22	**A**	29
	D	66



Scheme 5. Synthesis of quinoline derivatives **13–14**. *Reagents and Conditions:* (i) propargyl bromide, K_2CO_3, acetone, r.t., 24 h.

Table 1
Adjusting the glycosylation reaction conditions.

Procedure	Glycosyl donor	Glycosyl acceptor	Donor/acceptor molar ratio	Product	Reaction time [h]	Tetraalkylammonium salt	Yield [%]
A	**5**	**11**	3:1	**19**	72	Bu_4NBr	49
			2:1				23
			1:1				12
B	**5**	**11**	1:3	**15**	24	Bu_4NBr	34
						Me_4NCl	44
						Me_4NBF_4	28
						Et_4NClO_4	24
						–	–
C	**5**	**11**	1:1.15	**15**	48	–	22
					24		22
					2		16



Scheme 6. Synthesis of glycoconjugates **23–30**. *Reagents and Conditions:* (i) $CuSO_4{\cdot}5H_2O$, NaAsc, *i*-PrOH, THF, H_2O, r.t., 24 h; (ii) 1. NaOMe, MeOH, r.t. 0.5 h; 2. Amberlyst-15.

NaOMe in methanol and avoided low yields of the desired products. In case of the trial of glycoconjugates **23** deprotection, full conversion of the starting material to the deprotected derivative **27** was unsuccessful despite an extended reaction time and the use of a larger amount of NaOMe.

Finally, both protected **23–26** and unprotected **27–30** glycoconjugates were obtained. The CuACC reaction proceeds with high yield and leading to the formation of only 1,4-disubstituted of 1,2,3-triazoles. The structures of all compounds were confirmed by means of NMR and MS spectra.

2.2. Biological studies

2.2.1. Inhibitory potential

The obtained glycoconjugates **15–30** have been evaluated for their inhibitory activity against commercially available β-1,4-GalT. To evaluate the activity of tested compounds, concentrations of substrate and product of enzymatic reaction in the reaction mixtures was determined by RP-HPLC method, which is a modification of the Vidal method [76]. This method uses UDP-Gal, a natural β-1,4-GalT substrate, as glycosyl donor and (6-esculetinyl) β–D–glucopyranoside (esculine) as glycosyl fluorescent acceptor. To accurately determine the activity of the compound, the amount of product formed in the reaction without the inhibitor (test reactions) is compared to the amount of product formed during the reaction with the addition of glycoconjugate as potential enzyme inhibitor carried out under the same conditions. All glycoconjugates were tested at 0.8 mM concentrations. Results presented in Table 3 indicate that none of the tested compounds **15–30** showed sufficient inhibitory activity against used in research β-1,4-GalT. However, it cannot be ruled out any mechanism of action at this step.

The results indicate that activity against β-1,4-GalT depends on the type of attached sugar and the presence of the protecting groups in the sugar moiety. However, the parent compounds **11** and **12** are not able to inhibit the enzyme, which may indicate that the sugar fragment is necessary for the proper acting of the compounds. Surprisingly we found that glycoconjugates derivatives of D-glucose (**19, 21, 27, 29**) are more active than analogs containing D-galactose unit. It is significant that ability of enzyme inhibition shows only glycoconjugates containing unprotected sugar part, while the derivatives with acetyl protection groups on the sugar unit show no activity. This is probably related to the fact that the hydroxy group protections cause that glycoconjugates to became too large to fit into the active site of enzyme.

Table 3
Bovine milk β-1,4-Galactosyltransferase I assay results.

Compound	Percentage of inhibition at 0.8 mM [%]
11	2 ± 0.32
12	5 ± 0.04
13	0
14	0
15	0
16	0
17	0
18	0
19	14 ± 0.35
20	0
21	20 ± 0.86
22	0
23	0
24	0
25	0
26	0
27	43 ± 0.39
28	16 ± 0.36
29	33 ± 0.87
30	12 ± 0.48

Compounds **27–30** in which the sugar unit is connected to the quinoline moiety by the *O*-methylene 1,2,3-triazole linker showed slightly increased activity compared to compounds **19–22** in which sugar unit is connected directly by a glycosidic bond to 8-HQ derivative.

2.2.2. Cytotoxicity studies

The cytotoxic activity of quinoline derivatives **11–14** as well as obtained glycoconjugates **15–30** was conducted on seven cell lines: HeLa (cervical cancer cell line), HCT 116 (colorectal carcinoma cell line), MCF-7 (human breast adenocarcinoma cell line), U-251 and Hs683 (glioblastoma cell lines), PANC-1 and AsPC-1 (pancreatic cancer cell lines). In these lines, overexpression of the glucose and galactose transporters was observed [77,78]. First, screening tests were carried out for all compounds on three tumor lines (HeLa, HCT 116 and MCF-7) and additionally their selectivity was tested on Normal Human Dermal Fibroblasts-Neonatal (NHDF-Neo). Tests were conducted for

Table 4
Screening of cytotoxicity of glycoconjugates derivatives of 8-hydroxyquinoline.

Compound	Activity IC_{50} [μM]*			
	HeLa**	HCT 116**	MCF-7***	NHDF-Neo**
11	> 800	> 800	0.24 ± 0.01	> 800
12	> 800	> 800	43.18 ± 1.78	346.77 ± 2.23
13	> 800	> 800	95.95 ± 4.29	> 800
14	> 800	> 800	223.63 ± 8.06	> 800
15	> 800	> 800	> 800	–
16	> 800	> 800	> 800	–
17	732.80 ± 28.18	> 800	> 800	–
18	> 800	638.0 ± 5.26	> 800	–
19	> 800	> 800	> 800	–
20	> 800	> 800	> 800	–
21	> 800	> 800	> 800	–
22	> 800	> 800	> 800	–
23	59.48 ± 3.55	69.0 ± 2.53	57.69 ± 3.32	57.37 ± 3.19
24	30.98 ± 1.80	22.7 ± 1.58	4.12 ± 0.03	31.91 ± 1.63
25	> 800	750.9 ± 28.93	> 800	–
26	> 800	457.7 ± 15.3	> 800	–
27	> 800	212.0 ± 7.71	185.34 ± 2.21	247.24 ± 11.64
28	339.35 ± 6.96	265.5 ± 5.02	254.94 ± 8.81	703.45 ± 17.30
29	> 800	> 800	> 800	–
30	> 800	> 800	> 800	–
Doxorubicin	1.2 ± 0.03	5.59 ± 0.14	0.67 ± 0.01	> 20

* Cytotoxic was evaluated using the MTT assay.
** Incubation time 24 h.
*** Incubation time 72 h.

Table 5
Cytotoxicity of glycoconjugates against selected cell lines.

Compound	Activity IC_{50} [μM]*			
	U-251**	Hs683**	PANC-1**	AsPC-1**
23	> 100	> 100	47.87 ± 2.97	> 100
24	37.37 ± 1.56	57.19 ± 0.84	30.31 ± 1.32	34.24 ± 0.43
25	> 100	> 100	> 100	> 100
26	> 100	> 100	> 100	> 100
27	> 100	> 100	> 100	> 100
28	> 100	> 100	> 100	> 100
29	> 100	> 100	> 100	93.28 ± 1.89
30	> 100	> 100	> 100	> 100
Doxorubicin	0.05 ± 0.01	0.04 ± 0.01	0.73 ± 0.09	0.86 ± 0.13

* Cytotoxic was evaluated using the MTS assay.
** Incubation time 72 h.

glycoconjugates solutions at concentrations range from 0.01 mM to 0.8 mM. For the most active compounds IC_{50} value was designated (Tables 4 and 5). The dependence of cell proliferation on the concentration of the potential inhibitor was compared to the results obtained for the starting quinoline derivatives **11** and **12** and the results are presented in Figs. 1a–c.

The results of the cytotoxicity assay indicate that the tested glycosides **15–22** were not toxic to the tested cell lines. Low cytotoxic activity is probably due to the use of the quinoline OH group to form a glycosidic linkage and the formation of steric hindrance hampering the chelation of metal ions. Whereas, some derivatives containing 1,2,3-triazole fragment, appeared to be active on the tested cell lines. The presence of a triazole fragment improves the activity of glycoconjugates, probably by improving the metal chelation capacity found in many types of cancers. Within tested compounds, glycoconjugates **23** and **24** showed promising results.

The most active compounds were derivatives whose structure was

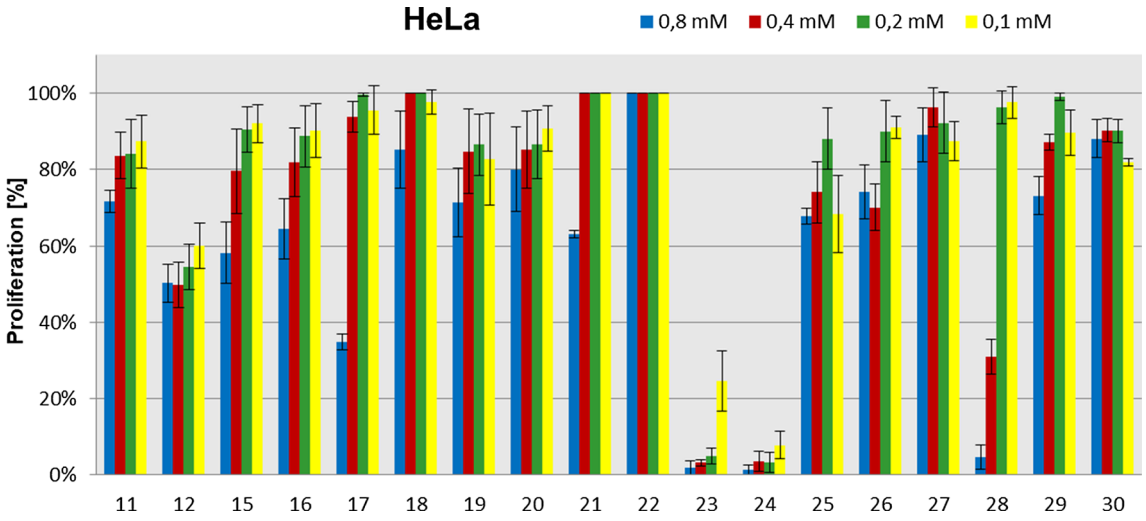


Fig. 1a. The dependence of HeLa cell proliferation on the concentration of the potential inhibitor.

