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Theoretical approaches to the design of biologically active compounds based on carbohydrates for medical applications

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Abstract. The study aimed to formulate theoretical grounds for the targeted design of glycosylated biologically active molecules with predictable pharmacological properties. The study methodology was based on a theoretical and analytical approach using *in silico* modelling, including prediction of bioavailability, polar surface and gastrointestinal absorption, as well as assessment of molecular interactions of glycosylated compounds with pharmacologically relevant targets. The results indicate that glycosyl residues such as N-acetylglucosamine and sialic acid increase the polar surface of the molecule from 48.9 to 112.4 square angstroms, which contributes to more efficient hydrogen bonding with receptor proteins. At the same time, a decrease in the distribution coefficient for octanol and water from 3.4 to 1.8 was observed, indicating a decrease in lipophilicity and more favourable pharmacokinetics. The modelled glycosylated compounds demonstrated a high degree of absorption in the gastrointestinal tract, in contrast to non-glycosylated analogues. The binding energy of the glycosylated molecules to the hyaluronic acid receptor and Galectin-3 lectin was in the range of -8.5 to -9.1 kilocalories per mole, indicating high affinity and stability of the complex. In comparison, the corresponding parameters for unmodified compounds ranged from -5.9 to -7.3 kilocalories per mole. The analysis also revealed a decrease in potential cytotoxicity and an increase in selectivity of action due to targeted interaction with receptor proteins. The data obtained confirm the importance of glycosylation as a strategy to improve the bioavailability, specificity and therapeutic efficacy of the molecules under development. The results are of practical importance for the rational design of medicinal molecules in which glycosyl fragments are used as active pharmacophore elements that increase the selectivity, stability and bioavailability of therapeutic compounds

Keywords: pharmacokinetics; molecular modelling; selectivity; receptor activity; biotargets; pharmacophore; bioavailability

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Introduction

In the context of growing drug resistance, limited selectivity of existing drugs, and the need to develop compounds with predictable pharmacological properties, the problem of structural design of biologically active molecules with targeted action is becoming particularly relevant. Modern medicinal chemistry faces a shortage of universal strategies that can simultaneously ensure high bioavailability, stability, and specificity of interaction with pharmacological targets. In this regard, a scientific problem arises: the lack of a comprehensive theoretical model that would provide the rational selection of structural components, such as glycosyl fragments, when creating new therapeutic agents.

One of the promising solutions to the problem is the use of carbohydrates as structural elements capable of modelling the pharmacological properties of a molecule. Natural mono- and oligosaccharides are characterised by high biocompatibility, metabolic stability and variability of functional groups, which makes them a versatile platform for molecular design. The inclusion of carbohydrate fragments provides targeted influence on pharmacokinetics and receptor specificity, especially concerning such targets as glucose transporter type 1 (GLUT1), Galectin-3, a β-galactoside-binding lectin, and the Cluster of Differentiation 44 (CD44) receptor, a membrane glycoprotein that interacts with hyaluronic acid [1].

In the post-Soviet scientific space, the topic of designing glycosylated compounds is being developed mainly in the pharmaceutical and chemical-biological fields. O. Akparalieva *et al.* [2] attempted to combine the synthesis of sulphonamide derivatives with a carbohydrate structure and the use of the Prediction of Activity Spectra for Substances software for preliminary computer screening of activity. The study not only highlighted the influence of glycosyl fragments on bioavailability but also raised the issue of the correlation between hydrophilicity and the proposed mechanism of action. In turn, V. Akhmetova [3] analysed the pharmacokinetic behaviour of glycosylated derivatives in the dissertation on changes in the metabolic rate depending on the nature of the carbohydrate component. The research demonstrated that glycosylation in Kyrgyz practice is perceived not only as a structural modification but also as a controlled tool for optimising pharmacological characteristics.

The use of carbohydrates as functional platforms in the therapy of malignant tumours is theoretically substantiated in several international publications. The review by A. Costa *et al.* [4] presented a structured presentation of the mechanisms of cellular uptake of glycosylated agents involving specific target proteins such as GLUT1, Galectin-3 and CD44. Notably, the study addressed carbohydrate fragments not as additive modules, but as full-fledged pharmacophores that determine the molecule delivery trajectory. The topic was further developed by N. Xavier *et al.* [5], proposing a classification of carbohydrate compounds according to the degree of structural similarity to natural analogues. The analysis of synthetic glycopeptides with immunomodulatory activity is also noteworthy: the study raises the question of the possibility of their adaptation for targeted delivery of anticancer agents. There is also a tendency to use carbohydrates not as an auxiliary element, but as the basis of a structure with specified biological functions.

The development of biologically active substances based on carbohydrates is impossible without the use of modern molecular modelling methods and highly specific synthetic approaches. A. Andreu *et al.* [6] conducted a detailed review of enzymatic strategies to produce glycosyl derivatives using engineered glycosyltransferases. The study emphasised that this route is not only environmentally friendly but also ensures strict control of the stereochemistry of the bond, which is considered a significant factor in the development of targeted drugs. Of additional value is the study by J. Markink [7], which uses machine learning for the automated design of carbohydrate ligands with affinity for target proteins. In contrast to the traditional Quantitative Structure-Activity Relationship approach, the study employed deep neural network architectures, which incorporate both spatial and electronic parameters of molecules.