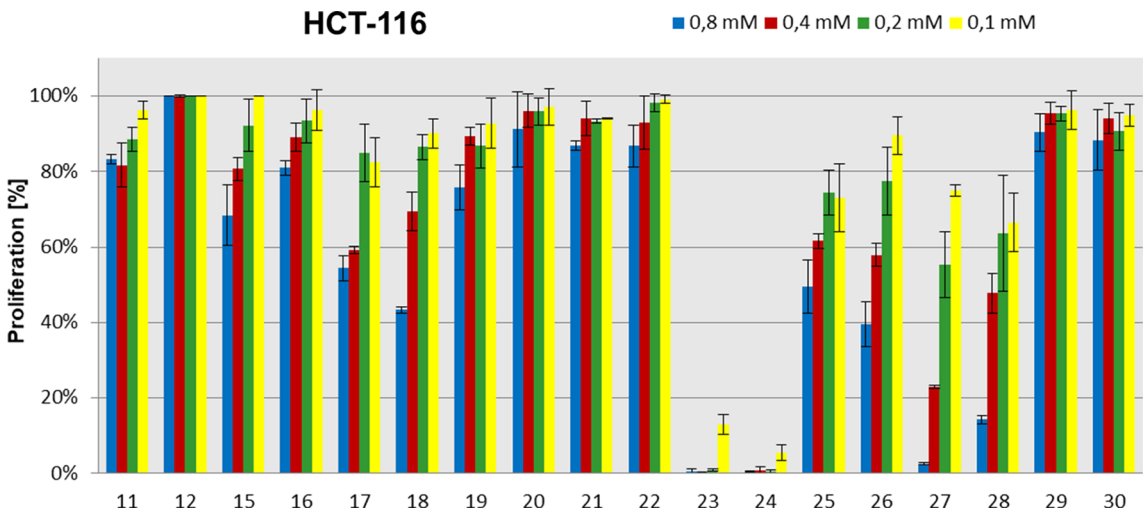


Fig. 1b. The dependence of HCT 116 cell proliferation on the concentration of the potential inhibitor.

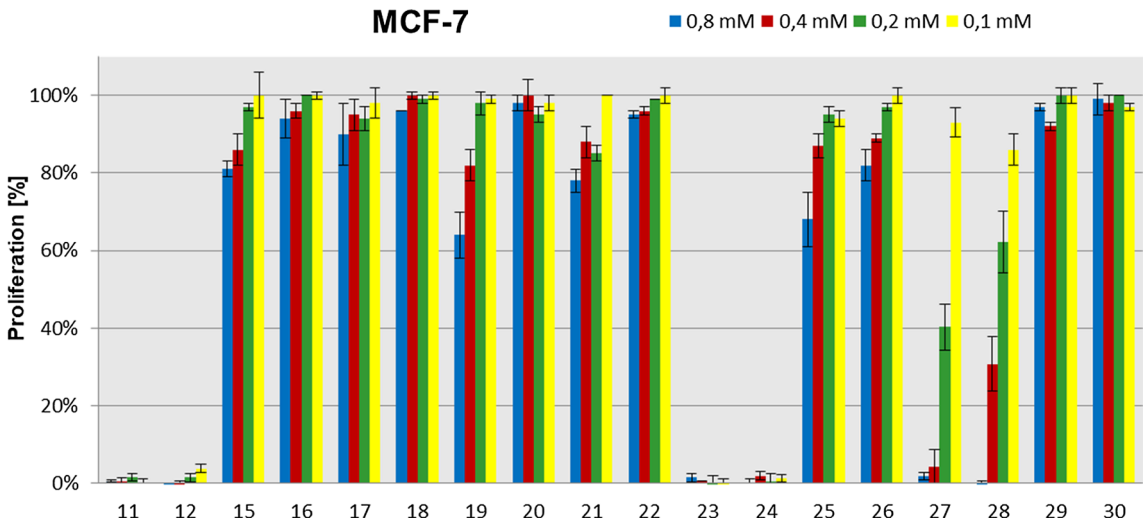


Fig. 1c. The dependence of MCF-7 cell proliferation on the concentration of the potential inhibitor.

based on the 8-HQ fragment (**23**, **24**, **27**, **28**). The same sugar derivatives but connected with 2-Me8-HQ units (**25**, **26**, **29**, **30**) were not able to inhibit cancer cell proliferation so much. On the other hand, the type of sugar unit did not significantly affect to the glycoconjugate activity. It is only important that in these units hydroxyl group were protected with an acetyl moiety. The important issue is the penetration of the compound to the body and the crossing of all biological barriers. Therefore, for these studies it is necessary to use compounds with protected sugar units in order to improve the lipophilicity of the glycoconjugates so that they can freely penetrate inside the cell, whereupon the esterases are able to remove the acyl groups.

It should be noted that it was also checked whether the sugar substrates used for glycoconjugate synthesis are capable of inhibiting the cancer cells proliferation. All these substrates appeared to be inactive on tested cell lines. Additionally, the IC_{50} values obtained for quinoline derivatives for three of the four tested cell lines are mostly higher than for their glycoconjugates, which confirms the assumption that attached sugar unit increases the absorption and distribution of the compound.

The studies on HCT 116 and MCF-7 deliver information about quinoline derivatives selectivity against both cell lines, and indicate on the higher sensitivities of colorectal cancer cells, mostly followed by MTT viability assays [79,80]. The mode of action is mostly explained with Topoisomerase II activity and DNA damage assay, chromatin and histons modifications, what results with cell cycle arrest and apoptotic cellular death induction, also in HeLa cells [81,82]. However, these findings do not precise how the active agents are downloaded into the cells. The chemical structure, most of tested compounds enable a transfer through the plasma membranes into the cytoplasm compartments. Although, the specific signaling pathway are usually activated, for quinoline derivatives the signal pathway of PI3K (phosphoinositide 3-kinase)-Akt (protein kinase B)-mTOR (rapamycin target protein) is one of the targets [80]. This specific transduction pathway regulates cell cycle and apoptosis, also processes, such as transcriptions, translations and proteins synthesis, influences general metabolisms [80]. Small quinoline derivatives are reported as inhibitors in PI3K-AKT-mTOR signaling pathway, what resulted with cell cycle arrest and apoptosis induction, with higher selectivity against MCF-7 than HCT 116 cells [80]. Glycoconjugates are more composite and structurally differ from quinoline precursors, so they probably cannot activate precise this specific cellular pathway, what resulted with lower cytotoxicity.

According to the idea that sugar-containing molecules may accumulate and act more effectively in cells that have high demand for sugars or relay on specific sugar metabolism we tested the glycoconjugates on additional cancer cell panel [83]. We selected cells that are known for their high demand for glucose as glioblastoma and pancreatic cancer [84]. Pancreatic cell's activity is regulated by glucose level. In pancreatic cancer the glucose metabolism determine morbidity

and malignancy of the tumor [85,86].

According to the results presented in the Table 5 compound **24** appeared most active among glycoconjugates that were tested against all additional cell lines, while **23** was active only against PANC-1.

3. Conclusion

In conclusion, a series of glycoconjugates derivatives of 8-HQ were obtained and their biological activity *in vitro* were tested. It turned out that the presence of both a sugar fragment and a 1,2,3-triazole linker in the structure was essential for biological activity. The *click-chemistry* approach in a simple, easily and inexpensive way leads to products with high yield, purity and selectivity. Obtained glycoconjugates were tested for their inhibitory potency against β-1,4-Galactosyltransferase as well as anticancer activity against wide bunch of cancer cell lines. Interestingly the conjugates designed on sugar moiety with free hydroxyl groups possessed some inhibitory potential contrary to their acetylated analogs. This result proves that only limited functionalization of the sugar core is allowed before final compound lost its recognition in biological system. On the other hand this activity do not correlate with antiproliferative activity of the compounds that were tested. Derivative of quinoline seemed to have better activity than quinaldines. Particularly acetylated sugar conjugates revealed interesting potential against breast cancer cells which appeared more vulnerable to quinoline derivatives. In other cell lines however several of the obtained compounds were at least ten times more active than the parent quinolines. As a result, these compounds could have valuable potential as therapeutic agents in the treatment of cancer diseases.

4. Experimental

4.1. General information

NMR spectra were recorded with an Agilent spectrometer at a frequency of 400 MHz using TMS as the internal standards and $CDCl_3$, CD_3OD or DMSO as the solvents. NMR solvents were purchased from ACROS Organics (Geel, Belgium). Chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hz. Optical rotations were measured with a JASCO P-2000 polarimeter using a sodium lamp (589.3 nm) at room temperature. Melting point measurements were performed on OptiMelt (MPA 100) Stanford Research Systems. Mass spectra were recorded with a WATERS LCT Premier XE system using electrospray-ionization (ESI) technique. Reactions were monitored by TLC on precoated plates of silica gel 60 F254 (Merck Millipore). TLC plates were inspected under UV light (λ = 254 nm) or charring after spraying with 10% solution of sulfuric acid in ethanol. Crude products were purified using column chromatography performed on Silica Gel 60 (70–230 mesh, Fluka), developed using toluene/EtOAc or $CHCl_3$/MeOH solvent systems. All evaporations were performed on a rotary evaporator under diminished pressure at 40 °C. Reversed phase HPLC analyses were performed using JASCO LC 2000 apparatus equipped with a reverse phase column (Nucleosil 100 C18, 5 µm, 25 × 0.4 cm; mobile phase: H_2O/MeCN 90:10, flow rate 0.8 mL/min) with a fluorescence detector (FP). Fluorescence for substrate and product was read at 385 nm excitation/540 nm emission. The absorbance on MTT assay was measured spectrophotometrically at the 570 nm wave lenght using a plate reader (Epoch, BioTek, USA).

1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose **3** [53], 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose **4** [53], 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** [54], 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide **6** [54], 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **7** [54], 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide **8** [54], β-D-glucopyranosyl azide **9** [55], β-D-galactopyranosyl azide **10** [55], 8-(2-propyn-1-yloxy)quinoline **13** [75] and 2-methyl-8-(2-propyn-1-yloxy)quinoline **14** [75] were prepared according to the respective published procedures. D-Glucose, D-galactose, 8-hydroxyquinoline and 8-hydroxyquinaldine are commercially available (Sigma-Aldrich). All used chemicals were purchased from Sigma-Aldrich, Fluka, Avantor and ACROS Organics and were used without purification. Bovine milk β-1,4-Galactosyltransferase I was purchased from Sigma-Aldrich.

4.2. Chemistry

4.2.1. Synthesis of glycoconjugates 15–22

Procedure A. 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide **6** (0.9 mmol, 369.0 mg) and quinoline derivative **11** (0.3 mmol, 43.5 mg) or **12** (0.3 mmol, 47.7 mg) were dissolved in dichloromethane (22 mL). K_2CO_3 (2.9 mmol, 400.8 mg) and TBABr (0.3 mmol, 96.7 mg) were added to this mixture, followed by water (12 mL) and methanol (12 mL). The resulting mixture was stirred for 72 h at room temperature. The reaction progress was monitored on TLC in an eluents system $CHCl_3$:MeOH (2:1). Then the two-phase system was separated, and the aqueous phase was washed repeatedly with dichloromethane (18 mL). The aqueous phase was concentrated in vacuo. The crude products were purified using column chromatography ($CHCl_3$:MeOH, gradient: 12:1 to 2:1) to give products **19–22**.

Procedure B. Ag_2CO_3 (0.5 mmol, 137.9 mg), Me_4NCl (0.5 mmol, 54.8 mg) and BMIm·BF_4 (1.5 mL) were added to a round-bottom flask and stirred for 1 h at room temperature. Then the quinoline derivative **11** (0.6 mmol, 87.0 mg) or **12** (0.6 mmol,95.4 mg) was added to this mixture, and after 20 min 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide **6** (0.2 mmol, 82.0 mg) was added. The resulting mixture was stirred for 24 h at room temperature. The reaction progress was monitored on TLC in an eluents system toluene:AcOEt (2:1). Then CH_2Cl_2 (5 mL) and H_2O (5 mL) were added, the two-phase system was separated, and the organic phase was washed with dichloromethane (3x5 mL). The combined organic phases were dried with dry $MgSO_4$, filtered and the filtrate was evaporated in vacuo. The crude products were purified using column chromatography (toluene:AcOEt, gradient: 8:1 to 1:1) to give products **15–18**.

Procedure C. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide **6** (1.2 mmol, 492.0 mg) and quinoline derivative **11** (1.4 mmol, 203.1 mg) or **12** (1.4 mmol, 222.7 mg) were dissolved in acetonitrile (15 mL), followed by addition of K_2CO_3 (5.5 mmol, 760.1 mg) and PEG 4000 (0.066 mmol, 264.0 mg). The resulting mixture was stirred for 48 h at room temperature. The reaction progress was monitored on TLC in an eluents system toluene:AcOEt (2:1 or 1:1). Then the reaction mixture was diluted with dichloromethane, filtered and the filtrate was evaporated in vacuo. The crude products were purified using column chromatography (toluene:AcOEt, gradient: 15:1 to 1:1) to give products **15–18**.

Procedure D. Per-*O*-acetylated glycosides **15–18** (0.375 mmol) was dissolved in methanol. Then 1 M solution of MeONa in MeOH (0.250 mmol, 250 µL) was added. Reaction was carried out for 0.5 h at room temperature. The reaction progress was monitored on TLC in an eluents system $CHCl_3$:MeOH (10:1). After the reaction was complete, the mixture was neutralized with Amberlyst-15, filtered and the filtrate was evaporated in vacuo. The crude products were purified using column chromatography (dry loading; $CHCl_3$:MeOH, gradient: 15:1 to 6:1) to give products **19–22**.

4.2.1.1. 8-Quinolinyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside 15.

Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide **5** and 8-hydroxyquinoline **11** according to **Procedure B** yield: 44% (41.8 mg), according to **Procedure C** yield: 22% (125.4 mg), product was obtained as a solid; m.p.: 155–159 °C; $[\alpha]_D^{27} = -56.1$ (c = 0.6, $CHCl_3$); HRMS (ESI-TOF): calcd for $C_{23}H_{26}NO_{10}$ ($[M+H]^+$): m/z 476.1557; found: m/z 476.1560; ^1H NMR (400 MHz, $CDCl_3$): δ 2.04, 2.05, 2.06, 2.10 (4 s, 12H, CH_3CO), 3.84 (ddd, 1H, J = 2.5 Hz,

J = 5.0 Hz, J = 10.0 Hz, H-5_{Glu}), 4.19 (dd, 1H, J = 2.5 Hz, J = 12.2 Hz, H-$6a_{Glu}$), 4.30 (dd, 1H, J = 5.0 Hz, J = 12.2 Hz, H-$6b_{Glu}$), 5.23 (dd, 1H, J = 9.3 Hz, J = 10.0 Hz, H-4_{Glu}), 5.33–5.50 (m, 3H, H-1_{Glu}, H-2_{Glu}, H-3_{Glu}), 7.40–7.48 (m, 3H, H-3_{Chin}, H-5_{Chin}, H-7_{Chin}), 7.57 (dd, 1H, J = 2.4 Hz, J = 7.0 Hz, H-6_{Chin}), 8.14 (dd, 1H, J = 1.6 Hz, J = 8.4 Hz, H-4_{Chin}), 8.90 (dd, 1H, J = 1.7 Hz, J = 4.2 Hz, H-2_{Chin}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.70, 20.75, 20.77, 20.93, 62.09, 68.61, 71.54, 72.20, 72.81, 100.85, 117.30, 121.68, 123.58, 126.41, 129.63, 135.93, 141.13, 149.89, 152.63, 169.50, 169.73, 170.38, 170.65.

4.2.1.2. 8-Quinolinyl-2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside ***16***. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide **6** and 8-hydroxyquinoline **11** according to **Procedure B** yield: 37% (35.2 mg), according to **Procedure C** yield: 42% (239.5 mg), product was obtained as a solid; m.p.: 120–122 °C; $[\alpha]_D^{25}$ = −40.6 (c = 1.7, $CHCl_3$); HRMS (ESI-TOF): calcd for $C_{23}H_{26}NO_{10}$ ($[M+H]^+$): *m/z* 476.1557; found: *m/z* 476.1559; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 2.03, 2.04, 2.10, 2.19 (4 s, 12H, CH_3CO), 4.04 (ddd, 1H, J = 1.1 Hz, J = 6.7 Hz, J = 7.0 Hz, H-5_{Gal}), 4.18 (dd, 1H, J = 6.7 Hz, J = 11.2 Hz, H-$6a_{Gal}$), 4.25 (dd, 1H, J = 7.0 Hz, J = 11.2 Hz, H-$6b_{Gal}$), 5.18 (dd, 1H, J = 3.4 Hz, J = 10.5 Hz, H-3_{Gal}), 5.38 (d, 1H, J = 8.0 Hz, H-1_{Gal}), 5.47 (dd, 1H, J = 1.1 Hz, J = 3.4 Hz, H-4_{Gal}), 5.72 (dd, 1H, J = 8.0 Hz, J = 10.5 Hz, H-2_{Gal}), 7.40–7.49 (m, 3H, H-3_{Chin}, H-5_{Chin}, H-7_{Chin}), 7.57 (dd, 1H, J = 3.2 Hz, J = 6.3 Hz, H-6_{Chin}), 8.14 (dd, 1H, J = 1.7 Hz, J = 8.3 Hz, H-4_{Chin}), 8.91 (dd, 1H, J = 1.7 Hz, J = 4.2 Hz, H-2_{Chin}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.80, 20.83, 21.08, 21.10, 61.47, 67.14, 68.96, 71.03, 71.20, 101.44, 117.07, 121.74, 123.48, 126.49, 129.69, 136.15, 144.70, 149.90, 152.77, 169.90, 170.37, 170.44, 170.49.

4.2.1.3. 2-Methyl-8-quinolinyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside ***17***. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide **5** and 8-hydroxyquinoline **12** according to **Procedure B** yield: 27% (26.4 mg), according to **Procedure C** yield: 29% (170.2 mg), product was obtained as a solid; m.p.: 132–139 °C; $[\alpha]_D^{25}$ = −73.6 (c = 1, $CHCl_3$); HRMS (ESI-TOF): calcd for $C_{24}H_{28}NO_{10}$ ($[M+H]^+$): *m/z* 490.1713; found: *m/z* 490.1707; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05, 2.06, 2.07 (4 s, 12H, CH_3CO), 2.75 (s, 3H, CH_3), 3.85 (ddd, 1H, J = 2.6 Hz, J = 5.0 Hz, J = 9.8 Hz, H-5_{Glu}), 4.20 (dd, 1H, J = 2.6 Hz, J = 12.2 Hz, H-$6a_{Glu}$), 4.28 (dd, 1H, J = 5.0 Hz, J = 12.2 Hz, H-$6b_{Glu}$), 5.23 (dd, 1H, J = 9.4 Hz, J = 9.8 Hz, H-4_{Glu}), 5.35 (dd, 1H, J = 9.3 Hz, J = 9.4 Hz, H-3_{Glu}), 5.46–5.53 (m, 2H, H-1_{Glu}, H-2_{Glu}), 7.30 (d, 1H, J = 8.4 Hz, H-3_{Chin}), 7.34–7.41 (m, 2H, H-5_{Chin}, H-7_{Chin}), 7.52 (dd, 1H, J = 2.6 Hz, J = 6.9 Hz, H-6_{Chin}), 8.02 (d, 1H, J = 8.4 Hz, H-4_{Chin}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.73, 20.79, 20.97, 25.67, 62.17, 68.71, 71.56, 72.15, 72.91, 100.89, 117.18, 122.51, 123.20, 125.47, 127.87, 136.06, 140.43, 152.18, 158.59, 169.56, 169.64, 170.47, 170.72.

4.2.1.4. 2-Methyl-8-quinolinyl-2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside ***18***. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide **6** and 8-hydroxyquinoline **12** according to **Procedure B** yield: 45% (44.0 mg), according to **Procedure C** yield: 51% (299.4 mg), product was obtained as a solid; m.p.: 134–138 °C; $[\alpha]_D^{25}$ = −57.0 (c = 1, $CHCl_3$); HRMS (ESI-TOF): calcd for $C_{24}H_{28}NO_{10}$ ($[M+H]^+$): *m/z* 490.1713; found: *m/z* 490.1715; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03, 2.04, 2.06, 2.18 (4 s, 12H, CH_3CO), 2.75 (s, 3H, CH_3), 4.06 (ddd, 1H, J = 1.0 Hz, J = 6.6 Hz, J = 6.8 Hz, H-5_{Gal}), 4.19 (dd, 1H, J = 6.6 Hz, J = 11.2 Hz, H-$6a_{Gal}$), 4.26 (dd, 1H, J = 6.8 Hz, J = 11.2 Hz, H-$6b_{Gal}$), 5.16 (dd, 1H, J = 3.4 Hz, J = 10.5 Hz, H-3_{Gal}), 5.39 (d, 1H, J = 8.0 Hz, H-1_{Gal}), 5.47 (dd, 1H, J = 1.0 Hz, J = 3.4 Hz, H-4_{Gal}), 5.75 (dd, 1H, J = 8.0 Hz, J = 10.5 Hz, H-2_{Gal}), 7.29 (d, 1H, J = 8.4 Hz, H-3_{Chin}), 7.34–7.41 (m, 2H, H-5_{Chin}, H-7_{Chin}), 7.51 (dd, 1H, J = 2.1 Hz, J = 7.4 Hz, H-6_{Chin}), 8.01 (d, 1H, J = 8.4 Hz, H-4_{Chin}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.75, 20.77, 21.05, 25.66, 61.52, 67.16, 68.99, 71.03, 71.08, 101.51, 116.73, 122.49, 123.02, 125.45, 127.82, 135.99, 140.38, 152.42, 158.53, 169.74, 170.36, 170.40, 170.46.

4.2.1.5. 8-Quinolinyl-β-D-glucopyranoside ***19***. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide **5** and 8-hydroxyquinoline **11** according to **Procedure A** yield: 49% (45.1 mg). Starting from 8-quinolinyl-tetra-*O*-acetyl-β-D-glucopyranoside **15** according to **Procedure D** yield: 41% (73.1 mg), product was obtained as a solid; m.p.: 193–196 °C; $[\alpha]_D^{25}$ = −99.0 (c = 1.1, $CH_3OH/CHCl_3$ 9:1); HRMS (ESI-TOF): calcd for $C_{15}H_{18}NO_6$ ($[M+H]^+$): *m/z* 308.1134; found: *m/z* 308.1132; ^{1}H NMR (400 MHz, CD_3OD): δ 3.45 (dd, 1H, J = 8.9 Hz, J = 9.6 Hz, H-4_{Glu}), 3.56 (dd, 1H, J = 8.9 Hz, J = 9.4 Hz, H-3_{Glu}), 3.57 (ddd, 1H, J = 2.2 Hz, J = 6.0 Hz, J = 9.6 Hz, H-5_{Glu}), 3.72 (dd, 1H, J = 7.8 Hz, J = 9.4 Hz, H-2_{Glu}), 3.73 (dd, 1H, J = 6.0 Hz, J = 12.0 Hz, H-$6b_{Glu}$), 3.96 (dd, 1H, J = 2.2 Hz, J = 12.0 Hz, H-$6a_{Glu}$), 5.06 (d, 1H, J = 7.8 Hz, H-1_{Glu}), 7.49–7.60 (m, 4H, H-3_{Chin}, H-5_{Chin}, H-6_{Chin}, H-7_{Chin}), 8.34 (dd, 1H, J = 1.7 Hz, J = 8.4 Hz, H-4_{Chin}), 8.84 (dd, 1H, J = 1.7 Hz, J = 4.3 Hz, H-2_{Chin}); ^{13}C NMR (100 MHz, CD_3OD): δ 62.64, 71.58, 74.80, 77.26, 78.51, 103.17, 114.51, 122.60, 123.01, 128.46, 131.03, 138.47, 140.27, 150.24, 153.85.