The issue of structural modification of carbohydrates to optimise the pharmacological properties remains the focus of modern glycochemistry. L. Pan *et al.* [8] considered carbohydrates as a basis for the construction of polymeric carriers that enhance the penetration of the active substance into target cells. The novelty of the article lies in the systematisation of nanotechnological solutions aimed at increasing the solubility and prolonging the action of glycosylated compounds. In turn, N. Wang *et al.* [9] emphasised phosphorylated sugars, demonstrating that phosphorus groups can stabilise the structure of the molecule and increase resistance to enzymatic hydrolysis. Both studies emphasise that the efficiency of carbohydrates as a building block can be significantly enhanced by targeted functionalisation.

Scientific publications devoted to the design of carbohydrate-based biologically active compounds, as a rule, fragmentarily consider the structural and functional features of glycosylated components without a comprehensive analysis of the possibilities of their targeted use in medicinal chemistry. The study aimed to develop theoretical approaches to the creation of glycosylated compounds with pharmacologically relevant properties. The study objectives were to identify the structural regularities that determine the biopharmaceutical profile of carbohydrate-containing molecules, to evaluate the methods used for the modelling, and to review attempts to experimentally substantiate the proposed theoretical approaches.

Materials and Methods

The study was conducted within the framework of a theoretical and analytical approach with elements of *in silico* modelling for computer prediction of biological activity, pharmacokinetic properties and molecular interaction of compounds based on the chemical structure and with the use of published experimental and patent data for comparative analysis and verification of theoretical conclusions. At the level of general theoretical analysis, a set of logical and methodological techniques was used, each method being applied to solve specific problems related to the theoretical substantiation of the design of glycosylated biologically active compounds. In particular, the structural analysis covered the classification of glycosyl residues (aldose, ketose, amino sugars), types of glycosidic bonds (O-, N-, S-couplings) and the configuration features, assessing the potential impact of these parameters on receptor selectivity and biopharmacological properties.

As part of the applied stage of modelling, 10 molecular structures were analysed: 5 glycosylated compounds modified with various carbohydrate fragments (α-D-glucose, β-D-galactose, N-acetylglucosamine, sialic and glucuronic acids), as well as 5 corresponding non-glycosylated analogues identical in terms of the basic skeleton of the molecule. The structures were selected based on the comparability criterion, which ensured an objective comparison of key pharmacokinetic and receptor parameters such as topological polar surface area (TPSA), lipophilicity coefficient (LogP), gastrointestinal absorption (GI absorption), and binding energy to biotargets such as GLUT1 transporter, CD44 receptor, and Galectin-3 lectin.

Induction was used to summarise data extracted from experimental and patent sources, and deduction was used to theoretically test hypotheses within the framework of drug-receptor models using molecular docking performed in AutoDock Vina (via PyRx) with an RMSD threshold of 2 Å and an active site size of 22 × 22 × 22 Å. The comparison method was used for a reasonable comparison of glycosylated and non-glycosylated biologically active compounds at the stage of theoretical modelling. This approach was used for a structural and functional assessment incorporating key pharmacokinetic (LogP, TPSA, GI absorption) and pharmacodynamic parameters (affinity, binding energy, cytotoxicity, selectivity).

In the logical structure of the study, the synthesis method was used to combine theoretical and modelling data with patent information, which formulated a conceptual framework linking the structure of glycosyl residues to their putative biological activity. The results were summarised at the final stage to compare the theoretical conclusions with the data from molecular modelling and visual analysis of the complexes. The empirical and patent base of the study was formed based on publications from 2005-2024, selected by keywords ("glycosylation", "glycomimetics", "glycoengineering") in Scopus, PubMed and SpringerLink, with priority given to papers containing data on biologically active glycosylated compounds. Two patents US11261477B2 [10] and US10087236B2 [11] were selected as representative sources: the first describes methods of targeted glycosylation of small molecules using engineered glycosyltransferases and the impact on biopharmaceutical properties, the second describes approaches to glycan engineering of antibodies with a demonstration of the effect of the structure of carbohydrate fragments on pharmacokinetics and receptor specificity.

For the theoretical evaluation of glycosylated compounds, the online tools Prediction of Activity Spectra for Substances Online, SwissADME and PubChem Sketcher were used. The former was used to predict the spectrum of biological activity based on the structure of the molecules, the latter to calculate pharmacokinetic parameters (LogP logarithm of the octanol/water distribution coefficient, TPSA, GI absorption), and the latter to generate structures and SMILES formats. The integrated use of these platforms made it possible to conduct a preliminary *in silico* analysis without laboratory tests.

Results and Discussion

Structural features of glycosylated derivatives as objects of pharmacological modelling

The results of the theoretical analysis demonstrated that the most common glycosyl residues such as α-D-glucose, β-D-galactose, N-acetylglucosamine, sialic and glucuronic acids differ in size, configurational flexibility and ability to form hydrogen bonds, which directly affects their pharmacophore function. In particular, the inclusion of α-D-glucose in the structure of low molecular weight compounds contributed to an increase in solubility, improving pharmaceutical availability. On the contrary, N-acetylglucosamine demonstrated a higher level of polarity (TPSA>100 $Å^2$) and resistance to enzymatic deglycosylation, which makes it particularly valuable in the development of stabilised antibodies.

The *in-silico* modelling results indicated a potential dependence of the metabolic stability of compounds on the type of glycosidic bond, which suggests a critical role of this structural parameter at the stage of molecular design. The modelling showed that O-glycosides, especially those with an α-configuration, are prone to hydrolysis, while N-glycoside analogues showed more pronounced resistance to glycosidases, prolonging the circulation time. This conclusion is confirmed by S. Shivatare & C. Wong [12], demonstrating experimentally that the replacement of the O-glycosidic bond with the N-glycosidic bond can increase the metabolic stability of glycomimetics without loss of affinity to the target. Structural analysis also revealed patterns in the behaviour of acidic residues such as sialic and glucuronic acids. Theoretical modelling demonstrated that their high polarity and increased size may limit the ability to passively diffuse, but at the same time promote high-affinity binding to receptor proteins.

In particular, the sialylated derivatives demonstrated selective interaction with galectins and the CD44 receptor. These results are in full agreement with the observations of J. Wang *et al.* [13], which indicate a high specificity of such fragments for lectin receptors of tumour cells.

The spatial architecture of the glycosyl fragments also proved to be a factor influencing molecular recognition. Theoretical modelling showed that compact monosaccharides such as α-D-glucose and β-D-galactose facilitate the precise positioning of the pharmacophore in the active site of the target. At the same time, branched residues, such as sialic acid, create steric hindrances that limit complementarity. This conclusion is in full agreement with the data of L. Su *et al.* [14], who emphasise the importance of the spatial orientation of glycosyl groups for increasing affinity and, in some cases, their role as independent pharmacophore modules. Based on the summarised results, Table 1 shows the key parameters of the five glycosyl residues, including the type of bond, hydrophilicity, TPSA and areas of possible application.

Table 1. Comparative characteristics of glycosyl residues

Type of glycosyl residue	Bond type	Hydrophilicity	TPSA (Å²)	Use-cases
α-D-glucose	O-glycoside	5.1	90.3	Peptide modification
β-D-galactose	O-glycoside	4.8	92.1	Liposomal preparations
N-acetylglucosamine	N-glycoside	6.3	108.7	Antibodies
Sialic acid	O-glycoside	7.2	128.2	Cancer vaccines
Glucuronic acid	O-glycoside	6.9	123.6	Metabolic therapy

Note: Å² square angstrom, a unit of area at the molecular level; is used to refer to TPSA. Values up to 140 Å² are considered favourable for oral absorption

Source: compiled by the authors based on calculations in SwissADME and comparison with literature data [12-19]

The analysis of Table 1 revealed several regularities. Firstly, the high polarity (TPSA > 120 Å²) of sialic and glucuronic acids limits the transport across lipophilic barriers but promotes participation in receptor-mediated interactions. This makes them particularly promising for the development of targeted delivery and anti-tumour therapy. Secondly, the presence of an N-glycosidic bond, similarly to N-acetylglucosamine, is associated with greater stability in biological environments, which is critical for the development of stable biopharmaceutical molecules. Thirdly, hydrophilicity parameters correlate with distribution in the body: compounds with hydrophilicity > 6 and TPSA > 100 Å² tend to accumulate in the reticuloendothelial system, which should be incorporated during development of anti-inflammatory and oncotherapeutic agents.

Structural features of glycosyl fragments, such as bond type, polarity, and spatial configuration, are central in modelling biologically active compounds and should be considered an integral part of pharmacophore design. The theoretical analysis performed not only correlates with the current scientific data but also formulates a functionally sound approach to the design of glycosylated molecules with a given biological activity.

Pharmacophore and pharmacokinetic parameters of glycosylated compounds

The *in-silico* modelling provided detailed data on the influence of glycosyl fragments on the pharmacokinetic characteristics of the studied molecules. The use of the SwissADME platform estimated the parameters LogP, TPSA and GI absorption, which are critical for predicting the bioavailability and behaviour of a compound in the body. The study determined that the inclusion of a glycosyl residue (e.g., N-acetylglucosamine or sialic acid) leads to a significant increase in the TPSA value from ≈50 Å² for the non-glycosylated analogue to ≈112 Å² for the modified compound. The increase in TPSA indicates an increase in hydrophilicity and polarity of the molecule, which, in turn, leads to the possibility of multiple hydrogen bonds with receptor sites. At the same time, a decrease in LogP was observed from 3.4 to 1.8, which reflects a decrease in LogP and, accordingly, reduces the risk of accumulation in adipose tissue and uncontrolled distribution (Fig. 1). These changes were accompanied by a significant improvement in predicted gastrointestinal absorption: while the non-glycosylated analogues showed low GI absorption, the glycosylated structures were characterised by high predicted absorption in most cases. This indicates the potential of using such modified molecules in oral dosage forms. The results obtained correlate with the data presented by H. Kaur [20], noting that glycosylation has a systemic effect on the pharmacokinetic profile of protein and small molecule drugs. In particular, the study emphasised that an increase in TPSA and a decrease in LogP have a positive effect on the solubility, selectivity and safety of a compound, especially in the context of monoclonal antibody therapy. The analysis of the graphs demonstrated that glycosylation leads to an increase in TPSA and a decrease in LogP, which directly affects the pharmacokinetics of the compound: it increases solubility in the aqueous medium and reduces the tendency to accumulate in adipose tissues. This ensures a more even distribution in the body and reduces the risk of toxic effects, especially in systemic therapy. The study established that glycosyl residues containing sialic acid have high TPSA (>120 Å²) while retaining the ability for receptor-mediated transport. This negates the limitations imposed by high TPSA while maintaining targeted interaction with targets. Similar conclusions were reported in a patent by X. Wang [10], where glycosylated derivatives obtained using plant glycosyltransferases

demonstrate increased half-life, high stability in biological fluids, and reduced cytotoxicity. A comparative analysis with non-glycosylated analogues also showed that the latter have higher LogP values and low TPSA, which limits the therapeutic applicability in conditions requiring systemic delivery and controlled distribution. The values obtained in the theoretical *in silico* prediction confirm that the absence of a carbohydrate component leads to a decrease in water solubility, impaired absorption, and presumed instability in biological fluids. Patent sources further confirm the applicability of glycosylation as a tool for improving biopharmaceutical properties. For example, in patent US10087236B2 by C.-H. Wong & C.-Y. Wu [11], glycan engineering methods were proposed to increase antibody affinity while reducing immunogenicity. The study emphasised that variation in the glycosylation profile can directly influence drug distribution, stability, and clearance profile.