4.2.1.6. 8-Quinolinyl-β-D-galactopyranoside ***20***. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl bromide **6** and 8-hydroxyquinoline **11** according to **Procedure A** yield: 34% (31.3 mg). Starting from 8-quinolinyl-tetra-*O*-acetyl-β-D-galactopyranoside **16** according to **Procedure D** yield: 41% (73.1 mg), product was obtained as a solid; m.p.: 200–205 °C; $[\alpha]_D^{25}$ = −43.8 (c = 0.8, $CH_3OH/CHCl_3$ 9:1); HRMS (ESI-TOF): calcd for $C_{15}H_{18}NO_6$ ($[M+H]^+$): *m/z* 308.1134; found: *m/z* 308.1135; ^{1}H NMR (400 MHz, CD_3OD): δ 3.67 (dd, 1H, J = 3.5 Hz, J = 9.9 Hz, H-3_{Gal}), 3.77–3.89 (m, 3H, H-5_{Gal}, H-$6a_{Gal}$, H-$6b_{Gal}$), 3.95 (d, 1H, J = 3.5 Hz, H-4_{Gal}), 4.06 (dd, 1H, J = 7.7 Hz, J = 9.9 Hz, H-2_{Gal}), 5.01 (d, J = 7.7 Hz, H-1_{Gal}), 7.50–7.60 (m, 4H, H-3_{Chin}, H-5_{Chin}, H-6_{Chin}, H-7_{Chin}), 8.35 (dd, 1H, J = 1.7 Hz, J = 8.4 Hz, H-4_{Chin}), 8.85 (dd, 1H, J = 1.6 Hz, J = 4.3 Hz, H-2_{Chin}); ^{13}C NMR (100 MHz, CD_3OD): δ 62.57, 70.24, 72.12, 74.18, 77.40, 103.88, 114.59, 122.53, 122.97, 128.44, 130.98, 138.46, 140.24, 150.16, 153.88.

4.2.1.7. 2-Methyl-8-quinolinyl-β-D-glucopyranoside ***21***. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide **5** and 8-hydroxyquinaldine **12** according to **Procedure A** yield: 21% (20.2 mg). Starting from 2-methyl-8-quinolinyl-tetra-*O*-acetyl-β-D-glucopyranoside **17** according to **Procedure D** yield: 68% (124.7 mg), product was obtained as a solid; m.p.: 206–210 °C; $[\alpha]_D^{24}$ = −109.4 (c = 1, $CH_3OH/CHCl_3$ 9:1); HRMS (ESI-TOF): calcd for $C_{16}H_{20}NO_6$ ($[M+H]^+$): *m/z* 322.1291; found: *m/z* 322.1293; ^{1}H NMR (400 MHz, CD_3OD): δ 2.74 (s, 3H, CH_3), 3.45 (dd, 1H, J = 8.8 Hz, J = 9.6 Hz, H-4_{Glu}), 3.54 (ddd, 1H, J = 2.3 Hz, J = 6.4 Hz, J = 9.6 Hz, H-5_{Glu}), 3.56 (dd, 1H, J = 8.8 Hz, J = 9.4 Hz, H-3_{Glu}), 3.71 (dd, 1H, J = 7.8 Hz, J = 9.4 Hz, H-2_{Glu}), 3.72 (dd, 1H, J = 6.4 Hz, J = 12.1 Hz, H-$6a_{Glu}$), 3.95 (dd, 1H, J = 2.3 Hz, J = 12.1 Hz, H-$6b_{Glu}$), 5.03 (d, J = 7.8 Hz, H-1_{Glu}), 7.41–7.48 (m, 3H, H-3_{Chin}, H-5_{Chin}, H-7_{Chin}), 7.52 (dd, 1H, J = 2.5 Hz, J = 7.0 Hz, H-6_{Chin}), 8.19 (d, 1H, J = 8.5 Hz, H-4_{Chin}); ^{13}C NMR (100 MHz, CD_3OD): δ 24.56, 62.63, 71.54, 74.88, 77.41, 78.49, 103.39, 115.34, 122.74, 124.00, 127.37, 129.29, 138.55, 140.03, 153.24, 159.90.

4.2.1.8. 2-Methyl-8-quinolinyl-β-D-galactopyranoside ***22***. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl bromide **6** and 8-hydroxyquinaldine **12** according to **Procedure A** yield: 29% (27.9 mg). Starting from 2-methyl-8-quinolinyl-tetra-*O*-acetyl-β-D-galactopyranoside **18** according to **Procedure D** yield: 66% (121.1 mg), product was obtained as a solid; m.p.: 208–212 °C; $[\alpha]_D^{25}$ = −87.4 (c = 1, $CH_3OH/CHCl_3$ 9:1); HRMS (ESI-TOF): calcd for $C_{16}H_{20}NO_6$ ($[M+H]^+$): *m/z* 322.1291; found: *m/z* 322.1292; ^{1}H NMR (400 MHz, CD_3OD): δ 2.72 (s, 3H, CH_3), 3.68 (dd, 1H, J = 3.4 Hz, J = 9.8 Hz, H-3_{Gal}), 3.75–3.88 (m, 3H, H-$6a_{Gal}$, H-5_{Gal}, H-$6b_{Gal}$), 3.94 (d, 1H, J = 3.4 Hz, H-4_{Gal}), 4.07 (dd, 1H, J = 7.8 Hz, J = 9.8 Hz, H-2_{Gal}), 4.97 (d, J = 7.8 Hz, H-1_{Gal}), 7.38–7.52 (m, 4H, H-3_{Chin}, H-5_{Chin},

H-6$_{Chin}$, H-7$_{Chin}$), 8.17 (d, 1H, J = 8.5 Hz, H-4$_{Chin}$); ^{13}C NMR (100 MHz, CD_3OD): δ 24.55, 62.53, 70.20, 72.22, 74.34, 77.35, 104.09, 115.38, 122.69, 123.97, 127.35, 129.25, 138.52, 140.03, 153.31, 159.85.

*4.2.2. Synthesis of glycoconjugates **23–30***

To a solution of *O*-acetylated glycosyl azides **7** or **8** (0.5 mmol, 186.6 mg) or deprotected glycosyl azides **9** or **10** (0.5 mmol, 102.5 mg) and 8-(2-propyn-1-yloxy)quinoline **13** (0.5 mmol, 91.5 mg) or 2-methyl-8-(2-propyn-1-yloxy)quinoline **14** (0.5 mmol, 98.5 mg) in THF (5 mL) : *i*-PrOH (5 mL), $CuSO_4{\cdot}5H_2O$ (0.1 mmol, 25.0 mg) dissolved in H_2O (2.5 mL) and sodium ascorbate (0.2 mmol, 39.6 mg) dissolved in H_2O (2.5 mL) were added to this mixture. The reaction mixture was stirred for 24 h at room temperature. The reaction progress was monitored on TLC in an eluents system $CHCl_3$:MeOH (20:1 or 2:1). Mixture was concentrated in vacuo and purified using column chromatography (dry loading; toluene:AcOEt, 2:1 and $CHCl_3$:MeOH, 100:1 for fully protected glycoconjugates or $CHCl_3$:MeOH, gradient: 50:1 to 2:1 for glycoconjugates with unprotected sugar part) to give products **23–30**.

*4.2.2.1. 8-((1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)quinoline **23**.*. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **7** and 8-(2-propyn-1-yloxy)quinoline **13**, product was obtained as a solid. Yield: 99% (275.3 mg); m.p.: 162–164 °C; $[\alpha]_D^{25} = -33.3$ (c = 1.0, $CHCl_3$); HRMS (ESI-TOF): calcd for $C_{26}H_{29}N_4O_{10}$ ($[M+H]^+$): *m/z* 557.1884; found: *m/z* 557.1885; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80, 2.00, 2.05, 2.06 (4 s, 12H, CH_3CO), 3.97 (ddd, 1H, J = 2.1 Hz, J = 5.0 Hz, J = 10.1 Hz, H-5$_{Glu}$), 4.12 (dd, 1H, J = 2.1 Hz, J = 12.7 Hz, H-6a$_{Glu}$), 4.23 (dd, 1H, J = 5.0 Hz, J = 12.7 Hz, H-6b$_{Glu}$), 5.21 (dd ~ t, 1H, J = 9.6 Hz, J = 10.1 Hz, H-4$_{Glu}$), 5.36–5.43 (m, 2H, H-3$_{Glu}$, H-2$_{Glu}$), 5.54 i 5.59 (qAB, 2H, J = 13.2 Hz, CH_2), 5.85 (d, 1H, J = 9.1 Hz, H-1$_{Glu}$), 7.25–7.27 (m, 1H, H-7$_{Chin}$), 7.39–7.48 (m, 3H, H-3$_{Chin}$, H-5$_{Chin}$, H-6$_{Chin}$), 7.98 (s, 1H, H-5$_{Triaz}$), 8.13 (dd, 1H, J = 1.5 Hz, J = 8.3 Hz, H-4$_{Chin}$), 8.95 (dd, 1H, J = 1.4 Hz, J = 4.0 Hz, H-2$_{Chin}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.11, 20.50, 20.52, 20.68, 61.51, 62.76, 67.68, 70.34, 72.68, 75.12, 85.78, 110.10, 120.43, 121.69, 121.92, 126.65, 129.54, 135.99, 140.37, 144.80, 149.43, 153.80, 168.73, 169.27, 169.92, 170.50.