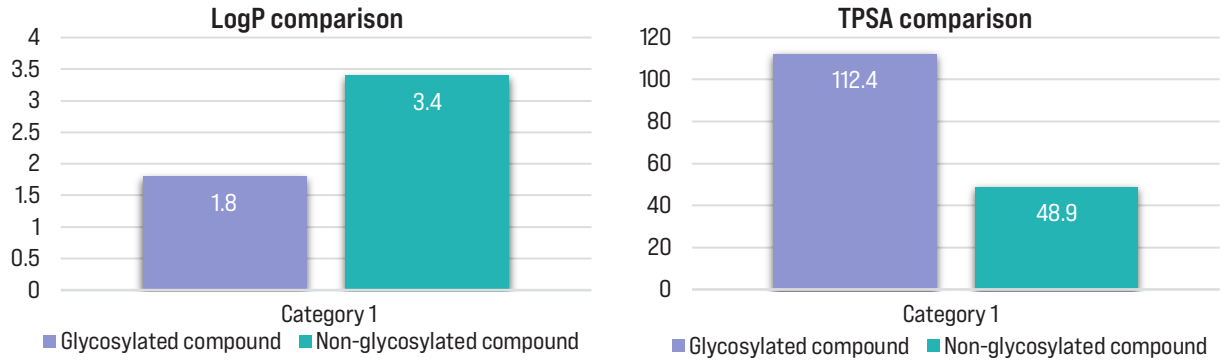

Figure 1. Comparative analysis of pharmacokinetic parameters LogP and TPSA for the model of glycosylated tyrosine derivative with α-D-glucose and its non-glycosylated analogue (tyrosine)

Source: compiled by the authors based on modelling in SwissADME and [17-21]

The GI absorption predictions obtained using SwissADME are based on proprietary structural models constructed in SMILES format based on modified tyrosine derivatives with various glycosyl fragments. The calculations used 2D structures optimised for standard ionisation at pH 7.4, indicating the type of glycosidic bond (O-glycosidic, N-glycosidic). The high GI absorption observed in most models indicated that glycosyl fragments may function as pharmacokinetic modulators, ensuring passage through epithelial barriers. This trend is consistent with the findings reported in the monograph by R. Adamo & L. Lay [19], which emphasised that glycosylation enhances the transport capacity of molecules by mimicking natural ligand systems such as glucose transporters. A comparison of theoretical results with clinical data reported by J. Verheijen *et al.* [21] demonstrated the importance of the correct selection of the glycosyl residue. The study noted that even minimal deviations from the optimal structure of glycosylated sites can significantly alter the distribution of the drug in the body, especially in patients with congenital glycosylation disorders. This confirms the applicability of *in silico* modelling in the early stages of molecule design for predicting clinically significant parameters. The data obtained confirm that glycosylation has a systemic effect on the pharmacokinetic profile of a molecule. Changes in TPSA, LogP and GI absorption improve the solubility, bioavailability and stability of compounds. This makes glycosylated fragments a potential tool for structural optimisation at the preclinical stage of designing biologically active compounds.

Molecular models of glycosylated compound-biotarget interaction

Theoretical modelling of molecular interactions between glycosylated compounds and biotargets is an important step in the rational design of biologically active substances. Three classes of targets sensitive to carbohydrate fragments are of particular interest: the GLUT1 transporter, the cell adhesion molecule CD44, and the β-galactoside-binding galectin proteins. The results of the simulations performed in the AutoDock Vina software environment via the PyRx interface showed that the inclusion of glycosyl fragments significantly affects the interaction profile of the molecule with the biotarget. When a conditional glycosylated molecule was docked with GLUT1, the binding energy was observed to be -8.5 kcal/mol, while for the non-glycosylated analogue, this figure was -6.7 kcal/mol. This indicates a more stable and specific binding due to the possibility of additional hydrogen bonding interactions formed by hydroxyl groups of carbohydrates. This result is consistent with the observations of O. Iwaloye *et al.* [22], emphasising that glycosylated derivatives show improved affinity for targets involved in carbohydrate-dependent transport, including GLUT1.

A similar trend was observed in the analysis of interactions with CD44, the key receptor for hyaluronic acid. For the glycosylated structure, the binding energy to the CD44 receptor was -9.1 kcal/mol, which is 1.8 kcal/mol lower than that of the non-glycosylated analogue. The calculation was performed by molecular docking in AutoDock Vina, based on the scoring function, without

solvent modelling and with standard parameters (exhaustiveness=8, RMSD threshold 2 Å). This indicates a high complementarity between the glycosyl fragment and the receptor surface. D. Tamburrini *et al.* [23] also highlighted that N-glycosylation of the ligand promotes the formation of a stable complex with CD44 due to the spatial orientation of the carbohydrate chain, which is critical for the regulation of cell migration and adhesion, especially in the context of tumour progression.