*4.2.2.2. 8-((1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)quinolone **24**.*. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide **8** and 8-(2-propyn-1-yloxy) quinoline **13**, product was obtained as a solid. Yield: 76% (211.3 mg); m.p.: 165–170 °C; $[\alpha]_D^{25} = -24.0$ (c = 1.0, $CHCl_3$); HRMS (ESI-TOF): calcd for $C_{26}H_{29}N_4O_{10}$ ($[M+H]^+$): *m/z* 557.1884; found: *m/z* 557.1884; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83, 1.99, 2.03, 2.20 (4 s, 12H, CH_3CO), 4.11 (dd, 1H, J = 6.3 Hz, J 11.1 Hz, H-6a$_{Gal}$), 4.17 (dd, 1H, J = 5.9 Hz, J = 11.1 Hz, H-6b$_{Gal}$), 4.20 (m, 1H, H-5$_{Gal}$), 5.23 (dd, 1H, J = 3.3 Hz, J = 10.3 Hz, H-3$_{Gal}$), 5.50–5.62 (m, 4H, H-2$_{Gal}$, H-4$_{Gal}$, CH_2), 5.83 (d, 1H, J = 9.3 Hz, H-1$_{Gal}$), 7.27 (m, 1H, H-7$_{Chin}$), 7.40–7.48 (m, 3H, H-3$_{Chin}$, H-5$_{Chin}$, H-6$_{Chin}$), 8.06 (s, 1H, H-5$_{Triaz}$), 8.14 (d, 1H, J = 8.0 Hz, H-4$_{Chin}$), 8.96 (d, 1H, J = 2.8 Hz, H-2$_{Chin}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.19, 20.47, 20.64, 61.25, 62.87, 66.86, 67.89, 70.83, 74.01, 86.29, 110.12, 120.40, 121.68, 121.99, 126.68, 129.53, 136.00, 140.40, 144.74, 149.43, 153.86, 168.85, 169.79, 169.98, 170.31.

*4.2.2.3. 2-Methyl-8-((1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)quinolone **25**.*. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **7** and 2-methyl-8-(2-propyn-1-yloxy) quinoline **14**, product was obtained as a solid. Yield: 80% (228.1 mg); m.p.: 195–200 °C; $[\alpha]_D^{25} = -37.6$ (c = 1.0, $CHCl_3$); HRMS (ESI-TOF): calcd for $C_{27}H_{31}N_4O_{10}$ ($[M+H]^+$): *m/z* 571.2040; found: *m/z* 571.2039; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81, 2.01, 2.05, 2.07 (4 s, 12H, CH_3CO), 2.86 (s, 3H, CH_3), 3.98 (ddd, 1H, J = 2.1 Hz, J = 4.9 Hz, J = 10.1 Hz, H-5$_{Glu}$), 4.13 (dd, 1H, J = 2.1 Hz, J = 12.6 Hz, H-6a$_{Glu}$), 4.27 (dd, 1H, J = 4.9 Hz, J = 12.6 Hz, H-6b$_{Glu}$), 5.22 (dd ~ t, 1H, J = 9.3 Hz, J = 10.1 Hz, H-4$_{Gal}$), 5.37–5.45 (m, 2H, H-3$_{Gal}$, H-2$_{Glu}$), 5.58 i 5.62 (qAB, 2H, J = 13.4 Hz, CH_2), 5.85 (d, 1H, J = 9.0 Hz, H-1$_{Glu}$), 7.23–7.28 (m, 1H, H-7$_{Chin}$), 7.34 (d, 1H, J = 8.4 Hz, H-3$_{Chin}$), 7.37–7.41 (m, 2H, H-5$_{Chin}$, H-6$_{Chin}$), 8.06 (s, 1H, H-5$_{Triaz}$), 8.07 (d, 1H, J = 8.4 Hz, H-4$_{Chin}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.11, 20.50, 20.52, 20.67, 25.39, 61.51, 63.18, 67.68, 70.33, 72.70, 75.11, 85.77, 111.15, 120.34, 122.06, 122.75, 125.98, 127.81, 136.86, 139.17, 145.02, 152.93, 158.31, 168.68, 169.28, 169.93, 170.51.

*4.2.2.4. 2-Methyl-8-((1-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)quinolone **26**.*. Starting from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide **8** and 2-methyl-8-(2-propyn-1-yloxy) quinoline **14**, product was obtained as a solid. Yield: 87% (248.0 mg); m.p.: 178–183 °C; $[\alpha]_D^{25} = -17.4$ (c = 1.0, $CHCl_3$); HRMS (ESI-TOF): calcd for $C_{27}H_{31}N_4O_{10}$ ($[M+H]^+$): *m/z* 571.2040; found: *m/z* 571.2043; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84, 1.99, 2.03, 2.20 (4 s, 12H, CH_3CO), 2.83 (s, 3H, CH_3), 4.10 (dd, 1H, J = 6.3 Hz, J = 10.6 Hz, H-6a$_{Gal}$), 4.17 (dd, 1H, J = 5.9 Hz, J = 10.6 Hz, H-6b$_{Gal}$), 4.20 (m, 1H, H-5$_{Gal}$), 5.23 (dd, 1H, J = 3.3 Hz, J = 10.3 Hz, H-3$_{Gal}$), 5.50–5.63 (m, 4H, H-2$_{Gal}$, H-4$_{Gal}$, CH_2), 5.82 (d, 1H, J = 9.3 Hz, H-1$_{Gal}$), 7.24 (dd, 1H, J = 2.4 Hz, J = 6.5 Hz, H-7$_{Chin}$), 7.33 (d, 1H, J = 8.2 Hz, H-3$_{Chin}$), 7.37–7.41 (m, 2H, H-5$_{Chin}$, H-6$_{Chin}$), 8.04 (d, 1H, J = 8.2 Hz, H-4$_{Chin}$), 8.08 (s, 1H, H-5$_{Triaz}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.21, 20.48, 20.63, 20.65, 25.62, 61.22, 63.36, 66.86, 67.90, 70.86, 74.00, 86.31, 111.02, 120.37, 121.97, 122.66, 125.82, 127.79, 136.49, 138.71, 145.08, 153.25, 158.29, 168.81, 169.80, 169.98, 170.30.

*4.2.2.5. 8-((1-(β-D-Glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy) quinoline **27**.*. Starting from β-D-glucopyranosyl azide **9** and 8-(2-propyn-1-yloxy)quinoline **13**, product was obtained as a solid. Yield: 83% (161.1 mg); m.p.: 213–218 °C; $[\alpha]_D^{25} = -9.6$ (c = 1.0, DMSO); HRMS (ESI-TOF): calcd for $C_{18}H_{21}N_4O_6$ ($[M+H]^+$): *m/z* 389.1461; found: *m/z* 389.1461; ^{1}H NMR (400 MHz, DMSO): δ 3.26 (m, 1H, H-2$_{Glu}$), 3.37–3.50 (m, 3H, H-3$_{Glu}$, H-4$_{Glu}$, H-5$_{Glu}$), 3.70 (m, 1H, H- 6a$_{Glu}$), 3.83 (m, 1H, H-6b$_{Glu}$), 4.71 (t, 1H, J = 5.9 Hz, 6-OH), 5.15 (d, 1H, J = 5.5 Hz, OH), 5.27 (d, 1H, J = 4.9 Hz, OH), 5.35 (s, 2H, CH_2) 5.43 (d, 1H, J = 6.0 Hz, OH), 5.61 (d, 1H, J = 9.3 Hz, H-1$_{Glu}$), 7.44 (dd, 1H, J = 4.7 Hz, J = 9.0 Hz, H-7$_{Chin}$), 7.51–7.58 (m, 3H, H-3$_{Chin}$, H-5$_{Chin}$, H-6$_{Chin}$), 8.32 (dd, 1H, J = 2.0 Hz, J = 8.2 Hz, H-4$_{Chin}$), 8.54 (s, 1H, H-5$_{Triaz}$), 8.82 (dd, 1H, J = 1.6 Hz, J = 4.3 Hz, H-2$_{Chin}$); ^{13}C NMR (100 MHz, DMSO): δ 60.70, 61.64, 69.56, 72.02, 76.98, 80.01, 87.53, 109.73, 119.97, 121.86, 124.25, 126.75, 129.03, 135.78, 139.63, 142.45, 148.96, 153.87.

*4.2.2.6. 8-((1-(β-D-Galactopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy) quinoline **28**.*. Starting from β-D-galactopyranosyl azide **10** and 8-(2-propyn-1-yloxy)quinoline **13**, product was obtained as a solid. Yield: 78% (151.4 mg); m.p.: 233–236 °C; $[\alpha]_D^{25} = 6.0$ (c = 1.0 DMSO); HRMS (ESI-TOF): calcd for $C_{18}H_{21}N_4O_6$ ($[M+H]^+$): *m/z* 389.1461; found: *m/z* 389.1459; ^{1}H NMR (400 MHz, DMSO): δ 3.49–3.61 (m, 3H, H-3$_{Gal}$, H-2$_{Gal}$, H-4$_{Gal}$), 3.71–3.80 (m, 2H, H-5$_{Gal}$, H-6a$_{Gal}$), 4.05–4.13 (m, 1H, H-6b$_{Gal}$), 4.64 (d, 1H, J = 5.5 Hz, OH), 4.75 (t, 1H, J = 5.9 Hz, 6-OH), 5.02 (d, 1H, J = 5.5 Hz, OH), 5.29 (d, 1H, J = 6.0 Hz, OH), 5.36 (s, 2H, CH_2), 5.55 (d, 1H, J = 9.2 Hz, H-1$_{Gal}$), 7.44 (dd, 1H, J = 4.4 Hz, J = 7.4 Hz, H-7$_{Chin}$), 7.51–7.58 (m, 3H, H-3$_{Chin}$, H-5$_{Chin}$, H-6$_{Chin}$), 8.32 (dd, 1H, J = 1.8 Hz, J = 8.3 Hz, H-4$_{Chin}$), 8.47 (s, 1H, H-5$_{Triaz}$), 8.83 (dd, 1H, J = 1.8 Hz, J = 4.1 Hz, H-2$_{Chin}$); ^{13}C NMR (100 MHz, DMSO): δ 60.51, 61.68, 68.54, 69.32, 73.69, 78.54, 88.15, 109.74, 119.96, 121.85, 123.76, 126.74, 129.03, 135.77, 139.64, 142.62, 148.97, 153.87.

*4.2.2.7. 2-Methyl-8-((1-(β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl) methoxy)quinolone **29**.*. Starting from β-D-glucopyranosyl azide **9** and 2-methyl-8-(2-propyn-1-yloxy)quinoline **14**, product was obtained as a solid. Yield: 92% (185.0 mg); m.p.: 162–167 °C; $[\alpha]_D^{25} = -20.4$ (c = 1.0, DMSO); HRMS (ESI-TOF): calcd for $C_{19}H_{23}N_4O_6$ ([M

+H] $^{+}$): *m/z* 403.1618; found: *m/z* 403.1618; ^{1}H NMR (400 MHz, DMSO): *δ* 2.62 (s, 3H, CH_3), 3.21–3.50 (m, 4H, H-2_{Glu}, H-3_{Glu}, H-4_{Glu}, H-5_{Glu}), 3.65–3.73 (m, 1H, H-$6a_{Glu}$), 3.78–3.85 (m, 1H, , H-$6b_{Glu}$), 4.67 (t, 1H, *J* = 5.5 Hz, 6-OH), 5.15 (d, 1H, *J* = 4.2 Hz, OH), 5.29 (bs, 1H, OH), 5.35 (s, 2H, CH_2), 5.43 (d, 1H, *J* = 5.8 Hz, OH), 5.60 (d, 1H, *J* = 9.3 Hz, H-1_{Glu}), 7.38–7.50 (m, 4H, H-3_{Chin}, H-5_{Chin}, H-6_{Chin}, H-7_{Chin}), 8.19 (d, 1H, *J* = 8.4 Hz, H-4_{Chin}), 8.54 (s, 1H, H-5_{Triaz}); ^{13}C NMR (100 MHz, DMSO): *δ* 24.91, 60.68, 61.48, 69.53, 72.03, 76.96, 79.98, 87.51, 110.01, 119.81, 122.47, 124.31, 125.66, 127.32, 135.96, 139.11, 142.51, 153.37, 157.28.