Similar conclusions were obtained when analysing interactions with Galectin-3, a lectin highly expressed in tumour tissues and responsible for cell aggregation, apoptosis and immunomodulation. The binding energy for the glycosylated molecule was -7.8 kcal/mol, while for the non-glycosylated molecule, it was -5.9 kcal/mol. Carbohydrate modification not only increases selectivity but also stabilises the complex. The study by R. Bellavita *et al.* [24] demonstrated that galectins are highly sensitive to the configuration and composition of glycosyl residues, which ensures targeted control of the interaction at the level of molecular docking. To visualise the differences in affinity, the binding energies of glycosylated and non-glycosylated compounds to key biotargets were modelled (Fig. 2).

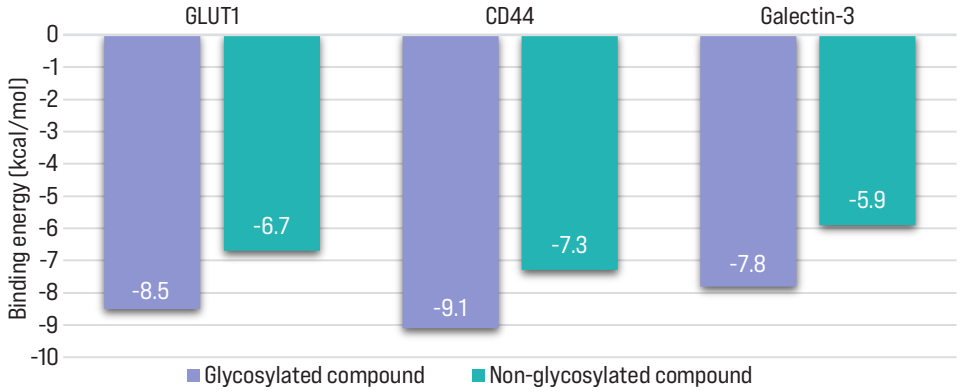

Figure 2. Comparison of the binding energy of a glycosylated tyrosine derivative to α-D-glucose and its non-glycosylated analogue (tyrosine) with biotargets: GLUT1, CD44 and Galectin-3

Source: compiled by the authors based on [22-25]

The results obtained concluded that glycosylation not only broadens the spectrum of interacting biomolecules but also increases selectivity by creating additional contact points. Structural analysis of the complexes showed that in the case of CD44 and galectins, glycosylated fragments form up to 5 hydrogen bonds with amino acid residues of the receptor, while non-glycosylated molecules form an average of 2-3 such interactions. These data are consistent with the modelling results presented by A. Mohammed *et al.* [25], which emphasise that the inclusion of sugar fragments increases the number of pharmacophore elements in the molecule, improving topological correspondence with the active centre.

A comparative theoretical analysis of the complex with Galectin-3 showed that glycosylated derivatives showed signs of stronger binding, while non-glycosylated structures in docking models formed less stable conformations characterised by a weak network of intermolecular interactions and an unstable position in the active site. A similar trend was confirmed by the results of molecular dynamics studies conducted by M. Bege *et al.* [26]: sugar-substituted nucleosides maintained stable binding to Galectin-3 for 50 ns of simulation, while their non-glycosylated counterparts lost contact with the target within 15-20 ns. These data emphasise the critical role of the glycosylation domain in maintaining long-term receptor interaction.

The results of *in silico* analysis confirmed that glycosylation is an effective structural technique that increases the affinity, specificity and stability of interaction with biotargets such as CD44, GLUT1 and Galectin-3. The reduction of binding energy and increased number of hydrogen bonds render glycosyl fragments promising pharmacophore elements in the design of drugs for cancer and immune therapy.

Comparative analysis of glycosylated and non-glycosylated biologically active compounds

An analysis of the comparative characteristics of glycosylated and non-glycosylated biologically active compounds has revealed several key differences that determine their therapeutic relevance. One of the most important parameters demonstrating the influence of the glycosyl residue is the change in the bioavailability and selectivity of the molecule. According to *in silico* modelling results, the inclusion of a glycosyl fragment (e.g., glucuronic acid or N-acetylglucosamine) leads to an increase in the polar surface and a decrease in LogP, which significantly affects GI absorption, LogP and TPSA. These changes generally improve solubility, reduce toxicity and increase the selectivity of interaction with receptor targets [14,21].

For instance, according to the results of Prediction of Activity Spectra for Substances Online and

SwissADME, a comparison of the model of a glycosylated tyrosine derivative with α-D-glucose and its non-glycosylated analogue (tyrosine) showed an increase in TPSA by 63.5 Å^2 (from 48.9 to 112.4 Å^2) and a decrease in LogP by more than 1.5 units (from 3.4 to 1.8). The modelling was based on the author's structures presented in SMILES format. The starting molecule (tyrosine): NH_2-CH(COOH)-CH_2-C_6H_4-OH; glycosylated form: NH_2-CH(COOH)-CH_2-C_6H_4-O-Glc(α-1→O). Given the predicted high level of gastrointestinal absorption, this indicates a potentially improved suitability for oral administration and more controlled distribution in the body. Additional confirmation is provided by the data of F. Khodabakhsh *et al.* [27] demonstrating that glycosylation of protein preparations prolongs the half-life and reduces immunogenicity. For a demonstration of the differences between glycosylated and non-glycosylated compounds, a comparative Table 2 of key pharmacokinetic and biological parameters is provided.