*4.2.2.8. 2-Methyl-8-((1-(β-D-galactopyranosyl)-1H-1,2,3-triazol-4-yl) methoxy)quinoline **30**.*. Starting from β-D-galactopyranosyl azide **10** and 2-methyl-8-(2-propyn-1-yloxy)quinoline **14**, product was obtained as a solid. Yield: 56% (112.6 mg); m.p.: 206–211 °C; $[\alpha]_D^{25} = -38.0$ (c = 1.0, DMSO); HRMS (ESI-TOF): calcd for $C_{19}H_{23}N_4O_6$ ([M +H] $^{+}$): *m/z* 403.1618; found: *m/z* 403.1624; ^{1}H NMR (400 MHz, DMSO): *δ* 2.63 (s, 3H, CH_3), 3.47–3.60 (m, 3H, H-3_{Gal}, H-2_{Gal}, H-4_{Gal}), 3.70–3.79 (m, 2H, H-$6a_{Gal}$, H-5_{Gal}), 4.04–4.10 (m, 1H, H-$6b_{Gal}$), 4.63 (d, 1H, *J* = 5.4 Hz, OH), 4.72 (t, 1H, *J* = 5.8 Hz, 6-OH), 5.02 (d, 1H, *J* = 5.6 Hz, OH), 5.28 (d, 1H, *J* = 6.0 Hz, OH), 5.36 (s, 2H, CH_2), 5.54 (d, 1H, *J* = 9.2 Hz, H-1_{Gal}), 7.38–7.50 (m, 4H, H-3_{Chin}, H-5_{Chin}, H-6_{Chin}, H-7_{Chin}), 8.19 (d, 1H, *J* = 8.4 Hz, H-4_{Chin}), 8.46 (s, 1H, H-5_{Triaz}); ^{13}C NMR (100 MHz, DMSO): *δ* 24.90, 60.46, 61.50, 68.48, 69.29, 73.67, 78.49, 88.12, 110.02, 119.79, 122.45, 123.87, 125.63, 127.31, 135.94, 139.12, 142.63, 153.37, 157.26.

4.3. Biological assays

4.3.1. Bovine milk β-1,4-Galactosyltransferase I assay

β-1,4-GalT activity was assayed using UDP-Gal, a natural β-1,4-GalT glycosyl donor type substrate, and (6-esculetinyl) β-D-glucopyranoside (esculine) as glycosyl fluorescent acceptor. The reaction mixtures contained reagents in the following final concentrations: 50 mM citrate buffer (pH 5.4), 100 mM $MnCl_2$, 20 mg/mL BSA, 2 mM esculine, 0.4 mM UDP-Gal and 10 μL MeOH or methanolic solution of potential inhibitors **15–30** at 0.8 mM concentration. Assays were performed in a total volume of 200 μL. The enzymatic reactions were started by the addition of 8 mU β-1,4-GalT and incubated at 30 °C for 60 min. After that, the reaction mixture was diluted with water to a volume of 500 μL and then was placed in a thermoblock set at 90 °C for 3 min. After denaturation, the solutions were centrifuged at 10 °C for 30 min at 10,000 rpm. The supernatant was filtered using syringe filters (M.E. Cellulose filter, Teknokroma®, 0.2 μm × 13 mm). The filtrate was injected into RP-HPLC system. The percentage of inhibition was evaluated from the fluorescence intensity of the peaks referring to product (6-esculetinyl) 4′-*O*-β-D-galactopyranosyl-β-D-glucopyranoside).

4.3.2. Cell lines

The culture media were purchased from EuroClone, HyClone, MP Biomedicals and Pan Biotech. Fetal bovine serum (FBS) was delivered by Eurx, Poland and Antibiotic Antimycotic Solution (100×) by Sigma-Aldrich, Germany. The human cell line HeLa and MCF-7 were obtained from collections at the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, branch in Gliwice, Poland, as kindly gift from dr Monika Pietrowska and prof. Wiesława Widłak. Normal Human Dermal Fibroblasts-Neonatal, NHDF-Neo were purchased from LONZA (Cat. No. CC-2509; NHDF-Neo, Dermal Fibroblasts, Neonatal; Lonza, Poland). HCT 116 and Hs683 were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). U-251, PANC-1, and AsPC-1 were bought from Sigma-Aldrich, Germany. The culture media consisted of RPMI 1640 or DMEM + F12 medium, supplemented with 10% or 12% fetal bovine serum and standard antibiotics.

4.3.3. MTT assay

A lifespan of the cells was assessed with an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) test (Sigma-Aldrich). The cells were seeded in the 96-well plates with concentration of 1×10^4 or 5×10^3 cells per well. The cells culture were incubated for 24 h at 37 °C in a humidified atmosphere of 5% CO_2. Then the culture medium was removed, replaced with solution of the tested compounds in medium and incubated for further 24 h or 72 h. After that, medium was removed and the MTT solution (50 μL, 0.5 mg/mL in RPMI 1640 without phenol red) was added. After 3 h of incubation, the MTT solution was removed and the acquired formazan was dissolved in isopropanol:HCl system. Finally, the absorbance at the 570 nm wave length was measured spectrophotometrically with the plate reader. The experiment was conducted in three independent iterations with four technical repetitions. Tests were conducted at concentrations tested compounds range from 0.01 mM to 0.8 mM solutions. For the most active compounds IC_{50} values were calculated using CalcuSyn. The IC_{50} parameter was defined as the compound concentration that was necessary to reduce the proliferation of cells to 50% of the untreated control.

4.3.4. MTS assay

The antiproliferative activity of selected compounds was tested on glioblastoma (U-251 and Hs683) and pancreatic cancer (PANC-1 and AsPC-1) cell lines with the MTS assay (Promega). The cells at concentration 5×10^3 per well were seeded into 96-well plates and cultured for 24 h under standard conditions (37 °C in a humidified atmosphere of 5% CO_2). After this time, medium was removed and supplied solutions of tested compounds with varying concentrations. The cell were incubated for 72 h. After this time the medium had been changed for 100 μL one without phenol red, 20 μL MTS dye [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium], and incubated for 1 h (in case of PANC-1 for 3 h). The optical product were qualitatively determined by measurement of the absorbance at 490 nm. The results were calculated as IC_{50} values using GraphPad Prism 5. Each experiment in triplicate was repeated at least three times.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary material

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References

[1] L. Costantino, D. Barlocco, Privileged structures as leads in medicinal chemistry, Curr. Med. Chem. 13 (2006) 65–85, https://doi.org/10.2174/092986706775197999.
[2] C.D. Duarte, E.J. Barreiro, C.A.M. Fraga, Privileged structures: a useful concept for the rational design of new lead drug candidates, Mini Rev. Med. Chem. 7 (2007) 1108–1119, https://doi.org/10.2174/138955707782331722.
[3] Anjali, D. Pathak, D. Singh, Quinoline: a diverse therapeutic agent, IJPSR 7 (2016) 1–13, https://doi.org/10.13040/IJPSR.0975-8232.7(1).25-30.
[4] R. Musiol, An overview of quinoline as a privileged scaffold in cancer drug discovery, Exp. Op. Drug Disc. 12 (2017) 583–597, https://doi.org/10.1080/17460441.2017.1319357.
[5] Y. Song, H. Xu, W. Chen, P. Zhan, X. Liu, 8-Hydroxyquinoline: a privileged structure with a broad-ranging pharmacological potential, Med. Chem. Commun. 6 (2015) 61–74, https://doi.org/10.1039/C4MD00284A.

[6] V. Oliveri, G. Vecchio, 8-Hydroxyquinolines in medicinal chemistry: A structural perspective, Eur. J. Med. Chem. 120 (2016) 252–274, https://doi.org/10.1016/j.ejmech.2016.05.007.

[7] L. Cahoon, The curious case of clioquinol, Nat. Med. 15 (2009) 356–359, https://doi.org/10.1038/nm0409-356.

[8] B. Regland, W. Lehmann, I. Abedini, K. Blennow, M. Jonsson, I. Karlsson, M. Sjögren, A. Wallin, M. Xilinas, C.G. Gottfries, Treatment of Alzheimer's disease with clioquinol, Dement. Geriatr. Cogn. Disord. 12 (2001) 408–414, https://doi.org/10.1159/000051288.

[9] C.M. Darby, C.F. Nathan, Killing of non-replicating *Mycobacterium tuberculosis* by 8-hydroxyquinoline, J. Antimicrob. Chemother. 65 (2010) 1424–1427, https://doi.org/10.1093/jac/dkq145.

[10] P.A. Enquist, Å. Gylfe, U. Hägglund, P. Lindström, H. Norberg-Scherman, Ch. Sundin, M. Elofsson, Derivatives of 8-hydroxyquinoline—antibacterial agents that target intra- and extracellular Gram-negative pathogens, Bioorg. Med. Chem. Lett. 22 (2012) 3550–3553, https://doi.org/10.1016/j.bmcl.2012.03.096.

[11] J. Novakowa, E. Vlkova, B. Bonusova, V. Rada, L. Kokoska, *In vitro* selective inhibitory effect of 8-hydroxyquinoline against bifidobacteria and clostridia, Anaerobe 22 (2013) 134–136, https://doi.org/10.1016/j.anaerobe.2013.05.008.

[12] P. Hongmanee, K. Rukseree, B. Buabut, B. Somsri, P. Palittapongarnpim, In Vitro Activities of Cloxyquin (5-Chloroquinolin-8-ol) against *Mycobacterium tuberculosis*, Antimicrob. Agents Chemother. 51 (2007) 1105–1106, https://doi.org/10.1128/AAC.01310-06.

[13] H. Jiang, J.E. Taggart, X. Zhang, D.M. Benbrook, S.E. Lind, W.Q. Ding, Nitroxoline (8-hydroxy-5-nitroquinoline) is more a potent anti-cancer agent than clioquinol (5-chloro-7-iodo-8-quinoline), Cancer Lett. 312 (2011) 11–17, https://doi.org/10.1016/j.canlet.2011.06.032.

[14] W.Q. Ding, B. Liu, J.L. Vaught, H. Yamauchi, S.E. Lind, Anticancer activity of the antibiotic clioquinol, Cancer Res. 65 (2005) 3389–3395, https://doi.org/10.1158/0008-5472.CAN-04-3577.

[15] A.Y. Shen, S.N. Wu, C.T. Chiu, Synthesis and cytotoxicity evaluation of some 8-hydroxyquinoline derivatives, J. Pharm. Pharmacol. 51 (1999) 543–548, https://doi.org/10.1211/0022357991772826.

[16] S. Zhai, L. Yang, Q.C. Cui, Y. Sun, Q.P. Dou, B. Yan, Tumor cellular proteasome inhibition and growth suppression by 8-hydroxyquinoline and clioquinol requires their capabilities to bind copper and transport copper into cells, J. Biol. Inorg. Chem. 15 (2010) 259–269, https://doi.org/10.1007/s00775-009-0594-5.