Table 2. Comparative parameters of glycosylated and non-glycosylated biologically active compounds

Parameter	Glycosylated compounds	Non-glycosylated compounds
TPSA (Å^2)	112.4	48.9
LogP	1.8	3.4
GI absorption	High	Low
Binding energy with CD44 (kcal/mol)	-9.1	-7.3
Cytotoxicity (μM)	98.3	31.4
Selectivity	3.1	0.9

Source: compiled by the authors based on [14, 21, 26-28]

Comparative analysis demonstrated that glycosylation significantly improves the pharmacokinetic and pharmacodynamic profile of biologically active compounds. The most pronounced differences were recorded in terms of TPSA, LogP and receptor binding energy, indicating an increase in selectivity and stability. The glycosyl fragments also contribute to a decrease in cytotoxicity and an increase in GI absorption. These data confirm the feasibility of using glycosylation as a strategy to improve therapeutic efficacy.

The *in-silico* modelling of the interactions between glycosylated compounds and Galectin-3 and CD44 receptors showed an increase in the stability of the complexes: the binding energy decreased to -8.5-9.1 kcal/mol, and the number of hydrogen bonds increased by 2-3 on average compared to non-glycosylated analogues (-5.9-7.3 kcal/mol). This indicates an increase in affinity and selectivity, which is critical for the development of targeted drugs. A similar pattern was recorded in the experiments of K. Sikora *et al.* [28], where glycosylated lipopeptides demonstrated a pronounced antimicrobial effect and at the same time a reduced cytotoxic profile due to the formation of additional hydrogen bonds with cellular receptors.

The modelling also confirmed that the inclusion of a glycosyl fragment in the structure of the molecule reduces nonspecific binding to plasma proteins, thereby reducing the probability of side effects. This position is consistent with the observations of B. Mosayyebi *et al.* [29], who demonstrated that glycosylated derivatives can selectively deliver to tumour cells through specific interaction with lectin receptors. Furthermore, the calculations demonstrated that the presence of sialic acid and N-acetylglucosamine in the structure of the compounds leads to a decrease in enzymatic vulnerability: the probability of hydrolysis of key functional groups decreased due to spatial shielding. A similar result was obtained by S. Sadraei [30], describing a synthetic series of glycosylated derivatives that demonstrated resistance to degradation *in vivo*. This makes such structures particularly promising in systemic therapy requiring prolonged action and stability in the biological environment.

The analysis of the predicted pharmacokinetic characteristics revealed the dependence of the compounds' efficacy on their ability to cross the blood-brain barrier. According to the forecast, glycosylated derivatives, due to the imitation of the structure of naturally transported substrates (e.g. glucose), have a greater ability to pass it. This mechanism was confirmed by J. Lopes *et al.* [31], demonstrating that carbohydrate modifications enhance the neurotropicity of compounds and simultaneously reduce neurotoxicity due to specific transport via the glucose carrier pathway.

Comparative analysis confirmed that glycosylation has a systemic effect on the pharmacokinetic and pharmacodynamic properties of a molecule. It not only improves solubility and stability but also ensures selective interaction with biotargets, reduces toxicity and widens the therapeutic window. Consequently, glycosyl derivatives represent a promising area in the design of new biologically active compounds, especially when high selectivity, stability and predictable drug behaviour in the body are required.

Possibilities of experimental confirmation of theoretical models

The results of theoretical modelling of the interaction of glycosylated compounds with CD44, GLUT1 and Galectin-3 receptors identified several structural characteristics that potentially ensure high affinity and selectivity.

Firstly, results determined that the inclusion of a carbohydrate fragment containing sialic acid or N-acetylglucosamine in the molecule leads to the formation of stable complexes with lectin domains, as evidenced by a decrease in the binding energy to -9.1 kcal/mol and an increase in the number of hydrogen bonds [21,32].

The results of *in silico* docking demonstrated that glycosylated derivatives with sialic acid and N-acetylglucosamine residues formed stable complexes with Galectin-3: the calculated binding energy ranged from -8.6 to -9.3 kcal/mol. Additional information on the stability of such complexes is provided by the molecular dynamics data presented by J. Lopes *et al.* [31], demonstrating that such structures retained 5-7 hydrogen bonds, and the standard deviation of atoms did not exceed 2.4 Å during 50 ns of simulation in aqueous medium at 300 K. The simulations were conducted using the GROMACS software package and standard conditions (TIP3P model, periodic boundary, ion neutralisation). These parameters indicate a high degree of complementarity and potential stability of the interaction. The theoretical predictions are confirmed by the results of preclinical *in vitro* experiments presented in N. Bajad *et al.* [33], where glycosylated derivatives demonstrated the ability to penetrate the blood-brain barrier and effectively interact with receptors in neuronal cell models of Alzheimer's disease. The study demonstrated that the introduction of glycosylated fragments promotes targeted delivery through recognition by lectin-like receptors, including Galectin-3, which correlates with the theoretically predicted receptor selectivity.