[17] W.Q. Ding, S.E. Lind, metal ionophores – an emerging class of anticancer drugs, IUBMB Life 61 (2009) 1013–1018, https://doi.org/10.1002/iub.253.

[18] M.E. Helsel, K.J. Franz, Pharmacological activity of metal binding agents that alter copper bioavailability, Dalton Trans. 44 (2015) 8760–8770, https://doi.org/10.1039/c5dt00634a.

[19] V. Prachayasittikul, S. Prachayasittikul, S. Ruchirawat, V. Prachayasittikul, 8-Hydroxyquinolines: a review of their metal chelating properties and medicinal applications, Drug Des. Dev. Ther. 7 (2013) 1157–1178, https://doi.org/10.2147/DDDT.S49763.

[20] G.J. Brewer, Copper control as an antiangiogenic anticancer therapy: lessons from treating Wilson's disease, Exp. Biol. Med. 226 (2001) 665–673 https://www.ncbi.nlm.nih.gov/pubmed/11444102.

[21] A. Gupte, R.J. Mumper, Elevated copper and oxidative stress in cancer cells as a target for cancer treatment, Cancer Treat. Rev. 35 (2009) 32–46, https://doi.org/10.1016/j.ctrv.2008.07.004.

[22] V. Milacic, P. Jiao, B. Zhang, B. Yan, Q.P. Dou, Novel 8-hydroxylquinoline analogs induce copper-dependent proteasome inhibition and cell death in human breast cancer cells, Int. J. Oncol. 35 (2009) 1481–1491, https://doi.org/10.3892/ijo_00000467.

[23] A. Barilli, C. Atzeri, I. Bassanetti, F. Ingoglia, V. Dall'Asta, O. Bussolati, M. Maffini, C. Mucchino, L. Marchiò, Oxidative stress induced by copper and iron complexes with 8-hydroxyquinoline derivatives causes paraptotic death of HeLa cancer cells, Mol. Pharmaceut. 11 (2014) 1151–1163, https://doi.org/10.1021/mp400592n.

[24] E.C. Calvaresi, P.J. Hergenrother, Glucose conjugation for the specific targeting and treatment of cancer, Chem. Sci. 4 (2013) 2319–2333, https://doi.org/10.1039/C3SC22205E.

[25] G.J. Seifert, Nucleotide sugar interconversions and cell wall biosynthesis: how to bring the inside to the outside, Curr. Op. Plant Biol. 7 (2004) 277–284, https://doi.org/10.1016/j.pbi.2004.03.004.

[26] V. Oliveri, G. Vecchio, Glycoconjugates of quinolines: application in medicinal chemistry, Mini-Rev. Med. Chem. 16 (2016) 1185–1194, https://doi.org/10.2174/1389557516666160505115634.

[27] V. Oliveri, G.I. Grasso, F. Bellia, F. Attanasio, M. Viale, G. Vecchio, Soluble sugar-based quinoline derivatives as new antioxidant modulators of metal-induced amyloid aggregation, Inorg. Chem. 54 (2015) 2591–2602, https://doi.org/10.1021/ic502713f.

[28] W. Li, Z.W. Zhang, S.X. Wang, S.M. Ren, T. Jiang, Synthesis and analysis of potential DNA intercalators containing quinoline-glucose hybrids, Chem. Biol. Drug. Des. 74 (2009) 80–86, https://doi.org/10.1111/j.1747-0285.2009.00831.x.

[29] T.A. Chupakhina, A.M. Katsev, V.O. Kur'yanov, Synthesis and investigation of antimicrobial activity of 8-hydroxyquinoline glucosaminides, Russ. J. Bioorg. Chem. 38 (2012) 422–427, https://doi.org/10.1134/S106816201204005X.

[30] V. Oliveri, A. Puglisi, M. Viale, C. Aiello, C. Sgarlata, G. Vecchio, J. Clarke, J. Milton, J. Spencer, New cyclodextrin-bearing 8-hydroxyquinoline ligands as multifunctional molecules, Chem. Eur. J. 19 (2013) 13946–13955, https://doi.org/10.1002/chem.201300237.

[31] V. Oliveri, M.L. Giuffrida, G. Vecchio, C. Aiello, M. Viale, Gluconjugates of 8-hydroxyquinolines as potential anti-cancer prodrugs, Dalton Trans. 41 (2012) 4530–4535, https://doi.org/10.1039/c2dt12371a.

[32] V. Oliveri, M. Viale, G. Caron, C. Aiello, R. Gangemi, G. Vecchio, Glycosylated copper(II) ionophores as prodrugs for β-glucosidase activation in targeted cancer therapy, Dalton Trans. 42 (2013) 2023–2034, https://doi.org/10.1039/c2dt32429f.

[33] V. Oliveri, M. Viale, C. Aiello, G. Vecchio, New 8-hydroxyquinoline galactosides. The role of the sugar in the antiproliferative activity of copper(II) ionophores, J., Inorg. Biochem. 142 (2015) 101–108, https://doi.org/10.1016/j.jinorgbio.2014.09.017.

[34] G. Pastuch-Gawołek, K. Malarz, A. Mrozek-Wilczkiewicz, M. Musioł, M. Serda, B. Czaplińska, R. Musioł, Small molecule glycoconjugates with anticancer activity, Eur. J. Med. Chem. 112 (2016) 130–144, https://doi.org/10.1016/j.ejmech.2016.01.061.

[35] A.E. Rashad, W.A. El-Sayed, A.M. Mohamed, M.M. Ali, Synthesis of new quinoline derivatives as inhibitors of human tumor cells growth, Arch. Pharm. Chem. Life Sci. 8 (2010) 440–448, https://doi.org/10.1002/ardp.201000002.

[36] L.B.de.O. Freitas, T.F. Borgati, R.P. de Freitas, A.L.T.G. Ruiz, G.M. Marchetti, J.E. de Carvalho, E.F.F. da Cunha, T.C. Ramalho, R.B. Alves, Synthesis and antiproliferative activity of 8-hydroxyquinoline derivatives containing a 1,2,3-triazole moiety, Eur. J. Med. Chem. 84 (2014) 595–604, https://doi.org/10.1016/j.ejmech.2014.07.061.

[37] S. Areti, S. Bandaru, Ch.P. Rao, Triazole-linked quinoline conjugate of glucopyranose: selectivity comparison among Zn^{2+}, Cd^{2+}, and Hg^{2+} based on spectroscopy, thermodynamics, and microscopy, and reversible sensing of Zn^{2+} and the structure of the complex using DFT, ACS Omega 1 (2016) 626–635, https://doi.org/10.1021/acsomega.6b00277.

[38] D. Dheer, V. Sing, R. Shankar, Medicinal attributes of 1,2,3-triazoles: Current developments, Bioorg. Chem. 71 (2017) 30–54, https://doi.org/10.1016/j.bioorg.2017.01.010.

[39] M. Meldal, C.W. Tornøe, Cu-catalyzed azide-alkyne cycloaddition, Chem. Rev. 108 (2008) 2952–3015, https://doi.org/10.1021/cr0783479.

[40] P. Thirumurugan, D. Matosiuk, K. Jozwiak, Click chemistry for drug development and diverse chemical–biology applications, Chem. Rev. 113 (2013) 4905–4979, https://doi.org/10.1021/cr200409f.

[41] S.P. Mantoani, T.P.C. Chierrito, A.F.L. Vilela, C.L. Cardoso, A. Martínez, I. Carvalho, Novel triazole-quinoline derivatives as selective dual binding site acetylcholinesterase inhibitors, Molecules 21 (2016) 193–204, https://doi.org/10.3390/molecules21020193.

[42] H.C. Kolb, K.B. Sharpless, The growing impact of click chemistry on drug discovery, DDT 8 (2003) 1128–1137, https://doi.org/10.1016/S1359-6446(03)02933-7.

[43] C.A.G.M. Weijers, M.C.R. Franssen, G.M. Visser, Glycosyltransferase-catalyzed synthesis of bioactive oligosaccharides, Biotechnol. Adv. 26 (2008) 436–456, https://doi.org/10.1016/j.biotechadv.2008.05.001.

[44] Ch. Breton, S. Fournel-Gigleux, M.M. Palcic, Recent structures, evolution and mechanisms of glycosyltransferases, Curr. Opin. Struct. Biol. 22 (2012) 540–549, https://doi.org/10.1016/j.sbi.2012.06.007.

[45] L.L. Lairson, B. Henrissat, G.J. Davies, S.G. Withers, Glycosyltransferases: structures, functions, and mechanisms, Annu. Rev. Biochem. 77 (2008) 521–555, https://doi.org/10.1146/annurev.biochem.76.061005.092322.

[46] I. Brockhausen, M. Benn, S. Bhat, S. Marone, J.G. Riley, P. Montoya-Peleaz, J.Z. Vlahakis, H. Paulsen, J.S. Schutzbach, W.A. Szarek, UDP-Gal: GlcNAc-R β1,4-galactosyltransferase—a target enzyme for drug design. Acceptor specificity and inhibition of the enzyme, Glycoconj. J 23 (2006) 525–541, https://doi.org/10.1007/s10719-006-7153-x.

[47] X. Qian, M.M. Palcic, Glycosyltransferase inhibitors, Carbohydrates in Chemistry and Biology, WILEY-VCH Verlag GmbH, 2000, pp. 293–312, , https://doi.org/10.1002/9783527618255.ch56.

[48] S. Wang, J.A. Cuesta-Seijo, D. Lafont, M.M. Palcic, S. Vidal, Design of glycosyltransferase inhibitors: pyridine as a pyrophosphate surrogate, Chem. Eur. J. 19 (2013) 15346–15357, https://doi.org/10.1002/chem.201301871.

[49] K. Kumamoto, Y. Goto, K. Sekikawa, S. Takenoshita, N. Ishida, M. Kawakita, R. Kannagi, Increased expression of UDP-galactose transporter messenger RNA in human colon cancer tissues and its implication in synthesis of Thomsen-Friedenreich Antigen and Sialyl Lewis A/X determinants, Cancer Res. 61 (2001) 4620–4627 https://www.ncbi.nlm.nih.gov/pubmed/11389099.

[50] R.D. Murray, A. Ailabouni, L.A. Heitlinger, B.U.K. Li, H.J. McClung, P. Powers, J. Gutt, L. Kien, Galactose-containing carbohydrates are preferentially absorbed in the neonatal pig colon, Pediatr. Res. 39 (1996) 656–660, https://doi.org/10.1203/00006450-199604000-00016.

[51] R.C. Evans, S. Fear, D. Ashby, A. Hackett, E. Williams, M. van der Vliet, F.D.J. Dunstan, J.M. Rhodes, Diet and colorectal cancer: an investigation of the lectin/galactose hypothesis, Gastroenterology 122 (2002) 1784–1792, https://doi.org/10.1053/gast.2002.33659.

[52] R.S. Haber, A. Rathan, K.R. Weiser, A. Pritsker, S.H. Itzkowitz, C. Bodian, G. Slater, A. Weiss, D.E. Burstein, GLUT1 glucose transporter expression in colorectal carcinoma: a marker for poor prognosis, Cancer 83 (1998) 34–40, https://doi.org/10.1002/(SICI)1097-0142(19980701)83:1<34::AID-CNCR5>3.0.CO;2-E.

[53] Q.R. Yang, W.H. Qiao, S.M. Zhang, J.P. Qu, D.L. Liu, Synthesis and characterization of a new cationic galactolipid with carbamate for gene delivery, Tenside Surf. Det. 5 (2010) 294–299, https://doi.org/10.3139/113.110080.

[54] H. Rajaram, M.K. Palanivelu, T.V. Arumugam, V.M. Rao, P.N. Shaw, R.P. McGeary, B.P. Ross, 'Click' assembly of glycoclusters and discovery of a trehalose analogue that retards Aβ40 aggregation and inhibits Aβ40-induced neurotoxicity, Bioorg. Med. Chem. Lett. 24 (2014) 4523–4528, https://doi.org/10.1016/j.bmcl.2014.07.077.

[55] I. Shin, H. Jung, M. Lee, Chemoselective ligation of maleimidosugars to peptides/protein for the preparation of neoglycopeptides/neoglycoprotein, Tetrahedron Lett. 42 (2001) 1325–1328, https://doi.org/10.1016/S0040-4039(00)02286-3.

[56] M. Jacobsson, J. Malmberg, U. Ellervik, Aromatic *O*-glycosylation, Carbohydr. Res. 341 (2006) 1266–1281, https://doi.org/10.1016/j.carres.2006.04.004.
[57] U. Aich, D. Loganathan, Stereoselective single-step synthesis and X-ray crystallographic investigation of acetylated aryl 1,2-*trans* glycopyranosides and aryl 1,2-*cis* C2-hydroxy-glycopyranosides, Carbohydr. Res. 341 (2006) 19–28, https://doi.org/10.1016/j.carres.2005.10.010.
[58] Y.S. Lee, E.S. Rho, Y.K. Min, B.T. Kim, K.H. Kim, Practical β-stereoselective *O*-glycosylation of phenols with penta-*O*-acetyl-β-D-glucopyranose, Carbohydr. Chem. 20 (2001) 503–506, https://doi.org/10.1081/CAR-100106933.
[59] T. Zenkoh, H. Tanaka, H. Setoi, T. Takahashi, Solid-phase synthesis of aryl *O*-glycoside using aqueous base and phase transfer catalyst, Synlett 6 (2002) 867–870, https://doi.org/10.1055/s-2002-31926.
[60] T.J. Wadzinski, A. Steinauer, L. Hie, G. Pelletier, A. Schepartz, S.J. Miller, Rapid phenolic *O*-glycosylation of small molecules and complex unprotected peptides in aqueous solvent, Nat. Chem. 10 (2018) 644–652.
[61] Y. Li, H. Mo, G. Lian, B. Yu, Revisit of the phenol *O*-glycosylation with glycosyl imidates, BF_3·OEt_2 is a better catalyst than TMSOTf, Carbohydr. Res. 363 (2012) 14–22, https://doi.org/10.1016/j.carres.2012.09.025.
[62] M.J. Thompson, E.J. Hutchinson, T.H. Stratford, W.B. Bowlerb, G.M. Blackburna, Sugar conjugates of fulvestrant (ICI 182,780): efficient general procedures for glycosylation of the fulvestrant core, Tetrahedron Lett. 45 (2004) 1207–1210, https://doi.org/10.1016/j.tetlet.2003.11.140.
[63] Q. Qin, D.-C. Xiong, X.-S. Ye, Additive-controlled stereoselective glycosylations of 2,3-oxazolidinone protected glucosamine or galactosamine thioglycoside donors with phenols based on preactivation protocol, Carbohydr. Res. 403 (2015) 104–114, https://doi.org/10.1016/j.carres.2014.07.004.
[64] S.G. Duron, T. Polat, C.H. Wong, N-(Phenylthio)-ε-caprolactam: A new promoter for the activation of thioglycosides, Org. Lett. 6 (2004) 839–841, https://doi.org/10.1021/ol0400084.
[65] W.R. Roush, X.F. Lin, A highly stereoselective synthesis of aryl 2-deoxy-β-glycosides via the Mitsunobu reaction, J. Org. Chem. 56 (1991) 5740–5742, https://doi.org/10.1021/jo00020a003.
[66] N. Lucchetti, R. Glimour, Reengineering chemical glycosylation: direct, metal-free anomeric *O*-arylation of unactivated carbohydrates, Chem. Eur. J. 24 (2018) 16266–16270, https://doi.org/10.1002/chem.201804416.
[67] H. Ye, C. Xiao, Q.-Q. Zhou, P.G. Wang, W.-J. Xiao, Synthesis of phenolic glycosides: glycosylation of sugar lactols with aryl bromides via dual photoredox/Ni catalysis, J. Org. Chem. 83 (2018) 13325–13334, https://doi.org/10.1021/acs.joc.8b02129.
[68] R.A. Tromp, S.S.G.E. van Boom, C.M. Timmers, S. van Zutphen, G.A. van der Marel, H.S. Overkleeft, J.H. van Boom, J. Reedijk, The β-glucuronyl-based prodrug strategy allows for its application on β-glucuronyl-platinum conjugates, J. Bioorg. Med. Chem. Lett. 14 (2004) 4273–4276, https://doi.org/10.1016/j.bmcl.2004.06.015.
[69] K. Yoshida, Y. Kanoko, K. Takao, Kinetically controlled α-selective O-glycosylation of phenol derivatives using 2-nitroglycals by a bifunctional chiral thiourea catalyst, Asian J. Org. Chem. 5 (2016) 1230–1236, https://doi.org/10.1002/ajoc.201600307.
[70] E.R. Palmacci, P.H. Seeberger, Synthesis of *C*-aryl and *C*-alkyl glycosides using glycosyl phosphates, Org. Lett. 3 (2001) 1547–1550, https://doi.org/10.1021/ol0158462.
[71] A. Vasella, New reactions and intermediates involving the anomeric center, Pure Appl. Chem. 63 (1991) 507–518, https://doi.org/10.1351/pac199163040507.
[72] I.J. Talisman, V. Kumar, J. Razzaghy, S.V. Malhotra, *O*-Glycosidation reactions promoted by in situ generated silver *N*-heterocyclic carbenes in ionic liquids, Carbohydr. Res. 346 (2011) 883–890, https://doi.org/10.1016/j.carres.2011.03.007.
[73] V.O. Kur'yanov, U.S. Priskoka, T.A. Chupakhina, V.Y. Chirva, A phase-transfer glucosamination of phenols catalyzed by polyethylene glycol, Russ. J. Bioorg. Chem. 31 (2005) 335–336, https://doi.org/10.1007/s11171-005-0042-4.
[74] H.C. Kolb, M.G. Finn, K.B. Sharpless, Click chemistry: diverse chemical function from a few good reactions, Angew. Chem. Int. Ed. 40 (2001) 2004–2021, https://doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.
[75] Y. Wu, M. Pan, Y. Dai, B. Liu, J. Cui, W. Shi, Q. Qiu, W. Huang, H. Qian, Design, synthesis and biological evaluation of LBM-A5 derivatives as potent P-glycoprotein-mediated multidrug resistance inhibitors, Bioorg. Med. Chem. 24 (2016) 2287–2297, https://doi.org/10.1016/j.bmc.2016.03.065.
[76] S. Vidal, I. Bruyère, A. Malleron, C. Augé, J.P. Praly, Non-isosteric C-glycosyl analogues of natural nucleotide diphosphate sugars as glycosyltransferase inhibitors, Bioorg. Med. Chem. 14 (2006) 7293–7301, https://doi.org/10.1016/j.bmc.2006.06.057.
[77] C.C. Barron, P.J. Bilan, T. Tsakiridis, E. Tsiani, Facilitative glucose transporters: Implications for cancer detection, prognosis and treatment, Metabolism 65 (2016) 124–139, https://doi.org/10.1016/j.metabol.2015.10.007.
[78] C. Granchi, F. Minutolo, Anticancer agents that counteract tumor glycolysis, Chem. Med. Chem. 7 (2012) 1318–1350, https://doi.org/10.1002/cmdc.201200176.
[79] N. Wang, M. Świtalska, M.Y. Wu, K. Imai, T.A. Ngoc, C.Q. Pang, L. Wang, J. Wietrzyk, T. Inokuchi, Synthesis and in vitro cytotoxic effect of 6-amino-substituted 11H- and 11Me-indolo[3,2-c]quinolines, Eur. J. Med. Chem. 78 (2014) 314–323, https://doi.org/10.1016/j.ejmech.2014.03.038.
[80] Z. Xiao, F. Lei, X. Chen, X. Wang, L. Cao, K. Ye, W. Zhu, S. Xu, Design, synthesis, and antitumor evaluation of quinoline-imidazole derivatives, Arch. Pharm. Chem. Life Sci. 351 (2018) 1–11, https://doi.org/10.1002/ardp.201700407.
[81] Y.L. Chen, Ch.H. Chung, I.L. Chen, P.H. Chen, H.Y. Jeng, Synthesis and cytotoxic activity evaluation of indolo-, pyrrolo-, and benzofuro-quinolin-2(1H)-ones and 6-anilinoindoloquinoline derivatives, Bioorg. Med. Chem. 10 (2002) 2705–2712, https://doi.org/10.1016/S0968-0896(02)00111-6.
[82] Ch. Chen, X. Hou, G. Wang, W. Pan, X. Yang, Y. Zhang, H. Fang, Design, synthesis and biological evaluation of quinoline derivatives as HDAC class I inhibitors, Eur. J. Med. Chem. 133 (2017) 11–23, https://doi.org/10.1016/j.ejmech.2017.03.064.
[83] J. Kim, C.V. Dang, Cancer's molecular sweet tooth and the Warburg effect, Cancer Res. 66 (2006) 8927–8930, https://doi.org/10.1158/0008-5472.CAN-06-1501.
[84] D.K. Podolsky, K.J. Isselbacher, Cancer-associated galactosyltransferase acceptor: inhibition of transformed cell and tumor growth, Cancer 45 (1980) 1212–1217 http://www.ncbi.nlm.nih.gov/pubmed/6766800.
[85] C.R. Dates, T. Fahmi, S.J. Pyrek, A. Yao-Borengasser, B. Borowa-Mazgaj, S.M. Bratton, S.A. Kadlubar, P.I. Mackenzie, R.S. Haun, A. Radominska-Pandya, Human UDP-Glucuronosyltransferases: Effects of altered expression in breast and pancreatic cancer cell lines. Cancer Biol. Ther. 16 (2015) 714–723, https://doi.org/10.1080/15384047.2015.1026480.
[86] L. Yilmaz, E. Borazan, T. Aytekin, I. Baskonus, A. Aytekin, S. Oztuzcu, Z. Bozdag, A. Balik, Increased UGT1A3 and UGT1A7 expression is associated with pancreatic cancer, Asian Pac. J. Cancer Prev. 16 (2015) 1651–1655, https://doi.org/10.7314/APJCP.2015.16.4.1651.