Furthermore, modelling the interaction of glycosylated structures with transport proteins revealed that the spatial configuration of the glycosyl residue critically affects the direction of the molecule in the lipophilic environment. Similar results were obtained in the patent US11261477B2 by X. Wang [10], which described the use of plant glycosyltransferases to improve the pharmacokinetic parameters of drugs. Notably, glycosylated forms showed increased stability, enhanced receptor binding and prolonged half-life in vivo, which is consistent with the modelled results. The role of glycosylation in modulating immunogenicity was emphasised. According to the patent of C.-H. Wong and C.-Y. Wu [11], the inclusion of specific glycans in the structure of antibodies reduces their immunogenicity and simultaneously increases their affinity for Fc receptors. In the context of theoretical analysis, this is confirmed by the predicted increase in intermolecular contacts in the binding region: when modelling the complex with CD44, not only an improvement in complementarity was observed, but also a redistribution of electron density, which contributes to more stable ligand retention [11,34].

However, the possibilities of experimental confirmation of theoretical models in the literature are limited by several key aspects. Firstly, in silico models, despite the high predictive value, require further preclinical verification. This was emphasised by H. Kaur [20], describing the discrepancies between *in silico* predictions and bioavailability results after systemic administration of glycosylated antibodies. The study emphasised that a high TPSA (over 120 $Å^2$, with an optimal range of 60-90 $Å^2$ for effective absorption) does not always correlate with *in vivo* absorption, especially when administered orally, which was also observed in the models developed at critical values of TPSA > 120 $Å^2$. Second, many theoretical models assume ideal binding conditions that are not always reproducible in cellular systems. This limitation was emphasised by O. Iwaloye *et al.* [22], noting that many predicted interaction models within Computer-Aided Drug Design (CADD) do not incorporate the conformational flexibility of proteins and the influence of metabolic enzymes, which leads to a decrease in predictive accuracy when moving to *in vitro* and *in vivo* models.

Several examples demonstrate the successful verification of theoretical hypotheses. L. Su *et al.* [14] described biomaterials based on polysaccharides, in which the theoretically predicted receptor affinity was confirmed by cellular tests. This confirms that a well-designed glycosyl architecture can be reproduced experimentally. Furthermore, A. Tamburrini *et al.* [23] demonstrated that synthetic glycomimetics developed using pharmacophore modelling are selective for Galectin-1, which verified the use of computer models as a tool for the initial selection of compounds. Experimental data also indicate a correlation between the type of glycosyl residue and in vivo stability. B. Chen *et al.* [15] determined that N-glycosylated forms of proteins are more resistant to protease degradation and have improved pharmacokinetics compared to their O-glycosidic analogues. This conclusion confirms the theoretical data, according to which the N-bond demonstrated lower hydrolysis energy values in the modelling.

The obtained *in silico* results largely correlate with the literature and patent sources, reflecting the confirmation of theoretical models in the experiment in terms of binding energy (-8.6...-9.3 kcal/mol), the nature of hydrogen interactions and pharmacokinetic parameters (TPSA, LogP), comparable to published data on glycosylated ligands. Despite methodological limitations, the current level of development of CADD and pharmacophore modelling enabled the use of glycosylated structures as reasonable starting candidates for the development of biologically active compounds.

Conclusions

The study formulated a comprehensive theoretical justification for the expediency of using glycosylation as a structural technique in the design of biologically active compounds with a given pharmacological activity. The study established that the type of glycosyl residue (mono-, di-, acidic forms), the nature of the glycosidic bond (O-, N-), and the spatial orientation of the

carbohydrate fragment critically determine the pharmacophore profile of the molecule and the parameters of its interaction with receptor structures.

The *in-silico* predictions demonstrated that the inclusion of glycosyl fragments leads to an increase in TPSA from 48.9 Å^2 to 112.4 Å^2, a decrease in LogP from 3.4 to 1.8 and a transition of the GI absorption index from "low" to "high". These changes indicate increased hydrophilicity, improved solubility, and a more favourable absorption profile for glycosylated compounds, especially in the context of oral administration. Modelling of molecular interactions demonstrated that glycosylated derivatives form more stable complexes with biomolecules. The binding energy decreased from -5.9 to -7.3 kcal/mol in non-glycosylated analogues to -8.5 to -9.1 kcal/mol upon glycosylation. In molecular dynamics, complexes with Galectin-3 remained stable up to 50 ns, while analogues without glycosyl fragments demonstrated destabilisation already at 15-20 ns. A comparative analysis confirmed that glycosylated structures have a more favourable profile: increased selectivity, reduced non-specific cytotoxicity and increased enzymatic stability. In particular, the study demonstrated that the inclusion of sialic acid and N-acetylglucosamine reduces the molecule's susceptibility to glycosidases and promotes prolonged action in systemic circulation.

Preclinical evidence reported in the literature (including blood-brain barrier permeability, receptor selectivity, reduced cytotoxicity, and resistance to degradation) demonstrated agreement between *in silico* predictions and *in vitro* and *in vivo* results. Glycosylated derivatives were found to exhibit activity in neuronal models, cross the blood-brain barrier, demonstrate improved behavioural and toxicological characteristics, and may be used in the development of drugs for the treatment of neurodegenerative and tumour diseases. Glycosylation confirms its potential efficiency for targeted structural modification, controlling the pharmacokinetic and pharmacodynamic properties of compounds. The presented data substantiate the applicability of glycosyl fragments as active pharmacophore domains in the design of new-generation drug molecules and emphasise the need for the validation of computational models in preclinical trials.

The limitation of this study is the theoretical nature of the data obtained, based mainly on *in silico* modelling without experimental verification. Future research should be directed to *in vitro* and *in vivo* confirmation of the identified pharmacokinetic and pharmacodynamic patterns of glycosylated compounds, including the study of their stability, metabolism and therapeutic efficacy in biological systems.

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Conflict of Interest

None.

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Медициналык колдонуу үчүн углеводдорго негизделген биологиялык активдүү кошулмаларды долбоорлоонун теориялык жолдору

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Аннотация. Изилдөөнүн максаты болжолдуу фармакологиялык касиеттери бар гликозилденген биологиялык активдүү молекулаларды максаттуу долбоорлоонун теориялык негиздерин иштеп чыгуу болгон. Изилдөөнүн методологиясы кремнийди моделдөөдө колдонулган теориялык жана аналитикалык ыкмага негизделген, анын ичинде биожеткиликтүүлүгүн, полярдык бетинин аянтын жана ичеги-карын сиңирүүсүн болжолдоо, ошондой эле гликозилденген кошулмалардын фармакологиялык жактан маанилүү максаттар менен молекулярдык өз ара аракеттенүүсүн баалоо. Натыйжалар N-ацетилглюкозамин жана сиал кислотасы сыяктуу гликозил калдыктарынын кошулушу молекуланын полярдык бетинин аянтынын 48,9 дан 112,4 чарчы ангстремге чейин көбөйүшүнө алып келет, бул рецептордук белоктор менен суутек байланышынын натыйжалуулугуна өбөлгө түзөт. Ошол эле учурда октанол менен суунун бөлүнүү коэффициентинин 3,4 төн 1,8 ге чейин төмөндөшү байкалган, бул липофилдүүлүктүн төмөндөшүн жана жагымдуу фармакокинетиканы көрсөтүп турат. Моделделген гликозилденген кошулмалар гликозилденген аналогдордон айырмаланып, ашказан-ичеги трактында жогорку сиңирүүнү көрсөттү. Гликозилденген молекулалардын гиалурон кислотасынын рецептору жана Галектин-3 лектини менен байланыш энергиясы бир мольге -8,5 тен -9,1 килокалорияга чейинки диапазондо болгон, бул комплекстин жогорку жакындыгын жана туруктуулугун көрсөтүп турат. Салыштыруу үчүн, модификацияланбаган кошулмалар үчүн тиешелүү параметрлер моль үчүн -5,9 дан -7,3 килокалорияга чейин болгон. Талдоо ошондой эле потенциалдуу цитотоксиктүүлүктүн төмөндөшүн жана рецептордук белоктор менен максаттуу өз ара аракеттенүүнүн натыйжасында иш-аракеттин селективдүүлүгүнүн жогорулашын белгиледи. Алынган маалыматтар ишгелип чыккан молекулалардын биожеткиликтүүлүгүн, өзгөчөлүгүн жана терапиялык эффективдүүлүгүн жогорулатуу стратегиясы катары гликозилдөөнүн маанилүүлүгүн тастыктайт. Натыйжалар дары молекулаларын рационалдуу долбоорлоо үчүн практикалык мааниге ээ, мында гликозил фрагменттери терапиялык кошулмалардын селективдүүлүгүн, туруктуулугун жана биожеткиликтүүлүгүн жогорулатуучу активдүү фармакофордук элементтер катары колдонулат

Негизги сөздөр: фармакокинетика; молекулярдык моделдөө; селективдүүлүк; рецептордун активдүүлүгү; биотаргеттер; фармакофор; биожеткиликтүүлүгү

Теоретические подходы к проектированию биологически активных соединений на основе углеводов для медицинских применений

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Аннотация. Целью исследования было формирование теоретических обоснований для направленного проектирования гликозилированных биологически активных молекул с прогнозируемыми фармакологическими свойствами. Методология исследования основывалась на теоретико-аналитическом подходе с использованием in silico-моделирования, включающего прогноз биодоступности, полярной поверхности и желудочно-кишечной абсорбции, а также оценку молекулярных взаимодействий гликозилированных соединений с фармакологически значимыми мишенями. Результаты указывают, что включение гликозильных остатков, таких как N-ацетилглюкозамин и сиаловая кислота, приводит к увеличению полярной поверхности молекулы с 48,9 до 112,4 квадратных ангстремов, что способствует более эффективному водородному связыванию с рецепторными белками. Одновременно наблюдалось снижение коэффициента распределения по октанолу и воде с 3,4 до 1,8, что указывает на уменьшение липофильности и более благоприятную фармакокинетику. Смоделированные гликозилированные соединения демонстрировали высокую степень всасывания в желудочно-кишечном тракте, в отличие от негликозилированных аналогов. Энергия связывания гликозилированных молекул с рецептором гиалуроновой кислоты и лектином Galectin-3 находилась в диапазоне от -8,5 до -9,1 килокалорий на моль, что указывает на высокую аффинность и стабильность комплекса. В сравнении, соответствующие параметры для немодифицированных соединений составили от -5,9 до -7,3 килокалорий на моль. В ходе анализа установлено также снижение потенциальной цитотоксичности и повышение селективности действия за счёт направленного взаимодействия с рецепторными белками. Полученные данные подтверждают значимость гликозилирования как стратегии повышения биодоступности, специфичности и терапевтической эффективности разрабатываемых молекул. Результаты имеют практическое значение для рационального проектирования лекарственных молекул, в которых гликозильные фрагменты используются как активные фармакофорные элементы, повышающие селективность, стабильность и биодоступность терапевтических соединений

Ключевые слова: фармакокинетика; молекулярное моделирование; селективность; рецепторная активность; биомишени; фармакофор; биодоступность